ROSEN'S
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Concepts and Clinical Practice

9th Edition

Rosen's Emergency Medicine

Concepts and Clinical Practice

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MV

It is both humbling and a privilege to be associated with this text and those who started it all— Rosen, Marx, Walls, and Hockberger—the founders of our discipline.

RDZ

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Preface to the Ninth Edition

When we began planning for this ninth edition, we challenged ourselves to make substantial and meaningful improvements to a book that has become the trusted standard in our field. With broad and rapid changes occurring in health care and information sciences, we recognized that relevance is not an accidental or passive concept. To advance in relevance and consolidate the book's position as the defining reference in our specialty, we carefully and deliberately undertook bold changes that we know make the book at once fresh, directive, and current in a way we have never before dared.

First, we created a substantially enhanced role for our editors, one that would demand a great deal more of their time, creativity, and energy. This helped us build a substantially different team of editors, a perfectly balanced blend of those with great experience with prior editions and those who would bring new ideas and challenge our assumptions. Ron Walls was asked to serve as Editor-in-Chief, with Bob Hockberger in his long-standing role as senior editor. Marianne Gausche-Hill, a highly respected academic emergency physician with service as editor on four previous editions, stepped up to complete our senior editorial ranks. At the editor level, Dr. Andy Jagoda returns and is joined by six brilliant new editors drawn from academic programs from coast to coast—Drs. Katherine Bakes, Jill Baren, Timothy Erickson, Amy Kaji, Michael VanRooyen, and Richard Zane. This dynamic and innovative editorial team has dramatically redrawn our text's blueprint by preserving what has served our readers the best, such as well-written discussions of the pathophysiologic basis of illness and injury, while moving in entirely new directions in providing pithy, clear, and succinct recommendations for diagnosis and treatment.

We collectively determined that all references prior to 2010 have been sufficiently long in the public domain that they no longer warrant citation. The infrequent exception to this is for guidelines that were issued in 2007 or later and have not been reissued or supplanted since. Strict adherence to our referencing policy required authors to diligently provide well-researched and detailed updates to their chapter content, based on only the most recent and relevant medical literature. In cases in which the literature is controversial or unclear, we have used the combined experience and expertise of our authors and editors to present cogent analyses of diagnostic and treatment options, make specific recommendations, and give the reader clear indications of the preferred actions. This makes the book much more immediately relevant for emergency clinicians. We recognize that emergency medicine is practiced by specialist emergency physicians, other physicians, residents and other trainees, and a variety of nonphysician practitioners, so were careful to ensure that we are addressing all these groups with the same concise, highest quality information and recommendations.

We revisited page counts for every chapter, adjusting allocations where indicated, and added new chapters on several important topics. We focused anew on consistency and redundancy, enhancing the former and minimizing the latter. We moved some chapters to online access only, allowing us to add new topics of interest, such as drug therapy for older patients, and have provided a rich array of dynamic videos and images, especially in emergency ultrasound. We substantially expanded and reorganized the pediatric emergency medicine section, introducing dedicated pediatric chapters on airway management, procedural sedation, and drug therapy. We introduced significant new material on emergencies in the pregnant woman, the patient with cancer, and a variety of other highly important clinical conditions. And, in every possible case, we insisted on adherence to referencing and writing requirements, a focus on relevant directive information, and appropriate use of prose and illustrations to provide the perfect balance of depth, breadth, and ready accessibility.

We are enormously proud of the result, a different, more readable "*Rosen,*" preserving the gravitas earned over 30 years as the most important book in our specialty while embracing the modern era of emergency medicine practice and research and an entirely new generation of learners and practitioners. For those who have owned prior editions, we appreciate your loyalty over so many years and hope to reward it with a significantly improved and useful companion for your continuing learning and practice of this great specialty. For our newer readers, welcome, and thank you for inspiring us to make significant changes to an iconic and timeless part of our academic heritage.

Ron M. Walls
Robert S. Hockberger
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How This Medical Textbook Should Be Viewed by the Practicing Clinician and Judicial System

The editors and authors of this text strongly believe that the complex practice of medicine, vagaries of human diseases, unpredictability of pathologic conditions, and functions, dysfunctions, and responses of the human body cannot be defined, explained, or rigidly categorized by any written document. *Therefore, it is neither the purpose nor intent of our textbook to serve as an authoritative source on any medical condition, treatment plan, or clinical intervention, nor should our textbook be used to rigorously define a standard of care that should be practiced by all clinicians.*

Our written word provides the physician with a literature-referenced database and a reasonable clinical guide combined with practical suggestions from individual experienced practitioners. We offer a general reference source and clinical road map on a variety of conditions and procedures that may confront emergency clinicians who are experienced in emergency medicine practice. This text cannot replace physician judgment, cannot describe every possible aberration, nuance, clinical scenario, or presentation, and cannot define rigid standards for clinical actions or procedures. *Every medical encounter must be individualized, and every patient must be approached on a case-by-case basis.* No complex medical interaction can possibly be reduced to the written word. The treatments, procedures, and medical conditions described in this text do not constitute the total expertise or knowledge base expected to be possessed by all emergency clinicians. Finally, many of the described complications and adverse outcomes associated with implementing or withholding complex medical and surgical interventions may occur, even when every aspect of the intervention has been standard or performed correctly.

The editors and authors of Rosen's Emergency Medicine: Concepts and Clinical Practice, Ninth Edition

SECTION ONE
Critical Management Principles

CHAPTER 1
Airway

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PRINCIPLES

Background

Airway management is the cornerstone of resuscitation and is a defining skill for the specialty of emergency medicine. The emergency clinician has primary airway management responsibility, and all airway techniques lie within the domain of emergency medicine. Although rapid sequence intubation (RSI) is the most commonly used method for emergent tracheal intubation, emergency airway management includes various intubation techniques and devices, approaches to the difficult airway, and rescue techniques when intubation fails.

Anatomy, Physiology, and Pathophysiology

The decision to intubate should be based on careful patient assessment and appraisal of the clinical presentation with respect to three essential criteria: (1) failure to maintain or protect the airway; (2) failure of ventilation or oxygenation; and (3) the patient's anticipated clinical course and likelihood of deterioration.

Failure to Maintain or Protect the Airway

A patent airway is essential for adequate ventilation and oxygenation. If a patient is unable to maintain a patent airway, the airway should be established by using airway maneuvers such as repositioning, chin lift, jaw thrust, or insertion of an oral or nasal airway. Likewise, the patient must be able to protect against the aspiration of gastric contents, which carries significant morbidity and mortality. Historically, the presence of a gag reflex has been advocated as a reliable indicator of the patient's ability to protect the airway, but this has been definitively proven to be unreliable because the gag reflex is absent in 12% to 25% of normal adults, and there is no evidence that its presence or absence corresponds to airway protective reflexes or predicts the need for intubation. The patient's ability to swallow or handle secretions is a more reliable indicator of airway protection. The recommended approach is to evaluate the patient's level of consciousness, ability to phonate in response to voice command or query, which provides information about the integrity of the upper airway and level of consciousness, and ability to manage his or her own secretions (eg, pooling of secretions in the oropharynx, absence of swallowing spontaneously or on command). In general, a patient who requires a maneuver to establish a patent airway or who easily tolerates an oral airway requires intubation for airway protection, unless there is a temporary or readily reversible condition, such as an opioid overdose.

Failure of Ventilation or Oxygenation

Gas exchange, both oxygenation and removal of carbon dioxide, is required for vital organ function. Ventilatory failure that is not reversible by clinical means or persistent hypoxemia despite maximal oxygen supplementation is a primary indication for intubation. This assessment is clinical and includes an evaluation of the patient's general status, oxygen saturation by pulse oximetry, and ventilatory pattern. Continuous capnography also can be helpful but is not essential if oximetry readings are reliable. Arterial blood gases (ABGs) generally are not required to determine the patient's need for intubation. In most cases, clinical assessment, including pulse oximetry with or without capnography, and observation of improvement or deterioration in the patient's clinical condition lead to a correct decision. ABG results are rarely helpful, are time-consuming to obtain, and may be misleading, causing a false sense of security and delay in intubating a deteriorating patient. If obtained, they should be interpreted carefully in the context of the patient's clinical status. Patients who are clinically improving despite severe or apparently worsening ABG alterations may not require intubation, whereas a rapidly tiring asthmatic may require intubation, even though ABG values are only modestly disturbed.

The need for prolonged mechanical ventilation generally mandates intubation. An external mask device, continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BL-PAP), have all been used successfully to manage patients with exacerbations of chronic obstructive pulmonary disease (COPD) and congestive heart failure, obviating the need for intubation (see Chapter 2) but, despite these advances, many patients who need assisted ventilation or positive pressure to improve oxygenation require intubation.[1,2]

Anticipated Clinical Course

Certain conditions indicate the need for intubation, even without an immediate threat to airway patency or adequacy of ventilation and oxygenation. These conditions are characterized by a moderate to high likelihood of predictable airway deterioration or the need for intubation to facilitate a patient's evaluation and treatment. Intubation may be indicated relatively early in the course of certain overdoses. Although the patient initially may be protecting the airway and exchanging gas adequately, intubation is advisable to guard against the strong likelihood of clinical deterioration, which can occur after the initial phase of care when the patient is no longer closely observed. A patient who has sustained significant multiple traumatic injuries may require intubation, even if the patient is ventilating normally through a patent airway and has adequate oxygen levels. For example, a multiple trauma

patient with hypotension, open femur fracture, and diffuse abdominal tenderness warrants early intubation, even if the patient is initially awake and alert, without airway injury or hypoxemia. Active resuscitation, pain control, need for invasive procedures and imaging outside of the emergency department (ED), and inevitable operative management dictate the need for early airway control. In addition, a patient with penetrating neck trauma may have a patent airway and adequate gas exchange. Nevertheless, early intubation is advisable when there is evidence of vascular or direct airway injury because these patients tend to deteriorate, and increasing hemorrhage or swelling in the neck will compromise the airway and confound later attempts at intubation.

The common thread among these indications for intubation is the anticipated clinical course. In each case, it can be anticipated that future events may compromise the patient's ability to maintain and protect the airway or ability to oxygenate and ventilate, and waiting until these occur may result in a difficult airway.

Identification of the Difficult Airway

In most patients, intubation is technically easy and straightforward. Although early ED-based observational registries reported cricothyrotomy rates of about 1% for all intubations, more recent studies have shown a lower rate, less than 0.5%.[3] As would be expected with an unselected, unscheduled patient population, the ED cricothyrotomy rate is greater than in the operating room, which occurs in approximately 1 in 200 to 2000 elective general anesthesia cases.[4] Bag-mask ventilation (BMV) is difficult in approximately 1 in 50 general anesthesia patients and impossible in approximately 1 in 600. BMV is difficult, however, in up to one-third of patients in whom intubation failure occurs, and difficult BMV makes the likelihood of difficult intubation four times higher and the likelihood of impossible intubation 12 times higher. The combination of failure of intubation, BMV, and oxygenation in elective anesthesia practice is estimated to be exceedingly rare, roughly 1 in 30,000 elective anesthesia patients.[4] These numbers cannot be extrapolated to populations of ED patients who are acutely ill or injured and for whom intubation is urgent and unavoidable. Although patient selection cannot occur, as with a preanesthetic visit, a preintubation analysis of factors predicting difficult intubation gives the provider the information necessary to formulate a safe and effective plan for intubation.

Preintubation assessment should evaluate the patient for potential difficult intubation and difficult BMV, placement of and ventilation with an extraglottic device (EGD; see later discussion), and cricothyrotomy. Knowledge of all four domains is crucial to successful planning. A patient who exhibits obvious difficult airway characteristics is highly predictive of a challenging intubation, although the emergency clinician should always be ready for a difficult to manage airway, because some difficult airways may not be identified by a bedside assessment.[5]

Airway difficulty exists on a spectrum and is contextual to the provider's experience, environment, and armamentarium of devices. Airways predicted to be difficult when using a traditional laryngoscope may not prove to be difficult when a videolaryngoscope is used. Some patients may have a single minor anatomic or pathophysiologic reason for airway difficulty, whereas others may have numerous difficult airway characteristics. Although both sets of patients represent potential intubation challenges, the latter group would likely have crossed a threshold beyond which neuromuscular blockade would be avoided because a so-called can't intubate and can't oxygenate failed airway may ensue. In these cases, a preferred approach would include topical anesthesia, parenteral sedation, and intubation without the use of a neuromuscular blocking agent (NBMA). Occasionally, RSI remains the preferred method, despite a concerning bedside assessment, when it is part of a planned approach to the difficult airway. This may include use of a double setup, in which a rescue approach, such as cricothyrotomy, is simultaneously prepared in the event of intubation failure. Regardless of the results of a reassuring bedside assessment for airway difficulty, significant challenges may be encountered with intubation and bag mask ventilation and the clinician must be prepared for unanticipated difficulty.

Difficult Direct Laryngoscopy: LEMON

Glottic visualization is paramount in emergency airway management. With direct laryngoscopy (DL), if the vocal cords can be seen (Cormack and Lehane [CL] grade I or II view; Fig. 1.1), the chance of intubation success is high. However, when the glottic aperture cannot be visualized (CL grade III or IV), intubation success is less likely. Very few of the difficult airway markers thought to limit DL access have been scientifically validated, yet applying them in combination can provide a reasonable assessment of anticipated airway difficulty. Videolaryngoscopy, on the other hand, rarely fails to provide adequate laryngeal visualization, so characterization of difficult videolaryngoscopy predictors may not be possible. Like DL, adequate video views are highly correlated with intubation success, although the strength of this association can depend on the device used and operator experience.[3,6,7] Whether DL or videolaryngoscopy is planned, a standard screening process for difficulty should be undertaken with every patient. Our recommended approach uses the mnemonic *LEMON* (Box 1.1).

***L*—Look Externally.** The patient first should be examined for external markers of difficult intubation, which are determined

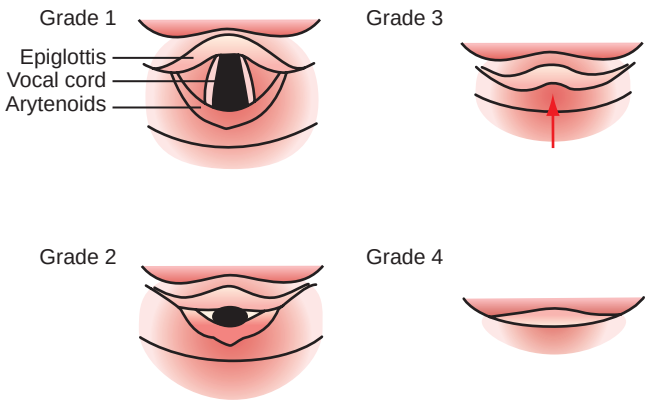

Fig. 1.1. Cormack and Lehane grading system for glottic view. (Modified from Walls RM, Murphy MF, editors: Manual of emergency airway management, ed 4, Philadelphia, 2012, Lippincott, Williams & Wilkins; with permission.)

BOX 1.1

LEMON Mnemonic for Evaluation of Difficult Direct Laryngoscopy

Look externally for signs of difficult intubation (by gestalt)
Evaluate 3-3-2 rule
Mallampati scale
Obstruction or *o*besity
Neck mobility

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.

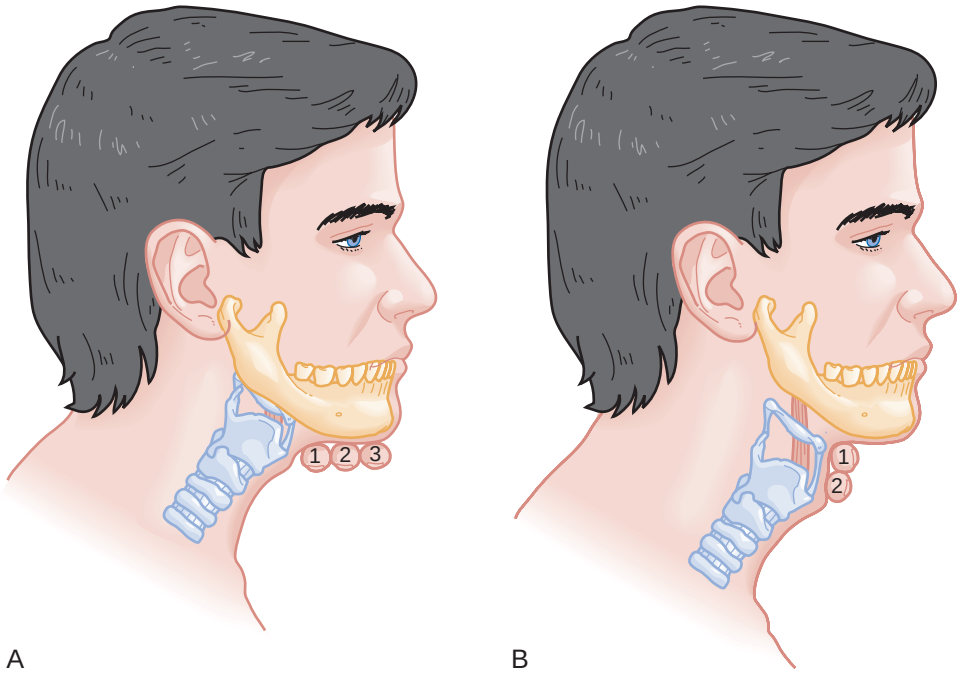

Fig. 1.2. Final two steps of the 3-3-2 rule. A, Three fingers are placed along the floor of the mouth, beginning at the mentum. B, Two fingers are placed in the laryngeal prominence (Adam's apple). (Modified from Murphy MF, Walls RM: Identification of difficult and failed airways. In Walls RM, Murphy MF, editors: Manual of emergency airway management, ed 4, Philadelphia, 2012, Lippincott, Williams & Wilkins; the 3-3-2 rule copyright © 2012 by The difficult airway course: emergency; and Lippincott Williams & Wilkins, publishers, Manual of emergency airway management.)

based simply on the intubator's clinical impression or initial gestalt. For example, the severely bruised and bloodied face of a combative trauma patient, immobilized in a cervical collar on a spine board, should (correctly) invoke an immediate appreciation of anticipated difficult intubation. Subjective clinical judgment can be highly specific but insensitive and so should be augmented by other evaluations whether or not the airway appears to be challenging.

***E*—Evaluate 3-3-2.** The second step in the evaluation of the difficult airway is to assess the patient's airway geometry to determine suitability for DL. Glottic visualization with a direct laryngoscope necessitates that the mouth opens adequately, the submandibular space is adequate to accommodate the tongue, and the larynx be positioned low enough in the neck to be accessible. These relationships have been explored in various studies by external measurements of mouth opening, oropharyngeal size, neck movement, and thyromental distance. The 3-3-2 rule is an effective summary of these assessments.[8] The 3-3-2 rule requires that the patient be able to place three of his or her own fingers between the open incisors, three of his or her own fingers along the floor of the mandible beginning at the mentum, and two fingers from the laryngeal prominence to the underside of the chin (Fig. 1.2). A patient with a receding mandible and high-riding larynx is impossible to intubate using DL because the operator cannot adequately displace the tongue and overcome the acute angle for a direct view of the glottic aperture In practice, the operator compares the size of his or her fingers with the size of the patient's fingers and then performs the three tests.

***M*—Mallampati Scale.** Oral access is assessed with the Mallampati scale (Fig. 1.3). Visibility of the oral pharynx ranges from complete visualization, including the tonsillar pillars (class I), to no visualization at all, with the tongue pressed against the hard palate (class IV). Classes I and II predict adequate oral access, class

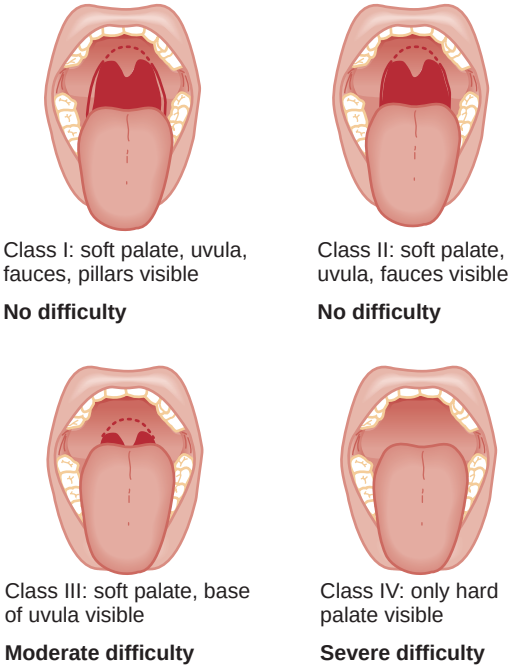

Fig. 1.3. The Mallampati scale, classes I to IV, assesses oral access for intubation. (From Whitten CE: Anyone can intubate, ed 4, San Diego, CA, 2004; with permission.)

III predicts moderate difficulty, and class IV predicts a high degree of difficulty. A meta-analysis has confirmed that the four-class Mallampati score performs well as a predictor of difficult laryngoscopy (and, less so, of difficult intubation), but the Mallampati score alone is not a sufficient assessment tool. A Mallampati score necessitates an awake compliant patient to perform the assessment in the way in which it was originally described. Nearly 50%

of ED patients cannot willingly perform this assessment, but it can be improvised by using a direct laryngoscope blade as a tongue depressor in obtunded or uncooperative patients.[9]

***O*—Obstruction or Obesity.** Upper airway (supraglottic) obstruction may make visualization of the glottis, or intubation itself, mechanically impossible. Conditions such as epiglottitis, head and neck cancer, Ludwig's angina, neck hematoma, glottis swelling, or glottic polyps can compromise laryngoscopy, passage of the endotracheal tube (ETT), BMV, or all three. Examine the patient for airway obstruction and assess the patient's voice to satisfy this evaluation step. Although obesity alone may not be an independent marker of difficult direct laryngoscopy, it likely contributes to challenges in other areas of airway management. Nevertheless, obese patients generally are more difficult to intubate than their nonobese counterparts, and preparations should account for this and for the more rapid oxyhemoglobin desaturation and increased difficulty with ventilation using BMV or an EGD (see later).

***N*—Neck Mobility.** Neck mobility is desirable for any intubation technique and is essential for positioning the patient for optimal DL. Neck mobility is assessed by flexion and extension of the patient's head and neck through a full range of motion. Neck extension is the most important motion, but placing the patient in the full sniffing position provides the optimal laryngeal view by DL.[10] Modest limitations of motion do not seriously impair DL, but severe loss of motion, as can occur in ankylosing spondylitis or rheumatoid arthritis, for example, may make DL impossible. Cervical spine immobilization in trauma patients artificially reduces cervical spine mobility, but DL is still highly successful in this group of patients.[7]

A similar mnemonic, *LEMONS*, has been described, with the "S" referring to the patient's oxygen saturation. Although not a direct contributor to difficulty with DL, a low starting oxygen saturation will result in a shorter period of safe apnea and a truncated time to perform laryngoscopy and successful endotracheal tube placement. As noted, identification of a difficult intubation does not preclude use of an RSI technique. The crucial determination is whether the emergency clinician judges that the patient has a reasonable likelihood of intubation success, despite the difficulties identified, and that ventilation with BMV or an EGD will be successful in case intubation fails (hence, the value of the BMV and EGD assessments; see Boxes 1.2 and 1.3).

Difficult Bag-Mask Ventilation: MOANS

Attributes of difficult BMV have largely been validated and can be summarized with the mnemonic *MOANS* (Box 1.2).

- ***M***ask seal compromise or difficulty
- ***O***bstruction (particularly supraglottic obstruction, but can be present anywhere in the airway) or ***O***besity (because of redundant upper airway tissues, chest wall weight, and resistance of abdominal mass)
- Advanced ***A***ge (best judged by the physiologic appearance of the patient, but age older than 55 years increases risk)
- Edentulous patients ("***N***o teeth"), which independently interferes with mask seal
- ***S***tiffness or resistance to ventilation (eg, asthma, COPD, pulmonary edema, restrictive lung disease, term pregnancy)—may contribute to increased difficulty with BMV

The difficulty with BMV of the edentulous patient is the basis of the advice often cited for patients with dentures: "teeth out to intubate, teeth in to ventilate." Another approach involves placing the mask inside the patient's lower lip. This may limit air leak in patients without teeth and eliminates the risk of aspiration associated with dental prosthetics or rolled gauze (Fig. 1.4).[11] Difficult BMV is not uncommon but, with proper technique, it usually is successful. A review by Kheterpal et al of more than 50,000 patients undergoing elective anesthesia has found that impossible BMV is exceptionally rare (0.2%) and is associated with neck changes secondary to radiation therapy, presence of a beard, male gender, history of sleep apnea, and Mallampati class III or IV airway.[11a] Impossible BMV was five times more likely if one of these factors was present and 25 times more likely with four or more.

Difficult Extraglottic Device Placement: RODS

Placement of an EGD, such as a laryngeal mask airway (LMA), Combitube, or similar upper airway device, often can convert a can't intubate, can't oxygenate situation to a can't intubate, can oxygenate situation, which allows time for rescue of a failed airway (see following section). Difficulty achieving placement or ventilation with an EGD can be predicted by the mnemonic *RODS*. Fortunately, if the emergency clinician has already performed the LEMON and MOANS assessments, only the *D* for distorted anatomy remains to be evaluated (Box 1.3). EGDs are placed blindly and have a mask or balloon structure that, when inflated, obstructs the oropharynx proximally and esophageal inlet distally, permitting indirect ventilation. Distorted upper airway anatomy can result in a poor seal and ineffective ventilation.

Difficult Cricothyrotomy: SMART

Difficult cricothyrotomy can be anticipated whenever there is limited access to the anterior neck or obscured laryngeal

BOX 1.2

MOANS Mnemonic for Evaluation of Difficult Bag-Mask Ventilation

Mask seal
Obstruction or obesity
Aged
No teeth
Stiffness (resistance to ventilation)

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.

Fig. 1.4. Mask ventilation in edentulous patients can be performed by placing the lower rim of the mask on the inside of the patient's lower lip to improve mask seal. (Courtesy Dr. Tobias Barker.)

BOX 1.3

RODS Mnemonic for Evaluation of Difficult Extraglottic Device Placement

Restricted mouth opening
Obstruction or obesity
Distorted anatomy
Stiffness (resistance to ventilation)

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.

BOX 1.4

SMART Mnemonic for Evaluation of Difficult Cricothyrotomy

Surgery
Mass (abscess, hematoma)
Access/anatomy problems (obesity, edema)
Radiation
Tumor

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.

landmarks and can be remembered by the mnemonic *SMART* (Box 1.4). Prior surgery, hematoma, tumor, abscess, scarring (as from radiation therapy or prior injury), local trauma, obesity, edema, or subcutaneous air each has the potential to make cricothyrotomy more difficult. Perform an examination for the landmarks needed to perform cricothyrotomy as part of the preintubation difficult airway assessment of the patient. Point-of-care ultrasound has been used at the bedside to locate the cricothyroid membrane, thereby allowing the emergency clinician to mark the location on the surface of the neck in high-risk cases. The emergency clinician should not avoid performing a rescue cricothyrotomy when indicated, even in the presence of predicted difficulty.

Measurement and Incidence of Intubation Difficulty

The actual degree to which an intubation is difficult is highly subjective, and quantification is challenging. The CL system is the most widely used system for grading a laryngoscopic view of the glottis, which grades laryngoscopy according to the extent to which laryngeal and glottic structures can be seen (see Fig. 1.1). In grade 1 laryngoscopy, all or nearly all of the glottic aperture is seen; in grade 2, the laryngoscopist visualizes only a portion of the glottis (arytenoid cartilages alone or arytenoid cartilages plus part of the vocal cords), in grade 3 only the epiglottis is visualized and, in grade 4, not even the epiglottis is visible.

Fewer than 1% of stable patients undergoing DL during elective anesthesia yield a grade 4 laryngoscopy, a finding associated with an extremely difficult intubation with. Grade 3 laryngoscopy, which represents highly difficult intubation, is found in less than 5% of patients. Grade 2 laryngoscopy, which occurs in 10% to 30% of patients, can be subdivided further into grade 2a, in which the arytenoids and a portion of the vocal cords are seen, and grade 2b, in which only the arytenoids are seen. Intubation failure occurs in 67% of grade 2b cases but in only 4% of grade 2a cases.

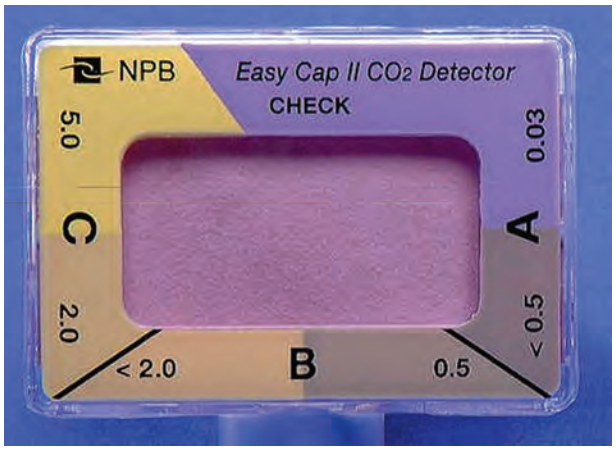

Fig. 1.5. End-tidal CO_2 detector before application. The indicator is *purple*, which indicates failure to detect CO_2. This also is the appearance when the esophagus is intubated.

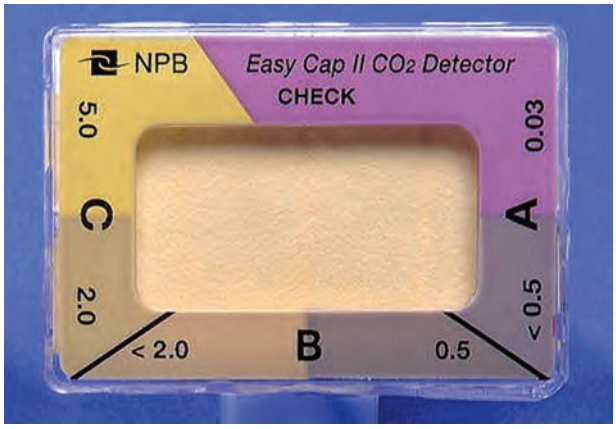

Fig. 1.6. Positive detection of CO_2 turns the indicator *yellow*, indicating tracheal placement of the endotracheal tube.

Outside of the operating room, the rate of difficulty may be higher. In a recent review of emergency adult inpatient intubations, as many as 10% were considered difficult (grade 3 or 4 CL direct view or more than three attempts required).[12] The incidence of difficult ED intubations is unknown but is likely much higher Approximately 80% of all grade 2 laryngoscopies are grade 2a; the rest are grade 2b. First-attempt intubation success drops off significantly as the glottic view transitions from a grade 2a to 2b; however, a grade 1 view is associated with virtually 100% intubation success. An alternative system, POGO (percentage of glottic opening), also has been proposed and validated but has not been widely used or studied. The incidence of difficult intubation, and the predictors thereof, are largely based on the use of conventional DL and are not applicable to videolaryngoscopy.

Confirmation of Endotracheal Tube Placement

Immediately after intubation, the intubator should apply an end-tidal carbon dioxide ($ETCO_2$) detection device to the ETT and assess it through six manual ventilations. Disposable colorimetric $ETCO_2$ detectors are highly reliable, convenient, and easy to interpret, indicating adequate CO_2 detection by color change (Figs. 1.5 and 1.6) and determining tracheal and esophageal intubation in patients with spontaneous circulation. The persistence of detected CO_2 after six manual breaths indicates that the tube is within the airway, although not necessarily within the trachea. CO_2 is detected with the tube in the mainstem bronchus, trachea, or supraglottic

space. Correlation of $ETCO_2$ detection with the depth markings on the ETT, particularly important in pediatric patients, confirms tracheal placement. Rarely, BMV before intubation or ingestion of carbonated beverages may lead to the release of CO_2 from the stomach after esophageal intubation, causing a transient false indication of tracheal intubation. Washout of this phenomenon universally occurs within six breaths.

Although colorimetric $ETCO_2$ measurement is highly sensitive and specific for detecting esophageal intubation, caution is required for patients in cardiopulmonary arrest. Insufficient gas exchange may prevent CO_2 detection in the exhaled air, even when the tube is correctly placed within the trachea. In patients in cardiopulmonary arrest, a CO_2 level greater than 2%, which is the threshold for color change on colorimetric capnometers, should be considered definitive evidence of correct ETT placement, but the absence of such CO_2 cannot be used reliably as an indicator of esophageal intubation. Recent resuscitation guidelines have suggested continuous quantitative measurement of $ETCO_2$ during cardiac arrest to gauge the efficacy of cardiopulmonary resuscitation.[13] This circumstance arises in approximately 25% to 40% of intubated cardiac arrest patients. In all other patients, absence of CO_2 detection indicates failure to intubate the trachea, and rapid reintubation is indicated.

When $ETCO_2$ detection is not possible, tracheal tube position can be confirmed with other techniques. One approach involves point-of-care ultrasound. In live patient and cadaver studies, ultrasonography performed over the cricothyroid membrane or upper trachea has accurately confirmed ETT position in the trachea, especially during intubation.[14,15]

Another method of tube placement confirmation is the aspiration technique, based on the anatomic differences between the trachea and esophagus. The esophagus is a muscular structure with no support within its walls and is therefore collapsible when negative pressure is applied. The trachea is held patent by cartilaginous rings and thus is less likely to collapse when negative pressure is applied. Vigorous aspiration of air through the ETT with the ETT cuff deflated results in occlusion of the ETT orifices by the soft walls of the esophagus, whereas aspiration after tracheal placement of the tube is easy and rapid.

Bulb or syringe aspiration devices may be used in patients in cardiac arrest who have no detectable CO_2. Although such devices are highly reliable at detecting esophageal intubation (sensitivity > 95%), false-positives, in which a correctly placed tracheal tube is incorrectly identified as esophageal, can occur in up to 25% of cardiac arrest patients. Aspiration devices may be useful in the out-of-hospital setting when poor lighting hampers colorimetric $ETCO_2$ determination. They also are good backup devices when cardiac arrest confounds attempts to assess placement with $ETCO_2$. Detection of expired CO_2 is more reliable and is the standard for confirmation of tracheal placement of an ETT and for early detection of accidental esophageal intubation. Aspiration devices have a valuable but secondary role. Also, a bougie can be placed through the center of an ETT to corroborate tube location further. A bougie that can be passed deeply through the tube, with little or no resistance, suggests an esophageal intubation because the bougie has likely passed beyond the tube and into the stomach. If the ETT is in the trachea, the tip of the bougie will become wedged after only a few inches, likely in the right mainstem bronchus, and a vibration from contact with the anterior tracheal rings may be transmitted to the operator's fingertips.

Accordingly, $ETCO_2$ detection, with aspiration, bougie, or an ultrasound technique as backup, should be considered the primary means of ETT placement confirmation. Secondary means include physical examination findings, oximetry, and radiography. The examiner should auscultate both lung fields and the epigastric area. Pulse oximetry is indicated as a monitoring technique in all critically ill patients, not just those who require intubation. Oximetry is useful in detecting esophageal intubation but may not show a decreasing oxygen saturation for several minutes after a failed intubation because of the oxygen reservoir (preoxygenation) created in the patient before intubation. Although chest radiography is universally recommended after ETT placement, its primary purpose is to ensure that the tube is well positioned below the cords and above the carina. A single anteroposterior chest radiograph is not sufficient to detect esophageal intubation, although esophageal intubation may be detected if the ETT is clearly outside the air shadow of the trachea. In cases in which doubt persists, a fiberoptic scope can be passed through the ETT to identify tracheal rings, another gold standard for confirmation of tracheal placement.

MANAGEMENT

Decision Making

Algorithms for emergency airway management have been developed and provide a useful guide for planning intubation and rescue in case of intubation failure. The algorithm assumes that a decision to intubate has been made and outlines such an approach. The approach is predicated on two key determinations that are to be made before active airway management is initiated (Fig. 1.7). The first determination is whether the patient is in cardiopulmonary arrest or a state of near arrest and is likely to be unresponsive to direct laryngoscopy. Such a patient—agonal, near death, in

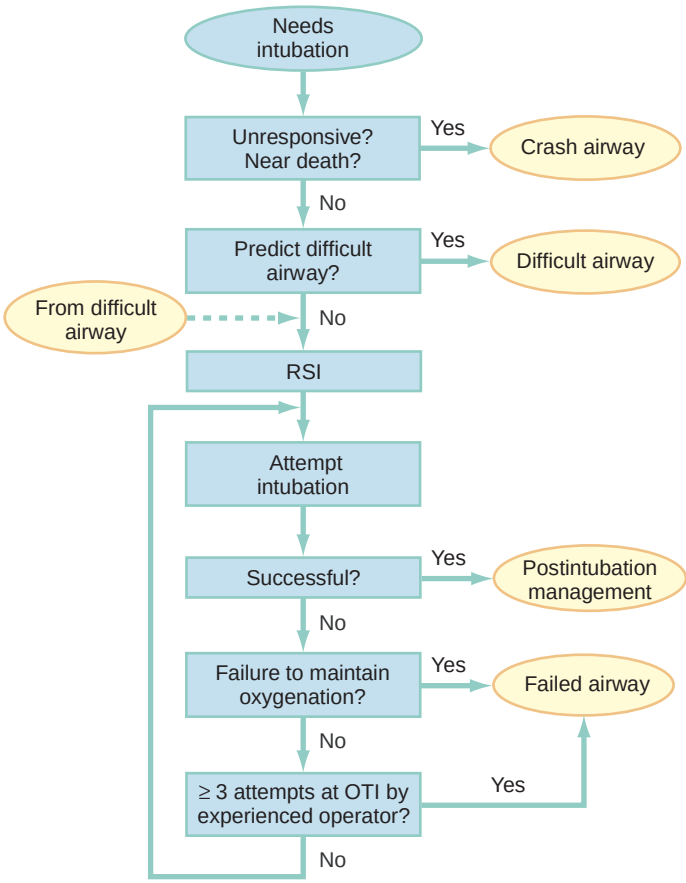

Fig. 1.7. Main emergency airway management algorithm. *OTI,* Orotracheal intubation; *RSI,* rapid sequence intubation. (Modified from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF, editors: Manual of emergency airway management, ed 4, Philadelphia, 2012, Lippincott, Williams & Wilkins; copyright © 2012, The difficult airway course: emergency; and Lippincott, Williams & Wilkins, publishers.)

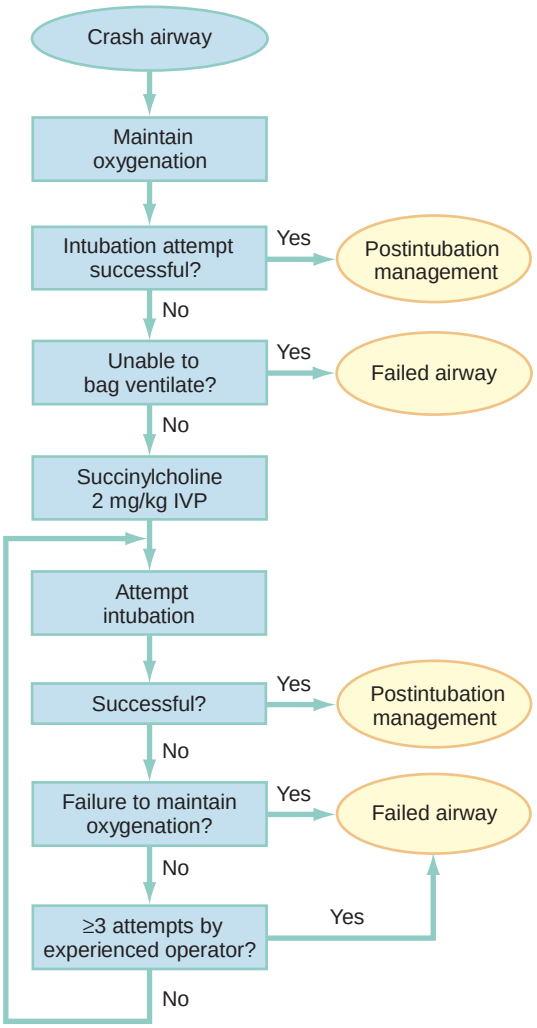

Fig. 1.8. Crash airway algorithm. *IVP,* Intravenous push. (Modified from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF, editors: Manual of emergency airway management, ed 4, Philadelphia, 2012, Lippincott, Williams & Wilkins; copyright © 2012, The difficult airway course: emergency; and Lippincott, Williams & Wilkins, publishers.)

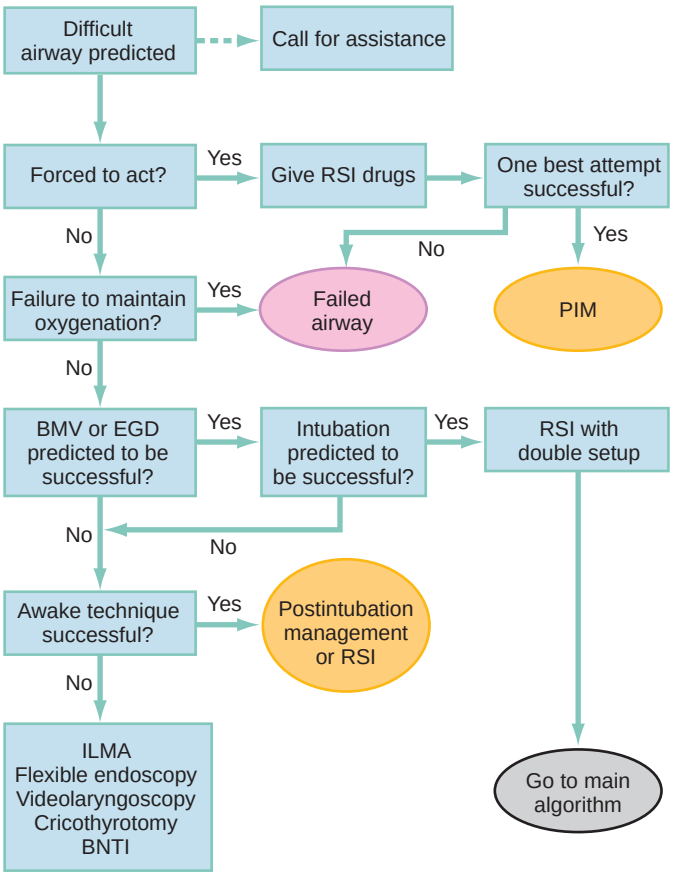

Fig. 1.9. Difficult airway algorithm. *BMV,* Bag-mask ventilation; *BNTI,* blind nasotracheal intubation; *DL,* direct laryngoscopy; *EGD,* extraglottic device; *ILMA,* intubating laryngeal mask airway; *PIM,* postintubation management; *RSI,* rapid sequence intubation. (Modified from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF, editors: Manual of emergency airway management, ed 4, Philadelphia, 2012, Lippincott, Williams & Wilkins; copyright © 2012, The difficult airway course: emergency; and Lippincott, Williams & Wilkins, publishers.)

circulatory collapse—is deemed a crash airway patient for the purposes of emergency airway management and is treated using the crash airway algorithm by an immediate intubation attempt without use of drugs; this can be supplemented by a single large dose of succinylcholine if the attempt to intubate fails, and the patient is thought not to be sufficiently relaxed (Fig. 1.8). If a crash airway is not present, a decision of whether the patient represents a difficult intubation, as determined by the LEMON, MOANS, RODS, and SMART evaluations is made and, if so, the difficult airway algorithm is used (Fig. 1.9).

For patients who require emergency intubation but who have neither a crash airway nor a difficult airway, RSI is indicated. RSI provides the safest and quickest method of achieving intubation in such patients.[3,16] After administration of RSI drugs, intubation attempts are repeated until the patient is intubated or a failed intubation is identified. If more than one intubation attempt is required, oxygen saturation is monitored continuously and, if saturation falls to 90% or less, BMV is performed until saturation is recovered for another attempt. If the oxygen saturation continues to fall, despite optimal use of BMV or EGD, a failed airway exists. This is referred to as a can't intubate, can't oxygenate scenario. A failed airway also is defined as three unsuccessful attempts at laryngoscopy because subsequent attempts at laryngoscopy by the same clinician are unlikely to succeed. The three failed laryngoscopy attempts are defined as attempts by an experienced clinician using the best possible patient positioning and technique. Three attempts by a physician trainee using a direct laryngoscope may not count, necessarily, as best attempts if an experienced emergency clinician is available or videolaryngoscopy has not yet been attempted. Also, if the emergency clinician ascertains after even a single attempt that intubation will be impossible (eg, grade 4 laryngoscopic view with DL, despite optimal patient positioning and use of external laryngeal manipulation), and no alternative device (eg, videolaryngoscope, intubating LMA) is available, a failed airway is present. The failed airway is managed according to the failed airway algorithm (Fig. 1.10).

Difficult Airway

The perception of a difficult airway is relative, and many emergency intubations could be considered difficult. Deciding whether to treat the airway as a typical emergency airway or whether to use the difficult airway algorithm is based on the degree of perceived difficulty, operator experience, armamentarium of airway devices available, and individual circumstances of the case. The LEMON, MOANS, RODS, and SMART assessments provide a systematic framework to assist in identifying the potentially difficult airway.

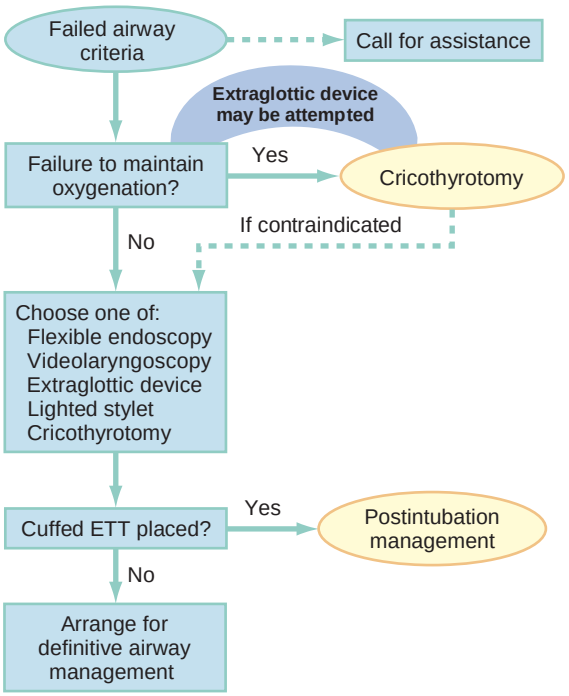

Fig. 1.10. Failed airway algorithm. *ETT,* Endotracheal tube. (Modified from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF, editors: Manual of emergency airway management, ed 4, Philadelphia, 2012, Lippincott, Williams & Wilkins; copyright © 2012, The difficult airway course: emergency; and Lippincott, Williams & Wilkins, publishers.)

When preintubation evaluation identifies a potentially difficult airway (see Fig. 1.9), the approach is based on the premise that NMBAs generally should not be used unless the emergency clinician believes that (1) intubation is likely to be successful and (2) oxygenation can be maintained via BMV or EGD should the patient desaturate during a failed intubation attempt. The one exception to this recommendation occurs in the forced to act scenario.

A forced to act imperative permits RSI, even in a highly difficult airway situation in which the operator is not confident of the success of laryngoscopy or of sustaining oxygenation. This usually occurs in the setting of a rapidly deteriorating patient with an obviously difficult airway and a presumed clinical trajectory of imminent arrest. Although this is not yet a crash airway situation, the operator is forced to act—that is, there is a need to act immediately to intubate before orotracheal intubation quickly becomes impossible or the patient arrests. The patient retains sufficient muscle tone and voluntary effort (including combative behavior induced by hypoxia) to require administration of drugs before intubation can be attempted. Consider an agitated patient with rapidly advancing anaphylaxis or angioedema, a morbidly obese patient in severe, end-stage status asthmaticus, or an intensive care unit (ICU) patient with inadvertent or premature extubation, respiratory failure, and difficult airway. Within seconds to minutes, perhaps before a full difficult airway assessment can be done or preparations can be completed for an alternative airway approach (eg, flexible endoscopy), the patient's rapid deterioration signals impending respiratory arrest. This is a unique situation in which the operator may be compelled to take the one best chance to secure the airway by rapidly administering RSI drugs, despite obvious airway difficulty, and attempting intubation before the airway crisis has advanced to the point that intubation is impossible or delay has caused hypoxic arrest. If laryngoscopy fails, the RSI drugs have optimized patient conditions for cricothyrotomy or insertion of an alternative airway device, depending on the operator's judgment.

Therefore, in the difficult airway algorithm, the first determination is whether the operator is forced to act. If so, RSI drugs are given, a best attempt at laryngoscopy is undertaken and, if intubation is not successful, the airway is considered failed, and the operator moves immediately to the failed airway algorithm. In the vast majority of difficult airway situations, however, the operator is not forced to act, and the first step is to ensure that oxygenation is sufficient to permit a planned orderly approach to airway management. If oxygenation is inadequate and cannot be made adequate by supplementation with BMV, the airway should be considered a failed airway. Although inadequate oxygenation should be defined on a case by case basis, oxygenation saturation falling below 90% is the accepted threshold, because this represents the point at which hemoglobin undergoes a conformational change, more readily releases oxygen, and increases the pace of further desaturation. Oxyhemoglobin saturations in the mid-80s, if holding steady, might be considered adequate in some circumstances, particularly if the patient is chronically hypoxemic. When oxygenation is inadequate or dropping, the failed airway algorithm should be used because the predicted high degree of intubation difficulty, combined with failure to maintain oxygen saturation, is analogous to the can't intubate, can't oxygenate scenario.

When oxygenation is adequate, however, the next consideration is whether RSI is appropriate, on the basis of the operator's assessment of the likelihood of (1) successful ventilation with BMV or EGD in case intubation is unsuccessful and (2) the likelihood of successful intubation by laryngoscopy. If the operator judges laryngoscopy likely to succeed and is confident that he or she can oxygenate the patient if intubation fails, RSI is performed. In such cases, a double setup can be used in which RSI is planned and preparations are simultaneously undertaken for rescue cricothyrotomy or another rescue technique. If the operator is not confident of successful intubation by RSI and time allows, an awake technique can be used. In this context, awake means that the patient continues to breathe and, although intravenous sedation and analgesia may be administered, can cooperate with caregivers. The patient is prepared by applying topical anesthesia with atomized or nebulized lidocaine, ideally preceded by a drying agent such as glycopyrrolate. Titrated doses of a sedative and analgesic agents (or ketamine, which provides both actions) may be required for the patient to tolerate the procedure. Once this is accomplished, a number of different devices can then be used to attempt glottic visualization, although flexible bronchoscopes and videolaryngoscopes are preferable. If the glottis is adequately visualized, the patient can be intubated at that time or, in a stable difficult airway situation, the emergency clinician may proceed with planned RSI, now assured of intubation success. If the awake laryngoscopy is unsuccessful, the patient can be intubated with any of numerous techniques shown in the last box in Fig. 1.9. For each of these methods, the patient is kept breathing but is variably sedated and anesthetized. The choice among these methods depends on clinician experience and preference, device availability, and patient attributes.

Failed Airway

Management of the failed airway is dictated by whether the patient can be oxygenated. If adequate oxygenation cannot be maintained with rescue BMV, the rescue technique of first resort is cricothyrotomy (see Fig. 1.10). Multiple attempts at other methods in the context of failed oxygenation only delay cricothyrotomy and place the patient at increased risk for hypoxic brain injury. If an alternative device (ie, an EGD such as an LMA or Combitube) is readily available, however, and the operator judges it to be an appropriate device for the patient's anatomy, single attempt can

be made to use it simultaneously with preparations for immediate cricothyrotomy as long as initiation of cricothyrotomy is not delayed. If early indications are that an EGD is effective and oxygenation improves, cricothyrotomy can wait; however, the operator must constantly reassess EGD function and oxygenation status. If the EGD subsequently fails, cricothyrotomy must begin without delay.

If adequate oxygenation is possible, several options are available for the failed airway. In almost all cases, cricothyrotomy is the definitive rescue technique for the failed airway if time does not allow for other approaches (ie, preservation of oxygenation) or if they fail. The fundamental difference in philosophy between the difficult and failed airway is that the difficult airway is planned for, and the standard is to place a definitive airway (cuffed ETT) in the trachea. The failed airway is not planned for, and the standard is to achieve an airway that provides adequate oxygenation to avert hypoxic brain injury. Some devices used in the failed airway (eg, EGDs) are temporary and do not provide definitive airway protection.

Methods of Intubation

Although many techniques are available for intubation of the emergency patient, four methods are the most common, with RSI being the most frequent approach.[3,16]

Rapid Sequence Intubation

RSI is the cornerstone of modern emergency airway management and is defined as the nearly simultaneous administration of a potent sedative (induction) agent and NMBA, usually succinylcholine or rocuronium, for the purpose of tracheal intubation. This approach provides optimal intubating conditions and has long been thought to minimize the risk of aspiration of gastric contents. A systematic review of the literature in 2007 failed to prove that RSI results in a lower incidence of aspiration than other techniques, but the authors correctly noted that virtually no studies have ever been designed to measure this precise endpoint. RSI is nevertheless the most widely used technique for emergency intubation of patients without identifiable difficult airway attributes, with recent large registry data showing that it is used in 85% of all emergency department intubations.[3,16]

The central concept of RSI is to take the patient from the starting point (eg, conscious, breathing spontaneously) to a state of unconsciousness with complete neuromuscular paralysis, and then to achieve intubation without interposed assisted ventilation. The risk of aspiration of gastric contents is thought to be significantly higher for patients who have not fasted before induction. Application of positive-pressure ventilation can cause air to pass into the stomach, resulting in gastric distention and likely increasing the risk of regurgitation and aspiration. The purpose of RSI is to avoid positive-pressure ventilation until the ETT is placed correctly in the trachea, with the cuff inflated. This requires a preoxygenation phase, during which mixed alveolar gases (mostly nitrogen) within the lungs' functional residual capacity are replaced with oxygen, permitting at least several minutes of apnea (see later discussion) in a healthy normal body habitus adult before oxygen desaturation to less than 90% ensues (Fig. 1.11).

Use of RSI also facilitates successful endotracheal intubation by causing complete relaxation of the patient's musculature, allowing better access to the airway. Finally, RSI permits pharmacologic control of the physiologic responses to laryngoscopy and intubation, mitigating potential adverse effects. These effects include further elevations in intracranial pressure (ICP) in response to the procedure and to the sympathetic discharge resulting from laryngoscopy (Box 1.5). RSI is a series of discrete steps, and every step should be planned (Box 1.6).

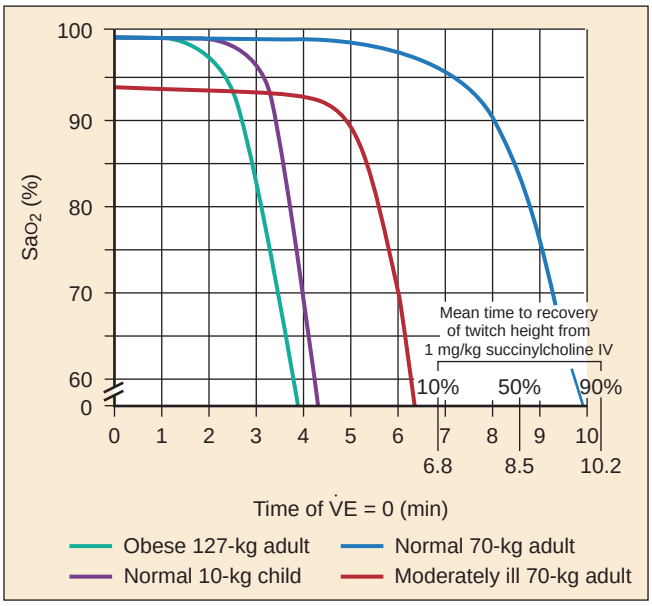

Fig. 1.11. Desaturation time for apneic, fully preoxygenated patients. Children, patients with comorbidity, and obese patients desaturate much more rapidly than healthy normal adults. The box on the lower right side of the graph depicts time to recovery from succinylcholine, which in almost all cases exceeds safe apnea time. Note also the precipitous decline of oxygen saturation from 90% to 0% for all groups. *VE,* Expired volume. (Modified from Benumof JL, Dagg R, Benumof R: Critical hemoglobin desaturation will occur before return to unparalyzed state following 1 mg/kg intravenous succinylcholine. Anesthesiology 87:979–982, 1997.)

BOX 1.5

Pretreatment Agents for Rapid Sequence Intubation[a]

Reactive airway disease: Albuterol, 2.5 mg, by nebulizer. If time does not permit albuterol nebulizer, give lidocaine 1.5 mg/kg IV.
Cardiovascular disease: Fentanyl, 3 µg/kg, to mitigate sympathetic discharge
Elevated ICP: Fentanyl, 3 µg/kg, to mitigate sympathetic discharge and attendant rise in ICP

ICP, intracranial pressure.
[a]Given 2–3 min before induction and paralysis.

BOX 1.6

The Seven Ps of Rapid Sequence Intubation

1. ***P****reparation*
2. ***P****reoxygenation*
3. ***P****retreatment*
4. ***P****aralysis with induction*
5. ***P****ositioning*
6. ***P****lacement of tube*
7. ***P****ostintubation management*

Preparation. In the initial phase, the patient is assessed for intubation difficulty, unless this has already been done, and the intubation is planned, including determining dosages and sequence of drugs, tube size, and laryngoscope type, blade, and size. Drugs are drawn up and labeled. All necessary equipment is

assembled. All patients require continuous cardiac and pulse oximetry monitoring. At least one and preferably two good-quality intravenous lines should be established. Redundancy is always desirable in case of equipment or intravenous access failure. Most importantly, a rescue plan for intubation failure should be developed at this time and made known to the appropriate members of the resuscitation team.

Preoxygenation. Administration of 100% oxygen for 3 minutes of normal tidal volume breathing in a normal healthy adult establishes an adequate oxygen reservoir to permit 6 to 8 minutes of safe apnea before oxygen desaturation to less than 90% occurs (see Fig. 1.11). Additional preoxygenation does not improve arterial oxygen tension. The time to desaturation to less than 90% in children, obese adults, late-term pregnant women, and patients who are acutely ill or injured is considerably shorter. Desaturation time also is reduced if the patient does not inspire 100% oxygen. Nevertheless, adequate preoxygenation usually can be obtained, even in ED patients, to permit minutes of apnea before there is oxygen desaturation to less than 90%. Preoxygenation is also essential to the no-bagging approach of RSI. If time is insufficient for a full 3-minute preoxygenation phase, eight vital capacity breaths with high-flow oxygen can achieve oxygen saturations and apnea times that match or exceed those obtained with traditional preoxygenation. Desaturation time in obese patients can be prolonged by preoxygenating with the patient in a head-up position and by continuing supplemental oxygen (via nasal cannula at a flow rate of 5–15 L/min) after motor paralysis and during laryngoscopy until the ETT is successfully placed. In obese patients, it extends the time to desaturation to 95% from 3.5 to 5.3 minutes.[17,18] This so-called apneic oxygenation takes advantage of a physiologic principle termed *aventilatory mass flow*.[19] Even though patients are paralyzed during RSI, circulation is unaltered. The constant diffusion of alveolar oxygen into the pulmonary circulation creates a natural downward gradient promoting passive oxygen movement from the patient's upper airway into the gas-exchanging portions of the lungs. Oxygen saturation monitors permit earlier detection of desaturation during laryngoscopy, but preoxygenation remains an essential step in RSI.

Pretreatment. During this phase, drugs are administered 3 minutes before the administration of succinylcholine and an induction agent to mitigate the adverse physiologic effects of laryngoscopy and intubation on the patient's presenting condition. Pretreatment approaches have evolved over time. Periodic reappraisals of the available literature have whittled the pretreatment approach down to the bare essentials with a focus on optimizing patient physiology prior to any intubation attempts. Older practices, such as the routine use of atropine for intubation of small children, have largely been abandoned.

Intubation is intensely stimulating and results in a sympathetic discharge, or reflex sympathetic response to laryngoscopy (RSRL). In patients suffering from a hypertensive emergency, sympatholysis with fentanyl (3 mcg/kg IV) administered 3 minutes before RSI can optimize the patient's hemodynamics by attenuating spikes in blood pressure and shear forces, both of which are considered undesirable in patients with elevations of intracranial pressure (ICP), aortic disease, acute coronary syndromes and neurovascular emergencies.

Patients with reactive airways disease can exhibit worsening pulmonary mechanics after intubation as a result of bronchospasm. Controversy exists regarding whether lidocaine (1.5 mg/kg IV) confers any additional benefit, beyond albuterol, and should be considered optional at best. Asthmatic patients being intubated in the ED for status asthmaticus will have received albuterol before intubation, and it is unlikely in these patients that lidocaine has any additive protective effect and is not recommended. Lidocaine has a vanishing role in emergency airway management and may disappear completely in the near future (see Box 1.5).

Paralysis With Induction. In this phase, a potent sedative agent is administered by rapid intravenous (IV) push in a dose capable of producing unconsciousness rapidly. This is immediately followed by rapid administration of an intubating dose of an NMBA, either succinylcholine at a dose of 1.5 mg/kg IV or rocuronium, 1 mg/kg. It is usual to wait 45 seconds from when the succinylcholine is given and 60 seconds from when rocuronium is given to allow sufficient paralysis to occur. The results from two large meta-analyses have revealed that intubating conditions provided by each drug are equivalent as long as rocuronium is dosed between 1.0 and 1.2 mg/kg IV.

Positioning. The patient should be positioned for intubation as consciousness is lost. Usually, positioning involves head extension, often with flexion of the neck on the body. Although simple extension may be adequate, a full sniffing position with cervical spine extension and head elevation is optimal if DL is used.[10] The Sellick maneuver—application of firm, backward pressure over the cricoid cartilage with the goal of obstructing the cervical esophagus and reducing the risk of aspiration—had long been recommended to minimize the risk of passive regurgitation and hence aspiration, but is no longer recommended. The Sellick maneuver is incorrectly applied by a variety of operators, making laryngoscopy or intubation more difficult in some patients, and aspiration often occurs despite use of the Sellick maneuver. In many patients, the cervical esophagus is positioned lateral to the cricoid ring in a relationship that is exaggerated by posterior pressure, rarely resulting in esophageal obstruction. Accordingly, we do not recommend routine use of the Sellick maneuver, and it should be considered optional, applied selectively, and released or modified early if the laryngeal view is poor or tube passage is difficult. After administration of an induction agent and NMBA, although the patient becomes unconscious and apneic, BMV should not be initiated unless the oxygen saturation falls to 90%.

Placement of Tube. Approximately 45 to 60 seconds after administration of the NMBA, the patient is relaxed sufficiently to permit laryngoscopy. This is assessed most easily by moving the mandible to test for mobility and absence of muscle tone. Place the ETT during glottic visualization with the laryngoscope. Confirm placement, as described earlier. If the first attempt is unsuccessful but oxygen saturation remains high, it is not necessary to ventilate the patient with a bag and mask between intubation attempts. If the oxygen saturation is approaching 90%, the patient may be ventilated briefly with a bag and mask between attempts to reestablish the oxygen reservoir.

Postintubation Management. After confirmation of tube placement by $ETco_2$, obtain a chest radiograph to confirm that mainstem intubation has not occurred and to assess the lungs. If available, place the patient on continuous capnography. In general, long-acting NMBAs (eg, pancuronium, vecuronium) are avoided; the focus is on optimal management using opioid analgesics and sedative agents to facilitate mechanical ventilation. An adequate dose of a benzodiazepine (eg, midazolam, 0.1–0.2 mg/kg IV) and opioid analgesic (eg, fentanyl, 3–5 μg/kg IV, or morphine, 0.2–0.3 mg/kg IV) is given to improve patient comfort and decrease sympathetic response to the ETT. Propofol infusion (5–50 μg/kg/min IV) with supplemental analgesia is an effective method for managing intubated patients who do not have hypotension or ongoing bleeding and is especially helpful for management of neurologic emergencies because its clinical duration of action is very short (<5 minutes), allowing frequent neurologic examinations. An NMBA is added only if appropriate use of

TABLE 1.1

Sample Rapid Sequence Intubation Using Etomidate and Succinylcholine

TIME	STEP
Zero minus 10 min	Preparation
Zero minus 5 min	Preoxygenation—100% oxygen for 3 min or 8 vital capacity breaths
Zero minus 3 min	Pretreatment—as indicated
Zero	Paralysis with induction • Etomidate, 0.3 mg/kg • Succinylcholine, 1.5 mg/kg
Zero plus 30 s	Positioning—Sellick maneuver optional
Zero plus 45 s	Placement • Laryngoscopy and intubation • End-tidal carbon dioxide confirmation
Zero plus 2 min	Postintubation management • Sedation and analgesia as indicated • Initiate mechanical ventilation • NMBA only if needed after adequate sedation, analgesia

NMBA, Neuromuscular blocking agent.

sedation and analgesia fail to control the patient adequately or when ventilation is challenging because of by muscular activity. Table 1.1 presents a sample RSI protocol using etomidate and succinylcholine. Zero refers to the time at which the induction agent and succinylcholine are pushed.

Delayed Sequence Intubation

Delayed sequence intubation (DSI) is a new technique proposed to maximize preoxygenation in preparation for intubation.[20] Agitation, delirium, and confusion can make attempts at preoxygenation challenging, if not impossible, when a patient is unable to comply with conventional modes of supplemental oxygenation, such as a face mask or BL-PAP. DSI considers preoxygenation a procedure and uses dissociative doses of ketamine (1.0 mg/kg IV) as procedural sedation to accomplish this. A small, ED- and ICU-based multicenter observational study showed post-DSI oxygen saturations significantly higher than pre-DSI levels. Additionally, there were no noted adverse outcomes or desaturations when intubation eventually took place in this limited case series. More investigation is required to determine the possible indications for and safety of DSI when performed in various ED settings.

Blind Nasotracheal Intubation

Historically, blind nasotracheal intubation (BNTI) was used extensively in the ED and out-of-hospital setting, but it has fallen out of favor largely because of the superiority of RSI. Prehospital intubation success between RSI and BNTI favors RSI, and ED studies have shown that RSI is superior.[3,16]

In the ED, BNTI rarely, if ever, should be used and is reserved for patients in whom the presence of a narrowly defined type of difficult airway makes RSI undesirable or contraindicated, and alternatives (eg, flexible endoscope) are not available. A review of nearly 9000 ED intubations has shown that nasal intubation was used in only 5% of intubations performed from 1997 to 2002.[16] A current registry of more than 17,500 adult ED intubations between 2002 and 2012 has revealed that this is now less than 0.5%.[3]

Awake Oral Intubation

Awake oral intubation is a technique in which sedative and topical anesthetic agents are administered to permit management of a difficult airway without neuromuscular blockade. Sedation and analgesia are achieved in a manner analogous to that for painful procedures in the ED. Topical anesthesia may be achieved by spray, nebulization, or local anesthetic nerve block. Various sedative agents can be used but ketamine, which provides dissociative anesthesia, analgesia, maintenance of protective airway reflexes, and minimal respiratory depression, is often the best choice (see later, "Pharmacologic Agents"). Aliquots of ketamine at a dose of 0.5 mg/kg IV, titrated to the desired level of sedation and procedural tolerance, is an effective method. Dexmedetomidine (Precedex), a centrally acting alpha receptor blocker, has been used successfully, alone or in combination with benzodiazepines, for awake airway evaluations.[21] A typical dose is 1.0 mg/kg IV infused over 5 to 10 minutes. After the patient is sedated, and topical anesthesia has been achieved, gentle direct videolaryngoscopy or flexible endoscopic laryngoscopy is performed to determine whether the glottis is visible and intubation possible. If the glottis is visible, the patient may be intubated during initial laryngoscopy, or the operator, confident that the glottis can be visualized, may opt to perform RSI to benefit from pretreatment, induction, and paralysis, as might be the case in a head-injured patient.

Awake oral intubation is distinct from the practice of oral intubation with a sedative or opioid agent to obtund the patient for intubation without neuromuscular blockade. This latter technique can be referred to as intubation with sedation alone or, paradoxically, nonparalytic RSI. Intubating conditions and first-attempt success achieved even with deep anesthesia are significantly inferior to what is achieved when neuromuscular blockade is used.[3] In general, the technique of administering a potent sedative agent to obtund the patient's responses and permit intubation in the absence of neuromuscular blockade is ill-advised and inappropriate for endotracheal intubation in the ED, unless performed as part of an awake intubation (see earlier), during which lesser amounts of sedation are typically used.

Oral Intubation Without Pharmacologic Agents

The arrested or near death patient may not require pharmacologic agents for intubation, but even an arrested patient may retain sufficient muscle tone to render intubation difficult. If the glottis is not adequately visualized, administration of a single dose of succinylcholine alone may facilitate laryngoscopy (see earlier, "Decision Making"). Success rates for intubating unconscious unresponsive patients are variable but approach those achieved with RSI, presumably because the patient is in a similar physiologic state (ie, muscle relaxation, no ability to react to laryngoscopy or tube insertion).[3,16] This does not apply to patients who are unconscious from neurologic catastrophe or trauma and those who have overdosed or have other medical causes of coma who warrant an induction agent and are intubated with standard RSI procedures (see earlier).

Pharmacologic Agents

Neuromuscular Blocking Agents

NMBAs are highly water-soluble, quaternary ammonium compounds that mimic the quaternary ammonium group on the acetylcholine (ACh) molecule. Their water solubility explains why they do not readily cross the blood-brain barrier or placenta. NMBAs are divided into two main classes, depolarizing and nondepolarizing agents. The depolarizing agent succinylcholine exerts its effects by binding noncompetitively with ACh receptors on the

motor endplate, causing sustained depolarization of the myocyte while preventing transmembrane potentials from reforming and resisting further stimulation from ACh. The other major class of NMBA comprises the competitive, or nondepolarizing, agents, which bind competitively to ACh receptors, preventing access by ACh and preventing muscular activity. The competitive agents are of two pharmacologically distinct types, steroid-based agents (aminosteroid compounds) and benzylisoquinolines. Each of these basic chemical types has distinct properties, but only aminosteroid compounds are used in the ED.

Succinylcholine. Succinylcholine is a combination of two molecules of ACh. Succinylcholine is rapidly hydrolyzed by plasma pseudocholinesterase to succinylmonocholine, which is a weak NMBA, and then to succinic acid and choline, which have no NMBA activity. Pseudocholinesterase is not present at the motor endplate and exerts its effects systemically before the succinylcholine reaches the ACh receptor. Only a small amount of the succinylcholine administered survives to reach the motor endplate. Succinylcholine is active at the motor endplate until it diffuses away. Decreased plasma pseudocholinesterase activity can increase the amount of succinylcholine reaching the motor endplate, prolonging succinylcholine block, but this is of little significance in the emergency setting because the prolongation of action rarely is significant, reaching only 23 minutes at the extreme.

Uses and Dosing. Succinylcholine is rapidly active, typically producing intubating conditions within 45 seconds of administration by rapid IV bolus injection. The clinical duration of action before spontaneous respiration is 6 to 10 minutes (see Fig. 1.11). Full recovery of normal neuromuscular function occurs within 15 minutes. The combination of rapid onset, complete reliability, short duration of action, and absence of common serious side effects has kept succinylcholine as the drug of choice for most ED intubations. Time-trended surveillance of ED intubation practices has suggested that succinylcholine is slowly being replaced by rocuronium.[3] The use of a competitive or nondepolarizing NMBA for RSI may be desirable when succinylcholine is contraindicated and in certain other settings. The appropriate dose of succinylcholine for emergency airway management is 1.5 mg/kg IV. Although the effective dose at which paralysis is achieved in 95% of patients (ED_{95}) for succinylcholine paralysis is much lower (0.3 mg/kg), the onset of muscle paralysis is excessively long at these lower doses and is not compatible with emergency intubation. Excellent intubating conditions are best achieved when succinylcholine is dosed at 1.5 mg/kg. Multiple studies have confirmed that the dose of succinylcholine is based on the patient's total body weight (TBW) and is not adjusted (downward), regardless of the degree of obesity.[22]

Cardiovascular Effects. As an ACh analogue, succinylcholine binds to ACh receptors throughout the body, not just at the motor endplate. It is difficult to separate the effects of succinylcholine on the heart caused by direct cardiac muscarinic stimulation from those caused by stimulation of autonomic ganglia by succinylcholine and from the effects induced by autonomic responses to laryngoscopy and intubation. Succinylcholine can be a negative chronotrope, especially in children, and sinus bradycardia may ensue after succinylcholine administration. Sinus bradycardia is treated with atropine, if necessary, but is usually self-limiting. Some pediatric practitioners recommend pretreatment with atropine for children younger than 1 year, but there is no evidence for benefit, and we do not agree with this recommendation. Adults may develop bradycardia after administration of a second dose of succinylcholine. Other cardiac dysrhythmias, including ventricular fibrillation and asystole, have been reported with succinylcholine, but it is impossible to distinguish the effects of the drug itself from those caused by the intense vagal stimulation and catecholamine release that accompany laryngoscopy and intubation. In addition, many of these catastrophic complications occur in critically ill patients, further confounding attempts to identify whether the illness or any particular drug or procedure is the cause.

Fasciculations. The depolarizing action of succinylcholine results in fine chaotic contractions of the muscles throughout the body for several seconds during the onset of paralysis in over 90% of patients. Muscle pain occurs in approximately 50% of patients who receive succinylcholine. Although it is has been thought that muscle pains are reduced or abolished by prior administration of a defasciculating dose of a competitive NMBA, the evidence is not conclusive. Use of 1.5 mg/kg of succinylcholine results in less fasciculation and less myalgia than occur with 1 mg/kg.

Hyperkalemia. Succinylcholine has been associated with severe fatal hyperkalemia when administered to patients with specific predisposing clinical conditions (Table 1.2). The mechanism whereby severe hyperkalemia occurs is related to receptor upregulation on the postsynaptic muscle membrane. When a muscle is deprived of ACh stimulation for several days, receptor upregulation occurs, causing an increase in receptor density and a change of receptor subtypes on the muscle surface. ACh receptors are primarily K^+ ion channels, and at-risk patients can have an immediate massive efflux of potassium as these newly recruited receptors are depolarized by succinylcholine. This occurs predominantly at the site of injury but may also occur in tissue remote from the original insult.[23] Although the hyperkalemia occurs within minutes after administration of succinylcholine and may be severe or fatal, the patient's vulnerability to succinylcholine-induced hyperkalemia starts as early as 3 days but does not become significant until more than 5 days after the inciting injury or burn, because receptor upregulation production of protein subunits takes time develop.

Succinylcholine remains the agent of choice for RSI in acute burn, trauma, stroke, and spinal cord injury if intubation occurs earlier than 5 days after onset of the condition. If doubt exists regarding the onset time, succinylcholine should be replaced with a competitive NMBA, usually rocuronium. Degenerative neuromuscular disorders, denervation syndromes, or primary myopathies (eg, multiple sclerosis, amyotrophic lateral sclerosis, Duchenne muscular dystrophy) can be particularly troubling, however, because the risk begins the onset of the disease and continues indefinitely, regardless of the apparent stability of the symptoms. In patients with denervation caused by a sudden discreet injury or ischemic insult (eg, stroke, spinal cord injury), the upregulated receptors eventually regress, and the patient can safely receive succinylcholine beginning 6 months after the original insult.

Potassium release does not occur to any significant extent in the general population. Succinylcholine is not contraindicated in renal failure but probably should not be used in patients with known or presumed hyperkalemia (often in the setting of missed

TABLE 1.2

Conditions Associated With Hyperkalemia After Succinylcholine Administration

CONDITION	PERIOD OF CONCERN
Burns > 10% BSA	>5 days until healed
Crush injury	>5 days until healed
Denervation (stroke, spinal cord injury)	>5 days until 6 mo postinjury
Neuromuscular disease (ALS, MS, MD)	Indefinitely
Intraabdominal sepsis	>5 days until resolution

ALS, Amyotrophic lateral sclerosis; *BSA,* body surface area; *MD,* muscular dystrophy; *MS,* multiple sclerosis.

dialysis) sufficient to be manifest on the electrocardiogram (ECG). Treatment for succinylcholine-induced hyperkalemia is the same as for any other hyperkalemic emergency.

Masseter Spasm. Succinylcholine has rarely been reported to cause masseter spasm, primarily in children and young adults. The clinical significance of this phenomenon is unclear, but administration of a competitive NMBA terminates the spasm. Severe persistent spasm should raise suspicion of malignant hyperthermia.

Malignant Hyperthermia. Succinylcholine has been associated with malignant hyperthermia, a perplexing syndrome of rapid temperature rise and rhabdomyolysis. Malignant hyperthermia occurs in genetically predisposed individuals who receive certain volatile anesthetic agents or succinylcholine. The condition is extremely rare and has not been reported in the context of ED intubation. Treatment consists of cessation of any potential offending agents, administration of dantrolene (1–2.5 mg/kg IV every 5 minutes, to a maximum dose of 10 mg/kg IV), and attempts to reduce body temperature by external means. A national malignant hyperthermia hotline is available for emergency consultation at 1-800-644-9737 (then dial 0).

Competitive Agents. Competitive NMBAs are classified according to their chemical structure. The aminosteroid agents include pancuronium, vecuronium, and rocuronium. Vecuronium neither releases histamine nor exhibits cardiac muscarinic blockade and is an excellent agent for the maintenance of neuromuscular blockade when this is desirable. Rocuronium is the best agent for use in RSI when succinylcholine is contraindicated. In a study of ED intubations performed with rocuronium or succinylcholine, first-pass intubation success was independent of the NMBA used.[24]

Rocuronium. When a patient has a contraindication to succinylcholine, rocuronium bromide is the paralytic agent of choice. At a dose of 1.0–1.2 mg/kg IV, rocuronium achieves intubating conditions similar to those of succinylcholine, lasts approximately 50 minutes, and has been used in the ED with success.[3] Intubating level paralysis may take 15 to 20 seconds longer than with succinylcholine, and the operator should allow 60 seconds to elapse before attempting intubation when rocuronium is used. There are no absolute contraindications to rocuronium. In the ED, dosing in morbidly obese patients should be based on actual TBW. Although adequate intubating conditions can be obtained when ideal body weight (IBW) is used, this concept is only pertinent to the anesthesiologist who may be titrating neuromuscular blockade to a short anesthetic time. Paralysis will be of sufficient duration, regardless of which weight-based dosing regimen is used, that the emergency clinician will need to have managed the airway successfully before spontaneous respirations return. The potential for inferior intubating conditions using IBW dosing makes this approach undesirable. However, in the subset of critically ill patients who require frequent, serial, neurologic examinations, the more prolonged duration of paralysis with rocuronium may make it less desirable than succinylcholine for routine use.

Paralysis After Intubation. After intubation, prolonged paralysis may be desired to optimize mechanical ventilation; however, current management is based on use of deep sedation and analgesia, with neuromuscular paralysis used only when necessary to maintain ventilatory control. If neuromuscular blockade is required, vecuronium (0.1 mg/kg IV) can be given, but longer term neuromuscular blockade is not to be undertaken without ensuring appropriate sedation and analgesia of the patient and a means to ensure that ongoing sedation and analgesia are adequate. Prolonged paralysis without adequate sedation occurs in up to 20% of patients following RSI in the ED.[25] A sedating dose of a benzodiazepine, such as midazolam (0.1 mg/kg IV), combined with an opioid analgesic, such as fentanyl (3–5 μg/kg IV) or morphine (0.2–0.3 mg/kg IV), is required to improve patient comfort and decrease sympathetic response to the ETT. A sedative strategy using propofol (0.1 mg/kg/min IV) is common, especially in head-injured patients, because of its beneficial cerebroprotective profile and rapid resolution of anesthesia that allows frequent neurologic reassessments. With appropriate attention to achieving optimal sedation and analgesia, ongoing use of an NMBA usually is not necessary.

Induction Agents

A patient with any degree of clinical responsiveness, including reactivity to noxious stimuli, should receive a sedative or induction agent at the time of administration of any NMBA. Patients who are deeply unconscious and unresponsive may require only a reduced dose of an induction agent if the unconscious state is caused by drugs or alcohol, which are themselves general anesthetic agents. Patients who are unconscious because of a central nervous system insult should receive a full induction dose of an appropriate agent to attenuate adverse responses to airway manipulation. Induction agents also potentiate the effect of the NMBA and improve intubation conditions because the intubation is often initiated on the leading edge of paralysis, and the relaxation effects of the induction agent are additive to those of the NMBA.

Etomidate. Etomidate is an imidazole derivative that has been in use since 1972. Its activity profile is similar to that of thiopental, with rapid onset, rapid peak activity, and brief duration, but it is remarkable in its lack of adverse hemodynamic effects. Emergency clinicians have high confidence in etomidate and, over the last decade, have chosen it for more than 90% of all ED intubations.[3] The induction dose is 0.3 mg/kg IV. Because etomidate is able to decrease ICP, cerebral blood flow (CBF), and cerebral metabolic rate without adversely affecting systemic mean arterial blood pressure and cerebral perfusion pressure (CPP), it is an excellent induction agent for patients with elevated ICP, even in cases of hemodynamic instability. Etomidate may cause brief myoclonus, but this is of no clinical significance when administered for RSI. A single dose of etomidate has been shown to reduce serum cortisol levels transiently and blunt the adrenal response to adrenocorticotropic hormone (ACTH) by reversibly inhibiting 11β-hydroxylase, a key synthetic enzyme in the glucocorticoid pathway. Since discovering this mechanism, much debate has emerged regarding etomidate's impact on survival in sepsis patients. Data from retrospective studies are conflicting, but a recent meta-analysis of 18 prospective observational and controlled trials has shown no mortality effect from a single dose of etomidate in septic patients.[26,27] Recent prospective randomized trials looking at undifferentiated ICU admissions and those specifically involving individuals with septic shock have shown that single-dose etomidate has no effect on outcome.[28] Ironically, much of the original criticism of etomidate arose from the hypothesis that the adrenocortical response to exogenous corticotropin predicts outcome in patients with septic shock, a theory that has since been discredited.[28a] The most comprehensive study of the role of exogenous corticosteroids in septic shock has failed to show any benefit, casting further doubt about any possible mortality effect of a single dose of etomidate. Pending a properly constructed, prospective, randomized clinical trial, there is not sufficient evidence to support the recommendation that etomidate be avoided in patients with septic shock. In fact, etomidate's superior hemodynamic profile makes it an excellent choice in these and other unstable patients.

Ketamine. Ketamine, a phencyclidine derivative, has been widely used as a general anesthetic agent since 1970. After an IV dose of 1 to 2 mg/kg, ketamine produces loss of awareness within 30 seconds, peaks in approximately 1 minute, and has a clinical

duration of 10 to 15 minutes. As a dissociative anesthetic agent, ketamine induces a cataleptic state rather than a true unconscious state. The patient has profound anesthesia but may have her or his eyes open. Protective airway reflexes and ventilatory drive usually are preserved.

The principal uses of ketamine in emergency airway management are as a sedative agent for awake intubation (eg, flexible bronchoscope) and as the induction agent during RSI for patients with acute severe asthma or hemodynamic instability. Because of its superior hemodynamic profile, ketamine is an excellent alternative to etomidate for a hemodynamically unstable patient, such as a patient with sepsis or multiple trauma. Although comparative human evidence is lacking, ketamine probably has less propensity to exacerbate hemodynamic instability than any other agent, even etomidate. However, all sedative induction agents, including ketamine, can provoke further hypotension or cardiovascular collapse in patients with profound refractory shock or those with depressed myocardial contractility and catecholamine depletion. In these settings, dosages are reduced to 50% or 25% of the usual dose. In patients with status asthmaticus, etomidate, propofol, or another induction agent can be used, with the notable exception of sodium thiopental, which releases histamine. Ketamine has some bronchodilatory effects and also can cause catecholamine release, so it may be useful for intubation and intermittent administration as part of sedation for mechanical ventilation in patients with severe asthma, although no outcome studies have clearly demonstrated its superiority.

Controversy exists regarding the use of ketamine in patients with elevated ICP because it may increase the cerebral metabolic rate, ICP, and CBF. The evidence that ketamine can produce harm in this way is conflicting, however, and may be outweighed in trauma patients because of its overall favorable hemodynamic profile.[29] Ketamine does not appear to be harmful in children when given in procedural doses to patients with known elevated ICP and may actually lower ICP.

Because it may cause release of catecholamines and increase blood pressure, ketamine should be avoided in traumatic brain injury (TBI) patients with elevated blood pressure. However, we recommend the use of ketamine or etomidate during RSI for induction of patients with TBI and hypotension or risk factors for hypotension. Ketamine may produce unpleasant emergence phenomena, especially disturbing or frightening dreams in the first 3 hours after awakening. These reactions, which are more prominent in adults than in children, in women than in men, in patients receiving larger doses, and in certain personality types, may be mitigated by benzodiazepine administration.[30] Patients who undergo RSI with ketamine should receive a benzodiazepine (eg, lorazepam, 0.05 mg/kg, or midazolam, 0.1 mg/kg) as part of postintubation management.

Propofol. Propofol is a highly lipophilic alkylphenol with γ-aminobutyric acid (GABA) receptor stimulation activity. Its primary use in the emergency setting has been for postintubation sedation in head-injured patients; however, it increasingly has been used as an induction agent during RSI.[3] It reduces ICP and cerebral oxygen usage and is indicated for patients with elevated ICP caused by a medical or traumatic emergency. Because of the propensity of propofol to cause hypotension through vasodilation and direct myocardial depression, the dosage is reduced or the drug is avoided altogether in hemodynamically compromised patients. The usual induction dose of propofol is 1.5 mg/kg IV, but reduced dosages should be used in older patients or those with hemodynamic compromise or poor cardiovascular reserve. Propofol is delivered in a soybean oil and lecithin vehicle and should not be used for patients with allergies to these substances. Although propofol has traditionally been avoided in patients with egg allergy, it is likely safe unless a history of anaphylaxis to egg protein exists. Propofol causes pain at the site of administration in as many as 60% of patients. Using a proximal (antecubital) vein in lieu of a distal venous injection site is the most important preventive measure. Pretreatment with IV lidocaine, coadministration of lidocaine mixed with propofol, and pretreatment with opioids or ketamine have all been shown to limit this common adverse reaction.[31]

Other Induction Agents. Given the widespread acceptance and familiarity with etomidate, propofol, and ketamine, other drug classes such as barbiturates and benzodiazepines are infrequently used as induction agents for RSI. In North America, nearly all emergency intubations are performed with one of those three agents.[3] Rapidly acting barbiturates, such as thiopental, are highly lipid-soluble and readily cross the blood-brain barrier, acting on the GABA receptor neuroinhibitory complex to depress central nervous system activity. The last US-based manufacturer of sodium thiopental stopped production, and imports into the United States are severely restricted, but it is still in use in some areas outside of North America. Of the benzodiazepines, only midazolam is used as an induction agent, a role for which it is inferior to other, more commonly used agents, such as etomidate and propofol. The usual induction dose for midazolam is 0.2 to 0.3 mg/kg IV. At a dose of 0.3 mg/kg IV, midazolam produces loss of consciousness in about 30 seconds (but may take up to 120 seconds) and has a clinical duration of 15 to 20 minutes. Midazolam is a negative inotrope and should be used with caution in hemodynamically compromised and older patients, for whom the dose can be reduced to 0.1 or 0.05 mg/kg. Onset is slower at these reduced doses.

Dexmedetomidine (Precedex) has gained popularity as a solo agent, or in combination with benzodiazepines, for procedural sedation and awake intubation.[21] The typical loading dose is 1 mg/kg IV over 5 to 10 minutes. At therapeutic levels, it has a minimal effect on the respiratory drive or protective airway reflexes but its use is limited by bradycardia and hypotension. It has not been studied as an induction agent during RSI, and its slow loading rate would likely keep it from being effective in that situation.

Special Clinical Circumstances

This section will discuss several specific clinical scenarios that often warrant modification of the airway management plan. Pediatric airway management is discussed in Chapter 161.

Status Asthmaticus

RSI is the recommended technique for intubation of a patient in status asthmaticus. Difficult airway considerations are complex in an asthmatic patient because of impending respiratory arrest and the patient's inability to tolerate attempts at awake intubation. When a difficult airway is identified, intubation preparation should begin early, so that awake methods, such as flexible endoscopic intubation, may be retained as options. Even when a difficult airway is identified in an asthmatic patient, however, RSI usually is the intubation method of choice. Ventilation with a BMV or EGD may be difficult because of high airway resistance, and the technique should be optimized with the use of a low tidal volume and respiratory rate, with a high inspiratory flow rate. Reducing the respiratory rate to allow for adequate exhalation, even at the expense of retaining CO_2, is recommended to prevent the development of auto-PEEP, known as breath stacking, which can compromise ventilation and cause barotrauma.

The asthmatic patient has highly reactive airways, and steps should be taken to minimize any additional bronchospasm that may occur during intubation. The bronchoconstriction that occurs with ETT placement is thought to be neurally mediated,

and local anesthetics, particularly lidocaine, have been studied as a way to blunt this airway reflex. We had previously recommended lidocaine to suppress the reflexive bronchospasm and coughing that occurs in response to airway manipulation in asthmatic patients, but there have been no high-level human studies supporting these beneficial effects, particularly in patients who have received a β_2-agonist. High-dose, inhaled β-agonists, such as albuterol, provide maximal protection against reactive bronchospasm during intubation and are indicated for asthmatics with or without active bronchospasm. Ketamine has bronchodilatory properties and may mitigate bronchospasm in patients who are not intubated and in patients who are already intubated and are not improving with mechanical ventilation. Although studies to date have been limited, ketamine is also a reasonable induction agent for the emergency intubation of patients with status asthmaticus (Table 1.3).

Hemodynamic Consequences of Intubation

Laryngoscopy and intubation are potent stimuli for the reflex release of catecholamines. This RSRL produces a modest increase in blood pressure and heart rate and is of little or no consequence in otherwise healthy patients. The RSRL is of potential clinical significance in two settings, acute elevation of ICP and certain cardiovascular diseases (eg, intracerebral hemorrhage, subarachnoid hemorrhage, aortic dissection or aneurysm, ischemic heart disease). In these settings, the reflexive release of catecholamines, increased myocardial oxygen demand, and attendant rise in mean arterial blood pressure and heart rate may produce deleterious effects. The synthetic opioids (eg, fentanyl) and β-adrenergic blocking agents (eg, esmolol) are capable of blunting the RSRL and stabilizing heart rate and blood pressure during intubation. In patients at risk from acute blood pressure elevation, administration of fentanyl (3 μg/kg) during the pretreatment phase of RSI attenuates the heart rate and blood pressure increase. The full sympatholytic dose of fentanyl is much higher, but limiting the dose minimizes the likelihood of precipitating or worsening hypoventilation. Because fentanyl reduces sympathetic tone, it should not be given to patients with hemodynamic compromise (eg, bleeding, volume depletion, sepsis). The administration of 3 μg/kg is safer than larger doses and can be supplemented with an additional 3 μg/kg immediately after intubation if greater sympathetic blockade is desired or hypertension and tachycardia persist. Fentanyl should be given over 60 seconds to prevent hypoventilation or apnea.

TABLE 1.3

Rapid Sequence Intubation for Status Asthmaticus

TIME	STEP
Zero minus 10 min	Preparation
Zero minus 5 min	Preoxygenation (as possible) • Continuous albuterol nebulizer • 100% oxygen for 3 min or eight vital capacity breaths, or highest flow oxygen possible
Zero minus 3 min	Pretreatment—albuterol, 2.5 mg nebulized, or lidocaine, 1.5 mg/kg[a]
Zero	Paralysis with induction • Ketamine, 1.5 mg/kg • Succinylcholine, 1.5 mg/kg
Zero plus 30 s	Positioning
Zero plus 45 s	Placement • Laryngoscopy with intubation • End-tidal carbon dioxide confirmation
Zero plus 2 min	Postintubation management • Sedation and analgesia • NMBA only if required after adequate sedation, analgesia • In-line albuterol nebulization • Additional ketamine as indicated

[a]Only if not already pretreated with β-agonists.
NMBA, Neuromuscular blocking agent.

Elevated Intracranial Pressure

When the ICP is elevated as a result of head injury or acute intracranial catastrophe, there are two considerations—maintaining CPP (by avoiding excessive hypotension) and minimizing supranormal surges in the mean arterial blood pressure (MAP), which can increase ICP. Normally, cerebrovascular autoregulation maintains a constant CBF over a wide range of systemic blood pressures, but this action may be lost in conditions that elevate ICP. Maintenance of the systemic MAP at 100 mm Hg or higher supports CPP and reduces the likelihood of secondary injury. Therefore, the RSI induction agent for a patient with suspected elevated ICP should be selected and dosed to minimize the likelihood of exacerbation of hypotension. In patients with suspected or documented elevation of ICP, control of RSRL is desirable to avoid further elevation of ICP. Fentanyl (3 μg/kg) given as a pretreatment drug is the best choice for this purpose in the emergency setting.

Although evidence has suggested a separate reflex that increases ICP in response to laryngoscopy and intubation, and IV lidocaine was formerly recommended for this purpose, evidence is weak, and no further evidence has developed. Therefore, we no longer recommend lidocaine in this setting. Similarly, RSRL and the ICP response to intubation make blind nasotracheal intubation inadvisable for brain injury patients.

In emergency patients who may have elevated ICP, the emergency clinician should choose an induction agent that balances a favorable effect on cerebral dynamics and ICP with a stable systemic hemodynamic profile. We recommend etomidate, although propofol is also a good option when there is no hemodynamic compromise (Table 1.4).

Hypotension and Shock

In critically ill and injured patients, induction agents have the potential to exaggerate preexisting hypotension and, in some cases, precipitate circulatory collapse. Peri-intubation cardiac arrest, typically pulseless electrical activity (PEA), complicates up to 4% of emergency RSIs.[3] Risk factors in ED populations include advanced age (>70 years), COPD, and shock on arrival.[32-34] In patients with profound shock, all induction agents have the potential to exacerbate hypotension. Shock-sensitive RSI hinges on three primary management principles—volume resuscitation prior to induction (if time permits), reduced dose induction agent administration, and pretreatment with peri-intubation pressor agents (Table 1.5).

When time allows, patients with hypotension should be administered isotonic fluid boluses or packed red blood cells (PRBCs) to maximize preload, increase blood pressure, and allow more pharmacologic options during RSI. Phenylephrine hydrochloride (Neo-Synephrine; 50–100 μg IV push) administered prior to the induction agent can limit hypotensive effects. In addition, induction agent selection should be limited to etomidate or ketamine only, and the dose should be reduced by 50%. Attention to these details can reduce the incidence of cardiovascular peri-intubation adverse events.

TABLE 1.4

Rapid Sequence Intubation for Elevated Intracranial Pressure

TIME	STEP
Zero minus 10 min	Preparation
Zero minus 5 min	Preoxygenation (as possible) — 100% oxygen for 3 min or eight vital capacity breaths
Zero minus 3 min	Pretreatment—fentanyl, 3 μg/kg (slowly)
Zero	Paralysis with induction • Etomidate, 0.3 mg/kg • Succinylcholine, 1.5 mg/kg[a]
Zero plus 30 s	Positioning
Zero plus 45 s	Placement • Laryngoscopy with intubation • End-tidal carbon dioxide confirmation
Zero plus 2 min	Postintubation management—sedation and analgesia; consider propofol to permit frequent reexamination NMBA only if required after adequate sedation, analgesia

[a]May substitute rocuronium, 1 mg/kg, for succinylcholine.
NMBA, Neuromuscular blocking agent.

TABLE 1.5

Rapid Sequence Intubation for Hypotension and Shock

TIME	STEP
Zero minus 10 min	Preparation—isotonic fluid boluses or blood products
Zero minus 5 min	Preoxygenation (as possible)—100% oxygen for 3 min or eight vital capacity breaths
Zero minus 3 min	Pretreatment—phenylephrine hydrochloride (Neosynephrine), 50–100 μg IV push (if still hypotensive after IVFs or blood)
Zero	Paralysis with induction • Ketamine, 0.5–0.75 mg/kg OR Etomidate, 0.1–0.15 mg/kg • Succinylcholine, 1.5 mg/kg IV
Zero plus 30 s	Positioning
Zero plus 45 s	Placement • Laryngoscopy with intubation • End-tidal carbon dioxide confirmation
Zero plus 2 min	Postintubation management—continued volume resuscitation

Potential Cervical Spine Injury

Historically, most patients with suspected blunt cervical spine injury were intubated orally by direct laryngoscopy with in-line cervical spine immobilization, whether done as an awake procedure or with neuromuscular blockade. However, with this approach, glottic views can be inadequate, and excessive lifting force often is required. Patients with known cervical spine fractures are optimally managed with a flexible bronchoscope to minimize cervical spine motion; however, in the emergency setting, a videolaryngoscope should be used and, if not available, a direct laryngoscope also can be used. A videolaryngoscope provides superior laryngeal views without excessive lifting force or cervical spine movement and has higher intubation success rates when compared with conventional direct laryngoscopy.

The intubating laryngeal mask airway (ILMA) also may result in less cervical spine movement during intubation than direct laryngoscopy, although the need for a blind intubation devices has been decreasing with the advent of videolaryngoscopy.[3] Other devices have also shown promise for safe intubation of patients with cervical spine injury. A fluoroscopic study in which intubation with the Shikani optical stylet (SOS; Clarus Medical, Minneapolis) was compared with DL has shown significantly less cervical spine movement with the SOS but a slightly longer intubation time (28 vs. 17 seconds). Video-enhanced rigid stylets, such as the Clarus Video System (CVS) are also effective tools for patients in cervical collars.[35] The Airtraq and Pentax Airway Scope are curved intubation devices that integrate an ETT channel and either a viewing lens or a video screen to facilitate intubation. Both devices have shown high levels of intubation success and minimal cervical spine motion compared with direct laryngoscopy. In the absence of a coexistent blunt traumatic mechanism or a neurologic examination indicating spinal cord injury, cervical spine immobilization for intubation of patients with penetrating head and neck trauma rarely is indicated. It is not proven whether patients with gunshot or shotgun injuries to the head or neck are at risk of exacerbation of cervical cord injury during intubation, and there is no report of such a patient, with or without clinical evidence of spinal cord injury, who was injured by intubation. In addition, cervical spine immobilization in patients with penetrating neck injuries may be harmful. A large retrospective review of more than 45,000 trauma patients with penetrating injuries has found that those in whom prehospital cervical collars were applied were two to three times more likely to die. Delays in transport and patient assessment and added difficulty for airway procedures were postulated as potential contributors.[36]

Airway Devices and Techniques

Direct Versus Video Laryngoscopy

The inherent limitations of DL make glottic visualization less likely when compared to video instruments.[6,37] Videolaryngoscopes offer the ability to visualize the glottis without creating a direct line of sight, thus making irrelevant many of the issues that complicate DL. Although DL remains an acceptable technique for tracheal intubation, there is mounting evidence of the clear superiority of modern video devices, and DL increasingly is relegated to the role of a standby device.[3]

Videolaryngoscopes

Modern laryngoscopes incorporate video imaging into specially designed laryngoscope blades to provide glottic visualization superior to that of a direct laryngoscope, without the need to create a straight-line visual axis through the mouth. Videolaryngoscopes can be separated into two large groups based on shape—those that use traditional laryngoscope geometry complemented by a video viewing device (which also can be used as direct laryngoscopes), and those with specially curved or angulated blades, designed specifically for use in a video system and not suitable for DL. This classification system is important because intubating mechanics and success differ between the two groups. Nevertheless, regardless of type, videolaryngoscopes provide superior glottic views and greater first-pass success when compared with direct laryngoscopes, particularly when the airway is difficult or when a nonexpert operator is performing the intubation.[6,7,37,38]

For routine intubation of nondifficult airways by expert intubators, success rates with direct laryngoscopy often can match those obtained with a videolaryngoscope.[7] Because emergency intubations are by definition emergent and cannot be rescheduled, operator experience varies, and airways are often difficult, videolaryngoscopy is the first-choice modality for emergency intubations.

The GlideScope videolaryngoscope system (GVL; Verathon, Seattle) uses a modified Macintosh blade with a straightened, angulated, and elongated tip enclosing a proximally placed camera to provide a wide-angle view of the glottis and surrounding anatomy, even in patients with difficult airways. Video images are transmitted to a high-resolution display that can record still pictures and video clips. Handle and blade sizes range from neonate to obese adult. The GlideScope Ranger is an ultraportable version of the device, designed for use in the out-of-hospital environment. One large series of out-of-hospital intubations has shown that the Ranger significantly reduces the number of attempts needed to intubate compared with DL.[39] The GlideScope Cobalt is a system designed for a single use, without the need for cleaning (Fig. 1.12). It consists of a flexible video wand insert that fits inside a disposable, single-piece transparent blade called a stat and comes in sizes comparable to those for the standard GlideScope. The added bulk created by the stat can make it harder to maneuver in emergency patients and may reduce intubation success compared to the standard GVL blade.[40] The newest generation GlideScope handles are made of lightweight titanium, with a narrower side profile (Fig. 1.13). The placement of the camera distally along the blade to create a viewing field essentially negates the obstructive potential of the tongue, so GlideScope laryngoscopy and most other hyperangulated videolaryngoscopy is performed with the blade introduced in the midline of the mouth and advanced around the tongue, with very little lifting. A proprietary rigid, preformed stylet is available for use with the GlideScope, or a malleable stylet can be shaped to match the exaggerated curve of the GlideScope blade. The rigid stylet is less likely to deform during intubation attempts and allows the operator better ETT control on the video screen. Either stylet may be used, and data are conflicting regarding the advantage provided with a rigid stylet; however, one ED-based investigation has suggested that intubation success is higher with the rigid stylet compared with a standard malleable stylet.[41,42] When compared with DL, the GlideScope provides an equivalent or superior glottic view and has a very high intubation success rate.[7] Traditional predictors of difficult direct laryngoscopy likely will not apply to videolaryngoscopy because most are based on limitations of creating a direct line of sight, which is not part of videolaryngoscopy.[43]

Fig. 1.12. GlideScope Cobalt system uses a high-resolution digital display, includes single-use Stats (blade sheaths) that cover the video baton, and can record still images and video clips through internal and removable storage devices. (Courtesy Verathon, Seattle.)

Although the view is universally better with all videolaryngoscopes, the GlideScope's impact on first-pass success has been less clear. A recent large meta-analysis of more than 12 studies has shown that GVL is superior in obtaining full glottic views but, for experienced laryngoscopists, first-pass success was not superior to conventional laryngoscopy.[7] In ED patients, GVL was associated with a lower first-attempt success rate than DL, although the groups were not matched.[3] Single-center ED observational studies, however, have shown that the GlideScope is superior to DL for intubating ED patients, and success has increased over time.[37,44] The GlideScope causes less cervical spine movement than conventional DL and provides better glottic exposure in patients with strict cervical spine precautions. The C-MAC videolaryngoscope (Fig. 1.14; Karl Storz Endoscopy, Tuttlingen, Germany)

Fig. 1.13. GlideScope Titanium handles incorporate similar video elements in a lightweight titanium blade with a narrower side profile. Connection to the video display is made by a USB-style cord. (Courtesy Verathon, Seattle.)

Fig. 1.14. The C-MAC videolaryngoscope (Karl Storz Endoscopy, Tuttlingen, Germany) uses an integrated complementary metal oxide semiconductor (CMOS) video chip to capture a video image from near the distal tip of an otherwise conventional laryngoscope blade. The image is conveyed to a video screen, where it is viewed by the intubator. (From Walls RM, Murphy MF, eds: Manual of emergency airway management, ed 4, Philadelphia, 2012, Lippincott, Williams & Wilkins; with permission.)

Fig. 1.15. King Vision videolaryngoscope integrates a single-use, curved video blade attached to a top-mounted display. The blades come in two versions, those with endotracheal tube channels, for advancing the endotracheal tube, and those without. (Courtesy Calvin A. Brown III, MD.)

Fig. 1.16. The Clarus Video System incorporates a curved stylet containing a CMOS chip video camera surrounding by a malleable but rigid protective metal sheath. Images are displayed on a video screen attached to the handle. The screen can swivel for optimal viewing as the stylet is inserted into the mouth. (Courtesy Clarus Medical, Minneapolis.)

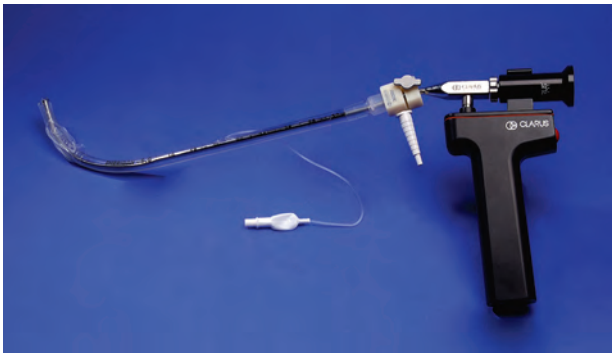

Fig. 1.17. The Shikani optical stylet (SOS) with endotracheal tube mounted. The eyepiece and battery pack are at the *right*. (Courtesy Clarus Medical, Minneapolis, MN.)

incorporates a complementary metal oxide semiconductor (CMOS) video chip into a range of laryngoscope blades to enhance glottic views. Images are displayed on a high-resolution monitor, with image- and video-saving capabilities. The traditionally shaped C-MAC blade can be used as a direct laryngoscope by a trainee while a supervisor observes the video output, providing an excellent tool for teaching DL. One ED-based direct comparison of the C-MAC and GVL has suggested that they perform similarly during emergency intubation.[45] Compared to DL the C-MAC provides better visualization of the glottic inlet, higher rates of first-pass success, and outperforms DL when rescuing a failed first attempt using DL.[3,6,46]

The King Vision videolaryngoscope (King Systems, Noblesville, IN) is a single-use, lightweight device with a detachable (and reusable) screen that sits on top of a disposable video blade (Fig. 1.15). There are two blade types, one with an integrated tube channel and one without; the latter requires the operator to place the ETT manually. In simulated difficult airways using cadaveric subjects, the King Vision results in higher success rates and faster tube placement compared to DL.[47] The McGrath Series 5 is a cordless videolaryngoscope with an integrated screen and handle configuration.

There are several other models of videolaryngoscopes with various sizes and features, such as disposable sheaths or blades, and at various price points.[48,49] Individual evaluation of these devices is important in selecting the best videolaryngoscope for an individual practitioner or practice group. In 2012, videolaryngoscopes were chosen as the first device for airway management in nearly 40% of all intubations.[3] Overall, videolaryngoscopy offers the promise of transforming laryngoscopy and has the potential to render DL obsolete.

Fiberoptic and Video Intubating Stylets

Several semirigid fiberoptic and video intubating stylets also are available. The SOS is the most studied of these, although a newer video device (Clarus Video System, Clarus Medical, Minneapolis; Figs. 1.16 and 1.17) based on the same principles likely will perform as well as or better than its fiberoptic forerunner. The ETT is placed over a semirigid stylet, consisting of a metal sheath with a distally placed video image acquisition system, then advanced through the mouth and over the tongue in the midline and into the trachea under fiberoptic or video visualization. The SOS appears to cause less movement of the cervical spine than conventional laryngoscopy during intubation with inline stabilization (Fig. 1.16). A smaller version, the Levitan scope (Clarus Medical), uses a light-emitting diode (LED)–illuminated fiberoptic stylet to facilitate intubation by direct laryngoscopy. The device is recommended by the manufacturer to facilitate first-pass success when a limited glottic view is obtained by DL. In the only study comparing the Levitan scope with the gum elastic bougie, however, the two devices achieved similar success.

Flexible Intubating Scopes

Intubation using a flexible endoscope is an important option for certain difficult airways, particularly in those with distorted upper airway anatomy, such as angioedema or blunt anterior neck trauma. These scopes long relied on fiberoptic technology, but this has largely been supplanted by miniaturized, high-quality video systems (Fig. 1.18). After appropriate patient preparation, the endoscope is passed through the vocal cords under continuous visualization, serving as an introducer for an ETT, which is then placed through the glottis. Flexible endoscopic examination also is used for airway assessment to determine whether intubation is needed, such as for patients with smoke inhalation or supraglottitis. Intubation of morbidly obese patients, those with distorted airway anatomy (eg, penetrating or blunt anterior neck injury), or those with a fixed cervical spine deformity can be achieved with the flexible endoscope with topical anesthesia and judicious sedation, thus preserving the patient's ability to breathe until intubation has been achieved. Scopes also have been used successfully to intubate through an ILMA, and video systems likely would work well in this application also.

Fig. 1.18. New video flexible bronchoscopes are now available and integrate fully with the C-MAC high-resolution display. (Courtesy Karl Storz Endoscopy, Tuttlingen, Germany.)

Fig. 1.19. The Ambu aScope is a new, fully disposable video flexible bronchoscope with an integrated suction port and working channel for suctioning and instillation of local anesthetic. Airway images are viewed via a reusable digital display. (Courtesy Calvin A. Brown III, MD.)

There is a significant learning curve for flexible endoscopic intubation, and proficiency with this device requires training and practice. Fortunately, endoscopic examination of the upper airway to the level of the vocal cords is a similar skill set as that needed to maneuver the scope through the cords to intubate. This is an important alternative method to obtain real-life experience with insertion and manipulation of the scope. Only approximately 1% of ED patients are managed with a flexible bronchoscope, possibly reflecting reluctance to select this instrument if the operator does not feel sufficiently trained or competent. Flexible bronchoscope intubations are the method of choice for most patients with upper airway obstruction.[3] The role of flexible endoscopic intubation in the ED will likely expand as obesity increases in the population and, increasingly, difficult airways are handled in the ED without backup. The transition from fiberoptic to CMOS video technology will make these flexible scopes more durable and less prone to fogging, both desirable attributes for emergency intubation. Although the cost required to purchase and maintain a flexible endoscope can make it challenging for some emergency departments, single-use flexible videoscopes, such as the Ambu aScope (Ambu, Columbia, MD), provide a less costly option (Fig. 1.19). Emergency clinicians should have immediate access to flexible endoscopes and should acquire training and regular practice in their use.

Extraglottic Devices

Laryngeal Mask Airways. LMAs collectively include a number of commercially available ovoid, silicone mask devices designed to seal above the glottis and permit ventilation through a central channel with a standard bag. There are several models available, and attributes differ among the models, but use and success rates are very similar. The most widely used is the original LMA. Reusable and single-use configurations, conventional and intubating formats, are offered by several manufacturers. The mask is inserted blindly into the pharynx and then inflated, providing a seal that permits ventilation of the trachea with minimal gastric insufflation. In elective anesthesia, the LMA has an extremely high insertion success rate and low complication rate, including a low incidence of tracheal aspiration. Evaluations of LMA insertion by experienced and inexperienced personnel consistently have shown ease of insertion, high insertion success rates, and successful ventilation. The LMA may be a viable alternative to endotracheal intubation for in-hospital or out-of-hospital treatment of cardiac arrest, particularly when responders are inexperienced airway managers. At a minimum, the device may serve a temporizing role equal or superior to BMV until definitive airway management can be achieved. The LMA Supreme (Teleflex Inc., Morrisville, NC) is a more robust LMA with a rigid angled tube, similar to an ILMA; it offers an orogastric tube channel and higher seal pressures than the standard LMA. This likely is the best version for general ED use.

A noninflatable LMA, the i-gel (Intersurgical, Berkshire, England), has a viscous gel cuff and does not require inflation (Fig. 1.20). It is available in a variety of sizes for adults and pediatric patients. The device is placed blindly, and insertion depths are marked on the side of the device. It has an integrated bite block and channel for passage of an orogastric tube. Initial experience with the device, even with minimally trained novice users, has been promising, with high insertion success rates and shorter insertion times when compared with the LMA or laryngeal tube airway.[50]

The ILMA is designed to facilitate intubation through the mask after correct placement (Fig. 1.21). It differs from the LMA in two main ways. First, the mask is attached to a rigid, stainless steel ventilation tube that is curved almost to a right angle, and the mask incorporates an epiglottic elevator at its distal end. Placement of the ILMA results in successful ventilation in almost 100% of cases and successful subsequent intubation in 95%. The ILMA can also be used for ventilation and intubation in obese patients, with similarly high success rates. The ILMA has a special ETT and stabilizer rod to remove the mask over the ETT

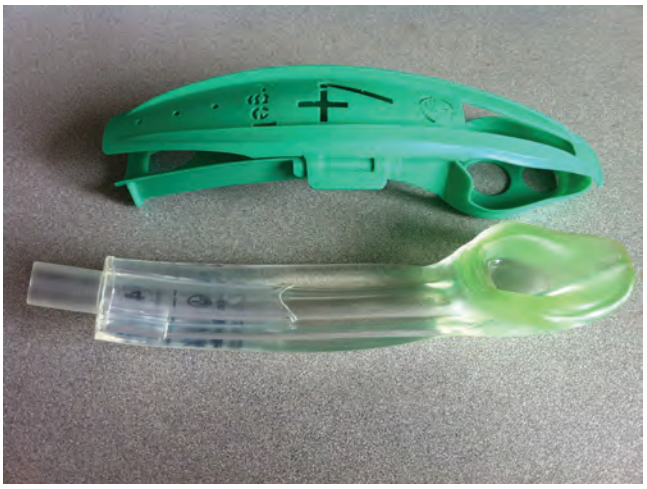

Fig. 1.20. The i-gel mask airway (Intersurgical, Berkshire, England) does not have an inflatable cuff and is available in sizes from infant to adult. (Courtesy Dr. Calvin A. Brown, III.)

Fig. 1.21. The intubating laryngeal mask airway is modified to facilitate insertion of an endotracheal tube after placement and ventilation have been achieved. The epiglottic elevator *(arrowhead)* lifts the epiglottis to allow passage of the special endotracheal tube *(arrow)*.

after intubation has been accomplished, but intubation can be comparably successful with a conventional polyvinylchloride (PVC) ETT.

The ILMA is a better device than the standard LMA for use in the ED because it facilitates rescue ventilation and intubation. Intubation through the ILMA has compared favorably in terms of success with DL and is superior in the hands of novice intubators. When the ILMA is placed, intubation can be performed blindly or guided by a lighted stylet or fiberoptic scope. The ILMA comes only in sizes 3, 4, and 5 and so is not suitable for use in patients weighing less than about 30 kg (≈66 lb). For smaller patients, the standard LMA, which has sizes down to size 1 (infant), should be used. Intubation can be achieved through the standard LMA, but the success rate is significantly less than with the ILMA. As experience with the LMA and ILMA grows, it is likely that there will be increasing adoption of the LMA as a primary airway management technique by nonhospital first responders, and the ILMA has been gaining attention as a primary rescue device in the ED. Newer LMA-style devices, the Ambu air-Q and Aura-I, can act as standard LMAs for ventilation and oxygenation but can facilitate blind intubation with standard adult endotracheal tubes. Both work well intubating a difficult airway, especially when augmented by flexible endoscopy.[51]

In the ED, the primary use of the LMA or ILMA is as a rescue technique to provide a temporary airway when intubation has failed, bag ventilation is satisfactory, and the patient has been paralyzed and may require prolonged ventilation or be in need of immediate airway management. In such cases, the LMA is one of numerous acceptable devices. In the can't intubate, can't ventilate situation, cricothyrotomy is indicated, but an ILMA may be placed rapidly in an attempt to achieve ventilation (converting the situation to can't intubate, can ventilate), as long as this is done in parallel with preparations for cricothyrotomy and does not delay initiation of a surgical airway. The standard LMA may also offer advantages for providing ventilation in unconventional positions, such as when the patient is lying on his or her side. In the out-of-hospital setting, where concerns about esophageal placement of ETTs have focused interest on methods used for airway management, the LMA and Combitube offer excellent placement and ventilation characteristics and may be preferable to endotracheal intubation in this setting, especially when intubation is relatively infrequently performed.[53] If the patient is in a difficult position in terms of intubation access, the LMA may facilitate more rapid ventilation.

Other Extraglottic Devices. In addition to LMAs, which sit above the glottis, there are several other types of EGDs. These are inserted blindly posterior to and beyond the laryngeal inlet to provide oxygenation and ventilation through side ports while inflatable balloons occlude the pharynx above and the esophageal inlet below. Because of their positioning behind the larynx, these often are called retroglottic devices. The prototype for these devices is the esophagotracheal Combitube. The Combitube is a plastic double-lumen tube with one lumen functioning as an airway after esophageal insertion and the other lumen functioning as a tracheal airway. The tube is placed blindly into the esophagus, and proximal and distal balloons are inflated sequentially through different ports. The balloons prevent escape of ventilatory gases upward through the pharynx or downward through the esophagus. The tube is placed into the esophagus, as designed, almost 100% of the time, but both lumens are patent, so ventilation is still possible if the tube has been placed inadvertently into the trachea. It comes in two sizes and is used only in patients taller than 48 inches.

The King laryngeal tube airway (King LT; King Systems) has a single port through which distal and proximal low-pressure balloons are inflated as a single step (Fig. 1.22). The distal balloon, when seated correctly, obstructs the cervical esophagus, and the larger proximal balloon obstructs the hypopharynx, preventing regurgitation of air. A newer version of the King LT has a posterior channel that accepts a nasogastric tube, which can be passed through the device into the stomach for aspiration of gastric contents. The King LT is disposable, rapidly placed, easy to use by operators of various skill levels and has seal pressures similar to those of standard LMAs.[52] All extraglottic devices can be safely left in place for 4 hours without mucosal pressure damage. Another device, the Rusch EasyTube (Teleflex, Morrisville, NC), is similar in concept and appearance to the Combitube but is available in 41 Fr and a smaller 28-Fr size for smaller patients. All retroglottic devices are primarily a substitute for endotracheal intubation for non–ETT-trained personnel, but are also used by advanced airway managers as a way to oxygenate and ventilate patients during crash and failed airway scenarios. These devices should be considered temporary measures, do not protect against aspiration, and should be exchanged for a definitive airway as soon as possible.

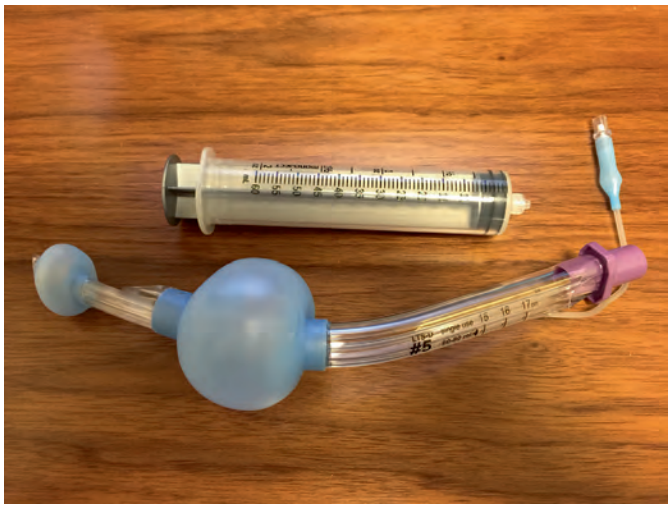

Fig. 1.22. King laryngeal tube incorporates two cuffs but inflates with a single bolus of air. There is a channel in the back for passage of an orogastric tube. It is available in a variety of adult and pediatric sizes.

Fig. 1.23. Melker universal cricothyrotomy kit. (Courtesy Cook Critical Care, Bloomington, IN.)

Surgical Airway Management

Needle Cricothyrotomy With Transtracheal Jet Ventilation

With the advent of newer airway devices, especially videolaryngoscopes, surgical airway management, which always has been distinctly uncommon, is required even less frequently.[3] Needle cricothyrotomy, which involves the insertion of a large needle (ideally, a large catheter designed for this purpose) through the cricothyroid membrane into the airway for transtracheal ventilation, may have a limited role in pediatric airway management (see Chapter 161). However, it is rarely, if ever, the right choice for an adult airway emergency and will not be discussed further here.

Cricothyrotomy

Cricothyrotomy is the creation of an opening in the cricothyroid membrane through which a cannula, usually a cuffed tracheostomy tube, is inserted to permit ventilation. The techniques and variations thereof have been well described elsewhere.[53] When surgical airway management is required, cricothyrotomy is the procedure of choice in the emergency setting, where it is faster, more straightforward, and more likely to be successful than tracheotomy.

Cricothyrotomy is indicated when oral or nasal intubation is impossible or fails and when BMV or EGD cannot maintain adequate oxygen saturation (the can't intubate, can't ventilate situation). Previous large series have established that the incidence of cricothyrotomy is approximately 1% of all ED intubations, with the highest rates seen in trauma patients.[16] More recent ED-based intubation surveillance has suggested that the rate of salvage cricothyrotomy—a surgical airway performed after another technique was attempted first—has dropped and is now approximately 0.3%.[3] Cricothyrotomy is relatively contraindicated by distorted neck anatomy, preexisting infection in the neck, and coagulopathy; these contraindications are relative, however, and establishment of the airway takes precedence over all other considerations. The procedure should be avoided in infants and young children, in whom anatomic limitations make it exceedingly difficult. Studies have suggested that approximately five practice cricothyrotomies on a simulator or animal model are sufficient to achieve at least baseline capability with the procedure, although training intervals for skill maintenance have not been well defined.

A number of commercial kits and devices are used to perform percutaneous cricothyrotomy. Percutaneous cricothyrotomy with the Seldinger technique appears comparable to formal open cricothyrotomy in terms of ease of learning and success rates. Patients with clear landmarks are the best candidates for this procedure because patient obesity or altered anatomy may lead to paratracheal tube placement. In patients with indistinct landmarks or for novice operators, standard open cricothyrotomy may be more successful. Bougie-assisted cricothyrotomy, during which a bougie is placed through the cricoid incision and used as a guidewire for ETT placement, may also improve surgical airway success for inexperienced practitioners. The safety and effectiveness of the many cricothyrotomy kits and devices have not been clearly established. Only two percutaneous cricothyrotomy sets currently on the market have the ability to place a cuffed tracheostomy tube. One is a dedicated Seldinger cricothyrotomy set; the other is a combination set that has all necessary equipment for a Seldinger percutaneous cricothyrotomy or standard surgical cricothyrotomy (Melker universal cricothyrotomy kit; Cook Critical Care, Bloomington, IN; Fig. 1.23).

OUTCOMES

Phase II of the National Emergency Airway Registry study (NEAR II) of almost 9000 ED intubations has reported that most patients were intubated by emergency clinicians using RSI, with overall success rates of 96%.[16] The NEAR classification system characterizes potentially adverse occurrences during intubation as adverse events. In the NEAR study, the overall rate of adverse events was 12%, with recognized esophageal or mainstem intubation and hypotension being the most common.[7] Phase III of the NEAR project has reported on more than 17,500 adult ED intubations over an 11-year period (2002–2012).[3] This latest multicenter report has revealed that first-attempt success (FPS) was 83%. However, over the course of data collection, this significantly increased from 80% in the first 3 years to 86% during the last 3 years. Emergency clinicians managed 95% of all patients, and 99% were successfully intubated within three attempts. Adverse event rates (12%) were identical to those of NEAR II, with recognized esophageal intubation and hypotension requiring IV fluids being the most common. The incidence of cricothyrotomy dropped from 0.9% to 0.5%. No studies have evaluated the long-term outcome of intubated ED patients.

KEY CONCEPTS

- Anticipating the clinical course of the patient's condition and assessing the likelihood of deterioration are crucial to the decision to intubate, especially if the patient is to leave the ED for a period of time (eg, interfacility transfer, diagnostic testing).
- Assessment of the patient for potential difficulty with intubation, bag-mask ventilation (BMV), ventilation using an extraglottic device (EGD), and cricothyrotomy is an essential step before a neuromuscular blockers is administered. The mnemonics *LEMON, MOANS, RODS* and *SMART* can serve as useful aids.
- In the absence of a crash patient (agonal, unresponsive to laryngoscopy) or difficult airway, rapid sequence intubation (RSI) is the airway management method of choice for ED patients.
- Tube placement confirmation using end-tidal CO_2 ($ETCO_2$) is essential after intubation; failure to detect adequate quantities of exhaled CO_2 is evidence of esophageal intubation until proven otherwise.
- Videolaryngoscopy has transformed intubation by eliminating many of the traditional anatomic barriers to direct laryngoscopy. Practitioners responsible for emergency airway management should transition their routine airway management from direct laryngoscopy to videolaryngoscopy.
- Cricothyrotomy is indicated in the can't intubate, can't oxygenate failed airway situation and should be performed without hesitation once this has been identified. Delays may increase the likelihood or severity of hypoxic injury to the patient.
- Emergency airway management is evolving, and modern intubators should be aware of these fundamental changes. Videolaryngoscopy is replacing direct laryngoscopy as the tool of choice for emergency airway management. Etomidate is used in more than 90% of all RSIs, and rocuronium use has been increasing. EGDs, such as laryngeal mask airways, are continually evolving, offering additional options for rescue oxygenation of the failed airway.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 1: QUESTIONS & ANSWERS

1.1. Which of the following is considered unreliable for assessing the need to establish an artificial airway?
- **A.** Absence of a gag reflex
- **B.** Absence of swallowing on command
- **C.** Level of consciousness
- **D.** Patient's ability to phonate
- **E.** Pooling of secretions in the oropharynx

Answer: A. The gag reflex can be absent in up to 25% of normal adults. Moreover, there is no evidence that the presence or absence of a gag reflex corresponds to a patient's ability to protect his or her airway. It should therefore not be used as an indicator of the need for intubation.

1.2. Which of the following is the most reliable overall method for confirmation of correct tube placement after endotracheal intubation?
- **A.** Bulb aspiration
- **B.** Chest and gastric auscultation
- **C.** Chest radiography
- **D.** Detection of colorimetric or quantitative end-tidal carbon dioxide ($ETCO_2$)
- **E.** Measurement of exhaled volume

Answer: D. Detection of $ETCO_2$ after endotracheal intubation is the most reliable of the options listed for the confirmation of tube placement. (A fiberoptic scope passed through the endotracheal tube, with visualization of the tracheal rings, is the gold standard but is not generally required.) Limitations of colorimetric CO_2 detection should be appreciated in cardiac arrest patients. In these situations, a bulb aspiration device may provide helpful information, even though this technique is generally not as reliable as $ETCO_2$ detectors. The other listed options, traditional as they may be, are prone to failure and should not be relied on for confirmation of tube placement.

1.3. During rapid sequence intubation (RSI), what is the optimal time to wait between the administration of a pretreatment drug and administration of the induction agent and neuromuscular blocking agent?
- **A.** 1 minute
- **B.** 2 minutes
- **C.** 3 minutes
- **D.** 4 minutes
- **E.** 5 minutes

Answer: C. Three minutes is considered the optimal time to wait between the administration of a pretreatment drug and administration of the induction agent. If the clinical situation does not allow for this length of time between administrations, there may still be some benefit to administration of the pretreatment agent.

1.4. In which of the following conditions is succinylcholine contraindicated?
- **A.** Acute burn < 5 days
- **B.** Acute head injury secondary to motor vehicle accident
- **C.** Acute spinal cord injury < 5 days
- **D.** Renal failure with a serum potassium level of 4.7 mEq/L
- **E.** Stable multiple sclerosis

Answer: E. Succinylcholine has been associated with severe fatal hyperkalemia when administered in specific clinical circumstances. The risk of succinylcholine-induced hyperkalemia in patients with denervation syndromes begins with the onset of disease and continues indefinitely. With respect to acute burns, trauma, stroke, spinal cord injury, and intraabdominal sepsis, the risk of hyperkalemia with succinylcholine use becomes evident 5 days after the onset of injury or disease process. Succinylcholine is not contraindicated in renal failure; however, known elevations in the potassium level may warrant use of another neuromuscular blocking agent.

1.5. Which of the following conditions prevents reliable use of colorimetric capnometers for the detection of esophageal intubation in 25% to 40% of cases?
- **A.** Acute asthma exacerbation
- **B.** Cardiac arrest
- **C.** Chronic obstructive pulmonary disease exacerbation
- **D.** Head trauma
- **E.** Pneumonia

Answer: B. Colorimetric capnometers detect CO_2 and can be used to confirm tracheal intubation. The absence of CO_2 detection indicates failure to intubate the trachea and necessitates reintubation, except in the low-perfusion state of cardiac arrest, when quantities of CO_2 returned to the lungs may be insufficient to produce a color change in the capnometer. This situation occurs in 25% to 40% of intubated cardiac arrest patients. The placement of the tube needs to be confirmed by clinical means, revisualizing placement, or the tube needs to be removed and the patient reintubated.

1.6. Until how long after an acute burn is succinylcholine considered safe to use for RSI?
- **A.** 30 minutes
- **B.** 12 hours
- **C.** 24 hours
- **D.** 48 hours
- **E.** 5 days

Answer: E. Succinylcholine can produce severe (and fatal) elevations in serum potassium levels after administration in patients with burns. However, this vulnerability to succinylcholine-induced hyperkalemia is not clinically significant until at least 5 days after the acute burn. As a result, succinylcholine remains the paralytic of choice if rapid sequence intubation occurs less than 5 days after the burn.

CHAPTER 2

Mechanical Ventilation and Noninvasive Ventilatory Support

Todd A. Seigel

PERSPECTIVE

Invasive and noninvasive ventilation are essential components in the management of critically ill patients. Some patients require support for respiratory failure or as part of comprehensive management of critical illness, whereas other patients require assistance primarily for airway protection. The reasons for initiating ventilatory support are varied and will influence ventilation strategy, hemodynamics, sedation strategy, and subsequent clinical course.

The decision to intubate is discussed in Chapter 1 and in other chapters throughout this text in the context of individual conditions. This chapter describes the modalities and techniques of noninvasive and invasive mechanical ventilation.

PRINCIPLES OF MECHANICAL VENTILATION

Physiology of Positive-Pressure Breathing

Spontaneous breathing in normal patients is based on the initiation of negative intrathoracic pressure. It is mediated by contraction and relaxation of the diaphragm in concert with the intercostal muscles. Contraction of the diaphragm and intercostal muscles increases the intrathoracic volume, creating negative pressure in the chest cavity and causing inhalation, whereas relaxation of the diaphragm and recoil of the chest wall decreases intrathoracic volume, which increases pressure in the chest cavity and results in passive exhalation. The amount of force required to generate adequate inspiration is influenced by the work of breathing; when the work of breathing increases, patients may be unable to generate enough negative force to sustain successful respiration and will require ventilatory support. Unlike spontaneous breathing, invasive and noninvasive mechanical ventilation are based on the delivery of humidified air with positive pressure. The amount of positive pressure required for adequate ventilation is dependent on the patient's respiratory effort, ranging from mild assistance to full support. Inhalation occurs by driving air into the lungs under positive pressure; air is passively exhaled when the chest wall recoils.

Transition from negative-pressure breathing to positive-pressure breathing affects cardiovascular and pulmonary physiology and can have significant clinical consequences. Pressure changes in the thoracic cavity directly affect pressures in the chambers of the heart. During spontaneous inspiration, decreased intrathoracic pressure augments venous return and preload. Cardiac output is increased, and there is an increased pressure gradient between the left ventricle and aorta. With the initiation of positive-pressure ventilation (PPV), the opposite occurs—venous return is diminished, cardiac output falls, and there is a decreased pressure gradient between the left ventricle and aorta. Relative hypotension can occur after ventilatory support has been initiated, and this may be exaggerated in patients with clinical hypovolemia or vasodilatory states.

Invasive Mechanical Ventilation: Control Variable and Ventilator Mode

The primary considerations regarding initiation of mechanical ventilation relate to how each breath should be delivered. This includes how a breath is defined, the size, duration, and frequency of the breath, and the degree of interaction the patient has with the ventilator.

How the ventilator defines a breath is referred to as the control variable. The ventilator can give breaths based on delivery of a set pressure or a set volume, referred to as pressure-controlled ventilation (PCV) and volume-controlled ventilation (VCV), respectively. The amount of time over which the breath is delivered is defined as the inspiratory time, and the speed at which air travels through the circuit is defined as inspiratory flow rate.

In PCV, a set amount of pressure is applied to the airway to expand the lungs for a specified amount of time. During PCV, the target pressure and inspiratory time are set by the provider, whereas the delivered tidal volume and inspiratory flow rate vary as functions of dynamic lung compliance and airway resistance. Ability to control the pressure delivered to the lungs is particularly useful to prevent barotrauma, which is described in more detail below. In addition, because inspiratory flow is not fixed, PCV may improve ventilator synchrony in intubated patients with a high respiratory drive. A significant disadvantage of PCV is that as tidal volume changes with acute changes in lung compliance, it can neither be guaranteed nor limited. PCV offers advantages over VCV in clinical conditions in which control of airway pressure is strictly mandated. This includes patients with the potential to develop dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEP) such as patients with severe asthma or respiratory failure from chronic obstructive pulmonary disease (COPD).

In VCV, a breath is defined by delivery of a set tidal volume to the lungs. Inspiratory volume and flow rate are set by the provider, and inhalation ends once a preset tidal volume has been delivered. The inspiratory time is a function of the set flow rate. Lung pressure—peak inspiratory pressures (PIPs) and end-inspiratory alveolar pressures—vary based on lung compliance and set tidal volume. The main benefit to the use of VCV is the ability to control tidal volume and minute ventilation, but VCV may cause spikes in peak pressures when compliance of the respiratory system is poor. Clinically, poor respiratory system compliance occurs in conditions that increase lung or chest wall stiffness, including pulmonary edema, acute respiratory distress syndrome (ARDS), pneumothorax, and obesity.

The choice between pressure-cycled ventilation and volume-cycled ventilation is driven by the underlying indication for mechanical ventilation. Volume-cycled ventilation should be used when strict control of tidal volume is mandated. Specifically, this includes patients with known ARDS, in whom low tidal volume strategies have been proven to reduce mortality. In addition,

TABLE 2.1

Features of Pressure Control Versus Volume Control

	SET PARAMETERS	VARIABLE PARAMETERS	CLINICAL IMPLICATIONS	CLINICAL CONDITIONS
Pressure-controlled ventilation (PCV)	Pressure target, inspiratory time, RR, PEEP	Tidal volume, inspiratory flow rate	Controls airway pressure, but tidal volume becomes a function of lung compliance (no guaranteed tidal volume or minute ventilation). Allows estimation of end-inspiratory alveolar pressure based on ventilator settings. Variable inspiratory flow helpful for patients with high respiratory drive	Severe asthma COPD, salicylate toxicity
Volume-controlled ventilation (VCV)	Tidal volume, RR, inspiratory flow pattern, inspiratory time	PIP, end-inspiratory alveolar pressure	Guaranteed delivery of tidal volume, but may result in high or injurious lung pressures. End-inspiratory alveolar pressure cannot be reliably estimated and must be measured (plateau pressure)	ARDS, obesity, severe burns

ARDS, Acute respiratory distress syndrome; *COPD,* chronic obstructive pulmonary disease; *PIP,* peak inspiratory pressure; *PEEP,* positive end-expiratory pressure; *RR,* respiratory rate.

patients with decreased chest wall compliance should be placed on VCV to ensure that adequate tidal volume is delivered. This includes patients with morbid obesity or severe chest wall burns. Conversely, in conditions in which strict control of airway pressure is desired, pressure-cycled ventilation should be used. As detailed earlier, this occurs most often in patients with asthma or COPD. In addition, because inspiratory flow is not limited in pressure-cycled ventilation, this strategy may be preferred to volume-cycled ventilation in patients with a high respiratory drive such as patients with salicylate overdose. For patients who do not require strict control of pressure or volume, similar ventilation mechanics can generally be achieved with pressure-cycled or volume-cycled ventilation (Table 2.1).

Newer ventilators can deliver breaths that combine volume and pressure strategies, referred to as dual-control ventilation. A common dual-control method of ventilation is pressure-regulated volume control (PRVC). A variation of volume control, PRVC is set to deliver a specific tidal volume while simultaneously minimizing airway pressure. Unlike with strict volume control, pressure is measured and modulated by the ventilator with each breath to ensure the delivery of the preset tidal volume. In addition, a pressure limit is set, and the ventilator sounds an alarm when that pressure has been exceeded. Theoretically, this combines the advantages of pressure and volume control to ensure the delivery of a specific tidal volume while the airway pressure is monitored. That said, because the ventilator is set to deliver a specific tidal volume, the disadvantages of volume-cycled ventilation persist. In addition, elevations in airway pressure are still possible and must be addressed if acute changes in respiratory system compliance occur. This mode of ventilation has not been specifically studied but likely does not offer significant advantage over traditional volume- or pressure-cycled ventilation, particularly if strict parameters for airway pressure are desired.

The term *ventilator mode* refers specifically to the amount of respiratory support provided by the ventilator. The most common ventilator modes can be categorized on the basis of how often the ventilator will initiate a breath for the patient and can be divided broadly into continuous mechanical ventilation (CMV), intermittent mechanical ventilation (IMV), and continuous spontaneous ventilation (CSV). CMV and IMV are intended to provide patients with a specific minimum number of preset breaths as defined by the ventilator and can be delivered via pressure or volume control methods. Conversely, in CSV, no mandatory breaths are delivered to a patient; the size and rate of the breaths are determined by the effort of the patient and are augmented with applied pressure to the airway. These methods are compared in Table 2.2. Other, more complex modes of ventilation include proportional assist ventilation (PAV) and airway pressure release ventilation (APRV), although these generally are not used in the emergency department (ED).

CMV is intended to provide full ventilatory support for patients with little or no spontaneous respiratory activity continuous delivery of preset breaths. However, if a patient generates negative pressure, representing respiratory effort, on CMV, that breath will be assisted by the ventilator. For this reason, CMV is also referred to as assist-control (A/C) ventilation. In this mode, patients can trigger a breath at any rate but will always receive at least the preset number of breaths. Notably, when a patient initiates a breath, the assisted breath that he or she receives is the full volume breath as set on the ventilator. For the promotion of ventilator synchrony, a spontaneous patient-initiated breath will take priority over a preset breath, meaning that if the ventilator is set to deliver 12 breaths/min, a breath is provided every 5 seconds in the absence of spontaneous inspiratory effort. When the patient makes a spontaneous effort, the ventilator provides an additional breath and the timer resets for another 5 seconds. A/C ventilation is the most useful initial mode of mechanical ventilation in ED patients, because many patients are initially paralyzed and sedated and do not interact with the ventilator. One of the biggest challenges with A/C ventilation, however, is that patient-initiated breaths are not proportional to patient effort; when inspiratory effort is detected, a full-sized breath is delivered. Clinically, this requires adequate sedation of patients when ventilated in the A/C mode to prevent spontaneous respiratory efforts that will result in hyperventilation, air trapping, hypotension, and poor ventilator synchrony.[1]

Synchronized intermittent mandatory ventilation (SIMV) provides intermittent ventilatory support to patients by delivering mandatory and spontaneous breaths. In SIMV, a mandatory breath is given at a preset rate, but the breath is synchronized as much as possible with spontaneous patient effort. Similar to A/C, the patient will receive at least the minimum number of preset mandatory breaths; if the patient provides no effort, the preset number of breaths will be given. If a patient has a rate of spontaneous respirations lower than the set rate, the ventilator will provide the preset number of full breaths but will deliver as many as possible in synchrony with patient effort. In these scenarios, there is little difference between A/C and SIMV. If a patient has a rate of spontaneous respirations higher than the preset rate, the patient receives all preset full breaths at the set rate, but additional

TABLE 2.2

Selecting Ventilator Strategy: Features of Potential Options

MODE	PARAMETERS SET BY PROVIDER	CLINICAL SCENARIO
CONTINUOUS MECHANICAL VENTILATION (CMV)		
Assist-control (A/C)	Pressure or volume control, RR	Paralyzed or deeply sedated patient, sedated patients with intermittent spontaneous respiratory effort; can lead to hyperventilation
INTERMITTENT MANDATORY VENTILATION (IMV)		
Synchronized intermittent mandatory ventilation (SIMV)	Pressure or volume control, RR (backup rate)	Patients with regular but poor spontaneous respiratory effort; if used in deeply sedated patients, set RR will need to be higher
CONTINUOUS SPONTANEOUS VENTILATION (CSV)		
Pressure-support ventilation (PSV)	Level of pressure support, PEEP	Spontaneously breathing patients with good respiratory effort requiring minimal ventilatory support
Continuous positive airway pressure (CPAP)	Level of CPAP	Alert, spontaneously breathing patients with immediately reversible causes of respiratory distress; COPD and ACPE are classic indications for noninvasive ventilation
Bi-level positive airway pressure (BL-PAP)	IPAP and EPAP	Similar to CPAP

ACPE, acute cardiogenic pulmonary edema; *COPD,* chronic obstructive pulmonary disease; *EPAP,* expiratory positive airway pressure; *IPAP,* inspiratory positive airway pressure; *PEEP,* positive end-expiratory pressure; *RR,* respiratory rate.

breaths generated by the patient will be at a volume determined by his or her respiratory effort. Additional breaths can be given via pressure support (see later). SIMV is useful for patients who are sedated but who have weak respiratory efforts and combats some of the challenges of using A/C in awake patients. The delivery of extra breaths consistent with patient respiratory effort attenuates the effects of air trapping and hyperventilation and may promote patient comfort.

CSV, in contrast to A/C or SIMV, delivers a breath only on a patient-initiated trigger. On a ventilator, the only way to eliminate mandatory delivery of preset breaths is via pressure support ventilation (PSV); therefore, CSV and PSV are essentially the same for patients who remain intubated with no intrinsic spontaneous respiratory effort. PSV is designed to support patients' spontaneous respiratory effort by delivering an applied pressure to the airway on the trigger of a breath. The amount of pressure required to support a full breath is variable and depends on the patient's ability to overcome the work of breathing. When inspiratory flow stops, signaling the end of inhalation, pressure support ceases and exhalation is allowed to proceed spontaneously. The level of pressure support is the only parameter determined by ventilator settings; inspiratory flow, inspiratory time, and tidal volume are determined by patient effort. This mode of ventilation most closely resembles normal spontaneous breathing and, for this reason, promotes patient control and comfort. In the ED, PSV is rarely used for intubated patients because most patients who require intubation are unable to breathe spontaneously and effectively and may have failed noninvasive support before intubation. PSV may prove to be most useful in awake and interactive patients who have been intubated for temporary airway protection rather than for respiratory failure. If PSV is used, careful monitoring and ventilatory alarms are needed to ensure against undetected hypoventilation or apnea.

Positive End-Expiratory Pressure

Regardless of the ventilatory mode chosen, PEEP is often used during invasive mechanical ventilation. PEEP refers to the maintenance of positive airway pressure after the completion of passive exhalation. During acute respiratory failure, lung volumes are typically decreased; the application of PEEP increases functional residual capacity (FRC), improves oxygenation, and decreases intrapulmonary shunting. The use of PEEP also reduces portions of nonaerated lung that may contribute to the development of ventilator-induced lung injury. Notably, PEEP increases intrapulmonary and intrathoracic pressures and may affect pulmonary and cardiovascular physiology. Potential adverse effects of PEEP include decreased cardiac output, lung overdistention, and pneumothorax.

Applied PEEP must be specifically differentiated from intrinsic PEEP (iPEEP, or auto-PEEP), which may result from improper assisted ventilation when adequate time is not allowed between breaths for complete exhalation. This is discussed later.

Noninvasive Techniques

Noninvasive positive-pressure ventilation (NPPV) is the delivery of CSV via sealed mask rather than endotracheal tube. As with PSV, the ventilator is set to provide a defined level of pressure when a patient takes a breath; inspiratory flow and inspiratory time are completely patient-mediated. The most common types of noninvasive ventilation in the ED are continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BL-PAP). BiPAP, a term commonly used for BL-PAP, is the proprietary name of a portable device that uses this method of noninvasive ventilation rather than a term for the ventilation itself (Philips Respironics, Murrysville, PA). CPAP provides constant positive pressure throughout the respiratory cycle, whereas BL-PAP alternates between higher pressure during inspiration (IPAP) and lower pressure during expiration (EPAP). Although, strictly speaking, CPAP applies positive pressure to the airway during inspiration, the amount of inspiratory assistance is minimal. Conversely, just as with invasive mechanical ventilation, IPAP augments patient respiratory effort by decreasing the work of breathing during inspiration, whereas EPAP acts as PEEP to maintain FRC and alveolar recruitment. Notably, although PEEP, CPAP, and EPAP all represent positive airway pressure at the end of expiration, PEEP, by convention, refers to pressure applied during invasive mechanical ventilation, whereas CPAP is the application of positive pressure (invasively or noninvasively) during spontaneous breathing. The terms are occasionally used interchangeably.

MANAGEMENT

Decision Making: Noninvasive Versus Invasive Ventilation

The decision to intubate carries significant implications for patients, including potentially life-threatening complications related to airway management and subsequent complications related to intensive care unit (ICU) care. NPPV is an appealing option for patients requiring ventilatory assistance with potentially reversible conditions when tracheal intubation is not immediately necessary or as a therapeutic adjunct for patients with "do-not-intubate" directives.[2] In appropriately selected patients, NPPV obviates intubation in more than 50% of cases and improves survival. Relative contraindications include decreased level of consciousness, lack of respiratory drive, increased secretions, hemodynamic instability, and conditions such as facial trauma that would prevent an adequate mask seal. Although the need for emergent intubation is generally a contraindication to treatment with noninvasive ventilation, noninvasive ventilation has been shown to improve preoxygenation prior to intubation when compared to standard methods of oxygen delivery.[3,4] If NPPV is initiated, patients should be reassessed frequently for progress of therapy, tolerance of the mode of support, and any signs of clinical deterioration that would indicate a need for intubation.

Patients most likely to respond to NPPV in the ED are those with more readily reversible causes of respiratory distress such as COPD exacerbation or cardiogenic pulmonary edema in which fatigue is a significant factor. Robust evidence has supported the use of NPPV for both conditions. In patients with acute COPD exacerbations, NPPV decreases the need for subsequent intubation with a number needed to treat (NNT) of 4, decreases hospital length of stay, and improves mortality (NNT = 10) when compared with standard therapy.[5] Treatment failure, defined as a subsequent need for intubation, is predicted by a Glasgow Coma Scale score of less than 11, sustained arterial pH less than 7.25, and tachypnea greater than 35 breaths/min.[3] A recent large study has confirmed prior findings regarding the benefit of NPPV over invasive ventilation, but highlighted the need for appropriate patient selection in that a failed trial of NPPV was associated with higher mortality when compared to patients who received immediate intubation.[6]

In patients with acute cardiogenic pulmonary edema (ACPE), NPPV reduces the work of breathing while simultaneously improving cardiac output. The application of NPPV causes elevations in intrathoracic pressure that decrease left ventricular (LV) ejection pressure and LV transmural pressure, which results in afterload reduction. In addition, decreases in RV preload may improve LV compliance via ventricular interdependence. Compared with standard therapy, multiple studies and several meta-analyses have confirmed a decreased need for intubation, as well as decreased mortality for patients with ACPE treated with NPPV. Benefits were found to be independent of whether patients received CPAP or BL-PAP and, despite suggestions from early clinical data, no increased rate of acute myocardial infarction occurred in patients receiving any form of NPPV.[7-9] Although either modality can be used, a recent ED-based study has suggested faster clinical improvement with BL-PAP.[10] Specific predictors of failure of NPPV in those with congestive heart failure (CHF) have not been systematically examined.

Evidence regarding the use of NPPV in other patients with respiratory compromise, including asthma and pneumonia, is limited. Several small studies have suggested that NPPV may be beneficial for patients with acute asthma exacerbations by improving lung function, decreasing bronchodilator requirements, and shortening overall hospital length of stay, suggesting a potential role for NPPV in these patients.[11,12] Studies have failed to establish a definitive role for NPPV in pneumonia, and the presence of pneumonia has been shown to be an independent risk factor for failure of noninvasive ventilation.[13] In a recent trial of NPPV for pneumonia, increased heart rate and decreased $Pao_2/Fio2$ ratio after 1 hour of therapy predicted failure of NPPV. In addition, the duration of NPPV prior to intubation was associated with in-hospital mortality, suggesting that early intubation is preferable for patients who do not rapidly improve on noninvasive therapy.[14]

Approach to Initial Ventilator Settings

Noninvasive Ventilation

Initial settings for noninvasive ventilation should be determined by the amount of ventilatory assistance required by the patient, as well as patient comfort and cooperation with therapy. The first consideration in the use of NPPV is whether to provide support in the form of CPAP or BL-PAP. As described earlier, there is no clear benefit of one over the other. Support may be provided by a full-face (oronasal) mask or nasal mask; this choice is determined by patient comfort, ability of the patient to cooperate, and the need for the patient to cough effectively or speak. Notably, nasal masks have been associated with higher leak rate and decreased patient comfort[3]; therefore, I recommend a full-face mask as the first method for novice patients. Inspiratory support (IPAP) is initiated at 10 cm H_2O and expiratory support (EPAP) at 5 cm H_2O. Subsequent titration of these parameters is based on the patient's clinical response, particularly pressure tolerance, respiratory rate, and oxyhemoglobin saturation. Although blood gas analysis is confirmatory, improvements in the patient's clinical condition can be observed by decrease in work of breathing, good patient-ventilator synchrony, and patient report. If required, EPAP and IPAP can be adjusted by 1 to 2 cm H_2O at a time based on the clinical response. If the work of breathing is unchanged, increases in IPAP can reduce hypercarbia by increasing tidal volume and minute ventilation, and increases in EPAP can improve oxygenation by combating atelectasis and promoting alveolar recruitment. IPAP greater than 20 cm H_2O should be avoided, because it can be uncomfortable and can cause gastric insufflation.

Mechanical Ventilation of the Intubated Patient

For the intubated patient, initial ventilator settings should facilitate ventilation that improves gas exchange, promotes ventilator synchrony, and minimizes the potential for complications. For an apneic or paralyzed patient, full ventilatory support is required; therefore, A/C is the recommended mode of initial ventilation for emergent patients. Specific required settings depend on whether the patient is receiving PCV or VCV, but the principles underlying the selection of settings are similar. Reasonable initial ventilator settings should deliver a tidal volume of 6 to 8 mL/kg of estimated ideal body weight (IBW) at rate of 12 to 14 breaths/min. If VCV is used, tidal volume can be set directly and, if PCV is used, tidal volume is determined by adjusting the targeted pressure to be delivered. Regardless of VCV or PCV, initial pressure targets should not exceed 30 cm H_2O. The initial Fio_2 should be set at 1.0 but generally can be adjusted down quickly to maintain an oxygen saturation of 90% or greater. PEEP is routinely given and is set initially at 5 cm H_2O.[1] Settings for specific clinical conditions such as status asthmaticus are discussed later.

Ongoing Management

Mechanical ventilation requires monitoring and regular adjustment to ensure appropriate gas exchange, safe delivery of desired tidal volume, and prevention of barotrauma and acid-base

derangement. Changes to ventilator settings are guided dynamically by multiple factors, including pulse oximetry, end-tidal carbon dioxide ($ETCO_2$) measurement, ventilation pressures, and blood gas levels. For the adequacy of ventilation to be monitored, capnography must be used, and arterial blood gases should be measured 15 to 20 minutes after the initiation of ventilatory support to correlate $ETCO_2$ with PCO_2. Notably, venous blood gas levels generally correlate well with the pH of arterial samples, although this correlation may be unreliable in critically ill patients.[15]

The correlation of PCO_2 between venous and arterial samples is less reliable.[16,17] Although there is variation in agreement between capnography and blood gas values, capnography generally correlates well with the PCO_2 of arterial samples and should be used for ventilator adjustment after initial correlation has been established. Recent data have confirmed the importance of continuous capnography, demonstrating a decrease in the use of blood gases and resultant, significant cost savings.[18] If capnography is difficulty to perform or otherwise noncorrelative, arterial blood gas determination remains the definitive test for evaluating PaO_2 and PCO_2. Minute ventilation can subsequently be altered by adjusting the tidal volume or respiratory rate. To avoid oxygen toxicity, FIO_2 should be reduced at the earliest opportunity to the lowest level that provides acceptable oxygen saturation (>90%). In many cases, increases in PEEP will allow better oxygenation for a given FIO_2 but may worsen hypotension or increase intrathoracic pressure.

In addition to maintaining adequate gas exchange, care should be taken to ensure that that pressure in the ventilator circuit (including the lungs) is appropriate. The two main measurements of pressure during mechanical ventilation are the PIP and plateau pressure (Pplat). The PIP measures the maximum amount of pressure in the ventilator circuit during a breath cycle. It reflects lung compliance and airway resistance, including resistance in the circuit itself. In PCV, because pressure limits are preset, the PIP is the sum of the set pressure target and PEEP. In this case, PIP also reflects the maximum amount of pressure in the alveoli, an important determinant in the development of ventilator-induced lung injury (VILI). In VCV, PIP can be influenced greatly by airway resistance and therefore is not reflective of the maximal alveolar pressure. Rather, maximal alveolar pressure is determined on the ventilator at the end of inspiration by means of an inspiratory hold. At the end of inspiration, flow in the circuit stops; therefore, there is no pressure from resistance in the circuit. Pplat is measured at that time, so it represents maximal end-inspiratory alveolar pressure in VCV.

Acute increases in measured pressure indicate increased airway resistance or changes in compliance of the respiratory system (eg, those associated with pneumothorax) and can indicate potentially dangerous clinical deterioration. Notably, acute changes in resistance or compliance that are seen directly in VCV as increased pressure would manifest as an acute decreases in tidal volume if the patient were on PCV (where pressure has been previously set). Decreases in lung pressure, conversely, indicate decreased resistance or decreased airflow in the ventilatory circuit and should prompt investigation of the ventilator circuit for leaks. Large or sudden decreases in pressure suggest disconnection of the ventilator circuit or unintended extubation. For patients with underlying respiratory failure secondary to increased airway resistance such as in asthma or COPD, more gradual decreases in PIP are associated with clinical improvement.

Sedation and Analgesia of the Ventilated Patient

Aside from specific ventilator management, considerations in the care of the intubated patient include analgesia and sedation, potential neuromuscular paralysis, and secretion management. After intubation, the primary goals of care in the ED are sustained, effective ventilation and patient comfort. Intubation, mechanical ventilation, and paralysis are a significant cause of pain and anxiety for patients, and analgesia and sedation are required to promote patient comfort and patient-ventilator synchrony. In initiating sedation (see later), sedation should be titrated to comfort and therapeutic goals, avoiding oversedation and undersedation. The desired level of sedation will differ based on patient tolerance and the clinical scenario; assuming that comfort is maintained, lighter sedation may be useful in patients requiring serial neurologic examinations, whereas deep sedation is required for any patient who is paralyzed. Several clinical scales, including the Richmond Agitation-Sedation Scale (RASS), have been established and validated for this purpose. Sedation should be maintained at the highest RASS score at which the patient is comfortable (between 0 and −5) and should be serially readdressed. Any paralyzed patient should remain deeply sedated (Table 2.3). Recent ED-based data have demonstrated that the use of rocuronium during rapid sequence intubation (RSI) is associated with increased time to adequate sedation, as well as decreased overall dose of sedation, when compared to patients intubated with succinylcholine.[19,20] This is likely because emergency clinicians wrongly ascribe the patient's inability to move or respond to adequate sedation, rather than to the paralysis. When rocuronium is used for RSI, additional sedation should be immediately administered after intubation confirmation.

After RSI, additional neuromuscular blocking agents (NBMAs) should generally be used only when poor ventilator synchrony interferes with ventilation sedation and analgesia. This may be particularly true in patients with ARDS, in whom the use of NMBAs has been associated with shorter duration of ventilation and improved mortality.[21] With proper sedation and analgesia, however, neuromuscular blockade usually is not required. If

TABLE 2.3

Richmond Agitation-Sedation Scale (RASS)

SCORE	TERM	DESCRIPTION
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, but movements not aggressive or vigorous
0	Calm	Alert and calm
−1	Drowsy	Not fully alert, but has sustained awakening (>10 sec)
−2	Light sedation	Briefly awakens with eye contact to voice (<10 sec)
−3	Moderate sedation	Movement or eye opening to voice but no eye contact
−4	Deep sedation	No response to voice but movement or eye opening with physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Adapted from Ely EW, et al: Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; 289:2983-2991.

needed, single doses of longer acting agents such as rocuronium and vecuronium should be used; note that impaired hepatic or renal function may increase duration of paralysis.

Analgesia is achieved by generous doses of opioid medications; fentanyl and morphine remain the most commonly used agents for analgesia in critically ill patients.[22] Opioids are associated with dose-dependent respiratory depression, a side effect that may be particularly beneficial for patients experiencing ventilator dyssynchrony. Morphine and fentanyl can be used for analgesia, although dosage requirements will vary based on tolerance and drug metabolism. Sedation and analgesia should therefore be titrated with a standard sedation scale, as discussed earlier. Notably, the active metabolite of morphine (morphine-6-glucuronide) is cleared renally and has potent sedative effects. For this reason, fentanyl may be preferred in patients with renal insufficiency. Remifentanil is an ultra–short-acting opiate that is metabolized by nonspecific plasma esterases. The predictable metabolism and short half-life of remifentanil have made it a choice for analgesia, and studies have demonstrated decreased duration of ventilation with remifentanil compared with longer acting opiates when used for analgesia in the ICU.[23]

Sedation after intubation can be accomplished via multiple pharmacologic modalities. In the ICU, benzodiazepines remain a common choice for sedation, with lorazepam and midazolam being the most commonly used agents.[24] Although data regarding postintubation sedation in the ED are limited, a large retrospective study has found that fewer than 50% of all ED patients received any sedation following RSI in the ED. When sedation was administered, benzodiazepines were the most common agents used.[25]

Benzodiazepines exert dose-dependent clinical effects by binding γ-aminobutyric acid (GABA) receptors, first producing anxiolysis and then sedation and hypnosis.[26] Benzodiazepines also cause respiratory depression, which is potentiated by concomitant opioid administration. Therefore, a sedation regimen of opioids and benzodiazepines may improve ventilator dyssynchrony while providing anxiolytic and amnestic effects. Benzodiazepines can be administered as repeated boluses or by continuous infusion although, in critically ill patients, benzodiazepines have altered pharmacokinetics that result in tissue accumulation and prolonged sedation. This is particularly true in obese patients and patients with renal or hepatic insufficiency. For this reason, sedation with benzodiazepines should be attempted with intermittent bolus administration before a continuous infusion is used.

Propofol is lipophilic, and the ability of the drug to penetrate the blood-brain barrier rapidly and distribute into peripheral tissues is responsible for the rapidity and short duration of its clinical effect.[24] Similar to benzodiazepines, propofol binds to the GABA receptor to induce sedation. Unlike benzodiazepines, the clearance of propofol is minimally affected in critically ill patients. In addition, propofol can precipitate hypotension by increasing venous capacitance, a side effect that is exaggerated in hypovolemic patients. Thus, propofol should be given as an infusion rather than as a bolus, initiated at low doses (0.1 mg/kg/min) and titrated to the desired level of sedation. In comparison to benzodiazepines, continuous infusions of propofol have been demonstrated to decrease the duration of mechanical ventilation, suggesting that propofol may confer benefit when compared with benzodiazepines in the sedation regimen for mechanically ventilated patients.

Other medications for the sedation of ventilated patients in the ED include dexmedetomidine and haloperidol. Dexmedetomidine is a centrally acting α_2-agonist with sedative and analgesic properties, largely distinguished from other sedative agents by a negligible impact on respiratory drive, even with simultaneous opioid administration. It is administered as a loading dose, followed by a continuous infusion, and can precipitate bradycardia and relative hypertension. Studies have demonstrated dexmedetomidine to be beneficial in facilitating the use of noninvasive ventilation, as well as awake fiberoptic intubations.[27,28] When dexmedetomidine was compared with a continuous infusion of midazolam, several large, multicenter evaluations demonstrated that dexmedetomidine was associated with a shorter duration of mechanical ventilation, as well as decreased sedation-associated delirium.[29] Although not systematically studied in ventilated ED patients, dexmedetomidine has emerged as an alternative sedation strategy for critically ill patients and may be considered as an alternative to traditional modalities in clinical settings in which agitation or anxiety limit therapeutic goals.

Haloperidol, commonly used as a sedative for agitated patients, can also be used as an adjunct to traditional sedation regimens in mechanically ventilated patients. Haloperidol may be particularly useful for patients who remain acutely agitated after receiving large doses of other sedative medications, especially because it does not affect hemodynamics. Notably, however, haloperidol does not have any analgesic or amnestic properties and cannot be used as a single therapeutic modality for sedation in critically ill patients.

Other ED considerations in the care of the ventilated patient include secretion management and steps to reduce the development of ventilator-associated pneumonia (VAP). Management of secretions is achieved via regular endotracheal suctioning, recognizing a balance between secretion clearance and the disruption of ventilation. In addition, a nasogastric or orogastric tube should be placed for gastrointestinal decompression. Finally, evidence has demonstrated benefit in the prevention of VAP from placing the patient in the semirecumbent position by elevating the head of the bed. Limited data have suggested that the use of so-called VAP care bundles, including elevation of the head of the bed, have decreased the incidence of VAP in the ICU; this may warrant further study to determine benefit in the ED.[30] A meta-analysis has also demonstrated a decrease in the incidence of VAP with continuous aspiration of subglottic secretions. This is done via a specialized endotracheal tube used for this purpose and, although not routinely used in the ED, this technique may be a direction for future investigation.[31]

Complications

Although initiated as a lifesaving intervention, PPV carries the risk of significant complications. As highlighted earlier, the initiation of PPV and elevated intrathoracic pressure can be associated with relative hypotension, and any subsequent changes in end-inspiratory alveolar pressures or PEEP during the management of ventilation may have hemodynamic consequences.

PPV also has a direct impact on the lungs. Whether delivered as a set volume or set pressure, invasive PPV forcibly distends the lung and can be injurious. Injuries from elevated lung volume or lung pressure are known as volutrauma and barotrauma, respectively, and contribute to the development of VILI. VILI is mitigated by limiting pathologic stretch on the alveoli; studies have supported that maximum safe end-inspiratory alveolar pressures are 30 to 32 cm H_2O, although this continues to be actively researched. Barotrauma can also manifest overtly with pneumothorax or pneumomediastinum, but this is relatively uncommon.

Another potential complication of PPV is the development of iPEEP (auto-PEEP). Particularly problematic in patients with obstructive lung disease, iPEEP is the accumulation of end-expiratory volume and end-expiratory pressure that occurs when exhalation cannot be fully completed. In patients with obstructive lung disease, expiratory flow is limited secondary to small airway obstruction and diminished elastic recoil. The time required for full exhalation may be significantly longer than norma, and, in patients receiving mechanical ventilation, exhalation may not be complete before the next delivered breath. This phenomenon,

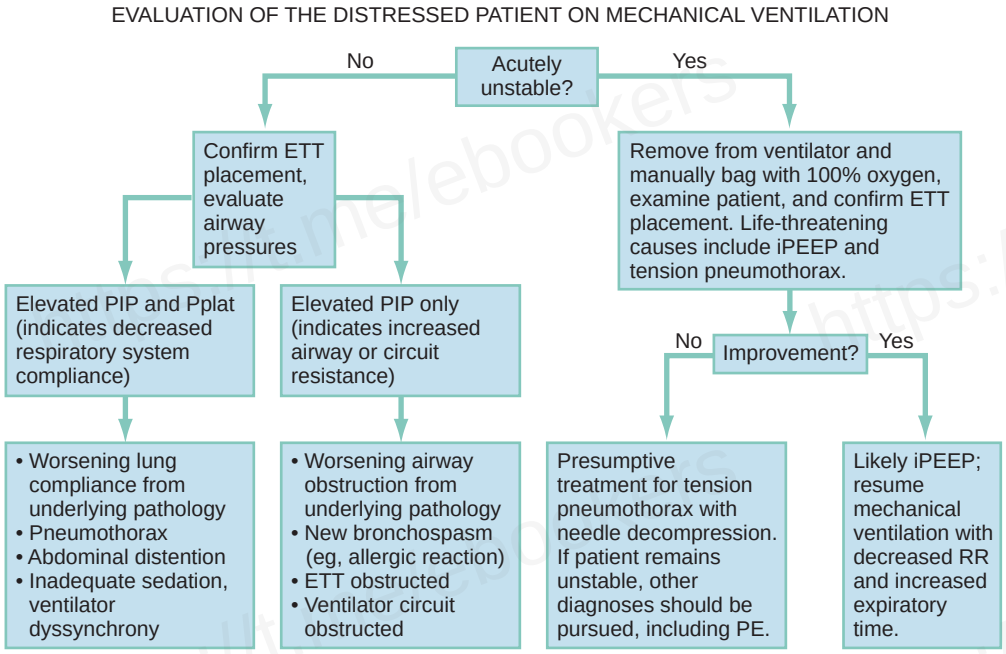

Fig. 2.1. Algorithm for evaluation of the distressed patient on mechanical ventilation.

termed *breath stacking*, results in dynamic hyperinflation. iPEEP results in unexpectedly high PIPs, difficulty in ventilation, hypotension, and potential circulatory collapse. Ventilation difficulty caused by iPEEP can be improved by decreasing the respiratory rate or inspiratory time, both of which facilitate increased time for exhalation.

Troubleshooting the Ventilator

When a patient's condition suddenly deteriorates during mechanical ventilation, a systematic approach should be applied to assess for life-threatening conditions (Fig. 2.1). The first step in evaluating the ventilated patient who has a change in clinical status is to assess vital signs. Patients with acute hemodynamic compromise or acute hypoxia should be removed from the ventilator and bagged manually on 100% oxygen. Tension pneumothorax, increased iPEEP, and accidental extubation are the most life-threatening concerns in this situation and must be expeditiously addressed. While the patient is bagged, the chest should be examined to ensure bilateral breath sounds. Changes in breath sounds may indicate a pneumothorax or migration of the endotracheal tube. Clinical examination, oxygen saturation, and $ETCO_2$ monitoring can be used as surrogates for tube placement, but suspicion of inadvertent extubation should prompt direct visualization. Acute hypotension can be precipitated by extreme elevations in intrathoracic pressure; compromise from iPEEP will improve once the patient has been disconnected from the ventilator, whereas hypotension from a tension pneumothorax will not be relieved. If the patient's condition remains unstable after she or he has been disconnected from the ventilator circuit, a tension pneumothorax should be treated presumptively with needle decompression and eventual chest tube placement. Although unlikely, it is possible that a patient could sustain bilateral pneumothoraces, and this should be considered. If the patient remains unstable after chest decompression, sources for decompensation unrelated to the ventilator are pursued.

Acute distress without hemodynamic changes can be precipitated by multiple factors, mechanical and physiologic (Table 2.4). The initial evaluation should begin by confirming the position and patency of the endotracheal tube before other diagnoses are investigated, including evaluation of the tracheal balloon. Once tube placement has been confirmed, the next step in the evaluation of ventilator-related causes of distress should focus on airway pressures. Acute decreases in PIP indicate discontinuity in the ventilator circuit, which could include inadvertent extubation. Patients with increased PIP can be considered in two categories—those with concomitant increases in Pplat and those with unchanged Pplat. If both PIP and Pplat acutely increase, this suggests decreased compliance of the respiratory system. Elevated PIP with unchanged Pplat indicates problems with increased airway resistance in the lungs or ventilator circuit. Specific conditions that cause decreased respiratory system compliance or increased airway resistance are detailed in Fig. 2.1.

TABLE 2.4

Troubleshooting the Ventilator: Potential Causes of Acute Respiratory Distress

WITH HEMODYNAMIC COMPROMISE: IMMEDIATELY DISCONTINUE MECHANICAL VENTILATION	
Increased intrinsic positive end-expiratory pressure (iPEEP)	
Tension pneumothorax	
Massive pulmonary embolus	
WITHOUT HEMODYNAMIC COMPROMISE: SEARCH FOR UNDERLYING CAUSE	
MECHANICAL	**PHYSIOLOGIC**
Endotracheal tube migration into bronchus	Worsening lung compliance
Endotracheal tube obstruction	Worsening airway obstruction
Endotracheal tube cuff leak	Abdominal distention
Inadvertent extubation	Pulmonary embolus
Discontinuity in ventilator circuit	Pain or inadequate sedation

Special Clinical Circumstances

Although generalizations can be made regarding ventilatory management in the ED, certain clinical circumstances merit specific discussion.

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Strategies for managing intubated patients with COPD focus on improving gas exchange while minimizing iPEEP. Reduction of iPEEP is achieved by decreasing airway resistance with bronchodilators and corticosteroids, as well as ensuring adequate expiratory time during mechanical ventilation. Adequate expiratory time is achieved by decreasing respiratory rate, tidal volume, and inspiratory time. Adequate oxygenation (saturation of 90%) is achieved while minimizing barotrauma by deliberately reducing minute ventilation, so-called permissive hypercapnia. No data have suggested the advantage of PCV over VCV, and either method can be used. The ideal ratio of inspiratory-to-expiratory time (I/E ratio) is variable, but should initially be set at 1:4. Studies in asthmatics have suggested that expiratory times longer than 4 seconds have minimal impact on airflow. iPEEP can also result in poor patient-ventilator synchrony, causing inadequate gas exchange. Unlike in patients with acute asthma (see below), applied PEEP should be used in patients with COPD; it can be set initially at 5 cm H_20.[32] Initially, deep sedation and analgesia (or sometimes paralysis) are required to prevent ventilator asynchrony and permit effective ventilation. Corticosteroids often are indicated (see Chapter 64). NBMAs are avoided, if possible, because patients receiving both NMBAs and corticosteroids are at higher risk for polymyopathy of critical illness and subsequent increased mortality.

Status Asthmaticus

Concerns in ventilating the acute asthmatic generally parallel those for patients with COPD, with small notable differences. In acute asthma, respiratory failure is a result of airway obstruction and airway inflammation. Furthermore, unlike COPD, airway obstruction is much less dynamic and occurs predominantly in the large airways. In addition, acute inflammatory changes throughout the lung contribute to decreased lung compliance, which has a direct impact on lung pressures during ventilation. Strategies should focus on low respiratory rates, with emphasis on maximizing expiratory time. The use of PEEP has been debated and is largely thought to contribute to increased lung pressure. Although no studies have definitively supported VCV over PCV, decreased lung compliance and potential iPEEP may make the delivery of adequate tidal volumes with PCV difficult. This is especially problematic for patients with severe, acute respiratory acidosis, for whom adequate ventilation is essential. Recommendations for ventilator settings include VCV with tidal volumes of 6 to 8 mL/kg IBW, respiratory rate of 10 to 15 breaths/min, and little (5 cm H_2O) or no PEEP. Decreased inspiratory time allows greater expiratory time and, in VCV, is achieved by increasing the inspiratory flow rate. Increases in inspiratory flow rate, however, will increase airway pressures, emphasizing the interplay of inspiratory time, tidal volume, and airway pressure.

Acute Respiratory Distress Syndrome

ARDS represents a spectrum of inflammatory lung disease characterized by heterogeneous noncardiogenic pulmonary edema, hypoxia, and diffuse lung consolidation. The severity of ARDS is classified as mild, moderate, or severe and is defined by the ratio of arterial oxygen concentration to the fraction of inspired oxygen (Pao_2/Fio_2). Notably, this definition was refined in 2012, and the term *acute lung injury* was eliminated.[33] ARDS can be caused by pulmonary or extrapulmonary insult, including VILI. Recent epidemiologic data from cohorts of ED patients with sepsis have suggested that although ARDS is uncommon on initial presentation to the ED, the development of ARDS after ED admission is not.[34-36] The impact of ventilation in the ED on the development of lung injury or ARDS is unclear.[37] Nonetheless, the development of VILI has been associated with lung overdistention and alveolar injury, and attention to ventilation strategy in the ED is warranted. Studies have confirmed that decreased tidal volumes are of clear benefit in the management of patients with ARDS. Most studies examining low tidal volume ventilation strategies, including the landmark ARDSnet trial in 2000, used 6- to 7-mL/kg tidal volumes based on IBW, although studies with 7 mL/kg did not demonstrate a difference in mortality. A meta-analysis of these data has concluded that tidal volumes below 7 mL/kg and Pplat less than 31 cm H_2O confer mortality benefit in patients with ARDS, although more recent work has suggested that low tidal volume ventilation may improve outcome for patients without lung injury as well, including halting progression to ARDS.[37-40] The level of PEEP in patients with ARDS continues to be actively researched and, although higher levels of PEEP have been demonstrated to improve oxygenation, they have not reduced mortality.[41] Therefore, in patients with ARDS ($Pao_2/Fio_2 < 300$), a low tidal ventilation strategy should be used. Initial ventilator settings should be volume-cycled, with tidal volumes based on 6 mL/kg of IBW. Although there have been no specific studies examining ventilation strategies for ED patients without evidence of ARDS, studies from other populations have suggested a benefit of lung protective ventilation for all patients; I recommend this strategy for all patients receiving mechanical ventilation in the ED. That said, despite the potential benefit, recent observational data have suggested that adherence to lung-protective ventilation strategies in the ED is just over 50%.[36]

OUTCOMES

Because of the heterogeneity of ventilation strategies and clinical reasons for respiratory failure, no studies have shown the superiority of one ventilation method over another; considerations in initiating mechanical ventilation are individualized and serially reevaluated. Nonetheless, certain conclusions regarding outcomes can be made. Data have clearly indicated the effectiveness of NPPV in preventing intubation for patients with COPD and ACPE, and these benefits have resulted in decreased admission to the ICU and decreased mortality. In addition, increased alveolar volumes and pressures have been shown to contribute to VILI and increase mortality in patients with ARDS. Although the benefit of decreased tidal volume ventilation on the prevention of lung injury in patients with normal lungs has not been proven, emerging data have suggested that strategies of mechanical ventilation in the ED can improve the subsequent clinical course of critically ill patients.

Finally, although the treatment of mechanically ventilated patients usually extends beyond the ED, delays in ICU admission can have significant implications on ED management of the critically ill ventilated patient because the role of emergency clinicians extends beyond acute stabilization toward ongoing clinical management.[42] In addition, when boarding times are long, patients intubated solely for airway protection may be candidates for extubation in the ED if the initial insult has been reversed.

KEY CONCEPTS

- There have been no demonstrated outcomes differences between BiPAP and CPAP. After appropriate patient selections, begin NIPPV with an inspiratory pressure setting of 10 cm of water and expiratory pressure of 5 cm of water and evaluate frequently for tolerance and need to titrate up or down.
- Pressure controlled (PC) ventilation delivers breaths at a predetermined pressure, which might result in low volume delivery, while volume controlled (VC) delivers a predetermined inspiratory volume, which might lead to excessive pressures. Continuous mandatory ventilation (CMV) delivers a required number and volume of breaths per minute while synchronized intermittent-mandatory ventilation (SIMV) synchronizes mandatory breaths with spontaneous breaths.
- Noninvasive ventilatory support is often adequate for reversal of impending respiratory failure and should considered as the first-line therapy for patients with exacerbations of chronic obstructive pulmonary disease and acute cardiogenic pulmonary edema in whom immediate intubation is not required. When non-invasive ventilation is attempted for patients with pneumonia, it should be abandoned in favor of intubation with mechanical positive-pressure ventilation unless the patient is clearly improving. Prolonged use of non-invasive ventilation that ultimately fails is associated with worse outcomes for patients than when intubation is undertaken earlier.
- Invasive mechanical ventilation is not without consequence and requires dynamic, ongoing management. After intubation, blood gas analysis should be performed to confirm appropriate ventilation and provide correlation with noninvasive monitoring of oxyhemoglobin saturation and end-tidal CO2. In addition, positive pressure can have adverse hemodynamic consequences. Elevated lung pressures can be deleterious and plateau pressure should be maintained below 30 cm H2O whenever possible, by adjusting ventilator settings. Progressive elevation in ventilation pressures prompts consideration of ventilator circuit obstruction, obstruction at any point of the airway, increased bronchospasm, mainstem intubation, tension pneumothorax or hemothorax, increased chest wall resistance (from a constricting device or intrinsic chest wall), or rigidity (as from high doses of fentanyl). Suddenly reduced ventilation pressures are often accompanied by increasing hypoxemia and indicate ventilator circuit leak or faulty connection, endotracheal tube cuff leak, accidental extubation, or esophageal intubation.
- The Richmond Agitation Sedation Score (RASS) or a similar scoring system should be used to manage sedation and analgesia of the mechanically ventilated patient to avoid unnecessary use of prolonged neuromuscular blockade. When RASS is used, a target score of -2 to 0 avoids both over and under sedation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

https://t.me/ebookers

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CHAPTER 2: QUESTIONS & ANSWERS

2.1. Which of the following is the most important consideration in the decision to initiate noninvasive positive-pressure ventilation (NPPV)?

A. Degree of acidosis
B. Degree of respiratory distress
C. Hemodynamic profile
D. Level of consciousness
E. Underlying etiology of respiratory failure

Answer: B. Although NPPV will be helpful for many patients in distress, the need for emergent intubation is an absolute contraindication to NPPV. Both hemodynamic profile and level of consciousness are important determinants in the decision to implement NPPV, but both are relative (rather than absolute) contraindications to its use. Patients with chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema (ACPE), and asthma are more likely to show benefit with NPPV than patients with pneumonia, but NPPV can be initiated for any patient with respiratory distress. Patients with hypoxia or hypercarbia may be acidemic, but the decision to initiate NPPV will be predicated on mental status and work of breathing rather than on degree of acidosis alone.

2.2. Which of the following is a potential adverse effect of positive-pressure ventilation?

A. Decreased mean intrathoracic pressure
B. Decreased ventilation/perfusion ratio
C. Increased cardiac output
D. Increased glomerular filtration rate
E. Increased work of breathing

Answer: E. Positive-pressure ventilation (PPV) is associated with several complications. Some of these can quickly become life-threatening. This reality underscores the importance of familiarization with the common problems that arise as a result of PPV. Most complications result from changes in thoracic physiology

when positive pressure is present for part or all of the respiratory cycle. Potential adverse effects of PPV include an increased work of breathing because of asynchrony or improperly set triggers, an increase in intrathoracic pressure, decreased venous return to the heart and decreased cardiac output, an increased ventilation/perfusion ratio, air trapping and intrinsic positive end-expiratory pressure, barotrauma, decreased renal blood flow and glomerular filtration rate with fluid retention, nosocomial infections of the lungs and sinuses, respiratory alkalosis, and agitation and increased respiratory distress.

2.3. What is the primary physiologic effect of applying positive end-expiratory pressure (PEEP) during mechanical ventilation?
- **A.** Decrease cardiac output
- **B.** Decrease intrapulmonary shunting
- **C.** Decrease ventilation/perfusion mismatch
- **D.** Increase functional residual capacity
- **E.** Increase partial pressure of oxygen (Pao_2)

Answer: D. Although all of these effects can be attributed to the application of PEEP, its primary physiologic effect is to increase functional residual capacity (FRC) by maintaining patency of injured or flooded alveoli that would otherwise collapse at the end of exhalation. Increasing the FRC may improve both oxygenation and lung compliance. PEEP increases Pao_2 at a constant fraction of inspired oxygen (Fio_2) by decreasing intrapulmonary shunting and ventilation/perfusion mismatch. One of the potential adverse effects to PEEP is decreased cardiac output.

2.4. Regarding a patient who develops acute distress on mechanical ventilation, which of the following is the most accurate?
- **A.** Accidental extubation is a common cause of increased airway pressure.
- **B.** Anaphylaxis would cause immediate increases in both peak inspiratory pressure (PIP) and plateau pressure (Pplat).
- **C.** All patients in distress should be immediately removed from the ventilator and bagged.
- **D.** Compared to patients with restrictive lung disease, patients with obstructive lung disease are more likely to decompensate because of inappropriately set respiratory rate.
- **E.** Presumptive needle thoracostomy is indicated for all hemodynamically unstable patients.

Answer: D. One of the most life-threatening complications of mechanical ventilation is loss of adequate cardiac output because of elevated intrathoracic pressure from intrinsic PEEP (iPEEP). Intrinsic PEEP can be precipitated by a respiratory rate that is too high, which does not allow patients to fully exhale before the delivery of another breath. Patients with obstructive lung disease such as COPD or acute asthma are particularly sensitive to this phenomenon, also known as "breath stacking." Although patients with restrictive lung disease may develop iPEEP with an inappropriate respiratory rate, this is much more likely to occur in patients with obstructive conditions. If patients are not hemodynamically unstable, they do not need to be removed from the ventilator, and in hemodynamically unstable patients, pneumothorax should only be presumptively treated if removing the patient from the ventilator does not improve the situation. Accidental extubation is a common cause of decreased airway pressures, and although anaphylaxis would cause increases in PIP, it would not typically cause increases in Pplat.

CHAPTER 3

Pain Management

James R. Miner | John H. Burton

PRINCIPLES

Background and Importance

Pain-related complaints represent the primary cause of concern in as many as 70% of patients presenting to the emergency department (ED) setting.[1] Uncontrolled pain should be considered a medical emergency. The estimated degree of pain experienced by a patient should play a role in the determination of a patient's overall acuity and urgency for therapy. Pain estimations, using both provider- and patient-derived scales, should be obtained and recorded to determine not only the presence of pain but the response to pain therapy. Although pain can be present in a wide variety of physical and psychosocial situations, it is typically present in the context of tissue injury. Pain can therefore be assumed to be present in patients with physically apparent disease or injury, even in those who cannot effectively communicate their condition. Important terms relating to analgesic practices are listed in Box 3.1.

A wide variety of options are available for the effective treatment of pain. Despite having treatments available for acute and chronic pain therapy, the treatment of pain can be difficult and is often one of the most challenging and frustrating aspects of the practice of emergency medicine.[1-9]

Patients' perceptions of their ED care are highly influenced by pain treatment. Satisfaction with emergency care often depends on the techniques and timeliness of analgesia, as well as the discharge plans for pain relief. In every interaction with a patient in pain, a balance must be achieved between relief of patient suffering and the diagnosis and treatment of the underlying medical condition.

A growing body of evidence has supported the importance of pain management as a central aspect for disease treatment. Unrelieved pain is associated with a variety of potentially negative physiologic outcomes, including increases in sympathetic outflow, peripheral vascular resistance, myocardial oxygen consumption, and the production of carbon dioxide. Other adverse effects of unrelieved pain include hypercoagulability, decreases in gastric motility, and immune function impairment. Poorly treated acute pain can promote the development of chronic pain syndromes and vegetative symptoms, as well as increase the need for pain management during any recovery period.[10-12] Pain during serial medical procedures may increase if successful analgesia was not provided during initial procedures.[8,13] It is also likely that a patient's experience of pain increases his or her ability to perceive pain from similar stimuli in the future.[14]

As an affirmation of the recognized importance of pain management in health care, the Center for Medicare and Medicaid Services and The Joint Commission for accreditation of health care organizations require hospitals to develop quality improvement efforts related to acute pain management, in addition to comprehensive programs for the measurement, documentation, and treatment of pain.[8,13]

Anatomy, Physiology, and Pathophysiology

Pain can be generally described by the terms *nociceptive* and *neuropathic*. Nociceptive pain results from the activation of sensory neurons that signal pain (nociceptors) in response to noxious stimuli. Neuropathic pain results from signal-processing changes in the central nervous system (CNS). Neuropathic pain is usually described as burning, tingling, or shooting sensations, and includes neuropathies and deafferentiation. Both nociceptive and neuropathic pains involve peripheral and central sensitization with a complex array of mediators to sensitize peripheral nociceptors and perpetuate thalamic signals (Fig. 3.1). At each level in the physiologic process of pain production or transmission, interventions and therapeutic opportunities should be considered to alter the process with a goal of improving the patient's pain experience.

Pain Conduction Pathways

Pain perception can be divided into four separate processes (see Fig. 3.1): pain detection (transduction), pain transmission, pain modulation, and pain expression (perception).

Pain Detection

The somatosensory system is responsible for the detection of pain as well as tactile, proprioceptive, and thermal sensations. Receptors responsible for the detection of pain are termed *nociceptors*. Nociceptors include sensory nerves that are capable of detecting mechanical, thermal, or chemical stimulation. Several different subtypes of nociceptors are present in cutaneous tissues, including mechanoreceptors, polymodal nociceptors (PMNs), and a variety of thermoreceptors.

The threshold of activation of a nociceptor can be modulated—increased or decreased—by a variety of chemical mediators, including prostaglandin, cyclic adenosine monophosphate, leukotrienes, bradykinins, serotonin, substance P, thromboxanes, platelet-activating factor, and endorphins. This change in nociceptor activation thresholds is termed *peripheral sensitization*. Trigger points, for example, are areas of frequent or constant low-level sensory stimulation (eg, scar tissue or a degenerative joint) that have developed peripheral sensitized nociceptors that perceive pain from otherwise innocuous stimuli.

Information Transmission

Peripheral Nerve Fibers. All sensory neurons are composed of a cell body located in the dorsal root ganglia. The dorsal root ganglia are connected by nerve axon fibers with sensory receptors located in a number of body sites, including dermatomes (cutaneous input), sclerotomes (input from bones), and myotomes (input from muscle). The discrete areas covered by each nerve provide a sensory map of the body surface.

Peripheral nerve fibers can be classified by the roles of each fiber group (Table 3.1). A-δ and C fibers fibers are responsible for the transmission of pain. A-δ fibers transmit sharp, initial pain; C fibers, in contrast, transmit dull, aching, or burning pain. The pain transmitted by A-δ fibers persists only as long as the initial stimulus is in effect, whereas C fiber pain persists longer than the initial stimuli, rendering a prolonged pain sensory experience. The relative concentration of nerve fiber types, both C and A-δ varies by body tissue.

Pain Transmission

Dorsal Horn. The dorsal horn is the gray matter of the posterior aspect of the spinal cord (Fig. 3.2). The dorsal horn acts as an integration system in which sensory input is filtered, attenuated, or amplified before being relayed to other spinal segments or the cortex.

The dorsal horn is a processing center for incoming information and is extensively involved in the modulation of nociceptive input. Afferents from visceral, muscle, bone, and cutaneous areas converge in the dorsal horn and likely account for the cutaneous transmissions associated with painful visceral, muscular, or bony stimuli.

Differentiation between innocuous stimuli and nociceptor input occurs in the dorsal horn by stimuli received in cells referred to as wide dynamic range neurons (WDRNs). WDRNs receive modulating input from a variety of chemical pathways, such as opioids, substance P, or inflammatory factors. These cells also receive modulating input from efferent and afferent neuronal pathways.

Visceral Pain. The quantity and type of stimuli that produce pain varies among visceral structures. The myocardium, for example, is sensitive to ischemia but not mechanical stimulation. Tissues in the intestine may be severed, crushed, or burned without pain; however, traction or distention produces pain sensations in this area.

The quality of visceral pain is unique from somatic pain. Somatic pain is initially sharp, later becoming burning or throbbing in nature as the response is modulated. In contrast, visceral pain tends to start as poorly localized, dull, and aching, with pronounced autonomic activation. These sensations may then

BOX 3.1

Definitions of Terms Related to Analgesia

Allodynia—pain from a stimulus that does not normally provoke pain
Amnestic—an agent that suppresses the formation of memories
Local anesthesia—creates an area of insensibility to pain by injection of a local anesthetic agent
Analgesia—relief from pain
Hypnotic—agent that promotes the onset of sleep
Narcotic—term with legal implications describing opioid agents together with various central nervous system depressant drugs of abuse
Nociceptor—receptor that is sensitive and responsible for transmitting pain stimuli
Noxious stimulus—stimulus that is damaging or potentially damaging and results in sensation of pain
Opiate—naturally occurring derivative of opium alkaloid that binds opiate receptors and produces effects similar to those of the endogenous endorphins
Opioid—naturally occurring or semisynthetic derivative of opium alkaloid (includes all opiates) that binds opiate receptors and produces effects similar to those of endogenous endorphins
Pain—unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage
Procedural sedation—pharmacologic induction of a state of sedation or dissociation with amnesia for pain control during a painful procedure
Sedative—agent that decreases a patient's level of awareness

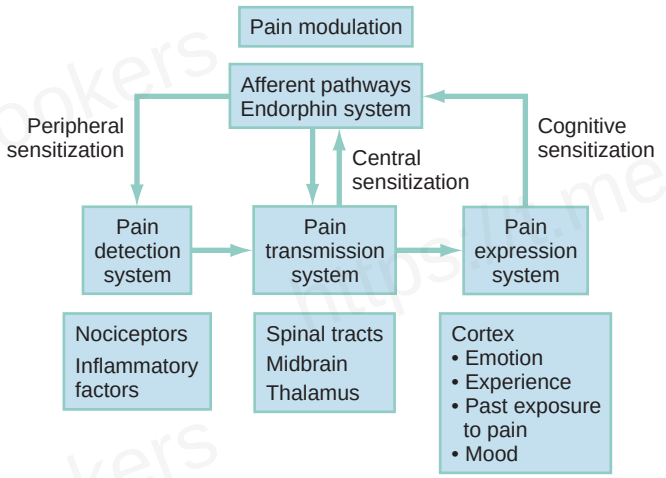

Fig. 3.1. The pain system algorithm.

TABLE 3.1

Peripheral Nerve Fibers

FIBER	FUNCTION	MYELIN	MEAN DIAMETER (mm)	ASCENDING TRACT	CONDUCTION VELOCITY (m/s)
A-α	Skeletal muscle motor	Deep	12–20	Ipsilateral dorsal column	70–120
A-β	Light touch and pressure	Superficial	5–15	Contralateral spinothalamic tract	30–70
A-γ	Motor	Superficial	6–8	Ipsilateral dorsal column	15–30
A-δ	Sharp pain (mechanoreceptors, thermoreceptors, PMNs)	Superficial	1–4	Contralateral spinothalamic tract	12–30
B	Sympathetic		1–3	Preganglionic	3–15
C	Long-lasting burning pain	Superficial	0.5–1.5	Contralateral spinothalamic tract	0.5–2

Adapted from Paris PM, Uram M, Ginsburg MJ: Physiological mechanisms of pain. In Paris PM, Stewart RD, editors: Pain management in emergency medicine, Norwalk, CT, 1988, Appleton & Lange.

develop into sharp, localized, referred pain. This progression is likely due to the varying ratios of A to C fibers, which are 1:10 in visceral nerves and 1:2 in cutaneous nerves.

Visceral pain often produces referred pain. For example, periumbilical pain is often associated with appendicitis. This referred pain sensation occurs due to visceral afferents supplying the small bowel and traveling through the celiac ganglia and splanchnic nerves to enter the spinal cord at T10. This input sensitizes the dorsal horn at T10, leading to sensitization of all the dorsal horn nociceptive neurons and ultimately leading to the perception of pain in the T10 dermatome. As appendicitis progresses, the pain localizes to the right lower quadrant as inflammation extends to the parietal peritoneum with the same nerve supply as the overlying dermatome.

Ascending Tracts Associated With Pain. Fibers carrying pain impulses exit the dorsal horn and ascend the spinal cord to the brain. The predominant pathways for pain conduction through the spinal cord are the spinothalamic, spinomesencephalic, and spinoreticular tracts, located in the anterolateral aspect of the spinal cord (Fig. 3.3; see Fig. 3.2).

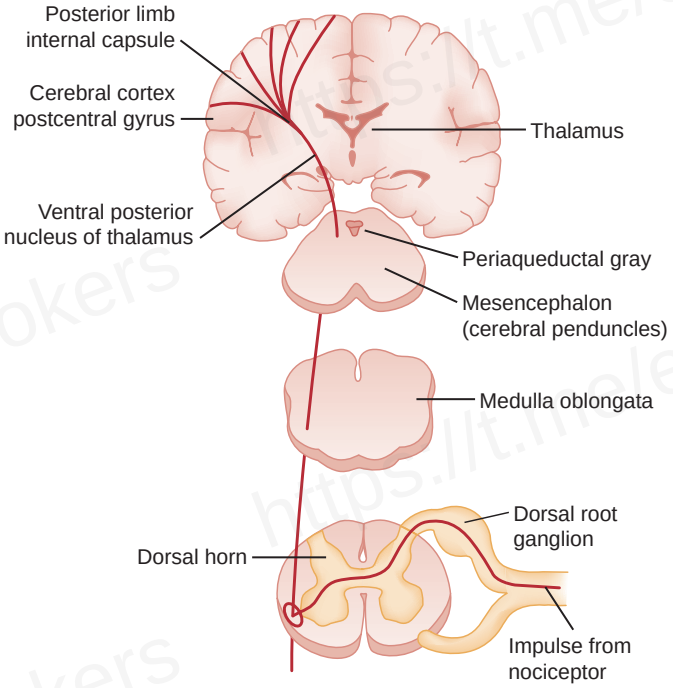

Fig. 3.2. Spinal tracts.

Pain Modulation

Impulses from nociceptors are modulated by descending tracts in the spinal cord. The two primary descending pathways appear to be serotonergic and noradrenergic. These pathways originate in the midbrain (periaqueductal gray matter and locus ceruleus) and medulla (nucleus raphe magnus and nucleus reticularis gigantocellularis) and are transmitted to the spinal cord via the dorsolateral funiculus.

Electrical stimulation of descending pathways produces analgesia comparable to that produced with opioids. Stimulation of the thalamus can also produce analgesia. Inputs to this system come from the frontal cortex, limbic system, hypothalamus, reticular system, locus ceruleus, and spinal cord. Multiple neurotransmitters are involved in these pathways, including serotonin, norepinephrine, and substance P. It is believed that the activation of this system is responsible for effects such as placebo, acupuncture, and transcutaneous electrical nerve stimulation (TENS) units, as well as stress-associated pain tolerance.

Central Sensitization

Central sensitization involves the amplification of nociceptive signals. Central sensitization is mediated by a number of substances, such as nitric oxide, glutamate, substance P, aspartate, prostaglandins, leukotrienes, norepinephrine, and serotonin. It can occur in the presence of chronic pain or can be the result of damage at any point along the pain transmission system. Central sensitization is described in the setting of traumatic and degenerative conditions of the spinal cord and brainstem and can be associated with thalamic strokes, multiple sclerosis, Parkinson's disease, Arnold-Chiari formation, and cervical stenosis.

Pain Expression

The transduction, transmission, and modulation of pain stimuli develop the perception of the subjective emotional experience of pain. Many factors other than the stimulation of nociceptors influence the final perception of pain. The discrete cognitive processes and pathways involved in the interpretation and experience of painful stimuli still remain a mystery and are affected by factors such as cultural expectations, personality, experiences, and underlying emotional state. Many of these factors, and therefore

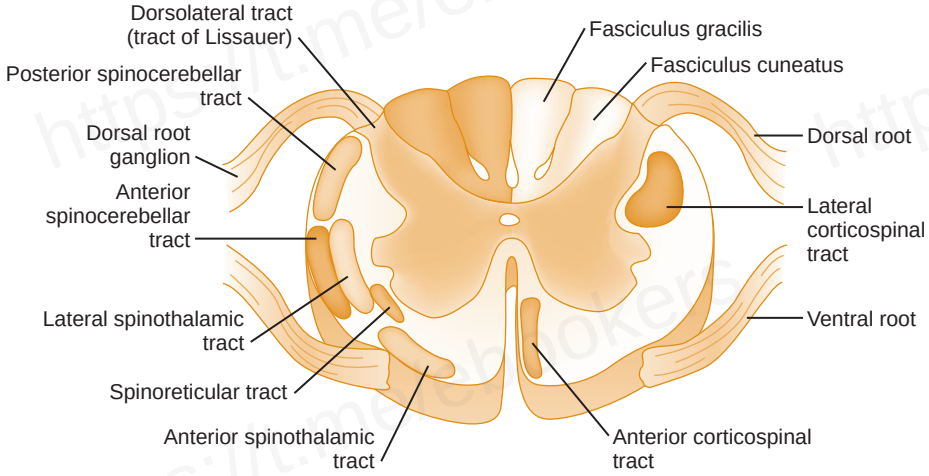

Fig. 3.3. Spinal cord.

the subsequent perception of pain, can be greatly influenced by pharmacologic and nonpharmacologic interventions.

For drugs such as nitrous oxide and low-dose opioids, much of their analgesic effect is on the cognitive interpretation and emotional reaction to pain rather than on transmission of the pain stimulus. Noninvasive techniques (eg, distraction, hypnosis) can limit pain perceptions and increase tolerance. Changes how a person experiences pain, based on previous experiences and learned behaviors, are referred to as cognitive sensitization.

Reflex Responses to Pain

There are two types of reflex responses to nociceptor input, spinal segmental (or suprasegmental) and cortical. Spinal reflexes are generated by the transmission of nociceptive impulses from the dorsal horn to motor and autonomic neurons in the spinal cord, provoking a range of responses, including tachycardia, vasoconstriction, paralytic ileus, and muscle spasm (Box 3.2). Suprasegmental reflexes are transmitted through ascending tracts to the brainstem, hypothalamus, and cortex, where withdrawal reflexes and autonomic responses occur in connection with conscious responses. The autonomic reflex responses to pain are variable and cannot be used to quantify pain in an individual.

Endorphin System

The endorphin system is a neuroendocrine system that serves to modulate responses to pain and stress. The endorphin system consists of widely scattered neurons that produce three types of opioids—beta-endorphin, met- and leu-enkephalins, and dynorphins. These opioids act as neurotransmitters and neuromodulators at three major classes of receptors—mu, delta, and kappa—and produce analgesia as well as counter the stress response (Table 3.2).

Under normal circumstances, the endorphin system serves to decrease pain and stress after a person has adequately dealt with the inciting noxious stimuli. The endorphin system normally is a responsive system that can have an increased or decreased effect to produce the appropriate response to a painful event. Like other neuroendocrine systems, increasing stimulation by endorphins produces feedback inhibition on their own circulating levels. During prolonged periods of pain with high levels of stimulation, the system can become less responsive and less effective at modulating the pain response.

Like their endogenous counterparts, opiates act at chemical receptors to produce analgesia and undesirable side effects. As these drugs are given over a prolonged period, they inhibit the endogenous endorphin system, blunting the response to pain and stress and decreasing the overall endorphin effect. As these drugs are withdrawn, the normal effects of the endorphin system resume.

Acute Versus Chronic Pain

Acute pain is usually associated with an identifiable pathologic condition and serves an adaptive function by warning the individual that an illness or injury exists. This sequence will motivate the person to cease activity that is causing the pain, look for a cause, seek help, and avoid the stimulus in the future.

Acute pain becomes chronic pain when the pain pattern persists, in changed or unchanged form, after the original physiologic insult has apparently resolved. All chronic pain starts as acute pain, but only small subsets of patients with acute pain develop chronic pain (Table 3.3). The physiologic transition from acute to chronic pain is a complex process, with physiologic and psychosocial components. In many cases, the development of chronic pain is likely related to the treatment of acute pain.

Acute pain serves an important purpose in that it stimulates a person to protect the injured area and seek help. Also, the neurochemical factors that contribute to acute pain acknowledgment will generally initiate and support recruitment of tissue repair mechanisms. As an injury heals, these adaptive responses may become maladaptive if the pain persists because this cycle can lead to a decreased range of motion, decreased function of the area and, ultimately, an increased susceptibility to injury and pain. Pain also causes a stress response that is initially adaptive in the face of injury. A prolonged stress response, however, causes an impaired immune system, hypercoagulable state, sleep disturbances, anxiety, and depression.

BOX 3.2

Reflex Responses to Pain

INCREASED SYMPATHETIC TONE
Vasoconstriction producing increased peripheral resistance
Increased cardiac output from increased stroke volume and heart rate
Increased blood pressure
Increased metabolic rate and oxygen consumption
Decreased gastric tone and gastric emptying (may progress to ileus)
Decreased urinary tract tone (may lead to urinary retention)

ENDOCRINE RESPONSES
Decreased insulin production
Increased cortisol levels
Increased antidiuretic hormone levels
Increased growth hormone levels
Increased renin, angiotensin II, aldosterone levels
Increased glucagon levels
Increased catecholamine levels

RESPIRATORY RESPONSES
Hyperventilation

CORTICAL RESPONSES
Anxiety and fear

TABLE 3.2

Opioid Receptors

OPIOID RECEPTOR CLASS	EFFECTS	ASSOCIATED ENDOGENOUS ENDORPHIN
Mu 1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential	Beta-endorphin
Mu 2	Respiratory depression, CV and GI effects, miosis, urinary retention	Beta-endorphin
Delta	Spinal analgesia, CV depression, decreased brain and myocardial oxygen demand	Enkephalin
Kappa	Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system	Dynorphin, beta-endorphin
Epsilon	Hormone	Beta-endorphin
Gamma	Dysphoria, psychomimetic effects	Beta-endorphin

CV, Cardiovascular; GI, gastrointestinal.

TABLE 3.3

Acute Versus Chronic Pain

PARAMETER	ACUTE PAIN	CHRONIC PAIN
Inciting factor	Associated pathology present and recovery is expected	Associated pathology not identifiable or not expected to improve; recovery unpredictable or not expected
Relation to healing	Pain improves as the injury heals; limitation of activity due to pain assists healing	Neither pain nor injury expected to improve; pain may limit activities that could improve condition
Psychosocial effects	Limited to acute stress reaction	Negative effects a prominent feature of disease
Treatment	Analgesics, immobilization	Psychosocial aspects must be addressed; analgesics play a smaller role

Chronic pain is very common. A large number of patients with chronic pain are seen in the ED. It can be difficult to determine the point at which an adaptive pain response becomes maladaptive, and the progression from acute pain to chronic pain occurs.

MANAGEMENT

Decision Making

Pain Assessment

The early accurate recognition and assessment of a patent's pain are the most important aspects of effective acute pain management. When pain is inadequately treated, inaccurate assessment is very likely the root cause of the problem.

The degree to which a person experiences pain is a complex and subjective interaction between the physical stimulus and patient's cognitive and emotional state. It is clear, however, that the degree of pain a patient perceives is not directly determined by the degree of physiologic injury. Patients in the ED with relatively identical injuries may experience and display completely different amounts of pain.[5,6,15] Therefore, pain treatments, analgesic requirements, and the way in which a patient describes pain cannot be uniformly described based on the nature of a patient's injury.

The assessment of pain depends on the patient's ability to communicate the nature of the painful experience to the emergency clinician and the emergency clinician's ability to obtain this information. Unfortunately, there is no objective test or physiologic index to measure pain reliably. Objective observations, such as hypertension, diaphoresis, or tachycardia, do not correlate well with the degree of pain present. Because pain cannot be objectively measured, an emergency clinician's assessment depends on communication with the patient—verbal and nonverbal. Barriers to communication between patients and emergency clinicians, including linguistic, socioeconomic, and cultural differences, limit the ability to assess pain effectively.

Oligoanalgesia

Because effective treatment is based on the assessment of pain, patients who have difficulty communicating are at particular risk of undertreatment of their pain (oligoanalgesia). Groups at particular risk for oligoanalgesia include infants and children, patients whose cultural and linguistic background differs significantly from the treating emergency clinician, and patients who are developmentally delayed, cognitively impaired, under severe emotional stress, or mentally ill.

There are a variety of reasons why patients do not receive adequate analgesia from health care providers. These include the ineffective assessment of pain, misconceptions about the safety and efficacy of various treatments, and the effect of analgesic interventions on a patient's evaluation. In the ED, there may be a significant delay to providing adequate pain control.[2,6,16,17] Additionally, when opioids are used, they are often given in subtherapeutic doses.[4,8,13,18,19]

Pain Measurement

The use of numeric rating scales, using a verbal 0 to 10 score (none to worst imaginable), are ubiquitous in the ED and other settings, where acute pain is managed or invoked (Fig. 3.4). Visual analogue scales, usually consisting of a 10-cm straight line with anchors at either extreme, are frequently used in research to provide continuous data for analysis. These scales offer little practical advantage over verbal reports in the clinical setting. Routine verbal or visual pain scale assessment encourages emergency clinicians to communicate with patients to assess their pain and to evaluate responses to analgesic intervention attempts.

Children require alternative communication techniques to acknowledge and relate pain. The FACES pain scales are designed for children younger than 7 years. This scale has a series of cartoon faces expressing a range of emotions, from happiness to severe distress. The child is asked to point to the face that corresponds to how he or she feels. The FACES pain scale, and others like them, require less of an abstract reference than numeric and verbal scales and are useful in pain assessment for toddlers and cognitively impaired adults.

In preverbal children, observer-derived scales may be used. These include scales such as the Modified Pre-Verbal, Early Verbal Pediatric Pain Scale (M-PEPPS), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), and CRIES scale for neonates. These scales use a scoring system for observed criteria that is reproducible among trained observers, making them useful for research. These scales appear to have little clinical utility compared to the emergency clinician's or parents' overall impression of the child's pain.

Pain scores have gained acceptance as the most accurate and reliable measure of assessing a patient's pain and response to pain treatment. Pain treatment should be targeted to a goal of reducing the pain score (eg, by 50%, below 4/10, or referred to as mild/moderate or severe) rather than a specific (maximum) analgesic dose.

Treatment Groups

The approach to patients in pain should begin with a characterization of pain patients into four unique treatment groups: (1) chronic pain; (2) recurrent pain; (3) chronic pain of malignancy and neuropathic pain; and (4) acute pain. Therapy for groups other than those with acute pain should focus on a long-term, multidisciplinary approach that includes the emergency clinician and ED as part of a patient's ongoing comprehensive strategy (Box 3.3). Acute and chronic pain patients have different physiologic

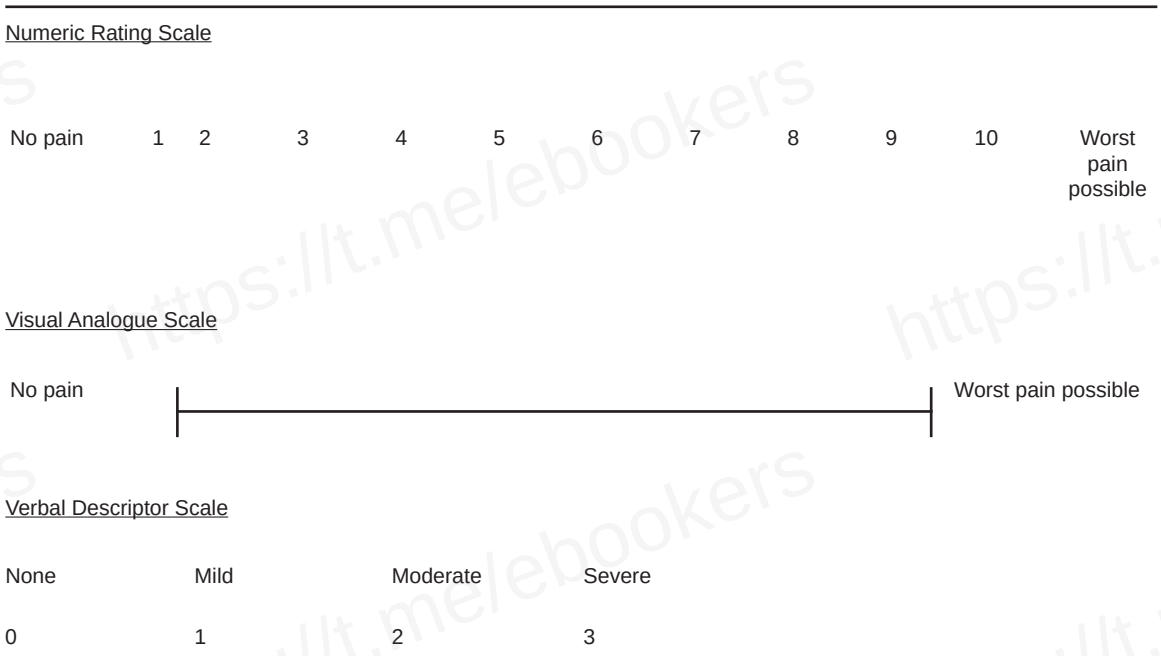

Fig. 3.4. Pain scales.

BOX 3.3

Common Outpatient Analgesic Agents by Pain Type

ACUTE PAIN

1. Acetaminophen
2. Nonsteroidal antiinflammatory drugs (NSAIDs)
3. Opioids used in combination with NSAIDs and acetaminophen
4. Oxycodone
5. Hydrocodone

CHRONIC PAIN

1. NSAIDs
2. Tramadol
3. Opioids used in combination with NSAIDs and acetaminophen[a,b]
4. Oxycodone, long-acting preparation, or for breakthrough pain
5. Tricyclic antidepressants

NEUROPATHIC PAIN

1. Gabapentin
2. Tricyclic antidepressants
3. Carbamazepine

[a]A variety of opioid and acetaminophen combination agents are available.
[b]Chronic opioid management should be managed by the primary outpatient physician.

causes and thus require different treatment approaches based on their specific site and mechanism of affect (Fig. 3.5).

Chronic Pain. The assessment of pain in the absence of acute or obvious physical injury requires a great deal of communication skill on the part of the emergency clinician and patient. Many patients with chronic pain develop experiences, some adaptive and others maladaptive, in describing their pain and interacting with emergency clinicians to receive pain treatment. Many behaviors such as exaggerating symptoms or attempting to manipulate providers are developed around the patient's expectations for obtaining pain therapy or pain relief. These behaviors, combined with the negative psychosocial effects and sense of futility associated with chronic pain, can complicate the evaluation process and care of chronic pain patients.

The assessment of chronic pain can represent some of the most challenging situations to obtain an accurate clinical history. Patients who are having a difficult time describing their pain should be encouraged with detailed questions about the pain, combined with multiple examples, comparisons, and summarizing statements, to facilitate accurate communication. Assuring the patient that the questions are intended to aid understanding and enable treatment of symptoms as effectively as possible can facilitate the development of a common goal and help establish the trust necessary to develop an effective treatment strategy.

Patients with chronic pain can present with an exacerbation of their chronic pain in the setting of ongoing therapy or with untreated chronic pain due to a gap or lack of chronic care. These scenarios require different treatment approaches. For chronic pain patients with an exacerbation in their pain exceeding the pain control of their usual treatment strategy, treatment can be approached in a fashion similar to that for acute pain. The goal for these patients should be to control the exacerbation and return the patient to baseline function.

Many patients with chronic pain are in comprehensive treatment programs, most of which involve a so-called contract with respect to the provision of their pain management. For such patients, a review of the pain management plan in the medical records, or contact with the health care provider who typically manages the patient's treatment plan, is a critical element in determining the best short-term strategy in the ED.

Patients with chronic pain who have a gap in their baseline treatment or who have never established appropriate treatment for chronic pain require an approach that addresses the need for establishment of a chronic, consistent treatment plan. Patients with no ongoing treatment plan should have a basic chronic pain treatment plan implemented during their ED visit. This should consist of acetaminophen, if not contraindicated, and a nonsteroidal antiinflammatory drug (NSAID), if tolerated. Tramadol may be helpful in certain cases. Adjuvants appropriate for neuropathic or central pain may be added, if appropriate. Opioids for chronic pain, whether for a patient already on a treatment plan

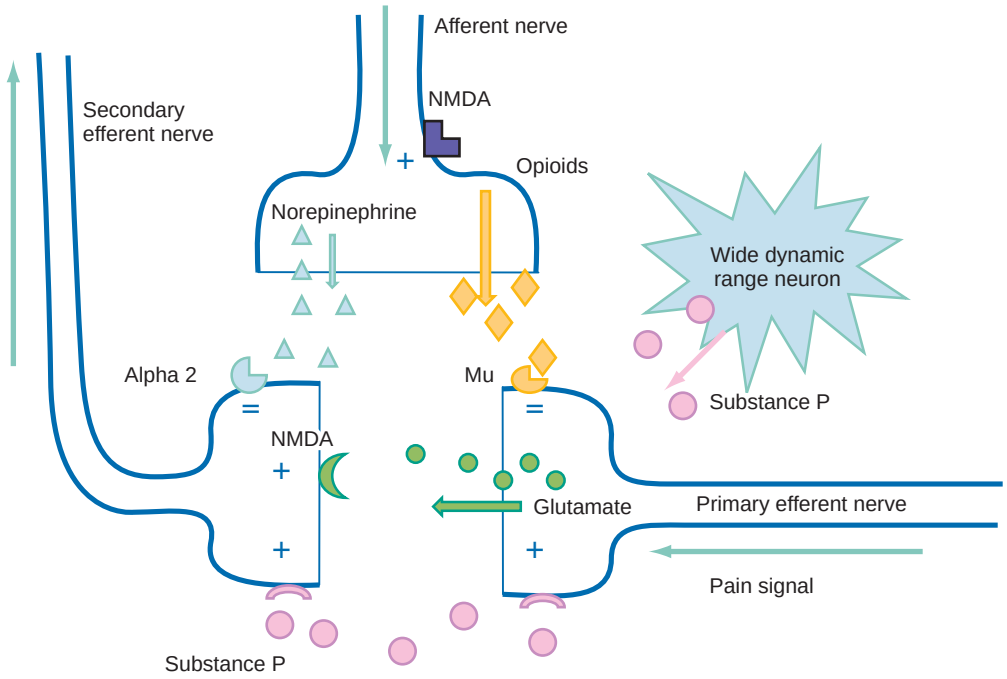

Fig. 3.5. Neurotransmitters and receptors at the dorsal root ganglion. *Mu,* Opioid receptor; *NMDA, N*-methyl-D-aspartate.

or without a treatment plan, rarely are indicated in the ED care of the chronic pain patient, with the exception of patients who are in care for pain related to advanced malignancy (see below.) Opioids should neither be administered nor prescribed unless their need is verified with the clinician responsible for the patient's chronic pain management plan. In general, opioids for chronic pain management are the domain of providers in ambulatory pain centers or primary care physicians who will follow the patient's therapy, response, and compliance. There is often difficulty communicating with the patient, who may have received opioids at many EDs, including the one currently being visited; establishment of a departmental policy empowers emergency clinicians to administer or prescribe opioids for chronic pain syndromes, without judging the patient.

Recurrent Pain. Recurrent pain is a subset of chronic pain; the term describes patients who have symptoms with repeated episodes of similar pain. Recurrent pain can include such disorders as back pain, myofascial pain syndrome, migraine syndrome, sickle cell disease, and inflammatory bowel disease. The approach to the treatment of recurrent pain in the ED incorporates elements of the treatment of acute pain and of chronic pain, and prevention of recurrent pain events must be considered as part of the treatment strategy. These therapies may integrate nonpharmacologic approaches, such as physical therapy for back pain, in addition to the use of preventive medications.

Chronic Pain of Malignancy. Chronic pain due to malignancy is approached differently from other causes of chronic pain. Chronic malignant pain is similar to acute pain in its relation to ongoing nociceptive stimulation and similar to chronic pain in its duration and psychobehavioral effects. The medications used, for the most part, are similar to those used for acute pain. Psychosocial effects of the pain of malignancy must be addressed as part of an effective treatment strategy.

Patients with a significant change in the pattern of their chronic pain caused by cancer or a terminal illness, as with other chronic pain patients, should be evaluated for a new process to account for the pain. Opioids, especially in long-acting or transdermal preparations, should be used liberally to bring pain relief for patients with terminal illnesses.

Neuropathic Pain. *Complex regional pain syndrome* (CRPS) is a term that includes most sympathetically maintained neuropathic pain. CRPS type 1 (often referred to as reflex sympathetic dystrophy) develops after an injury and typically follows the distribution of a peripheral nerve. It is associated with hyperalgesia, allodynia, changes in skin blood flow, and sympathetic dysfunction. This syndrome develops during the healing and recovery phases of acute painful injuries and is generally described as a burning, tingling sensation in the area of the previous injury, but not in a specific nerve distribution; it is likely related to ongoing painful stimulation leading to the development of self-sustaining modulation of the pain transmission system. CRPS type 2, commonly referred to as causalgia, is associated with burning pain and allodynia in the distribution of an injured nerve, with no association with sympathetic symptoms. Opioids are ineffective in preventing CRPS after an injury has occurred. Clonidine, N-methyl-d-aspartate receptor antagonists, and γ-aminobutyric acid (emergency clinician) receptor agonists are more effective in the treatment of CRPS than opioids. Gabapentin is generally considered a first-line agent, with pregabalin used for patients who cannot tolerate its sedating effects.[20]

Antidepressants have effects on neuropathic pain that appear to be distinct from mood effects. For patients with chronic pain thought to be unrelated to central or neuropathic origins, other antidepressants, such as selective serotonin reuptake inhibitors, may be safer and more effective.

Several anticonvulsants, including gabapentin, phenytoin, carbamazepine, and valproic acid, are described for neuropathic pain with lancinating or burning properties. Carbamazepine is used most frequently for trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy. Gabapentin is described for both types of CRPS, postherpetic neuralgia, and diabetic neuropathy.

Acute Pain. Symptomatic treatment of pain should be initiated promptly, titrated to an acceptable level of relief, and continued while the investigation for a cause is proceeding. Fig. 3.6

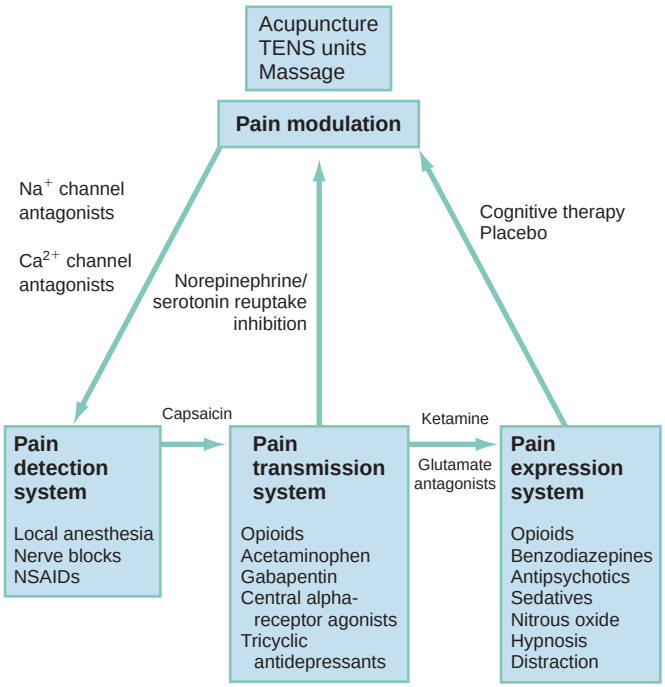

Fig. 3.6. Sites for pain treatment algorithm. *NSAID,* Nonsteroidal anti-inflammatory drug; *TENS,* transcutaneous electrical nerve stimulation.

presents a common approach to acute pain in the ED setting, beginning at triage with the assessment of pain type and severity and then progressing to clinical assessment, with therapeutic suggestions.

When the cause of acute pain is uncertain, immediate relief of pain occurs in parallel with initial efforts to establish the diagnosis. It is inappropriate to delay analgesic use until a diagnosis has been made. There is no evidence that the administration of adequate doses of opioid analgesia to establish patient comfort impairs the emergency clinician's ability to diagnose the cause of an acutely painful condition. On the contrary, the administration of analgesia may enhance the accuracy of the physical examination and patient assessment.

Pharmacologic Therapy

Opioid Analgesic Agents

In 1680, Sydenham wrote that "Among the remedies it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium." Centuries later, this statement is still accurate, with titrated opioids considered to be the therapeutic foundation for severe acute pain.

The beneficial effects of opioids have been well documented for centuries, as have their toxicity and potential for abuse. Unfortunately, opioids are often poorly used in clinical practice. Concerns regarding opioid toxicity or dependence and a poor understanding of the pharmacokinetics of the drugs have led to inadequate dosing and excessively infrequent dosing intervals. The safety of the short-term use of opioids for acute pain, in terms of toxicity and likelihood of causing future dependence, is established. Opioids are the first-line agents in the management of acute severe pain (Table 3.4). This safety is not well established in relation to the treatment of mild or moderate pain, however. The effectiveness of opioids relative to that of nonopioid analgesics, and a similar comparison of potential adverse effects, including the potential for abuse, argues against their use in mild pain and for sharp limits on their use for moderate pain. To prevent the overuse and misuse of opioids, the quantity and strength of the opioids prescribed should closely match the anticipated duration of the severe pain, and the patient should be transitioned off the opioid analgesia at the earliest appropriate opportunity. For most short-term acute pain episodes, such as a fracture, 3 to 5 days of opioid analgesia is sufficient, pending outpatient follow-up evaluation.

Mechanism of Action and Toxic Effects. Opioids bind to specific endorphin system receptors located throughout the nervous system. These receptors suppress pain detection peripherally, modify pain transmission in the spinal cord and thalamus, and alter pain perception at the level of the cortex. A variety of endorphin receptors are defined (see Table 3.2). The unique actions of opioids are determined by the specific binding properties of the agent to the various receptors.

Side effects can limit the success of opioid therapy, particularly in the acute treatment setting. The occurrence of side effects varies among individual patients and opioid agents. Tolerance of many side effects develops shortly after the initiation of therapy.

The most common side effect of opioids is constipation. Constipation is attributed to opiate binding of receptors located in the antrum of the stomach and proximal small bowel. Constipation can be anticipated with long-term opioid use (more than a few days). An active laxative, such as senna, lactulose, or bisacodyl, should be prescribed, as needed.

Nausea and vomiting can occur with the administration of opioids, especially in opioid-naïve patients. It is often difficult to distinguish whether nausea and vomiting are caused by the opioid or the acute pain for which it is administered. Routine coadministration of an antiemetic with the opioid, once an almost universal practice, is not necessary. Nausea and vomiting in the context of persistent acute pain after opioid administration may require an additional opioid and antiemetic, such as promethazine, prochlorperazine, or ondansetron.

Immunoglobulin-mediated allergies are rare for morphine and other opioids. Many patients will experience mild pruritus of the trunk and face after parenteral administration. This side effect is related to histamine release from opioid receptors on mast cells and does not constitute an allergy. To a varying degree, opioids destabilize mast cells in a dose-dependent fashion, causing histamine release and resultant urticaria, pruritus, and orthostatic hypotension. This reaction may appear as localized urticaria tracking up a vein after intravenous (IV) administration of an opioid, especially morphine. Rarely, bronchospasm may be seen in patients with reactive airway disease or atopy. This effect usually subsides rapidly, with no treatment required, although the symptoms can be controlled with the administration of an antihistamine.

Sedation and respiratory depression can occur with opioid administration for acute pain. Opioids decrease medullary sensitivity to carbon dioxide, resulting in respiratory depression. The combination of opioids with other sedating agents, such as benzodiazepines, will increase the likelihood of respiratory depression. Patients with underlying hepatic or renal dysfunction are also at increased risk because of their inability to clear opiates normally, resulting in the accumulation of active metabolites and a higher risk for sedation or respiratory depression.

Pain is a very effective stimulant of respiratory drive, rendering respiratory depression rare in the context of acute severe pain. Fear of respiratory depression should not deter the emergency clinician from treating pain adequately, although monitoring patients receiving significant doses of narcotics is advised. It should be noted that patients who had previously tolerated a dose of an opioid may develop respiratory depression if the source of acute pain is removed, such as by local anesthesia or the reduction and stabilization of a fracture. Transient respiratory depression

TABLE 3.4

Opioid Analgesics

ANALGESIC AGENT	INITIAL DOSE		DURATION OF ACTION	EQUIPOTENT DOSE		COMMENTS
	PARENTERAL	ORAL		IV	PO	
Morphine	0.1 mg/kg	0.5 mg/kg	3–4 h	10 mg	50 mg	Standard opioid for comparison
Hydromorphone	0.015 mg/kg	0.075 mg/kg	2–4 h	1.5 mg	7.5 mg	Inactive metabolites advantageous to patients with renal or hepatic disease
Methadone	0.1 mg/kg	0.2 mg/kg	4–8 h	10 mg	20 mg	Used for opioid addiction therapy and chronic pain; half-life longer than duration of action
Fentanyl	1.5 μg/kg	3 μg/kg	0.5–1.5 h	100 μg	NA	Oral dose actually transmucosal absorption rather than ingestion; metabolites inactive; transcutaneous patches used for chronic pain
Oxycodone	0.1 mg/kg	0.15 mg/kg	3–4 h	10 mg	15 mg	Excellent bioavailability, so it is an effective oral agent for acute pain
Codeine	1.3 mg/kg	2.5 mg/kg	2–4 h	130 mg	200 mg	Side effect to analgesia ratio is undesirable; pronounced peripheral effects—constipation, nausea and vomiting, cough suppression
Hydrocodone	NA	5–15 mg	3–4 h	NA	30 mg	Commonly used in preparations with acetaminophen; more potent than codeine
Meperidine	0.75 mg/kg	3 mg/kg	2–3 h	75 mg	300 mg	Toxic metabolite normeperidine accumulates at normal doses; generally should not be used for acute analgesia
Oxymorphone	0.01 mg/kg	0.1 mg/kg (PR)	3–4 h	1 mg	10 mg	Rectal dosing more predictable than other agents
Alfentanil	10–20 μg/kg	NA	8–12 min	1 mg	NA	Short duration due to redistribution; duration of action increases with size of dose
Sufentanil	0.1 μg/kg	NA	1–1.5 h	10 μg	NA	Minimal cardiovascular side effects
Remifentanil	0.5–1 μg/kg	NA	4–6 min	50 μg	NA	Used as a continuous infusion
Nalbuphine	0.4 mg/kg	0.1 mg/kg	3–4 h	40 mg	NA	Mixed agonist-antagonist; decreased respiratory depression relative to other opioids; limited analgesic effect; used during perinatal period

IV, Intravenous; *NA,* not applicable; *PO,* by mouth; *PR,* per rectum.

from opioids usually responds to simple verbal or tactile stimulation and, uncommonly, requires more aggressive interventions.

Tolerance and physical dependence are common effects of the prolonged use of opioids. Physical dependence is defined as the occurrence of an opioid withdrawal syndrome following abrupt cessation, rapid dose reduction, or administration of an antagonist. Tolerance is a phenomenon that occurs after prolonged exposure to opioids and is characterized by the diminution of an opioid's effect over time. Normal expected results of the prolonged use of opioids should be accounted for in planning their use for extended periods and do not represent addiction. Patients who require prolonged treatment with opioids (>5–10 days with regular dosing) will require tapering doses as their painful condition improves to prevent withdrawal. Neglecting to address this issue early in a patient's treatment can lead to difficulties with safe and tolerable treatment termination.

Addiction is a potential risk associated with prolonged opioid use and often limits use. The term addiction refers to a neurobiologic disease, with many factors influencing its development and manifestations. Addiction is characterized by compulsive drug use, continued use despite harm, and craving. The term *pseudoaddiction* describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications and otherwise seem to engage in inappropriate drug-seeking behaviors. Behaviors such as illicit drug use and deception can occur in the patient's efforts to obtain relief (Box 3.4). Pseudoaddiction can be distinguished from true addiction in that it resolves when pain is effectively treated.

BOX 3.4

Addiction Behaviors

BEHAVIORS TYPICALLY SPECIFIC TO ADDICTION

- Injecting oral formulations
- Concurrent abuse of alcohol or illicit drugs
- Selling or diversion of prescription drugs
- Prescription forgery
- Obtaining drugs from nonmedicinal sources
- Repeated dose escalation
- Repeated visits to other EDs without informing prescriber
- Drug-related deterioration in function at work or socially
- Repeated resistance to changes in therapy, despite evidence of adverse drug effects

BEHAVIORS LESS SPECIFIC TO ADDICTION

- Aggressive complaining about the need for more drug
- Drug hoarding during periods of reduced symptoms
- Requesting specific drugs
- Openly acquiring drugs from other medicinal sources
- Occasional dose escalation or noncompliance
- Unapproved use of a drug to treat another symptom
- Resistance to change in therapy associated with tolerable side effects, with expression of anxiety related to the return of severe symptoms

ED, Emergency department.

Drug-Seeking Behavior. Some patients feign or exaggerate pain to receive opioids to abuse medications or sell them to others, defined as diversion. Opioid abuse and diversion is a growing problem, and the rapid growth in the number of opioid prescriptions has played a large role in rising rates of abuse and diversion.[21-25] In recognition of diversion and abuse, many states have developed prescription monitoring programs that allow for an exchange of information among providers to detect frequent opioid prescriptions.[26-33] Prescription-monitoring programs are effective in reducing the number of opioid prescriptions given to patients at risk for abuse or diversion as long as providers consider these data as a routine and integrated practice for patient care. Some states require consultation with the registry before prescribing opioids, but EDs may be exempted from this requirement because of patient flow issues.

A physician's impression of behaviors believed to be associated with patient drug-seeking is associated with a reduction in the treatment of the patient's pain (see Box 3.3).[34] Unfortunately, prescriber perceptions are often complicated by differences between the health care provider and patient in regard to factors such as socioeconomic class, ethnic and racial background, and age, making them frequent sources of bias in the treatment of pain. Care must be taken to recognize these factors and consider their impact on treatment decisions. A thorough evaluation of drug-seeking behavior for a patient includes a review of medical records, prescription registries, and contact with other providers (eg, hospitals, primary care physicians), as available and appropriate. Unless confirmation can be derived through such an evaluation, a patient with apparent acute pain, as from a new injury, should be given the benefit of the doubt and treated as though her or his pain is legitimate. Patients with chronic conditions that can cause acute pain, such as dental caries, some gastrointestinal (GI) syndromes, or long-standing back pain, should be offered alternative pain management approaches, such as nerve block, nonopioid analgesia, or symptomatic treatment with antispasmodic agents until they can resume care with their usual health care providers.

Primary providers, chronic pain specialists, and others should note patient contracts, prescription details, and patterns of possible nontherapeutic drug-seeking behavior in the medical record, using objective terms and descriptions. Patients with repetitive episodes of drug-seeking events may benefit from a multidisciplinary review to establish specific recommendations for their care when they present to anyone other than their primary pain provider. Patients who are noncompliant with their treatment contract, and those who are known to be abusing or diverting opioid medications, should not be prescribed opioid medications from the ED.

Administration of Pain Control. The goal of opioid administration is to attain effective analgesia, with minimal adverse effects. The effects of opioids vary widely among individuals. There is no ceiling effect to their potency. There is also no standard, fixed, or weight-related dose that will consistently produce a given clinical effect. The correct dose that a particular patient requires at a particular time can only be determined by repeated assessment of the degree of pain relief and adverse effects. The use of opioids, therefore, requires titration based on frequent and accurate assessments (Fig. 3.7). The most effective and safe way to achieve pain relief is to use a deliberate IV titration.

The intramuscular (IM) route of administration of opioids has several disadvantages and is not advised for the treatment of acute pain (Box 3.5). The principal limitation of the IM route is its inability to titrate specific doses to desired treatment effects effectively. The time to achieve significant pain relief from an IM injection varies substantially for each patient and offers no therapeutic advantage over an oral medication dosing strategy.

BOX 3.5

Disadvantages of Intramuscular Opioid Administration

Pain on injection
Delayed onset of action
Inability to predict therapeutic effect
Inability to titrate dosage
Diurnal variation in level achieved
Disease state may affect level achieved
Level dependent on intramuscular injection site

Most patients with mild to moderate pain are best treated with oral (PO) opioids. If pain is severe, or if the patient is expected to require multiple doses of an agent for management, an IV route of administration is desirable. If an IV line cannot be established, and the patient cannot tolerate PO medications, the subcutaneous (SC) route is preferable to the IM route. SC injection is less painful than IM injection, with a similar onset of pain relief.

Opioids can be delivered through an oral transmucosal or intranasal mucosal route. Buprenorphine can be given via a sublingual route; whereas fentanyl is available in an impregnated sweetened matrix called Fentanyl Oralet (PO transmucosal fentanyl citrate). Nasal fentanyl, butorphanol, and sufentanil also produce rapid clinical effects via nasal mucosal absorption.

The optimal use of IV opioids requires the administration of an initial loading dose followed by assessment of the analgesic effect. Frequent (every 5–15 minutes) repeated doses should be administered until analgesia is achieved, followed by doses at regular intervals to prevent the return of significant discomfort (see Fig. 3.7).

Specific Agents

Morphine. IV morphine is often the first choice for treatment of acute severe pain in ED patients. Morphine is the opioid analgesic agent with which all other opioids are compared. When administered via the IV route, morphine reaches a peak of action in 15 to 20 minutes, with a half-life of 1.5 to 2 hours in healthy young adults and slightly longer in older adults. Its duration of action is 3 to 4 hours. An appropriate loading dose of morphine for acute severe pain is 0.1 to 0.15 mg/kg IV of ideal body weight, augmented by repeated doses of approximately half the initial dose every 5 to 15 minutes, depending on the severity of the pain and patient response.

Morphine is effective by oral administration; however, only 20% of the ingested morphine dose will reach tissues after first-pass metabolism, requiring a dose adjustment approximately five times that of an equipotent IV dose. The formerly held belief that morphine causes more smooth muscle spasm than other opioids, rendering it inappropriate for the treatment of patients with biliary or renal colic, has been thoroughly discredited.

Morphine is primarily metabolized by conjugation into a three- and six-conjugate forms in the liver. The three-conjugate form (normorphine) has no opioid analgesic activity and has rarely been associated with CNS side effects (eg, tremors, myoclonus, delirium, seizures). This risk is greatest in older patients and those with renal insufficiency, although it is generally not an issue in the ED. The six-conjugate form morphine metabolite is a strong mu and delta receptor agonist. This form plays an important role in the efficacy and duration of clinical effects.

Meperidine. Meperidine (Demerol), although once widely used, has several disadvantages compared with morphine and other parenteral opioids. Meperidine has no indication for use in the ED, and many hospitals have removed it from their

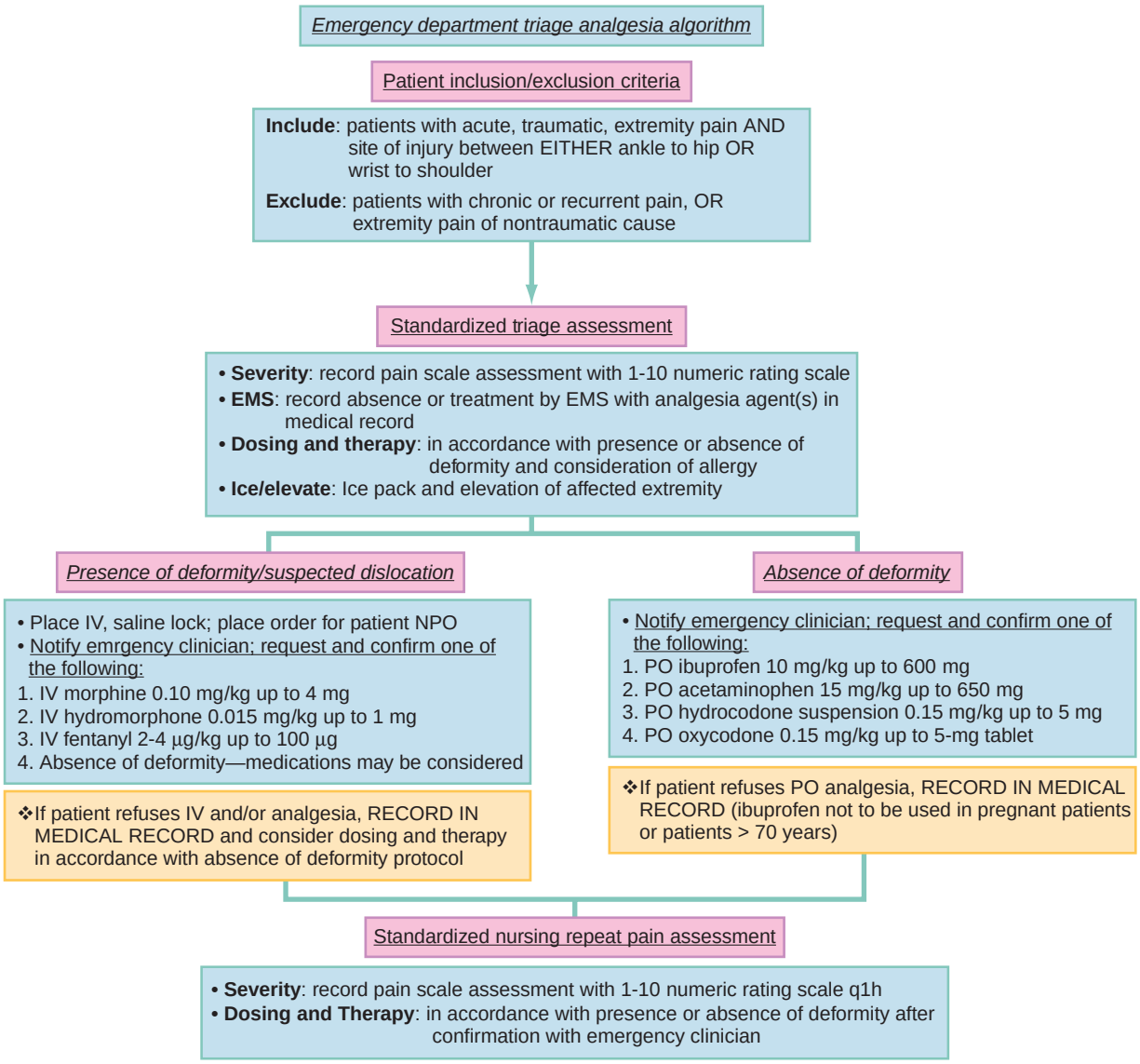

Fig. 3.7. Emergency department triage analgesia algorithm. *EMS,* Emergency medical services.

formularies. It should not be administered or prescribed in the ED. The greatest disadvantage of meperidine is that it is metabolized by the cytochrome P450 system to the active metabolite, normeperidine. Normeperidine can cause CNS toxicity at therapeutic meperidine doses. Normeperidine has a half-life of 12 to 16 hours and blocks muscarinic receptors, resulting in significant anticholinergic effects, including agitation and delirium. These effects may lead to seizures, hallucinations, and psychosis as the metabolite accumulates. Therefore, meperidine is never the first-line drug for any condition, and it should not be used or prescribed in the ED for the management of pain.

Hydromorphone. Hydromorphone is a semisynthetic derivative of morphine that is a potent analgesic agent, increasingly used in the management of acute pain in the ED.[18,35-37] Hydromorphone is the P450 metabolite of hydrocodone and is approximately seven times more potent than morphine, with a similar duration of action. Although 7 mg of morphine is roughly equivalent to 1 mg of hydromorphone, the nursing staff is more likely to administer low milligram doses of hydromorphone to patients with acute pain than higher, equipotent doses of morphine. Care should therefore be taken not to dose hydromorphone excessively, given the propensity for staff to believe that repeated doses of 1 to 2 mg of hydromorphone are relatively benign.

Pruritus, nausea, and vomiting may occur less frequently with hydromorphone administration than with morphine at equianalgesic doses. Hydromorphone is primarily conjugated in the liver to hydromorphone-3-glucuronide (H3G), an inactive metabolite, and is excreted through the renal system. As a result, hydromorphone is better tolerated than morphine, particularly in older patients and those with hepatic impairment. Patients with renal insufficiency may be at some risk of neurotoxicity after prolonged exposure due to H3G accumulation. Patients allergic to morphine do not consistently have cross-reactivity with hydromorphone. Hydromorphone can be given via the IV, SC, PR (per rectum), or PO route.

Fentanyl. Fentanyl is a synthetic opioid that is highly lipophilic; it produces analgesia within 1 to 2 minutes following IV infusion. Fentanyl redistributes rapidly, and its duration of therapeutic action is approximately 30 to 60 minutes.

Fentanyl is metabolized by the P450 system into inactive metabolites. Drug accumulation and toxicity may occur after tissue saturation following a prolonged infusion, but this is unlikely to occur during acute therapy. The short duration of action for fentanyl makes it highly titratable and ideal for use in patients who require serial examinations, such as trauma patients with possible occult head injury.

Fentanyl causes less histamine release than morphine and is associated with fewer peripheral effects at an equianalgesic dose. Fentanyl is an excellent choice for treating pain in patients with bronchospastic lung disease or a history of opioid-associated pruritus. Fentanyl is more frequently associated with respiratory depression than morphine. Patients receiving fentanyl infusions should be monitored with direct observation, supplemented by pulse oximetry.

The ED use of fentanyl is associated with a very low incidence (1.1%) of serious complications. High or repeated fentanyl doses may produce muscle rigidity. This side effect, so-called rigid chest syndrome, usually occurs with anesthetic doses greater than 15 μg/kg, but also has been reported during use for procedural sedation; it may be so severe that it interferes with respiration. Rigid chest attributed to fentanyl is exceedingly rare at doses typically used for acute analgesia. Chest rigidity, when observed to occur, generally responds to naloxone, but neuromuscular blockade may be necessary if naloxone reversal is not successful.

Fentanyl can be administered IV, transmucosally, or transdermally. Nebulized or intranasal fentanyl has been described for the treatment of acute pain in patients without IV access at doses of 3 mcg/kg.[38]

Oxycodone. Oxycodone is a strong opioid agonist that is highly bioavailable in an oral form. Oxycodone is widely sold in combination with acetaminophen or aspirin as well as by itself and is also available in long-acting PO formulations. Oxycodone for acute pain should be prescribed in the noncombination form—that is, as pure oxycodone—to allow a balance between oxycodone and a nonopioid medication. Baseline administration of a nonopioid medication, supplemented by titrated doses of oxycodone, will achieve the optimal effect, with the fewest side effects. Oxycodone bioavailability is much higher than other opioids. It is quickly and efficiently absorbed, which may be a causative factor in its high abuse potential.

Oxycodone is not available in a parenteral form in the United States, although studies have demonstrated its IV form to be equianalgesic to morphine. Similar to other opioids, the analgesic effects of oxycodone are dose-dependent. A 15-mg oxycodone dose has similar efficacy to 10 mg of IV morphine. The onset of action of PO oxycodone is approximately 20 to 30 minutes.

Oxycodone undergoes hepatic metabolism into oxymorphone, a strong opioid agonist that principally accounts for its analgesic effects. Similar to codeine, approximately 10% of patients do not metabolize oxycodone well and are unable to generate the functional metabolite, oxymorphone. This defect in metabolism renders these patients unable to achieve clinically meaningful pain relief with typical dosing strategies and may require very large doses to achieve analgesia. This effect can also be caused by agents that compete with oxycodone for CYP2D6 metabolism, such as neuroleptics, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Cases of serotonin syndrome have been reported when serotonin reuptake inhibitors and oxycodone are given together, likely due to this metabolic interaction.

Hydrocodone. Hydrocodone is metabolized in the liver to hydromorphone and is typically given orally. Hydrocodone provides greater pain relief when combined with acetaminophen or NSAIDs than either component alone. Hydrocodone combinations are less effective than oxycodone-acetaminophen combinations. Hydrocodone clinical analgesia effects typically last 4 hours, with typical dosing of 5 to 20 mg. As with oxycodone, hydrocodone should be prescribed in pure form, not in a combination agent, to allow individual titration of opioid and nonopioid analgesics.

Codeine. Codeine is a weak opioid receptor agonist, usually prescribed in combination with acetaminophen, but has little, if any, role in the modern ambulatory treatment of pain. Codeine is thought to exert its effects through metabolism into morphine and other active hepatic metabolites.

Approximately 10% of the population metabolizes codeine poorly. The effect of this genetic trait is a reduction in active analgesic metabolites and an enhancement in deleterious side effects, including nausea, constipation, and pruritus. Although often historically prescribed for mild to moderate pain, codeine is a poor choice for analgesia due to its tendency to cause side effects, particularly nausea, cramping, and constipation, at doses that provide minimal analgesia. Despite its weak opioid receptor agonist characteristics, codeine has been widely abused.

Methadone. Methadone has several unique features that distinguish it from other opioids. It has no known neurotoxic or active metabolites and has high bioavailability. In addition to being a strong opioid agonist, methadone also has N-methyl-d-aspartate antagonist and serotonin reuptakeitesnguish it from othMethadone has a slow elimination half-life of 27 hours due to its lipophilicity and tissue distribution. This slow clearance of methadone is the basis for its use in maintenance therapy, given that it can delay the onset of opioid withdrawal symptoms for up to 24 hours. The duration of its analgesic effects is closer to 6 to 8 hours. The discrepancy between the duration of action of analgesia and duration of the prevention of withdrawal symptoms is due to the biphasic elimination of the drug and its redistribution.

Naloxone. Naloxone is an opioid antagonist that reverses the effects of opioids and is used in the setting of adverse, opioid-induced events, such as opioid overdose. It can precipitate physiologic withdrawal in patients who are opioid-dependent. The duration of action of naloxone is approximately 45 minutes, which is shorter than that of most opioids, and care must be taken to monitor for the recurrence of opioid adverse events following this time period. Naloxone can be given IV, IM, SC, or via an endotracheal tube, but is typically given in titrated doses of 0.2 mg IV until reversal of any adverse opioid effect is observed. In the setting of adverse events from opioid treatment, usually respiratory depression, careful titration allows for the smallest dose possible to be administered so that its analgesic effect of the opioid. Naloxone, 0.4-mg autoinjectors, are available for outpatient use to prevent overdose complications. Early results of distributing these autoinjectors to opioid-dependent patients have shown that they are effective in preventing overdose complications.

Tramadol. Tramadol is a synthetic oral analgesic that is a weak mu agonist, with some serotonin and norepinephrine reuptake qualities. Its analgesic properties are thought to be primarily due to mu receptor agonist activity. Tramadol-induced analgesia is partially reversed by naloxone, suggesting that other properties play a role in its therapeutic effects. Tramadol, as a selective mu agonist without kappa agonist effects, should not cause physiologic dependence, although tramadol use is associated with abuse. Tramadol should be used with caution in patients addicted to opioids.

Tramadol is metabolized in the liver by the cytochrome P450 system. One of its metabolites, M1, has a greater mu receptor affinity than tramadol and has an elimination half-life of 9 hours. Tramadol appears to have effects on GABA, norepinephrine, and serotonin receptors and the reuptake of the neurotransmitters. These properties may serve to activate descending pain modulation pathways.

Compared with traditional opioids, low-dose tramadol has a more favorable side effect profile and may present a lower risk of addiction with chronic use. The most common tramadol side effects are nausea, vomiting, dizziness, orthostatic hypotension, and sedation. These side effects are seen in as many as 17% of patients using the drug for chronic pain, with slightly lower rates in patients receiving controlled-release versions. Tramadol lowers the seizure threshold and therefore provokes isolated seizures in

selected patients. The use of tramadol with other serotonergic medications (eg, selective serotonin receptor inhibitors, monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitors) is associated with serotonin syndrome.

Tramadol is effective at low doses. At increasing doses, it is associated with nausea and vomiting, limiting its use to low doses and effectively creating a therapeutic ceiling to its clinical use. Tramadol, 37.5 mg, combined with acetaminophen, 325 mg, appears to have similar efficacy to hydrocodone, 5 mg, combined with acetaminophen, 325 mg. As with hydrocodone and oxycodone, tramadol should be prescribed in pure form, allowing accurate dosage adjustment from other agents.

Tapentadol. Tapentadol is a mu opioid agonist and norepinephrine reuptake inhibitor. It is thought to control acute pain via both these pathways. Tapentadol has similar efficacy to oxycodone for the treatment of acute pain, with less frequent nausea and vomiting. Its dual mechanism of action makes it a potentially effective drug for use in chronic pain, although it has not been studied for this.

Opioid Agonist-Antagonist Analgesic Agents. The agonist-antagonist group of opioids was synthesized in an attempt to provide analgesia with little or no respiratory depression or abuse potential. It is believed that the analgesia provided by these agents is caused by agonist action at the kappa receptors, whereas the ceiling for respiratory depression is created by mu receptor antagonism. Agonist-antagonist agents have rates of abuse similar to those for standard opioids and a ceiling effect to their analgesia that limits their use. Clinical application of these drugs is typically in situations in which brief, limited analgesia is needed and respiratory depression is the principal adverse concern, such as in the perinatal period.

Nalbuphine is a commonly used agonist-antagonist. The half-life of nalbuphine is 3.5 hours, and the effects of renal or hepatic disease on metabolism are not completely known. The usual therapeutic parenteral dose is 10 mg, which has an analgesic efficacy similar to morphine, 10 mg. As with all other opioids, the dose must be individualized for the specific patient and clinical needs.

Opioid Use for Acute Abdominal Pain. Historically, pain treatment was withheld from patients with abdominal pain to avoid confounding a diagnosis. These recommendations date from the turn of the 20th century, predating modern diagnostic techniques, and have no place in modern emergency care. Multiple studies have confirmed the safety of providing effective opioid analgesia to patients with undiagnosed abdominal pain.

Nonopioid Analgesic Agents

Acetaminophen. Acetaminophen is the first-line agent for the treatment of acute and chronic pain and is the safest pharmacologic option for pain in children and adults. It has a high toxic-to-therapeutic ratio and lacks significant drug interactions compared with other pain medications.

Although acetaminophen has been in use since the 1880s, its pharmacologic mechanism of action is unknown. Acetaminophen has known analgesic and antipyretic activity, with no known peripheral antiinflammatory effects. Its activity may be due to the inhibition of prostaglandin endoperoxide H_2 synthase and a cyclooxygenase isoenzyme centrally. It may also affect the activation of beta-endorphin centrally. The analgesic actions of acetaminophen are comparable in magnitude to those of NSAIDs. The analgesic effects of the combination of acetaminophen with an NSAID are additive.

Acetaminophen is metabolized in the liver primarily through conjugation to a sulfate or glucuronide. A minor pathway for the oxidative metabolism of acetaminophen produces the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). NAPQI requires glutathione for detoxification and elimination. Hepatic toxicity can occur when glutathione pathways are overwhelmed by an increase in NAPQI or a decrease in glutathione levels. Hepatic toxicity is rare with ingestions less than 10 g in a 24-hour period, unless underlying liver disease exists or there is concomitant ethanol abuse. In the latter cases, therapeutic doses can cause clinical hepatotoxicity.

Acetaminophen is generally well tolerated when used at therapeutic doses. Mild rashes are rarely reported, as is bone marrow suppression, manifested by neutropenia, thrombocytopenia, and agranulocytosis. Its use is associated with several important drug interactions. Many anticonvulsants, including phenytoin, barbiturates, and carbamazepine, induce hepatic microsomal enzymes. Increased conversion of acetaminophen to its toxic metabolite may occur in patients who are taking anticonvulsants, but this is rarely of clinical significance in the context of the usual doses for pain management.

Although uncommon, drug interactions resulting in an increased international normalized ratio (INR) have been reported for patients taking acetaminophen and warfarin, particularly among patients taking high doses of acetaminophen (>9100 mg/week). Chronic use of acetaminophen should be avoided in patients with hepatic or renal disease. Renal failure can worsen with acetaminophen use, but the mechanism is unknown. Patients with a history of salicylate hypersensitivity characterized by urticaria have an 11% cross-reactivity to acetaminophen, and the agent should be used with caution in this group.

For mild analgesia and fever reduction, acetaminophen is the first-line agent and is a first choice for use in combination with other agents, usually opioids, in the treatment of patients with more severe pain. The recommended dose of acetaminophen for an adult is 650 to 1000 mg every 4 to 6 hours, not to exceed 4000 mg/day.

Nonsteroidal Antiinflammatory Drugs

NSAIDs inhibit cyclooxygenase (COX) and, as a result, the synthesis of prostaglandin, a key mediator of inflammation. The analgesic effect of NSAIDs is peripherally mediated by decreasing prostaglandin levels and effectively raising the threshold of activation of nociceptors. NSAIDs have synergistic effects with opioids and can reduce the amount of opioids needed to achieve pain relief.

Two COX isoenzymes mediate prostaglandin synthesis. COX-1 is present in all cells and plays an important role in homeostatic functions. COX-2 is induced by injury or inflammation and generates prostaglandins as part of the inflammatory process. Nonselective NSAIDs inhibit both COX-1 and COX-2, which results in multiple beneficial effects (eg, reduction of inflammation, pain, fever) but also some important undesirable effects.

As a group, and because of their common use, NSAIDs are responsible for more serious drug-related side effects than any other class of analgesic drugs. The major side effects of NSAID analgesic agents are GI bleeding, renal failure, anaphylaxis, and platelet dysfunction. Most of these side effects occur in patients who are taking NSAIDs for chronic conditions. It is estimated that more than 100,000 hospital admissions and approximately 16,500 deaths each year from GI bleeding are related to NSAID use for osteoarthritis and rheumatoid arthritis. One survey has estimated that for every 100,000 people taking NSAIDs, there are 300 GI-related deaths, 5 hepatic-related deaths, 4 renal-related deaths, and some congestive heart failure–related deaths.

Bone and cartilage healing and repair during NSAID use is a concern in patients with acute fractures. There is limited evidence to suggest that prostaglandins promote bone formation and that

NSAIDs might inhibit the process. This issue has not been thoroughly pursued or established through properly conducted studies. There is no human subject evidence that short-term use of NSAIDs for analgesia after fracture is deleterious to healing.

COX also promotes the production of prostacyclin, a vasodilator that increases GI mucosal perfusion. In the stomach, COX-1 increases bicarbonate and mucus production, important for protecting the mucosal lining. Inhibition of COX-1 compromises these protective functions, predisposing patients to ulcerations and bleeding, which are then exacerbated by concomitant NSAID-induced platelet dysfunction.

COX-1 and COX-2 affect the cardiovascular system through the production of endothelial prostacyclin (vasodilatory) and thromboxane (platelet aggregation). Inhibition of COX-1 causes antiplatelet activity that may be cardioprotective by inhibiting thromboxane production more than prostacyclin. Inhibition of COX-2 inhibits prostacyclin production more than thromboxane and may produce prothrombotic effects, increasing the risk of cardiovascular events. In the case of nonselective COX inhibitors, these two effects appear to balance each other out, resulting in few changes in cardiovascular risk in studies of these drugs. In the case of selective COX-2 inhibitors, this may result in an increase in cardiovascular risk and has limited the use of these agents.

Prostaglandin produced by COX-1 causes renal vasodilation that maintains renal blood flow and the glomerular filtration rate (GFR). Inhibition of COX-1, especially in volume-depleted patients, can result in a decreased GFR and acute renal insufficiency. Sodium and water retention, hypertension, hyperkalemia, and acute renal failure may also ensue, particularly in patients with congestive heart failure.

The most common adverse effect of NSAIDs is GI mucosal injury. In patients taking NSAIDs continuously for 1 year, it has been found that 10% to 60% will develop abdominal pain, dyspepsia, or nausea and 2% to 4% will develop symptomatic ulcers. Risk factors include age, concomitant use of warfarin or corticosteroids, congestive heart failure, diabetes, and coronary artery disease. There is evidence that cytoprotective agents such as misoprostol and proton pump inhibitors reduce this risk. The relative risk for GI side effects varies with various NSAIDs and treatment strategies (Table 3.5).

TABLE 3.5

Risk of Serious Gastrointestinal Effects of Nonselective Nonsteroidal Antiinflammatory Drugs (NSAIDs)

NSAID	RELATIVE RISK OF SERIOUS GI TOXICITY
COX-2 inhibitor	0.6
Ibuprofen	1.0
Diclofenac	1.8
Sulindac	2.1
Naproxen	2.2
Indomethacin	2.4
Tolmetin	3.0
Piroxicam	3.8
Ketoprofen	4.2
Ketorolac	24.7
RISK REDUCTION WHEN ADDED TO IBUPROFEN	
Proton pump inhibitor	0.09
Misoprostol	0.57

GI, Gastrointestinal.

Drug Interactions With Nonsteroidal Antiinflammatory Drugs

Aspirin. NSAIDs may impair the cardioprotective effect of aspirin, although the available evidence is unclear and the use of daily aspirin for cardiac prophylaxis should not deter the prescribing of an NSAID for acute pain or inflammation.

Oral Anticoagulants. The antiplatelet effects of NSAIDs add to the anticoagulant properties of warfarin, compounding the risk of significant bleeding complications, especially from GI ulcers. Furthermore, NSAIDs displace protein-bound warfarin and cause subsequent increases in prothrombin times at a constant warfarin dose. NSAID use is generally avoided in patients who are taking warfarin.

Angiotensin-Converting Enzyme Inhibitors. Concurrent use of NSAIDs with angiotensin-converting enzyme (ACE) inhibitors may impair renal function and impair the antihypertensive effects of ACE inhibitors.

Diuretics. Patients who are taking diuretics have a greater risk of developing renal failure due to NSAID-mediated decreased renal blood flow. Also, the natriuretic response to diuretics depends in part on prostaglandin-mediated vasodilation.

Glucocorticoids. Patients on corticosteroids have an increased risk of peptic ulcer disease. NSAIDs should generally be avoided in patients concurrently taking glucocorticoids unless closely supervised by a physician.

Lithium. NSAIDs enhance lithium reabsorption and may directly reduce lithium excretion, leading to increased lithium levels. CNS symptoms (eg, drowsiness, confusion, vertigo, convulsions, tremors), cardiac dysrhythmias, and QRS widening are warnings of lithium toxicity. The lithium dosage should be reduced when an NSAID is prescribed.

Nonselective Cyclooxygenase Inhibitor Selection.

NSAIDs combine analgesia and antiinflammatory effects with low abuse potential and many different side effects compared to opioid agents. Oral NSAIDs can be as effective as oral opioids for mild to moderate pain. Parenteral NSAIDs offer little advantage over their PO forms. Different patients respond differently to the beneficial effects and side effects of different NSAIDs. Therefore, some individual experimentation may be necessary to determine the best NSAID choice for a particular patient. No particular NSAID has been proven to be superior for any indication. Drug selection should depend on availability, side effect profile, convenience, and cost. Patients at risk for adverse events using NSAIDs are listed in Box 3.6.

Ketorolac Tromethamine. Ketorolac was the first nonopioid analgesic agent available for parenteral use in the United States. For acute pain management, ketorolac is rarely indicated in the patient able to receive oral medications, given that 60 mg of ketorolac administered IM is not clinically superior to 800 mg of oral ibuprofen. Additionally, NSAID agents can be administered at a fraction of the cost of parenteral routes. The main indication for ketorolac use is in the early treatment of renal colic (accompanied by a loading dose of IV morphine) because of the difficulty in colic patients receiving and tolerating of oral medications.

Ibuprofen. Ibuprofen is the most widely used agent in the NSAID class. It is available over the counter in a variety of preparations, including tablet, liquid suspension, and suppository forms. Ibuprofen is rapidly absorbed from the upper GI tract and has minimal interaction with other medications. The adult analgesic dose is 400 mg. No NSAID is more effective as an analgesic than ibuprofen, 400 mg, including ibuprofen, 600 and 800 mg.

BOX 3.6

Patients at Risk for Adverse Events During Nonsteroidal Antiinflammatory Drug (NSAID) Therapy

1. Patients with dehydration, hypovolemia or who have impaired renal function are at increased risk for decreasing renal function or renal failure.
2. Patients with liver disease or congestive heart failure—in particular, those already taking ACE inhibitors, ARBs, or diuretics—in whom liver or heart conditions may worsen.
3. Older patients are at enhanced risk for GI and renal events.
4. Patients with asthma and known aspirin hypersensitivity are increased risk of bronchospasm.
5. Women in the third trimester of pregnancy—NSAIDs may prolong gestation or prematurely close the ductus arteriosus.
6. Patients who use tobacco or ethanol with a history of gastritis or peptic ulcer disease are at increased risk for peptic ulcer or GI bleed.

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *GI*, gastrointestinal.

Skeletal Muscle Relaxants. Skeletal muscle relaxants have been advocated as an adjunct to analgesics in the management of musculoskeletal pain with a spasm component, principally back pain. Despite the common use of skeletal muscle relaxants, little data exist supporting their role in the treatment of pain. Studies have demonstrated that muscle relaxants, such as cyclobenzaprine, are indistinguishable from ibuprofen in analgesic effect but have an increased side effect profile.

Skeletal muscle relaxants should not be used in the treatment of acute musculoskeletal pain as a substitute for proper doses of effective analgesics unless there is a high degree of anxiety accompanying the pain. Benzodiazepines are not recommended for the routine treatment of musculoskeletal pain. In patients exhibiting a great deal of muscle spasm with anxiety, a benzodiazepine such as diazepam, 5 mg tid, or lorazepam, 1 mg bid, may be an effective therapeutic adjunct. Benzodiazepines have hypnotic, anxiolytic, antiepileptic, and antispasmodic properties. Muscle relaxation with these agents is probably due to GABA-mediated presynaptic inhibition at the spinal cord level.

Nitrous Oxide–Oxygen Mixtures. The analgesic and anesthetic properties of nitrous oxide were discovered more than 200 years ago and is one of the original forms of patient-controlled analgesia. Nitrous oxide–oxygen mixtures can be used in the ED or the out-of-hospital care setting to reduce anxiety in patients and manage mild to moderate pain states. Combined with oxygen, a mixture of nitrous oxide and oxygen in a 50:50 ratio is safe when self-administered by the patient.

Nitrous oxide and oxygen administered by nasal mask have long been used by dentists for the treatment of pain and anxiety. Experience in emergency medicine with nitrous oxide–oxygen mixtures is greatest in the ratio of a 50:50 mixture with a self-administered, hand-held mask.

The mechanism of analgesia and anxiolysis with nitrous oxide have not been fully delineated. The nature of its analgesic effect appears to be similar to that of low-dose opioids, although some of the anxiolytic effects of nitrous oxide appear to have more in common with benzodiazepines than opioids. It has been postulated that nitrous exerts an effect on GABA receptors.

Nitrous preparations are often administered in a two-tank system, with a fixed-ratio nitrous oxide–oxygen mixture delivered to the patient through a demand valve activated with inhalation through a facemask or mouthpiece. A negative pressure of 3 to 5 cm H_2O must be produced within the mask or mouthpiece to activate the flow of gas, limiting the use of these devices in very small children. Having the patient hold the mask to the face allows him or her to titrate the dose to an effective level. In 10% to 15% of patients, nitrous oxide is ineffective. It is much more potent as an anxiolytic than as an analgesic agent and can be supplemented with other analgesics.

Nitrous oxide is a folate antagonist and is strictly contraindicated in pregnant patients. Advanced scavenger systems are necessary to allow the safe use of nitrous oxide in the ED to avoid accumulation and toxicity in health care workers, especially if pregnant. Nitrous oxide–oxygen mixtures are relatively or absolutely contraindicated in patients with a decreased level of consciousness who are unable to follow instructions. Patients with severe chronic obstructive pulmonary disease who retain CO_2 should be given nitrous oxide–oxygen mixtures carefully, given that the mixture contains 50% oxygen, which may predispose to hypercapnia. Because nitrous oxide diffuses into body cavities, it can worsen a pneumothorax or bowel obstruction.

Minor side effects of nitrous analgesic gas mixtures have been reported in 5% to 50% of patients. The most common adverse effect is lightheadedness, with paresthesias and nausea reported less frequently. No documented adverse hemodynamic effects have occurred with the self-administered forms of this agent. Side effects attributed to nitrous oxide usually resolve within minutes of discontinuation.

Ketamine. Ketamine is a drug that has typically been used primarily as a dissociative anesthetic for procedural sedation; it is one of the most effective and widely used drugs for procedural anesthesia worldwide. Ketamine has also been evaluated for low-dose use as an analgesic.[39-41] Low-dose ketamine has been shown to be similar to morphine in its analgesic effect when used alone and as an additive to opioids when used in conjunction with them at doses of 0.1 to 0.3 mg/kg IV (one-tenth to one-third of a typical dose used for dissociative sedation).

The principle side effects of ketamine are dysphoria, vomiting, and hypersalivation. Ketamine appears to be effective via the *N*-methyl-D-aspartate receptor, a different pathway from opioids, acetaminophen, or NSAIDS, giving it potential to affect analgesia when other agents are limited by their adverse effects. It is likely that the use of low-dose ketamine as an analgesic will likely increase as its role and safety are further explored.

Local Anesthesia

Mechanism of Action. Peripheral nerves are responsible for transmitting pain information from pain receptors to the spinal cord. Each fiber consists of an axon surrounded by a covering called the Schwann cell. A myelinated axon is one covered by the projection of a Schwann cell that wraps itself many times around the axon; hence, the term myelin sheath.

Local anesthetics are much more effective at penetrating unmyelinated or lightly myelinated fibers than heavily myelinated ones. This difference explains the finding that local anesthetic agents provide sensory block without motor neuron effects (see Table 3.1).

Local anesthetic agents reversibly block lipid membrane sodium channels and prevent the influx of sodium ions into the axon, blocking depolarization and the nerve action potential. After injection of a local anesthetic, tissue buffers increase the pH of the solution surrounding the agent, driving much of the water-soluble acidic form to its lipid-soluble nonionic form. The lipid-soluble phase of the drug is able to penetrate the axon lipid membrane, where it then ionizes and enters the sodium channel, blocking the ability of sodium to enter the cell.

TABLE 3.6

Characteristics of Common Local Anesthetic Agents

AGENT	POTENCY (LIPID SOLUBILITY)	DURATION OF ACTION (min)	ONSET	COMMENTS
Procaine	1	60–90	Slow	Solutions of 0.5%–2% used in infiltration and blocks
Tetracaine	8	180–600	Slow	Topical for ophthalmic use
Lidocaine	3	90–200	Rapid	Most commonly used agent; 1.5 times as toxic as procaine
Mepivacaine	2.4	120–240	Very rapid	Less potent and less toxic than lidocaine
Bupivacaine	8	180–600	Intermediate	Long-acting agent used in infiltration and blocks
Etidocaine	6	180–600	Rapid	Twice as toxic as lidocaine; used mostly in epidurals

Adapted from Paris PM, Weiss LD: Narcotic analgesics: the pure agonists. In Paris PM, Stewart RD, editors: Pain management in emergency medicine, Norwalk, CT, 1988, Appleton & Lange.

Classes of Local Anesthetic Agents. Local anesthetic agents are chemical compounds that consist of an aromatic and amine group separated by an ester (eg, procaine, chloroprocaine, tetracaine) or an amide (eg, lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine) intermediate chain. Esters are unstable in solution and are metabolized in the body by the plasma enzyme cholinesterase. The amides, after absorption into the body, are destroyed by enzymes in the liver. The main considerations in the clinical use of these agents are potency, duration of anesthesia, and speed of onset (Table 3.6). The lipid solubility of an agent determines its potency. Less potent local anesthetics must be given in more concentrated forms and in larger doses to achieve an equivalent effect.

The duration of anesthetic agent action is determined by its protein-binding affinity to protein in the sodium channel. The speed of onset of any local anesthetic agent is directly related to its diffusion through tissues to the nerve, as determined by its pKa (dissociation constant)—the pH at which 50% is ionized. After injection, the anesthetic agent is in two forms, ionized and nonionized. Only the nonionized form of the drug diffuses into nerves. Therefore, solutions with a low pK_a have a more rapid onset of anesthesia.

Low tissue pH (5 or 6) in surrounding infected tissue delays the onset of local anesthesia in cases such as abscess incision and drainage by keeping more of the agent in an ionized state. The onset of action can be hastened by the alkalinization of the solution carrying the drug, which also decreases its irritant effect (pain) on injection. This can be done clinically by adding sodium bicarbonate solution to the anesthetic at a ratio determined by the pK_a of the agent. Anesthetic agents, except cocaine, are vasodilators, which tend to shorten the duration of anesthesia. Injection of the solutions into vascular tissues not only shortens the duration of anesthesia but also increases systemic absorption and the chance of systemic toxicity when larger doses are used. Therefore, epinephrine is often added to local anesthetic solutions.

Allergic Reactions. True allergies to local anesthetics are rare. When an allergy to local anesthetics is reported, the offending substance is often one of the preservatives used. Because the amide agents and amino ester agents do not cross-react and use different preservatives, a patient may be given a medication from another class if the allergy history is consistent with a specific anesthetic group. In those patients who report they are allergic to all "-caine" anesthetic agents, and the allergy is believed to be legitimate, diphenhydramine can be used as an alternate agent. Diphenhydramine may be used with 1 mL of a 50-mg/mL ampule diluted with saline to 5 or 10 mL (1%–0.5% solution) for local infiltration or nerve block. Diphenhydramine may cause direct tissue toxicity and should be avoided in areas with poor collateral circulation.

TABLE 3.7

Guidelines for Maximum Doses of Commonly Used Local Anesthesia Agents[a]

AGENT	WITHOUT EPINEPHRINE (mg/kg)	WITH EPINEPHRINE (mg/kg)
Lidocaine HCl[b]	3–5	7
Mepivacaine HCl	8	7[c]
Bupivacaine HCl[d]	1.5	3

[a]All maximum doses should be reduced 20% to 25% in very young, old, and very sick patients.
[b]A lidocaine level of 0.5 to 2.0 g/mL may be reached for every 100 mg of lidocaine infiltrated for blocks.
[c]Epinephrine adds to the potential cardiac toxicity of this drug.
[d]Not to be used for pudendal blocks or IV regional anesthesia; not recommended for children younger than 12 years.
Adapted from Stewart RD: Local anesthesia. In Paris PM, Stewart RD, editors: Pain management in emergency medicine, Norwalk, CT, 1988, Appleton & Lange.

Local and Systemic Toxicity

Local Toxicity. Local anesthetic agents, depending on the concentration, can be directly toxic to tissue. Also, it is possible that the use of a vasoconstrictor in an anesthetic solution may produce a reduction in blood flow that could increase wound healing time and vulnerability of the wound to infection. However, this concept has never been formally demonstrated.

Systemic Toxicity. Systemic toxicity of local anesthetics occurs when a sufficient quantity of the drug accumulates in the body so that sodium channel blockade occurs in the heart or brain. There is a dose-related clinical progression of local anesthetic toxicity, from subtle neurologic symptoms to seizures to cardiovascular collapse.

All local anesthetics produce systemic toxicity at a sufficiently high blood or CNS concentration. Each local anesthetic has a range of therapeutic safety beyond which systemic toxicity is more likely to occur (Table 3.7). Overdosage of local anesthetics may occur more commonly in patients with large wounds and in patients with a low body mass index.

The more lipophilic anesthetic agents (eg, etidocaine, bupivacaine) are more cardiotoxic. Cardiac toxicity may also occur if epinephrine-containing anesthetics are inadvertently injected intravenously. Special care should be exercised in children and

when performing blocks known to produce high blood levels of the anesthetic agent (eg, intercostal). In pediatric patients, the maximum agent dose should be calculated before administration.

A wide variety of symptoms may be experienced from local anesthetic toxicity. These include lightheadedness, headache, tinnitus, paresthesias, muscle spasm, and confusion. In addition, benzocaine has been associated with methemoglobinemia. The degree to which CNS symptoms are experienced is directly related to the blood level of the local anesthetic.

CNS toxicity from anesthetic agents may result in seizures. A typical clinical progression usually begins with circumoral paresthesias, dysarthria, and a report of tinnitus or similar auditory phenomenon. These events may be followed by a decreased level of consciousness progressing to confusion, seizures, and coma. Longer acting, more potent agents (eg, bupivacaine, etidocaine) are more likely than lidocaine to cause CNS symptoms at lower blood levels. Local anesthetic-induced seizures should be treated with IV benzodiazepines and may be refractory to normal dosing of neuroleptic medications.

Local anesthetic agents also have direct effects on cardiac automaticity, conductivity, contractility, and vascular tone. Management of cardiovascular collapse caused by toxic levels of local anesthetic agents should follow standard advanced cardiac life support guidelines. Unless the overdose is massive, the toxicity should be relatively short-lived, given the redistribution of the lipophilic agents.

Reducing the Pain of Local Anesthetic Injection. Many techniques can be used to reduce the pain of anesthetic injection (Box 3.7). Distraction by manual methods such as scratching, jiggling, or repetitively pinching the skin during needle puncture or injection reduces the discomfort experienced during local anesthetic injection. Injecting the agent slowly is the principle method to reduce injection pain. Injection into the edges of a wound is less painful than injection through intact skin. Warming the anesthetic and the application of a topical anesthetic agent can also decrease the initial sensation associated with needle injection.

The addition of sodium bicarbonate to lidocaine prior to injection reduces anesthetic injection pain. A standard solution of sodium bicarbonate (8.4% in 50 mL) can be added to a syringe containing lidocaine in a ratio of 1:10 (eg, 1 mL bicarbonate to 10 mL lidocaine, or 0.5 mL to 5 mL). Buffered lidocaine can be stocked in the ED and is effective for up to 1 week.

Topical Anesthesia

Topical anesthetics are generally of two types, those that can be applied to intact skin and those used on open skin. Topical agents are particularly useful in pediatric patients intimidated by needles. These agents may help decrease the intensity of superficial stimuli. The long application time and limited analgesia are the principal drawbacks for these strategies. In some patients, however, the strategy of applying the topical anesthetic and delaying the procedure until there will be less pain can be an effective tool in controlling pain and the response to subsequent interventions.

BOX 3.7

Techniques to Reduce the Pain of Injection

- Buffering of local anesthetic agents
- Counterirritation
- Slower rate of injection
- Use of topical anesthetics
- Warming of solution
- Distraction techniques

Topical Anesthetics Applied to Intact Skin

Eutectic Mixture of Local Anesthetics. A eutectic mixture of local anesthetics (EMLA) is a mixture of lidocaine and prilocaine in an alkaline oil mixture in which the anesthetics are primarily in their nonionized form. This format allows diffusion through intact skin. The term eutectic refers to mixtures that result in a melting point higher than that of either agent alone.

For clinical use, an EMLA mixture should be applied to the desired area with an occlusive dressing 30 to 60 minutes before the procedure is performed. Heating EMLA for 20 minutes improves analgesia but is less effective than a routine 60-minute application, with or without heat. The duration of action after a 60-minute application is 1 to 5 hours.

Indications for the use of EMLA include venipuncture, arterial puncture, lumbar puncture, or arthrocentesis when a 30- to 60-minute delay in performing the procedure is not an impediment. EMLA can be applied in triage, particularly for pediatric patients, with an IV started later in the ED with little or no pain.

Ethyl Chloride and Fluoromethane Sprays. Ethyl chloride and fluoromethane sprays are occasionally used for superficial analgesia. The agents evaporate quickly and cool the skin, providing brief (<1-minute) local anesthesia due to the sensation. The induced analgesia is brief. Any injection or incision should be made immediately after the application of the agent.

Agents Applied to Mucosal Surfaces

Cocaine. Cocaine is unique among local anesthetic agents given that it is a potent vasoconstrictor in addition to being an anesthetic that can be applied to mucosal surfaces. Cocaine is frequently used in the nose, for which a 4% (40 mg/mL) solution provides rapid anesthesia for the treatment of epistaxis and other nasal procedures. Although the maximum safe dose is unknown, no more than 200 mg is typically applied in adults. Cocaine should not be used in patients with known coronary artery disease due to the potential for coronary artery vasoconstriction.

Lidocaine. Both 2% and 4% lidocaine solutions are available in a viscous matrix for use on mucosal surfaces. Gel lidocaine can be used in nasal procedures, including the passing of nasogastric tubes and gastric lavage tubes. It can also be used for urethral anesthesia during Foley catheter placement. To be effective, lidocaine gel preparations must be injected into the urethra with a catheter tip syringe and be in contact with the area for 5 to 20 minutes. Lidocaine spray (4% or 10%) is useful for upper airway anesthesia, including intranasal use for nasogastric tube insertion.

Tetracaine. Tetracaine is a potent ester used for surface anesthesia of the cornea. Tetracaine stings when placed in the eye, but only for 10 to 15 seconds, after which there is excellent corneal anesthesia.

Benzocaine. Almost insoluble in water, benzocaine remains on mucous membranes in the mouth and is commonly used to provide superficial analgesia for oral procedures and pain.

Agents Applied to Open Skin: Lidocaine, Epinephrine and Tetracaine. The combination of lidocaine, epinephrine, and tetracaine, 5 to 10 mL, may be applied to an open wound using sterile cotton, which is then covered and held in place for 10 to 20 minutes. Anesthesia has been described in approximately 85% of cases of wounds of the scalp and face and a lower percentage of extremity wounds. Application of the solution to mucous membranes (eye, intranasal) can result in toxic blood levels of tetracaine and should be avoided.

Nonpharmacologic Interventions

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) systems use electrical stimulation to induce analgesia, likely through the activation of descending sensory pathways and modulation of nociceptive signals at the level of the spinal cord (Figs. 3.5 and 3.6). TENS units include a pulse generator, amplifier, and electrodes. Studies have demonstrated varying degrees of effectiveness. These devices are rarely indicated for use in the ED.

Hypnosis

The induction of hypnosis allows patients to refocus attention away from pain and anxiety-producing stimuli to other images and feelings. Hypnosis can be used as an adjunct to pharmacologic interventions or as a substitute. Hypnosis can be induced with only brief interventions on the part of the health care provider. Hypnosis is usually not practical in the ED due to time constraints and distracting ambient noise.

Out-of-Hospital Analgesia

Out-of-hospital providers frequently encounter patients with painful conditions. Patients obtain pain relief more quickly when pain medications are initiated by out-of-hospital personnel, although pain control in this setting is challenging to perform adequately.

The out-of-hospital environment is less controlled than the ED, and information regarding a patient's underlying condition is more limited, making the safe administration of pain medications more difficult. As in the ED, establishing rapport with the patient, providing calm reassurance, and using careful movement and handling, including proper splinting, are the first steps to which pharmacologic support can be added. Pain can be assessed in the out-of-hospital setting using numeric and verbal rating scales, the same as would occur in the ED.

Protocols for the administration of fentanyl and morphine are available in most emergency medical services systems and are usually limited to single-dose therapy prior to obtaining orders from the medical control physician. Morphine, 0.1 mg/kg, is safe for out-of-hospital use and should be considered the first-line agent for severe pain, as it is in the ED. There is no difference in the relative value of using fentanyl or morphine as the initial agent for prehospital pain treatment.

OUTCOMES: TREATMENT ENDPOINTS

Pain is a subjective experience. In the ED, management of acute pain should specify an initial dose, with a repeat dose and interval determined through a specific desired endpoint, such as pain reduction measured by a standardized assessment tool (see Fig. 3.7). A reasonable endpoint is to achieve sufficient pain relief for the patient to be able to doze or carry on a normal conversation with providers or family members.

KEY CONCEPTS

- Acute pain is an urgent condition for the patient. Pain should be rapidly assessed, treated, and frequently reassessed in tandem with diagnostic evaluations (see Fig. 3.7).
- Therapy for acute pain is different than for chronic pain (see Box 3.3). Chronic pain treatment should be undertaken in consultation with the provider(s) responsible for the patient's long- term management. In general, opioid analgesic agents should not be administered in the ED or prescribed for outpatient therapy for chronic pain patients unless the plan is agreed to by the responsible outpatient provider.
- Titrated IV opioid analgesics are the principal therapeutic approach for the treatment of moderate and severe acute pain. When intravenous access is not indicated or attainable, SC administration is preferable to the IM route (see Box 3.5).
- Oral oxycodone, with an onset of action similar to that of IM or SC opioids, can be used for moderate pain when the IV route is not otherwise needed. Oxycodone and other oral opioids should be administered and prescribed as a single-drug preparation, not as part of a combination.
- Ambulatory treatment with opioids should be confined to the period of acute pain. Most opioid prescriptions from the ED for acute injury (eg, burr, fracture) should be for 3 to 5 days, after which the patient is transitioned to nonopioid analgesia or reevaluated by an outpatient provider.
- Acetaminophen and NSAIDs should be added to pain therapy, when not contraindicated. Their analgesic effects are additive to those of opioids and to each other.
- Morphine, fentanyl, and hydromorphone are the preferred parenteral opioid agents in the ED. Meperidine should not be used.
- There is no evidence to support the concept that diagnosis based on physical examination findings will be impaired by the administration of opioid pain medications to achieve reasonable patient comfort.
- There is no validity to the belief that morphine causes more smooth muscle spasm than other opioids. Morphine is safe and appropriate for patients with acute biliary or renal colic.
- Patients who are known to be diverting or abusing opioids should not be prescribed opioids for use as outpatients. Patients with chronic pain syndromes, or those with chronic conditions that may cause acute pain (eg, dental caries), should be offered alternative pain management options, and opioids generally should be avoided.
- Topical and local anesthetics can be used to treat pain associated with most ED procedures and should be considered for use in isolated painful conditions.
- Low tissue pH (5 or 6) in infected tissue impairs the effectiveness of local anesthesia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 3: QUESTIONS & ANSWERS

3.1. Which of the following statements is true regarding pain transmission?

A. Cardiac pain is transmitted via the sympathetic system.
B. Central poststroke neuropathic pain is associated with parietal infarcts.
C. Descending modulation of pain is mediated primarily through γ-aminobutyric acid (GABA).
D. Peripheral neurotransmitters include prostaglandins, histamines, and substance P.
E. The dorsal columns play no role in pain transmission.

Answer: A. As a general rule, all visceral pain is carried via sympathetic afferents to ganglia and then to the spinal cord. Prostaglandins, substance P, and histamine sensitize peripheral afferents but are not neurotransmitters. The dorsal column tracts can down-modulate ascending pain signals. Central poststroke pain is clinically seen most often after thalamic strokes. Descending tracts that modulate pain processing at the dorsal horn use norepinephrine and serotonin, with the effect of the former being most important regarding analgesia.

3.2. Which of the following analgesics is matched with the correct feature?

A. Fentanyl—prolonged QT interval on electrocardiography
B. Hydromorphone—active metabolites
C. Meperidine—muscle rigidity
D. Oxycodone—serotonin syndrome
E. Propoxyphene—anticholinergic toxicity

Answer: D. Oxycodone has been associated with serotonin syndrome when coadministered with selective serotonin reuptake inhibitor (SSRI) medications. The following are the other correct associations:

Meperidine—anticholinergic toxicity, active metabolites
Propoxyphene—prolonged QT interval on electrocardiography
Fentanyl—muscle rigidity (chest wall)
Hydromorphone—inactive metabolite

3.3. A 32-year-old male patient undergoing treatment for an ankle sprain returns to the emergency department (ED) because of inadequate pain relief from the medicines he was prescribed. He is currently taking oxycodone, 10 mg PO every 4 hours, and ibuprofen, 400 mg every 4 hours. What is the next most appropriate medicine to add to his pain treatment regimen?

A. Add acetaminophen, 650 mg q4h.
B. Add tramadol, 50 mg PO q4h.
C. Increase ibuprofen to 800 mg.
D. Increase oxycodone to 15 mg.
E. Replace oxycodone with hydrocodone, 15 mg PO q4h.

Answer: A. Acetaminophen provides additive analgesia to nonsteroidal antiinflammatory drugs (NSAIDs) and opioids, with few adverse effects at low doses, and it should be incorporated in acute pain treatment when not contraindicated. The pain-relieving effects of ibuprofen have not been shown to be greater when 800 mg is used versus 400 mg, so increasing the dose of ibuprofen is unlikely to improve pain relief and will increase the risk of adverse effects of the NSAIDs. An increased dose of oxycodone would result in improved pain relief but increases the risk of adverse effects; it should be tried after other nonopioid treatments have failed. In this case, acetaminophen should be attempted first before increasing the oxycodone dose. Tramadol may improve pain relief and would be additive to the opioid effect of the oxycodone but would not be indicated before acetaminophen because of its high rate of dizziness and nausea. The pain-relieving effects of opioids at equianalgesic doses usually do not vary among individuals, and switching from an equivalent dose of one opioid to another is unlikely to improve pain treatment. Changing to hydrocodone, therefore, would be unlikely to decrease the patient's pain.

CHAPTER 4

Procedural Sedation and Analgesia

Steven A. Godwin

PRINCIPLES

Background

The performance of diagnostic and therapeutic procedures is common in emergency care. Many of these interventions are often associated with significant pain and anxiety. Procedural sedation and analgesia (PSA) is a fundamental and required skill for emergency clinicians and an integral part of the core training of emergency medicine residents.[1,2] Although increased emotional stress is most evident in children, patients of all ages require dedicated management of pain and anxiety in the emergency department (ED).[1,3] This chapter will focus primarily on PSA in the adult population; Chapter 162 will provide specific guidance for PSA for children.

PSA improves the quality of patient care and satisfaction through the relief of pain and anxiety and by facilitating timely and successful therapeutic or diagnostic procedures.[4-12] These include fracture or joint reduction, incision and drainage of abscesses, cardioversion, tube thoracostomy, lumbar puncture, complex wound repair, and imaging studies in uncooperative patients.

Many of the agents used for PSA have the potential to cause significant respiratory, cardiovascular, or central nervous system (CNS) depression. The Joint Commission (TJC), Centers for Medicare and Medicaid Services (CMS), American College of Emergency Physicians (ACEP), and American Society of Anesthesiologists (ASA) have produced expert consensus and evidence-based guidelines concerning the use of PSA[1,13,14] (Box 4.1). Although controversy continues about credentialing and oversight of PSA outside the operating room at some individual institutions, the advent of these guidelines has led to PSA becoming a common ED procedure. The adoption of PSA as a standard procedure in the ED has been further enhanced by the availability of shorter acting, more effective drugs and noninvasive monitoring devices.

With the wide variety of patient populations and procedural needs, the ability to individualize PSA for each unique situation is a necessary skill. This can be best achieved through a detailed understanding of the preprocedural patient assessment, protocols delineating the required personnel and their roles, supplies and equipment required, specific drugs used (including their routes of administration, dosages, effects, interactions, and complications), consideration for special populations, and patient monitoring, recovery, and discharge criteria.

Terminology

The following terms are important for understanding the concepts presented in this chapter:

Anxiolysis is a state of decreased apprehension concerning a particular situation in which the patient's level of awareness does not change. Analgesia refers to the relief of pain without the intentional alteration of mental status, such as occurs in sedation. An altered mental state may be a secondary effect of the medications administered for this purpose.

Dissociation is a trancelike cataleptic state induced by an agent such as ketamine and characterized by a profound analgesia and amnesia. Protective reflexes, spontaneous respirations, and cardiopulmonary stability are retained. Sedation is a controlled reduction of environmental awareness.

Procedural sedation and analgesia is a technique of administering a sedative or dissociative agent, usually along with an analgesic, to induce a state that allows the patient to tolerate painful procedures while maintaining adequate spontaneous cardiorespiratory function. It is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently and continuously. The drugs, doses, and techniques used are not likely to produce a loss of the protective airway reflexes.

In 2001, TJC adopted the ASA definition of sedation and analgesia that was created to describe the continuum of sedation and analgesia better (Fig. 4.1). Although this actually is a continuum, the ASA has divided PSA into four distinct subgroups—minimal sedation, moderate sedation, deep sedation, and general anesthesia. A fifth category, dissociative sedation, has since been added[15] (Table 4.1). This new nomenclature is more intuitive, clear, and logical.

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive functions and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate sedation and analgesia (formerly called conscious sedation) refers to a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, alone or accompanied by light tactile stimulation. Reflex withdrawal from the painful stimulus is not considered a purposeful response. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is always maintained.

Dissociative sedation is a trancelike cataleptic state induced by the dissociative agent ketamine; it is characterized by profound analgesia and amnesia while protective airway reflexes, spontaneous respirations, and cardiopulmonary stability are maintained.

Deep sedation and analgesia describes a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to maintain ventilatory function independently may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even with painful stimulation. The ability to maintain ventilatory function independently is often impaired. Patients often require assistance in

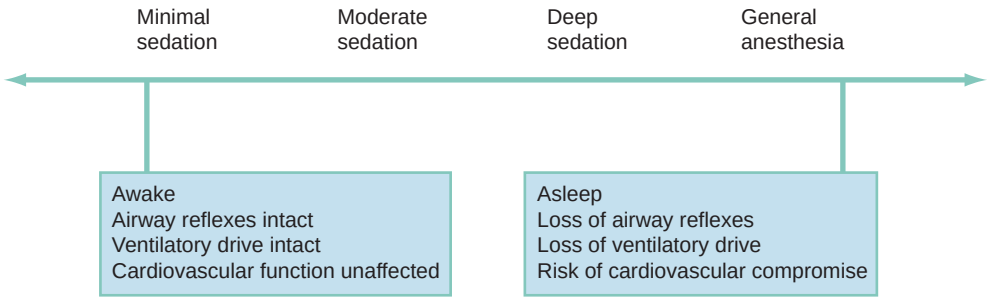

Fig. 4.1. Schematic representation of the sedation continuum. As increasing doses of nondissociative agents are given, patients move along the sedation continuum, experiencing a progressive decline in their level of consciousness and an increased risk of adverse respiratory and cardiovascular events. If medication administration continues, the patient will ultimately reach a state of general anesthesia, with loss of protective airway reflexes and ventilatory drive. The transition from one level of sedation to the next is often difficult to predict and varies from patient to patient.

TABLE 4.1

Definition of Levels of Sedation and Analgesia

PARAMETER	MINIMAL SEDATION (ANXIOLYSIS)	MODERATE SEDATION AND ANALGESIA (CONSCIOUS SEDATION)	DEEP SEDATION AND ANALGESIA	DISSOCIATIVE SEDATION	GENERAL ANESTHESIA
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response to repeated or painful stimulation	Unarousable, even with painful stimulus	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Adequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	Elevated	May be impaired

BOX 4.1

American College of Emergency Physicians Policy Statement on Sedation in the Emergency Department[a]

The American College of Emergency Physicians recommends the following:

- Emergency clinicians who have received the appropriate training and skills necessary to safely provide procedural sedation should be eligible for credentialing in all levels of procedural sedation.
- The decision to provide sedation and selection of the specific pharmacologic agents should be individualized for each patient by the emergency clinician and should not be otherwise restricted.
- Emergency clinicians and staff are expected to be familiar with the pharmaceutical agents they use and be prepared to manage their potential complications.
- To minimize complications, the appropriate drugs and dosages must be chosen and administered in an appropriately monitored setting, and a patient evaluation should be performed before, during, and after their use.
- Institutional and departmental guidelines related to the sedation of patients should include credentialing and verification of competency of providers, selection and preparation of patients, informed consent, equipment and monitoring requirements, staff training and competency verification, criteria for discharge, and continuous quality improvement.

[a]January 2011.
Adapted from American Society of Anesthesiologists Committee: Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology 114:495–511, 2011.

maintaining a patent airway, and positive-pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

The progression from minimal sedation to general anesthesia is a dynamic continuum that lacks distinct separation between stages. The transition from one level of sedation to the next is often difficult to predict and varies from patient to patient. The sedation continuum is not drug-specific, and levels from mild sedation to general anesthesia can be achieved with virtually all the PSA agents. Because of this, it is recommended that emergency clinicians administering PSA be competent in the skills required to treat patients who are in at least one level greater than the intended level of sedation.

Management

Decision Making

The approach to undertaking procedural sedation requires a diligent evaluation of a patient's specific conditions, which may

TABLE 4.2

American Society of Anesthesiologists Physical Status Classification

CLASS	DESCRIPTION	EXAMPLES	SEDATION RISK
I	Normal, healthy patient	No past medical history	Minimal
II	Mild systemic disease without functional limitations	Mild asthma, controlled diabetes	Low
III	Severe systemic disease with functional limitations	Pneumonia, poorly controlled seizure disorder	Intermediate
IV	Severe systemic disease that is a constant threat to life	Advanced cardiac disease, renal failure, sepsis	High
V	Moribund patient who may not survive without procedure	Septic shock, severe trauma	Extremely high

enhance or impede the effectiveness of procedural sedation. These factors include patient assessment, including the consideration of preprocedural fasting, need for appropriate personnel, supplies, and equipment, patient monitoring, and postprocedural recovery.

Patient Assessment. Although no outcome-based studies have demonstrated a clear benefit from presedation evaluation beyond vital signs, mental status, and airway and cardiopulmonary assessment, consensus guidelines have suggested that there may be an increased risk of adverse events in select subsets of patients. These include patients at the extremes of age, patients with difficult facial or neck anatomy or any other reason for potential intubation or bag-valve-mask ventilation difficulty, and patients with underlying significant disease states. A patient's general physical status is conventionally categorized according to the ASA's classification system (Table 4.2).[16] Most practice guidelines require that a history and focused physical examination be performed and documented before PSA. There have been no studies to support the need for routine diagnostic testing other than diagnostic testing driven by the patient's current status, including comorbidities.

The patient's age, current illness, or injury for which PSA is intended, underlying medical problems (eg, comorbidities), previous experiences or problems with PSA or general anesthesia, drug allergies and current medications, and tobacco, drug, and alcohol use are reviewed and recorded. A directed physical examination focuses on the vital signs, heart and lungs, and evaluation of the airway for potential difficulty providing bag-valve-mask ventilation or intubation.

A discussion including the risks, benefits, and potential side effects of PSA should be held with patients or their families before the procedure. Written consent is preferred, unless this is not possible due to issues related to the patient's clinical condition or access to the patient's medical surrogate. Not every patient is an appropriate candidate for PSA in the ED. Therefore, patient selection is important to the safety of the sedation. Depending on the clinical circumstances, a patient with an anticipated difficult airway or ASA classification of III or IV may require support of additional clinical resources. These resources can include additional nursing support or additional providers with expertise in procedural sedation, including emergency clinicians and/or anesthesiologist. At times, it may even be advisable to undertake the procedure under more controlled circumstances in the operating room with anesthesia.

Preprocedural Fasting. Evidence supporting the practice of preprocedural fasting in PSA has been extrapolated from patient populations undergoing general anesthesia. To date, there have been no published outcome-based studies demonstrating an increased risk of aspiration after a liquid or solid meal and no studies showing a benefit of fasting before PSA.[17-20] Despite the absence of literature to support this practice and its inevitable negative impact on timeliness of patient care and diagnosis, disagreement still exists as to how these societal guidelines are implemented at individual centers.[18]

Currently, for healthy patients undergoing elective procedures, the ASA recommends a period of 2 hours after ingestion of clear liquids, 4 hours after ingestion of breast milk, and 6 hours after ingestion of other liquids (eg, infant formula, nonhuman milk) or solids before PSA. Importantly, emergent sedations are noted as an exclusion from the fasting requirements within the framework of these same guidelines.[13] The extrapolated data from studies describing cases in which patients received sedation to the level of general anesthesia, followed by the manipulation of the airway during intubation and extubation, are not generalizable to the ED setting. PSA in the ED attempts to avoid both these specific situations.

In 2013, ACEP endorsed a level B recommendation—defined by the level of graded evidence equating to a moderate degree of certainly—regarding preprocedural fasting stating. It stated that providers should not delay procedural sedation in adult or pediatric patients in the ED based on fasting time. The recommendation further noted that preprocedural fasting for any duration has not demonstrated a reduction in the risk of emesis or aspiration during procedural sedation and analgesia.[1] Food intake should therefore not be considered a contraindication for administering PSA in the ED. Providers should consider the unique clinical and physiologic circumstances of each individual patient to identify challenges specific to that patient's needs.

Personnel. TJC and most institutional policies have suggested that PSA providers should have adequate training to administer the agents effectively and safely. This includes the skill to assess risk, dose, and administration of medications appropriately, monitor the patient's response to the medications given, and manage all potential complications.[1,8,21-24] This generally implies that PSA in the ED should be supervised by an emergency clinician or other appropriately trained and credentialed physician. It is also recommended that a qualified support person (eg, nurse, respiratory therapist) be present for continuous monitoring of the patient. Such a support person should focus on the patient's status and not take part in the procedure. He or she should also be able to recognize and respond to the complications of PSA. Although it is acceptable that they may also assist with minor interruptible tasks, they should have no other primary responsibilities that would interfere with the monitoring and documentation appropriate for the planned level of sedation from the start of the procedure to completion of the recovery phase.

Supplies and Equipment. PSA may result in an allergic reaction, oversedation, respiratory depression or, rarely, cardiopulmonary arrest. The incidence of these complications depends on patient selection, drugs used, rate and dosage of administration, and specific patient sensitivities. Consequently, appropriate equipment to monitor the patient's condition at all times, manage

BOX 4.2

Equipment for Procedural Sedation and Analgesia

- High-flow oxygen source
- Suction
- Airway management equipment
- Monitoring equipment
  - Pulse oximeter
  - ECG monitor, defibrillator, transcutaneous pacemaker
  - Blood pressure monitor
  - Capnography[a]
- Vascular access equipment
- Reversal agents
- Resuscitation drugs
- Adequate staff

[a]Capnography carries a level B recommendation by the American College of Emergency Physicians for use as an adjunct to pulse oximetry and clinical assessment to detect hypoventilation and apnea earlier than pulse oximetry and/or clinical assessment alone in patients undergoing procedural sedation and analgesia in the ED. It is also recommended by the American Society of Anesthesiologists for monitoring the presence of exhaled carbon dioxide during moderate or deep sedation, in addition to the continual observation of qualitative clinical signs of adequate ventilation.
ECG, Electrocardiogram.

airway complications, allergic reactions, and drug overdoses, and treat respiratory or cardiopulmonary arrest should be readily available. Supportive equipment includes oxygen, suction, patient-monitoring devices, basic and advanced airway management equipment, a monitor and defibrillator, advanced life support medications, reversal or rescue agents, and vascular access equipment (Box 4.2).

In most situations, the agents used for PSA in adult patients should be administered via the intravenous (IV) route. Nearly all adults undergoing PSA in the ED should therefore have an IV line placed before the procedure. This need in children is less clear and depends on the presence of comorbid conditions and choice and route of drug to be administered. In children, if the procedure is likely to be lengthy, or if multiple doses of drugs will be needed, an IV line should be strongly considered.

The requirement for supplemental oxygen, and its benefits during PSA, have not been well studied and remain somewhat unclear.[25] Supplemental oxygen may prevent hypoxemia in many patients; however, significant respiratory depression in these patients may not be detected because of their normal oxygen saturation. This may delay the recognition of respiratory compromise and hypercarbia when capnography is not used. On the other hand, transient hypercarbia is not harmful, and maintenance of adequate oxygen saturation is much more important. The use of capnography eliminates this issue, because ventilatory status is displayed continuously. I therefore recommend that supplemental oxygen be used while administering PSA to a patient in the ED.

Monitoring Devices and Techniques. The most important aspect of monitoring during PSA is the visual observation and assessment of the patient. The patient's ability to follow commands in response to varied levels of stimulation is useful in quantifying the level of consciousness. Furthermore, the patient's ventilatory rate may be readily assessed by direct observation, although depth of respiration or tidal volume is actually much harder to estimate clinically. Other components of monitoring, which should be documented, include determination of respiratory rate, heart rate, blood pressure, oxygen saturation, and cardiac rhythm and capnometry.[26-28] Pulse oximetry is a reliable and important monitoring modality, used in conjunction with close and continuous observation of the patient and his or her response to medications and procedures.

Although there is no outcome-based evidence that cardiac monitoring during PSA is of any benefit, it certainly is not harmful, is routinely available, and may be beneficial in certain cases. I recommend continuous electrocardiographic monitoring in older patients and in patients with a history of cardiovascular disease, hypertension, or dysrhythmia. In young healthy patients, without underlying significant disease, this may be safely replaced by continuous pulse oximetry, which also displays the heart rate but, in most cases, monitors capable of showing heart rate, blood pressure, and pulse oximetry will also easily facilitate cardiac rhythm monitoring.

Capnometry or capnography measures end-tidal carbon dioxide (CO_2) partial pressure and has been shown to detect cases of inadequate ventilation earlier than clinical assessment or detection of hypoxemia by oximetry.[29-33] Evidence has demonstrated that the use of capnography can significantly reduce hypoxemic events during procedures.[31] In July 2011, the ASA updated its procedural sedation standards to include capnography during moderate or deep sedation to evaluate the adequacy of ventilation in addition to continual observation of qualitative clinical signs.[34,35] In 2014, ACEP endorsed a level B recommendation that capnography may be used as an adjunct to pulse oximetry and clinical assessment to detect hypoventilation and apnea earlier than pulse oximetry and/or clinical assessment alone in patients undergoing procedural sedation and analgesia in the ED.[1]

We recommend that continuous capnography be used when deep sedation is planned, because respiratory depression is common in patients undergoing deep sedation. Although optional when only light sedation is planned, capnography may enhance patient safety by allowing the observer to recognize unintended oversedation and depression of respiratory rate or volume more rapidly.

The bispectral index (BIS) is monitored via a noninvasive device attached to the patient's forehead and determines the depth of sedation level via frontal lobe electroencephalographic measurements. It has been used in the operating room as an objective measure of sedation depth. Studies have hypothesized that its use may be beneficial in preventing oversedation in PSA and reducing the time to discharge. Early ED studies for its use in PSA to discriminate between mild to moderate and moderate to deep levels of sedation have not demonstrated a reliable advantage, nor has it been shown to be predictive of patients sedated to the point of general anesthesia as differentiated from those with lesser degrees of sedation. BIS monitoring has yet to demonstrate a beneficial role for emergency medicine use for routine PSA monitoring. Future studies, combined with advancement of current technology, may better define its potential role.

When transporting patients outside the ED for diagnostic procedures requiring PSA, every attempt should be made to provide the same level of monitoring during the transport and procedure as would be used within the department.

The highest risk of serious adverse events generally occurs within 5 to 20 minutes of receiving the last dose of IV medication and at the completion of procedures, when the patient remains sedated but is no longer receiving the painful stimulus. Similarly, patients undergoing prolonged procedures in which deeper sedation is desired to reduce motion (eg, magnetic resonance imaging [MRI]) are also at an increased risk. Patients should continue to be monitored closely at these times, and this should continue until clinical recovery has occurred.

Recovery. Monitoring as part of the PSA routine should continue until patients are spontaneously awake and able to function independently. Drowsy patients should not be left unattended, and appropriate measures to prevent falls should be taken.

Postprocedure Recovery and Discharge. Before discharge, baseline cognitive and motor functions should be achieved. The patient should be able to follow commands, speak clearly, and ambulate or sit unassisted (infants and children). Vital signs and respiratory status should be back to baseline and within normal limits. Residual pain should be addressed. Nausea should be minimal, and vomiting should be resolved. It is preferable that all patients, including adults, be sent home with a responsible adult but, if this is not possible, the patient should remain in the ED until a normal baseline has been achieved.[36,37]

Patients should be advised not to drive or participate in other dangerous activities for 12 to 24 hours. Despite the short clinical duration of most of the agents used, some patients may exhibit subtle signs of cognitive deficits and mild drowsiness. It is therefore preferable that they remain in the company of a responsible adult at home for 4 to 8 hours. For children, light play at home should be the extent of activities, with no bicycle riding, swimming, or other complex motor activity until the next day. An antiemetic and progressive diet is helpful if nausea or vomiting is experienced. Standard discharge instructions should also be provided for the presenting complaint, and all patients should be instructed to immediately return if any confusion or respiratory symptoms arise.

Pharmacologic Therapy

In selecting agents, consideration is given to the effects desired, risks and benefits, and logistics of administration for each situation. Unfortunately, the ideal agent does not exist. It would need to provide analgesia, anxiolysis, amnesia, and somnolence. It would have a rapid onset and offset, with predictable results, and would have no adverse effects.

The provider should have a clear understanding of the purpose and priorities of PSA so she or he can relate it to the procedure being performed. When the procedure is unpleasant but not painful (eg, endoscopy), pure sedation may be the desired endpoint, and agents such as benzodiazepines, barbiturates, etomidate, or propofol are sometimes used alone. These agents do not provide pain relief and should not be used as the sole agent when pain management is also desired. Analgesic agents such as opioids or nitrous oxide are often added to a sedative agent to provide analgesia for painful procedures. In contrast, ketamine, as a dissociative agent, may be an excellent single drug choice for painful or stimulating procedures in children and for some adult applications (eg, fracture reduction). Usually, a combination of analgesic and sedative agents is required. Caution is indicated, however, because their side effects are frequently potentiated.

The specific agents for PSA and dosage recommendations for adult patients are provided in Table 4.3. Their benefits and adverse effects are provided in Table 4.4. Individual agents are discussed in greater detail in the following sections.

Routes of Administration. The decision regarding the optimal route of administration should be determined by the procedure and requirements of the specific patient. In general, IV titration to the desired level of sedation and analgesia produces the most rapid, safest, and predictable results. Drugs given by the intramuscular (IM), oral, transmucosal, intranasal, or rectal route generally have a slower onset of action, are difficult to titrate, have unpredictable results, and may lead to prolonged sedation. These routes are rarely used for PSA in adults. In pediatric patients, however, the benefits of IV drug administration may be outweighed by the difficulty and distress to the patient in obtaining IV access. In this situation, drugs given by the alternative routes may be preferred (see Chapter 162). For example, ketamine has been shown to provide consistent and predictable results in children when given IM.[8,38] The use of nitrous oxide is limited to pediatric patients and special circumstances and is not fully

TABLE 4.3

Procedural Sedation and Analgesia Agents—Recommended Adult Starting Doses

AGENT	CLASS	MAIN EFFECT	ROUTE OF ADMINISTRATION	USUAL STARTING DOSE
Fentanyl	Opioid	Analgesia	Intravenous	1 μg/kg
Morphine	Opioid	Analgesia	Intravenous	0.1 mg/kg
Midazolam	Benzodiazepine	Sedation, amnesia	Intravenous	0.05 mg/kg
Methohexital	Barbiturate	Sedation, amnesia	Intravenous	1 mg/kg
Pentobarbital	Barbiturate	Sedation	Intravenous	2 mg/kg
		Amnesia	Intramuscular	4 mg/kg
Ketamine	Phencyclidine derivative	Dissociation, analgesia, sedation, amnesia	Intravenous Intramuscular	1–2 mg/kg 4.5 mg/kg
Etomidate	Imidazole derivative	Sedation, amnesia	Intravenous	0.1 mg/kg
Propofol	Alkylphenol derivative	Sedation, amnesia, antiemetic	Intravenous	0.5 mg/kg
Ketofol	Ketamine-propofol combination	Sedation, dissociation, amnesia, analgesia	Intravenous	Ketamine-propofol—1:1 mixture Initial dose of 0.075 mL/kg given as 0.75 mg/kg over 15–30 s; then repeat if needed at half-dose with 0.375 mg/kg after 1–3 min to achieve desired sedation
Alfentanil	Opioid analogue	Analgesia	Intravenous	3–8 μg/kg over 3 min, then 3 μg/kg q5–20 min
Remifentanil	Semisynthetic mu opioid receptor	Analgesia	Intravenous	0.1–0.15 μg/kg/min infusion Supplemental boluses: 1–2-μg/kg increments
Dexmedetomidine	α_2-Adrenergic agonist	Analgesia, sedation	Intravenous	1 μg/kg over 10 min, then 0.2–0.7 μg/kg/h

TABLE 4.4

Procedural Sedation and Analgesia Agents—Benefits and Adverse Effects

AGENT	ROUTE(S) OF ADMINISTRATION	ONSET (min)	DURATION (min)	ADVANTAGES	ADVERSE EFFECTS
Fentanyl	Intravenous, transmucosal	1–2 10–30	30–40 60–120	Rapid onset Short duration ↓Histamine release Minimal CV effects	Respiratory depression Rigid chest syndrome
Morphine	Intravenous	10	240–360	Longer lasting	Hypotension Respiratory depression
Midazolam	Intravenous, intramuscular, oral, rectal, intranasal	1–2 10–15 15–30 10–30 10–15	30–60 60–120 60–90 60–90 45–60	Rapid onset Short duration Easy to titrate Multiple routes	Respiratory depression
Methohexital	Intravenous, rectal	<1 5–10	4.7 20–60	Rapid onset Short duration Airway reflexes maintained	Respiratory depression Apnea Hypotension
Pentobarbital	Intravenous	1–2	30–60	Rapid onset Airway reflexes maintained	Respiratory depression Apnea Hypotension Prolonged recovery
Ketamine	Intravenous, intramuscular, oral, rectal, intranasal	1 5 30–45 5–10 5–10	15 15–30 120–240 15–30 30–120	Airway reflexes maintained No respiratory depression Predictable	Emergence phenomena Emesis Laryngospasm ↑ICP and ↑IOP
Etomidate	Intravenous	<1	5–10	Rapid onset Short duration Minimal CV effects Cerebroprotective	Respiratory depression Myoclonus Adrenal suppression
Propofol	Intravenous	<1	8–10	Rapid onset Short duration Antiemetic Cerebroprotective	Respiratory depression Hypotension Injection pain
Ketofol	Intravenous	1–3	10–15	Rapid onset Reduction in repeat dosing Reduction in emesis	Recovery agitation Respiratory depression Increased HR
Alfentanil	Intravenous	Immediate	10–15	Rapid onset Short duration Minimal CV effects	Respiratory depression and which can be increased with used as supplement to propofol
Remifentanil	Intravenous	3–6	5–10	Rapid onset Short duration Minimal CV effects	Respiratory depression
Dexmedetomidine	Intravenous	10–15 after initial loading infusion	5–8 half-life; 2-h terminal elimination	Rapid onset Short duration Minimal ventilatory effects	Bradycardia Hypotension

CV, Cardiovascular; *HR,* heart rate; *ICP,* intracranial pressure; *IOP,* intraocular pressure.

discussed in this chapter. It has a predictable behavior when used as a sole inhalational PSA agent in children but is also frequently used as an analgesic adjunct to a sedating agent.[39]

Drugs should be administered by titrated slow IV bolus to minimize hypotension or respiratory depression in many situations. It is important to allow adequate time between doses to achieve and assess peak effect before an additional dose is given. Lower initial doses should be chosen in sensitive patients or when drugs from multiple classes are being administered. Ketamine is considered the exception because, unlike the other agents described, it possesses a threshold response rather than an additive dose-response continuum. Smaller doses of ketamine cause analgesia and disorientation. Dissociation occurs when a dosage threshold of 1 to 1.5 mg/kg IV in adult patients or 1.5 to 2.0 mg/kg in younger pediatric patients is reached. Higher doses have not been shown to enhance or deepen the sedation.

Opioids. Parenteral opioids are commonly used as analgesics before painful procedures are performed. For PSA, an opioid is rarely optimal as a single agent, and most emergency clinicians

combine an opioid with a sedative-amnestic agent to balance sedation-amnesia and analgesia with the least likelihood of respiratory depression. One preferred method of establishing adequate analgesia for a painful procedure when using combined agents is addressing the pain requirements initially in the medication sequencing and then adding the anxiolytic for sedation. The most commonly used opioids in the ED for PSA are fentanyl and morphine. These are often combined with benzodiazepines such as midazolam for moderate sedation and are used in smaller doses to provide analgesia during deep sedation with etomidate or propofol. Meperidine historically was used for PSA but is no longer recommended because seizures are commonly associated with the accumulation of its long-lasting metabolite, normeperidine.

Fentanyl. Fentanyl has many advantages as an analgesic agent for PSA, given its rapid onset of action, short duration of activity, lack of histamine release, and favorable cardiovascular profile.[40,41] Fentanyl rapidly crosses the blood-brain barrier and produces analgesia in as little as 90 seconds. Serum levels rapidly decline from peak concentrations because of extensive tissue uptake followed by hepatic metabolism. It has a duration of action of 30 to 40 minutes; the peak respiratory depressant effect of a single IV dose of fentanyl is 5 to 15 minutes following injection. These properties permit the titration of multiple small doses to the desired clinical effect. Because fentanyl readily creates a reservoir in adipose tissue, accumulated large doses may result in a progressively increasing duration of effect. This does not generally occur in doses less than 10 μg/kg. For deep sedation, a single dose of 1 to 2 μg/kg of fentanyl is often given before the sedating agent. After adequate pain relief has been achieved, a smaller dose of a sedative agent may then be added and titrated to effect. Respiratory depression is minimized in this fashion. For moderate sedation, fentanyl can be titrated, along with a sedative agent such as midazolam, depending on whether the emergency clinician thinks that more sedative effect (midazolam) or analgesic effect (fentanyl) is required. Dosage should begin at 1 μg/kg and be slowly titrated upward every 1 to 2 minutes, until the desired level of analgesia has been achieved. Sufficient analgesia for painful procedures under moderate sedation usually is accomplished with doses of 2 to 3 μg/kg and under deep sedation with 1 to 2 μg/kg. Lower doses should be used in older patients or when other CNS depressants have been previously administered (eg, ethanol).

Respiratory depression is more likely at higher doses, when the drug is given rapidly, or when it is combined with other CNS depressants, such as benzodiazepines or alcohol. Other side effects may include vomiting and pruritus, although these are less common than with other opioids. Hypotension and bradycardia are rare but may occur with high doses. These adverse effects may be readily reversed by naloxone. Chest wall rigidity and glottic spasm, which may make ventilation difficult, are unique complications seen with high doses (anesthetic) of fentanyl not used for PSA and when given rapidly (generally > 7 μg/kg). In the rare event of chest wall rigidity, symptoms may not reliably be antagonized by naloxone and may necessitate neuromuscular blockade and intubation to enable adequate ventilation.

Morphine. Morphine is poorly lipid-soluble and penetrates the blood-brain barrier more slowly after small bolus injections. A period of 10 to 30 minutes is required before its peak effects are seen although, when used for PSA, morphine performs in a similar fashion to fentanyl, with comparable recovery times. A general starting dosage of 0.1 mg/kg is commonly used and then titrated to desired effect, as with fentanyl. Morphine has much more histamine release and therefore is more likely to produce hypotension, especially in preload-dependent patients. This fact, combined with its slow peak onset time, make it a less ideal opioid for use in PSA. It has a similar potential as other opioids for producing respiratory depression, especially when used with other CNS depressants, such as benzodiazepines. Morphine undergoes hepatic metabolism to an active metabolite, followed by renal excretion. Insufficiency of either organ system may lead to increased serum half-life.

Benzodiazepines. Benzodiazepines are potent amnestic, hypnotic, and anxiolytic medications. They also have anticonvulsant and muscle relaxant properties but do not have analgesic effects. Because of this, they are commonly coadministered with an analgesic agent, such as fentanyl or morphine. They may be given IV, IM, via the oral (PO) or intranasal (IN) route or per rectum (PR) but are virtually always used via the IV route for PSA in adults. Midazolam is the most commonly used agent because of its favorable pharmacokinetics.

Midazolam. Midazolam has many advantages for PSA, given its rapid onset of action and short duration of action compared with other benzodiazepines. Its stronger amnestic properties are an added advantage to other benzodiazepines. The starting IV dose is 0.05 mg/kg. Children may need slightly higher doses. The onset of sedation is generally within 1 to 2 minutes, and the duration of action is 30 to 60 minutes. Alternatives to the IV route are often used in children, including IM, PR, IN, and PO routes. Midazolam has been shown to be an extremely safe and effective agent for PSA, both alone and when used in combination with fentanyl.[40,41]

Side effects include dose-dependent hypoventilation and hypoxemia. Apnea and hypotension are uncommon but occur more often at high doses or when other CNS depressants, such as opioids, are used. Headache, nausea, emesis, coughing, and hiccups have been shown to occur, although rarely. Lower doses should be used when other agents such as analgesics are given concomitantly or given to older adults. Prolonged effects may be seen in older adults or those with liver dysfunction owing to decreased hepatic or first-pass metabolism. Midazolam is highly lipophilic, and its effects may be greatly amplified in obese patients, resulting in an increased plasma half-life of up to 8 hours with high or repetitive doses. Chronic alcohol users who do not have liver dysfunction may require relatively high doses of midazolam to achieve the same clinical effects as a result of cross-tolerance.

Barbiturates. Barbiturates are also potent hypnotics, with amnestic and anticonvulsant effects. They do not have analgesic properties. Therefore, the barbiturates pentobarbital, thiopental, and methohexital have been more commonly used for brief painless procedures. Methohexital has been combined with an analgesic for use in orthopedic procedures. However, because these agents have been replaced with other better tolerated and titratable short-acting agents, we do not recommend the routine use of barbiturates for procedural sedation in adults; see Chapter 162 for a discussion of their indications in children.

Ketamine. Ketamine is a well-studied, safe, and predictable agent for use in the pediatric population for PSA.[8,11,42] Increasingly, it has also gained popularity for use in adults for PSA.[40,43] It is a derivative of the street drug phencyclidine and is classified as a dissociative agent. It causes disruption between the thalamoneocortical and limbic systems, preventing the higher centers from perceiving visual, auditory, or painful stimuli. Because of this, ketamine leads to profound analgesia, amnesia, and catalepsis. It does not produce unconsciousness, but rather a trancelike state. Patients often experience nystagmus, roving eye movements, and random movements of the extremities, unrelated to painful stimuli. Parents who observe a procedure in which ketamine is used may be disturbed at seeing this and should be forewarned.

Ketamine has several advantages over other PSA agents. The most notable are its profound analgesic effect and lack of

significant respiratory depression. The protective airway reflexes, such as coughing, swallowing, and muscular tone of the tongue and pharynx, are preserved or slightly enhanced. Its use further leads to blockade of catecholamine reuptake, and blood pressure is generally well supported. It also induces bronchial smooth muscle relaxation and is well tolerated in patients with reactive airway disease. It has a fast onset and offset and is predictable when given by the IV or IM route. After administration, it is rapidly distributed and taken up by the cerebral tissues. The effects are maintained until the drug redistributes into the peripheral tissues and is metabolized by the liver. As a result, repeat doses are well tolerated in longer procedures. However, emergency clinicians should be aware that this might lead to longer recovery times and increased incidence of emesis.

Ketamine may be given by multiple routes but is administered almost exclusively by the IV route in adults. After an IV dose of 1 to 2 mg/kg, a dissociative state results in approximately 1 minute, with duration of action of approximately 15 minutes. Complete recovery generally requires 1 to 2 hours. Similar cataleptic results may be seen with IM administration of 4 to 5 mg/kg in approximately 5 minutes, with effects lasting 15 to 30 minutes. For pediatric sedation, ketamine is generally administered by the IV or IM route but may also be given via the PO, PR, or IN route. These other routes are infrequently used because of variable onset of action, slow offset, and less predictable results.

The most common side effect seen with ketamine is the emergence phenomenon. This occurs in approximately 15% of patients and is typically a mild reaction. The patient awakens with unpleasant vivid dreams or hallucinations or reports nighttime awakenings as a result of unpleasant dreams for several days after the administration of ketamine. Less than 1% to 2% of patients have significant emergence agitation. This is more commonly seen in female patients, adolescents, or adults and in those with underlying psychiatric disorders. Its rare occurrence, especially in children, should not limit the use of ketamine when indicated. Some have previously suggested concurrent administration of midazolam to mitigate this reaction, but studies have failed to support this practice, and the most recent clinical practice guideline updates do not recommend this practice in children.[1,7,44,45] The routine concomitant use of a benzodiazepine when administering ketamine sedation is therefore not recommended, unless it is judged to be of benefit for preprocedural anxiety. Benzodiazepines are useful for treating an emergence phenomenon if it occurs during the recovery phase. Emesis is the most common side effect, and concomitant dosing with a benzodiazepine and an antiemetic has been shown to reduce its incidence. Other side effects seen with ketamine use during sedation include transient apnea and laryngospasm.[46] These are also rare but have been suggested to be more common with rapid IV administration or with larger doses. Doses given slowly, at a rate of 0.5 mg/kg/min, may further limit these events. Ketamine also stimulates tracheobronchial and salivary secretions. In any patient undergoing airway examination (eg, fiberoptic laryngoscopy), pretreatment with glycopyrrolate, 0.01 mg/kg given 10 minutes before the ketamine, may be beneficial. Because airway reflexes are maintained, this generally is not a concern in other patients. Prophylactic pretreatment with anticholinergics is unnecessary, and this practice is no longer recommended.[8,47] Postrecovery nausea and vomiting are also frequently seen but are generally short-lived and respond well to typical antiemetics, such as ondansetron.

Because of the potential for catecholamine-mediated hypertension and tachycardia, ketamine should also be avoided in those with significant cardiovascular or coronary artery disease. Ketamine also increases intraocular pressure and should be avoided in those with open globe injuries. Ketamine is contraindicated in patients with psychosis, even when well controlled.

Sedative-Hypnotics

Etomidate. Etomidate is a short-acting, sedative-hypnotic agent that is structurally unrelated to the other PSA agents and has no analgesic properties. Its use leads to the very rapid onset of profound sedation and hypnosis by enhancing neurotransmission at γ-aminobutyric acid (GABA) receptors. Etomidate has been used for deep sedation because of its rapid onset, short duration of action and, most importantly, minimal effects on respiratory and cardiovascular function.[42,48,49]

After IV administration, sedation occurs in approximately 1 minute, and patients recover in 5 to 10 minutes. Etomidate induces deep sedation that borders on general anesthesia with higher doses and may be more difficult to titrate than the other sedative-hypnotics. It is generally administered IV, with an initial dose of 0.1 mg/kg given slowly over 1 to 2 minutes. Additional doses of 0.05 to 0.1 mg/kg may be administered every 2 to 3 minutes until the desired level of sedation has been achieved. Smaller initial doses should be considered when etomidate is combined with analgesic agents or given to older adults. Because it has little effect on the cardiovascular system and is cerebroprotective, it is an excellent choice for patients who have the potential for the development of hemodynamic instability or increased intracranial pressure.

Adverse effects that may limit its usefulness include apnea, respiratory depression, myoclonus, nausea, vomiting, and adrenal suppression.[50-52] These side effects are more common with rapid IV administration, when higher doses are used, and in older patients. Myoclonus is the most common side effect and is typically described as mild and brief but, at times, may be severe enough to interfere with the procedure. Although respiratory depression is rare and generally transient, few patients may require brief periods of assisted ventilation. Vomiting is unlikely with doses administered in the ED. Etomidate suppresses adrenal function by inhibiting 11-β-hydroxylase activity. Although some debate exists, this is generally not clinically relevant with a single sedating dose.[51,53]

Propofol. Propofol is another ultra–short-acting sedative-hypnotic that is structurally unrelated to the other PSA drugs and has no analgesic properties. It has an extremely rapid onset, short duration of action, and predictable efficacy for inducing deep sedation.[a]

Sedation quickly clears completely, permitting superior titration and earlier recovery and discharge. Propofol also possesses potent antiemetic properties and decreases intracranial pressure. Because of its properties, propofol is a highly desirable and widely used agent for deep sedation in the ED. It does not provide analgesia, however, and should be preceded by an opioid for painful procedures. As with all sedative agents, the addition of an opioid may increase the risk of deeper than anticipated sedation, respiratory depression, apnea, and hypotension, and smaller starting doses are recommended.

Propofol is administered with an initial IV bolus dose of 0.5 to 1 mg/kg that is then titrated every 1 to 3 minutes by 0.25- to 0.5-mg/kg aliquots to the desired sedation level. Children may require slightly higher weight-adjusted doses than adults. The onset of sedation occurs in less than 1 minute, and patient recovery occurs in 10 minutes. For procedures lasting longer than this, additional boluses of 0.5 mg/kg may be administered, or a continuous infusion of 3 to 6 mg/kg/hour may be titrated to the desired level of sedation. Smaller doses should be used when sedating older patients or when administering propofol to patients pretreated with analgesics.

Adverse effects include dose-dependent respiratory depression, apnea, hypotension, and pain on injection. Other agents, such as opioids, may intensify these effects. In most cases, apnea is

[a]References 3, 4, 7, 9, 21, 43, 54, and 55.

transient, and patients will not experience a significant decrease in their oxyhemoglobin level before recovering their respiratory function. This underscores the value of supplemental oxygen administration during sedation. If the oxygen saturation decreases to the low 90s, the patient may require a brief period of assisted ventilation. Propofol commonly results in a transient decrease in systolic and diastolic blood pressures, which rarely necessitates fluid administration and is well tolerated by healthy patients. The hypotensive effect is exaggerated in older adults and in patients with hypovolemia, and the initial dose of propofol should be reduced to 0.25 to 0.5 mg/kg in such patients. Pain associated with propofol injection occurs in most patients and can be reduced with small infusions of IV lidocaine before its administration. Despite these concerns, propofol has been shown to be reliable and safe when used with proper monitoring in the ED setting.

Ketamine Plus Propofol. Ketamine is commonly combined with propofol (known as ketofol) for PSA; although originally studied in children, its use has been expanded to adults. The two completely different agents are thought to have synergistic effects that balance each other's deficits while decreasing the overall dose of propofol. Ketamine provides the analgesic effects that propofol lacks. Furthermore, ketamine's cardiorespiratory stimulating effects provide a balance to the respiratory depression and hypotension caused by propofol. Also, vomiting and recovery hallucinations from ketamine are potentially mitigated by the antiemetic and hypnotic effects of propofol.[a]

In several recent studies, ketofol was not shown to be clinically superior to either agent used alone with regard to respiratory depression or airway complications.[41,44,57] There was statistically significant benefit in provider satisfaction, sedation quality, and decreased emesis and a clinically insignificant improvement in recovery time. Patients receiving ketofol frequently require less redosing due to the extended effects of the ketamine to maintain a similar depth of sedation. Although the use of this combination is extremely popular, it cannot be currently recommended as superior to propofol, propofol plus fentanyl, or ketamine, with or without ondansetron.

Ultra—Fast-Acting Agents. Reports and studies addressing agents such as alfentanil and remifentanil in PSA in the ED are limited. Alfentanil is an ultra–short-acting analogue of fentanyl that has been described for PSA in the ED.[59] This agent has been used in anesthesia and has also been found to be safe and effective when added to propofol for PSA in the ED. Emergency clinicians should be aware that patients who receive supplemental alfentanil may require additional stimulation to induce ventilation during ED PSA and may have extended recovery periods.[59] Although alfentanil is safe when added to propofol, the combination has not been shown to provide any additional benefit.

Remifentanil is an ester derivative of fentanyl and also has ultra–short-acting sedative and analgesic properties. Traditionally used in general anesthesia for sedation and analgesia, it has been described in brief reports for ED PSA.[60,61] It has the unique advantage of being metabolized by esterases present in interstitial tissues and red blood cells, and therefore its metabolism is independent of hepatic or renal dysfunction. It can have significant respiratory depression, but the patient is still often responsive to verbal commands.

Dexmedetomidine is a newer sedative agent for use in the ED. To date, literature supporting its use in the ED has been limited to a few case reports in the PSA population in the ED.[62] It acts as a highly selective α-adrenergic agonist with sedative, anxiolytic, and analgesic properties. Dexmedetomidine induces natural sleep to create its sedative effects. It has been mainly administered via infusion and has been used safely and successfully to facilitate fiberoptic intubation, gastrointestinal (GI) procedures and cardioversions. More intensive care unit (ICU) reports have demonstrated its use as a preferred sedative agent for mechanically ventilated patients. It may be considered for use with sedation of patients who are insensitive to the usual doses of benzodiazepines.

Reversal and Rescue Agents. Careful titration of medications to the desired level of sedation is generally the goal in PSA. At times, however, unanticipated deeper levels of sedation may be reached, and respiratory depression or apnea may be experienced. Airway repositioning, supplemental oxygen, and bag-valve-mask ventilation may be required. If these periods are prolonged, partial or complete reversal of agents such as opioids or benzodiazepines may be necessary. Elective reversal of PSA after completion of the procedure is not recommended.

Naloxone. Naloxone is a competitive antagonist of opioids and has been effectively used for the reversal of opioid-induced respiratory depression during PSA. It has a rapid onset of action and a mean plasma half-life of approximately 45 minutes, although its clinical effects last only 15 to 30 minutes. Resedation is generally not a problem for patients who have been given short-acting opioids such as fentanyl or morphine in doses recommended for PSA. Nevertheless, these patients should be observed for a minimum of 1 hour after the administration of naloxone. It is especially important for patients who have received large doses of fentanyl to ensure that redistribution of fentanyl within the body does not result in the recurrence of sedation.

Naloxone may be administered via the IV, IM, subcutaneous, or endotracheal route, but it is almost universally given IV. The smallest dose necessary to restore respiratory effort should be used because reversal of the opioid's respiratory depressant effect is matched by reversal of the analgesia. The initial dosage depends on the patient and the specific goals desired. For partial reversal, titrated doses of 0.1 to 0.2 mg may be used every 1 to 2 minutes to desired effect. Complete reversal is almost never desirable and requires doses of 1 to 2 mg. Similar doses may be used for children. In patients who are opioid-dependent, these doses may precipitate an acute withdrawal state. Smaller initial doses should be considered. Large doses of naloxone may also make it more difficult to control postprocedural pain. Naloxone use has little risk, but pulmonary edema, seizure, and dysrhythmia rarely have been reported.

Flumazenil. Flumazenil is a competitive antagonist of benzodiazepines. Although it reverses the sedation effect of benzodiazepines, it is not as effective for reversing respiratory depression. In general, when oversedation occurs, brief support of ventilation permits the patient to recover sufficient spontaneous respiration without the need for reversal. Flumazenil has a rapid onset of action in 1 to 2 minutes, peak effect in 5 to 10 minutes, and individually variable clinical duration of 30 to 90 minutes. Continuous patient monitoring must be ensured when flumazenil is used to reverse respiratory depression associated with longer lasting benzodiazepines because resedation is likely. Flumazenil has also been shown to be effective in reversing paradoxical excitement in children.

It is generally titrated in doses of 0.1 to 0.2 mg IV every 1 to 2 minutes to the desired effect. A maximum dose of 1 mg is generally sufficient. Common pediatric doses of 0.02 mg/kg are generally used, with a maximum of 0.2 mg. It should be used with extreme caution in patients with benzodiazepine dependence or a history of seizures because it may precipitate life-threatening status epilepticus refractory to common treatment. Routine reversal is not recommended.

[a]References 7, 41, 44, 45, and 56-58.

TABLE 4.5

Adult Drug Selection Strategies

PROCEDURE TYPE	EXAMPLES	RECOMMENDATION	ALTERNATIVES	COMMENTS
Nonpainful	Radiologic imaging	Midazolam (intravenous)	Propofol (intravenous)	Midazolam has considerable support and safety.
Low pain, high anxiety	Central line placement Lumbar puncture	Midazolam (intravenous)	Propofol (intravenous) Ketamine (intravenous)	Analgesia may be accomplished frequently with local or topical agents.
High pain, high anxiety	Fracture or joint reduction Abscess drainage Burn débridement Cardioversion Chest tube placement	Midazolam + fentanyl (intravenous) Propofol + fentanyl (intravenous) Ketamine (intravenous, intramuscular)	Etomidate + fentanyl (intravenous) Propofol + ketamine (intravenous)	There are far more data supporting the safety of fentanyl and midazolam, although the other choices have significant support.

Drug Selection and Administration

When choosing a strategy for PSA, it is important to consider the type of procedure being performed (painful or not), length of the procedure, specific procedural requirements (anxiolysis vs. immobility), and whether sedation may need to be prolonged (Table 4.5). The need for IV access generally is an issue only in small children. Planned adjuncts, such as topical, local, or regional anesthesia, are also considered. Patient factors, including age, medications, alcohol and drug use, and comorbid conditions, are considered when selecting the agent and initial dose. Procedures necessitating sedation may be broadly divided into three categories—nonpainful procedures requiring immobilization (eg, CT, MRI); low-pain, high-anxiety procedures (eg, laceration repair, lumbar puncture); and highly painful, high-anxiety procedures (eg, fracture or joint reduction, tube thoracostomy, abscess drainage, cardioversion).

For brief nonpainful procedures requiring complete immobilization, IV midazolam and propofol are excellent choices, and etomidate is a reasonable alternative. For longer procedures, oral or rectal midazolam or propofol infusion is reasonable.

For briefly painful procedures requiring minimal to moderate sedation, and when topical or local anesthetics may be used (eg, for reduction of a glenohumeral dislocation for which intraarticular lidocaine will be used), midazolam is a reliable and safe choice. IV propofol, preceded by a modest dose of fentanyl, is an excellent choice for brief painful procedures requiring deep sedation (eg, cardioversion, joint reduction, other highly painful procedures). Ketamine by the IV and IM routes has been extensively studied in children and is highly effective, with a large margin of safety for children and adults. The same may be said for IV midazolam plus fentanyl in the adult and pediatric populations.

KEY CONCEPTS

- Safe, effective PSA requires high-level skills and information and sound protocols, including patient monitoring.
- Patients should be discharged in the company of a responsible adult and should remain with a responsible adult for 4 to 8 hours after recovery and discharge.
- Propofol is the agent of choice for deep sedation in the ED but requires supplementation with an opioid analgesic when a painful procedure is planned.
- Absence of a preprocedure fasting period is not a contraindication to procedural sedation for an emergent and/or time-sensitive condition.
- Pulse oximetry is mandatory during sedation, and end-tidal CO_2 should be monitored if moderate or deep sedation is the goal. Oxygen should be administered to patients undergoing procedural sedation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 4: QUESTIONS & ANSWERS

4.1. When do most adverse events associated with emergency department procedural sedation occur?
- **A.** During the manipulation or intervention
- **B.** 5 to 20 minutes after the last sedative dose
- **C.** 20 to 30 minutes after the last sedative dose
- **D.** 30 to 60 minutes after the last sedative dose
- **E.** 60 to 90 minutes after the last sedative dose

Answer: B. High-risk times are 5 to 20 minutes after the last medication administration and at the completion of the procedure, when there is no longer a painful stimulus but the patient remains sedated.

4.2. Which of the following modalities has proven most effective for monitoring patients undergoing procedural sedation?
- **A.** Capnometry or capnography
- **B.** Cardiac rhythm monitoring
- **C.** Continual direct visual observation of qualitative clinical signs
- **D.** Documented respiratory rate
- **E.** Pulse oximetry

Answer: C. The patient's ability to follow commands in response to varied levels of stimulation and direct observation of the ventilatory status have been the most reliably documented methods of assessing the level of consciousness during procedural sedation. Pulse oximetry is a reliable adjunct, but it identifies hypoventilation late, especially when used with supplemental oxygen. Cardiac monitoring has been shown to be helpful in older patients or in those with a history of cardiac disease, but there is no evidence that it is of any benefit in young healthy patients. End-tidal carbon dioxide (CO_2) monitoring has been shown to be useful to detect inadequate ventilation earlier than oximetry, especially when direct observation of the patient is difficult, but no studies have demonstrated an effect on clinical outcome to date. The American Society of Anesthesiologists (ASA) has updated its procedural sedation standards to include capnography during moderate or deep sedation, in addition to the continual observation of qualitative clinical signs. Respiratory rate alone is an insensitive indicator of the adequacy of ventilation.

4.3. Which of the following statements is most accurate regarding the use of fentanyl for procedural sedation?
- **A.** Chest wall rigidity is a common occurrence but may be reversed with naloxone.
- **B.** For deep sedation, a single dose of 1 to 2 μg/kg IV is often given before sedation to achieve good pain control. A smaller dose of sedative agent may then be added and titrated to effect.
- **C.** Rapid IV administration is generally safe.
- **D.** Respiratory depression is less likely with fentanyl than with an equipotent dose of morphine.
- **E.** Sufficient analgesia is generally attained with dosages of 5 to 10 μg/kg intravenous (IV).

Answer: B. For deep sedation, less respiratory depression is generally observed if a single pain-relieving dose of fentanyl is used before sedation, followed by small titrated doses of a sedative agent. Sufficient analgesia is generally attained with fentanyl dosages of 1 to 2 μg/kg IV. Rapid IV administration of large doses is more likely to precipitate respiratory depression or arrest. Chest wall rigidity is very rarely seen and generally only with large, rapid, IV boluses of more than 7 μg/kg IV. If severe chest wall rigidity syndrome is precipitated, it often requires paralysis to ventilate the patient adequately. It is not reversed with naloxone. Equivalent dosages of morphine show more histamine release and hypotension than fentanyl but have similar respiratory depression potential.

4.4. Which of the following agents is matched with the correct associated side effect?
- **A.** Etomidate—limited (30-minute) duration of sedation
- **B.** Ketamine—laryngospasm
- **C.** Methohexital—venoirritation
- **D.** Pentobarbital—seizures
- **E.** Propofol—myoclonus

Answer: B. Ketamine has been associated with laryngospasm in children younger than 3 months and those with a respiratory infection. The following are the other correct associations:
Methohexital—seizures
Propofol—venoirritation
Pentobarbital—30-minute duration
Etomidate—myoclonus

4.5. Which of the following statements regarding the use of ketamine is false?
- **A.** Benzodiazepine coadministration has not been shown to reduce the incidence of emergence phenomenon in children.
- **B.** Despite increased secretions, airway reflexes are generally well maintained.
- **C.** Hypotension is common.
- **D.** Profound analgesic and sedative effects occur with minimal respiratory depression.
- **E.** Repeat doses are well tolerated in longer procedures.

Answer: C. Ketamine increases the release of catecholamines on administration and supports blood pressure well. It also decreases smooth muscle tone in the bronchial tree and may have a benefit in patients with reactive airways disease. Several studies have failed to show benefit with the concurrent administration of low to moderate dosages of benzodiazepines in preventing emergence phenomenon in children. These studies have shown a slightly increased risk of side effects. Their routine use is discouraged and should be reserved for the actual treatment of severe emergency phenomenon.

4.6. Which of the following statements regarding the use of propofol is true?
- **A.** Propofol has a long duration of action and provides significant analgesia.
- **B.** Propofol has significant antiemetic properties.
- **C.** Propofol is cerebroprotective.
- **D.** Propofol is well tolerated in volume-depleted patients.
- **E.** The use of ketofol (ketamine in combination with propofol) is clinically superior to the use of propofol alone.

Answer: B. Propofol is an ultra–short-acting, sedative-hypnotic, cerebroprotective agent with no analgesic but profound antiemetic properties. Its adverse effects include dose-dependent respiratory depression, apnea, hypotension, and pain on injection. Preload-dependent patients are particularly susceptible to hypotension. Its combined use with ketamine is common. The two agents are thought to have synergistic effects that balance each other's deficits. Their combined use has been shown to improve provider satisfaction, sedation quality, and decrease emesis but has not been shown to be clinically superior to either agent used alone in regard to respiratory depression, airway complications, or improved recovery times.

4.7. Which of the following statements is true regarding the need for fasting before procedural sedation?

A. A 6-hour period of fasting is required after the ingestion of liquids or solids before procedural sedation.

B. Preprocedural fasting is required in all cases.

C. The recommendation for preprocedural fasting is based on controlled trials involving patients undergoing procedural sedation.

D. The risk of vomiting and loss of the airway protective reflexes is an extremely rare occurrence during procedural sedation.

E. There is an increased risk of aspiration during procedural sedation after a liquid or solid meal.

Answer: D. The ASA currently recommends a period of 2 hours after ingestion of clear liquids, 4 hours after ingestion of breast milk, and 6 hours after the ingestion of other liquids or solids before the performance of procedural sedation. This recommendation is based on expert consensus and has been extrapolated from data on patients receiving general anesthesia and manipulation of the airway during intubation and extubation. There are no published studies showing an increased risk of aspiration after a liquid or solid meal nor benefits of fasting before procedural sedation. Large studies have shown no clinically significant differences with airway complications, emesis, or other adverse effects among groups of patients stratified by their preprocedural fasting status. The risks of procedural sedation should be balanced against the risks of delaying a time-sensitive procedure.

CHAPTER 5

Monitoring the Emergency Patient

Anthony M. Napoli | Ken Deitch

This chapter focuses on these monitoring modalities: noninvasive blood pressure measurement, pulse oximetry, and use of the end-tidal carbon dioxide ($ETCO_2$) measurement. Fetal monitoring after trauma and cerebral function monitoring are also briefly discussed.

BLOOD PRESSURE MEASUREMENT

Principles

Blood pressure measurement by sphygmomanometer is the most common method of noninvasively measuring arterial pressure by indirectly measuring systolic, diastolic, mean arterial, and pulse pressures. The pulse pressure is important because it closely resembles stroke volume when accounting for arterial compliance and resistance. At a given arterial compliance (C), stroke volume (SV) is associated with corresponding changes in pulse pressure: C = SV/PP. Therefore, blood pressure closely represents the interplay of cardiac output and overall systemic vascular resistance, making it an important screening and surrogate monitoring tool in emergency department (ED) patients.

Decision Making

Blood pressure monitoring remains a standard and important ongoing measure of changes in the physiologic adaptation to stress and serves as a dynamic measure and singular predictor of adverse outcomes in medical and surgical patients. For example, patients who present to the ED with sepsis are six times more likely to progress to septic shock if they have even a single episode of hypotension.[1] Similar results have been shown in trauma patients, for whom apparently isolated hypotension is associated with increased mortality.[2]

Devices and Techniques

Traditional blood pressure measurement by sphygmomanometry can be obtained by Doppler, palpation, auscultation, and oscillometric methods. Although palpation only allows for systolic pressure determination, it is useful in noisy environments (such as emergency medical services [EMS] transport), where measurement by oscillometric means may be difficult. Doppler is particularly helpful in identifying the presence of a systolic pulse in hypotensive patients or in internally (ie, atherosclerosis) or externally (ie, compartment syndrome) flow-limited extremities. Auscultation, otherwise known as manual blood pressure measurement, has remained a common, generally reliable, and reproducible method of blood pressure measurement for over 100 years, since its discovery. This method relies on placing the stethoscope at the antecubital fossa, inflating the blood pressure cuff, and then slowly deflating the cuff while noting the pressure at which auscultation of the pulse returns (systolic blood pressure) and when it disappears (diastolic blood pressure). Auscultation generally underestimates the systolic blood pressure and overestimates the diastolic pressure. Although accuracy has improved with standardization of the technology, this technique is occasionally prone to significant inaccuracy. The quality of the device, cuff size, body positioning, arm positioning, and relaxation are all components of the measuring technique that can affect the accuracy. Clinical circumstances such as obesity, dysrhythmias, and extremes of age (young children and older adults) may also affect the accuracy.

The ease of use of oscillometric blood pressure measurement makes this modality ideal for ED noninvasive monitoring. The oscillometric technique measures oscillations in the pressure during deflation of the cuff; the maximal point of oscillation represents the mean arterial pressure. This is the most common noninvasive method of measuring blood pressure in the ED and is commonly called the automatic blood pressure. This method has several advantages over auscultation, including less susceptibility to noise, less resource usage, and regular measurement intervals, and specific placement of a transducer over the artery is unnecessary. Comparisons of auscultation and oscillometric measurement with intraarterial measurement have found relatively good agreement, with automated pressures slightly overestimating manual systolic pressures with moderate precision in hemodynamically stable patients.

Other methods of providing continuous, noninvasive blood pressure monitoring often rely on partial radial artery compression or arterial loading counterpressure and offer results comparable to those of an arterial catheter, with the benefit of added mobility. Newer continuous, noninvasive blood pressure monitors have the advantage of providing additional advanced hemodynamic measures, such as stroke volume and cardiac output,[3] which may be beneficial in critically ill patients.

The gold standard, and the most accurate method of measuring blood pressure, remains the intraarterial catheter. However, this method is invasive and time intensive, and carries the infrequent but real risk of arterial injury or thrombosis. Common situations in which invasive arterial monitoring may be of benefit include (1) persistent or recurrent hemodynamic instability, (2) monitoring of conditions or treatments that result in large fluid or blood pressure shifts, (3) frequent arterial blood sampling, and (4) expected inaccuracies in noninvasive blood pressure management (eg, because of obesity or dysrhythmias).

PULSE OXIMETRY

Principles

Pulse oximetry is widely used for ED and out-of-hospital patient monitoring. It provides a real-time assessment of oxygen saturation and objective insight into dynamic changes in patient physiology, as well as the effectiveness of interventions as related to oxygenation. Since widespread adoption nearly 35 years ago, it is now become regarded as the fifth vital sign.

Decision Making

ED use of pulse oximetry was adapted from anesthesiology practice, which demonstrated less frequent and shorter episodes of desaturation and earlier recognition of hypoxia during or after

anesthesia. In the ED, pulse oximetry is largely used for the initial triage of patients or in the monitoring and management of patients who are sedated or critically ill, particularly with respiratory distress or during endotracheal intubation. In the latter case, pulse oximetry has been shown to reduce the frequency of hypoxic episodes. Arterial oxygen saturation (Sao_2) values at or below 96% have been shown to be 100% sensitive for the detection of hypoxia (partial pressure of arterial oxygen [Pao_2] < 70 torr), although such a cutoff can be different in patients with obstructive lung disease.

Devices and Techniques

Pulse oximetry is based on the premise that the concentration of an absorbing substance can be determined if the characteristic wavelength of that substance, intensity of the light transmitted through the substance, and distance of transmission are known (Beer-Lambert Law). Pulse oximetry devices use two light-emitting diodes (LEDs) that give off light at wavelengths characteristic of oxyhemoglobin and deoxyhemoglobin (660 and 940 nm). These wavelengths are absorbed at different rates depending on clinical conditions, and the fractional difference between the two wavelengths is measured and reflected in the pulse oximetry. Because the absorption characteristics of tissue, arterial blood, and venous blood are static over a cardiac cycle, the beat to beat alterations that occur in pulsatile blood can be isolated, and the static components can be filtered out through measurement of transmitted light several hundred times per second. Measurements can be made on the ears or fingers, although the fingers are generally better in patients with poor perfusion.

Pulse oximetry measures the percentage of arterial hemoglobin that is in the oxyhemoglobin state. It reflects the amount of oxygen that hemoglobin is carrying as a percent of the maximum it can carry; this is commonly known as the oxygen saturation as measured by pulse oximetry (Spo_2). Pulse oximetry does not measure the Pao_2; however, hemoglobin-bound oxygen represents the larger reservoir of oxygen in the blood. An understanding of the oxyhemoglobin dissociation curve and relationship between Sao_2 and Pao_2 makes it possible to advance monitoring capacity using this noninvasive continuous monitor to replace intermittent arterial blood draws. Although the two measures correlate well, their relationship is nonlinear. Pulse oximeters are generally accurate between 80% and 100% saturation, but large changes in the Spo_2 can occur with small changes in the Pao_2 in hypoxic patients. Below this range, the role is reversed, and large changes in Pao_2 may occur with small changes in Spo_2. Pulse oximetry retains its usefulness because in the no-hypoxic range, the relationship generally is linear and, once clinically important hypoxia exists, there is no significantly different clinical response to a pulse oximeter reading of 85% or 65%. In this way, pulse oximetry is an ideal tool for screening and continuous monitoring.

Pulse oximetry has several important clinical limitations. By design, pulse oximeters measures only two wavelengths. At these wavelengths, traditional pulse oximeters are unable to distinguish oxyhemoglobin and deoxyhemoglobin from two important dyshemoglobinemias, methemoglobin (MetHb) and carboxyhemoglobin (COHb). Multiwavelength CO oximeters are now available that can distinguish the four wavelengths.[4] In the setting of a significant MetHb or COHb exposure, the pulse oximeter will read falsely elevated levels of Sao_2, even at relatively high exposures, because it cannot distinguish oxygenated or deoxygenated hemoglobin from these other dyshemoglobinemias. In heavy smokers, COHb levels of 3% to 15% can commonly be found, but this has little impact on the reported Spo_2. Signal artifact is probably the most common technical limitation to adequate measurement. Other limitations include low perfusion states, which lead to a low pulsatile component and subsequent impaired measurement accuracy, ambient light, deep skin pigmentation, methylene blue, and nail polish. Signal averaging limits the impact of motion artifact and improves its accuracy.

Determination of the Spo_2 may obviate the need for repeated, invasive arterial sampling to determine oxygen saturation (and to some degree Pao_2), but it does not adequately provide insight into the pH or partial pressure of carbon dioxide ($Paco_2$). These latter two data points can be obtained by venous blood sampling and use of continuous capnography. More importantly, Spo_2 does not aid in determining the adequacy of ventilation when significant hypercapnia may precede hypoxia, and supplemental oxygen may mask hypoventilation. This is one of the many uses of $ETco_2$ measurement.

END-TIDAL CARBON DIOXIDE MONITORING

Principles

Capnography is the graphic record, represented as a waveform, or capnogram, of the instantaneous CO_2 concentrations in respired gases during a respiratory cycle. Near-instantaneous measurement of the pattern of each breath and concentration of exhaled carbon dioxide allows the emergency clinician to determine the baseline ventilatory status and track changes over time. Capnometry is defined as the quantitative measurement of $ETco_2$, displayed as a number without a waveform. Colorimetric detectors use color scales to estimate ranges of $ETco_2$ but are not sufficiently accurate to give precise quantitative measurements. Their use is therefore limited to confirmation of correct endotracheal tube (ETT) placement and its continuous location in the trachea. Capnography has broad application in the ED during procedural sedation and monitoring of critically ill or intubated patients, and also is used in the out-of-hospital setting to monitor intubated and sedated patients.

CO_2 monitors are configured as sidestream or mainstream, depending on the location of the photoelectric detector or sensor. Mainstream devices measure CO_2 directly from the airway, with the sensor attached directly to the ETT. Sidestream devices, more commonly used by EMS personnel and in the ED, aspirate a sample of gas through tubing into a sensor located inside the monitor and are used for intubated and nonintubated patients. They are lightweight and may be integrated into a nasal-oral cannula that simultaneously samples CO_2 and delivers low-flow oxygen, allowing for continuous oxygen delivery during procedural sedation and analgesia.

Colorimetric CO_2 detectors use pH-sensitive filter paper impregnated with metacresol purple, which changes color from purple (<4 mm Hg CO_2) to tan (4–15 mm Hg CO_2) to yellow (>20 mm Hg CO_2), depending on the concentration of CO_2 (see Chapter 1). The indicator, housed in a plastic casing, is inserted between the ETT and ventilator bag and detects changes on a breath by breath basis.

Anatomy and Pathophysiology

Although the concentrations of CO_2 can be displayed continuously throughout the respiratory cycle—by convention only the maximum CO_2 concentration at the end of each tidal breath—the $ETco_2$, is ordinarily displayed. In patients with normal cardiopulmonary function, there is a close correlation between the alveolar CO_2 ($Paco_2$) and arterial CO_2 ($Paco_2$). The $ETco_2$ is usually 2 to 5 mm Hg less than the $Paco_2$ because of the dilution of the end-tidal gases by physiologic dead space gas. Conditions that affect ventilation-perfusion ratios (including pulmonary embolism), cardiac arrest, hypovolemia, obstructive lung disease, and lateral decubitus position can widen the Pa–$ETco_2$ gradient. Several studies, however, have shown high concordance between $ETco_2$

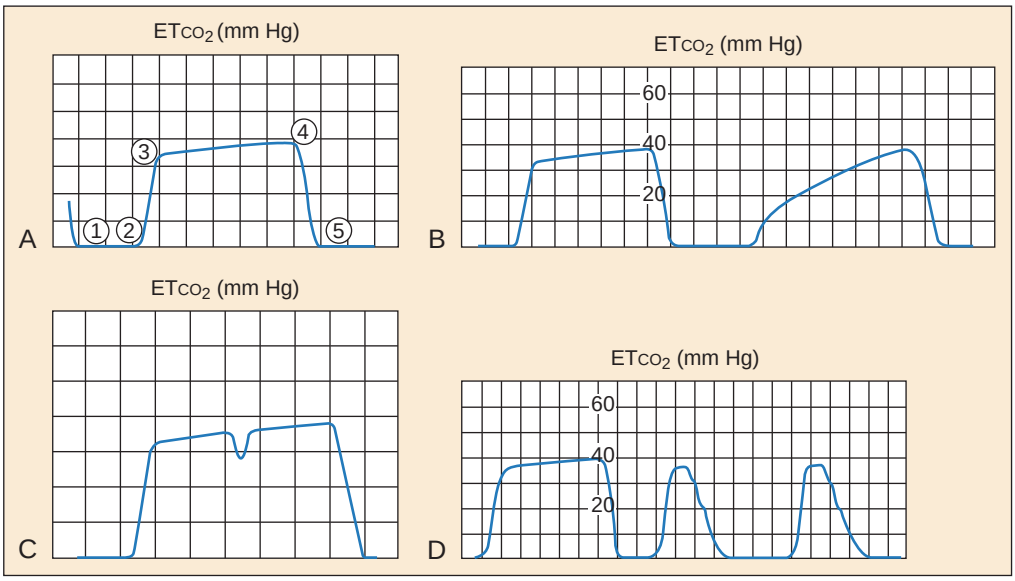

Fig. 5.1. A, Four phases of a normal capnogram. *1-2,* The carbon dioxide–free portion of the respiratory cycle. *2-3,* The rapid upstroke of the curve, representing the transition from inspiration to expiration and the mixing of dead space and alveolar gas. *3-4,* The alveolar plateau, representing the alveolar gas rich in carbon dioxide and tending to slope gently upward with the uneven emptying of the alveoli. *4-5,* The respiratory downstroke, which is a nearly vertical drop to baseline. B–D, See text for explanation. *$ETCO_2$,* End-tidal carbon dioxide.

and $Paco_2$ in adult asthmatics and in children with moderate and severe respiratory distress from bronchiolitis, asthma, and pneumonia. Analysis of the shape of the capnogram can yield valuable diagnostic information.

A normal capnogram has four phases (Fig. 5.1A):

1. Phase 1-2 represents a CO_2-free portion of the respiratory cycle. Usually, this is the inspiratory phase, although it may represent apnea or a disconnection of the device from the patient. An elevation of this baseline above zero implies rebreathing of CO_2, as in increased dead space in the circuit or contamination of the sensor.
2. Phase 2-3, the rapid upstroke of the curve, represents the transition from inspiration to expiration and the mixing of dead space and alveolar gas. Prolongation of phase 2-3 (see Fig. 5.1B) occurs with obstruction to expiratory gas flow (eg, obstructive lung disease, bronchospasm, kinked ETT) or leaks in the breathing system.
3. Phase 3-4, the alveolar plateau, represents the predominance of CO_2-rich alveolar gas in the breath stream and tends to slope gently upward with the uneven emptying of alveoli. Point 4 (the $ETco_2$) represents the maximum CO_2 concentration in each breath and is the number that appears on the monitor. The slope of this phase can be increased by the same obstructive factors that increase the slope of phase 2-3 and is also a normal physiologic variation in pregnancy. A dip in the plateau indicates a spontaneous respiratory effort during mechanical ventilation, as in hypoxia, hypercarbia, or inadequate anesthesia (see Fig. 5.1C).
4. Phase 4-5, the inspiratory downstroke, is a nearly vertical drop to baseline. This slope can be prolonged and blend in with the expiratory phase in endotracheal cuff leaks (see Fig. 5.1D). Abnormal respiratory patterns that are fast or chaotic limit the usefulness of $ETco_2$ monitoring because characteristic waveform patterns are difficult to discern.

Management

Capnography is used in the ED for intubated and nonintubated patients. For intubated patients, it provides information regarding respiratory function and ventilator settings and gives immediate notification of accidental extubation. Postintubation, an $ETco_2$ waveform demonstrating all four phases indicates that the endotracheal tube is through the vocal cords and is not obstructed. In patients who are not in cardiac arrest, qualitative colorimetric $ETco_2$ or quantitative capnography provides nearly 100% sensitivity and specificity for endotracheal placement. In contrast, using clinical signs to verify endotracheal tube placement is unreliable, with a high rate of false-positive results. $ETco_2$ can help monitor tube position continuously in the trachea during transport and is an accepted standard of care by the American Society of Anesthesiology and other organizations. During cardiac arrest, $ETco_2$ reflects the degree of pulmonary blood flow as alveolar ventilation and basal metabolism are constant, so that it can be used to gauge effectiveness of cardiopulmonary resuscitation (CPR) and return of spontaneous circulation (see Chapter 8).[5,6]

In addition to uses in resuscitation, capnography can also be used to monitor patients with active seizures and maintain appropriate $ETco_2$ levels in patients with elevated intracranial pressure. Along with visualizing tracheal rings on bronchoscopy, capnography is the other gold standard used to confirm intubation of the trachea (see Chapter 1).

Capnography in Spontaneously Breathing Patients

Rapid Assessment of Critically Ill Patients. Airway, breathing, and circulatory assessment of critically ill patients can be rapidly determined through the use of $ETco_2$ values and the capnogram. The presence of a normal capnogram denotes a patent airway and spontaneous breathing, and normal $ETco_2$ levels indicate adequate ventilation and perfusion. Unlike pulse oximetry and electrocardiography, capnographic measurement is airway based and therefore is not subject to motion artifact. It also provides reliable readings in low-perfusion states. Capnography is the only ventilation monitoring modality that is accurate and reliable in patients with active generalized seizures. Capnographic data (capnogram, $ETco_2$, respiratory rate) can be used to distinguish among actively seizing patients with apnea (flatline waveform, no $ETco_2$ readings, no chest wall movement), ineffective

ventilation with low–tidal volume breathing (small capnograms, low $ETCO_2$), and effective ventilation (normal capnogram, normal $ETCO_2$).

Capnography can also rapidly detect the common airway, respiratory, and central nervous system complications associated with nerve agents used in chemical terrorism, including apnea, upper airway obstruction, laryngospasm, bronchospasm, and respiratory failure.[5]

Assessment and Measurement of Response to Treatment in Patients With Acute Respiratory Distress. Capnography provides dynamic monitoring of ventilatory status in patients with acute respiratory distress, such as from asthma, bronchiolitis, chronic obstructive pulmonary disease (COPD), congestive heart failure, and cystic fibrosis. By measuring $ETCO_2$ and respiratory rate with each breath, capnography provides instantaneous feedback on the clinical status of the patient. Respiratory rate is measured directly from the airway via a nasal-oral cannula, providing a more reliable reading than impedance respiratory monitoring. In upper airway obstruction and laryngospasm, for example, impedance monitoring detects chest wall movement, interprets this as a valid breath, and displays a respiratory rate, even though the patient is not ventilating. In contrast, capnography detects no ventilation and shows a flatline capnogram.

Bronchospasm in obstructive lung disease leads to upward slanting of the expiratory plateau of the capnogram (Fig. 5.2, *middle panel*). Changes in $ETCO_2$ over time and the slope of this phase of the capnogram have been shown to correlate well with spirometric measurements (forced expiratory volume in 1 second [FEV_1] and peak expiratory flow rate [PEFR]). Capnography has the advantage of being independent of effort, gender, age, and height and is a useful objective measure in asthmatic patients who are unable to cooperate with spirometry (eg, young children, ventilated patients, patients in acute respiratory distress). Capnography can also be used to distinguish obstructive from restrictive lung disease. Characteristic capnographic patterns associated with restrictive and obstructive lung disease are shown in Fig. 5.2 *(bottom panel)*. A recent pilot study has shown early promise in a computerized algorithmic approach for the classification of waveform shapes differentiating congestive heart failure and COPD with a high degree of sensitivity and specificity.[7]

During Procedural Sedation and Analgesia. Capnography can also detect the common adverse airway and respiratory events associated with procedural sedation and analgesia (see Chapter 4). Central and obstructive apnea can be almost instantaneously detected by capnography. Capnography is the earliest indicator of airway or respiratory compromise and displays an abnormally high or low $ETCO_2$ 5 to 240 seconds before pulse oximetry detects a falling oxyhemoglobin saturation, especially in patients receiving supplemental oxygen. A low $ETCO_2$—that is, hypopneic hypoventilation—is commonly seen with sedative-hypnotic agents (especially propofol) and during deep sedation, represents low–tidal volume breathing (airway dead space remains constant but tidal volume decreases), and should not be misinterpreted as hyperventilation.

The use of capnography during procedural sedation in adults and children is associated with significantly lower rates of hypoxia. Early recognition of respiratory depression allows for earlier airway interventions and results in lower rates of hypoxia in patients undergoing procedural sedation (see Chapter 4).

Rapid Assessment of Obtunded or Unconscious Patients. Obtunded or unconscious patients, with or without psychomotor agitation, includes those with alcohol intoxication, intentional or unintentional drug overdose, postictal patients, and agitated patients treated with benzodiazepines, who may have respiratory depression, impaired ventilation, and hypoxia. Capnography may differentiate between postictal patients with effective ventilation and those with ineffective ventilation, as well as providing continuous monitoring of ventilatory trends over time to identify patients at risk for respiratory depression and respiratory failure.[8,9]

Rapid Assessment of Patients With Severe Illness. This includes those with sepsis, diabetic ketoacidosis, and dehydration. In addition to its established uses for assessment of ventilation and perfusion, capnography is a valuable tool for evaluating metabolic status. Studies have shown a positive linear correlation between $ETCO_2$ and serum bicarbonate ion (HCO_3^-) levels in those with diabetes and gastroenteritis; $ETCO_2$ can be used as an indicator of metabolic acidosis in these patients (Figs. 5.3 and 5.4). As a patient becomes acidotic, the HCO_3^- level decreases and a compensatory respiratory alkalosis develops, with an increase in minute ventilation and a resultant decrease in $ETCO_2$. The more acidotic the patient, the lower the HCO_3^-; the higher the respiratory rate, the lower the $ETCO_2$. Furthermore, $ETCO_2$ can be used to distinguish diabetics with ketoacidosis (metabolic acidosis, compensatory tachypnea, low $ETCO_2$) from those without (nonacidotic, normal respiratory rate, normal $ETCO_2$). A similar association between $ETCO_2$ and HCO_3^- has been demonstrated in

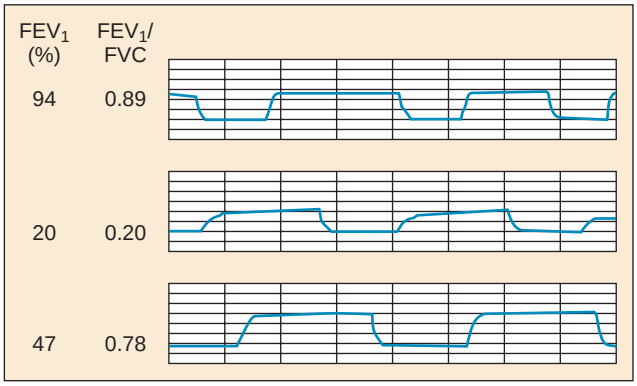

Fig. 5.2. Capnogram shape in normal subjects *(top panel),* patients with bronchospasm *(middle panel),* and those with obstructive and restrictive *(bottom panel)* lung disease. *FEV_1,* Forced expiratory volume in 1 second; *FVC,* forced vital capacity.

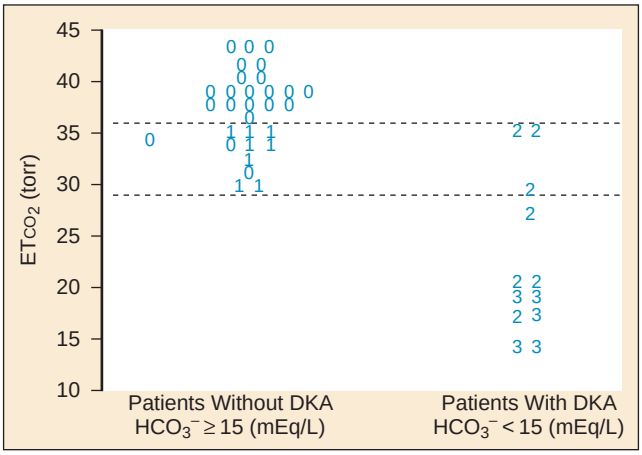

Fig. 5.3. Predictive value of end-tidal carbon dioxide ($ETCO_2$) in detecting metabolic acidosis in diabetics. *DKA,* Diabetic ketoacidosis; *HCO_3^-,* bicarbonate ion.

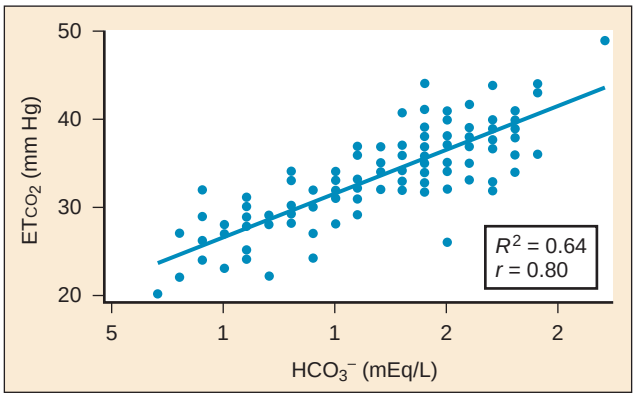

Fig. 5.4. End-tidal carbon dioxide ($ETCO_2$)/serum bicarbonate ion (HCO_3^-) correlation in gastroenteritis. *r,* Correlation coefficient; R^2, coefficient of determination for multivariate analysis.

children with gastroenteritis. $ETCO_2$ may not, however, be useful in management of other metabolic derangements such as sepsis and has not been shown to be a useful endpoint for resuscitation in early, goal-directed therapy for sepsis.

CEREBRAL FUNCTION MONITORING

Principles

The bispectral index (BIS) is used to monitor, analyze, and process a patient's electroencephalogram during sedation to produce a single number, the BIS score. This unitless number, values from 0 to 100, is used as an indicator of the depth of sedation, with 0 representing electroencephalographic silence and 100 a fully awake adult.

BIS monitoring has been studied in the ED in an attempt to objectify sedation endpoints by titrating to a target BIS score. However, the evidence of its ability to reflect depth of sedation reliably is conflicting. More importantly, the threshold beyond which ventilatory compromise occurs has not been determined, further limiting the usefulness of routine BIS monitoring for sedation in the ED. BIS monitoring reliably distinguishes patients undergoing procedural sedation and analgesia who were sedated to the point of general anesthesia from those with lesser degrees of sedation, but does not discriminate mild to moderate sedation from moderate to deep sedation. The use of BIS monitoring during procedural sedation is discussed in Chapter 4.

Another technology that monitors cerebral function is cerebral oximetry. Cerebral tissue oxygenation (ie, regional oxygen saturation [rSo_2]) is measured by near-infrared spectroscopy monitoring of the nonpulsatile signal component, reflecting tissue circulation of the cerebral vasculature. This technology has been primarily studied in the operating room. It does not work as an early warning device, and its use in the ED is limited.

FETAL MONITORING

Principles

A small but significant percentage of all pregnancies (6%–7%) are complicated by traumatic and/or accidental injury. Trauma represents the leading nonobstetric cause of death and carries a mortality rate of 6% to 7%.[10] Most traumatic injuries are motor vehicle accidents, but assaults, domestic abuse, and falls are also common. Uterine contractions occur in almost 50% of patients, although preterm labor and preterm delivery are much less common—5% to 15% and 1% to 2% of the time, respectively. However, peripartum complications and early preterm birth are difficult to predict after trauma. As a result, the Eastern Association for the Surgery of Trauma recommendations include cardiotocographic monitoring for a minimum of 6 hours after trauma in women at more than 20 weeks' gestation. In addition to serial examination, fetal monitoring allows for the identification of uterine contractions and nonreassuring heart rate changes.

Although the optimal period of monitoring has not been determined, further monitoring is recommended when abnormalities are identified or serial examination findings warrant it. Emergency clinicians generally do not monitor for cardiotocographic findings and, as a result, term or near-term pregnancies are generally transferred for such monitoring. ED bedside ultrasonography is available more commonly and can demonstrate fetal heart rate and movement. However, ultrasonography requires intermittent examinations, has limited ability to track fetal heart tones, and is unable to measure uterine contractions. Ongoing fetal monitoring in a third-trimester pregnancy after trauma is typically accomplished by admission or observation by the obstetric service.

Monitor Alarms and Limits

Continuous vital sign monitoring, with alarm thresholds that notify staff regarding changes in physiologic conditions, has become a routine part of ED care. Although these alarms are designed to be highly sensitive, their lack of specificity has the potential to desensitize staff and reduce alarm effectiveness in identifying important changes in the clinical condition (ie, nuisance alarms). Continuous monitoring in select patient populations, such as those with low-risk chest pain, has limited usefulness, with less than 1% of alarms resulting in a change in clinical management. A multidisciplinary team-based approach that focuses on identifying optimal application of monitoring, standardizing alarm limits and the staff response, and using improved alarm technology has the potential to improve patient safety and enhance workplace efficiency and satisfaction.[11]

KEY CONCEPTS

- Monitoring modalities, when used appropriately, help identify the effectiveness of interventions, predict deterioration, track the patient's clinical course, and inform clinical decision making.
- Noninvasive blood pressure monitors remain the standard for ongoing measurement of dynamic change. A single episode of hypotension is predictive of subsequent hemodynamic compromise. Despite generally high accuracy and dependability of blood pressure monitoring devices, manual blood pressure may be required at times to verify sudden changes in blood pressure measurements or when readings fluctuate rapidly, suggesting inaccuracy of the automated device.
- Due to the nonlinear relationship of the oxyhemoglobin dissociation curve, pulse oximeters are helpful for screening and monitoring patients but are not an accurate measure of Pao_2 in hypoxic patients and thus should be used with caution.
- In the setting of MetHb or COHb exposure, the pulse oximeter may read falsely elevated, so a CO oximeter is necessary to distinguish oxygenated and deoxygenated blood from other dyshemoglobinemias.

KEY CONCEPTS—cont'd

- Capnography supplements oximetry by providing useful information regarding pathologic conditions and response to therapy. It is highly correlated with cardiac output and therefore is a good indicator of the adequacy of cardiopulmonary resuscitation in arrest victims.
- Capnography is also useful in spontaneously breathing patients. It can be a good indicator of perfusion, ventilatory response to therapy in respiratory distress patients, adequacy of ventilation during procedural sedation, and rapid assessment and response to therapy in patients with metabolic derangements.
- Monitoring modalities, when used appropriately, help identify the effectiveness of interventions, predict deterioration, track the patient's clinical course, and inform clinical decision making.
- Noninvasive blood pressure monitors remain the standard for ongoing measurement of dynamic change. A single episode of hypotension is predictive of subsequent hemodynamic compromise. Despite generally high accuracy and dependability of blood pressure monitoring devices, determining blood pressure manuallly may be required at times to verify sudden changes in blood pressure measurements or when readings fluctuate rapidly, suggesting inaccuracy of the automated device.
- Due to the nonlinear relationship of the oxyhemoglobin dissociation curve, pulse oximeters are helpful for screening and monitoring patients but are not an accurate measure of Pa_{O_2} in hypoxic patients and thus should be used with caution.
- In the setting of MetHb or COHb exposure, the pulse oximeter reading may be falsely elevated; thus, a CO oximeter is necessary to distinguish oxygenated and deoxygenated blood from other dyshemoglobinemias.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 5: QUESTIONS & ANSWERS

5.1. A 27-year-old firefighter presents with a headache, chest pain, and severe shortness of breath after working at the scene of a house fire. The physical examination is remarkable for a blood pressure of 155/90 mm Hg, heart rate of 110 beats/min, respiratory rate of 28 breaths/min, oxygen (O_2) saturation of 98% on room air, and clear lungs. The chest radiograph is unremarkable. Which of the following may be responsible for a normal O_2 saturation despite such respiratory stress?

A. Carboxyhemoglobin
B. Cyanide
C. Melanin
D. Methemoglobin
E. Methylene blue

Answer: A. Pulse oximetry is based on differences in the optical transmission spectrum of oxygenated and deoxygenated hemoglobin. Pulse oximeters measure the pulse variation in red and infrared light transmitted through a tissue bed. Data averaged over several arterial pulse cycles are then presented as saturation. Carboxyhemoglobin (COHb) contributes to light absorption and causes errors in oximetry readings. The pulse oximeter senses COHb as though it were mostly oxyhemoglobin and provides a falsely high reading.

5.2. A 17-year-old male presents with fatigue, bluish-colored skin, and mild shortness of breath. He has recently been to the dentist to have his molars removed and reports that his only medications are ibuprofen and multiple applications of over-the-counter topical pain relief. The physical examination is remarkable for a blood pressure of 137/85 mm Hg, heart rate of 95 beats/min, respiratory rate of 20 breaths/min, and O_2 saturation of 85% on room air. The chest radiograph is unremarkable. Which of the following is most likely responsible for this O_2 saturation in the context of this presentation?

A. Carboxyhemoglobin
B. Cyanide
C. Lactate
D. Methemoglobin
E. Methylene blue

Answer: D. As with carboxyhemoglobin, methemoglobin (MetHb) contributes to pulse oximetry light absorption and causes an error in oximetry readings. MetHb produces a large pulsatile absorbance signal at red and infrared wavelengths. This forces the absorbance ratio toward unity, which corresponds to an oxygen saturation measured by pulse oximetry (Spo_2) of 85%. Thus, with high levels of MetHb, the Spo_2 is erroneously low when the arterial saturation is higher than 85% and erroneously high when the arterial saturation is less than 85%.

5.3. Which of the following conditions would lead to a prolongation of the rapid upstroke phase of the capnography curve?

A. Bronchospasm
B. Pneumothorax
C. Pregnancy
D. Pulmonary embolism
E. Sepsis

Answer: A. The rapid upstroke phase of the capnography curve represents the transition from inspiration to expiration and the mixing of dead space and alveolar gas. Prolongation of this phase occurs with obstruction to expiratory gas flow (eg, obstructive lung disease, bronchospasm, kinked endotracheal tube) or leaks in the breathing system.

5.4. Which of the following may lead to false-negative results when capnometry is used to confirm intubation of the trachea?

A. Bicarbonate infusion
B. Cardiac arrest
C. Chronic obstructive pulmonary disease
D. Pneumothorax
E. Pulmonary embolism

Answer: B. Capnometry can confirm intubation of the trachea but may give false-negative results in cardiac arrest if delivery of carbon dioxide (CO_2) from the periphery to the lungs is sufficiently diminished. Misleading end-tidal CO_2 ($ETco_2$) readings causing false-positive results can occur with esophageal intubation after bag-mask ventilation and ingestion of carbonated beverages or antacids. However, detection of $ETco_2$ usually ceases after six breaths and, if capnography is used, the tracings look abnormal. $ETco_2$ is also falsely elevated for 5 to 10 minutes after injection of sodium bicarbonate. In nonarrest settings, the $ETco_2$ approaches 100% sensitivity and specificity in confirming correct tube placement.

CHAPTER 6

Shock

Michael A. Puskarich | Alan E. Jones

PRINCIPLES

Background and Importance

In philosophic terms, shock can be viewed as a transition between life and death. Whether shock results from hemorrhage, sepsis, or cardiac failure, mortality rates exceed 20%.[1,2] In scientific lexicon, shock results from the widespread failure of the circulatory system to oxygenate and nourish the body adequately. At the cellular level, shock alters mitochondrial energy transfer and evokes the production and accumulation of toxic chemicals. The emergency clinician identifies shock by linking the qualitative clinical impression, synthesized from the patient's history of present illness, age, health status, and general appearance, to quantitative data, including vital signs, laboratory tests, urine output, and measurements of systemic oxygenation. When the clinical impression and quantitative data suggest widespread organ hypoperfusion, emergent resuscitation is used to restore tissue oxygenation and substrate delivery to prevent deterioration into a vicious cycle of systemic inflammation, organ dysfunction, and death. Anaphylaxis and its treatment are discussed in Chapter 109.

For years, shock has been classified into four broad categories based on Blalock's 1934 description—hematologic, vasogenic, cardiogenic, and neurologic. This basic organization scheme remains useful today for discussions of pathophysiology. For discussions of management, a system based on the requisite treatment response is more clinically useful. Box 6.1 outlines five categories of shock that generally have specific mechanisms and treatments. The epidemiology of shock in the emergency department (ED) context is diverse and evolving. Traumatic, cardiogenic, or septic shock are diagnosed in fewer than 3% of ED patients. Our understanding of the metabolic, systemic, and inflammatory responses that occur in all types of circulatory shock and the specific pathophysiology of the major causes of shock has led to dramatic increases in the early identification and treatment of these states, with resultant improvement in outcomes.

Anatomy, Physiology, and Pathophysiology

At the subcellular level, shock first affects the mitochondria. Mitochondria function at the lowest oxygen tension in the body, but they consume almost all the oxygen used by the body. More than 95% of aerobic chemical energy comes from mitochondrial combustion of fuel substrates (fats, carbohydrates, ketones) plus oxygen into carbon dioxide (CO_2) and water. Mitochondria have therefore been referred to as the canaries in the coal mine because they are affected first in conditions of inadequate tissue perfusion. When mitochondria have inadequate oxygen, the cell catabolizes fuels to lactate, which accumulates and diffuses into the blood. In the setting of hypoxia, mitochondria are unable to provide sufficient energy to maintain cellular processes and, at a certain point, an irreversible series of intracellular cascades leads to cellular dysfunction, organ failure, and ultimately death.

Specific Causes

Hemorrhagic Shock

Hemorrhagic shock results from a rapid reduction in intravascular blood volume from any cause. Rapid hemorrhage generally causes an increase in the strength of cardiac contraction and heart rate (HR), followed by baroreceptor activation and peripheral vasoconstriction. Typically, an initial slight increase in the diastolic blood pressure (BP) with a narrowing of the pulse pressure progresses to a decrease in ventricular filling and cardiac output, causing a reduction in systolic BP. This response varies considerably with cardiopulmonary status, age, and presence of vasoactive medications. The responses of HR and BP are therefore notoriously variable in hemorrhage, so no firm conclusion can be made at the bedside about the presence, absence, or degree of hemorrhagic shock by simple evaluation of the HR and BP.

Even before the cardiac output begins to decline, blood flow is directed away from noncritical organs and tissues, and their cells produce and release lactic acid. Consequently, acidemia often precedes any significant decrease in cardiac output. However, the blood contains bicarbonate ions that buffer the blood pH, keeping it near neutral, even as lactic acid accumulates. The base deficit—amount of strong base that would have to be added to 1 L of blood to normalize the pH—represents an index of how far the bloodstream has dipped into this reserve. A normal base deficit is more positive than −2 mEq/L. The arterial and venous blood base deficit can become more negative early in hemorrhage, even while blood pH and BP remain normal. The base deficit, therefore, crudely represents the physiologic endpoint that distinguishes trivial blood loss from clinically significant hemorrhage. In addition to chemical buffering, the body responds to small reductions in arterial pH by activating brainstem chemoreceptors, which increase minute ventilation, leading to reduced partial pressure of carbon dioxide in the arterial blood ($Paco_2$), providing an additional means of compensating for evolving acidosis.

With progressive blood loss, cardiovascular reflexes can no longer sustain adequate filling of the vasculature, and frank hypotension supervenes. Arterial hypotension is generally and arbitrarily defined as an arterial BP less than 90 mm Hg. Usually coincident with the development of hypotension, the compensatory chemical and respiratory buffering mechanisms become overwhelmed, resulting in acidosis. The hypothalamic-pituitary-adrenomedullary axis is activated, releasing stress hormones and inducing glycogenolysis, lipolysis, and mild hypokalemia. Significant traumatic hemorrhage in otherwise normal ED patients, therefore, will generally cause an arterial lactate concentration greater than 4.0 mmol/L, $Paco_2$ less than 35 mm Hg, mild hyperglycemia (150–170 mg/dL) and mild hypokalemia (3.5–3.7 mEq/L). Although hemorrhagic hypotension reduces lung perfusion, arterial hypoxemia should not be attributed simply to blood loss, but instead should prompt investigation for aspiration, airway obstruction, alveolar consolidation, or lung injury.

BOX 6.1

Five Categories of Shock According to Primary Treatment of Causes and Problems

PRIMARILY INFUSION OF VOLUME

Hemorrhagic shock
- Traumatic
- Gastrointestinal
- Body cavity

Hypovolemia
- Gastrointestinal losses
- Dehydration from insensible losses
- Third-space sequestration from inflammation

VOLUME INFUSION AND VASOPRESSOR SUPPORT

Septic shock
Anaphylactic shock
Central neurogenic shock
Drug overdose

IMPROVEMENT IN PUMP FUNCTION BY INFUSION OF INOTROPIC SUPPORT OR REVERSAL OF THE CAUSE OF PUMP DYSFUNCTION

Myocardial ischemia
- Coronary artery thrombosis
- Arterial hypotension with hypoxemia

Cardiomyopathy
- Acute myocarditis
- Chronic diseases of heart muscle (ischemic, diabetic, infiltrative, endocrinologic, congenital)

Cardiac rhythm disturbances
- Atrial fibrillation with rapid ventricular response
- Ventricular tachycardia
- Supraventricular tachycardia

Septic shock with myocardial failure (hypodynamic shock)

Overdose of negative inotropic drug
- Beta blocker
- Calcium channel antagonist

Structural cardiac damage
- Traumatic (eg, flail mitral valve)
- Ventriculoseptal rupture
- Papillary muscle rupture

IMMEDIATE RELIEF FROM OBSTRUCTION TO CARDIAC OUTPUT

Pulmonary embolism
Cardiac tamponade
Tension pneumothorax

Valvular dysfunction
- Acute thrombosis of prosthetic valve
- Critical aortic stenosis

Congenital heart defects in newborn (eg, closure of patent ductus arteriosus, with critical aortic coarctation)

Critical idiopathic subaortic stenosis (hypertrophic obstructive cardiomyopathy)

SPECIFIC ANTIDOTES DUE TO CELLULAR OR MITOCHONDRIAL POISONS

Carbon monoxide
Methemoglobinemia
Hydrogen sulfide
Cyanide

The second phase of organ injury from hemorrhagic shock occurs during resuscitation. The acute phase of hemorrhage initiates the inflammatory cascade, and resuscitation unleashes these volatile inflammatory mediators on the body, inducing organ injury. During resuscitation, neutrophils become more aggressive, binding to the lung endothelium and causing capillary leakage that characterizes acute respiratory distress syndrome (ARDS). Inflammatory cytokines are liberated, causing additional cellular damage and compounded by persistent microischemia in numerous organs due to an imbalance between vasodilation by nitric oxide (NO) and vasoconstriction by endothelins. The liver demonstrates centrilobular injury, demonstrated clinically by elevated transaminase levels, whereas the kidney may manifest acute spasm of the preglomerular arterioles, with resultant acute tubular necrosis. A growing body of evidence has suggested that resuscitation from hemorrhage exerts greater injury on the heart than the actual hypotensive insult.

Septic Shock

Although historically presented as the archetype of vasogenic or distributive shock, in reality the clinical course of septic shock is much more complex and varies over the course of the disease, with variables degrees of intravascular volume depletion, peripheral vasodialation, and impaired cardiac function. Septic shock can be produced by infection with any microbe, although in half or more of cases of septic shock, no organism is identified. One well-known mediator of sepsis is lipopolysaccharide (LPS), contained in the outer cell membrane of gram-negative bacteria; however, gram-positive organisms are now the primary cause of sepsis in hospitalized patients, indicating that the pathophysiology of sepsis cannot be explained simply by the response to LPS.

Septic shock often causes three major effects that must be addressed during resuscitation—hypovolemia, cardiovascular depression, and induction of systemic inflammation. Septic shock produces relative and absolute hypovolemia, reducing right ventricular filling. Absolute hypovolemia results from gastrointestinal volume loss, tachypnea, sweating, and decreased fluid intake during development of the illness. Further relative hypovolemia results from increasing venous capacitance in conjunction with increased capillary leak and resultant loss of intravascular volume into third spaces. Septic shock causes direct myocardial depression. Measurements of cardiac contractility have shown that mechanical function becomes impaired early in the course of septic shock, even in the hyperdynamic stages. Circulating mediators, myocardial cellular injury from inflammation, and deranged metabolism interact synergistically to injure the heart during septic shock, and specific cytokines (most notably tumor necrosis factor alpha [TNF-α] and interleukin-1 beta [IL-1β]), overproduction of NO by inducible nitric oxide synthase (iNOS), and possibly impairment in mitochondrial oxidative phosphorylation, may all play a role. Similar to hemorrhagic shock, systemic inflammation causes capillary leak in the lung, resulting in ARDS. Widespread systemic inflammation likely plays a role in the development and persistence of multisystem organ failure in sepsis through microvascular and mitochondrial dysfunction. Clinical trials to date have yet to demonstrate the effectiveness of specific or general antiinflammatory therapies in mitigating this response, and the treatment of septic shock relies primarily on the reversal of shock, supportive care, and source control.

Cardiogenic Shock

Cardiogenic shock results when more than 40% of the myocardium becomes dysfunctional from ischemia, inflammation, toxins, or immune injury. Otherwise, cardiogenic shock essentially produces the same circulatory and metabolic alterations as those that are observed with hemorrhagic shock. Undoubtedly, impaired baseline cardiac function can contribute to the development of circulatory shock secondary to infection, hemorrhage, or vasodilatory drug overdose. However, when shock results from a pure cardiac cause, severe left ventricular dysfunction will be evident on echocardiography early in the course. Patients with severe underlying dysfunction are far more likely to have a cardiogenic cause of shock than patients with normal or moderate left ventricular dysfunction.

Neurogenic Shock

Neurogenic shock results from interrupted sympathetic and parasympathetic input from the spinal cord to the heart and peripheral vasculature, typically resulting from acute traumatic injury. Traditionally, it has been described as peripheral vasodilation in conjunction with bradycardia. However, ED patients with shock from acute spinal injury actually manifest a range of heart rates and peripheral vascular resistance, most likely due to variable location of injury and the balance between disrupted efferent sympathetic and parasympathetic tone.[3] As a result, no single presentation adequately summarizes patients with neurogenic shock. It is likely that the downstream pathophysiologic consequences of persistently impaired perfusion mimic those of cardiogenic and hemorrhagic shock.

MANAGEMENT

Decision Making

Patients presenting to the the ED in shock frequently have no obvious cause. Rapid recognition of shock requires the integration of information from the immediate history and physical examination and is strongly supported by the presence of a worsening base deficit or lactic acidosis. In general, patients with shock exhibit a stress response; they are ill appearing, asthenic, pale, often sweating, usually tachypneic, and often have a weak and rapid pulse (Box 6.2). In all patients with shock, HR, BP, and oxyhemoglobin saturation are continuously monitored. HR can be normal or low in shock, especially in cases complicated by prescribed drugs that depress HR. BP initially can be normal because of adrenergic reflexes. Noninvasive measurement of BP may be inaccurate in severe hypotensive states, and insertion of an arterial pressure monitoring line improves the ability to monitor the dynamic response to therapy, which is particularly important if vasoactive medications are administered. BP and HR correlate poorly with the cardiac index (CI) in shock and often underestimate the severity of systemic hypoperfusion. Moreover, children with hypovolemic shock frequently demonstrate a normal BP until they rapidly deteriorate.

Urine output provides an excellent indicator of vital organ perfusion and is readily available with insertion of a Foley catheter. Measurement of urine output, however, requires 30 to 60 minutes for accurate determination of whether output is normal (>1.0 mL/kg/h), reduced (0.5–1.0 mL/kg/h), or severely reduced (<0.5 mL/kg/h), and is of limited use in patients with preexisting renal disease. Arterial or venous lactate concentration and the base deficit provide accurate assessment of global perfusion status. A lactate concentration greater than 4.0 mM or base deficit more negative than −4 mEq/L indicates circulatory insufficiency severe enough to cause subsequent multiple organ failure.[4] A downward trend of the serum lactate concentration or upward trend of the base deficit, with correspondingly improving vital signs and urine output, reliably gauge the adequacy of resuscitation and prognosis in shock from any cause. A rising lactate concentration (or refractory hypotension, with worsening base deficit), despite ongoing resuscitation, calls for more intensive measures. Once the empirical criteria for circulatory shock have been discovered, the next step is to consider the cause of the shock. Fig. 6.1 shows a potential sequence of decisions to help arrive at a diagnosis in a patient with undifferentiated shock.

The history, vital signs, and physical examination documented by prehospital providers can be useful in ED evaluation and management. Patients with prehospital hypotension, whether of medical or traumatic origin, have up to a fourfold higher in-hospital mortality rate than patients without hypotension.[5]

On physical examination, dry mucous membranes suggest dehydration, whereas jugular venous distention suggests congestive cardiac failure or right ventricular strain from pulmonary embolism (PE). Muffled heart sounds with jugular venous distention suggest cardiac tamponade, whereas a loud, machine-like, systolic murmur indicates acute rupture of a papillary muscle or interventricular septum. Diffuse rhonchi suggest bronchospasm, cardiac failure, or PE. Abdominal tenderness may indicate peritonitis, intestinal perforation, or occult trauma. The presence of melanotic stool on rectal examination indicates gastrointestinal hemorrhage. The neurologic examination documents responsiveness, cognition, and presence of any focal deficits and can be a means of clinically assessing end-organ perfusion. In children, documentation should include response to parents, appropriateness of crying, symmetry of grimace, symmetry of extremity movements, and motor tone.

Laboratory, radiographic, and other ancillary data can be useful to assess tissue and vital organ perfusion and diagnose injury from trauma, find the source of infection with sepsis, or identify the cause of cardiac failure. Chest radiography, electrocardiography, finger stick glucose measurement, complete blood count (CBC), urinalysis, serum electrolyte levels, and kidney and liver function tests are indicated for most patients with suspected shock. Arterial blood gas determination provides the base deficit and allows correlation of arterial gas tensions (Pao_2 and $Paco_2$) with those measured by pulse oximetry and capnography. Serum lactate level measurement is performed as early as possible in patients with suspected shock; venous or arterial lactate concentrations can be used. If the peripheral venous lactate level is used, the effect of time, storage temperature, and tourniquet use have no significant effect if the measurement is done within 15 minutes after the sample was obtained. Cardiac and abdominal bedside ultrasound scanning can screen for inadequate central venous volume, occult hemoperitoneum, abdominal aortic aneurysm, left ventricular failure, and cardiac tamponade. A systematic ultrasound protocol can significantly improve the

BOX 6.2

Empirical Criteria for Diagnosis of Circulatory Shock[a]

- Ill appearance or altered mental status
- Heart rate > 100 beats/min
- Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
- Arterial base deficit < –4 mEq/L or lactate level > 4 mM/L
- Urine output < 0.5 mL/kg/h
- Arterial hypotension > 30 min duration, continuous

[a]Regardless of cause. Four criteria should be met.

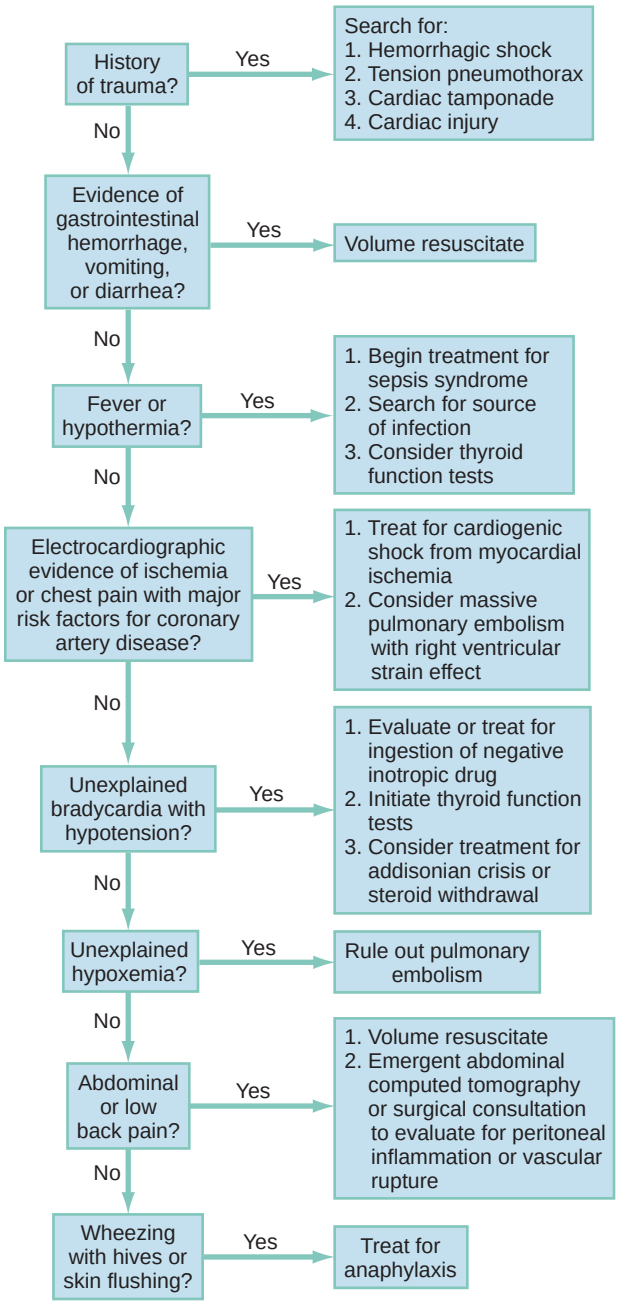

Fig. 6.1. Flow diagram to classify undifferentiated shock.

emergency clinician's ability to accurately diagnose the cause of undifferentiated shock in ED patients, and the finding of hyperdynamic left ventricular function in patients with undifferentiated shock strongly suggests sepsis.[6,7]

Consensus definitions of shock show the spectrum of hypoperfusion for the following three common causes of shock (Box 6.3):

1. *Hemorrhagic shock.* The American College of Surgeons has divided hemorrhagic shock into four stages, depending on the severity of blood loss and physiologic response to this loss, but such arbitrary divisions are of little value and are not accurate reflections of degree of hemorrhage in clinical practice.[8] A more useful approach defines hemorrhagic shock as being present when systemic hypoperfusion manifests as lactic acidosis or increasing base deficit with concomitant organ dysfunction.

BOX 6.3

Definitions and Criteria for Septic, Hemorrhagic, and Cardiogenic Shock

SEPTIC SHOCK

Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the following:

1. Temperature > 38°C or < 36°C
2. Heart rate > 90 beats/min
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. White blood cell count > 12,000/mm^3, < 4,000/mm^3, or > 10% band neutrophilia

Severe Sepsis

SIRS with suspected or confirmed infection and associated with organ dysfunction or hypotension; organ dysfunction may include presence of lactic acidosis, oliguria, and/or altered mental status.

Septic Shock

SIRS with suspected or confirmed infection with hypotension despite adequate fluid resuscitation requiring vasopressor support; septic shock should still be diagnosed if vasopressor therapy has normalized blood pressure.

HEMORRHAGIC SHOCK

Simple Hemorrhage

Suspected bleeding with pulse rate < 100 beats/min, normal respiratory rate, normal blood pressure, and normal base deficit

Hemorrhage with Hypoperfusion

Suspected bleeding with base deficit < –4 mEq/L *or* persistent pulse rate > 100 beats/min

Hemorrhagic Shock

Suspected bleeding, with at least four criteria listed in Box 6.2

CARDIOGENIC SHOCK

Cardiac Failure

Clinical evidence of impaired forward flow of the heart, including presence of dyspnea, tachycardia, pulmonary edema, peripheral edema, and/or cyanosis

Cardiogenic Shock

Cardiac failure plus four criteria listed in Box 6.2

2. *Septic shock.* International consensus definitions distinguish septic shock from its precursor conditions—systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis.[9] SIRS is often a precursor of shock, but the nonspecific criteria for SIRS are found in a large variety of conditions, many of which are benign, so the clinical context is vital to understanding the significance of these physiologic variations. Although a consensus definition of septic shock requires persistent hypotension after fluid resuscitation, initiation of treatment for empirically diagnosed severe sepsis or septic shock should not await the onset of hypotension. The incorporation of an indicator of tissue hypoperfusion (Box 6.4) into the clinical assessment may improve identification of hypoperfusion, particularly in subtle cases.[10]
3. *Cardiogenic shock.* Cardiogenic shock should be thought to be present whenever cardiac failure (ischemic, toxic, or obstructive) causes systemic hypoperfusion that manifests as lactic acidosis with organ dysfunction.

Box 6.5 presents the general treatment approach for these three common causes of shock.

BOX 6.4

Variables Indicating Tissue Hypoperfusion

Hypotension
Tachycardia
Low cardiac output
Dusky or mottled skin
Delayed capillary refill
Altered mental state
Low urine output
Low central venous oxygen saturation
Elevated lactate level

BOX 6.5

Clinical Management Guidelines for Three Common Causes of Shock

HEMORRHAGIC SHOCK

- Ensure adequate ventilation and oxygenation.
- Provide immediate control of hemorrhage, when possible (eg, traction for long bone fractures, direct pressure), and obtain urgent consultation as indicated for uncontrollable hemorrhage.
- Initiate judicious infusion of isotonic crystalloid solution (10–20 mL/kg).
- With evidence of poor organ perfusion and 30-min anticipated delay to hemorrhage control, begin packed red blood cell (PRBC) infusion (5–10 mL/kg).
- With suspected massive hemorrhage, immediate PRBC transfusion may be preferable as the initial resuscitation fluid.
- Treat coincident dysrhythmias (eg, atrial fibrillation with synchronized cardioversion).

CARDIOGENIC SHOCK

- Ameliorate increased work of breathing; provide oxygen and positive end-expiratory pressure (PEEP) for pulmonary edema.
- Begin vasopressor or inotropic support; norepinephrine (0.5 μg/min) and dobutamine (5 μg/kg/min) are common empirical agents.
- Seek to reverse the insult (eg, thrombolysis, percutaneous transluminal angioplasty).
- Consider intraaortic balloon pump counterpulsation for refractory shock.

SEPTIC SHOCK

- Ensure adequate oxygenation; remove work of breathing.
- Administer 20 mL of crystalloid/kg or 5 mL of colloid (albumin)/kg, and titrate infusion based on dynamic indices, volume responsiveness, and/or urine output.
- Begin antimicrobial therapy; attempt surgical drainage or débridement.
- Begin PRBC infusion for hemoglobin level <7 g/dL.

If volume restoration fails to improve organ perfusion, begin vasopressor support with norepinephrine, infused at 0.5 μg/min.

Monitoring Perfusion Status

Patients with cardiac failure or renal failure may benefit from closer measurement of dynamic variables of fluid responsiveness that can be measured from an arterial line (eg, stroke volume variation or stroke volume index) or a central venous line (central venous pressure [CVP]).[11] A triple-lumen catheter allows for accurate measurement of the CVP, although the clinical utility of these measurements has been debated. However, a triple-lumen catheter also allows for safe infusion of vasopressors in hypotensive patients unresponsive to an initial fluid bolus, as well as more rapid simultaneous infusion of intravenous (IV) fluids and antibiotics in patients with limited IV access. In children, a 3- or 5-Fr bilumen catheter can be placed in the femoral vein with few complications. If unable to attain adequate peripheral or central venous access rapidly in patients with shock, intraosseous (IO) access should be established, because it is easy and can provide a temporary method of administering fluid resuscitation and medications to adults and children. However, IO access should be considered a bridge to definitive IV access due to the risk of complications with prolonged usage in the inpatient setting. If vasoactive medications are administered, additional peripheral IV catheters will be required for infusion of crystalloid and other treatments. Many patients with renal disease or cancer have indwelling catheters in place. In patients with empirical criteria for shock, this catheter should be used for IV access, unless satisfactory access has already been established at other anatomic sites. In EDs where the standard practice is not to use these ports at the request of other emergency clinicians, a specific hospital policy and training session should be developed to make an exception in the case of circulatory shock. In general, failure to administer fluids rapidly and in sufficient quantity outweighs considerations about preservation of the line for future therapy.

Quantitative Resuscitation

Quantitative resuscitation, also called goal-directed therapy, goal-oriented resuscitation, or hemodynamic optimization, was first described in 1988 and refers to the practice of resuscitating patients to predefined physiologic endpoints indicating that systemic perfusion and vital organ function have been restored. Since that time, many studies have evaluated the efficacy of such a therapeutic approach to shock and have confirmed its benefit for reducing mortality. For many years, in the intensive care unit (ICU), clinicians have relied on the use of the pulmonary artery catheter to help optimize left ventricular filling indices, but data supporting the efficacy of this practice on patient-centered outcomes such as mortality are lacking. There is insufficient evidence to support the use of pulmonary artery catheters for ED patients, and their significant complication rate, in the context of uncertain or no benefit, leads us to recommend against their routine use.

Lactate clearance refers to serial measurements of the venous or arterial lactate level and is calculated according to the following formula:

$$([\text{Lactate}_{\text{initial}} - \text{lactate}_{\text{delayed}}]/\text{lactate}_{\text{initial}}) \times 100$$

Lactate clearance has been shown to be equivalent to central venous oxygen saturation as an endpoint of early septic shock resuscitation.[12] Lactate clearance measurements are easily obtained from peripheral venous blood and are a preferred endpoint of resuscitation. If the lactate concentration has not decreased by 10% to 20% 2 hours after resuscitation has begun, additional steps are undertaken to improve systemic perfusion. Resuscitation should continue until the lactate concentration drops below 2 mM/L.[13]

Mixed venous oxygen saturation ($S\bar{v}O_2$) measurements reflect the balance between oxygen delivery and oxygen consumption. The $S\bar{v}O_2$ can be used as a surrogate for CI—targeting an $S\bar{v}O_2$ of 65% is equivalent to reaching a CI of 2.5–3.5 L/min/m^2—as a therapeutic endpoint in critically ill patients. Although $S\bar{v}O_2$ requires the use of a pulmonary artery catheter, the central venous oxygen saturation ($Sc\bar{v}O_2$) drawn from the central circulation has been shown to parallel changes or trends over time and is the

preferable method for pulmonary artery catheter placement in the ED.

Quantitative resuscitation, which incorporates multiple indices of circulatory and oxygenation status, has been shown in meta-analyses to reduce mortality and morbidity in ED patients with severe sepsis or septic shock significantly when instituted as early in the disease course as is practical. In such an approach, patients are resuscitated early, within the first 6 hours, to achieve normalization of markers of volume status, perfusion, and adequate oxygen delivery (Fig. 6-2). The first description of an ED-based quantitative resuscitation strategy targeted specific volume, perfusion, and oxygen delivery endpoints and was termed *early goal-directed therapy* (EGDT).[14] Recently, three large multicenter trials did not demonstrate a mortality advantage for patients receiving the complex and invasive physiologic interventions associated with EGDT as compared to the appropriate volume resuscitation and targeted therapies that constitute the current usual care of shock.[11,15,16] Patients in these studies received 2 to 4 L early volume resuscitation and relatively prompt antibiotic administration, suggesting that early recognition and initiation of fluid and antibiotic therapy, in conjunction with close monitoring and thoughtful care, may be more important than the use of invasive measurements to attain the specific resuscitation goals suggested by earlier studies.

Pharmacology

Volume Replacement

Most patients with shock can be fully resuscitated with peripheral venous access established with at least two 18-gauge two catheters. The goal in volume replacement is slightly elevated left ventricular end-diastolic volume, which is difficult to measure in the ED. Historically, CVP has been used to estimate right ventricular filling pressure and is used in some quantitative resuscitation algorithms. However, CVP measurement does not accurately reflect left ventricular end-diastolic volume, and CVP poorly predicts the hemodynamic response to a fluid challenge. Thus, assessment of fluid responsiveness and fluid resuscitation should not be based solely on CVP. A better approach would include the use of the clinical response to fluid resuscitation, such as increases in urine output, BP, and decreasing lactate concentrations, alone or in combination with CVP measurements. In patients for whom fluid resuscitation may be associated with higher risk of harm (eg, severe systolic heart failure), the use of dynamic variables of fluid responsiveness that can be measured from an arterial line (eg, stroke volume variation, stroke volume index, passive straight leg raise) may be beneficial over empirical fluid boluses, but their use in the ED has not been studied.

Crystalloids. Standard treatment for hemorrhagic shock historically consisted of rapidly infusing several liters of isotonic crystalloid in adults or three successive 20-mL/kg boluses in children. Recent studies have endorsed the concept of delayed resuscitation or hypotensive resuscitation for hemorrhagic shock (see Chapter 33). No study to date has demonstrated the survival benefit of one type of crystalloid versus another; therefore, the choice of fluids may be less important than scrupulous monitoring for adequate tissue perfusion. Although a single Australian study has suggested an association between use of chloride-rich solutions and subsequent renal dysfunction in ICU patients, the study solutions included colloids as well as crystalloids and were not randomized, so any causative inference is not justified.[17] Normal saline or lactated Ringer's solution may be used for volume replacement during resuscitation, with no evidence clearly supporting one over the other. Accordingly, the selection of isotonic crystalloid solution may be based on institutional, departmental, or individual preferences. Initial volume replacement consists of the rapid infusion of 20 to 25 mL of isotonic crystalloid per kilogram.

Colloids and Hypertonic Saline. Colloids, including albumin, have been used in patients with hemorrhage, but at considerable increase in cost and without effect on morbidity or mortality. Colloids offer the theoretic advantage of a high osmotic pressure, which should help maintain normal intravascular volume. Initial resuscitation fluid treatment with hypertonic saline or hypertonic saline and dextran, compared with normal saline, has not been found to result in superior 28-day survival.[18]

In the setting of septic shock, initial fluid resuscitation should consist of serial boluses of IV isotonic crystalloid as long as the patient continues to demonstrate a positive hemodynamic response to fluid loading. Persistent hypotension, despite 30 mL/kg of IV fluid, indicates the need to add vasopressors to the resuscitation (see below). If patients require large volumes of crystalloid (>4 L), we recommend adding 5- to 10-mL/kg boluses of a natural colloid (eg, albumin), rather than additional isotonic crystalloid alone, until volume responsiveness is achieved.[19] We do not recommend use of synthetic colloids, such as hydroxyethyl hetastarch, which have recently been demonstrated to be associated with a higher risk of renal failure.[20] The infusion of hemoglobin-based blood substitutes as alternatives to packed red blood cells (PRBCs) for the resuscitation of hemorrhagic shock has been extensively studied and is associated with significant increased risk of death and myocardial infarction; we recommend against their use.

Blood Products. In the setting of hemorrhage or a critically low hemoglobin level (<7g/dL), if criteria for shock persist despite crystalloid infusion (see Box 6.2), we recommend transfusion of PRBCs (1–2 units in adults or 5–10 mL/kg in children). Fully crossmatched blood is safest and is always preferable unless the patient's need is considered sufficiently urgent to justify the use of type-specific or even uncrossmatched blood. Use of the latter is generally confined to patients with hemorrhagic shock with persistent, severe, arterial hypotension and massive or uncontrolled hemorrhage. O-negative blood is used in women of childbearing age, and O-positive blood is used in all others (see Chapter 111). If patients require more than 2 units of PRBCs for hemorrhage, we recommend a balanced resuscitation using PRBCs, fresh-frozen plasma, and platelets in a 1 : 1 : 1 ratio, which is associated with better hemostasis and lower death due to exsanguination by 24 hours.[1]

The goal hemoglobin target for patients with septic shock in the acute resuscitation window, generally defined as the first 6 hours following presentation, remains controversial. A recent large randomized controlled trial (RCT) in ICU patients with septic shock found similar rates of ischemic events, use of life support, and 90-day mortality among patients transfused at a threshold of 7 g/dL as compared to 9 g/dL.[6] Thus, we recommend transfusion of PRBCs at a threshold of 7 g/dL in patients with septic shock unless specific contraindications exist or patients refuse transfusion.

Vasopressors

The primary goal of vasopressor support is to increase cardiac output and oxygen delivery to vital organs when crystalloid resuscitation alone is inadequate. To reduce the potential for limb damage from extravasation from a peripheral IV injection, vasoactive medications are optimally administered through a central venous catheter, although this is not always feasible in the acute setting. Patients with septic shock who remain hypotensive after

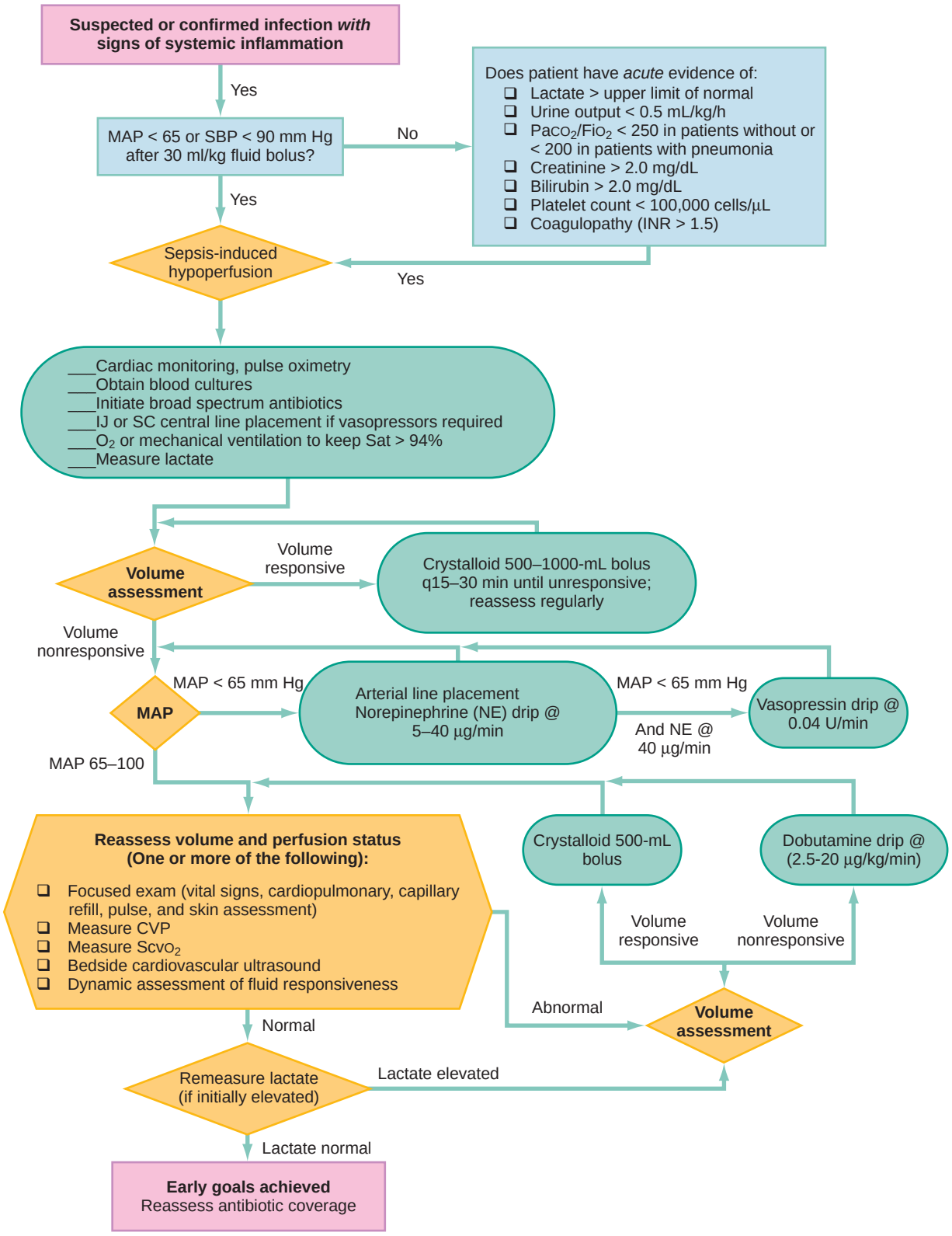

Fig. 6.2. Flow diagram outlining an example of a formalized resuscitation strategy. This figure illustrates the sequential targeting of preload, afterload, oxygen supply, and demand matching for sepsis-induced hypoperfusion. The protocol outlines specific hemodynamic and physiologic parameters that the emergency clinician should seek to attain within the first 6 hours of care. This protocol is focused on resuscitation and should be used in conjunction with standard clinical care for patients with suspected infection, such as appropriate diagnostic studies, to determine the focus of infection and appropriate antimicrobial agents to treat the infection. *HCT,* Hematocrit; *ICU,* intensive care unit; *IJ,* internal jugular; *INR,* international normalized ratio; *MAP,* mean arterial pressure; *NS,* normal saline; $Paco_2$, partial pressure of carbon dioxide, arterial; *Sat,* peripheral oxygen saturation; *SBP,* systolic blood pressure; *SC,* subclavian; $Scv\bar{o}_2$, central venous oxygen saturation; *SIRS,* systemic inflammatory response syndrome; *WBC,* white blood cell count.

a 30-mL/kg fluid bolus generally require vasopressor support. Several randomized trials and a meta-analysis have suggested that norepinephrine (5–30 μg/min) is associated with improved efficacy and lower rates of adverse effects, making norepinephrine the vasopressor of choice for correction of hypotension in septic shock.[7] In patients who remain in shock after initial crystalloid boluses, norepinephrine should be initiated at a rate of 0.05 μg/kg/min and titrated at 3- to 5-minute intervals until the mean arterial pressure is greater than 65 mm Hg or the systolic BP is greater than 90 mm Hg. There are no clear data regarding an absolute maximum dose, but generally there is little or no additional pressor effect once a dose of 30 μg/min has been reached. Vasopressin can be added as a second vasopressor agent when norepinephrine reaches the maximum dose of 30 μg/min. Vasopressin should be administered at a fixed rate of 0.03 to 0.04 units/min and should not be titrated. A trial of vasopressin cessation can be attempted once the patient demonstrates improving hemodynamics over at least a 6-hour period. Except in cases of a prolonged stay in the ED, vasopressors will not be stopped until the patient is in the ICU. Following vasopressor initiation, particularly in patients who require high or rapid upward titration of the vasopressor dose, patients should be reassessed for their responsiveness to additional fluid boluses through the use of dynamic variables or empirical 500-mL boluses, with careful attention to the clinical response. Vasopressor support, along with crystalloid therapy, is continued until the patient can maintain the blood pressures listed without vasopressor support, which can be tested at the bedside by weaning the vasopressor agent at a rate of 2 to 3 μg/min every 5 to 10 minutes.

Inotropes

Dobutamine may also be used with norepinephrine to increase cardiac output and maintain adequate oxygen delivery in cardiogenic and septic shock. In the setting of cardiogenic shock, dobutamine may be indicated by some combination of hypotension, cool extremities, poor urine output, and elevated lactate level. In the setting of septic shock, if the lactate level does not decrease at least 10% and/or the measured $Sc\bar{v}O_2$ does not reach 70%, despite fluid resuscitation and vasopressor administration (see earlier), dobutamine can be added at a dose of 2 μg/kg/min and titrated every 5 to 10 minutes, to a maximum of 20 μg/kg/min. Due to stimulation of vasodilating peripheral beta receptors, dobutamine does have the potential to decrease the BP, so careful attention to a patient's individual response is necessary. If simultaneous BP and inotropic support is necessary for septic shock, epinephrine alone, 0.2 μg/kg/min starting dose, provides similar outcomes and adverse event rates as a combination of norepinephrine plus dobutamine. When norepinephrine is the first pressor initiated and an inotrope is indicated, we recommend the addition of dobutamine, with the ability to titrate each agent individually. However, it is acceptable as an alternative to discontinue the norepinephrine and initiate epinephrine infusion to provide vasopressor and inotropic support via a single agent.

Antimicrobial Therapy

Treatment of the infection with antimicrobial therapy and, where necessary, surgical drainage (see later, "Source Control"), should be instituted as soon as practical in cases of septic shock.[10] Current evidence does not support an absolute time requirement for administration but, when septic shock is the working diagnosis in the ED, we recommend initiation of appropriate antibiotics as soon as practical after the diagnosis is made, ideally within 4 hours of ED presentation. When there is no focus of infection identified in a patient with presumed septic shock, a semisynthetic penicillin with a β-lactamase inhibitor, in combination with a fluoroquinolone and vancomycin, is a rational empirical choice. One such regimen would include piperacillin-tazobactam, 4.5 g IV every 6 hours, plus levofloxacin, 750 mg IV every 12 hours, and vancomycin, 30 mg/kg (maximum dose, 2 g) given every 12 hours, adjusted as appropriate for trough levels and renal failure.

Patients with neutropenia and sepsis syndrome are at particular risk for progressive sepsis, organ failure, and death. Neutropenia can be suspected in patients who have recently undergone chemotherapy, and these patients often know that they are neutropenic. Antimicrobial administration is particularly urgent for these patients and should occur rapidly after blood cultures are obtained, in parallel with crystalloid administration. Antibiotic considerations for the neutropenic patient are discussed in Chapter 115. Chemotherapy patients with sepsis represent a special challenge because the pathophysiology may be complicated by anemia, thrombocytopenia, dehydration from vomiting, and the effects of adjunctive steroid therapy. Chemotherapy patients often have indwelling catheters, which predispose them to more unusual causes of sepsis, including gram-positive bacteria and fungi (see Chapters 115 and 187).

Corticosteroids

There is no evidence for high-dose, short-course corticosteroid therapy in unselected patients with septic shock. Most current guidelines recommend that low-dose hydrocortisone be administered only to patients receiving chronic steroid replacement and in patients with refractory shock, despite adequate fluid and vasopressor support. Even this is only marginally supported, if at all, by scientific evidence. Corticotropin stimulation testing is no longer considered of value.

Special Cases

Systemic thrombolytic therapy is indicated in patients with shock from pulmonary embolism (see Chapter 78) without contraindications.[21] Specific treatments for shock as a result of poisoning with vasoactive medications and other toxins are discussed in the relevant chapters in this text.

Devices and Procedures

Ventilation

Rapid sequence intubation is the preferred method of airway control in most patients with refractory shock (see Chapter 1). Tissue hypoperfusion leads to increasing fatigue of the muscles of respiration, and respiratory failure commonly supervenes in patients with persistent shock. Intubation prevents aspiration, increases oxygenation, treats acute respiratory failure, provides initial treatment for metabolic or hypercarbic acidemia, and protects the patient who will be sent to an uncontrolled environment (eg, for testing). Intubation also reduces the work of breathing, which, in the patient with hypoperfusion, further exacerbates lactic acidemia. Strenuous use of accessory respiratory muscles can increase oxygen consumption by 50% to 100% and decrease cerebral blood flow by 50%. More importantly, if the patient has increased airway resistance (eg, bronchospasm with anaphylaxis) or a decrease in lung compliance (eg, pulmonary edema, ARDS), a more negative intrathoracic pressure must be generated to fill the lungs with each inspiration. The greater suction effect is also exerted on the left ventricle, impeding its ability to eject and increasing functional afterload. Positive-pressure ventilation removes this impedance and can improve ventricular function and cardiac output up to 30%. The use of etomidate for patients with septic shock is discussed in Chapter 1.

Source Control

Controlling hemorrhage remains the cornerstone of treating hemorrhagic shock, and evidence continues to support immediate surgery when direct vascular control cannot otherwise be obtained (see Chapters 33 and 41). Gastrointestinal bleeding may require urgent endoscopy, often in the ED or ICU, and aortic rupture requires emergency consultation by a vascular surgeon. In septic shock related to an abscess, aggressive infection (eg, necrotizing fasciitis; see Chapter 129) or wound (eg, toxic shock syndrome; see Chapter 130), removal of the infectious stimulus through surgical intervention should proceed as soon as practical.

Intraaortic Balloon Pumps and Percutaneous Coronary Intervention

The use of intraaortic balloon counterpulsation and percutaneous coronary intervention in selected patients with cardiogenic shock or acute cardiovascular emergencies is discussed in Chapter 68.

Pericardiocentesis and Thrombectomy

Shock caused by mechanical obstruction can be managed by direct intervention. Large, acute pericardial effusions should be managed with pericardiocentesis. Surgical thrombectomy for massive pulmonary embolism is performed rarely. Direct thrombolysis via interventional radiology, however, has been gaining acceptance as a therapeutic option in patients with shock, particularly if systemic thrombolytics are contraindicated.

OUTCOMES

Outcomes for patients with shock vary with the underlying cause of the shock state and the premorbid or comorbid status of the patient. Outcomes have progressively improved, with emphasis on early diagnosis and treatment. In general, persistent hypotension (refractory shock) is associated with worse outcomes. Patients meeting consensus definitions for hemorrhagic shock have a mortality rate of about 20%,[1] whereas this exceeds 40% in septic and cardiogenic shock.[2]

KEY POINTS

- Circulatory shock can occur with normal arterial blood pressure, and not all patients with arterial hypotension have circulatory shock.
- A base deficit more negative than –4 mEq/L or a serum lactate level greater than 4.0 mmol/L warrants a presumptive diagnosis of shock.
- Urine output is a reliable index of vital organ perfusion in patients with suspected shock. Normal urine output is 1.0 mL/kg/h. Output less than 0.5 mL/kg/h indicates severe renal hypoperfusion.
- A combination of a worsening base deficit, increasing lactate level, and low urine output represents persistent or worsening circulatory shock.
- Early initiation of fluid resuscitation, with pressor support as needed, and appropriate antimicrobial therapy improve the outcomes in patients with septic shock.
- The use of defined physiologic endpoints to measure systemic perfusion during resuscitation (quantitative resuscitation) improves outcomes for ED patients with shock.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 6: QUESTIONS & ANSWERS

6.1. Which of the following is considered one of the empirical criterion for the diagnosis of circulatory shock?
- **A.** Partial pressure of carbon dioxide ($Paco_2$) < 40 mm Hg
- **B.** Partial pressure of oxygen (Pao_2) < 55 mm Hg
- **C.** Serum lactate level < 4 mM/L
- **D.** Systolic blood pressure (SBP) < 100 mm Hg
- **E.** Urine output < 0.5 mL/kg/h

Answer: E. Four of the following criteria should be met for the diagnosis of circulatory shock:
1. Ill appearing or altered mental status
2. Heart rate > 100 beats/min
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. Arterial base deficit < −4 mEq/L or lactate level > 4 mM/L
5. Urine output < 0.5 mL/kg/h
6. Arterial hypotension > 20 min duration

6.2. Which of the following, when present and in the setting of suspected or confirmed infection, helps distinguish severe sepsis from systemic inflammatory response syndrome?
- **A.** Heart rate > 90 beats/min
- **B.** Hypotension
- **C.** $Paco_2$ < 32 mm Hg
- **D.** Temperature < 36°C
- **E.** >10% band neutrophilia

Answer: B. The diagnosis of severe sepsis is made in patients who meet the criteria for systemic inflammatory response syndrome (SIRS) with suspected or confirmed infection and associated with organ dysfunction or hypotension. The organ dysfunction mentioned may include the presence of lactic acidosis, oliguria, and/or altered mental status. The diagnosis of SIRS is made when two or more of the following are present:
1. Temperature > 38°C or < 36°C
2. Heart rate > 90 beats/min
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. White blood cell count > 12,000/mL, < 4,000/mL, or > 10% band neutrophilia

6.3. An 18-year-old unrestrained driver is transported to the emergency department (ED) after being thrown from his vehicle during a motor vehicle collision. He was intubated in the field and received an intravascular bolus of 3 L of normal saline before arrival to the ED. His initial Glasgow Coma Score (GCS) is 7, and his blood pressure on arrival is 80/50 mm Hg. Which of the following would be the most appropriate to initiate immediately on arrival to the ED?
- **A.** Dobutamine
- **B.** Dopamine
- **C.** Hetastarch
- **D.** Norepinephrine
- **E.** Packed red blood cell (PRBC) transfusion

Answer: E. In patients with signs of hemorrhagic shock and suspected central nervous system trauma or GCS < 9, immediate PRBC transfusion should be initiated. This assists with volume expansion and oxygen delivery to the brain. Pressors and positive inotropes will be of little benefit before volume replacement, and hetastarch has no proven benefit for initial resuscitation in head injury patients.

CHAPTER 7

Brain Resuscitation

Craig A. Williamson | William J. Meurer

PRINCIPLES

Background

Despite our recognition of the brain's dominant role in determining the quality of life, modern medicine's ability to intervene and reverse neuronal injury remains limited. Consequently, modern techniques of brain resuscitation are focused on restoring cerebral homeostasis and mitigating the effects of secondary brain injuries. Hypoxic-ischemic injury following cardiac arrest can be seen as a model of global ischemic disease, and recent advances in understanding of its pathophysiologic mechanisms have led to improvements in neurologic outcomes. Although hypoxic-ischemic injury represents a so-called pure form of brain ischemia, its underlying pathology has significant overlap with other cerebral injuries, such as stroke and traumatic brain injury. Thus, many of the physiologic principles of brain resuscitation following cardiac arrest are applicable to these conditions. This chapter, therefore, reviews the pathophysiology of ischemic brain injury and discusses therapies for improving neurologic recovery following cardiac arrest and other critical neurologic illnesses in which cerebral ischemia may occur.

Anatomy, Physiology, and Pathophysiology

The human brain consists of 10 billion neurons, each with multiple connections to other cells, totaling an estimated 500 trillion synapses. Although the brain constitutes only 2% of body weight, it receives 15% of the body's cardiac output and accounts for 20% of the body's overall oxygen use. Although no mechanical or secretory work is performed by the brain, energy expenditures include the synthesis of cellular constituents (eg, an estimated 2000 mitochondria are reproduced each day by each cell) and neurotransmitter substances, axoplasmic transport of these substances, and transmembrane pumping of ions.

When the brain is deprived of adequate blood flow, the resulting ischemia is characterized by a bewildering array of interrelated physiologic and cellular responses that ultimately result in neuronal cell death (Fig. 7-1).[1] Although this complex cascade of events can be triggered by periods of ischemia lasting only a few minutes, the resulting neuronal death is usually delayed by hours or days. Furthermore, the biology of cerebral cell death after global cerebral ischemia follows the pattern of delayed cerebral cell death that follows stroke, traumatic brain injury, and other forms of hypoxic or toxic brain injury, with slight variations. Increased understanding of the brain's response to injury during the period between insult and neuronal cell death will eventually allow more specific brain resuscitation therapies.

Elevated Intracranial Pressure

Intracranial pressure (ICP) is an important consideration in ischemic brain injury because cerebral ischemia can directly result in ICP elevation. This occurs because the failure of oxidative phosphorylation depletes adenosine triphosphate (ATP) stores, which results in an inability to maintain osmotic gradients actively. Increased intracellular osmolarity leads to water influx and the development of cytotoxic edema, which usually peaks 48 to 72 hours after injury. By decreasing cerebral perfusion pressure (CPP), elevated ICP is also an important contributor to secondary brain injury. This relationship is discussed in further detail below; additional information on ICP management is contained in the pharmacology, devices, and techniques sections.

To understand the pathophysiology of elevated ICP, it should be noted that the skull is a rigid container whose relatively noncompressible contents include the brain (~80%), blood (~10%), and cerebral spinal fluid (CSF; ~10%). According to the Monro-Kellie hypothesis, any addition to the volume of one of these components—for example, increased brain volume due to cerebral edema—must be offset by a reduction in the volume of the other contents or the ICP will rise.

Typically, adaptation to increased intracranial volume is initially accomplished by shifting CSF from the intracranial to spinal subarachnoid compartment. Approximately two-thirds of cerebral blood volume is contained in the cerebral veins and dural sinuses, and this venous capacitance can be reduced to accommodate increased intracranial volume further. Unfortunately, these mechanisms are sometimes quickly exhausted, resulting in decreased compliance and a significant increase in ICP. This may occur rapidly with acute cerebral injury or slowly with mass lesions such as tumors.

In its final stages, uncontrolled intracranial hypertension will result in downward herniation of the cerebellar tonsils through the foramen magnum, thereby compressing critical cardiorespiratory centers in the medulla. Prior to or concurrently with this, elevated ICP can exacerbate ischemic injury by reducing cerebral blood flow. CPP is equal to the mean arterial pressure (MAP) minus ICP. As ICP increases, CPP decreases, which is compensated for by cerebral arteriolar vasodilation. Unfortunately, this vasodilation may increase cerebral blood volume, which can additionally increase ICP and further reduce CPP. This vicious cycle is one of the primary inciting factors for the prolonged periods of refractory ICP elevation known as plateau or Lundberg A waves.

MANAGEMENT

Decision Making

Standard management of ischemic brain damage involves restoring cerebral blood flow (CBF) and preventing secondary insult. Most treatments have not been studied in prospective, randomized, controlled trials, but have been supported by clinical experience and limited experimental data. Although proposed and experimental neuroprotectant therapies are generally aimed at specific molecular interventions in the pathophysiology of ischemic brain injuries, as yet none of these have proven effective in clinical trials. In the case of ischemic injury following cardiac arrest, the most comprehensive review and consensus guideline statement on care of patients with post–cardiac arrest syndrome

has come from the International Liaison Committee on Resuscitation and its constituent bodies, with the endorsement of the American College of Emergency Physicians, Society for Academic Emergency Medicine, Society of Critical Care Medicine, and Neurocritical Care Society.[2] Improvements in post–cardiac arrest care, through an inclusive multisystem approach, can increase the likelihood of meaningful recovery in these patients. Implementation of standardized protocols for postresuscitation care that include many or all of the following components have demonstrated increases in survival, with a favorable neurologic outcome of up to 30% in repeated (although poorly controlled) before and after studies.[3,4]

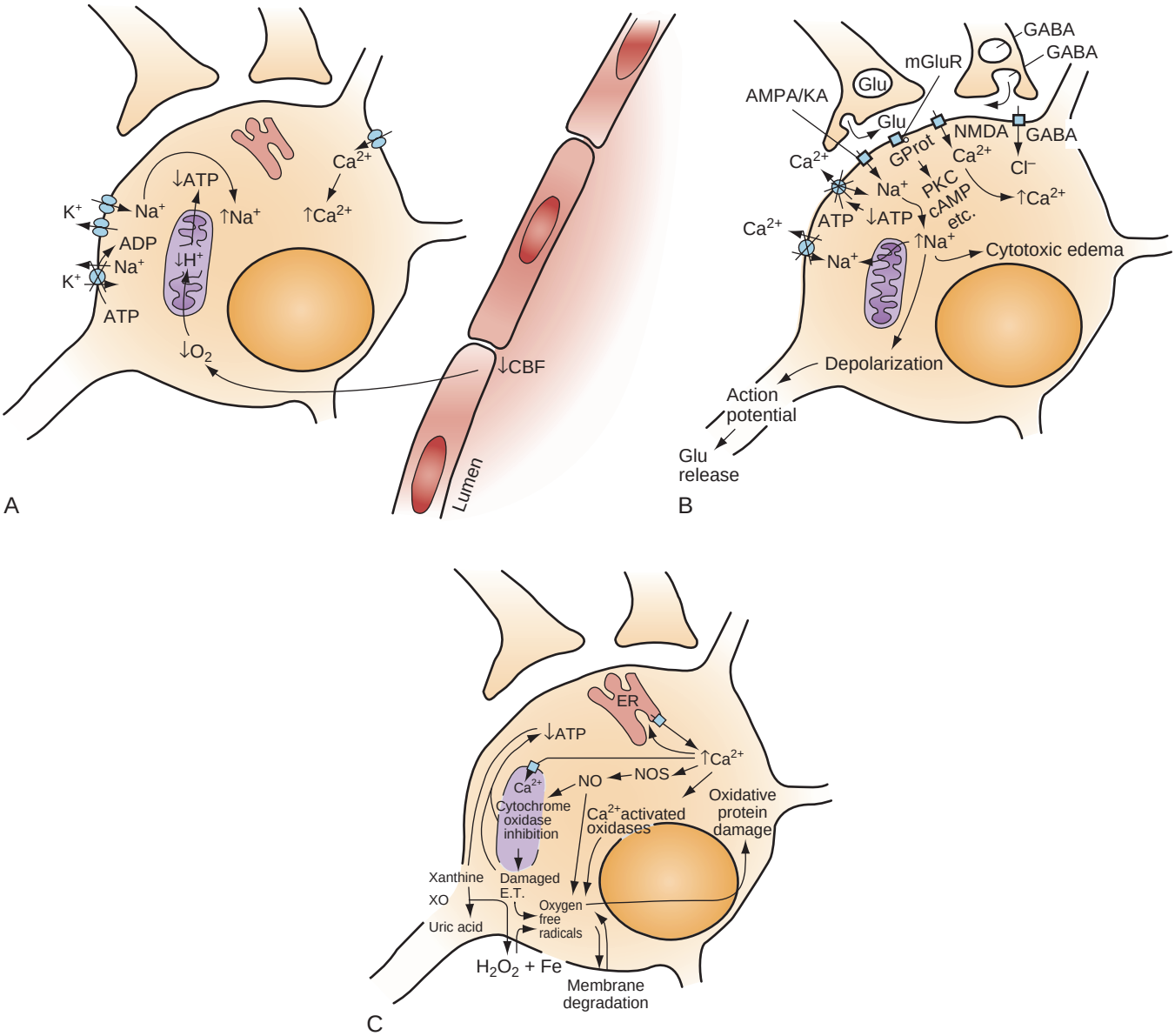

Fig. 7.1. Synopsis of events contributing to neuron cell death cascade after ischemia. **A,** Decreased cerebral flow (CBF) and arterial oxygen content during ischemia cause decreased adenosine triphosphate (ATP) production, failure of ATP-driven ion pump efflux of potassium ions (K^+), and influx of sodium ions (Na^+) and calcium ions (Ca^{2+}) through voltage-gated channels. *ADP,* adenosine diphosphate. **B,** Na^+ influx causes depolarization and glutamate (Glu) release, opening Glu receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate (KA) channels and exacerbating intracellular Na^+ overload. Increased Na^+ concentration ([Na^+]i) leads to cytotoxic edema. Glu-mediated *N*-methyl-D-aspartate (NMDA) channels allow intracellular Ca^{2+} overload. Insufficient ATP causes failure of energy-dependent Ca^{2+} pumps, and high [Na^+]i prevents removal of Ca^{2+} by Na^+/Ca^{2+} exchange pumps. γ-Aminobutyric acid (GABA) release can attenuate excitatory changes by opening a receptor-gated Cl^-. **C,** Increased [Ca^{2+}]i is amplified by calcium-induced release of Ca^{2+} from the endoplasmic reticulum (ER). Mitochondria may be injured attempting to buffer increasing [Ca^{2+}]i, resulting in further metabolic failure and diminished ATP. Ca^{2+} activates nitric oxide synthase (NOS), transforming it to nitric oxide (NO), which is amplified by NO activation of NOS. NO contributes to the formation of damaging oxygen free radicals and inhibits mitochondrial cytochrome oxidase function. ATP degradation to xanthine and then uric acid by xanthine oxidase (XO) yields hydrogen peroxide (H_2O_2), which reacts with iron to form dangerous oxygen radicals. Oxygen free radicals react with lipids in the cell membrane, which leads to membrane degradation and more free radicals. Oxygen free radicals also can damage proteins.

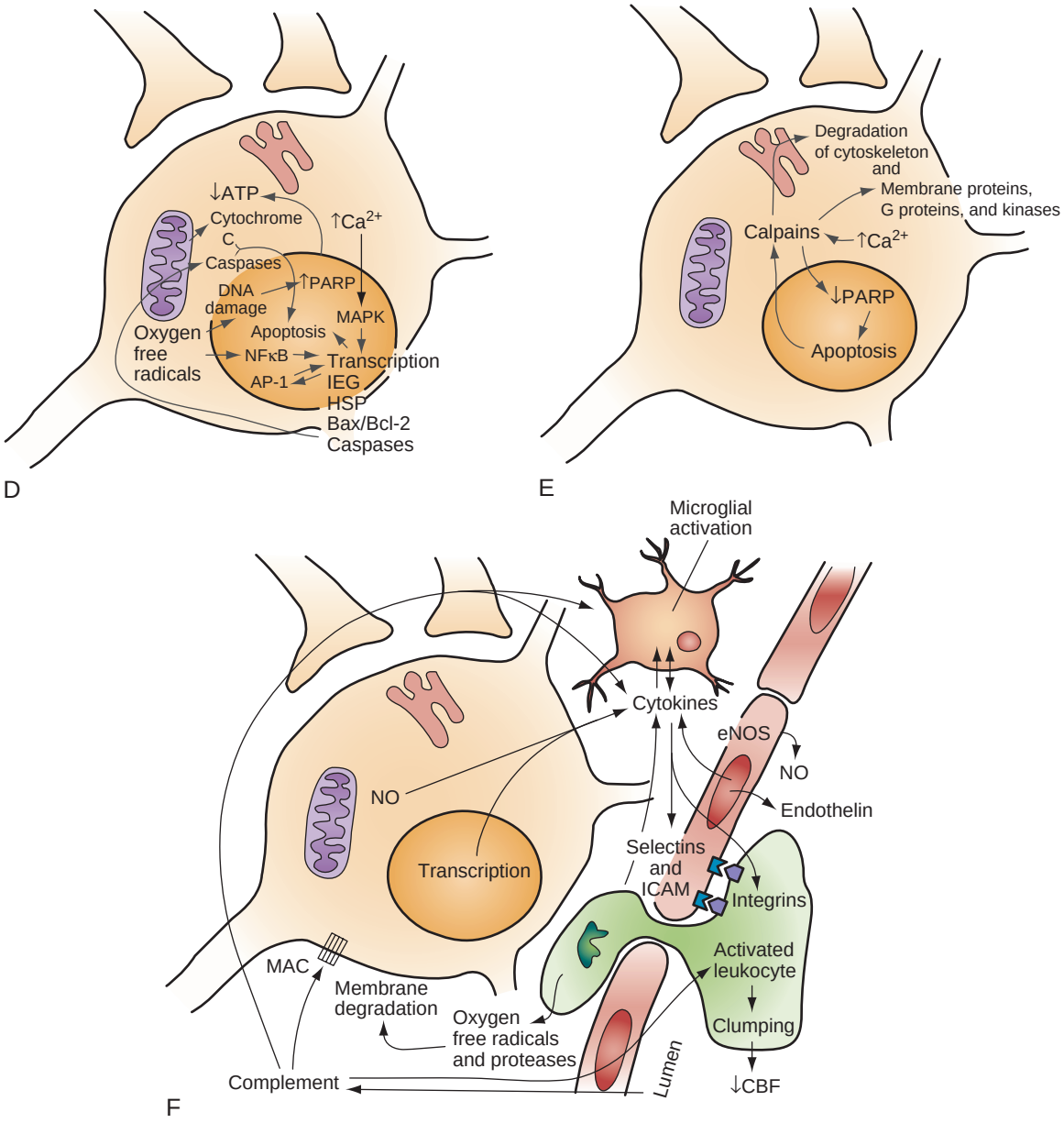

Fig. 7.1, cont'd. **D,** Ca^{2+} also activates kinase transcription factors, such as mitogen-activated protein kinase (MAPK). Oxygen radicals trigger nuclear factor κB (NFκB), another transcription factor. Many genes, including immediate early genes (IEGs), heat shock protein (HSP) genes, genes for caspases, and the *Bax/Bcl-2* systems, are activated. IEG products include AP-1, another transcription factor. Mitochondrial release of cytochrome c, existing and newly formed caspases, and other factors trigger apoptosis. DNA is damaged by oxygen free radicals and by endonucleases formed in apoptosis. DNA damage activates poly(ADP-ribose) polymerase (PARP), which further depletes ATP stores. **E,** Ca^{2+} and apoptosis activate calpains, proteases that degrade a variety of structural elements (eg, cytoskeletal and membrane proteins), signaling elements (eg, G proteins, kinases), and PARP. **F,** Transcription and NO contribute to the neuronal expression of cytokines, chemokines, and growth factors. These intercellular signals activate complement, epithelial cells, leukocytes, and microglia. Complement can amplify chemotactic signals, activate microglia directly, or cause cellular damage by creation of the membrane attack complex (MAC). Leukocyte integrins, epithelial cell selectins, and intercellular adhesion molecules (ICAMs) allow demargination. Activated leukocytes cause neuronal injury by releasing potent oxidants and protease. Cerebrovascular resistance may be affected by the epithelial release of NO and endothelin and by leukocyte clumping. *ADP,* Adenosine diphosphate; *[Ca^{2+}]i,* Ca^{2+} concentration; *cAMP,* cyclic adenosine monophosphate; *eNOS,* endothelial nitric oxide synthase; *E.T.,* enzyme trafficking; *mGluR,* metabotropic glutamate receptor; *PKC,* protein kinase C.

Pharmacology, Devices, and Techniques

Cardiopulmonary Resuscitation

In the event of cardiac arrest, return of spontaneous circulation is the first priority in cerebral resuscitation. The degree of brain injury after cardiac arrest depends on the duration of complete cerebral ischemia (the downtime, or time before the initiation of cardiopulmonary resuscitation [CPR]) and duration of relative ischemia that occurs during CPR and that may occur from cardiogenic shock preceding or subsequent to the period of cardiac arrest. Events occurring after the restoration of flow (eg, transient hypoxia, hypotension) also can exacerbate brain damage in this dynamic and important early resuscitation time period. Extensive

clinical evidence on hospital discharge rates and neurologic recovery rates supports the concept that success in resuscitation is inversely proportional to the duration of cardiac arrest. Although duration of arrest generally predicts outcome in the population of patients with sudden cardiac death, it cannot be used reliably to predict the outcome of individual patients. Modern brain resuscitation techniques focus on avoiding further secondary cerebral injury, which also affects outcome. Neurologic outcome of survivors is influenced by patient age, comorbidity and other individual characteristics.

The efficacy of closed chest CPR in generating adequate cerebral perfusion is somewhat controversial. Cardiac output during optimal standard closed chest CPR was previously estimated to be only 20% to 30% of normal, but more recent studies have suggested that higher cardiac outputs are possible in clinical practice and, unquestionably, effective CPR is essential to neurologic recovery after cardiac arrest.

Reperfusion

With cerebrovascular insults due to embolic or thrombotic mechanisms, randomized clinical trials have shown a benefit of revascularization in ischemic stroke. This is discussed in detail in Chapter 91).

Optimizing Perfusion and Oxygenation. Maintaining cerebral oxygen delivery is a mainstay of therapy after ischemic brain injury. Oxygen delivery requires a sufficiently high CPP, sufficiently low cerebrovascular resistance (CVR), and adequate blood oxygen saturation.

Hypotension can dangerously lower cerebral blood flow (CBF) and is associated with worse outcome following cardiac arrest and traumatic brain injury (TBI). Normally, a change in systemic blood pressure triggers corresponding changes in CVR, mediated by cerebral arterial vasodilation or vasoconstriction. This capacity, termed *cerebral autoregulation*, functions to maintain a constant CBF over a wide range of arterial blood pressures. Autoregulation is often lost in the injured brain and, as a result, perfusion of ischemic tissue becomes passively dependent on CPP. Consequently, hypotension can compromise CBF and result in significant additional brain damage. Therefore, low arterial pressures should be rapidly normalized, with intravascular volume administration and vasopressors used as needed. In the absence of prospective clinical trial data to guide decision making, current recommendations for cardiac arrest patients are to maintain a MAP of 65 to 100 mm Hg. Induced hypertension, once believed to enhance CPP, is not currently a standard therapy due to concerns related to disruption of the blood-brain barrier and worsening of vasogenic edema.

Blood pressure goals fundamentally differ in intracerebral hemorrhage (ICH), in which elevated blood pressure at presentation is common due to a physiologic pressor response. Hypertension is a known risk factor for hematoma expansion, yet the targeted blood pressure goal in these patients remains controversial due to uncertainty regarding perfusion to the brain tissue surrounding the hematoma (ischemic penumbra). A large, multicenter, randomized controlled trial has demonstrated that rapid lowering of the systolic blood pressure (SBP) to less than 140 mm Hg is safe and may have a small but meaningful benefit on neurologic outcome.[5] Consequently, we endorse immediate management with IV antihypertensives targeting an SBP less than 140 mm Hg. As in other conditions where there is a risk of secondary ischemic injury, hypotension should be diligently avoided by not allowing the MAP to drop below 65 mm Hg.

CVR is a critical determinant of CBF and may be affected by hyperventilation and microvascular patency. Although the cerebral circulation may lose its ability to adjust to blood pressure changes after ischemia, attenuated responsiveness to carbon dioxide and oxygen levels in arterial blood is generally present.[3] Carbon dioxide is a potent vasoactive agent, and lowering the arterial carbon dioxide partial pressure ($Paco_2$) by hyperventilation results in a rapid reduction of CBF of 2% for every 1-mm Hg decrease in the $Paco_2$. Because reductions in CBF reduce total cerebral blood volume, hyperventilation quickly lowers ICP. Induced hyperventilation can transiently abort brainstem herniation in the presence of critically elevated ICP until an alternative therapy can be initiated. However, the vasoconstriction and increased CVR caused by hyperventilation can lead to dangerous reductions in CBF, with resulting cerebral ischemia.[4] We recommend restricting the use of induced hyperventilation to the short-term treatment of immediately life-threatening cerebral herniation and severe intracranial hypertension that is not responsive to other measures, such as osmotic therapy. Chronic or prophylactic hyperventilation should not be used. Specific treatment for elevated ICP is described in the next section. In general, ventilation to maintain a $Paco_2$ of 35 to 40 mm Hg is safe and appropriate, and inadvertent hyperventilation should be avoided.

Normal arterial oxygen saturation following resuscitation from ischemic brain injury is a primary goal. The injured brain may not be able to compensate for hypoxia by augmenting CBF, and cerebral oxygen delivery may diminish rapidly as the oxygen content of blood decreases. Hyperoxia secondary to the use of high concentrations of oxygen, however, has also been shown to increase oxidative brain injury in animal models of cardiac arrest and resuscitation and is associated with increased mortality in stroke patients[5] and in post–cardiac arrest patients.[9] Normoxia or mild hyperoxia (arterial partial pressure of oxygen, Pao_2, of 80–120 mm Hg with oxyhemoglobin saturation percentage maintained in the high 90s) should be maintained through use of the lowest fraction of inspired oxygen (Fio_2) possible. Because hypoxia, hypocapnia, and hypercapnia must be avoided, controlled ventilation is appropriate in the period after resuscitation, with sedation and muscle relaxation if needed. Continuous oximetry and capnography, correlated with intermittent arterial blood gas determinations, will provide the information necessary to optimize ventilation parameters.

Elevated Intracranial Pressure

The presence of intracranial hypertension is suggested by certain imaging findings and clinical features. Relevant computed tomography (CT) findings include compressed basal cisterns, diffuse sulcal effacement, and diffuse loss of differentiation between the gray and white matter, although ICP can be elevated without any of these findings. Suggestive clinical features include papilledema, bilateral sixth nerve palsies, and new third nerve palsy in a comatose patient. Definitive diagnosis requires invasive ICP monitoring placement. The decision to place an ICP monitor should be guided by neurosurgery whenever consultation is available. Most data on the management of elevated ICP is derived from literature on TBI, a condition in which ICP elevation commonly occurs. Although support from randomized controlled trials is lacking, the Brain Trauma Foundation has published guidelines for ICP monitor placement, which we recommend following in TBI patients whenever possible. These call for ICP monitor placement in all patients with an abnormal head CT scan and severe brain injury, defined as a Glasgow Coma Score of 3 to 8. ICP monitoring is considered appropriate in the presence of a normal head CT when two of the following are present: (1) age older than 40 years; (2) unilateral or bilateral motor posturing; and (3) SBP less than 90 mm Hg.

Guidelines are not available for ICP monitoring in other conditions involving ischemic brain injury, such as stroke, where it is

generally not indicated. In particular, the clinical impact of intracranial hypertension due to anoxic brain injury following cardiac arrest is unclear and has not been studied in prospective trials. When cytoxic edema severe enough to cause ICP elevation develops, it portends a very poor prognosis. Consequently, invasive ICP monitoring is not recommended in the management of global ischemic injury following cardiac arrest.[2]

Medical Treatment. Medical treatment for elevated ICP has similarly not been proven effective in randomized controlled trials, and treatment protocols are primarily based on clinical experience and expert opinion. To ensure adequate cerebral perfusion, the MAP should be maintained above 65 mm Hg in all patients at risk for ICP elevation, and a CPP of 50 to 70 mm Hg should be targeted when ICP monitoring is available. Although the exact threshold for ICP treatment is unclear and may vary between individual patients, an ICP over 20 mm Hg has been associated with worse neurologic outcomes and should trigger treatment. Although there are many and somewhat diverse recommendations for the initial medical management of patients with elevated ICP, we suggest the following:

1. Position the patient with the head up by elevating the upper half of the bed or gurney to 30 degrees.
2. Maintain a neutral head and neck position to avoid jugular venous compression.
3. Treat fever. Administer antipyretics agents (eg, acetaminophen suppositories, 1000 mg every 6 hours) and use mist cooling as necessary, targeting a temperature at or below 37°C.
4. Minimize triggers of ICP increases.

   This is accomplished by treating and avoiding pain. We recommend titrated doses of a hemodynamically stable opioid medication, such as fentanyl 25 to 50 μg every 5 minutes, as needed. Cough or bucking of the ventilator also should be avoided; this is best accomplished by achieving adequate sedation and analgesia to permit mechanical ventilation, as described in Chapters 1 and 2. Propofol is our sedative agent of choice for this purpose because it decreases cerebral metabolic activity and thereby CBF, and rapidly clears for neurologic assessment, as needed. Propofol can cause or contribute to hypotension, which generally is avoided by dosage adjustment.
5. Initiate osmolar therapy.

   Osmolar therapy with mannitol or hypertonic saline can draw water across an intact blood-brain barrier and thereby lower ICP. Mannitol, 0.5 to 1 g/kg is given every 6 hours, up to a serum osmolality of 320 mOsm/kg. Treating with 30 mL of 23.4% normal saline appears to be at least as effective as mannitol at rapidly lowering ICP and reversing herniation, although a central line is necessary for safe administration; 30 to 60 mL can be given every 6 hours, up to a maximum serum sodium level of 160 meq/L. Because it is a potent diuretic, mannitol is preferred in cases of fluid overload, whereas hypertonic saline can be used as a resuscitative fluid.
6. Treat cases of refractory ICP elevation not amenable to the previous therapies.

   Induced coma with a barbiturate will further decrease CBF and lower ICP. Pentobarbital is started with a 10-mg/kg loading dose over 1 hour, followed by a continuous infusion of 0.5 to 5 mg/kg/h, titrated to achieve electroencephalographic burst suppression. Barbiturate administration is frequently accompanied by hypotension, which often requires vasopressors to maintain adequate CPP.
7. Mild induced hypothermia is an additional option in highly refractory cases.

   Endovascular or surface cooling devices should be used to target a temperature of 32° to 36°C, titrated to achieve ICP control. Once cooled, rapid rewarming should be avoided because this may precipitate a significant ICP elevation.

Surgical Treatment. Surgical options for the management of refractory ICP include decompressive craniectomy and evacuation of intracranial hematoma, when present, and should be guided by neurosurgical consultation. In the event of severe cytotoxic edema following middle cerebral artery stroke, there is a benefit of early (<36 hours) decompressive hemicraniectomy in patients younger than 60 years.[6] A bifrontal craniectomy is typically used to treat refractory ICP in TBI. Based on a recent randomized controlled trial that noted worse outcomes in TBI patients treated with very early craniectomy, we recommend reserving craniectomy for patients that have failed medical management, or as an urgent life-saving procedure when cerebral herniation is present in this population.[6a]

Maintenance of Body Temperature

Hyperthermia (or fever) exacerbates brain injury and worsens neurologic outcome.[17] Elevated body temperature increases cerebral metabolic demand by 8% to 13%/°C, escalates glutamate release, increases oxygen free radical production, and increases cytoskeletal and blood-brain barrier breakdown, with increased vasogenic edema. The core body temperature should be monitored in patients resuscitated from cerebral ischemia and measures should be initiated to prevent temperature increases in the postischemic period. In general, all temperature higher than 38°C should be treated aggressively with acetaminophen and surface cooling. Inducing therapeutic hypothermia has emerged as a therapy for comatose survivors of hypoxic-ischemic injury following cardiac arrest.

Resuscitative Mild Hypothermia

More than 50 years ago, hypothermia was first claimed to have a protective effect in global and focal brain ischemia. The neuroprotective mechanism is linked to a reduction of glutamate release, metabolic demand, free radical formation, and production of inflammatory cytokines. Cell signaling and genetic responses to cellular injury are also affected, and hypothermia may protect the brain from programmed neuronal cell death.

Mild hypothermia (32°–34°C) is easier to achieve and has fewer adverse effects than lower temperatures and has consistently been found to be neuroprotective in experimental models of cerebral ischemia. Two multicenter prospective, randomized controlled trials of mild hypothermia have shown marked improvements in neurologic outcome in comatose survivors of out-of-hospital cardiac arrest (Table 7.1).[18,19] In these trials, the number needed to treat to have one additional patient with a good neurologic outcome was only about seven. Evidence-based guidelines recommend cooling unconscious adult patients after cardiac arrest to 33°C for 12 to 24 hours.[7] Recent investigations in adults and children have compared therapeutic hypothermia of 33°C to targeted temperature management" (TTM) of 36°C.[8,9] The safety and efficacy of TTM versus therapeutic hypothermia were no different. There is strong biologic evidence from earlier clinical trials and animal models that 33°C provides better neuroprotection. The TTM trial did not provide evidence that one target was easier or safer than the other. Most patients included in these trials had immediate bystander CPR and, by extension, were likely to have less severe neurologic insults than cardiac arrest patient resuscitated in routine practice outside Europe. Given the evolving nature of the evidence in this area, we recommend protocols that cool to a target of 33°C; however, practicing emergency clinicians should work with their intensive care colleagues to develop local protocols. A definitive temperature control device, surface or endovascular, with a feedback loop temperature sensor is required, regardless of the target chosen.

TABLE 7.1

Clinical Outcomes in Randomized Controlled Trials of Hypothermia in Comatose Survivors of Cardiac Arrest

CLINICAL TRIAL	HYPOTHERMIA, *N* (%)	NORMOTHERMIA, *N* (%)	*P*
Yenari et al[a]	137	138	
• Good neurologic outcome[b]	75 (55)	54 (39)	$P < .01$
• Death	56 (41)	76 (55)	$P = .02$
Bernard et al[c]	43	34	
• Good neurologic outcome[d]	21 (49)	9 (26)	$P = .05$
• Death	22 (51)	23 (68)	$P = .14$

[a]Data from Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346(8):549–556, 2002.
[b]Good neurologic outcome here defined as recovery with no neurologic deficits or moderate disability but living independently and working at least part time at 6 months.
[c]Data from Bernard SA, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557–563, 2002.
[d]Good neurologic outcome here defined as recovery with moderate, minimal, or no neurologic deficits at hospital discharge and discharge to home or acute rehabilitation facility.

BOX 7.1

Abbreviated Protocol for Induced Hypothermia After Cardiac Arrest

- For access to a wide variety of detailed post–cardiac arrest care and hypothermia protocols collected by the University of Pennsylvania, see www.med.upenn.edu/resuscitation/hypothermia/protocols.shtml.
- Hypothermia is most effective as part of an institutional comprehensive post–cardiac arrest critical care program that begins in the emergency department (ED) and continues into the intensive care unit (ICU) and into recovery and rehabilitation.
- Early resuscitation, excellent cardiopulmonary resuscitation (CPR), rapid return of spontaneous circulation (ROSC), and quick transport to definitive care are fundamental. The value of prehospital cooling is unproven, but if cooling is initiated by emergency medical services (EMS), transport should be to an institution capable of maintaining hypothermia on arrival and avoiding any early (even transient) rewarming.

SKELETON PROTOCOL[a]

- Evaluate adult survivors of cardiac arrest by following institutional criteria for appropriateness of induced hypothermia.
- Begin cooling by rapidly infusing 2 L of cold (4°C) intravenous saline immediately after arrival or ROSC.
- Expose patient; avoid external warming—no blankets and no heated ventilator circuit.
- Place temperature-sensing urinary catheter and esophageal temperature probe. (Redundant monitoring allows esophageal temperature probe connection to cooling device and bladder temperature probe to patient monitoring system.)
- Initiate definitive cooling by endovascular temperature control device at maximal rate to target temperature of 33°C.
- Prevent shivering with sedation and nondepolarizing paralytic—bolus in the ED, bolus or drip in the ICU.
- Avoid hypotension and hypoxia.
- Most ED diagnostic evaluation, if needed, should follow initiation of cooling. (In patients with acute myocardial infarction [MI] who are going to primary coronary intervention, cooling should not delay door to balloon time. Cooling is initiated in the ED if there is time before the catheterization laboratory is ready; otherwise, cooling is initiated in the laboratory.)
- Admit to ICU.
- Continuous electroencephalographic monitoring for occult status epilepticus recommended. Treat seizures if present.
- Manage arterial blood gases in a consistent manner (may choose pH stat or alpha stat).
- At 24 hours after initiation of cooling, initiate rewarming to a target temperature of 36.5°C at a rate of 0.15°/h.
- Discontinue paralytics at the onset of warming. Control shivering with sedation, narcotics, and surface counterwarming.
- Lighten sedation as tolerated as rewarming progresses.
- Discontinue endovascular temperature control device after 48 hours (may use the device to maintain normothermia after rewarming is complete until it is removed).
- Remove or minimize sedation to allow neurologic evaluation before 72 hours to allow the best possible clinical prognostication at that time point; neurology consultation recommended.

[a]Modified from University of Michigan protocol.

The optimal method of cooling patients resuscitated from cardiac arrest has not been established (see Chapter 8). Animal experimentation and consensus recommendations have suggested that cooling should be initiated as early and rapidly as possible. Cooling may begin during the out-of-hospital phase of resuscitation and may even be initiated before return of spontaneous circulation. In the positive clinical trials, hypothermia at 33° ± 1°C was achieved by 2 or 8 hours after return of spontaneous circulation and was maintained for 12 or 24 hours. Patients are allowed to rewarm passively or with a combination of passive and active rewarming. Rebound hyperthermia is common with passive rewarming and should be avoided.

Clinical trials of mild hypothermia in adults and children with traumatic brain injury have generally been small and have shown variable results, but large multicenter trials evaluating the use of mild hypothermia as a neuroprotectant or treatment for elevated ICP are ongoing. Therapeutic hypothermia following ischemic stroke is not of proven benefit, and we do not recommend its use (Box 7.1).

Avoidance of Hyperglycemia

Postischemic hyperglycemia has detrimental effects on CBF, metabolism, edema formation, and neurologic outcome. Hyperglycemia after brain ischemia is strongly associated with worse outcomes in diabetics and nondiabetics. Because the brain is an obligate glucose consumer, brain resuscitation must balance hyperglycemia prevention with adequate cerebral glucose

availability. Cerebral microdialysis studies in humans have shown that tight glucose control (<120 mg/dL) is associated with low cerebral glucose and elevated lactate levels, which in turn are associated with increased mortality.[20] Current recommendations for glucose control following cardiac arrest are to avoid hypoglycemia and target a blood glucose level of less than 180 mg/dL. This can typically be achieved by the administration of subcutaneous insulin, although a continuous intravenous insulin infusion is sometimes necessary.[10] A multicenter clinical trial of intensive insulin therapy in acute ischemic stroke is currently underway.

Seizure Management

Although the prevention of seizures has not been demonstrated to improve neurologic recovery, seizures are clearly not desirable in the postischemic period. Seizures can result from global cerebral ischemia and may exacerbate underlying brain injury. Seizure activity can increase brain metabolism by 300% to 400%, worsening the mismatch between oxygen delivery and demand, with greater metabolic failure and neuronal loss and worsened neurologic outcome. When present, prolonged seizures or status epilepticus following cardiac arrest are strongly, although not invariably, associated with a poor neurologic outcome. Nonconvulsive status epilepticus has been reported after cardiac arrest; consequently, continuous electroencephalographic monitoring is frequently used in comatose survivors, and we recommend its use for patients who are paralyzed while receiving therapeutic hypothermia.[21] Electroencephalographic findings have been shown to predict neurologic outcome after cardiac arrest reliably and, in the future, electroencephalographic monitoring may be a core component in prognostication algorithms.[11]

We do not recommend the prophylactic use of anticonvulsant drugs in patients resuscitated from cardiac arrest, but seizures should be quickly and effectively treated. Lorazepam, 0.1 mg/kg, with a maximum rate of 2 mg/min, is the preferred first-line agent to abort seizures and should be followed by longer term treatment with an antiepileptic drug. Phenytoin, levetiracetam, or valproic acid are equally efficacious options based on current data. These are all available in IV formulations. Treatment is initiated with identical 20-mg/kg loading doses. In intracerebral hemorrhage, the prophylactic use of anticonvulsants has been associated with worse neurologic outcomes, and we concur with current guidelines that do not recommend their routine use.[12] In TBI, prophylaxis with phenytoin reduces seizures during the first 7 days, but not beyond, and has not been shown to improve outcome. There are limited data suggesting that prophylaxis with levetiracetam may be better tolerated than phenytoin, so 7 days of levetiracetam, 500 mg bid ,is our preferred regimen for prophylaxis in TBI patients.[13]

OUTCOMES

Cerebral ischemia is a frequently fatal and highly morbid condition, but the prognosis for its victims is not universally poor. An increasing body of data is providing more complete and precise estimates of the functional outcomes and quality of life of survivors, and the results are better than many emergency clinicians assume.

However, identification of reliable prognostic indicators of severe brain injury is hampered by the self-fulfilling prophecy, in which counseling provided to families of patients with a presumed poor prognosis leads to withdrawal of life-sustaining treatments, thereby seeming to confirm the poor prognosis. There is significant individual and institutional variation in the implementation of "Do not resuscitate" (DNR) orders and early withdrawal of life support, and these variations can profoundly affect our understanding of outcomes. In an important study using a large data set of patients with ICH, institution of DNR orders within 24 hours was strongly associated with mortality, independently of other known risk factors.[14] Consequently, recent ICH guidelines have emphasized the importance of avoiding assigning new DNR status within the first day of hospital presentation.[15] Prognostication in TBI, which disproportionately affects young adults, can be particularly difficult, and there are examples of good outcomes in spite of a prolonged hospital course and numerous poor prognostic indicators.[16]

On the other hand, prolonged survival with significant disability also may be a tragic outcome, and consideration of this may lead emergency clinicians and families to consider withdrawal of life support. This may account, in part, for the nihilism common among emergency clinicians treating patients with cardiac arrest. This may arise in part from the fact that most survivors of cardiac arrest are comatose at the time of admission and without early prognostic findings suggesting which patients will have a favorable outcome. The most recent American Academy of Neurology (AAN) guidelines (2006) for prognostication after cardiac arrest are driven by data from the pretherapeutic hypothermia era. These guidelines identified six factors that reliably predict poor outcome—absent pupillary response, corneal reflex, or motor response at 72 hours; neuron-specific enolase (NSE) level higher than 33 μm/L; myoclonic status epilepticus within 24 hours; and bilateral, absent, somatosensory evoked potentials. More recent data from patients undergoing therapeutic mild hypothermia have cast doubt on the reliability of several of these factors. In particular, NSE levels and motor responses at 72 hours have had poor predictive value in these patients. Additionally, a higher false-positive rate has been associated with absent corneal reflexes at 72 hours and early myoclonic status epilepticus. Further clinical studies and meta-analyses are needed to clarify reliable prognostic indicators.

Despite continued work to identify an imaging biomarker for outcome after cardiac arrest, there is no established role for early magnetic resonance imaging or CT in prognostication in survivors of cardiac arrest. In the near future, serum biomarkers of brain injury may identify the potential for neurologic recovery early in a patient's course and help guide therapy. Until early predictions of outcome can be made accurately, the emergency clinician should consider most survivors of cardiac arrest as having a significant chance of full recovery (14%–55%); however, patients with severe coma (motor plus brainstem four score below 4 in the absence of sedatives and paralytics) within 6 hours of resuscitation have a lower likelihood of recovery (5%–10%).

SUMMARY

Rapidly expanding knowledge about the pathophysiology of postischemic brain injury has stimulated the search for effective cerebral resuscitation therapies. Newly proven therapies such as resuscitative hypothermia will continue to be studied and will improve the outcomes of patients with ischemic brain injury in future years. Although experimental work has suggested many potentially promising brain resuscitation therapies, attention should also be paid to determining the benefits of existing standard therapies. Because of the complexity and interconnectedness of the pathophysiologic cascades that occur after cerebral ischemia, it is likely that a multifaceted therapeutic approach targeting mediators of secondary brain injury, rather than a single pharmacologic agent, is needed to reduce neurologic damage after cardiac arrest.

It is crucial that the emergency clinician recognize that the patient resuscitated from ischemic injury is, contrary to his or her outward appearance, in a dynamic stage of brain injury. At present, patients should be protected from further brain injury caused by hypotension, hypoperfusion, ICP elevation, hypoxia,

hyperthermia, hypoglycemia. hyperglycemia, and seizures. Comatose survivors of out-of-hospital cardiac arrest should now also undergo resuscitative hypothermia or targeted temperature management. In the future, cerebral resuscitation may also involve other specific pharmacologic interventions to derail the process whereby brain cells slowly die after ischemic brain injury.

KEY CONCEPTS

- Neuronal injury is a dynamic process that continues for hours or days after an ischemic insult to the brain.
- Hypotension and hypoperfusion should be avoided by maintaining MAP > 65 mm Hg and CPP of 50–70 mm Hg.
  - Normoxia or mild hyperoxia, with Pa_{O_2} of 80–120 mm Hg and oxyhemoglobin saturations in the high 90s, should be maintained. Hypoxia and significant hyperoxia should be avoided.
  - ICP elevation can further exacerbate ischemic brain injury. Initial management should include optimizing patient positioning while providing adequate analgesia and sedation. Management should then be escalated in a stepwise fashion to include hypertonic therapy, deep sedation with barbiturates, hypothermia, and surgery as needed.
  - Hyperventilation decreases cerebral blood flow and should be avoided by targeting a Pa_{CO_2} of 35–40 mm Hg. In the event of life-threatening cerebral herniation or significant ICP elevation, therapeutic hyperventilation is appropriate only as a short-term intervention bridging to more definitive therapy (ie, craniectomy).
  - Hyperglycemia worsens neurologic outcome. Subcutaneous or IV insulin should be used to maintain a glucose level <180 mg/dL.
  - When present, seizures should be promptly aborted using IV lorazepam, followed by treatment with IV phenytoin, valproic acid, or levetiracetam, with an initial 20-mg/kg loading dose. The prophylactic administration of antiepileptic drugs is not recommended, except for 7 days immediately following TBI. Levetiracetam, 500 mg bid, is a preferred agent.
  - Fever is an important mediator of secondary brain injury and all temperatures >38°C should be treated promptly with acetaminophen and surface cooling.
- Comatose survivors of out-of-hospital cardiac arrest should be rapidly cooled in the ED, maintained at a constant target of 33°–36°C in an ICU setting for 24 hours after resuscitation, and receive targeted temperature management to prevent hyperthermia after this period.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 7: QUESTIONS AND ANSWERS

7.1. To maximize cerebral blood flow, a patient with a normal intracranial pressure who is undergoing resuscitation should be ventilated to maintain a partial pressure of carbon dioxide ($Paco_2$) within what range?

A. 20 to 25 mm Hg
B. 25 to 30 mm Hg
C. 30 to 35 mm Hg
D. 35 to 40 mm Hg
E. 40 to 45 mm Hg

Answer: D. Carbon dioxide is a potent vasoactive agent, and lowering of the $Paco_2$ by hyperventilation results in rapid reduction of cerebral blood flow (CBF). Because reductions in CBF reduce total cerebral blood volume, hyperventilation may transiently abort brainstem herniation in the presence of critically elevated intracranial pressure (ICP) until osmotherapy or ventriculostomy can be initiated. When ICP is not elevated, however, the vasoconstriction and increased cerebrovascular resistance (CVR) caused by hyperventilation can cause potentially dangerous reductions in CBF. In general, ventilation to maintain a $Paco_2$ between 35 and 40 mm Hg is safe and appropriate.

7.2. True or false? Induced hypothermia for comatose survivors of ventricular fibrillation is a class 1A recommendation in the 2010 American Heart Association Emergency Cardiac Care/Advanced Cardiac Life Support Guidelines.

Answer: True.

7.3. Select the best answer. Which of the following statements is false?

A. Early magnetic resonance imaging (MRI) and serum biomarkers have a clearly established role in determining the prognosis of patients within 48 hours after cardiac arrest.
B. In a study from the Resuscitation Outcomes Consortium, median survival to hospital discharge among all patients with emergency medical services (EMS) responses for cardiac arrest was 8.4%.
C. In cardiac arrest patients who survive to hospital admission, 14% to 55% have good long-term outcomes.
D. The vast majority of 1-year survivors of cardiac arrest are neurologically intact.

Answer: Statement A is false. The role of early imaging, neurophysiologic testing, and serum biomarkers in predicting outcome has not yet been clearly established at any time point, especially not within 48 hours.

7.4. True or false? A patient with return of spontaneous circulation after 15 minutes of cardiac arrest has likely already suffered substantial neuronal cell death.

Answer: False. Although a cascade of cellular pathways will have been triggered, the resulting neuronal cell death is usually delayed by hours or days.

7.5. Select the best answer. Which of the following is associated with worse neurologic outcomes in comatose survivors of cardiac arrest?

A. All of these
B. Hyperthermia
C. Hypotension
D. Hypoxia
E. Only hypotension and hyperthermia

Answer: Statement A is the best answer. Hypotension, hypoxia, and hyperthermia (as well as hyperglycemia and seizures) are all associated with worse neurologic outcomes in comatose survivors of cardiac arrest.

CHAPTER 8

Adult Resuscitation

Michael C. Kurz | Robert W. Neumar

PRINCIPLES

Background

It is estimated that out-of-hospital cardiac arrest affects approximately 326,000 patients each year in the United States (an estimated annual incidence of 100/100,000).[1] Of these, approximately 176,000 are treated by emergency medical services (EMS).[1] Most EMS-treated, out-of-hospital cardiac arrests occur at home (70%) and are unwitnessed (50%).[2] The proportion of EMS-treated cardiac arrest patients with an initial rhythm of ventricular fibrillation (VF) has declined over time to approximately 20%.[1,2] Furthermore, the number of patients receiving bystander cardiopulmonary resuscitation (CPR) remains low, averaging 45%.[1,2] Bystander automated external defibrillators (AEDs) are applied in only 1% of home arrests and 8% of arrests in public settings.[2]

The most recent epidemiologic data from cardiac arrest registries have indicated that the survival rate of hospital discharge for EMS-treated, out-of-hospital cardiac arrest is about 11%.[2] However, tremendous regional variability in survival to hospital discharge after EMS-treated cardiac arrest has been reported, ranging from 3% to 17%. For the subset of patients who achieve return of spontaneous circulation (ROSC) long enough to be admitted to the hospital, there is significant interinstitutional variability in survival, ranging from 19% to 59%. Of patients surviving to hospital discharge, independent of neurologic status on presentation, 78% have good neurologic function (cerebral performance category of 1 or 2).[2] For comatose postcardiac arrest patients meeting study inclusion criteria for hypothermia-targeted temperature management (TTM), the reported survival rate with good neurologic function is approximately 50%.[3] The entire system of care affects patient outcomes, and the variability in outcomes across the country likely reflects local and regional variability in how well these systems function.

Anatomy, Physiology, and Pathophysiology

Understanding the underlying causes of cardiac arrest helps direct therapy and diagnostic testing during resuscitation and in the immediate post–cardiac arrest period (Table 8.1). Cardiac arrest caused by VF or pulseless ventricular tachycardia (pVT) usually has a primary cardiac origin. Coronary artery disease is a common pathologic condition found in patients who experience out-of-hospital cardiac arrest, and multiple observational studies have demonstrated disease rates comparable to those of patients undergoing clinically indicated coronary angiography.[4,5] Less common are inherited syndromes associated with sudden cardiac death due to ventricular dysrhythmias, including hypertrophic cardiomyopathy, Brugada's syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and arrhythmogenic right ventricular cardiomyopathy.[1] Pulseless electrical activity (PEA) and asystole may also occur as presenting rhythms in patients with a cardiac cause of arrest. These rhythms can occur in response to respiratory insufficiency secondary to cardiac dysfunction or to deterioration of VF or pVT when cardiac arrest is prolonged, or they may develop in response to resuscitation treatments such as defibrillation.

Primary respiratory failure generally causes initial hypertension and tachycardia, followed by hypotension and bradycardia and progressing to PEA, VF, or asystole. Circulatory obstruction (eg, tension pneumothorax, pericardial tamponade) and hypovolemia generally manifest with initial tachycardia and hypotension, progressing through bradycardia to PEA, but also may deteriorate to VF or asystole.

Other less common causes for cardiac arrest include electrolyte disturbances, drug toxicity, and electrocution. The most common metabolic cause of cardiac arrest is hyperkalemia, which is usually seen in patients with renal failure. Hyperkalemia results in progressive widening of the QRS complex, which can deteriorate to pVT, VF, asystole, or PEA. Other electrolyte abnormalities (eg, hypomagnesemia, hypermagnesemia, hypokalemia) may lead to significant dysrhythmias, but the frequency with which they cause cardiac arrest has not been documented and is likely very low. Cardiac arrest from drug toxicity has specific characteristics, depending on the presenting toxidrome. Specific therapy directed at drug toxicity is essential but may not be immediately effective, and prolonged resuscitation efforts involving a method that provides adequate perfusion may be needed. Electrocution causes cardiac arrest through primary dysrhythmias or apnea. Alternating current in the range of 100 mA to 1 A (household and light industry) generally causes VF, whereas currents greater than 10 A (heavy industry or electrical transmission infrastructure) can cause ventricular asystole. Lightning produces a massive direct current electrocution that can result in asystole and prolonged apnea (see Chapter 134).

Hypothermia-induced cardiac arrest can manifest with any electrocardiographic rhythm, and successful resuscitation depends on rapid rewarming, which often requires invasive measures (eg, intravascular rewarming, peritoneal or thoracic lavage, or venous-arterial extracorporeal membrane oxygenation [VA-ECMO]; see Chapter 132). Once circulation is restored, patients should be warmed to 32° to 34°C (90°–93°F) for patients without contraindications to targeted temperature management following cardiac arrest.[6] Drowning is a form of asphyxia usually resulting in bradyasystolic arrest. Because drowning often is accompanied by hypothermia, the victim may benefit from prolonged resuscitation efforts, similar to resuscitation efforts for hypothermia.

MANAGEMENT

Decision Making

Most cardiac arrest cases managed in the emergency department (ED) initially occur outside the hospital. An increasing number of first responders, nontraditional providers (eg, teachers, flight attendants), and public venues (eg, airports, casinos, sports arenas, schools) are being equipped with AEDs. When coupled with regional and statewide campaigns to improve bystander CPR rates, including hands-only[7] and dispatcher-assisted CPR,[8] dramatic resuscitation rates have been achieved in communities

TABLE 8.1

Common Causes of Nontraumatic Cardiac Arrest

GENERAL	SPECIFIC	DISEASE OR AGENT
Cardiac		Coronary artery disease Cardiomyopathies Structural abnormalities Valve dysfunction
Respiratory	Hypoventilation	CNS dysfunction Neuromuscular disease Toxic and metabolic encephalopathies
	Upper airway obstruction	CNS dysfunction Foreign body Infection Trauma Neoplasm
	Pulmonary dysfunction	Asthma, COPD Pulmonary edema Pulmonary embolus Pneumonia
Circulatory	Mechanical obstruction	Tension pneumothorax Pericardial tamponade Pulmonary embolus
	Hypovolemia	Hemorrhage
	Vascular tone	Sepsis Neurogenic
Metabolic	Electrolyte abnormalities	Hypokalemia or hyperkalemia Hypermagnesemia Hypomagnesemia Hypocalcemia
Toxic	Prescription medications	Antidysrhythmics Digitalis beta blockers Calcium channel blockers Tricyclic antidepressants
	Drugs of abuse	Cocaine Heroin
	Toxins	Carbon monoxide Cyanide
Environmental		Lightning Electrocution Hypothermia or hyperthermia Drowning or near-drowning

CNS, Central nervous system; *COPD,* chronic obstructive pulmonary disease.

where lay public providers feel empowered to respond within the first few minutes of arrest.[9] Programs that fail to improve rates of bystander CPR or AED use within this critical time window are unlikely to achieve increased survival rates.

Advanced life support) units staffed by paramedics often have standing orders to follow advanced cardiac resuscitation protocols. In cases of cardiac arrest refractory to properly performed advanced prehospital measures, the patient may be pronounced dead at the scene if appropriate protocols have been outlined within the system.[10] However, if advanced hospital-based resuscitation strategies such as extracorporeal cardiopulmonary resuscitation (ECPR) and percutaneous coronary intervention (PCI) are available during mechanical CPR, then transport to a comprehensive resuscitation center may still be warranted.[11,12] In systems where patients are transported in cardiac arrest, mechanical CPR has the potential to result in better quality chest compression during transport and is likely to be safer for EMS providers.[13]

In the ED, the management of cardiac arrest occurs in an orchestrated effort by a health care team led by an emergency clinician who can monitor the efficacy and response to therapeutic interventions. It is often difficult to determine the cause of cardiac arrest at presentation. Although a differential diagnosis can be formulated based on history, physical examination, and electrocardiographic rhythm on arrival, key information often is not available or is unreliable. The differential diagnosis potentially can be narrowed by the patient's age, underlying diseases, and medications, when known.

History and Physical Examination

Historical information from the family, bystanders, and EMS personnel provides key information regarding cause and prognosis. Information surrounding the event includes whether the arrest was witnessed, time of arrest, what the patient was doing (eg, eating, exercising, trauma), possibility of drug ingestion, time of initial CPR, initial electrocardiographic rhythm, and interventions by EMS providers. Important past medical history includes baseline health, previous heart, lung, or renal disease, malignancy, hemorrhage, and infection, and risk factors for coronary artery disease and pulmonary embolism. The patient's current medications and allergies also should be obtained, if possible.

Physical examination of a cardiac arrest patient is necessarily focused on a few key goals: (1) ensuring the adequacy of airway maintenance and ventilation; (2) confirming the diagnosis of cardiac arrest; (3) finding evidence of the cause; and (4) monitoring for complications of therapeutic interventions. This examination occurs in descending order of importance, simultaneously with therapeutic interventions, and is repeated frequently to assess for response to therapy and occurrence of complications (Table 8.2).

Cardiopulmonary arrest is defined by the triad of unconsciousness, apnea, and pulselessness. The pulse is palpated in a large artery (carotid or femoral). If any question exists about the diagnosis of pulselessness, CPR should be initiated. With sudden onset of cardiac arrest, as in VF, loss of consciousness occurs within 15 seconds, although agonal gasping respirations may persist for several minutes. Primary respiratory arrest results in transient tachycardia and hypertension due to mounting hypoxia, loss of consciousness, bradycardia, and pulselessness.

After the initial minutes of cardiac arrest, the physical examination may provide little evidence of the duration of arrest. Pupils dilate within 1 minute but constrict if CPR is initiated immediately and performed effectively. Dependent lividity and rigor mortis develop after hours of cardiac arrest. Temperature is an unreliable predictor of duration of cardiac arrest because it does not decrease significantly during the first hours of arrest. Moderate to severe hypothermia may cause cardiac arrest or be caused by prolonged arrest.

Monitoring

Traditional monitoring during CPR has relied on evaluation of the electrocardiogram (ECG) in one or more leads and palpation of carotid or femoral artery pulses. Although the lack of a palpable pulse during CPR may indicate inadequate forward flow, the degree of forward flow cannot be estimated accurately in the presence of a palpable pulse because pressures generated during CPR may be transmitted equally to the venous and arterial vasculatures. In addition, myocardial blood flow does not depend on the palpated arterial pressure during chest compression (CPR systole), but rather on the difference between aortic and right atrial pressures during relaxation (CPR diastole), which is defined

TABLE 8.2

Physical Examination Findings[a]

PHYSICAL EXAMINATION	ABNORMALITIES	POTENTIAL CAUSES
General	Pallor	Hemorrhage
	Cold	Hypothermia
Airway	Secretions, vomitus, or blood	Aspiration
		Airway obstruction
	Resistance to positive-pressure ventilation	Tension pneumothorax
		Airway obstruction
		Bronchospasm
Neck	Jugular venous distention	Tension pneumothorax
		Cardiac tamponade
		Pulmonary embolus
	Tracheal deviation	Tension pneumothorax
Chest	Median sternotomy scar	Underlying cardiac disease
Lungs	Unilateral breath sounds	Tension pneumothorax
		Right mainstem intubation
		Aspiration
	Distant or no breath sounds or no chest expansion	Esophageal intubation
		Airway obstruction
		Severe bronchospasm
	Wheezing	Aspiration
		Bronchospasm
		Pulmonary edema
	Rales	Aspiration
		Pulmonary edema
		Pneumonia
Heart	Diminished heart tones	Hypovolemia
		Cardiac tamponade
		Tension pneumothorax
		Pulmonary embolus
Abdomen	Distended and dull	Ruptured abdominal aortic aneurysm or ruptured ectopic pregnancy
	Distended, tympanitic	Esophageal intubation
	Gastric insufflation	
Rectal	Blood, melena	Gastrointestinal hemorrhage
Extremities	Asymmetrical pulses	Aortic dissection
	Arteriovenous shunt or fistula	Hyperkalemia
Skin	Needle tracks or abscesses	Intravenous drug abuse
	Burns	Smoke inhalation
		Electrocution

[a]Indicating potential cause of cardiac arrest and complications of therapy.

as the coronary perfusion pressure (CPP). Electrocardiographic monitoring during cardiac arrest indicates the presence or absence of electrical but not mechanical activity. Although these two monitoring modalities may be the best attainable in certain circumstances, they do not provide reliable information regarding the effectiveness of CPR and interventions or prognosis.

Unfortunately, no ideal monitoring technique provides all the information that might be desired during resuscitation, and the modalities discussed below can be challenging to initiate during CPR. A brief overview is provided of CPP, end-tidal carbon dioxide (ET_{CO_2}), and central venous oxygen saturation (Scv_{O_2}) monitoring, which, if available, can be used to detect inadequate CPR with high specificity (Table 8.3). In addition, several of these techniques are useful in the immediate post–cardiac arrest period.

Arterial Blood Pressure and Coronary Perfusion Pressure

Successful resuscitation of the arrested heart depends on generating adequate CPP during CPR, which has been directly correlated with myocardial blood flow. Animal and human studies have indicated that a minimum CPP of 15 mm Hg is necessary to achieve ROSC if initial defibrillation attempts have failed. Unfortunately, CPP monitoring is rarely feasible in ED resuscitations of cardiac arrest patients because it requires an indwelling arterial pressure catheter and central venous catheter, both transduced properly to provide simultaneous readings.

Invasive arterial blood pressure monitoring alone can be helpful in guiding resuscitation and should be used when an indwelling arterial pressure catheter is already in place. When adequate personnel are available, it is often feasible to cannulate the femoral artery during CPR, especially with ultrasound guidance. Human studies have shown that radial or femoral arterial relaxation pressures reliably reflect aortic relaxation pressures during CPR In one ED-based study, all patients who achieved ROSC had arterial relaxation pressure during CPR that reached or exceeded 17 mm Hg. Titrating resuscitation efforts to arterial relaxation (diastolic) pressure is less reliable than CPP because improper CPR (eg, leaning on chest during CPR diastole and

TABLE 8.3

Indicators of Inadequate Blood Flow During Cardiopulmonary Resuscitation

MONITORING TECHNIQUE	INDICATOR
Carotid or femoral pulse	Not palpable
CPP	<15 mm Hg
Arterial relaxation (diastolic) pressure	<20–25 mm Hg
$PETCO_2$	<10 mm Hg
$ScvO_2$	<40%

CPP, Coronary perfusion pressure; *$PETCO_2$*, partial pressure of CO_2 in exhaled air at the end of expiration; *$ScvO_2$*, central venous oxygen saturation.

hyperventilation) can cause undetected elevations in the right atrial pressure, reducing coronary perfusion.

Despite these limitations, it is reasonable to titrate resuscitation efforts to achieve an arterial relaxation (diastolic) pressure of 20 to 25 mm Hg or more when invasive arterial pressure monitoring is available.[14,15] Invasive arterial pressure monitoring during CPR may also be useful to distinguish PEA with or without mechanical heart contraction, detect ROSC, and assist in serial arterial blood gas monitoring. Although arterial and central venous catheters are usually placed in the post–cardiac arrest phase of care, from 10% to 20% of patients initially achieving ROSC will rearrest, making these modalities helpful during the patient's subsequent resuscitation.[16]

End-Tidal Carbon Dioxide

The partial pressure of CO_2 in exhaled air at the end of expiration ($PETCO_2$) can be a reliable indicator of cardiac output during CPR. This is most reliably measured through waveform capnography after endotracheal intubation. $PETCO_2$ depends on CO_2 production, alveolar ventilation, and pulmonary blood flow (ie, cardiac output) and correlates well with CPP and cerebral perfusion pressure during CPR. Therefore, when minute ventilation is held constant (a desirable but often unmet goal) and no exogenous CO_2 is introduced (eg, with sodium bicarbonate [$NaHCO_3$] administration), only increased cardiac output during CPR and ROSC significantly increase $PETCO_2$. Resuscitation after cardiac arrest is likely to fail if $PETCO_2$ values of 10 mm Hg or more are not achieved. Therefore, values less than 10 mm Hg should prompt the clinician to enhance the quality of CPR, improving compression rate, depth, or recoil.

$PETCO_2$ monitoring also can aid in the diagnosis and treatment of PEA. Patients in a state of PEA with mechanical heart activity may have pulsatile flow that simply cannot be detected by palpation of a pulse. In such cases, $PETCO_2$ levels may be elevated, even without compressions. Use of cardiac ultrasound in such cases can identify corresponding cardiac activity. In these cases, volume expansion or the use of vasopressors and inotropes is indicated. $PETCO_2$ monitoring also is useful in rapidly detecting the success of tension pneumothorax decompression, pericardiocentesis for pericardial tamponade, and fluid resuscitation for hypovolemia. ROSC causes immediate and significant increases in $PETCO_2$. Therefore, $PETCO_2$ monitoring can detect ROSC at any time during the chest compression cycle, providing valuable guidance for pharmacologic therapies and minimizing the need for a pulse check when organized rhythms are detected (Fig. 8.1).

Finally, $PETCO_2$ monitoring is valuable in patients after ROSC to monitor endotracheal tube placement (waveform capnography recommended), titrate minute ventilation to avoid hyperventilation, and detect sudden hemodynamic deterioration.

Central Venous Oxygen Saturation

Central venous oxygen saturation, $ScvO_2$, when available, provides an additional method to monitor the adequacy of resuscitative measures. The mixed venous blood oxygen saturation in the pulmonary artery ($S\bar{v}O_2$) represents the oxygen remaining in the blood after systemic extraction. Studies have shown a close correlation between $ScvO_2$ and $S\bar{v}O_2$ during CPR. Because oxygen consumption remains relatively constant during CPR, as does arterial oxygen saturation (SaO_2) and hemoglobin, changes in $ScvO_2$ reflect changes in oxygen delivery by means of changes in cardiac output.

Although used most commonly in the intensive care unit (ICU) setting, multilumen oximetric $ScvO_2$ catheters are placed in the same manner as regular central venous catheters and can be used to monitor $ScvO_2$ continuously in real time. $ScvO_2$ values normally range from 60% to 80%. During cardiac arrest and CPR, these values range from 25% to 35%, indicating greatly enhanced oxygen extraction of tissues owing to the inadequacy of oxygen delivery during CPR. Failure to achieve an $ScvO_2$ of 40% or greater during CPR has had a negative predictive value for ROSC of almost 100%. $ScvO_2$ also helps to detect ROSC rapidly without interruption of chest compressions, because ROSC will result in a rapid increase in $Scvo_2$ as oxygen delivery to tissues dramatically increases. $ScvO_2$ monitoring is also useful in the post–cardiac arrest period for hemodynamic optimization and for recognition of any sudden deterioration in the patient's clinical condition.

PHARMACOLOGIC THERAPY

Pharmacologic therapy during CPR improves the proportion of patients who achieve ROSC.[17] However, there is yet to be a randomized prospective placebo-controlled clinical trial that has been adequately powered to determine if pharmacologic therapy during CPR improves long-term survival or neurologic outcome. Therefore, the primary focus of advanced life support remains early defibrillation and high-quality CPR, guided by physiologic monitoring.

For ongoing resuscitation of arrest rhythms that fail to respond to CPR and defibrillation, intravenous (IV) or intraosseous (IO) access should be obtained so that vasopressor therapy (typically, epinephrine 1.0 mg, IV or IO) can be administered and repeated every 3 to 5 minutes. Simultaneous administration of epinephrine and vasopressin does not improve the outcome relative to epinephrine alone, regardless of presenting rhythm. When intravascular pressure monitoring is available, it is reasonable to titrate vasopressor therapy during CPR to achieve a CPP of more than 15 mm Hg or arterial relaxation pressure more than 20 to 25 mm Hg.

For refractory VF or pVT, antidysrhythmics can be administered up to their maximum loading dose. Amiodarone (300 mg IV) is the only antidysrhythmic agent that has been shown to improve the rate of VF conversion to a perfusing rhythm.

Other medications that may be of value in special cases include magnesium sulfate in torsades de pointes and hypomagnesemia, calcium chloride in hyperkalemia, $NaHCO_3$ in tricyclic antidepressant overdose, and 50% dextrose in water in documented hypoglycemia.[6] Routine administration of atropine outside the setting of bradycardia is not beneficial.

DEVICES AND TECHNIQUES

Echocardiography

The main usefulness of echocardiography is diagnostic, especially in patients with PEA. Echocardiography distinguishes organized pulseless cardiac activity that does or does not result in mechanical

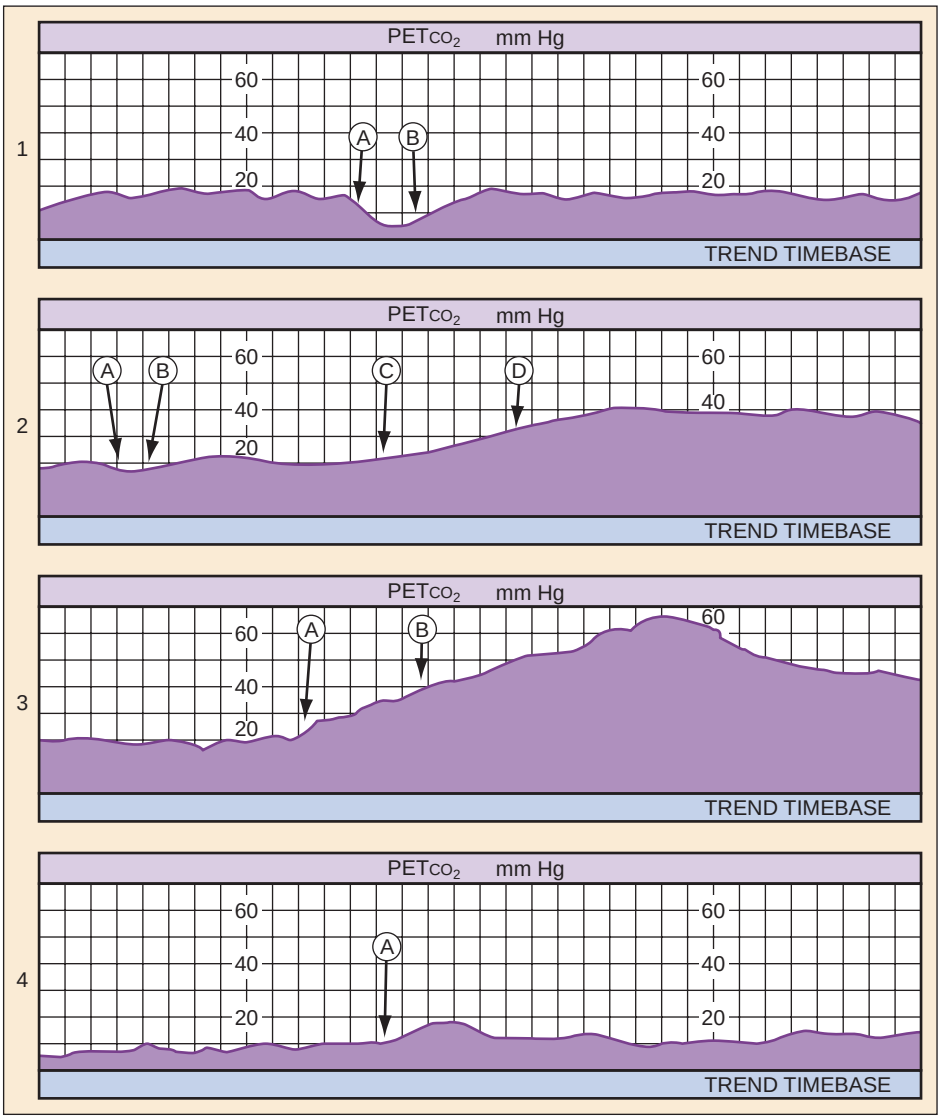

Fig. 8.1. Capnogram tracings of end-tidal carbon dioxide partial pressure ($PETCO_2$) during human cardiopulmonary resuscitation (CPR). **1,** Effect of rescuer fatigue is shown at point A. Point B shows the effect of changing to a fresh rescuer. **2,** Patient with pseudoelectromechanical dissociation. At point A, the patient is pulseless but has a persistent $PETCO_2$ value of 20 mm Hg without CPR, at point B, CPR is restarted, at point C, dopamine infusion is started, and at point D, CPR is stopped and a pulse is palpated. **3,** Sudden increase in $PETCO_2$ (point A) heralds the return of spontaneous circulation; pulses are palpated at point B. **4,** Point A shows a transient increase in $PETCO_2$, such as occurs during bolus administration of sodium bicarbonate.

heart contraction. It also may be helpful in diagnosing mechanical causes of PEA such as tension pneumothorax, pericardial tamponade, and pulmonary embolism. Echocardiography also is useful in guiding pericardiocentesis. In the postarrest period, echocardiography could prove to be valuable in evaluating myocardial dysfunction and determining the need for mechanical assistance of the failing heart.[18]

Laboratory Testing

Intermittent arterial and venous blood sampling for gas or chemistry analysis is of limited use during CPR. Typical blood gas findings during CPR demonstrate venous respiratory acidosis and arterial respiratory alkalosis. SaO_2 is usually greater than 94% during CPR and is of little value in titrating resuscitation therapy, except in the case of massive pulmonary embolism or unrecognized esophageal intubation. Although $ScvO_2$ indicates adequacy of CPR, a single measurement may not be as useful as continuous, oximetric $ScvO_2$ monitoring.

Other laboratory studies during CPR are typically not available in time to guide therapy, but may serve to confirm a diagnosis following successful resuscitation. Serum electrolyte levels may be ordered to rule out hyperkalemia, hypokalemia, hypomagnesemia, hypercalcemia, and hypocalcemia; however, empirical therapy should be initiated immediately if a high clinical suspicion exists. Hemoglobin levels may indicate hemorrhage, but the initial hemoglobin value may be normal, even in acute exsanguinating hemorrhage, owing to a lack of rapid vascular and interstitial compartment equilibration.

Resuscitation

Restoration of adequate cardiac function is the defining factor of ROSC, but restoration of good neurologic function is the defining

factor of successful resuscitation. The likelihood of achieving both these goals decreases with every minute that the patient remains in cardiac arrest. Although many interventions are specific to the presenting electrocardiographic rhythm, most therapeutic modalities and monitoring techniques are used in all rhythms, making separate algorithms redundant.

Interventions should be performed rapidly and efficiently to maximize the chances of a good neurologic outcome. The quality of CPR is perhaps the most underappreciated component of the resuscitation effort. Important quality performance measures include compression rate (100–120 compressions/min), compression depth (5–6 cm), chest compression fraction (ie, CPR performed 80 out of every 100 seconds of the pulseless interval), full chest recoil (no residual leaning between compressions), and ventilation rate (10 breaths ventilations/min).[14] Furthermore, hyperventilation has been shown to be common, and more than 10 ventilations/min are unnecessary and reduce cardiac output during CPR.[14] A 30:2 compression-to-ventilation ratio is currently recommended for health care professionals in all adult resuscitation scenarios until an advanced airway has been established.[14] Once an advanced airway is secured, CPR should be performed continuously, without pausing for ventilation, while providing one ventilation every 6 seconds (10 ventilations/min).[15] As indicated earlier, if $PETCO_2$ is to be helpful as an indicator of cardiac output during CPR, minute ventilation should be relatively constant. Although recent evidence has suggested that chest compression–only CPR is no less effective than traditional CPR when performed by bystanders in the out-of-hospital setting, trained providers who are willing and able to provide ventilations should do so.[19] Although oxygen uptake from the lungs is low during CPR, oxygen remaining in the functional residual capacity of the lung will be continuously consumed as CPR progresses, if not replenished. The exception to this is when inadequate personnel are present to provide compressions, ventilation, and other resuscitative measures. Intubation should be performed only when capable personnel are available and without interruption of chest compressions. Use of supraglottic airway adjuncts may be beneficial alternatives for airway management in the out-of-hospital phase of resuscitation to minimize interruptions to chest compressions.

In addition to monitoring specific CPR performance parameters, physiologic monitoring, if available, can help optimize CPR quality for the individual patient (see Table 8.3). If the inadequacy of CPR is recognized early in the resuscitation despite optimized therapy, the physician in charge may consider more invasive measures such as ECPR or coronary angiography and PCI with ongoing chest compressions if these modalities are readily available and there is significant potential for survival with good neurologic function. After prolonged arrest, however, clear indications that CPR is inadequate (based on appropriate monitoring techniques) can be a contributing factor in the decision to cease resuscitation efforts. Fig. 8.2 depicts an algorithm for the management of cardiac arrest. Interventions specific to each rhythm are discussed in the following sections.

Defibrillation

VF and pVT are treated identically because they are generally caused by the same mechanisms and respond to the same interventions. Traditional monophasic defibrillators have almost completely been replaced by defibrillators using biphasic waveforms. With biphasic defibrillation, the energy required for successful defibrillation, the so-called defibrillation threshold, is lower than with monophasic defibrillation. The biphasic waveform increases the likelihood of initial defibrillation success and decreases the likelihood of post–countershock myocardial dysfunction. Despite documented advantages of lower defibrillation threshold and reduced myocardial injury with the use of biphasic defibrillation, data are currently inadequate to conclude that any specific waveform (biphasic or monophasic) is superior to any other in achieving ROSC or survival to hospital discharge. New defibrillation technologies have stimulated a reevaluation of optimal defibrillation strategies. Current consensus suggests that the most effective strategy is delivery of single countershocks at optimal energy levels, with minimal pauses in CPR.[15] This is facilitated by the placement of defibrillation pads early in the resuscitation sequence, thus not requiring a pause while defibrillation paddles and conducting gel are placed for each shock. Health professionals should use the manufacturer-recommended countershock energies for biphasic defibrillators because these range from 120 to 360 J and are device-specific.[15] The recommended energy for a single monophasic defibrillation is 360 J.[16] There is no evidence that the use of higher energies or dual-sequential external defibrillation—simultaneously defibrillating from two separate, unlinked devices—in the setting of refractory VF improves survival to hospital discharge.[20]

A patient who develops VF or pVT while on a cardiac monitor may remain conscious for 15 to 30 seconds. The patient should be encouraged to cough vigorously until a defibrillator is available. This cough CPR has been demonstrated to keep patients conscious for up to 1 minute or longer. If the patient is unresponsive, chest compressions should be initiated immediately and continued until a defibrillator is available. Defibrillation without antecedent CPR is most likely to result in ROSC when administered in the first 2 minutes of arrest. However, beyond this interval, there has been no demonstrated difference in outcomes with a brief period (30–60 seconds), as compared to a longer period (180 seconds). of CPR, before first analysis of cardiac rhythm in a large, multicenter randomized trial.[21] The current consensus favors delivering a single countershock with minimal pause in chest compressions.[15] Defibrillation is followed immediately by the resumption of chest compressions for 2 minutes before a rhythm check and additional defibrillation, as appropriate.[14]

Therapy for refractory VF and pVT includes high-quality CPR, administration of vasopressors and antidysrhythmic agents, and repeated countershocks. If a patient is defibrillated into a different pulseless rhythm such as PEA or asystole, subsequent treatment should be modified to address those specific rhythms.

Pulseless Electrical Activity

PEA is defined as coordinated electrical activity of the heart (other than VT or VF) without a palpable pulse. This group of dysrhythmias includes electromechanical dissociation (EMD), in which no myocardial contractions occur, and pseudo-EMD, in which myocardial contractions occur but are inadequate, and no pulse can be palpated. Although distinguishing EMD from pseudo-EMD may be useful in determining cause and guiding treatment, in most cases of primary PEA there is a natural progression from hypotension to pseudo-EMD to EMD.

True EMD is the result of a primary disorder of electromechanical coupling in myocardial cells. It often is associated with abnormal automaticity and conduction, resulting in bradycardia and a wide QRS complex. Although the mechanism of uncoupling is unclear, it usually is associated with global myocardial energy depletion and acidosis resulting from ischemia or hypoxia. True EMD typically occurs after defibrillation following prolonged VF and is associated with hyperkalemia, hypothermia, and drug overdose.

Pseudo-EMD caused by global myocardial dysfunction is a transient state in the progression to EMD and has the same cause. An additional cardiac cause of pseudo-EMD is papillary muscle and myocardial wall rupture, in which the ventricle continues to contract but forward flow is greatly diminished. Pseudo-EMD also

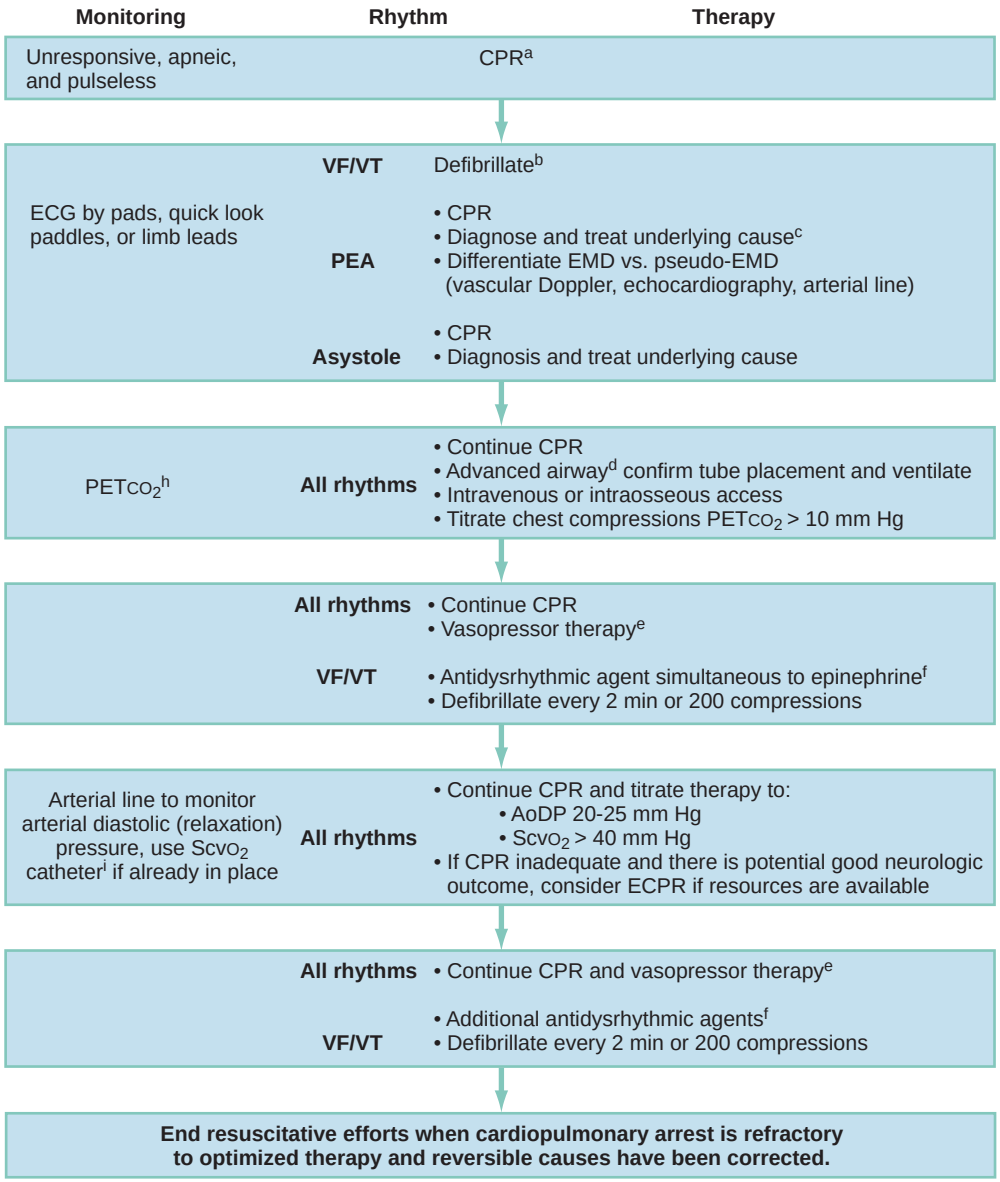

Fig. 8.2. Emergency treatment algorithm for treatment of cardiac arrest. [a]If arrest is witnessed and known to be of short duration, immediate rhythm assessment and defibrillation or ventricular fibrillation/ventricular tachycardia *(VF/VT)* precede cardiopulmonary resuscitation *(CPR)*. [b]Biphasic defibrillation should use manufacturer-recommended energy versus monophasic defibrillation (360 J). [c]See Table 8.4. [d]Endotracheal intubation or supraglottic airway, when feasible, with minimal interruption in chest compressions. [e]Epinephrine, initial dose of 1 mg IV or IO. Repeat every 3 to 5 minutes. Subsequent doses may be increased up to 0.1 mg/kg. An alternative to epinephrine is vasopressin, 40 U, via IV push. The dose (40 U) can be repeated once in 3 minutes, followed by the administration of epinephrine every 3 to 5 minutes. [f]Amiodarone, 300 mg via IV push, followed by 150 mg every 30 minutes. Lidocaine is an alternative antidysrhythmic if amiodarone is not available; magnesium sulfate, 1 to 2 g via IV push in torsades de pointes or known hypomagnesemia, may be given. [h]Changes in the partial pressure of end-tidal carbon dioxide ($PETCO_2$) may not be predictive of myocardial blood flow in the setting of high-dose vasopressor therapy. [i]Invasive monitoring should be performed only if adequate personnel are available and if it would not delay therapeutic interventions. *AoDP,* Aortic diastolic pressure; *ECG,* electrocardiogram; *EMD,* electromechanical dissociation; *PEA,* pulseless electrical activity; *$ScvO_2$,* central venous oxygen saturation.

may be caused by primary supraventricular tachycardia. Additional extracardiac causes of pseudo-EMD include hypovolemia, tension pneumothorax, pericardial tamponade, and massive pulmonary embolism. Pseudo-EMD of extracardiac origin most often has narrow complex tachycardia initially, which can progress to bradycardia, with conduction abnormalities and QRS widening.

Treatment of PEA requires all general resuscitation measures, including CPR, intubation with assisted ventilation, IV access, and repeated administration of vasopressors. Initial assessment also should include vascular Doppler ultrasound, echocardiography, or $PETCO_2$ monitoring to distinguish EMD from pseudo-EMD. This is important because volume loading or continuous vasopressor infusion, which is not typically used in routine cardiac arrest resuscitation, may be helpful in cases of pseudo-EMD. In contrast, the routine use of atropine during PEA, previously a mainstay of drug therapy, is not indicated. PEA thought to result from a supraventricular tachycardia (SVT) should be immediately cardioverted. These interventions alone are generally inadequate, unless the underlying cause of PEA is primary respiratory arrest

TABLE 8.4

Diagnosis and Treatment of Common Causes of Pulseless Electrical Activity

CAUSE	DIAGNOSIS	PALLIATIVE THERAPY	DEFINITIVE THERAPY
Hypovolemia	Response to volume infusion	Volume infusion	Hemostasis if hemorrhage
Hypoxia	Response to oxygenation	Oxygenation, assisted ventilation	Treat underlying cause
Cardiac tamponade	Echocardiogram; jugular venous distention	Pericardiocentesis	Thoracotomy and pericardiotomy
Tension pneumothorax	Asymmetric breath sounds, tracheal deviation	Needle thoracostomy	Tube thoracostomy
Hypothermia	Rectal temperature		Warm peritoneal or thoracic lavage, venoarterial ECMO
Pulmonary embolus	Risk factors or evidence of deep venous thrombosis	Venoarterial ECMO	Lytic therapy, pulmonary embolectomy
Drug overdose	History of drug ingestion	Drug-specific	Drug-specific
Hyperkalemia	History of renal failure or elevated serum potassium level	Calcium chloride, insulin and glucose, sodium bicarbonate	Hemodialysis
Acidosis	Arterial blood gas	Hyperventilation, sodium bicarbonate	Treat underlying cause

ECMO, Extracorporeal membrane oxygenation.

or SVT. Successful resuscitation of patients with PEA hinges on rapid diagnosis and treatment of the underlying cause. Physical examination may provide valuable clues to the underlying cause (Table 8.4). In hypoxia and hypovolemia, the diagnosis is based on response to empirical therapy, whereas other causes such as pericardial tamponade, tension pneumothorax, and hypothermia can be definitively diagnosed during resuscitation.

Asystole

Asystole represents complete cessation of myocardial electrical activity. Although asystole may occur early in cardiac arrest as a consequence of progressive bradycardia, asystole generally represents the end-stage rhythm after prolonged cardiac arrest caused by VF or PEA. Because the potential exists for an organized rhythm or VF to appear as asystole in a single lead—if the rhythm vector is completely perpendicular to the lead vector—asystole should be confirmed in at least two limb leads. Although asystole may be difficult to distinguish from extremely fine VF, routine countershock of asystole has not been shown to improve survival.

Treatment of asystole requires general resuscitation measures, including CPR, intubation with assisted ventilation, IV access, and repeated administration of vasopressors. Available evidence has indicated that routine administration of atropine is not beneficial. Extensive research has shown that asystole in the out-of-hospital setting seldom responds to pacing. To be effective, pacing must be initiated within several minutes of arrest.

Extracorporeal Cardiopulmonary Resuscitation

Despite lack of supporting evidence from randomized trials, use of ECPR or venoarterial ECMO as a rescue therapy for refractory adult and pediatric in-hospital cardiac arrest is a well-established practice in many specialized centers. Observational and case-control studies have suggested benefit in selected patients with refractory out-of-hospital cardiac arrest, reporting rates of survival with good neurologic function ranging from 11% to 33%.[11,22-24] Timely arterial and venous access, placement of cannulas, and initiation of ECPR support is critical to success. When used, ECPR is most successful when flow is initiated within 60 minutes of cardiac arrest onset.[22] Survivors typically require 2 to 5 days before they can be being successfully weaned from ECMO support.[22] Common complications include coagulopathy, hemorrhage, limb ischemia, vascular injury, renal replacement therapy, and stroke. The implementation of an ECPR program for refractory out-of-hospital cardiac arrest is expensive and resource-intensive and requires a significant amount of training and coordination among EMS providers, receiving EDs, designated specialties, and participating ICUs to be successful. More research is needed to determine the feasibility and value proposition of implementation outside of specialized centers.

OUTCOMES

Post–Cardiac Arrest Care

Resuscitation of a cardiac arrest victim does not end with ROSC. Management includes rapid diagnosis and treatment of the disorders that caused the arrest and complications of prolonged global ischemia. Simultaneous management of these two entities makes caring for a post–cardiac arrest patient particularly challenging. A comprehensive, goal-directed program of post–cardiac arrest care is necessary to optimize survival and neurologic recovery.[25]

Hypothermic Targeted Temperature Management

Hypothermic targeted temperature management (HTTM) in comatose survivors of cardiac arrest has been shown to improve survival and functional outcome in two modestly sized, prospective randomized clinical trials. These studies enrolled only comatose survivors of out-of-hospital cardiac arrest that was witnessed arrest and had an initial rhythm of VF. The time to achieve target temperature (<34°C [93.2°F) ranged from less than 2 hours to a median of 8 hours (interquartile range, 4–16 hours), suggesting a broad therapeutic window. HTTM was maintained for 12 to 24 hours, followed by gradual rewarming over 12 to 24 hours. A subsequent large, multicenter international randomized clinical trial of post–cardiac arrest HTTM included all presenting rhythms except unwitnessed asystole and found that outcomes with a target temperature of 33°C (91.4°F) were not superior to those with a target temperature of 36°C (96.8°F).[3] In this study, target temperature was maintained for 28 hours, followed by gradual

rewarming at 0.5°C (32.9°F)/hr and then maintenance of temperature below 37.5°C (99.5°F) for 72 hours post-ROSC. Although these parameters provide guidelines within which post–cardiac arrest HTTM is effective, additional preclinical and clinical data are needed to determine the optimal method of temperature control, time to achieve target temperature, target temperature, duration of therapy, and rate of rewarming. We recommend that emergency clinicians provide HTTM to comatose adult patients who achieve ROSC following cardiac arrest, independently of presenting cardiac rhythm (shockable vs. nonshockable) and location (OHCA [out-of-hospital cardiac arrest] vs. IHCA [in-hospital cardiac arrest]). Furthermore, emergency clinicians should select and maintain HTTM at a constant temperature between 32° and 36°C (89.6° and 96.8°F) for 24 hours after achieving that target temperature.[25]

Although there are no absolute contraindications, relative contraindications may include another obvious reason for coma (eg, drug overdose, status epilepticus), known end-stage terminal illness, and a preexisting do-not-resuscitate status. In each of the two randomized HTTM trials, the rates of complications, including bleeding, were not statistically different between groups. Specifically, thrombolytic therapy does not preclude the use of hypothermia.

When the decision is made to treat the comatose post–cardiac arrest patient with HTTM, efforts to achieve and maintain target temperature should begin in the ED, when feasible. However, prehospital cooling after ROSC using cold IV saline has not been shown to improve outcomes in two prospective randomized clinical trials.[26,27] In the ED, practical methods of rapidly inducing hypothermia include ice packs (applied to the neck, inguinal areas, and axilla), fan cooling of dampened exposed skin, cooling blankets underneath and on top of the patient, and disabling of ventilator warming circuits. Rapid IV infusion of limited volumes (1–2 L) of 4°C (39.2°F) saline facilitates induction of hypothermia, but additional measures are needed to maintain hypothermia.

No one cooling strategy or device has been demonstrated to result in superior clinical outcomes.[28] A number of automated surface cooling devices are now available that use chest and thigh pads and continuous temperature feedback from bladder or esophageal temperature probes. Although more invasive, automated endovascular cooling systems are also available that require placement of a central venous catheter and offer tighter control of temperature at target (SD [standard deviation] usually <0.3°C [32.5°F]).[29]

Shivering, which inhibits cooling, can be prevented with sedation and neuromuscular blockade. If neuromuscular blockade is continued during the maintenance phase of therapeutic hypothermia, continuous electroencephalographic monitoring is strongly encouraged to detect seizures, a common occurrence in post–cardiac arrest patients (5%–20%).[25] Target core body temperature is best monitored by an indwelling, temperature-sensitive bladder catheter or esophageal temperature probe. Although the optimal duration of post–cardiac arrest hypothermia is unknown and may be related to the total ischemic time,[30] target temperatures are typically actively maintained for at least 24 hours, followed by gradual rewarming over 12 to 16 hours.[25] Postarrest hypothermia is also discussed in Chapter 7.

Coronary Angiography and Primary Percutaneous Coronary Intervention

An immediate concern in a comatose cardiac arrest survivor is whether the patient has an acute coronary syndrome (ACS). Diagnosing ACS in an unconscious patient after cardiac arrest presents a unique challenge. A standard 12-lead ECG should be obtained as soon as feasible after ROSC, with additional right-sided and/or posterior leads as indicated. In one study, 50% of patients achieving ROSC after out-of-hospital cardiac arrest were found to have acute coronary occlusion on cardiac catheterization; more than 10% of them did not have ST segment elevation. Subsequent studies have reported that successful, immediate PCI is associated with improved hospital survival in post–cardiac arrest patients, with or without ST segment elevation.[31]

Immediate PCI is indicated for post-ROSC patients with demonstrated ST segment elevation myocardial infarction (STEMI) and should progress via established systems of care.[9,25] OHCA patients are often initially comatose, but this should not be a contraindication to consider immediate angiography and PCI. Although the initiation of TTM should not delay PCI, it can often be accomplished simultaneously and in concert with interventional cardiology.[25] When there is a high clinical suspicion of ACS without STEMI demonstrated on an ECG, rapid post-ROSC angiography and PCI, when indicated, have been associated with improved survival to hospital discharge when a noncardiac cause for OHCA is not obvious.[32]

When PCI is indicated but not available, transfer of post–cardiac arrest patients to a center capable of PCI or fibrinolytic therapy should be considered. Relative exclusion criteria for fibrinolytic therapy unique to the post–cardiac arrest patient include evidence of significant CPR trauma such as pneumothorax, flail chest, or pulmonary contusion with hemorrhage. The effects of TTM on the efficacy and complications of fibrinolytic therapy in postarrest patients have not been formally studied. However, an initial randomized TTM trial where fibrinolytics were given to approximately 50% of enrolled subjects demonstrated no increase in complications compared to controls.

Although the immediate post–cardiac arrest period is characterized by a hypocoagulable state, it is rapidly replaced by a hypercoagulable state for up to 72 hours as the post-ROSC surge of activated protein C abates.[33] Dual anticoagulant and antiplatelet therapy (aspirin and a P2Y12 inhibitor) should be strongly considered for postcardiac patients with diagnosed or suspected ACS in the absence of contraindications.[34,35] Recent clinical evidence has suggested that ticagrelor results in more effective platelet inhibition than clopidogrel in post–cardiac arrest patients treated with HTTM.[36] There is no proven benefit of prophylactic antiarrhythmic therapy or continuous infusion of an antiarrhythmic drug that has been associated with restoration of a stable rhythm during CPR. Concomitant therapies (eg, nitrates, beta blockers) are best performed in conjunction with careful hemodynamic monitoring. If indicated, IV preparations of nitrates and short-acting beta blockers (eg, esmolol) should be used because they have a brief duration of action and are easily titrated. In patients with new left bundle branch block, right bundle branch block with left anterior or posterior hemiblock, second-degree type II block, or third-degree block, transthoracic pacing pads should be applied in case they are needed to treat bradycardic rhythms. Placement of a transvenous pacing catheter may be considered, but is less commonly done with the increasing use and demonstrated efficacy of transthoracic cardiac pacing.

Inadequate oxygen delivery (DO_2) causes cells to convert to anaerobic metabolism, resulting in increased lactate production (dysoxia). Continued resuscitation efforts are aimed at optimizing DO_2 to prevent subsequent multiorgan dysfunction and recurrent arrest. However, supranormal arterial oxygen partial pressure (>300 mm Hg) can exacerbate oxidative brain injury during the first minutes to hours after cardiac arrest. Therefore, the fraction of inspired oxygen (FIO_2) can be titrated to the minimum concentration required to maintain an arterial oxyhemoglobin saturation around 94%. This level of oxygenation avoids detrimental hyperoxia while ensuring appropriate oxygen delivery.[37]

Serum lactate levels provide an indirect measure of whether DO_2 is adequate to prevent anaerobic metabolism. A single lactate

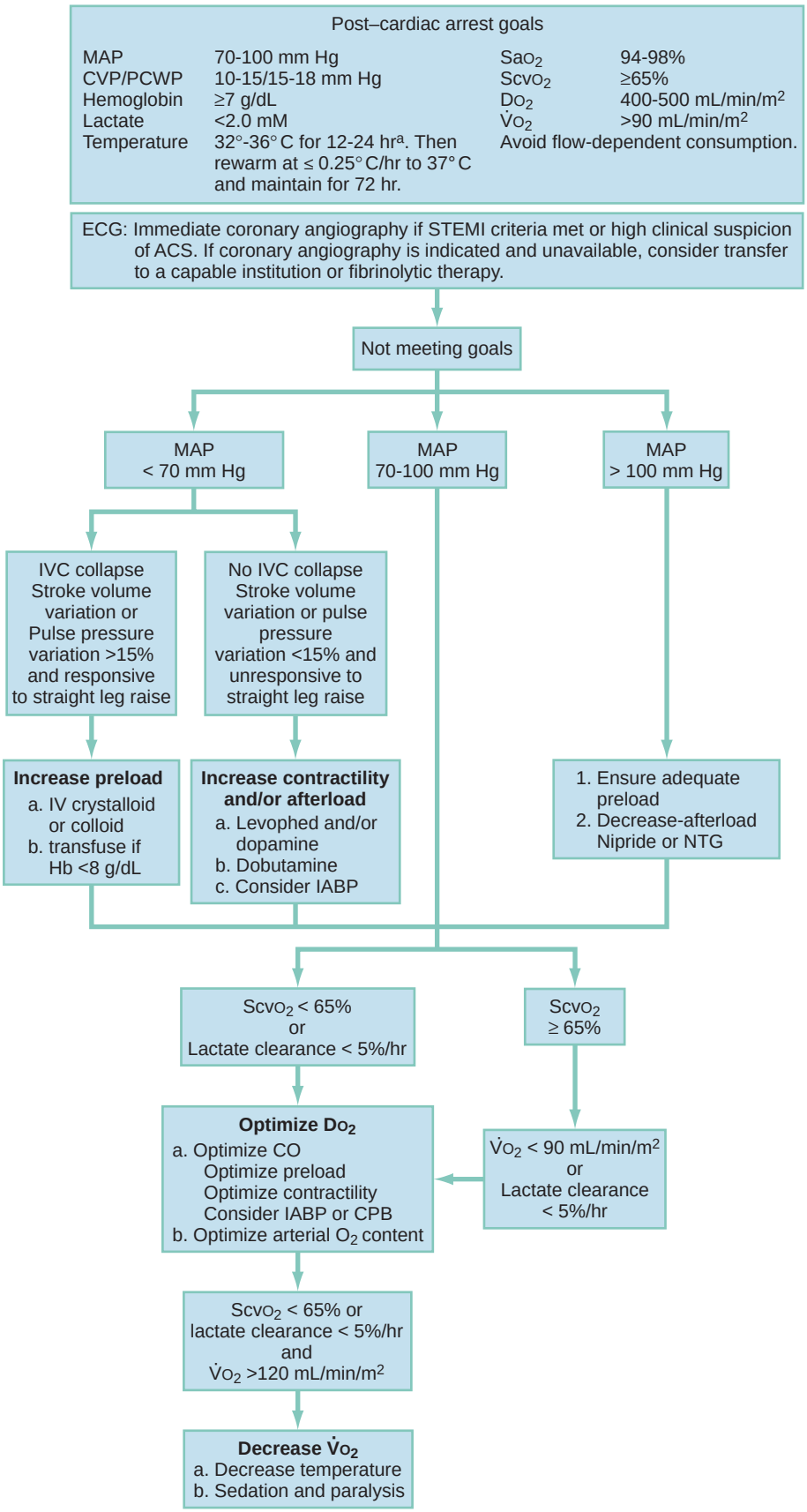

Fig. 8.3. Goal-directed postarrest treatment algorithm. [a]Hypothermic targeted temperature management (HTTM) is indicated in comatose survivors of witnessed cardiac arrest who had a presenting rhythm of ventricular fibrillation. It may also be effective in patients resuscitated from other cardiac arrest presentations. Relative contraindications include uncontrolled bleeding, preexisting coagulopathy, another obvious reason for coma (eg, drug overdose, status epilepticus), known end-stage terminal illness, and a preexisting do-not-resuscitate status. [b]Initiation of HTTM is not a contraindication to thrombolytic therapy. *CPB,* cardiopulmonary bypass; *CVP,* central venous pressure; D_{O_2}, oxygen delivery; *ECG,* electrocardiogram; *Hb,* hemoglobin; *IABP,* intraaortic balloon pulsation; *MAP,* mean arterial pressure; *MI,* myocardial infarction; *NTG,* nitroglycerin; *PCWP,* pulmonary capillary wedge pressure; *PTCA,* percutaneous transluminal angioplasty; Sa_{O_2}, arterial oxygen saturation; Scv_{O_2}, central venous oxygen saturation; $\dot{V}_{O_2}$, oxygen consumption.

level is almost universally elevated after resuscitation from cardiac arrest. Detection of ongoing lactate production requires monitoring of serial lactate levels. Insufficient DO_2 also causes increased oxygen extraction, resulting in decreased mixed venous oxygen saturation ($S\bar{v}O_2$). Low $S\bar{v}O_2$ coupled with persistently elevated lactate levels indicates inadequate DO_2. Patients with prolonged duration of CPR and those who have received high-dose vasopressor therapy during CPR may develop impaired tissue oxygen extraction. In such patients, $S\bar{v}O_2$ is abnormally high (venous hyperoxia) in the presence of inadequate DO_2 and likely represents a state of severe systemic shunting resulting in an increase in nonnutritive blood flow. Lactate levels in these cases are persistently elevated. Treatment includes carefully reducing any continuous infusion of vasopressors and providing more aggressive volume loading. The use of guided vasodilator therapy to recruit underperfused tissue beds, as well as consideration of mechanical adjuncts such as an intraaortic balloon pump or VA-ECMO, may also be necessary in this situation.

The use of combined hemodynamic and metabolic endpoints to guide resuscitation in the ED has been shown to improve the outcome of patients with septic shock states. Because the post–cardiac arrest condition represents a complex state of cardiovascular shock, the use of such goal-directed therapy is inherently valuable to reduce mismatches of oxygen delivery and consumption that cannot be determined by a simple physical examination and vital signs.

The use of goal-directed hemodynamic therapy is relatively straightforward and can be frequently accomplished via noninvasive means. Bedside ultrasound can be used to visualize the left ventricle in real time, allowing for direct assessment of cardiac index and myocardial wall function. Furthermore, in mechanically ventilated patients, volume responsiveness can also be reliability evaluated by measuring the inferior vena cava collapse[38,39] or passive leg raise.[40] These dynamic noninvasive measures can guide volume expansion to maximize preload without inducing pulmonary edema.

When sonographic measures are unavailable, the placement of a supradiaphragmatic central venous catheter may be used to give further clinical context for intractable shock. If $ScVO_2$, a reliable surrogate for $S\bar{v}O_2$, is abnormally low (<65%), but hemoglobin and SaO_2 values are normal, cardiac output is insufficient. Although central venous pressure (CVP) has limitations in certain disease states (eg, pulmonary hypertension), a CVP less than 8 mm Hg can be generally relied on to be fluid-responsive, and augmenting CVP to levels between 10 and 15 mm Hg ensures adequate preload in most patients. If intravascular volume is adequate and the patient has a mean arterial pressure of at least 65 mm Hg, unmet resuscitation goals should prompt therapy with an inotropic agent such as dobutamine while reperfusion strategies or mechanical adjuncts are considered.

The response to DO_2-optimizing interventions can be monitored by continuous or serial $ScVO_2$ measurements and serial lactate levels. An increase in $ScVO_2$, coupled with a decrease in lactate levels, indicates improved DO_2. An unchanging $ScVO_2$ level indicates the need to continue to increase delivery. Persistently elevated lactate levels and a low $ScVO_2$, despite maximum pharmacologic support and volume management, signal the need for additional interventions to optimize DO_2. Similarly, in patients with venous hyperoxia and elevated levels of lactate, the combination of these findings indicates severe microvascular dysfunction, which also leads to the accumulation of oxygen debt incompatible with survival. If oxygen debt continues to accumulate, the patient will be at increased risk of developing multisystem organ failure or death. Fig. 8.3 provides a goal-directed guide to care of the postarrest patient.

Hospital protocols and systems can be designed to ensure prompt transfer of post–cardiac arrest patients from the ED to the cardiac catheterization laboratory or an ICU, where intensive monitoring can guide subsequent therapy to achieve optimal patient outcomes. Unless prompt transfer to the ICU is anticipated and achieved, comprehensive post–cardiac arrest care should be initiated in the ED.

KEY CONCEPTS

- CPR quality is critical to successful resuscitation from cardiac arrest. Important benchmarks of quality CPR include compression rate between 100 and 120 compressions/min, compression depth of 5 to 6 cm, chest compression fraction of 80% or more, full chest recoil, and ventilation rate of 10 breaths/min.
- Restoration of adequate cardiac function is the defining factor of ROSC. Restoration of good neurologic function is the defining factor of successful resuscitation.
- Resuscitation of a cardiac arrest victim does not end with ROSC. Rapid diagnosis and proper management of the pathologic conditions that precipitated and resulted from the arrest, as well as goal-directed post–cardiac arrest care, can improve outcome.
- Immediate PCI is indicated in patients with demonstrated ST segment elevation MI following ROSC without regard to neurological status.
- Hypothermic targeted temperature management (32°–36° C [89.6°–96.8° F] for 24 hours) is the first and only post-ROSC intervention that has been shown to improve survival and functional outcome of comatose cardiac arrest survivors.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 8: QUESTIONS & ANSWERS

8.1. Which of the following statements regarding the epidemiology of out-of-hospital cardiac arrest is true?

A. Most patients surviving to hospital discharge will have persistent neurologic deficits.

B. Of patients successfully resuscitated and admitted to the hospital, 75% will survive to hospital discharge.

C. Return of spontaneous circulation with subsequent hospital admission occurs in less than 3% of cases.

D. Ventricular fibrillation is estimated to be the initial rhythm in more than 50% of all cases.

E. With the application of therapeutic hypothermia, up to 50% of successfully resuscitated patients may survive to hospital discharge with return to prearrest function.

Answer: E. It is estimated that 176,000 patients are treated for out-of-hospital cardiac arrest each year in the United States. The proportion of emergency medical services (EMS)–treated cardiac arrest patients with an initial rhythm of ventricular fibrillation (VF) has declined over time to 20% in recent US studies. There is tremendous variability in survival to hospital discharge after EMS-treated cardiac arrest, ranging from 3% to 16.7%. Recent US data have indicatd an average survival rate to hospital discharge of 11%. Of patients surviving to hospital discharge, independent of neurologic status on presentation, 78% have good neurologic function.

8.2. A 75-year-old man presents with return of spontaneous circulation (ROSC) after 2 minutes of VF and successful defibrillation by EMS. The patient is unresponsive to verbal and painful stimuli. Vital signs on arrival are pulse, 120 beats/min, blood pressure, 130/70 mm Hg, respiratory rate, 10 breaths/min, temperature, 36°C (96.8°F), and oxygen saturation, 94%. The patient has intravenous access. The next most appropriate examination or procedure is:

A. Anteroposterior (AP) chest radiograph

B. Arterial blood gas (ABG)

C. Comprehensive neurologic examination

D. Electrocardiography
E. Oxygen via nonrebreather mask

Answer: D. Acute coronary syndrome is a common cause of out-of-hospital cardiac arrest. Electrocardiography should be performed as soon as possible after ROSC to evaluate for ST segment elevation. Because it is impossible to determine survival or neurologic status in the immediate postarrest period, ST segment elevation myocardial infarction (STEMI) should be treated aggressively with percutaneous coronary intervention (PCI) independently of coma or other laboratory values such as those provided on ABG analysis. Oxygen saturations above 94% are adequate for tissue perfusion, and hyperoxia may be harmful. AP chest radiographs may be important to evaluate ventilatory status if the patient is unstable.

8.3. Which chest compression/ventilation ratio is recommended during adult resuscitation efforts performed by health care professionals before placement of an advanced airway?
A. 10:1
B. 20:1
C. 20:2
D. 30:2
E. None. Evidence has shown that chest compression–only cardiopulmonary resuscitation (CPR) is the most effective for health care providers.

Answer: D. A 30:2 compression/ventilation ratio is currently recommended for health care professionals in all adult resuscitation scenarios. Although recent evidence has suggested that chest compression–only CPR is effective when performed by bystanders in the out-of-hospital setting, there is inadequate evidence to recommend this as an alternative strategy for health care professionals, except when inadequate personnel are present to provide compressions, ventilation, and other resuscitative activities.

8.4. Which of the following statements regarding hypothermic targeted temperature management in comatose survivors of cardiac arrest is true?
A. Gradual rewarming should occur over 4 hours.
B. Pregnancy is an absolute contraindication.
C. Prolonged pharmacologically induced paralysis is often required to control shivering.
D. Target core body temperature should be 32° to 36° C.
E. To achieve benefit, the target temperature must be reached in less than 30 minutes.

Answer: D. Induction of prolonged HTTM in comatose survivors of cardiac arrest has been shown to improve survival and functional outcome. A target temperature in the range of 32° to 36° C (89.6°–96.8° F) should be selected and maintained. The time to achieve this temperature has not been clearly defined, and it has been suggested that there is a broad therapeutic window. In the studies showing a benefit, maintenance of hypothermia occurred for 12 to 24 hours, followed by gradual rewarming over 12 to 24 hours. There are no absolute contraindications to induced hypothermia after arrest. Shivering, which inhibits cooling, can be prevented with sedation and pharmacologic paralysis. However, prolonged paralysis should be avoided because of the risk of unrecognized seizure activity in post–cardiac arrest patients.

8.5. For end-tidal pressure of carbon dioxide ($PETCO_2$) to be a reliable indicator of cardiac output during cardiac arrest., which of the following must be present?
A. Mechanical chest compression must be performed.
B. The patient must be in asystole.
C. Patient must be normothermic
D. The patient must have an endotracheal tube and relatively constant minute ventilation.
E. Vasopressor therapy cannot be used.

Answer: D. Although $PETCO_2$ will change in direct relationship to cardiac output, alterations in minute ventilation will concentrate or dilute the fixed amount of expired CO_2, influencing the $PETCO_2$ measured independently of cardiac output. Therefore, for $PETCO_2$ to be a reliable indicator of cardiac output, minute ventilation must be held relatively constant. In addition, all studies demonstrating the relationship between $PETCO_2$ and cardiac output have been performed with an endotracheal tube in place. The relationship of $PETCO_2$ and cardiac output during CPR is not dependent on rhythm, mechanisms of chest compressions, or temperature. High-dose vasopressor therapy can cause a decreased in cardiac output during CPR, despite increased myocardial blood flow, which results in a decreased $PETCO_2$.

CHAPTER 9

Fever in the Adult Patient

Frederick C. Blum | Michelle H. Biros

PERSPECTIVE

Epidemiology

Morbidity and mortality rates from febrile illnesses vary dramatically with age. Younger adults with fever usually have benign self-limited disease, with less than 1% mortality. The challenge in this group is to identify the rare meningitis or septic condition when confronted with a predominance of self-limited viral and focal bacterial diseases. Patients older than 65 years, or those with chronic disease who have fever, represent a group at high risk for serious disease. Morbidity and mortality rates in this group are significant. From 70% to 90% are hospitalized, and 7% to 9% die within 1 month of admission.[1] Infection is the most common cause of fever in these patients, and most of these infections are bacterial in nature. Three body systems—the respiratory tract, urinary tract, and skin and soft tissue—are the target for more than 80% of these infections.[1,2] The relative mortality and morbidity rates for any given infection are much higher in the geriatric population. For example, older adults are at 5 to 10 times greater risk for urinary tract infections and 15 to 20 times greater risk for appendicitis.[1] Even viral illnesses that are generally not fatal, such as influenza, can be highly lethal in older adults.

Pathophysiology

Body temperature is normally controlled within a narrow range by the preoptic area of the hypothalamus. This range is usually 36.0° to 37.8°C (96.8°–100.0°F). There is a circadian rhythm within this range, with lower temperatures in the morning and higher temperatures in the late afternoon. Fever occurs when this normal range is reset to a higher value.

There is no consensus on the threshold core temperature that defines fever. The Centers for Disease Control and Prevention define fever as a core temperature greater than 37.8°C in the absence of fever-reducing medication. Others use a value of 38.0°C to define fever. However, there is near-universal agreement that a core body temperature of 38.3°C (100.9°F) represents a fever.[3]

Fever is distinct from hyperthermia. Hyperthermia is an elevation of the temperature related to the inability of the body to dissipate heat. Most cases of temperatures higher than 41.0°C (105.8°F) are a result of hyperthermia, but febrile illness also is considered.

In the anterior hypothalamus, neurons directly sense the blood temperature. Temperature is subsequently controlled by a combination of vasomotor changes, shivering, changes in metabolic heat production, and behavioral changes.

Fever may be produced by a number of endogenous and exogenous substances termed *pyrogens*. Endogenous pyrogens include a variety of cytokines released by leukocytes in response to infectious, inflammatory, and neoplastic processes. Exogenous pyrogens include a large number of bacterial and viral products and toxins. Toxins induce fever by stimulating cells of the immune system to release endogenous pyrogens. These cytokines, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor, and interferon, travel to the hypothalamus and induce the production of prostaglandin E_2 (PGE_2).

PGE_2 raises the set point of the temperature range by a combination of effects, including peripheral vasoconstriction, increased metabolic heat production, shivering, and behavioral changes that conserve heat. Fever is maintained as long as the levels of endogenous pyrogens and PGE_2 are high. There is also a variety of other humoral and neural pathways that modulate this basic response.[4] Cyclooxygenase inhibitors, such as aspirin, decrease fever by blocking the production of PGE_2. Age, malnutrition, immunosuppression, and chronic disease may also blunt the febrile response.

Moderate elevations of the body temperature may serve to aid host defenses by increasing chemotaxis, decreasing microbial replication, and improving lymphocyte function. Elevated temperatures directly inhibit the growth of certain bacteria and viruses.[5] Fever also results in certain increased physiologic costs to the host, including increased oxygen consumption, metabolic demands, protein breakdown, and gluconeogenesis. These costs are particularly problematic in older adults, who typically have a smaller margin of reserve for any given body system. It is well established that the ability to develop fever in older adults is somewhat impaired. Older adults also are known to have lower baseline temperatures than younger adults.[4] It has not been shown that treatment of fever with antipyretics has a beneficial effect on outcome or prevents complications.[5] An intensive care unit (ICU)–based study compared intravenous acetaminophen to placebo in febrile critically ill patients. There was no difference in 28- or 90-day mortality.[6] Treatment to reduce fever often makes febrile patients feel more comfortable, however.

The initial step in the process of fever is resetting of the thermostatic set point in the hypothalamus to a higher temperature while the actual body temperature remains normal. This mismatch of the thermostat with the "sensed" body temperature causes the patient to feel chilled (chills). If the chills are reported early to a caregiver and the temperature is taken, it is usually found to be normal or minimally elevated. To the examiner's touch, the patient's skin temperature will feel normal. The patient remains chilled until the body temperature rises to near the (elevated) hypothalamic set point. At this point, the patient no longer

TABLE 9.1

Differential Diagnoses—Infectious Causes

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Respiratory	Bacterial pneumonia with respiratory failure	Bacterial pneumonia, peritonsillar abscess, retropharyngeal abscess, epiglottitis	Otitis media, sinusitis, pharyngitis, bronchitis, influenza, tuberculosis
Cardiovascular		Endocarditis, pericarditis	
Gastrointestinal	Peritonitis	Appendicitis, cholecystitis, diverticulitis, intraabdominal abscess	Colitis or enteritis
Genitourinary		Pyelonephritis, tuboovarian abscess, pelvic inflammatory disease	Cystitis, epididymitis, prostatitis
Neurologic	Meningitis, cavernous sinus, thrombosis	Encephalitis, brain abscess	
Skin and soft tissue		Cellulitis, infected decubitus ulcer, soft tissue abscess	
Systemic	Sepsis or septic shock, meningococcemia		

experience chills and feels euthermic—but may feel fatigued or ill—but, to the caregiver, the skin temperature or thermometer reading is now elevated. The sequence of chills followed by febrile illness is the basis of the (incorrect) popular belief that getting chilled leads to infection (typically pneumonia). When the thermostatic set point is reduced to normal, the patient suddenly feels hot and sweats until the body temperature falls to match the set point, now normal.

DIAGNOSTIC APPROACH AND ALGORITHM

Diagnostic Approach

Differential Considerations

The complete differential diagnosis for the patient in the emergency department (ED) with fever is extensive. The major infectious and noninfectious causes are summarized in Table 9.1 and Box 9.1, respectively. The vast majority of serious causes are infectious in origin. Immediate threats to life are from decompensated shock (usually septic), respiratory failure (related to shock or pneumonia), or central nervous system infection (meningitis). Some critical noninfectious causes of fever also exist (see Box 9.1), but these are relatively rare and frequently do not occur with fever as the primary symptom.

A primary medical decision in acute febrile illness is based on assessment of the patient's stability (Fig. 9.1). Patients with life-threatening signs and symptoms, including significant alterations in mental status, respiratory distress, and cardiovascular instability, may require rapid and vigorous treatment. Prompt airway management and initiation of monitoring, intravenous access, fluid resuscitation, supplemental oxygen, and respiratory support are often necessary, despite incomplete information concerning the cause of the fever. Sustained temperatures above 41.0°C are rare but can be damaging to neural tissue and require rapid cooling (eg, misting, fans, cooling blankets).

In the younger otherwise healthy patient with fever, immediate threats to life such as toxic or septic shock, meningitis, meningococcemia, and peritonitis should be considered and treated empirically. In older, chronically ill patients with fever, most of the serious illnesses originate from infections in the respiratory tract, genitourinary tract, and skin and soft tissues.[2] Meningitis, although less common, can also be a significant cause of morbidity and mortality in this group.

BOX 9.1

Differential Diagnosis—Noninfectious Causes of Fever

CRITICAL DIAGNOSES
Acute myocardial infarction
Pulmonary embolism or infarction
Intracranial hemorrhage
Cerebrovascular accident
Neuroleptic malignant syndrome
Thyroid storm
Acute adrenal insufficiency
Transfusion reaction
Pulmonary edema

EMERGENT DIAGNOSES
Congestive heart failure
Dehydration
Recent seizure
Sickle cell disease
Transplant rejection
Pancreatitis
Deep vein thrombosis

NONEMERGENT DIAGNOSES
Drug fever
Malignancy
Gout
Sarcoidosis
Crohn disease
Postmyocardiotomy syndrome

Pivotal Findings

Although the differential diagnosis of fever is broad, most of the treatable causes are of infectious origin. Most of these causes of fever may be diagnosed by careful history and physical examination alone.[7] Age and the presence of underlying medical conditions can substantially influence the evaluation and subsequent decision making regarding management.

An approach to the diagnosis and management of the healthy, otherwise stable adult patient with acute febrile illness is shown

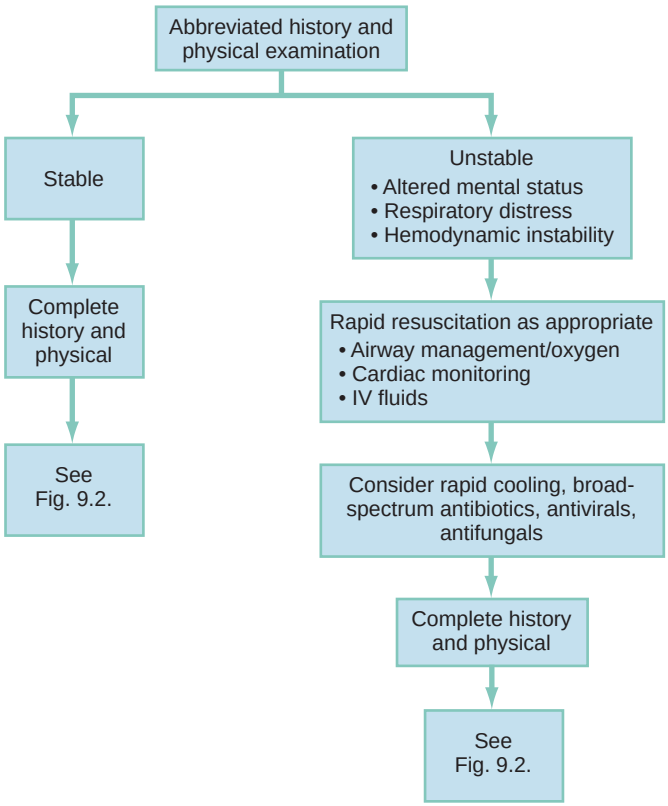

Fig. 9.1. Approach to the critically ill febrile adult patient. *IV,* Intravenous.

in Fig. 9.2. In younger and otherwise healthy adults, self-limited, localized bacterial infections or benign systemic viral infections are usually the cause of fever. The challenge with this group is to identify the rare life-threatening illness, such as meningococcemia, meningitis, or systemic methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

In the older or chronically ill population, fever is frequently a sign of severe illness. Usually, the cause is infectious. In addition to the most common infectious causes of illness (eg, respiratory, urinary, or skin sources), infections such as meningitis, cholecystitis, appendicitis, and diverticulitis are considered and may cause atypical signs and symptoms in older adults or immunosuppressed patients. In these populations, subtle changes in behavior may be the only sign of severe infection. Abnormal vital signs, especially significant tachypnea and hypotension, may portend a complicated and severe course. Of the cases of functional decline in nursing home patients, 75% are a result of infection.[1,2]

Symptoms

The onset of the fever, its duration and magnitude, and any associated symptoms help identify possible causes and severity of illness. Localizing symptoms such as dysuria or productive cough are especially helpful. The timing of the fever and its patterns may implicate certain diseases (eg, malaria). Recent or remote travel, chronic illnesses, past surgeries, hospitalizations, and treatment modalities may raise the suspicion of exotic or nosocomial infections. The presence of prosthetic heart valves or any indwelling device may be critical to the diagnosis. With the emergence of community-acquired MRSA, it is important to seek a history of skin infections in close family members or other close contacts. MRSA should also be considered in military personnel, prisoners, and persons involved in competitive sports that involve close contact.[8]

Also important in the medical history is a list of all the patient's medications, including any antipyretic medications. Family members are frequently an important source of information for older and very young patients.

Atypical symptoms of illness are common in older patients. Pneumonia or urinary tract infection in the older patient may be heralded only by a change in mental status, difficulty ambulating, or some other functional decline. Dysuria, frequency, and flank pain often are absent entirely in older adults with a urinary tract infection. Patients with pneumonia may inconsistently demonstrate productive cough or shortness of breath. Other frequent but nonspecific symptoms include anorexia, weight loss, weakness, lethargy, nausea, and recurrent falls.[1,2] A history of cancer with recent chemotherapy or radiation therapy may be a clue to leukopenia or another immunodepressed state. Assessment of the patient's baseline mental and physical function often relies on the reports of others who know the patient well.

Signs

The presence and magnitude of fever are important elements of the examination, but the older, very young, or chronically ill patient may not mount a febrile response to significant infection. Temperatures may fluctuate, and rechecks may be necessary.

Although the most accurate measure of core body temperature is thought to be via the thermistor of a pulmonary artery catheter, in the ED, rectal temperature measurements or, when a Foley catheter is indicated, bladder thermistors are the most practical and accurate.[9] Axillary and tympanic temperatures often are unreliable. Oral temperatures may be transiently distorted by recent ingestion of hot or cold liquids, smoking, or hyperventilation. For example, rectal temperatures are typically 0.7° to 1.0°C higher than oral temperatures.[10]

Fever is inconsistently associated with tachycardia and tachypnea. As a rough estimate, the heart rate may increase by 10 beats/min for each 0.55°C- (1°F-) rise in temperature. Relative bradycardia may be caused by medications such as beta blockers, but also can suggest factitious or drug-related fevers, typhoid fever, brucellosis, or leptospirosis. Frank bradycardia may occur with rheumatic fever, Lyme disease, viral myocarditis, and endocarditis. The respiratory rate may increase 2 to 4 breaths/min/°C. More significant tachypnea may be caused by respiratory infection or the acidosis related to shock.

In many patients, the examination is directed by the patient's localization of symptoms. The head and neck examination focuses on treatable foci of infection, such as otitis media, sinusitis, pharyngitis, peritonsillar abscess, retropharyngeal abscess, and dental infections. A muffled, so-called hot potato voice with severe sore throat may be a clue to adult epiglottitis or upper airway abscess. Fundoscopy rarely may reveal evidence of disseminated candidiasis, miliary tuberculosis, endocarditis, toxoplasmosis, or leukemia.

The neck is examined for lymphadenopathy, masses, or thyroid pathology (thyromegaly or mass). Nuchal rigidity or pain on flexion of the neck is a useful sign for meningismus, if present, but may not be prominent in many patients, particularly the very young or debilitated patient, even if meningitis is present. Conversely, cervical arthritis or Parkinson disease may cause preexisting nuchal rigidity.

The lungs are examined for rales, pleural rubs, or dullness to percussion. Localized rales or rhonchi may be subtle clues to the presence of pneumonia. The presence of concomitant chronic obstructive pulmonary disease or congestive heart failure, as

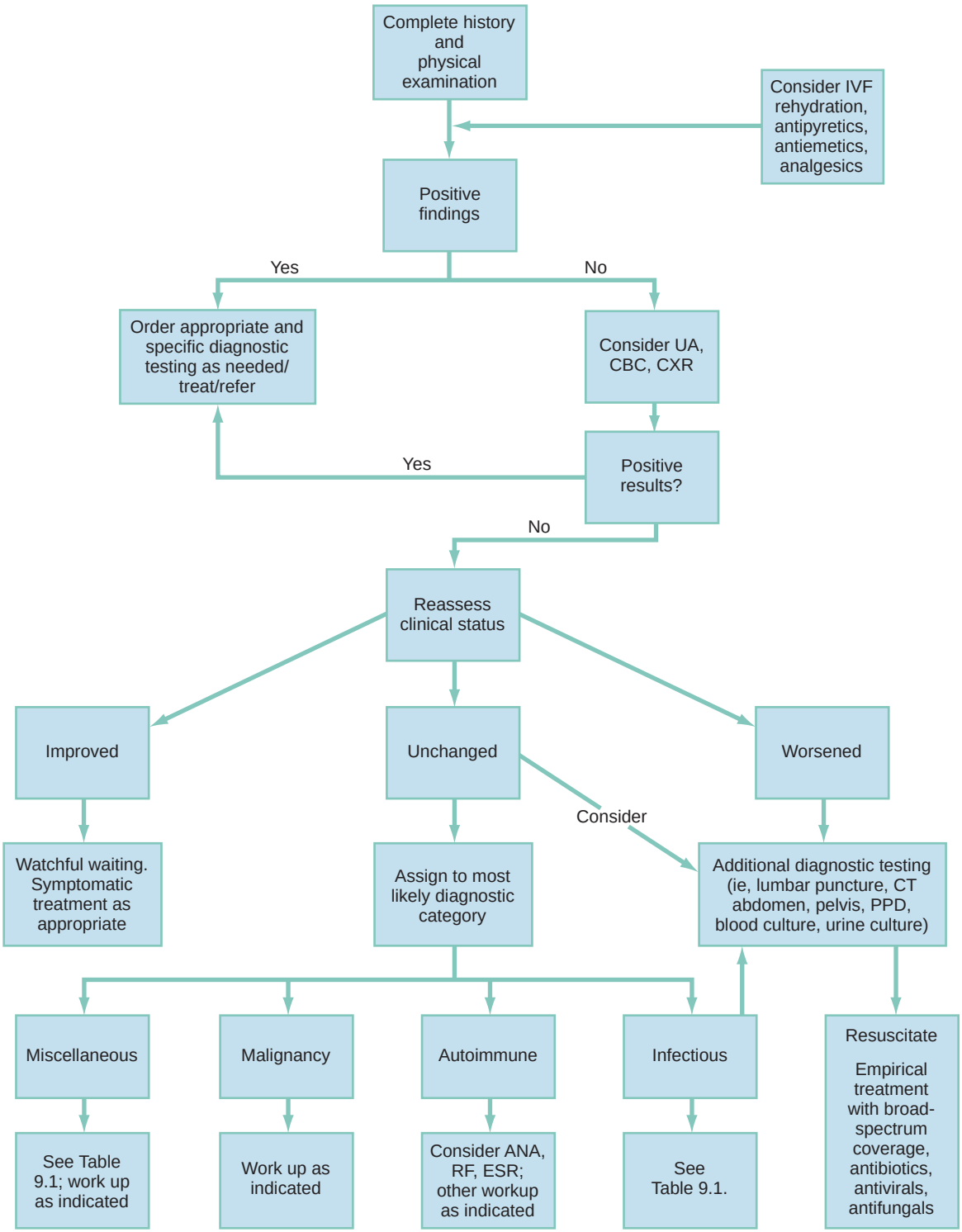

Fig. 9.2. Approach to the stable adult with an acute febrile illness. *ANA,* Antinuclear antibody; *CBC,* complete blood count; *CT,* computed tomography; *CXR,* chest x-ray; *ESR,* erythrocyte sedimentation rate; *IVF,* intravenous fluids; *PPD,* purified protein derivative; *RF,* rheumatoid factor; *UA,* urinalysis. (Modified from Holder BM, Ledbetter C: Fever of unknown origin: an evidence-based approach. Nurse Pract 36:46–52, 2011.)

well as poor respiratory effort, may hamper the diagnosis of pneumonia in older adults. The heart is examined for pericardial rubs or new murmurs.

The abdominal examination may be deceptively benign in older patients, patients with diabetes, or patients taking immunosuppressive drugs or steroids. When indicated by history or other findings, a rectal examination should be performed to check for evidence of enteritis, perirectal abscess, or prostatitis. The external genitalia examination may reveal evidence of a Bartholin abscess, urethral or vaginal discharge, or evidence of epididymitis or orchitis. In women, symptoms of lower abdominal pain, vaginal discharge, and dyspareunia suggest the need for a pelvic examination to evaluate for pelvic inflammatory disease or tuboovarian abscess.

The skin and extremities should be evaluated for rash, petechiae, joint inflammation, or evidence of soft tissue infection. In the absence of trauma, tenderness over the long bones or the spine may be evidence of osteomyelitis or neoplastic processes. Older adults and bedridden patients should be checked for the presence of pressure sores or decubitus ulcers.[2]

Ancillary Testing

Ancillary testing is directed by the history and physical examination. The two most useful ancillary tests, especially in older patients, are urinalysis and chest radiography. Chest radiographs are often helpful in the diagnosis of pulmonary infection but may be difficult to interpret in the patient with concurrent chronic obstructive pulmonary disease, congestive heart failure, dehydration, or other chronic lung disease. Urinalysis, although not foolproof, is highly accurate for detecting urinary tract infection, especially in men. Although the white blood cell count has been almost universally used in the evaluation of febrile patients, it lacks the degree of sensitivity and specificity to be of discriminatory value. The white blood cell count may incorrectly indicate serious infection when none is present or may be normal in the presence of life-threatening infection.[11] Other indirect tests of infection and inflammation, such as the erythrocyte sedimentation rate, are also plagued with irregular sensitivity and poor specificity. Gram staining of appropriate specimens may be helpful, and cultures may be ordered, although the results do not influence emergency evaluation and treatment. With the emergence of MRSA, it has become increasingly important to obtain cultures from soft tissue skin abscesses in patients considered at risk for MRSA infection. In older or chronically ill patients with acute fever of unknown origin, blood and urine cultures are frequently appropriate. Outpatient blood cultures should rarely, if ever, be done. A patient ill enough to require blood cultures from the ED generally requires hospitalization and empirical antibiotic coverage. Cerebrospinal fluid evaluation should be considered when mental status changes are evident, or if headache, meningismus, or other unexplained neurologic symptoms are present and cannot be clearly accounted for by infection outside the central nervous system. Thyroid function studies may be helpful when thyroid storm is suspected. Arterial or venous blood gas studies may help identify patients with critical disease who require prompt treatment.

Plain films of the abdomen are rarely indicated. Abdominal computed tomography (CT) is helpful if appendicitis, diverticulitis, cholecystitis, intestinal obstruction, perforated hollow viscus, or intraabdominal abscess is suspected. Ultrasonography may be helpful in the patient with potential cholecystitis.

Cranial CT scanning may be indicated before lumbar puncture in febrile patients with focal neurologic findings or a suspected embolic source, such as endocarditis, to exclude mass lesions such as a tumor or brain abscess. Neither CT scanning nor lumbar puncture should delay administration of antibiotics in patients with suspected meningitis.

Diagnostic Algorithm

The differential diagnoses of infectious causes of fever are summarized in Table 9.1. The differential diagnoses of noninfectious causes of fever are listed in Box 9.1. However, differences in patient characteristics can cause different manifestations of the same illness. For example, pneumonia or a urinary tract infection manifests in and is tolerated by an 80-year-old very differently from that of a young adult. A careful history and physical examination, along with strategic ancillary testing, will allow the emergency clinician to determine when a critical condition is present and will determine the operational tempo of subsequent evaluation and treatment.

EMPIRICAL MANAGEMENT

Temperatures higher than 41.0°C can result in damage to neuronal tissue and require prompt and vigorous treatment with antipyretics and external cooling measures. Heat illness, a spectrum of disorders due to environmental heat exposure, can result in extreme hyperpyrexia and lead to heat stroke. Urgent external cooling with fans, mist, and other modalities are required and are discussed in Chapter 133. There is no evidence for an improved outcome by routine use of antipyretic therapy, such as acetaminophen, in patients without extreme temperature elevation, but it is not harmful, and patients often feel better when their temperature is lowered.[5] Intravenous acetaminophen is as effective as oral acetaminophen and may be used in patients who are unable to take oral medication.[11] Patients with signs and symptoms of sepsis require prompt evaluation and treatment. Sepsis is characterized by the systemic inflammatory response syndrome (SIRS), defined by the presence of two or more of these criteria: temperature greater than 38°C or less than 36°C; heart rate greater than 90 beats/min; respiratory rate greater than 20 breaths/min or $Paco_2$ less than 32 mm Hg; and leukocyte count greater than 12,000/μL, less than 4,000/μL, or more than 10% immature (band) forms. The reliability of SIRS has increasingly been questioned, and patients meeting the definition of sepsis using SIRS criteria must be further clarified because a patient with SIRS may have a mild, self-limiting infection or may have a more severe infection with the potential to progress to severe sepsis. Patients with severe sepsis or septic shock require aggressive management, including intravenous fluid administration and prompt antibiotic therapy (see Chapter 130).

Patients with evidence of respiratory failure from shock or pneumonia require ventilatory support. Soft tissue infections of the head and neck may compromise the airway because of mechanical obstruction. These may require acute intervention to provide a secure airway.

In many cases, early empirical antibiotic therapy is appropriate. The choice of antibiotics is based on the likely cause of the fever as well as concomitant conditions, such as absolute neutropenia and end-stage renal disease. If a specific infection is subsequently identified, antibiotic therapy should be specific to that infection. With clinically severe illness in the absence of a clear source of infection, broad-spectrum coverage of gram-positive and gram-negative aerobic and anaerobic bacteria is indicated. In acutely ill febrile patients, especially those who are immunocompromised, antiviral and antifungal treatment are also frequently indicated.

DISPOSITION

Localized bacterial infections can often be treated with outpatient oral antibiotics. Relatively young, healthy patients with systemic viral illness can also be treated on an outpatient basis. These illnesses are often accompanied by vomiting and poor oral intake, and treatment in the ED with antipyretics, antinausea medications, and intravenous hydration may help prepare the patient for a successful outpatient course.

When no clear infection is identified in older patients or those with chronic illness, such as diabetes or chronic renal failure, admission to the hospital often is necessary to elucidate the possible causes of the presentation further. In this subset of patients, a diligent search for evidence of bacterial infection is required. Also, admission to an inpatient unit or ED observation unit may be advisable when fever or other systemic symptoms accompany a suspected MRSA infection. In patients with unexplained severe febrile illness, blood and urine cultures and broad-spectrum antibiotics are indicated to treat possible life-threatening

infection until a specific disease process or pathogen is identified. Indwelling devices, such as percutaneous intravenous access ports, frequently require culture and may need to be removed. Neutropenic patients with fever require prompt treatment with broad-spectrum parenteral antibiotics, pending results of cultures. Patients with unstable vital signs or life-threatening infections may require admission to a special care unit if they cannot be adequately stabilized in the ED before admission.

KEY CONCEPTS

- Younger adults with fever usually have benign self-limited disease, with low mortality. The challenge in this group is to identify the rare meningitis or septic condition when confronted with a predominance of self-limited viral and focal bacterial illness.
- For older patients, immunosuppressed patients, or those with chronic disease, fever indicates a high risk for serious disease. Temperature elevation may be minimal in these patients, who often are unable to mount a significant febrile response to serious infection. Bacterial infection is the most common cause of fever in these patients. Three body systems—the respiratory tract, urinary tract, and skin and soft tissue—are the target for more than 80% of these infections.
- Atypical symptoms of illness are common in older febrile patients. Altered mental status, difficulty with ambulation, frequent falls, and general functional decline may be the only signs of serious infection in older patients.
- The white blood cell count is not a discriminatory test for patients with fever, may incorrectly indicate serious infection when none is present, or may be normal in the presence of life-threatening infection.
- In febrile patients with serious signs and symptoms, early empirical antibiotic therapy is often appropriate. The choice of antibiotics is based on the likely cause of the fever as well as concomitant conditions, such as absolute neutropenia and end-stage renal disease.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 9: QUESTIONS AND ANSWERS

9.1. Which three body systems are the target of more than 80% of bacterial infections in patients older than 65 years?

A. Central nervous system, respiratory system, genitourinary system
B. Central nervous system, respiratory system, skin and soft tissue
C. Central nervous system, urinary system, skin and soft tissue
D. Respiratory system, gastrointestinal system, genitourinary system
E. Respiratory system, genitourinary system, skin and soft tissue

Answer: E. Patients older than 65 years who present with fever represent a group at high risk for serious disease. Morbidity and mortality in this group are significant. Between 70% and 90% are hospitalized, and 7% to 9% die within 1 month of admission. Infection is the most common cause of fever in these patients, and most of these infections are bacterial in nature. More than 80% of these infections originate from the respiratory system, genitourinary system, and skin and soft tissue.

9.2. A 65-year-old man presents after "briefly collapsing" at a nearby bus stop. On arrival, he is confused, opens his eyes spontaneously, and follows simple commands. A medical information card found in his wallet reveals a history of hypertension and gout. Vital signs reveal a blood pressure of 95/50 mm Hg, heart rate of 95 beats/min, respiratory rate of 24 breaths/min, temperature of 41.5°C, and arterial oxygen saturation (Sao_2) of 95%. His finger-stick glucose level is normal. Pertinent physical examination findings include pallor, dry mucous membranes, Glasgow Coma Score (GCS) of 14, and ataxia. An intravenous bolus of normal saline is started. Which of the following is the most appropriate next step in the management of this patient?

A. Administer broad-spectrum antibiotics.
B. Mist the patient with water and place him in front of a fan.
C. Obtain a head CT scan.
D. Obtain an electrocardiogram.
E. Perform a lumbar puncture.

Answer: B. In terms of initial resuscitative efforts, the most significant finding in this patient is a temperature of 41.5°C. Almost all cases of temperatures higher than 41.0°C (107°F) are due to hyperthermia rather than to fever. Sustained temperatures higher than 41.0°C (106°F) are rare but can be damaging to neural tissue and require rapid, aggressive, cooling measures, such as misting the patient with tepid water and placing him or her in front of a fan, immersion in cool water, or application of cooling blankets. Each of the other four options could potentially be performed during this patient's stay in the ED; however, the immediate focus is on temperature reduction.

9.3. Of the cases of functional decline in nursing home patients, 75% are due to which of the following?

A. Congestive heart failure
B. Coronary artery disease
C. Dementia
D. Infection
E. Traumatic injuries secondary to falls

Answer: D. Of the cases of functional decline (eg, difficulty ambulating, anorexia, decreased activity, new urinary incontinence) in nursing home patients, 75% are due to infection.

9.4. An 85-year-old man is brought to the ED by his daughter, who says that he has had a fever and has been eating less than normal for 2 days. The patient has a history of hypertension and severe dementia. He can provide no useful information. His present temperature was recorded by the triage nurse to be 38.5°C (101°F). The remainder of his vital signs are within normal limits. The only abnormal findings on physical examination are slightly dry mucous membranes, confusion, and poor social interaction. The daughter confirms his mental status to be at baseline. Which of the following are the two most important ancillary tests to perform in this patient?

A. Blood culture and urine culture
B. Urinalysis and chest radiography
C. Urinalysis and white blood cell count
D. White blood cell count and chest radiography
E. White blood cell count and urine culture

Answer: B. The two most important ancillary tests in the evaluation of fever in the adult patient, and especially in older patients, who frequently have atypical presentations, are urinalysis and chest radiography. Chest radiographs are often helpful in the diagnosis of pulmonary infection but may be difficult to interpret in the patient with chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), or other chronic lung disease. Urinalysis, although not foolproof, is highly accurate for urinary tract infection, especially in men. Although the white blood cell count is almost universally used in the evaluation of febrile patients, it lacks sufficient sensitivity and specificity to be of discriminatory value. Cultures are ordered in selected patients; however, the delay in obtaining results precludes any influence in emergency evaluation and treatment. Other tests that have relevance in select patients with fever include Gram staining, cerebrospinal fluid (CSF) analysis, thyroid function studies, ultrasonography, and computed tomography (CT) of the abdomen or head.

CHAPTER 10

Weakness

Raveendra S. Morchi

PERSPECTIVE

The complaint of weakness is common in emergency department (ED) patients and may be vague, subjective, and difficult to characterize. Up to 10% of ED visits are for generalized weakness, with a preponderance of the complaint among older adults.[1] Over half of these patients are identified as having a serious condition, and the diagnoses span cardiovascular, pulmonary, metabolic, and infectious causes. The approach to generalized weakness includes an evaluation of causes of malaise or weakness due to other physiologic and psychological causes, including infection, dehydration, electrolyte disorders, cardiovascular disease, cancer, and even depression. Conditions that lead to the perception of weakness must therefore be differentiated from true loss of neuromuscular power. This chapter focuses on the initial evaluation of the generalized complaint of weakness and specific evaluation of acute neuromuscular weakness. The latter may be focal or generalized and may originate in central or peripheral nerves, the neuromuscular junction (NMJ), or myofibers themselves. Other chapters provide more detail on peripheral nerve (Chapter 97) and neuromuscular disorders (Chapter 98).

Epidemiology

The epidemiology of weakness is closely linked to the epidemiology of other diseases and medical conditions. Although weakness can be a presenting problem at all ages, patients who are older or chronically ill are more likely to develop weakness.[2] Advanced diabetes, cardiovascular and pulmonary diseases, chronic infectious diseases, and cancer may produce neuromuscular weakness through secondary effects on the brain and neuromuscular system. Brain, spinal cord, peripheral nerve, and neuromuscular causes of weakness are much less common than weakness secondary to other medical conditions.

Pathophysiology

There are a number of physiologic considerations for the patient with diffuse weakness (Box 10.1). Alterations in plasma volume or composition, decrease in red cell numbers or cardiac function, drop in systemic vascular resistance, increased metabolic demand (infection, toxin, endocrinopathy), and mitochondrial dysfunction (severe sepsis) can all produce nonlocalized weakness via inadequate substrate delivery or utilization by neurons and cardiac or skeletal myofibers. A global depression in central nervous system (CNS) activity from sedative effect or stimulant withdrawal can also present as generalized weakness. Focal weakness confined to one area in the face or body (left, right, distal, or proximal) indicates a localized problem arising within the corresponding area of the central or peripheral nervous system.

Lesions involving the motor areas of the cerebral hemispheres may cause unilateral weakness, and lesions in the cerebral cortex outside the motor area may cause receptive or expressive aphasias and complex cerebral motor deficits such as apraxia. These are covered in Chapter 91. Peripherally, the spinal nerves extend from the anterior horn of the spinal cord and represent the anatomic origins of the lower motor neuron (LMN). The neuroanatomic distinction between LMNs and upper motor neurons (UMNs) is essential in localizing lesions.

DIAGNOSTIC APPROACH AND ALGORITHM

Conditions that affect the UMN produce signs that include spasticity to extension in the upper extremities, spasticity to flexion in the lower extremities, hyperreflexia, pronator drift, Hoffmann's sign, and Babinski's sign (upgoing toes). UMN signs signify a lesion within the cerebral cortex or corticospinal tract (CST) of the brainstem or spinal cord. Although these findings are not always detectable in the acute period, the presence of even one of them indicates pathology within the CNS.

Weakness caused by LMN dysfunction is often accompanied by flaccidity, decreased reflexes, fasciculations, or muscle cramps. Lesions in the anterior horn of the spinal cord and its axonal extensions at the nerve root and peripheral nerve produce these findings. Conditions that have only peripheral effects at the NMJ and muscle have preserved reflexes.

Differential Considerations

In the diffusely weak patient, consideration is first given to a systemic deficiency in substrate delivery to the nervous system or skeletal muscle unit. The emergency clinician should explore an appropriately detailed history regarding circumstances at onset, progression, exacerbating or alleviating factors, and any fluctuations in severity that may help discern if weakness is a result of cardiovascular disease, pulmonary insufficiency, metabolic disturbance, concurrent infection, toxic ingestion, medication imbalance, or cancer. Review of systems can reveal orthopnea and symptoms of congestive heart failure in the fatigued patient with significant cardiac disease, chronic blood loss in the anemic patient, or incontinence in an older adult with a urinary tract infection.

Vital sign abnormalities, including tachycardia, tachypnea, fever, hypothermia, or hypotension, prompt immediate intervention and a search for a systemic cause of the weakness. A general physical examination, including organ systems, skin, and mucous membrane examinations, may provide evidence of systemic disease. A cardiovascular examination can give the emergency clinician a sense of the adequacy of delivery of substrate to brain and muscle. In such patients, the neurologic examination will not demonstrate focal changes of the central or peripheral nervous system.

If by history, physical examination, and bedside ancillary testing the patient does not appear to have derangements in intravascular volume or cardiopulmonary function, metabolic abnormalities, or a source of infection, the investigation turns to a neural or primary muscular cause for weakness. Usually, these patients will have some asymmetric finding on their neurologic examination. The critical and emergent diagnoses for neuromuscular weakness are listed in Table 10.1.

BOX 10.1

Nonneurologic Weakness

Alterations in plasma volume (dehydration)
Alterations in plasma composition (glucose, electrolytes)
Derangement in circulating red blood cells (anemia or polycythemia)
Decrease in cardiac pump function (myocardial ischemia)
Decrease in systemic vascular resistance (vasodilatory shock from any cause)
Increased metabolic demand (local or systemic infection, endocrinopathy, toxin)
Mitochondrial dysfunction (severe sepsis or toxin-mediated)
Global depression of the central nervous system (sedatives, stimulant withdrawal)

TABLE 10.1

Critical and Emergent Causes of Neuromuscular Weakness

DIAGNOSIS	FEATURES
CRITICAL DIAGNOSES	
Cerebral cortex or subcortical	Ischemic or hemorrhagic cerebrovascular accident (CVA)
Brainstem	Ischemic or hemorrhagic CVA
Spinal cord	Ischemia, compression (disk, abscess, or hematoma)
Peripheral nerve	Acute demyelination (Guillain-Barré syndrome)
Neuromuscular junction	Myasthenic or cholinergic crisis Botulism Tick paralysis Organophosphate poisoning
Muscle	Rhabdomyolysis
EMERGENT DIAGNOSES	
Cerebral cortex or subcortical	Tumor, abscess, demyelination
Brainstem	Demyelination
Spinal cord	Demyelination (transverse myelitis) Compression (disk, spondylosis)
Peripheral nerve	Compressive plexopathy (hematoma, aneurysm) Paraneoplastic vasculitis uremia
Muscle	Inflammatory myositis

Diagnostic Algorithm

Generalized weakness can be explored by determining the adequacy of circulation. This includes an evaluation of cardiac function (signs of ischemia or infarction), red cell numbers, oxygen saturation, and systemic vascular tone. Next, assess plasma volume and its composition. Dehydration and altered nutrient (glucose), electrolyte (Na, K, Ca), or waste product (CO_2, urea, bilirubin, ketoacid) levels can produce diffuse weakness. If substrate delivery and plasma composition appear sufficient, consider disturbances of cellular metabolic machinery secondary to an endocrinopathy, toxin, or mitochondrial dysfunction in the setting of infection. Although generalized weakness can present deceptively as a focal deficit, particularly in areas already weakened by prior neurologic insult, focal findings, such as lateralizing weakness, numbness, gait instability, or cranial nerve defects, should prompt a more detailed exploration of a potential neurologic cause.

Critical Diagnoses

Deciphering focal loss of muscle power means following the pattern of a patient's weakness from the cortical neuron down through the CNS, peripheral nervous system (PNS), NMJ, and myofibers (Fig. 10.1). Common clinical patterns of weakness can be classified and assessed as discussed in the following sections.

Unilateral Weakness

Combination of Arm, Hand, or Leg With Ipsilateral Facial Involvement. This presentation is generally caused by a lesion in the contralateral cerebral cortex or the CSTs coursing down the corona radiata and forming the internal capsule. Mild forms can be limited to a loss of dexterity and coordination with hand movements. Moderate loss of power is termed *paresis,* and complete loss of motion is termed *plegia*. UMN signs are useful corroborative findings but may not always be present. Sensory disturbances commonly occur over the areas of weakness. Look for associated neglect, visual field cut, or expressive or receptive aphasia to localize the problem to the cortex. Patients with equal loss of strength to the face, hand, and leg are more likely to have a subcortical lesion disrupting all these fibers as they funnel close together in the internal capsule. Concomitant headache is suggestive of a brain hemorrhage or mass lesion. Sudden onset of this weakness pattern implies hemorrhage or ischemia, whereas a gradual onset may be seen in demyelination (eg, multiple sclerosis, acute demyelinating encephalomyelitis) or neoplasm (eg, metastases, astrocytoma, oligodendroglioma, ependymoma).

Combination of Arm, Hand, or Leg With Contralateral Facial Involvement. This pattern indicates a brainstem lesion. A careful cranial nerve (CN) examination can provide more clues. If the patient has contralateral facial findings, there will likely be ptosis (CN III or sympathetic fibers) or a facial droop with forehead involvement (CN VII nucleus). Signs of CN V, VI, VIII, IX, or XII dysfunction will help localize to a particular level within the brainstem.[1] Cerebellar findings or nystagmus may also be present on examination. Sensory disturbances can parallel the weakness, and some patients will report double vision, trouble swallowing, slurred speech, vertigo, or nausea and vomiting. The CST courses ventrally through the brainstem, and extremity weakness with UMN signs in the involved limbs may accompany brainstem lesions. Depressed consciousness can also occur if the brainstem reticular activating system is involved. The two main underlying processes that cause unilateral extremity weakness with contralateral facial involvement are vertebrobasilar insufficiency and demyelinating diseases.

Combination of Arm, Hand, or Leg Without Facial Involvement. Before a patient is placed in this category, a careful examination of facial symmetry is required to determine that subtle facial droop or effacement of the nasolabial fold is not present. If there is truly no facial involvement, the source of extremity weakness without facial involvement is most likely to be a result of one of these processes:

- A lesion in the medial, contralateral, cerebral homunculus (over the area where the lower extremity is represented)
- A discrete internal capsule or brainstem lesion involving only the corticospinal rather than the corticobulbar tracts
- Brown-Séquard internal capsule or brainstem lesion if the patient also has contralateral hemibody pain and temperature sensory disturbances below the level of motor weakness

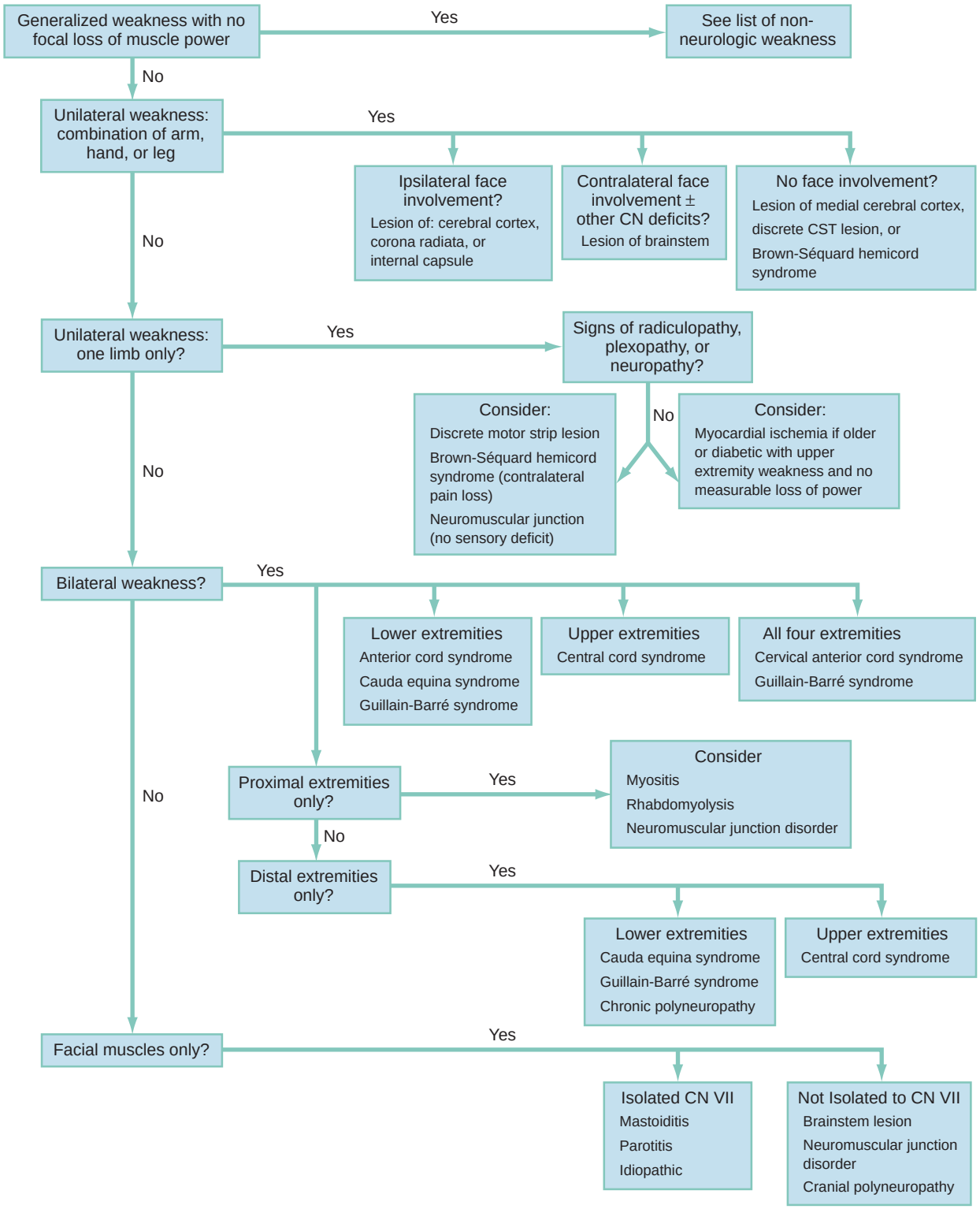

Fig. 10.1. Common Clinical Patterns of Weakness, Classified and Assessed.

One Limb Only (Monomelic Weakness, Monoparesis, or Monoplegia). Isolated weakness of one extremity is usually caused by a spinal cord or peripheral nerve lesion. Examination for UMN signs in the affected limb will help uncover rare monomelic presentations of CNS lesions. If UMN signs such as hyperreflexia or spasticity are present, a careful evaluation is performed for facial weakness or involvement of the contralateral or other ipsilateral limb as indicative of a central process. If weakness is in the entirety of one lower limb, one should ensure that the patient does not have a contralateral pinprick level indicative of Brown-Séquard hemicord syndrome. Monomelic weakness is often the result of a radiculopathy, plexopathy, peripheral neuropathy, or NMJ disorder. See Table 10.1 for emergent and critical peripheral nervous system diagnoses.

The examination for monomelic weakness presentations includes detailed strength testing and determination of whether weakness localizes to one ventral nerve root myotome or one particular peripheral nerve within the limb. Reflexes with a

BOX 10.2

Nonemergent Causes of Peripheral Neuropathy

Connective tissue disorder
External compression (entrapment syndrome, compressive plexopathy)
Endocrinopathy (diabetes)
Paraneoplastic syndromes
Toxins (alcohol)
Trauma
Vitamin deficiency

peripheral nerve disorder will be diminished, not hyperactive. Although radiculopathies can occasionally be purely motor, most peripheral lesions have some sensory component to their presentation; therefore, a careful sensory examination in the distribution of dorsal nerve root dermatomes and peripheral nerves is essential. See Box 10.2 for a list of nonemergent causes of peripheral neuropathy.

If suspicion is low for a UMN source of isolated extremity weakness, reflexes are intact, and there are no sensory deficits to suggest a nerve or root problem, NMJ disorders are considered. In such cases, the weakness is often mild, fluctuating, and worse later in the day. It usually involves the proximal arm or leg muscles, wrist extensors, finger extensors, or ankle dorsiflexors. NMJ disorder–induced weakness with only monomelic symptoms will be an uncommon diagnosis in the ED. In older patients and others with significant cardiac risk factors, myocardial ischemia is considered if arm sensory symptoms or arm weakness that does not demonstrate measurable loss of motor power is reported.

Bilateral Weakness

Lower Extremities Only (Paraparesis or Paraplegia). The first consideration with this presentation pattern is a spinal cord lesion. If this is the case, UMN signs may be absent in the acute period. Because the lateral spinothalamic tracts (LSTs) run in proximity to the CST, patients with bilateral lower extremity weakness frequently have alterations to their perception of pain or temperature. Examination may reveal a loss of pinprick sensation to a particular spinal level within the thoracic cord or terminal first lumbar segment. The lesion may be as high as T2 without producing upper extremity findings. The main causes of anterior cord syndrome are external compression, ischemia, or demyelination. In the absence of UMN signs or a clear thoracic pinprick level, evaluation of perianal sensation, rectal tone, and urinary retention can identify deficits that point to cauda equina syndrome—compression of peripheral nerve roots running below the termination of the spinal cord. If the physical examination does not support a cord syndrome or cauda equina compression, the patient may have a peripheral neuropathy affecting the longest nerve tracts first. The acute presentation that is most concerning is Guillain-Barré syndrome (GBS). Rapid demyelination of peripheral nerves can result in symmetric weakness ascending from the feet. Sensory findings parallel the weakness, and reflexes should be decreased at some point in the patient's clinical course.

Upper Extremities Only. This central cord pattern localizes to the central portion of the cervical spinal cord where corticospinal fibers designated for hand and arm strength are located. The patient may have pinprick sensory loss over the upper extremities from the involvement of crossing sensory axons destined for the contralateral LST. However, light touch sensation, mediated by the posterior columns, should remain intact. Causes of central cord syndrome include cervical spine hyperextension injuries and syringomyelia.

All Four Extremities Without Facial Involvement (Quadriparesis or Quadriplegia). The obvious concern with this pattern is for a cervical spinal cord injury or process, but the patient is first assessed for medical conditions that produce global weakness. The more dense the extremity weakness, the more likely it is that the patient has a cervical spinal cord problem. Although all four extremities will test poorly for muscle strength, there is frequently some discrepancy between the lower and upper limbs in quadriparesis.

Determination of sensory dermatomes by pinprick testing in the arms and hands, along with strength testing of specific myotomes, will allow localization of the level within the cervical spinal cord. One physical examination confounder with disorders that cause cord compression or ischemia is that upper extremity myotomes corresponding to the site of spine involvement will actually have LMN signs of flaccid weakness and decreased reflexes because anterior horn cells are involved at this particular level. However, UMN signs may be elicited below that level. A C5 lesion, for example, can cause diminished biceps reflexes but exaggerated triceps and patellar reflexes.

Bilateral extremity weakness may occur in patients with GBS that has ascended from the lower extremity peripheral nerve myelin sheaths to the upper extremities. In this case, the lower limbs are usually weaker than the upper limbs.

Proximal Portions of Extremities Only. Provided that there are no UMN signs and no sensory deficits, this pattern points to a myofiber disorder. Patients may report general fatigue or trouble raising the arms above the head, climbing stairs, or rising from a chair. The common acute and progressive causes of proximal muscular weakness are inflammatory diseases such as polymyositis or dermatomyositis, or necrosis, as in rhabdomyolysis from 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. Muscles are commonly but not always tender to palpation. Myositis patients can also have dysarthria and dysphagia from weakness of the pharyngeal muscles. Airway protective mechanisms may eventually be compromised.

Chronic or recurrent myofiber pathology includes abnormalities to anchoring proteins supporting fibrils to the cytoskeleton and cell membrane (eg, muscular dystrophies), dysfunctional ion channels responsible for depolarization of the muscle fiber cell (channelopathies such as hyperkalemic and hypokalemic periodic paralysis), or impaired ability to use carbohydrate and lipid energy sources (eg, metabolic myopathies, mitochondrial myopathies). The presentation of these varied conditions ranges from insidious and progressive to sudden onset and episodic. Occasionally, a patient with an NMJ disorder will demonstrate proximal extremity or neck muscle weakness mimicking myofiber disease.

Distal Portions of Extremities Only. This pattern is almost always caused by a peripheral neuropathy (see Box 10.2). Patients will have weakness and poor coordination, with fine movements of their feet or hands. If this type of distal weakness is present in both lower extremities only, the patient will most likely have a chronic peripheral neuropathy or an acute demyelinating neuropathy (GBS). The patient will also have some sensory disturbance over the feet. Examination for perianal sensory deficits or issues with fecal or urine continence will help exclude the compressive polyradiculopathy of cauda equina syndrome as a cause of bilateral distal lower extremity weakness. If only the fingers and hands are involved, evaluation for central cord syndrome is performed. Bilateral lower cervical radiculopathies or symmetrical polyneuropathies are possible but much less likely.

Facial Weakness Without Extremity Involvement

Isolated facial weakness will appear in one of two forms.

Unilateral Facial Droop. If the weakness is a result of a CN VII problem, unilateral weakness in the upper and lower halves of the face should be present on examination. Causes for an isolated CN VII neuropathy are Bell's palsy, mastoiditis, and parotitis. The examination must confirm that there is no extremity involvement and that other CNs, cerebellar testing results, and visual fields are normal. This will ensure that a brainstem lesion is not causing the weakness.

Facial Weakness Not Limited to Cranial Nerve VII and Muscle of Expression. This will include some combination of ptosis, binocular diplopia, dysarthria, or dysphagia. It can be caused by a brainstem lesion, multiple cranial neuropathies, or NMJ problem. If there are no cerebellar findings, visual field deficits, sensory disturbances, or extremity UMN signs, posterior cerebral circulation and brainstem disorders are less likely, and an NMJ disorder is more likely. Dysfunction of one or more ocular, facial, or pharyngeal muscles will be the most common presentation for NMJ pathology. The history may indicate that the facial weakness is acute and progressive (botulism) or chronic and fluctuating (myasthenia gravis). Signs of these diseases can be determined by examining extraocular motion, facial expression, and soft palate rise. Generalized fatigue is often reported, and neck, extremity, and respiratory muscle weakness caused by involvement of these neuromuscular units may be present on examination.

Patients with an abnormality of the presynaptic release of acetylcholine (eg, botulism, Eaton-Lambert syndrome, organophosphate poisoning) can have autonomic ganglia involvement and hence abnormal pupillary response to light, dry mouth, fluctuations in heart rate and blood pressure, anhidrosis, or gastrointestinal and bladder dysmotility.

Facial weakness from cranial polyneuropathy manifests with more than one CN deficit not localizing to a brainstem level and without any other long tract signs. These patients may have a variant of GBS or irritation of multiple CNs after they have exited the brainstem and pierced through inflamed meninges or malignant skull base metastases.

PIVOTAL FINDINGS

These are found in patients who present with lower extremity weakness, with the consideration of GBS localizing to a brainstem level, and without any other long tract sign. Close monitoring of respiratory symptoms, including tachypnea or shallow respirations, should prompt evaluation for potential respiratory failure from diaphragmatic, intercostal, and accessory muscle fatigue. Consideration should be given to quantify respiratory effort with pulmonary function tests, intensive care unit (ICU) admission, and possible mechanical ventilation.

In any patient with a sudden onset of focal weakness, a vascular cause (occlusion or hemorrhage) should be strongly considered until proven otherwise by an adequate imaging study. The presence of a severe headache with unilateral weakness, or midline back pain with lower extremity weakness, alerts the emergency clinician to a compressive space-occupying lesion.

Patients with UMN signs have weakness that localizes to the spinal cord CST or above and are considered to have an emergent problem. They may be at risk for progression to sympathetic autonomic failure or obtundation from enlarging space-occupying spinal or cerebral lesions, respectively. The presence of anorectal or bladder insufficiency without another explanation suggests a UMN or cauda equina lesion. Laboratory tests are most useful for excluding nonneuromuscular causes of weakness (electrocardiography, measurement of hemoglobin, glucose, electrolytes, troponin, and lactate levels, urinalysis). Two exceptions are the creatinine kinase level in inflammatory myositis and potassium level in channelopathies.

MANAGEMENT

The ED management of neuromuscular weakness is based on evaluating the underlying cause and managing the complications of weakness. Airway protection in obtunded patients or those with upper airway compromise is paramount. Neck and pharyngeal muscle weakness, for example, may herald a risk for aspiration. Diaphragmatic weakness and inadequate hypopharyngeal muscle control or respiratory muscle fatigue should prompt definitive airway protection by endotracheal intubation. During rapid sequence intubation (RSI), succinylcholine should be avoided in suspected cases of progressive denervation of muscle of more than a 3-day duration due to receptor upregulation and the risk for severe hyperkalemia. In this situation, we recommend rocuronium, a nondepolarizing neuromuscular blocking agent.

New quadriparesis or quadriplegia and hypotension without another cause is assumed to be caused by failure of autonomic sympathetic fibers in the cervical spinal cord. Consider a volume load and pressor support in addition to emergent imaging of this area. Although new weakness localizing to the spinal cord calls for immediate imaging, weakness from the spinal roots down does not always necessitate imaging in the ED unless cauda equina syndrome is suspected. Patients with suspected GBS need pulmonary function testing in addition to admission to a critical care setting for further management. An infectious or metabolic trigger is sought in patients with myasthenic crisis. If the patient is currently on acetylcholinesterase inhibitors, consideration should be given to a cholinergic crisis. Be aware of medications that may worsen weakness in patients with NMJ disease (eg, aminoglycosides, quinolones, beta blockers). Rhabdomyolysis is treated with aggressive fluid resuscitation and intervention directed at the primary cause, if known.

DISPOSITION

Patients with generalized weakness should receive treatment and disposition based on the underlying diagnosis, ranging from discharge home after intravenous rehydration to ICU admission, with invasive hemodynamic monitoring and multiorgan support.

Patients with identified central vascular lesions, thrombotic or hemorrhagic, should be aggressively managed in the inpatient setting. Patients with mild LMN or myofiber weakness of benign origin may be discharged with close follow-up, provided that the condition is not thought to be progressing rapidly. Those with more severe or progressive LMN or myofiber weakness and any patient with new UMN weakness should be admitted for further testing. Patients with suspicion for ascending paralysis should be admitted to an ICU setting for close respiratory observation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

REFERENCE

1. Querol-Pascual MR: Clinical approach to brainstem lesions. Semin Ultrasound CT MR 31:220–229, 2010.

CHAPTER 10: QUESTIONS AND ANSWERS

10.1. A 65-year-old man with a history of atrial fibrillation, on warfarin, with a supratherapeutic international normalized ratio (INR) of 4, presents with sudden onset right leg weakness and back pain. On examination, he is tachycardic to 108 beats/min and has 3/5 weakness to the right hip flexors and extensors, knee flexors and extensors, as well as ankle dorsiflexion and great toe extension. However, ankle plantar flexion is preserved.. His knee reflexes are absent, but Achilles reflexes are normal. He has a normal Babinski reflex and no spasticity. He has sensory deficits throughout the anterior and posterior parts of his proximal leg as well as the anterior lower leg and dorsum of the foot. His posterior lower leg and plantar surface, however, have normal sensation. Rectal tone is normal, and there is no urinary retention. His most likely diagnosis is:

A. Anterior cord syndrome from epidural hematoma
B. Cauda equina syndrome
C. Guillain-Barré syndrome
D. Hemorrhagic anterior cerebral artery (ACA) distribution stroke
E. Retroperitoneal hematoma with lumbar plexopathy

Answer: E. This patient has a spontaneous retroperitoneal hematoma compressing the lumbar nerve plexus.

10.2. A 45-year-old man has had gradual onset of progressive weakness to his face and trouble swallowing for 2 days. On examination, he has bilateral ptosis with dilated, poorly reactive pupils, bilateral upper and lower facial muscle weakness, poor soft palate rise, and slurred speech. His oral mucosa is dry. Arms and legs have 5/5 strength. He has no sensory deficits. He has a palpable distended bladder. His symptoms have not abated since onset, and they are getting worse. The most likely diagnosis is:

A. Brainstem stroke
B. Botulism
C. Muscular dystrophy
D. Myasthenia gravis
E. Organophosphate poisoning

Answer: B. This patient has acute onset of progressive neuromuscular junction weakness. He has autonomic findings of abnormal pupil response to light, dry oral mucosa from decreased salivary production, and a distended bladder. These imply that his problem is with the release of acetylcholine (ACh) rather than the nicotinic receptor. The latter would not have autonomic findings. The most appropriate cause of acute onset, progressive impairment in the release of ACh, as listed in the choices, is botulism.

10.3. A 23-year-old woman presented with the sudden onset of weakness to her face, arm, and leg 2 hours ago. On examination, she has weakness to her upper and lower face on the left. She cannot abduct her left eye. She has 3/5 strength to her upper and lower extremities on her right side. She has a right pronator drift and an upgoing toe on the right. Sensation is decreased in her right upper and lower extremities as well. There is no aphasia, neglect, or visual field deficit. The most likely diagnosis is:

A. Midbrain stroke because of cardioembolic stroke
B. Middle cerebral artery (MCA) distribution stroke
C. Multiple sclerosis
D. Myasthenia gravis
E. Pons stroke because of vertebral dissection

Answer: E. This patient has acute onset of crossed face and extremity weakness, with upper motor neuron (UMN) signs in the extremities. Both upper and lower extremities are affected, which makes a corticospinal tract (CST) lesion more likely than a cerebral cortex lesion. Her left-sided facial weakness is representative of a peripheral cranial nerve (CN) VII that is actually due to infarction of the CN VII nucleus in the brainstem. The CN VI deficit on that side is due to proximity of this nucleus as well. The CST runs just anterior to these nuclei within the brainstem. These CN nuclei lie in the pons.

10.4. A 21-year-old man awoke this morning with weakness to his right hand and right foot. He admits to drinking heavily the night before and falling asleep on the floor. On examination, he appears well, with weakness to right wrist extension and thumb extension, as well as sensory deficits over the dorsal surface of his hand and first and third digits. He also has weakness to ankle dorsiflexion and great toe extension on the right. He has sensory deficits over the anterior lower leg and the dorsum of his foot. Biceps and ankle reflexes are intact, he has no pronator drift, and his toes are downgoing. His most likely diagnosis is:

A. Brainstem stroke
B. Brown-Séquard syndrome
C. Compressive neuropathy
D. MCA distribution stroke
E. Polyradiculopathy secondary to disk disease

Answer: C. He has radial nerve and peroneal nerve palsies because of compression while lying passed out on the floor for an unspecified time.

10.5. A 70-year-old man has had trouble swallowing and progressive weakness of his hands over the past 2 months. On examination, his speech is slurred, his voice is nasal, and he has fasciculations to his face, tongue, and over his pectoralis muscles and deltoids bilaterally. He has 4/5 strength to shoulders, biceps, triceps, and hand grip bilaterally. Stiffness to extension is present at both elbows. He has bilateral pronator drift and 3+ biceps reflexes. He tends to smile inappropriately. He has no sensory symptoms. The most likely diagnosis is:

A. Amyotrophic lateral sclerosis (ALS)
B. Brainstem stroke
C. Chronic demyelinating polyneuropathy
D. Parkinsonism
E. Polymyositis

Answer: A. This patient has lower motor neuron (LMN) signs (fasciculations) and UMN signs (pronator drift and increased reflexes) in similar distribution. The combination of upper and lower motor neuron involvement make ALS the leading diagnosis among those listed. His dysphagia and inappropriate smiling are due to a release of the medulla from upper motor neuron regulation.

CHAPTER 11

Cyanosis

Madonna Fernández-Frackelton

PERSPECTIVE

Cyanosis is a blue or purple appearance of the skin or mucous membranes. This clinical finding is caused by inadequately oxygenated blood perfusing peripheral tissues or the presence of abnormal hemoglobin forms, which are unable to bind oxygen or supply adequate oxygen to end organs and tissues.

Epidemiology

Cyanosis is a relatively rare presenting chief complaint in the emergency department (ED) and is usually noted in patients with a hypoperfused state or known cardiopulmonary disease, including congenital heart disease. Although carbon monoxide poisoning and cyanide toxicity result in inadequate hemoglobin oxygenation and tissue hypoxia, these entities typically do not present with the clinical finding of cyanosis and are discussed in other chapters.

Pathophysiology

Cyanosis is evident on physical examination when the absolute amount of desaturated (unoxygenated) hemoglobin in the circulating capillary blood is elevated to approximately 5 g/dL. It is not caused by a percentage of desaturated total hemoglobin mass or decreased amount of oxyhemoglobin. For this reason, patients with a relatively low hemoglobin level exhibit cyanosis at a much lower partial pressure of oxygen (Pao_2) and arterial oxygen saturation (Sao_2) than those with normal hemoglobin levels. Cyanosis is an insensitive indicator of tissue oxygenation. Its presence suggests hypoxia, but its absence does not exclude it.

Abnormal hemoglobin forms contribute significantly to cyanotic disease. Under normal conditions, red blood cells (RBCs) contain hemoglobin with iron in the reduced ferrous state (Fe^{2+}). Ferrous iron binds oxygen readily to create oxyhemoglobin, and it reverts to the ferrous state when oxygen is released. The iron molecule may be oxidized to the ferric state (Fe^{3+}), spontaneously or by oxidative stress, to produce methemoglobin. This reaction impairs the ability of hemoglobin to bind and transport oxygen to and carbon dioxide from the tissues. The oxygen dissociation curve is shown in Fig. 11.1

A number of variables can increase or decrease the hemoglobin affinity for oxygen. Methemoglobin shifts the curve to the left, resulting in tissue hypoxia and lactic acid production. Methemoglobin normally accounts for less than 1% of total hemoglobin.[1] Cyanosis results when more than 1.5 g/dL of methemoglobin is present (~10%–25% of the total hemoglobin). Methemoglobin has a dark purple-brown or chocolate brown color, even when exposed to room air. It is normally reduced to ferrous (Fe^{2+}) hemoglobin primarily by nicotinamide adenine dinucleotide (NADH)–cytochrome b5 reductase, an enzyme system present within RBCs. A secondary system dependent on nicotinamide adenine dinucleotide phosphate (NADPH) reductase uses glutathione production and glucose-6-phosphate dehydrogenase (G6PD) to reduce methemoglobin to ferrous hemoglobin. This secondary pathway normally plays a minor role but is accelerated by methylene blue.[1]

Primary methemoglobinemia is the result of congenital errors in enzyme metabolism caused by diminished levels of NADH reductase or an abnormally functioning enzyme. Patients may have cyanosis in a stable compensated state. Acquired methemoglobinemia occurs when methemoglobin production (hemoglobin oxidation) is increased beyond the capacity of NADH reductase activity. This is usually a result of a drug reaction. See Box 11.1 for common causes. Newborns are at risk for methemoglobinemia because their NADH reductase activity is relatively low compared with that of adults.

DIAGNOSTIC APPROACH

Differential considerations for patients with cyanosis are listed in Box 11.2.

Pivotal Findings

Symptoms

The onset, duration, time of day of symptoms, and any previous episodes should be noted. Precipitating factors may include exposure to cold air or water, high altitude, or exercise in patients with a history of cardiopulmonary disease. Additional history should include known congenital heart disease or cardiopulmonary disease, hypercoagulable states, and any family history of cyanotic or hematologic disease. A history of home or occupational exposures to fumes or chemicals should be obtained, including aniline, azo dyes (phenazopyridine [Pyridium]), phenacetin, and nitrates.[2] A drug history should be reviewed, including use of prescription and over-the-counter medications, health food supplements, and herbal or alternative preparations. The potential of pseudocyanosis resulting from exposure to dyes, heavy metals, or topically absorbed pigments should be explored.

In infants, congenital heart disease is suggested by difficulty feeding, sweating, lethargy, poor weight gain, or respiratory distress. Episodic cyanotic events, or tet spells, may be seen in children with tetralogy of Fallot—ventricular septal defect, overriding aorta, pulmonic stenosis or atresia, and right ventricular hypertrophy with outlet obstruction. These patients have cyanosis, tachypnea, and anxiety owing to decreased pulmonary blood flow, with shunting of unoxygenated blood into the peripheral circulation.

Signs

There is significant interobserver variability in detecting cyanosis on physical examination. Room lighting and temperature may affect examination of the skin and mucous membranes. A patient's natural skin tone, thickness, and pigmentation also may alter findings.

Central cyanosis is often secondary to the shunting of venous unsaturated hemoglobin into the arterial circulation or the

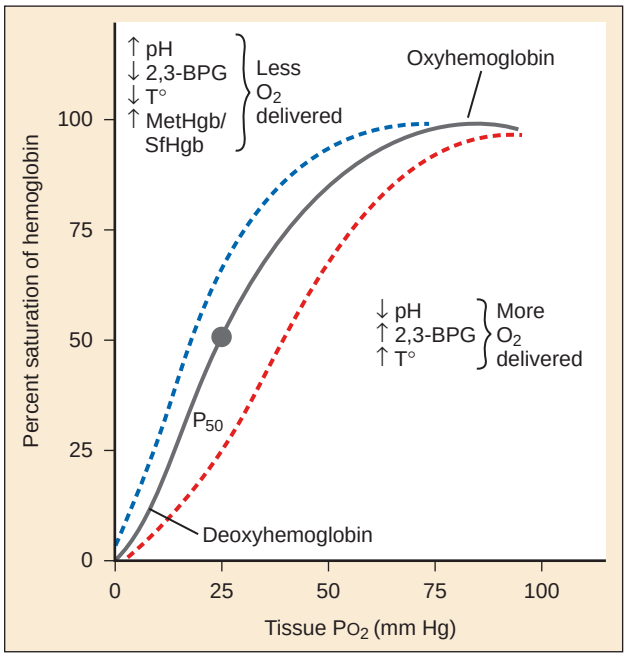

Fig. 11.1. Hemoglobin-oxygen dissociation curve. The solid line represents percent of hemoglobin (Hgb) saturation at a given Pa_{O_2}. The *red dotted line* represents factors that favor O_2 delivery to the tissues, so that at a given Pa_{O_2}, the Hgb saturation drops and O_2 is released. Muscle tissue is an example of lactic acid production and elevated temperature shifting the curve to the right, which favors the release of O_2. The *blue dotted line* represents a shift to the left with higher O_2 binding at any given Pa_{O_2}. Higher pH and lower temperatures, as in pulmonary capillary beds, favor more O_2 binding. Methemoglobin has a high affinity for oxygen molecules and does not readily release O_2 to the peripheral tissues. This shifts the normal oxygen dissociation curve to the left, resulting in hypoxia and lactic acid production. Lactic acid being produced in the tissues should facilitate O_2 release; however, the high affinity of methemoglobin for O_2 prevents this normal process. *2,3-BPG,* 2,3-Bisphosphoglycerate; *P_{O_2},* partial pressure of oxygen; *P_{50},* oxygen half- saturation pressure of hemoglobin; *T°,* temperature. (Redrawn from Koeppen BM, Stanton BA: Berne & Levy physiology, ed 6, St. Louis, 2008, Mosby.)

presence of abnormal hemoglobin. Central cyanosis is best seen on perioral skin, oral mucosa, or conjunctivae.

Peripheral cyanosis is secondary to vasoconstriction and slow flow of normally oxygenated hemoglobin in arterial blood, allowing for greater oxygen extraction by the tissues. Peripheral cyanosis affects capillary beds and typically is seen in the extremities and nail beds. Differential cyanosis may occur in the upper or lower (or the right or left) half of the body, with the remainder of the body appearing well oxygenated. This form of cyanosis is usually seen in patients with cyanotic heart disease with multiple anomalies.

Vital signs should be obtained from all patients. Temperature is typically normal. Blood pressure and heart rate vary, depending on the cause and acuity of cyanosis. Upper airway obstruction and other signs of respiratory insufficiency should be sought. Intermittent apnea in infants suggests central nervous system immaturity or a central lesion. Infants with cyanosis, increased respiratory depth, periodic apnea episodes, or diaphoresis with feeding may have congenital heart disease. Tachypnea (>60 breaths/min) in a newborn is nonspecific but may indicate a pulmonary disorder, congenital heart disease, infection, metabolic disorder, or gastrointestinal or central nervous system pathology.

The general appearance and mental status are evaluated. The head, eyes, ears, nose, and throat examination may reveal central cyanosis. Fundoscopic examination may detect dilated tortuous veins and papilledema in patients with cyanotic congenital heart disease.[3] Jugular venous distention may be seen on the neck examination in patients with pulmonary edema.

The chest examination may reveal crackles, wheezing, or inadequate ventilation. Heart sounds should be assessed for tachycardia, abnormal rhythm, or gallops and the presence and quality of murmurs, especially in the newborn. Central pulse strength should be noted. The abdomen should be examined for the presence of hepatosplenomegaly, pulsatile mass, or abdominal bruit.

Extremity examination includes evaluation of the nail beds for peripheral cyanosis, strength and symmetry of distal pulses, and capillary refill. Evidence of chronic vascular disease, such as hair loss and temperature difference, should be noted. Clubbing of the nails may occur because of increased soft tissue and expansion of the capillary beds (Fig. 11.2). Clubbing may be idiopathic or hereditary but is usually the result of chronic hypoxemic states, such as cyanotic heart disease, infective endocarditis, pulmonary disease (eg, chronic obstructive pulmonary disease, cystic fibrosis) and some gastrointestinal disorders (eg, cirrhosis, Crohn's disease,

BOX 11.1

Common Causes of Methemoglobinemia

HEREDITARY

Hemoglobin M
NADH methemoglobin reductase deficiency (homozygote and heterozygote)
G6PD deficiency

ACQUIRED

Medications

Amyl nitrite
Antineoplastics (eg, cyclophosphamide, ifosfamide, flutamide)
Dapsone
Local anesthetics (eg, benzocaine, lidocaine, prilocaine)
Nitroglycerin
Nitroprusside
Phenacetin
Phenazopyridine (Pyridium)
Quinones (eg, chloroquine, primaquine)
Sulfonamides (eg, sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)

Chemical Agents

Aniline dye derivatives (eg, shoe dyes, marking inks)
Butyl nitrite
Chlorobenzene
Fire (heat-induced denaturation)
Food adulterated with nitrites
Food high in nitrates
Isobutyl nitrite
Naphthalene (mothballs)
Nitrophenol
Nitrous gases (seen in arc welders)
Paraquat
Silver nitrate
Trinitrotoluene
Well water (nitrates)

Pediatric Cases

Reduced NADH methemoglobin reductase activity in infants (<4 mo)
Seen in association with low birth weight, prematurity, dehydration, acidosis, diarrhea, and hyperchloremia

G6PD, Glucose-6-phosphate dehydrogenase; *NADH,* reduced nicotinamide adenine dinucleotide.
Modified from Goldfrank LR: Toxicologic emergencies, ed 9, New York, 2010, McGraw-Hill.

BOX 11.2

Differential Diagnosis of Cyanosis

I. Peripheral cyanosis
  A. Low cardiac output states
    1. Shock
    2. Left ventricular failure
    3. Hypovolemia
  B. Environmental exposure (cold)
    1. Air or water
  C. Arterial occlusion
    1. Thrombosis
    2. Embolism
    3. Vasospasm (Raynaud's phenomenon)
    4. Peripheral vascular disease
  D. Venous obstruction
  E. Redistribution of blood flow from extremities
II. Central cyanosis
  A. Decreased arterial oxygen saturation
    1. High altitude (>8000 ft)
    2. Impaired pulmonary function
      a. Hypoventilation
      b. Impaired oxygen diffusion
      c. Ventilation-perfusion mismatching
        (1) Pulmonary embolism
        (2) Acute respiratory distress syndrome
        (3) Pulmonary hypertension
      d. Respiratory compromise
        (1) Upper airway obstruction
        (2) Pneumonia
        (3) Diaphragmatic hernia
        (4) Tension pneumothorax
        (5) Polycythemia
  B. Anatomic shunts
    1. Pulmonary arteriovenous fistulae and intrapulmonary shunts
    2. Cerebral, hepatic, peripheral arteriovenous fistulae
    3. Cyanotic congenital heart disease
      a. Endocardial cushion defects
      b. Ventricular septal defects
      c. Coarctation of aorta
      d. Tetralogy of Fallot
      e. Total anomalous pulmonary venous drainage
      f. Hypoplastic left ventricle
      g. Pulmonary vein stenosis
      h. Tricuspid atresia and anomalies
      i. Premature closure of foramen ovale
      j. Dextrocardia

regional enteritis). Thrombotic events should also be considered in patients with skin and nail bed hemorrhages or end-organ damage (eg, eye, kidney).

A neurologic examination is performed, focusing on mental status, symmetry of motor and sensory function, and any gross deficit.

Laboratory and Ancillary Testing

The complete blood count is performed to assess for erythrocytosis, polycythemia, or anemia.[4] A peripheral smear assesses RBC morphology and fragments, as well as the white blood cell differential count. A D-dimer level is indicated if pulmonary embolism (PE) is suspected as the cause of observed circulatory shock.[5]

The peripheral blood typically appears chocolate brown in color. Normally, a small drop of blood placed on a white sheet or filter paper will turn bright red when exposed to 100% oxygen. No change in color is highly suggestive of methemoglobinemia.[6]

Fig. 11.2. Symmetric clubbing. Shown here are equal cyanosis and clubbing of the hands and feet resulting from transposition of the great vessels and a ventricular septal defect without patent ductus arteriosus.

Interpretation of pulse oximetry is problematic in the setting of cyanosis (see Chapter 5). Assessment of peripheral pulses and capillary refill time can help determine whether poor circulation is the cause of low pulse oximetry. Pulse oximetry measures the light absorbance of tissue at two wavelengths, 660 nm (red, reduced hemoglobin) and 940 nm (infrared, oxyhemoglobin). The ratio of these two readings is the basis of the pulse oximetry calculation. Methemoglobin absorbs well at both wavelengths, resulting in a saturation reading of approximately 85%, regardless of the actual Pao_2 and Sao_2 values.[7]

Arterial blood gas testing assesses Sao_2, often sampled when the patient is breathing room air (see Fig. 11.1). CO-oximetry measurements should be specifically ordered if carbon monoxide exposure or methemoglobinemia is suspected. Sulfhemoglobin is reported as methemoglobin on CO-oximetry so, if sulfhemoglobinemia is possible, measured oxygen saturation should be specifically determined. Devices designed to measure methemoglobin levels noninvasively (eg, pulse CO-oximetry) may be useful but have decreasing accuracy at lower Sao_2 levels (<95%) and higher methemoglobin levels (>14%).[8,9]

Other Diagnostic Modalities

Imaging

A chest radiograph should be ordered to evaluate lung fields for consolidation, infiltrates, effusions, and pulmonary edema. An abnormal cardiac silhouette and mediastinum may suggest congenital heart disease. In patients thought to have PE, an elevated D-dimer level may indicate the need for lower extremity venous Doppler ultrasound, computed tomography (CT) pulmonary angiography or, rarely, ventilation-perfusion scanning.

Electrocardiography and Echocardiography

An electrocardiogram should be obtained on all patients with a new presentation of cyanosis to assess for dysrhythmia and acute ischemic changes. Right axis deviation or right ventricular hypertrophy may be seen with significant cardiopulmonary disease (eg, cor pulmonale, acute pulmonary hypertension). An

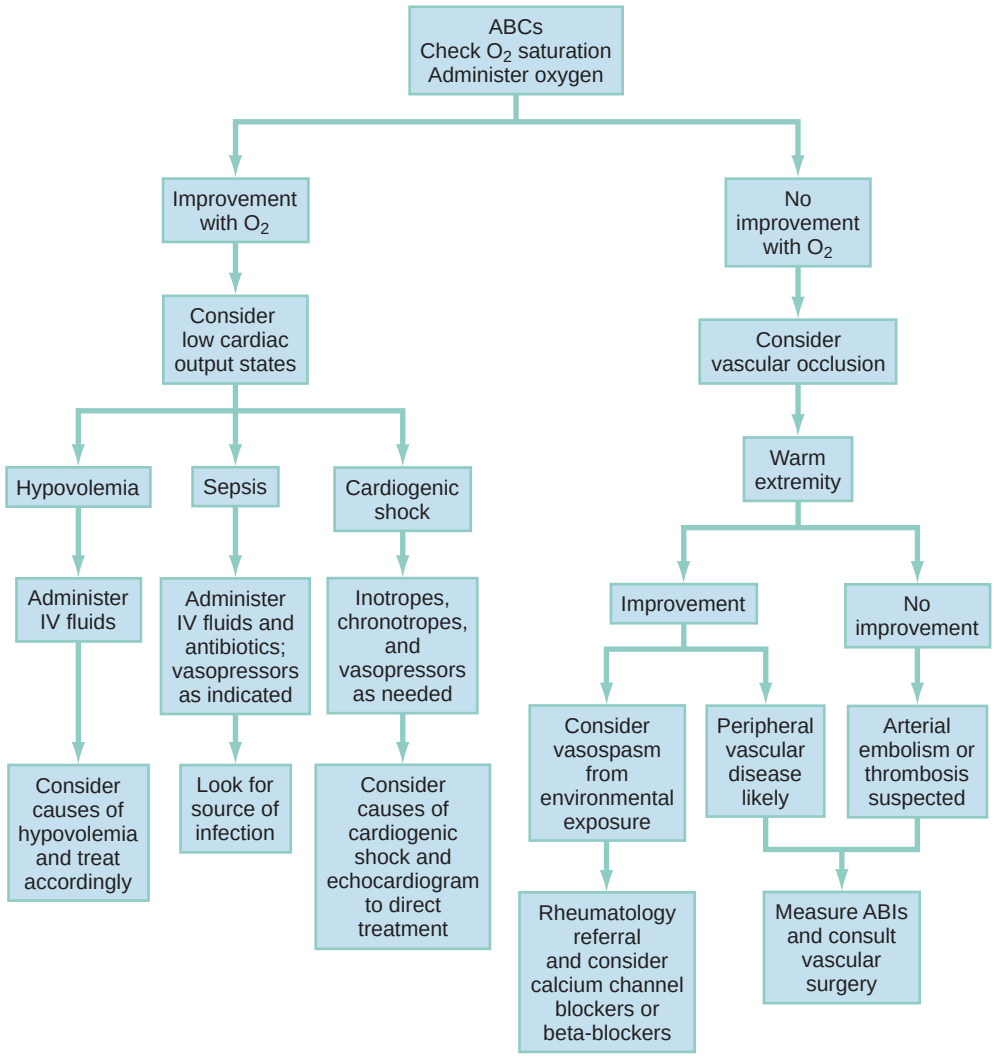

Fig. 11.3. Algorithmic approach to peripheral cyanosis. *ABCs,* Airway, breathing, circulation; *ABI,* ankle-brachial index; *IV,* intravenous.

echocardiogram may be useful in detecting septal defects in infants or valvular disease in infants and adults.

DIFFERENTIAL ALGORITHMS

Figures 11.3 and 11.4 outline approaches to the differential diagnosis and treatment of peripheral and central cyanosis, respectively. During the initial assessment, the emergency clinician should initiate oxygen therapy and follow steps to determine the cause of cyanosis. Clinical improvement with oxygen suggests diffusion impairment. Patients who do not respond to high-flow oxygen are more likely to have ventilation-perfusion ratio abnormalities, such as shunting from pulmonary consolidation or congenital heart disease with right-to-left shunting. Cardiac size and silhouette on a chest radiograph may suggest the presence of congenital heart disease. If heart size is normal, impaired pulmonary function, pulmonary embolus, or other noncardiac causes should be considered. If no improvement occurs with 100% oxygen therapy, the patient's respiratory status should be reassessed and tension pneumothorax or upper airway obstruction considered. Pulmonary embolus should be considered and CT pulmonary angiography performed. If a patient exhibits no respiratory distress and remains resistant to oxygen therapy, cardiac shunting or abnormal hemoglobin forms should be considered and treated accordingly. Superior vena cava (SVC) syndrome should be suspected in patients with central cyanosis with facial, neck, and upper extremity swelling, with venous distention and plethora.

Critical Diagnoses

Acute cardiovascular and respiratory compromise are considered in patients with cyanosis and symptoms or signs of shock. The differential diagnosis includes acute heart failure, acute coronary syndrome, and hypovolemic or cardiogenic shock. In addition, consider acute respiratory insufficiency or failure, massive PE, exacerbation or decompensation in a patient with known congenital heart disease, or the first presentation of pediatric congenital heart disease.

Emergent Diagnoses

Methemoglobinemia is an infrequent cause of cyanosis but should be considered in patients without a history or physical findings suggestive of cardiovascular or pulmonary disease.

Sulfhemoglobinemia is a rare cause of cyanosis, usually occurring after exposure to hydrogen sulfide from organic sources, medications that are sulfonamide derivatives, or gastrointestinal sources (bacterial overgrowth). Strong consideration should be given to sulfhemoglobin toxicity in patients with cyanotic findings

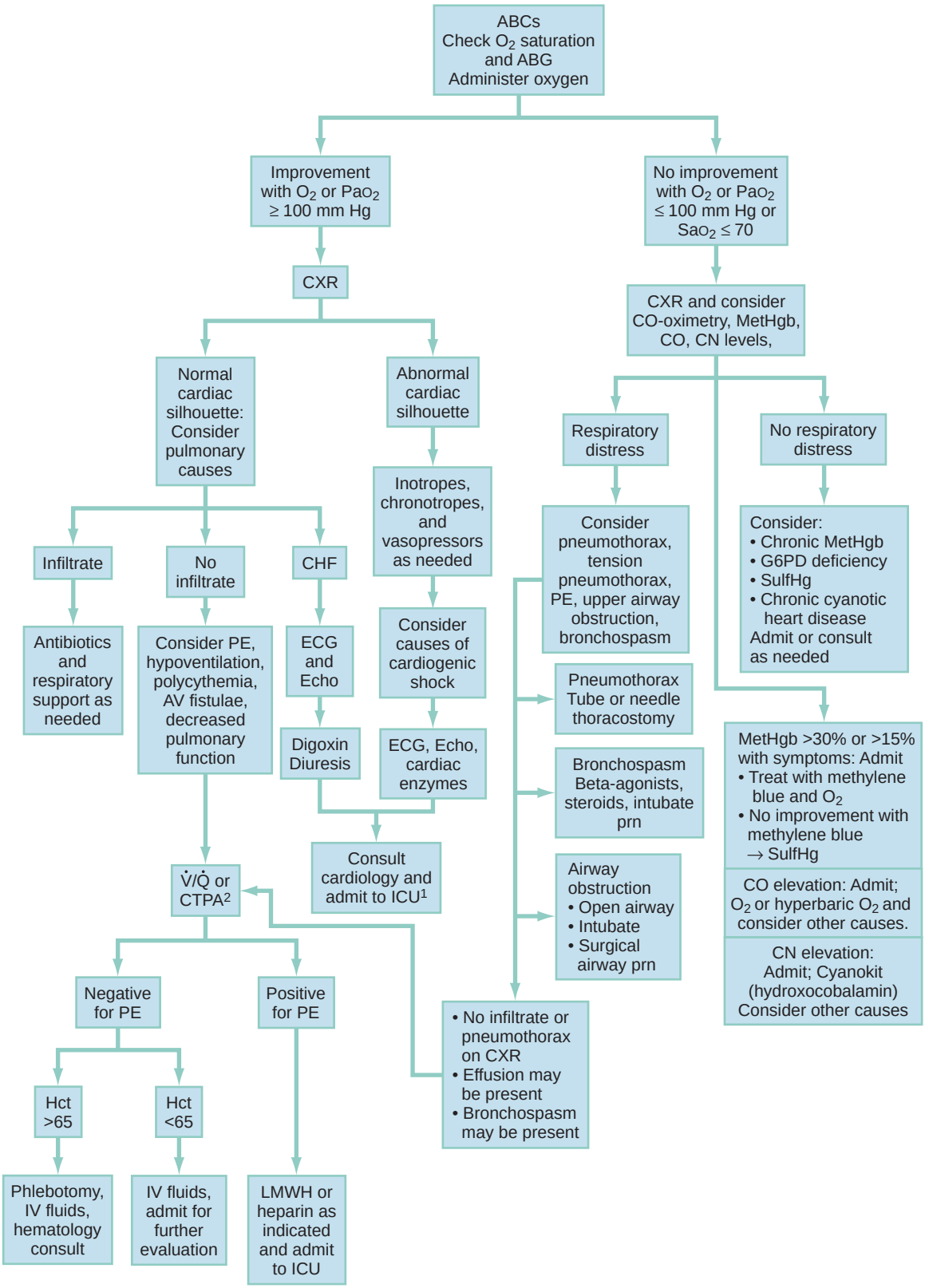

Fig. 11.4. An algorithmic approach to central cyanosis. *ABCs,* Airway, breathing, circulation; *ABG,* arterial blood gas; *AV,* arteriovenous; *CHF,* congestive heart failure; *CN,* cyanide; *CO,* carbon monoxide; *CTPA,* computed tomography pulmonary angiography; *CXR,* chest radiograph; *ECG,* electrocardiography; *Echo,* echocardiography; *G6PD,* glucose-6-phosphate dehydrogenase; *Hct,* hematocrit; *ICU,* intensive care unit; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *MetHgb,* methemoglobin; O_2, oxygen; Pao_2, partial pressure of arterial oxygen; *PE,* pulmonary embolus; *prn,* as needed; *RA,* room air; Sao_2, arterial oxygen saturation; *SulfHg,* sulfhemoglobin; V̇/Q̇, ventilation-perfusion scan. [1]Patients with chronic cyanotic heart disease may not require ICU care or even hospital admission. Disposition should be discussed with the patient's cardiologist.[2] The V̇/Q̇ ratio may be determined when CTPA is unavailable or contraindicated.

and methemoglobin on CO-oximetry but who do not improve with methylene blue treatment.[10]

Polycythemia is defined as an elevated RBC mass from one of three causes. Polycythemia vera is a disorder of bone marrow stem cells with increased RBC mass, cyanosis, and splenomegaly. Patients may demonstrate hyperviscosity syndrome. Secondary polycythemia occurs with an appropriate or inappropriate increase of erythropoietin, physiologic response to chronic hypoxemia (<92% oxygen saturation), cyanotic congenital heart disease, cigarette smoking, or high-altitude exposures. Relative polycythemia is an increased RBC mass, often resulting from dehydration or reduced plasma volume.

Finally, vascular disease, such as Raynaud's phenomenon, may cause peripheral cyanosis. Raynaud's phenomenon occurs in 15% of the population, with a female predominance. Patients have an abnormal response to excessive cold or emotional stress, causing vasoconstriction, profound cold sensitivity, and recurrent events of sharply demarcated pallor or cyanosis of the digits (Fig. 11.5). Usually, the cutaneous arterial capillary beds of the fingers and toes are affected,[11] but the tongue, ear, and other distal areas may also be affected.

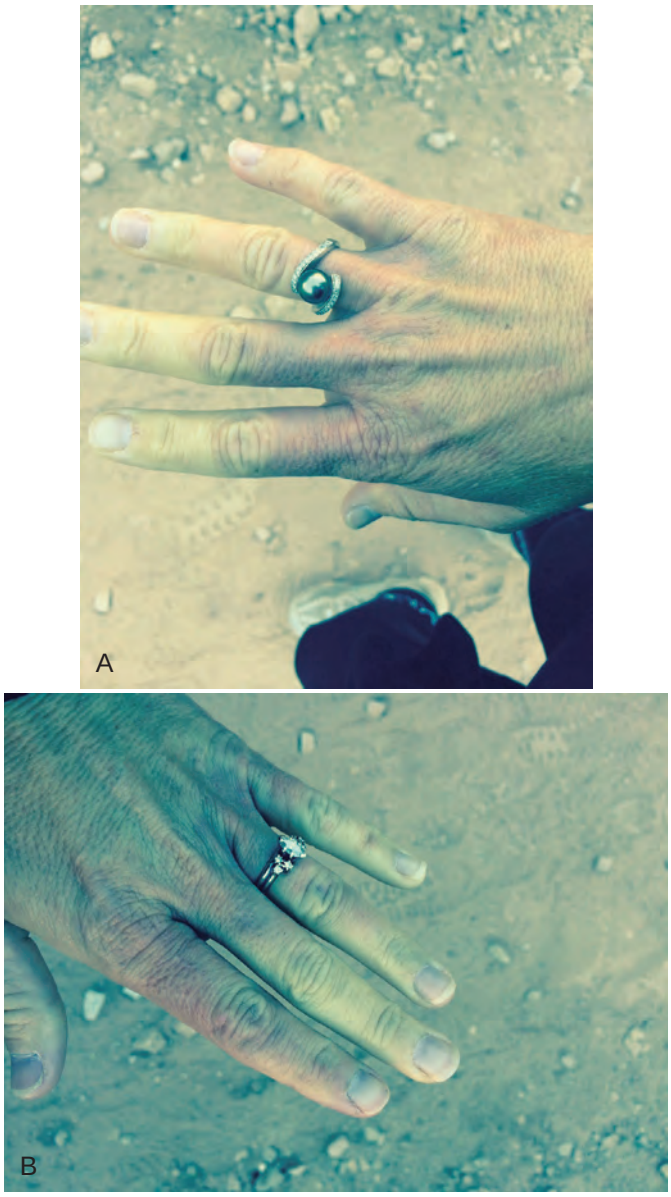

Fig. 11.5. A, B, Raynaud's phenomenon due to cold exposure.

EMPIRICAL MANAGEMENT

Administration of high-flow oxygen is the first therapy for patients with cyanosis. Any clinical improvement, or lack thereof, should be noted. Thereafter, consider an abnormal hemoglobin level and toxin-induced cyanosis because the administration of appropriate antidotes and systemic therapies may decrease morbidity.

Intravenous (IV) fluid resuscitation should be initiated in patients with hypovolemia. Treatment of congestive heart failure, arrhythmias, or poor cardiac output should occur as clinical conditions indicate. We recommend cardiology consultation for patients with congenital heart disease, who often have very abnormal responses to oxygen and conventional fluid therapy. If oxygenation compromise is sufficient to cause ischemic chest pain, prompt correction of the underlying hemoglobin abnormality is undertaken simultaneously with conventional treatment of the ischemia. Although several specific treatments are discussed here, the cause of the cyanosis may be elusive, and hospitalization is required in all but chronic stable cases.

Specific Strategies

Methemoglobinemia and Sulfhemoglobinemia

If cutaneous exposure to an inciting agent (ie, aniline dye) has occurred, complete decontamination with soap and water is recommended. The staff should use appropriate protective equipment. Urgent treatment with oxygen and methylene blue (1–2 mg/kg IV over 5 minutes) is indicated for patients with symptomatic hypoxia (eg, dysrhythmias, angina, respiratory distress, seizures, coma) or methemoglobin levels greater than 30%. Sulfhemoglobinemia is suggested when the laboratory reports an elevated methemoglobin level and the patient does not respond to methylene blue. Sulfhemoglobinemia is irreversible for the life of the erythrocyte. Treatment of sulfhemoglobinemia is supportive in addition to removing the causative agent. Transfusion of RBCs and exchange transfusion have been described as a treatment, but there are no controlled studies of this modality.[10]

Other Causes of Cyanosis

Acute therapy for patients with symptomatic hyperviscosity syndrome and secondary polycythemia includes phlebotomy and volume expansion with isotonic crystalloid. The goal of therapy is to achieve a normal hematocrit (45%).[4] Long-term therapy is focused on the underlying cause, and patients require referral to a hematologist.

Patients with SVC syndrome require further evaluation for a mediastinal mass or vascular abnormality. Conservative management with oxygen and elevation of the head of the bed often provide significant symptomatic relief. Vascular stenting may be necessary, and radiation or chemotherapy may be indicated in cases caused by malignancy.

The Raynaud's phenomenon is treated by warming the affected digits and extremities. Systemic vasodilating agents (eg, calcium channel blockers [nifedipine] or nitrates, endothelin antagonists, statins, phosphodiesterase inhibitors, botulinum toxin) may be useful in the acute setting, although data are limited.[11] If there is no improvement of peripheral cyanosis with warming and administration of 100% oxygen, arterial insufficiency or occlusion may be present. In cases of critical limb ischemia, IV heparin should be considered in consultation with a vascular surgeon. Embolic sources, such as endocarditis and abdominal aortic aneurysms, should be considered. Vascular bypass, intraarterial thrombolysis, or stenting may be indicated.

Carbon monoxide and cyanide poisoning do not typically cause cyanosis and are covered elsewhere.

PATIENT DISPOSITION

Admission

All patients with a first episode of cyanosis or an uncertain cause require hospitalization. Cardiology consultation and referral are recommended for children with a first episode of congestive heart failure and newly diagnosed or suggested congenital heart disease. A surgical consultation and intervention are indicated for acute arterial occlusion from embolic or thrombotic sources. Multiple consultations may be appropriate for patients with SVC syndrome, including a vascular surgeon, interventional radiologist, oncologist, and radiation oncologist.

Discharge

Patients with peripheral cyanosis from vasospasm, those with asymptomatic methemoglobinemia less than 15%, and stable patients with primary pulmonary disease may be treated as outpatients after several hours of monitoring in the ED. Follow-up should occur within 24 hours unless the patient has a previous diagnosis of chronic cyanosis. Instructions should clearly state that if the cyanosis worsens, or if dyspnea, altered mentation, or chest pain occurs after discharge, the patient should return immediately to the ED. Any precipitating agents should be removed.

KEY CONCEPTS

- Cyanosis occurs as a result of an absolute amount of desaturated hemoglobin rather than a percentage; anemic patients exhibit cyanosis at a lower Pa_{O_2} than those with normal hemoglobin levels.
- Central cyanosis is due to a shunting of unsaturated (venous) hemoglobin to the arterial circulation, whereas peripheral cyanosis is due to vasoconstriction or slow flow of normally oxygenated hemoglobin to the peripheral tissues.
- Methemoglobin has a chocolate brown color, even when exposed to room air.
- The pulse oximeter for patients with methemoglobinemia typically reads 85%, regardless of the Pa_{O_2} or Sa_{O_2}.
- Congenital heart disease is a prime diagnostic consideration in all infants presenting with cyanosis
- Toxic exposures, particularly to aniline dyes and local anesthetics, are considered in acute cyanosis.
- Sulfhemoglobin is reported as methemoglobin on CO-oximetry; patients with methemoglobinemia on CO-oximetry who do not respond to methylene blue treatment likely have sulfhemoglobinemia.
- Clinical improvement of the cyanotic patient with supplemental oxygen suggests a diffusion impairment as the cause.
- All patients with a first episode of cyanosis or an uncertain cause require hospitalization.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 11: QUESTIONS AND ANSWERS

11.1. Which of the following statements regarding methemoglobin is true?
- **A.** Methemoglobin begins to produce cyanosis when its concentration reaches 25% of total hemoglobin.
- **B.** Methemoglobin changes from dark purple to light red when exposed to room air.
- **C.** Methemoglobin normally accounts for 5% of total hemoglobin.
- **D.** Methylene blue accelerates the reduction of methemoglobin to hemoglobin.
- **E.** The primary method of reducing methemoglobin to hemoglobin is glucose-6-phosphate dehydrogenase (G6PD)–dependent.

Answer: D. Methemoglobin normally accounts for less than 1% of total hemoglobin. Cyanosis results when MORE than 10% to 15% of the total hemoglobin is methemoglobin, which has a dark purple-brown color, even when exposed to room air. Methemoglobin is reduced to ferrous hemoglobin primarily by reduced nicotinamide adenine dinucleotide (NADH)–cytochrome b5 reductase, an enzyme system present in red blood cells. A secondary reduced nicotinamide adenine dinucleotide phosphate (NADPH)–dependent system uses glutathione production and G6PD to reduce methemoglobin to hemoglobin. This secondary pathway normally plays a minor role but is accelerated by methylene blue.

11.2. Which of the following conditions produces peripheral cyanosis?
- **A.** Diaphragmatic hernia
- **B.** High altitude > 8000 ft
- **C.** Hypovolemia
- **D.** Impaired oxygen diffusion
- **E.** Pulmonary hypertension

Answer: C. Peripheral cyanosis is secondary to vasoconstriction and A slow flow of normally oxygenated hemoglobin in arterial blood, allowing for greater oxygen extraction by the tissues. Hypovolemia causes a low-flow state that can produce peripheral cyanosis. The remaining options would cause a central cyanosis secondary to decreased arterial oxygen saturation.

11.3. Which of the following conditions produces central cyanosis?
- **A.** Hypothermia
- **B.** Raynaud's phenomenon
- **C.** Shock
- **D.** Venous insufficiency
- **E.** Ventricular septal defect

Answer: E. Central cyanosis is caused by decreased arterial oxygen saturation, shunting of venous unsaturated hemoglobin into the arterial circulation, or the presence of abnormal hemoglobin. A ventricular septal defect causes shunting of deoxygenated blood from the right side of the heart to the left, with resultant decreased arterial oxygen saturation and central cyanosis. The remaining options would cause a peripheral cyanosis.

11.4. In the cyanotic patient, clinical improvement with supplemental oxygen is most suggestive of which of the following underlying processes?
- **A.** Arterial emboli
- **B.** Congenital heart disease with right-to-left shunting
- **C.** Hyperventilation
- **D.** Impaired oxygen diffusion
- **E.** Ventilation-perfusion mismatching

Answer: D. Clinical improvement with oxygen suggests diffusion impairment. Patients who do not respond to oxygen are more likely to have ventilation-perfusion ratio abnormalities, such as shunting from pulmonary consolidation or congenital heart disease with right-to-left shunting. Arterial emboli will be affected by supplemental oxygen.

11.5. Which of the following statements regarding polycythemia is correct?
- **A.** Polycythemia is defined as an elevated hemoglobin level.
- **B.** Polycythemia vera may result from an increase in the erythropoietin level.
- **C.** Patients may present with hyperviscosity syndrome.
- **D.** Relative polycythemia occurs from high-altitude exposures.
- **E.** Secondary polycythemia is often due to dehydration.

Answer: C. Polycythemia is defined as an elevated red blood cell (RBC) mass resulting from one of three causes. Polycythemia vera is a disorder of bone marrow stem cells with increased RBC mass, cyanosis, and splenomegaly. Patients may present with hyperviscosity syndrome. Secondary polycythemia occurs with an appropriate or inappropriate increase of erythropoietin, a physiologic response to chronic hypoxemia, cyanotic congenital heart disease, cigarette smoking, or high-altitude exposures. Relative polycythemia is an increased RBC mass, often resulting from dehydration or reduced plasma volumes.

11.6. Soon after receiving topical upper airway anesthesia with benzocaine, a patient becomes tachypneic and complains of chest pain. The patient is noted to be cyanotic. Supportive measures are initiated, and CO-oximetry reveals a methemoglobin level of 40%. Which of the following should be administered?
- **A.** Benadryl
- **B.** Hyperbaric oxygen
- **C.** Methylene blue
- **D.** Nitroglycerin
- **E.** Thrombolytics

Answer: C. Local anesthetics such as benzocaine, lidocaine, and prilocaine can cause an acquired methemoglobinemia. Urgent treatment with oxygen and methylene blue is indicated in such patients, especially when accompanied by symptomatic hypoxia (eg, dysrhythmias, angina, respiratory distress, seizures, coma) and methemoglobin levels greater than 30%.

11.7. An otherwise healthy 35-year-old woman presents with headache, mild shortness of breath, and central cyanosis. She is currently taking trimethoprim-sulfamethoxazole and phenazopyridine for a urinary tract infection. She does not improve with supplemental oxygen. Her chest radiograph is normal. CO-oximetry shows a methemoglobin level of 28%. Her medications are withheld. The patient shows no improvement after 2 mg/kg of methylene blue is administered. Ongoing management should include which of the following treatments?

A. Calcium channel blockers
B. Hydroxycobalamin
C. Phlebotomy
D. Sodium thiosulfate
E. Supportive care

Answer: E. This patient has likely has sulfhemoglobinemia, a rare complication of the medication phenazopyridine (Pyridium). Standard CO-oximetry will report sulfhemoglobin as methemoglobin. Both sulfamethoxazole and phenazopyridine can also cause methemoglobinemia. Patients with an elevated methemoglobin level and no response to methylene blue likely have sulfhemoglobinemia, which is less severe than methemoglobinemia and only requires supportive care. Phlebotomy is the treatment for polycythemia. Sodium thiosulfate and hydroxycobalamin are both used to treat cyanide toxicity, and calcium channel blockers may be used to treat peripheral cyanosis resulting from vasospasm (Raynaud's phenomenon).

11.8. Acute treatment for symptomatic hyperviscosity syndrome includes which of the following?

D. Heparin
E. Methylene blue
C. Nifedipine
A. Phlebotomy
B. Warm compresses

Answer: A. Patients with polycythemia and other conditions that increase the viscosity of blood may present with symptomatic hyperviscosity syndrome. Acute therapy for these patients includes phlebotomy and volume expansion with isotonic crystalloid. The goal of therapy is a normal hematocrit. Long-term therapy is focused on the underlying cause, and patients typically require referral to a hematologist.

CHAPTER 12

Syncope

Robert A. De Lorenzo

PERSPECTIVE

Syncope is the sudden transient loss of consciousness with a loss of postural tone. It is a common presenting complaint in the emergency department (ED). Despite improved understanding of risk and outcomes, consensus on the diagnostic approach and disposition remains elusive. This is in part because of the varied causes of syncope and lack of definitive diagnostic studies available and because of confusion and lack of standard terminology to describe the disorder. Diagnostic accuracy relies largely on the synthesis of patient risk factors and reported symptoms, with limited reliance on the physical examination and ancillary testing.

Epidemiology

The prevalence of syncope in the general population is approximately 19%, with only half consulting a physician for evaluation. Syncope accounts for up to 3% of ED visits. Patients presenting to the ED for syncope appear to have a higher likelihood of a serious underlying cause than those presenting to other ambulatory settings. The admission rate is variable across EDs, with almost 50% of patients admitted to an inpatient or observation unit.[1] Persons aged 65 years and older account for 80% of such admissions. The mortality rate at 1 month depends on the cause of syncope and comorbid conditions and can be nearly 5%.[1] Up to 15% of children experience at least one episode of syncope.

Risk factors for syncope include cerebrovascular disease, cardiac medications, and hypertension. Most causes of syncope are benign and have favorable outcomes. Patients with preexisting cardiovascular disease and syncope from any cause are at the greatest short- and long-term risk of mortality. In patients with a cardiac history, 1 year after a syncopal episode, over one-third of the 7.6% death rate has been found to be cardiac related. Age, congestive heart failure, and coronary artery disease are key predictors of mortality in patients with syncope.[2] In contrast, there is no increased risk of cardiovascular morbidity or mortality associated with neurally mediated (vasovagal), orthostatic, and medication-related syncope. Recurrence of syncope may be as high as 50% and is not correlated with age or gender.

Benign causes of syncope predominate in adolescents and young adults. Prospective outcome studies in children are incomplete, but it has been suggested that mortality rates are extremely low. Significant trauma may result from syncope and can contribute to increased risk of morbidity and mortality, particularly in older adults. The overall US medical cost of syncope has been estimated at $2.4 billion annually.

Pathophysiology

The final common pathway resulting in syncope is dysfunction of both cerebral hemispheres or the brainstem (reticular activating system), usually from acute hypoperfusion. Reduced blood flow may be regional (cerebral vasoconstriction) or systemic (hypotension). Loss of consciousness results in loss of postural tone, with the resulting syncopal episode. Less severe derangements may result in sensations of presyncope (near-syncope) or lightheadedness. Thus, presyncope and syncope may be considered on a continuum with shared causes, mechanisms, and outcomes.[3] By definition, syncope is transient; therefore, the cause of central nervous system (CNS) dysfunction should likewise be transient. Persistent causes of significant CNS dysfunction may result in coma or depressed consciousness (see Chapter 13).

Hypoperfusion resulting in an approximately 35% or more reduction in cerebral blood flow usually produces unconsciousness, and any mechanism that adversely affects the components of perfusion (eg, cardiac output, systemic vascular resistance, blood volume, regional vascular resistance) can cause or contribute to syncope. The cause of syncope can be divided into three major classifications: neurally (or reflex) mediated, orthostatic hypotension mediated, and cardiovascular mediated. Causes of transient loss of consciousness that do not fall into the major syncope classifications presumably operate under different mechanisms; these include seizures, hypoglycemia, certain toxins and metabolic derangements, hyperventilation, primary neurologic conditions, and psychiatric disorders.

DIAGNOSTIC APPROACH

Differential Considerations

The potential causes of syncope are numerous and can be categorized according to their primary mechanism (Box 12.1). The first differential diagnostic consideration is to distinguish syncope from other causes of an apparent sudden loss of consciousness, especially seizure and uncommon disorders such as cataplexy. When syncope is established as the working diagnosis, the life-threatening causes, primarily cardiovascular in origin, are considered first. The principal serious causes of syncope are dysrhythmias, myocardial dysfunction, and sudden interruption of right ventricular outflow by pulmonary embolism. Cerebrovascular disease, principally subarachnoid hemorrhage, is less frequently encountered, but equally serious. Toxic and metabolic abnormalities may induce syncope through alterations in blood pressure or cardiac rhythm. Structural cardiac lesions, such as critical aortic stenosis, can also cause sudden loss of consciousness. Dissection of the thoracic aorta rarely manifests primarily as syncope.

Pivotal Findings

Most cases of syncope arise from benign causes, so the evaluation is largely focused on identifying those cases caused by serious pathology. The patient's history, particularly the setting of the syncope (eg, postmicturition, venipuncture), patient position (eg, sitting, standing), prior episodes, and presence or absence of prodromal symptoms, are central to separating benign from serious causes of the syncopal episode. Young, healthy patients with clearly benign syncope, occurring in a compatible setting and preceded by prodromal symptoms, as disclosed by a thorough history, require little more than a physical examination for anemia or other benign exacerbating factors. All other patients require

BOX 12.1

Causes of Syncope and Transient Loss of Consciousness

SYSTEMIC HYPOPERFUSION RESULTING IN CNS DYSFUNCTION

Cardiovascular System–Mediated

Outflow Obstruction
Mitral, aortic, or pulmonic stenosis
Hypertrophic cardiomyopathy
Atrial myxoma
Pulmonary embolism
Pulmonary hypertension
Cardiac tamponade
Congenital heart disease

Reduced Cardiac Output
Tachycardia
- Supraventricular tachycardia
- Ventricular tachycardia
- Ventricular fibrillation
- Wolff-Parkinson-White syndrome
- Torsades de pointes

Bradycardia
- Sinus node disease
- Second-degree and third-degree AV block
- Prolonged QT syndrome
- Brugada's syndrome
- Pacemaker malfunction
- Implanted cardioverter-defibrillator malfunction

Other Cardiovascular Disease
Aortic dissection
Myocardial infarction
Cardiomyopathy

Neurally Mediated (Neurocardiogenic)
Reflex syncope (vasovagal)
- Emotion
- Pain
- Instrumentation
- Valsalva—elevated intrathoracic pressure, weightlifting; tussive, sneeze

Situational
- Carotid sinus sensitivity (necktie, shaving syncope)
- Postexercise
- Gastrointestinal—swallowing, vomiting, defecation
- Postmicturition

Orthostatic Mediated
Volume depletion
- Anemia—hemorrhage

Primary autonomic failure
Secondary autonomic failure
Drug-induced

FOCAL HYPOPERFUSION OF CNS STRUCTURES

Cerebrovascular disease
Hyperventilation
Subclavian steal
Subarachnoid hemorrhage
Basilar artery migraine
Cerebral syncope

CNS DYSFUNCTION WITH NORMAL CEREBRAL PERFUSION

Hypoglycemia
Hypoxemia—asphyxiation
Seizure
Narcolepsy
Psychogenic
- Anxiety disorder
- Conversion disorder
- Somatization disorder
- Panic disorder
- Breath-holding spells

Toxic
- Drugs
- Carbon monoxide
- Other agents

Undetermined causes

AV, Atrioventricular; *CNS,* central nervous system.

further diagnostic evaluation. The yield of an electrocardiogram (ECG) is generally low; however, it is broadly recommended in all other cases (see below) and has the additional advantages of being noninvasive and relatively inexpensive. The clinical examination (history and physical examination) alone can suggest the diagnosis in 45% of cases. For a large portion of the remainder, however, a clear diagnosis for the syncope may not be established in the ED.

Symptoms

Symptoms can often suggest the diagnosis, although the relative weight of the history diminishes in older patients and in those not able to remember clearly the events leading up to the loss of consciousness. The patient is asked to describe the character of the syncopal event. Witnesses may be able to supplement and corroborate the patient's incomplete recall, and that history should be solicited. Key characteristics include the rate of onset (gradual or abrupt), position on symptom onset (eg, standing, sitting, supine), and duration and rate of recovery. Abrupt onset, occurrence while sitting or supine, and duration of more than a few seconds are usually ascribed to serious, often cardiac, causes of syncope, but firm data are lacking. Similarly, incomplete or near-syncope may be perceived as less serious, but mortality appears to be similar.[3] The diagnostic approach to presyncope is therefore the same as for syncope.

Additional history regarding the events preceding the syncope is helpful. Occurrence during significant exertion suggests outflow obstruction, whereas occurrence after exercise or prolonged exposure to heat stress suggests orthostasis. The myriad mechanisms that may mediate a neurocardiogenic response, including significant emotional events, micturition, eating, bowel movements, emesis, and movement or manipulation of the neck causing stimulation of the carotid sinus, should be addressed. Occurrence in a supine position or the presence of acute palpitations is relatively specific for syncope of cardiac origin. Seizures may be preceded by an aura and followed by a typical postictal state.

Events during the syncopal episode do not usually clarify the cause. Tonic-clonic movements, related to inadequate cerebral perfusion, can occur in any form of syncope, including benign neurally mediated causes, and should be differentiated from the prolonged activity with subsequent postictal depression of consciousness seen in seizure disorders (see Chapter 92). Trauma from a fall, although important to address, may distract the examiner from evaluating for the underlying syncope that caused the injury.

The postsyncopal events should be queried. Symptoms consistent with a postictal state are characteristic of seizures. Initial vital signs and cardiac monitoring by out-of-hospital medical providers may provide clues to primary cardiac dysrhythmias.

Associated symptoms can offer potentially important clues. Chest pain or dyspnea can suggest myocardial ischemia, aortic dissection, or pulmonary embolism. Diaphoresis and lightheadedness are nonspecific but, if prominent and accompanied by a graying of vision, may suggest orthostasis or neurally mediated causes. Tongue biting and incontinence of urine or stool suggest seizures.

The past medical history is critical in stratifying risk.[2] Congestive heart failure is a key determinant of increased short- and long-term mortality in the setting of syncope.[2] Prior coronary artery or cerebrovascular disease, diabetes, hypertension, and other significant chronic diseases also appear to increase the risk of mortality after syncope.

Certain medications are well established to be associated with syncope (Box 12.2). QT interval–prolonging agents, beta blockers, insulin, and oral hypoglycemics, in particular, deserve attention because of the likelihood of repeated syncope without careful medication monitoring.

Signs

The physical examination focuses primarily on the elements affecting the cardiovascular and neurologic systems. Specific findings are detailed in Table 12.1. Signs of orthostasis should be sought in all cases in which this mechanism is suggested. Carotid massage is safe and occasionally revealing; it is indicated in patients for whom the history is suggestive of carotid sinus hypersensitivity. Rectal examination for gross blood or melena is recommended if anemia or gastrointestinal hemorrhage is suspected.

BOX 12.2

Medications That May Induce Syncope

Cardiovascular agents
Beta blockers
Vasodilators—beta blockers, calcium channel blockers, nitrates, hydralazine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, phenothiazines, phosphodiesterase inhibitors
Diuretics
Central antihypertensives (eg, clonidine, methyldopa)
Other antihypertensives (eg, guanethidine)
QT-prolonging agents (eg, amiodarone, disopyramide, flecainide, procainamide, quinidine, sotalol)
Other antidysrhythmics
Psychoactive agents
Anticonvulsants (eg, carbamazepine, phenytoin)
Antiparkinsonian agents
Central nervous system depressants (eg, barbiturates, benzodiazepines)
Monoamine oxidase inhibitors
Antidepressants
Narcotic analgesics
Sedating and nonsedating antihistamines
Cholinesterase inhibitors (eg, donepezil, tacrine, galantamine)
Drugs with other mechanisms
Drugs of abuse (eg, cannabis, cocaine, alcohol, heroin)
Digitalis
Insulin and oral hypoglycemics
Neuropathic agents (vincristine)
Nonsteroidal antiinflammatory drugs
Bromocriptine

TABLE 12.1

Directed Physical Examination in Syncope

SYSTEM	PIVOTAL FINDING	SIGNIFICANCE
Vital signs	Pulse rate and rhythm	Tachycardia, bradycardia, other dysrhythmias
	Respiratory rate and depth	Tachypnea suggests hypoxia, hyperventilation, or pulmonary embolus
	Blood pressure	Shock may cause decreased cerebral perfusion; hypovolemia or medication use may lead to orthostasis
	Temperature	Fever from sepsis may cause volume depletion and orthostasis
Skin	Color, diaphoresis	Signs of decreased organ perfusion
Head, eyes, ears, nose, and throat	Tenderness and deformity	Signs of trauma
	Papilledema	Increased intracranial pressure, head injury
	Breath	Ketones from ketoacidosis
Neck	Bruits	Identify presence of cerebrovascular disease
	Jugular venous distention	Right-sided heart failure from myocardial ischemia, tamponade, pulmonary embolism
Lungs	Breath sounds, crackles, wheezes	Infection, left-sided heart failure from myocardial ischemia, rarely pulmonary embolism
Heart	Systolic murmur	Aortic stenosis, hypertrophic cardiomyopathy
	Rub	Pericarditis, tamponade
Abdomen	Pulsatile mass	Abdominal aortic aneurysm
Rectum	Stool for gross blood or melena	Anemia, gastrointestinal bleed
Pelvis	Uterine bleeding, adnexal tenderness	Anemia, ectopic pregnancy, hypovolemia
Extremities	Pulse equality in upper extremities	Subclavian steal, thoracic aortic dissection
Neurologic	Mental status, focal neurologic findings	Seizure, stroke, or other primary neurologic disease

Ancillary Studies

The chief diagnostic adjunct in evaluating syncope is the 12-lead ECG (Table 12.2). It has an overall diagnostic yield of 2% to 9%.[4] In patients younger than 40 years without evidence of cardiovascular disease, the yield is far lower. It is warranted in all cases of syncope except in young, otherwise healthy patients with a clear history and setting for benign, neurally mediated (vasovagal) syncope. Dysrhythmias, preexcitation, and a shortened PR or prolonged corrected QT interval may be identified on the 12-lead ECG. Continuous limb lead monitoring of the ECG in the ED may also identify transient dysrhythmias. A right bundle branch block in association with ST elevation in leads V_1 through V_3 suggests Brugada syndrome. Ischemia or cardiac hypertrophy may be revealed. An ECG showing a right ventricular strain pattern may suggest pulmonary embolism, whereas diffuse ST elevation or electrical alternans helps diagnose pericarditis or pericardial tamponade.

Routine hematologic and urine studies have limited usefulness in the evaluation of syncope and are generally not indicated. When suggested by the history and physical examination findings, however, selective use of the complete blood count, serum electrolyte and glucose levels, urine drug screen, and pregnancy test may identify or exclude some uncommon causes of syncope (see Table 12.2). Chest radiography, bedside pulmonary ultrasound, with or without serum B-type natriuretic peptide (BNP) testing are warranted if heart failure is suspected or known by history. Other than seizure or intracranial hemorrhage, primary neurologic events rarely are the cause of apparent syncope. Cranial computed tomography is indicated only when intracerebral hemorrhage is suspected on the basis of sudden syncope with accompanying headache, particularly of sudden onset, or in the presence of abnormalities on neurologic examination.[4]

In otherwise healthy patients who are reliable historians, in whom a benign dysrhythmia such as episodic supraventricular tachycardia or atrial fibrillation is suspected, outpatient Holter or prolonged event monitoring of the ECG may be helpful. In patients with significant underlying cardiac disease or when a significant dysrhythmia is a possible cause of the syncope, continuous monitoring, echocardiography, or cardiovascular stress testing may be helpful in the inpatient or ED observation unit setting. Depending on the results of the initial evaluation, electrophysiologic studies or coronary artery imaging may be indicated. Electroencephalography is useful only when a seizure episode is suspected. Tilt table testing, although infrequently used in the United States, may have diagnostic value in older patients and children in whom chronic orthostatic hypotension is possible. Orthostatic vital signs, although unreliable in the evaluation of volume status, may be helpful when positional changes are accompanied by typical presyncopal symptoms and a significant rise in heart rate or fall in blood pressure. A schematic of selected diagnostic testing strategies for syncope is depicted in Figure 12.1.

TABLE 12.2

Ancillary Studies in Syncope

STUDY	INDICATION
12-lead ECG	Obtained as a screen on most patients; cardiac dysrhythmia, conduction abnormality, ischemia, cardiomyopathy
Orthostatic vital signs	Orthostatic hypotension or bradycardia
Hemogram	Anemia
Electrolytes, serum	Metabolic abnormality
Glucose, serum or blood	Hypoglycemia
D-dimer, serum	Pulmonary embolism
Cardiac biomarkers, serum	Myocardial infarction
B-type natriuretic peptide (BNP), serum	Congestive heart failure
Prolactin, serum	Seizure
β-hCG	Pregnancy
Toxicologic screen	Drug-related syncope
Arterial blood gas	Acid-base disturbance, hypoxemia
Chest x-ray examination	Thoracic aortic dissection, congestive heart failure
Cranial CT or MRI	New-onset or focal seizure, trauma, intracranial hemorrhage
Echocardiography	Cardiac outflow obstruction, tamponade, thoracic dissection
Ventilation-perfusion scan	Pulmonary embolism
CT pulmonary angiography	Pulmonary embolism, thoracic aortic dissection
Abdominal ultrasound or CT	Abdominal aortic aneurysm
Pelvic ultrasound	Ectopic pregnancy
TESTS USUALLY PERFORMED AS PART OF INPATIENT OR OUTPATIENT EVALUATION	
Prolonged monitoring of the ECG	Dysrhythmia
Echocardiography	Heart failure, cardiomyopathy, valvular disease
Exercise and chemical stress ECG	Myocardial ischemia
Cardiac and coronary artery imaging	Myocardial ischemia
Electrophysiologic study	Dysrhythmia
Carotid ultrasound	Stroke, TIA
Head-up tilt table test	Orthostatic hypotension
Electroencephalography	Seizures

CT, Computed tomography; *ECG,* electrocardiogram; *β-hCG,* human chorionic gonadotropin; *MRI,* magnetic resonance imaging; *TIA,* transient ischemic attack.

DIAGNOSTIC ALGORITHM

The critical diagnoses to consider are listed in Box 12.3.The emergent causes of syncope are protean and are included in Box 12.1. Many other causes, such as neurally mediated and reflex-associated syncope, have benign mechanisms.After stabilization and assessment, the clinical features coupled with onset and recovery can suggest the cause (Table 12.3). A logical approach to the history, physical examination, and diagnostic testing is depicted in Figure 12.2. The emphasis is on risk stratification because the short-term mortality risk in syncope is primarily related to structural cardiac disease, heart failure, and dysrhythmias.

EMPIRICAL MANAGEMENT

Syncope is by definition a transient event, so most patients are asymptomatic on presentation. Patients with significantly abnormal vital signs, recurrent syncope, or associated symptoms of a concerning nature, such as chest pain, hypotension, abdominal or back pain, or shortness of breath, should undergo rapid evaluation.

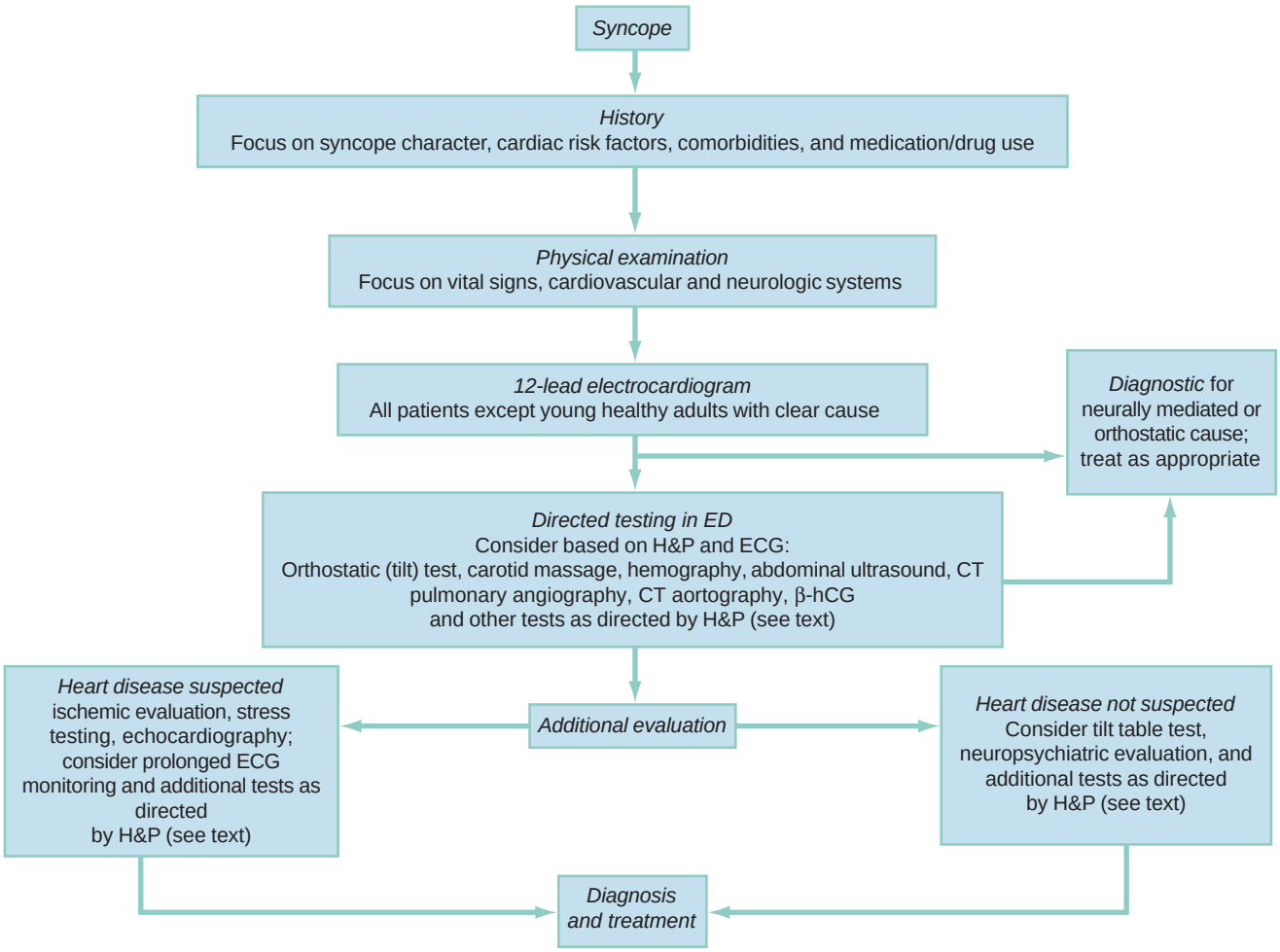

Fig. 12.1. Management algorithm for patients with syncope. *CT,* Computed tomography; *ECG,* electrocardiography; *β-hCG,* human chorionic gonadotropin; *H&P,* history and physical (examination).

BOX 12.3

Critical Diagnoses to Consider in Syncope

Myocardial infarction
Life-threatening dysrhythmias
Thoracic aortic dissection
Critical aortic stenosis
Hypertrophic cardiomyopathy
Pericardial tamponade
Abdominal aortic aneurysm
Massive pulmonary embolism
Subarachnoid hemorrhage
Stroke (cerebrovascular accident)
Toxic-metabolic derangements
Severe hypovolemia or hemorrhage
Ruptured ectopic pregnancy
Sepsis

Patients with critical diagnoses are stabilized in the ED and admitted to the intensive care unit (ICU) or other appropriate inpatient unit. Those with emergent diagnoses are typically admitted to telemetry units or, in selected cases, ED observation units capable of expedited cardiovascular risk stratification strategies, such as a cardiac stress test. Patients with nonemergent diagnoses can be treated as outpatients, generally in a primary care setting.

Multiple guidelines and decision rules have been proposed to aid in risk stratification and, although derivation studies have shown promise, none have performed acceptably in rigorous validation testing.[5-9] Existing prediction rules should not be strictly applied because they fail to show superior sensitivity, specificity, or prognosis for short-term outcomes when compared to the emergency clinician's clinical judgment (gestalt).[2,10,11] However, prediction rules provide a useful framework for estimating short- and medium-term risk and can inform clinical decision making (Box 12.4)

Hospitalization is required for patients with chest pain, unexplained shortness of breath, history of congestive heart failure, or significant valvular disease.[6] Patients with electrocardiographic evidence of ventricular dysrhythmias, ischemia, significantly prolonged QT interval, or new bundle branch block are also generally admitted.[11] The emergency clinician should consider monitoring patients with any of the following indications: age older than 65 years, preexisting cardiovascular or congenital heart disease, family history of sudden death, serious comorbidities such as diabetes, or exertional syncope.

The ED evaluation of syncope is often inconclusive. After a history, physical examination, and 12-lead ECG, up to 50% of patients do not have a firm diagnosis.[11] A stepwise algorithmic approach can improve diagnostic accuracy. Men younger than 45 years and women younger than 55 years and without worrisome symptoms, signs, or electrocardiographic findings are generally at very low risk for adverse outcome and can be treated on an outpatient basis. The recurrence rate while driving is less than 1%,

TABLE 12.3

Clinical Features of Common and Serious Causes of Syncope

CAUSE	ONSET AND RECOVERY	FEATURES
Dysrhythmia	Typically, abrupt onset and rapid recovery	Classic presentation uncommon; past cardiac history, risk factors for CAD more common in older adults; implanted pacemaker or cardioverter-defibrillator
Cardiac outflow obstruction	Exertion causes abrupt symptoms; rapid recovery with rest	Murmurs not always audible; mechanical valves warrant close monitoring
Myocardial infarction	Exertion or at rest; recovery often incomplete with chest pain persisting	Past cardiac history, risk factors for CAD; chest pain and shortness of breath common but frequently absent in diabetics and older adults
Pulmonary embolism	Abrupt onset; recovery often incomplete with dyspnea persisting	Chest pain, dyspnea, hypercoagulable state, DVT, pregnancy
Thoracic aortic dissection	Spontaneous; recovery often incomplete with chest or upper back pain persisting	Tearing chest pain; associated with hypertension, Marfan syndrome, cystic medial necrosis
Abdominal aortic aneurysm	Spontaneous onset; recovery often incomplete, with abdominal pain persisting	Abdominal or low back pain; associated with peripheral vascular disease
Pericardial tamponade	Penetrating chest trauma or thoracic cancers	Beck's triad of hypotension, JVD, muffled heart sounds
Anomalous left coronary artery	Onset with exercise, Valsalva maneuver	Left coronary artery arises from pulmonary artery; usually detected in childhood
Subarachnoid hemorrhage	Rapid onset; sentinel event may resolve	Focal neurologic findings; thunderclap—worst headache; nuchal rigidity
Vertebrobasilar insufficiency	Posture change or neck movement	Vertigo, nausea, dysphagia, dysarthria, blurry vision common associated symptoms
Hypovolemia	Bleeding, emesis, heat stress, dehydration; gradual onset	Orthostatic hypotension
Anemia	Bleeding, often occult or gradual from menses or gastrointestinal sources; iron deficiency or decreased red blood cell production	Orthostatic hypotension commonly associated
Hypoglycemia	Gradual onset; incomplete spontaneous recovery	Diabetes, ingestion or injection of hypoglycemics or insulin; diaphoresis, confusion, anxiety
Hypoxemia	Usually gradual onset; spontaneous recovery if asphyxiating circumstance is reversed	Carbon monoxide, natural gas, sewer gas, bleach-ammonia mix
Subdural hematoma	Onset with or after trauma (which may be trivial in high-risk patients)	Older adults, alcoholics, patients on anticoagulants at greater risk
Air embolus	Diving	Hyperbaric oxygen a key treatment
Pulmonary hypertension	Associated with myocardial infarction or pulmonary embolus	Risk factors for myocardial infarction or pulmonary embolism
Drug syncope	Medication associated with syncope	Consider illicit and alternative drug use; older adults at risk for polypharmacy, drug interactions
Ruptured ectopic pregnancy	Patient often unaware of pregnancy	Abdominal pain, abnormal tenderness; positive β-hCG test
Sepsis	Overt or insidious infectious prodrome	Fever, markers of infection
Seizure	Abrupt or with aura; postictal state common	Past history common
Carotid sinus sensitivity	Carotid sinus sensitivity; rapid onset and recovery	Shaving, necktie, sudden neck movement; carotid massage may provoke symptoms
Reflex syncope	Gastrointestinal, genitourinary, or thoracic stimulation	Urination, defecation, cough, eating, swallowing, weightlifting
Neurally mediated (vasovagal)	Emotion, pain are common triggers; upright posture; gradual onset; rapid recovery once supine	Prodrome of lightheadedness, graying or blurring of vision, nausea, sweats common
Hyperventilation	Emotion, pain; gradual onset; patient often unaware of rapid respirations	Perioral tingling, carpopedal spasms, extremity numbness
Narcolepsy	Often spontaneous	Known history
Basilar artery migraine	Specific triggers often known to patient	Visual prodrome often absent; more common in young women; vertigo and nausea common
Trigeminal or glossopharyngeal neuralgia	Sudden onset; specific triggers often known to patient	Lancinating pain in characteristic location

TABLE 12.3

Clinical Features of Common and Serious Causes of Syncope—cont'd

CAUSE	ONSET AND RECOVERY	FEATURES
Subclavian steal	Moving affected arm	Thoracic outlet syndrome
Psychogenic	Variable	Anxiety or psychiatric history; diagnosis by examining symptom pattern and excluding organic cause
Breath-holding	Deliberate breath-holding	Usually toddlers or young children
Drop attack	Unpredictable	Not true syncope—no loss of consciousness; usually older adults; loss of tone, ataxia, vertigo

CAD, Coronary artery disease; *DVT,* deep vein thrombosis; *hCG,* human chorionic gonadotropin; *JVD,* jugular venous distention; *TIA,* transient ischemic attack.

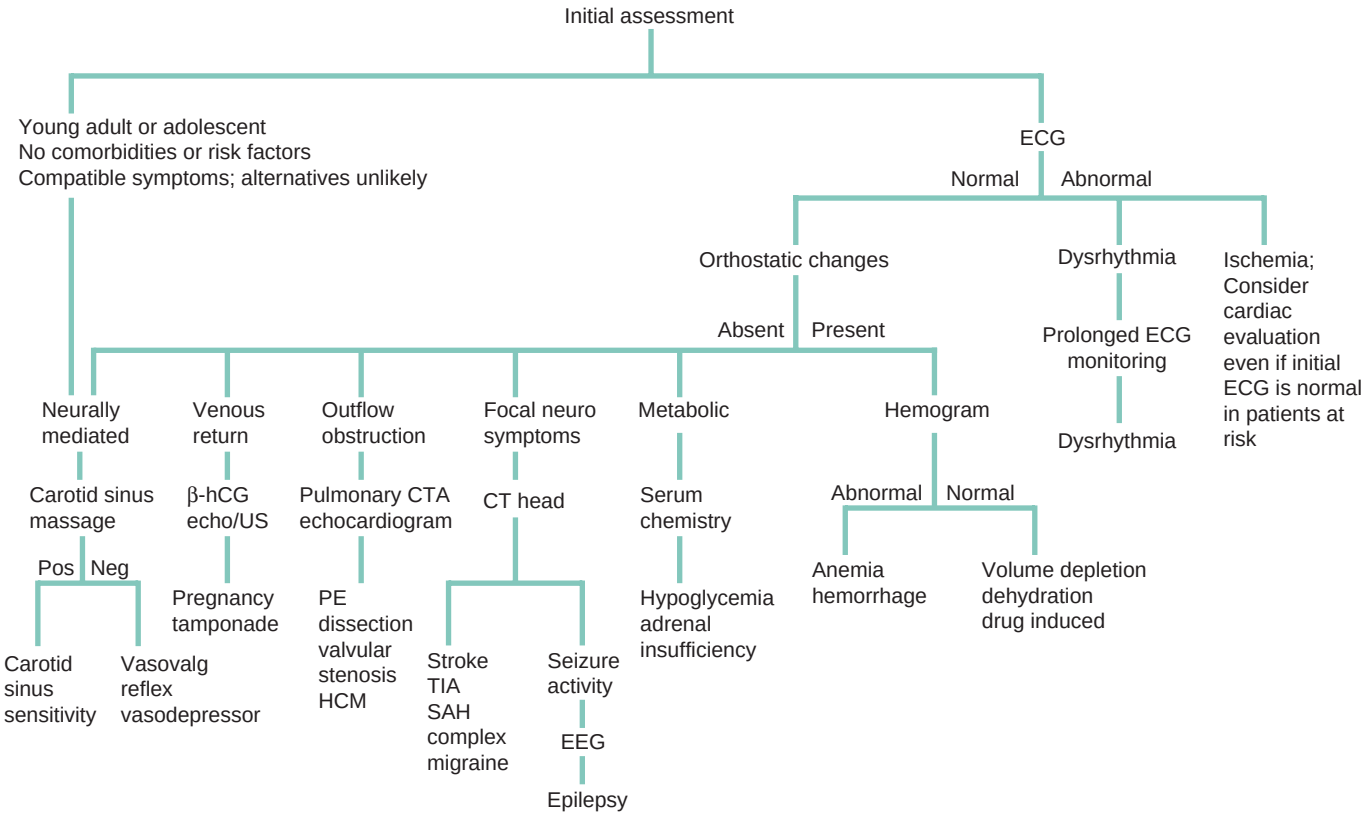

Fig. 12.2. Diagnosis algorithm for syncope. *β-hCG,* human chorionic gonadotropin; *CTA,* computed tomography angiography; *EEG,* electroencephalography; *HCM,* hypertrophic cardiomyopathy; *Neg,* negative; *PE,* pulmonary embolism; *Pos,* positive; *SAH,* subarachnoid hemorrhage; *TIA,* transient ischemic attack; *US,* ultrasound.

BOX 12.4

Selected Potential Markers of Increased Short-Term Risk[a]

Age > 65 yr
Male gender
History of congestive heart failure
History of cardiovascular disease or serious dysrhythmia
History of structural heart disease
Family history of early (<50 yr) sudden death
Syncope without prodrome
Exertional syncope
Syncope during supine position
Dyspnea or shortness of breath
Hypotension—systolic blood pressure < 90 mm Hg
Abnormal ECG
Anemia with hematocrit <30% or hemoglobin <90 g/L

[a]Identified from proposed prediction rules and published guidelines. Markers have not performed sufficiently well in rigorous validation studies to be recommended as conclusive indicators of short-term risk, however, they may inform clinical decision-making. See text.

and long-term mortality is comparable to age- and gender-matched cohorts, so discharged patients generally should not be restricted from this activity. The risk while engaging in other activities, such as working at heights, has not been studied.

KEY CONCEPTS

1. The pathophysiology of syncope is dysfunction of both cerebral hemispheres or the brainstem (reticular activating system), usually from acute hypoperfusion. Reduced blood flow may be regional (cerebral vasoconstriction) or systemic (hypotension). Loss of consciousness results in loss of postural tone, with the resulting syncopal episode.
2. Presyncope (near-syncope) or lightheadedness are less severe symptoms and may be considered on a continuum with syncope and share causes, mechanisms, and outcomes.
3. The potential causes of syncope are protean. The first differential diagnostic consideration is to distinguish syncope from other causes of an apparent sudden loss of consciousness, especially seizure and uncommon disorders such as cataplexy.
4. Most cases of syncope arise from benign causes, so the history is largely focused on identifying those cases caused by serious pathology. The past medical history, particularly cardiovascular disease and heart failure, is a key factor in determining future risk of morbidity and mortality.
5. The physical examination of syncope focuses primarily on the elements affecting the cardiovascular and neurologic systems.
6. The chief diagnostic adjunct in evaluating syncope is the 12-lead ECG. It should be obtained on nearly all patients. Studies suggest an overall diagnostic yield of 2% to 9%.
7. Routine hematologic, chemistry, urine, and imaging studies have limited usefulness in the evaluation of syncope and are generally not indicated unless directed by specific factors in the history or physical examination.
8. Disposition of syncope patients can be informed through identification of factors suggesting increased risk of short-term mortality. Predication rules and scoring systems have not yet been validated or shown to be superior to physician gestalt and should not be used alone.
9. Hospitalization is required for patients with chest pain, unexplained shortness of breath, history of congestive heart failure, significant valvular disease, or serious ECG findings. Admission is recommended for patients with factors indicating high-risk of short-term mortality.
10. Men younger than 45 years and women younger than 55 years and without worrisome symptoms, signs, or electrocardiographic findings are generally at very low risk for adverse outcome and can often be treated on an outpatient.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 12: QUESTIONS AND ANSWERS

12.1. Which of the following statements regarding the epidemiology of syncope is true?

A. Of athletes who die during exercise, 30% have had a prior episode of syncope.
B. People younger than 65 years account for 50% of all patients admitted for syncope from the emergency department.
C. Syncope in adolescents is typically secondary to significant pathology.
D. Syncope in the general population has a prevalence of approximately 1%.
E. Women have an increased risk of recurrence of syncope.

Answer: A. The prevalence of syncope in the general population is approximately 19%. This accounts for 0.8% of emergency department (ED) visits. Approximately 32% of these patients are admitted, and people aged 65 years or older account for 80% of such admissions. Recurrence of syncope may be as high as 50% and is not associated with age or gender. Benign causes of syncope predominate in adolescents and young adults. Approximately 30% of athletes who die during exercise, however, have had a prior episode of syncope as a sentinel event.

12.2. Syncope resulting from serious pathology is usually caused by which of the following?

A. Cerebrovascular disease
B. Dysrhythmias and myocardial ischemia
C. Pulmonary embolism
D. Structural cardiac lesions
E. Toxic-metabolic abnormalities

Answer: B. The principal serious causes of syncope are dysrhythmias and myocardial ischemia. Cerebrovascular disease, principally subarachnoid hemorrhage, is less frequently encountered but equally serious. Toxic-metabolic abnormalities may induce syncope through alterations in blood pressure or cardiac rhythm. Structural cardiac lesions, such as critical aortic stenosis, and sudden interruption of right ventricular outflow by pulmonary embolism, can also cause sudden loss of consciousness.

12.3. Which of the following findings suggest that a patient presenting with syncope can be safely discharged from the ED?

A. Anemia
B. History of congestive heart failure (CHF)
C. Hypotension
D. Normal ECG findings
E. Shortness of breath

Answer: D. A normal electrocardiogram in a patient without other significant risk factors (eg, advanced age, preexisting congestive heart failure, shortness of breath) may be considered for outpatient disposition.

CHAPTER 13

Depressed Consciousness and Coma

Charles Lei | Clay Smith

PERSPECTIVE

Coma is defined as a state of profoundly decreased arousal, resembling sleep. Comatose patients exhibit variable reflex behaviors and cannot be aroused with external stimuli. Stuporous or lethargic patients have a decreased level of awareness and also may have a decreased level of consciousness, but these patients can be aroused with external stimuli.

Epidemiology

Depressed consciousness is commonly encountered in daily emergency medicine practice, affecting patients of all ages. Patients may present with a wide spectrum of severity, ranging from sleepiness to frank obtundation. Most cases are the result of a metabolic derangement, usually a glucose disorder or drug overdose or adverse effect, but other common causes include traumatic brain injury, systemic or central nervous system (CNS) infection, ischemic or hemorrhagic stroke, intracranial mass and, rarely, psychiatric illness. Patients with depressed consciousness represent true emergencies because the differential diagnosis includes life-threatening causes that must be rapidly diagnosed and reversed, if possible. An understanding of relevant neuroanatomy and pathophysiology facilitates our understanding of how consciousness is affected in the setting of disease (Fig. 13.1).

Pathophysiology

Consciousness refers to awareness of self and one's relation to the environment and consists of arousal and awareness. To maintain normal consciousness, the brain requires a constant flow of sensory input and the ability to process this information. Visual, auditory, olfactory, gustatory, visceral, and somatosensory inputs are all synthesized and interpreted by the brain simultaneously. Disruption in this flow of information or inability to process it may lead to depressed consciousness. This may occur at the cortical or subcortical level, and the clinical presentation varies considerably depending on the location of the insult.

Consciousness depends on intact cortical function. The cortex is responsible for the content of consciousness, or awareness. Meanwhile, arousal is initiated by the subcortical structures, including the brainstem nuclei, thalamus, basal forebrain, hypothalamus and, most notably, the ascending reticular activating system (ARAS). ARAS neurons are located predominately in the pons and midbrain, connect to the thalamus, and project to the cortex. Consequently, damage to the dorsal brainstem, thalamus, or axonal projections to the cortex, or extensive injury to bilateral cortices, may result in depressed consciousness or coma.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of depressed consciousness and coma is broad (Table 13.1) and potentially involves dysfunction in any area of the brain, from the cortex to the brainstem. It may be the result of a global insult causing massive cortical neuronal dysfunction or a small injury to a critical area of the brainstem responsible for arousal. Most cases have toxic, metabolic, or infectious causes; of these, toxins are the most common. Structural brain diseases account for the remainder of cases. Common, largely reversible causes of depressed consciousness and coma, along with their clinical findings and emergency treatment, are listed in Table 13.1.

Special consideration is needed for specific populations of patients. Older patients are often prescribed multiple medications and are subject to accidental overdose, drug-drug interactions, and adverse drug reactions. Seemingly minor infections, such as a urinary tract infection, upper respiratory infection, or viral gastroenteritis, may cause depressed consciousness or coma. In addition, immunocompromised patients are susceptible to opportunistic infections that are uncommon in the general patient population. Immunocompromise may result from acquired immunodeficiency syndrome (AIDS) or may be seen in patients receiving chemotherapy or biologic agents (eg, for rheumatologic illness or inflammatory bowel disease). Psychogenic causes of coma are uncommon, and caution is advised when making this diagnosis.

In practice, the cause of coma is often apparent from the history and physical examination, but keeping a broad initial differential diagnosis may prevent premature fixation that could lead to diagnostic error. Although the differential diagnosis is broad in an undifferentiated comatose patient, a careful history and clues from the physical examination will often lead to a short list of possibilities, focused evaluation, and rapid initiation of treatment.

Pivotal Findings

Symptoms

A patient with depressed consciousness is unlikely to provide a reliable history. Historical information elicited from alternate sources, such as witnesses, family members, friends, emergency medical services (EMS) personnel, or law enforcement officers, usually guides the diagnostic evaluation. The time course of the patient's alteration in consciousness should be established. An abrupt onset of coma suggests a stroke, seizure, cardiac event, or poisoning, whereas a more gradual onset of symptoms suggests an infectious process, metabolic disorder, or enlarging intracranial mass. EMS personnel are trained to gather information at the scene and can provide valuable details about the circumstances surrounding the discovery of the patient, such as the presence of empty pill bottles, suicide note, or possibility of environmental exposures.

Family members or caregivers may have information regarding the patient's recent symptoms, which can offer important diagnostic clues. For example, a preceding, severe, sudden-onset headache suggests an intracranial hemorrhage, cerebral venous sinus thrombosis, or cervical artery dissection, a preceding fever or infection may suggest encephalitis, or a history of depression may

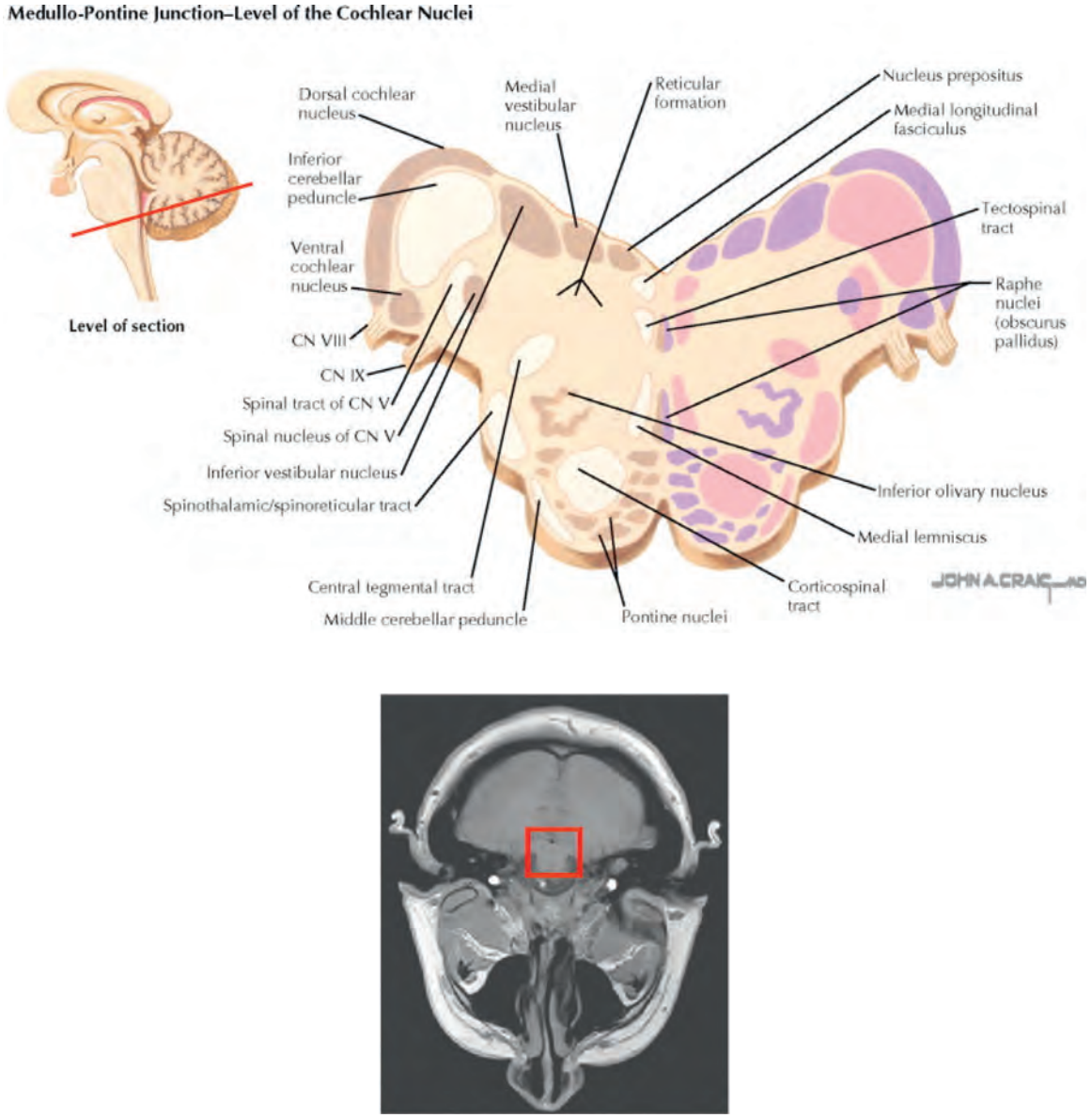

Fig. 13.1. Relevant anatomy showing the ascending reticular activating system and adjacent structures important for arousal. *CN*, Cranial nerve. (From www.netterimages.com. © 2018 Elsevier Inc. All rights reserved.)

suggest a drug overdose or adverse effects of psychotropic drugs. The patient's medication history should be carefully reviewed for any recent changes to her or his medication regimen or dosages. A history of taking over-the-counter or alternative medications should also be obtained.

The patient may be carrying additional pieces of information, such as a card in the wallet containing a list of medical conditions and/or medications or a medical alert bracelet or necklace. If the patient can be reliably identified by a family member or photo identification card, the medical record may be accessed for additional medical history. In addition, the patient's pharmacy may be contacted to obtain an accurate medication list.

Signs

After necessary stabilization measures have been instituted, the patient should be evaluated systematically, starting with an assessment of vital signs, including the oxygen saturation and blood glucose level. An elevated temperature suggests an infection but is also seen in some medical conditions and drug intoxications (eg, salicylates); a lower temperature is seen in environmental exposure but also in medical conditions such as sepsis and hypothyroidism. Hypotension with depressed consciousness indicates shock, with resultant cerebral hypoperfusion. Hypertension may be a sign of intoxication (eg, with cocaine or phencyclidine) or withdrawal (eg, from alcohol or opiates), cerebral or brainstem infarction, subarachnoid hemorrhage, posterior reversible encephalopathy syndrome (PRES), or elevated intracranial pressure (ICP). The combination of hypertension and bradycardia, known as the Cushing reflex, suggests severe elevation in ICP. Bradycardia may also be the result of a myocardial conduction abnormality, cardiac ischemia, or overdose from medications such as beta blockers, calcium channel blockers, cardiac glycosides, or clonidine. Many medical conditions can cause tachycardia and altered mental status, including sepsis, medications with stimulant or anticholinergic effects, severe anemia, hypovolemia, thyrotoxicosis, and acute structural brain injury.

Alterations in respiratory rate, pattern, or depth are usually caused by primary CNS abnormalities and toxic or metabolic disorders. Kussmaul's breathing consists of deep labored respirations

TABLE 13.1

Critical and Emergent Diagnoses of Coma

DIAGNOSIS	CAUSE	FINDINGS	TREATMENT	COMMENTS
METABOLIC				
Critical diagnoses	Hypoglycemia	Diaphoresis, insulin pump	$D_{50}W$, 50 mL	
	Hyperglycemia (DKA, HHS)	Tachypnea, nausea, vomiting, abdominal pain, dehydration	Isotonic fluid, insulin	
	Beri-beri	Hypothermia, hypotension	Thiamine, 100 mg IV	
	Adrenal crisis	Weakness, weight loss, hypotension, hyperpigmentation	D_5NS volume repletion, correct hypoglycemia; hydrocortisone, 100 mg IV	Expect hyperkalemia as well
	Pituitary apoplexy	Sudden headache, visual impairment, multihormonal dysfunction	Treat electrolyte abnormalities; hydrocortisone, 100 mg IV	May have pituitary adenoma; consult neurosurgery
	Sepsis	SIRS criteria, poor end-organ perfusion, delirium	Isotonic fluid, appropriate antibiotics, source control	
Emergent diagnoses	Wernicke's encephalopathy	CN III or VI palsies, nystagmus, sluggish pupillary response, anisocoria, gait instability, peripheral neuropathy	Thiamine replacement	Often seen in alcoholic or severely malnourished patient; seldom in hyperemesis gravidarum
	Hyponatremia	Progressive confusion, headache, anorexia, seizure	Free water restriction, hypertonic saline if seizing	Side effect of many medications
	Hyperammonemia	Lethargy, irritability, vomiting, seizure, poor feeding	Monitor protein intake, hemodialysis	Seen in liver disease, inborn error of metabolism, or as side effect of valproic acid or bariatric surgery
	Hypercalcemia	Lethargy, polyuria, AKI, constipation	Isotonic fluid	Causes nephrogenic DI; suspect malignancy
	Uremia	Nausea, vomiting, anorexia, fatigue, ammonia breath	Treat hyperkalemia, hemodialysis	Check ECG for hyperkalemia changes
	Hepatic encephalopathy	Fetor hepaticus, asterixis, ascites, stigmata of cirrhosis	Lactulose	Rule out sepsis, GI bleeding, SBP
	Thyrotoxic crisis	Fever, tachycardia, sweating, diarrhea	Isotonic fluid; propranolol 1 mg IV; propylthiouracil 600 mg PO	May also need to treat adrenal insufficiency
	Myxedema coma	Sluggishness, weight gain, edema, depression, hair loss, constipation	Thyroxine, 500 μg IV; hydrocortisone, 100 mg IV	May be precipitated by acute illness
	Heat stroke	Hyperpyrexia (>41.1°C [106°F]), flushing, exertion in heat, dehydration	Isotonic fluid, evaporative cooling	Also in older adults with comorbidities unable to seek cool environment
	High altitude cerebral edema	Rapid ascent, headache, confusion, psychosis	Rapid descent from altitude, hyperbaric oxygen; dexamethasone 10 mg IV	More common above 3500 m
TOXIC				
Critical diagnoses	Hypoglycemic agents	Older adult with worsening renal function, intentional overdose	$D_{50}W$, 50 mL; octreotide, 50–100 μg IV q8h if refractory hypoglycemia	Frequent lethal overdose in children with one pill; admit these patients, young or old
	Opioids	Stupor, apnea, miosis, needle tracks	Naloxone, 0.4 mg IV, up to 10 mg IV	Check skin for fentanyl patches
	Simple asphyxiants	Sudden lightheadedness, collapse, syncope	100% oxygen	Leaking CO_2 tank in enclosed space (eg, walk-in freezer); also nitrogen, helium, or argon gas
	Carbon monoxide	Combustion of fuel in enclosed space, headache, confusion, malaise, nausea	100% oxygen, hyperbaric oxygen per toxicology	Multiple people may be affected simultaneously; consider hyperbaric oxygen, especially during pregnancy
	Histotoxic hypoxia	Confusion, seizure, collapse, hydrogen sulfide smells like rotten eggs, cyanide (bitter almond smell) may result from combustion of plastics	100% oxygen; hydroxycobalamin, 70 mg/kg (or 5g) IV for cyanide	Consider cyanide in any house or car fire
	Methemoglobinemia	Use of medications, such as topical anesthetics or dapsone, cyanosis, pulse oximeter 85%	100% oxygen; methylene blue, 1–2 mg/kg IV	Also may result from severe diarrhea in children

Continued

TABLE 13.1

Critical and Emergent Diagnoses of Coma—cont'd

DIAGNOSIS	CAUSE	FINDINGS	TREATMENT	COMMENTS
Emergent diagnoses	Sedatives	Alcohol, benzodiazepines, and many others may be the culprit	Supportive	Avoid flumazenil
	Toxic alcohols	Nausea, vomiting, intoxication, early osmolar gap then anion gap acidosis, renal failure	Fomepizole, 15 mg/kg IV load; correct electrolyte abnormalities; isotonic fluid, 500 mL/h	Consult nephrology and toxicology to consider hemodialysis
	Inhalants	Often young, paint on hands and/or face, diplopia, slurred speech, cardiac dysrhythmia	Check ECG and monitor on telemetry; definitive airway if lip or tongue edema	Inhalants may be cold, may cause frostbite and edema to mucous membranes and hands
	Psychiatric medications	Hypotension, wide QRS	High-dose sodium bicarbonate for tricyclic antidepressant overdose	
	Anticonvulsants	Confusion, slurred speech, elevated drug levels	Supportive measures	Hyperammonemia may occur with valproic acid use
	Anticholinergics	Hyperpyrexia, pupillary dilation, urinary retention, visual hallucinations	Pyridostigmine rarely used; benzodiazepines may help in severe agitation	
	Clonidine	Bradycardia, hypotension, somnolence	Naloxone up to 10 mg IV, then 2–4 mg/h infusion	
	Beta blockers	Bradycardia, hypotension, hypoglycemia, seizure	Glucagon, 5 mg IV; epinephrine 1–4 μg/min; atropine 0.5 mg IV; transcutaneous or transvenous pacing	Discuss IV lipid infusion with toxicology
	Salicylates	Nausea, vomiting, tinnitus, delirium, hyperpnea, anion gap metabolic acidosis with mixed respiratory alkalosis	D_5W with 150 mEq/L sodium bicarbonate; correct hypokalemia; consider hemodialysis	May come from oil of wintergreen or other nonaspirin source
	Neuroleptic malignant syndrome	Hyperpyrexia, muscular rigidity, delirium, autonomic instability	Cooling, isotonic fluid, benzodiazepines	Pharmacologic paralysis with nondepolarizing agent if severe
	Serotonin syndrome	Multiple serotonergic agents, hypertension, tachycardia, hyperreflexia, muscular rigidity, tremor, nausea, diarrhea	Isotonic fluid; check CK; cyproheptadine 12 mg PO; benzodiazepines	Pharmacologic paralysis with nondepolarizing agent if severe
STRUCTURAL				
Critical diagnoses	Hemorrhage	Headache; hypertension; sudden onset; neurologic deficits	CT without contrast, reversal of anticoagulation	Early neurosurgical consultation for possible evacuation
	Cortical infarct	Sudden unilateral neurologic deficits	CT without contrast to rule out hemorrhage, neurology consultation, consider tPA and intraarterial clot retrieval	tPA contraindications must be excluded; tPA, 0.9 mg/kg IV, not to exceed 90 mg total dose; administer 10% of total dose as initial IV bolus over 1 min and remainder infused over 60 min
	Cerebellar infarct	Sudden vertigo; nausea; ataxia; dysarthria	Consider tPA as above	Neurosurgery consult if severe edema to consider decompressive craniectomy

AKI, Acute kidney injury; *CK*, creatine kinase; *CN*, cranial nerve; *CO_2*, carbon dioxide; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *$D_{50}W$*, 50% dextrose in water; *D_5NS*, 5% dextrose in normal saline; *DI*, diabetes insipidus; *DKA*, diabetic ketoacidosis; *ECG*, electrocardiogram; *EEG*, electroencephalogram; *EVD*, external ventricular drain; *GI*, gastrointestinal; *HHS*, hyperosmolar hyperglycemic state; *ICP*, intracranial pressure; *IV*, intravenous; *MRV*, magnetic resonance venogram; *PO*, per os (orally); *q8h*, every 8 hours; *SBP*, spontaneous bacterial peritonitis; *SIRS*, systemic inflammatory response syndrome; *tPA*, tissue plasminogen activator.

and can be seen in patients with severe metabolic acidosis, particularly diabetic ketoacidosis. Cheyne-Stokes respiration, a cyclic breathing pattern in which episodes of gradually increasing and then decreasing respiratory rate are separated by brief apneic periods, is associated with stroke and heart failure.

After an assessment of the patient's vital signs, a complete head to toe physical examination is performed. The head should be inspected for signs of trauma, such as a scalp laceration or hematoma, periorbital ecchymosis (raccoon eyes), retroauricular ecchymosis (Battle sign), hemotympanum, or cerebrospinal fluid (CSF) otorrhea or rhinorrhea. The hydration of the oral mucous membranes and quantity of salivary secretions provide information regarding the patient's volume status and may indicate a specific toxidrome. Laceration or contusion of the tongue suggests a recent seizure.

The patient's cervical spine is immobilized if there is suspicion for a neck injury. The presence of meningismus raises suspicion for meningitis, subarachnoid hemorrhage, and space-occupying CNS lesions. Stridor indicates obstruction of the large airways and is usually caused by infection, anaphylaxis, trauma, or foreign

body aspiration. Goiter in a patient with altered mental status suggests underlying myxedema coma or thyroid storm.

The cardiovascular system is evaluated for rate or rhythm disturbances, murmurs, and signs of volume depletion or overload. Abnormal lung sounds, retractions, and impairments in chest wall excursion indicate a pulmonary cause of depressed consciousness. Examination of the abdomen may reveal ascites or hepatosplenomegaly, suggesting a hepatic cause of coma or a pulsatile mass indicating the presence of an abdominal aortic aneurysm. Bladder distension and decreased bowel sounds suggest an anticholinergic toxidrome. A rectal examination should be performed to assess for gastrointestinal bleeding and retained foreign bodies.

The patient should be fully undressed to evaluate the skin for needle track marks, medication patches, rashes, and/or signs of trauma or infection. The presence of jaundice, palmar erythema, spider angiomata, or caput medusa in a patient with altered mental status should raise concern for hepatic encephalopathy. Petechiae or purpura can be seen in patients with meningococcemia, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, or vasculitis. Unusual odors emanating from the patient may provide additional diagnostic clues.

The main objectives of the neurologic examination are to determine the depth of coma, identify lateralizing deficits, and assess for brainstem dysfunction. The examination should proceed systematically and include an evaluation of the patient's level of consciousness, cranial nerves, brainstem reflexes, and motor responses. The patient's level of consciousness should be assessed with stimuli of increasing intensity. Auditory stimuli, such as a verbal cue or loud noise, may be used first. If the patient does not exhibit a response to auditory stimuli, noxious stimuli may be applied, such as a sternal rub, nail bed compression, or pressure on the medial aspect of the supraorbital ridge or posterior aspect of the mandibular ramus.

Level of consciousness may also be evaluated using a coma scale. The two most widely used scales are the Glasgow Coma Scale (GCS; Table 13.2) and Full Outline of UnResponsiveness (FOUR) score (Table 13.3).[1] Although originally developed for patients with traumatic brain injury, the GCS is commonly applied to all patients presenting with altered mental status. The GCS has considerable limitations because it does not account for abnormalities in brainstem function and may not detect subtle changes in the neurologic examination. The FOUR score has been validated in a variety of clinical settings and has higher interrater reliability than the GCS. The FOUR score incorporates a more detailed assessment of brainstem reflexes and has greater predictive value than the GCS in intubated patients and those with very low GCS scores.[2,3] The utility of both coma scales can be maximized by reporting the scores of each element and total score.

The cranial nerves are tested, with particular attention paid to the eyes. The size, reactivity, and symmetry of the pupils can provide important diagnostic clues. Pinpoint pupils that are minimally reactive or unreactive to light may be a result of damage to the pons, usually from hemorrhage or infarction. Pupillary dilation with loss of pupillary reactivity in a comatose patient should raise concern for an expanding intracranial mass with transtentorial herniation, resulting in compression of the oculomotor nerve or injury to the midbrain. Drugs and other toxins can also cause miosis (eg, opioids, clonidine, organophosphates) or mydriasis (eg, amphetamines, tricyclic antidepressants). Fixed, mid-size pupils can be seen in severe midbrain injury and may be the first sign of brain death.

Eye position and movement are also noted. Forced deviation of the eyes, usually in the horizontal plane, may indicate an ipsilateral hemispheric or contralateral pontine lesion. Seizures can also cause horizontal eye deviation, typically away from the cerebral lobe containing the seizure focus. Horizontal disconjugate gaze can be seen in patients who are sedated, drowsy, or intoxicated and in those with metabolic disorders. Disconjugate gaze in the vertical plane, also known as skew deviation, strongly suggests a lesion in the cerebellum or brainstem. Spontaneous conjugate roving eye movements indicate bihemispheric dysfunction and relatively intact brainstem. Nystagmus in an unresponsive patient may be a sign of nonconvulsive status epilepticus (NCSE), brainstem dysfunction, or overdose (eg, from anticonvulsants, lithium, ketamine, ethanol, phencyclidine).

A funduscopic examination may yield additional diagnostic information. The presence of a subhyaloid hemorrhage should raise suspicion for aneurysmal subarachnoid hemorrhage. Papilledema and retinal hemorrhages are associated with increased ICP and malignant hypertension. Ultrasound measurement of the optic nerve sheath diameter has been reported to predict the presence of elevated ICP accurately.[4]

Brainstem function is evaluated through the various brainstem reflexes, including the oculocephalic reflex (doll's eyes), oculovestibular reflex (cold caloric testing), corneal reflex, and gag reflex. Provided that there is no suspicion for cervical spine injury, the

TABLE 13.2

Glasgow Coma Scale

PARAMETER	RATING	SCORE
EYE OPENING		
Open before stimulus	Spontaneous	4
Open after spoken or shouted request	To voice	3
Open after fingertip stimulus	To pain	2
No opening at any time, no interfering factor	No response	1
Closed by local factor	Not testable (NT)	NT
BEST VERBAL RESPONSE		
Correctly gives name, place, and date	Oriented	5
Not oriented but communicates coherently	Confused	4
Intelligible single words	Inappropriate words	3
Only moans or groans	Incomprehensible sounds	2
No audible response, no interfering factor	No response	1
Factor interfering with communication	NT	NT
BEST MOTOR RESPONSE		
Obeys two-part request	Obeys commands	6
Moves hand across body or above clavicle to stimulus	Localizes pain	5
Bends arm at elbow rapidly, features not predominantly abnormal	Withdraws from pain	4
Bends arm at elbow, features clearly predominantly abnormal	Flexion to pain	3
Extends arm at elbow	Extension to pain	2
No movement in arms or legs, no interfering factor	No response	1
Paralyzed or other limiting factor	NT	NT

Modified from Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. Lancet 2:81–84, 1974.

TABLE 13.3

Full Outline of UnResponsivness (FOUR) Score

RESPONSE	SCORE
EYE RESPONSE	
Eyelids open or opened, tracking, or blinking to command	4
Eyelids open but not tracking	3
Eyelids closed but open to loud voice	2
Eyelids closed but open to pain	1
Eyelids remain closed with pain	0
MOTOR RESPONSE	
Thumbs-up, fist, or peace sign	4
Localizing to pain	3
Flexion response to pain	2
Extension response to pain	1
No response to pain or generalized myoclonus status	0
BRAINSTEM REFLEXES	
Pupil and corneal reflexes present	4
One pupil wide and fixed	3
Pupil or corneal reflexes absent	2
Pupil and corneal reflexes absent	1
Absent pupil, corneal, and cough reflex	0
RESPIRATION	
Not intubated, regular breathing pattern	4
Not intubated, Cheyne-Stokes breathing pattern	3
Not intubated, irregular breathing	2
Breathes above ventilator rate	1
Breathes at ventilator rate or apnea	0

oculocephalic reflex is tested by rotating the head from side to side in the horizontal plane. In a patient with a normally functioning brainstem, the eyes will move in a direction opposite the head movement and appear to maintain visual fixation on a single point in space. Brainstem dysfunction should be suspected if the eyes remain in midposition with respect to the bony orbits and move in unison with the head. Conscious patients can usually suppress the oculocephalic reflex. Caloric testing of the oculovestibular reflex is a more sensitive test for brainstem dysfunction and cannot be resisted voluntarily. After cerumen impaction and tympanic membrane perforation have been excluded, the patient's head is elevated to 30 degrees up from the horizontal and ice water is infused into the external auditory canal. In a comatose patient with an intact brainstem, the stimulus results in sustained conjugate deviation of the eyes toward the ear being irrigated. Absence of a response to the irrigation should raise suspicion for brainstem dysfunction. In response to caloric testing, conscious patients experience not only tonic deviation of the eyes toward the stimulated ear but also nystagmus (with the fast phase away from the side of irrigation), severe vertigo, nausea, and vomiting. The presence of nystagmus is suggestive of wakefulness and psychogenic unresponsiveness.

The corneal reflex is tested by gently touching the edge of the cornea with a wisp of cotton and observing for blinking of the eyes. The gag reflex is elicited by stimulating the posterior pharynx and observing for brisk elevation of the soft palate and bilateral contraction of the pharyngeal muscles. Because the gag reflex is symmetrically diminished or absent in a subset of normal individuals, the test is most informative when the response is asymmetric.

Motor function is assessed by observing any spontaneous movements and testing the motor responses to verbal commands and noxious stimuli. Purposeful movements should be distinguished from reflex activity. Examples of purposeful movements include following commands and localization of or withdrawal from painful stimuli. Reflexive responses include decorticate posturing, characterized by adduction of the shoulders and flexion of the elbows, wrists, and fingers, and decerebrate posturing, which consists of shoulder adduction, elbow extension, and forearm pronation. Although usually associated with focal brain lesions, posturing reflexes can also be seen in systemic conditions affecting the CNS, such as toxic and metabolic disorders.

Muscle tone, assessed by passive manipulation of the extremities, is usually decreased in structural brain disease but not affected in most metabolic conditions. Generalized muscle rigidity occurs in patients with neuroleptic malignant syndrome and malignant hyperthermia. Myoclonus may be a sign of NCSE, hepatic or renal dysfunction, or hypercarbic respiratory failure.

Ancillary Testing

Laboratory evaluation of a patient with depressed consciousness should begin with point of care measurement of the serum glucose level to confirm or exclude hypoglycemia. A comprehensive metabolic panel should be carried out to identify metabolic acidosis, renal or hepatic dysfunction, and any electrolyte derangements, such as hyponatremia or hypercalcemia. In a patient with metabolic acidosis, a widened anion gap suggests possible ketosis (eg, from diabetes, alcohol ketoacidosis, starvation), lactic acidosis (eg, from sepsis, hypoperfusion, cyanide poisoning), uremia, or intoxication (eg, with methanol, ethylene glycol, salicylates). Anion gap in the context of poisoning is discussed in Chapter 139. A complete blood count may reveal profound anemia or thrombocytopenia, but this would not account for the depressed mental status, unless as a cause of intracranial hemorrhage or severe hypotension. Although an elevated white blood cell count can be a marker of infection, it is nonspecific and rarely helpful in discerning the cause of altered mental status. An abnormally low white blood cell count, however, suggests an immunocompromised state and should raise suspicion for infection or malignancy. An elevated prothrombin or partial thromboplastin time can be seen in blood dyscrasias, liver disease, and anticoagulant use.

Urinalysis can provide valuable diagnostic information. A high urine specific gravity suggests dehydration. Glucosuria can be seen in diabetic ketoacidosis and hyperosmolar hyperglycemic state. Detection of white blood cells, leukocyte esterase, and nitrites in the urine indicates a urinary tract infection. The presence of calcium oxalate crystals is associated with ethylene glycol ingestion.

Serum salicylate and acetaminophen levels should be determined if toxicity is suspected, such as a case of an unexplained anion gap acidosis or hepatic failure. Other toxicologic tests, such as the serum ethanol level and urine drug screen, are unlikely to significantly affect the acute management of a patient with depressed consciousness. Blood gas analysis can be used to rapidly assess acid-base balance and identify hypoxia or hypercarbia. Co-oximetry should be included if carbon monoxide poisoning or methemoglobinemia is suspected. Due to its poor sensitivity and specificity, the serum ammonia level has little utility in the evaluation of altered mental status. Ammonia concentrations can be elevated in a variety of nonhepatic conditions, such as valproic acid toxicity and inborn errors of metabolism, and can be normal

in patients with hepatic encephalopathy. Thyroid function studies can help confirm myxedema coma or thyrotoxicosis. Blood and urine cultures should be tested if there is concern for infection. CSF analysis should be undertaken if CNS pathology such as infection or hemorrhage is suspected. Neuroimaging should be performed prior to lumbar puncture to exclude an intracranial mass lesion.

Noncontrast computed tomography (CT) of the brain, because of its wide availability and rapid acquisition, is the imaging modality of choice for the initial evaluation of a patient with depressed consciousness. It should be obtained in patients with preceding head trauma, those with suspected structural brain disease, and those in whom the diagnosis is not identified by other means. Noncontrast cranial CT may identify intracranial hemorrhage, hydrocephalus, cerebral edema, or mass lesion, and may reveal signs of ischemic stroke or elevated ICP. CT angiography (CTA) of the head and neck should be performed if brainstem dysfunction is suspected on neurologic examination. It can provide valuable information regarding the cerebral vasculature and aid in the diagnosis of an intracranial aneurysm, arteriovenous malformation, cerebral venous thrombosis, and basilar or vertebral artery stenosis or occlusion.

Due to bone artifact, CT has limited utility in the visualization of the posterior fossa. In comparison, magnetic resonance imaging (MRI) of the brain is better for identifying structural lesions in this region. MRI also provides greater anatomic differentiation of cortical and brainstem structures and is superior to CT for detecting early ischemic stroke, visualizing the arterial system, and identifying infectious, inflammatory, and neoplastic processes. However, MRI is less practical than CT because of cost, accessibility, and the length of time needed to acquire each study, which limits the ability to monitor and access a critically ill patient.

Chest radiography may identify pneumonia, pneumothorax, tumor, or foreign body, and may reveal signs of aortic dissection or congestive heart failure.

An electrocardiogram may diagnose cardiac ischemia, a conduction block, or an arrhythmia. It may also provide supporting evidence for an electrolyte abnormality (potassium or calcium), a drug ingestion (tricyclic antidepressant), hypothermia, or structural brain injury.

Electroencephalography (EEG) should be performed to evaluate for NCSE, which can manifest de novo and present with coma or persist after cessation of convulsive seizures.[5] An EEG is also indicated in seizure patients who have received sedative or paralytic medications to assess for ongoing seizure activity. See Chapter 92.

DIAGNOSTIC ALGORITHM

Critical and emergent diagnoses that require immediate consideration, evaluation, and treatment are listed in Table 13.1. Information from the history, physical examination, and initial battery of tests guides the direction of imaging and additional testing. Neuroimaging is performed next, but not before treating emergent causes, such as hypoglycemia or opioid toxicity. An algorithmic approach to the diagnosis and management of patients with depressed consciousness is presented in Fig. 13.2. This approach allows diagnostic assessment and therapeutic intervention to proceed in parallel.

EMPIRICAL MANAGEMENT

The management of comatose patients should begin immediately on arrival, before a definitive diagnosis is established. Management prioritizes oxygenation and perfusion while the diagnostic evaluation is initiated. A complete set of vital signs, including pulse oximetry, should be obtained. Care should be taken to avoid hypoxia and hyperoxia because both are deleterious.[6] A goal oxygen saturation of 96% is acceptable and avoids both extremes. Intravenous (IV) access is established and cardiac monitoring initiated. A rapid bedside glucose level is determined and hypoglycemia treated immediately. Rapid treatment of hypoglycemia will lead to reversal of coma due to neuroglycopenia. An empirical trial of naloxone will lead to rapid reversal of opioid toxicity, as well as several other medication overdoses (see Chapter 156). We recommend administering an initial naloxone dose, 0.4 mg IV, and increasing up to 10 mg IV if necessary. Effective reversal with naloxone may obviate the need for endotracheal intubation in these patients. In cachectic malnourished patients, women with severe hyperemesis gravidarum, alcoholics, or other patients with suspected thiamine deficiency, empirical administration of thiamine 100 mg IV is recommended.

If initial management efforts do not promptly result in improvement, the patient's ability to protect and maintain a patent airway should be reassessed. Failure to oxygenate, ventilate, or protect the airway are indications for intubation. GCS scores inversely correlate with aspiration risk, but GCS alone does not accurately predict which patients will maintain protective airway reflexes. Patients with a GCS score higher than 8 cannot be considered safe or not at risk for aspiration.[7] Consider the history, examination, and ability of future providers caring for a patient to perform an airway intervention successfully, should it become necessary, when making the decision to intubate or not. We recommend endotracheal intubation in most patients with coma and a GCS score of 8 or lower and for any patient thought not to be capable of sustained airway self-maintenance and protection.

Prior to intubation, a detailed neurologic examination is performed, with particular attention to assessing brainstem function. Once the airway has been reassessed and secured as needed, we recommend treating patients with undifferentiated coma and clinical suspicion for meningitis (ie, fever, other signs of infection, sepsis, rash) empirically with ceftriaxone, 2000 mg IV, prior to CT imaging. Additional antibiotics such as vancomycin may be added if local pneumococcal resistance rates are high, an indwelling venous catheter is present, or a hospital-acquired pathogen is suspected. If encephalitis is suspected, empirical acyclovir, 800 mg IV, is recommended.

If the head CT or CTA is diagnostic, notify the appropriate consultant (neurosurgery or neurology) and arrange for definitive management. In all patients with brain injury of any type, especially those with signs of herniation, general principles of neuroprotective care are recommended (Box 13.1; see Chapter 7).

If the head CT or CTA is nondiagnostic, determine if there are any other emergent conditions that could be treated and potentially reversed. The differential diagnosis is listed in Fig. 13.2 and may be easily recalled using the mnemonic shown.

Once the initial diagnostic evaluation has been completed and initial management is underway, most patients will require definitive treatment in an intensive care unit. The disposition will

BOX 13.1

Principles of Neuroprotective Resuscitation

- Elevate head of bed to 30° if there is no suspicion for thoracic spine injury.
- Avoid constricting ties or collars around neck.
- Avoid hypoxia and hyperoxia.
- Maintain end-tidal CO_2 at 35 cm H_2O.
- Avoid hypotension.
- Avoid hyperthermia.
- Prevent and treat seizure activity.

CO_2, Carbon dioxide; *H_2O*, water.

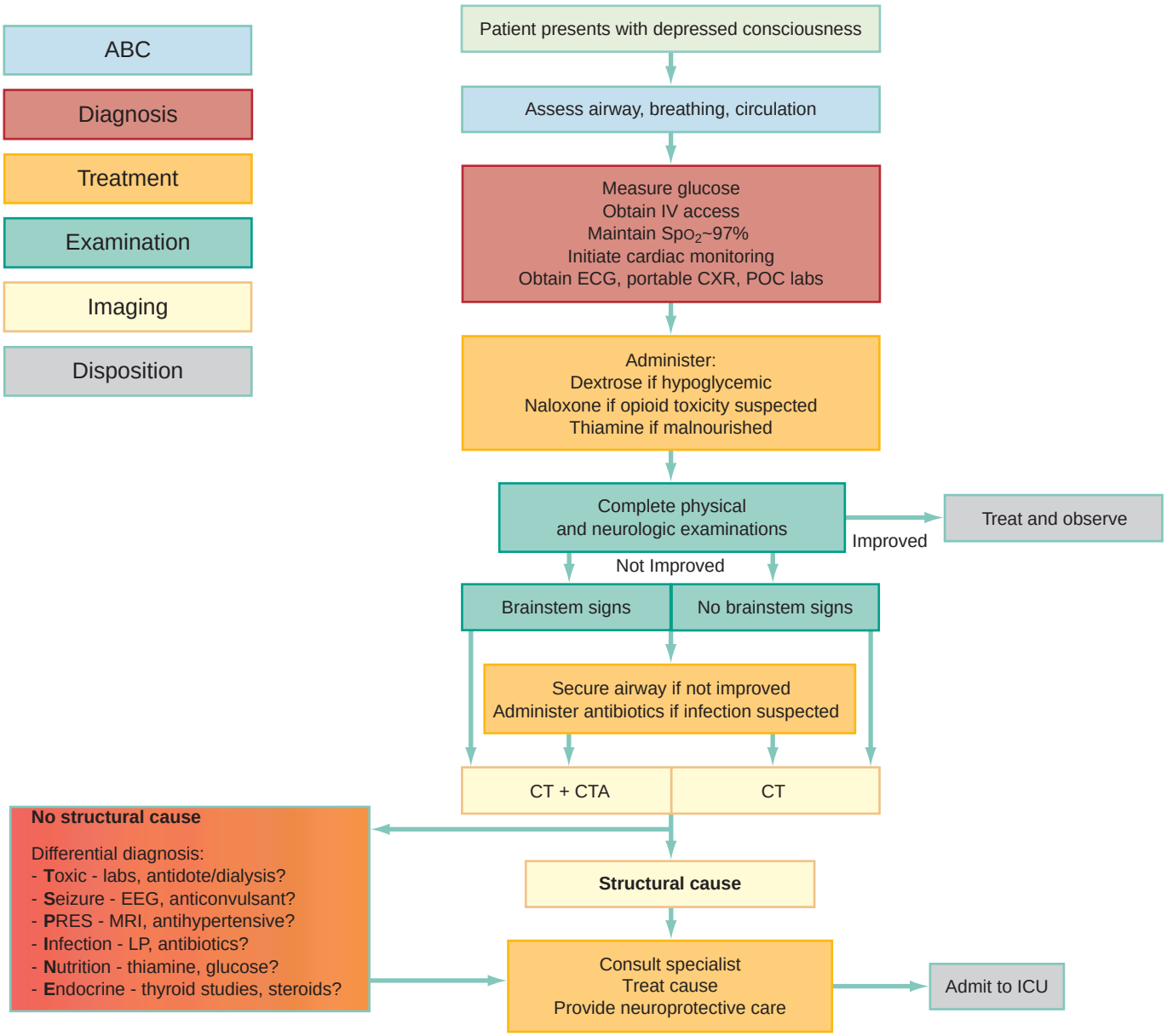

Fig. 13.2. Algorithm for diagnostic and management approach to depressed consciousness and coma. *ABC*, airway, breathing, circulation; *CT*, computed tomography; *CTA*, computed tomography angiography; *CXR*, chest x-ray; *ECG*, electrocardiogram; *EEG*, electroencephalogram; *ICU*, intensive care unit; *IV*, intravenous; *LP*, lumbar puncture; *MRI*, magnetic resonance imaging; *POC*, point of care; *PRES*, posterior reversible encephalopathy syndrome; *SpO_2*, oxygen saturation.

depend on what is discovered during the evaluation. Patients found to have a structural abnormality on imaging potentially requiring neurosurgical intervention must be rapidly transferred to a facility with neurosurgical capabilities if not available at the initial location.

Many patients with toxic or metabolic causes (eg, opioid overdose, hypoglycemia) of depressed consciousness may be rapidly treated and stabilized in the emergency department and some may be safely discharged home after a period of observation. Patients with alcohol or recreational drug intoxication and no other discernible cause of depressed consciousness may be discharged when clinically sober. Most patients, even if the level of consciousness markedly improves with initial treatment, will require admission to the hospital or observation unit.

KEY CONCEPTS

- Consciousness consists of arousal (subcortical) and awareness (cortical).
- Damage to the dorsal brainstem, thalamus, or axonal projections to the cortex, or extensive injury to bilateral cortices, may result in depressed consciousness or coma.
- Toxic, metabolic, and infectious causes of coma make up 65% of cases; of these, toxins are the most common. Structural brain diseases make up most of the remaining 35% of cases.
- An abrupt onset of coma suggests a stroke, seizure, cardiac event, or poisoning.

KEY CONCEPTS—cont'd

- A patient with depressed consciousness is unlikely to provide a reliable history. Historical information should be elicited from other available sources, such as EMS and family.
- The neurologic examination includes an evaluation of level of consciousness, cranial nerves, brainstem reflexes, and motor responses.
- Pinpoint pupils may represent a pontine infarct or intoxication from opioids, clonidine, or cholinergic medications.
- Hypoglycemia and hypoxia are two easily identified and reversible causes of coma.
- An empirical trial of naloxone will lead to rapid reversal of opioid toxicity and other medication overdoses.
- Nonconvulsive status epilepticus should be suspected in cases of coma of undetermined cause and is diagnosed by EEG.
- Most patients with coma will require intensive care. Transfer patients if the cause of coma is not treatable in the current facility (eg, structural lesion requiring neurosurgery).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 13: QUESTIONS & ANSWERS

13-1. In infants, what is the most common cause of a depressed level of consciousness?
- **A.** Accidental toxic ingestion
- **B.** Hypoxia
- **C.** Infection
- **D.** Inborn errors of metabolism
- **E.** Physical abuse

Answer: C. Causes of a depressed level of consciousness vary with patient age. In infants, infectious causes of depressed consciousness are most common; however, trauma secondary to physical abuse and metabolic derangements from inborn errors of metabolism can be seen. Accidental toxic ingestions are often seen in younger children but are very uncommon in infants. Young adults and adolescents are more likely to present after recreational drug use or trauma. Finally, older adults are particularly vulnerable to infectious causes, medication changes, and alterations in their living environments.

13-2. What Glasgow Coma Scale (GCS) score would be given to an adult patient who opens the eyes to painful stimuli, speaks in an incomprehensible manner, and withdraws to pain?
- **A.** 6
- **B.** 7
- **C.** 8
- **D.** 9
- **E.** 10

Answer: C. Using the GCS, this patient would receive 2 points for eye opening to pain, 2 points for verbal response consisting of incomprehensible words, and 4 points for withdrawing to painful stimuli.

13-3. What GCS score would be given to a pediatric patient who opens the eyes and flexes the extremities to painful stimuli and who is persistently irritable?
- **A.** 6
- **B.** 7
- **C.** 8
- **D.** 9
- **E.** 10

Answer: C. Using the GCS, this patient would receive 2 points for eye opening to pain, 3 points for persistently being irritable, and 3 points for flexion to painful stimuli.

13-4. Awareness of one's self or surroundings defines which of the following?
- **A.** Cognition
- **B.** Consciousness
- **C.** Judgment
- **D.** Memory
- **E.** Orientation

Answer: B. Consciousness is defined as the awareness of one's self or surroundings; it is made up of arousal and cognition. Cognition is the combination of orientation, the accurate perception of what is experienced, judgment, the ability to process input data to generate more meaningful information, and memory, the ability to store and retrieve information.

CHAPTER 14

Confusion

J. Stephen Huff

PERSPECTIVE

The term *confusion* connotes an acute alteration in higher cerebral functions, such as memory, attention, or awareness. The ability to sustain and focus attention is impaired. Confusion is a symptom, not a diagnosis. The degree of confusion may fluctuate, as may the patient's level of consciousness. Implicit in the definition is a recent change in behavior. Chronic mental status changes such as dementia have a different clinical chronology. Other forms of altered mentation include states of diminished alertness on the coma spectrum; these presentations may result from some of the same pathophysiologic processes causing confusion and are discussed in Chapter 13. Confusion may range in severity from a mild disturbance of short-term memory to a global inability to relate to the environment and process sensory input. This extreme state is termed *delirium* (see Chapter 94).

Confusion has many causes, and an orderly approach is necessary to discover the causative diagnosis. The assessment of mental status and cognitive impairment in older emergency department (ED) patients is an important part of their evaluation and has been proposed as a key quality indicator by the Society for Academic Emergency Medicine Geriatric Task Force.[1] The absence of a chief complaint of altered mental status should not reassure the emergency clinician that an acute mental status change is absent. History from family or caregivers, structured physical examination, and use of a specific assessment tool may be needed to detect the presence of confusion.

Epidemiology

Physicians underestimate the incidence of confusion in patients. Confusion is often accepted as an incidental or secondary component of another condition. A patient with injuries from a motor vehicle crash or with dyspnea may be confused, but the primary condition overshadows the underlying abnormal mental status. When confusion exists as an isolated or unexplained finding, it is more likely to receive full and immediate consideration by the emergency clinician. Confusion is estimated to be present in 2% of ED patients, 10% of all hospitalized patients, and 50% of older hospitalized patients. Delirium in older ED patients is an independent predictor of increased mortality within 6 months.[2]

Pathophysiology

Conceptually, consciousness is divided into elements of alertness or arousal and elements constituting the content of consciousness. Confusion is largely a problem of the content portion of consciousness. Any underlying clinical process that disrupts optimal central nervous system (CNS) functioning can result in confusion. Global CNS dysfunction usually results from substrate deficiencies (eg, hypoglycemia, hypoxemia), neurotransmitter dysfunction, presence of, or withdrawal from a CNS drug or toxin, or circulatory dysfunction. Sepsis syndrome is also associated with encephalopathy.[3] Compounding this problem is the concept that the reserve of cognitive function varies from individual to individual; individuals with a preexisting impairment may become confused after even minor changes in their normal physiologic state.

DIAGNOSTIC APPROACH

Differential Considerations

Certain critical and emergent diagnoses require prompt recognition (Box 14.1). Four groups of disorders encompass most causes of confusion: (1) systemic diseases secondarily affecting the CNS; (2) primary intracranial disease,; (3) exogenous toxins; and (4) drug withdrawal states (Box 14.2).

In general, schizophrenia and other psychiatric disorders do not present with confusion and cognition, including orientation and attention, are normal in these patients unless psychosis or agitation is severe (see Chapter 100). The term *psychosis* implies a disorder of reality testing and thought organization severe enough to interfere with normal daily functioning. Psychosis is a nonspecific syndrome, and careful evaluation is required to differentiate between psychiatric and medical origins (eg, drug intoxication, other systemic process; Table 14.1).

Focal cortical dysfunction, such as from tumor or stroke, typically does not cause confusion although, occasionally, receptive or expressive dysphasia may be mistaken for confusion. Occasionally, other focal neurologic abnormalities may mimic a confusional state. A person with a new visual field deficit and visual neglect from stroke or intracranial mass may have difficulty ambulating in familiar surroundings and may be labeled as confused, but this reflects focal neurologic injury and not a confusional state from global CNS dysfunction. Frontal lobe dysfunction from stroke, subdural hematoma, or tumor may result in personality changes and the report of confusion by family or friends. Careful assessment of mental status assists in resolving the diagnostic dilemma.

Likewise, subcortical or brainstem dysfunction usually results in a diminished level of alertness and consciousness, not confusion. A person with a new visual field deficit and visual neglect may have difficulty ambulating in familiar surroundings and may be labeled as confused but, in this case, it reflects a focal neurologic injury. Frontal lobe dysfunction from stroke, subdural hematoma, or tumor may result in a change in personality that may be reported as confusion by family or friends.

Pivotal Findings

A patient with confusion is evaluated through a focused history, physical examination, and rapid bedside screening assessment tools. Response to specific therapies (eg, dextrose, naloxone) may identify critical causes. Additional evaluation may include laboratory testing and diagnostic imaging, which are usually confirmatory of one of a number of suspected conditions. Examples of pivotal historical findings that provide the key to the diagnosis include new medications, preceding infection, history of head trauma, history of seizures, and time course of symptom onset. Examples of pivotal physical findings include altered vital signs, evidence of head trauma, focal neurologic deficits, loss of

BOX 14.1

Critical and Emergent Diagnoses

CRITICAL
Failure to oxygenate
Failure to ventilate
Hypoglycemia
Elevated intracranial pressure with impending herniation

EMERGENT
Systemic diseases
- Electrolyte and fluid disturbance
- Endocrine disease—thyroid, adrenal

Note: These represent a partial diagnosis; causes are myriad. "Critical" in this case means conditions that need immediate assessment and correction within moments, such as oxygenation and ventilation problems or hypoglycemia. Because confusion represents central nervous system failure, other problems may be considered critical as well and may necessitate intensive care unit admission, depending on their severity.

BOX 14.2

Major Categories: *Differential Considerations*

Primary intracranial disease
Systemic diseases secondarily affecting the central nervous system
Exogenous toxins
Drug withdrawal

TABLE 14.1

Findings to Help Differentiate Between Organic and Functional Causes of Confusion

ORGANIC	FUNCTIONAL (PSYCHIATRIC)
HISTORY	
Acute onset	Onset over weeks to months
Any age	Onset age, 12–40 yr
MENTAL STATUS EXAMINATION	
Fluctuating level of consciousness	Alert
Disoriented	Oriented
Attention disturbances	Agitated, anxious
Poor recent memory	Poor immediate memory
Hallucinations—visual, tactile, auditory	Hallucinations, usually auditory
Cognitive changes	Delusions, illusions
PHYSICAL EXAMINATION	
Abnormal vital signs	Normal vital signs
Nystagmus	No nystagmus
Focal neurologic signs	Purposeful movement
Signs of trauma	No signs of trauma

attention, preservation of orientation, and presence of a toxic syndrome (so-called toxidrome).

Symptoms

Confusion is frequently reported by caregivers and family members rather than by the patient. Families may articulate the complaint as confusion but also may describe rambling, disorientation, speaking to persons not there, patient's inability to find his or her way around familiar surroundings, or simply "not being right." An essential goal of the history is to determine when the patient last exhibited normal thinking and behavior and what normal is for the particular patient.

The initial task in evaluating the patient is to define the symptoms and severity of confusion. The specific behaviors that are of concern to the patient or caregivers should be delineated. Often, the family is the most valuable source for information; a physician or other caregiver with an established relationship with the patient also may be helpful. The duration of the confusion, recent changes in medications, and recent illnesses are important points in the clinical history. Hallucinations are not unique to psychiatric illness and can commonly occur in confusion states, especially delirium. Hallucinations in delirium tend to be visual, with or without auditory components, powerful, fleeting, and poorly organized. A history of medication or substance abuse and any recent changes, especially cessation of benzodiazepines or ethanol, should be sought.

Signs

The general physical examination may suggest a cause of confusion or altered mental status, such as congestive heart failure, pneumonia, or signs of illicit drug use. Fever suggests an infection as the cause of altered mental status and should prompt a search for the source, particularly urinary tract infection in the older patient. New focal neurologic findings suggest a possible mass lesion or stroke, but these would manifest with confusion only if global cortical dysfunction were caused by surrounding cerebral edema or elevated intracranial pressure by severe mass effect. Aphasia, fluent or nonfluent, is a focal sign suggesting a lesion in the dominant cerebral hemisphere. In confusional states, speech may be abnormal and is often incoherent, and the rate of speech may be rapid or slowed.

Identification of the elements of a toxidrome, such as serotonin syndrome, may assist in the identification of a drug effect as the cause of confusion prompting intervention or consultation. A careful inspection of the skin, especially in dependent areas such as the buttocks, may reveal a culprit skin infection. In some patients, confusion may be subtle, and an informal assessment of mental status and cognitive abilities may fail to detect abnormalities. Emergency clinicians often fail to perform a formal assessment for confusion or delirium, although studies have shown that delirium in older adults often goes unrecognized unless a structured assessment is performed. Casual conversation and basic questions about orientation will not detect confusion or delirium in all patients. A simple screening test is needed that goes beyond simple orientation and the apparent ability to carry on a normal conversation.

Attention deficit is the common denominator in confusional states. Patients with normal attention function should be able to perform digit repetition forward (five or six digits) and backward (four digits). Additionally, spelling a commonly used word backward ("world" is frequently used) or listing the months of the year in reverse order is an accurate screening test.[4,5] We recommend answering orientation questions, performing forward and backward digit repetition, and reciting the months of the year in reverse order as a brief screening examination.

The tools traditionally used by consultants for assessing cognitive impairment or dementia such as the Mini-Mental State Examination (MMSE) will show low performance in confused patients because an ability to sustain attention is required for these tasks. The MMSE (Fig. 14.1) was created as a screening instrument for cognitive impairment such as dementia, and many test items require focus and attention. If additional testing is performed in

the ED to assess cognition, we prefer the Quick Confusion Scale (QCS; Fig. 14.2), which was developed and tested in ED patients. This tool objectively measures elements of the patient's mental status in 2 to 3 minutes and correlates well with the MMSE. Most patients do not require more detailed evaluation during the ED phase of their care.

There are other simple tests that have been proposed for screening for delirium in older patients. The geriatric emergency department guidelines recently approved by emergency medicine and geriatric professional societies recommend a two-step approach.[6] First, an assessment known to be sensitive in detecting delirium is recommended to be performed by ED personnel (Fig. 14.3). The delirium triage screen assesses level of consciousness by observation and assesses attention by a simple question (backward spelling of five-letter word). If this triage screen is positive, a

ORIENTATION TO TIME
"What is the date?"

REGISTRATION
"Listen carefully. I am going to say three words.
You say them back after I stop.
Ready? Here they are . . .
HOUSE (pause), CAR (pause), LAKE (pause).
Now repeat those words back to me."
[Repeat up to 5 times, but score only the first trial.]

NAMING
"What is this?" [Point to a pencil or pen.]

READING
"Please read this and do what it says."
[Show examinee the words on the stimulus form.]
CLOSE YOUR EYES

Fig. 14.1. Mini-Mental State Examination sample items. (Reproduced by special permission of the publisher, Psychological Assessment Resources [PAR], from the Mini-Mental State Examination, by Marshal Folstein and Susan Folstein. Copyright © 1975, 1998, 2001 by Mini Mental LLC; published 2001 by Psychological Assessment Resources. Further reproduction is prohibited without permission of PAR. The MMSE can be purchased from PAR, Inc., by calling [800] 331-8378 or [813] 968-3003.)

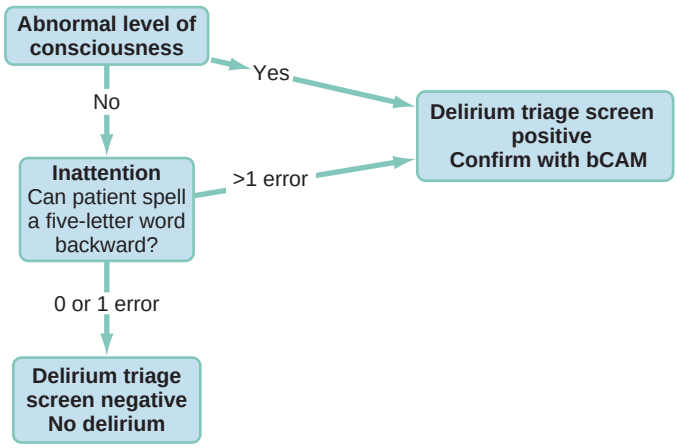

Fig. 14.3. Delirium triage screen. *bCAM,* Brief confusion assessment method. (Modified from American College of Emergency Physicians; American Geriatrics Society; Emergency Nurses Association; Society for Academic Emergency Medicine; Geriatric Emergency Department Guidelines Task Force: Geriatric emergency department guidelines. Ann Emerg Med 2014;63:e7–e25.)

ITEM	SCORE (highest number in category indicates correct response; decreased scoring indicates increased number of errors)	WEIGHT	SCORE
What year is it now?	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
What month is it?	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
Repeat phrase and remember it: "John Brown, 42 Market Street, New York"			
About what time is it? (answer correct if within the hour)	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
Count backward from 20 to 1	0, 1, or 2 (score 2 if correct; 1 if 1 error; score 0 if more than 2 errors)	x1	
Say the months in reverse	0, 1, or 2 (score 2 if correct; 1 if 1 error; score 0 if more than 2 errors)	x1	
Repeat the memory phrase (each underlined portion is worth 1 point)	0, 1, 2, 3, 4, 5 (score 5 if correctly performed; each error drops score by one)	x1	
		TOTAL	_____

Final score is sum of the totals; score less than 15 suggests the presence of altered cognition and need for further assessment.

Fig. 14.2. Quick Confusion Scale.

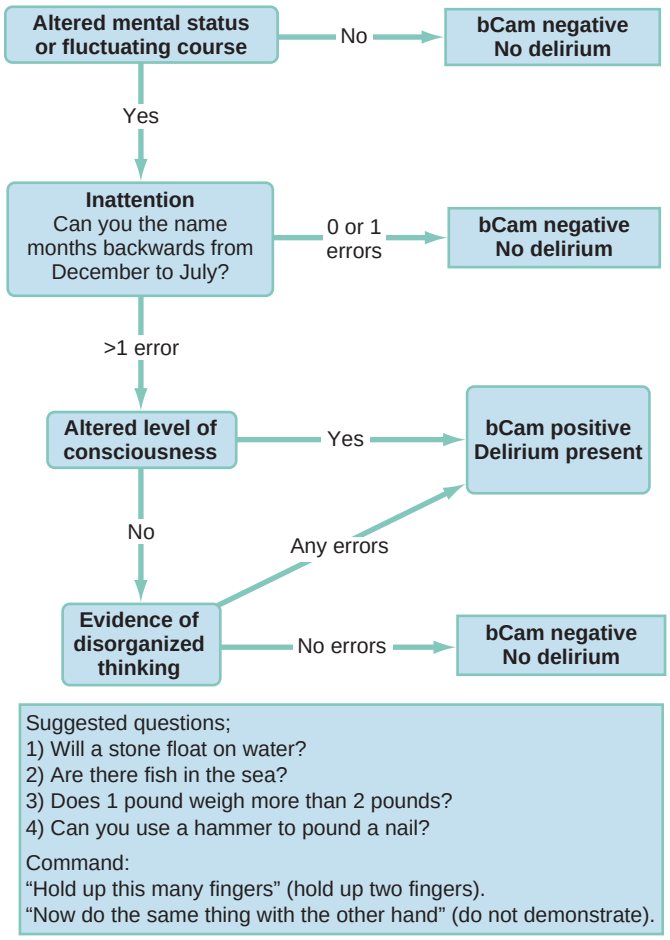

Fig. 14.4. Brief confusion assessment method (bCAM).

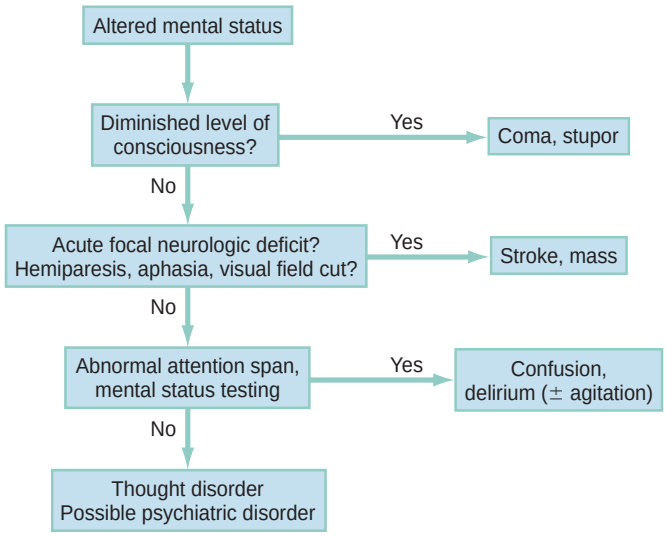

Fig. 14.5. Diagnostic algorithm for confusion.

more specific evaluation is recommended. The guidelines recommend a modification of the confusion assessment method, termed the *brief confusion assessment method* (bCAM) as a second test. This assesses four features—mental status by history or examination, further assessments of attention, level of consciousness, and orderly thinking (Fig. 14.4).

Ancillary Testing

Synthesis of information from the history and physical examination guide the emergency clinician in the choice of laboratory tests most likely to yield valuable diagnostic information. Pulse oximetry may reveal hypoxia or bedside glucose testing may reveal hypoglycemia or hyperglycemia. In the presence of fever, chest radiography and urinalysis often reveal the source of the infection causing the altered mentation. In older patients, urinalysis should be performed whether or not fever or typical symptoms are present. Serum chemistry tests for liver function may help identify hepatic encephalopathy. If there are clinical findings or a history suggestive of hypothyroidism, thyroid testing is indicated (see Chapter 120).

Electrocardiography is indicated in older patients because myocardial infarction may manifest atypically as confusion. The complete blood count, although commonly determined, is unlikely to provide useful diagnostic clues unless profound anemia is suspected. White blood cell counts may be elevated, normal, or low, without specificity as to the presence or nature of a disorder. Arterial blood gas testing is rarely indicated or useful unless pulse oximetry is not reliable.

If common and simple tests do not identify a cause, advanced diagnostic testing may be indicated. The clinical situation and overall condition of the patient determine the speed and direction of evaluation and whether the tests are obtained in the ED. Additional laboratory work is often of decreasing yield but serum ammonia and calcium levels and selected drug and toxicologic testing may be ordered in this second tier of evaluation. Blood and urine cultures are obtained in the febrile patient when hospital admission is anticipated and a clear infectious source is not evident. Paracentesis or thoracentesis may be appropriate if ascites or a new pleural effusion is present.

Cranial computed tomography (CT) scanning is often done to screen for CNS lesions in the absence of another identified source of the confusion. Unanticipated abnormalities are uncommonly found, although focal findings on examination increase the yield of neuroimaging.

Lumbar puncture may allow discovery or exclusion of CNS infection if no other source has been identified. Cerebrospinal fluid examination may clarify a diagnosis of meningitis, encephalitis, or subarachnoid hemorrhage.

If the cause of confusion remains unclear, or if the patient is unable to function safely in their current environment, admission is recommended for observation, and additional evaluation with consideration of obtaining magnetic resonance imaging or electroencephalography.

DIAGNOSTIC ALGORITHM

Certain critical and emergent diagnoses require prompt recognition for morbidity or mortality to be prevented (Box 14.1). The diagnosis of confusion implies the exclusion of other states of altered mental status, such as a decompensated psychiatric syndrome (Fig. 14.5).

The first step in assessing a patient with confusion is to ensure that the critical reversible causes are identified and addressed (eg, hypoxia, hypercarbia, hypoglycemia; Fig. 14.6). A complete set of vital signs, including temperature and oxyhemoglobin saturation, and a bedside blood glucose level should be determined promptly. Next, an assessment for delirium is performed using the confusion assessment method (CAM) score. If delirium is suspected, the underlying medical or surgical cause must be sought, including pneumonia, urinary tract infection, other systemic infection, CNS lesion, and drug toxicity. If the patient's CAM score is negative, a cognitive assessment should be performed, looking for evidence of an underlying dementia.

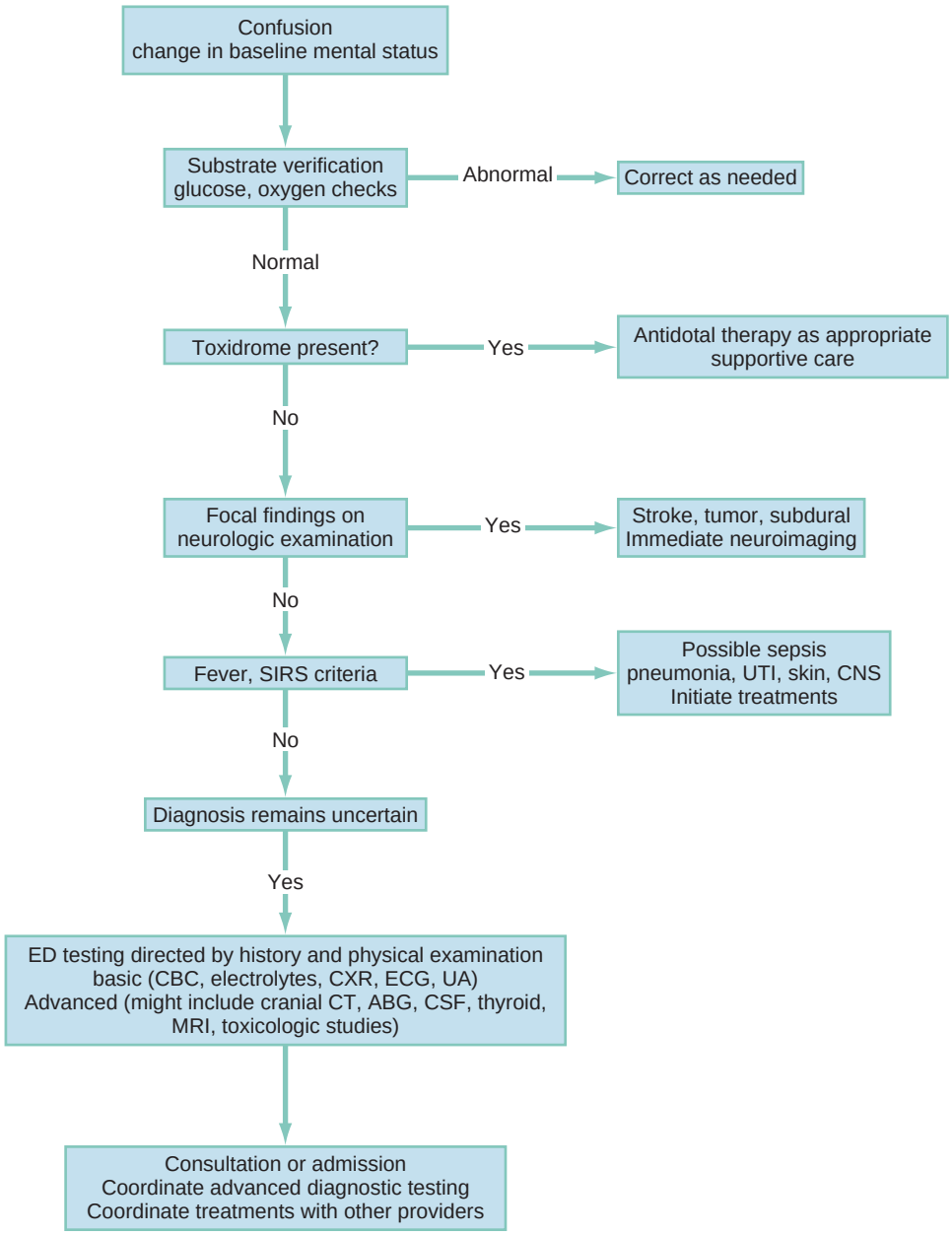

Fig. 14.6. Management algorithm for confusion. *ABG,* Arterial blood gases; *CBC,* complete blood count; *CNS,* central nervous system; *CT,* computed tomography; *CSF,* cerebrospinal fluid; *CXR,* chest x-ray; *ECG,* electrocardiogram; *ED,* emergency department; *MRI,* magnetic resonance imaging; SIRS, *UA,* urinalysis; *UTI,* urinary tract infection.

The history and physical examination search for precipitating factors underlying the onset of the confusional state. Investigations continue until the patient is stabilized, a likely diagnosis is discovered, or consultation and admission are deemed necessary. Focal neurologic findings suggesting stroke, tumor, or some other mass lesion prompt immediate neuroimaging. If the examination is nonfocal, the presence of systemic inflammatory response syndrome (SIRS) criteria or fever may lead to the discovery of an infectious cause of the confusion.

Postictal confusion is common in patients with seizures but should improve within 20 to 30 minutes. If the patient remains unconscious or confused after a seizure, the possibility of ongoing or intermittent seizure activity (ie, nonconvulsive seizures) should be entertained, and neurologic consultation and electroencephalography should be considered.

If the cause of confusion remains uncertain, admission to an inpatient or observation unit is considered for further evaluation. Ideally, care is promptly coordinated with consultants and admitting physicians.

EMPIRICAL MANAGEMENT

Oral or intravenous glucose therapy is indicated if an abnormally low blood glucose level is discovered. In adults, 25 g dextrose (50 mL of 50% dextrose) is commonly administered, and the bedside glucose level is checked again. Thiamine, 100 mg IV, is recommended at the time of dextrose administration. Hypoxia and hypocapnia are addressed with noninvasive or invasive strategies tailored to the patient's presentation. If a toxidrome is present, treatment is directed toward the specific toxin or syndrome.

Confused or agitated patients should be protected from harming themselves or others. Close observation may need to be supplemented by medications or physical restraint. Family members may offer valuable assistance in observing and comforting the patient. Environmental manipulations such as dim lighting or providing a quiet environment may be helpful. Confinement or physical restraint may be necessary at times but should be used with careful adherence to institutional guidelines. Benzodiazepines, butyrophenones, or newer antipsychotic medications may be used if necessary to decrease agitation, but any of these might confound evaluation of the confusional state. No studies allow precise recommendation but in adults we recommend midazolam, titrated beginning with 1 to 2 mg IV or 5 mg IM.

Age-appropriate antibiotic treatment for coverage of causes of sepsis tailored to the patient's comorbidities may be considered in ill febrile patients while a definitive evaluation is in progress. If a CNS infection is suspected, age-guided empirical antibiotic treatment without delay for lumbar puncture is recommended (see Chapter 99).

In patients with a prolonged postictal period or who are suspected of being in nonconvulsive status epilepticus, empirical treatment with lorazepam, 1 mg IV, up to a maximum of 10 mg, may be considered pending consultation and additional testing (see also Chapters 15 and 92).

KEY CONCEPTS

- Confusion is a symptom, not a diagnosis.
- Focal cortical dysfunction, such as from tumor or stroke, typically does not cause confusion.
- Any underlying clinical process that disrupts optimal central nervous system (CNS) functioning can result in confusion.
- Emergent causes of confusion that need immediate detection and treatment include hypoglycemia, hypoxemia, hypotension, sepsis, and toxic ingestions.
- Assessment of attention is fundamental for the assessment of patients with confusion.
- The confusion assessment method (CAM) is a validated tool for identifying patient with delirium.
- Delirium often goes unrecognized unless a structured assessment tool is used.
- Midazolam is useful for managing undifferentiated agitation while the diagnostic evaluation is in progress.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 14: QUESTIONS & ANSWERS

14.1. A 70-year-old man with a chief complaint of confusion is brought to the emergency department by his family. Which of the following initial assessments should be included?

A. All of these
B. Blood pressure
C. Pulse oximetry
D. Rapid bedside glucose testing
E. Temperature

Answer: A. Confusion may result from shock states, hypoglycemia, and hypoxia. Evaluation for these conditions is a priority. Confusion is a symptom rather than a medical condition, and reversible remedial causes should be investigated.

14.2. A variety of screening tests may aid in the detection of confusion. Which of the following conditions may inhibit performance of these tests?

A. Attention impairment
B. Cortical blindness
C. Disorientation
D. Hemiparesis
E. Long-term memory impairment

Answer : A. Deficiency in attention span will impair performance of all tests of cognitive performance. If the patient cannot attend to simple tasks, more detailed testing is not possible.

14.3. A 30-year-old patient is brought to the emergency department for evaluation of odd behavior. Which of the following characteristics might suggest a psychiatric cause for the behavior?

A. Auditory hallucinations
B. Disorientation
C. Fever
D. Olfactory hallucinations
E. Visual hallucinations

Answer: A. Auditory hallucinations are common in psychiatric illness. If hallucinations are present in organic causes of delirium, they are usually visual, tactile, or olfactory. Orientation is generally preserved with primary psychiatric disorders unless psychosis or severe impairment is present.

14.4. Postictal confusion is common in patients with seizures, but if improvement in consciousness does not occur within 20 to 30 minutes after seizure cessation, which of the following conditions should be considered?

A. all of these
B. electrolyte abnormalities
C. head injury
D. hypoglycemia
E. nonconvulsive or subtle status epilepticus

Answer: A. For a patient with a generalized convulsive seizure, termination of the seizure activity should be followed by improvement of mental status within a short period of time. For the patient with persistently altered consciousness or prolonged confusion, consider causes of provoked seizures with prolonged altered mental status or persistence of subtle seizures.

CHAPTER 15

Seizures

Charles V. Pollack, Jr. | *Felipe Teran Merino*

PERSPECTIVE

Seizures are episodes of abnormal neuronal excitation and are generally a manifestation of an underlying process. The goal of the emergency clinician is to differentiate a seizure from a seizure mimic and identify causes that are reversible. Epilepsy is defined as recurrent unprovoked seizures caused by a genetically determined or acquired brain disorder; it is not an appropriate term for seizures that occur intermittently or predictably after a known insult, such as alcohol intoxication and withdrawal.[1] Status epilepticus is characterized by seizures lasting more than 5 minutes or recurrent seizures, without return to baseline mental status.[2]

Generalized convulsive seizures are often self-limiting but, if sustained, require prompt treatment to minimize complications. Nonconvulsive seizure activity and nonconvulsive status epilepticus may be relatively obscure in their presentation and should be suspected in patients with altered behavior or coma of undetermined cause.[3]

Epidemiology

More than 10% of the US population will experience at least one seizure during their lifetime; however, only 3% will be diagnosed with epilepsy. Alcohol and other intoxications and central nervous system pathologies, such as tumor, stroke, trauma, or infection, are common causes of seizures in adults.

Seizures are classified based on cause (primary or secondary), effect on mentation, and motor activity. Primary seizures are unprovoked and not linked to an inciting event. Secondary seizures may be caused by trauma, illness, intoxications and poisonings, metabolic disturbances, and cerebral tumors.[4,5] A generalized seizure is defined as abnormal neuronal activity in both cerebral hemispheres, which results in an alteration in the level of consciousness. Generalized seizures may be further divided into tonic-clonic, absence, atonic, and myoclonic. Focal seizures usually involve one cerebral hemisphere, thereby preserving consciousness, although these seizures may progress and cause an altered sensorium. Some seizures are impossible to classify because of inadequate or inaccurate description of the ictal activity.[2,6]

Convulsive seizures are characterized by uncontrolled, rhythmic motor movements and can affect part or all of the body. Patients with nonconvulsive seizures may manifest automatisms, confusion, altered mental status, abnormal behavior, or coma.

Status epilepticus has been classically defined as at least 30 minutes of persistent seizures or a series of recurrent seizures without intervening return to full consciousness. The time criterion has been shortened to 5 minutes, with recognition that the duration of seizure activity is related to outcome and that the likelihood of achieving seizure cessation with typical treatments decreases with ictal duration.[2,4] Common causes of status epilepticus in adults are shown in Box 15.1. See Chapter 92 for a more detailed discussion of seizures.

Pathophysiology

Seizures occur when the abnormal, increased electrical activity of initiating neurons activates adjacent neurons and propagates via a process termed *recruitment,* following contiguous paths or extending along diverse integrated circuits that are deep and may cross the midline. When the abnormal impulse extends below the cortex to deeper structures, the reticular activating system in the brainstem may be affected, altering consciousness. In generalized seizures, the focus often is subcortical and midline, which explains the prompt loss of consciousness and bilateral involvement.

Seizures are typically self-limited; at some point the hyperpolarization subsides and the bursts of electrical discharges from the focus terminate. This cessation may be related to reflex inhibition, neuronal exhaustion, or alteration of the local balance of neurotransmitters between the excitatory acetylcholine and the inhibitory γ-aminobutyric acid (GABA).

Focal seizures may represent a similar pathophysiologic process, in which less recruitment occurs and the ictal activity does not cross the midline. Because of the more limited focus of abnormal activity, convulsive motor activity may not be the predominant clinical manifestation. Chapter 92 presents a further discussion of the pathophysiology of seizures.

DIAGNOSTIC APPROACH

Differential Considerations

Because a diagnosis of seizure has major consequences for the patient—including loss of driving privileges and exposure to potentially toxic medicines—the first diagnostic task in the emergency department (ED) is to determine whether the patient has actually experienced a seizure.[7] Once a seizure is suspected, there must be a search for underlying precipitants. New-onset seizures or a change in seizure patterns in epileptics may be the primary manifestation of serious underlying diseases, and should prompt a focused evaluation. The differential diagnoses to consider when evaluating for seizure are listed in Box 15.2. Neurogenic seizures must be differentiated from seizure mimics, which include syncope, dysrhythmia, migraine, decerebrate posturing from increased intracranial pressure, dystonic drug reactions, tetanus, strychnine poisoning, and psychogenic events.

Syncope, including simple vasovagal syncope, can be associated with occasional twitching movements or even a brief, more generalized convulsion, which can be misdiagnosed as a seizure. This is referred to as convulsive syncope. Myoclonic activity is brief (usually a few seconds) and recovery is as for any other syncopal event, without any postictal altered mental status or confusion. Generalized, sustained (more than a few seconds) tonic-clonic movements, tongue biting, or postictal amnesia are rare with convulsive syncope, and should be presumed to represent a nonsyncopal generalized seizure. When put in the context of when and where the event occurred, the duration of the event,

BOX 15.1

Causes of Status Epilepticus in Adults

METABOLIC DISTURBANCES
Hepatic encephalopathy
Hypocalcemia
Hypoglycemia or hyperglycemia
Hyponatremia
Uremia

INFECTIOUS PROCESSES
Central nervous system abscess
Encephalitis
Meningitis

WITHDRAWAL SYNDROMES
Alcohol
Antiepileptic drugs
Baclofen
Barbiturates
Benzodiazepines

CENTRAL NERVOUS SYSTEM LESIONS
Acute hydrocephalus
Anoxic or hypoxic insult
Arteriovenous malformations
Brain metastases
Cerebrovascular accident
Eclampsia
Head trauma: acute and remote
Intracerebral hemorrhage
Neoplasm
Posterior reversible leukoencephalopathy

INTOXICATION
Bupropion
Camphor
Clozapine
Cyclosporine
Flumazenil
Fluoroquinolones
Imipenem
Isoniazid
Lead
Lidocaine
Lithium
MDMA
Metronidazole
Synthetic cannabinoids
Theophylline
Tricyclic antidepressants

BOX 15.2

Differential Considerations for a Seizure or Seizure-like Event

The following diagnoses may have presentations that can be difficult to differentiate from seizure activity:

CARDIAC
Vasodepressive (vagal) syncope
Orthostatic syncope
Cardiogenic syncope

NEUROLOGIC
Stroke, transient ischemic attack
Atypical migraine
Movement disorders
Mass lesions

TOXICOLOGIC
Intoxication, inebriation
Oversedation, overanalgesia
Extrapyramidal symptoms

METABOLIC
Hypo-, hyperglycemia
Thyrotoxicosis
Delirium tremens

INFECTIOUS
CNS infections
Tetanus

PSYCHIATRIC
Pseudoseizure
Panic attacks
Cataplexy

type of movements, and presence or absence of a postictal state, convulsive syncope usually is easily differentiated from seizure.

Migraine with an aura can be confused with nonconvulsive seizures. This is compounded by the finding that many migraine patients have abnormal electroencephalograms (EEGs). Basilar migraine can result in loss of consciousness, making the differentiation even more difficult. These patients will almost always have a history of migraine, often with similar presentation. When the event is the first that the patient has experienced, differentiation can be difficult, and the event should be presumed to be a seizure until this has been excluded by further evaluation and testing.

Psychogenic seizures (pseudoseizures) are functional events with a clinical presentation mimicking neurogenic seizures. There is no corresponding alteration in electroencephalographic activity. These events are often conversion reactions and are not under the patient's conscious control. Up to 30% of patients referred to specialized epilepsy clinics for evaluations are ultimately diagnosed with psychogenic seizures, often with a delay of many years before the correct diagnosis is made. Psychogenic seizures often last longer than neurogenic events, and there usually is a brief or no postictal period. Patients can often recall events during psychogenic seizures, which would be diagnostic because this is not possible in neurogenic generalized seizures. Psychogenic seizures are classically manifested by forward-thrusting pelvic movements and head turning from side to side. Avoidance of noxious stimuli or gaze deviation away from the examiner are also suggestive that an event is psychogenic in origin. On laboratory testing, psychogenic seizure patients do not have a metabolic acidosis, which is nearly universal in those with generalized convulsive seizures.

Pivotal Findings

History and physical findings can be useful in differentiating seizure from other acute medical conditions. Retrograde amnesia, lateral tongue biting, and urinary incontinence are all suggestive of a neurogenic event however they are not specific and have been also reported in psychenic seizures. Patients may experience an aura, which in essence is a focal seizure that then often generalizes. Auras are clinically defined by the area of the brain involved. Examples include alterations in sensation, autonomic deregulation such as sweating and flushing, aphasia, a sense of déjà vu, and

automatisms, such as lip smacking, repeated swallowing or uttering verbal phrases, or picking at clothing.

Symptoms

History taking in the patient with seizure is directed by two main questions. First, "Was the incident truly a seizure?" This is important because of the broad differential diagnosis for seizures (see Box 15.2) and the frequency of inaccurate descriptions of seizure-like activity from laypersons. In general, ictal events have five properties:

1. Abrupt onset: History should focus on any evidence of an aura.
2. Brief duration. Seizures rarely last longer than 90 to 120 seconds, although bystanders may overestimate the duration. Status epilepticus is the important exception.
3. Alteration of consciousness. Generalized seizures are manifest by loss of consciousness; focal seizures are often accompanied by an alteration in consciousness.
4. Purposeless activity. Automatisms and undirected tonic-clonic movements are common in ictal events. Tonic-clonic movements are rhythmic and generally do not involve head shaking.
5. Postictal state. This is an acute confusion state that typically occurs with all seizure types except focal and absence. This interval represents the transition from the ictal state back to the patient's baseline mental status. It can last from minutes to hours, depending on which specific region of the brain triggered the seizure, seizure duration, age, and use of an antiepileptic drug (AED).

The second question to direct the history is, "Does this patient have a history of seizures?" If there is a documented history of seizures, ED evaluation may be limited to identifying precipitants and obtaining an AED level, when available. The history should focus on clinical factors known to decrease the seizure threshold, such as recent illness or trauma, drug or alcohol use, sleep deprivation, potential adverse drug-drug interactions with AEDs, medication noncompliance, recent change in anticonvulsant dosing regimens, or change in ictal pattern or characteristics.

Signs

The physiologic alterations associated with convulsive ictal activity include hypertension, tachycardia, and tachypnea from sympathetic stimulation. These signs typically resolve quickly after the seizure activity ceases. With more prolonged convulsions, skeletal muscle damage, lactic acidosis and, rarely, rhabdomyolysis may ensue. Autonomic discharges and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting (with aspiration risk), tongue biting, and airway compromise. All these signs are helpful discriminators in the differential evaluation of seizure-like spells, although the presence or absence of these findings neither confirms nor excludes seizure occurrence. Evidence of physical injury should be sought.

After the seizure activity has ceased, resting vital signs are evaluated. Fever and underlying infection can cause seizures, although there may be a low-grade temperature elevation immediately after a convulsive generalized seizure. Tachypnea, tachycardia, or an abnormal blood pressure that persists beyond the immediate postictal period may indicate toxic exposure, hypoxia, or a central nervous system lesion. Pertinent physical findings may include nuchal rigidity, stigmata of substance abuse, lymphadenopathy suggestive of human immunodeficiency virus (HIV) disease or malignancy, dysmorphic features, or skin lesions. The examination should also focus on potential adverse sequelae of convulsive seizures, such as head trauma, oral and tongue injury, posterior shoulder dislocation, or back pain.

Finally, a complete neurologic examination is performed. A persistent focal deficit after a seizure (eg, Todd's paralysis) often indicates the focal origin of the event but also can be evidence of an underlying stroke. Hyperreflexia and a positive Babinski reflex that resolve are indications that a seizure occurred. The patient should be carefully examined for signs of ongoing subtle convulsive or nonconvulsive status epilepticus, especially when there is prolonged postictal depression of consciousness.

Ancillary Testing

Laboratory Testing

The serum glucose level should be determined in every seizing or postictal patient; women of reproductive age should be tested for pregnancy. If the diagnosis of seizure is uncertain, lactic acidosis may be detectable for up to 1 hour after the seizure resolves. Blood drawn in the field should be sent to the laboratory, along with blood drawn on arrival in the ED, if possible. Presence of a lactic acidosis in the field sample that resolves on ED testing supports a seizure diagnosis. Patients with a significant change in seizure pattern (eg, a substantial increase in seizure frequency despite medication compliance), or with an abnormal neurologic examination should undergo a more thorough laboratory assessment. The serum sodium level is the most important electrolyte to assess. Drug levels are appropriate in patients known or thought to be taking AEDs. Febrile patients should be evaluated for the source of the fever, including consideration of lumbar puncture.

For medically ill adults (eg, those with diabetes, cancer, or liver disease or those taking medications that can affect serum electrolyte levels) and in patients with a first-time seizure or substantial change in seizure pattern, serum electrolyte levels, including calcium and magnesium, are indicated. Liver function tests may be helpful if the history or physical examination suggests hepatic disease. Directed toxicology screens should be performed if substance abuse (particularly cocaine, amphetamines, and other sympathomimetic agents) or supratherapeutic use of aspirin or acetaminophen is suspected. Many drug of abuse screening tests do not detect agents such as synthetic cannabinoids, which can cause seziures.[8] Headache may be a feature of the patient's postictal state but, otherwise, the presence of fever and headache or sudden onset of headache is an indication for computed tomography (CT), lumbar puncture, or both.

Imaging Studies

An emergent cranial CT scan is indicated when a serious structural lesion is suspected on clinical grounds, including presence of a new focal deficit, persistent altered mental status, fever, recent trauma, persistent headache, history of cancer, anticoagulant use, suspicion or known history of acquired immunodeficiency syndrome (AIDS), age older than 40 years, and partial complex seizure.[2,9] If magnetic resonance imaging (MRI) is readily available, it can be used instead of CT in most patients; MRI is more sensitive than CT and yields useful additional diagnostic and prognostic information. It is unlikely, however, that CT will miss a substantial CNS lesion. MRI is likely most useful in patients with a normal CT but recurrent seizure or focal electroencephalographic abnormalities.[9]

In the fully recovered patient without headache and with normal mental status and neurologic examination findings who has had a single brief seizure, a cranial CT scan can be performed in the ED or at a follow-up visit at the discretion of the treating physician.

The literature on head CT imaging for first-time, nonfebrile seizures in children has been inconclusive.[8] Emergent neuroimaging is indicated for children with medical or surgical comorbidities or in cases of focal seizures in children younger than 3 years, discussed in Chapter 174.[2]

Electroencephalography

Obtaining an EEG is often logistically challenging in the ED, but can be invaluable for patients in whom the diagnosis is unclear or who remain altered. EEG is useful to diagnose nonconvulsive status epilepticus, monitor seizure activity after intubation and neuromuscular blockade, and help differentiate seizures from other nonneurologic presentations.

DIAGNOSTIC ALGORITHM

In patients suspected of having had a seizure, the first step is to determine whether the history from the patient or bystander(s) supports the diagnosis. Critical causes of seizures with specialized treatments include eclampsia, toxic ingestion (eg, isoniazid, tricyclic antidepressants), hypoglycemia, hyponatremia, and increased intracranial pressure. Box 15.3 presents the critical and emergent diagnoses that must be considered; Fig. 15.1 presents a diagnostic algorithm.

If the patient has a history of seizures, directed questions should be made to characterize the type of seizure. Information regarding the onset, presence of aura, type of seizure, and duration of ictal and postictal periods is key to determining whether the seizure is similar to previous seizures. If the seizure appears typical for the patient, the emergency clinician should identify if the patient is on an AED and inquire about potential triggers that can lower the seizure threshold, such as sleep deprivation, infections, and medications. If the patient is taking an AED for which a serum level can be measured (eg, phenytoin, carbamazepine, valproic acid) and found to be subtherapeutic, then additional medication can be given via the intravenous (IV) or oral (PO) route. The patient can then be discharged, with continued outpatient evaluation with the neurologist or primary care physician.

If the patient does not have a history of prior seizures, the diagnostic approach is directed to assess for potential precipitants, such as toxic ingestions, history of immunosuppression, pregnancy, or head trauma. Fingerstick blood glucose, pregnancy test in women, and serum sodium level are the most helpful laboratory tests. An ECG can identify characteristic changes from some toxic ingestions and evidence of risk for dysrhythmias (eg, accessory pathways, prolonged QTc). An obviously gravid patient may increase suspicion for eclampsia, but the condition can occur up to 8 weeks postpartum. A head CT scan can identify traumatic and atraumatic lesions or signs of increased intracranial pressure.

BOX 15.3

Critical and Emergent Diagnoses to Consider in a Patient With Seizure

CRITICAL DIAGNOSES

Status epilepticus, regardless of cause
Nonconvulsive status epilepticus
Seizures with specialized treatments
- Eclampsia
- Toxic ingestion (eg, isoniazid [INH], tricyclic antidepressants)
- Hypoglycemia
- Hyponatremia
- Increased intracranial pressure

EMERGENT DIAGNOSES

Infection
Posttraumatic seizures
Serious mimics of seizure activity (eg, cardiogenic syncope)

Patients who arrive at the ED with ongoing seizure activity or who experience recurrent seizures without recovering from the postictal period are in status epilepticus. These patients generally require a full metabolic evaluation, complete blood count, and head CT. Up to 15% of patients who are successfully treated for convulsive status epilepticus remain in nonconvulsive status epilepticus; therefore, there should be a low threshold for obtaining a bedside EEG, especially if the postictal period is prolonged or automatisms are noted.

EMPIRICAL MANAGEMENT

Prehospital Management

The prehospital management of the patient with seizures focuses on prompt recognition and treatment of hypoxia, hypotension, and hypoglycemia. Simultaneously, the patient should be protected from injury and, if possible, placed in a lateral decubitus position to reduce aspiration risk. Large retrospective reviews and expert consensus do not support the routine use of cervical spine immobilization unless there is high suspicion for head and neck trauma.[1] A nasopharyngeal airway devices may optimize oxygenation.

Because most seizures are of brief duration and self-limited, little intervention is generally required. Patients who are still seizing by the time of emergency medical services (EMS) arrival should be suspected to be in status epilepticus and priority should be on rapid administration of a benzodiazepine. Well-designed trials have shown the efficacy and safety of early administration of benzodiazepines during prehospital care.[10,11] Intramuscular (IM) midazolam can be quickly administered; there is evidence that it is superior to IV lorazepam in adults and noninferior in children.[11] Based on ease of administration and comparable outcome to IV lorazepam, we recommend IM midazolam as the first-line intervention is the field management of status epilepticus (Table 15.1 for dosing). We do not recommend the use of rectal diazepam in managing status because absorption is erratic and not as dependable as other routes.

Emergency Department Management

Patients who are actively seizing in the ED should be placed in a monitored bed. Management simultaneously focuses on identifying reversible causes, such as hypoxia and hypoglycemia, and initiating pharmacologic treatment. See Table 15.1 and Fig. 15.2.

For the seizing patient, ensuring central nervous system (CNS) perfusion and oxygenation is the priority. Oropharyngeal airways are contraindicated because they may induce gagging and vomiting and may damage the teeth or tongue. Oxygen may be administered to supplement immediate oxygenation and in preparation for possible rapid sequence intubation. Suction should be available but used carefully.

Lorazepam is the first-line treatment unless there is no vascular access, in which case we recommend midazolam IM.[12,13] If the patient continues to seize despite initial therapy with lorazepam, second-line medications should be given. These include phenytoin, 20 mg/kg IV (at a maximum rate of 50 mg/min to avoid hypotension and arrhythmias), fosphenytoin (a water-soluble prodrug of phenytoin) at 20 phenytoin equivalents (PE)/kg IM or IV (maximum rate of 150 mg/min), and valproic acid, 20 to 40 mg/kg IV, administered at a rate of 3 to 6 mg/kg/min. If seizures continue, an additional half-loading dose of phenytoin, fosphenytoin, or valproic acid can be given.[13] Although limited evidence exists, IV levetiracetam, bolus 1000 to 3000 mg over 15 minutes in adults, and 20 to 60 mg/kg, at a rate of 2 to 5 mg/kg/min 20 to 60 mg/min over 15 minutes in children, has been recommended.[12,13]

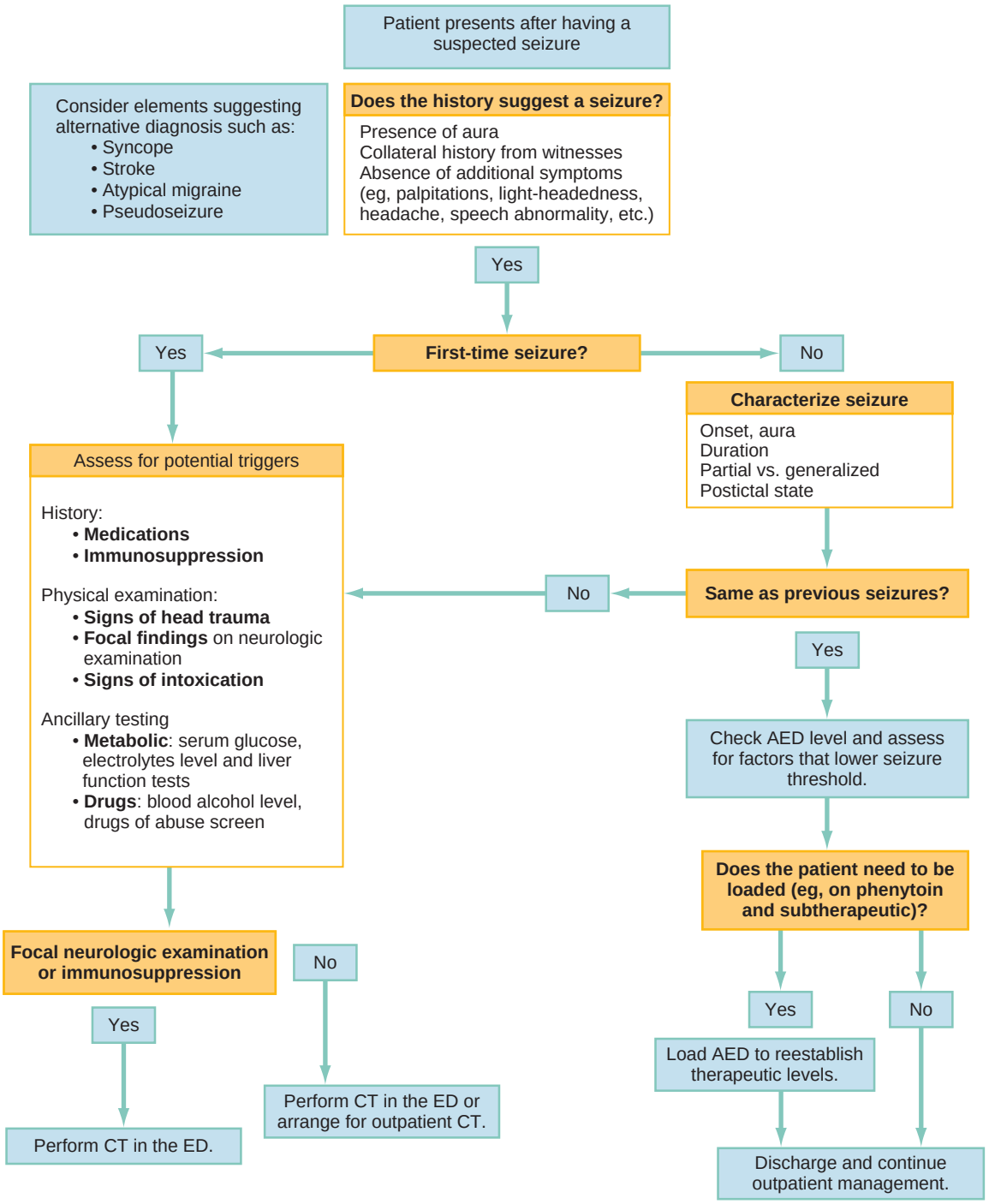

Fig. 15.1. Diagnostic algorithm for the patient with seizure in the emergency department. *AED,* Antiepileptic drug; *CT,* computed tomography,

If seizure activity continues, a careful reassessment should be done to identify reversible underlying processes, such as bleeding, drug overdose, and metabolic abnormalities that could have been missed until this point. Preparations for endotracheal intubation and administration of third-line therapies are indicated. Concomitantly, specific seizure syndromes should be considered in patients at risk. For example, isoniazid overdose can cause prolonged seizures refractory to benzodiazepines and requires pyridoxine to terminate the seizures. In seizing female patients of childbearing age, eclampsia may be the cause, and IV magnesium is the treatment of choice. Eclamptic seizures refractory to magnesium may respond to benzodiazepines or barbiturates, with or without phenytoin. Children and psychiatric patients at risk for water intoxication may be hyponatremic and require hypertonic saline therapy.

Third-line therapies for status epilepticus include pentobarbital, 5 mg/kg IV at a rate of 1 to 5mg/kg/hr and then a 0.5 to 3.0-mg/kg/hr infusion as needed, phenobarbital, 20 mg/kg IV at 50 to 75 mg/min, midazolam, 0.2 mg/kg and then 0.1 to 0.4 mg/kg/hr, or propofol, 2 mg/kg IV at 2 to 5 mg/kg/hr and then a 5- to 10-mg/kg/hr infusion, as needed. Patients in status epilepticus should be admitted to the intensive care unit and have continuous electroencephalographic monitoring, which will be key to titrating the dosing of sedation for seizure termination.

TABLE 15.1

Medications Used in the Abortive Treatment of Ongoing Seizure Activity in the Emergency Department

MEDICATION	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
INITIAL THERAPY			
Diazepam	5 mg IV, up to a max of 20 mg, or 10–20 mg PR	0.2–0.5 mg/kg IV/ET or 0.5–1.0 mg/kg PR (max, 20 mg)	May repeat in 10 min; monitor respiratory status.
Lorazepam	2 mg IV at 2 mg/min, up to a max of 10 mg	0.05–0.1 mg/kg IV (max 2 mg)	Preferred IV benzodiazepine; may repeat in 10 min; monitor respiratory status.
Midazolam	5 mg, up to a max of 10 mg; IV, IM, IN	0.2 mg/kg IV, IM, IN (max, 5 mg)	Preferred IM benzodiazepine; may repeat in 10 min; monitor respiratory status.
SECOND-TIER TREATMENTS			
Phenytoin	20-mg/kg IV infusion at 50 mg/min (25 mg/min in patients with cardiac history)	20-mg/kg IV infusion at rate of 1 mg/kg/min	May cause hypotension and dysrhythmia; May give additional 5–10 mg/kg 10 minutes after the loading dose
Fosphenytoin	20 PE/kg IV infusion at 150 mg/min, or 20 PE/kg IM	20 PE/kg IV at rate of 3 mg PE/kg/min	May give an additional 5 PE/kg 10 min after loading dose
Valproic acid	20–40 mg/kg IV at 3–6 mg/kg/min infusion	20–40 mg/kg IV at 1.5–3 mg/kg/min infusion	May give additional dose of 20 mg/kg 10 min after loading dose
Levetiracetam	1000–3000 mg over 15 min	20–60 mg/kg at rate of 2–5 mg/kg/min	Efficacy and safety data come from small studies.
THIRD-TIER TREATMENTS			
Pentobarbital	5–15 mg/kg IV loading dose at 50 mg/min, then 0.5–5 mg/kg/hr infusion as needed	5–15 mg/kg loading dose at maximum rate of 50 mg/min	Titrate to EEG; intubation and hemodynamic support required
Phenobarbital	20 mg/kg IV at 50–100 mg/min	20 mg/kg IV at 50–100 mg/min	Intubation required; may give additional 5–10 mg/kg 10 min after loading dose
Midazolam	0.2- mg /kg IV loading dose, then 0.05–2 mg/kg/hr	0.2-mg/kg IV loading dose, then 0.05–2 mg/kg/hr	Titrate to EEG; monitor respiratory status
Propofol Infusion	1–2 mg/kg IV loading dose; start at 1–2 mg/kg/hr and increase rate by 0.3–0.6 mg/kg/hr every 5 min	1–2-mg/kg IV loading dose; start at 1–2 mg/kg/hr and increase rate by 0.3–0.6 mg/kg/hr every 5 min	Intubation required; use with caution in doses >4.8 mg/kg/hr

EEG, Electroencephalogram; *ET,* endotracheal; *IM,* intramuscular; *IV,* intravenous; *IN,* intranasal; *PR,* per rectum.
Second- and third-tier treatments adapted from Brophy GM, Bell R, Claassen J, et al; Neurocritical Care Society Status Epilepticus Guideline Writing Committee: guidelines for the evaluation and management of status epilepticus. Neurocrit Care 17:3–23, 2012.

Disposition

The appropriate disposition of a patient presenting to the ED with a seizure or history of a recent seizure must be individualized according to the underlying illness, likelihood of recurrence, indications for maintenance pharmacologic therapy, and state reporting regulations.

Patients may be discharged home with early referral to a neurologist if they have a normal neurologic examination findings, no significant medical comorbidities, and no known structural brain disease, do not require the use of an AED, did not require more than one dose of a benzodiazepine in the ED, and are thought to have sufficient resources to comply reliably with follow-up instructions.[14] When the diagnosis is uncertain and close follow-up is unlikely, longer observation or admission for observation should be considered.

Patients discharged home from the ED should receive state-specific guidance regarding driver's license privileges, warning about potentially dangerous activities (eg, swimming, climbing ladders and heights, operating machinery), and information for prompt follow-up with a neurologist.

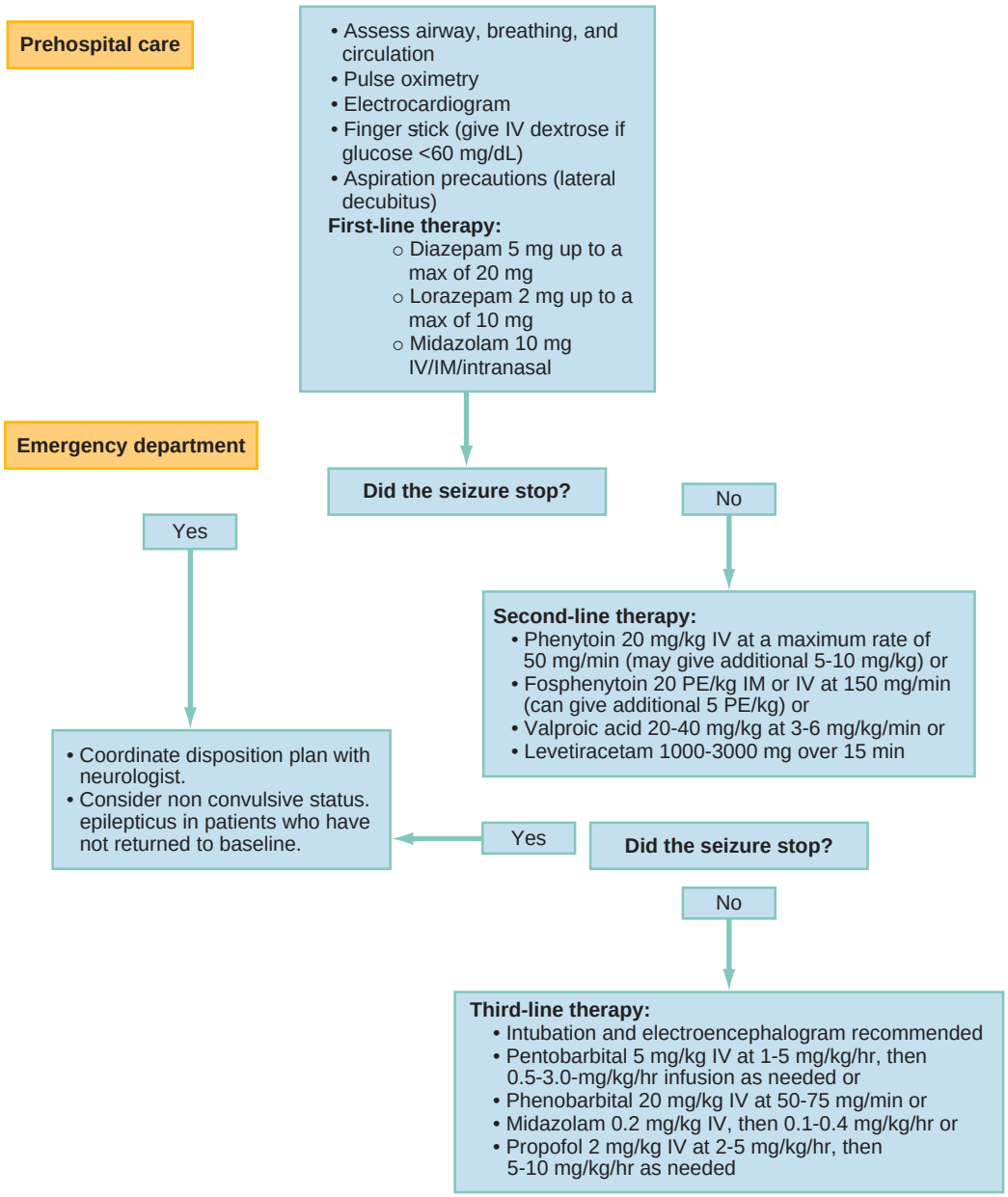

Fig. 15.2. Management algorithm for status epilepticus.

KEY CONCEPTS

- The differentiation between seizures and other causes of altered mention or abnormal motor activity is not always straightforward and may require synthesizing the history, physical examination, laboratory results, and imaging data.
- Beginning in the out-of-hospital setting, patients with possible seizure activity should be protected from injury and assessed for hypoglycemia.
- Status epilepticus is defined as seizures lasting more than 5 minutes or repeat seizures while still postictal.
- Primary abortive therapy for seizures in the ED setting includes lorazepam; if diazepam is used in status epilepticus, it should be immediately followed by a loading dose of phenytoin, fosphenytoin, or valproic acid.
- Neuroimaging is recommended for patients with seizures who have head trauma, persistently abnormal mental status, focal neurologic abnormality, or HIV infection.
- Nonconvulsive status epilepticus should be considered in patients with a prolonged postictal state or otherwise unexplained coma.
- Patients with a first-time seizure who have no known structural brain pathology, normal serum glucose and sodium levels, and normal neurologic examination can be discharged from the ED with appropriate outpatient follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 15: QUESTIONS & ANSWERS

15.1. Which of the following is a generalized seizure disorder characterized by lack of a postictal state?
- **A.** Atonic seizure disorder
- **B.** Clonic seizure disorder
- **C.** Myoclonic seizure disorder
- **D.** Temporal lobe epilepsy
- **E.** Tonic-clonic seizure disorder

Answer: A. Atonic seizure disorder, also known as atonic drop attack ictus, is notable among the generalized seizure disorders because of its lack of postictal state. Postictal states may be seen following tonic-clonic, clonic, and myoclonic seizures. Temporal lobe epilepsy is a focal, instead of generalized, seizure disorder.

15.2. What is the most common metabolic cause of seizure activity?
- **A.** Hypercalcemia
- **B.** Hyperglycemia
- **C.** Hypermagnesemia
- **D.** Hypocalcemia
- **E.** Hypoglycemia

Answer: E. Seizure activity secondary to metabolic derangements is most commonly caused by hypoglycemia. The only treatment required in this situation may be intravenous (IV) glucose. Prolonged seizure activity may also cause hypoglycemia so that the cause and effect relationship may sometimes be reversed, and further therapy may be required.

15.3. A 15-year-old girl is brought to the emergency department for evaluation of a recent seizure. While awaiting laboratory results, she begins to have further seizure activity. Which of the following is the optimal first-line agent to terminate her seizure activity?
- **A.** Fosphenytoin
- **B.** Lorazepam
- **C.** Phenobarbital
- **D.** Phenytoin
- **E.** Valproic acid

Answer: B. Benzodiazepines are the optimal first-line agents for stopping seizure activity in patients of all ages. Available agents include lorazepam, diazepam, and midazolam. Phenytoin is recommended as second-line therapy for adults with persistent seizure activity. The prodrug, fosphenytoin, can be administered more quickly, can be given intramuscularly, and has less of a tendency to cause hypotension. Second-line therapy for children is phenobarbital. Third-line therapy is pentobarbital, propofol, or a benzodiazepine infusion. Valproic acid should be considered for patients who are on chronic valproic therapy and whose levels are subtherapeutic.

15.4. A 24-year-old man is brought to the emergency department by emergency medical services (EMS). The patient's mother reports that she found her son seizing on the floor of her living room approximately 30 minutes before arrival at the hospital. Two months ago, the patient returned from Mexico, where he had been incarcerated for 6 months. The mother reports that during the past 2 months she has seen her son consistently take his seizure medicine and several other pills for a "bad lung infection" he got in Mexico. She cannot remember the names of any of the medications. Several doses of IV lorazepam have been administered, with no effect on the patient's seizure activity. Which of the following medications would be the most effective in aborting his seizure activity?
- **A.** Diazepam
- **B.** Magnesium sulfate
- **C.** Phenytoin
- **D.** Pyridoxine
- **E.** Valproic acid

Answer: D. Several historical clues in this scenario point to tuberculosis being the "bad lung infection" in this patient. In patients with seizures that are refractory to benzodiazepines, isoniazid (a common medication for tuberculosis) overdose is a possibility and should be considered. Pyridoxine is the only fully effective pharmacologic treatment for toxic isoniazid seizures, although benzodiazepines have been shown to suppress seizure activity in some cases.

15.5. A mother arrives with her 10-year-old daughter (41 kg) who has been seizing for at least 10 minutes. The patient has a history of epilepsy, and a home dose of rectal diazepam has been ineffective. The mother states that the child has been in her usual state of good health until the seizure began, and there has been no history of trauma. Which of the following is the most appropriate initial action?
- **A.** Administer 10 mg midazolam intramuscularly.
- **B.** Consult neurology to obtain a bedside electroencephalogram.
- **C.** Endotracheal intubation with vecuronium and etomidate.

D. Establish vascular access and administer 2 mg of lorazepam.
E. Obtain an immediate computed tomography scan of the head.

Answer: A. Early, aggressive benzodiazepine administration is associated with decreased morbidity and mortality in status epilepticus. Intramuscular midazolam is superior to intravenous lorazepam; in addition, the dose of lorazepam is inadequate. Endotracheal intubation may ultimately be required, but is a secondary priority; use of a long-acting neuromuscular blockade agent, such as vecuronium, should be avoided. Cranial computed tomography may or may not be needed in this patient, depending on the response to benzodiazepine therapy. Bedside electroencephalograms are most useful in diagnosing nonconvulsive status epilepticus.

15.6. Paramedics present with a 24-year-old woman with a history of epilepsy after a seizure. She is somnolent but easily arousable and oriented to self and year. Her vital signs are normal, there are no signs of trauma, and an empty expired bottle of phenytoin is found in her purse. Her prehospital finger stick blood glucose level is 163 mg/dL. Which of the following treatment options is most correct?
A. Administer 20 mg/kg fosphenytoin intramuscularly and observe the patient until she returns to baseline.
B. Establish vascular access, and administer 4 mg lorazepam IV.
C. Establish vascular access, obtain a phenytoin level, and administer 1 to 2 mg lorazepam IV if the patient begins to seize.
D. Place the patient in a monitored setting, establish vascular access, and withhold diagnostic tests and treatments unless patient's condition changes.

Answer: C. Medication noncompliance is a frequent cause of seizures in adults with epilepsy. It is recommended to check phenytoin levels before administering additional drug. Because the patient is not in status epilepticus, a low dose of benzodiazepines can be considered for patients who begin to seize while undergoing a period of observation.

15.7. Which of the following is not part of the routine emergency department evaluation and treatment of a 21-year-old healthy woman with a first seizure?
A. Discharge, with early outpatient neurology follow-up
B. Evaluation of serum electrolyte levels
C. Initiation of antiepileptic drug therapy.
D. Performance of cranial computed tomography

Answer: C. Adults presenting with a first seizure should undergo cranial computed tomography and evaluation of serum electrolyte and glucose levels because abnormalities would likely influence disposition while identifying potentially life-threatening conditions. For otherwise healthy adults with normal findings after evaluation, early outpatient follow-up can be considered. In some cases, initiation of antiepileptic drugs can be considered after a first seizure; however, this should be done in consultation with the neurologist responsible for outpatient follow-up.

15.8. Which of the following findings is uniformly reliable when trying to differentiate a seizure from a syncopal episode?
A. Loss of bowel or bladder continence
B. None of these
C. Report of nonpurposeful rhythmic movements from bystanders
D. Tongue biting
E. Transient confusion after the event

Answer: B. Unfortunately, although all the findings listed are seen more commonly with seizures than with syncope, all can occur in patients with syncope. Atonic seizures, commonly called drop attacks, are not followed by a postictal state.

CHAPTER 16

Dizziness and Vertigo

Andrew K. Chang

PERSPECTIVE

Dizziness is an extremely common yet complex neurologic symptom that reflects a disturbance of normal balance perception and spatial orientation. Patients use the term *dizziness* to describe a variety of experiences, including sensations of motion, weakness, lightheadedness, unsteadiness, emotional upset, and depression. Dizziness is categorized into vertigo, near syncope, disequilibrium, and nonspecific dizziness. Vertigo is an illusion of motion, typically described as the room spinning; near syncope is feeling faint or lightheaded; disequilibrium is a sense of unsteadiness when walking; and nonspecific dizziness is generally thought to be related to a polysensory disorder with an anxiety component. Acute vestibular syndrome is used to describe a clinical condition in which dizziness develops acutely, is constant, persists longer than a day, and is accompanied by nausea or vomiting, unsteady gait, nystagmus, and intolerance to head motion.

Although common causes of dizziness (such as, benign paroxysmal positional vertigo [BPPV] and vestibular neuritis) can often be readily diagnosed via history and specific diagnostic tests, a precise diagnosis is not always possible even after imaging and neurology consultation. Although one study showed that fewer than one in 500 patients discharged with a diagnosis of dizziness or vertigo experienced a major vascular event in the month after discharge, another study found that patients discharged from the emergency department (ED) with a diagnosis of dizziness or vertigo had a twofold higher risk of a vascular event, such as stroke, on 3-year follow-up.[1,2] Thus, the challenge for the emergency clinician is to identify the patient with a dangerous underlying disorder from the many others who have benign causes.

Pathophysiology

The maintenance of equilibrium and awareness of the body in relationship to its surroundings depend on the interaction of the visual, proprioceptive, and vestibular systems. Input from these three systems is connected to the cerebellum by way of the vestibular nuclei in the brainstem. Any disease that causes a mismatch of information from any two of these systems may give rise to symptoms of vertigo.

The vestibular apparatus helps maintain head position and stabilize head movement. It is housed in the inner ear, or labyrinth, which lies embedded in the petrous portion of the temporal bone. The vestibular apparatus consists of three semicircular canals and two otolithic structures (the utricle and the saccule). The semicircular canals and the utricle are connected to each other and contain endolymph. The semicircular canals provide information about movement and angular momentum, whereas the utricle (via otoliths, which are calcium carbonate particles attached to hair cells) provides information about head tilt and linear acceleration.

The semicircular canals are paired (left and right ears) structures that normally respond to motion in a symmetrical manner. With inner ear disease, the resting discharge or the discharge stimulated by motion can be altered in one ear. This alteration produces asymmetrical responses and results in the perception of vertigo. For example, freely moving otoliths that are inappropriately located within the semicircular canals, as in BPPV, can produce positional vertigo as the otoliths move under the influence of gravity and inappropriately signal that the head is turning when it is not.

Impulses leave the vestibular apparatus by the vestibular part of the acoustic nerve (cranial nerve [CN] VIII), enter the brainstem just below the pons and anterior to the cerebellum, and proceed to the four vestibular nuclei of the brainstem and to the cerebellum. From there, impulses travel along two pathways that contribute to the clinical manifestations of vertigo: (1) the medial longitudinal fasciculus (MLF) and (2) the vestibulospinal tract, which connect to the motor neurons that supply the muscles of the extremities. In individuals with healthy vestibular systems, these connections allow the eyes to compensate for body movement in different directions and to maintain a visual axis that is stable with respect to the environment. However, patients with a defective vestibular apparatus may experience false steps or other body movements, which is different from true ataxia, as they attempt to correct for an imagined change in position. Connections between the vestibular nuclei and the autonomic system account for the perspiration, nausea, and vomiting that commonly accompany an attack of vertigo. Connections between the vestibular nuclei and the cerebellum account for the modulating influence of this organ on motor activity.

Nystagmus occurs when the synchronized vestibular information becomes unbalanced. Typically, it results from unilateral vestibular disease, which causes asymmetrical stimulation of the medial and lateral rectus muscles of the eye. This unopposed activity causes a slow movement of the eyes toward the side of the stimulus, regardless of the direction of deviation of the eyes. Then the cerebral cortex corrects for these eye movements and rapidly brings the eyes back to the midline, only to have the process repeated. By convention, the direction of nystagmus is denoted by the direction of the fast "cortical" component.

Near-syncope is due to the global reduction of blood flow to the brain. Because people rise from the supine and sitting positions frequently throughout the day, a complicated neural reflex has evolved such that the central nervous system (CNS) puts out a stimulus causing vasoconstriction and hence preservation of blood flow to the brain upon standing. When the reflex fails or is interfered with (eg, orthostatic hypotension, vasovagal syndrome, and environmental factors), pallor, nausea, rubbery legs, diaphoresis, and constriction of the visual field occur.

Disequilibrium occurs due to a disruption between the sensory inputs and motor outputs, and this often results in an unsteady gait. Disequilibrium is usually a disease of older adults because there is an age-related decline in the ability of the CNS to process sensory inputs, as well as a decline in control of postural reflexes. Disequilibrium is often exacerbated by unfamiliar surroundings, uneven ground, or poor lighting. Cervical spondylosis is a common cause and leads to spinal cord myelopathy. Patients have poor proprioception in the legs leading to a stiff-legged gait.

TABLE 16.1

Pathophysiology of Selected Causes of Peripheral Vertigo

DIAGNOSIS	PATHOPHYSIOLOGY
Benign paroxysmal positional vertigo (BPPV)	Otoliths inappropriately displaced from utricle into semicircular canals (posterior >> horizontal > anterior)
Vestibular neuritis and labyrinthitis	Inflammation (possibly viral) of the vestibular nerve
Ménière's disease	Endolymphatic hydrops (excessive endolymph in the inner ear)
Perilymph fistula	Abnormal opening between the middle and inner ear

BOX 16.1

Causes of Vertigo

PERIPHERAL CAUSES

Benign paroxysmal positional vertigo (BPPV)
Vestibular neuritis (or neuronitis)/labyrinthitis
Ménière's disease
Foreign body in ear canal
Acute otitis media
Perilymphatic fistula
Trauma (labyrinth concussion)
Motion sickness
Acoustic neuroma

CENTRAL CAUSES

Vertebral basilar artery insufficiency
Cerebellar hemorrhage or infarction
Tumor
Migrainous vertigo
Multiple sclerosis
Post-traumatic injury (temporal bone fracture, postconcussive syndrome)
Infection (encephalitis, meningitis, brain abscess)
Temporal lobe epilepsy
Subclavian steal syndrome

The mechanism of nonspecific dizziness is poorly understood but is thought to result from impaired central integration of sensory signals. Patients sometimes have difficulty describing their dizziness and are often in a hypervigilant state. Their exaggeration of reactions to normal changes may induce psychological stress. Table 16.1 lists the pathophysiology for selected causes of peripheral vertigo.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis for peripheral and central vertigo is summarized in Box 16.1. More detailed information is given on selected causes in Table 16.2. A symptom-based approach to categorizing dizziness identifies four categories: (1) vertigo, (2) near syncope, (3) disequilibrium, and (4) nonspecific dizziness. Unfortunately, this approach is imprecise and new categorization systems have been proposed. One system uses three general categories: (1) acute severe dizziness (eg, vestibular neuritis, stroke), (2) recurrent attacks of dizziness (eg, Ménière's disease, transient ischemic attack (TIA), and (3) recurrent positional dizziness (eg, BPPV, cerebellar tumor, multiple sclerosis). Another system uses a "timing and triggers" approach, resulting in four categories: (1) acute vestibular syndrome (eg, vestibular neuritis, cerebellar stroke), (2) spontaneous episodic vestibular syndrome (eg, Ménière's disease, vertebrobasilar insufficiency [VBI]), (3) triggered episodic vestibular syndrome (eg, BPPV), and (4) chronic vestibular syndrome (eg, polysensory dizziness, psychiatric syndromes, posterior fossa lesions).[3] Neither of these approaches has been prospectively validated or systematically studied as a diagnostic paradigm, but they provide an alternative way of thinking about dizziness and vertigo.

If the patient has true vertigo, then the cause is either a peripheral lesion, such as from the vestibular system, or a central process, such as cerebrovascular disease or a neoplasm. This distinction is important because peripheral disorders are generally benign, whereas central disorders usually have serious consequences. Box 16.1 lists causes of peripheral and central vertigo. Table 16.3 summarizes the different characteristics of peripheral and central vertigo.

Pivotal Findings

Symptoms

Vertigo is described as the environment spinning; however, any sensation of disorientation in space or sensation of motion can qualify as vertigo. Vertigo is generally associated with some degree of nausea, vomiting, pallor, and perspiration. Peripheral vertigo is not associated with a change in mentation or syncope. A sensation of imbalance often accompanies vertigo, and this can be difficult to distinguish from true instability, disequilibrium, or ataxia, findings of which indicate a higher likelihood of a central process.

The time of onset and the duration of vertigo are important clues to the cause. For example, episodic vertigo produced primarily by a change in position and lasting less than a minute suggests BPPV. A patient with BPPV often thinks his vertigo is constant, because every time he moves his head, he gets vertigo. By teasing out how long each *individual* episode of vertigo lasts, the physician will be led to the correct diagnosis of BPPV. Acute vestibular syndrome has an arbitrary cutoff of continuous vertigo for at least 1 day, in part to help differentiate acute vestibular syndrome from attacks of Ménière's disease or prolonged migrainous vertigo.

The presence of auditory symptoms suggests a peripheral cause of the vertigo, usually on the side of end-organ disturbance. Acoustic neuroma, which can rarely cause vertigo, is usually associated with progressive unilateral hearing loss, typically of several months' duration. Hearing loss, vertigo, and tinnitus form the characteristic triad of Ménière's disease. Labyrinthitis is differentiated from vestibular neuritis in that the former is associated with hearing loss.

Head injury can cause vertigo occasionally from intracerebral injury and more commonly from labyrinth concussion. Neck injury can cause vertigo from vertebral artery dissection, resulting in posterior circulation ischemia.

Associated neurologic symptoms such as imbalance, dysarthria, or numbness raise the likelihood of TIA and stroke. Although the vast majority of patients with isolated dizziness/vertigo do not have TIA or stroke, they can be the only initial symptoms of cerebellar and other posterior circulation bleeds, TIAs, and infarction. In these cases, diagnostic testing is directed by assessment of risk based on the history and physical examination.[4] Older age, male sex, hypertension, coronary heart disease, diabetes, and atrial fibrillation put patients at higher risk for TIA and stroke. Many medications (such as, aminoglycosides, anticonvulsants, alcohols, quinine, quinidine, and minocycline) have direct vestibulotoxicity.

TABLE 16.2

Selected Causes of Peripheral and Central Vertigo

CAUSE	HISTORY	ASSOCIATED SYMPTOMS	PHYSICAL
PERIPHERAL			
1. Benign paroxysmal positional vertigo (BPPV)	Short-lived (typically less than 30 seconds), positional, fatigable episodes; more often in older adults.	Nausea, vomiting	Certain positions can precipitate vertigo. Positive result on Hallpike test (posterior semicircular canal) or supine roll test (horizontal canal).
2. Vestibular neuritis/ labyrinthitis	Vertigo may develop suddenly or evolve over several hours, usually increasing in intensity for hours, then gradually subsiding over several days but can last weeks. Can be worsened with positional change. Sometimes history of viral infection precedes initial attack. Highest incidence is found in third and fifth decades.	Nausea, vomiting	Spontaneous nystagmus beating away from the side of the lesion may be present in the first few hours. Positive head impulse test. Hearing is normal in vestibular neuritis; hearing loss for labyrinthitis.
3. Ménière's disease	Recurrent episodes of severe rotational vertigo usually lasting hours. Onset usually abrupt. Attacks may occur in clusters. Long symptom-free remissions.	Nausea, vomiting, tinnitus, hearing loss (hearing loss required for diagnosis)	Positional nystagmus is not present; hearing loss
CENTRAL			
1. Vascular disorders			
A. Vertebrobasilar insufficiency (VBI)	Should be considered in any patient of advanced age with isolated new-onset vertigo without an obvious cause. More likely with history of atherosclerosis. Can occur with neck trauma. May be preceded by an episode usually lasting minutes.	Often headache; usually neurologic symptoms including dysarthria, ataxia, weakness, numbness, double vision; tinnitus and hearing loss uncommon but possible	Neurologic deficits usually present, but initially neurologic examination can be normal.
B. Cerebellar hemorrhage	Sudden onset of severe symptoms.	Headache, vomiting, ataxia	Signs of toxicity. Dysmetria, true ataxia. Ipsilateral sixth cranial nerve palsy may be present.
C. Occlusion of posterior inferior cerebellar artery (Wallenberg's syndrome)	Vertigo associated with significant neurologic complaints.	Nausea, vomiting, loss of pain and temperature sensation, ataxia, hoarseness	Loss of pain and temperature sensation on the side of the face ipsilateral to the lesion and on the opposite side of the body, paralysis of the palate, pharynx, and larynx. Horner's syndrome (ipsilateral ptosis, miosis, and decreased facial sweating).
2. Head trauma	Symptoms begin with or shortly after head trauma. Positional symptoms most common type after trauma. Self-limited symptoms that can persist weeks to months.	Usually mild nausea	Occasionally, basilar skull fracture.
3. Migrainous vertigo	Vertigo attacks can occur during the headache (in one study of 33 patients 24% always had headache with vertigo and 67% had headache sometimes with vertigo) but often occur during the headache-free interval. Most patients have a family history of migraine. Syndrome usually begins in adolescence.	Imbalance, head motion intolerance, photophobia, phonophobia, oscillopsia	No residual neurologic or otologic signs are present after attack.
4. Multiple sclerosis	Vertigo presenting symptom in 7% to 10% and appears in the course of the disease in a third. Onset may be severe. Disease onset usually between ages of 20 and 40. Often history of other attacks with varying neurologic signs or symptoms.	Nausea and vomiting, which may be severe	May have horizontal, rotary, or vertical nystagmus. Nystagmus may persist after the vertiginous symptoms have subsided. Internuclear ophthalmoplegia (INO) highly suggestive for multiple sclerosis. INO is diagnosed when, on eye movement, the adducting eye shows little to no movement while the abducting eye moves normally.

TABLE 16.3

Characteristics of Peripheral and Central Vertigo

CHARACTERISTIC	PERIPHERAL	CENTRAL
Onset	Sudden	Gradual or sudden
Intensity	Severe initially, often decreasing over time	Mild in most but can be severe in stroke and multiple sclerosis
Duration	Intermittent episodes lasting seconds to less than a minute for BPPV; continuous and lasting hours to days for vestibular neuritis	Usually weeks, months (continuous) but can be seconds or minutes with vascular causes, such as with posterior circulation TIA
Direction of nystagmus	Usually torsional and upbeat (fast phase beating toward forehead) in classic posterior canal BPPV; horizontal in horizontal canal BPPV; horizontal-torsional in vestibular neuritis/labyrinthitis	Purely vertical, spontaneous and purely torsional, direction-changing on lateral gaze, downbeating (fast phase beats toward nose)
Effect of head position	Induces vertigo (BPPV); worsens vertigo (vestibular neuritis)	Usually little change but can worsen with head position change
Associated neurologic findings	None	Usually present
Associated auditory findings	May be present, including tinnitus (Ménière's disease) and hearing loss (labyrinthitis)	Rarely

BPPV, Benign paroxysmal positional vertigo; *TIA,* transient ischemic attack.

Physical Examination

Vital Signs. The vital signs, including orthostatic changes, may be the key to identifying a cardiovascular etiology or drug effect as the cause of dizziness. When subclavian steal syndrome is suspected, which also can cause VBI, the pulse and blood pressure should be checked on both sides.

Head and Neck. Carotid or vertebral artery bruits suggest atherosclerosis and risk for TIA or stroke. The vertebral artery can be auscultated in the supraclavicular region.

Fluid in the middle ear as a result of a middle ear infection may cause mild vertigo, as can occlusion of the eustachian tubes associated with an upper respiratory tract infection or descent barotrauma. A perforated or scarred eardrum may indicate a perilymphatic fistula, especially if the history includes previous trauma.

Examination of the eyes is critical in assessing a patient with vertigo. Pupillary abnormalities may indicate third cranial nerve or descending sympathetic tract involvement. Papilledema suggests increased intracranial pressure. Relatively subtle extraocular movement abnormalities can be the only clue to a cerebellar hemorrhage. A sixth cranial nerve palsy ipsilateral to the hemorrhage may result from early brainstem compression by the expanding hematoma. Internuclear ophthalmoplegia, which indicates brainstem pathology, is recognized when the eyes are in a normal position on straight-ahead gaze, but on eye movement the adducting eye (CN III) is weak or shows no movement while the abducting eye (CN VI) moves normally (although often displaying a coarse nystagmus). This finding indicates an interruption of the MLF on the side that demonstrates third cranial nerve weakness and is virtually pathognomonic of multiple sclerosis.

Abnormal nystagmus is the cardinal sign of inner ear disease and the principal objective evidence of abnormal vestibular function. Positional nystagmus, induced by changing the position of the head, strongly suggests an organic vestibular disorder, typically BPPV. Noting the characteristics of the nystagmus can help to differentiate benign peripheral causes from serious central causes (see Table 16.3). Central causes of nystagmus are more likely when the pattern of nystagmus is purely vertical, downbeating (fast phase beating toward the nose), non-fatigable, direction changing with gaze, or spontaneous pure torsional. Severity of nystagmus is directly related to the degree of acute vestibular hypofunction that occurs. Spontaneous nystagmus usually occurs in severe cases. In mild cases, vestibular asymmetry is less prominent, so spontaneous nystagmus may be subtle or present only for the first few hours. After that it may be only detectable when the patient looks away from the damaged ear or if the examiner performs a head impulse test.

Neurologic Examination. The presence of cranial nerve deficits suggests a space-occupying lesion in the brainstem or cerebellopontine angle, such as an acoustic neuroma, which can rarely manifest with vertigo.

Cerebellar function is tested several ways. Dysmetria is the inability to arrest a muscular movement at the desired point and should be assessed with finger-to-finger or finger-to-nose pointing. Dysdiadochokinesia (an inability to perform coordinated muscular movement smoothly) is assessed with rapid alternating movements.

Gait assesses ataxia, which when of recent and relatively sudden onset suggests cerebellar hemorrhage or infarction in the distribution of the posterior inferior cerebellar artery or the superior cerebellar artery. Ataxia that is slowly progressive suggests chronic cerebellar disorders. True ataxia may be difficult to discern from the unsteadiness that occurs when a patient with significant vertigo attempts to walk, although other findings (such as, nystagmus and dysmetria) can help narrow the differential diagnosis. This examination is performed when the patient is both sitting and standing, because truncal ataxia, which is seen in midline cerebellar lesions, may become obvious only when the patient has to sit, stand, or walk unaided. Any marked abnormality (eg, consistent falling or a grossly abnormal gait) should suggest a central lesion, especially in a patient whose vertiginous symptoms have subsided. Patients with an acute peripheral vestibular lesion typically can stand, although they will likely veer toward the side of the lesion. Patients with central vertigo often cannot stand without support. The main features of a cerebellar gait are a wide base, unsteadiness, irregularity of steps, tremor of the trunk, and lurching from side to side. The unsteadiness is most prominent on arising quickly from a sitting position, turning quickly, or stopping suddenly while walking. Patients with gait ataxia also cannot perform heel-to-toe walking.

Positional Testing. Positional testing can confirm the diagnosis of BPPV. The Hallpike test, also known as the *Dix-Hallpike*

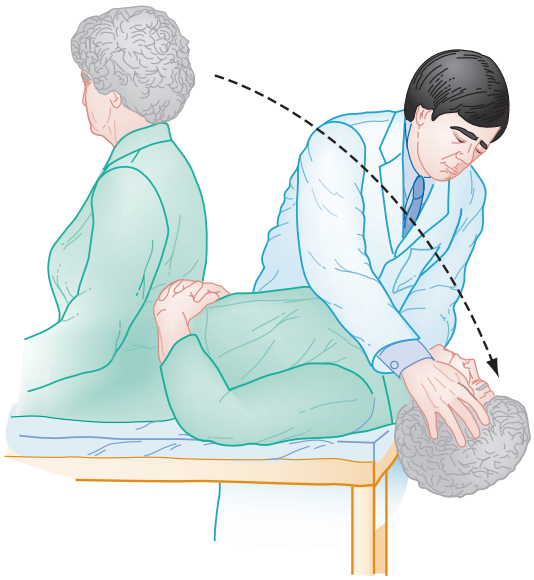

Fig. 16.1. Testing for positional vertigo and nystagmus.

test or the *Nylen-Barany test,* confirms the diagnosis of posterior canal BPPV, which is the most common variant of BPPV.[5] This test should be reserved for those patients suspected of positional vertigo, and caution should be exercised in performing it in patients with acute vestibular syndrome (acute and constant dizziness, nausea or vomiting, unsteady gait, nystagmus, and intolerance to head motion lasting more than a day) whose main differential diagnosis include vestibular neuritis and stroke.[6] Some evidence indicates that provocative testing may lead to a nonspecific worsening of symptoms in these patients, which could be misinterpreted as diagnostic of a peripheral disorder before stroke has been adequately excluded. Thus, if a patient is actively experiencing vertigo during history taking and there has been no immediate prior head movement, then the Hallpike test should not be performed because this history is inconsistent with BPPV, which requires head movement to elicit symptoms.

The Hallpike test is performed with the patient sitting up. The examiner turns the patient's head 45 degrees to one side and then moves the patient from the upright seated position to a supine position with the head overhanging the edge of the gurney (Fig. 16.1). The patient is queried for the occurrence of vertigo, and the eyes are observed for nystagmus after a latency period on the order of a few seconds. In a patient with classic posterior canal BPPV, the nystagmus usually lasts 5 to 30 seconds and is combined upbeating (the fast phase beats toward the forehead) and ipsilateral torsional (the top pole beating toward the downward ear). The patient is then brought back up to the seated position, and the test is repeated with the head turned 45 degrees to the other side. Findings are summarized in Box 16.2.

In general, if the patient has posterior canal BPPV, only one side should be positive during the Hallpike test, although it is theoretically possible to have otoliths inappropriately located in both right and left posterior semicircular canals. Assuming unilateral involvement, the downward ear indicates the involved side, which is the side to start with when treating with the curative bedside Epley maneuver. If the patient pre-identifies the side that causes the symptoms, we test the opposite side first, and this should result in a negative Hallpike test. We then test the other side and, if positive, continue on to complete the Epley maneuver. (The first step of the Epley maneuver is the first part of the Hallpike test, which involves turning the head 45 degrees to the involved side and then laying the patient with the head hanging over the edge of the gurney.)

BOX 16.2

Classic Findings During Hallpike Test in Posterior Canal Benign Paroxysmal Positional Vertigo

Latency (delay in nystagmus and vertigo once in head-hanging position) of approximately 3 to 10 seconds, although delay can take up to 30 seconds on rare occasions
Reproduction of vertigo symptoms in head-hanging position
Upbeat (fast phase toward forehead) and torsional nystagmus (usually toward the downward ear)
Vertigo and nystagmus escalates in head-hanging position, then slowly resolves over 5 to 30 seconds
Nystagmus and vertigo may reverse direction when patient returns to sitting position
Nystagmus and vertigo decrease with repeated testing (fatigability)

If the Hallpike test is negative or seems to be positive bilaterally, one can use the supine roll test to test for the horizontal canal variant of BPPV.[7,8] The patient starts in the supine position and unlike the Hallpike test, the head does not need to overhang the edge of the gurney. The head is then turned 90 degrees to each side. With a positive test, the patient will have reproduction of symptoms and horizontal nystagmus with the head turned in either direction. The side that is involved is the one with the more intense symptoms and more dramatic nystagmus. Note that the nystagmus will change direction, but this is due to a change in head position and not from a change in gaze direction and so is not concerning for a central cause of vertigo. A video of a case involving failed attempts at the barbeque roll to treat horizontal BPPV, followed by conversion to posterior canal BPPV after a Gufoni maneuver (with resultant cure using the Epley maneuver), can be found at www.youtube.com/watch?v=iOJOArGmepM.

The head impulse, or head-thrust test, is used to diagnose vestibular neuritis and labyrinthitis. The physician stands face to face with the patient and places both hands on the sides of the patient's head. The patient stares at the examiner's nose while the examiner rapidly turns the patient's head approximately 10 degrees to one side. Normally the patient's eyes should keep focusing on the examiner's nose. If there is a problem with the vestibular nerve, the eyes will temporarily move along with the head. A corrective saccade will then occur, in which the eyes jerk back toward the midline. If a saccade is seen, this denotes a positive head-thrust test result and indicates vestibular nerve dysfunction. In general, eliciting a positive head impulse test indicates a benign peripheral cause of vertigo, such as vestibular neuritis. The head must be turned rapidly because a false negative test may result otherwise, leading to incorrectly suspecting a central cause.

HINTS. *HINTS* (*H*ead *I*mpulse test, *N*ystagmus, *T*est of *S*kew) is a bedside oculomotor examination test that has been proposed as a way to differentiate central from peripheral vertigo in patients with acute vestibular syndrome. The majority of such patients will have vestibular neuritis, but the HINTS examination may help to identify the smaller numbers who are suffering from stroke or other central causes of vertigo.

The first part of HINTS is the head impulse test and as described earlier, a corrective saccade indicates a positive test and is more reassuring for vestibular neuritis. The second part (nystagmus) refers to a direction change of nystagmus on eccentric gaze. For example, when the patient looks to the left, the fast component beats to the left; and when the patient looks to the right, the fast component beats to the right. This direction-changing nystagmus may indicate a stroke in a patient with acute vestibular

TABLE 16.4

Differentiating Benign Paroxysmal Positional Vertigo From Vestibular Neuritis/Labyrinthitis

	BENIGN PAROXYSMAL POSITIONAL VERTIGO	VESTIBULAR NEURITIS/LABYRINTHITIS
Age	More common in older adults	More common in younger patients
Hearing loss	None	None in vestibular neuritis; hearing loss in labyrinthitis
Frequency of symptoms	Episodic (occurs with certain movements of the head)	Constant
Hallpike test	Positive usually on one side only with upbeat and torsional nystagmus and reproduction of vertigo symptoms	Symptoms may be worsened in head-hanging position (*Note:* It is advised not to administer Hallpike test in a patient with a clinical history consistent with vestibular neuritis or labyrinthitis.)
Head impulse test	Negative (*Note:* It is advised not to administer head impulse test in a patient with a clinical history consistent with BPPV.)	Positive (corrective saccade seen)
Epley maneuver	Highly effective	Ineffective
Recurrence	Frequent	Rare (2% to 11%)

BPPV, Benign paroxysmal positional vertigo.

syndrome. The third part (test of skew) refers to vertical ocular misalignment during alternate cover testing and its presence is suggestive of brainstem strokes.[9] Using HINTS requires experience and practice, and it should only be used in patients with a first ever episode of constant vertigo from acute vestibular syndrome as was required in the clinical studies involving the HINTS exam. For example, applying the head impulse test in a patient who is dizzy from BPPV would result in a negative test and may cause the emergency physician to incorrectly conclude that the patient's dizziness could be from a central cause of vertigo. In general, performing both the Hallpike test and the HINTS examination on the same patient is not appropriate. Instead, BPPV and acute vestibular syndrome should be distinguished from each other by history and by the presence of spontaneous nystagmus.

Ancillary Testing

Most routine laboratory testing is not helpful in the evaluation of a vertiginous patient except for a finger-stick blood glucose test. Blood counts and blood chemistries are helpful if the dizziness is described as lightheadedness. An electrocardiogram can evaluate for myocardial ischemia or dysrhythmia as a potential cause.

Radiologic Imaging. Acute vertigo by itself does not warrant urgent computed tomography (CT) or magnetic resonance imaging (MRI) in all patients, particularly patients in whom a clear picture of peripheral vertigo emerges, such as with BPPV. Risk factor assessment can be helpful in deciding which patients warrant imaging: Older age, male sex, hypertension, coronary artery disease, diabetes, and atrial fibrillation put patients at higher risk for more serious causes of dizziness and vertigo.

If cerebellar hemorrhage, cerebellar infarction, or other central lesions are suspected, emergent CT or MRI of the brain is indicated. MRI, when available, has become the diagnostic modality of choice for posterior fossa (cerebellum, medulla, and pons) lesions, as well as for rare causes of vertigo, including acoustic neuroma and multiple sclerosis.

DIAGNOSTIC ALGORITHM

Most cases of vertigo are of peripheral origin and are not usually life-threatening. BPPV and vestibular neuritis are likely the most common peripheral causes of vertigo encountered in the ED. However, they are diagnosed and treated very differently. Table 16.4 helps to differentiate between these two diagnoses (Fig. 16.2).

EMPIRICAL MANAGEMENT

Management is based on an accurate diagnosis that distinguishes the serious central causes of vertigo from the less serious peripheral causes. Any suggestion of cerebellar hemorrhage warrants immediate imaging with CT or MRI and neurosurgery consultations. VBI should be considered in any patient of advanced age or at high risk of cerebrovascular disease who presents with isolated, new-onset vertigo without an obvious cause. Because of the possibility of progression of new-onset VBI in the first 24 to 72 hours, hospital or observation unit admission and consideration of early magnetic resonance angiography (MRA) are reasonable, even in a stable patient. Changing or rapidly progressive symptoms suggest impending posterior circulation occlusion. If CT or MRI excludes hemorrhage as the source of the patient's symptoms, an immediate neurologic consultation, further imaging (such as, angiography), and possible anticoagulation are indicated.

Canalith repositioning maneuvers, such as the Epley maneuver, are extremely effective in treating BPPV, including in the ED setting.[10] The Epley maneuver, which is used to treat posterior semicircular canal BPPV, involves four to five sequential rotations of the head, holding each position for approximately 30 seconds or until the nystagmus and vertigo resolves, as demonstrated in Figure 16.3. Failure of the Epley maneuver is usually due to one of two problems: First, the head is lifted too high during the third step of the Epley maneuver, in which the patient rolls onto his side and looks toward the ground. Second, the Epley maneuver is often inappropriately applied to a patient who has vestibular neuritis, which is distinct from BPPV (see Table 16.4).

The "barbecue roll" is a simple maneuver that can be used to treat the horizontal canal variant of BPPV, which is diagnosed by the supine roll test. The patient lies flat on the gurney with the head turned 90 degrees to the involved side. The head is then rotated in 45-degree intervals away from the involved side (each turn is held approximately 30 seconds or until nystagmus and vertigo resolve). Eventually the patient needs to turn over into the prone position. The maneuver is completed once the head has returned to the original starting position. The Gufoni maneuver is an alternative treatment for the horizontal canal variant (see http://careguides-videos.med.umich.edu/media/Gufoni+Left+Horizontal-Geotropic/1_3sii1rw8/20345631).

Two relatively recent practice guidelines were published that included information on the use of medications to treat BPPV. One found no evidence to support a recommendation of any medication in the routine treatment of BPPV.[11] The other

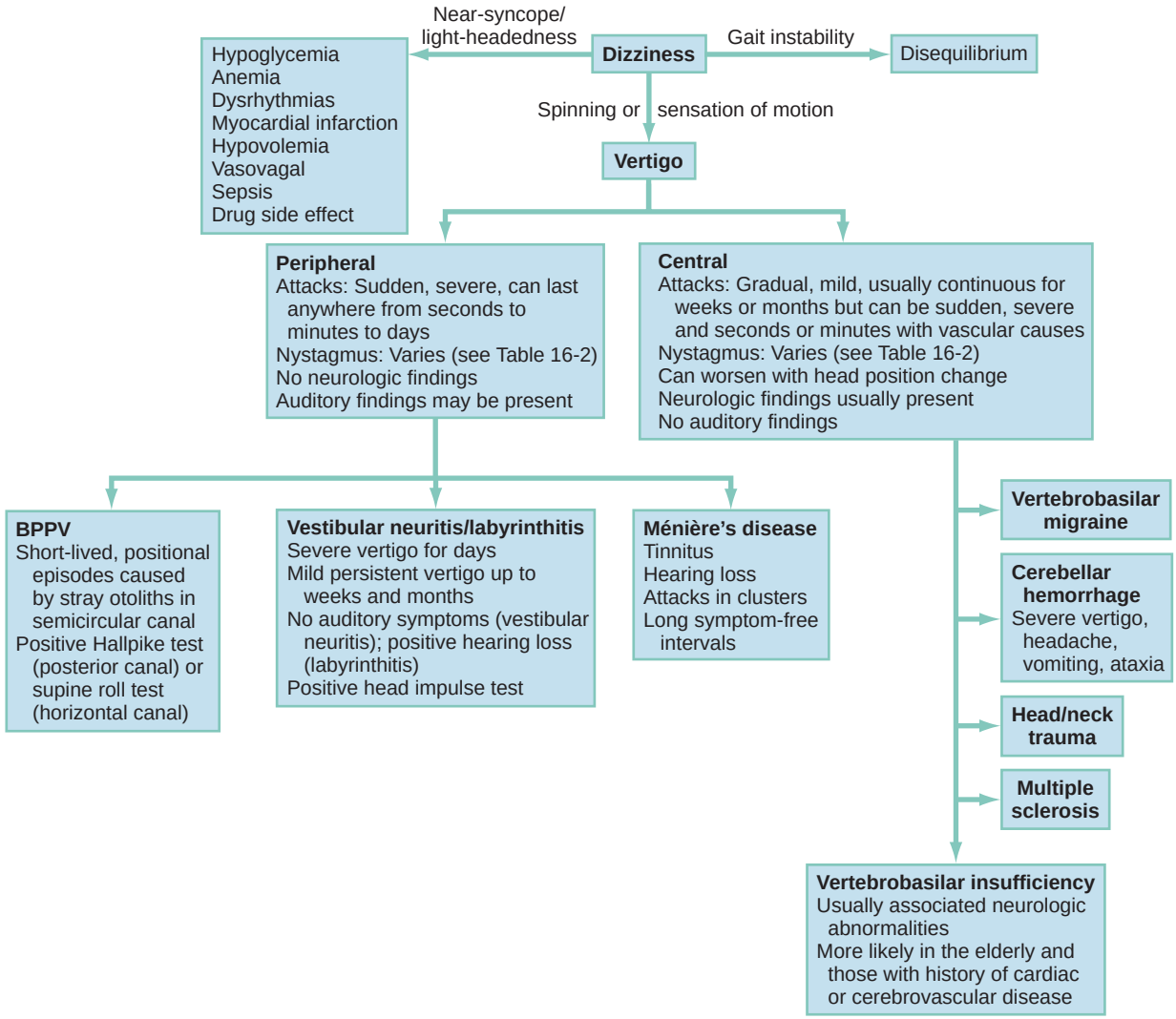

Fig. 16.2. Diagnostic algorithm for dizziness and vertigo. *BPPV,* Benign paroxysmal positional vertigo.

concluded that clinicians should not routinely treat BPPV with vestibular suppressant medications.[12] However, both guidelines were from specialty societies whose patients often have chronic and likely milder forms of BPPV than patients who develop acute BPPV and come to the ED. For ED patients who are actively vomiting or cannot tolerate canalith repositioning maneuvers and for those with other causes of acute vertigo (such as, vestibular neuritis), it is reasonable to administer vestibular suppressants.

Most vestibular suppressants are antiemetic medications (Table 16.5), which not only suppress nausea and vomiting but also decrease the sensation of vertigo. Although promethazine (Phenergan) is likely the most effective parenteral vestibular suppressant, the U.S. Food and Drug Administration (FDA) has given intravenous use of promethazine a black box warning, and it is now recommended to be administered only in intramuscular or oral forms.[13] Trials using various agents including dimenhydrinate, lorazepam, and droperidol have given mixed results. We recommend intravenous ondansetron as the first line intravenous medication for symptomatic vertigo. Patients with intractable vertigo and vomiting that are unresponsive to antiemetics can be given an intravenous benzodiazepine, such as 1 to 2 mg of intravenous lorazepam. However, it is generally not recommended to discharge patients with oral benzodiazepines, especially in patients with vestibular neuritis and labyrinthitis because these patients undergo a process of vestibular habituation, in which the vestibular system learns to adapt to the mismatch of information it is receiving, and benzodiazepines can interfere with this process.

Meclizine (Antivert) 25 mg every 4–6 hours can be given in the ED, although its time of onset is approximately 1 hour. Because it can exacerbate symptoms in patients with non-vertiginous types of dizziness, it should be reserved for patients with BPPV who have failed the Epley maneuver or for patients who have an alternative diagnosis of peripheral vertigo, such as vestibular neuritis. Transdermal scopolamine has shown disappointing results for treatment of peripheral vertigo but may be considered a third-line option.

Vestibular neuritis, which is inflammation of the eighth cranial nerve, is thought to have a similar mechanism to Bell palsy.[14] Patients typically have severe vertigo for 1 to 2 days with gradual resolution over weeks to months. Nystagmus may be spontaneous during the first several hours of symptoms, and patients will have a positive head impulse test. Although the evidence is weak, corticosteroids are possibly helpful using a 22-day taper of methylprednisolone beginning with a dose of 100 mg each morning.[15] Antivirals, such as valacyclovir, are not helpful in the treatment of vestibular neuritis. Until certainty is reached, we recommend steroid treatment with prednisone (or methylprednisolone) with a gradual taper over 2 to 3 weeks, although shared decision making with the patient is an acceptable alternative.

Some cases of Ménière's disease have been treated successfully with vasodilation and diuretic therapy. Diets low in sodium and

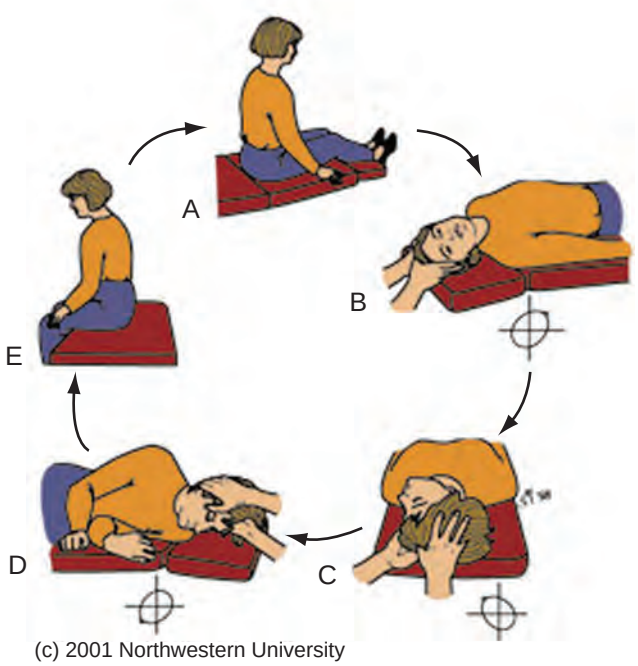

Fig. 16.3. A to **E,** The Epley maneuver for benign paroxysmal peripheral vertigo, also known as the *particle repositioning* or *canalith repositioning procedure.* (Image used with permission of Timothy C. Hain, Professor of Neurology, Feinberg School of Medicine, Northwestern University, www.dizziness-and-balance.com/disorders/bppv/bppv.html.)

TABLE 16.5

Medications for Acute Vertigo

DRUG	USUAL STARTING DOSAGE	ANTIEMETIC ACTION
Promethazine (Phenergan)	25 mg IM, PO, PR (black box warning for IV administration)	Moderate
Ondansetron (Zofran)	4 mg IV, SL/PO, IM	Prominent
Dimenhydrinate (Dramamine)	50 mg IM, IV, PO	Moderate
Prochlorperazine (Compazine)	10 mg IV, IM, PO, PR	Prominent
Droperidol (Inapsine)	2.5 mg IM (black box warning for IV administration)	Prominent
Metoclopramide (Reglan)	10 mg IV, IM, PO	Prominent
Lorazepam (Ativan)	1 mg IV, IM, PO	Mild
Diazepam (Valium)	2.5 to 5.0 mg IV, IM, PO	Mild
Meclizine (Antivert)	25 mg PO	Mild
Scopolamine (Transderm-Scop)	0.2 mg transdermal patch, IM, PO	Moderate

IM, Intramuscular; *IV,* intravenous; *PO, per os* (by mouth); *PR,* per rectum; *SL,* sublingual.

caffeine and cessation of smoking also have been helpful. However, the diagnosis of Ménière's disease requires documentation of hearing loss, so this is not a diagnosis that can be typically made during an ED visit.

DISPOSITION

Documented or suspected VBI or cerebellar hemorrhage or infarction require diagnostic evaluation, treatment, and, usually, hospitalization. In patients older than age 55 with vascular risk factors, admission for observation and imaging of cerebral vasculature should be considered if the diagnosis is not certain. Most younger patients with peripheral causes of vertigo can be discharged from the ED after symptoms have been controlled. Some patients with peripheral vertigo may have such severe symptoms (eg, intractable vomiting, inability to walk) despite medications that they require hospital admission for intravenous hydration, vestibular suppressants, and antiemetics. Reassessment of neurologic examination findings and response to therapy are important to ensure that the vertigo is not of central origin. Discharged patients should receive primary care, neurology, or otolaryngology follow-up, particularly if symptoms are not significantly improved within 72 hours or are worsening despite symptomatic treatment.

KEY CONCEPTS

1. Associated neurologic complaints, such as imbalance, dysarthria, or numbness raise the likelihood of TIA or stroke as the cause of a patient's dizziness/vertigo.
2. Benign paroxysmal positional vertigo (BPPV) requires head movement to elicit symptoms. Consequently, the Hallpike test should *not* be performed if the patient is actively symptomatic during history taking (and the patient's head has not been recently moved) because such a history is inconsistent with BPPV.
3. When performing the Hallpike test, the head should be turned to the side 45 degrees prior to laying the patient back into the head-hanging position.
4. A positive Hallpike test should elicit upbeating nystagmus.
5. The Epley maneuver is used to treat posterior semicircular canal BPPV, which is the most common subtype of BPPV.
6. Central causes of nystagmus are more likely when the pattern of nystagmus is purely vertical, downbeating (fast phase beating toward the nose), non-fatigable, direction changing with gaze, or spontaneous pure torsional.
7. The presence of auditory symptoms suggests a peripheral cause of the vertigo.
8. Acute vestibular syndrome is diagnosed when dizziness develops acutely; is constant; is accompanied by nausea or vomiting, unsteady gait, nystagmus, and intolerance to head motion; and persists for longer than a day.
9. Neck injury can cause vertigo from vertebral artery dissection, resulting in posterior circulation ischemia.
10. Abnormal nystagmus is the cardinal sign of inner ear disease and the principal objective evidence of abnormal vestibular function.
11. *HINTS* (*H*ead *I*mpulse test, *N*ystagmus, *T*est of *S*kew) is a bedside oculomotor examination test that has been proposed as a way to differentiate central from peripheral vertigo in patients with a first ever onset of constant vertigo from acute vestibular syndrome.
12. Meclizine (Antivert) has a time of onset of approximately 1 hour.
13. Do not prescribe benzodiazepines to patients with vestibular neuritis or labyrinthitis who are discharged home. Such medications can interfere with the process of vestibular rehabilitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 16: QUESTIONS & ANSWERS

16.1. Which maneuver should be used to treat benign paroxysmal positional vertigo (BPPV) of the horizontal semicircular canal?
- **A.** Barbeque roll
- **B.** Epley maneuver
- **C.** Hallpike test
- **D.** Head impulse test

Answer: A. The Epley maneuver is used to treat posterior canal BPPV. The Hallpike test is used to diagnose posterior canal BPPV. The head impulse test is used to diagnose vestibular neuritis and labyrinthitis. The supine roll test, in which the patient lies flat on the gurney and the head is turned to each side, is used to diagnose horizontal canal BPPV, whereas the barbeque roll maneuver is used to treat the horizontal variant of BPPV.

16.2. Which of the following examination findings requires further testing and/or consultation with a specialist?
- **A.** Direction changing nystagmus on change in head position
- **B.** Direction changing nystagmus on change in lateral gaze
- **C.** Positive head impulse test
- **D.** Torsional upbeat nystagmus during Hallpike test

Answer: B. Direction changing nystagmus on change in gaze is concerning for a central cause of vertigo and makes up part of the HINTS test.

16.3. Internuclear ophthalmoplegia most often suggests a diagnosis of:
- **A.** Horizontal canal BPPV
- **B.** Labyrinthitis
- **C.** Multiple sclerosis
- **D.** Vestibular neuritis

Answer: C. Internuclear ophthalmoplegia is diagnosed when, on eye movement, the adducting eye shows little to no movement while the abducting eye moves normally. In a vertigo patient, this finding is virtually pathognomonic for multiple sclerosis.

16.4. Which of the following is a central cause of vertigo?
- **A.** Labyrinthitis
- **B.** Ménière's disease
- **C.** Vertebrobasilar insufficiency
- **D.** Vestibular neuritis

Answer: C. All the other causes are peripheral.

16.5. Continuous vertigo of what duration is used to define acute vestibular syndrome?
- **A.** 1 hour
- **B.** 8 hours
- **C.** 24 hours
- **D.** 1 week

Answer: C. Acute vestibular syndrome has an arbitrary cutoff of continuous vertigo for at least 1 day in part of help differentiate acute vestibular syndrome from attacks of Ménière's disease or prolonged migrainous vertigo.

CHAPTER 17

Headache

Christopher S. Russi | Laura Walker

PERSPECTIVE

Headache is consistently among the top reasons for visit to the emergency department (ED). The vast majority of patients who have a primary complaint of headache do not have a serious medical cause for the problem. Most common primary headache etiologies are benign, such as tension headache and migraine. A minority of headaches will be secondary to an underlying medical or surgical condition; a patient may present with headache due to a serious life-threatening disease requiring prompt diagnosis and treatment. The low incidence of serious disease can create a "needle in the haystack" phenomenon, and headache is disproportionately represented in emergency medicine malpractice claims despite widespread overuse of imaging for benign headache conditions. Although representing only 0.5% to 6% of presentations of acute headache to the ED, the most important and commonly encountered life-threatening cause of severe sudden head pain is subarachnoid hemorrhage (SAH).[1] Unfortunately, this is a diagnosis that is also missed on first presentation over 25% of the time.[2] The other significant, potentially life-threatening causes of headache occur even less frequently. As is the case for SAH, these other serious disorders (ie, meningitis, carbon monoxide poisoning, temporal arteritis, acute angle-close glaucoma, intracranial hemorrhage [ICH], cerebral venous sinus thrombosis, and increased intracranial pressure) can often be linked with specific historical elements and physical findings that facilitate their diagnosis.

Pathophysiology

The brain parenchyma is insensitive to pain. The pain-sensitive areas of the head include the meninges, the arteries and veins supplying the brain, and the various tissues lining the cavities within the skull. The ability of the patient to specifically localize head pain is often poor. Much of the pain associated with headache, particularly with vascular headache and migraines, is mediated through the fifth cranial nerve. Such pain may proceed back to the nucleus and then be radiated through various branches of the fifth cranial nerve to areas not directly involved. Inflammation in a specific structure (eg, periapical abscess, sinusitis, or trigeminal neuralgia) is much easier to localize than the relatively diffuse pain that may be generated by tension or traction headaches. Pains in the head and neck may easily overlap. They should be thought of as a unit when complaints of headache are considered.

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

The differential diagnosis of headache is complex due to the large number of potential disease entities and the diffuse nature of many types of pain in the head and neck region (Table 17.1). In evaluating the patient with a primary complaint of headache, the top priority is to exclude the causes with significant morbidity and mortality: SAH, ICH, meningitis, encephalitis, and mass lesions. Carbon monoxide is an exogenous toxin, the effects of which may be reversible by removing the patient from the source and administering oxygen. Carbon monoxide poisoning is a rare example of a headache in which relatively simple interventions may quickly improve a critical situation; however, returning the patient to the poisoned environment without a diagnosis could be lethal (see Chapter 153).

Pivotal Findings

Physical findings may be minimal or nonspecific, even in serious causes of headache, so the history is the pivotal part of the evaluation (Table 17.2).

1. Determine the *pattern and the onset* of the pain. Patients may remember having had frequent and recurrent headaches similar to the one they have on the current ED visit; a marked variation in the headache pattern can signal a new or serious problem. A rapid and severe onset of pain ("thunderclap") has been associated with serious causes of headache, and this warrants strong consideration of a cerebrovascular etiology.[3] Slow onset of headache should not be solely relied on to rule out a potentially life-threatening cause, and the nature of the onset usually is not possible to ascertain if the headache came on during sleep.

   Almost all studies dealing with subarachnoid bleeding report that patients moved from the pain-free state to severe pain within seconds to minutes. The thunderclap headache is common in acute presentations of SAH but is not highly specific. If the patient with moderate or severe headache can indicate the precise activity in which he or she was engaging at the time of the onset of the headache, the suddenness of onset warrants consideration of SAH. Careful questioning about the onset of headache may lead to the correct diagnosis of SAH, even if the pain is improving at the time of evaluation.
2. The patient's *activity at the onset of the pain* may be helpful. Headaches that come on during exertion have a relationship to vascular bleeding.[4] Additionally, although the syndrome of postcoital headache is well known, coitus is also recognized as an activity associated with SAH, so a pattern of previous postcoital headache is key, as is understanding whether the current headache fits that pattern. Postcoital headaches require the same evaluation on initial presentation as any other exertion-related head pain.
3. If there is a history of head trauma, the differential diagnosis shifts markedly toward epidural and subdural hematoma, traumatic SAH or intraparenchymal hemorrhage, skull fracture and closed head injuries, such as concussion and diffuse axonal injury.
4. The *intensity of head pain* is difficult to quantify objectively. Almost all patients who come to the ED consider their headaches to be severe. Use of a pain scale with appropriate explanation may help differentiate patients initially but has more value in monitoring their response to therapy. Rapid resolution

TABLE 17.1

Headache Etiologies and Associated Spectrum of Severity of Disease by System

ORGAN SYSTEM	CRITICAL	EMERGENT	NONEMERGENT
CNS, neurologic, vessels	SAH Carotid dissection Venous sinus thrombosis	Shunt failure Traction headaches Tumor or mass Subdural hematoma Reversible cerebral vasoconstriction syndrome	Migraine, various types Vascular headache, various types Trigeminal neuralgia Post-traumatic (concussion) Post LP headache
Toxic/metabolic, environmental	Carbon monoxide poisoning	Mountain sickness	
Collagen vascular disease	Temporal arteritis		
Ocular/ENT		Glaucoma	Sinusitis Dental problems TMJ disease
Musculoskeletal			Tension headache Cervical strain
Allergy			Cluster or histamine headaches
Infectious disease	Bacterial meningitis Encephalitis	Brain abscess	Febrile headaches, non-neurologic source
Pulmonary or oxygen		Anoxic headache Anemia	
Cardiovascular		Hypertensive crisis	Hypertension (rare)
Unspecified		Preeclampsia IIH	Effort-dependent or coital headaches

CNS, Central nervous system; *ENT,* ear, nose, and throat; *IIH,* idiopathic intracranial hypertension; *LP,* lumbar puncture; *SAH,* subarachnoid hemorrhage; *TMJ,* temporomandibular joint.

TABLE 17.2

Signs and Symptoms of Various Headache Etiologies

SYMPTOM	FINDING	POSSIBLE DIAGNOSIS
Sudden onset of pain	"Thunder clap" with any decreased mentation, any positive focal finding, meningismus or intractable pain	SAH, cervical artery dissection, cerebral venous thrombosis
Sudden onset of pain	Recurrent thunder clap episodes, may be associated with stroke-like symptoms	Reversible cerebral vasoconstriction syndrome
"Worst headache of my life"	Associated with sudden onset	SAH, cervical artery dissection, cerebral venous thrombosis
Near syncope or syncope	Associated with sudden onset	SAH, cervical artery dissection, cerebral venous thrombosis
Increased with jaw movement	Clicking or snapping; pain with jaw movement	TMJ disease
Facial pain	Fulminant pain of the forehead and area of maxillary sinus; nasal congestion	Sinus pressure or dental infection
Forehead and/or temporal area pain	Tender temporal arteries	Temporal arteritis
Periorbital or retro-orbital pain	Sudden onset with tearing	Temporal arteritis or acute angle closure glaucoma

SAH, Subarachnoid hemorrhage; *TMJ,* temporomandibular joint.

of pain in the ED, either from time or therapy, should not be relied on to rule out serious causes of headache.[5]

5. The *character of the pain* (eg, throbbing, pressure), although sometimes helpful, may not be adequate to differentiate one type of headache from another.
6. The *location of head pain* at onset and as the pain progresses is helpful when the patient can identify a specific area. It is certainly useful to direct the examination to evaluate for externally visible contributing factors, such as an infectious process. Unilateral pain is more suggestive of migraine or localized inflammatory process in the skull (eg, sinus) or soft tissue. Muscle tension headache often starts at the base of the skull and can extend over the entire head, following the occipital-frontal aponeurosis. Temporal arteritis, temporomandibular joint (TMJ) disease, dental infections, and sinus infections frequently have a highly localized area of discomfort. Meningitis, encephalitis, SAH, and even severe migraine, although intense in nature, are usually more diffuse in their localization.

BOX 17.1

Emergent Causes of Headache and Associated Risk Factors

1. Carbon monoxide poisoning
   a. Breathing in enclosed or confined spaces with engine exhaust or ventilation of heating equipment
   b. Multiple household members with the same symptoms
   c. Wintertime and working around machinery or equipment producing carbon monoxide (eg, furnaces)
2. Meningitis, encephalitis, abscess
   a. History of sinus or ear infection or recent surgical procedure
   b. Immunocompromised state
   c. General debilitation with decreased immunologic system function
   d. Acute febrile illness—any type
   e. Extremes of age
   f. Impacted living conditions (eg, military barracks, college dormitories)
   g. Lack of primary immunization
3. Temporal arteritis
   a. Age >50
   b. Females more often than males (4 : 1)
   c. History of other collagen vascular diseases (eg, systemic lupus)
   d. Previous chronic meningitis
   e. Previous chronic illness, such as tuberculosis, parasitic or fungal infection
4. Glaucoma—acute angle closure
   a. Not associated with any usual or customary headache patterns
   b. History of previous glaucoma
   c. Age >30
   d. History of pain increasing in a dark environment
5. Increased intracranial pressure
   a. History of previous benign intracranial hypertension
   b. Presence of cerebrospinal fluid (CSF) shunt
   c. History of congenital brain or skull abnormalities
   d. Female gender
   e. Obesity
6. Cerebral venous sinus thrombosis
   a. Female gender
   b. Pregnancy, peripartum, hormone replacement therapy or oral contraceptive use
   c. Prothrombotic conditions
7. Reversible cerebral vasoconstriction syndrome
   a. Episodic sudden severe pain, with or without focal neurological findings or seizure
   b. Recurrent episodes over a period up to several weeks
   c. Exposure to adrenergic or serotonergic drugs
   d. Postpartum state
8. Intracranial hemorrhage (ICH)
   a. Subarachnoid hemorrhage (SAH)
      i. Sudden and severe pain; "worst headache of life"
      ii. Acute severe pain after sexual intercourse or exertion
      iii. History of SAH or cerebral aneurysm
      iv. History of polycystic kidney disease
      v. Family history of SAH
      vi. Hypertension—severe
      vii. Previous vascular lesions in other areas of the body
      viii. Young and middle-aged
   b. Subdural hematoma
      i. History of alcohol dependency with or without trauma
      ii. Current use of anticoagulation
   c. Epidural hematoma
      i. Traumatic injury
      ii. Lucid mentation followed by acute altered mentation or somnolence
      iii. Anisocoria on physical examination

7. *Exacerbating or alleviating factors* may be important. Patients whose headaches rapidly improve when they are removed from their environment or recur each time they are exposed to a particular environment (eg, basement workshop) may have carbon monoxide poisoning. Most other severe causes of head pain are not rapidly relieved or improved when patients get to the ED. Intracranial infections, dental infections, and other regional causes of head pain tend not to be improved or alleviated before therapy is given.
8. *Associated symptoms and risk factors* may relate to the severity of headache but rarely point to the specific causes (Box 17.1). Nausea and vomiting are nonspecific symptoms seen in both primary and secondary headaches, but they are rare in simple muscle tension headache. Migraine headaches, increased intracranial pressure, temporal arteritis, and glaucoma can all manifest with severe nausea and vomiting, as can some systemic viral infections with headache. Such factors may point toward the intensity of the discomfort but are not specific in establishing the diagnosis. Immunocompromised patients are at risk for unusual infectious causes of headache, which may present with deceptively low grade symptomatology. Toxoplasmosis, cryptococcal meningitis, and abscess are very rare but may be seen in patients with a history of human immunodeficiency virus (HIV) or other immunocompromised state. This subset of patients may have a serious central nervous system infection without typical signs or symptoms of systemic illness (eg, fever and meningismus).

   Another special population to considers is the pregnant and peripartum woman, in whom preeclampsia, idiopathic intracranial hypertension (IIH), and reversible cerebral vascular syndrome should be considered, as well as the even more serious causes of headache including venous sinus thrombosis, pituitary apoplexy, cervical artery dissection, and stroke.[5-7]

   Patients on medications containing estrogen are also at higher risk for thrombotic events, such as cavernous venous thrombosis, and this should be considered in the differential diagnosis.
9. A *prior history of headache,* although helpful, does not rule out current serious problems. One important consideration is the association of migraine headaches and stroke, with particular consideration of carotid dissection.[8] Previous evaluation for serious disease can be useful to guide the current evaluation. Prior visits to an ED or outpatient setting, computed tomography (CT), magnetic resonance imaging (MRI), and other forms of testing can provide support for, or help rule out, a specific diagnosis. Patients with migraine, cluster, and tension headaches tend to have stereotypical recurrent patterns. Adherence to these patterns is also helpful in deciding the degree to which a patient's symptoms are pursued.

Signs

There are signs that may be elicited on physical examination that can be particularly high yield. For example, deficits of extraocular movements localizing to cranial nerves (CNs) III, IV, and VI may indicate the presence of increased intracranial pressure due to mass lesion or IIH. When headache is associated with an acutely red eye, this finding should prompt consideration of acute angle closure glaucoma and further investigation with testing of

intraocular pressure. Any focal neurological deficit found on examination, regardless of subtlety, warrants further investigation. Not all signs associated with headache contribute greatly to final determination of diagnosis, but they may serve as cues for further consideration of a serious intracranial process. Nausea and vomiting are often associated with migraine, but they are also associated with intracranial mass, acute angle closure glaucoma, intracranial bleeding, and carbon monoxide poisoning. Additional physical findings associated with various forms of headache are listed in Table 17.3.

Ancillary Testing

The vast majority of headache patients do not require additional testing (Table 17.4). Advanced imaging should be directed toward the specific disease of concern in the differential diagnosis and not

TABLE 17.3

Signs and Symptoms Associated With Different Headache Etiologies

SIGN	FINDING	POSSIBLE DIAGNOSES
General appearance	Nonfocal mental status changes	Meningitis, encephalitis, SAH, subdural hematoma, anoxia, increased intracranial pressure, carbon monoxide poisoning
	Mental status changes with focal findings	Intraparenchymal bleed, tentorial herniation, stroke
	Severe nausea, vomiting	Increased intracranial pressure, acute-angle closure glaucoma, SAH, carbon monoxide poisoning
Vital signs	Hypertension with normal heart rate or bradycardia	Increased intracranial pressure, SAH, tentorial herniation, intraparenchymal bleed, preeclampsia, reversible cerebral vasoconstriction syndrome
	Tachycardia	Anoxia, anemia, febrile headache, exertional or coital headache
	Fever	Febrile headache, meningitis, encephalitis
HEENT	Tender temporal arteries	Temporal arteritis
	Increased intraocular pressure	Acute angle closure glaucoma
	Loss of venous pulsations on funduscopy or papilledema	Increased intracranial pressure, mass lesions, subhyaloid hemorrhage, SAH, cerebral venous thrombosis
	Acute red eye (severe ciliary flushing) and poorly reactive pupils	Acute angle closure glaucoma
Neurologic	Enlarged pupil with third nerve palsy	Tentorial pressure cone, mass effect (aneurysm, bleed, abscess, or tumor)
	Lateralized motor or sensory deficit	Stroke, subdural hematoma, epidural hematoma, hemiplegic or anesthetic migraine (rare), reversible cerebral vasoconstriction syndrome, central venous thrombosis
	Balance and coordination deficits	Cervical artery dissection, acute cerebellar hemorrhage, acute cerebellitis (mostly children), chemical intoxication of various types
	Extraocular movement deficits (CN III, IV, and VI)	Mass lesion, neurapraxia (post-traumatic headache), IIH

CN, Cranial nerve; *HEENT,* head, eyes, ears, nose, and throat; *IIH,* idiopathic intracranial hypertension; *SAH,* subarachnoid hemorrhage.

TABLE 17.4

Diagnostic Findings in Emergent Causes of Headache

TEST	FINDING	DIAGNOSIS
Erythrocyte sedimentation rate (ESR)	Significant elevation	Temporal arteritis
Electrocardiogram (ECG)	Nonspecific ST/T wave changes	SAH Increased intracranial pressure
Complete blood count (CBC)	Severe anemia	Anoxia
Computed tomography (CT) scan: Head	Increased ventricular size	Increased intracranial pressure
	Blood in subarachnoid space	SAH
	Blood in epidural or subdural space	Epidural or subdural hematoma
	Bleeding into parenchyma of brain	Intraparenchymal hemorrhage
	Areas of poor vascular flow	Pale infarct
	Structural, mass lesion	Traction headache secondary to mass effect
Lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis	Increased opening pressure	IIH Mass lesion Shunt failure Cryptococcal meningitis
	Increased protein	Tumor or other structural lesions, infection
	Increased RBCs	SAH
	Increased WBCs	Infection
	Positive Gram's stain	Infection
	Decreased glucose	Infection

IIH, idiopathic intracranial hypertension; *RBC,* red blood cell; *SAH,* subarachnoid hemorrhage; *WBC,* white blood cell.

as a default process in the investigation of headache in general. For example, a head CT scan is not indicated for muscle tension headache or recurrent migraine, and it may not be sufficient to assess for cerebral venous thrombosis or for a posterior circulation stroke. A CT scan performed within 6 hours of onset of headache has been shown to be sufficiently sensitive to exclude the diagnosis of SAH when using a third-generation CT scanner. Outside this window, sensitivity declines, and additional testing must be undertaken for appropriate evaluation for SAH.[9]

Lumbar puncture (LP) with measurement of the opening pressure and cerebrospinal fluid (CSF) analysis is indicated when assessing for an infectious process, such as meningitis or encephalitis, IIH, or SAH. Although evidence for this is scant, it is widely believed that LP may increase the likelihood of herniation in certain cases with elevated intracranial pressure caused by a mass lesion. This is the genesis of the common dictum of "CT before LP" when a mass lesion or abscess is a consideration. In reality, this concern is likely misguided, and the compelling reason to obtain a CT scan first in such patients is that it may provide the diagnosis and make the LP unnecessary.

DIAGNOSTIC ALGORITHM

Key elements of the history of present illness, past medical history, and examination are used to narrow the differential diagnosis and choose the appropriate diagnostic pathway. Figure 17.1 outlines a diagnostic algorithm for assessment of headache patients.

If it is clear from the evaluation that the diagnosis is a primary headache disorder (eg, migraine) or of minor severity and gradual onset (eg, typical tension headache) with normal neurological examination findings, then symptomatic treatment is provided without need for further diagnostic evaluation.

If the history or examination findings are clearly indicative of a particular etiology (eg, angle closure glaucoma), then directed testing is indicated—in this case, intraocular pressure determination.

It is cases in which there are highly concerning elements of history but no definitive diagnosis that are the most challenging in terms of choosing the appropriate evaluation. Indications of patients at higher risk for serious cause of headache who are candidates for more comprehensive evaluation include (1) sudden onset of headache, (2) patient description of the headache as "the worst ever," (3) altered mental status, (4) meningismus, (5) unexplained fever, (6) focal neurological deficit on examination, (7) symptoms refractory to appropriate treatment or worsening despite treatment, (8) onset of headache during exertion, (9) history of immunosuppression, or (10) pregnancy or peripartum state. In these potentially critically ill patients, head CT scan is indicated, and a LP often is needed for those in whom imaging does not reveal the etiology of their symptoms.

Sequential evaluation of the patient's condition and assessment of ancillary data will confirm a working diagnosis or trigger a reconsideration of alternatives, including more serious conditions (Table 17.5).

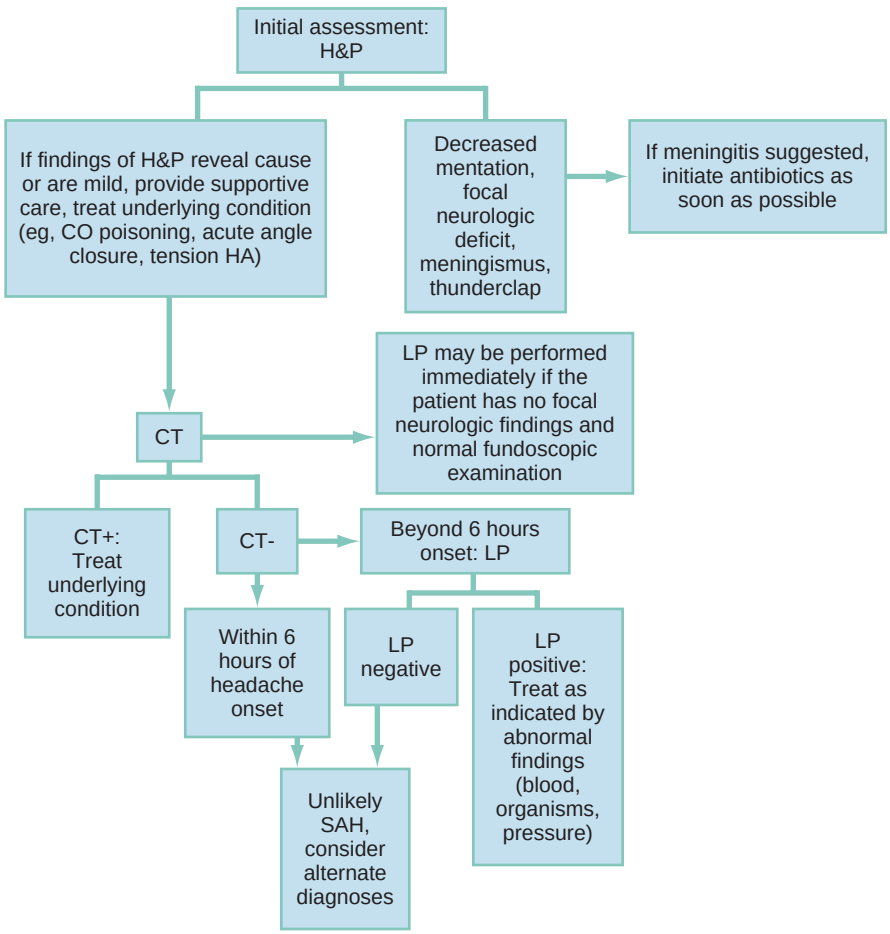

Fig. 17.1. Evaluation algorithm for presentation of headache. *CO,* Carbon monoxide; *CT,* computed tomography; *H&P,* history and physical examination; *HA,* headache; *LP,* lumbar puncture; *SAH,* subarachnoid hemorrhage.

TABLE 17-5

Causes and Differentiation of Potentially Catastrophic Illness Manifesting With Nontraumatic Headache

DISEASE ENTITIES	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORT HISTORY	PREVALENCE
Carbon monoxide poisoning	Usually gradual, subtle, dull, nonfocal throbbing pain	May wax and wane as individual leaves and enters the involved area of carbon monoxide; throbbing may vary considerably	Exposure to engine exhaust, old or defective heating systems, most common in winter months	Rare
Subarachnoid hemorrhage (SAH)	Sudden onset, "thunderclap," severe throbbing	Symptoms variable; may present from relatively asymptomatic to altered mental status or focal neurological deficit	History of polycystic kidney disease; history of HTN	Uncommon
Meningitis, encephalitis, abscess	Gradual; as general symptoms increase, headache increases. Nonfocal pain	Decreased mentation prominent, irritability prominent. With abscess, focal neurologic findings may be present	Recent infection, recent facial or dental surgery or other ENT surgery, unimmunized state	Uncommon
Temporal arteritis	Pain often develops over a few hours from mild to severe, almost always localized to temporal area(s)	Decreased vision, nausea, vomiting may be intense and confound diagnosis	Age over 50; other collagen vascular diseases or inflammatory diseases	Uncommon
Acute angle closure glaucoma	Sudden in onset	Nausea, vomiting, decreased vision	History of glaucoma; history of pain increasing in dark areas	Rare
Increased intracranial pressure syndromes	Gradual, dull, nonfocal	Vomiting, decreased mentation	History of CSF shunt or congenital brain or skull abnormality	Uncommon

CSF, Cerebrospinal fluid; *ENT,* ear, nose, and throat; *HTN,* hypertension.

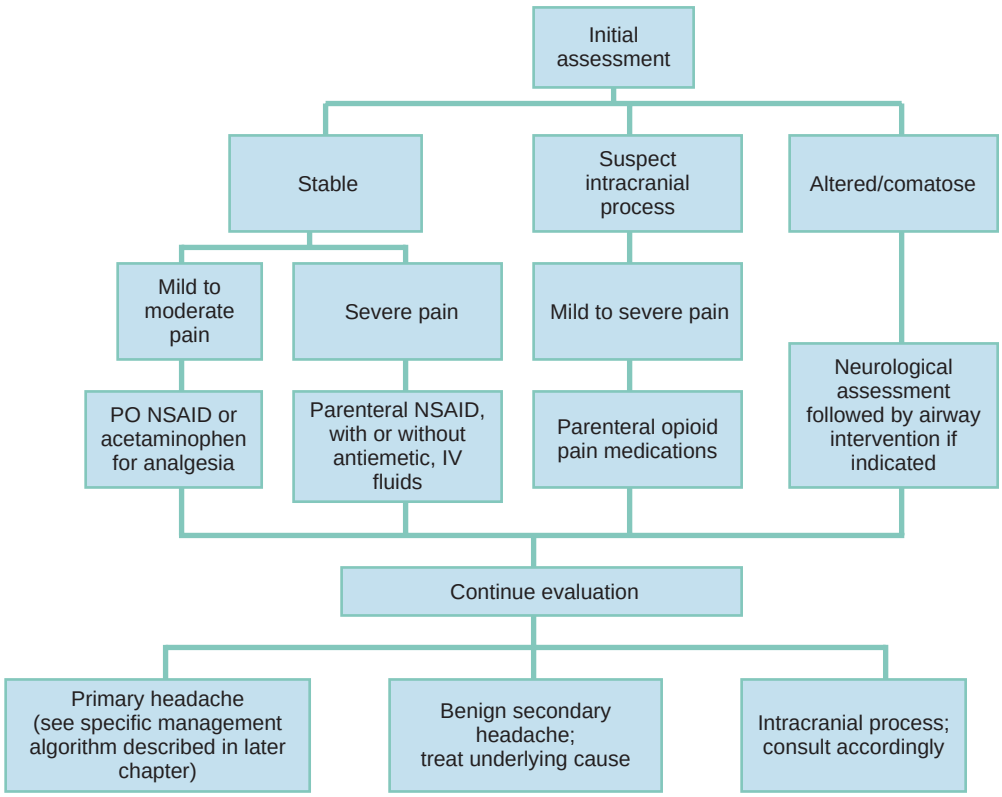

Fig. 17.2. Management algorithm. *IV,* intravenous; *NSAID,* nonsteroidal antiinflammatory drug; *PO, per os* (by mouth).

EMPIRICAL MANAGEMENT

Headache, although a frequent chief complaint, is a nonspecific symptom. The speed and intensity of the initial evaluation and treatment are guided by the presentation and the patient's mental status. Figure 17.2 represents a management algorithm with immediate management pending completion of a full diagnostic evaluation.

For purposes of the initial assessment, headache can be divided into two categories: (1) accompanied by altered mental status and (2) without altered mental status. Whenever a patient's mental status is impaired, brain tissue is initially assumed to be

compromised. The principles of cerebral resuscitation address the seven major causes of evolving brain injury: (1) lack of substrate (glucose, oxygen), (2) cerebral edema, (3) intracranial mass lesion, (4) endogenous or exogenous toxins, (5) metabolic alterations (fever, seizure), (6) ischemia, or (7) elevated intracranial pressure.

Pain is mitigated as soon as possible. The pain medication of choice depends on the working diagnosis of the patient's headache. For nonspecific mild to moderate headache, oral nonsteroidal antiinflammatory medication is appropriate in analgesic doses (eg, 500 mg of naproxen). Opioids are not first-line management for any type of headache pain, except when ICH (including SAH) is thought to be present.

Other than symptomatic relief of pain, empirical treatment does not precede diagnostic studies in most cases, because the treatment must be targeted to the specific cause of the headache. A significant exception to this is when bacterial meningitis is a consideration. Treatment of bacterial meningitis is time-sensitive, and empirical antibiotics should be administered as soon as possible and before results are available to confirm the diagnosis.

Disposition

Patients who are not thought to have a serious cause for their head pain requiring hospitalization but who are without a specific diagnosis are provided with appropriate return precautions and recommendations for follow-up care. Some patients many benefit from beginning a headache journal to facilitate further outpatient evaluation.

KEY CONCEPTS

- When a patient with a known headache disorder presents with a change in the pattern of the headache, evaluate for potential serious causes.
- The physical examination in the headache patient focuses on cranial nerves (CNs) II, III, IV, and VI.
- Opioid medication is almost never the analgesic of choice for headache. Simple headache is treated with nonsteroidal analgesic medication, and specific antimigraine therapies are used for migraine.
- Most patients with headache do not require neuroimaging. When obtained, neuroimaging should be tailored to the specific elements of the differential diagnosis of concern.
- The differential diagnosis of sudden severe headache includes subarachnoid or other intracranial hemorrhage (ICH), cerebral venous thrombosis, and cervical artery dissection.
- In those patients for whom there is concern for subarachnoid hemorrhage (SAH), a normal head CT scan obtained using a high resolution scanner within 6 hours of onset is sufficient to rule out SAH. Patients outside this window require lumbar puncture (LP) to achieve appropriate sensitivity in the evaluation.
- Antibiotics should be given prior to LP being performed when bacterial meningitis is suspected.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 17: QUESTIONS & ANSWERS

17.1. The most appropriate initial evaluation of a patient with nontraumatic headache is:
- **A.** CT scan of brain
- **B.** EEG
- **C.** MRI scan of brain
- **D.** Thorough neurological evaluation
- **E.** Trial of NSAIDs for pain relief

Answer: D. A thorough neurological examination may reveal deficits not seen on gross evaluation, prompting expansion of the differential diagnosis to include more concerning etiologies. Depending on the history and remainder of the physical, a normal neurological examination may be reassuring and obviate need for advanced imaging studies.

17.2. In the setting of headache, the presence of nausea and vomiting are diagnostic of which of the following as an underlying cause?
- **A.** Glaucoma
- **B.** Increased intracranial pressure
- **C.** Migraine
- **D.** Temporal arteritis
- **E.** None of the above

Answer: E. Nausea and vomiting are completely nonspecific. Migraine headaches, increased intracranial pressure, temporal arteritis, and glaucoma can all be manifested by severe nausea and vomiting, as can some systemic viral infections with headache. Such factors may point toward the intensity of the discomfort but are not specific in establishing the diagnosis.

17.3. Which of the following causes of headache has a constellation of risk factors that include age older than 50 years, female gender, history of lupus, and previous chronic meningitis?
- **A.** Abscess
- **B.** Encephalitis
- **C.** Increased intracranial pressure
- **D.** SAH
- **E.** Temporal arteritis

Answer: E. Risk factors associated with temporal arteritis include age older than 50 years; female gender (ratio 4 : 1); history of other collagen vascular diseases, such as lupus; previous chronic meningitis; and previous chronic illness, such as tuberculosis, parasitic infection, and fungal infection.

17.4. A history of polycystic kidney disease is an associated risk factor for which of the following potentially catastrophic causes of headache?
- **A.** Cerebral venous sinus thrombosis
- **B.** Increased intracranial pressure
- **C.** SAH
- **D.** Subdural hematoma
- **E.** Temporal arteritis

Answer: C. A history of polycystic kidney disease is a risk factor for SAH. Other historical details and risk factors for SAH are sudden severe pain, acute severe pain after sexual intercourse or straining, history of SAH or cerebral aneurysm, family history of SAH, severe hypertension, previous vascular lesions in other areas of the body, and being young or middle aged.

CHAPTER 18

Diplopia

Kama Guluma

PERSPECTIVE

Epidemiology

Diplopia, or double vision, is of two types, monocular and binocular. For patients who present to the emergency department (ED) with diplopia, most cases are binocular, with cranial nerve (especially sixth nerve) palsies being among the most common causes. The remainder (≈15%) are monocular.

Pathophysiology

Monocular diplopia, or double vision that persists in one affected eye, even with the other one closed, is an ophthalmologic problem related to distortions in the light path. Binocular diplopia, or double vision that resolves when either eye is closed, is the result of a misalignment in the visual axes and has a wide range of causes. These can be organized in a progression from the eye distally to the brainstem proximally. The process responsible might involve oculomotor muscle dysfunction, cranial nerve (CN) dysfunction, or intranuclear or supranuclear lesions in the brainstem or above. In a recent, prospective observational study of 260 ED patients presenting with binocular diplopia, a secondary cause of the diplopia was delineated in 36% and, of these, the most frequent diagnoses were stroke (45%), multiple sclerosis (18%), brain tumors (12%), and cerebral aneurysms (8%).[1]

DIAGNOSTIC APPROACH

Differential Considerations

The causes of diplopia are myriad, ranging from relatively benign to significantly pathologic. The clinical approach in the ED entails sorting out those that may result in rapid and profound morbidity from those that are less acute. Table 18.1 outlines some key causes of diplopia prioritized by immediate acuity, with mechanism and distinguishing features.

Binocular diplopia may be due to a mechanical orbitopathy, a palsy of one or more of the oculomotor cranial nerves, a proximal neuroaxial process involving the brainstem and related cranial nerves, or a systemic neuromuscular process.

Monocular diplopia is an ophthalmologic problem related to distortions in the light path from dry eyes, a corneal irregularity, cataract or lens dislocation[2] or, rarely, from retinal wrinkles involving the macula.

A restrictive mechanical orbitopathy can be caused by orbital myositis, trauma, or infection (abscess), or from craniofacial masses, any of which can directly restrict movement of a single eye. A restrictive orbitopathy is identified by characteristic symptoms and signs combined with the absence of any other focal neurologic deficits. Often involving only a single extraocular muscle, orbital myositis may be a manifestation of a variety of steroid-responsive conditions such as Wegener's granulomatosis, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, sarcoidosis, rheumatoid arthritis, or idiopathic orbital inflammatory syndrome (orbital pseudotumor).

Graves' orbitopathy is the most common cause of ocular myopathy in older adults, will affect at least 50% of patients with Graves' disease,[3] and is bilateral in at least 85% of cases. The patient presenting with thyroid-related diplopia will likely have a preexisting diagnosis of Graves' disease, but may present with isolated diplopia prior to the onset of systemic symptoms (and diagnosis).[3]

The oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) cranial nerves innervate the muscles that move the eye. With regard to an oculomotor cranial nerve palsy, CN VI is the most commonly affected, followed by CN III, and then CN IV.[2] An isolated simple mononeuropathy in CN III, IV, or VI may be from a demyelinating process (eg, multiple sclerosis[4]), hypertensive or diabetic vasculopathy, or compression. Each nerve has characteristic predilections to which it is vulnerable. In adults, CN III is usually affected by diabetic or hypertensive vasculopathy. Aneurysms in the posterior communicating (most common), basilar, superior cerebellar, posterior cerebral, and cavernous internal carotid arteries are a close second.[5] CN IV is usually affected by trauma from abutting against the tentorium, typically not an isolated symptom or finding, followed by vascular causes. Due to its length, CN VI is the most common nerve to be affected by tumors, elevated intracranial pressure, and microvascular ischemia.[6]

A cavernous sinus infection, mass, or vasculitis may affect CN III, IV, and VI simultaneously (orbital apex syndrome), but typically affects CN VI first because it traverses through the cavernous sinus, as opposed to within its wall, like CNs III and VI. Causes include carotid-cavernous fistula, inflammatory vasculitides such as giant cell arteritis, Tolosa-Hunt syndrome (a rare idiopathic vasculitis), or tumor or infiltration (eg, lymphoma, sarcoidosis) in the orbital apex.[7] A complex palsy in the cavernous sinus may also be iatrogenic due to intravascular injection or diffusion of anesthetic along tissue planes into the pterygoid venous plexus from an intraoral dental anesthetic nerve block.[8] Herpes zoster ophthalmicus is a well-described cause of orbital apex syndrome.[9-11]

A focal brainstem lesion may be from multiple sclerosis (as a clinically isolated syndrome, of which 68% manifest as diplopia).[4] A more diffuse but localized brainstem process may be caused by brainstem tumor, brainstem lacunar stroke,[2] impending basilar artery thrombosis, vertebral artery dissection, or ophthalmoplegic migraine.[3] A vertebral artery dissection may present with diplopia alone, as can an impending basilar artery thrombosis, which can also result in a coma.[12]

A more diffuse process involving the brainstem and/or CNs III, IV, and VI may be infectious, autoimmune, neurotoxic, or metabolic, and involve other neurologic structures, resulting in additional symptoms and signs. Possibilities include basilar meningoencephalitis (cryptococcal,[13] carcinomatous, or viral[14]), at times with the diplopia being the only symptom,[15] botulism,[16] an autoimmune process such as Miller-Fisher or Guillain-Barré syndrome,[17] and Wernicke's encephalopathy, in which the ophthalmologic manifestations are due to metabolically induced lesions in the pontine tegmentum, abducens nucleus, and oculomotor nucleus.[18]

TABLE 18.1

Important Causes of Diplopia

DIPLOPIA-CAUSING ENTITY	MECHANISM AND MORTALITY	DISTINGUISHING FEATURES
TIER 1—CRITICAL		
Basilar artery thrombosis	Impending thrombosis of the basilar artery with brainstem ischemia; untreated mortality, 70%–90%	Vertigo, dysarthria, other cranial nerve involvement; risk factors for stroke
Botulism	Toxin inhibits release of acetylcholine at cholinergic synapses and presynaptic myoneural junctions; untreated mortality, 60%	Dysarthria, dysphagia, autonomic dysreflexia, pupillary dysfunction
Basilar meningitis	Infection; untreated mortality, close to 100% if bacterial (15%–20% if treated)	Headache, meningismus, fever
Aneurysm	Enlarging aneurysm directly compresses cranial nerve; untreated rupture risk = 1%/yr (3.5%/yr for previously ruptured); mortality, 26%–67%/rupture	CN III palsy with pupillary involvement
TIER 2—EMERGENT		
Vertebral dissection	Dissection causes vertebrobasilar ischemia; acute untreated mortality, 28% (2%–5% if neurologically asymptomatic)	Neck pain, vertigo; risk factors for vertebral dissection
Myasthenia gravis	Autoantibodies develop against acetylcholine (ACh) nicotinic postsynaptic receptors; untreated crisis mortality, 42% (5% if treated)	Fluctuating muscle weakness, ptosis, and diplopia worsen with activity, improve with rest
Wernicke's encephalopathy	Thiamine-dependent metabolic failure and tissue injury; untreated mortality, 20%	Nystagmus, ataxia, altered mental status, ophthalmoplegia; alcoholism and nutritional deficiency
Orbital apex syndrome, cavernous sinus process	Inflammation or infection in the orbital apex or cavernous sinus directly affects oculomotor cranial nerves; acute mortality low unless infectious and complicated by meningitis	Combination of palsies of CN III, IV, or VI, with retro-orbital pain, conjunctival injection, possible periorbital, facial numbness
TIER 3—URGENT		
Brainstem tumor	Tumor involvement at the supranuclear level; acute mortality low (long-term mortality variable)	Skew deviation—vertical diplopia, internuclear ophthalmoplegia
Miller-Fisher syndrome	Autoantibodies develop to a cranial nerve ganglioside, GQ1b; acute mortality low (if fully differentiated from GBS; mortality, 2%–12% if GBS)	Ophthalmoplegia, ataxia, areflexia
Multiple sclerosis	Demyelinating lesions; acute mortality low	Internuclear ophthalmoplegia
Thyroid myopathy (Graves' disease)	Autoimmune myopathy; acute mortality low in regard to ocular complaints	Proptosis, restriction of elevation and abduction of the eye, signs of Graves' disease
Ophthalmoplegic migraine	Inflammatory cranial neuropathy; low mortality, self-limited disease	Ipsilateral headache, CN (usually III) palsy
Ischemic neuropathy	Microvascular ischemia; mortality low, self-limited disease	Isolated CN palsy (pupil-sparing if CN III)
Orbital myositis, pseudotumor	Autoimmune or idiopathic myositis; acute mortality low in regard to ocular complaints	Eye pain, restriction of movement, periorbital edema; exophthalmos and chemosis when more severe
Orbital apex mass	Tumor, infiltration, or mass effect in orbital apex or cavernous sinus directly compresses oculomotor cranial nerves; acute mortality low	A combination of palsies of CN III, IV, or VI and possible periorbital, facial numbness, with retro-orbital pain, proptosis, signs of venous congestion

Snake envenomations and tick paralysis can, on rare occasions, present with isolated diplopia, with diplopia being an early and frequent manifestation of neurotoxicity from certain snake venoms.[19] Diplopia may also be part of a paraneoplastic syndrome, but the prototypical neuromuscular cause of diplopia is myasthenia gravis. The initial symptoms are ocular in 85% of myasthenia cases, due to diplopia in 14% of cases. In addition, the symptoms of myasthenia gravis are solely ophthalmologic in almost 20% of patients.[20] However, patients with myasthenia will typically present with diplopia in the setting of a preestablished diagnosis, which facilitates a determination, if not immediate recognition, of the cause.

Pivotal Findings

There are four aspects of questioning the help formulate the differential diagnosis in diplopia: (1) timing of onset and symptoms; (2) directionality and orientation of the diplopia; (3) presence of pain; and 4) presence of other associated symptoms.[2] In terms of the timing of onset, a truly sudden onset suggests an ischemic cause, cerebrovascular or microvascular, especially if the intensity or degree of diplopia was maximal at onset. A fluctuation of symptoms over time may suggest transient ischemic attacks or an impending stroke, but more generally implies a neuromuscular disease.[2] Regarding the directionality of the diplopia, the

directions of gaze that elicit or worsen the diplopia and the general orientation of that diplopia—that is, horizontal, vertical, torsional—should be carefully determined to localize the problem. Finally, symptoms associated with the diplopia (eg, pain, neurologic or neuromuscular symptoms) are critical to forming a differential diagnosis, if not making the diagnosis. The presence of pain suggests an inflammatory or infectious process and narrows the differential significantly.

The patient complaining of diplopia should have a thorough neurologic examination, with attention to the cranial nerves and an evaluation of the six cardinal movements of gaze. Each extraocular muscle (and the nerve that supplies it) has a maximal action in a specific direction, and the evaluation of gaze should therefore specifically follow the configuration of a six-limbed asterisk, or an H (Fig. 18.1). The patient should also undergo a careful pupillary and facial examination, looking for signs of pupillary asymmetry, ptosis, lid lag, conjunctival injection or chemosis, periorbital swelling, or proptosis and overall head positioning.

The acuity of onset and presence or absence of pain can be used to prestratify diagnostic possibilities, as shown in Fig. 18.2, especially with regard to vascular, potentially ischemic events.

Symptoms

Monocular Cause. This is present only if the patient complains that the diplopia persists in the affected eye with the normal eye closed.

Mechanical Orbitopathy. A structural restriction of motion of a single eye, typically gradual in onset, may cause diplopia in a single or multiple directions of gaze, depending on the type and extent of muscular involvement. A sensation of mass effect, discomfort, or pain in the culprit eye is a characteristic symptom. If

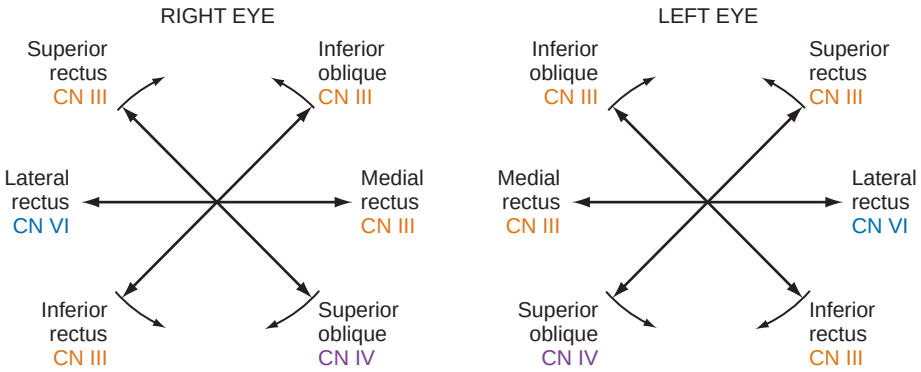


Fig. 18.1. Cardinal movements of the eyes, with the oculomotor muscles that create them and the nerves that supply those muscles. *Small curved arrows* denote intorsion or extorsion of the eye by the muscle indicated. *CN,* Cranial nerve.

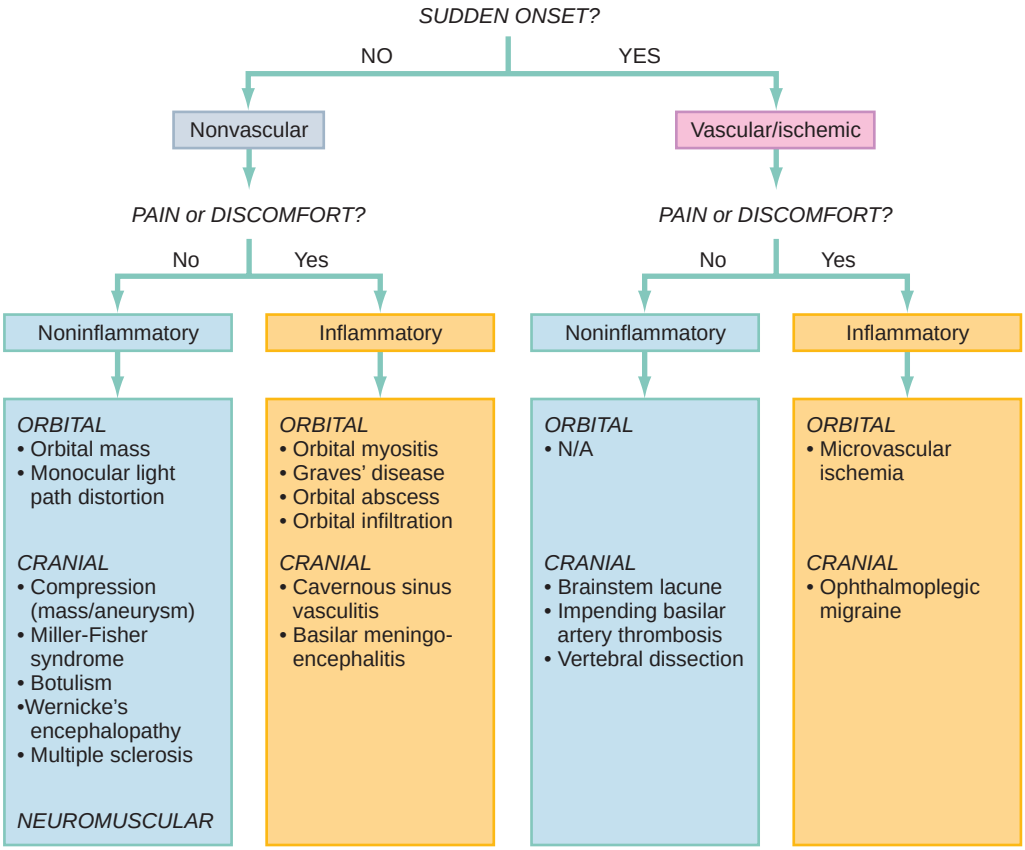


Fig. 18.2. Prestratification of the differential diagnosis in a patient presenting with diplopia.

the cause is infectious, the patient may have a history of a fever. Diplopia that is worse in the morning suggests Graves' myopathy, presumably due to the venous congestion of the ocular muscle associated with being supine.

Isolated Oculomotor Nerve Palsy. The patient with a CN III palsy typically reports diplopia in all directions of gaze, except on lateral gaze to the affected side. A CN IV palsy resulting in rotational double vision makes descending stairs, reading, and watching television in bed difficult. Diplopia that worsens on lateral gaze to one direction implies an issue with CN VI on that side.[2] A patient with diplopia from an isolated palsy of CN III, IV, or VI will typically not have other associated symptoms. Pain and speed of onset are differentiators; a sudden isolated CN III, CN IV, or CN VI palsy associated with orbital discomfort in a patient with chronic diabetes or hypertension strongly suggests that microvascular ischemia is the cause, with a caveat that with a CN III palsy, a headache frequently accompanies aneurysmal compression.[21]

The diplopia from a problem involving the cavernous sinus or orbital apex, unlike an isolated mononeuropathy, may manifest as a combination of any of the gaze abnormalities noted above, because more than one cranial nerve may be involved. It may be gradual in onset and associated with retroorbital pain or blurred vision due to venous congestion. Because branches of the trigeminal nerve travel though the orbital apex, the patient may have associated ipsilateral periorbital facial numbness or dysthesia.[7]

Neuroaxial Process Involving the Brainstem and Related Cranial Nerves. A focal brainstem lesion (eg, in multiple sclerosis) may result in isolated diplopia. However, localized brainstem lesions such as those from mass effect or ischemia typically also result in so-called neighborhood symptoms and signs from anatomically contiguous involvement, of which double vision may be the most prominent and therefore the presenting complaint (see Box 18.1). It is therefore important to screen for those other symptoms and signs actively. Additional symptoms of nausea, vertigo, or slurred speech are concerning for an impending basilar artery occlusion, especially if symptoms are sudden in onset, painless, and fluctuate, or a brainstem mass, if gradual in onset and progressive over days. A young person with an ophthalmoplegic migraine may present in a similar fashion to someone with a brainstem stroke but will typically develop an associated ipsilateral headache.

Diplopia from a more diffuse neurologic syndrome that happens to involve the brainstem and cranial nerves is usually gradual in onset and manifests with various other discordant symptoms. A gradually evolving combination of double vision, slurred speech, and problems swallowing suggests foodborne botulism,[16] especially if additional symptoms of dry mouth, nausea, and diffuse muscle weakness are present. Double vision, clumsiness, and altered mentation in a patient with chronic alcoholism, malnutrition, or history of bariatric surgery should raise the possibility of Wernicke's encephalopathy.[18] Diplopia and other cranial nerve symptoms, together with headache, photophobia, stiff neck, and/or fever, are suspicious for a basilar meningoencephalitis.

Neuromuscular Disorder. Diplopia that is variably triggered in multiple directions, and without a distinct structural or neuropathic cause evident, implies a neuromuscular cause such as myasthenia gravis. A mild neuromuscular manifestation of myasthenia may present with a diplopia isolated to one direction, however. Diplopia from neuromuscular disease generally fluctuates over time[2] and, in myasthenia gravis, worsens with fatigue and improves with rest.[22] There may be associated symptoms of proximal muscle weakness (eg, difficulty holding arms above the head or climbing stairs), shortness of breath, or difficulty swallowing.

Signs

Monocular Cause. With monocular diplopia—typically a problem with abnormal refraction—the diplopia from the affected eye should resolve when a pinhole is used, unless it is due to a retinal abnormality.

Mechanical Orbitopathy. Signs of a structural orbitopathy or myositis include proptosis, periorbital swelling, edema, conjunctival or scleral hyperemia, and palpebral swelling involving a single eye. Diplopia due to a mass in the orbit may appear as a clean, ordinal mechanical diplopia, in which having the patient attempt to look in the direction of the problem induces the most diplopia, with an axis of visual image separation parallel to the direction of the gaze (as can at times be seen in patients with significant periorbital swelling from trauma). In contrast, diplopia due to a process in any of the individual extraocular muscles, except for the lateral or medial recti muscles, may present in a messy eccentric or torsional manner based on the direction of pull of and therefore restriction by each muscle (see Fig. 18.1). There is a mismatch between the primary direction of diplopia and primary direction of movement, possibly improved by head tilt. Although findings may mimic a neurogenic palsy to some extent, the signs induced on testing extraocular eye movements will not reflect the stereotyped deficits typical of palsies of the oculomotor cranial nerves. Ocular myositis can be distinguished from a neurogenic palsy in that it abruptly restricts eye movement away from the muscle, whereas a cranial nerve palsy smoothly and progressively impairs movement toward the weakened muscle. Stigmata of Graves' disease include lid lag, diffuse conjunctival edema, and vascular injection[3] and, because it typically affects the inferior and medial recti muscles first, restriction of elevation and abduction of the eye. Patients with thyroid-related diplopia may tilt their head back to accommodate for the restriction of upward gaze by the thickened inferior rectus muscle.[2]

Isolated Oculomotor Nerve Palsy. Palsies from an isolated mononeuropathy of the oculomotor nerve will present with typical findings, as outlined in Fig. 18.3. CN III also innervates the levator palpebrae superioris muscle, which lifts the upper eyelid, and provides parasympathetic innervation to two intrinsic ocular muscles, the ciliary and constrictor pupillae muscles, which

BOX 18.1

Lacunar Stroke Syndromes Presenting With Diplopia

Weber syndrome (midbrain lacune)—ipsilateral CN III palsy and contralateral hemiparesis
Benedikt syndrome (midbrain lacune)—ipsilateral CN III palsy and contralateral tremor or dysmetria
Claude syndrome (midbrain lacune)—ipsilateral CN III palsy and contralateral weakness, tremor, and ataxia
Millard-Gubler syndrome (pontine lacune)—ipsilateral CN VI palsy, ipsilateral facial weakness (CN VII), contralateral arm and leg weakness
Foville's syndrome (pontine tegmentum)—ipsilateral CN VI palsy, ipsilateral facial weakness (CN VII), contralateral ataxia and hemiparesis
One-and-a-half syndrome (CN VI nuclei, paramedian pontine reticular formation)—bilateral CN VI (abduction) palsies with a unilateral adduction palsy

Adapted from Friedman DI. Pearls: diplopia. Semin Neurol 30:54–65, 2010; and Lewandowski CA, Rao CP, Silver B: Transient ischemic attack: definitions and clinical presentations. Ann Emerg Med 52:S7–S16, 2008.

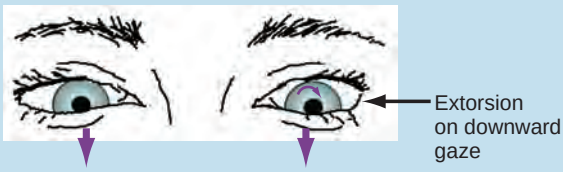
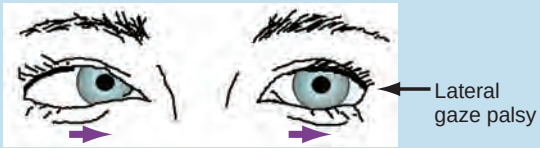
NERVE PALSY	MUSCLE(S) "OFF"	SYMPTOMS	EXAMINATION FINDINGS
Normal	N/A	N/A	
Oculomotor (CN III)	Medial, inferior, and superior rectii muscles • Inferior oblique muscle • Levator palpebrae (eyelid) • Ciliary and constrictor pupillae muscles (pupil)	Multidirectional horizontal and vertical diplopia, except on lateral gaze to the affected side • Eyelid "droop"	
Trochlear (CN IV)	Superior oblique muscle	Rotational diplopia that worsens on looking down and toward the nose	
Abducens (CN VI)	Lateral rectus muscle	Horizontal diplopia on gaze toward the affected side	

Fig. 18.3. Corresponding muscle dysfunction, symptoms and examination findings for each oculomotor cranial nerve palsy. *CN,* Cranial nerve.

constrict the pupil. An isolated CN III palsy presents with diplopia in all directions of gaze, except on lateral gaze to the affected side and an eye that is deviated down and out, with a dilated pupil, and ptosis. Typically seen in older patients with vascular risk factors such as diabetes and hypertension, diplopia due to microvascular ischemia may present with an isolated CN III palsy associated with pain, classically sparing the pupil, whereas that from compression (ie, from an aneurysm) is associated with pupillary mydriasis due to compression of pupillomotor parasympathetic fibers in the exterior of the nerve. The so-called rule of the pupil—more of a guideline than a rule—states that an otherwise complete CN III palsy (complete ptosis, completely down and out), with normal pupillary size and reactivity, rules out compression as the source. However, the presence of pupillary involvement does not rule in mechanical compression as the cause. A large case series of patients with CN III palsies revealed that over 50% of patients with diabetic microvascular ischemia had pupillary involvement, possibly from concomitant autonomic neuropathy, although pain was more common with CN III palsies from aneurysms (94% of cases) than from diabetic microvascular ischemia (69% of cases).[21] A rotational diplopia that worsens on looking down and toward the nose implies a superior oblique (CN IV) palsy. An abducens nerve (CN VI) palsy may present with bilateral findings, because elevated intracranial pressure from a brain tumor or malfunction ventriculoperitoneal shunt may be the cause.[23]

In contrast to a mononeuropathy, the combination of ipsilateral palsies of CN III, IV, and VI from an orbital apex or cavernous sinus process will typically present with additional findings—together called orbital apex syndrome—of exophthalmos, chemosis, and injection. Sensory deficits corresponding to the ophthalmic (V1) and maxillary (V2) divisions of the trigeminal nerve may be present, given their course through the orbital apex.

Neuroaxial Process Involving the Brainstem and Related Cranial Nerves. Vertical diplopia without the torsional component seen with CN IV palsy, called a vertical skew deviation, suggests a brainstem lesion. An internuclear ophthalmoplegia, suggested by an inability to adduct the eye on one side in the contralateral direction during lateral gaze that resolves during convergence, implicates a lesion in the medial longitudinal fasciculus (MLF) such as that typically found in patients with multiple sclerosis.[2] In multiple sclerosis, diplopia may present alone as a clinically isolated syndrome[4] or may be associated with a host of additional heterogeneous neurologic findings that typify this disorder (eg, optic neuritis, with blurred vision and eye pain, or focal motor or sensory abnormalities). A brainstem lacunar stroke may present as any of a number of identifiable syndromes (see Box 18.1). An impending basilar occlusion may present with additional symptoms of nystagmus, dysmetria, gait ataxia, and dysarthria.

A brainstem or cranial neuropathy that is part of a more diffuse neurologic syndrome may present with a stereotypical assortment of additional associated deficits. With foodborne botulism, patients have a descending flaccid paralysis that begins with multiple cranial nerve palsies. There may also be autonomic signs such as dry mouth, ileus, postural hypotension, respiratory muscle weakness, and pupillary abnormalities.[16] Patients with Miller-Fisher syndrome may present with an isolated ophthalmoplegia, considered a forme fruste of the disease, but more typically have the classic triad of ophthalmoplegia, ataxia, and areflexia. Muscle weakness should not be present[17]; if it is, the case is better classified as Guillain-Barré syndrome with

ophthalmoplegia.[17] Most patients with Wernicke's encephalopathy have ocular abnormalities, including nystagmus and ophthalmoplegia (usually from a CN VI palsy), typically associated with the classic triad of nystagmus, altered mental status, and ataxia. A fever suggests the possibility of an infectious process such as basilar meningoencephalitis.

Neuromuscular Disorder. The stigmata of neuromuscular disease such as muscle atrophy or weakness may be apparent on physical examination. Patients with myasthenia gravis may have unilateral or bilateral ptosis, weakness on forced eyelid closure, and generalized muscle weakness, but with normal reflexes and no sensory abnormalities. About 50% present with isolated ocular abnormalities.[22] The diplopia may represent a myasthenic crisis, possibly associated with occult respiratory muscle weakness and ventilatory insufficiency.[24]

Ancillary Testing

The patient with monocular diplopia should undergo a slit lamp and funduscopic examination and may need an evaluation by an ophthalmologist. A monocular cause of diplopia will not typically require an extensive neuroophthalmologic evaluation.

In the patient with a suspected or evident mechanical orbitopathy, a magnetic resonance imaging (MRI) scan of the orbits with gadolinium can allow an assessment for enlargement or enhancement in extraocular muscles and orbital structures, although a contrast-enhanced cranial computed tomography (CT) scan with fine cuts through the orbit can be used as a second-line option.[25] The same imaging paradigm applies to localization of the process within the cavernous sinus or orbital apex, because it will highlight infiltrative, inflammatory, or compressive pathology.[25]

For an isolated neuropathy of CN III, IV, or VI presenting without evidence of an aneurysm, the optimal study is MRI of the brain and orbits with gadolinium, high-resolution cuts through the brainstem, and fat-suppressed orbital imaging to assess for inflammation, neoplasm, or demyelination along the course of the nerves.[25] If an aneurysm is suspected, the imaging modality chosen (typically magnetic resonance angiography [MRA] and CT angiography) should be standard for that required to assess for an aneurysm; this is detailed in other chapters in this text specifically devoted to the topic.

If myasthenia gravis is suspected, a bedside test that can be performed is the ice test. An ice-filled glove or bag is applied to the patient's closed eye or eyes, held there for about 5 minutes, withdrawn, and any improvement in ptosis (typically ≈5 mm) or diplopia noted. Cold temperatures mitigate the effect of myasthenia-related acetylcholine receptor blockade by decreasing cholinesterase activity and promoting the efficacy of acetylcholine at the endplate. The bedside tests with the highest sensitivities for ocular myasthenia gravis are fatigability on sustained upgaze (sensitivity, 80%; specificity, 63%) and the ice test (sensitivity, 80%; specificity, 25%).[22] An edrophonium (Tensilon) challenge can also be performed, if the drug is available.

DIAGNOSTIC ALGORITHM

The critical, emergent, and urgent diagnoses applicable to each of the differential considerations noted are outlined in Table 18.1. The refinement of the differential diagnosis for the ED patient with diplopia involves determining the exact nature of the diplopia and functional location of the defect and screening for associated symptoms and findings that may suggest the underlying cause. Most of this diagnostic resolution is done at the bedside, followed by targeted neuroophthalmologic imaging, as indicated. The diagnostic challenge, in a context of cost-effective and efficient resource utilization, tends to be "Where do I look? … and for what? … and with which tool?" This challenge can be addressed, as reflected in the diagnostic algorithm in Fig. 18.4, using a phased systematic approach that incorporates the following queries, taking into consideration the symptoms and signs described earlier (see "Pivotal Findings"):

1. Is the diplopia monocular?
2. Is the diplopia due to a restrictive, mechanical orbitopathy?
3. Is the diplopia due to a palsy of the oculomotor cranial nerves (CN III, IV, VI) in a single eye?
4. Is the diplopia due to a neuroaxial process involving the brainstem and related cranial nerves?
5. Is the diplopia due to a neuromuscular disorder?

The first key assessment is to determine if diplopia is purely monocular. If it is, the evaluation essentially ends with ophthalmologic considerations. In contrast, if the diplopia is determined to be binocular, the next question is whether or not there is a simple mechanical orbitopathy, from an inflammatory, traumatic, neoplastic, or infectious mass effect directly restricting the movement of a single eye. If both eyes are involved, thyroid disease (Graves' orbitopathy) is a consideration. If an orbital mechanical problem is clearly apparent, with no neuroophthalmologic findings (including ptosis, pupillary abnormality, and anisocoria) or neurologic findings (including cranial nerve abnormalities), the initial evaluation can proceed along these lines.

If the diplopia does not appear to be strictly mechanical, the next question is whether there is a unilateral oculomotor cranial nerve palsy in the oculomotor (CN III), trochlear (CN IV), or abducens (CN VI) nerve, either as an isolated simple mononeuropathy from compression or microvascular ischemia or ipsilateral involvement of more than one of these oculomotor nerves (from mass, inflammation, or infection in the posterior orbit or cavernous sinus; orbital apex syndrome). An older diabetic patient with a classic presentation of mononeuropathy from microvascular ischemia will typically not need neuroimaging because the yield regarding another pathology is very low.[6,26] If there is any equivocation, however, it would not be unreasonable to pursue this in the ED because a small percentage of patients with risk factors for microvascular ischemia (eg, hypertension, diabetes, smoking) may have a cause other than microvascular ischemia.[6,27]

Assuming that a unilateral process limited exclusively to the orbit or oculomotor cranial nerves is not clearly identifiable, the next option is a neuroaxial process involving the brainstem and related cranial nerves, as one of the following: (1) a focal lesion in the brainstem (eg, from multiple sclerosis); (2) a more diffuse but still localized brainstem process (eg, from a brainstem tumor, brainstem lacunar stroke, impending basilar artery thrombosis, vertebral artery dissection, or ophthalmoplegic migraine); or (3) as part of a more diffuse neurologic syndrome involving the brainstem and/or CNs III, IV, and VI due an infectious, autoimmune, neurotoxic, or metabolic process involving other neurologic structures (eg, basilar meningoencephalitis, foodborne botulism, Miller-Fisher or Guillain-Barré syndrome, Wernicke's encephalopathy). It should be kept in mind that diplopia may be the first, primary, or only symptom of any of these, and that neuropathic signs suggesting a focal brainstem process may actually be a mild or early presentation of a diffuse neurologic syndrome.

Finally, if the presentation of the diplopia does not fit into an anatomically congruent process or central nervous system (CNS), a neuromuscular cause such as myasthenia gravis or tick paralysis may be involved.

EMPIRICAL MANAGEMENT

Because the treatment of diplopia depends entirely on the cause, there are few primary treatments for diplopia in the ED, as opposed to addressing whatever secondary disorder is causing it. Such approaches are outlined elsewhere in this text.

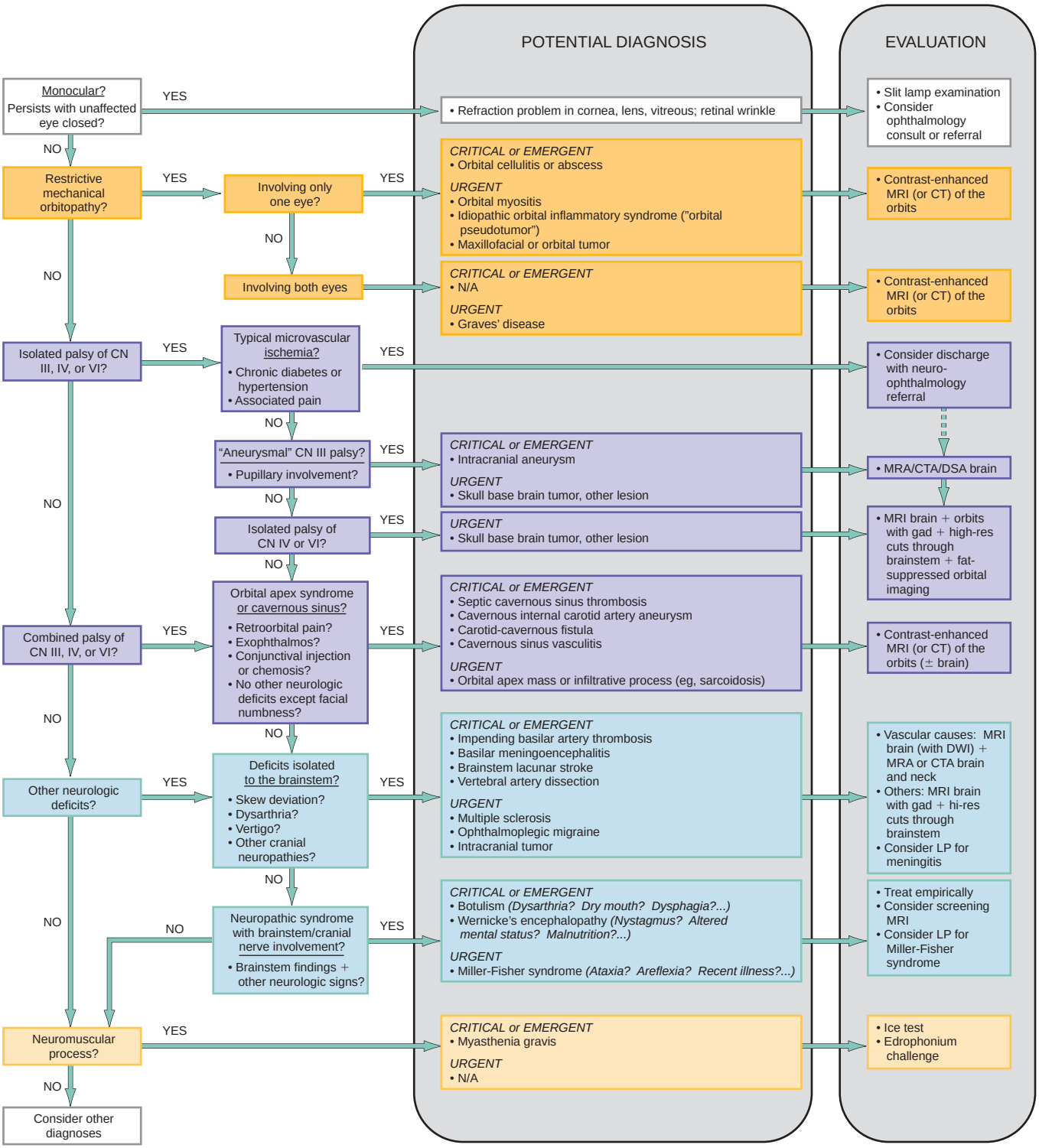


Fig. 18.4. Algorithm for the diagnostic approach to diplopia in the ED, a guideline. *CN,* Cranial nerve; *CNS,* central nervous system; *CT,* computed tomography; *CTA,* CT angiography; *DSA,* digital subtraction angiography (conventional angiography); *DWI,* diffusion-weighted imaging; *gad,* gadolinium; *High-res,* high-resolution; *LP,* lumbar puncture; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging.

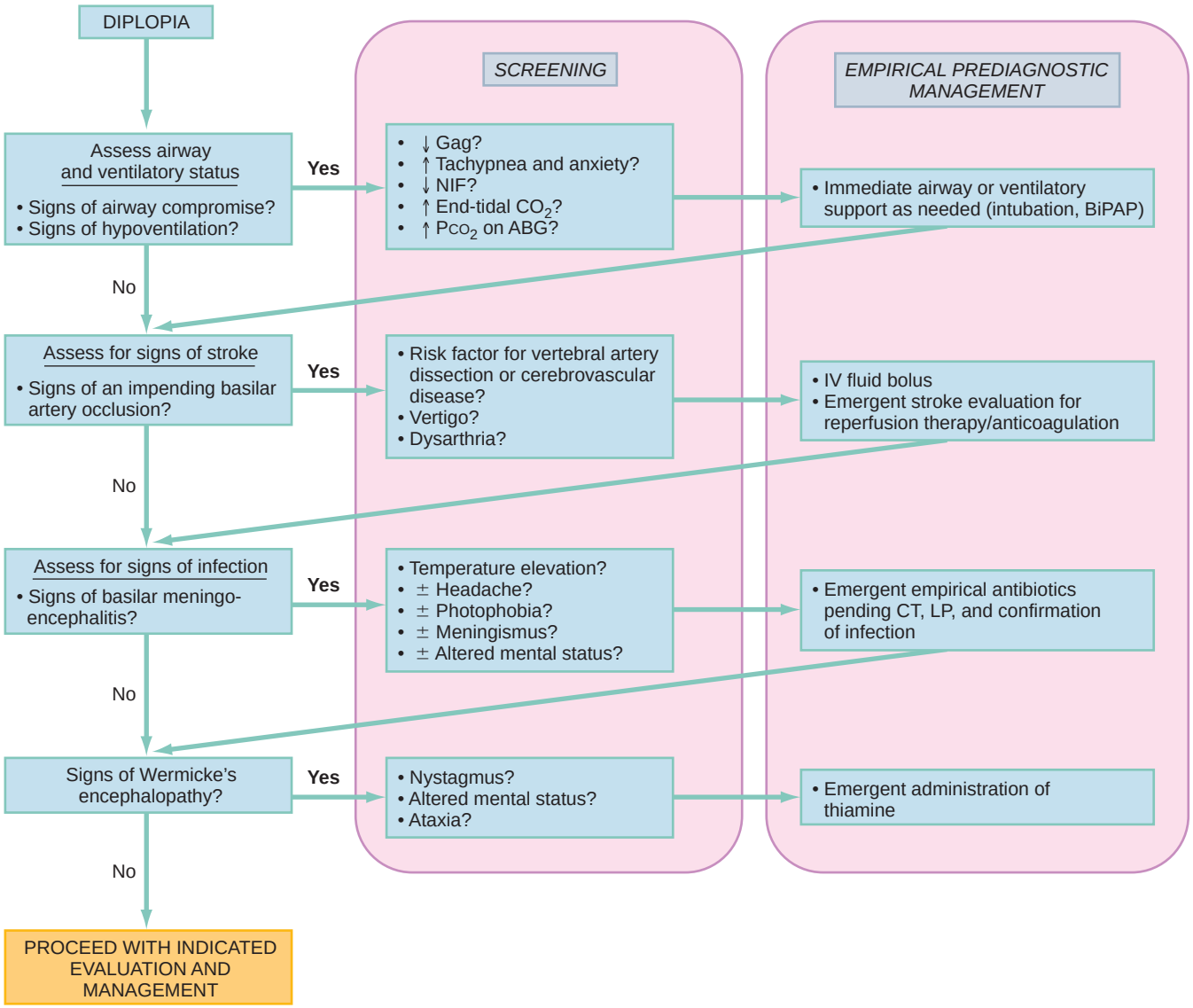


Fig. 18.5. Algorithm for the initial stabilization of the patient with diplopia in the ED, a guideline. *ABG,* Arterial blood gas; *BiPAP,* biphasic positive airway pressure; *CO_2,* carbon dioxide; *pCO_2,* partial pressure of carbon dioxide; *CT,* computed tomography (of the cranium); *LP,* lumbar puncture; *NIF,* negative inspiratory force.

Management Algorithm

Certain emergent therapeutic measures may be indicated in the context of potentially serious underlying causes, as outlined in the algorithm in Fig. 18.5. The priority is to consider imminent threats to CNS tissue viability such as an impending basilar artery thrombosis and then consider rapidly evolving threats to CNS tissue viability such as meningoencephalitis or Wernicke's encephalopathy and institute indicated treatments empirically as, or even before, the evaluation gets underway.

The patient with diplopia will typically require admission for further evaluation and treatment of the underlying disorder, unless diagnosed with a low-acuity condition such as microvascular ischemia. A CN III or VI palsy from microvascular ischemia is generally self-limited; the pain usually resolves after a few days, and complete spontaneous resolution is the norm, occurring in up to 95% of patients. These patients can typically be discharged home, with close outpatient follow-up.

KEY CONCEPTS

- Monocular diplopia persists in one affected eye, even with the other one closed. It is an ophthalmologic problem related to refractory distortions in the light path or from buckling of the retina.
- Binocular diplopia resolves when either eye is closed and is the result of a misalignment in the visual axes.
- Four lines of questioning that help formulate the differential diagnosis of binocular diplopia are as follows: (1) cadence of onset and symptoms (a sudden onset suggests an ischemic event; a fluctuation of symptoms suggests transient ischemic attacks, impending stroke, or neuromuscular disease); (2) directionality and orientation of the diplopia (horizontal, vertical, torsional); (3) presence of pain, which suggests an inflammatory or infectious process, and (4) the presence of other associated symptoms, which suggest a larger disease process (eg, infection, CNS ischemia, neuromuscular disease).
- The diagnostic approach to diplopia entails a methodical consideration of (1) a monocular (refractive) problem, which, when excluded, leads to consideration of (2) a simple restrictive, mechanical orbitopathy, which, when excluded, leads to consideration of (3) a palsy of one or more of the oculomotor cranial nerves, and then (4) a more proximal neuroaxial process involving the brainstem and related cranial nerves; if all else is excluded, then (5) a systemic neuromuscular process.
- An isolated CN III palsy presents with diplopia in all directions of gaze, except on lateral gaze to the affected side, and an eye that is deviated down and out, with a dilated pupil, and ptosis. Microvascular ischemia (typically seen in patients with diabetes), classically spares the pupil. A CN IV palsy results in rotational diplopia that worsens on looking down and toward the nose. A CN VI palsy results in diplopia that worsens on lateral gaze toward the problematic side.
- Simultaneous ipsilateral involvement of more than one of the CN III, IV, or VI nerves from mass, inflammation, or infection in the posterior orbit or cavernous sinus (orbital apex syndrome) may cause a combination of palsies and is associated with retroorbital pain or blurred vision due to venous congestion and possibly ipsilateral numbness or dysesthesia from involvement of the ophthalmic (V1) and maxillary (V2) trigeminal branches that travel though the orbital apex.
- Diplopia from a neuroaxial process involving the brainstem and related cranial nerves may present as (1) a focal lesion in the brainstem (eg, from multiple sclerosis), (2) a more diffuse but still localized brainstem process (eg, from a brainstem tumor or lacunar stroke, impending basilar artery thrombosis, vertebral artery dissection, or an ophthalmoplegic migraine), or (3) as part of a more diffuse neurologic syndrome involving the brainstem and oculomotor nerves (eg, from an infectious, autoimmune, neurotoxic, or metabolic process).
- The diplopia in myasthenia gravis is associated with ptosis, gets worse as the patient fatigues, and improves with rest or on placing ice over the eye.
- The empirical treatment of conditions causing diplopia, instituted even before testing for specific entities is begun, is directed toward imminent threats to airway and ventilation (eg, with botulism and myasthenia gravis), immediate threats to CNS tissue viability (eg, with basilar artery thrombosis or stroke), and rapidly evolving threats to CNS tissue viability (eg, with meningoencephalitis or Wernicke's encephalopathy).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 18: QUESTIONS & ANSWERS

18.1. A 65-year-old man with a long-standing history of diabetes and hypertension presents with sudden onset of persistent diplopia that began a few hours before arrival. He describes left retro-orbital discomfort, and his examination is notable for a left eye that is deviated laterally and downward, with a palsy of movement medially and upward. He also has a left-sided ptosis but no conjunctival injection, chemosis, or proptosis. His pupils are equal in size at 4 mm, round, and equally reactive to light in both a direct and consensual reflex, and his examination is otherwise unremarkable. What is the most likely cause of the diplopia?

A. Brain tumor
B. Cerebral aneurysm
C. Microvascular ischemia
D. None of these
E. Orbital apex syndrome

Answer: C. Based on examination, this is a patient who has a pupil-sparing CN III (third nerve) palsy. Because his pupillary examination is normal, with an otherwise complete CN III palsy, the so-called rule of the pupil applies. The palsy is very unlikely to be due to external compression from a brain tumor, aneurysm, or orbital apex process. It is a typical presentation of microvascular ischemia, to which the patient is predisposed, given his history of diabetes and hypertension.

18.2. A 56-year-old woman presents with recurrent episodes of diplopia that have been ongoing for a week. She describes double vision that gradually comes and goes, typically worse at the end of the day, with no particular direction or orientation to the diplopia. The patient's coworker, who is present in the emergency department (ED) with her, states that the patient's eyes "looked droopy" during an animated staff meeting they attended that afternoon but look normal now. The patient also describes waxing and waning general muscular weakness that has also been present this past week but denies any other symptoms and states that when she rests, she feels better. With which entity are her symptoms most consistent?

A. Botulism
B. Hypothyroidism
C. Miller-Fisher syndrome
D. Myasthenia gravis
E. None of the above

Answer: D. The patient and coworker are describing what appears to be an activity-related diplopia, with generalized muscle weakness and lack of other focal symptoms, all very suggestive of a possible neuromuscular process (myasthenia gravis). Miller-Fisher syndrome would not be associated with muscle weakness and would not wax and wane. Botulism would typically have a more progressive course, with other associated bulbar symptoms. Diplopia may be associated with hypothyroidism if it is a presentation of or treatment complication of Graves' disease but would not change so markedly with activity.

18.3. A 76-year-old man with hypertension, hypercholesterolemia, and diet-controlled diabetes presents with a sudden onset of diplopia that developed 30 minutes before arrival. Medics state that the patient's wife reported that he suddenly began staggering around the room, unable to bear weight on his left side. On examination, the patient has normal vital signs except for mild hypertension and has a right CN III palsy, with left arm and leg weakness. He has no airway complaints and denies any pain. What is the most appropriate initial response?

A. Checking blood gas levels and assess the patient's negative inspiratory force
B. Emergent treatment with botulinum antitoxin
C. Initiating broad-spectrum antibiotics to cover upper respiratory pathogens
D. Initiating clinical measures to address an acute ischemic stroke
E. A and B

Answer: D. The paroxysmal onset of the patient's symptoms, with focal neurologic symptoms and signs, suggests an ischemic event. His crossed deficits and discrete CN III palsy suggest localization in the brainstem.

18.4. Which constellation of symptoms is most concerning for foodborne botulism?

A. Double vision, headache, and right leg weakness
B. Double vision, left eye discomfort, and periorbital swelling
C. Double vision, neck pain, and vertigo
D. Double vision, nystagmus, and confusion
E. Double vision, slurred speech, difficulty swallowing, and dry mouth

Answer: E. Double vision, slurred speech, difficulty swallowing, and dry mouth would be present with foodborne botulism.

18.5. A 45-year-old man presents with progressively worsening double vision associated with right-sided, retro-orbital pain. His examination reveals mild conjunctival injection of the right eye, palsies of CNs III, IV, and VI on that side, some ptosis, a slightly decreased visual acuity to the right eye compared to the left, and mild sensory loss to the right infraorbital maxillary area. Which of the following initial imaging modalities should be used to evaluate the patient?

A. Computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the brain and neck
B. Contrast-enhanced CT or magnetic resonance imaging (MRI) of the brain, with fine cuts through the orbit
C. Diffusion-weighted MRI of the brain and brainstem
D. Digital subtraction angiography (DSA)
E. Noncontrast computed tomography of the brain

Answer: B. The combined palsy of multiple oculomotor cranial nerves on one side, with no other neurologic deficits apart from mild facial numbness corresponding to the maxillary branch of the trigeminal nerve, especially with the ocular findings and decreased visual acuity, suggests an orbital apex or cavernous sinus problem. The most optimal study would be that outlined in answer B. The risk in using the studies outlined in the other answers is that pathology might be missed because they are not dedicated to the orbits and cavernous sinus.

CHAPTER 19

Red and Painful Eye

Alan A. Dupré | John M. Wightman

PERSPECTIVE

Epidemiology and Pathophysiology

Most eye complaints are not immediately sight-threatening and can be managed by an emergency clinician; however, some require immediate recognition, emergent intervention, and consultation. Ocular injuries are one of the leading causes of visual impairment and blindness worldwide.[1] More patients with postoperative complications can be expected to present to the emergency department (ED) as more outpatient ophthalmological surgeries are performed. Nontraumatic diseases, such as glaucoma and peripheral vascular disease leading to retinal ischemia, are more common with advancing age.

The external and internal anatomy of the eye is depicted in Figure 19.1. The globe has a complex layer of blood vessels in the conjunctiva, sclera, and retina. Redness reflects vascular dilation and may occur with processes that produce inflammation of the eye or surrounding tissues. Eye pain may originate from the cornea, conjunctiva, iris, vasculature, or optic nerve. Each is sensitive to processes causing irritation or inflammation.

DIAGNOSTIC APPROACH

Rapid and accurate triage is the most critical consideration in the approach to the red and painful eye. A few problems should be considered critical, because they can rapidly lead to progressive visual loss without immediate intervention in the ED. Emergent conditions require expeditious triage and treatment. Urgent conditions should be managed in the ED before discharge. The remainder of conditions are those, such as conjunctivitis and spontaneous subconjunctival hemorrhage, where time to treatment has little effect on patient comfort or outcome.

Visual acuity has been called "the vital sign of the eye." Only a few situations preclude early and accurate visual acuity testing. Patients with complaints of contamination with an acid, alkali, or other caustic substance; sudden visual loss, especially if unilateral and painless; and significant trauma, especially with retrobulbar hematoma causing orbital compartment syndrome, should have only a gross visual acuity examination performed as interventions are simultaneously prepared. When not being actively examined or treated, injured eyes should be protected with a rigid shield to prevent inadvertent pressure that could cause additional damage.

Differential Diagnosis Considerations

The diagnostic approach to the red or painful eye typically begins with categorization into traumatic and nontraumatic causes. Patients almost always can report whether or not their eye was injured, even indirectly, such as injury from reflected sunlight.

Traumatic pain and redness can be caused by caustic fluids and solid materials, low-velocity contact with a host of materials that can fall or be rubbed into the eye, higher velocity blunt-force impacts to the orbit or globe, or potentially penetrating injuries. Caustic contamination is discussed elsewhere. Other traumatic complications that must be considered early in the course of care include retrobulbar hematoma, abscess, or emphysema with orbital compartment syndrome and suspicion of an open globe from either blunt or penetrating trauma.

The first triage question for any eye complaint should be, "Did anything get in your eye?" If so, attempt to identify the nature of the substance or foreign body. Specifically, this question seeks to quickly identify eyes that may have been exposed to a caustic substance. Patients exposed to acids, alkalis, and other caustic substances require rapid decontamination before additional evaluation to potentially prevent permanent loss of visual acuity.

The possibility of an open globe must be considered following any traumatic injury regardless of the mechanism. Findings may be obvious, subtle, or occult. Blunt trauma may frankly rupture the globe. Penetrating trauma can result from obvious causes identified through determining the events leading to injury, but it can also be unknown to the victim, such as walking near a person hammering metal or using a high-speed grinder yet not realizing a tiny ballistic metal fragment may have penetrated the eye.

Causes of nontraumatic pain and redness are diverse but are mostly infectious and inflammatory, although these may be due to processes intrinsic to the globe and adjacent structures or be due to ocular manifestations of systemic illness (eg, giant-cell arteritis). Exposure history and review of systems may be helpful when infection is suspected (eg, concomitant upper respiratory tract infections making a viral etiology of conjunctivitis more likely). Questions related to recent surgery and contact lens wear and cleaning practices should not be overlooked. Therefore, nontraumatic eye complaints typically require a more detailed history than would be necessary following a known injury.

Not all visual disturbances are due to conditions that cause ocular inflammation resulting in pain or redness. One that is critical to identify in the triage process is central or branch retinal artery occlusion. Only a rapid funduscopic examination to identify the problem and immediate intervention will afford even a chance to restore sight. This condition is readily apparent as a diffusely pale retina with indistinct or unseen retinal arteries (Fig. 19.2). Because it does not typically present with either pain or external signs (such as, redness), diagnosis and treatment are detailed in Chapter 61. Diplopia is covered in Chapter 18.

Pivotal Findings

Measurement of the patient's best corrected visual acuity (ie, with glasses on if available) with each eye individually provides vital information when evaluating eye complaints and may be prognostic in some situations. Only a few situations discussed earlier preclude obtaining visual acuity using a chart. Decreased visual acuity caused by abnormal refraction (eg, chronic myopia) can be detected by using a pinhole device during acuity testing, because central vision remains intact in refraction conditions. If there is a non-refractory problem, such as retinal edema or aqueous hemorrhage causing the acuity deficit, pinhole testing will show no improvement in the (poor) visual acuity.

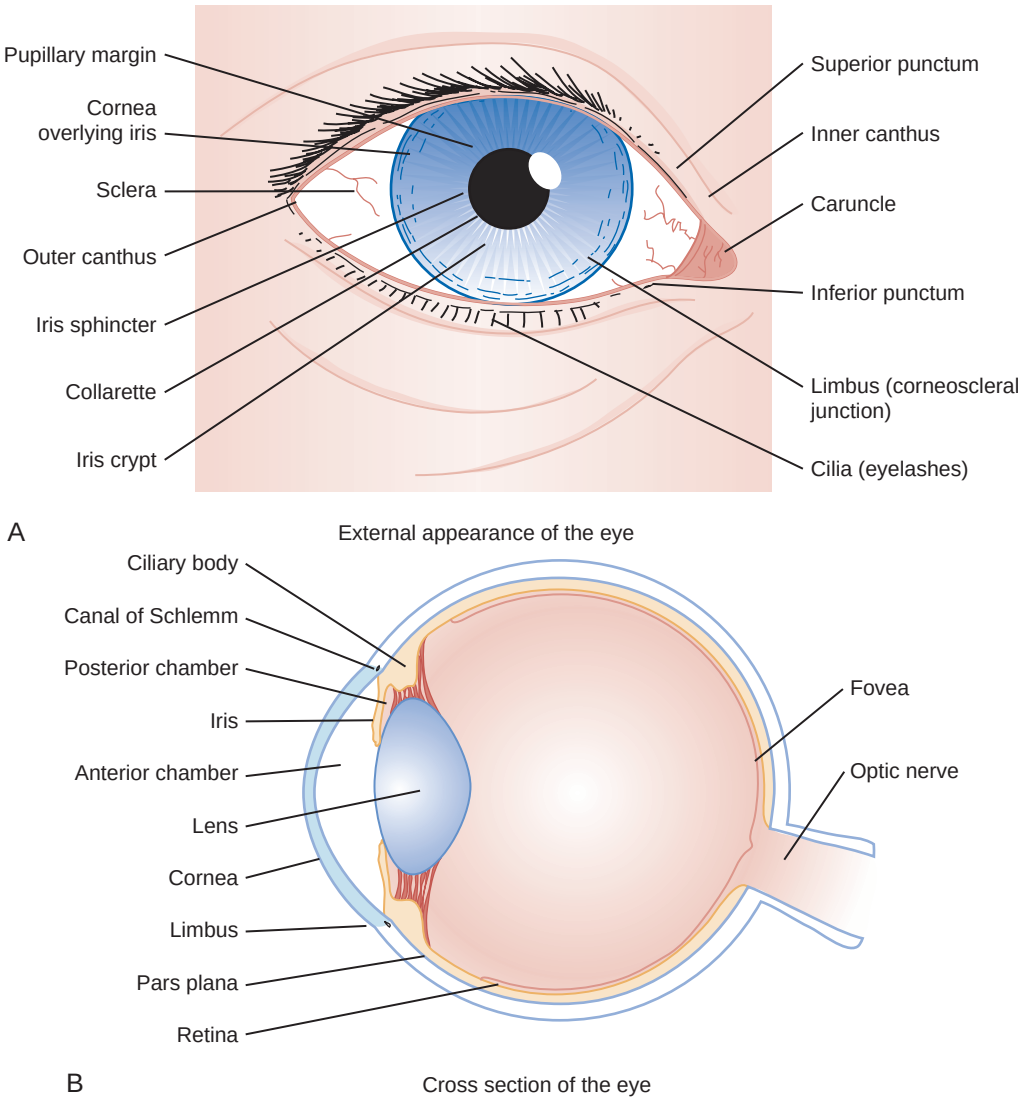

Fig. 19.1. External **(A)** and internal **(B)** anatomy. (From Ragge NK, Easty DL: Immediate eye care, St Louis, 1990, Mosby-Year Book.)

Symptoms and signs that are more likely to be associated with a serious diagnosis in patients with a red or painful eye are listed in Box 19.1.

Symptoms

When the presenting complaint is pain, the first step is to characterize it: itching, burning, dull pain, sharp pain, diffuse, or localized. Two historical factors are particularly important: suddenness of onset and perception of a foreign body. Itching tends to be more often due to irritation by blepharitis, conjunctivitis, or dry eye syndrome. Burning is associated with these conditions and with other mostly superficial problems, such as irritation of a pterygium or pinguecula, episcleritis, or limbic keratoconjunctivitis. A foreign-body sensation, particularly when it can be localized, is a strong indicator of corneal origin to the pain (foreign body, corneal abrasion, ulcer, or viral or ultraviolet keratitis). Sharp pain generally results from abnormalities of the anterior eye, such as corneal origin pain and uveitis. Dull pain, which may be severe, is usually generalized throughout the eye (and may be reported as "headache"). It is typically a manifestation of increased intraocular pressure (IOP) (such as, with acute angle closure glaucoma), vitreous infection (such as, endophthalmitis), or the pain is referred from an extra orbital process (such as, sinusitis, migraine headache, or temporal arteritis). Acute orbital compartment syndrome, caused by retro-orbital hematoma, presents with intense pain and progressive visual loss. These patients often present with head trauma that precludes them reporting pain, emphasizing the importance of physical examination.

Rarely is there a chief complaint of redness that is not accompanied by pain, itching, irritation, or foreign body sensation. Completely asymptomatic "red eye" is almost always a spontaneous subconjunctival hemorrhage, which is benign but often alarming to the patient. Spontaneous subconjunctival hemorrhage may follow coughing or straining, but it most often occurs without any identifiable precipitating event and is simply noticed by the patient when looking in a mirror.

Symptomatic red eye commonly causes bulbar or limbal injection of the conjunctiva. Free blood noted behind the bulbar conjunctiva (ie, subconjunctival hemorrhage) or in the anterior chamber (ie, hyphema) may be spontaneous or post-traumatic. Spontaneous subconjunctival hemorrhage is painless, and the presence of pain raises concern for a more serious cause of the hemorrhage, such as direct globe injury or a retrobulbar process. Hyphema of sufficient size to be noted by the patient or bystander usually presents with pain and blurred vision.

Other subjective findings may be transient and detected only by a thorough history. The patient may have symptoms of lid

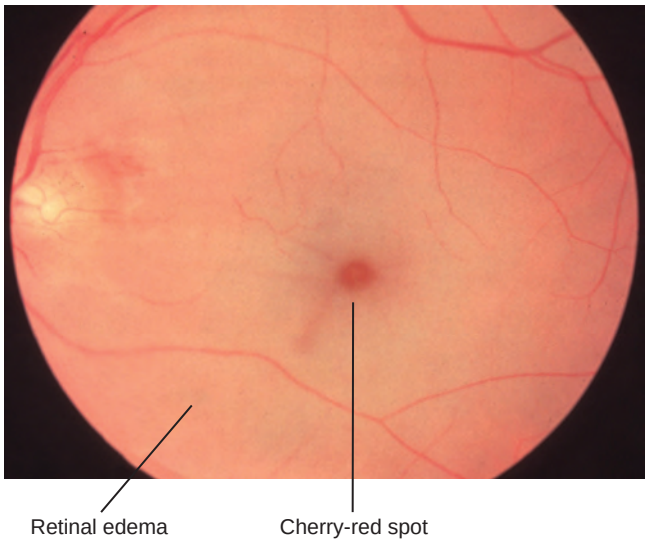

Fig. 19.2. Key funduscopic findings in acute central retinal artery occlusion include general pallor of the retina (except for a characteristic cherry-red spot where the perfused choroid shows through the thinner fovea) and attenuation of retinal arteries (possibly with retinal veins preserved as in the photograph). (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary illustrated manual of ophthalmology, ed 2, Philadelphia, 2004, WB Saunders, p 297.)

BOX 19.1

Pivotal Findings More Likely Associated With a Serious Diagnosis in Patients With a Red or Painful Eye

Severe ocular pain
Persistently blurred vision
Exophthalmos (proptosis)
Reduced ocular light reflection
Corneal epithelial defect or opacity
Limbal injection (also known as, ciliary flush)
Pupil unreactive to a direct light stimulus
Wearer of soft contact lenses
Neonate
Immunocompromised host
Worsening signs after 3 days of pharmacologic treatment

Adapted and reprinted with permission from Trobe JD: The physician's guide to eye care, San Francisco, 2001, Foundation of the American Academy of Ophthalmology.

swelling, tearing, discharge, crusting, discomfort on blinking, or sensitivity to light. Lid swelling can be caused by inflammatory and noninflammatory processes. Concurrent erythema and tenderness of the lid favors the former. In the absence of trauma or other external irritant (eg, contact dermatitis from eye makeup), inflammatory processes include primary lid problems, such as hordeolum (ie, stye) or blepharitis, as well as extension from concomitant conjunctivitis or cellulitis in orbital or periorbital structures. When pain is present, tearing is usually secondary. Discharge and crusting are most commonly associated with conjunctivitis, whether allergic, chemical, viral, or bacterial. Blepharitis, dacryocystitis, and canaliculitis are other inflammatory processes that may create a discharge and subsequent crusting.

A history of eyelids sticking together, particularly in the morning, is commonly cited as clinical evidence of bacterial, as opposed to viral, conjunctivitis, but this is unreliable. Even when lid sticking is combined with absence of itch and lack of history of conjunctivitis, large studies have failed to show diagnostic correlation between lid sticking and bacterial infection. Similarly, in the pediatric population (younger than 18 years old), lid sticking plus mucoid or purulent discharge show only fair correlation with proven bacterial infection. The hazards of equating lid sticking with bacterial infection are underscored by the fact that viral conjunctivitis, particularly caused by subtypes of adenovirus, can cause dramatic symptoms with mucopurulent discharge, lid sticking, keratitis symptoms, and lid inflammation. In many studies, lack of viral cultures precludes consideration of copathogens or bacterial culture of nonpathogenic flora.

Additional past ocular history questions are listed in Box 19.2.

BOX 19.2

Past Ocular History Questions

1. Are contact lenses used? If so, what type, how are they cleaned, and how old are the lenses? How often is the lens solution changed?
2. Are glasses worn? If so, when was the last assessment for adequate refraction? Does the patient endorse a subjective change in vision?
3. Has previous eye injury or surgery occurred?
4. What is the patient's usual state of health? Does the patient have any systemic diseases that may affect the eye?
5. What medications are being taken?
6. Are there any known or suspected allergies?

BOX 19.3

Complete Eye Examination

*V*isual acuity (best possible using correction)
*V*isual fields (tested by confrontation)
*E*xternal examination
    Globe position in orbit
    Conjugate gaze
    Periorbital soft tissues, bones, and sensation
*E*xtraocular muscle movement
*P*upillary evaluation (absolute and relative)
*P*ressure determination (tonometry)
Slit-lamp examination
Funduscopic examination

Adapted from Wightman JM, Hurley LD: Emergency department management of eye injuries. Crit Decis Emerg Med 12:1-11, 1998.

Signs

A complete eye examination usually includes eight components, although many patients require only a limited or directed eye examination, depending on the presentation. The mnemonic *VVEEPP* (pronounced "veep") plus slit-lamp and funduscopic examinations represent these components (Box 19.3). We recommend slit-lamp examination for any complaint involving trauma and for any medical presentation involving foreign-body sensation or alteration of vision. Funduscopic examination is usually pursued if there is visual loss, visual alteration, clouding of vision, or suggestion of serious pathology in the history and initial physical examination. A thorough physical examination can be conducted in the following order.

Visual Acuity

The initial determination of a patient's visual acuity provides a baseline from which deterioration or improvement may be

followed. It is also predictive of functional outcome after ocular trauma. Visual acuity is quantitatively assessed by use of a Snellen chart test at a distance of 20 feet (6 m) or a Rosenbaum chart at a distance of 14 inches. Young patients who cannot yet read letters and numbers should be tested with an Allen chart that depicts easily recognizable shapes. Each eye is tested separately with the opposite eye carefully covered. Patients who present without their prescribed corrective lenses may be evaluated by having them view the chart through a pinhole eye cover, which improves most refractive errors in vision.

If the patient cannot distinguish letters or shapes on a chart, visual acuity must be determined qualitatively. Any printed material suffices. The result may be recorded as, for example, "patient able to read newsprint at 3 feet." If this is not possible, visual acuity is recorded as:

- Unable/able to count fingers (CF)
- Unable/able to perceive hand motion (HM)
- Unable/able to perceive light (LP)

Visual Field Testing

Confrontation is the most common method of testing visual fields in the ED, but it is unreliable for detection of anything short of an extensive field deficit. On the other hand, visual field examination rarely adds useful information in the evaluation of the acutely red and painful eye. Detection of a scotoma usually represents a retinal problem. However, glaucoma may cause scotomata that can be crescent-shaped, involve just the binasal visual fields, or affect all peripheral vision. Hemi- or quadrantanopia is more commonly a problem of the neural pathways to the brain.

External Examination

Gross abnormalities are assessed by a visual inspection of both eyes simultaneously. Findings may be more apparent if compared with the opposite side. Fractures of maxillofacial bones are associated with ocular injuries, some of which require immediate intervention by an ophthalmologist.[2]

Globe position is part of the external examination. Subtle exophthalmos and enophthalmos are rare and best detected by looking inferiorly, tangentially across the forehead, from over the patient's scalp. Exophthalmos may have traumatic or nontraumatic causes but is due to increased pressure or a space-occupying lesion within the orbit, which may manifest as pain. Medical causes include cellulitis or intraorbital or lacrimal tumors. Hyperthyroidism may cause enlargement of extraocular muscles.

The most important cause of exophthalmos in the ED is orbital compartment syndrome, which pushes the globe forward, stretching the optic nerve and retinal artery and increasing IOP. The resulting microvascular ischemia is sight-threatening if sufficiently severe and persistent. Orbital emphysema and inflammation caused by a retained foreign body behind the eye are other causes of exophthalmos. Other signs of orbital compartment syndrome include limited eye movement and a relative afferent pupillary defect (RAPD) described under ancillary testing. If retrobulbar hemorrhage is the cause, blood often dissects anteriorly to fill the subconjunctival potential spaces.

The discovery of exophthalmos should prompt ocular tonometry measurements to determine the urgency of intervention. Trauma, particularly penetrating globe injury with extrusion of vitreous, can cause the globe to recede into the orbit, but the most common cause of enophthalmos is actually pseudo-enophthalmos when the contralateral globe is proptotic.

Inspection also involves examination of the upper and lower palpebral sulci for foreign bodies or other abnormalities. The lower sulcus is easily viewed after manual retraction of the lower lid toward the cheek and having the patient gaze upward. The upper sulcus is inspected by pulling its lashes directly forward and looking under the lid with white light. The lid can then be everted by pressing a cotton-tipped applicator in the external lid crease and folding the lid margin over the applicator.

Fig. 19.3. Injection of the palpebral and bulbar conjunctiva plus hypertrophy of Bruch's glands in the lower eyelid. (Photograph courtesy of Dr. John Wightman.)

Conjunctivitis, with conjunctival injection and discharge, is a common diagnosis following evaluation of patients with red and painful eyes. The presence of punctate "follicles" (ie, hypertrophy of lymphoid tissue in Bruch's glands) along the conjunctival surfaces of one or both lower lids has been touted to be relatively specific for a viral etiology (Fig. 19.3). Indeed, the "typical" viral "pink eye" used to be called *acute follicular conjunctivitis.*[3] Trachoma, a chronic keratoconjunctivitis caused by *Chlamydia trachomatis,* is one notable nonviral cause of this follicular hypertrophy.

Any discharge present is assessed as serous, mucoid, or purulent. Both viral and bacterial infection can cause mucoid or purulent discharge, so it is not possible to clinically distinguish viral from bacterial conjunctivitis on this basis alone.

A red eye in a neonate or infant is always abnormal. It is usually caused by corneal abrasion or infection. Corneal abrasions can also be a cause of inconsolable crying in an infant. Fluorescein examination helps to identify traumatic abrasions and herpes keratitis acquired from the birth canal or transmitted from a caregiver's fingers.

Extraocular Muscle Function

Limitation of ocular movement in one eye may be detected by having the patient follow the examiner's finger or a bright light through the cardinal movements of gaze. The eyes may move in a disconjugate fashion, or the patient may admit to diplopia if asked. Diplopia on extreme gaze in one direction may indicate entrapment of one of the extraocular muscles within a fracture site, but more often is caused simply by edema or hemorrhage related to the injury and is functional rather than actual entrapment. In the absence of trauma, diplopia is rarely associated with redness or pain.

Pupillary Evaluation

The pupils are inspected for abnormalities of shape, size, and reactivity. These examinations are conducted with light specifically directed into the pupil and by means of the swinging flashlight test.

Blunt or penetrating trauma, previous surgery (eg, iridotomy for cataract extraction), and synechiae from prior iritis or other inflammatory condition are the most common causes of irregularly shaped pupils.

Asymmetrically sized pupils may represent normal or pathologic conditions. Physiological anisocoria is a slight difference in pupil size that occurs in up to 10% of the population. Topical or systemic medications, drugs, and toxins may cause abnormal pupillary constriction or dilation.

Pathologic reasons for failure of one pupil to constrict with a direct light stimulus include globe injury, abnormalities of afferent or efferent nerves, and paralysis of the ciliaris or sphincter pupillae muscles in the iris. Potentially serious problems, which also cause pain and redness, include uveitis and acute angle-closure glaucoma.

While examining the pupils, the anterior chambers can be visually inspected for hyphema or hypopyon. Blood in the anterior chamber is usually the result of direct ocular trauma and may be associated with traumatic mydriasis or an obvious tear of the iris. If penetration and rupture can be reasonably excluded, the hyphema should be graded and IOP determined. Inability to view posterior structures through the anterior blood may necessitate radiologic or ultrasonographic imaging.

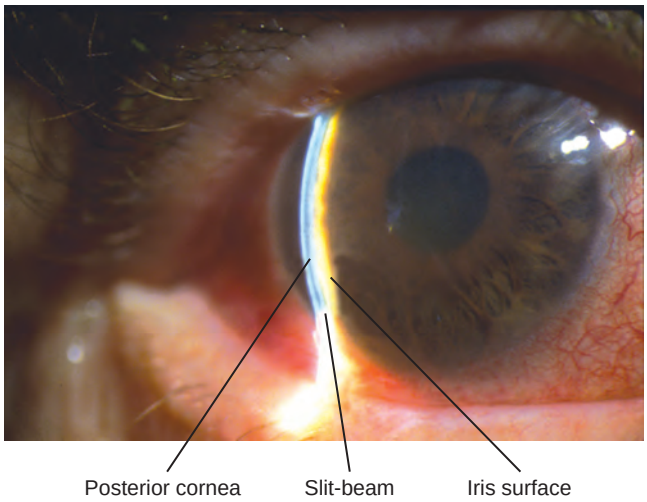

Fig. 19.4. Primary angle-closure glaucoma with very shallow anterior chamber and iridocorneal touch (no space between slit-beam views of cornea and iris). (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary illustrated manual of ophthalmology, ed 2, Philadelphia, 2004, WB Saunders.)

Ancillary Testing

Physical examination can be augmented by a number of additional tests to assess the relative amount of light reaching the retina or being converted into neural signals, determine the IOP, and visually inspect the anterior and posterior globe with magnification. Imaging of internal anatomy and pathology can be accomplished at the bedside or in the radiology suite.

Swinging Flashlight Test

The swinging flashlight test is used to determine whether a RAPD exists (see https://youtu.be/soiKbngQxgw). It is described in Chapter 61. A RAPD may be partial or complete and due to inhibition of light transmission to the retina because of vitreous hemorrhage, loss of some or all of the retinal surface for light contact because of ischemia or detachment, or the presence of lesions affecting the prechiasmal optic nerve (eg, optic neuritis).

Pressure Determination

Ocular tonometry is usually the last examination performed in the ED. Common methods of determining the IOP in the ED include use of electronic, manual (eg, Schiøtz), or applanation tonometers. IOPs in the 10 to 20 mm Hg range are considered normal. Causes of intraocular hypertension include glaucoma in its many forms, suprachoroidal hemorrhage, and space-occupying retrobulbar pathology. Acute angle-closure glaucoma is a relatively rare but an important critical diagnosis to make in the ED. Patients present with pain, the onset of which is often sudden in low-light conditions causing pupillary dilation through contraction and thickening of the iris peripherally. The iris becomes immobile and often irregular, and the pupil is commonly fixed at 5 to 6 mm in diameter. Inability of the pupil to constrict may result in photophobia, and accommodation may be affected. These reactions and the increased IOP can lead to frontal headache, nausea, and vomiting. As inflammation progresses, limbal injection of the conjunctiva is almost universally seen. Figure 19.4 demonstrates many of these findings. Patients presenting with IOPs exceeding 20 mm Hg should have ophthalmological consultation. Rapid treatment is usually not necessary unless the pressure exceeds 30 mm Hg.

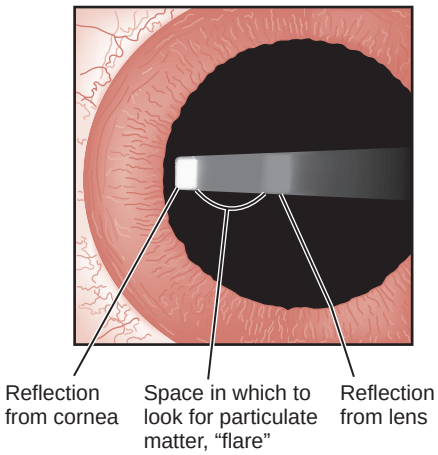

Fig. 19.5. Technique of slit-lamp examination with a short, narrow light beam projected from an extreme temporal angle across the contrasting black pupil to better find cells or "flare" indicative of acute anterior uveitis. (From Ragge NK, Easty DL: Immediate eye care, St Louis, 1990, Mosby-Year Book.)

Slit-Lamp Examination

The slit lamp is used to examine anterior eye structures. It permits a magnified, binocular view of the conjunctivae and anterior globe for diagnostic purposes and to facilitate delicate procedures. It allows depth perception in otherwise clear structures, such as the cornea, aqueous humor, and lens. Figure 19.5 shows the typical appearance of an angled slit beam reflecting from and passing through the cornea. Components of the slit-lamp examination are found in Box 19.4.

Fluorescein examination with cobalt blue light from the slit lamp identifies corneal defects. Fluorescein is not taken up by intact corneal epithelium but concentrates in areas where corneal epithelium is breached by abrasion, foreign body, or ulcer (Fig. 19.6). If the patient cannot sit in front of a slit lamp, a Wood's lamp may be used for magnification and an alternative light source instead. When corneal perforation is suggested, Seidel's test can be used as described in Chapter 61 (see https://www.youtube.com/watch?v=GlFcAv0DR4c).

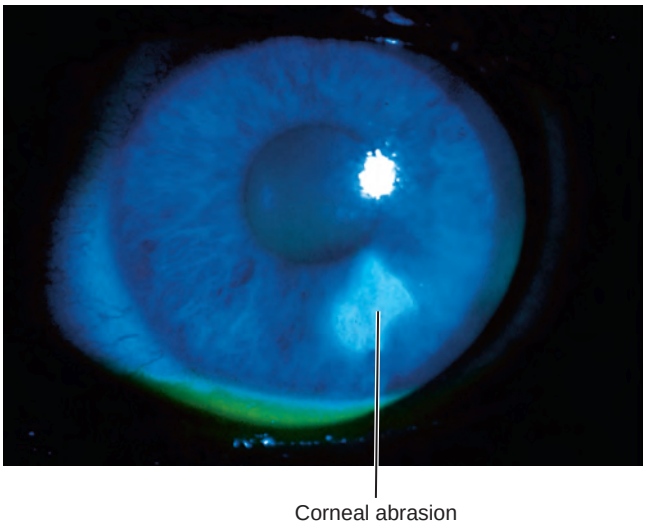

Fig. 19.6. Corneal abrasion demonstrating fluorescein pooling of a small inferior epithelial defect. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary illustrated manual of ophthalmology, ed 2, Philadelphia, 2004, WB Saunders.)

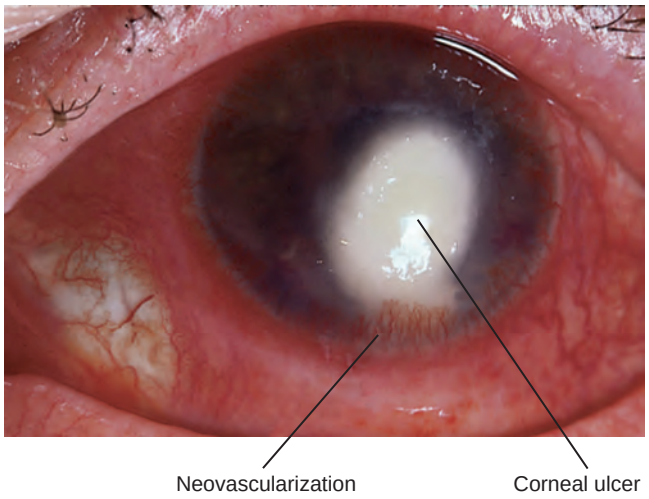

Fig. 19.7. Bacterial keratitis demonstrating a large, central *Streptococcus pneumoniae* corneal ulcer. Note the dense, white corneal infiltrate and the extreme conjunctival injection. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary illustrated manual of ophthalmology, ed 2, Philadelphia, 2004, WB Saunders.)

BOX 19.4

Slit-Lamp Examination

1. **Lids and lashes** inspected for blepharitis, lid abscess (ie, hordeolum) and internal or external pointing, and dacryocystitis.
2. **Conjunctiva and sclera** inspected for punctures, lacerations, and inflammatory patterns.
3. **Cornea** (with fluorescein in some cases) evaluated for abrasions, ulcers, edema, foreign bodies, or other abnormalities.
4. **Anterior chamber** evaluated for the presence of cells (eg, red and white blood cells) and "flare" (diffuse haziness related to cells and proteins suspended in aqueous humor) representing deep inflammation. Hyphema from surgery or trauma, hypopyon, or foreign bodies may also be noted.
5. **Iris** inspected for tears or spiraling muscle fibers noted in acute angle-closure glaucoma.
6. **Lens** examined for position, general clarity, opacities, and foreign bodies.

BOX 19.5

Causes of Inability to Visualize a Red Reflex or the Otic Fundus

1. Opacification of the cornea, most commonly by edema secondary to injury or infection
2. Hyphema or hypopyon within the anterior chamber
3. Extremely miotic pupil
4. Cataract of the lens
5. Blood in the vitreous or posterior eye wall
6. Retinal detachment

Ulcers can be large and easy to visualize (Fig. 19.7) or small and difficult to detect. They are best identified under slit-lamp examination by noting a denuding of epithelium with surrounding edema. Edema, in the form of increased interstitial water, is seen as whitish clouding of the normally clear tissue in the base of and adjacent to the lesion. This is best identified without fluorescein staining.

Direct Funduscopic Examination

Funduscopy is used to examine posterior eye structures. Emergency physicians most commonly perform a nondilated funduscopic examination, because there are several eye conditions in which dilation may be harmful (eg, angle-closure glaucoma). Iridodialysis, lens dislocation, and conditions requiring early intervention are usually identifiable along the visual axis. Inability to obtain a red reflex or visualize the fundus of the eye can be due to the causes listed in Box 19.5.

In the absence of trauma, few posterior findings are associated with chief complaints of external redness. Findings associated with visual loss include pallor of the retina indicating ischemia, "cupping" of the optic disk indicating glaucoma, indistinctness of disk margins indicating papilledema or optic neuritis or neuropathy, air or plaque emboli in retinal arteries, and a host of other signs indicating more chronic ocular or systemic pathology not normally amenable to management in the ED.

Topical Anesthetics

Relief of discomfort after instillation of a topical anesthetic can be used as a diagnostic test for a superficial source of pain. In general, abolition of pain by local anesthetic drops indicates pain of corneal origin. Modest but incomplete relief suggests a conjunctival process. Intraocular pain, including pain associated with uveitis, is not diminished by local anesthetic solution.

Imaging

A penetrating wound that violates the sclera may be immediately obvious. In other cases, the penetration may have occurred elsewhere in the head or neck then reach the orbit posterior to the orbital septum to injure the globe. In these cases, computed tomography (CT) or plain radiography is used to determine the presence of an intraocular or intraorbital foreign body.

Ultrasonography can be used in the ED when patient condition may preclude movement to the radiology suite, and it can be

highly accurate in identifying ocular foreign bodies. In experienced hands, ultrasonography is an excellent bedside modality for evaluating pathology of the globe. Ultrasonography can be used to evaluate abnormalities of the anterior chamber, iris, ciliary body, lens, vitreous, retina, choroid, posterior wall, and optic nerve.

Although plain radiography may directly identify facial fractures, or indirectly suggest fractures by detecting an air-fluid level in the orbit or fluid in the paranasal sinuses, CT is now considered the preferred modality for evaluating orbital trauma. Magnetic resonance imaging (MRI) clearly delineates orbital and retroorbital structures but is less rapidly obtained with no advantages over CT in trauma, is contraindicated in cases of suspected metallic foreign body, and is reserved for ocular issues felt to be of neurological origin.[4,5] All imagining modalities should be considered complementary to each other when employed in appropriate settings.

Laboratory Testing

Laboratory tests, such as a complete blood count, are generally not necessary in the evaluation of the red and painful eye. One notable exception is the evaluation of temporal arteritis. Temporal arteritis may present with eye pain and decreased visual acuity, but there may be no injection or other physical alteration of the eye. An erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are generally elevated in the acute phase, although one or both may be normal in up to 5% of biopsy-proven cases of temporal arteritis.[6] We do recommend obtaining CRP and ESR in cases of suspected temporal arteritis.

Microbiologic cultures are rarely ordered in the ED, but an ophthalmologist may request them in select circumstances.

DIAGNOSTIC ALGORITHM

A recommended algorithmic approach to the patient with an acutely red or painful eye is provided in Fig. 19.8.

Critical Diagnoses

Critical diagnoses require immediate intervention in the ED. Ophthalmological consultation is mandatory but should not delay potentially sight-saving procedures. Critical ophthalmologic diagnoses that do not present with redness or pain are discussed in Chapter 61. Because of its prognostic value, a quick visual acuity should be obtained while the patient is being triaged and subsequently managed.

Caustic injury to the eye can rapidly lead to a destructive keratoconjunctivitis if the agent is not removed immediately (Fig. 19.9). Intervention is initiated on history alone, before any other examination is performed. Early and copious irrigation is indicated. Many patients have already undergone extensive irrigation at the job site, but when the exposure has occurred in the home, irrigation prior to arrival in the ED is uncommon. Alkaline caustic agents cause a liquefactive necrosis of the cornea by progressively reacting with the corneal layers, and destruction is severe and relentless. Acid injury causes coagulation necrosis, which tends to limit the depth of injury. Both types require copious irrigation with any clean, relatively neutral fluid (eg, tap water, normal saline, and so on). Continuous irrigation until the pH of the tears is neutral is the only effective method to terminate these chemical reactions. A normal pH and post-irrigation examination (except expected conjunctival injection) does not mandate that an ophthalmologist respond to the ED. Any other post-treatment abnormalities do necessitate the presence of an ophthalmologist.

Orbital compartment syndrome can occur whenever intraorbital pressure increases to the point of causing dysfunction of the optic nerve. IOP can be used as a surrogate measure of intraorbital pressure when this can be safely measured. Retrobulbar hematoma is usually caused by orbital trauma, but it can also occur spontaneously in patients with coagulopathy. Retrobulbar abscess or emphysema can also occur. Elevated IOP in any of these conditions implies an orbital compartment syndrome and constitutes a surgical emergency.[7] Intervention in the ED requires decompressing the orbit by performing lateral canthotomy and cantholysis (see https://youtu.be/bUAagMd_Q8A) to relieve the pressure on the optic nerve, and should be performed within 2 hours of injury for the best chance of sight recovery.[7] These patients should be examined by an ophthalmologist as soon as possible afterward.

Patients with acute angle closure glaucoma (see earlier) require prompt medical intervention to decrease IOP in the ED and urgent ophthalmologic consultation (see Chapter 61). Follow-up can be decided based on the patient's response to therapy and discussion with the ophthalmologist.

Emergent Diagnoses

Most emergent diagnoses involve some kind of inflammation secondary to trauma, infection, or systemic disease. These include keratitis, anterior uveitis, scleritis, and endophthalmitis. Any of these may be complications of surgical procedures, and an appropriate ophthalmological history must be obtained. Consultation with an ophthalmologist is appropriate for all emergent diagnoses.

If penetrating ocular trauma is confirmed, or if the possibility persists after evaluation, an ophthalmological consultation is indicated.

Keratitis is treated with topical anesthesia, which provides immediate (but temporary) relief of pain, thus reinforcing the corneal origin of the process and facilitating examination and definitive diagnosis.

Following thorough irrigation, thermal and chemical burns must receive a careful slit-lamp examination for potential full-thickness injury. If this is not found, superficial corneal burns may be treated similarly to abrasions. If full-thickness injury is identified, immediate ophthalmological consultation is indicated.

Corneal ulcerations caused by overuse of contact lenses are treated with prophylactic antibiotics and avoidance of the lenses for at least 72 hours. We recommend follow-up with an ophthalmologist or optometrist before contact lens use is resumed.

Infections of the cornea with herpes simplex virus can rapidly lead to opacification and significant visual loss. It is most commonly recognized by a characteristic dendritic pattern of fluorescein pooling under blue light (Fig. 19.10). Anterior uveitis, which includes iritis and iridocyclitis, often occurs secondary to a traumatic injury or infectious process or can be associated with serious systemic immune diseases, such as adult and juvenile rheumatoid arthritis, sarcoidosis, and ankylosing spondylitis. We recommend urgent ophthalmologic evaluation, either in the ED or by immediate evaluation in an ophthalmological clinic, for these conditions.

Scleritis is commonly idiopathic, but may be associated with a systemic inflammatory process, such as a connective tissue disease, gout, or infection (eg, Lyme disease, syphilis, tuberculosis). Episcleritis is a somewhat more common, superficial, and more benign inflammation. Both are discussed in Chapter 61.

Endophthalmitis usually results from an infection of structures inside the globe. It is most common following penetrating trauma but may begin after hematogenous seeding from a remote or systemic infection, particularly in immunocompromised hosts. Unless it is detected early and is responsive to antimicrobial therapy, endophthalmitis is a devastating process that frequently requires enucleation.

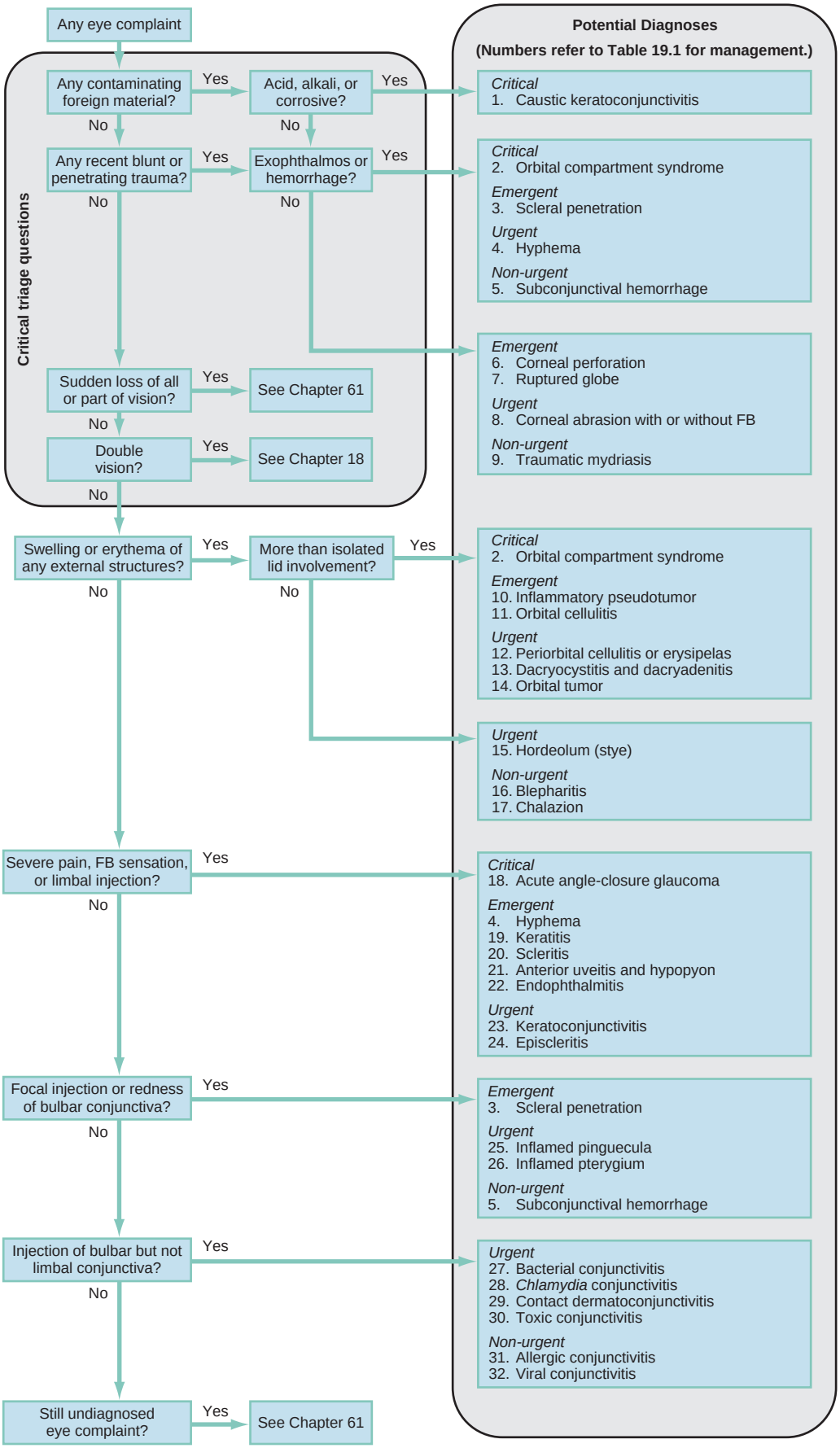

Fig. 19.8. Diagnostic algorithm for red and painful eyes. Numbers next to diagnoses correspond to Table 19.1 for management of each condition. *FB,* Foreign body.

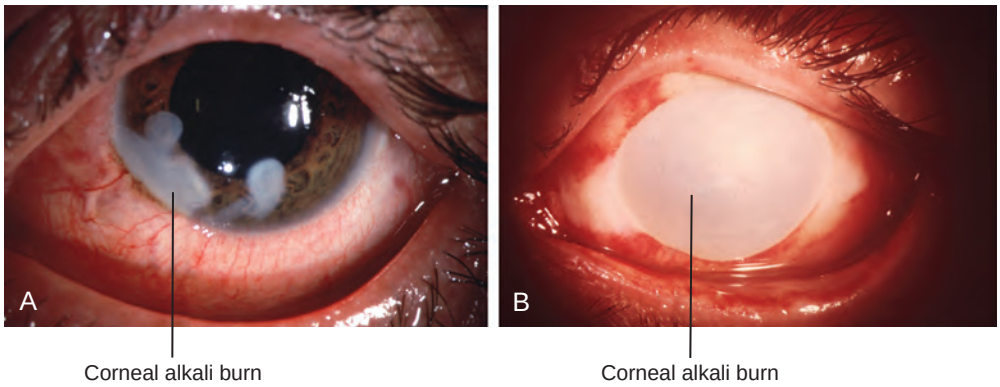

Fig. 19.9. A, Alkali burn demonstrating corneal burns and conjunctival injection on the day of the accident. **B,** Complete corneal tissue destruction 7 days after alkali burn. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary illustrated manual of ophthalmology, ed 2, Philadelphia, 2004, WB Saunders.)

Urgent Diagnoses

Foreign bodies on the cornea or under the lid are removed, as described in Chapter 61.

Superficial corneal abrasions, once universally patched, are now known to heal spontaneously without need for patching, prophylactic antibiotics, or prophylactic tetanus immunization.

Patients with hyphema are placed with head of bed elevated to 30 degrees, and they receive systemic analgesia and, if required, antiemetics, with emergent ophthalmologic consultation (see Chapter 61). Medications affecting platelet function should be avoided. If the iris is not injured, a long-acting cycloplegic agent (eg, topical homatropine) may be recommended to prevent repetitive motion of the iris. After consultation by ophthalmology, outpatient therapy and follow-up often are sufficient for management with simple (eg, acetaminophen) analgesia for pain. We recommend a rigid shield to protect the eye during sleep, but this should not be worn during the day. Patching is not otherwise needed. The patient should see the ophthalmologist or return to the ED if the patient experiences an increase in pain or decrease in visual acuity.

Fig. 19.10. Fluorescein pooling in the dendritic-shaped lesions of herpes simplex keratitis. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary illustrated manual of ophthalmology, ed 2, Philadelphia, 2004, WB Saunders.)

EMPIRICAL MANAGEMENT

Management of the specific entities listed in the diagnostic algorithm presented in Figure 19.8 is presented in Table 19.1. Specific management of ophthalmologic conditions is also discussed in Chapter 61.

Critical and emergent conditions are treated as described earlier. All other ocular emergencies are generally diagnosable in the ED, and treatment is initiated based on the diagnosis made. Caustic exposures receive copious irrigation, but all chemical or liquid exposures should undergo irrigation unless 1 hour has passed since exposure and the patient is completely asymptomatic at the time of evaluation.

Foreign bodies are removed, along with all fine particulate matter. Irrigation is advisable after foreign body removal if there is suspicion of remaining, very fine, foreign substance. After irrigation, conjunctival injection is common, but symptoms are expected to be mild. Patching is not indicated. Patients with significant symptoms after foreign body removal or with corneal abrasion may benefit from a topical nonsteroidal antiinflammatory analgesic solution or dilute topical local anesthetic drops for 24 hours.[8,9]

An algorithm for the treatment of acute conjunctivitis is presented in Figure 19.11. We do not recommend topical antimicrobial or corticosteroid treatment for conjunctivitis or keratoconjunctivitis (see Chapter 61). This is an area in which antibiotic misuse is widespread. There is no good medical evidence to support the requirements of most daycare and school facilities to mandate antibiotic treatment for acute conjunctivitis before returning to activities with other children. First, some causes of "pink eye" are not infectious. Second, in patients enrolled in clinical trials for acute infectious conjunctivitis, bacteria continue to be cultured many days after treatment is started, and viruses continue to be shed for 2 weeks or more with or without antibiotics. Unless a patient with conjunctivitis might potentially expose an immunocompromised individual, there is no medical reason not to return to daycare or school with or without treatment. If bacterial, only direct eye-to-hand-to-eye exposure will result in transmission. If viral, others have likely already been exposed. Finally, regardless of etiology, complications in healthy children are extraordinarily rare.[10]

Topical acyclovir, 3% ointment, is indicated for herpes keratitis, in conjunction with ophthalmologic or infectious disease consultation. Azithromycin is indicated for trachoma, again with consultation.

Topical antimicrobial prophylaxis is similarly not indicated for superficial epithelial defects of the cornea, although this also is

Text continued on p. 182

TABLE 19.1

Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 19.8*

POTENTIAL DIAGNOSIS	MANAGEMENT	CONSULTATION	DISPOSITION
1. Caustic keratoconjunctivitis	Immediate and copious irrigation with tap water or sterile normal saline until tear-film pH = 7. Solids: Lift particles out with dry swab before irrigation Acids: Minimum of 2 L *and* 20 minutes Alkalis: Minimum of 4 L *and* 40 minutes	Ophthalmologist must come to ED if there is any abnormal visual acuity or objective finding on examination after sufficient irrigation, with exception of expected injection of conjunctiva secondary to treatment.	May discharge only if tear film pH = 7 *and* no findings on examination except conjunctival injection, then ophthalmologist can reevaluate next day.
2. Orbital compartment syndrome: Exophthalmos (proptosis), decreased visual acuity, painful or limited ocular mobility, and increased IOP	Measure IOP unless possibility of ruptured globe. IOP >30 mm Hg may require emergent needle aspiration or lateral canthotomy and cantholysis in ED.	IOP >20 mm Hg may be surgical emergency, may add medications used in glaucoma #18 to decrease IOP before decompression in ED. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	Admit all cases of retrobulbar pathology causing increased IOP. Others might be candidates for discharge depending on cause of problem.
Retrobulbar hematoma: Occurs due to trauma, coagulopathy, or thrombocytopenia and associated with possible dissection of blood to potential space under bulbar conjunctiva	Hematoma: Correct any coagulopathy or thrombocytopenia.		
Retrobulbar emphysema: Occurs with forceful sneeze or occasionally happens spontaneously and associated with possible dissection of air to potential space under bulbar conjunctiva	Emphysema: Antibiotic prophylaxis to cover sinus flora.		
Retrobulbar abscess: Occurs with contiguous or occasionally hematogenously disseminated infection and associated with possible dissection of pus to potential space under bulbar conjunctiva	Abscess: Antibiotics as in orbital cellulitis (see #11).		
3. Scleral penetration: Localized redness at site of entry plus possible teardrop pupil, blood in anterior chamber or loss of red reflex	Protect eye from further pressure, provide pain relief, and prevent vomiting. Parenteral antibiotic and tetanus prophylaxis.	Ophthalmologist must come to ED if there is any concern for globe penetration.	Admit for continuation of antibiotics and possible procedural intervention.
4. Hyphema: Pain, decreased visual acuity, gross or microscopic blood in anterior chamber, may be associated with dilated and fixed pupil following blunt trauma Graded by amount of blood: • Percentage of vertical diameter of anterior chamber when blood layers with patient in upright position • Microhyphema shows no layering and only suspended red blood cells	First rule out open globe. May require ultrasound if cannot visualize posterior structures. Measure IOP unless possibility of ruptured globe. IOP >30 mm Hg may require acute treatment as in glaucoma (see #18). If IOP >20 mm Hg and no iridodialysis, may use cycloplegic to prevent iris motion.	Discuss findings and use of ε-aminocaproic acid and steroids, other medical therapy, best disposition, and follow-up examination by ophthalmologist within 2 days. Some patients may be admitted for observation, bed rest, head elevation, and frequent medication administration.	Most patients can be discharged with careful instructions to return for any increased pain or change in vision. Patients should decrease physical activity and sleep with an eye shield in place. Eyes should be left open while awake so that any change in vision can be immediately recognized. PO NSAIDs or narcotics should be given for analgesia.
5. Subconjunctival hemorrhage: Red blood beneath clear conjunctival membrane	Exclude coagulopathy or thrombocytopenia if indicated by history.	None required if no concerns for underlying ocular pathology and no acute complications.	Reassure patient that discoloration should resolve over 2 to 3 weeks.
6. Corneal perforation: Direct visualization of full-thickness injury or positive Seidel's test	Protect eye from further pressure, provide pain relief, and prevent vomiting. Parenteral antibiotic and tetanus prophylaxis.	Ophthalmologist must come to ED to evaluate.	Admit for continuation of antibiotics and procedural intervention.

TABLE 19.1

Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 19.8*—cont'd

POTENTIAL DIAGNOSIS	MANAGEMENT	CONSULTATION	DISPOSITION
7. Ruptured globe: Misshaped cornea or globe following trauma	Protect eye from further pressure, provide pain relief, and prevent vomiting. Parenteral antibiotic and tetanus prophylaxis.	Ophthalmologist must come to ED to evaluate.	Admit for continuation of antibiotics and procedural intervention.
8. Corneal abrasion: History of direct trauma or foreign body plus direct visualization of defect in the corneal epithelium using white light, or fluorescein and blue light; any surrounding corneal edema indicates a concomitant keratitis (see #19)	Antibiotic prophylaxis with polymyxin-B/trimethoprim solution 1 drop every 3 hours while awake and erythromycin ointment while sleeping.	Discuss plan for follow-up in 1 to 3 days.	May discharge if no other findings. No patch.
9. Traumatic mydriasis: Nonreactive dilated pupil without any other identifiable eye abnormalities following blunt trauma	None once other abnormalities of the eye, cranial nerves, and brain have been reasonably excluded.	Discuss plan for follow-up evaluation of slowly developing hyphema and ensure resolution.	May discharge if no other findings.
10. Inflammatory pseudotumor: Nonspecific idiopathic retrobulbar inflammation with eyelid swelling, palpebral injection of conjunctiva, chemosis, proptosis, blurred vision, painful or limited ocular mobility, binocular diplopia, edema of optic disk, or venous engorgement of retina	Measure IOP. Evaluate for infection, diabetes mellitus, and vasculitis with CBC, BMP, UA, and CRP or ESR. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	IOP >20 mm Hg may be surgical emergency, may add medications used in glaucoma #18 to decrease IOP before decompression in ED.	May discharge if no systemic problems, no findings of particular concern on CT, and IOP ≤20 mm Hg. Start high-dose PO steroids after discussion with ophthalmologist, and ensure reevaluation in 2 to 3 days.
11. Orbital cellulitis: Eyelid swelling, redness and warmth of skin overlying orbit, tenderness of skin overlying bone palpebral injection of conjunctiva, and chemosis; differentiated from periorbital cellulitis by *presence* of any finding of fever, ill appearance, blurred vision, proptosis, painful or limited ocular mobility, binocular diplopia, edema of optic disk, or venous engorgement of retina	Measure IOP and rule out orbital compartment syndrome. Start parenteral antibiotics with second-generation cephalosporin (eg, cefuroxime, cefoxitin, or cefotetan) or with ampicillin/sulbactam to cover sinus and skin flora. Alternatives are ticarcillin/clavulanate, piperacillin/tazobactam, vancomycin, or clindamycin + third-generation cephalosporin (eg, cefotaxime or ceftriaxone).	IOP >20 mm Hg may be surgical emergency, may add medications used in glaucoma #18 to decrease IOP before decompression in ED. Obtain blood cultures and start antibiotics. Axial and coronal CT of orbits and sinuses to rule out FB, retrobulbar abscess, orbital gas, subperiosteal abscess, osteomyelitis, and changes in cavernous sinus. Consider LP.	Admit all cases of orbital cellulitis.
12. Periorbital cellulitis or erysipelas: Eyelid swelling, redness and warmth of skin overlying orbit, tenderness of skin overlying bone, palpebral injection of conjunctiva, and chemosis; differentiated from orbital cellulitis by *absence* of any other finding listed in #11	First rule out orbital cellulitis (see #11). PO antibiotics for sinus and skin flora if not admitting.	Ophthalmologist may admit if systemically ill, case is moderate or severe, or no social support for patient.	May discharge mild cases with PO antibiotics. Ophthalmologist must reevaluate next day to ensure no orbital extension.
13. Dacryocystitis and dacryadenitis: Eye tearing and inflammation of lower eyelid inferior to lacrimal punctum finding redness and tenderness over nasal aspect of lower lid and adjacent periorbital skin	First rule out orbital cellulitis (see #11) and periorbital cellulitis (see #12). Inspect for obstruction of punctum by SLE, may express pus by pressing on sac, PO antibiotics for nasal and skin flora if not admitting.	Ophthalmologist may admit if systemically ill, case is moderate or severe, or no social support for patient. Ask about culturing before prescribing medications if admitting, and then may add medications used in glaucoma #18 to decrease IOP before decompression.	May discharge mild cases with PO analgesics and antibiotics (eg, amoxicillin/clavulanate), and instructions to apply warm compresses to eyelids for 15 minutes and gently massage inner canthal area four times a day.
14. Orbital tumor: Blurred vision, proptosis or other displacement of globe, painful or limited ocular mobility, or binocular diplopia (but can be asymptomatic)	Measure IOP. Evaluate for extraocular signs of malignancy. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	IOP >20 mm Hg may be surgical emergency, prescribe to decrease IOP in ED. Ophthalmologist may want MRI, MRA, or orbital ultrasonography.	Based on findings and discussion with consultant.

Continued

TABLE 19.1

Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 19.8*—cont'd

POTENTIAL DIAGNOSIS	MANAGEMENT	CONSULTATION	DISPOSITION
15. Hordeolum (stye): Abscess in eyelash follicle or modified sebaceous gland at lid margin: *external* or *internal* based on side of lid margin that abscess is pointing	External: Warm compresses often all that is needed, may prescribe anti-*Staphylococcus* ointment twice daily. Internal: PO antibiotics for β-lactamase–positive *Staphylococcus* such as amoxicillin/clavulanate	Outpatient referral only for treatment failure after 2 weeks.	Discharge with instructions to apply warm compresses to eyelids for 15 minutes and gently massage abscess four times a day.
16. Blepharitis: Inflammation of eyelid margins often associated with crusts on awakening, FB sensation, and tearing	None except artificial tears for dry eye.	Outpatient referral only for treatment failure after 2 weeks.	Discharge with instructions to apply warm compresses to eyelids for 15 minutes four times a day and scrub lid margins and lashes with mild shampoo on washcloth twice daily.
17. Chalazion: Inflammation of meibomian gland causing subcutaneous nodule within the eyelid	None.	Outpatient referral only for treatment failure after 2 weeks.	Discharge with instructions to apply warm compresses to eyelids for 15 minutes and gently massage nodule four times a day.
18. Acute angle-closure glaucoma: Sudden-onset eye pain and blurred vision that may be associated with frontal headache, nausea, and vomiting; anterior eye may manifest shallow or closed angle between iris and cornea, pupil fixed at midsize, or limbal injection of conjunctiva	Administer medications below in ED if IOP >30 mm Hg. Decrease production of aqueous humor: • Timolol 0.5% 1 drop • Apraclonidine 1% 1 drop q8hr • Dorzolamide 2% 1 drops *or* if sickle cell disease or trait, then methazolamide 50 mg PO Decrease inflammation: • Prednisolone 1% 1 drop every 15 minutes four times Constrict pupil: • Pilocarpine 1%–2% 1 drop after IOP <50, then repeat in 15 minutes Consider establishing osmotic gradient: • Mannitol 2 g/kg IV	Discuss any IOP >20 mm Hg with ophthalmologist.	Based on findings and discussion with consultant, which primarily depends on speed of onset and response to treatment.
19. Keratitis (abrasion or UV injury): Pain, FB sensation, blepharospasm, tearing, photophobia, epithelial disruption on inspection under white light, or fluorescein pooling under blue light; SPK appears as stippling of corneal surface (often lower two thirds of cornea if due to light exposure); if neglected for a time, may have surrounding edema appearing as white "cloudiness" in clear tissue	First rule out corneal penetration either grossly or employing Seidel's test. Relieve pain and blepharospasm with topical anesthetic. Inspect all conjunctival recesses and superficial cornea for any foreign material that can be removed by irrigation or manually lifted from surface.	Ophthalmologist must come to ED if there is any concern for globe penetration. Otherwise consult for follow-up examination in 1 to 2 days.	May discharge cases not infected or ulcerated. May provide topical antibiotic prophylaxis using polymyxin B combinations with bacitracin (ointment) or trimethoprim (solution). Erythromycin, gentamicin, and sulfacetamide are less desirable single-agent alternatives. PO NSAIDs or narcotics for analgesia. No patch.

TABLE 19.1

Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 19.8*—cont'd

POTENTIAL DIAGNOSIS	MANAGEMENT	CONSULTATION	DISPOSITION
Keratitis (ulceration): Symptoms and signs as described above; ulceration from complications of contact wear has "scooped out" epithelium with surrounding edema appearing as white "cloudiness" in clear tissue	Relieve pain and blepharospasm with topical anesthetic. *Staphylococcus* and *Streptococcus* species still most common organisms, but *Pseudomonas* greater percentage in existing infections (especially contact lens wearer), so prescription with topical fluoroquinolone is preferred.	Discuss with ophthalmologist any potential need to débride or culture before starting antibiotic.	Based on findings and discussion with consultant. Typical ciprofloxacin dosing is 2 drops q15min for 6 hours, then 2 drops q30min day and night for remainder of day 1 until seen by consultant the next day. Typical moxifloxacin dosing is 1 drop q15min for 1 hr, then 1 drop q1hr day and night until seen by consultant the next day. For large ulcerations or ulcers near the visual axis, a fortified antibiotic, such as tobramycin, may be added.
Keratitis (herpetic infection): Symptoms and signs as described above Look for other signs of herpes, varicella, zoster (or CMV infection in immunocompromised patient) Look for "dendritic" defects of cornea with fluorescein under blue light	Relieve pain and blepharospasm with topical anesthetic. Prescribe acyclovir 3% ointment, trifluridine 1% solution, or vidarabine ointment. Varicella-zoster and CMV not normally given antivirals if immunocompetent.	Discuss with ophthalmologist any potential need to débride or culture before starting antiviral.	Based on findings and discussion with consultant. Typical vidarabine or acyclovir dosing is five times a day for 7 days, then taper over 2 more weeks. Typical trifluridine dosing is 1 drop every 2 hours for 7 days, then taper over 2 more weeks. PO NSAIDs or narcotics for analgesia. No patch.
20. Scleritis: Progressively increasing eye pain with radiation to ipsilateral face and decreasing vision, photophobia, tearing, and possible pain with eye motion	Decrease inflammation with PO NSAIDs.	Discuss findings and use of topical or PO steroids.	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2 to 3 days.
21. Anterior uveitis and hypopyon: Eye pain, photophobia, tearing, limbal injection of conjunctiva, and cells or flare in anterior chamber; hypopyon is layering of white cells (pus) in anterior chamber	First rule out glaucoma with IOP measurement. Prescribe in ED if IOP >20 mm Hg. Otherwise okay to dilate pupil with 2 drops of cyclopentolate 1%.	Discuss findings and use of prednisolone acetate 1% (frequency determined by ophthalmologist but range is every 1 to 6 hours).	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2 to 3 days. Patients with hypopyon are generally admitted.
22. Endophthalmitis: Progressively increasing eye pain and decreasing vision, diminished red reflex, cells and flare (and possibly hypopyon) in anterior chamber, chemosis, and eyelid swelling	Empirical parenteral antibiotic administration with vancomycin and ceftazidime to cover *Bacillus, enterococcus,* and *Staphylococcus* spp. Ciprofloxacin or levofloxacin are used when others contraindicated.	Ophthalmologist must admit for parenteral and possibly intravitreal antibiotics.	Admit all cases of endophthalmitis.
23. Keratoconjunctivitis: Conjunctivitis with subepithelial infiltrates in cornea causing pain and decreased vision, possibly with halos reported	Treat for conjunctivitis by likely etiologic category (see #25 to #30).	Discuss findings and use of prednisolone acetate 1% (frequency determined by ophthalmologist).	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2 to 3 days.
24. Episcleritis: Rapid onset of localized pain, injection of episcleral vessels, and localized tenderness	Relieve irritation with artificial tears and decrease inflammation with ketorolac drops.	Outpatient referral only for treatment failure after 2 weeks.	May discharge patient with PO NSAIDs alone or in combination with topical ketorolac drops.
25. Inflamed pinguecula: Inflammation of soft yellow patches in temporal and nasal edges of limbal margin 26. Inflamed pterygium: Inflammation of firmer white nodules extending from limbal conjunctiva onto cornea	Decrease inflammation with naphazoline or ketorolac drops.	Outpatient referral only for treatment failure after 2 weeks.	Discharge to follow-up with ophthalmologist for possible steroid therapy or surgical removal.

Continued

TABLE 19.1

Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 19.8*—cont'd

POTENTIAL DIAGNOSIS	MANAGEMENT	CONSULTATION	DISPOSITION
27. Bacterial conjunctivitis: Hyperpurulent discharge not typical of common "pink eye" and more commonly unilateral in adults; inflammation of eyelid margins associated with lid edema, chemosis, and possibly subconjunctival hemorrhage, but usually little or no follicular "cobblestoning"	Topical polymyxin-B/trimethoprim in infants and children, because more *Staphylococcus* spp. Topical sulfacetamide or gentamicin clinically effective in 90% of uncomplicated adult cases. Use topical fluoroquinolone if *Pseudomonas* possible.	Culture drainage and ophthalmology consult in all neonates and those at risk for vision loss or systemic sepsis. *Neisseria gonorrhoeae* can be rapidly sight-threatening.	Discharge uncomplicated cases with 10 days of topical antibiotics in both eyes, regardless of laterality of apparent infection. Use ointments in infants and drops in others.
28. *Chlamydia* conjunctivitis: Often bilateral palpebral injection of conjunctiva in neonate or other individual at risk for sexually transmitted disease	Empirical PO azithromycin for *Chlamydia.* Consider empirical parenteral ceftriaxone for concurrent *N. gonorrhoeae.*	Culture drainage and consult ophthalmology in all neonates and those at risk for vision loss or systemic sepsis.	Discharge uncomplicated cases on 5 days of PO azithromycin.
29. Contact dermatoconjunctivitis: Localized lid and conjunctival redness and swelling 30. Toxic conjunctivitis: Diffuse conjunctival injection, chemosis, and lid edema	Irrigation with tap water or sterile normal saline. Decrease irritation with naphazoline drops.	Outpatient referral only for severe cases or treatment failure after 2 weeks.	Identify offending agent and avoid subsequent exposure. Discharge uncomplicated cases on continued naphazoline.
31. Allergic conjunctivitis: Often bilateral palpebral injection of conjunctiva and chemosis that may be seasonal and associated with other allergic symptoms, such as rhinitis	Decrease irritation with naphazoline drops.	Outpatient referral only for treatment failure after 2 weeks.	Identify antigen if possible. Consider treating other allergic symptoms with PO antihistamines.
32. Viral conjunctivitis: Often bilateral palpebral injection of conjunctiva and follicular cobblestoning of inner surface of lower lid; inflammation of eyelid margins often associated with crusts on awakening, FB sensation, and tearing	Decrease irritation with artificial tears, naphazoline, or ketorolac drops.	Culture drainage, and consult ophthalmology in all neonates and those at risk for vision loss or systemic sepsis.	Ask about pregnant mothers, infants, and immunocompromised individuals in close contact. Discharge uncomplicated cases with instructions on respiratory and direct-contact contagion for 2 weeks.

BMP, Basic metabolic profile (includes electrolytes, glucose, and renal function tests); *CBC,* complete blood count; *CMV,* cytomegalovirus; *CRP,* C-reactive protein; *CT,* computed tomography; *ED,* emergency department; *ESR,* erythrocyte sedimentation rate; *FB,* foreign body; *IOP,* intraocular pressure; *IV,* intravenous; *LP,* lumbar puncture; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *NSAID,* nonsteroidal antiinflammatory drug; *PO, per os* (by mouth); *SLE,* slit-lamp examination; *SPK,* superficial punctuate keratitis; *spp.,* species; *UA;* urinalysis; *UV,* ultraviolet.
*Antibiotic choices should be based on current practice.

common practice despite an absence of supporting evidence. There is also no evidence supporting the practice of administering tetanus immunization to patients with superficial corneal abrasions, other than as a general public health measure. On the other hand, true open wounds of the adnexa or globe do require tetanus prophylaxis if the patient's immunization status is not up to date.

Mydriatic and cycloplegic agents are also commonly prescribed but rarely are indicated. Their use is discussed in Chapter 61. Mydriatic agents are contraindicated in patients with narrow-angle glaucoma. Larger corneal lesions sometimes require a cycloplegic agent for pain relief, but this should be prescribed only for the few patients experiencing refractory iris spasm and not prophylactically.[11]

Treatment of bacterial keratitis and endophthalmitis is described in Chapter 61.

Most ED patients with eye complaints are candidates for discharge and, if indicated, follow-up in the ED or with an ophthalmologist in 1 to 2 days. Others may require referral only if there is lack of resolution or treatment fails. A few patients require admission for procedural intervention, parenteral antibiotic regimens, management of intractable pain, or further diagnostic evaluation. General consultation and disposition considerations for the most important entities are outlined in Table 19.1.

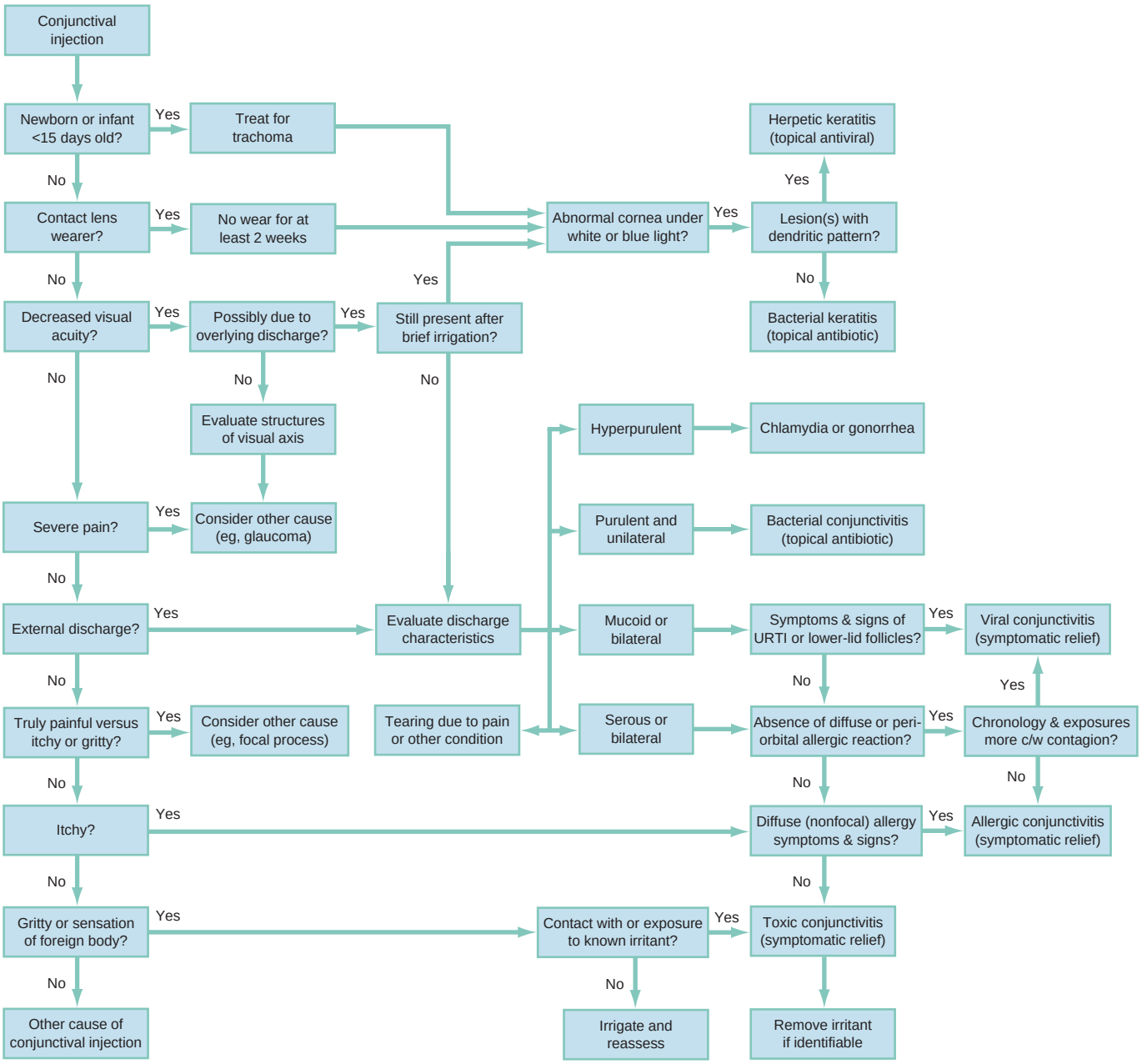

Fig. 19.11. Diagnostic algorithm for suspected acute conjunctivitis. *c/w,* Consistent with; *URTI,* upper respiratory tract infection.

KEY CONCEPTS

- Critical diagnoses, such as caustic injury, orbital compartment syndrome, and acute angle closure glaucoma, require immediate treatment and ophthalmology consultation.
- Prompt and prolonged irrigation is advised for patients who experience caustic injury to the eye.
- Headache and nausea may be prominent symptoms in patients with acute angle-closure glaucoma.
- Complete abolition of a foreign body sensation after instillation of local anesthesia solution indicates a high likelihood of a superficial corneal lesion.
- Keratitis, inflammation of the cornea, is most commonly caused by a viral infection, but may also be caused by recent ultraviolet light exposure, chemical injury, or hypoxic injury from contact lens use.
- A localized corneal defect with edematous, inflammatory changes may signal corneal ulceration.
- A corneal dendritic pattern may signal a herpetic infection, which can progress to corneal opacification and visual loss.
- Pain, consensual photophobia, peri-limbic conjunctival infection, and a miotic pupil that is caused by ciliary spasm could signal iritis, which is inflammation of the iris and ciliary body, or uveitis, inflammation of the iris, ciliary body, and also choroids. The cause may be trauma or underlying autoimmune disease. The presence of cells and flare in the anterior chamber can help identify these conditions.
- Conjunctivitis is usually self-limited and rarely requires antibiotic treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 19: QUESTIONS & ANSWERS

19.1. Cupping of the optic disk is most commonly seen in which of the following?
- **A.** Glaucoma
- **B.** Graves' disease
- **C.** Pseudotumor
- **D.** Retinal detachment
- **E.** Retrobulbar hematoma

Answer: A. Cupping of the optic disk results from increased intraocular pressure (IOP) and is seen quite frequently in patients with glaucoma, especially those with long-standing, uncontrolled disease.

19.2. A patient who normally wears contact lenses is diagnosed with bacterial conjunctivitis. Which of the following is the preferred treatment in this patient?
- **A.** Bacitracin
- **B.** Chloramphenicol
- **C.** Erythromycin
- **D.** Moxifloxacin
- **E.** Sodium sulfacetamide

Answer: D. Patients who wear contact lenses are at increased risk for infections with *Pseudomonas* and, in the setting of bacterial conjunctivitis, should be prescribed a quinolone (eg, ciprofloxacin or moxifloxacin) barring any contraindications.

19.3. Which of the following provides the longest maximum duration of cycloplegia?
- **A.** Atropine
- **B.** Cyclopentolate
- **C.** Homatropine
- **D.** Scopolamine
- **E.** Tropicamide

Answer: A. Atropine has a maximum duration of action of 14 days. This is followed by scopolamine with a maximum duration of 7 days, homatropine with 3 days, cyclopentolate with 24 hours, and tropicamide with 6 hours.

19.4. A 15-year-old boy presents to the ED after having been shot in the face with a BB gun. He has a solitary penetrating wound just inferior to his left eye. His visual acuity in the left eye is limited to light perception, but he reports having normal vision prior to the injury. He has significant proptosis of his left eye, and his fundus is clearly seen with direct ophthalmoscopy. Intraocular pressure (IOP) of the affected eye is 50 mm Hg. His mental status is normal. What is the most appropriate next step in the management of this patient?
- **A.** CT scan of the head and face
- **B.** ED observation with repeated neurologic examinations
- **C.** Lateral canthotomy and inferior cantholysis
- **D.** Next-day referral to ophthalmology
- **E.** Plain radiography of the face

Answer: C. The described patient likely has a retrobulbar hematoma with visual acuity changes and an elevated IOP. The elevated IOP with a clear funduscopy are findings consistent with no penetration into the globe. Although CT scan of the head and face is indicated to further delineate specific injuries, lateral canthotomy and inferior cantholysis is emergently necessary for orbital decompression in an attempt to salvage visual function. This sight-saving procedure should not be delayed more than 2 hours after injury when severe findings (decreased visual acuity and significantly increased IOP) are present. Likewise, ophthalmology consultation would be indicated emergently. Plain films of the face would prove of little use in the evaluation of this patient, as would prolonged ED observation.

19.5. A 68-year-old woman presents with a sudden, painless, and complete vision loss in her right eye. Upon funduscopic examination of her right eye, she is noted to have a diffusely pale retina with indistinct vessels and a cherry-red fovea centralis. Her left eye is normal. Which of the following is the most likely diagnosis?
- **A.** Acute angle closure glaucoma
- **B.** Central retinal artery occlusion
- **C.** Retinal detachment
- **D.** Tay-Sachs disease
- **E.** Temporal arteritis

Answer: B. Acute central retinal artery occlusion is characterized by a diffusely pale retina with indistinct or unseen retinal arteries in a patient with sudden, painless, and usually complete visual loss in one eye. Although temporal arteritis can precipitate an occlusion of the retinal artery as one mechanism leading to visual loss and therefore manifest the same findings on funduscopy, this condition is not painless. Patients with temporal arteritis typically have excruciating pain over or in the region of their temporal arteries. Acute angle closure glaucoma is also typically associated with severe pain and has ocular manifestations unlike the ones presented in this case. The funduscopic examination in a patient with retinal detachment reveals a translucent retina that has lifted away from the underlying pigment epithelium. Finally, although patients with Tay-Sachs disease do have a cherry-red fovea, the remainder of the retina is not diffusely pale with poorly visualized vessels. Moreover, Tay-Sachs disease is manifested in the early part of life and would not first be coming to clinical attention in a 68-year-old patient.

19.6. A professional boxer presents to the ED after having been punched in the right eye during a boxing match 1 hour ago. He complains of decreased vision in the affected eye and is noted to have significant periorbital swelling and

proptosis. Intraocular pressure (IOP) is 35 mm Hg in his right eye. Which of the following is the most likely diagnosis?
A. Orbital cellulitis
B. Orbital compartment syndrome
C. Periorbital cellulitis
D. Post-traumatic glaucoma
E. Traumatic iritis

Answer: B. The most important cause of post-traumatic proptosis in the ED is the development of retrobulbar hematoma. This is characterized by hemorrhage within the bony orbit and behind the globe. With significant bleeding, an orbital compartment syndrome can occur in which the globe is pushed forward, the optic nerve and retinal artery are stretched and compressed, and the IOP is increased. This is a potentially sight-threatening condition that requires expedient diagnosis and management if the vision is to be salvaged.

19.7. A collection of pus in the anterior chamber of the eye is known as which of the following?
A. Cotton-wool spot
B. Dacryocystitis
C. Hyphema
D. Hypopyon
E. Keratitis

Answer: D. A collection of layered pus in the dependent portion of the anterior chamber is called a *hypopyon.*

19.8. Which of the following results from inflammation of a meibomian gland?
A. Blepharitis
B. Chalazion
C. Dacryocystitis
D. Erysipelas
E. Hordeolum

Answer: B. Inflammation of a meibomian gland with the subsequent formation of a subcutaneous nodule within the eyelid is known as a *chalazion.* This condition typically resolves spontaneously over several days. Authorities often recommend warm compress application and gentle massage of the nodule several times a day, although there is no evidence supporting this. If complete resolution does not occur with 2 weeks, the patient should be referred to an ophthalmologist.

19.9. Which of the following pathogens causes a characteristic dendritic lesion on the cornea?
A. *Chlamydia trachomatis*
B. Coxsackievirus
C. Herpes simplex virus
D. *Neisseria gonorrhoeae*
E. *Pseudomonas aeruginosa*

Answer: C. Herpes simplex virus causes a characteristic corneal dendritic lesion that is readily seen during slit-lamp examination under blue light as fluorescein stain pools in the defect. The importance of recognizing this lesion and diagnosing HSV infection of the eye is tremendous, because infections of the cornea with HSV can rapidly lead to corneal opacification and permanent loss of vision.

CHAPTER 20

Sore Throat

Amy H. Kaji

PERSPECTIVE

Epidemiology

Sore throat and throat-related complaints[1] are among the most common presenting complaints, not just in emergency departments (EDs) but also in outpatient care settings in the United States.[1,2] Although individuals of all ages commonly develop sore throat, some subtypes of pharyngitis and peripharyngeal disorders are more common in children and adolescents. For example, the epidemiology of group A streptococcal pharyngitis is characteristic in that it is primarily a disease of children 5 to 15 years of age and is rarely seen in those younger than 3 years.

Pathophysiology

Sore throat, or pharyngitis, is generally caused by inflammation in the soft tissue of the pharynx. There are three anatomically distinct regions of the pharynx—the nasopharynx, oropharynx, and hypopharynx (Fig. 20.1). Pathology involving one site usually involves the others, but inflammation at any of these levels can manifest as a sore throat. The nasopharynx encompasses the area superior to the oral cavity, between the base of the skull and soft palate. The eustachian tubes, connecting the middle ear and pharynx, open into this space. The oropharynx is the region directly visible on examination, lying behind the oral cavity, between the uvula and hyoid, including the vallecula and epiglottis. Laterally, it is defined by the tonsillar pillars. The hypopharynx is the most caudal aspect of the pharynx. It lies inferior to the epiglottis and terminates where the aerodigestive paths become distinct, at the esophagus and larynx; the vocal cords define the inferior pole. If one looks directly at a patient, this region is posterior and slightly superior to the thyroid cartilage. There are several important potential spaces surrounding the pharynx; disease in the retropharyngeal and submandibular spaces can manifest as pain and, ultimately, airway compromise.

The terms *pharyngitis* and *tonsillitis* are often used interchangeably; however, the tonsils are distinct lymph tissue located throughout the pharynx. Waldeyer's tonsillar ring, or the pharyngeal lymphoid ring, consists of the pharyngeal (adenoids), tubal, palatine, and lingual tonsils. The palatine tonsils are located on the sides of the oropharynx, between the palatoglossal and palatopharyngeal arches. These immunologic masses are commonly implicated in sore throat and are referred to colloquially as the tonsils. Regional infections, viral and bacterial, commonly trigger inflammatory changes in this collection of lymphatic tissue. Whereas inflammation and swelling of the soft tissues in the oropharynx are the most likely cause in patients with a sore throat, any of the anatomic structures or surfaces within the nasopharynx or hypopharynx can be affected by disease leading to a sore throat. Cranial nerves IX and X supply sensory innervation to the region.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis for sore throat presentations is extremely broad, but major categories to consider in order of frequency include infectious and noninfectious (neoplastic, inflammatory, traumatic) and referred pain from acute coronary syndrome.

Pivotal Findings

Symptoms and Signs

The evaluation of sore throat begins with a simultaneous assessment of the airway and the patient's general appearance. The general appearance should be assessed, with attention to hydration status and markers of systemic toxicity. Patients, particularly children, with significant pain from uncomplicated pharyngitis often have difficulty with oral intake and may become dehydrated. Fever and mild tachycardia are common vital sign derangements in pharyngitis and do not typically indicate dangerous pathology. A prolonged fever (>5–7 days) in children may also be associated with Kawasaki disease.[3]

Patients with airway compromise often sit upright or lean forward, with the neck extended and jaw thrust forward, and appear restless and distressed. Drooling may indicate an inability to swallow oral secretions and thus inflammation or pathology in the oropharynx or hypopharynx may be present. Drooling is a sign of an advanced airway process, requiring prompt preparation for detailed evaluation and intervention. The presence of a muffled voice should prompt consideration of a supraglottic threat to airway patency. The floor of the mouth should be visualized and, when indicated, the submental region palpated as a brawny induration or tenderness in this area is classically associated with Ludwig's angina (Table 20.1). Stridor, a high-pitched noise heard on inspiration, suggests a process involving the glottic or infraglottic structures. Stridor indicates partial obstruction, a true airway emergency except when occurring in young children (<10 years) with croup (see Chapter 167). Stridor is associated with ominous conditions such as epiglottitis, retropharyngeal abscess, and angioedema, and the severity, rate of onset, and progression of symptoms may help indicate the urgency of any required intervention. Patients who have a mass lesion causing sore throat symptoms may have associated dysphagia or odynophagia, hoarseness, weight loss, and lymphadenopathy. Those who have acute coronary syndrome with referred throat pain may have associated chest pain, dyspnea, or diaphoresis.

Direct visualization of the pharynx is typically the most helpful portion of the encounter; thus, complete and unencumbered visualization of the pharyngeal structures is mandatory. Lingual resistance may require coaching or stimulation of a gag reflex, and trismus or pain will often require analgesia. If impressive tonsillar

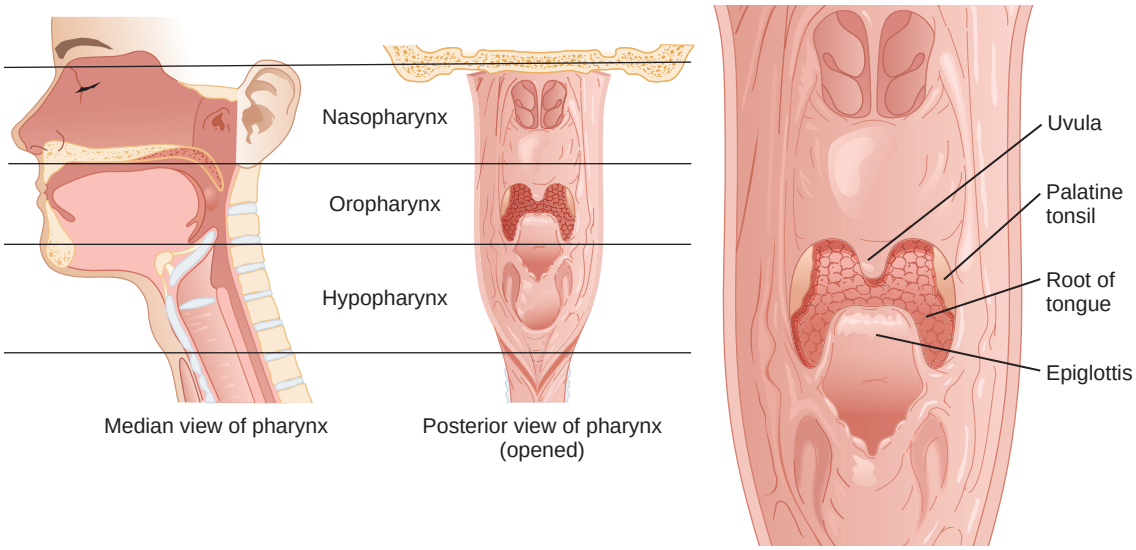

Fig. 20.1. Anatomy of the nasopharynx, oropharynx, and hypopharynx.

TABLE 20.1

Differential Diagnosis for Sore Throat

INFECTIOUS CAUSES				
	AEROBIC			
VIRAL	Common	Uncommon	ANAEROBIC	OTHER
Rhinovirus	*Streptococcus pyogenes* (GABHS)	*Haemophilus influenzae*	*Bacteroides* spp.	*Candida* spp.
Adenovirus	GABHS	*Haemophilus parainfluenzae*		
Peptostreptococcus spp.	*Coccidioides* spp.			
Coronavirus	Non–group A streptococcus	*Corynebacterium diphtheriae*	*Peptococcus* spp.	
Herpes simplex virus 1, 2	*Neisseria gonorrhoeae*	*Streptococcus pneumoniae*	*Clostridium* spp.	
Influenza A, B	*Neisseria meningitides*	*Yersinia enterocolitica*	*Fusobacterium* spp.	
Parainfluenza	*Mycoplasma pneumoniae*	*Treponema pallidum*	*Prevotella* spp.	
Cytomegalovirus	*Arcanobacterium haemolyticum*	*Francisella tularensis*		
Epstein-Barr virus	*Chlamydia trachomatis*	*Legionella pneumophila*		
Varicella-zoster virus	*Staphylococcus aureus*	*Mycobacterium* spp.		
Hepatitis virus				

NONINFECTIOUS CAUSES		
SYSTEMIC	TRAUMA, MISCELLANEOUS	TUMOR
Kawasaki disease	Penetrating injury Angioneurotic edema	Tongue
Stevens-Johnson syndrome	Retained foreign body Anomalous aortic arch	Larynx
Cyclic neutropenia	Laryngeal fracture Calcific retropharyngeal tendinitis	Thyroid
Thyroiditis	Retropharyngeal hematoma	Leukemia
Connective tissue disease	Caustic exposure	

GABHS, Group A beta-hemolytic streptococci.

erythema or exudates are observed in a symmetric distribution, and the patient has no signs of airway involvement, acute tonsillitis is present, and further investigation is rarely warranted. There are various scoring systems, the most well-known of which is the Centor criteria system (Table 20.2),[4] which incorporate components of the history and physical examination to generate an estimate of the likelihood of group A streptococcal infection (GAS). The four Centor criteria are history of fever, tonsillar exudates, tender anterior cervical adenopathy, and absence of cough. A later modification added a fifth criterion (subtract 1

TABLE 20.2

Modified Centor Criteria[a] and Likelihood of Streptococcal Infection

CRITERIA:	HISTORY OF FEVER	TONSILLAR EXUDATES	TENDER CERVICAL LAD	COUGH ABSENT
# OF CRITERIA PRESENT		GABHS		
1		1%		
2		17%		
3		35%		
4		51%		

[a]Subtract 1 point for age >45 yr.
GABHS, group A beta-hemolytic streptococci; *LAD,* lymphadenopathy.

point for age >45 years). Using the criteria, the prevalence of GAS is about 50% in patients with scores of 4 or higher, one third with a score of 3, less than 20% with a score of 2, 10% with a score of 1, and near zero with a score of 0 or −1. In contrast, visualization of ulcerations, or presence of rhinorrhea, sneezing, or conjunctivitis point more to a viral cause of the pharyngitis. Unilateral swelling and contralateral uvular deviation, typically without exudates, suggest peritonsillar abscess. Involvement of the entire oropharynx indicates pharyngitis. If, however, the patient has significant symptoms and no oropharyngeal pathology on examination, evaluation for disease in the hypopharynx, especially epiglottitis, by direct or indirect visualization is indicated. Other potential sinister causes for when a patient presents with significant symptoms and a relatively normal oropharyngeal examination include retropharyngeal abscess and parapharyngeal abscess.

Ancillary Testing

In the context of acute pharyngitis, diagnostic testing with the rapid antigen detection test (RADT) or culture is helpful to distinguish between GAS and non-GAS pharyngitis (particularly viral causes) for the purpose of selecting patients who may benefit from antimicrobial therapy. If the patient has a clear-cut viral cause for the pharyngitis, with oral ulcers, cough, rhinorrhea, and hoarseness, then no testing (or treatment) for GAS is indicated. Additionally, because of the rarity of GAS and rheumatic fever in children younger than 3 years, testing is also generally not indicated in this age group. Unfortunately, even with the use of the Centor criteria, clinical features alone often do not allow the emergency clinician to discriminate GAS from viral pharyngitis reliably, and the overprescribing of inappropriate antimicrobial therapy for viral pharyngitis contributes to the undesirable adverse effects of (unnecessary) antibiotics and to antimicrobial resistance. The primary reasons for treating patients with culture-proven GAS in the setting of acute pharyngitis are to decrease the risk of suppurative (eg, peritonsillar abscess, cervical lymphadenitis, mastoiditis, possibly internal jugular septic thrombophlebitis) and nonsuppurative (acute rheumatic fever) complications of GAS.[5] Additionally, antimicrobial treatment may decrease the duration and severity of illness and reduce the risk of transmission to close contacts. Although many western industrialized nations, where rheumatic fever tends to be exceedingly rare, have abandoned this approach because the inaccuracy and risks of testing and treatment seem to outweigh benefits, the Centers for Disease Control and Prevention (CDC) and Infectious Disease Society of America (IDSA) guidelines of 2012 recommend a combination of clinical assessment and bacteriologic testing, with the goal of treating with antibiotics for proven or strongly suspected GAS.[6] Because the sensitivity of the RADT is only approximately 70% to 90%, the IDSA recommends that for children and adolescents, a negative RADT should be followed up with a throat culture. In contrast, a positive RADT does not warrant follow-up throat culture testing because of its high specificity (95%). The IDSA does not recommend that a negative RADT be followed up with a throat culture in adults, in whom the incidence of GAS and risk of subsequent rheumatic fever is extremely low, when compared to children and adolescents.

Heterophile antibody testing for mononucleosis, testing for acute retroviral syndrome, and other possibilities may also be considered in patients with an extended clinical course, unusual features, or treatment failure, largely to exclude other causes and to ensure appropriate advice regarding issues such as contagion and activity limitations (see Chapters 62 and 122).[7,8]

Imaging

Although radiographic imaging has long been recommended for evaluation of the epiglottis and structures in the hypopharynx, direct visualization of the structures of interest by examination is preferable, providing definitive diagnosis, assessment of airway threats, and the ability to plan for or perform endotracheal intubation. In adults with possible epiglottitis, particularly those with severe symptoms such as drooling, distress, or muffled voice, examination via nasopharyngoscopy at the bedside or via laryngoscopy in the operating room setting is the best approach. Examination of this sort, however, should occur under a so-called double setup, with availability of and preparation for an emergent rescue airway, usually cricothyrotomy, because manipulation of the irritated upper airway tissues may precipitate laryngospasm and obstruction. Endoscopic examination also allows identification of other life-threatening causes beyond infection such as foreign bodies, polyps, and angioedema. If there is concern for epiglottitis but upper airway examination by endoscopy is not possible (eg, equipment unavailable) and the patient has a stable airway, plain film radiography may be useful to assess for changes such as the thumb sign—widening of the epiglottis silhouette (Fig. 20.2).[9] The approach to pediatric airway infection, including epiglottitis, is described in Chapters 167 and 168.

Ultrasound is another technology with applications for the detection of neck masses from tumors and hypopharyngeal conditions, including epiglottitis. In a convenience sample of adults, the epiglottis was easily visualized and measured in males and females,[10] and recent case reports, as well as a small, controlled ED study of ultrasound for epiglottitis, have suggested that this noninvasive bedside tool may prove useful.[10,11]

In a child or adult with signs and symptoms of a deep neck infection such as retropharyngeal abscess and whose airway security has been ensured, the most useful imaging modality is computed tomography (CT) of the neck. The lateral neck x-ray examination is a relatively sensitive test for this disease, so in lower risk patients a normal film (no widening of the prevertebral space, normal lordotic curve of the spine, and absence of soft tissue air)

Fig. 20.2. Soft tissue lateral neck x-ray demonstrating thumb sign or widening of the epiglottis silhouette *(arrow)*.

Fig. 20.3. CT scan of retropharyngeal abscess.

can be a useful risk stratification tool.[12] Ultimately, however, CT is the definitive evaluation for deep neck infection (Fig 20.3). It is highly accurate at detecting infection in the deep tissues, but its ability to differentiate between cellulitis and abscess is variable.[13] Also, CT may help discern tumors or hemorrhage from abscesses and delineate invasion of nearby structures. In children with a sore throat and visible inflammatory neck mass, ultrasound diagnosis can be definitive.

DIAGNOSTIC ALGORITHM

Critical and Emergent Diagnoses

Box 20.1 outlines critical diagnoses and emergent diagnoses that have the potential to cause airway compromise that may warrant specific intervention. For example, in patients with Ludwig's angina, securing the airway, promptly initiating antibiotic treatment and fluid resuscitation, and obtaining prompt evaluation by an otolaryngologist may be lifesaving. If there are signs of airway compromise or impending airway compromise in addition to preparing for advanced airway management, the emergency clinician should immediately move to a detailed intraoral physical examination, ideally while initiating any available consultations such as otolaryngology or surgical services. This examination should concentrate on the detection of masses such as sublingual edema, visible abscess, and foreign bodies. If such a mass can be visualized, disease-specific decisions about imaging, potential airway management, or surgical procedures (eg, abscess drainage) can be made.

In patients without signs of airway compromise, the pace of execution can be more deliberate; a primary question is whether or not findings consistent with pharyngitis are visible. If exudates, erythema, or cobblestoning of the posterior pharyngeal wall is evident, pharyngitis is likely present. At this point, consideration of less common causes (eg, gonococcal infection, mononucleosis) should be explored by concentrating on features in the history such as recent exposures and duration, and the possibility of extremely rare entities (eg, Lemierre's syndrome) may be entertained as well.[14] In the absence of unusual features that predispose to these diagnostic possibilities, pharyngitis is likely to be viral or streptococcal in origin and may be empirically managed as such.[15]

BOX 20.1

Critical and Emergent Diagnoses in Patients Presenting With Sore Throat

CRITICAL DIAGNOSES
Epiglottitis causing airway compromise
Retropharyngeal or parapharyngeal abscess causing airway compromise
Peritonsillar abscess causing airway compromise
Ludwig's angina
Angioedema
Croup causing stridor at rest
Lemierre's syndrome from septic internal jugular septic thrombophlebitis
Acute coronary syndrome presenting with referred throat pain

EMERGENT DIAGNOSES
Trauma causing a nonexpanding neck hematoma
Mass lesion in the neck causing sore throat
Epiglottitis, retropharyngeal, parapharyngeal, or peritonsillar abscess not causing airway compromise

URGENT DIAGNOSES
Group A streptococcal pharyngitis

EMPIRICAL MANAGEMENT

Fig. 20.4 shows a clinical algorithm for the initial management of the sore throat presentation. Airway compromise and impending airway compromise, when present, must be addressed first. Infectious syndromes suggesting severe systemic illness or sepsis should be treated accordingly. Patients who clinically appear to have no potential for airway compromise and no signs of invasive or systemic disease can be managed according to presumptive causes.

Usually, sore throat will be caused by viral pharyngitis, in which case pain management with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) is the mainstay of care and the most important initial step in empirical management. Regimented administration of these agents, rather than the use of as-needed approaches that fail to prevent or interrupt spiraling pain, is often helpful. Two recent systematic reviews have concluded that acute pharyngitis, including GAS pharyngitis, should not routinely be treated with antibiotics.[16,17] It is thought that the decline of rheumatic fever may be unrelated to trends in antibiotic

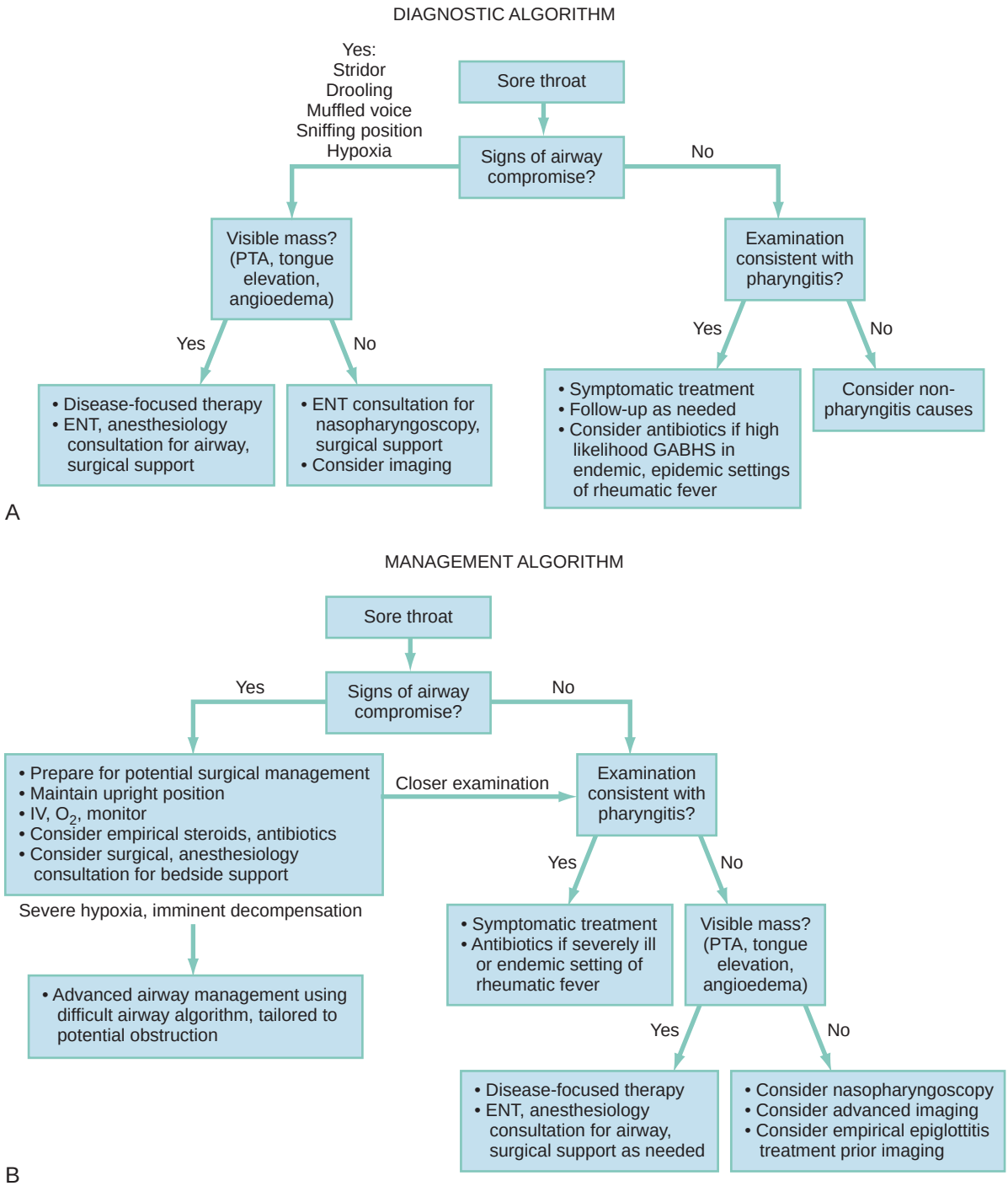

Fig. 20.4. Clinical approach to the patient with sore throat, diagnosis and management. *ENT,* Ear-nose-throat; *GABHS,* Group A beta-hemolytic streptococci; *IV,* intravenous; *PTA,* peritonsillar abscess.

use, but rather is a result of factors associated with industrialization, including improved living conditions, access to care, hygiene, and nutrition.[18] This explains the current epidemiology of rheumatic fever, a disease that is extremely rare in developed nations but continues to be an important public health threat in developing regions worldwide.[19,20] Notably, adverse events caused by antibiotics are common and frequently result in ED visits, and the overuse of antibiotics for self-limiting conditions such as upper respiratory tract infections remains rampant.[21] Indeed, the inappropriate prescription of antibiotics for viral pharyngitis in the United States has remained unchanged over time in recent decades, even despite extensive public health messaging to reduce the problem.[22] Thus, for public health reasons and prevention of unnecessary individual harm, antibiotics should be avoided in the management of viral pharyngitis.

Education of patients, who will often expect or desire antibiotics, is a key part of management. Education should provide a careful explanation of the following: (1) the self-limited nature of viral pharyngitis; (2) the lack of symptomatic or other benefit with antibiotics; and (3) the potential harm of antibiotics (eg, individual and population resistance, fungal infections in women, rashes, gastrointestinal effects, recurrence of pharyngitis, occasionally dangerous allergic reactions). It is often most important to emphasize that symptom reduction can be achieved with the

BOX 20.2

Antibiotic Regimens for Proven Group A Streptococcal Pharyngitis

Benzathine penicillin G, intramuscular, 600,000 U for <27 kg and 1.2 million U for >27 kg
Pencillin V oral, 50 mg/kg/day qid × 10 days
Amoxicillin, 40 mg/kg/day tid × 10 days
If penicillin-allergic:
Clindamycin, 7 mg/kg/dose tid (maximum, 300 mg/dose) × 10 days
Cephalexin, 20/mg/kg dose bid (maximum, 500 g/dose) × 10 days
Azithromycin, 12 mg/kg/day (maximum dose, 500 mg) × 5 days

various interventions that target pain control—for example, NSAIDs.[23]

However, major organizations such as the IDSA and CDC support targeted testing and antimicrobial therapy for proven GAS pharyngitis and tonsillitis.[6] Moreover, because eradicating GAS from the pharynx with appropriate antibiotic administration may reduce the duration and severity of illness, decrease the risk for suppurative and nonsuppurative complications, and reduce infectivity and transmission to close contacts, I recommend treatment with intramuscular benzathine penicillin G or a 10-day course of oral penicillin VK because of proven efficacy and low cost. See Box 20.2 for antibiotic regimens and alternative agents for those who are allergic to penicillin. For severe pharyngitis causing difficulty swallowing, corticosteroid therapy reduces pain and duration of pain, with most studies using 0.6 mg/kg (maximum dose, 10 mg) of dexamethasone, orally or parenterally, in a single dose.[24] Opioid pain medication rarely is indicated, and the presence of such severe pain may indicate a more severe syndrome such as abscess or epiglottitis, requiring additional evaluation. Proper pain management allows patients to reestablish nutritional balance, achieve and maintain a hydrated state, and ingest medications, as necessary.

In the setting of clinical pharyngitis, a fluctuant unilateral peritonsillar mass should be drained whenever possible. Drainage in such cases constitutes definitive care.[23] Although there are no data to support or refute the administration of antibiotics in cases of unilateral swelling and redness that appears not to be fluctuant (ie, so-called peritonsillar cellulitis), I recommend the same antibiotics that are used for GAS pharyngitis for these patients (see Box 20.2). For patients with manifestations of severe, systemic illness (ie, those requiring hospitalization or with impending airway compromise), antibiotic coverage for streptococcal and anaerobic bacteria may theoretically be helpful. I recommend the administration of parenteral clindamycin (900 mg tid) and a third-generation cephalosporin such as ceftriaxone (50 mg/kg or 1 g bid), although no firm evidence is available to support or refute this practice. Other specific empirical therapies or consultation may be necessary for severe or unusual presentations of disease.

Finally, the great majority of patients will be able to manage their condition on an outpatient basis. For those with actively present or potentially impending airway threat, surgical intensive care settings are often appropriate, although this will depend on nursing ratios, local comfort level with airway management, and ability for the patient to be monitored closely in alternate settings. In such cases, as well as in cases of confirmed deep space infection (eg, neck abscess, parapharyngeal abscess, Ludwig's angina), surgical consultation for potential operative management or for imaging modalities such as nasopharyngoscopy is generally important and helpful. Some patients with pharyngitis may also benefit from inpatient management, usually those with systemic illness who are unable to tolerate oral therapies or nutrition.

KEY CONCEPTS

- Sore throat is a chief complaint that can represent life-threatening diagnoses and extreme challenges for the emergency clinician, primarily in the form of airway threats and/or deep space infections.
- The five modified Centor criteria award 1 point for each of the following: (1) history of fever; (2) presence of exudates; (3) presence of anterior cervical adenopathy; and (4) absence of cough, and subtract 1 point for (5) age older than 45 years. Patients with scores of −1 to 1 are very unlikely to have GAS infection. Scores of 4 or 5 correspond to a 50% likelihood of GAS, which drops to approximately 30% with a score of 3 and below 20% with a score of 2.
- Physical examination is central to detecting airway threats and determining diagnosis.
- The absence of physical findings during oropharyngeal examination in the setting of severe sore throat symptoms suggests that lower structures may be involved, and endoscopic examination of the upper airway is advisable.
- Antibiotics are more harmful than helpful for patients with viral pharyngitis, which is self-limiting.
- For GAS-proven pharyngitis, a single injection of penicillin or 10-day course of oral penicillin is recommended to decrease the duration of symptoms, transmission to close contacts, and prevention of the rare suppurative and nonsuppurative sequelae.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 20: QUESTIONS & ANSWERS

20.1. When a patient presents to the emergency department (ED) complaining of a sore throat, which is the most valuable component of the diagnostic evaluation?
- **A.** Computed tomography (CT) evaluation of the soft tissues
- **B.** Direct visualization of the oropharynx
- **C.** Plain film radiography
- **D.** Serologic testing

Answer: B. Direct visualization of the pharynx is typically the most helpful portion of the encounter. Thus, complete and unencumbered visualization of the pharyngeal structures is mandatory. Lingual resistance may require coaching or stimulation of a gag reflex, and trismus or pain will often require analgesia. If impressive tonsillar erythema or exudates are observed in a symmetric distribution, and the patient has no signs of airway involvement, acute tonsillitis is present, and further investigation is rarely warranted.

20.2. Historically, there was emphasis on determining whether infectious pharyngitis was bacterial or viral in origin. Many industrialized countries have abandoned the search for group A streptococci in the context of pharyngitis for the following reason(s):
- **A.** All of these.
- **B.** Antibiotics do not improve the symptoms associated with viral pharyngitis.
- **C.** Risks of treatment outweigh benefits.
- **D.** The prevalence of rheumatic fever is exceedingly rare in industrialized nations.

Answer: A. The great majority of cases are viral in origin, and suppurative complications following streptococcal infection are easily treated and occur too rarely to justify routine use of antibiotics. Rheumatic fever is a disease that is extremely rare in developed nations. Additionally, adverse events caused by antibiotics are common and frequently result in ED visits.

20.3. A 40-year-old man presents with a complaint of sore throat. He is febrile, 102° F (39° C), reports considerable pain with swallowing, and has a moderate sensation of tightness in his throat. On examination, you note that the patient is sitting up; you observe only mild erythema to the tonsillar tissue. What should be the next step?
- **A.** Discharging patient home with a prescription for nonsteroidal antiinflammatory drugs (NSAIDs)
- **B.** Intramuscular injection of penicillin
- **C.** Nasopharyngoscopy at the bedside
- **D.** Sending the patient to radiology for a CT scan of the neck

Answer: C. The severity of his symptoms, which are disproportionate to the physical examination, is concerning for other more sinister diagnoses such as epiglottitis, parapharyngeal abscess, and retropharyngeal abscess.

20.4. A healthy 20-year-old, nonsexually active female presents with a complaint of a sore throat. She is febrile and mildly tachycardic. On evaluation, she looks uncomfortable but is in no distress. She has cervical adenopathy, and direct visualization of the oropharynx reveals symmetric tonsillar erythema and diffuse exudates. Ideal management for this patient would include which of the following?
- **A.** Ceftriaxone, 250 mg IM once
- **B.** Ibuprofen, 400 mg every 4 to 6 hours, dexamethasone (Decadron). 10 mg once, and acetaminophen-oxycodone (Percocet), 5/325 mg qid PRN
- **C.** Ibuprofen 400 mg every 4 to 6 hours, penicillin G IM once
- **D.** Unasyn (Ampicillin-sulbactam), 3 g IV, and incision and drainage

Answer: C. Usually, sore throat is caused by acute pharyngitis, in which case pain management with acetaminophen or NSAIDs is the mainstay of care and the most important initial step in empirical management. The Centor criteria, incorporating components of the history and physical examination to generate an estimate of group A streptococci (GAS), are listed in Table 20.2 with the results of one classic study, and this patient would be a candidate for antibiotic treatment.

CHAPTER 21

Hemoptysis

Calvin A. Brown III

PERSPECTIVE

Epidemiology

Hemoptysis is defined as the expectoration of blood from the respiratory tract below the vocal cords. Most cases seen in the emergency department (ED) are mild episodes of small-volume hemoptysis, typically consisting of either blood-tinged sputum or minute amounts of frank blood, most often associated with bronchitis. Although hemoptysis is commonly seen in the ED, only 1% to 5% of hemoptysis patients have massive or life-threatening hemorrhage. Many definitions exist, but *massive hemoptysis* is generally accepted as 100 to 600 mL of blood loss in any 24-hour period, which can result in hemodynamic instability, shock, or impaired alveolar gas exchange and has a mortality rate approaching 80%.

Large, contemporary series of patients with massive hemoptysis are lacking, and most causative data originate from small, often rural, studies in which tuberculosis (TB) and bronchiectasis are responsible for the majority of cases. In developed nations, cancer, cystic fibrosis, arteriovenous malformations, anticoagulant use, and postprocedural complications play more prominent roles. Pediatric hemoptysis is rare but can be caused by infection, congenital heart disease, cystic fibrosis, or bleeding from a preexisting tracheostomy. Major causes of hemoptysis are listed in Box 21.1.

Pathophysiology

Minor hemoptysis typically originates from tracheobronchial capillaries that are disrupted by vigorous coughing or minor bronchial infections. Conversely, massive hemoptysis nearly always involves disruption of bronchial or pulmonary arteries, which are the two sets of vessels that constitute the lung's dual blood supply. Bronchial arteries, which are direct branches from the thoracic aorta, are responsible for supplying oxygenated blood to lung parenchyma, and disruption of these vessels from arteritis, trauma, bronchiectasis, or malignant erosion can result in sudden and profound hemorrhage. Although small in caliber, the bronchial circulation is a high-pressure system and the culprit in nearly 90% of the cases of massive hemoptysis requiring embolization. Pulmonary arteries, although transmitting large volumes of blood, do so at much lower pressures and, unless affected centrally, are less likely to cause massive hemoptysis.

Nearly all causes of hemoptysis have a common mechanism—vascular disruption within the trachea, bronchi, small-caliber airways, or lung parenchyma. Modes of vessel injury include acute and chronic inflammation (from bronchitis and arteritis), local infection (especially lung abscesses, TB, and aspergillosis), trauma, malignant invasion, infarction following a pulmonary embolus, and fistula formation (specifically aortobronchial fistulae).

In the 1960s, nearly all cases of massive hemoptysis were a result of TB, bronchiectasis, or lung abscess. Each of these has since decreased in frequency, whereas pneumonia and bleeding diathesis have become more prevalent.

Bronchiectasis, a chronic necrotizing infection resulting in bronchial wall inflammation and dilation, is one of the most common causes of massive hemoptysis worldwide. As tissue destruction and remodeling occur, rupture of nearby bronchial vessels can result in bleeding. Bronchiectasis can complicate chronic airway obstruction, necrotizing pneumonia, TB, or cystic fibrosis. Broncholithiasis, the formation of calcified endobronchial lesions following a wide array of granulomatous infections, is an uncommon problem with a similar propensity to erode nearby vessels. Hemorrhage control often requires surgical intervention.

Iatrogenic hemoptysis complicates 2% to 10% of all endobronchial procedures, especially percutaneous lung biopsies. Right (pulmonary artery) heart catheterization using a Swan Ganz catheter can cause iatrogenic pulmonary artery perforation especially in patients with pulmonary hypertension. Although this complication is rare, the mortality is between 50% to 70%.[1,2] Diffuse alveolar hemorrhage can be seen with autoimmune vasculitides, such as Wegener's granulomatosis, systemic lupus erythematosus (SLE), and Goodpasture's syndrome. An uncommon cause of hemoptysis occurs when ectopic endometrial tissue within the lung results in monthly catamenial episodes of bleeding. Less common causes include pulmonary hereditary telangiectasias and hydatidiform infections. Any episode of hemoptysis can be exacerbated by coagulopathy and thrombocytopenia.

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

First, the clinician should be convinced that the source of the bleeding is pulmonary. Distinguishing hemoptysis from hematemesis is accomplished by the clinician working with the patient to clarify details of the history, particularly differentiation between coughing and vomiting or spitting. Nasal, oral, or hypopharyngeal bleeding may contaminate the tracheobronchial tree, mimicking true hemoptysis. The clinician should closely inspect the nasopharynx and oral cavity to exclude this possibility. Gastric or proximal duodenal bleeding can similarly mimic hemoptysis, and differentiating a gastrointestinal (GI) source of bleeding is especially important because further evaluation and management of these two pathologies follow divergent pathways. In unclear cases, inspection and pH testing may help to distinguish GI from tracheobronchial hemorrhage. Unless an active, brisk upper GI hemorrhage is present, the acidification of blood in the stomach results in fragmentation and darkening, producing specks of brown or black material often referred to as *coffee-ground emesis.* Pulmonary blood appears bright red or as only slightly darker clots and is alkaline.

Inflammatory disorders that secondarily involve the lungs or pulmonary vasculature include Wegener's granulomatosis, Goodpasture's syndrome, and SLE, and a history of these should be elicited. Any risk factors for platelet dysfunction, thrombocytopenia, and coagulopathy should be noted, as should, conversely, any

BOX 21.1

Differential Diagnosis of Hemoptysis

AIRWAY DISEASE
Bronchitis (acute or chronic)
Bronchiectasis
Neoplasm (primary and metastatic)
Trauma
Foreign body

PARENCHYMAL DISEASE
Tuberculosis (TB)
Pneumonia, lung abscess
Fungal infection
Neoplasm

VASCULAR DISEASE
Pulmonary embolism
Arteriovenous malformation
Aortic aneurysm
Pulmonary hypertension
Vasculitis (Wegener's granulomatosis, systemic lupus erythematosus [SLE], Goodpasture's syndrome)

HEMATOLOGIC DISEASE
Coagulopathy (cirrhosis or warfarin therapy)
Disseminated intravascular coagulation (DIC)
Platelet dysfunction
Thrombocytopenia

CARDIAC DISEASE
Congenital heart disease (especially in children)
Valvular heart disease
Endocarditis

MISCELLANEOUS
Cocaine
Postprocedural injury
Tracheal-arterial fistula
SLE

hypercoagulable states that might contribute to venous thromboembolic disease.

Primary or metastatic cancer can cause hemoptysis by erosion into pulmonary and bronchial vessels. Recent percutaneous or transbronchial procedures can cause immediate or delayed postprocedural bleeding, and any recent history of trauma should also be noted. A pertinent travel history to areas in which TB or pulmonary paragonimiasis is endemic is crucial.

A history of chronic alcoholism, cancer, and pulmonary fungal infections are other critical historical elements, because these independently predict increased in-hospital mortality.[3]

Pivotal Findings

Symptoms

Although patient reports of bleeding severity can be inaccurate, an estimate of the rate, volume, and appearance of expectorated blood should be obtained. Additional pertinent history includes prior episodes of hemoptysis or parenchymal pulmonary disorders, including bronchiectasis, recurrent pneumonia, chronic obstructive pulmonary disease, bronchitis, TB, and fungal infection.

Signs

A targeted examination may suggest the location and cause of bleeding but does so in less than 50% of cases. Focal adventitious breath sounds in a febrile patient may indicate pneumonia or pulmonary abscess. A new heart murmur, especially in a febrile patient, may reflect endocarditis causing septic pulmonary emboli. A rash might hint at underlying rheumatologic disorders, such as SLE or vasculitis. Symptoms and signs of deep venous thrombosis suggest pulmonary embolism. Ecchymoses and petechiae can indicate coagulopathy and thrombocytopenia, respectively.

Ancillary Testing

Initial laboratory studies include a complete blood count, coagulation tests, and a type and crossmatch for packed red blood cells. Renal function tests should be performed if vasculitis is suggested or contrast computed tomography (CT) is planned. Plain chest radiography plays a limited role in evaluating patients with minor hemoptysis. Although chest x-rays can screen for causes of hemoptysis (including infection and malignancy), their sensitivity is poor and often cannot identify the source of bleeding, a critical step in triage and management (see the Empirical Management section). Up to half of hemoptysis patients with a normal chest radiograph will have positive findings on chest CT.

When there is massive hemoptysis, plain films localize the site of hemorrhage in as many as 80% of patients; however, high-resolution CT of the chest is the principle diagnostic test for investigating both bronchial and non-bronchial causes of massive hemoptysis. A chest CT scan should be obtained in the high-risk patient (ie, smokers, oncology patients) or in any patient with moderate to severe bleeding even if the initial chest radiograph is normal. CT localization of hemorrhage can expedite bronchoscopic evaluation and guide subsequent interventional procedures.

CT is diagnostically comparable to conventional angiography but less invasive and more rapidly available. Angiography is the first-line study when the cause of the hemoptysis is known (eg, malignancy), bronchial artery hemorrhage is suspected or when angiography-assisted embolization therapy is contemplated. Successful embolization rates range to 95%.

DIAGNOSTIC ALGORITHM

Critical Diagnoses

Box 21.2 shows critical diagnoses and emergent diagnoses. Proper management hinges not only on standard resuscitative measures but also specific therapies, such as reversal of coagulopathy or emergent surgical intervention. For example, in patients with preexisting tracheostomies, new hemoptysis (especially within 3 to 4 weeks of surgery) often represents a tracheo-innominate artery fistula (TIF) for which the need for hemorrhage control is immediate and can often be accomplished in the ED.

Although management decisions hinge on the volume and rate of bleeding, the initial diagnostic strategy is the same for all patients with hemoptysis (Fig. 21.1). Patients with trace hemoptysis or blood tinged sputum only and a classic story for viral bronchitis may not require laboratory or radiology investigation of any type. For all others, the initial screening test obtained in the ED is a chest x-ray. Since the advent of high-resolution CT, radiologic evaluation has had an integral role in the evaluation and treatment of patients with hemoptysis. Unless the initial chest radiograph is diagnostic or the patient is hemodynamically unstable, a chest CT should be obtained. Further management decisions should be guided by the CT results and made in conjunction with pulmonary and thoracic surgery consultants.

Bronchoscopy

Early bronchoscopy may be the right option because it facilitates both localization of bleeding and therapeutic intervention. Chest CT is as diagnostically accurate as bronchoscopy in locating bleeding peripheral vessels not accessible by a flexible bronchoscope. Chest CT can be used to identify the site of bleeding to determine whether angiography is indicated. There may be little added benefit to bronchoscopy before interventional angiography if the bleeding source has already been accurately identified on CT.

EMPIRICAL MANAGEMENT

Figure 21.2 outlines the management algorithm for patients with hemoptysis. Although hemodynamic instability can occur as a result of hemorrhage, the most lethal sequela of massive hemoptysis is hypoxia, which results from the ventilation-perfusion mismatch that follows submersion of the small airways and alveoli with blood.

All patients with massive hemoptysis should have multiple large bore peripheral intravenous lines placed. Volume resuscitation should begin immediately for patients with ongoing bleeding or shock. Coagulopathy, in the setting of severe bleeding, should be reversed by infusing 2 to 4 units of fresh frozen plasma (FFP) and 10 mg of intravenous vitamin K. Prothrombin complex concentrates (PCCs) have been successful in reversing warfarin-induced intracranial hemorrhage, but there is no information to guide the use of PCC in patients with severe hemoptysis.[4] Patients with thrombocytopenia should have a platelet transfusion with a goal platelet count of 50,000 to 60,000.

If a TIF is suspected, the emergency clinician should immediately attempt to overinflate the tracheostomy balloon in an effort to tamponade the bleeding. If this fails, the tracheostomy tube should be removed, the patient should be orally intubated, and the operator's index finger should be placed through the tracheostomy hole with pressure applied at the sight of bleeding (Fig. 21.3).

Aortobronchial artery fistulae are highly lethal; but if caught early, general resuscitative measures should be undertaken in addition to immediate consultation with or transfer to an endovascular surgeon. Pulmonary embolus only rarely affiliated with massive hemoptysis. When trace hemoptysis accompanies pulmonary embolism, usual care with anticoagulation is standard treatment.

Hemoptysis as a complication of disseminated intravascular coagulation (DIC) should be treated following the general management guidelines for DIC. Treatment of DIC remains controversial; but when bleeding is present thrombocytopenia with platelet counts less than 50,000, transfusion is indicated. FFP and cryoprecipitate have been advocated to replace factors lost due to consumptive coagulopathy.

Patients with a known or suspected lateralizing source of bleeding should be placed in the "bleeding lung-down" position such that the bleeding lung is more dependent, promoting continued protection and ventilation of the unaffected lung and improved oxygenation. If intubation is required, a large diameter

BOX 21.2

Critical and Emergent Diagnoses in Patients Presenting With Hemoptysis

CRITICAL DIAGNOSES

Disseminated intravascular coagulopathy (DIC)
Tracheo-innominate artery fistula (TIF)
Aortobronchial fistula
Iatrogenic (postprocedural) hemoptysis
Pulmonary embolism

EMERGENT DIAGNOSES

Trauma
Bronchiectasis
Pneumonia
Abscess/fungal infection
Oral anticoagulant overdose
Endocarditis

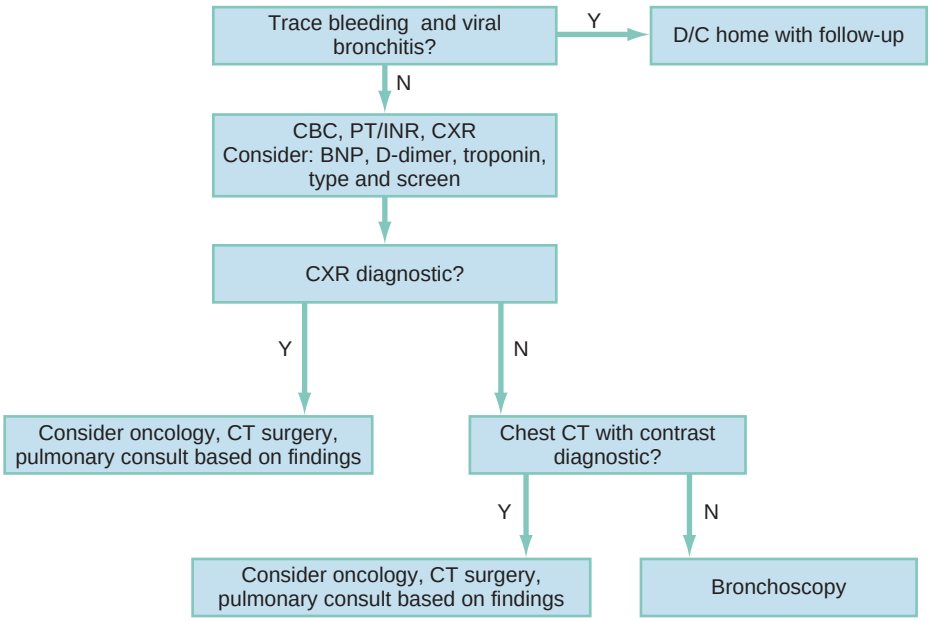

Fig. 21.1. The emergency department (ED) diagnostic approach to hemoptysis. *BNP,* B-type natriuretic peptide; *CBC,* complete blood count; *CT,* computed tomography; *CXR,* chest x-ray; *D/C,* discharge; *INR,* international normalized ratio; *PT,* prothrombin time.

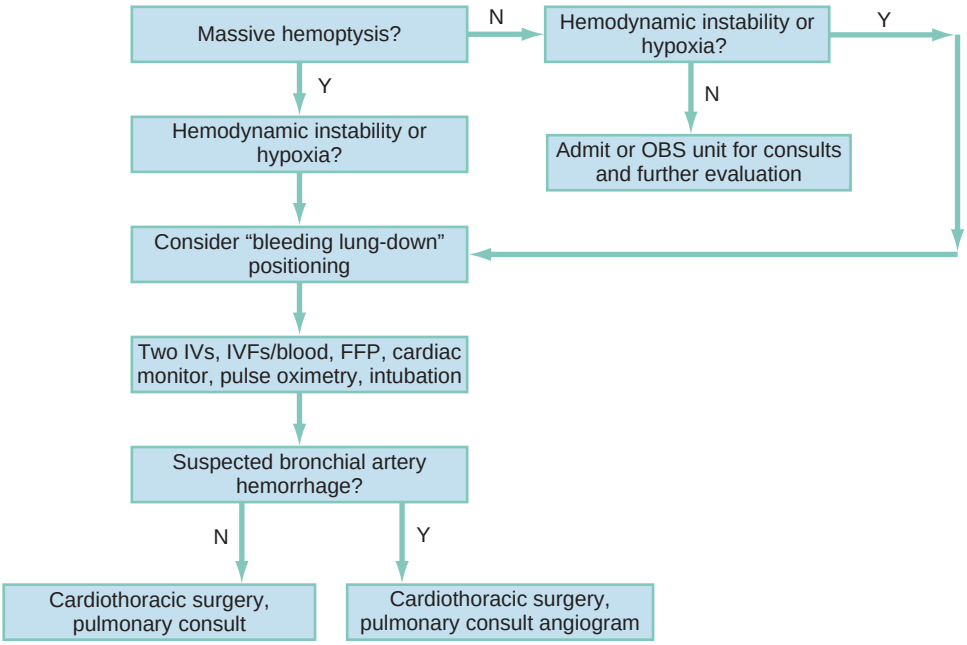

Fig. 21.2. The emergency department (ED) management approach to hemoptysis. *IV,* Intravenous; *IVF,* intravenous fluid; *FFP,* fresh frozen plasma; *OBS,* observation.

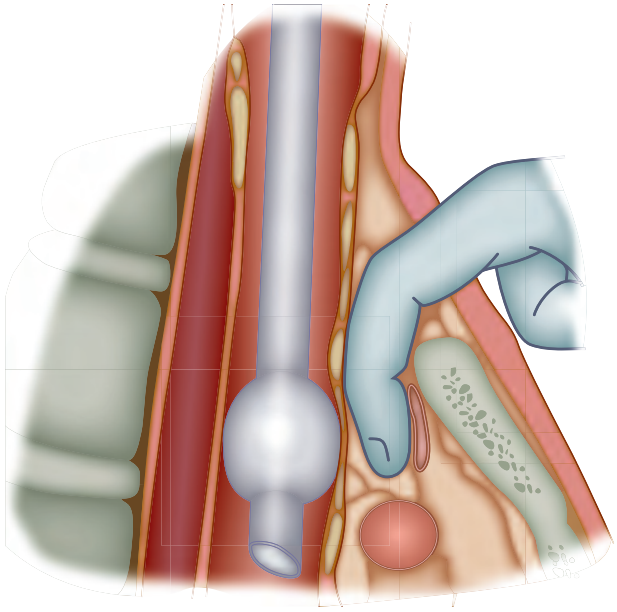

Fig. 21.3. Pressure placed by the clinician's finger through the tracheostomy hole occluding the tracheo-innominate artery.

(8.0) endotracheal tube should be used to facilitate emergent flexible bronchoscopy.

If the patient has marginal hemodynamic status, the intubation should proceed with a "shock-sensitive" strategy focusing on preload maximization with isotonic fluids or blood, reduced dose induction agents and peri-intubation pressors, such as phenylephrine (Neo-Synephrine) (see Chapter 1). In selected cases of confirmed left-sided bleeding, a single-lumen right-mainstem intubation often can be successfully performed through advancement of the tube in the neutral position or use of a 90-degree rotational technique, during which the tube is rotated 90 degrees in the direction of desired placement and advanced until resistance is met. Left-mainstem intubations are more difficult but may be attempted when the bleeding site is the right lung and simple lung-down positioning is not sufficient to stabilize the patient's airway and oxygenation.

When these measures fail or the hemoptysis is life-threatening, anesthesia consultation is sought for consideration of placement of double-lumen endotracheal tubes for lung isolation. The correct positioning of blindly placed double-lumen tubes is difficult and requires confirmation by auscultation and fiberoptic bronchoscopy, both of which are severely impaired by massive hemoptysis. Complications of double-lumen tubes include unilateral and bilateral pneumothoraces, pneumomediastinum, carinal rupture, lobar collapse, and tube malposition.

Fiberoptic bronchoscopy, in addition to being one of the first diagnostic maneuvers, is a first line therapeutic option as well. Balloon and topical hemostatic tamponade, thermocoagulation, and injection of vasoactive agents can all effectively control arterial bleeding. Optimal timing for bronchoscopy remains conjectural. Although stable patients with mild to moderate bleeding may benefit from early bronchoscopy, in unstable patients or those with brisk hemorrhage, bronchoscopy may facilitate airway management but is less likely to control bleeding.

Bronchial arterial embolization is an effective first-line therapy for massive hemoptysis and is the procedure of choice for patients either unable to tolerate surgery or in whom bronchoscopy has been unsuccessful. Hemostatic rates range from 85% to 98%, but as many as 20% to 50% of patients have early episodes of repeat bleeding. The risk of delayed bleeding may exist for up to 36 months. To guide therapy, initial localization of bleeding by bronchoscopy or CT is preferred. Rare complications include arterial perforation and dissection.

Emergency thoracotomy, in the operating room, is reserved for life-threatening hemoptysis or for persistent, rapid bleeding that is uncontrolled by bronchoscopy and percutaneous embolization. Although lung resection for massive hemoptysis carries with it high morbidity and mortality, it is a permanent solution to ongoing life-threatening hemoptysis. Pulmonary arterial hemorrhage from tumor necrosis represents a surgical emergency.

Healthy patients with blood-streaked sputum or intermittent small-volume hemoptysis in the context of an acute or subacute respiratory infection with resolved hemoptysis and normal vital signs do not require imaging beyond plain chest radiography and

can be discharged. High-risk patients (such as, those with known lung cancer, pulmonary vascular abnormalities, or coagulopathy with minor hemoptysis) and all patients with moderate or large amounts of hemoptysis should undergo emergent chest CT scan. There is little value in obtaining a plain chest radiograph before CT, and a plain x-ray film should not be obtained if chest CT is planned regardless of the findings on the plain film. Brief hospitalization or admission to an observation unit for bronchoscopy should be considered. All patients with massive hemoptysis require admission to an intensive care unit and expedited multidisciplinary treatment involving the emergency physician, pulmonologist, and thoracic surgeon.

KEY CONCEPTS

- Hemoptysis is caused by infection, trauma, cancer, coagulopathy, or as a complication of invasive pulmonary procedures.
- Plain radiographs are the initial screening test in most cases of massive hemoptysis, although CT scans are more sensitive and can supplant plain chest x-rays as the initial diagnostic test.
- Bronchial artery embolization is highly effective with hemostasis rates ranging from 85% to 95%.
- With massive hemoptysis, hypoxia is the more immediate concern than volume resuscitation, and early intubation to ensure adequate oxygenation is paramount.
- If a tracheo-innominate artery fistula (TIF) is suspected, then overinflation of the tracheostomy balloon or digital pressure at the site of bleeding should be performed for immediate hemorrhage control.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 21: QUESTIONS & ANSWERS

21.1. What is the most common cause of trace hemoptysis (blood-tinged sputum)?
- **A.** Bronchiectasis
- **B.** Bronchitis
- **C.** Cancer
- **D.** Congestive heart failure
- **E.** Pulmonary embolism

Answer: B. The most common cause of small-volume hemoptysis is bronchitis.

21.2. Disruption of which of the following vessels is responsible for the vast majority of cases of massive hemoptysis?
- **A.** Aorta
- **B.** Bronchial arteries
- **C.** Pulmonary arteries
- **D.** Pulmonary veins
- **E.** Tracheobronchial capillaries

Answer: B. Massive hemoptysis almost exclusively involves one of the two sets of vessels that constitute the lung's dual blood supply. Bronchial arteries, direct branches from the thoracic aorta, are responsible for supplying oxygenated blood to the lung parenchyma. Disruption of these vessels can result in sudden and profound hemorrhage. Although small in caliber, the bronchial circulation is a high-pressure system and the cause in nearly 90% of the cases of massive hemoptysis requiring embolization. Although they transmit large volumes of blood, pulmonary arteries are at much lower pressure and, unless affected at a very central location, are less likely to cause massive hemoptysis. Trace hemoptysis typically originates from tracheobronchial capillaries that become disrupted with vigorous coughing or minor bronchial infections.

21.3. Which of the following statements regarding the evaluation of hemoptysis is true?
- **A.** Chest computed tomography (CT) should not be obtained in patients with massive hemoptysis if this delays initiation of bronchoscopy.
- **B.** Chest CT should be obtained in any patient with moderate bleeding even if the initial chest radiograph is normal.
- **C.** Conventional angiography is the preferred diagnostic test to detect both bronchial and non-bronchial arterial causes of massive hemoptysis.
- **D.** High-resolution multidetector CT, even with recent advances in technology, remains diagnostically inferior to angiography.
- **E.** In patients with massive hemoptysis, plain films accurately localize the site of hemorrhage in less than 50% of patients.

Answer: B. In patients with massive hemoptysis, plain films may localize the site of hemorrhage in as many as 80% of patients. However, high-resolution multidetector CT of the chest is the principal diagnostic test to detect both bronchial and non-bronchial arterial causes of massive hemoptysis. CT is diagnostically comparable with, but less invasive than, conventional angiography, which currently is done as a combined diagnostic/therapeutic modality. A chest CT scan should be obtained in high-risk patients (smokers and oncology patients) or in any patient with moderate-to-severe bleeding even if the initial chest radiograph is normal. CT localization of hemorrhage can expedite bronchoscopic evaluation or guide subsequent interventional procedures.

21.4. A 50-year-old man presents after an episode of hemoptysis. He describes coughing up several large clots of dark blood. During his evaluation, he coughs and expectorates approximately 5 mL of clotted blood. The patient's vital signs are normal, and no abnormalities are noted on physical examination. His chest radiograph is normal. Which of the following is the most appropriate next step in the management of this patient?
- **A.** Admission to an observation unit
- **B.** Consultation for bronchoscopy
- **C.** Consultation for percutaneous embolization
- **D.** Discharge home with follow-up in 24 hours
- **E.** Obtain chest CT scan

Answer: E. Since the advent of high-resolution CT, radiologic evaluation has had an integral role in the evaluation and management of patients with hemoptysis. Unless the initial chest radiograph is diagnostic or the patient is hemodynamically unstable, a chest CT scan should be obtained in most cases. Further management strategy should occur in conjunction with pulmonary and thoracic surgery consultants, guided by the CT results.

21.5. A 58-year-old man with a single lung transplant presents to the emergency department (ED) with what appears to be large-volume hemoptysis. He was just discharged from the endoscopy suite, where he had a number of surveillance biopsies performed. He looks pale and diaphoretic with an initial oxygen saturation of 71%. After placement of an intravenous line and supplemental oxygen, the next most appropriate step is:
- **A.** Blood transfusion
- **B.** Contrast-enhanced CT scan of the chest
- **C.** Intubation
- **D.** Thoracic surgery consultation

Answer: C. This patient is profoundly hypoxic, will need imaging outside of the ED, and invasive procedures. All resuscitative and procedural efforts will be futile without intubation and maximal oxygenation.

CHAPTER 22

Dyspnea

Sabina A. Braithwaite | Debra Perina

PERSPECTIVE

Dyspnea is the term applied to the sensation of breathlessness and the patient's reaction to that sensation. It is an uncomfortable awareness of breathing difficulties that in the extreme manifests as "air hunger." Dyspnea is often ill defined by patients, who may describe the feeling as shortness of breath, chest tightness, or difficulty breathing. Dyspnea results from a variety of conditions, ranging from nonurgent to life-threatening. Neither the clinical severity nor the patient's perception correlates well with the seriousness of underlying pathology and may be affected by emotions, behavioral and cultural influences, and external stimuli.[1]

The following terms may be used in the assessment of the dyspneic patient:

Tachypnea: A respiratory rate greater than normal. Normal rates range from 44 cycles/min in a newborn to 14 to 18 cycles/min in adults.

Hyperpnea: Greater than normal minute ventilation to meet metabolic requirements.

Hyperventilation: A minute ventilation (determined by respiratory rate and tidal volume) that exceeds metabolic demand. Arterial blood gases (ABGs) characteristically show a normal partial pressure of oxygen (Po_2) with an uncompensated respiratory alkalosis (low partial pressure of carbon dioxide [Pco_2] and elevated pH).

Dyspnea on exertion: Dyspnea provoked by physical effort or exertion. It often is quantified in simple terms, such as the number of stairs or number of blocks a patient can manage before the onset of dyspnea.

Orthopnea: Dyspnea in a recumbent position. It usually is measured in number of pillows the patient uses to lie in bed (eg, two-pillow orthopnea).

Paroxysmal nocturnal dyspnea: Sudden onset of dyspnea occurring while reclining at night, usually related to the presence of congestive heart failure.

Epidemiology

Dyspnea is a very common presenting complaint among emergency department (ED) patients of every age. Causes vary widely, and range from benign, self-limited conditions to critical pathology that can produce short-term mortality and long-term morbidity.[2,3]

Pathophysiology

The actual mechanisms responsible for dyspnea are only beginning to be specifically described. Normal breathing is controlled both centrally by the respiratory control center in the medulla oblongata and peripherally by chemoreceptors located near the carotid bodies, but there are numerous sensory inputs that affect the feeling of dyspnea, including pulmonary stretch receptors and mechanoreceptors in the diaphragm and skeletal muscles.[4] Imbalances among these inputs can be perceived as dyspnea and may manifest as increased work of breathing, due to increased lung resistance or decreased compliance in asthma or chronic obstructive pulmonary disease (COPD). Alternatively, the imbalances of these inputs may also manifest as increased respiratory drive—ie, resulting from severe hypoxemia, acidosis, or centrally acting stimuli (toxins, central nervous system events).[5]

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

Dyspnea is subjective and has many different potential causes. The differential diagnosis can be divided into acute and chronic causes, of which many are pulmonary. Other causes include cardiac, metabolic, infectious, neuromuscular, traumatic, and hematologic conditions (Table 22.1).

Pivotal Findings

Symptoms

Patient descriptions of dyspnea vary significantly and generally correlate poorly with severity, although the complaint of dyspnea alone is predictive of mortality.

Duration of Dyspnea. Chronic or progressive dyspnea usually denotes primary cardiac or pulmonary disease.[6] Acute dyspneic spells may result from asthma exacerbation; infection; pulmonary embolus; intermittent cardiac dysfunction; psychogenic causes; or inhalation of irritants, allergens, or foreign bodies.

Onset of Dyspnea. Sudden onset of dyspnea should lead to consideration of pulmonary embolism (PE) or spontaneous pneumothorax. Dyspnea that builds slowly over hours or days may represent a flare of asthma or COPD; pneumonia; recurrent, small pulmonary emboli; congestive heart failure; or malignancy.

Positional Changes. Orthopnea can result from left-sided heart failure, COPD, or neuromuscular disorders. One of the earliest symptoms seen in patients with diaphragmatic weakness from neuromuscular disease is orthopnea.[7] Paroxysmal nocturnal dyspnea is most common in patients with left-sided heart failure but also occurs in COPD.[6] Exertional dyspnea commonly is associated with COPD but also can be seen with poor cardiac reserve and abdominal loading. Abdominal loading, caused by ascites, obesity, or pregnancy, leads to elevation of the diaphragm, resulting in less effective ventilation and dyspnea.

Anxiety or overwhelming fear, particularly if it precedes the onset of dyspnea, may point to panic attack or psychogenic dyspnea, but organic causes should be considered first. PE or myocardial infarction may cause isolated dyspnea with or without associated chest pain, particularly if the pain is constant, dull, or visceral.[8] Pain that is sharp and worsened by deep breathing but not by movement may indicate pleural effusion, pleurisy,

TABLE 22.1

Differential Diagnoses for Acute Dyspnea

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Pulmonary	Airway obstruction Pulmonary embolus Noncardiogenic edema Anaphylaxis Ventilatory failure	Spontaneous pneumothorax Asthma Cor pulmonale Aspiration Pneumonia (CAP score >70)	Pleural effusion Neoplasm Pneumonia (CAP score ≤70) COPD
Cardiac	Pulmonary edema Myocardial infarction Cardiac tamponade	Pericarditis	Congenital heart disease Valvular heart disease Cardiomyopathy
PRIMARILY ASSOCIATED WITH NORMAL OR INCREASED RESPIRATORY EFFORT			
Abdominal		Mechanical interference Hypotension, sepsis from ruptured viscus, bowel obstruction, inflammatory or infectious process	Pregnancy Ascites obesity
Psychogenic			Hyperventilation syndrome Somatization disorder Panic attack
Metabolic or endocrine	Toxic ingestion DKA	Renal failure Electrolyte abnormalities Metabolic acidosis	Fever Thyroid disease
Infectious	Epiglottitis	Pneumonia (CAP score >70)	Pneumonia (CAP score ≤70)
Traumatic	Tension pneumothorax Cardiac tamponade Flail chest	Simple pneumothorax, hemothorax Diaphragmatic rupture Neurologic injury	Rib fractures
Hematologic	Carbon monoxide or cyanide poisoning Acute chest syndrome	Anemia	
PRIMARILY ASSOCIATED WITH DECREASED RESPIRATORY EFFORT			
Neuromuscular	CVA, intracranial insult Organophosphate poisoning	Multiple sclerosis Guillain-Barré syndrome Tick paralysis	ALS Polymyositis Porphyria

ALS, Amyotrophic lateral sclerosis; *CAP,* community-acquired pneumonia; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *DKA,* diabetic ketoacidosis.

or pleural irritation from pneumonia or PE. Spontaneous pneumothorax also may produce sharp pain with deep breathing that is not worsened by movement.

Signs

Physical signs in dyspneic patients may be consistent with specific illnesses (Table 22.2). For example, fever suggests an infectious cause, somnolence or obtundation may indicate hypercarbia, agitation can be associated with hypoxia, and trauma may produce dyspnea through various injuries. Physical findings found in specific diseases also can be grouped according to presenting patterns (Table 22.3). Some findings have improved predictive value for specific pathologies when combined with laboratory testing in validated risk stratification tools.[9-11]

Ancillary Testing

Specific findings obtained from the history and physical examination should be used to determine which ancillary studies are needed (Table 22.4). Bedside oxygen saturation determinations, or selective use of ABGs when oximetry is not reliable, are useful in determining the degree of hypoxia and the need for supplemental oxygen or assisted ventilation. In patients with abnormal values, a venous blood gas (VBG) is a less painful alternative to ABG to determine pH.[12] VBG is less reliable for P_{CO_2} or accurate numeric correlation to arterial hypercapnia, although a normal venous P_{CO_2} has a strong negative predictive value, and values greater than 45 mm Hg are highly sensitive in predicting arterial hypercarbia.[13,14] The more invasive ABG is useful when an accurate P_{CO_2} or P_{O_2} is important. An additional resource for quickly assessing ventilatory status is noninvasive waveform capnography. End-tidal carbon dioxide (ET_{CO_2}) values correlate well with arterial carbon dioxide (CO_2), and the shape of the capnogram can be helpful in assessing the adequacy of ventilations, as well as underlying causes of the dyspnea (see Chapter 5).[15] An electrocardiogram may be useful if history or physical examination findings suggest heart failure, ischemic cardiac disease, dysrhythmia, or pulmonary hypertension. Bedside ultrasound is useful to rapidly assess multiple parameters that can focus and guide therapy. For example, thoracic ultrasound can quickly visualize pleural effusion, pulmonary edema with B lines, pneumothorax when "sandy beach" and "comet tail" signs are absent, cardiac dysfunction by evaluating myocardial contractility and estimating ejection fraction (EF), or pericardial effusion and tamponade.[16,17] Abdominal ultrasound can assess

TABLE 22.2

Pivotal Findings in Physical Examination

SIGN	PHYSICAL FINDING	DIAGNOSES TO CONSIDER
Vital signs	Tachypnea	Pneumonia, pneumothorax
	Hypopnea	Intracranial insult, drug or toxin ingestion
	Tachycardia	PE, traumatic chest injury
	Hypotension	Tension pneumothorax
	Fever	Pneumonia, PE
General appearance	Cachexia, weight loss	Malignancy, acquired immune disorder, mycobacterial infection
	Obesity	Hypoventilation, sleep apnea, PE
	Pregnancy	PE
	Barrel chest	COPD
	"Sniffing" position	Epiglottitis
	"Tripoding" position	COPD or asthma with severe distress
	Traumatic injury	Pneumothorax (simple, tension), rib fractures, diaphragmatic injury, flail chest, hemothorax, pulmonary contusion
Skin and nails	Tobacco stains or odor	COPD, malignancy, infection
	Clubbing	Chronic hypoxia, intracardiac shunts, or pulmonary vascular anomalies
	Pallid skin or conjunctivae	Anemia
	Muscle wasting	Neuromuscular disease
	Bruising	Chest wall: Rib fractures, pneumothorax
	Diffuse: Thrombocytopenia, chronic steroid use, anticoagulation	
	Subcutaneous emphysema	Rib fractures, pneumothorax, tracheobronchial disruption
	Hives, rash	Allergic reaction, infection, tick-borne illness
Neck	Stridor	Upper airway edema or infection, foreign body, traumatic injury, anaphylaxis
	JVD	Tension pneumothorax, COPD or asthma exacerbation, fluid overload or CHF, PE, cardiac tamponade
Lung examination	Wheezes	CHF, anaphylaxis
	Bronchospasm	
	Rales	CHF, pneumonia, PE
	Unilateral decrease	Pneumothorax, pleural effusion, consolidation, rib fractures or contusion, pulmonary contusion
	Hemoptysis	Malignancy, infection, bleeding disorder, CHF
	Sputum production	Infection (viral, bacterial)
	Friction rub	Pleurisy
	Abnormal respiratory pattern (eg, Cheyne-Stokes)	Intracranial insult
Chest examination	Crepitance or pain on palpation	Rib or sternal fractures
	Subcutaneous emphysema	Pneumothorax, tracheobronchial rupture
	Thoracoabdominal desynchrony	Diaphragmatic injury with herniation; cervical spinal cord trauma
	Flail segment	Flail chest, pulmonary contusion
Cardiac examination	Murmur	PE
	S_3 or S_4 gallop	PE
	S_2 accentuation	PE
	Muffled heart sounds	Cardiac tamponade, pericardial effusion
Extremities	Calf tenderness, Homans' sign	PE
	Edema	CHF
Neurologic examination	Focal deficits (motor, sensory, cognitive)	Stroke, intracranial hemorrhage causing central abnormal respiratory drive; if long-standing, risk of aspiration pneumonia
	Symmetrical deficits	Neuromuscular disease
	Diffuse weakness	Metabolic or electrolyte abnormality (hypocalcemia, hypomagnesemia, hypophosphatemia), anemia
	Hyporeflexia	Hypermagnesemia
	Ascending weakness	Guillain-Barré syndrome

CHF, Congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *JVD,* jugular venous distention; *PE,* pulmonary embolism.

TABLE 22.3

Diagnostic Table: Patterns of Diseases Often Resulting in Dyspnea

DISEASE	HISTORY (DYSPNEA)	ASSOCIATED SYMPTOMS	SIGNS AND PHYSICAL FINDINGS	TESTS
Pulmonary embolism	HPI: Abrupt onset, pleuritic pain, immobility (travel, recent surgery) PMH: Malignancy, DVT, PE, hypercoagulability, oral contraception, obesity	Diaphoresis, exertional dyspnea	Tachycardia, tachypnea, low-grade fever	Pulse oximetry, ABG (A-a gradient), D-dimer ECG (dysrhythmia, right-sided heart strain) CXR (Westermark sign, Hampton's hump), spiral CT, MRV Pulmonary angiogram Ultrasound positive for DVT
Pneumonia	Fever, productive cough, chest pain	Anorexia, chills, nausea, vomiting, exertional dyspnea, cough	Fever, tachycardia, tachypnea, rales or decreased breath sounds	CXR, CBC, sputum and blood cultures
Bacterial	SH: Tobacco use			Pulse oximetry Waveform capnography if altered mental status; ABG if capnography unavailable and acid-base derangement or hypercarbia suspected
Viral	Exposure (eg, influenza, varicella)			
Opportunistic	Immune disorder, chemotherapy			
Fungal or parasitic	Exposure (eg, birds), indolent onset	Episodic fever, nonproductive cough		
Pneumothorax	Abrupt onset: Trauma, chest pain, thin males more likely to have spontaneous pneumothorax	Localized chest pain	Decreased breath sounds, subcutaneous emphysema, chest wall wounds or instability	CXR: Pneumothorax, rib fractures, hemothorax Ultrasound: Pneumothorax, pleural effusion
Simple				Ultrasound positive for pneumothorax
Tension	Decompensation of simple pneumothorax	Diaphoresis	JVD, tracheal deviation, muffled heart sounds, cardiovascular collapse	Clinical diagnosis: Requires immediate decompression. May verify via bedside ultrasound
COPD or asthma	Tobacco use, medication noncompliance, URI symptoms, sudden weather change PMH: Environmental allergies FH: Asthma	Air hunger, diaphoresis	Retractions, accessory muscle use, tripoding, cyanosis "Shark fin" capnograph	CXR: Rule out infiltrate, pneumothorax, atelectasis (mucus plug) Ultrasound: Distinguish from heart failure Waveform capnography
Malignancy	Weight loss, tobacco, or other occupational exposure	Dysphagia	Hemoptysis	CXR, chest CT: Mass, hilar adenopathy, focal atelectasis
Fluid overload	Gradual onset, dietary indiscretion or medication noncompliance, chest pain PMH: Recent MI, diabetes, CHF	Worsening orthopnea, PND	JVD, peripheral edema, S_3 or S_4 gallop, new cardiac dysrhythmia, hepatojugular reflux	CXR and/or ultrasound: Pleural effusion, interstitial edema, Kerley B lines, cardiomegaly ECG: Ischemia, dysrhythmia BNP
Anaphylaxis	Abrupt onset, exposure to allergen	Dysphagia	Oral swelling, stridor, wheezing, hives	

A-a, Alveolar-arterial; *ABG,* arterial blood gas; *BNP,* B-type natriuretic peptide; *CBC,* complete blood count; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *CT,* computed tomography; *CXR,* chest x-ray examination; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *FH,* family history; *HPI,* history of present illness; *JVD,* jugular venous distention; *MI,* myocardial infarction; *MRV,* magnetic resonance venography; *PE,* pulmonary embolism; *PMH,* past medical history; *PND,* paroxysmal nocturnal dyspnea; *SH,* social history; *URI,* upper respiratory infection.

TABLE 22.4

Ancillary Testing in the Dyspneic Patient

CATEGORY	TEST	FINDINGS AND POTENTIAL DIAGNOSES
Laboratory	Pulse oximetry, selective ABG use	Hypoxia, hyperventilation (muscular weakness, intracranial event)
	Waveform capnography	CO_2 retention (COPD, sleep apnea), obstructive or restrictive pulmonary pattern
		Metabolic versus respiratory acidosis (DKA, ingestions)
		A-a gradient (PE)
		Elevated carboxyhemoglobin (inhalation injury or CO poisoning)
	Complete blood count	WBC
		Increase: Infection, stress demargination, hematologic malignancy
		Decrease: Neutropenia, sepsis
		Hgb, Hct: Anemia, polycythemia
		Smear: Abnormal Hgb (ie, sickling), inclusions
		Platelets: Thrombocytopenia (marrow toxicity)
		Chemistry
		BUN, Cr: Acute or chronic renal failure
		K, Mg, Phos: Low levels resulting in muscular weakness
		Glucose: DKA
		D-dimer: Abnormal clotting activity
		BNP: Heart failure, PE
		Troponin: Cardiac ischemia or infarct
Cardiac	ECG	Ischemia, dysrhythmia, $S_1Q_3T_3$ (PE), right-sided heart strain
	Echocardiogram	Pulmonary hypertension, valvular disorders
		Wall motion abnormalities related to ischemia, intracardiac shunts
Radiologic	Chest radiograph	Bony structures: Fractures, lytic lesions, pectus, kyphoscoliosis
		Mass: Malignancy, cavitary lesion, infiltrate, foreign body
		Diaphragm: Eventration, elevation of hemidiaphragm, bowel herniation
		Mediastinum: Adenopathy (infection, sarcoid), air
		Cardiac silhouette: Enlarged (cardiomyopathy, fluid overload)
		Soft tissue: Subcutaneous air
		Lung parenchyma: Blebs, pneumothorax, effusions (blood, infectious), interstitial edema, local consolidation, air bronchograms, Hampton's hump, Westermark's sign
	Scan	PE
	Pulmonary angiogram	PE, intervention (thrombolysis)
	CT	Mass lesion, adenopathy, trauma, PE
	MRI	PE, bony and soft tissue lesions, vascular abnormality
	Soft tissue neck radiograph	Epiglottitis, foreign body
	Ultrasound	Pneumothorax, pleural effusion, impaired cardiac function or pericardial effusion
Fiberoptic	Bronchoscopy	Mass lesion, foreign body
		Intervention (stenting, biopsy)
	Laryngoscopy	Mass lesion, edema, epiglottitis, foreign body

A-a, Alveolar-arterial; *ABG,* arterial blood gas; *BNP,* B-type natriuretic peptide; *BUN,* blood urea nitrogen; *CO,* carbon monoxide; *CO_2,* carbon dioxide; *COPD,* chronic obstructive pulmonary disease; *Cr,* creatinine; *CT,* computed tomography; *DKA,* diabetic ketoacidosis; *ECG,* electrocardiogram; *Hct,* hematocrit; *Hgb,* hemoglobin; *K,* potassium; *Mg,* magnesium; *MRI,* magnetic resonance imaging; *PE,* pulmonary embolism; *Phos,* phosphate; *WBC,* white blood cell.

intravascular volume by quantifying inferior vena cava size and compressibility.[18] Extremity ultrasound can reveal deep venous thrombosis.[19]

Serum electrolytes may confirm metabolic acidosis or a less common cause, such as hypokalemia, hypophosphatemia, or hypocalcemia. A complete blood count may identify severe anemia or thrombocytopenia associated with sepsis. The white blood cell count is not sufficiently sensitive or specific to be of discriminatory value.

Expanded availability of specific blood biomarkers relevant to emergent evaluation of dyspnea provides improved immediate decision support and allows for short- and long-term prognostication.[20,21] These include cardiac markers and D-dimer assay, which are useful in pursuing causes, such as cardiac ischemia or venous thromboembolic disease. B-type natriuretic peptide (BNP) analysis adds both diagnostic and prognostic value for several causes of dyspnea, including heart failure, PE, and ischemic cardiac disease.[22]

If venous thromboembolism is suspected, D-dimer testing, with or without chest computed tomographic angiography, duplex venous ultrasonography, or, rarely, ventilation-perfusion scanning, is performed on patients preselected based on clinical decision rules.[23] If dyspnea is believed to be upper airway in origin, direct or fiberoptic laryngoscopy or a soft tissue lateral radiograph of the neck may be useful.

DIAGNOSTIC ALGORITHM

The range and diversity of pathophysiologic conditions that produce dyspnea render a simple algorithmic approach difficult. The primary branch point is the determination of whether the dyspnea primarily is cardiopulmonary or toxic-metabolic in origin. After initial assessment, stabilization and symptom relief in critical patients, findings from the history, physical examination, and ancillary testing are collated to match patterns of disease that produce dyspnea. This process is updated periodically as new information becomes available. Table 22.3 presents recognizable patterns of disease for common dyspnea-producing conditions, along with specific associated symptoms.

Critical Diagnoses

Several critical diagnoses should be promptly considered to determine the best treatment options to stabilize the patient. Tension pneumothorax is a critical condition that is diagnosed by history and physical examination. If a dyspneic patient has no breath sounds on one side, ipsilateral hyper-resonance, severe respiratory distress, hypotension, and oxygen desaturation, prompt decompression of presumptive tension pneumothorax is indicated. Jugular venous distension may or may not be apparent and its absence does not rule out the condition. Bedside ultrasonography can confirm pneumothorax in less obvious cases. If dyspnea and stridor indicate upper airway obstruction, early, definitive assessment, and intervention occur in the ED or operating room. Complete obstruction by a foreign body warrants the Heimlich maneuver until the obstruction is relieved or the patient is unconscious, followed rapidly by direct laryngoscopy for foreign body removal. Heart failure and pulmonary edema can produce dyspnea and respiratory failure and require prompt intervention to support ventilation and gas exchange if severe. Significant dyspnea and wheezing in anaphylaxis require immediate use of parenteral epinephrine in addition to supportive measures. Severe bronchospastic exacerbations of asthma at any age may lead rapidly to respiratory failure and arrest and should receive vigorous attention, including continuous or frequent administration of a beta-agonist aerosol and steroid therapy.[24] Ultrasound may also be of benefit in rapidly distinguishing between COPD and heart failure, as well as other pathologies.[25,26] As mentioned earlier, waveform capnography is a valuable adjunct for assessing the severity and determining the cause of respiratory distress. Presumptive anticoagulation or even thrombolytics may be appropriate in patients with suspected significant PE even prior to diagnostic testing.

Emergent Diagnoses

Asthma and COPD exacerbations can result in marked dyspnea with bronchospasm and decreased ventilatory volumes.[27] Sudden onset of dyspnea with a decreased oxygen saturation on room air accompanied by sharp chest pain may represent PE. Dyspnea accompanied by decreased breath sounds and tympany on percussion on one side is seen with spontaneous pneumothorax. Dyspnea associated with decreased respiratory effort may represent a neuromuscular process, such as multiple sclerosis, Guillain-Barré syndrome, or myasthenia gravis. Unilateral rales, cough, fever, and dyspnea usually indicate pneumonia.

Figure 22.1 provides an algorithm for assessment and stabilization of a dyspneic patient. The initial division is based on the degree of breathing effort associated with the symptoms. The most critical diagnoses are considered first, and appropriate intervention undertaken.

All patients experiencing dyspnea, regardless of possible cause, should be promptly evaluated in the treatment area. Bedside pulse oximetry readings should be obtained, and the patient placed on a cardiac monitor. If the pulse oximetry result is less than 94% on room air, supplemental oxygen either by nasal cannula or mask should be considered, depending on the degree of desaturation. In patients with somnolence or obtundation, hypercarbia and respiratory failure should be considered as possible etiologies. If necessary, ventilation should be assisted manually or mechanically, either noninvasively for the short term, or with the patient tracheally intubated for airway protection for prolonged ventilation.[28]

Decreased mental alertness, inability to speak in more than one-syllable words, or certain types of body positioning signal the presence of significant respiratory distress and the need for rapid intervention. After the airway has been secured, rapid assessment of the patient's appearance and vital signs can help determine the need for further stabilization and the cause of the dyspnea can be further investigated.

Empirical Management

The management algorithm for dyspnea (Fig. 22.2) outlines the approach to treatment for most identifiable diseases. Unstable patients or patients with critical diagnoses must be stabilized and may require admission to an intensive care unit. Emergent patients who have improved with ED management may be admitted to an intermediate care unit. Patients diagnosed with urgent conditions in danger of deterioration without proper treatment or patients with severe comorbidities, such as diabetes, immunosuppression, or cancer, may also require admission for observation and treatment.

Most patients in the nonurgent category can be treated as outpatients if medical follow-up can be arranged. If dyspnea persists despite therapy and no definitive cause has been delineated, the preferred course of action is hospitalization for observation and ongoing evaluation. If no definitive diagnosis can be obtained and the symptoms have abated, the patient may be discharged with medical follow-up and instructions to return if symptoms recur.

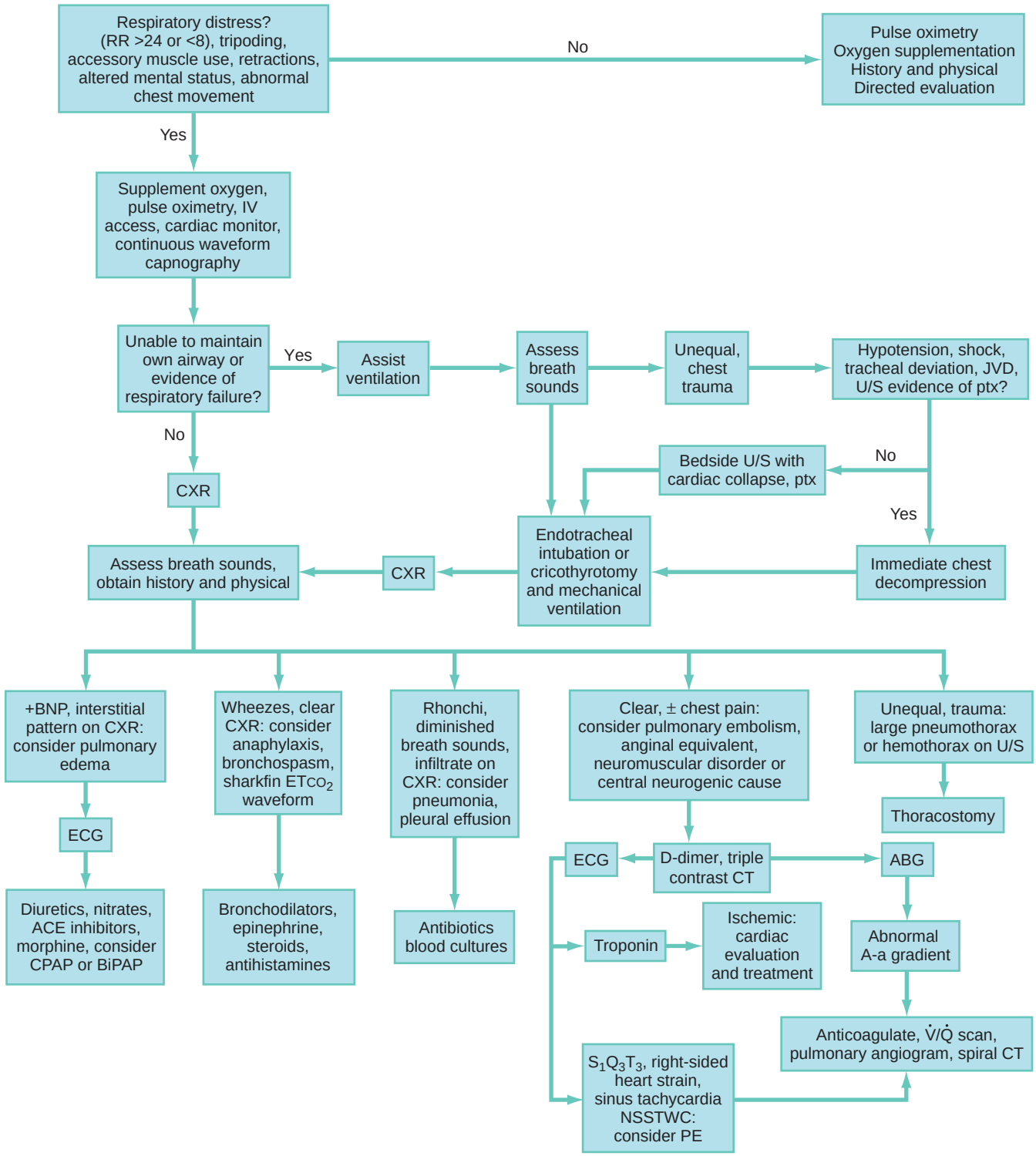

Fig. 22.1. Rapid assessment and stabilization of a dyspneic patient. *A-a,* arterial-alveolar; *ABG,* arterial blood gas; *ACE,* angiotensin-converting enzyme; *BiPAP,* biphasic positive airway pressure; *BNP,* B-type natriuretic peptide; *CPAP,* continuous positive airway pressure; *CT,* computed tomography; *CXR,* chest x-ray; *ECG,* electrocardiogram; *$ETCO_2$,* end-tidal carbon dioxide; *IV,* intravenous; *JVD,* jugular venous distention; *NSSTWC,* nonspecific ST wave changes (on ECG); *PE,* pulmonary embolism; *ptx,* pneumothorax; *RR,* respiratory rate; V̇/Q̇, ventilation-perfusion ratio; *U/S,* ultrasound.

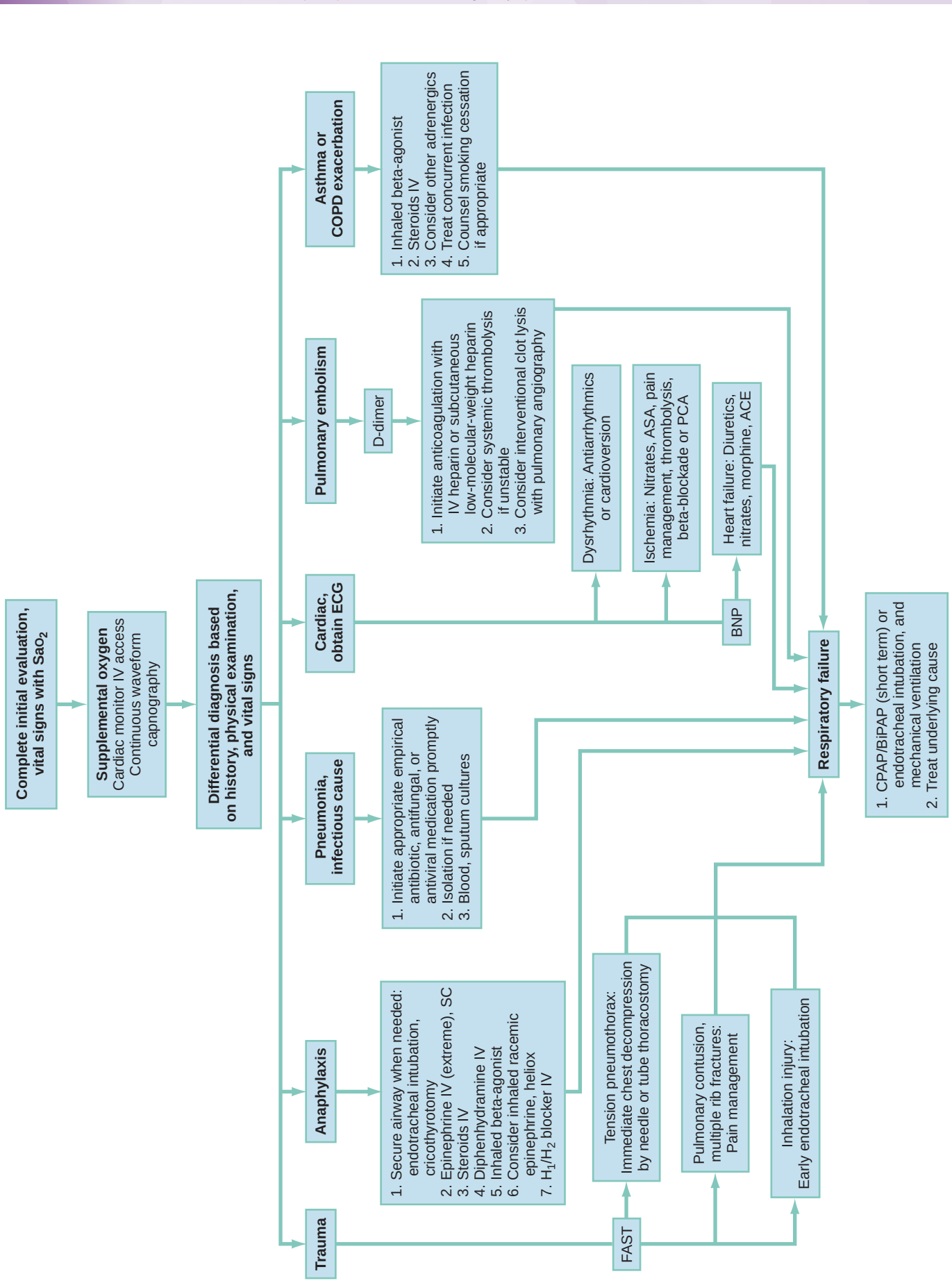

Fig. 22.2. Clinical guidelines for emergency department (ED) management of dyspnea. *ACE,* angiotensin-converting enzyme; *ASA,* acetylsalicylic acid; *BNP,* B-type natriuretic peptide; *COPD,* chronic obstructive pulmonary disease; *CPAP/BiPAP,* continuous positive airway pressure/biphasic positive airway pressure; *ECG,* electrocardiogram; *FAST,* focused assessment with sonography in trauma; *IV,* intravenous; *PCA,* patient-controlled analgesia; SaO_2, arterial oxygen saturation; *SC,* subcutaneously.

KEY CONCEPTS

- Dyspnea results from a variety of conditions, ranging from nonurgent to life-threatening. Neither the clinical severity nor the patient's perception correlates well with the seriousness of underlying pathology.
- Dyspnea is subjective and the differential diagnosis can be divided into acute and chronic causes, of which many are pulmonary. Other causes include cardiac, metabolic, infectious, neuromuscular, traumatic, and hematologic conditions.
- Chronic or progressive dyspnea usually denotes primary cardiac or pulmonary disease. Acute dyspneic spells may result from asthma exacerbation; infection; pulmonary embolus; intermittent cardiac dysfunction; psychogenic causes; or inhalation of irritants, allergens, or foreign bodies.
- All patients experiencing dyspnea, regardless of possible cause, should be promptly evaluated in the treatment area. Bedside pulse oximetry readings should be obtained, and the patient placed on a cardiac monitor.
- If the pulse oximetry result is less than 95% on room air, the patient should be placed on supplemental oxygen either by nasal cannula or mask, depending on the degree of desaturation.
- If necessary, breathing should be assisted with manual or mechanical ventilation, either noninvasively for the short term, or with the patient tracheally intubated for airway protection for prolonged ventilation.
- Unstable patients or patients with critical diagnoses must be stabilized and require admission to an intensive care unit. Emergent patients who have improved in the ED may be admitted to an intermediate care unit. Most patients in the nonurgent category can be treated as outpatients if medical follow-up can be arranged.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 22: QUESTIONS & ANSWERS

22.1. Hyperpnea is best defined by which of the following?
- **A.** A respiratory rate greater than normal
- **B.** A tidal volume that exceeds metabolic demands
- **C.** Decreased end-tidal carbon dioxide levels
- **D.** Elevated functional residual capacity
- **E.** Greater-than-the-normal minute ventilation necessary to meet metabolic demands

Answer: E. Hyperpnea is greater-than-the-normal minute ventilation necessary to meet metabolic demands.

22.2. Stridor is most likely due to:
- **A.** Bronchospasm
- **B.** Guillain-Barré syndrome
- **C.** Laryngeal edema
- **D.** Malignancy
- **E.** Pulmonary embolism

Answer: C. Stridor is an upper airway noise caused by airway narrowing. Of the given options, stridor is most likely due to laryngeal edema.

22.3. A 34-year-old male was struck repeatedly with a pipe in the right chest. He becomes acutely more dyspneic during emergency medical services (EMS) transport and becomes clammy, hypotensive, and more tachycardic on arrival to the emergency department (ED). Examination reveals tachypnea, crepitance, and subcutaneous air over the right chest, with decreased breath sounds. The most appropriate next action is:
- **A.** 1-L intravenous (IV) fluid bolus
- **B.** Needle chest decompression of the right chest
- **C.** Perform portable chest radiograph
- **D.** Provide supplemental oxygen by non-rebreather mask
- **E.** Rapid sequence intubation (RSI) and endotracheal intubation

Answer: B. Needle chest decompression is indicated for management of a likely tension pneumothorax. If ultrasound is immediately available, it can be used to confirm pneumothorax, but in this patient, who is in cardiovascular collapse, immediate intervention is necessary.

22.4. A 49-year-old female presents with acute onset of dyspnea. Which of the following findings is most suggestive of a primary cardiac etiology?
- **A.** Hampton's hump on chest radiograph
- **B.** Positive amino-terminal pro–B-type natriuretic peptide (NT-proBNP)
- **C.** Positive D-dimer
- **D.** Positive Homans' sign
- **E.** S1Q3T3 on electrocardiography (ECG)

Answer: B. Positive NT-proBNP. Although this may be positive with heart failure or pulmonary embolism (PE), this is the best choice. S1Q3T3, Hampton's hump, D-dimer, and Homans' sign are more associated with PE than primary cardiac etiology.

CHAPTER 23

Chest Pain

James E. Brown

PERSPECTIVE

Approximately 6 million patients visit the emergency department (ED) each year with complaints of chest pain, constituting 9% of all patients seen in EDs in the United States.[1] From 1999 to 2008, the total number of ED patients with noninjury complaints increased by 22%, whereas the percentage of patients with chest pain decreased slightly.[2] Chest pain is a symptom caused by several life-threatening as well as non–life-threatening diseases and has a broad differential diagnosis. It is complicated by a frequent disassociation between intensity of symptoms and signs and seriousness of underlying pathology.

Epidemiology

The epidemiology of the critical diagnoses causing chest pain varies widely. Acute coronary syndrome (ACS), aortic dissection, pulmonary embolism (PE), pneumothorax, pericarditis with tamponade, and esophageal rupture are potentially catastrophic causes of chest pain. These are discussed in the relevant chapters in this text. Chest pain that is atypical or of unclear cause is a daily presentation in virtually every ED—large or small, academic or community, urban, suburban, or rural.

Pathophysiology

Afferent fibers from the heart, lungs, great vessels, and esophagus enter the same thoracic dorsal ganglia. Through these visceral fibers, each organ produces the same indistinct quality and location of pain. The quality of visceral chest pain varies widely and is described as "burning," "aching," "stabbing," or "pressure." Because dorsal segments overlap three segments above and below a level, disease of a thoracic origin can produce pain anywhere from the jaw to the epigastrium. Radiation of pain is caused by somatic afferent fibers synapsing in the same dorsal root ganglia as the thoracic viscera. This stimulation can confuse the patient's central nervous system into misperceiving that the pain originates in the arms, shoulders, or neck.

DIAGNOSTIC APPROACH

Differential Considerations

Because of the indistinct nature of visceral pain, the differential diagnosis of chest pain is broad and includes many of the most critical diagnoses in medicine and many nonemergent conditions (Table 23.1).

Rapid Stabilization and Assessment

All patients, except those with obvious benign causes of chest pain, undergo electrocardiography as soon as possible after reporting their pain. The electrocardiogram (ECG) should be read for acute myocardial infarction (MI) by the emergency clinician promptly after it is completed. Patients with positive electrocardiographic findings and those considered at high risk are triaged directly to the treatment area and monitored.

In clinical evaluation of the patient, the initial questions are "Should I intervene now?" and "What are the life-threatening possibilities in this patient?" The answers are usually apparent within the first few minutes after assessment of the patient's appearance, ECG, and vital signs. If a patient has unilateral chest pain, respiratory distress, shock, and unilateral reduction or absence of breath sounds, emergent intervention with needle or tube thoracostomy is required. In addition, patients with severe derangements in vital signs require stabilizing treatment during a search for the precipitating cause. Patients with respiratory distress require prompt intervention and lead the emergency clinician to consider a more serious cause of the pain (Fig. 23.1; also see Chapter 22).

Symptomatic derangements in vital signs are addressed. If vital signs are stable, a focused history and physical examination are performed. Many patients also require a chest radiograph to evaluate the chest pain. If myocardial ischemia is suspected, aspirin and nitroglycerin may be appropriate. Patients with pain, findings suggestive of aortic dissection, and significant hypertension are candidates for immediate reduction of blood pressure (see Chapter 75). Patients with low voltage on the ECG, diffuse ST segment elevation, elevated jugular venous pressure on examination, and signs of shock should undergo prompt bedside cardiac ultrasound to evaluate for pericardial tamponade.

Pivotal Findings

The broad and complex nature of chest pain defies application of a simple algorithm. An organized approach to a patient with chest pain is essential, however, to ensure that all causes are evaluated appropriately. The history and physical examination are key to diagnosis. Information pertinent to the differential diagnosis is obtained through the directed history, physical examination, and ECG in 80% to 90% of patients.

History

The patient is asked to describe the character of the pain or discomfort. Descriptions such as "squeezing," "crushing," or "pressure" lead the emergency clinician to suspect a cardiac ischemic syndrome, although cardiac ischemia can also be characterized by nonspecific discomfort, such as "bloating" or "indigestion." "Tearing" pain that may migrate from the front to back or back to front is the classic description in aortic dissection. "Sharp" or "stabbing" pain is seen more in pulmonary and musculoskeletal diagnoses. Patients reporting a "burning" or "indigestion" type of pain may initially be thought to have a gastrointestinal condition, but owing to the visceral nature of chest pain, patients with all causes of pain may report any of the preceding descriptions. Of note, descriptors may vary among ethnic groups; for example, "sharp" may mean "severe."

Additional history about the patient's activity at the onset of pain may be helpful. Pain occurring during exertion suggests an

TABLE 23.1

Differential Diagnosis of Chest Pain

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Cardiovascular	Acute myocardial infarction Acute coronary ischemia Aortic dissection Cardiac tamponade	Unstable angina Coronary spasm Prinzmetal's angina Cocaine-induced pericarditis or myocarditis	Valvular heart disease Aortic stenosis Mitral valve prolapse Hypertrophic cardiomyopathy
Pulmonary	Pulmonary embolus Tension pneumothorax	Pneumothorax Mediastinitis	Pneumonia Pleuritis, tumor, pneumomediastinum
Gastrointestinal	Esophageal rupture (Boerhaave's syndrome)	Esophageal tear (Mallory-Weiss) Cholecystitis Pancreatitis	Esophageal spasm Esophageal reflux Peptic ulcer, biliary colic
Musculoskeletal			Muscle strain, rib fracture arthritis, tumor, costochondritis, nonspecific chest wall pain
Neurologic			Spinal root compression, thoracic outlet, herpes zoster, postherpetic neuralgia
Other			Psychological, hyperventilation

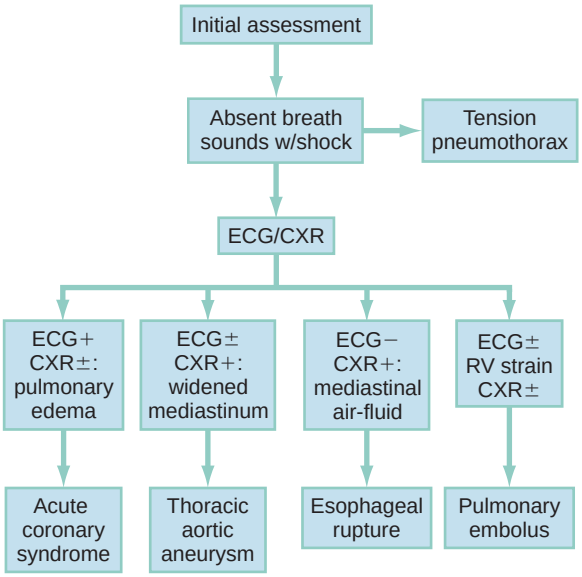

Fig. 23.1. Initial assessment of critical diagnoses. *CXR,* Chest x-ray study; *ECG,* electrocardiogram; *RV,* right ventricular.

ischemic coronary syndrome, whereas progressive onset of pain at rest suggests an acute MI. Pain of sudden onset is more typical with aortic dissection, PE, or pneumothorax. Pain after meals is more indicative of a gastrointestinal cause.

The severity of pain is commonly quantified with a 1 to 10 pain scale. Alterations in pain severity are documented at times of onset, at peak, at present, and after intervention.

The location of the discomfort is described. Pain that is localized to a small area is more likely to be somatic versus visceral in origin. Pain localized at the periphery of the chest is more likely to have a pulmonary rather than cardiac cause. Lower chest or upper abdominal pain may be of cardiac or gastrointestinal origin.

Any description of radiation of pain should be noted. Transthoracic pain through to the back should suggest aortic dissection or gastrointestinal causes, especially pancreatitis, cholecystitis, or posterior ulcer. Inferoposterior myocardial ischemia may also manifest primarily as thoracic back pain. Radiation to the arms, neck, or jaw increases the likelihood of cardiac ischemia. Pain located primarily in the back, especially interscapular back pain that migrates to the base of the neck, suggests aortic dissection.

Duration of pain is another important historical factor. Pain that lasts a few seconds or minutes is rarely of cardiac origin. Pain that is exertional but abates with a few minutes of rest may be a manifestation of cardiac ischemia. Pain that is maximal at onset may be caused by aortic dissection. Pain that is not severe and persists over the course of days is less likely to be of serious origin than pain that is severe or has a stuttering or fluctuating course.

The emergency clinician should consider aggravating or alleviating factors. Pain that worsens with exertion and improves with rest is more likely related to coronary ischemia. Pain related to meals is more suggestive of a gastrointestinal cause. Pain that worsens with respiration is seen more often with pulmonary, pulmonary vascular, pericardial, and musculoskeletal causes.

Other associated symptoms may suggest the visceral nature of the pain (Table 23.2). Diaphoresis is uncommonly associated with somatic pain unless it is severe. such as rib fractures, so the presence of diaphoresis should prompt a search for a serious or visceral cause and points away from a chest wall origin. Hemoptysis, a classic PE sign, is rarely seen. Near-syncope and syncope suggest a higher likelihood of a cardiovascular cause or PE. Dyspnea is seen in cardiovascular and pulmonary disease. Nausea and vomiting may be seen in those with cardiovascular and gastrointestinal complaints.

A history of prior pain and diagnosis of that episode may facilitate the diagnostic process, but the emergency clinician should not allow the prior diagnosis to form an anchoring bias and be misled. A prior history of cardiac testing, such as stress testing, echocardiography, or angiography, may be useful in determining if the current episode is suggestive of cardiac disease. Similarly, patients with previous spontaneous pneumothorax or PE are at increased risk of recurrence.

The presence of risk factors for a particular disease is primarily of value as an epidemiologic marker for large population studies (Box 23.1). In the ED, presence of risk factors in an individual patient without established disease has minimal or no effect on the clinical likelihood (pretest probability) of a specific disease process.

Physical Examination

Specific findings may be found with a variety of causes (Table 23.3).

TABLE 23.2

Significant Symptoms of Chest Pain

SYMPTOM	FINDINGS	DIAGNOSIS
Pain	Severe, crushing, pressure, substernal, exertional, radiation to jaw, neck, shoulder, arm	Acute MI, coronary ischemia, unstable angina, coronary spasm
	Tearing, severe, radiating to or located in back, maximum at onset, may migrate to upper back or neck	Aortic dissection
	Pleuritic	Esophageal rupture, pneumothorax, cholecystitis, pericarditis, myocarditis
	Indigestion or burning	Acute MI, coronary ischemia, esophageal rupture, unstable angina, coronary spasm, esophageal tear, cholecystitis
Associated syncope or near-syncope		Aortic dissection, PE, acute MI, pericarditis, myocarditis
Associated dyspnea (SOB, DOE, PND, orthopnea)		Acute MI, coronary ischemia, PE, tension pneumothorax, pneumothorax, unstable angina, pericarditis
Associated hemoptysis		PE
Associated nausea, vomiting		Esophageal rupture, acute MI, coronary ischemia, unstable angina, coronary spasm, esophageal tear, cholecystitis

DOE, Dyspnea on exertion; *MI,* myocardial infarction; *PE,* pulmonary embolism; *PND,* paroxysmal nocturnal dyspnea; *SOB,* shortness of breath.

BOX 23.1

Risk Factors Associated With Potentially Catastrophic Causes of Chest Pain

Acute coronary syndromes
- Past or family history of coronary artery disease
- Age
  - Men >33 yr
  - Women >40 yr
- Diabetes mellitus
- Hypertension
- Cigarette use or possible passive exposure
- Elevated cholesterol (low-density lipoprotein [LDL]) or triglyceride levels
- Sedentary lifestyle
- Obesity
- Postmenopausal
- Left ventricular hypertrophy
- Cocaine abuse

Pulmonary embolism
- Prolonged immobilization
- Surgery >30 min in last 3 mo
- Prior deep vein thrombosis or pulmonary embolus
- Pregnancy or recent pregnancy
- Pelvic or lower extremity trauma
- Oral contraceptives with cigarette smoking
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Obesity
- Past medical or family history of hypercoagulability

Aortic dissection
- Hypertension
- Congenital disease of the aorta or aortic valve
- Inflammatory aortic disease
- Connective tissue disease
- Pregnancy
- Arteriosclerosis
- Cigarette use

Pericarditis or myocarditis
- Infection
- Autoimmune disease (eg, systemic lupus erythematosus)
- Acute rheumatic fever
- Recent myocardial infarction or cardiac surgery
- Malignancy
- Radiation therapy to mediastinum
- Uremia
- Drugs
- Prior pericarditis

Pneumothorax
- Prior pneumothorax
- Valsalva's maneuver
- Chronic lung disease
- Cigarette use

Ancillary Studies

The two most commonly performed studies in patients with chest pain are chest radiography and 12-lead electrocardiography (Table 23.4). Electrocardiography should be performed within 10 minutes of arrival in all patients with chest pain or potential angina equivalent in whom myocardial ischemia is a possibility.[3,4] This generally includes all male patients 33 years and older and female patients older than 39 years who report pain from the umbilicus to the mandible, unless a noncardiac cause is readily apparent. Rapid acquisition of the ECG facilitates the diagnosis of acute MI and expedites the National Heart, Lung, and Blood Institute's recommended door to treatment times from arrival to percutaneous coronary intervention (PCI) or thrombolytic therapy in acute MI. Patients with a new injury pattern on the ECG (Table 23.5) or new ischemic electrocardiographic changes should have appropriate therapy instituted at this point (Fig. 23.2; see also Chapter 68). An ECG showing right ventricular strain

TABLE 23.3

Pivotal Findings in Physical Examination

SIGN	FINDING	DIAGNOSES
Appearance	Acute respiratory distress	PE, tension pneumothorax, acute MI, pneumothorax
	Diaphoresis	Acute MI, aortic dissection, coronary ischemia, PE, esophageal rupture, unstable angina, cholecystitis, perforated peptic ulcer
Vital signs	Hypotension	Tension pneumothorax, PE, acute MI, aortic dissection (late), coronary ischemia, esophageal rupture, pericarditis, myocarditis
	Tachycardia	Acute MI, PE, aortic dissection, coronary ischemia, tension pneumothorax, esophageal rupture, coronary spasm, pericarditis, myocarditis, mediastinitis, cholecystitis, esophageal tear (Mallory-Weiss)
	Bradycardia	Acute MI, coronary ischemia, unstable angina
	Hypertension	Acute MI, coronary ischemia, aortic dissection (early)
	Fever	PE, esophageal rupture, pericarditis, myocarditis, mediastinitis, cholecystitis
	Hypoxemia	PE, tension pneumothorax, pneumothorax
Cardiovascular examination	Significant difference in upper extremity blood pressures	Aortic dissection
	Narrow pulse pressure	Pericarditis (with effusion)
	New murmur	Acute MI, aortic dissection, coronary ischemia
	S_3-S_4 gallop	Acute MI, coronary ischemia
	Pericardial rub	Pericarditis
	Audible systolic "crunch" on cardiac auscultation (Hamman's sign)	Esophageal rupture, mediastinitis
	JVD	Acute MI, coronary ischemia, tension pneumothorax, PE, pericarditis
Pulmonary examination	Unilateral diminished or absent breath sounds	Tension pneumothorax, pneumothorax
	Pleural rub	PE
	Subcutaneous emphysema	Tension pneumothorax, esophageal rupture, pneumothorax, mediastinitis
	Rales	Acute MI, coronary ischemia, unstable angina
Abdominal examination	Epigastric tenderness	Esophageal rupture, esophageal tear, cholecystitis, pancreatitis
	Left upper quadrant tenderness	Pancreatitis
	Right upper quadrant tenderness	Cholecystitis
Extremity examination	Unilateral leg swelling, warmth, pain, tenderness, or erythema	PE
Neurologic examination	Focal findings	Aortic dissection
	Stroke	Acute MI
	Coronary ischemia	Aortic dissection, coronary spasm

JVD, jugular venous distention; *MI,* myocardial infarction; *PE,* pulmonary embolism.

TABLE 23.4

Ancillary Testing of Patients With Chest Pain

TEST	FINDING	DIAGNOSIS
ECG	New injury	Acute MI, aortic dissection
	New ischemia	Coronary ischemia, coronary spasm
	RV strain	PE
	Diffuse ST segment elevation	Pericarditis
CXR	Pneumothorax with mediastinal shift	Tension pneumothorax
	Wide mediastinum	Aortic dissection
	Pneumothorax	Esophageal rupture, pneumothorax
	Effusion	Esophageal rupture
	Increased cardiac silhouette	Pericarditis
	Pneumomediastinum	Esophageal rupture, mediastinitis
ABG	Hypoxemia, A-a gradient	PE
Spiral CT or $\dot{V}/\dot{Q}$ scan	High probability or any positive in patient with high clinical suspicion	PE

A-a, Alveolar-arterial; *ABG,* arterial blood gas; *CT,* computed tomography; *CXR,* chest x-ray examination; *ECG,* electrocardiography; *MI,* myocardial infarction; *PE,* pulmonary embolism; *RV,* right ventricular; *$\dot{V}/\dot{Q}$,* ventilation-perfusion.

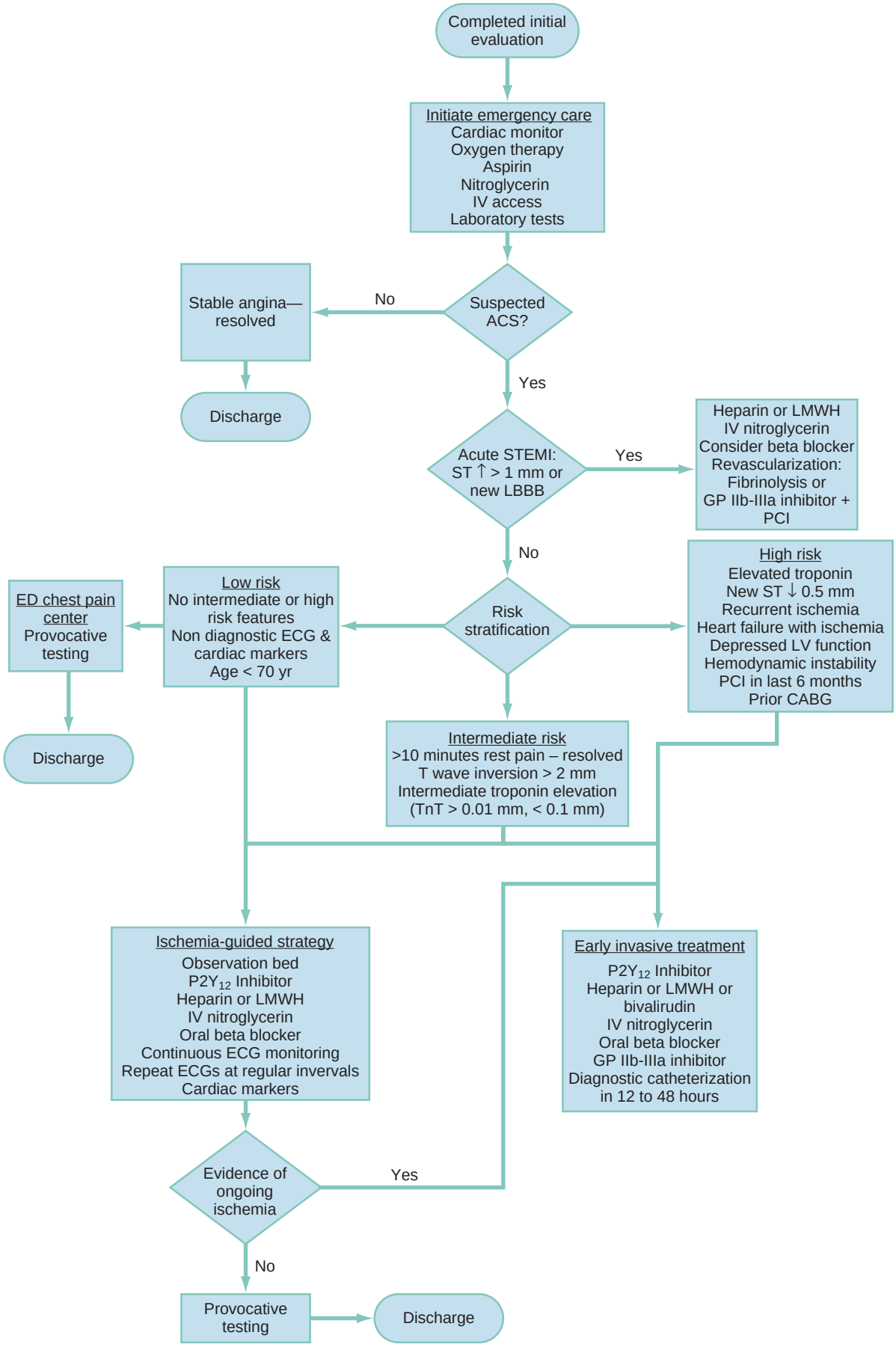

Fig. 23.2. Clinical guidelines for emergency department management of chest pain of myocardial ischemic origin. *ACS,* Acute coronary syndrome; *CABG,* coronary artery bypass graft; *ECG,* electrocardiogram; *ED,* emergency department; *GP,* glycoprotein; *IV,* intravenous; *LBBB,* left bundle branch block; *LMWH,* low-molecular-weight heparin; *LV,* left ventricular; *PCI,* percutaneous coronary intervention; *STEMI,* ST segment elevation myocardial infarction. (Adapted from Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: e344.)

pattern, in the appropriate setting, should raise the clinical suspicion for PE.[5] Diffuse ST segment elevation helps confirm the diagnosis of pericarditis.[6]

Chest radiography is performed for patients with a possibly serious cause of chest pain. Pneumothorax, pneumonia, empyema, and pleural effusion are definitively diagnosed at this point. A wide mediastinum or ill-defined aortic knob increases the clinical suspicion for acute aortic dissection. Pleural effusion, subcutaneous air, or mediastinal air-fluid level may be seen in esophageal rupture. An increased cardiac silhouette may indicate pericarditis or cardiomyopathy.

Pneumomediastinum is seen with esophageal rupture and mediastinitis. A serum D-dimer assay may help discriminate patients with PE from those with a possible gastrointestinal cause. A low serum D-dimer level in a patient without a high pretest probability of PE effectively excludes the diagnosis.[7] Patients with a low pretest probability who meet certain defined criteria do not require further testing (see Chapter 78).

Patients at high pretest probability for PE should undergo diagnostic imaging.[8] High pretest probability warrants initiation of anticoagulation (eg, with heparin or low-molecular-weight heparin) therapy in the ED before the imaging study in the absence of a contraindication.[9]

Patients with suspected thoracic aortic dissection may be evaluated by computed tomography (CT) angiography, transesophageal echocardiography, or magnetic resonance imaging. Selection of the imaging modality depends on the patient's clinical status and availability of the test modality.

A high-resolution (>64 slice) CT scanner can be used to rule out all the life-threatening causes of chest pain. Although ACS, PE, and thoracic dissection (the so-called triple rule-out) are the causes most commonly discussed, pneumothorax, mediastinitis, and pericardial effusions are also diagnosed with CT.

Laboratory testing is useful in the evaluation of ACS. An elevated troponin level in the correct clinical setting is synonymous with acute MI and is embedded in the universal definition of MI. Troponins (I and T), when elevated, identify patients with ACS who have the highest risk for an adverse outcome. Sensitivity for acute MI at 4 hours is approximately 50%, rising to nearly 100% by 12 hours. Creatine kinase (CK) and CK-MB are used only if determination of the troponin level is unavailable.[10]

TABLE 23.5

Electrocardiographic Findings in Ischemic Chest Pain

	FINDINGS
Classic myocardial infarction	ST segment elevation (>1 mm) in contiguous leads; new LBBB Q waves > 0.04-sec duration
Subendocardial infarction	T wave inversion or ST segment depression in concordant leads
Unstable angina	Most often normal or nonspecific changes; may see T wave inversion
Pericarditis	Diffuse ST segment elevation; PR segment depression

LBBB, left bundle branch block.

DIAGNOSTIC TABLE

After the patient is stabilized and assessment is completed, the findings are matched to the classical and atypical patterns of the seven potentially critical diseases causing chest pain. This matching process is continuous while the patient is evaluated and the response to therapy is monitored. Any inconsistency in findings with the primary working diagnoses necessitates a rapid review of the pivotal findings and the potential diagnoses (Table 23.6).

EMPIRICAL MANAGEMENT

The management of ACS is discussed in Chapter 68. Fig. 23.3 outlines the approach to treatment of critical noncardiac diagnoses. Patients with critical diagnoses generally are admitted to the intensive care unit. Patients with emergent diagnoses typically are

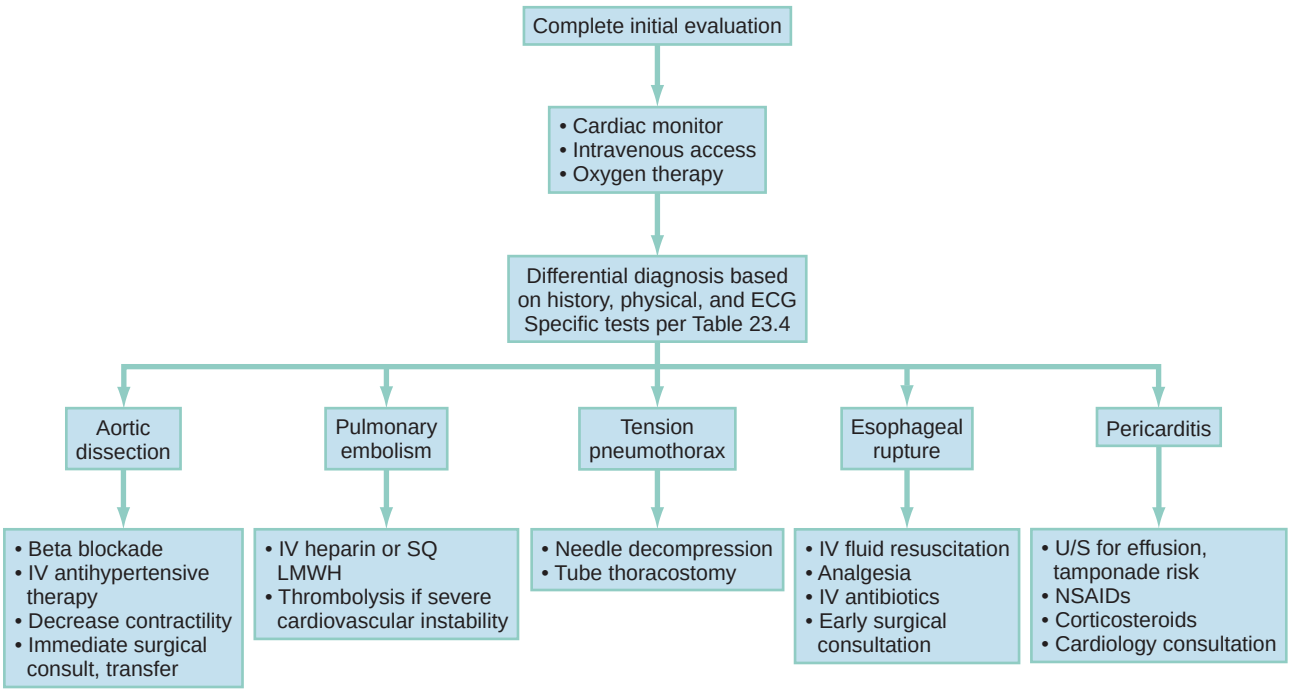

Fig. 23.3. Clinical guidelines for emergency department management of chest pain from potentially catastrophic nonmyocardial origins. *ECG,* Electrocardiogram; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *NSAIDs,* nonsteroidal antiinflammatory drugs; *SQ,* subcutaneous; *U/S,* ultrasound.

TABLE 23.6

Causes and Differentiation of Potentially Catastrophic Illness Manifesting With Central Chest Pain or Discomfort

	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN EMERGENCY DEPARTMENT	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
Myocardial infarction	Discomfort is usually moderately severe to severe and rapid in onset. May be more "pressure" than pain. Usually retrosternal, may radiate to neck, jaw, both arms, upper back, epigastrium, and sides of chest (left more than right). Lasts more than 15–30 min and is unrelieved by NTG.	Diaphoresis, nausea, vomiting, dyspnea.	May be precipitated by emotional stress or exertion. Often comes on at rest. May come on in early awakening period. Prodromal pain pattern often elicited. Previous history of MI or angina. Age >40 years, positive risk factors, and male sex increase possibility.	Common.	Patients are anxious and uncomfortable. Blood pressure usually is elevated, but normotension and hypotension are seen. The heart rate is usually mildly increased, but bradycardia can be seen. Patients may be diaphoretic and show peripheral poor perfusion. There are no diagnostic examination findings for MI, although S_3 and S_4 heart sounds and new murmur are supportive.	ECG changes (new Q waves or ST segment–T wave changes) occur in 80% of patients. CK-MB and troponins are helpful if elevated, but may be normal.	Pain may be reported as "indigestion" or "unable to describe." Other atypical presentations include altered mental status, stroke, angina pattern without extended pain, severe fatigue, syncope. Elderly may have weakness, congestive heart failure, or chest tightness. 25% of nonfatal MIs are unrecognized by patient. The pain may have resolved by the time of evaluation.
Unstable angina	Changes in pattern of preexisting angina with more severe, prolonged, or frequent pain (crescendo angina). Pain usually lasts >10 min. Angina at rest lasting 15–20 min or new-onset angina (duration <2 mo) with minimal exertion. Pattern of pain change important in gauging risk for AMI. Unpredictable responses to NTG and rest.	Often minimal. May have mild diaphoresis, nausea, dyspnea with pain. Increasing pattern of dyspnea on exertion.	Not clearly related to precipitating factors. May be a decrease in amount of physical activity that initiates pain. Previous history of MI or angina. Older than 40 years, presence of risk factors, and male sex increase probability.	Common.	Nonspecific findings of a transient nature; may have similar cardiac findings as in MI, especially intermittent diaphoresis.	Often no ECG or enzyme changes. Variant angina (Prinzmetal's) has episodic pain, at rest, often severe, with prominent ST segment elevation.	May be pain-free at presentation. Full history is essential. Fewer than 15% of patients hospitalized for unstable angina go on to acute MI. May respond to NTG. May manifest similarly to non–Q wave infarction.
Aortic dissection	90% of patients have rapid-onset severe chest pain that is maximal at beginning. Radiates anteriorly in chest to the back interscapular area or into abdomen. Pain often has a "tearing" sensation and may migrate.	Neurologic complications of stroke, peripheral neuropathy, paresis or paraplegia, abdominal and extremity ischemia possible.	Median age, 59 yr. History of hypertension in 70%–90% of patients. 3:1 ratio, males to females. Marfan syndrome and congenital bicuspid aortic valves have increased incidence.	Rare.	Often poorly perfused peripherally but with elevated BP. In 50%–60% of cases, there is asymmetric decrease or absence of peripheral pulses; 50% of proximal dissections cause aortic insufficiency. Other vascular occlusions—coronary (1%–2%), mesentery, renal, spinal cord. New-onset pericardial friction rub or aortic insufficiency murmur supportive of diagnosis.	ECG usually shows left ventricular hypertrophy, nonspecific changes. Chest film shows abnormal aortic silhouette (90%). Aortic angiography has diagnostic accuracy of 95%–99%. Transesophageal echocardiogram, CT, MRI most useful in screening.	Rare for patient to be pain-free. May have neurologic complications. Physical examination findings may be minimal. Dissection into coronary arteries can mimic MI. Ascending aortic aneurysms are more often approached surgically. Descending are generally managed medically.

Pulmonary embolism	Pain is more often lateral pleuritic. Central pain is more consistent with massive embolus. Abrupt in onset and maximal at beginning. May be episodic or intermittent.	Dyspnea and apprehension play a prominent role, often more than pain. Cough accompanies about 50% of cases. Hemoptysis occurs in <20%. Angina-like pain may occur in 5%.	Often some period of immobilization has occurred (eg, postoperative). Pregnancy, oral contraceptives, heart disease, and cancer are all risk factors. Previous DVT or PE is the greatest risk factor.	Uncommon in ambulatory patients but common in departments with high volumes of older or medically complex patients.	Patients are anxious and often have respiratory rate >16 breaths/min. Tachycardia, inspiratory rales, and an increased pulmonic second sound are common. Fever, phlebitis, and diaphoresis are seen in 30%–40% of patients. Wheezes and peripheral cyanosis are less common.	Arterial blood gases show Po_2 <80 mm Hg in 90%. Widened A-a gradient is helpful. Chest film is usually normal, although 40% show some volume loss, oligemia, or signs of consolidation caused by pulmonary infarction. Lung perfusion scan rules out, if truly negative.	Patients may have dyspnea, with or without bronchospasm. Acute mortality rate is 10%. Emboli usually from lower extremities above knee, prostate or pelvis venous plexus, right side of heart. May be subtle cause of COPD exacerbation.
Pneumothorax	Pain is usually acute and maximal at onset. Most often lateral pleuritic, but central pain can occur in large pneumothorax.	Dyspnea has a prominent role. Hypotension and altered mental states occur in tension pneumothorax.	Chest trauma, previous episode, or asthenic body type.	Infrequent.	Decreased breath sounds, increased resonance on percussion. Elevated pressure in neck veins occurs in tension pneumothorax.	Chest film definitive. Inspiratory and expiratory films may enhance contrast between air and lung parenchyma. Tension pneumothorax should be diagnosed on physical examination.	May be subtle in COPD, asthma, cystic fibrosis. Can be complicated by pneumomediastinum.
Esophageal rupture	Pain usually is preceded by vomiting and is abrupt in onset. Pain is persistent and unrelieved, localized along the esophagus, and increased by swallowing and neck flexion.	Diaphoresis, dyspnea (late), shock.	Older individual with known gastrointestinal problems. History of violent emesis, foreign body, caustic ingestion, blunt trauma, alcoholism, esophageal disease.	Rare.	Signs of lung consolidation, subcutaneous emphysema may be present.	Chest film usually has mediastinal air, a left-sided pleural effusion, pneumothorax, or a widened mediastinum. pH of pleural effusion < 6.0. Diagnosis supported by water-soluble contrast esophagram or esophagoscopy.	Patient may be in shock state. This entity often considered late in differential diagnostic process.
Pericarditis	Dull, aching recurrent pain unrelated to exercises or meals, or it may be a sharp, stabbing, pleuritic-type pain that does not change with chest wall motion. May be severe. Not relieved by NTG.	Dyspnea, diaphoresis.	Pain is often worse when supine but improves sitting up. Often preceded by viral illness or underlying disease (SLE or uremia).	Rare. Tamponade even more rare complication.	Friction rub may be heard, often fleeting, position-dependent (50% of patients).	ECG pattern typical for ST segment elevation across the precordial leads. Erythrocyte sedimentation rate may be elevated.	More common in 20- to 50-year-olds. May have associated tachycardias, ventricular dysrhythmias. Idiopathic most common (80%). Treated with aspirin, NSAIDs.

A-a, Alveolar-arterial; *AMI,* acute myocardial infarction; *BP,* blood pressure; *CK-MB,* an isoform of creatine kinase; *COPD,* chronic obstructive pulmonary disease; *CT,* computed tomography; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *MI,* myocardial infarction; *MRI,* magnetic resonance imaging; *NSAID,* nonsteroidal antiinflammatory drug; *NTG,* nitroglycerin; *PE,* pulmonary embolus; Po_2, partial pressure of oxygen; *SLE,* systemic lupus erythematosus.

admitted to the hospital, most often on telemetry units. Patients with nonemergent diagnoses are usually treated as outpatients. Hospitalization is required in certain cases, particularly when patients have other comorbid conditions.

Frequently, no definitive diagnosis is established. Any patient with almost any type of chest pain may be having coronary ischemia, PE, or aortic dissection. When a clear pattern does not emerge to allow the emergency clinician to make an alternative diagnosis confidently, or if the pattern of symptoms clearly is not compatible with a serious disorder, such as coronary ischemia, continued evaluation, hospitalization, or observation admission may be the best course.

KEY CONCEPTS

- Tension pneumothorax is a clinical diagnosis, treated with needle decompression, followed by tube thoracostomy.
- Patients with suspected ACS are risk-stratified by history, ECG, and troponin levels. Those with ST segment elevation myocardial infarction (STEMI) undergo fibrinolysis or percutaneous transluminal coronary angioplasty (PTCA). Those with non–ST segment elevation myocardial infarction (NSTEMI) do not require immediate PTCA. Those with a nondiagnostic ECG and troponin level are managed with observation.
- Thoracic dissection is diagnosed with CT angiography. The initial management of dissection is with urgent control of heart rate, followed by lowering of blood pressure. Further management, medical or surgical, depends on the location of the dissection.
- Pulmonary embolism is diagnosed using a combination of serum D-dimer measurement and imaging, usually CT angiography. Patients with a low pretest probability and normal D-dimer level do not have pulmonary embolism as the cause of their chest pain presentation.
- Patients with pericardial effusions undergo echocardiography to evaluate for cardiac tamponade. Those with signs of shock may require emergent pericardicentesis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 23: QUESTIONS & ANSWERS

23.1. A patient presents with the sudden onset of unilateral chest pain, followed almost immediately by respiratory distress. He is noted to have a blood pressure of 75/45 mm Hg, pulse of 130 beats/min, and decreased breath sounds on the right side of his chest. What is the most appropriate initial step in the management of this patient?
A. Administer intravenous (IV) antibiotics.
B. Infuse a 2-L bolus of normal saline.
C. Obtain a chest radiograph.
D. Obtain an electrocardiogram (ECG).
E. Perform a tube thoracostomy.

Answer: E. Tension pneumothorax is a critical diagnosis that must be made and remedied, if present, in the first few moments of the rapid stabilization and assessment phase of any patient encounter. If a patient presents with chest pain, respiratory distress, shock, and unilateral reduction or absence of breath sounds, immediate intervention with needle or tube thoracostomy is required.

23.2. A 65-year-old man with a past medical history of prostate cancer presents with chest pain. His blood pressure is 60/40 mm Hg, and his pulse is 145 beats/min. The ECG shows diffuse ST segment elevation, and cardiomegaly is seen on his chest radiograph. What is the most appropriate first step in the management of this patient?
A. Administration of dobutamine
B. Administration of dopamine
C. Cardiac catheterization
D. Cardiac ultrasonography
E. Thrombolysis

Answer: D. Prompt bedside cardiac ultrasonography would be the most appropriate next step in the management of this patient, who presents with symptoms and signs of pericardial effusion with tamponade. If confirmed by ultrasonography, immediate pericardiocentesis would logically follow in an effort to reverse the signs of shock in this patient. Other signs that could accompany the presentation are low voltage on the ECG and elevated jugular venous pressure on examination.

23.3. A "tearing" sensation is classically described for which of the following causes of chest pain?
A. Aortic dissection
B. Coronary spasm
C. Esophageal rupture
D. Mallory-Weiss tear
E. Pneumothorax

Answer: A. "Tearing" pain that may migrate from the front to back or back to front is classically described in aortic dissection. Descriptions such as "squeezing," "crushing," or "pressure" lead to the suspicion of a cardiac ischemic syndrome, although cardiac ischemia can be characterized by nonspecific discomfort, such as "bloating" or "indigestion." "Sharp" or "stabbing" pain is seen more in pulmonary and musculoskeletal diagnoses. Patients complaining of a burning- or indigestion-type of pain may initially be suspected of having a gastrointestinal cause; however, because of the visceral nature of chest pain, all causes of pain may present with any of the preceding descriptions.

23.4. Uremia is a risk factor associated with which of the following causes of chest pain?
A. Acute coronary syndrome
B. Aortic dissection
C. Pericarditis
D. Pneumothorax
E. Pulmonary embolism

Answer: C. Uremia is a risk factor for the development of pericarditis. Other risk factors associated with the development of pericarditis include infection, autoimmune disease, acute rheumatic fever, recent myocardial infarction or cardiac surgery, malignancy, radiation therapy to the mediastinum, and prior pericarditis.

23.5. A narrow pulse pressure is more closely associated with which of the following diagnoses?
A. Acute myocardial infarction
B. Aortic dissection
C. Pericarditis with effusion
D. Pneumothorax
E. Pulmonary embolism

Answer: C. A narrow pulse pressure is a pivotal finding in the diagnosis of pericarditis with associated pericardial effusion. Other characteristic, but less specific, potential findings in the patient with pericarditis include hypotension, tachycardia, fever, and jugular venous distention (JVD). The more specific finding of pericardial rub is also heard in some patients with pericarditis.

23.6. The finding of Hamman's sign is most consistent with which of the following?
A. Cholecystitis
B. Mediastinitis
C. Pericarditis

D. Pulmonary embolus
E. Unstable angina

Answer: B. Hamman's sign is an audible systolic "crunch" heard on cardiac auscultation that is produced by the heart moving against air in the mediastinum. This can be heard in conditions such as esophageal rupture, mediastinitis, and pneumomediastinum.

23.7. Right ventricular strain on the ECG of a patient complaining of chest pain would be most consistent with which of the following diagnoses?
A. Acute myocardial infarction
B. Coronary ischemia
C. Coronary spasm
D. Pericarditis
E. Pulmonary embolus

Answer: E. In the setting of chest pain, right ventricular strain as evidenced on the ECG is highly suspicious for pulmonary embolus.

23.8. The ECG finding of PR segment depression would be more commonly found in which of the following causes of chest pain?
A. Pericarditis
B. Pulmonary embolus
C. ST segment elevation myocardial infarction (STEMI)
D. Subendocardial infarction
E. Unstable angina

Answer: A. The electrocardiographic findings most commonly associated with pericarditis are diffuse ST segment elevation and PR segment depression. The ECG in patients with unstable angina is most often normal or nonspecific. T wave inversion may be seen in these patients. The characteristic ECG findings with subendocardial infarction are T wave inversion and/or ST segment depression in concordant leads. Classic STEMI is manifested electrocardiographically by ST segment elevation (>1 mm) in contiguous leads, a new left bundle branch block (LBBB), or Q waves 0.04 second or more in duration. Many possible electrocardiographic findings are associated with pulmonary embolus, usually manifestations of right ventricular strain.

CHAPTER 24

Abdominal Pain

Kurt A. Smith

PERSPECTIVE

Abdominal pain is often diagnostically challenging. The nature and quality of the pain may be difficult for the patient to convey. Physical examination findings are variable and can be misleading. The location and severity of the pain may change over time. What seems like benign symptoms may represent a life-threatening condition; conversely, patients with severe symptoms may carry a relatively benign diagnosis.

Epidemiology

Abdominal pain is an extremely common emergency department (ED) presentation and is most often a symptom of a benign process. In certain populations of patients, however, the ratio of serious causes to benign causes is much higher than in the average young, healthy adult. These patients require a more diligent search for potentially serious disorders, masquerading as routine abdominal pain, often involving advanced imaging or prolonged observation. Box 24.1 identifies patients at higher risk for serious pathology when presenting with abdominal pain.

Older patients with acute abdominal pain are more likely to have a serious process as the cause of their pain. Conditions such as appendicitis, diverticulitis, ruptured abdominal aneurysm, and mesenteric ischemia are more common in this population, may manifest atypically, and can be rapidly progressive. Decreased diagnostic accuracy, coupled with increased probability of severe disease results in increased mortality in elderly patients with abdominal pain.

Presentations in the immunocompromised patient may be highly variable and subtle and are discussed in Chapter 187. Disproportionately mild symptomatology, atypical physical findings (such as, lack of focal tenderness), or misleading laboratory findings (eg, elevated transaminases, elevated or depressed white blood cell [WBC] counts) may confound making the diagnosis.

Patients with prior bariatric surgery are at particular risk for adhesions, internal hernias, and anastomotic breakdown. Evaluation of these patients often requires consultation by a bariatric surgeon.

Abdominal pain in women involves a broader differential diagnosis that includes the reproductive tract thus requiring a more in-depth diagnostic testing evaluation. Pelvic organs may be the source of pathology in both the pregnant and the non-pregnant patient. Abdominal pain in the context of a positive pregnancy test warrants special concern for ectopic pregnancy or atypical presentation of routine disease, especially appendicitis. During pregnancy, the uterus becomes an abdominal rather than a pelvic organ and may displace the normal intraperitoneal contents, adding complexity to the evaluation of these patients. Pregnancy also adds consideration of possible harm to the fetus in determining appropriate imaging modalities.

Pathophysiology

Pathology in the gastrointestinal and genitourinary tracts remains the most common source of pain perceived in the abdomen. Evaluation of the entire patient history and physical examination is important, however, because abdominal pain also can arise from a multitude of extra-abdominal causes, particularly diseases of the thorax and spinal nerve roots, or a systemic disorder, such as diabetic ketoacidosis. Abdominal pain is perceived through one or more of three distinct pain pathways: visceral, somatic, and referred.

Visceral pain result from stimulation of autonomic nerves invested in the visceral peritoneum surrounding internal organs and is usually the earliest manifestation of a disease process. Distention of hollow organs by fluid or gas and capsular stretching of solid organs by edema, blood, masses, or abscesses are the most common stimuli. This discomfort is poorly characterized and difficult to localize. If the involved organ is affected by peristalsis, the pain often is described as intermittent, crampy, or colicky. In general, visceral pain is perceived from the abdominal region that correlates with the embryonic somatic segment, as follows:

- *Foregut* structures (stomach, duodenum, liver, gallbladder, and pancreas) are associated with *upper abdominal pain.*
- *Midgut* derivatives (small bowel, proximal colon, and appendix) are associated with *periumbilical pain.*
- *Hindgut* structures (distal colon and genitourinary tract) are associated with *lower abdominal pain.*

Visceral pain is poorly localized and can be perceived in a location remote from the actual disease process. Localization occurs with the extension of the disease process beyond the viscera, which allows engagement of somatic sensation, and the location of the pathologic process becomes more reliable. A classic example is that of the early periumbilical (visceral) pain of appendicitis. When the parietal peritoneum becomes involved, the (somatic) pain localizes to the right lower quadrant of the abdomen.

Somatic pain occurs with irritation of the parietal peritoneum. This is caused by infection, chemical irritation, injury, hemorrhage, or another inflammatory process. Sensation is conducted by the peripheral nociceptive nerves in the area. Figure 24.1 illustrates some more typical pain locations corresponding to specific disease entities. Somatic pain is often described as intense and constant.

Referred pain is defined as pain felt remotely from its source because peripheral afferent nerve fibers from many internal organs enter the spinal cord through nerve roots that also carry fibers from other locations, as illustrated in Figure 24.2. This confounds interpretation of the location of noxious stimuli for the brain. Both visceral pain and somatic pain can manifest as referred pain. Understanding the pathophysiology of referred pain broadens the differential diagnosis to include adjacent anatomical areas: the thorax for upper abdominal pain, and the hips and retroperitoneum for lower abdominal pain. Examples of referred pain are epigastric pain associated with an inferior myocardial infarction, shoulder pain associated with free peritoneal blood irritating the diaphragm, pain originating from the hips being experienced as pelvic pain, and lower lobe pneumonia causing upper abdominal pain. Finally, some metabolic disorders and "toxidromes" may manifest with abdominal pain.

BOX 24.1

Patients at Higher Risk for Serious Underlying Disorders

Age older than 60 years old
Previous abdominal surgery including obesity surgery
History of inflammatory bowel disease
Recent instrumentation (eg, colonoscopy with biopsy)
Known abdominal/pelvic/retroperitoneal malignancy
Active chemotherapy
Immunocompromised, including low dose prednisone
Fever, chills, systemic symptoms
Women of childbearing age
Recent immigrants
Language or cognitive barrier

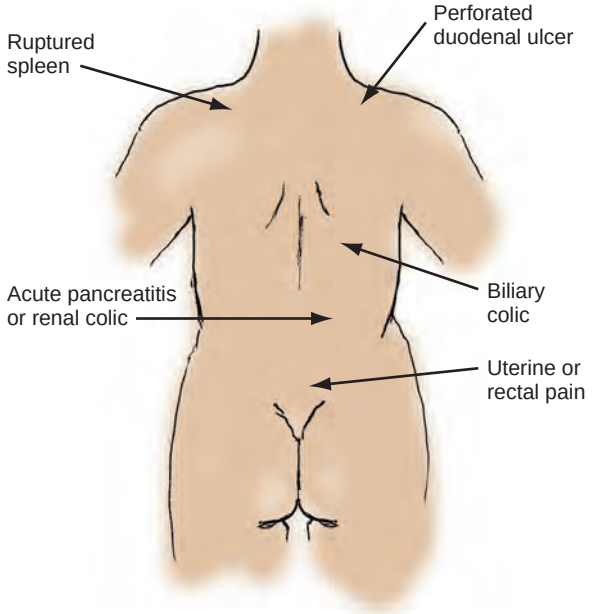

Fig. 24.2. Common locations of referred pain from abdominal cause.

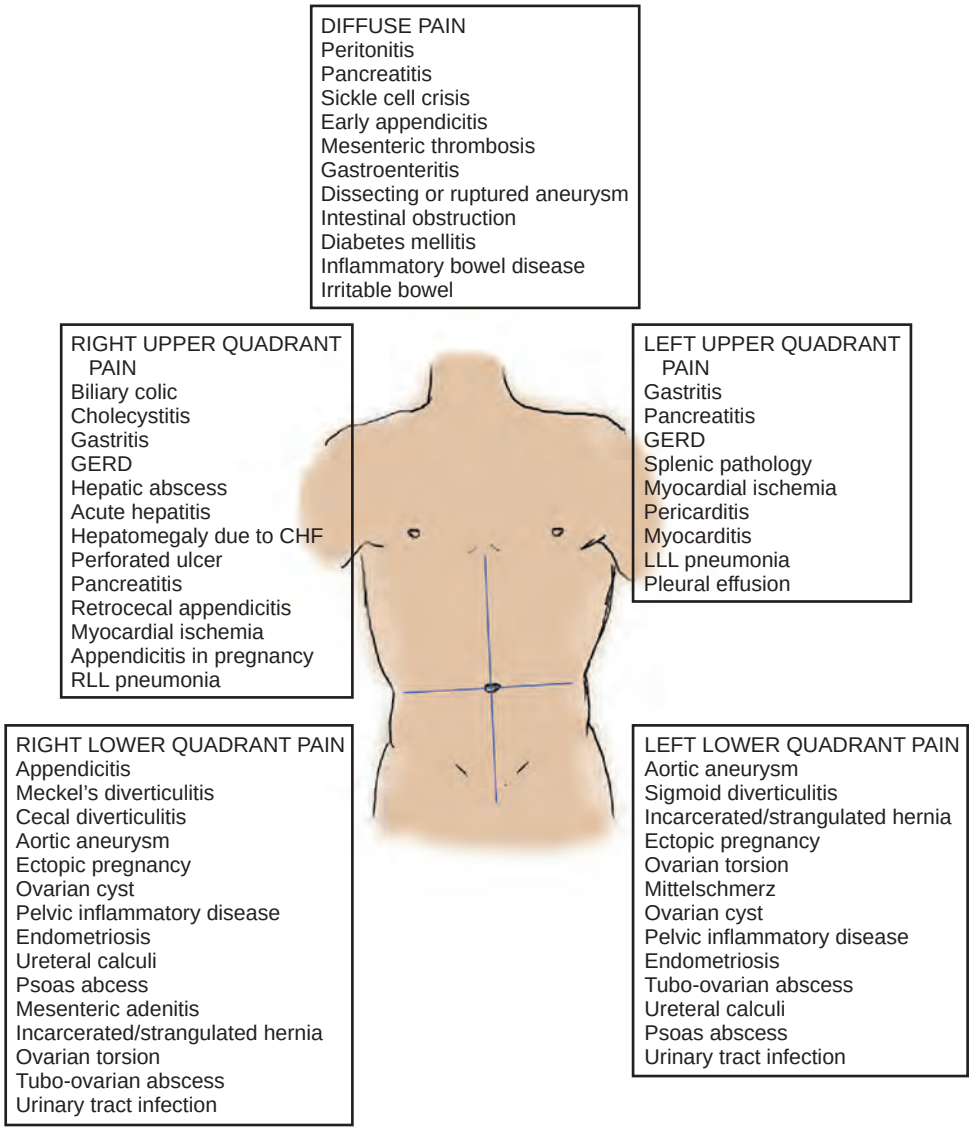

Fig. 24.1. Differential diagnosis of acute abdominal pain by location. *CHF,* Congestive heart failure; *GERD,* gastroesophageal reflux disease; *LLL,* left lower lobe; *RLL,* right lower lobe.

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

The differential diagnosis of abdominal pain is divided into abdominopelvic (intraperitoneal, retroperitoneal, and pelvic) causes (eg, appendicitis, cholecystitis, pancreatitis) and non-abdominopelvic processes (eg, pneumonia, myocardial infarction, ketoacidosis, toxicologic, abdominal wall pain). Table 24.1 lists important potentially life-threatening nontraumatic causes of abdominal pain. This group represents the major causative disorders likely to be associated with hemodynamic compromise and for which early therapeutic intervention is critical. More common emergent conditions that cause abdominal pain are listed in Table 24.2.

Rapid Assessment and Stabilization

Although most patients with abdominal pain do not have hemodynamic instability, patients with vital sign abnormalities require prompt evaluation and resuscitation. Elders and immunocompromised patients may present with normal vital signs despite life-threatening etiologies and, therefore, warrant particular scrutiny. Signs of volume depletion indicate the need for volume replacement, which may be oral or parenteral. Hemodynamic instability caused by conditions such as ruptured abdominal aortic aneurysm, massive gastrointestinal hemorrhage, ruptured ectopic pregnancy, ruptured spleen, and hemorrhagic pancreatitis may necessitate blood or blood product replacement.

Bedside ultrasonography can be used to quickly evaluate patients for free intraperitoneal fluid, volume status, and presence of aortic pathology. Ultrasound assessment is part of the initial physical examination and can be invaluable in guiding treatment and disposition. Early surgical consultation is indicated when there is identified intra-abdominal hemorrhage (hemodynamic compromise plus ultrasound evidence of intraperitoneal fluid), suspected aortic aneurysm rupture, or free air within the peritoneum.

Pivotal Findings

Symptoms

A careful and focused history is central to determining the source of abdominal pain. Language and cultural differences may influence accurate communication and mutual understanding; therefore use of an appropriate medical interpreter is essential key component of evaluation of a non-English speaking patient.

In general, abrupt onset and progressive symptoms and severe pain, especially if accompanied by nausea, vomiting, or diaphoresis, suggest a serious underlying cause. Localization and pain migration also are helpful components of the pain history, because they can highlight specific processes. Diffuse pain, particularly crampy pain that migrates and has periods of minimal or no symptoms, generally is nonsurgical. Poorly localized pain may represent the early visceral component of a surgical process, however, so progression of symptoms is important. Colicky pain is indicative of hollow viscus distention, and duration and time of colic may give clues to the identity of the culprit organ, as displayed in Figure 24.3.

The severity and descriptive nature of the pain are subjective, but a few descriptions are classic, for example:

- The diffuse, severe, colicky pain associated with severe nausea in bowel obstruction
- The "pain out of proportion to examination" (ie, severe pain that is not readily reproduced with palpation) observed in patients with mesenteric ischemia

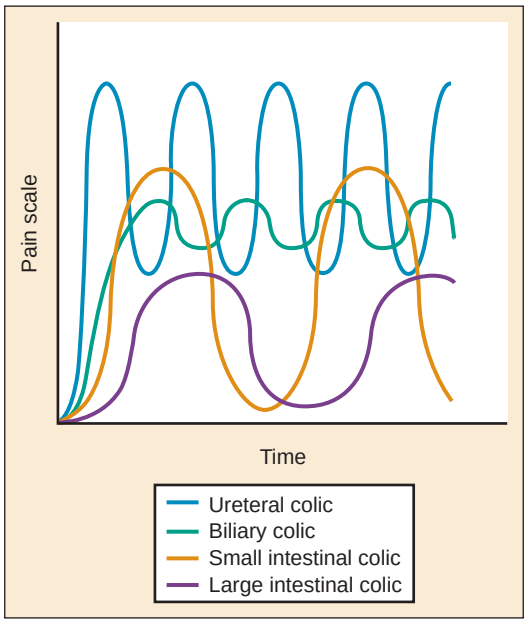

Fig. 24.3. The characteristics of colicky abdominal pain.

- The radiation of pain from the epigastrium straight through to the midback, almost invariably accompanied by nausea and vomiting associated with acute pancreatitis
- The radiation of pain to the left shoulder or independent pain in the left shoulder associated with splenic pathology, diaphragmatic irritation, or free intra-peritoneal fluid
- The onset of pain associated with syncope seen in ruptured aortic aneurysm or ruptured ectopic pregnancy

A thorough review of the patient's past medical history and medications frequently provides key information. A history of immunocompromised state or immunosuppressive medications may point to infection. A patient undergoing anticoagulation therapy or taking nonsteroidal antiinflammatory drugs (NSAIDs) may point to gastrointestinal bleeding. Diabetics may be experiencing abdominal pain as a feature of ketoacidosis. A patient undergoing chronic opioid therapy may have constipation or even a bowel obstruction. A patient with previous abdominal surgery may have adhesions with obstruction. Inflammatory bowel disease may lead to fistula, perforation, or abscess.

Signs

The objective evaluation begins with measurement of the vital signs. Significant tachycardia and hypotension are indicators that hypovolemia or sepsis may be present. Tachypnea in the absence of hypoxemia may be an indication of metabolic acidosis from gangrenous viscera or sepsis, or simply a catecholamine-induced reaction to pain. Elevated temperature is associated with intra-abdominal infections. Although important, vital signs may be misleading and should be interpreted in the context of the entire presentation. Tachycardia may develop late for various reasons in hypovolemia. Temperature often is normal in elderly patients with laparotomy-proven intraperitoneal infections, or patients with sepsis also may demonstrate hypothermia.

A thorough abdominal examination is an essential part of evaluating abdominal pain. This requires properly positioning the patient supine and exposing the abdomen. The examination begins with inspection for any signs of trauma, bruising, or skin lesions. Ask the patient to localize the area of maximal tenderness by pointing with one finger, and then examine each quadrant of the abdomen individually, examining the culprit area last.

TABLE 24.1

Critical Causes of Abdominal Pain

CAUSE	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TOOL(S)
Ruptured ectopic pregnancy	Occurs in females of childbearing age. No method of contraception prevents ectopic pregnancy. Approximately 1 in every 100 pregnancies.	Risk factors include nonwhite race, older age, history of STD or PID, infertility treatment, intrauterine contraceptive device placed within the past year, tubal sterilization, and previous ectopic pregnancy.	Severe, sharp constant pain localized to the affected side. More diffuse abdominal pain with intraperitoneal hemorrhage. Signs of shock may be present. Midline pain tends not to be ectopic pregnancy.	Shock or evidence of peritonitis may be present. Lateralized abdominal tenderness. Localized adnexal tenderness or cervical motion tenderness increases the likelihood of ectopic pregnancy. Vaginal bleeding does not have to be present.	β-hCG testing is necessary in all females of childbearing age (10 to 55 years old); combined with ultrasonography, preferably transvaginal in early pregnancy, usually is diagnostic. FAST examination is useful in evaluating for free fluid in patients with shock or peritonitis.
Ruptured or leaking abdominal aneurysm	Incidence increases with advancing age. More frequent in men. Risk factors include HTN, DM, smoking, COPD, and CAD.	Exact cause is undetermined. Contributing factors include atherosclerosis, genetic predisposition, HTN, connective tissue disease, trauma, and infection.	Patient is often asymptomatic until rupture. Acute epigastric and back pain is often associated with or followed by syncope or signs of shock. Pain may radiate to back, groin, or testes.	Vital signs may be normal (in 70%) to severely abnormal. Palpation of a pulsatile mass is usually possible in aneurysms 5 cm or greater. The physical examination may be nonspecific. Bruits or inequality of femoral pulses may be evident.	Abdominal plain films are abnormal in 80% of cases. Ultrasound can define diameter and length but can be limited by obesity and bowel gas. FAST examination can be helpful in evaluating for leak by looking for free fluid. Spiral CT test of choice in stable patients.
Mesenteric ischemia	Occurs most commonly in elders with CV disease, CHF, cardiac dysrhythmias, DM, sepsis, and dehydration. Mortality is 70%. Mesenteric venous thrombosis is associated with hypercoagulable states, hematologic inflammation, and trauma.	20% to 30% of lesions are nonocclusive. The causes of ischemia are multifactorial, including transient hypotension in the presence of preexisting atherosclerotic lesion. The arterial occlusive causes (65%) are secondary to emboli (75%) or acute arterial thrombosis (25%).	Pain can be severe and colicky starting in the periumbilical region and then becomes diffuse. Often associated with vomiting and diarrhea. Sometimes postprandial ie, "mesenteric or abdominal angina."	Early examination results can be remarkably benign in the presence of severe ischemia. Bowel sounds are often still present. Rectal examination is useful because mild bleeding with positive guaiac stools can be present.	Often a pronounced leukocytosis is present. Elevations of amylase and creatine kinase levels are seen. Metabolic acidosis caused by lactic acidemia is often seen with infarction. Plain radiographs are of limited benefit. CT, MRI, and angiography are accurate to varying degrees.
Intestinal obstruction	Peaks in infancy and in the elderly. More common with history of previous abdominal surgery.	Adhesions, carcinoma, hernias, abscesses, volvulus, and infarction. Obstruction leads to vomiting, "third spacing" of fluid, or strangulation and necrosis of bowel.	Crampy diffuse abdominal pain associated with vomiting.	Vital signs are usually normal unless dehydration or bowel strangulation has occurred. Abdominal distention, hyperactive bowel sounds, and diffuse tenderness. Local peritoneal signs indicate strangulation.	Elevated WBC count suggests strangulation. Electrolytes may be abnormal if associated with vomiting or prolonged symptoms. Abdominal radiographs and CT are useful in diagnosis.
Perforated viscus	Incidence increases with advancing age. History of peptic ulcer disease or diverticular disease common.	More often a duodenal ulcer that erodes through the serosa. Colonic diverticula, large bowel, and gallbladder perforations are rare. Spillage of bowel contents causes peritonitis.	Acute onset of epigastric pain is common. Vomiting in 50%. Fever may develop later. Pain may localize with omental walling off of peritonitis. Shock may be present with bleeding or sepsis.	Fever, usually of low grade, is common; worsens over time. Tachycardia is common. Abdominal examination reveals diffuse guarding and rebound. "Board-like" abdomen in later stages. Bowel sounds are decreased.	WBC count is usually elevated owing to peritonitis. Amylase may be elevated; LFT results are variable. The upright radiographic view reveals free air in 70% to 80% of cases with perforated ulcers.

TABLE 24.1

Critical Causes of Abdominal Pain—cont'd

CAUSE	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TOOL(S)
Massive gastrointestinal bleeding	More common in older adults ages 40 to 70.	History of peptic ulcer disease, gastritis, or liver disease; prior GI bleeding history. Not typically caused by Mallory-Weiss tears, which typically can occur in the stomach but rarely cause severe bleeding.	Nausea and vomiting typically occur with upper GI bleeds with hallmark coffee-ground or hematemesis; lower GI bleeds associated with poorly localized discomfort and bright red blood per rectum; slow transit can lead to melena.	Non-focal abdominal tenderness; large bleeds may result in tachycardia and hypotension with enough blood loss. Hemoglobin/hematocrit is rarely abnormal in acute, massive bleeds.	Stool or gastric guaiac if there is a question of bleeding; massive bleeds may require emergent consultation by gastroenterology or surgery to intervene.
Acute pancreatitis	Peak age is adulthood; rare in children and elders. Male preponderance. Alcohol abuse and biliary tract disease are risk factors.	Alcohol, gallstones, hyperlipidemia, hypercalcemia, or endoscopic retrograde pancreatography causing pancreatic damage, saponification, and necrosis. ARDS, sepsis, hemorrhage, and renal failure are secondary.	Acute onset of epigastric pain radiating to the mid-back. Nausea and vomiting are common. Pain disproportionate to physical findings. Adequate volume repletion is important in the initial therapy.	Low-grade fever is common. Patient may be hypotensive or tachypneic. Some epigastric tenderness is usually present. Because pancreas is retroperitoneal organ, guarding or rebound not present unless condition is severe. Flank ecchymosis or periumbilical ecchymosis may be seen if process is hemorrhagic.	Serum lipase is the test of choice. Ultrasound examination may show edema, pseudocyst, or biliary tract disease. CT scan may show abscesses, necrosis, hemorrhage, or pseudocysts. Ultrasound is recommended to assess for gallstones while CT is recommended if severe acute pancreatitis is suspected.

ARDS, Acute respiratory distress syndrome; *β-hCG,* beta-human chorionic gonadotropin; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *CT,* computed tomography; *CV,* cardiovascular; *DM,* diabetes mellitus; *FAST,* focused assessment with sonography in trauma; *GI,* gastrointestinal; *HTN,* hypertension; *LFT,* liver function test; *MRI,* magnetic resonance imaging; *PID,* pelvic inflammatory disease; *STD,* sexually transmitted disease; *WBC,* white blood cell.

TABLE 24.2

Emergent Causes of Abdominal Pain

CAUSATIVE DISORDER OR CONDITION	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TEST(S)
Gastric, esophageal, or duodenal inflammation	Occurs in all age groups.	Caused by gastric hypersecretion, breakdown of mucoprotective barriers, infection, or exogenous sources.	Pain is epigastric, radiating or localized, associated with certain foods. Pain may be burning. In some cases, exacerbation in supine position.	Epigastric tenderness without rebound or guarding. Perforation or bleeding leads to more severe clinical findings.	Uncomplicated cases are treated with antacids or histamine H_2 blockers before invasive studies are contemplated. Gastroduodenoscopy is valuable in diagnosis and biopsy. Testing for *Helicobacter pylori* with blood or biopsy specimens. If perforation is suspected, an upright chest radiograph is obtained early to rule out free air. CT may be beneficial.

Continued

TABLE 24.2

Emergent Causes of Abdominal Pain—cont'd

CAUSATIVE DISORDER OR CONDITION	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TEST(S)
Acute appendicitis	Peak age in adolescence and young adulthood; less common in children and elders. Higher perforation rate in women, children, and elders and in pregnancy. Mortality rate is 0.1% but increases to 2% to 6% with perforation.	Appendiceal lumen obstruction leads to swelling, ischemia, infection, and perforation.	Epigastric or periumbilical pain migrates to RLQ over 8 to 12 hours (50% to 60%). Later presentations associated with higher perforation rates. Pain, low-grade fever (15%), and anorexia (80%) common; vomiting less common (50% to 70%).	Mean temperature 38° C (100.5° F). Higher temperature associated with perforation. RLQ tenderness (90% to 95%) with rebound (40% to 70%) in majority of cases. Rectal tenderness in 30%.	Leukocyte count is nonspecific and may be normal or elevated. If elevated, may or may not show left shift. Urinalysis may show sterile pyuria. CT is sensitive and specific. US may have use in those with normal body habitus (non-obese), women, pregnancy, and children with RLQ pain.
Biliary tract disease	Peak age 35 to 60 years old; unlikely in patients younger than 20. Female-to-male ratio of 3:1. Risk factors include multiparity, obesity, alcohol intake, and use of birth control pills.	Passage of gallstones causes biliary colic. Impaction of a stone in cystic duct or common duct leads to cholecystitis or cholangitis.	Crampy RUQ pain radiates to right subscapular area. Prior history of pain is common. May have nausea or postprandial pain. Longer duration of pain favors diagnosis of cholecystitis or cholangitis.	Temperature is normal in biliary colic, elevated in cholecystitis and cholangitis. RUQ tenderness, rebound, and jaundice (less common) may be present.	WBC is count elevated in cholecystitis and cholangitis. Lipase and liver function tests may help differentiate this from gastritis or ulcer disease. US shows wall thickening, pericholecystic fluid, stones, or duct dilatation. Hepatobiliary scintigraphy diagnoses gallbladder function.
Ureteral colic	Average age for first episode is 30 to 40 years old, primarily in men. Prior history or family history of stones is common.	Family history, gout, *Proteus* infection. Renal tubular acidosis and cystinuria lead to stone formation.	Acute onset of flank pain radiating to groin. Nausea, vomiting, and pallor are common. Patients are usually writhing in pain.	Vital signs are usually normal. Tenderness on CVA percussion with benign abdominal examination.	Urinalysis usually shows hematuria. Noncontrast CT is sensitive and specific. US with fluid bolus useful diagnostically.
Diverticulitis	Incidence increases with advancing age, affects males more often than females. Recurrences are common.	Colonic diverticula may become infected or perforated or cause local colitis. Obstruction, peritonitis, abscesses, fistulae result from infection or swelling.	Change in stool frequency or consistency commonly reported. LLQ pain is common. Associated with fever, nausea and vomiting; rectal bleeding may be seen.	Fever usually of low grade. LLQ pain without rebound is common. Stool may be heme positive.	Results on most tests usually normal. Plain radiographs not indicated. CT is diagnostic, but diagnosis is often made clinically, without imaging.
Acute gastroenteritis	Seasonal. Most common misdiagnosis of appendicitis. May be seen in multiple family members. History of travel or immunocompromise. Most common GI disease in the United States.	Usually viral. Consider invasive bacterial or parasitic cause in prolonged cases, in travelers, or immunocompromised patients.	Pain usually poorly localized, intermittent, crampy, and diffuse. Diarrhea is key element in diagnosis; usually large volume, watery. Nausea and vomiting usually begin before pain.	Abdominal examination usually nonspecific without peritoneal signs. Watery diarrhea or no stool noted on rectal examination. Fever is usually present.	Usually symptomatic care with antiemetics and volume repletion. Heme-positive stools may be a clue to invasive pathogens. Key is not using this as a "default" diagnosis and missing more serious disease.
Constipation and obstipation	More common in females, elders, the very young, and patients on narcotics.	Idiopathic or hypokinesis secondary to disease states (low motility) or exogenous sources (diet, medications).	Abdominal pain; change in bowel habits.	Variable, nonspecific without peritoneal signs. Rectal examination may reveal hard stool or impaction.	Radiographs may show large amounts of stool. This is a diagnosis of exclusion.

CT, Computed tomography; *CVA,* costovertebral angle; *GI,* gastrointestinal; *LLQ,* left lower quadrant; *RLQ,* right lower quadrant; *RUQ,* right upper quadrant; *US,* ultrasonography; *WBC,* white blood cell.

Tenderness in one quadrant often corresponds with the location of the diseased organ, which will direct the evaluation (see Fig. 24.1). Some disease processes may manifest with pain that is not exclusively within one specific quadrant, such as the suprapubic pain of a urinary tract infection or the midepigastric pain of a gastric ulcer. Although most patients with proven appendicitis have right lower quadrant abdominal tenderness, some patients, particularly elders, those with immunocompromise, and women with advanced pregnancy do not.

A rectal examination has limited use in the evaluation of abdominal pain, except when there is suspicion of gastrointestinal hemorrhage (which usually is not associated with pain), prostatitis, or perirectal disease. The main utility of the rectal examination is in the detection of melena or heme-positive stool, anal fissures or fistulae, stool impaction, or the empty vault associated with bowel obstruction. Rectal examination has not been shown to increase diagnostic accuracy for any cause of abdominal pain, including appendicitis.

For female patients, abdominal evaluation should include a pelvic examination when there is pain or tenderness below the umbilicus. Findings on pelvic examination help differentiate an abdominal from a pelvic source, thus guiding the selection of imaging modality. Pelvic ultrasound examination is superior to computed tomography (CT) scanning in evaluating uterine and ovarian pathology, whereas CT is superior for evaluation of suspected intra-abdominal pathology. Although the pelvic examination may guide the initial choice of imaging modality, overlap in examination findings is common. For example, a patient with right lower quadrant tenderness may have both right adnexal tenderness and tenderness over McBurney's point, necessitating exclusion of both appendicitis and tubal or ovarian pathology. The diagnosis felt most likely guides the selection and sequencing of imaging.

In most male patients with abdominal pain, a urogenital examination is important. Diseases such as prostatitis, orchitis, and epididymitis commonly cause abdominal pain in males. Testicular torsion is notoriously under-diagnosed as a cause of lower abdominal pain in adolescents and young men. Furthermore, inguinal hernias are more common in males, with the possibility of strangulation or incarceration in the inguinal canal.

In view of the evolving nature of abdominal pain, repetitive examinations are useful. This is common practice with respect to suspected appendicitis and has improved the diagnostic accuracy in patients with atypical presentations.

Ancillary Testing

Urinalysis and testing for pregnancy are perhaps the most time- and cost-effective adjunctive laboratory tests available. Urinalysis results are interpreted within the context of the patient's clinical picture. Pyuria, with or without bacteriuria, often may confirm the diagnosis of urinary tract infection but also is present in a variety of other conditions, such as appendicitis. Similarly, hematuria is present in the vast majority of patients with nephrolithiasis but also may be seen with cystitis, a much less serious condition, or renal vein occlusion, a much more serious disorder.

A complete blood count (CBC) is often useful in the evaluation of patients with abdominal pain. Of these, the WBC is the most often referenced, despite its lack of diagnostic accuracy. A WBC count seldom contributes to the correct diagnosis of a patient with abdominal pain and often is misleading. Despite the association of elevated WBC counts with many infectious and inflammatory processes, the WBC count is neither sufficiently sensitive nor specific to be considered a discriminatory test to help establish or exclude a specific cause for the pain. The WBC count is within normal range in a significant percentage of patients with serious (surgical) pathology and may be elevated in patients with benign conditions, including gastroenteritis. The CBC is not entirely without use, however. A depressed WBC count may indicate immunocompromise, reduced hematocrit may indicate blood loss, and thrombocytopenia may identify patients with sepsis, alcoholism, or other disorders. Serum electrolytes, even in the presence of protracted emesis or diarrhea, are frequently normal, but excessive electrolyte losses in vomiting and diarrhea can lead to a contraction alkalosis from excessive chloride and potassium loss, indicating the need for volume replenishment, if that is not otherwise clinically obvious. Blood glucose, anion gap, and serum ketone determinations are useful in distinguishing diabetic ketoacidosis. Ultimately, serum electrolytes are useful adjuncts in assessing the patient but rarely provide a diagnosis.

Liver enzymes and coagulation studies are helpful only in a small subset of patients with suspected liver disease. If pancreatitis is suspected, the most useful diagnostic test is a serum lipase elevated to at least double the normal value. Serum amylase is not as reliable as serum lipase and is no longer used for the diagnosis of acute pancreatitis. Serum lactate levels are elevated in states leading to decreased tissue or organ perfusion, such as sepsis. Lactate often is elevated late in bowel ischemia, but a normal lactate level cannot be used to exclude bowel ischemia.[1]

Plain radiography of the abdomen has limited usefulness in the evaluation of acute abdominal pain and should be performed only when bowel obstruction or a radiopaque foreign body is suspected and there is no intent to obtain a CT scan. For suspected perforated hollow viscus, an upright chest radiograph is a better study than an abdominal film to rapidly assess for free air, but the primary role for a chest radiograph is to exclude or diagnose an intrathoracic cause of the patient's presentation. CT of the abdomen has become the imaging modality of choice with non-obstetric, non-biliary abdominal pain, and should be the first modality used when imaging is required. The CT scan visualizes both intraperitoneal and retroperitoneal structures and has a high degree of accuracy. When biliary or female reproductive disease is suspected, ultrasound is a superior modality.

CT has increased diagnostic utility in elderly patients for several reasons. The elderly with abdominal pain is significantly more likely to require surgery and have an increased mortality compared with younger adults. Furthermore, evaluation of abdominal pain in elders often is more challenging because of difficulties in history taking, unreliable or variable findings on physical examination (including vital signs), physiologic age-related changes, and comorbid conditions. In the elderly population, CT results change management or disposition decisions in a significant proportion of patients.

Technologic advances have improved image acquisition and resolution, and several studies have shown that intravenous (IV) contrast alone is adequate in the evaluation of most suspected pathologic processes, such as solid organ or bowel wall disease. CT with IV contrast alone also has been shown to be sensitive and specific for the confirmation or exclusion of acute appendicitis. The exclusion of oral contrast in these patients can significantly decrease time to disposition and improve patient satisfaction; however, sensitivity and specificity of all CT studies tends to increase with the addition of different contrast media. In looking for appendicitis, for example, several studies have shown that oral and IV contrast increases sensitivity and specificity, but only marginally above CT without contrast.[2] Oral contrast is more valuable in assessing for ulceration, perforation, or inflammatory bowel disease; and IV contrast is useful in determining inflammation and increased vascularity. Protocols tend to be specific to the machines available at an institution and radiologist preference but should be tailored to getting accurate diagnosis in a time-sensitive fashion.

Controversy also surrounds the use of CT with regard to radiation exposure that patients receive. Several studies have attempted

TABLE 24.3

Common Critical and Emergent Uses of Bedside Ultrasound in Abdominal Pain

REGION	USE
CRITICAL	
Pelvic	Identification of ectopic pregnancy with or without hemorrhage
Aorta	Measurement of the cross-sectional diameter of the abdominal aorta to determine the presence of an abdominal aortic aneurysm
FAST	Detection of free intraperitoneal fluid indicating hemorrhage, pus, or extrusion of gut contents
EMERGENT	
Pelvic	Identification of an intrauterine pregnancy or ovarian torsion
Biliary/RUQ	Gallstones or a dilated common bile duct, which may be a clue to the presence of choledocholithiasis Pericholecystic fluid or gallbladder wall thickening, which may be indicative of cholecystitis
Renal	Hydronephrosis indicating possible obstructive uropathy
FAST	Free intraperitoneal fluid indicating ascites or hemorrhage
Cardiac	Inferior vena cava distention or collapse as an indicator of volume status

FAST, Focused assessment with sonography for trauma; *RUQ,* right upper quadrant.

to quantify the radiation exposure associated with CT, but in reality there variation in dosage among different types of CT studies and imaging protocols. Studies estimate an abdominal CT with IV contrast to produce a dose of 10 to 50 millisieverts (mSv), enough to increase the estimated lifetime risk of cancer to 1 in 470 in a 20-year-old woman. Although patients may feel more confident when CT imaging was part of their ED evaluation, they typically have a very poor understanding of the radiation dose involved.[4] CT is an important adjunct in ED care, but the decision to scan is carefully weighed against the patient's history, physical examination findings, age, and gender. In particular, a patient with a history of chronic undifferentiated abdominal pain, multiple previous CT scans, and alternative diagnoses may benefit from observation as opposed to another CT scan.

Bedside transabdominal and transvaginal ultrasonography have emerged as extremely useful adjuncts, decreasing time to diagnosis of life-threatening abdominopelvic conditions. Useful indications are shown in Table 24.3. The results of sonographic examinations are operator dependent, and misdiagnosis can occur because of failure to detect or identify pathology, incorrect identification of normal anatomy as pathologic, or over interpretation of correctly identified findings (eg, the mere presence of gallstones does not confirm that cholelithiasis is the cause of the pain).

DIAGNOSTIC ALGORITHM

Critical Diagnoses

The differential diagnosis considerations with abdominal pain include a significant number of potentially life- or organ-threatening entities, particularly in the setting of a hemodynamically unstable or toxic-appearing patient. A diagnostic algorithm for initial assessment is shown in Figure 24.4. Severely ill patients require timely resuscitation and expeditious evaluation for potentially life-threatening conditions. A focused history and examination should be conducted, and the patient should be placed in a monitored acute care area well equipped for airway control, quick IV access, and fluid administration. Only then should appropriate diagnostics be initiated (bedside focused assessment with sonography in trauma [FAST], aorta ultrasound assessment, and radiographic, electrocardiographic, and laboratory studies). Table 24.1 lists critical diagnoses that should be considered with abdominal pain in order to facilitate appropriate early diagnosis and treatment.

Women of reproductive age with abdominal pain should undergo pregnancy testing early, and a known pregnancy or a positive result on urine or serum pregnancy testing associated with abdominal pain in the first trimester should be considered to represent an ectopic pregnancy until proven otherwise. If evidence of hemorrhage is present, early obstetric consultation and diagnostic ultrasonography should be prioritized. Bedside transabdominal sonography may identify free intraperitoneal fluid during the evaluation of shock, which generally is sufficient evidence to justify operative intervention in the context of a positive pregnancy test and appropriate history and physical examination findings.

Emergent Diagnoses

Despite the limitations already described, the approach to the differential diagnosis of abdominal pain generally is based on the location of maximum tenderness. Figure 24.1 shows locations of subjective pain and maximal tenderness on palpation related to various underlying causes. In women of childbearing age, a positive result on pregnancy testing may indicate ectopic pregnancy, but the entire spectrum of intra-abdominal conditions remains in the differential diagnosis. When the very broad differential diagnosis list is compartmentalized by both history and physical examination, ancillary testing should proceed to either confirm or support the clinical suspicion. Common emergent diagnoses of abdominal pain are listed in Table 24.2.

Despite the significant variety of tests available, close to one half of the patients in the ED with acute abdominal pain will have no conclusive diagnosis. It is incumbent on the clinician to reconsider the extra-abdominal causes of abdominal pain with special consideration in elders and immunocompromised patients, before arriving at the diagnosis of "nonspecific abdominal pain."

EMPIRICAL MANAGEMENT

The main therapeutic goals in managing acute abdominal pain are physiologic stabilization, mitigation of symptoms (eg, nausea and pain), and expeditious diagnosis, with consultation if required. An algorithm for management is presented in Figure 24.5.

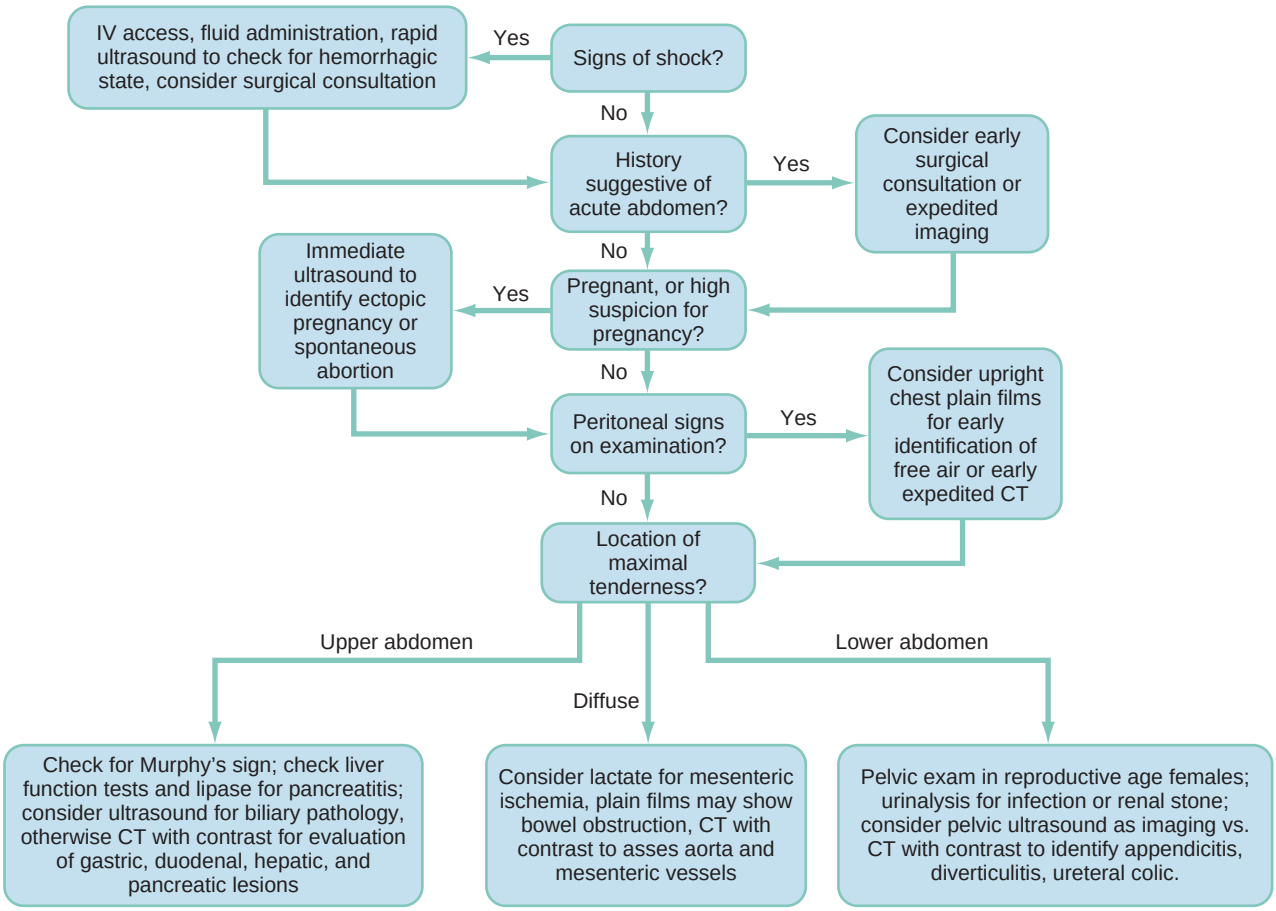

Fig. 24.4. Diagnostic algorithm for abdominal pain. *CT,* Computed tomography; *IV,* intravenous.

There is no evidence to support withholding analgesics from patients with acute abdominal pain to preserve the accuracy of subsequent abdominal examinations; in fact, the preponderance of evidence supports the opposite.[5] Pain relief may facilitate the diagnosis in patients ultimately requiring surgery. In the acute setting, analgesia usually is accomplished with intravenously titrated opioids. IV ketorolac, the only parenteral NSAID available in North America, is useful for both ureteral and biliary colic, as well as some gynecologic conditions, but is not recommended for general treatment of undifferentiated abdominal pain. Ketorolac has been shown to cause increased bleeding times in healthy volunteers and should be avoided in patients with gastrointestinal bleeding or potential surgical candidates.

Aside from analgesics, a variety of other medications may be helpful to patients with abdominal pain. The burning pain caused by gastric acid may be relieved by antacids. Antiemetics can be helpful for nausea and vomiting. The 5-HT antagonists, such as ondansetron, produce excellent results with minimal side-effects. Other agents, such as promethazine, prochlorperazine, or droperidol, also can be useful, but the mixed anticholinergic and antihistamine properties of these medications can cause sedation and extrapyramidal side effects. Extra-pyramidal side effects can be treated, if necessary, with diphenhydramine, benztropine, or benzodiazepines. Gastric emptying by nasogastric tube with suction is not indicated routinely for patients with small bowel obstruction but may relieve symptoms in those with intractable vomiting.

If intra-abdominal infection is suspected, broad-spectrum antibiotic therapy should be initiated promptly. Abdominal infections are often polymicrobial, and coverage for enteric gram-negative, gram-positive, and anaerobic bacteria is indicated. In the choice of antibiotic or combination, the following should be considered:

- Unless local antibiotic resistance dictates otherwise, a second-generation cephalosporin, such as cefotetan, 2 g, or cefoxitin 2 g; or a quinolone, usually ciprofloxacin, 400 mg, or levofloxacin, 500 mg; is combined with metronidazole, 500 mg, for the initiation of antibiotics in the ED. Alternatively, a non-cephalosporin, β-lactam agent with a β-lactamase antagonist, such as ampicillin-sulbactam, 3 g, piperacillin-tazobactam, 3.375 g, or ticarcillin-clavulanate 3 g, provide excellent gram positive and negative, aerobic and anaerobic coverage and are effective as single agents.
- Many enteric gram-negative bacilli mutate rapidly to produce β-lactamases that are poorly antagonized by specific drug combinations containing clavulanate, sulbactam, or tazobactam. Carbapenems, such as imipenem, 1 g, meropenem, 1 g, or cefepime, 1 g, are preferable for patients who have recently received other antibiotics.

Whether to provide coverage for *Enterococcus* species is a subject of debate, and the decision to treat for these bacteria specifically can be made after consultation. Immunocompromised patients may require antifungal agents (see Chapter 187).

Disposition

Because up to 40% of patients with acute abdominal pain receive the diagnosis of nonspecific abdominal pain, decisions regarding disposition are difficult. Categories for disposition may include surgical versus nonsurgical consultation and management, admission for observation, and discharge to home with follow-up

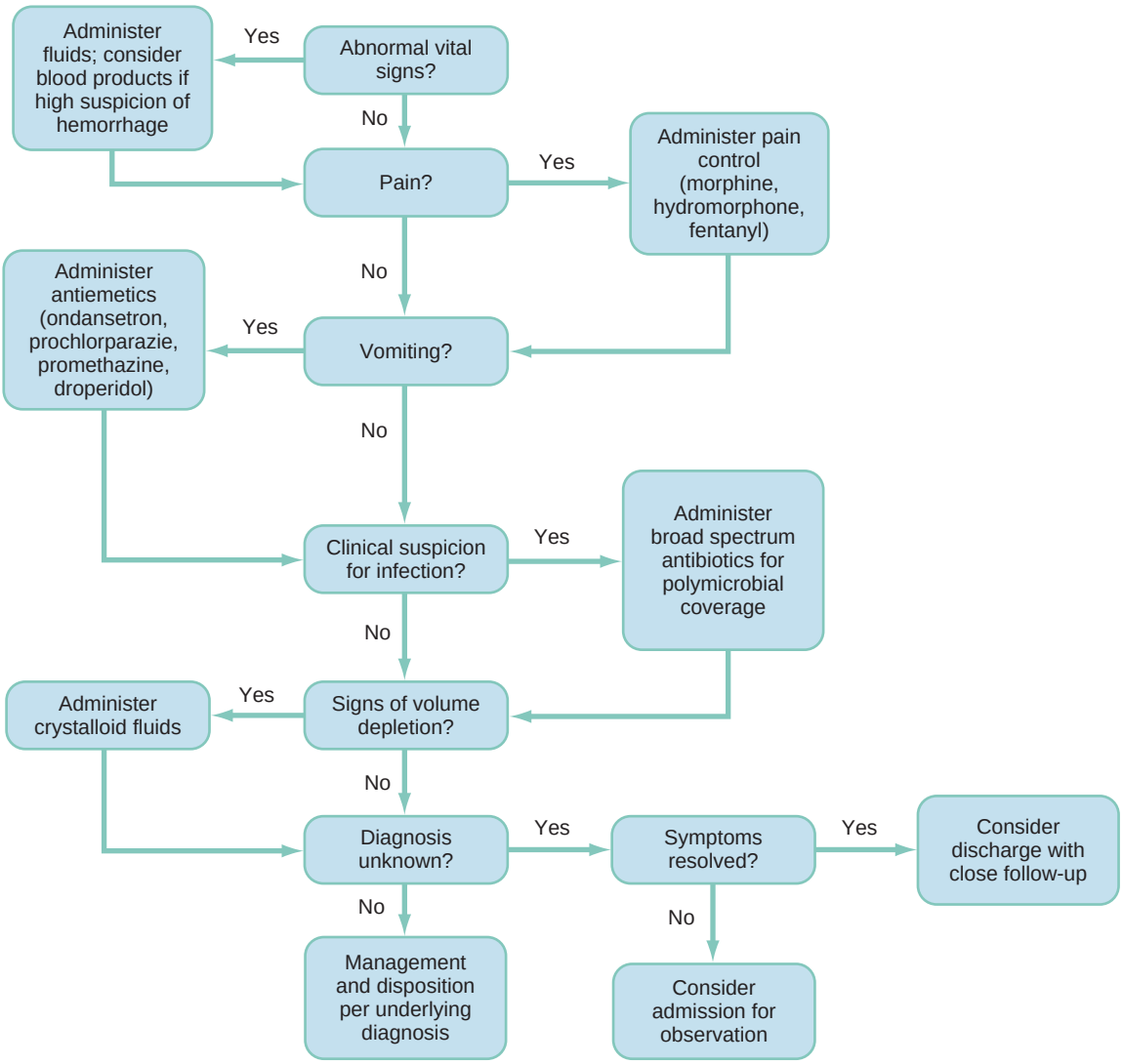

Fig. 24.5. Management algorithm for abdominal pain.

evaluation. The decision to admit a patient to an observation unit or a hospital bed factors in the following:

- History, examination findings, or ancillary tests suspicious for underlying disease
- A high likelihood of disease progression
- A high likelihood of adverse outcome if a diagnosis is missed
- Difficulty in the patient arranging appropriate and timely follow-up
- Ability and reliability of the patient to return if disease progresses

Clinically stable patients may be discharged from the ED with appropriate follow-up care, possibly to include repeated physical examination or additional diagnostic imaging if indicated.

In the case of nonspecific abdominal pain that is considered potentially worrisome, CT scan, observation (ie, in the ED observation unit), or follow-up reevaluation after 12 to 24 hours are all are valid options.

Before discharge of a patient with an undiagnosed cause of nonspecific abdominal pain, several conditions should be met. The abdominal examination findings should not indicate serious organ pathology or peritoneal irritation, and the patient should have normal or near-normal vital signs. Pain and nausea should be controlled, and the patient should be able to take fluids by mouth. If a patient is to be discharged home without a specific diagnosis, clear instructions should be given and include the following information:

- What to do for relief of symptoms or to maximize chances of resolution of the condition (eg, avoiding exacerbating food or activities, how to take any medications prescribed)
- Under what circumstances, with whom, and how soon to seek follow-up evaluation
- Under what conditions to seek more urgent care or return to the ED

KEY CONCEPTS

- Certain patients with abdominal pain, including elder patients, women of reproductive age, the immunocompromised, patients with cancer, and those who have undergone prior surgery (especially bariatric surgery) are more likely to harbor a serious diagnosis for their abdominal pain presentation and more often require imaging than their otherwise healthy counterparts.
- Early bedside ultrasound is indicated for patients with signs of shock. Ultrasound may identify aortic aneurysm or free intra-peritoneal blood, indicating the need for rapid surgical intervention.
- The WBC count is non-diagnostic in the evaluation of patients with abdominal pain, and neither elevation nor normal range results should be considered confirmatory of a diagnostic impression.
- Ultrasound is superior to CT scanning for the diagnosis of pain originating in the biliary tract or pelvis. Most abdominal pain can be diagnosed with non-contrast or IV contrast only CT scan.
- Plain radiographs are rarely useful, and should only be obtained in the rapid detection of free air or obstruction, when there is no intent to proceed to CT scan if the radiograph is positive or negative.
- Pain medication does not impede diagnosis and should not be withheld during diagnostic evaluation.
- Close to half of all patients with abdominal pain will not get a definitive diagnosis in the ED. Select populations may be suitable for discharge with appropriate close follow-up.
- First line antibiotics for serious intraperitoneal infections should be broad spectrum, including anaerobic coverage, such as piperacillin/tazobactam 3.375 g or ciprofloxacin 500 mg plus metronidazole 500 mg.

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CHAPTER 24: QUESTIONS & ANSWERS

24.1. Referred pain from pancreatitis is commonly localized to what anatomic area?
- **A.** Left flank
- **B.** Left shoulder
- **C.** Midback
- **D.** Rectum
- **E.** Right shoulder

Answer: C. Pain from acute pancreatitis is usually localized in the epigastric area and radiates to the midback. Pain from spleen is usually referred to the left shoulder, while a perforated ulcer may refer to the right shoulder. Uterine or rectal pain is commonly referred to the low back.

24.2. Which of following disease processes does not usually cause colicky pain?
- **A.** Diarrhea
- **B.** Gallstone
- **C.** Intestinal obstruction
- **D.** Pancreatitis
- **E.** Ureteral stone

Answer: D. Colicky pain is described as "waxing and waning" and usually arises from hollow organs, such as the gallbladder, ureters, or small/large intestines. Pain from pancreatitis is usually constant and severe.

24.3. Bedside ultrasonography is helpful in making which of the following diagnoses?
- **A.** Cholecystitis
- **B.** Free intraperitoneal hemorrhage from trauma
- **C.** Hydronephrosis from ureteral stone
- **D.** Ruptured abdominal aneurysm
- **E.** Ruptured ectopic pregnancy
- **F.** All of the above

Answer: F. Clinician-performed ultrasonography is a useful tool in the diagnosing all the above disease processes.

24.4. What intraabdominal processes are best visualized on ultrasound rather than CT?
- **A.** Biliary and ovarian
- **B.** Biliary and perirectal
- **C.** Gastric and hepatic
- **D.** Hepatic and splenic
- **E.** Ovarian and small bowel

Answer: A. Ultrasonography is more sensitive in detecting biliary pathology, which can be more subtle on CT scans, as well as assessing for flow in ovarian torsion.

24.5. Which of the following populations warrants more careful evaluation for abdominal pain?
- **A.** Immunocompromised patients
- **B.** Patients older than 65 years
- **C.** Patients with a language or communication barrier
- **D.** Patients with prior bariatric surgery
- **E.** Pregnant women
- **F.** All of the above

Answer: F. All of the above patients have been shown to exhibit increased complications and morbidity when presenting with abdominal pain.

CHAPTER 25

Jaundice

Todd Andrew Taylor | Matthew A. Wheatley

PERSPECTIVE

Epidemiology

Jaundice is the manifestation of elevated serum bilirubin; thus an understanding of the metabolism of bilirubin is fundamental for the evaluation and management of the emergency department (ED) patient with jaundice. Recently, hepatitis A and B immunizations have altered the traditional population of patients with jaundice because they have significantly decreased the prevalence of these diseases.

Pathophysiology

Normal Bilirubin Metabolism

Bilirubin is generated from heme products, primarily senescent red blood cells. A small portion is derived from myoglobin and maturing erythroid cells. Within the reticuloendothelial system, heme is oxidized to biliverdin, which is then converted to bilirubin. Unconjugated bilirubin forms a tight but reversible bond with albumin in circulation. It is passively taken into the hepatocytes, where it undergoes glucuronidation and at this point has become conjugated bilirubin. This conjugated fraction is secreted into the biliary system and emptied into the gut. Colonic bacteria metabolize the majority of the bilirubin to urobilinogen and stercobilin. Stercobilin is excreted in the stool (causing the stool to turn brown), and urobilinogen is reabsorbed and excreted in the urine. The remaining conjugated bilirubin is deconjugated and reenters the portal circulation to be taken up again by the hepatocytes (enterohepatic circulation). In the laboratory, conjugated bilirubin and unconjugated bilirubin are reported as direct and indirect fractions, respectively.

Abnormalities in Bilirubin Metabolism

Clinical jaundice is usually not evident until the total serum bilirubin concentration rises above 2.5 mg/dL. It is observed in tissues with high albumin concentrations, for example, the skin and eyes. It is absent in albumin-poor fluids, such as tears or saliva. The physiology of bile metabolism may be altered in three principal areas: (1) overproduction of heme products (hemolysis); (2) failure of the hepatocyte to take up, conjugate, and excrete bilirubin (hepatocellular dysfunction); or (3) obstruction of biliary excretion into the intestine. Unconjugated bilirubin that is not bound to albumin can cross the blood-brain barrier, causing adverse neurologic effects ranging from subtle developmental abnormalities to encephalopathy and death. Conditions that favor the unbound fraction of unconjugated bilirubin, including hemolysis, hypoalbuminemia, acidemia, and drugs that bind competitively to albumin, increase the risk of neurotoxicity. Conjugated bilirubins are not neurotoxic, although they may indicate serious disease.

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

The three major diagnostic categories to consider in the patient with jaundice are liver injury or dysfunction (cholestasis), biliary obstructive disorders, and disorders of hemolysis. Figure 25.1 outlines a laboratory-based approach to differentiating among these three categories.

Pivotal Findings

The pivotal findings related to history, physical examination, and ancillary testing are listed in Figure 25.2.

Symptoms

Patients may be asymptomatic at presentation or have nonspecific symptoms, such as pruritus, malaise, or nausea. There are a few symptom complexes that can help narrow the differential diagnosis. Jaundice with abdominal pain suggests biliary obstruction or significant hepatic inflammation. New-onset painless jaundice is the classic presentation for a neoplasm involving the head of the pancreas. Patients may complain of ill-fitting clothing because of weight loss or increasing abdominal girth related to ascites. The patient or caregiver may note subtle personality changes or frank confusion, suggestive of hepatic encephalopathy.

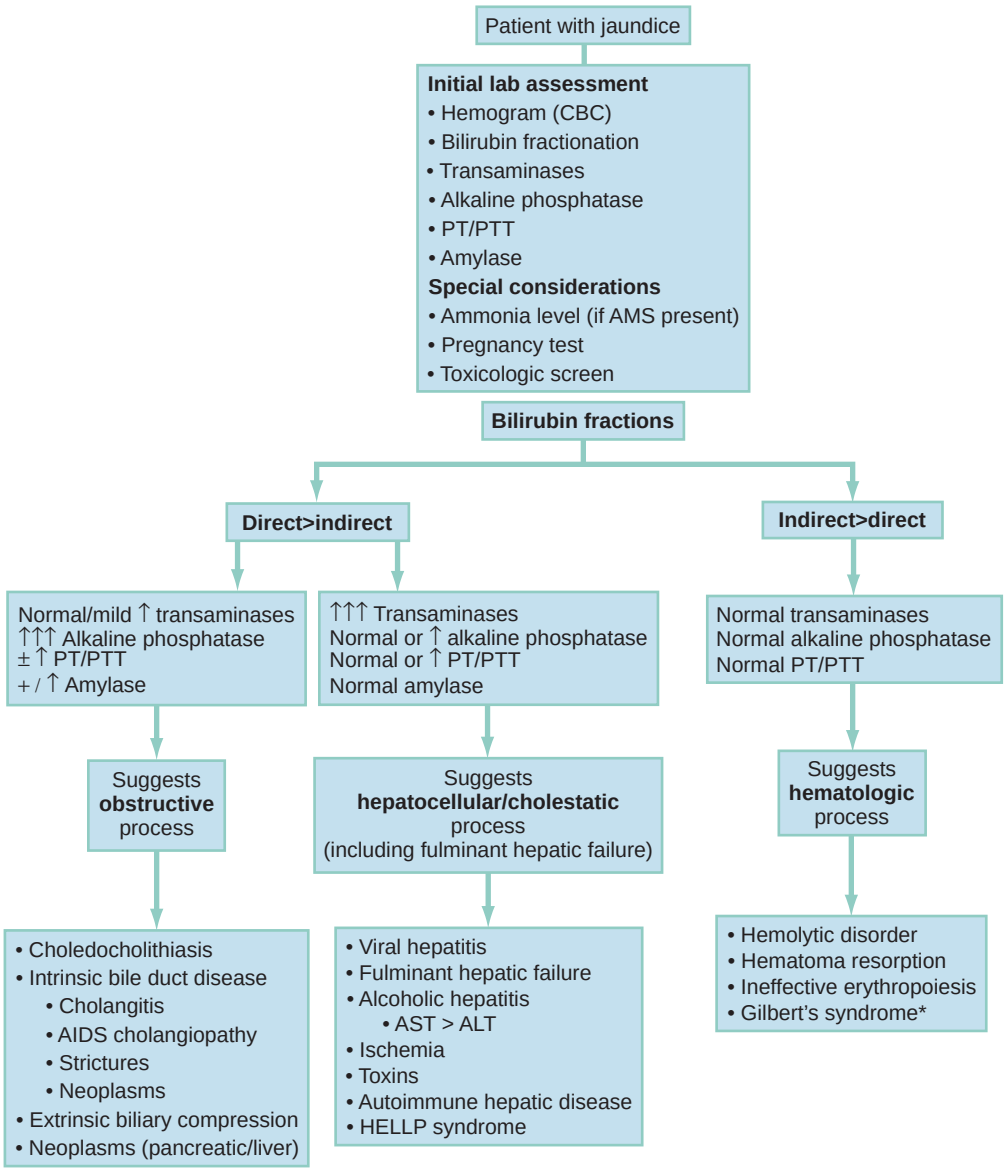
Signs

Pertinent physical examination findings are summarized in Figure 25.2. Examination of the skin and the abdomen is particularly helpful in narrowing the differential diagnosis.

Skin findings can point to acute or chronic liver disease. Jaundice is first apparent sublingually, in the conjunctiva and on the hard palate. From there, it spreads caudally; however, the extent of cephalocaudal progression does not accurately reflect the serum bilirubin concentration. Adequate lighting is necessary to detect the initial presentation of jaundice. Cutaneous findings of chronic liver disease include angiomas, excoriations from pruritus, and caput medusa.

The abdominal examination should begin with a thorough visual inspection. A distended or protuberant abdomen can indicate the presence of ascites. On palpation, an enlarged, tender liver suggests hepatic inflammation or engorgement caused by biliary obstruction. An enlarged nontender liver is concerning for malignant infiltration. A nonpalpable liver can indicate fibrosis caused by cirrhosis. A palpable gallbladder, a rare finding, suggests chronic cholestasis or malignancy. The presence of splenomegaly suggests hemolysis, malignancy, or portal hypertension.

Neurologic examination of the jaundiced patient may show depressed mental status, indicating hepatic encephalopathy or cerebral dysfunction caused by sepsis. Asterixis is a specific finding



*A benign hereditary condition characterized by hyperbilirubinemia and jaundice due to inadequate hepatic conjugation of bilirubin.

Fig. 25.1. Laboratory approach to differential diagnosis of jaundice. *AIDS,* Acquired immunodeficiency syndrome; *ALT,* alanine aminotransferase; *AMS,* altered mental status; *AST,* aspartate aminotransferase; *CBC,* complete blood count; *HELLP,* hemolysis, elevated liver enzymes, and low platelets; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

of hepatic encephalopathy. Table 25.1 addresses the clinical stages of hepatic encephalopathy.

Laboratory Tests

Figure 25.2 lists the laboratory tests that are helpful in the evaluation of a patient with jaundice. Serum gamma-glutamyl transpeptidase (GGT) rises in parallel with alkaline phosphatase in the setting of liver disease.[1] Although alkaline phosphatase also can be elevated in diseases affecting bone or placenta, the concomitant increase in serum GGT or 5′-nucleotidase confirms a hepatic source. A reticulocyte count and evaluation of the peripheral blood smear may identify hemolysis. In cases of unexplained hepatocellular injury, a quantitative acetaminophen level may be helpful. Hepatitis serologies are indicated when the presentation suggests viral illness. Bedside stool guaiac testing should be considered assesses for the presence of gastrointestinal bleeding, because patients with gastrointestinal bleeding will have an elevated ammonia level. This is secondary to the excess nitrogen load from the blood being converted into ammonia by the intestinal bacteria. Both glucose and ammonia metabolism can be altered in the presence of hepatocellular injury, and patients with altered mental status should have these levels determined. The degree of elevation in serum ammonia does not correlate directly with the level of hepatic encephalopathy. Ascitic fluid should be analyzed in patients with new-onset ascites and in those with established ascites but new complaints of fever, abdominal pain, gastrointestinal bleeding, hepatic encephalopathy, hypotension, or renal failure. Cell count and differential diagnosis, albumin, and total protein concentration are sufficient initial screening tests. If the etiology of the ascites is unknown, determining the serum ascites albumin gradient (SAAG) is helpful in determining the cause of ascites. The SAAG value is obtained by taking the albumin level in the ascetic fluid and subtracting it from the albumin level in

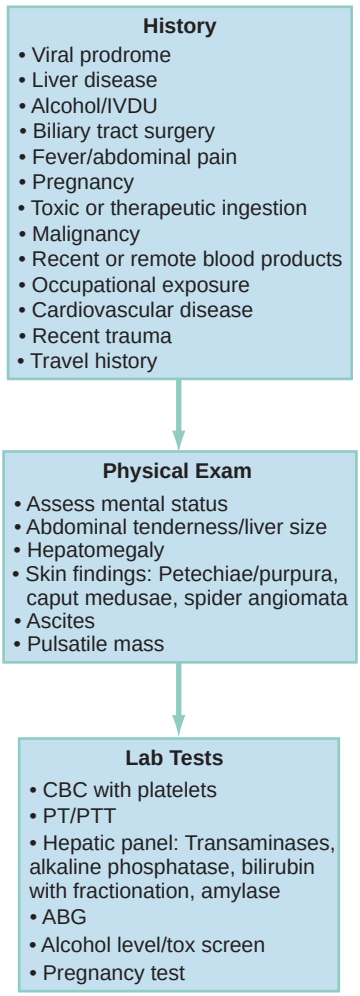


Fig. 25.2. Pivotal points in the assessment of the jaundiced patient. *ABG,* Arterial blood gas; *CBC,* complete blood count; *IVDU,* intravenous drug use; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *tox,* toxicology.

TABLE 25.1

Clinical Stages of Hepatic Encephalopathy

CLINICAL STAGE	INTELLECTUAL FUNCTION	NEUROMUSCULAR FUNCTION
Subclinical	Normal examination findings, but work or driving may be impaired	Subtle changes in psychometric testing
Stage 1	Impaired attention, irritability, depression, or personality changes	Tremor, incoordination, apraxia
Stage 2	Drowsiness, behavioral changes, poor memory, disturbed sleep	Asterixis, slowed or slurred speech, ataxia
Stage 3	Confusion, disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
Stage 4	Stupor and coma	Dilated pupils and decerebrate posturing; oculocephalic reflex

From Fitz G: Systemic complications of liver disease. In Feldman M, Sleisenger M, editors: Gastrointestinal and liver disease, Philadelphia, 1998, WB Saunders.

the serum. A value of greater than or equal to 1.1 g/dL is found in patients with portal hypertension. There are many causes of portal hypertension, including cirrhosis, liver failure, and heart failure. A value of less than 1.1 g/dL can be found in patients with lupus or pancreatitis. SAAG can diagnose portal hypertension, thereby rapidly narrowing the differential diagnosis.

In the setting of suspected bacterial peritonitis, fluid culture is also necessary; Gram stain is rarely helpful. Ascites with a polymorphonucleocyte (PMN) count >250 mm^3 is an indication for antibiotics (cefotaxime 2 grams). Two sets of blood cultures should be performed for patients with fever and jaundice. If there is evidence of gastrointestinal bleeding with hemodynamic instability or severe anemia, a type and crossmatch should be performed.

Imaging

When indicated, abdominal imaging can help narrow the differential diagnosis of jaundice, especially in patients for whom biliary obstruction is a concern. The primary role of imaging is in the characterization of obstructive biliary disease. The first choice of study depends on the clinical presentation. Ultrasonography is generally superior for visualization of the gallbladder and ducts, but both ultrasonography and computed tomography (CT) are highly sensitive in diagnosing obstruction. The choice of imaging procedure depends on the pretest probability that there is biliary obstruction and that the obstruction is malignant. For patients with painless, progressive jaundice and without suspicion of hepatocellular injury (eg, hepatitis, alcoholism), malignant obstruction has a high pretest probability, so CT is the preferred method owing to its improved sensitivity in locating the site of the obstruction, determining resectability, and assessing for disseminated disease. Patients with a high likelihood of biliary disease and benign obstruction are best screened with ultrasonography. Ultrasonography is less expensive and less invasive than either magnetic resonance cholangiography or endoscopic ultrasound but has a lower sensitivity in identifying common bile duct stones.[2] Ultrasonography with Doppler flow can detect obstruction in the hepatic, portal, and splenic veins. Sonographic features of cholecystitis are discussed in Chapter 90. In patients with low or intermediate clinical likelihood of mechanical obstruction, ultrasonography is the preferred initial modality to evaluate whether or not biliary obstruction is present. CT is preferred if the entire abdomen needs to be evaluated.

DIAGNOSTIC ALGORITHM

The differential diagnosis considerations for jaundice are broad; there are critical and emergent causes that should be ruled in or out in the ED (Table 25.2). Patients are considered in a critical state if they have jaundice and any of the following: altered level of consciousness, hypotension, fever with abdominal pain, or active bleeding.

Further characterization of the cause of jaundice involves analysis of the laboratory studies (see Fig. 25.1). Indirect bilirubinemia points to a hematologic cause, whereas direct bilirubinemia indicates hepatobiliary pathology. Elevated direct bilirubin with transaminase elevation is indicative of hepatocellular inflammation or injury. Prolongation of prothrombin time (PT) indicates significant hepatocellular dysfunction. Elevated alkaline phosphatase with elevated direct bilirubin suggests extrinsic biliary obstruction.

Patients with suspected biliary obstruction should undergo ultrasonography and/or CT in the ED to determine the cause and site of the obstruction. The most common causes of biliary obstruction are biliary stones, benign and malignant stenoses.[3]

TABLE 25.2

Jaundice: Differential Diagnosis of Critical and Emergent Diagnoses

SYSTEM	CRITICAL	EMERGENT	NONEMERGENT
Hepatic	Fulminant hepatic failure Toxin Virus Alcohol Ischemic insult Reye's syndrome	Hepatitis of any cause with confusion, bleeding, or coagulopathy Wilson's disease Primary biliary cirrhosis Autoimmune hepatitis Liver transplant rejection Infiltrative liver disease Drug induced (isoniazid, phenytoin, acetaminophen, ritonavir, halothane, sulfonamides) Toxin ingestion or exposure	Hepatitis with normal mental status, normal vital signs, and no active bleeding
Biliary	Cholangitis	Bile duct obstruction (stone, inflammation, stricture, neoplasm)	
Systemic	Sepsis Heatstroke	Sarcoidosis Amyloidosis Graft-versus-host disease	Post-traumatic hematoma resorption Total parenteral nutrition
Cardiovascular	Obstructing AAA Budd-Chiari syndrome Severe congestive heart failure	Right-sided congestive heart failure Veno-occlusive disease	
Hematologic-oncologic	Transfusion reaction	Hemolytic anemia Massive malignant infiltration Inborn error of metabolism Pancreatic head tumor Metastatic disease	Gilbert's syndrome Physiologic neonatal jaundice
Reproductive	Preeclampsia or HELLP syndrome Acute fatty liver of pregnancy	Hyperemesis gravidarum	Cholestasis of pregnancy

AAA, Abdominal aortic aneurysm; *HELLP,* hemolysis, elevated liver enzymes, low platelets.

The identification of critical or emergent causes of jaundice requires the clinician to recognize patterns in the patient's signs, symptoms, and ancillary testing. For instance, patients with a triad of jaundice, encephalopathy, and coagulopathy (international normalized ratio [INR] >1.5) have acute hepatic failure.[4] Fever, right upper quadrant pain, and jaundice can indicate biliary obstruction with infection (eg, cholangitis, cholecystitis, or hepatitis). Ascites with abdominal tenderness raises suspicion for spontaneous bacterial peritonitis (SBP). Rapid onset of hepatomegaly and ascites can point to portal vein thrombosis (Budd-Chiari syndrome).

EMPIRICAL MANAGEMENT

General supportive and specific therapies depend on the presumptive cause of the jaundice (Fig. 25.3). If coagulopathy is known or suspected, compressible sites and ultrasound guidance should be used for central venous access. Coagulopathy in the context of acute hemorrhage should be corrected with fresh frozen plasma, and blood volume repletion accomplished with packed red blood cells.

If ascites is present and SBP is suspected, paracentesis is diagnostic. The presence of more than 250 polymorphonuclear cells per cubic millimeter of ascitic fluid is diagnostic for SBP. The empirical antibiotic of choice is a third-generation cephalosporin (eg, cefotaxime). If the patient has a history of cirrhosis and is taking a nonselective beta blocker, it should be discontinued because it has been shown to increase mortality in patients with SBP.[5]

Patients with jaundice and transaminases out of proportion to elevation of alkaline phosphatase have a hepatocellular injury pattern. Treatment of hepatic encephalopathy is described in Chapter 90. Patients with fulminant hepatic failure should be admitted to the intensive care unit or transferred to a hospital with expertise in severe liver disease. Acetaminophen toxicity and indications for *N*-acetylcysteine therapy are discussed in Chapter 148. There is some evidence suggesting *N*-acetylcysteine offers a mortality benefit in non-acetaminophen induced acute liver failure. However, the evidence is weak and we do not recommend its use in this context.[6,7]

In the absence of liver failure, patients with encephalopathy, coagulopathy, or unstable vital signs should be admitted. There are no clear guidelines to indicate what level of hepatic or biliary dysfunction requires inpatient management. We recommend hospitalization or placement into observation status for patients with new-onset jaundice and transaminases approaching 1000 IU/L, bilirubin approaching 10 mg/dL, or evidence of coagulopathy, because these laboratory abnormalities suggest significant hepatic dysfunction. Patients with hepatitis or cholestatic jaundice may be managed as outpatients if they have a normal mental status, stable vital signs, ability to take oral fluids, no evidence of acute bleeding or significant coagulopathy, and no complicating infectious process. Intravenous fluids and antiemetics may be required in the ED. Alcohol and medications with potential hepatotoxicity, particularly acetaminophen, should be avoided.

Fever, abdominal pain, and obstructive jaundice suggest ascending cholangitis (Fig. 25.4). Antibiotic recommendations for ascending cholangitis are discussed in Chapter 90. In addition to antibiotics, patients should be resuscitated with intravenous fluids as necessary and have any metabolic derangements corrected. Because biliary excretion of most antibiotics is compromised in the setting of obstruction, all patients will require biliary

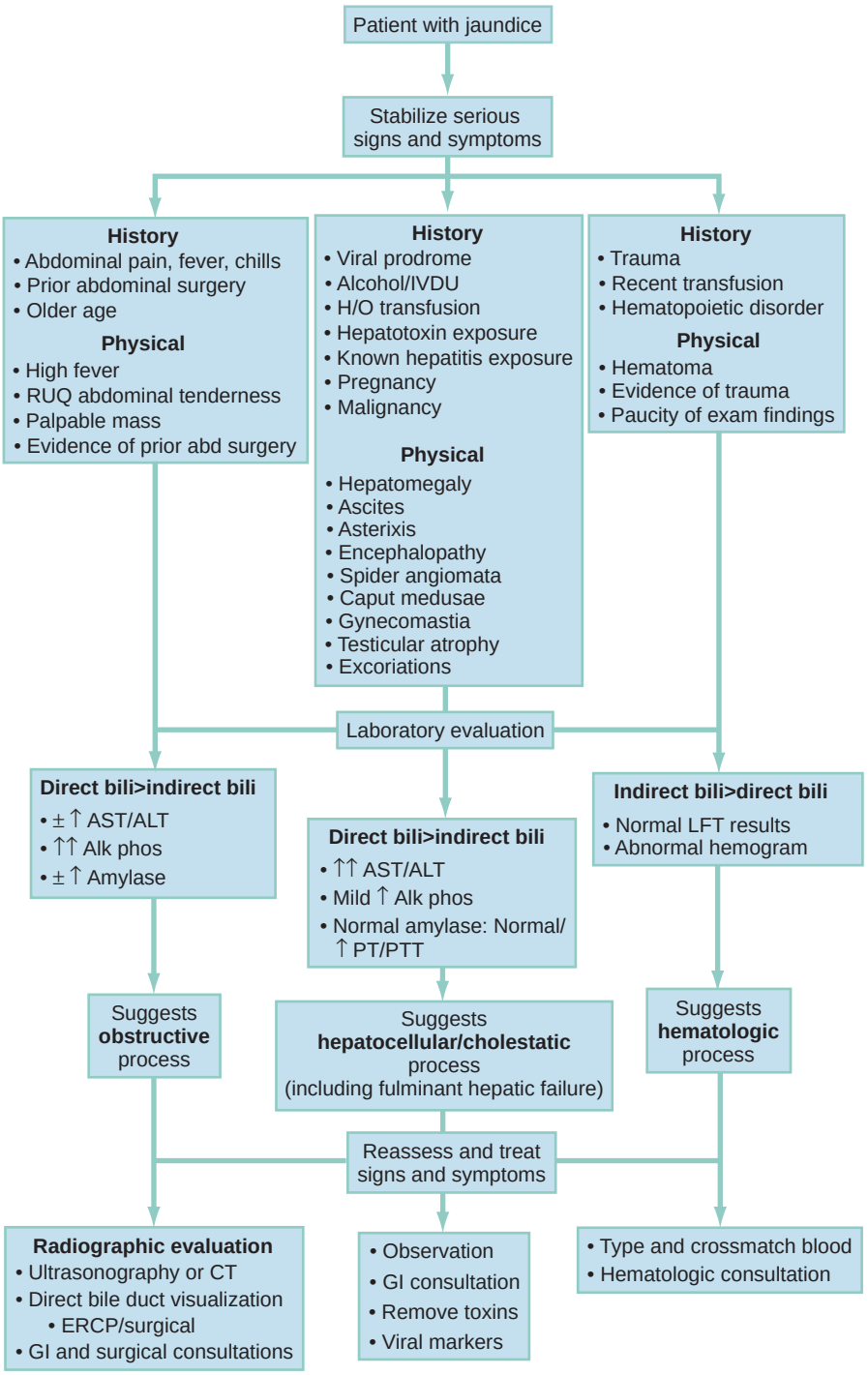


Fig. 25.3. Management of the patient with jaundice. *abd,* Abdominal; *Alk phos,* alkaline phosphatase; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *bili,* bilirubin; *CT,* computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *GI,* gastrointestinal; *H/O,* history of; *IVDU,* intravenous drug use; *LFT,* liver function test; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RUQ,* right upper quadrant.

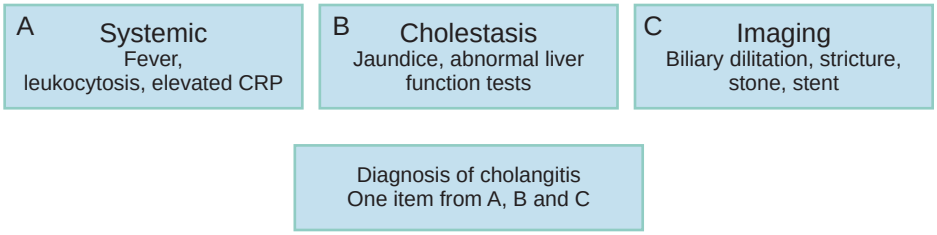


Fig. 25.4. Tokyo Guidelines for diagnosis of acute cholangitis. *CRP,* C-reactive protein. (Redrawn from Kimura Y, Takada T, Kawarada Y, et al: Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo Guidelines. J Heptaobiliary Pancreat Surg 14: 15-26, 2007.)

drainage. This generally should be done urgently but may be deferred 24 to 48 hours in stable patients. Drainage can be accomplished by endoscopic, percutaneous, or open surgical approaches. Prompt consultation with general surgery or gastroenterology is necessary to determine which approach and timing are appropriate.

Patients with extrahepatic obstructive jaundice without cholangitis should also be admitted for drainage. Endoscopic retrograde cholangiopancreatography (ERCP) is therapeutic for benign obstructions, such as gallstones or strictures. Patients with obstructive jaundice caused by malignancy also benefit from biliary decompression, whether operative or endoscopic. Malignancy with jaundice heralds more advanced disease and increased morbidity and mortality.

In general, patients with uncomplicated cholecystitis should receive intravenous fluids in the ED, parenteral analgesics and antiemetics as needed, and should be hospitalized. Antibiotic therapy for acute cholecystitis is discussed in Chapter 90. These patients should undergo emergent imaging and consultation with a surgeon or gastroenterologist.

Patients with confirmed or suspected choledocholithiasis, stones in the common bile duct, require admission for possible ERCP or cholecystectomy.[13] Neither CT nor ultrasonography is 100% sensitive in identifying a common bile duct stone, but they are reasonably sensitive in identifying a dilated common bile duct, which is highly suggestive of obstruction.

In patients with anemia, the management is based largely on the etiology. In immune-mediated hemolytic anemia, the decision to transfuse should be based on the patient's ability to oxygenate and the ability to institute alternative treatments. An urgent hematology consultation is recommended (see Chapter 121). In the case of drug-induced hemolytic anemia, the mainstay of treatment involves removal of the offending agent. For patients with glucose-6-phosphate deficiency, blood transfusions are rarely indicated, and the focus of management should be on avoiding oxidative stressors and maintaining urine output to prevent renal failure. Patients with hemoglobinopathies rarely require transfusion therapy unless they have severe anemia without evidence of reticulocytosis. Fluids, oxygen, and analgesics can be given for an acute crisis.

KEY CONCEPTS

- Clinical jaundice is usually not evident until the total serum bilirubin concentration rises above 2.5 mg/dL.
- Bile metabolism may be altered when there is an overproduction of heme products (hemolysis); failure of the hepatocyte to take up, conjugate, and excrete bilirubin (hepatocellular dysfunction); or obstruction of biliary excretion into the intestine.
- Unconjugated bilirubin that is not bound to albumin can cross the blood-brain barrier, causing adverse neurologic effects; conjugated bilirubin is not neurotoxic.
- New-onset painless jaundice is the classic presentation for a neoplasm involving the head of the pancreas.
- Jaundice is first apparent sublingually, in the conjunctiva and on the hard palate.
- In cases of unexplained hepatocellular injury, a quantitative acetaminophen level may be helpful.
- If the etiology of the ascites is unknown, getting the serum ascites albumin gradient (SAAG) will aid in determining the cause of ascites and presence of portal hypertension.
- Ultrasonography is the preferred initial modality to evaluate whether or not biliary obstruction is present, whereas CT is preferred if malignant obstruction is suspected or the entire abdomen needs to be evaluated.
- Elevated direct bilirubin with transaminase elevation is indicative of hepatocellular inflammation or injury.
- Diagnosis of spontaneous bacterial peritonitis (SBP) is >250 neutrophil count. Treatment is cefotaxime 2 grams.
- Hyperemesis gravidarum can elevate liver enzymes up to 20 times the normal amount, including mildly elevated bilirubin.
- Intrahepatic cholestasis of pregnancy is an idiopathic cause of jaundice that occurs in the third trimester.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 25: QUESTIONS & ANSWERS

25.1. A 56-year-old male presents with fever, distended abdomen, and a bedside ultrasound that shows ascites. A paracentesis is performed and the results indicate that the patient has spontaneous bacterial peritonitis (SBP). What daily medication should be stopped upon admission?
A. Amlodipine
B. Crestor
C. Lactulose
D. Metoprolol

Answer: D. Beta Blocker use in pts with cirrhosis with SBP should be discontinued because it has been shown to increase mortality.

25.2. A 43-year-old female presents with 1 month of abdominal swelling. On examination she has a diffusely swollen abdomen with a fluid wave. The patient appears to have new onset ascites. In order to help determine the etiology, you obtain the serum ascites albumin gradient (SAAG). Which value is consistent with cirrhosis?
A. 0.25 g/dL
B. 0.5 g/dL
C. 1 g/dL
D. 1.5 g/dL

Answer: D. A (SAAG) value of greater than or equal to 1.1 g/dL is found in patients with portal hypertension. There are many causes of portal hypertension, including cirrhosis, liver failure, and heart failure.

25.3. A 48-year-old male with a history of cirrhosis presents with 3 days of abdominal pain and fever. On examination, he is febrile and has an abdominal examination that is diffusely tender with guarding. The decision is made to do a paracentesis to evaluate for spontaneous bacterial peritonitis (SBP). What is the best treatment for SBP?
A. Cefotaxime and discontinue beta blockers
B. Ceftriaxone and dexamethasone
C. Ceftriaxone and discontinue beta blockers
D. Ciprofloxacin and metronidazole

Answer: A. The empirical antibiotic of choice is a third-generation cephalosporin (eg, cefotaxime). If the patient has a history of cirrhosis and is taking a nonselective beta blocker, it should be discontinued because it has been shown to increase mortality in patients with SBP.

25.4. A 41-year-old male with a history of cirrhosis presents with fever, abdominal distension, and confusion. A paracentesis is performed in the evaluation of spontaneous bacterial peritonitis (SBP). What is the diagnostic criteria found in the ascetic fluid that confirms SBP?
A. Neutrophil count >100
B. Neutrophil count >250
C. WBC >100
D. WBC >250

Answer: B. The presence of more than 250 polymorphonuclear cells per cubic millimeter of ascitic fluid is diagnostic for SBP.

25.5. A 55-year-old female presents with 1 month of diffuse abdominal swelling and pain. She reports a long history of alcohol use. In the evaluating this patient for jaundice, how high does the bilirubin have to be to become clinically apparent, and what area of the body does jaundice appear first?
A. 2 mg/dL; nail beds
B. 2 mg/dL; sclera
C. 2.5 mg/dL; skin
D. 2.5 mg/dL; sublingual

Answer: D. Clinical jaundice is usually not evident until the total serum bilirubin concentration rises above 2.5 mg/dL. Jaundice is first apparent sublingually, in the conjunctiva and on the hard palate.

CHAPTER 26

Nausea and Vomiting

Joshua Guttman

PERSPECTIVE

Nausea and vomiting are most commonly associated with primary gastrointestinal (GI) disorders but may also occur with systemic conditions. Nausea and vomiting may be of benign origin or may be associated with life-threatening conditions, and treatment is directed both at symptomatic relief and at the underlying cause. Vomiting may also result in serious sequelae (Table 26.1). Classification by duration and frequency of the vomiting (acute, recurrent, chronic, or cyclic) may assist in determination of the underlying cause.

Epidemiology

Nausea and vomiting represent 4% of emergency department (ED) chief complaints and often are present in patients whose chief complaint is abdominal pain, among many other conditions. The most common causes of nausea and vomiting are GI disorders. Nausea and vomiting may also represent disorders outside the GI tract, such as hyperemesis gravidarum, intracranial lesions and infections, myocardial infarction, diabetic ketoacidosis, and drug toxicities.

Pathophysiology

The act of vomiting is divided into three phases: nausea, retching, and actual vomiting. Nausea may occur without retching or vomiting, and retching may occur without vomiting. The exact neural pathways mediating nausea are not clear, but they are likely to be the same pathways that mediate vomiting. Mild activation of the pathways may result in nausea, whereas more intense stimulation results in vomiting. During nausea there is an increase in tone in the musculature of the duodenum and jejunum, with a concomitant decrease in gastric tone; this leads to reflux of intestinal contents into the stomach. There is often associated hypersalivation, repetitive swallowing, and tachycardia.

Retching is characterized as rhythmic, synchronous contractions of the diaphragm, abdominal muscles, and intercostal muscles that occur against a closed glottis, without the expulsion of gastric contents.

Vomiting is the forceful expulsion of gastric contents through the mouth. There is contraction of the external oblique and abdominal rectus muscles, and the hiatal portion of the diaphragm relaxes; this increases the pressure in the abdominal and the thoracic compartments. There is contraction of the pyloric portion of the stomach. Simultaneously, there is relaxation of the gastric fundus, cardia, and upper esophageal sphincter as the vomitus is brought up and out the mouth. The glottis closes to prevent aspiration.

The complex act of vomiting is coordinated by the *vomiting center* located in the lateral reticular formation of the medulla. The efferent pathways from the vomiting center are mainly through the vagus, phrenic, and spinal nerves (Fig. 26.1). These pathways are responsible for the integrated response of the diaphragm, intercostal muscles, abdominal muscles, stomach, and esophagus. The vomiting center is activated by afferent stimuli from a variety of sources. These include (1) visceral afferent impulses directly from the GI tract; (2) visceral afferent impulses from outside the GI tract, including the biliary system, peritoneum, pharynx, genitalia, and heart; (3) extramedullary central nervous system (CNS) afferents, including the vestibular system; and (4) the chemoreceptor trigger zone (CTZ) (Fig. 26.2), which is located in the area postrema, the floor of the fourth ventricle. Part of this area is located outside of the blood-brain barrier, enabling it to respond to endogenous and exogenous substances that activate vomiting (see Fig. 26.2).

The discovery of various neurotransmitters and their receptor sites within the medulla has improved the understanding and development of therapeutic agents. The CTZ area is rich in dopamine D_2 receptors and serotonin receptors, and the lateral vestibular nucleus is rich with cholinergic and histamine receptors. Serotonin receptors are also widely found in the GI tract. These receptor sites are targets for the various medications that are used to treat nausea and vomiting.

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

The differential diagnosis for nausea and vomiting is particularly broad in scope; almost any organ system can be involved. *Acute* vomiting is defined as episodic vomiting that occurs for less than 1 week and is associated with acute conditions, whereas chronic vomiting, which occurs for a period longer than 1 week, is associated with motility disorders, effects of systemic treatments (such as for cancer), neuropsychiatric conditions (eg, bulimia) and neurologic conditions. Discrete episodes of intractable vomiting with intervening asymptomatic periods are considered *cyclic*. Common causes of nausea and vomiting are outlined in Table 26.2, and a differential diagnosis is presented in Tables 26.3 and 26.4.

Pivotal Findings

Symptoms

A thorough history, including past medical history, medications, and social history will generally elicit the etiology of vomiting. The content and color of the vomitus may help determine its cause (Table 26.5). Although coffee ground emesis usually suggests a slower bleeding rate than bright red blood, this cannot be relied upon in all cases. The history should be directed at assessing for both the causes of vomiting, as well as its sequelae.

Timing and duration of the vomiting may be important. Symptoms occurring primarily in the morning may suggest increased intracranial pressure. Delayed vomiting more than 1 hour after eating suggests gastric outlet obstruction or gastroparesis. Vomiting of material eaten more than 12 hours previously is pathognomonic for outlet obstruction.

Associated symptoms are helpful: Vomiting with diarrhea is generally due to an infectious gastroenteritis but may also be

TABLE 26.1

Potential Sequelae of Vomiting

SEQUELAE	ETIOLOGY
Hypovolemia	Loss of water and sodium ions in vomitus
Metabolic alkalosis	Loss of hydrogen ions in vomitus
Hypokalemia	Loss of potassium in urine
Mallory-Weiss tears	Forceful retching or vomiting causing a 1 cm to 4 cm tear in the mucosa and submucosa; the cause of 3% of deaths from upper GI bleeds
Boerhaave's syndrome	Perforation of the esophagus due to increased intraesophageal pressure during forceful retching or vomiting There is free passage of esophageal contents into the mediastinum, causing a chemical mediastinitis, leading to superinfection, sepsis, multiorgan failure, and death It is a surgical emergency The mortality rate is 50% if surgical repair is not performed within 24 hours
Aspiration pneumonitis and pneumonia	A concern in patients with baseline poor mental status and pulmonary findings after an episode of vomiting

GI, Gastrointestinal.

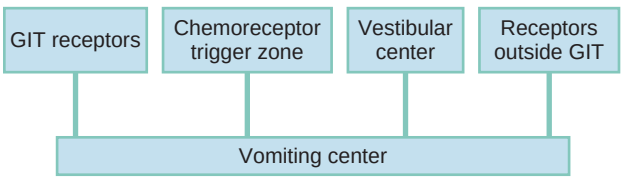


Fig. 26.1. Vomiting process. *GIT,* Gastrointestinal tract.

present in mesenteric ischemia or other GI surgical emergencies. Vomiting with abdominal pain is generally caused by diseases of the GI system. Chronic headaches with nausea and vomiting should raise suspicion of elevated intracranial pressure. Vomiting without preceding nausea is typical of CNS pathology. The *social history* should include inquiries about alcohol or other substance use. The *past medical history* will reveal the presence of any GI disease or previous surgeries. Finally, a thorough *medication list,* including over-the-counter drugs and supplements, should be elicited.

A history of *similar episodes* should be elicited. A history of stereotypical episodes of nausea and vomiting lasting hours to days, with symptom-free intervals may lead to a diagnosis of cyclical vomiting syndrome. In patients with a history of cyclical vomiting, heavy, chronic use of cannabis is important to elicit, because it may lead to a diagnosis of cannabis hyperemesis syndrome.[1] Symptoms are similar to cyclic vomiting syndrome; however patients will note temporary relief with a hot shower.[1] Onset of the syndrome is often delayed years after chronic marijuana use has begun.

Signs

The examination should begin with an overall assessment of the patient's status, including an assessment for volume depletion. The history will direct the examination to the appropriate body systems (Table 26.6). The eye examination may reveal nystagmus, which may indicate cerebellar pathology, peripheral vertigo, or drug intoxication. Oral examination may reveal loss of dental enamel commonly seen with bulimia. Abdominal examination, with appropriate testing for occult blood in the stool, may reveal ascites, distention, hernias, abdominal tenderness and masses, or hyperactive or hypoactive bowel sounds. Neurological examination (including funduscopic examination) may be important if a central cause is considered. Provocative testing in patients with suspected benign paroxysmal positional vertigo may elicit vomiting or nystagmus, suggesting this diagnosis (see Chapter 16). Symptoms of depression or anxiety may suggest a psychiatric origin to the vomiting; however, this is a diagnosis of exclusion and rarely is made in the ED.

Ancillary Studies

Testing is determined by the differential diagnosis based on the history and physical examination:

- Serum electrolytes and creatinine: Measurement of serum electrolytes and creatinine is not indicated in most cases of vomiting. Patients with a history of prolonged or severe vomiting, or with clinical evidence of dehydration requiring volume replacement, should undergo electrolyte testing to assess for hypokalemia, hypochloremia, contraction alkalosis, or other sequelae of protracted vomiting. Creatinine may help assess pre-renal dysfunction.
- Serum lipase: Lipase determination is indicated in cases of suspected pancreatitis, based on the patient's complaint of (often severe) epigastric pain and the presence of tenderness.
- Urine tests: A urine pregnancy test should be performed in all women of childbearing age with nausea and vomiting. A urine analysis may show leukocyte esterase and nitrites as evidence of an urinary tract infection. Ketones may support a diagnosis of diabetic ketoacidosis or prolonged starvation state. Hematuria indicates a possible renal calculus.
- Liver function and ammonia tests: Liver function tests are indicated in cases of suspected hepatitis or biliary disease. Ammonia testing is useful if liver failure is suspected.
- Serum drug levels: Serum drug levels may be important in determining the cause of nausea and vomiting in patients on digoxin, salicylates, or acetaminophen, especially in elders who are taking medication without supervision. Specific serum drug levels should be drawn only if knowledge of the drug level would alter the patient's management.
- Ultrasound: A bedside abdominal ultrasound evaluates for cholelithiasis, cholecystitis, renal colic, appendicitis, and small bowel obstruction (SBO). Additionally, an assessment of the inferior vena cava may be helpful in monitoring patients with suspected dehydration.
- Abdominal computed tomography (CT): Abdominal CT scan is indicated in patients with a suspected SBO or surgical cause, such as appendicitis, when not diagnosed by ultrasound.
- Cranial imaging: CT or magnetic resonance imaging (MRI) may be indicated to evaluate for intracranial etiologies of nausea and vomiting. When occipital headache is accompanied by hypertension and vomiting, a CT or an MRI should be obtained to evaluate for cerebellar hemorrhage. For other posterior fossa pathologies, such as cerebellar infarction, MRI is preferred.
- Chest imaging: A chest x-ray may reveal subdiaphragmatic air in a patient with a perforated viscus, but abdominal CT is far superior when perforation or other serious intra-abdominal pathology is suspected. For patients with suspected Boerhaave's syndrome, a chest radiograph is used to assess for a pneumomediastinum, but, again, CT is the preferred modality when this condition is suspected.

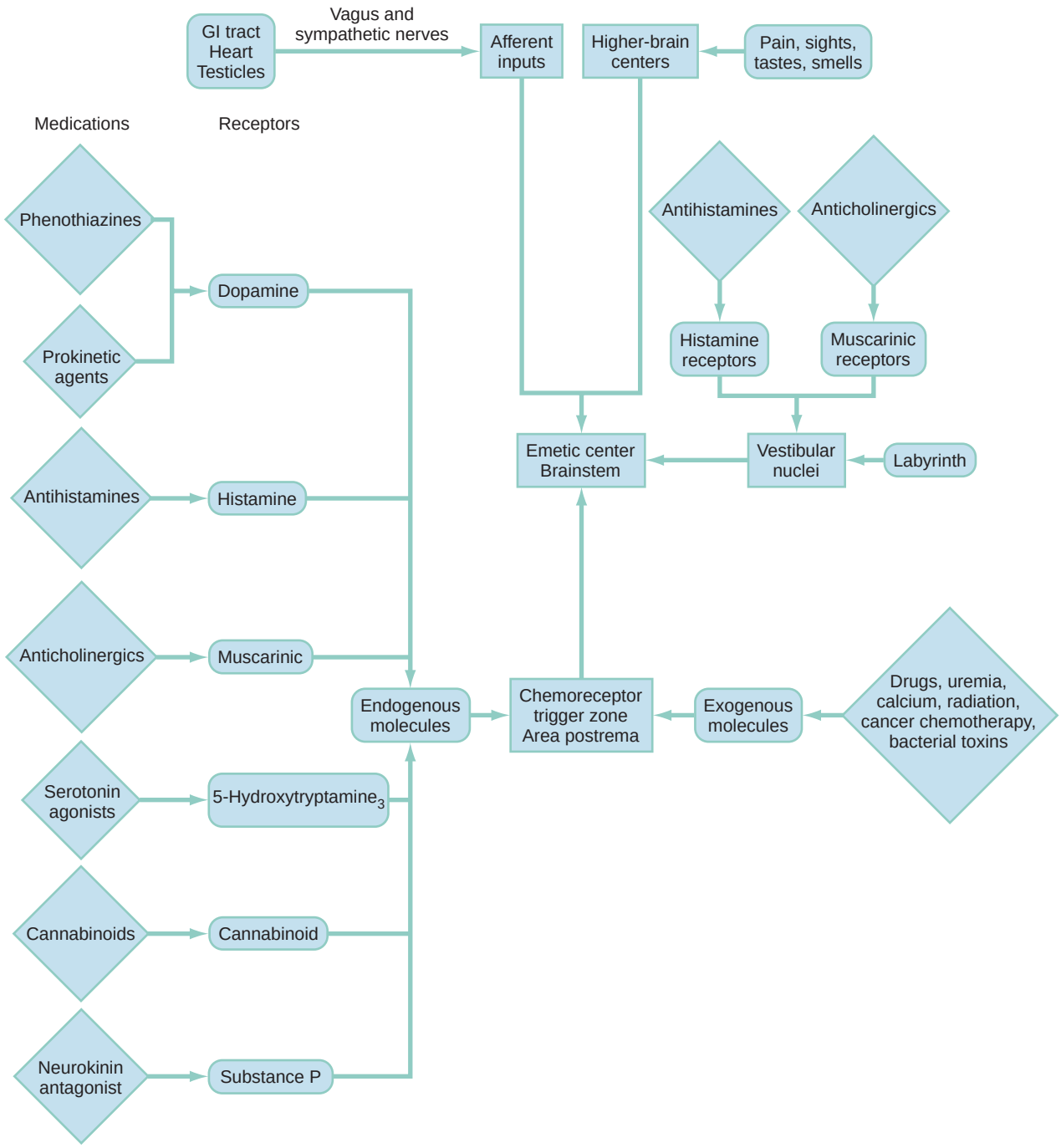


Fig. 26.2. Pathophysiology of nausea and vomiting. *GI,* Gastrointestinal.

DIAGNOSTIC ALGORITHM

Patients presenting with vomiting should be rapidly assessed to ascertain if a potentially critical diagnosis is present (see Table 26.4). A diagnostic algorithm is shown in Figure 26.3.

The evaluation begins by determining whether the patient is stable or unstable. If the patient is deemed to be unstable or critically ill, oxygenation is provided as needed, intravenous (IV) access and monitoring are is established, and any vital sign disturbances are addressed. A brief history and directed physical examination are performed concomitantly to determine the most likely causes, with evaluation and management prioritized to those causes.

If the patient is stable, a more thorough history and physical examination is performed. Empirical therapy, laboratory and radiologic testing are directed by results of the history and examination. Patients with volume depletion requiring IV replacement require serum electrolyte and renal function determination. In addition, patients with associated severe abdominal pain receive IV analgesics and antiemetics as needed, and have additional blood sent for liver function tests and lipase. If sepsis or shock is considered, obtain a serum lactate level. Most patients with severe pain and tenderness will require abdominal imaging. Patients with a history of abdominal surgery and decreased stool output are evaluated for SBO. Patients with severe headache or neurological deficits (not thought to be due to a primary headache disorder)

TABLE 26.2

Disorders Commonly Associated With Vomiting

DISORDER	CLASS	HISTORY	PREVALENCE	PHYSICAL EXAMINATION	USEFUL TESTS	COMMENTS
Nausea and vomiting of pregnancy (NVP)	Acute	Vomiting may occur in the morning or throughout the day. Associated breast tenderness. NVP typically starts in weeks 4 to 7, peaks in weeks 10 to 16, and disappears by week 20. Vomiting that begins after week 12 or continues past week 20 should prompt a search for another cause.	Very common Affects 75% of all pregnancies	Benign abdomen	Urine pregnancy test Serum electrolytes, urine ketones to exclude hyperemesis gravidarum	Consider NVP in all females of childbearing age. Prognosis for mother and infant is excellent. NVP is associated with a decreased risk of miscarriage, fetal growth retardation, and fetal mortality.
Hyperemesis gravidarum	Acute	Severe, protracted form of NVP. No universally accepted definition of the disease. Generally accepted hallmarks include 5% weight loss, ketonuria, and electrolyte disturbance. Hyperemesis is associated with multiple gestation, molar pregnancy, and nulliparity.	Uncommon Affects <1% of pregnancies	Signs of dehydration Benign abdomen	β-hCG Urinalysis for ketones Serum electrolytes Ultrasound examination to exclude molar pregnancy or multiple gestations (if not already performed this pregnancy)	Most studies have found no adverse outcomes for the fetus. A few studies, however, have shown a correlation with fetal growth retardation.
Gastroenteritis	Acute	Fever, diarrhea, and crampy abdominal pain. Vomiting and pain occur early, usually followed by diarrhea within 24 hours.	Very common	Benign abdomen	Usually not necessary	Early gastroenteritis, when only vomiting and periumbilical pain are present, may be confused with early appendicitis. Diarrhea is usually in the diagnosis of gastroenteritis.
Gastritis	Acute	Epigastric pain, belching, bloating, fullness, heartburn, and food intolerance. Use of NSAIDs or ETOH common.	Very common	Mild epigastric tenderness may be present.	Lipase and pregnancy test may be necessary to exclude other diagnoses	Removal of inciting agent along with antacid therapy will resolve symptoms in most patients.
Peptic ulcer disease (PUD)	Acute Chronic	Epigastric pain present in 90% of cases. Classically, duodenal ulcer pain is relieved by food, whereas gastric ulcer pain is made worse. Presence of severe pain should raise suspicion of perforation.	Very common	Mild epigastric tenderness	Hemoglobin and hemoccult testing if bleeding is suspected Upright abdominal film if perforation is suspected	Three major causes of PUD are NSAIDs, *Helicobacter pylori* infection, and hypersecretory states.
Biliary disease		Abdominal pain may be midepigastric or RUQ. Onset frequently after a fatty meal. May have history of similar episodes in the past.	Very common	RUQ tenderness present in most cases. If instructed to breathe deeply during palpation in the RUQ, the patient experiences heightened tenderness and inspiratory arrest (Murphy's sign).	WBCs Lipase Serum bilirubin LFTs RUQ ultrasound examination	Normal temperature, WBCs, and spontaneous resolution of symptoms suggest biliary colic. Fever, Murphy's sign, elevated WBCs, and suggestive ultrasound indicate cholecystitis.
Myocardial infarction (MI)	Acute	Patients typically have substernal chest pain that may radiate to left arm or jaw. Often associated with dyspnea, diaphoresis, or dizziness.	Common	Patients often are anxious and in distress from pain. No diagnostic examination findings.	ECG (new Q waves, ST segment changes, or T wave inversions) troponin	Not all patients have chest pain. A subset of patients, particularly diabetics and elders, may have only nausea, vomiting, and epigastric discomfort.

Continued

TABLE 26.2

Disorders Commonly Associated With Vomiting—cont'd

DISORDER	CLASS	HISTORY	PREVALENCE	PHYSICAL EXAMINATION	USEFUL TESTS	COMMENTS
Diabetic ketoacidosis (DKA)	Acute	Polydipsia and polyuria occur early. Without treatment, altered mental status and coma may develop. In patients with long-standing diabetes, DKA may be triggered by infection, change in medication trauma, MI, or surgery.	Common	"Fruity" breath odor results from serum acetone. Tachypnea occurs with attempts to "blow off" carbon dioxide to compensate for metabolic acidosis. Signs of dehydration may be present. Severe cases often manifest with altered mental status or coma.	Serum glucose Electrolytes Urine ketones VBGs	DKA may be the first manifestation of diabetes in some patients. These patients often do not recognize the importance of polydipsia and polyuria. They often report only nausea, vomiting, and epigastric pain.
Pancreatitis	Acute Chronic	Presenting symptom is epigastric pain, which often radiates to the back. Most cases are caused by gallstones or alcoholism.	Common	Epigastric tenderness is present. Associated paralytic ileus may cause abdominal distention and decreased bowel sounds. Frank shock may be present in severe cases.	Lipase WBCs Serum glucose LDH AST Hematocrit BUN Calcium VBGs	Criteria correlating with higher mortality: *At admission*—age >55 years old, WBCs >16,000/mm^3, glucose >200 dL, base deficit >4, LDH >350 IU/L, AST >250 U/L *Within 48 hours*—Hct drop of 10%, BUN >2 mg/dL, Po_2 4 L
Appendicitis	Acute	Abdominal pain classically begins in periumbilical region and later moves to right lower quadrant. Anorexia is common.	Common	Localized tenderness over right lower quadrant. Low-grade fever may be present.	WBCs Ultrasound Abdominal CT	Early appendicitis can be a difficult diagnosis to make. It is still frequently missed on the first physician encounter.
Bowel obstruction	Acute Chronic	Classically, abdominal pain consists of intermittent cramps occurring at regular intervals. The frequency of the cramps varies with the level of the obstruction; the higher the level, the more frequent the cramps. The location of the pain also varies with the level of the obstruction; high obstruction causes epigastric pain, midlevel obstruction causes periumbilical pain, colonic obstruction causes hypogastric pain.	Common	Abdominal distention, mild diffuse tenderness, and high-pitched "tinkling" bowel sounds may be present. Thorough search for hernias should be performed.	Electrolytes Lactate Abdominal ultrasound Abdominal CT	Adhesions, hernias, and tumors account for 90% of bowel obstructions. Other causes include intussusception, volvulus, foreign bodies, gallstone ileus, inflammatory bowel disease, stricture, cystic fibrosis, and hematoma.
Carbon monoxide (CO) poisoning	Acute	Headache is usually present. CO poisoning often occurs during winter months when furnaces are turned on. Family members may have similar symptoms if they also have been exposed.	Uncommon	No reliable signs of early CO poisoning	CO level	Because CO is a tasteless, odorless gas, patients may not realize they have been exposed. It is important to keep a high index of suspicion during the cold months.
Boerhaave's syndrome	Acute	Patients may have neck, chest, or epigastric pain. Forceful, protracted vomiting usually causes the tear. Most cases follow a bout of heavy eating and drinking. Other reported causes include childbirth, defecation, seizures, and heavy lifting.	Uncommon	Tachypnea, tachycardia, and hypotension may be present. Escaped air from the esophagus may produce subcutaneous emphysema. Air in the mediastinum produces a "crunching" sound as the heart beats (Hamman's sign).	CXR may show pleural effusion, widened mediastinum, pneumothorax, or pneumomediastinum. Esophagogram with water-soluble contrast is definitive.	The classic presentation includes forceful vomiting, severe chest pain, subcutaneous emphysema, and multiple CXR findings. There is a growing body of evidence that most cases do not have this "classic" picture. In more subtle presentations, the diagnosis can be difficult to make.

AST, Aspartate aminotransferase; *β-hCG,* beta-human chorionic gonadotropin; *BUN,* blood urea nitrogen; *CT,* computed tomography; *CXR,* chest radiography; *ECG,* electrocardiogram; *ETOH,* ethyl alcohol; *Hct,* hematocrit; *LDH,* lactate dehydrogenase; *LFT,* liver function test; *NSAID,* nonsteroidal antiinflammatory drug; Po_2, partial pressure of oxygen; *RUQ,* right upper quadrant; *VBG,* venous blood gases; *WBC,* white blood cell.

TABLE 26.3

Causes of Nausea and Vomiting

ACUTE	CHRONIC	EPISODIC	CYCLICAL
Ischemic bowel	Chronic pancreatitis	Cholelithiasis	Cyclical vomiting syndrome
Ruptured viscus	Gastroparesis	IBD	Cannabinoid hyperemesis syndrome
Cholangitis	PUD	IBS	
Cholecystitis/ cholelithiasis	Gastritis	Gastritis	
Bowel obstruction	Gastric outlet obstruction	BPPV	
Appendicitis	CNS tumor	Motion sickness	
Peritonitis	Raised ICP	Chemotherapy	
Acute pancreatitis	Migraine	DKA	
PUD	Drug toxicity	Uremia	
Gastroenteritis	Bulimia	Pregnancy	
Hepatitis	Carbon monoxide		
Food poisoning	Pregnancy		
Intracerebral bleed			
Meningitis			
Cerebellar infarct			
Drug toxicity			
Drug withdrawal			
Renal colic			
Gonadal torsion			
Pyelonephritis			
Myocardial infarction			
Sepsis			
Carbon monoxide			
Alchohol intoxication			
Alcohol withdrawal			

BPPV, Benign paroxysmal peripheral vertigo; *CNS,* central nervous system; *DKA,* diabetic ketoacidosis; *IBD,* inflammatory bowel disease; *IBS,* inflammatory bowel syndrome; *ICP,* intracranial pressure; *PUD,* peptic ulcer disease.

will have neuroimaging performed, and patients with suspected myocardial infarction will have an electrocardiogram (ECG) and cardiac enzyme testing.

If an emergent cause of nausea and vomiting is confirmed or highly suspected based on the initial evaluation and ancillary testing, then appropriate management is undertaken. Patients who are generally well and have a low likelihood of a serious cause, whose symptoms are controllable, but for whom the diagnosis is still unclear, should have follow-up arranged within 24 to 48 hours for reevaluation if symptoms persist or more urgently if symptoms worsen or a new, concerning symptom, such as blood in the stool or vomit, fever, or localized pain, develops.

Patients who have a suspected or confirmed nonemergent diagnosis are treated with antiemetic medications, with specific

TABLE 26.4

Differential Diagnosis of Nausea and Vomiting

ETIOLOGIC CATEGORY	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Gastrointestinal (GI)	Boerhaave's syndrome Ischemic bowel GI bleeding Ruptured viscus Cholangitis	Gastric outlet obstruction Pancreatitis Cholecystitis Bowel obstruction or ileus Appendicitis Peritonitis Spontaneous bacterial peritonitis	Gastritis Gastroparesis Peptic ulcer disease Inflammatory bowel disease Biliary colic Hepatitis Gastroenteritis Food poisoning Inflammatory bowel syndrome
Neurologic	Intracerebral bleed Meningitis	Meningitis CNS tumor	Migraine
Vestibular	Cerebellar infarct	Raised ICP Suppurative labyrinthitis	BPPV
Endocrine	DKA	Adrenal insufficiency Uremia	Thyroid disorder
Pregnancy		Hyperemesis gravidarum	Nausea and vomiting of pregnancy
Drug toxicity	Acetaminophen Aspirin	Digoxin Theophylline	
Therapeutic drug use			Aspirin Antibiotics Erythromycin Ibuprofen Chemotherapy
Drugs of abuse		Alcohol withdrawal	Narcotics Narcotic withdrawal Alcohol
Genitourinary	Gonadal torsion		Urinary tract infection Nephrolithiasis
Miscellaneous	Myocardial infarction Sepsis Organophosphate poisoning	Carbon monoxide Electrolyte disorders	Motion sickness Labyrinthitis

BPPV, Benign paroxysmal peripheral vertigo; *CNS,* central nervous system; *DKA,* diabetic ketoacidosis; *ICP,* intracranial pressure.

TABLE 26.5

Differential Diagnosis Based on Content of Vomitus

COLOR/CONTENT OF VOMITUS	DIAGNOSES
Bright red blood	Peptic ulcer Gastritis Esophageal varices Aortoenteric fistula Esophageal rupture Duodenal or gastric tumors Mallory-Weiss syndrome Dieulafoy's lesion Foreign body
Coffee grounds	Peptic ulcer Gastritis Esophageal varices Duodenal or gastric tumors Mallory-Weiss syndrome
Undigested food	Gastric outlet obstruction Achalasia Esophageal stricture Foreign body
Feces	Small bowel obstruction Large bowel obstruction
Bilious (adults)	Small bowel obstruction Large bowel obstruction

TABLE 26.6

Physical Examination of the Patient With Nausea and Vomiting

ORGAN SYSTEM	FINDING	SUGGESTED DIAGNOSES
General	Poor skin turgor Dry mucous membranes	Dehydration
Vital signs	Fever	Gastroenteritis, cholecystitis, appendicitis, hepatitis Bowel perforation
	Tachycardia, orthostatic changes	Dehydration
HEENT	Nystagmus	Labyrinthitis Vertebrobasilar insufficiency Cerebellar infarct or bleed CPA tumor
	Papilledema	Increased ICP from CNS tumor or bleeding
Neck	Goiter	Thyroid disease
Lungs	Rales	Pneumonia
Heart	Arrhythmia Murmur	Acute myocardial infarction or other cardiac pathology
Abdomen	Abdominal distention	Bowel obstruction, gastroparesis
	Peristaltic waves High-pitched bowel sounds	Gastric outlet obstruction Bowel obstruction
	Decreased bowel sounds	Ileus
	Hernias or surgical scars	Possible bowel obstruction
	Peritoneal signs	Appendicitis, cholecystitis Perforated viscus
Neurologic	Abnormal mental status Cerebellar findings Cranial nerve findings	CNS pathology

CNS, Central nervous system; *CPA,* cerebellopontine angle; *HEENT,* head, eyes, ears, nose, throat; *ICP,* intracranial pressure.

management directed at the underlying cause. Patients with cyclical or recurrent vomiting syndromes do not require any particular diagnostic testing in the ED and should be managed in consultation with the patient's primary care physician. However, care should be taken to avoid anchoring on the patient's previous diagnosis of cyclical vomiting syndrome and should seek corroborative information from the patient, the medical record, family members, or the primary physician to ensure that the pattern of the presentation fits the patient's syndrome and to exclude alternate emergent causes of vomiting.

EMPIRICAL MANAGEMENT

Symptomatic relief of nausea, vomiting, or pain should not await identification of the underlying cause. Decreased oral intake with concomitant fluid loss (by vomiting) causes dehydration. If the patient is mildly or moderately dehydrated and is able to take oral liquids, a solution containing sodium, carbohydrate, and water is recommended. Many sports drinks contain the proper balance of these elements. Patients who are severely dehydrated or in whom intake of oral fluids is not possible or is contraindicated should be given IV crystalloid solution (usually normal saline) and electrolyte abnormalities corrected. Placement of a nasogastric tube is not indicated, except in patients with bowel obstruction.

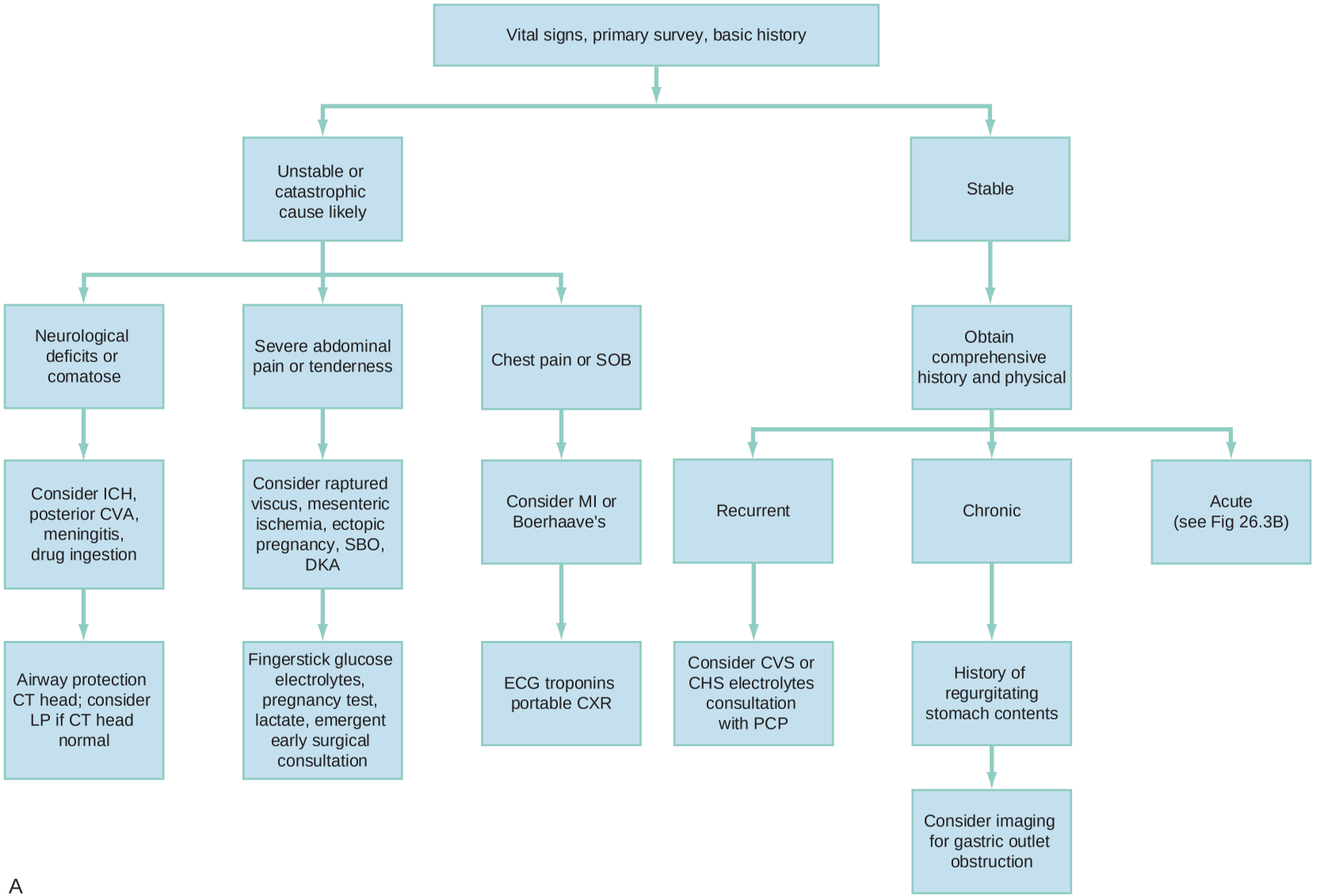
The need for antiemetics and the response to therapy may be measured with scales similar to those used for pain assessment, such as the visual analog scale and the verbal categorical scale.

Patients presenting to the ED with nausea or vomiting may have a known etiology with specific treatment aimed toward treating the underlying cause. These are discussed in the Specific Situations section.

For the patient with either non-obstructive GI causes or undifferentiated nausea and vomiting, there is very limited evidence to support one agent over another. A large, randomized trial of ED patients with undifferentiated nausea and vomiting found no difference in the primary outcome of reduction of symptoms between metoclopramide 20 mg IV, ondansetron 4 mg IV, or saline placebo.[2] There was a decreased need for rescue antiemetics in patients who received metoclopramide; however, these patients also had more side effects. These findings were similar to previous smaller trials, where various commonly used medications were compared and no statistically significant difference between the various medications were found.[2-3] Children, pregnant patients, and hemodynamically unstable patients were excluded from all studies. When comparing the raw data of all the randomized controlled trials, decreased nausea scores were associated with increasing amount of IV saline given.[2] Although this has not been formally studied, IV fluids alone may be an effective treatment for nausea and vomiting.

The pharmacologic management of patients with nausea and vomiting is outlined in Table 26.7, and a management algorithm is shown in Figure 26.4. To allow the physician to tailor the appropriate choice for each patient, the pharmacologic therapies available may be classified into serotonin antagonists, histamine antagonists, muscarinic antagonists, and dopamine antagonists.

The serotonin antagonists, particularly ondansetron, are considered first line therapies for most cases of nausea and vomiting in the ED, except in specific situations discussed later. Other



A

Fig. 26.3. A and **B,** Approach to the patient with nausea and vomiting. *BMP,* Basic metabolic panel; *CT,* computed tomography; *CVA,* Cerebrovascular accident; *CVS,* cyclical vomiting syndrome; *CXR,* chest x-ray; *DKA,* diabetic ketoacidosis; *ECG,* electrocardiogram; *ICH,* intracranial hemorrhage; *LFT,* liver function test; *LP,* lumbar puncture; *MI,* myocardial infarction; *PCP,* phencyclidine; *SBO,* small bowel obstruction; *SOB,* shortness of breath; *US,* ultrasound; *VBG,* venous blood gas.

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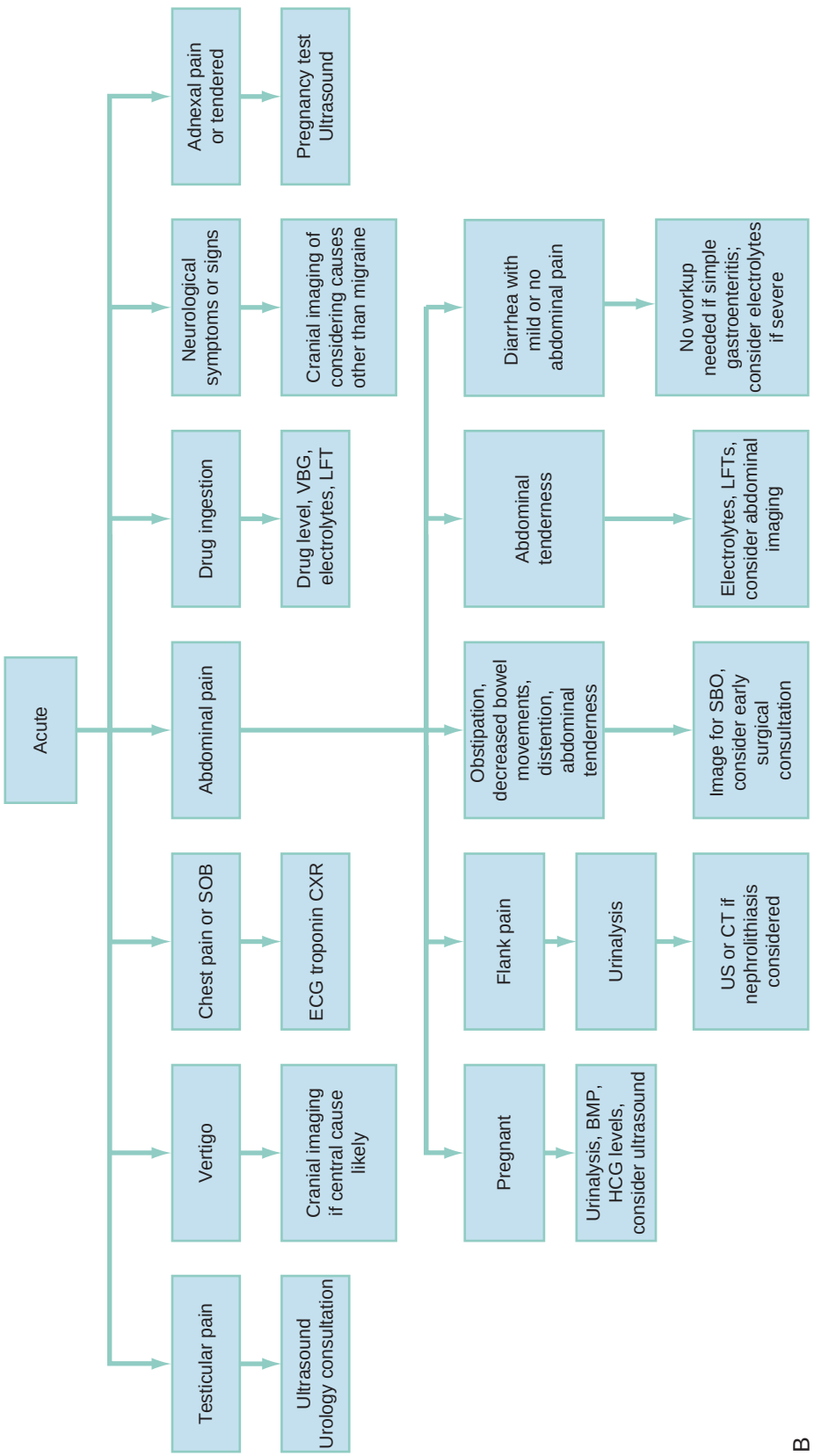

B

Fig. 26.3., cont'd

TABLE 26.7

Commonly Used Medications for the Treatment of Nausea and Vomiting

MEDICATION	CLASS	SITE OF ANTIEMETIC ACTION	DOSAGE	ADVERSE EFFECTS
Ondansetron (Zofran)	Serotonin antagonist	5-HT_3 receptor at CTZ and vagus nerve terminal in GIT	*Adult:* Usual: 4 to 8 mg IV single dose, may go up to 16	May cause headache, dizziness, and musculoskeletal pain.
Metoclopramide (Reglan)	Dopamine and serotonin antagonist	D2 and 5-HT_3 receptors in CTZ. D2 in stomach and LES	*Adult:* 10 to 20 mg IM or IV, may repeat every 6 hours	May cause dystonic reactions, tardive dyskinesia (black box warning), neuroleptic malignant syndrome, restlessness, drowsiness, diarrhea.
Prochlorperazine (Compazine)	Dopamine antagonist	D1 and D2 receptor in CTZ	*Adult:* 5 to 10 mg IM or PO; 2.5 to 10 mg IV every 4 hours as needed; 25 mg by rectum every 12 hours as needed	May cause lethargy, hypotension, extrapyramidal effects, dystonic reactions, sedation, and feelings of restlessness. Rarely neuroleptic malignant syndrome, blood dyscrasias, and cholestatic.
Promethazine (Phenergan)	Antihistamine	H1 receptor in CTZ, minimal D2	*Adult:* 12.5 to 25 mg IV, IM, PO, or by rectum every 4 hours as needed	Extravasation may cause severe tissue injury (black box warning). May cause sedation, dry mouth, dizziness, blurred vision.
Dimenhydrinate (Dramamine, Gravol)	Antihistamine	H1 receptor in GIT and CTZ	25–50 mg IV, IM, or PO every 6 hours as needed	Drowsiness, light-headedness.

CTZ, Chemoreceptor trigger zone; *GIT,* gastrointestinal tract; *IM,* intramuscularly; *IV,* intravenously; *LES,* lower esophageal sphincter; *PO,* per os (by mouth).

serotonin antagonists (such as, granisetron) are available but have not been studied in the ED and therefore cannot be recommended over ondansetron. The initial dose of ondansetron is 4 to 8 mg IV. A single dose of up to 16 mg is considered safe in the non-elderly population. In the elderly, it is recommended that the initial dose should not exceed 8 mg infused over at least 15 minutes. Ondansetron at higher doses and faster infusion rates may cause QT prolongation in older patients.[4] For most patients, there are few or no side effects of the serotonin receptor antagonists and, if they occur, are mild. If the patient is known to have a long QT or is at risk of developing long QT syndrome, then it is best to reserve ondansetron as a second line agent. Ondansetron has also been associated with serotonin toxicity when given concurrently with other serotonergic agents.[5]

Metoclopramide (Reglan) is the other first line agent for use in the ED. Metoclopramide is an excellent general-purpose antiemetic. As a prokinetic agent, it is useful in patients with gastroparesis and other dysmotility syndromes. The initial dose of metoclopramide is 10 to 20 mg IV/intramuscular (IM).

The phenothiazines, prochlorperazine (Compazine) and promethazine (Phenergan), have historically been first-line agents and are still widely used as general-purpose antiemetics. In one study, prochlorperazine was found to be a superior to promethazine. Although both of these agents are sedating, promethazine is more sedating than prochlorperazine and is associated with more extra-pyramidal effects. Due to increased side effects, these medications are considered third line in the ED.

The anti-psychotic medication, droperidol, is also considered effective in the treatment of nausea and vomiting. In one randomized control trial, droperidol was found to be superior to other first-line agents.[6] Droperidol has generally fallen out of favor in the ED due to the black box warning on QT prolongation. An ECG should be performed prior to administration to check for QT prolongation. A dose of 1.25 mg IV is sufficient in most patients. The dose may be repeated in 60 minutes if needed.

For patients with undifferentiated nausea and vomiting or those without specific causes listed in the special situations below, start with ondansetron 4 mg IV. It is inexpensive and generally well tolerated. IV crystalloid should also be given if there are no contraindications. A repeat 4 mg IV dose should be given initially if there is no response. If there is there is still an inadequate response, than metoclopramide 10 mg IV should be given, with a repeat dose of metoclopramide after 30 minutes, if needed. A poor response to the above antiemetics should prompt the clinician to consider an underlying mechanical GI obstruction inducing the symptoms, and this should be addressed if present.

If ondansetron and metoclopramide have not been effective and a mechanical obstruction is unlikely, consider using droperidol in a patient at low risk of adverse effects from the droperidol. Begin with 1.25 mg IV, and the dose may be repeated if no effect is seen within 30 minutes. If droperidol is not considered safe, then the next drug of choice should be prochlorperazine. A single dose of 10 mg IV is appropriate. If sedation is desired, promethazine may be given prior to trying prochlorperazine. For most patients, begin with promethazine 12.5 mg IV, which may be repeated in 30 minutes if tolerated. In patients who may not tolerate sedation, such as elderly patients, those with underlying respiratory diseases, or those with other sedating medications, begin at 6.25 mg IV, which may be incrementally increased as tolerated. Dimenhydrinate may be given instead of promethazine, but they should not be given together due their sedating effects.

Finally, patients who remain highly symptomatic after these medications should be admitted to the hospital for continued management and evaluation for the etiology of the vomiting.

Special Situations

Opioid-Induced Vomiting

Antiemetic medications are frequently used in the mistaken belief that they reduce the incidence of nausea and vomiting when opioid analgesics are administered in the ED for pain control. Studies have demonstrated that the incidence of nausea and vomiting related to opioid administration in the ED is low and that these medications have little efficacy in reducing nausea and vomiting.

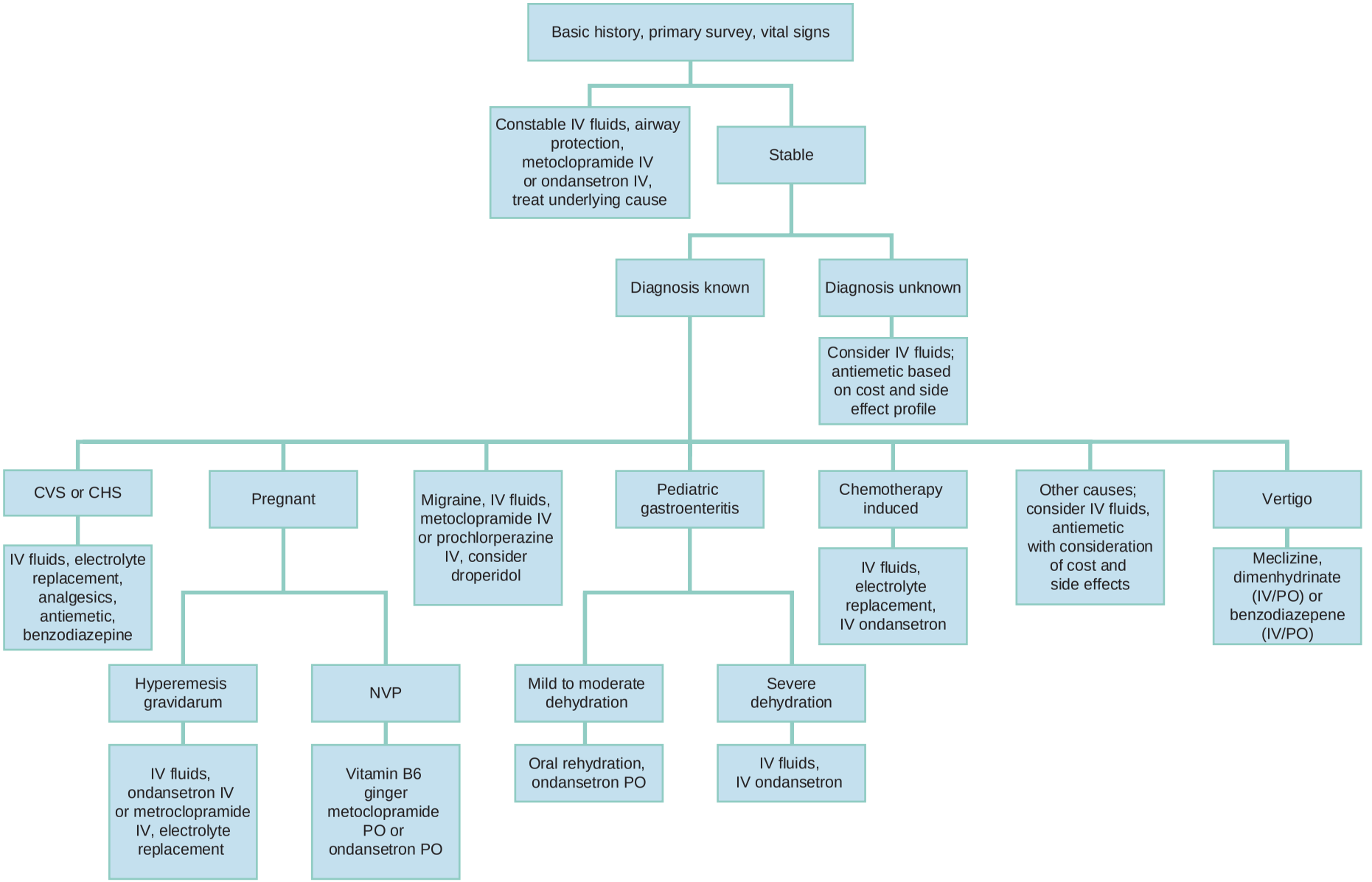

Fig. 26.4. Management algorithm for the patient with nausea and vomiting. *CHS,* cannabinoid hyperemesis syndrome; *CVS,* cyclical vomiting syndrome; *IV,* intravenous; *NVP,* nausea and vomiting of pregnancy; *PO, per os* (by mouth).

Headache

Patients with nausea or vomiting associated with a headache should be given metoclopramide as the first line agent. Metoclopramide will treat the both the headache, as well as the nausea and vomiting. Ondansetron may cause headache and therefore is not appropriate as a first line agent. If metoclopramide is ineffective, then prochlorperazine may be used a second line agent, because it has also shown to be effective in the treatment of headaches. Finally, droperidol is effective for headaches and for nausea and vomiting and should be considered if the first two agents fail.

Pregnancy

Many agents, both pharmacologic and non-pharmacologic have been evaluated in the treatment of nausea and vomiting of pregnancy and hyperemesis gravidarum. A recent Cochrane review concluded that there was insufficient high quality evidence to recommend one agent over another. Agents that have shown to be more effective when compared to placebo include ginger, vitamin B6 (pyridoxine), vitamin B6 combination products (such as, doxylamine with pyridoxine), ondansetron, and metoclopramide. Studies comparing ondansetron to metoclopramide have not shown a difference in effectiveness.[7] Although the quality of the evidence is poor, there may be an association between ondansetron use and fetal malformations in the first trimester.[8]

In pregnant patients presenting with nausea and vomiting, metoclopramide 10 mg IV should be the first line agent. Ondansetron should be reserved as a second line agent. If the pregnant patient is discharged from the ED, then a vitamin B6 combination product should be prescribed if her symptoms return.

Chemotherapy

Chemotherapy-related nausea and vomiting may be seen in ED patients. The chemotherapy-induced nausea and vomiting may be acute (up to 24 hours) or delayed (after 24 hours). Ondansetron is the first line agent and should be given at repeated doses. Start with 4 mg IV and repeat every 30 minutes up to 16 mg IV. A single dose of dexamethasone 10 mg IV should be added if the vomiting is refractory to the ondansetron.

Cyclical Vomiting

Patients with cyclical vomiting syndrome may be difficult to manage. They should receive IV hydration and may require high doses of an antiemetic medication, although once again, none of which has been deemed superior to another. Benzodiazepines are recommended in this condition, because inducing sleep often terminates the episode, especially if antiemetic therapy fails to abort the episode and admission is considered.[9]

Although the evidence is primarily anecdotal, patients with cannabis hyperemesis syndrome should be treated with IV fluids, an antiemetic medication, and frequent hot showers. Patients should be advised to abstain from marijuana use, because that is the only known cure. Patients with a history of cannabis hyperemesis syndrome have been shown to relapse if they resume marijuana use, even after a long period of abstention.

Vertigo

Antihistamines are useful in nausea and vomiting associated with motion sickness and vertigo. Agents such as dimenhydrinate (Gravol, Dramamine) and meclizine (Antivert) directly inhibit vestibular stimulation and vestibular-cerebellar pathways. Their anticholinergic effect also may contribute to their effectiveness in vertigo and motion sickness. Antihistamines have some role as general antiemetics but are better used in the prevention of motion sickness. The most common side effects of antihistamines are drowsiness, blurred vision, dry mouth, and hypotension.

DISPOSITION

Hospital admission is appropriate when the patient has a significant underlying disease, has an unclear diagnosis and responds poorly to fluid and antiemetic therapy, continues to experience uncontrolled emesis refractory to medication, or is at the extremes of age with poor response to treatment. More difficult disposition decisions are related to patients in whom the diagnosis is unclear and prospects for timely follow-up are poor. Discharge may be considered if no serious underlying illness is present, the response to fluid and antiemetic therapy is good, the patient is able to take clear liquids before discharge, and the prospects for follow-up and observation at home are favorable.

Close follow-up often is advisable for discharged patients, preferably with their primary care physician, in 24 to 48 hours. At discharge, the patient is prescribed medications as needed and is advised to restart oral intake with small feedings of a liquid diet with gradual return to a normal diet. Clear instructions are given to return to the ED if there is a recurrence, change, or deterioration in symptoms.

Causes for nausea and vomiting frequently remain undiagnosed. Some cases declare themselves or resolve over time; reevaluation and close follow-up are fundamental in the care for patients with continuing symptoms.

KEY CONCEPTS

- Nausea and vomiting can result from a primary problem in the GI tract but can also be secondary to problems in the neurological, vestibular, urogenital, and cardiac systems.
- Associated symptoms and a medication/drug history are the most helpful in narrowing the differential diagnosis in the acutely vomiting patient.
- Laboratory studies are not required in all patients who vomit. Patients with severe or protracted vomiting, sufficient to require IV rehydration, should have their electrolytes and renal function determined and corrected.
- In a patient with undifferentiated nausea or vomiting or vomiting due to non-obstructive GI disease, ondansetron is the first line antiemetic.
- Although evidence is limited, metoclopramide is the antiemetic of choice in hyperemesis gravidarum and vomiting associated with headache; ondansetron is the drug of choice in chemotherapy induced vomiting.
- Antiemetics should not be prescribed routinely in patients receiving opioid analgesia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 26: QUESTIONS & ANSWERS

26.1. Which of the following metabolic derangements is most likely in a patient with severe, protracted vomiting?
- **A.** Hypochloremic, hypokalemic, metabolic alkalosis
- **B.** Hypochloremic, hypokalemic, metabolic acidosis
- **C.** Hyperchloremic, hypokalemic, metabolic alkalosis
- **D.** Hyperchloremic, hypokalemic, metabolic acidosis
- **E.** Hyperchloremic, hyperkalemic, metabolic acidosis

Answer: E. Severe, protracted vomiting can cause a hypochloremic, hypokalemic, metabolic alkalosis. The metabolic alkalosis is produced by loss of hydrogen ions in the vomitus. Many factors serve to maintain the alkalosis including volume contractions, hypokalemia, chloride depletion, shift of extracellular hydrogen ions into cells, and increased aldosterone. Hypokalemia is produced primarily by loss of potassium in the urine. The metabolic alkalosis leads to large amounts of sodium bicarbonate being delivered to the distal tubule. Secondary hyperaldosteronism from volume depletion causes reabsorption of sodium and excretion of large amounts of potassium in the urine.

26.2. Antihistamines would most effectively control the nausea and vomiting caused by which of the following conditions?
- **A.** Chemotherapy administration
- **B.** Digoxin ingestion
- **C.** Gastritis
- **D.** Gastroparesis
- **E.** Labyrinthitis

Answer: E. Antihistamines are useful in nausea and vomiting associated with labyrinthitis, motion sickness, and vestibular disorders by directly inhibiting vestibular stimulation and vestibular-cerebellar pathways. Their anticholinergic effect may also contribute to their effectiveness in vertigo and motion sickness.

26.3. A 35-year-old man is given 10 mg of IV prochlorperazine for treatment of nausea. Fifteen minutes after the administration of medication, he displays protrusion of his tongue, difficulty speaking, intermittent contractions of his facial muscles, and anxiety. Which of the following would be the most appropriate next step in the management of this patient?
- **A.** Administer benztropine mesylate
- **B.** Administer haloperidol
- **C.** Five-point physical restraints
- **D.** Rapid sequence intubation
- **E.** Repeat dose of prochlorperazine

Answer: A. The described patient is experiencing a dystonic reaction to prochlorperazine (Compazine). Drug-induced dystonic reactions most commonly occur with antipsychotic, antidepressant, and antiemetic medications. Administration of an anticholinergic medication such as benztropine mesylate (Cogentin) or diphenhydramine (Benadryl) is the treatment of choice and typically aborts the reaction. Benzodiazepine administration may occasionally be necessary if the previously mentioned medications are ineffective. Artificial airway placement and use of restraints are rarely required. Further dopamine receptor blockade with haloperidol or additional doses of the offending agent would not prove useful.

26.4. Where is the principal site of action of the serotonin receptor antagonist ondansetron?
- **A.** Area postrema
- **B.** Basal ganglia
- **C.** GI tract
- **D.** Hypothalamus
- **E.** Vestibular system

Answer: A. The serotonin receptor antagonists such as ondansetron, granisetron, and tropisetron are a class of agents that have generated much interest secondary to their effect on chemotherapy-induced emesis. Their principal site of action is the area postrema, which is located in the lateral reticular formation of the medulla. They also exert some effect on receptors of the GI tract; however, this is secondary to their effect in the area postrema.

26.5. What is the most common cause of nausea and vomiting in the adult population?
- **A.** Acute gastroenteritis
- **B.** Drug side effects
- **C.** Febrile systemic illness
- **D.** Motion sickness
- **E.** Pregnancy

Answer: B. In adult medicine, nausea and vomiting are caused most often by medications. When considering the entire population (pediatrics and adults), the three most common causes of nausea and vomiting are acute gastroenteritis, febrile systemic illnesses, and drug effects.

CHAPTER 27

Gastrointestinal Bleeding

David A. Meguerdichian | Eric Goralnick

PERSPECTIVE

Upper and lower gastrointestinal bleeding (GIB) are defined based on their location relative to the ligament of Treitz in the terminal duodenum, so esophagus, stomach, and duodenum origin bleeds are upper and all others are lower. Upper GIB (UGIB) mortality rates have remained constant at about 15% over the past 2 decades despite advances in medical therapy, intensive care unit (ICU) management, endoscopy, and surgery. This is most likely due to the increasing proportion of older patients, who may die due to comorbid conditions, and increases in cirrhotic and variceal patients. The lower GIB (LGIB) mortality rate is approximately 4%. Predictors include age older than 70 years, intestinal ischemia, comorbid illness, coagulation defects, transfusion of packed red blood cells, and male gender.

DIAGNOSTIC APPROACH

Differential Considerations

The characteristics of the GIB, age of the patient, and social factors can all help determine the cause. UGIB can routinely manifest as bloody or coffee-ground–like vomit termed *hematemesis* or as dark, tarry stools termed *melena.* In older adults, peptic ulcer disease, esophagitis, and gastritis account for most cases. Younger patients typically present with Mallory-Weiss tears, GI varices, and gastropathy (Table 27.1). As a whole, peptic ulcer disease makes up more than 50% of all acute cases of UGIB seen in the emergency department (ED).[1] In pediatric patients, gastric and duodenal ulcers, esophagitis, gastritis, esophageal varices, and Mallory-Weiss tears account for most cases of UGIB, in descending order of frequency.

LGIB usually produces bright red or maroon blood per rectum, termed *hematochezia.* LGIB may be classified according to pathophysiologic cause—inflammatory, vascular, oncologic, traumatic, or iatrogenic. Anorectal sources, such as hemorrhoids, are the most common causes of LGIB in all age groups. In adults, the most common sources of hematochezia are colonic diverticula and angiodysplasia. Other noteworthy causes include colitis caused by ischemia, infection, and inflammatory bowel disease. Among older patients with cardiovascular disease, ischemic colitis as a cause for LGIB has been increasing. Although uncommon, a brisk UGIB may present as hematochezia and be mistaken for a bleed from a lower GI source. Up to 14% of bleeds characterized as hematochezia are due to such lesions and are associated with higher transfusion rates, surgical interventions, and mortality. Major causes of LGIB in children include anorectal fissures and infectious colitis. Bleeding can also be caused by intussusception and Meckel's diverticulum in infants and toddlers. Despite diagnostic advances for all ages, the source of GIB is not identified in nearly 15% of patients.

Death from exsanguination resulting from GIB is rare. However, there are two causes of GIB that may rapidly cause death if not recognized and mitigated, esophageal varices and aortoenteric fistula. The former, which typically arises from portal hypertension usually caused by alcoholic cirrhosis, is the single most common source of massive UGIB and has a mortality rate of 30%. The latter is caused when an abdominal aortic aneurysm or, more commonly, an aortic graft adheres to and erodes through a bowel wall. Aortoenteric fistula is a rare but rapidly fatal cause of GIB, with the mortality of an untreated fistula of nearly 100%. Aortoenteric fistula is a primary consideration in patients with GIB and known abdominal aortic aneurysms or aortic grafts until an alternative bleeding source is identified. Prompt surgical consultation is warranted when aortoenteric fistula is a likely diagnosis.

Finally, in the differential considerations, one must determine whether the blood is actually of GI origin. Epistaxis, dental bleeding, or red food coloring can mimic the appearance of hematemesis. Bismuth-containing medications and iron supplements can create melanotic-appearing (but guaiac-negative) stools. Vaginal bleeding, gross hematuria, and red foods (eg, beets) can all be mistaken for hematochezia (Box 27.1). Unless an alternative diagnosis is clearly evident, the appropriate approach is to continue with the evaluation for GIB.

Pivotal Findings

The history centers on the GI tract and on the timing, quantity, and appearance of the bleeding. Relevant comorbid conditions should be reviewed as well (Box 27.2). The extent of the history will be dictated by the severity of the complaint and hemodynamic stability of the patient on ED arrival. Reviewing the patient's vital signs, appearance of the stool, and basic laboratory studies will help identify the bleeding source and guide treatment.

Symptoms

A useful starting point for the emergency clinician is to determine the time of onset, duration of symptoms, and relevant supporting historical facts. Often, the degree of bleeding is better gauged by assessing symptoms associated with significant intravascular loss, such as weakness, shortness of breath, angina, orthostatic dizziness, confusion, palpitations, and report of cool extremities. Blood loss more than 800 mL will usually result in the onset of these complaints, with severe symptoms being described at a threshold greater than 1500 mL. Such symptoms indicate a decreased oxygen-carrying capacity that often accompanies significant blood loss and should prompt a thorough and expeditious evaluation and resuscitation.

The context of the bleeding can help explain its cause. For example, if a patient complains of bright red blood per rectum after several days of constipation and straining, that presentation suggests an anorectal source. Alternatively, a patient with hematemesis after several earlier episodes of retching would lead one to suspect an esophageal tear. Finally, a patient with easy bruising and recurrent gingival bleeding might suggest an underlying coagulopathy.

Efforts should be made to quantify the amount of blood lost during the bleeding event. Patients may describe the passage of large clots, blood changing the toilet bowl water red, or simply streaks of blood on the toilet paper. The patient's recollection of

TABLE 27.1

Common Causes of Gastrointestinal (GI) Bleeding in Adults and Children

CAUSE	ADULTS	CHILDREN
Common causes of upper GI bleeds	Peptic ulcers (gastric more than duodenal) Gastric erosion Esophagogastric varices Mallory-Weiss tears Esophagitis Gastric cancer	Duodenal ulcers Gastric ulcers Esophagitis Gastric erosion Esophageal varices Mallory-Weiss tears
Common causes of lower GI bleeds	Diverticular disease Angiodysplasia Colitis (inflammatory, infectious, ischemic) Anorectal sources Neoplasm Upper GI bleeding	Anorectal fissure Infectious colitis Inflammatory bowel disease Juvenile polyps Intussusception Meckel's diverticulum

BOX 27.1

Alternative Diagnoses or Mimics of Gastrointestinal Bleeding

Melena
- Ingestion of bismuth medications
- Ingestion of activated charcoal

Hematemesis
- Nasopharyngeal bleeding (eg, nosebleeds, dental bleeding)
- Ingestion of red drinks or food

Hematochezia
- Vaginal bleeding
- Gross hematuria
- Partially digested red food (eg, red beets, red grapes)

BOX 27.2

Characteristics of Patients With High-Risk Gastrointestinal Bleeds

Medication use
- Aspirin
- Nonsteroidal antiinflammatory drugs
- Steroids
- Anticoagulants (warfarin, heparin)
- Chemotherapeutic agents

History of peptic ulcer disease
Known liver disease, cirrhosis
Advanced age (>60 yr)
Alcoholism
Current smoker
Chronic medical comorbidities
- Congestive heart failure
- Diabetes
- Chronic renal failure
- Malignancy
- Coronary artery disease

History of abdominal aortic aneurysm graft

BOX 27.3

Key Historical Information for Patients With Gastrointestinal Bleeds (GIBs)

- Events prior to or leading up to the bleeding episode
- Severity, frequency, and quantity of the bleeding episode
- Appearance and color of the bleed
- Medical history, including risk factors for GIB:
  - Prior bleeding episodes and any identified source
  - Medication use that may increase the risk of GIB
  - Social factors that may increase the risk of GIB
- Symptoms patient is experiencing with the bleeding episode

the bleed and its amount is usually poorly quantified and inaccurate.

Classifying the blood as hematemesis, melena, or hematochezia provides the initial clue to the source of bleeding. Vomiting of fresh blood or blood with the appearance of coffee grounds strongly suggests a UGI source. The passage of melena, dark digested stools, also suggests likely UGIB. In contrast, the presence of hematochezia, bright red or maroon stools, usually signifies LGIB. There are exceptions, however. In a hemodynamically unstable patient, bright red blood per rectum can represent brisk UGIB. Hematemesis rarely can arise from a source in the LGI tract that is proximal to an obstruction. Although the definitive cause and location of the bleed will usually be determined by the gastroenterologist, the emergency clinician uses the history to make a reasoned determination of the likely source and help guide the initial diagnostic evaluation.

Relevant Medical History

A review of the patient's relevant medical history and risk factors for bleeding should note whether a patient has had similar bleeding before and the location of the causative lesion (Box 27.3). This is especially important with UGIB because most of these presentations are caused by rebleeding of previously identified sources. Next, identification of relevant comorbid diseases helps risk-stratify these patients in the context of their bleed. Patients with GIB and a history of coronary artery disease, congestive heart failure, liver disease, or diabetes have a higher mortality and therefore may require earlier or more extensive interventions.

A review of the patient's medications should pay particular attention to gastrotoxic substances, anticoagulants, and antiplatelet drugs. Medications such as nonsteroidal antiinflammatory drugs (NSAIDs), aspirin, warfarin, clopidogrel, corticosteroids, and certain chemotherapeutic agents are known to increase the risk of GIB by as much as threefold. In addition, reviewing the patient's social history can identify activities that increase risk for GIB. Alcohol abuse is associated with gastritis and peptic ulcer disease. It can also result in cirrhosis, portal hypertension and, ultimately, esophageal variceal bleeding. Smoking cigarettes results in slower healing and greater recurrence of ulcers. These two social habits are also closely associated with GI malignancy—another, albeit rare, risk factor for GIB.

Signs

Hypotension and tachycardia can suggest moderate hypovolemia and can be the early indicators of impending shock. Normal vital signs do not preclude the possibility of a severe bleed. Orthostatic vital signs, although frequently used historically, are insufficiently sensitive or specific to be of value in determining volume status in the context of acute blood loss.

Mental status is evaluated for signs of poor cerebral perfusion. Generalized pallor in a hemodynamically stable patient might indicate the anemia of a subacute or chronic GIB; in the unstable patient, pallor might reinforce the impression of malperfusion caused by massive blood loss. Cold clammy skin on the extremities signal significant volume loss consistent with hemorrhagic shock. Ecchymoses or petechiae suggest a coagulopathy. Finally, jaundice, palmar erythema, or spider angiomata suggests the possibility of UGIB from esophageal varices.

The abdomen is carefully examined for subtle findings that can help identify the source of bleeding. Hyperactive bowel sounds are a nonspecific finding, but might indicate UGIB, because intraluminal blood is a known cathartic that can stimulate peristalsis. Tenderness to palpation can be seen in many cases of peptic ulcer disease. Severe diffuse tenderness on examination warrants the consideration of bowel ischemia, mechanical obstruction, ileus, or bowel perforation. Evidence of peritonitis merits a rapid surgical consultation for possible operative management. The abdominal examination may also show further signs of portal hypertension with the presence of hepatomegaly, ascites, or caput medusae. The rectal examination helps determine the type of bleeding and should be performed in most patients with GIB. The examination should include evaluation of the external anus, digital rectal examination and, when local bleeding is thought to be the cause, anoscopy for hemorrhoids, polyps, or fissures.

Ancillary Testing

Occult Blood and Guaiac Bedside Testing

In patients with suspected UGIB, guaiac testing can be performed at the bedside to evaluate for occult blood, even when stool appears normal. The test makes use of the pseudoperoxidase activity found in hemoglobin. When hydrogen peroxide is dripped onto the guaiac paper containing the stool sample, an oxidative reaction rapidly turns the paper blue. The test can actually be positive for up to 2 weeks after an acute bleed and thus is more useful for diagnosing chronic occult bleeding. Uncommonly, false-positive results can be triggered by ingestions of red meat, turnips, horseradish, vitamin C, methylene blue, and bromide preparations. Iron- and bismuth-containing medications can cause dark stools that will be guaiac-negative. Similar testing is available for gastric contents but testing of UGI aspirates and vomitus is less reliable than testing of an LGI sample, and we do not recommend it. The clinical impression of an UGIB should override any testing. The diagnostic and prognostic limitations of nasogastric (NG) tube insertion are discussed below.

Laboratory Studies

Laboratory studies can assist in the risk stratification of GIB. Minimum testing should include evaluation of the patient's hemoglobin and blood urea nitrogen (BUN) levels, coagulation studies, and platelets. The hemoglobin level does not immediately decline in the setting of an acute bleed, because whole blood is lost. Changes in hemoglobin levels are typically seen after 24 hours, when there is hemodilution from shifting extravascular fluids and intravenous (IV) hydration with crystalloid. Nevertheless, acute hemoglobin levels less than 10 g/dL have been positively correlated with higher rates of rebleeding and mortality. Blood transfusion is indicated in a patient with GIB when their hemoglobin level is acutely less than 7 to 8 g/dL, they are experiencing vigorous blood loss, or they require further resuscitation beyond 2 L of crystalloid due to unstable vital signs. An even lower threshold for transfusion is indicated in older adults and those with significant comorbidities, such as coronary artery disease.[2]

Absorption of digested blood breakdown products into the circulatory system from the gut causes elevation of BUN levels. The BUN level can also be elevated from prerenal azotemia in the setting of hypovolemia. A BUN-to-creatinine ratio greater than 36 when the patient does not have renal failure has a sensitivity of 90% in predicting GIB, but specificity is very low, at 27%.[3] Coagulation studies, particularly prothrombin time, monitor for coagulopathy in the context of blood loss and replacement. This becomes especially important in patients with liver disease or those taking therapeutic anticoagulants such as warfarin.

Other laboratory tests rarely are useful in patients with GIB. Electrolyte abnormalities may be present in patients with repeated or prolonged episodes of vomiting or diarrhea. Leukocytosis often is present because of the stress response to acute blood loss and should not be considered to represent underlying infection unless other indications of infection are present. The serum lactate level is elevated when circulatory shock is present or, much less commonly, from gut ischemia, if that is the cause of the GI blood loss.

Blood is sent to the blood bank for a type and screen if the patient is stable and for crossmatching if blood loss is brisk or the patient is hemodynamically unstable or has significant comorbidities, especially heart disease. If the patient is highly unstable, transfusion of non–crossmatched blood may be necessary.

Electrocardiography

Because GIB and its subsequent anemia can reduce the oxygen-carrying capacity of blood, patients should be screened for signs of myocardial ischemia. We recommend obtaining an electrocardiogram for all patients older than 40 years, those with any symptoms of ischemia, and those with known coronary artery disease who are at higher risk for ischemic events. Electrocardiographic findings consistent with myocardial ischemia likely represent demand ischemia rather than coronary thrombosis and are treated with restoration of adequate circulatory volume, including blood, if needed.

Imaging

Emergent imaging of the chest or abdomen in the ED setting is rarely indicated in the patient with acute GIB. When bowel perforation is suspected on the basis of peritoneal findings on examination, abdominal computed tomography (CT) is the imaging test of choice. Abdominal plain radiographs are of no value for patients with GIB, except in the rare case where bowel obstruction is strongly suspected. In the absence of clinical findings consistent with perforation or bowel ischemia, CT of the solid abdominal organs is not indicated and does not alter the acute management and disposition of the patient with a GIB.

When endoscopy is not possible or cannot locate the hemorrhage source, CT angiography (CTA) is the principle diagnostic imaging tool and has the benefit of allowing for therapeutic options via embolization. CTA has a sensitivity of 85% and specificity of 92% for detecting acute GIB. Conventional angiography is indicated in a very small proportion of cases of GIB and requires a hemorrhage rate of greater than 0.5 mL/min to detect the bleed. Although also potentially therapeutic, angiography has a high complication rate, including acute renal failure, contrast reactions, and bowel infarction. Angiography has a sensitivity of 46% and specificity of 100% for acute bleeds (Fig. 27.1).

Tagged red blood cell imaging or nuclear scintigraphy involves erythrocyte injection to detect indolent or elusive bleeding and is primarily useful in the inpatient setting. Scanning must be performed within 2 hours of injection to localize bleeding accurately[3] (Fig. 27.2).

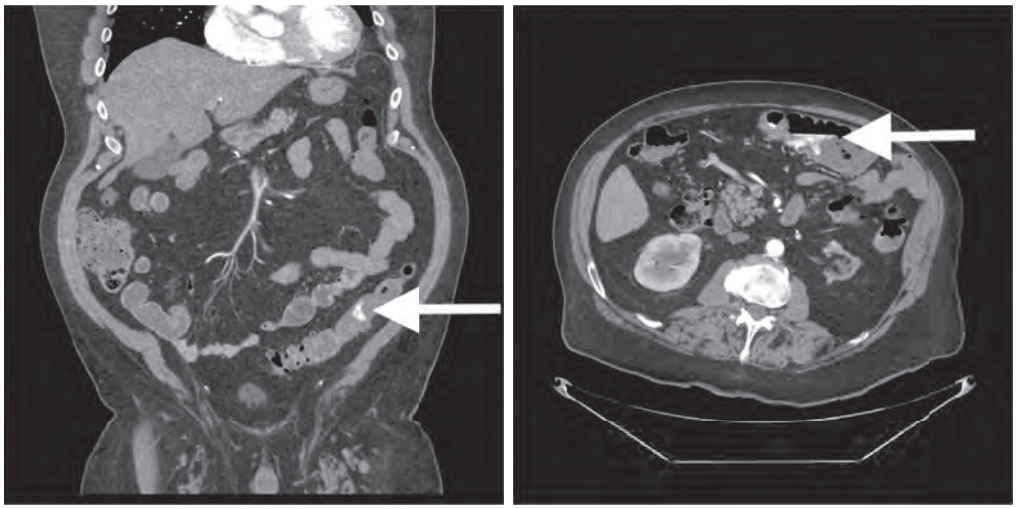

Fig. 27.1. Axial and coronal images from CT angiograms demonstrating extravasation of contrast material within the colon from a bleeding diverticulum. (Courtesy Wendy B. Landman, MD; Department of Radiology Brigham and Women's Hospital.)

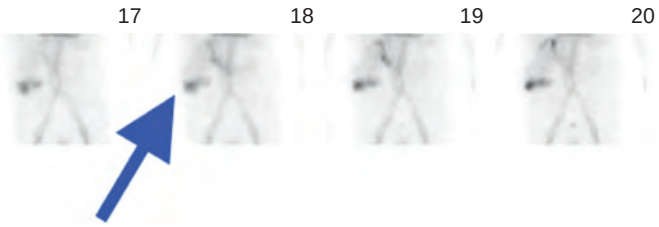

Fig. 27.2. Technetium 99m-labeled red blood cell scintigraphy demonstrating focus of increased activity in the ascending colon with antegrade transit into the hepatic flexure and transverse colon. (Courtesy Wendy B. Landman, MD; Department of Radiology Brigham and Women's Hospital.)

With numerous approaches available, the American College of Radiology has developed an appropriateness rating scale to help guide emergency clinicians in the use of specific interventions and imaging modalities for patients presenting with GIB (Table 27.2).

DIAGNOSTIC ALGORITHM

The diagnostic approach to the GIB patient involves a number of key decision points. First, the emergency clinician should assess the patient's general appearance, vital signs, and volume status. This initial assessment can help categorize the patient as stable or unstable. If the patient is unstable, resuscitation begins with the immediate placement of two large-bore IV catheters (18 gauge or larger) or central venous catheter placement and crystalloid infusion, with the aim of establishing and maintaining adequate tissue perfusion. This does not equate to restoration of normal blood pressure, however, and maintaining a systolic blood pressure in the range of 100 mm Hg is a good initial resuscitative goal. Endpoints of adequate resuscitation would include evidence of adequate perfusion of skin, urine output greater than 1 mL/kg/hr, and normal mental status.

The second decision point involves use of the history and physical examination findings to determine if the patient has UGIB or LGIB. These details will help risk-stratify the GIB patient further and establish the differential diagnosis. Once the presumptive origin of the bleed has been determined, the emergency clinician should consider the anticipated hospital course of the patient.

TABLE 27.2

American College of Radiology Appropriateness Rating Scale[a]

TREATMENT OR PROCEDURE	RATING	COMMENTS
Transcatheter arteriography, intervention	8	Allows for embolization if positive on arteriography
Diagnostic, therapeutic colonoscopy	4	Challenging in an unstable patient
Surgery	5	Appropriate if bleeding site localized
Nuclear medicine scan	1	More appropriate for hemodynamically stable patient
CTA abdomen	5	Continuing to emerge as an appropriate option when the bleeding source is unknown
MRI abdomen	1	Not appropriate in hemodynamically unstable patients

Note: Rating scale from 1 to 9, with 1 = least appropriate and 9 = most appropriate.

[a]For evaluation and treatment of LGIB in an actively hemodynamically unstable patient. From Millward S: ACR Appropriateness Criteria on treatment of acute nonvariceal gastrointestinal tract bleeding. J Am Coll Radiol 36:2667–2774, 2008.

The third decision point relies on the severity of the UGIB or LGIB to determine the ED management and disposition.

A later section of this chapter (see "Disposition") discusses risk stratification and hospitalization recommendations. In general, patients who are young, reliable, and hemodynamically stable, with a clear source of bleeding (eg, a minor bleed in a clear context of a Mallory-Weiss tear), can be discharged after an observation period of 12 hours in the ED or ED observation unit. The patient who has been properly resuscitated in the ED and remains hemodynamically stable will require urgent GI consultation, so admission to a medical inpatient unit or observation unit for further evaluation and management is indicated. LGIB patients who are hemodynamically stable, are reliable, have no significant risk factors, and have a clearly visualized source of bleeding on

examination can be safely discharged to follow-up with their outpatient provider.

Unstable UGIB will require emergent gastroenterology consultation, consideration of intubation if shock or hemorrhage is severe, and admission to an ICU for continued resuscitation and emergent endoscopy. Unstable LGIB patients require emergent surgical consultation. Management initially centers on proper resuscitation with fluids, blood products, and admission to the ICU.

MANAGEMENT

Empirical Treatment

Rapid identification of the bleeding source (ie, upper vs. lower GI tract), risk stratification, resuscitation, consultation, and disposition are the integral elements of this process. Massive bleeding, active hematemesis, hypoxia, severe tachypnea, and/or altered mental status may mandate tracheal intubation for protection and to supplement tissue oxygenation. Fig. 27.3 presents a combined diagnostic and management algorithm.

Resuscitation

Hemodynamic instability and estimated volume loss should guide initial resuscitation efforts. Patients should be placed on pulse oximetry and should receive supplemental oxygen with prompt crystalloid resuscitation through two peripheral, large-bore IV catheters. Cardiac telemetry should be initiated because demand ischemia and myocardial infarction may occur in patients with significant GIB.

Blood Product Transfusion

Continued hemodynamic instability or ongoing hemorrhage dictate the need for blood transfusion. Factors such as age, comorbidities (eg, ischemic heart disease, peripheral vascular disease, heart failure), baseline hemoglobin and hematocrit levels, and evidence of cardiac, renal, or cerebral hypoperfusion should be considered when determining transfusion quantity. Blood transfusion is immediately indicated in patients with GIB who have a hemoglobin level acutely less than 7 to 8 g/dL, are experiencing vigorous blood loss, or require further resuscitation beyond 2 L of crystalloid to maintain a systolic blood pressure in the range of 100 mm Hg.

Coagulopathy, especially in patients with underlying liver disease or those requiring massive transfusions, should be corrected promptly. We recommend either a 1:1:1 or a 1:1:2 ratio of plasma to platelets to packed RBC.[4]

Nasogastric Aspiration and Lavage

NG tube placement with aspiration or gastric lavage is not indicated for the evaluation of GIB.[5] Despite its long time role, with advocates citing diagnostic and prognostic value, evidence has confirmed that it is not useful for either of these purposes. The sensitivity of NG aspiration and lavage for predicting later recurrence or worsening of UGIB is low, and the negative likelihood ratio in patients with melena or hematochezia without hematemesis is poor.[6] Up to 15% of patients without blood or coffee-ground material in NG aspirates have been found to have high risk lesions on endoscopy. NG tube placement is not a benign procedure and has been associated with complications, including pain, aspiration, pneumothorax, pharyngeal or esophageal perforation, and gastric lesions. Occasionally, a consulting gastroenterologist may wish to place an NG tube in hopes of improving endoscopic visibility (and accuracy) by evacuating gastric contents and blood but, absent such an indication, we do not recommend placement of an NG tube in patients with suspected UGIB.

Sengstaken-Blakemore Tube

A bedside balloon tamponade should only be considered in exsanguinating patients with likely variceal bleeding when endoscopy is not immediately available. Complications are common and significant, but tube placement is indicated in the appropriate patient population due to the high mortality of uncontrolled bleeding. Insertion of these tubes is a rarely performed procedure, and emergency clinicians have resorted to novel approaches, including indirect laryngoscopy with a GlideScope, to aid placement.[7]

Pharmacologic Agents

Several medications may improve GIB outcomes. Proton pump inhibitor (PPI) infusions have long been a staple of acute GIB therapy, but evidence has contradicted their necessity in the emergent setting. A recent systematic review has found no evidence to suggest that PPI therapy affects clinically important outcomes such as mortality, rebleeding, or subsequent surgery.[8] However, the infusion of high-dose PPIs before endoscopy has been proven to accelerate the resolution of signs of bleeding in ulcers and reduce the need for endoscopic sclerotherapy and thermocoagulation. Therefore, we recommend initiating IV dosing of an 80-mg bolus of omeprazole, followed by 8 mg/hr by continuous IV infusion for 3 days. High-dose oral PPIs, such as esomeprazole, 40 mg bid, have been shown in Asian populations to reduce the risk of rebleeding, need for surgery, and risk of death, but additional data are needed to determine whether those findings are generalizable to Western patients. If oral therapy proves equivalent to IV therapy, oral PPI therapy would decrease cost, dosage, and supply shortfalls.[9]

Somatostatin and octreotide, synthetic analogues, are splanchnic vasoconstrictors that reduce portal hypertension and the risk of persistent bleeding, rebleeding, and transfusion requirements in patients with variceal bleeding. Octreotide should be empirically administered to patients presenting with an acute GIB and history of significant liver disease, variceal bleeding, or alcoholism or with abnormal liver function tests. Octreotide is given as a 50-µg bolus followed by 50 µg/hr continuous IV infusion. Octreotide is not indicated for presumed nonvariceal bleeding. Although an older meta-analysis purported to show benefit for patients with nonvariceal GIBs who were treated with somatostatin, the individual studies were poor, and there is insufficient evidence to support its use.

Vasopressin, administered by continuous IV infusion, also reduces splanchnic blood flow and portal hypertension. However, we do not recommend its use due to the risk of significant complications, including myocardial and mesenteric ischemia and infarction.

Definitive Management

Consultation

Patients with hemodynamic instability and severe bleeding of a presumed upper GI source should have emergent gastroenterology consultation. Severe LGIB warrants emergent surgical consultation.

Endoscopy

Upper endoscopy is the most effective diagnostic and therapeutic intervention for UGIB, achieving hemostasis in greater than 90% of cases. Endoscopic hemostasis decreases rates of rebleeding,

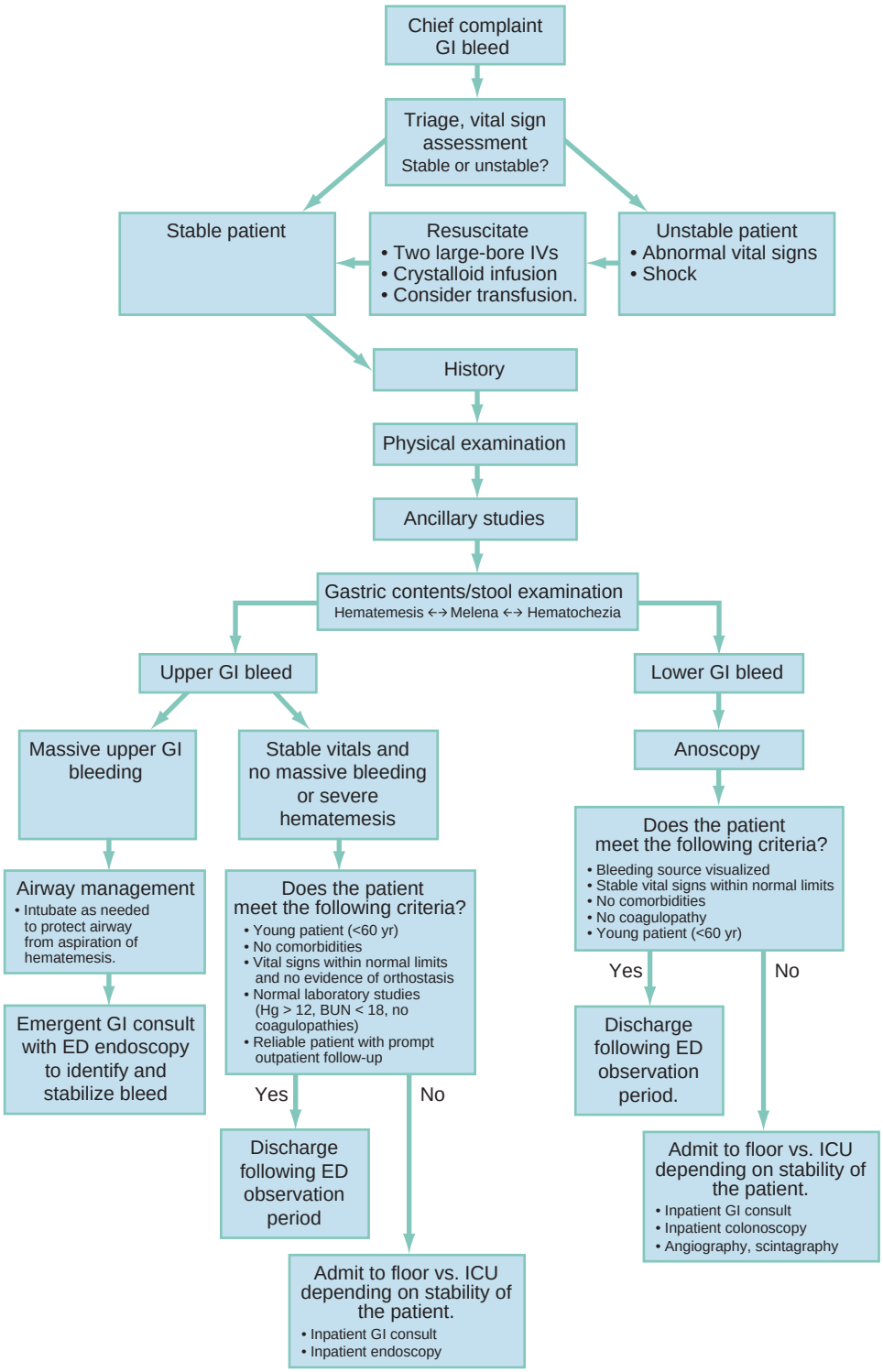

Fig. 27.3. Diagnostic and management strategies for gastrointestinal bleeding. *BUN,* Blood urea nitrogen; *ED,* emergency department; *GI,* gastrointestinal; *Hg,* hemoglobin; *ICU,* intensive care unit; *IV,* intravenous.

mortality, and urgent surgery. Endoscopic treatments include injection therapy (eg, saline, vasoconstrictors, sclerosing agents, tissue adhesives, or a combination), thermal therapy with the use of contact methods, such as multipolar electrocoagulation and heater probe, or noncontact methods, such as argon plasma coagulation and mechanical therapy, principally endoscopic clips. Endoscopy within 13 hours of bleeding reduces mortality in high-risk patients.[10]

Colonoscopy

Urgent colonoscopy has variable diagnostic value for the identification of a bleeding source in LGIB. Lesion visualization is maximized by bowel preparation with polyethylene glycol in brisk, but not severe, hemorrhage. Consultation with a surgeon or gastroenterologist guides decision making with regard to the need for urgent colonoscopy.

TABLE 27.3

Blatchford Score[a]

ADMISSION RISK MARKER	SCORE COMPONENT VALUE
Blood urea nitrogen level (mg/dL)	
≥18.2 to <22.4	2
>22.4 to <28	3
>28 to <70	4
>70	6
Hemoglobin level for men (g/dL)	
>12 to <13	1
≥10 to <12	3
<10	6
Hemoglobin level for women (g/dL)	
≥10 to <12	1
<10	6
Systolic blood pressure (mm Hg)	
≥100 to <109	1
>90 to <99	2
<90	3
Other markers	
Pulse rate ≥100 beats/min	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Heart failure	2

[a]Range of scores is from 0 to 23, with high risk >0.

TABLE 27.4

Clinical Rockall Risk Score[a]

VARIABLE	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Age	<60	60–79	>80	
Shock	No shock	Pulse >100 SBP >100	SBP <100	
Co-morbidity			CHF, IHD, major morbidity	Renal failure, liver failure, metastatic cancer

[a]Scores are calculated without endoscopic findings, and patients with scores >0 are considered at high risk for developing adverse outcomes (eg, recurrent bleeding, death).
CHF, Congestive heart failure; *HR,* heart rate; *IHD,* ischemic heart disease; *SBP,* systolic blood pressure.

DISPOSITION

There are currently no well-validated clinical decision rules for emergency clinicians to aid in resource allocation and disposition decisions for GIB patients. However, several risk scoring systems, including the Blatchford and Rockall systems, can aid emergency clinicians in stratifying UGIB patients into low- and high-risk groups for adverse outcomes, with high-risk patients defined as those who require a blood transfusion or endoscopic or surgical intervention during their admission. The Blatchford scoring system (Table 27.3) and clinical (or pre-endoscopic) Rockall scoring system (Table 27.4) are two methods that solely use clinical and laboratory data to risk-stratify patients. In a retrospective review of 354 patients, the Blatchford scoring system was 99.6% sensitive and the clinical Rockall scoring system was 90.2% sensitive at identifying patients as high risk.

Our recommendation is to use the Blatchford or Rockall scoring systems as general guidelines, understanding that these clinical decision rules may not be sensitive enough to predict which patients are high risk. High-risk UGIB patients require admission for inpatient monitoring, assessment, and consultation for definitive diagnosis and treatment.

Patients at low risk for recurrent or worsening UGI bleed can be discharged to home if they meet all the following criteria: no significant comorbid diseases (eg, ischemic heart disease, congestive heart failure, hepatic disease); normal vital signs; normal or trace positive results on stool guaiac testing; normal hemoglobin and hematocrit levels; good support systems; proper understanding of signs and symptoms of significant bleeding; immediate access to emergent care; and arranged follow-up within 24 hours. Low-risk patients deemed appropriate candidates for discharge should be given clear instructions reviewing the signs and symptoms of significant GIB and when to contact their primary care physician or return to the ED. Specific educational guidelines should include information regarding the likely source of bleeding, medication side effects, alcohol abstinence, and discontinuation of the use of aspirin and NSAIDs. These patients require early follow-up for a specific evaluation.

There are no clear guidelines on risk stratification for the outpatient management of LGIB patients, other than clear identification of a local anal source of the bleeding, such as a hemorrhoid or fissure. Most LGIB patients, therefore, are hospitalized or placed in an observation unit for further evaluation. Lower GI bleeding not clearly due to hemorrhoids, fissure, or proctitis may require nuclear medicine imaging or coloscopy.

KEY CONCEPTS

- Several risk scoring systems, including the Blatchford and Rockall scoring systems, can help emergency clinicians stratify UGIB patients into low- and high-risk groups for adverse outcomes, with high-risk patients defined as those who require a blood transfusion or endoscopic or surgical intervention during their admission.
- Patients who are not at high risk and are without comorbid diseases, have normal vital signs, normal or trace positive results on stool guaiac testing, normal hemoglobin and hematocrit levels, good support systems, proper understanding of signs and symptoms of significant bleeding, and access to emergent care and 24-hour follow up may be discharged.
- Nasogastric lavage is an uncomfortable procedure that has low sensitivity and is not indicated in the acute management of UGI bleeding.
- IV administration of proton pump inhibitors, such as pantoprazole, 40 mg IV bid, should be initiated in the emergent setting for patients with significant UGIB. Alternatively, in patients with significant acute GIB, we recommend an 80 mg IV bolus of omeprazole followed by 8 mg/hr continuous infusion for 3 days.
- A BUN-to-creatinine ratio greater than 36 in the setting of no renal failure can be highly suggestive of UGIB.
- Electrocardiography should be performed in older adults or those with known coronary artery disease who are at higher risk for demand ischemia in the setting of hypotension or anemia due to a GIB.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 27: QUESTIONS & ANSWERS

27.1. Which of the following cannot clinically mimic hematemesis?
- **A.** Dental bleeding
- **B.** Bismuth-containing medication
- **C.** Oral trauma or injury
- **D.** Red food coloring
- **E.** Severe epistaxis

Answer: B. When evaluating a patient with an upper gastrointestinal (GI) bleed, one must consider other potential causes that are not related to the GI tract. Epistaxis, dental bleeding, oral trauma, and red food coloring can mimic the appearance of hematemesis. Bismuth-containing medication can create melanotic-appearing, guaiac-negative stools, so this presentation is not truly consistent with the findings of hematemesis and a possible upper GI bleed.

27.2. A 56-year-old man presents with nausea, vomiting, and hematemesis since early this morning. He reports vomiting a combination of coffee-ground emesis and, more recently, bright red blood. His past medical history is significant for heavy alcohol use and known esophageal varices. On arrival, he is pale and diaphoretic. His vitals are remarkable for a blood pressure of 90/54 mm Hg and a regular heart rate of 118 beats/min. What is the most appropriate initial step in management?
- **A.** Consult a gastroenterologist for immediate endoscopy.
- **B.** Perform a rectal examination to confirm a gastrointestinal bleed.
- **C.** Perform electrocardiography to evaluate a cardiac cause for the patient's presentation.
- **D.** Perform emergent abdominal plain radiography to evaluate the cause of the GI bleed.
- **E.** Place two large-bore intravenous catheters and begin crystalloid resuscitation.

Answer: E. If a patient with a reported GI bleed is unstable, the initial step in management involves resuscitation with the immediate placement of two large-bore intravenous catheters (18 gauge or larger) and crystalloid infusion. Other diagnostic measures, such as performing electrocardiography or imaging, can be carried out after the initial step of gaining venous access and initiating resuscitation. It is important to note that abdominal plain films are rarely helpful in patients with GI bleeding unless bowel obstruction is suspected. Gastroenterology consultation is an important part of this patient's care plan; however, it is not the first step in management after the evaluation.

27.3. A 65-year-old man presents with weakness, fatigue, melena, and increasing amounts of coffee-ground emesis over the last 24 hours. The patient has a known history of cirrhosis and heavy alcohol abuse. On examination, he is pale and diaphoretic and has rectal findings showing a combination of melena and hematochezia. His vital signs show a blood pressure of 75/40 mm Hg and a regular heart rate of 125 beats/min. You place two large-bore intravenous (IV) catheters and attempt to resuscitate the patient with crystalloid, but the patient shows no improvement after 2 L of fluid. At this point, the management of this patient should include all of the following, except which one?
- **A.** Emergent gastroenterology consultation for endoscopy
- **B.** Emergent intensive care unit (ICU) consultation for admission, further evaluation, and monitoring
- **C.** Placement of a nasogastric (NG) tube with gastric lavage
- **D.** Transfusion of 1 unit of fresh frozen plasma (FFP) for every 4 units of packed red blood cells
- **E.** Transfusion of packed red blood cells

Answer: C. Placement of an NG tube in suspected upper GI bleed is not recommended. The sensitivity of this modality for predicting upper GI bleed is low, and there is a negative likelihood ratio in patients with melena or hematochezia. Along with this, NG tube placement has been associated with severe complications, including aspiration, pneumothorax, perforation, and development of gastric lesions. Transfusion of packed red blood cells and FFP is indicated here because the patient is hemodynamically unstable and likely to be suffering from coagulopathy resulting from his liver disease. Both GI and ICU consultation should be pursued because the patient will require endoscopy and close monitoring.

27.4. Which of the following statements regarding the epidemiology of GI bleeding is correct?
- **A.** LGIB affects a larger portion of patients than does UGIB.
- **B.** LGIB requiring admission is more common in adults than in children.
- **C.** Most deaths secondary to GI bleeding occur in patients older than 60 years.
- **D.** Overall mortality has remained the same over the past 20 years.
- **E.** UGIB is more common in women than in men.

Answer: C. The overall mortality of GI bleeding is approximately 13% to 14% and has not changed significantly since the 1960s. LGIB affects a smaller portion of patients and results in proportionally fewer hospital admissions than UGIB. GI bleeding can occur in individuals of any age but usually affects people in their

40s through 70s (mean age, 59 years). Most deaths caused by GI bleeding occur in patients older than 60 years. UGIB is more common in men than in women (2:1), whereas LGIB is more common in women. Significant UGIB requiring admission is more common in adults, whereas LGIB requiring admission is more common in children.

27.5. What is the most common cause of significant upper GI bleeding in adults?
A. Duodenitis
B. Esophagitis
C. Gastric erosions
D. Peptic ulcer disease
E. Varices

Answer: D. The most common cause of significant upper GI bleeding in adults is peptic ulcer disease. In descending order of frequency, this is followed by gastric erosions, varices, Mallory-Weiss tear, esophagitis, and duodenitis.

27.6. What is the most common cause of significant lower GI bleeding in adults?
A. Cancer
B. Diverticular disease
C. Inflammatory bowel disease
D. Rectal disease
E. Upper GI bleeding

Answer: B. The most common cause of significant lower GI bleeding in adults is diverticular disease. In descending order of frequency, this is followed by angiodysplasia, upper GI bleeding, cancer or polyps, rectal disease, and inflammatory bowel disease.

27.7. What is the most common cause of upper GI bleeding in children?
A. Esophageal varices
B. Esophagitis
C. Gastric and duodenal ulcers
D. Gastritis
E. Mallory-Weiss tear

Answer: C. Gastric and duodenal ulcers are the most common cause of upper GI bleeding in children. In descending order of frequency, this is followed by esophagitis, gastritis, esophageal varices, and Mallory-Weiss tear.

27.8. What is the most common cause of lower GI bleeding in children?
A. Anorectal fissure
B. Infectious colitis
C. Inflammatory bowel disease
D. Intussusception
E. Polyps

Answer: A. Anorectal fissure is the most common cause of lower GI bleeding in children. In descending order of frequency, this is followed by infectious colitis, inflammatory bowel disease, polyps, intussusception, and Meckel's diverticulum.

27.9. Which of the following has been shown to decrease rebleeding occurrences effectively in patients treated for upper GI bleeding secondary to esophageal varices?
A. Cimetidine
B. Famotidine
C. Octreotide
D. Omeprazole
E. Vasopressin

Answer: C. Octreotide is a useful addition to endoscopic sclerotherapy and decreases rebleeding occurrences. Patients with documented esophageal varices and acute upper GI bleeding should be treated with an intravenous infusion of DAM, 50 μg/hr, for a minimum of 24 hours while being observed in the intensive care unit.

27.10. Emergent surgical consultation should be obtained in a patient with GI bleeding and which of the following?
A. Esophageal varices
B. History of abdominal aortic graft
C. Initial systolic blood pressure < 100 mm Hg
D. Liver disease
E. Transfusion requiring 4 units of blood

Answer: B. Emergent surgical consultation is needed for patients who have abdominal aortic grafts and who present to the emergency department with GI bleeding because of the possibility of an aortoenteric fistula. Consultation with a surgeon should be obtained if it appears that more than 5 units of blood is required to achieve hemodynamic stability or if there is reasonable suspicion that operative intervention may be needed. This is especially true for patients older than 65 years. Patients with a history of varices, persistent postural changes in heart rate, or significant bright red blood per rectum are more likely to require surgery than patients without these findings.

CHAPTER 28

Diarrhea

Nicole Lazarciuc

PERSPECTIVE

Diarrhea is a clinical symptom of numerous infectious and noninfectious diseases. It encompasses mild presentations requiring supportive treatment to that of severe dehydration resulting in septic shock or even death. New challenges emerge as immunosuppression, global traveling, and comorbid conditions affect the assessment and management of patients. The evaluation requires a systemic approach that narrows diagnostic considerations and directs testing and management.

Epidemiology

Despite advances in care, diarrhea continues to be a major global health concern. According to the World Health Organization (WHO), there are over 1.7 billion cases of diarrhea every year; it is responsible for 760,000 deaths in children annually. In the United States, there are 179 million cases of acute diarrheal illness each year resulting in over 900,000 hospitalizations.[1] Unlike the developing world where children are at the greatest risk, 83% percent of deaths attributed to acute diarrhea occur in adults greater than 65 years old. Norovirus (caliciviruses), of which more than 100 different strains are identified, independently accounts for 50% of diarrheal illnesses in the United States. Media headlines continue to highlight outbreaks of infectious diarrhea on cruise ships and in nursing homes, schools, and hospitals. Hospital acquired *Clostridium difficile* and norovirus infection are the most prevalent causes of fatal illness from diarrhea. Diarrhea continues to be a source of hours of lost work and a cause of significant morbidity and mortality.

In the United States, *C. difficile* infection has become a leading cause of gastroenterologic hospitalization and death accounting for direct annual costs of 3.4 billion dollars.[2] There has been an increase in both incidence and severity of *C. difficile* infection in the last decade. Intravenous (IV) administration of antibiotics prior to emergency department (ED) discharge has been associated with an increase in antibiotic-associated diarrhea.[2] Vulnerable populations at risk of life-threatening illness include patients at the extremes of age, the immunologically compromised, and those with iatrogenic disease.

Pathophysiology

Diarrhea is defined as a change in normal bowel movements with passage of three or more stools per day or at least 200 g of stool per day.[3] *Acute diarrhea* lasts for 14 days or less, *persistent diarrhea* is defined as lasting for greater than 14 days, and *chronic diarrhea* continues for 30 days or longer.[1]

Diarrhea-associated illnesses are divided into two main categories: infectious and noninfectious. Infectious causes of diarrhea account for 85% of cases, with noninfectious causes accounting for the remainder. Causes of infectious diarrhea include viruses (70%), bacteria (24%), and parasites (6%) (Box 28.1).[4]

Acute diarrhea presentations are usually infectious and self-limited. They are generally caused by viral or bacterial pathogens. Persistent diarrhea often results from enteric pathogens that are bacterial or protozoan. Chronic diarrhea is frequently noninfectious and consequently requires further investigation to determine its source.

The small and large bowels absorb 99% of daily gastrointestinal tract secretions produced and liquids ingested. Reducing water absorption by 1% can result in diarrhea. Four major pathologic processes can contribute to this decreased absorption in the gut:

- *Secretory diarrhea* is caused by pathogens that produce cytotoxins, which can increase cellular permeability leading to the oversecretion of water and electrolytes. The majority of ED presentations of diarrhea result from this pathologic secretory process. Medications, endocrine disorders, and neoplasms constitute several of the noninfectious causes of secretory diarrhea (Box 28.2).
- *Inflammatory diarrhea* (invasive or dysentery) is attributed to another distinct pathologic mechanism. Cellular damage of the intestinal mucosa leads to hypersecretion of water, electrolytes, blood, mucus, and plasma proteins. Most frequently, inflammatory diarrhea is caused by invasive bacterial and parasitic pathogens (see Box 28.1). Noninfectious causes of inflammatory diarrhea consist of chemotherapy, radiation therapy, inflammatory bowel disease, and autoimmune disorders. Systemic symptoms, fecal leukocytes, and fecal erythrocytes are typically present on evaluation.
- *Osmotic diarrhea* occurs with the ingestion or malabsorption of osmotically active solutes. The solutes themselves lead to the movement of water into the intestinal lumen, and the gut is unable to reabsorb this massive volume. Osmotic laxatives and the effect of carbohydrate malabsorption are examples of this process. Steatorrhea results from the osmotic effects of lipids not absorbed in malabsorption and maldigestion syndromes.
- *Abnormal motility* is yet another mechanism that may cause diarrhea. However, although usually a component of chronic diarrhea, it can also play a role in presentations of acute diarrhea. Hypermotility decreases the contact time between luminal contents and the absorbing mucosa. The consequence of which is limited water and electrolyte reabsorption.

DIAGNOSTIC APPROACH

A thorough patient evaluation includes inquiries regarding travel, immunizations, medications, recent antibiotic use, hospitalization, and sick contacts. Duration of symptoms, volume, frequency, consistency or presence of blood in the stool, ability to tolerate oral intake, and accompanying systemic symptoms, such as fever, vomiting, or abdominal pain are key components in the patient assessment. Social history should include contact with nursing home residents, hospital employment, or exposure to those who are immunocompromised.

Differential Diagnosis Considerations

The differential diagnosis of a patient presenting with diarrhea to the ED can be categorized as acute infectious or chronic diarrhea

BOX 28.1

Causative Agents of Infectious Diarrhea

VIRAL (60% OF CASES)*
Astrovirus
Calicivirus
Coronavirus
Cytomegalovirus†
Enteric adenovirus
Hepatitis A through G
Herpes simplex virus
HIV enteropathy
Norwalk-like agents
Norwalk virus
Pararotavirus
Picornavirus
Rotavirus
Small round viruses

BACTERIAL (20% OF CASES)*
Invasive†
Aeromonas species
Campylobacter species
Clostridium difficile
Enteroinvasive *Escherichia coli*
Mycobacterium species
Plesiomonas shigelloides
Salmonella species
Shigella species
Vibrio fluvialis
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica
Yersinia pseudotuberculosis

Toxigenic
Food Poisoning With Preformed Toxins
Bacillus cereus
Clostridium botulinum
Staphylococcus aureus

Toxin Formation After Colonization
Aeromonas hydrophila
Clostridium perfringens
Enterohemorrhagic *E. coli*† O157:H7
Enterotoxigenic *E. coli*
Klebsiella pneumoniae
Shigella species
Vibrio cholerae

Other Bacteria
*Parasitic (5% of cases)**
Protozoa
Balantidium coli†
Blastocystis hominis
Cryptosporidium
Cyclospora
Dientamoeba fragilis
Entamoeba histolytica†
Entamoeba polecki
Enteromonas hominis
Giardia lamblia
Isospora belli
Microsporidia
Sarcocystis hominis

Helminths
Angiostrongylus costaricensis
Anisakiasis
Ascaris lumbricoides
Diphyllobothrium latum
Enterobius vermicularis
Hookworms
Schistosoma species
Strongyloides stercoralis
Taenia species
Trichinella spiralis
Trichuris trichiura

HIV, Human immunodeficiency virus.
*% indicates the estimated contribution to total cases.
†Associated with fever, abdominal pain, and fecal red blood cells or white blood cells.

BOX 28.2

Causes of Noninfectious Diarrhea

TOXINS
Drugs
ACE inhibitors
Alprazolam (Xanax)
Antacids (magnesium)
Antibiotics
Antidepressants
Antiepileptic drugs
Antihypertensives
Antiparkinson drugs
Beta-blockers
Caffeine
Cardiac antiarrhythmics
Chemotherapy agents
Cholesterol-lowering drugs
Cholinergic agents
Cholinesterase inhibitors
Colchicine
Digitalis
Diuretics
Fluorouracil
Fluoxetine (Prozac)
Histamine H_2-receptor antagonists
Hydralazine
Lactulose
Laxatives, cathartics
Levodopa
Lithium
NSAIDs
Neomycin
Podophyllin
Procainamide
Prostaglandins
Quinidine
Ricinoleic acid
Theophylline

BOX 28.2

Causes of Noninfectious Diarrhea—cont'd

Thyroid hormone
Valproic acid

Dietetic Foods
Mannitol
Sorbitol
Xylitol

Fish-Associated Toxins
Amnestic shellfish poisoning
Ciguatera
Echinoderms
Neurotoxic shellfish poisoning
Paralytic shellfish poisoning
Scombroid
Tetrodotoxin

Plant-Associated Toxins
Herbal preparations
Horse chestnut
Mushrooms—*Amanita* species
Nicotine
Other plant toxins
Pesticides—organophosphates
Pokeweed
Rhubarb
Miscellaneous
Allergic reactions
Carbon monoxide poisoning
Ethanol
Heavy metals
Monosodium glutamate (MSG)
Opiate withdrawal

GASTROINTESTINAL PATHOLOGY
Appendicitis
Autonomic dysfunction
Bile acid malabsorption
Blind loop
Bowel obstruction
Celiac disease
Cirrhosis
Defects in amino acid transport
Diverticular disease
Familial dysautonomia
Fecal impaction
Fecal incontinence
Gastrointestinal bleed
Gastrointestinal cancer
Hirschsprung's disease
Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
Intussusception
Irritable bowel syndrome
Ischemic bowel
Lactose or fructose intolerance
Malabsorption syndromes
Malrotation
Postsurgical
Postvagotomy
Radiation therapy
Short gut syndrome
Small bowel resection
Strictures
Toxic megacolon
Tropical sprue
Volvulus
Whipple's disease

ENDOCRINE-RELATED CONDITIONS
Carcinoid syndrome (serotonin)
Hormonal hypersecretion
Hyperthyroidism (thyroid hormone)
Medullary carcinoma of the thyroid (calcitonin)
Pancreatic cholera (VIP)
Somatostatinoma (somatostatin)
Systemic mastocytosis (histamine)
Zollinger-Ellison syndrome (gastrin)

Endocrine Pathology
Adrenal insufficiency
Diabetes enteropathy
Hypoparathyroidism
Pancreatic insufficiency

SYSTEMIC ILLNESS AND OTHER CAUSES
Alcoholism
Amyloidosis
Connective tissue disease
Cystic fibrosis
Ectopic pregnancy
Hemolytic-uremic syndrome
Henoch-Schönlein purpura
Lymphoma
Otitis media—infants
Pelvic inflammatory disease
Pneumonia, sepsis
Pyelonephritis
Scleroderma, SLE
Severe malnutrition
Stevens-Johnson syndrome
Toxic shock syndrome
Wilson's disease
Miscellaneous
Factitious diarrhea
Runner's diarrhea

ACE, Angiotensin-converting enzyme; *NSAID,* nonsteroidal antiinflammatory drug; *SLE,* systemic lupus erythematosus; *VIP,* vasoactive intestinal polypeptide.

comprising infectious and noninfectious etiologies. Most viral and many bacterial agents cause self-limited secretory diarrhea that lasts less than 14 days and results in mild dehydration with minimal systemic symptoms. In the United States, one quarter of diarrheal presentations to the ED result from norovirus infection. Bacterial and protozoal agents less commonly cause diarrhea syndromes indistinguishable from norovirus infection with a nontoxic, self-limited course. Bacteria, parasites, and rarely viruses are the source of infectious persistent or chronic diarrhea. Bacterial pathogens include *Aeromonas, Campylobacter, C. difficile, Salmonella,* and *Mycobacterium tuberculosis. C. difficile* infection, once considered a nosocomial infection in the elderly population, is now reported in healthy ambulatory patients without recent antibiotic use.[5] Evidence indicates that an increase in virulence and alterations in gut flora have resulted in colonization by antibiotic resistant *C. difficile.* Parasitic sources that infect the colon include *Amoeba, Trichuris, Yersinia*, and *Schistosoma* species. *Giardia, Cryptosporidium, Cyclospora, Isospora*, and *Strongyloides*

are pathogens affecting the small intestine. Homosexual men have an increased probability of complicated protozoal diarrhea syndromes caused by *Giardia lamblia* and *Entamoeba histolytica*. Organ transplant patients are at increased risk compared to the general population for complicated diarrhea from *Cytomegalovirus*.

Chronic diarrhea in developing countries is most frequently attributed to a bacterial source. Conversely, in developed countries it is often caused by noninfectious disorders, such as irritable bowel syndrome, laxative abuse, malabsorption syndromes, and inflammatory bowel disease. Patients with human immunodeficiency virus (HIV) may initially present with chronic diarrhea. *Cryptosporidium, Microsporidia, Mycobacterium avium* complex, herpes simplex virus, *Isospora, Cyclospora*, and *Cytomegalovirus* are possible sources of chronic infectious diarrhea. Parasitic and helminthic infections are additional considerations.

There are numerous causes of noninfectious diarrhea (see Box 28.2), accounting for 15% of all cases of diarrheal illness. Clinically, it is often challenging to distinguish between infectious and noninfectious causes. Gastrointestinal bleeding, ischemic bowel, acute appendicitis, intussusception, ectopic pregnancy, and partial bowel obstruction all may present with diarrhea. The differential diagnosis for noninfectious diarrhea is lengthy, including toxic exposures or ingestions, adrenal insufficiency, hyperthyroidism, and hormone secreting tumors.

Pivotal Findings

Signs and Symptoms

Initial assessment of the patient focuses on oxygenation and perfusion with attention to volume status. Indications of hypovolemia and hypoperfusion include tachycardia, hypotension, dry mucosa, cool extremities, diaphoresis, poor skin turgor, decreased urine output, and mental status changes. Clinical signs and symptoms of anemia are pale conjunctiva, delayed capillary refill, pallor, and shortness of breath. A diarrhea associated acid-base disorder is suspected in patients with increased respiratory rate or Kussmaul's respirations. Patients presenting with systemic inflammatory response syndrome (SIRS) may be dehydrated or in septic shock. Bedside ultrasound can be employed to assess volume status. A patient with a collapsed inferior vena cava and a poorly filled, rapidly beating heart requires intervention and rehydration.[6]

Young, healthy adults may maintain a normal blood pressure and heart rate even in the setting of severe dehydration. The heart rate in patients who are taking anti-arrhythmic medications, beta-blockers or have pacemakers may be an unreliable indicator of volume status. Clinical signs of dehydration in the pediatric patient include sunken eyes, depression of the fontanel, reduced number of wet diapers, and decrease in alertness or activity. Following stabilization, a secondary survey is conducted in an attempt to further evaluate the patient and direct treatment.

The secondary survey assesses the patient's overall health condition, including the presence of fever and the potential for an acute abdomen. Focal abdominal pain in the setting of gastroenteritis may mimic an acute surgical abdomen. Serial abdominal examinations are often required. Rectal examination can detect melena, hematochezia, or fecal impaction. Gross blood may be indicative of invasive, infectious diarrhea, although there are other pathologic states that manifest with gastrointestinal bleeding, including inflammatory bowel disease. Parasitic infection may be accompanied by histamine-induced changes, such as urticaria or bronchospasm. Systemic findings of jaundice or scleral icterus demonstrate associated liver pathology. Clinical presentations of toxic syndromes (eg, cholinergic or sympathomimetic) may include diarrhea.

Ancillary Testing

In most cases of acute diarrhea, laboratory and diagnostic tests should be kept to a minimum. Testing is guided by the clinical severity of the illness, including abnormal vital signs, presence of comorbidities, or physical examination findings suggesting serious intra-abdominal disease or diarrhea related to serious systemic illness. A toxic appearance with fever, volume depletion, blood-containing or mucus-containing stools, frequent voluminous stools, peritoneal findings, and serious comorbidities, especially immune suppression or chronic inflammatory gastrointestinal disease, should prompt further investigation in order to guide appropriate therapy.

Blood Tests. Leukemoid reactions have been reported in *C. difficile* infections, although an isolated white blood cell count is not sensitive or specific enough to aid in diagnostic decision making.[7] Eosinophilia may be seen in parasitic infections with an extra-intestinal migration phase. Hemoglobin levels may be employed to screen for anemia secondary to blood loss. Abnormalities in platelets and coagulation may aid in identifying causes for gastrointestinal bleeding. A simple chemistry panel to check electrolytes and a blood urea nitrogen/creatinine ratio can be useful when hypovolemia is suspected or there has been substantial diarrhea. Liver function tests including aspartate transaminase (AST), alanine transaminase (ALT), and coagulation times are indicated when there is jaundice or other evidence of liver disease. Other laboratory studies are rarely indicated but may be obtained when there are particular findings. For example, a lipase level is indicated if the diarrhea is part of a syndrome that includes severe epigastric pain and tenderness accompanied by vomiting.

Lactate. An elevated lactate may aid in identifying and directing therapy in patients with dehydration, severe sepsis, or causes of noninfectious diarrhea (eg, mesenteric ischemia, gastrointestinal bleeding).

Hemoccult and Fecal Cell Count. Fecal leukocytes are not specific or sensitive enough as the sole criteria to determine which patients should be treated with antibiotics. Inflammatory diarrhea of varied causes, including bacterial or parasitic infection and noninfectious sources, may demonstrate red and white blood cells visualized on stool examination. The presence of fecal leukocytes does not identify which patients would benefit from empirical antibiotic therapy. A positive stool guaiac should not be used in isolation to initiate antibiotic therapy. Blood without fecal leukocytes is present in amebiasis, malignancy, fissures, hemorrhoids, bowel ischemia, and primary gastrointestinal bleeding.

Assays for Fecal Calprotectin and Fecal Lactoferrin. The assays for fecal calprotectin and fecal lactoferrin produced by leukocytes are not indicated. These tests are not useful in guiding ED patient evaluation, treatment, or disposition, even though they are reasonably sensitive markers, 83% and 75% respectively, of acute bacterial diarrhea.[8]

***Clostridium difficile* Toxin Assay.** This test is indicated if the patient is immunocompromised, or reports recent antibiotic use, hospitalization, nursing home residence, or employment in a health care setting, or significant diarrhea (>6/day) for several days. Diarrhea associated with *C. difficile* most commonly occurs during or closely following the completion of the antibiotic course. Cephalosporins, penicillins, and clindamycin are most frequently implicated, but all antibiotic use places patients at risk for an infection. Quantitative polymerase chain reaction (PCR) is the most sensitive functional toxin assay and is the assay of choice for diagnosis of *C. difficile* infection.

Escherichia coli O157:H7 Toxin Assay. This assay is indicated when there is a known outbreak or if the presentation occurs in an endemic area. The assay also is indicated for patients with suspected hemolytic-uremia syndrome.

Stool Culture for Bacteria. Tests for pathogenic enteric bacteria including *Campylobacter, Salmonella,* and *Shigella* species using a sterile sample are generally not indicated in the ED, given their low sensitivity and delayed results. However, the tests are helpful for patients being admitted to hospital with toxic appearance, immunocompromise, or advanced age. Stool culture also is indicated for patients with persistent or chronic diarrhea not previously tested for these pathogens.

Stool Examination for Ova and Parasites. These tests generally are not indicated in the ED. They may be useful in patients with chronic diarrhea *(E. histolytica* and *Cryptosporidium),* patients with history of travel to, or recent immigration from, developing countries *(Cryptosporidium, Giardia,* and *Cyclospora),* patients with exposure to infants in daycare centers *(Cryptosporidium* and *Giardia),* and patients with HIV infection *(E. histolytica* and *Giardia).*

Giardia Antigen Assay and Serologic Testing for Amebiasis. *Giardia* antigen assay and serologic testing for amebiasis are indicated for patients exposed to poor sanitation, those with immune compromise, a history of travel to developing countries, recent camping with ingestion of stream or spring water, and those with daycare exposures.

Radiographic Studies. Plain radiography rarely is indicated. If peritonism is present and abdominal perforation is suspected, abdominal computed tomography (CT) scan with (at least) IV contrast is the imaging modality of choice. If intestinal obstruction is suspected, an abdominal plain film may confirm the diagnosis but should only be done if there is certainty that more specific causative diagnosis by CT scan will not be required. If specific diagnosis is required, the abdominal plain film is omitted and CT scan is performed. CT, similarly, is useful for diagnosis of fistula, mesenteric ischemia, inflammatory bowel disease, and acute surgical diagnoses, such as appendicitis. If biliary disease is suspected, abdominal ultrasound is preferred to CT scan, and ultrasound can often diagnosis appendicitis without the need for ionizing radiation.

Gastrointestinal Referral. Patients with chronic diarrhea should be referred to their primary care doctor or a gastroenterologist for further diagnostic testing, much of which is beyond the scope of the ED (endoscopy, biopsy, stool studies).

DIAGNOSTIC ALGORITHM

Unlike many presenting symptoms and signs, critical and emergent diagnoses for patients with diarrhea depend much more on the effects of the diarrhea (hypovolemia, renal compromise) and patient comorbidity (immune compromise, advanced age, inflammatory bowel disease) than on the cause of it.

Critical Diagnoses

Patients with diarrhea and unstable vital signs are suspected of having a critical condition and are evaluated for hypovolemic, septic, or hemorrhagic shock, and drug toxicity (eg, cholinergic poisoning). They require rapid resuscitation, including IV fluids, while the underlying etiology is investigated. Laboratory studies should include a creatinine to assess renal status, hemoglobin to assess for gastrointestinal bleeding or hemoconcentration, and a lactate to assess for organ perfusion. An elevated white blood cell count is nonspecific but can be associated with *C. difficile* infection, invasive causes of diarrhea, or simply the stress effects of the illness and volume loss. Even viral infectious diarrhea perceived as "self- limited" may result in life-threatening illness in those patients presenting with severe dehydration.

If vomiting accompanies diarrhea or if the patient appears jaundiced, liver function tests may help delineate other causes of diarrhea, including infectious hepatitis. At particular risk are the elderly, pediatric populations, and the immunocompromised. Plain films are of little or no use, but CT imaging of the abdomen is indicated if perforation or major vascular disease (aorto-enteric fistula, bowel ischemia) is suspected.

Emergent Diagnoses

In patients who have stable vital signs and are nontoxic appearing, the duration of diarrhea guides the ED evaluation (Table 28.1). In elderly patients, those with recent hospitalization, or history of being immunocompromised, laboratory evaluation includes testing for electrolyte levels and renal function and for *C. difficile,* which often is undiagnosed on first presentation (Fig. 28.1). Discussion with the patient's physician regarding presentation, evaluation, and plan is important to coordinate follow-up and outpatient monitoring, especially for patients with multiple comorbidities. Well appearing patients that do not have any concerning findings or risk factors (history of immunosuppression, recent hospitalization, nursing home stay) do not need any laboratory testing or intervention. In these patients, the specific causative diagnosis for the diarrhea illness is not important, because the treatment is supportive and the course is generally self-limited. Well appearing patients with low-grade fever do not require testing in the ED unless *C. difficile* is suspected, but outpatient follow-up should be arranged and strict return precautions should be provided.

EMPIRICAL MANAGEMENT

Oral rehydration is the treatment choice for mild fluid loses (see Fig. 28.1) and can be accomplished with sports beverages, commercial rehydration solutions, or a balanced clear liquid diet at home. For less developed areas, the WHO has outlined an oral rehydration solution (WHO-ORS) that can be made by dissolving the following in 1 L of clean water: 3.5 g of sodium chloride, 2.9 g of trisodium citrate or 2.5 g of sodium bicarbonate, 1.5 g of potassium chloride and 20 g of glucose or 40 g of sucrose. Studies in infants 7 to 120 days with probable sepsis and diarrhea demonstrate that 10 mg daily oral zinc supplementation combined with antibiotic therapy improves outcomes.[9]

The choice of rehydration fluids is dependent on the extent of dehydration and the underlying health of the patient. In otherwise healthy patients with mild dehydration, fluids including sports drinks and diluted fruit juices may be supplemented with soups, broths, or crackers. However, these "clear liquids" may contain excess sugars and insufficient sodium content, resulting in an osmotic diarrhea. Caffeine should be avoided because it increases cyclic adenosine monophosphate levels and may lead to a secretory diarrhea.

Pathogens responsible for acute diarrhea may rarely cause a transient lactase deficiency causing malabsorption and osmotic diarrhea if milk is ingested. Patients should be cautioned that if persistent diarrhea appears to be related to dairy product ingestion, these products should be avoided for 2 weeks. Foods that have high fat content delay gastric emptying. The *BRAT* (bananas, rice, apples, toast) diet is often recommended, because it is relatively constipating (bananas, apple peel) and nonstimulating (bland diet). The pectin, such as is found in apple peel, is the

TABLE 28.1

Factors Increasing Probability of Non-Benign Diarrhea

FACTOR	SPECIFIC PATHOGEN(S) AND OTHER CONSIDERATIONS
Presentation to a health care facility	Degree of illness overall greater in patients seeking evaluation; increased probability of "not norovirus" cause to 50%
Travel history	Especially foreign travel and to endemic areas of dysenteric disease
Recent hospitalization	*Clostridium difficile* from antibiotic exposure
Day care attendance	Rotavirus, *Shigella, Giardia*
Nursing home residence	*C. difficile,* medication side effects, tube feedings, ischemic colitis, fecal impaction, and overflow diarrhea
Wilderness exposure	*Giardia* or *Cryptosporidium*
Antibiotic therapy	*C. difficile,* antibiotic side effects
Raw shellfish, farm animals and fair livestock, pet reptiles or amphibians, petting zoos	*Salmonella* species, *Escherichia coli* O157:H7, and non-O157 Shiga toxin–producing *E. coli, Vibrio* species
Epidemic of multiple patients with a short time of onset	Norovirus; less commonly, *Campylobacter jejuni, Salmonella* species, *Cryptosporidium*
Acute vomiting and diarrhea after eating suspected contaminated food	*Bacillus cereus, Clostridium botulinum*, *Staphylococcus aureus*
Epidemic of severe gastroenteritis traced to eggs, poultry, meat, or dairy products	*C. jejuni*, *Salmonella* species
Homosexuality (males)	*Giardia lamblia*, *Entamoeba histolytica*
Abdominal pain, nausea, vomiting, bloody stool, fever, rectal pain, tenesmus	Severe bacterial infections: *Salmonella, Campylobacter, Shigella,* EPEC, *Yersinia* or *Vibrio* species Also consider surgical abdomen, gastrointestinal bleeding, inflammatory bowel disease
Diarrhea (>7 to 14 days' duration)	Protozoa and microsporidia, *C. difficile, Campylobacter,* Shiga toxin–producing *E. coli*
Hemolytic uremic syndrome	*E. coli* O157:H7 or other species
Stool WBC count	Not reliable for diagnosis of bacterial cause
Colonic ulcerations	Inflammatory bowel disease
Proctitis	Bacterial cause highly probable
Pseudomembranes	Toxic megacolon, *C. difficile*
Chronic disease (eg, cirrhosis, DM)	Complicated course expected with any form of diarrheal illness
Organ transplantation	Abnormally severe illness from rotavirus and adenovirus Increased frequency of *Cytomegalovirus* Severe illness from dysenteric diarrhea Spore-forming protozoa and microsporidia
HIV infection, other immunodeficiency disorders	Severe illness from common bacteria, spore-forming protozoa, and microsporidia Increased frequency of *Cytomegalovirus* and *Mycobacterium avium* complex

DM, diabetes mellitus; *EPEC,* enteropathogenic *E. coli*; *HIV,* human immunodeficiency virus; *WBC,* white blood cell.

"pectate" in bismuth subsalicylate (Kaopectate), a common, nonsystemic symptomatic anti-diarrhea agent. Bananas also provide potassium.

Patients who are severely dehydrated receive IV fluid replacement with normal saline or lactated Ringer's solution, which generally is given by bolus (1 to 2 L) followed by infusion at 300 to 500 mL/hour until the patient is well hydrated and passing normal or dilute urine. Fluid replacement rates are reduced for patients with heart failure. Pediatric patients receive an initial bolus of 20 mL/kg of normal saline, which may be repeated. Special attention should be given to electrolyte repletion. Specific treatment should then be directed toward the suspected cause. In addition to IV fluids, IV antibiotics and blood components may be indicated.

In the ED, antibiotic therapy is often empirical in that specific pathogens causing infectious diarrhea are rarely identified (see Box 28.1). Viral and noninvasive bacterial gastroenteritis are most frequently self-limited and require supportive therapy. Empirical antibiotic treatment is initiated in patients suspected of having an invasive process.[9] Guidelines recommend ciprofloxacin, 500 mg orally twice a day, or levofloxacin (Levaquin) 500 mg orally once daily for 3 to 5 days for systemically ill appearing adults.[10] Fluoroquinolones should be avoided in pregnant patients. Oral antibiotics in acute episodes of traveler's diarrhea result in a reduction in the duration of diarrhea compared to placebo, although there is an increase in minor side effects.[11]

C. difficile treatments include metronidazole 500 mg orally three times daily for 10 to 14 days as initial treatment, or oral vancomycin 125 mg four times daily for 10 to 14 days. Evidence indicates that from 1996 to 2005, *C. difficile* infections tripled. Although the initial antibiotic response rates are high, recurrence rates are approximately 35% in weeks 1 to 8; following retreatment, recurrence occurs in 50% to 65% of patients. The high recurrence rate has propelled the employment of a unique

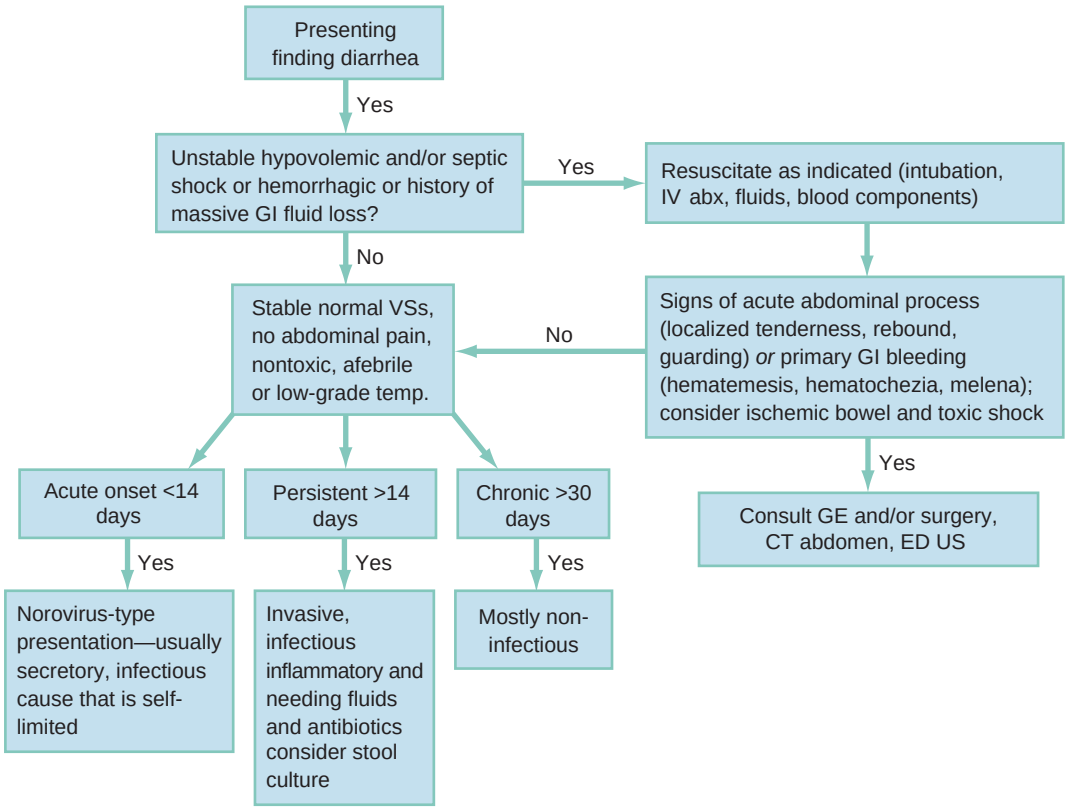


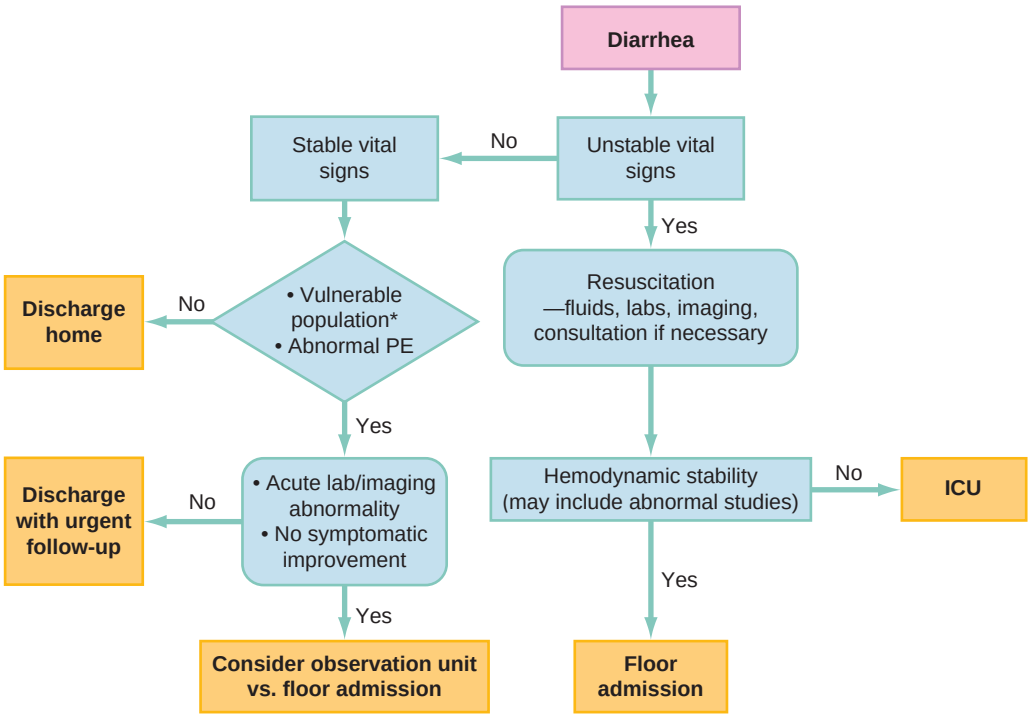
Fig. 28.1. Diagnostic algorithm. *Abx,* antibiotics; *CT,* computed tomography; *ED,* emergency department; *GE,* gastroenterologist; *GI,* gastrointestinal; *IV,* intravenous; *temp.,* temperature; *US,* ultrasonography; *VS,* vital sign.

microbial replacement therapy, *fecal microbiota transplant*, in the treatment of patients with recurrent *C. difficile* infections.[12] Antibiotic treatment of severe gastroenteritis in children has been associated with the development of hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura in those testing positive for enterohemorrhagic *E.coli* O157:H7. *Salmonella, Shigella,* and *Campylobacter* have also been implicated. Pediatric patients should initially be given supportive care and, if possible, antibiotic therapy should be tailored to culture results.

Nontoxic patients with acute viral gastroenteritis may benefit from antimotility agents and often obtain significant relief of symptoms. In adults, an initial dose of loperamide 4 mg orally with subsequent doses of 2 mg (not to exceed 16 mg in 24 hours) is the safest and most effective medication with relief of symptoms achieved more rapidly than with bismuth subsalicylate (Pepto-Bismol). In the pediatric population, the use of loperamide or diphenoxylate with atropine has rarely been associated with the precipitation of toxic megacolon and hemolytic-uremic syndrome. Antimotility agents should be used with caution in patients who are high risk (such as, the elderly) and those with recent hospitalization or antibiotic use.

Probiotics have been proposed as an alternative to antibiotic therapy for diarrhea, although as of yet there is no consensus on dosage or frequency of specific products. Oral ingestion of lactobacillus and other bacteria are effective in restoring the normal gastrointestinal flora that is disrupted during diarrhea illness. The use of probiotics appears to reduce stool frequency and shorten the duration of acute infectious diarrhea by 1 day.[13] Evidence demonstrates a protective effect of probiotics in preventing *C. difficile*–associated diarrhea. It is safe and effective when used as an adjunct to antibiotics in immunocompetent patients.[14]

The causative agent of diarrhea is often not identified in the ED and an empirical management strategy is needed (Fig. 28.2). Patients with uncomplicated, acute diarrhea can be discharged home after careful assessment and symptomatic treatment. Viral agents and many forms of bacterial gastroenteritis are self-limited with patients requiring supportive therapy. Following initial resuscitation, hospitalization is necessary in patients with severe dehydration, hemodynamic instability, or toxic appearance. Intensive care unit (ICU) level of care is recommended in patients presenting in septic shock or severe sepsis despite continued resuscitation. In patients with multiple comorbidities who are being discharged home with likely uncomplicated diarrhea, it is imperative to arrange for outpatient follow-up. Outlining specific return precautions to the ED is essential prior to the discharge of any patient.



*Immunocompromised, elderly, recent antibiotic use (see Table 28.1)

Fig. 28.2. Approach to disposition. *ICU,* Intensive care unit; *PE,* physical examination.

KEY CONCEPTS

- Hospital acquired *C. difficile* and norovirus infection are the most prevalent causes of fatal illness from diarrhea in the United States.
- Key elements of the history in the patient with diarrhea include recent travel, immunosuppression, hospitalization, and antibiotic use.
- Acute diarrhea is most often viral and treated with supportive therapy.
- Fluids with excess sugar, caffeine, and high fat content should be avoided in patients with diarrhea.
- In nontoxic patients, loperamide, initial dose of 4 mg and subsequent doses of 2 mg after each loose stool (not to exceed 16 mg in 24 hours), is safe and effective in providing symptom control.
- Ciprofloxacin 500 mg orally twice daily or levofloxacin (Levaquin) 500 mg once daily are effective empirical treatments for systemically ill appearing adults with suspected traveler's diarrhea.
- *C. difficile* treatments include metronidazole 500 mg orally three times daily for 10 to 14 days as initial treatment or vancomycin 125 mg four times daily orally for 10 to 14 days.
- Quantitative PCR is sensitive in testing for *C. difficile.*
- Use of probiotics reduces stool frequency and shortens duration of acute infectious diarrhea.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 28: QUESTIONS & ANSWERS

28.1. What is the most common pathogenic cause of diarrheal illnesses in the United States?
A. Adenoviruses
B. *Escherichia coli*
C. Noroviruses
D. Rotaviruses
E. *Salmonella*

Answer: C. The two major categories of diarrhea-associated illness are infectious and noninfectious. Infectious causes represent approximately 85% of cases, whereas noninfectious causes represent only 15%. By far, the most common pathogens causing infectious diarrheal illnesses in the United States are noroviruses. The more than 100 different strains of noroviruses are responsible for 90% of diarrheal illnesses in the United States.

28.2. What is the most common type of diarrhea seen in emergency departments (EDs)?
A. Dysenteric diarrhea
B. Inflammatory diarrhea
C. Invasive diarrhea
D. Osmotic diarrhea
E. Secretory diarrhea

Answer: E. Diarrhea results from one or more of four different pathologic processes that are characteristic of the primary cause and contribute to the decreased absorption in the gut. Secretory diarrhea is caused by pathogens that produce cytotoxins that increase cellular permeability and cause the oversecretion of water and electrolytes. Noninfectious causes of secretory diarrhea include medications, toxic substances, endocrine disorders, and neoplasias. Most cases of diarrhea encountered in the ED are secretory. Inflammatory diarrhea, also described as invasive diarrhea or dysentery, results from cellular damage to the intestinal mucosa, leading to the secretion of water, electrolytes, blood, mucus, and plasma proteins. Osmotic diarrhea occurs with the ingestion or malabsorption of osmotically active solutes. These solutes cause the osmotic shift of water into the intestinal lumen to the extent of overwhelming the gut's ability to reabsorb it. Abnormal motility is generally seen in patients with chronic diarrhea but is always a component of acute diarrhea. Hypermotility decreases contact time between luminal contents and the absorbing mucosa, thereby limiting water and electrolyte absorption.

28.3. An otherwise healthy 25-year-old man presents with a 3-day history of diarrhea. He reports associated anorexia, weight loss, shortness of breath, and itching. On physical examination, he is noted to have diffuse erythematous wheals on his skin, and pulmonary examination reveals bilateral wheezing. Of the following, which is the most likely cause of his diarrhea?
A. Bacillus cereus
B. Enteric adenovirus
C. *Giardia lamblia*
D. Rotavirus
E. Vibrio vulnificus

Answer: C. Hives and bronchospasm in this patient point to excessive histamine release. In the setting of diarrhea, histamine release would most likely result from a parasitic infection. This is not common; however, it should be considered in patients presenting with diarrhea and histamine-induced skin changes. Of the choices listed, *Giardia lamblia* is the only parasite.

28.4. Evaluation of stool for ova and parasites would prove least beneficial in which of the following subsets of patients presenting with diarrhea?
A. Patients concurrently taking clindamycin
B. Patients returning from a trip to Russia
C. Patients with chronic diarrhea
D. Patients with human immunodeficiency virus (HIV) infection
E. Patients working in daycare centers

Answer: A. The assessment of stool for ova and parasites is not routinely recommended in most cases of diarrheal illness. This study is used in patients with chronic diarrhea *(Entamoeba histolytica* and *Cryptosporidium);* patients with a history of travel to developing countries, particularly to Nepal or areas of Russia *(Cryptosporidium, Giardia,* and *Cyclospora);* patients with exposure to infants in daycare centers *(Cryptosporidium* and *Giardia);* and patients with HIV infection *(E. histolytica* and *Giardia).* Patients with diarrhea who are concurrently taking clindamycin would benefit most from testing for *Clostridium difficile* toxin.

28.5. Which of the following antibiotics is recommended for the empirical treatment of systemically ill-appearing adults with diarrhea?
A. Azithromycin
B. Ciprofloxacin
C. Metronidazole
D. Trimethoprim-sulfamethoxazole
E. Vancomycin

Answer: B. The current recommendation for empirical treatment of a systemically ill-appearing adult is ciprofloxacin 500 mg orally twice a day or levofloxacin 500 mg orally every 24 hours for 3 to 5 days. Fluoroquinolones are efficacious against most organisms

that cause dysenteric illnesses and have been shown to be more effective than trimethoprim-sulfamethoxazole. Fluoroquinolones should not be administered to pregnant patients or children younger than 18 years old.

28.6. Which of the following causes of diarrhea is more common among children who attend daycare than among those who do not?
A. *Campylobacter*
B. *Escherichia coli*
C. *Salmonella*
D. *Shigella*
E. Yersinia

Answer: D. Daycare attendance increases the probability of a patient having non-benign diarrhea caused by *Shigella, Giardia,* or rotavirus.

28.7. Homosexual men are at increased risk of diarrhea caused by which of the following protozoal pathogens?
A. *Blastocystis hominis*
B. *Cryptosporidium*
C. *Giardia lamblia*
D. *Isospora belli*
E. *Microsporidia*

Answer: C. Homosexual men have increased probability of complicated protozoal diarrhea syndromes caused by *Giardia lamblia* and *Entamoeba histolytica*.

28.8. Compared with the general population, diarrheal illnesses in organ transplant patients are more frequently caused by which of the following?
A. Coronavirus
B. *Cytomegalovirus*
C. Herpes simplex virus
D. Norwalk virus
E. Rotavirus

Answer: B. Patients with organ transplants are at increased risk for complicated diarrhea caused by *Cytomegalovirus.*

CHAPTER 29

Constipation

Jan M. Shoenberger

PRINCIPLES

The term *constipation* refers to a symptom or complex of symptoms and not a specific diagnosis. Patients and health care providers often define constipation differently. Most health care providers define constipation based on stool frequency. Patients often use the term *constipation* to describe a broad set of complaints, including straining, hard or infrequent stools, pain during a bowel movement, a feeling of incomplete evacuation, or abdominal bloating. Constipation may be acute (new for the patient) or chronic. *Chronic constipation* is defined as the presence of symptoms for at least 3 months. In clinical practice, attempting to identify the cause of the symptoms often results in the best chance of effective treatment and helps determine disposition. A definitive diagnosis often is not possible in the emergency department (ED), and appropriate follow-up evaluation should be arranged. When constipation becomes severe with constant pain, some clinicians use the term *obstipation.* Obstipation represents the progression of the symptom of constipation toward bowel obstruction.

Although constipation may be the final diagnosis for some patients presenting to the ED with abdominal pain, providers should be cautious when reaching this conclusion. Other more serious causes of abdominal pain must be excluded, especially when a patient has abnormal vital signs or marked or localized tenderness on physical examination of the abdomen.

Epidemiology

In adults, constipation is more common in women, the elderly, those with high body mass index, sedentary individuals, and those with low socioeconomic status. A consistent trend of increasing prevalence of constipation is observed with age, with significant increases after the age of 70 years. The high prevalence among elderly patients is multifactorial and related to a diet low in fiber, sedentary habits, multiple medications, and various disease processes that impair neurologic and motor control.

Pathophysiology

Normally the gastrointestinal tract is presented with 9 to 10 L/day of secretions and ingested fluids. The small intestine usually absorbs all of this except for approximately 500 mL. The colon mixes the ileal effluent, ferments and salvages the unabsorbed carbohydrate residues, and desiccates the contents to form stool. The process of stool transport and evacuation is complex and is regulated by neurotransmitters, intrinsic colonic reflexes, and a multitude of learned and reflex mechanisms that are not fully understood. Constipation may result from structural, metabolic, mechanical, neurologic, or behavioral disorders that affect the colon or anorectum either directly or indirectly.[1-3]

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

Causes of constipation are divided into *primary* (no apparent external cause) and *secondary* causes (Box 29.1). These two groupings have some overlap. In the ED, patients most commonly have acute constipation resulting from side effects of medications or avoidance of defecation secondary to presence of painful perianal lesions, such as fissures, hemorrhoids, or perirectal abscesses. Ruling out emergent conditions related to constipation is the priority. Severe, chronic constipation causing fecal impaction in the large bowel leading to pressure necrosis and perforation can cause a condition referred to as *stercoral perforation*.[4] This is typically diagnosed on computed tomography (CT) scan.

Pivotal Findings

Symptoms

A thorough, detailed history usually identifies the most likely cause of the patient's constipation. Start by defining what the patient means by "constipation." Essential information includes the presence or absence of serious symptoms and signs, such as fever, anorexia, nausea, vomiting, blood in the stool, anemia, weight loss of more than 10 pounds, a family history of colon cancer, onset of constipation after the age of 50, and acute onset of constipation in an elderly patient. Diet and dietary changes are noted.

Additional elements of the history are directed toward elucidating a possible cause. Questions about the character of the stools may reveal a decrease in caliber of the stool, suggesting possible mass lesion, or diarrhea alternating with constipation, which may indicate irritable bowel syndrome. The review of systems should include questions regarding associated symptoms if no obvious cause is elicited in the history. Questions directed at associated neurologic symptoms, activity level, and status of comorbid diseases may provide clues to contributing factors. A medication history should include any recent changes in dosage of any prescription medications, herbal agents, and over-the-counter (OTC) medications.

Many patients experience constipation as a side effect of a medication or drug of abuse with opioids being the most commonly implicated. Because elderly patients are at particular risk for constipation and are sometimes prescribed opioids for pain, they are a particular group who should be warned about constipation and given instructions to prevent and treat it. Other drugs that may cause constipation include iron supplements, calcium channel blockers, and antidepressants.

Signs

The physical examination should begin with a general inspection of body habitus and nutritional status and then focus on the

BOX 29.1

Causes of Constipation

CONGENITAL
Hirschsprung's disease
Imperforate anus
Anorectal atresia
Aganglionosis

PRIMARY CAUSES (FUNCTIONAL DISORDERS)
Idiopathic slow transit
Irritable bowel syndrome

SECONDARY CAUSES

Neurologic
Chronic diseases (multiple sclerosis, Parkinson's disease)
Spinal cord injury

Metabolic
Diabetes
Hypercalcemia
Hypokalemia
Hypothyroidism
Hypomagnesemia

Myopathies
Systemic sclerosis
Amyloidosis

Structural
Obstructing tumor or stricture
Intussusception
Rectocele
Rectal prolapse

Medication Side Effect (Most Common Listed Here)
Opiates
Iron or calcium supplements
Calcium channel blockers
Antidepressants
Diuretics
Antipsychotics
Anticholinergics
Antiepileptics
Antiparkinson drugs

Psychological
Abuse (psychological, physical, sexual)
Eating disorders (bulimia, anorexia nervosa)
Affective disorders

Others
Dehydration
Immobility
Pregnancy
Postoperative pain
Dietary factors

Adapted from Chatoor D, Emmanuel A: Constipation and evacuation disorders. Best Pract Res Clin Gastroenterol 23:517, 2009.

abdominal and rectal examinations. The abdominal examination in constipation is usually normal, and abnormal findings (such as, tenderness, a mass, distention, or possibly evidence of obstruction) prompt further directed evaluation. Bowel sounds should be auscultated and typically are normal.

Anorectal inspection may reveal fissures, hemorrhoids, or rectal prolapse. The digital rectal examination should include palpation for impacted stool or mass, and the presence or absence of pain should be noted. Having the patient bear down may be helpful in assessing sphincter function and may reveal milder forms of prolapse. The quantity and the characteristics of the stool should be recorded. Testing the stool for occult blood may yield additional information, although straining with stooling can produce local anal lesions and bleeding. If results of occult blood testing are positive, diverticular disease, carcinoma, and local anal bleeding from repeated attempts at straining all are possibilities. The rectal examination alone should not be used to confirm or exclude the presence of constipation.

Ancillary Testing

The majority of patients who visit the ED with a chief complaint of constipation do not need any testing. Plain abdominal radiography is of almost no value, and patients whose history and examination suggest a need for imaging should undergo ultrasound or CT scan, depending on the working differential diagnosis. Although constipation can cause cramping and abdominal pain, plain radiographs documenting an increased stool load in the constipated patient should not be used to rule out more serious underlying causative disorders, especially if the patient has a significant amount of abdominal pain or tenderness on examination. Several studies have shown that interpretation of abdominal films in the evaluation of constipation is highly variable, subjective, and can lead to misdiagnosis.[1,5]

Clinical laboratory studies are not routinely indicated in the evaluation of constipation. When blood is found in the stool, a hemoglobin level or complete blood count (CBC) may reveal an accompanying anemia, which may suggest an occult carcinoma or recurrent blood loss from localized colon disease, like diverticulosis. The white blood cell count is nonspecific and not helpful.

Patients with acute constipation for which the cause is not readily apparent should receive symptomatic treatment, with referral for outpatient evaluation and reassessment as needed. The patient in the ED with chronic constipation and no alarming signs or symptoms should receive empirical treatment without any ancillary testing. Outpatient tests may eventually include blood tests to investigate metabolic or endocrine causes and possibly specialized tests, such as colonic transit studies and anorectal manometry.[2]

DIAGNOSTIC ALGORITHM

The approach to the patient with constipation starts with assessing whether or not this symptom is accompanied by the additional symptom of abdominal pain. If such pain is present, the evaluation should be geared toward this symptom, which may ultimately reveal the cause of the constipation. Constipation may itself cause abdominal pain; however, this should be a diagnosis of exclusion once other, more serious potential causative disorders have been ruled out.

Figure 29.1 presents a diagnostic algorithm. If the physical examination reveals a structural or mechanical cause (such as, pain from hemorrhoids, fissures, or mass lesion), the appropriate treatment or referral is indicated; the constipation will resolve once the cause is addressed. If no obvious cause is found on examination, then determination of the presence or absence of stool in the rectal vault may be helpful. History will be very helpful in differentiating among causes, such as medication side effect and possible neurologic disease.

Constipation is rarely associated with morbidity or mortality. Most bad outcomes are a result of missed diagnosis of bowel obstruction or perforation. These conditions are generally diagnosed through physical examination, plain radiographs, and CT scan if needed. Surgical consultation is needed for suspected perforation and obstruction.

EMPIRICAL MANAGEMENT

Treatment of acute constipation is directed toward identifying the underlying cause and providing symptom relief. Prevention of further episodes of constipation may include recommending increased fluid intake, increased exercise, increased dietary fiber, and, if necessary, additional sources of bulk in the form of synthetic bulking agents. These interventions will not usually help the acutely constipated patient in the short term. Therapeutic choices and recommendations for patients should be customized based on patient preferences, as well as history of efficacy of treatments used in the past. Specific recommendations may also include withholding a causal medication, management of an anal fissure, or draining of a perirectal abscess. Stool softeners (eg, docusate sodium), although commonly recommended to patients, should not be used as a first-line agent for most patients with constipation. Docusate has not been shown to be any more effective than placebo in relieving acute constipation, although it may be somewhat helpful in patients with anal fissures or hemorrhoids, because it may make defecation less painful.[3]

Specific agents for symptomatic treatment of constipation are listed in Table 29.1. There are five main classes of commonly used laxatives. These are softeners, bulking agents (fiber), osmotic agents, stimulants, and the new peripherally acting μ-opioid

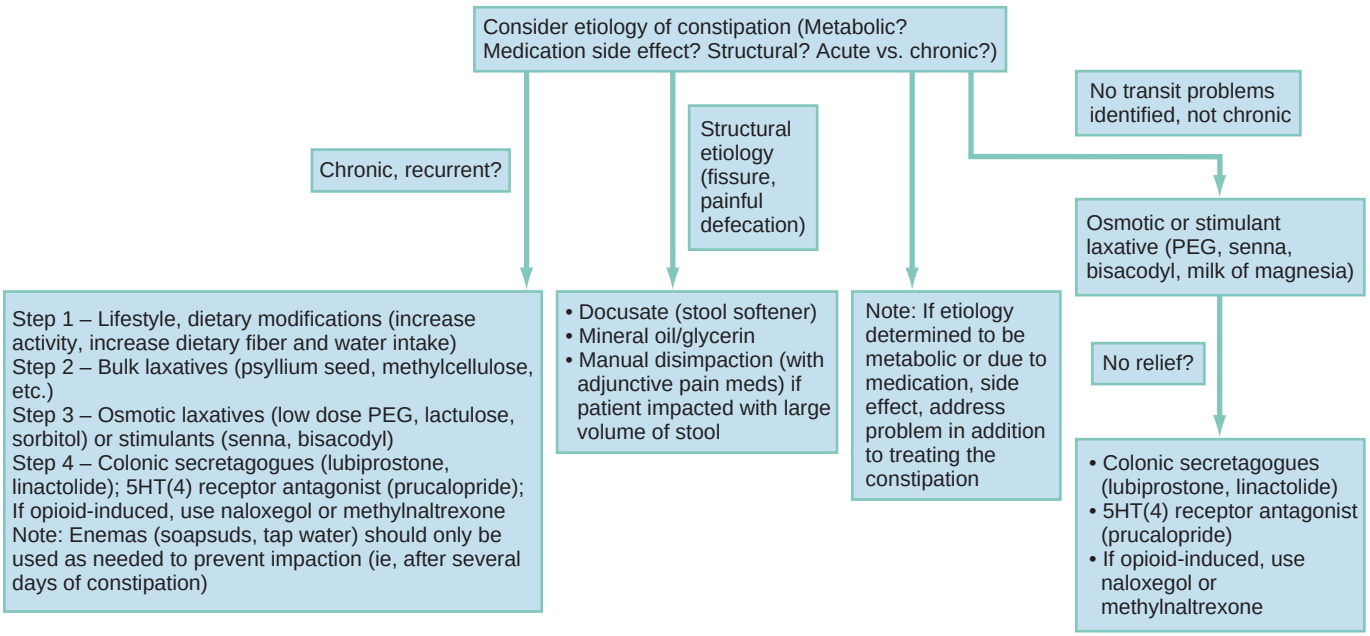

Fig. 29.1. Algorithmic approach to the diagnosis of constipation. *5HT(4),* 5-hydroxytryptamine(4); *PEG,* polyethylene glycol.

TABLE 29.1

Preparations Used in the Symptomatic Treatment of Constipation

MEDICATION	MAXIMAL RECOMMENDED DOSAGE	ONSET OF ACTION	COMMENTS
Bulk laxatives			Indigestible fiber attracts water, which leads to larger, softer fecal mass.
Psyllium (Metamucil)	Titrate up to 20 g	12–72 hours	Natural fiber that undergoes bacterial degradation, which may contribute to bloating and flatus. Should be taken with plenty of water to avoid intestinal obstruction.
Methylcellulose (Citrucel)	Titrate up to 20 g		Semisynthetic cellulose fiber that is relatively resistant to colonic bacterial degradation.
Polycarbophil (Fibercon)	Titrate up to 20 g		Synthetic fiber of polymer of acrylic acid, resistant to bacterial degradation.

Continued

TABLE 29.1

Preparations Used in the Symptomatic Treatment of Constipation—cont'd

MEDICATION	MAXIMAL RECOMMENDED DOSAGE	ONSET OF ACTION	COMMENTS
Osmotic laxatives			Draw water into the intestines along osmotic gradient.
Magnesium or sodium salts			
Magnesium hydroxide (milk of magnesia)	30–45 mL once daily	1–6 hours	A small percentage of magnesium is absorbed—use caution in patients with renal insufficiency and in children.
Magnesium citrate	150–300 mL as needed	3–6 hours	
Sodium phosphate (Fleet Phospho-Soda)	20–45 mL with 12 oz of water as needed		Hyperphosphatemia may result if patient has renal insufficiency. Commonly used before colonoscopy.
Poorly absorbed sugars			
Lactulose	15–30 mL once or twice a day	24–48 hours	Synthetic disaccharide not absorbed by the small intestine. Gas and bloating common.
Sorbitol	15–30 mL once or twice a day		Poorly absorbed by small intestine.
Polyethylene glycol and electrolytes (GoLYTELY, MiraLax)	17 g two or three times a day	12–24 hours	Organic polymers that are poorly absorbed and not metabolized by bacteria; thus may cause less bloating and cramping. Can be mixed with noncarbonated beverages.
Stimulant laxatives			Stimulate intestinal motility or secretion.
Senna (Senokot, Ex-Lax)	8–34 mg daily	6–12 hours	Stimulates secretion and motility of small intestine and colon.
Bisacodyl (Dulcolax, Correctol)	5–10 mg daily		
Stool softeners			Increase water penetration and soften stool.
Docusate sodium (Colace)	100 mg twice a day; some use higher doses	24–48 hours	In many studies, no better than placebo. Not recommended as first-line or solo therapy.
Mineral oil (Fleet mineral oil)	5–15 mL orally at night		Provides lubrication for the passage of stool. Long-term use is not recommended. Lipid pneumonia can occur in patients predisposed to aspiration.
Newer agents			
Lubiprostone (Amitiza)	24 μg once or twice per day	1 hour	Used in CIC.
Linaclotide (Linzess)	145 mcg orally once daily in CIC and 290 mcg orally once daily in IBS-C		Used in IBS-C and CIC.
Methylnaltrexone (Relistor)	8–12 mg SC every other day		Used in opioid-induced constipation.
Naloxegol (Movantik)	25 mg orally once daily		Used in opioid-induced constipation.

CIC, Chronic idiopathic constipation; *IBS-C,* irritable bowel syndrome with constipation; *SC,* subcutaneously.

receptor antagonists. These agents aid defecation by decreasing stool consistency, stimulating colon motility, or both. There are also several new pharmacologic classes being used or investigated for the treatment of constipation in specific groups of patients.[6]

A group of patients that often experiences constipation are those who are on chronic, medically necessary medications that cause constipation (eg, opioids in patients with chronic pain or cancer). These patients should be on bowel regimens designed to prevent constipation, which usually include such measures as high levels of dietary fiber (eg, added prunes or figs), as well as daily administration of stimulant laxatives. An advance in the treatment of refractory opioid-induced constipation has been the development of peripherally acting μ-opioid receptor antagonists. There are two drugs in this category—methylnaltrexone (Relistor), which is administered subcutaneously, and naloxegol (Movantik), which is orally administered.[7] These drugs selectively block the gastrointestinal μ-opioid receptors without compromising central mediated effects of opioid analgesia or precipitating withdrawal. The use of this class of drugs in the treatment of opioid-induced constipation was recently supported in a systematic review and can be used in the ED for patients in whom standard therapies have failed.[8]

Enemas are sometimes necessary if laxatives have failed to provide relief or if the patient has a large volume of stool in the lower colon or rectum that cannot be expelled. Warm tap-water enemas are the safest choice. For immediate relief, manual disimpaction may be necessary in some patients, especially in elders with large amounts of stool present in the rectal vault. In rare cases, disimpaction may need to be performed with procedural sedation.

KEY CONCEPTS

- Constipation is a common patient concern and rarely has an emergent condition associated with it.
- Evaluation of the patient with constipation requires a detailed history (with particular attention to medication history), physical examination (including rectal examination) and rarely requires labs or imaging.
- Treatment of constipation includes addressing underlying etiologies and recommending the correct agent based on the etiology.
- Stool softeners (docusate sodium), although commonly prescribed, are ineffective and are rarely indicated.
- Osmotic agents or stimulants can be used to treat the majority of patients who present with constipation.
- Patients who have a large amount of stool in the rectum can be treated with an enema, which acts by distending the rectum and helps soften the stool to facilitate passage. For some with particularly recalcitrant stool, manual disimpaction may be required.
- Plain abdominal radiographs are of little or no use in diagnosing constipation or other, more serious abdominal disorders that may present as constipation, and should be used highly selectively, if at all.
- Patients with opioid-induced constipation that is refractory to other standard laxatives, may benefit from peripherally acting μ-opioid receptor antagonists.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 29: QUESTIONS & ANSWERS

29.1. Which of the following statements regarding constipation is correct?
- **A.** Chronic constipation is defined as the presence of symptoms for at least 2 weeks.
- **B.** Constipation is a disease is increasing in frequency.
- **C.** Constipation is more common in men than in women.
- **D.** Obstipation refers to severe constipation with constant pain.
- **E.** The incidence of constipation is lower in patients with a high body mass index.

Answer: D. Obstipation refers to constipation has become severe with constant pain. Obstipation represents the progression of symptoms toward bowel obstruction. Constipation is a symptom, not a disease. Chronic constipation is defined as the presence of symptoms for at least 3 months. Constipation is more common in women than in men, those with higher body mass index, and in elderly patients.

29.2. A previously healthy, 50-year-old woman presents with a 1-day history of constipation associated with hard stools and increased straining. The physical examination (including rectal examination) is normal. Which of the following is the most appropriate next step in the evaluation and management of this patient?
- **A.** Laboratory evaluation of serum electrolytes
- **B.** Obtain abdominal radiograph series
- **C.** Obtain urinalysis
- **D.** Order colonic transit studies
- **E.** Prescribe a laxative agent

Answer: E. The majority of patients who present with a chief complaint of constipation do not need testing. Patients with acute constipation for which a cause is not readily apparent should be treated symptomatically and referred for outpatient evaluation and reassessment if needed.

29.3. Which of the following medications is the most likely cause of constipation in a patient with an otherwise non-concerning history and physical examination?
- **A.** Acetaminophen
- **B.** Albuterol
- **C.** Famotidine
- **D.** Hydrocodone
- **E.** Naproxen

Answer: D. Opioids are the most common class of medications to cause constipation. The other medications listed do not commonly cause constipation as a side effect.

29.4. A 25-year-old human immunodeficiency virus (HIV)-positive man presents with a 3-day history of constipation. He also reports a perianal mass has been slowly increasing in size during the past 3 months and has become painful in the past week. He has no other complaints. Physical examination reveals perianal condyloma acuminata with one area of tenderness, friability, and erosion. There is no evidence of infection, and stool can be palpated in the rectal vault during digital examination. Which of the following oral agents would be most beneficial for the symptomatic improvement of constipation in this patient?
- **A.** Docusate sodium
- **B.** Mineral oil
- **C.** Psyllium
- **D.** Senna
- **E.** Sorbitol

Answer: B. Oral mineral oil lubricants are particularly helpful in patients who have acute painful perianal lesions. The softening and coating of the stool can make passage much easier and less painful. Although not listed as an option, another consideration in this patient would be suppositories, which are especially helpful in patients who tend to have trouble expelling soft stool from the rectum. Glycerin suppositories may have a soothing effect and be helpful in patients with constipation caused by local, painful perianal lesions.

29.5. Which of the following agents used in the treatment of constipation is contraindicated in patients who are at increased risk for aspiration?
- **A.** Magnesium citrate
- **B.** Mineral oil
- **C.** Polyethylene glycol
- **D.** Psyllium
- **E.** Senna

Answer: B. Mineral oil is contraindicated in patients with swallowing problems or patients particularly debilitated who are at increased risk for aspiration, because this could ultimately lead to lipid pneumonia if aspirated.

CHAPTER 30

Acute Pelvic Pain

Ari M. Lipsky | Danielle Hart

PERSPECTIVE

Epidemiology

Acute pain caused by pelvic pathology is common, and the presenting complaint may be diffuse or lower abdominal pain, pelvic pain, or low back pain. A patient with chronic pelvic pain may also have an acute process related to the chronic condition or arising de novo.

Over one-third of reproductive age women will experience nonmenstrual pelvic pain. Among diagnoses for women with pain caused by gynecologic disorders in the emergency department (ED), pelvic inflammatory disease (PID) and lower genital tract infections (eg, cervicitis, candidiasis, Bartholin's abscess) account for almost 50%. Other common diagnoses are menstrual disorders, noninflammatory ovarian and tubal pathology (including cysts and torsion), and ectopic pregnancy. Ectopic pregnancy accounts for up to 20% of diagnoses among women presenting with vaginal bleeding or abdominal pain in the first trimester of pregnancy.

Younger patients and those with multiple sexual partners are more likely to have PID, and a previous episode increases the likelihood of a subsequent episode.[1] The risk of ectopic pregnancy is higher in women who have had PID, pelvic surgery, prior ectopic pregnancy, or are using an intrauterine device. Heterotopic pregnancy is of special concern in women undergoing assisted reproduction. Common nongynecologic diseases such as appendicitis, diverticulitis, urinary tract infection, and urolithiasis remain important considerations in the woman with acute pelvic pain. Box 30.1 lists conditions accounting for most cases of pelvic pain in women.

Some causes of pelvic pain may lead to serious sequelae. PID carries the short-term risk of tubo-ovarian abscess and the long-term risks of impaired fertility, chronic pelvic pain, and increased predisposition to ectopic pregnancy. Rupture of an ectopic pregnancy or hemorrhagic ovarian cyst may be life-threatening. Unrecognized abuse may also have serious or lethal consequences.

Pathophysiology

The female pelvis contains the vagina, uterus, fallopian tubes and ovaries, ureters and urinary bladder, and sigmoid colon and rectum, as well as components of the vascular and musculoskeletal systems. Although pelvic pain often originates from the reproductive organs, it may arise from any structures that lie adjacent to or course through the pelvis. Visceral pain afferents supplying the pelvic organs have common innervation with the appendix, ureters, and colon. Their significant overlap makes accurate localization difficult for both patient and emergency clinician. Pain may be initiated by inflammation, distention, or ischemia of an organ, or by spillage of blood, pus, or other material into the pelvis. Pain may become more localized when the afferent nerves in the parietal peritoneum adjacent to an affected organ are stimulated.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of pelvic pain is broad (see Box 30.1). Most causes of pelvic pain fit into three categories: (1) reproductive tract; (2) urinary tract; and (3) intestinal tract. Because a subset of pelvic pain is found only in pregnancy, the pregnancy test is a key branch point in the diagnostic process. Potential pregnancy-related disorders can be divided into complications of early pregnancy and complications that occur further along in pregnancy. Although the specific cause of pelvic pain cannot always be determined at the initial ED visit, an organized approach usually leads to the confirmation or exclusion of disorders most likely to result in significant morbidity and/or mortality.

Pivotal Findings

It is unlikely that any particular finding on history or physical examination, summarized in Table 30.1, is reliable enough to make or exclude a particular diagnosis conclusively, so ancillary testing beyond a pregnancy test is commonly required in the evaluation of patients with acute pelvic pain.

The pelvic examination may at times provide crucial information. However, some findings on bimanual examination are subjective and may be unreliable; they are perhaps most helpful in localizing the process to one side or the other or in helping to plan the initial evaluation. There are not sufficient data to select reliable women in whom the pelvic examination need not be performed, although the pelvic examination may be deferred in patients who are planned to undergo immediate imaging (usually ultrasound) for a suspected critical condition such as ruptured ectopic pregnancy. Depending on imaging results, a subsequent speculum or bimanual pelvic examination may or may not be necessary.

A sequential approach can progressively narrow the diagnostic possibilities until a reasonable provisional diagnosis is reached.

Symptoms

The location of pain and pattern of radiation often are helpful in focusing the differential diagnosis toward a specific cause or group of causes. Lateral pelvic pain is often related to a process in the tube or ovary. However, with right-sided pain, appendicitis is considered, and in left-sided pain (especially in patients >40 years), the differential diagnosis includes diverticulitis and colitis. Urolithiasis may also manifest as lateral pelvic pain, especially when the stone is at the ureterovesicular junction, or as pain radiating to the labia or vaginal area. Central pelvic pain usually is caused by processes involving the uterus, bladder, or both adnexae. Pain radiating to the rectum may be secondary to pooling of fluid or blood in the cul-de-sac. Diffuse pain may occur with a central or bilateral process such as PID or with diffuse peritonitis from infection or intraabdominal hemorrhage.

Information regarding the onset and duration of pain may be useful. Patients with uncomplicated appendicitis (without

BOX 30.1

Causes of Pelvic Pain in Women

REPRODUCTIVE TRACT
Ovarian torsion
Ovarian cyst
Pelvic inflammatory disease
Salpingitis
Tubo-ovarian abscess
Endometritis
Endometriosis
Uterine perforation
Uterine fibroids
Dysmenorrhea
Neoplasm

PREGNANCY-RELATED
First Trimester
Ectopic pregnancy
Threatened abortion
Nonviable pregnancy
Ovarian hyperstimulation syndrome

Second and Third Trimesters
Placenta previa
Placental abruption
Round ligament pain
Labor or Braxton-Hicks contractions
Uterine rupture

INTESTINAL TRACT
Appendicitis
Diverticulitis
Ischemic bowel
Perforated viscus
Bowel obstruction
Incarcerated or strangulated hernia
Fecal impaction or constipation
Inflammatory bowel disease
Gastroenteritis
Irritable bowel syndrome

URINARY TRACT
Pyelonephritis
Cystitis
Ureteral stone

VASCULAR
Septic pelvic thrombophlebitis
Ovarian vein thrombosis
Sickle cell disease
Pelvic congestion syndrome

MUSCULOSKELETAL
Muscular strain or sprain
Hernia
Abdominal wall hematoma
Pelvic fracture

NEUROLOGIC OR PSYCHIATRIC
Depression
Domestic violence
Sexual abuse
Abdominal migraine
Herpes zoster

perforation or abscess) typically are seen within 48 hours of symptom onset. Sudden-onset pain suggests acute intrapelvic hemorrhage, cystic rupture, ovarian torsion, or ureterolithiasis. Gradual-onset pain is more consistent with inflammation such as in PID or appendicitis. PID-associated pain generally begins gradually during or immediately following menses, whereas ovarian cyst pain peaks at midcycle and, if associated with rupture, is of sudden onset. Ovarian cyst pain may also fluctuate through several menstrual cycles before rupture. Chronic or recurrent pain is consistent with endometriosis, recurrent ovarian cysts, or persistent ovarian mass. The quality of pain may differentiate the crampy intermittent pattern of muscular contractions along a hollow viscus (arising from uterine, ureteral, or bowel pathology) from the steady progressive pain associated with inflammatory or neoplastic causes.

Fever and chills are more common with an infectious process. Nausea and vomiting occur more frequently when the process originates within the gastrointestinal tract but may also accompany any pain of visceral origin such as ovarian torsion, ureteral colic, and pregnancy or any severe pain. Dysuria occurs in many local vulvar and vaginal processes such as herpesvirus infection, candidiasis, and other types of vulvovaginitis, but urinary urgency typically signals an irritated bladder or urethra and should focus attention on the urinary tract.

Information about the patient's last menstrual period, pattern of menses, and sexual activity pattern may be useful but does not necessarily exclude pregnancy. In a pregnant patient, the obstetric history may provide some helpful diagnostic clues. Recurrent spontaneous abortion or previous ectopic pregnancy increases the likelihood of these conditions, respectively. Patients who are actively undergoing infertility treatment are at increased risk for ectopic pregnancy, heterotopic pregnancy, ovarian torsion, and ovarian hyperstimulation syndrome. Round ligament pain is usually noted in the second trimester. Postpartum patients are at increased risk for endometritis.

The presence, quantity, and duration of associated vaginal bleeding should be ascertained (see Chapters 31 and 178). In a nonpregnant patient, bleeding may be associated with abnormal uterine bleeding (eg, from PID, ovulatory dysfunction, cancer) or trauma (eg, vaginal laceration due to pelvic fracture, direct vaginal irritation or trauma). In a pregnant patient, bleeding may also be associated with a subchorionic hemorrhage in an otherwise viable pregnancy, ectopic pregnancy, nonviable intrauterine pregnancy (IUP) (which may continue to cause bleeding after expulsion of the uterine contents, especially if any products of conception are retained), or later in pregnancy with placenta previa or abruption. In some cases, the amount of bleeding may be substantial enough to necessitate blood transfusion and surgical intervention. The presence of vaginal discharge (color, consistency, odor) should also be ascertained.

Sexual history is important, with emphasis on recent sexual contact and previous history of sexually transmitted disease. A history of any recent gynecologic procedures should be obtained because the onset of pelvic pain shortly after uterine instrumentation increases the possibility of uterine perforation or infection. All women should be interviewed in private to permit disclosure of sensitive information such as sexual history, pregnancy, recent abortion, and abuse.

TABLE 30.1

Differentiation of Common or Potentially Catastrophic Causes of Pelvic Pain

CAUSATIVE DISORDER OR CONDITION	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN ED	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
Ectopic pregnancy (critical if ruptured)	Classically severe, sharp, lateral pelvic pain, but severity, location, and quality highly variable	Vaginal bleeding (often mild, can be absent)	Missed period; history of previous ectopic pregnancy, infertility, pelvic surgery, PID, or IUD use	Common	Classically, unilateral adnexal tenderness, adnexal mass, CMT	Pelvic US, quantitative β-hCG, T&C, laparoscopy	Cannot reliably exclude diagnosis based on history and physical examination; severe pain, hypotension, or peritonitis suggests rupture.
Ruptured ovarian cyst (emergent—critical with significant hemorrhage; otherwise, urgent)	Abrupt moderate to severe lateral pain	Light-headedness if bleeding is severe; rectal pain arises from fluid in cul-de-sac.		Rupture—common; significant hemorrhage—uncommon	Hypotension and tachycardia if blood loss is significant; possible peritonitis	Pelvic US, CBC, T&C	Physical examination findings often do not correlate with volume of blood in pelvis at US.
Ovarian torsion (emergent)	Acute onset of moderate to severe lateral pain	Nausea and vomiting	History of ovarian mass or cyst	Uncommon	Adnexal mass and tenderness, possible peritonitis	US with Doppler flow studies, laparoscopy	Torsion can be intermittent.
Appendicitis (emergent)	Duration often <48 hr, generalized followed by localized RLQ pain	Low-grade fever, nausea, anorexia	Migration of pain to RLQ from center, abdominal pain before vomiting	Common	RLQ tenderness, possible peritonitis	US, CT, or MRI	Early in course, tenderness may be minimal or poorly localized.
PID, TOA (TOA: emergent; PID: urgent-emergent)	Without TOA, pain usually bilateral; may manifest acutely within 48 hr, but PID may also be chronic.	Fever, vaginal discharge	Vaginal discharge, history of PID, history of unprotected intercourse or multiple partners	PID— common; TOA—uncommon	Pus from cervical os, CMT, adnexal tenderness; peritonitis suggests TOA or severe PID	CBC, ESR, CRP, pelvic US, laparoscopy, cervical cultures, cervical smear for WBCs	History and physical examination may be inaccurate for diagnosis, particularly in patients with subacute presentation.

UTI (urgent)	Pain with urination; patient may have flank pain from associated pyelonephritis.	Urinary urgency and frequency; fever and vomiting if patient has associated pyelonephritis	Recent urologic procedure, prior history of UTI	Common	Suprapubic tenderness, flank tenderness, and fever with pyelonephritis	Urinalysis, urine culture (if recurrent or complicated)	WBCs can be present in urine with PID and appendicitis; RBCs present in urine with hemorrhagic cystitis.
Ureteral colic (urgent)	Acute onset, manifests within hours; pain is lateral, usually moderate to severe. Often radiates into the groin or costovertebral angle or flank	Nausea and vomiting	Prior history of stones	Common	Patient often appears uncomfortable, but physical examination can be otherwise unremarkable.	Urinalysis— hematuria present in ≈80% of cases; renal ultrasound for hydronephrosis; abdominal CT	If stone is at ureterovesicular junction, patient can have localized pain that can mimic appendicitis or other acute pelvic pathology.
Unruptured ovarian cyst or tumor	Lateral ache, gradual onset	Often minimal	Prior history of similar pain	Common	Lateral pelvic tenderness, with or without a mass	Pelvic US	
Endometriosis	Unilateral or bilateral pelvic pain, often recurrent	Dysmenorrhea, dyspareunia.	Prior history of same type of pain in association with menstrual cycle	Common	Unilateral or bilateral adnexal tenderness, occasionally pelvic mass present, peritoneal findings uncommon	Pelvic US, laparoscopy	Symptoms can mimic other types of pelvic pathology; laparoscopy often is needed for confirmation.

CBC, Complete blood count; *CMT,* cervical motion tenderness; *CRP,* C-reactive protein; *CT,* computed tomography; *ED,* emergency department; *ESR,* erythrocyte sedimentation rate; *β-hCG,* β-human chorionic gonadotropin; *IUD,* intrauterine device; *MRI,* magnetic resonance imaging; *PID,* pelvic inflammatory disease; *RBC,* red blood cell; *RLQ,* right lower quadrant; *T&C,* type and crossmatch; *TOA,* tubo-ovarian abscess; *US,* ultrasonography; *UTI,* urinary tract infection; *WBC,* white blood cell.

Signs

The physical examination is directed toward the abdomen and pelvis. Pelvic examination is performed in almost all patients, including pregnant patients at less than 20 weeks' gestation. Pregnant patients beyond 20 weeks' gestation with complaints of vaginal bleeding should undergo transabdominal pelvic ultrasound for placental localization before the pelvic examination (see Chapter 178), should have a fetal heart rate measured and documented, and may need timely obstetric consultation.

Abnormal vaginal discharge may be seen in a variety of conditions, including vaginitis, cervicitis, endometritis, PID, and retained foreign body. Cervical motion tenderness usually indicates reproductive tract inflammation but also occurs with irritation of adjacent structures (eg, cystitis, appendicitis). An open os is most consistent with an incomplete or inevitable abortion, but does not definitively exclude an ectopic pregnancy. A large uterus in a nonpregnant patient may indicate fibroids. Fundal tenderness is often difficult to distinguish from cystitis but may suggest PID, endometritis, or necrotic fibroids. Unilateral adnexal masses and tenderness are suggestive of an ovarian cyst, ectopic pregnancy, tubo-ovarian abscess, or ovarian torsion.

The constellation of cervical motion tenderness, uterine tenderness, and adnexal tenderness is classically associated with PID, although only one sign is required to initiate treatment in certain clinical settings per recent Centers for Disease Control and Prevention (CDC) guidelines (2015).[2]

Ancillary Testing

A pregnancy test is required in almost all patients of childbearing age with a complaint of abdominal or pelvic pain, irrespective of sexual history or reported contraception use. Very few exceptions to this rule exist such as documented hysterosalpingectomy or a woman who is known to be pregnant. A positive test result may indicate current or recent intrauterine or extrauterine pregnancy or, rarely, molar pregnancy or cancer. Urinalysis of a clean-catch specimen may identify nitrites and pyuria from a urinary tract infection, or hematuria, consistent with urolithiasis or hemorrhagic cystitis. The absence of hematuria does not exclude the possibility of a ureteral stone, although it lowers the likelihood, and mild pyuria may be seen in extravesicular conditions such as appendicitis. Urinalysis should be performed in all pregnant patients with pelvic pain, even if their symptoms do not include urinary tract complaints, because urinary tract infection, including asymptomatic bacteriuria, is associated with significant morbidity for both mother and fetus.

Patients who may be hemorrhaging internally or externally should have their hemoglobin level checked, and type and crossmatching should be performed if the hemorrhage is substantial. Pregnant patients with concern for fetomaternal transfusion (eg, vaginal bleeding) also require blood typing to identify Rh-negative patients who will require Rho(D) immune globulin.

Bedside ultrasound is a core part of the evaluation of most women with pelvic pain and, along with the history and physical examination, should be considered as an integral part of the initial examination.[3] Patients with a positive pregnancy test result should undergo a bedside ED ultrasound or formal ultrasound examination to evaluate for ectopic pregnancy. Identification of a definite IUP by ultrasound imaging excludes ectopic pregnancy with a high degree of certainty in patients who are not undergoing assisted reproduction. Conversely, a patient with a positive pregnancy test in whom a definite IUP cannot be seen is presumed to have an ectopic pregnancy until proven otherwise. In addition, the presence of a gestational sac alone is not sufficient to confirm an IUP; experienced sonographers may use the double decidual sac sign, but it is recommended that less experienced sonographers visualize a yolk sac or embryo for definitive ultrasonographic confirmation of an IUP. A complex adnexal mass, tubal ring, extrauterine yolk sac or embryo, or free fluid is indicative of a probable ectopic pregnancy. The presence of free intraabdominal fluid on ultrasound with a negative urine pregnancy test is consistent with hemorrhage or a ruptured hemorrhagic ovarian cyst. Regardless of cause, intraabdominal free fluid is presumed to be blood and should be addressed expediently.

DIAGNOSTIC ALGORITHM

The algorithm in Fig. 30.1 is designed to focus further testing and progress to a rational provisional diagnosis. It is not unusual, however, to pursue evaluation of gynecologic and intraabdominal causes of pain in parallel, as when the initial history and physical examination do not provide clear direction. It is also possible for common diseases to manifest in uncommon ways, for more than one disease to be present, or for a positive finding not to explain the entirety of the patient's presentation. For example, patients with an abnormal urinalysis may have appendicitis, pregnant patients may also have ovarian torsion or appendicitis, and simple ovarian cysts may be asymptomatic. Tests are therefore interpreted in the context of the individual patient's presentation. With certain diseases such as endometriosis, definitive testing is not available in the ED, and the patient's history may be the most important discriminator.

After an initial history and physical examination, the pregnancy test determines the subsequent priorities, although pregnant patients are not immune to non–pregnancy-related diagnoses. For example, if a threatened abortion is most likely (ie, there is an IUP on ultrasound imaging), unilateral pain may prompt further evaluation for torsion. An empty uterus on ultrasound imaging, or any ultrasound study that cannot confirm a definite IUP, could be consistent with an ectopic pregnancy, spontaneous abortion, or very early normal pregnancy. Patients past 20 weeks' gestation will likely require observation with fetal monitoring.

Nonpregnant patients with pain that seems to be gynecologic in nature should be assessed for hemorrhage from a ruptured, hemorrhagic ovarian cyst, for ovarian torsion, and for infection, including cervicitis, endometritis, PID, salpingitis, and tubo-ovarian abscess (see Chapters 88 and 90). Although the history and physical examination often are sufficient to diagnose infection, ultrasound assessment is helpful if torsion, tubo-ovarian abscess, or ruptured hemorrhagic cyst is suspected. Ultrasound findings also may support a diagnosis of PID if evidence of salpingitis is noted or a diagnosis of a simple ruptured cyst if a characteristic ovarian appearance is combined with the presence of a small amount of free fluid. Although not as reliable as CT, ultrasound may be able to identify appendicitis.

It is difficult to differentiate some gynecologic origins of pain from intraabdominal causes (eg, right ovarian pathology from appendicitis), so ancillary testing may require an ultrasound study, CT, or both. If the cause is most likely gynecologic, an ultrasound examination of the pelvis, and subsequently the appendix, is reasonable. These studies may be followed by CT if the ultrasound findings are unremarkable and the presentation remains consistent with appendicitis or other concerning diagnoses. Pelvic US performed after CT is unlikely to yield additional useful information.[4] When ultrasound is nondiagnostic in a pregnant patient suspected of having appendicitis, we recommend magnetic resonance imaging (MRI), which avoids the risks of progression of the disease during a prolonged observation period and obviates the need for ionizing radiation from CT.[5] Patients whose pain does not seem to be from the reproductive tract often have urinary infections or stones, abdominal sources of pain (see Chapter 24), or musculoskeletal pathology, or may be victims of

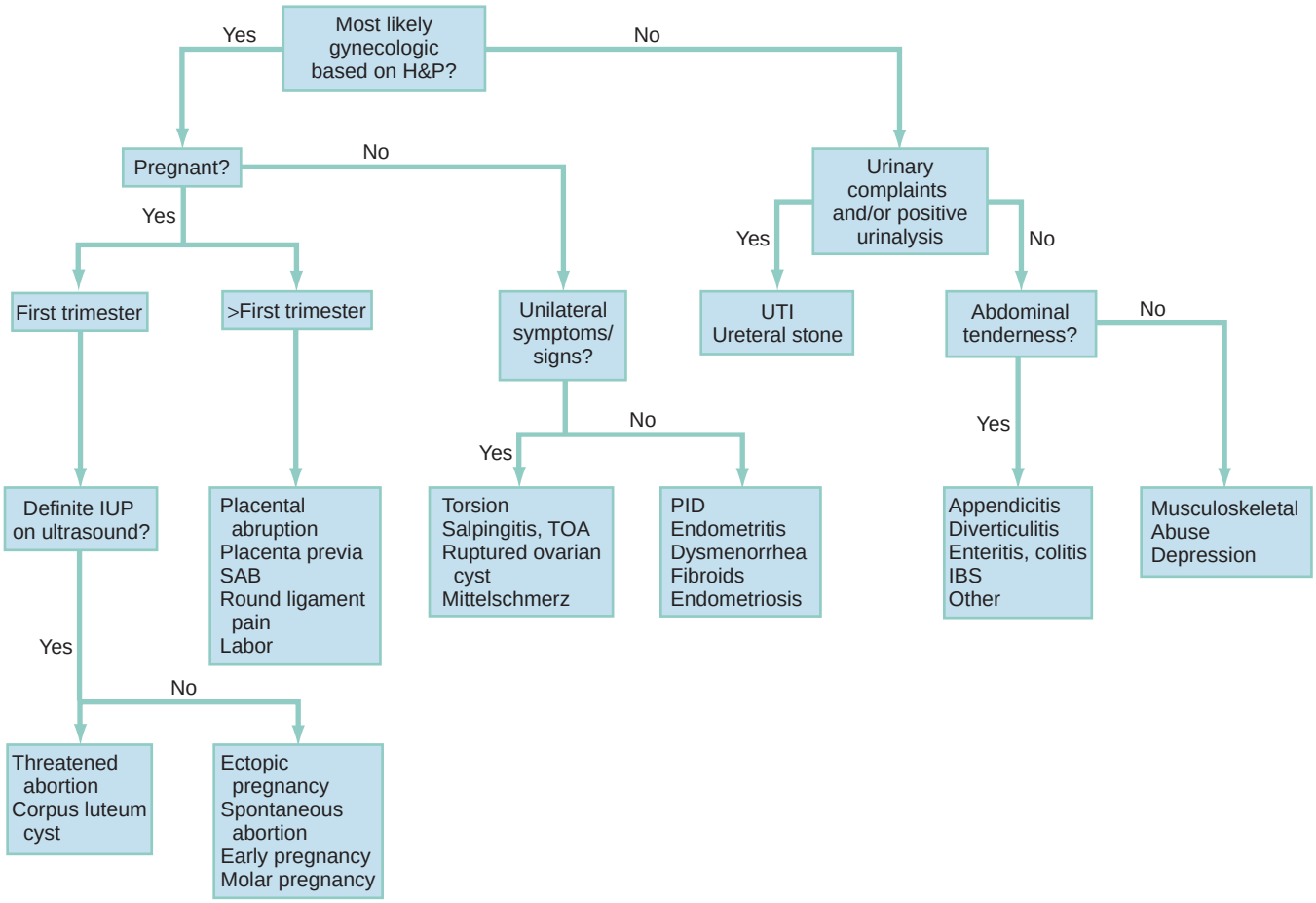

Fig. 30.1. Diagnostic algorithm for acute pelvic pain; see text for details. *H&P,* History and physical; *IBS,* irritable bowel syndrome; *IUP,* intrauterine pregnancy; *PID,* pelvic inflammatory disease; *SAB,* spontaneous abortion; *TOA,* tubo-ovarian abscess; *UTI,* urinary tract infection.

abuse or have depression. Vascular or neuropathic causes of pain are possible but less common.

If the available data do not make sense or conflict with the clinical gestalt, the following three steps should be considered;

1. Ensure that emergent, life-threatening diagnoses have been addressed (eg, ectopic pregnancy).
2. Reassess whether the presentation may be atypical (eg, reconsider appendicitis).
3. If emergent causes are unlikely and sufficient consideration was given to less likely disorders without uncovering a cause, address the possibility of depression or abuse. Follow-up planning for all patients is recommended.

EMPIRICAL MANAGEMENT

An algorithm for the management of patients with acute pelvic pain is presented in Fig. 30.2. Patients in extremis are most likely hemorrhaging, although on occasion septic shock may be the cause. Ectopic pregnancy, placental abruption, and hemorrhagic ovarian cyst may cause life-threatening hemorrhage, with no or minimal vaginal bleeding. Patients with these disorders need rapid treatment with fluid and blood products and may require surgical intervention before stabilization can be achieved. A bedside ultrasound generally will help the emergency clinician reach these presumptive diagnoses expediently. Septic shock may be a consequence of abdominal or pelvic processes and may require general surgical and gynecologic consultations, as well as admission to an intensive care setting.

We recommend early administration of analgesia for patients with significant pain, a practice that greatly improves patient comfort and the reliability of the physical examination, which is otherwise hampered by the patient's extreme pain, tenderness, or both. For severe pain, intravenous opioids such as morphine or hydromorphone are rapid and effective, titratable, and generally considered safe in pregnancy. After critical and emergent diagnoses have been excluded, well-appearing patients for whom a definitive or reasonable provisional diagnosis is reached may be discharged with close follow-up and appropriate treatment and precautions. Pregnant patients at a stage of fetal viability (20 weeks' gestation or as per institutional guidelines) should be referred to the obstetric service for fetal monitoring before discharge. Pregnant patients who have suffered abdominal trauma, especially those later in pregnancy, should undergo monitoring before discharge (see Chapter 182).

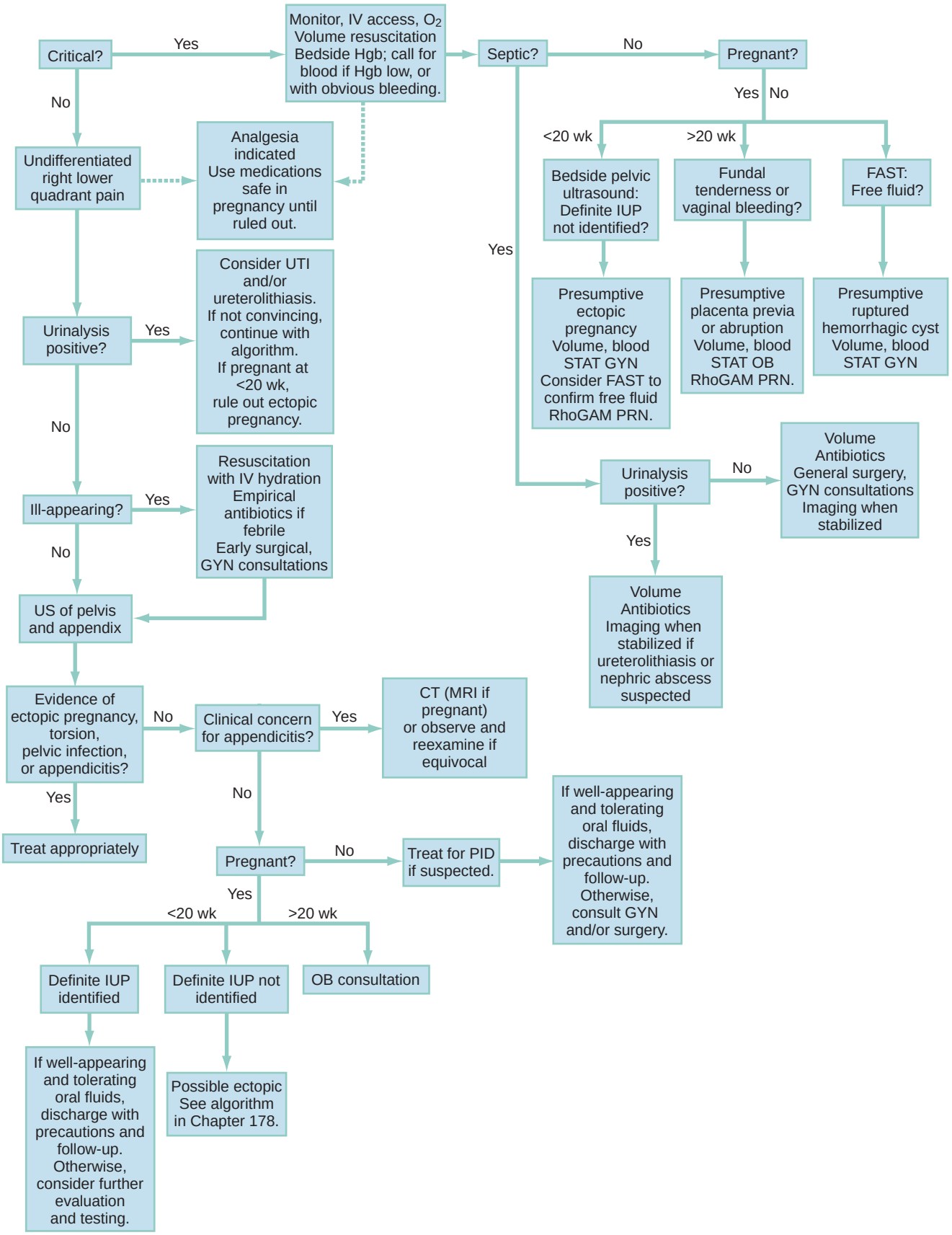

Fig. 30.2. Management algorithm for acute pelvic pain illustrating critical patients and right lower quadrant pain presentations. *CT,* Computed tomography; *FAST,* focused assessment with sonography for trauma; *GYN,* gynecology; *Hgb,* hemoglobin; *IUP,* intrauterine pregnancy; *IV,* intravenous; *MRI,* magnetic resonance imaging; *OB,* obstetric; *PID,* pelvic inflammatory disease; *STAT,* immediately; *US,* ultrasound; *UTI,* urinary tract infection.

KEY CONCEPTS

- Acute pelvic pain in women is often from a gynecologic source, but urinary and intraabdominal sources are also common. Less frequently, the pain may arise from vascular, musculoskeletal, neurologic, or psychiatric sources.
- Potentially lethal diagnoses associated with acute pelvic pain include ectopic pregnancy, ovarian cyst with significant hemorrhage, and domestic violence; highly morbid conditions presenting with acute pelvic pain include pelvic inflammatory disease and ovarian torsion.
- Nearly all women of childbearing age with pelvic pain should have a pregnancy test performed, and most also require a pelvic ultrasound examination.
- Ectopic pregnancy should be excluded in the pregnant patient with pelvic pain. Bedside ultrasound is an excellent test for confirming an intrauterine pregnancy (IUP); it excludes ectopic pregnancy with a high degree of certainty in patients who are not undergoing assisted reproduction.
- In the nonpregnant patient, the pain of PID generally begins gradually and during menses. Ovarian cyst–associated pain is maximal at midcycle, and is usually gradual and cyclic, although it may be sudden and severe if rupture has occurred.
- Pregnant patients with acute pelvic pain may also have non–pregnancy-related disorders; appendicitis, nephrolithiasis, and ovarian torsion remain in the differential diagnosis.
- Many patients with acute pelvic pain require imaging as part of their assessment. If a gynecologic source is suspected, begin with an ultrasound and then progress to CT or MRI, if needed. The presence of an ovarian cyst on imaging does not necessarily explain the patient's pain, and further evaluation may be required.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 30: QUESTIONS & ANSWERS

30.1. Which of the following is most true regarding the evaluation of patients with pelvic pain?

A. Ancillary testing can be limited to a urine pregnancy test in most patients.
B. Bimanual examinations have been shown to result in highly reliable findings, with substantial interobserver agreement.
C. Patients typically localize visceral pain with a high degree of accuracy.
D. Thorough history taking is adequate to exclude most life-threatening conditions.
E. None of these.

Answer: E. It is rare that any particular finding on history or physical examination is reliable enough to make or exclude a particular diagnosis conclusively in patients presenting with pelvic pain, so ancillary testing (beyond a simple pregnancy test) is commonly required in the evaluation of these patients. The bimanual examination may, at times, provide important information. Unfortunately, however, findings on pelvic examination are somewhat subjective and unreliable and may serve more to localize the process to one side or the other rather than diagnose it or even limit it to the reproductive organs. Although pelvic pain often originates from the reproductive organs, it may arise from any structures that lie adjacent to or course through the pelvis. Visceral pain afferents supplying the pelvic organs have common innervation with the appendix, ureters, and colon. Their significant overlap makes accurate localization difficult for both patient and emergency clinician.

30.2. A 26-year-old patient presents with right lower quadrant (RLQ) abdominal pain. She states her last menstrual period was 8 weeks ago. Bimanual pelvic examination reveals tenderness in the RLQ and right adnexal area. The patient's vital signs include a regular pulse of 120 beats/min and a blood pressure of 110/68 mm Hg. Urinalysis is unremarkable, and the urine pregnancy test is positive. What is the most appropriate next test?

A. Cervical cultures
B. Complete blood count (CBC)
C. Computed tomography (CT)
D. Magnetic resonance imaging (MRI)
E. Pelvic ultrasonography

Answer: E. This follows the algorithms in Figs. 30.1 and 30.2. The most life-threatening pathology requiring urgent or emergent intervention is hemorrhage from a ruptured ectopic pregnancy. A pelvic ultrasound scan is rapid, especially when using bedside ultrasonography, and is the first step in an evaluation of a suspected ruptured ectopic pregnancy.

30.3. A 30-year-old woman presents with lower abdominal pain. She has lower abdominal, uterine, bilateral adnexal, and cervical motion tenderness on pelvic examination. She has a negative urine pregnancy test and urinalysis. What is the most appropriate next step in the patient's management?

A. Await cervical culture results.
B. Obtain a CBC.
C. Obtain a CT scan.
D. Perform a pelvic ultrasound.
E. Treat with antibiotics.

Answer: E. The constellation of uterine tenderness, bilateral adnexal tenderness, and cervical motion tenderness is classically associated with pelvic inflammatory disease (PID), particularly when the pain onset is during or just after menstruation. The diagnosis may be made, however, without the presence of all three signs, and treatment may be initiated with only one sign in an at-risk patient, as given in the 2015 Centers for Disease Control and Prevention (CDC) guidelines.

30.4. A 35-year-old woman undergoing infertility treatment presents with severe lower left quadrant (LLQ) abdominal pain and tenderness isolated to the left adnexal area on pelvic examination. The urine pregnancy test is positive, and the urinalysis is unremarkable. Rapid bedside ultrasonography reveals an intrauterine pregnancy with a gestational age of 6 weeks, 5 days, and moderate free pelvic fluid. Which diagnoses should be further investigated at this time?

A. Ectopic pregnancy
B. Heterotopic pregnancy
C. Round ligament pain
D. Simple ovarian cyst
E. None of these

Answer: B. Women who are actively undergoing infertility treatment are at increased risk for ectopic pregnancy, heterotopic pregnancy, ovarian torsion, and ovarian hyperstimulation syndrome.

CHAPTER 31

Vaginal Bleeding

Joelle Borhart

PERSPECTIVE

Epidemiology

Abnormal uterine bleeding occurs in women of all ages and is the most common reason that women seek gynecologic care.[1] Abnormal vaginal bleeding in nonpregnant women is rarely life-threatening, but may herald serious underlying pathology, such as cancer. Bleeding as a complication of pregnancy poses significant risk of morbidity and mortality to the fetus and mother.

Pathophysiology

Nonpregnant Patients

The mean time between menstrual periods is 28 days (±7 days), with menstruation generally lasting for 5 days. It is considered abnormal to bleed for more than 7 days. On average, 35 mL of blood is lost per menstruation; a loss of more than 80 mL is abnormal.[2]

There has been an important change in the accepted nomenclature used to describe abnormal bleeding in nonpregnant women. Since 2011, the American Congress of Obstetricians and Gynecologists (ACOG) has recommended the PALM-COEIN classification system, which uses the all-inclusive term *abnormal uterine bleeding* (AUB) and divides the causes of AUB into structural and nonstructural causes. Structural causes include ***p***olyps, ***a***denomyosis, ***l***eiomyomas, and ***m***alignancy (**PALM**). Nonstructural causes include ***c***oagulopathy, ***o***vulatory dysfunction, ***e***ndometrial, ***i***atrogenic, and ***n***ot yet classified causes (**COEIN**).[3,4] The use of the term *dysfunctional uterine bleeding* is no longer recommended.

Approximately 50% of cases of excessive menstruation fall under the nonstructural PALM-COEIN category of ovulatory dysfunction, which includes anovulatory bleeding. If a woman does not ovulate, there is no corpus luteum to produce progesterone, which results in estrogen being unopposed. Unopposed estrogen causes the endometrium to proliferate to the point at which it becomes unstable and begins to break down, causing irregular and unpredictable bleeding to occur. Heavy bleeding can also occur in the setting of regular ovulation (ovulatory bleeding).

Benign structural causes such as leiomyomas (fibroids) were classically thought to cause heavy bleeding by increasing endometrial surface area and disrupting the endometrial vascular supply and the ability of the uterus to contract to stop bleeding. Recent evidence has shown that aberrantly regulated growth factors may also play a role in fibroid-related bleeding.[5] Cervical polyps, which commonly occur in multiparous women in their 40s and 50s, are friable and prone to bleeding.[6]

Pregnant Patients

Pregnant women may experience bleeding throughout their pregnancy. In early pregnancy, ectopic pregnancy causes hemorrhage into the fallopian tube by disrupting of the blood supply to the ectopic gestational sac. Also, the size of the growing gestational sac can rupture through the tubal wall.

After the 20th week of pregnancy, vaginal bleeding can be caused by placenta previa, in which the placenta completely or partially covers the internal cervical os. As the lower part of the uterus becomes thinner during the third trimester in preparation for labor, bleeding can occur. Placental abruption causes bleeding when the placenta tears away from the uterine wall. This can occur spontaneously or secondary to abdominal trauma, with transmission of forces to the uterus. It is important to note that a large amount of concealed blood can be retained between the detached placenta and uterus, and the extent of the hemorrhage may not be fully appreciated until delivery.[7] The most significant risk factor for abruption is a history of abruption in prior pregnancies (10-fold increased risk). An increased incidence is also seen in pregnancies complicated by hypertensive disorders, including preeclampsia, eclampsia, the HELLP (***h***emolysis, ***e***levated ***l***iver enzymes, and ***l***ow ***p***latelets) syndrome, and abnormal implantation of the placenta (eg, placenta previa, accreta, increta, percreta). Smoking and cocaine use also increase the risk for abruption.

In the immediate postpartum period (first 24 hours), bleeding is usually the result of uterine atony if the uterus fails to contract. Atony is more likely to occur with conditions that overdistend the uterus, such as a large for gestational age fetus, polyhydramnios, and multiparity. Prior history of postpartum hemorrhage, prolonged labor, induced labor, augmentation of labor with oxytocin, and instrumentation delivery also increase the risk of postpartum hemorrhage.[7,8] After 24 hours postpartum, retained products of conception (POCs) is the most common cause of bleeding.

DIAGNOSTIC APPROACH

Differential Considerations

In nonpregnant women, the differential diagnosis is extensive (Box 31.1), and it is helpful to categorize the differential diagnosis by the age of the patient. In prepubescent girls, causes of vaginal bleeding include vaginitis, foreign bodies, sexual abuse, tumors, and trauma. In adolescent girls, the most common cause of abnormal vaginal bleeding is persistent anovulation due to immaturity of the hypothalamic-pituitary-ovarian axis.[9] Underlying bleeding disorders and coagulopathies, such as von Willebrand disease, may also first present in adolescence. Sexually transmitted infections may also cause abnormal bleeding in this age group. For women in their reproductive years, structural lesions such as polyps and fibroids frequently cause abnormal bleeding. Black women are more likely to have fibroids, and they experience disproportionally more morbidity from heavy bleeding.[5] Endocrine causes, such as polycystic ovarian syndrome, should be considered in women with signs of androgen excess—obesity, acne, hirsutism. In perimenopausal woman, anovulatory cycles become common as ovarian function declines. Endometrial atrophy is the most common cause of abnormal bleeding in postmenopausal women; however, cancer should be considered until proven otherwise.

BOX 31.1

Differential Diagnosis of Abnormal Uterine Bleeding In Nonpregnant Females

STRUCTURAL CAUSES

Polyps
Fibroids
Malignancy
Hyperplasia
Endometriosis

NONSTRUCTURAL CAUSES

Coagulopathies
- von Willebrand disease
- Factor XI deficiency
- Thrombocytopenia
- Idiopathic thrombocytopenic purpura

Endocrine
- Polycystic ovarian syndrome
- Hypothyroidism
- Hyperprolactinemia
- Adrenal hyperplasia
- Cushing's disease

Weight loss, extreme exercise
Stress
Obesity
Trauma
- Sexual abuse

Infections
- Sexually transmitted infection
- Tuboovarian abscess
- Vaginitis

Systemic disease
- Liver disease
- Kidney disease

Foreign bodies
Medications
- Antiepileptics
- Antipsychotics
- Anticoagulants
- Hormonal medications
- Steroids

Intrauterine device

NOTE: Divide patients with vaginal bleeding into groups based on age when formulating a differential diagnosis.
From Borhart J: Emergency department management of vaginal bleeding in the nonpregnant patient. Emerg Med Pract 15:1–20, 2013.

Regardless of age, review a patient's medication list for drugs that are known to cause abnormal bleeding (eg, antiplatelet agents, anticoagulants), antiepileptic agents (especially valproic acid), and typical and atypical antipsychotics and steroids can cause abnormal uterine bleeding.

For pregnant women with vaginal bleeding, the differential diagnosis can be refined based on whether the bleeding occurs in early or late pregnancy or postpartum. For patients with vaginal bleeding in early pregnancy (before the 20th week of gestation and prior to fetal viability), the differential diagnosis includes miscarriage, ectopic pregnancy, implantation bleeding, molar pregnancy, and ruptured corpus luteum cyst. Bleeding in early pregnancy is common, affecting up to 20% of pregnancies. Miscarriage, defined as the spontaneous termination of pregnancy before the 20th week of gestation is also common; approximately 50% of women with early bleeding will miscarry. Miscarriages are described as threatened, missed, inevitable, incomplete, or complete depending on the status of the internal cervical os and if any POCs have been passed. The most concerning diagnosis in patients with bleeding in early pregnancy is ectopic pregnancy, a pregnancy implanted outside the uterus. Ectopic pregnancy is the leading cause of first-trimester maternal death[10] and is common among patients presenting with pain or bleeding in the first trimester of pregnancy. Risk factors for ectopic pregnancy include pelvic inflammatory disease, previous ectopic pregnancy, prior tubal surgery, use of an intrauterine device, and endometriosis. An important subgroup of patients are women undergoing assisted reproduction or in vitro fertilization (IVF). These patients are at increased risk for heterotopic pregnancies, which is a simultaneous intrauterine pregnancy (IUP) and ectopic pregnancy.[11] Heterotopic pregnancies are rare in the general population.

Vaginal bleeding after the 20th week of pregnancy is less common, occurring in approximately 4% of pregnancies. Bleeding complications in late pregnancy generally occur in the third trimester and include placenta previa, placental abruption, and uterine rupture.

Pivotal Findings

Symptoms

Begin by eliciting the timing and duration of bleeding. Volume of blood loss is difficult to quantify because historical features, such as the frequency of changing a sanitary pad or tampon, have not been shown to predict blood loss consistently. Normal menstrual blood does not clot; therefore, the presence of clots indicates heavy bleeding. A report of dizziness, syncope, or weakness could also indicate significant blood loss. Associated symptoms such as abdominal pain, fever, vaginal discharge or odor, and postcoital bleeding could indicate a possible sexually transmitted infection or pelvic inflammatory disease. Postcoital bleeding can also indicate a cervical lesion, and occurs more commonly in pregnancy due to increased cervical blood flow. A history of trauma should be noted. Vaginal injuries can be sustained in a number of ways and range in severity from minor contusions to deep lacerations. The most common mechanism of genital injury in adult women is coitus.[12] In pregnancy, blunt trauma, such as falls, motor vehicle accidents, and interpersonal violence, is associated with a significantly increased risk of maternal and fetal morbidity and mortality.

Signs

For any patient presenting with vaginal bleeding, begin by determining the patient's hemodynamic status and performing a complete abdominal and pelvic examination. The pelvic examination may reveal the source of bleeding because masses, polyps, ulcers, foreign bodies, and evidence of trauma or inflammation may be visualized. After the 20th week of pregnancy, a pelvic examination should be deferred until after an ultrasound has been performed to exclude placenta previa as the cause of bleeding. In pregnant patients of sufficient gestational age, the fetal heart rate and fundal height should also be assessed. Fetal heart rate can be measured using the M mode on bedside ultrasound as opposed to Doppler because this is thought to transmit less acoustic energy to the fetus. Fetal cardiac activity may be measured as early as 6 weeks. Uterine size can be estimated by palpating the fundus. The uterus is palpable at the level of the umbilicus at 20 weeks. The fetal age is more than 24 weeks (ie, viable) if the uterus can be felt at least four fingerbreadths above the umbilicus. This method may be less reliable in multiple pregnancies or other conditions that might affect the distention of the uterus or abdomen, such as large fibroids, polyhydramnios, oligohydramnios, intrauterine growth restriction, and obesity.[13] Bedside ultrasound can also be used to estimate fetal age.

Ancillary Testing

Pregnancy status is an essential data point in the evaluation of any woman of reproductive age presenting with vaginal bleeding. Other critical laboratory tests in hemodynamically unstable patients include complete blood count, type and crossmatching of blood, coagulation studies and, if pregnant, a quantitative β-human chorionic gonadotropin (β-hCG) level determination.

Bedside ultrasound has become increasingly used in the emergency department (ED) evaluation of pregnant women with vaginal bleeding to determine whether an IUP is present. A yolk sac is the first sonographic evidence of a definite IUP and can be visualized using transvaginal ultrasound, beginning around the 5th week of pregnancy. *Pregnancy of unknown location* (PUL) is the term used to categorize pregnancy in a woman with a positive pregnancy test when no pregnancy can be visualized using transvaginal ultrasound.[11] In this case, the quantitative β-hCG level has traditionally been used to determine if the level is in the discriminatory zone. The discriminatory zone is the level of β-hCG in which an IUP, if present, should be seen consistently. For transvaginal ultrasound, the discriminatory zone is generally accepted as from 1000 to 2000 IU/mL. However, the value of the discriminatory zone has recently been called into question because it is not as reliable at excluding a viable pregnancy as previously thought.[14] Multiple studies have reported that a normal intrauterine pregnancy not visualized on ultrasound is possible if β-hCG levels are above the discriminatory zone.[15,16] Therefore, caution should be used when interpreting a single β-hCG measurement because a normal gestation could potentially be disrupted. It is appropriate to repeat transvaginal ultrasound and β-hCG measurements in hemodynamically stable patients instead of initiating medical or surgical intervention for possible ectopic pregnancy based on the discriminatory zone alone. There is no β-hCG level at which an ectopic pregnancy could be completely ruled out.

Additional testing for the stable, nonpregnant ED patient, such as thyroid and other hormonal studies, is usually performed on an outpatient basis. This also includes a complete pelvic ultrasound because the results will rarely change ED management.

DIAGNOSTIC ALGORITHM

The single most important determination to make when evaluating a woman with vaginal bleeding is to determine if she is pregnant or nonpregnant (Fig. 31.1). If the patient is not known to be pregnant or immediately postpartum, a urine pregnancy test should be performed. Next, determine the age of the pregnancy in weeks. The most critical diagnoses to make in patients less than 20 weeks pregnant are ectopic and heterotopic pregnancies. Bedside ultrasound is useful to establish if an IUP is present. If the ultrasound is indeterminate, a quantitative β-hCG determination can help risk-stratify the patient further. Usually, the diagnosis will be threatened miscarriage.

For patients of more than 20 weeks gestation, the crucial diagnoses to make are placenta previa, placental abruption, uterine rupture, and arteriovenous malformation. Ultrasound should be performed before a pelvic examination in these patients.

For nonpregnant patients, the pelvic examination may reveal a cause of bleeding but, for most women in the emergency department, no cause will be identified. These patients will be diagnosed

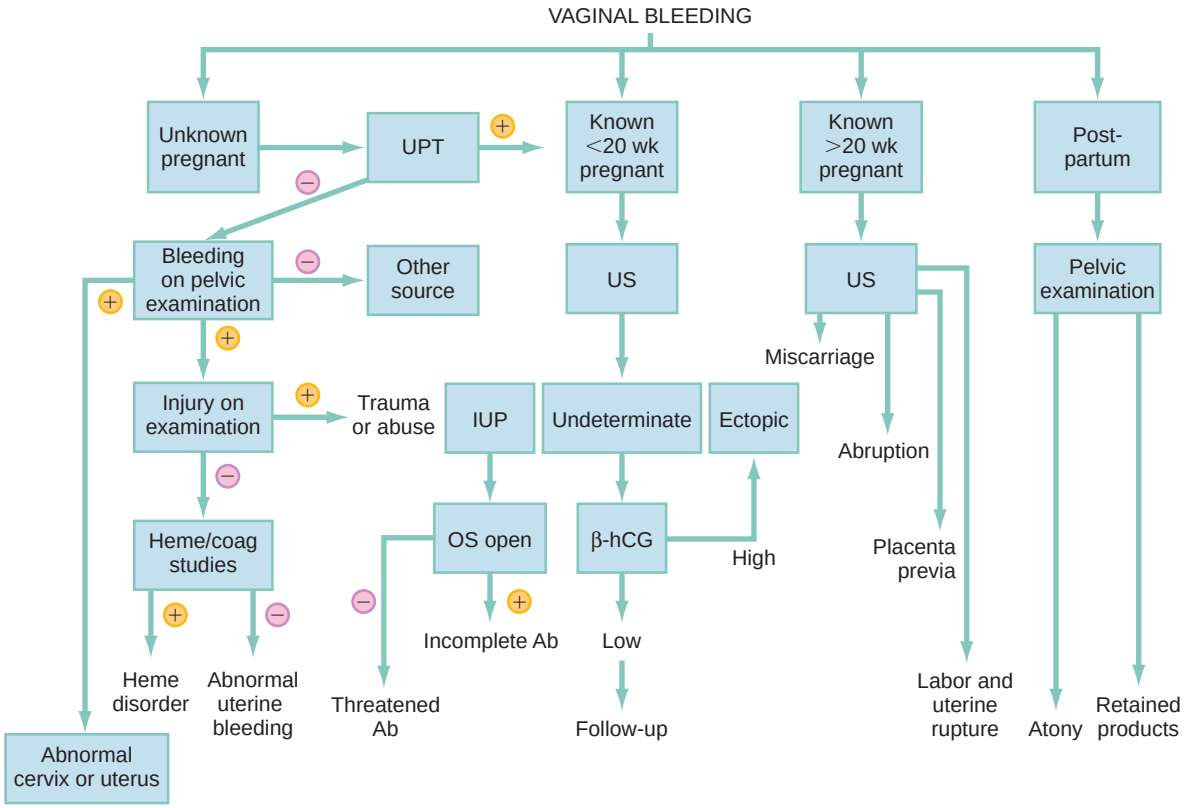

Fig. 31.1. Diagnostic algorithm for patient with vaginal bleeding. *Ab,* Abortion; *β-hCG,* β-human chorionic gonadotropin; *coag,* coagulation; *DUB,* dysfunctional uterine bleeding; *IUP,* intrauterine pregnancy; *OS,* cervical os; *UPT,* urine pregnancy test; *US,* ultrasonography.

with abnormal uterine bleeding and should be referred for further gynecologic testing.

EMPIRICAL MANAGEMENT

Patients with hemodynamic instability unresponsive to crystalloid fluid resuscitation require blood transfusion (Fig. 31.2). For women of childbearing age, use Rh-negative blood if the Rh status of the patient is unknown. In addition to hemodynamic stabilization for severe bleeding in nonpregnant women, high-dose intravenous conjugated estrogen (Premarin) is considered first-line treatment and may be administered every 4 to 6 hours for up to 24 hours (suggested dose, 25 mg). If bleeding continues, the vagina may be packed with long continuous gauze. Alternatively, a Foley catheter may be inserted transvaginally into the uterus to tamponade bleeding. Vaginal packing and catheters may be left in place for up to 24 hours.

Treatment of stable nonpregnant patients includes nonhormonal treatments such as nonsteroidal antiinflammatory drugs (NSAIDs). Despite their varying degree of platelet activity inhibition, NSAIDs decrease blood loss by reducing endometrial prostaglandin levels and promoting vasoconstriction in the uterus. Different types of NSAIDs appear to be equally effective at reducing bleeding.[17] Hormonal treatments such as monophasic oral contraceptive pills are also frequently used to temporize a heavy bleeding episode and are typically prescribed as a taper. Hormonal treatment is likely to be most effective for women with suspected anovulatory bleeding. Any of the monophasic pills containing less than 35 μg of ethinyl estradiol can be used; a common low-dose regimen is one pill twice daily for 5 days and then one pill daily for the remainder of the pack.[18] Contraindications to the use of estrogen include a history of a thromboembolic event or stroke, pregnancy, active liver disease, severe uncontrolled hypertension, and women older than 35 years who smoke. High-dose, progestin-only treatment is a frequently used alternative therapy for women with contraindications to estrogen. A common regimen is medroxyprogesterone acetate (Provera) 10 mg, once daily, for 10 days[19] (Table 31.1).

All unstable pregnant and postpartum patients should be managed in close consultation with an obstetrician. Patients with viable pregnancies may require emergency cesarean section. Unstable patients with confirmed or suspected ectopic pregnancies, heterotropic pregnancies, or previable IUPs may also require operative management. Stable patients with threatened, missed, incomplete, or inevitable miscarriages may be managed expectantly or may require dilation and evacuation or curettage. Rh status should be checked and RhoGAM treatment should be initiated in the ED for patients who are Rh-negative. The management of pregnant patients is discussed in detail in Chapters 178 to 182.

DISPOSITION

Most nonpregnant patients presenting to the ED with vaginal bleeding can be discharged home with timely gynecology follow-up. Adolescents with abnormal bleeding most likely have anovulatory cycles but should be evaluated for a possible underlying bleeding disorder. Perimenopausal and menopausal women with abnormal bleeding should have expedited follow-up because they are considered to have a malignancy until proven otherwise. If sexual abuse is suspected in prepubertal girls, a safe environment for the patient must be ensured before considering discharge. Any patient with significant or symptomatic bleeding should be admitted to the hospital.

Pregnant patients with ruptured ectopic or heterotopic pregnancies, placenta previa, placental abruption, or uterine rupture should be admitted to the hospital. Stable patients with threatened, inevitable, incomplete, or missed miscarriage can often be managed expectantly as outpatients, with close gynecology follow-up.

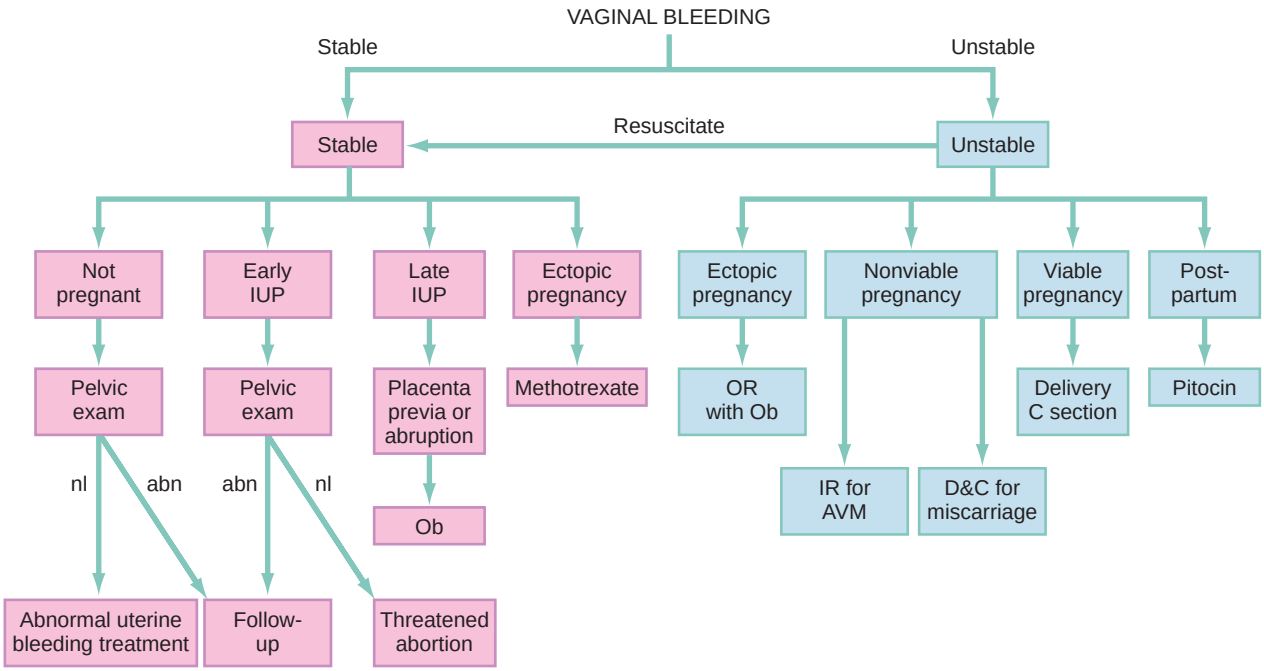

Fig. 31.2. Empirical management of the patient with vaginal bleeding. *abn,* Abnormal; *AVM,* arteriovenous malformation; *D&C,* dilation and curettage; *DUB,* dysfunctional uterine bleeding; *exam,* examination; *IR,* interventional radiology; *nl,* normal; *Ob,* obstetrician; *OR,* operating room.

TABLE 31.1

Pharmacologic Treatment Regimens for Acute Abnormal Uterine Bleeding

DRUG	SUGGESTED DOSE[a]	CONTRAINDICATIONS AND CAUTIONS[b]
Hormonal treatments (conjugated equine estrogen)	25 mg IV every 4–6 h until bleeding stops, up to 24 h	• Contraindicated in patients with active or past thromboembolic disease, breast cancer, or liver disease • Use with caution in patients with cardiovascular or thromboembolic risk factors
Combination oral contraceptive pills	Monophasic oral contraceptive pills containing <35 μg ethinyl estradiol recommended): One pill tid PO for 7 days *or* One pill bid PO for 5 days, then one pill qd until pack is finished	• Contraindicated in women >35 y who smoke • Contraindicated in women who have a history of deep vein thrombosis or pulmonary embolism, breast cancer, liver disease, known thromboembolic disorders, pregnancy, ischemic heart disease, cerebrovascular disease, or uncontrolled hypertension
Progestin-only oral contraceptive pills (medroxyprogesterone acetate)	20 mg tid PO for 7 days *or* 10 mg qd PO for 10 days	• Contraindicated in patients with active or past deep vein thrombosis or pulmonary embolism, liver disease, or breast cancer
NSAIDs		• NSAIDs contraindicated in patients with advanced renal disease • Use NSAIDs with caution in patients with history of GI ulcers or GI bleed
Ibuprofen	200–400 mg tid or qid PO for 5 days	
Mefenamic acid	500 mg tid PO for 4 or 5 days or until bleeding stops	
Naproxen	500 mg PO initially, then 250 mg tid or qid for 5 days	

[a]Other dosages and schedules also may be effective.
[b]Partial list of contraindications. The US Food and Drug Administration's labeling contains exhaustive lists of contraindications for each of these treatments. In making treatment decisions for women with abnormal uterine bleeding, emergency clinicians should consider the risks of treatment against the risk of continued bleeding on a case by case basis.
GI, gastrointestinal; *IV,* intravenous; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PO,* by mouth.
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KEY CONCEPTS

- Pregnancy status is the single most important determination to make when evaluating a woman with vaginal bleeding.
- There are many causes of abnormal bleeding in nonpregnant patients. Most nonpregnant patients presenting to the ED with vaginal bleeding can be safely discharged home, with timely gynecology follow-up.
- The use of the term *dysfunctional uterine bleeding* is no longer recommended; instead, use the term *abnormal uterine bleeding.*
- Hormonal and nonhormonal treatments can be initiated in the ED to temporize an acute bleeding episode in a nonpregnant patient until she can follow up with her gynecologist.
- Vaginal bleeding is common in early pregnancy. Most patients will be diagnosed with threatened miscarriage, but ectopic pregnancy should always be considered at any level of serum β-hCG.
- Vaginal bleeding after the 20th week of pregnancy is less common and is often associated with significant morbidity and mortality for the mother and fetus. These patients should be managed in close consultation with an obstetrician.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 31: QUESTIONS & ANSWERS

31.1. What is the leading obstetric cause of maternal mortality?

A. Domestic violence
B. Ectopic pregnancy
C. Placental abruption
D. Postpartum hemorrhage
E. Septic abortion

Answer: D. Postpartum hemorrhage is the leading cause of maternal mortality. Within the first 24 hours after delivery, this is usually caused by uterine atony. After 24 hours, the cause is frequently retained products of conception.

31.2. A 30-year-old woman in the eighth week of her first gestation reports a 1-day history of crampy lower abdominal pain and scant vaginal bleeding. Vaginal examination reveals a minimal amount of dark blood oozing through a closed cervical os. Endovaginal ultrasonography confirms an intrauterine pregnancy of 8 weeks' gestation. The fetus has good cardiac activity. What is the most appropriate diagnosis for this patient?

A. Incomplete abortion
B. Inevitable abortion
C. Missed abortion
D. Normal pregnancy
E. Threatened abortion

Answer: E. Bleeding during pregnancy is common but should not be considered normal. The symptoms and findings in this patient lead to a diagnosis of threatened abortion, which is described as bleeding of intrauterine origin before the completion of 20 weeks' gestation, without dilation of the cervix, and without expulsion of products of conception. Patients with threatened abortion may or may not have uterine contractions. An incomplete abortion is the expulsion of some, but not all of the products of conception, which would be a complete abortion, before the completion of 20 weeks' gestation. An inevitable abortion is defined as bleeding of intrauterine origin before the completion of 20 weeks' gestation, with dilation of the cervical os but without expulsion of THE products of conception. Missed abortion refers to retained products of conception after demise of the embryo or fetus.

31.3. A 30-year-old woman who is 26 weeks pregnant describes a 1-hour history of painless vaginal bleeding after tripping and falling from a standing height. Her vital signs are normal, and physical examination of the abdomen reveals a nontender uterus with a fundal height 1 cm above the umbilicus. Of the following, which would be the most appropriate next step in evaluating this patient?

A. Abdominal MRI
B. Bimanual examination
C. Sterile speculum examination
D. Ultrasound

Answer: D. Painless vaginal bleeding after the 20th week of pregnancy is suggestive of placenta previa. Pelvic examination (speculum or bimanual) should be deferred until ultrasound has excluded placenta previa as the cause of bleeding.

CHAPTER 32

Back Pain

Brian Niall Corwell

PERSPECTIVE

Back pain is the most common musculoskeletal chief complaint in the emergency department (ED) and the second most common symptom-related complaint for the primary care physician (PCP). It is an enormous source of health care expenditures and lost productivity and causes more disability globally than any other condition.[1-3] In the great majority of patients, back pain has a benign course; however, the goal of ED assessment is to separate the common benign causes of back pain from those that could result in significant morbidity or mortality if not promptly recognized. The key to accurate clinical decision making is performance of a thorough history and physical examination, with focus on the identification of potential markers of serious disease that will be referred to as key clinical findings (and sometimes as red flags; Box 32.1).

Epidemiology

Over 85% of patients with acute low back pain, defined as lasting less than 6 weeks, are ultimately diagnosed with mechanical or nonspecific back pain or pain in the absence of a known specific pathology (eg, neoplastic, infectious, cauda equina syndrome, fracture, or inflammatory cause).[4] Only about 1 in 50 ED patients with lower back pain will require hospitalization or observation.[5]

A thorough history and physical examination usually identify the roughly 2% of patients with an emergent diagnosis, including aortic dissection, abdominal aortic aneurysm (AAA), cauda equina syndrome, epidural abscess, osteomyelitis, or malignancy. Spinal carcinoma is uncommon in the general population with back pain (0.7%) but, in patients with systemic cancer, approximately 5% to 30% will have spinal metastasis, and as many as 70% of patients with a known primary tumor have spinal metastatic disease at autopsy.[6]

The World Health Organization (WHO) defines nonspecific back pain as back pain having no known underlying identifiable pathology and no apparent relative tissue damage. Nonspecific back pain may arise in almost any patient, but has increased likelihood in patients who smoke or are obese, sedentary, or of advanced age.[5,7,8]

Until recently, nonspecific low back pain was believed to be a self-limited condition, much like the common cold. However, research over the past decade has indicated that low back pain may become a chronic condition for many.[9,10] Although patients with acute low back pain generally have improvement in pain and disability in the first 6 weeks, improvement appears to slow thereafter, and recurrences are common, often worsening over time.[10] Most patients with chronic back pain (defined as lasting >3 months) will experience persistence or a recurrence within 12 months.[9,11] In an ED population, there is substantial morbidity and ongoing analgesic use at 1 week and 3 months after the initial visit, greatest in those with chronic back pain and greater baseline disability.[12,13]

Pathophysiology

Back pain may be caused by a vascular, visceral, infectious, mechanical, or rheumatologic process. Pain may originate from the spinal cord, nerve root, vertebral column, surrounding musculature, or an extraspinal origin (including thoracic, abdominal, or pelvic organs). The pathophysiology of nonradicular musculoskeletal low back pain is frequently indeterminate; possible causes may include muscle or ligament injuries, degenerative spinal disease, and disk herniation. Disk herniation occurs when the tough outer disc layer (annulus fibrosis) thins and tears, and the inner gelatinous material (nucleus pulposus) prolapses, inflames, and compresses a nerve root. This herniation may be anywhere on the continuum from asymptomatic to severely painful. Clinical symptoms are typically self-limited, with a high rate of spontaneous improvement and low likelihood of progression to a neurologic emergency. The natural history of disk herniation is that pain from pressure and nerve irritation improves as local inflammation subsides. The size of the disk protrusion may naturally decrease over time.

Although we commonly consider disk herniation and radiculopathy together, herniation is usually asymptomatic and likely only causes symptoms of sciatica occasionally. Radiculopathy is a clinical diagnosis of nerve root irritation and compression leading to symptoms in the distribution of the affected lumbar or sacral nerve root, such as numbness, weakness, or paresthesia. The most common causes are disk herniation and foraminal stenosis caused by spondylotic degeneration.

This natural resolution of symptoms in disk disease is in contrast to spinal stenosis, which tends to persist or worsen over time. Thickening of the ligamentum flavum and other degenerative changes with age contribute to spinal stenosis. The spinal cord ends at L1 in the adult, where it gives rise to the cauda equina. Compressive lesions above the cauda equina cause upper motor neurologic signs. Compression of the cauda equina leads to lower motor neurologic findings.

Referred pain is perceived in a location other than that of the noxious stimulation. Irritation in a visceral organ frequently produces pain that may be perceived in somatic structures some distance away, such as a symptomatic AAA being felt as low back pain or ureteral colic being perceived as flank pain.

There are two proposed mechanisms for this phenomenon. The dermatomal model states that pain is usually referred to a structure that developed within the same embryonic segment or dermatome as the structure in which the pain originates. The convergence model states that pain may also be referred from the convergence of visceral and somatic pain fibers in dorsal horn neurons that project to the somatosensory cortex. It has been proposed that convergent connections from deep tissues to dorsal horn neurons may not be present initially, but are opened by nociceptive input from skeletal muscle and referral to myotomes outside the lesion due to a spread of central sensitization to adjacent spinal segments. It is for this reason that pain from intra-abdominal pathology can be referred as flank pain, back pain, or groin pain.

BOX 32.1

Key Clinical Findings in the History and Physical Examination

HISTORICAL INFORMATION

Recent significant trauma
History of cancer
Anticoagulant use
Intravenous drug use
History of prolonged glucocorticoid use
History of osteoporosis
History of abdominal aortic aneurysm
Patient > 50 yr
Unrelenting night or rest pain
Unexplained weight loss
Recent bacterial infection
Immunocompromised status
Failure to improve after 6 wk of conservative therapy

PHYSICAL EXAMINATION

Abnormal vital signs—hypotension, hypertension, tachycardia, fever
Unequal blood pressure readings in the upper extremities
Murmur of aortic insufficiency
Pulse deficit or circulatory compromise of the lower extremities
Pulsatile abdominal mass
Urinary retention
Urinary or stool incontinence
Loss of rectal sphincter tone
Severe or progressive neurologic deficit
Focal lower extremity weakness
New ataxia or difficulty walking

BOX 32.2

Differential Considerations in Acute Low Back Pain

EXTRASPINAL CAUSES

Chest—aortic dissection, bacterial endocarditis, pulmonary embolism, pneumonia, pleural effusion
Abdominal—ruptured or expanding aortic aneurysm, esophageal disease, penetrating peptic ulcer disease, pancreatitis, pancreatic cancer, biliary colic, cholecystitis, cholangitis
Genitourinary—renal colic, prostatitis, perinephric abscess, pyelonephritis, ovarian torsion or tumor, pelvic inflammatory disease, endometriosis
Musculoskeletal—acute muscle strain, acute ligamentous injury
Other—herpes zoster, retroperitoneal hemorrhage, psoas abscess, nonspecific low back pain

SPINAL CAUSES

Cauda equina syndrome, spinal epidural abscess or hematoma, spinal fracture, transverse myelitis, traumatic fracture, pathologic fracture, vertebral osteomyelitis, infectious diskitis, ankylosing spondylitis, spondylolysis or spondylolisthesis, disc herniation, degenerative disease (discs, facet joints), isolated sciatica, spinal stenosis

II. DIAGNOSTIC APPROACH

Differential Considerations

The emergency clinician should evaluate for potentially life-threatening and disabling causes of back pain. These can be broken down into two main categories: (1) spinal causes, such as epidural abscess or compressive mass, spinal column injury with cord or root compression, and cauda equina syndrome; and (2) extraspinal causes, such as thoracic aortic dissection and ruptured AAA (Box 32.2).

Pivotal Findings

A careful, thorough history and physical examination are invaluable. Technologically sophisticated radiologic and laboratory studies are not a substitute for a detailed history and physical examination. This approach will help categorize patients into stable and unstable categories (Fig. 32.1). Certain findings will guide the additional evaluation for patients with neurologic deficits and more serious spinal or visceral sources (Table 32.1). The most important elements of the history, physical examination, and diagnostic testing are to answer two questions:

- Is there evidence of extraspinal or systemic disease?
- Is there evidence of neurologic compromise?

Symptoms

As with any patient who complains of pain, symptoms should be characterized by the basic historical elements of the episode, such as the intensity, onset, character, severity, location, presence of radiation, exacerbating and alleviating factors, and presence of key clinical finding signs and symptoms (see Box 32.1). Most episodes of lower back pain will resolve or significantly improve within 4 to 6 weeks[11]; therefore, lack of significant improvement in 6 to 8 weeks is also a warning sign.

Presence of an individual key clinical finding does not necessarily correspond to a specific pathology; rather, it prompts the emergency clinician to a more serious underlying condition that may require further investigation. Many of these key clinical findings have poor or untested diagnostic accuracy and have meaning only in the context of the complete history and findings in a particular patient. Blindly allowing the presence of these individual findings to guide diagnostic treatment will lead to potentially unnecessary, misleading, and costly investigations in most patients. In one study, 80% of patients with back pain had at least one of these key clinical findings, despite a prevalence of serious disease of less than 1%. On the other hand, if there are no key clinical findings, one can be 99% confident that serious spinal disease had not been missed.[14] Presence of multiple key clinical findings often is an indication for further investigation, which may be initiated in the ED or on an ambulatory basis, depending on the patient. In an ED population, four of the important variables associated with serious outcomes include (1) pain worse at night, (2) decreased lower extremity sensation, (3) use of anticoagulants, and (4) pain persisting despite appropriate treatment.[15]

Different causes of acute low back pain have different distinguishing characteristics (see Table 32.1). Typical nonspecific back pain is unilateral. Pain may radiate to the buttocks or posterior thigh but not past the knee, implying muscle or ligamentous strain or disk disease without associated nerve involvement. Pain is increased with movement and is relieved by rest, and there are no complaints of numbness, weakness, or bowel or bladder dysfunction. Inflammatory back pain (spondyloarthritis) is insidious in onset, affects younger patients (<40 years), improves with exercise but not with rest, and causes pain at night, with improvement on arising. Peripheral nerve pain may be described as "pins and needles" or "burning" as opposed to nerve root pain, which is transient and very sharp, relieved with recumbent positioning and exacerbated by a Valsalva maneuver. Pain from disk herniation is relieved by lying supine and is worsened by a Valsalva maneuver, coughing, sneezing, and positions that produce increased pressure on annular fibers, such as prolonged sitting, standing, and bending

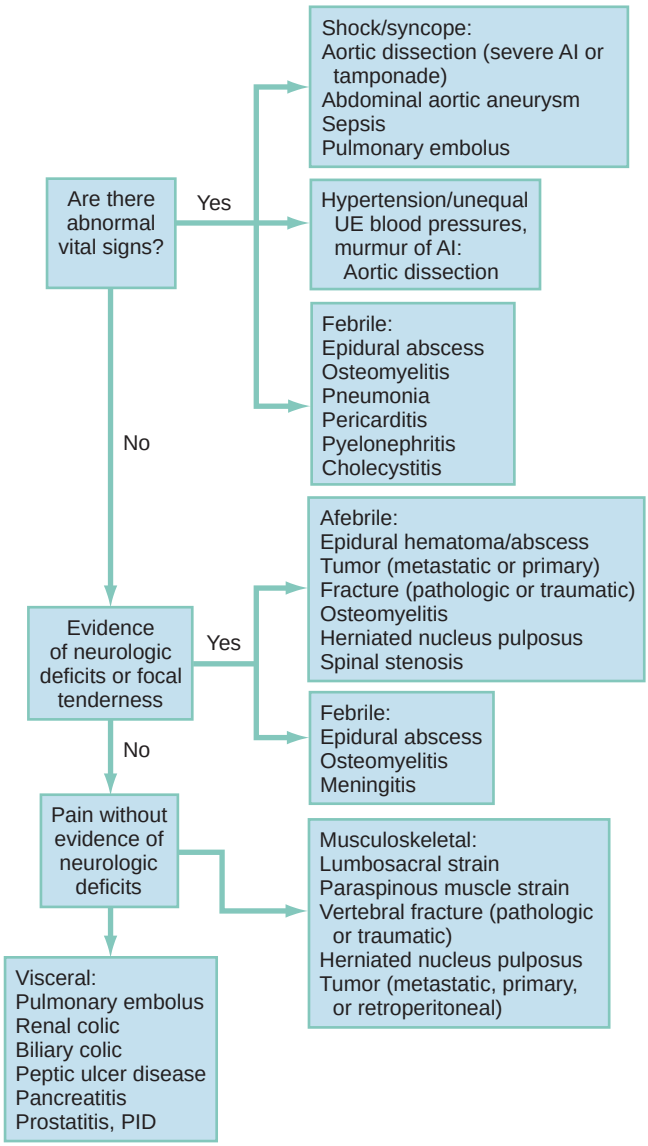

Fig. 32.1. Rapid assessment of acute low back pain. *AI,* Aortic insufficiency; *PID,* pelvic inflammatory disease; *UE,* upper extremity.

postures. Discogenic pain is typically worse with flexion, whereas pain from spondylolysis is aggravated by facet loading, which occurs in extension. Radicular pain follows a dermatomal distribution and indicates nerve root compression or irritation. Radicular pain involving the sciatic nerve (sciatica) is sharp or burning. It radiates laterally or posteriorly down the leg distal to the knee, usually to the foot or ankle, and may also be associated with numbness or weakness. Multi–nerve root pathology or the presence of bilateral symptoms is a potential indicator of a spinal mass lesion or large central disk herniation, which compresses multiple descending nerve roots within the spinal canal.

Epidural compression syndromes—spinal cord compression, cauda equina syndrome, and conus medullaris syndrome—can have a bimodal onset, acute (hours) or gradual (weeks or even months). Cauda equina syndrome usually occurs from a large lower lumbar disk herniation or by smaller prolapses in the presence of spinal stenosis. Other causes include infection, neoplasms, epidural hematoma, and trauma. There are three typical presentations: (1) acute onset of symptoms in those without a previous history of back problems; (2) acute bladder dysfunction in those with a history of low back pain and sciatica; or (3) gradual progression of symptoms in those with chronic back pain and sciatica.[16] Epidural compression symptoms are mainly neurologic in origin and include bilateral leg pain, urinary retention with overflow incontinence, fecal incontinence or decreased rectal tone, erectile dysfunction, saddle anesthesia, and progressive and severe distal leg numbness or weakness. It is important to determine the cause of the urinary incontinence by differentiating true overflow incontinence from cases in which pain or physical limitations have prevented timely use of the bathroom.

The age of the patient is an important initial consideration. Tumors and infections appear with higher frequency in patients younger than 18 or older than 50 years. Younger patients are at increased risk of spondylolysis and spondylolisthesis. In the older patient with a first episode of back pain, or back pain distinctly different from prior episodes, consider an AAA as a potential cause. Although AAA as a cause is rare in the overall population of patients with back pain, isolated low back pain is one of the classic presentations of a contained ruptured AAA (see Chapter 76). Vigilance is required to differentiate renal colic patients from AAA in older patients because both groups may present with back pain associated with nausea, diaphoresis, or syncope, and hematuria may be present in either condition. Features significantly associated with vertebral fractures include female gender, history of osteoporosis, older age (>50, 64, or 70 years, depending on the guideline), prolonged steroid use, and substantial trauma.[14,17,18] Disk herniation is unusual in those younger than 18 years and is rare in the fibrotic disks of older adults. In older patients, typically those older than 60 years, spinal stenosis is suggested by lower back pain with radiculopathy that is worsened with walking and prolonged standing (back extension). This is because erect posture narrows the cross-sectional area of the central canal and neural foramina. It is relieved by forward flexion (shopping cart sign), which increases spinal canal diameter, temporarily relieving the stenosis. Spinal stenosis causes diffuse intermittent burning, cramping pain in the back, motor weakness, reflex changes, and radiating pain in the buttocks, thigh, and legs, with associated paresthesias. This symptom constellation is termed *neurogenic claudication* (also called pseudoclaudication) and is caused by neurologic compression, unlike vascular claudication, which is caused by arterial insufficiency, may have abnormal pulses, and is relieved by rest.

Immunocompromised patients, diabetics, intravenous drug users (IVDUs), those with recent spinal instrumentation or indwelling devices (eg, epidural catheters, spinal stimulators, vascular access) and those with a recent bacterial infection (eg, pneumonia, urinary tract infection) are at increased risk of a spinal bacterial infection. Recent gastrointestinal or genitourinary procedures may also cause a transient bacteremia, leading to an infectious cause of the patient's back pain. A patient with current or recent IVDU and back pain should be assumed to have an abscess or vertebral osteomyelitis until proven otherwise.

Patients with cancer also represent another high-risk group. Spinal epidural metastasis can be the initial presentation of malignancy or may occur in patients with a known primary malignancy. Spinal metastases usually arise in the posterior aspect of the vertebral body, with subsequent invasion of the epidural space. The spine is the third most common site for metastatic disease, most often involving the thoracic (70%) and lumbar spines (20%). The most common metastatic diseases affecting the spine are those of the lung, breast, prostate, kidney, and thyroid, lymphoma, and multiple myeloma. Patients present with back pain that can be intermittent and often responsive to nonsteroidal antiinflammatory drugs (NSAIDs) initially, but worsens over time. History may also reveal pain at night, rest pain, pain in multiple areas of the spine, or unexplained weight loss.[17,19] Sudden severe pain raises concern for a pathologic fracture.

Back pain associated with pain in other locations should prompt consideration of an extraspinal cause. Association with

TABLE 32.1

Classic Findings in Selected Serious Causes of Acute Back Pain

FINDINGS	DIAGNOSES	HISTORY	IMPORTANT PHYSICAL EXAMINATION FINDINGS	ANCILLARY TESTING	COMMENTS
CRITICAL					
Vascular	Aortic dissection	Often sudden-onset, tearing, severe pain; associated nausea, vomiting, acute anxiety common; syncope and chest pain can occur.	Associated diaphoresis, unstable vital signs; hypertension common; unequal upper extremity blood pressure; new-onset aortic insufficiency murmur; central and peripheral neurologic deficits secondary to ischemia	Choice of CT, aortography, transesophageal echo, MRI; depends on patient stability and availability of equipment	More common as cause of thoracic back pain, but low back pain may be only complaint
	Abdominal aortic aneurysm (ruptured, expanding)	Pain may radiate to back, flank, or testicle; syncope may be present.	Pulsatile abdominal mass, abdominal bruits; hypoperfusion	Bedside US; if stable, abdominal CT with contrast; plain films may show calcified, enlarged, aortic contour	Can also mimic renal colic, GI bleeding, diverticulitis, myocardial infarction; 30% of signs are misdiagnosed.
Infectious	Spinal epidural abscess	At-risk population with diabetes, chronic renal failure, IV drug use, alcoholism, cancer, recent spinal surgery, trauma, recent bacterial infection, bacteremia as risk factors	Fever (50%), back pain (75%); focal neurologic deficits are late findings (<50% of patients); all three (classic triad) present in 15%; localized body tenderness along spine; rare cauda equina–like syndrome	CBC (elevated WBC in 60%), ESR, CRP, blood cultures useful but insensitive and nonspecific; MRI modality of choice; CT or myelography can be used; search for source of infection; *Staphylococcus aureus* common cause (70%)	Manifests as mass-occupying lesion compressing spinal cord; may be hematoma, malignancy, disk; often begins as focal pyogenic infection in disk; biopsy may be necessary.
Mechanical	Epidural compression syndrome (eg, cauda equina syndrome, neoplastic cord compression)	Usually history of back pain, cancer; symptoms may develop over hours; sciatica (96%), micturition dysfunction (89%), defecation dysfunction (47%)	Urinary retention, fecal incontinence; saddle anesthesia (81%), bilateral leg pain; lower extremity weakness with hyporeflexia	Evaluate postvoid residual; MRI with or without contrast; if unavailable, then CT	Can result in severe dysfunction; emergent condition caused by compression of lumbosacral nerve roots
	Spinal fracture with cord impingement, or unstable fracture	Acute onset, localized pain; usually trauma history; older adults or those with chronic steroid use with osteoporosis also at risk	Bone tenderness, radicular, or cord compression findings	Plain films initially, then CT or MRI	Symptoms, signs depend on level
	Epidural hematoma	Usually patient with coagulation disorder, hereditary or acquired (eg, anticoagulants); may occur after epidural anesthesia	Radicular findings (neurologic defects); neurologic pattern similar to abscess	MRI, CT, or myelography	Can also occur in AV malformations
EMERGENT					
Infectious	Vertebral osteomyelitis	At-risk group similar to that for epidural abscess; onset may be insidious; back pain, tenderness, and stiffness may precede neurologic findings by significant time period.	Fever, other constitutional symptoms; localized body tenderness of two adjacent vertebrae	CBC, blood cultures, generally low yield and nonspecific; plain films diagnostic in 80%–95%, but MRI more accurate and detailed	Biopsy may be necessary for diagnosis; *S. aureus* most common—start antibiotic

TABLE 32.1

Classic Findings in Selected Serious Causes of Acute Back Pain—cont'd

FINDINGS	DIAGNOSES	HISTORY	IMPORTANT PHYSICAL EXAMINATION FINDINGS	ANCILLARY TESTING	COMMENTS
Immune	Transverse myelitis	Back pain, neurologic deficits; Almost 50% of patients worsen maximally in 24 h	Partial or total loss of sensory, motor, autonomic, and sphincter function below level of the lesion; leg weakness more common, arm involvement is rare; bladder (bowel control) affected in most patients	Goal is to rule out mass lesion compressing the cord; thought to be autoimmune origin; MRI imaging modality of choice; contrast CT, CT myelography may be performed	May be associated with multiple sclerosis, SLE, sarcoidosis; also associated with Lyme disease, Epstein-Barr virus, other viral (eg, herpes, enterovirus) or bacterial (eg, tuberculosis, syphilis) infections
Mechanical	Back pain with neurologic deficits; Intervertebral disk herniation; spinal stenosis; spinal fractures without cord impingement; malignancy; sciatica with potential for nerve root compression	Most patients recall atraumatic mechanisms (eg, lifting, twisting); Common complaints—stiffness, tenderness, decreased range of motion	Positive straight leg raise test; muscular weakness, sensory deficits; absent or diminished deep tendon reflexes	Plain films not indicated; CT or MRI performed for complete assessment when cauda equine syndrome, osteomyelitis or diskitis, mass, cord hematoma, or cord compression suspected	Search for key clinical findings (see Table 32.1) to rule out serious underlying disease.

AV, Arteriovenous; *CBC,* complete blood count; *CT,* computed tomography; *echo,* echocardiogram; *GI,* gastrointestinal; *MRI,* magnetic resonance imaging; *SLE,* systemic lupus erythematous; *US,* ultrasound.

TABLE 32.2

Physical Examination for Lumbar Nerve Root Compromise

DISK SPACE	NERVE ROOT	SENSORY TESTING	REFLEX	STRENGTH AND MOTOR TESTING	SCREENING EXAMINATION
L3-4	L4	Test from the medial lower leg and foot down to the medial surface of the great toe (not including the first web space).	The corresponding reflex is the patellar reflex.	Test with knee extension (quadriceps), ankle inversion and dorsiflexion.	Squat and rise
L4-5	L5	Test from the lateral lower leg, dorsum of the foot, and first web space.	There is no reliable reflex to test L5.	Test with great toe dorsiflexion (extensor hallucis longus).	Heel walking
L5-S1	S1	Test from the lateral foot and ankle.	The corresponding reflex is the Achilles reflex.	Test with foot plantar flexion.	Toe walking

chest or abdominal symptoms may indicate a visceral cause, such as vascular or solid organ pathology. Unilateral flank symptoms may have a renal or retroperitoneal origin, and thoracic level pain can emanate from the chest or pleura. Because most benign back pain is tolerable, worsened with activity, and improved with rest or lying still, symptoms such as severe night pain (especially deep bony pain) and severe unrelenting pain that is not relieved by rest, recumbency, or appropriate analgesic treatment are concerning for nonmusculoskeletal causes, such as malignancy or infection. Other pertinent history considerations should include past and present work history (a history of repeated loading would suggest a mechanical cause), medications (anticoagulants are associated with epidural and retroperitoneal hematomas, steroids are associated with infection and compression fractures), hematuria (nephrolithiasis, pyelonephritis, ruptured AAA), and colic (nephrolithiasis, cholelithiasis). Previous atherosclerotic or vascular disease may suggest aortic disease, and sudden-onset, severe back pain suggests a vascular cause. Direct trauma may suggest contusion, strain, or fracture. Resulting splenic, hepatic or retroperitoneal bleeding may lead to referred pain to the back.

Signs

The physical examination includes a review of the patient's general appearance and vital signs, examination of the thorax, abdomen, and extremities, detailed examination of the back, and complete neurologic examination of the lower extremities (see Table 32.1). Lumbar spine pathology is frequently manifested in the lower extremities in the form of altered reflexes, sensation, and muscle strength (Table 32.2).

Abnormal or unstable vital signs may indicate an extraspinal cause of the back pain (eg, hypotension and tachycardia with ruptured AAA, hypertension with aortic dissection). Fever, present in approximately 50% of patients with osteomyelitis or spinal epidural abscess, indicates potential infection. The absence of fever, however, does not exclude a spinal infection.

Observe the patient's gait and movement in the examining room because a normal gait provides important reassurance regarding the patient's central and peripheral neurologic function.

- Does the patient move cautiously, protecting himself or herself, or move freely, appearing to be in little pain?
- Is the gait shortened, asymmetric, or antalgic?

Musculoskeletal back pain usually is mild to moderate in intensity, rarely accompanied by visceral symptoms (eg, diaphoresis, nausea, vomiting), and prompts the patient to be still. Patients presenting with extreme pain, restlessness, writhing, or visceral symptoms or signs more likely have an emergent cause. Perform cardiac and pulmonary auscultation, carry out an abdominal examination (for tenderness, bladder distention, aneurysm, or masses), and palpate for symmetry of peripheral pulses. Abdominal ultrasound can evaluate for AAA or renal colic. Examine the hips for musculoskeletal tenderness, deformity, or inflammatory focus other than the back.

The patient's back should be fully exposed and inspected for signs of infection, trauma, or the rash of herpes zoster. The midline spinous processes should be inspected for redness, swelling, or warmth and then palpated for tenderness, which suggests fracture or infection (sensitivity, 86%; specificity, 60%). Pain during lumbar flexion suggests discogenic pain, whereas pain on lumbar extension suggests facet disease. Paraspinal muscle spasm should be noted but is not diagnostic of any particular condition.

The distal neurologic examination targets the three most common locations for disk herniation—L4, L5, and S1. A vast majority of herniated disks affect the L4-5 or L5-S1 interspaces, causing impingement on the L5 (most common) and S1 nerve roots. At each level, the emergency clinician should test corresponding muscle strength, sensation, and reflexes. When possible, motor testing of the legs is best done with the patient standing. It can be difficult to differentiate true motor weakness from apparent weakness caused by pain during motor testing. Because many muscles have innervations from multiple roots, strength may be preserved despite significant involvement of a single nerve root. Sensory fields can also have considerable overlap, so examine areas that are exclusively served by an individual nerve. True sensory loss is best tested with pinprick rather than light touch. Isolated sensory loss or the absence of a reflex is not considered to be a progressive neurologic deficit and must be correlated with the patient's clinical picture. See Table 32.2 for nerve root levels and corresponding examination findings. Of note, ankle reflexes decrease with age, lost in nearly 50% of those older than 80 years. This loss is usually symmetric, so unilateral absence may signify pathology.

Mid and upper lumbar nerve root impingement likely has a higher prevalence than previously reported and is found with increasing frequency in older adults with spinal stenosis. Pathology at the higher lumbar spine (L1, L2, L3) will cause acute back pain, with radiation to the groin or anterior thigh, weakness with hip flexion (iliopsoas), and anterior thigh sensory changes in the corresponding dermatome. A partial knee bend while bearing weight on one leg and then the other indicates normal hip, buttock, and thigh muscle strength. There are no individual reflexes for the L1-3 lumbar levels. Those with pathology at the lower sacral levels (S2-5) will have sacral or buttock pain that radiates down the posterior leg or into the perineum and can have difficulties with penile erection (S2-4), abnormal perianal sensation (S3-5), anal wink (S2-4), rectal tone (S2-5), and bladder function (S2-4). Assessment of perianal sensation is extremely important for the diagnosis and prognosis of epidural compression syndrome. A digital rectal examination (DRE) is not a routine part of the physical examination but should be performed in those with suspicion of progressive neurologic findings (eg, epidural compression syndrome). Check the anal wink and bulbocavernosus reflex and perform a Babinksi test in these high-risk patients. A Babinksi sign (positive plantar reflex) is extension of the great toe, with flexion and splaying of the other toes. The presence of clonus, hyperreflexia, or Babinski sign indicates an upper motor neuron lesion.

Testing for urinary retention using a postvoid residual (PVR) volume assessment by ultrasound or catheterization is highly sensitive and specific for cauda equina syndrome. Normal PVR volumes are less than 30 mL, so large PVR volumes (>100 mL) indicate a denervated bladder and suggest significant neurologic compromise. If bladder catheterization is performed, one can test for trigone sensitivity by gently pulling on the catheter, which should produce the urge to micturate. This can help distinguish those with a true neurologic deficit from those with pain-associated retention.[16]

Straight leg raise (SLR) tests for disk herniation causing nerve root compression (sensitivity, 72%–97%; specificity, 11%–66%). SLR has a positive predictive value (PPV) of 67% to 89% and a negative predictive value (NPV) of 33% to 57% in patients with a high probability of having a disk herniation versus a PPV of 4% in patients with a low probability based on the absence of neurologic symptoms or sciatica. To perform this test, the patient is positioned supine, with the legs fully extended. The emergency clinician places one hand under the ankle and the other hand on the knee (to maintain leg extension). With the patient relaxed, the emergency clinician slowly lifts the patient's leg by flexing the leg at the hip until pain is elicited or end range is reached. Test each leg separately. A positive test causes or reproduces radicular pain below the knee of the affected leg when the leg is elevated between 30 and 70 degrees. Care should be taken that the patient is not actively helping in lifting the leg and that the knee remains straight throughout the examination.

A further positive finding occurs if radicular symptoms are elicited when the leg is then lowered until pain is eased and the ipsilateral ankle is dorsiflexed (Braggard's sign). Pain at less than 30 degrees, more than 70 degrees, or with reproduction of pain only in the back, hamstring, or buttock region, does not constitute a positive test result. Pain referred to the affected leg when the opposite asymptomatic leg is tested, called a positive crossed SLR, is highly indicative of nerve root irritation from a herniated disk (specificity, 85%–100%; sensitivity, 29%).[20] In cases where the patient is reluctant or unwilling to lie supine for SLR testing, the seated SLR or slump test should be attempted. The patient sits at the edge of the examination table and slumps forward while flexing the neck and trunk. This is followed by knee extension and ankle dorsiflexion. A positive test reproduces radicular pain.

Waddell's examination findings can aid in distinguishing between true pathologic back pain and nonorganic back pain; it can be remembered by the mnemonic DORST—***d***istraction, ***o***verreaction, ***r***egional disturbances, ***s***imulation tests, ***t***enderness). Waddell's signs, especially if three or more are present, correlate with malingering and functional complaints (physical findings without anatomic cause). Superficial, nonanatomic, or variable tenderness during the physical examination suggests a nonorganic cause. Provocative maneuvers such as axial loading of the head or passive rotation of the shoulders and pelvis in the same plane should not elicit low back pain. There may be a discrepancy between the symptoms reported during the supine and seated SLR tests. The seated version of the test, sometimes termed the *distracted SLR,* can be performed while distracting the patient or appearing to focus on the knee. Furthermore, radicular pain elicited at a leg elevation of less than 30 degrees is suspicious because the nerve root and surrounding dura do not move in the neural foramen until an elevation of more than 30 degrees is reached. Sensory and motor findings suggestive of a nonorganic cause include stocking, glove, or nondermatomal sensory loss or weakness that can be characterized as "give-way," jerky, or cogwheel

weakness. Finally, gross overreaction is suggested by exaggerated, inconsistent, painful responses to a stimulus. These signs can be used in the evaluation of select patients and are merely a component of a comprehensive physical examination. They should never be used independently because they lack the sensitivity and specificity to rule out true organic pathology.

ANCILLARY TESTING

Ancillary testing is not indicated in the absence of concerning findings, and routine (nonemergent) use of computed tomography (CT), magnetic resonance imaging (MRI), or laboratory testing should be discouraged. Blind diagnostic testing may lead to false-positive results and further unnecessary evaluations and interventions.

Laboratory Tests

Laboratory testing, consisting of the determination of the white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level is indicated for clinical suspicion of infection or malignancy, new-onset back pain with a history of malignancy, or multiple risk factors for cancer. In cases of spinal infection, the sensitivity of an elevated WBC count is poor (35%–61%), but the ESR (76%–95%) and CRP (82%–98%) are more sensitive and may help guide further evaluation or consideration of other entities. Incorporation of ESR and CRP values into an ED decision guideline may improve diagnostic delays and help distinguish patients in whom MRI may be performed on a nonemergent basis.[21] Infection is very unlikely in patients with an ESR less than 20 mm/h. An elevated ESR (>20 mm/h) is nonspecific for infection, however, and also may indicate occult malignancy (sensitivity, 78%; specificity, 67%). Urinalysis (UA) may be useful in suspected cases of renal disease with referred back pain (eg, nephrolithiasis, pyelonephritis, urinary tract infection). Blood cultures may be sent when there is a significant concern for an infectious cause, such as an epidural abscess, but this will not affect immediate decision making.

Imaging

Imaging, like laboratory testing, is not indicated in the absence of concerns for malignancy, fracture, infection, or epidural compression syndrome. Although the added diagnostic value of modern neuroimaging is significant, unnecessary imaging only serves to increase the cost of the visit and length of stay and subject the patient to unnecessary radiation. Multiple evidence-based clinical practice guidelines have recommended avoiding routine spinal imaging for nontraumatic acute lower back pain in the absence of severe or progressive neurologic deficits or signs and symptoms that suggest a serious underlying condition. Although patient satisfaction is reportedly higher when imaging is performed, this is likely because the negative imaging provided a reassuring explanation for the patient, one that could, instead, have been provided by a thoughtful reassuring discussion by the emergency clinician. Early imaging is not useful and does not affect outcomes for pain, function, quality of life, or overall patient-related improvement. Across all age ranges, including older adults, imaging does not change the management of uncomplicated mechanical low back pain compared with usual care being provided without routine imaging.[22,23] Despite this, a substantial portion of ED patients with lower back pain undergo nonindicated imaging.[23]

Plain films are rarely of use in the evaluation of nontraumatic back pain unless pathologic fracture is suspected. Most patients who require imaging will undergo CT or MRI. Plain films are indicated for new onset of lower back pain in a patient with a history of cancer, strong clinical suspicion for cancer, risk factors for pathologic vertebral fracture, and trauma. Anteroposterior (AP) and lateral films provide reasonable detail in showing fractures, particularly in the lumbar spine. Additional views are only indicated if spondylolysis or spondylolisthesis is suspected. If evidence of neurologic emergency exists, bypass plain films and proceed directly to CT or MRI. For example, only a small minority of patients with malignant spinal cord compression will have the level of compression correctly identified on plain radiographs.

In general, CT provides superior imaging of bone and only moderate detail of soft tissue, whereas MRI gives excellent detail of soft tissue and only moderate detail of bone. CT is increasingly used as a primary screening modality for moderate to severe spine trauma because it is superior to plain film for the detection of vertebral fractures and other bony pathology, especially fractures involving posterior spine structures, bone fragments within the spinal canal, or spinal malalignment. CT provides reasonable contrast resolution and can identify root compressive lesions, such as disk herniations, in the vast majority of cases. CT with myelography (or with intravenous [IV] gadolinium) may be used if there is concern for epidural abscess, epidural compression, or vertebral osteomyelitis in patients who are otherwise unable to have a MRI. CT cannot identify intrathecal pathology and is less sensitive than MRI in the detection of early inflammatory or infectious processes, neoplasm, or paraspinal soft tissue lesions.

With the exception of the evaluation of acute trauma, MRI will identify almost all pathologic states that could benefit from surgical management. MRI is the modality of choice for evaluation of spinal infectious lesions (sensitivity and specificity > 90%), malignancy (sensitivity, 90%; specificity, 95%), disk herniation, and epidural compression syndrome (sensitivity and specificity > 90%).[18] MRI in the ED is indicated for those patients with lower back pain in whom spinal infection, cauda equina syndrome, and/or severe or progressive neurologic deficits are suspected. Without these clinical indications, MRI does not improve clinical outcomes (eg, pain, daily function, health status) and may actually worsen them, resulting in increased rates of subsequent interventions (eg, lumbosacral injections, back surgery) and increased health care expenditures.[14,24-27]

MRI is too sensitive and not specific enough to screen for other presentations of back pain in the ED and has no role in the evaluation of chronic lower back pain without strong clinical consideration of emergent pathologic causes. In patients with chronic, nonradicular back pain, MRI findings are not related to disability or pain intensity.[28] Disk disease is a component of normal aging and is a very nonspecific finding. In fact, one in four asymptomatic persons younger than 60 years and one in three older than 60 years will have MRI findings of a herniated disk. Over 50% of asymptomatic patients are identified as having a bulging disk on MRI. Furthermore MRI studies have shown that almost two-thirds of herniated disks regress or resolve over 6 months. Thus, imaging can reveal pathoanatomic abnormalities that have little or no correlation with patient symptoms.[29]

DIAGNOSTIC ALGORITHM

Critical Diagnoses

Following the history and physical examination, patients with acute low back pain can be divided into three main categories: (1) those with extraspinal causes (chest, abdominal, or retroperitoneal); (2) those with critical or emergent spinal pathology (eg, from tumor, infection, or epidural compression syndrome); and (3) those with nonspecific lower back pain, sciatica, or spinal stenosis. (see Box 32.2) The first priority is to rule out nonspinal pathology, such as an AAA. The next step is to exclude the presence of serious spinal pathology, such as epidural compression syndrome or abscess. The final priority is to decide whether the

patient has musculoskeletal or nerve root pain. In the absence of radicular pain, the pain is classified as nonspecific low back pain.

Most patients seen in the ED will have nonspecific low back pain, and no laboratory testing or imaging is indicated. A smaller group of patients will have radiculopathy or spinal stenosis. In the absence of key clinical findings or progressive neurologic symptoms, treatment will generally mirror that of nonspecific low back pain, and MRI can be delayed for 4 to 6 weeks and coordinated by the PCP if they are candidates for surgery or interventional pain management (eg, epidural steroid injections). Most patients with sciatica recover without surgery.

Following the history and physical examination, the minority of patients who have multiple key clinical findings or a moderate to high probability of a critical or emergent condition will require further urgent evaluation and management aimed at identifying and treating the underlying cause. This care is started in the ED and usually consists of an MRI evaluation. The degree of neurologic impairment, duration, and rate of worsening dictate whether these tests are performed on an urgent or emergent basis. If the motor loss in a muscle segment is rapidly progressive or 3/5 or less, MRI and spine surgery consultation should be undertaken emergently. If motor loss is subacute, stable, and with 4/5 strength, it is possible to wait 1 or 2 days for imaging, with surgical follow-up soon after. This should be arranged with the PCP, radiologist, and surgeon. The patient is instructed to return immediately if worsening weakness occurs.

Spinal epidural abscess remains a very challenging diagnosis to make. Almost 50% of patients are initially misdiagnosed and average two ED visits before admission. Do not rely on the classic triad of fever, back pain, and neurologic deficits because all three components are present only 15% of the time and fever is only present in 50% to 66% of patients at presentation. ESR and CRP values may help in risk stratification. Perform MRI when a moderate to high pretest probability exists (eg, use of IV drugs with new back pain and unexplained fever), regardless of a normal WBC count and neurologic examination and the absence of fever.[18] Preoperative neurologic function is a good predictor of final outcome. Those with few to no risk factors, normal WBC, ESR, CRP, and plain films, and a normal neurologic examination can be managed with close follow-up and appropriate discharge instructions.

Like spinal epidural abscess, cord compression (eg, cauda equine syndrome) is another critical condition in which delayed diagnosis is common, and neurologic function at the time of diagnosis is the primary determinant of the ultimate outcome. Unfortunately, no constellation of symptoms or examination findings is 100% sensitive. No single symptom predicts the radiographic finding of cauda equina syndrome with an accuracy greater than 65%.[30] The probability of significant epidural spinal compression without urinary retention is highly unlikely, although it should be noted that postvoid residual volume can be increased in patients on opioid analgesics. MRI of the lumbosacral spine should be ordered from the ED if there is moderate to high suspicion. Contrast enhancement is not necessary in most cases, but when an infiltrative cause is suspected, such as from infection or metastasis, contrast may be useful. The MRI should include the entire spine to evaluate for falsely localizing sensory levels because clinically silent multilevel involvement is common, and there is a 10% risk of distant asymptomatic metastasis, which may affect subsequent treatment (eg, cervical lesion causing a thoracic sensory level). Fewer than 25% of patients with malignant spinal cord compression have a sensory level within three vertebrae of the true compression level, as demonstrated on an MRI scan. Early initiation of glucocorticoids in consultation with the treating spinal surgeon should follow when the diagnosis is suspected, rather than waiting hours for confirmatory testing. Neoplastic epidural spinal cord compression is a true emergency and requires prompt diagnosis and treatment for the best possible patient outcome. ED management includes early MRI, pain control, and high-dose corticosteroids, with specialty consultation for radiation therapy and/or surgical decompression.

A systematic approach to the patient with cancer and back pain is accomplished by categorizing patients into two groups based on signs and symptoms:

1. Patients with sudden or rapid change in their back pain, development of new or progressive signs or symptoms suspicious for epidural compression (eg, bowel or bladder incontinence, weakness, loss of reflexes, multiroot findings), especially the development of bilateral severe sciatica.

These patients are at high risk for rapid deterioration and should be evaluated and treated as previously discussed for possible emergent epidural compression syndrome in the ED.

2. Patients with back pain but without changes in neurologic status should have plain films and ESR and CRP determinations in the ED. If these are abnormal, or any change in neurologic status occurs, obtain an MRI scan within 24 hours (inpatient or outpatient).

If there is any bony pathology, advanced imaging with MRI or CT is indicated on an outpatient basis within the next several days. If plain films are normal, further evaluation is not emergent. Patients must be closely followed by their PCP for improvement and lack of progressive symptoms. A follow-up appointment should occur within 1 week.

Finally, some patients without known cancer have key clinical findings suggestive of malignancy, such as unexplained weight loss or back pain that is worse at night. As previously discussed, these patients require further risk stratification with plain radiographs and laboratory testing, including a WBC count, ESR, and CRP.[18] With normal test results, these patients can be referred to their PCP for further evaluation. With abnormal diagnostic results, such as a bone lesion on plain film or an extremely elevated ESR, urgent MRI should be performed on an outpatient basis within the next week.

Empirical Management

In general, the recommended role of the emergency clinician in the management of acute lower back pain is to identify whether significant pathology is present, and establish a correct diagnosis while avoiding excessive investigation. Subsequent goals include initiating appropriate treatment, providing analgesia, and educating the patient. The initial empirical management of acute back pain depends on the presenting vital signs and the patient's overall appearance. Figure 32.2 details the specific management considerations for treatment.

Show support by acknowledging the patient's pain and providing reassurance that back pain is very common, the pain does not indicate ongoing harm or serious pathology, and most patients eventually experience spontaneous improvement. Care should be taken to avoid negative or confusing messages. An example of this would be avoiding language that might frighten the medically naïve patient (eg, ruptured disk) and imply a serious abnormality when none exists.[31,32] Provide a full explanation of the diagnosis, evaluation, treatment plan, and expected time course for recovery in terms that the patient understands. Patients should be educated about why they are not undergoing laboratory or radiographic studies and should be reassured of the likely benign course of the pain. Most patients can be convinced by education and an explanation of radiation dosing and associated deleterious effects. This approach will help avoid misperceptions of substandard care or subsequent unnecessary return visits within 48 hours when symptoms are still present. For some patients, chronic, recurrent back pain is a long-term issue, and they may visit the ED during an acute exacerbation. These patients still require a thorough

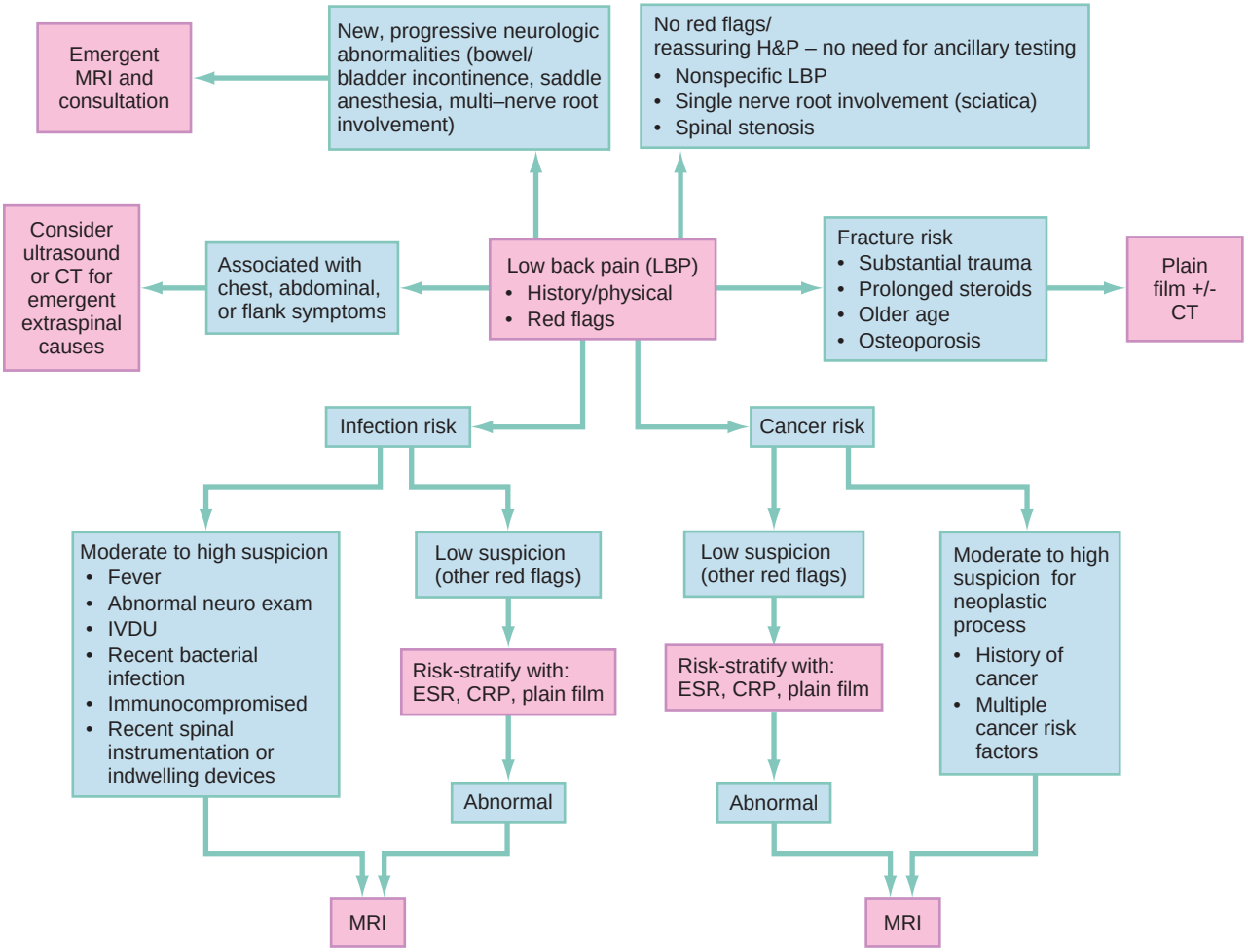

Fig. 32.2. Management of acute low back pain. *AAA,* Abdominal aortic aneurysm; *ADLs,* activities of daily living; *ASAP,* as soon as possible; *CBC,* complete blood count; *CRP,* C-reactive protein; *CT,* computed tomography; *ECG,* electrocardiogram; *echo,* echocardiogram; *ED,* emergency department; *ESR,* erythrocyte sedimentation rate; *exam,* examination; *H&P,* history and physical examination; *IVDU,* intravenous drug use; *MRI,* magnetic resonance imaging; *neuro,* neurologic; *NSAIDs,* nonsteroidal antiinflammatory drugs.

examination and review of key clinical findings to risk-stratify them better and guide ED evaluation. Labelling these patients without performing a thorough investigation can have dangerous consequences. For example, cauda equina syndrome is often seen in those with a prior history of back pain or sciatica.

One of the most important goals of treatment is to provide an acceptable level of analgesia while the underlying condition resolves, or ameliorate the suffering of those patients who await definitive therapy. Emergency clinicians also should be alert to racial bias in treatment of back pain.[33] Despite numerous studies and recommendations, few if any treatments have been proven effective for the management of low back pain. Patients' expectations are known to influence the outcome of treatment, and this process can begin in the ED. Advice and information about back pain, carefully selected and presented, can have a positive effect on patients' beliefs and clinical outcomes.[32] Setting a goal that a pain-free expectation is less realistic than pain improvement may be beneficial. Avoid making unnecessary presumptive diagnoses, and avoid the medicalization of benign conditions by ordering unnecessary tests. This behavior, coupled with the overprescription of analgesics, particularly opioids, fosters a belief on the part of the patient of the existence of serious pathology for an otherwise benign condition.

Nonpharmacologic analgesia can include the use of heat or cold externally applied to the lower back. There is better evidence for the benefits of heat than ice for the treatment of lower back pain. First-line pharmacologic therapy includes nonopioid analgesics (eg, acetaminophen, NSAIDs). Some studies have called into question the efficacy of acetaminophen for acute lower back pain, despite its universal recommendation as a first-line analgesic.[34-36] When using acetaminophen, dosing should start at the maximal recommended doses.

There is little to no benefit of adding high-dose acetaminophen to NSAID therapy. Parenteral NSAID analgesia is rarely indicated and is no more effective than an equivalent dose of an oral NSAID. Lidocaine transdermal patches (Lidoderm) are a safe, nonsedating, effective treatment option for acute and subacute back pain.

Despite claims to the contrary, there is no convincing evidence for the benefit of so-called muscle relaxants, such as cyclobenzaprine and carisoprodol, for acute back pain, and we do not recommend their use.[37] These medications have a high incidence of significant side effects, such as anticholinergic effects, dizziness, and sedation, thereby limiting their use. When simple analgesia is not sufficient, despite a reasonable trial with proper dosing, and the patient has prominent symptoms of sleep disturbance and anxiety related to the pain, a benzodiazepine may be prescribed

as an adjunct to nonopioid analgesia. Their effect, if any, likely is based on their anxiolytic and sedative properties, which may promote sleep and synergize pain relief. Sleep quality is related to subsequent lower back pain intensity,[38] so benzodiazepines may be beneficial, with limited side effects, when taken at bedtime. There is no clear benefit of oral glucocorticoids prescribed in the ED in regard to low back pain (with or without sciatica), activity level, or ability to return to work.[39]

If the pain is severe, IV opioids such as morphine or hydromorphone are the preferred analgesic and should be given in a titrated fashion. However, opioids should be considered a second-line alternative and are best used for those experiencing severe acute back pain with inadequate control with nonopioid analgesics.[40] When administering opioids, frequently reassess the patients until an adequate response is reached, and then transition to oral agents in preparation for discharge.

Despite back pain being the most common indication for opioid prescription in an ED population, routine use of opioids for acute or chronic back pain is not recommended.[41] Also, although opioids are effective for relieving pain, they do not improve functional status. When prescribed, opioids should be combined with NSAIDs, taken on a fixed dosing schedule at the lowest dose possible, and taken only for a limited, clearly defined period (eg, <1 week). The emergency clinician should always consider the known side effects of opioids (eg, constipation, confusion, sedation), especially in older adults, in addition to the individual patient's risk for opioid misuse, abuse, or diversion.

In summary, for patients with mild pain, NSAIDs are the first-line medication unless contraindicated, in which case acetaminophen is preferred. For patients with severe pain, add a low-dose opioid on a fixed dosing schedule for 2 to 3 days. These patients may also benefit from the addition of a benzodiazepine if the pain, sleep disturbance, and anxiety remain prominent.

With chronic back pain, however, opioid efficacy is less clear and should be carefully considered in the absence of a new acute condition. In the chronic back pain population, prescription opioid abuse is epidemic, and aberrant medication taking occurs in up to 25% of cases. Compared to placebo, opioids do improve pain and function in the short-term for chronic lower back pain.[42] However, although opioids and NSAIDs are effective for chronic lower back pain, opioids do not confer a greater benefit with regard to pain or disability.[43] For such patients, NSAIDs are indicated as first-line treatment, and opioids should be considered as an adjunct for short-term pain relief only and should be avoided whenever possible.[44,45] Opioids should not be prescribed to patients with chronic musculoskeletal pain in the ED (see Chapter 3). They should be referred to a pain management center, where epidural glucocorticoid injections and other potential treatments may be provided.

The disposition of patients with back pain depends on their diagnosis. Patients with a life-threatening or disabling cause require emergent treatment, consultation, and admission. Patients with acute cord compression from a fracture, disk protrusion, abscess, or hematoma require urgent surgical evaluation initiated in the ED. Patients with cancer and intractable bone pain may also require admission for pain control. Patients with epidural abscess will also require administration of IV antibiotics and likely surgical consultation. Almost all patients with nonspecific lower back pain can be discharged from the ED with PCP follow-up. In rare circumstances, severe ongoing pain, despite treatment, or inadequate support at home may necessitate admission to the hospital or the ED observation unit.

Although patients should avoid vigorous exercise and provocative activities, complete rest should be avoided. Bed rest has been proven to be deleterious to successful recuperation from back pain, leading to less functional recovery and slightly increased pain than for those advised to remain ambulatory. Remaining active will also help with muscle spasm and atrophy. However, patients with severe pain may be able to do little beyond navigating between the bedroom, bathroom, and kitchen. The perception of activity as a trigger may predispose patients to experience additional disability. It should be made clear that ongoing pain does not imply ongoing harm. Recommend continuing daily activities and gradually increasing specific exercises, as tolerated. Clarify that back pain does not need to be totally alleviated before the patient can return to work. Returning to work should be based on consideration of the actual work duties of the patient. Those with jobs involving heavy manual labor may benefit from time away from work if no light duty options are available, and ED work notes should make this distinction clear. All patients with back pain evaluated in the ED who are not admitted should be given clear discharge instructions, with unambiguous indications to return to the ED immediately with symptoms such as new or progressive leg weakness, bowel or bladder dysfunction, or saddle anesthesia.

KEY CONCEPTS

- Acute low back pain is a common, costly, recurring, and painful condition that often has no recognizable or dangerous cause. Most low back pain is nonspecific and improves without laboratory evaluation or imaging.
- The vast majority of patients can be properly managed by their PCP and do not require ED consultation or specialty referral.
- A focused history should be elicited from patients with lower back pain, with the goal of uncovering high-risk features that would predispose the patient to an emergent or life- threatening situation. The physical examination should focus on the lower extremity neurologic examination, including testing of strength, sensation, and reflexes.
- Imaging and laboratory studies are rarely indicated following the history and physical examination and are only indicated when there is evidence of neurologic deficit or multiple key clinical findings suggesting a dangerous or systemic pathologic cause.
- Adherence to published guidelines will decrease the use of improper laboratory studies and imaging, thereby lowering costs, reducing ED throughput, and improving overall patient care.
- MRI in the ED should only be ordered when there is strong consideration of a serious or progressive neurologic lesion or spinal infection. When a critical or emergent diagnosis is strongly suspected, MRI and spine surgery consultation should be undertaken emergently.
- Patients who have low back pain emergencies are generally classified in two five groups: (1) past medical history of malignancy and new back pain, with neurologic findings; (2) back pain and symptoms of epidural compression syndrome; (3) back pain with symptoms suggesting an infectious cause; (4) back pain with gross muscle weakness or paralysis; and (5) back pain and bilateral or multiple nerve root involvement.

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The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 32: QUESTIONS & ANSWERS

32.1. What would be the most likely cause of back pain in a 48-year-old patient with bilateral leg pain and weakness, urinary retention, decreased rectal tone, and saddle anesthesia?

A. Abdominal aortic aneurysm
B. Bone metastasis
C. Epidural abscess
D. Herniated disk
E. Primary bone tumor

Answer: D. The listed symptoms and signs describe cauda equina syndrome, which is usually caused by a large central herniated disk. Other less common causes include tumor and infection.

32.2. What percentage of herniated disks regress or completely resolve over 6 months?

A. 5%
B. 33%
C. 50%
D. 66%
E. 90%

Answer: D. Serial magnetic resonance imaging (MRI) studies have shown that 66% of herniated disks regress or resolve over 6 months. This high percentage argues for early conservative therapy and argues against early MRI or computed tomography (CT) imaging.

32.3. A 35-year-old man presents with severe back pain that radiates down his right leg. He reports that while lifting a heavy box at work 2 weeks ago, he felt a "pop" in his lower back. He has not been able to return to work since the injury occurred. The patient spoke with his lawyer and was told to come directly to the emergency department to get an MRI. He denies having any other symptoms and reports no significant past medical history. During the

physical examination, the patient is asked to lie on his back, with his knees extended. His right leg is elevated and, at 50 degrees, he reports severe pain running down the lateral aspect of his right leg to his foot. The patient is then asked to sit with his knees flexed and legs hanging over the side of the bed. His legs are passively extended, with no production of pain. The remainder of the physical examination is normal. What is the most appropriate next step in managing this patient?
A. CT of the lumbar spine
B. Discharge home
C. Emergent neurosurgical consultation
D. MRI of the lumbar spine
E. Radiography of the lumbar spine

Answer: B. Several aspects of this scenario point to malingering. The most convincing relates to the physical examination findings. The straight leg raise (SLR) is the classic test for sciatic nerve root irritation. The absence of a positive result generally rules out nerve root irritation. To perform the SLR, the patient is positioned supine, knee extended, and leg elevated until pain is elicited. A positive result is pain radiating down the leg below the knee in a dermatomal distribution when the leg is elevated between 30 and 70 degrees. In a patient who may be malingering, the SLR can be performed with the patient sitting on the side of the bed with knees flexed. Passively straightening the legs in this position should produce equally positive results if true nerve root irritation exists.

32.4. Disk herniation with involvement of the L5 nerve root will present with which of the following findings?
A. Decreased or absent ankle jerk
B. Decreased patellar reflex
C. Diminished sensation of the lateral small toe
D. Impaired plantar flexion
E. Weakness with extension of the great toe

Answer: E. Involvement of the L5 nerve root presents with weakness, with extension of the great toe, decreased sensation in the first web space, and normal reflexes. An S1 radiculopathy is characterized by diminished sensation of the lateral small toe, impaired plantar flexion, and decreased or absent ankle jerk. The patellar reflex is associated with L2-4.

32.5. A history of intravenous (IV) drug use increases the risk for which of the following causes of acute back pain?
A. Abdominal aortic aneurysm
B. Epidural hematoma
C. Malignancy
D. Transverse myelitis
E. Vertebral osteomyelitis

Answer: E. Vertebral osteomyelitis and spinal epidural abscess are diagnosed most frequently in an at-risk population that includes patients with a history of diabetes, chronic renal failure, IV drug use, alcoholism, cancer, AND recent surgery or trauma.

32.6. Plain films have the highest utility in diagnosing which of the following?
A. Abdominal aortic aneurysm
B. Epidural hematoma
C. Spinal stenosis
D. Transverse myelitis
E. Vertebral osteomyelitis

Answer: E. Plain films are diagnostic in 80% to 95% of cases of vertebral osteomyelitis. There is limited usefulness with any of the other conditions listed.

32.7. Spinal epidural abscess is most commonly caused by which of the following pathogens?
A. *Mycobacterium tuberculosis*
B. Pseudomonas aeruginosa
C. Staphylococcus aureus
D. Staphylococcus epidermidis
E. Streptococcus pyogenes

Answer: C. *S. aureus* causes 70% of spinal epidural abscesses.

CHAPTER 33

Multiple Trauma

Eric A. Gross | Marc L. Martel

PRINCIPLES

Emergency clinicians play a vital role in the stabilization, diagnosis, and treatment of trauma patients. The management of trauma patients involves complex, decisive, leadership ability and technical skill. For the multiply or severely injured patient, a team approach is necessary, capitalizing on a strong clinical partnership between emergency medicine and surgery. An effective trauma response also requires timely consultation, access to other trauma-related specialties, especially neurosurgery and orthopedic surgery, and coordination with anesthesiology to ensure prompt and safe transfer to the operating room.

Epidemiology

Motor vehicle collisions (MVCs) are the leading cause of trauma-related mortality in people aged 1 to 44 years.[1] Firearm deaths are a significant concern unique to the United States (see Chapter e2). In 2012, there were almost 33,000 deaths by firearms.[1] The economic cost of traumatic injuries and death is estimated in the hundreds of trillions of dollars, which includes medical costs and lost productivity.[2] Between 2000 and 2012, primarily because of increased seat belt use, the motor vehicle fatality rate declined almost by one-third, to fewer than 11 deaths/100,000 population.[3]

ANATOMY AND PHYSIOLOGY

In contrast to penetrating trauma from knife wounds, in which injuries can be expected to occur only along the track of the weapon, injuries inflicted by gunshot wounds depend on several factors. The amount of tissue damage is related to the kinetic energy of the bullet, which is a factor of the bullet weight (caliber) and velocity. Gunshot wounds cause trauma to the surrounding tissue by direct laceration, crush injury, shock waves, and cavitation—the displacement of tissue forward and radially. Because of these dynamic forces, high-velocity weapons, such as rifles, cause more widespread injuries than low-velocity weapons, such as handguns. Similar to knives, handgun bullets and shotgun pellets (from long range) generally cause injury based on direct laceration and crush generated by the missile along its track. Shotgun wounds from close range are characterized by massive tissue injury.

Injury patterns can differ significantly between adults and children subjected to similar mechanisms of trauma. Pediatric trauma is discussed in Chapter 165.[4-7]

Older patients commonly sustain extremity, craniofacial, and closed head injuries. Most of these occur as the result of a fall or MVC. Unintentional injury was the fourth leading cause of death in 2013.[1] Older trauma patients typically have comorbid illnesses, may be taking relevant medications (especially anticoagulants) and also have normal, age-related changes in organ system function. These factors can increase susceptibility to injury, morbidity, and mortality.

Pathophysiology

In blunt trauma victims, the mechanism of injury can be associated with particular injury patterns. These are listed in Table 33.1. Knowledge of these associations can help the provider evaluate for injuries that may not be readily identified on the initial examination.

CLINICAL FEATURES

Primary Survey

The primary survey should be performed in a standardized fashion immediately after the patient arrives in the emergency department (ED). The goal of the primary survey is to diagnose critical, life-threatening injuries rapidly and begin treatment at the time of diagnosis. Figs. 33.1, 33.2, and 33.3 show the recommended algorithms for the evaluation of airway, breathing, and circulation. Fig. 33.4 describes special considerations between blunt and penetrating mechanisms that should be considered during the primary survey.

Traumatic causes of a compromised airway, such as by a neck or maxillofacial injury, are typically easily recognized. In the absence of obvious direct trauma involving the airway, airway management decisions are based on the overall patient condition and anticipated clinical course (see Chapter 1).

Inadequate ventilation, which may lead to respiratory acidosis, can be noted by the rate and quality of respirations. Pulse oximetry will detect inadequate oxygenation, which may manifest clinically as agitation and restlessness. Assessment for injuries that may compromise oxygenation, ventilation, or both requires careful inspection and auscultation of the chest. Signs of such compromising injury include increased work of breathing, tachypnea, penetrating wounds, subcutaneous emphysema, chest wall instability, flail segments, tracheal deviation, and distended neck veins. See Fig. 33.2.

Assessment of hemodynamic and circulatory status (see Fig. 33.3) follows evaluation of the airway and ventilation. Clinical indicators of adequate perfusion include normal mental status, skin color and temperature, heart rate, blood pressure, and capillary refill. However, a normal finding for any single sign does not rule out significant hemorrhage or even shock. Mental status changes associated with hypoperfusion can include anxiety, agitation, and depressed consciousness. Cool pale skin or extremities

TABLE 33.1

Blunt Trauma Mechanisms and Associated Injuries

MECHANISM OF INJURY	ADDITIONAL CONSIDERATIONS	POTENTIAL ASSOCIATED INJURIES
MOTOR VEHICLE COLLISIONS		
Head-on collision		Facial injuries Lower extremity injuries Aortic injuries
Rear end collision		Hyperextension injuries of cervical spine Cervical spine fractures Central cord syndrome
Lateral (T-bone) collision		Thoracic injuries Abdominal injuries—spleen, liver Pelvic injuries Clavicle, humerus, rib fractures
Rollover	Greater chance of ejection Significant mechanism of injury	Crush injuries Compression fractures of spine
Ejected from vehicle	Likely unrestrained Significant mortality	Spinal injuries
Windshield damage	Likely unrestrained	Closed head injuries, coup and countercoup injuries Facial fractures Skull fractures Cervical spine fractures
Steering wheel damage	Likely unrestrained	Thoracic injuries Sternal and rib fractures, flail chest Cardiac contusion Aortic injuries Hemothorax, pneumothorax
Dashboard involvement or damage		Pelvic and acetabular injuries Dislocated hip
Restraint or seat belt use		
Proper three-point restraint • Lap belt only • Shoulder belt only	Decreased morbidity	Sternal and rib fractures, pulmonary contusions Chance fractures, abdominal injuries, head and facial injuries and fractures Cervical spine injuries and fractures, "submarine" out of restraint devices (possible ejection)
Air bag deployment	Front end collisions Less severe head and upper torso injuries Not effective for lateral impacts More severe injuries in children (improper front seat placement)	Upper extremity soft tissue injuries and fractures Lower extremity injuries and fractures
PEDESTRIAN VERSUS AUTOMOBILE		
Low speed (braking automobile)		Tibia and fibula fractures, knee injuries
High speed		Waddel's triad—tibia and fibula or femur fractures, truncal injuries, craniofacial injuries Thrown pedestrians at risk for multisystem injuries
Bicycle • Automobile-related		Closed head injuries Handlebar injuries • Spleen or liver lacerations • Additional intra-abdominal injuries • Consider penetrating injuries
• Non–automobile-related		Extremity injuries Handlebar injuries

TABLE 33.1

Blunt Trauma Mechanisms and Associated Injuries—cont'd

MECHANISM OF INJURY	ADDITIONAL CONSIDERATIONS	POTENTIAL ASSOCIATED INJURIES
FALLS	LD_{50}, 36–60 ft	
Vertical impact		Calcaneal and lower extremity fractures Pelvic fractures Closed head injuries Cervical spine fractures Renal and renal vascular injuries
Horizontal impact		Craniofacial fractures Hand and wrist fractures Abdominal and thoracic visceral injuries Aortic injuries

LD_{50}, Height of fall that would be fatal for 50% of those falling.

with delayed capillary refill suggest inadequate perfusion and shock. A normal heart rate, blood pressure, or both can be present, despite significant hemorrhage. Conversely, tachycardia may be seen without significant volume loss.

Traditionally, direct pressure to external bleeding sites has been advocated, and the use of tourniquets has been discouraged. The use of direct pressure on the bleeding site remains first-line therapy, but there is good evidence to support the early use of tourniquets for massive extremity hemorrhage that is not otherwise easily controlled.[8-10] Similarly, studies of newer hemostatic agents have shown potential application in combat and out-of-hospital settings.[11,12]

Early intravenous (IV) access is required in the assessment of circulation. We recommend two large-bore (14- or 16-gauge) IV catheters. Routine IV access may be difficult or unobtainable in certain cases. Intraosseous vascular access can be obtained rapidly in pediatric and adult patients and allows the safe infusion of large amounts of fluid or blood products. Compact, battery-operated intraosseous drills are commonly available, and their use has been well established. Ultrasound-guided peripheral venous access by nurses and emergency clinicians should be considered in patients when blind peripheral attempts are unsuccessful. Central venous access may also be indicated in the appropriate clinical scenario or based on the emergency clinician's discretion. The use of ultrasound (US) has been shown to increase successful vein cannulation and decrease complications in the placement of central venous lines in pediatric patients and adults.[13-15] Central venous pressure measurements may be used to direct resuscitative efforts, but should not delay definitive care. Real-time US of the vena cava can be performed much more quickly by assessing its size and the degree of respiratory variation to determine adequacy of resuscitation.[16] We recommend that an extended, focused, abdominal sonography in trauma (eFAST) examination be performed on all patients at the transition point from the primary to secondary survey.

Secondary Survey

The goals of the secondary survey are to obtain pertinent historical data about the patient and injury and identify and manage all significant injuries by performing a systematic, complete examination. An AMPLE (***a***llergies, ***m***edications, ***p***ast medical history, ***l***ast meal, ***e***nvironments and events) history should be obtained. Trauma is a dynamic process, requiring frequent reassessment of the the patient's level of consciousness, airway, circulatory, and pain status throughout the ED phase of management. If deterioration occurs, a complete reevaluation of the primary survey should be initiated. Features of the secondary survey, with critical and emergent diagnoses, are listed in Table 33.2. Concurrently with the primary and secondary survey, oxygenation is enhanced as necessary, appropriate IV access is established, and volume resuscitation (as needed) commences. On completion of the secondary survey, laboratory and more extensive radiographic evaluations commence.

DIFFERENTIAL DIAGNOSES

The differential diagnosis of injuries to the airway or chest that might compromise the airway or breathing is finite. In contrast, circulation problems have a variety of potential causes. Figs. 33.2 and 33.3 outline the approach to emergent diagnoses in the critically ill trauma patient. The early assessment of a trauma patient's circulatory status is crucial and includes hemorrhage control. An algorithmic approach is designed to localize the cause, as well as direct intervention. In penetrating trauma, the bleeding site(s) and therefore the differential diagnosis of circulatory problems is relatively limited as compared to the patient who has sustained significant blunt trauma. In victims of blunt trauma, the goal of management often focuses on localizing the injury: (1) to obvious external hemorrhage; (2) to long bone fractures; (3) to pelvic fractures; or (4) to internal hemorrhage.

The goal of the initial assessment in the ED is to determine whether the patient is in shock. If so, the decision making process turns to an assessment of volume status. If the patient is hypovolemic, immediate resuscitation is initiated. Hemorrhagic shock prompts the emergency clinician to locate the source immediately and target interventions, with ongoing reassessment.

Although mechanisms of injury alone cannot be relied on to predict all injuries caused by blunt major trauma,[7] common patterns of injuries can be anticipated and specifically assessed in ED patients (see Table 33.1). Although these injuries may be present, there is frequently significant overlap between mechanism and injury. In this section, the differential diagnoses of various presentations are discussed.

Victims of trauma often present with altered mental status. Although acute neurologic injuries are the primary consideration, a variety of nontraumatic entities may also affect the patient's presentation or be present in isolation. These include acute intoxication with drugs or alcohol, preexisting medical conditions (eg, hypoglycemia, hyponatremia) and behavioral and mental health conditions. A breath alcohol test or serum alcohol level is indicated for the trauma patient with altered mental status, although waiting for the results should not delay emergent head

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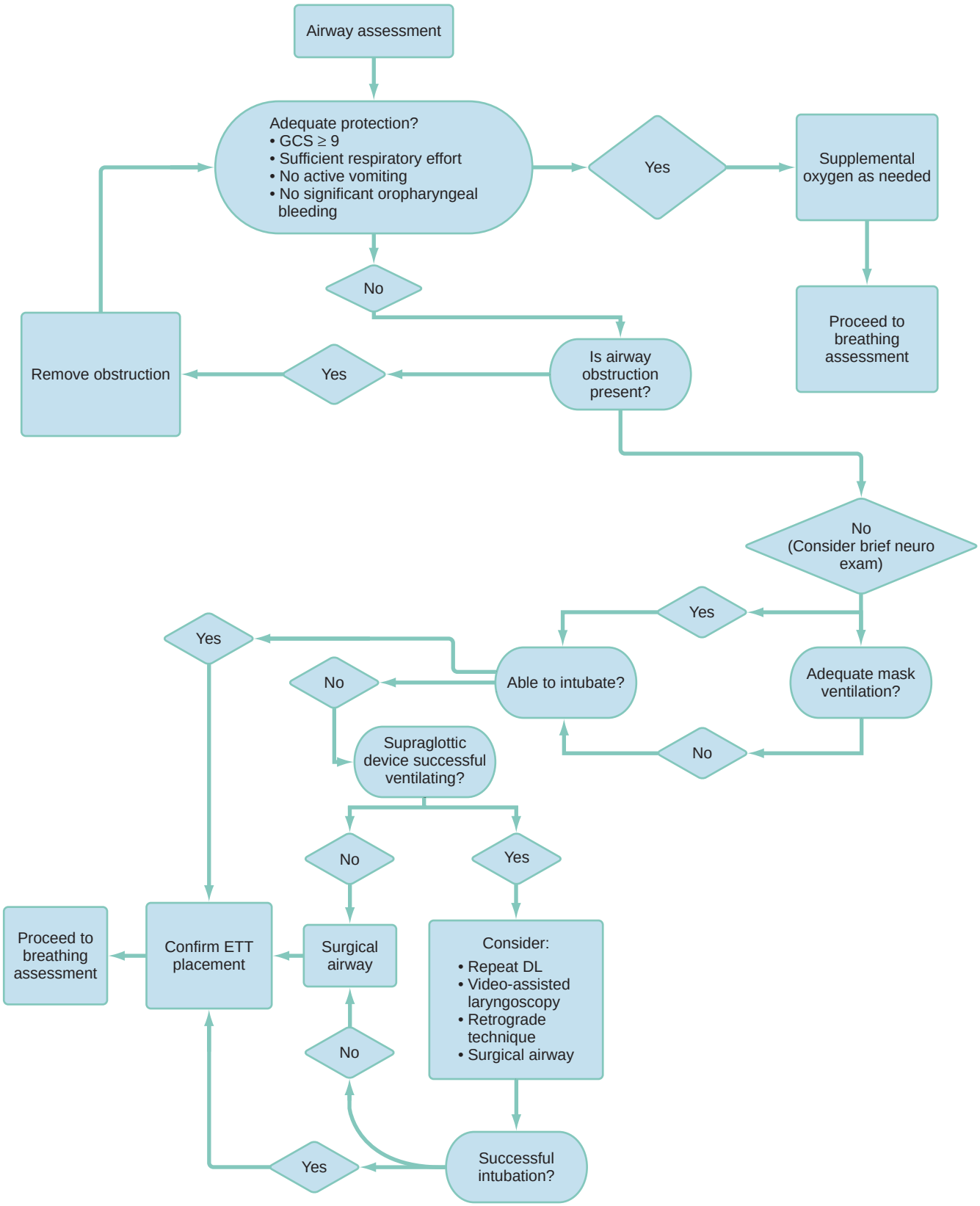

Fig. 33.1. Airway assessment algorithm. *DL,* Direct laryngoscopy; *ETT,* Endotracheal tube; *neuro,* neurologic.

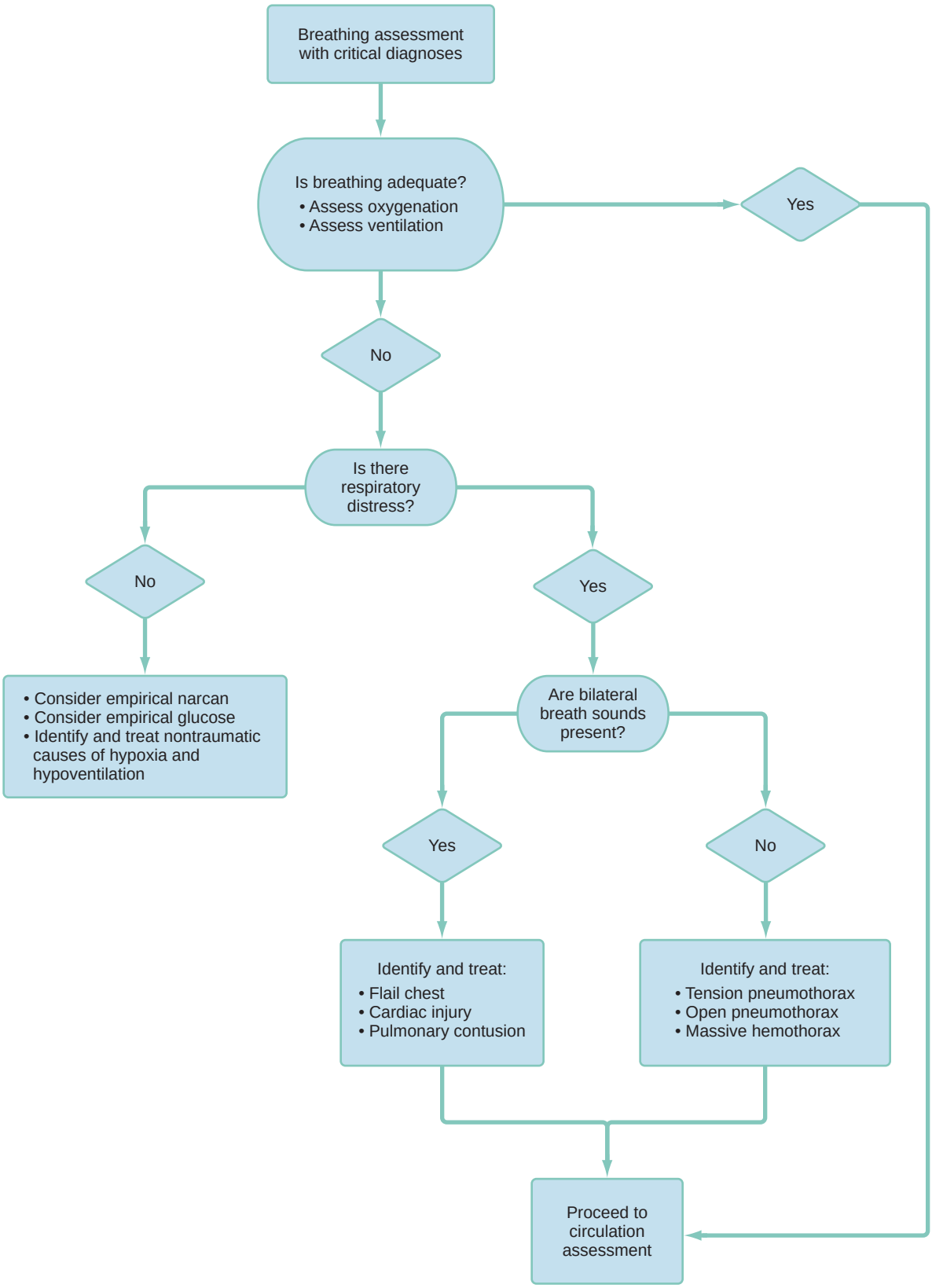

Fig. 33.2. Breathing assessment algorithm.

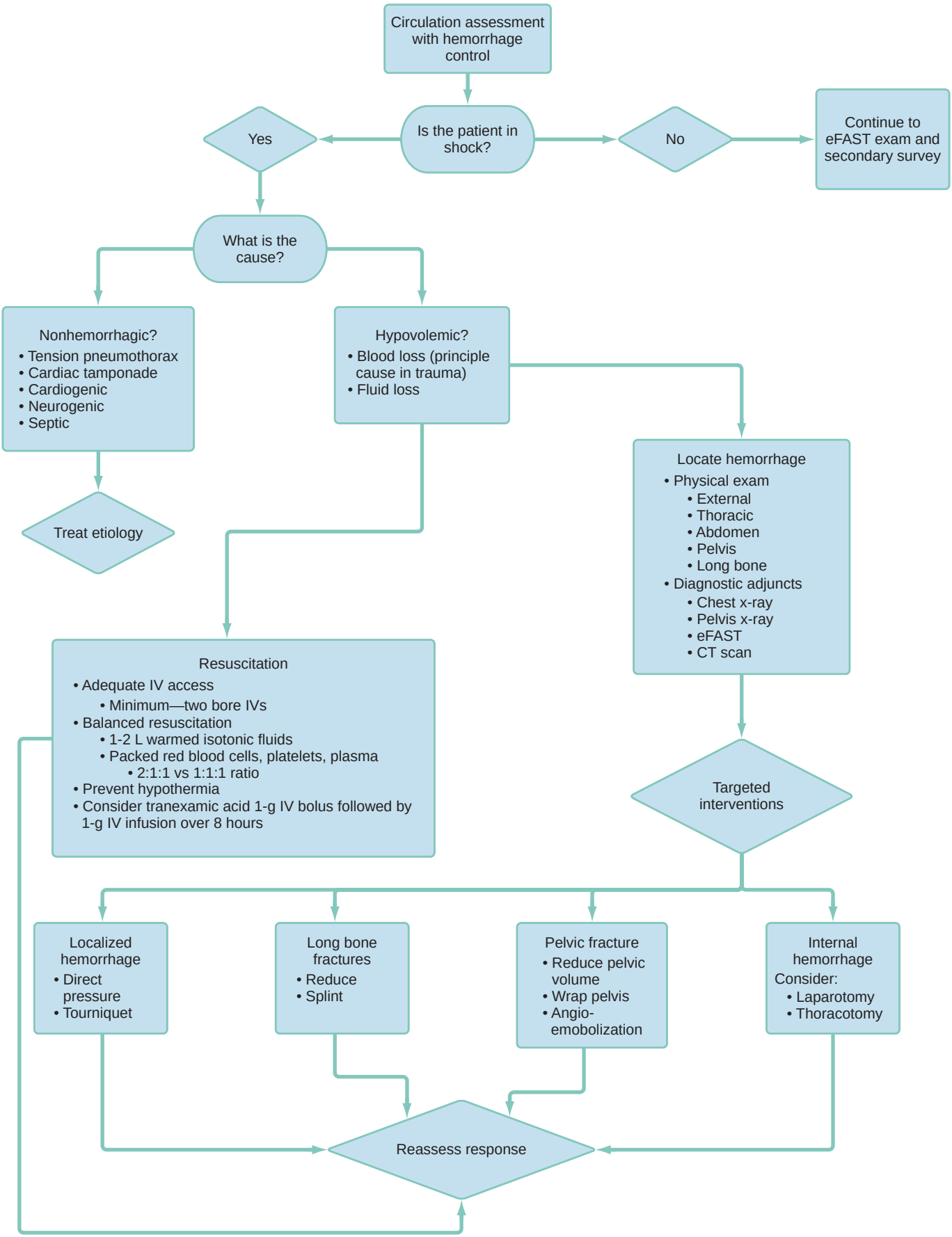

Fig. 33.3. Circulation with hemorrhage control algorithm. *CT,* Computed tomography; *eFAST,* extended, focused, abdominal sonography in trauma; *exam,* examination.

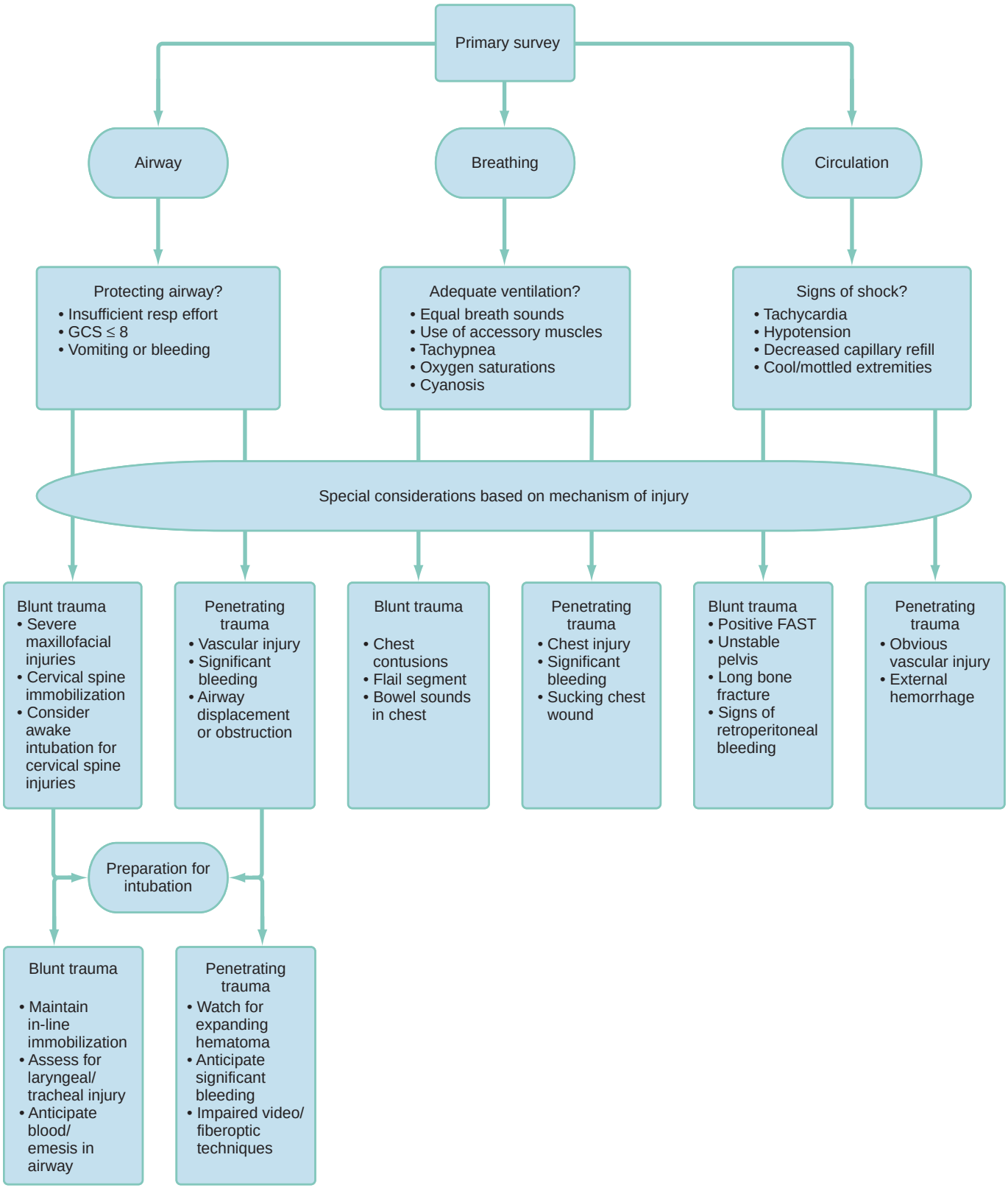

Fig. 33.4. Special considerations of the primary survey. *FAST,* Focused, abdominal sonography in trauma; *GCS,* Glasgow Coma Scale.

TABLE 33.2

Secondary Survey of Trauma Patients

REGION OR SYSTEM	ASSESSMENT OR EXAMINATION	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES
General	Level of consciousness	GCS ≤ 8	
	Glasgow Coma Scale (GCS) score	Focal motor deficit	
	Specific complaints		
Head	Pupils (size, shape, reactivity, visual fields)	Herniation syndrome	Globe rupture
	Contusions		
	Lacerations		
	Evidence of skull fracture (hemotympanum, Battle's sign, raccoon eyes, palpable defects)		Open skull fracture Cerebrospinal fluid leak
Face	Contusions		
	Lacerations		
	Midface instability	Airway obstruction due to bleeding	Facial fractures
	Malocclusion		Mandible fracture
Neck (maintain cervical immobilization)	Penetrating injury, lacerations		
	Tracheal deviation	Carotid injury	
	Jugular venous distention	Pericardial tamponade	
	Subcutaneous emphysema	Tracheal, laryngeal fracture	
	Hematoma	Vascular injury	
	Midline cervical tenderness	Cervical fracture, dislocation	
Chest	Respiratory effort, excursion	Impending respiratory failure	
	Contusions		Cardiopulmonary injury
	Lacerations		Intrathoracic injury
	Focal tenderness, crepitus		Rib fractures
	Subcutaneous emphysema	Flail chest	Pneumothorax
	Heart tones (muffled)	Cardiac tamponade	
	Breath sounds (symmetric)	Tension pneumothorax	Pneumothorax Hemothorax
Abdomen, flank	Contusions		Solid, hollow viscous injury
	Penetrating injury, lacerations	Intra-abdominal hemorrhage	Solid, hollow viscous injury
	Tenderness	Intra-abdominal hemorrhage	Solid, hollow viscous injury
	Peritoneal signs	Abdominal catastrophe	
Pelvis, genitourinary	Contusions	Pelvic hemorrhage	
	Lacerations		Urogenital injury
	Stability, symphyseal tenderness	Unstable pelvic fracture	
		Pelvic hemorrhage	
	Blood (urethral meatus, vaginal bleeding, hematuria)	Unstable pelvic fracture	Urethral injury
	Rectal examination	Colorectal injury (bleeding)	Urethral injury (high-riding prostate)
Neurologic, spinal cord	Midline bony spinal tenderness	Spinal fracture, dislocation	
	Mental status	Epidural hematoma	Cerebral contusions
		Subdural hematoma	Shear injury
	Paresthesias		Spinal cord injury, contusion
			Nerve root injury
	Sensory level	Spinal fracture, dislocation	
	Motor function, including sphincter tone	Spinal fracture, dislocation	
Extremities	Contusions	Compartment syndrome	Rhabdomyolysis
	Lacerations	Vascular injury	
	Deformity	Neurovascular injury	Fracture
	Focal tenderness		Fracture
	Pulses	Arterial injury	
	Capillary refill	Hemorrhagic shock	
		Arterial injury	
	Evaluation of compartments	Compartment syndrome	

computed tomography (CT) when serious head trauma is suspected. Hypoglycemia causes depression of mental status and can be an inciting factor in major trauma. Point of care glucose testing is commonly performed by prehospital providers, but normal glucose levels should be confirmed after arrival in the ED. Minor mechanisms of injury with significant mental status changes may be a clue to a concomitant nontraumatic cause of altered mental status in these patients. Chronic medication use and comorbidities may contribute to the incidence of traumatic injuries and complicate the ED management of these patients. In addition to oral or injectable agents used to control diabetes, medications used for hypertension may result in bradycardia or transient hypotension, with decreased levels of consciousness as the cause of trauma. Use of diuretics or anticholinergic medications or psychiatric illness may lead to hyponatremia. Seizures have a postictal state and also may result in (usually minor) injury, but major trauma can result from seizures occurring while driving or those causing a fall from heights or submersion in water. Anticoagulants present a high risk state for any patient sustaining trauma, and patients on warfarin or newer anticoagulants or antiplatelet agents should undergo neuroimaging with even minor mechanisms of injury.

Hypotension is a significant finding in the acute trauma patient, and all such patients warrant a thorough evaluation for acute hemorrhagic shock. If hypotension persists and no clear source of hemorrhage is identified, other causes of hypotension must be considered. Neurogenic shock, associated with a spinal cord injury, is the next most likely cause when paralysis is identified. Acute myocardial infarction and cardiogenic shock due to severe myocardial contusion or underlying cardiac abnormalities, or hypotension caused by preexisting sepsis or blood loss (eg, gastrointestinal [GI] bleed), are considered if hypotension is present and no clear cause has been identified.

Finally, a critical tenet of trauma management is to avoid distraction by what might appear as an obvious injury. Traumatic amputations, gaping wounds, complex open fracture dislocations, and combative patient behavior frequently distract providers from their structured trauma evaluation. Approaching patients in a systematic way, using the primary and secondary surveys, will help prevent overlooking significant acute injuries. Similarly, complete exposure and a head to toe examination of the trauma patient will identify otherwise occult injuries, which may be concealed on the back or may be in the axilla or perineum.

DIAGNOSTIC TESTING

Laboratory Evaluation

Laboratory testing in the trauma patient should be guided by clinical assessment and the needs of the individual patient. Used wisely, these studies may provide an objective measure of the adequacy of resuscitation, guide transfusion decisions, assess for coagulopathy, provide baseline information for ongoing assessment, and detect and aid in the management of comorbid conditions, such as renal insufficiency and diabetes. Electrolyte levels, liver function studies, international normalized ratio (INR), urinalysis, blood typing and screening (or crossmatching, depending on severity of injury) and lactate levels or base deficit should be determined in all critically ill trauma patients. A pregnancy test should be performed in all female trauma patients of childbearing age. Serum β-human chorionic gonadotropin (β-hCG) testing can avoid the delays in obtaining a urine specimen.

Lactate level, base deficit, and anion gap determinations can help identify subclinical hypoperfusion and track the adequacy of resuscitation. [17-20] Central venous oxygenation also has been used to assess adequacy of resuscitation.[21] Research into earlier markers of hypoperfusion continues.[22] We recommend determining the serum lactate level to evaluate for adequacy of resuscitation in trauma patients with abnormal vital signs suggestive of hypovolemia or altered mental status or other individuals for whom clinical assessment may be unreliable—older patients, those with comorbid conditions or medications that may affect vital signs (eg, beta blockers), or those with mechanisms with high risk for occult injury (see Table 33.1).

A type and screen are indicated for those patients with abnormal vital signs thought to be due to injury or mechanisms with risk for occult injury. A crossmatch should be ordered in those with persistently abnormal vital signs. If transfusion is needed prior to crossmatched blood being available, the provider can temporize with type-specific blood or type O-negative in women of childbearing age or type O-positive in other populations.

An INR should be ordered in all critically injured patients, those with ongoing hemorrhage requiring transfusion, and those on anticoagulants. The INR, however, does not provide a rapid comprehensive picture of the clotting process. In patients with extensive bleeding or undergoing massive transfusion, thromboelastrography (TEG) or thromboelastometry (ROTEM) testing is used to aid the early diagnosis of trauma coagulopathies and direct blood and blood product transfusion. These evaluations are most beneficial for patients undergoing massive transfusion.[23]

In the noncritical patient, determination of electrolyte levels can be reserved for those with underlying medical conditions for whom assessing or monitoring those values will be helpful. A complete blood count provides baseline information important for those at risk for ongoing bleeding or history of anemia. Liver function testing and serum lipase level determination should be carried out when blunt hepatic or pancreatic injury (eg, handlebar injury) is likely or comorbid conditions, including alcoholism, exist.

Radiographic Evaluation

Before the advent of CT scanning and advances in our understanding of the limitations of imaging, virtually all significantly injured patients underwent portable, plain radiographic imaging of their cervical spine, chest, and pelvis. This has now been largely supplanted by the selective use of portable plain radiography, bedside ultrasound (eFAST), and advanced imaging, usually CT scanning.

An eFAST examination should be performed on all patients with multisystem trauma or isolated trauma to the torso. Sonographic evidence of free intra-abdominal, intrathoracic, or pelvic hemorrhage, pneumothorax, and pericardial effusions or cardiac tamponade directs management of the patient. A positive abdominal scan for free fluid in hypotensive patients can identify those in need of emergent laparotomy, with good sensitivity.[24] The sensitivity for injury may not be as high in the pediatric population,[25] but in adult and pediatric populations, the absence of intraperitoneal blood on bedside US does not rule out intra-abdominal injury.[26,27] US evaluation of the inferior vena cava is useful for assessing volume status, but is not part of the eFAST examination.[16,28,29] Further discussion and suggested algorithms are found in Chapter 39.

Cervical spine imaging by plain radiographs in the trauma bay is of very limited value and has been largely supplanted by cervical spine imaging by CT. Patients with neurologic deficits are presumed to have spinal cord injury until proven otherwise, and a so-called normal cervical spine radiograph is not sufficient to rule out injury; spinal precautions should be continued.[30] We recommend using the NEXUS (***N**ational **E**mergency **X**-Radiography **U**tilization **S**tudy*) criteria, which include absence of posterior midline tenderness, focal neurologic deficit, altered mental status, intoxication, or distracting injury.[31] When a patient is not cleared by the NEXUS criteria, a CT scan of the cervical spine should be

obtained.[32] If the neurologic examination is normal, a normal CT scan of the cervical spine is sufficient to exclude injury; further imaging is not necessary.[33-36] Further diagnostic algorithms regarding spine imaging can be found in Chapter 36.

Imaging of the chest early in the evaluation of the multiple trauma patient can provide important information about potentially life-threatening injuries. US is superior to a supine portable chest x-ray as the initial screening tool for pneumothorax and hemothorax.[37-39] We recommend that thoracic US be used in the initial screening of the blunt trauma patient with a significant mechanism of injury to identify life-threatening pneumothorax or hemothorax. If US is not available, portable chest x-ray should be used as the initial screening modality. A normal chest x-ray does not exclude intrathoracic injury; sensitivity for intrathoracic injury is low.[40,41] Injuries not detected by chest x-ray, however, generally do not result in worse outcomes. Chest CT should be performed in those with significant chest pain, dyspnea, sternal tenderness, or abnormal thoracic US or chest x-ray findings. Chest CT is not required in asymptomatic blunt trauma victims with a normal chest x-ray.[42-45]

There is evidence that thoracic imaging can be avoided altogether in blunt trauma patients with very low risk of thoracic injury. The criteria for obtaining imaging in one large validation study are age older than 60 years, rapid deceleration mechanism, chest pain, intoxication, abnormal alertness and mental status, distracting painful injury, and tenderness to chest wall palpation. This rule has a sensitivity of 99.8% and negative predictive value of 98.5%.[46] However, these criteria have not been adopted on a wide scale. Adoption of these or modified criteria may occur by consensus among the key services involved (typically, emergency medicine, trauma surgery, radiology) at the local level as a way to decrease costs and radiation exposure.

In patients with a stab wound to the chest and an initial normal thoracic US or chest x-ray, routine use of chest CT is not indicated.[47,48] Asymptomatic patients can undergo a repeat chest x-ray in as little in 1 hour, rather than the traditional 6 hours after an initial normal chest x-ray, to exclude significant pathology.[47]

Pelvic fractures can cause significant hemorrhage, and early recognition of fracture and closure of the pelvic space can mitigate hypotension in these patients. In hemodynamically unstable patients, a portable pelvic x-ray should be obtained in the trauma bay. The sensitivity for an anteroposterior pelvic x-ray to identify all possible fractures is not high; however, an abnormal x-ray showing an open book fracture or vertical displacement of the posterior pelvis should alert the emergency clinician to the need for a pelvic binder and possible embolization or surgical fixation to control ongoing pelvic hemorrhage. Hemodynamically stable patients with pelvic tenderness or a distracting injury, or those with severe mechanisms of injury and altered mental status, should have their pelvis imaged. If the patient is undergoing CT of the abdomen and pelvis as part of the trauma assessment, we recommend using the bone windows of the CT scan rather than obtaining a pelvic x-ray.[49,50] Hemodynamically stable patients who are awake, alert, and asymptomatic, with a normal pelvic physical examination, do not require pelvic x-rays.[51,52] Similar studies have suggested the same for pediatric patients.[53,54] Further discussion of pelvic trauma can be found in Chapter 48.

In blunt multiple trauma victims, imaging with an abdominal-pelvic CT scan (AP-CT) is recommended for those with abdominal pain or tenderness, significant mechanism of injury (see Table 33.1), abnormal eFAST examination, gross hematuria, or unreliable examination (eg, altered mental status, distracting injury, head injury). The presence of a seat belt sign is associated with an internal abdominal injury (IAI) and should prompt a CT scan.[55] Blunt multiple trauma victims who have a Glasgow Coma Scale (GCS) score of 15, normal abdominal physical examination, negative eFAST, and normal laboratory results can forego a CT scan; however, they should have a period of observation, repeat eFAST examination, and repeat hemoglobin level determination.[55,56]

Indications for imaging of the head, spine, and extremities are covered in the respective chapters. Patients with moderate or severe head injury should have their head imaging completed as soon as possible after the primary survey, eFAST examination, and brief secondary survey. Imaging of the thoracic and lumbar spines and extremities can be delayed until other life-threatening injuries have been investigated and managed.

MANAGEMENT

Out-of-Hospital Management

Management of the trauma patient frequently begins before arrival in the ED by first responders. The goals of out-of-hospital care include intervention in immediately life-threatening injuries, prevention of additional injury, and rapid transport to trauma centers for definitive care.

Most life-threatening injuries that require intervention by out-of-hospital providers are related to airway, breathing, and circulation (the ABCs). Endotracheal intubation may be required for patients with severe trauma, particularly head trauma with coma, and for those with significant trauma when transport times may be prolonged. Tension pneumothorax compromises ventilation and perfusion and requires needle or other thoracostomy when suspected. Systemic hypotension with impaired end-organ perfusion necessitates restoration of intravascular volume to a level sufficient to provide perfusion, but not and attempt to restore normal blood pressure.

Preventing additional injury requires an awareness of not only clinically evident abnormalities but also potentially more serious injuries. Coordinated extrication and transport with cervical immobilization, spinal precautions, intensive hemodynamic monitoring, and stabilization of fractures to prevent neurovascular compromise are examples of assuming the most serious injuries exist in multiple trauma patients.

Emergency Department

Because multiple trauma patients have a variety of injuries from varying mechanisms, the initial focus is directed at overall resuscitative care, with emphasis on performing interventions in the optimal sequence.

For level 1 trauma centers, the American College of Surgeons (ACS) requires the presence of a board-certified general surgeon to be present in the hospital 24 hours each day. The trauma surgeon is expected to be present in the ED no later than 15 minutes after arrival of trauma patients to the ED (Box 33.1).[57] As the specialty of emergency medicine has evolved, and the number of residency-trained and board-certified emergency clinicians has increased, the need for a surgeon for all trauma patients has been increasingly debated; outcomes are equivalent when the trauma team is led by a surgeon or an emergency clinician.[58] Most trauma resuscitations in the community are performed by emergency clinicians, with consultation by a surgeon or surgical subspecialist based on identified injuries.

The priorities in the treatment of trauma patients are similar to those for any other life-threatening condition. Securing the airway, maintaining ventilation, controlling hemorrhage, and treating shock are the first priorities.

The goals of airway management are threefold—airway protection, adequate oxygenation, and adequate ventilation. The decision to intubate may go beyond these three tenets because the potential for deterioration in clinical status should be taken into account. Patients may have an obvious need for early intubation identified during the primary survey. Others will have serious

BOX 33.1

American College of Surgeons Requirements for the Presence of a Surgeon in Major Resuscitations

A surgeon should be present in the emergency department on trauma patient arrival or within 15 minutes if any of the following major criteria are found:

- Confirmed hypotension (systolic blood pressure < 90 mm Hg)
  - Gunshot wounds to the neck, chest, abdomen or proximal extremities
  - Intubated patients transferred from the scene
- Respiratory compromise requiring an emergent airway
- Penetrating gunshot wound to the neck, chest, abdomen, or pelvis
- Glasgow Coma Scale score < 8 attributed to trauma
  - At the discretion of the emergency clinician

injuries detected later in their evaluation or will have deteriorated and require intubation. Still others will require intubation based on their overall clinical course and constellation of injuries, rather than for any one clear indication.

Airway protection is necessary for many trauma patients. Airway obstruction necessitates immediate intervention. Obstruction from debris, blood, or vomitus may be removed with suction. Neck or facial trauma may cause more complicated problems. Swelling, distorted anatomy, and hematoma formation may all contribute to impending obstruction. Early airway control is safest because these conditions may rapidly worsen. The inability to protect the airway adequately, such as in patients with depressed levels of consciousness, is another indication for intubation. Airway control is recommended for patients with depression of consciousness sufficient to compromise airway protection (usually cited as a GCS score <9).[59] Alcohol intoxication can be an important confounder in the early neurologic assessment of these patients. In patients who do not immediately require airway protection, close observation over time for neurologic recovery to a normal state is necessary.

As a general rule, all trauma patients initially should be placed on supplemental oxygen. When oxygenation on room air is adequate, low-flow (3 L/min) nasal cannula oxygen is sufficient. When oxygenation is compromised, face mask oxygen at a high flow rate is required. Restoring adequate oxygenation has a direct effect on the outcome of many trauma patients, particularly head-injured patients. Maintenance of the arterial oxygen concentration (Pao_2) above 60 mm Hg has been recommended by the Brain Trauma Foundation, a recommendation that has not changed since 2007. Certain ventilatory problems, such as pneumothorax or hemothorax, may require tube thoracostomy in addition to intubation. Placement of the chest tube before undertaking intubation, if possible, may improve the patient's hemodynamic status and decrease the risk of serious deterioration related to the use of intubating medications and initiation of positive pressure ventilation.

If the patient's condition allows, a detailed neurologic examination is important before administering neuromuscular blocking agents, which may confound later evaluation. Correlation of head CT scan findings with neurologic status is critical to making any decisions regarding operative intervention for intracranial hemorrhage. Also, documentation of neurologic function or deficit is essential in the setting of a potential spine injury. Most patients will not have been cleared of cervical spine injury before intubation, so in-line spine stabilization and the most gentle possible technique are important. We recommend videolaryngoscopy with rapid sequence intubation as the primary method to secure the airway in the severely traumatized patient[60-62] (see Chapter 1). Videolaryngoscopy has been shown to reduce spine movement and generally achieves superior laryngeal views when compared with conventional direct laryngoscopy. When a potentially unstable spine injury has been identified, some emergency clinicians prefer to use a flexible bronchoscope for intubation. Overall, the choice of intubation technique will be based on the clinical scenario and emergency clinician's determination of what is most likely to accomplish the desired task in his or her hands. Blind nasotracheal intubation is undesirable in the trauma patient. Nasotracheal intubation using a flexible bronchoscope may be valuable in patients with a suspected airway or unstable cervical spine injury, performed as part of a prepared awake intubation (see Chapter 1).

A surgical airway is indicated in cases of failure of or contraindication to intubation. Cricothyrotomy is the preferred method, although it is performed in a small minority of all trauma cases requiring airway management, and the incidence has been decreasing because of the availability of better alternative rescue devices when intubation fails. When cricothyrotomy is required, we recommend the use of the four-step method or the no-drop cricothyrotomy technique, as described in Chapter 1. A variety of devices for percutaneous cricothyrotomy are also available, but only those using the Seldinger technique are sufficiently reliable and safe.

Control of external hemorrhage and rapidly establishing IV access are essential early steps in the management of the acute trauma patient. This has been discussed earlier (see "Primary Survey").

The choice of fluids for resuscitation includes crystalloid, colloid, and blood products. Fluid replacement is generally based on a 3:1 ratio of fluids to blood loss. There are few clinically significant differences between lactated Ringer's and normal saline solutions.[60,63] The debate regarding the choice of colloids versus crystalloids for resuscitation is ongoing. No indisputable advantages of colloids have been demonstrated.[64] Therefore, the less expensive and more readily available crystalloids are the mainstay of treatment. No clear benefit to the use of hypertonic saline has been established.[65] Current Advanced Trauma Life Support (ATLS) guidelines standardize the ratio of replacement fluids to loss and recommend 2 L of crystalloid be infused in all patients in shock, followed by blood products. O-positive blood should be used, except in women of childbearing age. Type-specific blood should be used when available, but emergent transfusion should not be delayed. Massive transfusion protocols are commonly used for patients with severe hemorrhagic shock. Recent data have suggested that the use of a 1:1:1 ratio of plasma, platelets, and red blood cells may result in earlier hemostasis, although no significant difference in mortality was noted.[66] We recommend the use of a 1:1:1 or 1:1:2 ratio of blood products based on specific institutional policies and procedures. Other transfusion ratios are less effective in resuscitation. The use of the antifibrinolytic agent tranexamic acid has been shown to decrease mortality in trauma patients at risk of major bleeding if given within the first hour following injury.[8-10] Any trauma patient with clinically significant hemorrhage, or those who present in shock, should receive 1 g of tranexamic acid over 10 minutes, followed by a 1-g infusion over 8 hours. Mortality benefits of tranexamic acid have been shown when administered up to 3 hours after trauma, but earlier administration (within 1 hour) is superior.

In the severely injured, hypotensive trauma patient, restoration of normal blood pressure may be undesirable. The concept of permissive hypotension is based on the premise that resuscitation to a normal blood pressure may increase bleeding from an uncontrolled hemorrhage site or even from a site that is tenuously contained and not actively hemorrhaging. In permissive

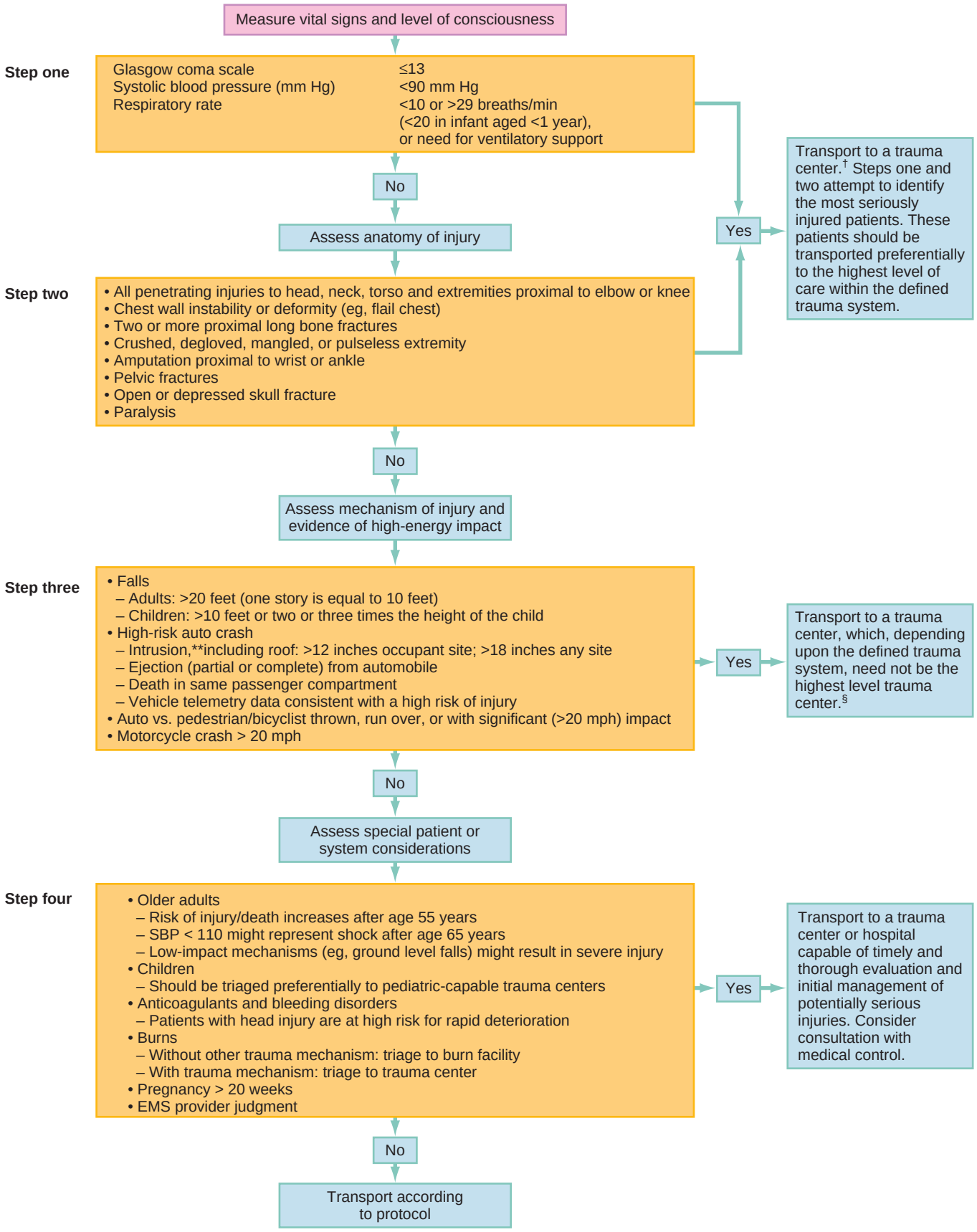

Fig. 33.5. Triage decision scheme. *EMS,* Emergency medical services. (Adapted from American College of Surgeons, Committee on Trauma: Resources for the optimal care of the injured patient, Chicago, 2012, American College of Surgeons.)

hypotension, mean arterial pressure (MAP) is restored to a goal of approximately 50 mm Hg. Data have shown that this strategy leads to less blood product use, less bleeding, and lower incidence of coagulopathy.[11,12] Permissive hypotension is contraindicated in the management of traumatic brain injury because of the risk of hypoperfusion.[13-15] Rather than any particular MAP target, restoration of adequate tissue perfusion, with normal mentation or, more importantly, normalization of tissue oxygen saturation (Sto_2) monitoring, is the clinically relevant endpoint in the resuscitation of the trauma patient.[67-69]

The role of ED thoracotomy (EDT) has become more selective to limit futile resuscitation efforts and minimize risk to providers. Patients with penetrating trauma who undergo cardiac arrest while in transport or in the ED are most likely to benefit from EDT. In contrast, cardiac arrest patients with blunt trauma, prolonged cardiopulmonary resuscitation (CPR), or delayed transport times generally have dismal outcomes that are not altered by EDT.[70] Most institutions have protocols in place outlining criteria regarding when EDT should be performed. The National Association of EMS Physicians and ACS Committee on Trauma have published guidelines for withholding or terminating resuscitation efforts in out-of-hospital traumatic cardiac arrest patients. As a result, these guidelines often limit the transport of patients who would not likely benefit from EDT. Patients who may not be transported include any blunt trauma patient without vital signs at the scene, apneic or pulseless penetrating trauma victims without other signs of life, patients undergoing more than 15 minutes of CPR, and patients with transport times of more than 15 minutes after arrest.[71-73] Suggested algorithms for the application of EDT are outlined in Figs. 33.5, 33.6, and 33.7. EDT is discussed further in Chapter 38. When EDT is performed, the goal is to manage rapidly correctable traumatic injuries and allow for transfer to the operating room for definitive intervention.

To assess disability, a rapid assessment of the patient's neurologic status is necessary early in the ED course. If intubation is necessary early in the patient's treatment, perform a brief neurologic examination, including level of consciousness, tone and motor ability for all four extremities (eg, spontaneous, purposeful, withdrawal to pain), anal sphincter tone (if obtunded or evidence of paralysis), and any lateralizing signs, prior to administration of the paralytic and induction agent.

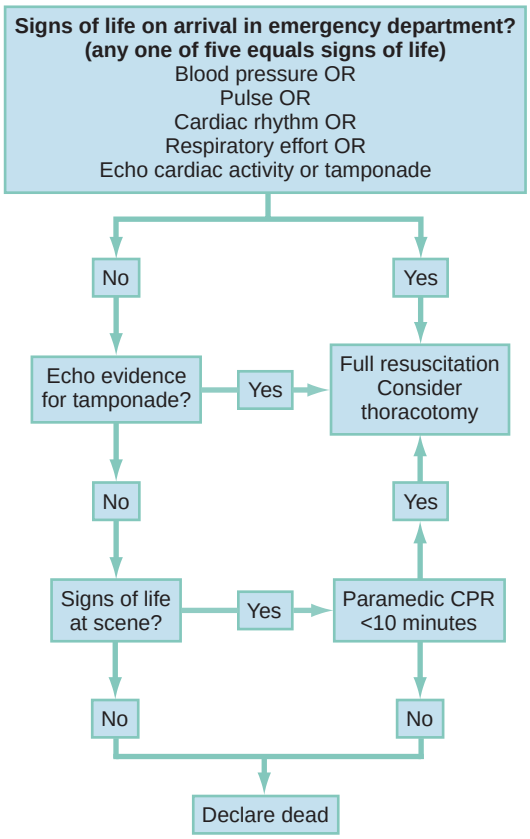

Fig. 33.6. Penetrating chest trauma—emergency department thoracotomy algorithm. *CPR,* Cardiopulmonary resuscitation; *Echo,* echocardiographic.

DISPOSITION

The decision to admit the patient or transfer to a tertiary care facility should be coordinated based on available resources, consultation with the trauma surgeon, and consideration of institutional and regional guidelines. The ultimate disposition is dictated by a number of factors, including the patient's condition, nature of the injury, and availability of surgeons, subspecialists, and anesthesiologists. Possible dispositions include transfer to the operating room, admission to the surgical service, limited observation in the ED, and transfer to another hospital. The level of care and monitoring established in the ED should be maintained throughout transfer. All equipment and medications needed for resuscitation and maintenance of vital functions should be available during the transfer, as should qualified personnel to oversee the patient's care.

In cases of interhospital transfers, emergency clinicians at the two institutions should carefully coordinate all arrangements. Stabilizing measures are begun before the patient's transfer, but decompensation in transit should be anticipated. Qualified personnel and necessary resuscitative equipment should accompany the patient. The compelling reason for transferring a patient with life-threatening trauma is the lack of resources or personnel to care for a patient's particular injuries. Transfer should not be delayed for nonessential diagnostic procedures. All documentation and results of ancillary testing should accompany the patient in transfer.

In certain circumstances, the multiple trauma patient may not need admission or interhospital transfer. The decision to discharge these patients is evaluated carefully because many traumatic injuries may manifest in a delayed manner. When discharge is considered, thorough ED evaluation is necessary, with resources in place to ensure an optimal outcome—surgical consultation, where appropriate, attending radiologist support for image interpretation, and timely scheduled follow-up on an outpatient basis.

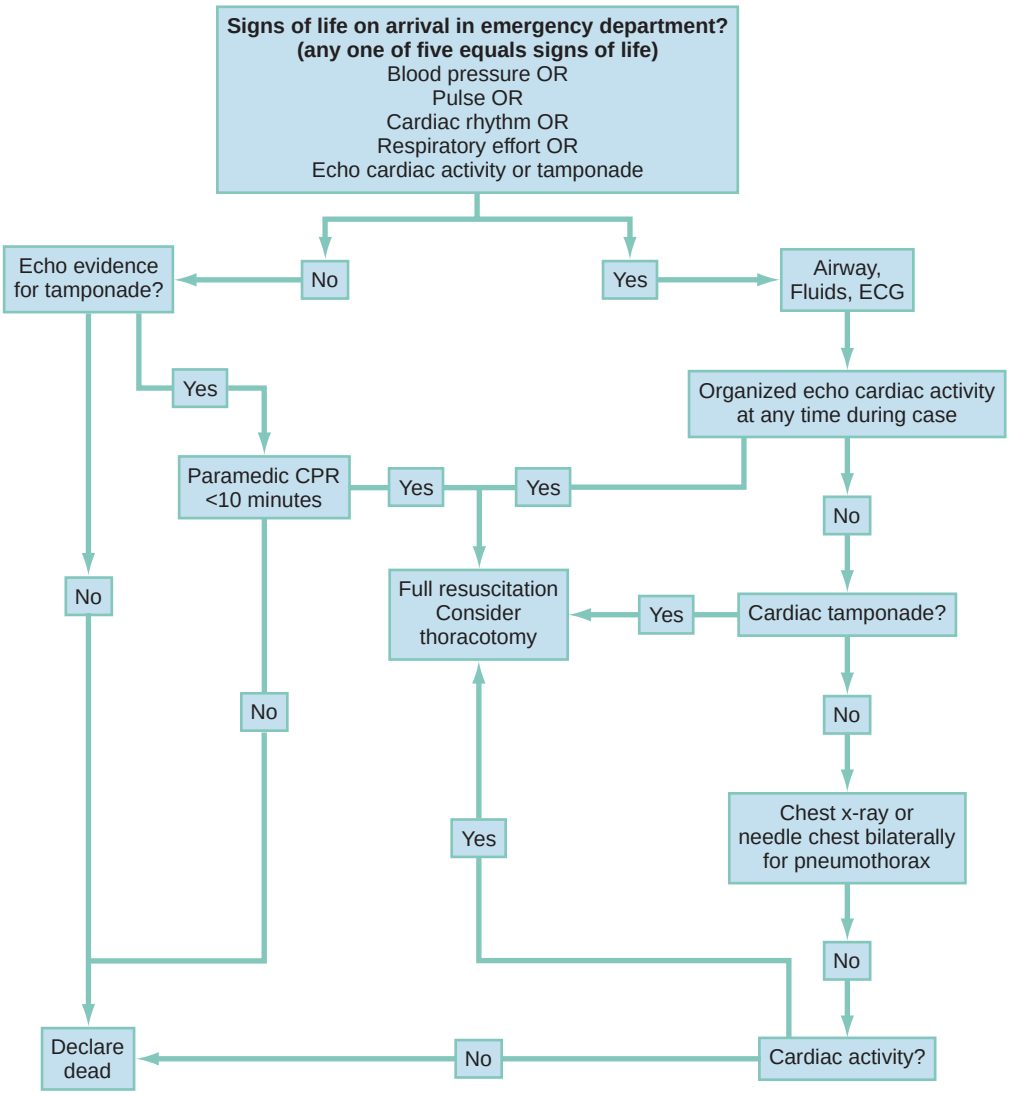

Fig. 33.7. Blunt chest trauma emergency department thoracotomy algorithm. *CPR,* Cardiopulmonary resuscitation; *ECG,* electrocardiogram; *Echo,* echocardiographic.

KEY CONCEPTS

- Immediately after a trauma patient arrives in the ED, the primary survey should be performed in a standardized fashion. The goal of the primary survey is to identify and initiate the treatment of critical, life-threatening injuries rapidly.
- The eFAST examination should take place early in the evaluation of the trauma patient, ideally as part of the primary survey. Thoracic examination of the trauma patient by ultrasound is more accurate than plain radiography.
- Any patient with potentially life-threatening injuries should have blood typing and screening performed. When transfusion is indicated, blood products should be transfused in a 1:1:1 or 1:1:2 ratio of plasma to platelets to packed red blood cells.
- Tranexamic acid is indicated for patients with evidence of significant hemorrhage or shock and is given as a 1-g bolus followed by a 1-g infusion over 8 hours. Results are best if started within 1 hour of injury but benefit may occur when it is given within 3 hours.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 33: QUESTIONS & ANSWERS

33.1. A 33-year-old mother and her 2-year-old-son are brought in by paramedics after they were both hit by a car moving at 15 mph. Although mother and child had an identical mechanism of injury, the son would be at greater risk for all the following injuries, with the following exception:
A. Head injury
B. Hypothermia
C. Intra-abdominal injury
D. Multisystem injury
E. Posttraumatic stress disorder

Answer: E. Injury patterns can differ significantly between adults and children subjected to similar mechanisms of trauma. The major anatomic distinctions relate to the smaller size and surface area, larger head-to-body ratio, and less protected abdominal cavity of the child. As a result, children are more vulnerable to multisystem injury in blunt trauma, including significant head and intra-abdominal injuries, as well as being at greater risk for hypothermia.

33.2. Which of the following is the goal of the primary survey?
A. Determine which consultations should be obtained.
B. Do an AMPLE (***a***llergies, ***m***edications, ***p***ast medical history, ***l***ast meal, ***e***nvironments and events) history.
C. Obtain pertinent historical data from the paramedics.
D. Perform a radiographic evaluation.
E. Rapidly identify critical life-threatening diagnoses and begin treatment at the time of the diagnosis.

Answer: E. The emergency clinician should use a standardized approach to the initial evaluation of these patients. Following the Advanced Trauma Life Support (ATLS) algorithm of ABCs in the primary survey allows the timely identification of critical diagnoses and intervention without delay. The primary survey should be performed in a standardized fashion immediately after the patient arrives in the emergency department. The goal of the primary survey is to identify critical, life-threatening diagnoses rapidly and begin treatment at the time of diagnosis. The goals of the secondary survey are to obtain pertinent historical data about the patient and injury as well as evaluate and treat injuries not found on the primary survey. An AMPLE history should be obtained.

33.3. An 89-year-old man who was a restrained front seat passenger with a history of hypertension, anxiety disorder, and dementia is being evaluated after a head-on collision. His home medications include an angiotensin-converting enzyme (ACE) inhibitor for the hypertension, lorazepam for the anxiety, and olanzapine (Zyprexa) for the dementia. The patient does not have any complaints but is noted to have a blood pressure of 80/50 mm Hg and heart rate of 100 beats/min. In evaluating the patient, you should suspect that the asymptomatic hypotension is most likely due to which of the following?
A. Antihypertensive medication use
B. Antipsychotic medication use
C. Benzodiazepine use
D. Blood loss

Answer: D. Lower extremity weakness, gait disturbances, decreased visual acuity, and the use of psychotropics, antihypertensives, and sedatives have been associated with falls in older adults, resulting in major injury. The use of these medications, particularly antihypertensives, should not be considered causative in trauma patients with hypotension until acute hemorrhage has been ruled out. In addition, anticoagulants, antiplatelet drugs, and aspirin are commonly prescribed, and their effects should be suspected and reversed, if warranted.

33.4. A critically injured, multisystem trauma patient has blood sent to the laboratory. The appropriate tests may determine the adequacy of resuscitation and need for blood transfusion. Hypoperfusion and inadequate resuscitation may be indicated by abnormalities in all except which of the following?
A. Anion gap
B. Base deficit
C. Central venous oxygen saturation
D. Lactate level
E. Magnesium

Answer: E. Laboratory markers can help identify patients who may not appear acutely ill but do have hypoperfusion, as well as track the adequacy of resuscitation. Lactate level, base deficit, and anion gap also predict outcome in the trauma patient. Following changes in the central venous oxygen saturation may also be worthwhile; low values in hemodynamically stabilized trauma patients have been shown to worsen outcome.

33.5. A severely injured, hypotensive trauma patient is being considered for permissive hypotension because she has a contained retroperitoneal hematoma and is not actively hemorrhaging. In permissive hypotension, the mean arterial pressure is restored to a goal of 50 mm Hg. Which of the following should help you decide against using permissive hypotension?
A. Age > 80 years
B. Age < 10 years
C. Associated traumatic brain injury
D. Hemoglobin of 10 g/dL
E. Intoxication

Answer: C. In the severely injured, hypotensive trauma patient, restoration of normal blood pressure may be undesirable. The concept of permissive hypotension is based on the concern that resuscitation to normal blood pressures may increase bleeding from a site that is contained and not actively hemorrhaging. In permissive hypotension, the mean arterial pressure (MAP) is restored to a goal of about 50 mm Hg. Studies have shown that this strategy leads to less blood product use, less bleeding, and lower incidence of coagulopathy. However, the provider should be aware that permissive hypotension is contraindicated in the management of traumatic brain injury because of the risk of hypoperfusion.

CHAPTER 34

Head Trauma

Linda Papa | Scott A. Goldberg

PRINCIPLES OF DISEASE

Background and Importance

Head trauma is a broad term describing an external trauma to the craniofacial area of the body from blunt, penetrating, blast, rotational, or acceleration-deceleration forces, the term *head injury* refers to a clinically evident injury on physical examination and is recognized by the presence of ecchymosis, lacerations, or deformities, and the term *traumatic brain injury* (TBI) indicates an injury to the brain itself.

Head trauma accounts for approximately 1.5 million emergency department (ED) visits annually in the United States; one-third of these are children younger than 14 years. Falls and motor vehicle collisions (MVCs) account for almost 75% of head trauma in the civilian population.[1] TBI caused by blasts has resulted in disproportionate morbidity to combatants in the recent wars in Iraq and Afghanistan.[2,3] As veterans return to the United States, the number of patients experiencing the consequences of TBI continues to increase.

Gunshot wounds (GSWs) to the head are particularly lethal; the overall mortality rate is estimated to be 90%, with 70% of deaths occurring at the scene.[4] However, in a subset of these patients with good initial neurologic function, survival approaches 75%.

The ultimate survival and neurologic outcome of the brain-injured patient depends on the extent of TBI occurring at the time of injury (primary injury) and the effects of systemic insults (secondary injury), such as those caused by hypotension and hypoxia. Thus, clinical care of patients with TBI emphasizes early management to minimize the occurrence of secondary brain injury. Emergency clinicians influence the incidence and severity of primary brain injury only through injury prevention programs (see Chapter e2).

A number of terms describing mild traumatic brain injury (MTBI) have been used in the past, including minor, minimal, grade I, class I, and low risk. The American Congress of Rehabilitation Medicine defines a patient with MTBI as one who has a Glasgow Coma Scale (GCS) score of 13 to 15, with traumatically induced physiologic disruption of brain function, as manifested by at least one of the following: (1) any period of loss of consciousness less than 30 minutes; (2) any loss of memory for events immediately before or after the accident (posttraumatic amnesia should last <24 hours); (3) any alteration in mental state at the time of the accident (eg, feeling, dazed, disoriented, or confused); and (4) focal neurologic deficits that may or may not be transient (Box 34.1).

Individuals with MTBI are acutely at risk for serious intracranial injuries. Up to 17% of patients with suspected MTBI in the ED have abnormal computed tomography (CT) scans. Although the incidence of life-threatening lesions that require neurosurgical intervention in suspected MTBI is only about 1%, these patients have an important risk of subsequent deterioration from intracranial bleeding. If these cases are recognized and treated early, a full recovery is likely; if not, severe disability or death may ensue.

The GCS score was not originally intended for use in MTBI patients,[5] and some authors have suggested that patients with a GCS score of 13 or 14 be excluded from the mild category and placed into the moderate-risk group due to the higher risk of neurosurgical intervention.[6] However, a patient who is intoxicated from drugs and alcohol may present with a GCS score of 13 to 14. Furthermore, over 10% of patients who become comatose start with a GCS score of 15. Patients can deteriorate from an expanding intracranial hematoma after what appears clinically to be a MTBI. Among MTBI patients, those with GCS scores trending downward (worsening neurologic status) are at higher risk of neurosurgical intervention and have a less favorable outcome than those with GCS scores trending upward (improving neurologic status).[7,8]

Anatomy and Pathophysiology

Scalp and Cranium

The scalp consists of five tissue layers (Fig. 34.1). The skull is comprised of the frontal, ethmoid, sphenoid, and occipital bones and two parietal and two temporal bones. Each bone consists of solid inner and outer layers separated by a layer of cancellous bone tissue (the diploë). In adults, the bones of the skull average 2 to 6 mm in thickness; the bones in the temporal region are usually the thinnest of the skull. The cranial bones form a smooth outer surface of the skull, but within the cranial vault are many bone protrusions and ridges. Contrecoup injuries and contusions far from the site of head impact occur as the brain strikes against uneven bone surfaces. After the first few months of life, the cranial bones begin to fuse, ultimately forming the rigid, nonexpendable cranial vault. The inner aspect of the skull is lined with the periosteal dura, which is a thick connective tissue layer that adheres closely to the bone surface. The inner meningeal layer of the dura is the outermost covering of the brain. This dural membrane reflects back on itself to make folds within the cranial space. These folds serve to protect and compartmentalize different components of the brain. The midline falx cerebri separates the two cerebral hemispheres from each other. The tentorium cerebelli partitions the cerebellum and brainstem from the cerebral hemispheres. The U-shaped free margin of this dural fold is important in the pathology of the transtentorial herniation syndromes. Within the margins of the dural reflections, the two dural layers separate to form large dural venous sinuses. Injury to the dural sinuses is associated with significant morbidity and mortality because of the potential for uncontrolled hemorrhage.

Brain and Cerebrospinal Fluid

The brain is a semisolid structure that weighs approximately 1400 g (3 lb) and occupies approximately 80% of the cranial vault, with the remaining space occupied primarily by vasculature

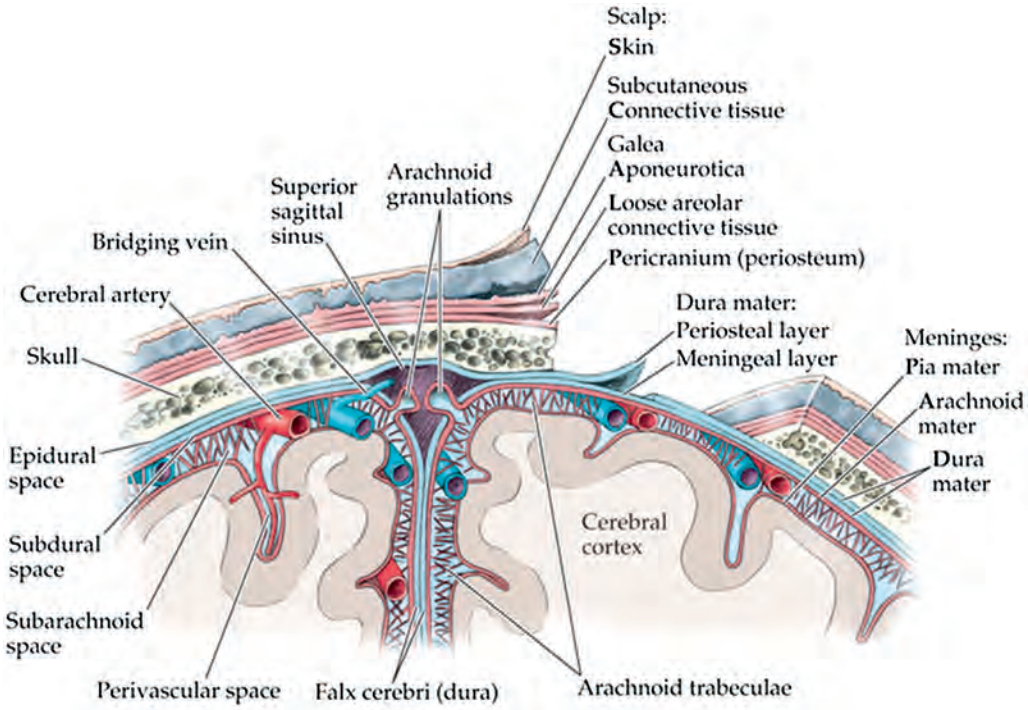


Fig. 34.1. Layers of the soft tissues, skull, and meninges. The dermis is the outermost layer and is among the thickest layers of skin on the body. The underlying subcutaneous tissue contains the hair follicles and rich blood supply of the scalp. The galea, made of tough fascial tissue, contains the occipitofrontalis and temporoparietalis muscles, which move the scalp backward and forward, elevate the eyebrows, and wrinkle the forehead. Under the galea is a loose areolar tissue layer. The deepest layer of the scalp, the pericranium, is firmly adhered to the skull. (From Blumenfeld H: Neuroanatomy through clinical cases, Sunderland, 2002, Sinauer Associates, Incorporated.)

BOX 34.1

Definition of Mild Traumatic Brain Injury

According to the American Congress of Rehabilitation Medicine, a person with mild traumatic brain injury (MTBI) is a patient with a GCS of 13–15 who has had a traumatically induced physiologic disruption of brain function, as manifested by at least one of the following:

1. Any period of loss of consciousness less than 30 min
2. Any loss of memory for events immediately before or after the accident (posttraumatic amnesia should last <24 hr)
3. Any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused)
4. Focal neurologic deficit(s) that may or may not be transient

and cerebrospinal fluid. The brain is covered by three distinct membranes—the meningeal dura, arachnoid layer, and pia (Fig. 34.2). The location of traumatic hematomas relative to these membranes defines the pathologic condition and determines the consequences of the injury.

The brain is suspended in the cerebrospinal fluid (CSF), which provides some physical buffering for the brain during trauma. CSF is produced by the choroid plexus, located primarily in the lateral ventricles of the brain. CSF passes from the ventricular system into the subarachnoid space that surrounds the brain and spinal cord. The normal pressure exerted by the CSF is 65 to 195 mm H_2O or 5 to 15 mm Hg.

The blood-brain barrier (BBB) maintains the microenvironment of the brain tissue and CSF. Extracellular ion and neurotransmitter concentrations are regulated by movement across this barrier. When the BBB is intact, the ability of neuroactive drugs

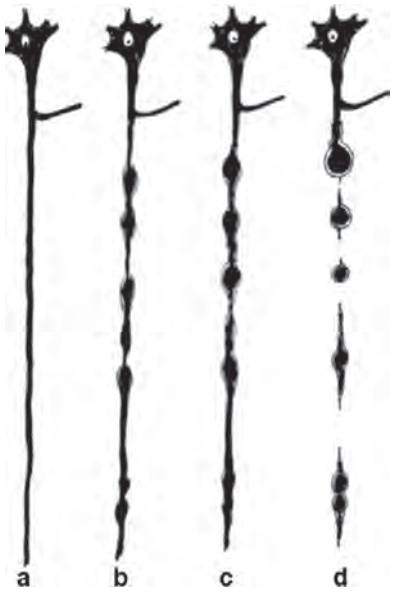


Fig. 34.2. Diffuse axonal injury (DAI), otherwise known as traumatic axonal injury (TAI), is characterized by axonal stretching leading to axolemmal disruption, ionic flux, neurofilament compaction, and microtubule disassembly, resulting in axonal swelling and disconnection. Axonal swelling and disconnection can lead to axon death. **a,** Normal neuron, **b, c,** Axon reaction to increasing stretch. **d,** Retraction balls have formed, and aggregates of axonal material lie along the course of the axon. (From Peerless SJ, Rewcastle NB: Shear injuries of the brain. CMAJ 96:577–582, 1967.)

to penetrate into the brain tissue usually depends on their lipid solubility. However, the biomechanics of a brain injury or posttraumatic cerebral edema can cause a disruption of the BBB for up to several hours after the insult. Prolonged disruption of the BBB further contributes to the development of posttraumatic vasogenic cerebral edema and higher maximum intracranial pressure.[9]

Cerebral Hemodynamics and Increased Intracranial Pressure

The brain has an extremely high metabolic rate, using approximately 20% of the entire oxygen consumed by the body and requiring approximately 15% of the total cardiac output. In the normal brain, cerebral blood flow (CBF) is maintained at constant levels. Optimal regional CBF is maintained by the ability of the cerebral vessels to alter their diameter in response to changing physiologic conditions. The responses of the cerebral vasculature to changing physiologic conditions protect the brain by increasing the delivery of oxygen to tissue, enhancing the removal of metabolic end products, and allowing nearly instantaneous adjustments to meet changing metabolic demands. Hypertension, alkalosis, and hypocarbia promote cerebral vasoconstriction, whereas hypotension, acidosis, and hypercarbia cause cerebral vasodilation.

Cerebral vasoactivity is also very sensitive to changes in the partial pressures of carbon dioxide and oxygen (P_{CO_2} and P_{O_2}, respectively). The response to changes in P_{CO_2} is nearly linear between P_{CO_2} values of 20 and 60 mm Hg. In this range, lowering P_{CO_2} by as little as 1 mm Hg decreases the diameter of cerebral vessels by 2% to 3%, corresponding to an overall change in CBF of 1.1 mL/100 g of tissue/min. This is the physiologic rationale for intentional hyperventilation in the setting of rapid and marked increases in intracranial pressure (ICP). Hyperventilation causes P_{CO_2} to fall, resulting in cerebral vasoconstriction, but this is no longer recommended as a mechanism for reducing ICP. The cerebral vessels also respond to changes in P_{O_2}. As P_{O_2} declines, cerebral vessels dilate to ensure adequate oxygen delivery to brain tissue. When brain injury occurs, increased CBF, vascular dilation, and a disrupted BBB promote vasogenic edema and can further increase ICP.[9] Thus, avoiding or reversing hypoxia is essential in managing the brain-injured patient.

CBF also depends on the cerebral perfusion pressure (CPP), which is the pressure gradient across the brain. CBF remains fairly constant when CPP is 50 to 160 mm Hg. This is referred to as autoregulation and occurs with a mean arterial pressure (MAP) of 60 to 150 mm Hg. The determinants of CPP are MAP and the resistance to CBF produced by the mean systemic venous pressure and ICP. Because ICP is higher than mean systemic venous pressure, ICP effects predominate, and CPP can be approximated as follows:

$$CPP = MAP - ICP$$

If CPP falls below 40 mm Hg, autoregulation is lost and CBF declines, resulting in tissue ischemia and altered cerebral metabolism. Avoidance of hypotension or elevation in ICP in the head-injured patient helps ensure that CPP can be maintained.

The recommended target CPP value for improved outcomes is between 60 and 70 mm Hg. Whether 60 or 70 mm Hg is the minimum optimal CPP threshold is unclear and may depend on the patient's autoregulatory status.[10]

Increased Intracranial Pressure

Increased ICP is defined as CSF pressure greater than 15 mm Hg (or 195 mm H_2O) and is a frequent consequence of a severe TBI. Initially, as ICP increases as a result of a traumatic mass lesion or edema, CSF is displaced from the cranial vault to the spinal canal, offsetting the increased blood or brain volume. When this compensatory mechanism is overwhelmed, the elastic properties of the brain substance allow tissue compression to provide buffering for the increasing pressure. Depending on the location and rate of mass expansion and edema formation, the intracranial compensatory mechanisms can accommodate an increased volume of 50 to 100 mL. Beyond that, even small changes in intracranial relationships, such as from vasodilation, CSF obstruction, or areas of focal edema, may increase ICP. If ICP increases to the point at which CPP is compromised, vasoparalysis occurs and autoregulation is lost. The CBF then depends directly on the systemic MAP. With the loss of autoregulation, massive cerebral vasodilation occurs. Systemic pressure is transmitted to the capillaries, contribute to vasogenic edema, and further increase ICP.

ICP above 22 mm Hg is associated with increased mortality and warrants treatment.[10] Methods to reduce elevated ICP include use of osmotic and diuretic agents and CSF drainage. Simple techniques to reduce ICP include head of bed elevation to 30 degrees and keeping the neck in a neutral position.[11] Therapeutic hyperventilation, once almost universally used, is potentially harmful and is now used only in as a temporizing measure for a select group of patients for whom other measures are not available or have failed. If ICP is not controlled, herniation will occur, resulting in brainstem compression and cardiorespiratory arrest.

Cushing's Reflex

Progressive hypertension associated with bradycardia and diminished respiratory effort is a specific response to acute, potentially lethal increases in ICP. This response is called Cushing's reflex or Cushing's phenomenon, and its occurrence indicates that the ICP has reached life-threatening levels. However, only one-third of cases of life-threatening increased ICP manifest the full triad of hypertension, bradycardia, and respiratory irregularity.

Definitions and Patterns of Injury

Traumatic Brain Injuries: Severe, Moderate, and Mild

Traditionally, TBI has been separated into the three broad categories of mild, moderate, and severe, primarily based on the GCS score following resuscitation and stabilization. Severe brain injury is defined as a TBI with a postresuscitation GCS score of 8 or lower, moderate as a GCS score of 9 to 12, and mild as a GCS score of 13 to 15. Overall, 80% of patients sustain MTBIs, 10% moderate brain injuries, and 10% severe brain injuries (Table 34.1).[1] The term *concussion* is commonly used to describe MTBIs in sports.

The degree of brain injury following a MTBI or concussion also depends on the primary mechanism and magnitude of injury, secondary insults, and the patient's genetic and molecular response.[12] Primary damage is caused by the initial impact or force that although not usually as evident as severe TBI, may lead to smaller contusions, hematomas, axonal damage, and microvascular injury. Following a MTBI without evidence of lesions on computed tomography (CT) scans, there is a decrease in cerebral flow over the ensuing hours and days after injury,[13] as well as cortical neurometabolic abnormalities.[14,15] Traumatic axonal injury (TAI) is also an important determinant of outcome.[16-18]

Increasing evidence has suggested that a single MTBI can produce long-term gray and white matter atrophy, precipitate or accelerate age-related neurodegeneration, and increase the risk of developing Alzheimer's, Parkinson's, and motor neuron disease.[19,20] In addition, repeated episodes of MTBI can provoke the development of chronic traumatic encephalopathy (CTE), a term used to describe clinical changes in cognition, mood, personality,

TABLE 34.1

Traumatic Brain Injury (TBI) as a Portion of All Injuries and Emergency Department (ED) Visits

		ALL INJURIES		TRAUMATIC BRAIN INJURIES		
PARAMETER	ALL VISITS	NO.	PERCENT OF ALL VISITS	NO.	PERCENT OF ALL INJURIES	PERCENT OF ALL VISITS
ED visits[a]	96,839,411	28,697,028	29.6	1,364,797	4.8	1.4
Hospitalizations[b]	36,693,646	1,826,548	5.0	275,146	15.1	0.7
Deaths	2,432,714	169,055	6.9	51,538[c]	30.5	2.1
Total	135,965,771	30,692,631	22.6	1,691,481	5.5	1.2

[a]Persons who were hospitalized, died, or were transferred to another facility were excluded.
[b]In-hospital deaths and patients who transferred from another hospital were excluded.
[c]28 mortality records (from 2002-2006) were omitted because of missing age information.
Adapted from Faul M XL, Wald MM, Coronado VG: Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002-2006, Atlanta, 2010, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, pp 1–74.

behavior, and/or movement occurring years following concussion.[21,22] CTE has recently been found to occur after other causes of repeated head trauma, suggesting that any repeated blows to the head, such as those that occur in American football, hockey, soccer, and professional wrestling, in military personnel, and in victims of physical abuse, can also lead to neurodegenerative changes.[20,22,23]

Direct and Indirect Injuries

Direct Injury. Direct head trauma occurs when the head is struck, or its motion suddenly arrest by, an object. The resulting damage to the skull and brain depends on the consistency, mass, surface area, and velocity of the object striking the head. Direct injury can also be caused by compression of the head. External signs of trauma are frequently noted at the site of application of the impact or compression force. The skull initially bends inward at the point of contact. If the force is sufficient, a skull fracture can occur. The cranium absorbs some of the applied energy, whereas some energy is transmitted to the brain by shock waves that travel distant to the site of impact or compression. With sufficient and prolonged application of compression force, the ability of the skull to absorb the force is overcome, and multiple linear skull fractures occur. These resulting fractures can be depressed if a high-energy rapid compression force is applied to a small area of the skull. The extent of direct injury depends on the vasoelastic properties of the underlying region of brain tissue, duration of the force applied, magnitude of the force reaching the brain tissue, and surface area of the brain that is affected.

Indirect Injury. In indirect brain injury, the cranial contents are set into motion by forces other than the direct contact of the skull with an object. A common example is an acceleration-deceleration injury. No direct mechanical impact is sustained, but the cranial contents are set into vigorous motion. As the bridging subdural vessels are strained, subdural hematomas (SDHs) may result.

Differential acceleration of the cranial contents occurs, depending on the physical characteristics of the brain region. As one brain region slides past another, shear and strain occur. These movements result in diffuse injuries, such as a concussion or TAI. Additional injury occurs as the movement of the intracranial contents is abruptly arrested, and the brain strikes the skull or a dural structure. Contrecoup contusions are an example of this injury. In penetrating injury, the object produces pressure waves that can strike structures distal to the path of the missile.

Neurochemical Cascade

There can be secondary insults mediated through physiologic events, which can decrease the supply of oxygen and energy to the brain tissue, or a cascade of cytotoxic events, mediated by many molecular and cellular processes. These events include activation of inflammatory responses, imbalances of ion concentrations (eg, potassium, calcium), an increase in the presence of excitatory amino acids (eg, glutamate), dysregulation of neurotransmitter synthesis and release, imbalance in mitochondrial functions and energy metabolism, and production of free radicals.[24]

Penetrating Head Trauma

The morbidity and mortality from missile injuries to the head depend on the intracranial path, speed of entry, and size and type of the penetrating object. Projectiles that cross the midline or geographic center of the brain, pass through the ventricles, or come to rest in the posterior fossa are associated with extremely high mortality. High-velocity wounds are associated with greater mortality than low-velocity injuries. Large missiles or missiles that fragment within the cranial vault are usually fatal. The design of the bullet and its fragmentation potential (capacity to deform or fragment) also contribute to final tissue destruction and patients' morbidity and mortality.

Tangential wounds are caused by an impact that occurs at an oblique angle to the skull. If the missile has high velocity but low energy, it can travel around the skull, under the scalp, without passing through the skull. Intracranial damage, primarily cortical contusions, can occur at the initial site of impact secondary to pressure waves generated by the impact. Although many patients with tangential GSWs have a GCS score of 15 on presentation, up to 24% also have intracranial hemorrhage, and 16% sustain skull fractures.[25]

Most civilian penetrating brain injuries are penetrating missile wounds, which are produced by moderate- to high-velocity projectiles discharged at close range. The penetrating object may travel through the entire skull, bounce off the opposite inner table of the skull and ricochet within the brain, or stop somewhere within the cranial cavity.

As the bullet passes through the brain, a tissue cavity as much as 10 times the diameter of the missile is created. A percussion shock wave is also created, lasting 2 milliseconds but causing little tissue destruction. The wounding capacity of a firearm is related to the kinetic energy of its missile on impact and how much energy is dissipated. Low-velocity missiles tend to be deflected by

intracranial structures. The final track is therefore erratic and occasionally bears no relation to the exit or entrance site of the missile.

Scalp Wounds

The large blood vessels of the scalp do not fully constrict if they are lacerated and can be the source of substantial blood loss. Because the areolar attachments to the rest of the scalp are loose, scalp avulsions frequently occur through this layer. Subgaleal hematomas can become large because blood easily dissects through the loose areolar tissue. Hemostasis may be difficult to achieve, and blood loss may be significant to the point of causing hemodynamic compromise.

Skull Fractures

Skull fractures are local injuries caused by direct impact to the skull. Although the presence of a skull fracture does not always indicate underlying brain injury, the force required to fracture the skull is substantial, and all patients with skull fractures must be carefully evaluated to ensure that no additional injury is present. The pattern, extent, and type of skull fracture depend on the force of the impact applied and ratio of the impact force to the impact area. Clinically significant features of skull fractures include intracranial air, association with an overlying scalp laceration (open skull fracture), depression below the level of the skull's inner table, and location over a major dural venous sinus or middle meningeal artery.

Linear Fractures

A linear skull fracture is a single fracture that goes through the entire thickness of the skull. Linear skull fractures are clinically important if they cross the middle meningeal groove or major venous dural sinuses; they can disrupt these vascular structures and cause the formation of epidural hematomas (EDHs). Most other linear skull fractures are not clinically significant.

Sutural diastasis is the traumatic disruption of a cranial suture. In adults, sutural diastasis often involves the coronal or lambdoid sutures. Sutural diastasis usually occurs when a linear fracture extends into the suture line, and it is rare after sutures have undergone bone fusion. Comminuted skull fractures, which are multiple linear fractures that radiate from the impact site, usually suggest a more severe blow to the head than that producing a single linear fracture. A linear vault fracture substantially increases the risk of intracranial injury.

Depressed Fractures

Depressed skull fractures are usually caused by direct-impact injury with small blunt objects, such as a hammer or baseball bat. Most depressed skull fractures occur over the parietal or temporal regions. These fractures are clinically important because they predispose to significant underlying brain injury and to complications of head trauma, such as infection and seizures.

Basilar Fractures

Basilar fractures are linear fractures at the base of the skull, usually occurring through the temporal bone. Patients with basilar fractures are at risk for extra-axial hematomas because of the proximity of the fracture to the middle cerebral artery. Dural tears, resulting from a basilar skull fracture, may produce a communication among the subarachnoid space, paranasal sinuses, and middle ear. This offers a route for the introduction of infection into the cranial cavity and is suggested by a CSF leak. These fractures are the result of considerable impact force and are highly associated with an underlying brain injury.

Extra-Axial and Intra-Axial Intracranial Injuries

Extra-axial refers to injury or bleeding that occurs within the skull but outside of the brain tissue. Intra-axial injury or bleeding occurs within the brain tissue itself. Extra-axial intracranial lesions include epidural hematoma, subdural hematoma, traumatic subarachnoid hemorrhage, and subdural hygroma. Intra-axial intracranial lesions include traumatic axonal injury, cerebral and cerebellar contusions, and cerebral and cerebellar hematomas.

Extra-Axial Injury

Epidural Hematoma. An EDH is bleeding that occurs between the inner table of the skull and dura. Most EDHs result from a direct-impact injury that causes a forceful deformity of the skull. Often, a fracture occurs across the middle meningeal artery, or vein, or a dural sinus. The temporoparietal region is the most likely site for an EDH. The high arterial pressure of the bleeding vessel dissects the dura away from the skull, permitting hematoma formation.

EDH is primarily a disease of the young and accounts for up to 5% of all patients who have experienced TBI.[26] EDHs are rare in older adults and children younger than 2 years because of the close attachment of the dura to the skull in both patient populations.

Subdural Hematoma. A SDH is a hemorrhage that occurs between the dura and brain and is usually caused by acceleration-deceleration injuries. SDH occurs most commonly in patients with brain atrophy, such as alcoholic or older patients, because bridging vessels traverse greater distances than in patients with no atrophy. As a result, the vessels are more likely to rupture with rapid movement of the head. Once they are ruptured, blood can fill the potential space between the dura and arachnoid. SDH is much more common than EDH, occurring in up to 30% of patients with severe head trauma. The slow bleeding of venous structures delays the development of clinical signs and symptoms. As a result, the hematoma compresses the underlying brain tissue for prolonged periods and can cause significant tissue ischemia and damage. Approximately 20% of patients will present with a bilateral SDH. The prognosis of SDH does not entirely depend on the size of the hematoma but rather on the degree of brain injury caused by the pressure of the expanding hematoma on underlying tissue or by other intracranial injuries. Mortality is highest in older adults, patients who have a GCS score of 8 or less, and those with signs of acute herniation syndrome on initial ED presentation. Posterior fossa SDHs make up less than 1% of all reported SDHs. They are caused by occipital trauma that tears bridging vessels or venous sinuses and have a very poor prognosis.

Traumatic Subarachnoid Hemorrhage. A traumatic subarachnoid hemorrhage (SAH) is blood within the CSF and meningeal intima and probably results from tears of small subarachnoid vessels. Traumatic SAH is detected on the first CT scan in up to one-third of patients with severe TBI and ultimately is identified in almost 50% of patients with severe head trauma. It is therefore the most common CT scan abnormality seen after head trauma. Data from the National Traumatic Coma Data Bank have demonstrated a 60% unfavorable outcome in severely brain-injured patients when traumatic SAH is present compared with a 30% unfavorable outcome when it is not present. Traumatic SAH also is considered a risk factor for early mortality.[27]

Subdural Hygroma. A subdural hygroma (SDHG) is a collection of clear, xanthochromic blood-tinged fluid in the dural space. The pathogenesis of an SDHG is not certain. It may result from a tear in the arachnoid that permits CSF to escape into the dural space or effusions from injured vessels through areas of abnormal permeability in the meninges or in the underlying parenchyma. They may accumulate immediately after trauma or in a delayed manner.

Intra-Axial Injury

Diffuse Axonal Injury and Traumatic Axonal Injury. Prolonged traumatic coma not caused by mass lesions or ischemic insult is thought to result from diffuse axonal injury (DAI).[28] Although the term *diffuse axonal injury* has been widely adopted, the distribution of axonal injury is usually not diffuse but multifocal. Axonal injury occurs on a spectrum, with milder cases primarily localized. Furthermore, DAI has been used to describe axonal injury from nontraumatic causes in other neurologic conditions. Accordingly, the term *traumatic axonal injury* is preferred, particularly in milder cases. In more severe cases, when the axonal injury is more diffuse, the term *diffuse traumatic axonal injury* can be used.

In TAI, axons sustain a primary insult in which they are torn (axotomy) or stretched, and secondary insults lead to axonal swelling and disconnection and can lead to axon death (see Fig. 34.2).[29] Moreover, acute uncoupling of cerebral blood flow, metabolism, and apoptosis are thought to be the important factors linked to axonal cell death after TAI.[13,30]

Most patients with TAI present with persistent traumatic coma that begins immediately at the time of trauma; however, some patients may recover consciousness briefly before lapsing into prolonged coma. Because diagnostic studies cannot predict the extent of the axonal damage, the severity of the injury is determined by the clinical course. Clinical grades of diffuse TAI have been based on length of coma: (1) grade 1 (mild)—ccoma for 6 to 24 hours; (2) grade II (moderate)—coma for longer than 24 hours but not decerebrate; (3) grade III (severe)—coma for longer than 24 hours and decerebrate or flaccid. Currently, no early clinical or biomarker predictor exists that differentiates patients with mild, moderate, or severe diffuse TAI. Experimental laboratory data have indicated that neurons can partially repair and regenerate damaged axons.[29,31]

Cerebral Contusions. Contusions are bruises on the surface of the brain, usually caused by impact injury. Most often, contusions occur at the poles and inferior surfaces of the frontal and temporal lobes, where the brain comes into contact with bone protuberances in the base of the skull. If the contusion occurs on the same side as the impact injury, it is a coup injury; if it occurs on the opposite side, the contusion is a contrecoup injury. Contusions also often develop in the brain tissue that underlies a depressed skull fracture. Multiple areas of contused tissue may be produced with a single impact, often in association with other intracranial injuries. Contusions are produced when parenchymal blood vessels are damaged, resulting in scattered areas of petechial hemorrhage and subsequent edema. Contusions develop in the gray matter on the surface of the brain and taper into the white matter. Often, subarachnoid blood is found overlying the involved gyrus. With time, the associated hemorrhages and edema of a contusion can become widespread and serve as a nidus for hemorrhage or swelling, thus producing a local mass effect. Compression of the underlying tissue can cause local areas of ischemia, and tissue infarction is possible if the compression is significant and unrelieved. Eventually, these ischemic areas become necrotic, and cystic cavities form within them.

Intracerebral Hematoma. Intracerebral hematomas (ICHs) are formed deep within the brain tissue and are usually caused by shearing or tensile forces that mechanically stretch and tear deep small-caliber arterioles as the brain is propelled against irregular surfaces in the cranial vault. Resulting small petechial hemorrhages coalesce to form ICHs, with 85% in the frontal and temporal lobes. An ICH is often found in the presence of extra-axial hematomas and, in many patients multiple ICHs are present. Isolated ICHs may be detected in as many as 12% of all patients with severe head trauma.

Intracerebellar Hematoma. Primary traumatic intracerebellar hematomas are rare but can occur after a direct blow to the occipital area. Often, these patients have an associated skull fracture, posterior fossa EDH or SDH, or supratentorial contrecoup hematomas and contusions.

Primary and Secondary Brain Injuries

The acute clinical picture of the patient with TBI is dynamic and represents the sum of primary and secondary injury.

Primary Brain Injury

A primary brain injury is mechanical damage that occurs at the time of head trauma and includes brain lacerations, hemorrhages, contusions, and tissue avulsions. On the microscopic level, primary injury causes permanent mechanical cellular disruption and microvascular injury. Other than the evacuation of traumatic hematomas, no specific intervention exists to repair or reverse primary brain injury.

Following the primary injury, there is a cascade of events at the cellular and molecular level that continues for hours to days that contribute further to the brain injury. This secondary brain injury results from intracellular and extracellular derangements that lead to alterations in cell function and propagation of injury through processes such as depolarization, excitotoxicity, disruption of calcium homeostasis, free radical generation, BBB disruption, ischemic injury, edema formation, and intracranial hypertension.[32] Animal and human studies have revealed a complicated series of neurochemical, neuroanatomic, and neurophysiologic reactions after brain injury (Fig. 34.3). The cell has some compensatory mechanisms to protect itself from widespread damage, such as endogenous free radical scavengers and antioxidants. However, these systems are quickly overwhelmed, and the functional and structural integrity of the cell is threatened. Investigational agents aimed at specific steps in the destructive processes have suggested that some aspects of secondary brain injury may be reversed or modified. Multiple ongoing brain injury trials have been performed with numerous investigational therapeutic interventions; to date, none have proved useful in the clinical setting.[32,33]

Secondary Systemic Insults

The final neurologic outcome after head trauma is influenced by the extent and degree of secondary brain injury. In turn, the amount of secondary brain injury depends on certain premorbid and comorbid conditions, such as the age of the patient and trauma-related systemic events.[34] A primary goal in the emergency care of a head trauma patient is prevention or reduction of systemic conditions that are known to worsen outcome after TBI, such as hypotension, hypoxia, anemia, and hyperpyrexia.[34,35]

Hypotension. Defined as SBP less than 90 mm Hg, this has been found to have negative impact on severe brain injury outcome. Systemic hypotension reduces cerebral perfusion, thereby potentiating ischemia and infarction. Hypotension is

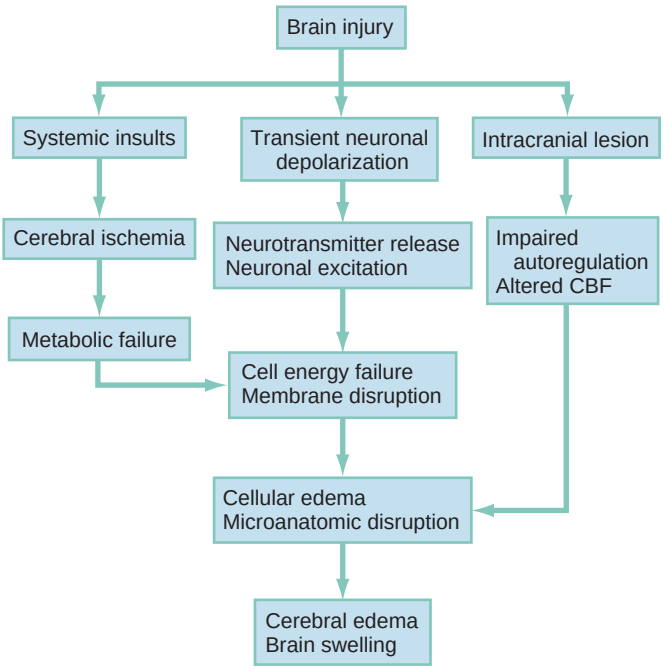


Fig. 34.3. Contributing events in the pathophysiology of secondary brain injury. *CBF,* Cerebral blood flow.

associated with a near-doubling of the mortality from TBI and worse outcomes for patients who survive.[10]

Hypoxia. Defined as a Po_2 less than 60 mm Hg, this occurs often in the brain-injured patient. Causes include the following: (1) transient or prolonged apnea caused by brainstem compression or injury after the traumatic event; (2) partial airway obstruction caused by blood, vomitus, or other debris in the airway of the traumatized patient; (3) injury to the chest wall that interferes with normal respiratory excursion; (4) pulmonary injury that reduces effective oxygenation; and (5) ineffective airway management, such as the inability to bag-valve-mask or intubate the patient in an effective or timely manner. When hypoxia is documented, the overall mortality from severe TBI may double.[10] Hyperoxia also is associated with worse outcome after traumatic brain injury.[36,37]

Hypocarbia and Hypercarbia. Hypocarbia ($Paco_2 \leq$ 35 mm Hg) and hypercarbia ($Paco_2 \geq 46$ mm Hg) are each associated with increased mortality following TBI. Hypercarbia causes cerebral vasodilation, with a resultant increase in cerebral edema and ICP, and thus is associated with a worsened neurologic outcome.[38,39] Hyperventilation to induce hypocarbia has been discredited for patients with elevated ICP; current patient management emphasizes maintenance of normal to slightly reduced $Paco_2$ levels.

Anemia. Anemia caused by blood loss can be detrimental to the head-injured patient by reducing the oxygen-carrying capacity of the blood, thus reducing the amount of necessary substrate delivered to the injured brain tissue. When anemia (hematocrit, 30%) occurs in patients with severe brain injury, the mortality rate increases.[34] Other potential reversible causes of systemic insult in brain injury include hypercarbia, coagulopathy, and seizures.[34]

Hyperpyrexia. Hyperpyrexia (core body temperature > 38.5° C [101.3° F]) is also correlated with worse outcomes after TBI, its magnitude and its duration seem to contribute. The exact mechanism whereby it causes damage likely involves increased metabolism in injured brain areas, thus recruiting blood flow, with a resultant increase in ICP.[34]

Altered Levels of Consciousness

Consciousness is the state of awareness of the self and environment, and it requires intact functioning of the cerebral cortices and reticular activating system (RAS) of the brainstem. A patient who has sustained TBI typically has an altered level of consciousness (LOC), but reversible conditions that can alter mental status, such as hypoxia, hypotension, or hypoglycemia, should be corrected as they are identified. Head trauma patients may be hypoxic from injury to respiratory centers or from concomitant pulmonary injury. Hypotension from other associated injuries can compromise CBF and affect consciousness. Global suppression may result from an intoxicant consumed before the injury, hypoglycemia, posttraumatic seizure (PTS), or postictal period after a seizure from any cause. With increasing ICP from brain swelling or an expanding mass lesion, brainstem compression and subsequent RAS compression can occur.

Cerebral Herniation Syndromes

Cerebral herniation occurs when increasing cranial volume and ICP overwhelm the natural compensatory capacities of the central nervous system (CNS; Fig. 34.4). When the signs of herniation syndrome are present, however, mortality approaches 100% without rapid implementation of temporizing emergency measures and definitive neurosurgical therapy.

Uncal Herniation

The most common clinically significant traumatic herniation syndrome is uncal herniation, a form of transtentorial herniation. Uncal herniation is often associated with traumatic extra-axial hematomas in the lateral middle fossa or the temporal lobe. As compression of the uncus begins, the third cranial nerve (CN) is compressed; anisocoria, ptosis, impaired extraocular movements, and a sluggish pupillary light reflex develop on the side ipsilateral to the expanding mass lesion. As the herniation progresses, compression of the ipsilateral oculomotor nerve eventually causes ipsilateral pupillary dilation and nonreactivity.

Initially in the uncal herniation process, motor examination findings can be normal, but contralateral Babinski responses develop early. Contralateral hemiparesis develops as the ipsilateral peduncle is compressed against the tentorium. With continued progression of the herniation, bilateral decerebrate posturing eventually occurs; decorticate posturing is not always seen with the uncal herniation syndrome.

In a certain percentage of TBI patients, the contralateral cerebral peduncle is forced against the opposite edge of the tentorial hiatus. Hemiparesis is then detected ipsilateral to the dilated pupil and mass lesion. This is termed *Kernohan's notch syndrome* and causes false-localizing motor findings. As uncal herniation progresses, direct brainstem compression causes additional alterations in the LOC, respiratory pattern, and cardiovascular system. Mental status changes may initially be subtle, such as agitation, restlessness, or confusion, but soon lethargy occurs, with progression to frank coma. The patient's respiratory pattern may initially be normal, followed by sustained hyperventilation. With continued brainstem compression, an ataxic respiratory pattern develops. The patient's hemodynamic status may change, with rapid fluctuations in blood pressure and cardiac conduction. Herniation that is uncontrolled progresses rapidly to brainstem failure, cardiovascular collapse, and death.

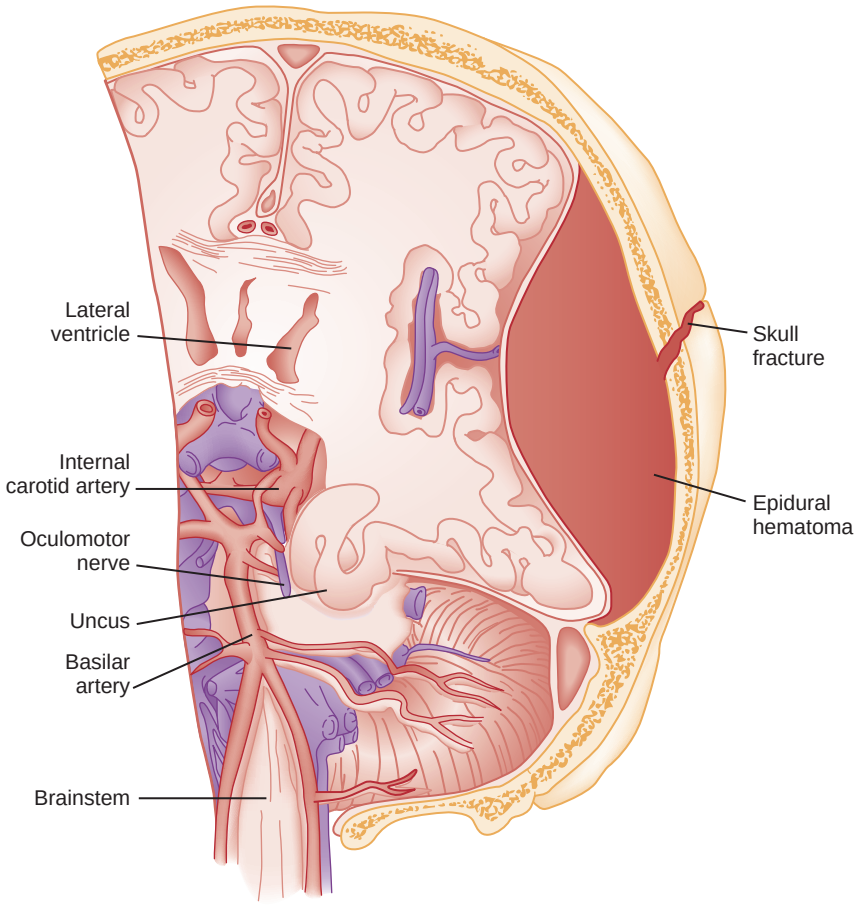


Fig. 34.4. Anterior view of transtentorial herniation caused by large epidural hematoma. A skull fracture overlies the hematoma. (From Rockswold GL: Head injury. In Tintinalli JE, et al editors: Emergency medicine, New York, 1992, McGraw-Hill, p 915.)

Central Transtentorial Herniation

Less common than uncal transtentorial herniation, the central transtentorial herniation is demonstrated by rostrocaudal neurologic deterioration caused by an expanding lesion at the vertex or frontal or occipital pole of the brain. Clinical deterioration occurs as bilateral central pressure is exerted on the brain from above. The initial clinical manifestation may be a subtle change in mental status or decreased LOC, bilateral motor weakness, and pinpoint pupils (2 mm). Light reflexes are still present but are often difficult to detect. Muscle tone is increased bilaterally, and bilateral Babinski's signs may be present. As central herniation progresses, both pupils become midpoint and lose light responsiveness. Respiratory patterns are affected, and sustained hyperventilation may occur. Motor tone increases. Decorticate posturing is elicited by noxious stimuli. This progresses to bilateral decorticate and then spontaneous decerebrate posturing. Respiratory patterns initially include yawns and sighs and progress to sustained tachypnea, followed by shallow slow and irregular breaths immediately before respiratory arrest.

Cerebellotonsillar Herniation

Cerebellotonsillar herniation occurs when the cerebellar tonsils herniate downward through the foramen magnum. This is usually the result of a cerebellar mass or large central vertex mass causing the rapid displacement of the entire brainstem. Clinically, patients demonstrate sudden respiratory and cardiovascular collapse as the medulla is compressed. Pinpoint pupils are noted. Flaccid quadriplegia is the most common motor presentation because of bilateral compression of the corticospinal tracts. Although mortality is high, timely neurointensive care and neurosurgical intervention results in recovery to a minimal or moderate level of disability in over 50% of patients.

Upward Transtentorial Herniation

Upward transtentorial herniation occasionally occurs as a result of an expanding posterior fossa lesion. The LOC declines rapidly. These patients may have pinpoint pupils from compression of the pons. Downward conjugate gaze is accompanied by the absence of vertical eye movements.

MODERATE AND SEVERE TRAUMATIC BRAIN INJURY

Clinical Features and History

Although the history may be delayed by the need for emergent resuscitation and stabilization, details regarding the mechanism of injury, circumstances surrounding the injury, and any concomitant drug or alcohol use should be solicited. The patient, prehospital providers, or any witnesses should be queried as to loss of consciousness or seizure activity. The patient should be asked about recall of the incident and the time periods before and after and about any symptoms, including severe headache, nausea, vomiting, or amnesia. The past medical history should be obtained, with particular attention to coagulopathies such as hemophilia. In

addition, the patient's medications, particularly anticoagulant or antiplatelet agents, should be determined. If there has been a change in the patient's GCS score, this should be noted.

The patient's current LOC, as well as that immediately before and after the injury and at the arrival of first responders, should be determined. Worsening mental status or deteriorating GCS scores since the injury indicate the presence of moderate to severe injury. Witnessed seizures or apnea should be reported. If the patient is now awake but was unconscious at some point, it should be determined if the patient has returned to baseline mental status.

Common Presentations of Specific Lesions

Epidural Hematoma

The classic presentation of an EDH is described as head trauma producing a decreased LOC followed by a so-called lucid interval. Although the patient's consciousness is less decreased during the lucid interval, a completely normal mental status may not return before a second episode of decreased consciousness occurs. The lucid interval is not pathognomonic for an EDH and occurs in patients who sustain other expanding mass lesions. Approximately 47% of patients with EDHs present classically. The development of symptoms and signs of EDH is entirely dependent on how quickly the EDH is developing within the cranial vault. Patients with an EDH often complain of a severe headache, sleepiness, dizziness, nausea, and vomiting. A small EDH may remain asymptomatic, but this is rare.

If the EDH is rapidly detected and evacuated, the functional outcome is excellent. Because of their rapid formation, EDHs from arterial bleeding are usually detected within hours after injury and often earlier in children. EDHs that develop from a dural sinus tear develop more slowly, and clinical manifestations may be delayed, with resultant delays in detection.

A posterior fossa EDH is the result of direct occipital trauma resulting in a skull fracture that disrupts a venous sinus is the usual cause, and most patients have external evidence of occipital injury. Most patients become symptomatic within 24 hours after injury, with complaints of headache, nausea, vomiting, and nuchal rigidity. Most patients eventually have a decreased LOC.

Subdural Hematoma

The patient's clinical presentation depends on the amount of brain injury sustained at the time of trauma and the rate of SDH expansion. If the patient with an SDH was rendered unconscious at the time of trauma, the prognosis is poor; these patients often have concurrent TAI. The signs and symptoms after injury that produces an SDH are initially related to the other intracranial injuries that may have been sustained and then to the slow expansion of the SDH. SDHs are classified by the time to clinical presentation. Acute SDHs are symptomatic within 24 hours after trauma. Patients with acute SDHs often have a decreased LOC. Most patients with an SDH have a GCS score less than 8. Approximately 12% to 38% of patients will have a lucid period at some point in their presentation. The overall mortality of patients who have an SDH and require surgical intervention is 40% to 60%.

A chronic SDH becomes symptomatic 2 weeks or more after trauma. The signs and symptoms may be very subtle or nonspecific, but many patients demonstrate unilateral weakness or hemiparesis. Patients with unilateral chronic SDH have more frequent occurrence of hemiparesis than those with bilateral chronic SDH.[40] Most report an altered LOC, but some patients are unable to recall the trauma or describe only a minor injury. A chronic SDH may have initially been a small asymptomatic SDH that eventually expanded owing to a combination of recurrent hemorrhage and escape of plasma into the hematoma. At some point, a critical mass is reached, and the chronic SDH becomes symptomatic.

Clinical manifestations of posterior SDH vary but usually include nausea, vomiting, headache, and decreased LOC. Occasionally, CN palsies may be found, as well as nuchal rigidity, cerebellar signs and symptoms, and papilledema.

Traumatic Subarachnoid Hemorrhage

An increased incidence of skull fractures and contusions is found in patients with a traumatic SAH (tSAH) compared with patients with no tSAH. The amount of blood within the tSAH correlates directly with the outcome and inversely with the presenting GCS score. Patients may complain of headache and photophobia.

Subdural Hygroma

Clinically, an SDHG cannot be distinguished from other mass lesions. Often, patients have a decreased LOC or focal motor deficits. They may complain of headaches, nausea, and vomiting. The ICP can increase because of the mass effect, and signs of increased ICP may be present.

Traumatic Axonal Injury

The duration of loss of consciousness or coma following injury is directly related to the extent of axonal pathology in the brainstem.[28] Even with extensive axonal pathology in the white matter, there may be little or no loss of consciousness if the brainstem is relatively spared. Therefore, it appears that the distribution, rather than the overall extent, of axonal pathology is important in determining consciousness immediately following TBI.[41]

Cerebral Contusion

The clinical presentation of patients with contusions is frequently delayed. They may have sustained only a brief loss of consciousness, but the duration of posttraumatic confusion and obtundation may be prolonged. If contusions occur near the sensorimotor cortex, focal neurologic deficits may be present. Many patients with significant contusions make uneventful recoveries, but contusions may cause significant neurologic problems, including increased ICP, PTSs, and focal deficits.

Intracerebral Hematoma

The clinical effects of intracerebral hematomas depend on size and location and whether the bleeding is continuing. ICHs have been reported with all degrees of severity of head trauma. More than 50% of patients with ICH sustain loss of consciousness at the time of impact. The patient's subsequent LOC depends on the severity of the impact and coexisting lesions. Combined with contusions, other concurrent lesions, and subsequent perilesion edema, an ICH can produce substantial mass effects and precipitate a herniation syndrome (Fig. 34.5).

Traumatic Intracerebellar Hematoma

The clinical presentation of an isolated traumatic cerebellar hematoma is similar to that of other posterior lesions. When other traumatic lesions are present, the picture may be confusing.

Physical Examination

In the setting of head trauma and suspected brain injury, management should be guided by the principles of trauma resuscitation.

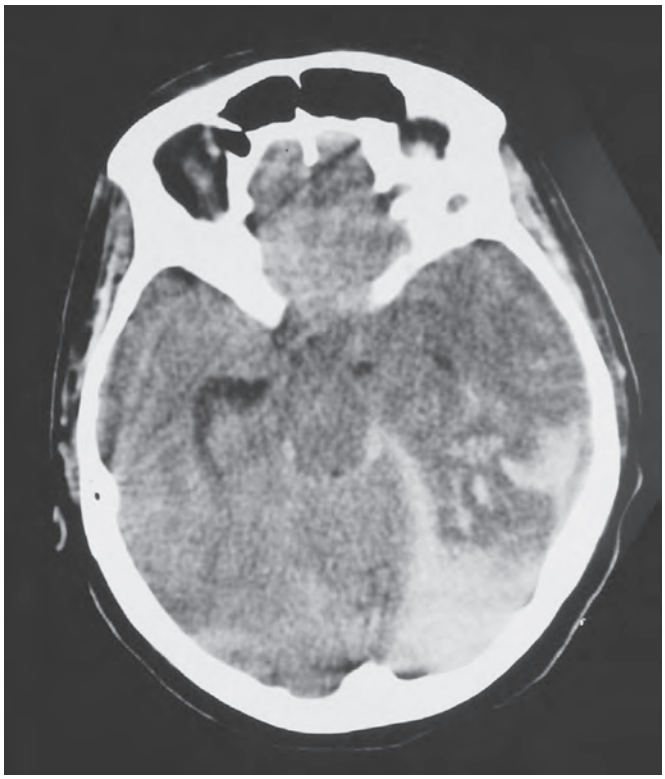


Fig. 34.5. Non–contrast-enhanced computed tomography (CT) scan of intracerebral hematoma and contusion in the left occipital region. The scan also shows layering of a tentorial subdural hematoma. Mass effect and early uncal herniation are visible as well.

A primary survey focusing on airway, breathing, and hemorrhage control should be performed expeditiously. After immediate life threats are adequately addressed, a secondary survey should evaluate for underlying head injury, brain injury, and neurologic compromise.

The head and neck should be carefully examined for external signs of trauma that may have also produced an underlying TBI. A scalp laceration, contusion, abrasion, or avulsion may overlie a depressed skull fracture. The clinical examination for a depressed skull fracture may be misleading. The mobility of the scalp can result in nonalignment of the fracture with an overlying scalp laceration. As a result, the skull underlying the laceration may be normal, with the depressed area several centimeters away. Scalp swelling may interfere with physical examination findings and hide any palpable bone defects. The signs and symptoms of a depressed skull fracture depend on the depth of depression of the free bone piece. About 25% of patients sustaining a depressed skull fracture report loss of consciousness. Neurologic deficits may be present, depending on the extent of underlying brain tissue injury.

Basilar skull fractures are often diagnosed by the clinical examination (Box 34.2), and the physical examination should evaluate for such signs as hemotympanum, periauricular or periorbital ecchymoses, and clear otorrhea or rhinorrhea. In the case of an impalement injury, the penetrating object should be left in place to be removed at surgery. Patients with basilar fractures are at risk for extra-axial hematomas because of the proximity of the fracture to the middle cerebral artery. Basilar fractures can compress and entrap the CNs that pass through the basal foramina, dislocate the bones of the auricular chain, and disrupt the otic canal or cavernous sinuses with subsequent injury to CNs III, IV, and V. Fractures of the sphenoid bone can disrupt the intracavernous internal carotid artery, creating the potential for the formation of pseudoaneurysms or carotid venous fistulae. The diagnosis of a basilar skull fracture is based on associated clinical signs and symptoms (see Box 34.2).

BOX 34.2

Clinical Characteristics of Basilar Skull Fractures

Blood in ear canal
Hemotympanum
Rhinorrhea
Otorrhea
Battle's sign (retroauricular hematoma)
Raccoon sign (periorbital ecchymosis)
Cranial nerve deficits
Facial paralysis
Decreased auditory acuity
Dizziness
Tinnitus
Nystagmus

The percentage of concurrent cervical spine injury in patients with severe head trauma ranges up to nearly 20%.[42] Often, other spinal regions are also injured. The neck should be evaluated for evidence of a cervical spine fracture. Carotid artery dissections caused by a hyperflexion-extension neck injury can occasionally be detected by auscultation of a carotid bruit. In these patients, a careful neurologic examination should assess for subtle asymmetry between the carotid arteries. Finally, all patients should undergo a thorough secondary evaluation after initial stabilization, evaluating for additional injuries, including an evaluation for spinal cord pathology.

Acute Neurologic Examination

General. The goals of the acute neurologic assessment of head trauma patients include detection of life-threatening injuries and identification of neurologic changes in the immediate posttrauma period. An accurate neurologic assessment in this period serves as a basis for comparison in subsequent examinations. An efficient neurologic examination in the emergency setting includes evaluation of mental status, GCS score, pupillary size and responsiveness, and motor strength and symmetry. If a formal GCS measure is not possible or is difficult because of comorbid confounders, the patient's mental status should be described in as much detail as possible. Declining mental status after head trauma suggests increasing ICP from an expanding mass lesion or worsening cerebral edema, which may rapidly become life-threatening. The strongest predictors of outcome following moderate and severe TBI are age, pupillary reactivity, and GCS motor score. Additional predictors include CT characteristics, hypotension, hypoxia, laboratory parameters (eg, glucose, hemoglobin levels), and extracranial injuries.[43]

Glasgow Coma Scale. The GCS is a 15-point scale used in an attempt to quantify the patient's LOC and is an objective method of following the patient's neurologic status (Table 34.2). It was originally developed during a time when CT scanning was not available to communicate changes in neurologic status in comatose patients with TBI (Fig. 34.6). The score assigns points based on the patients best eye opening (spontaneous opening = 4 to no response = 1), motor response (obeys commands = 6 to no response = 1), and verbal response (oriented = 5 to no response = 1). Due to its ease of use, it has been adopted in the routine

TABLE 34.2

Glasgow Coma Scale

RESPONSE	SCORE	SIGNIFICANCE
EYE OPENING		
Spontaneously	4	Reticular activating system intact; patient may not be aware
To verbal command	3	Opens eyes when told to do so
To pain	2	Opens eyes in response to pain
No eye opening	1	Does not open eyes to any stimuli
VERBAL STIMULI		
Oriented, converses	5	Relatively intact CNS, aware of self and environment
Disoriented, converses	4	Well-articulated, organized, but disoriented
Inappropriate words	3	Random exclamatory words
Incomprehensible	2	Moaning, no recognizable words
No verbal response	1	No response or intubated
MOTOR RESPONSE		
Obeys verbal commands	6	Readily moves limbs when told to
Localizes to painful stimuli	5	Moves limb in an effort to remove painful stimuli
Flexion withdrawal	4	Pulls away from pain in flexion
Abnormal flexion	3	Decorticate rigidity
Extension	2	Decerebrate rigidity
No motor response	1	Hypotonia, flaccid—suggests loss of medullary function or concomitant spinal cord injury

CNS, Central nervous system.

assessment of all trauma patients, including those with MTBI who are not comatose.[5] However, the GCS score can reflect impairment from conditions other than brain injury, such as distracting injuries, intoxication from drugs and alcohol, hypoxemia, and sedative medications. Furthermore, patients can deteriorate from an expanding intracranial hematoma after what appears clinically to be a mild brain injury. Although TBI is often categorized into mild, moderate, and severe based on the GCS score, it really represents a spectrum of injury.

Pupillary Examination. An evaluation of the patient's pupil size and responsiveness is performed early in the initial assessment of the head-injured patient. Pupillary asymmetry, the loss of the light reflex, or a dilated pupil suggests herniation syndrome as increasing pressure on the CN III results in compromise of the parasympathetic fibers and pupillary dilation on the affected side. However, use of the pupillary examination for localization of an intracranial lesion is neither sensitive nor specific. Further, traumatic mydriasis, resulting from direct injury to the eye and periorbital structures, may confuse the assessment of the pupillary responsiveness. As with the GCS score, a change in pupillary response is more indicative of intracranial pathology than the initial findings.

Motor Examination. The patient's acute motor examination assesses for strength and symmetry. Paralysis obscures involuntary reflexes; attempts should be made to perform the motor examination before paralytic agents are given. If the patient is not cooperative or is comatose, motor movement should be elicited by the application of noxious stimuli. Any movement should be recorded. Voluntary purposeful movement must be distinguished from abnormal motor posturing.

Decorticate posturing is abnormal flexion of the upper extremity and extension of the lower extremity. The arm, wrist, and elbow slowly flex, and the arm is adducted. The leg extends and rotates internally, with plantar flexion of the foot. Decorticate posturing implies injury above the midbrain. Decerebrate posturing is the result of a more caudal injury, and therefore is associated with a worse prognosis. The rate of decerebrate posturing increases significantly in the presence of midbrain lesions.[44] The arms extend abnormally and become adducted. The wrist and fingers are flexed, and the entire arm is internally rotated at the shoulder. The neck undergoes abnormal extension, and the teeth may become clenched. The leg is internally rotated and extended, and the feet and toes are plantar-flexed.

Brainstem Function. In the acute setting, brainstem activity is assessed by the patient's respiratory pattern, pupillary size, and eye movements. The oculocephalic response (doll's eyes maneuver) tests the integrity of the pontine gaze centers. This response should not be elicited until cervical spine fractures have been ruled out. The oculovestibular response (cold water calorics) also permits assessment of the brainstem. Comatose patients no longer demonstrate nystagmus when cold water is placed in the ear canal; the only response is tonic deviation of the eyes toward the instilled cold water. This response is dampened by cerumen or blood in the patient's ear canal, and the tympanic membrane needs to be intact for this test to be performed.

In the severely head-injured patient, the CN examination is often limited to the pupillary responses (CN III), gag reflex (CNs IX and X), and corneal reflex (CNs V and VII). Facial symmetry (CN VII) can sometimes be assessed if the patient grimaces with noxious stimuli. In patients who are awake and cooperative, a formal CN examination should be performed.

Differential Diagnosis

In the context of trauma, conditions presenting with an altered LOC include seizures and associated postictal state, intoxication with alcohol or drugs, and systemic trauma resulting in hypoxemia or hypoperfusion. A patient's mental status may also be impaired by sedatives or motor function may be altered by neuromuscular blocking agents administered prior to ED arrival. However, intra-axial and extra-axial lesions may cause alterations in mental state and may coexist with other traumatic injuries. Head trauma may result in confounding injuries to other parts of the head or neck, including skull or facial bone fractures, cervical spine or spinal cord injuries, eye injuries, otolaryngeal injuries, and damage to blood vessels within the neck. Although a GCS score of 15 does not exclude the possibility of brain injury, a decreasing GCS score suggests an expanding intracranial lesion, which may be intracerebral or subdural or epidural. Signs include worsening headache, focal neurologic signs, confusion, and lethargy, which may progress to coma. Presentation of a subdural hemorrhage may be acute, subacute, or chronic. Epidural or intracerebral hemorrhages have an acute abrupt presentation, which may be delayed by minutes to hours from the initial injury. Patients with an epidural hemorrhage may have a lucid interval following a brief loss of consciousness or period of confusion. A skull fracture may be accompanied by underlying traumatic pathology, including brain contusions, dural tears, and vascular trauma. Given the proximity of the middle meningeal artery to the temporal bones, consider extra-axial hematomas (especially EDH) if there are signs of a basilar skull fracture. Decorticate posturing implies injury above

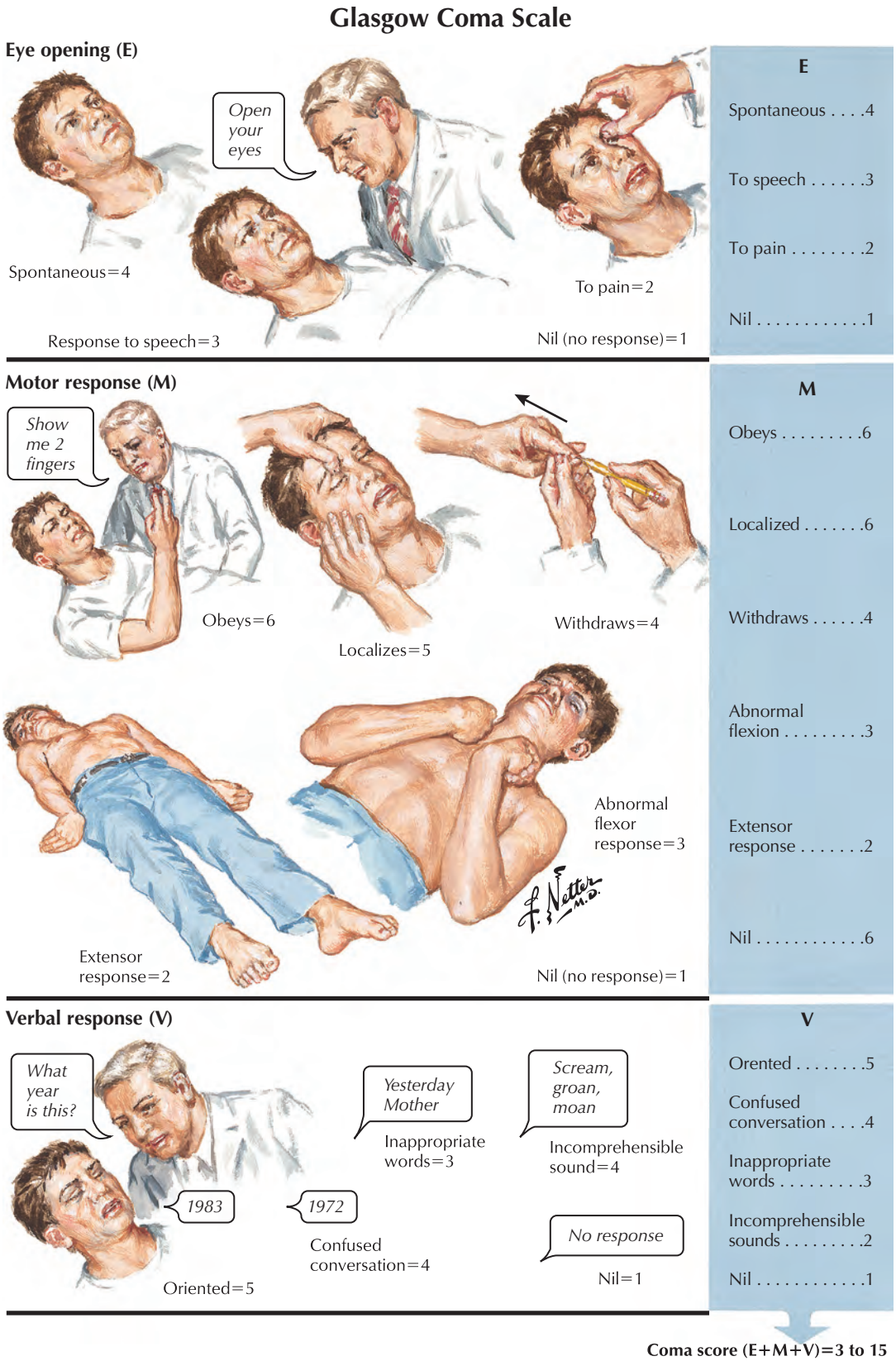


Fig. 34.6. How to calculate a Glasgow Coma Scale (GCS) score. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

the midbrain, whereas decerebrate posturing is suggestive of a midbrain lesion. Pupil inequality and unilateral motor deficits may help localize a lesion. In vulnerable populations, consider nonaccidental trauma in all patients with brain injury. Furthermore, consider traumatic brain injury in all patients with head trauma and advanced age or those on anticoagulant or antiplatelet agents, regardless of symptoms. With age, the brain atrophies and creates more space within the cranial vault for blood to accumulate, so older adults can have significant hemorrhage and not show signs of deterioration.

Diagnostic Testing

Laboratory Tests

Routine laboratory tests are generally not needed for patients with isolated mild TBI in the acute setting, except for a bedside glucose test in patients with altered mental status and determination of the blood alcohol level in patients suspected of alcohol intoxication and head trauma. Suspicion of a systemic insult as the cause of the head trauma, such as when a diabetic patient sustains a MVC after losing consciousness from hypoglycemia, warrants directed testing for culprit conditions. Coagulation studies are indicated in patients with coagulopathies (eg, hemophilia, Von Willebrand disease), suspected liver disease, and those on anticoagulants. Ancillary laboratory tests that may provide useful information in the subsequent management of the patient include a urine toxicology screen, blood alcohol level, complete blood count, and electrolyte levels. In severe TBI patients, coagulation parameters (eg, platelet count) can indicate a worse prognosis.[45]

Neuroimaging

Skull Radiography. Skull radiography after head trauma rarely is indicated and has long been replaced by cranial computed tomography (CT), which is the cornerstone of imaging for acute head trauma. Although patients with clinical signs of skull fracture have a substantially increased incidence of intracranial lesions, numerous studies have shown that skull radiographs are neither sensitive nor specific for intracranial injury. When the clinical examination shows evidence of skull fractures, CT should be performed. Although plain skull radiographs were used in the past to localize missile fragments or ascertain penetration of the skull, CT also is the radiologic test of choice for penetrating head trauma.[46] The bone windows of the CT scan can detect skull fractures (including basilar fractures). CT defines the precise location of the missile, its intracranial path, the presence of bone or missile fragments, extra-axial or intracerebral blood collections or other traumatic lesions, and pneumocephalus. Skull radiographs for adults with MTBI are not recommended.

Computed Tomography. Noncontrasted CT of the head is the diagnostic standard for identifying intracranial injury in the ED. This scan delineates acute intra-axial and extra-axial bleeding, cerebral swelling, ischemic infarction caused by hypoxia after trauma, evidence of increased ICP, and pneumocephalus. It is sensitive for demonstrating mass effect, ventricular size and configuration, bone injuries, and acute hemorrhage, regardless of location (ie, parenchymal, subarachnoid, subdural, or epidural spaces).[47] Follow-up CT should be performed if there is any clinical deterioration.

Pneumocephalus. This is often associated with missile wounds that penetrate the sinuses but can be caused by free air sucked into the penetration cavity behind the projectile. All tangential GSWs should be evaluated with a head CT scan secondary to the high incidence of associated intracranial injury.[25] Angiography may be indicated to better discern location referable to key vascular structures. Pneumocephalus is also associated with open skull fractures.

Epidural Hematoma. On CT scan, an EDH appears hyperdense, biconvex, ovoid, and lenticular. The EDH does not usually extend beyond the dural attachments at the suture lines. The margins are sharply defined, and the hematoma usually bulges inward toward the brain (Fig. 34.7). EDHs of mixed density on CT may be actively bleeding. The temporoparietal region is the most likely site for an EDH. An EDH is usually unilateral, and 20% of patients have other intracranial lesions, usually SDHs or contusions. The deterioration of a patient who has an EDH from arterial bleeding can be rapid and dramatic.

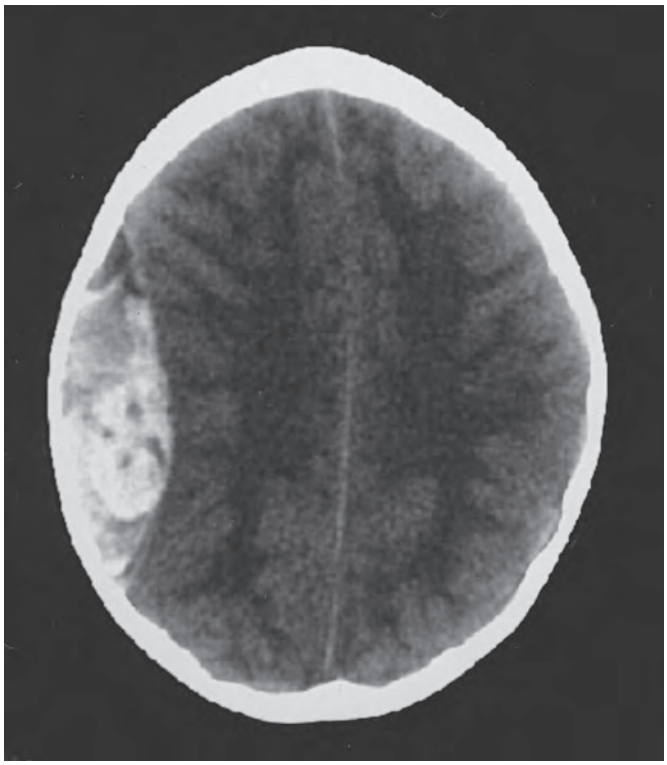


Fig. 34.7. Non–contrast-enhanced CT scan of acute epidural hematoma at the level of right midconvexity. There is an associated mass effect and moderate midline shift.

A posterior fossa EDH is the most common traumatic mass lesion of the posterior fossa and accounts for 5% of EDHs. On CT scan, a posterior fossa EDH looks similar to other EDHs, but may cross the midline and extend above the tentorium to the supratentorial compartment (Fig. 34.8).

Subdural Hematoma. Unlike EDHs, SDHs often extend beyond the suture lines (Fig. 34.9). An SDH may follow the contour of the tentorium and be detected within the interhemispheric fissure (Fig. 34.10). Many patients with an acute SDH also show CT evidence of intracerebral lesions contralateral to the SDH. A subacute SDH is symptomatic between 24 hours and 2 weeks after injury. It may appear hypodense or isodense on CT scans. Contrast increases the detection of isodense lesions. Patients complain of a headache, altered mental status, or focal deficits.

On a CT scan, a chronic SDH may appear isodense or hypodense to brain parenchyma. Indirect evidence of the lesion includes a midline shift, effacement of the ipsilateral cortical sulci, and ventricular compression. Contrast may increase the likelihood of identifying a chronic SDH that has become isodense. On a CT scan, blood of various ages is seen as a mixed-density lesion. On a magnetic resonance imaging (MRI) scan, a chronic SDH appears hyperdense.

Posterior fossa SDHs are caused by occipital trauma and, on a CT scan, they do not cross the midline or extend above the tentorium. The outcome of a posterior SDH is very poor.

Traumatic Subarachnoid Hemorrhage. A noncontrast CT scan allows the diagnosis to be made, with increased density noted within the basilar cisterns. Blood can also be seen within the interhemispheric fissures and sulci. The amount of blood within the tSAH correlates directly with the outcome and inversely with the presenting GCS score.

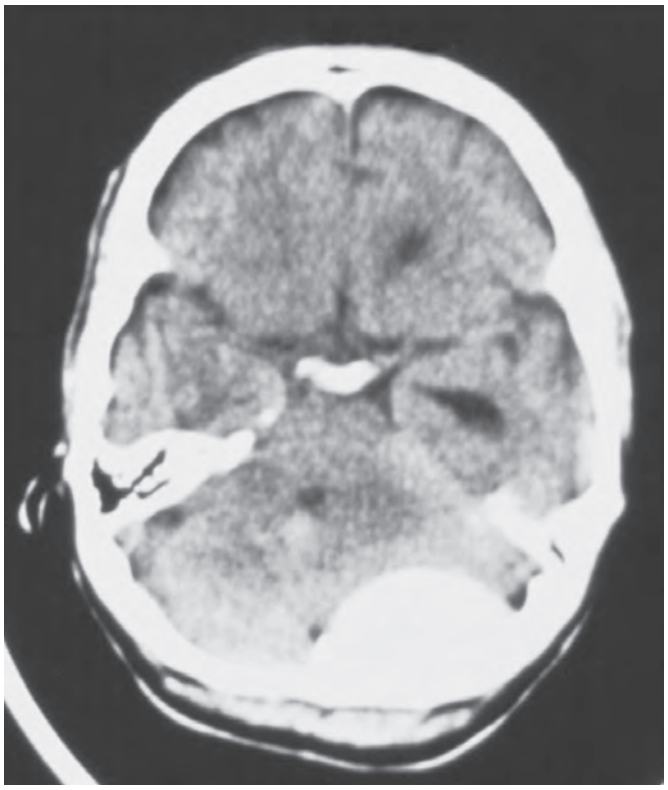


Fig. 34.8. Non–contrast-enhanced CT scan of large left posterior fossa, epidural hematoma. The size of the lesion at this high level suggests that it crosses into the supratentorial compartment. This lesion is often associated with occipital bone fracture that disrupts transverse sinus.

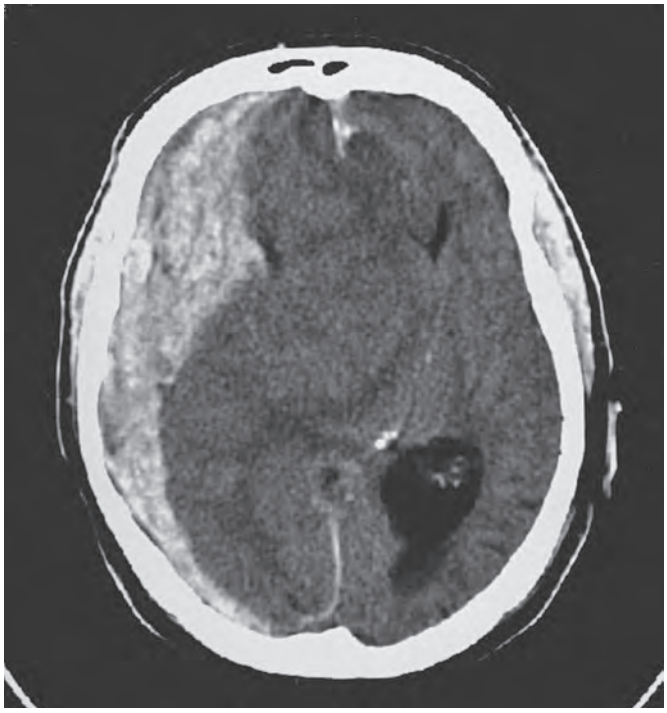


Fig. 34.9. Non–contrast-enhanced CT scan of acute right temporal subdural hematoma. There is acute bleeding and delayed bleeding, which explains the mixed density. Mass effect is large, with a midline shift measuring approximately 2.7 cm right to left. The right lateral ventricle has been obliterated.

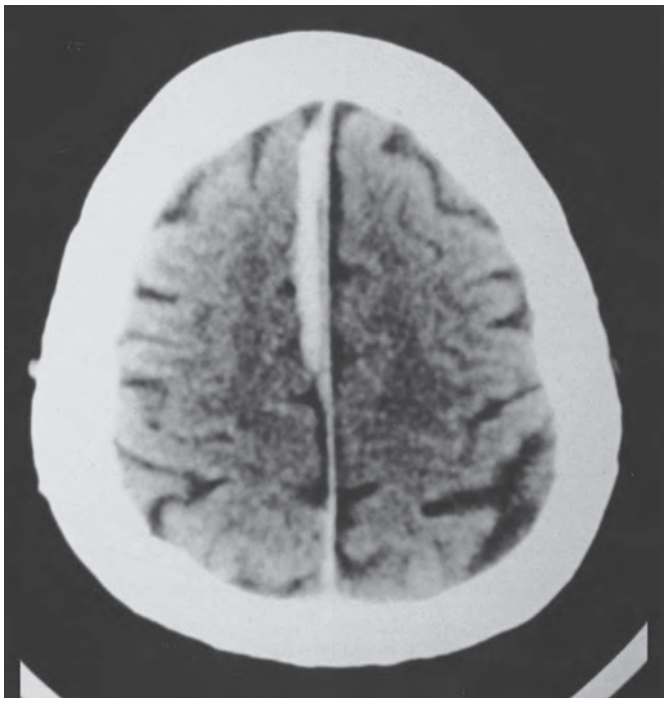


Fig. 34.10. Non–contrast-enhanced CT scan of intrahemispheric acute subdural hematoma.

Subdural Hygroma. On CT, SDHGs appear crescent shaped in the extra-axial space; the density is the same as that of CSF. Bilateral SDHGs are common.

Diffuse Axonal Injury/ Traumatic Axonal Injury. Diffuse TAI is the most common CT finding after severe head trauma, estimated to occur in over 50% of all comatose head trauma patients. However, in milder cases, there is no specific acute focal traumatic lesion noted on a head CT scan or on structural MRI scan. Occasionally, small petechial hemorrhages in proximity to the third ventricle and within the white matter of the corpus callosum or internal capsule of the brainstem are detected.[28] An intraventricular hemorrhage on the initial CT scan has been reported to be an early predictor of DAI lesions in the corpus callosum on MRI.[48] Although histopathologic examination of postmortem brain tissue[28] is the gold standard for diagnosing TAI, advanced MRI neuroimaging techniques, such as diffusion tensor imaging (DTI), may help assess white matter integrity (Fig. 34.11).[49]

Cerebral Contusions. Non–contrast-enhanced CT is the best diagnostic test to discover contusions in the early posttraumatic period. These appear heterogeneous and irregular because of mixed regions of hemorrhage, necrosis, and infarction. Often, the surrounding edematous tissue appears hypodense. By posttrauma days 3 and 4, the blood located within the contusions has begun to degrade, and structural MRI becomes more useful.

Intracerebral Hematoma. An intracerebral hematoma may be detected on the first CT scan immediately after injury but often is not seen for several hours or days. Unlike contusions, ICHs are usually deep in the brain tissue and often become well demarcated over time. On CT scan, an ICH appears as a well-defined hyperdense homogeneous area of hemorrhage (Fig. 34.12).

Traumatic Intracerebellar Hematoma. Often, these patients have an associated skull fracture, posterior fossa EDH or SDH, or supratentorial contrecoup hematomas and contusions.

Cerebral Edema. On CT scans, diffuse edema manifests as bilateral compression of the ventricles, loss of definition of the cortical sulci, or effacement of the basal cisterns (Fig. 34.13). Focal

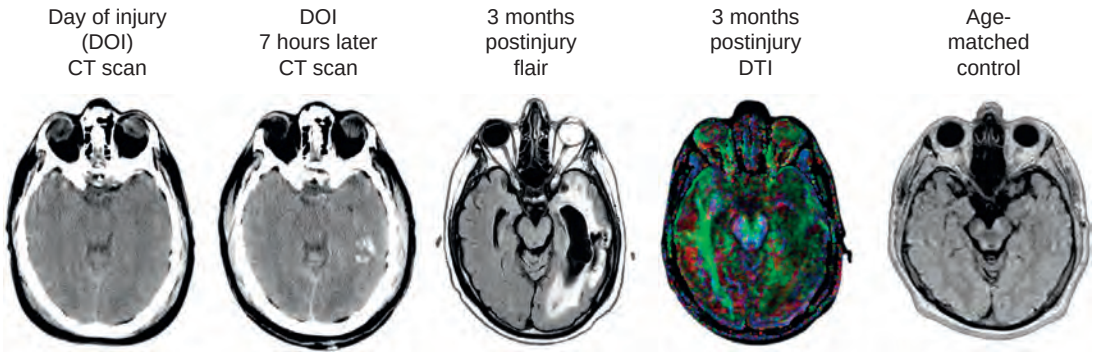


Fig. 34.11. Sequential scan findings in severe traumatic brain injury (TBI) with traumatic axonal injury (TAI). In the ED, on initial day of injury (DOI) CT imaging, the scan on the *far left* shows primarily generalized edema but, by 7 hours, distinct intraparenchymal hemorrhages appear, particularly within the left temporal lobe. By 3 months postinjury, TAI and intraparenchymal hemorrhages result in massive degenerative effects, reflected in temporal horn dilation and markedly abnormal white matter signal differences throughout the temporal and occipital lobes on the fluid-attenuated inversion recovery (FLAIR) sequence. Temporal horn dilation is also evident in the right temporal lobe as well, reflective of the generalized atrophy. The loss of white matter integrity is more distinctly observed using diffusion tensor imaging (DTI), where there is no coherent direction noted in the left temporal region; even though the right temporal lobe exhibits atrophic changes, the inferior occipitotemporal fasciculus (*arrow*) is distinctly visible. The control MRI scan is a T1 image showing symmetric temporal lobe morphology with the normal slitlike appearance of the temporal horns. (Adapted from Bigler ED, Maxwell WL: Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. Brain Imaging Behav 6:108–136, 2012.)

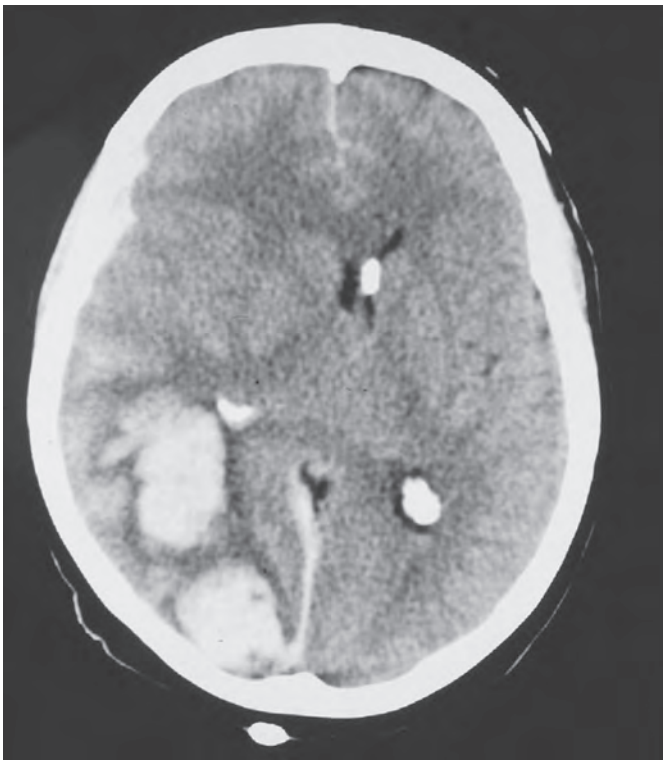


Fig. 34.12. Non–contrast-enhanced CT scan of right occipital and temporal intracerebral hematomas, surrounded by mild edema and hemorrhagic contusion. A small, intrahemispheric, subdural hematoma is visible in the posterior interhemispheric fissure. Midline shift is obvious. A ventriculostomy has been placed and is visible as high-density image within the ventricles.

Fig. 34.13. Non–contrast-enhanced CT scan showing diffuse cerebral edema. Loss of gray-white differentiation in the brain parenchyma is present. Bilateral compression of the ventricles has occurred, with loss of cortical sulci.

edema adjacent to traumatic mass lesions demonstrates decreased density on CT scans compared with normal tissue.

Rotterdam Computed Tomography Score. The Rotterdam score was developed to determine the risk for mortality in traumatic brain injury. It is based on initial noncontrast CT findings of basal cistern compression, midline shift, presence of an epidural hematoma, and the presence of intraventricular blood and/or traumatic subarachnoid hemorrhage (Box 34.3).

Management

Out-of-Hospital Care

The out-of-hospital management of the head-injured patient should focus on preventing or minimizing secondary brain injury.

BOX 34.3

Rotterdam Score of Initial Noncontrast Computed Tomography for Predicting 6-Month Mortality Following Traumatic Brain Injury[a]

1. Basal cistern effacement
   0 = none
   1 = partially effaced (compressed)
   2 = completely effaced (compressed)
2. Midline shift
   0 = no shift or ≤5 mm
   1 = >5 mm
3. EDH (epidural hematoma)
   0 = EDH present
   1 = no EDH
4. IVH (intraventricular hemorrhage) or SAH (subarachnoid hemorrhage)
   0 = neither present
   1 = either present
   2. Add 1 to score

Total score = 1–6 points

[a]Probability of mortality at 6 mo postinjury based on score:
1 ≥ 0%
2 ≥ 7%
3 ≥ 16%
4 ≥ 26%
5 ≥ 53%
6 ≥ 61%

The two major systemic insults are hypotension and hypoxia. Interventions should be aimed at maintenance of oxygenation and prevention of hypotension through directed fluid resuscitation and control of hemorrhage.

Airway. Controversy exists regarding the benefits of out-of-hospital intubations in patients with brain injuries. In systems with short transport times, and in patients in whom an oxygen saturation more than 90% can be maintained with supplemental oxygen, field intubation is of questionable benefit and may potentially lead to worse outcomes.[50-52] Although unsuccessful attempts at field intubations may add to out-of-hospital time and increase the risk of aspiration or hypoxia, patients who are hypoxic or are unable to maintain their airway have improved outcomes in terms of mortality and neurologic outcome with field intubation.[50,52]

The ultimate goal in the field is to prevent or minimize hypoxia. Out-of-hospital airway protocols balance the risks of emergency intubation in an uncontrolled setting with the need to secure an at-risk airway and prevent hypoxia. If oxygenation can be maintained and transport time is short (most urban settings), definitive airway management should be delayed until arrival in the ED.[53] If endotracheal intubation is undertaken in the field, it should be performed by skilled practitioners with a rigorous quality assurance program and continuous provider training. All advanced airway placement should be confirmed with quantitative end-tidal capnography ($ETCO_2$), which dramatically improves the detection of improperly placed airway devices and inadvertent hyperventilation by field providers. Prehospital endotracheal intubation is associated with poorer prognosis in children and should be avoided in this population (see Chapter 165).

Hypotension. Avoiding and managing hypotension are critical elements of the prehospital treatment of the head-injured patient. The secondary survey of the head-injured patient should include a search for external signs of head trauma. Scalp lacerations may bleed a large volume into a bulky dressing, and a less bulky dressing should be used with firm constant manual pressure applied to avoid excessive blood loss. Any other ongoing external hemorrhage should be expeditiously addressed and controlled. Although permissive hypotension may be beneficial in some trauma patients, it is detrimental in the setting of brain injury.[54]

Agitation. Many severely head-injured patients are initially combative or agitated. Transporting an agitated patient who is fighting against physical restraints may exacerbate physical injury, cause an increase in ICP, and interfere with appropriate stabilization and management. Management of agitation in the out-of-hospital setting mirrors that used in the ED, as described below.

Emergency Department Management

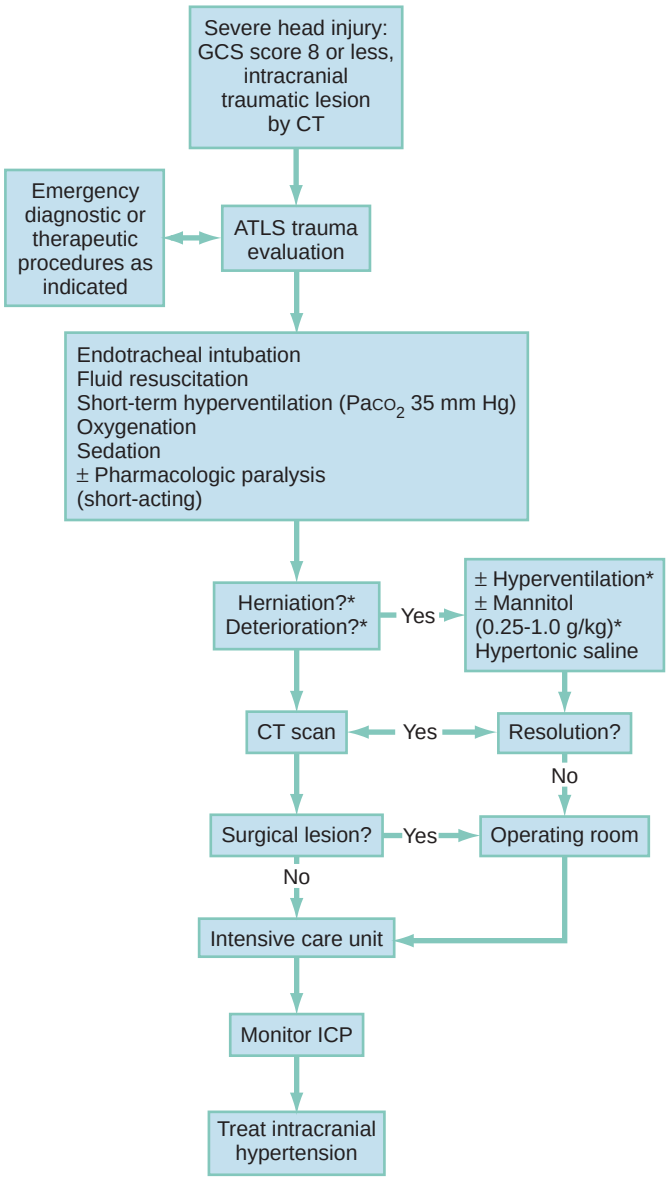
General. In the ED phase of patients with severe head trauma, management is in accordance with ATLS (Advanced Trauma Life Support) protocols. Monitoring of vital signs should be continuous, such as respiratory status (pulse oximetry, capnography) heart rate, blood pressure, and temperature. Tetanus status should be determined and prophylaxis given, as appropriate. Pregnancy status in women of childbearing age should be verified.

Airway. Primary airway compromise in the setting of head trauma may result from craniofacial or neck trauma, bleeding, or vomiting. Secondary airway compromise may also result from brain injury, as in the case of loss of brainstem reflexes, patient agitation, severe systemic hypotension, or alterations in mental status. In either case, the airway should be secured early to protect against aspiration and prevent secondary brain injury as a result of hypoxia or hypercarbia (Fig. 34.14).

If possible, a rapid but detailed neurologic examination should be performed before the patient is given any sedative or neuromuscular blocking agent. This focused examination includes careful recording of the elements of the GCS, characterization of movement of all four extremities (to command, purposeful response to pain, localizing pain, withdrawal, posturing), tone, and pupillary reflexes. These elements are essential in correlating CT findings with clinical injury and are also useful in following the patient's progression. The drug selection and technique of intubation for the head-injured patient is discussed in Chapter 1.

Hypotension. If hypotension is detected at any time in the emergent management of a potentially brain-injured patient, a cause other than the brain injury should be sought (see Chapter 33). Systemic hypotension has profound implications for neurologic outcomes. In fact, a single episode of hypotension doubles mortality risk. As such, fluids or blood transfusion should be delivered to maintain a SBP of at least 90 mm Hg. Maintaining the SBP above 100 mm Hg may be considered to decrease mortality and improve outcome.[10]

Brain-Directed Hyperosmolar Therapy. If there are signs of impending herniation syndrome, such as deepening coma, a newly asymmetric pupil, or other substantially diminishing neurologic parameters, we recommend the use of osmotic diuretics, such as mannitol or hypertonic saline (HTS). Mannitol is the time-honored mainstay for the control of elevated ICP in acute severe TBI.[10] Mannitol (0.25–1 g/kg) can effectively reduce cerebral edema by producing an osmotic gradient that reduces brain volume and provides increased space for an expanding hematoma or brain swelling. The osmotic effects of mannitol occur within minutes and peak approximately 60 minutes after bolus administration. The ICP-lowering effects of a single bolus may last for 6 to 8 hours. Mannitol is also an effective volume expander and, in the presence of hypovolemic hypotension, may aid in maintaining



*Only in the presence of signs of herniation or progressive neurologic deterioration not attributable to extracranial factors.

Fig. 34.14. Treatment options for initial resuscitation of a patient with a severe head injury. *ATLS,* Advanced Trauma Life Support; *CT,* computed tomography; *GCS,* Glasgow Coma Scale; *ICP,* intracranial pressure; *$Paco_2$,* partial pressure of arterial carbon dioxide. (From Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care; AANS/CNS; J Neurotrauma 24[Suppl 1]:S1–106, 2007.)

the systemic blood pressure required for adequate cerebral perfusion. It also promotes CBF by reducing blood viscosity and microcirculatory resistance. It is an effective free radical scavenger, reducing the concentration of oxygen free radicals that may promote cell membrane lipid peroxidation.

HTS also has been used effectively to reduce ICP in TBI. Few comparative data exist on brain-directed osmotic therapy, however. Selection of mannitol versus HTS should be made on an institutional basis, so that providers across various specialties (eg, emergency medicine, trauma surgery, neurosurgery, anesthesiology) provide consistent care.[55,56]

HTS given as bolus therapy is more effective than mannitol in lowering cumulative and daily ICP elevations after severe TBI, but it does not improve mortality.[55,57] Proposed benefits of HTS include reducing secondary injury through effects on cellular modulation, decreasing cerebral edema, improving peripheral perfusion, and decreasing ICP through vasoregulatory mechanisms[58] and upregulation of proinflammatory and prothrombotic mediators. Numerous clinical studies have demonstrated that HTS can significantly reduce ICP; however, the total number of enrolled patients in these trials is small, and interpretation is complicated by variation in protocols, HTS concentration, and rate of administration.[10,55,58-60]

Among patients with severe TBI not in hypovolemic shock, initial resuscitation with hypertonic saline or hypertonic saline-dextran, compared with normal saline, was found not to result in superior 6-month neurologic outcome or survival.[61,62] Mannitol can produce renal failure or hypotension if given in large doses. It may also induce a paradoxical effect of increased bleeding into a traumatic lesion by decompressing the tamponade effect of a hematoma. Potential adverse events associated with HTS include renal failure, central pontine myelinolysis, and rebound ICP elevation.[60] Osmotic therapy should be guided by findings on ICP monitoring. Prior to initiation of such monitoring, brain-directed osmotic therapies should be reserved for patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes.[10]

Osmolar therapy with mannitol or hypertonic saline can draw water across an intact BBB and thereby lower ICP. Mannitol, 0.25 to 1 g/kg, is given every 6 hours, up to a serum osmolality of 320 mOsm/kg. Treatment with 30 mL of 23.4% HTS appears to be at least as effective as mannitol at lowering ICP rapidly and reversing herniation, although a central line is necessary for safe administration. Hypertonic saline (23.4%), 30 to 60 mL, can be given every 6 hours, up to a maximum serum sodium level of 160 mEq/L. Because it is a potent diuretic, mannitol is preferred in cases of fluid overload, whereas HTS can be used as a resuscitative fluid; a 3% or 23.4% solution can be used.[63]

Hyperventilation. Under normal conditions, $Paco_2$ is the most powerful determinant of CBF and, between a range of 20 and 80 mm Hg, CBF is linearly responsive to $PaCO_2$. Formerly, so-called therapeutic hyperventilation was recommended as a method to reduce ICP. Unfortunately, however, this reduction in ICP is accomplished by reducing CBF, which is important in meeting the brain's metabolic demands. A low $Paco_2$, therefore, and the resulting low CBF, may result in cerebral ischemia, whereas high $Paco_2$ levels can result in cerebral hyperemia and high ICP. Normal ventilation is currently the goal for severe TBI patients in the absence of cerebral herniation, and $Paco_2$ is maintained in the normal range, from 35 to 45 mm Hg.[10] In the case of life-threatening cerebral herniation or significant ICP elevation, therapeutic hyperventilation is appropriate only as a short-term intervention, bridging to more definitive therapy (eg, craniectomy). Therefore, hyperventilation is recommended only as a temporizing measure for the reduction of elevated ICP and should not be used for routine management or prophylaxis. Hyperventilation should be avoided during the first 24 hours after injury when CBF is often critically reduced. If hyperventilation is used, jugular venous oxygen saturation (Sjo_2) or brain tissue O_2 partial pressure ($Btpo_2$) measurements are recommended to monitor oxygen delivery.[10,64] The neurologic effects of hypocapnia are illustrated in Fig. 34.15.

Cranial Decompression. In patients with impending herniation who do not respond to osmotic therapy and hyperventilation, particularly those with a history of so-called talk and deteriorate after head trauma, emergency cranial decompression may temporarily reverse or arrest the herniation syndrome.[65,66] Emergency trephination may allow enough time for a patient to

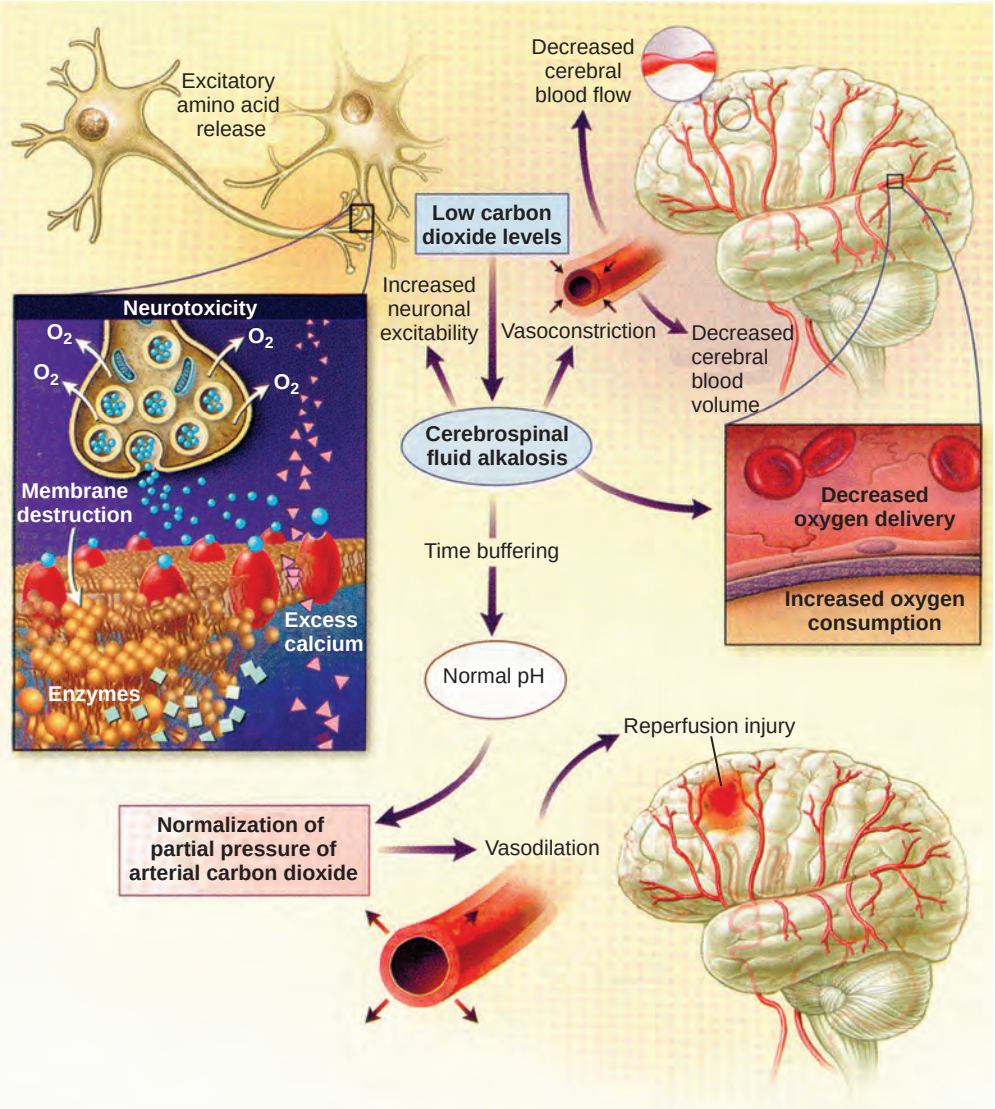


Fig. 34.15. Neurologic effects of hypocapnia. Systemic hypocapnia results in cerebrospinal fluid alkalosis, which decreases cerebral blood flow, cerebral oxygen delivery and, to a lesser extent, cerebral blood volume. The reduction in intracranial pressure may be lifesaving in patients in whom the pressure is severely elevated. However, hypocapnia-induced brain ischemia may occur because of vasoconstriction (impairing cerebral perfusion), reduced oxygen release from hemoglobin, and increased neuronal excitability, with the possible release of excitotoxins, such as glutamate. Over time, cerebrospinal fluid pH and hence cerebral blood flow gradually return to normal. Subsequent normalization of the partial pressure of arterial carbon dioxide can then result in cerebral hyperemia, causing reperfusion injury to previously ischemic brain regions. (From Laffey JG, Kavanagh BP: Hypocapnia. N Engl J Med 347:43–53, 2002.)

undergo a formal craniotomy in the operating room. However, most patients presenting unconscious have sustained diffuse massive brain injury, with no focal lesion amenable to emergency decompression. Patients with erratic or absent respiratory effort, bilateral fixed and dilated pupils, no spontaneous eye movements, and decerebrate posturing do not benefit from emergent burr holes. Furthermore, placement of a burr hole is a blind invasive procedure, and the chances of localizing the expanding lesions are uncertain. Trephination should be undertaken only after confirmation of an extradural collection by neuroimaging[67] and only by, or under the guidance of, an emergency clinician with specific training.

Decompressive craniectomy (DC) is the surgical removal of the skull bone and has been performed for the purpose of relieving elevated ICP, with outcome improvement in some TBI patients.[68,69] Bifrontal DC has been used in severe TBI patients with diffuse injury (without mass lesions) who have ICP elevation to more than 20 mm Hg for more than 15 minutes within a 1-hour period, refractory to first-tier therapies. There is no evidence for improved outcome, as measured by the Glasgow Outcome Scale-Extended (GOS-E) score, at 6 months postinjury.[10] However, this procedure has been demonstrated to reduce ICP and to minimize days in the intensive care unit (ICU). A large frontotemporoparietal DC (not <12 × 15 cm or 15 cm diameter) is recommended over a small frontotemporoparietal DC for reduced mortality and improved neurologic outcomes in patients with severe TBI.[10]

Hemostatic Agents. Patients taking warfarin may be managed with prothrombin complex concentrate, fresh-frozen plasma), or vitamin K. Reversal of warfarin-associated anticoagulation is discussed in Chapter 114. There is inadequate evidence to support the routine use of platelet transfusion for intracranial hemorrhage for patients taking preinjury antiplatelet medications

(eg, aspirin, clopidogrel).[70] Idarucizumab, a reversal agent against dabigatran, is approved for emergency surgery and urgent procedures or in life-threatening or uncontrolled bleeding. Although studies are lacking in the setting of TBI, when significant intracranial bleeding is identified in patients with acute TBI who are taking dabigatran, we recommend reversal with idarucizumab. The recommended dose for idarucizumab is 5 g (2.5 g/vial) administered intravenously as two consecutive 2.5-g infusions or as a bolus injection by injecting both vials consecutively, one after another, via syringe.

Recombinant factor VIIa (rFVIIa) is a hemostatic agent that was originally developed to treat bleeding in hemophiliacs. Limited military experience led to interest in the use of rFVIIa for traumatic intracerebral hemorrhage as well.[71,72] However, results of clinical trials are mixed, and there has been no convincing evidence of benefit for this expensive agent in traumatic intracranial hemorrhage in the absence of preexisting coagulopathy. We do not recommend routine use of rFVIIa for patients with traumatic intracranial hemorrhage.[72,73]

When given early after injury (within 3 hours), tranexamic acid (TXA) has demonstrated benefit in trauma with hemorrhage without increasing the risk of adverse events.[74-76] The use of TXA is discussed in Chapter 33. Tranexamic acid is of no benefit for patients with isolated head trauma or head trauma without significant systemic hemorrhage and may even be harmful. TXA should not be used in this population.

Induced Hypothermia. Hyperpyrexia worsens outcome after severe TBI, and guidelines emphasize maintaining normothermia with antipyretic medications and cooling devices.[34] Induced therapeutic hypothermia has been proposed to decrease ICP, including reducing proinflammatory cytokines and stabilizing the BBB. However, the routine use of hypothermia for the treatment of TBI has met with mixed results in adult and pediatric populations.[77-79] Although hypothermia remains a significant area of research and promise for patients with severe and moderate TBI, the available scientific evidence is inconclusive with regard to improved mortality or morbidity.[80] Some studies have shown the potential for benefit,[77] but a recent randomized trial has shown that therapeutic hypothermia for severe TBI does not improve the neurologic outcomes or risk of mortality compared with strict temperature control.[78] Similarly, in another randomized trial in patients with an elevated ICP of more than 20 mm Hg, therapeutic hypothermia plus standard care to reduce ICP id not result in outcomes better than those with standard care alone.[81] We do not recommend the routine use of therapeutic hypothermia for the treatment of TBI.

Seizure Prophylaxis. Acute symptomatic seizures may occur as a result of severe traumatic brain injury (TBI). Such PTSs are classified as early when they occur within 7 days of injury or late when they occur after 7 days following injury. Posttraumatic epilepsy (PTE) is defined as recurrent seizures more than 7 days following injury. Up to 12% of all patients who sustain blunt head trauma and 50% of those with penetrating head trauma develop early PTSs.[46,82] Although the occurrence of seizures in the immediate posttrauma period is not predictive of future epilepsy, early seizures can cause hypoxia, hypercarbia, release of excitatory neurotransmitters, and increased ICP, potentially worsening secondary brain injury.

Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS, but phenytoin is recommended to decrease the incidence of early PTS (within 7 days of injury), when the overall benefit is thought to outweigh the risk of complications associated with such treatment.[10,83] Early PTSs have not been associated with worse outcomes,[10] but the use of prophylactic anticonvulsants in penetrating brain injuries is recommended for 7 days postinjury.[46] There is insufficient evidence to recommend levetiracetam over phenytoin; we recommend phenytoin for early PTSs and toxicity.[10]

If the patient is actively seizing, benzodiazepines are administered as effective, rapid-acting, first-line anticonvulsants. Lorazepam (0.05–0.1 mg/kg IV) is the preferred agent for aborting seizures because of its high effectiveness and prolonged duration of action. Diazepam (0.1–0.2 mg/kg) or midazolam (0.05–0.1 mg/kg) is an effective alternative. For long-term anticonvulsant activity, phenytoin (18–20 mg/kg IV) or fosphenytoin (phenytoin equivalents, 15–18 mg/kg) can be given. Fosphenytoin has the advantages of rapid administration, smaller volume of fluid for the dose delivered, and less potential for hypotension than phenytoin.

Antibiotic Prophylaxis. Although the practice was once widespread, there is no evidence to support the use of antibiotic prophylaxis for the prevention of meningitis or other infection in patients with blunt basilar skull fractures, with or without evidence of CSF leakage.[84,85] Penetrating brain injury, however, is a different matter. Contamination with skin, bone, hair, and tissue occurs and may be widespread when there is cavitation caused by the missile as it passes through the brain.[46] Evidence supports the use of intravenous (IV) prophylactic, broad-spectrum antibiotics to cover for staphylococci, gram-negative bacilli, and anaerobes for penetrating craniocerebral trauma. Although there are several potential antibiotic regimens, a combination of vancomycin, 1 g bid, gentamycin, 80 mg tid, and metronidazole, 500 mg qid, will provide adequate coverage.[86,87]

Patients undergoing ICP monitoring are reported to have related infection rates as high as 27%.[88] For external ventricular drains (EVDs), routine catheter exchanges has been replaced by attention to proper care during insertion, CSF sampling techniques and, in some cases, prophylactic IV antibiotics. In a single-institution study, bundle implementation (including hand hygiene, prophylactic antibiotics, sterile technique, hair removal for dressing adherence, skin preparation using iodine and isopropyl alcohol, full surgical attire for the surgeon and other bedside providers), together with an antimicrobial-impregnated catheter, dramatically decreased EVD-related infections. We recommend training and situational awareness of best practices for infection control, assisted by checklists. However, there is insufficient evidence at this time to recommend antibiotic-impregnated EVDs for minimizing infection.

Other Therapies

Corticosteroids. Corticosteroids have no benefit for patients with head trauma, and in fact demonstrate an increase in adverse events, including infection, gastrointestinal bleeding and mortality. In patients with severe TBI, high-dose methylprednisolone is associated with increased mortality and is contraindicated.[10]

Barbiturates. Barbiturate therapy has historically been used in severely brain-injured patients to reduce cerebral metabolic demands of the injured brain tissue and reduce elevated ICP. However, barbiturates also can cause a decrease in SBP. Compared with placebo, barbiturates offer no mortality benefit; furthermore, any benefit of decrease in ICP is offset by the risk of hypotension.[89] The only remaining value of barbiturates in TBI is the use of high-dose barbiturate therapy to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.[10] Prophylactic administration of barbiturates to induce burst suppression measured by electroencephalography is not recommended.

Monitoring of Intracranial Pressure and Cerebral Spinal Fluid Drainage. Management of severe TBI patients using information from ICP monitoring is recommended to reduce

in-hospital and 2-week postinjury mortality.[10] However, management of EVD systems in patients with severe TBI remains a controversial topic. An EVD in a closed position allows for monitoring of ICP, whereas in an open position drainage of CSF can occur. Practice patterns regarding whether the EVD should be maintained in a closed or open position vary widely based on a number of variables, including patient age, institutional resources, and physician preferences. Continuous CSF drainage is a relatively common practice in the pediatric population. In adults, there is variability in practice with three options: (1) continuously monitoring ICP and only intermittently draining for ICP elevations; (2) intermittently monitoring ICP with continuous drainage of CSF; or (3) continuously monitoring ICP with continuous drainage of CSF.[90,91] An EVD system zeroed at the midbrain with continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent use. The use of CSF drainage to lower ICP in patients with an initial GCS less than 6 during the first 12 hours after injury may be considered.[10]

Glucose Control and Nutrition. Hyperglycemia and hypoglycemia are associated with worsened outcomes following a severe TBI, but the optimal glucose target and best treatment regimen is yet to be determined.[10] The complex interaction of the body with nutritional support is magnified during illness, particularly after severe TBI. Severe TBI is associated with increased energy expenditure early after injury. Guidelines recommend feeding patients to attain basal caloric replacement, at least by the fifth day and, at most, by the seventh day postinjury is recommended to decrease mortality.[10] Furthermore, transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia.[10]

Erythropoietin. In a recent multicenter randomized controlled trial of patients with moderate to severe TBI, erythropoietin did not reduce the number of patients with severe neurologic dysfunction or increase the incidence of deep venous thrombosis of the lower limbs. There was no effect on mortality at 6 months. It is not recommended for use at this time.[92]

Progesterone. Progesterone has been shown to improve neurologic outcome in early-phase trials involving patients with TBI. In a double-blind, multicenter clinical trial, progesterone was administered to TBI patients with moderate to severe TBI within 4 hours of injury. Progesterone did not improve outcomes in patients with TBI over placebo.[93] These findings are consistent with a recent meta-analysis.[94] Progesterone is not recommended for treatment of TBI.

Hyperbaric Oxygen Therapy. Hyperbaric oxygen therapy following severe, acute TBI provides the injured brain with an increased partial pressure of oxygen and theoretically reduces cerebral edema.[95] However, although the pooled results of several small studies have suggested some benefit in terms of survival, the clinical significance is questionable. Thus, the use of hyperbaric oxygen therapy for the treatment of TBI injury cannot be recommended.[95]

Management of Specific Injuries

Scalp Wounds. If blood loss is brisk, rapid hemostasis is a priority. Initially, hemostasis may be achieved by the application of a temporary, tight pressure dressing, allowing prompt attention to other priorities. Alternatively, a stapler may be used to staple the scalp laceration rapidly to control bleeding. The wound later can be reopened for proper irrigation and reclosure. Other methods to achieve hemostasis include direct digital compression of the bleeding vessel against the skull, infiltration of the wound edges with lidocaine plus epinephrine, and clamping or ligation of identified bleeding vessels. The best approach is repair with sutures or staples because the closure will assist in tamponade. In stable patients, closure of the wound, after proper débridement and irrigation, is the most effective way to stop a bleeding scalp laceration and prevent the tissue crush injury that may occur if other compressive methods are used for too long.

Once hemostasis is obtained, the wound should be irrigated to rinse away any debris. The emissary vessels of the subgaleal layer of the scalp drain directly into the diploë veins of the skull. These in turn drain into the venous sinuses. Contaminated or infected scalp wounds, therefore, have the potential to cause serious intracranial infections. Blood clots and other debris should be removed and the galea and underlying cranium palpated to detect any remaining debris, disruptions, or bone step-offs. Shear injuries to the scalp may deposit contaminants at sites distant from the apparent injury. The complexity of stellate lacerations often interferes with thorough inspection and débridement, making them particularly susceptible to infection. Digital exploration of a scalp wound should be performed gently; if done too vigorously, comminuted or depressed bone pieces may be depressed further.

It is easy to confuse a disruption in the galea or tear in the periosteum with a skull fracture. The base of the laceration should therefore be directly visualized. Clipping away a small area of hair parallel to the edges of the wound may facilitate this. Alternatively, an antibiotic ointment can be applied to the hair immediately surrounding the wound and used to plaster the hair away from the injury site. If hair is accidentally embedded within the repaired laceration, it can delay healing by producing an inflammatory reaction or by serving as a nidus of infection. If the laceration begins on the forehead and extends upward beyond the hairline, surrounding hair should not be removed. Removal obliterates a useful landmark for cosmetic closure and may result in malalignment of the two laceration edges.

Several studies have evaluated the use of staples versus sutures to close scalp lacerations that do not involve the galea. For adult and pediatric scalp lacerations that begin beyond the hairline, staples have been shown to be cheaper, take less time, and have the same outcome than sutures if used in the appropriate manner. However, staples cannot be used to close the galea and may not be effective alone when hemostasis is a problem. Large lacerations of the galea are closed to prevent the edges of the wound from pulling apart as the muscles within the galea contract. The skin, dermis, and galea can usually be repaired in a single layer with interrupted or vertical mattress sutures of 3-0 nylon or polypropylene.[96] Recently, an alternative method of scalp laceration closure has been described, in which bundles of the patient's hair on each side of the wound are twisted together and then secured with tissue glue.[96] This may provide another method of effective repair and prevent the need to remove the closure material after the wound has healed, particularly in the pediatric population. Because of the rich blood supply of the scalp, even very large scalp avulsions may remain viable. If the avulsion remains attached to the rest of the scalp by a tissue bridge, it should be reattached to the surrounding tissue. If the avulsion is completely detached from the scalp, it should be treated as any other amputated part and reimplanted as soon as possible.

Scalp abrasions are often contaminated with pieces of dirt or other debris. The wound should be cleaned as thoroughly as possible and inspected for puncture wounds or other areas that penetrate beyond the superficial layers of the skin to ensure the removal of unsuspected foreign bodies. A careful inspection often reveals a small scalp laceration within the abraded area. Systemic antibiotics are usually not needed for carefully managed scalp wounds because rapid healing is facilitated by the rich blood supply of the scalp. However, special consideration may be given to large or highly contaminated wounds, bite wounds, and immunocompromised patients.

Skull Fractures. A noncontrast head CT scan with bone windows has become the imaging modality of choice for patients

with suspected skull fractures or to identify intracranial foreign bodies. Plain radiographs can be useful when CT is not available.

Linear Fractures. Linear skull fractures are clinically important if they cross the middle meningeal groove or major venous dural sinuses; they can disrupt these vascular structures and cause the formation of EDHs. No specific intervention is necessary for linear skull fractures if a noncontrast CT scan reveals no underlying brain injury. Patients with no evidence of intracranial injury on CT and no other significant extracranial injuries should be observed in the ED for 4 to 6 hours prior to discharge. If there is any suspicion or clinical evidence of brain injury, patients should be admitted for observation. Those with intracranial injuries should have an emergent neurosurgical consultation. Patients with simple linear skull fractures may demonstrate concussive symptoms or other evidence of mild TBI and should be provided appropriate discharge instructions (see later, "Mild Traumatic Brain Injury: Disposition").

Depressed Fractures. When a depressed fracture occurs, traumatic impact drives the bone piece below the plane of the skull. The edges of the depressed portion of skull may become locked underneath the adjacent intact bone and fail to reduce into their anatomic position. As a result, the depressed piece of bone can penetrate tissue and lacerate the dura. Fractures in which the free piece of bone is depressed deeper than the adjacent inner table of the skull require surgical elevation. Depressed skull fractures are usually open fractures with disruption of the galea, which can often be felt with palpation of the skull. However, this examination should be done cautiously to avoid driving a depressed bone fragment deeper into the cranium. The clinical examination for a depressed skull fracture may be misleading. The mobility of the scalp can result in nonalignment of the fracture with an overlying scalp laceration. As a result, the skull underlying the laceration may be normal, with the depressed area several centimeters away. Scalp swelling may interfere with the physical examination findings and hide any palpable bone defects.

Depressed fractures may be difficult to visualize on plain skull radiographs. The free piece of bone demonstrates increased or double density because it often overlaps the nonfractured bone, or it is rotated from the rest of the adjacent cranium. Tangential views of the skull may increase the ability to visualize the fracture. However, CT scanning with bone windows, if available, remains the imaging modality of choice.

An open depressed skull fracture, as well as any type of penetrating skull injury, increases the risk for developing intracranial and meningeal infection and seizures and should receive prophylaxis.[97] Patients with depressed skull fractures should be admitted for continued observation. Patients with open (compound) cranial fractures depressed greater than the thickness of the cranium should undergo operative intervention to prevent infection. They may be treated nonoperatively if there is no clinical or radiographic evidence of dural penetration, significant intracranial hematoma, depression greater than 1 cm, frontal sinus involvement, gross cosmetic deformity, wound infection, pneumocephalus, or gross wound contamination. Nonoperative management of closed (simple) depressed cranial fractures is a treatment option. For all open depressed skull fractures, we suggest that prophylactic antibiotics be given for 5 to 7 days to prevent the risk of subsequent CNS infection. Suggested antibiotics are identical to those for penetrating head trauma.

Basilar Skull Fractures. Basilar fractures are the result of considerable impact force and are highly associated with underlying brain injury. Emergency clinicians should be suspicious of an epidural hematoma in patients with a temporal bone basilar skull fracture. All patients with basilar skull fractures should be admitted for observation, regardless of the need for surgical intervention. A systematic review and meta-analysis of antibiotic prophylaxis following basilar skull fracture has concluded that routine prophylaxis is not supported by the available evidence, whether or not there is evidence of CSF leakage.[84,85] We do not recommend routine antibiotics for basilar skull fractures unless the patient is immunocompromised.[84,85] Most CSF leaks resolve spontaneously within 1 week, with no complications.[98] If the leak persists beyond 7 days, the incidence of bacterial meningitis increases significantly; prophylactic antibiotics should be given in such cases. Antibiotic selection is identical to that for penetrating head trauma. If a patient with a previously diagnosed CSF leak returns to the ED later with fever, the diagnosis of meningitis should be strongly suspected and appropriate evaluation (ie, lumbar puncture) and antibiotic treatment initiated immediately. Treatment of posttraumatic meningitis is discussed in Chapter 99.

Extra-Axial Lesions

Epidural Hematoma. Expert consensus guidelines support rapid surgical evacuation for any patient who has mass effect on a CT scan or progressive neurologic deterioration. Indications for urgent surgical evacuation include epidural hematomas larger than 30 cm^3, regardless of the patient's GCS score, as well as comatose patients with an acute EDH and anisocoria on pupillary examination. For patients with acute EDH who are awake and have no focal neurologic deficits, nonsurgical management is based on the size of the hematoma (<30 cm^3), thickness of the clot (<15 mm), and degree of midline shift (<5 mm). In those managed nonoperatively, close neurologic observation in a neurosurgical center is required, and the first repeat CT scan should be obtained within 6 to 8 hours postinjury.

Subdural Hematoma. Because of associated brain injury caused by the SDH, the delay in clinical signs and symptoms, and the more advanced mean age of the at-risk population, the mortality associated with SDH is much higher than that associated with EDH. Pupil inequality, motor deficit, and other signs consistent with increased brain swelling may be present on the initial examination. If the patient is deeply comatose at presentation, with flaccidity and without signs of brainstem activity, he or she may best be served by simply providing supportive care. Subsequent management decisions should be discussed with the patient's family and attending neurosurgeon. A small SDH (only a few millimeters thick at its widest point on CT scan) often is amenable to serial observations of the patient's status and appearance of the SDH on CT scan. Even a small SDH may be accompanied by extensive brain tissue damage that can cause an increase in ICP sufficient to precipitate a herniation syndrome.

Indications for surgical evacuation include acute SDHs with a thickness more than 10 mm or a midline shift of more than 5 mm on a CT scan, regardless of the patient's GCS score. Other parameters for surgical evacuation include a worsening GCS score (≥2 points from the time of injury to hospital admission) in comatose patients, asymmetric or fixed and dilated pupils, and persistent elevation in ICP. Most patients with subacute SDH require surgical evacuation of the lesion.

The treatment of chronic SDHs is controversial. Symptomatic chronic SDHs require surgical evacuation. Most patients have a good outcome after surgery. Overall, the mortality from surgically drained chronic SDH approaches 5%, with decreased survival in older adults.[99]

Traumatic Subarachnoid Hemorrhage. If there is no other brain injury, tSAH does not generally carry a poor prognosis. The most serious complication of tSAH is worsening of cerebral vasospasm, which may be severe enough to induce cerebral ischemia. Posttraumatic vasospasm is common, occurring approximately 48 hours after injury and persisting for up to 2 weeks. Vasospasm following TBI is characterized by a different time course, duration, and associated profile of risk factors than those of aneurysmal SAH (aSAH).[100] Although, no treatments have been shown to affect outcomes conclusively in tSAH, calcium channel

blockers, such as nimodipine and nicardipine, have been used in the acute ICU setting to prevent or reduce vasospasm after tSAH.[100] However, we do not recommend the routine use of calcium channel blockers in tSAH. Patients with severe TBI and large amounts of SAH may benefit from serial noninvasive monitoring and institution of therapy in the setting of radiographic or clinical deterioration.

Subdural Hygroma. If SDHGs are asymptomatic, observation is reasonable. Otherwise, they are surgically evacuated. Mortality approaches 20% and appears to depend on the severity of other intracranial injury.[101]

Intra-Axial Lesions

Cerebral Contusion. In one series of patients with brain contusions who initially received conservative treatment, 45% had significant progression on CT, and 19% required surgical intervention.[102] Patients with lower GCS scores and larger cerebral contusions are at higher risk for hemorrhagic progression and the need for delayed surgical decompression.[102] Hemorrhagic progression of a contusion generally occurs within the first 12 hours, but may occur as late as 3 to 4 days after head trauma. Small contusions that progress are usually clinically silent and are unlikely to require surgical decompression.

Intracerebral Hematoma. Many patients with an ICH require emergent intervention or surgery to lower elevated ICP. Mortality is low in patients who are conscious before surgery, whereas in unconscious patients, mortality approaches 45%. ICHs that bleed into the ventricles or cerebellum also carry a high mortality rate.

Intracerebellar Hematoma. Acute management should first address the most clinically significant lesion. Mortality from isolated traumatic intracerebellar hematoma is very high. Emergent neurosurgical consultation is indicated.

Complications and Outcome

Seizures

PTSs are classified as early when they occur within 7 days of injury or late when they occur after 7 days following injury. PTE is defined as recurrent seizures more than 7 days following injury. In patients with severe TBI, the rate of a clinical PTS may be as high as 12%, whereas that of subclinical seizures detected on electroencephalography may be as high as 20% to 25%.[10] The risk factors for early PTS include GCS score of 10 or lower, immediate seizures, posttraumatic amnesia lasting longer than 30 minutes, linear or depressed skull fracture, penetrating head injury, subdural, epidural, or intracerebral hematoma, cortical contusion, age 65 years or younger, or chronic alcoholism.[82] Rates of PTE are substantially higher than the risk of developing epilepsy in the general population. The risk factors for PTE include severe TBI, early PTSs prior to discharge, acute intracerebral hematoma or cortical contusion, posttraumatic amnesia lasting longer than 24 hours, age older than 65 years, and premorbid history of depression.[82]

Early PTSs, within 24 hours of injury, are usually brief and are probably caused by transient mechanical and neurochemical changes within the brain. In the 24 to 48 hours after trauma, seizures are caused by worsening cerebral edema, small hemorrhages, or penetrating injuries. PTSs are common in children and can be precipitated by MTBI but are more common in moderate and severe TBI.[103,104] Acute PTS prophylaxis in the ED is recommended for penetrating brain injury.[46,105] Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS from a nonpenetrating injury. Phenytoin is recommended to decrease the incidence of early PTS (within 7 days of injury), when the overall benefit is thought to outweigh the complications associated with such treatment. However, early PTSs have not been associated with worse outcomes.[10] Newer agents, such as levetiracetam, have been assessed for this purpose as well.[106] However, at present, there is insufficient evidence to recommend levetiracetam over phenytoin regarding efficacy for preventing early PTSs and toxicity.[10] The decision to maintain the head trauma patient on long-term anticonvulsant therapy during the recovery period depends on the patient's subsequent course. Long-term seizure prophylaxis is not indicated for all patients who have had PTSs in the acute or subacute period.[10] Prophylactic anticonvulsants are not recommended to prevent late PTSs.[10,107,108]

Central Nervous System Infections

Meningitis After Basilar Fractures. Posttraumatic meningitis is caused by a variety of microbes, depending on the portal of bacterial entry. Patients have typical signs and symptoms of meningitis, including fever, altered mental status, and occasional focal neurologic signs. In patients with a CSF leak after basilar fracture, early meningitis (ie, within 3 days of injury) is usually caused by pneumococci. Treatment of posttraumatic meningitis is discussed in Chapter 99.

Brain Abscess. Brain abscesses develop infrequently after penetrating missile injuries to the head. Abscesses can also develop after open depressed skull fractures if bone fragments are not removed or as a postoperative complication. Posttraumatic CSF fistulae and fractures that disrupt air-filled sinuses predispose to the formation of brain abscesses. Clinical manifestations include headaches, nausea, vomiting, declining mental status, signs of increased ICP, and new focal neurologic findings in patients who had been improving after trauma. Evaluation and treatment of brain abscess are discussed in Chapter 99.

Cranial Osteomyelitis. Cranial osteomyelitis can occur after penetrating injury to the skull. The clinical manifestations include pain, tenderness, swelling, and warmth at the infected site. More than 50% of cases are obvious on plain skull radiographs. Technetium bone scans can help in the diagnosis when the skull radiographs are negative, but false-positive bone scans occur in patients with previous trauma or craniotomy. Adding a gallium scan helps differentiate infection from other causes of a positive technetium scan. Patients with posttraumatic cranial osteomyelitis require surgical débridement and removal of the infected bone. Antibiotic choice is determined by culture results. If systemic symptoms are present, an underlying subdural or epidural empyema is often present.

Medical Complications

There are several systemic manifestations of TBI that can occur in the absence of any specific organ injury or systemic infection. The nature and severity of these manifestations depend mainly on the severity of the brain injury.

Disseminated Intravascular Coagulation. The injured brain is a source of tissue thromboplastin that activates the extrinsic clotting system. Disseminated intravascular coagulation (DIC) can develop within hours after any injury disrupting brain tissue. Cerebral intravascular coagulation is a universal response to TBI and is found in tissues from surgical specimens of human cerebral contusions. Coagulation abnormalities, including systemic DIC, are detected in over 50% of severe TBI patients.[109] Isolated severe TBI patients who develop coagulopathy have higher mortality rates than isolated severe TBI patients without coagulopathy.[110] DIC not only increases morbidity and mortality after severe TBI, it increases the risk of delayed intracranial hemorrhage. If a stable

patient with DIC suddenly deteriorates, a repeat CT scan should be obtained to rule out hemorrhage.

The extent of tissue destruction determines the degree of DIC that develops. The diagnosis is based on abnormalities in the international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), platelets, plasma fibrinogen levels, and fibrin degradation products. Patients with coagulopathy or abnormal platelet function require interventions to correct these.[111] Furthermore, patients with moderate or severe head trauma are at extremely high risk to experience venous thromboembolic events (VTEs) after admission to the hospital. Recent evidence has suggested that patients with moderate or severe head trauma can be safely treated with low-molecular-weight heparin to reduce the risk of VTEs without significantly increasing the risk of intracerebral hematoma expansion.[112]

Neurogenic Pulmonary Edema. Neurogenic pulmonary edema can develop minutes to days after head trauma.[113] It leads to an increase in extravascular fluids in the lungs, which causes hypoxia and decreased lung compliance. Theories on its pathophysiology include the following: (1) catecholamine surge or blast from the TBI, resulting in increased intravascular pressure, increased capillary permeability, and hydrostatic edema[114]; and (2) a systematic inflammatory reaction leading to endothelial damage and vasogenic edema. Treatment of acute lung injury in TBI is challenging because measures such as hypercapnia, fluid restriction, and prone ventilation (which raises ICP) that are routinely used to treat lung injury are contraindicated in TBI.[113] Positive end-expiratory pressure (PEEP) is commonly used to reduce lung fluids. Although PEEP is thought to increase ICP by reducing venous return, studies have shown that with adequate intravascular volume and MAP, PEEP does not adversely affect ICP and may reduce ICP by improving cerebral oxygenation. Furthermore, controlling ICP also appears to reduce the neurogenic stimulation that may contributes to this edema. Close ICP and ventilator management are essential to improved outcomes in patients with acute lung injury secondary to TBI.

Cardiac Dysfunction. A variety of cardiac rhythm, rate, and conduction abnormalities are detected after TBI. Harvey Cushing noted a connection between cardiac dysrhythmias and intracranial bleeding in the early 20th century. Many brain-injured patients with cardiac dysfunction have concurrent myocardial injury from underlying disease or chest injury. However, brain injury can cause primary cardiac dysfunction. High levels of circulating catecholamines have been measured in head-injured patients, with increased sympathetic nervous system activation.[115,116] Cardiac rhythm abnormalities have been reported in up to 70% of all patients with tSAH and more than 50% of all patients with traumatic intracranial hemorrhage.[115] In SAH, the cardiac dysrhythmias may result from autonomic nervous system dysfunction that subsequently affects ventricular polarization.

The most common cardiac dysrhythmia after TBI is supraventricular tachycardia, but many other rhythms have been observed. Findings on the electrocardiogram include diffuse large upright or inverted T waves, prolonged QT intervals, ST segment depression or elevation, and U waves. The primary goal in the emergency management of cardiac dysfunction after head trauma is ensuring adequate tissue perfusion and avoiding hypoxia. Dysrhythmias in head-injured patients often resolve as ICP is reduced.

Disposition

All patients with moderate TBI should be admitted for a period of observation, even with an initial, apparently normal CT scan. Frequent neurologic checks should be initiated, and a repeat CT scan is indicated if the patient's condition deteriorates or fails to improve over the first 48 hours after trauma. In patients with persistent symptoms of headache, confusion, or memory difficulties, delayed MRI may define lesions in the regions related to cognition that cannot be seen on CT. Although not useful in the acute setting, MRI has prognostic value during subsequent care and assists in directing the future rehabilitation of these patients.

All patients with moderate to severe head trauma require imaging to determine the extent and nature of the brain injury and necessity of neurosurgical intervention. Neurosurgical consultation should be obtained as soon as possible to help direct the patient's subsequent management. Moderate and severely head-injured patients require admission to an institution capable of intensive neurosurgical care and acute neurosurgical intervention. If this is not available at the receiving hospital, the patient should be transferred to an appropriate institution.

MILD TRAUMATIC BRAIN INJURY

Clinical Features and History

As with moderate and severe TB, a comprehensive history includes information from the patient, prehospital personnel, family members and witnesses about the mechanism of injury, events before and after the injury, age, comorbidities, coagulopathies (eg, hemophilia, Von Willebrand disease, hepatic insufficiency, use of anticoagulants), consumption of alcohol or drugs, changes in mental status or deteriorating GCS scores, previous TBI or concussion, symptoms of other potential injuries, and TBI symptoms (including postconcussive symptoms). By definition, the diagnosis of MTBI is largely clinical. It is not uncommon for MTBI symptoms to dissipate by the time patients reach the ED. It is important to ask patients specifically about symptoms of disorientation, confusion, amnesia, or disordered awareness, with or without loss of consciousness. A number of MTBI patients do not experience a loss of consciousness and, if they do, it is difficult to quantify unless there are witnesses. Patients may report headache, dizziness (vertigo or imbalance), lack of awareness of surroundings, and nausea and vomiting. Patients may also complain of mood and cognitive disturbances, sensitivity to light and noise, impaired verbal memory, delayed language comprehension, and slowed speech and exhibit balance problems.

Alert patients are questioned regarding cervical spine pain. Immobilization is indicated until cervical spine injury is excluded.

Physical Examination

The general physical examination is as for the patient with moderate or severe head injury, as described earlier. A more detailed neurologic examination is often possible in patients with mild MTBI who are able to interact with the examiner and cooperate with the examination. The examination includes evaluation of the cranial nerves, because CN injuries can occur in MTBI, particularly in conjunction with skull base fractures.[117] Assess for anosmia and hyposmia, because the olfactory nerve (CN I) is one of the most common CNs affected after MTBI.[117] This may be done by having the patient smell ground coffee or a citrus-scented beverage or cleaning agent. The facial nerve (CN VII) and oculomotor nerves (CNs III, IV, and VI) are also frequently injured, so assess for facial paralysis, change in taste, and/or diplopia. In MTBI, CNs IV and VI are more commonly injured than CN III.[117] CN VII palsy may indicate a fracture of the temporal bone, particularly if it occurs in association with decreased hearing (CN VIII). Hearing impairment can be one of the more subtle deficits seen after TBI.[118] Facial pain (CN V) and occipital neuralgia may also occur in association with MTBI. Assess coordination, balance, and gait. MTBI patients often can have difficulty with the finger-nose-finger test and will use slow purposeful movements to complete the task.

Romberg testing may demonstrate significant sway. Vestibular problems can affect balance and gait.[119] Assess sensation, motor strength, symmetry, and reflexes. Note if the patient displays a peculiar flat affect, appears devoid of emotion, and speaks in a slow monotone voice without inflection, which may indicate damage to the prefrontal cortex or frontal lobes.[120]

Differential Diagnosis

MTBI (GCS score of 13–15) is characterized by symptoms of confusion and amnesia, with or without preceding loss of consciousness. The differential diagnosis, in the context of trauma, therefore includes intoxication (drugs, alcohol, medications), posttraumatic seizures and postictal state, hypoglycemia, and other injuries that may impair a patient's ability to communicate, such as hypoxemia or hypoperfusion (from extracranial injuries), facial bone fractures, cervical spine or spinal cord injuries, injuries to the eyes or tympanic membranes, laryngeal or vocal cord injuries, and vascular injuries of the neck. Patients can deteriorate from an expanding intracranial hematoma after what appears clinically to be a MTBI, even if the patient presents with a GCS score of 15. In such a case, the injury would be reclassified as moderate or severe TBI.

Prior to the trauma, patients may have experienced a syncopal episode, seizure, or cardiac event that produced a loss of consciousness that led to the subsequent trauma. For example, an MVC may have resulted from the driver becoming distracted or incapacitated by important symptoms suggestive of an unrelated disorder. Therefore, potential precipitants to the trauma should also be considered in the differential diagnosis.

An MTBI or concussion may go unrecognized in the ED, especially if symptoms are transient or if more visible injuries dominate the assessment. An underlying dementia or psychiatric illness may make it very difficult to distinguish an MTBI from baseline cognitive or mental dysfunction. Other conditions that could cofound the diagnosis include stroke, encephalopathies (eg, hepatic, uremic), delirium from alcohol or drug withdrawal, neurologic conditions (eg, Parkinson's or Alzheimer's disease, autism), and infection or sepsis. Even low-mechanism trauma should alert the emergency clinician to the possibility of brain injury in susceptible populations. A thorough medical evaluation is critical.

Diagnostic Testing

Neuroimaging in the Emergency Department With Computed Tomography

CT imaging of the head is the diagnostic standard for identifying intracranial injury in the ED. However, CT is associated with exposure to ionizing radiation and higher health care costs.[121] Therefore, a number of clinical decision rules have been prospectively derived and validated to identify patients at risk for neurosurgical intervention and intracranial lesions on CT scan in adult patients with suspected MTBI in the ED. These include the New Orleans Criteria (NOC), Canadian Computed Tomography Head Rule (CCHR), and National Emergency X-Radiography Utilization Study II (NEXUS-II; Box 34.4). Others have developed guidelines based on available evidence, including the American College of Emergency Physicians clinical policy on neuroimaging of adult ED patients with MTBI (ACEP), National Institute for Health and Clinical Excellence (NICE), Neurotraumatology Committee of the World Federation of Neurosurgical Societies (WFNS), Scandinavian Neurotrauma Committee, and Scottish Intercollegiate Guidelines Network (SIGN). Although most of the rules and guidelines produce high sensitivities for detecting neurosurgical intervention and intracranial lesions, the specificities are variable. Additional clinical decision rules have been developed for use in the pediatric population (see Chapter 165).[122]

The most widely researched clinical decision rules for MTBI are the CCHR and NOC, with external validation studies in the United States and internationally.[123-126] The CCHR was developed for use in patients with a GCS score of 13 to 15; it divides clinical variables into high- and medium-risk categories. The NOC was developed for use in patients with a GCS score of 15 only and is composed of seven clinical variables. For injuries requiring neurosurgical intervention, both the CCHR and NOC have a high sensitivity (99%–100%) but the CCHR has a much higher specificity (CCHR, 48%–77%; NOC, 3%–31%).[127] For identification of traumatic intracranial lesions on CT, the CCHR and NOC have a high sensitivity (CCHR, 80%–100%; NOC, 95%–100%) but specificity is higher with the CCHR.[127] In terms of potential for CT reduction, adherence to the NOC results in an increase in head CT use; adherence to the CCHR results in a decrease in head CT use compared to current practice.[124] Imaging of patients in this population should follow a validated guideline. Clinicians in emergency medicine, trauma surgery, neurosurgery and, as indicated, neurology, should review the relevant guidelines (CCHR, NOC) and select the system thought to be most applicable for their setting and patient population. Oversight should ensure that cases not following the adopted guidelines are reviewed and feedback is provided to emergency clinicians.

BOX 34.4

Clinical Decision Rules for Neuroimaging in Adults With Mild Traumatic Brain Injury

CANADIAN COMPUTED TOMOGRAPHY HEAD RULE (CCHR)

High-Risk Injury (May Require Neurologic Intervention)

1. GCS score < 15 at 2 hr after injury
2. Suspected open or depressed skull fracture
3. Any sign of basal skull fracture (hemotympanum, raccoon eyes, CSF otorrhea or rhinorrhea, Battle's sign)
4. Vomiting ≥ two episodes
5. Age ≥ 65 years

Medium-Risk Injury (May Have Important Brain Injury on CT)

6. Amnesia before impact ≥ 30 min
7. Dangerous mechanism (pedestrian struck by vehicle, occupant ejected from vehicle, fall from elevation >3 feet [five stairs])

NEW ORLEANS CRITERIA (NOC)

1. Headache
2. Vomiting
3. Age > 60 yr
4. Drug or alcohol intoxication
5. Persistent anterograde amnesia
6. Trauma above the clavicle
7. Seizure

NEXUS II CRITERIA

1. Evidence of significant skull fracture
2. Scalp hematoma
3. Neurologic deficit
4. Altered level of alertness
5. Abnormal behavior
6. Coagulopathy
7. Persistent vomiting
8. Age ≥ 65 yr

CSF, Cerebrospinal fluid; *GCS,* Glasgow Coma Scale.

Other Neuroimaging Modalities

Structural MRI. CT is the imaging modality of choice for initial screening to exclude serious traumatic intracranial lesions in MTBI. However, many patients who develop persistent symptoms and cognitive deficits have no detectable abnormalities on CT. MRI is better than CT in detecting posttraumatic ischemic infarctions, subacute nonhemorrhagic lesions and contusions, axonal shear injury, and lesions in the brainstem or posterior fossa. Structural MRI, particularly at a 3-T strength, improves structural sensitivity, can be performed when neurologic findings cannot be explained by CT,[128] and is particularly valuable in assessing the brainstem, posterior fossa, and brain parenchyma adjacent to the calvaria.[129] Structural MRI (without contrast) can also be used for the evaluation of TBI-related symptoms in the subacute and chronic phases of injury.[128]

Susceptibility-Weighted Imaging. A significant advancement in the imaging of MTBI has been the development of susceptibility-weighted imaging (SWI). This technique is an imaging method that grew out of and is part of MRI. It uses differences in magnetic susceptibility between tissues and is particularly helpful for the evaluation of TAI and punctate hemorrhages in the deep subcortical white matter not visible on CT or structural MRI scans. It takes about 4 minutes to image the entire brain and, in the ED, SWI detects additional lesions 30% of the time compared to CT and structural MRI.[130] The number and volume of SWI hemorrhagic lesions correlate with clinical outcome.[131]

Diffusion Tensor Imaging. DTI uses MRI technology to analyze the movement of water molecules in the white matter of the brain and also provides the opportunity to perform tractography—visualization of major white matter pathways—to assess damaged nerve fiber tracts.[16] DTI detects white matter abnormalities and underlying cognitive deficits when conventional imaging is normal[132] and may be a sensitive marker of TAI in MTBI at acute and chronic stages of its clinical course.[133]

Computed Tomography Angiography and Magnetic Resonance Angiography. Vascular imaging such as CT angiography and MR angiography are not recommended routinely for patients with MTBI unless there is suspicion of a traumatic vascular injury, such as pseudoaneurysm, dissection, or uncontrolled hemorrhage. Typically vascular injuries occur with penetrating trauma, skull base fractures, blunt neck trauma, and/or skull base or cervical spine fractures. Independent predictors of arterial injury in blunt trauma include cervical facet subluxation or dislocation, fracture lines approaching an artery, and high-impact injury mechanisms.[134]

Ancillary Studies

Laboratory Testing. Laboratory tests are not needed for patients with isolated MTBI except for a bedside glucose level in those with a GCS score less than 15. Coagulation parameters such as INR, PT, and PTT are indicated for those with inherent coagulopathies or suspected liver disease and those on anticoagulants.

Although not in clinical use at this time, glial fibrillary acidic protein (GFAP) is a promising brain-specific biomarker for MTBI in adults and children (Fig. 34.16).[135-140] GFAP is released into serum following a MTBI within 1 hour of injury,[135,138,140] and its level is elevated in MTBI patients with axonal injury, as evidenced by MRI at 3 months postinjury.[136] It can remain elevated for seven days post-injury.[140a] In adults and children, studies have shown that serum GFAP levels distinguish MTBI patients from trauma patients without TBI and detect intracranial lesions on CT with a sensitivity of 94% to 100%.[135,138-140]

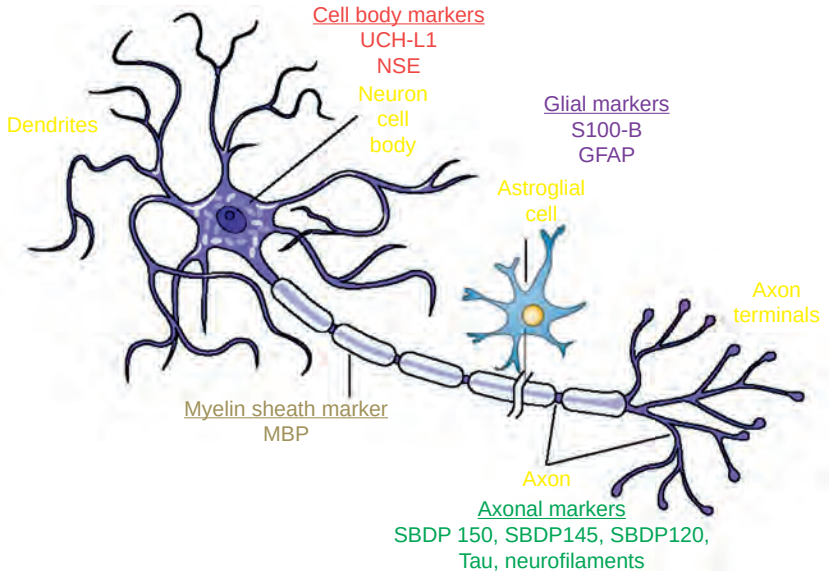


Fig. 34.16. Neuron and neuroanatomic locations of potential TBI biomarkers. S100β is the major low-affinity calcium binding protein in astrocytes that helps regulate intracellular levels of calcium. Glial fibrillary acidic protein (GFAP) is a monomeric intermediate protein found in the astroglial skeleton and in white and gray brain matter and is strongly upregulated during astrogliosis. Neuron-specific enolase (NSE) is one of the five isozymes of the gycolytic enzyme enolase found in central and peripheral neuronal cell bodies. UCH-L1 is highly abundant in neurons and was previously used as a histologic marker for neurons. Alpha II-spectrin is the major structural component of the cortical membrane cytoskeleton and is particularly abundant in axons and presynaptic terminals. Tau is an intracellular, microtubule-associated protein that is highly enriched in axons. Neurofilaments are heteropolymeric components of the neuron cytoskeleton. (From Papa L: Exploring serum biomarkers for mild traumatic brain injury. In Kobeissy F, editor: Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects in brain injury models. London, 2015, CRC Press, p 303.)

Neuropsychological Testing. Neuropsychological testing is used to assess cognitive function after MTBI and is commonly used following sports concussion. Although not routinely done in the ED, referral to a neuropsychologist is warranted for patients having persistent symptoms following a concussion.

Disposition

Most patients with MTBI can be discharged from the ED with a normal examination and after a reasonable period of ED observation (4–6 hours) or following a negative head CT scan, except in the presence of therapeutic anticoagulation, when more prolonged observation, up to 12 hours, sometimes with repeat head CT, is warranted.[141] If the emergency clinician decides that the patient with MTBI can be sent home, an appropriate early follow-up should be arranged. Providing patients and families with educational information about postconcussive syndrome and what to expect after injury helps improve outcome. Patients should also be given contact information for the brain injury association in their state. State brain injury associations can connect patients and families with support groups, programs, and professionals who understand the injury (www.biausa.org/mild-brain-injury.htm).

Patients should be discharged with instructions describing the signs and symptoms of acute and delayed complications of MTBI, have access to a telephone, and be monitored in the acute posttrauma period by a responsible sober adult. All discharge instructions should be written and told to a responsible third party. Warning signs for acute deterioration, such as inability to waken the patient, severe or worsening headaches, somnolence or confusion, restlessness, unsteadiness, or seizures, difficulties with vision, vomiting, fever, or stiff neck, urinary or bowel incontinence, and weakness or numbness involving any part of the body should prompt the caregiver to seek immediate medical help. If any doubt exists regarding the safety of the discharged patient with MTBI, a brief inpatient observation period (12–24 hours) is advisable.

If resources allow, prolonged ED observation may be practical in some circumstances. For example, intoxicated patients with MTBI who otherwise fulfill low-risk criteria should undergo serial evaluations in the ED until clinical sobriety is achieved. In these patients, a CT scan may be unnecessary, and ED observation is beneficial.

If a patient with MTBI returns to the ED because of persistent symptoms, delayed complications of injury should be sought. If a CT scan was not initially obtained, the intensity of symptoms may guide the decision to obtain a CT scan at the second visit. If a negative scan was initially obtained, the likelihood of the subsequent development of an intracranial lesion is exceedingly low.[7,8] The decision to rescan is more complex in patients from certain subgroups who may be considered more likely to develop delayed complications. These include patients on anticoagulation, those with preexisting neurologic injuries that may obscure an examination, and those with previous neurosurgical procedures (eg, ventriculoperitoneal shunts). The literature about repeat CT scanning in MTBI suggests that patients who are unchanged or improving neurologically do not benefit from a repeat CT, but repeat imaging is indicated to assess a deteriorating patient.[7,8]

Complications

In addition to being at risk for serious intracranial injuries, patients with a suspected MTBI can have elusive axonal injuries[15,142] and, over the long term, can suffer impairment of physical, cognitive, and psychosocial functioning.[143] It has been reported that more than one-third of MTBI patients do not resume work until 1 to 3 months after their injury, and lingering cognitive complaints are reported by as many as 15% of patients 1 year postinjury.[144] Recovery can also be complicated by psychiatric or substance abuse problems, health problems, concurrent orthopedic and/or traumatic injuries, chronic pain, lack of family and social support, unemployment, and litigation.[145]

Postconcussive Syndrome

Postconcussive syndrome (PCS) refers to a constellation of symptoms that include somatic (headache, dizziness, vertigo, nausea, fatigue, sensitivity to noise and light), cognitive (difficulties with attention, concentration, and memory) and affective complaints (irritability, anxiety, depression, emotional lability) that occur following a MTBI or concussion and persist beyond the expected recovery period. Affected patients commonly report headache, dizziness, memory or concentration difficulties, irritability, sleep disturbances, dizziness, and depression. There appears to be psychological and structural components to postconcussive syndrome, because patients with a history of migraines, depression, or anxiety are more likely to experience postconcussive syndrome.[146] The severity and duration of postconcussive symptoms may correlate with the abnormalities found with early functional imaging.[147] Studies of ED patients have indicated that as many as 30% of patients with a discharge diagnosis of MTBI will have symptoms at 3 months postinjury, and up to 15% will continue to be symptomatic at 1 year postinjury. In the ED, patients with more severe symptoms, such as prolonged amnesia, dizziness, headache, anxiety, noise sensitivity, or trouble with verbal recall have been shown to be at a higher risk of developing postconcussive syndrome.[148] Other factors that have been identified as conferring an increased risk for the development of PCS symptoms include prior MTBI, history of depression and/or anxiety, multiple injuries, forgetfulness or poor memory, noise and/or light sensitivity, and history of migraine.[149,150] There are a wide range of treatments being studied, including cognitive and behavioral therapies, medications, devices, dietary supplements, return to activity and rest and others.[151]

Seizures

Posttraumatic seizures occur in fewer than 1% of MTBI patients, and acute antiseizure prophylaxis is not indicated.[152,153] The cumulative incidence of posttraumatic epilepsy in the first 3 to 5 years after discharge is about 4% for patients with MTBI.[153] PTE usually develops within the first 2 years after injury. Prophylactic treatment with anticonvulsants does not prevent delayed-onset PTE and is not recommended.[154]

Posttraumatic Transient Cortical Blindness

Posttraumatic transient cortical blindness syndrome is characterized by transient visual loss, normal pupillary response, and normal funduscopic examination within hours following MTBI. This syndrome has been reported mainly in children. In most cases, vision returns to normal within minutes to hours (usually within 24 hours) following injury and leaves no neurologic sequelae. Headache, confusion, irritability, anxiety, nausea, and vomiting are common related symptoms. Although the mechanism for the transient blindness is unknown, it has been suggested that it is an abnormal vascular response to trauma, with resultant transient hypoxia and cerebral dysfunction.

Special Populations With Mild Traumatic Brain Injury

Mild Traumatic Brain Injury and Concussion in Sports

It has been estimated that 3.8 million concussions occur in the United States annually from organized and recreational sports.[155] Football, ice hockey, soccer, and lacrosse tend to have the highest

concussion incidence rates when calculated by athlete exposure.[155] Although concussion is under the umbrella of MTBI, the term *concussion* is typically used to describe MTBI in athletes. It has been suggested that sports-related concussions are associated with less disability and more rapid recovery than concussions in non-athletes. However, neuroimaging has suggested similar patterns of neuronal disruption for sports- and nonsports-related MTBI.[156] Athletes are more vulnerable to the deleterious long-term effects of MTBI because they are often subjected to repetitive trauma and greater levels of physical exertion during recovery.[156] Only recently has chronic traumatic encephalopathy (CTE) come to public attention due to autopsy findings in high-profile athletes.[157] Originally identified in boxers,[21] CTE has recently been found to occur after other organized sports, including US football, hockey, soccer, and professional wrestling.[20,22,23] Meta-analyses of neuropsychological outcomes following MTBI have suggested that recovery from impairments in the general population takes longer (weeks to months) than in athletes who tend to show recovery within 2 to 14 days following concussion. Among athletes there is a tremendous motivation to return to play. As a result, athletes often underreport symptoms, return to their regular activities prematurely, and may create the impression that they recover more quickly than they actually do.[156]

Second-impact syndrome is thought to be an exceedingly rare yet catastrophic, and sometimes fatal, consequence of repeated MTBI in sports occurring within a short period of time (days). It is defined as occurring when "an athlete who has sustained an initial head trauma, most often a concussion, sustains a second head trauma before symptoms associated with the first have fully cleared,"[158] leading to diffuse cerebral swelling. The controversy surrounding second-impact syndrome is whether a repeated head trauma is required to cause it or whether the brain swelling is the result of a single blow to the head.[159] Most reported cases of this entity, including the index case, actually sustained a single blow and did not involve a "second" impact. Furthermore, many reported cases had evidence of other structural brain injuries, such as acute subdural hematomas, in addition to the cerebral swelling. Based on the published case studies, the two groups of athletes at a higher risk of this entity are boxers and children and adolescents. Accordingly, the Centers for Disease Control and Prevention (CDC) has developed the HEADS UP Concussion in Youth Sports initiative to offer information about preventing, recognizing, and responding to a concussion to coaches, parents, and athletes involved in youth sports.

In 2013, several new or updated clinical practice guidelines and position statements were published on the diagnosis, treatment, and management of MTBI and concussion in sports. Three of these guidelines were produced by the American Medical Society for Sports Medicine,[160] American Academy of Neurology,[161] and Zurich Consensus working group.[162] It was agreed that concussion is a clinical diagnosis that is ideally made by a licensed health care provider with experience in the evaluation and management of patients with a concussion. Any athlete suspected of having a concussion should be immediately removed from play. Graded symptom and clinical sign checklists can be useful, particularly if they can be compared to preseason data.[163] The Sport Concussion Assessment Tool, third edition (SCAT3), is a standardized tool for evaluating injured athletes for concussion and can be used in athletes 13 years of age and older. It replaces the original SCAT and SCAT2, published in 2005 and 2009, respectively[162] (http://bjsm.bmj.com/content/ 47/5/259.full.pdf). The SCAT3 takes 15 to 20 minutes to complete and computes a composite score comprised of the GCS, Standardized Assessment of Concussion (SAC) score (cognitive and physical evaluation, delayed recall), and balance assessment score (modified Balanced Error Scoring System [BESS]). For children from 5 to 12 years of age, the Child-SCAT3 is used (http://bjsm.bmj.com/content/47/5/ 263.full.pdf). The SCAT3 also includes a page of information to be given to the athlete and parents after discharge.

When evaluating an athlete with suspected MTBI or concussion in the ED, obtain a comprehensive history, taking into account additional information from parents, coaches, teammates, and eyewitnesses, such as mechanism of injury, events after the injury, changes in mental status or deteriorating GCS scores, prior MTBI or concussion, current symptoms (including postconcussive symptoms), and symptoms of other potential injuries (eg, cervical spine injury). As with any trauma patient, perform a thorough examination looking for other signs of trauma, and remember to evaluate for cervical spine injury. The neurologic examination should include an assessment of pupillary reactivity, cognitive functioning, and gait and balance. As with all MTBI patients, monitoring of the injured athlete with serial assessments is critical, because signs and symptoms may evolve over hours after injury. A head CT scans is not routinely recommended but should be considered if there is clinical suspicion of a traumatic intracranial lesion. Before return to play, a gradual, a stepwise increase in general physical activity, followed by sports-specific activities, is recommended. Progression to more strenuous steps is only recommended if the athlete is asymptomatic at the current level of activity (Table 34.3). Ideally, a multidisciplinary approach to assessment and management is used, with the inclusion of sports medicine specialists from various subspecialties, as

TABLE 34.3

Graduated Return to Play Protocol

REHABILITATION STAGE	FUNCTIONAL EXERCISE AT EACH STAGE OF REHABILITATION	OBJECTIVE OF EACH STAGE
1. No activity	Symptom–limited physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming, or stationary cycling, keep intensity to <70% of maximum predicted heart rate; no resistance training	Increase heart rate
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer; no head impact activities	Add movement
4. Noncontact training drills	Progression to more complex training drills, for example, passing drills in football and ice hockey; may start progressive resistance training	Exercise, coordination, and cognitive load
5. Full-contact practice	After medical clearance, participate in normal training activities	Restore athlete's confidence; coaching staff assesses functional skills
6. Return to play	Normal game play	

Adapted from McCrory P, Meeuwisse WH, Aubry M, et al: Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. J Athl Train 48:554–575, 2013.

appropriate for the athlete's symptoms and signs.[164] Because many states have passed laws regarding concussion management in organized youth sports, it is good practice for emergency clinicians to familiarize themselves with the laws of the state in which they are practicing.[155]

Key recommendations of all three recent position statements have stated that any athlete suspected of having a concussion should not be allowed to return to play on the day of the injury.[160-162] Athletes with concussion should not return to play until they have been evaluated by a licensed health care provider with expertise in concussion management. Head CT should only be considered if intracranial lesions are suspected. Furthermore, there should be a gradual stepwise increase in physical activity.[164]

Military Personnel and Blast Injury

Mild TBI is also a common injury among soldiers who have participated in combat. Explosive blast brain injury is becoming recognized as a distinct entity from the penetrating form of blast injury and closed brain injury.[165] In recent US conflicts in Iraq and Afghanistan, over 60% of combat casualties were from explosive blast, mostly from improvised explosive devices (IEDs).[166] Other mechanisms included falls, motor vehicle accidents, fragment shrapnel, and bullet wounds. In an explosive blast, the primary injury to the brain occurs when the physical forces emanating from a detonation impart loading on the head and consequently the brain. The definition of MTBI from the American Congress of Rehabilitation Medicine is currently being applied to explosive blast TBI (including loss of consciousness, amnesia, altered mental status, and focal neurologic deficit).[165] A soldier who has been exposed to a blast may lack overt evidence of a head injury, such as lacerations, bruising, or hematomas. Recognizing an MTBI acutely is important so that the soldier can receive appropriate medical attention and be removed from combat-related duty to avoid another TBI.[166] After the first blast exposure, many soldiers do not recognize that they may have been injured, and thus will not seek medical care. The first indication of injury may be persistent postconcussive symptoms, such as headaches, vertigo, short-term memory loss, and difficulty concentrating and multitasking.[166] The clinical presentation of explosive blast MTBI can be confounded by the considerable overlap between the symptoms of MTBI and posttraumatic stress disorder (PTSD), such as mood fluctuations, sleep disturbances, and difficulty concentrating. Both may occur in the same individual. PTSD symptoms usually include bursts of anger, irritability, hypervigilance, and increased startle response.[165]

Anticoagulated Patients

Patients on Anticoagulant Medications. Most clinical decision making rules exclude patients who are taking anticoagulants such as warfarin (vitamin K antagonists), antiplatelet medications (aspirin, clopidogrel), and non–vitamin K antagonists (factor IIa or Xa inhibitors). Overall, there is a higher incidence of intracranial bleeding in TBI patients on anticoagulants following head trauma, with an incidence of up to 22% in patients with MTBI.[167-169] As a result, most practice guidelines propose that patients who sustain head trauma and are on anticoagulation treatment should undergo a CT scan without contrast and should have the INR determined, because an initial INR greater than 3 confers a much higher risk of intracranial bleeding.[168-170] Some guidelines advocate observation for the first 24 hours following MTBI, along with a second CT scan.[168] However, intracranial bleeding can be delayed beyond the first 24 hours in 1% to 3% of anticoagulated patients and can present as late as 4 weeks following injury.[168-172] Antiplatelet medications are more likely to lead to immediate traumatic intracranial hemorrhage (12%) compared with patients receiving warfarin (5%), who are more likely to have delayed bleeding.[169] In anticoagulated patients with a negative CT scan, routine admission is not required.[173] Admission should be considered for anticoagulated patients with a high risk for delayed bleeding (eg, supratherapeutic INR), those with significant comorbidities, those who live alone, and those who cannot return to the hospital in a timely manner should symptoms of delayed bleeding appear.[173,174] This underscores the importance of detailed patient instructions on discharge from the hospital.[171]

Patients with therapeutic anticoagulation and a negative initial head CT scan do not need to have their anticoagulation reversed.[175] Patients on warfarin with traumatic intracranial lesions should undergo reversal with fresh-frozen plasma or prothrombin complex concentrates, and vitamin K should also be initiated in the ED.[176] However, the transfusion of platelets in patients on antiplatelet medications does not reduce mortality. Dabigatran can be reversed with hemodialysis, but rivaroxaban and apixaban cannot.[177] Idarucizumab, a Fab fragment of a monoclonal antibody directed specifically against dabigatran, was approved by the US Food And Drug Administration in 2015 for emergency surgery and urgent procedures and for life-threatening or uncontrolled bleeding. The recommended dose for idarucizumab is 5 g (2.5 g/vial), administered as two consecutive 2.5-g IV infusions or bolus injection by injecting both vials consecutively, one after another, via syringe. Andexanet alfa is a class-specific antidote targeted to reverse the oral direct factor Xa inhibitors as well as the indirect inhibitor, enoxaparin; ciraparantag is a universal antidote targeted to reverse the direct thrombin and factor Xa inhibitors, as well as the indirect inhibitor, enoxaparin.[178] Studies evaluating these antidotes in the setting of TBI are currently lacking.

Patients With Inherent Bleeding Disorders. The most serious site of bleeding for children and adults with inherent bleeding disorders, such as hemophilia, is the CNS. Intracranial hemorrhage in patients with hemophilia can occur spontaneously or following mild head trauma. Over 50% of hemophiliacs with MTBI who have intracranial bleeding are initially asymptomatic, with a normal neurologic examination. Therefore, patients with inherent bleeding disorders should undergo head CT following a MTBI.[179] There should be a low threshold for factor replacement (eg, factor VIII or IX, cryoprecipitate, fresh-frozen plasma) in patients with severe hemophilia or in those with MTBI symptoms, even prior to performing head CT.[180]

Head Trauma in Older Adults

Older patients have increased morbidity and mortality from TBI and have higher rates of intracranial injuries following head trauma.[1,181,182] They also experience MTBI more frequently than severe TBI. Furthermore, frequent falls put them at risk for repetitive brain injury. Within 7 months following a mild or moderate TBI, older patients can show a decline in language, memory, executive function, activities of daily living, and mood compared with their preinjury functioning and compared to controls.[183] Accordingly, older adults with preinjury warfarin or clopidogrel use are at an increased risk for unfavorable long-term neurologic outcomes compared with similar patients without preinjury use of these medications.[184]

With age, the brain atrophies and creates more space within the cranial vault for blood to accumulate before symptoms appear. Moreover, with atrophy, comes stretching of bridging veins that may tear and lead to subdural hematomas more easily. Therefore, older adults can have significant hemorrhage into their brain and not show signs of deterioration, especially if their baseline cognitive functioning is impaired. Occult intracranial hemorrhages occur in over 2% of older patients with head trauma.

Alcohol abuse is one of the most prevalent comorbid conditions found in older patients admitted to the hospital with TBI,[185] so screening for alcohol abuse in older patients with head trauma is recommended.[186] Elder abuse is an important consideration in this population as well and should be assessed during the ED evaluation.[187]

The presence of comorbid medical conditions, use of anticoagulants, preexisting cognitive deficits, polypharmacy, alcohol consumption, and unique physiology of the aging brain make it challenging for the emergency clinician to detect brain injury.[186] Even low-mechanism falls should prompt health care providers to consider the possibility of brain injury in older patients. Many clinical decision rules recommend CT for patients older than 60 to 65 years following any suspected MTBI. Reducing the risk of falls in older adults can reduce the risk of TBI.[188] Particular attention needs to be given to polypharmacy, drug interactions, safety issues in the living environment, risk of elder abuse, and covert alcohol consumption.[186,188]

KEY CONCEPTS

- *Head trauma* is a broad term describing an external trauma to the craniofacial area of the body from blunt, penetrating, blast, rotational, or acceleration-deceleration forces, the term *head injury* refers to a clinically evident injury on physical examination, and the term *brain injury* indicates an injury to the brain itself.
- TBI is often categorized into mild (GCS score, 13–15), moderate (GCS score, 9–12), and severe (GCS score, 3–8), but this actually represents a spectrum of injury. Patients with a presentation GCS score of 13 to 15 who are stable or improving are exceedingly unlikely to have CT findings that warrant intervention.

Severe and Moderate Traumatic Brain Injuries

- Secondary systemic insults such as hypoxia and hypotension worsen neurologic outcome and should be corrected as soon as detected.
- Noncontrast head CT is the imaging modality of first choice when TBI is suspected.
- The motor component of the GCS is the strongest predictor of outcome following TBI.

Penetrating Head Trauma

- Anticonvulsant prophylaxis with phenytoin and broad-spectrum antibiotics should be given to patients with penetrating brain injuries for 7 days postinjury.

Mild Traumatic Brain Injury

- Patients can deteriorate from an expanding intracranial hematoma after what appears clinically to be MTBI, and should undergo serial evaluations, including serial GCS scoring.
- An MTBI can be easily overlooked when an alert patient presents with other more obvious traumatic injuries. Specifically, ask patients about symptoms of disorientation, confusion, amnesia, or disordered awareness (with or without loss of consciousness).
- Imaging of patients in this population should follow a validated guideline, such as the Canadian CT Head Rule and New Orleans Criteria. Emergency clinicians should work collaboratively to select the system thought to be most applicable for their setting and patient population.
- Alcohol and drug use affects the GCS score and significantly obscures the neurologic examination. Intoxicated individuals are high-risk patients.
- Most patients with MTBI can be discharged from the ED with a normal examination and after a reasonable period of ED observation (4–6 hours) or following a negative head CT.
- Patients should be discharged with instructions describing the signs and symptoms of acute and delayed complications of MTBI. All discharge instructions should be written and relayed to a responsible third party.

Special Populations

- Any athlete suspected of having a concussion should be immediately removed from play.
- Athletes with concussion should not return to play until they have been evaluated by a licensed health care provider with expertise in concussion management. There should be a gradual stepwise increase in physical activity.
- Older adults can have significant hemorrhage into their brain and not show signs of deterioration, especially if their baseline cognitive functioning is impaired. Patients older than 60 years should have a CT scan obtained.
- Falls in older adults, including low-mechanism falls, should prompt health care providers to consider the possibility of brain injury.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 34: QUESTIONS & ANSWERS

34.1. Injured brain ischemia may be seen with partial pressure of carbon dioxide (Pco_2) levels below what value?
A. 35 mm Hg
B. 30 mm Hg
C. 25 mm Hg
D. 20 mm Hg

Answer: D. Cerebral vasculature is exquisitely sensitive to Pco_2 levels. The degree of vasoconstriction below a Pco_2 of 20 mm Hg may be so severe as to induce ischemia. Modest hyperventilation to a target of 30 to 35 mm Hg is recommended once acute resuscitation is completed.

34.2. Which of the following statements is true regarding cerebral blood flow (CBF), cerebral perfusion pressure (CPP), and intracranial pressure (ICP)?
A. CBF autoregulation is lost below a CPP of 60 mm Hg.
B. CPP closely parallels diastolic blood pressure.
C. Normal ICP is 65 to 195 mm Hg.
D. CPP = mean arterial pressure (MAP) − ICP.
E. The only resistance to CBF is ICP.

Answer: D. CBF depends on CPP, which is the blood flow pressure gradient. CBF resistance is provided by mean systemic venous pressures and ICP, predominantly by the latter. CPP closely parallels MAP offset by ICP; thus, the formula CPP = MAP − ICP. ICP is estimated clinically by the central venous pressure unless a ventricular catheter is in place and ICP can be directly determined. CBF autoregulation is lost below a CPP of 40 mm Hg. Normal ICP is 5 to 15 mm Hg or 65 to 195 mm H_2O.

34.3. Which of the following parameters are associated with a worsened outcome after traumatic brain injury (TBI)?
A. Both D and E
B. Core body temperature > 37.5° C (99.5° F)
C. None of the above
D. Partial pressure of oxygen (Po_2) < 60 mm Hg
E. Systolic blood pressure < 90 mm Hg

Answer: A. The following are associated with worsened outcomes after TBI:
Hematocrit (Hct) < 30%
Temperature > 38.5° C (101.3° F)
Systemic blood pressure (SBP) < 90 mm Hg
Po_2 < 60 mm Hg

34.4. A 27-year-old man presents after a motor vehicle collision (MVC) with a severe closed head trauma. On examination, you calculate a Glasgow Coma Scale (GCS) score of 5 and a left dilated pupil, with a sluggish pupillary reflex compared with the right. What other finding will your examination likely reveal?
A. Left carotid bruit
D. Left foot weakness
E. Loss of controlled pain/temperature sensation
B. Right carotid bruit
C. Right-sided hemiparesis

Answer: C. Uncal herniation is the most common posttraumatic herniation syndrome. The initial pressure compresses the third cranial nerve (CN III), causing ipsilateral pupillary sluggishness, ptosis, anisocoria, and impaired extraocular movements. Contralateral hemiparesis can develop early after an initial normal motor examination. In some cases, the contralateral uncus is compressed, resulting in ipsilateral weakness (Kernohan notch syndrome).

34.5. A 24-year-old man presents with a closed head injury after a MVC. The physical examination is remarkable for a sluggish left pupil, right-sided hemiparesis, and a GCS score of 12. What should be the next step in this patient's management?
A. 3% hypertonic saline IV
B. Intubation and hyperventilation
C. Mannitol, 1 g/kg IV
D. Methylprednisolone IV
E. Pentobarbital IV

Answer: B. The most rapid effect on ICP reduction is achieved via intubation and moderate hyperventilation to a Pco_2 of 30 to 35 mm Hg. The effect peaks within minutes and should be considered a short-term intervention, with an expected ICP reduction of 25%. Prolonged hyperventilation may be dangerous. Steroids may worsen outcome after TBI. Mannitol is generally efficacious and exerts an effect within minutes and lasts hours. Other neuroprotective effects include volume expansion, viscosity reduction, CBF improvement, and free radical scavenging. Hypertonic saline data are encouraging but inconclusive; stronger data exist in the pediatric literature. Barbiturates exert a modest ICP-lowering effect because of their lowering of the cerebral metabolic rate and oxygen demand.

34.6. What is the minimum time after becoming asymptomatic that an individual should refrain from playing sports after a concussion if no loss of consciousness (LOC) or prolonged posttraumatic amnesia occurred at the time of injury?
A. 24 hours
B. 48 hours
C. 1 week
D. 2 weeks
E. 1 month

Answer: C. All current recommendations for return to play after a sports-related concussion state that players with concussion should not return to play for at least 1 week after they have become asymptomatic. This is usually increased to at least a symptom-free month for an extended LOC or prolonged posttraumatic amnesia occurring at the time of the concussion.

34.7. A 15-year-old boy presents after being hit in the head with a baseball. He has a GCS score of 7 and a large hematoma of his scalp, anterior and superior to his right ear. In addition, he is noted to have unequal pupils and a sluggish papillary light reflex of the right eye. Which of the following is most likely in this patient?
A. Central transtentorial herniation
B. Cerebellotonsillar herniation
C. Downward transtentorial herniation
D. Uncal herniation
E. Upward transtentorial herniation

Answer: D. Uncal herniation is often associated with traumatic extra-axial hematomas in the lateral middle fossa of the temporal lobe. The classic signs and symptoms are caused by compression of the ipsilateral uncus of the temporal lobe on the U-shaped edge of the tentorium cerebelli as the brain is forced through the tentorial hiatus. As compression of the uncus begins, CN III is compressed; anisocoria, ptosis, impaired extraocular movements, and a sluggish pupillary light reflex develop on the side ipsilateral to the expanding mass lesion. This phase may last for minutes to

hours, depending on how rapidly the expanding lesion is changing. As the herniation progresses, compression of the ipsilateral oculomotor nerve eventually causes ipsilateral pupillary dilation and nonreactivity.

Initially, in the uncal herniation process, the motor examination can be normal, but contralateral Babinski responses develop early. Contralateral hemiparesis develops as the ipsilateral peduncle is compressed against the tentorium. With continued progression of the herniation, bilateral decerebrate posturing eventually occurs; decorticate posturing is not always seen with the uncal herniation syndrome. In some patients, the contralateral cerebral peduncle is forced against the opposite edge of the tentorial hiatus. Hemiparesis is then detected ipsilateral to the dilated pupil and mass lesion, termed *Kernohan notch syndrome*, and causes false-localizing motor findings. As uncal herniation progresses, direct brainstem compression causes additional alterations in the LOC, respiratory pattern, and cardiovascular system. Mental status changes may initially be subtle, such as agitation, restlessness, or confusion, but soon lethargy occurs, with progression to frank coma. The patient's respiratory pattern may initially be normal, followed by sustained hyperventilation. With continued brainstem compression, an ataxic respiratory pattern develops. The patient's hemodynamic status may change, with rapid fluctuations in blood pressure and cardiac conduction. Herniation that is uncontrolled progresses rapidly to brainstem failure, cardiovascular collapse, and death.

34.8. Central pontine myelinolysis is a potential adverse event associated with the administration of which of the following medications?

A. Etomidate
B. Hypertonic saline
C. Mannitol
D. Methylprednisolone
E. Pentobarbital

Answer: B. Central pontine myelinolysis is a potentially adverse event associated with hypertonic saline administration.

CHAPTER 35

Facial Trauma

Ryanne J. Mayersak

PRINCIPLES

Background and Importance

A complex structure vital to the function of the person, the face is comprised of airway openings, entry to the gastrointestinal tract, and special sensory organs, including the eyes, ears, and nose. Facial functioning is essential for eating, speaking, and effective nonverbal communication. The appearance and attractiveness of the face have significant implications for social interactions,[1] sexual attraction, and self-esteem. In one study, patients who had sustained facial trauma experienced long-term sequelae, including unemployment, incarceration, marital difficulties, and negative body image.[2]

Apart from the immediate threat to the patient's airway and special sense organs, injuries to the face can have serious implications for the patient's mental health[3] and future functioning.[4] Posttraumatic patients with facial injuries often describe physical, financial, social, and psychological loss.[5,6] Multiple studies have demonstrated an association between facial trauma and psychological symptoms such as anxiety, depression, and posttraumatic stress disorder.[7,8] Some institutions are now including screening evaluations regarding supportive interventions, as well as initiating support groups and online resources for facial trauma patients.[9,10]

Although the emergency clinician's first goal is to address life-threatening problems successfully, the care of facial injuries is aimed at optimizing the patient's function and cosmetic appearance. Four main specialties—ophthalmology, plastic surgery, otolaryngology, and oral and maxillofacial surgery—participate in the care of facial injuries. Early consultation with the appropriate specialist can expedite the care of facial injuries.

Anatomy of the Face

The face is a complex hollow space encapsulated by a bony structure overlaid with muscle and skin. It includes several special sensory organs—the eyes, ears, nose, and mouth.

Bones

The posterior portions of the face form the anterior wall of the calvaria, placing the face and its features in an intimate relationship with the structures of the central nervous system. The anterior facial skeleton is composed of the frontal bone, nasal bones, zygomata, maxillary bones, and mandible (Fig. 35.1). The sphenoid, ethmoid, lacrimal, vomer, and temporal bones lie deep within the facial structure, providing support and important sites for muscular attachments, including the muscles of mastication, speech, and deglutition. This musculature is innervated by cranial nerves IX and X.

Nerve Supply

The most anterior muscle layer includes the muscles of facial expression innervated by the seventh cranial nerve (CN), which lies just inferior to the external auditory canal. The trigeminal nerve (CN V) supplies sensation to the face through three major divisions (I–III). The ophthalmic division (CN V1) supplies the upper third of the face, including the eye and nose down to the tip. The maxillary division (CN V2) provides sensory innervation to the midface and includes the infraorbital nerve. The mandibular division (CN V3) supplies sensation to the lower third of the face.

Ears

The skeleton of the pinna is cartilage covered in closely apposed skin and rolled into a helical shape with a second ridge, the antihelix, defining the inner concha. The external auditory canal, middle ear, cochlea, semicircular canals, and superior origin of the eustachian tube all lie within the temporal bone.

Eyes

The bony orbit is composed superiorly of the frontal bone. The zygoma forms the lateral wall and lateral floor of the orbit. The medial floor and anteromedial wall are formed by the maxilla. The lacrimal and ethmoid bones complete the medial wall, where the orbit is at its most delicate. The medial wall of the orbit forms the lateral walls of the intranasal space.

Nose

The nose serves as a major entryway for air and is composed of cartilage and bone covered by skin, with mucosa lining the internal surface. Alar cartilage arches over the entrances to the symmetric, mucosa-lined nares, separated by the anterior cartilage of the septum. Superiorly, the nasal bones create the bridge of the nose. With the head held in a neutral upright position, the floor of the nose is perpendicular to the ground and leads back into the nasopharynx, passing the turbinates laterally and bony septum medially. The ethmoid bone lies superiorly and crosses midline, behind the nasal bridge, to form the superior portion of the bony nasal septum and cribriform plate. The vomer makes up the inferior portion of the bony septum, and the palatine process of the maxillary bone forms the posterior floor of the nose and hard palate.

Air-containing sinuses are structural features unique to the facial skeleton. They warm and humidify inhaled air and form chambers that create the unique tone of the human voice. These sinuses develop over the period of human growth. At birth, only the ethmoid air cells and mastoid antrum are aerated. The sphenoid sinus and remainder of the mastoid air cells become aerated at approximately age 3 years. Frontal sinuses form at approximately age 6 years, and maxillary sinuses are not fully developed until age 10 years.

Mouth

The mouth serves as an entryway for the respiratory and gastrointestinal tracts. With the mouth in the closed position, the tongue

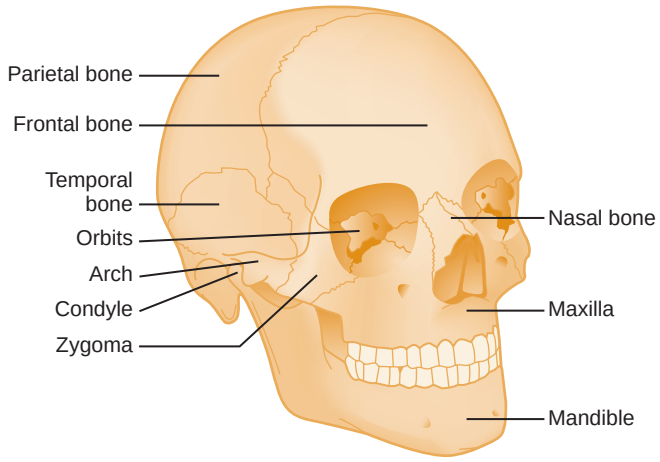

Fig. 35.1. Bones of the facial skeleton.

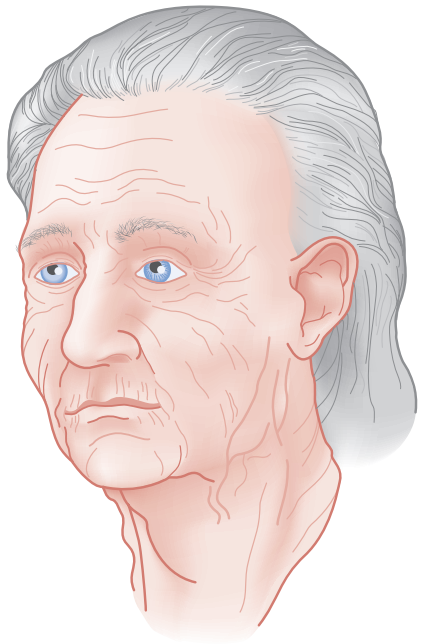

Fig. 35.2. Langer's lines—lines of facial expression.

fills the oral cavity. Single rows of teeth lie within the alveolar ridges of the maxilla and mandible. With the mouth closed, the teeth in normal individuals occlude, with the lower row lying just internal to the upper row. The "usual" occlusion for individuals varies widely; the patient's perception may be the best determinant of whether or not the teeth are meeting as usual. Anterior to the teeth is the vestibule, a fold of mucosa and flexible soft tissue that allows the lips to remain closed while various motor movements occur behind them. The mandible is a U-shaped bone that forms the chin and completes the lower facial skeleton. Containing the lower row of teeth, the body of the mandible meets in midline at the symphysis, which is completely fused by age 2 years. Posterior to the last molar, the bone turns to form the angle of the jaw and continues upward as the ramus of the mandible. At the most superior point of the ramus is the articular surface of the condyle, separated from the superior surface of the temporomandibular joint (TMJ) by an intervening meniscus of fibrocartilage. Anterior to the condyle lies a thin projection, the coronoid process, which provides the insertion point for the temporal muscle.

Temporomandibular Joint

The TMJ is complex, with the condyle of the mandible undergoing rotation and translation anteriorly during normal mouth opening. The function of the TMJ is preserved by a meniscus, which overlies the condyle. Essentially, the joint between the meniscus and condyle is a hinged joint, allowing rotation, and the joint between the meniscus and temporal bone is a sliding joint, allowing translation. A formal, thick joint capsule does not exist at the anteromedial portion of the joint; loose, relatively weak synovial tissue is positioned here to allow translation to occur.

Soft Tissue, Vasculature, and Specialized Glands

The skin of the face is among the thinnest of the body, draping over the underlying musculature. Facial skin falls visibly into predictable creases with age, following Langer's lines (Fig. 35.2). At the mouth, nares, and palpebral fissures, the skin is contiguous with the mucosa lining these structures. The skin of the lips is particularly thin and lined with vascular papillae, which give the lips their vermilion hue. Lips are particularly important as part of communication; understanding their movement can allow language without sound (lip reading).

The face is a highly vascular structure, which can have grave implications for the treatment of facial injuries. With the exception of the ophthalmic artery, the superficial blood supply comes from the external carotid artery via the facial, superficial temporal, and maxillary arteries (Fig. 35.3). Soft tissue injuries and fractures that involve these vessels can lead to significant hematomas or exsanguinations. Because the face has extensive anastomotic connections across the midline and between arterial territories, however, ligation of major branches causes minimal ischemia.

Buried within the structure of the face are a series of glandular structures and ducts that are susceptible to injury. In the eye, the lacrimal glands lie within the orbits, superior and lateral to the globes, and secrete tears through ductules into the folds of the conjunctiva. The liquid flows medially into the puncta of the lacrimal canaliculi and drains into the lacrimal sac and then, via the nasolacrimal duct, into the nasopharynx.

The salivary system consists of the parotid, sublingual, and submandibular glands. The parotid is the largest of these glands, lying just anterior to the ear and wrapping around the mandible. The parotid is superficial to the masseter muscle and drains via Stensen's duct, a 5-cm tube that curves around the anterior edge of the masseter to enter the mouth opposite the second upper molar. In normal subjects, this duct is large enough to be palpated with the masseter clenched (Fig. 35.4). The sublingual glands lie entirely within the floor of the mouth and drain into the mouth via ductules. They surround the ducts draining the submandibular glands (Wharton's ducts). The body of the submandibular gland is folded around the mylohyoid muscle so that a portion lies within the floor of the mouth and a portion lies external to it. The submandibular (Wharton's) ducts run from the external portion of the gland to empty into the mouth on either side of the frenulum of the tongue.

Pathophysiology

The basic mechanism of all injury is the transfer of energy, most often kinetic, to the structures of the body. When the energy overcomes the tolerance of the underlying tissue, injury results. Trauma traditionally has been classified as blunt or penetrating, but in many cases the effect is a combination of the two, such as the forehead injury (contusion and complex laceration) resulting from a child's fall against the sharp corner of a coffee table. The likelihood of injury is related to the amount of energy transferred and condition of the underlying tissue. Significant injury

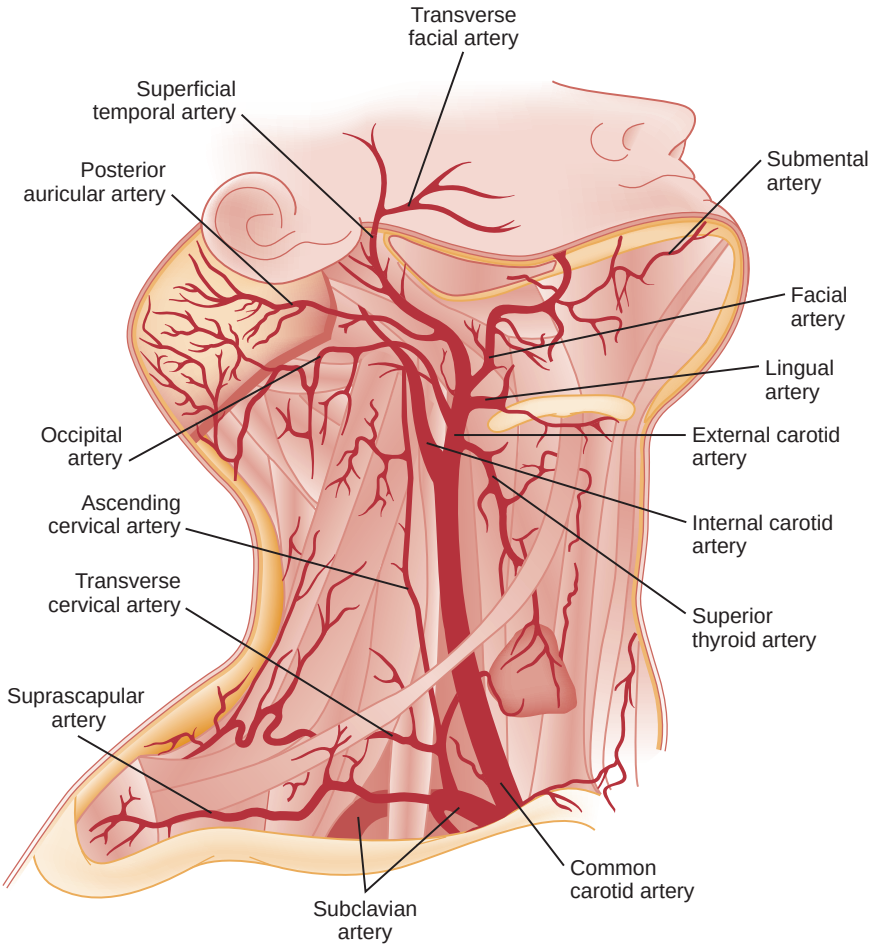

Fig. 35.3. Vessels of the face. (Adapted from Gray H: Gray's anatomy, Philadelphia, 1918, Lea & Febiger.)

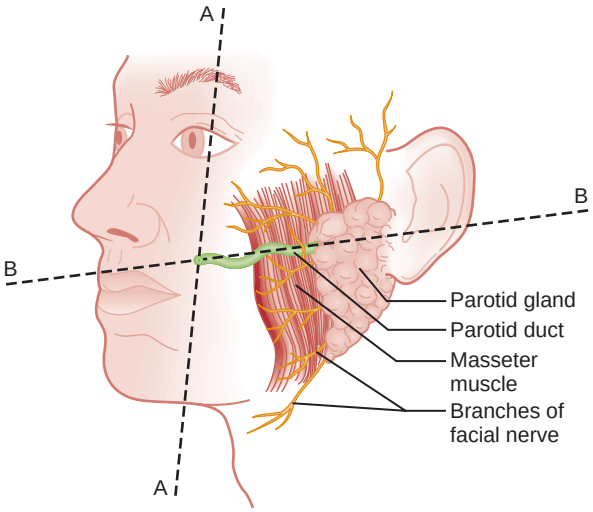

Fig. 35.4. Parotid gland and duct (Stensen's), with the surrounding branches of the facial nerve. Line B approximates the course of the duct, which enters the mouth at the junction of lines A and B.

may result when an 80-year-old falls from standing to a carpeted floor, but it is more likely to result when the face strikes the steering wheel or dashboard in a high-speed motor vehicle collision (MVC).

The mechanism can be broken down into low-energy events, such as a fall from standing or walking into the corner of a piece of furniture, and high-energy events, such as an MVC. Understanding the mechanism of injury can help predict not only the severity of the facial injury but also the risk of associated cervical or brain injuries.

Traditional teaching had been that the face protects the brain from injury, and that patients with facial trauma are less likely to have a significant brain injury. This does not appear to be correct. Instead, recent work has suggested a significant increase in risk for brain injury among blunt trauma patients with facial fractures.[11-13]

The association between cervical injury and facial injury is unclear. The traditional teaching has been that the presence of a facial injury should increase the suspicion of an injury to the cervical spine. However, most of the studies supporting this idea are assessments of the incidence of cervical spine injury in patients with facial injury.[14] When more sophisticated methods are used to assess any association between the two while correcting for the mechanism of injury, patients with facial injury appear to be less likely to have a significant cord injury, and there is no relationship with bony spinal injury. In the setting of multiple facial fractures, a large study of over 1 million trauma subjects in the United States and Puerto Rico found cervical spine injury prevalence ranged from 7% to 11%, whereas with an isolated facial injury, cervical spine injury ranged from 4.9% to 8%.[15] Thus, in a particular patient, cervical and brain injuries should be considered based on the mechanism of injury and presentation of the patient without allowing the presence or absence of a facial injury to change the level of suspicion.

Penetrating trauma to the face from gunshots, stab wounds, blast debris, or impalement is often obvious and dramatic (Fig. 35.5). The astute emergency clinician should search avidly for

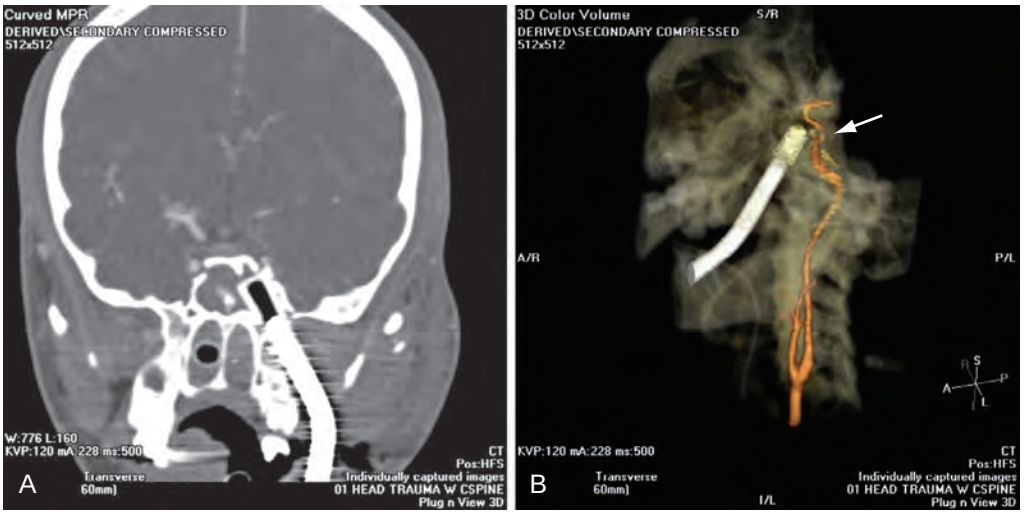

Fig. 35.5. Impalement by a turn signal lever. Computed tomography (CT) scan (**A**) and three-dimensional reconstruction (**B**) from a patient impaled through the face into the cranial cavity by the turn signal lever from his steering column when his vehicle rolled over in a single-car crash. The color three-dimensional reconstruction reveals a significant injury to the facial artery *(arrow)*.

associated intracranial, spinal, or vascular injuries, which are common in these cases.[13] Facial penetration from pellets (BBs) or small blast debris or shrapnel may be less obvious, and the emergency clinician should be alert to the possibility based on the history and should carefully search for small skin lesions. Recreational hobbies such as paintball and new law enforcement weapons that use so-called alternative ammunition, which can have substantial kinetic energy, have caused significant facial and upper body trauma.[16]

Clinical Features

History

The history can provide information about the mechanism of the patient's injury. The emergency clinician, however, should be alert to limitations of the history in cases in which the patient's consciousness is altered by a head injury or intoxication, there is an issue of secondary gain, the police are involved, or abuse is suspected. Patients with a clear sensorium are able to describe the events leading up to the injury and localize pain, deficits in motor or sensory function, and abnormalities of vision, hearing, taste, or smell. Although the association between facial trauma and brain or cervical spine injury has been debated, these possibilities should be considered, and the patient should be questioned regarding headache, peripheral weakness, numbness, and/or paresthesias.

Physical Examination

Many facial injuries can be identified by simple inspection. During the primary assessment, attention is initially on the patient's airway, and inspection of the oropharynx is an essential first step. Airway compromise is often a result of intraoral trauma, and the examiner should note excessive bleeding, drooling, dysphonia, swelling of the tongue or posterior pharynx, and presence of avulsed teeth. When the patient is stabilized, a secondary survey should include a systematic examination of all facial structures and functions. Bony prominences should be palpated for abnormal motion, bony crepitus, tenderness, or step-off. Tenderness and massive swelling associated with facial trauma may preclude reliable palpation of a fracture. Consequently, areas of significant swelling should be imaged radiographically. Assessment of bony integrity includes testing for a possible Le Fort fracture. The upper incisors are grasped and pulled anteriorly. Movement of the upper alveolar ridge (type I), midface (type II), or entire face (type III) indicates a fracture (Fig. 35.6). Wounds may need to be palpated for underlying bony injury or foreign objects; anesthesia may be required for a thorough examination within the wound. Complex lacerations involving the cartilage of the nose or ear, eyelids, lacrimal apparatus, eyebrows, or vermilion border of the lips should be identified because their repair requires special techniques.

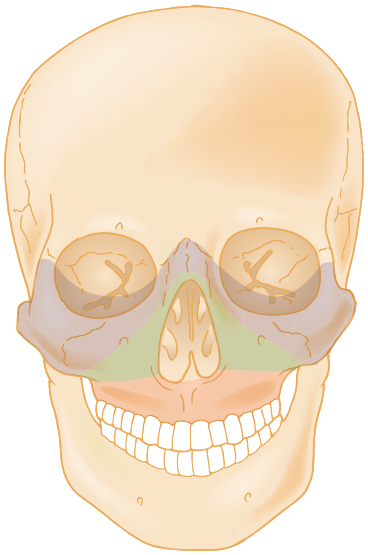

Fig. 35.6. Le Fort classification. Le Fort type 1 is shaded in *red*, Le Fort type II is shaded in *green*, and Le Fort type III is shaded in *blue*.

Eyes and Orbits. In addition to the examination of lacerations and contusions, the face should be evaluated for symmetry. The appearance of the zygomata may be evaluated by looking at the patient from above. This technique also draws attention to the relative position of the eyeballs. Orbital fractures may result in enophthalmos, and a large retrobulbar hematoma (Fig. 35.7) may cause exophthalmos. The anterior chamber of the globe should

Fig. 35.7. Retrobulbar hematoma. (From Nickson C: Bashed, blind, and bulging. http://lifeinthefastlane.com/ophthalmology-befuddler-033-2.)

be inspected for hyphema or globe rupture. A complete examination of the eye requires specific testing. If the patient is able to cooperate, visual acuity should be documented. Contact lenses should be removed. In the event of a significant potential chemical exposure, the pH of the eye may need to be measured. Fluorescein examination of the eye should be performed if there is any concern about corneal abrasion. Victims of MVCs often have particles of glass in the conjunctiva or on the cornea, and these should be sought and removed. Extraocular motions should be tested. Blowout fractures of the orbit may result in diplopia on upward gaze, secondary to entrapment of the inferior rectus muscle or anesthesia of the midface and upper lip in the distribution of the second division of the CN V, secondary to neurapraxia resulting from a fracture through the infraorbital foramen or compression by a local hematoma (Fig. 35.8).

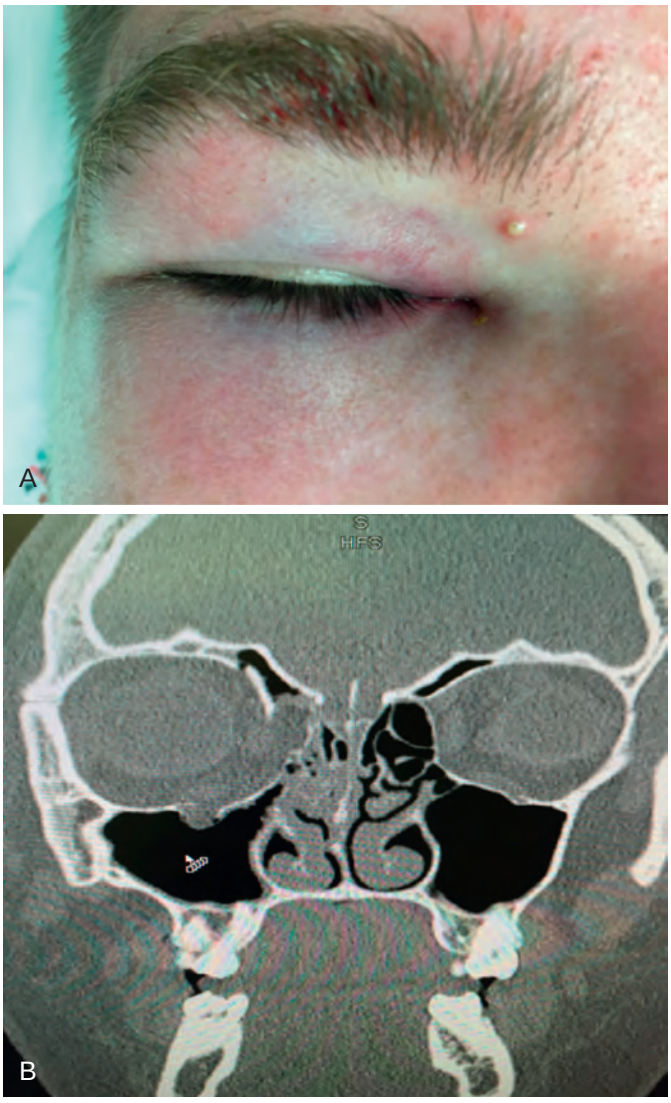

Fig. 35.8. Blowout fracture. **A,** Periorbital swelling and ecchymosis with an eyebrow laceration related to a blowout fracture. **B,** CT scan of a blowout fracture.

Oropharynx. The integrity of the mouth and nasal complex may be evaluated by listening to the patient's speech. A muffled or hoarse voice may indicate occlusion of the nose or nasopharynx, whereas dysarthria may indicate a mandibular fracture, tongue injury, or neurologic problem. Oral injury may result in progressive airway compromise, and dysphonia should alert the emergency clinician to the possible need for active airway management. The intraoral examination includes inspection of the palate, teeth, tongue, and gums and palpation with a gloved finger—the latter only if the patient is able to cooperate. The range of motion of the mandible should be determined. If the maximal incisor opening is less than 5 cm, a mandibular fracture may be present. Trismus is likely to indicate a fracture or significant hematoma within the face. If awake, the patient's impression about the normalcy of bite occlusion is a more sensitive determinant of a fracture of the mandible than the emergency clinician's impression. Being able to perform a tongue blade test (grasping and holding a tongue blade between the teeth while the examiner pulls gently) is associated with a greatly reduced probability of mandibular fracture. If the patient is able to crack the tongue blade by biting on both sides of the mouth, the negative predictive value for a mandibular fracture is greater than 92%.[17] Injury to the parotid area should raise suspicion of disruption of Stensen's duct. The opening of the duct opposite the second upper molar should be examined for bleeding while the gland is compressed. If blood is expressed from the duct or the severed ends of the duct are identified within a facial wound, specialized repair over a stent is required to prevent formation of a cutaneous fistula.

Ears. Otoscopy is performed to evaluate the integrity of the external canal, look for hemotympanum, and assess for otorrhea. Clear fluid from the ear after trauma should raise the possibility of a cerebrospinal fluid (CSF) leak. At the bedside, a drop of the fluid may be placed onto filter paper. A rapidly advancing halo of clear fluid around red blood defines a positive test result. This is a quick bedside test with good sensitivity (>86%) as long as the mix is approximately 50:50 between blood and other fluid, but it does not differentiate between CSF and saline, saliva, or other clear fluids.[18] Leaks can also be detected easily by β_2-transferrin electrophoretic examination, high-resolution computer tomography (HRCT), magnetic resonance cisternography with contrast, and surgical exploration; however, some of these methods can be timely, costly, or invasive.[18,19]

The ear should be inspected for subcutaneous hematomas (Fig. 35.9) because these need to be drained.

Nose. The nose is palpated for tenderness, crepitus, or abnormal movement; then each naris is held closed in turn to ensure that the patient is able to breathe through either side. The septum should be examined visually to look for septal hematoma (Fig. 35.10), which appears as a large purple mass extending from the

Fig. 35.9. Auricular hematoma. (From Hanna P: Top 7 worst cauliflower ears in MMA history. www.fightofthenight.com/articles/top-5-worst-cauliflower-ears-in-mma-history.)

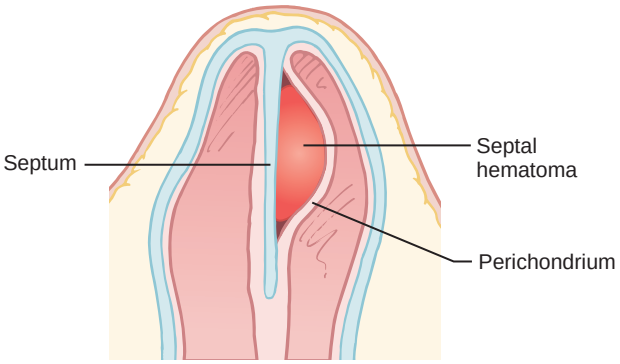

Fig. 35.10. Septal hematoma.

septum. If there is any concern about CSF rhinorrhea, the aforementioned filter test may be performed.

Neurologic Examination

Light touch should be tested for all three branches of CN V. Motor function (CN VII) can be examined by having the patient actively wrinkle the forehead, fully open and close the eyelids, smile widely, and bare the teeth. Asymmetry of these movements indicates a potential nerve injury. Peripheral injuries to CN VII should cause discernible weakness in the forehead as well as the orbital and oral musculature, whereas central injuries will result in preserved forehead function because of crossing fibers distal in the course of the nerve. CN V (the ophthalmic branch of the trigeminal nerve) and CN VII can be assessed by testing the corneal reflex in an altered or uncooperative patient.

DIFFERENTIAL DIAGNOSIS BASED ON ANATOMIC SITE

Soft Tissue Injuries and Lacerations

Soft tissue injuries to the face present an acute cosmetic concern for the patient. Areas may be contused, lacerated, abraded, or any combination of the three. When cleaned of any debris, abrasions may be covered in a thin layer of antibiotic ointment and left exposed or covered (as much as possible, given their location). Patients with significant tattooing will benefit from topical lidocaine for anesthesia before vigorous scrubbing is begun to remove the embedded material. Careful attention should be paid to removing all the embedded material as soon as possible because epithelialization requires the creation of a new wound to remove debris later. For contusions, ice and sleeping with the head elevated may limit the degree of swelling anticipated on days 2 and 3. The patient should be cautioned to anticipate the development of periorbital swelling, ecchymosis, or both over time as a result of gravity when the primary contusion has been to the brow, forehead, or bridge of the nose.

The most appropriate person to close an open wound may be the emergency clinician or a consultant. Decisions about which wounds to close personally and which to ask a consultant to repair are based on the personal judgment of the emergency clinician. Factors that may be considered in the decision include resource availability, size, shape, depth, and location of the wound, and the time commitment that careful, cosmetic wound closure can entail for the emergency clinician in a busy emergency department (ED). The patient's priority with facial lacerations is cosmesis, and therefore a patient may request specialty services for even minor wounds. Children and patients with behavioral problems may require sedation to allow sufficient control for a cosmetic repair. Repair of facial wounds in uncooperative patients who are acutely intoxicated may be delayed until they become sober enough to cooperate for the procedure.

After anesthesia has been achieved, wounds should be explored for depth, foreign bodies, and underlying fractures. Irrigation may not be necessary in simple, clean facial wounds closed within 6 hours. For nongaping wounds smaller than 3 cm, a single-layer closure may be sufficient.[20,21] For gaping wounds deeper than the dermis, subcuticular buried sutures of absorbable materials should be placed to close any potential space and relieve any tension on the skin. For skin closure, tissue adhesive is faster and less painful, results in equal cosmetic results in adults and children, and can be used to close the skin over deeper sutures.[20,22] Compared with sutures, tissue adhesive has the additional benefit of not requiring later removal, but care must be taken not to glue the eye, nares, or mouth closed unintentionally.

Antibiotics are not required for simple facial wounds, which rarely become infected. Bite wounds, wounds with any evidence of devascularization, wounds through and through the buccal mucosa, wounds involving the cartilage of the ear or nose, and wounds with extensive contamination (particularly with barnyard or fecal matter) are exceptions to this rule.

The choice of antibiotic therapy will likely be an evolving topic in light of the emergence of community-associated, methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Among spontaneous skin infections requiring an ED visit, the prevalence of CA-MRSA is now significant for adults and children.[23] In addition, it appears that the incidence of such spontaneous infections requiring ED care is also increasing. However, current literature does not suggest choosing antibiotics with MRSA coverage for wound prophylaxis. If prophylactic antibiotic therapy is needed, the antibiotic should be selected based on the normal bacterial flora associated with the affected site.[20,23]

Mouth

Lip lacerations are common and require special consideration to maintain the appearance of the lip edge or vermilion border and natural architecture of the philtrum. Because infiltration of even a small volume of local anesthetic may distort and blanch the soft tissue, marking the vermilion border (with nonpermanent ink or a scratch of a sterile needle) before anesthesia facilitates a cosmetic repair. To minimize any divots and maximize cosmesis and function, wounds that include the muscular layer should be closed in multiple layers. Skin may be closed with nylon or other nonabsorbable sutures; the lip and mucosa should be closed with absorbable sutures. Lip lacerations are not amenable to closure with wound adhesives.

Through-and-through lacerations of the mouth should be closed in layers, beginning with the intraoral mucosa and working outward in layers toward the skin. After closure of the mucosal layer, copious irrigation of the external wound is indicated to remove lingering bacteria that otherwise would be incorporated into the wound. Prophylactic treatment with penicillin has been shown to decrease the risk of infection after significant through-and-through lacerations. Lacerations that approach the parotid (Stensen's) or submandibular (Wharton's) duct should be evaluated before intervention for ductal integrity. Saliva milked from the gland should be thin and clear and exit the duct readily. If a duct is involved or there is any doubt, a facial specialist should be consulted for evaluation and repair.

Small lacerations of the tongue or oral mucosa do not require repair. Lacerations that gape (including deep tongue lacerations), collect food, and are likely to heal with a significant divot or thick scar that may hinder eating and speaking functions require repair. Deep or gaping lacerations of the tongue or oral mucosa should be closed (in layers, if necessary) with absorbable sutures that do not require removal. To facilitate repair, an assistant may be needed to expose the laceration by grasping the tongue between gauze and holding a segment outside the mouth. Some advocate placing a thick temporary suture through the distal tongue (after appropriate anesthesia) to facilitate this exposure. Discharge instructions for intraoral lacerations, whether or not they are repaired, should include gentle cleansing (swish and spit) with a mild antiseptic.

Perioral Burns

Young children use their mouths to explore their environment and may lick electrical outlets or bite electrical cords. The wet oral mucosa provides little electrical resistance, and the current penetrates to deeper structures, often causing a partial or full-thickness burn at the commissure of the lip. These children need a systemic evaluation for other electrical injuries (see Chapter 134); this discussion is limited to the evaluation and treatment of facial wounds. Perioral burns resulting from electrical injury can result in severe cosmetic problems and microstomia. The initial appearance of the wound may be misleadingly trivial; edema and necrosis progress over several days and, even with healing, the defect may become disfiguring. Traditionally, a more acute concern has been bleeding from the labial artery when the maturing burn eschar separates from underlying structures about 4 weeks postburn, and it was previously recommended that patients be admitted for close monitoring. In general, current practice is discharge with close observation at home and follow-up with otolaryngology specialists, plastic surgery specialists, or both to address cosmesis. Large wounds can cause significant early difficulty with eating, however, and patients may require placement of a nasogastric tube for the maintenance of nutrition. Initial ED treatment of the wound aims at treating discomfort and keeping the area clean.

Treatment of these injuries include early oral splinting (microstomia prevention appliance) and minimal surgical débridement, followed by scar revision and excision of the burned area at 1-year postsurgery.[24] Later reconstructive repair may be required to preserve mouth opening, eating, and speech clarity. Early involvement of consultants is indicated, even when the burn seems to be trivial. The possibility of abuse or neglect should be considered when a child is presented with a perioral burn.

Cheeks

Contusions of the cheek should raise concern for an underlying zygomatic or maxillary fracture. Lacerations of the lateral cheek may involve the parotid gland or Stensen's duct. Failure to identify and repair ductal injury results in retention of salivary fluid and enlargement of the gland or formation of a cutaneous fistula. Lacerations in the area anterior to the tragus may include injury to the facial nerve, and a careful neurologic examination should be carried out before closure. Langer's lines change from mostly horizontal in the superior cheek to diagonal at the nasolabial fold, then curve convexly around the mouth; these changes should be taken into consideration when débridement is required as part of a complex repair.

Nose

Because of its anterior position, soft tissue injuries to the nose are common. Almost any trauma can result in epistaxis. In general, epistaxis is controllable by pinching the cartilaginous anterior nose closed between two fingers and holding compression for approximately 10 minutes. If it is not controlled, anterior packing is indicated. Intranasal inspection is required in any nasal injury to assess for a septal hematoma, which appears as a dark purple or bluish mass against the septum. Hematomas require drainage because they are associated with necrosis of the septum if left untreated. Simple incision and expression of the clot followed by anterior packing are sufficient. Traditional teaching has been that any patient with nasal packing should receive prophylactic antibiotics to cover *Staphylococcus* and *Streptococcus* spp. to prevent sinusitis and toxic shock syndrome. Toxic shock syndrome is a rare but measurable complication of postoperative nasal packing, occurring in approximately 16/100,000 cases; the incidence with primary packing is unknown. There is no evidence that prophylactic antibiotics change the risk of developing toxic shock syndrome or sinusitis in postoperative or primary packing; the few studies that have been done have had sample sizes far too small to show an effect. Based on this, systemic prophylactic antibiotics are unnecessary with nasal packing. A topical antibiotic, such as chlorhexidine-neomycin (Naseptin), could be used and is a more cost-effective alternative.[25]

Because of the location and structure of the nasal bridge, fractures of the thin bones of this area are common. Patients with contusion or tenderness over the bridge of the nose may be assumed to have a fracture of the nasal bones. If the nose is acceptably straight on initial evaluation, there is no septal hematoma, epistaxis is controlled, and the patient is able to breathe out of each naris, no further evaluation is required emergently for isolated nasal injuries. Although radiographs of the nasal bones are still in use, they have no clinical value.[26,27]

Swelling over the bridge often precludes determination of the acceptability of the appearance at the time of injury. The patient may be provided with a referral for outpatient specialty follow-up in 3 to 5 days if the appearance at that time, when the swelling has improved, is unacceptable. In a series of surgically repaired simple nasal bone fractures, septal fractures were present in more than 50% of cases. CT did not provide any advantage in diagnosing septal fractures and should be reserved for evaluating patients suspected of having other, more complex fractures.[28,29]

Children with nasal fractures may have premature closure of sutures and uneven growth, particularly of the vomeroseptal line. In a child, no imaging studies are indicated, but a consultant should evaluate swelling and tenderness over the nose, preferably within 4 days of the injury.[30]

Simple lacerations of the nasal skin may be closed with sutures or tissue adhesive. If needed, anesthesia may be achieved with a nerve block of the infraorbital or supratrochlear nerves. The large pores typically present in the area of the nasal ala increase the likelihood of stitch abscesses after laceration closure in this area. Closure with an absorbable running subcuticular suture may limit the risk of this outcome. If involved, the cartilaginous portions of the ala should be closed in a separate layer with absorbable 4-0 sutures. For lacerations through and through the nose, repair

should be carried out from the mucosal layer outward, with copious irrigation between layers.

Ears

Blunt trauma to the ear may cause hematoma formation in the subperichondrial potential space. Such hematomas are the prelude to the development of a so-called cauliflower ear and should be drained by aspiration. Re-accumulation of the hematoma is prevented with a compressive dressing of the ear, but reexamination is crucial, and re-aspiration should be performed as necessary.

Ear lacerations often involve the cartilage. The ear may be anesthetized with a field block; 1% lidocaine without epinephrine can be used as a local anesthetic for direct infiltration of the ear. 1% lidocaine with epinephrine can be utilized for a regional block. Simple skin wounds may be closed in a single layer. Lacerations to the underlying cartilage should be repaired with absorbable material. If there is significant degloving or loss of overlying tissue, a consultant should be involved; portions of aural cartilage may be saved temporarily in a distant dermal pocket for later reconstruction. Because cartilage is avascular, chondritis, when it occurs, requires extensive débridement and is disfiguring. No randomized trials have been performed, but when the cartilage of the pinna requires repair, antibiotic prophylaxis covering typical skin flora as well as *Pseudomonas* is recommended. Compressive ear dressings (splints) are indicated after any significant repair. Ear injuries occurring before age 1 year or injuries to both ears in children are rare and should raise the suspicion of abuse.[30]

Eyes

Simple eyelid lacerations may be repaired in a single layer. Wound adhesives should be used with great caution anywhere near the eye; care must be taken not to glue the eyelids open or shut. Lacerations that involve deeper structures, loss of tissue, or the lid margin should be referred to a consultant. The integrity of the lacrimal apparatus can be assessed by instilling fluorescein into the eye and assessing for dye in the wound. A consultant should handle any injury to the sac or lacrimal duct.

Eyebrow lacerations are common because of the overhanging supraorbital ridge. Careful wound exploration should be performed to assess the integrity of the underlying bony structure. No shaving should be performed because the brow hairs may not regrow, and the hairs are necessary for realignment. If débridement is required, it should be done parallel to the hair follicles (skived) rather than perpendicular to the skin. This approach minimizes the bald area of the scar. Closing the deeper muscular layers preserves the normal expressive function of the brow. Injuries to the globe are discussed in Chapter 71.

Fractures and Dislocations

For the emergency clinician, the key to facial fractures is accurate diagnosis and appropriate referral. Many nondisplaced or minimally displaced facial fractures may be handled on an outpatient basis, with definitive repair or fixation delayed several days. In adults, fractures develop firm fibrous union within approximately 10 to 14 days; however, definitive repair is performed most easily before day 7. Fractures to the face of young children are relatively rare and may be incomplete or greenstick fractures. Fibrous union in these cases is rapid; early reduction (within 3 days) is recommended.

Broad-spectrum antibiotics against the typical sinus and nasal pathogens are indicated for open fractures and fractures that violate a sinus. Patients with fractures through the nasoethmoid (NOE) complex that violate the maxillary bones or floor of the orbit should be cautioned to avoid sneezing and blowing the nose because these activities force air out into the soft tissues of the face.

Surgical repair of simple nasal fractures may be performed closed and the nose splinted internally or packed. Repair of fractures of the floor of the orbit, when necessary, may require the placement of a silicone patch to occlude the opening into the maxillary sinus. Operative repair of most other fractures of the face is performed with the use of small metal plates (microplates), screws, or wires to stabilize fragments by attaching them to unbroken segments of bone. Efforts are made to return the features to their unfractured locations and to regain facial symmetry, if possible. Complex facial fractures may have to be repaired in a staged fashion, depending on the patient's degree of illness and amount and quality of the bone remaining. Much of this surgery is best accomplished when the fragments are still freely mobile but initial swelling has been reduced, on postinjury days 3 to 5.

Forehead

Fractures through the superior forehead may occur above the level of the frontal sinus. These are actually skull fractures rather than facial fractures and should be addressed with special attention to risk of injury to the underlying brain. Unlike other skull fractures, frontal skull fractures often require repair for cosmesis alone. More often, fractures in this area involve the anterior portion of the frontal sinus. If even minimally displaced, these fractures require elevation for cosmesis. Fractures through the anterior wall of the frontal sinus are likely to continue through the posterior wall, and CT should be performed to look carefully for this complication; if present, a CSF leak should be assumed until proved otherwise. CSF leaks into the frontal sinus may also manifest in a delayed manner, days or years after the initial injury; with many frontal sinus fractures, complex repair or obliteration may be required to treat this complication.[27]

Orbit

The most common simple fracture of the orbit is a blow-out fracture of the orbital floor, often caused by a fisted blow or ball striking the globe, increasing intraorbital pressure enough to force orbital contents through the floor. This injury may happen without other significant bony facial injury. When displaced, the bony fragments sag into the underlying maxillary sinus. If the inferior rectus muscle is entrapped in the defect, the patient is unable to elevate the globe on the affected side, resulting in diplopia on upward gaze. Stretch or compression of the infraorbital nerve, which passes through the floor, may cause anesthesia over the anteromedial cheek and upper lip. Because signs of entrapment may result from contusion and edema and be self-limited, immediate repair is not necessary, but careful follow-up is required. Repair typically is performed 1 or 2 weeks after the injury for persistent enophthalmos or diplopia. Because of the acute limitation in the visual field, discharge instructions for patients with acute diplopia should include patching for comfort and a request not to drive until the diplopia is resolved.

Fractures of the medial orbital wall, through the lamina papyracea, are often associated with nasal injury or a more general midface fracture, particularly with telescoping of the midfacial skeleton. Herniation of orbital contents into the ethmoids may occur. Patients with orbital fractures with a medial component are more likely to have ocular signs of diplopia or exophthalmos than patients with fractures that did not involve the medial wall. Fractures involving the superior orbit include the base of the frontal sinus, and all the concerns about the anterior skull mentioned previously apply. Herniation of orbital structures into the frontal sinus is rare but can occur.

Fig. 35.11. CT scan of fractures of the left orbital floor *(top arrow)* and left lateral maxillary wall *(bottom arrow).* There is streak artifact from dental devices.

Fig. 35.12. Coronal slice from maxillofacial CT scan of a patient with blunt facial trauma. Acute comminuted fractures of the outer table of bilateral frontal bones, bilateral nasal bones, bony nasal septum, nasal spine, bilateral orbital floor, bilateral lateral and medial orbital walls, roof of the right orbit, posterior wall of the right sphenoid sinus, bilateral pterygoid plates, and anterior, medial and posterolateral walls of the bilateral maxillary sinuses are noted. There is extraconal air bilaterally. There is near-complete opacification of bilateral maxillary sinuses and bilateral ethmoid air cells with hyperdensity within, suggestive of blood products. There is opacification of bilateral frontal and sphenoid sinuses with hyperdensity within, suggestive of blood products. Endotracheal and orogastric tubes are noted.

Many orbital fractures involve more than one wall of the orbit and may be present in a constellation with complex midface fractures (Fig. 35.11). Several classification schemes aimed at improving communication among emergency clinicians, radiologists, and maxillofacial surgeons have been proposed, but no classification system has been generally accepted.

Injury to the orbit, particularly fractures, can cause a hematoma to form within the orbit, behind the globe. If significant in size, a retro-orbital hematoma can elevate retro-orbital pressure, causing acute exophthalmos and a compartment syndrome of the retro-orbital space. Stretch on the retinal artery limiting flow to the retina or neurapraxia of the retinal nerve may cause decreased visual acuity or blindness. Orbital emphysema (Fig. 35.12) associated with fractures of the medial wall or floor rarely results in a space-filling lesion with the same effect. This is a true emergency; drainage of the air or blood via lateral canthotomy with cantholysis is indicated to save the patient's vision. Needle aspiration of entrapped air may also be attempted, but this may be best left to a consultant, given the proximity of the globe.

Midface

Tripod (or trimalar) fractures are among the simplest fractures of the midface and include fractures of three bones—the lateral orbit, zygoma, and maxilla (Fig. 35.13). Typically caused by a direct blow, these fractures are often displaced and require operative stabilization. If left untreated, the area may sink posteriorly and inferiorly, giving an unacceptable appearance of facial asymmetry emphasized by the inferior position of the orbit and malar flattening. On the initial physical examination, there may be a large contusion over the cheekbone, enophthalmos, or malocclusion of the upper teeth. Fractures through the anterior wall of the maxillary sinus may denervate the maxillary teeth because the dentoalveolar nerves run in tunnels in this area.

More complex fractures of the midface are classified with the Le Fort system, although many complex fractures defy this simple system. Other classification systems exist. One system has divided the face into a matrix of vertical and horizontal beams to describe the fracture patterns. Another system has utilized CT findings to describe low- and high-impact fractures. Despite the Le Fort system's limitations in describing comminuted, complex fracture patterns, it is still the most accepted classification method used. All Le Fort fractures involve the pterygoid plate, and the injury pattern can be unilateral, bilateral, or a combination. A Le Fort I fracture involves a transverse fracture through the maxilla above the roots of the teeth and may be unilateral or bilateral. Patients may report malocclusion, and the maxilla may be mobile when the upper teeth are grasped and rocked. A Le Fort II fracture is typically bilateral and pyramidal in shape. It extends superiorly in the midface to include fractures of the nasal bridge, maxilla, lacrimal bones, orbital floor, and rim. In these cases, the nasal complex moves as a unit with the maxilla when the teeth are grasped and rocked. In the current age of CT scanning, in which the full extent of comminution can be appreciated, simple Le Fort III fractures are rare but essentially involve fracturing of the connections between the elements of the skull and face (craniofacial dysjunction). These fractures start at the bridge of the nose, extend posteriorly along the medial wall of the orbit (ethmoids), along the floor of the orbit (maxilla), and through the lateral orbital wall, and finally break through the zygomatic arch. Intranasally, they extend through all the lesser bones to the base of the sphenoid and frequently are associated with a CSF leak.

Significant force to the bridge of the nose may fracture the deep NOE complex without creating a formal Le Fort pattern. CT is the initial test of choice in this setting. Fractures to the central portion of the ethmoid bone (cribriform plate) are likely to be associated with a CSF leak and commonly result in anosmia.

If possible, patients with a CSF leak should have the head elevated 40 to 60 degrees. Head elevation minimizes the intracranial

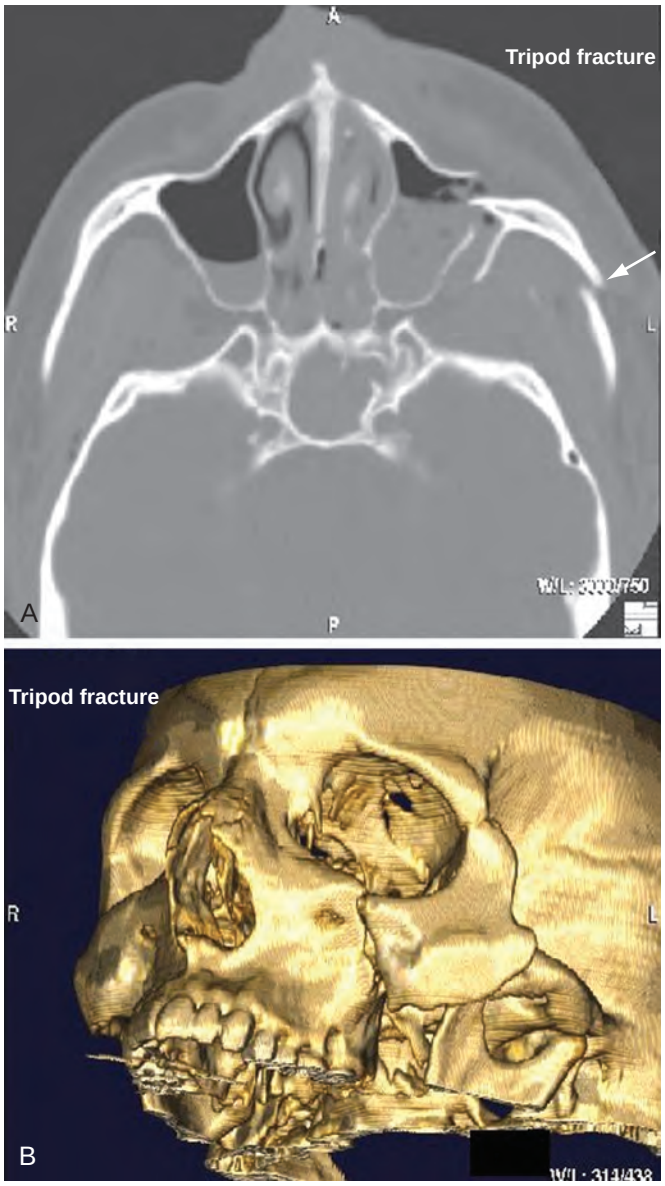

Fig. 35.13. Tripod fracture. **A,** CT scan. **B,** Three-dimensional reconstruction.

pressure, with the idea of decreasing the flow and allowing the leak to seal. Often, these patients are treated with antibiotics; however, this practice is controversial, and most of the studies supporting it involve small, local case series. Although the evidence is equivocal, it is recommended that appropriate prophylactic antibiotics be used in patients who may be immunosuppressed, have an indwelling device, or have an open contaminated wound. Neurosurgeons should be involved in the care of patients with CSF leaks, although many leaks will resolve spontaneously.[31,18]

Fractures involving the deeper structures of the midface may be associated with significant bleeding into the nose or oropharynx. Anterior nasal packing may be performed safely in the adult patient with multiple trauma. Even a 10-cm anterior pack should not reach the skull base in a skeletally mature person. Significant or massive bleeding into the posterior nasopharynx presents a complex problem and occurs in less than 1% of patients with midface fractures. It may be treated with nasal packing and immediate fracture reduction.[32] Unless the anatomy is well understood and the skull base known to be intact, the use of a long balloon catheter (Foley) should be avoided for the control of posterior bleeding. The unintended positioning of these items within the intracranial or intraspinal space during blind nasal insertion has been well documented and, when the face is grossly distorted, preinsertion measurement or other methods of preventing this outcome have not been adequately tested.[32] There are no reports of the intracranial placement of commercial catheters designed for posterior epistaxis, but if the midface is significantly distorted or telescoped, they may be long enough to reach the intracranial space. An alternative method for containing posterior nasal bleeding is to provide compression by packing the area with gauze by hand from the oropharynx after intubation.

Zygoma

Isolated fractures of the zygoma are relatively rare, usually the result of a direct blow, and often displaced. Because the condyle of the mandible may disturb zygomatic fragments while moving, fractures with significant displacement are likely to result in trismus or discomfort with mouth opening. Surgical repair is usually required to return the cheekbone to an acceptable position.

Mandible

Fractures of the mandible can result from any significant force applied to its U shape. Because of its shape, multiple fractures may result from a single blow, and the fracture sites may be distant from the site of impact. Depending on the location of the fractures, the patient may have trismus (fractures of the coronoid process, neck, or rami), dental malocclusion, swelling, and tenderness intraorally or externally. Anesthesia of the lower lip may occur if there is damage to the inferior dental nerve.

Fractures of the symphysis, body, angle, or rami usually require early splinting, typically by the placement of arch bars to accomplish interdental fixation, commonly known as wiring the jaw shut. Fixation limits fracture motion, decreases the patient's discomfort and, if the fracture is minimally displaced, may provide complete fracture care. Impacted and nondisplaced fractures occasionally are treated with only a soft diet, and fractures of the coronoid alone usually require no intervention, but these decisions should be made in consultation with an oral surgeon or other specialist. Arch bars may be placed in the ED or operating room, typically placed by a specialist. Fracture reduction may require the extraction of teeth adjacent to the fracture line. Patients with open fractures require antibiotics and usually hospitalization. When the fractures are closed and adequate stabilization can be obtained, elective operative repair can be performed as an outpatient procedure in 3 to 5 days.

In one study, 17% to 22% of pediatric patients 4 to 11 years old developed facial growth disturbances after a fractured mandible and required later orthognathic surgery for correction. Children younger than 4 or older than 11 years were much less likely to develop this complication.[30] Because of the frequency of this complication, children in this age group who have sustained a blow to the chin and who have any trismus or tenderness over the TMJ should be assessed carefully with Panorex imaging for a condylar fracture and referred appropriately.

Dental and Alveolar Trauma

Trauma to the teeth may occur with or without other facial injury. In the setting of caries, tooth fractures may occur with eating relatively soft foods. Tooth fractures are classified by the Ellis system. Class I fractures involve only the enamel of the tooth, are not painful, and can await dental evaluation on an outpatient basis. Class II fractures expose the yellow dentin and may be painful. These also can await dental care but may be covered with a dressing of calcium hydroxide and aluminum foil. Class III fractures

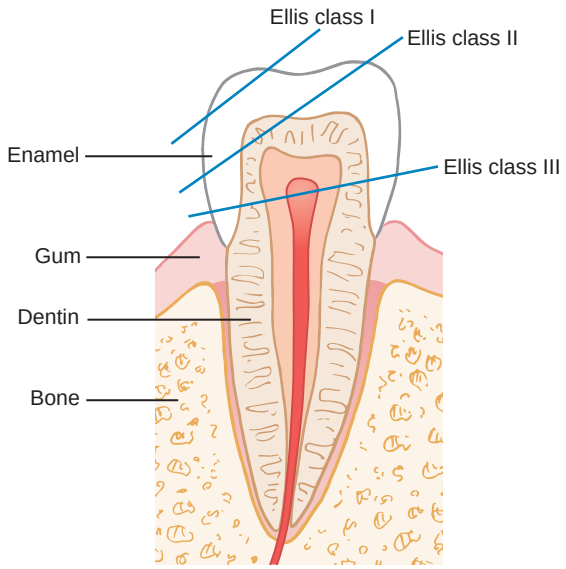

Fig. 35.14. Ellis classification of tooth fractures.

expose the dental pulp, seen as a red line or dot, and are exquisitely painful. These require early evaluation by a dentist or endodontist (Fig 35.14).

Sufficient energy to the area avulses teeth from their sockets. Multitrauma patients, particularly patients who are intoxicated, required to be supine for cervical spine immobilization, or neurologically impaired, should have avulsed or mostly avulsed teeth removed from the mouth and placed externally in saline as an aspiration precaution. In a critically ill multitrauma patient, avulsed teeth should be among the lowest priorities and are reimplanted only if the care of other injuries allows it, and there is no risk of aspiration if the teeth loosen.

To perform a reimplantation, the emergency clinician disturbs the socket as little as possible, gently rinses off the tooth (the root should not be wiped), and places it into the socket where it clicks into place. If the tooth is only partially avulsed, extruded, or laterally luxated, it should not be removed; it should be reimplanted or relocated. Intruded teeth should not be manipulated. Reimplantation can be painful and may require local anesthesia with a regional dental block. Alternatively, the area of a single socket may be anesthetized by placing approximately 0.5 mL of 1% lidocaine with epinephrine is used for oral nerve blocks into the buccal sulcus and gum on the outer side of the alveolar ridge. After reimplantation, the tooth requires stabilization with acrylic splint or wiring to the adjacent teeth. Appropriate antibiotics such as penicillin and a tetanus booster shot should be given, as well as dental follow-up for possible root canal if the reimplantation does not take.[33,34]

Reimplanted teeth may or may not take acutely, but it can take weeks to assess the final success of reimplantation. The extra-alveolar time, periodontal state, and storage process seem to play a critical role in the initial success.[34,35] Teeth that are successfully reimplanted in 20 to 30 minutes have fewer complications, including signs of inflammation and bone resorption. Studies also have shown that age is a factor in root resorption of teeth that have prolonged avulsion times. A significantly higher rate of root resorption in patients between the ages of 8 and 17 years when compared to 17- to 39-year-olds has been reported, as well as a complication prevalence of 57% to 80%.[34-36]

In children, the front maxillary incisors are usually avulsed. After reimplantation, these teeth may ankylose and fail to grow out normally, requiring later extraction or orthodontic intervention for cosmesis. This situation is most common in children aged 6 to 10 years with avulsed adult teeth.[37]

Fig. 35.15. Left comminuted fracture of the parasymphyseal mandible involving the alveolar ridge and extending to the root of the first mandibular molar. An endotracheal tube is also present.

Avulsed teeth missing after significant trauma should be carefully sought, including via a chest x-ray examination. In an acute event, the patient may not recall aspirating a tooth; this is more likely if the patient is intoxicated or neurologically impaired. If the tooth is below the diaphragm on the film, it does not require retrieval. Teeth lodged in a bronchus or the esophagus require bronchoscopic or endoscopic retrieval. Aspirated teeth result in pulmonary abscess formation unless removed.

Fractures through the alveolar ridge may result in a group of teeth being dislodged and out of position, often leaning inward. These teeth require stabilization with wire or acrylic splinting after fracture reduction has returned the teeth to their correct location. The involved teeth may or may not survive after such a fracture, and careful follow-up with a dentist or oral surgeon is required (Fig. 35.15).

Temporomandibular Joint

Trauma to the TMJ may tear the meniscus or injure the collateral ligaments holding it in a normal position. This injury can cause the meniscus to fail to translate normally, resulting in clicking or popping as it catches up to the condyle or inability to open the mouth fully because the meniscus fails to translate completely. Patients without fracture but with acute pain and difficulty with mouth opening should be placed on soft foods, asked not to yawn or struggle to open their mouths widely, and referred to an oral surgeon with expertise in TMJ pathology. Pediatric patients with posttraumatic internal derangements of the TMJ are prone to asymmetry of facial growth and retrognathia.

Because of the anatomy and function of the joint, anterior dislocation of the TMJ can occur after widely yawning, laughing, kissing, singing, or other activities that involve spontaneous wide opening of the mouth. When the condyle is out, spasm of the muscles of mastication prevents spontaneous reduction. Significant trauma is more likely to cause a fracture-dislocation. Simple dislocation may be unilateral or bilateral, and the patient may report being unable to close the mouth. In unilateral dislocation, the jaw is rotated laterally away from the affected joint; bilateral dislocation causes significant protrusion of the jaw. The jaws of these patients are often open so widely that they cannot swallow their secretions and are actively drooling. Speech is often garbled by the patient's inability to touch the tongue to the roof of the mouth or maxillary teeth. There is a depression in the area of the affected TMJ on inspection of the patient's face.

If the mechanism of injury suggests a fracture, the area should be imaged with plain x-ray or Panorex examination before reduction is attempted. For reduction of a simple dislocation, the patient should be seated upright. For leverage to be maximized,

the best position may be for the patient to be seated in a regular chair, with the operator standing in front of the patient. As in dislocations of other joints, adequate analgesia and sedation are required for success. With the thumb or index finger placed into the buccal sulcus on either side of the mouth, the angle of the jaw is pressed downward while the symphysis is rotated (chin) upward and backward. Care should be taken not to place fingers along the crowns of the teeth; when relocation occurs, spasm of the muscles of mastication snaps the mouth shut with force. If this is the only location possible for the emergency clinician's fingers, gauze wrappings should be placed to protect them.

DIAGNOSTIC TESTING

Imaging

The choice of imaging for facial fractures depends on the patient's stability, patient's ability to cooperate, and availability of various options. The two main options are plain x-ray examination for isolated injuries and CT. Fractures are better visualized with CT than with magnetic resonance imaging (MRI), so MRI is not an optimal imaging choice. In patients in whom a fracture or penetrating injury is obvious from the physical examination, HRCT is the imaging modality of choice.[28] For a complete evaluation, CT scans of the face should include axial, coronal, and sagittal reconstructions. Interpreting facial CT scans is an art that requires attention to bones, sinuses, orbital contents, and soft tissue and is best handled by a radiologist.

CT is now the first choice for all patients in whom a midface fracture is suspected. However, when no scanner is available, and in patients with a low to moderate pretest probability of a midface or maxillary fracture and who are stable and able to cooperate, the current recommendation is for a single screening view (Water's or occipitomental view), followed by CT if the film is positive for a fracture or air-fluid level in any sinus.[27]

The U shape of the mandible and presence of nearby bony structures make isolating the mandible on flat film impossible. Simple radiographs of the mandible are less sensitive than Panorex radiographs and particularly tend to miss fractures of the condyle (Fig. 35.16). If available, Panorex imaging is indicated for a first episode of TMJ dislocation, isolated mandibular fractures, dental fractures, or fractures of the alveolar ridge. In children, if fracture of the condyle is suspected, coronal CT is more sensitive and specific than Panorex studies.[30] Although the traditional teaching has been that the mandible's shape results in two fractures if it is fractured at all, a case series using CT evaluation has found that 42% of mandibular fractures are unifocal.[36]

For patients with complex fractures, new imaging techniques may help improve surgical planning and esthetic outcomes. In displaced orbital fractures, use of CT data to measure orbital volumes has shown that after repair, an orbital volume greater than 4% larger than on the unfractured side is associated with visible postoperative enophthalmos. This method seems to be useful in predicting which patients might benefit from operative repair. In conjunction with more standard two-dimensional facial CT scans, three-dimensional CT scans seem to improve the diagnosis and aid preoperative planning for patients with complex fractures of the midface (Fig. 35.17).[38,39]

Blunt cerebrovascular injury (BCVI) incidence is still not fully known in the trauma setting. CT angiography (CTA) should be used as a screening and diagnostic tool when evaluating for BCVI. This is an evolving area in which 20% of injuries are still missed until patients become symptomatic and are often outside the therapeutic window, with devastating neurologic consequences. BCVI requires a high index of suspicion and should be considered in any patient with a cervical spine fracture, neurologic examination that does not fit the diagnostic picture, and patients with Horner's syndrome, LeFort II or III fractures, skull base fractures, or soft tissue injuries of the neck. The gold standard for diagnosis is angiography; however, CTA should be considered as part of the initial trauma evaluation protocol[40,41] (Fig. 35.18).

Patients with tenderness and swelling isolated to the bony bridge of the nose who do not have a septal hematoma, can breathe through each naris, and have a straight nose do not require nasal bone radiography in the ED because imaging results would not alter treatment. If these criteria are not met, early reduction by a specialist or referral for surgical intervention may be indicated, and evaluation by plain films (for truly isolated injuries) or CT scanning (if concern for other injuries exists) is indicated. Plain x-ray examination may also be performed in the setting of legal concerns. If there is concern for a foreign body in a superficial wound, two standard x-ray views (Water's and Caldwell's, or occipitofrontal view) are indicated to triangulate the position of the observed foreign material.

Patients with suspected ocular injuries may benefit from bedside ultrasound as a noninvasive and cost-effective diagnostic tool, particularly if there is a need for urgent operative management of other injuries and no time for a dedicated facial CT. One case study used bedside ultrasonography for the diagnosis of a retrobulbar hematoma and termed the findings of conical deformation of the ocular globe's posterior aspect as the *guitar pick sign*.[42] The different acoustic impedances of the orbit's anatomic structures make this modality operator-friendly, and an ultrasound of the eye can readily detect lens dislocation, vitreous

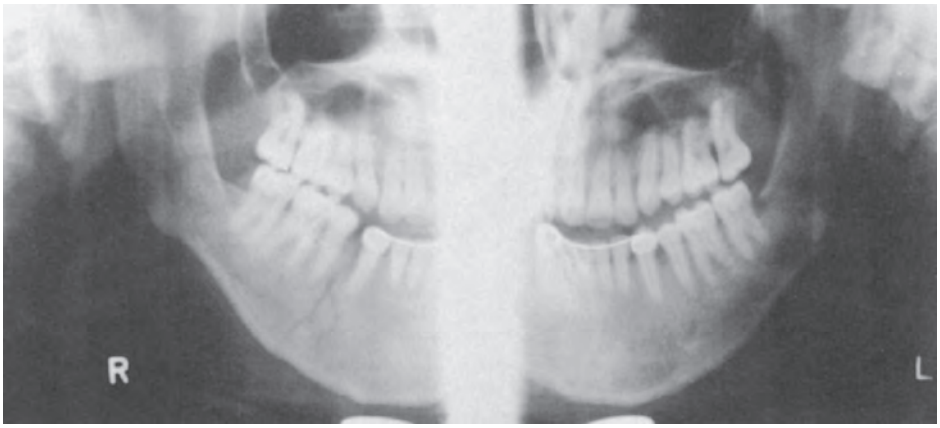

Fig. 35.16. Panoramic radiograph of the mandible shows fractures through the left angle and right body. A dental appliance is in place on the lower incisors.

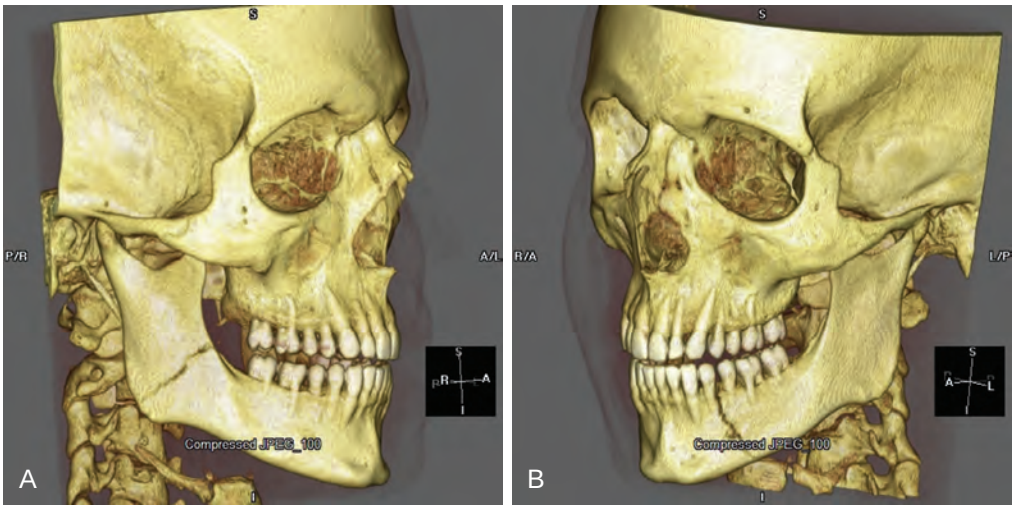

Fig. 35.17. A, B, Three-dimensional CT reconstructions of minimally displaced mandibular fractures in the same patient as in Fig. 35.5.

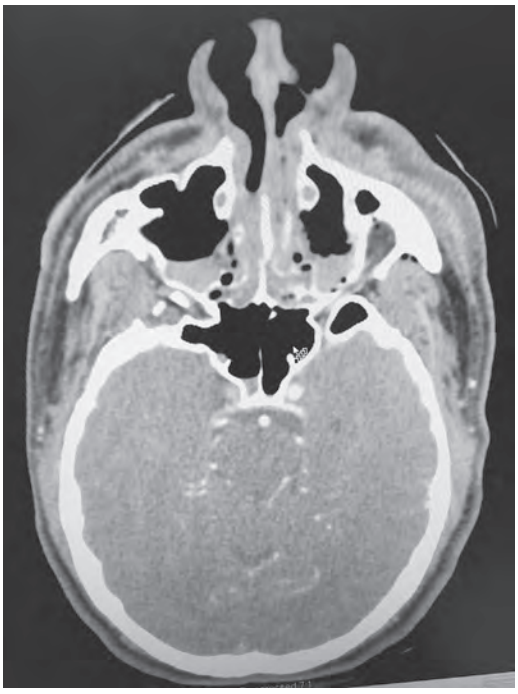

Fig. 35.18. CT angiography slice of the head and neck from a moped accident patient. There is no flow seen in the right internal carotid artery, suggestive of a blunt cerebrovascular injury.

hemorrhage, retinal detachment, and globe rupture (Figs. 35.19 and 35.20). The operator should position the transducer in a transverse orientation, scanning in a cephalad to caudad direction, making sure to scan the entire anatomy of the eye, and using special care to minimize the pressure exerted over the eye, especially when evaluating for a specific ocular emergency. Prior findings have suggested that high-resolution ultrasound has at least a 94% correlation with axial and coronal CT imaging in the detection of orbital fractures and emphysema.[43]

MANAGEMENT

Management of facial injuries occurs within the overall resuscitation of the patient. Unless the airway is threatened or exsanguination is a concern, treatment of most facial injuries can be deferred until more life-threatening injuries have been stabilized. Care of the patient with penetrating trauma to the face should center on standard trauma care, with initial attention focused on maintenance of a patent airway, adequate ventilation, and systemic perfusion.

Out-of-Hospital Care

The indications for airway management of a patient with a facial injury are the same as those for other patients. Does the patient have a currently patent airway and, if so, can the patient be expected to maintain it without intervention? If the answer to either question is "no," the patient needs to be intubated. If other injuries preclude the patient from ventilating appropriately, intubation is also required.

Patients with expanding hematomas after facial injury present a special dilemma. Injuries to the facial vasculature may cause significant hematomas that can extend into the neck or down to the supraclavicular area. Such hematomas greatly distort the normal anatomy of the pharynx and neck, making intubation and cricothyroidotomy particularly difficult. If the patient has a patent airway, he or she can speak without difficulty, and the transport time is expected to be short, no intervention should be performed. and the receiving institution should be notified so that planning can begin for a difficult airway. If intubation must occur in the field, awake orotracheal intubation should be considered. If certified in its use, emergency medical services personnel should be ready to perform a surgical airway as needed. Gunshot wounds to the lower third of the face are particularly likely to require intubation for airway protection, and a significant proportion of these require a surgical airway.[44]

In the setting of significant facial trauma, active bleeding can obscure the view and make intubation considerably more difficult. Double suctioning may be required, which involves an assistant holding one suction catheter in the posterior oropharynx while the operator uses a second device more anteriorly or inferiorly, as needed during the procedure. Conversely, patients with fractures of the mandible may be easier to intubate because increased mobility of the mandible may allow wider opening of the mouth.

Patients with multiple injuries should be resuscitated following Advanced Trauma Life Support (ATLS) protocol, and those who require intubation should have a LEMON assessment (Box 35.1) followed by rapid-sequence intubation, which has a higher success rate and fewer complications. Some alternative airway techniques may include submental or submandibular intubations

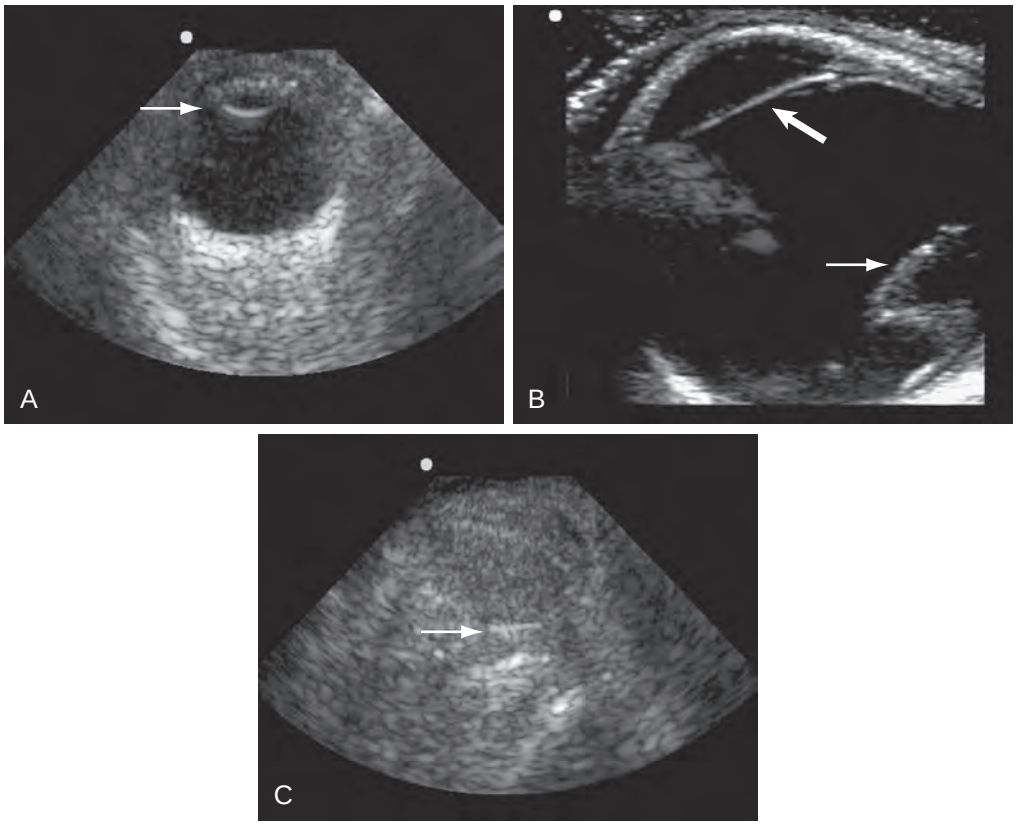

Fig. 35.19. Bedside sonograms of the eye. In each image, a small *white dot* is placed to identify the front of the eye, and *thin arrows* identify the lens. **A,** Normal eye. **B,** Detached retina. The large arrow is pointing to the lens of the eye, and the smaller arrow is pointing to the detachment. **C,** Ruptured globe *(arrow).* (Courtesy Dr. Keith Boniface.)

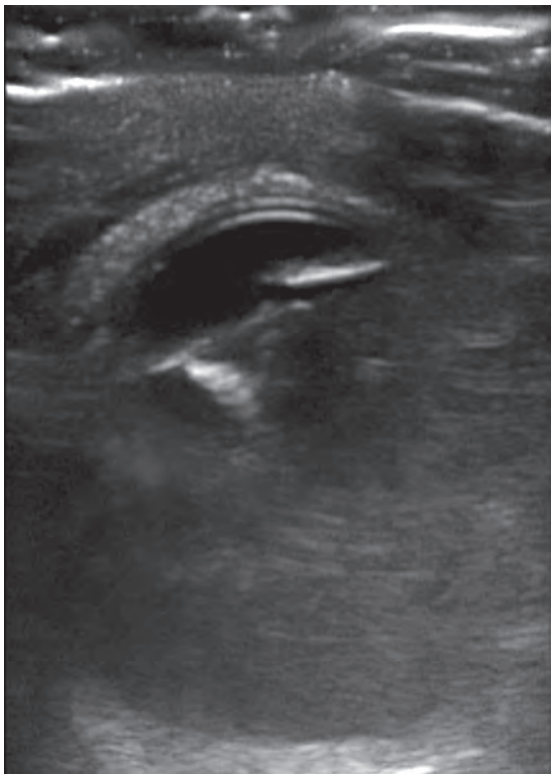

Fig. 35.20. Ultrasound image of a globe rupture with lens dislocation. At the top of the image, the cornea is visible, and just below that is the dislocation, with hemorrhage visible posteriorly.

BOX 35.1

LEMON Criteria[a]

L = Look externally (facial trauma, large incisors, beard or mustache, large tongue)
E = Evaluate the 3-3-2 rule (incisor distance, 3 fingerbreadths; hyoid-mental distance, 3 fingerbreadths; thyroid to mouth distance, 2 fingerbreadths)
M = Mallampati (Mallampati score > 3)
O = Obstruction (presence of any condition such as epiglottitis, peritonsillar abscess, trauma)
N = Neck mobility (limited neck mobility)

[a]Patients in the difficult intubation group have higher LEMON scores.

or anesthesiology-assisted intubations with the use of adjuncts such as the GlideScope or lighted stylet.[44-51]

Control of local bleeding is the other significant out-of-hospital consideration in facial trauma. In many areas, external compression is sufficient to control bleeding during transport. Epistaxis and significant intraoral bleeding can be more difficult to treat. Even in the setting of significant nasal trauma, the soft portions of the nares can be compressed to stop anterior nasal bleeding. In an awake alert patient with intraoral bleeding, 4- × 4-inch gauze packing may be placed into the buccal space to provide control. If these maneuvers are insufficient, and the patient's injuries require spinal immobilization, intubation may be a necessary first step to control intraoral or nasopharyngeal bleeding. After

intubation, large amounts of gauze can be placed via the mouth into the oropharynx and nasopharynx to obtain control via direct pressure.

If out-of-hospital personnel suspect a ruptured globe, special protection against compression of the eye (eg, eye cup, noncontact shielding) should be provided in the field. Avulsed parts, including the ears, tip of the nose, teeth, or completely avulsed flaps, should be transported with the patient in saline-soaked gauze.

Completely avulsed teeth should be removed and carried with the patient during transport. Neurologically normal, nonintoxicated patients may be able to carry avulsed teeth in their mouths, held between the gum and buccal mucosa. Patients who are not neurologically normal, are intoxicated, require cervical spine immobilization, are nauseated, or cannot be transported upright should not be transported with avulsed teeth held in the mouth. In such cases, the risk of aspirating the teeth outweighs any other concerns, and the teeth should be transported in a container with sterile saline. Incompletely avulsed teeth should be left in place and not manipulated.

Emergency Department Treatment

General Measures

The initial evaluation in the ED should re-address the question of intubation. In the setting of significant distortion of the mouth, oropharynx, or upper neck by avulsion or hematoma, the awake fiberoptic method may optimize the chances of a successful intubation. When there is significant distortion of the oropharynx or larynx, a laryngeal mask airway may not achieve a sufficiently tight fit to allow ventilation. Emergent cricothyroidotomy is the procedure of choice if endotracheal intubation is impossible.

Unless there is life-threatening hemorrhage from the face, facial injuries can be safely left to the secondary survey after the airway has been secured. The emergency clinician should avoid being distracted by a facial injury and search intensively for head, neck, chest, abdominal, pelvic, and extremity injuries. In-depth ocular examinations and other special testing should not be performed until other serious injuries have been managed emergently.

Significant bleeding can often be controlled by compression. If compression fails, hemostasis can be achieved in the ED by ligation of the relevant vessel. Great care should be taken, however, not to clamp or tie structures blindly deep within the face because serious iatrogenic injury of nerve or ductal structures could result. Massive uncontrollable bleeding from facial fractures occurs rarely and is best treated with arterial embolization, if available.[52] Intraarterial vasopressin has recently been suggested as an option for hemostasis.[52] Tranexamic acid may also show promise in controlling hemorrhage from facial trauma.[53]

In the rare case of a patient acutely exsanguinating from a facial wound, the external carotid artery can be emergently ligated. This ligation is best accomplished with surgical assistance.

Bite wounds, gross contamination, or significant tattooing from foreign bodies should be addressed definitively as soon as possible, given the needs of the patient's other injuries. Definitive treatment of simple soft tissue injuries can be left for 24 hours, if needed, after irrigation and temporary approximation. Ideally, facial fractures are treated early, before significant swelling occurs, or after several days, when return of more normal facial contours can aid in the repair. The need for tetanus prophylaxis should be considered for all open wounds. If the injury is an animal bite, the need for rabies prophylaxis should be considered. Because the rabies virus is transmitted to the brain along nerve axons, and symptomatic disease theoretically may occur sooner with wounds of the head, face, and neck, initiating rabies treatment within 5 days of the injury is recommended.

Because lead poisoning has been reported from the ingestion of shotgun pellets in patients with primarily facial injuries, consideration should be given to looking for the presence of pellets in the gastrointestinal tracts of these victims. A plain x-ray film of the abdomen suffices. Early endoscopic removal of the pellets should limit future toxicity.

The final part of the physical examination when dealing with facial trauma is the importance of documentation. Facial injuries may be evidence of assault, domestic violence, or child abuse. Careful documentation of findings, including photographs, drawings, or both, not only communicates initial findings to other practitioners but also can provide crucial legal evidence because many of these cases have forensic implications or result in litigation.

DISPOSITION

The decision to discharge or admit patients with facial trauma depends on their associated injuries, general injury severity, and plans for treatment. In general, the emergency clinician can handle the initial resuscitation and stabilization of patients with facial trauma. It is recommended that early consultation with the appropriate surgical specialists happen once the patient has been stabilized. Antibiotics should be considered in cases of severe facial trauma or open fractures. Patients with isolated facial trauma that has been repaired or stabilized and with no airway issues are usually discharged with close follow-up.

KEY CONCEPTS

The face is central to the patient's ability to breathe, eat, and communicate. Injuries to the face can have serious psychological and psychosocial consequences.

- Facial injuries may be prevented by the appropriate use of seat belts, child restraints, air bags, helmets, and mouth and face guards.
- The epidemiology of facial injury is changing, with an increasing proportion of injuries occurring as a result of interpersonal violence. A careful history is required, and the possibility of abuse should be considered for every patient.
- Shock from facial trauma is rare and results only from obvious external bleeding. Facial injuries should not distract the emergency clinician from aggressively searching for other causes of shock.
- Assertive management of the airway is indicated in a patient with significant facial injuries. Surgical management (cricothyroidotomy) may be required, particularly with gunshot wounds.
- Directed facial CT scanning is the best imaging technique in patients with obvious injuries.
- Definitive treatment may be delayed, if necessary, to allow other serious injuries to be addressed.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 35: QUESTIONS & ANSWERS

35.1. Stensen's duct enters the mouth most closely to which tooth?

A. First lower molar
B. First upper molar
C. First upper premolar
D. Second lower molar
E. Second upper molar

Answer: E. The salivary system consists of the parotid, sublingual, and submandibular glands. The parotid is the largest of these glands, lying just anterior to the ear and wrapping around the mandible. The parotid is superficial to the masseter muscle and drains via Stensen's duct, a 5-cm tube that curves around the anterior edge of the masseter to enter the mouth opposite the second upper molar. The sublingual glands lie entirely within the floor of the mouth and drain into the mouth via ductules. They surround the ducts draining the submandibular glands (Wharton's ducts). The body of the submandibular gland is folded around the mylohyoid muscle so that a portion lies within the floor of the mouth and a portion lies external to it. The submandibular (Wharton's) ducts run from the external portion of the gland to empty into the mouth on either side of the frenulum of the tongue.

35.2. Which term is used to describe bilateral transverse fractures through the maxilla above the roots of the teeth?

A. Craniofacial disjunction
B. Le Fort I fracture
C. Le Fort II fracture
D. Le Fort III fracture
E. Trimalar fracture

Answer: B. Tripod (or trimalar) fractures are among the simplest fractures of the midface and include fractures of three bones—the lateral orbit, zygoma, and maxilla. More complex fractures of the midface are classified using the Le Fort system, although many complex fractures defy classification with this system. A Le Fort I fracture involves a transverse fracture through the maxilla above the roots of the teeth and may be unilateral or bilateral. Patients may complain of malocclusion, and the maxilla may be mobile when the upper teeth are grasped and rocked. A Le Fort II fracture is typically bilateral and pyramidal in shape. It extends superiorly in the midface to include the fracture of the nasal bridge, maxilla, lacrimal bones, orbital floor, and rim. In these cases, the nasal complex moves as a unit with the maxilla when the teeth are grasped and rocked. Le Fort III fractures involve fracturing the connections between the elements of the skull and face (craniofacial disjunction). These fractures start at the bridge of the nose and extend posteriorly along the medial wall of the orbit (ethmoids), along the floor of the orbit (maxilla) and through the lateral orbital wall, and finally break through the zygomatic arch. Intranasally, they extend through all the lesser bones to the base of the sphenoid and frequently are associated with a cerebrospinal fluid (CSF) leak.

35.3. Treatment for a patient with a blowout fracture can include all the following recommendations except which one?

A. Application of cold compress to reduce swelling
B. Appropriate oral antibiotic
C. Discouraging nose blowing to avoid creating or exacerbating any orbital emphysema
D. Use of decongestants to help keep the sinuses clear of any draining fluid
E. Use of steroid eye drops to help decrease any inflammation in the affected eye

Answer: A. The use of steroid eye drops should not be initiated by the emergency clinician for a blowout fracture. Antibiotic prophylaxis against the potential sequelae of sinusitis, orbital cellulitis, and other more malignant intracranial infections is appropriate, as would be the use of decongestants and the avoidance of any activities that would exacerbate orbital emphysema.

CHAPTER 36

Spinal Injuries

Amy H. Kaji | Robert S. Hockberger

PRINCIPLES

Background and Importance

According to the National Spinal Cord Injury Statistical Center, motor vehicle collisions (MVCs) account for 37% of all spinal injuries.[1] Speeding, alcohol intoxication, and failure to use restraints are major risk factors. The next most common cause of spinal cord injury (SCI) is falls, followed by acts of violence (primarily gunshot wounds) and sporting activities. Approximately 80% of victims are male, and the average age at injury is 42.6 years. The lifetime cost to care for SCI victims ranges from $1 million if older than 50 years, with incomplete motor function, to over $4 million for those younger than 25 years, with complete paraplegia. The total cost to society from lifelong medical expenses and lost productivity for all ages and types of spinal injuries is estimated to be more than $5 billion. The devastating emotional and psychological impact is incalculable.

Injuries of the soft tissues supporting the cervical spine can result in chronic pain and disability. The term *whiplash-associated disorder* (WAD) has been used to describe these injuries because of the flexion-extension movement of the neck that results from rear-end MVCs, the most common cause of a WAD. Due to the large number of people sustaining these injuries, the annual costs associated with a WAD exceed $230 billion, which is more than the combined costs associated with spinal cord and brain injuries caused by MVCs.[2]

Anatomy and Physiology

The human spine consists of 33 bony vertebrae—7 cervical, 12 thoracic, 5 lumbar, 5 sacral (fused into one), and 4 coccygeal (usually fused into one; Fig. 36.1). These 26 individual units are separated from one another by flexible intervertebral disks and connected to form a single functioning unit by a complex network of ligaments (Fig. 36.2). The vertebral column protects the spinal cord, which extends from the midbrain to the level of the second lumbar vertebra.

Spinal injuries involve fractures in 85% of cases. Of these, 10% are ligamentous injuries without fracture, and 5% are SCIs without a radiographic abnormality (SCIWORA), in which the spinal cord is injured directly without radiographic evidence of bony or ligamentous injury. Stability of a spinal injury refers to the resistance to displacement of fracture fragments or, in the case of ligamentous injury, the entire vertebral unit. There are several classification systems for assessing the stability of subaxial spinal column injuries, including the Allen Ferguson classification, Association for Osteosynthesis classification, Dennis Classification, and thoracolumbar injury classification and severity score for thoracolumbar injuries. According to a survey of the members of Spine Trauma Study Group of the International Spinal Cord Society, practical implementation is evenly distributed among the classification systems.[3] The three parallel vertical column model proposed by Denis[2] depicts the anterior column as being formed by alternating vertebral bodies and intervertebral disks surrounded by the annulus fibrosus capsule and anterior longitudinal ligament. The middle column consists of the posterior part of the annulus fibrosus and posterior vertebral wall, posterior longitudinal ligament, spinal cord, paired laminae and pedicles, articulating facets, transverse processes, nerve roots, and vertebral arteries and veins. The posterior column consists of the spinous processes, nuchal ligament, interspinous and supraspinous ligaments, and ligamentum flavum. Disruption of a single column usually preserves stability but does not preclude an SCI from displaced fracture fragments. Disruption of two columns results in an injury that is stable in one direction but unstable in another (eg, stable in flexion but unstable in extension). Disruption of all three columns produces a highly multidirectional unstable injury.

Pathophysiology

Classification of Spinal Column Injuries

Acute spinal injuries are classified according to the mechanism of trauma—flexion, flexion-rotation, extension, and vertical compression (Table 36.1).

Flexion. Pure flexion injuries involving the C1-C2 complex can cause unstable atlanto-occipital or atlantoaxial joint dislocation, with or without an associated fracture of the odontoid (Fig. 36.3). The basion-axial interval (BAI) and basion-dens interval (BDI) are normally less than 12 mm. A value greater than 12 mm is suggestive of an atlantoaxial joint dislocation (Fig. 36.4). Calculating the ratio of the distance from the basion to midvertical portion of the posterior laminar line of the atlas over the distance from the opisthion to midvertical portion of the posterior surface of the anterior ring of the atlas (Fig. 36.5) indicates subluxation if the ratio is greater than 1. These injuries are considered unstable because of their location and the relative lack of muscle and ligamentous support.

In pure flexion injuries below C2, a longitudinal pull is exerted on the strong nuchal ligament complex, which usually remains intact. Most of the force is expended on the vertebral body anteriorly, causing a simple wedge fracture. Radiographically, there is a diminished height and increased concavity of the anterior border of the vertebral body, increased density of the vertebral body resulting from bony impaction, and prevertebral soft tissue swelling (Fig. 36.6). Because the posterior column remains intact, this injury is usually stable. However, spinal instability may occur with severe wedge fractures (loss of more than half the vertebral height) or multiple adjacent wedge fractures.

A flexion teardrop fracture results when severe flexion forces cause anterior displacement of a wedge-shaped fragment (resembling a teardrop) of the anteroinferior portion of the involved vertebral body (Fig. 36.7). This injury, which is associated with neurologic injury, is highly unstable because the anterior and posterior ligaments are commonly disrupted.

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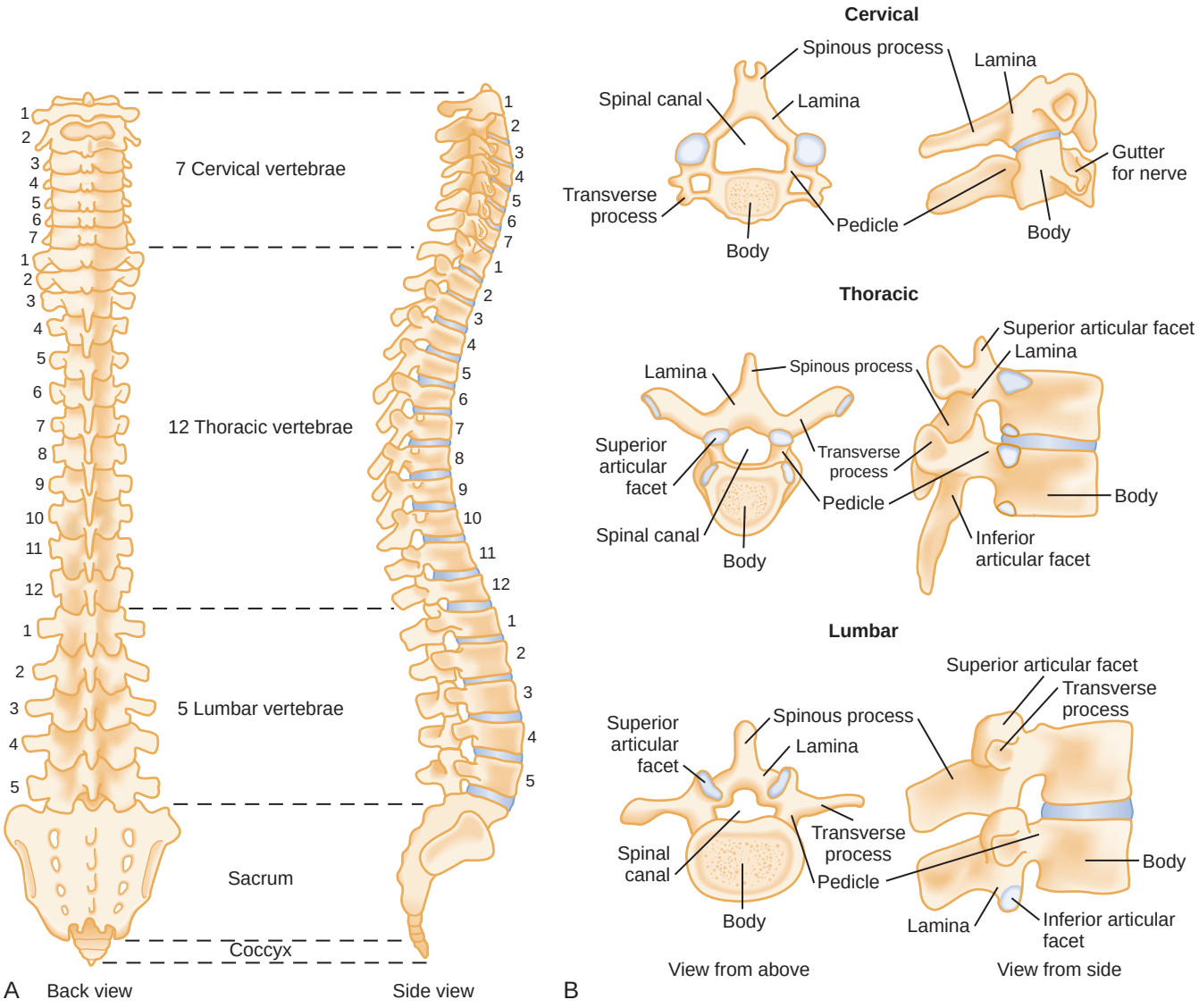
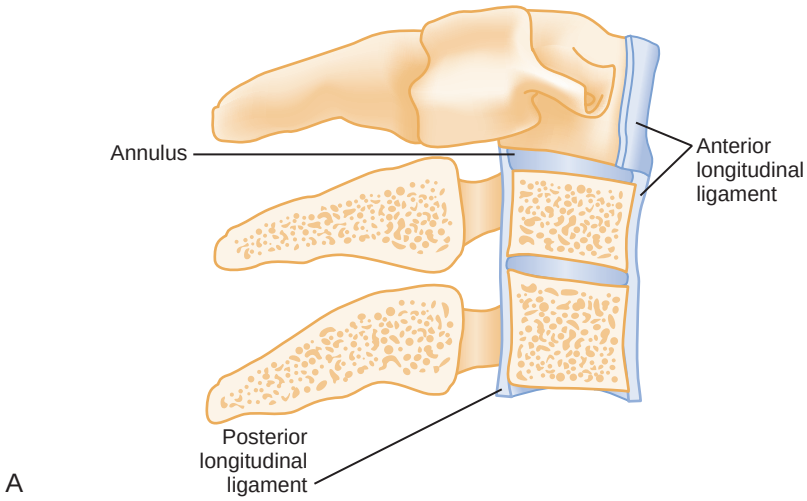


Fig. 36.1. **A,** Vertebral column. **B,** Typical vertebrae.



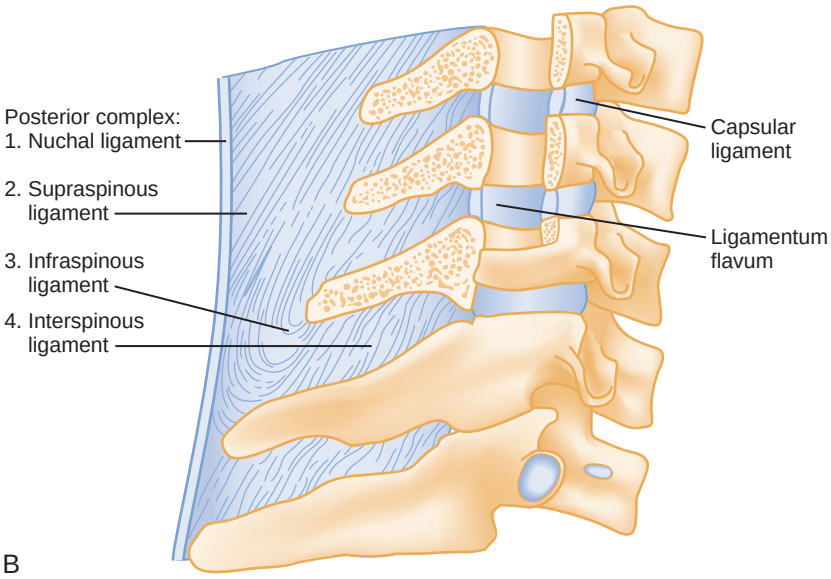


Fig. 36.2. **A,** Ligaments of the anterior column. **B,** Ligaments of the posterior column.

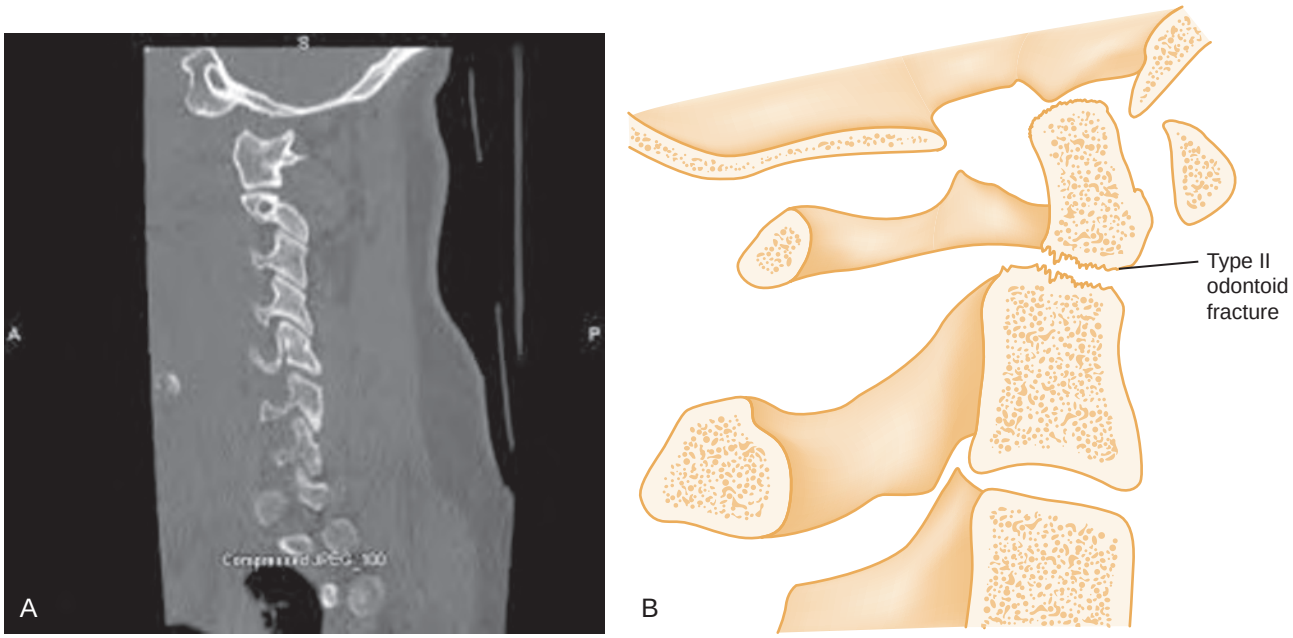


Fig. 36.3. A, B, Odontoid fracture with anterior dislocation. Mechanism—flexion with shearing; stability— unstable.

TABLE 36.1

Classification of Spinal Injuries

MECHANISM OF SPINAL INJURY	STABILITY
FLEXION	
Wedge fracture	Stable
Flexion teardrop fracture	Extremely unstable
Clay shoveler's fracture	Stable
Subluxation	Potentially unstable
Bilateral facet dislocation	Always unstable
Atlanto-occipital dislocation	Unstable
Anterior atlantoaxial dislocation with or without fracture	Unstable
Odontoid fracture with lateral displacement fracture	Unstable
Fracture of transverse process	Stable
FLEXION-ROTATION	
Unilateral facet dislocation	Stable
Rotary atlantoaxial dislocation	Unstable
EXTENSION	
Posterior neural arch fracture (C1)	Unstable
Hangman's fracture (C2)	Unstable
Extension teardrop fracture	Usually stable in flexion; unstable in extension
Posterior atlantoaxial dislocation, with or without fracture	Unstable
VERTICAL COMPRESSION	
Bursting fracture of vertebral body	Stable
Jefferson fracture (C1)	Extremely unstable
Isolated fractures of articular pillar and vertebral body	Stable

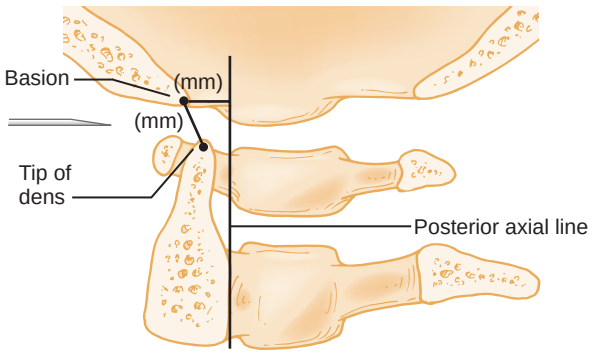


Fig. 36.4. The basion-axial interval (BAI) and basion-dens interval (BDI) are normally less than 12 mm.

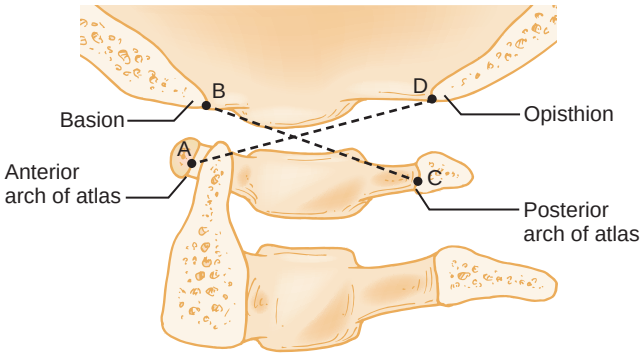


Fig. 36.5. The Power's ratio.

Fig. 36.6. **A,** Lateral view of a wedge fracture of C5 with angulation. Mechanism—flexion; stability—mechanically stable. **B,** Note the anterior wedging of the C4 vertebral body and angulation of C4 on C5.

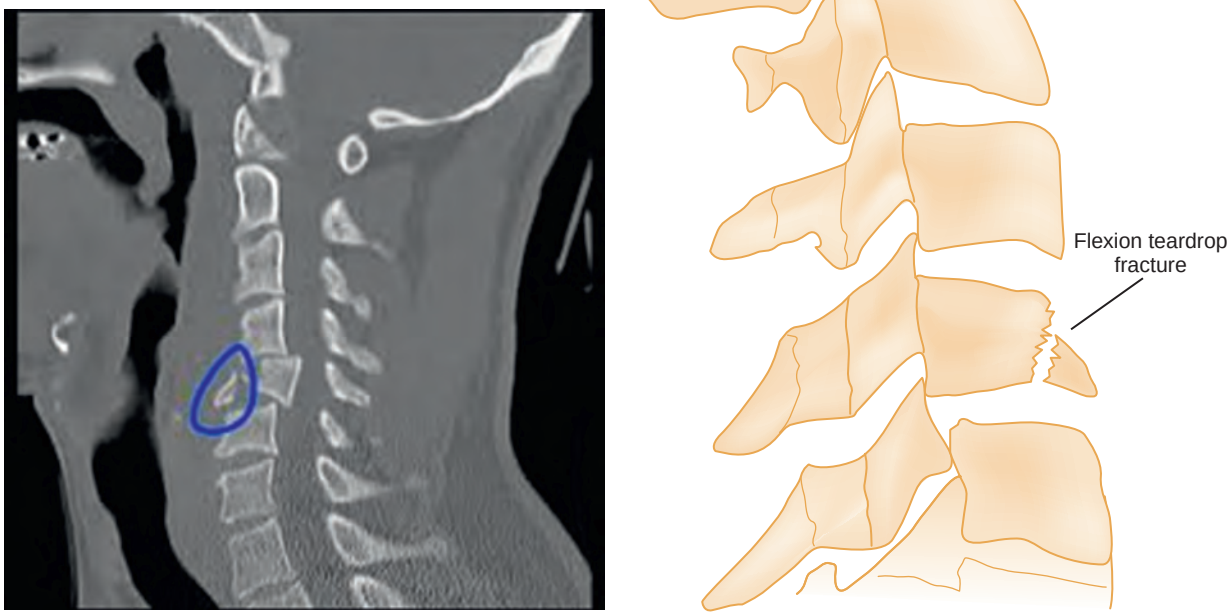


Fig. 36.7. **A, B,** Lateral view of a teardrop fracture. Mechanism—flexion; stability—unstable. The fractured fragment off the C5 body resembles a teardrop.

The clay shoveler's fracture is an oblique fracture of the base of the spinous process of one of the lower cervical vertebrae (Fig. 36.8). The injury derives its name from the fracture caused by the abrupt head flexion that clay miners experienced when lifting a heavy shovelful of clay and having the clay stick to the shovel. This force, transmitted through the supraspinous ligament, results in an avulsion fracture of the spinous process. Today, this fracture is seen after direct trauma to the spinous process and after sudden deceleration MVCs that result in forced neck flexion. Because this injury involves only the spinous process, it is stable and requires no treatment beyond symptomatic care.

Pure spinal subluxation occurs when the ligamentous complexes rupture without an associated bony injury. This injury begins posteriorly in the nuchal ligament and proceeds anteriorly to involve other ligaments (Fig. 36.9). Although rarely associated with neurologic damage, this injury is potentially unstable.

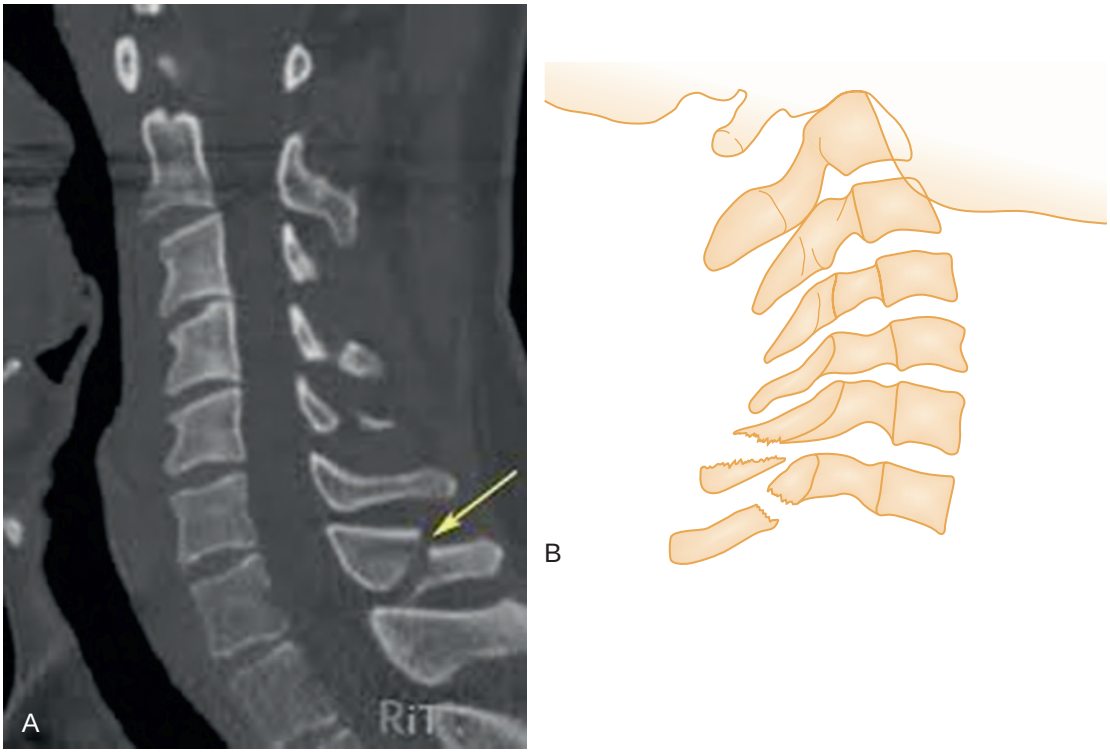


Fig. 36.8. A, B, Clay shoveler's fracture. Mechanism—flexion; stability—mechanically stable. Note the avulsed fragment off the tip of the C7 spinous process in an underpenetrated lateral view (*arrow*).

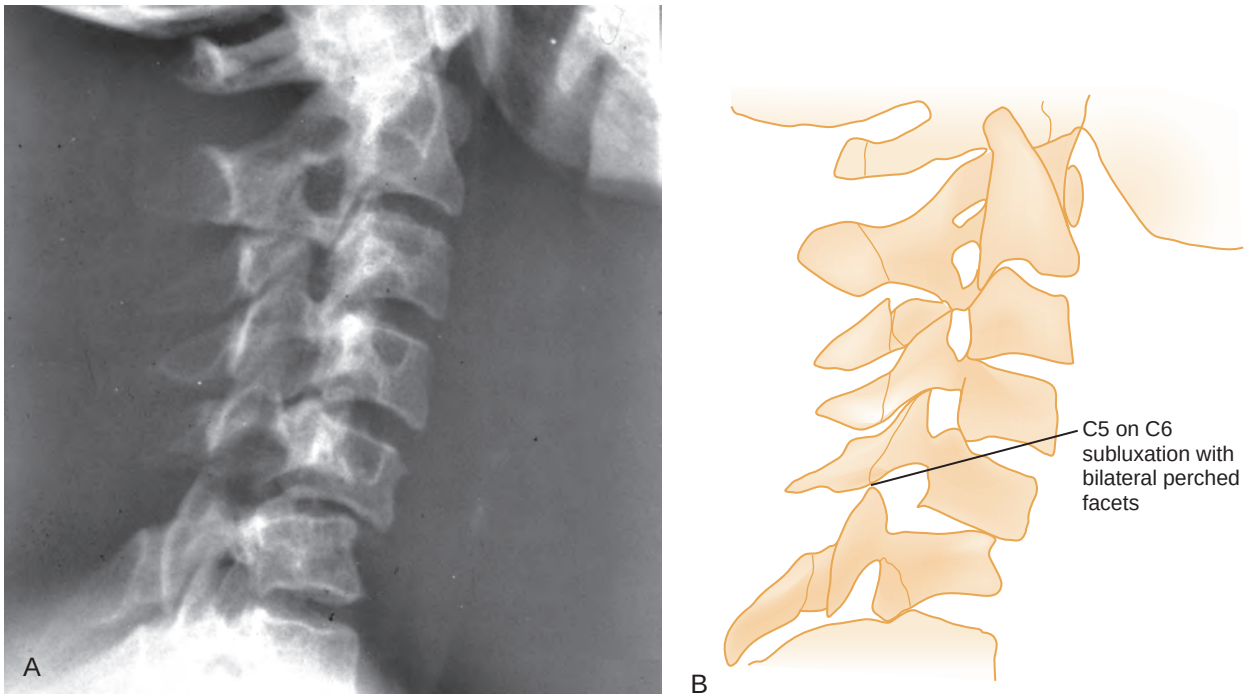


Fig. 36.9. A, B, Subluxation with bilateral perched facets at C5 and C6. Mechanism—flexion; stability—unstable. Lateral view shows severe subluxation of C5 on C6.

Bilateral facet dislocations occur when a greater force of flexion causes soft tissue disruption to continue anteriorly to the annulus fibrosis of the intervertebral disk and anterior longitudinal ligament, resulting in extreme instability. The forward movement of the spine causes the inferior articulating facets of the upper vertebra to pass upward and over the superior facets of the lower vertebra (Fig. 36.10), resulting in anterior displacement of the spine above the level of injury.

Shear Injury. Trauma to the head directed in an anteroposterior (AP) direction may result in fracture of the odontoid process above the transverse ligaments (type I) or, more commonly, at the base of the odontoid process where it attaches to C2 (type II; Fig. 36.11). Slight angulation of the force may result in extension of the fracture into the body of C2 (type III; Fig. 36.12). Type I odontoid fractures are usually stable because they are an avulsion injury to the odontoid tip. However, if traction forces injure the apical and alar ligaments, the fracture may be unstable. Type II odontoid fractures are, by definition, unstable and are often complicated by nonunion. Type III odontoid fractures are also mechanically unstable because they can extend laterally into the superior articular facet of the atlas.

Flexion-Rotation. Rotary atlantoaxial dislocation is an unstable injury visualized best on open-mouth odontoid radiographs (Fig. 36.13) or a computed tomography (CT) scan. When the x-ray image reveals symmetric basilar skull structures, a unilateral magnified lateral mass confirms a C1-C2 dislocation.

A unilateral facet dislocation is caused by both flexion and rotation. The rotational component of this injury occurs around one of the facet joints, which acts as a fulcrum. Simultaneous flexion and rotation cause the contralateral facet joint to dislocate, with the superior facet riding forward and over the tip of the inferior facet and coming to rest within the intervertebral foramen. In this position, the dislocated articular mass is mechanically locked in place, making this a stable injury even though the posterior ligament complex is disrupted.

Any cervical fracture or dislocation may cause torticollis however torticollis may also be caused by a benign process such as a muscle spasm. It may be difficult to differentiate the two

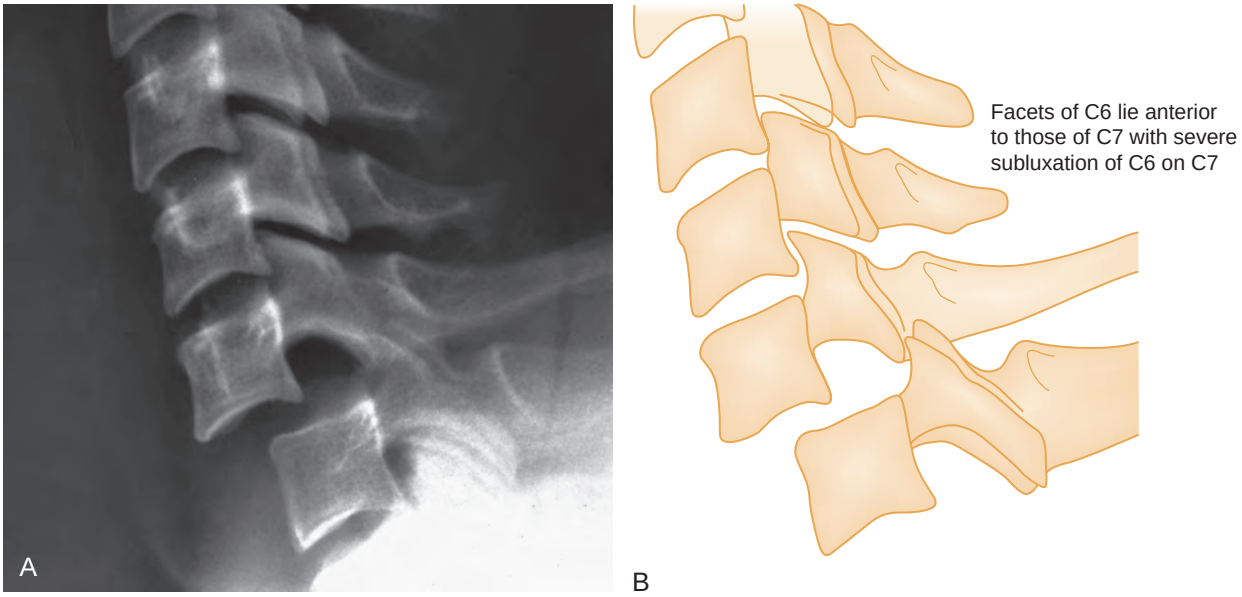


Fig. 36.10. A, B, Bilateral facet dislocation. Facets of C6 lie anterior to those of C7, with severe subluxation of C6 on C7.

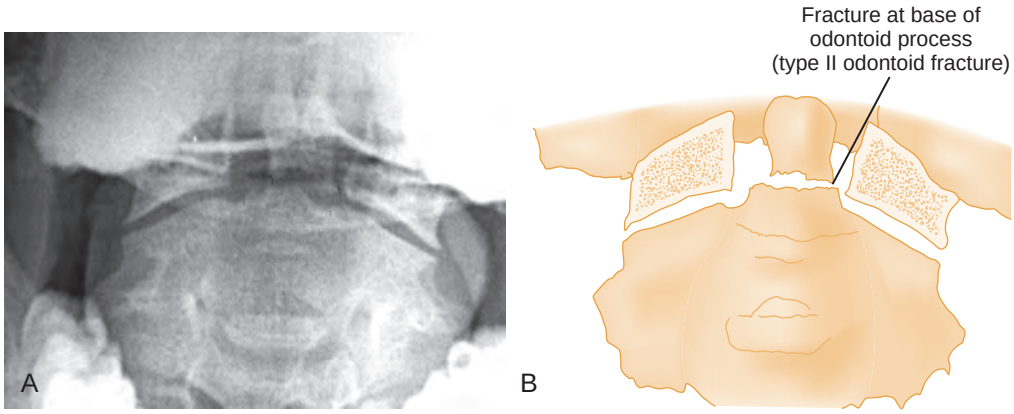


Fig. 36.11. A, B, Odontoid fracture with lateral displacement. Mechanism—flexion; stability—unstable. The tip of the odontoid process is laterally displaced in this lateral flexion injury.

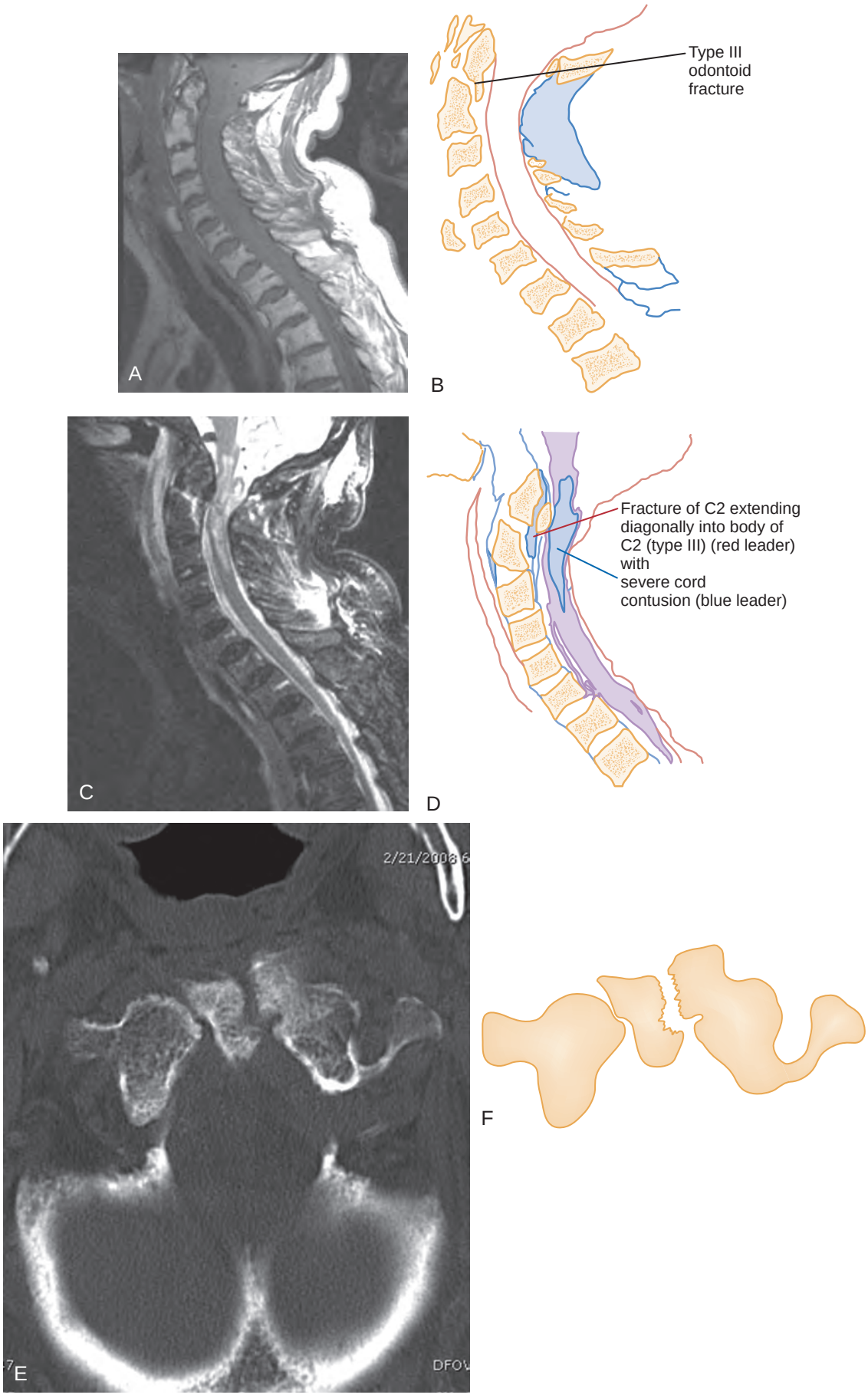


Fig. 36.12. **A–F**, Odontoid fracture, type III.

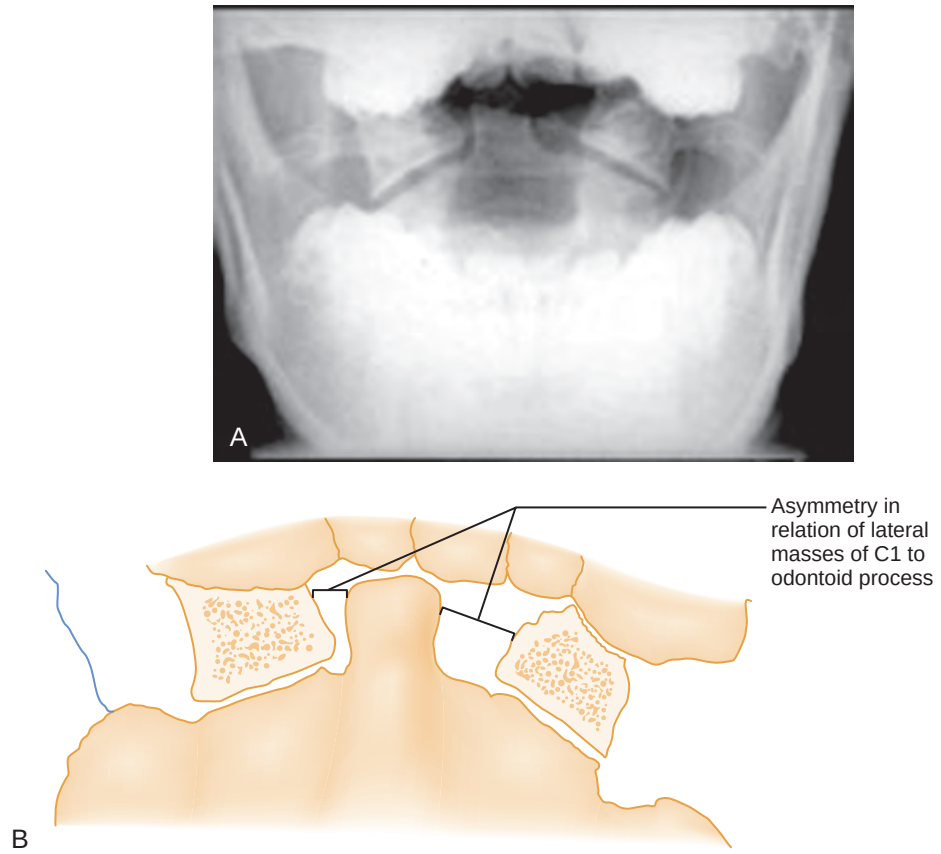


Fig. 36.13. A, B, Rotatory subluxation of C1 on C2. Mechanism—rotation; stability—unstable. There is marked asymmetry in the relationship of the lateral masses of C1 to the odontoid process. Rotation causes the right lateral mass to appear slightly larger (farther from the x-ray film) than the left (closer to the x-ray film).

Fig. 36.14. Unilateral facet dislocation on CT.

and in the setting of trauma, CT (Fig. 36.14) or oblique radiographs may be necessary to demonstrate the dislocated facet joint (Fig. 36.15).

Due to the varying shapes of the articular processes, different types of flexion-rotation injuries result. In the cervical region, where articular processes are small and almost horizontal, unilateral facet dislocations occur, whereas in the lumbar region, in which articular processes are large and nearly vertical, unilateral facet dislocation is rare. Instead, one or both articular processes fracture, and the upper vertebra swings forward. Commonly seen in the thoracolumbar and lumbar regions, this rotation fracture-dislocation is unstable (Fig. 36.16).

Extension. Fracture of the posterior neural arch of the atlas (C1) results from compression of the posterior elements between the occiput and spinous process of the axis (C2) during forced neck extension (Fig. 36.17). Although the anterior arch and transverse ligament remain intact, this fracture is potentially unstable because of its location.

The hangman's fracture, or traumatic spondylolysis of C2, occurs when the cervicocranium—the skull, atlas, and axis functioning as a unit—is hyperextended as a result of abrupt deceleration. Bilateral fractures of the pedicles of the axis occur with or without dislocation (Fig. 36.18). Although unstable, cord damage is often minimal because the AP diameter of the neural canal is greatest at C2, and the bilateral pedicular fractures permit spinal canal decompression. Originally described in victims of hanging injury, today it is most often the result of head-on MVCs.

The extension teardrop fracture occurs when abrupt extension of the neck causes the anterior longitudinal ligament to pull the anteroinferior corner of a vertebral body away from the remainder of the vertebra, producing a triangular fracture that is radiographically similar to the flexion teardrop fracture. Often occurring in lower cervical vertebrae (C5–C7) from diving accidents, this injury may be associated with a central cord syndrome (see later) and is caused by the ligamentum flavum buckling into the spinal cord. Because the posterior elements remain intact, this injury is stable in flexion but potentially unstable in extension.

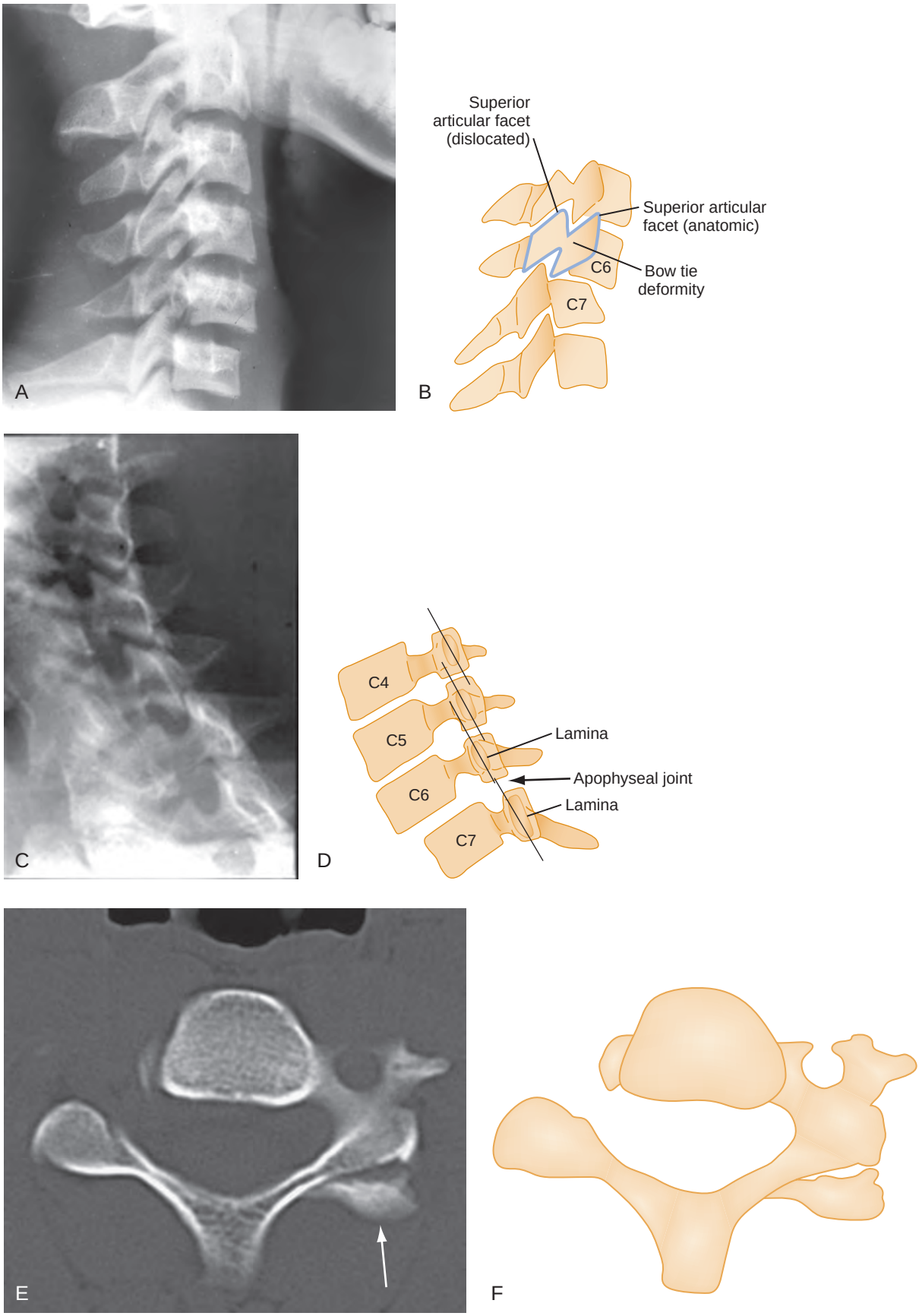


Fig. 36.15. Unilateral facet dislocation. Mechanism—flexion and rotation; stability—stable. **A, B,** Lateral view showing one dislocated articular facet of C5 lying anterior to the corresponding facet of C6 and creating a bowtie deformity. The C5 vertebral body is subluxed anteriorly on C6. **C, D,** Oblique view of unilateral facet dislocation with the lamina of C6 projecting into the neural foramen. **E, F,** CT scan showing facet dislocation. The inferior facet (*arrow*) lies posterior to the superior facet.

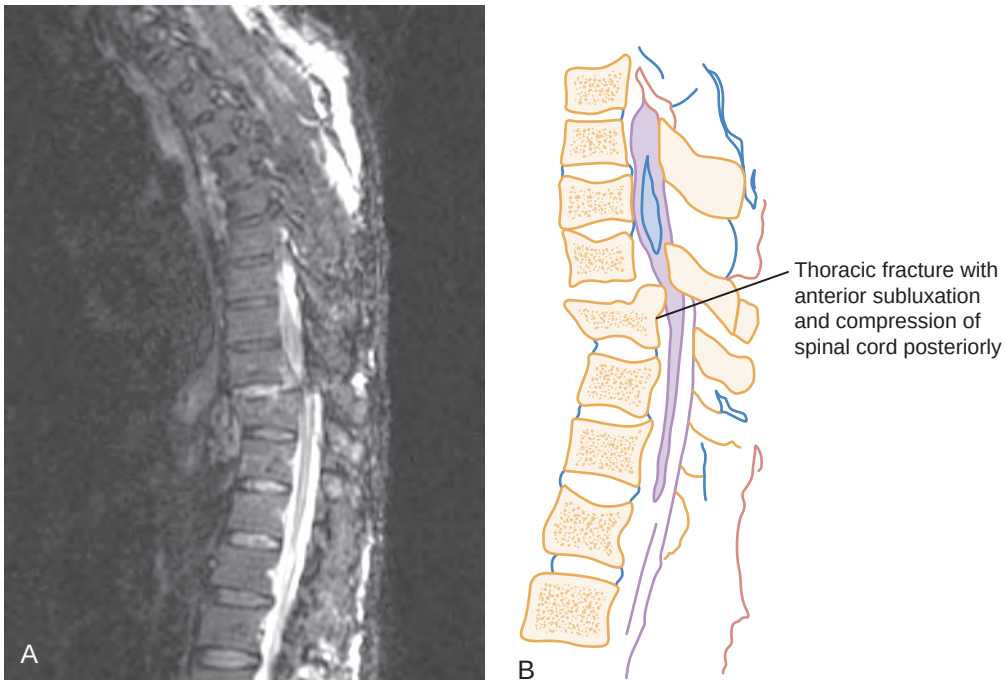


Fig. 36.16. **A**, **B,** MRI scan showing fracture-dislocation of the thoracic spine.

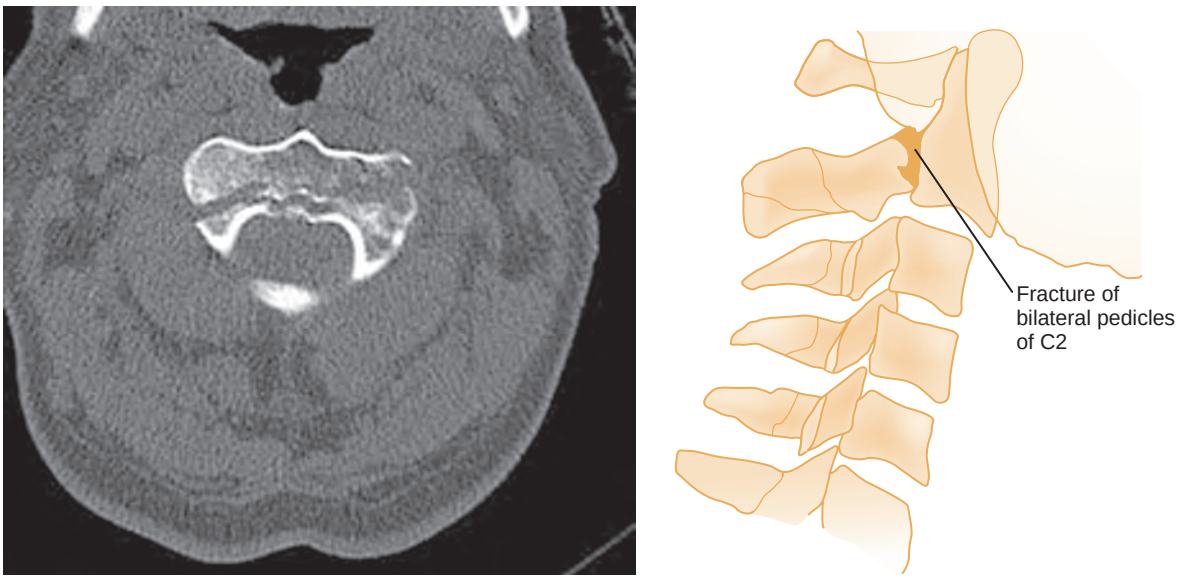


Fig. 36.17. **A, B,** CT scan of posterior neural arch fracture of C1. Mechanism—extension; stability—unstable. The fracture line is well visualized.

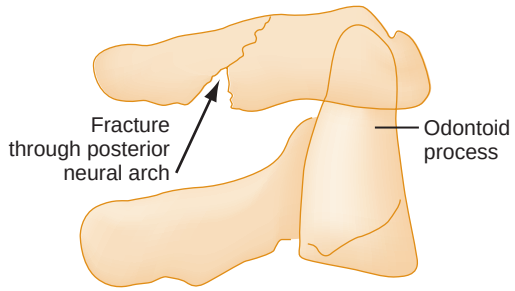


Fig. 36.18. Hangman's fracture. Mechanism—extension; stability—unstable. Fracture lines extending through the pedicles of C2 are well visualized. Retropharyngeal soft tissue swelling is apparent.

Vertical Compression. Vertical compression injuries occur in the cervical and lumbar regions, which are capable of straightening at the time of impact. When forces are applied from above (skull) or below (pelvis or feet), one or more vertebral body endplates may fracture. The nucleus pulposus of the intervertebral disk is forced into the vertebral body, which is shattered outward, resulting in a burst fracture (Fig. 36.19). Sagittal CT cuts and a lateral radiograph will demonstrate a comminuted vertebral body, and there will typically be greater than 40% compression of the anterior vertebral body, which helps differentiate it from the simple wedge fracture. Coronal CT cuts and a frontal radiograph demonstrate a characteristic vertical fracture of the vertebral body. This is a stable fracture because all the ligaments remain

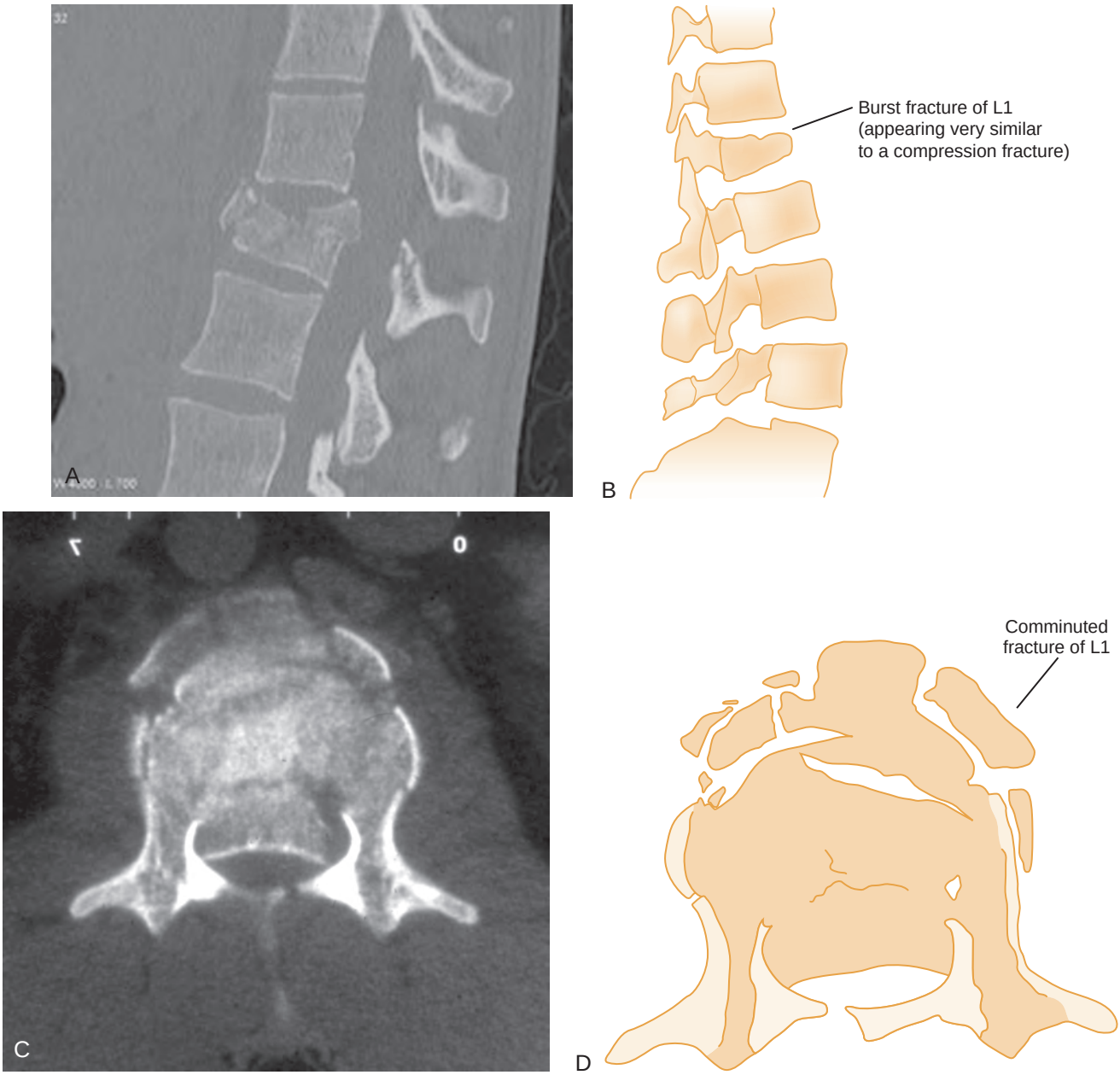


Fig. 36.19. Burst fracture of a vertebral body. Mechanism —vertical compression and flexion; stability—unstable**. in the right place? A**, **B,** Lateral CT scan showing a burst fracture of L1, appearing very similar to a compression fracture. Mechanism—flexion; stability—usually stable. **C, D,** CT scan of L1 in the same patient showing comminution of the fracture and retropulsion of fragments into the spinal canal.

intact. However, fracture fragments may impinge on or penetrate the ventral surface of the spinal cord and cause an anterior cord syndrome (Fig. 36.20).

An extremely unstable injury, the C1 Jefferson fracture occurs when a vertical compression force is transmitted through the occipital condyles to the superior articular surfaces of the lateral masses of the atlas, driving the lateral masses outward, disrupting the transverse ligament and resulting in fractures of the anterior and posterior arches of the atlas (Fig. 36.21). The lateral film may demonstrate a widening of the predental space between the anterior arch of C1 and the odontoid, or dens. The open-mouth view will demonstrate a bilateral offset of right and left lateral masses of C1 relative to the lateral masses of C2. A fracture should be diagnosed when the sum of the offset distances from the right and left sides exceeds 7 mm. However, when the fragments are minimally displaced, the Jefferson fracture is difficult to recognize.

Rarely, vertical compression fractures may result in isolated fractures of the articular pillar or vertebral body, exhibiting vertical and oblique lines of fracture.

Classification of Spinal Cord Injuries

Primary Spinal Cord Injury. The spinal cord may be injured by three broad categories of injury patterns. First, penetrating trauma or massive blunt trauma with disruption of the vertebral column causes transection of neural elements. Because neurons within the central nervous system do not regenerate, such injuries are irreversible. Less severe blunt trauma may have similar effects resulting from a displaced bony fragment or herniated disk injuring the cord.

Second, when patients with cervical osteoarthritis and spondylosis, particularly older adults, are subjected to forcible cervical

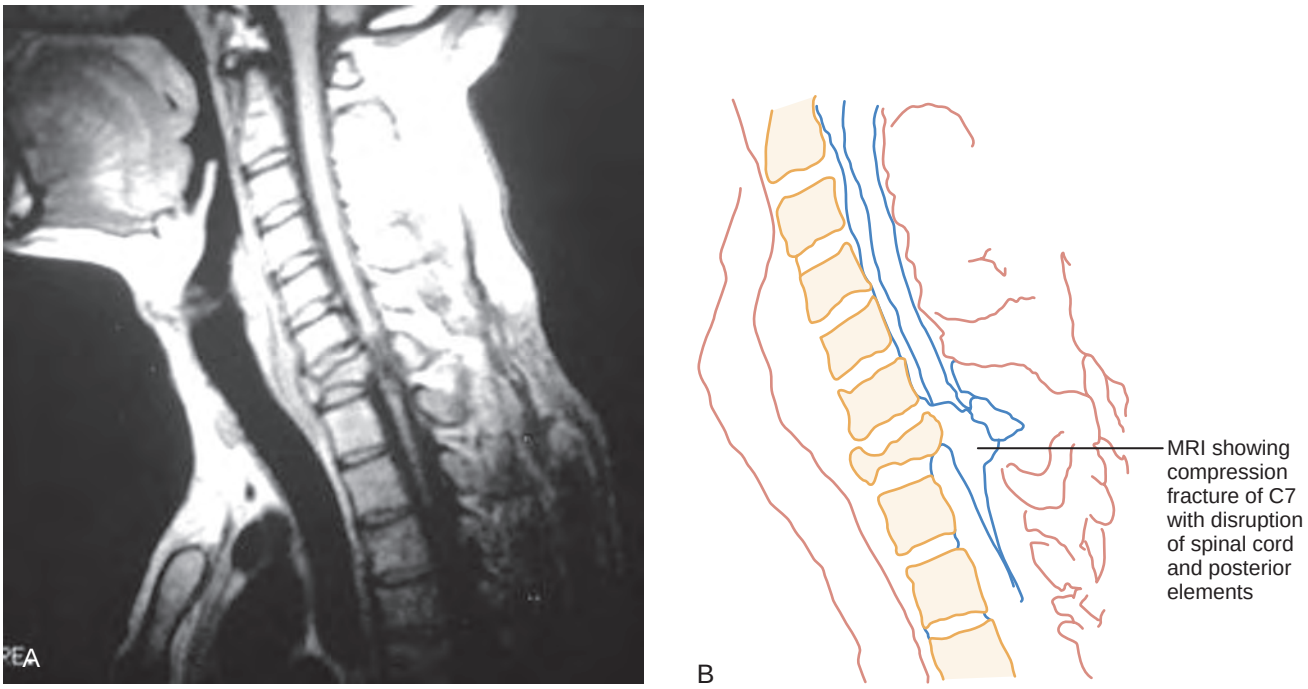


Fig. 36.20. A, B, MRI scan showing a burst fracture of C7 with complete spinal cord disruption.

spine extension, the spinal cord may be injured secondary to compression between an arthritically enlarged anterior vertebral ridge and a posteriorly located hypertrophic ligamentum flavum (Fig. 36.22). This injury frequently results in a central cord syndrome.

The third mechanism is primary vascular damage to the spinal cord. The spinal cord may be compressed by an extradural hematoma, particularly in patients who are on anticoagulants or have bleeding disorders. Vascular injuries should also be suspected when there is a discrepancy between the clinically apparent neurologic deficit and known level of spinal injury. For example, a lower cervical dislocation may compress the vertebral arteries as they travel within the spinal foramina of the vertebrae, resulting in thrombosis of the anterior spinal artery that originates from both vertebral arteries at C1 (Fig. 36.23). On physical examination, such an injury may erroneously appear to be localized to the level of C1 or C2. Also, the great radicular artery of Adamkiewicz, originating from the aorta and entering the spinal canal at the level of L1, sends branches as cephalad as T4. Therefore, a lumbar fracture or dislocation can produce a neurologic deficit as high as T4.

Secondary Spinal Cord Injury. The maximum neurologic deficit after blunt spinal cord trauma is often not seen on initial examination and may, instead, progress over many hours. Studied extensively in animal models, the histopathology of secondary SCI is now thought to be due to a complex cascade of biochemical events that result in progressive ischemia of gray and white matter during the postinjury period (Fig. 36.24). Other factors, such as hypoxia, hypotension, hyperthermia, and hypoglycemia, also affect the ultimate extent of SCI.

Classification of Cervical Soft Tissue Injuries

Blunt force trauma can injure one or more of the soft tissues of the neck, including ligaments, muscles, intervertebral disks, zygapophysial facet joints, dorsal root ganglia, and vertebral artery. Although injuries of these tissues have been documented in biomechanical, animal, and human autopsy studies, a validated diagnostic test is only available for facet injuries.[4,5] The cardinal symptom of a WAD is neck pain, but neck stiffness, neck and arm paresthesias, and dizziness are commonly reported. Table 36.2 shows the Quebec Task Force classification of WADs, the most common classification used worldwide.[2]

TABLE 36.2

Quebec Task Force Classification of Whiplash-Associated Disorders

GRADE	DESCRIPTION
0	Whiplash injury but no pain, symptoms, or signs
1	Delayed neck pain, minor stiffness, nonfocal tenderness only, no physical signs
2	Early onset of neck pain, focal neck tenderness, spasm, stiffness, radiating symptoms
3	Early onset of neck pain, focal neck tenderness, spasm, stiffness, radiating symptoms and signs of neurologic deficit
4	Neck complaint (grade 2 or 3 above) and fracture dislocation

(Adapted from Sterling S: Physiotherapy management of whiplash-associated disorders [WAD]. J Physiother 60:5–12, 2014.)

CLINICAL FEATURES

Neurologic Evaluation

The initial neurologic evaluation of a patient with a suspected spinal injury should begin with observation. Careful inspection, beginning with the head and proceeding downward, may reveal signs of possible spinal involvement. Significant head and facial trauma have a 5% to 10% incidence of associated cervical spine injuries. Scapular contusions suggest a rotation or flexion-rotation injury of the thoracic spine. Chest and neck abrasions from

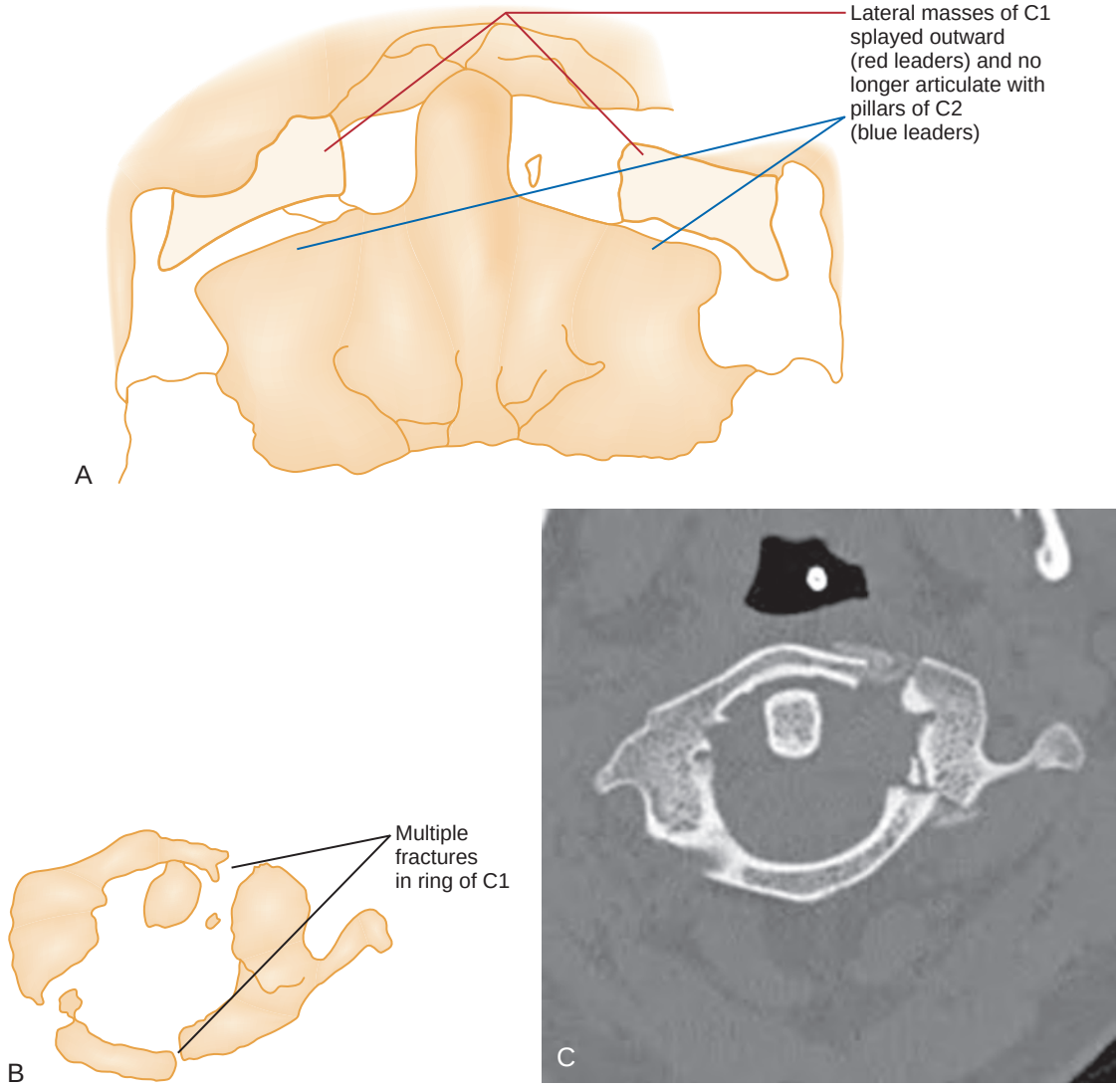


Fig. 36.21. Jefferson fracture. Mechanism— vertical compression; stability— unstable. **A, B,** Bilateral lateral displacement of the lateral masses of C1 with respect to the articular pillars of C2 confirms a Jefferson fracture and differentiates it from fracture of the posterior neural arch of C1 on an anteroposterior view. **C,** CT scan of C1 showing two fracture sites in the ring of C1, with lateral displacement of the lateral mass on the left.

automobile shoulder belts and lower abdominal markings from lap belts indicate possible blunt carotid and vertebral injuries, as well as spinal, intrathoracic, and intra-abdominal injuries. As occurs with falls from considerable heights, injuries to the gluteal region, calcaneal fractures, and severe ankle fractures suggest a compression type of spinal injury.

Because the diaphragm is innervated by the phrenic nerve, which originates at C3-C4, an abdominal breathing pattern may provide an important clue to an upper cervical injury. The presence of Horner's syndrome, characterized by unilateral ptosis, miosis, and anhidrosis, may result from disruption of the cervical sympathetic chain, usually between C7 and T2. Priapism may occur with severe SCI, and it is often associated with spinal shock, which is a transient reflex depression of the spinal cord below the level of the injury.

The emergency clinician should speak with the patient during the examination because it provides the patient with reassurance and the emergency clinician with valuable information. Patients may experience pain in the sensory dermatome corresponding to the injured spinal level. For example, a C2 lesion may cause occipital pain, whereas discomfort in the trapezius muscle, particularly in the absence of signs of local trauma, suggests a C5 injury. The past medical history is important because certain conditions predispose patients to cervical injury. For example, Down syndrome patients are predisposed to atlanto-occipital dislocation, whereas rheumatoid arthritis patients are prone to rupture of the C2 transverse ligament.

Palpation of the entire spine and paraspinal musculature may reveal areas of tenderness, deformity, or muscle spasm. A step-off may be appreciated with severe subluxation. Widening of an interspinous space indicates a tear in the posterior ligament complex and a potentially unstable spinal injury.

The motor activity of the body is complex. Because a single motion is often governed by muscles innervated by multiple spinal segments, localizing a spinal lesion based solely on motor function is extremely difficult. Testing the presence and strength of those motions outlined in Table 36.3, however, provides a rapid baseline assessment. When a deficit is noted, the motor and neurologic examination should be repeated because progression of dysfunction may occur. Even the most minimal of motor

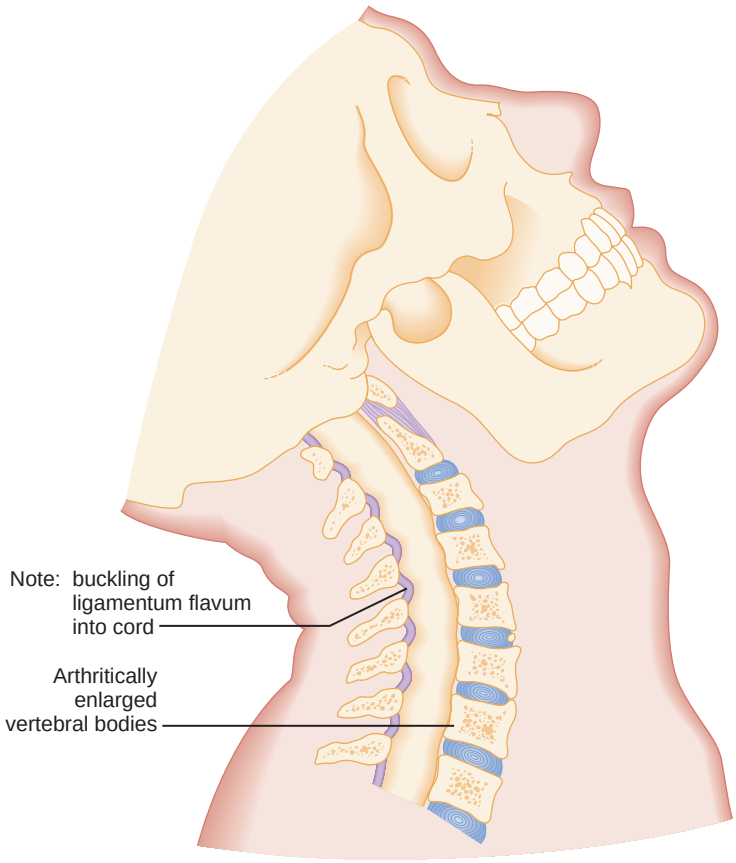


Fig. 36.22. Older patients subjected to extension forces can sustain cervical spinal cord injury as a result of compression of the spinal cord between the posterior hypertrophic ligamentum flavum and arthritically enlarged anterior vertebral bodies.

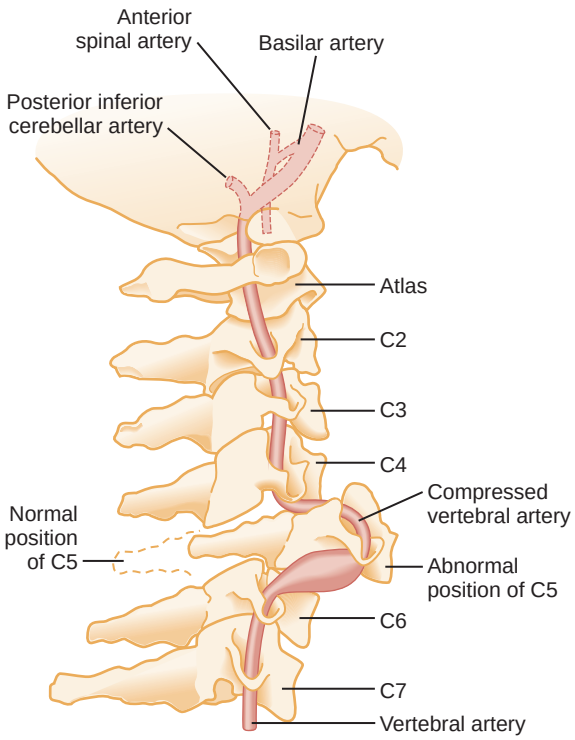


Fig. 36.23. Mechanism of vascular injury of the spinal cord resulting from cervical vertebral injury.

TABLE 36.3

Spinal Motor Examination

LEVEL OF LESION	RESULTING LOSS OF FUNCTION
C4	Spontaneous breathing
C5	Shrugging of shoulders
C6	Flexion at elbow
C7	Extension at elbow
C8-T1	Flexion of fingers
T1-T12	Intercostal and abdominal muscles[a]
L1-L2	Flexion at hip
L3	Adduction at hip
L4	Abduction at hip
L5	Dorsiflexion of foot
S1-S2	Plantar flexion of foot
S2-S4	Rectal sphincter tone

[a]Localization of lesions in this area is best accomplished with the sensory examination.

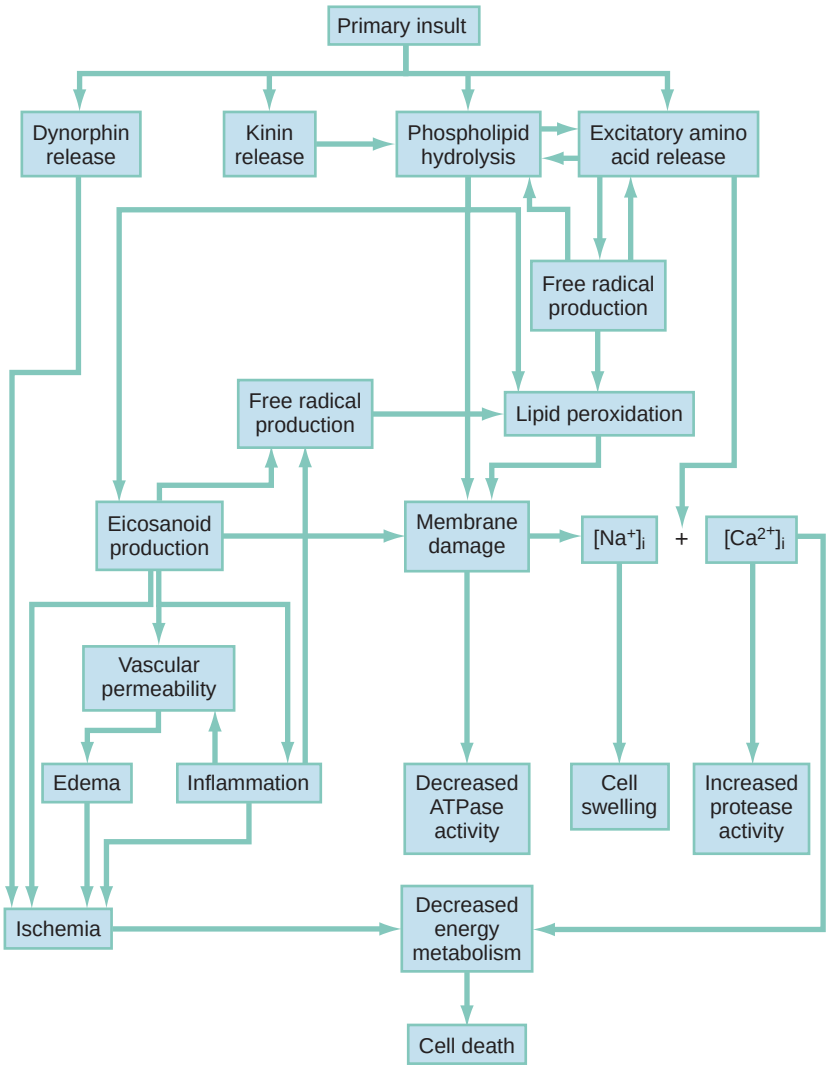


Fig. 36.24. Speculative paradigm of secondary pathophysiologic events after primary traumatic injury to the spinal cord. Ca^{2+}, Calcium ion; Na^{+}, sodium ion.

TABLE 36.4

Spinal Reflex Examination

LEVEL OF LESION (AT OR ABOVE)	RESULTING LOSS OF REFLEX
C6	Biceps
C7	Triceps
L4	Patellar
S1	Achilles

response should be elicited and documented, because any response improves prognosis. A slight toe flicker in an otherwise paralyzed individual indicates that the patient may again eventually walk unassisted.

The presence of cord-mediated deep tendon reflexes can be helpful as a localizing diagnostic aid (Table 36.4). Typically, muscle paralysis associated with intact deep tendon reflexes indicates an upper motor neuron (spinal cord) lesion, whereas paralysis associated with absent deep tendon reflexes indicates a lower motor neuron (nerve root or cauda equina) lesion. This differentiation is important because the latter condition may be caused by a surgically correctable lesion. After the initial period of areflexia, reflexes gradually return after 1 to 3 days and, after 1 to 4 weeks, patients with SCI will manifest characteristic hyperreflexia and spasticity. Reflexes are typically absent during the initial phase of spinal shock in the emergency department (ED), however.

Sensory function can be quickly evaluated through the use of a structured approach (Table 36.5) or graphic dermatome chart (Fig. 36.25). After locating an area of hypesthesia, one should move the sensory stimulus from areas of decreased sensation outward, rather than the reverse, because patients are more sensitive to the appearance of sensation than to its disappearance. This test should be performed first with a cotton swab to assess sensitivity to light touch, a posterior column function. A pin should be used to assess pain, which is an anterior spinothalamic tract function. Even in the presence of complete motor paralysis, the presence of islands of preserved sensation within an affected dermatome or below the level of dysfunction indicates potential for functional recovery. An accurate baseline sensory examination is imperative because cephalad progression of hypesthesia is the most sensitive indicator of deterioration. When this is observed in the cervical region, one should anticipate impending respiratory failure and preemptively secure the airway.

TABLE 36.5

Spinal Sensory Examination

LEVEL OF LESION	RESULTING LEVEL OF LOSS OF SENSATION
C2	Occiput
C3	Thyroid cartilage
C4	Suprasternal notch
C5	Below clavicle
C6	Thumb
C7	Index finger
C8	Small finger
T4	Nipple line
T10	Umbilicus
L1	Femoral pulse
L2-L3	Medial aspect of thigh
L4	Knee
L5	Lateral aspect of calf
S1	Lateral aspect of foot
S2-S4	Perianal region

Spinal Cord Lesions

Complete Spinal Cord Lesions

A complete spinal cord lesion is defined as total loss of motor power and sensation distal to the site of an SCI. Functional motor recovery is rare with a complete cord syndrome that persists for longer than 24 hours. Before making the diagnosis of a complete cord syndrome, however, two points should be considered. First, any evidence of minimal cord function, such as sacral sparing, excludes the patient from this group. Signs of sacral sparing include perianal sensation, preserved rectal sphincter tone, and flexor toe movement. Any of these signs indicates a partial lesion, usually a central cord syndrome, and the patient ultimately may have substantial functional recovery, including bowel and bladder control and eventual ambulation.

Second, a complete spinal cord lesion may be mimicked by a condition termed *spinal shock,* which may persist for a few weeks. Spinal shock results from a concussive injury to the spinal cord that causes total neurologic dysfunction distal to the site of injury. The end of spinal shock is heralded by the return of the bulbocavernosus reflex, which is a normal cord-mediated reflex elicited by placing a gloved finger in the patient's rectum and then squeezing the glans penis or clitoris or by tugging gently on the Foley catheter. An intact reflex results in rectal sphincter contraction. Absence of this reflex indicates the presence of spinal shock, during which time the patient's prognosis cannot be accurately assessed.

Incomplete Spinal Cord Lesions

Approximately 90% of incomplete spinal injuries can be classified as one of three clinical syndromes—the central cord syndrome, Brown-Séquard syndrome, and anterior cord syndrome (Fig. 36.26). The most common is the central cord syndrome, often seen in patients with degenerative arthritis who suffer neck hyperextension. The ligamentum flavum buckles into the cord, resulting in a concussion of the central gray matter in the pyramidal and spinothalamic tracts. Because fibers innervating distal structures are located in the spinal cord periphery, the upper extremities are more severely affected than the lower extremities. The prognosis is variable, but more than 50% of patients with central cord syndrome become ambulatory and regain bowel and bladder control, as well as some hand function.

The Brown-Séquard syndrome, or hemisection of the spinal cord, usually results from penetrating trauma but may also be seen after lateral mass fractures of the cervical spine. Patients with this lesion have ipsilateral loss of position and vibration sense, as well as motor paralysis, but also have contralateral loss of pain and temperature sensation distal to the level of injury. Because the fibers of the lateral spinal thalamic tract cross at a different level, the pain and temperature loss may be found variably one or two segments above the lesion. Virtually all patients maintain bowel and bladder function and unilateral motor strength, and most become ambulatory.

The anterior cord syndrome results from hyperflexion injuries causing cord contusion by the protrusion of a bony fragment or herniated disk into the spinal canal or by laceration or thrombosis of the anterior spinal artery. This syndrome is characterized by paralysis and hypalgesia below the level of injury, with preservation of posterior column functions, including position, touch, and vibratory sensations. Suspicion for an anterior cord syndrome warrants prompt neurosurgical consultation because it is a potentially surgically correctable lesion. After surgical intervention, patients have variable degrees of recovery during the first 24 hours but little improvement thereafter.

Several less common spinal cord syndromes may result from direct injury to the cervicomedullary junction and upper cervical segments or from vertebral artery occlusion resulting from severe hyperextension (Fig. 36.27). The posteroinferior cerebellar artery syndrome may produce dysphagia, dysphonia, hiccups, nausea, vomiting, dizziness or vertigo, and cerebellar ataxia. The Dejeune onion skin pattern of analgesia of the face is caused by damage to the spinal trigeminal tract. Horner's syndrome results from damage to the cervical sympathetic chain and is characterized by ipsilateral ptosis, miosis, and anhidrosis. Injuries below the L2 level can result in an acute cauda equina syndrome, characterized by perineal or bilateral leg pain, bowel or bladder dysfunction, perianal anesthesia, diminished rectal sphincter tone, and lower extremity weakness.

The syndrome of SCIWORA is seen primarily in younger children but may occur in any age group. In fact, there is increasing evidence that SCIWORA has been underreported in adults.[6] The mechanism is unclear but has been ascribed to the increased ligamentous elasticity seen in the young, leading to transient spinal column subluxation, stretching of the spinal cord, and vascular compromise. Patients often experience a brief episode of upper extremity weakness or paresthesias followed by neurologic deficits that appear hours to days later. The prognosis for patients with SCIWORA is variable, depending on the degree of neurologic impairment and rate of resolution

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of spinal injuries includes peripheral nerve injuries that may mimic sensory or motor deficits from a central lesion. For example, compression of the superficial peroneal nerve from a fibular fracture may result in a foot drop, but impingement of a lumbar spinal nerve root from a lumbar vertebral fracture could also result weakness in dorsiflexion. As noted, ligamentous injury in SCIWORA is also a consideration, especially if no fractures are found on imaging. Muscle contusions and strains around the neck, thorax, and lumbosacral regions would also be part of the differential diagnosis. Finally, a diagnosis of exclusion, conversion disorder can result in apparent

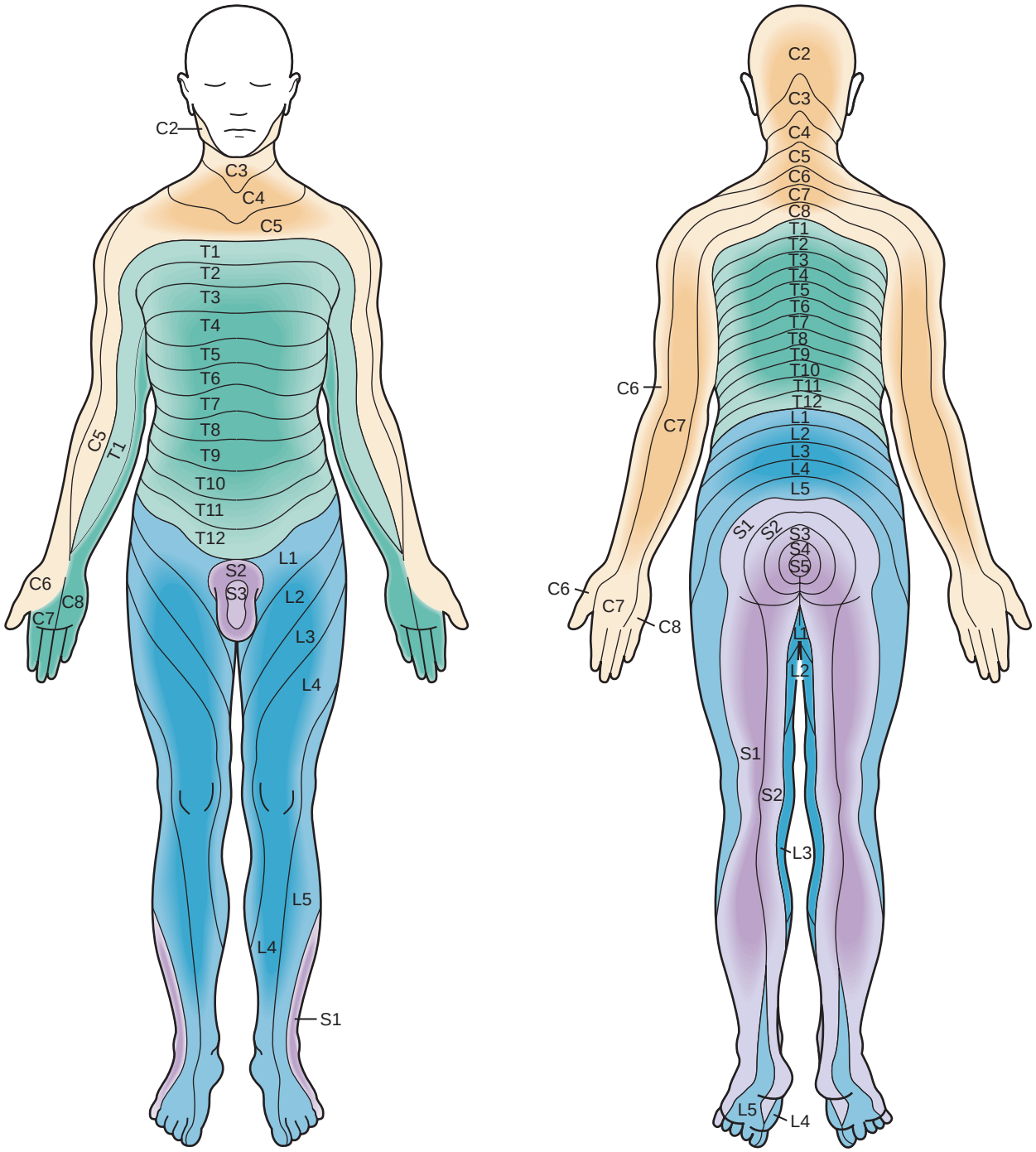


Fig. 36.25. Sensory dermatomes.

manifestations of sensory and motor deficits that may initially be confused and attributed to spinal injuries.

DIAGNOSTIC TESTING

Radiographic Evaluation

Indications

Emergency clinicians have historically taken a liberal approach to imaging the cervical spine in the setting of trauma because failure to recognize an SCI may result in devastating neurologic consequences. In an effort to standardize clinical practice and guide emergency clinicians to be more selective in radiographic imaging without jeopardizing patient care, two clinical decision rules have been developed. Use of selective but safe imaging modality may decrease overall health care costs, reduce radiation exposure, and decrease complications (eg, aspiration and pressure trauma to skin) associated with the patients lying flat on a backboards with a rigid collar. The first rule to be developed, the National Emergency X-Radiography Utilization Study (NEXUS) Low-Risk Criteria (NLC), was based on a multicenter prospective observational study involving almost 35,000 trauma patients seen at 21 EDs in the United States. The decision instrument required patients to meet five criteria to be classified as having a low probability of injury: (1) no midline cervical tenderness; (2) no focal neurologic deficit; (3) normal alertness; (4) no intoxication; and (5) no painful, distracting injury. The decision rule identified all but 8 of

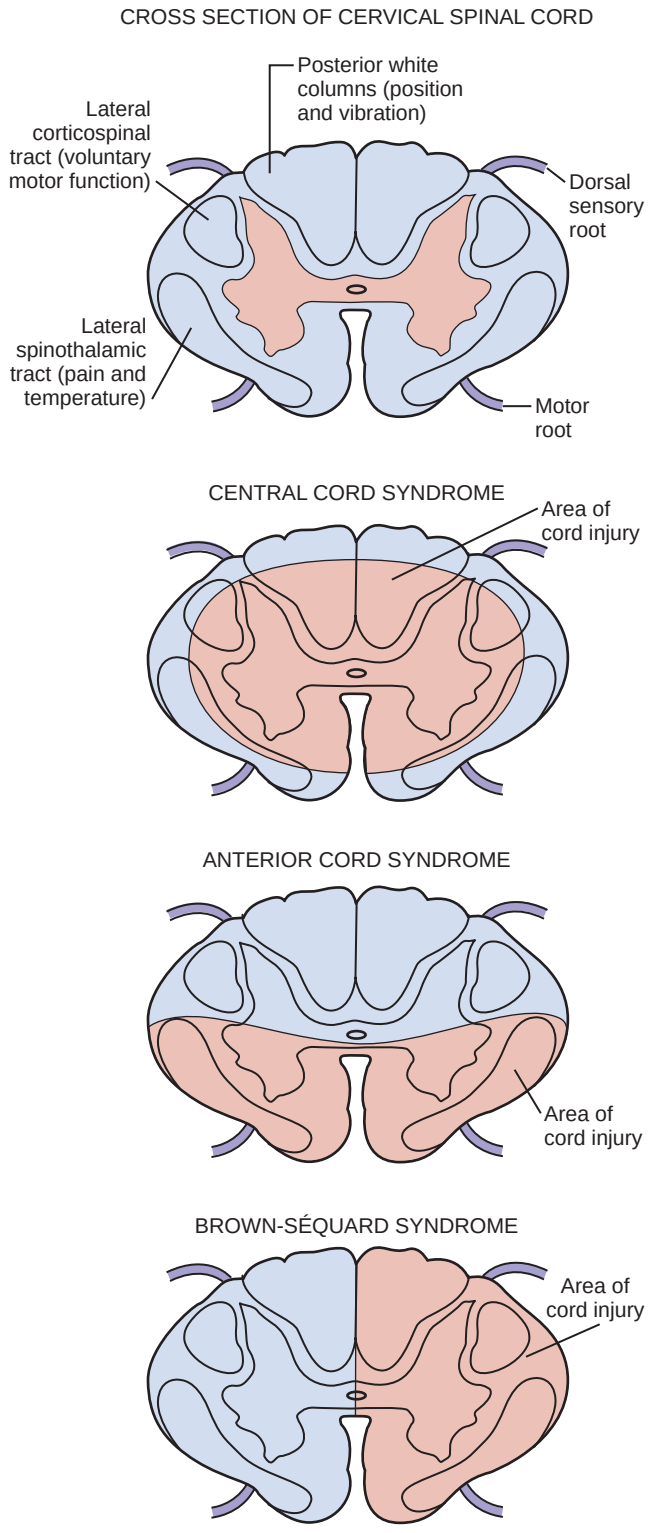


Fig. 36.26. Incomplete spinal cord syndromes.

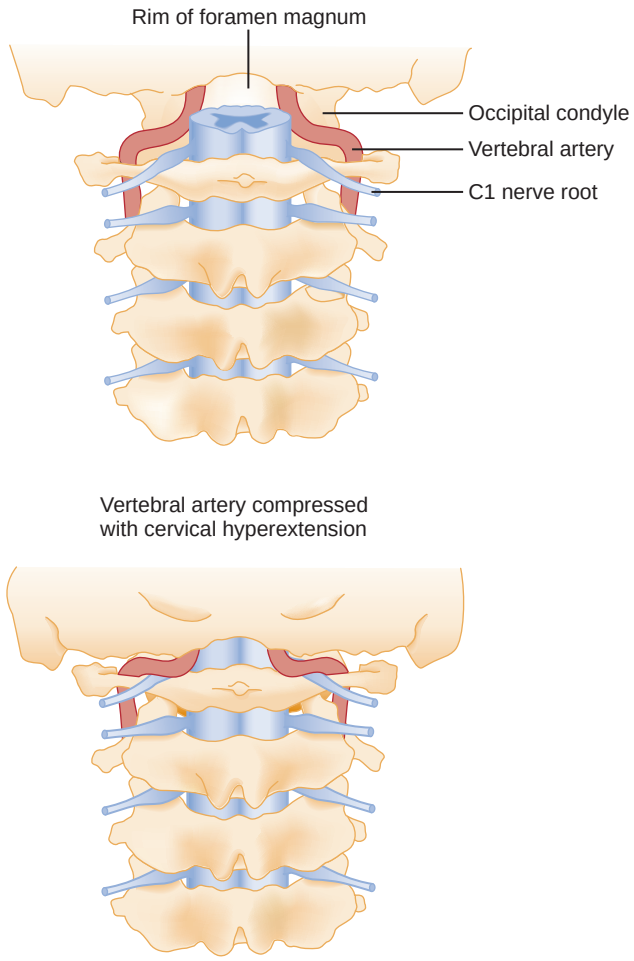


Fig. 36.27. Mechanism of vertebral artery injury in extension injuries of the cervical spine.

the 818 patients who had spinal injuries. Two of these patients had a clinically significant injury, only one of whom required surgical stabilization, and neither sustained a permanent neurologic injury. Sensitivity, specificity, and negative predictive value of the NLC were 99.6%, 12.9%, and 99.8%, respectively.

Owing to concerns about the low specificity of the NLC, the Canadian C-Spine Rule (CCR) was developed using 25 selected clinical predictor variables associated with spine injury. In 2003, the CCR was prospectively studied and compared with the NLC in nine Canadian tertiary care hospitals. Of 8283 patients, 162 were found to have clinically significant injuries, and the sensitivity, specificity, and negative predictive values of the CCR were, respectively, 99.4%, 45.1%, and 100%.The CCR is composed of the following three questions:

1. Are there any high-risk factors that mandate radiography?
2. Are there any low-risk factors that allow safe assessment of range of motion?
3. Is the patient able to rotate his or her neck actively 45 degrees to the left and right?

According to the CCR, patients with no high-risk factors, any low-risk factor, and the ability to rotate the neck do not require radiographic evaluation. High-risk factors include age older than 65 years, a dangerous mechanism of injury (eg, fall from a height >1 m, axial loading injury, high-speed MVC [>100 km/hr], rollover, ejection, motorized recreational vehicle or bicycle collision), or the presence of paresthesias. Low-risk factors include simple rear-end vehicle crashes, to a sitting position in the ED, ambulatory at any time, delayed onset of neck pain, and absence of midline neck tenderness. Although the NEXUS criteria are more widely used in the United States, there is controversy regarding which of the two rules to implement; a systematic review demonstrated better diagnostic accuracy for the CCR.[7] There are methodologic differences in the respective study designs, such as different inclusion and exclusion criteria.[8] Nonetheless, both rules have been well-validated and are sensitive, and the use of either rule decreases the number of unnecessary radiographs while rarely missing clinically significant injuries.

Cervical Plain Radiographs

Due to the widespread availability and superior test characteristics of CT in the United States, spinal plain radiographs are now rarely obtained, especially when CT is ordered to visualize a different body part. Furthermore, plain radiographs have been shown to be inadequate to visualize the entire cervical spine in up to 72% of cases, thus necessitating CT. However, plain radiographs are often used outside the United States, and there is increasing concern regarding cost and exposure to medical radiation from CT. When compared to plain radiographs, CT respectively confers a 10- to14-fold increase in radiation exposure to the skin and thyroid.

Thus, in light of cost and radiation exposure, plain radiographs of the cervical spine may be preferentially obtained in patients who sustain a relatively minor mechanism of injury but fail the NLC and CCR criteria, and do not warrant CT of the head or other body parts. On plain radiographs, the C7-T1 vertebrae may be obscured in muscular or obese patients, as well as in patients with spinal lesions causing paralysis of the muscles that act to depress the shoulders. In this case, a swimmer's view of the lower cervical vertebrae, or CT, is often needed. The cross-table lateral view of the cervical spine is the most helpful x-ray, but its inadequacy as the sole view is well documented. The diagnostic yield is significantly increased when the AP and odontoid views are included. The NLC has shown that a technically adequate three-view trauma series will fail to diagnose significant spinal injury in only 0.07% of patients with injuries and in only 0.008% of patients with unstable injuries. Note that once CT is performed, however, plain radiographs do not add any further clinically relevant information and should not be obtained.

Cross-Table Lateral View. The inspection of the lateral cervical spine film should be methodical and complete. It is helpful to remember the ABCs of interpreting the lateral film, where A stands for alignment, B for bony abnormalities, C for cartilage space assessment, and s for soft tissues.

To check alignment, two imaginary lines are drawn that connect the anterior and posterior margins of the vertebral bodies, the anterior and posterior contour lines. A third line, the spinolaminal line, connects the bases of the spinous processes extending to the posterior aspect of the foramen magnum (Fig. 36.28). All three lines should form a smooth, continuous lordotic curve, and any disruption of these lines suggests a bony or ligamentous injury. An exception to this rule is the pseudosubluxation of C2 and C3, which is commonly seen in infants and children. This phenomenon is attributed to immature muscular development and a hypermobile spine. Thus, if a high cervical injury is suspected in a child, the posterior cervical line, which connects the points bisecting the bases of the spinous processes of C1 and C3, should be used (Fig. 36.29). If the base of C2 lies more than 2 mm anterior or posterior to the posterior cervical line, an injury at that level should be suspected. On the lateral view, the predental space, which is the distance between the anterior aspect of the odontoid process and posterior aspect of the anterior ring of C1, should not exceed 3 mm in an adult or 5 mm in a child (Fig. 36.30). A widening of this space may indicate a Jefferson fracture of C1.

Subtle signs of cervical subluxations and dislocations can be identified through cartilage space assessment. A slight anterior or posterior widening of the intervertebral or interspinous space may be the only clue to an unstable dislocation.

Finally, the soft tissues of the retropharyngeal space should be assessed for prevertebral swelling and hemorrhage, often the only radiographic signs of spinal injury. The retropharyngeal space, measured from the anterior border of the body of C2 to the posterior wall of the pharynx, should not exceed 6 mm in children or adults. At the level of C3 and C4, this should not exceed 5 mm or should be less than half the width of the vertebral body at that level (see Fig. 36.30). Below the level of C4, the prevertebral soft tissue space is widened by the esophagus and cricopharyngeal muscle. The retrotracheal space, measured from the anterior border of the body of C6 to the posterior wall of the trachea, should not exceed 22 mm in adults or 14 mm in children younger than 15 years. In children younger than 2 years, the retropharyngeal space may normally appear widened during expiration; therefore, inspiratory films should be obtained. Air in the prevertebral space may indicate rupture of the esophagus or some portion of the respiratory tree, and anterior bulging of the prevertebral fat stripe is an excellent sign of an underlying bony or soft tissue injury.

Odontoid View. The open-mouth or closed-mouth view of the atlas and axis can be helpful in diagnosing Jefferson and odontoid fractures. Nonfusion of the odontoid in children and congenital anomalies of the odontoid in adults may mimic fractures.

Anteroposterior View. The AP spinal film completes the spinal series. Connecting imaginary dots placed at the base of each spinous processes should form a straight line, and the laryngeal and tracheal air shadows should be midline. The regular outline of the lateral masses should be verified, and the pedicles viewed

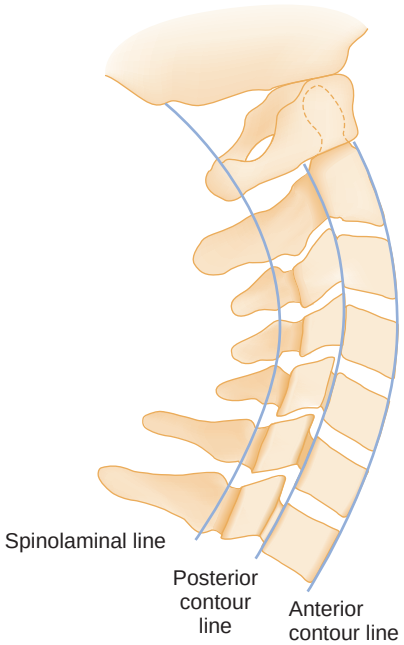


Fig. 36.28. Normal structural relationships of the lateral cervical spine.

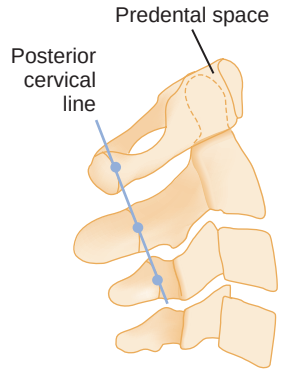


Fig. 36.29. Posterior cervical line of a normal lateral spine.

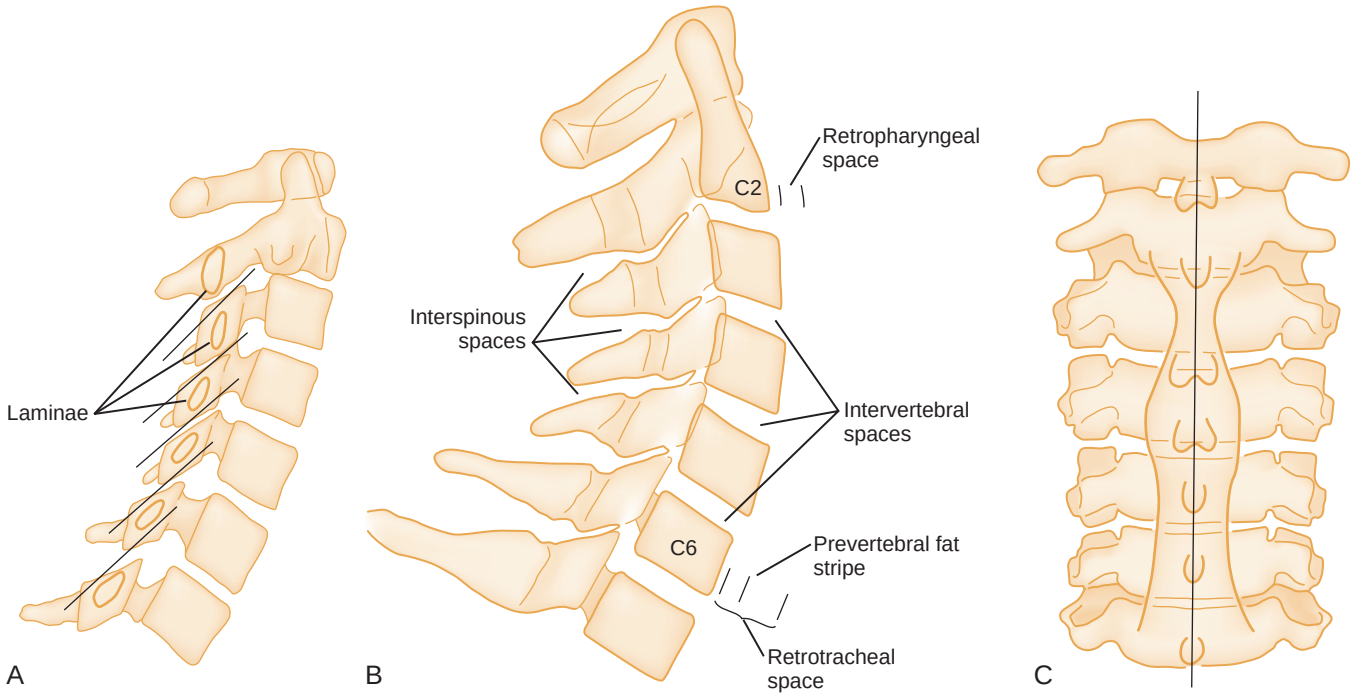


Fig. 36.30. **A**, Normal structural relationships of the cervical spine laminae in an oblique view form a so-called shingles on a roof appearance. **B,** In the lateral view, the intervertebral spaces and interspinous spaces should be compared with the spaces above and below for asymmetry and important clues in flexion and extension injuries. The retropharyngeal and retrotracheal soft tissues are measured at the C2 and C6 levels for swelling. **C,** Normal relationship between soft tissues and bony structures of the cervical spine in the lateral and anteroposterior (AP) views. **C,** In the AP view, the tracheal and laryngeal air shadows should be within the midline. A straight line should connect points bisecting the spinous processes. If such is not the case, rotatory injuries are suspected.

end-on can be checked for fracture. Widening of the interpedicular distance compared with adjacent vertebrae suggests a burst fracture (Fig. 36.31). Bulging of the mediastinal stripe may be the only evidence of a thoracic vertebral body fracture, which may cause hemorrhage that produces mediastinal widening on the chest x-ray.

Flexion and Extension Views. Flexion-extension (F/E) views are rarely indicated in the acute evaluation of a patient presenting to the ED after acute trauma, but may be useful when there is concern for ligamentous injury and magnetic resonance imaging (MRI) is not available. F/E views should be obtained only in patients who are alert and able to articulate the presence of pain, numbness, or paresthesias, because such symptomatology may indicate instability. The NEXUS investigators demonstrated that 86 of 818 patients(10.5%) ultimately found to have cervical injury underwent F/E testing. Although two patients had bony injuries and four patients had subluxations demonstrated only on F/E views, all six patients had other injuries apparent on routine radiographs.

F/E views are also deemed inadequate for interpretation in nearly one-third of studies.[8] A more recent review of 1000 F-E radiographs revealed that 80% of the films did not demonstrate the C7-T1 junction or had less than a 30-degree range of motion.[9] In the acute setting, F/E radiographs have been reported to have unacceptably high false-positive and false-negative rates because of concomitant muscle spasm. Delayed F/E views obtained 1 week after injury may be helpful, but they have little value in the ED when the CT scan is negative.[10] Thus, we do not recommend obtaining F/E radiographs in the ED unless there is concern for ligamentous instability in an alert evaluable patient, and MRI is not available. Such evaluation should occur in consultation with, and images should be obtained under the supervision of, a spine or trauma surgeon.

Advanced Imaging: Computed Tomography and Magnetic Resonance

The CT scan is the technique of choice for the evaluation of acute cervical spine trauma because of its superior test characteristics and time efficiency in the radiology department when compared to plain radiography. CT permits examination without moving the patient from the supine position and is thus preferable in terms of fracture stabilization, airway control, and other life support measures. CT can also identify bony fragments, acute disk herniation, foreign body, paraspinal hematoma, or extramedullary hematoma. Thus, routine plain radiographs in many centers are reserved for the alert patient with minor trauma. In addition to those undergoing CT imaging of other body parts, CT may be preferred when plain radiographs are difficult to interpret because of abnormal anatomy, such as in older adults with degenerative disease or the patient with rheumatoid arthritis. Additionally, rotational and distraction injuries resulting in atlanto-occipital dislocations may be missed on plain x-ray. For patients who have a severe mechanism of injury, unless CT is not available, we support the practice guidelines from the Eastern Association for the Surgery of Trauma, which recommend that CT from the occiput to T1 be used as the primary screening. Because fractures in contiguous and noncontiguous vertebrae are fairly common, CT scans should be obtained to visualize the entire cervical spine.

Fractures involving the transverse foramina or C1-C3 are associated with vertebral artery dissection or thrombosis in up 22% of cases, as well as basilar artery stroke. When such fractures are identified, we recommend further study by magnetic

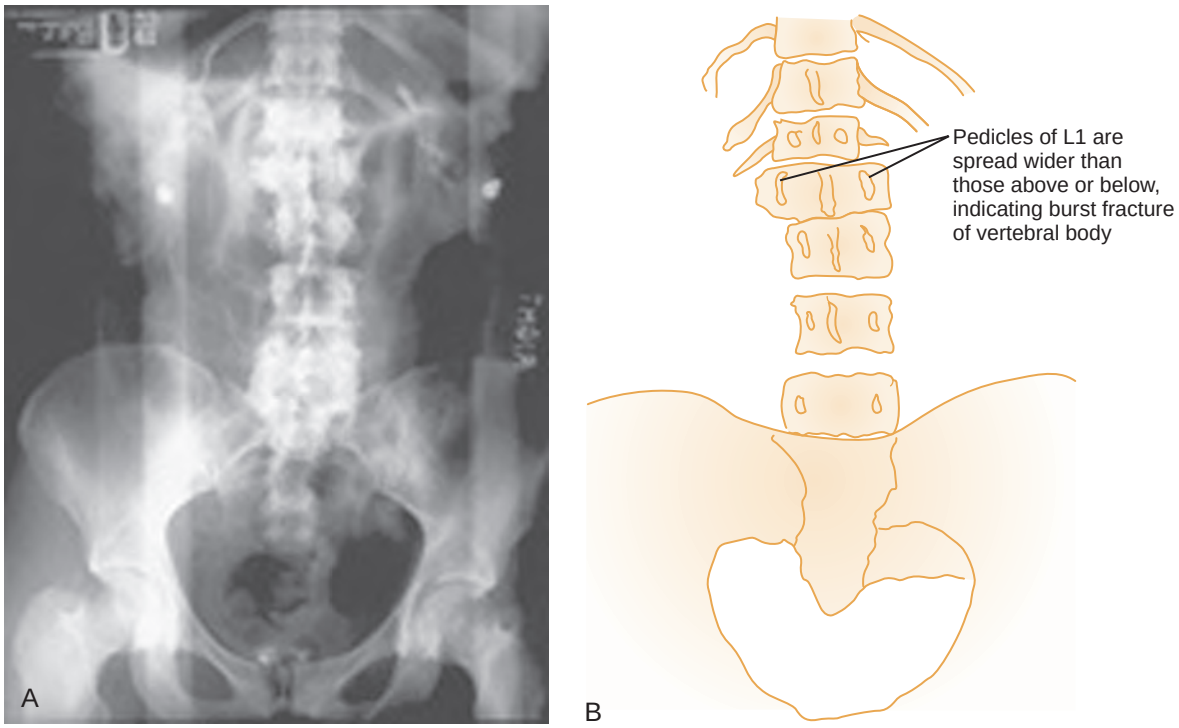


Fig. 36.31. **A**, **B,** Burst fracture of L1. An anteroposterior radiograph shows increased distance between the pedicles of L1 in comparison to adjacent vertebrae. An intravenous pyelogram showed renal injury on the left.

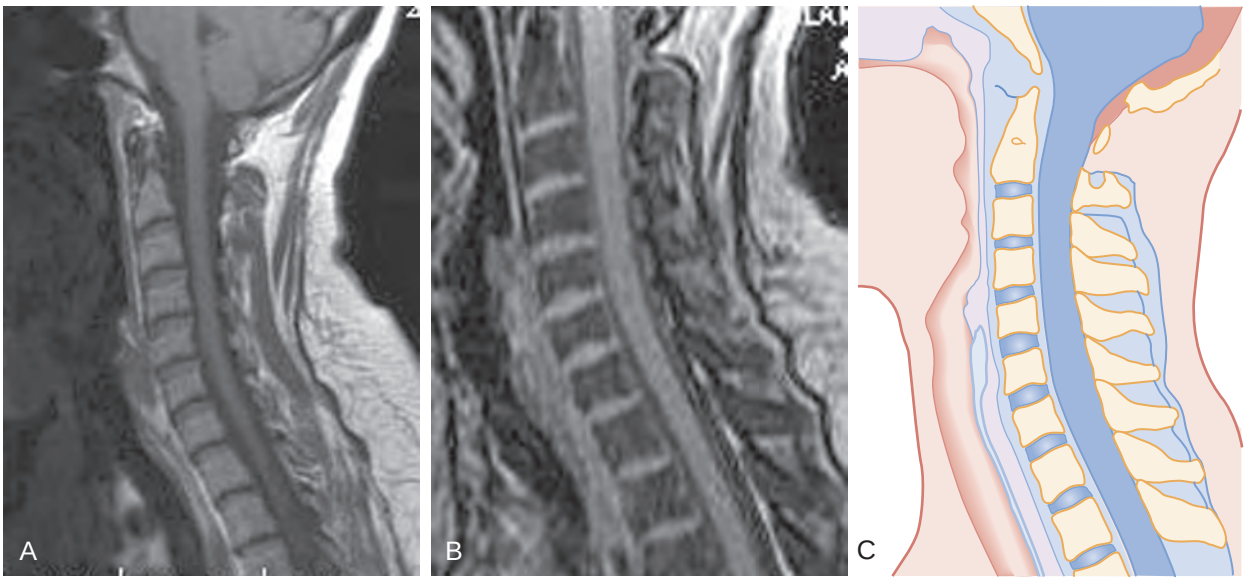


Fig. 36.32. Normal sagittal magnetic resonance images of the cervical spine. **A,** T1-weighted and flip angle (**B**) scans. **C,** Cervical spine.

resonance angiography (MRA), CT angiography (CTA), or four-vessel angiography.

Vertebral images reconstructed from CT scans of the abdomen and pelvis obtained for the evaluation of chest and abdominal injuries provide sufficient data to screen for spinal fractures. CT is also thought to be adequate to clear cervical spines, even in the obtunded blunt trauma patient; in fact, a meta-analysis of 10 studies involving 1850 obtunded trauma patients has demonstrated a negative predictive value and specificity greater than 99%,[11] whereas a single-center cohort study of 83 patients demonstrated a sensitivity and specificity of 100% for CT in detecting unstable cervical spine injuries compared to MRI.[12,13]

Although CT has a higher sensitivity than MRI to detect fractures and dislocations at the craniocervical junction, as well as fractures of the posterior elements, MRI, with its superior resolution and lack of ionizing radiation, has the primary advantage of the ability to image nonosseous structures directly, including intramedullary and extramedullary spinal abnormalities that potentially cause neurologic deficit (Fig. 36.32). Its major impact has therefore been in demonstrating potentially surgically correctable lesions, including acute disk herniation, ligamentous injury, bony compression, epidural and subdural hemorrhages, and vertebral artery occlusion. MRI can identify three separate patterns of SCI, including acute cord hemorrhage, cord edema or

contusion, and mixed cord injury. Patients with cord edema or contusion show significant neurologic improvement, whereas those with cord hemorrhage (Fig. 36.33) fare far worse. MRI can also diagnose a developing intramedullary (posttraumatic) syrinx or subarachnoid cystic changes (Fig. 36.34). MRI is also the best diagnostic imaging modality for SCIWORA. Thus, a patient who demonstrates neurologic deficit or persistent neck pain suggesting ligamentous injury or an occult spine injury, should undergo an expedited MRI, regardless of a normal CT scan or plain radiograph (Fig. 36.35).

There are risks to performing an MRI, however, such as aspiration, secondary brain injury, and the difficulty of monitoring and resuscitation in the MRI suite. In addition, MRI cannot be used when MRI-incompatible life support, monitoring systems, pacemakers, cerebral aneurysm clips, and cervical traction devices are used, although MRI-compatible support systems exist. In the obtunded or unreliable patient, MRI may not be necessary to exclude unstable injuries if the CT scan is normal. A recent prospective study of the use of cervical spine CT in 402 obtunded patients reported a sensitivity of greater than 99%.[14]

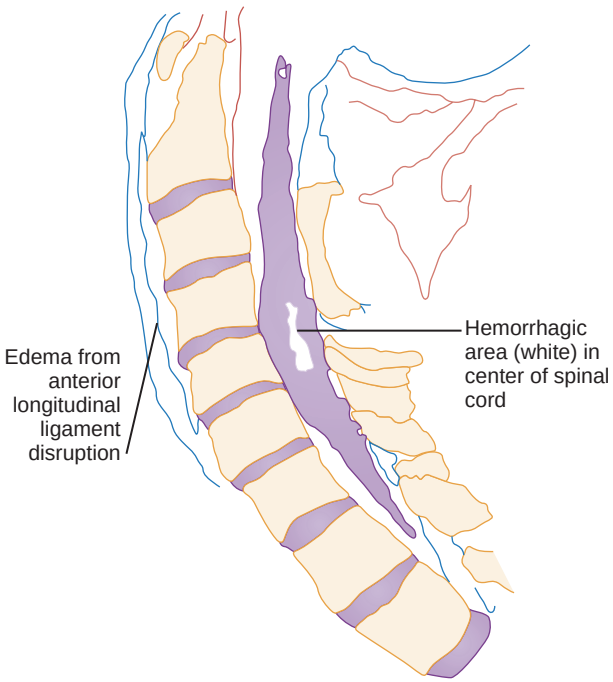


Fig. 36.33. MRI scan showing a small area of central cord hemorrhage and anterior and posterior ligamentous disruption.

MANAGEMENT

Spinal injury should be suspected in all trauma victims with an unknown or suggestive mechanism of injury associated with complaints of neck or back pain, evidence of significant head or facial trauma, spinal tenderness, signs of focal neurologic deficit, impaired consciousness, potentially distracting injuries, or unexplained hypotension (Fig. 36.36).

Spinal Column Stabilization

Out-of-Hospital Care

Prehospital personnel are well versed in the care of the patient with a potentially traumatized spine, and all emergency medical services (EMS) incorporate these principles. The traditional approach to immobilization requires the use of a backboard, rigid cervical collar, and supportive blocks on both sides of the head. In the past, a concerning mechanism of injury called for automatic and routine initiation of such spinal immobilization at the scene. However, it has been noted that many trauma patients are unnecessarily immobilized by EMS, and immobilization is not a benign intervention. For example, in addition to resulting in prolonged on-scene time and delayed transport to definitive care, the backboard can lead to pressure ulcers, increased pain, and decreased functional respiratory residual capacity. Also, the cervical collars can hide other injuries, such as lacerations and hematomas, and have even been found to result in worsening vertebral distraction injuries.[15] There is also ample evidence that EMS providers can safely apply spinal assessment guidelines, such as NEXUS.

Emergency Department

Trauma victims are assessed as described in Chapter 33 while maintaining immobilization. If the patient's spine can be clinically cleared by use of the NEXUS criteria or CCR, the immobilization device may be removed. If the trauma victim was wearing a helmet and the helmet was not removed in the field, the face mask, helmet, and any sports padding (eg, shoulder pads on hockey or football players) may be carefully removed while immobilization is maintained. Ideally, at least two or three providers should be present to perform the task of helmet removal. Once the helmet and shoulder pads have been removed, a rigid collar should be placed if the patient's cervical spine cannot be cleared by use of the NEXUS criteria or CCR.

Patients with probable spinal injury who are conscious and cooperative should be immobilized until imaging has been performed. Patients who are uncooperative because of head injury, drug or alcohol intoxication, hypotension, or presence of multiple painful injuries require a deliberate approach, including the use of chemical and mechanical restraints. Suspected thoracic and lumbar spinal injuries are best managed by keeping the patient supine and immobile. The goal of stabilization in cervical spine trauma is to immobilize the neck and body because any movement may extend the initial injury. If the patient is not already immobilized on a backboard, the torso should be firmly anchored to the examining table by straps or rolled sheets. Sedation, drug-induced paralysis, and intubation may be required for patients who pose a danger to themselves because of excessive movement and whose injuries otherwise will likely require intubation. Paralysis and intubation are not used simply to control patient

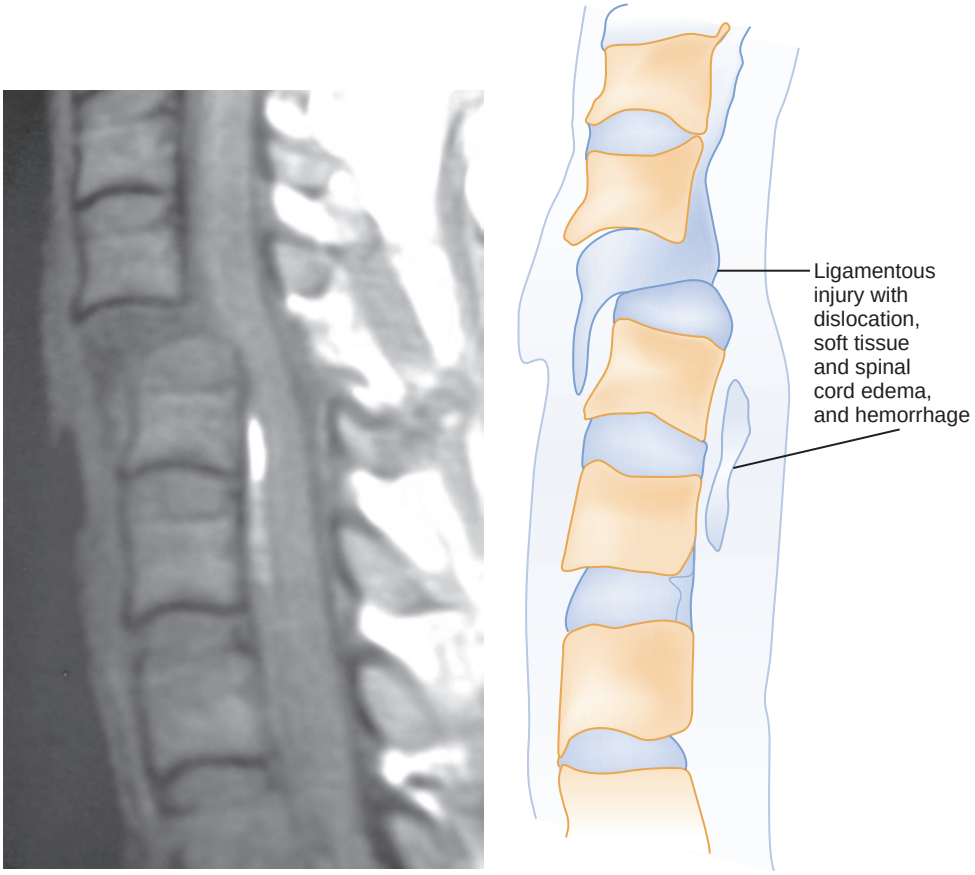


Fig. 36.34. MRI scan showing posttraumatic syrinx of the spinal cord.

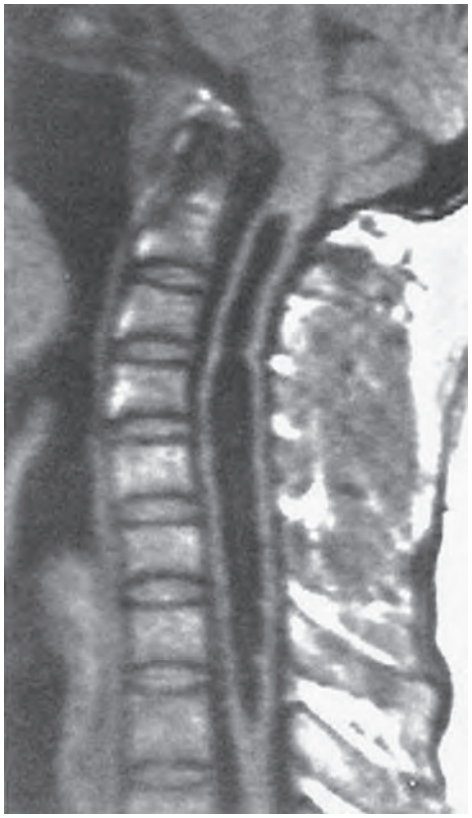


Fig. 36.35. Anteroposterior longitudinal ligament disruption. A sagittal MRI scan demonstrates ligamentous disruption between C4 and C5, with blood tracking in the anterior spinal canal.

movement or lack of cooperation. Spinal precautions should be maintained in patients with an altered sensorium until the presence of an injury can be excluded clinically or radiographically. Suctioning should be readily available to prevent aspiration. Vomiting patients should be placed on their side by logrolling while spinal alignment is maintained.

Airway Management

Cervical spine injuries often require early intubation as part of the resuscitation. Lesions above C3 may rapidly progress to respiratory paralysis, and the spread of edema from a lower injury may cause delayed phrenic nerve paralysis, as well as ascension of the neurologic injury above the level of C3. Cervical injuries may be associated with airway obstruction from retropharyngeal hemorrhage or edema or maxillofacial trauma.

Airway management of the trauma patient, including those with suspected spine injury, is discussed in Chapter 1.

Spinal Shock

Spinal shock is characterized by the temporary loss of neurologic function and autonomic tone below the level of an acute spinal cord lesion. Patients usually exhibit flaccid paralysis with loss of sensation, deep tendon reflexes, and urinary retention, along with bradycardia, hypotension, hypothermia, and intestinal ileus. Recovery from spinal shock, which may last from less than 24 hours to more than 2 weeks, is heralded by the return of the bulbocavernosus reflex.

Neurogenic hypotension, caused by loss of vasomotor tone and lack of reflex tachycardia, is a diagnosis of exclusion in the trauma victim. It should not be considered the cause of hypotension

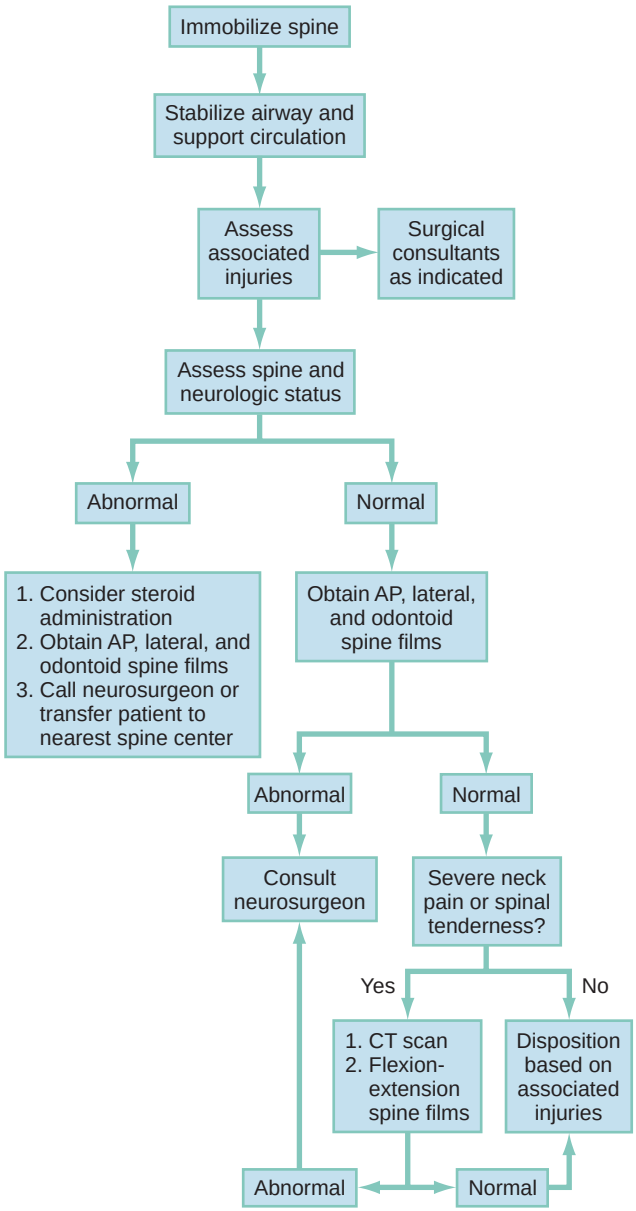


Fig. 36.36. Approach to a patient with suspected cervical spine injury. *AP,* Anteroposterior; *CT,* computed tomography.

unless the patient is flaccid and areflexic, reflex tachycardia and peripheral vasoconstriction are absent and, most important, the possibilities of coexisting hemorrhagic shock, cardiac tamponade, or tension pneumothorax have been eliminated.

Although there is no evidence for an optimal mean arterial pressure (MAP), we recommend initiating the resuscitation of hypotensive trauma victims with a balanced crystalloid fluid infusion, as outlined in Chapter 33. Most cases of pure neurogenic hypotension are mild (eg, systolic blood pressure > 90 mm Hg) and may not require fluid resuscitation or will respond to modest amounts of fluid. Severe neurogenic hypotension(eg, systolic blood pressure < 70 mm Hg), seen in 20% to 30% of cases, usually occurs with high cervical injuries associated with total or near-total loss of neurologic function. Because hypotension can lead to hypoperfusion and secondary spinal cord ischemia, prolonged severe hypotension (systolic blood pressure < 70 mm Hg) should be prevented and treated. Fluid resuscitation is often ineffective in such patients and may result in fluid overload. Thus, when there is persistent hypotension despite fluids, we recommend vasopressor support with norepinephrine to be started at 0.05 μg/kg/min and titrated upward to a maximum dose of 1 μg/kg/min to achieve an MAP of 85 mm Hg.[16]

Pharmacologic Treatment for Incomplete Cord Injury

Delayed biochemical damage contributes to ongoing tissue loss and worsening neurologic function in SCI. Thus, numerous neuroprotective and neuroregenerative treatment strategies, including pharmacologic treatment, hypothermia, and decompression,[17-19] have been investigated in laboratory animal studies and human clinical trials. Substantial media attention was prompted by case reports of athletes, such as the Buffalo Bills tight end Kevin Everett, who underwent therapeutic hypothermia and was subsequently able to walk just 3 months after his treatment. Since 2010, there has been one prospective case series of 20 patients,[17] two retrospective case series,[20,21] and one case report.[19] In all these studies, the patients had surgical decompression in addition to the hypothermia treatment (32°–34° C [89.6°–93.2° F) for 6 to 48 hours and, although there appeared to be some association of hypothermia with improvement in the American Spinal Injury Association Impairment Scale, this cannot be considered evidence in support of the use of therapeutic hypothermia for acute spinal cord injury. Reported complications from hypothermia induction include pneumonia, thrombocytopenia, and atrial fibrillation. The Miami Project to Cure Paralysis is a phase 1 study currently being conducted at the University of Miami and should be able to help delineate the risks and benefits better, as well as the duration of hypothermia.[22] At this time, hypothermia should be considered experimental.

Methylprednisolone, once widely recommended for use on the basis of extremely weak evidence, has been found to have no benefit and is likely, on balance, to be harmful. It is no longer recommended or used for acute spinal cord injury.

Associated Injuries

Cardiopulmonary

Although cardiopulmonary deterioration in a trauma victim is usually the result of hemorrhagic shock or direct injury to the heart or lungs, pulmonary edema may also occur in response to brain injury and SCI. Spinal cord trauma stimulates an intense sympathetic discharge with two subsequent effects. First, pulmonary capillary endothelial cells are disrupted, leading to the pulmonary capillary leak syndrome, in which pulmonary edema occurs in the presence of normal pulmonary artery pressures (<18 mm Hg). Second, marked increases in afterload may lead to pulmonary edema associated with high pulmonary artery pressures (>18 mm Hg) from ventricular dysfunction. Excessive fluid resuscitation can also contribute to pulmonary edema. Later in the recovery period, many SCI patients suffer from alternating episodes of low and high blood pressure, often with labile heart rates, termed *autonomic dysreflexia*.[23] The treatment for this is primarily supportive by addressing causative factors, such as bladder distention, pain, and hydration status.

Gastrointestinal and Genitourinary

If SCI renders the abdominal examination unreliable, an abdominal CT scan or ultrasound is often necessary. In the acute stages of SCI, the gastrointestinal tract and bladder become atonic. Thus, a nasogastric tube should be placed to prevent gastric distention and a Foley catheter inserted to prevent bladder distention and monitor fluid output. Because gastrointestinal bleeding from

stress ulcers occurs in 2% to 20% of spinal trauma patients, ulcer prophylaxis with histamine H2 receptor antagonists or proton pump inhibitors should be initiated.

Skin

Denervated skin is extremely susceptible to pressure necrosis, and sores can develop in less than 1 hour on unpadded spinal carts. Therefore, backboards should be removed as soon as possible. Padding pressure areas with sheepskin or foam can help minimize decubitus ulcers.

Definitive Treatment and Prognosis

The role of prompt surgical intervention in the management of spinal injuries is currently limited to relieving spinal cord impingement caused by foreign bodies, herniated disks, bony fracture fragments, or epidural hematoma. Surgery may be necessary later to stabilize severe bony injuries or reduce spinal dislocations. The timing of surgical intervention is controversial because there are no well-designed studies that have determined whether early (<12 hours) versus late decompression is beneficial.

Once almost uniformly fatal, major spinal injury caused death from pulmonary complications or sepsis from skin necrosis or urinary infection. The advent of antibiotic therapy made long-term survival not only possible but also expected. Today, patients with SCIs are best managed at a regional spine injury center, where a team of neurosurgeons, orthopedic surgeons, psychologists, and physical therapists can initiate rehabilitation. Specialized SCI treatment centers offer patients a chance to return to a productive life within the limits of their disability. With the exception of patients with high cervical lesions (above C5), most patients attain sufficient independence to live outside of high-level care environments.

DISPOSITION

Cervical Soft Tissue Injuries

Patients with cervical soft tissue injuries of the spine who have only mild to moderate discomfort without neurologic impairment or abnormal radiographic findings (WAD class 1 or 2) are best managed as outpatients. Discharge instructions should include educating the patient that pain often increases over the first 24 to 48 hours but that the symptoms will begin to dissipate thereafter. We recommend treatment with analgesics, such as acetaminophen, 650 to 1000 mg/dose, up to qid. Although analgesic doses of a nonsteroidal antiinflammatory drug, such as ibuprofen, 400 to 600 mg/dose, is also reasonable, there is ample evidence that acetaminophen, which has fewer adverse effects on the gastrointestinal and renal systems, is equally effective, and there is no indication for antiinflammatory treatment. Additionally, we do not recommend medications with purported muscle relaxant properties, such as cyclobenzaprine, because they have not been found to provide additional benefit and have an adverse side effect profile (principally anticholinergic effects and drowsiness.).[24] Finally, referral for follow-up with a primary care physician is indicated because up to 50%of patients experiencing neck pain after trauma will continue to have symptoms at 1 year. This is more likely in patients with WAD class 3 but can occur in patients with class 2 and rarely class 1. Box 36.1 lists the prognostic indicators of poor functional recovery in patients with a WAD.

BOX 36.1

Prognostic Indicators of Poor Functional Recovery Following Whiplash-Associated Disorders

FACTORS WITH CONSISTENT EVIDENCE FOR BEING PROGNOSTIC INDICATORS FOR POOR RECOVERY

- Initial pain levels > 5.5/10
- Initial disability levels: NDI > 29%
- Symptoms of posttraumatic stress
- Negative expectations of recovery
- High pain catastrophizing
- Cold hyperalgesia

FACTORS WITH CONSISTENT EVIDENCE OF NOT BEING PROGNOSTIC INDICATORS

- Accident-related features (eg, collision awareness, position in vehicle, speed of accident)
- Findings on imaging
- Motor dysfunction

FACTORS WITH INCONSISTENT EVIDENCE

- Older age
- Female gender
- Neck range of movement
- Compensation-related factors

NDI, Neurological Disability Index.
Adapted from Sterling S: Physiotherapy management of whiplash-associated disorders (WAD). J Physiother 60:5–12, 2014.

Minor Fractures

Most patients with spinal fractures require hospitalization. Patients with isolated cervical vertebral body compression or spinous process fractures may be managed as outpatients if there is no evidence of neurologic impairment or associated ligamentous instability, and the degree of patient distress is not severe. Appropriate follow-up should be arranged for all patients because even minor spinal injuries may be associated with prolonged disability from chronic pain.

For patients with minor wedge fractures (<10% compression of the anterior vertebral body height) who do not have an associated ileus or neurologic deficit, outpatient management may be possible. However, most wedge fractures of the thoracic and lumbar spines are usually best managed in the hospital for several reasons. First, patients with these injuries usually have marked discomfort, often requiring parenteral opioid analgesia. Second, significant force is generally required to fracture thoracic or lumbar vertebrae, and associated intrathoracic or abdominal injuries are common. Third, lower thoracic and lumbar fractures are associated with prolonged and occasionally delayed gastrointestinal ileus, requiring continuous nasogastric suction. Finally, older adults who have vertebral fractures and only minor associated injuries may require admission to facilitate assessment of fall risks and expedite rehabilitation.

KEY CONCEPTS

- The anterior cord syndrome, characterized by paralysis and hypalgesia below the level of injury, with preservation of position, touch, and vibration, results from hyperflexion injuries causing cord contusion, by the protrusion of a bony fragment or herniated disk into the spinal canal, or by laceration or thrombosis of the anterior spinal artery. Suspicion for an anterior cord syndrome warrants prompt neurosurgical consultation because it is a potentially surgically correctable lesion.
- In the awake, evaluable trauma patient, the NEXUS or CCR decision rules may be used to determine the need for radiographic imaging.
- In the awake, evaluable trauma patient, unless the patient has a very minor trauma mechanism (or CT is not available), CT is preferred over plain radiography, especially if CT is being performed on other body parts.
- Neurogenic hypotension, caused by loss of vasomotor tone and lack of reflex tachycardia, is a diagnosis of exclusion in the trauma victim. It should not be considered the cause of hypotension unless the patient is flaccid and areflexic, reflex tachycardia and peripheral vasoconstriction are absent and, most importantly, the possibilities of coexisting hemorrhagic shock, cardiac tamponade, or tension pneumothorax have been eliminated.
- Because neurogenic hypotension can lead to hypoperfusion and secondary spinal cord ischemia, prolonged, severe hypotension (systolic blood pressure < 70 mm Hg) should be prevented and treated. When there is persistent hypotension despite fluid resuscitation, we recommend vasopressor support with norepinephrine to be started at 0.05 μg/kg/min and titrated upward to a maximum dose of 1 μg/kg/min to achieve an MAP of 85 mm Hg.
- Methylprednisolone or any other steroid is not beneficial in the treatment of acute spinal cord injury and should not be used.
- Emergency department management of SCI includes care to prevent pressure ulcers, bladder distention, and gastric distention.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 36: QUESTIONS & ANSWERS

36.1. Which of the following is a stable cervical spine fracture?
- **A.** Anterior atlantoaxial dislocation without fracture
- **B.** Bilateral facet dislocation
- **C.** Flexion teardrop
- **D.** Jefferson fracture
- **E.** Unilateral facet dislocation

Answer: E. See Table 36.1 for a classification of spinal injuries according to stability.

36.2. A 28-year-old man is brought to the emergency department (ED) after a rollover motor vehicle collision (MVC). He is moderately hypotensive, unable to flex his elbows, and has diffuse lower extremity paralysis. What is the likely site of the lesion?
- **A.** C4
- **B.** C5
- **C.** C6
- **D.** C7
- **E.** C8

Answer: C. See Table 36.2.

36.3. Which of the following statements regarding high-dose methylprednisolone after spinal cord injury is true?
- **A.** Dexamethasone is superior to methylprednisolone if a concurrent closed head injury is present.
- **B.** High-dose methylprednisolone should not be used to treat spinal cord injury.
- **C.** It is efficacious after penetrating injury if given within 4 hours.
- **D.** It is efficacious in cases of spinal shock.
- **E.** It is more efficacious after thoracic than after lumbar injuries.

Answer: B. Evidence that high-dose methylprednisolone is a clinically efficacious intervention in the management of acute, blunt, partial spinal cord injury is lacking and, because of severe side effects, should not be used.

36.4. A 27-year-old man presents after a high-speed rollover MVC. The physical examination is remarkable for T8 motor-sensory deficit and a moderately distended abdomen that is nontender. Vital signs are heart rate, 108 beats/min, blood pressure, 88/40 mm Hg, respiratory rate, 22 breaths/min, temperature, 35°C (95°F), and oxygen (O_2) saturation, 96%. Which of the following tests or treatments is indicated?
- **A.** Baseline laboratory tests and observation
- **B.** Computed tomography (CT) scan of the abdomen
- **C.** Intravenous phenylephrine infusion
- **D.** Packed red blood cell transfusion
- **E.** Thoracolumbar spine films

Answer: B. Spinal cord injury often renders the abdominal examination unremarkable. CT, ultrasonography, diagnostic peritoneal lavage, or some combination is necessary to rule out intra-abdominal injury.

36.5. A 23-year-old man presents after a rollover MVC. He is brought by emergency medical services (EMS) from the scene fully restrained on a backboard, with a cervical collar. The physical examination is remarkable for moderate symmetric numbness below the neck, symmetric arm and leg weakness, intact reflexes, and diminished rectal tone. Vital signs are heart rate, 94 beats/min, blood pressure, 80/46 mm Hg, respiratory rate, 24 breaths/min, and O_2 saturation, 96%. Which of the following treatment sequences is most indicated?
- **A.** Crystalloid to CT scan to phenylephrine
- **B.** Crystalloid to focused assessment with sonography for trauma (FAST) examination to transfusion
- **C.** Crystalloid to phenylephrine to transfusion
- **D.** Dopamine to crystalloid to CT scan
- **E.** Transfusion to phenylephrine

Answer: B. Spinal shock should not be considered the cause of hypotension unless the patient is flaccid and areflexic. Crystalloid

is the first step regardless of the traumatic hypotensive cause. The possibilities of coexisting hemorrhagic shock, cardiac tamponade, tension pneumothorax, or other life-threatening injuries should first be addressed. The absence of vasomotor activity in patients with neurogenic hypotension may mask the usual presentation of these life-threatening injuries. In this case, the lack of flaccidity and presence of reflexes argues for a nonneurogenic cause for the hypotension.

CHAPTER 37

Neck

Ilene Claudius | Kim Newton

PRINCIPLES

Background

Trauma to the neck comprises a spectrum of injuries ranging from incidental to life threatening and can include airway occlusion, hemorrhagic shock, or acute neurologic/vascular injury. Airway compromise can rapidly ensue, challenging even the most experienced clinician. Stable-appearing patients may harbor insidious injuries associated with high morbidity and mortality if not recognized and treated in a timely manner.

Neck trauma is divided into three major mechanisms: blunt, penetrating, and strangulation/hanging. These mechanisms can be further categorized anatomically into injuries of the laryngotracheal, pharyngoesophageal, and vascular systems. Each has unique features and will be discussed separately.

Anatomy

The neck is a complex, closed anatomic area, dense with vital structures and invested with fascia, creating several compartments. Because of this, vascular injury with hemorrhage may be contained by fascial planes and neighboring structures, leading to occult, life-threatening anatomic distortion, making evaluation and airway management extremely difficult. Anatomically, the neck is divided into anterior and posterior triangles. The *anterior triangle* is densely packed with vital structures including neurovascular and aerodigestive tracts. It is bordered anteriorly by the midline, posteriorly by the sternocleidomastoid muscle, and superiorly by the lower edge of the mandible. The *posterior triangle* is bounded by the sternocleidomastoid muscle anteriorly, the clavicle inferiorly, and the anterior border of the trapezius muscle posteriorly. Excluding spinal trauma, injury to this region often has a more favorable prognosis because of the relative paucity of vital structures.

Historically, for evaluation of penetrating neck trauma, the neck has been divided into *Zones I, II,* and *III* (Fig. 37.1), and the location of an injury within one of these zones guided the management approach. It is useful to maintain an understanding of the neck zones for the purposes of communication with other providers. Many current algorithms use zone driven protocols for diagnostics and management. As technology has continued to improve, multi-detector computed tomography angiography (MDCTA) has become the gold standard for the initial screening of most symptomatic, stable penetrating neck injuries. Use of MDCTA has also demonstrated that penetrating neck injury can span multiple zones not evident from the surface wound, making the surface zone location less relevant, and allowing for more rapid and accurate nonsurgical evaluation than in the past.[1,2] Some practitioners and institutions have abandoned the zone system of nomenclature, but others have continued to use it. Either approach (traditional zone based or modern no-zone) have been shown to be safe and effective. The decision to use one system versus the other will be provider and institution specific, driven by clinical preference and consideration of available resources.[3] *Zone I* (base of neck) extends superiorly from the sternal notch and clavicles to the cricoid cartilage. It includes the thoracic outlet below the cricoid cartilage. Injury to this region can affect both neck and mediastinal structures. *Zone II* (midneck) is the area between the cricoid cartilage and the angle of the mandible. Zone II injuries are therapeutically distinct because they lie in the most exposed region of the neck, making them accessible to direct surgical intervention with access to both proximal and distal vascular control. *Zone III* (upper neck) extends from the angle of the mandible to the base of the skull. As with zone I injuries, proximal and distal vascular control in this region is difficult to achieve (Box 37.1).

Two fascial layers, the superficial fascia and the deep cervical fascia, cover neck structures. The superficial fascia covers the platysma muscle and is located just below the skin. The deep cervical fascia is divided into three parts: the *investing layer* surrounds the neck and splits to encase the sternocleidomastoid and trapezius muscles; the *pretracheal layer* adheres to the cricoid and thyroid cartilages and travels caudally deep to the sternum to insert on the anterior pericardium; and the *prevertebral layer* envelops the cervical prevertebral muscles and extends to form the axillary sheath, which covers the subclavian artery. The pretracheal fascia is clinically important because of its connection from the neck to the anterior mediastinum. Missed aerodigestive injuries can result in mediastinitis because of this anatomic continuity. The carotid sheath is made of portions from all three divisions of the deep cervical fascia. The *platysma muscle,* sandwiched between the superficial and deep cervical fascia, envelopes the anterolateral neck. If the platysma muscle is violated, injury to deep structures should be suspected, and platysmal violation is used to separate superficial, unimportant injuries from those warranting evaluation of the deep structures at risk.

Pathophysiology

Penetrating injuries are most often gunshot wounds (GSWs) or stab wounds (SWs). GSWs are further divided into high-velocity and low-velocity injuries. High-velocity missiles (military-style weapons and hunting rifles) easily penetrate soft tissue and bone. Their pathway is generally predictable, causing both direct injury along the path of travel and remote injury via blast effect. Blast or cavitation effect pertains to moderate or high velocity missiles and is caused by the immediate release of kinetic energy as the bullet enters the tissue. Cavitation can lead to extensive soft tissue damage beyond that caused directly by the bullet's path. Low-velocity injuries result from missiles that travel at significantly slower speed and tend to produce erratic pathways, with injuries often demonstrating no direct relationship to the location of the entrance or exit wounds.[4] Lower-velocity projectiles cause less severe clinical injury than high velocity projectiles, but injuries can be life-threatening, nevertheless. In the past decade, the overall mortality rate for penetrating neck trauma has been reported to be around 5% in civilian victims, comparable to the rate seen in war casualties.[1,5]

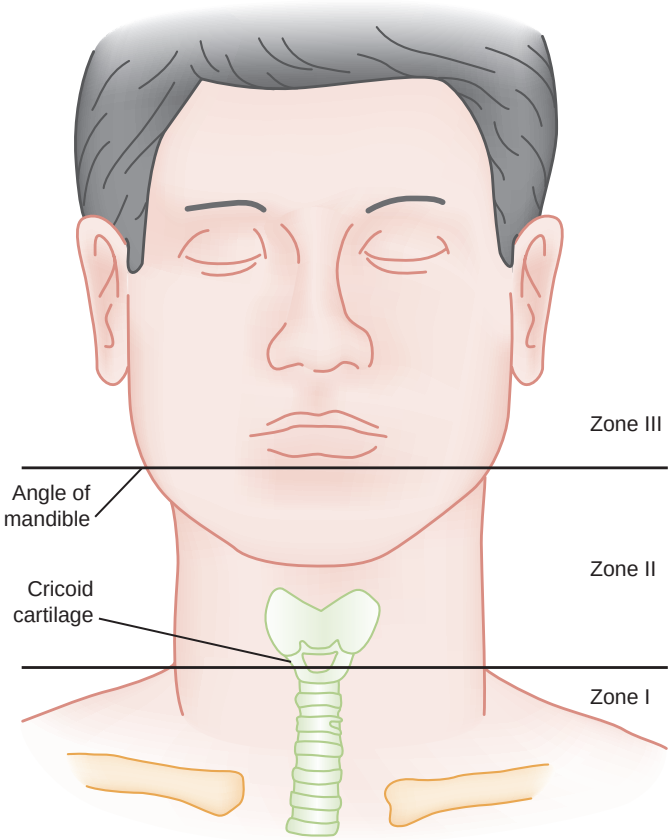

Fig. 37.1. Zones of the neck.

Blunt neck trauma most frequently results from motor vehicle collisions (MVCs) but can occur after assaults, "clothesline" injuries, strangulation, and sports injuries.

Transcervical gunshot wounds (TC-GSWs) represent a subset of penetrating neck trauma that has been associated with an almost threefold increase in the incidence of serious injury compared with GSWs that do not cross the midline (80% vs. 30%). The most common injuries are to vascular structures and the spinal cord. The decision whether to practice mandatory exploration for these injuries or to use a selective surgical approach with appropriate diagnostic studies and serial examinations is institution specific, and either approach is reasonable.

CLINICAL FEATURES

Patients with neck injury can manifest numerous signs and symptoms, but many are nonspecific and there may be minimal external evidence of injury apparent during early assessment, even when there are serious underlying injuries. Frequent examination and a methodical approach to evaluation are crucial to ensure that serious, occult injuries do not go undetected or evolve to the point that they threaten the patient's airway, circulation, or life. Symptoms and signs of particular importance are dyspnea, dysphonia, stridor, drooling, hematoma, significant external bleeding, bruit, neurological deficit, or shock.

DIFFERENTIAL DIAGNOSIS

With neck trauma, typically the differential diagnosis is limited to injury of the structures of the neck: aerodigestive, vascular, neurological, and glands, and, less commonly, the spinal column or cord, thoracic structures, and brain. The incidence of these injuries from penetrating neck trauma is listed in Table 37-1.

TABLE 37.1

Incidence of Injuries in Penetrating Neck Trauma

LOCATION	NUMBER (1275 TOTAL)	PERCENTAGE*
Arterial	320	12.8
Venous	281	11.3
Tracheolaryngeal	253	10.1
Pharyngoesophageal	240	9.6
Spinal cord	76	3
Neurologic, other	85	3.4
Thoracic duct	20	0

*Incidence based on other reported series.
From McConnell DB, Trunkey D: Management of penetrating trauma to the neck. Adv Surg 27:97, 1994.

BOX 37.1

Vascular and Other Contents in Neck Zones

ZONE I
Proximal common carotid artery
Vertebral artery
Subclavian artery
Major vessels of upper mediastinum
Apices of lungs
Esophagus
Trachea
Thyroid
Thoracic duct
Spinal cord

ZONE II
Carotid artery
Vertebral artery
Larynx
Trachea
Esophagus
Pharynx
Jugular vein
Vagus nerve
Recurrent laryngeal nerve
Spinal cord

ZONE III
Distal carotid artery
Vertebral artery
Distal jugular vein
Salivary and parotid glands
Cranial nerves IX to XII
Spinal cord

DIAGNOSTIC TESTING

Diagnostic testing in the emergency department (ED) will apply primarily to the stable patient. Patients with neck injury should be thought of as in terms of whether or not they will require emergent or urgent surgical intervention in the operating room (OR). They can generally be divided into four categories: (1) hemodynamically unstable, (2) hard signs of injury with or without hemodynamic instability, (3) hemodynamically stable with soft signs of injury, and (4) asymptomatic. Patients in either

of the first two categories will most likely go to the OR emergently or urgently. If a patient displays hard signs of injury (defined later), but remains hemodynamically stable, they may go directly to the OR or undergo evaluation and imaging and then be taken to the OR for surgical exploration. Despite variability in the definition of hemodynamic instability, any blood pressure (BP) lower than 90 mm Hg should be considered unstable.[6] Diagnostic testing is indicated for stable patients exhibiting soft signs of injury and, sometimes, for those who present asymptomatically. Airway stabilization should always be of primary concern, and this is discussed in detail in the Management section.

Patients with penetrating neck injury are evaluated for the presence of soft or hard signs of aerodigestive or neurovascular injury during the primary and secondary survey (Box 37.2). Definitions of hard signs of injury vary. Hard signs equate with the need for immediate surgical or endovascular intervention. Not all patients with hard signs are hemodynamically unstable, yet even stable patients will likely need expeditious surgical intervention in the OR. Hard signs are indicative of injury to either the aerodigestive or neurovascular structures. Hard signs of aerodigestive injury include air bubbling from the wound, substantial subcutaneous emphysema, or airway compromise. Hard signs of neurovascular injury include significant hematoma (whether pulsatile or not) significant hemoptysis, active bleeding, shock unresponsive to fluid, decreased or absent radial pulse, vascular bruit or thrill, or cerebral ischemia. Institution specific factors (availability of imaging and surgery subspecialties, for example) determine which variation of these hard signs selects patients for immediate transport to an OR. Despite hard signs being an indication for expedited transfer to the OR, there are times when some pre-OR diagnostic imaging might be helpful in the otherwise stable patient. An example of this would be head and neck computed tomography angiography (CTA) to identify whether unilateral neurological deficit in a MVC victim is caused by injury to the carotid artery or to the brain.

Soft signs of injury (see Box 37.2) necessitate further diagnostic evaluation but are less likely than hard signs to require surgical exploration. Ancillary testing is dependent on several parameters, including location of injury, specific signs and symptoms (soft signs), resource availability, and institution-specific protocols. The most common study obtained is CTA. Other diagnostic tests for particular presentations can include plain radiographs of the neck or chest (primarily to locate the missile or fragments), contrast esophagography, flexible or rigid endoscopy, laryngoscopy or flexible nasopharyngoscopy, duplex ultrasound, magnetic resonance angiography (MRA) or conventional angiography. Indications for these ancillary, diagnostic tests will be addressed under the specific anatomic injury further in this chapter.

Researchers historically remained divided as to whether patients lacking both hard and soft signs required further diagnostic evaluation. Two large prospective studies of patients with penetrating neck wounds found that physical examination and symptoms were reliable in determining which stable patients needed vascular or esophageal diagnostic studies. Currently, management varies in these asymptomatic patients from serial examination and observation to diagnostic studies, such as CTA. The age of the patient, availability of both imaging studies and personnel, ability to perform serial assessment of the wound, and patient's social situation need to be considered in making this decision.

BOX 37.2

"Soft" and "Hard" Signs of Penetrating Neck Trauma

SOFT SIGNS
Minor hemoptysis
Hematemesis
Dysphonia, dysphagia
Subcutaneous or mediastinal air
Nonexpanding hematoma
Oropharyngeal bleeding
Neurological findings
Proximity wound

HARD SIGNS
Rapidly expanding/pulsatile hematoma
Massive hemoptysis
Air bubbling from wound
Severe hemorrhage
Shock not responding to fluids
Decreased or absent radial pulse
Vascular bruit or thrill
Stridor/hoarseness or airway compromise
Cerebral ischemia
+/– Massive subcutaneous emphysema

MANAGEMENT

The evaluation of penetrating neck trauma depends on the anatomic zone of injury, clinical presentation, and hemodynamic stability. Early management is based on whether the patient requires immediate surgery, extensive evaluation for injury to the deep structures of the neck (airway, digestive, vascular, neurological), serial evaluation and observation, or discharge after ED evaluation.

Whenever feasible, patients with neck injury should be transported to a trauma center. Despite a stable initial appearance, airway compromise can ensue rapidly, and intervention is essential at the first sign of airway threat, ideally before respiratory symptoms develop. Necessary stabilization procedures should be initiated during transport to the ED when possible rather than at the scene to avoid delays in definitive care.

Airway

Airway management is the highest initial priority in any patient with neck trauma. Bag mask ventilation may be hazardous because it may force air into injured tissue planes, resulting in massive subcutaneous emphysema and subsequent airway distortion or, rarely, air embolus. Aside from obvious injury to the airway or overt airway distress or compromise, the clinician should look for signs of impending or future compromise of the airway. These can include neck hematoma, upper airway hemorrhage or hematoma, voice change or significant subcutaneous emphysema, any of which can progress to distort or occlude the airway. These are all considered indications for early airway stabilization (see also Chapter 1).

Although the ideal technique to secure a definitive airway for patients with neck trauma has been heavily debated, orotracheal intubation with rapid sequence intubation (RSI) has been shown to be safe and effective and should be considered the first-line airway technique in the emergent situation, preferably using a video laryngoscope.[7] Video laryngoscopy confers advantage through improved glottic views and less need for neck manipulation.[8,9] If the cervical spine must remain immobilized during orotracheal intubation, an assistant should hold inline stabilization of the head and neck. Relative contraindications to RSI include significant anatomical disruption of the face or neck, massive hematemesis, or concern that RSI will not succeed and

the patient will not be successfully oxygenated using a bag and mask, laryngeal mask airway, or other device. If time and resources allow, fiberoptic laryngoscopy may be preferable; however, this procedure requires skill with endoscopy and is not feasible when there is significant bleeding.[10] Institution-appropriate rescue and surgical airway equipment should be available if standard orotracheal intubation fails.

Blind nasotracheal intubation has been associated with serious complications, including false passage, and is contraindicated in patients with penetrating neck trauma. If endotracheal intubation is not possible, cricothyrotomy may be required (see Chapter 1).

Breathing

When the airway has been stabilized, breathing assessment is standard, with consideration of the associated risk of hemothorax or pneumothorax, seen primarily with penetrating zone I injuries.

Circulation

Open wounds should be covered and sufficient compression applied to control bleeding and prevent air embolus without occluding the airway or blood flow to the brain. Wounds with active bleeding or blood clots should not be probed because massive hemorrhage can ensue. Ideally, bleeding is controlled by direct pressure. Blind clamping of active bleeding sites should be avoided because of the high concentration of neurovascular structures in the neck. Intravenous (IV) access is best placed on the uninjured side, avoiding the ipsilateral neck or upper extremity.

Occasionally, exsanguination from penetrating trauma in the ED is imminent. In those cases, direct pressure on the wound is first-line treatment, followed by insertion of fingers into the wound or packing the wound to facilitate compression if direct pressure alone is unsuccessful. Occasionally, these measures will fail, particularly in zone III wounds. Insertion of a 16- or 18-French ballooned catheter into the wound with inflation of the balloon to tamponade bleeding during transport to the operating suite may be helpful.[11]

Cervical Spine

The placement of a cervical collar is unnecessary in most cases of penetrating neck trauma without neurological deficits. One large series found an overall incidence of 0.4% unstable cervical spine injuries in patients who had sustained penetrating neck injury.[12] Cervical collars can obscure neck pathology and preclude adequate examination. In any patient with blunt neck or multisystem trauma, and in particular if altered, there should be greater concern for occult or overt cervical spine injury.

Thoracotomy

In patients presenting to the ED with cardiopulmonary resuscitation (CPR) in progress, the indication for resuscitative thoracotomy is CPR for less than 15 minutes with penetrating neck trauma or less than 10 minutes of CPR with any blunt trauma. Arrest in the ED, or profound, refractory shock are also indications in either scenario. Mortality from resuscitative thoracotomy for any type of blunt trauma resulting in CPR is exceedingly high with survival rates cited in the 1% to 2% range.[13]

Venous/Arterial Air Embolism

Venous air embolism (VAE) causes profound shock or cardiopulmonary arrest unresponsive to fluids or thoracotomy. If VAE is suspected, placing the patient in a head-down, left lateral decubitus position will cause intra-cardiac air to accumulate in the apex of the right ventricle. If shock persists, aspiration of air from the apex of the right ventricle either by use of an ultrasound-guided pericardiocentesis needle or under direct visualization after ED thoracotomy can be lifesaving. Neurologic sequela or any otherwise unexplained stroke-like syndrome should prompt consideration of arterial air embolism. Controversy surrounds the best patient position when considering the diagnosis of arterial air embolus, and there are no large trials to provide a definitive answer. Because arterial emboli can lead to cerebral edema, we recommend placing the patient in a neutral position after cardiac aspiration is completed and vital signs restored.

Nasogastric Tubes

Placement of a nasogastric tube (NGT) is relatively contraindicated in patients with penetrating neck injury and should be avoided if at all possible. Exceptions are when placement is required to decompress a stomach distended by positive pressure ventilation to permit improved respiratory support. Ideally, placement is deferred until after intubation, because it may no longer be deemed necessary, and, if necessary, can be inserted gently and with endoscopic guidance, if available. The NGT aspirate may be helpful because bloody aspiration implies visceral injury.

PHARYNGOESOPHAGEAL TRAUMA

PRINCIPLES

Epidemiology

Esophageal injuries are rare, and most are due to penetrating trauma and involve the cervical segment.[14] Injury from blunt trauma is typically associated with hyperextension or cervical spine fractures.[15]

Pathophysiology

Early diagnosis of esophageal injury is crucial because spillage of orogastric contents with bacterial contamination can lead to florid inflammation, abscess, and mediastinitis. Delayed diagnosis of esophageal injuries contributes to their mortality rate of up to 20%.[16-18]

CLINICAL FEATURES

In penetrating trauma, air leaking out through the wound site is the most compelling indicator of an underlying esophageal or airway injury. Otherwise, there are no pathognomonic signs of esophageal injury. Soft signs of injury include hematemesis, odynophagia, dysphagia, subcutaneous emphysema, and blood in the saliva or NGT aspirate (see earlier discussion of placement of NGT). Other associated findings include dyspnea, hoarseness, stridor, cough, pain and tenderness in the neck, and resistance to passive neck movement. Physical examination is unreliable in diagnosing esophageal injury, and a normal examination does not exclude aerodigestive injury.[19] However, absence of any symptoms or soft signs, coupled with a normal physical examination makes esophageal injury extremely unlikely, and serial evaluation can replace any other further diagnostic testing in this setting, depending on institution-specific protocols.

DIAGNOSTIC TESTING

Timely diagnosis is associated with decreased morbidity and mortality, with poorer outcomes found in patients treated beyond

24 hours from the time of injury.[20] Plain films of the neck and chest alone are inadequate but may suggest esophageal perforation if pneumomediastinum, hydrothorax, or retropharyngeal air is present.

Contrast esophagography, which requires the patient's cooperation, has a sensitivity of 90% for esophageal injuries. Typically, water-soluble contrast (eg, diatrizoate meglumine and diatrizoate sodium [Gastrografin]) is used. Barium has greater sensitivity, but has more danger associated with extravasation. A thin barium swallow can be used to increase sensitivity if the Gastrografin swallow is negative. Flexible endoscopy follows a negative contrast esophagography study. This combination of tests has a sensitivity approaching 100%.[11]

Sole reliance on CTA, without oral contrast, for diagnosis of esophageal injuries is currently not supported by the literature. Although computed tomography (CT) scan can be useful to look at the wound track or trajectory of a bullet to determine if a proximity wound is likely, its sensitivity is variable and is as low as 50%.[15,19] Extravasation of contrast is rarely seen, and non-oral contrast CT depends on visualization of indirect signs, such as paraesophageal air or fluid, esophageal wall thickening, or edema.[20] In patients in whom the pre-test suspicion is low, CT demonstration of a wound track distant from the esophagus may be sufficient. In higher risk injuries, addition of a contrast swallowing study is recommended. If available, thin (5 mm) section contrast CT esophagography has test characteristics comparable to standard barium swallow and is an alternative option.[21] Additionally, evaluation for vascular or airway injury is recommended prior to repair of the esophageal damage; half of patients with penetrating esophageal injuries will have a concurrent laryngotracheal injury.[22]

MANAGEMENT

When esophageal injury is suspected, broad-spectrum antibiotics with anaerobic coverage (eg, piperacillin and tazobactam IV 3.375 grams every 6 hours) should be administered, and the patient should receive nothing by mouth. Preoperative placement of an NGT under endoscopic guidance may reduce the spillage of gastric contents into the wound. Any uncontained perforation of the esophagus requires prompt surgery, whereas small contained perforations may be candidates for observation and reimaging.[23]

Esophageal stents are gaining popularity for certain nontraumatic perforations and may have applications in trauma as well.[17,23] Isolated pharyngeal injury can be managed nonoperatively in the majority of cases.

LARYNGOTRACHEAL TRAUMA

PRINCIPLES

Laryngotracheal injuries account for less than 1% of all trauma injuries, but a substantial proportion of immediate mortality. Most blunt laryngotracheal injuries result from direct blunt force sustained in MVCs, often without a shoulder restraint, in which the extended neck strikes the steering wheel or dashboard and the larynx is compressed between the fixed object and the cervical spine. Other mechanisms leading to laryngotracheal injuries include clothesline injuries, improperly fitting shoulder harnesses, near hanging, assaults, athletic events, attempted strangulation, and iatrogenic wounds.

The cricoid cartilage is the only complete solid ring in the larynx. Fractures of the cricoid cartilage can lead to death through acute airway obstruction and are the most serious laryngeal injuries. Calcification of the laryngeal cartilages begins during the teenage years. The degree of airway obstruction after blunt trauma to the larynx is inversely related to the degree of cartilage calcification, putting children at highest risk of respiratory compromise after injury.[24] These injuries can lead to long-term sequelae, including recurrent pneumonia, dyspnea, voice change, dysphagia, laryngeal stenosis, and chronic pain, and risk and severity of sequelae increases with delayed or missed diagnosis.

CLINICAL FEATURES

Not all surgically significant laryngotracheal injuries will manifest clinically at the time of initial evaluation in the ED, particularly in the case of blunt trauma.[25] Bubbling or air leakage from a neck wound signals injury to the respiratory tract and is considered a hard sign of laryngotracheal injury. Massive subcutaneous air and crepitus over the larynx (caused by laryngeal fracture) represent laryngotracheal injury until proven otherwise. A clothesline mechanism of injury makes laryngotracheal injury more likely than other blunt mechanisms. Other clinical features of laryngotracheal injury include dysphonia, aphonia, dyspnea, stridor, hemoptysis, subcutaneous emphysema, laryngeal crepitus, neck tenderness or pain over the larynx, a visible neck wound, or loss of anatomic landmarks secondary to hematoma. However, each individual finding occurs in fewer than 50% of cases.[26] Pain with tongue movement or rotation of the head implies injury to the hyoid bone or laryngeal cartilage.[27] Patients with laryngotracheal injury may be unable to tolerate lying flat.[28] Soft tissue surrounding the injury can serve as a makeshift air conduit, and minimize respiratory distress initially, even with complete laryngotracheal separation.[29] Because blunt laryngotracheal injuries are often seen in association with multisystem trauma, they can be easily overlooked; however, they portend a higher mortality and often mandate early airway management.

DIAGNOSTIC TESTING

Plain radiographs, if performed, should be evaluated for extraluminal air, edema, foreign bodies, and fracture or disruption of the cartilaginous laryngeal structures. Laryngoscopy or flexible nasopharyngoscopy allows direct evaluation of laryngeal integrity. With appropriate local anesthesia, laryngoscopy is well tolerated by most patients, even those in cervical spine immobilization collars. Anesthesia and preparation for an emergent airway should precede laryngoscopy in the semi-stable patient, because instrumentation-related irritation and cough can cause sudden laryngospasm or airway disruption.[29] Rigid endoscopy is useful to evaluate injury distal to the larynx but is performed in the OR under general anesthesia.

With a sensitivity approaching 100%, CT scanning is the imaging modality of choice, providing detailed information about laryngeal integrity and the surrounding region.[30] When soft tissue anterior neck injury is suspected, 1-mm cuts of the larynx should be obtained and multiplanar reconstructions performed to optimize the study. CT is useful for assessing airway diameter and vocal cord integrity, as well as for detecting fractures of the hyoid bone, disrupted laryngeal or tracheal cartilages, significant exolaryngeal or endolaryngeal hematoma, and dislocations of the cricothyroid or cricoarytenoid joints. It is less useful for the detection of mucosal perforations, degloving injuries of the cartilage with denuded mucosa, certain types of minor laryngotracheal separation, particularly when there are poorly calcified pediatric cartilaginous structures. Typically, injuries missed by CT scan are unlikely to require surgical management.[31]

Widespread access to ultrasound has led to an increase in its use for trauma patients. Whereas some advocate ultrasound to detect blunt laryngotracheal injuries such as laryngotracheal separation, larger studies are needed before we can recommend this modality.

MANAGEMENT

Airway compromise in patients with laryngotracheal trauma can be immediate or delayed. Because delayed airway occlusion can be rapid and life-threatening, these patients require close monitoring. When laryngotracheal injury is suspected, early laryngoscopy is indicated to identify injuries and determine the need to secure the airway.[25] When emergent airway management is required, the approach should be individualized, based on the suspected injuries, the patient's overall status, and the ability to tolerate examination by laryngoscopy under local anesthesia, without or without sedation. If available, an awake, fiberoptic-guided oral intubation is likely the best route.[25,32] If this is not feasible given the status of the patient, or availability of equipment and operator, and anatomy is reasonably preserved, "awake" intubation using a video laryngoscope (see Chapter 1) is a good alternative. If an awake technique is not feasible, the best approach often is a single attempt at orotracheal intubation under a "double set-up," using RSI, but with preparations in place to move immediately to a surgical airway (cricothyroidotomy or tracheostomy) if intubation is not successful on the first attempt.[33] The airway lumen may be compromised by edema or hematoma, so endotracheal tubes of varying sizes, including several sizes smaller than would normally be used for the patient, should be prepared for use. A tube one size smaller than what is typically used is a good first selection.

Most patients can be intubated in a standard fashion, but the laryngoscope (unless a flexible scope is used) is not capable of visualizing the airway below the vocal cords, so the tube must be placed very gently and guided down the airway with the least contact or friction. This will minimize the possibility of completing a partial laryngotracheal separation or creating a false passage. Depending on the location and extent of the injury, tracheostomy may be preferred over cricothyrotomy because of the potential for the latter to further damage an injured larynx. When the airway is managed in the OR, tracheostomy is preferred. In the ED, management is often more time pressured, and cricothyroidotomy, provided the anatomy is preserved, usually is preferred, because it is faster and easier to perform. In cases with a large neck wound, intubation can be performed through the wound, provided the trachea can be visualized.

Complete laryngotracheal separation is often fatal. If complete laryngotracheal separation is present with distal retraction of the trachea, orotracheal intubation is unlikely to be successful, but may be tried, as described earlier, using a small (cuffed) tube and gentle technique, if flexible endoscopy is not available. If a surgical approach is chosen, after vertical incision in the neck, tracheal hooks can be used to recover the distal end of the trachea, and tracheostomy performed at the fourth or fifth tracheal ring to avoid the larynx. Blind nasotracheal intubation or use of positive pressure supraglottic ventilation (eg, bag/mask or laryngeal mask airway) is contraindicated in these injuries. The risk of decompensation with intubation, the condition of the patient, and the available resources/consultants must all be weighed carefully.

For the majority of injuries, a period of hospitalization for observation is required. Patients with no identifiable injury, beyond laryngeal tenderness, but who had a significant mechanism of injury (significant energy transfer to the larynx) can be observed for 12 hours in the ED or an ED observation unit and discharged home if no additional symptoms or signs develop, voice and swallowing are normal, and discomfort is minimal and abating. These patients should have their first 6 hours of observation in the ED to ensure stability before transfer to the observation unit for the remainder of their visit.[25] Most small mucosal injuries, hematomas, and nondisplaced fractures can be managed conservatively with analgesia, humidified air, elevation of the head of the bed, antibiotics, steroids, antireflux medications, vocal rest, and a clear diet. Unstable patients or those with higher-grade injuries require surgical repair.

VASCULAR TRAUMA

PRINCIPLES

The great vessels of concern in the neck include the carotid, subclavian, and vertebral arteries and the internal and external jugular veins. Morbidity and mortality occurs via exsanguination, hematoma expansion with subsequent airway distortion and compromise, direct vessel injury leading to vascular occlusion, or embolization of a foreign body (eg, shotgun pellet to brain or heart). Delayed-onset, evolving, central neurologic deficits in a patient with any neck trauma should prompt assessment of the carotid arteries for dissection.

Penetrating Injury

Arterial injuries, including extravasation, pseudoaneurysm, occlusion, dissection, and atrioventricular fistula formation, occur in 25% of all penetrating neck wounds, and 37% of deep penetrating neck wounds have some vascular injury.[2,34] Vessels are injured directly in most cases, although the blast effect can cause indirect intimal injury. Mortality rates range from 10% to 50%.

Blunt Injury

Blunt cerebrovascular injuries (BCVIs) are rare, occurring in less than 2% of blunt trauma victims.[35,36] Mortality rates for blunt cervical vascular injuries range to 60%.[37] The internal carotid artery is the most frequently injured artery, followed by the vertebral artery.[38] Blunt trauma to the cervical vessels can result in a spectrum of arterial injuries, including intimal tears, thrombosis, dissection, and pseudoaneurysm.[37] Embolization can then occur from a thrombus that develops at the injury site. The most common mechanism for blunt internal carotid artery injury is sudden, forceful hyperextension and lateral rotation of the neck. This mechanism can cause stretching of the carotid artery over the transverse processes of the upper cervical vertebrae, resulting in intimal injury.[37] Other mechanisms responsible for this type of injury include direct blunt force to the side of the neck, intraoral trauma, and basilar skull fractures involving the petrous or sphenoid portions of the carotid canal. Blunt carotid artery injuries most often result from MVCs but have also been reported after fights, athletic events, seat belt injuries, and strangulations. Vertebrobasilar arterial injuries may follow relatively minor trauma, such as chiropractic neck manipulation, but most commonly occur in association with fractures of the spinal column.

CLINICAL FEATURES

Penetrating Injury

Hard signs of arterial injury include active hemorrhage, hematoma that is expanding or is pulsatile, new bruit, fluid-unresponsive shock, massive hematemesis or hemoptysis, or appropriate focal neurologic deficits. Over 80% of patients with penetrating neck trauma and hard signs of vascular neck or aerodigestive injury (air leaking through injury site or significant subcutaneous emphysema) will have vascular or aerodigestive injuries identified. By contrast, fewer than 20% of patients with soft signs of vascular injury (non-pulsatile, nonexpanding hematomas, minor

hemoptysis) or aerodigestive injury (eg, dysphonia, dysphagia, any subcutaneous emphysema) will have a significant injury to either of these systems confirmed. For patients with neither hard nor soft signs, the likelihood of significant injury approaches zero, even when there is a wound in proximity to a vital structure, attesting to the value of risk-stratification of penetrating neck trauma patients based on the presence of physical examination findings.[39] The decision to obtain diagnostic studies or to observe the asymptomatic patient with isolated neck trauma, particularly one with a wound proximal to a vascular structure, is guided by institutional policy and practice, and depends on the availability of imaging, ability of the provider to assess the patient, and potential for ongoing observation both in the ED and following discharge at home.

Blunt Trauma

Half the patients with dissection from blunt trauma are neurologically asymptomatic. When symptomatic, carotid injuries cause either transient or fixed contralateral sensory or motor deficits, aphasia, dysphasia, and Horner syndrome, whereas vertebral injuries can cause ataxia, vertigo, emesis, and visual field deficits.[40] Neurological symptoms are often delayed. Most symptoms develop 10 to 72 hours post-injury with a median of 12.5 hours.[38,40] Up to one-third of patients may not develop deficits for more than 24 hours.[35] Delay in onset of neurological sequelae of weeks to years has been reported. Any unexplained focal neurologic abnormality after blunt or penetrating trauma involving the head or neck should prompt consideration of vascular injuries. Similarly, patients with arterial epistaxis are at risk and should be evaluated.

Because of the potential for delay in symptom onset and catastrophic outcome, screening of asymptomatic patients with associated injuries has become standard. Cervical spine injury, mandible fracture, basilar skull fracture, high injury severity score, and low ED Glasgow Coma Score (GCS; below 6 or 8) have been found independently predictive of a BCVI in an otherwise asymptomatic patient.[41] Cervical spine injury is the strongest risk factor, with an associated BCVI in up to 45% of isolated cervical spine fractures.[42,43] Screening criteria differ slightly between authors, centers, and organizations, and those from the Western and Eastern Trauma Associations are listed in Table 37.2.[44,45] Unfortunately, screening guidelines, such as the Eastern Association for the Surgery of Trauma (EAST) screening criteria, typically miss about 20% of injured patients.[46] Expanding these criteria to include all cervical spine fractures and select patients with complex facial fractures or mandible fractures may increase sensitivity of clinical criteria for BCVI screening.[41,46,47] At a minimum, screening should be performed in patients with cervical spine fractures or injuries in C1 to C3, transverse foramen fracture at any level, low GCS, LeFort II or III fracture, basilar skull fracture involving the petrous bone, and patients with an appropriate mechanism of hyperextension or hyperflexion with rotation and significant injuries to the head, face, and neck.

Seat-belt signs, or visible abrasions on the neck, are often a concern for physicians evaluating these injuries. Firstly, a "seat-belt sign" should be differentiated from a large hematoma, which is of greater concern. Secondly, several authors have included "seat-belt sign" in the list of variables evaluated, without proving them contributory in multivariate analysis. In two recent studies focused specifically on the impact of the seat-belt sign, no vascular injury was found in a single patient with an isolated seat-belt sign without signs of vascular injury or criteria for asymptomatic screening.[48,49]

In children, the rate of BVCI is lower, likely about 0.4%.[50] Evaluation and management mirrors that of the adult patient.

TABLE 37.2

Trauma Association Criteria for Blunt Cerebrovascular Injury Screening

	WESTERN TRAUMA ASSOCIATION	EASTERN TRAUMA ASSOCIATION
Symptomatic	Arterial hemorrhage from the neck, mouth, nose, ears Large or expanding cervical hematoma Cervical bruit in patient <50 years old Focal neurological deficit Evidence of cerebral infarct Neurologic deficit incongruous with CT/MRI findings	Unexplained neurological injury Arterial epistaxis
Asymptomatic	Cervical hyperextension or hyperflexion with rotation Direct cervical trauma Intraoral trauma Basilar skull fracture involving the carotid canal LeFort II or III Head injury with GCS <6 Fracture of C1 to C3 Vertebral body or transverse foramen fracture, subluxation, or ligamentous injury at any level Hanging with cerebral anoxia Seat-belt sign or clothesline injury with significant cervical pain, swelling, AMS	GCS <9 Petrous bone fracture Diffuse axonal injury Cervical spine fracture (especially C1-3, transverse foramen, or subluxation/rotational component) LeFort II or III fracture

AMS, altered mental status; *CT,* computed tomography; *GCS,* Glasgow Coma Score; *MRI,* magnetic resonance imaging.

DIAGNOSTIC TESTING

Penetrating Trauma

Traditionally, for cases without overt hard signs of vascular injury, the less accessible zones I and III were evaluated radiographically, whereas the more surgically accessible zone II injuries underwent operative exploration. However, many patients with penetrating mechanisms will have injuries outside of the zone cutaneously affected.[1]

CTA has a 90% to 100% sensitivity and 99% to 100% specificity for vascular injury in penetrating neck trauma.[39,51,52] Both direct CT signs (wall irregularity, contrast extravasation, lack of vascular enhancement, and caliber changes) and indirect signs (sheath hematoma, bone or bullet fragments <5 mm from a major vessel) are used in diagnosis.[2] CTA may help surgical planning in the stable patient with loss of the carotid pulse lacking neurologic deficits or a new bruit.[11] However, it is primarily useful in evaluating patients with soft signs of injury, as patients with hard signs will typically need operative management.

Blunt Trauma

Historically, conventional arteriography (digital subtraction angiography [DSA]) has been used extensively to detect vascular injury in patients with both blunt and penetrating injuries. DSA should include the intracranial portion of the carotid artery with zone III injuries or suspected blunt cervical trauma. Zone I injuries should include the aortic arch with its branches.

Sensitivity and specificity are nearly 100% and complication rates are less than 2%.[53]

For blunt trauma, CTA has become standard, and few patients with a negative CTA develop adverse neurological outcomes.[54,55] However, its sensitivity is still substantially lower when compared to DSA (51% to 89%).[54,56-58] Nearly 80% of the lesions missed by CTA are grade 2 or higher.[56] False positives are frequently reported as well. Therefore, for patients in whom the pre-test probability is high and a CTA is therefore unexpectedly negative, further testing (eg, DSA) should be undertaken unless clinical evaluation suggests the contrary.

Other Radiographic Options

Although not indicated in most cases of suspected vascular injury, plain films can occasionally be useful. Anteroposterior and lateral neck films can help determine a bullet trajectory. Chest radiographs allow evaluation of the mediastinum and identification of hemothorax or pneumothorax.

Duplex ultrasonography has shown variable performance in the evaluation of cervical vascular injury in patients with both penetrating and blunt trauma, risking misses of zone I and zone III injuries. For penetrating injury, carotid duplex Doppler has higher sensitivity, but for symptomatic dissection patients without obvious evidence of stroke, sensitivity of ultrasound is inadequate.

MRA has additional distinct disadvantages that include remote location in many centers, the contraindication of metallic foreign bodies (bullet fragments), length, cost, availability, and the inability to directly visualize the neck during the procedure for expanding hematoma. Reports of sensitivity are variable, but it is likely equivalent to that of CTA for carotid injury and possibly inferior for vertebral dissections.

MANAGEMENT

The goals of management are twofold: repair of acute life-threatening hemorrhage and prevention of stroke. Mortality in patients suffering a stroke following a vascular injury is significantly higher than those who do not (34% vs. 7%).[56]

Penetrating Injury

The ideal management strategy for injuries of the vascular system resulting from penetrating trauma has not been determined, although surgical repair is common. In cases with brisk hemorrhage or those in whom reperfusion might convert an ischemic infarction to a hemorrhagic infarction in patients with profound neurologic deficit, some prefer selected ligation over repair. Vertebral artery injuries are often more amenable to endovascular repair.[59]

Blunt Injury

Treatment options for blunt arterial injuries depend in part on the mechanism, type of injury, and location of the lesion. Injuries are typically graded as 1 (intimal irregularity with <25% narrowing), 2 (dissection or intramural hematoma with ≥25% narrowing), 3 (pseudoaneurysm), 4 (occlusion), and 5 (transection with extravasation). Treatment modalities include anticoagulation, surgery, and observation. Anticoagulation is widely used for dissection, although there is no convincing evidence that it clearly improves outcome. For anticoagulation, antiplatelet agents and heparin have comparable injury healing rates, and no difference was noted between outcomes in patients given heparin, aspirin, or a combination of aspirin and clopidogrel.[60] Because of high complication rates in trauma patients, treatment should be initiated with appropriate consultation with vascular surgery or neurosurgery. Surgical treatment includes ligation, resection, thrombectomy, endovascular stent placement, and, in the case of severe hemorrhage in a small vessel with collateral circulation, transarterial embolization. Endovascular stent therapy is less invasive than surgery and considerably easier to perform in less surgically accessible regions. In non-randomized studies, endovascular stents were typically used in higher-grade lesions, with comparable outcomes to medical management. Stent patients are generally managed with a week of heparin, followed by 6 months of aspirin or a combination of aspirin and clopidogrel.[61] For low-grade lesions, particularly dissection, long-term occlusion outcomes are better with anticoagulation and antiplatelet therapy compared to stenting.[62] Appropriate treatment reduces stroke rate from about one-quarter of patients to 3.9%.[40] Repeat imaging in 7 to 10 days assesses recannulation, as well as pseudoaneurysm formation. Enlarging or symptomatic pseudoaneurysms merit treatment, particularly in patients with questionable follow-up.

NERVOUS SYSTEM, GLANDULAR, AND RETROPHARYNGEAL INJURIES

The brachial plexus, peripheral nerve roots, cervical sympathetic chain, the spinal cord, and cranial nerves VII, IX, X, XI, and XII are vulnerable to trauma. Neurologic deficit can also result from vascular injury with subsequent cerebral ischemia. Complete cord injury can result in spinal (neurogenic) shock with paraplegia, bradycardia, and hypotension. Brown-Séquard syndrome (hemisection of the spinal cord) arises with ipsilateral hemiplegia and contralateral sensory deficit. Cervical spine fractures and cord injuries are most commonly found in GSWs (1.35% and 0.94%, respectively), followed by direct blunt trauma. Either injury is rare from SWs (0.12% and 0.11%).[63] Brachial plexus, spinal root, and peripheral nerve injuries have been reported after neck trauma and can result in both sensory and motor deficits. Phrenic nerve injury may compromise spontaneous respiration by causing ipsilateral diaphragmatic paralysis. Hoarseness can result from direct laryngeal trauma but also from injury to the recurrent laryngeal nerve, which branches off the vagus nerve (cranial nerve X), leading to vocal cord paralysis. Sixty percent of patients with transection of the cervical trachea will experience recurrent laryngeal nerve damage.[64]

Other less common injuries have been reported in association with neck trauma with variable signs and symptoms. Thoracic duct injuries are less likely to be apparent initially and are frequently diagnosed intraoperatively or after chylothorax develops. Glandular wounds, including those of the thyroid, parathyroid, and salivary glands, are reported rarely. Thyroid rupture or hemorrhage can occur, with an expanding hematoma causing increasing respiratory distress over the 24 hours following an injury.[65,66] Isolated retropharyngeal hematomas, typically from a whiplash mechanism, are also extremely rare but can result in life-threatening airway compromise.[67]

NEAR HANGING AND STRANGULATION

PRINCIPLES

The terms *hanging* and *strangulation* are often used interchangeably, with hanging being a subset of strangulation. *Judicial* hanging victims classically fell at least the height of their body, whereas most suicides fall little to no distance and are termed *non-judicial*. *Complete hanging* refers to the victim who is freely suspended, while *incomplete hanging* refers to the partial suspension of the

victim's body with some part still in contact with the ground. *Typical hanging* refers to the ligature knot being midline directly under the occiput. *Atypical hanging* refers to all other knot placements. The maximal force is applied immediately opposite to the placement of the knot; therefore, typical hanging portends highest risk of arterial occlusion. *Near-hanging* is a common term referring to survivors of an attempted hanging.

Manual strangulation and *ligature strangulation* refer to external compression of the neck, usually by hands or ligature, but independent of the weight of the victim. *Postural strangulation,* generally seen in the younger pediatric population, refers to death sustained by the victim's body weight compressing the anterior neck against a firm object.

Judicial hanging involving an adequate fall distance results in forceful distraction of the head from the neck and body, and this leads to high cervical fractures, such as the classic hangman's fracture (fracture through both pedicles of C2), complete cord transection, and death. Non-judicial hangings frequently occur at less than 2.7 meters, usually inadequate to injure the cervical spine, except in the elderly population.[68-70]

In essentially all types of non-judicial strangulation, the ligature or external force causes venous congestion with stasis of cerebral blood flow leading to unconsciousness. Once the person is limp, the ligature or external force can tighten further, leading to complete arterial occlusion and ultimately to brain injury or death. Vagal reflexes resulting from pressure on the carotid body may contribute to fatal dysrhythmias, as may increased sympathetic tone from pericarotid sinus pressure. Compression of the airway does not play as significant a role.

Survivors of hanging can suffer sequelae in other systems; hypoxic-ischemic brain injury is the driving factor in the high mortality and neurologic morbidity. Pulmonary edema can occur from several mechanisms: *neurogenic* pulmonary edema from centrally mediated, massive sympathetic discharge; *postobstructive* from relief of the marked negative intrapleural pressure generated by forceful inspiratory effort against an extrathoracic obstruction; and *cardiogenic* pulmonary edema, which is increasingly recognized as a result of hanging-associated Takotsubo cardiomyopathy.[71]

CLINICAL FEATURES

External trauma may or may not be evident. Ligature marks, fingernail scratches, abrasions, and contusions are variably present on the external neck as well. *Tardieu spots* are highly correlated with asphyxial deaths; these petechial hemorrhages are seen in the conjunctiva, mucous membranes, and skin cephalad to the ligature marks.

Thyroid cartilage fractures and/or hyoid bone fractures are seen in approximately half of all non-judicial hanging deaths.[70] More commonly seen with manual strangulation, cricoid cartilage fractures are rarely reported in suicidal hangings, and there are few survivors.[72] These are significant less common (≈7%) in survivors of near-hanging.

Vascular injury leading to delayed neurologic sequelae after near-hanging is rare. Carotid injury occurs in only a tiny fraction of near-hangings. In a study of 56 survivors of manual strangulation, 16% of whom lost consciousness and 63% of whom had a neck hematoma, no laryngeal, hyoid, or vascular damage was identified on magnetic resonance imaging (MRI).[73]

DIAGNOSTIC TESTING

Suggested radiographic evaluation for hanging or strangulation with suspected injury includes head CT and neck CTA.

MANAGEMENT

Techniques for managing the airway are as for other blunt neck trauma. The addition of positive end-expiratory pressure is often necessary, especially when pulmonary edema or acute respiratory distress syndrome (ARDS) develops. Full resuscitative effort is warranted even in the unconscious patient, because full recovery is possible. The altered or comatose patient should be assumed to have cerebral edema with elevated intracranial pressure, and cerebral resuscitation measures should be initiated.

Definitive studies providing guidelines for the management of hypoxic brain injury specifically related to near-hanging or strangulation injuries are lacking. Case series indicate a potential role for induced mild hypothermia in comatose survivors of strangulation.[74,75] One study demonstrated a 43% rate of survival to discharge and 6% return of neurological function in hanging patients treated with hypothermia after arrest.[76] Case reports have suggested use of thrombolysis for carotid injury related stroke in survivors of near-hanging, although this is not widely studied.[77] However, the data are not sufficient at this point to recommend either for clinical practice.

DISPOSITION

Most patients with penetrating or blunt neck trauma warrant admission to the hospital, especially when their condition justifies further diagnostic studies, surgery, or intensive care. All patients with platysma muscle violation should be admitted to the surgical service or the observation unit for ongoing observation, regardless of their stability. Careful observation should be maintained for patients with blunt neck injury, because they can manifest delayed signs and symptoms of visceral or vascular injury with serious consequences. Some patients may require transfer to trauma centers, if required services are not available at the initial receiving facility. Pediatric trauma victims fare better when transferred directly to a trauma center.[78,79]

KEY CONCEPTS

- Neck trauma results from three major mechanisms: blunt injury, penetrating injury, or near hanging or strangulation. Platysma violation defines a penetrating injury.
- The external neck is divided into zones I, II, and III. Zone designation has anatomic, diagnostic, and management implications in penetrating trauma, but use of computed tomography angiography (CTA) has greatly simplified the approach to the evaluation. Many injuries involve more than one zone.
- Zone I and III respectively encompass the thoracic inlet and base of skull, and penetrating injuries to these regions risk more occult vascular injury.
- Airway stabilization is the first priority in neck trauma. In most instances, flexible endoscopy is preferred, if possible, but orotracheal rapid sequence intubation (RSI), using a double set-up is also a valid approach. A surgical airway option should be available.
- Cervical spine injury in penetrating neck trauma without neurological deficits is extremely rare.
- Esophageal injuries are uncommon but represent the most frequently missed neck injury. Delays in diagnosis carry an extremely high mortality.
- Hard signs of vascular injury following penetrating trauma include rapidly expanding or pulsatile hematoma, massive hemoptysis, severe

KEY CONCEPTS—cont'd

hemorrhage, shock not responding to fluids, decreased or absent pulse, vascular bruit or thrill, respiratory distress, and/or cerebral ischemia. Hard signs of aerodigestive injury include air bubbling from wound or extensive subcutaneous emphysema. Typically, patients with hard signs require prompt surgical intervention.

- Blunt vascular injuries are often asymptomatic but can present with immediate or delayed neurological sequelae. Cerebral ischemia, aphasia, dysphagia, Horner syndrome, ataxia, vertigo, visual field defects, and emesis should prompt consideration of anterior or posterior circulation vascular injury.
- Seat-belt signs should be differentiated from neck hematomas (the latter being of greater concern). The literature does not support an isolated cervical seat-belt sign as a sign of vascular injury.
- CTA is more than 90% sensitive for the detection of vascular injury with penetrating neck trauma but less sensitive for identifying vascular injury in blunt trauma. Digital subtraction angiography (DSA) is indicated for patients with high pre-test probability of injury but a normal CTA.
- A leading cause of in-hospital death following near-hanging or strangulation are pulmonary complications, including pulmonary edema, which has three primary etiologies: postobstructive, neurogenic, and cardiac.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 37: QUESTIONS & ANSWERS

37.1. The presence of which of the following signs after penetrating neck trauma would indicate a likely benefit from surgical intervention?
A. Decreased or absent radial pulse
B. Small degree of hemoptysis
C. Horner syndrome
D. Muffled voice
E. Stable hematoma

Answer: A. "Hard" signs of penetrating neck trauma are the presence of an expanding hematoma, severe active bleeding, shock not responding to fluids, decreased/absent radial pulse, vascular bruit/thrill, cerebral ischemia, and airway obstruction. Most patients with hard signs benefit from surgical intervention.

37.2. Which of the following statements regarding airway management after penetrating neck trauma is true?
A. Awake fiberoptic intubation is the first-line technique.
B. Bag-valve-mask ventilation should be high tidal volume, low rate.
C. Cervical spine immobilization is typically unnecessary.
D. Nasotracheal intubation position is relatively contraindicated in neck trauma.
E. Preintubation nasogastric tube (NGT) placement may be lifesaving.

Answer: C. Unless there is concomitant blunt injury or evidence of spinal cord injury, cervical immobilization is not needed. Classic oral intubation after rapid sequence intubation (RSI) is the technique of choice and is successful in almost all cases. Although rarely a first line choice, nasotracheal intubation has been used successfully in these trauma patients. Gentle bag-valve-mask technique with low pressures is indicated to avoid venous air embolism (VAE) and subcutaneous emphysema. NGT placement, if done at all, should be gentle and placed after intubation.

37.3. A 21-year-old male presents after a small-caliber gunshot wound (GSW) to the left neck. He is hypotensive, hypoxic, and lethargic, but physical examination is remarkable only for a small zone I penetrating wound on the left side, with no gross swelling or crepitus. Oral intubation and rapid crystalloid infusion fail to improve his blood pressure (BP) or oxygen saturation. A portable chest radiograph is negative. While still in the emergency department (ED), his systolic blood pressure (SBP) drops to the 30s and is fluid unresponsive. What is the most appropriate next step in management?
A. Computed tomography (CT) scan of the neck and chest
B. Dopamine infusion at 20 μg/kg/min
C. Emergent blood transfusion
D. Emergent surgical consultation for neck exploration
E. Resuscitative thoracotomy

Answer: E. After penetrating trauma, the presence of profound shock or cardiopulmonary arrest unresponsive to fluids should prompt the initiation of a resuscitative ED thoracotomy. During that procedure, options C and D should already be in place, but this patient is too unstable to be transported to CT scan and while in extremis, should remain in the ED for the thoracotomy. Another consideration if the thoracotomy does not yield hemodynamic improvement is that of a venous air embolus.

CHAPTER 38

Thoracic Trauma

Ali S. Raja

Many causes of early deaths (within the first 30 to 180 minutes) resulting from thoracic trauma are preventable and include tension pneumothorax, cardiac tamponade, airway obstruction, and uncontrolled hemorrhage.

Approximately 75% of patients with thoracic trauma require only simple tube thoracostomy and volume resuscitation, and the initial care and disposition of these patients is usually performed by emergency clinicians. Care of severe thoracic trauma is multidisciplinary in nature, involving trauma surgeons, cardiothoracic surgeons, and intensivists. Improved understanding of underlying physiologic mechanisms, newer imaging modalities, minimally invasive approaches, and pharmacologic therapies have contributed to decreasing morbidity and mortality in patients with thoracic injuries.

Injury location and type dictates both assessment and management. This chapter is organized into sections for chest wall, pulmonary, tracheobronchial, diaphragmatic, cardiovascular, and esophageal injuries.

CHEST WALL INJURY

RIB FRACTURE

Principles

Background and Importance

The susceptibility to rib fracture increases with age. These injuries can be exquisitely painful, but their importance lies not in the fracture itself, which generally is self-limiting and will heal, but rather associated complications, particularly pneumothorax, hemothorax, pulmonary contusions, and post-traumatic pneumonia. Rib fractures in children are discussed in Chapter 165.

Anatomy and Physiology

An intact chest wall, protected by its rib cage, is necessary for normal ventilation. Outward expansion of the thorax by the respiratory muscles with descent of the diaphragm creates negative intrathoracic pressure. This allows passive air entry into the lungs during inspiration. Chest trauma, particularly blunt trauma, can severely disturb the physiology of respiration. Fortunately, most individuals have substantial respiratory reserve and can tolerate significant chest wall injury with adequate support.

Flail chest results when three or more adjacent ribs are fractured at two points, allowing a free segment of the chest wall to move in paradoxical motion (Fig. 38.1), with the flail segment moving inward with inspiration and outward with expiration. It can also occur with costochondral separation or vertical sternal fracture in combination with rib fractures. Underlying pulmonary contusion is considered to be the major cause of respiratory insufficiency with flail chest, and it is therefore one of the most serious chest wall injuries (Fig. 38.2). In addition, flail chest can be associated with a variety of other injuries, including hemopneumothorax, liver or spleen lacerations, and mediastinal injury.

Pathophysiology

Ribs usually break at the point of impact or at the posterior angle or posterolateral area, which is structurally the weakest area. The 4th through 9th ribs are most commonly involved. Ribs 1 to 3 are short and relatively protected, and ribs 9 to 12 are longer and more mobile at the anterior end. This confers the relative resistance to fracture of the "high" and "low" ribs. Fractures occur more easily in older adults than younger adults or in children, due to the progressive inelasticity of the chest wall that develops through aging.

The true danger of rib fracture involves not the rib itself but the potential for penetrating injury to the pleura, lung, liver, or spleen. Fractures of ribs 9 to 11 are also associated with intra-abdominal injury. Right-sided rib fractures are associated with hepatic injury and left-sided rib fractures with splenic injury. Injury severity is indicated by the number of rib fractures. The presence of two or more rib fractures at any level is associated with a higher incidence of internal injuries than with a single, isolated fracture. Patients older than 65 years old with multiple rib fractures have a greater incidence of pneumonia and a higher mortality compared their younger counterparts.

Clinical Features

Rib fracture is often a clinical diagnosis, with severe point tenderness, bony crepitus, ecchymosis, and muscle spasm over the rib being the most common findings. Also, bimanual compression of the thoracic cage remote from the site of injury (barrel compression test) usually produces pain at the site of fracture. Injury to the parenchyma may be detected by assessing the respiratory rate, oxyhemoglobin saturation, respiratory effort, effectiveness of ventilation, and pulmonary sounds.

Flail chest is characterized by paradoxical motion of a portion of the chest wall during respiration, and is usually obvious on physical examination. Unless the patient is unconscious, there will be severe pain, splinting, tenderness, and crepitus. Paradoxical chest wall motion is a product of negative intrathoracic pressure, and is obscured if the patient has been intubated and is receiving positive-pressure ventilation. For such patients, the diagnosis is usually evident on examination of the integrity of the chest wall (compression, crepitus).

Differential Diagnoses

Patients with suspected rib fracture have always sustained trauma, thus focusing the evaluation. Patients with significant, potentially multisystem trauma require a thorough trauma evaluation (see Chapter 33). Rib fracture, costochondral separation, and rib contusion may present in similar fashion, and it is not critical to identify a single, isolated rib fracture. Patients with multiple suspected fractures are at higher risk for intrathoracic injury and also for later decompensation and complications. Important diagnoses to consider include chest wall or clavicle fracture (especially sternal fracture), pulmonary injuries (pulmonary contusion/

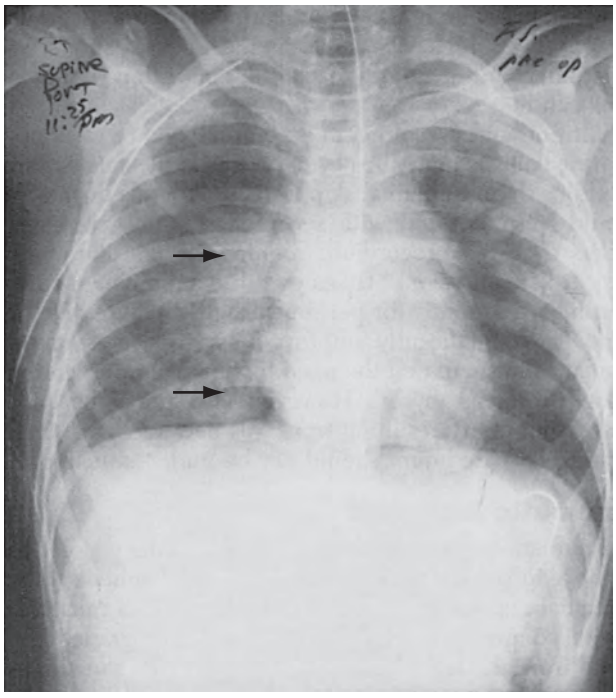

Fig. 38.1. Bilateral alveolar infiltrates *(arrows)* suggesting pulmonary contusion. Pneumopericardium and pneumomediastinum are also present.

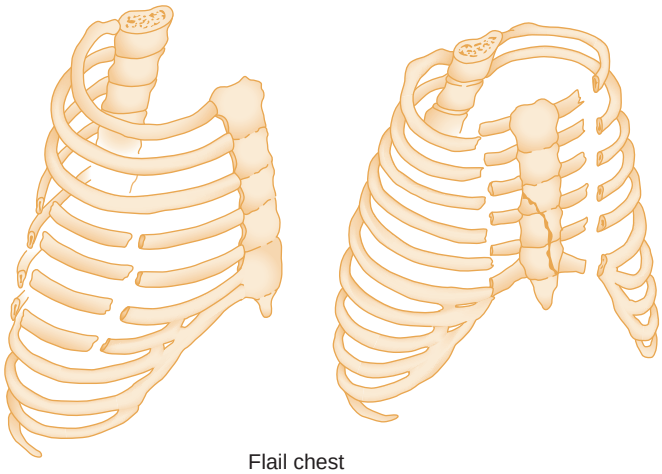

Fig. 38.2. Flail chest. Fracture of several adjacent ribs in two places with lateral flail or central flail segments.

laceration, pneumothorax, or hemothorax), tracheobronchial injury, diaphragmatic injury, cardiovascular injury (cardiac contusion or aortic injury), or esophageal injury. This broad differential diagnosis holds true for most patients with thoracic trauma, given the close proximity of the organs involved and the similar mechanisms behind most of the injuries in this chapter.

Diagnostic Testing

Many patients with relatively minor thoracic trauma are evaluated and managed exclusively based on physical findings, and they do not require imaging. When the injury is significant enough to raise concern for underlying pulmonary injury, imaging is required. Because rib fractures are managed expectantly, imaging should be reserved for patients in whom multiple rib fractures, underlying pulmonary injury, or comorbid pulmonary status (eg,

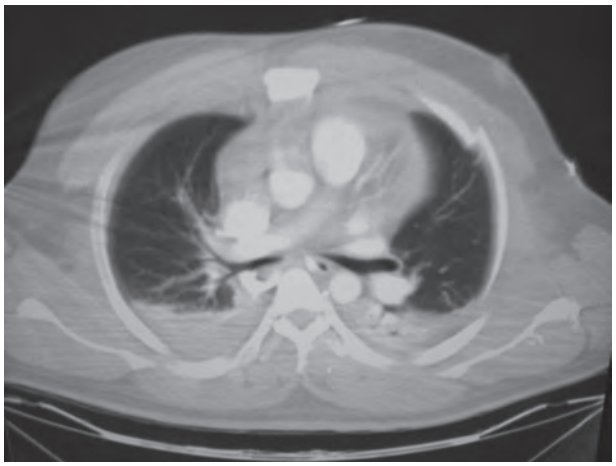

Fig. 38.3. Multiple rib fractures seen on chest computed tomography (CT) scan. (Also note presence of bilateral hemothoraces.)

BOX 38.1

NEXUS-Chest Computed Tomography Criteria for Chest Computed Tomography After Blunt Trauma

Abnormal chest x-ray
Rapid deceleration mechanism (defined as fall >20 feet or motor vehicle collision >40 mph)
Distracting painful injury
Chest wall tenderness
Sternal tenderness
Thoracic spine tenderness
Scapular tenderness

From Rodriguez RM, Langdorf MI, Nishijima D, et al: Derivation and validation of two decision instruments for selective chest CT in blunt trauma: a multicenter prospective observational study (NEXUS Chest CT). PLoS Med 12(10):e1001883, 2015.

chronic obstructive pulmonary disease [COPD]) is a concern. A plain chest radiograph will identify only about 50% of single-rib fractures; its greatest value is in identifying or excluding significant intrathoracic and mediastinal injuries. Rib series and expiratory, oblique, and cone-down views should not be used routinely. If additional imaging is required beyond a standard upright posteroanterior and lateral chest x-ray, a computed tomography (CT) scan should be obtained (Fig. 38.3). A CT scan is not indicated to confirm suspected isolated rib fracture, but it will identify multiple-level fractures and associated pulmonary injury, such as pneumothorax or hemothorax, with much greater accuracy than additional chest x-ray views.

In an attempt to limit unnecessary use of diagnostic ionizing radiation, the National Emergency X-Radiography Utilization Study (NEXUS) group derived and validated a decision instrument to guide the use of chest CT in patients with blunt trauma.[1] The NEXUS-Chest CT derivation and validation studies, performed at eight trauma centers in the United States, enrolled 11,477 patients. In the validation phase, their decision instrument had a sensitivity of 95.4%, a negative predictive value of 93.9%, and a specificity of 25.5% for all thoracic injuries. The results were even more impressive for major clinical injuries, with both sensitivity and negative predictive value approaching 100% (99.2% and 99.8%, respectively). We recommend that CT scan not be obtained for patients sustaining blunt trauma who do not meet any of the seven NEXUS-Chest CT criteria (Box 38.1).[2]

Management

Respiratory decompensation is the primary indication for endotracheal intubation and mechanical ventilation for patients with multiple rib fractures. Obvious problems, such as hemopneumothorax or severe pain, should be corrected before intubation and ventilation are presumed necessary. In the awake and cooperative patient, noninvasive continuous positive airway pressure (CPAP) by mask may obviate the need for intubation.[3] In general, the most conservative methods for maintaining adequate oxygenation and preventing complications should be used. Adequate analgesia is of paramount importance in patient recovery and may contribute to the return of normal respiratory mechanics.

Treatment of acute rib fractures is based on adequate pain relief and the maintenance of pulmonary function. Outdated management techniques involving stabilization of the flail segment by positioning the person with the injured side down or placing a sandbag on the affected segments have been discredited. These interventions actually inhibit expansion of the chest and produce increased atelectasis of the injured lung. Instead, oxygen should be administered, cardiac and oximetry monitors applied, and the patient observed for signs of an associated injury, such as tension pneumothorax.

Otherwise well patients with single rib fractures are managed with opioid and non-opioid analgesia. These injuries can be severely painful, and regular opioid medication, particularly at bedtime, is usually necessary for up to a week. Thereafter, simple analgesia with acetaminophen or a nonsteroidal anti-inflammatory analgesic generally will suffice. Continuing daily activities and deep breathing should be stressed to ensure ventilation and prevent atelectasis. It is helpful to advise patients to wait 30 to 45 minutes after taking their pain medications before performing deep breathing exercises, ideally with an incentive spirometer.

The greater the number of fractured ribs is, the higher the mortality and morbidity rates. Hospitalization should be considered for patients with three or more fractured ribs, despite the lack of other identified injuries, to receive pulmonary therapy, repeated evaluation, and appropriate effective analgesia. Elderly patients with six or more fractured ribs should be treated in intensive care units owing to high morbidity and mortality.

Multiple rib fractures in trauma patients are associated with significant morbidity and mortality. Intercostal nerve blocks with a long-acting anesthetic, such as bupivacaine with epinephrine, may relieve symptoms up to 12 hours. Other alternatives for hospitalized patients include patient-controlled analgesia, parenteral opioids, and thoracic epidural analgesia.

For flail segments, consultation with a trauma or thoracic surgeon is essential to plan for surgical intervention. Early operative internal fixation of the flail segment results in a speedier recovery, decreased complications, and better cosmetic and functional results, and it is cost-effective.[3] Indications for open fixation for flail chest include patients who are unable to be weaned from the ventilator secondary to the mechanics of flail chest, persistent pain, severe chest wall instability, and a progressive decline in pulmonary function.[4]

The patient with flail chest should be treated in the emergency department (ED) as if pulmonary contusion exists regardless of whether mechanical ventilation is used.

Disposition

Most rib fractures heal uneventfully within 3 to 6 weeks, and patients should expect a gradual decrease in their discomfort during this period. However, in addition to the complications of hemopneumothorax, atelectasis, pulmonary contusion, and pneumonia, rib fractures can result in post-traumatic neuroma, empyema, nonunion, or costochondral separation.[5] These rare complications are painful and heal slowly (if at all). Patients with blunt trauma and multiple rib fractures should be observed for 12 to 24 hours to ensure that occult vascular or intrapulmonary injuries are not present and then considered for discharge, with the full understanding that the rib fractures themselves will require a prolonged recovery period and close follow-up.

The outcome of flail chest is a function of associated injuries. Because many different physiologic mechanisms have been implicated in flail chest, there is no consensus about hospital treatment. The cornerstones of therapy include pulmonary physiotherapy, effective analgesia, selective use of endotracheal intubation and mechanical ventilation, and close observation for respiratory compromise.

STERNAL FRACTURE

Principles

Background and Importance

Sternal fractures and dislocations are caused primarily by anterior blunt chest trauma (eg, motor vehicle collisions [MVCs] or bicycle accidents when the chest strikes the steering wheel or handlebars). Risk factors for sternal fracture from blunt trauma include types of vehicular passenger restraint systems and patient age. Restrained passengers are more likely than unrestrained passengers to sustain sternal fracture, likely related to the central location of the shoulder portion of the restraint. Cardiac complications, such as myocardial contusion, occur rarely, and there is no association between sternal fracture and aortic rupture. Although sternal fractures may occur in the context of major blunt chest trauma, the presence of a sternal fracture itself does not imply other major life-threatening conditions.

Pathophysiology

During rapid deceleration from a frontal impact, the forward thrust of the body against the fixed seat belt across the sternum can result in a fracture. The location of the sternal fracture varies depending on the position of the belt, patient size, the magnitude of the impact, and the vector of the forces.

Clinical Features

Patients with sternal fractures typically present with a history compatible with the injury, and anterior chest pain, point tenderness over the sternum, ecchymosis, soft tissue swelling, or palpable deformity.

Diagnostic Testing

When sternal fracture is suspected after a relatively minor mechanism of injury (eg, ground level fall or punch to the chest), posteroanterior and lateral chest radiography is sufficient to establish the diagnosis and for evaluation of the pulmonary structures. However, when more significant traumatic signs or symptoms are present (as per the NEXUS-Chest CT criteria)[1] or when plain radiography shows a displaced fracture or possible evidence of intrathoracic injury, we recommend obtaining a chest CT scan. Results will guide management of the sternal fracture and any associated mediastinal or other intrathoracic injuries.[6] Notably, there are also specific ultrasound views during, or in addition to, evaluation by extended focused assessment with sonography in trauma (E-FAST) that may be more sensitive than plain radiography for sternal fracture.[7]

Management

Treatment consists of providing adequate analgesia, as for rib fractures. In the absence of associated injuries, most patients with isolated sternal fractures who can achieve adequate pain control with oral medications can be safely discharged home. A small subset of patients with more severe sternal fractures may have severe pain and develop respiratory compromise or nonunion. These patients are best referred for operative fixation.

NONPENETRATING BALLISTIC INJURY

Principles

Background and Importance

Many law enforcement officers, emergency medical services personnel, and private security guards wear lightweight synthetic body armor for protection against gunshot injury. In addition, there have been a number of reports of armed robbers wearing such vests in anticipation of exchanging gunfire with police or security personnel. These vests are "bullet resistant" rather than "bulletproof," depending on the weapon being used against them. They are composed of many different combinations of synthetic fibers such as Kevlar, and so wearers who are shot often suffer nonpenetrating ballistic injuries rather than gunshot wounds.

Another type of nonpenetrating ballistic injury is caused by rubber bullets and beanbag shotgun shells. Rubber bullets have been used for many years by police agencies throughout the world for crowd dispersal and for nonlethal use of force. Beanbag shotgun shells are nylon bags filled with pellets, which are fired from a standard shotgun. Both of these projectiles have the potential to cause serious injury despite their classification of "nonmetal" or "less-than-lethal" use of force.

Pathophysiology

Bullet-resistant vests are usually capable of stopping penetration by the low-velocity missiles of most handguns, but the kinetic energy of the missile can be transmitted through the layers of protective cloth or armor and produce significant injury without penetration. The heart, liver, spleen, lung, and spinal cord are vulnerable to nonpenetrating ballistic injury that may occur despite innocent-appearing skin lesions.

Clinical Features

Patients who have been shot with "less-than-lethal projectiles" or with standard bullets while wearing bullet-resistant vests usually have erythema, ecchymosis, and marked tenderness to palpation over the affected area. There may be a projectile, such as a beanbag, still located in the wound. The area of tenderness and surrounding structures should be carefully palpated to identify any subcutaneous emphysema, crepitus, or bony step-offs.

Diagnostic Testing

Most patients with nonpenetrating ballistic injury do not require testing beyond a thorough physical examination. Those in whom there is concern for retained foreign body or underlying injury may need ultrasound examination, chest x-ray, or CT scan (as they might with other blunt trauma). However, patients with only superficial ecchymoses without clinical signs or symptoms of rib fracture, pneumothorax, hemothorax, or intrapleural/peritoneal penetration frequently require no additional testing.

Management

In patients in whom underlying injury has been excluded or it is of low clinical probability, management of nonpenetrating ballistic injury focuses on wound care, either of the ecchymotic area or of the superficial abrasion/laceration. Underlying injuries, when present, should be managed as noted elsewhere in this chapter.

Disposition

It is recommended that patients with all but the most superficial nonpenetrating ballistic injuries to the chest be observed closely for 4 to 6 hours to detect internal injuries that may manifest in a delayed manner.

PULMONARY INJURIES

PULMONARY CONTUSION AND LACERATION

Principles

Background and Importance

Pulmonary contusion is reported to be present up to 75% of patients with significant blunt chest trauma, most often from MVCs with rapid deceleration.[8] Pulmonary contusion can also be caused by high-velocity missile wounds and the high-energy shock waves of an explosion in air or water.

In addition to contusions, the lungs can also sustain lacerations. Although they are most often lacerated from penetrating injury, they may also be injured by the inward projection of a fractured rib or avulsion of a pleural adhesion.[9,10]

Pathophysiology

Pulmonary contusion is caused by an impact to the lung parenchyma followed by alveolar edema and hemorrhage but without an accompanying pulmonary laceration. The early diagnosis of pulmonary contusion is important if treatment is to be successful. Since its onset may be insidious, it should be suspected from a history of a high mechanism of injury (eg, a fall from height, an MVC, and other forms of significant trauma) rather than the initial chest radiograph.

Clinical Features

The clinical manifestations include dyspnea, tachypnea, cyanosis, tachycardia, hypotension, and chest wall bruising. There are no specific signs for pulmonary contusion or laceration, but hemoptysis may be seen. Moist rales or absent breath sounds may be heard on auscultation. Palpation of the chest wall commonly reveals fractured ribs. If flail chest is discovered, pulmonary contusion is commonly present.

Surprisingly, many of the worst contusions occur in patients without rib fractures. It has been theorized that the more elastic chest wall in younger individuals transmits increased force to the thorax. Although isolated pulmonary contusions can exist, they are associated with extrathoracic injuries in the majority of patients.

Diagnostic Testing

Laboratory

Hypoxemia frequently occurs with pulmonary contusions, and is often detected by a decreasing pulse oximetry reading. In patients

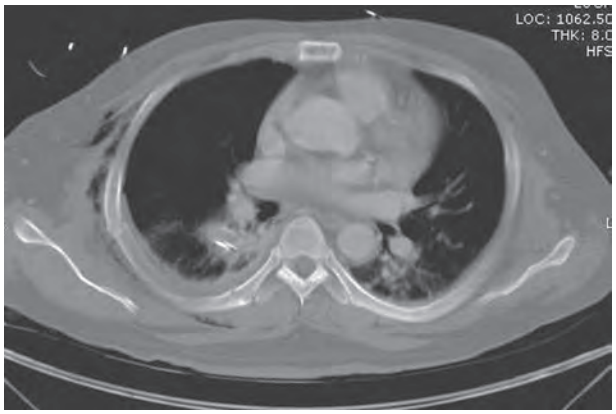

Fig. 38.4. Chest computed tomography (CT) scan showing bilateral alveolar infiltrates suggesting pulmonary contusion. There are also multiple rib fractures and subcutaneous emphysema.

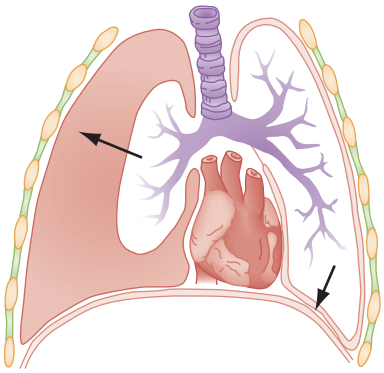

Fig. 38.5. Closed pneumothorax. Simple pneumothorax is present in the right lung with air in the pleural cavity *(left arrow)* and collapse of the right lung *(right arrow)*.

with thoracic injury and hypoxemia in whom other, more severe injuries (eg, pneumothorax) have been excluded, a pulmonary contusion should be suspected. In these patients, an arterial blood gases may be helpful in making the diagnosis, because a widening alveolar-arterial oxygen difference indicates a decreasing pulmonary diffusion capacity of the patient's contused lung, and it is one of the earliest and most accurate means of assessing the current status, progress, and prognosis.

Radiology

Typical radiographic findings can begin to appear within minutes of injury and range from patchy, irregular, alveolar infiltrate to frank consolidation (Fig. 38.4). Although these changes may be present on the initial examination, they are almost always present within 6 hours. The rapidity of changes on chest x-ray visualization usually correlates with the severity of the contusion or laceration. Pulmonary contusion should be differentiated from acute respiratory distress syndrome (ARDS), with which it is often confused because the radiographic appearance of the two conditions may be similar. Contusion usually manifests within minutes of the initial injury, is usually localized to a segment or a lobe, is often apparent on the initial chest study, and tends to last 48 to 72 hours. ARDS is diffuse, and its development is usually delayed, with onset typically between 24 and 72 hours after injury.

The increased frequency of CT scans for blunt trauma patients has resulted in a corresponding increase in the diagnosis of pulmonary contusions and lacerations. CT scans have been shown to detect at least twice as many pulmonary contusions as plain radiographs, and one recent study found that isolated pulmonary contusions seen on CT only had a mortality of only 2.6% (compared to 4.7% for all patients with pulmonary contusion).[11]

Chest CT scan is particularly valuable to identify a pulmonary contusion in the acute phase after injury because plain chest x-ray films have a low sensitivity. Although CT scan may not be necessary to make the diagnosis of a pulmonary contusion that is evident on plain chest radiography, it may be helpful to further define the extent of the contusion and to identify other thoracic injuries. Occult pulmonary contusions are those that are initially visible only on CT scan, not plain radiographs, and usually involve less than 20% of the lung volume. These occult pulmonary contusions are not associated with a worse clinical outcome as compared with blunt trauma patients without pulmonary contusion.[11,12]

Management

Treatment for pulmonary contusion is primarily supportive.[12] As with flail chest, intubation and mechanical ventilation should be avoided if possible, because they are associated with an increase in morbidity, including pneumonia, sepsis, pneumothorax, hypercoagulability, and longer hospitalization.[13] In the rare case in which one lung has been severely contused *and is causing significant hypoxemia,* consideration should be given to intubating and ventilating each lung separately with a dual-lumen endotracheal tube and two ventilators. This allows for the difference in compliance between the injured and the normal lung and prevents hyperexpansion of one lung and gradual collapse of the other.

Management of patients with pulmonary contusions should include the restriction of intravenous (IV) fluids (to maintain intravascular volume within strict limits) and comprehensive supportive care consisting of vigorous tracheobronchial toilet, suctioning, and pain relief. These maneuvers may preclude the need for ventilator support and allow a more selective approach to both flail chest and pulmonary contusion.

Patients sustaining the force necessary to inflict a pulmonary contusion may also have pulmonary lacerations. Most of these are minor and rarely life-threatening, and they can usually be treated with continuous oxygen therapy, observation, or tube thoracostomy. Severe lacerations are associated with hemopneumothorax, multiple displaced rib fractures, and hemoptysis. Often, these life-threatening lacerations require thoracotomy with resection or tractotomy to control bleeding.

PNEUMOTHORAX

Principles

Background and Importance

Pneumothorax, which is the accumulation of air in the pleural space, is a common complication of chest trauma. It is reported to be present in 15% to 50% of patients who sustain significant chest trauma and is invariably present in those with transpleural penetrating injuries.

Pathophysiology

Pneumothorax can be divided into three types depending on whether air has direct access to the pleural cavity: (1) simple, (2) communicating, and (3) tension.

Simple Pneumothorax. A pneumothorax is considered simple (Fig. 38.5) when there is no communication with the atmosphere or any shift of the mediastinum or hemidiaphragm resulting from the accumulation of air. Traumatic simple pneumothorax is most often caused by a fractured rib that is driven inward, lacerating the pleura. It may also occur without a fracture

when the impact is delivered at full inspiration with the glottis closed, leading to a tremendous increase in intra-alveolar pressure and the subsequent rupture of the alveoli. A penetrating injury, such as a gunshot or stab wound, may also produce a simple pneumothorax if there is no free communication with the atmosphere (Fig. 38.6).

Communicating Pneumothorax. A communicating pneumothorax (Fig. 38.7) is associated with a defect in the chest wall and most commonly occurs in combat injuries. In the civilian sector, this injury is typically secondary to gunshot wounds. Air can sometimes be heard flowing sonorously in and out of the defect, prompting the term "sucking chest wound." The loss of chest wall integrity causes the involved lung to paradoxically collapse on inspiration and expand slightly on expiration, forcing air in and out of the wound. This results in a large functional dead space for the normal lung and, together with the loss of ventilation of the involved lung, produces a severe ventilatory disturbance.

Tension Pneumothorax. The progressive accumulation of air under pressure within the pleural cavity, with shift of the mediastinum to the opposite hemithorax and compression of the contralateral lung and great vessels, is the constellations of findings in tension pneumothorax (Figs. 38.8 and 38.9). It occurs when the injury acts like a one-way valve, prevents free bilateral communication with the atmosphere, and leads to a progressive increase of intrapleural pressure. Air enters on inspiration but cannot exit with expiration. The resulting shift of mediastinal contents compresses the vena cava and distorts the cavoatrial junction, leading to decreased diastolic filling of the heart and subsequent decreased cardiac output. These changes result in the rapid onset of hypoxia, acidosis, and shock.

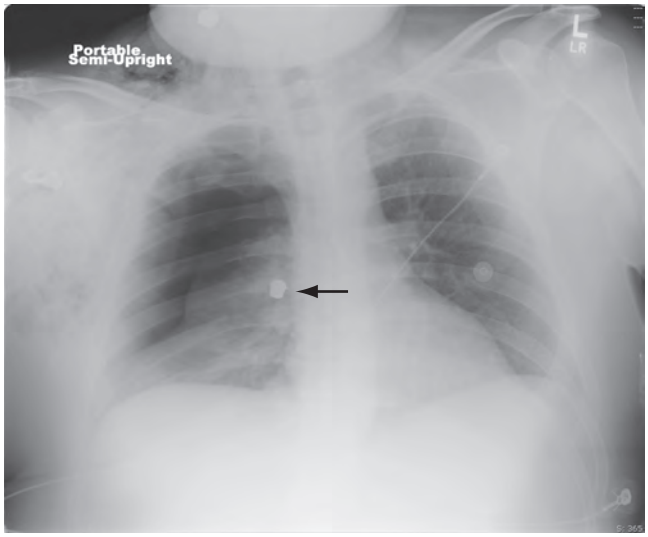

Fig. 38.6. Chest radiograph showing a moderate-sized right pneumothorax. A bullet *(arrow)* can be seen near the right mediastinum.

Clinical Features

Shortness of breath and chest pain are the most common presenting complaints of pneumothorax. The patient's appearance is highly variable, ranging from acutely ill with cyanosis and tachypnea to misleadingly healthy. The signs and symptoms are not always correlated with the degree of pneumothorax. The physical examination may reveal decreased or absent breath sounds and hyper-resonance over the involved side as well as subcutaneous emphysema, but small pneumothoraces may not be detectable on physical examination.

Patients with tension pneumothorax become acutely ill within minutes and develop severe cardiovascular and respiratory distress. They are dyspneic, agitated, restless, cyanotic, tachycardic, and hypotensive and display decreasing mental activity. The cardinal signs of tension pneumothorax are tachycardia, hypotension, oxyhemoglobin desaturation, jugular venous distention (JVD), and absent breath sounds on the ipsilateral side. However, JVD may not reliably be present with massive blood loss.

Diagnostic Testing

Because intrapleural air tends to collect at the apex of the lung, the initial chest radiograph should be an upright full inspiratory film if the patient's condition permits. An upright film will often reveal small pleural effusions that are not visible on supine films, and it also allows better visualization of the mediastinum. Although the chest radiograph has traditionally been the preferred initial study for diagnosing a simple pneumothorax, several studies have found that ultrasound has greater sensitivity for pneumothorax than chest radiography.[14,15] During the focused assessment with sonography in trauma (FAST) examination, pneumothorax will be detected well before chest radiography is performed. This may be particularly critical in the hypotensive

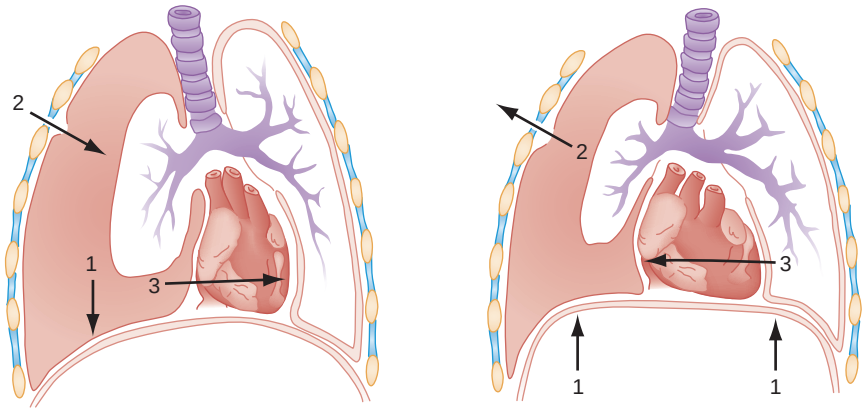

Fig. 38.7. Inspiration *(left):* The diaphragm contracts causing negative intrathoracic pressure *(arrow 1)* that draws air through the sucking chest wound in the pleural cavity *(arrow 2)* and causing the mediastinal structures to shift to the patient's left *(arrow 3).* Expiration *(right):* The diaphragm recoils *(arrow 1)* causing air to exit the chest *(arrow 2)* and allowing the mediastinum to shift back to normal position *(arrow 3).* The collapsed lung paradoxically shrinks on inspiration and expands on expiration.

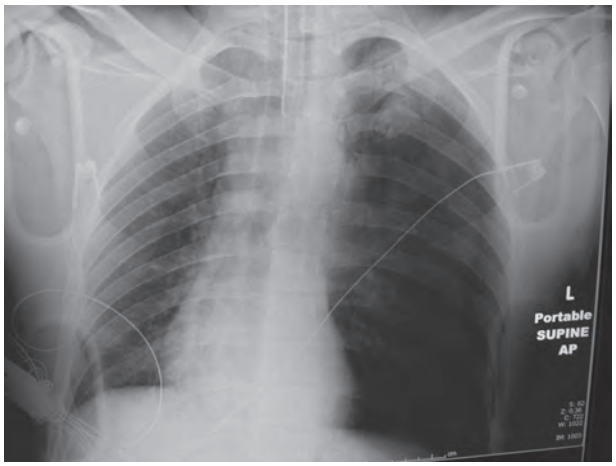

Fig. 38.8. Tension pneumothorax seen in intubated patient.

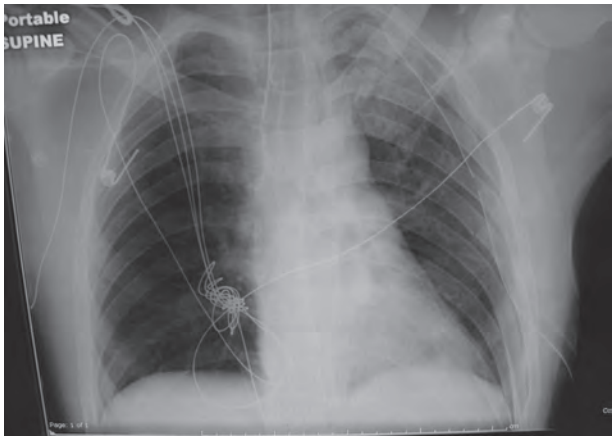

Fig. 38.9. Resolution of the tension pneumothorax shown in Figure 38.7 with placement of a left-sided tube thoracostomy.

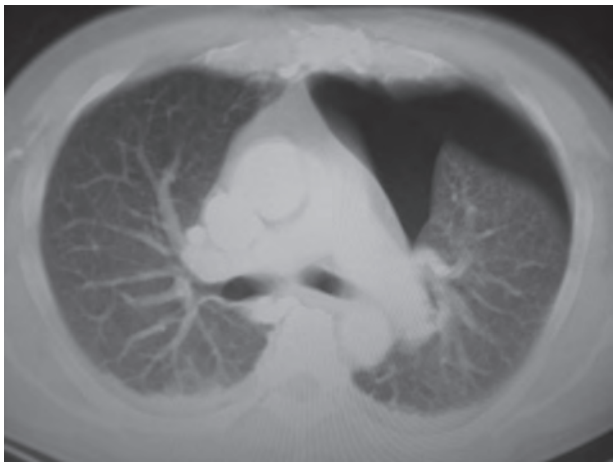

Fig. 38.10. Occult pneumothorax. Large left-sided pneumothorax visible on chest computed tomography (CT) scan, which was not visible on chest x-ray film.

BOX 38.2

Indications for Tube Thoracostomy

Traumatic cause of pneumothorax (except asymptomatic, apical pneumothorax)
Moderate to large pneumothorax
Respiratory symptoms regardless of size of pneumothorax
Increasing size of pneumothorax after initial conservative therapy
Recurrence of pneumothorax after removal of an initial chest tube
Patient requires ventilator support
Patient requires general anesthesia
Associated hemothorax
Bilateral pneumothorax regardless of size
Tension pneumothorax

From Dougall AM, et al: Chest trauma—current morbidity and mortality. J Trauma 17:547, 1977.

poly-trauma patient with oxyhemoglobin desaturation for whom tension pneumothorax is one of myriad considerations as the cause of the unstable state. Suspicion of tension pneumothorax on the basis of clinical findings is indication for immediate tube thoracostomy. Treatment should not be delayed pending a confirmatory chest radiograph. Ultrasound can confirm the presence of a pneumothorax within the first minutes of the patient's arrival, and identification of a pneumothorax in a patient with pulmonary and hemodynamic compromise is also considered confirmatory empirical evidence of tension pneumothorax requiring thoracostomy. Even without ultrasound confirmation, clinical suspicion of tension pneumothorax is justification for tube thoracostomy, because delay can be hazardous.

Occult Pneumothorax

A pneumothorax that is absent on the initial chest radiograph but is identified on subsequent chest or abdominal CT is called an *occult pneumothorax*. Occult pneumothorax is being diagnosed more frequently given the increased use of CT (Fig. 38.10).[16-18]

Management

An asymptomatic patient who suffers a low-velocity penetrating trauma (typically a stab wound) and who has negative initial imaging can be safely observed, typically for 6 hours.[16] If the initial imaging was a CT scan, the patient may be safely discharged after the period of observation. If the initial imaging was via x-ray, a delayed chest x-ray should be performed prior to discharge.

Simple Pneumothorax

Treatment of a simple pneumothorax depends on its cause and size. Small isolated apical pneumothoraces due to stab wounds may be observed without intervention. However, this conservative method seldom has application in multisystem trauma, and a chest tube should be inserted immediately upon any sign of deterioration.

Similarly, small occult pneumothoraces found only on CT scan in hemodynamically stable patients without symptoms can be managed with observation and do not need treatment, even if the patient is placed on positive-pressure ventilation.[17-19]

Any moderate to large pneumothorax should be treated with a chest tube. The indications for tube thoracostomy (chest tube) are listed in Box 38.2. The preferred site for insertion is the fourth or fifth intercostal space at the midaxillary line. This lateral placement of the tube is preferred not only because it is more efficient, but also because it does not produce an easily visible cosmetic defect, as does the anterior site at the second interspace at the midclavicular line. With multisystem trauma in which hemothorax is likely, a large chest tube (36-F to 40-F in adults and 16-F to 32-F in children) should be used. Conversely, spontaneous pneumothoraces or those due to minor or isolated injuries can be treated with smaller chest tubes.

Care is taken to be certain the vent holes along the side of the tube are all inside the chest cavity. A radiopaque line along the side of the tube with interruptions at these drainage holes helps greatly in radiographically interpreting tube position. The tube should be attached to a water seal drainage system that allows reexpansion of the pneumothorax. If there is significant air leak or a large hemothorax, the tube may be connected to a source of constant vacuum at 20 to 30 cm H_2O for more rapid reexpansion.

Tube thoracostomy does have some potentially serious complications, including the formation of a hemothorax, pulmonary edema, bronchopleural fistula, pleural leaks, empyema, subcutaneous emphysema, infection, intercostal artery laceration, contralateral pneumothorax, and parenchymal injury.[20,21] A recent meta-analysis was unable to find sufficient evidence for or against the use of empirical antibiotics with all tube thoracostomy placements to prevent empyema or pneumonia, especially those needed for spontaneous pneumothoraces. However, for patients with multisystem trauma or hemothorax, the data was suggestive of a benefit. We recommend routine intravenous antibiotic administration in these patients, specifically cefazolin 1 to 2 g given prior to—or within 1 hour of—chest tube insertion. Vancomycin (1 g) or clindamycin (600 mg) are appropriate alternatives in patients in whom cephalosporins are inappropriate.[22]

Communicating Pneumothorax

For a patient with a communicating pneumothorax in the out-of-hospital setting, the defect should be covered immediately, which helps convert the condition to a closed pneumothorax, eliminating the major physiologic abnormality. Either a partially occlusive dressing or a commercial vented chest seal can be applied; care should be taken to continually assess for conversion of the injury to a tension pneumothorax, especially in patients who are intubated and undergoing positive-pressure ventilation.[23-25] The wound should never be packed, because the negative pressure during inspiration can suck the dressing into the chest cavity. These considerations are not as important once the patient is in the ED, where formal tube thoracostomy can be performed. Positive-pressure ventilation can then be initiated, if needed, without the fear of producing a tension pneumothorax, and the patient can be prepared for definitive surgical repair.

Tension Pneumothorax

When the diagnosis of tension pneumothorax is suspected clinically, the pressure should be relieved immediately with needle thoracostomy, which is performed by inserting a large-bore (14-gauge or larger) catheter, at least 5 cm in length, through the fourth or fifth interspace laterally or the second or third interspace anteriorly on the involved side. Recent studies have suggested that some catheters may not be of sufficient length to penetrate the pleural space.[26,27] So, we recommend the lateral approach if it is accessible. This method can be easily performed in the field, allowing vital signs to improve during transport or preparation for a tube thoracostomy.[28]

In the ED, it may be just as expeditious to insert a chest tube (or even perform a "finger thoracostomy," without actually inserting the chest tube) as it is to perform a needle thoracostomy, depending on the availability of equipment. Regardless, even if a needle thoracostomy is performed on a patient with suspected tension pneumothorax in the ED, a chest tube should emergently follow.

The intubated patient in the ED who is receiving positive-pressure ventilation and external cardiac compressions is at particular risk for developing tension pneumothorax. Fractured ribs from cardiopulmonary resuscitation (CPR) can penetrate lung parenchyma and cause pneumothorax. Positive-pressure ventilation then increases intrapleural pressure and produces a tension pneumothorax. The earliest sign of this complication is an increase in resistance to ventilation. If the patient has vital signs, the blood pressure will fall and the central venous pressure (CVP) will rise. Misplacement of an endotracheal tube does not result in tension pneumothorax but, rather, asymmetry of breath sounds. If tension pneumothorax is suggested, the clinician should proceed with empirical emergent therapy.

HEMOTHORAX

Principles

Background and Importance

Hemothorax, which is the accumulation of blood in the pleural space after blunt or penetrating chest trauma, is a common complication that may produce hypovolemic shock and dangerously reduce vital capacity. It is commonly associated with pneumothorax and extrathoracic injuries.

Pathophysiology

Hemorrhage from injured lung parenchyma is the most common cause of hemothorax, but this tends to be self-limited unless there is a major laceration. Specific vessels are less often the source of hemorrhage, with intercostal and internal mammary arteries causing hemothorax more often than hilar or great vessels. Bleeding from the intercostal arteries may be brisk, however, because they branch directly from the aorta.

Clinical Features

Depending on the rate and quantity of hemorrhage, varying degrees of hypovolemic shock will be manifested. Patients may present in respiratory distress and be tachycardic and hypoxemic. Breath sounds may be diminished. The diagnosis should also be remembered as a potential complication of central line placement, and considered—along with pneumothorax—in patients who present with these symptoms after the procedure.

Diagnostic Testing

The *upright* chest radiograph remains the primary diagnostic study in the acute evaluation of hemothorax. A hemothorax is noted as meniscus of fluid blunting the costophrenic angle and tracking up the pleural margins of the chest wall when viewed on the upright chest x-ray film. Blunting of the costophrenic angles on upright chest radiograph requires at least 200 to 300 mL of fluid. The supine view chest film is less accurate but, unfortunately, is often the only film available because of the patient's unstable condition. In the supine patient, blood layers posteriorly, creating a diffuse haziness that can be rather subtle (or appear to be a pulmonary contusion), depending on the volume of the hemothorax (Fig. 38.11). With massive hemothorax, the large volume of blood can create a tension hemothorax, with signs and symptoms of both obstructive and hemorrhagic shock (Fig. 38.12).

As is the case with pneumothoraces, ultrasound has greater sensitivity than supine chest radiography in the detection of hemothoraces.[29] Given this, early bedside ultrasonography should routinely be performed in patients with thoracic trauma, regardless of findings on supine radiography. Additional imaging via chest CT (Fig. 38.13) should be performed if indicated by the NEXUS-Chest CT criteria as discussed earlier,[1] because it may detect hemothorax or other associated injuries (Fig. 38.14).

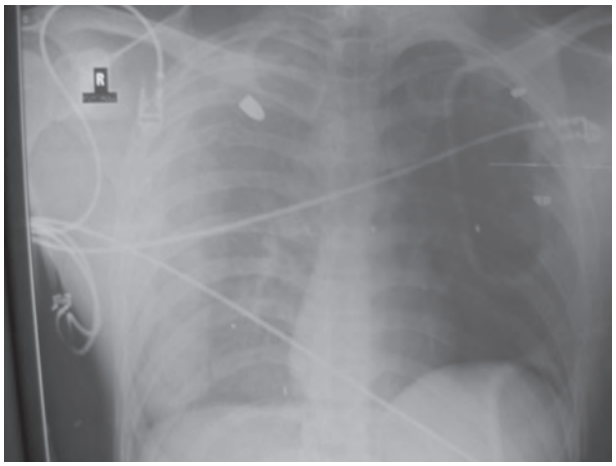

Fig. 38.11. Hemothorax secondary to gunshot wound. Note haziness over right hemithorax with bullet seen in right upper lobe.

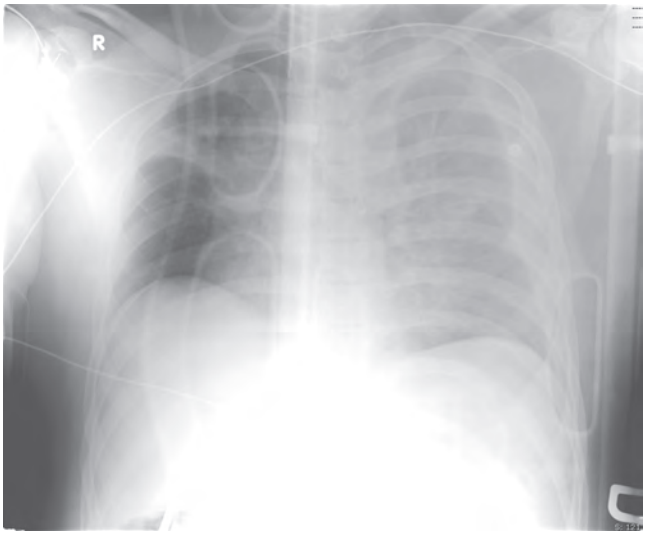

Fig. 38.12. Tension hemothorax.

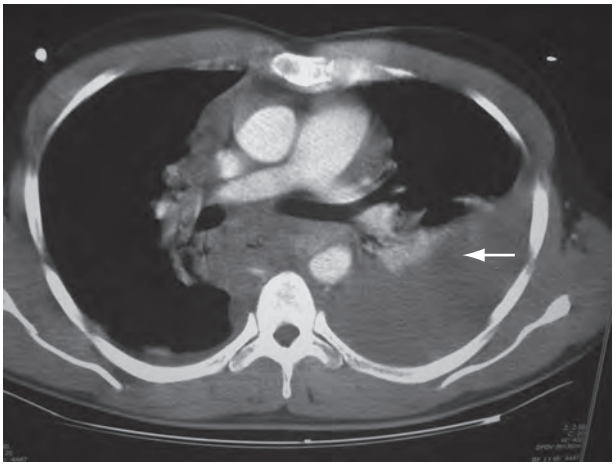

Fig. 38.13. Left-sided hemothorax visible on chest computed tomography (CT) scan *(arrow)*.

Management

Treatment of hemothorax consists of restoring the circulating blood volume, controlling the airway as necessary, and evacuating the accumulated blood. Tube thoracostomy allows constant monitoring of the blood loss, and serial chest radiographs help monitor lung reexpansion. A large-bore tube (36-F to 40-F) should be inserted in the fifth interspace at the anterior axillary line and connected to underwater seal drainage and suction (20 to 30 mL H_2O).

Although small hemothoraces may be observed in stable patients, a moderate hemothorax or any hemothorax in an unstable or symptomatic patient requires tube thoracostomy. Severe or persistent hemorrhage requires thoracostomy or open thoracotomy. Studies are required to better delineate the size of a hemothorax detected on CT scan that requires tube thoracostomy drainage.

Autotransfusion has been successfully used in tube thoracostomy. Autotransfusion also eliminates the risk of incompatibility reactions and transmission of certain diseases, such as hepatitis C. Because the majority of blood loss occurs immediately after tube thoracostomy placement, autotransfusion apparatus should be immediately available in the ED.

Close monitoring of the initial and ongoing rate of blood loss should be performed. Immediate drainage of more than 1500 mL of blood from the pleural cavity is considered an indication for urgent thoracotomy, as is a continued output of at least 200 mL/hr for 3 hours.[17,30] General considerations for urgent thoracotomy are outlined in Box 38.3.

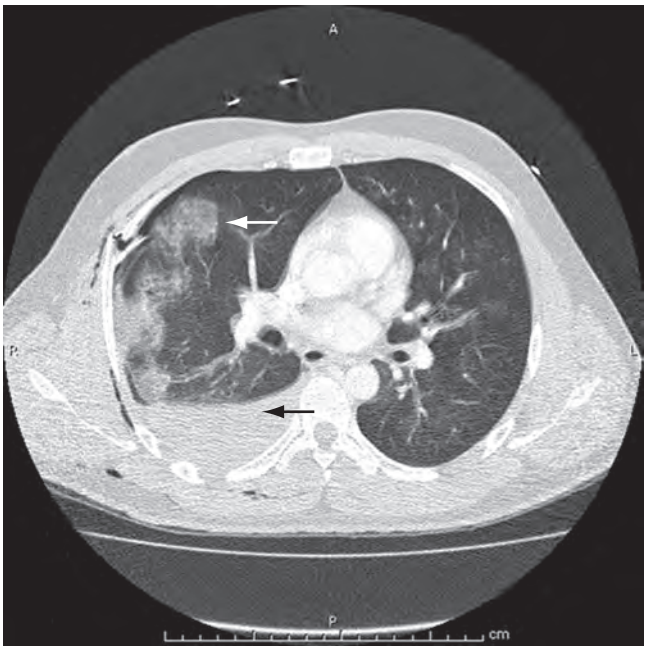

Fig. 38.14. Rib fracture resulting in pneumothorax, with associated hemothorax *(bottom arrow)* and pulmonary contusion *(top arrow)* seen on chest computed tomography (CT) scan.

TRACHEOBRONCHIAL INJURY

PRINCIPLES

Background and Importance

Tracheobronchial injuries may occur with either blunt or penetrating injuries of the neck or chest. MVCs are the most frequent mechanism causing tracheobronchial injury, accounting for more than half of all cases.

Although there has been an increase in the occurrence of tracheobronchial disruption, it is still a relatively rare injury, occurring in fewer than 3% of patients with significant chest injury. Its

BOX 38.3

Indications for Thoracotomy

Initial thoracostomy tube drainage is more than 20 mL of blood per kilogram.
Persistent bleeding at a rate greater than 7 mL/kg/hr is present.
Increasing hemothorax seen on chest x-ray films.
Patient remains hypotensive despite adequate blood replacement, and other sites of blood loss have been ruled out.
Patient decompensates after initial response to resuscitation.

associated mortality rate is reported to be approximately 10%, although mortality rates are significantly affected by associated injuries and the timing of diagnosis and surgical repair.

Pathophysiology

Tracheobronchial injuries caused by knife wounds develop almost exclusively from wounds in the cervical trachea (see Chapter 37), whereas gunshot wounds may damage the tracheobronchial tree at any point. Intrathoracic injury to the tracheobronchial tree occurs most commonly from blunt trauma. These injuries may result from direct blows, shearing stresses, or burst injury. A direct blow to the neck may crush the cervical trachea against the vertebral bodies and transect the tracheal rings or cricoid cartilage. Shear forces on the trachea will produce injury at the carina and the cricoid cartilage, which are its relatively fixed points.

Sudden deceleration of the thoracic cage pulls the lungs away from the mediastinum, producing traction on the trachea at the carina. When the elasticity of the tracheobronchial tree is exceeded, it ruptures. It has also been suggested that if the glottis is closed at the time of impact, the sudden increase in intrabronchial pressure will rupture the tracheobronchial tree. Regardless of the mechanism, more than 80% of these injuries occur within 2 cm of the carina.

CLINICAL FEATURES

Massive air leak through a chest tube, hemoptysis, and dramatic or increasing subcutaneous emphysema should suggest the diagnosis of major airway damage. Subcutaneous emphysema is typically the most common physical finding. Auscultation of the heart may reveal Hamman's crunch if air tracks into the mediastinum. Hamman's crunch is a crunching, rasping sound that is synchronous with the pulse and is best heard over the precordium. It is the result of the heart beating against air-filled tissues. Patients with tracheobronchial disruption have one of two distinct clinical pictures. In the first group of patients, the wound opens into the pleural space, producing a large pneumothorax. A chest tube fails to evacuate the space and reexpand the lung, and there is continuous bubbling of air (persistent leak) in the underwater seal device (Fig. 38.15).

In the second group of patients, there is complete transection of the tracheobronchial tree but little or no communication with the pleural space. A pneumothorax is usually not present. The peribronchial tissues support the airway enough to maintain respiration, but within 3 weeks, granulation tissue will obstruct the lumen and produce atelectasis. These patients are relatively free of symptoms at the time of injury; but weeks later, they have unexplained atelectasis or pneumonia. Radiographic signs in either group of patients are pneumomediastinum, extensive subcutaneous emphysema (Fig. 38.16), pneumothorax, fracture of the upper ribs (first through fifth), air surrounding the bronchus, and obstruction in the course of an air-filled bronchus.

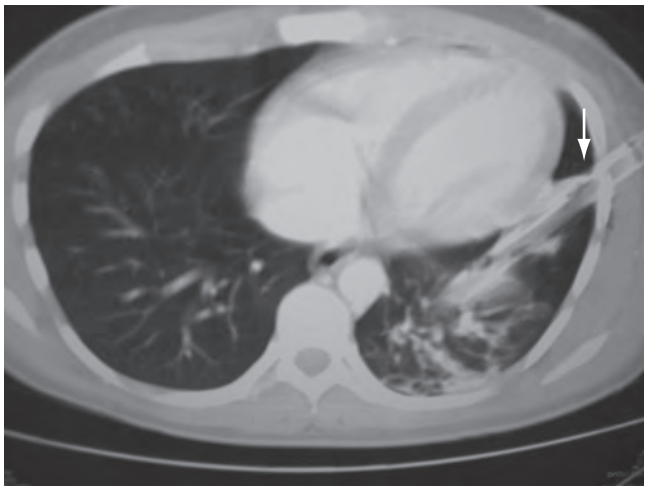

Fig. 38.15. Penetration of lung parenchyma by tube thoracostomy *(arrow),* with large residual pneumothorax, visible on computed tomography (CT) scan.

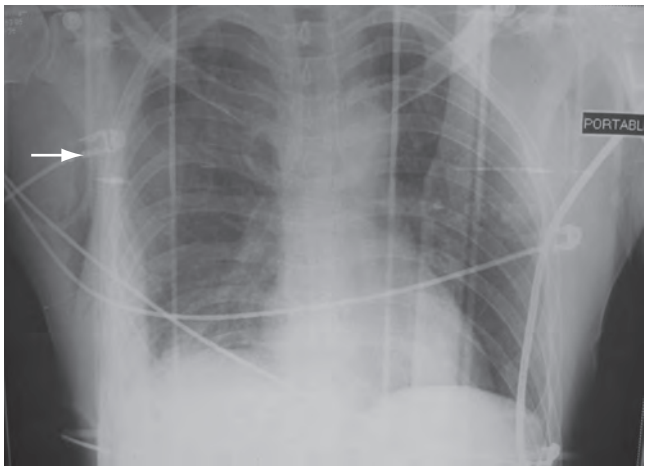

Fig. 38.16. Multiple rib fractures with extensive subcutaneous emphysema *(arrow),* with no pneumothorax seen.

DIAGNOSTIC TESTING

When tracheobronchial injury is suspected, bronchoscopy should be performed. Flexible endoscopic bronchoscopy is the most preferred and reliable means of establishing the diagnosis and determining the site and extent of the injury. However, CT scan has been shown to have high sensitivity in detecting tracheobronchial injury. Bronchopleural fistula (a communication between a bronchus and the lung parenchyma) can occur as a complication of tracheobronchial disruption and in some cases has been treated successfully via the fiberoptic bronchoscope. A mediastinal fluid collection, evidence of mediastinitis, or both may be noted on chest CT.

MANAGEMENT

If diagnostic bronchoscopy is performed, endotracheal intubation can be performed over the bronchoscope to ensure that the tube passes safely beyond the site of injury. Blind intubation should not be attempted. If intubating using a video laryngoscope (or

conventional laryngoscope), the tube is advanced slowly and gently to avoid creating a false passage or converting a partial tracheal tear to a complete tear.

The standard treatment for tracheobronchial injury has been thoracotomy with intraoperative tracheostomy and surgical repair of the disrupted airway. However, conservative medical treatment of such injuries can be considered for patients with tracheal tears less than 2 cm and without esophageal prolapse, mediastinitis, or massive air leakage.[30]

DIAPHRAGMATIC INJURY

PRINCIPLES

Background and Importance

Diaphragmatic rupture is present in 1% to 6% of major thoracic injuries. Diaphragmatic rupture occurs most commonly after blunt thoracoabdominal trauma, such as occurs in MVCs or falls from heights, but can also occur from penetrating trauma.

Pathophysiology

Diaphragmatic hernia is a herniation of abdominal structures into the thoracic cavity through a defect on the diaphragm, with a potential risk of strangulation of abdominal viscera, especially the small bowel. Signs and symptoms may not occur during the initial admission and may be delayed for as long as months to years, with a significant mortality rate.

Three-quarters of cases of diaphragmatic rupture secondary to blunt trauma occur on the left side, the remainder on the right, presumably due to the protective effect of the liver on the right side. Only about 5% of cases are bilateral. With penetrating injury, diaphragmatic injury occurs at the site of the penetration but may be occult.

In cases of blunt injury, the raised pressure within the abdominal cavity causes the diaphragmatic tear, and a pressure difference of generally 5 to 10 mm Hg forces the abdominal organs through the diaphragmatic defect. Because blunt trauma can cause multiple organ injuries, these coexisting injuries can mask the more silent diaphragmatic injuries, and diaphragmatic rupture may be initially overlooked. Over time, negative intrathoracic pressure generated by inspiration tends to draw abdominal contents into the thorax. This effect is lost with the use of intubation and positive-pressure ventilation.

DIAGNOSTIC TESTING

Accurate diagnosis of traumatic diaphragmatic hernia is essential because prompt surgical repair is the treatment of choice, but plain chest radiography alone is poorly sensitive for diaphragm rupture.

In patients with blunt trauma, CT examination of the abdomen and chest can be very useful for the evaluation of diaphragmatic injury, although injury site and type affect its sensitivity. Nevertheless, CT can demonstrate findings consistent with diaphragmatic injury, including diaphragmatic discontinuity, intrathoracic herniation of abdominal contents, and waist-like constriction of abdominal viscera (the "collar sign").

In patients with penetrating left thoracoabdominal trauma, the incidence of herniation of abdominal contents is sufficiently high that thoracoscopy or laparoscopy is recommended for the diagnosis and repair of a diaphragmatic injury. Even in patients with right-sided penetrating lesions (which do not typically result in herniation because of the protective effect of the dome of the liver), evaluation of both sides of the diaphragm with laparoscopy or thoracoscopy is recommended.

MANAGEMENT

Diaphragmatic injuries may be markers of severity and predictors of serious associated injuries in trauma and should be surgically repaired. The treatment of choice is surgery. CT scan should identify the site and extent of herniation, herniated organs, complications, and damage to associated organs. Although they are not without complications, laparoscopy and thoracoscopy may be used for diaphragmatic hernia repair.

The incidence of diaphragmatic involvement after penetrating left-sided thoracoabdominal injury is high, making nonoperative, expectant management of these patients potentially unsafe.

CARDIOVASCULAR TRAUMA

BLUNT CARDIAC TRAUMA

Blunt cardiac injury usually results from high-speed MVCs in which the chest wall strikes the steering wheel. Other causes, such as falls from heights, crushing injuries, blast injuries, and direct blows, are less common. The diagnosis of a blunt injury to the heart remains elusive because of the usual concomitant serious injuries to other body organs and, more important, because there is no gold standard for making the diagnosis.

The importance of detecting blunt myocardial injury lies in the recognition of associated potentially fatal complications. Life-threatening dysrhythmias, conduction abnormalities, congestive heart failure, cardiogenic shock, hemopericardium with tamponade, cardiac rupture, valvular rupture, intraventricular thrombi, thromboembolic phenomena, coronary artery occlusion, ventricular aneurysms, and constrictive pericarditis have all been reported as complications.

Blunt cardiac trauma may be viewed as part of a continuous spectrum (ie, myocardial concussion, contusion, infarction, and rupture). Myocardial concussion occurs when a blunt injury to the interior chest produces a "stun" response in the myocardium. No permanent cellular injury occurs, but transient clinical effects may result. Myocardial contusion is the least severe form of injury that can be demonstrated pathologically. Cellular injury occurs with extravasation of red blood cells into the muscle wall, along with localized myocardial cellular necrosis. Permanent myocardial damage is rare. Infarction typically occurs with traumatic occlusion or disruption of a coronary artery. Cardiac rupture is obviously the most severe form of blunt cardiac injury.

MYOCARDIAL CONCUSSION

Principles

Background and Importance

The terms *myocardial concussion* or *commotio cordis* are used to describe an acute form of blunt cardiac trauma that is usually produced by a sharp, direct blow to the midanterior chest that stuns the myocardium and results in brief dysrhythmia, hypotension, and loss of consciousness. It is a rare event and primarily occurs in adolescents, especially those playing sports involving hard spherical objects (eg, baseballs, hockey pucks, and so on).

Pathophysiology

Animal models of commotio cordis have determined that it is much more likely to occur if the impact occurs during early ventricular repolarization.[31] Additionally, flat objects and softer balls (eg, tennis or soccer) are less likely to cause commotio cordis than smaller balls.[32] Once this dysrhythmia occurs, it can result in a non-perfusing rhythm, such as asystole or ventricular

fibrillation, and irreversible cardiac arrest. There are, however, a number of documented cases of successful resuscitation with both rapid provision of CPR and the use of an automated external defibrillator (AED).[33]

Clinical Features

Commotio cordis has a characteristic mechanism (blunt chest trauma) and presentation (sudden collapse). Notably, the disease itself is defined by a lack of structural cardiac damage, and so more severe trauma (such as that necessary to cause cardiac contusion or rupture, as described later) is incongruent with the diagnosis.

Diagnostic Testing

Laboratory Tests and Electrocardiogram

Patients who present with the characteristic mechanism and presentation above and who have shockable rhythms on electrocardiogram (ECG) (or who were defibrillated by an AED) can be presumed to have commotio cordis if there is no evidence of structural heart damage on echocardiography or CT. Laboratory evaluation of serum electrolyte and cardiac biomarker levels may identify additional contributors to their presentation, but these will typically be normal.

Management

The initial treatment of patients with commotio cordis should follow standard advanced cardiac life support (ACLS) algorithms, ideally with initiation of bystander CPR and early defibrillation (especially at sporting events). Barring any other more severe cardiac injuries (discussed later), commotion cordis does not require any specific interventions.

Disposition

In patients who survive the dysrhythmia of commotio cordis and are not found to have more severe traumatic cardiac injury, a short period of observation is appropriate. Although there is a paucity of evidence as to the duration of this observation period, we recommend 6 to 12 hours of telemetry monitoring. After this, patients may be discharged, although they should not return to play until additional outpatient cardiac testing (eg, stress testing, cardiac magnetic resonance imaging [MRI], and pharmacologic testing for primary conductive disorders, if indicated) is performed.[33]

MYOCARDIAL CONTUSION

Principles

Background and Importance

Myocardial contusion is a very poorly understood and nebulous condition. Decades of research and widely varied clinical practice have failed to produce a consensus regarding its diagnosis, complication rate, and proper disposition.

Pathophysiology

Several mechanisms have been postulated by which the heart may be injured in cases of blunt trauma. A direct blow to the chest transmits energy through the ribs to the spine. When a large force is applied to the chest wall, the sternum is displaced posteriorly and the heart is compressed between the sternum and vertebrae or an elevated diaphragm. Either can presumably result in cardiac injury. Increased intrathoracic pressure from a direct blow to the chest may contribute to the injury. In addition, compression of the abdomen and pelvis may displace abdominal viscera upward and result in cardiac injury.

Clinical Features

Myocardial contusion manifests clinically as a spectrum of injuries of varying severity. Although the majority of patients with myocardial contusion have external signs of thoracic trauma (eg, contusions, abrasions, palpable crepitus, rib fractures, or visible flail segments), the absence of identifiable thoracic injury decreases the likelihood of myocardial contusion but does not exclude it. Virtually every known intrathoracic and chest wall injury has been associated with myocardial contusion. The most sensitive but least specific sign of myocardial contusion is sinus tachycardia, which is present in approximately 70% of patients with documented myocardial contusions and is a very common vital sign in trauma patients. A reduction in cardiac output, which can be clinically insignificant or manifest as pronounced cardiogenic shock, may occur in patients with significant cardiac contusion.

Diagnostic Testing

Unfortunately, there is not an agreed upon gold standard diagnostic definition for myocardial contusion. Clinical evidence is often nonspecific, especially in the setting of multiple traumas. Many tests and definitions have been proposed over the years, but none has emerged as definitive.

Laboratory Tests and Electrocardiogram

Electrocardiogram. Because of its anterior position in the thorax and proximity to the sternum, the right ventricle is far more likely to be injured than the left ventricle. The standard 12-lead ECG is relatively insensitive to right ventricular damage, as demonstrated by pathologic evidence of cellular damage in patients with normal ECGs. A cardiac contusion usually results in moderate right ventricular damage with only minor electrical changes, which can easily be missed on ECG. Right-sided ECGs (the addition of V_4R) have not been found to be of any benefit.

The ECG for patients with myocardial contusion often shows evidence of dysrhythmia, conduction disturbance, or ischemia. Dysrhythmias or ECG changes also can be caused by significant hypoxia as a result of pulmonary injuries or blood loss, which resolve once the hypoxemia or blood loss has been corrected.

A few cases of delayed life-threatening dysrhythmia have been reported up to 12 hours after injury, and patients may develop less lethal dysrhythmias up to 72 hours after injury. The onset of ECG changes may be delayed up to 48 hours after injury, but all ECG changes usually resolve in 4 to 60 days. The presence of ECG abnormalities is neither specific enough to confirm the diagnosis of myocardial contusion nor reliable enough to predict subsequent complications, but a newly abnormal ECG (arrhythmia/heart block or ischemic changes) warrants admission for continuous ECG monitoring.[34]

Cardiac Biomarkers. Because creatine kinase (CK) is nonspecifically increased in trauma patients owing to associated skeletal muscle injury, and CK-MB levels have also been found to be falsely elevated in multi-trauma patients, the troponin assay is the preferred cardiac biomarker for testing.

The combination of a normal troponin level and a normal 12-lead ECG has a negative predictive value sufficient to "rule out" myocardial contusion, and these patients do not need any other evaluation or monitoring specific for myocardial contusion.[34]

Imaging

Although echocardiography provides a means to directly visualize cardiac structures and chambers and can be very useful to rule out structurally significant myocardial injuries (eg, wall motion or valvular abnormalities), it should not be routinely used as a primary screening modality for blunt cardiac injury. Rather, echocardiography should be reserved for patients in whom myocardial contusion is suspected (based on ECG or troponin level) and who have unexplained hypotension or arrhythmias.[34]

Management

Treatment of a suspected myocardial contusion is similar to that of a myocardial infarction (MI): saline lock (if IV fluids are not otherwise indicated), cardiac monitoring, administration of oxygen if hypoxic, and analgesic agents. Dysrhythmias are typically transient and do not require treatment. Serious dysrhythmias, such as ventricular tachycardia or atrial flutter should be treated with appropriate medications as per current ACLS guidelines. No data exist to support prophylactic dysrhythmia suppression. Measures should be taken to treat and prevent any conditions that increase myocardial irritability (eg, metabolic acidosis). Thrombolytic agents and aspirin are contraindicated in the setting of acute trauma. In rare instances, there may be an acute MI associated with trauma, which can arise from lacerations or blunt injury to the coronary arteries. These cases should be managed by percutaneous coronary intervention (PCI), with cardiothoracic surgery for definitive repair as indicated.

In the setting of depressed cardiac output caused by suspected or confirmed myocardial contusion, judicious fluid administration to augment preload is warranted (eg, 200 to 250 mL boluses every 15 minutes to a maximum of 1 to 2 L). A dobutamine infusion may be useful once preload has been optimized. While intra-aortic balloon counterpulsation has been used successfully in refractory cardiogenic shock, the priority is to ascertain that the decreased cardiac output is not the result of other undiagnosed traumatic injuries, particularly aortic rupture.

The prognosis of a patient with myocardial contusion depends on the character and magnitude of the initial trauma, the size and location of the contusion, the preexisting condition of the coronary arteries, and, most importantly, with the number of associated serious injuries. Recovery without complications is the usual course.

Disposition

Patients with suspected myocardial contusion who have a normal troponin level and a normal ECG do not have the diagnosis. Myocardial contusions resulting in ECG changes or troponin elevations necessitate telemetry observation or in-hospital monitoring, depending on the patients' other injuries. Markedly abnormal ECGs, troponin elevations, or hypotension warrant echocardiography and cardiology consultation.

MYOCARDIAL RUPTURE

Principles

Background and Importance

High-speed MVCs are responsible for most cases of traumatic myocardial rupture, which is almost always fatal. Approximately one-third of these patients have multiple chamber rupture, and one-fourth have an associated ascending aortic rupture. Approximately 20% of patients survive at least 30 minutes, theoretically long enough to get them to the cardiac surgery operating room if the injury is recognized immediately and the center is capable.

Anatomy and Physiology

Myocardial rupture refers to an acute traumatic perforation of the ventricles or atria, but it may also include a pericardial rupture or laceration or rupture of the interventricular septum, interatrial septum, chordae, papillary muscles, valves, and lacerated coronary arteries. A delayed rupture of the heart may also occur weeks after nonpenetrating trauma, probably as a result of necrosis of a contused or infarcted area of myocardium.

The chambers most commonly involved in cardiac rupture are the ventricles, with right ventricular rupture being most common. Ruptures of the atria are less common, with right atrial rupture being more common than left. Multiple chamber involvement occurs in 20% of patients. Twenty percent of nonsurvivors have concomitant aortic rupture.

Pathophysiology

A rupture occurs during closure of the outflow tract when there is ventricular compression of blood-filled chambers by a pressure sufficient to tear the chamber wall, septum, or valve. This is the most likely mechanism for ventricular rupture when injury occurs in diastole or early systole concomitant with maximal ventricular distention. The atria are most susceptible to rupture by sudden compression in late systole when these chambers are maximally distended with venous blood and the atrial ventricular valves are closed. Other proposed mechanisms of rupture include: (1) deceleration shearing stresses acting on the "fixed" attachment of the inferior and superior vena cava at the right atrium; (2) upward displacement of blood and abdominal viscera from blunt abdominal injury that causes a sudden increase in intracardiac pressure; (3) direct compression of the heart between the sternum and vertebral bodies; (4) laceration from a fractured rib or sternum; and (5) complications of a myocardial contusion, necrosis, and subsequent cardiac rupture.

Because of the mechanisms involved in cardiac rupture, associated multisystem injuries are common. More than 70% of reported survivors of myocardial rupture have other major associated injuries, including pulmonary contusions, liver and spleen lacerations, closed head injuries, and major fractures.

The immediate ability of the patient to survive cardiac rupture depends on the integrity of the pericardium. Two-thirds of patients with cardiac rupture have an intact pericardium and are protected from immediate exsanguination. These patients may survive for a brief period but will then develop significant hemopericardium and pericardial tamponade. One-third of patients with cardiac rupture have associated pericardial tears and succumb promptly to exsanguination.

Clinical Features

The clinical presentation of a patient who has sustained a myocardial rupture is usually that of cardiac tamponade or severe hemorrhage. Rarely, a patient is seen with a large hemothorax, hypotension, and hypovolemia, obscuring the diagnosis by mimicking a serious pulmonary or other intrathoracic injury. A patient with an intact pericardial sac and developing tamponade displays physical findings of tamponade, usually with subsequent clinical deterioration. Initial inspection of the torso may reveal little more than a bruised area over the sternum or no external physical evidence. More often, however, signs of significant chest trauma or other associated injuries will be present, indicating a mechanism of injury that could result in myocardial rupture. Auscultation may reveal a harsh murmur, known as a *bruit de moulin,*

which has been classically described as sounding like a splashing mill wheel. This is caused by pneumopericardium.

Diagnostic Testing

Early use of ED ultrasound may facilitate the early diagnosis of cardiac rupture and pericardial tamponade. The combination of shock and JVD in a patient with blunt chest trauma should immediately suggest pericardial tamponade or tension pneumothorax, both conditions rapidly assessable by bedside ultrasound. In patients with coexistent hemorrhage from other injuries, JVD may be absent. Other considerations include myocardial contusion, superior vena cava obstruction, and ruptured tricuspid valve. Sonographic visualization of pericardial fluid in this setting should be followed by emergent thoracotomy (Fig. 38.17).

A chest radiograph may be helpful in patients suspected of having sustained trauma severe enough to cause myocardial rupture. Although this study usually does not help diagnose cases of myocardial rupture, it notes the presence of other intrathoracic injuries (eg, hemothorax, pneumothorax, and signs of possible aortic dissection). An increase in the size of the cardiac silhouette more commonly reflects preexisting disease or valvular incompetence with chamber enlargement caused by increased filling pressures. ECG changes may occur with myocardial injury, but these are often nonspecific. Bedside echocardiography in the ED should be performed in any case of suspected cardiac rupture, pericardial tamponade, a previously undiagnosed murmur, or shock unexplained by other causes (eg, exsanguination).

Management

When nonhospital medical personnel evaluate a patient who has sustained blunt chest trauma, they should concentrate on rapid transport and observe for any signs of pericardial tamponade. If examination is consistent with tension pneumothorax, this should be treated with needle decompression.

In the ED, treatment of patients with a myocardial rupture is directed toward immediate decompression of cardiac tamponade and control of hemorrhage. Pericardiocentesis may be effective in cases of a small rupture, but it is usually performed as a diagnostic or temporizing therapeutic procedure until surgical correction can be undertaken. Emergency thoracotomy and pericardiotomy may be required in the ED if the patient has rapidly deteriorating vital signs or a cardiac arrest. After emergency thoracotomy and pericardiotomy, the myocardial rupture should be controlled until the patient can be transported to the operating room for definitive repair. Hemorrhage from a ruptured atrium can often be controlled by finger occlusion or application of a vascular clamp. Insertion of a Foley catheter through the defect, followed by inflation of the balloon and traction on the catheter, may also control the bleeding. Ventricular rupture can usually be controlled by direct digital pressure or by suturing with nonabsorbable vascular sutures.

Cardiopulmonary bypass is required in only 10% of successful repairs of myocardial rupture. Therefore, for patients with suspected myocardial rupture, it is appropriate to undertake emergency thoracotomy in institutions that have qualified surgeons but no immediate access to cardiopulmonary bypass.

Fig. 38.17. Echocardiogram demonstrating pericardial fluid with cardiac tamponade.

PENETRATING CARDIAC TRAUMA

Penetrating cardiac injuries are one of the leading causes of death in the setting of urban violence, with patients who survive to hospital arrival having a mortality rate of almost 80%. Improvements in emergency medical services, along with an emphasis on rapid transport, are responsible for an increasing number of cardiac injury patients arriving in impending or full cardiopulmonary arrest at busy urban trauma centers.[35] The proportion of gunshot wounds versus stab wounds varies widely in reported case series, depending on the location of the trauma center.

The right ventricle is affected more often (43%) than the left ventricle (34%) owing to its anterior anatomic location. The left or right atrium is affected in 20% of cases. One-third of penetrating cardiac wounds affect multiple chambers, and survival is much worse in these cases.[36] In 5% of cases, a coronary artery is lacerated, although these injuries usually involve a distal segment of the artery and rarely produce significant acute MI when they are ligated. More proximal coronary artery lacerations require coronary bypass. Rarely, the interventricular septum, a valve, papillary muscle, or chordae tendineae are lacerated, producing an acute shunt or valvular insufficiency. These lesions are poorly tolerated and can quickly produce massive pulmonary edema and cardiogenic shock.[37]

Two conditions may occur after penetrating heart injury: (1) exsanguinating hemorrhage if the cardiac lesion communicates freely with the pleural cavity, or (2) cardiac tamponade if the hemorrhage is contained within the pericardium. Patients with exsanguinating wounds frequently die before they reach medical attention, or they have rapidly progressive hemorrhagic shock on presentation, culminating in cardiac arrest. This presentation is most typically seen in patients sustaining gunshot wounds to the heart. Cardiac tamponade is a life-threatening condition but appears to offer some degree of protection and increased survival in patients with penetrating cardiac wounds. These patients often require immediate resuscitation by emergency department thoracotomy (EDT) if they meet the criteria listed in Box 38.4.

BOX 38.4

Indications for Emergency Department Thoracotomy

PENETRATING TRAUMATIC CARDIAC ARREST

Cardiac arrest at any point with initial signs of life in the field
Systolic blood pressure below 50 mm Hg after fluid resuscitation
Severe shock with clinical signs of cardiac tamponade

BLUNT TRAUMA

Cardiac arrest in the emergency department (ED)

ACUTE PERICARDIAL TAMPONADE

Principles

Background and Importance

The reported incidence of acute pericardial tamponade is approximately 2% in patients with penetrating trauma to the chest and upper abdomen; it is rarely seen after blunt chest trauma. It occurs more commonly with stab wounds than with gunshot wounds, and 60% to 80% of patients with stab wounds involving the heart develop tamponade. Patients with acute pericardial tamponade can deteriorate in minutes, but many can be saved if proper steps are taken.

Pathophysiology

The primary feature of a pericardial tamponade is an increase in intrapericardial pressure and volume. As the volume of the pericardial fluid encroaches on the capacity of the atria and ventricles to fill adequately, ventricular filling is mechanically limited, and thus the stroke volume is reduced. This results in decreased cardiac output and ultimately diminished arterial systolic blood pressure and decreased pulse pressure. As little as 60 to 100 mL of pericardial blood may produce the clinical picture of tamponade. Concomitantly, CVP rises because of the mechanical backup of blood into the vena cava.

Several compensatory mechanisms then occur. The heart rate and total peripheral resistance rise in an attempt to maintain adequate cardiac output and blood pressure. A less effective compensatory response, resulting in a greater rise in CVP, is an increase in venomotor tone caused by contractions of the smooth muscles within the wall of the vena cava.

The diagnosis of pericardial tamponade should be suspected in any patient who has sustained a penetrating wound or blunt trauma to the thorax or upper abdomen. One is never certain of the trajectory of the bullet or the length, force, and direction of a knife thrust on initial evaluation. Obviously, wounds directly over the precordium and epigastrium are more likely to produce a cardiac injury resulting in tamponade than those in the posterior or lateral thorax. Nevertheless, it is assumed that a penetrating wound, particularly a gunshot wound, anywhere in the thorax or upper abdomen may have injured the heart. Rapid bedside echocardiography, performed as part of the standard FAST examination, easily detects a pericardial effusion causing cardiac tamponade.

Clinical Features

Patients with cardiac tamponade may initially appear deceptively stable if the rate of bleeding into the pericardial space is slow or if the pericardial wound allows intermittent decompression. Other patients may complain primarily of difficulty breathing, which suggests pulmonary rather than cardiac pathology.

The physical findings of pericardial tamponade—hypotension, distended neck veins, and, rarely, distant or muffled heart tones (known as *Beck's triad*)—may be difficult to identify clinically, especially in the midst of a major resuscitation with concomitant hypovolemia, when the neck veins may be flat. Although the most reliable signs of pericardial tamponade are an elevated CVP (>15 cm H_2O) in association with hypotension and tachycardia, bedside echocardiography performed as part of the FAST examination rapidly diagnoses pericardial tamponade (by identifying pericardial fluid with concomitant tamponade physiology) and has largely replaced the use of CVP measurements to make the diagnosis. Echocardiography also distinguishes pericardial tamponade versus tension pneumothorax when the triad of elevated CVP, hypotension, and tachycardia is present.

Acute pericardial tamponade may be seen with three distinct clinical pictures. If the hemorrhage is confined to the pericardial space, the patient is initially normotensive but will have a tachycardia and elevated CVP. If untreated, most of these patients go on to develop hypotension. If significant hemorrhage has occurred outside the pericardial sac, either through a tear in the pericardium or from associated trauma, the clinical picture is that of hypovolemic shock with hypotension, tachycardia, and a low CVP. If the CVP rises to a level of 15 to 20 cm H_2O with volume replacement but hypotension and tachycardia persist, pericardial tamponade should be considered. The third clinical picture is that of an intermittently decompressing tamponade due to intermittent hemorrhage from the intrapericardial space, partially relieving the tamponade. The clinical picture may wax and wane depending on the intrapericardial pressure and volume and total blood loss. In general, this condition is compatible with a longer survival than are the first two clinical presentations.

Pulsus paradoxus is defined as an excessive drop in systolic blood pressure during the inspiratory phase of the normal respiratory cycle. This sign may be an additional clue to the presence of pericardial tamponade, but it is often difficult to measure during an intensive resuscitation or in the presence of shock.

Diagnostic Testing

Radiology

Ultrasound. Ultrasound enables rapid, accurate, and noninvasive diagnosis of pericardial tamponade. This study can be performed at the bedside in the ED during the initial resuscitation of the patient as part of the FAST examination.[38] Although the sonographic definition of tamponade is the simultaneous presence of pericardial fluid and diastolic collapse of the right ventricle or atrium, the presence of pericardial fluid in a patient with chest trauma is highly suggestive of pericardial hemorrhage (see Fig. 38.17). An indirect sonographic sign of tamponade is the demonstration of a dilated inferior vena cava in a hypotensive patient. EDs in which cardiac ultrasonography is performed with subcostal and long parasternal views have reported a sensitivity and specificity of nearly 100% for the detection of pericardial effusion. Because ultrasound is noninvasive and extremely accurate, its immediate availability in the initial phase of major trauma resuscitation can be very helpful in detecting pericardial fluid before the patient deteriorates hemodynamically.

Radiography. The radiographic evaluation of the cardiac silhouette in acute pericardial tamponade generally is not helpful, unless a traumatic pneumopericardium is present. Because small volumes of hemopericardium lead to tamponade in the acute setting, the heart will typically appear normal. This is in contrast to the "water-bottle" appearance of the heart with chronic pericardial effusion. Usually the latter condition is tolerated for a long period.

Electrocardiography

Many ECG changes of pericardial tamponade have been described in the literature, but few are diagnostic, and each is more likely to be seen with chronic rather than acute tamponade. For example, electrical alternans (in which the morphology and amplitude of the P, QRS, and ST-T waves in any single lead alternate in every other beat [Fig. 38.18]) has been reported to be a highly specific marker of pericardial tamponade. The postulated cause is the mechanical oscillation of the heart in the pericardial fluid, which is called the *swinging heart phenomenon.* Echocardiographic

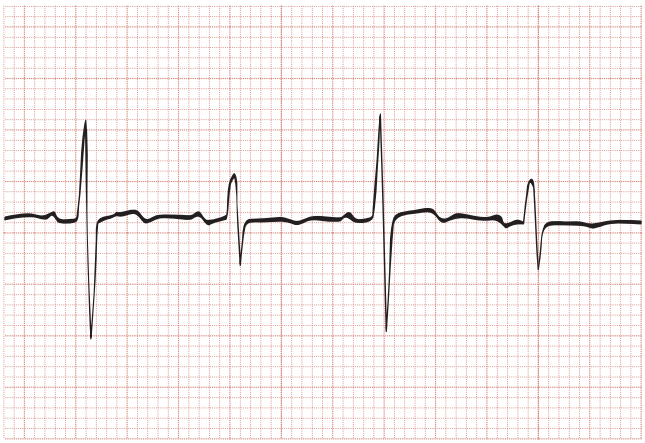

Fig. 38.18. Lewis (S5) lead electrocardiogram (ECG) revealing total electrical alternans of the QRS complexes. (From Sotolongo RP, Horton JD: Total electrical alternans in pericardial tamponade. Am Heart J 101:853, 1981.)

studies have revealed that when fluid accumulates to a critical extent, the frequency of cardiac oscillation may abruptly decrease to half the heart rate. The cardiac position will alternate, with the heart returning to its original position with every other beat, and thus electrical alternans may be seen. Electrical alternans, when present, is pathognomonic for tamponade. However, it is much more common in chronic pericardial effusions that evolve into a tamponade, and it is rarely seen in acute pericardial tamponade. Notably, however, low amplitude of the QRS complexes may be seen as a result of the presence of pericardial effusion.

Management

Field treatment for cases of pericardial tamponade is essentially the same as that outlined for any victim of major trauma. The diagnosis of tamponade should be suspected by the location of penetrating wounds or by the patient's poor response to vigorous volume resuscitation. Tension pneumothorax, which is much more common, mimics certain aspects of acute pericardial tamponade. If the patient is in extremis or the clinical condition rapidly deteriorates, consideration should be given to performing a needle thoracostomy, which, if not therapeutic, suggests pericardial tamponade in the appropriate clinical presentation by virtue of "diagnosis of exclusion." Expedient transport to the nearest trauma center should be paramount.

Upon ED arrival, volume expansion with crystalloid solution via two or three large-bore (14- or 16-gauge) catheters should be established immediately. The presence of a pneumothorax or hemothorax, which is often associated with penetrating cardiac trauma, is treated expeditiously with tube thoracostomy. Bedside echocardiography should be performed as quickly as possible to establish the diagnosis of pericardial tamponade, which then should be followed by emergent surgical repair.

There is increasing controversy regarding the role of pericardiocentesis. In the past, it was recommended that pericardiocentesis be performed for both diagnostic and therapeutic reasons. Aspiration of as little as 5 to 10 mL of blood may result in dramatic clinical improvement. However, it should be emphasized that pericardiocentesis is not a benign or invariably successful procedure. Blood in the pericardial space tends to be clotted, and aspiration may not be possible. Possible complications include the production of pericardial tamponade, the laceration of coronary artery or lung, and induction of cardiac dysrhythmias. Whenever possible, pericardiocentesis should be performed under sonographic guidance, because this approach will increase the success rate and decrease the incidence of complications. A pigtail catheter may be introduced into the pericardial space for repeated aspirations while preparations are underway to quickly transport the patient to the operating room for definitive therapy. If pericardiocentesis is unsuccessful or the clinical status deteriorates, and if acute pericardial tamponade remains important in the differential diagnosis, thoracotomy should be performed as quickly as possible.[39] Patients with penetrating cardiac injury invariably require surgical repair. The location (operating room vs. ED) and timing (immediate vs. urgent) depend on the patient's clinical status.

Fig. 38.19. Emergency department thoracotomy (EDT).

Emergency Department Thoracotomy

EDT is a drastic, dramatic, and potentially lifesaving procedure in which emergency clinicians should be proficient. Although the procedure is not described in detail here, a few technical points merit discussion. A left lateral incision is preferred because it is rapidly accomplished; allows the best exposure of the heart, aorta, and left hilum; and facilitates open cardiac massage and internal defibrillation (Fig. 38.19). With right-sided or multiple injuries, it may be necessary to extend the incision across the sternum and right chest wall, creating a "clamshell" incision. The internal mammary arteries need to be ligated if this maneuver restores effective perfusion. After the heart is sufficiently exposed, the pericardium is vertically incised anterior to the phrenic nerve. Release of a tamponade may rapidly restore cardiac output. The heart is then delivered through the pericardium, and penetrating wounds are identified.

There are several alternatives for repairing cardiac wounds. Small wounds can be compressed by digital pressure to control bleeding en route to the operating room. If the injury is quite large, balloon tamponade can be achieved by applying gentle traction on a Foley catheter inserted into the wound with the balloon inflated with saline. This can temporarily stop the hemorrhage to allow suture repair of the injury (cardiorrhaphy) or to gain time while the patient is transferred to the operating room

for a more definitive surgical procedure. Lacerations of the atria can be temporarily controlled with a vascular clamp.

Suture of cardiac wounds over pledgets is the time-honored and effective technique but is technically more difficult and more time-consuming. The use of a monofilament suture, such as 2-0 Prolene, is recommended. Some trauma surgeons recommend stapling cardiac wounds with standard skin staplers because this technique may be much quicker and equally effective in closing these wounds.

Care is taken to avoid ligating coronary arteries during the repair. Direct insertion of a large-bore catheter (eg, a 5-French catheter) into the left atrial appendage provides a route for rapid infusion of fluids. If the heart is empty or the patient fails to respond to rapid fluid administration, the aorta is cross-clamped to divert cardiac output to the brain and heart. Prolonged ischemia and severe acidosis often result in post-resuscitation myocardial depression with ineffective contraction and diminished cardiac output. Thus the cross-clamp should be temporarily released every 30 to 45 minutes to minimize ischemic complications.

Indications for Emergency Department Thoracotomy. Although it is often tempting to perform EDT on all traumatic arrest victims in the ED, there are many cases in which patients have virtually no chance of survival. In addition, EDT is costly; requires the undivided attention of all personnel in the ED, diverting care from other, more salvageable patients in critical condition; and poses a risk to ED personnel for injury from needle sticks and other blood-contaminated exposures.

Evidence-based guidelines from the Eastern Association for the Surgery of Trauma recommend that EDT be performed on patients who lose pulses but who initially presented to the ED with signs of life after *penetrating* thoracic trauma (see Box 38.4). They conditionally recommend EDT for both patients who present to the ED without signs of life after *penetrating* thoracic trauma and patients who present to the ED with signs of life after *blunt* injury, and recommend against EDT in patients who sustain *blunt* injury and present to the ED pulseless.[39] It is worth emphasizing that EDT is a temporizing measure and should only be performed if definitive treatment is a viable option in the setting to which the patient presents.

BLUNT AORTIC INJURY

Principles

Background and Importance

Blunt aortic injury is a life-threatening injury, usually resulting from sudden deceleration, usually from automobile crashes. Other mechanisms of injury include pedestrians struck by automobiles, motorcycle crashes, airplane crashes, and falls from heights. Despite the improvement in and increased use of restraint systems, the overall incidence of blunt aortic injury associated with fatal automobile crashes has remained unchanged over the past decade.

Blunt aortic injury includes a spectrum of lesions, ranging from a small intimal tear to frank rupture, which usually causes rapid lethal hemorrhage. The most common sites of injury are the aortic isthmus and the ascending aorta just proximal to the origin of the brachiocephalic vessels. Sixty percent to 90% of patients with blunt aortic injury die at the site of accident or within hours of hospital admission. However, an increasing number of patients arrive at a treatment facility because of improvements in out-of-hospital care, more appropriate resuscitation in the field, and rapid transportation to a trauma center. The early survival rate of such patients depends on the initial resuscitation and/or the timeliness and correct choice of diagnostic procedures. A rapid and accurate diagnosis is thus mandatory to optimize treatment and maximize odds of survival.

Pathophysiology

The descending thoracic aorta is relatively fixed and immobile because of its tethering by intercostal arteries and the ligamentum arteriosum. With sudden deceleration, the more mobile aortic arch swings forward, producing a shearing force or "whiplash effect" on the aorta at the isthmus. A bending stress at the isthmus, created by sudden lateral oblique chest compression, may also result in rupture by causing flexion of the aortic arch on the left mainstem bronchus and the pulmonary artery. Forces created by the whiplash effect or lateral oblique compression may not be sufficient to provoke aortic tears. It is now postulated that those injuries may be caused by inferior and posterior rotation of anterior thoracic osseous structures (manubrium, first rib, and medial clavicles), pinching and shearing the interposed aorta as they strike the vertebral column.

Rupture of the ascending aorta just distal to the aortic valve likely occurs through a different mechanism. At the time of rapid deceleration and chest compression, the heart is displaced into the left posterior chest, which causes a shearing stress just above the aortic valve. A sudden increase in intra-aortic pressure, "the water hammer effect," may cause an explosive rupture of the aorta at this location. Involvement of the coronary ostia with coronary artery occlusion may occur in association with tears to the ascending arch. The intraluminal pressure tolerance of the aorta may be exceeded in a high-speed MVC.

A total of 80% to 90% of aortic tears occur in the descending aorta at the isthmus, just distal to the left subclavian artery (Fig. 38.20). Less common sites of involvement are the ascending aorta, the distal descending aorta at the level of the diaphragm, the midthoracic descending aorta, and the origin of the left subclavian artery. Although ruptures of the ascending aorta are much less common than those of the descending aorta, they have a 70% to 80% incidence of associated lethal cardiac injuries. This is in contrast to ruptures at the isthmus, which have a 25% incidence of associated cardiac injuries. Lethal cardiac injuries commonly

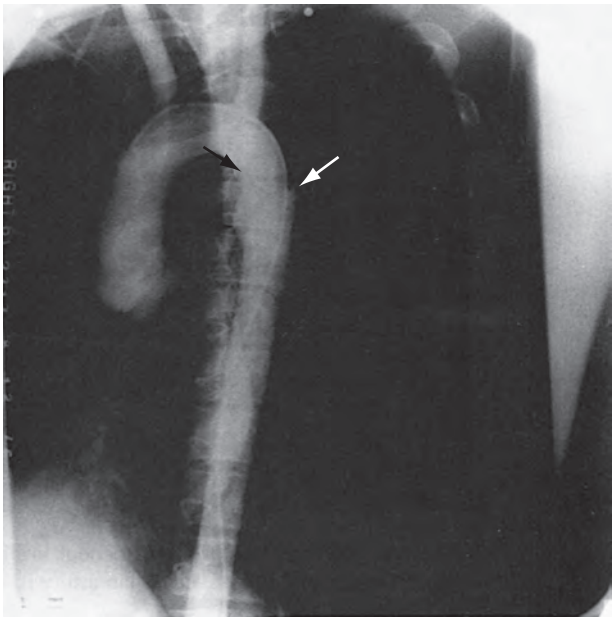

Fig. 38.20. Aortogram shows tear in aorta *(arrows)* at the most common location, at or just distal to takeoff point of left subclavian artery, which is not visualized.

include pericardial tamponade, aortic valve tears, myocardial contusion, or coronary artery injuries. Passenger ejection, pedestrian impact, severe falls, and crush injuries commonly result in ascending thoracic aortic ruptures. Survival long enough to be evaluated in the ED is rare among patients who sustain an ascending aortic rupture.

Aortic rupture may occur from causes other than high-speed MVC deceleration. Rupture has been documented as a complication of external cardiac massage and has been known to occur after fracture-dislocations of the thoracic spine, presumably as a result of direct shearing force. Vertical deceleration injuries resulting from falls can cause a rupture of the ascending aorta by producing an acute lengthening of the ascending aorta. This is the likely mechanism responsible for aortic rupture in the setting of airplane and elevator accidents. Direct kicks by animals, crush injuries, sudden burial by landslide, and air bag deployment have also been reported as causes of aortic rupture. Direct compression of the compliant thorax has been postulated to contribute to aortic rupture in children. Displaced fractures of the sternum, ribs, and clavicle have also been shown to directly lacerate the aorta.

Clinical Features

The possibility of aortic disruption should be considered in every patient who sustains a severe deceleration injury, because approximately 30% of surviving patients with blunt aortic injury will die within the first 24 hours without treatment. This is especially true if the automobile was moving in excess of 45 mph or if there is evidence of severe blunt force to the chest (eg, from a damaged steering wheel). In the case of any moderate- or high-speed MVC, it is imperative that paramedics carefully evaluate the extent of damage to the vehicle, the complaints of the victims, and the physical manifestations of blunt chest trauma. This information should be promptly relayed to the emergency clinician.

Despite the severe nature of the injury, the clinical manifestations of an aortic rupture are often deceptively meager. Associated pulmonary, neurologic, orthopedic, facial, and abdominal injuries are commonly present. Coexisting injuries can mask the signs and symptoms of an aortic injury or divert the physician's attention away from the more lethal aortic rupture. The absence of any external evidence of a chest injury does not eliminate the possibility of an aortic tear. One-third to one-half of patients reported in the literature have no external signs of chest trauma.

The most common symptom is interscapular or retrosternal pain. It is often found in nontraumatic aortic dissection but is present in only 25% of patients with a traumatic aortic disruption. Other symptoms described in the literature but uncommonly present include dyspnea resulting from tracheal compression and deviation, stridor or hoarseness caused by compression of the laryngeal nerve, dysphagia caused by esophageal compression, and extremity pain caused by ischemia from decreased arterial flow.

Clinical signs are uncommon and nonspecific. Generalized hypertension, when present, may be an important clinical sign. Sympathetic afferent nerve fibers, located in the area of the aortic isthmus, are capable of causing reflex hypertension as a response to a stretching stimulus. The presence of a harsh systolic murmur over the precordium or posterior interscapular area may be heard in up to one-third of patients. The murmur is thought to result from the turbulent flow across the area of transection. A less commonly encountered physical finding is a swelling at the base of the neck caused by the extravasation of blood from the mediastinum, which results in an increased neck circumference or a pulsatile neck mass. Other clinical signs suggestive of aortic rupture include lower extremity pulse deficit and lower extremity paralysis. Initial chest tube placement output in excess of 750 mL is also suggestive of aortic rupture, especially if the hemothorax is left sided. However, the physical examination is neither sensitive nor specific for aortic injury.

Diagnostic Testing

Chest Radiography

Radiography of the chest can be a valuable tool when aortic rupture is suspected. An increase in the width of the superior mediastinum is the most sensitive sign and is found in the majority of aortic ruptures (Fig. 38.21).

However, specificity of this radiologic sign may be as low as 10%; mediastinal widening may be caused by venous bleeding from a clavicle, thoracic spine, or sternal fracture; pulmonary contusions; a previous mediastinal mass; a misplaced CVP catheter; or magnification caused by the anteroposterior and supine position of a portable chest radiograph. Hence the sign is not pathognomonic for aortic rupture. Every effort should be made to obtain a standard upright inspiratory posteroanterior film, if clinically feasible, before a mediastinum is declared abnormal, to avoid false-positive interpretations. However, although mediastinal widening may be indicative of aortic rupture, its absence does not preclude the injury. Up to nearly half of patients with blunt aortic injury may have a normal mediastinum on chest radiography.[40] Given this, we recommend the use of chest CT scanning in patients with suspected aortic rupture, regardless of x-ray findings.[40]

Chest Computed Tomography Scan

Chest CT scanning is the gold standard test for blunt aortic injury and has replaced aortography as the test of choice. CT scans have almost 100% sensitivity and specificity for rapidly detecting aortic injury while requiring only IV contrast administration (Figs. 38.22 and 38.23). A normal aortic contour on CT, even in the presence of a mediastinal hematoma, has been shown to be highly accurate in excluding thoracic aortic disruption (Figs. 38.24 and 38.25).[41]

As a result of the improvements in CT scanning technology, more subtle aortic lesions are now being identified, which has led to the term "minimal aortic injury." A minimal aortic injury is defined as an aortic injury with an intimal flap less than 1 cm, and no or minimal periaortic mediastinal hematoma. Up to 10% of patients with blunt aortic injury diagnosed on CT scan may have

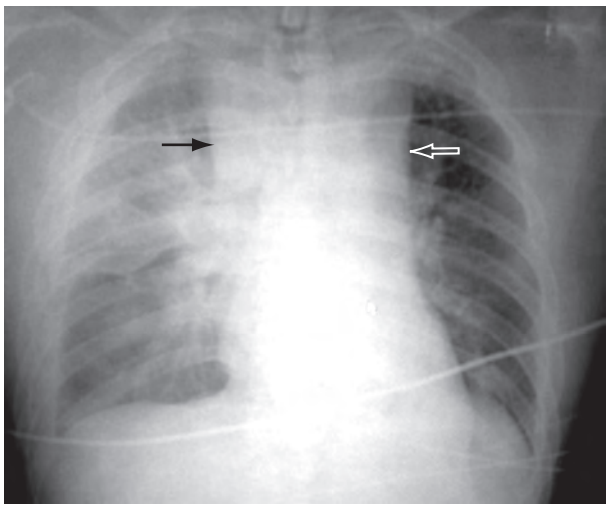

Fig. 38.21. Anteroposterior radiograph of the chest showing wide mediastinum *(arrows)*.

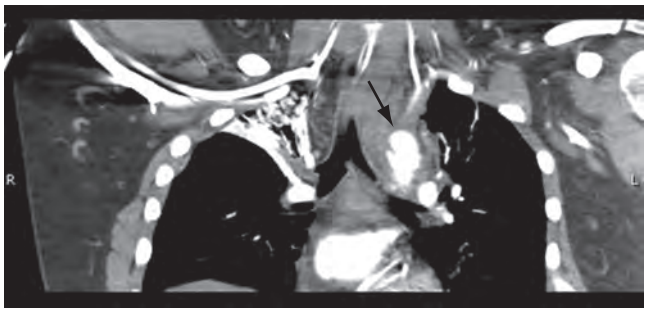

Fig. 38.22. Chest computed tomography (CT) scan showing aortic intimal tear with surrounding mediastinal hematoma *(arrow).*

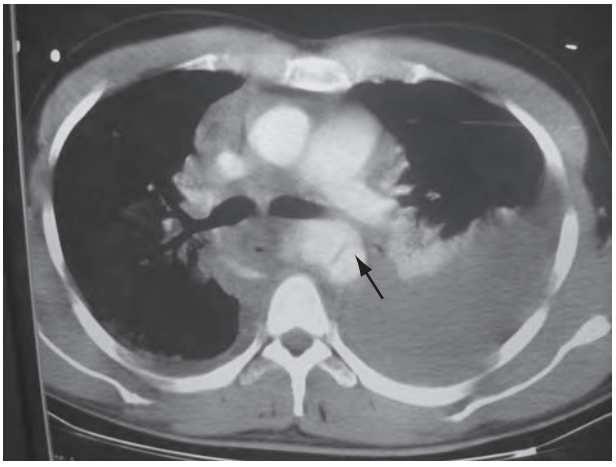

Fig. 38.23. Chest computed tomography (CT) scan demonstrating periaortic hemorrhage and an intimal flap *(arrow).*

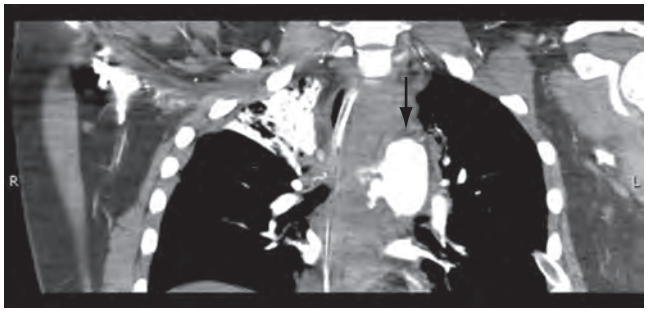

Fig. 38.24. Chest computed tomography (CT) scan showing aortic injury with active extravasation *(arrow).*

a minimal aortic injury.[42] It is felt that minimal aortic injuries carry a relatively low risk of rupture. Although at least two grading systems linking CT findings of blunt aortic injury to outcomes have been developed, neither has been externally validated.[43,44] In lieu of a validated decision instrument, we recommend following these patients with serial CT scans. If the injury is associated with significant thrombus, periaortic hematoma, lumen encroachment, or pseudoaneurysm, the patient can be treated via endograft.

Management

Stabilization and Empirical Therapy

Due to the ever-present risk of sudden rupture and exsanguination, repair of the aortic injury should be performed as soon as the diagnosis is made. Management of the patient with multiple injuries who has documented rupture of the thoracic aorta

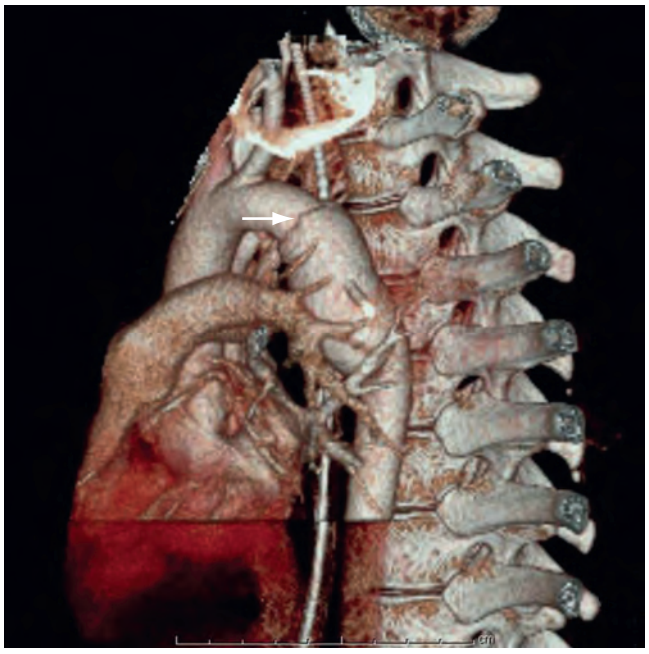

Fig. 38.25. Three-dimensional reconstruction of chest computed tomography (CT) scan showing aortic injury *(arrow).*

depends on the nature of associated injuries. Endovascular or surgical repair of the aortic rupture should be delayed in the presence of life-threatening intracranial or intra-abdominal injury or profuse retroperitoneal hemorrhage.[40] Consideration for delay of the procedure should be made for patients at high risk for infection (eg, those who have extensive body surface burns, contaminated large open wounds, established sepsis, or severe respiratory insufficiency caused by thoracic trauma).

Careful regulation of blood pressure is mandatory until definitive surgical repair can be performed. If operative repair is delayed, the systolic blood pressure should be maintained between 100 and 120 mm Hg. The objective of lowering the blood pressure is to decrease the shearing jet effect of an elevated pulse pressure, thus decreasing the possibility of continued adventitial dissection and subsequent free rupture.

Esmolol, a short-acting titratable beta-blocker, is ideally suited for this purpose because, unlike nitroprusside sodium, it decreases the pulse pressure and minimizes the shearing effect on the intact adventitia of the aorta.[45] Esmolol can be initiated with a bolus of 0.5 mg/kg over 1 minute, followed by an infusion of 0.05 mg/kg/min (titrated upward in 0.05 mg/kg/min increments to a maximum of 0.3 mg/kg/min). If blood pressure is not adequately controlled, nitroprusside sodium can be added as a second agent, beginning at a dose of 0.25 to 0.5 mcg/kg per minute.

Definitive Management

Many surgical techniques have been described since the first successful repair by Passaro and Pace in 1959.[46] The pathologic condition found dictates the type of repair, and a synthetic graft is often required because of extensive tension on the vessel walls or jagged torn ends of the vessel. However, open repair can have associated complications of stroke, paraplegia, and renal failure due to aortic clamp time.

Endovascular Repair. A number of studies indicate that success rates and complication rates are likely better than those of traditional open surgical repairs and that the risk of major surgery and subsequent paraplegia from prolonged aortic clamping is significantly reduced with endovascular repair. Current

guidelines recommend endovascular treatment for patients without contraindications.[40]

ESOPHAGEAL PERFORATION

PRINCIPLES

Background and Importance

The classic description of esophageal perforation resulting from forceful vomiting was published in 1724 by Boerhaave, and from 1724 to 1941 the occurrence of Boerhaave's syndrome was almost uniformly fatal.[47] In 1941 the first successful surgical treatment, a drainage procedure, was reported, and in 1947 the first successful closure of a ruptured esophagus was described. Since then, improved surgical techniques, greater physician awareness leading to a more prompt diagnosis, the availability of more effective antibiotics, and better general supportive measures have reduced the mortality to approximately 20%. Mortality data cited for perforation are affected by several variables, such as location (with perforations of the thoracic segment having the highest mortality rate), mechanism of injury, time elapsed between injury and diagnosis, the presence of preexisting esophageal disease, and general health of the patient.

Pathophysiology

The anatomic feature responsible for the prolonged morbidity and high mortality associated with esophageal perforation is the lack of an esophageal serosal covering that allows perforation at any level direct access to the mediastinum. Perforations in the upper or cervical esophagus enter the retropharyngeal space, where fascial planes extend from the base of the skull to the bifurcation of the trachea. Perforations in the midesophagus and lower esophagus enter directly into the mediastinum. Only the thin mediastinal pleura prevents free access to the entire pleural cavity, and this barrier is commonly overcome by continued drainage and the massive exudative inflammatory reaction induced by chemical and bacterial mediastinitis. When the mediastinal pleura are penetrated, the negative pressure generated by respiratory efforts tends to increase soilage by promoting drainage from the gastrointestinal tract into the mediastinum and pleural space.

When esophageal rupture results from forceful emesis, as in cases of Boerhaave's syndrome, the intrinsic weakness of the left posterior distal esophagus is important. Other areas (including cervical, midthoracic, and infradiaphragmatic sites) have been reported only rarely to rupture secondary to emesis. In addition, the esophagus has three areas of anatomic narrowing: (1) the cricopharyngeal muscle near the esophageal introitus, (2) the level at which the esophagus crosses the left mainstem bronchus and the aortic arch, and (3) the gastroesophageal junction. In the absence of a preexisting esophageal disease (such as, carcinoma), it is unusual for a perforation caused by a foreign body to occur anywhere other than at these three sites. Foreign bodies may cause perforation by direct penetration, pressure, or chemical necrosis.

CLINICAL FEATURES

The most reliable symptom of an esophageal injury is pleuritic pain localized along the course of the esophagus that is exacerbated by swallowing or neck flexion (Fig. 38.26). Pain may be located in the epigastrium, substernal area, or back; usually worsens over time; and may migrate from the upper abdomen to the chest. As the infectious process worsens, dyspnea usually ensues.

The early physical signs of an esophageal perforation are sparse. As air and caustic contaminated material move through the esophageal tear into the mediastinum and pleural space, and before any subcutaneous air is palpable at the root of the neck, the mediastinal air may impart a nasal quality to the voice. Mediastinal air may surround the heart and produce a systolic

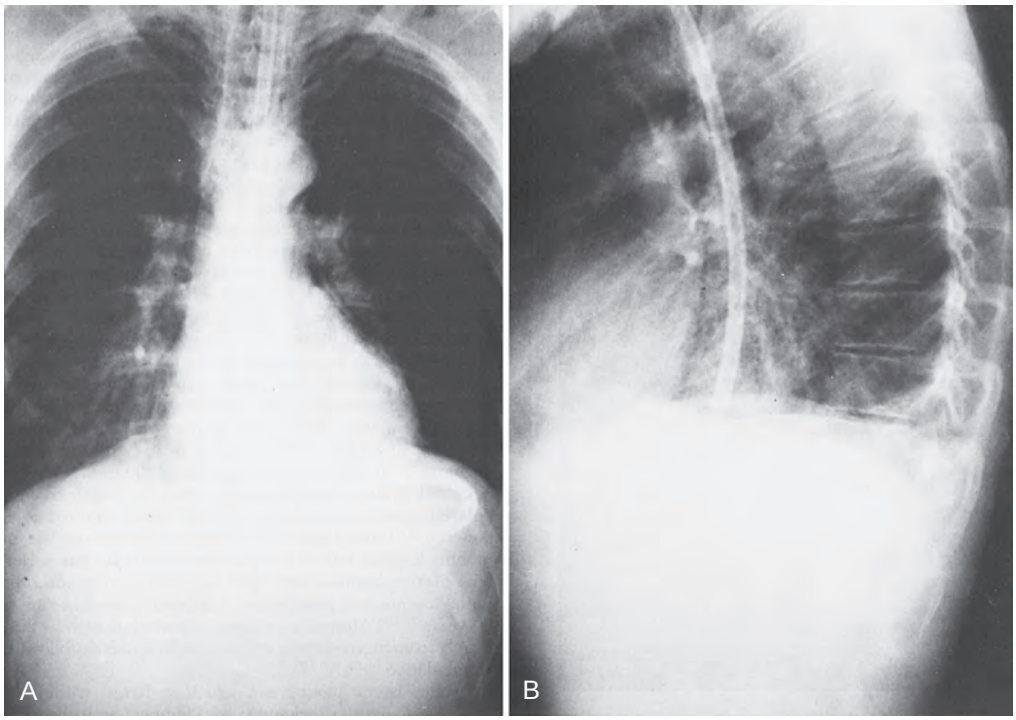

Fig. 38.26. A, Chest radiograph of a 36-year-old man with acute onset of pleuritic chest pain after forceful vomiting. **B,** Chest radiograph shows mediastinal and subcutaneous air typical of ruptured esophagus. Mediastinum is not yet widened, and there is no soilage of the pleural cavity.

BOX 38.5

Most Common Causes of Esophageal Perforation

Iatrogenic
Foreign bodies
Caustic burns
Blunt or penetrating trauma
Spontaneous rupture (post emetic or Boerhaave's syndrome)
Postoperative breakdown of anastomosis

crunching sound (Hamman's crunch). As air and fluid move into the pleural space, signs of a hydropneumothorax or an empyema may develop. Eventually the air travels into the subcutaneous tissues, dissecting into the neck, where subcutaneous emphysema may first become evident. This classic sign is present in only approximately 60% of patients, however, and in the absence of a tracheal injury, it may occur in only 30%. The most common causes of an esophageal perforation are shown in Box 38.5.

Iatrogenic

Most esophageal perforations are iatrogenic, most commonly as a complication of instrumentation. The rigid endoscope is the most common offender, particularly when general anesthesia is used. Although use of the flexible endoscope has made this complication less likely, the total number of perforations has increased as more procedures are performed. Injuries tend to occur near the cervical esophagus as the endoscope is inserted. Endoscopic procedures that are too vigorous in the presence of a corrosive burn or carcinoma are also a common cause of iatrogenic esophageal injury. In the ED, nasotracheal or nasogastric intubations are the most common causes of iatrogenic perforation, with the perforation usually occurring in the pyriform sinus.

The use of an esophageal obturator airway was also associated with occasional esophageal trauma, specifically midesophageal perforation. Use of the esophageal obturator airway's successors, the laryngotracheal Combitube and the King airway, do not seem to be associated with trauma more severe than occasional esophageal abrasions or contusions.

Foreign Bodies

Foreign bodies can cause an esophageal injury by direct laceration, by pressure necrosis, or during endoscopic removal. Small perforations tend to seal without sequelae, but pressure necrosis or lacerating injuries provide ample access to the mediastinum. Foreign bodies usually lodge in the cervical esophagus. In children younger than 4 years old, the cricopharyngeal narrowing is the usual point of foreign body impaction. After 4 years old, most objects pass this region and traverse the remaining normal esophagus. In adults, a foreign body impaction, especially in cases of repeated episodes, raises the possibility of a stricture and warrants further investigation.

Caustic Burns

Caustic burns of the esophagus occur from intentional or accidental ingestion of acid or alkali. There are two peaks of incidence: (1) from 1 to 5 years old, which is when ingestion is usually of a small amount of material and accidental, and (2) in the teens and 20s, when larger quantities are ingested during suicide attempts. Symptoms include hematemesis, respiratory distress, vomiting, drooling, or the presence of oropharyngeal lesions on physical examination.

The liquefaction necrosis classically resulting from strong alkali burns (pH >12) is more likely to cause esophageal perforation than the coagulation necrosis resulting from strong acid burns (pH <2). Individuals ingesting alkali substances with a pH less than 11.5 rarely sustain injuries more serious than superficial mucosal burns. Acid ingestions cause damage more frequently in the stomach than in the esophagus.

Endoscopy within the first 6 to 18 hours may be used to determine the extent of the injury and to guide therapy. Although admission after significant ingestion is the rule, some authors suggest that in the setting of accidental ingestion in children and in the absence of symptoms, endoscopy and admission may not be indicated. Esophagoscopy is commonly undertaken to ascertain the presence or absence of esophageal injury. Advancing the esophagoscope beyond the first burn in the esophagus increases the risk of perforation and is a common iatrogenic cause of esophageal perforation.

Penetrating and Blunt Trauma

Because of its well-protected position posteriorly, esophageal trauma is rare and usually not an isolated injury. Cervical esophageal injuries are the most common because of a lack of protection by the bony thorax, and the trachea is the most common associated site of injury. In some cases, the esophageal injury may be overlooked initially because of the dramatic presentation of a patient with a tracheal injury.

Typical symptoms seen in cervical esophageal injuries include neck pain, dysphagia, cough, voice changes, and hematemesis. Physical findings may include neck tenderness, resistance to flexion, crepitus, or stridor. In one large series, the most common life-threatening problem in the ED was compromise of the airway. Most of these cases were handled with rapid sequence intubation, but a significant number (12%) of patients required cricothyroidotomy.

If the patient's condition is stable, a preoperative esophagogram with a water-soluble agent should precede any endoscopy. Although chest and neck radiograph and CT also may be used to diagnose this injury, emergent bedside flexible endoscopy seems to be the test of choice to confirm negative findings on esophagography (especially in the setting of penetrating trauma). Operative repair is indicated in most of these injuries (>90%) and should be done as quickly as possible to avoid the development of fistulae, mediastinitis, or abscess formation.

Spontaneous Rupture

Spontaneous esophageal rupture, post-emetic rupture, and *Boerhaave's syndrome* are synonymous terms. This esophageal injury is associated with a poor prognosis because the forces required to rupture the esophagus result in almost instantaneous and massive mediastinal contamination. The distal esophagus is the usual site of injury, with a longitudinal tear occurring in the left posterolateral aspect. More than 80% of these injuries occur in middle-aged men who have ingested alcohol and large meals. Increases in intra-abdominal pressure resulting from blunt trauma, seizures, childbirth, laughing, straining at stool, and heavy lifting have all been reported to cause this injury.

DIAGNOSTIC TESTING

The diagnosis of esophageal perforation is aided by consideration of clinical circumstances. In patients with classic Boerhaave's syndrome, emesis is followed by severe chest pain, subcutaneous emphysema, and cardiopulmonary collapse. Development

BOX 38.6

Clinical Conditions That May Mimic Esophageal Perforation

Spontaneous pneumomediastinum
Aortic aneurysm (thoracic)
Pulmonary embolus
Perforated peptic ulcer
Myocardial infarction (MI)
Pancreatitis
Mesenteric thrombosis
Cholecystitis
Pneumonia

of these signs and symptoms after instrumentation of the esophagus or removal of an esophageal foreign body is relatively straightforward. One-third of cases of perforated esophagus are atypical, however. A careful history and physical examination supplemented by appropriate imaging studies enable the clinician to diagnose a subtle case at an early stage. In considering any of the diagnoses listed in Box 38.6, a perforated esophagus should also be considered.

Radiology

The radiographic examination usually suggests the diagnosis of an esophageal perforation. The classic chest radiograph findings are mediastinal air (with or without subcutaneous emphysema), left-sided pleural effusion, pneumothorax, and widened mediastinum. Lateral views of the cervical spine may reveal air or fluid in the retropharyngeal area that is characteristic of a cervical esophageal perforation but also is found when perforations in the lower parts of the esophagus release air or fluid that dissects superiorly (Fig. 38.27). Water soluble diatrizoate meglumine (Gastrografin) is preferred for visualization in cases of suspected esophageal perforation. It does not obscure visualization during subsequent endoscopy, and it produces less mediastinal soiling than barium. Then, if no leak is found, a barium study may be undertaken to better define the mucosal detail.

Endoscopy

Endoscopy, similar to contrast studies, is not an infallible aid in establishing the presence or absence of an esophageal perforation. The size and location of the perforation and the skill of the endoscopist are important factors in the low incidence of false-negative studies. If the accuracy of the endoscopy is in doubt, an esophagogram should be performed. Helical CT with dilute oral contrast has been reported as a safer, faster, and less manpower-intensive diagnostic examination. Some of the abnormalities that may be seen on CT scan include extraluminal air, periesophageal fluid, esophageal thickening, and extraluminal contrast. These CT findings may be the first clue to the correct diagnosis of esophageal perforation.

MANAGEMENT

Early diagnosis can best be accomplished if one is aware of the pathophysiology and clinical settings in which esophageal perforations occur. Time is crucial in minimizing the mortality and morbidity of this condition. If the diagnosis is strongly suggested or confirmed, management should include broad-spectrum antibiotics (covering oral flora), volume replacement, and airway maintenance.[48] An emergency surgical consultation should be obtained because prognosis worsens as time passes, with mortality almost doubling in the first 12 hours.

Fig. 38.27. Lateral view of the cervical spine revealing air in the retropharyngeal area *(arrow)*.

Although operative therapy is standard, nonoperative therapy is an option for patients with well-contained perforations, with minimal mediastinal involvement, and without evidence of sepsis. In such cases, the patient is placed on *nil per os* (nothing by mouth) (NPO) status for at least 72 hours, broad-spectrum antibiotics are initiated, and usually total parenteral nutrition treatment is begun. The use of nasogastric tubes should be discouraged, because they may increase gastroesophageal reflux and worsen the contamination of the mediastinum.

KEY CONCEPTS

- Even relatively minor chest wall injuries, such as rib fractures, may result in serious complications in elderly patients and patients with preexisting pulmonary disease if adequate analgesia and close follow-up care are not provided.
- Unless there are abnormalities on the electrocardiogram (ECG) or an elevated serum troponin level, there is no need to pursue the diagnosis of myocardial contusion with more sophisticated tests.
- Many patients with myocardial rupture or traumatic aortic rupture survive to reach the hospital and can be salvaged with rapid diagnosis and intervention.
- Pericardial tamponade can be diagnosed accurately before hemodynamic decompensation occurs by standard cardiac ultrasound performed by emergency clinicians.
- Chest computed tomography (CT) scan is the test of choice for blunt aortic injury even in the presence of normal chest radiographs.
- The NEXUS-Chest CT criteria can be used to determine the need for chest CT in patients with blunt trauma.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 38: QUESTIONS & ANSWERS

38.1. An 18-year-old man presents after a motor vehicle collision (MVC) in which he was ejected from the vehicle. The paramedics have been administering bag-valve-mask ventilation en route because of respiratory distress and now report increased resistance with ventilations. The patient has decreased breath sounds on the left. His blood pressure is 80/40 mm Hg, and his pulse is 145 beats per minute. His respirations are agonal, with a rate of 5 breaths per minute. Which of the following is the most appropriate next step in the management of this patient?

A. Anteroposterior chest radiograph
B. Emergency department thoracotomy (EDT)
C. Endotracheal intubation
D. Needle decompression
E. Tube thoracostomy

Answer: D. This clinical scenario depicts a patient with a tension pneumothorax. He has decreased blood pressure, decreased breath sounds, and, most important, an increased resistance to ventilation, which is the earliest sign of the development of a tension pneumothorax. Immediate decompression with a large-bore needle is the correct initial management in this condition.

38.2. Which of the following is the most sensitive electrocardiogram (ECG) manifestation of myocardial contusion?
A. Biphasic T wave
B. Left bundle branch block
C. Right bundle branch block
D. Sinus tachycardia
E. Transient ST segment elevation

Answer: D. Sinus tachycardia is present in approximately 70% of patients with documented myocardial contusion and is the most sensitive sign for this condition. It is, however, also the least specific.

38.3. A patient presenting with blunt thoracic trauma complains of shortness of breath and chest pain. On physical examination, he is tachypneic with chest wall bruising and moist rales on the right side on auscultation. Which of the following is the least likely finding?
A. Consolidation within 6 hours of injury
B. Diffuse patchy alveolar infiltrates on chest radiograph in 24 hours
C. Low partial arterial pressure of oxygen (Pao_2) on arterial blood gas sampling
D. Patchy alveolar infiltrate on chest radiograph within minutes of injury
E. Rib fractures

Answer: B. This patient has physical findings consistent with pulmonary contusion. All answers are correct except B. Delayed onset of diffuse alveolar infiltrates is more consistent with acute respiratory disease syndrome (ARDS). The development of ARDS is diffuse and usually delayed, with onset typically between 24 and 72 hours after injury.

38.4. A 55-year-old man complains of chest wall pain after a high-speed motor vehicle collision (MVC). He has ecchymosis of the left lateral chest wall. You notice that there is outward movement of the left lateral chest wall on expiration. Which of the following statements regarding this patient's problem is *not true*?
A. Chest radiograph likely demonstrates parenchymal contusions.
B. Intubation splints the chest wall internally.
C. Multiple rib fractures are likely.
D. Positioning of patient with injured side down improves symptoms.
E. The cornerstone of treatment is pulmonary physiotherapy.

Answer: D. This patient has a flail chest. Out-of-hospital or emergency department (ED) stabilization of the flail segment, by positioning the person with the injured side down or placing a sandbag on the affected segments, has been abandoned. Endotracheal intubation and positive-pressure ventilation will internally splint the chest wall, making the flail segment difficult to detect on physical examination. The cornerstones of therapy include pulmonary physiotherapy, effective analgesia, selective use of endotracheal intubation and mechanical ventilation, and close observation for respiratory compromise.

38.5. A 50-year-old woman is brought in by emergency medical services on a backboard after a motor vehicle collision (MVC), complaining of shortness of breath. She has decreased breath sounds on the right side of the chest. A chest tube is placed, with a return of 200 mL of blood in the first hour, 200 mL in the second hour, and 350 mL in the third hour. What is the next step in the management of this patient?
A. Check coagulation profile
B. Conservative management and transfusion as needed
C. Emergency thoracotomy
D. External fixation of rib fractures
E. Insertion of a second thoracostomy tube

Answer: C. Immediate drainage of more than 1500 mL of blood from the pleural cavity is usually considered an indication for urgent thoracotomy. Perhaps even more predictive of the need for thoracotomy is a continued output of at least 200 mL/hr for 3 hours.

38.6. A 37-year-old man presents with chest pain after a motor vehicle collision (MVC). He states that his chest hit the steering wheel. On initial evaluation, the patient is without fractures of the ribs or sternum, but there is a small chest wall contusion. The initial chest radiograph is negative, and the electrocardiogram (ECG) shows nonspecific ST-T wave changes. What is the next step in the emergency management of this patient?
A. Admit to telemetry for 23-hour observation
B. Discharge home after repeat ECG and troponin at 6 hours
C. Discharge home after repeat ECG in 1 hour
D. Discharge home if echocardiogram is negative
E. Discharge home if initial troponin is negative

Answer: B. In patients who have minor injuries and are otherwise asymptomatic, elevated troponin levels and minor ECG abnormalities do not necessarily indicate a clinically significant myocardial contusion. Very few of these patients will develop complications. However, normal troponin level (4 to 6 hours after injury), along with normal (or unchanged) ECGs, correlate with minimal risk of cardiac complications. Echocardiography is rarely required in this low-risk subset of patients who have minor injuries and are otherwise asymptomatic.

38.7. A 30-year-old woman presents intubated by emergency medical services on a backboard with C spine immobilization. She was found unresponsive and hypotensive after a front-end collision. She was the driver of the vehicle and unbelted. Despite fluid resuscitation, the patient continues to be tachycardic and hypotensive. On physical examination, you note jugular venous distention (JVD) and a harsh murmur that sounds like a splashing mill wheel. An electrocardiogram (ECG) reveals electrical alternans. Which of the following statements is true regarding the patient's underlying problem?
A. Echocardiogram will reveal diastolic collapse of the right ventricle and fluid in the pericardium.
B. Focused assessment with sonography in trauma (FAST) will demonstrate echogenicity in Morrison's pouch.
C. Patchy consolidation will be seen on chest radiograph.
D. Pericardiocentesis is not indicated.
E. She will have a negative focused abdominal sonogram.

Answer: A. Early use of emergency department (ED) ultrasonography may facilitate the early diagnosis of cardiac rupture and pericardial tamponade. The combination of shock and JVD (or an elevated central venous pressure [CVP]) in a patient with blunt chest trauma should immediately suggest pericardial tamponade.

CHAPTER 39

Abdominal Trauma

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PRINCIPLES

Background

The management of abdominal trauma relies on applying knowledge and organization to key clinical features and the timely use of diagnostic procedures. Advancements in imaging have helped to decrease missed or delayed diagnoses, yet abdominal injuries can be notoriously occult, requiring both diligence and vigilance to achieve the best outcomes.[1]

Penetrating Abdominal Trauma

Whether by accident or intention, penetrating trauma can result from a wide variety of weapons or instruments, and certain elements of therapy vary accordingly. The careful integration of physical examination and certain diagnostic procedures, notably local wound exploration (LWE), ultrasonography, computed tomography (CT), laparoscopy, and in rare instances, diagnostic peritoneal tap (DPT), now provides an accurate and reliable means of determining whether laparotomy should be undertaken. The approach varies according to the clinical status of the patient, the instrument responsible for injury, and the site of penetration. Nonoperative management has gained favor predominantly for stab wounds, though also for carefully selected gunshot wounds, with the intent to reduce the incidence of and morbidity from nontherapeutic laparotomies.[2,3]

Wounds from stabbing implements occur nearly three times more often than from firearms, but the latter are responsible for 90% of penetrating trauma mortality. The small intestine, colon, and liver are the most likely organs to sustain injury after penetrating trauma. The highest risk of death from penetrating abdominal injury occurs among African Americans in the 15- to 34-year-old age range, followed by Hispanic persons in that same age group. The rate for non-Hispanic whites is greatest at 75 years of age and older. The predominant intent is homicide among African Americans and suicide among non-Hispanic whites.

The use of firearms in the United States contributes heavily to the morbidity and mortality of trauma. The number of homicides committed with firearms exceeds the number of homicides resulting from all other forms of violence combined. More than 850,000 American civilians were killed by bullets in the 20th century.[4] Please see Chapter e2 for a more complete discussion of injury prevention.

Blunt Abdominal Trauma

Despite advances in imaging, blunt injuries carry a greater risk of mortality than penetrating injuries because they are more difficult to diagnose and are commonly associated with severe trauma to multiple intraperitoneal organs and extra-abdominal systems. Historical data may be incomplete, absent, or presumptive. The symptoms and signs can be unreliable and obfuscated by head injury, alcohol, or other toxins. The likelihood of extra-abdominal systems trauma adds further complexity, underscoring the need for a carefully organized approach.

The spleen is the organ most often injured; and in nearly two thirds of these cases, it is the only damaged intraperitoneal structure. The liver is the second most commonly injured intra-abdominal organ, and injury to any hollow viscus is uncommon by comparison, with the intestine is the most likely hollow viscus to be damaged. Most cases of blunt abdominal trauma are caused by motor vehicle collisions, whereas blows to the abdomen and falls make up a minority of blunt abdominal trauma cases.

Anatomy and Physiology

The abdominal cavity and its contents can be reached not only through the anterior abdominal wall and lower chest but also through the flank, back, and buttocks. Rarely, missiles lodge intraperitoneally after traversing proximal extremities, as well. The *anterior abdomen* is defined as that region between the anterior axillary lines from the costal margins to the groin creases. The *low chest* begins at the nipple line or fourth intercostal space anteriorly and the inferior scapular tip or seventh intercostal space posteriorly, and then extends down to the inferior costal margins. The *flank* is between the anterior and posterior axillary lines bilaterally from the inferior scapular tip to the iliac crest. The *back* is between the posterior axillary lines, beginning at the inferior scapular tip and extending down to the iliac crest. The intraperitoneal cavity is vulnerable when penetration occurs as high as the fourth intercostal space anteriorly and the sixth or seventh laterally and posteriorly because the diaphragm can ascend to this level during expiration. Simultaneous thoracic and abdominal penetration can be found in 20% to 40% of cases of abdominal thoracic trauma. Scrutiny of entrance and exit sites, as well as wound tracts, is imperative.

Pathophysiology

Penetrating Abdominal Trauma

Penetrating abdominal injuries predominantly are caused by knives and firearms. Injuries caused by impalement objects, such as fences, stakes, or similar objects are treated as stab wounds. Various propelled missiles from lawn mowers or other machinery are managed as gunshot wounds, based on their velocity. Fragmentation injuries produced by grenades and bombs are rare in this country, but industrial explosions can produce similar injuries, and blunt abdominal trauma from blast effect can coexist in this setting. Domestic terrorist acts may involve improvised bombs that are loaded with shrapnel, such as BBs, ball bearings, or nails, with penetrating abdominal trauma often the least dramatic of the injuries.[5]

The liver, followed by the small bowel, is the organ most often damaged by stab wounds, in keeping with the location and surface area of these structures. The frequency of organ injury caused by gunshot wounds is greatest for small bowel, followed by the

colon, and then the liver. Typically, multiple organ injuries are sustained.

Stab Wounds. A variety of implements besides knives can induce stab wounds, which occur most commonly in the upper quadrants. Nearly one quarter of cases have multiple wounds, and up to 10% of cases involve the chest. Most stab wounds do not cause an intraperitoneal injury, although the incidence varies with the implement used and the direction of entry. Anterior stab wounds penetrate the peritoneum in approximately 70% of cases but inflict a visceral injury in only half of these.[2] Left lower chest wounds are associated with a 17% incidence of intraperitoneal damage in addition to the high rate of thoracic and diaphragmatic injuries, whereas right lower chest wounds have a much lower incidence of 0% to 4%. Abdominal entries from the flank and back have reported incidences of up to 44% and 15%, respectively. The liver and spleen are the viscera most commonly damaged in cases of back and flank wounds, but the injury pattern cannot be well predicted by the site of entry in the abdominal wall.

Gunshot Wounds: Ballistics. The science of ballistics is complex, but a few basic principles are helpful in understanding the pathophysiologic processes. The magnitude of the injury is proportional to the amount of kinetic energy imparted by the bullet to the victim, according to the following equation:

$$E = \frac{7000\,mv^2}{2\,ga}$$

where E is the kinetic energy (in foot-pounds), m is the mass of the bullet, v is the velocity of the bullet (in ft/s), and ga is gravitational acceleration (in ft/s). The degree of injury depends on the mass of the bullet and the square of its velocity, although the resistance and viscoelastic properties of the tissue affect the resultant injury, as well. Missile velocities are categorized as low (slower than 1100 ft/s), medium (1100 to 2000 ft/s), and high (faster than 2000 to 2500 ft/s). Impact velocity is the most important determinant of wounding capability, which depends on the distance between the firearm and the victim, the muzzle velocity, and characteristics of the missile. At medium and high velocities, the missile has an explosive effect and creates a temporary passage in the tissue along its course, directly proportional to the specific gravity of the penetrated tissue. This sudden formation of a tract displaces nearby organs and vascular structures, and bone and viscera may be fractured or torn without being directly struck by the missile. Several cases of an intraperitoneal injury caused by a bullet that remained extraperitoneal throughout its entire course have been reported. Solid viscera, such as the liver and spleen, are more vulnerable to this effect.

High-Velocity Missiles. Wounds from high-velocity missiles involve additional problems. External contaminants tend to be dragged into the wound, high-velocity bullets can fragment internally, and closure of the tract immediately after the bullet's passage may lead to an underestimation of tissue damage. A missile at any velocity can fragment after contact with bone and cause additional multiple trajectories and injuries, which makes assumptions regarding bullet tracts dangerous in the assessment of the patient. Civilian wounds usually result from low-velocity handguns, but there has been a trend toward more destructive weapons.

Shotgun Wounds. Because of the ballistic shape of the individual pellets, a rapid falloff in velocity occurs, making this weapon ineffective in producing severe wounds at long distances. An initial muzzle velocity of 1300 ft/s drops to 950 ft/s within 20 yards, a decrease of 25%. At close range (<15 yards), however, the shotgun is extremely lethal, which has implications for patient care. Although the kinetic energy depends on the pellet's size, the number of striking pellets, the type and amount of powder, and the barrel choke (constriction), the most important clinical variable is the distance between the shotgun and the victim. At a distance of 10 yards (9 meters), 19% of the pellets cluster in a 9-inch (23 cm) diameter circle if fired from a full choke (maximum constriction) barrel. At a distance of 20 yards (18 meters), the circle is approximately double that diameter. Because the kinetic energy is proportional to the square of the velocity, a 25% loss of velocity at 20 yards (18 meters) results in a significant decrease in the damage produced by the blast.

Shotgun wounds have been previously classified in three groups according to the range and pattern of distribution. More recently, classification has been according to the pattern of injury on the victim. Based on distance from the weapon to the victim, type I wounds involve a long range (>7 yards or 6.4 m) and a penetration of subcutaneous tissue and deep fascia only. Type II wounds occur at a distance of 3 to 7 yards (2.7 to 6.4 m) and may create a large number of perforated structures. Type III wounds occur at point-blank range (<3 yards or 2.7 m) and involve a massive destruction of tissue. When categorized by pattern, type I wounds produce a spread greater than 25 cm in diameter; type II, 10 to 25 cm in diameter; and type III, less than 10 cm in diameter. Close-range shotgun wounds, in addition to the shot, force external contaminants (eg, clothing and parts of the shell wadding) into the wounds. Type III wounds carry a substantial mortality risk.

Blunt Abdominal Trauma

Sudden and pronounced rises in intra-abdominal pressures created by outward forces, such as lap-belt-only restraints, can cause rupture or burst injury of a hollow organ. Compression of abdominal viscera between the applied force to the anterior wall and the posterior thoracic cage or vertebral column produces a crushing effect. Solid viscera are especially vulnerable to this injury, which is why liver and spleen injury are so common in blunt abdominal trauma. Crush injuries are more likely to occur with the lax abdominal wall characteristics of elderly or intoxicated patients. Finally, acceleration and deceleration cause organs and vascular pedicles to shear at the relatively fixed points of attachment.

Seatbelt Injuries. Unrestrained passengers are at unequivocally greater risk of intra-abdominal injury than their restrained counterparts. The three-point shoulder-lap belt is the most effective restraining system and is associated with the lowest incidence of abdominal injuries. However, abdominal injuries are still ascribed to combined shoulder-lap belt systems. The shoulder belt component can lead to right-sided and left-sided rib fractures for the driver and front seat passenger, respectively, with potential for injury to underlying abdominal viscera, particularly in the case of improper underarm usage of the shoulder belt.

Injuries resulting from solitary lap belts are most often to the abdomen. The pathogenesis is usually the compression of bowel between the belt and the vertebral column, resulting in a contusion or perforation of the intestines or a tear of the mesentery. Approximately one fourth of these patients develop evidence of a hemoperitoneum secondary to mesenteric lacerations. In the remainder, the intestinal injury most commonly involves the jejunum, and the initial signs and symptoms are often absent or considered insignificant. Subsequent delays in diagnosis of up to 8 weeks have rarely been reported. The "seatbelt sign," contusion or abrasion across the lower abdomen, is found in less than one third of patients with abdominal injuries caused by lap belts. Its presence, however, is highly correlated with intraperitoneal

pathologic lesions. Rupture of the diaphragm can also occur in cases of high speed frontal impact.[6] Rare cases of acute abdominal aortic dissection with incomplete or complete occlusion have been described, and injuries to the lumbar spine are not uncommon.

Iatrogenic Injuries. Abdominal injuries may be sequelae of various medical procedures. External cardiac compressions, manual chest thrusts to clear an airway obstruction, and the Heimlich maneuver can cause rib fractures and injury to abdominal viscera. Misadventure with tube thoracostomy can cause injury to the liver or spleen because of unrecognized elevation of the diaphragm or improper technique or placement of the tube. Peritoneal lavage, paracentesis, and peritoneal dialysis can cause vascular penetration or bowel perforation. A liver biopsy can lead to a hemoperitoneum or a biloma, whereas endoscopic procedures of the bowel may cause a hollow viscus perforation and peritonitis.[7] Colonoscopy can cause splenic injury and hemoperitoneum, and although specific mechanisms and risk factors are unclear, does not necessarily seem to be associated with biopsy.[8]

Clinical Features

The patient's history may be unobtainable, elusive, or temporarily deferred while resuscitative measures are carried out. When the situation permits and a reliable source is available, certain information is valuable. The patient's ability to relate the course of events may be compromised by head or spinal cord injury, alcohol intoxication, developmental delay, psychiatric illness, and any number of toxins that will affect the clinician's assessment of the patient. At times, the trauma may have preceded the onset of symptoms by days, weeks, or even years, and may have been forgotten or considered trivial by the patient. This is particularly true of delayed presentation of diaphragmatic hernia related to a prior penetrating lower chest injury. Witnesses at the scene, particularly paramedical personnel, often provide the most reliable data.

Appreciation of comorbid medical conditions, particularly cardiovascular disease and coagulopathies, optimizes fluid and blood component therapy. When a prehospital care team or transferring hospital is involved, the vital signs, physical assessment, prehospital course, and response to therapy should be obtained. Clinical records and laboratory and radiologic studies obtained at an outlying hospital should be carefully reviewed.

Abdominal pain is the most obvious symptom of abdominal trauma. A hematic, infectious, acidic, or enzymatic irritation of the peritoneum produces pain. The pain may be clearly present at the outset or delayed for hours to days. The perception communication of such pain may be dulled or ineffectual, or the perception of pain may be impaired by a spinal cord injury or an underlying medical problems. Occasionally, intense, competing pain at another body site dominates and distracts both the patient and physician away from the abdomen. Abdominal pain can be localized, because it sometimes is in the left upper quadrant with a splenic injury, or diffuse, such as in septic peritonitis subsequent to bowel perforation.

Pain need not be localized to the abdomen, and irritation of the diaphragm by hemoperitoneum can cause referred pain to the right and left shoulder tips or neck, particularly when the patient has been in the Trendelenburg position. This most often is a marker of hepatic or splenic injury. Pain can also be referred to the testicle in the setting of retroperitoneal injury and is seen most commonly with urogenital and duodenal trauma.

A variety of other extraabdominal symptoms may be present as well. If substantial enough, volume loss may produce orthostatic or frank dizziness, light-headedness, and confusion. Nausea and vomiting can accompany peritoneal irritation or hypovolemia, or can result from an obstruction, such as following a duodenal hematoma. Dyspnea sometimes occurs with gastric distention or diaphragmatic irritation or when abdominal contents herniate into the chest, impairing respiratory dynamics.

Penetrating Abdominal Trauma

Stab Wounds. The number of stabs inflicted, type and size of the instrument, posture of the victim relative to the direction of assault, estimated blood loss at the scene, time of injury, and response to fluids help to gauge the nature and severity of injuries. However, a significant proportion of victims of stab wounds are found under the influence of alcohol or another drug making an accurate history a futile effort and potentially compromising the validity of symptoms and signs.

Gunshot Wounds. Clinically helpful information for gunshot wound victims includes the weapon used, its distance from the victim when shot, the position of the victim in relationship to the weapon when fired, the suspected number of shots, the blood loss at the scene, the amount and type of field fluids administered, and the vital signs during the prehospital course.

Blunt Abdominal Trauma

Clinically relevant information for passengers in motor vehicle crash includes the nature of the crash; extent of damage to the car; the patient's location within the car; whether the patient struck the steering wheel; whether seat belts were used and, if so, what type; and whether front or side air bags were deployed. The magnitude of injury to pedestrians varies with the speed and size of the striking vehicle. A triad of injuries to the torso, cranium, and lower aspect of the lower extremity has been well described, and pathologic lesions discovered in two of these sites should prompt careful attention to the third. Motorcycle crashes can be placed in one of four categories: frontal, lateral or angular ejection, or "laying the bike down." Different pathologic lesions can be projected based on the offending mechanism.

Physical Examination

Abdominal trauma provokes a wide spectrum of presentations that range from seemingly insignificant symptoms and signs to severe shock and coma. Evidence of abdominal tenderness, peritoneal irritation, gastrointestinal hemorrhage, and hypovolemia not attributable to extra-abdominal causes represents most of the signs suggestive of an intraperitoneal injury. These signs may be initially absent or obscure but may emerge during serial examinations.

The physical examination of a hemodynamically unstable patient is performed coincident with therapy, but care and thoroughness are not precluded by these circumstances. When an obvious intracranial, thoracic, or orthopedic injury is present, abdominal symptoms or findings may be obscured, and abdominal injury should be considered. Chest trauma is a risk factor for coincident intraperitoneal injury. This is particularly true in cases of suspected blunt trauma accompanied by a head injury, coma, or obtunded mental status resulting from drugs or alcohol.

After removal of the patient's clothing, abdominal examination occurs as part of the secondary survey (see Chapter 33).

Acute hypotension resulting from hemorrhage is most often from a solid visceral or vascular injury. Traumatic pancreatitis may evolve to produce significant third-space fluid loss but is virtually never the sole cause of acute shock. When unexplained hypotension accompanies significant blunt trauma, one should assume the presence of intraperitoneal hemorrhage until it is excluded. A known extra-abdominal source of hemorrhage does

not mitigate the need to evaluate the peritoneal cavity. Solitary cranial or spinal injury should not be considered the sole cause of shock until intra-peritoneal injury has been excluded.

In cases of penetrating trauma, inspecting the abdomen for entrance and exit wounds may help determine the path of injury. Distention can occur as a result of hemoperitoneum or pneumoperitoneum, gastric dilation, or ileus secondary to peritoneal irritation. An ecchymotic discoloration of the flanks (Gray-Turner sign) or umbilicus (Cullen's sign) indicates retroperitoneal hemorrhage, but these signs are usually delayed for 12 hours to several days. Abdominal contusions can result from various implements; and when caused by lap-seat belts, they herald abdominal injuries in one third of cases. Presence or absence bowel sounds does not reliably identify or exclude the presence of intra-abdominal injury.

Although palpation elicits local or generalized tenderness in the vast majority of alert patients with an intra-abdominal visceral injury, it is less reliable in patients with altered mental status. However, physical examination can be unreliable even in conscious, responsive patients. Local and generalized rebound tenderness and rigidity can be signs of peritoneal irritation but occur less commonly. These signs lack specificity and can be found with lower rib fractures and contusions of the thoracoabdominal wall as well. Rarely, encapsulated bleeding into regions walled off by blood clots or adhesions can form palpable intra-abdominal masses; these usually appear at least several hours later. Severe contusions of the abdominal wall can cause tenderness and voluntary guarding that is localized and usually exacerbated by use of the affected muscle. A palpable mass can represent a rectus hematoma or ventral hernia.

Rectal examination, once a routine part of trauma assessment, rarely, if ever, provides clinical useful information and is not indicated in the vast majority of trauma patients. This is particularly true in conscious patients of both sexes, for whom rectal examination is uncomfortable, unnecessary, and potentially humiliating. The sole remaining value of rectal examination is as part of the neurological assessment (for anal sphincter tone) for patients with identified neurological deficit believed to be caused by spinal cord injury.

Although the presence of physical findings makes intraperitoneal injury more likely, their absence does not preclude serious pathology, and no finding is exclusively diagnostic of a specific injury. Extended observation and the use of certain laboratory procedures greatly help prevent erroneous or missed diagnoses.

Penetrating Abdominal Trauma

Stab Wounds. Serial physical examination performed by the same observer is useful in appropriately staffed and experienced centers, particularly with patients who are alert, communicative, and neurologically intact. The presence of intoxicants does not necessarily preclude reliance on examination but may decrease its value until sobriety is regained. Even among patients with evidence of shock, peritonitis, or evisceration after penetrating trauma to the abdomen exploratory laparotomy fails to reveal intraperitoneal organ injury in over 10% of cases.[3] In contrast, up to one third of patients with significant intra-abdominal injuries have no suggestive physical signs, particularly when a retroperitoneal injury has occurred.

Gunshot Wounds. As with blunt or other modes of penetrating trauma, there are limitations to physical examination of patients with abdominal gunshot wounds. Up to 20% of patients with a documented intraperitoneal injury have no peritoneal signs before exploration, whereas objective physical findings suggestive of intra-abdominal damage may be present in up to 15% of patients in whom laparotomy reveals no injury.

Blunt Abdominal Trauma

Overall, the accuracy of the physical examination in patients with blunt abdominal trauma is only 55% to 65% because the initial presentation may be deceptively benign. The most reliable symptoms and signs in alert patients are pain, tenderness, and peritoneal findings, particularly when risk factors for abdominal injury are present. When altered sensorium intercedes, the physical signs become less reliable. Frequent evaluations by the same examiner are indicated even in alert patients, but especially in sensorium-altered patients, particularly as their mental status and sensorium normalize.

DIFFERENTIAL DIAGNOSES

Trauma Versus Medical Condition

Medical and traumatic pathologic conditions can be coincident or lead one to the other. For instance, hypoglycemia or a generalized convulsive seizure may precipitate a motor vehicle collision, and the patient's altered mental status may incorrectly be ascribed to closed head injury, delaying diagnosis of the medical condition. Patients with infectious mononucleosis can experience splenic rupture after relatively trivial trauma, and presentation may be delayed. Finally, patients with premorbid coagulopathy or who are on therapeutic anticoagulation may sustain serious intracranial or intra-abdominal hemorrhage from otherwise unimpressive trauma (see Chapters 33 and 34).

Single Versus Multisystem Trauma

Emergency clinicians should be wary and not miss the proverbial forest for the trees. For instance, the pedestrian struck by a car who has an alleged isolated tibial-fibular fracture may well harbor significant intra-abdominal pathology, irrespective of a nontender abdomen.

Single Versus Multiple Intraperitoneal Organ Injury

There has been an increasing trend toward nonoperative management of known intraperitoneal solid organ injury, specifically of the spleen and liver.[9,10] However, coincident hollow viscus pathologic lesions may exist but not be discernible initially on clinical examination or diagnostic studies. In addition, patients without solid organ pathology who have increasing amounts of free peritoneal fluid or tenderness warrant careful consideration for hollow viscus damage.

Intraperitoneal Injury Versus Necessary Laparotomy

Formerly, suspicion or knowledge of any intraperitoneal injury mandated laparotomy. Now, diagnostic effort is appropriately aimed at determining whether surgery is necessary or whether the injury is self-limited and does not require repair.

DIAGNOSTIC TESTING

Ultrasonography

Extended focused assessment with sonography for trauma (E-FAST) examination is indicated in all poly-trauma patients and all patients with suspected abdominal injury, whether by blunt or penetrating mechanism. Ultrasonography's primary role is detecting free intraperitoneal blood after blunt trauma. This is accomplished by an examination of Morrison's pouch, the

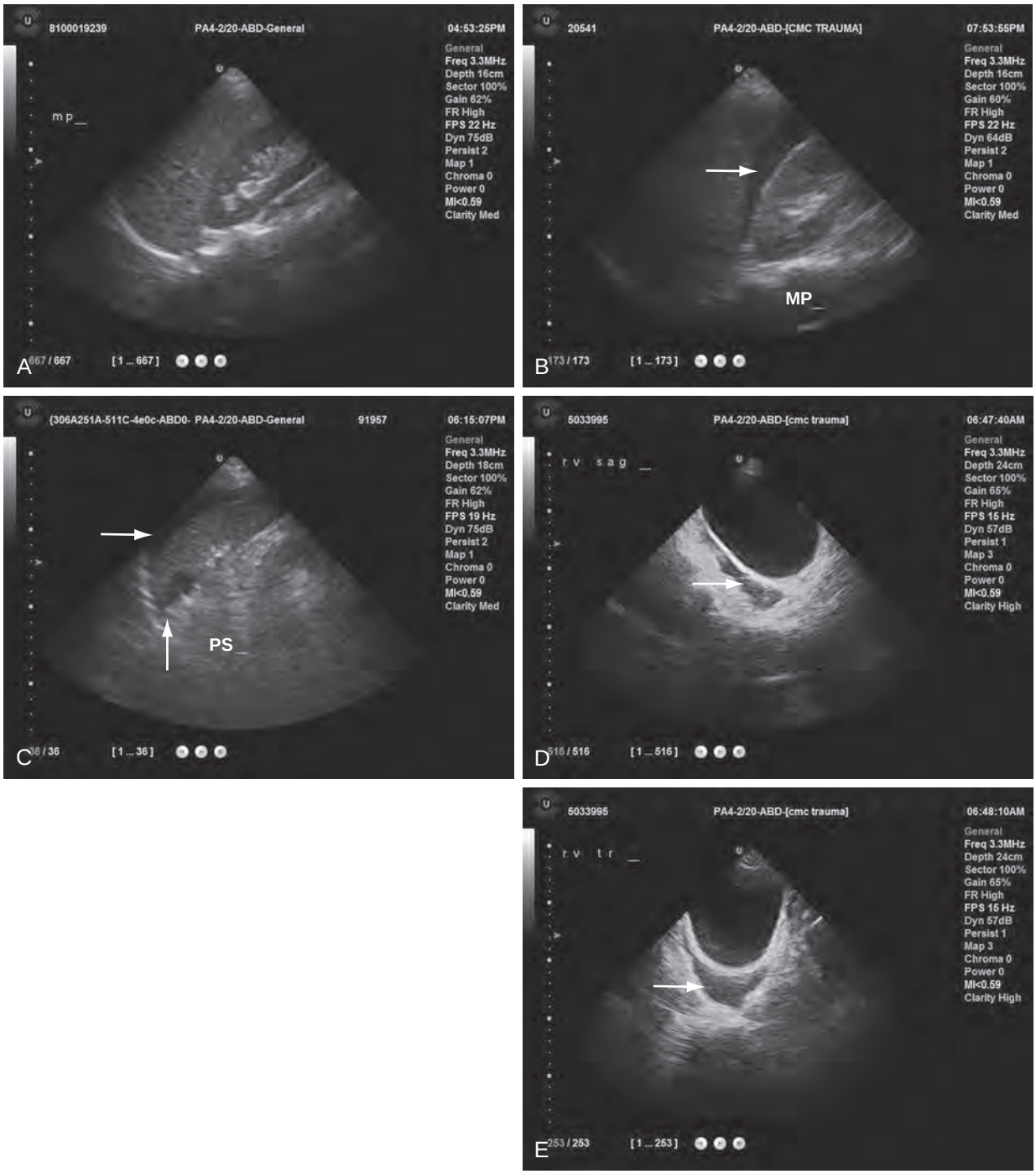

Fig. 39.1. **A,** Normal Morrison's pouch view. Note absence of an anechoic stripe, which would represent a fluid collection between the liver and kidney. **B,** Positive Morrison's pouch view. Note presence of an anechoic stripe representing a fluid collection between the liver and kidney *(arrow)*. **C,** Positive perisplenic view. Note anechoic fluid around spleen *(arrows)*. **D,** Positive fluid in the sagittal retrovesicular view *(arrow)*. Note anechoic stripe indicative of retroperitoneal fluid. **E,** Positive transverse retrovesicular view. Note anechoic area indicative of retroperitoneal fluid *(arrow)*.

splenorenal recess, and the pouch of Douglas, which are dependent portions of the intraperitoneal cavity where blood is likely to accumulate (Fig. 39.1). The thoracic portion of the examination detects pneumothorax, hemothorax, and pericardial effusion or tamponade (Fig. 39.2). Ultrasound applications in the trauma patient are discussed in Chapter e5. The E-FAST study is aimed precisely at the determinations described earlier and is limited for visualizing solid parenchymal damage, the retroperitoneum, or diaphragmatic defects.

Laboratory

Hematologic and chemical values are of limited use in the management of the acutely traumatized patient and should be considered adjuncts to diagnosis and not substitutes for clinical assessment. Laboratory assessment for patients with severe or multi-system trauma has historically relied on "trauma panels," which are a form of standing or automated order of myriad tests, the majority of which are not indicated. Both payers and

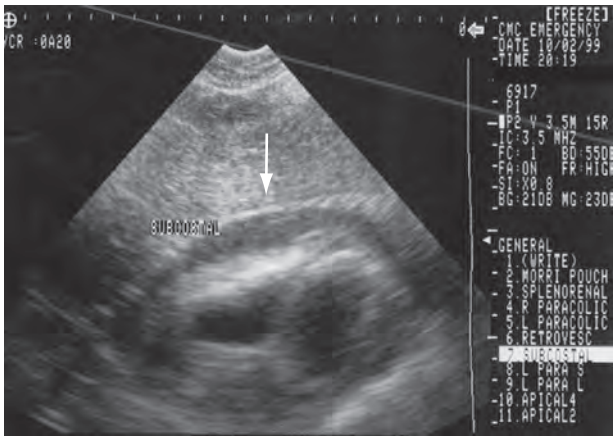

Fig. 39.2. Pericardial effusion seen on subcostal view *(arrow)*. The *white line* is the pericardium, and the anechoic space below represents a fluid collection in the pericardial space.

evidence-based practice argue strongly for the cessation of this wasteful and often clinically misleading practice. This is particularly true for patients with suspected abdominal trauma. Targeted laboratory evaluation, however, can provide significant guidance in the assessment and management of the traumatized patients.

Hematocrit

The hematocrit reflects baseline value, extent of and time from hemorrhage, exogenous fluid administration, and endogenous plasma refill. The last of these is a physiologic compensatory shift of extracellular fluid into the intravascular space, the intent of which is to restore the original blood volume. Based on a study of volunteers sustaining a 10% to 20% blood loss, this restoration requires over 24 hours for completion. Patients with hemorrhagic shock (at least 40%) demonstrate much faster plasma refill rates, with significant decreases in hematocrit within 90 minutes. Although easily measured, hematocrit is often a conundrum when viewed in isolation, and serial determinations are more helpful.

White Blood Cell Count

The white blood cell (WBC) count has little discriminatory value in cases of abdominal trauma, particularly its acute phase. The WBC count may be normal or may show a modest leukocytosis (12,000 to 20,000/mm^3 with or without left shift), which can occur in the setting of multisystem trauma as a result of stress-induced demargination in the absence of any intra-abdominal process, or as a result of tissue injury, acute hemorrhage, or peritoneal irritation.

Chemistry

Although included in many "trauma panels," neither serum amylase nor lipase is useful in the evaluation of acute abdominal trauma. Normal levels do not exclude a major pancreatic injury, and elevated values may be caused by any of an assortment of reasons in addition to an injured pancreas, including alcohol, drug toxicity, or systemic hypotension and pancreatic hypoperfusion without pancreatic injury. Elevated or rising levels may indicate damage but in themselves are not conclusive.[11] In all cases, clinical examination and status direct further investigation.

Metabolic acidosis in the setting of trauma can suggest the presence of hemorrhagic shock. This can be witnessed chemically as a decreased serum bicarbonate level, increased base deficit, or elevated lactate level. Although normal values do not exclude abdominal injury, abnormalities, such as a base deficit greater than or equal to 6, elevated lactate greater than 4 mmol/L, or increase over time in either of these indices, suggests perfusion compromise or injury.[12] These findings should be considered in clinical context, because the cause of the abnormalities may be extra-abdominal and trending of laboratory findings lags behind the clinical deterioration or improvement of the patient.

Elevated serum transaminases can result from hepatic trauma but do not distinguish minor contusions from severe injury. Alternatively, these may be symptomatic of alcohol-induced liver damage. Elevated liver transaminase levels may be useful for screening pediatric patients for intentional trauma (see Chapter 177).

Screens for ethanol and drugs are often used in trauma centers. Their utility in the management of abdominal trauma, per se, has not been established, particularly in patients with normal mental status. Positive study findings may prompt the emergency clinician to interdict and the patient to decrease the recidivistic use of ethanol or drugs, and physician intervention during this "teachable moment" has been shown to be effective.

TABLE 39.1

Diagnostic Studies in Blunt Abdominal Trauma

STUDY SCENARIO	PRIMARY PURPOSE	STUDY	COMPENSATORY
HEMODYNAMICALLY UNSTABLE			
General	IPH	FAST, DPA	—
Pelvic fracture	IPH	FAST, DPA[a]	—
HEMODYNAMICALLY STABLE			
General	OI[b,c], HVI	FAST, CT	DPL, SPEs
Nonoperative management[d]	OI	FAST, CT[e]	DPL,[f] SPEs
Closed head injury	OI	FAST, CT[e]	SPEs[g]
Blunt aortic injury	IPH	FAST	CT[h]

[a]Positive peritoneal aspirate necessitates laparotomy.
[b]To discover fluid or blood suggesting injury.
[c]FAST for OI much less reliable than for IPH.
[d]Institutional capability should be carefully considered.
[e]CT less reliable for HVI than for solid visceral injury.
[f]Complementary to CT if HVI suspected.
[g]SPEs are unreliable in the patient with CHI.
[h]May be more appropriate if helical CT is primary study for blunt abdominal injury or can be rapidly acquired.
CT, Computed tomography; *DPA,* diagnostic peritoneal aspiration; *DPL,* diagnostic peritoneal lavage; *FAST,* focused assessment with sonography in trauma; *HVI,* hollow viscus injury; *IPH,* intraperitoneal hemorrhage; *OI,* organ injury; *SPE,* serial physical examination.

Radiology

Resuscitation and initial stabilization measures precede abdominal radiographic studies. The purpose of diagnostic studies is twofold (Table 39.1): to discern or eliminate the presence of hemoperitoneum in the patient whose condition is critical and unstable to properly sequence management and, in less urgent circumstances, to demonstrate organ injury that requires operative repair. Basic plain radiography of the abdomen in the trauma bay is not indicated, except for missile location or identification. Portable chest x-ray examination has been a staple to screen for significant hemothorax or pneumothorax before the patient is transferred to the CT scanner, but this is largely being replaced by

the chest portions of the E-FAST examination, which has proven at least as sensitive and specific as portable chest radiography for both conditions.[13]

Hemodynamically stable patients who will undergo expedient abdominopelvic CT can forego pelvic radiographs in the trauma bay. Indications for pelvic radiography are discussed in Chapters 33 and 48. In patients whose evaluation, including E-FAST results, demonstrates likely intra-peritoneal injury requiring laparotomy, delay in operation to obtain further diagnostic radiology studies is permissible only when the patient has been stabilized and only if studies might aid in determining management.

Plain Radiographs

The chest radiograph and anteroposterior pelvic films can be invaluable in some cases of penetrating and blunt trauma, depending on the presentation and results of initial evaluation. Chest radiographs can provide extra-peritoneal causes of hypotension in the unstable patient. Plain abdominal films can demonstrate the location or presumed track of the missile(s) in gunshot and shotgun injury but are of little value in blunt trauma or non-projectile penetrating trauma, particularly if CT imaging of the abdomen is anticipated. If plain radiography of the abdomen is done, the finding of rib, pelvic, vertebral body, or transverse spinous process fractures in the blunt trauma patient warrants special consideration for nearby visceral damage.

Although free intraperitoneal air can be detected on plain films, the small amounts and location of air associated with small bowel injuries are seen more readily on CT. Free intraperitoneal air uncommonly can be generated by mediastinal or pulmonary injury, as well as by barotrauma, and its presence is not pathognomonic of hollow viscus perforation. Intraperitoneal air is mobile; in upright films, air is located under the diaphragm or the central tendon of the diaphragm anteriorly. In supine films, air tracks under peritoneal attachments, such as the falciform ligament and urachus, up to the anterior abdominal wall. On films in which the patient is in a lateral decubitus position, air is located in the superior flank and outlines the lateral liver edge. Extraperitoneal colonic perforations may extravasate air, which outlines the psoas muscle and perinephric region. All of these injuries are much more readily identified and localized on abdominal CT and thus remains the imaging modality of choice.

Foreign bodies and missiles are easily identified on abdominal films. Therefore their absence without a known exit wound warrants further search of other body cavities (eg, the chest, upper thighs, buttocks). A ricochet off the spine or pelvis into the chest or proximal extremities can occur. An entry into the vascular system may carry the object toward and into the right side of the heart or peripherally into the arterial tree. It may also find its way into the gastrointestinal tract and either produce obstruction or pass through unnoticed. Thus, the location of a bullet and its fragments may provide its primary value in suggesting if extraabdominal injuries are present.

Computed Tomography

CT scanning is the primary diagnostic imaging test for trauma. CT scanning can define the injured organ and the extent of the injury. It is most accurate for solid visceral lesions and discerns the presence, source, and approximate quantity of intraperitoneal hemorrhage (Fig. 39.3). It can demonstrate active bleeding from the liver or spleen and can be used to determine whether observation, therapeutic angiographic embolization, or open operative intervention is indicated. By minimizing the incidence of nontherapeutic laparotomies for self-limited injury to the liver or spleen, it decreases morbidity and cost.[10] CT scanning also evaluates the retroperitoneum (Fig. 39.4), an area not sampled by E-FAST, while simultaneously evaluating the vertebral column, and can be readily extended above or below the abdomen to visualize the thorax or pelvis. CT scanning also provides definitive evaluation for most possible injuries to the urinary tract, including renal artery injury.[14] It can also detect other vascular hemorrhage and obviate the need for angiography in some patients. Little additional information is provided by the addition of oral contrast, and most trauma centers use intravenous contrast alone, which decreases aspiration risk for the patient.

CT scanning, however, is relatively insensitive for injury of the pancreas, diaphragm, small bowel, and mesentery, although detection of these injuries is improving (Fig. 39.5). The last two are particularly worrisome because coincidental hollow viscus injury in patients with blunt trauma, although uncommon, is not rare, and increased morbidity and death can ensue if diagnosis is missed or the condition goes undetected for a prolonged period. Findings on CT scans, including the suspected quantity of hemoperitoneum or the presence of isolated free fluid, are not able to forecast well the need for operative intervention. Complications

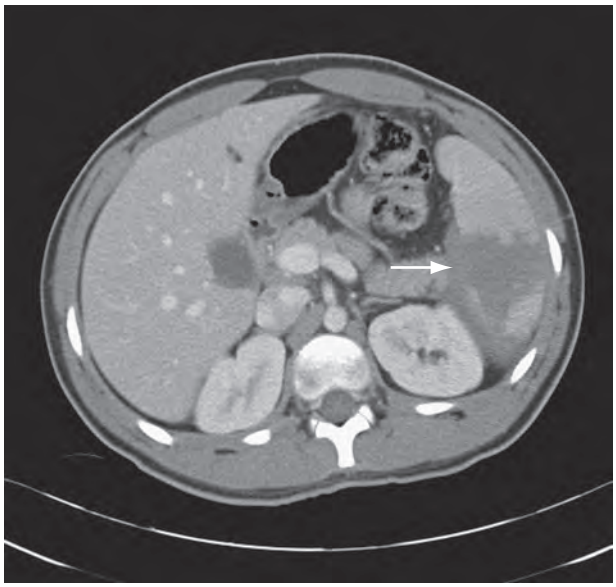

Fig. 39.3. Grade 4 splenic laceration.

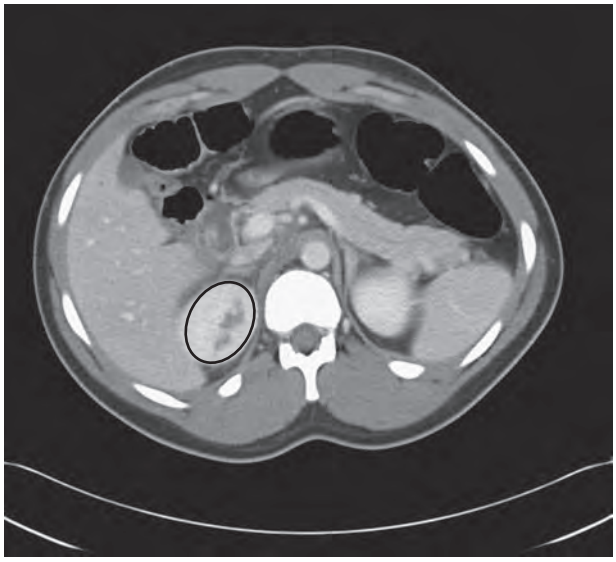

Fig. 39.4. Grade 3 right renal laceration *(encircled)*.

Fig. 39.5. A, Grade 4 splenic laceration *(black arrow)* with diaphragmatic rupture *(white arrow).* **B,** Small bowel edema concerning for hollow viscus injury *(encircled).*

may result from intravenous contrast administration, including contrast-induced nephropathy, and the patient is subjected to ionizing radiation, both of these factors compelling clinicians to be selective in ordering these studies. Finally, patients must be temporarily removed from the resuscitation area for the study to be accomplished, which can put the patient at risk in the case of rapid clinical deterioration. Nevertheless, CT scanning remains the cornerstone of diagnosis.

Increasingly, there is concern regarding the negative long-term effects from exposure to ionizing radiation resulting from medical imaging. Although direct evidence of increased cancer risk from CT scans has not yet been demonstrated, several methods are available to reduce radiation exposure. The scanner should be adjusted to the lowest possible setting without losing sensitivity in diagnosing intra-abdominal injury.[15] Attempted limiting scanning only through the region of abdominal tenderness turned out to be excessively insensitive for significant injury, and this practice is not recommended.[16] Digital images should accompany patients transferred between facilities, to avoid unnecessary repetition of the study.[17]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is usually impractical and sometimes impossible to perform in the acute phase of multiple blunt trauma. Currently, in acutely injured trauma patients, MRI should be reserved for the evaluation of spinal cord injuries and elusive diaphragmatic defects not amenable to laparoscopy or thoracoscopy in the fully stabilized patient.

MANAGEMENT

The field approach to multiple or serious trauma focuses on rapid transportation to a capable receiving emergency department (ED) and is discussed in Chapter 33. An emerging body of evidence has evolved around the concept of "permissive hypotension," where a mild degree of hypotension (mean arterial pressure >50 mm Hg) is tolerated to decrease unnecessary fluid resuscitation, which can worsen trauma-induced coagulopathy, hypothermia, and may increase the risk of destabilizing relatively "soft" clots. Although animal and some human data support this practice, definitive clinical trial evidence mandating the practice is currently lacking.

In the ED, assessment of abdominal injury is part of the general management of the trauma patient (see Chapter 33).

In patients who are intubated, have a massively distended abdomen, or in whom there is a high concern for stomach or duodenal injury, a nasogastric tube should be placed to decompress the abdomen, decrease the likelihood of aspiration, and determine whether blood is present, respectively. Placement of an orogastric tube is preferable in patients with midface or skull base fractures. Foley catheterization, once fairly routine, is reserved for unconscious patients, and those in shock, for whom urine output is an indicator of adequate end-organ perfusion. Thoracotomy and subsequent cross-clamping of the descending aorta have been used to stabilize patients with thoracoabdominal injuries and profound hypovolemic shock, but this is best undertaken as a temporizing rescue maneuver in the operating room when laparotomy identifies critical injuries not amenable to abdominal repair. ED thoracotomy for management of intra-abdominal injuries, even exsanguinating injuries, rarely is indicated, and the decision to undertake thoracotomy rests with the treating trauma surgeon.

Antibiotics, given prophylactically, are effective in decreasing the incidence of intra-abdominal sepsis. Intestinal perforation and soiling can occur with penetrating, and uncommonly with blunt trauma to the abdomen. A single preoperative dose of a broad-spectrum antibiotic or combination of antibiotics that covers both aerobic and anaerobic organisms, such as piperacillin-tazobactam 3.375 g intravenously, is recommended.

Penetrating Abdominal Trauma: Stab Wounds

Selective management of abdominal stab wounds is now well accepted because of the relatively low incidence of intraperitoneal injuries coupled with the success of various diagnostic strategies.[3,18] This strategy is based on the site of penetration, the clinical status of the patient, and the experience and judgment of the hospital institution and its personnel. Compared to the former practice of mandatory laparotomy, selective management has resulted in a tremendous reduction in unnecessary laparotomies and their associated morbidity, with minimal and acceptable loss in sensitivity for significant intraperitoneal injury.[3,18] Overall, the nontherapeutic laparotomy rate should be less than 15%.

Anterior Abdomen

In approaching the management of stab wounds to the anterior abdomen, the clinician is faced with three fundamental tasks. The first and most important is to determine whether clinical indications exist for emergent laparotomy. The presence of one or more of these indications, particularly in the context of an unstable patient, sets the course to exigent operation. If none is found, the clinician may address the second issue of whether the peritoneal cavity has been violated. If it can be definitively demonstrated that it has not, no further diagnostic evaluation is required, and the patient can be discharged after appropriate wound care. If the cavity has been violated, or if it cannot be determined whether the cavity has been violated, the third question is pursued: Does an intra-peritoneal injury exist and, if so, is laparotomy required? One general approach to abdominal stab wounds founded on these three queries is summarized in Figure 39.6. This algorithm is largely based on clinical indicators of injury, LWE, CT, and other radiologic modalities. Other strategies rely more heavily on other techniques, such as serial abdominal examinations or laparoscopy.

Step I: Clinical Indications for Emergent Laparotomy. Various clinical determinants can be used to determine the need for emergent laparotomy (Table 39.2) based on the likelihood of associated intra-abdominal injuries requiring surgical repair. These clinical determinants are summarized in the following list by reasons for immediate laparotomy, followed by clinical indications that require additional supportive evidence.

A: Emergent laparotomy immediately indicated

1. Hemodynamic compromise: This is the preeminent indication of the need for laparotomy in the setting of a stab wound and is the most likely reason that a patient will be taken urgently to the operating room without preliminary diagnostic studies.
2. Peritoneal signs: There is considerable debate over the reliability of peritoneal signs, particularly in the early post-injury period. Among physical examination findings, unequivocal peritoneal signs have the highest positive predictive value, whereas an entirely normal examination even in the presence of mild to moderate intoxication has the greatest negative predictive value for therapeutic laparotomy. In general, however, clear peritoneal signs indicate the need for laparotomy.
3. Evisceration: Patients with viscus evisceration sustain up to an 80% incidence of major intraperitoneal injury, and most surgeons will take these patients for exploratory laparotomy. In rare cases, for isolated omental evisceration without viscus evisceration and absence of free intraperitoneal blood on E-FAST examination, the surgeon may ligate, excise, and restore the omentum to the peritoneal cavity. This is done at the bedside in the trauma bay.
4. Left-sided diaphragmatic injury: Although rarely diagnosed acutely, left-sided diaphragmatic injury may be diagnosed through the observation of stomach or bowel in the left chest on bedside chest radiographs, and indicates the need for operative intervention.

B: Laparotomy only considered with additional clinical evidence

5. Gastrointestinal hemorrhage: Again, although rarely diagnosed because nasogastric tubes are rarely used in this clinical scenario, recovery of blood via a nasogastric tube or emesis may reflect a violation of the stomach or duodenum. However, blood without coincident peritoneal violation does not necessarily require surgical exploration.

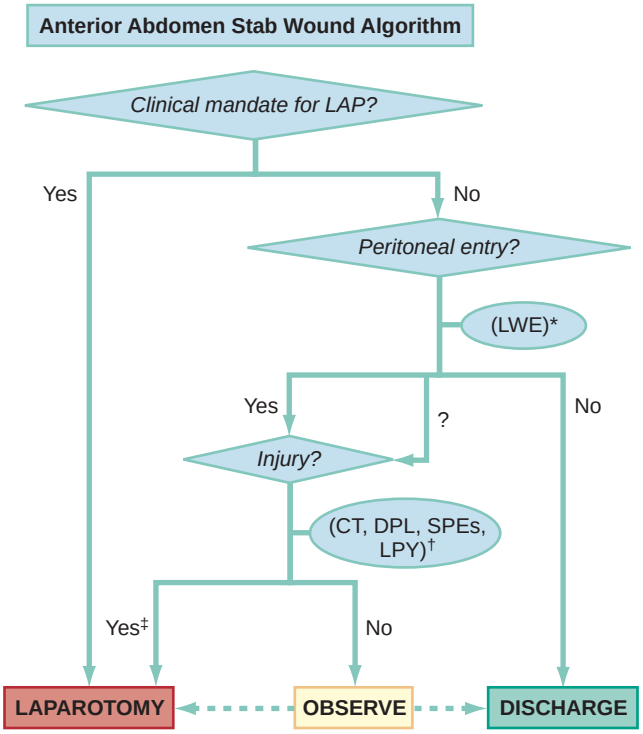

Fig. 39.6. Anterior abdomen stab wound algorithm. *LAP,* Laparotomy; *LWE,* local wound exploration.*Plain films, focused assessment with sonography in trauma (FAST), laparoscopy *(LPY),* and computed tomography *(CT)* can also assess peritoneal entry. †CT, diagnostic peritoneal lavage *(DPL),* serial physical examinations *(SPEs),* or LPY can be used in singular or complementary fashion, depending on the clinical scenario. ‡Expectant management of injuries is infrequently attempted.

TABLE 39.2

Clinical Indications for Laparotomy Following Penetrating Trauma

MANIFESTATION	PREMISE	PITFALL
EMERGENT LAPAROTOMY INDICATED		
Hemodynamic instability	Major solid visceral or vascular injury	Thorax or mediastinum, causal or contributory
Peritoneal signs	Intraperitoneal injury	Unreliable, especially immediately post injury
Evisceration	Additional bowel, other injury	No injury in one fourth to one third of stab wound cases
Diaphragmatic injury	Diaphragm	Rare clinical, radiographic findings
LAPAROTOMY REQUIRES ADDITIONAL CLINICAL EVIDENCE		
Gastrointestinal hemorrhage	Proximal gut	Uncommon, unknown accuracy
Implement in situ	Vascular impalement	Comorbid disease or pregnancy creates high operative risk
Intraperitoneal air	Hollow viscus perforation	Insensitive; may be caused by intraperitoneal entry only or may have cardiopulmonary source

Modified from Marx JA: Diagnostic peritoneal lavage. In Ivatury RR, Cayten CG, editors: The textbook of penetrating trauma, Baltimore, 1996, Williams & Wilkins.

6. Implements in situ: The conservative and widely held maxim is to remove implements in situ of the torso in the operating room. However, there is little evidence to support this practice and removal of such instruments in the ED under controlled circumstances, and in consultation with a surgeon, is reasonable.
7. Intraperitoneal air: See later.

Step II: Peritoneal Violation. If clinical indications for laparotomy are absent, a logical next step is assessing the wound tract itself. The presence of peritoneal violation can be determined by a variety of means. There is great value in establishing that a wound tract is superficial to the peritoneal, retroperitoneal, intrathoracic, and pericardial cavities. In this event, the patient can be discharged from the ED after receiving appropriate wound care. If a study is inconclusive, it should be assumed that one or more of these cavities has been violated and further means of assessment are required. The five methods of assessing whether the peritoneum is intact are as follows:

1. Evisceration: Evisceration of bowel or omentum is clear evidence of peritoneal entry. Although typically mandating laparotomy, exceptions exist (see earlier).
2. Intraperitoneal air: Although a finding of intraperitoneal free air on an upright chest or a lateral decubitus abdominal radiograph may indicate bowel perforation, it may simply establish that the implement has entered the peritoneal cavity and drawn air in with it. Therefore, although intraperitoneal air is a strong indication of peritoneal violation, it does not necessary imply bowel injury and is therefore not used in isolation to determine the need for emergent laparotomy. Rarely, a false-positive determination of peritoneal entry can be made when the actual source of intraperitoneal free air is the pulmonary tract.
3. LWE: This has been demonstrated to be an effective tool in determining if the peritoneal cavity has been penetrated.[3] Superficial wounds can be repaired if needed and the patient discharged from the ED.
4. Ultrasonography: E-FAST examination demonstrating hemoperitoneum, pneumoperitoneum, or pericardial effusion (see Fig. 39.2) identifies peritoneal penetration or injury. A negative E-FAST does not rule out peritoneal violation. Presence of intraperitoneal blood on ultrasonography precludes the need for LWE.
5. Laparoscopy or thoracoscopy in the operating room: This has compared favorably with LWE in assessing the wound tract but requires a surgeon's expertise and carries a greater risk of complications. Benefits include the ability to detect organ injury (including diaphragmatic injury) and simultaneously repair some injuries, thus decreasing negative and nontherapeutic laparotomy rates. Its primary use is in evaluating for diaphragmatic violation in left anterior lower chest stab wounds.

Step III: Injury Requiring Laparotomy. In this algorithm, patients requiring an operation on clinical grounds have proceeded to laparotomy, and those in whom peritoneal violations have been excluded are discharged home. The patients remaining have presumed or known peritoneal violation. The next consideration is whether injury exists that dictates operative repair, because organ injury is present in only just over 60% of patients with peritoneal violation.[2] In any case, patients who reach this stage of evaluation should be observed for at least 12 to 24 hours.

Initial CT scanning coupled with serial E-FAST, and physical examinations are used to identify significant wounds not initially obvious. Hollow viscus and occult diaphragmatic injuries remain the most frequently missed injuries on CT. Laparoscopy is performed when serial evaluation suggests possible, but not obvious, need for laparotomy.

Thoracoabdominal Penetration

Even a single stab wound to the low chest can violate the mediastinum, thoracic cavity, diaphragm, peritoneal cavity, and retroperitoneum. Nearly 20% of left thoracoabdominal stab wounds will be found to have diaphragmatic violation. When all thoracoabdominal wounds are considered, the risk of occult injury is 7%. Ultrasonography can be extremely useful by permitting quick assessment for hemopericardium and hemoperitoneum in the marginally stable patient if thoracotomy or laparotomy is not already clinically indicated. LWE of slash-type wounds may obviate the need for further evaluation, but the depth of investigation cannot be taken beyond the anterior rib margin to maximize safety and accuracy.

Diagnosis of diaphragmatic injury is particularly problematic. CT has sensitivity and specificity in the low 90% range for detecting diaphragmatic injury. However, equivocal scans should be followed up with more definitive management, such as laparoscopy or thoracoscopy.

Flank and Back

The incidence of retroperitoneal injuries after stab wounds to the flank and back is greater than with injury to the anterior wall. However, risk of intraperitoneal organ injury also is significant, ranging up to 40%. LWE is less accurate than in anterior wounds because the paraspinal muscles are quite thick, so the procedure is only useful if the wound is obviously superficial (such as, a slash wound). CT with intravenous contrast is the method of choice for evaluating wounds not identified to be clearly superficial. A negative CT scan, followed by serial examination over a period of 24 hours, can effectively exclude serious injury management of these patients.

Penetrating Abdominal Trauma: Gunshot Wounds

Unlike stab wounds, almost all gunshot wounds penetrate the peritoneal cavity and typically produce multiple organ injuries and a high incidence of hollow visceral injury. Accordingly, the risk of mortality is significantly greater and increases with the velocity of the missile. Missiles striking the low chest commonly penetrate both intrathoracic and abdominal structures, including the diaphragm.

Abdominal gunshot wounds enter the peritoneal cavity in approximately 80% of cases, and in more than 90% of those involving penetration, there is intraperitoneal damage. Although selective management is widely accepted for stab wounds, its application in the management of gunshot wounds is extremely limited, and therefore mandatory laparotomy generally is the rule, rather than the exception. First and foremost, are there clinical grounds for immediate operation? Second, if none exists, has peritoneal violation occurred? If the answer to either of these questions is yes, the patient is taken emergently to laparotomy with very few exceptions. If no peritoneal violation occurred, or it is unclear, admission for serial examinations is indicated (Fig. 39.7).

Step I: Clinical Indications for Laparotomy

If the patient is hemodynamically unstable, or peritoneal signs are present, the patient is taken immediately for operative intervention.

Step II: Peritoneal Violation

If is patient does not meet indications for immediate laparotomy, assessments are made to determine if peritoneal violation is

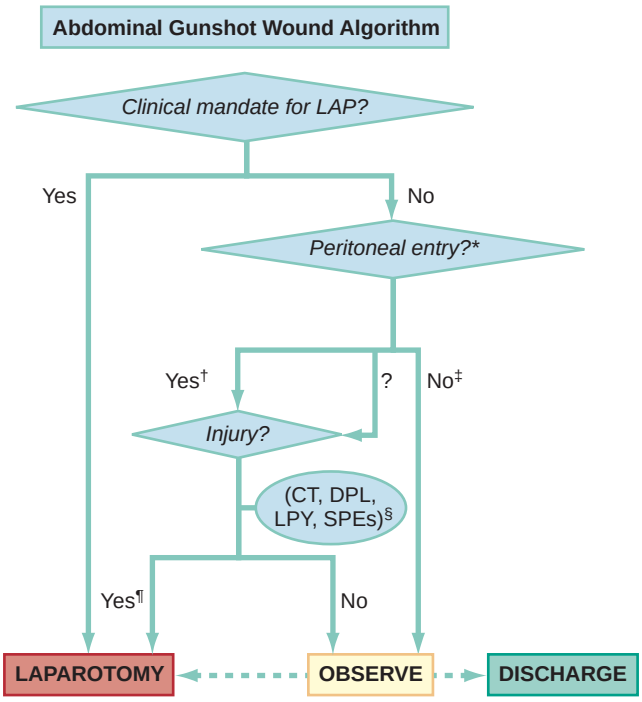

Fig. 39.7. Abdominal gunshot wound algorithm. *LAP,* Laparotomy.*Can be assessed by missile path, plain films, local wound exploration (LWE), ultrasonography, and laparoscopy. †Most centers proceed to laparotomy if peritoneal entry is suspected. ‡Patients with documented superficial and low-velocity injuries can be discharged; unknown-depth or high-velocity injuries require further tests or observation. §Computed tomography *(CT),* diagnostic peritoneal lavage *(DPL),* laparoscopy *(LPY),* or serial physical examinations *(SPEs)* can be used in singular or complementary fashion, depending on the clinical scenario. ¶Expectant management of injuries caused by gunshot wounds is rarely attempted.

present. Six methods are used to determine whether the missile has entered or traversed the peritoneal cavity:

1. Missile path: If the missile clearly just grazed the superficial tissue of the abdominal wall, it can be identified as non-penetrating.
2. Plain radiographs: An anteroposterior and lateral projection of the abdomen can assist in placing the missile in the peritoneal cavity, but such estimations are imprecise and are largely unhelpful in patients with through-and-through or multiple gunshot wounds.
3. LWE: This is used highly selectively in apparent grazing injuries or occasional injuries from handguns that appear to go through and through the lateral abdominal wall, well outside the confines of the peritoneum. If LWE confirms the path as superficial, violation has not occurred.
4. Ultrasonography: Presence of fluid on E-FAST indicates penetration, regardless of the impression one has derived from the apparent path of the missile.
5. Laparoscopy: Laparoscopy is used when peritoneal violation is known or suspected, but physical examination and E-FAST suggest that intraperitoneal injury is minimal or absent.
6. CT: CT has been helpful when trajectory is indeterminate and has extremely high sensitivity and specificity for identifying intra-abdominal injury. It can also identify the wound track, whether fragmentation has occurred, and indicate vascular structures at risk for injury, although this is more useful in neck wounds.

Thoracoabdominal

Half of the patients with gunshot wounds to the low chest have intraperitoneal injuries. Clinical indications for emergent or urgent laparotomy are as for abdominal gunshot wounds. CT scanning is highly accurate for identification of both chest and abdominal injury and should be obtained before the patient goes to the operating room, unless the patient's instability will not allow this.[19]

Flank and Back

CT scan is highly accurate for identification of retroperitoneal injury and is the diagnostic test of choice in a stable patient. Most patients are then taken to the operating room. In some cases of low velocity gunshot wound to the flank, laparoscopy or observation alone can be used if the CT scan shows no evidence of injury and the bullet track does not traverse any anatomically important structures.

Shotgun Wounds

Type I injuries can be effectively managed by reserving laparotomy for patients with clear peritoneal signs or progressive abdominal tenderness. Certain authors advocate an expectant approach to type II injuries, stating that small punctures of the bowel cause no wound eversion and no peritoneal leakage and will spontaneously close. A more prudent approach is to perform laparotomy in cases of these penetrating wounds, especially if there are signs of peritonitis. Reconstruction of abdominal wall defects may be required. Type III injuries are commonly associated with multiple organ injuries, shock, and pronounced tissue destruction, requiring hemostasis and extensive débridement.

Blunt Abdominal Trauma

In cases of blunt trauma, it is the exception when a patient undergoes laparotomy based on clinical grounds alone. Far more typically, one or a complementary battery of diagnostic tests are performed. The choice of these tests is influenced by the patient's hemodynamic status, the clinical scenario, and the institution's resources and preferences (Fig. 39.8).

The decision to perform immediate laparotomy after injury from a blunt mechanism is rarely determined solely by clinical parameters. Immediate transport to the operating room is reserved to patients with (Table 39.3):

1. Refractory hypotension in a patient with positive E-FAST examination for hemoperitoneum and absence of an unstable pelvic fracture
2. Obvious peritonitis with positive E-FAST examination
3. Evidence on E-FAST of intra-abdominal injury in the context of other life-threatening injuries, such as uncontrollable chest hemorrhage, which require transfer to the operating room

In patients who are hemodynamically stable, CT scanning is the diagnostic modality of choice, as outlined earlier.

Operative Versus Nonoperative Management

Patients with certain intraperitoneal injuries, even moderate- to high-grade liver or spleen trauma, often can be managed without laparotomy.[9,10] The patient with normal sensorium and minor to intermediate severity of mechanism is a superior candidate for expectant management. It is critical that an institution appraise its ability to manage such patients, which includes having experienced nursing staff, trauma surgeons, adequate blood resources, and radiologists and the ability for the patient to undergo laparotomy urgently if the need arises at any time of day or night.

Several pitfalls in the expectant approach are noteworthy. First, hollow viscera injury, when present, requires operative management. The ability of the CT scan to detect injury to these structures is discussed earlier. The patient with multisystem injury

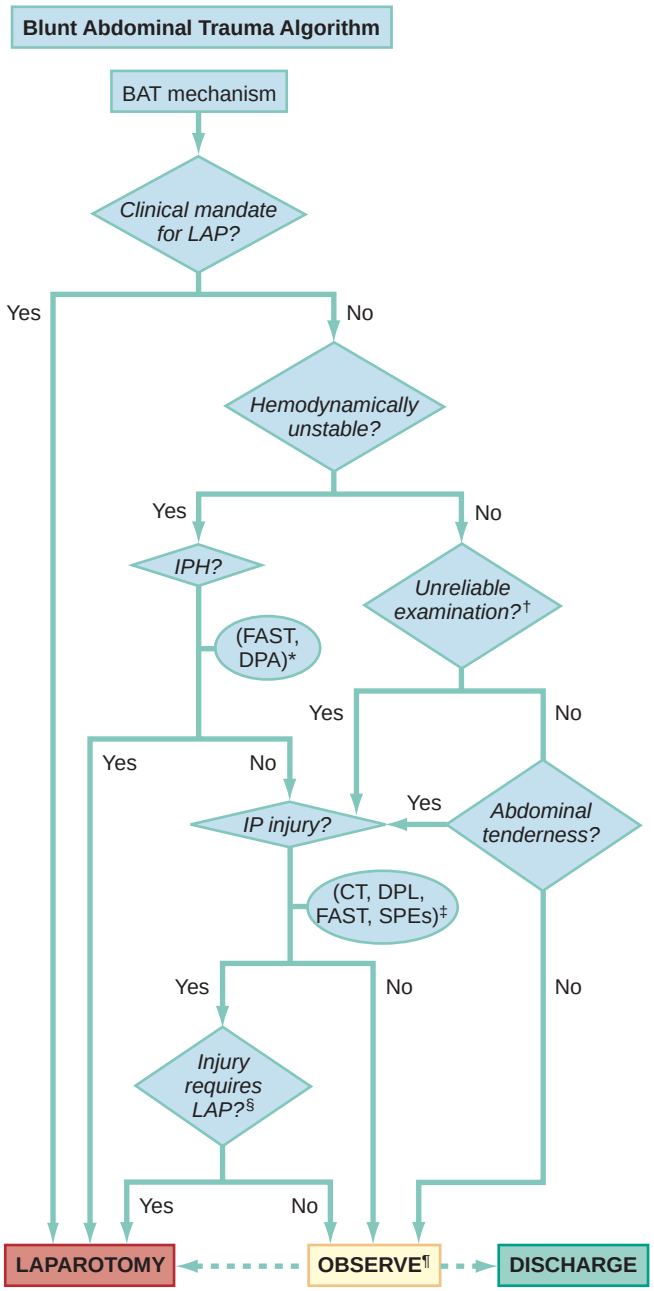

Fig. 39.8. Blunt abdominal trauma *(BAT)* algorithm. *CT,* Computed tomography; *DPL,* diagnostic peritoneal lavage; *FAST,* focused assessment with sonography in trauma; *IP,* intraperitoneal; *IPH,* intraperitoneal hemorrhage; *LAP,* laparotomy; *SPEs,* serial physical examinations. *Determined by unequivocal free intraperitoneal fluid on FAST or positive aspiration of blood on diagnostic peritoneal aspiration *(DPA).* †Can be unreliable because of closed head injury, intoxicants, distracting injury, or spinal cord injury. ‡One or more studies may be indicated. §Need for laparotomy is based on clinical scenario, diagnostic studies, and institutional resources. ¶Duration of observation should be 6 to 24 hours depending on whether diagnostic tests have been performed, the results of the tests, and clinical circumstances, including the absence of factors rendering the examination unreliable.

and, specifically, closed head trauma is most vulnerable to having delayed diagnosis of perforated intestinal injury because of delayed or impaired development of physical findings by abdominal examination. Second, expectant management may lead to increased use of blood products. Finally, this management approach will fail in those patients whose hemorrhage persists and is not amenable to therapeutic angiography and embolization. In such cases, the lag time from injury to operation may increase morbidity and mortality.

TABLE 39.3

Clinical Indications for Laparotomy After Blunt Trauma

MANIFESTATION	PITFALL
Unstable vital signs with strongly suspected abdominal injury	Alternate sources of shock
Unequivocal peritoneal irritation	Potentially unreliable
Pneumoperitoneum	Insensitive; may be caused by cardiopulmonary source or invasive procedures (diagnostic peritoneal lavage, laparoscopy)
Evidence of diaphragmatic injury	Nonspecific and insensitive, especially in penetrating trauma
Significant gastrointestinal bleeding	Uncommon, unknown accuracy

Pelvic Fracture

In the setting of pelvic fracture, the clinical triage determinant is the presence or absence of hemoperitoneum (Fig. 39.9). Although the sensitivity of E-FAST in patients with pelvic fractures may be decreased, it still serves as a tool to triage the patient to the next intervention. In an unstable patient, if the E-FAST is negative, then the patient should proceed to therapeutic angiography with the presumed diagnosis of a life-threatening retroperitoneal bleed. In all patients, early mechanical pelvic stabilization is advised (see Chapter 48), and CT scan followed by pelvic angiography and embolization are undertaken as early as possible in the context of the multiple injuries.

Multiple System Injury

It is not unusual to confront intraperitoneal hemorrhage in a patient with apparent closed head injury or suspected blunt aortic disruption or both. Repair of the abdomen is said to take precedence over that of the head and chest. However, these situations are highly complex, and decision-making is influenced by numerous and dynamic variables, and approaches to two of these situations are summarized in Figures 39.10 and 39.11. The key tenet is that a patient with known hemoperitoneum whose vital signs cannot be stabilized should undergo laparotomy to avoid exsanguination.

Bedside Procedures

Diagnostic Peritoneal Lavage

Once the mainstay of evaluation of the abdominal trauma patient to determine the presence of injury and the need for laparotomy, diagnostic peritoneal lavage now is largely of historic interest only. Its remaining role in trauma is limited to centers where ultrasound equipment is not available or the clinician is not trained to perform ultrasound.

Local Wound Exploration

LWE is used to determine whether an anterior stab wound has penetrated into the peritoneal cavity in a non-obese patient. The

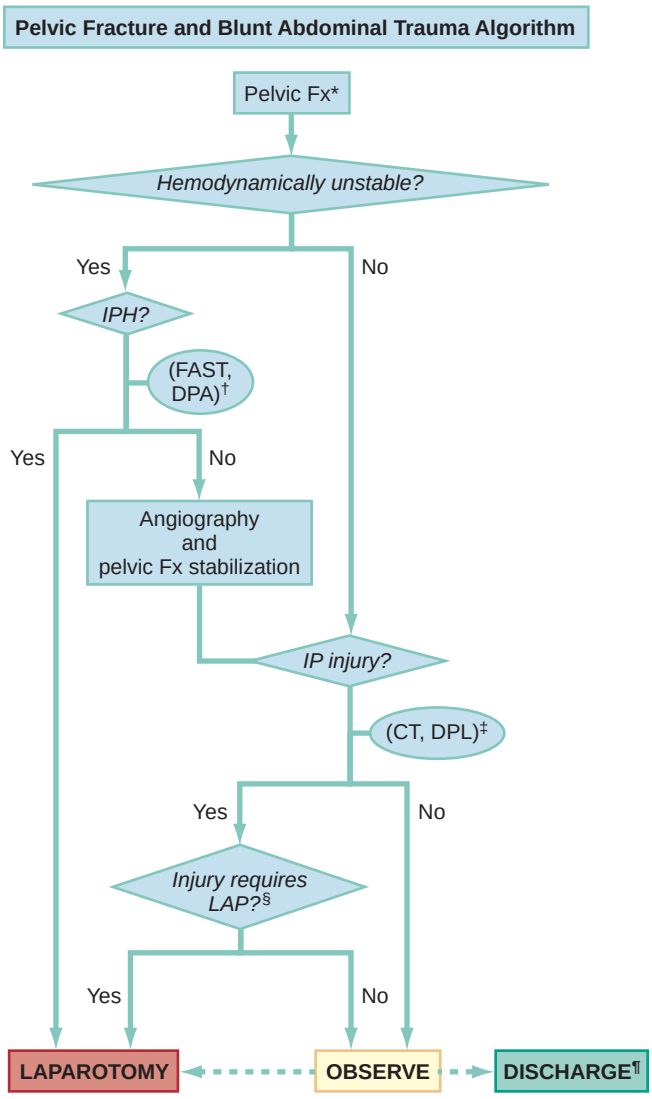

Fig. 39.9. Pelvic fracture *(Fx)* and blunt abdominal trauma algorithm. *CT,* Computed tomography; *DPL,* diagnostic peritoneal lavage; *FAST,* focused assessment with sonography in trauma; *IP,* intraperitoneal; *IPH,* intraperitoneal hemorrhage; *LAP,* laparotomy. *Certain pelvic fractures are more likely to cause pelvic vascular disruption and subsequent retroperitoneal hemorrhage. †Determined by unequivocal free intraperitoneal fluid on FAST or positive peritoneal aspiration on diagnostic peritoneal aspiration *(DPA).* ‡One or more studies may be indicated. Serial physical examinations are generally considered unreliable owing to the presence of pelvic fracture. §Need for laparotomy is based on clinical scenario, diagnostic studies, and institutional resources. ¶Discharge from the perspective of need for further consideration for laparotomy.

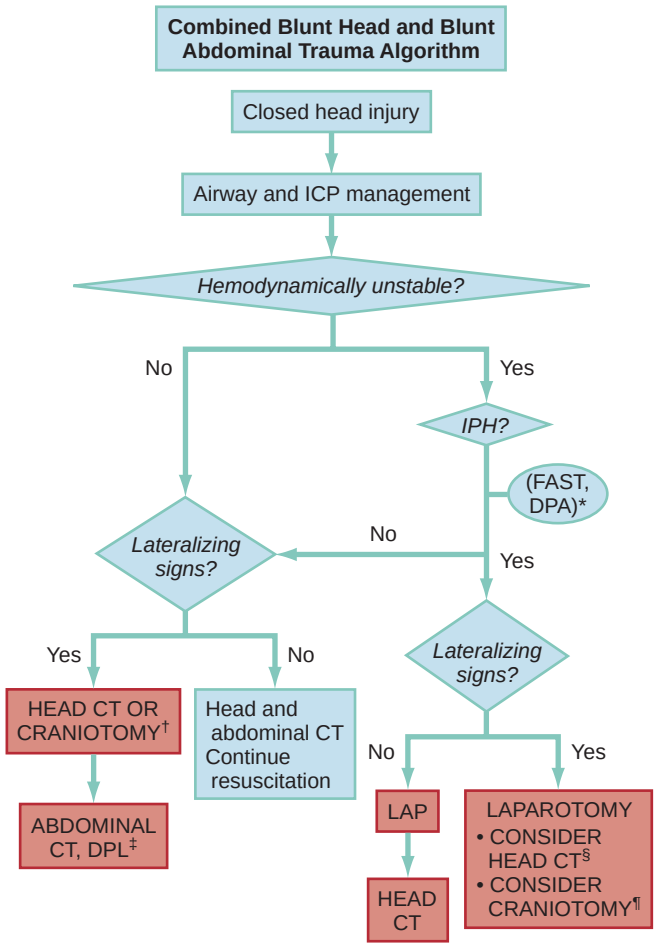

Fig. 39.10. Combined blunt head and blunt abdominal trauma algorithm. *CT,* Computed tomography; *ICP,* intracranial pressure; *IPH,* intraperitoneal hemorrhage. *Determined by unequivocal free intraperitoneal fluid on focused assessment with sonography in trauma *(FAST)* or positive peritoneal aspiration on diagnostic peritoneal aspiration *(DPA).* †Craniotomy or burr holes based on clinical picture and unavailability of computed tomography (CT). ‡Diagnostic peritoneal lavage *(DPL)* can be complementary to CT in determining hollow viscus injury. §Consider prelaparotomy *(LAP)* head CT based on clinical picture and availability of CT. ¶Consider craniotomy or burr holes simultaneous with laparotomy.

wound is infiltrated with a local anesthetic containing epinephrine then carefully visualized through each successive layer of tissue. Blind probing with digits, instruments, or cotton-tipped swabs is inaccurate, unless the peritoneal cavity is obviously freely entered. If LWE indicates that the peritoneum is not violated, the E-FAST is negative, and the patient is otherwise uninjured, the injury can be treated as a local abdominal wall injury, and the patient is treated and discharged. Indication of entry into the peritoneal cavity or inability to locate the end of the wound tract are indications for ongoing observation or abdominal CT scan (see Management).[3]

Wound explorations in patients with multiple entrances are not economical and require extensive effort, and it may be wiser to assume peritoneal penetration. Deep exploration over the thoracic cage is precluded by attendant complications to neurovascular structures and pleura. However, careful inspection of superficial chest wounds (eg, slash wound) is safe and can provide valuable data.

Therapeutic Angioembolization

Therapeutic angiography, a time-consuming procedure, is usually reserved for the unstable patient with blunt trauma and pelvic fracture in whom it can be used to embolize bleeding vessels (Fig. 39.12). Laparotomy and angioembolization for pelvic fractures with hemoperitoneum have shown no significant difference in regards to in-hospital mortality regardless of hemodynamic status.[20] It can also be a means of staunching solid visceral hemorrhage from blunt trauma, notably of the spleen. Nonoperative management has become standard in management of splenic injuries but is associated with increasing failure rates with increasing grades of injury, up to 44% with the highest-grade injuries. Successful nonoperative management increases significantly with the use of angioembolization, although higher-grade injuries are still more likely to fail nonoperative management than

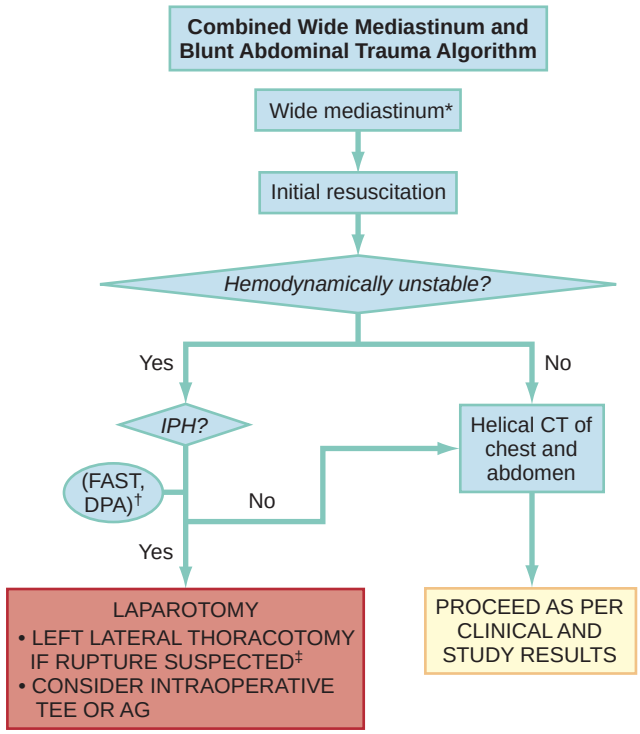

Fig. 39.11. Combined wide mediastinum and blunt abdominal trauma algorithm. *AG,* Aortogram; *CT,* computed tomography; *FAST,* focused assessment with sonography in trauma; *IPH,* intraperitoneal hemorrhage; *TEE,* transesophageal echocardiogram. *Preferably based on upright posteroanterior film and mechanism of injury; other radiographic signs or mechanism alone may signal need for evaluation. †Determined by unequivocal free intraperitoneal fluid on FAST or positive finding on diagnostic peritoneal aspiration *(DPA).* ‡Allows surgical access to majority of aortic disruption sites.

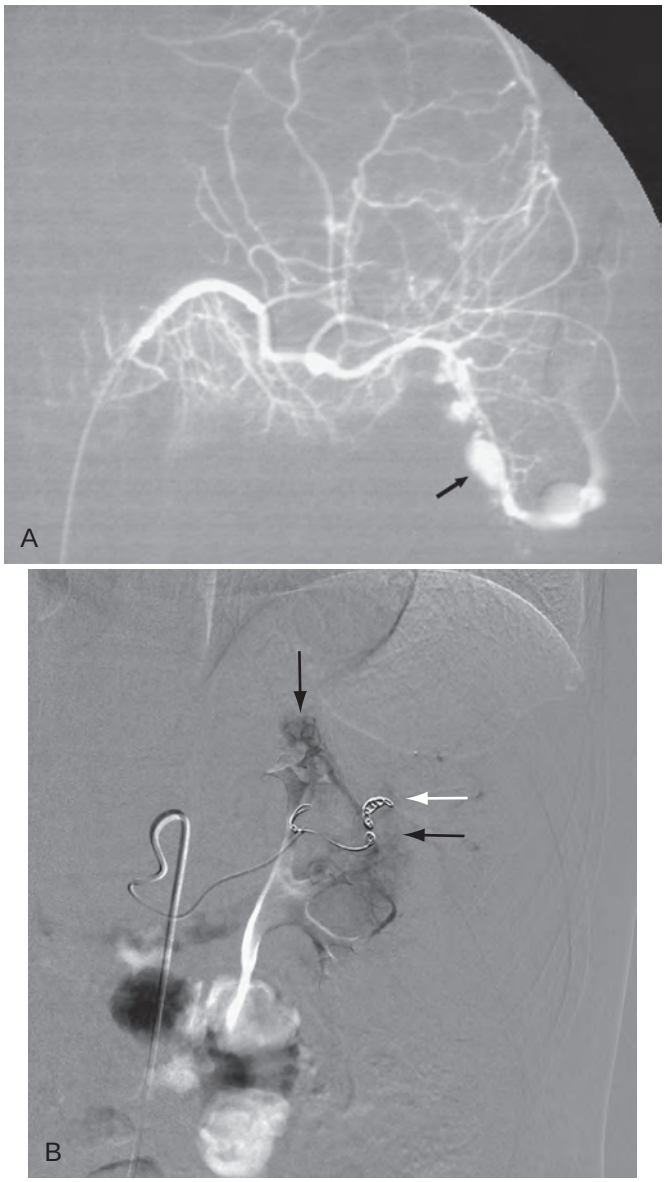

Fig. 39.12. **A,** Angiography of splenic laceration. Note the blush representing active hemorrhage *(arrow).* **B,** Angioembolization of renal laceration. Note coil in the splenic artery *(white arrow)* and blush representing active hemorrhage stemming from two branches *(black arrows).* (**A,** From Mauro MA: Image guided interventions, Philadelphia, 2008, Elsevier, p 835.)

lower-grade injuries. Angioembolization may have the added benefit over splenectomy of preserved splenic immunity in many cases, although further data are needed. Finally, angioembolization also has been used rarely for intraperitoneal and retroperitoneal hemorrhage after trauma by a penetrating mechanism.

DISPOSITION

Disposition will vary according to findings from the evaluation and the patient's clinical course. Stable patients without any identified injuries sustaining stab wounds (see Fig. 39.6) or blunt abdominal trauma (see Fig. 39.8) may be discharged home according to the algorithms provided. Patients sustaining penetrating wounds into the peritoneal cavity should either be admitted and followed with serial examinations or taken immediately to the operating room (see Figs. 39.6 and 39.7). Patients sustaining blunt abdominal trauma should be taken to the operating room or angioembolization suite (see Figs. 39.8, 39.9, 39.10, and 39.11), whereas stable patients with identified injuries can either be admitted for serial examinations or taken to the operating room, as necessary.

Consultation

Trauma is a multi-disciplinary condition. Early consultation with a general or trauma surgeon, or their involvement as part of a team response to severe trauma is a hallmark of an effective trauma hospital. Emergency clinicians provide care to the majority of abdominal trauma patients, and initial evaluation and resuscitation to an even greater proportion, but many injuries, as outlined earlier, require operative intervention or prolonged observation on an experienced service. Similarly, consultation with a radiologist may help to prioritize studies, avoid unnecessary studies, or obtain the vital information with the minimum exposure of the patient to ionizing radiation or contrast material.

Transfer

Patients with significant abdominal trauma whether blunt or penetrating should be transferred to a level I, II, or III trauma center as soon as possible after the threatening injury is identified, and without delay for time-consuming imaging studies that will not alter the need for transfer. Trauma patients in non-trauma hospitals with significant transfer times may require a stabilizing damage control laparotomy by a general surgeon before being transferred to a trauma center for definitive care.

KEY CONCEPTS

- The accuracy of physical examination is limited in cases of abdominal trauma. It is rendered less reliable by distracting injury, altered sensorium (eg, head trauma, alcohol or drug intoxication, developmental delay, psychiatric illness), and spinal cord injury.
- Stab and gunshot wounds frequently violate the lung parenchyma, diaphragm, mediastinum, intraperitoneal cavity, and retroperitoneum in some combination.
- Physical examination with E-FAST, followed by CT scan when indicated, provides accurate diagnosis for the majority of blunt and penetrating abdominal trauma patients.
- Emergent laparotomy is indicated for patients sustaining a stab wound in the setting of hemodynamic compromise, peritoneal signs, evisceration, or left-sided diaphragmatic injury. Patients not meeting these criteria undergo a combination of LWE, CT scan, serial examination and E-FAST, depending on the location of the wound
- Emergent laparotomy is indicated for patients sustaining a gunshot wound in the setting of hemodynamic compromise, peritoneal signs, or peritoneal violation. Patients not meeting these criteria undergo a combination of LWE, CT scan, serial examination and E-FAST, depending on the location of the wound.
- The critical determinant in hemodynamically unstable patients with pelvic fracture is the existence of active intraperitoneal hemorrhage. Discovery of this by E-FAST, CT scan, or peritoneal aspiration is an indication for laparotomy, whereas its absence prompts diagnostic and potentially therapeutic angiography.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 39: QUESTIONS & ANSWERS

39.1. The focused assessment with sonography in trauma (FAST) scan of a patient with blunt abdominal trauma shows a hypoechoic stripe in the pouch of Douglas. Which of the following is correct?

A. In the presence of hemodynamic instability, this indicates a need for laparotomy.
B. The patient needs to go for emergent laparotomy.
C. The patient requires repeat abdominal examinations and FAST examinations in the emergency department (ED).
D. There is at least 50 mL free fluid in the abdomen.
E. This indicates a ruptured bladder.

Answer: A. The pouch of Douglas is one of the areas of ultrasound inspection for a FAST examination. If free fluid is present and the patient is hemodynamically unstable, the patient should forego computed tomography (CT) scanning for the operating room. FAST examinations are effective in detecting as little as 100 mL of free fluid in the abdominal cavity.

39.2. An 18-year-old man presents after a moderate-velocity front-end vehicle collision. He has a blood pressure of 110/70 mm Hg, heart rate of 120 beats per minute, respiratory rate of 17 breaths per minute, and a Glasgow Coma Score (GCS) of 13. On physical examination, he has a tender abdomen and an unstable pelvis. A FAST examination is positive for free fluid in the abdomen. What should be the next step in this patient's management?

A. Admission to the trauma service for observation
B. Diagnostic peritoneal lavage (DPL) followed by laparotomy if 5 mL blood is aspirated
C. DPL followed by laparotomy if 10 mL of grossly bloody aspirate is obtained
D. Emergency laparotomy
E. ED observation for 12 hours with repeat FAST examinations

Answer: C. Although the sensitivity of FAST examinations for identifying intra-abdominal injuries requiring surgical intervention is not high, it still serves as a tool to triage patients to the next intervention. In an unstable patient, a positive FAST ultrasound scan is followed by a supraumbilical peritoneal aspirate. If this reveals 10 mL or more of blood, then the patient should expeditiously move to laparotomy.

39.3. Which of the following is *not* an advantage of CT scanning over diagnostic peritoneal lavage (DPL) in assessing patients with blunt abdominal trauma?

A. Identification of hemorrhage
B. Evaluation of genitourinary injury
C. Evaluation of retroperitoneum
D. Evaluation of unstable trauma patients
E. Quantification of hemorrhage

Answer: D. In most situations, CT scanning has supplanted DPL because of its higher predictive ability for operative lesions and the fact that it is noninvasive. CT scanning can define the injured organ and the extent of the injury. It is most accurate for solid visceral lesions and accurately discerns the presence, source, and approximate quantity of intraperitoneal hemorrhage. It can demonstrate active bleeding from the liver or spleen, and it can be used to determine whether therapeutic angiographic embolization is indicated. CT scanning also evaluates the retroperitoneum. In cases of blunt trauma, DPL's primary remaining use is the triage of the patient who is hemodynamically unstable and has multiple injuries with an equivocal FAST examination.

39.4. Which of the following statements regarding radiation exposure from CT scans in the setting of blunt abdominal trauma is false?

A. A single CT scan may increase the lifetime risk of cancer.
B. CT scans are never indicated in pregnancy, given the risk of radiation to the fetus.
C. Institutions should follow as low as reasonably achievable (ALARA) principles to mitigate radiation exposure.
D. Medical radiation may be responsible for 0.4 to 1% of all cancers in the United States.
E. Patients transferred to another facility should have attempts made to convey the images to the receiving facility as long as it does not negatively impact the patient's care.

Answer: B. Although there is a risk to the fetus with radiation, there may be situations where the risk of missed injury or exploratory laparotomy outweighs the risk of radiation to both mother and fetus. Patients being transferred to another facility should have attempts made to provide CT scans either in hard copy or digitally, to minimize repeat radiation exposure to the patient. Current estimates suggest at least 0.4% of all cancers in the United States are secondary to medical radiation, and a single CT scan may increase the lifetime risk of cancer. Facilities can minimize this risk by adopting ALARA principles.

39.5. A 27-year-old male presents 4 hours after an isolated stab wound to the anterior abdomen. His vital signs are heart rate 84 beats per minute and blood pressure 115/64, and the lactate level is 0.9 mg/dL. His focused assessment with sonography in trauma (FAST) examination is negative for free fluid. He denies alcohol and drug use and appears clinically sober. Which of the following statements regarding this patient's subsequent management is true?

A. A diagnostic peritoneal lavage (DPL) with 250,000 red blood cells per mm^3 indicates the need for admission and serial abdominal examinations.

B. A local wound exploration (LWE) that fails to demonstrate peritoneal violation means that the patient can be discharged from the emergency department (ED).

C. A negative computed tomography (CT) scan rules out the need for further evaluation.

D. The negative FAST examination rules out intra-abdominal injury requiring operative intervention.

E. The patient meets criteria for emergent laparotomy.

Answer: B. Simple anterior abdominal stab wounds that do not violate the peritoneum can be discharged from the ED after appropriate wound care (see Fig. 39-6). Not all anterior stab wounds meet indication for laparotomy, even in the presence of peritoneal penetration. A DPL of greater than 100,000 red blood cells (RBCs)/mm^3 is an indication for laparotomy in abdominal stab wounds. A negative FAST examination does not rule out significant intra-abdominal injury or even small-volume hemoperitoneum in either penetrating or blunt abdominal trauma. CT scans poorly visualize both the small bowel and diaphragm and cannot be used in isolation to rule out injury in penetrating abdominal trauma.

39.6. A 67-year-old female who is taking warfarin (Coumadin) for atrial fibrillation presents after a high-mechanism motor vehicle collision. Her heart rate is 142 beats per minute and blood pressure is 84/40 after 1 L of normal saline. Her Glasgow Coma Score (GCS) is 6, and her left pupil is 6 mm versus 3 mm on the right. Her physical examination is notable for a seat belt sign on the abdomen. Which of the following is *not* an acceptable approach to her initial assessment and treatment?

A. Perform a focused assessment with sonography in trauma (FAST) examination to evaluate for the presence of intra-abdominal fluid.

B. Perform chest and pelvic radiographs in the resuscitation bay.

C. Perform empirical craniotomy concurrently with laparotomy in the operating room after a positive diagnostic peritoneal aspiration.

D. Perform endotracheal intubation and begin mild hyperventilation.

E. Proceed to radiology for an emergent abdominal CT scan.

Answer: E. The patient is hemodynamically unstable, with suspected intra-abdominal injuries in conjunction with signs of herniation. CT scanning of the abdomen would be inappropriate in this patient. Several concurrent management options to stabilize the patient and determine the source of her hypotension are desirable (see Fig. 39.10). Endotracheal intubation allows airway control and possible hyperventilation to delay impending herniation. Chest and pelvic radiographs rule out other sources of ongoing hemorrhage and may support emergent laparotomy. A FAST examination can confirm the presence of intra-abdominal free fluid, which in the setting of hemodynamic instability is an indication for laparotomy. Finally, after confirmation of intra-abdominal blood by either digital pulse analyzer (DPA) or FAST, proceeding to the operating room, with or without emergent CT scanning of the head, are management options. If the head CT is foregone because of instability, empirical craniotomy is an acceptable management option.

39.7. Which of the following statements regarding splenic injuries in blunt abdominal trauma is false?

A. A CT scan with a grade IV splenic laceration indicates the need for laparotomy.

B. Angiographic embolization may preserve some of the immune function of the spleen, even in the setting of a grade V laceration.

C. Bedside focused assessment with sonography in trauma (FAST), although sensitive for intra-abdominal fluid, is a relatively poor test for the evaluation of solid organ injury.

D. CT scanning followed by serial abdominal examinations and hematocrits is a reasonable management option at experienced centers.

E. Mononucleosis increases the risk of splenic laceration from seemingly minor blunt abdominal trauma.

Answer: A. High-grade splenic lacerations, although having a higher rate of failed nonoperative or angiographic embolization management, do not represent a definitive indication for laparotomy. Mononucleosis does increase the risk of splenic laceration. Trauma can be so minor that the patient may have little recollection of the remote trauma responsible. Serial abdominal examinations, laboratory tests, and/or repeat FAST examinations are reasonable management options at experienced centers. Limited studies have suggested that angiographic embolization does preserve some of the immune function of the spleen compared with splenectomy. The FAST examination does not visualize solid organ injury effectively enough to eliminate the need for further evaluation with CT scanning in this case, especially because laparotomy is not necessarily indicated.

CHAPTER 40

Genitourinary System

Sanjay N. Shewakramani

PRINCIPLES

Background and Importance

Ten percent of trauma cases in the United States involve the genitourinary tract, and most of these injuries are not life-threatening. In fact, due to the anatomic protection of the kidneys, ureters, and bladder, as well as the mobile nature of the male external genitalia, isolated urologic injuries are uncommon in patients involved in major trauma. However, genitourinary trauma can cause significant, long-term morbidity, including renal insufficiency, chronic hypertension, incontinence, and sexual dysfunction. Additionally, traumatic renal injuries can be overlooked, due to the location of the kidneys and subtle presentation, with serious consequences for the patient.[1]

Almost three-quarters of all blunt injuries are caused by motor vehicle collisions, but seatbelts and air bags have been shown to result in substantially fewer high-grade renal injuries and, as a result, fewer nephrectomies.[2] Seatbelts and air bags can also cause injuries to the kidneys, although the benefits of these protective devices have been shown to outweigh the risks.[3] Forty percent of patients with renal trauma have a coexistent abdominal injury.

Blunt trauma is responsible for nearly all cases of pediatric renal trauma.[4] Kidney injuries are more common than injuries to the spleen, liver, pancreas, and bowel in this population. However, due to more conservative approaches in management, pediatric renal trauma now only rarely leads to nephrectomy.[3]

Due to the long, tubular nature of the ureter and its location in the retroperitoneum where it is well protected by the vertebrae and soft tissues, blunt traumatic injuries of the ureter are rare and virtually never occur in isolation. Most noniatrogenic ureteral injuries are due to penetrating mechanisms; the ureter is involved in up to 5% of penetrating injuries to the abdomen.[5]

After the kidney, the bladder is the most commonly injured genitourinary organ with blunt trauma; this happens most frequently from motor vehicle collisions, which are responsible for approximately 90% of cases.[6] Bladder injury most often occurs in the context of pelvic fractures or other intra-abdominal injuries, and the mortality rate in patients with blunt bladder trauma is therefore as high as 22%.[7] The bladder also is subject to penetrating injury through the abdomen, rectum, or buttocks. Up to 80% of patients with penetrating bladder injuries also suffer bowel injuries.[8]

Blunt trauma mechanisms, the majority of which are motor vehicle collisions, are responsible for approximately 90% of urethral injuries. Males are five times more likely than women to suffer urethral injuries due to the increased overall incidence of trauma in males, and the longer length and reduced mobility of the male urethra.[1] Similar to bladder injuries, significant blunt pelvic trauma is typically required to cause injuries to the urethra. As a result, concomitant injuries are often observed, with significant pelvic fractures or straddle-type injuries involved in the majority of cases.[9] Penetrating injuries to the urethra are rare and are suspected on the basis of the nature and trajectory of the penetrating object. Urethral trauma also can occur from misadventure during self-instrumentation, which is most often related to sexual activity. Urethral injury can cause significant morbidity, due to stricture formation, incontinence, impotence, and infertility, even if urethral injuries are appropriately diagnosed and treated.[10]

The external genitalia, particularly the scrotal contents, are subjected to direct injury, which happens most often in sports-related trauma. Minor external trauma may occur with consumer products (including zippers, sporting items, and furniture), and the large majority of these injuries are self-limited.[11] Severe injuries, including penile fractures and testicular rupture, are rare but generally require hospital admission. These injuries also can lead to long-term reproductive, physiologic, and psychological consequences.[1]

Although the overall rates are low in females, up to 8% of reported childhood trauma in girls involves the external genitalia.[12] Sexual abuse is much more commonly the cause than accidental trauma in this age group (see Chapter 177).[13]

Anatomy and Physiology

The genitourinary tract is divided into the upper tract (kidneys and ureters, including the renal pedicle), lower tract (bladder and urethra), and external genitalia (penis, scrotum, testicles, and vulva).

The kidneys are retroperitoneal organs that are encapsulated by fibrous tissue known as *Gerota's fascia.* They lie against the psoas muscles, are surrounded by the ribs and spinal column, and are well-cushioned by perinephric fat, leaving them fairly well-protected (Fig. 40.1). This explains why isolated renal injury is rare in trauma, because it often requires a significant mechanism to cause injury. However, the lower poles of the kidney do project inferior to the twelfth rib bilaterally, which makes them susceptible to trauma.[1] Due to their proportionately larger kidneys with less perirenal fat, weaker abdominal muscles, and a less rigid chest wall, children are at higher risk for renal injury.[14]

The renal pedicle—which includes the renal artery, renal vein, and the ureter—inserts into the kidney along the medial border, at the hilum. A longitudinal cross-section of the kidney reveals the outer renal cortex with inner medulla that compose the renal parenchyma (Fig. 40.2). These create and drain urine into the calyces, which flow into the renal pelvis, which then drains into the ureter.

The bladder is a muscular organ that lies in the abdomen at birth but descends into the pelvis at around 6 years old and is, thus, considered extraperitoneal. It is heavily protected by the bony pelvis, especially when it is not distended.[15] However, when distended, the dome of the bladder rises into the abdomen (as high as the umbilicus), making it more prone to both blunt and penetrating trauma. Posteriorly, the bladder connects to the ureters on the superior aspect, and in males, it is adjacent to the seminal vesicle and vas deferens on the inferior side. Loose connective tissue surrounds the bladder laterally.

The male urethra is approximately 22 cm in length when measured from the bladder to the urethral meatus (Fig. 40.3). The

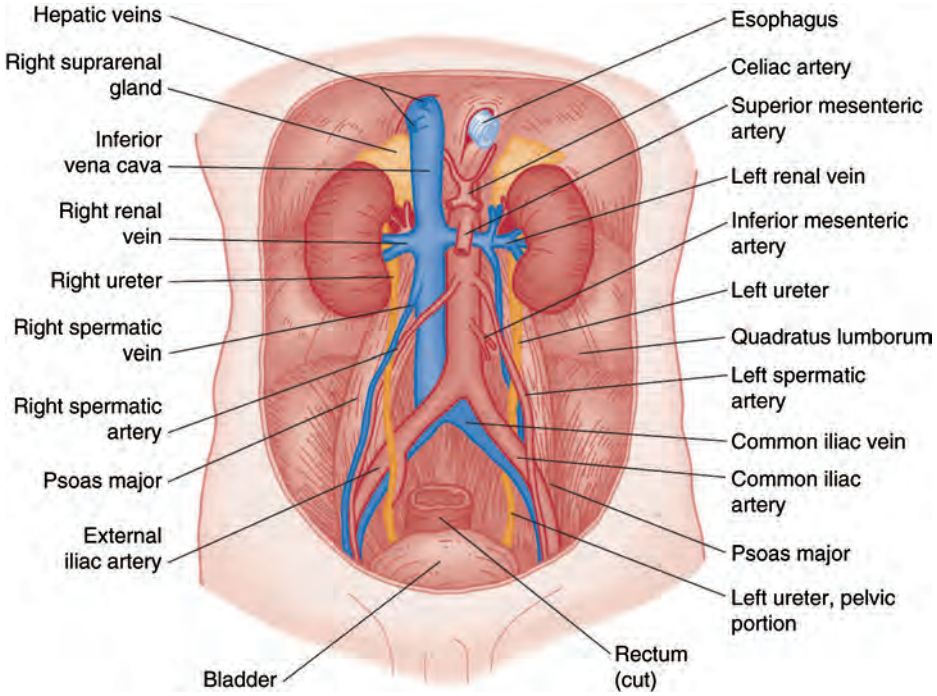


Fig. 40.1. Dissection of abdomen showing kidneys and ureters and their relationship to other anatomic features in the retroperitoneal space.

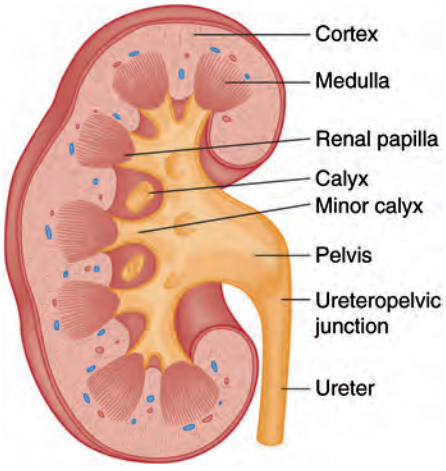


Fig. 40.2. Longitudinal section of kidney.

urogenital diaphragm divides the posterior urethra (comprised of the prostatic and membranous segments) from the anterior urethra (comprised of the bulbous and penile segments). The fossa navicularis is the slightly dilated segment of the penile urethra contained within the glans. Although the anterior urethra is more mobile, the posterior urethra is anchored to the anterior pubic arch by the puboprostatic ligaments. The female urethra is only approximately 5 cm long and is protected due to its close association with the vagina, which absorbs the majority of the force during trauma. In addition, the female urethra has no significant attachments, making it mobile, and reducing the likelihood of significant trauma.[16]

The testicles normally measure 5 × 3 × 2 cm each and are individually encapsulated by the fibrous tunica albuginea (Fig. 40.4). The encapsulated testicles are then surrounded by the tunica vaginalis, which has both a visceral and parietal surface. The potential space between these surfaces allows for hydroceles or even hematoceles to form. Each half of the scrotum contains a separate testicle, spermatic cord, and epididymis.

The penis is composed of two paired corpora cavernosa along the dorsal aspect and a corpus spongiosum along the ventral surface (Fig. 40.5). The corpora cavernosa are filled with venous sinusoids that surround a central artery and engorge with blood during an erection, whereas the corpus spongiosum surrounds the urethra and forms the glans penis on its distal aspect. Each of the three is surrounded by a separate fascial sheath, which also is referred to as the *tunica albuginea.* Buck's fascia, the deep fascia of the penis, immediately surrounds the three structures, and multiple other superficial fascial layers further surround Buck's fascia. The superficial and deep dorsal veins provide most of the venous drainage from the penis.

Pathophysiology

Because it is fixed in space only by the renal pelvis and pedicle, the kidney is prone to acceleration and deceleration injuries from blunt trauma. The American Association for the Surgery of Trauma (AAST) guidelines for grading blunt renal trauma are essentially unchanged since their creation in 1989, with grades III, IV, and V defined as "high grade" renal trauma (Table 40.1 and Fig. 40.6).[1] Lacerations and contusions typically occur from direct trauma, whereas renal artery avulsions can occur from deceleration mechanisms. Renal artery thrombosis can occur when the renal artery is compressed between the anterior abdominal wall and vertebral bodies.[17] Penetrating injuries, typically due to gunshot and stab wounds, can cause similar patterns of injury as blunt injuries.

Blunt injuries can cause trauma to the ureter either directly from compression against fractured bony structures (such as, transverse processes of lumbar vertebrae) or by deceleration mechanisms, which can cause a disruption at the ureteropelvic and ureterovesical junctions.[5] Due to their hyperextensible vertebral columns, children are more prone to deceleration mechanisms. Penetrating injuries are almost exclusively unilateral, and

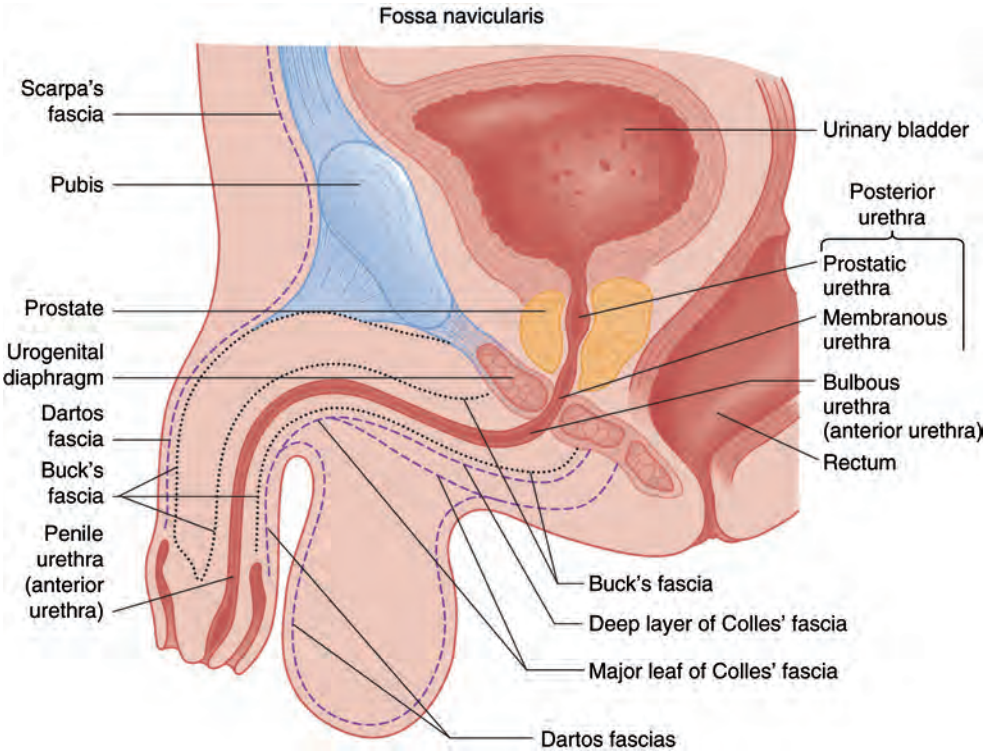


Fig. 40.3. Anatomy of male genitalia.

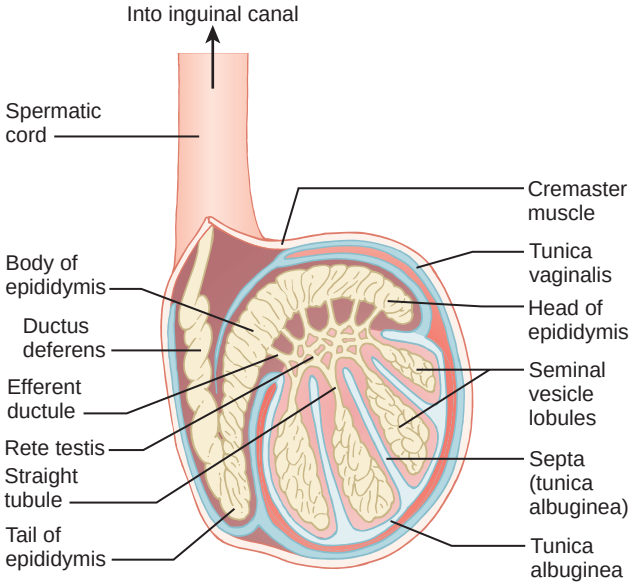


Fig. 40.4. Scrotal anatomy.

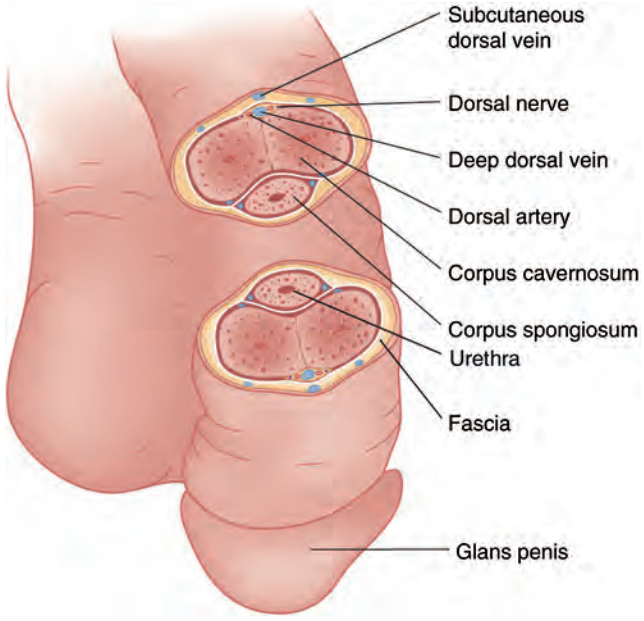


Fig. 40.5. Cross-sectional view of the penis.

gunshot wounds tend to cause more devascularization and potential ureteral necrosis than stab wounds, which usually involve only a short segment of the ureter.[8]

Bladder injuries range from mural contusions (representing 50% of injuries) to bladder ruptures, which are defined as lacerations through the entire wall of the bladder.[18] Ruptures are further classified into intraperitoneal bladder ruptures (IBRs) and extraperitoneal bladder ruptures (EBRs). Intraperitoneal injuries resulting from blunt trauma are typically caused by rupture of a distended bladder at its weakest point, which is the dome where it abuts the peritoneum. As a result, urine drains into the peritoneal cavity. EBRs, which account for the majority of bladder ruptures, occur as the result of direct compression, shear forces at the bladder base, or lacerations from bony spicules from pelvic fractures.[1,18] These ruptures result in urine draining into the pelvic cavity. Approximately 10% of bladder injuries are both intraperitoneal and extraperitoneal in nature.[1]

With blunt trauma to the pelvis, shearing forces transmitted through the urogenital diaphragm create tension along the urethra, most often between the anterior and posterior segments at the bulbomembranous junction. These forces occur commonly in unstable pelvic fractures, bilateral ischiopubic rami fractures, and symphysis pubis diastasis injuries. In fact, the combination of anterior pelvic ring fracture with sacroiliac joint disruptions posteriorly present with a concomitant posterior urethral injury

in approximately 25% of cases. Injuries can range from stretching, to partial lacerations, to complete disruptions of the urethra; the latter of which accounts for approximately 50% to 65% of urethral injuries.[19] The majority of these injuries involve the posterior urethra, and the most severe injuries are complex posterior injuries involving the bladder neck or rectum.[1]

Anterior urethral injuries, which are four times less common than posterior injuries, are often caused by blunt straddle-type injuries, which result in crushing of the bulbar urethra against the inferior aspect of the pubic bone (Fig. 40.7). These injuries occur more commonly in children and can be easily missed, potentially resulting in future strictures.[16] Gunshot wounds and other penetrating injuries involve the anterior urethra more commonly than the posterior urethra.[1]

TABLE 40.1

The American Association for the Surgery of Trauma Grading Scale for Classification of Renal Trauma

GRADE	TYPE	DESCRIPTION
I	Contusion Hematoma	Microscopic or gross hematuria Subcapsular, nonexpanding without parenchymal laceration
II	Hematoma Laceration	Nonexpanding perirenal hematoma confirmed to renal retroperitoneum <1 cm parenchymal depth of renal cortex without urinary extravasation
III	Laceration	>1 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation
IV	Laceration Vascular	Parenchymal laceration extending through the renal cortex, medulla, collecting system Main renal artery or vein injury with contained hemorrhage
V	Laceration Vascular	Completely shattered kidney Avulsion of renal hilum that devascularizes kidney

From Harper K, Shah KH: Renal trauma after blunt abdominal injury. J Emerg Med 45:400–404, 2013.

Besides testicular rupture, which is caused by disruption of the testicular tunica albuginea, blunt trauma can also lead to scrotal hematomas, testicular contusions, testicular fractures, testicular dislocation, or even traumatic testicular torsion and traumatic epididymitis.[20] In fact, significant injuries occur in up to 45% of all patients presenting with blunt trauma to the scrotum.[21] Testicular hematomas form within the testicle and may be associated with testicular rupture, whereas testicular fractures are defined as linear avascular areas within the testicular parenchyma without rupture of the tunica albuginea. Testicular dislocation occurs when blunt trauma forces the extra-scrotal migration of one or both testicles, although bilateral dislocations are rare. They migrate along the course of the spermatic cord and typically are found in the superficial inguinal area, but they can even be found in the suprapubic region.[22] Penetrating injuries often violate the tunica albuginea.[1]

Penile fractures, due to tears of the tunica albuginea, account for the majority of blunt penile injuries that present to the emergency department (ED). Blunt trauma can also lead to rupture of the dorsal veins or artery, resulting in local ecchymosis that can be easily mistaken for a penile fracture, and is therefore termed a *false penile fracture*.[23] Penetrating injuries to the penis involves the urethra in up to 29% of cases and can also result in penile amputation, which is more common in patients with a psychiatric history.[1,24]

Nonsexual genital injuries in females are most often due to straddle injuries in young girls, but other blunt and penetrating injuries do occur and are often more severe.[13] The labia are most frequently involved, as well as the perineum. Penetrating injuries can involve the rectum as well as urethra, and these deeper injuries

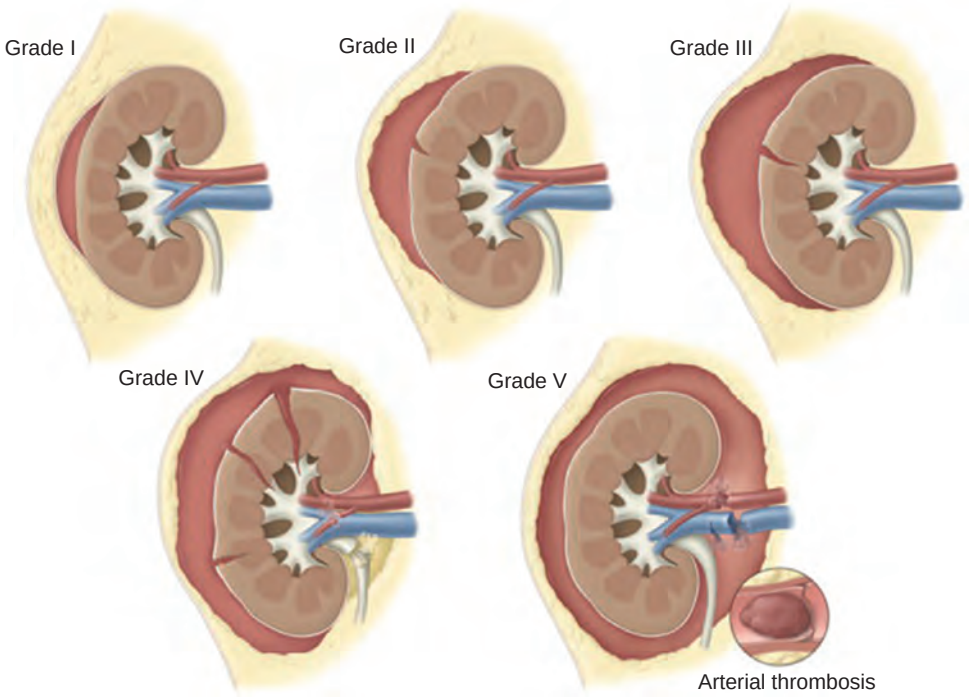


Fig. 40.6. Schematic of the American Association for the Surgery of Trauma (AAST) grading scale for renal trauma. (From Myers JB, Brant WO, Broghammer JA: High-grade renal injuries: radiographic findings correlated with intervention for renal hemorrhage. Urol Clin North Am 40:335–341, 2013.)

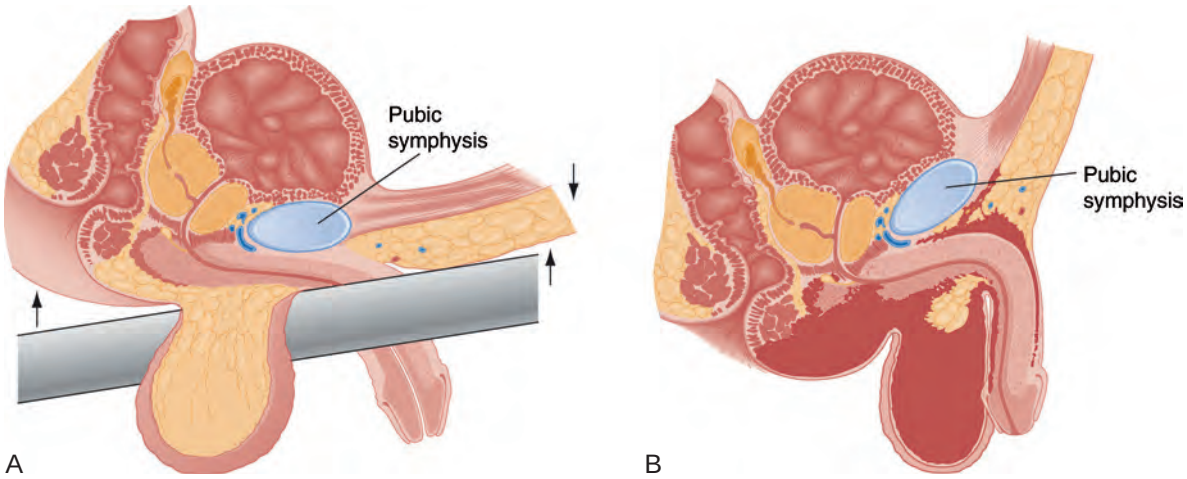


Fig. 40.7. Injury to the bulbous urethra due to straddle mechanism. **A,** Mechanism: Usually a perineal blow or fall astride an object, crushing the urethra against inferior edge of pubic symphysis. **B,** Extravasation of blood and urine enclosed within Colles' fascia. (From McAninch JW: Injuries to the genitourinary tract. In Tanagho EA, McAninch JW, editors: Smith's general urology, ed 14, Norwalk, CT, 1995, Appleton & Lange.)

can easily be missed in young girls if a thorough examination is not performed.[12]

The diagnostic and management approach to each organ varies, necessitating a basic understanding of the anatomy and traumatic pathophysiology of each individual organ. The majority of cases require early urologic consultation. The clinical features, diagnostic approach, and management guidelines for the specific organs are discussed in the following sections.

RENAL TRAUMA

Clinical Features

The history for patients with potential renal trauma includes the mechanism of injury for blunt trauma and the type of implement or weapon for penetrating injury. Significant genitourinary injury is rare in the absence of high energy blunt trauma, unless the trauma is localized to a full bladder or the external genitalia. Gross hematuria warrants careful evaluation for significant genitourinary injury, although the degree of hematuria does not necessarily correlate with the degree or grade of injury, and significant genitourinary trauma can occur without hematuria.[14] Renal injury requiring intervention is rare in the absence of gross hematuria or shock. Examination of the patient with multisystem trauma may reveal shock, flank tenderness, mass, or ecchymosis; loss of flank contour; obviously fractured ribs; abdominal tenderness; or an abdominal mass.[25]

Differential Diagnosis

Blunt or penetrating trauma can result in a range of injuries to the kidney and the vascular supply to the kidney, as shown in Table 40.1). Injuries to the renal parenchyma can cause contusions or lacerations within the kidney or hematomas surrounding the kidney. Vascular injuries can involve the renal artery or vein and vary in significance. Minor injuries to the vascular supply can lead to a contained hematoma, but hilar avulsion can result in complete devascularization of the kidney.[1]

Diagnostic Testing

Although significant renal injury can occur without causing hematuria, 95% of all patients with renal trauma have some hematuria on urinalysis, which is defined as more than five red blood cells per high power field. Patients with multisystem trauma, especially with evidence of blood loss, require a complete blood count and type and screen. Creatinine drawn within an hour of injury reflects renal function prior to the injury and, thus, serves as a baseline for future testing.[25]

Microscopic hematuria in a blunt trauma patient without shock is not an indication for renal imaging, even if there is evidence of local trauma (eg, costovertebral angle tenderness or localized ecchymosis). Although renal injury may uncommonly be identified on imaging for these patients, the injuries are mild and do not require intervention. Hemodynamic instability with evidence of intraperitoneal injury on abdominal examination, presence of pelvic fracture, a penetrating trauma mechanism, or presence of lower rib fractures, with or without hematuria, are indications for further investigation. Additionally, imaging is advisable for patients with gross hematuria, targeted to the entire urinary tract or localized to the lower tract (bladder and urethra), depending on the mechanism and location of the trauma.[1]

Computed tomography (CT) with intravenous (IV) contrast is the best modality to evaluate for renal injury with nearly 100% sensitivity and specificity. CT can evaluate for renal lacerations, hematomas, extravasation of contrast, devascularized renal segments, and urinary extravasation and thereby grade the severity of renal trauma (Fig. 40.8).[26] If there are concerns about collecting system injury (eg, ureteropelvic junction disruption, ureteral injury), delayed images should be performed 10 minutes after administration of contrast (Fig. 40.9).

Ultrasound can demonstrate renal injuries but has lower sensitivity and specificity than CT, and the quality of the study is operator dependent. It is also difficult to determine the depth and extent of renal lacerations, and it is often unclear if fluid seen surrounding the kidney on ultrasound represents urine or blood. However, unlike CT, ultrasound can be performed at the bedside if the patient is unstable. Management of the multisystem trauma patient and the patient with abdominal trauma is discussed in Chapters 33 and 39.

Management

Multisystem trauma is managed in collaboration with a general or trauma surgeon, and consultation with a urological surgeon often is indicated when there is injury to the urinary tract.

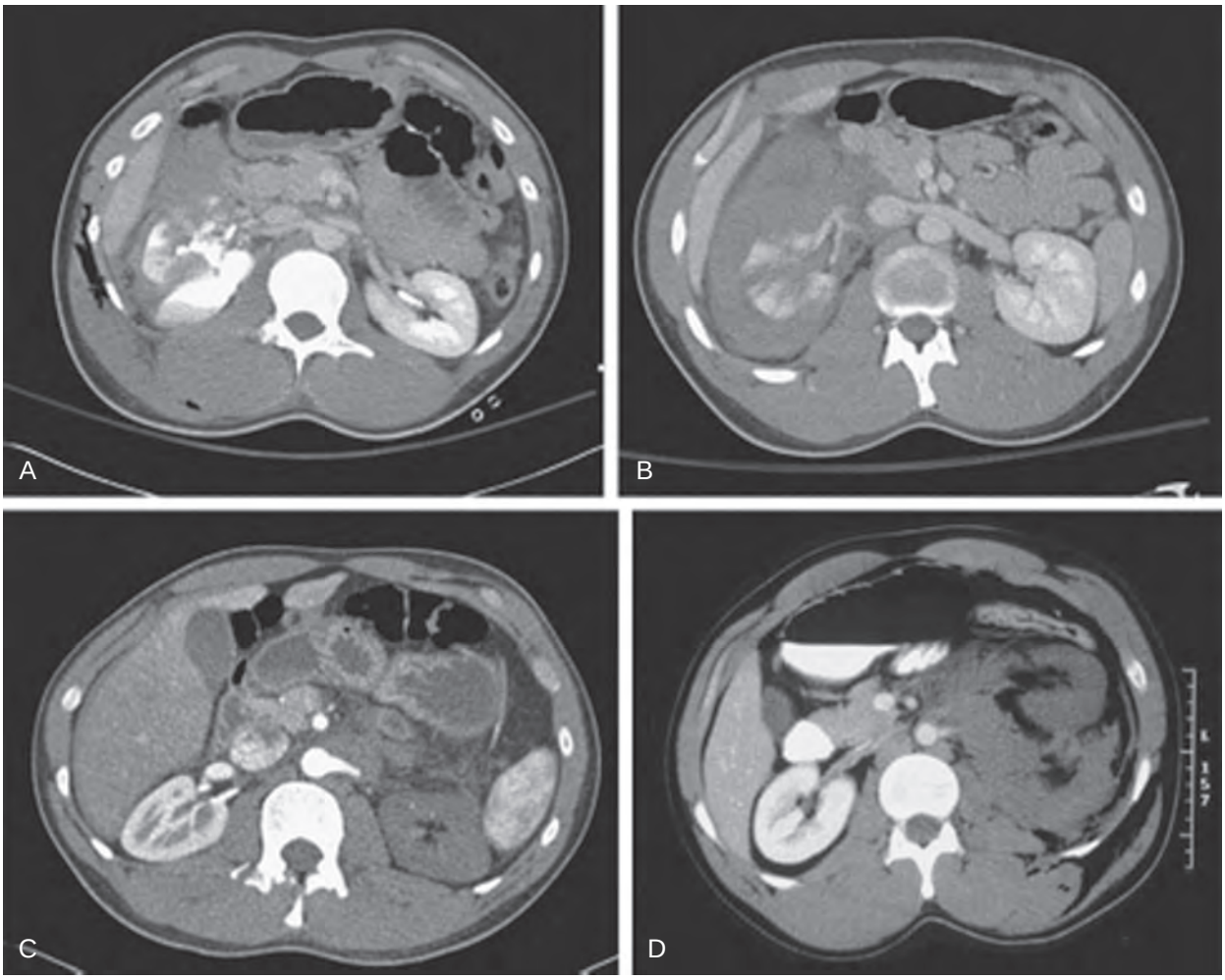


Fig. 40.8. High grade renal injuries. **A,** Grade IV injury with urinary extravasation. **B,** Severe grade IV laceration, also referred to as *shattered kidney.* **C** and **D,** Grade V injuries with devascularization of the affected kidney. (From Myers JB, Brant WO, Broghammer JA: High-grade renal injuries: radiographic findings correlated with intervention for renal hemorrhage. Urol Clin North Am 40:335–341, 2013.)

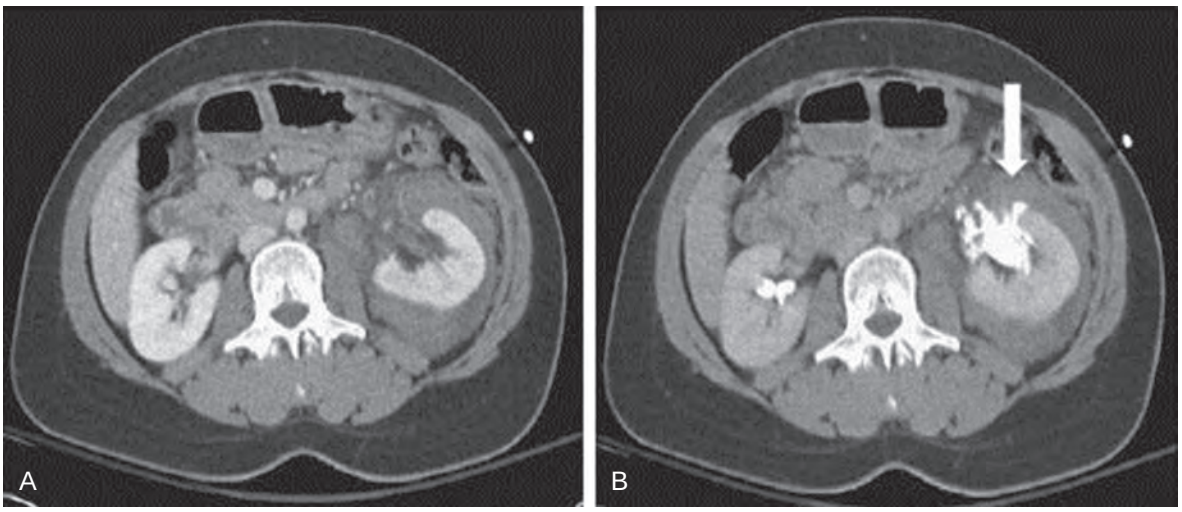
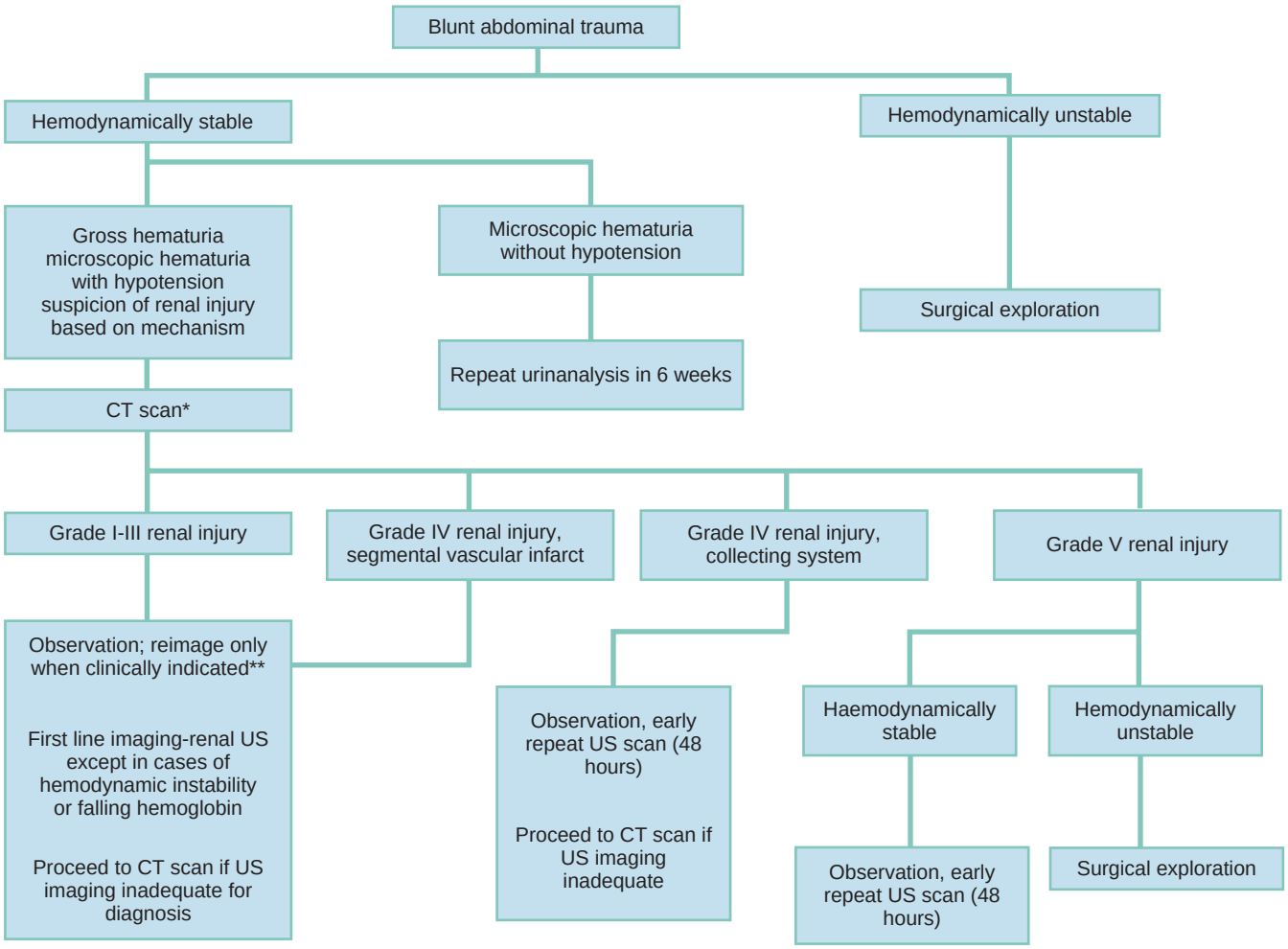


Fig. 40.9. A, Left-sided perinephric fluid collection suggests a collecting system injury on computed tomography (CT) images. **B,** Delayed images confirm a collecting system injury with contrast extravasation *(arrow)*. (From Hardee MJ, Lowrance W, Stevens MH, et al: Process improvement in trauma: compliance with recommended imaging evaluation in the diagnosis of high-grade renal injuries. J Trauma Acute Care Surg 74:558–562, 2013.)



* CT scan with and without IV contrast and delayed phase images

** Fever, progressive leukocytosis, hypertension, marked change in symptoms or physical exam

Fig. 40.10. Algorithm for imaging and management of renal trauma. *CT,* Computed tomography; *IV,* intravenous; *US,* ultrasound. (From Breen KJ, Sweeney P, Nicholson PJ, et al: Adult blunt renal trauma: routine follow-up imaging is excessive. Urology 84:62–67, 2014.)

Figure 40.10 represents an algorithm for the management of blunt trauma to the kidneys. After renal trauma is identified on imaging, hemodynamic instability determines the next step. If the patient is unstable despite fluid resuscitation, they should undergo surgical exploration. Patients found to have minor renal injuries (grade I to III) can be managed conservatively with observation and fluid resuscitation, whereas grade IV and V have a higher likelihood of needing operative intervention.[27]

Therapeutic options for blunt renal trauma include nephrectomy, ureteric stenting, percutaneous drainage, and arterial embolization.[28] Recent changes in management have focused on nonoperative therapy, leading to increased renal salvage. Surgical practice has shifted away from early exploration due to the high number of nephrectomies performed with early exploration. Thirty percent of patients with minor renal trauma undergoing exploration have nephrectomies, but if exploration is performed within 24 hours of arrival, over half undergo nephrectomy. Percutaneous transarterial embolization is being used with increased frequency even for high grade injuries to avoid nephrectomy.[27] This shift has been even more pronounced in the pediatric population, where the renal salvage rate now approaches 99%, and patients are treated with stent and nephrostomy if needed.[4] In contrast to blunt trauma, penetrating injuries to the kidney are often explored operatively. Approximately one-third of these patients will require a nephrectomy.[29]

Consideration has recently been given to further dividing grade IV injuries into IVa and IVb. The distinction is made because patients with grade IV injuries that have CT findings that reveal contrast extravasation, medial or complex lacerations, or hematomas larger than 3.5 cm require surgery more often than patients who do not.[30] In fact, patients with two or three of these criteria are 25 times more likely to require an intervention than those with zero or one of these findings.[31]

Patients with renal artery thrombosis are typically more stable and asymptomatic. Hypertension is often seen with thrombosis of the main renal artery but is rare with segmental artery thrombosis.[17] These injuries can result in devascularization of segments of the affected kidney but are also treated conservatively if possible.[32]

Complications of renal trauma include infection, urinary leak with resultant urinoma, loss of renal function, and hypertension. The most common complication is urinary tract infection.[33] In general, antibiotics should be considered for all patients with renal trauma to potentially avoid future urinary tract infections and perinephric abscess formation.[28] Grade III, IV, and V injuries are associated with a decrease in renal function of 15%, 30%, and 65%, respectively, after trauma.[34]

URETERAL TRAUMA

Clinical Features

Signs suggestive of ureteral injury include flank ecchymosis and occasionally gross hematuria with blunt trauma, and fractures of the transverse process of lumbar vertebrae are often seen. However, hematuria is seen in only half of patients and is usually microscopic. In addition, because over 20% of patients with ureteral injuries and blunt trauma have multisystem trauma with bony injuries (such as, pelvic and vertebral fractures) and hollow viscus injuries, they may not have complaints specific to the ureter, despite having a significant injury. Penetrating injuries of the ureter are often associated with injuries to the iliac vessels, which are often life-threatening. Given their subtle presentation, ureteral injuries do not declare themselves until later when patients present with sepsis (from urinary extravasation), hydronephrosis from obstruction, or a urinary fistula.[5]

Differential Diagnosis

Blunt trauma affecting the ureter can lead to stretching and resultant hematomas or, if more severe, partial or complete disruption of the ureteral wall. Penetrating injuries involving the ureter generally result in complete or partial transection.[5]

Diagnostic Testing

Hematuria is not a reliable indicator of ureteral trauma, because it is present in only 50% of patients. Blunt ureteral injury is rare, however, and further diagnostic evaluation for ureteral injury is reserved for patients with unexplained persistent hematuria or evidence of injury adjacent to the ureter, such as retroperitoneal vascular injury, vertebral fractures, or penetrating injuries near the flank. The best modality for diagnosing ureteral injury is IV contrast CT scan.[1]

IV pyelography/urography and retrograde pyelography were once used to diagnose ureteral injury, but they have been supplanted by CT scanning (Fig. 40.11). CT scan performed immediately after the administration of IV contrast can potentially miss ureteral injuries, and 10 minute delayed imaging (allowing for contrast to enter and pass through the ureter from the collecting system) is recommended. CT findings of ureteral injury include contrast extravasation, a delayed pyelogram, hydronephrosis, or lack of contrast distal to the ureteral injury.[1] Additionally, the presence of a transverse process fracture, perinephric stranding or hematomas, and low-density retroperitoneal fluid (representing urinary extravasation) should raise the concern for ureteral injury. If delayed CT imaging was not initially performed but ureteral injury is suggested by these findings, a plain film of the abdomen can be obtained 30 minutes after CT to assess for contrast extravasation into the pelvis. Alternatively, retrograde pyelography can be performed.[35]

Management

With minor injuries including contusions and partial lacerations, ureteral stenting is typically sufficient. However, débridement with anastomosis may be necessary with loss of a segment.[5] Additional options include percutaneous nephrostomy for unstable patients and ureteral reimplantation into the bladder. Nephrectomy is rare but sometimes necessary with more proximal injuries.[35]

Almost one-quarter of all patients develop a complication after ureteral injury, which are rarely life threatening but can occasionally lead to the loss of the affected kidney. Urinary leaks leading to sepsis or fistulas, as well as strictures, are among the most common complications, and are frequently seen when diagnosis of the initial injury is delayed.[35]

Fig. 40.11. Intravenous (IV) urography revealing an injury to the left distal ureter, resulting in contrast extravasation. (From Cutinha P, Venugopal S, Salim F: Genitourinary trauma. Surgery [Oxford] 31:362–370, 2013.)

BLADDER TRAUMA

Clinical Features

Unlike injuries to the ureter, hematuria is the hallmark of a bladder injury, with gross hematuria noted in 72% of patients with blunt trauma to the bladder, and up to 95% of patients with penetrating bladder trauma.[6] Other signs and symptoms include abdominal tenderness (approximately 60% of patients), blood at the urethral meatus, the inability to void, and ecchymosis in the perineum, thigh, or abdomen.[15]

Differential Diagnosis

Differentiating intraperitoneal from EBR is of utmost importance. Intraperitoneal injuries are most often caused by significant blunt force abdominal trauma in a patient with a distended bladder. Extraperitoneal injuries are usually associated with some form of pelvic trauma. Bladder injuries themselves can range from mural hematomas to through-and-through disruptions of the bladder wall, resulting in rupture.[15]

Diagnostic Testing

Other than urinalysis, laboratory evaluation is not useful in diagnosis of bladder injury.[1] Gross hematuria is present in the majority of cases; those without gross hematuria will have microscopic hematuria. High energy pelvic fractures, such as symphysis diastasis and displaced obturator ring fractures, should also raise the suspicion of bladder injury.[16]

All patients with gross hematuria and pelvic fracture should undergo cystographic imaging, due to the high likelihood of

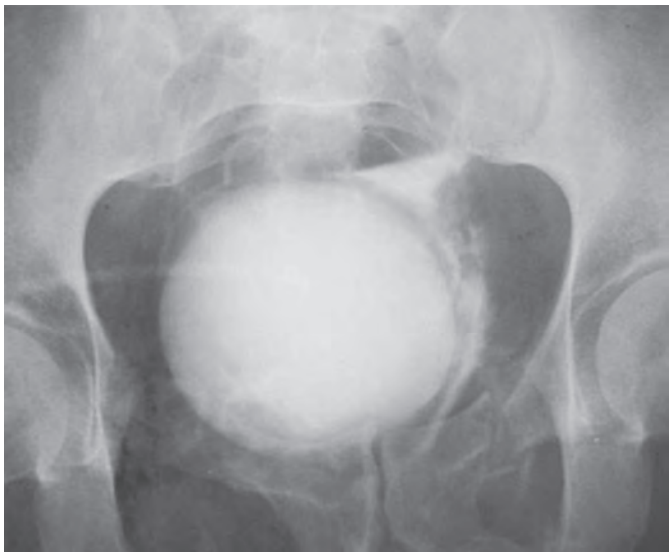


Fig. 40.12. Extraperitoneal bladder rupture (EBR) on retrograde cystography. Contrast extravasation is limited to the pelvis. (From Cutinha P, Venugopal S, Salim F: Genitourinary trauma. Surgery [Oxford] 31:362–370, 2013.)

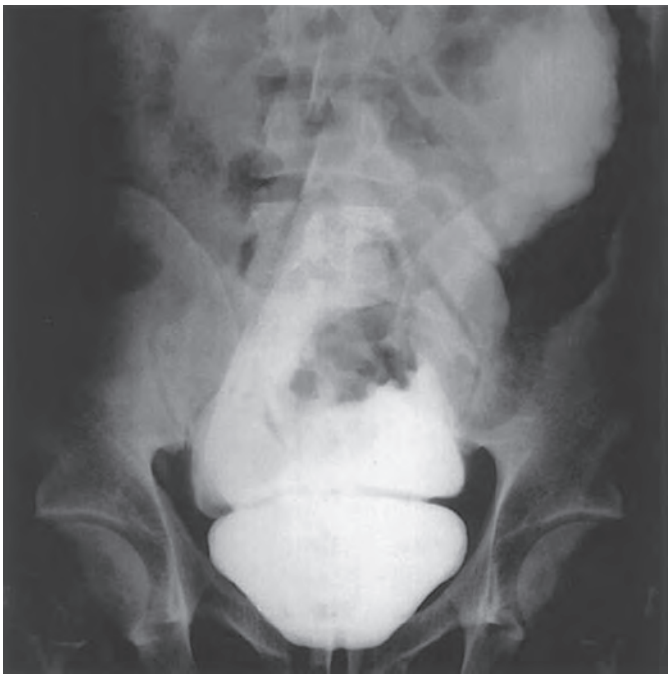


Fig. 40.13. Intraperitoneal bladder rupture (IBR) on retrograde cystography. Extravasating contrast can be seen outlining bowel. (From Cutinha P, Venugopal S, Salim F: Genitourinary trauma. Surgery [Oxford] 31:362–370, 2013.)

bladder injury.[1] Imaging is also indicated for patients with microscopic hematuria and either pelvic ring or obturator fractures, or with penetrating trauma to the pelvis.[18] CT scan performed with IV contrast alone does not sufficiently distend the bladder to evaluate for mural defects, leading to false negatives, and thus retrograde "stress" cystography must be performed.[6] This involves diluting 30 mL of water-soluble ionic contrast in a 500 mL bag of warmed saline. Approximately 300 to 400 mL of this solution is then introduced into the bladder via a Foley catheter using gravity.[18] Foley catheterization should not be performed unless the clinician is confident that urethral injury is not present (see discussion following). By distending the bladder, thrombi that may have formed along the bladder wall are dislodged, allowing for urinary extravasation. Images are then acquired to assess for rupture. Conventional cystography can assess for urinary extravasation (Figs. 40.12 and 40.13). However, CT is more sensitive (95%) and can evaluate for foreign body involvement from fractures or even bladder neck injuries. EBR may demonstrate a "molar tooth" appearance on cystography, which represents contrast tracking along the pelvic fascial planes (Fig. 40.14), whereas IBR reveals contrast material outlining the intraperitoneal structures (Fig. 40.15).[18]

Bedside ultrasonography has not been fully studied to assess for bladder rupture, although it does show promise (Fig. 40.16).[36] As with any evaluation using ultrasound, this technique is highly operator dependent, and findings are not necessarily specific.

Management

The distinction between EBR and IBR is important, because the management differs. Contusions and extraperitoneal injuries due to blunt trauma are typically managed conservatively with Foley catheterization, unless they are complicated by other intra-abdominal injuries, bladder neck injuries, bone fragments in the bladder wall, or if open reduction is performed on an associated pelvic fracture.[37] In contrast, given the extremely low likelihood of IBR and penetrating injuries healing with conservative therapy, almost all patients with these types of injuries are taken to the operating room for exploration and repair.[1] Without surgery, there is an extremely high likelihood of complications, which include infections and fistula formation.

Compared to patients with pelvic fracture alone, a concomitant bladder injury is associated with a 75% increase in mortality.[6] Due to the significant mechanism needed to cause an IBR, these injuries are associated with an approximate 20% mortality, which is twelve times more than is seen with isolated EBR.[6] Operative repair decreases the mortality risk by nearly 60%.[37] Additionally, intraperitoneal urinary extravasation can lead to delayed morbidity and mortality due to resultant infections, as well as ileus and chemical peritonitis. Extraperitoneal injuries can lead to fistula formation or infections as well but occur in the minority of cases. Penetrating rectal injuries leading to bladder involvement can result in abscess, bladder stones, urethral strictures, and fistulae.[38] The high likelihood of potential complications underscores the importance of performing retrograde cystography with an adequate amount of volume in order to diagnose all cases of bladder injury.

URETHRAL TRAUMA

Clinical Features

The "classic" presentation of posterior urethral injury includes blood at the urethral meatus, urinary retention, and a "high-riding" prostate on digital rectal examination (DRE). However, DRE is not a sensitive test, because the prostate can be obscured by a pelvic hematoma, which is common after pelvic fractures. Therefore, DRE should be focused on detecting rectal injuries, and it should not be used to diagnose urethral injury.[39] Other findings include swelling or ecchymosis of the perineum or penis (including "butterfly bruising" seen with anterior injuries that violate Buck's fascia; Fig. 40.17) and a distended bladder due to the inability to void.[35]

Blood at the urethral meatus is the most common sign, occurring in up to 90% of posterior injuries and 75% of anterior injuries. As a result, absence of blood at the meatus and the lack of a genital hematoma, bruising, or swelling decrease the likelihood of urethral injury. The degree of hematuria is not correlated with the

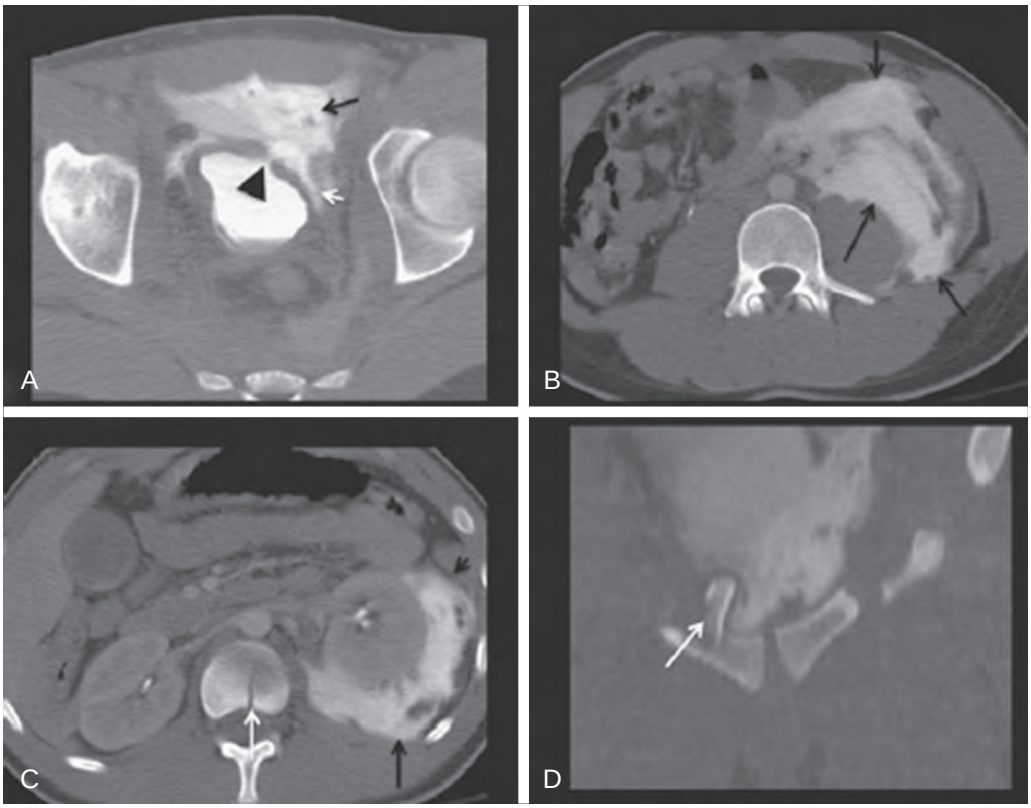


Fig. 40.14. Computed tomography (CT) cystography images from a complex extraperitoneal bladder rupture (EBR). **A,** The *arrowhead* overlying the bladder points to the location of extravasation into the perivesicular spaces. **B** and **C,** Contrast extravasation continues along the left retroperitoneum, extending into the perirenal space. **D,** The rupture was likely caused by the displaced ramus fracture fragment which is seen violating the bladder wall. There is an associated lumbar spine fracture noted in **C.** (From Avery LL, Scheinfeld MH: Imaging of male pelvic trauma. Radiol Clin North Am 50:1201–1217, 2012.)

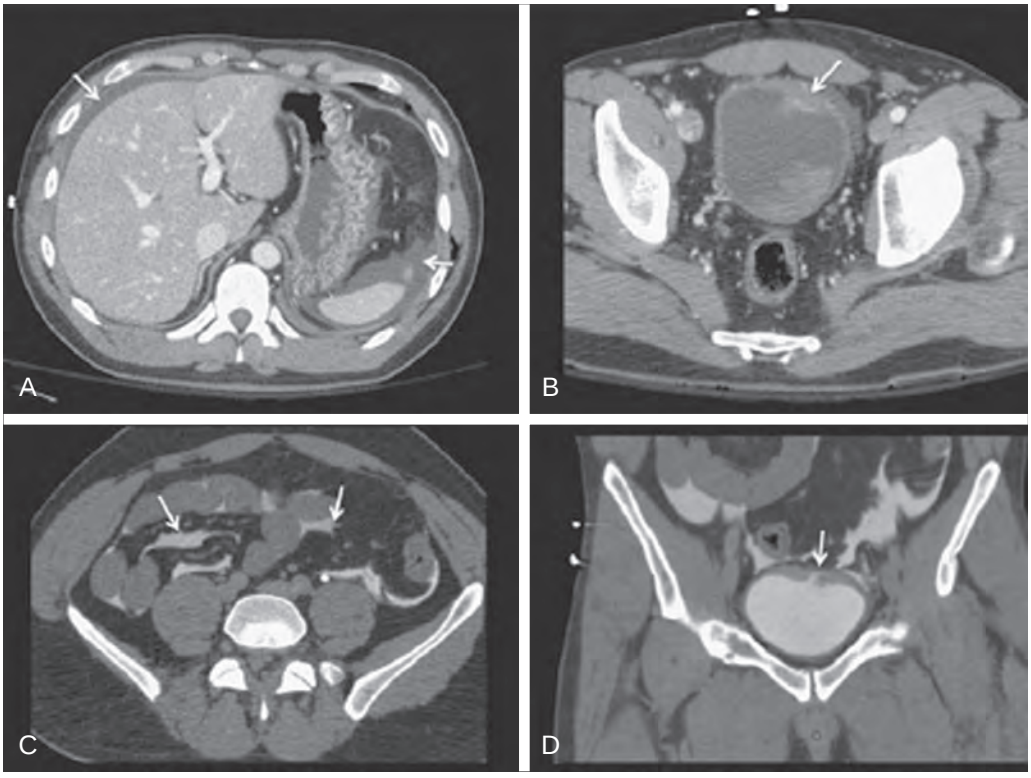


Fig. 40.15. Computed tomography (CT) images from a patient with intraperitoneal bladder rupture (IBR). **A** and **B,** Images acquired immediately after intravenous (IV) contrast administration reveal fluid around the liver and spleen, as well as clot within the bladder and left anterior bladder wall. CT cystography reveals intraperitoneal extravasation of contrast **(C)** with a disruption of the dome of the diaphragm **(D).** (From Avery LL, Scheinfeld MH: Imaging of male pelvic trauma. Radiol Clin North Am 50:1201–1217, 2012.)

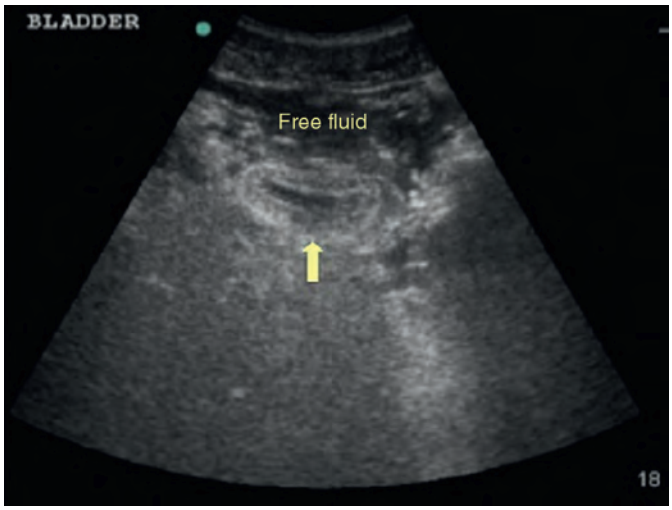


Fig. 40.16. Ultrasound image of bladder rupture. The bladder is contracted, with an irregular bladder wall posteriorly *(arrow),* and free fluid anteriorly. (From Wu TS, Pearson TC, Meiners S, et al: Bedside ultrasound diagnosis of a traumatic bladder rupture. J Emerg Med 41:520–523, 2011.)

Fig. 40.17. "Butterfly pattern" of ecchymosis of the scrotum and perineum. (From Mundy AR, Andrich DE: Urethral trauma. Part I: introduction, history, anatomy, pathology, assessment and emergency management. BJU Int 108:310–327, 2011.)

degree of injury; in fact, a transection can cause a minimal amount of microscopic hematuria, whereas a contusion can induce copious bleeding.[1]

Differential Diagnosis

Mild blunt-force injuries to the urethra can result in stretching of the urethra or a contusion of the wall. More severe injuries include partial or complete disruption of the wall. Penetrating injuries usually result in some sort of disruption of the lumen of the urethra. If complete disruption occurs, the amount of urethral separation is important, because more than 2 cm of disruption carries a worse prognosis.[1]

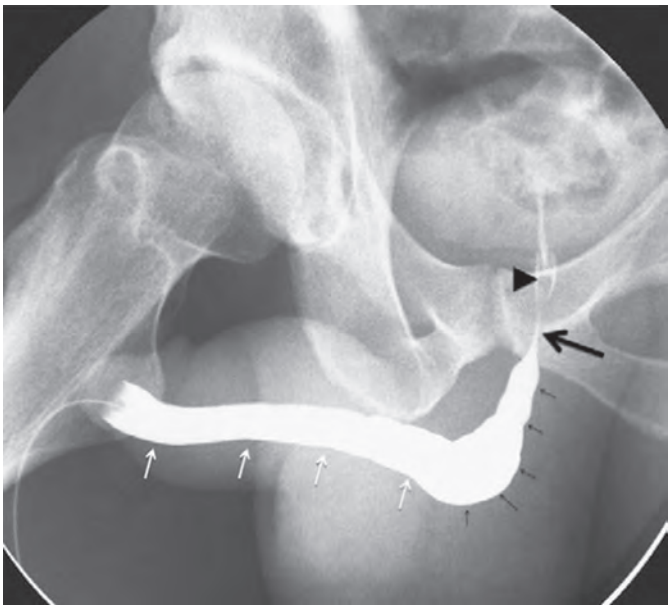


Fig. 40.18. Normal retro urethrogram. *White arrows* point to the penile urethra, and *black arrows* point to the bulbous urethra, which together form the anterior urethra. The posterior urethra is composed of the membranous urethra *(black arrow)* and the prostatic urethra *(black arrowhead).* (From Avery LL, Scheinfeld MH: Imaging of male pelvic trauma. Radiol Clin North Am 50:1201–1217, 2012.)

Diagnostic Testing

Retrograde urethrography (RUG) is the gold standard for diagnosing urethral injuries, and it should be performed if there is blood at the urethral meatus, or other findings consistent with urethral injury (eg, perineal or pelvic ecchymosis or swelling), prior to bladder catheterization (Fig. 40.18).[39] The technique for performing a RUG is detailed in Box 40.1 and depicted in Figure 40.19. A scout film that can demonstrate preexisting calcifications is important to avoid false positive diagnoses, and then it can be compared to post-contrast images.[39] Urethrography can determine the location (anterior and posterior) and extent (partial versus complete) of the injury, and it has excellent sensitivity and specificity. Figure 40.20 depicts a potential schematic of a urethral injury with the resultant RUG image. If a urinary catheter has already been placed, a pericatheter RUG can be performed by introducing a 3 Fr catheter into the fossa navicularis and then introducing a small amount of contrast.

CT scan with IV contrast only carries a sensitivity of 88% and specificity of 79%, confirming RUG as the gold standard. Ultrasonography and magnetic resonance imaging (MRI) also have limited utility in the diagnosis of urethral injury.[35]

Management

The immediate goal with urethral injury is to secure catheter drainage of the bladder.[1] Instrumenting a partially disrupted urethra with a Foley catheter can lead to complete disruption of the urethra. Additionally, continued extravasation of urine through a urethral laceration can lead to infection. Therefore, if a urethral injury is diagnosed, a suprapubic catheter should be placed as soon as possible.[39] Figure 40.21 details this procedure, which should be performed under ultrasound guidance, if possible, to avoid injury to the bowels.[40]

After suprapubic drainage is established, the surgical management of urethral injuries can be delayed in favor of treating other life-threatening injuries, except in the case of penetrating injuries or concomitant bladder neck injuries, which should be explored

BOX 40.1

Technique for Performing Retrograde Urethrography

1. A 16-Fr or 18-Fr Foley catheter or a hysterosalpingogram catheter is flushed with radiopaque contrast to avoid air bubbles.
2. The glans penis and urethral meatus are cleaned with antiseptic.
3. The catheter is inserted into the penis, and the balloon is partially inflated (1 to 2 mL) in the fossa navicularis.
4. The penis is then pulled laterally to straighten the urethra under moderate traction.
5. A precontrast "scout" image is obtained, because prostatic calcifications may be confused for extravasated contrast.
6. Under fluoroscopic visualization, 20 to 30 mL of contrast is injected with the goal of filling the entire urethra.
7. If spasm of the external sphincter prevents posterior urethral filling, slow, gentle pressure may allow opacification.
8. Static images are obtained to demonstrate the identified pathologic condition.

From Avery LL, Scheinfeld MH: Imaging of male pelvic trauma. Radiol Clin North Am 50:1201–1217, 2012.

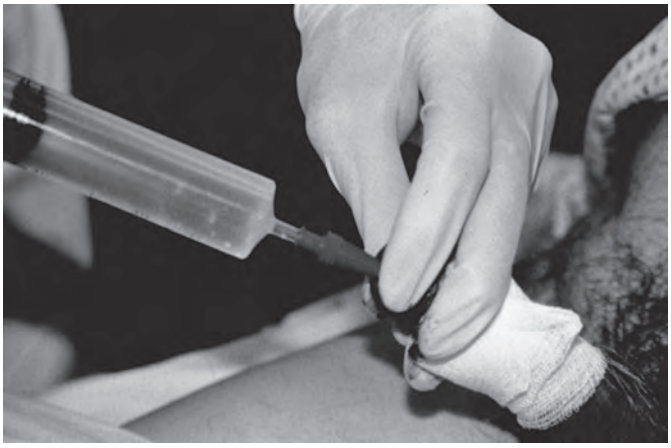


Fig. 40.19. Christmas tree adapter on the end of a 60-mL syringe has been gently placed inside the fossa navicularis in preparation for retrograde urethrography (RUG).

and débrided immediately. Delayed repair allows time for inflammation to decrease and is associated with lower rates of erectile dysfunction, urinary incontinence, and stricture formation.[9]

Complications of urethral injury include urethral stricture, urinary incontinence, and erectile dysfunction, which effects almost half of all men suffering urethral injuries.[9] Almost half of all children with pelvic fractures and associated urethral injury will exhibit erectile dysfunction at puberty. An even higher number is seen in patients with pubic diastasis.[41] The cause of erectile dysfunction is thought to be neurogenic in most cases, but it can be vasogenic or mixed in some cases.[42] In children, a higher risk is seen with urethral gap lengths more than 2.5 cm and lateral prostatic displacement.[41] A higher rate of future stress incontinence is seen in women with urethral trauma.[16]

GENITAL TRAUMA

Clinical Features

Patients with scrotal injuries may present immediately with swelling and pain, but note that patients with scrotal injuries often do not present acutely; in one study, patients had median presentation durations of 3 days.[20] Due to swelling, it is often difficult to distinguish between the different types of testicular injury on examination. Blunt force of at least 50 kg is needed to cause a rupture of the tunica albuginea with extrusion of the seminiferous tubules, resulting in testicular fracture.[20]

Penile injuries result in pain, swelling, and ecchymosis. In the setting of blunt or penetrating injuries, blood at the urethral meatus, gross hematuria, or the inability to void suggest a concomitant urethral injury.[1] False penile fractures present with the swelling and ecchymosis that is typically seen with penile fractures, but patients typically experience a more gradual detumescence and do not typically notice the popping sound that accompanies most cases of penile fracture (Fig. 40.22).[23] However, it is very difficult to make a clinical distinction between true and false penile fractures, and many of these cases still require exploration.

True penile fractures are relatively uncommon but are also likely underreported.[10] It is defined as a rupture of the tunica albuginea surrounding any of the three corpora of the penis.[43] The tunica albuginea stretches when the penis is erect, making it thin and inflexible, and thus more prone to rupture with lateral

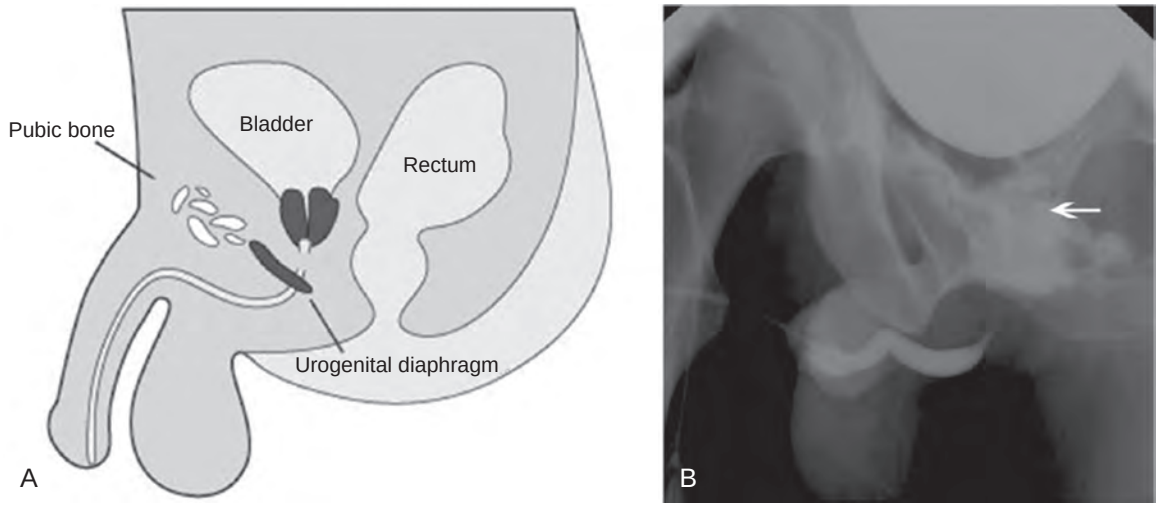


Fig. 40.20. Schematic representation of disruption of the membranous urethra **(A)** with retrograde urethrogram **(B)** revealing contrast extravasation above the urogenital diaphragm. (From Nicola R, Menias CO, Mellnick V, et al: Sports-related genitourinary trauma in the male athlete. Emerg Radiol 22[2]:157–168, 2015.)

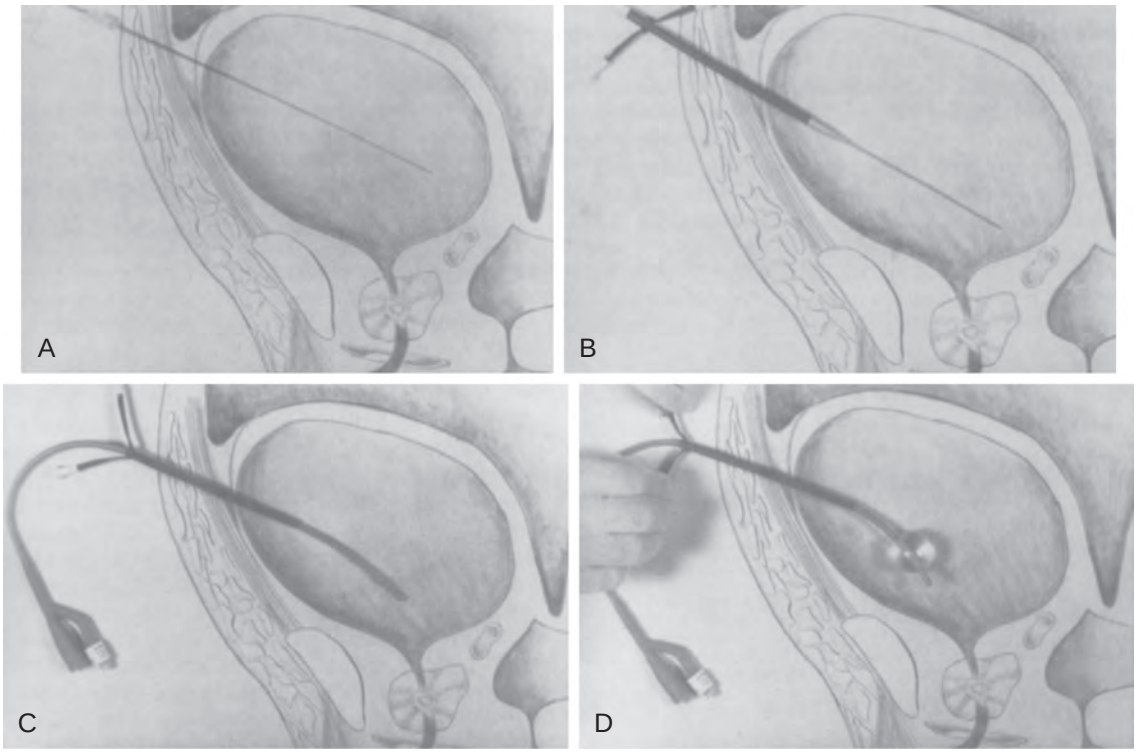


Fig. 40.21. Percutaneous placement of a suprapubic tube with peel-away sheath introducer. **A,** An 18-gauge needle is in the bladder. A guidewire is advanced through the needle. **B,** A dilator and peel-away sheath are advanced over the guidewire. **C,** The dilator and guidewire are removed. Through the peel-away sheath, an appropriately sized catheter can be introduced into the bladder. **D,** The balloon is inflated, and the sheath is pulled back and peeled away. (From O'Brien WM: Percutaneous placement of suprapubic with peel away sheath introducer. J Urol 145:1015, 1991.)

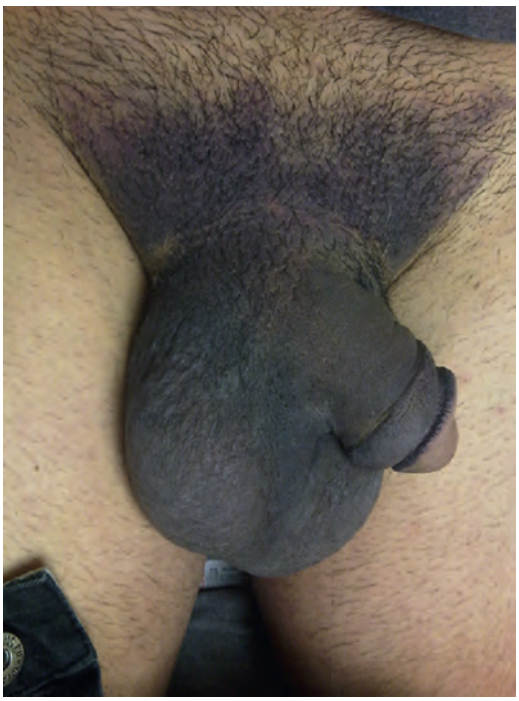


Fig. 40.22. Superficial dorsal vein rupture imitating penile fracture. (From Chang AJ, Brandes SB: Advances in diagnosis and management of genital injuries. Urol Clin North Am 40:427–438, 2013.)

Fig. 40.23. Penile fracture causing penile and scrotal ecchymosis and blood that has emanated from the urethral meatus, suggesting urethral injury. (From Hoag NA, Hennessey K, So A: Penile fracture with bilateral corporeal rupture and complete urethral disruption: case report and literature review. Can Urol Assoc J 5:E23–E26, 2011.)

bending.[44] In the Western hemisphere, penile fracture most often occurs when the penis slips out of the vagina during intercourse and is accidentally thrust against the perineum or pubic symphysis. However, in the Mediterranean and Middle-East, the most common cause is *taghaandan*—where the erect penis is forcibly pushed down to achieve detumescence.[45] Penile fractures are associated with urethral injuries in 10% to 20% of cases, and urethral injuries are more likely in cases of bilateral corporal fractures or when blood is noted at the urethral meatus (Fig. 40.23).[10] Patients with penile fracture experience immediate pain with

Fig. 40.24. Penile fracture and hematoma causing an "eggplant deformity." (From Mundy AR, Andrich DE: Urethral trauma. Part II: types of injury and their management. BJU Int 108:630–650, 2011.)

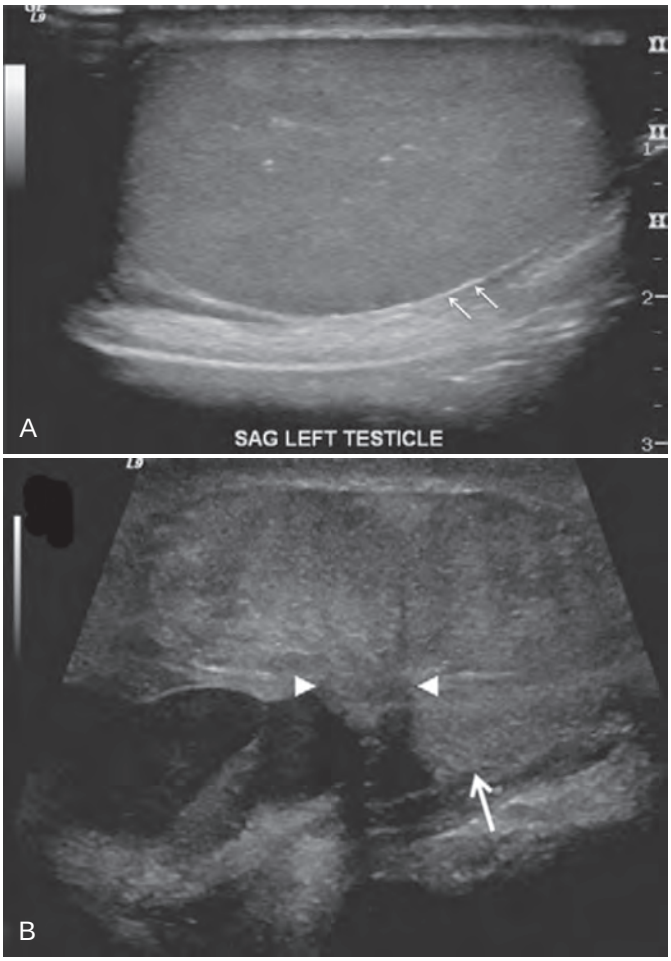


Fig. 40.25. A, Normal testicular ultrasound. *Arrows* define the thin tunica albuginea. **B,** Testicular rupture. *Arrowheads* point to a disruption in the tunica albuginea with extrusion of the seminiferous tubules. The *large arrow* indicates a hematocele. (From Avery LL, Scheinfeld MH: Imaging of male pelvic trauma. Radiol Clin North Am 50:1201–1217, 2012.)

rapid detumescence and a resultant penile hematoma with swelling. An audible popping sound is often heard as well.[43] Ecchymosis typically is present along the entire shaft of the penis; however, if Buck's fascia is also torn, a "butterfly pattern" (see Fig. 40.17) of ecchymosis can be seen in the perineal region.[46] The swelling and color caused by penile fractures can result in an "eggplant deformity," and the penis tends to deviate away from the damaged side (Fig. 40.24).[47] A defect in the tunica albuginea may be palpated along the shaft of the penis, which is known as *Rolling sign.*[24]

Injuries to the female genitalia can result in labial swelling or ecchymosis, but consideration should be given to performing procedural sedation or even general anesthesia to allow for adequate examination to assess the entire extent of their injuries, especially in young girls.[13] An examination under anesthesia is suggested for female patients who are younger than 10 years old who present with perineal bleeding, hematoma, or swelling resulting from falls, assaults, or playground activities. Studies have shown that thorough examinations are underperformed in this population, resulting in missed diagnoses, which can lead to significant morbidity.[12]

Differential Diagnoses

Blunt trauma to the scrotum can lead to testicular rupture, testicular dislocation, testicular fracture (parenchymal injury contained within the tunica albuginea), intraparenchymal contusions, hematoceles, or scrotal hematomas. Blunt trauma to the penis can cause penile fractures or false penile fractures. Urethral injury can sometimes occur as a result of blunt penile trauma. Penetrating injuries to the male genitalia often cause a disruption to the tunica albuginea of the penis or scrotum, but they can lead to amputation as well. Blunt trauma in females can cause labial and vaginal contusions, hematomas, and lacerations. Severe vulvar trauma, either from blunt or penetrating mechanisms, can lead to rectal injuries as well.[1]

Diagnostic Testing

Due to the external nature of the genitalia, diagnoses of genital trauma are usually made clinically, as opposed to other genitourinary trauma, which often require imaging studies. Scrotal injuries typically present with swelling, pain, bruising, lacerations, and/or skin loss. However, due to swelling, the examination can be limited.[48] Laboratory studies are not helpful, except for diagnosing concomitant injuries.

Imaging

Scrotal ultrasound is the imaging modality of choice when evaluating for testicular injury because of its accuracy, as well as its availability. The ability to evaluate flow using Doppler is extremely useful when determining viability and vulnerability of tissue. Along with testicular rupture, ultrasound can diagnose fractures, hematomas, hematoceles, and contusions. MRI can be used but is less practical given its long acquisition time and the limited availability. For testicular rupture, the sensitivity of ultrasonography approaches 100% and should focus on testicular echotexture, as well as the contour of the testicle. Irregularities of the contour or a discontinuity of the tunica albuginea suggest testicular rupture (Fig. 40.25).

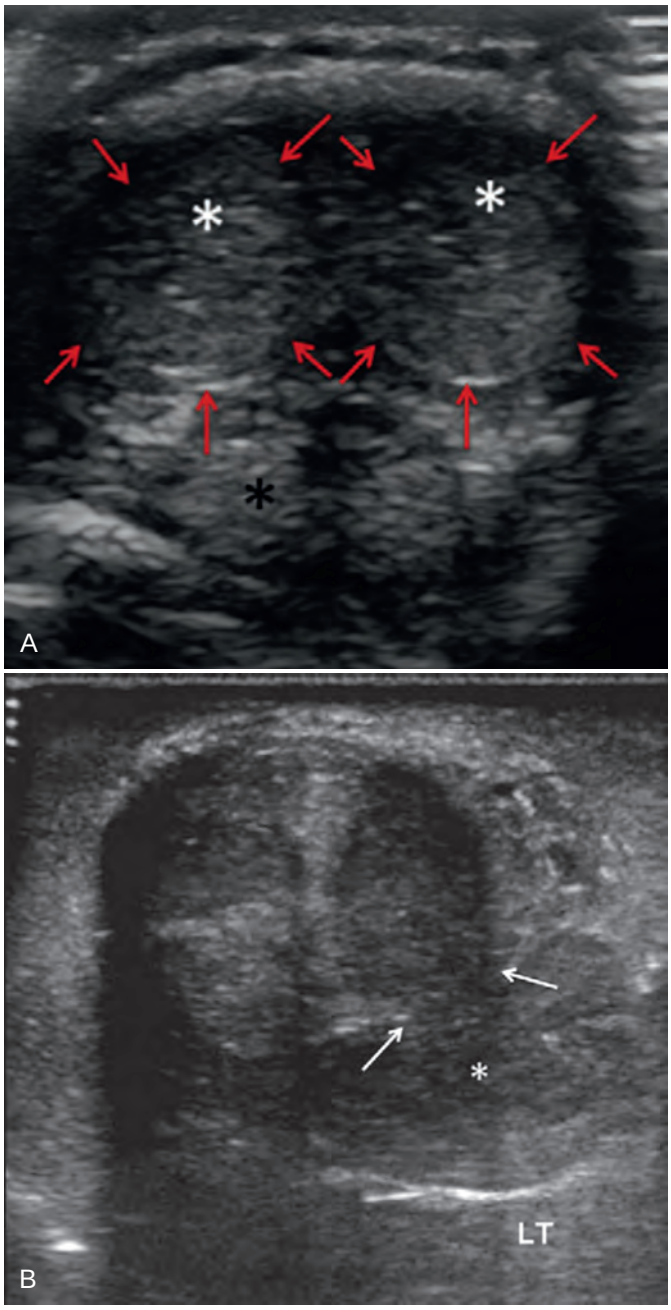


Fig. 40.26. A, Normal penile ultrasound. *Arrows* outline the tunica albuginea, asterisks overly the corpora cavernosa *(white asterisks)* and corpus spongiosum *(black asterisk).* **B,** Disruption of the tunica albuginea *(arrows)* and extruded corpus cavernosum tissue *(asterisk)* suggest penile fracture. (From Avery LL, Scheinfeld MH: Imaging of male pelvic trauma. Radiol Clin North Am 50:1201–1217, 2012.)

Ultrasound is also the preferred modality for penile imaging. It can diagnose penile fracture, but can also be used to evaluate the blood flow in penile arteries and veins. Unlike scrotal ultrasound, however, penile ultrasound is used less often, as the diagnosis of penile fracture is usually made clinically. Due to the extensive exploration required to evaluate for penile fracture, however, ultrasound is gaining more popularity because it can reveal a defect in the tunica albuginea with extruding hematoma, as well as assess blood flow in the arteries and veins (Fig. 40.26).

RUG should be considered if there are concerns about concomitant urethral injury (Fig. 40.27).[44]

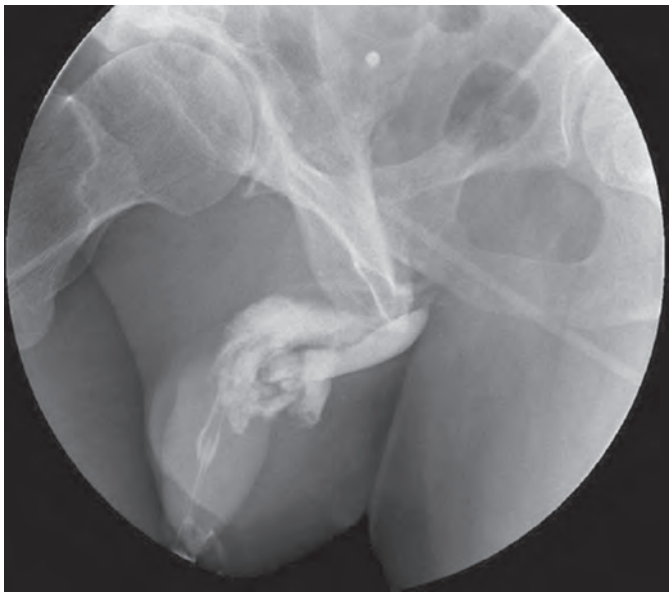


Fig. 40.27. Retrograde urethrogram revealing anterior urethral injury and contrast extravasation in the setting of a penile fracture. (From Cutinha P, Venugopal S, Salim F: Genitourinary trauma. Surgery [Oxford] 31:362–370, 2013.)

Management

Testicular and penile fractures require prompt urological consultation and surgery, and they are discussed in more detail later. With any type of penetrating injury to the scrotum or penis, surgical exploration is usually indicated to evaluate for injuries to deeper structures that could result in significant morbidity, unless the injury is extremely superficial.[49] Penile surgical exploration involves degloving the entire penis to allow for visualization of all structures. Prognosis after penile fractures is generally good, but cosmetic abnormalities can occur, even with prompt surgical repair.[50]

For testicular rupture, operative intervention focuses on débriding nonviable tissue and closing the tunica albuginea, although orchiectomy is performed if the testicle is deemed nonviable.[1] The rate of orchiectomy is low (10% to 20%) if exploration is performed within 72 hours, but if there is significant delay, the rate is significantly higher (45%).[20,21] The goal of surgery for testicular injuries is testicular salvage, although penetrating injuries still result in a 35% rate of orchiectomy due to testicular necrosis or unhealthy parenchyma.[49]

Typically, small scrotal hematomas respond well to rest and nonsteroidal antiinflammatory drug (NSAID) therapy. However, scrotal hematoceles and expanding or large scrotal hematomas may lead to testicular ischemia due to local pressure effects on blood vessels and, thus, may also require exploration.[48] Reduction of testicular dislocations should be attempted by applying gentle caudad pressure following the course of the spermatic cord. However, even if reduction is successful, ultrasound should be performed to evaluate for vascular compromise, and patients usually require future operative intervention in the form of orchiopexy to prevent testicular torsion.[22]

Amputations of either the testicles or penis require immediate surgical evaluation. In the interim, the amputated part should be wrapped in saline soaked gauze and then placed in a sealed bag, which can then be placed in another bag that is filled with ice.[1] The amputated part should never be placed directly on ice. Direct pressure is usually adequate to achieve hemostasis.

Injuries to the female genitalia may need the operating room for an examination (and repair) under anesthesia, or for extensive lacerations involving the labia, perineum, and posterior fourchette.[12] Again, the threshold for an examination under anesthesia should be extremely low, especially in the pediatric population.

Zipper injuries should be evaluated thoroughly for underlying trauma to the penis (or scrotum when involved). If the zipper is stuck, the cloth between the interlocked dentition of the zipper can be cut. However, if the penis is caught in the buckle of the fastener, unzipping can be attempted, and mineral oil may help with removal. However, if this proves unsuccessful, the medial bar of the zipper can be cut with bone or wire cutters to separate the face plates. Sometimes, however, circumcision or an elliptical incision of the penile skin must be performed to achieve release.[51]

Burns to the external genitalia are usually not seen in isolation, and the thin skin of the penis makes it quite vulnerable to full-thickness burns. Patients with burns that are not extremely superficial should be evaluated at a burn center as soon as possible.[47] More than 10% of these patients will need surgical débridement.[52] Superficial burns can be treated with topical therapies.[47]

Occasionally, patients will present with constricting rings that have created local ischemia and swelling, and attempts at removal should be made as quickly as possible to prevent tissue necrosis from ischemia.

Scrotal injuries leading to orchiectomy can be a source of infertility but can also alter hormonal function. Other complications include voiding dysfunction and erectile dysfunction.[49] Many of the complications of penile injury are cosmetic in nature, including penile curvature and plaque or nodule formation superficially after penile fracture, but the likelihood is significantly decreased with surgery.[43,50] Still, urethral injury can lead to stricture formation, penile abscess, permanent curvature, and painful erections, even if repair is successful.[53] A delay in diagnosing female genital injury can lead to urinary or fecal incontinence, chronic fissures, rectovaginal fistula, or even vaginal stenosis, highlighting the importance of a thorough physical examination.[12]

KEY CONCEPTS

- Microscopic or gross hematuria is suggestive of genitourinary trauma; however, the degree of hematuria does not correlate well with the severity of injury.
- The kidney is the most frequently injured genitourinary organ, and imaging should be considered in patients with gross hematuria or microscopic hematuria with hemodynamic instability.
- Delayed CT images after IV contrast should be obtained in patients with mechanism or findings suggestive of ureteral trauma. Blunt ureteral trauma is rare.
- CT scan with IV contrast is not sensitive for diagnosing bladder injury, and retrograde cystography should be obtained if there is any concern to allow proper distention of the bladder to allow for urinary extravasation.
- Pelvic fractures associated with hematuria strongly suggest urethral injury.
- Retrograde urethrography (RUG) should be performed in patients with pelvic fractures and hematuria, perineal ecchymosis or swelling, or those with blood at the urethral meatus, because passage of a Foley catheter blindly in these settings can worsen a preexisting urethral injury.
- Genital injury is rarely life threatening, but prompt diagnosis and evaluation is necessary to decrease the likelihood of future morbidity in these patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 40: QUESTIONS & ANSWERS

40.1. All of the following are associated with clinically significant blunt renal injuries in adult patients and would warrant further evaluation, except:

A. A sudden decelerating mechanism of injury in a patient without microhematuria
B. A sudden decelerating mechanism of injury in a patient without shock
C. Gross hematuria
D. Microscopic hematuria
E. Microscopic hematuria in a patient with shock

Answer: D. Renal injury requiring intervention is rare in the absence of gross hematuria or shock. Gross hematuria warrants careful evaluation for significant genitourinary injury, although the degree of hematuria does not necessarily correlate with the degree or grade of injury and significant genitourinary trauma can occur without hematuria. Microscopic hematuria in a blunt trauma patient without shock is not an indication for renal imaging, even if there is evidence of local trauma (eg, costovertebral angle tenderness or localized ecchymosis). Although renal injury may uncommonly be identified on imaging for these

patients, the injuries are mild and do not require intervention. Hemodynamic instability with evidence of intraperitoneal injury on abdominal examination, presence of pelvic fracture, a penetrating trauma mechanism, or presence of lower rib fractures, with or without hematuria, are indications for further investigation. Additionally, imaging is advisable for patients with gross hematuria, targeted to the entire urinary tract or localized to the lower tract (bladder and urethra), depending on the mechanism and location of the trauma.

40.2. A 27-year-old male presents after a motor vehicle collision complaining of abdominal pain. He was the restrained driver of a car struck on the driver's side by a delivery truck. His vital signs are blood pressure 118/72, heart rate 70 beats per minute, and respiratory rate 16 breaths per minute. Physical examination reveals left upper quadrant abdominal tenderness without guarding or rebound tenderness. There is no blood at the urethral meatus or scrotal hematoma. A Foley catheter is placed without difficulty and drains gross blood. A radiograph of the pelvis reveals fractures of the left superior and inferior pubic rami, and a focused assessment with sonography in trauma (FAST) examination reveals free fluid in the splenorenal pouch. Which of the following diagnostic strategies is most appropriate?

A. Intravenous (IV) contrast-enhanced computed tomography (CT) of the abdomen and pelvis with delayed images of the bladder after clamping the Foley catheter to allow the IV contrast to collect in the bladder
B. IV contrast-enhanced CT of the abdomen and pelvis with delayed images of the renal collecting system
C. IV contrast-enhanced CT of the abdomen and pelvis and retrograde CT cystogram
D. IV contrast-enhanced CT of the abdomen and pelvis and retrograde urethrogram
E. Retrograde cystogram followed by IV pyelogram

Answer: C. This patient has clinical features concerning for several possible injuries, including a splenic laceration, renal injury, and bladder rupture. Significant urethral injury is less likely, given the examination findings and ease of Foley catheter placement. Because the patient is stable without apparent indication for laparotomy, the most appropriate diagnostic evaluation would be IV contrast-enhanced CT of the abdomen and pelvis and retrograde CT cystogram. The former will evaluate for solid organ injury and the latter for bladder rupture. It is essential that cystography not be done in an antegrade fashion, because such studies (eg, injecting IV contrast material, clamping the Foley catheter, and allowing the examination to depend on antegrade filling of the bladder from renal excretion of progressively dilute contrast material) may produce incomplete and spurious findings because of inadequate distention of the bladder.

40.3. A 72-year-old male presents with flank and pelvis pain after he slipped and fell on an icy sidewalk. His examination reveals normal vital signs and abrasions over the left flank and left iliac crest and is otherwise unremarkable. He has grossly clear urine, but a urinalysis reveals 25 red blood cells per high-power field. Radiographs of the pelvis and hips reveal no fracture, and the patient is able to ambulate without difficulty. What is the most appropriate next step?

A. Obtain a renal ultrasound scan.
B. Obtain an IV contrast-enhanced CT of the abdomen and pelvis.
C. Perform a retrograde cystogram.
D. Perform a retrograde urethrogram.
E. Treat the patient's pain and discharge him home with outpatient urology follow-up in 1 week.

Answer: E. A significant genitourinary injury is unlikely, given the patient's history, physical examination, and urine findings. However, outpatient urology follow-up until microhematuria has cleared is advisable to be certain that it does not represent another more serious underlying (nontraumatic) condition.

40.4. A 35-year-old female presents after being stabbed with an ice pick during a robbery. Her examination is normal except for a 0.5-cm, hemostatic wound to the right flank at the level of the second lumbar vertebrae. Bedside ultrasonography reveals no free intra-abdominal fluid. Her urinalysis does not contain blood. What is the most appropriate next step?

A. Obtain a renal ultrasound scan.
B. Obtain an IV contrast-enhanced CT of the abdomen and pelvis, with additional images of the renal collecting system 10 minutes after contrast injection.
C. Perform a retrograde cystogram.
D. Perform a retrograde urethrogram.
E. Treat the patient's pain, counsel her on appropriate wound care, and discharge her home with outpatient urology follow-up in 1 week.

Answer: B. In cases of penetrating renal trauma, the presence or absence of hematuria is not a reliable predictor of upper urinary tract injury. The location of the penetrating injury in relation to the urinary tract is the most important determining factor in deciding the need for radiographic investigation. Therefore, the absence of hematuria in a patient with a gunshot or stab wound in proximity to the urinary tract does not eliminate the need for IV contrast-enhanced CT as the initial diagnostic examination. Significant injuries to the kidney and ureter may occur in penetrating trauma without hematuria. Additional images obtained at 10 minutes after contrast injection are indicated to evaluate for delayed contrast extravasation and to maximize the sensitivity of the study.

40.5. A 25-year-old male presents after an unfortunate incident resulting in a scrotal injury and a left testicle that was traumatically amputated (the patient brings the amputated testicle with him in a towel). All of the following would be indicated, except:

A. Analgesics for the patient
B. Emergent urological consultation
C. Place the amputated testicle directly on ice
D. Prepare the patient for possible operative exploration by the surgeon
E. Wrap the amputated testicle in saline soaked gauze

Answer: C. Amputations of either the testicles or penis require immediate surgical evaluation. In the interim, the amputated part should be wrapped in saline-soaked gauze, and then placed in a sealed bag, which can then be placed in another bag that is filled with ice. The amputated part should never be placed directly on ice. Direct pressure is usually adequate to achieve hemostasis.

40.6. A 30-year-old female presents after blunt abdominal trauma after a motor vehicle collision, and an ultrasound demonstrates free fluid. You suspect a bladder rupture. A true statement about this entity includes which of the following:

A. A bladder contusion may be successfully managed with Foley catheterization drainage.

B. Extraperitoneal bladder injuries are typically managed with surgical intervention.
C. It is unimportant to distinguish an intraperitoneal from an extraperitoneal bladder rupture (EBR).
D. Most patients with an intraperitoneal bladder rupture (IBR) will resolve with Foley catheter drainage.
E. Most penetrating bladder injuries will resolve with Foley catheter drainage.

Answer: A. The distinction between EBR and IBR is important, because the management differs. Contusions and extraperitoneal injuries due to blunt trauma are typically managed conservatively with Foley catheterization, unless they are complicated by other intra-abdominal injuries, bladder neck injuries, bone fragments in the bladder wall, or if open reduction is performed on an associated pelvic fracture. In contrast, given the extremely low likelihood of IBR and penetrating injuries healing with conservative therapy, almost all patients with these types of injuries are taken to the operating room for exploration and repair. Without surgery, there is an extremely high likelihood of complications, which include infections and fistula formation.

CHAPTER 41

Peripheral Vascular Injury

Ali S. Raja

PRINCIPLES

Background and Importance

Injury to the major peripheral arteries or veins may not always be life-threatening, but it invariably poses a threat to the viability of the affected limb. Historically, due to the rapidity of exsanguination, injury to major vessels was often fatal in the field; and most patients who survived to hospital arrival had relatively minor vascular injuries. However, with the advent of modern emergency medical service (EMS) systems with advanced extrication methods and rapid transport, more patients with major vascular injuries are reaching the emergency department (ED) alive. In addition, the incidence of both penetrating injuries from interpersonal violence and blunt injuries from motor vehicle–related trauma has increased dramatically over the past 50 years. Consequently, emergency clinicians are frequently confronted with critically ill patients harboring overt (or occult) peripheral vascular injuries.

Management of these vascular injuries has also evolved, with advances in diagnostic methods and surgical techniques. Treatment of vascular injuries before and during World War II resulted in limb amputation rates of 50% to 75%. Advances during the Korean and Vietnam wars reduced amputation rates to 5% to 15%, which approach the current rates of amputation for civilian injuries.

Tremendous progress has also been achieved in diagnostic and therapeutic techniques for dealing with peripheral vascular injuries, and several noninvasive diagnostic modalities have emerged as accurate alternatives to surgical exploration and angiography. These techniques are easily used in the ED, and the goal of timely detection and repair of serious vascular injuries is achievable in the majority of cases.

Peripheral vascular injuries are divided almost equally between blunt and penetrating mechanisms. In the United States, up to 90% of these injuries are a result of penetrating wounds, mainly because of the high rate of penetrating trauma in inner-city urban areas.[1] Major venous injuries are present in up to 50% of gunshot wound cases, and more than 80% of these have associated arterial injuries. In addition, due to the increased use of percutaneous endovascular diagnostic and therapeutic procedures, the incidence of iatrogenic vascular injuries has increased and accounts for up to one-third of all cases in some series.[2]

Anatomy and Physiology

The major vessels and their relevant anatomy are described in the following sections (Figs. 41.1 and 41.2).

Upper Extremity

The right subclavian artery arises from the brachiocephalic artery, and the left arises from the arch of the aorta. From their origin, they course posterior and inferior to the clavicles to the outer margins of the first ribs, where they become the axillary artery and vein. The left subclavian artery rises higher than the right and extends into the root of the neck.

The axillary artery courses from the lateral border of the first rib to the inferior border of the teres major muscle, where it becomes the brachial artery. The axillary vein runs medial to the artery. Due to the extensive anastomotic arterial connections around the shoulder joint, up to half of patients with axillary artery injuries will have palpable pulses as a result of collateral circulation. Because of the close proximity of the brachial plexus and the axillary vessels, significant denervation of the upper extremity can occur.

The brachial artery begins at the lower border of the teres major muscle and divides into the radial and ulnar arteries at the level of the proximal aspect of the radial head. The median and ulnar nerves and the basilic vein are in close proximity to the brachial artery. The profunda brachii artery is a major branch that arises slightly after the origin of the brachial artery and often contributes good collateral flow if the brachial artery is injured distal to this branch point.

The radial artery originates in the cubital fossa and runs superficially to the distal end of the radius, where it ultimately joins the deep branch of the ulnar artery to form the deep palmar arch of the hand. The ulnar artery begins in the cubital fossa and runs with the ulnar nerve anterior to the flexor retinaculum, at which point it joins the radial artery to form the superficial palmar arch of the hand.

Lower Extremity

The external iliac vessels become the common femoral vessels at the inguinal ligament. After giving off the profunda femoris artery in the femoral triangle, the femoral artery continues as the superficial femoral artery almost vertically to the adductor tubercle of the femur and enters the popliteal fossa as the popliteal artery. Extensive proximal collaterals are present around the hip joint, including the gluteal, obturator, and pudendal branches of the iliac artery.

The popliteal artery gives off the genicular branches in the popliteal fossa and then divides into the anterior and posterior tibial arteries at the lower border of the popliteus muscle. The peroneal artery arises from the posterior tibial artery slightly after its origin. The anterior and posterior tibial arteries and the peroneal artery form the trifurcation of the popliteal artery, and each runs with a corresponding vein and nerve in different compartments of the leg.

The popliteal artery divides into three branches—the anterior and posterior tibial and the peroneal arteries—at the inferior margin of the popliteal fossa. Injuries below the trifurcation at the knee may need repair if hard signs of arterial injury are apparent in the foot or if two of the three arteries are occluded. The most common blunt trauma cause of popliteal artery injury is a posterior knee dislocation in which bony elements directly lacerate or cause thrombosis of the artery. Anterior knee dislocations may cause excessive stretch on the popliteal vessels resulting in arterial

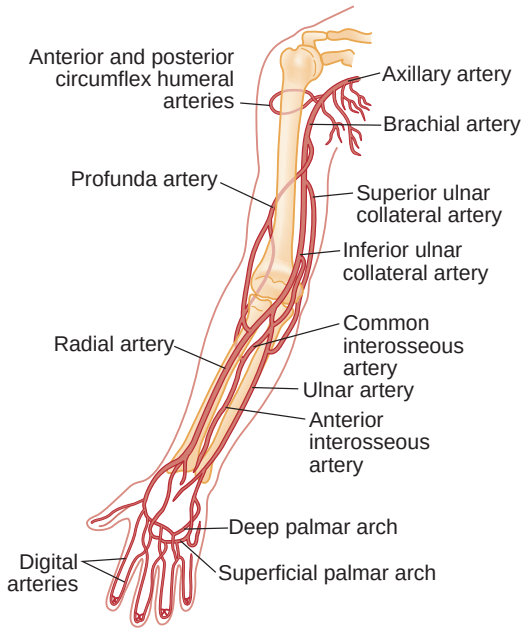

Fig. 41.1. Major arteries of the upper limb. (From Snell R, Smith M, editors: Clinical anatomy for emergency medicine, St Louis, 1993, Mosby.)

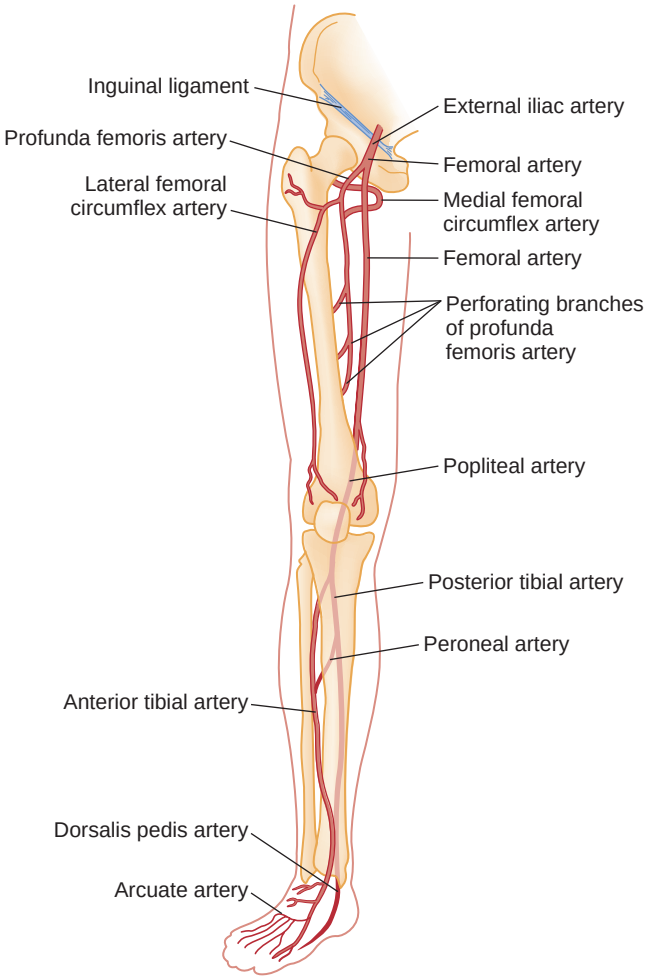

Fig. 41.2. Major arteries of the lower limb. (From Snell R, Smith M, editors: Clinical anatomy for emergency medicine, St Louis, 1993, Mosby.)

thrombosis, but this injury is relatively rare. Up to one-third of knee dislocations result in popliteal artery injury. Twenty-five percent of cases have an associated injury to the peroneal and posterior tibial nerves. A knee dislocation may reduce spontaneously, leaving little evidence of the original trauma, particularly in obtunded patients.

Pathophysiology

Blunt and penetrating types of trauma result in similar spectra of vascular injuries, although their mechanisms of injury differ. Although blunt vascular injuries are less common than penetrating injuries, they are often more severe and more commonly result in amputation because of associated injuries to nerves, bone, and soft tissue. Certain mechanisms of injury, such as animal bites that crush and lacerate vessels, can involve both penetrating and blunt mechanisms.

Penetrating Trauma

Gunshot wounds can cause direct arterial lacerations or transections, in addition to concussive injuries distal to the track of the bullet. These latter injuries tend to be tears in the intima of an artery, with subsequent thromboses that may not become apparent for hours to months after the injury. Bullets may ricochet off bone, making predicting trajectories less accurate than with stab wounds.

Stab wounds cause vascular injuries by completely or partially transecting vessels. Partial laceration of an artery may produce few symptoms of arterial insufficiency on initial evaluation but result in delayed complications. The vascular structures at risk can be predicted more reliably with stab wounds than with gunshot wounds by taking into consideration the anatomic location, causative implement, depth, and direction of the wound.

Shotgun wounds are less common than gunshot or stab wounds, but they can cause injuries varying from minor soft tissue wounds to massive destruction of soft tissue and bone, depending primarily on the range from which the shotgun was fired. The presence of multiple missiles ranging from 9 or 10 (buckshot) to dozens (birdshot) also complicates the evaluation of these injuries because of the many potential sites of potential vascular injury. In addition, close-range shotgun wounds (<3 yards) can cause significant blunt trauma to blood vessels, as well as a higher rate of bone and nerve injury than might occur with gunshot wounds. Migration of pellets or bullets proximally through the venous system to the heart, or migration through an artery with subsequent distal occlusion, has been reported frequently as a delayed complication.[3,4]

Blunt Trauma

Blunt injury involves either avulsion forces that can stretch vessels beyond their capacities or direct crushing injuries that disrupt vessel walls. In addition, fracture fragments resulting from blunt extremity trauma can lacerate or entrap vessels. These vascular injuries can range from small intimal tears to complete avulsions of arteries and nerves. Open avulsion injury of a limb is particularly severe because the skin, which is very pliable, is the final structure to tear. Once torn, it is inevitable that vessels and nerves will tear as well. Vascular injuries should also be suspected in patients with massive soft tissue avulsions or crush injuries, displaced long bone fractures, electrical or lightning injuries, and severe burns, as well as in those with compartment syndrome from trauma or prolonged immobilization as a result of stroke, coma, drug overdose, or other causes. Bites that are inflicted by large animals, such as dogs used by law enforcement, are particularly prone to arterial injury and wound complications.[5] Collateral

circulation may continue to perfuse the limb, but injuries that occur proximal to the collateral branch point—or that involve both the main trunk and collateral branches—will preclude adequate flow.

Distal ischemia results from the inability of tissues to continue aerobic metabolism. Eventually, anaerobic metabolism consumes all substrate, thereby resulting in the accumulation of lactic acid. As ischemia progresses, cellular integrity is lost and irreversible cell death occurs. A vicious cycle of tissue edema and further impairment of the blood supply occurs. When no specific measures are taken to cool the limb, it is said that the limb is undergoing "warm ischemia" at ambient temperature. After 6 hours of complete warm ischemia, 10% of patients will have irreversible damage; by 12 hours, 90% will have irreversible damage. Artificially cooling the limb to near freezing temperature ("cold ischemia") will reduce the metabolic demands and greatly prolong the tissue's tolerance of ischemia to 24 hours or more.

Two main types of vascular injury can result from trauma: *occlusive injuries* (transections, thromboses, and reversible spasm), in which all perfusion distal to the occlusion is lost, and *nonocclusive injuries* (intimal flaps, dissections, arteriovenous fistulae [AVF], and pseudoaneurysms), which include mechanical defects to vessel walls that may or may not lead to decreased distal blood flow.[6]

Complete Occlusive Injury

Transection. The most common vascular injury is complete transection, in which distal flow is effectively eliminated. Cleanly transected arteries will often retract and undergo spasm to minimize blood loss. With longitudinal arterial lacerations and venous injuries, blood loss cannot be minimized by this physiologic response, and therefore tend to result in greater blood loss. Pulsatile bleeding may quickly lead to exsanguinating hemorrhage and shock.

Thrombosis. Intraluminal thrombosis (Fig. 41.3) may occur in an injured artery acutely (within 24 hours) or may be delayed for many months. Acute thrombosis is initiated by stasis resulting from compression of the artery or from a disruption in the intima of an artery that becomes a nidus for thrombus formation. As the thrombus propagates, complete occlusion of the vessel can occur. Delayed thrombosis can occur months to years after injury if the injured vessel heals with stricture formation, resulting in decreased distal flow, followed by stasis and clot formation.

Reversible Arterial Spasm. The precise cause and incidence of significant reversible arterial spasm after trauma are unknown. In the case of arterial transection, arterial spasm is beneficial and limits hemorrhage. In other cases, however, the segmental arterial spasm occurs at some distance from the site of traumatic injury and can produce severe distal ischemia. Arterial spasm is particularly common in children. In many series, segmental arterial spasm is the most common arteriographic finding (Fig. 41.4). However, symptoms of ischemia should never be assumed to be a result of arterial spasm; that diagnosis is based on arteriographic results only.

Nonocclusive Injuries

Intimal Flap. An intimal flap occurs when there is a break in the vessel intima, generally from excessive stretch or concussive forces. Although flow is not altered by small flaps and the associated soft tissue wounds often appear benign initially, these intimal flaps may become a nidus for thrombosis that can occur hours to months after the initial injury.

Pseudoaneurysm. A true aneurysm contains all three layers of the vessel wall (intima, media, and adventitia) and rarely is caused by trauma. A pseudoaneurysm is formed following a tear in a vessel wherein the hemorrhage is contained by surrounding fascia and the resulting hematoma is gradually encased by a capsule of fibrous tissue, analogous in consistency to the adventitia of a normal vessel (Fig. 41.5). Because it is relatively thin walled, rupture of a pseudoaneurysm is a distinct possibility. In addition, because its diameter inevitably expands under arterial pressure

Fig. 41.3. Complete thrombosis *(arrow)* of the distal brachial artery after reduction of a posterior elbow dislocation. (Courtesy D. Demetreades, MD.)

Fig. 41.4. Acute arterial spam of the brachial artery. (From Arquilla B, Gupta R, Gernshiemer J, et al: Acute arterial spasm in an extremity caused by inadvertent intra-arterial injection successfully treated in the emergency department. J Emerg Med 19[2]:139-143, 2000.)

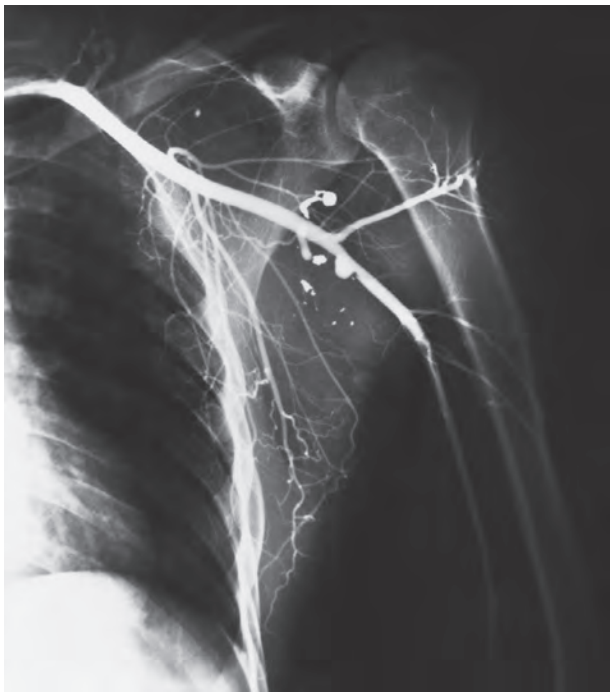

Fig. 41.5. Multiple small pseudoaneurysms of the axillary artery after penetrating injury. (Courtesy D. Demetreades, MD.)

over days to months, compression of adjacent tissue may result in neuropathy, venous obstruction with resultant peripheral edema and venous thrombosis, and even erosion into adjacent bone. The cavity of a pseudoaneurysm is in direct communication with the lumen of the vessel, so embolization of mural clots may produce distal arterial occlusion. Pseudoaneurysms may be diagnosed months to years after an injury when patients manifest symptoms of compression neuropathy or peripheral arterial embolism or for investigation of a soft tissue "tumor" that represents the growing aneurysm.

Arteriovenous Fistula. An AVF is formed when both an artery and an adjacent vein are injured. Higher-pressure arterial flow is directed into the lower-pressure vein, thereby diverting the blood supply to distal tissues and engorging the distal veins. Because the aperture of the fistula is often relatively narrow and thus results in turbulent flow, a bruit and palpable thrill are common diagnostic findings. Symptoms are primarily those of distal ischemia, but rarely, high-output congestive heart failure may occur when large central vessels are involved. Symptoms are often delayed for months, because it takes time for the fistula to mature.

Compartment Syndrome. Compartment syndrome is most common after crush injury or a long bone fracture but may also be seen after reperfusion of an ischemic limb. Initially, blood flow is diminished and the injury is considered nonocclusive. Progressive edema elevates tissue pressure above capillary pressure, thus ending arterial perfusion and initiating a cascade of events that results in compartment syndrome. The risk for this complication is increased when ischemia time is prolonged; in the presence of combined arterial and venous injury; after ligation or repair of a major artery or vein; or in the presence of significant soft tissue injury, frequently concomitant with a long bone fracture. After restoration of arterial flow to a previously ischemic limb, a cascade of reperfusion injury results from release of oxygen free radicals, lipid peroxidation, and influx of intracellular calcium.

TABLE 41.1

Clinical Features of Vascular Injury

HARD FINDINGS	SOFT FINDINGS
Pulsatile hemorrhage	History of significant hemorrhage at scene
Expanding hematoma	Nonexpanding hematoma
Absent distal pulses	Diminished pulse or ABI of injured extremity
Palpable thrill	Extremity peripheral nerve deficit
Audible bruit	Bony injury or proximate penetrating wound

ABI, Ankle-brachial index.

These mediators give rise to progressive cellular damage, edema, and necrosis, thereby propagating the vicious cycle that increases compartment pressure. Consequently, frequent reexamination of the limb is indicated to assess compartment pressure after arterial repair or in the high-risk circumstances listed earlier. Compartment syndrome is discussed in more detail in Chapter 42.

CLINICAL FEATURES

Detection and treatment of vascular injuries takes place within the context of the overall resuscitation of the patient according to established principles of trauma care.[7] If the source of bleeding is readily identifiable, it is compressed with digital pressure. Although control of active bleeding is being achieved in this manner, detection and treatment of other life-threatening injuries proceed concurrently. Peripheral vascular injury can occur coincident with other life-threatening trauma, which may take higher priority in resuscitation. In other cases, peripheral vascular injury may be the most serious or only injury, and evaluation and management of this type of injury can proceed directly. Many patients have no evidence of injury but are considered at risk for vascular injury because of penetrating wounds that traverse the course of major neurovascular bundles, or because they have sustained high-risk injuries, such as posterior knee dislocation. In addition, patients without acute trauma, but with symptoms of intermittent claudication or with unexplained peripheral embolization and a history of previous trauma to the limb should be suspected of having occult arterial injury.

Peripheral vascular injury can be divided into three categories by physical examination: hard findings, soft findings, and asymptomatic high-risk wounds based on the mechanism of injury.

Hard Findings of Vascular Injury

Many patients have classic "hard" findings of arterial injury, listed in Table 41.1. The incidence of arterial injury in patients with any hard finding is consistently greater than 90%, and the presence of these findings requires further investigation by emergency angiography/computed tomography angiography (CTA) or, more commonly, immediate surgical intervention, depending on the duration of warm ischemia and the overall status of the patient.[8,9]

Soft Findings of Vascular Injury

An additional group of patients have "soft findings" of vascular injury (see Table 41.1).[8,9] Up to 35% of patients with "soft" findings of vascular injury have positive angiographic studies, although only a small proportion of these injuries require emergency repair.

The significance of prolonged capillary refill (>2 seconds) is controversial; some experts find it to be a reliable sign of vascular injury (when combined with a pulse deficit) and consider delayed

capillary refill to be a valid "soft sign" of vascular injury. However, capillary refill is age, gender, and temperature dependent, and an arbitrary 2 second cutoff results in a significant false-positive rate, especially in older patients.[10] Delayed capillary refill by itself is an unreliable predictor of arterial injury, but the presence of delayed capillary refill in conjunction with a proximate penetrating injury or the presence of one or more soft signs warrants, at the least, repeated hourly examination.

Isolated penetrating injury to a peripheral nerve is commonly associated with vascular injury because of the close proximity of these structures within the neurovascular bundles. Vascular injury occurs in up to half of cases of penetrating peripheral nerve injury, and vice versa.[11] It can be difficult to distinguish whether pain, paresthesias, or paralysis are caused by a primary nerve injury, an associated vascular injury causing compression of the nerve, or compartment syndrome. In general, primary nerve injury occurs immediately at the time of injury, whereas vascular neuropathy occurs over minutes to hours after the injury.

Asymptomatic High-Risk Wounds

Major neurovascular bundles include large limb arteries proximal to critical branch points (Table 41.2). Proximity of a penetrating wound to a neurovascular bundle is defined variably as within 1 cm, 1 inch, or 5 cm. This concept is useful in evaluating patients with penetrating injury but without evidence of vascular injury. We consider penetrating wounds that occur within 1 cm of a major neurovascular bundle or whose presumed trajectory has crossed such a bundle to be sufficiently likely to produce an occult vascular injury that they warrant frequent (every 30 to 60 minutes) evaluation for the first 4 to 6 hours to ensure that a developing vascular injury is not missed within the warm ischemia window. Routine imaging is not, however, indicated based on proximity alone.

In addition, a small minority of patients with high-risk injuries, such as bites from large dogs or other animals, displaced fractures, crush injuries, or major joint dislocations (especially knee dislocation), may initially have occult vascular injuries that are not detected on physical examination. The risk of missing such injuries is that the traditional 6-hour window of warm ischemia time will be exceeded, or the patient will experience delayed complications resulting in limb loss. Patients with intimal flaps may be completely asymptomatic initially but can subsequently develop arterial thrombosis. Similarly, pseudoaneurysms progressively enlarge to produce compression of adjacent structures but may be very small and undetectable on initial physical examination. Consequently, these patients also should undergo serial physical examinations.

Due to their noncompressible location, blunt subclavian injuries can be particularly challenging. These are often associated with clavicular fracture or dislocation (however, contrary to long held belief, isolated first rib fracture is rarely combined with vascular injury unless posterior displacement occurs). Shear injury of the subclavian artery can occur as a result of a loose shoulder restraint during a motor vehicle collision (MVC). Interestingly, penetrating subclavian vein injuries are even more lethal than those to the artery, because in addition to massive blood loss, there is a relatively high risk of massive air embolism, which is frequently fatal.

Popliteal artery injuries can often be a result of knee dislocations, most of which will have spontaneously reduced. Patients showing complete ligamentous disruption of the knee on physical examination should be suspected of having a spontaneously reduced knee dislocation. Hemarthrosis may also be absent if the joint capsule is torn because blood can track into the fascial planes.

TABLE 41.2

Major Neurovascular Bundles

MAJOR ARTERY	PROXIMATE PLEXUS/NERVE
Axillary artery	Brachial plexus
Brachial artery	Median nerve
Radial artery	Median and radial nerves
Ulnar artery	Ulnar nerve
Femoral artery	Femoral nerve
Popliteal artery	Tibial nerve

History

In patients who achieve and maintain hemodynamic stability, a more comprehensive history can be obtained. Important historical points to note include the exact time and mechanism of the injury. The time of injury is important because of the significant morbidity that results from prolonged warm ischemia time. The mechanism is of clinical and often forensic importance in that injuries are frequently inflicted during a criminal act or in the workplace. Various mechanisms of injury may mandate special reporting and may alter the patient's ultimate disposition. Certain types of injuries, such as crush or bite wounds, are particularly prone to complications. The occupation, avocation, and hand dominance of the patient are pertinent to determine the best approach to achieve maximum functionality. Comorbid medical conditions may also be important. Patients who are immunocompromised because of diabetes, acquired immunodeficiency syndrome (AIDS), asplenia, cancer, or steroid use are at increased risk for infection and impaired wound healing. Patients with preexisting vascular insufficiency have more tenuous perfusion, are more susceptible to ischemia from elevated compartment pressure, and have a higher incidence of complications. As with most aspects of trauma care, patients whose sensorium is altered by head injury or intoxication, patients with spinal cord injury who cannot perceive pain, and those with significant painful distracting injuries will not reliably be able to report pain or paresthesias suggesting vascular insufficiency, so extra caution should be exercised in these cases.

Evidence of abdominal injury raises concern for injury to the iliac vessels, and virtually all iliac artery and vein injuries have associated trauma to the small or large intestine, bladder, solid viscera, or bony pelvis. The common and external iliac arteries are injured with equal frequency and more often than the internal iliac vessels. Approximately 80% of iliac vessel injuries are caused by penetrating trauma, and the remainder is mainly associated with pelvic fracture. Trauma to the iliac veins is responsible for massive bleeding in displaced pelvic fractures and often requires angiographic embolization.

Physical Examination

Despite advances in technology, meticulous physical examination in combination with comparison of blood pressures in the affected and unaffected limbs is the mainstay of diagnosis of vascular injury.[8] Physical examination is directed at discovering evidence of local wound complications and distal ischemia suggestive of vascular injury. Pulses in the affected extremity are palpated to compare strength and quality between the injured limb and its uninjured counterpart. Isolated detection of a diminished pulse distal to the site of injury merits further evaluation rather than immediate surgery, because palpation of pulses is a relatively

inaccurate means of predicting arterial injury.[12] False-positive findings of a pulse deficit may occur because of shock, in which all pulses are diminished; congenital absence of a pulse in one extremity; preexisting vascular disease; operator technique; or arterial spasm or compression. False-negative findings can occur with transmission of the pulse through a "soft clot," past an intimal flap, or through collateral circulation. Distal pulses can persist despite significant arterial injury. Compression of an artery by casts, splints, or dressings may produce a pulseless extremity, and these should be removed if there is evidence of ischemia. Symptoms of limb ischemia may be apparent with absent radial and brachial pulses. However, pulses are completely absent in only a third of cases, because collateral flow from the thyrocervical trunk may provide sufficient perfusion to avoid the symptoms and signs of ischemia.[1] Finally, although the pulse may be absent, the limb may be well perfused by collateral arterial supply, thus making immediate repair of the arterial injury less compelling. Comparative palpation of the injured and unaffected limbs can also detect differences in skin temperature that may suggest hypoperfusion. Testing two-point discrimination on the injured and unaffected limbs may help detect sensory deficits. Auscultation over the site of injury may reveal a bruit, which is present in more than half of patients with AVF. Repeated examination of any hematoma adjacent to a wound is indicated during the first 24 hours to determine whether it is expanding or pulsatile.

Despite the limitations just noted, reliance on the history and physical examination to triage patients to receive immediate surgery, imaging studies, or observation has been found to be relatively dependable, with a sensitivity and specificity for significant vascular injury both exceeding 90%.[8] However, studies of military casualties suffering blast injury or high-velocity gunshot wounds have found physical examination to be less reliable than in studies of civilian casualties, likely because of the high energy nature of military wounds.

Neurologic deficits in the upper extremity occur in more than half of patients. The most severe of these injuries is damage to the brachial plexus, which occurs in nearly half of patients with blunt injury.

DIFFERENTIAL DIAGNOSES

In many cases, peripheral vascular injury will be readily apparent by external bleeding or hematoma formation. In other cases, vascular injury is suspected by the location or nature of the trauma the patient sustained. In all patients, vascular injury is a cue to search for associated injuries, such as bony injuries, injuries to proximate nerves, and soft tissue injuries due to either direct trauma or compression secondary to compartment syndrome. Conversely, some cases of vascular injury may not be obvious on initial examination and should be sought when evaluating patients with potential deep vein thromboses, crush injuries, and other presentations of acute limb pain.

DIAGNOSTIC TESTING

Plain Radiography

Plain radiographs of the affected extremity are indicated to detect fractures, joint penetration, and foreign bodies. With gunshot wounds, the sum of the number of intact bullets seen on radiographs and the number of entrance and exit wounds in the body should be an even number. Rarely, bullets or shotgun pellets can deflect off bone and travel sufficiently far as to not be visible on the radiograph. Bullets or pellets can migrate distally and produce vascular occlusion or migrate proximally through the venous system to the heart. When there is concern for a missing projectile, broaden the radiographic search.

Pulse Oximetry and Near-Infrared Spectroscopy

Pulse oximetry has been found to be a relative insensitive means of identifying limb ischemia after trauma. Clearly, in the absence of a pulse, no reading can be obtained. Beyond that, pulse oximetry should not be considered a discriminatory or useful test for vascular injury. Measurement of tissue oxygenation by near-infrared spectroscopy (NIRS) to quantify muscle oxyhemoglobin showed early promise as a possible noninvasive and simple means of detecting vascular injury; however, small clinical studies have found contradictory results in use of NIRS for this indication.[13,14]

Handheld Doppler

Absent or diminished pulses in an injured extremity should be evaluated using a handheld Doppler. Arterial injury is suggested by absent Doppler signal, or by a change in the usual triphasic quality of the Doppler pulse to a biphasic or monophasic waveform, because the pulse is "damped" by partial occlusion.

Arterial Pressure Index and Ankle-Brachial Index

Measuring systolic blood pressure in the injured versus the uninjured extremity (arterial pressure index [API]) or measuring it in an injured leg at the ankle compared with brachial artery pressure (ankle-brachial index [ABI]) are both accurate means of screening for arterial injury. Systolic pressure is measured by inflating a standard blood pressure cuff proximal to the injury and recording handheld Doppler systolic pressure distal to the injury. The process is repeated on the uninjured limb (or the arm, if calculating an ABI), and a ratio of injured to uninjured systolic pressure is calculated. In general, a ratio less than 0.90 is considered abnormal and indicates need for further investigation. Clinical studies of API/ABI have shown promising results. In several studies, an API/ABI less than 0.90 yielded a sensitivity and specificity for the detection of vascular injury of over 95%, with correspondingly high positive and negative predictive values.[15]

Patients with suspected vascular injury who have an API/ABI of 0.90 to 0.99 merit observation for 12 to 24 hours for repeated physical examination and API measurements to detect potentially evolving injury. Patients with normal physical examination findings and a completely normal (greater than or equal to 1.0) API/ABI can be safely discharged from the ED, provided that there are no other injuries requiring admission.

However, reliance on the API/ABI to screen for arterial injury is not always possible. Comparisons cannot be made when both limbs are injured or when severe soft tissue disruption precludes placement of a blood pressure tourniquet. Certain arteries (eg, the profunda femoris, profunda brachii, and peroneal arteries) normally do not produce palpable pulses, and so API/ABI is of limited usefulness if injuries to these vessels are suspected. Shotgun wounds often are associated with normal API/ABI measurements despite multiple small arterial wounds; catheter-based angiography is the preferred diagnostic modality in this group.

Despite the limitations previously noted, API/ABI has proved effective in screening patients with proximity wounds. The vast majority of injuries missed by API/ABI heal spontaneously. Those that do not heal generally present within 3 months with signs of arterial injury and can be repaired electively.

Ultrasound

Bedside B-mode (real-time) ultrasound, particularly with color flow Doppler (see later), can reliably identify loss of arterial pulsation in major vessels. However, B-mode ultrasound cannot visualize certain anatomic areas accurately (eg, subclavian and

iliac vessels) because of inadequate tissue windows, and it is unreliable in detecting a fresh, relatively non-echogenic thrombosis or hematoma. As blood liquefies within a hematoma, it becomes echolucent and more readily distinguishable from surrounding tissues.

Doppler ultrasound interprets sound moving toward or away from the transducer as flow. Venous flow is heard as a low-pitched hum, whereas arterial flow has a higher-pitched triphasic quality. The combination of B-mode and Doppler ultrasound is called *duplex ultrasound* and has enhanced accuracy in examining blood vessels. Duplex scans showing a focal increase in peak systolic velocity suggest partial obstruction of the vessel. However, duplex scanning is slightly less accurate for detecting injuries that do not decrease flow, such as small pseudoaneurysms, AVF, and intimal flaps. Also, it is technically limited in examining certain anatomic areas, such as the profunda femoris and profunda brachii arteries and the iliac and subclavian vessels. Duplex ultrasound findings may be subtle, and as with other applications of ultrasound, its accuracy is operator dependent. Despite these limitations, the sensitivity of duplex ultrasound in comparison with standard angiography ranges from 83% to 100%, with a specificity of 99% to 100% and an accuracy of 96% to 100%.[16]

Color flow Doppler converts Doppler echoes into quantitated visual signals. Flow toward the transducer is seen as red, and flow away from the transducer is seen as blue. The intensity of the color (the number of pixels on the screen) is proportional to flow through the vessel. Small prospective studies have indicated a high rate of accuracy in detecting arterial injury with color flow Doppler. Absence of flow is readily apparent, but subtle injuries, such as intimal flaps and small pseudoaneurysms, can be more difficult to identify than with CTA. The overall sensitivity of color flow Doppler in detecting arterial injury is 50% to 90%, with a specificity of 95% to 99%. The sensitivity for detecting injuries requiring surgical repair is greater than 90% (Figs. 41.6 and 41.7).[9,17]

Computed Tomography and Magnetic Resonance Imaging

With a few important exceptions, CTA has largely replaced catheter-based angiography for the detection of peripheral

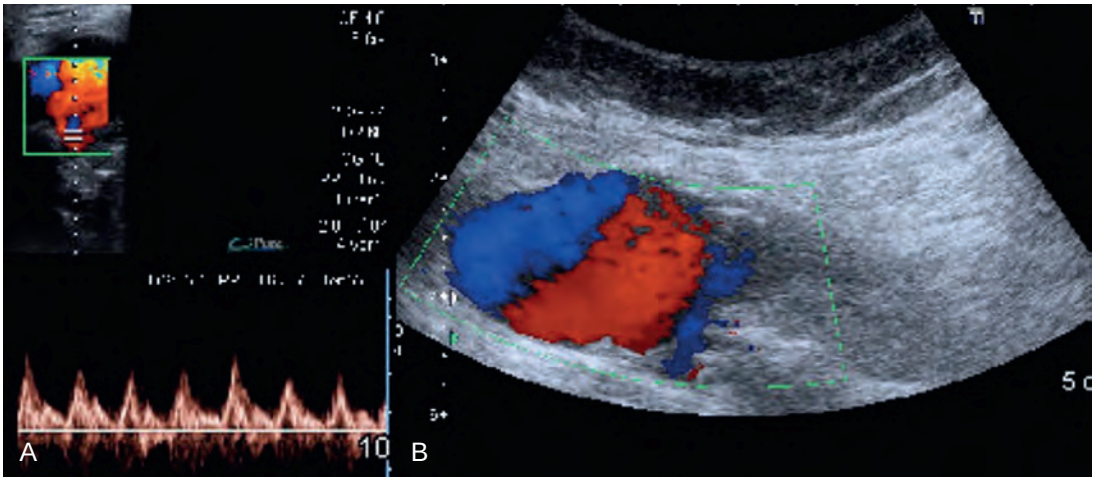

Fig. 41.6. Sonography of popliteal fossa with systolic bruit **(A)** and longitudinal color Doppler ultrasound **(B)** show arterial blood. (From Tejero-Garcia S, Lirola Criado JF, Ast MP, et al: Popliteal pseudoaneurysm after unicompartmental knee replacement: a case report. Knee 21[2]:597-599, 2014.)

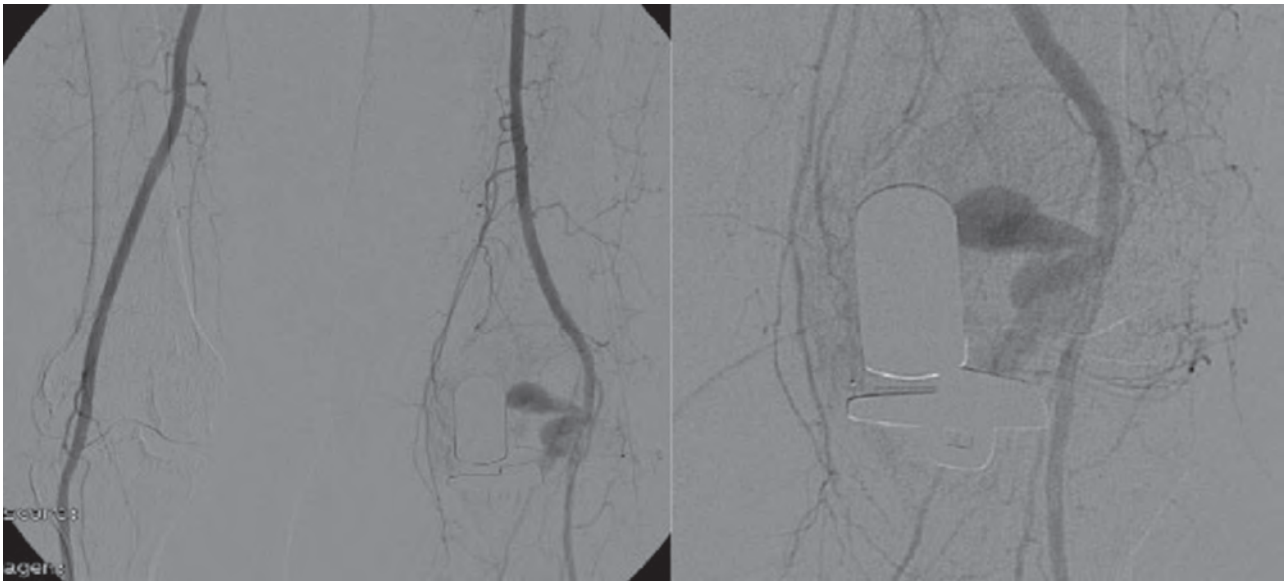

Fig. 41.7. Digital subtraction angiography of both popliteal arteries shows pseudoaneurysm on the *left (zoomed image on the right).* (From Tejero-Garcia S, Lirola Criado JF, Ast MP, et al: Popliteal pseudoaneurysm after unicompartmental knee replacement: a case report. Knee 21[2]:597-599, 2014.)

vascular injury in most trauma centers.[16] Multi-detector helical computed tomography (CT) scanners have proven very accurate for diagnosis of peripheral vascular injury in multiple series with a sensitivity of 93% to 100% and specificity of 87% to 100% compared with catheter-based angiography.[18-21] The advantages of CTA over catheter-based angiography are that it is noninvasive, readily available, and less costly and provides information on other injuries in the region being studied. However, there are several pitfalls to the use of CTA. Metallic artifact from bullets, orthopedic hardware, or other penetrating objects may obscure visualization of parts of a vessel, although with image reconstruction techniques, this problem can be largely overcome. Venous injuries may be missed depending on the phase of the contrast. The rapid image acquisition of current CT scanners makes timing of the contrast bolus more critical, and out-of-phase images may miss arterial injury. In practical terms, though, CTA is very useful in that it can be integrated into an overall plan for diagnostic imaging, including CT of the head and trunk, all of which can be accomplished rapidly.[19] Because of the enhanced detail, accuracy, and speed of image acquisition with 64 and greater slice CT scanners and the ability to perform three-dimensional reconstructions, this modality has become the standard imaging technique for suspected vascular injury. Magnetic resonance angiography (MRA) has been described and accurately detects vascular injuries but has yet to prove clinically useful.[22] MRI is also contraindicated in the presence of ferromagnetic foreign bodies.

Arteriography

Historically, catheter-based contrast angiography was used for diagnosing peripheral arterial injury. However, given the ready availability of CTA and additional steps necessary to obtain an angiography (transfer of the patient, activation of the angiography team, preparation of the angiography suite), CTA has replaced angiography as the initial diagnostic modality of choice in the ED.[23] Even those patients who may need intervention (embolization of pseudoaneurysms, endovascular stent insertion to bypass a dissection or AVF, and injection of thrombolytic agents to dissolve thrombus are routinely performed via intra-arterial catheter) are best served by obtaining a rapidly available CTA to establish the diagnosis.

Diagnosis of Specific Vascular Injuries

Although the aforementioned diagnostic strategies apply to vascular trauma overall, certain injuries bear particular mention.

For subclavian artery injury, the combination of physical examination and chest x-ray findings suggestive of subclavian injury (hemothorax, pneumothorax, apical pleural cap, or wide mediastinum) identifies nearly all injuries, and arteriography is not indicated in the absence of findings. When injury is suspected and the patient is unstable, operative intervention is indicated. If the patient's clinical condition permits, however, angiography can confirm the diagnosis and can locate the injury precisely. APIs are not reliable with proximal thoracic outlet injuries because of collateral arterial flow. Ultrasound techniques are also relatively inaccurate in detecting subclavian injuries because of interference by overlying gas-filled lung tissue. Therefore in cases in which the clinical diagnosis is equivocal (soft signs of injury or proximity wounds), arteriography (CTA or catheter based) is required to detect the injury.

No consensus has been reached on the diagnostic approach to detect popliteal artery injury resulting from documented or suspected knee dislocation. It is, of course, unreasonable to perform routine arteriography on every case of obvious or suspected knee dislocation. Although the exact diagnostic strategy is institution specific and dependent on available resources, our hospital's approach is to perform a CTA in cases of high-energy mechanisms of blunt trauma (eg, auto vs. pedestrian or MVC).[24] For lower energy blunt mechanisms, such as athletic injury, we perform serial clinical evaluations, including ABI. However, patients with *penetrating* trauma and more than one hard sign of popliteal artery injury can be taken directly to the operating room for repair, because delaying these cases to obtain a CTA is unnecessary.

MANAGEMENT

Management of peripheral vascular injury is part of the total care of the trauma patient, including control of active hemorrhage by direct digital pressure. Blind clamping of a bleeding vessel is not recommended because of the risk of crushing adjacent nerves; however, clamping a clearly visible vessel can be effective. Tourniquet use for up to 6 hours is safe and effective, and it has been associated with increased survival in patients with major limb trauma. Tourniquets should be applied if direct pressure is insufficient to control bleeding and left in place until definitive surgical control can be achieved.[25] Few complications are associated with the use of tourniquets, and almost all of these are transient.[26] In cases in which proximal and distal control of large-vessel injuries cannot be readily achieved in the ED, insertion of a Foley catheter into the wound and inflation of the balloon with sterile water can temporarily tamponade the bleeding. Intravenous lines should not be started in the injured extremity, because they may be ineffective in delivering resuscitation fluid or medication and because extravasation from an injured vein may increase compartment pressure. Serial hemoglobin determinations may indicate unexpected blood loss from occult vascular injury. Patients with significant blood loss should have blood typed and crossmatched and may require immediate transfusion for stabilization. Patients with significant vascular injury often remain hypotensive despite such infusion and require further volume infusion or blood transfusion.

The issue of hypotensive resuscitation is controversial with regard to major vascular injuries. A tenuous clot can form in an injured artery and prevent further blood loss as long as the patient remains hypotensive. Once arterial pressure reaches a critical but variable point, the clot may be expelled and massive blood loss can ensue. Therefore, when an arterial injury is inaccessible for occlusion by direct pressure, the target blood pressure for resuscitation should be lowered to a systolic pressure of approximately 90 mm Hg. Overly rapid fluid administration in the field or in the ED can produce transient intravascular hypervolemia and may ultimately increase the rate of blood loss. Closely monitor vital signs and the total volume of fluid infused.[27]

Once a vascular injury has been identified, a specific diagnostic and therapeutic strategy should be developed that is consistent with the severity of the injury, the presence of other injuries, and the resources available. In hospitals without the ability to perform vascular repair, transfer to a trauma center should be initiated early. In cases in which the transfer will involve a delay of several hours, cooling the ischemic limb will avoid exceeding the critical 6-hour cutoff for warm ischemia. To accomplish this, wrap the limb in towels, and apply ice in plastic bags around the limb, avoiding direct contact of the ice to the limb, which can result in frostbite.

Major Vascular Injuries

Major vascular injuries that compromise the viability of a limb should be repaired within 6 hours to avoid irreversible ischemic neuropathy and myonecrosis. Treatment of vascular injury has changed dramatically in the past 10 years. Endovascular treatment with self-expanding stents is currently the preferred technique for

repair of these injuries in stable patients, and the majority of arterial repairs in the United States are now done with this technique.

Upper Extremity Arterial Injuries

For brachial artery injuries, limb salvage rates have improved to nearly 100% owing to efficient out-of-hospital transport, improved surgical techniques, and shorter time to first antibiotic dose. Repair is indicated in all cases because the amputation rate is high with ligation.

Injuries to forearm vessels detected by arteriography or ultrasound do not need to be repaired unless there are signs of ischemia in the hand; "hard signs" of arterial injury, such as an expanding hematoma, pseudoaneurysm, or AVF; or injury to both radial and ulnar arteries. However, some authors recommend repairing all these injuries because of the risk of intermittent claudication or cold intolerance in patients who have one artery ligated. Certain patients are almost exclusively dependent on the ulnar arterial supply to the hand because of an underdeveloped deep palmar arch. Clearly, ulnar artery injuries should be repaired in these patients. Ultimately, the decision to repair an arterial injury is in the domain of the vascular surgeon. Compartment syndrome in the forearm is common after repair of proximal arteries and veins and may require fasciotomy.[28]

Lower Extremity Arterial Injuries

In patients with severe injuries to the lower extremities, an initial "damage control" laparotomy with temporary vascular shunting of the iliac vessels is often necessary as resuscitation continues. Distal ischemic complications occur in approximately one-third of repaired iliac arteries, and subsequent amputations are required in up to 20%.

Femoral artery injuries should be repaired as simple ligation of the common femoral artery results in amputation of the lower extremity in 80% of cases.

Factors that place patients at higher risk of amputation include severe soft tissue injury of the extremity, the presence of multiple fractures, major venous repair, or delay in repair exceeding 6 hours of warm ischemia time. Because of the high incidence of compartment syndrome with lower leg injuries, fasciotomy is required in half of cases, and some centers routinely perform fasciotomy in all such cases.[29]

Late Complications of Arterial Injury

Despite timely optimal repair of arterial injuries, approximately one in five patients experiences delayed complications requiring further surgical intervention, including delayed amputation. The most common of such complications is delayed thrombosis, which often occurs after many months as stenosis at the repair site progresses. Other complications include intermittent claudication, chronic pain or edema of the limb, and aneurysm formation in the graft.

Venous Injuries

Venous injuries may be primarily ligated if the patient's condition makes them unable to tolerate prolongation of surgery. However, the current trend is to repair major venous injuries if possible, particularly in the lower extremity, because wound healing is improved and the incidence of compartment syndrome, venous thrombosis, pulmonary embolism, and chronic edema is decreased. Extensive venous collaterals in the upper extremity make surgical repair less compelling.

Minor Vascular Injuries

Increasingly, minor nonocclusive vascular injuries are being treated expectantly. Criteria for observation of vascular injuries include low-velocity missile wounds, intact distal circulation, absence of active hemorrhage, and minimal arterial wall disruption on angiography if performed. Angiographic or CTA findings meeting these criteria include intimal flaps extending less than 5 mm and pseudoaneurysms smaller than 5 mm in diameter. Follow-up of these injuries with repeat angiography or ultrasound reveals that approximately 85% resolve spontaneously. Patients meeting these criteria can be monitored as outpatients for 3 months, with repeat physical examination and ultrasound to detect delayed complications. Most intimal flaps heal spontaneously, and asymptomatic injuries that do not disrupt perfusion of the limb can be treated conservatively with early administration of antiplatelet agents, such as clopidogrel or aspirin. However, almost all pseudoaneurysms ultimately require repair and, once discovered, should be repaired electively rather than undergoing continued observation. Failure to detect and repair occult arterial injuries in children often results in severe differential limb growth. Thus, a more aggressive policy of repairing arterial injuries that causes a relatively minor decrease in blood flow to a child's growing limb may be justified.

Arterial Spasm

Isolated arterial spasm usually reverses with conservative treatment (topical warm saline or topical nitroglycerin paste), but prolonged spasm may require infusion of vasodilators, such as nitroglycerin, calcium channel blockers, alpha-blockers, nitroprusside, specific prostaglandin inhibitors, or warm saline.

Antibiotics

Current guidelines call for empirical gram-positive and gram-negative antibiotic administration for all patients with peripheral vascular injuries associated with open fractures, as well as those with extensive soft tissue injury.[30] Appropriate coverage might include a first-generation cephalosporin (eg, cefazolin 1 to 2 g intravenously preoperatively) and gentamicin 5 to 7 mg/kg intravenously every 24 hours during the perioperative period.

DISPOSITION

Patients with confirmed injury to major vessels, equivocal findings on diagnostic tests, or symptoms of limb ischemia should be admitted to the hospital or ED observation unit for further investigation or serial physical examinations. Frequent vascular and neurological checks will be necessary in these patients, so step-down or intensive care unit levels of care may be necessary. Consultation with a vascular surgeon is indicated as soon as vascular injury is strongly suspected or the need for emergency operative repair established. Patients who are unstable because of vascular or other injuries may undergo further investigation or exploration in the operating room. If the treating hospital is incapable of performing vascular surgery or appropriate investigations, transfer to a trauma center should be initiated. Obtaining angiograms for proximity wounds in centers that are incapable of acting on positive results is unwise, because this may delay definitive care beyond the safe limits of warm ischemia time.

KEY CONCEPTS

- The overall condition of the patient determines the extent of emergency department (ED) evaluation and stabilization. Critically injured patients may require immediate surgery, which should not be delayed for confirmatory studies of obvious vascular injury.
- Arterial injury may be readily apparent or clinically occult. In patients with high-energy blunt mechanisms, computed tomography angiography (CTA) should be the initial diagnostic modality of choice. In patients with lower-energy mechanisms, serial physical examinations may be performed instead.
- Symptoms of arterial injury may be delayed by hours to months after the initial injury. Late onset of symptoms suggests delayed thrombosis, pseudoaneurysm or arteriovenous fistulae (AVF) formation, compartment syndrome, or intermittent claudication, resulting from stenosis or reliance on small-caliber collateral vessels for arterial perfusion.
- Compartment syndrome frequently develops in limbs with arterial injury, particularly injuries of the lower leg, and fasciotomy is often required.
- Many vascular injuries are amenable to endovascular treatment with self-expanding stents. This results in fewer complications, lower cost, and earlier discharge from the hospital.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 41: QUESTIONS & ANSWERS

41.1. An 18-year-old man presents complaining of left lower leg pain. He was involved in a motor vehicle collision (MVC) 1 month earlier and requires surgical repair of a left femur fracture. Which of the following is the *least* likely cause of the patient's symptoms?

A. Compartment syndrome
B. Intimal flap
C. Pseudoaneurysm
D. Thrombosis
E. Vessel stricture formation

Answer: A. Delayed thrombosis can occur months to years after injury if the injured vessel heals with stricture formation and decreased blood flow distally, followed by stasis and clot formation. Although flow is not altered by small intimal flaps, and the associated soft tissue wounds often appear benign initially, they may become a nidus for thrombosis that can occur hours to months after the initial injury. The cavity of a pseudoaneurysm is in direct communication with the lumen of the vessel, so embolization of mural clots may produce distal arterial occlusion. Patients with pseudoaneurysm are commonly seen months to years later with symptoms of compression neuropathy or peripheral arterial embolism. The delayed presentation of this patient makes compartment syndrome the least likely cause of his leg pain.

41.2. A 45-year-old man complains of right leg pain and edema shortly after surgery for a mid-shaft femur fracture. Physical examination reveals decreased distal pulses in the extremity. What is the most important diagnosis to consider in this patient?

A. Anemia causing poor tissue oxygenation
B. Compartment syndrome
C. Intimal flap
D. Pseudoaneurysm
E. Vessel stricture

Answer: B. After restoration of arterial flow to a previously ischemic limb, a cascade of reperfusion injury has been identified that results from release of oxygen free radicals, lipid peroxidation, and influx of intracellular calcium. These mediators give rise to progressive cellular damage, edema, and necrosis, thereby propagating the vicious cycle that increases compartment pressure.

41.3. After vascular injury to an extremity, how many hours are generally required before irreversible damage occurs?

A. 2 hours
B. 6 hours
C. 10 hours
D. 12 hours
E. 24 hours

Answer: B. Although individuals may vary, 6 hours of complete warm ischemia is generally considered the point at which irreversible nerve and muscle damage begins to occur. After 6 hours of warm ischemia, 10% of patients will have irreversible damage; by 12 hours, 90% will have irreversible damage. Artificially cooling the limb to just higher than freezing temperature will reduce the metabolic demands of ischemic tissues and greatly prolong the tissue's tolerance of ischemia to 24 hours or more.

41.4. A 25-year-old man who sustained a gunshot wound to the right leg has an ankle-brachial index (ABI) of 0.9. What is the most appropriate next step in this patient's management?

A. Admit for observation and repeat examinations.
B. Discharge the patient home with surgical follow-up.

C. Obtain an emergent computed tomography (CT) angiogram.
D. Obtain immediate vascular consultation.
E. Perform a Doppler ultrasound scan.

Answer: A. Patients with an ABI of 0.90 to 0.99 merit observation for 12 to 24 hours for repeat examinations and ABI measurements to detect evolving injury. In general, a ratio of less than 0.90 is considered abnormal and is an indication for further investigation, such as computed tomography angiography (CTA).

41.5. Which of the following is *least* likely to cause vascular injury to an extremity?
A. Close-range shotgun wound
B. Crush injury
C. Electrical injury
D. Gunshot wound from a long distance
E. Massive tissue avulsion

Answer: D. Close-range shotgun wounds can cause significant blunt trauma to vessels, as well as a higher rate of bone and nerve damage than gunshot wounds. An open avulsion injury to limb is particularly severe because the skin is the final structure to be disrupted, and there is inevitable injury to deeper vessels and nerves. Vascular injury must be suspected in patients with massive soft tissue avulsion or crush injury, displaced long bone fractures, and electrical or lightning injuries.

CHAPTER 42

General Principles of Orthopedic Injuries

Joel M. Geiderman | Dan Katz

MANAGEMENT PRINCIPLES

Although only rarely life-threatening, orthopedic injuries may threaten a limb or its function, and accurate early diagnosis and treatment can avert long-term complications. Many of these injuries can and should be treated definitively by the emergency clinician. Consultation with an orthopedist should be sought for the treatment of most long bone fractures, open fractures, injuries with joint violation, and injuries with neurovascular compromise and for follow-up of certain patients initially treated in the emergency department (ED).

When evaluating a potential orthopedic injury, 10 basic general principles should be considered:

1. Most orthopedic injuries can be inferred by understanding the chief complaint, age of the patient, mechanism of injury, and estimate of the amount of energy delivered.
2. A careful history and physical examination can predict radiographic findings with a high degree of accuracy. A presumptive diagnosis before a radiographic study may prompt the emergency clinician to order special views necessary to diagnose an injury correctly. Many fractures were accurately described before the advent of roentgenology (Table 42.1).
3. If a fracture is suggested clinically, but radiographic films appear negative, the patient should initially be treated with immobilization as though a fracture were present. Similarly, certain soft tissue injuries require prompt identification and follow-up and should be immobilized despite normal radiographic findings.
4. There are criteria for adequate radiographic studies; inadequate studies should not be accepted.
5. In general, when a fracture is suspected, radiographic studies should be performed before most reductions are attempted, except when a delay could be potentially harmful to the patient or in some field situations, such as neurovascular compromise or ischemic skin.
6. Neurovascular competence should be assessed and recorded prior to and following all reductions and after application of immobilization.
7. Patients must be checked for the ability to ambulate safely before discharge from the ED and should not be discharged unless safe transportation can be established.
8. Patients should receive explicit aftercare instructions before leaving the ED, covering areas such as monitoring for signs of neurovascular compromise or increasing compartment pressure, cast care, weightbearing, crutch use, and an explicit plan and timing for follow-up.
9. In a patient with multiple trauma, noncritical orthopedic injuries should be diagnosed and treated only after more threatening injuries have been addressed.
10. All orthopedic injuries should be described precisely and according to established conventions. When communicating with an orthopedic consultant, this may affect decisions regarding disposition of a patient and operative versus nonoperative management.

FRACTURES

Fracture Nomenclature

Describing orthopedic injuries with precise language according to established convention enables accurate clear communication with other parties. Terms commonly used to describe a fracture are listed in Box 42.1. A fracture is a break in the continuity of bone. Clinically, a history of loss of function, pain, tenderness, swelling, abnormal motion, and deformity suggests a fracture. Radiographic studies are the mainstay of diagnosis and are usually, although not always, confirmatory. At times, use of special views, radionuclide bone scans, computed tomography (CT), and/or magnetic resonance imaging (MRI) is necessary to confirm a clinical impression. These studies should be considered when the clinical evidence is at odds with the findings of routine radiography, although are rarely required emergently.

General Descriptors

Description of a fracture should begin by stating whether the fracture is closed or open. In a closed fracture, the skin and soft tissue overlying the fracture site are intact. The fracture is considered open if it is, or has been, exposed to the outside environment in any manner, which may not be immediately obvious. Occasionally, it may be difficult to determine whether a small wound in proximity to a fracture actually communicates with that fracture. Although some emergency clinicians advocate probing such a wound with a blunt sterile swab to establish a relationship, no study has established the safety, benefit, or accuracy of this maneuver. If doubt exists, an open fracture should be assumed to be present.

The next item that should be noted in the description of a fracture is the exact anatomic location, including the name of the bone, left or right, and standard reference points along the bone (eg, the humeral neck or posterior tibial tubercle). Long bones can be divided into thirds—proximal, middle, or distal—and these thirds, or the junction of any two of them (eg, the junction of the middle and distal thirds of the tibia), are used to describe fractures. The most descriptive language possible should be used. It is better to say "closed fracture of the right ulnar styloid" than "closed fracture of the right distal ulna" because the former conveys more precise anatomic information.

TABLE 42.1

Common Fracture Names and Their Origins

FRACTURE EPONYM OR NAME	DESCRIPTION	COMMENT
Aviator	Vertical fracture of the neck of the talus with subtalar dislocation and backward displacement of the body	First described in flyers during World War I; arises from forced dorsiflexion of the foot in flying accidents and in traffic accidents after a head-on collision
Barton	Intraarticular fracture-dislocation of the wrist	Considered complicated and unstable; requires surgical reduction in most cases; described by Barton in 1838 before the advent of radiography
Dorsal Barton	Oblique intraarticular fracture of the dorsal rim of the distal radius with displacement of the carpus along with the fracture fragment	Results from high-velocity impact across the articular surface of the radiocarpal joint, with the wrist in dorsiflexion at the moment of impact
Volar Barton	Wedge-shaped articular fragment sheared off the volar surface of the radius (volar rim fracture), displaced volarly along with the carpus	Similar mechanism as dorsal Barton but with wrist in volar flexion at time of injury; also referred to as reverse Barton's fracture; much rarer than dorsal Barton fracture
Bennett	Oblique fracture through base of the first metacarpal, with dislocation of the radial portion of the articular surface	Usually produced by direct force applied to the end of the metacarpal; dorsal capsular structures disrupted by the dislocation; marked tenderness along medial base of thumb
Bosworth	Fracture-dislocation of the ankle resulting in the fibula being entrapped behind the tibia	Rare injury, produced by severe external rotation force applied to the foot; physical examination reveals foot severely externally rotated in relation to the tibia
Boxer	Fracture of the neck of the fourth or fifth metacarpal	Results from striking a clenched fist into an unyielding object, usually during an altercation, or against a wall, out of frustration or anger
Chance	Vertebral fracture, usually lumbar, involving the posterior spinous process, pedicles, and vertebral body	Caused by simultaneous flexion and distraction forces on the spinal column, usually associated with use of lap seat belts; anterior column fails in tension, along with the middle and posterior columns; may be misdiagnosed as a compression fracture
Chauffeur	Solitary fracture of radial styloid	Occurs from tension forces sustained during ulnar deviation and supination of the wrist; name derived from occurrence in chauffeurs who suffered violent, direct blows to the radius incurred while turning the crank on a car, only to have it snap back, during previous eras
Clay shoveler	Fracture of the tip of the spinous process of the sixth or seventh cervical vertebra	First described in Australian clay shovelers who sustained a fracture of the spinous process by traction as they lifted heavy loads of clay
Colles	Fracture of the distal radius with dorsal displacement and volar angulation, with or without an ulnar styloid fracture	Most common wrist fracture in adults, especially in older adults; results from fall on an outstretched hand; also known as silver fork deformity, which accurately describes the gross appearance in the lateral view; first described by Colles in 1814, before the advent of radiography
Cotton	Trimalleolar fracture	Fracture of the lateral malleolus, fracture of the posterior malleolus, and either a fracture of the medial malleolus or disruption of the deltoid ligament, with visible widening of the mortise on ankle radiograph
Dashboard fracture	Fracture of the posterior rim of the acetabulum	Named for mechanism of injury—a seated passenger striking the knee on a dashboard, driving the head of the femur into the acetabulum
Dupuytren	Fracture-dislocation of the ankle	Results from a similar mechanism as the better known Maisonneuve fracture (ie, external rotation of the ankle), resulting in deltoid ligament rupture or medial malleolus fracture, diastasis of the inferior tibiofibular joint, and indirect fracture of the fibular shaft; Maisonneuve was a student of Dupuytren
Essex-Lopresti	Fracture of radial head with dislocation of the distal radioulnar joint	Results from longitudinal (axial) compression of the forearm
Galeazzi	Fracture of the shaft of the radius with dislocation of the distal radioulnar joint; ligaments of inferior radioulnar joint ruptured, head of ulna displaced from ulnar notch of the radius	Results from fall on outstretched hand, with the wrist in extension and the forearm forcibly pronated; inherently unstable, with tendency to redisplace after reduction

TABLE 42.1

Common Fracture Names and Their Origins—cont'd

FRACTURE EPONYM OR NAME	DESCRIPTION	COMMENT
Hangman	Fracture-dislocation of atlas and axis, specifically of pars interarticularis of C2 and disruption of C2-3 junction; separation occurs between second and third vertebral bodies from anterior to posterior side	Results from extreme hyperextension during abrupt deceleration; most common cause is the forehead striking the windshield of a car during a collision; a bit of a misnomer in that hanging usually produces death by strangulation rather than cord damage
Hume	Fracture of the proximal ulna associated with forward dislocation of the head of the radius	Essentially high Monteggia injury
Jefferson	Burst fracture of ring of C1, or atlas	Axial loading results in a shattering of the ring of the atlas; decompressive type of injury; associated with disruption of transverse ligament; unstable injury
Jones	Transverse fracture of the metatarsal base, occurring at least 15 mm distal to the proximal end of the bone, distal to the insertion of the peroneus brevis	Should not be confused with the more common avulsion fracture of fifth metatarsal styloid, produced by avulsion at the insertion of the peroneus brevis; Jones described the fracture that bears his name in 1902, after sustaining the injury himself while dancing.
Le Fort	Maxillary fracture	Types I, II, and III (see Chapter 42)
Le Fort-Wagstaffe	Avulsion fracture of the anterior cortex of the lateral malleolus	Rare pull-off injury of the fibular attachment of the anterior tibiofibular ligament
Lisfranc	Fracture located around the tarsometatarsal (Lisfranc) joint, usually associated with dislocation of this joint	Lisfranc, a field surgeon in Napoleon's army, described an amputation performed through the tarsometatarsal joint in a soldier who caught his foot in a stirrup when he fell off his horse; since then, the joint has borne his name.
Maisonneuve	Fracture of proximal third of fibula associated with rupture of the deltoid ligament or fracture of the medial malleolus and disruption of the syndesmosis	Results from external rotation of the ankle with transmission of forces through syndesmosis; proximally, the force is relieved by fracture of the fibula; described experimentally in 1840, before radiography
Malgaigne	Fracture of the ilium near the sacroiliac joint with displacement of the symphysis, or a dislocation of the sacroiliac joint with fracture of both ipsilateral pubic rami	Resultant pelvic injury is unstable; described by Malgaigne, based on clinical findings, in 1847
March	Fatigue, or stress, fracture of the metatarsal	Arises from long marches or other repetitive use trauma (eg, marathon running) or, less commonly, from single stumbling movements
Monteggia	Fracture of the junction of the proximal and middle thirds of the ulna associated with anterior dislocation of the radial head.	Usually caused by fall on outstretched hand along with forced pronation of forearm or by a direct blow on the posterior aspect of the ulna; reported by Monteggia in 1814
Nightstick	Fracture of ulna, radius, or both	Name derived from a citizen's attempt to protect himself from a police officer's baton or "nightstick" by offering the forearm
Piedmont	Closed fracture of the radius at the middle third–distal third junction, without associated ulnar fracture	Named for a series of cases presented at the Piedmont Orthopaedic Society of Durham, North Carolina
Pott	Definitions vary (see comment); usually a bimalleolar fracture or fracture of the distal fibula, 4–7 cm above the lateral malleolus	The exact fracture Pott described in 1769 is uncertain; clearly, it referred to a fracture of the lower fibula, usually associated with other fractures or dislocations about the ankle.
Rolando	Intraarticular fracture at base of metacarpal; frequently Y- or T-shaped, or may be severely comminuted	Produced by an axial load with the metacarpal in partial flexion; worse prognosis than a Bennett fracture and, fortunately, rarer
Salter-Harris	Epiphyseal fracture occurring in children or adolescents	Graded I–V, depending on degree of involvement and/or displacement of epiphysis and metaphysis (see text dealing with Salter-Harris fractures and Table 42.2)
Smith	Extraarticular fracture of the distal radius with volar displacement of distal fragment	Reverse of the Colles fracture but much more uncommon; sometimes referred to as a garden spade deformity; usually results from fall with force to back of hand; first described by Smith in 1847
Stener	Avulsion of the ulnar corner of the base of the proximal phalanx of the thumb	Bony equivalent of rupture of the ulnar collateral ligament, or so-called gamekeeper's thumb

Continued

TABLE 42.1

Common Fracture Names and Their Origins—cont'd

FRACTURE EPONYM OR NAME	DESCRIPTION	COMMENT
Teardrop	Wedge-shaped fracture of the anteroinferior portion of the vertebral body, displaced anteriorly	Commonly involves a ligamentous injury; may produce neurologic injury
Thurston Holland fragment	Triangular metaphyseal fragment that accompanies the epiphysis in Salter-Harris type II fractures	Described by Thurston Holland in 1929; the name is commonly hyphenated, although technically it should not be
Tillaux	Isolated avulsion fracture of the anterolateral aspect of the distal tibial epiphysis	Occurs in older adolescents (12–15 yr) after the medial parts of the epiphyseal plates close but before the lateral part closes; external rotation force places stress on anterior talofibular ligament; described by Tillaux in 1872

BOX 42.1

Fracture Description

IDENTIFICATION
Open versus closed
Exact anatomic location
Direction of fracture line
Simple, comminuted
Position (displacement, alignment)

ADDITIONAL MODIFIERS
Complete versus incomplete
Involvement of articular surface (%)
Avulsion
Impaction
- Depression
- Compression

SPECIAL SITUATIONS
Pathologic
Stress

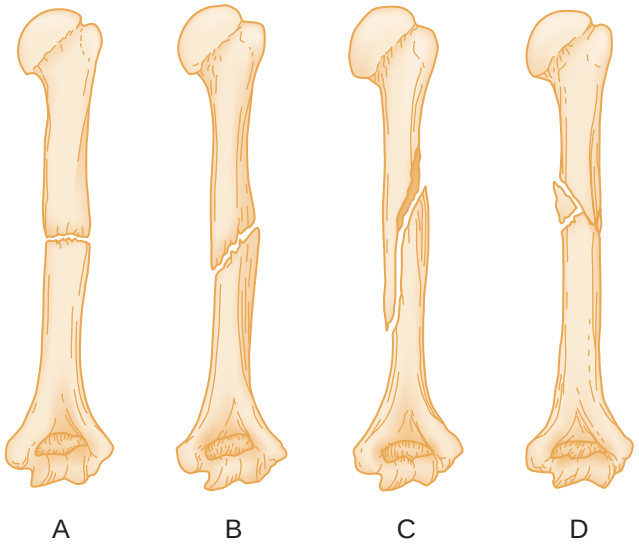


Fig. 42.1. Types of fractures. **A,** Transverse. **B,** Oblique. **C,** Spiral. **D,** Comminuted.

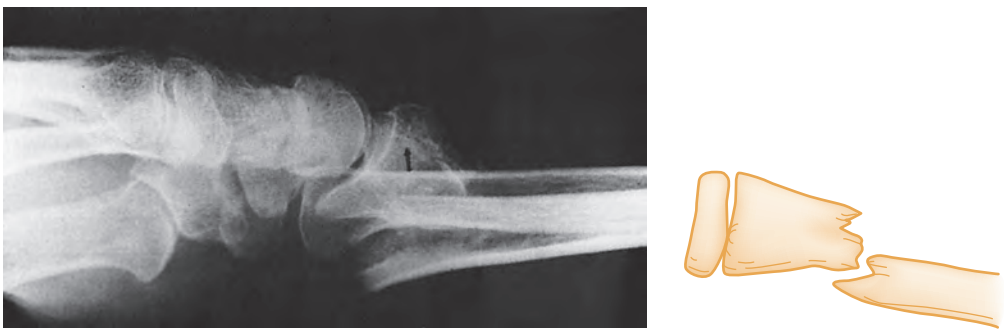


Fig. 42.2. Dorsal displacement of distal radius.

An additional modifier describes the direction of the fracture line in relation to the long axis of the bone in question. A transverse fracture occurs at a right angle to the long axis of the bone (Fig. 42.1A), whereas an oblique fracture runs oblique to the long axis of the bone (see Fig. 42.1B). A spiral fracture results from a rotational force and encircles the shaft of a long bone in a spiral fashion (see Fig. 42.1C). A fracture with more than two fragments is termed *comminuted* (see Fig. 42.1D).

The position and alignment of the fracture fragments (ie, their relationship to one another) should be described. Fragments are described relative to their normal position, and any deviation from normal is termed *displacement.* By convention, the position of the distal fragment is described relative to the proximal one. Displacement may be described as a quantitative measurement (ie, in millimeters) or as a percentage of the bone width. Fig. 42.2 shows a dorsal displacement of the fractured radius, and Fig. 42.3 shows lateral, or valgus, displacement of the distal tibia and fibula.

The terms *valgus* and *varus* are sometimes confusing. The term *alignment* refers to the relationship of the longitudinal axis of one fragment to another; deviation from the normal alignment is

termed *angulation.* The direction of angulation is determined by the direction of the apex of an angle formed by the two fracture fragments (Fig. 42.4). The term *valgus* denotes a deformity in which the the apex of the deformity points towards the midline. Conversely, the term *varus* denotes a deformity in which the apex of the angulation points away from the midline. The relative position or angulation of the distal fragment of a fracture may also be described with terms such as *radial* or *ulnar, dorsal* or *volar, anterior* or *posterior,* and *lateral* or *medial.* One should also be aware of rotational deformity, present when the distal fragment of a fracture is rotated to some degree along the axis of the bone itself. Especially in the digits of the hand, clinically apparent radial or ulnar deviation of a flexed finger can occur, and radiographs often underestimate the degree of clinical deformity and rotation present.

Descriptive Modifiers

A fracture is termed *complete* if it interrupts both cortices of the bone on orthogonal radiographic views and termed *incomplete* if one cortex remains intact. It should be noted whether a fracture extends into and involves an articular surface. Frequently, the percentage of articular surface involved can only be estimated; in some cases the percentage that is actually involved dictates the need to perform a surgical reduction. In general, it is important that the articular surface be restored to anatomic integrity to prevent consequent posttraumatic arthropathy.

The term *avulsion fracture* refers to a bone fragment that is pulled away from its normal position by the forceful contraction of a muscle (Fig. 42.5A) or the resistance of a tendon or ligament to a force in the opposite direction (see Fig. 42.5B). The term *impaction* refers to the forceful collapse of one fragment of bone into or onto another. In the proximal humerus, this collapse typically occurs in a telescoping manner, particularly in older patients, whose bones are soft and brittle. In the tibial plateau, impaction occurs frequently in the form of a depression (Fig. 42.6A and B) and, in the vertebral bodies, impaction frequently occurs in the form of compression (see Fig. 42.6C).

A fracture that occurs through abnormal or diseased bone is termed *pathologic.* A pathologic fracture is suggested whenever a fracture occurs from seemingly trivial trauma. Diseases that cause structural weakness predisposing to injury include primary or metastatic malignancies, bone cysts, enchondromata, and giant cell tumors. In addition, metabolic diseases such as osteomalacia, scurvy, rickets, and Paget's disease all alter bone density, which makes them susceptible to fracture. The term *pathologic* is also often applied to fractures through osteopenic bone when the demineralization is a result of disuse, as in polio. In contrast, fractures through osteoporotic bone of older adults usually are not described as pathologic; these are referred to as geriatric or insufficiency fractures.

When fractures occur in normal bones and a history of so-called trivial trauma is elicited, violence or battering should be suspected. Repeated low-intensity forces may lead to resorption of normal bone, resulting in a stress fracture. Other terms for this condition are *fatigue fracture* and *march fracture* (see Table 42.1). Most stress fractures occur in the lower extremities and affect individuals involved in activities such as running, basketball, aerobics, and dancing. There is often a history of functional pain leading up to the fracture. Extrinsic factors such as training regimens, type of equipment used, and nutrition habits, as well as intrinsic factors such as anatomic variation, muscle endurance, and hormonal factors, have all been associated with stress fractures. These injuries may not be recognizable on initial plain films; therefore, management should be based on the clinical diagnosis. The tibia, fibula, metatarsals, navicular, cuneiform, calcaneus, femoral neck, or femoral shaft may be involved.

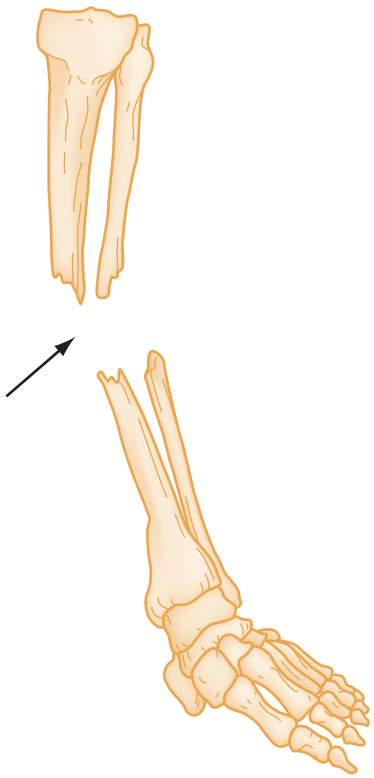


Fig. 42.3. Valgus displacement of the distal tibia and fibula. The distal segment is angled away from the midline of the body.

Fracture Eponyms

Many fractures were described before the advent of radiography and are described by an eponym rather than the exact bony injury.

Fig. 42.4. Volar angulation of a fractured radius (*arrow*).

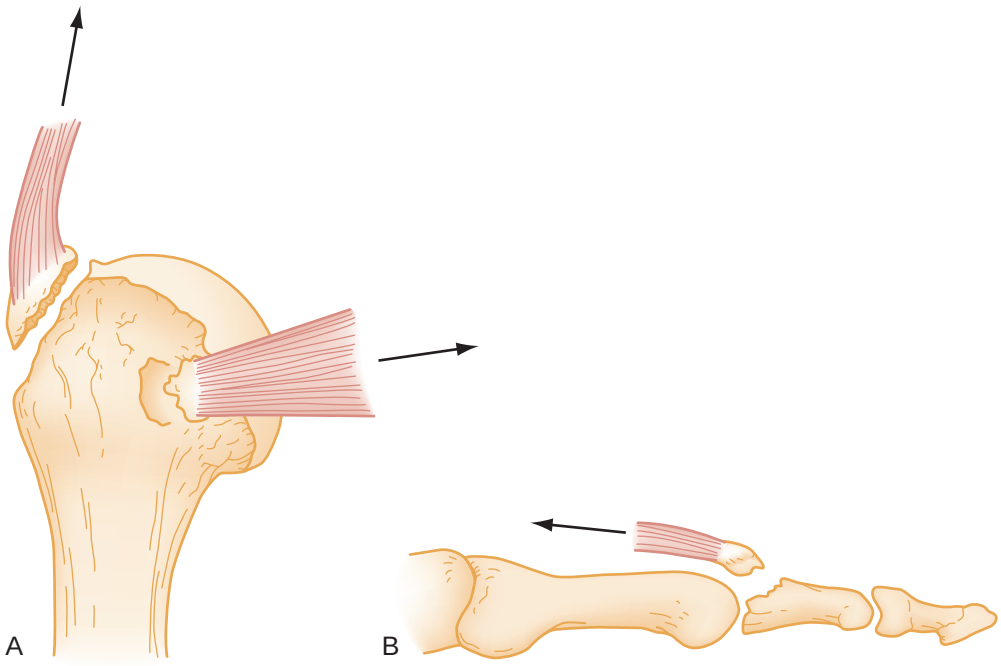


Fig. 42.5. Avulsion fractures. **A,** Musculotendinous avulsions of small bone fragments from the head of the humerus (*arrows*). **B,** Extensor tendon avulsion of bone from the base of the middle phalanx (*arrow*).

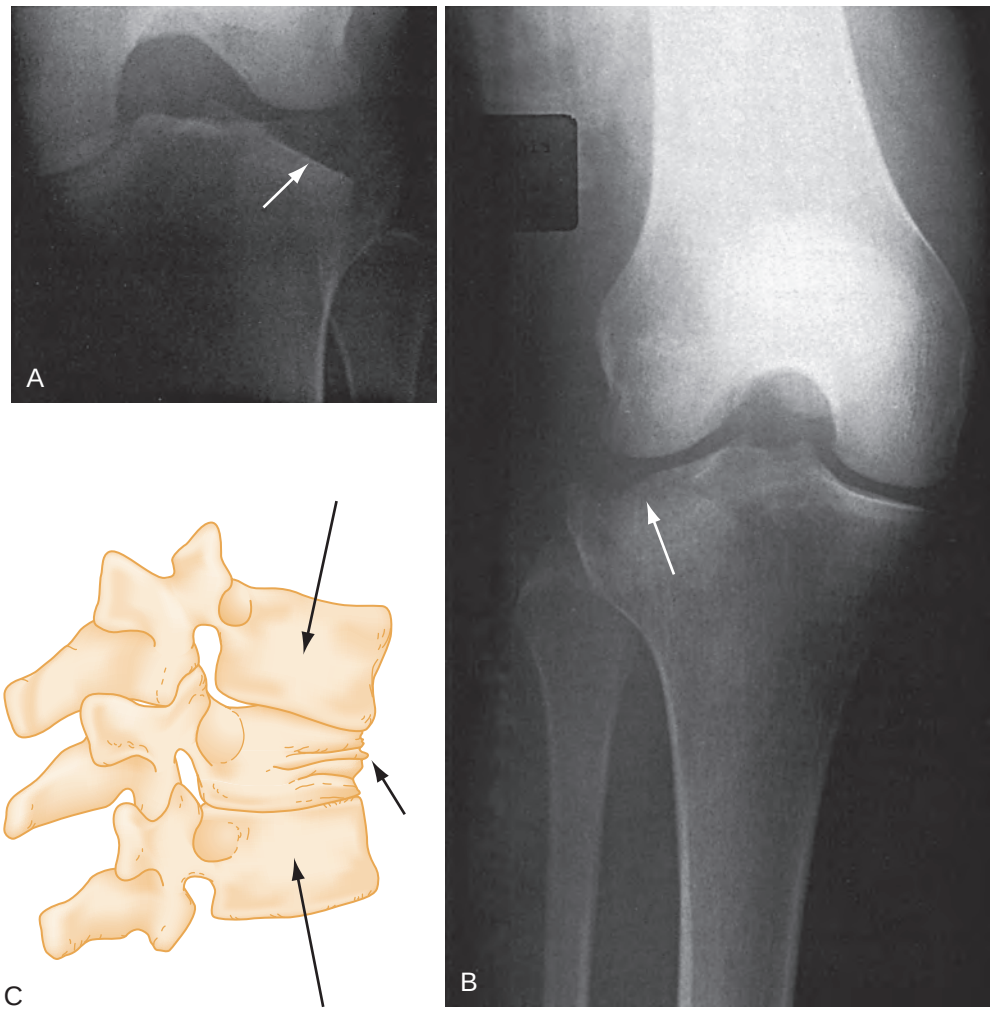


Fig. 42.6. **A, B,** Tibial plateau fracture. **C,** Vertebral body compression fracture (*arrows*).

These eponyms reflect the rich history of orthopedic care and, despite the objections of some, are still commonly used to describe orthopedic injuries (see Table 42.1).

Fracture Healing

The goal of fracture reduction is to realign bony fragments so that healing or union can take place, and normal function is restored. Rupture of vessels crossing the fracture line forms a hematoma, which eventually resorbs and provides the first continuity between the fragments. This procallus provides no structural rigidity for bearing stress but, with remodeling, callus is subsequently formed on the periosteal and endosteal surfaces of the bone, acting as a biologic splint. The callus completely ossifies and, over several months to 1 year, remodels and becomes indistinguishable from mature bone.

Radiographic studies conducted 10 to 14 days after injury show the bone surrounding the fracture line becoming more visible because of localized bone resorption and hyperemia during the inflammatory phase. After 2 to 4 weeks, soft tissue swelling has regressed, and callus first becomes visible, initially in a mottled pattern and then taking on a dense appearance. The callus undergoes organization, with peripheral margins becoming smooth as physically unstressed portions are resorbed.

In a healthy adult, the whole process from injury to consolidation takes about 2 months for the humerus and about 4 months for a large bone such as the femur. Oblique fractures tend to heal more quickly than transverse fractures. The rate of fracture healing is affected by many factors, including the type of bone (cancellous bone heals faster than cortical bone), degree of fracture and opposition, and systemic states, such as hyperthyroidism or illness requiring ongoing corticosteroid treatment. Appropriately timed weightbearing can increase the rate of ossification of callus, whereas premature or excessive weightbearing can create a nonunion.

On a radiograph, the presence of abundant bridging callus that is beginning to organize is usually associated with clinical union. If there is any suggestion of movement at the fracture site noted on clinical examination, union is regarded as inadequate. Several terms are used to denote abnormal healing. *Delayed union* is union that takes longer than usual for a particular fracture location; *malunion* occurs when a residual deformity exists; and *nonunion* is the failure of a fracture to unite. When nonunion results in a false joint, it is termed a *pseudarthrosis.*

If there is clinical evidence of stability, such as pain-free weightbearing, and radiographs demonstrate bridging bone on at least three cortices, a patient may resume activities of daily living with the injured extremity, even if the original fracture remains visible. The final process of complete radiographic consolidation can take several months.

Nomenclature and features of fractures in children are discussed in Chapter 175.

Diagnostic Modalities for Fractures

Plain Radiography

Conventional radiography is the mainstay for diagnosing fractures. In addition to confirming or excluding fractures, it can identify other pathologic conditions. With penetrating trauma, foreign bodies, air, and gas also may be detected.

Biplanar radiographs of an injured extremity should be obtained to delineate the bony injury fully. Conventional radiographic evaluation of long bones includes at least two orthogonal views, and an oblique view is also obtained if an injury adjacent to the joint is suspected. In certain locations, such as the phalanges, oblique views are necessary. If fracture is suspected despite negative radiographs, additional oblique views should be obtained. A fracture line is most visible when it is parallel to the x-ray beam and is invisible when it is exactly 90 degrees to the beam. To identify the extent of the fracture accurately, the entire bone should be visible on the image.

Each image is examined to ensure that proper technique has been used, and that no important area is omitted from the image. Overexposed images may fail to reveal an abnormality. Although some fine detail is lost on portable images, these are acceptable if the patient is unstable. Even with good technique, some fractures are not visible initially and do not appear until the margins of the fracture absorb. Absorption widens the radiolucent line, and a defect appears in 10 to 14 days. At that time, new bone produced beneath the periosteum at the margins of the fracture accentuates the fracture. Accordingly, if a fracture is suggested but is not visible at the initial visit, the injury should be treated as a fracture, reexamined clinically and radiographically in 10 to 14 days, and the patient should be informed of the rationale for this regimen.

Stress views of joints are occasionally used to evaluate the degree of ligamentous injury when other methods are not available.[1] The value of stress views is limited because pain may not allow sufficient stress to be applied, and there is a possibility of injuring an already traumatized structure further.

Comparison views with the contralateral bone may be useful in selected situations but should not routinely be obtained in pediatric examinations (see Chapter 175). It is reasonable to use comparison views in cases in which radiographs are inconclusive and when confusion arises specifically out of the need to distinguish between a possible fracture and normal developmental anatomy. Comparison views sometimes are helpful in adults when there is a question regarding the presence of accessory ossicles or nonfused bones (eg, bipartite patella), because these anomalies are usually bilateral. The bleeding that inevitably accompanies fractures may produce soft tissue swelling, which may impinge on or obliterate overlying muscle planes. Fat pads, such as in the elbow, may be displaced. Another useful sign is the fat-fluid level, which may accompany fractures extending into the knee joint. The fat-fluid level is visible, however, only if the cross-table technique is used.

The bones themselves should be examined systematically. Normal adult bones possess a smooth contour. A distinct angle is highly suggestive of a fracture. In an adult, a lucent line that interrupts the smooth contour and usually extends to the opposite side represents a typical fracture. Nutrient arteries may be confused with fractures but have different radiographic characteristics: they are fine, sharply marginated, and extend obliquely through the cortex and are less radiolucent than fractures. In addition, they do not extend to the opposite side of the bone. Pseudofractures can be created by soft tissue folds, bandages, or other overlying material or by a radiographic artifact called the Mach effect, which occurs at the margin of areas of differing density. If lucencies extend beyond the bones, the line is highly unlikely to represent a fracture.

Anomalous bones and calcified soft tissue likewise may be mistaken for fractures. Avulsions and small fracture fragments have an irregular surface that lacks well-corticated margins, and a defect in the adjacent bone is present, whereas anomalous ossification centers (accessory ossicles) and sesamoids are characterized by smooth cortical margins. Reference texts are useful in identifying and confirming these anomalies because they tend to occur in predictable locations. Compression fractures are represented by increased density rather than by a lucency. Finally, the most commonly missed fracture is the second fracture. One should be diligent in searching for additional fractures after discovering the first fracture on a study. In particular, certain paired fractures, such as the distal tibia and proximal fibula, should be sought out.

Special Imaging Techniques

Computed Tomography. Although conventional radiography remains the initial imaging study of choice for skeletal trauma, CT offers a more detailed and diagnostically sensitive evaluation of bones and joints. Two-dimensional multiplanar reconstruction in any chosen plane, and three-dimensional surface rendering techniques provide images with unprecedented quality, even in the presence of metallic implants or fixation devices.

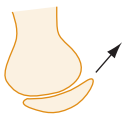
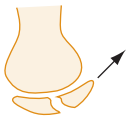
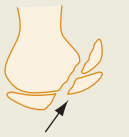
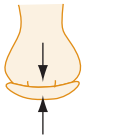
CT is used to confirm possible fractures or to define displacement, alignment, or fragmentation of fractures better. It is also useful in trauma to rule out a cervical spine fracture when plain films are equivocal and in noncompressive vertebral fractures to assess the number of fragments and their spatial relationship to the spinal canal. CT is used frequently to define the integrity of articular surfaces in the acetabulum, knee, wrist, or ankle and in Salter-Harris type IV fractures. In the multiple trauma patient requiring thoracic, abdominal, and pelvic CT imaging to rule out visceral injury, the soft tissue protocols may be adapted to acquire diagnostic bone images as well (Table 42.2). During imaging of the chest, abdomen, or pelvis, data sets are created from which the thoracolumbar spine and bony pelvis can be derived.[2]

Magnetic Resonance Imaging. MRI constitutes the most advanced noninvasive examination of orthopedic structures, delineating lesions of bone, cartilage, ligaments, and other structures, such as menisci, disks, and epiphyseal structures. MRI is expensive and time-consuming and should be reserved for cases in which the diagnosis is in doubt, and specific findings would alter the treatment urgently.

Ultrasound Imaging. Point of care ultrasound is an effective tool for the diagnosis of fractures when conventional radiography is unavailable. Through the use of point of care ultrasonography, fractures are visualized as an interruption of the linear bony cortex and may be clinically correlated during the physical examination of the affected area.[3] Ultrasound can be effective in the diagnosis of long bone fractures, orbital floor fractures, rib fractures, and occult fractures of the foot and ankle. Real-time ultrasound can be used during fracture reduction to confirm proper reduction and alignment of bony fragments.

TABLE 42.2

Salter-Harris Classification

TYPE	DESCRIPTION	DIAGRAM
I	Fracture extends through the epiphyseal plate, resulting in displacement of the epiphysis; this may appear merely as widening of the radiolucent area representing the growth plate.	
II	As above; in addition, a triangular segment of metaphysis is fractured.	
III	Fracture line runs from the joint surface through epiphyseal plate and epiphysis.	
IV	Fracture line occurs as in type III but also passes through adjacent metaphysis.	
V	This is a crush injury of the epiphysis; it may be difficult to determine by radiographic examination.	

Complications of Fractures

Infection (Osteomyelitis)

Any fracture communicating with the surface of the skin is termed an *open fracture.* Open fractures are treated as true, time-dependent orthopedic emergencies because of the risk of infection. The high morbidity associated with osteomyelitis dictates that therapy be initiated expeditiously, including parenteral administration of antibiotics as early as possible, emergent washout of debris, and coverage with a moist dressing.[4] The Gustilo-Anderson classification is used to describe the various types of open fractures (Box 42.2).

Currently, suggested therapy includes a first-generation cephalosporin, such as cefazolin, 1 to 2 g IV tid, for all open fractures, with the addition of an aminoglycoside, such as gentamicin, 1 to 1.7 mg/kg IV tid, for type II or III fractures. With farm injuries or other scenarios that predispose to the development of anaerobic infection, such as clostridial myonecrosis (gas gangrene), ampicillin or penicillin should be added to the antibiotic regimen. Early versus delayed débridement of open fractures and its subsequent effect on rates of infection has been a source of debate. Historic guidelines recommending débridement of open fracture wounds within 6 hours of injury were based on animal experiments conducted in the 1890s.[5] The timing of débridement—less than 6 hours versus more than 6 hours after injury—has not been proven to improve outcome, but general practice is to undertake débridement and irrigation of the wound within the first 24 hours of injury. Regardless, the goals of open fracture management should focus on early administration of antibiotics, tetanus prophylaxis, coverage of the wound, and splinting of the extremity.

BOX 42.2

Classification and Emergency Management of Open Fractures

GRADES

Grade I: Wound less than 1 cm long, punctured from below
Grade II: Laceration 5 cm long; no contamination or crush; no excessive soft tissue loss, flaps, or avulsion
Grade III: Large laceration, associated contamination or crush; frequently includes a segmental fracture
- IIIA: Involves extensive soft tissue stripping of bone
- IIIB: Periosteal stripping has occurred
- IIC: Major vascular injury present

MANAGEMENT

1. Control hemorrhage in field with sterile pressure dressing after carefully removing gross debris (eg, wood, clothing, leaves).
2. Splint without reduction, unless vascular compromise is present.
3. Irrigate with saline, cover with saline-soaked sponges after arrival in the emergency department.
4. Begin IV antibiotic prophylaxis, usually a first-generation cephalosporin for grade I, with the addition of an aminoglycoside for grades II and III.
5. Administration of tetanus prophylaxis, including tetanus immune globulin, for large crush wounds

Certain open fractures of the finger and toes present a notable exception to the previous recommendation. Such injuries, especially an open distal tuft fracture, are common when the phalanx of a finger or toe is subject to crush injury (eg, by a door) and there is a skin defect overlying a fractured bone. There is no evidence that antibiotic use reduces the infection rate for these fractures, which rarely, if ever, develop osteomyelitis. Vigorous irrigation and débridement are adequate primary treatment for open phalangeal fractures in fingers and toes with intact digital arteries and can be provided by the emergency clinician without consultation.

Hemorrhage

Because of the rich blood supply to the skeleton, fractures can result in large amounts of blood loss, shock, and death from exsanguination. In particular, certain pelvic fractures can cause great blood loss because adequate tamponade is not possible. In adults, blood loss can range from 100 mL from a forearm fracture to 3 L from a pelvic fracture (Table 42.3). Such hemorrhage can be controlled in part by early stabilization of the injured area through splinting, a binder, or skeletal traction.

Vascular Injuries

Vascular injuries characteristically are associated with certain fractures and may be limb-threatening. Fractures and dislocations (at the femorotibial articulation) of the knee result from tremendous force, which often injures the popliteal artery. Fracture of the femoral neck requires emergent reduction and fixation to protect the blood supply to the femoral head.[5] In the extremities, assessment of vascular injuries may be difficult. The initial survey should note the presence or absence of pulses and state of capillary filling. If an end artery is completely disrupted, the tissue distal to the injury may exhibit the classic five Ps: pain, pallor, pulselessness, paresthesias, and paralysis. Incomplete and subclinical injuries occasionally occur that initially may be asymptomatic and undetectable. Likewise, in an unconscious, multiply injured patient, major vascular injuries may not be obvious. The mechanism of injury and anatomy dictate the need to assess the possibility of an injured vessel. If pulses cannot be palpated, a Doppler stethoscope should be used to listen for blood flow. Even palpable pulses may be misleading because pulses may be normal in 10% to 20% of patients with significant arterial injuries. When pulses are present but the mechanism of injury suggests the possibility of vascular injury, additional diagnostic studies or surgical exploration may be necessary.[6] If a limb is clearly not perfused, operative vascular exploration and repair should take place promptly. Late complications of undiagnosed vascular injuries include thrombosis, arteriovenous fistulae, aneurysm, false aneurysm, and tissue ischemia with limb dysfunction. Delay of vascular injury repair is a risk factor for consequent amputation. The evaluation of peripheral vascular injuries is discussed in Chapter 41.

TABLE 42.3

Blood Loss Associated with Fracture in Adults

FRACTURE SITE	AMOUNT OF BLOOD LOSS (mL)
Radius and ulna	150–250
Humerus	250
Tibia and fibula	500
Femur	1000
Pelvis	1500–3000

Nerve Injuries

Nerves can be injured by blunt or penetrating trauma:

- Neurapraxia is the contusion or traction injury of an otherwise intact nerve, with disruption of the ability to transmit impulses. Paralysis, if present, is transient, and sensory loss is slight. Normal function usually returns to a neurapraxic nerve in weeks to months.
- In axonotmesis, crush or traction result in more severe injury to axons within an intact epineurium. Because the Schwann tubes remain in continuity, spontaneous healing is possible but slow.
- Neurotmesis is the severing of a nerve, usually requiring surgical repair.

Age, site, injured nerve, and delay between injury and repair have all been shown to influence prognosis after microsurgical repair. Because of proximity, specific nerve injuries characteristically accompany certain fractures (Table 42.4). For example, in the upper extremity, a distal radius fracture caused by a high-energy insult can be associated with acute dysfunction of the median nerve. Deteriorating neurologic function may necessitate temporary or definitive stabilization of a fracture.

When the nerve is completely severed, all functions are absent, including the following: superficial sensation to touch, pain, and temperature; deep sensation to muscle and joint movements, position, deep pressure, and vibration; motor supply and deep tendon reflexes (to distally innervated muscle groups); and response to electrical stimulation. For less severe injuries, any subjective change in sensation should be noted. Light touch is a good screening test. Two-point discrimination is a more sensitive examination and should be used routinely in evaluating digital nerves. The discrimination on the injured digit is then compared with the uninjured ones. A normal two-point discrimination value at the fingertip of an adult is 4 mm, or discrimination may be compared to a noninjured digit. Evaluation of the innervation of the hand is discussed in Chapter 43.

Compartment Syndrome

Compartment syndrome is a serious, acute, emergency complication that should be considered whenever significant pain and paresthesias occur in an extremity after a fracture within an enclosed osseofascial space (Table 42.5). The immediate threat is to the viability of nerve and muscle tissue within the involved compartment, but infection, gangrene, myoglobinuria, and renal failure also may ensue if the diagnosis is not made in timely fashion. Compartment syndrome is usually associated with a

TABLE 42.4

Nerve Injuries Accompanying Orthopedic Injuries

ORTHOPEDIC INJURY	NERVE AFFECTED
Distal radius	Median nerve
Elbow injury	Median or ulnar nerve
Shoulder dislocation	Axillary nerve
Sacral fracture	Cauda equina nerve
Acetabulum fracture	Sciatic nerve
Hip dislocation	Femoral nerve
Femoral shaft fracture	Peroneal nerve
Knee dislocation	Tibial or peroneal nerve
Lateral tibial plateau fracture	Peroneal nerve

TABLE 42.5

Life-Threatening or Limb-Threatening Emergencies

CONDITION	POSSIBLE ADVERSE OUTCOME
Open fracture	Osteomyelitis
Fracture or dislocation with major vascular disruption (especially popliteal)	Amputation
Major pelvic fracture	Exsanguination
Hip dislocation	Avascular necrosis of femoral head
Compartment syndrome	Ischemic contracture; myoglobinuria, renal failure

closed long bone fracture of the tibia, but it also is well described in the thigh, forearm, arm, hand, and foot.[7] In addition, compartment syndrome can occur with soft tissue trauma alone and even with open fractures. It also has been described in a host of unusual situations, including prolonged procedures in the lithotomy position, the tuck position (knees tucked to the chest for lumbar surgery), coma, spontaneous hemorrhage, extravasation of IV injections, and application of excessive traction in treatment of a fracture.

Pathophysiology. Increased pressure in a closed nonexpandable compartment essentially represents a mismatch between the volume of that space and its contents. As such, it may arise from one of three circumstances: (1) increased compartment contents; (2) decreased compartment volume; or (3) external pressure (Box 42.3). As tissue pressure increases, so does venous pressure, resulting in compromise of the local circulation and tissue hypoxia; this is believed to occur at pressures that are above normal diastolic pressure but below systemic arterial pressure because of a reduced arteriovenous gradient at the tissue level. The body responds by releasing histamine in an attempt to dilate capillaries and increase blood flow to the affected area. Histamine also increases capillary membrane permeability, resulting in a leak of proteins and fluid into the surrounding tissue and further increasing compartment pressure.

As tissue pressure continues to increase, venous blood flow is impaired as capillary perfusion pressure is exceeded. Finally, arterial capillary blood flow falls to a point at which the basic metabolic needs are no longer met, leading to ischemic necrosis of muscles and nerves within the compartment. An important concept in the management of compartment syndrome is that because local venous pressure cannot be significantly below local tissue pressure, and because elevation of a dependent limb decreases local arterial pressure by 0.8 mm Hg for each 1 cm of limb elevation, elevation of a limb with resultant reduction in the local arteriovenous gradient may be counterproductive and may exacerbate compartment syndrome. Vascular spasm seems to play an insignificant or minimal role in the development of compartment syndrome, as evidenced angiographically, where spasm has never been shown, and clinically, where it has been observed that distal pulses usually are maintained until late in the course.

Normal compartment pressure is 0 mm Hg. Microcirculation generally is impaired when tissue pressures reach 30 mm Hg or more; however, some patients can tolerate much higher compartment pressures without the development of compartment syndrome. Controversy exists over attempts to define compartment syndromes on the basis of specific tissue pressure. The tolerance to tissue ischemia varies among individuals because of shock, compensatory hypertension, altered tone in resistance vessels, preexisting vascular disease, and other unknown factors. Inadequate perfusion and relative ischemia begin when tissue pressure within a closed compartment increases to within 20 mm Hg of a patient's diastolic pressure or, more accurately, within 30 mm Hg of the mean arterial pressure. When tissue pressure equals or exceeds the patient's diastolic blood pressure, tissue perfusion effectively ceases. The development of muscle ischemia depends not only on the magnitude but also on the duration of elevated pressure. Intracompartmental pressures do not measure muscle

BOX 42.3

Causes of Compartment Syndrome

INCREASED COMPARTMENT CONTENT

Bleeding
- Major vascular injury
- Coagulation disorder
- Anticoagulant therapy

Increased capillary filtration
- Reperfusion after ischemia
  - Arterial bypass grafting
  - Embolectomy
  - Ergotamine ingestion
  - Cardiac catheterization
  - Lying on limb
- Trauma
  - Fracture
  - Convulsion
- Intensive use of muscle
  - Exercise
  - Seizures
  - Eclampsia
  - Tetany
- Burns
  - Thermal
  - Electrical
- Intraarterial drug injection
- Orthopedic surgery
  - Tibial osteotomy
  - Hauser's procedure
  - Reduction and internal fixation of fractures
- Snakebite

Increased capillary pressure
- Intensive use of muscles
- Venous obstruction
  - Phlegmasia cerulea dolens (ie, acute inflammation and edema of the legs)
  - Ill-fitting leg brace
  - Venous ligation
- Diminished serum osmolarity (ie, nephrotic syndrome)

DECREASED COMPARTMENT VOLUME

Closure of fascial defects
Excessive traction on fractured limbs

MISCELLANEOUS

Infiltrated infusion
Pressure transfusion
Leaky dialysis cannula
Muscle hypertrophy
Popliteal cyst

EXTERNAL PRESSURE

Tight casts, dressings, or air splints
Lying on limb

From Matsen FA III: Compartmental syndromes. New York, Grune & Stratton, 1980.

and nerve ischemia but rather suggest the existence of the proper setting for compartment syndrome.

Anatomic Considerations and Risk Factors. Compartment syndrome theoretically can develop in any location where neuromuscular tissue is contained in a limiting envelope. The condition has been reported in the leg, thigh, buttock, arm, forearm, and hand (Box 42.4). By virtue of its location and higher likelihood of sustaining high-energy trauma, the leg, particularly the anterior compartment, is most commonly involved. Higher rates of compartment syndrome are seen with open fractures than with closed fractures, despite the fascial rents that accompany open fractures. The higher energy of injury observed with open fractures, with resultant tissue trauma, swelling, and bleeding, may account for this observation.

Most patients with compartment syndrome have an associated long bone fracture, and fractures of the tibial shaft are particularly likely to cause increased compartment pressure. Up to one-third of patients, however, have only soft tissue injury without fracture. Compartment syndrome is more likely when there is a bleeding disorder or the patient is taking anticoagulants. Traffic accidents and sports activities are the most common mechanisms of injury.

Clinical Presentation. Compartment syndrome is a clinical diagnosis. In a conscious and fully oriented patient, pain that is disproportionate to the injury or physical findings is a hallmark finding in compartment syndrome. Pain often is characterized as deep, burning, and unrelenting and is difficult to localize. The need for increasing amounts of analgesics should not lead the emergency clinician automatically to the conclusion that the patient is drug-seeking; rather, it should serve as a prompt to the possibility that a compartment syndrome is developing or is present.

Pain on passive stretching of the muscle groups in the suggestive compartment is an important finding. In addition, active flexion of involved muscles may produce pain. Other reliable suggestive signs and symptoms are hypoesthesias and paresthesias in the distribution of nerves crossing the compartment or tenderness, tenseness, or sensation of tightness of the compartment.

Skin color, temperature, capillary refill, and distal pulses all are unreliable monitors for compartment syndrome because the pressure necessary to produce compartment syndrome is well below arterial pressure. Pallor and loss of pulses are late and ominous signs. Diminished pulses should suggest concomitant pathologic conditions responsible for reduced arterial flow. Although it is still frequently taught that the five Ps—pain, pallor, pulselessness, paresthesias, and paralysis—are signs and symptoms of compartment syndrome, this is generally not true. Rather, they are the signs of acute disruption of arterial flow. Subjective complaints are an important indicator of compartment syndrome. Patients who are not fully alert or cooperative are assessed with particular care.

Diagnostic Tests. Clinical examination remains the diagnostic cornerstone of acute compartment syndrome, which can then be confirmed by the measurement of compartment pressure. Compartment pressures can be measured with a commercially available monitor (Fig. 42.7). The two most common methods of determining compartment pressures are the slit catheter techniques and side port needle. The Stryker Intra-Compartmental Pressure Monitor (Stryker, Kalamazoo, MI) system is a hand-held digital device that is easy to use with minimal training. Care should be taken to zero the monitor in on the plane in which it will be inserted to account for the effects of gravity. It is also paramount that the appropriate compartment be measured. Pressures of less than 30 mm Hg generally do not produce compartment syndrome. When intracompartmental pressures exceed 30 mm Hg, or when the difference between diastolic blood pressure and compartment pressure (perfusion pressure, also known as the ΔP) is less than 30 mm Hg, fasciotomy may be indicated. Serial or continuous pressure measurements should be performed in cases that are not clear-cut. A rising or sustained elevated compartment pressure is superior to a single measurement as an indicator of acute compartment syndrome or the need for fasciotomy. A compartment pressure greater than 30 mm Hg and perfusion

BOX 42.4

Reported Anatomic Locations of Compartment Syndromes

LOWER EXTREMITY

Leg
Anterior compartment
Lateral compartment
Deep posterior compartment
Superficial posterior compartment

Thigh
Quadriceps compartment

Buttock
Gluteal compartment

UPPER EXTREMITY

Hand
Interosseous compartment

Forearm
Dorsal compartment
Volar compartment

Arm
Deltoid compartment
Biceps compartment

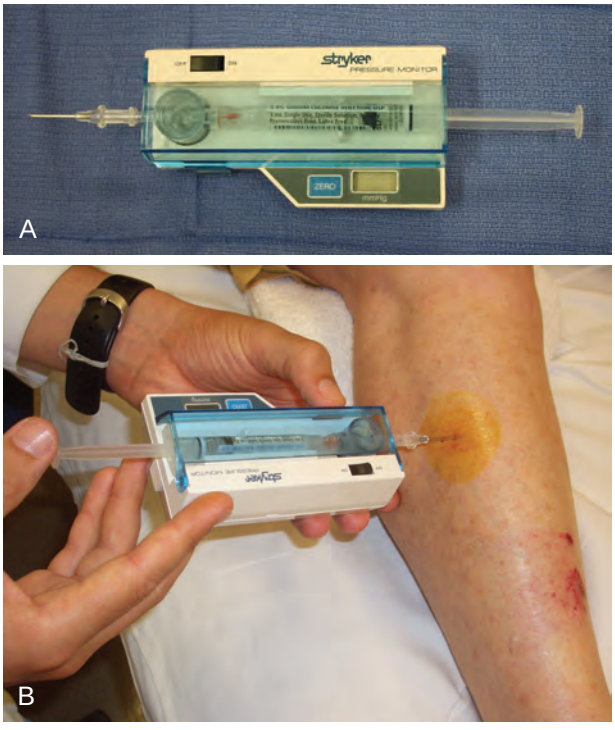


Fig. 42.7. A, Hand-held device for measuring compartment pressure. **B,** Device is inserted perpendicular to skin.

pressure less than 30 mm Hg have relatively poor specificity for compartment syndrome, and orthopedic consultation should be sought to help guide management.[8]

Doppler ultrasound is not useful in evaluating these patients because excellent arterial blood flow may be documented, even in the presence of a significant compartment syndrome. Newer devices based on near-infrared spectroscopy (NIRS) measurement of tissue oxygenation have proven effective experimentally in detecting compartment syndrome but will require validation in the clinical setting before widespread application.

Treatment, Complications, and Disposition. Complete fasciotomy is the only treatment that can reliably normalize elevated compartment pressure. Preparation for surgery is done as quickly as possible. Delaying fasciotomy for more than 12 hours often results in irreversible myonecrosis and nerve damage. While the patient is awaiting definitive treatment, the affected part should not be elevated above the level of the heart because this maneuver does not improve venous outflow and reduces arterial inflow. Slight dependency has been suggested to maximize the pressure head in the extremity.

Because tissue compartments are more pliable soon after injury, the rate of extremity swelling is greater in the immediate postinjury period and tends to peak at 36 to 48 hours after injury. Although compartment syndrome usually appears within 36 hours of injury, cases have been reported more than 2 weeks following injury.[9] Extremity swelling decreases over a similar duration. Rhabdomyolysis, hyperkalemia, and myoglobinuria may occur and should be managed aggressively to avoid renal failure. Lactic acid also is released from necrotic muscle tissue. Other complications include infection and tissue loss.

Delayed treatment results in loss of nerve and muscle function and eventual contracture formation. The magnitude of these disasters may be illustrated by the fact that in 2004, the average indemnity award in cases of missed compartment syndrome was nearly $426,000. Awards were proportional to the delay beyond 8 hours in performing fasciotomy and the number of the five Ps indicating ischemia that were present during the initial missed diagnosis. Thus, when the diagnosis of compartment syndrome is confirmed, fasciotomy should be done without delay.

Avascular Necrosis

Because of their blood supply, certain bones may undergo avascular necrosis after fracture, especially if fractures are comminuted and go untreated for any length of time. The femoral head, talus, scaphoid, lunate, and capitate are particularly prone to this complication. These injuries are described in subsequent chapters.

Fat Embolism Syndrome

Fat embolism refers to the presence of fat globules in the lung parenchyma and peripheral circulation after a long bone fracture or major trauma. The phenomenon of fat embolization is probably common as a subclinical event after long bone fracture. Intravascular fat droplets appear in nearly one of five patients admitted with major trauma, although not all patients are symptomatic or require treatment.

Fat embolism syndrome is a serious manifestation of fat embolism, occurring most commonly after long bone fractures (usually tibia and femur) in young adults and after hip fractures in older patients. Symptoms usually appear 1 to 2 days after an acute injury or after intramedullary nailing. Respiratory distress and hypoxemia are the earliest, most common manifestations. Acute respiratory distress syndrome (ARDS) may occur and is the usual cause of death. Neurologic involvement, presenting as restlessness, confusion, and/or deteriorating mental status, also is an early sign, as are thrombocytopenia and a petechial rash.[10] Fever, tachycardia, jaundice, retinal changes, and renal involvement may occur. Fat is seen in the urine in 50% of patients within 3 days of injury. The incidence of full-blown fat embolism syndrome varies from 0.5% to 2% in patients with isolated long bone fractures to 5% to 10% in patients with multiple fractures. Management of fat embolism syndrome is primarily supportive, usually in an intensive care unit. The mortality rate is 20%, but most patients recover without severe sequelae. No specific therapy has shown benefit.

Fracture Blisters

Fracture blisters are tense blisters or bullae that accompany high-energy injuries, with significant soft tissue swelling. They can occur anywhere but are most common in areas with thin soft tissue envelopes. The ankle, elbow, foot, and knee (in that order) are the most common sites; all these contain fewer hair follicles and sweat glands to anchor together the epidermal-dermal junction than other limb locations. Fracture blisters are believed, in many cases, to occur in the setting of increased underlying tissue pressure and may be a harbinger of compartment syndrome.

Early reduction and splinting with expedited surgical intervention reduces the incidence of fracture blister formation. In addition, the presence of a fracture blister requires an alteration of the surgical approach or delay in surgery. Most experts discourage incisions through a fracture blister because such incisions seem to increase infection and skin breakdown. Measures to perform early surgery after high-energy injuries and minimize increases in tissue pressures might reduce the incidence of this complication. Intact blisters should be covered with povidone-iodine solution and a sterile dressing. Unroofing the blister and applying coverage with silver sulfadiazine paste has been reported to decrease the incidence of complications.

Complications of Immobilization

Fractures frequently result in long periods of immobilization. Immobility may lead to multiple medical problems, especially in older patients, including pneumonia, deep venous thrombophlebitis, pulmonary embolism, urinary tract infection, wound infection, decubitus ulcers, muscle atrophy, stress ulcers, gastrointestinal hemorrhage, and psychiatric disorders (Box 42.5). Early ambulation is a major goal of optimal orthopedic care.

Damage Control Orthopedic Surgery

Over the past few decades, the management of the multiply injured trauma patient has changed considerably. Historically, patients with multiple injuries were treated nonoperatively because it was believed they were too ill to tolerate surgery. In the 1970s, literature began to appear suggesting adverse outcomes as a result of prolonged recumbency. In addition, operative fracture fixation techniques were evolving, and this led to the advent of early fracture stabilization and the notion of early total care of the polytrauma patient. During the 1990s, the concept of damage control surgery came to the forefront of trauma surgical care. The successful use of an abbreviated operation in patients with penetrating abdominal trauma to avoid the lethal triad of hypothermia, acidosis, and coagulopathy was reported in 1993, and the term *damage control* was coined. Similar principles were found to be applicable to the management of pelvic and long bone fractures in the polytrauma patient.

With this change in approach, early total care with immediate definitive fixation of all major fractures gradually shifted to early temporary fracture stabilization, resuscitation of the patient to a stable physiologic state, and then definitive fixation at a later time once the patient's physiology had been stabilized. Temporary

BOX 42.5

Complications of Fractures and Immobility

FRACTURES
Hemorrhage
Vascular injuries
Nerve injuries
Compartment syndrome
Volkmann's ischemic contracture
Avascular necrosis
Reflex dystrophy
Fat embolism syndrome

IMMOBILITY
Pneumonia
Deep venous thrombosis
Pulmonary embolism
Urinary tract infection
Wound infection
Decubitus ulcers
Muscle atrophy
Stress ulcers

fracture stabilization is usually accomplished by the application of external fixation devices to aid in hemorrhage control and tissue oxygenation, but the timing and optimal type of fracture surgery in the multiply injured trauma patient are still subjects of research.

SUBLUXATION AND DISLOCATIONS

Nomenclature

Abnormal forces applied to joints may result in the loss of continuity between two articulating surfaces. Partial loss of continuity is termed *subluxation,* and complete loss is termed *dislocation*. In general, dislocations are named for the major joint involved, as in a dislocated shoulder or hip. In three-bone joints, the injury is named for the joint involved if the disturbance involves the two major bones or, if the lesser bone is involved, the disturbance is named for that bone. Separation of the femur from the tibia is termed *dislocation of the knee,* whereas displacement of the patella from its normal articulation is termed *dislocation of the patella* (Fig. 42.8). At the elbow, separation of the olecranon from the humerus is termed a *dislocation of the elbow,* whereas separation of the radius from the humerus is termed *radial head dislocation.*

Dislocations and subluxations should be described according to the direction of the distal segment relative to the proximal segment or of the displaced bone relative to the normal structures. The injury shown in Fig. 42.9 is termed *dorsal dislocation of the interphalangeal joint of the thumb.* Disruption of articulation also may occur in combination with a fracture. The term *fracture-dislocation* is used to describe this combination. If the overlying skin is broken in any way, dislocations, subluxations, or fracture-dislocations are described as open and constitute the same emergency as an open fracture alone.

Assessment

In most cases of dislocation, severe to excruciating pain is present because the highly innervated joint capsule is stretched or torn. Movement of the joint exacerbates the pain. This useful sign is lost in an obtunded, intoxicated, or unconscious patient and may result in a missed diagnosis if a careful survey is not performed.

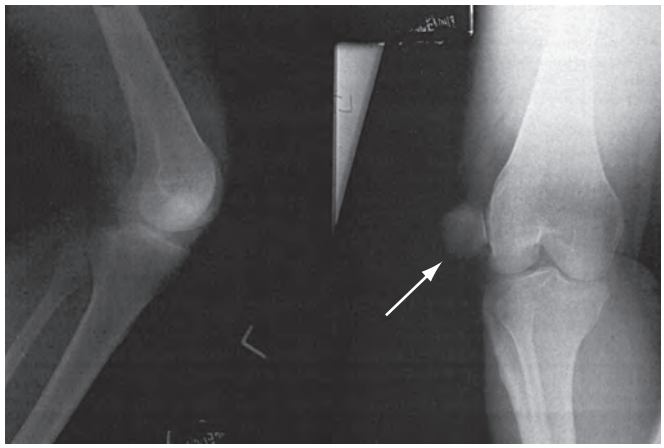


Fig. 42.8. Dislocation of the patella.

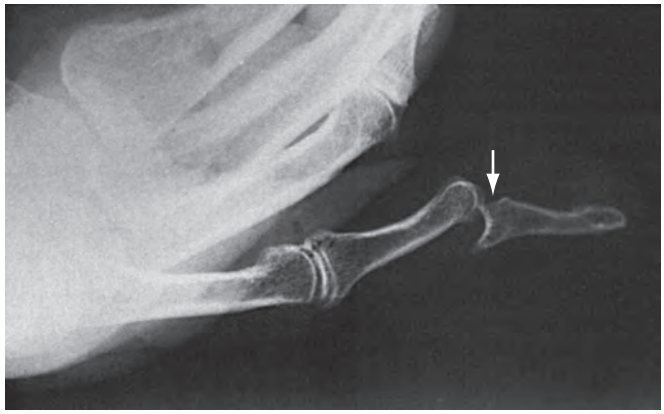


Fig. 42.9. Dorsal dislocation of the distal phalanx of the thumb (*arrow*).

Some dislocations, such as anterior shoulder dislocation, cause an obvious deformity, whereas others, such as posterior shoulder dislocation, may be subtle. Swelling of soft tissues also may obscure the diagnosis, such as in the tarsal-metatarsal region. Gentle passive testing of range of motion should be performed but never forced. Assessment for neurovascular function is similar to that for fracture. Certain dislocations (eg, knee) are so commonly associated with vascular injuries that a careful assessment of blood flow is important in evaluating these injuries.

Plain radiographic studies detect most dislocations, provided that the correct views are ordered. Radiographs should be performed before and after attempts at reduction of first-time or complicated dislocations unless there is neurovascular compromise. This confirms the diagnosis and ensures that associated fractures are documented before treatment is undertaken.

Treatment

Methods of relocating specific joints are reviewed in subsequent chapters, but a few basic principles apply. In general, a joint should be relocated as soon as possible. Over time, swelling and muscle spasm make reduction more difficult. Also, pain is not adequately relieved until the dislocation is reduced. In the hip, early reduction is mandatory to restore vascular supply and avert the complication of avascular necrosis. The general principle of reducing a dislocation is to stabilize the proximal bone and re-create and reverse the mechanism of injury, pulling the proximal end of the dislocated bone out and away from whatever is trapping it in its final resting place. This technique helps prevent interposition of soft tissues in the joint that can preclude reduction. As this maneuver is accomplished, the disarticulated surface is

manipulated back or may snap back spontaneously toward its normal anatomic position. Large joint relocation may require procedural sedation with parenteral analgesia. An emergency clinician–performed, ultrasound-guided regional nerve block can facilitate large joint relocations and is less resource-intensive than procedural sedation. Smaller joints may require local anesthesia or, on occasion, no anesthesia. Some joints cannot be reduced in the ED because the opposing muscles are contracting too forcefully, and general anesthesia is necessary to overcome these forces, or mechanical obstruction by a bony fragment or torn piece of cartilage, tendon, joint capsule, or skin requires surgical removal for reduction to occur.

SOFT TISSUE INJURIES

Sprains

Nomenclature

Ligamentous injuries resulting from an abnormal motion of a joint are termed *sprains.* A sprain is injury to the fibers of a supporting ligament of a joint. Sprains may be graded according to the severity of pathologic findings; clinically, however, the grades are often indistinct.

- First-degree sprains are characterized by minor tearing of ligamentous fibers, with resultant mild hemorrhage and swelling. Minimal point tenderness can be elicited. Stressing the ligament produces some pain, but there is no opening or abnormal joint motion.
- A second-degree sprain is a partial tear of a ligament, meaning that more fibers are torn than in the first-degree injury. Clinical findings include moderate hemorrhage and swelling, tenderness, painful motion, abnormal motion, and loss of function. There may be a tendency toward persistent instability and recurrence, and prevention of these complications is a major goal of treatment.
- A third-degree sprain describes the complete tearing of a ligament. Signs include a further exaggeration of the signs mentioned for second-degree sprain. In addition, stressing the joint, when possible and not limited by pain, reveals grossly abnormal joint motion, provided that this is not limited by pain or swelling.

Intraarticular analgesia and the evacuation of a hemarthrosis may be used to allow a more complete diagnosis of these injuries. Chronic joint instability may result if severe ligamentous injuries do not heal properly.

Assessment

The clinical presentation of a sprain of the extremity may be indistinguishable from that of a fracture. The injury frequently occurs during vigorous athletic activity, when forces applied in opposite directions result in a joint being stressed in an abnormal or exaggerated direction. The patient may complain of hearing a "snap" or a "pop" at the moment of injury and conclude that a fracture is present. Other patients report "seeing stars" or "almost passing out" at the moment the injury occurred and may still be in extreme pain, appearing pale and diaphoretic if seen shortly after the injury. Analgesia should be provided to these patients. Evaluation should include a careful history of the exact sequence of events at the time of injury and ascertaining the position of the extremity and the forces applied to it at that moment. A history of any sounds that accompanied the injury should be elicited. Examination of the joint should include stressing it to show abnormal motion. If radiographs are planned to rule out a fracture anyway, or if exquisite pain is produced by mild attempts to apply stress, it is probably better to delay stressing until films have verified the absence of a significant fracture. Plain radiography is indicated in some, but not all, cases to rule out a fracture.

Avulsion fractures may occur concomitantly with sprains. In children, epiphyseal fractures occur more commonly than ligamentous disruption because of the relative ligamentous strength compared with the ease of disrupting the epiphyses. Arthroscopy or MRI is indicated in the follow-up evaluation of some of these injuries (eg, for suspected cruciate ligament tears) when significant pain or disability is present.[11]

Treatment and Disposition

Specific management of sprains varies depending on the location and severity of the injury. In general, initial measures should include the traditional recommendations of ice, elevation, and analgesia. Nonsteroidal antiinflammatory drugs (NSAIDs) are effective analgesics in many patients. Several studies have found a more rapid decrease in swelling, increased exercise endurance, and earlier return to work with use of NSAIDs.[12]

Immobilization through the use of one of the following methods provides protection and comfort in the initial management of most injuries. Because the severity of injury is sometimes difficult to establish at the first visit, it is reasonable to immobilize the affected joint for the first 48 to 72 hours, after which the extent of injury can be better determined. At that time, early mobilization is often desirable, particularly in lateral ankle injuries, because this leads to earlier return to work and athletic activities and better preservation of proprioceptive neuromuscular function. Use of an inflatable air cast, alone or in conjunction with an elastic ankle wrap, has been shown to be effective in decreasing the symptomatic period. For lower extremity injuries, protected weightbearing with crutches provides patients with comfort and avoids motion of the impaired part. In older patients, safe ambulation sometimes cannot be accomplished, and a short hospitalization or respite in an acute rehabilitation or skilled nursing facility may be necessary.

For complete or nearly complete ligamentous disruption, urgent orthopedic consultation is mandatory. Less severe injuries can be followed up 3 to 7 days postinjury, when acute swelling has subsided. Physical therapy and rehabilitative exercises sometimes are begun at these visits and and can be continued for several weeks. Because ligaments are relatively avascular, healing is slow, and patients with significant sprains should be informed of this. Sprains should be diagnosed as precisely as possible and should not be trivialized. Too often after radiographs have ruled out fracture of an affected extremity, the term *sprain* is applied indiscriminately or the patient is told that the injury is only a sprain, a misleading expression that should be avoided. Aside from creating false expectations regarding recovery, mislabeling of injuries not clearly visible on ED images may lead to missed occult fractures in adults or epiphyseal injuries in children.

Strains

Nomenclature

A strain is an injury to a musculotendinous unit resulting from violent contraction or excessive forcible stretch. The term *pulled muscle* sometimes is used interchangeably with muscle strain. These injuries are graded in a manner similar to sprains.

- A first-degree (mild) strain is a minor tearing of the musculotendinous unit, characterized by minor swelling, local tenderness, and minimal restriction of movement.
- Findings increase along a continuum such that in a second-degree (moderate) strain, more fibers are torn, but without complete disruption; swelling, ecchymosis, and loss of strength are more marked.

- In a third-degree (severe) strain, the muscle or tendon is completely disrupted, with resultant separation of muscle from muscle, muscle from tendon, or tendon from bone.

An accompanying avulsion fracture may be present on radiographs in second- or third-degree injuries.

Assessment

Signs and symptoms include pain, ecchymosis, swelling, and loss of function. A force applied to the muscle, passive stress or active contraction, produces sharp pain at the site of injury, even as the injured muscle may be relatively comfortable at rest. A palpable defect sometimes is present at the site of a complete rupture, which usually involves the region of the muscle-tendon junction, or a bunching up of the muscle may be appreciated. Ultrasound had increasingly been used to diagnose an assortment of soft tissue injuries, including rotator cuff tears, tendon ruptures, and muscle tears. Among nonathletes, strains commonly are seen in patients who have overstressed a muscle group or tried to generate excessive force in an unconditioned muscle. Examples are the weekend gardener or mover who experiences lower back strain on Monday morning, the aerobics student who strains the rectus muscles, and the weightlifter with chest wall pain resulting from pectoralis major strain. These are usually first-degree injuries, and the onset is slow. Rapid acceleration (eg, in a tennis player) may result in a third-degree gastrocnemius or plantaris tear, whereas pushing off to jump is a common cause of rupture of the Achilles tendon in a basketball player. A sudden violent attempt at lifting by an older individual can result in a complete biceps brachii disruption. Sudden generation of forces, of which the thighs are capable, results in second-degree strain of the hamstrings, quadriceps, or thigh abductor muscles.

In athletes, generation of tremendous contraction forces coupled with excessive forcible stretching (while the body may be accelerating or planting) results in severe strains. Involvement of almost any muscle group is possible, and the onset of such injuries is usually acute. Immediate removal from activity, application of ice, and rest of the affected limb for 48 to 72 hours are usually advised for prevention of further injury. After a brief rest period, however, early mobilization and rehabilitation should be encouraged.

Treatment and Disposition

Treatment depends on the degree of disruption, location, and functional loss. Most first-degree injuries respond to rest, application of ice and, for some patients, analgesics in a few days. NSAIDs commonly are recommended and prescribed, although their efficacy for other than analgesic purposes is unproven.[12] Second-degree strains are treated similarly, with protection against aggravating activity required for longer periods. Third-degree strains receive similar initial treatment in the ED plus early orthopedic consultation. Some of these injuries are amenable to surgical repair, whereas others may be treated with immobilization. The muscle affected and the age, occupation, and activity level of the patient all are factors in deciding whether surgical intervention is appropriate. Early mobilization is an important tenet in the treatment of muscle strains; its timing may be based on the ability to stretch the injured muscle as much as the uninjured contralateral muscle and the use of the injured muscle without pain during basic movements.

Tendinitis and Tendinosis

Tendinitis is classically described as an inflammatory condition characterized by pain at tendinous insertions into bone, occurring in the setting of overuse. It is now believed that the pathophysiology of this condition is more complex than mere overuse, with the roles of load and use affecting the cell-matrix interaction. Contributing factors are those associated with aging, decreased blood supply and decreased tensile strength, muscle weakness and imbalance, insufficient flexibility as well as male gender, obesity (in weight-bearing joints), smoking, malalignments, training errors, and improper equipment. In addition, certain systemic diseases, including diabetes mellitus, chronic renal failure, rheumatoid arthritis, and systemic lupus erythematosus, steroid use, and occasionally fluoroquinolone use are associated with the development of tendinopathy.

The histopathology of tendinitis is characterized by the following: degeneration and disorganization of collagen fibers; infiltration by macrophages, plasma cells, and lymphocytes rather than leukocytes; and increased vascularity. Inflammatory changes are not a principal finding in tendinitis. This evolving understanding of tendinitis should, in the future, allow for more logical treatment of these injuries aimed at the underlying pathophysiology. It also has led some authors to propose that chronic painful conditions of the tendon should be referred to as tendinosis rather than tendinitis or by other terms previously used to describe this condition, including *tendonitis, degenerative changes, chronic tendinopathy,* and *partial rupture*. In this chapter, the terms *tendinitis* and *tendinosis* are used interchangeably.

Common sites for tendinitis are the rotator cuff of the shoulder, Achilles tendon, radial aspect of the wrist (de Quervain's tenosynovitis), and insertion of the hand extensors on the lateral humeral epicondyle (tennis elbow). Also commonly involved in athletes are the patellar tendon, particularly for those engaged in jumping sports, biceps femoris, semitendinosus, and semimembranosus (hamstring syndrome), posterior tibial tendon (shin splint syndrome), iliotibial band, and common wrist flexors (medial epicondylitis; involvement is seen in little league pitchers and golfers). In some locations, most commonly the shoulder, calcium deposition occurs along the course of the tendon, resulting in a painful condition termed *calcific tendinitis.* This condition also may occur in the wrist, hand, neck, hip, knee, ankle, or foot.

Physical examination reveals pain with motion and limitation of function and may include point tenderness and palpable crepitus over the involved tendon with motion. In general, a clinical test can be performed by forcible flexion of the involved muscle while keeping the point of insertion fixed or by operating the involved muscle against resistance. Either test should intensify the discomfort. Radiographs are usually negative. A small fleck of bone may suggest an avulsion, or the surface of the bone at the attachment may be roughened, indicating periostitis. Calcium deposits along the course of the tendon due to calcific tendonitis should not be confused with an avulsion fracture. Ultrasound is sometimes useful in confirming the diagnosis of tendinitis. Although a normal tendon is characterized by a relatively homogeneous pattern, tendinitis is characterized by one or more of the following features: loss of the fibrillar echotexture, focal tendon thickening, diffuse thickening, focal hypoechoic area, irregular or ill-defined borders, or microruptures.

There is little evidence to support any specific treatment for tendinosis. The classic approach consists of rest, ice, and NSAIDs initially, followed by rehabilitation, training, and control of force loads to prevent recurrences. Although NSAIDs may be useful for a brief period as an analgesic, no evidence exists that they significantly alter the pathophysiology of this condition, and no rationale exists for ordering them in antiinflammatory doses or for patients at any significant risk for complications from this class of drugs.[13] Peritendinous local infiltration of anesthetics and corticosteroids may be useful but should not be repeated frequently because it may cause susceptibility to tendon rupture. Injection therapy is especially useful in calcific tendinitis around the shoulder. Injection of steroids directly into the Achilles tendon should be avoided

because of reports of partial or complete rupture after even a single injection. Some cases of calcific tendinitis that do not respond to conservative therapy may require arthroscopic or open surgery.

Bursitis

Bursitis is a painful inflammation of the bursa that may be traumatic, infectious, or related to systemic illness. Commonly involved sites include the olecranon, greater trochanter of the femur, and prepatellar and anserine bursae around the knee. Physical findings are tenderness and swelling over the involved bursa. When accompanied by warmth and overlying erythema, an infection may be present. If infection is suggested, aspiration of the bursal fluid and Gram staining and culture are recommended. Otherwise, treatment may be conservative and is similar to treatment for tendinitis, with ice, NSAIDs, or steroid injections. Most patients can be treated as outpatients.

TREATMENT MODALITIES

Splinting and Bandaging

Suggested or confirmed fractures or dislocations should be splinted to avoid damage to muscles, nerves, vessels, and skin. Splinting also may restore blood flow to ischemic tissue by removing pressure caused by a bone fragment resting against a blood vessel. In addition, splinting may relieve the pain associated with movement of fracture fragments.

Field Care

Splinting should begin in the field because it reduces the risk of further neurovascular compromise, prevents a closed injury from potentially being converted to an open one during transport, reduces the patient's pain, and facilitates subsequent ED assessment and imaging. Numerous commercial devices are available, and most ambulances carry an assortment of immobilization devices (Fig. 42.10). Minimal equipment includes long and short backboards, cervical collars, sandbags, and extremity splints. A half-ring traction splint also is essential. Inflatable air splints are favored by some authors because they are convenient, easy to apply, transparent, and radiolucent and because they tamponade low-pressure bleeding. Others prefer to avoid these devices because theoretically they could contribute to the development of a compartment syndrome. If used, inflatable splints should be inflated only by mouth and to the point that still permits indentation by gentle finger pressure.

Field personnel should splint possible fractures before the patient is moved. Severely angulated long bone fractures should be reduced in the field before they are splinted. Splints should be applied in such a way as to immobilize the joints above and below the fracture site to avoid motion of the involved bone. The skin should be padded to avoid local necrosis, and the splint should be secured by use of a circumferential wrapping material. This material should allow for some expansion and should not be applied in a constricting manner.

Emergency Department Care

In the ED, the indications for splinting are the same as in the field. All splints should be checked and, if properly applied, need not be changed. If alternate traction is available, Hare traction that was applied in the field should be carefully removed in the ED because it may angulate femur fractures and result it decubitus ulcers over the ischium. Splinting or other immobilization is also used after diagnosis and treatment of injuries. In some cases, a splint is all that is needed for definitive treatment. Injuries other than sprains and fractures (eg, inflammatory and infectious processes, bites, burns, repaired injuries of muscle bellies or tendons) also benefit from immobilization. Splints also can be used to improve function, such as with wrist drop that accompanies radial nerve palsy. When the injury is immobilized, it is important to stress elevation of the affected part to avoid edema formation. Many different devices and materials are available. Some devices that are commonly used are described next.

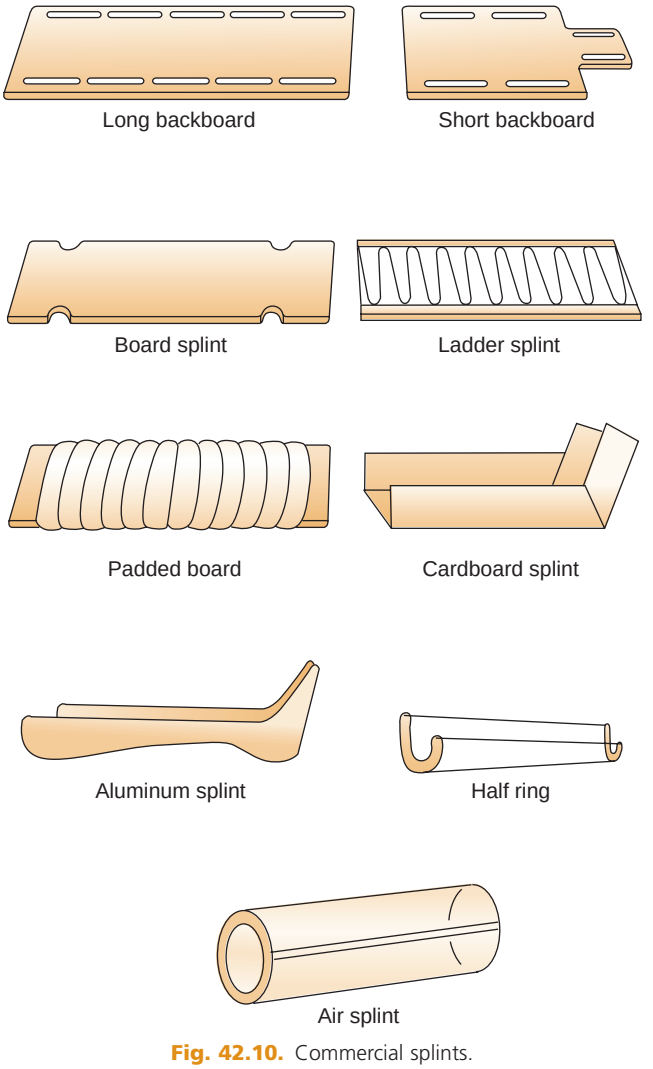


Fig. 42.10. Commercial splints.

Upper Extremity

Sling-and-Swathe and Velpeau Bandages. Sling-and-swathe and Velpeau bandages are useful in immobilizing the shoulder, humerus, and elbow. They are commonly used after reduction of dislocated shoulders and to treat impacted fractures of the humeral neck. The axillae should be padded and powdered to avoid skin maceration. A commercial shoulder immobilizer also is available and is useful after reduction of a shoulder dislocation. Its advantages are ease of application and ease of removal and reapplication by the patient for bathing. Although they may aid in healing, they are primarily placed for comfort and to decrease the incidence of re-injury.

Clavicle Fractures. Once commonly used for clavicle fractures, figure-of-eight clavicle splints have been abandoned because of an unfavorable benefit-risk profile. A simple sling of the arm

on the affected side is sufficient to support the clavicle, improving healing immobilization and relieving pain.

Plaster and Fiberglass Splints. Well-fitting, customized plaster splints can be fashioned easily to immobilize the elbow, forearm, wrist, and hand. The advantage of these splints is the ability to mold them to an exact size and shape (eg, along the ulnar side of the forearm and hand to immobilize a midshaft fourth or fifth metacarpal fracture, the so-called gutter splint). Several commercially available products consist of multiple layers of plaster or fiberglass strips, inside a covering of foam and flannel, on a continuous roll that can be applied to any length. While the splint is still wet, a bandage is wrapped over it, and the splint is molded and held in the desired position as the plaster or fiberglass resin hardens. Curing of the fiberglass and plaster splints produces an exothermic reaction. To avoid burns, lukewarm water should be used for the splint and adequate skin padding applied.

Forearm and Wrist Splints. Numerous preformed splints are available for splinting fractures of the distal forearm and wrist. They are lightweight, neat, and easy to apply and are easily removed and replaced by the patient (Fig. 42.11).

Lower Extremity

Splinting methods for various lower extremity fractures, including hip, femoral shaft, knee, and lower leg, are described in the respective chapters. Commercially available knee immobilizers can be used after acute injuries to provide firm but not rigid stabilization of the knee. The device is essentially a foam cylinder with medial and lateral aluminum stays, attached by Velcro straps, and spanning the upper thigh to upper ankle. This device is commonly used after trauma to let the knee cool off until a better physical examination or diagnostic study can be performed in a few days.

Fig. 42.11. Wrist splints.

Historically, the Jones dressing, a bulky dressing of cotton bandage and elastic wrap, applied in layers, was used for acute knee injuries, but it has been completely supplanted by knee immobilizers. The Jones dressing generally is used only after surgical procedures.

Ankle. Immobilization of the ankle can be accomplished by numerous means. Plaster or fiberglass splints can be used temporarily for the treatment of nondisplaced ankle fractures or severe sprains. These can be fashioned in the same manner as described for the upper extremity. An alternative method is to apply a full circular cast, bivalve it on either side, discard the anterior piece, and affix the posterior mold with an elastic bandage or bias-cut stockinette. Most ankle injuries should be splinted with the patient's ankle in neutral position. Injuries to the Achilles tendon, plantaris muscle, or gastrocnemius muscle initially should be treated with the foot held in slight equinus (plantar flexion) for comfort. The toes should be free to move distal to the metatarsophalangeal joints, and the proximal border should end below the tibial tubercle to avoid pressure on the peroneal nerve.

Adhesive strapping is an alternative method of ankle immobilization that provides good support and limitation of motion. Taping reportedly loses its protective properties with cyclic loading and sweating; although this is cited as a disadvantage, it may actually be helpful in encouraging and allowing early mobilization. This method is lightweight and not bulky, and a shoe can be worn over the material. Tape is applied in a noncontinuous manner, which allows for swelling and avoids constriction. First, the hair is shaved. Next, strips of tape are measured and torn off; 1.5- or 2-inch cloth-backed adhesive tape or Elastoplast is used. Elastoplast is an elastic-backed tape, constructed to stretch only in the longitudinal direction; this serves to spring the foot back automatically to a neutral position if the foot is plantar-flexed for any reason. The tape should be applied directly to the skin after a skin adherent, such as tincture of benzoin, is applied. The tape should lie flat because wrinkles may damage the skin (Fig. 42.12). The use of tape is associated with dermatologic complications, including itching or contact dermatitis, owing to adhesion of the tape to the skin. For moderate to severe lateral ankle sprains, a commercial mechanical support composed of molded plastic with Velcro straps (eg, AirCast Air Stirrup; DJO Global, Vista, CA) is more effective than elastic bandaging alone (Fig. 42.13).[14]

The treatment of ankle sprains is discussed in Chapter 51.

Casts

Plaster or synthetic (fiberglass) casts perform a function similar to splints in that they provide stability and pain relief. Casts are not mandatory for all fractures and, in situations in which they are, application is usually not an immediate necessity. Because they are circumferential, casts provide more effective immobilization of a fracture, but they require more skill and time to apply. Swelling and subsequent pressure under the cast are highest during the first 24 hours after injury. Complications of casting include compartment syndrome, thermal injury, pressure sores, bacterial and fungal infections (especially if a wound is present under the casted area), and pruritic dermatitis. Plaster is applied as strips or rolls of cloth impregnated with a hemihydrate of calcium sulfate. When this cloth is dipped in lukewarm water, a creamy paste is formed that can be molded into a cast. An exothermic reaction takes place that causes the plaster to harden and can burn the skin. Factors that have been shown experimentally to increase skin temperatures during plaster application are dip water temperatures greater than 24° C (75° F), cast thickness greater than eight sheets, and inadequate ventilation of the newly applied cast. Immersing the plaster in water for too short a time or squeezing too much water out also may lead to the generation

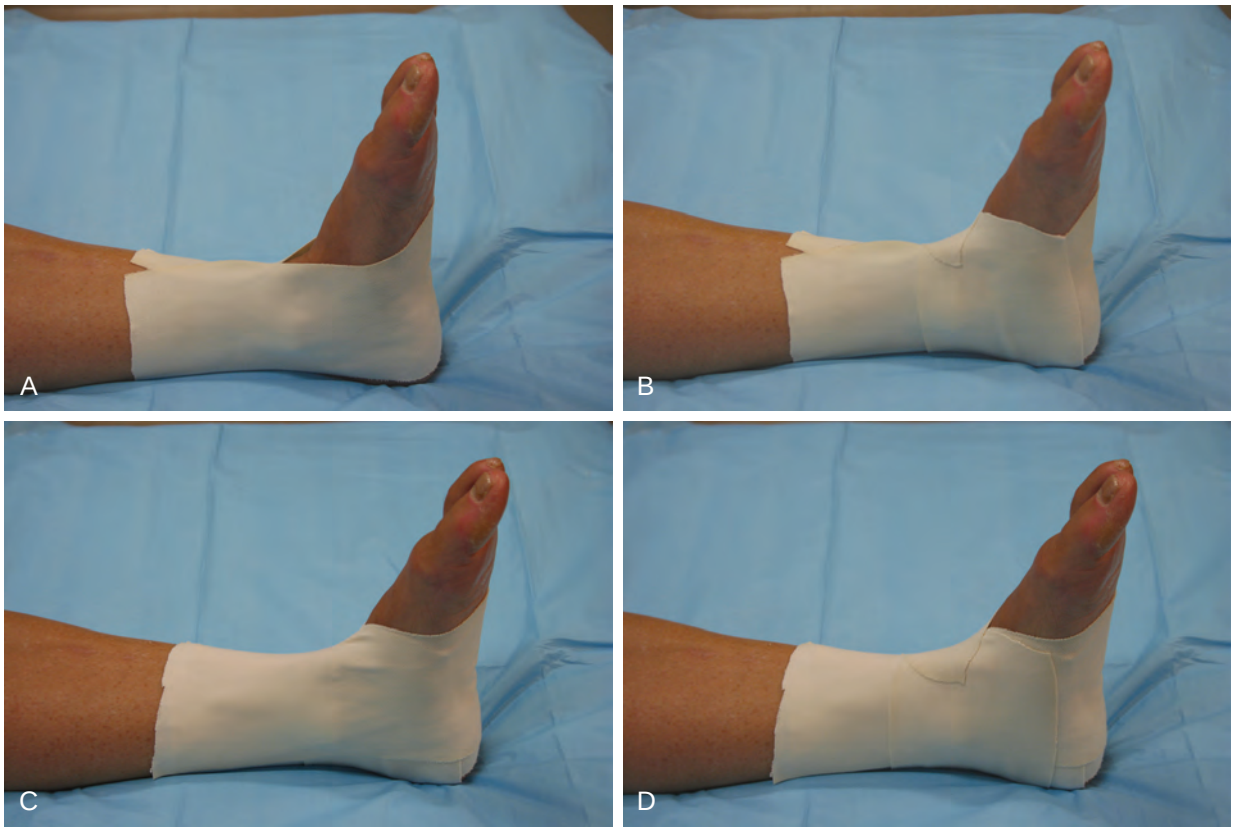


Fig. 42.12. **A–D,** Application of adhesive strips to immobilize the ankle.

Fig. 42.13. Air cast ankle support. **A,** Lateral view. **B,** Anterior view.

of excess heat. To avoid pressure on the skin and over bony prominences, stockinette and layers of cotton sheet wadding (Webril; Covidien, Minneapolis) are first applied snugly. Padding that migrates under a formed cast can be uncomfortable and result in pressure sores. Padding alone does not prevent burns.

Variations of the basic cast exist. A window may be placed in the cast, and the cutout area may be used for access to skin wounds that require care or observation during immobilization. Walking heels may be worked onto a lower extremity cast and should be placed in the center of the foot. Synthetic casts (fiberglass and other materials) are lightweight, durable, and water-resistant. In addition, their setting temperatures are significantly lower, and they are less likely to produce burns.

Patients with casts may visit the ED for complaints related to their casts; these usually are pain, local irritation, swelling, or numbness of the distal part. A cast that is too tight results in swelling, pain, coolness, and change in skin color of the distal parts. Pain also may be caused by the initial injury or by local pressure or may be a result of a developing compartment syndrome or wound infection. When a patient complains of pain, it is prudent to bivalve the cast and inspect the extremity. This is done by cutting the plaster and padding on each side and removing half the cast at a time, with the other half used as a mold to keep the extremity immobile. Afterward, the bivalved cast can be held together with bias-cut stockinette or elastic wrap until a new cast is applied. If relieving external pressure does not alleviate symptoms, the diagnosis of compartment syndrome should be considered. Casts may obscure wound infections, sources of sepsis, and even the source of tetanus.

Although once routine, we recommend basing the need for cast checks 1 day after initial application on the type and risk of the fracture and reliability of the patient and his or her access to follow-up care.

Thermal Therapy

Some confusion exists as to the role of cold versus heat therapy in the treatment of acute orthopedic injuries. Part of this confusion arises because heat may be more soothing to the patient. Icing or cooling is commonly recommended and used for acute orthopedic injuries to help reduce acute pain, despite a lack of evidence that the practice improves outcome by accelerating healing. Cold causes vasoconstriction, believed to limit blood flow and hemorrhage into the traumatized area. Metabolic requirements are reduced in cooled tissues, as is histamine, and less capillary breakdown occurs as a result. The sooner postinjury ice therapy is initiated, the more beneficial the reduction in metabolism will be. Reduced blood flow also should limit edema formation, and lower extravascular fluid pressure allows for better lymphatic drainage of injured areas. Generally, if ice is to be applied, we recommend that an insulating layer (even two layers of paper towel) be placed between the ice and skin, and that icing be continued for no longer than 30 minutes, with the skin allowed to rewarm completely between applications. Ice is likely to be most beneficial in the first 48 to 72 hours after injury.

Absolute contraindications to cryotherapy include severe cold allergy (with hives and joint pain) and Raynaud's phenomenon and disease. Relative contraindications include some rheumatoid conditions and paroxysmal cold hemoglobinuria, with renal dysfunction and secondary hypertension. Anesthetic skin in a paralyzed or comatose patient is at risk with ice therapy. Complications of cryotherapy can include skin burns and nerve damage but are rare, especially in the athletic population most at risk for serious injuries. Heat increases blood flow and the inflammatory response and edema. Warm tissues and cells have a higher metabolic rate and increased requirements for nutrients and oxygen.

KEY CONCEPTS

- Consultation with an orthopedist should be sought for the treatment of most long bone fractures, open fractures, injuries with joint violation, and injuries with neurovascular compromise.
- A careful history and physical examination can predict radiographic findings with a high degree of accuracy. A presumptive diagnosis before a radiographic study may prompt the emergency clinician to order special views necessary to diagnose an injury correctly.
- Open fracture management should focus on the early administration of antibiotics, tetanus prophylaxis, coverage of the wound, and splinting of the extremity. Suggested therapy for open fractures includes a first-generation cephalosporin, such as cefazolin, with the addition of an aminoglycoside for type II or III open fractures.
- Compartment syndrome is associated most commonly with a closed long bone fracture of the tibia but also is well described in the thigh, forearm, arm, hand, and foot and can occur with soft tissue trauma alone. Clinical examination remains the diagnostic cornerstone of acute compartment syndrome, which can then be confirmed by compartment pressure measurement.
- Because of their blood supply, certain bones may undergo avascular necrosis after fracture, especially if fractures are comminuted and go untreated for any length of time. The femoral head, talus, scaphoid, and capitate are particularly prone to this complication.
- Fat embolism syndrome is a serious consequence of fat embolism, occurring most commonly after long bone fractures in young adults (usually tibia and fibula) and after hip fractures in older patients. ARDS is the earliest, most common, and serious manifestation. Neurologic involvement, manifesting as restlessness, confusion, or deteriorating mental status, is also an early sign, as are thrombocytopenia and a petechial rash.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 42: QUESTIONS & ANSWERS

42.1. A 6-year-old girl presents complaining of pain in her right ankle after tripping and falling in the playground. On physical examination, you note that there is moderate swelling and diffuse tenderness of the lateral ankle joint, with good pulses and normal sensation. Radiographs of the ankle do not demonstrate an acute fracture or disruption of the growth plates. What is the next step in this patient's management?

A. Ace wrap, ice, pain medication, and orthopedic referral
B. Emergent orthopedic consult and preparation for the operating room
C. Orthopedic referral, ice, and pain medication
D. Splint, pain medication, and orthopedic referral
E. Urgent orthopedic consult, ice, and pain medication

Answer: D. A child with swelling and tenderness over an epiphysis (eg, of the lateral ankle) and a negative radiograph should be suspected to have an epiphyseal injury, rather than a sprain, because the epiphysis is weaker than the overlying ligaments.

42.2. Which of the following situations requires an emergent fasciotomy in the setting of a clinically suspected compartment syndrome?

A. Elevated tissue pressure within a closed compartment
B. Pain on passive stretching of the muscle group involved
C. Tissue pressure less than the diastolic pressure
D. Tissue pressure of 20 mm Hg
E. Tissue pressure within 30 mm Hg of the mean arterial pressure

Answer: A. Controversy exists regarding attempts to define compartment syndromes on the basis of specific tissue pressure. The tolerance to tissue ischemia varies among individuals because of shock, compensatory hypertension, altered tone in resistance vessels, and other unknown factors. Inadequate perfusion and relative ischemia begin when the tissue pressure within a closed compartment increases to within 20 mm Hg of a patient's diastolic pressure or, more accurately, within 30 mm Hg of the mean arterial pressure. When tissue pressure equals or exceeds the patient's diastolic pressure, tissue perfusion effectively ceases.

42.3. Which of the following is not a manifestation of fat embolism syndrome?

A. Altered mental status
B. Hematochezia
C. Petechial rash
D. Respiratory distress
E. Thrombocytopenia

Answer: B. Respiratory distress and hypoxemia are the earliest, most common manifestations of fat embolism syndrome. Acute respiratory distress syndrome (ARDS) may occur and is the usual cause of death. Neurologic involvement, manifesting as restlessness, confusion, or deteriorating mental status, also is an early sign, as are thrombocytopenia and a petechial rash. Fever, tachycardia, jaundice, retinal changes, and renal involvement may occur.

CHAPTER 43

Hand

Dana A. Stearns | David A. Peak

PRINCIPLES

Function of the hand may be impaired by injury or illness, particularly infection or inflammation. Effective and timely evaluation and treatment require an in-depth knowledge of the anatomy of the hand and wrist, including the vascular and nerve supply and location and functions of muscles and tendons acting on the joints in the hand. Serious injury, with potential long-term consequences, may appear innocuous until detailed functional testing reveals tendon or nerve disruption. Deep space infections, improperly treated, can cause permanent disability. Methodic evaluation will identify the conditions and injuries best managed in consultation with a hand surgeon (Box 43.1).

Anatomy

Five digits, including the thumb and four fingers, extend from the hand—the second digit (index finger), third digit (middle [long] finger), fourth digit (ring finger), and fifth digit (little finger; Fig. 43.1). Each finger contains three phalanges, the thumb only two. Each finger has a proximal (PIP) and distal (DIP) interphalangeal joint. The thumb has only a single interphalangeal (IP) joint. These joints articulate through 1 degree of freedom (flexion-extension). All digits possess a metacarpophalangeal (MCP) joint at the palmar interface, which articulates through two degrees of freedom (flexion-extension, adduction-abduction). The metacarpal bones are found in the palm and articulate with the eight carpal bones that in turn articulate with the radius. Two palmar muscular prominences assist with flexion, abduction, and opposition of the thumb (thenar eminence) and little finger (hypothenar eminence; Fig. 43.2).

The palmar aponeurosis (from the Greek, meaning flat tendon) is a dense tendinous extension from the volar forearm's palmaris longus muscle that creates a barrier between the tightly adherent skin surface and deeper neurovascular and musculotendinous structures (Fig. 43.3). Although the aponeurosis protects the deeper tissues from repetitive compressive or abrasive trauma, it also limits fluid extravasation and inflammatory edema, which can lead to increased compartmental pressures and neurovascular compromise. Horizontal and oblique skin creases are formed at the digital joint articulations (see Figs. 43.1 and 43.2). The organized epithelial ridging of the volar fingertip improves surface grip. Conversely, the hand's dorsum does not possess an aponeurosis. The skin is more loosely affixed across the dorsal surface (Fig. 43.4). Thus, a deep space process can easily extend posteriorly, giving the appearance of a dorsal-based process.

Eight carpal bones are arranged in two rows at the wrist. Together with interosseous ligaments, the flexor retinaculum holds them in an anterior concave orientation, creating a space known as the carpal tunnel, allowing the median nerve and volar forearm tendons to pass with minimal constriction. The carpal-metacarpal joint matrix is fixed in a volar concave position, allowing digital opposition, abduction, adduction, and grasp. The index and long finger metacarpals form an axis, around which the carpal (proximal) metacarpal (distal), and longitudinal volar arches are formed. The unique mobility of the thumb combine with these intrinsic arches to create longitudinal transverse and oblique palmar positions that enhance grasp (Fig. 43.5). The MCP joint articulation allows two degrees of freedom (flexion-extension, abduction-adduction). The distal aspect of the proximal and middle phalanges are bicondylar, creating a grooved and articular surface that provides stable flexion and extension. Each joint capsular matrix contains articular synovium. Alongside the MCP and IP joint capsules, lateral and medial collateral ligaments maintain joint alignment during motion. The IP collateral ligaments insert onto a fibrocartilaginous matrix across the volar base of the IP joint known as the volar plate. IP ligaments that are stretched due to injury may lead to joint instability. When IP ligaments are immobilized, they should be placed in a foreshortened position to ensure that proper joint alignment reduces future instability. Recovering MCP joints are best placed in flexion for the same reason (Fig. 43.6).

Pediatric phalangeal and thumb metacarpal bony epiphyses are located proximally, whereas the finger metacarpals are distal (see Fig. 43.1). They begin to appear radiographically between 10 and 24 months; fusion with radiographic evidence of skeletal maturity is age-specific and occurs during adolescence (ages 14–16 years).

Muscles and Tendons

Intrinsic hand musculature originates within the hand itself, whereas the extrinsic musculature extends from the volar and dorsal aspects of the forearm, with their tendons extending to insertion points on the hand and digits.

Intrinsic Musculature. There are four groups of intrinsic hand muscles—thenar, hypothenar, interosseous, and lumbrical. The thenar and hypothenar musculature assist with thumb and fifth digit flexion, abduction, and opposition. They take their origin on the palmar aspect of the carpal scaphoid, trapezium (thenar), pisiform, hamate (hypothenar) carpals, and flexor retinaculum (Fig. 43.7). They insert on the first and fifth metacarpal and proximal phalanges, respectively, and are named for their function. The interosseous muscles originate on the palmar and dorsal aspects of the metacarpal bones and insert on the ipsilateral side of the corresponding proximal phalanges (Fig. 43.8). The three palmar interosseous muscles adduct the index, ring, and little fingers against the long finger. The four dorsal interossei abduct these three digits away from the long finger. The lumbricals originate on the proximal finger metacarpal bones and tendon sheath of the corresponding flexor digitorum profundus (FDP) tendons. They insert on the tendinous-ligamentous matrix known as the extensor expansion that forms a hood over the PIP joints of the four fingers. The lumbricals assist with finger MCP joint flexion and IP joint extension (see Fig. 43.8).

BOX 43.1

Potential Limb-Threatening Conditions Requiring Immediate Intervention and Emergency Hand Consultation

- Compartment syndrome
- Crush injuries
- High pressure injection injury
- Open fracture
- Amputation
- Vascular injury
- Limb-threatening infection (includes bites and risk of tendon, neurovascular or joint)
- Burns—thermal, chemical (especially circumferential burns)
- Dislocations (eg, carpometacarpal joint fracture-dislocation)
- Complex fractures (angulated, oblique or malrotated fractures)

NON–LIMB-THREATENING CONDITIONS[a]

- Closed fractures
- Nerve injury
- Tendon injury
- Ligamentous injury
- Distal phalanx injury (includes amputation, tuft, nail bed)

[a]These conditions typically need definitive intervention and urgent consultation assistance with disposition (24–72 hr).
From Labs, JD: Standard of care for hand trauma: where should we be going? Hand 3:197–202, 2006.

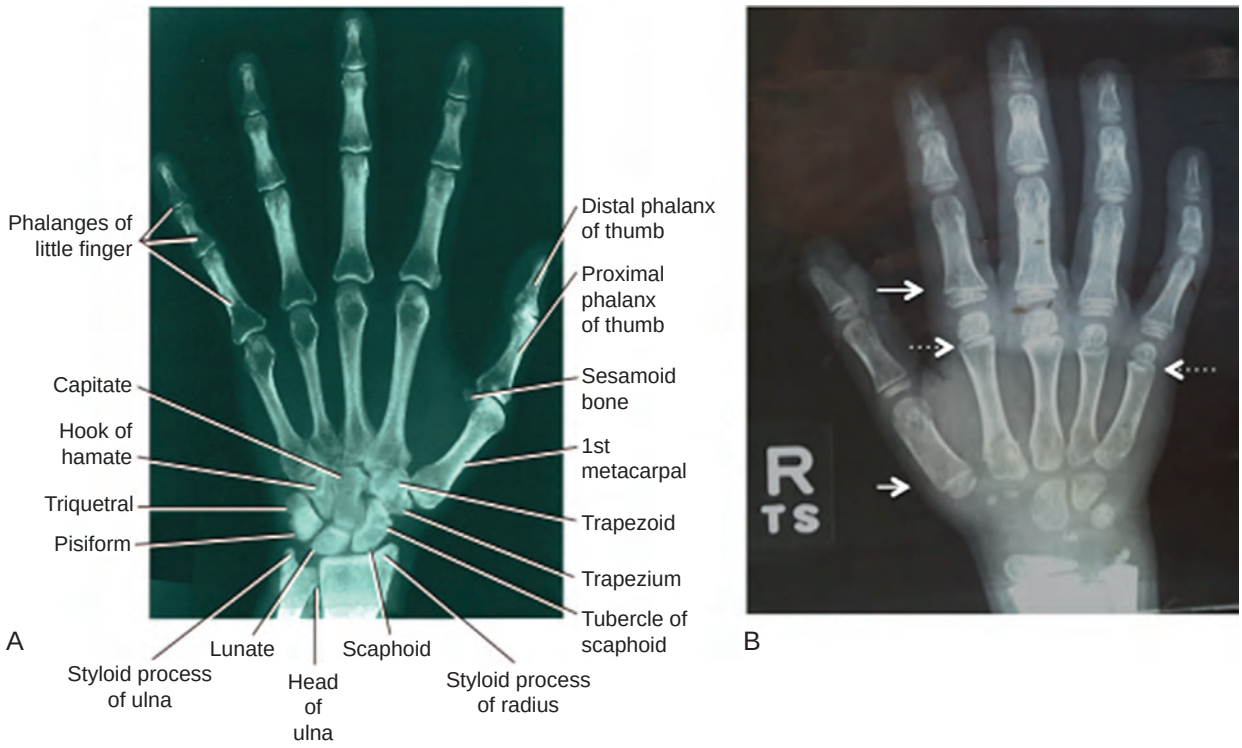

Fig. 43.1. A, Posteroanterior radiograph of the wrist and hand with the forearm pronated. The 8 carpal, 5 metacarpal, and 14 phalanges are labelled. **B,** Pediatric radiograph. Children's phalangeal and thumb metacarpal bony epiphyses are located proximally (*solid white arrows*), whereas the finger metacarpals are distal (*dashed white arrows*). (**A** from Snell RS, Smith MS: Clinical anatomy for emergency medicine, St. Louis, 1993, Mosby, p 650; **B** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

Extrinsic Musculature. The dorsal forearm contains wrist extensors and deviators, thumb extensor and abductors, and finger extensors. Each of these muscles are named for their function.

The volar forearm contains wrist flexors and deviators, as well as thumb and finger flexors. Their tendons pass to the carpal region inserting there and on associated proximal metacarpals or passing through the carpal tunnel and into the hand. The exception is the palmaris longus tendon; absent in up to 25% of the population, it passes anterior to the flexor retinaculum and forms the palmar aponeurosis (see Fig. 43.3). This tendon is commonly injured in soft tissue lacerations at the volar wrist.

Extensor Tendons. Nine extensor tendons pass from the dorsal forearm and cross the carpal wrist underneath the extensor retinaculum through six fibrous compartments that prevent bowing of the tendons during extension (Fig. 43.9). These compartments extend medially across the radius and ulna. The thumb's extensor pollicis longus tendon, contained in the third compartment, curves radially around a fibro-osseous prominence on the distal radius known as Lister's tubercle, passing to the dorsum of the thumb's distal phalanx and extending the thumb's DIP joint. This and the first compartment's tendons assist in the creation of the radial fossa known as the anatomic snuffbox,

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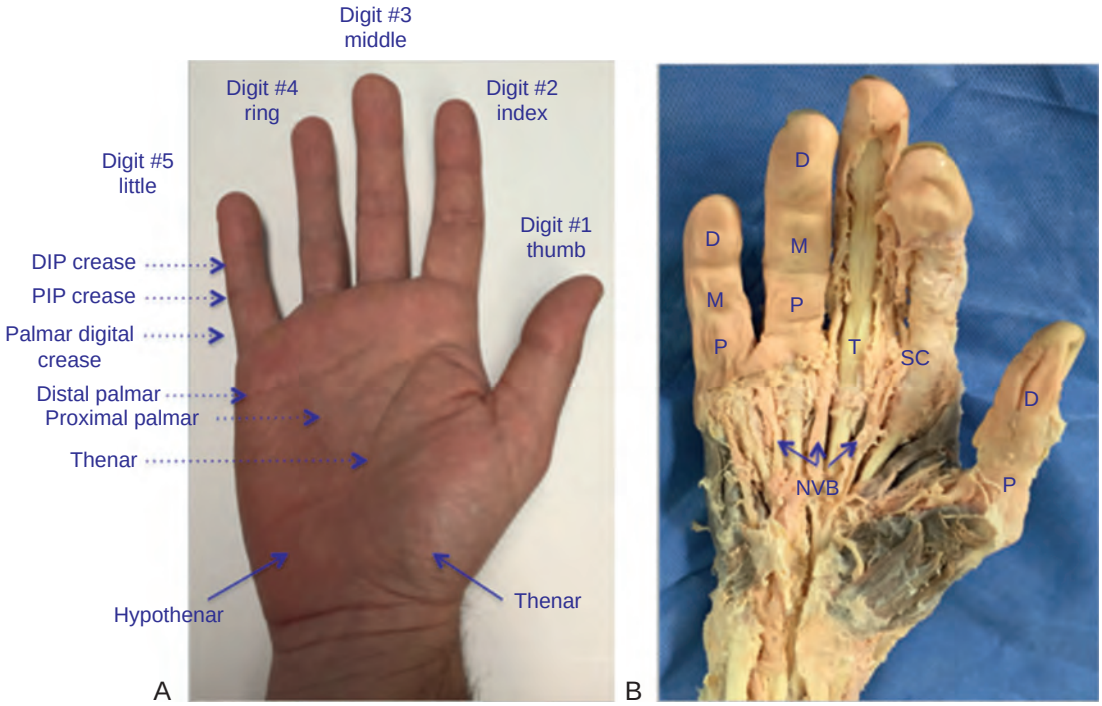


Fig. 43.2. Hand anterior, palmar-volar view. **A,** Superficial landmarks and nomenclature. Anatomic position places the thenar eminence and thumb lateral and farthest from the midline. Skin creases are created on the skin surface near joint articulations and labeled for their anatomical position. **B,** Close relationship of the neurovascular and musculotendinous structures and their proximity to the skin surface. The distal (D), middle (M), and proximal (P) finger and thumb phalanges are labeled. The neurovascular bundles (NVB) pass from the palm to each digit and travel alongside the digital tendons (T). Synovial sheaths surround the digital tendons and adhere to the anterior surface of the digital phalanges. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

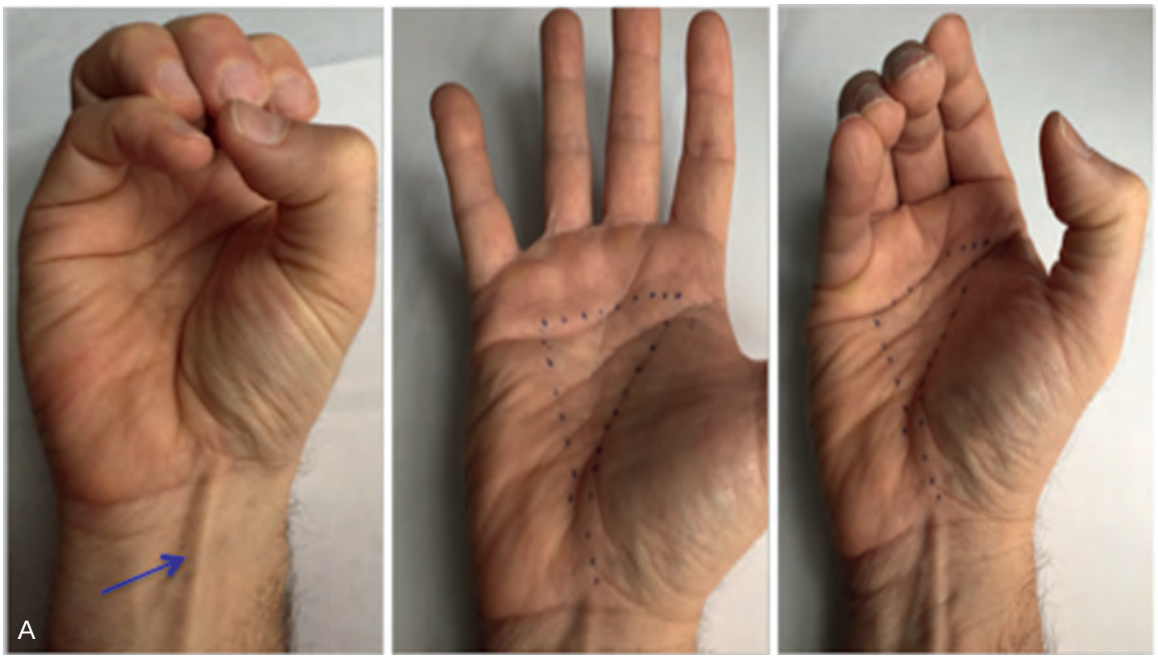
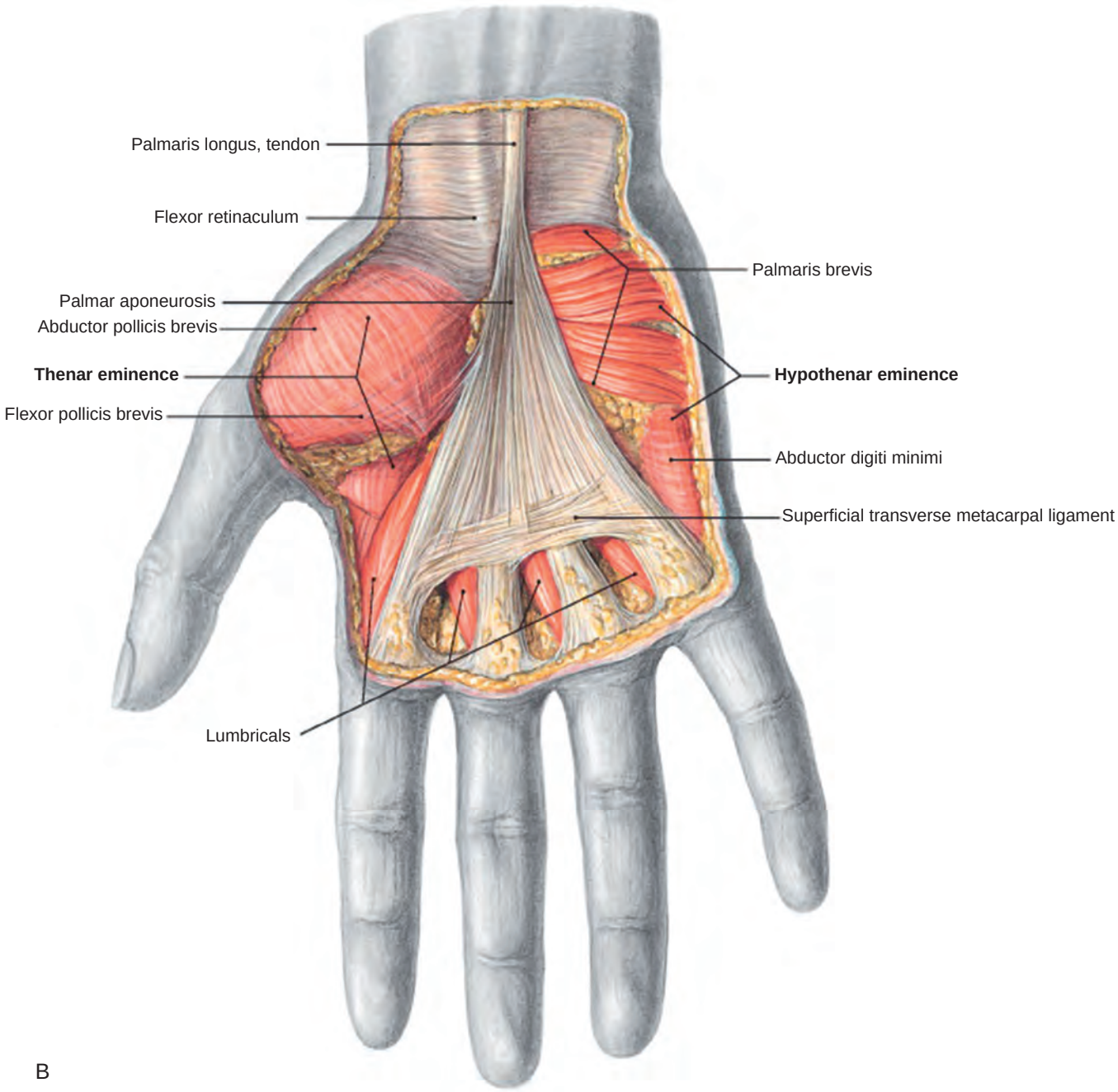


Fig. 43.3. Palmaris longus tendon—palmar aponeurosis, **A,** The palmaris longus tendon (*blue arrow*), absent in up to 25% of the population, contributes to the palmar aponeurosis (*dotted outlines*).



B

Fig. 43.3, cont'd. **B,** Superficial layer of muscles in the palm of the hand, right side, palmar view. There are three groups of muscles in the palm of the hand. On both sides of the palm, muscles of the thumb and fifth finger form the thenar and hypothenar, respectively. Between the two groups are the muscles of the palm of the hand. These three groups are arranged in three consecutive muscle layers. The neurovascular structures between these layers need to be considered when dissecting the palm of the hand. Located most superficially is the palmar aponeurosis, which consists of longitudinal and transverse fibers; the latter is prominent just below the metacarpophalangeal joints (superficial transverse metacarpal ligament). The palmar aponeurosis is fixed proximally to the flexor retinaculum and stretched by the palmaris longus. Distally, it is fixed to the tendinous sheaths of the finger flexors and to the ligaments of the metacarpophalangeal joints. At the thenar, the abductor pollicis brevis is located on the radial side and the flexor pollicis brevis is located ulnar to the abductor muscle. At the hypothenar, the palmaris brevis and abductor digiti minimi are superficial. **(A** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **B** from Paulsen F, Waschke J, editors: Upper extremity. In Sobotta atlas of human anatomy, vol 1, ed 15, Munich, 2013, Urban & Fischer, pp 130–245. © Elsevier, 2013.)

Fig. 43.4. Hand, dorsal view. **A,** Superficial landmarks and nomenclature. **B,** Distal (D), middle (M), and proximal (P) finger and thumb phalanges. The extensor tendon apparatus (T) passes to their respective digits along the dorsal surface of the bones, just deep to the skin and subcutaneous tissues. **C,** The skin is less loosely affixed across the dorsal surface. **D,** Significant dorsal swelling. The cause was an innocuous puncture wound to the first web space that extended posteriorly. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

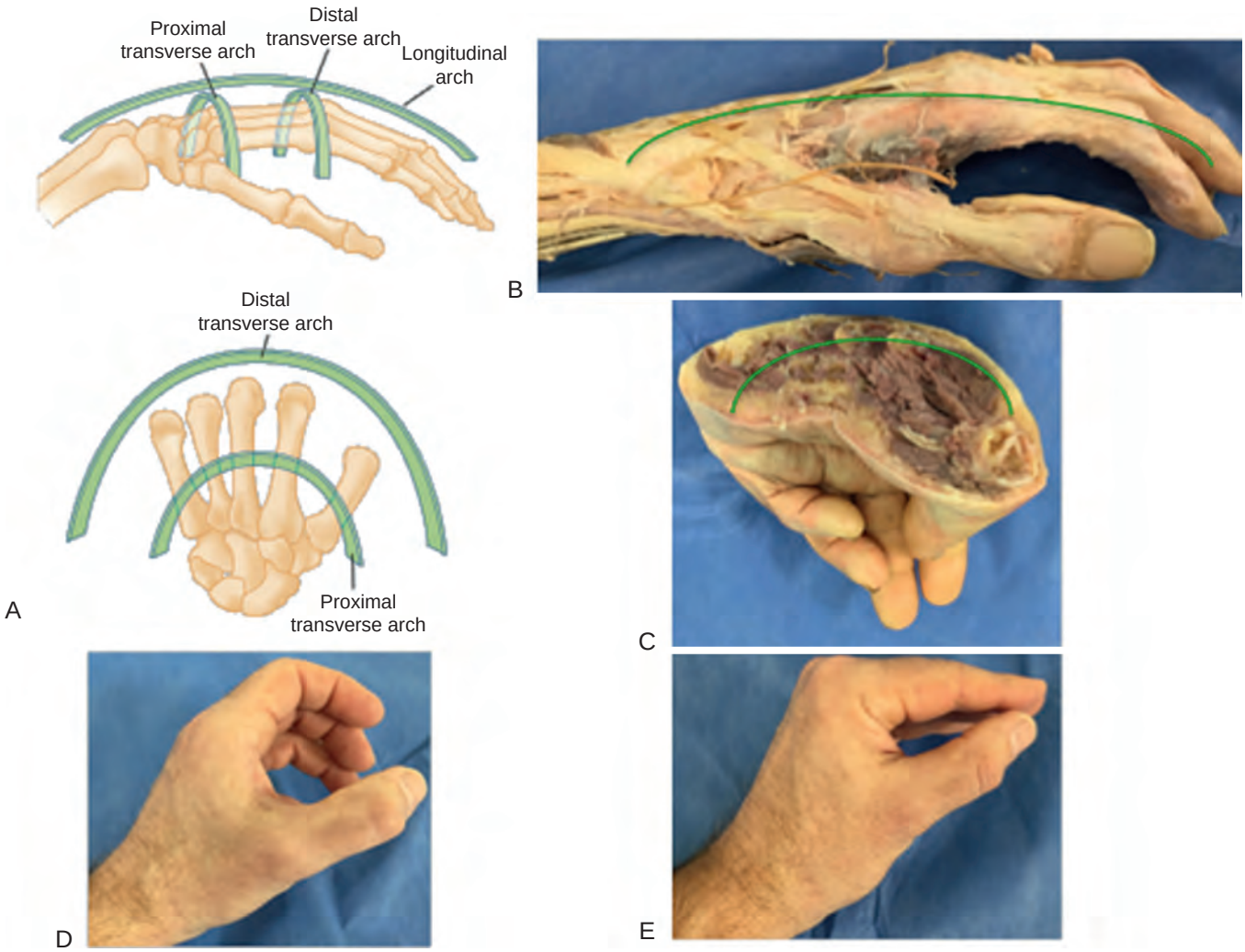


Fig. 43.5. **A,** Sagittal and transverse views of the longitudinal proximal and distal metacarpal arches. **B,** Longitudinal arch. **C,** Proximal transverse arch. **D, E,** Unique thumb articulations contribute to the intrinsic arches to create a broad range of grasp positions. (**A** from American Society for Surgery of the Hand: Regional review course in hand surgery syllabus, ed 10, Aurora, CO, 1990, American Society for Surgery of the Hand; **B–E** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

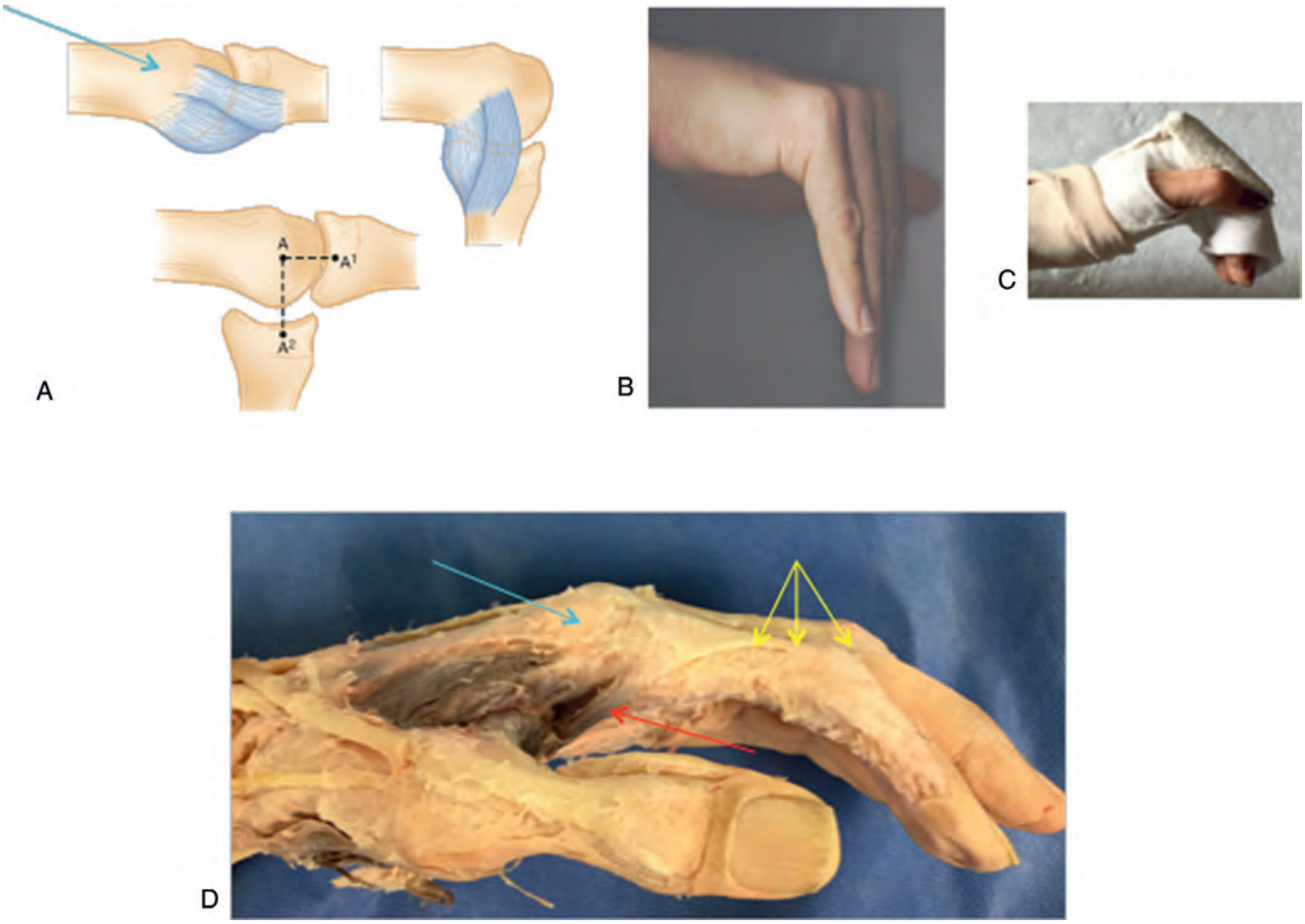


Fig. 43.6. **A,** The metacarpal head of the metacarpophalangeal (MCP) joint has an eccentric shape (*blue arrow*). The distance A-A^1 (MCP joint extension) is less than A-A^2 (MCP joint flexion), creating more collateral ligament tension with flexion than in extension. **B,** The lumbricals assist with finger metacarpophalangeal flexion and IP joint extension. **B, C,** When these ligaments are immobilized, they should be placed in a foreshortened position to reduce future joint instability and ensure proper alignment through its range of motion during rehabilitation. **C,** Recovering MCP joints are best placed in flexion and corresponding interphalangeal (IP) joints in extension. **D,** The lumbrical musculature takes origin on the tendon sheath of the corresponding flexor digitorum profundus (FDP) tendons (*red arrow*). They insert on the tendinous-ligamentous matrix known as the extensor expansion that forms a hood over the proximal interphalangeal (PIP) joints of the four fingers (*yellow arrows*). Note the eccentric shape of the metacarpal head of the MCP joint (*blue arrow*). (**A** from DeLee JC, Drez D Jr: Orthopedic sports medicine: principles and practice, ed 2, Philadelphia, 2003, Saunders; **B–D** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

Fig. 43.7. Thenar (T) and hypothenar (H) musculature (**A–C**) assist with thumb and fifth digital flexion (**D, H, I**), abduction (**E**), adduction (**H, I**), and opposition (**F, G**). Opposition is the best test for recurrent median nerve function. If the nerve is damaged, the thumb can no longer oppose to the fifth digit tip. **F, G** asked to oppose, the patient with this injury will adapt by flexing and adducting the thumb to the base of the fifth digit, indicative of injury (**H, I**). (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

Fig. 43.8. A, Four dorsal interossei serve to abduct the adjacent digits away from the middle finger. **B,** The three volar interossei adduct them against the middle finger. Both sets of muscles are innervated by the ulnar nerve. **C,** Paper pinch test creating forceful adduction to prevent a sheet of paper from being drawn from between the digits. **D,** With ulnar nerve dysfunction, the patient will adapt to create resistance by flexing the thumb interphalangeal (IP) joint to pinch the paper; this uses the median nerve (Froment's paper sign). **E, F,** Lumbrical function—flexion of the metacarpophalangeal (MCP) joint while extending the proximal interphalangeal (PIP) joint ("ta-ta" wave motion). (From Froment J: La préhension dans les paralysies du nerf cubital et le signe du pouce. Presse Med 1915; 23:409, 1915; and courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

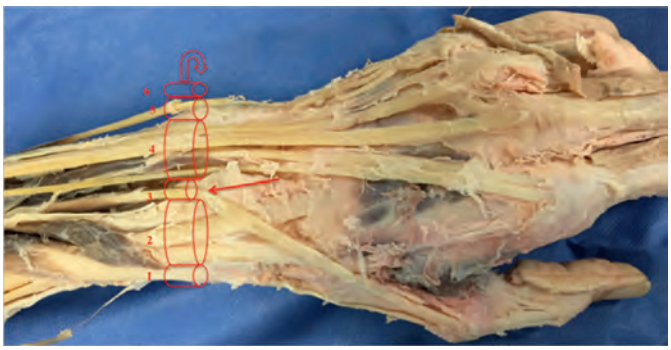


Fig. 43.9. Anatomic dissection exposing the six compartments for the dorsal forearm tendon after the extensor retinaculum has been removed. The sixth compartment is behind the fifth in this image and out of view. Note the bowing of the tendons after they have been released from the sheaths. *Compartment 1,* Abductor pollicis longus and extensor pollicis brevis; *compartment 2,* extensor carpi radialis longus and extensor carpi radialis brevis; *compartment 3,* extensor pollicis longus; *compartment 4,* extensor digitorum; *compartment 5,* extensor digit minimi; *compartment 6* (diagrammed but out of view, just medial to compartment 5), extensor carpi ulnaris. The *red arrow* notes the location of Lister's tubercle, allowing the extensor pollicis longus tendon to deviate radially towards the thumb. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

created when the thumb is extended and abducted (Figs. 43.10 and 43.11). The superficial branch of the radial nerve courses over this location. Within the snuffbox lies the cephalic vein (intern's vein), dorsal radial artery, and scaphoid carpal bone.

The extensor indicis and extensor digiti minimi tendons pass to the index and little fingers, providing each with independent extension function. The extensor indicis proprius and extensor digiti minimi can be independently tested by asking the patient to extend these digits after making a fist (Fig. 43.12). Juncturae tendineae connect adjacent tendons of the extensor digitorum communis (EDC) and extensor digiti minimi together in a horizontal and oblique orientation as these tendons approach the MCP joint. In addition to evenly spacing the tendons and stabilizing the MCP joints, the juncturae tendineae ensure continued individual MCP joint extension, even in the setting of traumatic transection of an extensor tendon.

The extensor complex on the dorsum of the four fingers is comprised of tendinous extensions from the extrinsic and intrinsic musculature (Fig. 43.13). As the EDC tendon crosses the MCP joint, it inserts onto the extensor apparatus joined by tendinous extensions from the interosseous and lumbrical musculature, creating the dorsal expansion (hood). The expansion divides into three bands—a central tendon (central slip) that inserts on the dorsal base of the middle phalanx and two lateral bands. The

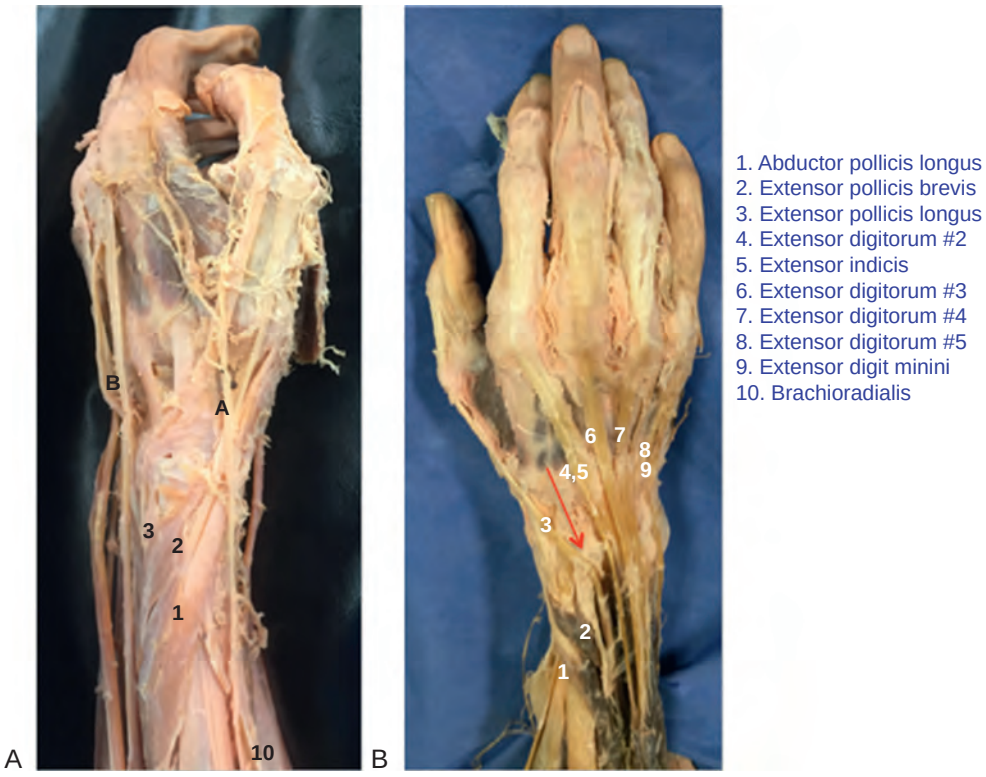


Fig. 43.10. A, B, Dorsal forearm tendons extending across the wrist and hand dorsum beyond the extensor retinaculum. **A,** The superficial branch of the radial nerve (A) extends beyond the brachioradialis in the forearm and crosses over the anatomic snuffbox to supply the radial aspect of the hand dorsum. Note the bowing effect on the extensor tendons (B) after the tethering effect of the extensor retinaculum has been removed. **B,** Note Lister's tubercle (*arrow*). (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

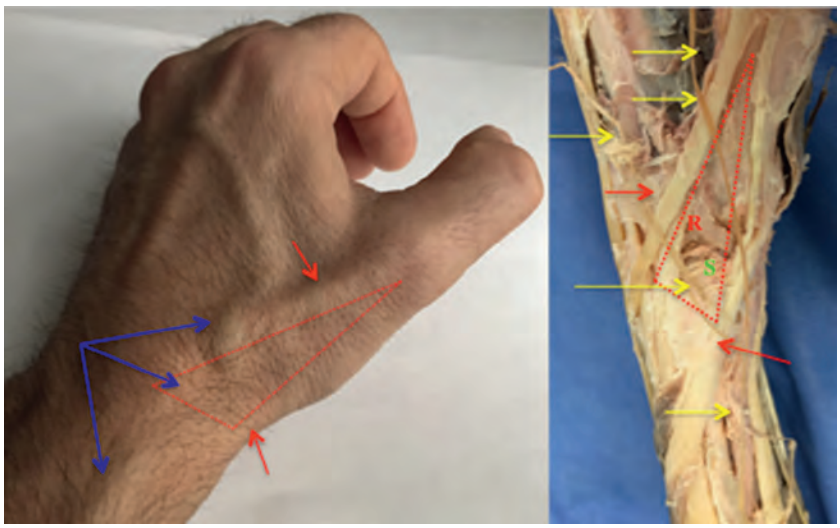


Fig. 43.11. Anatomic snuffbox. Shown are the borders of the anatomic snuffbox *(red triangles)* and abductor pollicis longus, extensor pollicis brevis, and extensor pollicis longus (*red arrows*). The area is best palpated when the thumb is abducted and the metacarpophalangeal (MCP) joint is extended, as shown in the image at *left*. Also shown are the cephalic (intern's) vein that passes over the snuffbox *(blue arrows). Right,* Superficial branch of the radial nerve supplying sensation to the hand dorsum (*yellow arrows*). The dorsal extension of the radial artery (*red R*) and scaphoid bone *(green S*) are palpable within the fossa. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

Fig. 43.12. A, Juncturae tendineae (JT; *red arrows*) connect the adjacent extensor digitorum communis (EDC) tendons together in a horizontal and oblique orientation and ensure metacarpophalangeal (MCP) joint extension of the second through fifth digits, even if a particular extensor tendon is transected. **B,** EDC, extensor indicis proprius (EIP), and extensor digiti minimi (EDM) extend over the metacarpal bones toward their respective fingers. The EIP and EDM are tested independently by extending these digits after making a fist (so-called hook 'em horns). (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

lateral bands combine with extensions of the lumbrical and interosseous tendons, cross the dorsum of the PIP joint, and insert on the dorsal base of the distal phalanx. The central and lateral bands are held in place by a transverse retinacular ligament, which serves to prevent the lateral bands from migrating anteriorly, resulting in paradoxical PIP joint flexion.

The EDC, interosseous, and lumbrical tendons coordinate PIP and DIP joint extension. The intrinsic tendons travel volar to the axis of rotation of the MCP joint to insert on the lateral bands of the extensor apparatus. This unique position allows the instrinsic muscles to act as flexors at the MCP joint and as extensors at the PIP and DIP joints. The long extensors act primarily to extend the MCP joints. The relationship between the long flexors, long extensors, and lumbricals is complementary and aids in examination of the function of the fingers. On the palmar side, the long tendons flex the IP joints, and the lumbrical flexes the MCP. On the dorsum, the reverse is the case: the long extensors extend the MCP, and the lumbricals extend the IP joints. This also helps explain why the preferred splinting position of MCP fractures is MCP flexion and PIP extension (see Fig. 43.13). Thumb extension is achieved through the use of the extensor pollicis longus (IP joint) and brevis (MCP joint).

Flexor Tendons. From the anterior forearm muscles, 12 tendons extend to the volar palm and digits. Facilitating wrist flexion and radial-ulnar deviation, the flexor carpi radialis, flexor carpi ulnaris, and palmaris longus tendons cross the carpal region to insert on the first metacarpal bone, fifth metacarpal bones, and palmar aponeurosis, respectively. The flexor digitorum superficialis (FDS), FDP, and flexor pollicis longus (FPL) tendons travel alongside the median nerve through the carpal tunnel and into the hand palm (Fig. 43.14). The FPL inserts on the volar aspect of the thumb's proximal distal phalanx. As its name implies, the FDS lies more superficially in the palm than the FDP tendons (Fig. 43.15). Uniquely, the FDS tendons bifurcate just proximal to their insertion points at the volar base of each finger's middle phalanx. This allows the FDP to pass through the gap and insert on the volar base of the corresponding finger's distal phalanx (Fig. 43.16). The lumbrical muscles originate on the corresponding fingers' FDP tendons as they cross the metacarpals (see Fig. 43.15). Along the volar aspect of the hand, synovial sheaths encase tendons, minimizing friction of motion (Fig. 43.17).

Each digit's muscle-tendon unit should be tested individually. Examination of extensor function involves observation of these digits separately and as a unit with the remaining digits. The flexor

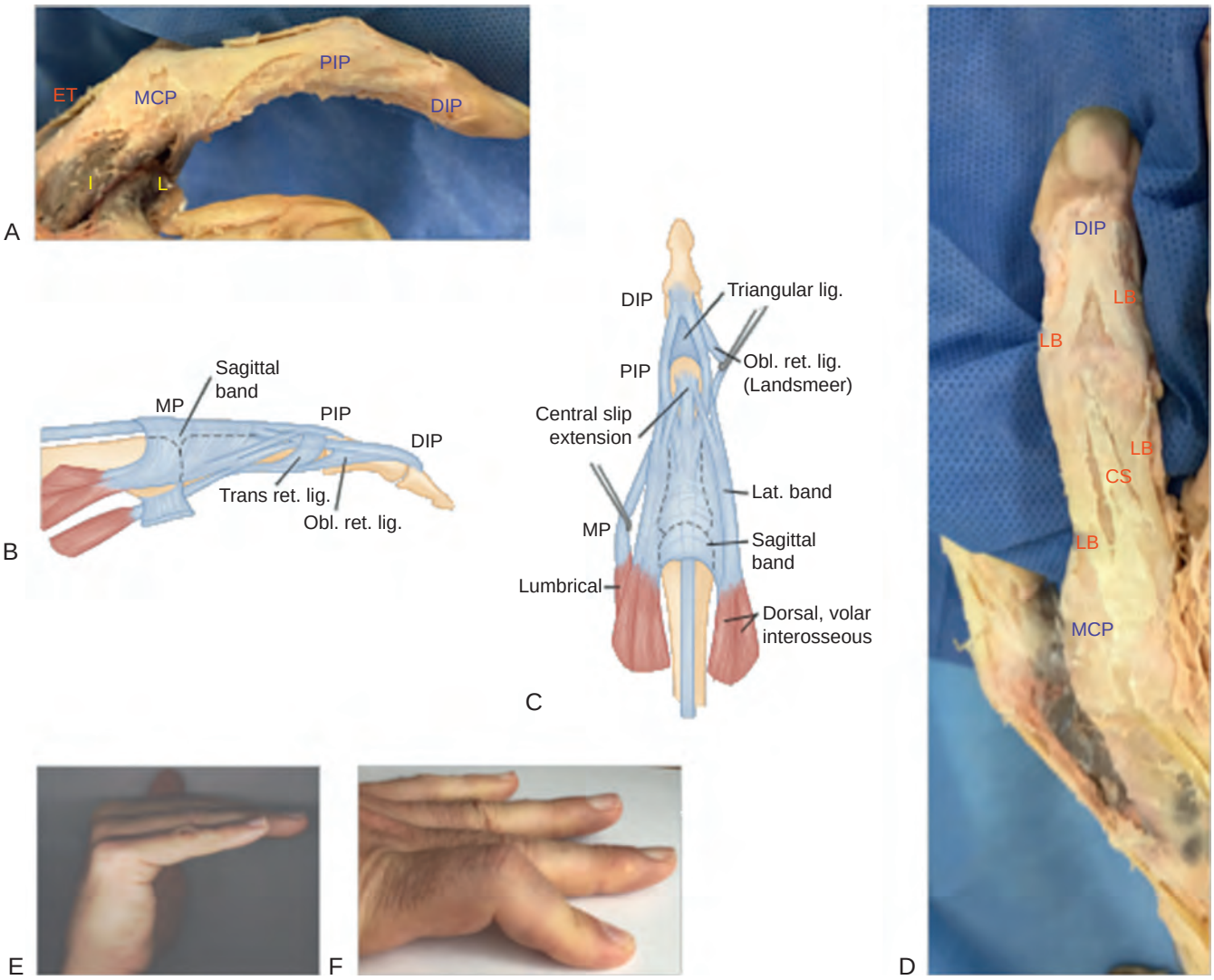


Fig. 43.13. Finger extensor complex. **A, B,** The extensor tendon (ET) at the metacarpophalangeal (MCP) joint is secured by a sagittal band originating from the volar plate and metacarpal ligaments to form the origin of the extensor hood or expansion. **A,** The intrinsic tendons from the lumbrical (L) and interosseous (I) muscles join the extensor mechanism along the proximal dorsal phalanx. **C, D,** The extension complex at the proximal interphalangeal (PIP) joint is comprised of a trifurcation of the extensor tendon into a central slip (CS), which inserts on the dorsal base of the middle phalanx and two lateral bands (LB). These lateral bands continue distally beyond the distal interphalangeal (DIP) joint to insert at the dorsal base of the distal phalanx. **C, E, F,** The PIP extension mechanism is maintained in place over the PIP joint by the transverse and triangular retinacular ligaments. These prevent the lateral bands from migrating anteriorly, resulting in paradoxical PIP joint flexion. **F,** The index finger's PIP joint is paradoxically flexed with DIP extension (boutonnière deformity). (**A, D–F** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **B, C** from Doyle JR: Extensor tendons—acute injuries. In Green DP, editor: Operative hand surgery, New York, 1993, Churchill Livingstone, p 1928.)

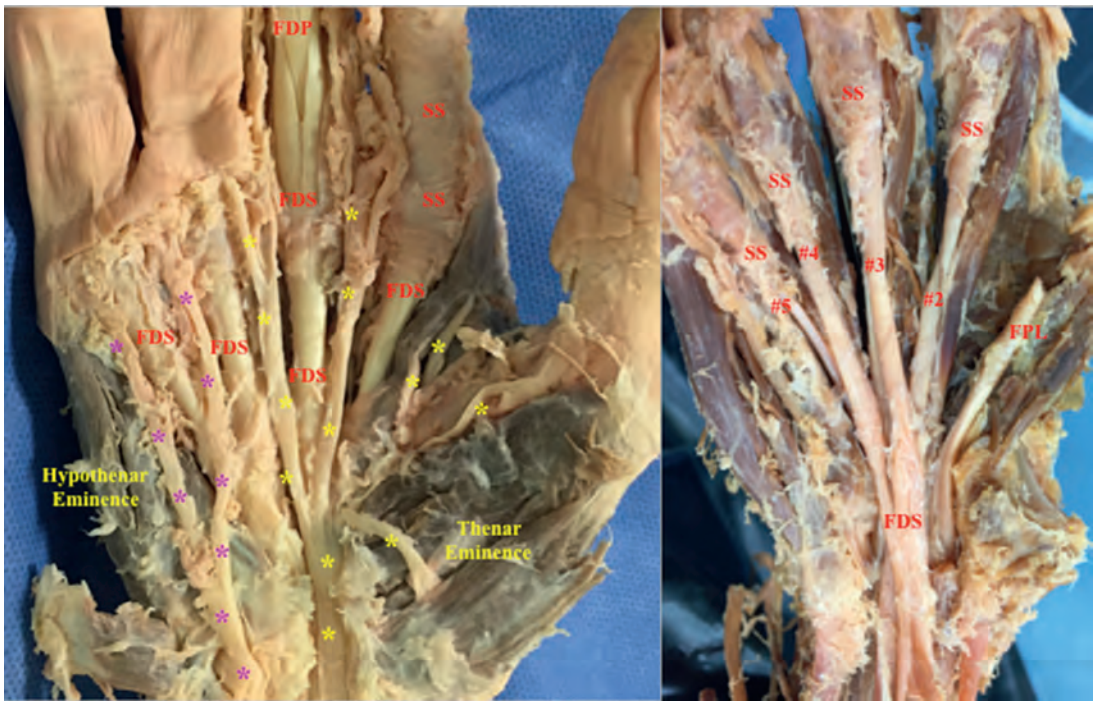


Fig. 43.14. The flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), and flexor pollicis longus (FPL) tendons travel alongside the median nerve (*yellow stars*) through the carpal tunnel and into the hand palm. The ulnar nerve (*purple stars*) enters the palm through Guyon's canal, just medial to the pisiform bone. The flexor tendons enter the synovial sheaths (SS) for each digit. Note the sheaths for the second through fourth digits begin just proximal to the respective MCP joints. The thumb and little finger's sheaths extend from the proximal palm and are surrounded by muscles of the thenar and hypothenar eminences. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

carpi radialis, flexor carpi ulnaris, and palmaris longus tendons can be tested by palpating the tendons while the patient is flexing the wrist against resistance. The flexor pollicis longus assists in flexion of the MCP and IP joints and is assessed by observing the thumb's IP joint flex against resistance.

Reduced resistance strength or increased pain and tenderness at a point along a tendon may suggest a partial tendon tear. Trigger finger can result from scarring of a previous tear and commonly occurs over the MCP joint. The patient may describe a pop or snap sensation as the tendon defect passes along the synovial sheath. At times, the patient may need to unlock the so-called trigger by palpating or ranging the affected digit with the opposite hand.

Synovial Spaces. Synovium-containing fibrous tissue sheaths provide lubrication for the flexor tendons as they pass the length of the digits to their insertions. Up to 100 degrees of flexion can occur at the PIP and 80 degrees at the DIP joints (Fig. 43.18; see Figs. 43.16 and 43.17). Adjacent bursae absorb repetitive and compressive forces. Tendons are largely avascular and depend on adjacent compartments for nutrition and homeostasis. The avascularity of the synovial sheaths and bursae promote the spread of infection. Extensor tendons, not encased in similar sheaths, are less prone to infectious tenosynovitis.

The synovial sheaths of the index, long, and ring fingers pass from the distal phalanx along the volar digit into the palm, end at the distal palmar crease, and do not communicate with one another. The sheath and bursa of the thumb's flexor pollicis longus tendon pass from the volar distal phalanx to the proximal palmar crease, where they may communicate with the adjacent radial bursa that resides in the palm and carpal tunnel (Fig. 43.19). A similar sheath and bursal space passes along the trajectory of the flexor digitorum tendons and communicates with the ulnar bursa in the palm and carpal tunnel. Infections involving the flexor synovial spaces of the index, middle, and ring fingers may extend along the volar aspect of the affected digit into the palm. Processes involving the thumb or little finger have the potential to extend into the carpal tunnel and may even communicate across to the opposite digit's space, producing a horseshoe infection.

Blood Supply

Arterial System. The radial and ulnar arteries, named for the forearm bones that they parallel, enter the carpal region at the wrist. The radial artery divides at the volar wrist. The superficial palmar branch moves anteriorly over the palmar carpal ligament and into the base of the thenar eminence, where it forms the superficial palmar arch. The radial artery passes to the dorsum of the trapezium bone between the radial styloid process and the scaphoid bone, where it emerges within the anatomic snuffbox and forms a dorsal carpal arch that parallels the extensor retinaculum. The deep branch passes into the hand palm between the first and second metacarpals to join the deep palmar arch (Fig. 43.20). The ulnar artery passes into the palm by crossing over the flexor retinaculum in a space created by the pisiform bone and palmar carpal ligament, known as Guyon's canal. As it emerges from the canal, the artery sends a deep branch that forms a collateral with the radial artery's deep palmar arch and continues anteriorly into the palm to form a collateral with the radial artery's superficial palmar arch (Fig. 43.21; see Fig 43.20). Individual pairs of palmar digital arteries extend from these arches along the radial and ulnar

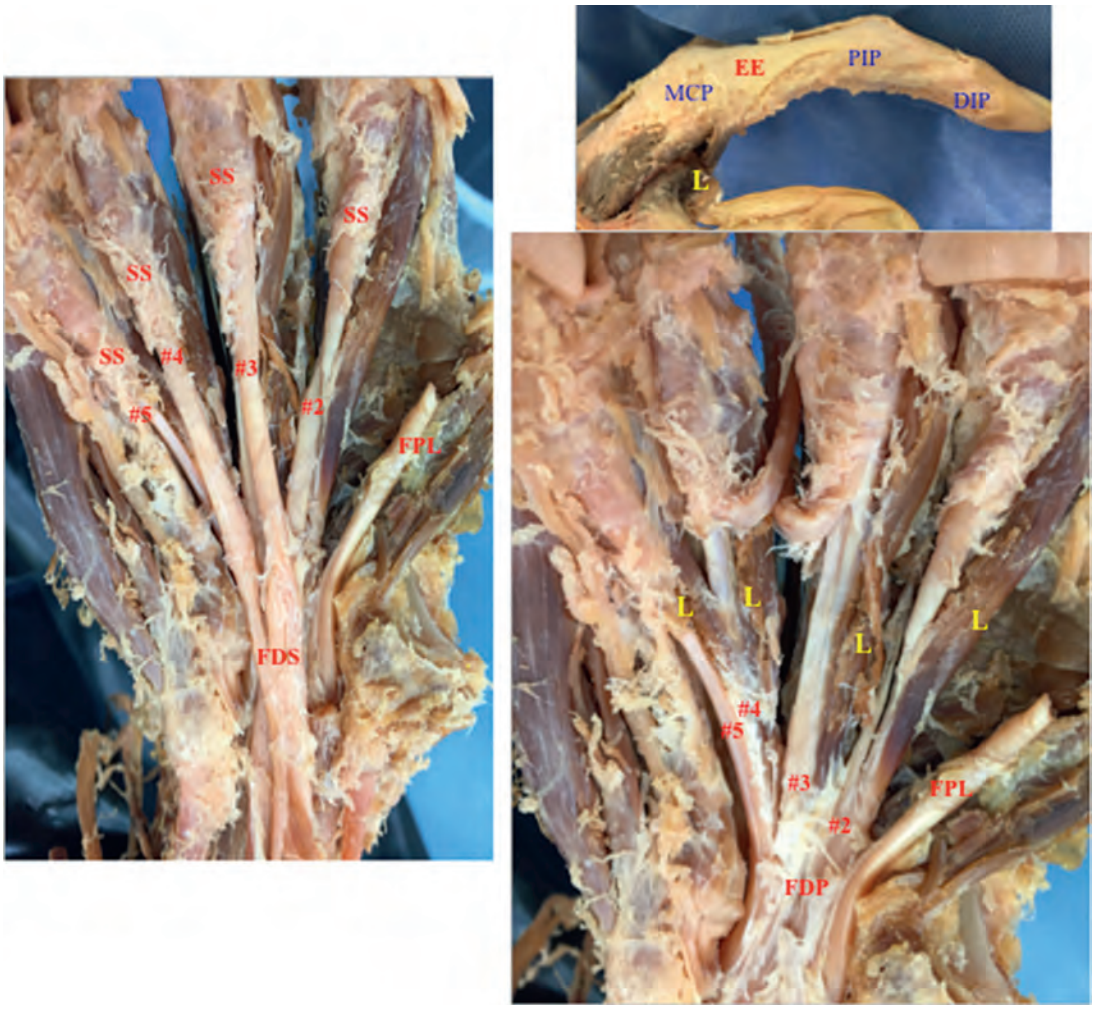


Fig. 43.15. The flexor digitorum superficialis tendons (FDS, 2–5) enter the palm through the carpal tunnel (tendons 3 and 4 tightly overlap anterior to tendons 2 and 5; the middle and ring fingers' FDS are more commonly involved than the index and little fingers with carpal penetrating injuries as a result) and remain just anterior to the flexor digitorum profundus (FDP) tendons (2–5) in the palm and proximal phalanx. The flexor pollicis longus (FPL) inserts on the volar aspect of the thumb's proximal distal phalanx. The fingers' lumbricals (L) originate on the FDP tendon as they cross the metacarpals. They insert on the tendinous-ligamentous matrix known as the extensor expansion (EE) that forms a hood over the PIP joints and dorsal proximal phalanges of the four fingers. The lumbricals assist with finger MCP flexion and IP joint extension. The flexor tendons are encased in fibrous tissue synovial sheaths (SS) as they pass the length of the digits to their insertions. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

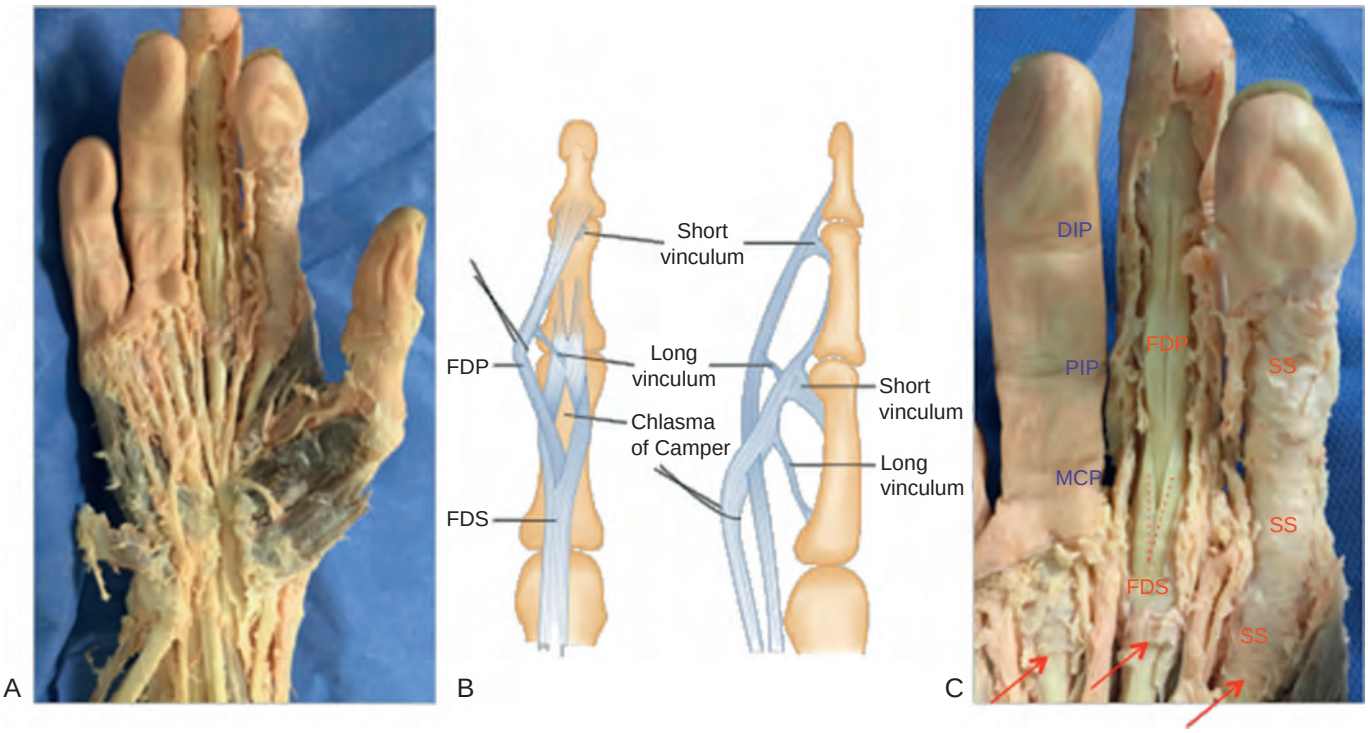


Fig. 43.16. A, The flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), and flexor pollicis longus (FPL) travel with the medial nerve through the carpal tunnel, extending through the palm towards their respective digits. **B,** Tendon trajectories of the FDS and FDP in the finger. **C,** The FDS tendons lie more superficially in the palm than the FDP tendons. The FDS tendons bifurcate just proximal to their insertion points at the volar base of each finger's middle phalanx (*red dotted lines*). This allows the FDP to pass through the gap and insert on the volar base of the corresponding finger's distal phalanx (joints labeled in *blue*). The FDS tendons are the first at risk with volar penetrating wounds involving the palm and proximal phalanges. The FDP tendon is particularly at risk with volar penetrating injuries of the middle and distal phalanges. Note the origin of synovial sheaths of the second through fourth digits (SS; *arrows*). (**A, C** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **B** from Schneider LH: Flexor tendon injuries, Boston, 1985, Little, Brown.)

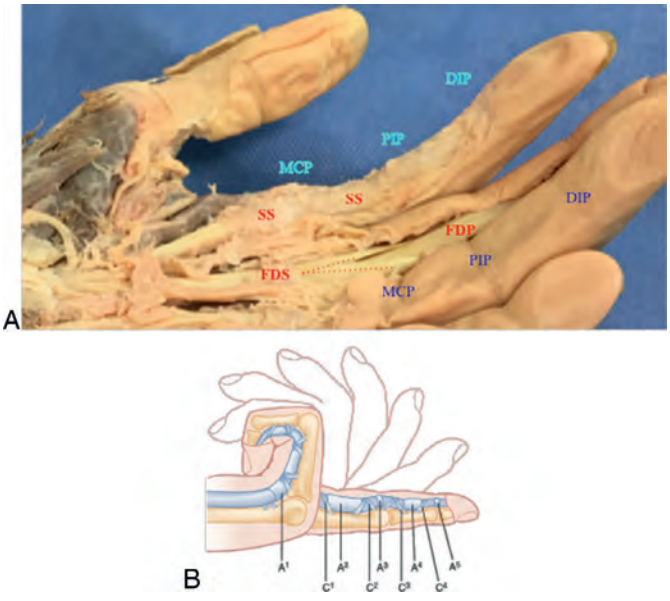


Fig. 43.17. A, Flexor tendon synovial sheath extending the length of the index and middle fingers along the volar digits. The middle finger sheath has been removed to expose the flexor tendons, as shown. The flexor digitorum superficialis (FDS) tendons bifurcate just proximal to their insertion points at the volar base of each finger's middle phalanx (*red dotted lines*). This allows the flexor digitorum profundus (FDP) tendon to pass through the gap and insert on the volar base of the corresponding finger's distal phalanx (joints labeled in *blue*). The FDS tendons are the first at risk with volar penetrating wounds involving the palm and proximal phalanges. The FDP tendon is particularly at risk with volar penetrating injuries of the middle and distal phalanges. Note the origin of synovial sheaths of the second digit (SS). **B,** Flexor pulley system. The pulleys are thickenings in the fibrous flexor sheath. There are five annular pulleys (transversely oriented fibers; A^1 to A^5). There are four cruciate pulleys (oblique, with some criss-crossing fibers; C^1 to C^4). The sheaths are tethered to the metacarpals and phalanges to create a pulley system and allow for up to 100 degrees of flexion at the PIP joint and 80 degrees at the DIP joint, as shown. (**A** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **B** courtesy Kleinert Kutz Hand Care Center, Louisville, KY.)

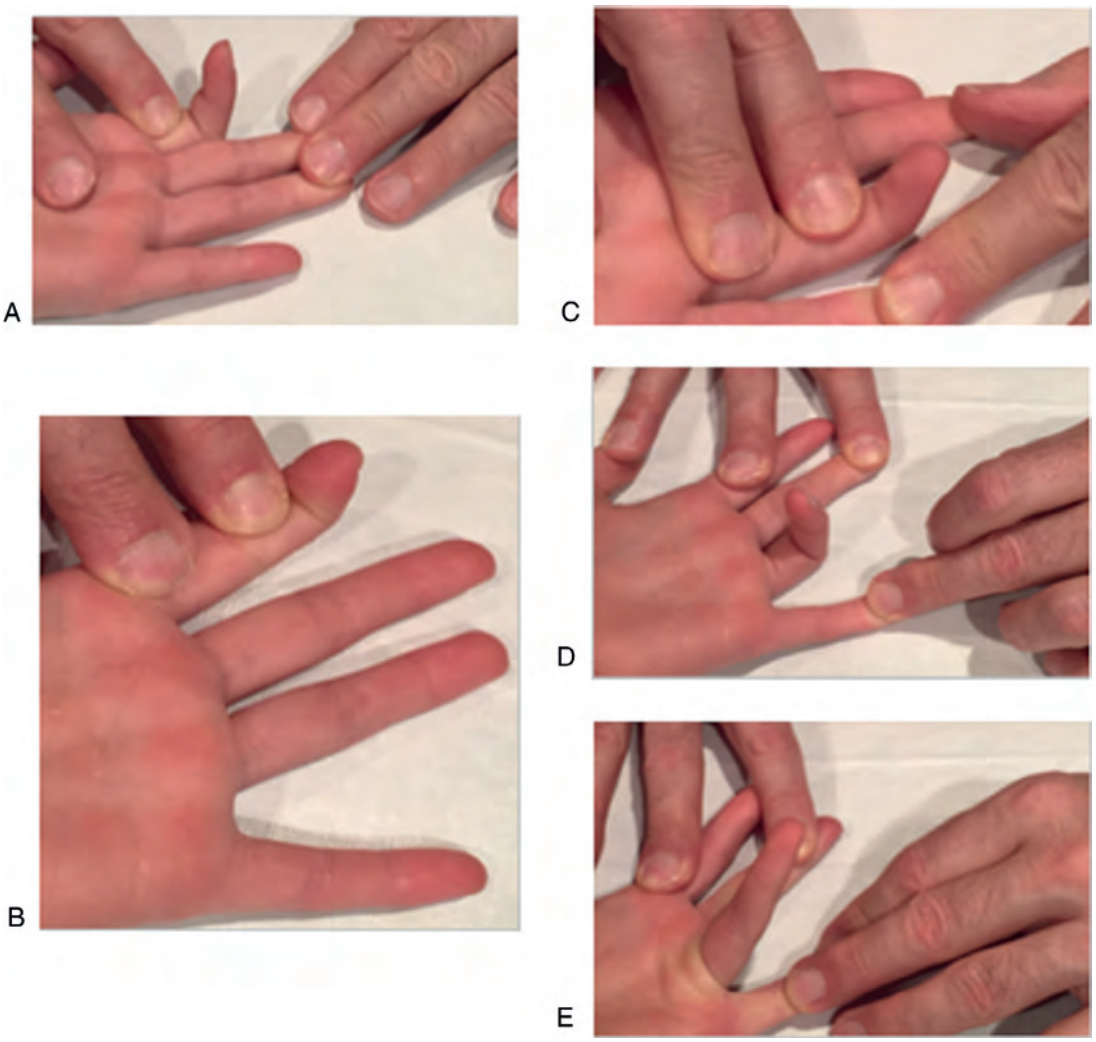


Fig. 43.18. Each digit's muscle and tendon unit should be tested individually. **A,** The index finger flexor digitorum superficialis (FDS) tendon is checked by asking the patient to flex the corresponding proximal interphalangeal (PIP) joint while the adjacent digits are held in extension by the examiner. **B,** Finger flexor digitorum profundus (FDP) function is assessed by asking the patient to flex the distal interphalangeal (DIP) joints of each digit individually while the corresponding PIP joints are stabilized in extension by the examiner. **C–E,** The ring finger's flexor digitorum profundus (FDP), FDS, and lumbrical functions are tested individually. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

aspects of each digit. This complex of collateral vessels helps maintain perfusion of the hand when the radial or ulnar artery is compromised.

Arterial circulation can be assessed at the bedside. Tissue color, temperature, and distal capillary refill of the injured hand should be compared alongside the unaffected hand. The modified Allen test, although less sensitive than other noninvasive radiologic modalities, is an easy and rapid bedside maneuver to assess and compare the distal radial and ulnar arteries (see Fig. 43.21).[1] After the examiner identifies the radial and ulnar pulses at the volar wrist, these are compressed, and the patient is asked to open and close the hand until the tissues are blanched from exsanguination. The examiner then releases one of the arteries, and vascular refill time is observed on the volar hand and digital tissue. The steps are repeated, and vascular refill is observed after release of the other artery. The refill times can be compared to each other, as well as to the unaffected hand. Each digit can be assessed in a similar fashion, because bilateral arterial injuries are at higher risk for poor outcome.[2]

Venous and Lymphatic Systems. Although the dorsal and superficial veins are numerous and varied in size and location, a common site for IV placement is the distal cephalic vein, located over the anatomic snuffbox and extending along the dorsum of the radius (see Fig. 43.11). The deep veins travel alongside the arteries, generally in a neurovascular bundle. The loose subcutaneous space on the dorsal hand contains much of the lymphatic system that drains next to the cephalic and basilic veins of the forearm, commonly resulting in dorsal swelling with hand infections.

Nerve Supply

Motor Innervation. The radial nerve (C6-C8 nerve roots) distribution on the hand and digits is entirely sensory (Fig. 43.22). The nerve passes from the brachial plexus into the posterior arm, where it divides into superficial and deep branches as it emerges from the radial groove at the elbow, between the brachialis muscle medially and brachioradialis muscle laterally.

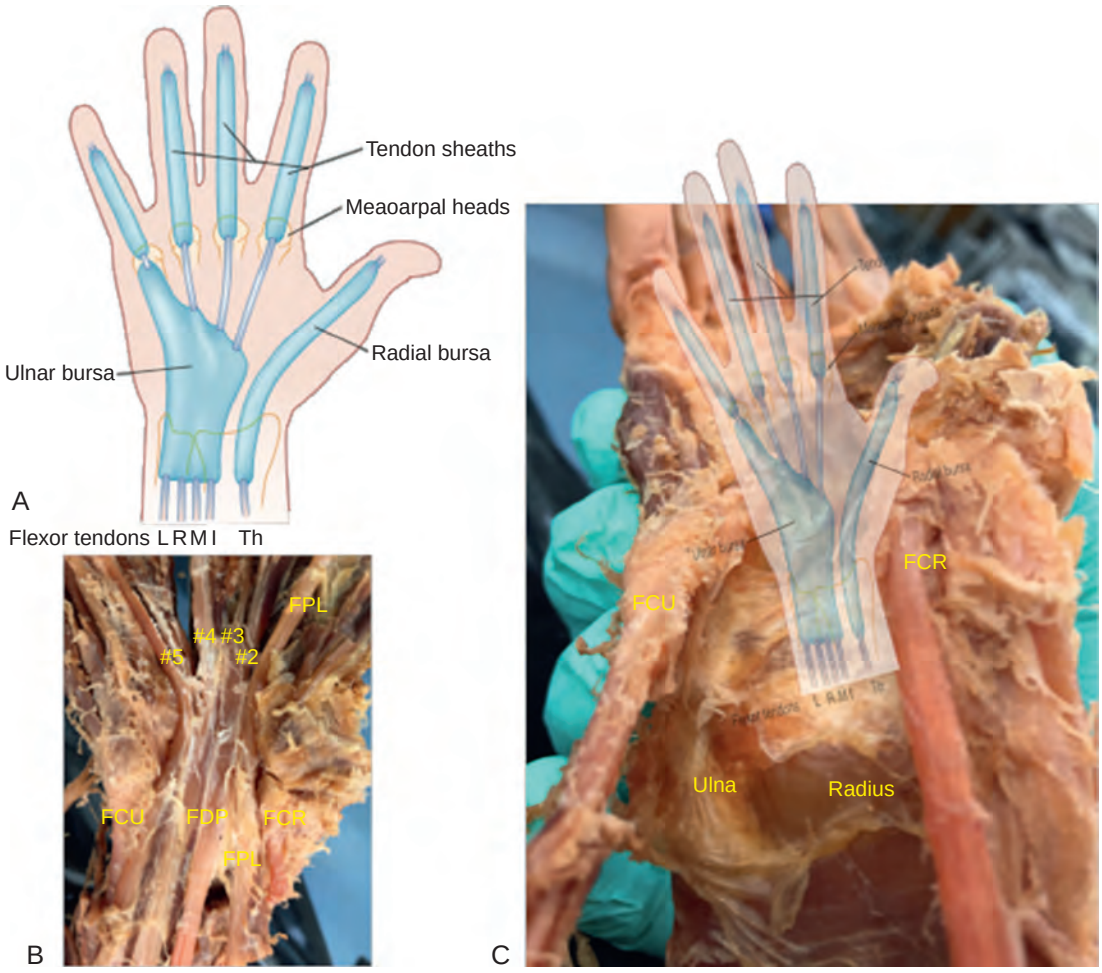


Fig. 43.19. **A,** The bursal sacs of the hand. The index, long, and ring finger bursae and sheaths pass between the distal phalanx, along the volar digit into the palm and the distal palmar crease. They do not communicate with one another. The thumb's bursa and sheath contain the flexor pollicis longus tendon and pass between the distal phalanx to the proximal palmar crease, where they may communicate with the adjacent radial bursa that resides in the palm and carpal tunnel. A similar sheath and bursal sac pass along the trajectory of the flexor digitorum tendons and communicate with the ulnar bursa in the palm and carpal tunnel. **B,** The flexor digitorum profundus (FDP) and flexor pollicis longus (FPL) tendons pass through the carpal tunnel into the hand palm. These structures are protected by the bursal sacs. **C,** The carpal tunnel, with contents removed. The flexor carpi ulnaris (FCU) and flexor carpi radialis (FCR) are left in place to show the anterior margins of the tunnel. **A** has been superimposed and made transparent to show the location of the carpal, palmar, and digital sacs and their orientation with the carpal tunnel. Infections involving the synovial spaces of the second to fourth digits may extend along the volar digit but generally terminate in the hand palm. Thumb or little finger bursal infections have the potential of extending into the carpal tunnel and, in some cases, can communicate across to the opposite digit's space, causing a horseshoe infection. (**A** from Siegel DB, Gelberman RH: Infections of the hand. Orthop Clin North Am 19:779–789, 1988; cadaveric images courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

The deep branch supplies motor innervation to the dorsal forearm muscles (wrist-digital extensors, digital abductors, and forearm supinator). Motor function can be tested by asking the patient to extend the wrist, thumb, or digits against resistance and comparing the action to the opposite side.

The median nerve (C5-T1 nerve roots) originates from the lateral and medial cords of the brachial plexus and extends along the medial arm, crossing the elbow anteriorly and entering the forearm. It supplies all the anterior forearm muscle, with the exception of the flexor carpi ulnaris and ulnar aspect of the flexor digitorum profundus (fourth and fifth digits). As the nerve passes through the carpal tunnel and extends into the palm, the recurrent median nerve branches off and takes a superficial course along the surface of the thenar eminence, making it susceptible to injury from lacerations (Fig. 43.23; see Figs. 43.14). Recurrent median nerve function is tested by demonstrating thumb opposition—placing the tip of the thumb against the tip of the fifth digit (see Fig. 43.7). The median nerve extends distally and also supplies the index and middle finger lumbricals.

The ulnar nerve (C7-T1) originates from the medial cord of the brachial plexus and extends along the medial arm, crossing the elbow posteriorly to the medial humeral epicondyle before entering the volar forearm. It supplies the flexor carpi ulnaris and ulnar aspect of the flexor digitorum profundus (fourth and fifth

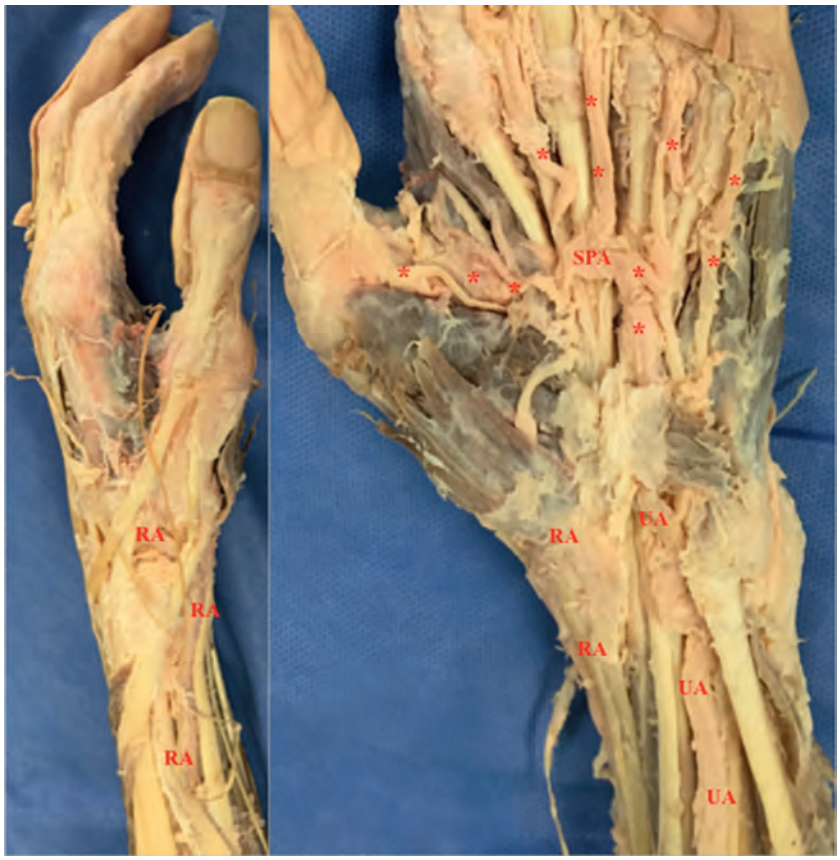


Fig. 43.20. The radial artery (RA) divides at the wrist sending a palmar branch over the palmar carpal ligament. Beyond the base of the thenar eminence it forms the superficial palmar arch (SPA) that contributes digital arteries *(red stars)*. The artery sends a deep branch past the dorsum of the trapezium bone between the radial styloid process and the scaphoid bone, where it emerges within the anatomical snuffbox. It creates a dorsal carpal arch that parallels the extensor retinaculum. A deep branch passes into the palm between the first and second metacarpals to create the deep palmar arch. The ulnar artery's path (UA) enters into the palm by crossing over the flexor retinaculum in a space created by the pisiform bone and the palmar carpal ligament, also known as Guyon's canal. The artery forms a collateral with both the superficial and deep palmar arches. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

digits). The nerve divides into volar and dorsal branches, just proximal to the pisiform bone (Fig. 43.24; see Fig. 43.14). The volar branch joins the ulnar artery at the ulnar tunnel (Guyon's canal) and enters the palm. The nerve supplies the hypothenar eminence, the fourth and fifth digital lumbricals, and interosseus intrinsics. Interosseus adduction is an accurate test of ulnar nerve motor function (see Fig. 43.8).

Sensory Distribution. The peripheral nerve supply to the hand and digits originate from the C5-T1 nerve roots that form the brachial plexus and its median, ulnar, and radial nerves. The terminal nerve patterns are important when examining a condition that appears to be isolated to the hand or digits, although overlap may occur along the borders of the classic distributions. The radial nerve is best tested at the first dorsal web space, median nerve at the fat pad of the index finger, and ulnar nerve at the little finger fat pad (Fig. 43.25).

Nerve damage in the setting of an acute injury may be difficult to assess. Sharp and dull testing results do not correlate well with subsequent findings at surgery; two-point discrimination is the test of choice in evaluating the hand and digits for sensory innervation. Two-point discrimination is not infallible, but consistent discrimination at a threshold distance comparable to the uninjured extremity makes significant nerve disruption unlikely. Significant variation from the uninjured hand, or threshold discrepancies wider than 5 mm on the fingertips, 1 cm on the palm, and 1.5 cm on the dorsum in the clinical context suggests sensory dysfunction. When there is doubt about whether innervation is intact, we recommend reexamination in 24 to 48 hours. Patients with hand injuries and subjective numbness or questionable two-point discrimination should receive an urgent referral and repeat evaluation within 1 week by a hand surgeon so that any nerve injury can be repaired within the required time window.

Fingertip

The fingertip is the portion of distal phalanx beyond the insertion of the flexor and extensor tendon insertions (Fig. 43.26). Adipose and fibrous connective tissue septa create the volar fat pad, containing sensory nerves and vascular collaterals from the digital neurovascular bundles.

Nail

This cornified epithelial plate takes origin from the nail root on the dorsum of the distal phalanx (see Fig. 43.26A and B). The

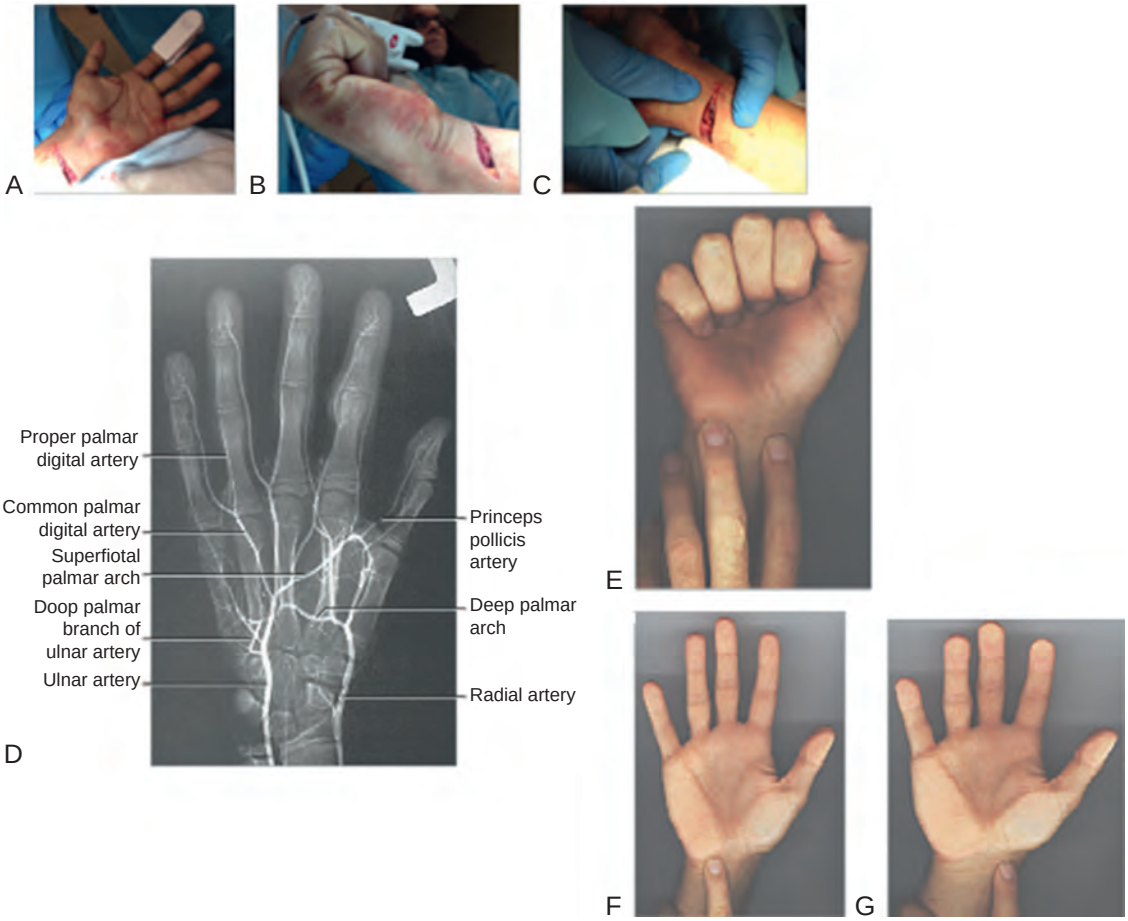


Fig. 43.21. A–C, Wrist and palmar lacerations require an assessment of the arterial circulation. **D,** Arteriogram of the hand. The ulnar artery is the principal contributor to the superficial palmar arch. **E–G,** The Allen test can be used as a rapid assessment of radial and ulnar arterial integrity. **E,** After the examiner identifies the radial and ulnar pulses at the volar wrist, they are compressed, and the patient is asked to open and close the hand until the tissues are blanched from exsanguination. **F,** The examiner then releases one of the arteries, and vascular refill is observed on the volar hand and digital tissue. **G,** The steps are repeated, and vascular refill is observed after the other artery is released. The refill times can be compared to each other as well as to the unaffected hand. (**A–C, E–G** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **D** courtesy Dr. D. Armstrong, Associate Professor of Radiology, University of Toronto, Ontario, Canada.)

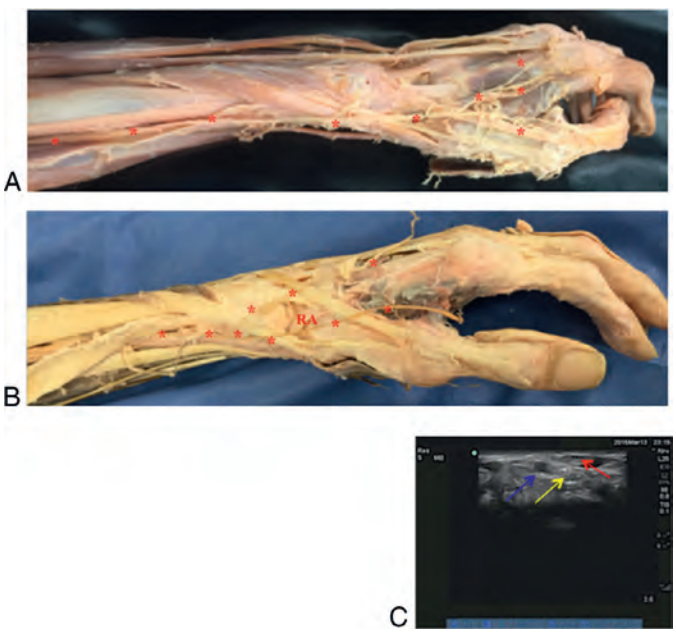


Fig. 43.22. A, B, Radial nerve (superficial branch; *red stars*) sensory distribution on the hand and digits proper is entirely sensory. The nerve emerges from under the brachioradialis tendon, passing over the anatomic snuffbox onto the hand dorsum. Note that the nerve branches several times at and beyond the anatomic snuffbox. The radial artery (RA) is identified within the anatomic snuffbox. **C,** Regional anesthesia of the radial nerve can be accomplished using ultrasound to identify the nerve two fingerbreadths proximal to the radial styloid process (cephalic vein, *blue arrow*; radial nerve, *yellow arrow*; brachioradialis tendon, *red arrow*). Care is taken to avoid injecting local anesthetic into the anatomic snuffbox because the distal RA passes through this area. (**A, B** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **C** courtesy Dr. V. Noble, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

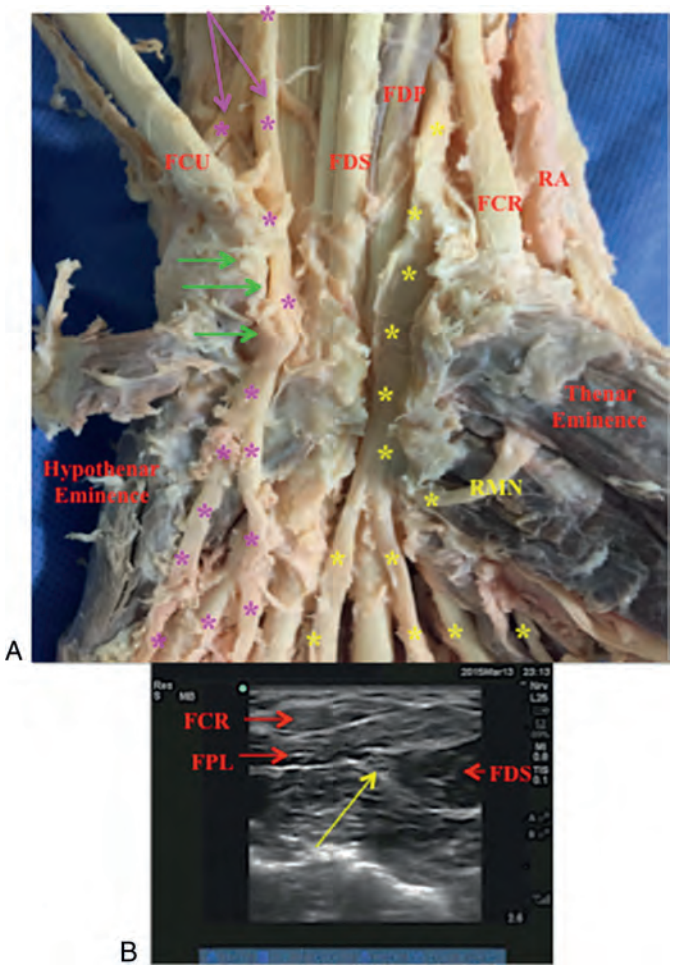


Fig. 43.23. Median nerve (*yellow stars*) passing through the carpal tunnel into the hand palm. Note the superficial location of the recurrent median nerve (RMN) passing over the thenar eminence. Lacerations involving the thenar eminence require testing the integrity of this nerve, specifically through thumb opposition against the fingertips of the adjacent fingers (see Fig. 43.7). **A, B,** Regional anesthesia using ultrasound requires identification of landmarks adjacent to the median nerve. The radial artery pulse (RA), lies just lateral to the flexor carpi radialis (FCR) tendon. The flexor pollicis longus (FPL) tendon lies just posterior to the FCR tendon and just radial to the median nerve. The flexor digitorum superficialis (FDS) tendons are located just medial to the nerve (**B,** *yellow arrow*). The ulnar nerve (*purple stars*) lies just lateral to the flexor carpi ulnaris tendon (FCU) and joins the ulnar artery as it passes through Guyon's canal, anterior to the carpal tunnel and lateral to the pisiform bone (*green arrows*). Note that the ulnar nerve divides proximally to the pisiform bone into dorsal and volar branches (*purple arrows*). (**A** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **B** courtesy Dr. V. Noble, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

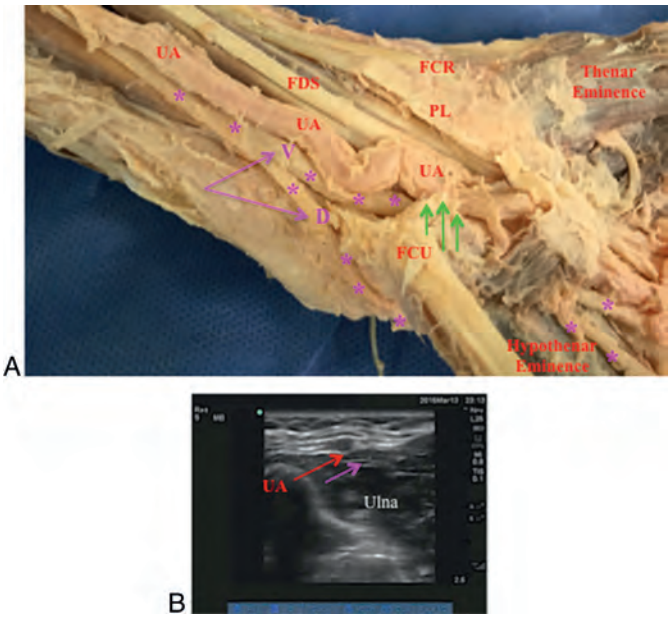


Fig. 43.24. **A,** The ulnar nerve (*purple stars*) travels just beneath the flexor carpi ulnaris (FCU, reflected) and medial to the ulnar artery (UA) in the forearm. It divides into a volar and dorsal branch (*purple arrows*, V and D) just proximal to the pisiform bone. The volar branch joins the UA at the ulnar tunnel (Guyon's canal; *green arrows*) and enters the palm. The nerve supplies the hypothenar eminence, dorsal branch the fourth and fifth digital lumbricals, and interosseus intrinsics. **B,** Ultrasound image of the ulnar nerve (*purple arrow*) lying just medial to the UA (*red arrow*) just proximal to the ulna. (**A** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **B** courtesy Dr. V. Noble, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

Fig. 43.25. Terminal nerve sensory distribution in the hand and digits. Overlap may occur along the borders of the classic distribution of terminal nerve sensation. Sensory distribution is shown by colors: median nerve *(blue)*, ulnar nerve *(purple)*, radial nerve *(red)*. *Yellow stars* indicate the best location within the distribution to test each terminal nerve exclusively. Index fingertip (median), little fingertip (ulnar) hand dorsum fist webspace (radial). (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

proximal nail fold extends out over the proximal ends of the nail plate to form the eponychium (cuticle), perionychium (sides), and distal hyponychium. The nail plate, normally pink due to its highly vascularized matrix below, has a proximal white semicircular line called the lunula. The nail plate appears blue with peripheral vasoconstriction or cyanotic conditions. The entire length of the nail bed contributes to the growth and migration of the nail plate, approximately 0.5 to 1.2 mm/wk. If the nail bed is not repaired adequately, scarring will cause abnormal nail plate growth that can result in an irregular, split, or absent nail, which can be disfiguring.

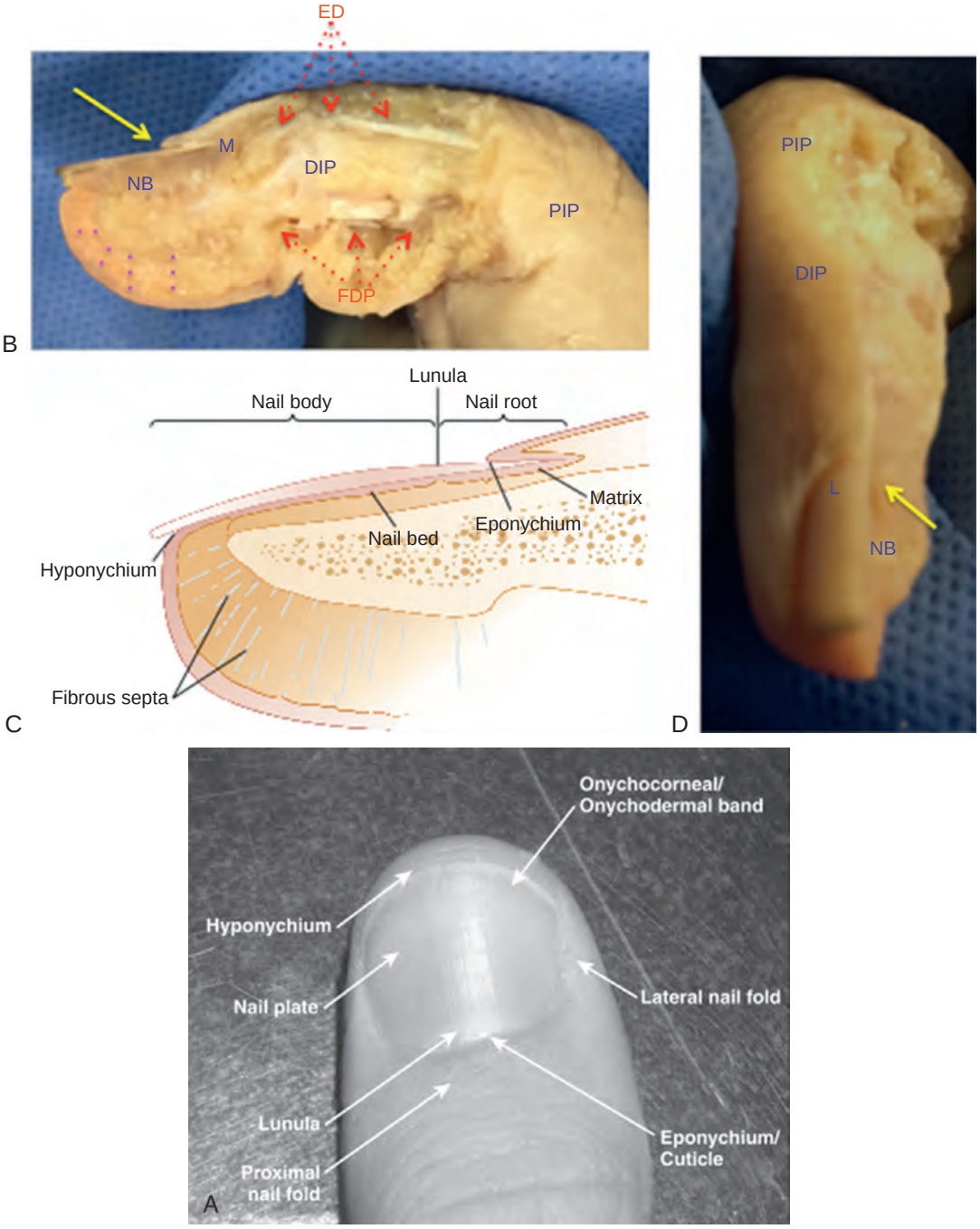


Fig. 43.26. **A,** Surface anatomy of the nail. **B–D,** The fingertip. **B,** The fingertip consists of soft tissues beyond to the flexor and extensor tendon insertions on the distal phalanx. The nail consists of specialized epithelium containing keratin, extending over the dorsum of the phalanx. The nail root is covered by the proximal nail fold, which extends out over the proximal ends of the nail plate to form the eponychium and cuticle (*yellow arrow*), the sides with perionychium, and the distal end, the hyponychium (**C**). The nail plate grows distally from the nail matrix (M) and the nail bed (**B** to **D**, approximately 0.5–1.2 mm/wk). **C**, The plate's lunula (L) is a white semicircular line just distal to the nail fold. **(A** from Bope ET, Kellerman RD, editors: Diseases of the skin. In Conn's current therapy 2015, Elsevier. pp 219–320, © 2015; **B, D** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **C** from Siegel DB, Gelberman RH: Infections of the hand. Orthop Clin North Am 19:779–789, 1988.)

CLINICAL FEATURES

Providers should note patient age, hand dominance, occupation, medical conditions, previous hand ailments, medications, allergies, and tetanus immunization status. Identify the location of pain, swelling, discoloration, timing of onset of symptoms and their progression, aggravating and alleviating factors, current resultant functional disability, and previous history of similar symptoms and interventions. In cases of trauma, important information includes accurate time and circumstances surrounding the incident, mechanism, symptom progression, hand positioning at the time of injury, and any treatments prior to the

current evaluation. With amputation, elapsed time since the incident, and the location and care of the amputated part, are important factors.

The upper extremity, at least from the elbow down, should be examined to avoid concurrent or associated proximal conditions (Box 43.2). Evaluation should include a thorough assessment of vascular integrity, skin integrity, and neurologic function, followed by skeletal and joint stability and musculotendinous function. Tendinous injury or bony deformities may not be evident until the area is examined throughout its range of motion. Digital or regional anesthesia may be necessary to assess for fracture stability, reduction, and stabilization adequately.

Assessment of open wounds requires knowledge of adjacent and underlying at-risk neurovascular, musculotendinous, and joint relationships. The emergency clinician will need adequate lighting, hemostasis, and the ability to compare tissues to the unaffected side. Wound length, depth, avulsion and tissue loss, flap viability, and contamination are should be considered when developing a management strategy.

BOX 43.2

General Physical Examination of the Hand

I. GENERAL APPEARANCE
A. Active hemorrhage
B. Amputations or avulsions
C. Position at rest

II. SKIN
A. Integrity
B. Moisture
C. Swelling (edema, hematoma?)
D. Discoloration
E. Inflammation
F. Scars

III. VASCULAR
A. Color and warmth
B. Pulses
C. Capillary refill
D. Allen test

IV. NEUROLOGIC
A. Motor function
   1. Ulnar nerve—finger abduction and adduction
   2. Radial nerve—wrist extension
   3. Median nerve—flexion of digits 1, 2, and 3; thumb opposition
B. Sensory function
   1. Ulnar nerve—volar tip of digit 5
   2. Median nerve—volar tip of digit 2
   3. Radial nerve—dorsum, first web space

V. BONE AND JOINT
A. Deformity
B. Local tenderness to palpation, passive range of motion
C. Tenderness with axial compression
D. Joint range of motion
E. Ligamentous stability—distal interphalangeal, proximal interphalangeal, and metacarpophalangeal joints

VI. MUSCULOTENDINOUS
A. Function of each muscle-tendon group
B. Strength against resistance
C. Tenderness with active motion

DIAGNOSTIC TESTING

Plain films are the most common and useful tools in the assessment of traumatic bony injury. In addition to posteroanterior, lateral. and oblique views, additional special views are used when seeking specific injuries. X-rays are obtained before and after closed fracture or joint reduction maneuvers.

Lacerations and puncture wounds with suspected retained foreign bodies, such as glass or metal, can be imaged with conventional radiography. Radiopaque materials are best seen with multiview plain films. Less dense materials such as plastics or wood may not be seen on plain radiographs and are best evaluated with bedside ultrasound. However, emergency ultrasound may fail to identify foreign bodies smaller than 3 mm.[3]

Computed tomography (CT) does not usually add significant information to conventional radiography in the trauma setting. CT scanning can show high resolution of the bony structures of the hand, but provides limited information regarding soft tissues such as muscles, tendons, and ligaments. CT may be helpful in the settings of complex, comminuted, or intraarticular fractures as well as highly suspicious clinical scenarios with the absence of fracture on plain films.

Magnetic resonance imaging (MRI) is rarely used in the evaluation of acute hand trauma. It provides visualization of soft tissues, including muscles tendons and ligaments, as well as the vascular system. It may be recommended as a follow-up modality to assess the carpal region and thumb more accurately when clinical suspicion is high for a complex avulsion fracture or ligamentous disruption.

MANAGEMENT OF SPECIFIC INJURIES

Traumatic Injuries

Due to the concentrated anatomy, a single mechanism of trauma can compromise multiple tissues. Lacerations (>50% of injuries) are the most common, followed by fractures (≈10%). Prehospital management of hand injuries should focus on control of hemorrhage and pain control via splinting or analgesia. Amputated parts should be gently irrigated if contaminated and placed in a clean, dry, waterproof container on ice during transport.

Fingertip Injuries

The fingertip accounts for over 60% of hand injuries in children and 10% of job-related injuries. Fractures and soft tissue injuries occur with crush mechanisms, and shearing injuries can cause lacerations, tissue avulsions, and complex defects. Burns and frostbite can result in permanent tissue loss. Management goals of preserving neurovascularity and digital length will optimize function and recovery.

Acute Nail Bed Injuries

Approximately 50% of perionychial crush injuries result in distal phalangeal or tuft fractures. Radiographs should be obtained when bone involvement is suspected. Shearing forces can result in a concurrent laceration or significant tissue loss.

Subungual Hematoma. Nail bed compression may result in local hemorrhage contained between the nail folds and nail, causing a minimally swollen but highly pressurized, painful, and tender hematoma (Fig. 43.27). DIP extensor tendon function should be assessed and radiographs obtained for unstable fingertips. Trephination reduces pain, but does not hasten healing or alter infection risk, so it is generally used for large hematomas extending over more than 50% of the nail. Trephination is

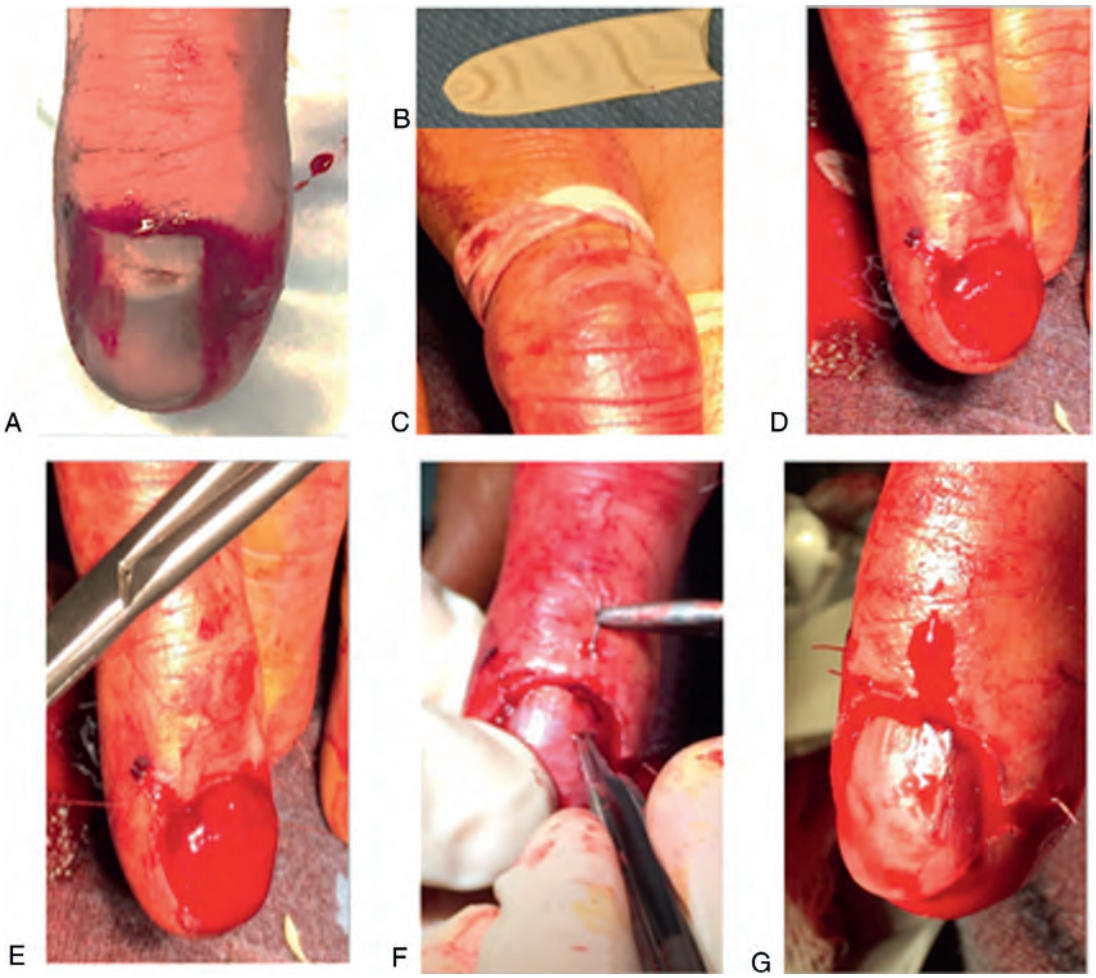


Fig. 43.27. Nail bed repair. **A,** Subungual hematomas with nail disruptions or skin fold lacerations generally require nail removal to repair concurrent eponychial laceration. **B, C**, The finger of a surgical glove can be used as a tourniquet after the tip has been removed. It can be rolled over the digit to secure hemostasis, as shown. **D,** Nail has been removed exposing eponychial laceration. **E,** Primary repair using interrupted 5-0 or 6-0 absorbable sutures. **F, G,** Nail is replaced into the nail fold and secured using sutures. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

accomplished using a heated, blunt-tipped needle device or disposable electrocautery unit to sear a hole through the nail, ensuring that pressure is light so that contact with the nail bed does not ensue. Multiple holes may be necessary to ensure adequate drainage. Alternatively, a hole can be drilled through the nail by the emergency clinician, who holds an 18-gauge needle by the hub, between the thumb and index finger, twirling it on its long axis rapidly and alternating direction. The bevel of the needle will drill a hole in the nail, avoiding the need for heat and the expense of electrocautery. Acrylic nails are potentially flammable and cautery is contraindicated. Concurrent distal phalangeal or ungual tuft fractures do not result in a difference in complications.

Traumatic subungual hematomas with nail disruptions or skin fold lacerations may have concurrent eponychial lacerations. Hematomas involving more than half the nail size have a 60% incidence of concurrent nail bed laceration, which increases to 95% if there is a distal phalanx fracture. When the nail and nail margins are intact, there is no significant difference in outcomes between nail trephination alone and formal nail bed repair, regardless of hematoma size. As a result, nail removal and repair of the nail bed is recommended only if the nail is broken or the nail edges are disrupted. Although the use of prophylactic antibiotics for open distal phalangeal fractures is controversial, we recommend managing grossly contaminated wounds or injuries in high-risk patients (eg, those who are immunocompromised) with Cephalexin 250 mg qid or 500 mg bid (pediatric 25 to 50 mg/kg per day in 2 to 4 divided doses) for 3 to 5 days or until hand surgery follow-up. Clindamycin 300 mg tid (pediatric 8 to 12 mg/kg/day PO divided into 3 or 4 equal doses) may be used for penicillin-allergic patients. For patients not meeting these criteria, advice regarding signs of infection, combined with reevaluation in 72 hours and beyond, as needed, suffices. The nail may be lost but should regenerate with an intact germinal matrix.

Nail Bed Lacerations. Repair of nail bed lacerations is also controversial (see Fig. 43.27). Nail removal for eponychium repair is unnecessary except with significant disruption of the nail, skin folds, gross contamination, or when the eponychium–nail matrix area is involved. Primary repair using 5-0 or 6-0 absorbable sutures minimizes subsequent nail deformity and reduces functional disability. Late reapproximation yields unpredictable results (see Fig. 43.27). The original nail can be used to splint and protect the healing eponychium, replaced into the nail fold and secured using sutures or tape. Nonadherent gauze may be substituted if the nail cannot be used.

Nail bed avulsions may result in cleavage of eponychium from the bed onto the underside of the avulsed nail. Small defects (<25%) may still heal secondarily on their own, whereas larger

defects are best managed by securing the nail onto the original avulsion site using through and through sutures at the edges.

Foreign Bodies in the Hand

Depending on their cause, penetrating wounds often have retained foreign bodies. A detailed history of how the injury occurred will help identify the likelihood of a foreign body. Wood splinters, in particular, are notorious for breaking off during the penetration or removal attempts. Penetration or laceration by broken glass similarly has a high incidence of a retained foreign body. Other materials include metal, sand particles, and organic materials, such as soil, grease, or paint. Suspicious clinical clues include sharp localized tenderness with wound palpation or manipulation, a palpable mass, or persistent draining wounds.

Radiographs and bedside ultrasound are useful for locating foreign material. However, small objects (<3 mm diameter) are difficult to detect by either modality. If there is strong suspicion of a foreign body despite negative plain films, and the wound is not amenable to exploration, a CT or MRI scan is obtained. MRI should not be used if the foreign body is metallic. Imaging is not required if the suspicion for retained foreign body is low, and plain radiographs and bedside ultrasound are negative. Similarly, further imaging is not required if the entire length and depth of the tissue defect can be visualized. When suspicion is low for a foreign body and advanced imaging is not performed, the patient is advised regarding follow-up for persistent pain, poor wound healing, or signs of infection within the first 7 days of injury.

In general, foreign bodies in the hand are best managed by removal in the emergency department (ED) or in the operating room. The exception is very small (≤3 mm) foreign bodies of an inert material (eg, glass, metal) that located where their continued presence likely carries a smaller risk of long-term problems than the tissue disruption from the removal procedure. Objects not requiring removal include small, inert foreign bodies not in close proximity to a joint, tendon, nerve, or vessel, objects that are unlikely to migrate into vital structures or the circulation, and those without tenderness on examination. The emergency clinician should explain to the patient why the dangers of removal outweigh the benefits. Indications for removal of foreign bodies include pain and tenderness limiting function, risk of systemic toxicity (eg, from lead), risk of infection, including deep space infection (eg, from wood, soil, contaminated material), and immediate risk to adjacent vital structures. Foreign bodies related to marine envenomation are discussed in Chapter 55. A superficial object that can be identified by gentle probing (eg, with a hemostat) or seen with minor exploration is removed in the ED. Deep wounds at risk for concurrent tendon, neurovascular, or joint injury will require hand surgery consultation for removal in the operating room (Box 43.3).

If the foreign body is small, not strategically located, and noncontaminated, and therefore does not require immediate removal, referral to a hand surgeon within 72 hours for further evaluation and possible delayed exploration is advised. The patient should be informed of the specific follow-up arrangements and indications for immediate return to the ED. If there is minimal or no evidence of concurrent contamination, the wound can be irrigated and closed primarily. As with other wounds, tetanus prophylaxis is administered following Centers for Disease Control and Prevention guidelines (see Chapter 52.) There is no high-quality evidence that antibiotic administration reduces infection in those in whom a foreign body is retained or has been removed. We recommend daily wound checks for 3 days to ensure that there is no evolving infection. If infection occurs, treatment consists of Cephalexin 250 mg qid or 500 mg bid (pediatric 25 to 50 mg/kg per day in 2 to 4 divided doses) for 7 days or until hand surgery follow-up. Clindamycin 300 mg tid (pediatric 8 to 12 mg/kg/day PO divided into 3 or 4 equal doses) may be used for penicillin-allergic patients.

BOX 43.3

Indications for Hand Service Consultation for Removal of Foreign Body in the Operating Room

- Large or multiple foreign bodies
- Evidence of tendon or neurovascular injury
- Penetration of deep space of the hand, including deep palmar, thenar, and hypothenar space
- Suspected joint penetration
- Presence of fracture or bone penetration
- Highly contaminated wound
- Immune compromised patient
- Lead foreign body
- Liquid foreign body (eg, paint)

Hand Fractures

Principles

The bones of the hand are the most commonly fractured bones in the entire body. The mechanism of injury often determines the nature of the fracture; direct blunt trauma is more likely to cause a transverse or comminuted fracture, whereas a twisting mechanism or axial loading is more likely to result in an oblique or spiral fracture. Associated injuries may include nerve, vascular, tendinous, and ligamentous injuries. Hand fractures are classified according to site and type of fracture, alignment, and whether the fracture is closed or open.

Transverse fractures are stable, although spiral, oblique, and comminuted fractures and fractures associated with dislocations are considered unstable. Most closed injuries can be managed in the ED with appropriate splinting, but unstable, open, intraarticular, and periarticular fractures usually require operative management. Reduction and splinting of fractures and dislocations is an essential management principal (Fig. 43.28). The duration of splinting should be no longer than necessary to avoid loss of mobility and flexibility. In general, splinting is done with the hand in the universal safe or functional position. In this position, the wrist is extended 15 to 30 degrees, the thumb is extended and abducted, with the other fingers in a relaxed positon of 60 degrees of flexion at the MCP, and minimal flexion (5–10 degrees) at the PIP and DIP joints. This position minimizes shortening of tendons and ligaments, and thus stiffness, during the splinting duration.

Clinical Features

Distal Phalanx Fractures. Fractures of the distal phalanx are the most common fractures of the hand and are frequently complicated by nail injuries. Fractures may be to the tuft, shaft, or base. Distal and tuft fractures can be quite painful because of soft tissue swelling in the highly innervated finger pad.

Fractures at the base of the distal phalanx often are caused by tendon avulsion. Avulsion injuries can be diagnosed clinically by local tenderness over the avulsion site and the inability to move the joint actively. Avulsion fractures are easily identifiable on plain radiographs.

Management. Tuft fractures heal without incident. Most distal phalangeal fractures are stable and nondisplaced and can be managed conservatively with elevation, analgesia, wound care for

Fig. 43.28. Hand—digital splints. A forearm volar cockup splint in resting, functional position is considered for temporary immobilization of soft tissue injuries, including tendon and neurovascular tissues, as well as minimally displaced metacarpal fracture. A dorsal slab may be added for improved stability. The wrist joint will remain capable of pronation and supination; hence, additional immobilization should be considered for concurrent injury. A Burkhalter splint includes a volar slab immobilizing the wrist at 30 degrees of extension and a dorsal slab crossing the metacarpophalangeal (MCP) joint to ensure 90 degrees of MCP flexion, allowing for improved stabilization and alignment of metacarpal fractures and MCP joint dislocations. A forearm sugar tong splint should be added when concurrent wrist injuries exist and the risk of a pronation-supination motion may create further complications. Thumb spica splint immobilization is indicated with the risk of a distal radius, scaphoid-first metacarpal and first MCP joint injury; splint immobilization includes 30 degrees of wrist extension and resting position of the first MCP. The thumb distal interphalangeal (DIP) joint is open and allowed to maintain opposition. An ulnar gutter is considered for minimally displaced fourth and fifth metacarpal joint, MCP joint, and proximal and middle phalangeal injuries. The wrist is immobilized in extension, with the digits in resting, intrinsic-plus positioning. Digital splinting is considered for stable stable middle distal phalangeal fractures and proximal interphalangeal (PIP) joint strains. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

soft tissue injuries (if present), and splinting. Nondisplaced distal phalangeal shaft fractures may be splinted in extension, using a simple distal phalangeal joint splint (leaving the PIP joint fully mobile) for 2 to 3 weeks for protection and comfort. Fractures with angulation, rotation, or displacement may require closed reduction under digital or metacarpal nerve block anesthesia, followed by volar splinting. Irreducible and open fractures require hand surgery consultation.

Avulsion-type fractures are managed like other closed tendon injuries, with splinting to reduce the tension on the fracture and referral to a hand surgeon for possible repair. Flexor tendon avulsion fractures (ie, the so-called Jersey finger because of the association with tackling sports) involving the flexor digitorum profundus require surgical repair. *Mallet finger* is the term applied to extensor avulsion fractures, but also may be caused by distal extensor tendon ruptures (Fig. 43.29). The injuries are be splinted in full extension (typically, 0–10 degrees extension) at the DIP joint for 6 to 8 weeks, followed by part-time splinting for an additional 4 to 6 weeks. We recommend hand surgery consultation within 7 days because some of these injuries require surgery

Fig. 43.29. Mallet finger—avulsion fracture involving the extensor tendon insertion on the proximal distal phalanx. **A, B,** A common mechanism is forced distal interphalangeal (DIP) joint flexion during active extension. Clinical characteristics include local tenderness and inability to extend the DIP joint actively. Plain films are used to identify the fracture. **C**, The true lateral image is most likely to reveal the fracture, a triangular avulsion fragment at the extensor aspect of the distal phalanx at the DIP (*arrow*). (Courtesy Dr. L. Avery, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston.)

and close supervision of the full-time splinting (eg, including during sleep, bathing) is necessary to ensure healing.

A Seymour-type metaphyseal fracture between the extensor tendon insertion dorsally and FDP tendon insertion volarly may be confused with a mallet finger. It is more common in the pediatric population when the physeal region may be weaker than the tendon insertion. No tendon injury is present, but the fracture causes an imbalance between the flexor and extensor forces. This will cause a flexion deformity at the level of the DIP and may be associated with a proximal nail avulsion. X-rays can help differentiate this fracture pattern from an avulsion injury. Seymour fracture management is controversial and requires consultation with a hand surgeon.

Complications. Distal phalanx and tuft fractures may be complicated by subungual hematoma or nail bed lacerations, and long-term nonunion, numbness, hyperesthesia, or chronic pain may ensue. Trauma to the nail bed may result in abnormal nail growth indefinitely.

Middle and Proximal Phalangeal Fractures. The middle phalanx has two important tendon insertion sites, the flexor digitorum superficialis, which divides and inserts along much of the volar surface of the phalanx, and the extensor tendon, which inserts on the proximal portion of the dorsal base (see Figs. 43.13, 43.15, and 43.17). Therefore, fractures at the neck of the middle phalanx usually result in volar angulation, whereas fractures of the base of the middle phalanx usually result in dorsal angulation.

Proximal phalangeal fractures typically have volar angulation due to extensor and interosseus muscle function. Hinge IP joint intraarticular fractures involving the condyles, base, or shaft are difficult to discern on AP radiographs and may require oblique views.

Fracture alignment may be assessed clinically by comparing the injured digit to the unaffected hand or adjacent normal fingers at rest and with motion of the MCP and PIP joints. Normally, when the fingers are loosely flexed, the nails of the digits should lie in the same parallel plane (Fig. 43.30), and all the fingers of a gently closed fist (except the thumb) should point to the scaphoid and radial styloid process.

Management. ED management includes appropriate analgesia, fracture reduction when necessary, splinting, and consultation with a hand surgeon, as needed.

Phalangeal fractures need precise anatomic alignment for good results. However, most fractures are nondisplaced and can be managed with dynamic splinting by "buddy-taping" to an adjacent finger for early protected motion (see Fig. 43.28). This allows for fracture healing and reduced stiffness. Management of unstable or displaced fractures depends on the ability to obtain closed reduction and anatomic alignment. Reducible fractures can be immobilized with gutter or anteroposterior (Burkhalter) splints. Spiral, oblique, comminuted, intraarticular, and nonreducible fractures should have a hand service consultation for possible open reduction and fixation.

Complications. Malunion, malrotation, and proximal phalangeal volar angulation may occur, requiring hand specialist consultation and referral for definitive operative management.

Metacarpal Fractures. Metacarpal fractures are common, representing one-third to one-half of all hand fractures.[4] Most injuries occur in male patients who have sustained the injury from punching with the dominant hand in a clenched fist. Falls are the most common mechanism for patients younger than 9 and older than 50 years. Important information for definitive management includes mechanism of injury, open versus closed condition, fracture stability, and reducibility.

Due to the need for functional mobility, the thumb, index, and middle fingers have little tolerance for deformity as compared to the ring and little fingers. Carpometacarpal (CMC) joint range of motion decreases across the cascade of digits from the thumb to little finger. The thumb, index, and middle fingers can accommodate far less degree of dorsal angulation (10–15 degrees) and still retain adequate function when fractured compared to the ring (40–45 degrees) and fifth digit (50–70 degrees). Rotational deformities are poorly tolerated by all digits. Except for simple boxer's fractures (see below), all metacarpal fractures should receive consultation or referral to a hand surgeon as part of the management plan.

Metacarpal Fractures of the Index, Middle, Ring, and Little Fingers. Examination may reveal local swelling, bony

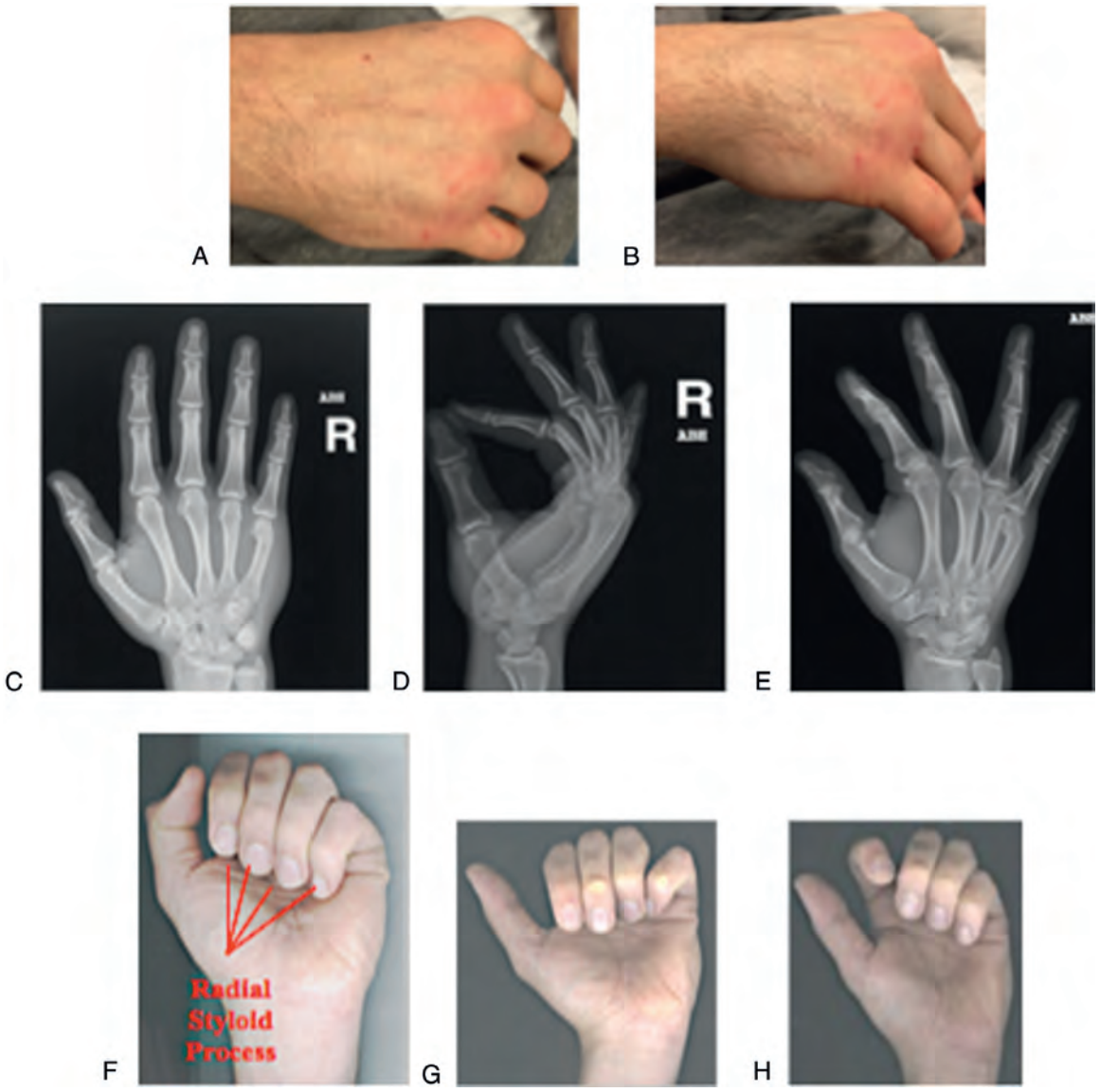


Fig. 43.30. Boxer's fracture. **A, B,** This patient arrived complaining of pain and swelling over his fourth and fifth digits hand after striking a concrete wall. The wounds should be carefully inspected for evidence of full thickness violation. Tetanus status should be assessed and updated as necessary. **C–E,** Radiographs reveal a fracture of the distal fifth metacarpal bone. It is important to assess for intraarticular involvement, comminution, location along the shaft of the metacarpal, associated joint dislocations, degree of angulation, and presence of rotation. AP, lateral, and oblique views are necessary. **F,** The patient may be unwilling to be examined until after analgesia is provided. A hematoma block or regional ulnar nerve block using a local anesthetic may assist with digital motion. When making a fist, the fingers should flex in alignment, with each knuckle adjacent to one another and each fingertip pointing toward the radial styloid process. Volar angulation of the distal metacarpal fragment will cause the DIP and PIP joints to be angled forward relative to the adjacent digits. **G, H,** Rotation of the distal metacarpal fragment will cause the affected digit to overlap or misalign, with the tip no longer pointing toward the radial styloid. (**A, B, F–H,** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **C–E,** courtesy Dr. L. Avery, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston.)

deformity, and tenderness to palpation or axial compression. Suspicious dorsal wounds should be considered as being caused by a fight bite and managed accordingly. Fourth and fifth metacarpal fractures may injure the ulnar nerve, causing intrinsic hand muscle weakness and digital numbness. Plain radiographs will reveal most fractures. CT imaging can assess displacement of intraarticular fractures.

The metacarpal neck is the most common fracture location, typically incurred from direct impaction resulting in dorsal angulation. A so-called boxer's fracture—metacarpal neck fracture of the fifth digit—is the most common type (see Fig. 43.30). The physical examination commonly reveals tenderness, with or without deformity. Metacarpal shaft fractures, usually from axial trauma, may be transverse or comminuted and cause dorsal angulation. Oblique and spiral fractures usually result from rotational torque and tend to shorten or rotate the digit (see Fig. 43.30). Less common injuries include the metacarpal head, caused by direct blunt trauma or crush injury, and metacarpal base, caused by torsion and associated with carpal bone injuries.

Management. Management of most stable, nondisplaced metacarpal fractures consists of reduction and splinting in the intrinsic-plus position, with the wrist extended 30 degrees, the

MCP joint flexed to 90 degrees with the PIP and DIP joints kept in extension (see Fig. 43.28). Postreduction radiographs should be obtained to ensure successful positioning, and follow-up arrangements with a hand surgeon should be made. Hand service consultation is recommended for irreducible, unstable, open, intraarticular fractures and any metacarpal rotational deformity.

Metacarpal base fractures commonly involve the carpal-metacarpal articulation, resulting in an intraarticular fracture or joint displacement. Because they frequently remain angulated and displaced with closed reduction alone, we recommend referral for definitive operative management by a hand surgeon.

Metacarpal shaft fractures may be reduced after adequate anesthesia with a hematoma or regional block. Goals of treatment include, less than 3 mm of metacarpal shortening, less than 10 degrees dorsal angulation for the index and middle fingers, less than 20 degrees for the ring and little fingers and elimination of a shaft rotational deformity. The 90-90 reduction method includes having the MCP, PIP, and DIP joints flexed to 90 degrees and application of dorsal pressure over the fracture, with immobilization in the intrinsic-plus position (see above). However, if reduction of dorsal angulation cannot be obtained, proper metacarpal length is not maintained, or digital malrotation is present, operative stabilization is necessary.

Metacarpal neck fractures, including the boxer's fracture, are commonly managed nonoperatively. Reduction goals for displaced metacarpal neck fractures is controversial. Consensus is that there should be less than a 15-degree angulation for the index or middle finger, up to 35 degrees for the ring finger, and 45 degrees for the fifth digit (acceptable ranges of 20–70 degrees from the second to fifth digits have been quoted). These fractures may be reduced using the 90-90 method with intrinsic-plus splint positioning. Malrotation and persistent angulation, despite reduction attempts are indications, for surgical intervention.

Metacarpal head fractures may be intraarticular and comminuted, with a high risk of fracture displacement and malrotation. These are best managed using instrinsic-plus or gutter splint immobilization and immediate hand service referral for operative repair.

Lacerations or puncture wounds over the MCP joint associated with fractures should be considered open and highly contaminated, requiring antibiotics and consultation with a hand surgeon for consideration of operative débridement, irrigation, and reduction.

Complications. Avascular necrosis, nonunion, misalignment, interosseous muscle or tendon injury or fibrosis, and chronic stiffness may occur. Patients with fractures of the metacarpal head and neck have been shown to have higher rates of violent behavior, anxiety, and personality disorders and are at risk for recurrent injury. Prevention strategies and/or psychiatric screening should be considered.

Metacarpal Fractures of the Thumb. Due to increased digital mobility, thumb metacarpal fractures are less common than finger metacarpals. Most fractures involve the base and are classified as extraarticular or intraarticular. Extraarticular fractures are more common and usually result from direct trauma or impaction. They may be transverse, oblique, and epiphyseal (in children). Examination may reveal thenar eminence swelling and ecchymosis. Transverse fractures are usually stable and can be managed with closed reduction and immobilization. Fractures of more than 30 degrees of angulation should undergo closed reduction and immobilized in abduction, with the IP joint extended in a thumb spica splint. Oblique extraarticular fractures are generally unstable, requiring hand service consultation for open reduction and fixation.

Bennett and Rolando fractures are two intraarticular fractures of the thumb base resulting from an axial force acting on a partially flexed metacarpal (Fig. 43.31). The more common Bennett fracture involves an intraarticular metacarpal base fracture combined with first CMC ligamentous disruption, causing dislocation or subluxation of the distal metacarpal shaft. The larger fragment is subluxed dorsally by the force of the abductor pollicis longus muscle, whereas the ulnar portion remains in place. Management includes reduction of the fracture dislocation and immobilization in a thumb spica splint, with outpatient hand service follow-up.

In a Rolando fracture, the thumb metacarpal is comminute, and thus carries a worse prognosis than the Bennett fracture. Although at times difficult to see on plain films, the classic radiographic Y- or T-shaped pattern is a typical configuration of comminution. Management includes thumb spica splint immobilization and hand service consultation for early follow up. Definitive treatment is controversial and depends on the severity of comminution at the base of the thumb and degree of displacement. Malunion is the most common late complication of metacarpal thumb fractures, followed by posttraumatic arthritis. Nonunion is rare.

Soft Tissue Injuries

Soft tissue injuries of the hand can result in disabling musculotendinous, neurovascular, and joint compromise, local and deep space infection, and retained foreign bodies. Standard principles of wound management including irrigation, exploration, removal of foreign material, débridement when necessary, consideration of primary versus delayed closure, and appropriate antibiotic prophylaxis. Closure of skin defects should be based on injury mechanism, wound age, size and location, degree of contamination, functional implications, and patient comorbidity.

High-risk injuries that should receive antibiotic prophylaxis include bites, puncture or avulsion wounds (with or without musculotendinous injury), injuries that penetrate a joint, bony or neurovascular involvement, and wounds with contaminated or devitalized tissue. Immunodeficiency (eg, diabetes mellitus) should also direct therapy. When clinically indicated, tetanus and rabies prophylaxis should be provided (see Chapters 52 and 123).

Dislocations and Ligamentous Injuries

Principles

Injured dorsal, collateral, or volar plate ligaments may be focally tender when palpated. Ligamentous injuries are classified as stretching with small tears (grade I), incomplete partial tears (grade II), or complete tears (grade III). With incomplete joint dislocation (ie, subluxation), the articular surfaces are only partially separated. A dislocation is complete when articular surfaces are completely separated.

Accurate assessment of joint stability includes testing passive and active ranges of motion. After a neurologic assessment, local or regional anesthesia may be needed to assist with the examination, because testing motor function may be limited by pain. The affected joint should be examined using passive range of motion to assess for stability. Full range assessment on the affected joint should include radial–ulnar and dorsal–volar stress in an extended and semi-flexed joint position to evaluate collateral and volar plate stability, respectively. Active stability can be evaluated by asking the patient to range the affected joint. Limitation of full range of motion or joint displacement suggests instability. The joint can be compared to that of the adjacent digit, as well as that of the unaffected hand. Plain and stress radiographs of the joint may confirm instability.

Adjacent soft tissues in grades I and II partial ligamentous injuries are commonly swollen, yet the joint remains stable with stressing, passive, and active motion. Stable joints are less likely to require surgical repair. Grade III complete ligamentous injuries

Fig. 43.31. First metacarpal base fractures. **A, B,** Bennett fracture (1882), an oblique intraarticular fracture of the base of the first metacarpal. A triangular-shaped fragment rests at the medial (ulnar) base of the metacarpal, held in place by multiple ligaments between the fragment and trapezium; the remaining metacarpal bone is displaced dorsally and laterally (radially) from the abductor pollicis muscle. **C, D,** Rolando fracture (1910), a comminuted intraarticular fracture of the first metacarpal base involving at least three fragments, typically forming a Y or T configuration. **D,** Comminuted intraarticular fracture, a worse prognosis than a Bennett fracture. This requires prompt immobilization and referral for best outcome. (Courtesy of Dr. L. Avery, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston.)

will be unstable during ranging and exhibit wide displacement on stress testing.

Interphalangeal Joint Injuries

Distal Interphalangeal Joint

Collateral and volar ligaments, as well as the flexor and extensor tendons, stabilize the DIP joint. For this reason, DIP dislocations about this joint are less common, often associated with open wounds. Prior to joint reduction, radiographs should be obtained to identify intraarticular or avulsion injuries. Local or regional anesthesia may be required. Dorsal pressure, combined with longitudinal and hyperextended traction, should be used to secure the joint, followed by splinting in the functional position. Avulsion fractures, volar plate tears, or tendon entrapment may prevent reduction and require operative repair. Open dislocations are managed with wound care, skin closure, splint immobilization, prophylactic antibiotics, and hand service referral.

Proximal Interphalangeal Joint

The proximal interphalangeal (PIP) joint is the most common joint dislocated in the hand. Although the extensor central slip provides additional dorsal stability as it inserts on the base of the middle phalanx, loading mechanisms may cause complete disruption of more than one ligament, resulting in middle phalangeal dislocation.

PIP dislocations are named for the direction of displacement of the middle phalanx. Dorsal dislocations without fracture, caused by hyperextension, are the most common. A volar plate fracture at the base of the middle phalanx may also occur (Fig. 43.32). Fractures involving more than 50% of the joint surface are unstable and often require surgical repair. Lateral radial or ulnar forces may rupture collateral volar ligaments, with a sixfold greater incidence of radial collateral rupture resulting in ulnar deviated dislocations. Rotational longitudinal compression of the middle phalanx may result in volar plate and collateral disruption. Such volar dislocations are uncommon, difficult to reduce, and may be

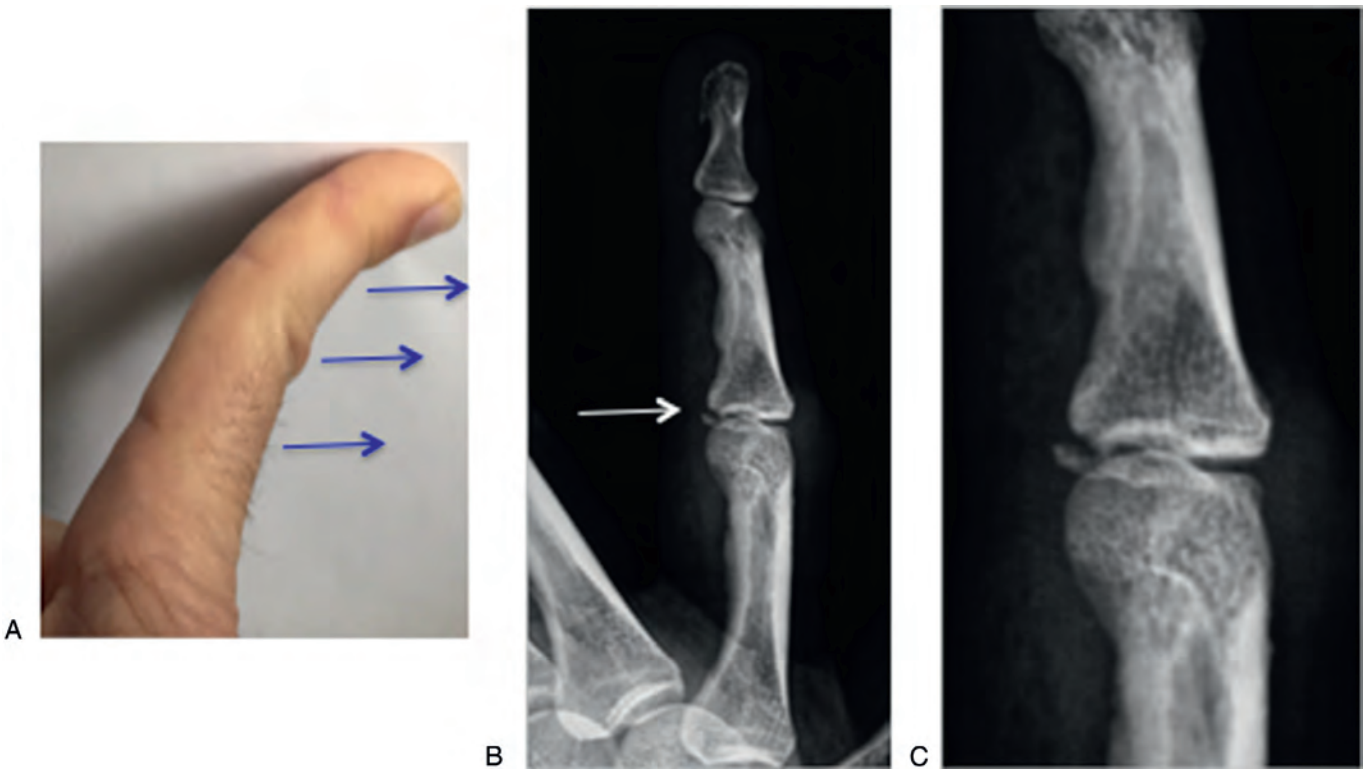


Fig. 43.32. Volar plate fracture. **A,** Axial loading can cause forced hyperextension of the proximal interphalangeal (PIP) joint (*arrows*) and create an avulsion fracture of the volar phalanx (**B,** *arrow*). **C**, Lateral radiographs can best identify the injury. When these ligaments are immobilized, they should be placed in a foreshortened position (dorsal reduction splint) to reduce future joint instability and ensure proper alignment through its range of motion during rehabilitation. (**A** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **B, C** courtesy Dr. L. Avery, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston.)

associated with central slip extensor tendon detachment, leading to a boutonnière deformity (see Fig 43.13).

Management. Radiographs can identify the type of dislocation, as well as associated fractures. Management should balance the importance of early motion to prevent long-term stiffness with the need to protect unstable injuries. Fractures involving more than one-third of the intraarticular surface commonly require surgical correction. Smaller fractures do not always require repair and may improve with 2 to 3 weeks of immobilization, followed by progressive range of motion. Reduction of dorsal and lateral PIP joint dislocation is accomplished using longitudinal traction and PIP hyperextension, followed by dorsal pressure on the proximal middle phalanx. Some volar dislocations may reduce successfully using longitudinal traction, with the MCP and DIP joints flexed. However, definitive management is controversial, and many will require open reduction.

Dorsal and lateral dislocations should be immobilized in 20 to 30 degrees of flexion or with an extension block splint—dorsal splint allowing flexion but restricting extension—for 2 to 3 weeks, followed by active movement. Reduced volar dislocations should be splinted in full extension. Open or irreducible dislocations, unstable reductions, dislocations with volar plate avulsion and intraarticular fractures involving more than 30% of the joint surface should receive hand service referral.

Injury to the Interphalangeal Joint of the Thumb

Thumb phalanges are stronger, but otherwise the joint is similar to a finger DIP joint. The collateral ligaments, volar plate, and some contribution from the extensor and flexor tendons insertions provide stability. Dorsal dislocations are most common. Dislocations should be reduced using digital nerve anesthesia, followed by splinting in the functional position in 2 to 3 weeks.

Metacarpophalangeal Joint Injury

The more condyloid shape of the MCP joint allows for abduction, adduction, flexion, and extension. Collateral and volar ligaments stabilize deep and superficial transverse metacarpal ligaments, which in turn stabilize the joint. The joint becomes more stable in a flexed position as the collateral ligaments are stretched across the articulation. MCP joints are most vulnerable to dorsal and lateral distracting forces; the most common dislocations are from hyperextension injuries. Simple dislocations are often subluxed, with the joint resting in at least 60 degrees of hyperextension, with tender, ecchymotic swelling. Complex dislocations are complete disarticulations; they are unstable, yet often appear less angulated than simple injuries. In addition to tender ecchymotic swelling, a palpable, displaced, metacarpal head dimples the palm. An interposed volar plate or sesamoid bone may prevent reduction. The Brewerton view (fingers flat on the radiograph plate, MCP joints flexed 65 degrees, and the beam angled from a point 15 degrees to the ulnar side of the hand) can identify concurrent bony injury.

Management. Hyperextension and longitudinal traction should be avoided because the volar plate of the MCP joint may become entrapped in the joint space. Rather, simple subluxed MCP joints should be reduced with the wrist in flexion, relaxing the flexor tendons, and applying direct dorsal pressure on the

proximal phalanx. To stabilize, the hand should be splinted with 90 degrees of MCP joint flexion (see Fig 43.28). Hand service referral should be requested for complex dorsal and volar dislocations because both may require operative reduction for stabilization.

Injury to the Metacarpophalangeal Joint of the Thumb

Due to its location and its mobile condyloid structure, the thumb MCP joint is far more likely to be injured than the remaining finger MCP joints. Forceful hyperextension can damage the volar plate, collateral ligament, and joint capsule, producing a dorsal phalangeal subluxation. Similar to the other MCP joints, complex dislocations may include phalangeal displacement into a bayonet position over the metacarpal and volar plate or sesamoid bone entrapment within the joint space.[5]

Management. Articular and avulsion fractures or displaced sesamoid bones may be visible on plain radiographs. As with other joints, local anesthesia or regional (eg, radial, median) nerve blocks can facilitate a painless reduction. Relaxed flexion of the wrist and thumb adduction, with IP joint flexion, may allow pressure on the dorsal proximal phalanx to reduce a dislocation. Ranging supports success, and the joint is then immobilized in functional position for hand service follow-up evaluation (see Fig 43.28). Significant collateral instability, complex (nonreducible), and open dislocations may require operative intervention.

Carpometacarpal Joint Injury

The CMC joint is comprised of eight carpal bones, their ligamentous communications, and the metacarpals, forming the hand's transverse metacarpal arch (see Fig. 43.5). Carpal flexor and extensor tendinous insertions add support to the palmar, interosseous, and dorsal ligaments. CMC injury is rare, unexpected, and easily missed. Injuries occur from high-impact trauma, including clenched fist injuries, falls, and motor vehicle collisions (MVCs). The fifth digital dorsal CMC joint dislocation is the most common injury. Dorsal swelling with focal CMC joint tenderness to motion and palpation should raise suspicion. Identification of fracture dislocations may be difficult on routine radiographs; oblique, Brewerton views, or CT scans may be needed for radiographic visualization.

Management. Closed reduction after adequate anesthesia may be attempted using traction and wrist flexion, followed by longitudinal force on the associated metacarpal base to restore length. Metacarpal head extension may assist with preserving the reduction while applying splint immobilization in the neutral position. Many of these injuries are unstable and need definitive operative fixation; hand service consultation should be obtained, especially for unstable or volar dislocations.

Injuries to the Carpometacarpal Joint of the Thumb.

Trapeziometacarpal joint dislocation, due to disruption of the dorsoradial ligament, may cause the thumb metacarpal joint to dislocate posteriorly. Radiographs may reveal concurrent articular fracture and confirm reduction. Thumb spica splint immobilization will stabilize the injury for hand service referral and possible operative management.

Ulnar Collateral Ligament Injuries

The thumb ulnar collateral ligament (UCL) injury (also known as gamekeeper's thumb or skier's thumb) was first described in Scottish gamekeepers who acquired their injuries through repeated forced abduction of the MCP joint, resulting in ligamentous injury at its insertion onto the proximal phalanx. The injury may be associated with an avulsion fracture and result in a complete or incomplete ligament tear (Fig. 43.33). Inadequate management and repeat injury may result in chronic disability. Skiing has become the most common cause of acute and chronic injury to the UCL. A Stener lesion occurs when the superficial portion of the ligament is drawn proximally. Ulnar deviation of the MCP joint allows the adductor pollicis tendon to interpose between the superficial and deep distal portion of the UCL ligament, resulting in improper healing in up to two-thirds of cases. Concurrent volar plate and joint capsule injuries may occur. Examination reveals swelling over the MCP joint and thenar eminence, with particular tenderness over the ulnar portion of the joint, as well as pain and weakness of thumb pinch. Valgus stress on the affected UCL, by applying a radial stabilizing force while gently abducting the joint, assists in diagnosis. UCL laxity (15 degrees > the unaffected thumb or >35 degrees overall) suggests a complete UCL rupture.[6] Because this diagnostic maneuver can lead to a Stener lesion, it should only be performed after radiographs are obtained to exclude a concurrent avulsion fracture.

Management. Partial UCL injuries may be managed with thumb spica immobilization and outpatient hand service referral. Surgical repair within 3 weeks of injury will result in good to excellent recovery in 90% of patients with Stener lesions or complete ligament rupture.

Radial Collateral Ligament Injuries.

A radial collateral ligament injury is caused by forced adduction. It is tenfold less common than an UCL injury, but can be equally debilitating, with loss of pinch strength and chronic pain. Management strategy is similar to that for UCL injuries, including a careful history, radiographs, varus stress testing, thumb spica immobilization, and hand service referral.

Tendon Injuries

Lacerations and puncture wounds, as well as crush and forced hyperextension, may result in a range of tendon injuries, including strain, complete rupture, and avulsion fracture. At rest, the balance of forces between digital flexors and extensor musculature results in a semiflexed or functional position, with a progressively greater degree of flexion from the index to the fifth fingers. If active ranging is present, but elicits discomfort along the tendon, a partial tear may exist. An injured finger with a greater or lesser degree of resting flexion when compared to adjacent digits, as well as that of the opposite hand, may indicate a tendon injury (Fig. 43.34). Meticulous, individual tendon function should be tested for motion against resistance. Initiating the test at maximal tendon stretch creates the greatest contraction strength for motion against resistance and can be compared to adjacent and opposite tendon function. Shorn tendons may retract proximally or distally into a wound, depending on hand positioning at the time of injury (eg, grasping versus extended). Thus, all tendons should be inspected throughout their entire range of motion during wound exploration.

Extensor Tendon Injuries

Principles. Lack of fibrous tendon sheaths and minimal amount of protective subcutaneous tissue make the extensor tendons over the hand dorsum prone to injury. The timing of definitive repair is controversial, but should generally be within 2 weeks of injury. Extensor tendon injuries have been grouped according to anatomic zones for assessing injury, consideration of repair techniques, and rehabilitation. Eight zones of tendon

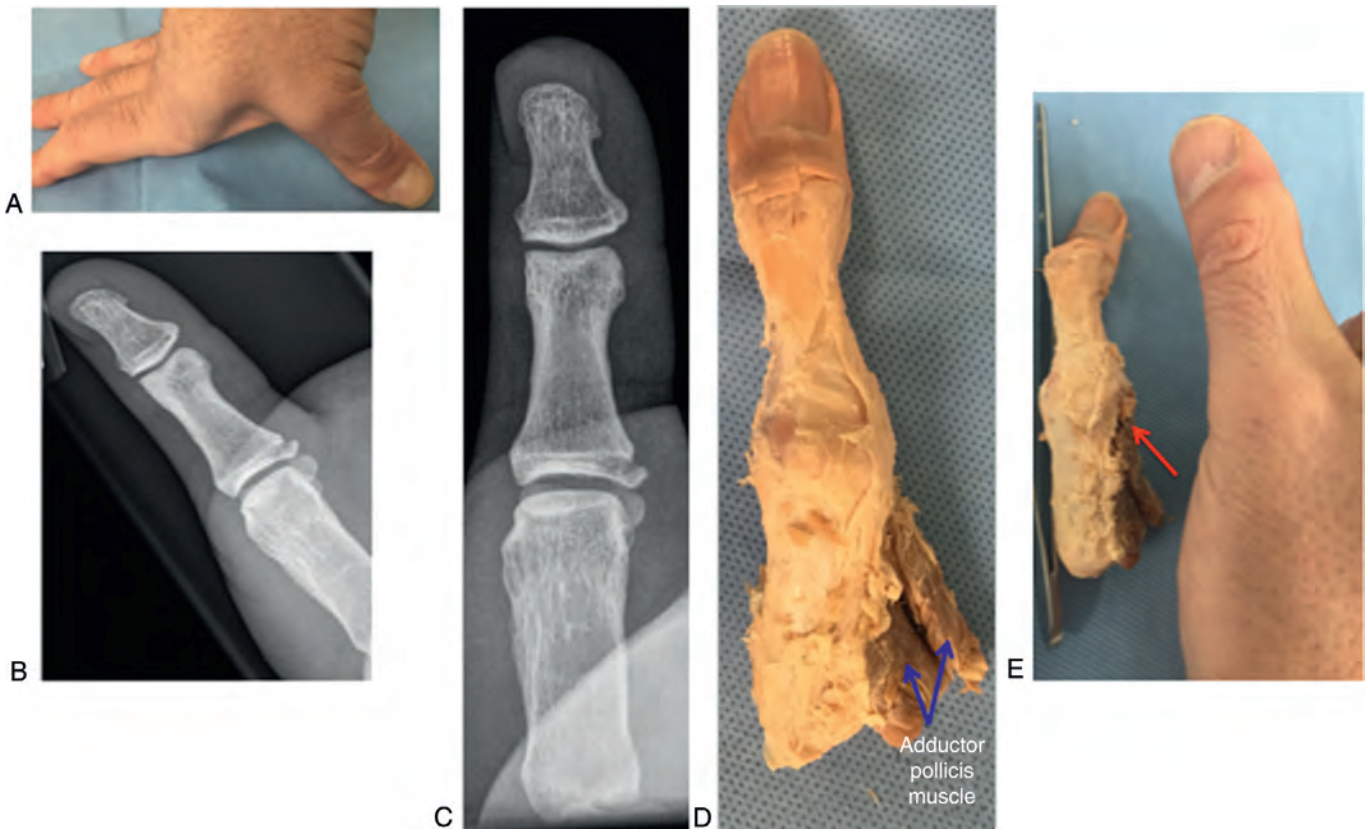


Fig. 43.33. Gamekeeper's thumb. **A,** Valgus and extension forces on an abducted first metacarpophalangeal (MCP) joint can result in ulnar collateral ligament injury. Symptoms include thenar ecchymosis, swelling, and MCP joint tenderness, with a weakened and unstable pincer grasp. **B, C,** Plain films should be obtained and reviewed before performing a radial stress test of the MCP joint assessing ligamentous integrity to avoid creating a Stener lesion. **D,** Ruptured collateral ligaments that are retracted proximally and from underneath the adductor pollicis muscle tendon produce a raised palpable mass proximal to the medial MCP joint. **E,** Anatomic defect on the cadaver specimen (*red arrows*). Compare the degree of ulnar collateral ligament (UCL) laxity to the opposite thumb; more than 40 degrees of laxity suggests a complete tear. Treatment requires thumb spica splint immobilization and urgent referral for repeat evaluation within 3 to 5 days; surgical repair is best performed within 3 weeks of injury. (**A, C, E** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **B, C** Dr. L. Avery, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston.)

trajectory have been defined, from the distal digit to the proximal forearm (Fig. 43.35; see Fig. 43.13). Partial and compete lacerations are repaired with a roll suture or figure-of-eight stitch with 5-0 nonabsorbable sutures (for zones I–IV) or 4-0 nonabsorbable sutures (for zone V and higher). Repair typically is performed by a hand surgeon, but may be done by the emergency clinician if properly trained, with follow-up by a hand surgeon.

Simple, clean tendon lacerations may be repaired in the ED if partial-thickness or full-thickness, with both ends easily visualized. However, because extensor tendon injuries are prone to functional impairment if not precisely repaired, and because structures are difficult to visualize without magnification and wound extension, we recommend that all injuries other than those easily visualized in zone VI be referred to a hand specialist by an urgent (1–3 day) follow-up appointment.[7] Prior to discharge, wounds should be thoroughly irrigated and the patient started on prophylactic antibiotics covering skin flora.

Clinical Features and Management

Zone I Extensor Injuries. This zone includes the conjoined extensor tendon over the DIP joint and its insertion at the dorsal distal phalanx. Partial tendon injuries may present with extension lag, with reduced strength on resistance testing. Complete transection of the tendon from open or closed trauma results in an unopposed flexed posture at the DIP joint.

Mallet finger, caused by forced flexion of the extended finger, is the most common sports-related tendon injury (see Fig. 43.29).[8] Up to one-third of mallet fingers have associated avulsion fractures. The DIP joint may be held in flexion at rest, with dorsal swelling and tenderness. Closed injuries benefit from early immobilization in extension, allowing PIP and MCP joint mobility. Most will improve within 6 to 8 weeks of immobilization. Open injuries, with partial or complete tendon laceration, are typically closed using 5-0 nonabsorbable sutures and the DIP joint splinted in extension for 6 to 8 weeks. Patients with chronic untreated mallet fingers may develop swan neck deformities from dorsally displaced lateral bands causing PIP joint hyperextension (Fig. 43.36).

Zone II Extensor Injuries. The extensor tendon's central and lateral bands pass over the middle phalanx in this region. The central band inserts on the middle phalanx and the lateral bands extend to the base of the distal phalanx. Rarely, lacerations transecting all the tendons will produce a mallet deformity. Treatment options are similar to those for zone I injuries.

Zone III Extensor Injuries. The second most common sports-related closed tendon injury involves the central tendon as it

Fig. 43.34. Flexor tendon injuries. **A, B,** In a normal resting position, the fingers and thumb are semiflexed, with the little finger having the greatest degree of flexion and index finger having the least. In the resting hand, a finger with a lesser degree of flexion than the contralateral digit of the opposite hand often indicates a flexor tendon injury. **C, D,** When both the flexor digitorum superficialis and flexor digitorum profundus tendons are lacerated, common in volar proximal phalangeal lacerations (*red dashed arrows*), the affected digits will assume a fully extended position. (**A, B** courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; **C, D** courtesy Dr. J. Jin, Department of Orthopedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston.)

passes dorsally over the PIP joint. Causes of closed injuries include forced flexion and extension and crush to the dorsum of the PIP joint. At this level, lacerations may involve the tendon and the joint, warranting careful wound examination through a full range of motion. A boutonnière deformity may result from damage and displacement of the extensor hood, as well as the attachments of the central tendon's lateral bands causing volar displacement and resulting in a paradoxical PIP joint flexion and DIP joint hyperextension (see Fig. 43.13). Diagnosis should be suspected with PIP joint swelling in flexion with concurrent DIP joint extension and tenderness along the tendon. The Elson test may identify a central slip rupture; with the patient's PIP joint in 90 degrees of flexion over the edge of a counter, the patient is asked to extend the middle phalanx actively. Weak extension with rigid DIP joint extension is suggestive of a central slip injury (Fig. 43. 37). Closed PIP joint injuries should be immobilized in extension, leaving the DIP joint free, with referral to a hand specialist. Patients with open injuries should receive prophylactic antibiotics, tetanus, and immediate hand service consultation.

Zone IV Extensor Injuries. Partial and complete tendon injuries over the proximal phalanx do not retract appreciably and can be repaired using 5-0 nonabsorbable sutures, followed by immobilization in a functional position.

Zone V Extensor Injuries. These injuries commonly involve the flexed finger MCP joints, Clenched fist injuries can be closed or open. Radiographs should be obtained to rule out metacarpal head and articular fractures. The inability to extend the MCP joint fully, with local swelling and tenderness, suggests tendon injury.

Unless proven otherwise, all open injuries over the MCP joint should be presumed secondary to a punch to the mouth or fight bite. A misleading history or innocuous wound appearance should not dissuade the examiner from making this diagnosis, because risk of infection is high and should be treated expeditiously with antibiotics and possible operative washout. Wounds should be left open, and patients should receive empirical antibiotics to cover *Staphylococcus aureus,* streptococci, *Eikenella corrodens* and anaerobes. We recommend the combination of a β-lactam and β-lactamase inhibitor such as amoxicillin-clavulanate, 875/125 mg (25 to 30 mg/kg/day) orally bid for 3 to 5 days or until hand surgery follow-up. For penicillin-allergic patients, clindamycin, 300 mg (8 to 12 mg/kg/day) tid, plus double-strength trimethoprim-sulfamethoxazole (8 to 10 mg/kg/day) bid, doxycycline, 100 mg

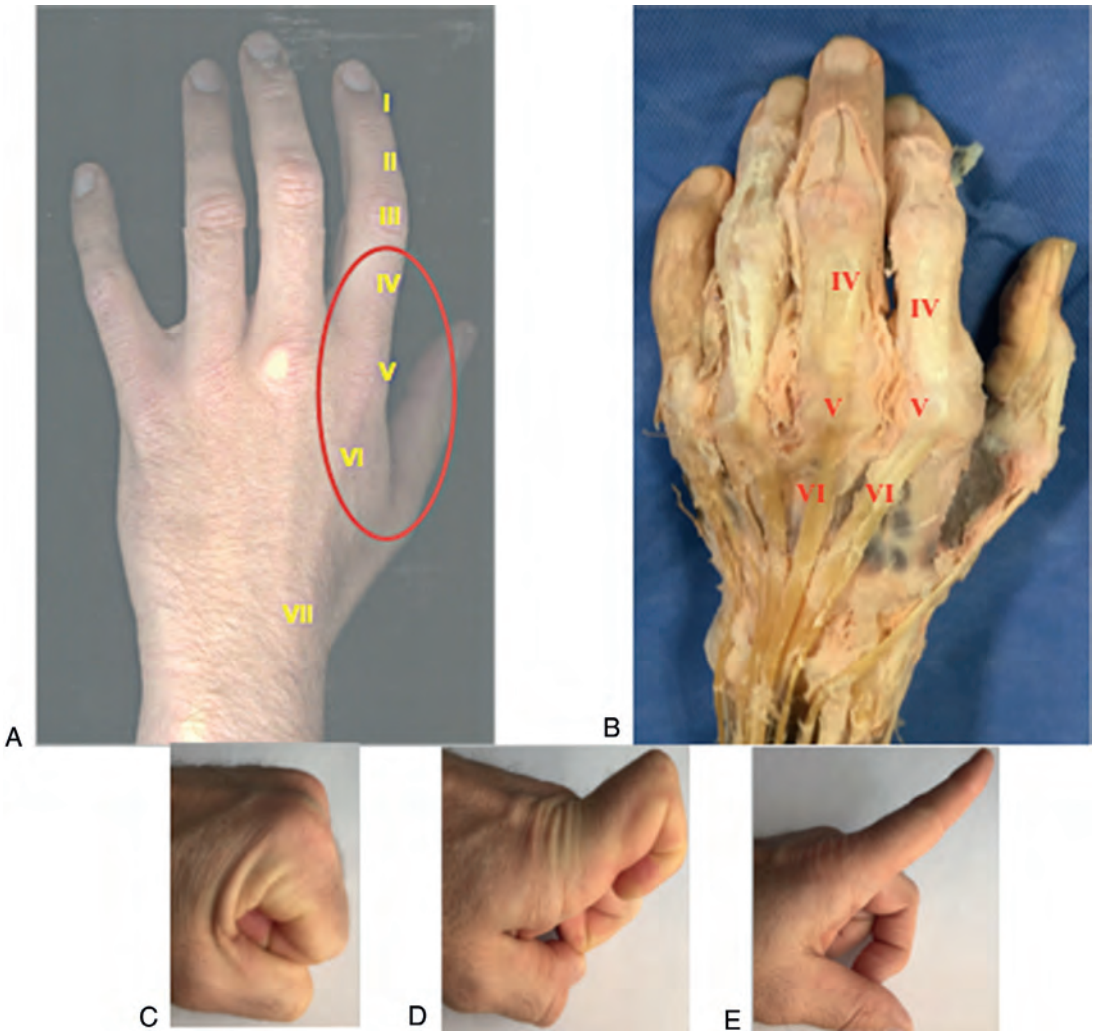


Fig. 43.35. Extensor tendon lacerations more than 75% will require repair. **A, B,** Emergency clinician safe zones include zones IV, V and VI. Repair may be done by the emergency clinician if properly trained and with hand service follow-up. All other zones will require hand specialist consultation. Primary tendon repair is contraindicated in high-risk lacerations (eg, fight bites). Tendon lacerations may undergo successful delayed repair up to 14 days. **C–E,** Tendon integrity should be examined through the digit's full range of motion because lacerations may be hidden from view. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

bid, or a fluoroquinolone (eg, ciprofloxacin) 500 mg (10 to 20 mg/kg/day) bid may be used. (Due to concern for potential cartilage erosion in the growing skeleton, the American Academy of Pediatrics recommends using alternatives to fluoroquinolones in children whenever possible.)

The incidence of associated tendon, joint, and bone injury is as high as 75%. Exploration of these open wounds through full range of motion may reveal an extensor tendon injury or violation of the joint capsule, warranting operative washout and repair. Lacerations caused by clean objects should have the skin closed and splinted, with the MCP joint and wrist in the functional position and referral for urgent hand specialist consultation.

Zone VI Extensor Injuries. Tendons over the metacarpal bone are superficial, necessitating meticulous examination through full range of motion and in isolation. Strength should be compared to adjacent digits and the opposite hand, recognizing that forces may be transmitted from the juncturae tendineae. Injuries in this zone should be splinted with the wrist and MCP joint in the functional position. Other than clean, easily visualized tendon injuries, which may be amenable to primary repair in the ED, patients should be referred to a hand specialist within 1 to 3 days to schedule definitive repair.

Zone VII and VIII Extensor Injuries. These tendon injuries involve the wrist and forearm and should be referred to hand service consultation for definitive management.

Flexor Tendon Injuries

Principles. Flexor tendon injuries of the hand are less common than extensor tendon injuries. The most common closed flexor tendon injury of the hand is an FDP tendon avulsion from the forceful extension of a flexed digit. The digit may rest in relative extension due to unopposed extensor function. Isolated joint function testing of should assess individual FDP, FDS, and lumbrical function. The volar hand is divided into five anatomic zones to assist with defining areas of injury and potential tissue involvement (Fig. 43.38).

Flexor tendon injuries are more difficult to treat than extensor tendon injuries and should be referred for hand specialist consultation. The intricacy of the hand's volar anatomy has given it the nickname of "no man's zone." This, combined with a high risk of complications, including tendon adhesions, precludes primary ED repair.

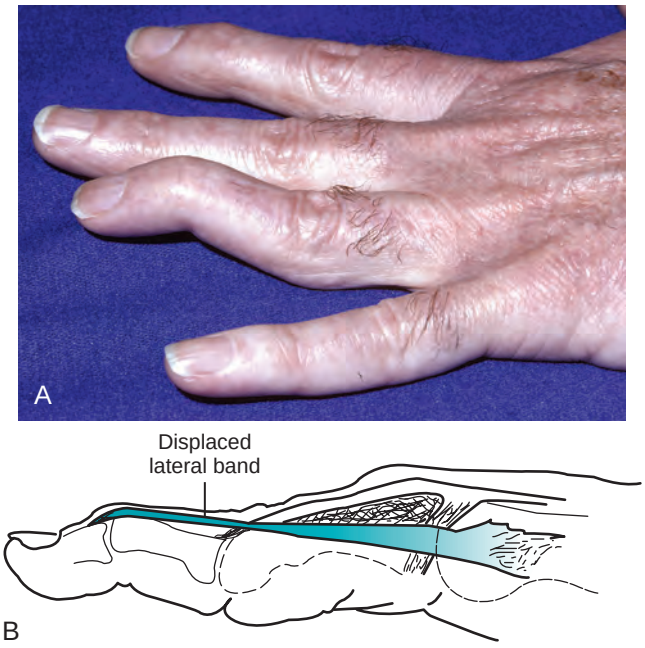


Fig. 43.36. Swan neck deformity (**A**) and diagram of the swan neck deformity (**B**). Lateral bands have displaced dorsal to the axis of the proximal interphalangeal joint, where they extend the joint and allow the distal interphalangeal joint to flex. (From Sokolove PE, Barnes DK: Extensor and flexor tendon injuries in the hand, wrist, and foot. In Roberts JR, editor: Roberts and Hedges' clinical procedures in emergency medicine Philadelphia, 2014, Saunders, pp 931–998; © Elsevier 2014.)

Zone I. The region includes the FDP tendon from the fingertip to the middle phalanx distal to the FDS tendon insertion.

Zone II. The FDP and FDS tendons extend between the middle phalanx and distal palmar crease. Proximal to zone II, the FDS tendons are superficial to the FDP tendon. The FDS tendon splits into two slips (Camper chiasm) across the proximal phalanx, allowing the FDP tendon to pass between them before the slips insert on the middle phalanx. A fibrocartilage matrix surrounds these tendons, creating a pulley mechanism that assists with isolated DIP and PIP flexion and prevents bowstringing.

Zone III. Known as the lumbrical zone, the region extends from the distal palmar crease to the distal edge of the flexor carpal ligament.

Zones IV and V. The carpal tunnel is included in zone IV. Zone V incorporates the proximal anterior forearm tendons and their distal musculature.

Clinical Features. Up to 90% of palmaris aponeurosis injuries are associated with tendinous and neurovascular injury, including injuries to arteries, median and ulnar nerves, FDS and FDP tendons, and lumbricals. Passive resting flexion should result in increasingly greater degrees of flexion from the index through little finger (see Fig. 43.34). Complete disruption of the FDP tendon results in an extended resting position of the DIP joint. Reduced pinch and grip strength may also occur. FDS tendon injuries may result in a reduced resting flexion at the PIP joint.

FDP and FDS tendons' strength and integrity should be tested separately. FDP tendon injury is suspected with subjective weakness or abnormal position of the hand at rest or pain and weakness with DIP joint flexion against resistance. Lacerations at the MCP joint crease may result in FDS tendon injury; as the FDS tendon bifurcates for the FDP tendon along the proximal phalanx, the FDP tendon paradoxically becomes the superficial tendon at the PIP joint crease (see Fig. 43.17). Therefore, wounds involving the PIP and DIP joint creases may involve the FDP tendon.

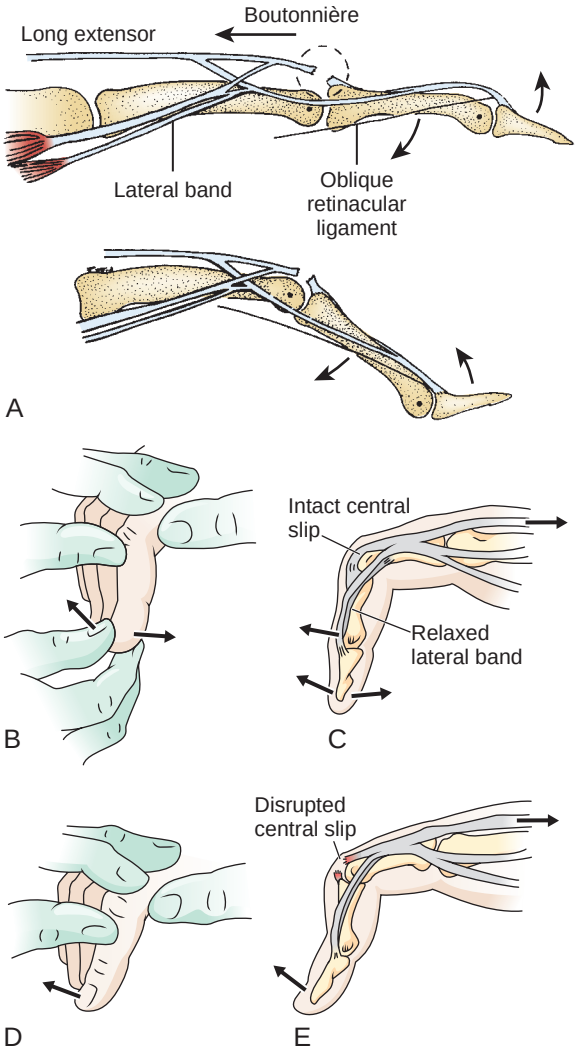


Fig. 43.37. A, Boutonnière deformity. **B–E,** The Elson test for early diagnosis of an acute rupture of the central slip of the extensor digitorum communis tendon. Such a rupture results in a boutonnière deformity, in which the distal interphalangeal joint is hyperextended, as shown. **B,** With the patient's finger flexed (over a straight edge) at the proximal interphalangeal (PIP) joint, the examiner palpates the dorsal surface of the middle phalanx. **C,** If the central slip is intact, PIP joint flexion causes the slip to tighten distally, thereby relaxing the lateral bands and allowing the distal phalanx to hyperextend (*arrows*). Thus, when the patient is asked to extend the digit, the examiner feels pressure that is being exerted by an intact central slip. **D, E,** If the central slip is disrupted, however, the examiner feels no pressure on the dorsum of the middle phalanx as the patient tries to extend the digit. It is possible for the patient to extend the injured finger successfully only by hyperextending (by action of the lateral bands; *arrows*). (From Sokolove, PE, Barnes DK: Extensor and flexor tendon injuries in the hand, wrist, and foot. In Roberts JR, editor: Roberts and Hedges' clinical procedures in emergency medicine Philadelphia, 2014, Saunders, pp 931–998; © Elsevier 2014.)

Finger FDP function is assessed by asking the patient to flex the DIP joints of each digit individually while the corresponding PIP joints are stabilized in extension by the examiner. Conversely, the FDS tendon of the individual finger is checked by asking the patient to flex the corresponding PIP joint while the adjacent digits are held in extension by the examiner (see Fig. 43.18). Because the FDP tendons share a common muscle belly in the forearm, extension of the adjacent digits will impede function of the tested finger's FDP tendon, thus allowing the FDS tendon to be tested independently. Normal anatomic variations this include an independent FDP tendon muscle belly of the index finger and

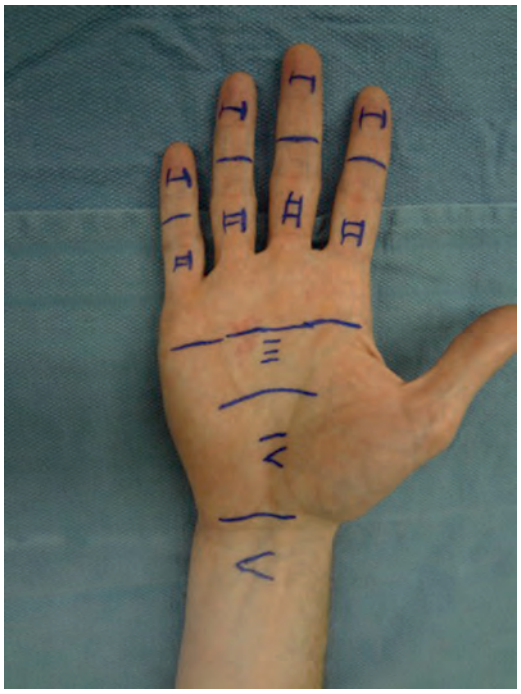


Fig. 43.38. Volar surface of the hand, with lines defining the borders of flexor tendon injury in zones I to V. (From Kenney RJ, Hammert WC: Physical examination of the hand. J Hand Surg 39:2324–2334, 2014.)

lack of an FDS tendon in the pinky finger; these variations tend to be bilateral.[9]

There are three classifications of FDP avulsion injuries. Type I results in retraction of the avulsed FDP tendon as far as the palm, compromising its vasculature. Operative repair should be accomplished urgently to prevent permanent damage. Types II and III injuries result in less severe tendon retraction and have more favorable operative outcomes.

Management. Management of flexor tendon injuries includes hemorrhage control, thorough examination, documenting concurrent nerve and tendon injury, radiographs to identify concurrent fracture or foreign material, irrigation, decontamination, and antibiotic and tetanus prophylaxis. Patients should receive hand service consultation for all flexor tendon injuries to assist with the decision for immediate or delayed primary repair. Emergent intervention may be needed with concurrent vascular injury, whereas delayed repair may be acceptable within days to weeks.[9] Optimal treatment remains controversial, so partial flexor tendon lacerations should also be referred early. Open wounds should be closed with 5-0 nonabsorbable sutures after decontamination, followed by immobilization of the hand, with the wrist in 30 degrees of flexion, MCP joint in 70 degrees of flexion, and IP joint in 10 to 15 degrees of flexion. Urgent follow-up evaluation and definitive operative management should be arranged with the hand service before discharge.

Complications. Timely identification, management, and consultation can lead to favorable outcomes. Adhesions, triggering, and bowstringing are potential complications.

Vascular Injuries

Vascular injuries may result from penetrating trauma such as puncture wounds, lacerations, injection injuries, and amputations. Blunt trauma, such as a crush injury, can create arterial thrombosis or false aneurysm.[2] The hand and its digits possess an excellent collateral supply, and isolated arterial injuries seldom result in ischemia. Pulsatile bleeding at the time of injury, even if bleeding has ceased at the time of evaluation, should raise concern for arterial injury. The neurovascular systems travel together within the palm and along the digits, and a careful neurologic evaluation should be performed to exclude concurrent nerve injury (see Figs. 43.23, 43.25, and 43.26).

Clinical findings may include pallor or cyanosis, delayed capillary refill, cool tissues, progressive pain or hyperesthesias, and reduced or absent pulses. The modified Allen test, pulse oximetry, or Doppler ultrasound may help assess regional vascular integrity. Ischemic pain is the most common initial complaint of patients with vascular insufficiency, often accompanied by pallor in the affected area.

Management

Meticulous physical examination is necessary to exclude occult vascular and concurrent nerve injury. Hand lacerations rarely cause life-threatening hemorrhage because the arteries usually retract and constrict. However, they may bleed briskly, especially in patients on antiplatelet or anticoagulation therapy. Injuries involving the palmar arches may be difficult to visualize in the ED and often require surgical exploration for hemorrhage control. Direct pressure, use of a blood pressure cuff inflated to 30 mm Hg above systolic pressure, or a tourniquet may help control bleeding. Clamps and hemostats should not be used to control bleeding because adjacent nerves and tendons may be crushed.

Arterial repair is not mandatory in isolated arterial injuries with a normal distal vascular examination. However, repair is indicated with tissue ischemia or associated nerve injury. If an artery is to be ligated, both ends should be closed, because these valveless vessels can back-bleed from collaterals. Radiographs and ultrasound may help identify the cause of palpable tender masses and differentiate among a retained foreign body, hematoma, infection, pseudoaneurysm, or arteriovenous fistula.

Nerve Injuries

Three classifications help define neural injuries resulting from blunt or penetrating trauma to the hand. The motor and sensory distributions distal to the injury should be carefully examined to identify nerve injuries (see Figs. 43.22 to 43.24). Neurapraxia is characterized by complete or partial dysfunction, commonly caused by prolonged compression or crush injury. The nerve's axon, sheath, and endoneurium remain intact. Complete recovery commonly occurs within days to weeks. Axonotmesis results from disruption of the axon and myelin sheath, resulting in distal axonal degeneration. The endoneurial tube remains intact, allowing the proximal axonal stump to regenerate along the tube at a rate of 1 to 3 mm/day. Functional recovery is variable. Penetrating wounds commonly result in neurotmesis, in which all or a portion of the nerve elements are separated. Axonal regeneration does not occur unless the severed components are reapproximated.[10]

Management

Patients with nerve injuries caused by blunt trauma should be splinted in the functional position and referred to a hand specialist to differentiate surgically amenable neurotmesis from conservatively treated axonotmesis. For penetrating trauma, hand service consultation should be obtained for injuries to the motor branches of the ulnar and median nerves, as well as digital sensory nerve injuries proximal to the DIP joint crease on the radial aspect of the index finger, the ulnar aspect of the little finger, and both sides of the thumb. Delayed primary repair may be needed in complex

injuries, allowing for adequate decontamination, débridement, and recession of inflammatory swelling prior to closure.

Complications

Peripheral nerve injury can result in permanent motor dysfunction, muscle atrophy, chronic paresthesias, neuromas, and sympathetic dystrophy.

Amputations

Principles

Complete or partial traumatic amputations constitute 0.1% to 1% of all hand injuries. With few exceptions, all completely amputated parts should be considered for replantation, and all partial amputations should be assessed for revascularization. Crushed, mangled, or multilevel digital amputations have poorer prognoses. Proximal amputations tolerate less ischemia time; distal injuries have a higher replantation success rate. Sharp, guillotine-like injuries fare better than avulsion or crush injuries.

Although successful replantation of digits after up to 40 hours of warm ischemia has been reported, cooling of the affected part extends the average tolerated ischemic time by approximately twofold; muscle and bone tolerate up to 12 and 24 hours of cold ischemia, respectively. Amputations involving the thumb, multiple digits, hand at the level of the wrist, and all amputations in children should always be evaluated for replantation (Box 43.4). Because thumb loss results in 40% loss of hand function, all thumb amputations should be considered for salvage, regardless of the level or mechanism of injury. Similarly, all amputations in children should be considered for replantation; microscopic inspection of vessels and nerves will guide the decision.

Management

General management goals include control of hemorrhage, salvage of neurologic and musculotendinous function, preservation of amputated tissues, wound care, and expeditious consultation. Gross contaminants can be removed by irrigation with normal saline. The amputated part should then be wrapped in normal saline–moistened gauze, sealed in a dry plastic bag, and placed on ice in an insulated container. The stump should be covered with saline-moistened sterile dressings and elevated to reduce edema and control bleeding. Patients should receive appropriate antibiotic and tetanus prophylaxis. Partial amputations with vascular compromise should be irrigated, dressed, and splinted. Cold packs may be placed around the dressings to prevent warm ischemia.

BOX 43.4

Classic Indications for and Contraindications to Replantation

INDICATIONS

- Multiple digits
- Thumb
- Wrist and forearm
- Sharp amputations with minimal to moderate avulsion proximal to the elbow
- Single digits amputated between PIP joint and DIP joint (distal to flexor digitorum superficialis [FDS] insertion)
- All pediatric amputations

CONTRAINDICATIONS

- Amputations in unstable patients secondary to other life-threatening injuries
- Multiple-level amputations
- Self-inflicted amputations
- Single-digit amputations proximal to FDS insertion

Complications

Amputation completion or revision may be indicated when vascularity is unsalvageable. Successful reimplantations may require additional operative revision or suffer from hypoesthesia, hyperesthesia, or chronic stiffness.

Fingertip Amputations

Principles. Any portion of the digit distal to the DIP joint is contained in the fingertip and is a common site of injury. Preservation of length and sensation are goals of care.

Classification. Amputations involving the distal phalanx and nail bed are divided into zones (Figs. 43.39 and 43.40; see Fig. 43.26). Zone I injuries preserve the bone and proximal two-thirds of the nail bed. In zone II injuries, two-thirds of the nail bed has been lost, with exposure of bone. In zone III injuries, the entire nail bed is absent, with significant bone exposure.

Management. Preservation of length, especially of the thumb, and maintenance of pulp to pulp pinch of the index finger are primary goals. Treatment includes early and thorough wound care, devitalized tissue débridement, and assessment of the need for surgical revision.[11,12] Wounds smaller than 1.0 cm without bone exposure may be managed through secondary intention healing in children and adults. Wounds with up to 0.5 cm of bony exposure may be managed by secondary granulation after dissection of the exposed bone below the soft tissue with a ronguer. Larger wounds with more bony exposure will often need operative revision. We recommend antibiotic prophylaxis for bone exposure because these wounds are considered contaminated.

Hand specialist consultation should be considered early for zones II and III injuries, as well as thumb or index finger involvement.[13,14] Management options include primary or delayed intervention, including wound closure, reimplantation, skin grafts, and a variety of flap revisions (see Fig. 43.40). Avulsion wounds may require a flap to cover bone adequately and add tissue bulk to the fingertip. Nail bed revision with preservation of a minimum 0.5 cm of nail bed distal to the lunula will allow nail adherence to the underlying matrix.

Complications. Nail deformity from matrix loss, despite repair, is common. Neurovascular damage may result in chronic fingertip hyper- or hypoesthesia, along with temperature intolerance. Close hand service follow-up is important to monitor recovery for maximal functional outcome and return to activity.

Ring Avulsion Injuries. A deceleration, such as a fall when a ringed finger catches on an object, can lead to results ranging from partial skin degloving to complete amputation. Hand service should be consulted to determine further management, including microvascular repair with replantation, complex flap transfer, graft, and primary amputation.

Mutilating Injuries. Lawnmower, carpentry saws, and wood chippers can create permanently disabling injuries. The most common injuries involve the dominant hand, including the index and middle fingers. Hand service should be consulted to identify opportunities to preserve limb length and function, especially in pediatric cases.

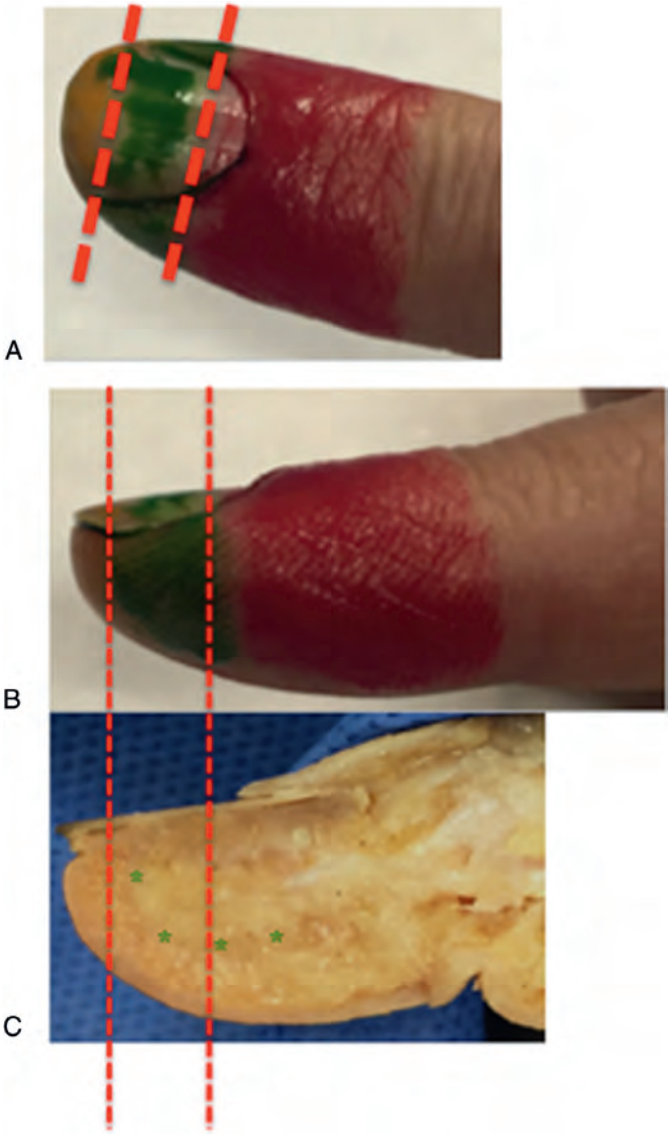


Fig. 43.39. Fingertip amputations. *Zone I,* Pulp, distal nail—healing by secondary intention. *Zone II,* Bone exposed—revision amputation soft tissue flap (eg, V-Y advancement flap). *Zone III,* Involving the eponychium. Most will require amputation of the distal phalanx at the DIP joint. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

High-Pressure Injection Injuries

Principles

Industrial equipment such as water, grease, paint, and sand injectors, with compressive forces of 2000 to 12,000 psi, are sufficient to penetrate skin, even from a distance. The nondominant hand, often involving the index finger, is the most common site of injury. The initial presentation may appear benign, creating false reassurance. Due to their high rate of deep tissue infection, high-pressure injuries commonly result in limb loss, with amputation rates as high as 48%. Prompt hand service evaluation is recommended because delay in care is associated with a higher complication rate.

Mechanical force–induced tissue injury, toxicity of the injected material, and resultant inflammation and compartment syndrome biomechanics may occur at multiple levels along the limb. The type of material injected, its volume, and velocity of injection determine the degree of the inflammatory response. Paint and solvents produce a large, early inflammatory response, resulting in a high percentage of amputations as compared to grease and other viscous compounds. The velocity of injection and site of tissue penetration determine dispersion risk. Distal sites (eg, fingertips) carry a worse prognosis than proximal sites.

Clinical Features

Initial symptoms may be minimal, with an entrance would appearing innocuous or even absent. However, the involved digit or hand can develop pain, swelling, pallor, and motion tenderness within hours. Careful serial examinations should be performed to document the extent of injury and associated evolving neurovascular dysfunction. Radiographs may help identify the degree of dispersion by identifying subcutaneous emphysema and radiopaque material.

Management

Emergent hand service consultation should be obtained to determine needed interventions, including decompression and débridement. Successful nonoperative management in the case of sterile water or air injection has been reported.[15] ED management includes broad-spectrum antibiotics, splinting, limb elevation, and tetanus prophylaxis. Parenteral analgesia is recommended over regional nerve blocks, which can add to tissue pressures and promote neurovascular compromise.

Compartment Syndrome in the Hand

Principles

Increased interstitial pressures within a closed compartment can lead to impaired microcirculatory perfusion and tissue injury. Common culprits include trauma (eg, displaced fractures, crush injuries) and injection-related injuries (eg, IV drug–abuse related injection, envenomations, iatrogenic extravasation of IV material, high-pressure injection injuries). Fascial planes separate the palm into 10 individual compartments (Fig. 43.41). The flexor surface of the digits are also compartmentalized by fascia and skin at flexor creases.

Clinical Features

Severe pain out of proportion to the injury may be the only initial abnormality. Hyperesthesia or hypoesthesia in the distribution of the nerve(s) passing through the affected compartment may be an early abnormal symptom. Soft tissue swelling may not be as impressive as the degree of pain. Pain and tenderness will be aggravated by active and passive stretching of the tissues associated with the affected compartment. With progression, patients may develop decreased motor function and progressive vascular compromise.

Management

Prompt diagnosis and definitive therapy increase the odds of a favorable outcome. The hand service should be emergently consulted for surgical decompression and débridement.[16] Envenomations should be treated with antivenins, when available, but should not delay surgical consultation.

Infections of the Hand

Paronychia

Principles. A paronychia is an infection involving the lateral nail fold, commonly caused by local trauma. It may evolve from

Fig. 43.40. Repair of fingertip amputations—V-Y flap closure for fingertip amputation. **A–D,** The Atosoy-Kleinert V-Y flap (1970) is a triangular, volar, V-shaped flap that is excised from the fat pad and advanced distally for reconstruction of the fingertip. It can be used to preserve length when the bone is exposed in a horizontal amputation. It cannot be performed with oblique injuries that amputate more volar tissues. **E, F,** Zone III fingertip injury involving the eponychium and nail matrix. The amputated material was harvested to fashion a transfer flap from the fat pad. **G, H,** After the remainder of the distal phalanx was amputated, the flap was used to close the wound, preserve length, and maintain digit function. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

local cellulitis to an abscess with lymphangitic extension. *S. aureus* (including methicillin-resistant *Staphylococcus aureus* [MRSA]) is the most common pathogen, followed by streptococci, *Pseudomonas*, gram-negative bacteria, and anaerobic flora; herpes simplex virus may mimic (ie, Herpetic whitlow; Fig. 43.42) or co-infect a paronychia.[17] Adults and children are prone to infections from oral flora, commonly from nail biting and digit sucking. Refractory cases may result from atypical mycobacterium or fungal infections. Inflammation originates along the cuticle alongside the fingernail, but may progress to involve the entire nail fold. The process may also extend to involve the proximal nail (ie, eponychium).

Management. Patients with local cellulitis without an abscess should be given oral antibiotics and instructed to soak the finger multiple times per day and keep it elevated. Those with local fluctuance should be drained by lifting the cuticle off the nail to release and drain the pus. More extensive lesions may require digital block followed by extended incision, parallel to the nail and under the eponychium (Fig. 43.43). To allow improved drainage in severe cases, up to 25% of the nail adjacent to the abscess can be excised from the nail bed, followed by irrigation and packing. Wound cultures are usually not indicated and antibiotics are not necessary unless there is extending cellulitis, lymphangitis, immunocompromised status, or recurrent infection. Most cases resolve with local wound care over 5 to 10 days. Complications may include osteomyelitis. Chronic indolent processes involving the perionychium may require prolonged treatment and should be referred to a hand surgeon or dermatologist.

Felon

Principles. A felon is an infection resulting from penetrating trauma involving the digital fat pad (the pulp) containing septations that extend vertically from the distal phalanx to the volar skin, creating a series of individual compartments, each of which can become inoculated. Local warmth and redness may progress to a swollen, throbbing, and tender pulp space from increased local pressure. Infection may persist despite surgical decompression and drainage attempts if all affected compartments are not treated. *S. aureus* (consider methicillin-resistant and methicillin-sensitive strains) is the most common isolated pathogen, although the cause may also be polymicrobial.

Management. After administering a digital block, a felon can be drained by an incision parallel to the length of the phalanx,

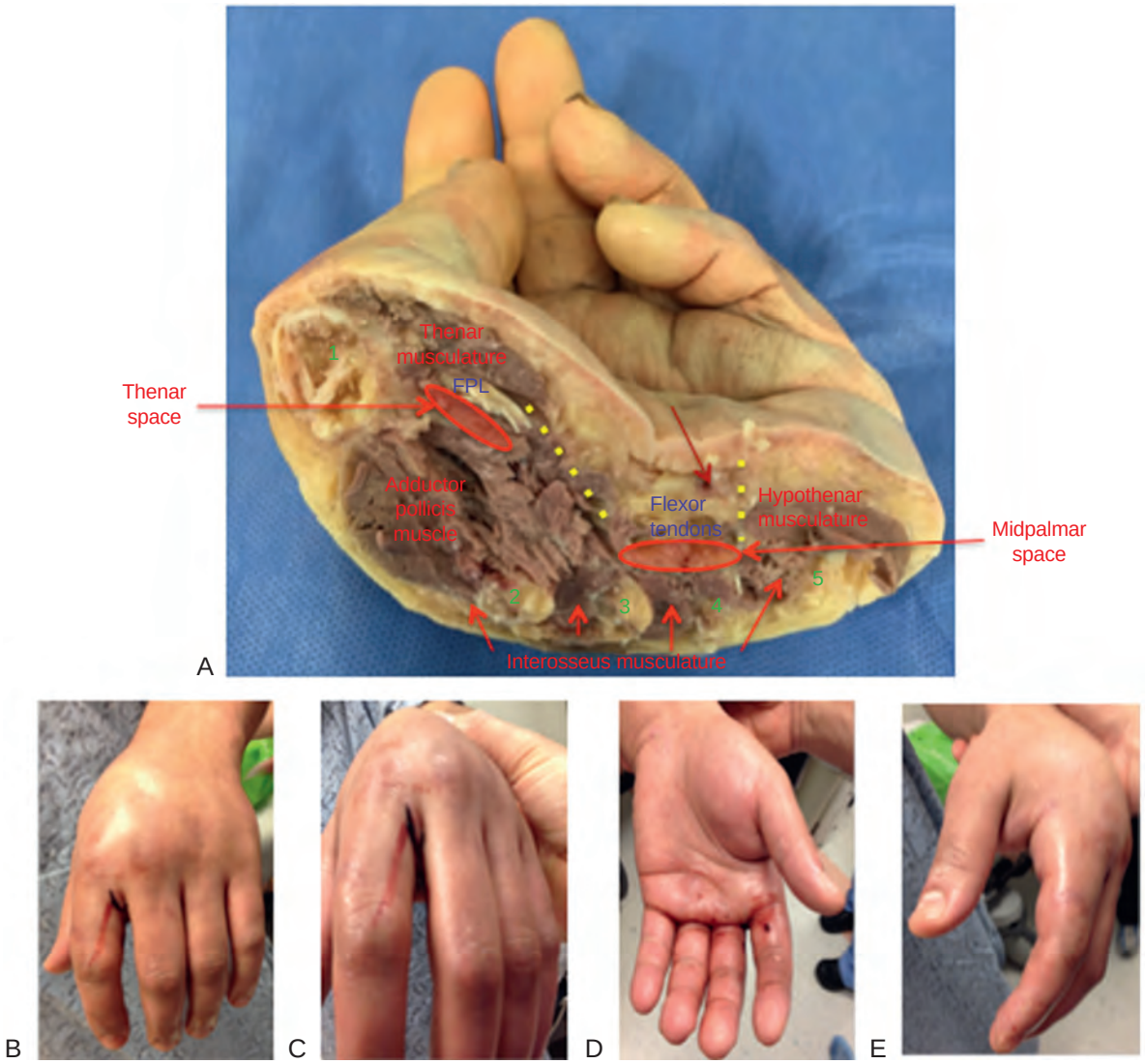


Fig. 43.41. Midpalmar spaces. **A,** Cadaver specimen revealing the midpalm and associated structures. Shown are the metacarpal bones of the thumb (1) and index (2), middle (3), ring (4), and little (5) fingers (*green*). The thenar and hypothenar eminence musculature is separated from the central palmar structures by midpalmar (oblique) and hypothenar fibrous septa (*yellow dotted lines*). The thenar adductor and interosseus muscle spaces lie between the metacarpal bones (*red*). The flexor pollicis longus (FPL) tendon and digital flexor tendons of the midpalm (*blue*) pass just anterior to the thenar and midpalmar spaces (*red ovals*). **B–E,** This patient presented with severe progressive painful swelling and hyperesthesias involving the first web space and index and middle fingers after a puncture wound to the second web space (*red arrow*). The patient suffered from a progressive deep space process involving the interosseus and thenar spaces, requiring operative débridement. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

from the base of the fat pad (≈5 mm distal to the DIP joint) to the free edge of the nail. To avoid pincher surfaces, the incision should be made dorsal to the neurovascular bundle along the radial aspect of the thumb and fifth digit, and the ulnar aspects of the second to fourth digits. The incision should be deep enough to open the septal loculations. Adhesions are then released (Fig. 43.44). Some emergency clinicians advocate the use of a paramedian longitudinal incision to decrease the risk of digital nerve. Fishmouth, hockey stick, or bilateral longitudinal through and through incisions should be avoided because they increase the risk of nerve injury and poor wound healing.

After irrigation, the wound should be packed, a bulky dressing applied, and the patient instructed to have the packing removed in 48 to 72 hours, with daily warm soaks to assist with secondary healing. Oral antibiotics such as cephalexin or dicloxacillin—or trimethoprim-sulfamethoxazole or clindamycin for suspected MRSA or penicillin allergy—should be given for at least 5 days.

Complications. Untreated felons can lead to skin necrosis, sinus tract formation, and chronic drainage. Dorsal spread can lead to phalangeal tuft necrosis and osteomyelitis. Deep incision may injure the flexor tendon sheath. Incision and drainage of structures crossing the DIP flexor crease increases the risk of infection spread, flexor tenosynovitis, septic arthritis, and proximal osteomyelitis. Incisions affecting the neurovascular bundle may result in vascular insufficiency, fingertip anesthesia, or neuroma. Longitudinal volar fat pad incisions can result in thick scarring and fingertip anesthesia.

Herpetic Whitlow

Principles. A self-limited manifestation of human herpes simplex type 1 or 2, herpetic whitlow is the most common viral infection of the hand, often involving the distal fat pad through direct contact of the digit with vesicles or open wounds. Common risks include patients with genital herpes infection and children with gingivostomatitis. Formerly health care workers were at particular risk, although this has been significantly reduced by the use of protective gloves and proper hand hygiene.

Clinical Features. Usually, a single digit is involved, with local erythema, swelling, and painful pruritus (see Fig. 43.42). Systemic symptoms are absent, although the affected area can become secondarily infected. Clear vesicular lesions evolve over the erythematous area, coalesce, and ulcerate over a 2-week period. This latter stage may appear similar to a felon or paronychia, prompting a consideration for incision and drainage. However, incision and drainage is contraindicated in herpetic whitlow because it can lead to viral dissemination and secondary infection.

Fig. 43.42. Herpetic whitlow on the finger of a child. Herpetic whitlow is sometimes misdiagnosed as cellulitis or blistering distal dactylitis or, depending on the distribution, paronychia. (From Mendoza N, Madkan V, et al: Human herpesviruses. In Bologna JL, Jorizzo JL, Schaffer JO, eds: Dermatology, ed 3, New York, 2012, Elsevier, pp 1321–1344.)

Diagnostic Testing. A diagnosis can be made clinically based on the overall appearance in the context of local recurrence and potential sources of inoculation. Although viral culture of the vesicular fluid has been the criterion standard because it can differentiate among herpes simples virus types with high specificity, the 24- to 48-hour turnaround time may be less optimal for disposition planning. The Tzanck smear of vesicle scrapings to identify Giemsa-stained viral inclusion multinucleated giant cells is insensitive. We recommend the more cost-effective and sensitive polymerase chain reaction (PCR) assay.

Management. Although lesions resolve spontaneously over a 3- to 4-week period, symptoms recur in up to 20% of cases. Goals of therapy include providing symptomatic relief and preventing transmission, especially oral and ocular inoculation. Topical antiviral therapy has not been shown to be of treatment or prophylactic benefit. Although oral acyclovir has been advocated for immunocompromised patients, the benefits remain less clear in immunocompetent patients.

Complications. Misdiagnosis of a bacterial cause such as felon or paronychia may lead to improper treatment. A careful history, search for concurrent vesicular lesions, and avoidance of local incision and drainage should be carried out. Viral culture or PCR assay should be considered in equivocal diagnoses, especially in immunocompromised patients.[18]

Tenosynovitis

Principles. Synovial space infections involve the flexor tendon sheaths and associated bursae (see Figs. 43.18 and 43.19). Double-walled sheaths contain a visceral layer adjacent to the tendon and a parietal layer, extending from the midpalmar crease to just proximal of the DIP joint. The thumb and fifth digit sheaths are continuous with the radial and ulnar palmar bursae. The radial bursa surrounds the flexor pollicis longus tendon; the ulnar bursa surrounds the flexor digitorum superficialis and flexor digitorum profundus tendons. These bursae communicate with each other in approximately 80% of the population, facilitating the spread of horseshoe infections. The sheaths and associated bursae of the second, third, and fourth digits end at the midpalmar crease and do not communicate with each other or the palm. *S. aureus*,

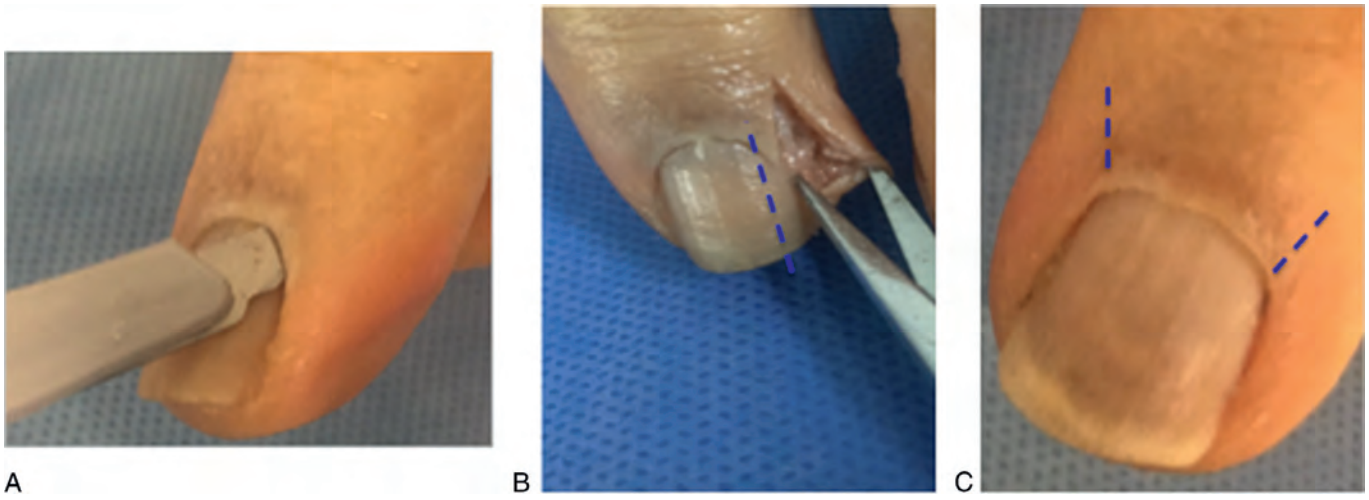


Fig. 43.43. Drainage of paronychia. **A,** The eponychial fold is elevated from the nail to facilitate local drainage. **B,** A lateral incision may be necessary to expose and drain an extended collection. The lateral aspect of the nail (*blue dashed line*) is removed if infection tracks below it. **C**, Two incisions are required (*blue dashed lines*) if the infection tracks across the proximal nail. This also facilitates proximal nail removal if the infection tracks below it. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

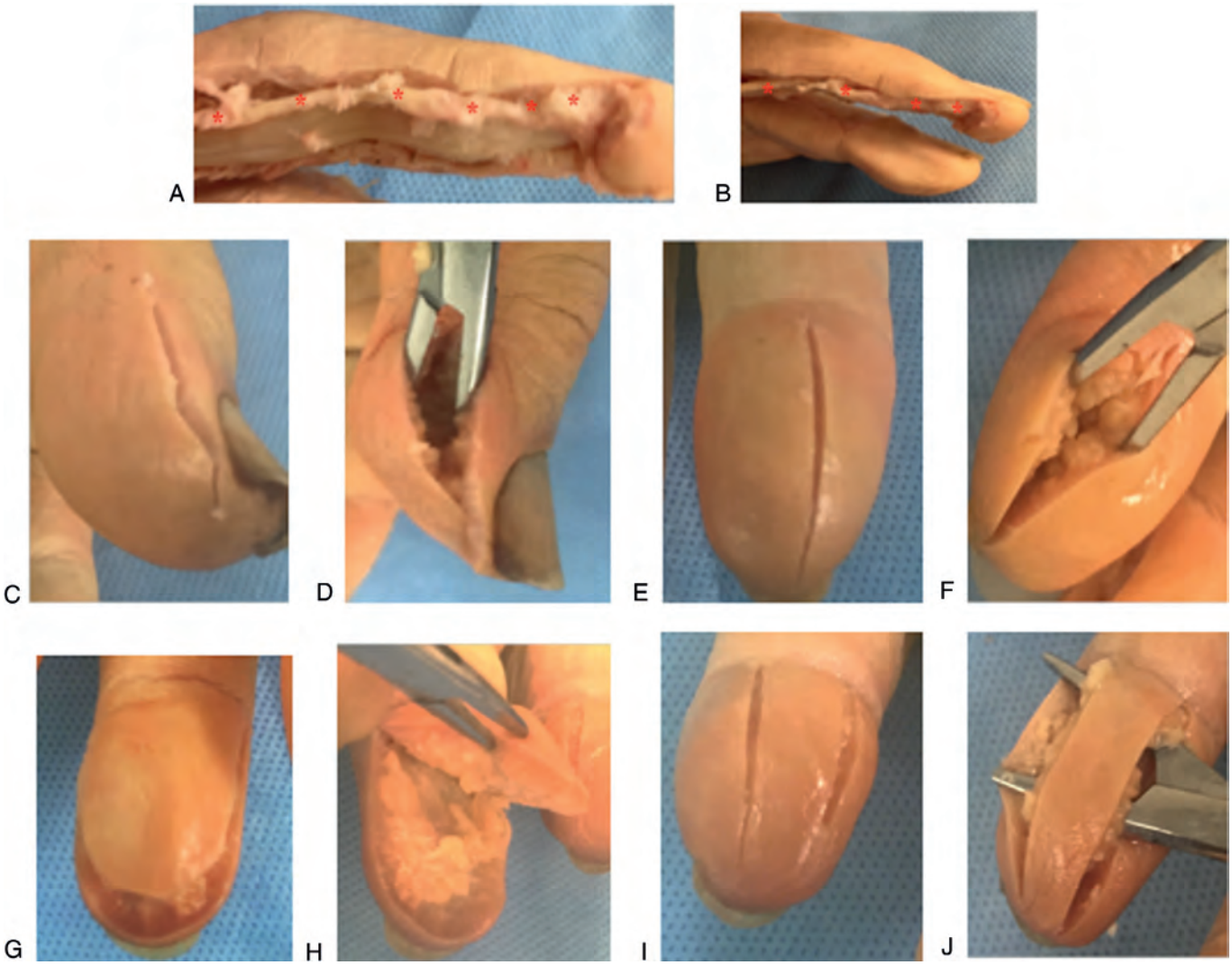


Fig. 43.44. Incision and drainage techniques for felon. **A, B,** Exposure of the digital neurovascular bundle extending toward the digit tip. Note that it passes 2 to 3 mm volar to the lateral nail bed. **C, D,** Unilateral longitudinal approach, the most commonly used technique. Blunt dissection follows to ensure that the septae are divided and loculations are freed. **E, F,** Longitudinal paramedian incision. Blunt dissection is used on either side of the incision to free the septae. **G, H,** Fishmouth incision. This technique is not advised. **E–J,** Parallel through and through incision, which also is not advised. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

streptococci, gram-negative organisms, and enterococci have been isolated from infections caused by penetrating injuries that violate the bursa and sheath or by hematogenous spread (eg, endocarditis). Infection can spread rapidly and proximally to involve the midpalmar, lumbrical (second, third, and fourth digits), thenar, and hypothenar compartments.

Clinical Features. Clinical manifestations of tenosynovitis were first described by Kanavel. These include the following: (1) palpable tenderness along the tendon sheath; (2) pain on passive extension of the digit; (3) symmetric digital swelling; and (4) digit fixed in a semiflexed position. Although all signs may not be present, the first two findings are the most useful and consistent clinical findings. Early recognition can prevent proximal spread of infection because progressive inflammation of the space can lead to microvasculature compromise and necrosis.

Management. Patients with flexor tenosynovitis require hospital admission, IV antibiotics, immobilization, elevation of the affected extremity, and hand service consultation for possible operative irrigation and drainage. Surgery should be considered in severe cases and for those who fail to improve after 24 hours of conservative treatment. The flexor sheath is rarely affected alone, and overlying cellulitic skin changes should raise concern for concurrent proximal bursa or midpalmar space involvement. Late presentations are common in immunocompromised patients (eg, diabetes mellitus) and in those suffering from peripheral neuropathy. In patients with infection after penetrating trauma, antibiotics should include antistaphylococcal coverage (eg, cephalexin or dicloxacillin; vancomycin, trimethoprim-sulfamethoxazole, or clindamycin for suspected MRSA or penicillin allergy). Gonococcal infections should be considered in sexually active persons with atraumatic presentations. In these cases, we recommend empirical treatment with ceftriaxone pending final test results, including samplings of mucosal sites.

Deep Space Infections

Principles. There are superficial and deep facial compartments in the hand that are potential spaces for the origin and spread of infection from penetrating wounds, communicating adjacent spaces, or hematogenous spread. The three superficial

spaces include the dorsal subcutaneous space, subaponeurotic space, and interdigital web space. Three anterior palmar spaces include the thenar, hypothenar, and midpalmar spaces (see Fig. 43.30). Common pathogens include *S. aureus*, streptococci, and coliforms.

Clinical Features. Concurrent subcutaneous involvement is the rule, not the exception, and the emergency clinician should consider a deep space process with a clinical context, such as penetrating trauma. Symptoms include pain out of proportion to the clinical findings and deep space tenderness with digital motion. When inflamed, the dorsal subaponeurotic space creates diffuse swelling and erythema on the hand dorsum but can be distinguished from simple cellulitis by noting concurrent tenderness on digital extension.

A palmar puncture wound, deep blister, or infected callus at the MCP joint can evolve into an interdigital web space infection termed a *collar button abscess*. Volar spread of infection is limited by the tight adherence of skin to the palmar aponeurosis. The infection extends dorsally to involve the dorsal subcutaneous tissues. The involved web space will appear swollen and tender, with its adjacent digits lying abducted.

Tenosynovitis of the first and second digits can extend into the thenar space, causing painful swelling of the thenar eminence and first web space. The thumb will be held in an abducted and flexed position. Midpalmar space infections may originate from tenosynovitis of the third, fourth, and fifth digits and present with pain and tenderness in the proximal palmar region, especially with motion of the fingers.

Management. Deep fascial space infections require hospital admission, IV antibiotics, immobilization, elevation, and hand service consultation to determine the need for operative exploration and drainage. Patients should receive IV antistaphylococcal coverage, such as cephalexin and dicloxacillin; vancomycin, trimethoprim-sulfamethoxazole, or clindamycin should be used for suspected MRSA or penicillin allergy.

Septic Arthritis

Principles. Infections are commonly caused by direct inoculation from penetrating injuries, spread from adjacent soft tissue infections (eg, felon, paronychia, tenosynovitis); hematogenous spread is a less common cause. *S. aureus* (MRSA and methicillin-sensitive *S. aureus*) and streptococci are common pathogens, whereas *Haemophilus influenzae*, *Pseudomonas aeruginosa*, coliforms, corynebacteria, and anaerobes are less common.[19] Gonococcal infection should be considered in sexually active patients presenting with atraumatic mono- or polyarticular arthritis.

Clinical Features. With progressive swelling, the joint assumes a semiflexed position to accommodate maximum volume. The overlying skin is commonly erythematous and warm. Unlike tenosynovitis, the joint itself, not the length of the overlying tendon sheath, is extremely tender and guarded, allowing minimal passive motion. The patient is often unwilling to mobilize the affected joint.

Management. Arthrocentesis should be performed on suspected joints using a 20-gauge or larger needle to aspirate viscous fluid. Relative contraindications to arthrocentesis include coagulopathy and overlying soft tissue infection. Admission, immobilization, elevation, and hand service consultation for joint irrigation and débridement or closed joint catheter irrigation should be considered. Patients should receive IV antistaphylococcal coverage, such as cephalexin or dicloxacillin; vancomycin, trimethoprim-sulfamethoxazole, or clindamycin should be used for suspected MRSA or penicillin allergy and ceftriaxone for suspected gonococcal infection.

Osteomyelitis

Open fractures and spread from adjacent soft tissue infections are common causes of hand osteomyelitis, with an incidence from 1% to 11%, far lower than in long bone injuries. Wounds with gross contamination, significant soft tissue injury, and severe skeletal trauma are at highest risk.

Clinical Features. Usually insidious, fever, localized soft tissue redness, swelling, warmth, and tenderness should raise suspicion, especially in immunocompromised patients. Children and infants may refuse to use the limb due to pain and tenderness (pseudoparalysis). Laboratory studies such as complete blood count, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, and cultures may increase suspicion in the clinical context, but do not have the sensitivity or specificity of bone biopsy or aspirate cultures.[20] Radiographic images may show overlying soft tissue edema as early as 3 to 5 days; periosteal elevation and early bone destruction may be seen at 14 to 28 days.

Management. Early hand specialist consultation is recommended for assistance with definitive management, which may include surgical débridement or hyperbaric oxygen therapy. Infectious disease consultation may be warranted, especially for immunocompromised patients.

Common pathogens resulting from trauma include *S aureus*, coliform bacilli, and *P. aeruginosa*. Primary coverage may include cephalexin, nafcillin, and fluoroquinolones. Alternatives include vancomycin for suspected MRSA and a third- or fourth-generation cephalosporin (eg, ceftazidime, cefepime) for suspected pseudomonal infection. For suspected hematogenous-induced osteomyelitis, whose pathogens include *S. aureus*, Enterobacteriaceae, streptococci, and *H. influenzae*, treatment should include a combination of a penicillinase-resistant synthetic penicillin and a third-generation cephalosporin. Alternate therapy includes vancomycin (for suspected MRSA) or clindamycin, a third-generation cephalosporin, and linezolid. Ciprofloxacin and rifampin may also be an appropriate combination therapy for adult patients. *S. aureus* and *Salmonella* spp. should be considered in patients with sickle cell anemia.

Nontraumatic Disorders of the Hand

Stenosing Tenosynovitis

Stenosing tenosynovitis (ie, trigger finger or thumb, texting tendinitis, so-called Game Boy thumb) is caused by nodular thickening of the flexor tendon sheath, leading to a focal stenosis that prevents smooth passage of the associated tendon. As a result, the patient experiences painful and delayed extension of the digit. Causes can be traumatic, infectious, rheumatologic, inflammatory, or congenital. The MCP joint is the most frequent location, with the middle and ring fingers most commonly involved. Patients often describe a click or popping sensation after having to extend the digit forcefully; eventually, the digit remains locked in place, requiring manual extension of the digit. Patients should be referred to a hand specialist. Temporizing therapy may include local injection of steroids and 1% lidocaine placed into the tendon sheath at the stenosis; the digit is then immobilized in extension.

Ganglion

A ganglion, the most common soft tissue tumor of the hand, is a synovial cyst consisting of degenerated collagenous connective

tissue that has herniated from a joint or tendon sheath. The condition grows insidiously, without a clear inciting event, and is common along flexor tendon sheaths and the wrist. Chief complaints include a dull ache and localized pain over the structure. Although large or tender ganglion cysts may be aspirated, they commonly recur and often require surgical arthroscopic or open excision for definitive removal. We recommend referral to a hand specialist.

KEY CONCEPTS

- Traumatic, infectious, and inflammatory conditions involving the hand are among the most commonly encountered problems in the ED.
- Obtaining a thorough history and performing a meticulous physical examination of the hand are paramount to the evaluation and development of an appropriate management strategy. Diagnostic imagery should be obtained with clinical suspicion.
- Timely and accurate evaluation and management yield the best functional outcomes with traumatic and infectious conditions of hand.
- Management of the acute hand condition should focus on maximizing function and minimizing long-term disability.
- Recognition of the need for hand specialist consultation or referral is extremely important for obtaining the best functional outcome for the patient.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 43: QUESTIONS & ANSWERS

43.1. A 25-year-old man presents with a painful laceration of the forearm following a bicycle accident. The laceration transects the supinator muscle. The patient's physical examination shows his fingers held in flexion at the metacarpophalangeal (MCP) joint and thumb held in adduction. Which anatomic structure has been injured?

A. Median nerve
B. Musculocutaneous nerve
C. Radial artery
D. Radial nerve
E. Ulnar nerve

Answer: D. Motor function of the radial nerve is tested by having the patient extend the wrist against resistance. Proximal injury to the radial nerve causes a condition known as wristdrop, in which the fingers are held in flexion at the MCP joints, and the thumb is adducted.

43.2. A young man presents after a fight complaining of a cut on his finger. On physical examination, you note a deformity to the distal second phalanx, with a laceration to the second MCP joint. What is the best management for this patient?

A. Antibiotics, splint, and follow-up with hand surgery
B. Irrigation, topical antibiotic, and splint
C. Radiography, hand surgery consult, and antibiotics
D. Radiography, laceration repair, and splint
E. Radiography, urgent hand surgery follow-up, and cephalosporin

Answer: C. Lacerations or puncture wounds over the dorsum of the MCP joint associated with a metacarpal head fracture should be considered open until proved otherwise. Such injuries are often caused by a clenched fist injury and are highly contaminated wounds. Emergent consultation with a hand surgeon for operative débridement and irrigation is recommended. Prophylactic coverage with a cephalosporin is routinely recommended, although those with highly contaminated wounds also should receive penicillin with a β-lactamase inhibitor and an aminoglycoside.

43.3. A 27-year-old woman was playing basketball and jammed her ring finger on the basketball. She presents with her ring finger held in flexion at the proximal interphalangeal (PIP) joint and hyperextension at the distal interphalangeal (DIP) and MCP joints. What is the next step in the management of this patient?

A. Splint PIP in extension, allowing free movement of DIP and MCP.
B. Splint PIP in extension, MCP in flexion.
C. Splint PIP in extension, with full immobilization of digit.
D. Splint PIP in slight flexion allowing free movement of DIP and MCP.
E. Splint PIP in 90 degrees of flexion and extension of DIP and MCP.

Answer: A. This patient presents with a boutonnière deformity, which is a disruption of the central tendon, causing disruption in the extensor mechanism of the finger. Patients with suspected closed central tendon injuries should be treated with splinting of the PIP joint in full extension for 5 or 6 weeks. Only the PIP joint should be immobilized, and passive and active DIP joint flexion is encouraged from the outset. Operative repair may be required for an acute, closed boutonnière injury associated with a displaced avulsion fracture and injury with volar PIP joint dislocation. Early referral to a hand surgeon is advised.

43.4. A mechanic presents with a complaint of right index finger fusiform swelling and pain following an injection injury with a grease gun. Which of the following approaches best describes the appropriate management?

A. Digital block, elevation, and urgent surgical consult
B. Digital block, splint, and outpatient antibiotics
C. Digital block, splint, and urgent surgical consult
D. Parenteral pain medication, splint, and emergent surgical consult
E. Parenteral pain medication, splint, and outpatient surgical evaluation

Answer: D. Initial emergency department (ED) management includes splinting, elevation, tetanus prophylaxis, analgesia, and broad-spectrum antibiotics. Digital blocks are contraindicated because of the potential for increased tissue pressure, which may aggravate vascular compromise. Emergent hand surgery consultation is warranted because most cases require early extensive surgical decompression and débridement.

43.5. Which of the following are diagnostic criteria for flexor tenosynovitis?
- **A.** Flexor contracture, flexor fluctuance, digit held in flexion, flexor erythema
- **B.** Flexor tendon tenderness, pain on passive flexion, symmetric swelling, digit held in flexion
- **C.** Flexor tendon tenderness, symmetric swelling, pain on passive extension, digit held in flexion
- **D.** Pain, paresthesias, pulselessness, pallor
- **E.** Pain out of proportion to physical examination

Answer: C. Four cardinal signs of acute flexor tenosynovitis (Kanavel's signs) are usually present and help differentiate tenosynovitis from other soft tissue infections in the hand: (1) tenderness along the course of the flexor tendon; (2) symmetric swelling of the finger; (3) pain on passive extension; and (4) a flexed posture of the finger. All four signs may not be present early in the course of infection.

43.6. How much angulation is acceptable in a metacarpal neck fracture?
- **A.** 20 degrees at index finger
- **B.** 25 degrees at middle finger
- **C.** 35 degrees at index finger
- **D.** 45 degrees at little finger
- **E.** 50 degrees at index finger

Answer: D. Generally, less than 15 degrees angulation is allowed in the index and long finger metacarpals; in the ring and little finger metacarpals, 35 and 45 degrees of angulation are allowed, respectively. Any rotational misalignment should be completely corrected.

43.7. A 30-year-old woman presents after getting her index finger caught in her car door. Examination of the finger reveals a dark red discoloration beneath the nail involving approximately 25% of the nail. The nail is intact and the nail margins are not disrupted. Radiographs are negative. What is the most appropriate management?
- **A.** Consult with hand surgery
- **B.** Nail trephination
- **C.** Oral pain medication, arrangements for follow-up
- **D.** Performance of a digital block
- **E.** Removal of the nail and repair of the nail bed laceration

Answer: C. Small subungual hematomas do not require drainage; the blood is incorporated into the nail and eventually removed with the free edge. Large (>50% of the nail) hematomas cause significant discomfort and should be removed by nail trephination.

43.8. A 42-year-old man presents with a painful swollen tip of his index finger. Four days earlier, he sustained a puncture wound to his fingertip. The physical examination is significant for tenderness, swelling, redness, and increased pressure in the distal pulp space of the affected finger. Which of the following is the best management strategy?
- **A.** Deep midline volar incision to the flexor tendon sheath
- **B.** Finger splint, oral antibiotics
- **C.** Fishmouth incision
- **D.** Intravenous antibiotics, emergent hand surgery consult
- **E.** Lateral incision along the ulnar aspect of the fingertip

Answer: E. Felons are traditionally managed with incision through the septa to drain and relieve pressure in septal compartments. Most felons can be drained by a single lateral incision. The incision should be made along the ulnar aspect of the index, middle, and ring fingers and the radial aspects of the thumb and little finger, avoiding pincher surfaces. Fishmouth incisions may destroy the blood supply to the fingertip. Any incision that is made too deeply and proximally can injure the flexor tendon sheath, initiating a tenosynovitis.

43.9. Which of the following statements regarding foreign bodies in the hand is true?
- **A.** A single radiograph is sufficient when looking for foreign bodies
- **B.** Hand foreign bodies should always be removed emergently.
- **C.** Magnetic resonance imaging (MRI) can improve the ability to detect foreign bodies.
- **D.** Most glass foreign bodies are radiographically occult.
- **E.** Wooden foreign bodies are readily visible on plain radiography.

Answer: C. Radiography is the best method for detecting radiopaque foreign bodies, including most glass. Radiographs should be taken using a soft tissue technique, with multiple views. Wooden foreign bodies are difficult to visualize radiographically. MRI, computed tomography (CT), and ultrasound can identify radiographically occult foreign bodies. Decisions regarding the necessity and timeliness of foreign body removal are based on the size and reactivity of the foreign body, proximity to vital structures, degree of wound contamination, and presence or absence of symptoms.

43.10. What is the proper ED management of a closed mallet finger injury?
- **A.** Splint the DIP and PIP joints in extension.
- **B.** Splint the DIP and PIP joints in extension and MCP joint in flexion.
- **C.** Splint the DIP joint in flexion.
- **D.** Splint the DIP joint in slight hyperextension.
- **E.** Splint the DIP and PIP joints in flexion.

Answer: D. The management of a closed mallet finger injury consists of maintaining continuous DIP extension for 6 to 8 weeks, allowing for tendon healing to occur. The DIP joint is immobilized in slight hyperextension, but the PIP and MCP joints are allowed to move freely. An excessive degree of hyperextension should be avoided because this can lead to skin necrosis on the dorsal surface of the DIP joint.

CHAPTER 44

Wrist and Forearm

David T. Williams | Hyung T. Kim

WRIST

PRINCIPLES

The wrist joint is broadly defined as the anatomic area from the distal radius and ulna bones of the forearm to the carpometacarpal junctions of the hand. It is anatomically and biomechanically complex, allowing for diverse functional capabilities. In the setting of trauma, this area is exposed, mobile, and at high risk of injury. Detailed knowledge of relevant anatomy, mechanism of injury, accurate clinical assessment, and radiograph interpretation are essential for proper emergent diagnosis and treatment.

ANATOMY AND PHYSIOLOGY

The wrist is composed of many complex articulations, including the radiocarpal, midcarpal, and distal radial ulnar joints (DRUJs), allowing for flexion, extension, abduction (radial deviation), adduction (ulnar deviation), and circumduction movements. Pronation and supination of the hand are primarily movements of the forearm occurring at the proximal radial ulnar joint and DRUJ.

The wrist includes the distal radius, ulna, and eight carpal bones, which are arranged in two transverse rows and are commonly referred to as the carpus (Fig. 44.1). Each carpal row contains four bones. The more mobile, proximal row, listed radial to ulnar, consists of the scaphoid, lunate, triquetrum, and pisiform bones and the distal row consists of the trapezium, trapezoid, capitate, and hamate bones.

The radius has three articular surfaces at the wrist—radiocarpal joint, DRUJ, and an interface with the triangular fibrocartilage complex (TFCC), also known as the articular disk. Only the distal radius articulates directly with the carpus via the scaphoid and lunate bones, which form the commonly referred to wrist joint. The ulna is separated from direct articulation with the proximal carpal row by the TFCC. This articular disk binds the distal ends of the radius, ulna, lunate, and triquetrum together. The DRUJ is a synovial pivot where the distal radius articulates and rotates around the relatively fixed ulna, and this joint is primarily stabilized by the TFCC.

Aside from the pisiform, which is considered to be a sesamoid bone embedded within the flexor carpi ulnaris (FCU) tendon, the carpus bones are lined by synovium that creates a continuous capsule throughout the intercarpal joints, distally to the metacarpal articulations. The only muscular insertions that occur throughout the carpus are the origin of the abductor digiti minimi from the pisiform and the point at which the FCU tendon inserts onto the hook of the hamate. As a result, nearly all carpal bone movements are passive, based on muscular insertions on the distal radius, ulna, and metacarpal bases.

The stabilizing ligaments of the wrist are divided into two major groups, the intrinsic and extrinsic ligaments. The intrinsic ligaments interconnect the individual carpal bones, and the extrinsic ligaments link the carpal bones to the distal radius, ulna, and metacarpals. The intrinsics are named for the adjacent bones to which they connect; the most important for maintaining carpal stability are the scapholunate and lunotriquetral ligaments. The extrinsics are divided into volar and dorsal groups. The volar extrinsic ligaments are divided into two V-shaped ligamentous bands called the proximal and distal arcades, which generally are thicker and stronger than the dorsal extrinsic ligaments and are the most important in providing stability to the wrist. Between these volar arcades is an area relatively devoid of ligamentous support, called the space of Poirier. This space enlarges when the wrist is dorsiflexed, and an injury to the joint capsule in this region can result in significant carpal instability (Fig. 44.2).

Most structures that cross the wrist joint are contained within individual compartments formed by the deep fascia of the wrist. On the dorsal surface of the wrist, the extensor tendons are divided by the extensor retinaculum into six compartments, each having a separate synovial sheath that extends proximally and distally to the retinaculum. On the volar surface of the wrist, the flexors of the digits and median nerve are contained within the carpal tunnel, which is formed by the flexor retinaculum superficially and its attachments to the carpal bones. Radially, the flexor retinaculum attaches to the scaphoid tubercle and ridge of the trapezium. On the ulnar side, it attaches to the pisiform and hook of the hamate. Both the trapezoid and capitate bones form the floor of the carpal tunnel. Radially and superficially to the carpal tunnel, the flexor carpi radialis tendon crosses the wrist joint in its own compartment.

The vascular supply to the wrist is provided by the radial and ulnar arteries, which join in a series of dorsal and palmar arches to supply the bones of the carpus. The intrinsic blood supply to most carpal bones enters the distal portion, leaving the proximal area at risk for devascularization and avascular necrosis (AVN) when fractured. This is particularly true for the scaphoid, capitate, and lunate bones, which receive their blood supply commonly from a single distal vessel (Fig. 44.3).

The wrist and hand are innervated by the radial, median, and ulnar nerves. The radial nerve and dorsal sensory branch of the ulnar nerve cross the dorsum of the wrist near the radial and ulnar styloids, respectively. The median nerve crosses within the carpal tunnel on the volar aspect of the wrist, just radial and deep to the palmaris longus tendon. The ulnar nerve is within Guyon's canal, between the pisiform and hook of the hamate (see Fig. 44.3). In the setting of trauma, motor and sensory function of the radial, median, and ulnar nerves may be assessed at the wrist and distally, based on common clinical examinations (Table 44.1).

CLINICAL FEATURES

The clinical examination of the patient with a wrist injury begins with a complete history, including the mechanism of injury and site of maximal pain or tenderness. Most wrist injuries are caused by a fall on the outstretched hand. The physical examination begins with inspection of the wrist, with the opposite uninjured wrist used as the normal reference; it includes an assessment of

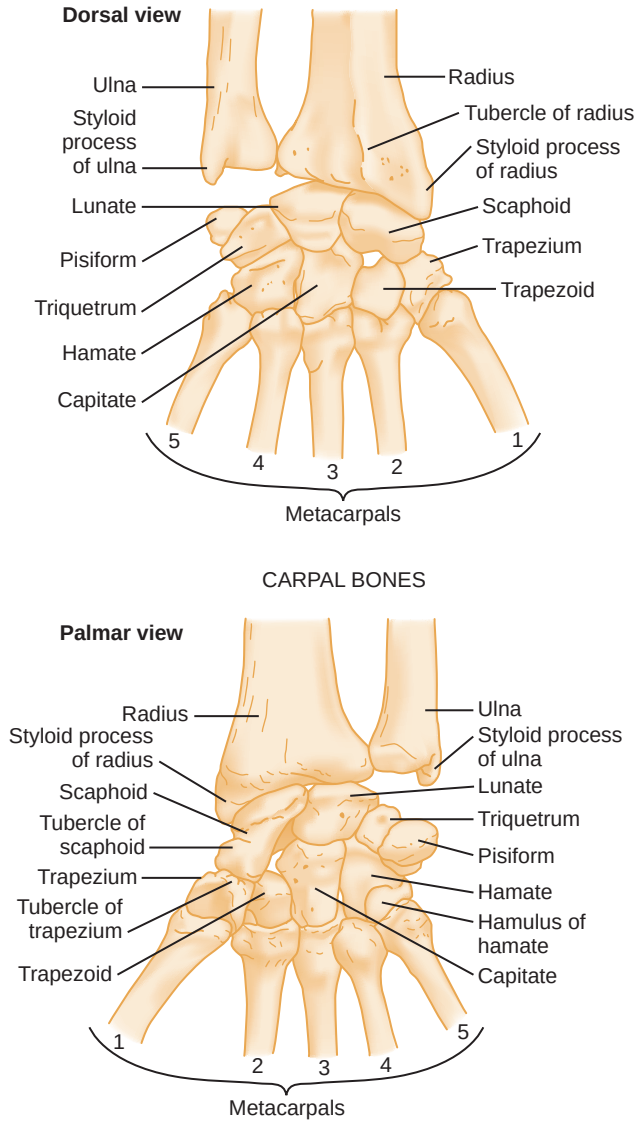

Fig. 44.1. Bones of the wrist. The wrist joint includes the distal articular surfaces of the radius and ulna and the proximal and distal carpal rows. (Adapted from Netter FH: Atlas of human anatomy, ed 3, Teterboro, NJ, 2003, Icon.)

the presence of swelling, discoloration, or obvious deformity and ability of the patient to move the joint through a normal range of motion.

Several bony prominences serve as useful landmarks; their locations are best described in relation to the two major lateral and medial reference points in the wrist, the radial and ulnar styloids, respectively. Just distal to the radial styloid is the anatomic snuffbox, bordered radially by the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons and ulnarly by the extensor pollicis longus (EPL) tendon. The body of the scaphoid is palpable within the snuffbox and is more prominent with the wrist in ulnar deviation. Lister's tubercle can be palpated on the dorsum of the wrist, just ulnar to the radial styloid. This is an important landmark because, notably, just distal to the tubercle lies the scapholunate joint, a common site of ligamentous injury in the wrist. With the wrist in neutral position, the capitate is palpable in a small depression found midway between the base of the middle metacarpal and Lister's tubercle. Bringing the wrist into flexion can bring the lunate forward into a palpable position at this same site. Lister's tubercle divides the second and third dorsal extensor compartments of the wrist and is also used as a primary landmark for radiocarpal arthrocentesis. Further ulnar on the dorsal side of the wrist from Lister's tubercle is the DRUJ. The triquetrum is palpable distal to the ulnar styloid in the proximal carpal row and can be made more prominent with radial deviation of the wrist.

On the volar aspect of the wrist, the scaphoid tubercle is palpable just distal and palmar to the radial styloid. It is felt as a rounded prominence at the base of the thenar muscles and is especially prominent when the wrist is extended. On the ulnar border of the wrist, the pisiform is palpable at the base of the hypothenar muscles, just distal to the wrist crease. In addition, approximately 1 cm distal and radial to this point, the prominence formed by the hook of the hamate can be palpated.

The clinical examination also includes an assessment of neurovascular status. Radial and ulnar pulses are easily palpable on the volar surface of the wrist, and the presence of adequate circulation should be assessed in injuries to the wrist.

TABLE 44.1

Median, Radial, and Ulnar Never Innervations and Clinical Examination

PARAMETER	MEDIAN	RADIAL	ULNAR
Innervation	Pronator teres Flexor carpi radialis Palmaris longus Flexor digitorum superficialis Flexor digitorum profundus Flexor pollicis longus Prone for quadrates	Brachioradialis Extensor carpi radialis longus Extensor carpi radialis brevis supinator Extensor digitorum Extensor digiti minimi Extensor carpi ulnaris Abductor pollicis longus Extensor pollicis longus Extensor pollicis brevis Extensor indicis	Flexor carpi ulnaris Flexor digitorum profundus Opponens digiti minimi Abductor digiti minimi flex Lumbricals 3 and 4 Dorsal interossei Palmar interossei Adductor pollicis Palmaris brevis
Motor	Thumb opposition Pincer function (thumb, index finger) Pronation A-OK sign	Wrist extension Finger extension Supination Thumbs-up sign	Finger abduction Finger abduction
Sensory	*Sensation* Index finger, volar tip Volar	*Sensation* First dorsal web space Dorsal	*Sensation* Little finger, volar tip Volar dorsal

DIAGNOSTIC TESTING: RADIOLOGY

Plain radiographs remain the cornerstone of emergent diagnosis of trauma to the wrist. Routine radiographic views include the posteroanterior (PA), lateral, and oblique projections, each obtained with the wrist in neutral position. Accurate interpretation of these views requires knowledge of the normal appearance and anatomic relationships of the distal radius, ulna, and carpal bones.

On a correctly positioned PA view of the wrist, the ulnar styloid rises from the lateral aspect of the distal ulna; the extensor

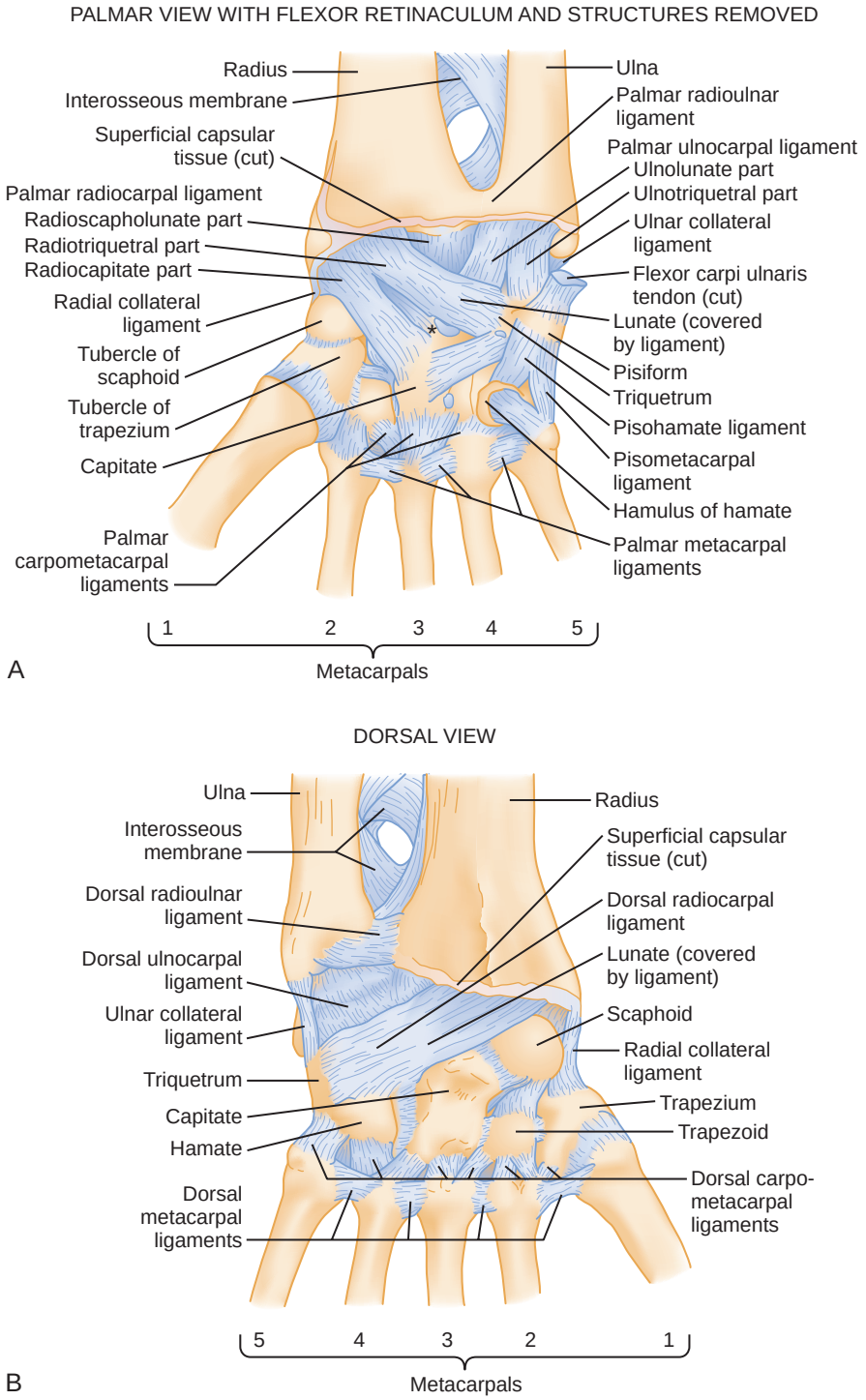

Fig. 44.2. Ligaments of the wrist. **A,** The volar extrinsic ligaments are most important in providing stability to the wrist. These include the radial collateral, radiocapitate, radioscaphoid, radiotriquetral, ulnotriquetral, capitotriquetral, and ulnar collateral ligaments. The space of Poirier (*) is a gap in the volar ligaments and the site of potential weakness. **B,** The intrinsic (intercarpal) ligaments connect the individual carpal bones. The most important of these are the scapholunate and lunotriquetral ligaments. (Adapted from Netter FH: Atlas of human anatomy, ed 3, Teterboro, NJ, 2003, Icon.)

carpi ulnaris (ECU) tendon groove should be visualized at, or radial to, its base. The radial styloid process extends beyond the end of the articular surface of the ulna by a normal distance of 9 to 12 mm. This normal difference in length is called the radial length measurement (Fig. 44.4). There may be some degree of ulnar variance that affects the radial length measurement on a PA radiograph. The distal articular surface of the ulna may terminate before, at, or distal to the radiolunate articulation as a result of wrist rotation, flexion, extension, anatomic variation, or injury. Neutral ulnar variance (as seen in Fig. 44.4) is described when the distal ulnar and radiolunate articular surfaces terminate at the same point. A positive ulnar variance (ulnar articulation is more distal) or negative ulnar variance (ulnar articulation is more proximal) is independent of styloid size and may be associated

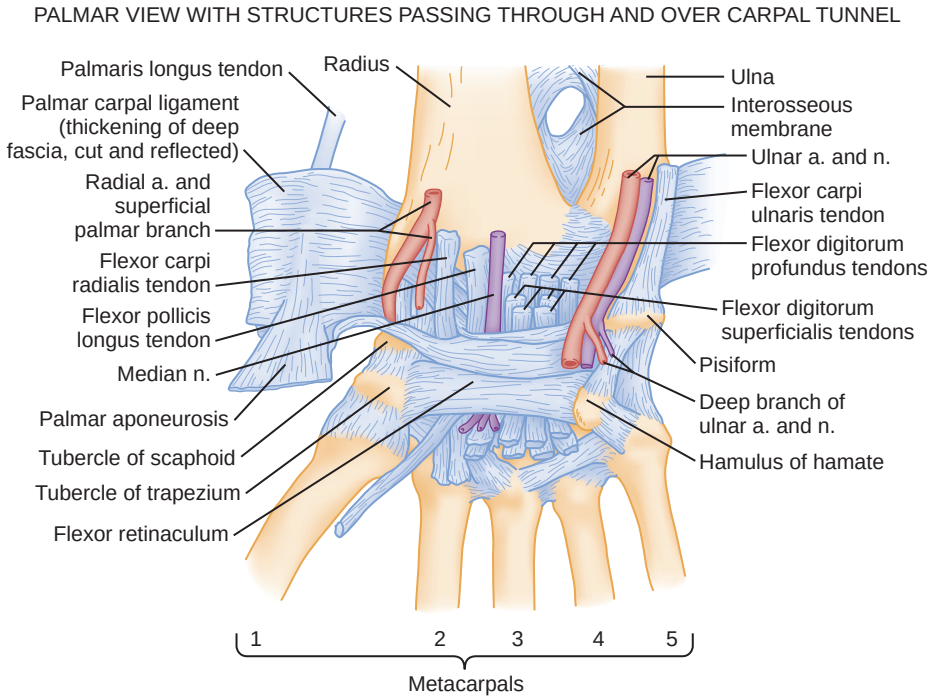

Fig. 44.3. Vascular supply to the wrist. Note the relationship of the ligaments to the neurovascular supply to the wrist. (Adapted from Netter FH: Atlas of human anatomy, ed 3, Teterboro, NJ, 2003, Icon.)

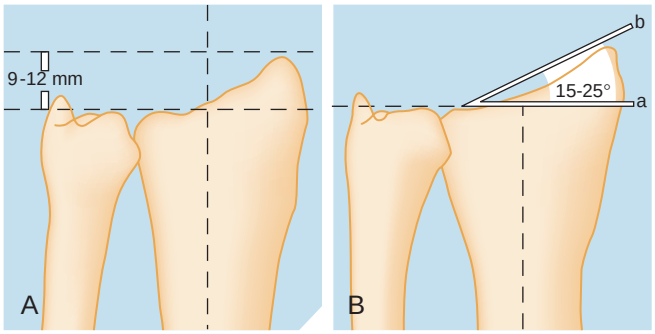

Fig. 44.4. Normal radiographic appearance of the wrist on a posteroanterior view. The ulnar styloid arises from the lateral aspect of the distal ulna, and the tendon groove for the extensor carpi ulnaris should be visualized at, or radial to, its base. **A,** Radial length measurement with neutral ulnar variance. The radial styloid extends 9 to 12 mm beyond the articular surface of the distal ulna. The ulna may terminate distal, at, or proximal to, the radiolunate articulation affecting radial length measurement with a positive, neutral, or negative variance, respectively. **B,** The ulnar slant of the distal radius (angle ab) normally measures 15 to 25 degrees. (From Greenspan A: Orthopedic radiology: a practical approach, ed 2, New York, 1992, Gower Medical.)

with wrist pathology (eg, ulnar impaction syndrome and Kienbock's disease, respectively). The ulnar slant of the articular surface of the radius, referred to as radial inclination, is visible on the PA view and normally measures 15 to 25 degrees (see Fig. 44.4). Both these measurements are important in assessing the degree of radial shortening seen in association with some fractures of the distal radius. The normal appearance of the carpus on the PA view shows an approximately equal distance (usually 1 to 2 mm) between each of the carpal bones, and opposing articular surfaces are parallel to one another (an arrangement known as parallelism). On radiographs, three smooth curves normally can be drawn along the carpal articular surfaces, known as carpal or Gilula's arcs (Fig. 44.5). Disruption of these curves or widening of the carpal spaces is an indication of carpal ligament disruption, instability, or fracture.[1]

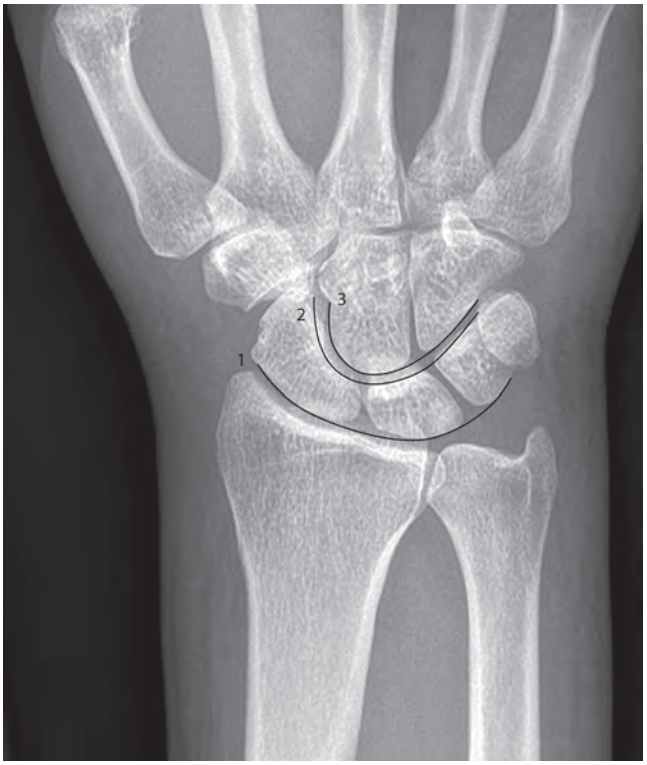

Fig. 44.5. Carpal (Gilula's) arcs. On a posteroanterior radiograph of the wrist, three arcuate lines (1 to 3) can be drawn along the articular surfaces. Although small indentations at joint lines may occur, a step-off or broken arc suggests fracture, ligamentous instability, or disruption of the wrist.

The normal volar tilt of the distal radial articular surface is visible on the lateral view of the wrist and typically measures 10 to 25 degrees (Fig. 44.6). Adequacy of a lateral view of the wrist is assessed based on the relationship among the scaphoid, pisiform, and capitate projections. The palmar cortex of the pisiform

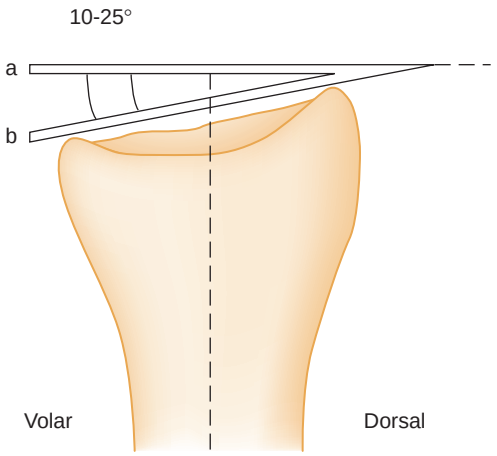

Fig. 44.6. Normal radiographic appearance of the wrist on a lateral view. The distal radius has a normal volar tilt (angle ab) of 10 to 25 degrees. (From Greenspan A: Orthopedic radiology: a practical approach, ed 2, New York, 1992, Gower Medical.)

Fig. 44.7. Normal S-P-C (scaphoid-pisiform-capitate) lateral view of the wrist. The palmar cortex of the pisiform (P) is shown bisecting the line between the palmar aspect of the scaphoid (S) and capitate (C) bones.

should project midway between the palmar margins of the distal pole of the scaphoid and capitate head, forming the S-P-C lateral (Fig. 44.7). The normal alignment of the distal radius with the lunate and capitate also is seen on the lateral view, which will show two concentric cups—the cup of the distal radius containing the lunate and the cup of the distal lunate containing the capitate. Ideally, the long axis of the radius, lunate, capitate, and third metacarpal should appear as a straight line on the lateral view, although the so-called normal alignment usually is within 10 degrees of this line (Fig. 44.8). The carpal alignment on the lateral view is defined further by the scapholunate angle, which should

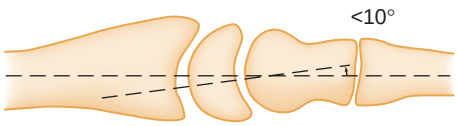

Fig. 44.8. Normal relationship of carpal bones on a lateral radiographic view. The concavity of the radius and lunate and convexity of capitate form three C-shaped areas *(stippled)* along a straight line that runs through the central axis of these bones.

measure 30 to 60 degrees, and capitolunate angle, which is 0 to 30 degrees (Fig. 44.9). Abnormalities in these angles are seen in patients with carpal ligament injuries and instability.

The soft tissues of the wrist also offer valuable clues to the presence of underlying bony injuries. It is estimated that on 90% of normal lateral radiographs of the wrist, the pronator quadratus line is visible as a linear, lucent, fat collection in the volar soft tissues just anterior to the distal radius (Fig. 44.10). Fractures of the distal radius or ulna result in a pronator quadratus sign representing volar displacement, anterior bowing, or complete obliteration of this line. Although this sign may suggest injury, a wide range of sensitivities has been quoted, so, its absence does not exclude a fracture.[2,3] A positive pronator quadratus sign has also been observed in soft tissue injuries, as well as infectious and inflammatory medical conditions.

Many wrist injuries are occult and may not be identified or clearly characterized by routine wrist radiographs.[1] Additional radiographic imaging of the wrist may assist the emergency clinician with diagnosis based on chief complaint, mechanism of injury, or physical examination findings, including specific areas of tenderness. In addition to the standard PA, lateral, and oblique wrist radiographs, adjunct imaging may include views with ulnar and radial deviation, maximal flexion, extension, carpal tunnel view, reverse (supinated) oblique, clenched fist PA, or anteroposterior (AP) views. Emergent patient-specific imaging helps delineate otherwise occult fractures or abnormal motion of the carpus resulting from ligamentous injuries further. When a scaphoid fracture is suspected, a pronated ulnar deviated view of the wrist, allows for better visualization of the bone along its long axis. The carpal tunnel view is performed with the wrist hyperextended and provides an axial volar image of bony margins. The carpal tunnel view and reverse (supinated) oblique help identify fractures involving the hook of the hamate and pisiform in the common clinical setting of hypothenar wrist trauma.[4] The clenched fist, both PA and AP views, drive the capitate, proximally, as a wedge, causing diastasis within the scapholunate joint and highlighting ligamentous instability when tenderness is present (Table 44.2). Although scapholunate width may be exaggerated on the AP, instability is suspected when either view shows a distance of 3 mm or greater. Wrist views taken in maximal flexion or extension are typically used in more chronic ligamentous issues, such as volar and dorsal intercalated segmental instability.[5]

Given the high incidence of occult injuries of the wrist, when radiographs are negative and significant pain persists, immobilization and a repeat examination, often accompanied by imaging, should be arranged after a period of 1 to 2 weeks. A thumb spica is usually added in the setting of suspected scaphoid fractures. Additionally, occult, fractures or soft tissue injuries may be diagnosed emergently, urgently, or on a routine basis with advanced computed tomography (CT) or magnetic resonance imaging (MRI) imaging protocols.[6-9] Emergent CT or MRI wrist imaging is rarely, if ever, indicated in the emergency department (ED). Although advanced imaging occasionally identifies an otherwise occult injury, management and outcomes generally are not affected by this new diagnosis. The best data exist for scaphoid fractures (discussed below), for which CT and MRI protocols are

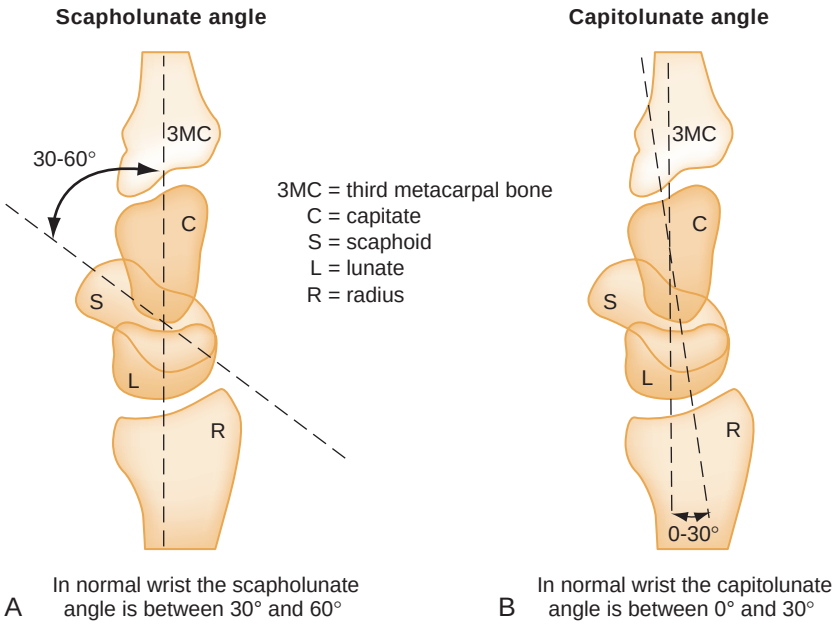

Fig. 44.9. **A,** The normal scapholunate angle is formed by the intersection of the longitudinal axes of the scaphoid and lunate and normally measures 30° to 60°. **B,** The normal capitolunate angle is formed by the intersection of the capitate and lunate central long axes and normally measures 0 to 30 degrees. (From Greenspan A: Orthopedic radiology: a practical approach, ed 2, New York, 1992, Gower Medical.)

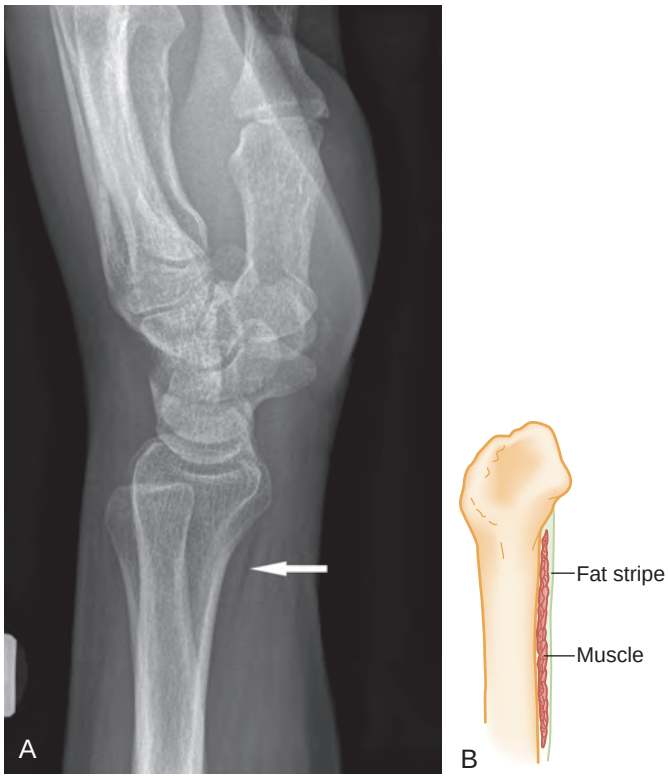

Fig. 44.10. The pronator quadratus fat pad. **A, B,** A narrow fat stripe *(arrow)* located on the volar surface of the radius is seen on the lateral view of the wrist. Although not highly sensitive, volar displacements, anterior bowing, or complete obliteration of this line caused by hematoma in the setting of trauma is suggestive of wrist injury or fracture.

approaching 100% sensitivity for injury. However, until more prospective and definitive research identifies clear value for emergent advanced imaging, we recommend immobilization, with follow-up in 1 to 2 weeks for reexamination and possible imaging at that time.

TABLE 44.2

Additional Radiographic Wrist Views

RADIOGRAPHIC VIEW	BENEFIT
Clenched fist (AP or PA)	Exposes scapholunate ligament injury; pushes capitate into proximal carpal row
Scaphoid (PA with ulnar deviation)	Elongates scaphoid; exposes wrist fractures
Carpal tunnel and reverse supinated oblique	Identifies fractures involving hamate and pisiform; identifies bony encroachment onto carpal tunnel

AP, Anteroposterior; *PA,* posteroanterior.

MANAGEMENT AND DISPOSITION

Carpal Injuries

Scaphoid Fractures

The scaphoid is the most commonly fractured bone of the carpus.[10,11] It accounts for approximately 70% of all carpal fractures and is typically seen in individuals 15 to 40 years of age.[11] Scaphoid fractures most commonly occur after a fall on the outstretched hand, causing hyperextension of the wrist.[11] These injuries are rare in skeletally immature patients because the carpus is composed entirely of cartilage at birth and remains predominantly cartilaginous until the adolescent years. In pediatric patients, although the physis of the radius is likely to fail first, scaphoid fractures, with and without a radial fracture have been observed. In older adults, a distal radius metaphysis fracture is more likely to occur. Scaphoid fractures are classified by their anatomic location and may be divided into three groups—fractures of the tuberosity and distal pole, waist, and proximal pole. Of these three patterns, fractures through the waist of the scaphoid are the most common, accounting for approximately 70% to 80% (Fig. 44.11).[11,12]

Fig. 44.11. Scaphoid wrist fracture. A posteroanterior view of the wrist in ulnar deviation (scaphoid view) illustrates a nondisplaced fracture of the scaphoid waist *(arrow)*.

Patients typically report radial-sided wrist pain distal to the styloid with decreased range of motion of the wrist and thumb. Classically, the physical examination reveals tenderness on palpation of the scaphoid within the anatomic snuffbox. For scaphoid tenderness to be elicited, a combination of maneuvers, such as ulnar deviation, palpation of the scaphoid tubercle volarly, a Watson's scaphoid shift test, axial compression of the first metacarpal, resisted supination of the wrist and a positive clamp sign, and subjective dorsal and volar radial pain illustrated by a thumb-index finger pinch on both sides of the wrist may have to be performed.[10-13] The first meta-analysis of the diagnostic accuracy of physical examination findings in ED adult patients with occult scaphoid fractures was published in 2014.[11] The conclusions of this study emphasized that except for the absence of snuffbox tenderness, which has a negative likelihood ratio of 0.15 for occult scaphoid fracture, physical examination findings lack accuracy to rule scaphoid fractures in or out, and no validated clinical decision rule exists.[11] Therefore, in an attempt to avoid complications associated with delayed diagnosis, occult fracture displacement, and AVN, any patient with suspected scaphoid fracture should receive splint immobilization and repeat imaging within 1 to 2 weeks.

Radiographic diagnosis of scaphoid fractures is often difficult. An additional ulnar-deviated PA view of the wrist may assist with fracture visualization. A visible bone lucency or cortical disruption may be absent, and a more subtle change, such as bowing, obliteration, or displacement of the scaphoid fat pad may be the only clue that a wrist injury is present. However, these signs are not even reliably present, and plain radiographs taken soon after injury fail to detect fracture in approximately 15% of scaphoid injuries.[7,14] Approximately one in four patients who presents with scaphoid tenderness, has initially negative x-rays, and is splinted, will subsequently be diagnosed with a scaphoid fracture.[11] Recent evidence has called into question the practice of immobilizing the

Fig. 44.12. Short arm, thumb spica splint. Common immobilization technique used for occult fractures of the scaphoid bone seen in a volar view. Note the optimal 10 degrees of wrist flexion and radial deviation, which assists in scaphoid immobilization.

wrist in all patients with suspected scaphoid injuries and has suggested that the use of more advanced imaging modalities is accurate and cost-effective and should be performed earlier rather than later. The cost of time off from work, serial casting, repeat physician evaluation, and office visits easily exceed that of MRI, CT, or bone scans for definitive diagnosis where these imaging modalities are readily available.[15,16] In addition to advanced imaging, clinical risk assessments and decision rules are being developed to help risk-stratify patients further.[13]

Radiographic imaging remains the cornerstone for the evaluation of acute wrist trauma and, historically, bone scans were used 72 to 96 hours after injury to detect occult scaphoid fractures. Although high sensitivities are quoted (97%), lower specificities, many false-positives, decreased effectiveness in older adults, and limited availability have tempered their use.[13,17] Macroradiography and ultrasound, including high-resolution sonography, have not approached the sensitivities and specificities observed with bone scintigraphy, CT, and MRI.[18,19] CT and MRI imaging allow emergency clinicians to diagnose most radiographically occult scaphoid fractures.[14] However, CT has not had the sensitivity required (93%) for diagnosing occult scaphoid fractures, nor alternative injuries, in the emergent setting, or that may still warrant wrist immobilization. As a result, CT may be used urgently for detailed bone imaging and operative planning, and it reveals the complications of fracture fragment displacement, malunion, and nonunion. Despite increased costs and more limited availability, MRI protocols have the advantage of allowing the diagnosis of alternative occult fractures or soft tissue injuries and are being used to detect scaphoid fractures, with purported sensitivity rates approaching 100%.[13,20-22] Research reflecting emergent diagnostic management of wrist trauma with advanced MRI imaging may suffer from clearly defined diagnostic criterion standards, incorporation, and temporal bias inflating sensitivities of clinically significant disease.[11] Despite extensive study and multiple adjunct imaging modality options, emergent advanced protocols remain investigational, calling for more prospective data.[11,13,19]

The definitive treatment for uncomplicated, nondisplaced scaphoid fractures is debated among orthopedic specialists, although trends toward screw fixation over cast immobilization are evident.[13] Emergency management typically involves immobilization in a thumb spica splint at 10 degrees of flexion with radial deviation, theoretically, used to stabilize fracture fragments of the scaphoid (Fig. 44.12). Most surgeons terminate the thumb spica at the interphalangeal joint line. Some specialists use a long arm (above the elbow) cast or splint, which prevents wrist pronation and supination for the first few weeks, while others prefer short arm immobilization.[23] In addition to flexion and extension, pronation and supination have been suggested to produce fracture displacement in the proximal carpal row. The duration

Fig. 44.13. Avascular necrosis of the scaphoid bone. A common complication of scaphoid fractures is avascular necrosis as a result of the distal to proximal osseous blood supply, displacement, or nonunion, resulting in chronic wrist pain and arthritis.

Fig. 44.14. Avascular necrosis of the lunate bone *(circle),* also known as Kienbock's disease, was formerly of unknown cause. However, prevailing theories support fracture of the lunate bone or compromised circulation as the most likely cause of disease.

of immobilization varies relative to the location of the fracture, but 6 to 12 weeks is common. More proximal fractures commonly require longer durations to ensure adequate healing. Variability in healing time is related directly to the pattern of blood supply to the scaphoid, which flows from the distal to proximal portion of the bone through the scaphoid tuberosity. This pattern of blood flow also accounts for the higher incidence of AVN and nonunion seen in more proximal fractures (Fig. 44.13). As a result of these complications, true scaphoid fractures require urgent orthopedic referral for consideration of operative treatment.

Lunate Fractures

Fractures of the lunate are relatively uncommon and represent fewer than 5% of all carpal fractures.[10] This injury occurs more commonly in persons with a congenitally short ulna, perhaps as a result of a compromised support for the TFCC. The usual mechanism of injury involves a fall on the outstretched hand, causing extreme dorsiflexion, with transmittal of the resultant force from the capitate to lunate. Patients have pain over the dorsum of the wrist, exacerbated by axial loading of the long finger metacarpal. On physical examination, tenderness may be elicited by palpation over the dorsum of the wrist in the depression felt just distal to Lister's tubercle.

Fractures of the lunate may be difficult to see on plain radiographs because of overlap of the distal radius, ulna, and other carpal bones. For this reason, and because of the risk of AVN in missed injuries, clinically suspected lunate fractures should be immobilized. Nondisplaced lunate fractures are treated with immobilization, and displaced injuries require open reduction and internal fixation (ORIF).[24] Lunate and perilunate dislocations are discussed later, in the section on carpal instability. Complications of lunate fractures include progression to carpal instability, nonunion, and AVN. Kienbock's disease, defined by AVN of the lunate, has a predictable pattern of bony collapse, carpal change, and degeneration. Although poorly understood, it apparently results from an a combination of vascular, anatomic, and traumatic mechanisms.[25,26] In well-established cases of Kienbock's disease, the lunate appears sclerotic and fragmented on radiographic examination, and ultimately the bone collapses, with resultant proximal migration of the capitate (Fig. 44.14). These changes cause secondary osteoarthritis of the radiocarpal joint, chronic wrist pain, and weakness. Treatment involves nonoperative and operative intervention, with correction of the articular abnormalities by lengthening the ulna or shortening the radius. In more advanced cases, excision and prosthetic replacement of the lunate or arthrodesis may be necessary.

Triquetral Fractures

Triquetrum injuries, second only to the scaphoid in incidence, account for approximately 15% of carpal fractures.[10] There are three main patterns observed, triquetral body and avulsion fractures volarly and as a dorsal cortical chip. Triquetral body and volar avulsion fractures are commonly associated with perilunate and lunate dislocations and, therefore, ligamentous injury should be considered. A fracture to the triquetral body is best seen on the AP radiograph, and urgent orthopedic referral is suggested. Dorsal triquetral chips appear to be an avulsion-type fracture with a more benign clinical course. The impact of a prominent ulnar styloid or proximal hamate bone against the triquetrum has been theorized as a possible mechanism of injury.[24] On physical examination, patients will have local tenderness, and swelling may be noted in this area. Although the fracture is best seen on the standard lateral view of the wrist as a small dorsal avulsion fragment, a more oblique pronated view may be necessary for

Fig. 44.15. Triquetral avulsion fracture. A minimally displaced triquetral avulsion or dorsal chip fracture (*arrow*) is seen on this lateral radiograph of the wrist.

Fig. 44.16. Pisiform fracture. A reverse supinated oblique radiograph of the wrist profiling the pisotriquetral joint demonstrates minimally displaced pisiform fracture *(arrow)* not typically seen on traditional posteroanterior, lateral, and oblique views.

visualization (Fig. 44.15). Treatment is with immobilization in a short arm splint or ulnar gutter with more routine orthopedic referral. Definitive treatment in a short arm cast usually results in an uncomplicated course, with prompt fracture healing over 4 to 6 weeks.

Pisiform Fractures

The pisiform is unique in the carpus because it is the only sesamoid-like bone and attaches to the FCU tendon, articulating on its dorsal surface with the triquetrum. Although pisiform injuries are rare, occurring in less than 1% of all carpal fractures, given the important role of forming the lateral wall of Guyon's canal, ulnar arterial damage and neurapraxias may be associated. Fractures of the pisiform usually occur from a fall on the outstretched hand but also may be seen after direct blows to the hypothenar eminence. This occurs from repetitive trauma when the palm of the hand is used in a hammer-like manner. On physical examination, there is tenderness over the ulnar aspect of the wrist, just distal to the volar crease. Paresthesias in the distribution of the ulnar nerve and hand clumsiness from intrinsic muscle dysfunction can occur. Pisiform fractures are poorly seen on routine wrist radiographs, are likely underreported; a reverse (supinated) oblique and carpal tunnel view allow for better visualization (Fig. 44.16).[4]

Nondisplaced fractures of the pisiform generally carry a good prognosis and are treated conservatively, with immobilization and orthopedic referral. Definitive treatment is with a short arm cast for 3 to 4 weeks. Most pisiform fractures with evidence of ulnar neurapraxia will resolve, but urgent orthopedic referral for consideration of surgical decompression is indicated. Pisiform fractures complicated by displacement, nonunion, and pain may also require excision.[27]

Hamate Fractures

Hamate fractures are rare and account for approximately 5% of all carpal bone fractures.[10,27] The hook or hamulus is the most common site of fracture, although articular surfaces and body fractures are also seen. Fracture of the hook usually occurs from a fall on the outstretched hand or from a direct blow to the palm. Typically, hook of the hamate fractures occur from those participating in racket or club sports (eg, tennis, golf, baseball). The use of hammers and vibration equipment (eg, jack hammers) is also a common mechanism, which can predispose workers to hamate fractures and ulnar canal and hypothenar hammer syndrome.[28] Patients may have isolated pain over the hypothenar eminence, associated decreased grip strength, or compromised distal perfusion. Pain may be localized directly on palpation of the hamate, 1 cm distal and radial to the pisiform. Hamate body and articular surface fractures are usually caused by increased load to the ring and little finger metacarpals. These fracture patterns are best seen on PA views of the wrist (Fig. 44.17). Standard wrist radiographs have poor sensitivity for hamate hook fractures, which are more easily seen on reverse, supinated oblique, and carpal tunnel views (Fig. 44.18). Confirmed hook of hamate fractures should be immobilized with ulnar outrigger and a thumb spica splint to limit traction from the transverse carpal ligament. Hook of hamate fractures may result in immediate or delayed ulnar arterial or nerve compromise, and flexor tendon rupture affecting the little finger has been documented. Displaced hook of the hamate fractures are frequently treated with operative resection, but immobilization has been successful for nondisplaced injuries. Vascular compromise or distal ischemia warrants emergent orthopedic consultation; otherwise, urgent follow-up is recommended.[27,28]

Fig. 44.17. Hamate fracture. Fracture of the articular surface of the hamate bone *(arrow)* is seen on this posteroanterior radiograph of the wrist.

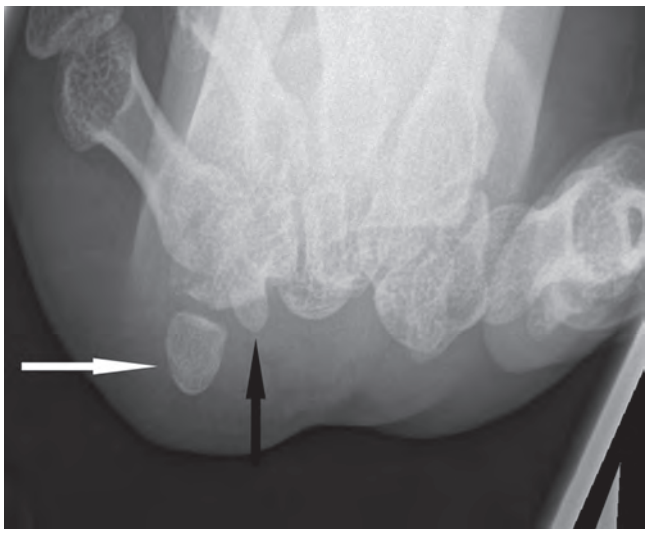

Fig. 44.18. Carpal tunnel view of wrist. The pisiform bone *(white arrow)* and hook of hamate or hamulus (*black arrow*) are better visualized on carpal tunnel views of the wrist when clinical hypothenar palmar wrist pain is present and fracture is suspected.

Trapezium Fractures

Fractures of the trapezium are also uncommon and represent approximately 4% of all carpal fractures.[10] There are two main types of fractures, those involving the body and trapezial ridge. A direct blow to the adducted thumb causes fracture through the body of the trapezium, with transmittal of the force by the base of the thumb metacarpal. Avulsion fractures of the trapezial ridge occur with forceful radial deviation or rotation of the wrist. On examination, patients report pain with movement of the thumb and on direct palpation of the trapezium, just distal to the scaphoid in the anatomic snuffbox. Although trapezium fractures may be seen on the AP view of the wrist, they are typically better visualized on oblique views (Fig. 44.19) and, unfortunately, are

Fig. 44.19. Trapezium fracture. An oblique view of the wrist shows an isolated, comminuted, intraarticular fracture of the trapezium body (*arrow*).

also commonly occult. These injuries are treated with immobilization in a thumb spica splint, and patients are given orthopedic referral. Nondisplaced fractures are immobilized in a circumferential cast for 6 weeks, whereas displacement or involvement of the carpometacarpal joint warrants urgent orthopedic referral for ORIF.

Capitate Fractures

The capitate lies in a central position in the distal carpal row and, because of this protected location, it is rarely fractured. When fracture does occur, the mechanism generally is a direct blow to the dorsum of the wrist. Fracture also may be seen in association with a perilunate dislocation after a fall on the outstretched dorsiflexed hand. Clinical examination reveals dorsal wrist pain and swelling, with localized tenderness on palpation of the capitate. Fractures usually are visible on the standard PA view of the wrist, although the lateral view may be helpful in determining the presence of rotation or displacement of the fracture fragment.

Nondisplaced isolated fractures of the capitate may be managed with immobilization in a short arm splint with thumb spica, with the patient given orthopedic referral. Urgent orthopedic referral for fractures with displacement and emergency consultation are indicated for associated carpal dislocation. Complications of nonunion and AVN of the proximal fragment are rare but do occur because the capitate receives its blood supply through its distal half.

Trapezoid Fractures

Trapezoid fractures are rare, usually seen in association with other carpal injuries, and account for only approximately 1% of all carpal fractures.[10] The typical mechanism of injury is a direct blow down the long axis of the index metacarpal, which may result in

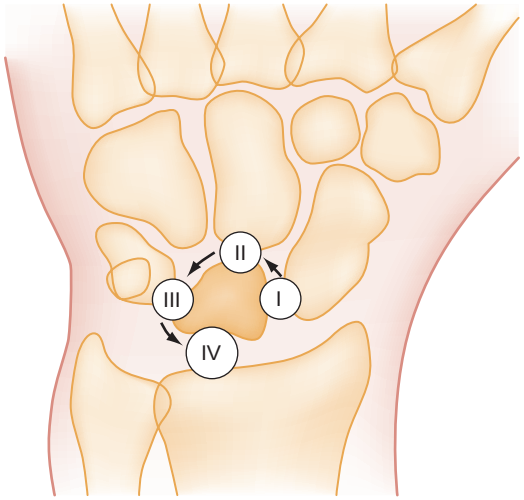

Fig. 44.20. Sequential stages of carpal dislocation. Each of four stages (I–IV) represents a sequential intercarpal ligament injury proceeding around the lunate. (From Greenspan A: Orthopedic radiology: a practical approach, ed 2, New York, 1992, Gower Medical.)

isolated fracture to the trapezoid or cause a dorsal fracture-dislocation. On clinical examination, pain and tenderness are localized over the dorsum of the wrist at the base of the second metacarpal. The fracture may be visible on routine PA views of the wrist; however, oblique views may be superior for visualization of the injury. Nondisplaced trapezoid fractures should be immobilized with a short arm splint and thumb spica, and patients are given an orthopedic referral. However, displaced fractures warrant urgent orthopedic referral for reduction and fixation.

Carpal Instability

Carpal ligamentous injury is caused by wrist hyperextension, ulnar deviation, and intercarpal supination.[29] The Mayfield classification of carpal instability is comprised of four distinct stages. Each stage represents a sequential intercarpal injury, beginning with scapholunate joint disruption and proceeding around the lunate, creating progressive carpal instability (Fig. 44.20). Each stage also may be associated with specific bony fractures, which, if present, should alert the emergency clinician to the possibility of an occult perilunate ligamentous injury. These associated injury patterns include fractures of the radial styloid, scaphoid, capitate, and triquetrum.

A stage I injury, or scapholunate dissociation, results in a characteristic widening of the scapholunate joint on the PA view, which has been called the Terry Thomas sign after the British comedian with a gap between his front teeth. This radiographic sign has been updated to reference more current celebrity figures and is also referred to as the Madonna sign or David Letterman sign. This injury pattern may be associated with a rotary subluxation of the scaphoid. Radiographically, the scaphoid is seen end-on, with the cortex of the distal pole appearing as a ring shadow, referred to as the signet ring sign (Fig. 44.21). Scapholunate dissociation may not be demonstrated on routine radiographs, so when the clinical examination reveals tenderness to palpation, suggesting ligamentous injury, additional stress views could be considered. Radiographs taken with a clenched fist and with ulnar deviation (the clenched fist AP view) accentuate widening of the scapholunate joint and are suggestive of disease when a gap larger than 2 mm is observed.[5]

A stage II injury, or perilunate dislocation, is seen best on the lateral view of the wrist. Although the lunate remains articulated to the distal radius, the capitate is dorsally dislocated. The PA view shows overlap of the distal and proximal carpal rows and also may show an associated scaphoid, radial styloid, or capitate fracture (Fig. 44.22).

Fig. 44.21. Scapholunate dissociation with scaphoid subluxation. Posteroanterior view of the wrist shows characteristic widening of the scapholunate joint *(black arrow),* known as the Terry Thomas sign, and a ring shadow over the scaphoid *(white arrow)* secondary to subluxation, known as the signet ring sign.

A stage III injury appears identical to a stage II injury but includes a dislocation of the triquetrum that is seen best on the PA view, with overlap of the triquetrum on the lunate or hamate. This injury may be associated with a volar triquetral fracture.

A stage IV injury, or lunate dislocation, results in a characteristic triangular appearance of the lunate on the PA view caused by the rotation of the lunate in a volar direction. This triangular appearance is known as the piece of pie sign. This rotation also is visible on the lateral view of the wrist, in which the lunate looks like a cup tipped forward and spilling its contents, referred to as the spilled teacup sign. On the lateral view, the capitate is seen to lie posterior to the lunate and often has migrated proximally to contact the distal radius (Fig. 44.23). Mayfield dislocations are associated with radial styloid, scaphoid, capitate, and volar triquetral avulsions and dislocations. This injury pattern, with or without spontaneous lunate reduction, should alert the emergency clinician to ligamentous damage.[30,31]

Patients with these carpal dislocation injuries typically have a history of a fall on the outstretched hand. They complain of pain and swelling over the dorsum of the wrist, with limited range of motion. On physical examination, tenderness to palpation is noted over the dorsum of the wrist, particularly in the region of the scapholunate ligament. Delayed scapholunate instability may be clinically elicited by a provocative maneuver, such as Watson's scaphoid shift test, which will increase pain and produce a clunk or snap. The test is performed by placing upward pressure on the scaphoid tuberosity while the hand is in ulnar deviation. In scapholunate instability, this action will cause the scaphoid to ride out of the radial fossa over the dorsal rim and, as the hand is moved back radially, a painful snap is produced.[32] In the setting of acute trauma, unfortunately, this test is too painful to perform.

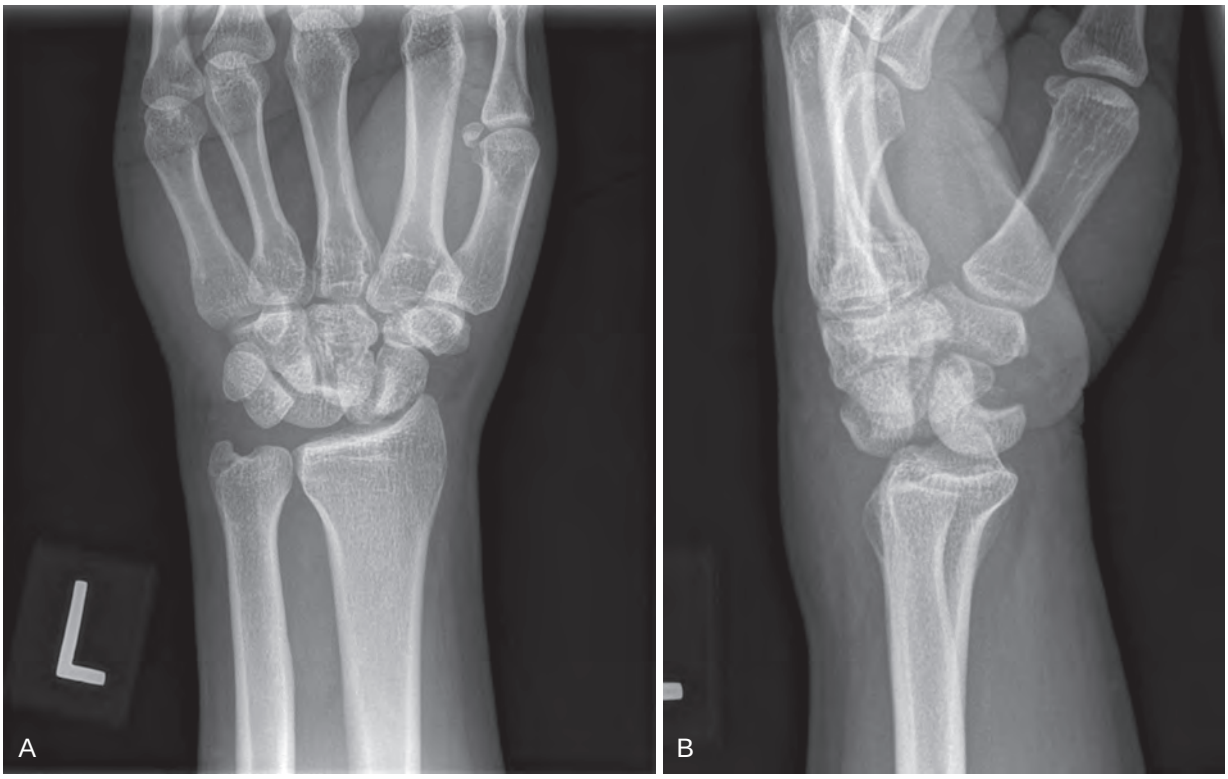

Fig. 44.22. Perilunate dislocation. **A,** This posteroanterior view of the wrist shows an abnormal-appearing lunate bone, obvious disruption of the normal carpal arcs, and commonly associated and, in this case, displaced scaphoid fracture. **B,** Lateral view shows a dislocated and dorsally displaced capitate bone in relation to the lunate. Of note, the lunate maintains its articular connection and alignment with the radius, suggesting perilunate dislocation.

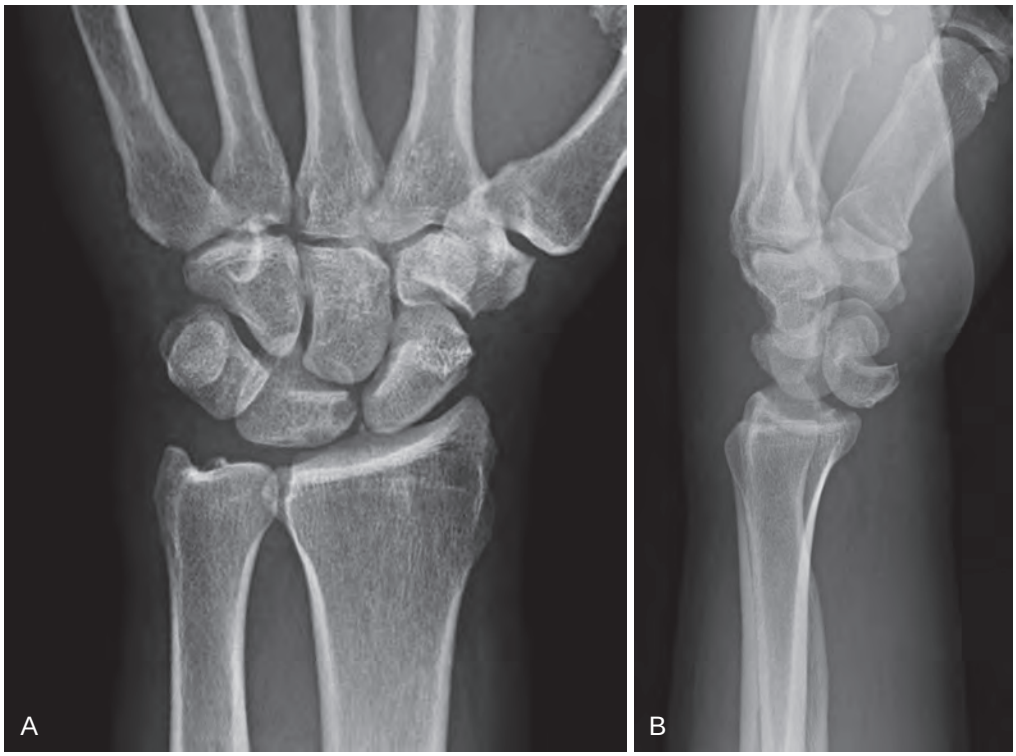

Fig. 44.23. Lunate dislocation. **A,** This posteroanterior view shows the characteristic triangular shape of the lunate bone during dislocation. **B,** Volar displacement of the lunate resembles a spilled teacup on the lateral view. Note the disrupted articulation between the lunate and distal radius and realignment of the radius, capitate, and metacarpals, suggesting lunate dislocation.

MRI has relatively low sensitivity and specificity for the diagnosis of scapholunate injury; arthroscopy remains the gold standard for diagnosis. Arthroscopy is considered to have superior detection ability for the internal derangement of wrist ligaments and a more accurate visualization of the articular surfaces.[32] With perilunate and lunate dislocations, visible deformity of the wrist also is apparent, and two-point sensation in the median nerve distribution often is diminished. Carpal dislocation injuries need emergent orthopedic consultation in the ED for reduction and stabilization. Complications of carpal dislocation injuries include median nerve injury and chronic carpal instability, with resultant degenerative arthritis.

Radiocarpal Instability and Dislocation

Although radiocarpal dislocations and fracture-dislocations are considered extremely rare, representing only 0.2% of all dislocations, some consider this diagnosis to be underreported.[33,34] High-energy trauma is the mechanism of injury; patients usually have many additional injuries and are commonly involved in polytrauma scenarios. Dislocations may be volar or dorsal, and ulnar translation of the carpal bones is much more common than radial translation. Emergent reduction of these injuries is paramount because of the extensive soft tissue damage and commonly associated distal neurovascular compromise.[35] Reduction is, however, commonly difficult to maintain in these complex and unstable injuries, which usually require ORIF. Emergent orthopedic consultation in the ED is indicated.

Distal Radius and Ulna Injuries

Distal radius and ulna fractures remain some of the most common injuries seen in EDs worldwide.[10,36,37] Women older than 50 years are most vulnerable and carry a 15% lifetime risk of this injury pattern.[38] Occurring, in general, from a ground level fall on the outstretched hand in older patients and from high-energy trauma in younger patients, these injuries are commonly closed, may have intraarticular involvement and displacement, and frequently require ED closed reduction, splinting, and outpatient orthopedic referral. Plain radiographs are typically adequate for the emergent diagnosis and management of these injuries; rarely is advanced imaging indicated. A neurovascular examination should be performed to exclude any median, radial, or ulnar neurapraxia and radial or ulnar arterial compromise caused by the deformity or fracture fragments. Indications for ED reduction include significant deformity, joint subluxation, and dislocation. Postreduction radiography and a neurologic examination are recommended. Open fractures, vascular compromise, or an acute carpal tunnel syndrome are indications for emergency surgical evaluation.[36,37] Open fractures should receive tetanus prophylaxis, toxoid, and immunoglobulin, as indicated, intravenous (IV) antibiotics, and surgical intervention. Numerous classification patterns have been devised, and the most commonly encountered fractures are discussed in the following sections.

Colles' Fracture

Colles' fracture, first described in 1814, is the most common wrist fracture seen in adults.[39] It is a transverse fracture of the distal radial metaphysis, which is dorsally displaced and angulated, causing the classic dinner fork deformity seen on physical examination. The fracture usually is located within 2 cm of the radial articular surface and may be associated with comminution and intraarticular extension into the radiocarpal or radioulnar joints. There is commonly an associated fracture of the ulnar styloid in 60% to 70% of cases, which may suggest concomitant injury to the TFCC.[40] The PA view may show extension of the fracture into the radioulnar or radiocarpal joints and the amount of intraarticular step-off and radial shortening present. The degree of dorsal displacement and angulation is best seen on the lateral view, with loss of the normal volar tilt of the distal radial articular surface (Fig. 44.24).

Many Colles' fractures require ED reduction for restoration of radial length, correction of dorsal angulation, especially when greater than 20 degrees and, optimally, restoration of anatomic volar tilt.[40] Closed reduction should be attempted by the emergency clinician using procedural sedation, local or regional anesthesia, or a combination of these options, followed by splint immobilization. Splinting should immobilize the wrist and allow for finger movement. Immediate circumferential casting, as well as overly tight splinting, should be avoided for at least 24 hours because edema from this injury may induce subsequent pain or neurovascular compromise.[36] This treatment may be definitive and, if successful, allows for outpatient orthopedic referral in most cases. Methods of local and regional anesthesia for distal radial fracture reduction include the classic hematoma block, IV regional anesthesia, known as the Bier block, and regional nerve blocks, including median, radial, ulnar, and brachial plexus approaches.[40] The hematoma block remains an easy effective method of anesthesia and may be performed by placing a 22-gauge needle in the dorsum of the distal radius, withdrawing until a fracture hematoma is encountered and then instilling 5 to 10 mL of 1% or 2% lidocaine, with or without the addition of a longer acting agent such as bupivacaine (Fig. 44.25).[41]

Of note, hematoma blocks may avoid the requirement for procedural sedation and decrease ED length of stay.[42] For pediatric distal radial fractures, local anesthesia should not be injected into the growth plate but is otherwise indicated.[36,37] Use of finger traps also is an effective means of obtaining the reduction to allow positioning for splinting (Fig. 44.26). The more comminuted and displaced the fracture, the higher the likelihood that operative reduction will be necessary. Common emergent indications for Colles' fracture reductions include any neurovascular compromise, significant deformity, soft tissue tension, tenting of the skin, and loss of volar tilt, with significant dorsal angulation (>20 degrees). Radial inclination greater than 15 degrees, volar tilt less than 20 degrees dorsally, radial shortening (positive ulnar variance) less than 5 mm, and intraarticular step-off less than 2 mm suggest general, not absolute, adequate emergent reduction parameters.[36,40] Loss of reduction will occur in many of these patients before follow-up, especially in comminuted, intraarticular fractures, and in older adults, for whom the long-term benefits of anatomic restoration appear less beneficial.[43] The American Academy of Orthopedic Surgeons has suggested surgical fixation of fractures with more than 3 mm of shortening, 10 degrees of dorsal tilt, and intra-articular step-off of more than 2 mm postreduction.[44,42]

Complications of Colles' fractures are seen most often in older patients and those with comminution, displacement, and inadequate fracture reduction.[36,40,43-45] Although radial and ulnar nerves may be compromised, median nerve injury is most common and may occur acutely from contusion, traction from displacement, transection from fracture fragments, nerve compression after closed reduction, overlying cast pressure, or secondary to acute carpal tunnel syndrome (ACTS; see later).[45] Thus, it is important to evaluate neurologic function before and after fracture reduction.

Smith's Fracture

Smith's fracture is a transverse fracture of the metaphysis of the distal radius, with associated volar displacement and angulation.[46] In some cases, the fracture may extend into the radiocarpal joint. On physical examination it is known as the garden spade

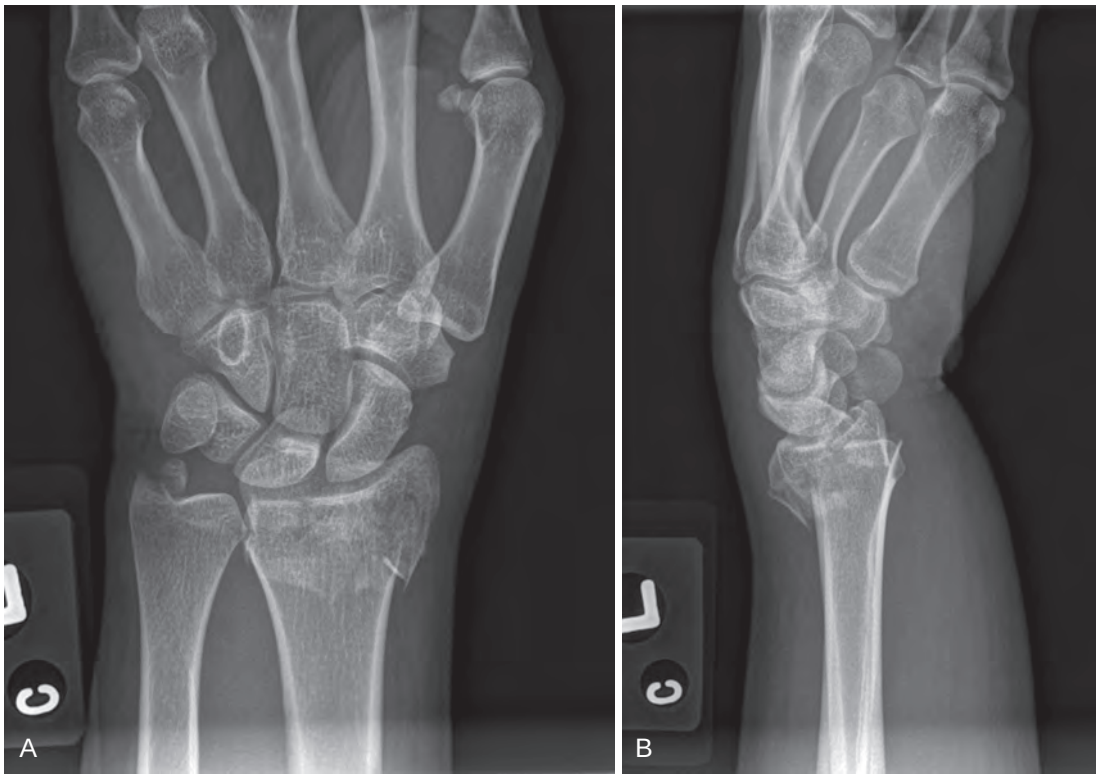

Fig. 44.24. Colles' fracture. **A,** Posteroanterior view shows fracture and shortening of the radius, intraarticular extension, and associated ulnar styloid fracture. **B,** Lateral view shows typical dorsal displacement and angulation of the radial fracture known as the dinner fork deformity.

Fig. 44.25. Hematoma block. Sterile preparation of the fracture area is performed, and local anesthetic is then introduced to the hematoma that surrounds the fracture site to assist with pain control during reduction.

deformity but, because displacement is opposite to that seen in Colles' fracture, Smith's fracture often is called a reverse Colles' fracture. The typical mechanism of injury involves a direct blow to the dorsum of the wrist or a fall onto the dorsum of the hand resulting in extreme palmar flexion. This fracture also may be seen after a fall backward on an outstretched hand, with the forearm in supination. The patient has a swollen painful wrist, which is deformed, with fullness visible on the volar aspect. The fracture is visible on PA and lateral radiographs of the wrist, but the lateral view best shows the degree of volar displacement and angulation (Fig. 44.27).

Treatment of this fracture involves closed reduction and immobilization in a splint, as discussed earlier. Unlike Colles' fracture, however, Smith's fracture is much more likely to be

Fig. 44.26. Finger traps. The distal radius reduction method typically involves traction followed by manipulation facilitated by the finger traps. Ten pounds of weight are hung from the elbow at 90 degrees of flexion for approximately 10 minutes before the reduction attempt.

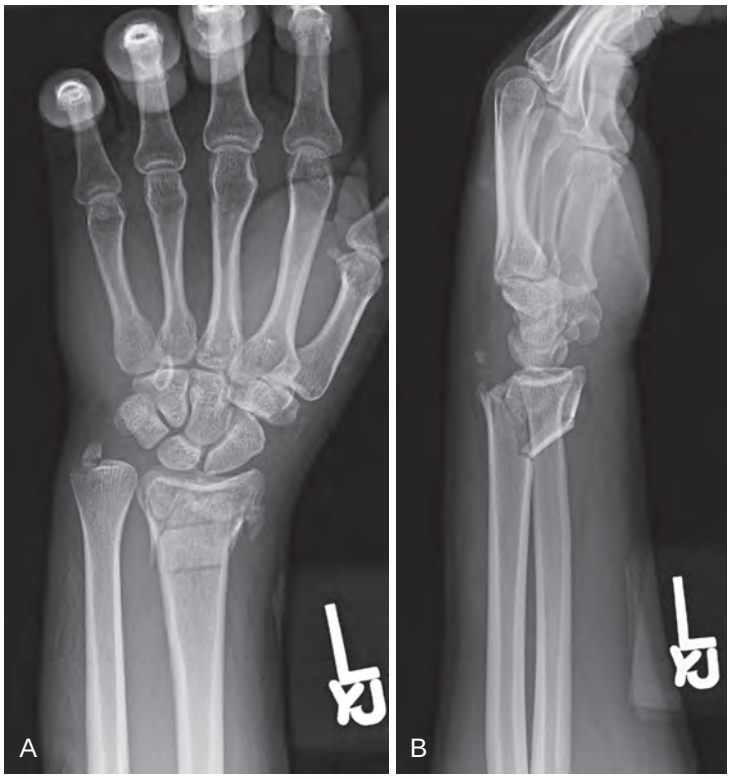

Fig. 44.27. Smith's fracture. **A,** Posteroanterior view shows a metaphyseal fracture of the radius, with shortening and associated ulnar styloid base fracture. **B,** Lateral view shows volar displacement of the distal fracture fragment along with the carpus.

unstable and to require operative repair and splint reduction; it also has an increased tendency to cause neurovascular compromise, specifically median nerve compression. Urgent orthopedic referral or emergent consultation is indicated based on the severity of angulation, neurovascular compromise, or associated soft tissue complications. Delayed tendon complications, including extensor pollicis longus entrapment and rupture, have been documented.[47] Similarly, prognosis is most favorable in patients with successful reduction and restoration of the normal radial length and volar tilt.[40]

Barton's Fracture

Barton's fracture is an oblique intraarticular fracture of the rim of the distal radius, with displacement and dislocation of the carpus along with the fracture fragment.[48,49] The fracture may involve the dorsal rim of the radius with dorsal carpal subluxation (classic Barton's fracture), or may involve the volar rim with volar carpal subluxation (volar Barton's fracture). These fractures are rare and account for only 1% of all distal radius fractures. The volar-anterior margin fracture is seen more often than the dorsal-posterior margin fracture.

The mechanism of injury for these fractures is a high-velocity impact across the articular surface of the radiocarpal joint, with the wrist in volar flexion (causing a volar rim fracture) or dorsiflexion (causing a dorsal rim fracture). Volar and dorsal rim fractures are easily visible on PA and lateral wrist radiographs; however, the lateral view best shows the degree of articular surface involvement and amount of associated fracture displacement (Fig. 44.28).

Treatment of these unstable fractures requires emergent orthopedic consultation for reduction and fixation. Closed reduction may be successful when performed under fluoroscopy, although most fractures require percutaneous pinning or ORIF to restore

Fig. 44.28. Volar Barton's fracture. Lateral radiograph of the wrist shows typical oblique intraarticular fracture of the volar rim of the radius, with associated displacement of the distal radial fragment and carpus dislocation.

the articular surface of the radius and stabilize the carpus accurately. Complications include posttraumatic arthritis of the radiocarpal joint and delayed carpal instability. Both complications are seen more commonly when reduction fails to achieve or maintain anatomic realignment of the radiocarpal joint surface.[49]

Hutchinson's Fracture

Hutchinson's fracture, or chauffeur's fracture, is an intraarticular fracture of the radial styloid. The mechanism of injury is usually a direct blow or fall resulting in trauma to the radial side of the wrist. The term *chauffeur's fracture* originated in the era of hand-cranked automobiles, when this injury occurred because of direct trauma to the radial side of the wrist from the recoil of the motor crank.[50] The fracture is seen best on the PA view of the wrist as a transverse fracture of the radial metaphysis, with extension through the radial styloid into the radiocarpal joint.

Nondisplaced fractures may be immobilized in a sugar tong splint, with the patient given urgent orthopedic referral; definitive treatment is in a short arm cast. However, displaced fractures, which are frequently associated with scapholunate ligament disruption, require open or closed reduction and fixation (Fig. 44.29). Because the radial styloid is the primary site of attachment for many of the ligaments of the wrist, accurate fracture reduction and union are crucial for wrist function. Posttraumatic arthritis is a common complication of radial styloid fractures and more common with displacement and scapholunate ligament disruption.

Distal Radioulnar Joint Disruption

Acute dislocation of the DRUJ can occur as an isolated injury, which is rare, or in association with a fracture to the distal radius (Colles' fracture), radial diaphysis (Galeazzi's fracture), or radial head (Essex-Lopresti injury).[50-52] Diagnosis often is difficult because when the injury occurs in isolation or is not suspected, plain radiographs commonly are reported as normal. Certain characteristic findings on clinical examination may constitute the only clue to the presence of this injury.

Fig. 44.29. Hutchinson's fracture. Posteroanterior radiographic view shows intraarticular fracture of the radial styloid with displacement and scapholunate dissociation, a common complication of untreated Hutchinson's fracture.

The typical mechanism of injury is a fall on the outstretched hand with hyperpronation, resulting in dorsal dislocation, or hypersupination, causing volar dislocation of the ulna.[50] Dorsal ulna dislocations are more common than volar dislocations.[10] Another mechanism known to cause DRUJ dislocation is the catching of the hand in rotating machinery, resulting in the same forcible hyperpronation or supination. This forcible rotation of the wrist causes disruption of the TFCC, the major stabilizer of the DRUJ, and may result in an associated avulsion fracture of the ulnar styloid.

Patients with this injury have a history of sudden onset of pain with a snapping sensation in the wrist, swelling, and limited range of motion. On examination, tenderness is present over the ulnar aspect of the wrist, with palpable crepitus on supination and pronation. With a dorsal dislocation of the ulna, the ulnar styloid appears more prominent than on the unaffected side, and significant pain and limitation of movement are noted on supination of the wrist. With a volar dislocation of the ulna, there is loss of the normal ulnar styloid prominence, with pain and limitation of movement on pronation. These characteristic clinical findings should alert the emergency clinician to the possibility of DRUJ disruption and prompt the appropriate investigations to confirm the presence or absence of injury.

Well-positioned lateral radiographs of the wrist may show the presence of a DRUJ dislocation with more than 20 degrees of dorsal angulation or volar displacement, but pain and inability of the patient to rotate the wrist fully may cause a false-negative result because a true lateral view cannot be obtained.[53] Fractures of the ulnar styloid base may increase suspicion regarding a DRUJ disruption. It also is important to assess for radial head fractures because this injury is commonly associated with DRUJ disruption and interosseous membrane rupture (see below, "Essex-Lopresti Lesion"). A DRUJ dislocation is seen on the PA view of the wrist showing significant overlap or widening of the distal radius and ulna (Fig. 44.30). If there is significant clinical suspicion of injury, and the radiographic appearance is normal, a CT scan may assist in the diagnosis.

Treatment of these injuries commonly requires orthopedic consultation for reduction and stabilization. Closed reduction with the forearm in supination followed by application of a long arm cast often is successful. Alternatively, open reduction frequently is necessary with volar dislocations because the ulnar head often is locked on the distal radius. Operative reduction also is necessary in dorsal dislocations to repair the associated injury to the TFCC. Immobilization in a long arm cast is maintained for 6 weeks.

SOFT TISSUE INJURIES OF THE WRIST

Carpal Tunnel and Acute Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy; it occurs at the wrist and results in compression of the median nerve. CTS is typically a chronic, progressive, repetitive overuse syndrome and has an overall lifetime incidence around 5%, with a female preponderance.[54-56] The transverse carpal ligament and volar surfaces of the carpal bones form the carpal tunnel. It is a rigid compartment that contains nine flexor tendons (flexor pollicis longus, four flexor digitorum superficialis, and four flexor digitorum profundus tendons) and the median nerve. CTS also can be associated with numerous systemic conditions, such as rheumatoid arthritis, hypothyroidism, diabetes mellitus, renal failure, congestive heart failure, acromegaly, and collagen vascular diseases. Each of these systemic diseases is thought to produce an increase in pressure within the carpal

Fig. 44.30. Distal radioulnar joint dislocation. Posteroanterior radiographic view shows an ulnar styloid base fracture suggestive of triangular fibrocartilage complex disruption and widening of the radius and ulna, consistent with distal radioulnar dislocation.

tunnel from thickening of the flexor synovia or transverse carpal ligament. Hormonal changes associated with pregnancy and menopause also are known to cause CTS, probably from retention of fluid in the soft tissues about the wrist.[56]

The classic symptoms include a gradual onset of numbness, paresthesia, and pain in the median nerve distribution (thumb, index, long and radial aspect of the ring finger; see Table 44.1). These symptoms often are bilateral and are worse during the night and after strenuous activities. Typically, patients report numbness and paresthesias on awakening that lessens when the hands are shaken or held in a dependent position. Pain may actually radiate proximal to the carpal tunnel, and symptoms may progress to include decreased grip strength, hand clumsiness, thenar atrophy, and trophic ulceration of the fingertips.[54] The differential diagnosis includes cervical radiculopathy and Raynaud's syndrome.

The most common provocative test supporting the diagnosis of CTS is the wrist flexion or Phalen test (Fig. 44.31).[57] This test is performed by asking the patient to flex the wrists fully for 60 seconds while holding the forearms in a vertical position. The test result is positive if paresthesia or numbness develops in the median nerve distribution. Other tests suggesting CTS are weakness observed on thumb abduction testing and Tinel's sign, which demonstrates pain or paresthesias elicited by light tapping or percussion over the median nerve at the wrist. Durkan's test, or the median nerve compression test, consists of the application of pressure directly over the median nerve at the carpal tunnel and may have the highest sensitivity and specificity for disease. However, no physical examination maneuver is completely reliable in making the diagnosis and is therefore more supportive when used in combination.[54]

Nerve conduction studies have traditionally been used to confirm the diagnosis. MRI and ultrasound are also being used

Fig. 44.31. Phalen's test.

for confirmation, but emergently the diagnosis of CTS is primarily clinical.[54,58]

Conservative (nonoperative) treatment for CTS yields variable results. Specific measures include splinting the wrist in a neutral position and administering cortisone injections in the carpal tunnel.[54,59] Splinting initially may be prescribed full time and then reduced to immobilization at night only. Five factors that lessen the likelihood of successful nonoperative treatment are (1) age older than 50 years, (2) symptom duration longer than 10 months, (3) constant paresthesias, (4) stenosing flexor tenosynovitis, and (5) positive Phalen's test result at less than 30 seconds. Nonsteroidal antiinflammatory drugs (NSAIDs) have proved to be of little benefit. Open or endoscopic surgical release of the flexor retinaculum to unroof the carpal tunnel is indicated when medical management fails.[60]

ACTS, which occurs over hours rather than weeks, months, or years, is much less common than the chronic, gradually progressive presentations of CTS requiring symptomatic relief, appropriate referral, and patient education. ACTS is more often directly related to fractures, fracture-dislocations, hemorrhagic conditions, infections, vascular disorders, and edema involving the wrist. Although the carpal tunnel is open at both ends, it has the physiologic properties of a closed compartment.[56] Distal radius fractures are likely the most common cause of ACTS; however, lunate and perilunate dislocations are associated, and even isolated carpal fractures and rupture of the EPL tendon have been documented as rare causes. Trauma resulting in an ACTS is typically relieved by closed reduction, and no reliable clinical method currently exists for differentiating acute median nerve compression in ACTS from concussive insult. In the absence of trauma, ACTS has occurred secondary to hemorrhagic, vascular and bleeding disorders and anticoagulant use. When ACTS has been diagnosed, orthopedic consultation is recommended for surgical decompression and release of the transverse carpal ligament.

de Quervain's Disease and Intersection Syndrome

De Quervain's disease and intersection syndrome, like CTS, have been grouped into the overuse or repetitive strain injury pattern category, sometimes referred to as work-related cumulative trauma in the occupational medical literature. The APL and EPB, both within the first dorsal extensor compartment of the wrist, are the tendons affected in de Quervain's disease. Traditionally known as a stenosing tenosynovitis, tendinitis, or tendovaginitis of the wrist, de Quervain's disease involves enlarged tendons, which may reach five times their original size, creating a stenosing tendinopathy. Clinically, patients report pain on the radial side of

the wrist, with ulnar deviation, thumb movements, weakened grip strength, or a combination of these symptoms. Onset is gradual and typically the result of increased use. There are no large epidemiologic studies, but de Quervain's disease is thought to be common, affecting women six times more frequently than men, typically at an age older than 40 years. Radiographs are useful in ruling out bony pathology, but the diagnosis may be made with physical examination only. Originally described in 1930, Finkelstein's test has long been considered to be a pathognomonic sign of de Quervain's disease.[61]

There are surprisingly few prospective randomized controlled studies with good methodologic quality regarding treatment of de Quervain's disease. Conservative interventions of rest, splinting, and NSAIDs are the first-line treatments for mild to moderate disease. Wrist splints with thumb spicas effectively immobilize the APL and EPB, but pain may return when inciting activity is resumed. As a result, ED management should consist of rest, splint immobilization, and anti-inflammatory doses of an NSAID, if not contraindicated. Injection of corticosteroid preparations into the dorsal extensor compartment of the wrist may be offered at follow-up with an orthopedic surgeon, rheumatologist, or primary care physician. Patients with refractory or severe cases of de Quervain's disease that interfere with activities of daily living undergo surgical release of the first dorsal extensor compartment of the wrist, with decompression of the APL and EPB tendons.

Intersection syndrome is another overuse tendinopathy that clinically manifests with pain on the radial side of the wrist, approximately 4 to 8 cm proximal to the site of de Quervain's disease. The condition is also known as peritendinitis crepitans or crossover or oarsman's syndrome. The mechanism of injury is secondary to rowing, weightlifting, or a repetitively resisted pulling action. Pathophysiologically, intersection syndrome occurs secondary to inflammation where the muscle bellies of the APL and EPB cross over the muscle bellies of the extensor carpi radialis longus and brevis proximal to the retinaculum. Physical examination findings include significant pain, soft tissue swelling, and crepitus with movement in more severe cases. Ultrasound findings may include thickened tendons or effusion, and radiographs are negative. The treatment for this disease is immobilization with a wrist splint and antiinflammatory medication, as specified for de Quervain's disease. Although surgical treatments have been described, this syndrome is typically self-limited.[62]

FOREARM

PRINCIPLES

Forearm injuries are common encounters in the ED. There is a bimodal age distribution of patients who suffer forearm injuries—children aged 6 to 15 years and adults older than 50 years.[63] In children, forearm fractures account for nearly 50% of all pediatric fractures and are on the rise due to an increase in sports activity and body mass index (BMI).[64] Please refer to pediatric fractures referenced within this text.

Mechanisms of injury for forearm fractures include falls on outstretched hands, direct blows to the area, or high-energy trauma, such as involvement in a motor vehicle collision. Evaluation of forearm injuries requires an understanding of the interdependent biomechanical relationship between the radius and ulna. These two bones articulate at the proximal and distal ends, which allows the radius to rotate around the ulna to provide pronation and supination. Because fracture of the radius or ulna can result in dislocation at the wrist or elbow, emergency clinicians should be vigilant when treating forearm fractures. Early diagnosis and prompt treatment of these injuries are critical to prevent loss of function.

ANATOMY

The forearm is a unique two-bone structure with the radius and ulna being bound at both ends by a ligamentocapsular structure. The proximal radioulnar joint (PRUJ) consists of an articulation between the radial head and ulna. The radial head, the primary stabilizer of the forearm combined with the annular, quadrate, radial, and ulnar ligaments, provides strong support at the PRUJ. At the DRUJ, the TFCC and anterior and posterior radioulnar ligaments support the articulation of the distal radius and ulna.[65] The interosseous membrane further stabilizes the forearm by providing a strong interconnection between the radius and ulna. The ulna is relatively straight and provides the rotational axis for the bowed radius to rotate around through various planes of motion. The supinator, pronator teres, and pronator quadratus muscles insert along the shaft of the radius and ulna to provide their named function, but they also are responsible for the deforming forces in forearm fractures.

The forearm is typically divided into three compartments—volar, dorsal, and mobile wad. The interosseous membrane divides the volar and the dorsal compartments, and the mobile wad is located laterally (Fig. 44.32). The volar compartment, which can be further divided into superficial and deep layers, contains the pronators and flexor muscles of the hands. The radial, ulnar, and anterior interosseus arteries and median, ulnar, and superficial radial nerves are also contained within the volar compartment. The dorsal compartment consists of the extensor muscles of the hand and posterior interosseous artery and nerve. The mobile wad is located in the proximal lateral aspect of the forearm and contains the brachioradialis, extensor carpi radialis longus, and extensor carpi radialis brevis.

CLINICAL FEATURES

Obtaining the history of the mechanism of injury is crucial in the initial assessment of a forearm injury. The most common mechanism of injury is an axial load applied to the forearm through the hand, which often leads to rotational displacement. Patients may present with obvious deformity and a significant amount of pain.

Physical examination of the forearm injury begins with visual inspection by evaluating for swelling along the injured area, obvious deformity, and evidence of lacerations. Gentle palpation can assist in localization of the injury, reveal crepitus in grossly unstable fractures, and allow assessment of skin turgor in the evaluation of compartment pressure. Significant swelling, as well as disproportionate pain, paresthesia, and paleness of skin, should alarm emergency clinicians regarding the development of compartment syndrome. Neurologic evaluation should include careful examination of motor and sensory function of the radial, ulnar, and median nerves. Assessment of the brachial, radial, and ulnar arteries should be part of the vascular examination. Please see pediatric fractures and compartment syndromes referenced within this text.

DIAGNOSTIC TESTING: RADIOLOGY

The radiologic evaluation of the forearm injury should begin with the AP and lateral views. It is essential to include wrist and elbow in the x-ray examination of the forearm to exclude any concomitant injuries to the DRUJ or PRUJ.

On the normal AP view of the forearm, a medially pointing radial styloid and laterally projecting biceps tuberosity of the proximal radius are visible. On the lateral view, the coronoid process of the proximal ulna points volarly, and the ulnar styloid lies dorsally (Fig. 44.33). Any deviation suggests an abnormal rotational or axial deformity. The normal radiologic findings of the forearm, including radiocarpal articulation angle, relationship

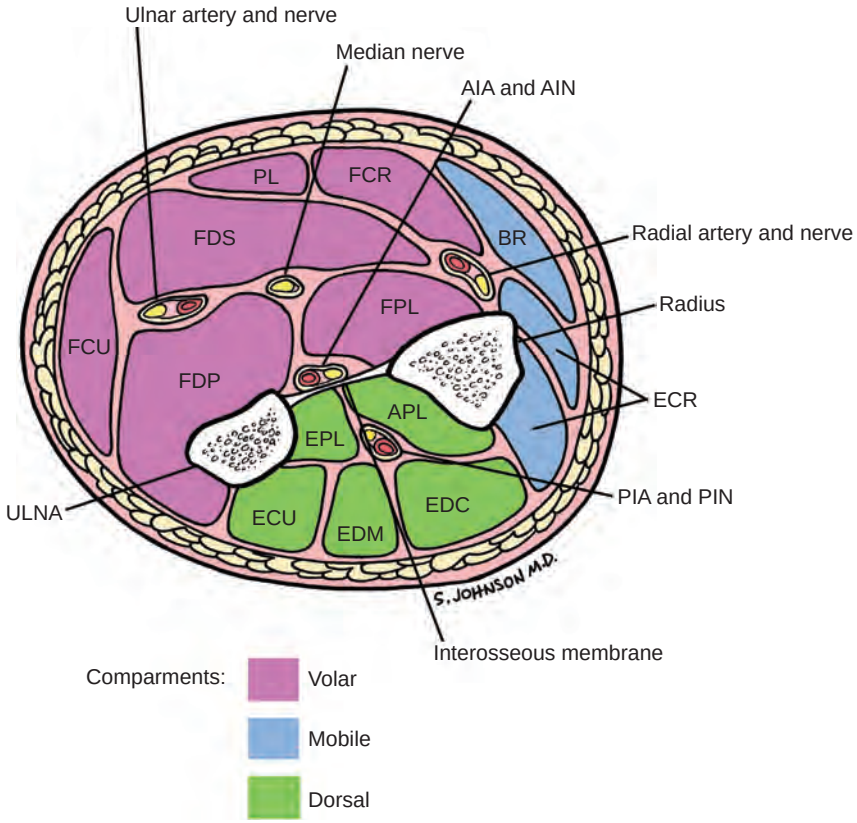

Fig. 44.32. Cross section of the forearm demonstrating the compartments and neurovascular structures. The volar compartment contains the flexor of hands and wrist, including the pollicis longus (PL), flexor digitorum superficialis (FDS), flexor carpi radialis (FCR), flexor pollicis longus (FPL), flexor digitorum profundus (FDP), and flexor carpi ulnaris (FCU), as well as the ulnar nerve, ulnar artery, median nerve, radial artery, superficial branch of the radial nerve, anterior interosseous artery (AIA), and anterior interosseous nerve (AIN). The dorsal and volar compartments are bordered by the interosseous membrane. The dorsal compartment contains finger extensors and long thumb abductor, as well as the posterior interosseous artery (PIA), posterior interosseous nerve (PIN), abductor pollicis longus (APL), extensor digiti minimi (EDM), extensor carpi ulnaris (ECU), extensor pollicis longus (EPL), and extensor digitorum communis (EDC). The mobile wad, which is often considered to be a third compartment, is composed of the extensor carpi radialis brevis and longus muscles (ECR) and brachioradialis (BR). (Courtesy Dr. S. Johnson.)

between radial styloid and ulnar styloid, and normal volar tilt of the radius, are described in the section on radiology of the wrist (see earlier).

Injury to the radial head can be evaluated by drawing a midaxis line through the radial shaft, neck, and head. This radial midaxis line should intersect the center of capitellum of the elbow on any radiologic view. Any variance from this alignment should raise suspicion regarding radial head dislocation (Fig. 44.34).

CT scans can be useful when there is a suspicion of extension of the fracture into the DRUJ or PRUJ on plain radiography. MRI is the study of choice for evaluation of soft tissues (eg, muscle, tendon, ligament) of the forearm, including the interosseous membrane. Ultrasound images can also help with evaluation of interosseous membrane injury[66] and to determine when pediatric forearm fractures have been adequately realigned after closed reduction.[67]

MANAGEMENT AND DISPOSITION

Forearm Injuries

Shaft Fractures of Radius and Ulna

Fractures involving both the radius and ulna, also known as both bone fractures, are common forearm injuries. Patients often have pain and obvious deformity of the forearm as a result of minor or major trauma. Careful physical examination is warranted to exclude any associated neurovascular injury or open fracture. Compartment syndrome should be considered in all patients with this type of injury. The initial radiologic evaluation should include not only AP and lateral radiographs of the forearm, but also dedicated wrist and elbow radiographs.

After initial evaluation, any open fractures should be irrigated with sterile normal saline to decrease contamination, and a sterile dressing should be applied, along with parental antibiotics, while awaiting operative management. Any grossly displaced fracture-dislocation should be reduced to improve alignment and prevent impending or ongoing neurovascular injury. Application of a sugar tong forearm splint should be made with an urgent referral to an orthopedist, as long as there is no evidence of open fracture or neurovascular compromise.[68]

Because nondisplaced radius and ulna fractures are extremely uncommon, most both bone fractures of the forearm in adults will require operative management.[69] Common complications of combined radius and ulna fractures are nonunion, malunion, infection, and neurovascular injury.

Ulna Shaft Fractures

Isolated fractures of the ulna shaft, known as nightstick fractures, are seen frequently in the ED. Patients often have pain and swelling over the medial aspect of the forearm, because the usual

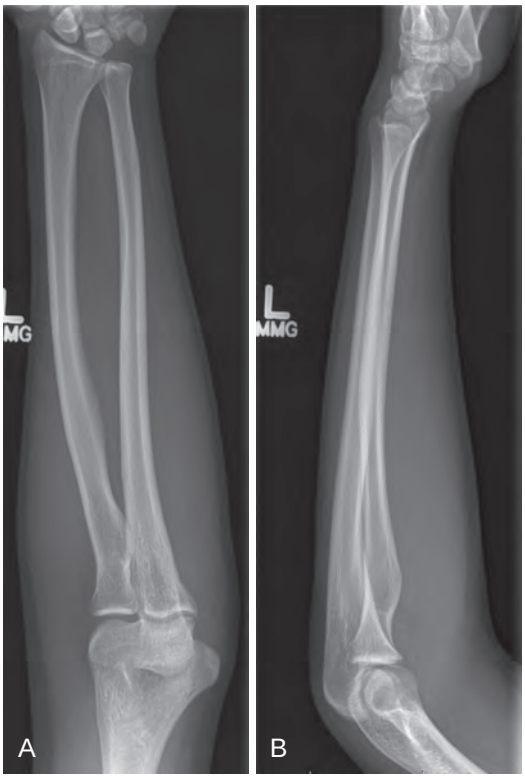

Fig. 44.33. Normal anteroposterior (**A**) and lateral (**B**) radiographic views of the forearm. Both bones should be visible for their entire length, and the radiograph should include the wrist and elbow joints.

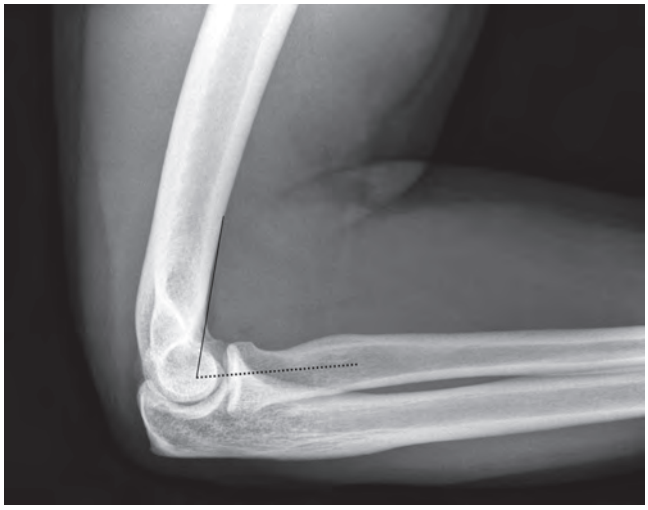

Fig. 44.34. Lateral radiographic view of a normal elbow. A line bisecting the proximal radial shaft also bisects the capitellum *(dotted line)*.

mechanism involves raising the arm overhead to protect it from a direct traumatic impact. Careful inspection of the skin is necessary; many patients have open fractures, given the superficial position of the ulna directly under the subcutaneous skin. The complete examination should include wrist and elbow examinations to exclude any associated injuries involving the PRUJ or DRUJ. The emergency clinician should be aware of potential instability at either articulation associated with fractures involving the proximal or distal third of the ulna.

Diagnosis of an ulna fracture is made through the findings on AP and lateral radiographs of the full-length forearm (Fig. 44.35). Although most isolated ulna fractures are considered stable, those

Fig. 44.35. Isolated ulna fracture (nightstick fracture). Anteroposterior (**A**) and lateral (**B**) radiographic images show isolated ulnar fracture.

with more than 50% displacement, more than 8 degrees of angulation, involvement of the proximal third of the ulna, or instability at the DRUJ or PRUJ are considered unstable fractures.[70] There are no absolute indications for operative management of isolated ulna shaft fracture; however, unstable fractures should be referred to an orthopedist urgently for possible ORIF because they carry a high risk of function loss, nonunion, malunion, and radioulnar synostosis.

Most stable ulna fractures heal without significant clinical sequelae. Stable fractures can be managed with 6 to 8 weeks of short arm, below-elbow immobilization with interosseous molding to limit radial angulation and prevent forearm rotation. Early mobilization with a removable forearm support achieve the earliest radiologic time to union and lowest rate of malunion. Above-elbow immobilization or long arm casting may be detrimental to the healing process, and they have been associated with nonunion and delayed union.[71]

Monteggia's Fracture

The ulna fractures associated with radial head dislocation are commonly known as Monteggia's fractures. In 1814, Giovanni Battista Monteggia specifically described a traumatic lesion involving the fracture of the proximal third of the ulna and anterior dislocation of the radius. In 1974, Bado redefined Monteggia's lesion and classified it to encompass various ulna fractures with concomitant radial head dislocation. The Bado classification divides the injury into four types depending on the location and angulation of the ulna fracture, along with the direction of the radial head dislocation.[72]

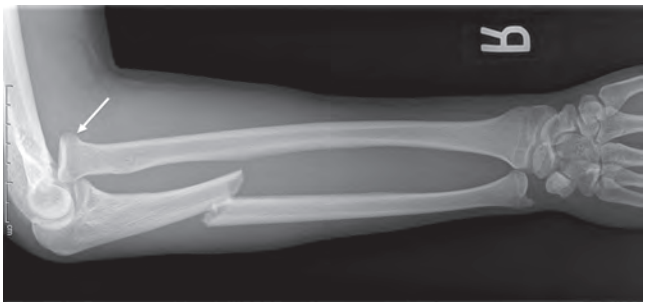

Fig. 44.36. Monteggia's fracture-dislocation. A fracture of the ulna diaphysis with anterior dislocation of the radial head *(arrow)* is shown in this lateral view of the forearm.

Patients with Monteggia's fracture often have fallen on an outstretched hand, resulting in hyperpronation. Direct posterior force on the ulna or a fall on the flexed elbow has also been implicated in the mechanism of the injury. Typically, patients have swelling and tenderness along the fracture site accompanied by a limited range of motion at the elbow and pain with pronation of the forearm. A dislocated radial head may be appreciated on palpation. Initial assessment of Monteggia's fracture should include complete neurologic examination because the posterior interosseous nerve (PIN), a deep branch of the radial nerve, can be injured. Because the PIN innervates the finger extensors along with the supinator, PIN injury is often manifested by weakness or paralysis of the thumb and/or finger extension.

The radiograph of the forearm reveals the obvious ulna fracture that often overshadows the subtle radial head dislocation (Fig. 44.36). A chronic, irreducible radial head dislocation can occur as a result of delay in diagnosis. Drawing the radiocapitellar line (RCL) through the head of the capitellum can prevent overlooking a proximal dislocation. The line should intersect the distal third of the capitellum on all views and confirm correct alignment. However, in young children, an RCL may not reliably bisect the capitellum in normal pediatric patients. An abnormal RCL should be suggestive of but not pathognomonic for an injury.[73]

Treatment of Monteggia's fracture depends on the age of the patient. Pediatric patients with this type of injury can be treated conservatively, with long arm casting in supination with acceptable reduction. However, most adult patients with this type of fracture should be referred to an orthopedic surgeon urgently for ORIF. Complications of Monteggia's fracture include malunion, nonunion, synostosis, stiffness, and nerve palsy. Early diagnosis and treatment of Monteggia's fracture are crucial in achieving good outcomes.[74,75]

Galeazzi's Fracture

Galeazzi's fracture refers to a fracture of the middle to distal third of the radius associated with injury to and dislocation of the DRUJ. It accounts for 3% to 7% of all forearm fractures.[76] Typically, Galeazzi's fracture results from a fall or motor vehicle collision as the patient attempts to brace for impact by stretching out the hand in hyperpronation. A direct blow to the dorsolateral aspect of the forearm is less common but also well recognized as a mechanism of injury for Galeazzi's fracture. Galeazzi's fracture is often overlooked as a simple radius fracture, yet it often results in diminished forearm range of motion, loss of function, weakness, and chronic pain.[77]

In addition to radiographic imaging, the history and clinical examination play a critical role in the diagnosis of Galeazzi's fracture because injuries to the DRUJ may not be obvious. Patients with Galeazzi's fracture have deformity at the site of the fracture

Fig. 44.37. Galeazzi's fracture-dislocation. The anteroposterior (**A**) and lateral (**B**) views of the forearm show an obvious fracture of the distal third of the radius, with severe displacement and an associated dislocation of the distal radioulnar joint *(arrow)*.

associated with swelling and tenderness. Meticulous attention is required in examining the wrist to evaluate for stability of the DRUJ. Instability of the DRUJ can range from obvious prominence of the ulnar head (associated with the subluxation or dislocation) to tenderness elicited at the wrist, which can be a subtle sign of DRUJ ligament injury.

AP and lateral radiographs of the entire forearm and wrist are essential to diagnose Galeazzi's fracture. Besides the obvious fracture of the radius at the middle to distal third, there will be other radiographic findings. On the AP view of the forearm, the space between the distal radius and ulna is widened (>2 mm) and the radius appears relatively shortened. In the lateral view, the dorsally angulated fracture of the radius can cause a dorsal displacement of the ulnar head. A fracture at the base of the ulnar styloid should raise the suspicion for DRUJ interruption (Fig. 44.37). Although not all radius shaft fractures are associated with DRUJ injury, previous studies have shown that at least 25% of all patients with radius fractures have DRUJ dislocation.[76] Therefore, patients with radius shaft fractures should be referred to an orthopedist for close follow-up.

Conservative management of Galeazzi's fracture in adults has been associated with poor outcomes. Due to deforming forces from different forearm muscles and loss of stability at the DRUJ, displacement of the alignment in the cast occurs, despite successful initial reduction. Galeazzi's fracture has been termed a *fracture of necessity* to imply that surgical intervention is pivotal for achievement of an ideal anatomic position and acceptable functional outcomes.[78] Any skeletally matured patients with this fracture should be referred to an orthopedist urgently for ORIF of the radius and associated repair of the DRUJ. In contrast, conservative treatment with closed reduction and long arm casting has been successful in children and rarely necessitates surgical

intervention.[76] Along with the common complications associated with forearm fractures, such as malunion and nonunion, the occurrence of subluxation and dislocation of the DRUJ can result in limited motion and chronic pain.[79]

Essex-Lopresti Lesion

The Essex-Lopresti lesion, or longitudinal radioulnar disassociation, refers to an unstable forearm as a result of a triad of injuries to the radial head, disruption of the interosseous membrane, and violation of the DRUJ. The patient often has fallen on an outstretched hand, resulting in transmission of a large axial loading force from the wrist to elbow. Consequently, the radial head, the primary forearm stabilizer, is fractured and displaced proximally. Disruption of the interosseous membrane and DRUJ also occurs and compromises the stability of the forearm.[80] In addition to localized pain along the elbow from a radial head fracture, patients with the Essex-Lopresti lesion have wrist and forearm pain, along with grip and pronation weakness.

The diagnosis of Essex-Lopresti lesion remains elusive because the standard AP and lateral views of the forearm often reveal only an isolated radial head fracture. Thus, the incidence of the lesion may be higher than previously appreciated.[81,82] The integrity of the interosseous membrane is difficult to assess based on a plain film. Subtle findings of positive ulna variance and a widened DRUJ are suggestive of longitudinal radioulnar dissociation. Obtaining a grip view and comparing the injured wrist with the contralateral wrist can be helpful in diagnosing an Essex-Lopresti lesion. MRI is the study of choice when clinical suspicion for an Essex-Lopresti lesion is high; however, ultrasound has recently been used more frequently to evaluate the integrity of the interosseous membrane.[66]

Once the diagnosis of Essex-Lopresti lesion has been made, the patient should be referred to an orthopedic surgeon for further surgical intervention. Many strategies have been proposed to repair Essex-Lopresti lesions, and the treatment option varies, depending on the chronicity of the injury. Radioulnar synostosis and loss of forearm rotation can result from longitudinal disassociation.[81,82]

KEY CONCEPTS

- On the PA radiograph of the wrist, three arcs, known as Gilula's lines, and equal spacing between carpus bones (1–2 mm), known as parallelism, assist in the radiographic diagnosis of carpal injury.
- In the setting of acute trauma, there is a high incidence of occult fractures and soft tissue injuries of the wrist. Because of the associated risk of malunion, nonunion, posttraumatic arthritis, and AVN if diagnosis is delayed, splint immobilization is recommended when radiographs are negative and pain persists. A thumb spica is usually added in the setting of suspected scaphoid and other carpal fractures. Follow-up for repeat physical examination, radiographs, or advanced imaging (eg, MRI, CT, or bone scan) is indicated.
- Routine wrist radiographs (AP, lateral, and oblique projections) fail to detect 15% of scaphoid fractures. Approximately one in four (25%) of splinted patients will subsequently be diagnosed with a scaphoid fracture.
- Triquetral dorsal chips are best seen on the standard lateral view of the wrist as a small avulsion fracture fragment, although a more oblique pronated lateral view may be necessary to visualize it.
- Hamate and pisiform fractures are better visualized with a carpal tunnel or reverse supinated oblique radiograph.
- Lunate dislocation results in a characteristic triangular appearance of the lunate on the PA view (so-called piece of pie sign) owing to rotation of the lunate in a volar direction. This rotation also is visible on the lateral view of the wrist, on which the lunate looks like a cup tipped forward and spilling its contents into the palm (spilled teacup sign).

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The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 44: QUESTIONS & ANSWERS

44.1. In the setting of acute trauma and negative radiographs of the wrist, which clinical examination method(s) is (are) used to detect occult scaphoid fractures?

A. All of these
B. Anatomic snuffbox tenderness
C. None of these
D. Scaphoid tubercle tenderness
E. Thumb metacarpal compression tenderness

Answer: A. In the setting of acute trauma and negative radiographs, tenderness to palpation within the anatomic snuffbox, on the scaphoid tubercle, or with thumb metacarpal compression are all suggestive of occult scaphoid fracture.

44.2. A 45-year-old man complains of wrist pain after falling on an outstretched hand. What injury is shown in this radiograph of the patient's wrist?

A. Barton's fracture
B. Lunate dislocation
C. Perilunate dislocation
D. Scaphoid fracture
E. Scapholunate dissociation

Answer: E. The radiograph shows the signet ring, or cortical ring sign, which refers to the rotary subluxation of the scaphoid and oval appearance of the tubercle in the anteroposterior (AP) view of the wrist. On a properly positioned radiograph, this sign is typically associated with scapholunate widening, suggesting ligamentous laxity or dissociation. The signet ring sign is also used to describe pulmonary computed tomography (CT) imaging of bronchiectasis in relation to a dilated bronchus and associated pulmonary artery.

44.3. A 55-year-old man complains of wrist pain after a fall onto an outstretched arm. There is pain and swelling along the carpal bones. Also noted is decreased two-point sensation distally on the tips of the index and middle digits. Which structure is most likely injured?

A. Median nerve
B. Radial artery
C. Radial nerve
D. Ulnar artery
E. Ulnar nerve

Answer: A. The median nerve courses through the carpal tunnel on the ventral aspect of the wrist. It provides sensation to most of the palm and thumb, half of the ring finger and, specifically, the tips of the index and middle digits. The median nerve is the most common neurapraxia associated with Colles' fractures.

44.4. Which nerve is commonly associated with Monteggia's fracture?

A. Muscular branch of the radial nerve
B. Posterior interosseous nerve
C. Deep branch of the ulnar nerve
D. Median nerve
E. Ulnar nerve

Answer B: Injury to the posterior interosseous nerve (PIN), a deep branch of the radial nerve, is commonly associated with Monteggia's fracture. Because the PIN innervates the finger extensors along with the supinator, associated injury is often manifested by weakness or paralysis of the thumb and/or finger extension.

CHAPTER 45

Humerus and Elbow

*Kelly Bookman**

PRINCIPLES

Injuries in the region of the elbow can be difficult to diagnose and have a high potential for complications and residual disability. Recognition of neurovascular and soft tissue complications improves the outcome in many of these injuries. Knowledge of the relevant anatomy, mechanisms of injury, and appropriate management techniques, as well as knowing when to refer to or consult with orthopedic specialists will improve outcomes. The essential anatomy of the elbow region, as it relates to acute injury, is shown in Figures 45.1 to 45.4.

CLINICAL FEATURES

History includes a description of the mechanisms of any traumatic event, pain characteristics including quality, duration, location, effects of movement, exacerbating or alleviating factors, severity, and radiation, in addition to concomitant injury or systemic complaint. Past medical history should include occupational factors and prior or chronic problems with the affected joint or other bones or joints. Numbness or weakness distal to the injury may indicate neurovascular injury. Pediatric orthopedic injuries, including those caused by abuse, are discussed in Chapters 165 and 177.

Examination begins with simple inspection and comparison with the contralateral limb. The position in which the extremity is held should be noted. Deformity may indicate fracture, dislocation, or hematoma. Range of motion may be evaluated, depending on the appearance of the extremity and suspicion of injury, but general manipulation of the acute injured extremity should be minimized gentle. Bony prominences are palpated with notation of specific areas of tenderness. Crepitus, bony deformity, and pain in an acutely injured limb are virtually diagnostic of a fracture. The radial head specifically is palpated for tenderness. Intra-articular elbow fractures, including those of the radial head, are universally associated with effusion (hemarthrosis). Elbow effusion is notoriously difficult to discern on examination but is readily identified on lateral radiographs (Fig. 45.5). The extremity also should be inspected for swelling, compromised circulation, or any wound that may indicate an open fracture.

In addition to the elbow region itself, examination incudes thorough evaluation of the distal neurovascular status of the extremity. The vascular status of the extremity is of highest priority. Presence of the brachial, radial, and ulnar pulses is confirmed by palpation. The ulnar pulse is more difficult to palpate than the radial pulse and is not palpable in some normal people. Although a warm hand with normal color suggests adequate tissue perfusion, a handheld Doppler device often is required to evaluate major vessel flow if significant swelling is present or if the pulses are not palpable. Poor perfusion may result from direct arterial injury, compression or kinking in the instance of significant displacement from a fracture or dislocation, or compartment syndrome. Identification of arterial compromise or injury warrants consultation with an orthopedic or vascular surgeon (see Chapter 41). Compartment syndrome is discussed in Chapter 42. Orthopedic consultation and measurement of compartment pressures is indicated for patients who are suspected of compartment syndrome. The radial, median, and ulnar nerve all transit the elbow in close proximity to major bony structures, so their motor and sensory functions require careful evaluation. The radial nerve can be tested by evaluating sensation to the dorsum of the hand and wrist extension. The median nerve should be tested for sensory function by assessing sensation at the lateral aspect of the thumb and for motor function by having the patient perform an "okay sign." The ulnar nerve serves the sensation of the palmar aspect of the fifth digit and motor function to the medial interosseous muscles, which can be tested by having the patient abduct the small finger from the ring finger against pressure.

When movement of the elbow is possible without significant pain, the range of motion of the elbow in all planes (ie, flexion-extension and pronation-supination) is determined. Inability to tolerate even minimal passive movement often indicates dislocation or severe fracture. With the forearm supinated, the normal range of motion is 0 degrees in full extension to 150 degrees in full flexion. A mild degree of hyperextension is normal in some individuals and should be symmetrical. With the elbow flexed at 90 degrees and the thumb facing up, the forearm normally supinates and pronates 90 degrees. Range-of-motion testing may be limited by pain and impossible with severe injuries and can be postponed until after radiographic evaluation.

Most elbow and humerus injuries are evaluated radiographically, although on occasion history and clinical examination alone are sufficient to make a diagnosis (eg, minor mechanism fall with minimal pain, full range of motion, and no significant bony tenderness). There are no validated clinical decision rules for the elbow, so radiography should be performed when there is moderate to severe pain, significant limitation in range of motion, obvious deformity, swelling or effusion, or significant tenderness over any of the bony prominences or the radial head. With the exception of children with obvious nursemaids' elbow (radial head subluxation), radiography should be used in virtually all pediatric elbow injuries with any bony tenderness on examination to assess for possible growth plate injury.

Routine views of the elbow include at least the anteroposterior and lateral views, with oblique views when necessary. Anteroposterior and oblique views are taken with the elbow extended. The lateral view is taken with the elbow in 90 degrees of flexion and the thumb pointing upward. Positioning of the elbow is important because anything but a true lateral view makes accurate interpretation of soft tissue findings and alignment difficult.

Most fractures in the elbow region are identifiable on plain film, but radial head and subtle supracondylar fractures may be difficult to visualize, and examination of the fat pads to identify effusion reduces the risk of missing them. The normal cortex of the radius is smooth and has a gentle continuous concave sweep. If consistent with history and physical findings, any disruption of this smooth arc is considered evidence of fracture. Abnormalities

*I would like to thank Thom Mayer, Joel M. Geiderman, and Sam S. Torbabi for their work on this chapter in previous editions.

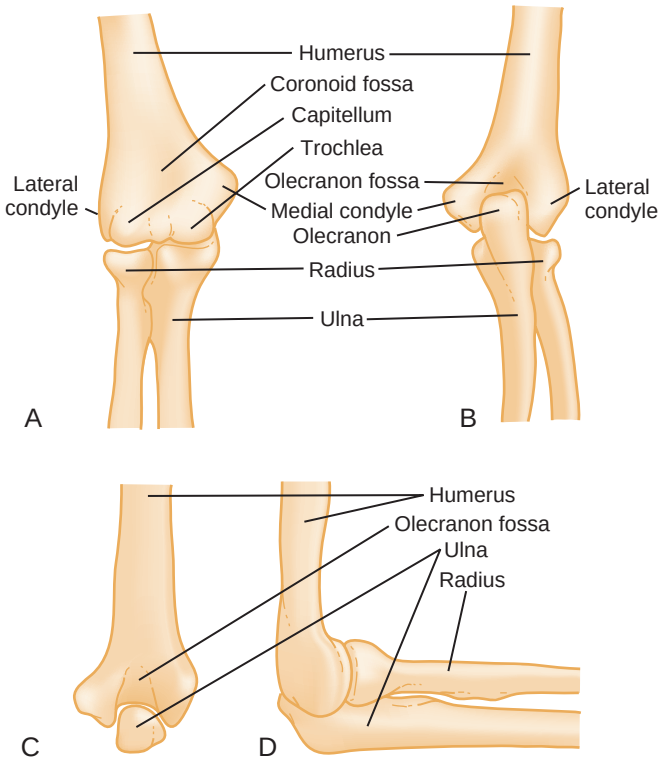


Fig. 45.1. Bony anatomy of distal humerus and elbow region. **A,** Anterior view. **B,** Posterior view. **C,** Posterior view, 90 degrees flexion. **D,** Lateral view. Right elbow is shown. (Adapted from Connolly JF: DePalma's management of fractures and dislocations. Philadelphia, 1981, WB Saunders.)

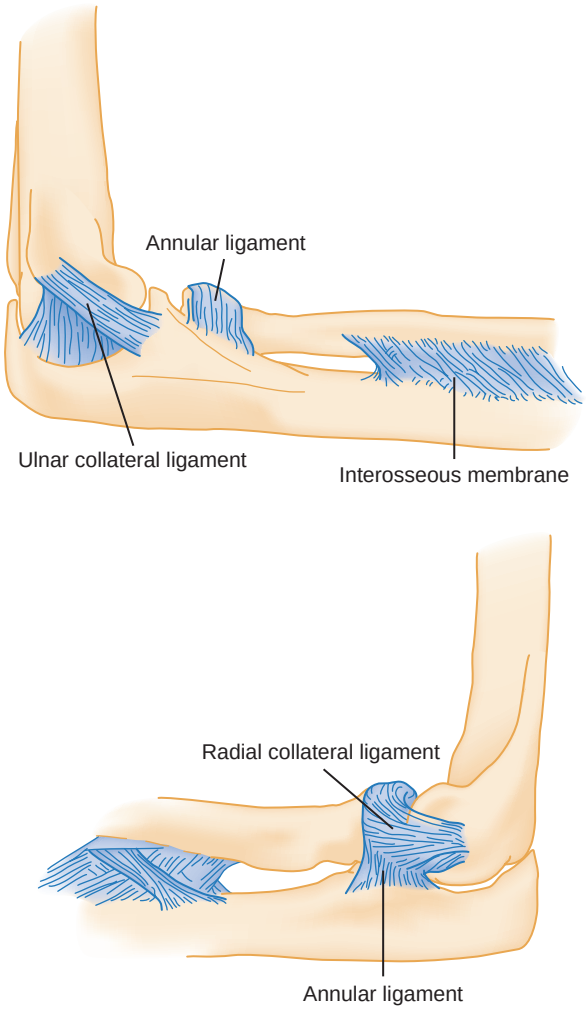


Fig. 45.2. Ligamentous structures of elbow. (From Simon R, Koenigsknecht S: Emergency orthopaedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

within the soft tissues on elbow films are particularly important and may be the only radiographic sign of a fracture. Normally, fat surrounding the proximal elbow joint is hidden in the concavity of the olecranon and coronoid fossae. The normal elbow has only a narrow strip of lucency anteriorly, parallel to the anterior surface of the distal humerus (the anterior fat pad), and there is no posterior fat pad. Injuries that produce intra-articular hemorrhage cause distention of the synovium and displace the fat out of the fossa, making the posterior fat pad visible on lateral radiographic views. This intra-articular swelling displaces the anterior fat farther anteriorly, where it takes the shape of a sail from a boat. The radiographic finding is commonly referred to as the "sail sign." Displacement of the posterior fat pad makes it visible on the lateral radiograph as a "posterior fat pad sign" (see Fig. 45.5). In the setting of trauma, more than 95% of patients with the "posterior fat pad" sign have intra-articular skeletal injury. These soft tissue findings occur even with subtle fractures, and when present in the setting of trauma, an occult fracture is considered to be present. In adults without an identifiable fracture on radiograph, fat pad signs most often indicate a radial head fracture, whereas in children a supracondylar fracture is the more likely underlying injury. In the absence of trauma, the presence of a fat pad suggests other causes of effusion (eg, inflammation, infection). The fat pad sign may be absent in fractures where the injury is severe enough to rupture the capsule.

DIFFERENTIAL DIAGNOSIS

Injuries in the region of the shaft of the humerus and about the elbow fall into several categories including fractures, dislocations/subluxations, and soft tissue disorders (Table 45.1).

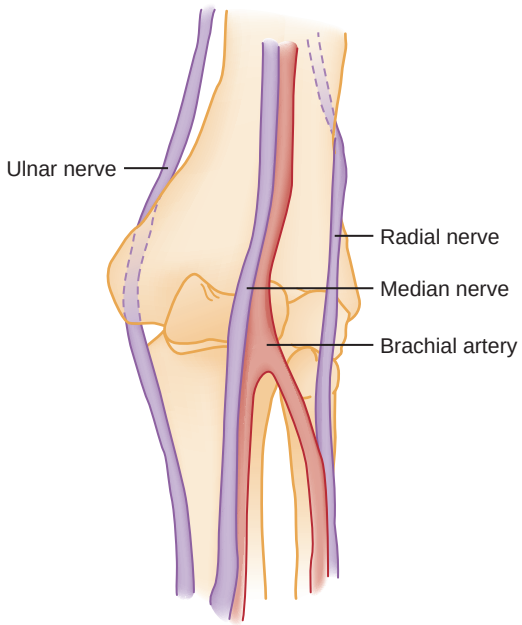


Fig. 45.3. Neurovascular structures of elbow region. Volar surface of left elbow is shown.

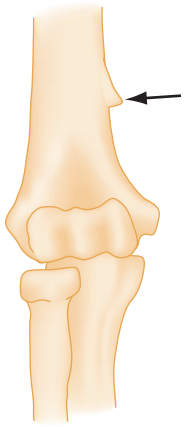
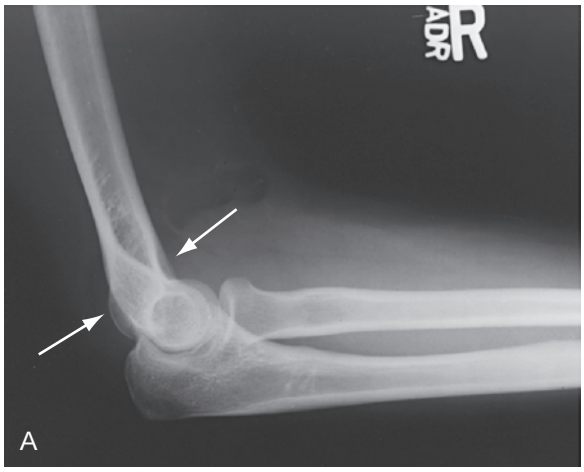


Fig. 45.4. Supracondylar process of the humerus *(arrow)* is present in approximately 2.5% of cases just proximal to the medial epicondyle. Volar surface of right elbow is shown.



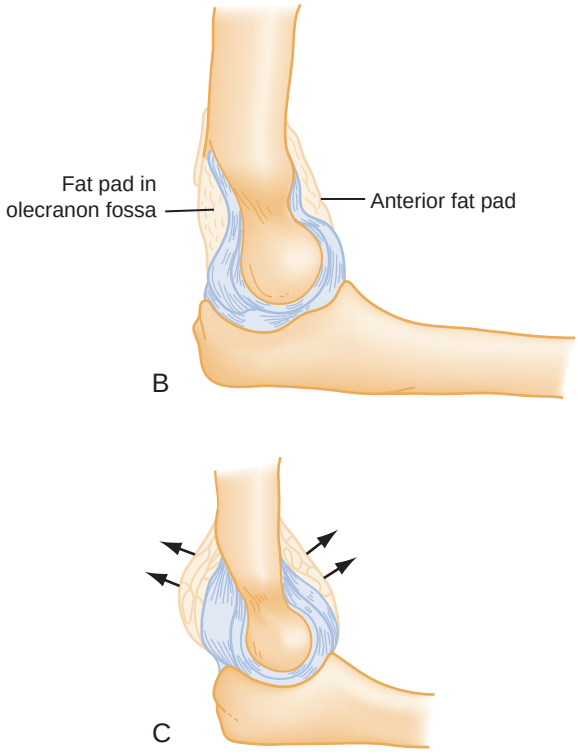


Fig. 45.5. **A,** Anterior and posterior fat pads on lateral study *(arrows).* **B,** The anterior fat pad is normally a thin radiolucent stripe; the posterior fat pad is now visible. **C,** An effusion displaces both fat pads. This posterior fat pad is now visible.

Fractures

Shaft of the Humerus

Clinical Features. Fractures of the humeral shaft commonly result from a direct blow to the arm, severe twisting, or a fall on an outstretched hand. Rarely, fractures may be caused by violent muscle contraction, such as occur when a javelin or baseball is thrown.[1] The shaft of the humerus most commonly fractures in the middle third in a transverse fashion. The patient reports localized pain, which is often severe in nature, and the arm is visibly swollen and cannot be used. When a fracture is complete, bony crepitus is felt in the shaft of the humerus with any manipulation of the arm. The arm may be shortened or rotated, depending on the displacement of the fracture fragments. When the fracture is incomplete, there is bony tenderness and swelling without obvious deformity.

Diagnostic Testing. Studies routinely should include the shoulder and elbow joints. The humerus is a common site for benign tumors, unicameral cysts, and primary bone malignancies, as well as a common site for metastatic disease. Thinning of the cortex and abnormal osteoblastic or osteoclastic activity are evidence of a pathologic fracture (Fig. 45.6). These fractures do not heal without concomitant treatment of the underlying pathologic condition.

Management. Isolated, closed fractures are treated conservatively with a high degree of success. Attempts at fracture reduction and external immobilization are unnecessary and sometimes detrimental to healing. Fractures that are nondisplaced or minimally displaced are immobilized by adding a coaptation, or "sugar-tong" splint, to the sling and swathe (Fig. 45.7). The coaptation splint is often replaced by a functional brace after the first 10 to 14 days. If the fracture is grossly displaced or comminuted, the hanging cast technique is preferable. This technique is especially effective with spiral fractures (Fig. 45.8). Care is taken not to make the cast too heavy because this would distract fracture fragments. The hanging cast has the disadvantage of using gravity for traction and requires that the patient remain upright at all times, including during sleep, a situation that many patients find intolerable. Neurovascular examination should be repeated and documented before and after the application of any splint or cast because loss of nerve function from entrapment of the nerve between fragments can occur after these interventions. Open reduction and internal fixation (Fig. 45.9) is necessary for open fractures, presence of multiple injuries that preclude mobilization, bilateral fractures, poor reduction, poor patient compliance, failure of closed treatment, and fractures through pathologic bone.[2,27] Although the success rate with nonoperative intervention is about 80%, patients should be included in treatment decisions regarding nonoperative versus operative intervention because operative intervention may decrease recovery time with earlier return to work.[3] For open fractures, the wound should be covered immediately with normal saline soaked gauze. Splinting can be done for comfort during patient manipulation but should be limited. Cephalexin (1 g intravenously) is given, and consultation is obtained by orthopedic surgery for emergent operative washout.

The most common complication, radial nerve injury, occurs in up to 25% of humerus fractures. Radial nerve injury causes wrist drop with loss of the ability to extend the fingers and thumb.[4] This nerve injury is most often a benign neurapraxia that resolves

TABLE 45.1

Injuries to Humerus and Elbow

INJURY SITE				MECHANISM/EXAMINATION		IMAGING
Humerus fractures						
	Shaft of the humerus fractures			Direct blow, severe twisting	Localized tenderness, may be shortened or rotated	Obvious fracture line
	Distal humerus fractures					
		Supracondylar (most common in children)				
			Extension	Fall on the outstretched hand when the elbow is either fully extended or hyperextended	Arm is held at the side and has a characteristic S-shaped configuration	Obvious fracture line or maybe the presence of a posterior fat pad or an abnormal anterior humeral line
			Flexion	Direct blow to the flexed elbow	Forearm is supported with the opposite hand with the elbow flexed to 90 degrees	Increase in the anterior angulation of the distal supracondylar fragment or gross displacement of the distal fragment proximal and anterior to the distal end of the proximal fragment
		Transcondylar (more common in elderly)		Mechanism of injury that is similar to that for supracondylar injuries	Localized tenderness	Fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface
			Extension	Mechanism of injury that is similar to that for supracondylar injuries	Localized tenderness	Fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface
			Flexion	Mechanism of injury that is similar to that for supracondylar injuries	Localized tenderness	Fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface
		Intercondylar		Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment
			Nondisplaced	Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment
			Separated	Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment
			Separated and rotated	Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment
			Combination with articular surfaces	Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment

Continued

TABLE 45.1

Injuries to Humerus and Elbow—cont'd

INJURY SITE				MECHANISM/EXAMINATION		IMAGING
		Condylar			Localized tenderness	Widening of the intercondylar distance
			Medial	Valgus force on the extended elbow	Localized tenderness	Widening of the intercondylar distance
			Lateral	Direct blow to the lateral aspect of the flexed elbow or a force that results in adduction and hyperextension with avulsion of the lateral condyle	Localized tenderness	Widening of the intercondylar distance
			Articular surface		Localized tenderness	Widening of the intercondylar distance
		Capitellum		Fall on outstretched hand	Localized tenderness, pain worse with flexion	Fragment lying anterior and proximal to the main portion of the capitellum
		Trochlea		Fall on outstretched hand	Localized tenderness with limited ROM	Fragment visible lying on the medial side of the joint, just distal to the medial epicondyle, signs of joint effusion
		Epicondylar		Fall on outstretched hand, repetitive valgus stress, direct blow	Elbow is held in flexion and any movement is resisted	A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow dislocation; evaluate for fracture fragments
			Medial	Fall on outstretched hand, repetitive valgus stress, direct blow	Elbow is held in flexion and any movement is resisted	A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow dislocation; evaluate for fracture fragments
			Lateral	Fall on outstretched hand, repetitive valgus stress, direct blow	Elbow is held in flexion and any movement is resisted	A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow dislocation; evaluate for fracture fragments
Radius/ulnar fractures						
	Radial head fracture			Fall on outstretched hand	Localized tenderness over radial head or pain with passive rotation of forearm	Range from subtle disruption of the gradual sweep of the radial neck and head surface to obvious displaced or comminuted fracture, positive fat pad sign
		Nondisplaced		Fall on outstretched hand	Localized tenderness over radial head or pain with passive rotation of forearm	Range from subtle disruption of the gradual sweep of the radial neck and head surface to obvious displaced or comminuted fracture, positive fat pad sign
		Displaced		Fall on outstretched hand	Localized tenderness over radial head or pain with passive rotation of forearm	Range from subtle disruption of the gradual sweep of the radial neck and head surface to obvious displaced or comminuted fracture, positive fat pad sign
		Comminuted		Fall on outstretched hand	Localized tenderness over radial head or pain with passive rotation of forearm	Range from subtle disruption of the gradual sweep of the radial neck and head surface to obvious displaced or comminuted fracture, positive fat pad sign
	Ulnar fracture					
		Olecranon fracture		Direct blow, forceful contraction of the triceps while the elbow is flexed during a fall can cause a transverse or oblique fracture through the olecranon	Localized tenderness, palpable separation at fracture site, inability to extend the elbow against force	Obvious fracture line
		Coronoid fracture		Direct blow, forceful contraction of the triceps while the elbow is flexed during a fall can cause a transverse or oblique fracture through the olecranon	Localized tenderness, palpable separation at fracture site, inability to extend the elbow against force	Obvious fracture line

Subluxations/ dislocations						
	Elbow dislocation					Obvious dislocation, must assess for concurrent fractures
		Posterior		Fall on the outstretched hand or wrist, the elbow being either extended or hyperextended	Elbow in flexion at approximately 45 degrees and have marked prominence of the olecranon	Obvious dislocation, must assess for concurrent fractures
		Anterior		Blow from behind to the olecranon while the elbow is in the flexed position	Upper arm appears shortened, the forearm elongated and supinated, the elbow is fully extended and the olecranon fossa is palpable posteriorly	Obvious dislocation, must assess for concurrent fractures
		Medial/lateral		Mechanism similar to that in posterior dislocations, with a vector of force displacing the ulna and radius as a unit either medially or laterally	Obvious deformity either medially or laterally	Obvious dislocation, must assess for concurrent fractures
	Radial head subluxation			Forearm pulled while in pronation with the elbow extended, direct blow, twisting	Arm held in passive pronation, with slight flexion at the elbow; refuses to move the arm, localized tenderness, swelling, ecchymosis and deformity are absent	Radiographs are not necessary and are rarely positive
Soft tissue						
	Epicondylitis			Repetitive pronation and supination of the forearm	Dull pain over lateral aspect of elbow, the lateral epicondyle or radiohumeral joint, increased by grasping or twisting motions	Radiographs normal or may have calcifications
	Olecranon bursitis			Repetitive minor trauma, inflammatory	Progressive pain, tenderness, and swelling over olecranon	None
	Bicep tendon rupture					
			Proximal	Repetitive microtrauma to the tendon	Visible defect at top of bicipital groove with bunching of the muscle distally, flexion of elbow produces pain at proximal insertion but flexion remains intact	None
			Distal	Extension force applied to the arm flexed at 90 degrees	Pain and tearing in the antecubital region, visible deformity and palpable defect of the biceps muscle belly with weakness of elbow flexion and supination	None

Fig. 45.6. Pathologic fracture of proximal humerus.

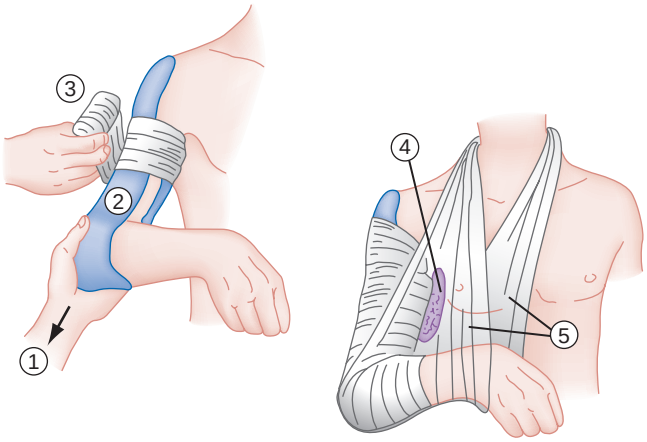


Fig. 45.7. Sugar-tong splint for humeral shaft fractures. Gentle traction is applied *(1)* as the splint is placed *(2)* from over the deltoid laterally, under the elbow, and up into the axilla. An elastic wrap holds the splint in place *(3)*. The axilla must be padded *(4)*, and a sling is used *(5)*. (Adapted from Connolly JF: DePalma's management of fractures and dislocations. Philadelphia, 1981, WB Saunders.)

spontaneously in over 90% of cases without operative intervention, although recovery may take 6 to 9 months.[4] Patients should be advised of this possible complication prior to discharge and follow-up with an orthopedic surgeon should be arranged before the patient leaves the emergency department (ED). Exploration and internal fixation are indicated if the radial nerve palsy develops after manipulation, because this is highly suggestive of nerve entrapment.[2] Radial nerve injuries associated with penetrating trauma or open fractures are likely to be caused by anatomical nerve disruption and usually warrant operative exploration. Median and ulnar nerve injuries are rare and usually secondary to penetrating trauma. Injuries to the brachial artery occur rarely and, if suspected, vascular surgery consultation is indicated, often with angiography or other vascular studies.

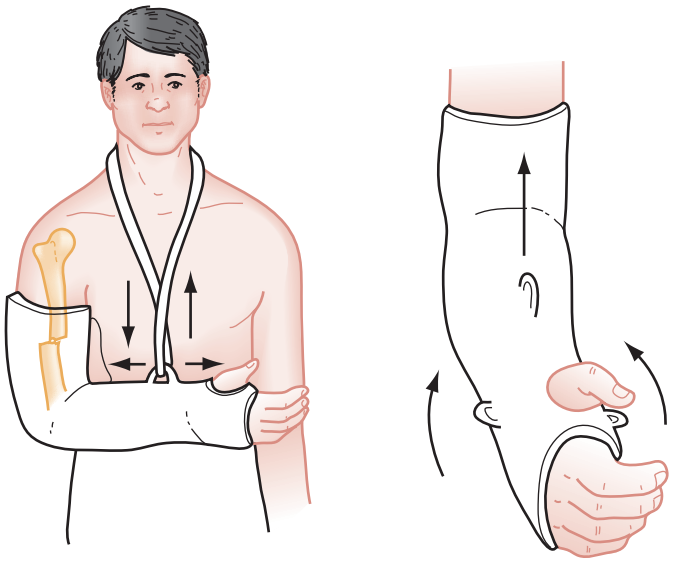


Fig. 45.8. Hanging cast technique.

Disposition. All patients with humeral shaft fractures should be referred to an orthopedic surgeon for further evaluation within 48 hours after the ED visit to ensure that the alignment has been maintained, no neurological deficits have emerged, and pain is adequately controlled. Emergent referral to an orthopedist is recommended for patients with evidence of radial nerve injury, severely displaced or comminuted fractures, open fractures, or fractures associated with forearm fractures in the same extremity.

Distal Humerus

Supracondylar Fractures. Distal humerus fractures that occur proximal to the epicondyles are called *supracondylar fractures.* This type of fracture is almost exclusively an injury of the immature skeleton, with a peak incidence in children 5 to 10 years old.[5] This injury rarely occurs after age 15 and accounts for approximately one half of all elbow fractures and one third of pediatric limb fractures. In children, the tensile strength of the collateral ligaments and joint capsule of the elbow is greater than that of bone. In adults, the reverse is true, and a fall or accident that would result in a supracondylar fracture in children would likely result in a posterior elbow dislocation in an adult. Supracondylar fractures are classified as either extension or flexion fractures, depending on the mechanism of injury and the displacement of the distal fragment. Of these injuries, 98% are of the extension type.

Extension Type Supracondylar Fractures

Clinical Features. Extension supracondylar fractures occur as a consequence of a fall on the outstretched hand when the elbow is either fully extended or hyperextended (eg, a fall off the "monkey bars"). The strong action of the triceps tends to pull and displace the distal fragment in a posterior and proximal direction. In children with extension-type supracondylar fractures, the arm is held at the side and has a characteristic S-shaped configuration, whereas with flexion-type supracondylar fractures, the forearm is supported with the opposite hand with the elbow flexed to 90 degrees. There may be anterior angulation of the sharp distal end of the proximal fragment into the antecubital fossa, which could injure the brachial artery and median nerve (Fig. 45.10). In most cases, however, the brachialis muscle protects the anterior neurovascular structures from injury. Because this fracture primarily

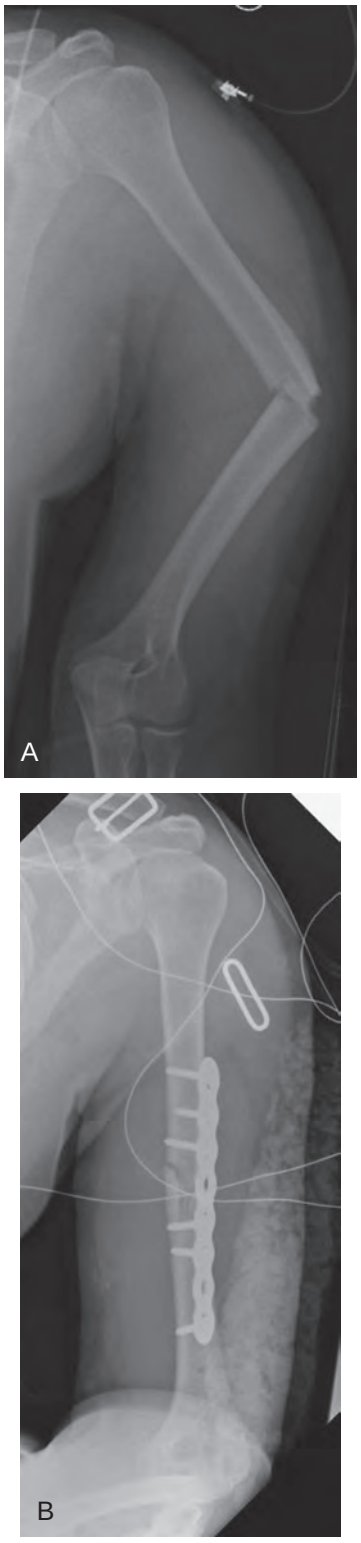


Fig. 45.9. Midshaft humerus fracture before **(A)** and after **(B)** open reduction and internal fixation.

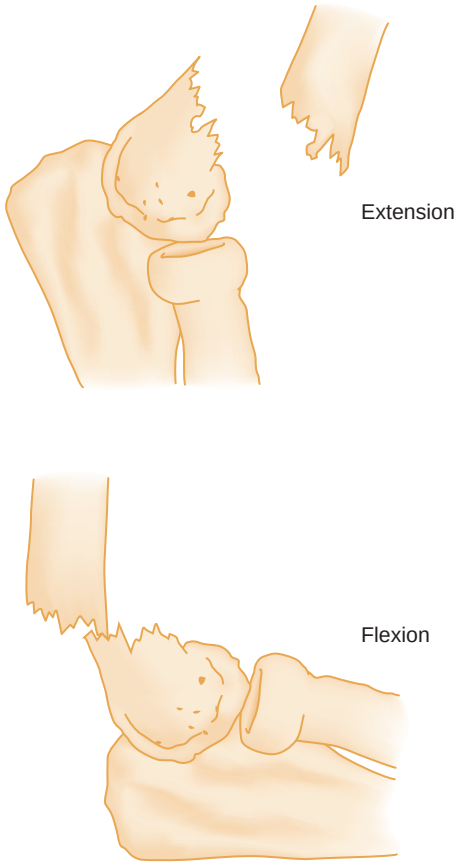


Fig. 45.10. Supracondylar fractures, extension and flexion. (Adapted from Simon R, Koenigsknecht S: Emergency orthopaedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

Fig. 45.11. Supracondylar fracture *(arrow)* with anterior and posterior fat pad.

occurs in children, 25% of supracondylar fractures are of the greenstick variety, with the posterior cortex remaining intact. Subtle changes (eg, the presence of a posterior fat pad or an abnormal anterior humeral line) may be the only radiographic clues to the presence of a fracture (Fig. 45.11). Ten percent of children lose the radial pulse temporarily, most often as a result of swelling and not direct brachial artery injury. Fracture reduction, avoiding flexing the elbow more than 90 degrees and elevating the arm help prevent secondary obstruction to arterial flow. Nerve injuries occur in 11% of these injuries, but the incidence increases to a range of 19% to 49% with increasing severity of fracture displacement.[6,7] The anterior interosseous nerve is the most commonly injured, followed by the radial, median, and ulnar nerves. Most deficits seen at the time of injury are

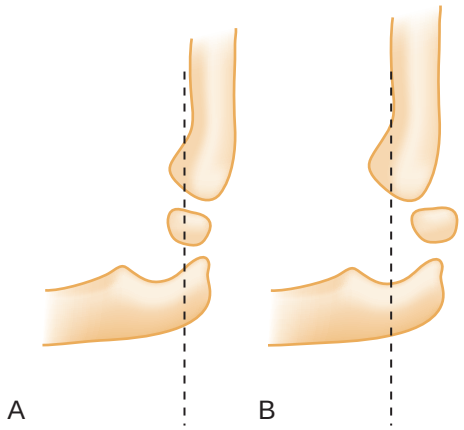


Fig. 45.12. A, A line drawn down the anterior surface of the humerus on a lateral film should transect the middle of the capitellum. **B,** With an extension supracondylar fracture, the line passes more anteriorly. (From Simon R, Koenigsknecht S: Emergency orthopaedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

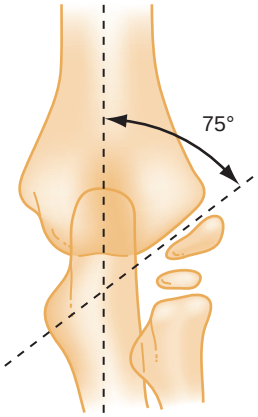


Fig. 45.13. Baumann's angle as measured on anteroposterior film. (From Worlock P: Supracondylar fractures of the humerus. J Bone Joint Surg Br 68:755, 1986.)

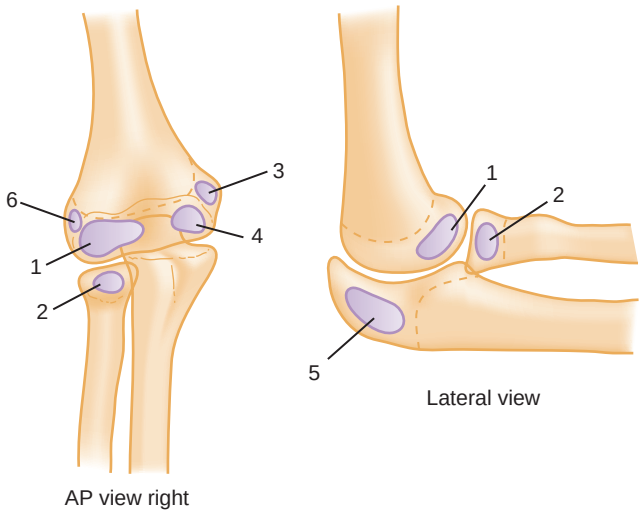


Fig. 45.14. Secondary growth centers of the elbow. *1,* Capitellum. *2,* Radial head. *3,* Medial epicondyle. *4,* Trochlea. *5,* Olecranon. *6,* Lateral epicondyle. (From Townsend DJ, Bassett GS: Common elbow fractures in children. Am Fam Physician 53:2031, 1996.)

TABLE 45.2

Ossification Centers of the Elbow: CRITOE

OSSIFICATION CENTERS	AGE OF APPEARANCE
Capitellum	1–2
Radial head	4–5
Internal (medial) epicondyle	4–5
Trochlea	8–10
Olecranon	8–9
External (lateral) epicondyle	10–11

BOX 45.1

Gartland Classification for Supracondylar Fractures in Children

Type I: Minimal or no displacement
Type II: Displacement of the fracture but with the posterior cortex intact
- Type IIA: No rotational component
- Type IIB: Some rotational component

Type III: Displaced, no cortical contact
- Type IIIA: No rotation of the fracture
- Type IIIB: Rotation present

neurapraxias that resolve with conservative management. Motor function returns within 7 to 12 weeks, whereas recovery of sensation may take more than 6 months.[6,8]

Diagnostic Testing. Two diagnostic aids in evaluating for possible supracondylar fractures include using the anterior humeral line and evaluating Baumann's angle. The anterior humeral line is a line drawn on a lateral radiograph along the anterior surface of the humerus through the elbow. Normally, this line transects the middle third of the capitellum (Fig. 45.12). With an extension supracondylar fracture, this line either transects the anterior third of the capitellum or passes entirely anterior to it. The abnormal relationship between the anterior-humeral line and capitellum may be the only evidence of a minimally displaced supracondylar fracture and is a presumptive finding of a fracture. Baumann's angle is the intersection of a line drawn on the anteroposterior film through the midshaft of the humerus and the growth plate of the capitellum defines an angle of approximately 75 degrees (Fig. 45.13).[9] Radiographic evaluation of the elbow in children is difficult because of the presence of multiple ossification centers (Fig. 45.14). Comparison views of the uninjured elbow are often helpful in distinguishing fractures from the normal epiphyses and ossification centers. Table 45.2 lists the typical age of first appearance and fusion of ossification centers.

Based on radiographic findings, supracondylar fractures are classified into four types: type I, minimal or no displacement; type IIA, displaced fracture, posterior cortex intact with no rotational component; type IIB, displaced fracture, posterior cortex intact with no rotational component; type III, totally displaced fracture, anterior and posterior cortex disrupted; and type IV, multidirectionally unstable due to complete circumferential periosteal disruption.[10]

Management and Disposition. Current treatment recommendations for supracondylar fractures from the American Academy of Orthopaedic Surgeons remain based on the modified Gartland classification (Box 45.1). Nondisplaced extension supracondylar fractures (type I) are immobilized primarily for comfort

and protection, because they are inherently stable. They are treated in a splint or cast flexed to 75 to 80 degrees with the forearm in neutral rotation.[6] Protected active range of motion is begun in approximately 3 weeks. Even without definite radiographic findings, a child with localized tenderness consistent with a supracondylar fracture should be splinted and referred for follow-up examination within 24 to 48 hours. An x-ray performed a few weeks after the injury may reveal periosteal new bone formation in the supracondylar region. Patients with type I fractures can be discharged safely from the ED with instructions to elevate the extremity, apply ice, and have a follow-up evaluation in 1 to 2 days. Fractures that require manipulation usually warrant admission to the hospital to ensure compliance and for neurovascular monitoring. Minimally displaced (type II) fractures that are stable after reduction can be treated with splinting or casting with the elbow flexed. Some authors recommend flexion to 110 to 120 degrees for this injury.[5,30,31] This position uses the intact posterior periosteum as a tension band to hold the reduction; however, if swelling or circulatory obstruction prevents this much flexion, it cannot and should not be used. The greater the flexion at the elbow, the greater is the chance of vascular impairment. When swelling peaks at 24 to 48 hours, the risk of vascular obstruction and compartment syndrome is the greatest. Occasionally, these injuries require percutaneous pinning to maintain stability, especially if a significant rotational component is present.[6] Percutaneous pinning of fractures after reduction has grown in popularity in recent years and is recommended for type IIB fractures with some studies showing better outcomes with pinning than without.[6,11,12] Type III totally displaced fractures generally are the result of more severe injuries that produce more swelling than type I or type II injuries. Displacement necessitates the reestablishment of length, increases the chance of varus deformity and increases the chances of interposed soft tissues and neurovascular injury. For all these reasons, patients with type III fractures require emergency orthopedic consultation in the ED and should be admitted to the hospital for frequent neurovascular checks and closed reduction by an orthopedist and percutaneous pinning. Open reduction may be necessary if closed reduction is unsuccessful.[6] Reduction in the ED is indicated only when the displaced fracture is associated with vascular compromise that threatens the viability of the extremity. Under these conditions, closed reduction should be attempted. After appropriate procedural sedation, an assistant fixes the arm of the patient. The physician grasps the patient's wrist and applies steady, firm traction in line with the long axis of the limb (Fig. 45.15A). The forearm is kept in the neutral, thumb-up position. While traction is maintained, correction of any medial or lateral displacement is accomplished with the other hand at the elbow (see Fig. 45.15B). If the distal fragment is displaced laterally, it is pushed inward; if it is displaced medially, it is pushed outward. After length has been restored and the angular deformity has been corrected, the thumb of the free hand is placed over the anterior surface of the proximal fragment with the fingers behind the olecranon. While traction is maintained, the elbow is gently flexed to just beyond 90 degrees (see Fig. 45.15C). Angulation is corrected to a normal carrying angle. Only one attempt should be made at manipulation. Multiple attempts increase the likelihood of neurovascular injury and swelling. If reduction is unsuccessful, simple traction on the extended elbow may restore vascular supply. When reduction is performed, follow-up radiographs are obtained to ensure adequate reduction and neurovascular function is checked at frequent intervals. Cylinder casts are not applied initially because they increase the risk of forearm ischemia; a posterior plaster splint provides safe and adequate immobilization. Type IV injuries require emergent orthopedic consultation for complicated operative intervention. These injuries represent a surgical challenge, but recent studies show that a satisfactory outcome can be obtained.[10]

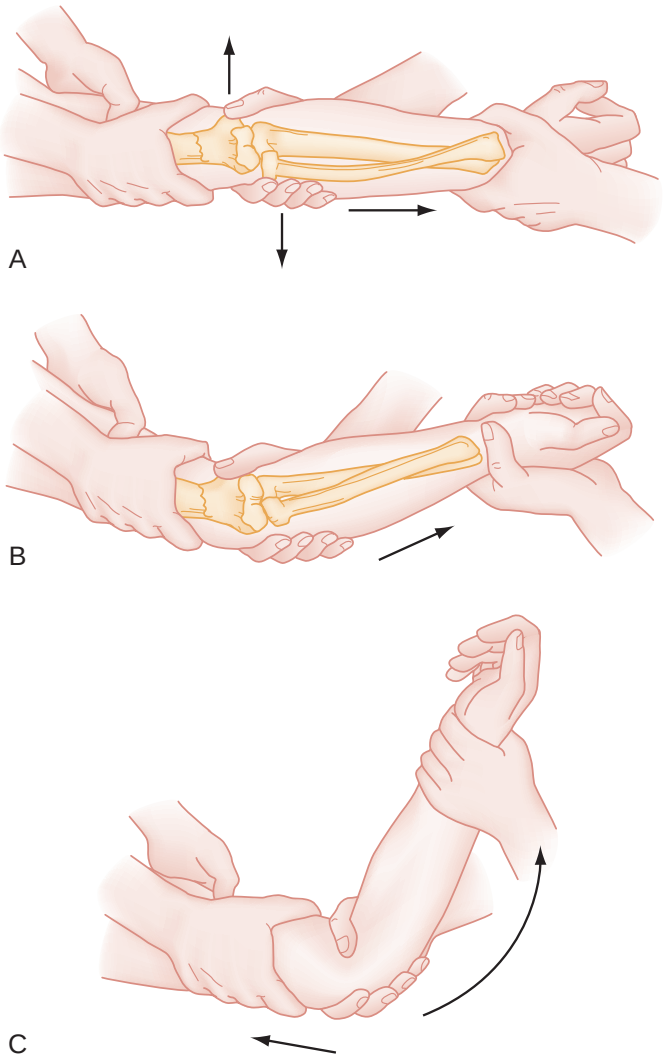


Fig. 45.15. A to **C,** Steps in reduction of displaced supracondylar fracture.

Flexion Type Supracondylar Fractures

Clinical Features. Flexion-type supracondylar injuries are much less common, with a reported frequency of about 2% of all supracondylar fractures.[13] The mechanism of injury is a direct blow to the flexed elbow.

Diagnostic Testing. Plain films may reveal a simple increase in the anterior angulation of the distal supracondylar fragment or gross displacement of the distal fragment proximal and anterior to the distal end of the proximal fragment. In the latter case, the distal end of the proximal fragment protrudes posteriorly. A line down the anterior humeral shaft (see earlier discussion in the Extension Type Supracondylar Fractures section) intersects the capitellum either normally or posteriorly in these fractures, depending on whether there is anterior displacement.[14] The most common complication is nerve injury with injury to the ulnar nerve, occurring in over 90% of all nerve inuries.[6] The radial and median nerves are rarely injured.

Management and Disposition. For flexion-type supracondylar injuries, when the posterior periosteum is torn, the anterior periosteum functions as a tension band with the arm in extension. In type I fracture, the periosteum is minimally displaced. These injuries do not need to be immobilized in extension. The elbow can be comfortably flexed and should be immobilized in a splint as with extension injuries. Type II and III injuries should be referred to an orthopedist immediately. Type II injuries are

Fig. 45.16. Type III supracondylar fracture with significant displacement of distal fragment.

manipulated into extension and then either in a long arm cast or with percutaneous pins. Type III injuries are treated with closed reduction and percutaneous pinning but will require open reduction if closed reduction fails (Fig. 45.16).[6]

Transcondylar Fractures

Clinical Features. Both extension and flexion types of transcondylar fractures have been described based on the position of the elbow when fractured. Extension types are the most common with a mechanism of injury that is similar to that for supracondylar injuries. In contrast to supracondylar fractures, however, the injury is more common in elderly individuals with fragile, osteoporotic bone.

Diagnostic Testing. Transcondylar (or dicondylar) fractures have a fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface (Fig. 45.17).

Management and Disposition. Transcondylar (or dicondylar) fractures are generally difficult to treat because the small distal fragment possesses little extra-articular bone, and only a small amount of bone contact is available for union.[14] Orthopedic consultation in the ED should be obtained for these injuries. Both internal fixation and elbow arthroplasty are viable operative options, with internal fixation now supplanting primary elbow arthroplasty as the mainstay of treatment for most cases.[15]

Intercondylar Fractures

Clincial Features. These injuries are rare and generally are seen in adults in their 50s and 60s.[12] The common mechanism of injury is direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end. Patients with intercondylar fractures complain of pain at the elbow, which on examination is tender to palpation. Neurovascular complications are not common with these injuries.

Diagnostic Testing. Good-quality anteroposterior and lateral radiographic views are essential in evaluating fracture displacement and comminution (Fig. 45.18). Intercondylar fractures are usually T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment (Fig. 45.19). The distal portion of the fracture extends to the articular surface of the distal humerus.

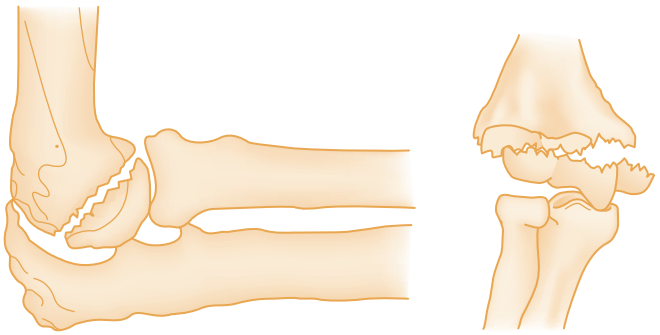


Fig. 45.17. Transcondylar fracture of distal humerus. (*Left,* From Ruiz E, Cicero J: Emergency management of skeletal injuries, St Louis, 1995, Mosby. *Right,* Adapted from Simon R, Koenigsknecht S: Emergency orthopaedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

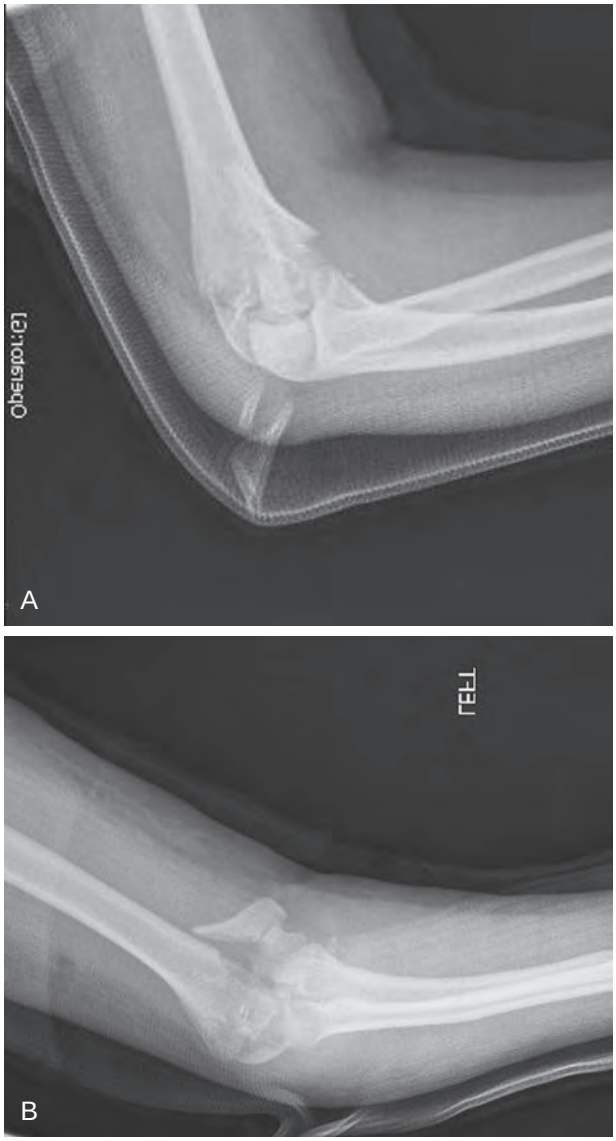


Fig. 45.18. Intercondylar fracture, type III. Lateral **(A)** and anteroposterior **(B)** views.

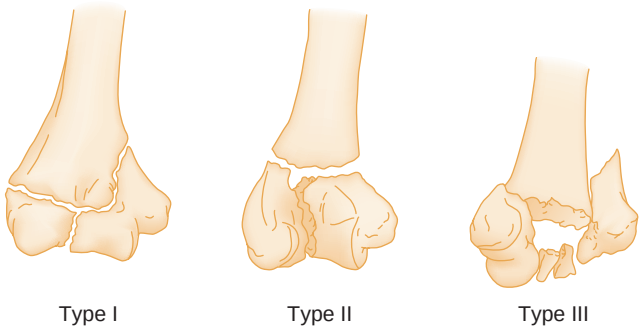


Fig. 45.19. Intercondylar T fractures, types I, II, and III. (From Connolly JF: DePalma's management of fractures and dislocations, Philadelphia, 1981, WB Saunders.)

Computed tomography may be used to delineate fracture patterns further.

Management and Disposition. Treatment of intercondylar fractures is difficult and complicated.[13,34] The goal of treatment is to reestablish articular congruity and alignment and to begin active motion as soon as possible, most often through open reduction with rigid internal fixation. Closed treatment is typically restricted to elderly patients, patients with medical conditions that prohibit surgery, and certain patients with nondisplaced fractures, although recent literature shows that both closed and open methods may have similar results in children.[16] These injuries all should be referred to an orthopedic surgeon immediately. As with supracondylar fractures, manipulation should be avoided unless limb-threatening ischemia is present. Traction across the elbow with the arm extended is helpful in restoring blood flow to an ischemic forearm.

Condylar Fractures

Clinical Features. Condylar fractures are rare in adults and typically involve the articular surface and the nonarticular portion of the distal humerus, including the epicondyle (Fig. 45.20). Lateral condylar fractures are uncommon, although more common than fractures of the medial condyle. The mechanism of injury is either a direct blow to the lateral aspect of the flexed elbow or a force that results in adduction and hyperextension with avulsion of the lateral condyle. Medial condylar fractures are rare and result from either a direct blow to the apex of the flexed elbow or a fall on the outstretched hand with the elbow forced into varus. The presentation of condylar fractures is similar to that of other distal humerus fractures, with swelling, tenderness, and crepitus localized over either the medial or the lateral elbow. On palpation, independent motion of the involved condyle may be appreciated. In lateral condylar fractures, findings may be accentuated with movement of the radius. In children, lateral condyle fractures are the second most common fractures involving the elbow, after supracondylar fractures.[17] The fracture has an age distribution similar to that of supracondylar fracture and occurs after a fall on the outstretched hand, with a varus stress applied to the extended arm. Tenderness and swelling are noted over the lateral aspect of the elbow. In general, children exhibit less swelling than with supracondylar fractures and neurovascular compromise is uncommon. Because of the location of the ulnar nerve, it is imperative to test its function when this fracture is present. Medial condylar fractures are associated with tenderness over the medial condyle and pain with flexion of the wrist against resistance. Medial condyle fractures are rare in children, comprising 1% to 2% of pediatric elbow fractures.[18] When they do occur, medial condyle fractures are considered type IV Salter-Harris injuries with physeal injury a possible outcome. The mechanism of injury is believed

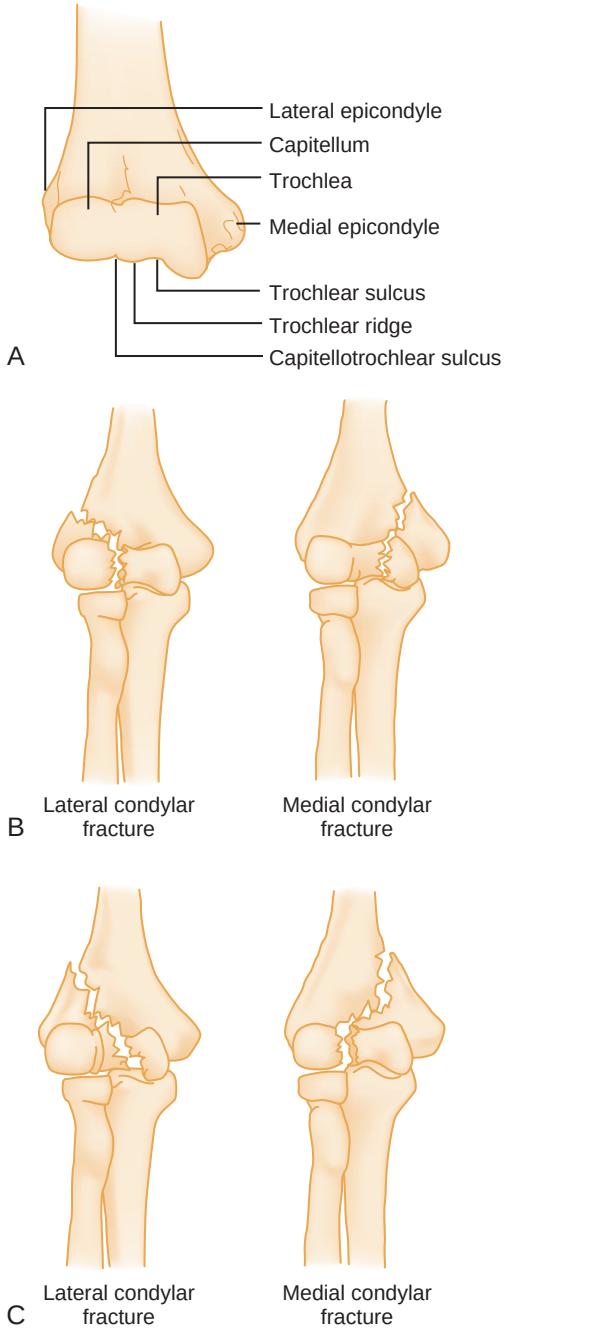


Fig. 45.20. Condylar fractures. **A,** Normal anatomy. **B,** Lateral trochlear ridge not in fracture fragment (stable). **C,** Lateral trochlear ridge included with fracture fragment (unstable). (Adapted from Simon R, Koenigsknecht S: Emergency orthopaedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

to be a valgus force on the extended elbow. The patient has tenderness and swelling over the medial aspect of the elbow.

Diagnostic Testing. Diagnosis is usually made on standard anteroposterior and lateral views, although an oblique view also may be helpful. These fractures are notoriously difficult to diagnose because fractures with minimal displacement are difficult to see radiographically and are often misdiagnosed as supracondylar humerus fractures. The status of the lateral trochlear ridge is the key to analyzing humeral condyle fractures. It may be involved with either medial or lateral condylar fractures and, when incorporated into the distal fragment, is far more likely to result in instability. On radiographic examination, lateral condylar

fractures show a widening of the intercondylar distance. The distal fragment is often displaced, most commonly posteriorly and inferiorly. Displaced distal fragments tend to be anterior and inferior because of the pull of the forearm flexors. For medial condoyle fractures, anteroposterior, lateral, and oblique films may show the fracture in older children, but because the trochlea does not ossify until about age 9, plain films in younger children do not show the fracture. Magnetic resonance imaging (MRI) may be necessary to confirm the diagnosis in these patients.

Management and Disposition. For condylar fractures, treatment depends on radiographic findings but much controversy exists about the accuracy of these findings and studies are being done to determine the best imaging method.[19] For nondisplaced or minimally displaced condylar fractures, immobilization of the flexed elbow in a long arm posterior plaster splint is sufficient. Surgical intervention is recommended for a fragment incarcerated within the elbow joint, open fracture, nerve injury, or gross elbow instability.[19] For fractures displaced more than 3 mm, surgical fixation is traditionally recommended, but there is some controversy around this with acceptable displacement ranging from more than 2 mm to 15 mm.[19] Due to the high rate of complications, orthopedic consultation should be sought for all adult condylar fractures. For lateral condylar fractures, the forearm should be supinated and the wrist extended to relieve the tension on the extensor muscle attachments. For medial condylar fractures, the reverse is true (ie, the forearm should be pronated and the wrist flexed). Nondisplaced lateral condyle fractures are treated nonoperatively with a cast, whereas fractures with any displacement require closed or open reduction with percutaneous pin fixation for 3 to 4 weeks.[17,37] For medial condyle fractures, operative treatment is indicated if displacement is greater than 2 mm; otherwise, conservative treatment is sufficient.

Capitellum and Trochlea Fractures

Clinical Features. Fractures of the capitellum and trochlea typically occur together, usually as a result of posterior dislocation of the elbow, with isolated fractures being less common. Injury to the capitellum occurs when the patient falls on an outstretched hand, forcing the radial head upward, similar to the motion of a piston, shearing off the capitellum into the radial fossa. Because the capitellum has no muscular attachments, the fragment may remain nondisplaced. More often the fragment is displaced usually anteriorly and occasionally posteriorly. A radial head fracture also may be present and should be clinically suspected because of this mechanism. The development of significant signs and symptoms may be delayed with capitellum fractures. Eventually, swelling within the capsule results in severe pain that manifests as well-localized tenderness on examination and flexion of the elbow increases pain. Isolated fractures of the trochlea are exceedingly rare because of the structure's protected position deep within the elbow joint. The shearing force of the ulna against the trochlea is associated more commonly with posterior elbow dislocation. The elbow is painful, with an effusion and limited range of motion because this is an intra-articular injury.

Diagnostic Testing. For capitellum fractures, a true lateral plain film usually shows the fragment lying anterior and proximal to the main portion of the capitellum (Fig. 45.21). In an isolated trochlear fracture, the radiograph shows a fragment visible lying on the medial side of the joint, just distal to the medial epicondyle, and signs of joint effusion are visible. The fracture may extend into the distal portion of the medial epicondyle.

Management and Disposition. Treatment of capitellum and trochlea fractures begins in the ED with a posterior splint, ice packs, elevation, compression, and analgesia. Accurate anatomic alignment, rigid internal fixation, and early mobilization are prerequisites for a good functional result.[20] Fractures of the articular surfaces can be treated nonsurgically only if radiographs show perfect anatomic alignment. Nondisplaced trochlea fractures may be treated with a posterior splint for 3 weeks, followed by early range-of-motion exercises. Displaced fractures should be treated operatively; fragments that can be internally fixed are repaired, whereas small fragments are excised. Immobilization should be minimized to 10 to 14 days.[39]

Fig. 45.21. Fracture of the capitellum.

Epicondylar Fractures

Clinical Features. Most epicondylar fractures involve the medial epicondyle. Medial epicondyle fractures are most common in children and adolescents and often involve the apophysis, which is the last ossification center to fuse in the distal humerus, usually after age 15. Fractures through this ossification center usually occur in adolescence and constitute 11% of pediatric elbow fractures.[15] These are not Salter-Harris injuries, because the apophysis is involved rather than the physis. The lateral epicondyle is almost level with the flattened outer surface of the lateral condyle giving it only minimal exposure to a direct blow and fracture is extremely rare. Medial epicondyle injuries occur from a variety of mechanisms. First, avulsion fractures are associated with posterior elbow dislocations in patients younger than 20 years in up to 50% of cases.[21] Avulsion fracture also may occur with severe or repeated stress, such as from arm wrestling or baseball pitching (Little Leaguer's elbow). Finally, a direct blow to the medial epicondyle can cause this injury. The elbow is held in flexion and any movement is resisted. Isolated fractures are associated with focal tenderness over the medial epicondyle. Use of the forearm flexors increases pain because their attachment is along the medial epicondyle. Ulnar nerve function should be evaluated as associated ulnar nerve palsy may be present with an entrapped fragment.

Diagnostic Testing. Simple fractures of the medial epicondyle are extra-articular injuries with limited soft tissue injury.[13] They generally do not produce a fat pad sign on the lateral radiographic view of the elbow. A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow

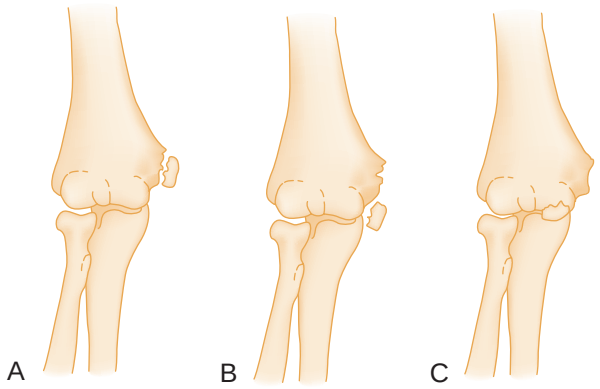


Fig. 45.22. Fractures of medial epicondyle. **A,** Minimal displacement. **B,** Marked displacement. **C,** Displacement into joint. (From Connolly JF: DePalma's management of fractures and dislocations, Philadelphia, 1981, WB Saunders.)

dislocation. Careful radiographic evaluation is especially important because fracture fragments may migrate into the joint space. If the fragment is overlying the joint line on radiographic examination, it should be considered intra-articular (Fig. 45.22). Radiographic detection of the intra-articular fragment is often difficult.[17] Fragments may be difficult to see on radiographs and a true anteroposterior view is difficult to obtain because of severe pain on extension. In an adolescent patient, there is a tendency to confuse the normal radiolucent epiphyseal growth plate with a fracture. In addition, minimally displaced fractures may be difficult to appreciate with radiographs and comparison films of the uninjured elbow may be necessary. If dislocation is present, repeat radiographs taken after reduction should be evaluated for fragment location.

Management and Disposition. For epicondylar fractures, if the fracture fragment is minimally displaced (<5 mm), treatment with a posterior splint is appropriate. To minimize distraction of the fragment by the forearm flexors, the elbow and wrist are flexed with the forearm pronated. Treatment of displaced fractures is controversial and often, the amount of displacement dictated the need for surgery, but results of operative and nonoperative treatment seem to be good regardless of the degree of displacement.[22] Some experts advocate surgery for patients who participate in high-performance athletic activities that involve the injured extremity but controlled studies are lacking.[17] Intra-articular fragments that cannot be removed from the joint by manipulation are an indication for surgery.[22] Emergent orthopedic consultation should be sought for these injuries. The rare lateral epicondylar fracture in adults was previously treated with immobilization, but more recent experience indicates that operative management is more successful.[41]

Olecranon

Clinical Features. Fractures of the olecranon may result most commonly from a direct blow as a result of a fall, a motor vehicle or motorcycle crash, or an assault. Less commonly, indirect force applied by forceful contraction of the triceps while the elbow is flexed during a fall can cause a transverse or oblique fracture through the olecranon. Olecranon fractures are uncommon in children. The anatomic integrity of the olecranon is essential for triceps strength and normal function of the elbow. Physical findings may include tenderness and pain over the olecranon, a palpable separation at the fracture site or the inability to extend the elbow against force. This last finding indicates complete discontinuity of the pulling mechanism and the consequent failure of

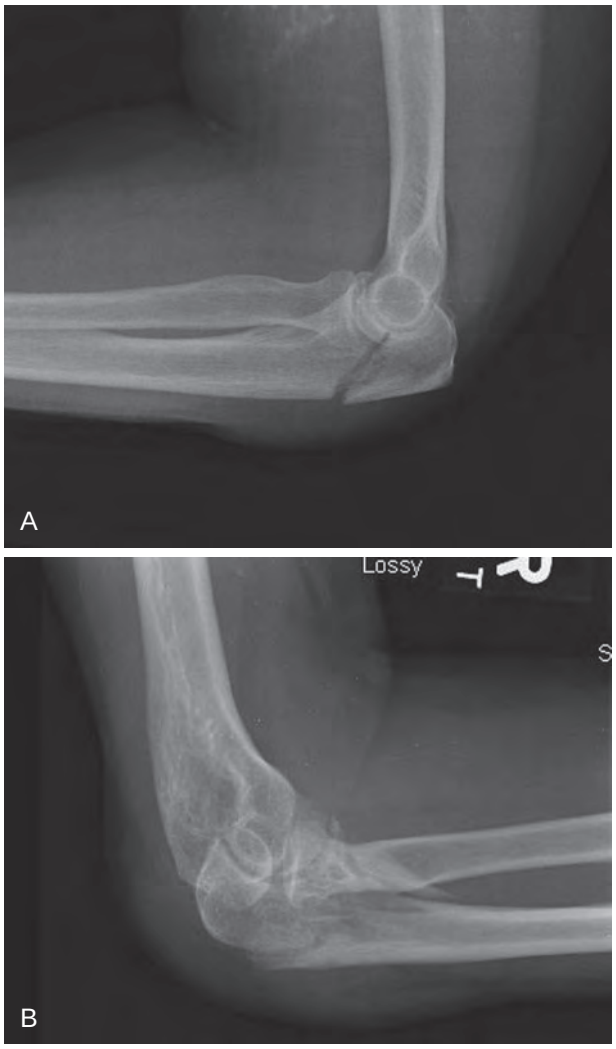


Fig. 45.23. A, Olecranon fracture with displacement. **B,** Fracture accompanied by radial head dislocation.

triceps function. The neurovascular status should be examined with special attention given to the ulnar nerve distribution. Loss of sensation over the palmar aspect of the fifth digit and hypothenar eminence or motor weakness in the interossei muscles of the hand suggests ulnar nerve injury. Symptoms of ulnar nerve injury occur in 10% of patients and in most cases the injury is an ulnar contusion that resolves spontaneously.

Diagnostic Testing. Lateral radiographic views are most helpful. In addition to the fracture, the degree of comminution, the extent of articular surface disruption and the amount of displacement in the 90-degree flexion position should be noted.

Management and Disposition. In olecranon fractures, non-displacement in the 90-degree flexion position indicates that the triceps aponeurosis is intact and prolonged immobilization is unnecessary. Displacement of more than 2 mm is considered an indication for surgery (Fig. 45.23A). A fracture line that increases in separation with flexion of the elbow is also considered a displaced fracture. When this fracture is associated with elbow dislocation, the plane of instability is located through the fracture site and the radiohumeral joint resulting in posterior displacement of the proximal fragment of the ulna and anterior dislocation of the radius and ulna as a unit (see Fig. 45.23B). Nondisplaced fractures can be treated conservatively on an outpatient basis with

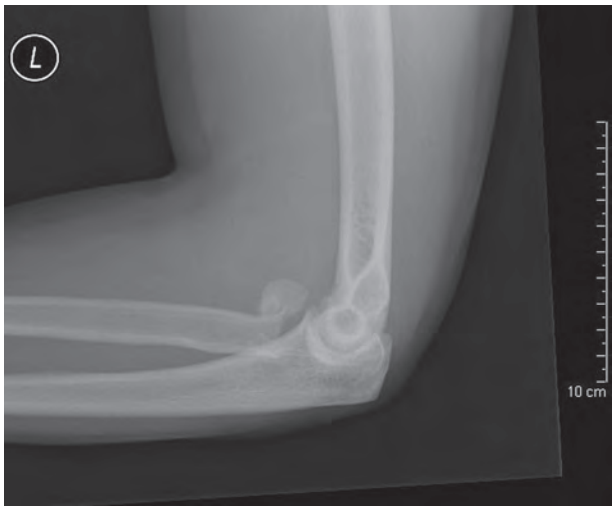


Fig. 45.24. Radial head fracture with displacement.

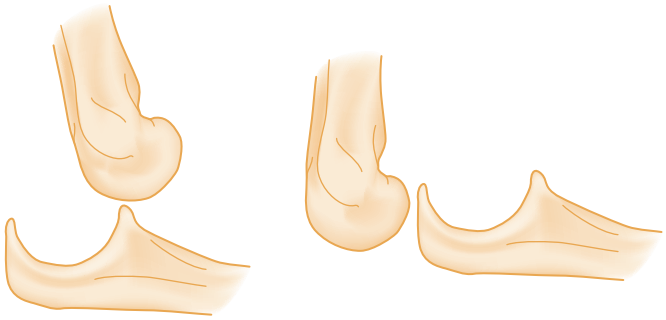


Fig. 45.25. Elbow dislocation, posterior and anterior. (Adapted from Simon R, Koenigsknecht S: Emergency orthopaedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

ice, compression, immobilization in 45 to 90 degrees of flexion and analgesia. Follow-up films should be performed at frequent intervals to ensure that subsequent displacement does not occur. Range-of-motion exercises can be started within 3 weeks in many cases. Displaced fractures or fracture-dislocations require open reduction and internal fixation and patients should be referred urgently to an orthopedist. Displaced fractures in elderly patients sometimes are treated conservatively but this should be left to the discretion of the consultant. Orthopedic referral also is necessary when ulnar nerve symptoms are present.

Radial Head and Neck

Clinical Features. Radial head and neck fractures, in general, are produced by an indirect mechanism, typically a fall on an outstretched hand. The radius transmits the force upward, driving the radial head against the capitellum and resulting in fracture of the weaker radial head or neck. Although the fracture of the radial head may be the only radiographic finding, damage to the articular surface of the capitellum and injury to the collateral ligament commonly occur. Displacement of the radial head fragment suggests considerable force and significant soft tissue injury. This injury is characterized by localized tenderness over the radial head or pain with passive rotation of the forearm.

Diagnostic Testing. Radiographic findings range from a subtle disruption of the usual gradual sweep of the radial neck and head surface to an obvious displaced or comminuted fracture (Fig. 45.24). Undisplaced fractures are notoriously difficult to see on radiographs. Tenderness coupled with a positive fat pad sign on the radiograph indicates that the injury should be treated as a radial head fracture even in the absence of a visible fracture. Radial head fractures are classified into four types: type I, undisplaced fractures; type II, marginal fractures (involving <30% of the articular surface) with more than 2 mm displacement, including impaction or angulation; type III, comminuted fractures of the entire radial head; and type IV, any of the previous types with elbow dislocation.[23]

Management and Disposition. In radial head and neck fractures, type I nondisplaced fractures are treated symptomatically with a brief period of sling support and early range-of-motion exercises (within 24 to 48 hours). Aspiration of the hemarthrosis from the joint space may give dramatic relief of pain and improve the range of motion. Based on a prospective randomized study, which found no benefit to bupivacaine instillation compared with simple aspiration, we do not recommend injection of bupivacaine into the joint.[24] Most patients with this injury recover well in 2 to 3 months. A few do poorly, however, with long-term pain, contracture, or inflammation. Type II injuries are usually treated similarly, with aspiration and immobilization in the ED, followed by a trial period of range-of-motion exercises. In these cases, aspiration of the joint not only relieve pain but also allow testing of the range of motion to identify entrapped fragments. Radial head excision is sometimes performed later if the patient fails to improve. Early excision is advised for type II fractures when a mechanical block is present and for most type III fractures. Long-term functional results after radial head excision are acceptable in most patients with relatively few having some functional disability after this procedure.[43] Treatment of type IV injuries is directed at the elbow dislocation as described next and for the specific radial head lesion.

Dislocations/Subluxations

Elbow

Clinical Features. The elbow is inherently subject to mechanical instability because of its anatomic structure and dislocations are common. The elbow is second only to the shoulder as the most commonly dislocated large joint. *Elbow dislocation* is a term usually used to describe a disruption of the relationship between the humerus and the olecranon. In general, the radius and ulna, bound together firmly by the annular ligament and interosseous membrane, displace as a unit. Most classifications refer to the abnormal position of the ulna relative to the humerus. The elbow most often dislocates posteriorly, although it may dislocate anteriorly, medially, or laterally (Fig. 45.25). Although rare, a *divergent dislocation,* which is a dislocation between the radius and ulna concurrently with the ulnohumeral type, can occur. Dislocation of the elbow requires considerable energy and is often associated with fractures of adjacent bony structures and a fracture-dislocation injury is referred to as a *complex elbow dislocation.*

The mechanism of injury of a posterior elbow dislocation is a fall on the outstretched hand or wrist, the elbow being either extended or hyperextended at the time of impact. A valgus stress usually also occurs. Patients hold the elbow in flexion at approximately 45 degrees and have marked prominence of the olecranon. Some elbow dislocations may reduce spontaneously prior to presentation in the ED where significant swelling and tenderness may be the only findings. Because elbow dislocations are associated with brachial artery and median nerve injuries, careful neurovascular examination is important especially prior to any

manipulation or reduction and should be repeated frequently. Radiographic evaluation is crucial before manipulation to rule out fractures that can mimic dislocation on examination. Several fractures, including fractures of the distal humerus, radial head, and coronoid process commonly occur in conjunction with dislocation, which need to be identified and treated when present. The most serious complication of elbow dislocation is vascular compromise. Severe disruption results in injury to the brachial artery in 5% to 13% of cases.[25] Vascular injury should be considered when a wide opening between the tip of the olecranon and the distal humerus is palpated or seen on a radiograph. The presence of distal pulses is not proof of an intact artery; and if a question of vascular compromise exists, emergent vascular studies or consultation is indicated. Median nerve traction injuries and entrapment have been reported. Recurrent dislocation of the elbow is rare. Medial and lateral elbow dislocations are produced by a mechanism similar to that in posterior dislocations, with a vector of force displacing the ulna and radius as a unit either medially or laterally. Anterior dislocations are rare and occur as a result of a blow from behind to the olecranon while the elbow is in the flexed position. Severe associated soft tissue trauma is often present, including avulsion of the triceps mechanism or vascular disruption, and these dislocations are frequently open. On examination, the upper arm appears shortened, the forearm elongated and supinated, the elbow is fully extended and the olecranon fossa is palpable posteriorly.

Diagnostic Testing. A radiographic example of posterior elbow dislocation before reduction is provided in Figure 45.26. The anteroposterior view is the important to be able to visualize medial or lateral dislocations.

Management and Disposition. Rapid reduction of complete elbow dislocations is important to relieve pain and to prevent circulatory embarrassment or cartilaginous damage. Reduction should be attempted as soon as possible, especially if there is neurovascular compromise, and orthopedic consultation is usually not necessary to proceed. Intra-articular injection of local anesthetic may provide adequate analgesia to allow for closed reduction, but procedural sedation is very helpful and often required to facilitate reduction. Posterior dislocations are reduced with an assistant immobilizing the humerus and applying counter traction while traction is applied to the distal forearm. The ideal position is for the elbow to be flexed at 30 degrees with the forearm supinated while distal traction is applied. When the capitellum slides over the coronoid process, a coupling sound occurs as the articular surfaces mesh. If reduction is unsuccessful with this technique, the physician should apply downward pressure at the proximal forearm and apply pressure behind the olecranon while maintaining inline traction. This downward force may help "unlock" the coronoid process, which may be trapped in the olecranon fossa. The joint is gently moved through its normal range of motion to check stability. As with all reductions, neurovascular status should be checked before and after any reduction attempt. Post reduction radiographs are required to access concomitant fractures of the coronoid process or radial head or, in children, separation of the medial epicondylar apophysis. Post reduction management includes immobilization in a posterior splint with the elbow in as much flexion as circulation allows along with a sling. Circular casting should be avoided initially. Patients can be discharged with instructions to apply ice, elevate, and watch for signs of vascular impairment. If the elbow is stable after reduction, gentle range-of-motion exercises may be initiated in 3 to 5 days. Unstable joints may require either prolonged immobilization in the presence of ligamentous instability or internal fixation for instability associated with fracture.[26] For medial and lateral elbow dislocations, reduction is carried out with the arm in slight extension but otherwise is similar to that for posterior dislocation. Care should be taken not to convert these to posterior dislocations during reduction. Complications and aftercare are the same as for posterior dislocations. Reduction of closed anterior dislocations is performed with distal traction of the wrist and a backward pressure on the forearm while the distal humerus is grasped. A click usually indicates that reduction has been achieved. These injuries have a higher incidence of vascular impairment than the more common posterior dislocation although ulnar nerve injuries are unusual.[27] Emergent orthopedic referral is standard for open injuries or when vascular disruption is suspected.

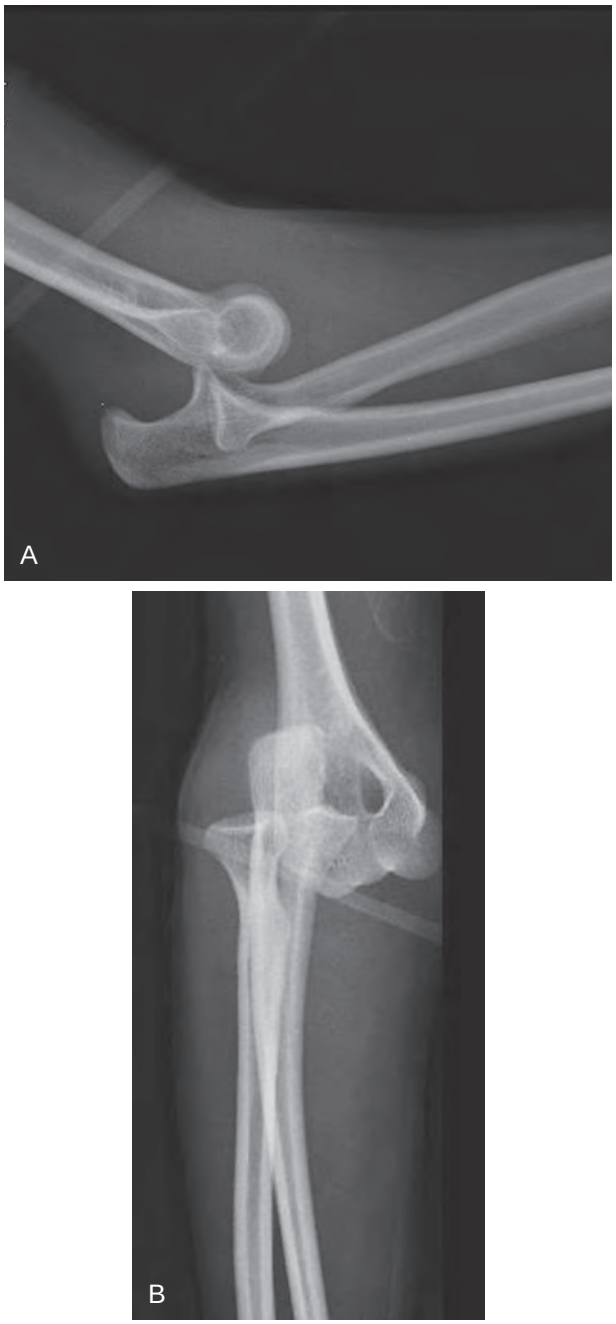


Fig. 45.26. Characteristic posterior dislocation of elbow, lateral **(A)** and anteroposterior **(B)** views.

Radial Head Subluxation

Clinical Features. Subluxation of the radial head (nursemaids' elbow) is a common injury, representing more than 20%

of upper extremity injuries in children. Children 1 to 4 years old are most often affected, although cases have been reported in children 6 months to 15 years old. Girls are affected more commonly than boys, and the left arm is more commonly affected than the right.[28] The classic history, which is present approximately half of the time, is that of the forearm being pulled while in pronation with the elbow extended with stretching of the annular ligament, allowing fibers to slip between the capitellum and the head of the radius, resulting in an inability of the child to supinate the arm.[29] By the age of 5, the annular ligament becomes thick and strong and thus is far less likely to tear or be displaced. Other mechanisms include direct trauma to the elbow or a twisting motion of the arm. In children younger than 6 months old, the mechanism of subluxation involves rolling over in bed that may trap the involved forearm under the body with resulting longitudinal traction on the joint. Clinically, the arm is held in passive pronation, with slight flexion at the elbow. The child is unable or unwilling to move the arm. Resistance to supination and tenderness on direct palpation over the head of the radius are present. Swelling, ecchymosis and deformity are absent.

Diagnostic Testing. When the history is suggestive of radial head subluxation, radiographs are not necessary and are rarely useful. If there is swelling or deformity, if there is an uncharacteristic history, if the child does not resume use of the arm after reduction, or if there is a possibility of nonaccidental trauma, appropriate radiographic studies are recommended. If palpation of the forearm, wrist, or humerus away from the elbow elicits reproducible tenderness, radiographs should be taken to exclude other diagnoses.

Management and Disposition. Reduction may be attempted in children with typical presentations and is safe even when the classic history is absent. Although historically, supination-flexion has been the method most commonly used, hyperpronation has a significantly higher reported success rate of reduction on the first attempt and is the recommended method for reduction.[30] With the hyperpronation method, the child's elbow is supported with moderate pressure applied to the radial head. The examiner then grips the child's distal forearm and hyperpronates the forearm, resulting in a click felt over the radial head (Fig. 45.27). In the supination-flexion method, reduction is achieved either by supination or pronation of the forearm while applying direct pressure over the radial head. With the supination method, the forearm is supinated while slight pressure on the radial head is applied with the examiner's thumb. In one continuous motion, the elbow is supinated and flexed with gentle axial pressure applied. A click often, but not always, is felt as the radial head reduces (Fig. 45.28). Many patients are asymptomatic within 5 to 10 minutes; 90% of patients regain use of the arm within 30 minutes. Because a fearful child often does not use even the successfully reduced limb, it is a good idea for the physician to leave the room and for parents to distract the child to show return of normal function. If function does not return within 24 hours, the patient should be reevaluated. After successful reduction, no additional treatment, immobilization, or activity reduction is necessary. Parents and caregivers should be instructed to avoid excessive traction on the child's forearm to prevent recurrent radial head subluxation. The recurrent radial head subluxation rate is approximately 20%.[31]

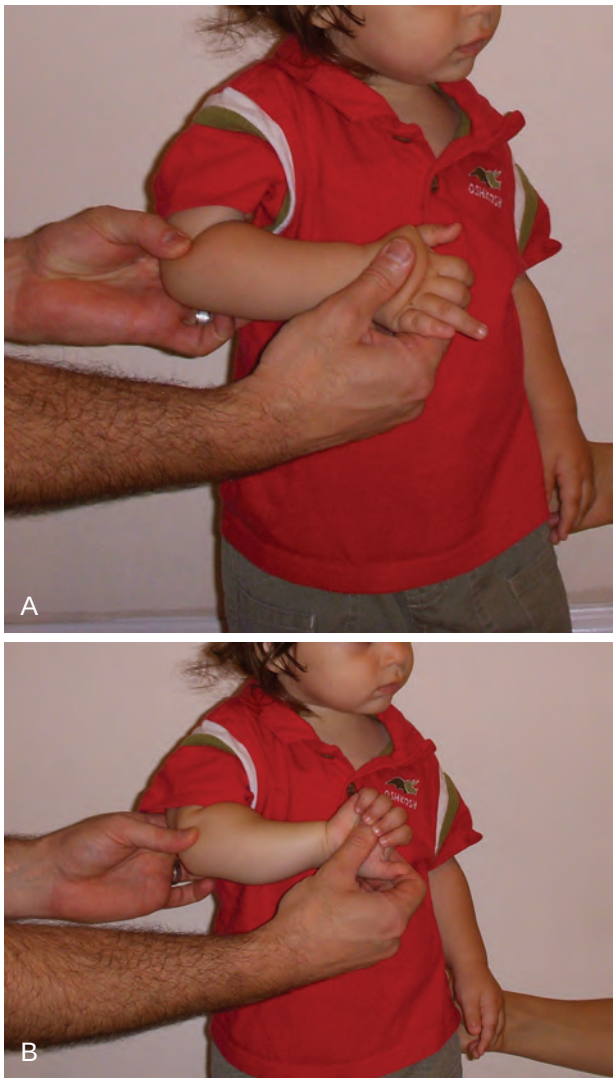


Fig. 45.27. Hyperpronation method of radial head subluxation reduction. **A,** Support elbow with pressure to radial head. **B,** Then hyperpronate the arm distally.

Soft Tissue Disorders

Epicondylitis

Clinical Features. *Epicondylitis* (tennis elbow) is a term first introduced in the 1880s to describe an inflammatory process that involves the radiohumeral joint or lateral epicondyle of the humerus. It is a common exercise-related syndrome, and the mechanism is thought to be repetitive pronation and supination of the forearm. The actual pathologic nature of this syndrome is unclear. Radiohumeral bursitis or synovitis, tendinitis of the common extensor tendon, periostitis of the lateral epicondyle, and entrapment by scar tissue of the radial nerve all have been suggested as causes of this syndrome. Histologically, the abnormality has been described as *angiofibroblastic hyperplasia,* a term subsequently modified to *angiofibroblastic tendinosis.* It is thought to be a degenerative process because of the paucity of acute inflammatory cells seen histologically.[32] Most cases are lateral, but medial tennis elbow and posterior tennis elbow have been reported, the former involving the pronator teres and flexor carpi radialis insertions and the latter involving the triceps tendon. Onset is usually gradual and patients report dull pain over the lateral aspect of the elbow over the lateral epicondyle or radiohumeral joint, increased by grasping or twisting motions. Supination and pronation against resistance may be painful, and pain can be elicited by stretching the wrist extensors. To test this, the elbow is extended, the forearm pronated and the wrist fully dorsiflexed.

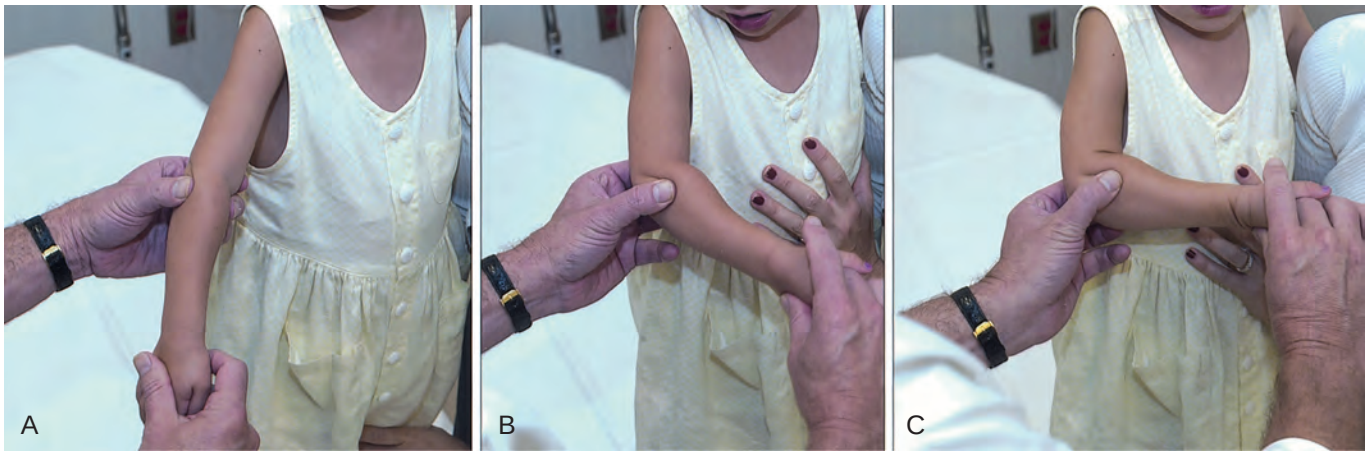


Fig. 45.28. Subluxation of the radial head. Method of reduction: Apply pressure to radial head **(A),** supinate the forearm **(B),** and flex elbow **(C),** in one continuous motion.

Diagnostic Testing. Radiographic findings may be normal, although with chronicity, calcifications may be present over the lateral epicondyle. Characteristic MRI findings also have been described, although MRI is not indicated emergently.

Management and Disposition. Traditional treatment includes protection, rest, ice, compression, elevation, and medication. Initial therapy includes avoidance of the inciting activity and immobilization with a sling. Nonsteroidal antiinflammatory drugs (NSAIDs) are often used, but their efficacy probably is limited to their analgesic rather than their antiinflammatory properties. Injection of a corticosteroid at the point of tenderness provides some pain relief in most patients.[32,48] Because corticosteroids weaken collagen, injection directly into the tendon and premature resumption of heavy loading of the tendon at the lesion should be avoided. Patients with pain that persists despite treatment and a rehabilitation program should be referred for possible surgery.[28] Modification of athletic technique is recommended after the symptoms subside.

Olecranon Bursitis

Clinical Features. Olecranon bursitis is commonly caused by repetitive minor trauma, such as leaning on the elbow during work activities. It also may result from an inflammatory process, such as gout or an infectious process within the bursa (septic bursitis). Septic olecranon bursitis occurs most commonly in patients engaged in work that predisposes to repetitive trauma to the elbow, such as gardening or plumbing. Although several bursae are located in the elbow region, the olecranon bursa is the one most often involved in an isolated pathologic process. Patients usually have progressive pain, tenderness and swelling over the olecranon. Some patients with septic bursitis have an abrupt onset instead, with a rapid increase in pain over a few hours and on examination, the septic bursa is typically swollen, hot, erythematous, and tender. Flexion is limited by pain brought on by tightening of the skin over the inflamed bursa. Minor breaks in the skin, frank abrasions, or healing lacerations over the bursa may be present. Noninfectious bursitis usually manifests with less warmth and erythema. The skin is intact and swelling may be the only finding.

Diagnostic Testing. The most important aspect of evaluation is the differentiation of a septic process from a benign inflammatory one, and this differentiation may be difficult on clinical grounds because considerable overlap exists in the histories and physical findings. If doubt exists, aspiration of the bursa should be performed and the aspirate sent for crystals, white blood cell (WBC) count, Gram's stain, and cultures. Unless the aspirate is frankly bloody, traumatic nonseptic olecranon bursitis usually has a leukocyte count lower than 1000 cells/mm^3, whereas septic bursal fluid usually has a count higher than 10,000 WBCs/mm^3.

Management and Disposition. Aspiration is diagnostic and therapeutic because relief of pressure relieves some of the pain. In cases of purulent bursitis, the bursa should be drained and appropriate antibiotics should be prescribed. Pending culture results, empirical antibiotics should include coverage for routine skin organisms, as well as methicillin-resistant *Staphylococcus aureus* (MRSA). Sulfamethoxazole/trimethoprim double-strength twice daily or doxycycline 100 mg should be used twice daily for 10–14 days. For patients with severe inflammation or who are immunocompromised, intravenous vancomycin 15 to 20 mg/kg per dose every 8 to 12 hours should be used. Bursitis refractory to aspiration and appropriate antibiotics may require incision and drainage. Noninfectious bursitis can be managed with a compression dressing, ice, NSAIDs, and avoidance of the inciting activity. Patients who have had their bursa aspirated should be rechecked within 24 to 48 hours to verify culture results and monitor their response to treatment.

Biceps Tendon Rupture

Clinical Features. Biceps tendon rupture occurs most commonly in the proximal portion of the long head of the biceps. It is most common in middle-aged athletes or physical laborers who sustain repetitive microtrauma to the tendon. Patients experience a snapping sound and pain in the anterior shoulder during strenuous activities that produce rapid loading of the muscle. Rupture also occurs distally, usually as an avulsion from the insertion on the radial tuberosity, although ruptures at the musculotendinous junction occasionally occur. Rupture of the distal biceps tendon occurs almost exclusively in men, most commonly between the ages of 40 and 60, and most often involves the dominant arm.[33,34] The inciting event is usually an unexpected extension force applied to the arm flexed at 90 degrees. The pathophysiology of tendon rupture is poorly understood, although tendon rupture generally occurs in the setting of underlying tendinosis. Diabetes, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, and steroid or fluoroquinolone therapy all may result in tendinosis. Smoking has been shown to be strongly associated with distal

biceps tendon rupture.[35] In proximal tendon rupture, the patient usually has a visible defect at the top of the bicipital groove with bunching of the muscle distally. Flexing of the elbow produces pain at the proximal insertion but flexion remains intact, because the short head of the biceps usually maintains its integrity. With distal ruptures, the patient reports pain and tearing in the antecubital region. Visible deformity and a palpable defect of the biceps muscle belly are present with weakness of elbow flexion and supination. If the tendon is completely ruptured, there is a bunching up of the muscle and this effect is accentuated when the patient attempts flexion.

Diagnostic Testing. Radiographs are not revealing and usually not necessary. MRI may be useful when a partial rupture is suggested but can be obtained in follow-up and is not indicated in the ED.

Management and Disposition. All patients require referral to an orthopedist within 72 hours for evaluation for early anatomic repair of complete ruptures. Partial ruptures occasionally respond to conservative treatment but often require surgical repair. The arm is splinted and the patient advised to apply ice and be given analgesics while awaiting orthopedic consultation.

KEY CONCEPTS

- Clinical decision rules for the elbow joint have not been validated. Radiographs should be obtained when there is limitation in range of motion, moderate to severe pain, obvious deformity, joint effusion, or significant tenderness or crepitus over any of the bony prominences or the radial head. The threshold for imaging should be lower in pediatric patients (with the exception of presentation consistent with radial head subluxation) owing to the presence of open growth plates and limitations to the physical examination.
- In children with wrist pain and traumatic mechanism of injury, the absence of a clear-cut explanation for the pain (eg, no abnormal radiographic findings) should prompt consideration of an elbow injury causing referred pain to the wrist.
- On lateral elbow x-ray, a small anterior fat pad, parallel to the anterior surface of the humerus, can be a normal finding. Any convex ("sail sign") anterior fat pad and all posterior fat pads are pathological and indicate presence of joint effusion. In the setting of trauma, almost all patients with the posterior fat pad sign of the elbow have intra-articular skeletal injury. In adults, a posterior fat pad sign is indicative of a radial head fracture, whereas in children, a supracondylar fracture is the probable underlying injury. In the absence of trauma, inflammation and infection also cause effusion with positive fat pad signs.
- Radial nerve injury is the most common complication of humeral fracture and occurs 20% of the time. This is most often a benign neurapraxia that resolves spontaneously, although recovery may take several months. Radial nerve injuries associated with penetrating trauma or open fractures are likely to represent anatomical disruption and usually warrant operative exploration.
- Generally the radius and ulna, bound together firmly by the annular ligament and interosseous membrane, displace as a unit and typically dislocate posteriorly.
- Biceps tendon rupture occurs almost exclusively in men, most commonly between ages 40 to 60, usually subsequent to an unexpected extension force applied to the arm flexed at 90 degrees. Smoking, diabetes, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, and steroid or fluoroquinolone therapy may predispose to this injury.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 45: QUESTIONS & ANSWERS

45.1. A 23-year-old man presents with arm pain and weakness after a gunshot wound to the left upper arm. Physical examination is remarkable for a small penetrating wound at the midlateral aspect of the biceps muscle, extensor weakness of the thumb and wrist, and intact distal pulses. Which of the following statements is true?

A. Angiography is indicated.
B. Cervical radiography is warranted.
C. Operative exploration is indicated.
D. The neurapraxia should resolve.
E. Urgent nerve conduction studies are indicated.

Answer: C. Radial nerve palsy resulting from penetrating injury or open fractures is often permanent and warrants operative exploration. Nerve conduction studies would not be abnormal until approximately 3 weeks post injury.

45.2. A 4-year-old boy is brought to the emergency department (ED) by his mother after falling from a swing set. He complains of right wrist pain and resists detailed examination of the arm. Radiographs are normal. What is the most appropriate next step in this patient's management?

A. Computed tomography (CT) scan of the wrist
B. Elbow radiograph
C. Reassurance
D. Splinting for 3 to 6 weeks
E. Triple-phase bone scan after 7 to 10 days

Answer: B. In children with wrist pain and traumatic mechanism of injury, the absence of a clear-cut explanation for the pain (eg, normal radiograph) should prompt suspicion for an elbow injury producing referred pain.

CHAPTER 46

Shoulder

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PRINCIPLES

The shoulder joint is a unique and complex articulation unit. It has the largest range of motion of any appendicular joint in the body and can be moved through a space that exceeds a hemisphere in extent.

Shoulder injuries are commonly encountered in emergency medicine and dislocations account for more than 50% of all major joint dislocations seen in the emergency department (ED). The shoulder can be injured by trauma (indirect or direct) or by overuse.[1]

In general, children are vulnerable to the same injuries as those incurred by adults; however, the presence of the epiphysis and its growth plate changes the pattern of injuries.[2] The strength of the joint capsule and its ligaments is two to five times greater than that of the epiphyseal plate. An injury that produces a sprain or dislocation in an adult often causes a fracture through the hypertrophic zone of the growth plate in a child. Most shoulder injuries in children can be treated conservatively, with a good prognosis for full return of function.[2]

Anatomy

The shoulder girdle connects the upper extremity to the axial skeleton (Fig. 46.1). The sternoclavicular joint (SCJ) represents the only true articulation between the upper extremity and the axial skeleton. The SCJ participates in all movements of the upper extremity and is the most moved joint in the body (Fig. 46.2). The superior mediastinum with its great vessels, trachea, esophagus, thoracic duct, lung apices, and other important structures is immediately posterior to the SCJ.

The clavicle is an S-shaped bone that acts as a strut to support the upper extremity and keep it away from the chest wall, also protecting the subclavian vessels and brachial plexus. The middle third, which is thin and untethered, is the most commonly fractured segment.[3]

The acromioclavicular joint (ACJ) connects the lateral end of the clavicle with the medial aspect of the acromion process (Fig. 46.3). The ACJ has little or no bony stability and is dependent on the associated ligaments and muscles for support.[4]

The scapula is a flat triangular bone that forms the posterior aspect of the shoulder girdle. The thin body of the scapula lies flat against the posterior thorax and widens laterally to form the glenoid fossa. The scapula's thickened borders are the attachment sites for 18 muscle origins and insertions.[5] The thick muscle coat and ability to recoil along the posterior chest wall protect the scapula from both direct and indirect trauma.

The glenohumeral articulation is a ball-and-socket–type joint that depends largely on associated capsule, muscles, and ligaments for stability (Fig. 46.4).[6] The absence of bony stability permits a range of motion greater than any other joint.

The proximal humerus articulates with the glenoid fossa and provides for the attachment of many important muscles. The rotator cuff stabilizes the glenohumeral joint (GHJ) and consists of the supraspinatus, infraspinatus, teres minor, and subscapularis muscles (Fig. 46.5). The long head of the biceps tendon originates from the supraglenoid tubercle and ascends over the humeral head to enter the arm via the bicipital groove (see Fig. 46.5). Long muscles that cross the articulation are involved primarily in movements of the GHJ. The pectoralis major, latissimus dorsi, and teres major muscles all insert into the humeral intertubercular groove. Displacements encountered with fractures of the humerus usually reflect the pull of these attached muscle groups. The proximal humerus is composed primarily of trabecular bone with a thin cortical shell. Changes in bone density with age increase the risk of fractures.[7]

The brachial plexus and subclavian vessels enter the shoulder girdle superiorly between the clavicle and the first rib, traverse under the coracoid process, and exit anterior to the inferior aspect of the GHJ as the median, ulnar, and radial nerves and axillary vessels. These nerves represent the final branches of the upper brachial plexus (nerve roots C5 to C8).

CLINICAL FEATURES

History

Most complaints involve some combination of pain, stiffness, instability, or weakness. Pain can result from many different conditions extrinsic and intrinsic to the shoulder. Extrinsic sources of shoulder pain include disorders of the cervical spine, thoracic outlet myocardium, as well as symptoms referred from processes causing diaphragmatic irritation.

For intrinsic conditions, the most important factors to determine are the time and mechanism of injury (traumatic or overuse), the precise location of the pain, and associated sensorimotor complaints. Shoulder pain also can manifest in an insidious manner, unrelated to any precipitating factor. In these instances, the duration, location, character, and aggravating and alleviating factors of the pain should be noted.

Stiffness usually manifests as a restricted range of motion resulting from an underlying painful condition of the shoulder. Instability can be chronic or acute and seen in the form of an obvious subluxation or dislocation or a sensation of the shoulder almost "going out." A rotator cuff tear or an underlying nerve lesion usually causes significant shoulder weakness.

Physical Examination

The shoulder should be inspected from the anterior, posterior, and lateral positions in addition to the axilla. Any obvious deformity, ecchymosis, laceration, swelling, or hematoma should be noted.

Palpation of the shoulder should be performed systematically, beginning at the SCJ and moving laterally to the ACJ. Next, the scapula, GHJ, and humerus are palpated. Any point tenderness, crepitus, swelling, or deformity should be noted.

Active and passive ranges of motion should be tested although this may be limited due to acute pain. Active range of motion is best determined with the patient in the sitting position to

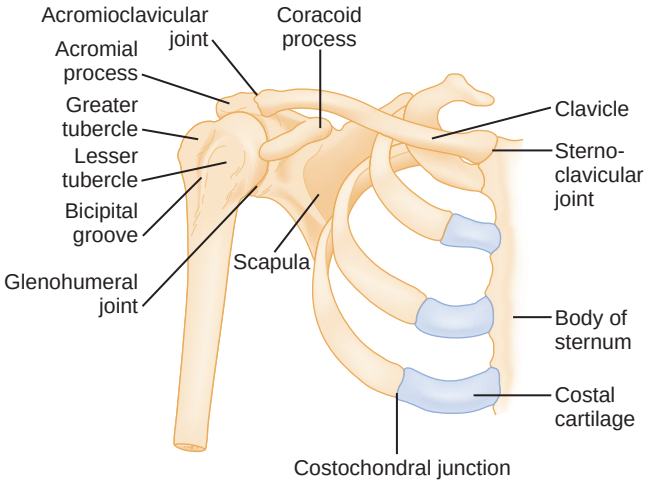

Fig. 46.1. Anatomy of the shoulder girdle. It consists of three bones: the clavicle, humerus, and scapula; three joints: the acromioclavicular, glenohumeral, and sternoclavicular joints; and one pseudoarticulation: the scapulothoracic pseudoarticulation. (From Roy S, Irwin R: Sports medicine: prevention, evaluation, management and rehabilitation, Englewood Cliffs, NJ, 1983, Prentice Hall.)

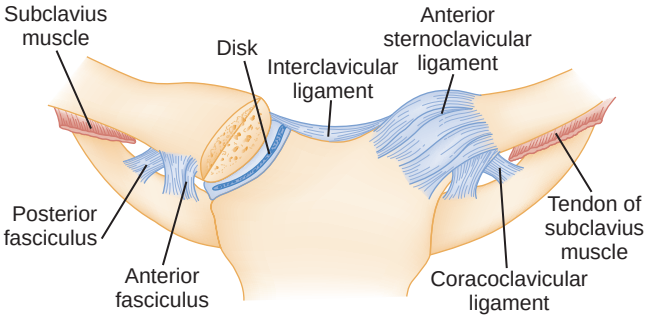

Fig. 46.2. The sternoclavicular joint (SCJ) is stabilized by several ligaments. (Redrawn from DePalma AF: Surgery of the shoulder, ed 3, Philadelphia, 1983, JB Lippincott.)

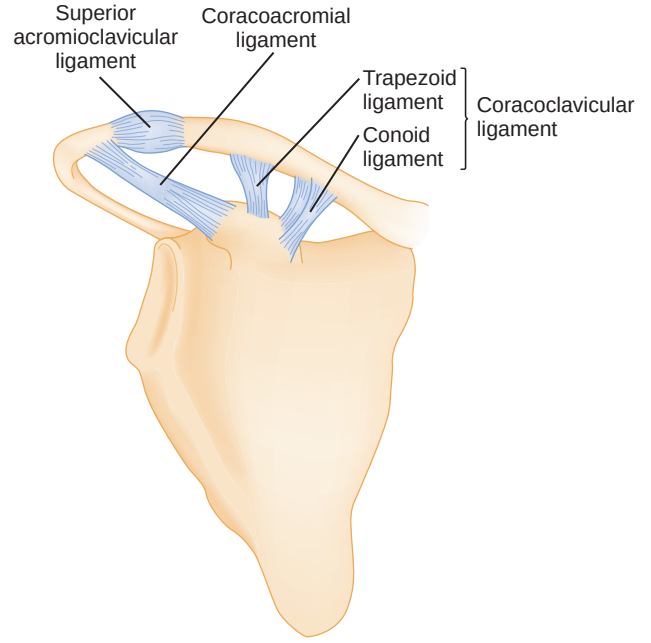

Fig. 46.3. Ligaments of the acromioclavicular joint (ACJ). (Redrawn from DePalma AF: Surgery of the shoulder, ed 3, Philadelphia, 1983, JB Lippincott.)

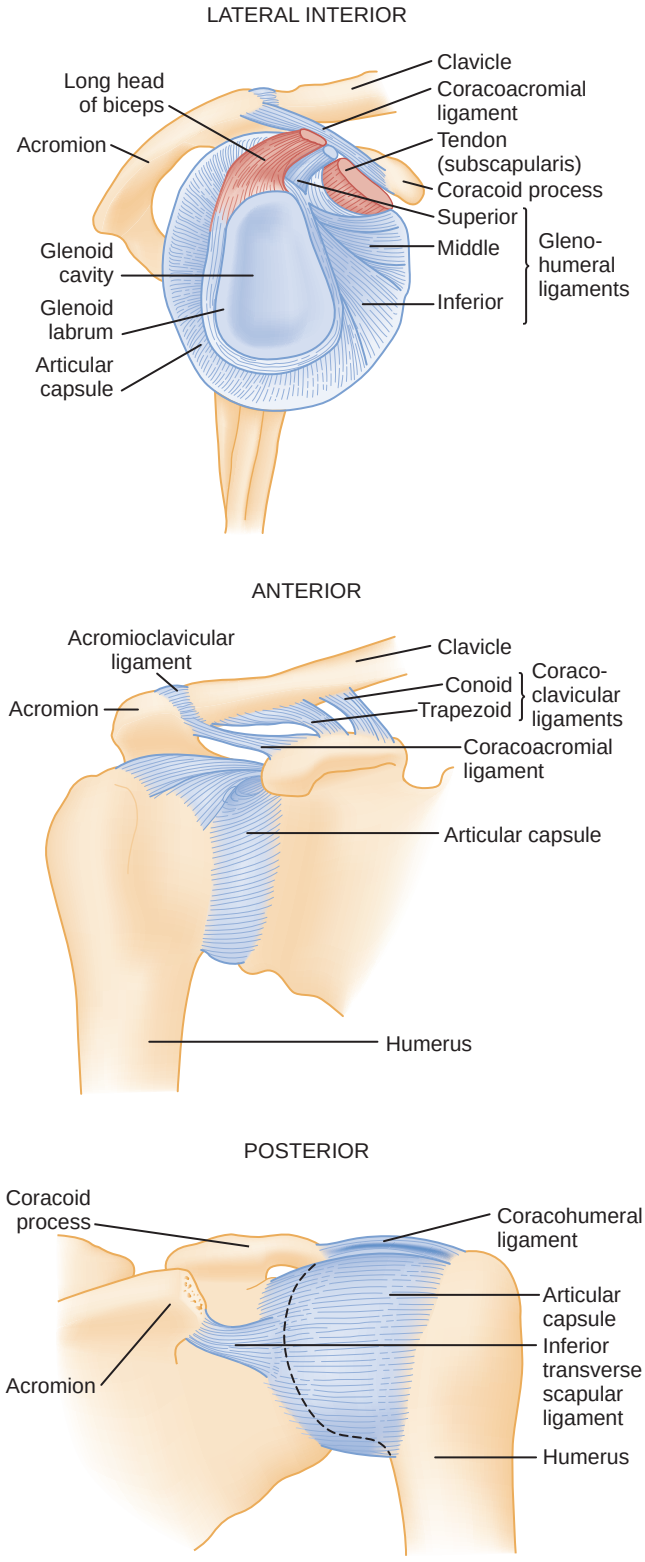

Fig. 46.4. Anatomy of the glenohumeral joint (GHJ). A synovial membrane extends from the glenoid fossa to the humeral head. Overlying the synovial membrane is a loose and redundant fibrous capsule. Anteriorly, the capsule is thickened to form the superior, middle, and inferior glenohumeral ligaments. The anterior band of the inferior glenohumeral ligament is the most important restraint to anterior glenohumeral dislocations.

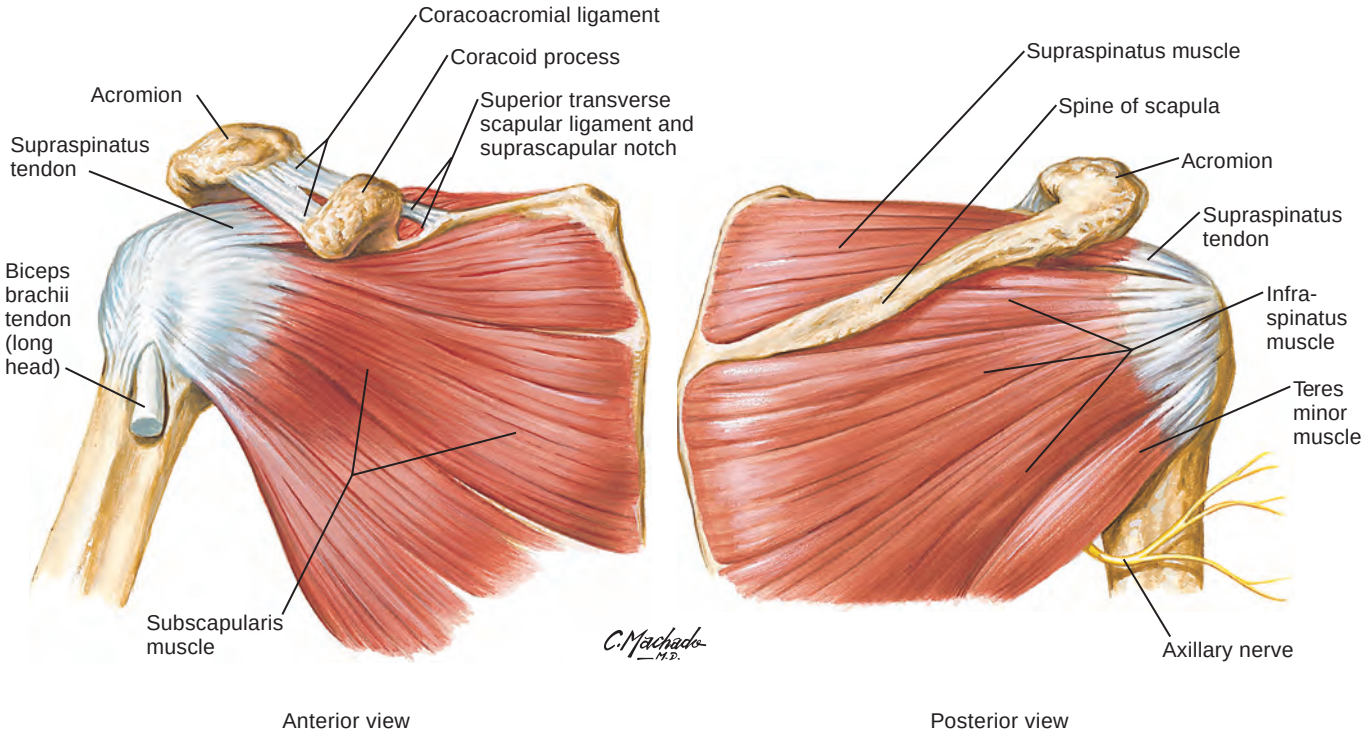

Fig. 46.5. The rotator cuff: anterior view, posterior view, and the four muscles—subscapularis, supraspinatus, infraspinatus, and teres minor. (Netter illustration from www.netterimages.com. Copyright 2016 Elsevier Inc. All rights reserved.)

TABLE 46.1

Sensory and Motor Components of the Brachial Plexus

SPINAL LEVEL	SENSORY AREA	MUSCLE
C2 to C4	—	Trapezius
C5	Lateral arm	Deltoid
C6	Lateral forearm and thumb	Biceps
C7	Tip of long finger	Thumb extensors
C8	Tip of little finger and medial forearm	Finger flexors
T1	Medial arm	Hand interossei

eliminate the contributions of the lumbar spine and lower extremity joints. Passive range of motion is best evaluated in the supine position. The degrees of abduction, forward flexion, extension, and internal and external rotation should be compared with those for the unaffected extremity. In addition, observe the motion of the scapulothoracic articulation. After 45 degrees of abduction, the scapula moves approximately 1 degree for every 2 degrees of glenohumeral motion. Specific strength tests for the rotator cuff include resisted internal rotation (subscapularis), resisted external rotation (infraspinatus and teres minor), and the empty can test (supraspinatus). The empty can test is performed with the patient resisting downward pressure with their arm raised forward to 90 degrees, with arm extended and pronated, such that the thumb is down (as if pouring out a can of liquid).

The examination is completed with an assessment of the neurovascular function. A complete sensory (light touch and pinprick) and full motor examination of the brachial plexus should be performed (Table 46.1). The radial pulse should be checked, although collateral circulation may preserve this despite an underlying vascular injury. The presence of pallor, paresthesias, or a significant hematoma should raise concern for a vascular injury. The neurovascular examination should be repeated after any manipulation in the ED.

DIAGNOSTIC TESTING

Radiology

The initial assessment of traumatic injuries includes a three-view trauma series of radiographs consisting of true anteroposterior (45-degree lateral), transscapular lateral ("Y" view), and axillary lateral views. The true anteroposterior view is preferred over standard anteroposterior views, because it shows the GHJ without any bony overlap. Standard anteroposterior views obtained with the joint in internal and external rotation profile the lesser and greater tuberosity and are more useful in the evaluation of soft tissue conditions.

Orthogonal views include the axillary lateral, transscapular lateral, and apical oblique. The preferred view is the axillary lateral, which projects the GHJ in a cephalocaudal plane helping to define the position of the humeral head with the glenoid fossa and identify lesions of the coracoid process, humeral head, and glenoid rim. The difficulty in obtaining this view is commonly due to pain has led to the popularity of the transscapular view. Advantages of this projection include its simplicity, reproducibility, and clear delineation of anatomic structures. In this view, the scapula is projected as a Y, with the body forming the lower limb and the coracoid and acromion processes forming the upper limbs. The humeral head normally is superimposed over the glenoid, which is located at the junction of the three limbs. This view is particularly useful in identifying anterior and posterior glenohumeral dislocations. The apical oblique view (obtained by having the patient stand bending forward, and angling the central ray 45 degrees caudally) shows the GHJ in a unique coronal

projection. This view is easy to obtain and been found to be useful in evaluating for Hill-Sachs lesions in shoulder dislocations, and displacement and angulation of proximal humerus fractures.

Physical examination is typically sufficient to diagnose most shoulder injuries, however, when indicated, plain radiographs are the mainstay of the radiologic examination in the ED. In selected circumstances, additional bone and soft tissue details may be obtained via computed tomography (CT) or magnetic resonance imaging (MRI). Bedside ultrasonography is emerging as a reliable screening and diagnostic imaging modality for selected conditions, in particular fractures of the clavicle, and soft tissue injuries, such as biceps tendon rupture and rotator cuff tears.[8-10]

SPECIFIC INJURIES

Fractures

Clavicle

Principles. The clavicle accounts for 3% to 5% of all fractures with a 2:1 male to female ratio and is the most commonly fractured bone in children. Clavicular fractures are classified anatomically and mechanistically into three groups. Fractures of the medial third are uncommon (5%) and occur as a result of a direct blow to the anterior chest. Fractures of the middle third are the most frequent (Fig. 46.6), accounting for 80% of all injuries. The usual mechanism of injury involves a direct force applied to the lateral aspect of the shoulder as a result of a fall, sporting injury, or motor vehicle collision (MVC). Fractures of the lateral third (15%) result from a direct blow to the top of the shoulder and are classified further into three subtypes.[3] Type I fractures are stable and minimally displaced because the coracoclavicular ligament remains intact. Type II fractures are associated with a torn coracoclavicular ligament and have a tendency to displace because the proximal fragment lacks any stabilizing forces (Fig. 46.7). Type III injuries involve the articular surface.

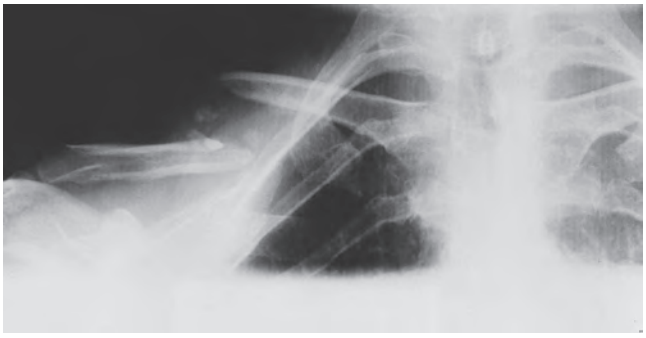

Fig. 46.6. Displaced midclavicular fracture.

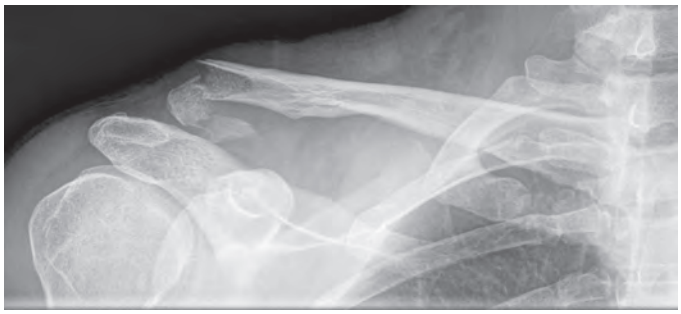

Fig. 46.7. Type II lateral clavicular fracture and torn coracoclavicular ligament. (Courtesy Erik Foss, MD.)

Clinical Features. The patient has pain over the fracture site, and the affected extremity is held close to the body. This positioning is a result of the effect of gravity and the pull of the muscles (pectoralis major, latissimus dorsi, sternocleidomastoid) on either side of the fracture site. The head is often tilted toward the injured side in an attempt to relax the effects of these displacing muscular forces. Ecchymosis, crepitus, and a palpable or visible deformity may be noted over the fracture site. Examine for any tenting of the skin, because this can cause progression to an open fracture. Although rarely present, it is prudent to evaluate for associated neurovascular and pulmonary injury due to close proximity of the subclavian vessels, brachial plexus, and apex of the lung.[11]

Diagnostic Testing. Clavicle-specific plain radiographs may be required to confirm the presence of a fracture, although most clinically significant fractures are diagnosed on chest or shoulder radiographs. Fractures in children, can be reliably diagnosed or ruled out by bedside ultrasound, decreasing the exposure to radiation (Fig. 46.8).[9]

Management. Principles of initial management for simple fractures include pain control, some form of immobilization primarily for comfort, and proper follow-up care. In addition to oral analgesics, pain associated with clavicle fractures can also be managed with an ultrasound-guided superficial cervical plexus block in the ED.[12] Fractures of the clavicle are adequately immobilized with a simple sling. Figure-of-eight bandages are no longer recommended.[13] Emergent orthopedic consultation should be sought for open fractures or fractures associated with neurovascular injuries, skin tenting, or interposition of soft tissues. More urgent orthopedic consultation (before 72 hours) is recommended for type II lateral clavicle fractures, because these fractures have up to a 30% incidence of nonunion and may require surgical repair.[3] Severely comminuted or displaced fractures of the middle third (defined as over 18 mm of initial shortening) are associated with a higher incidence of nonunion and long-term functional deficits and so should be referred for early orthopedic evaluation for consideration of operative reduction.[11,14] Additional risk factors associated with nonunion in midclavicular fractures include smoking, female sex, and advancing age.[15]

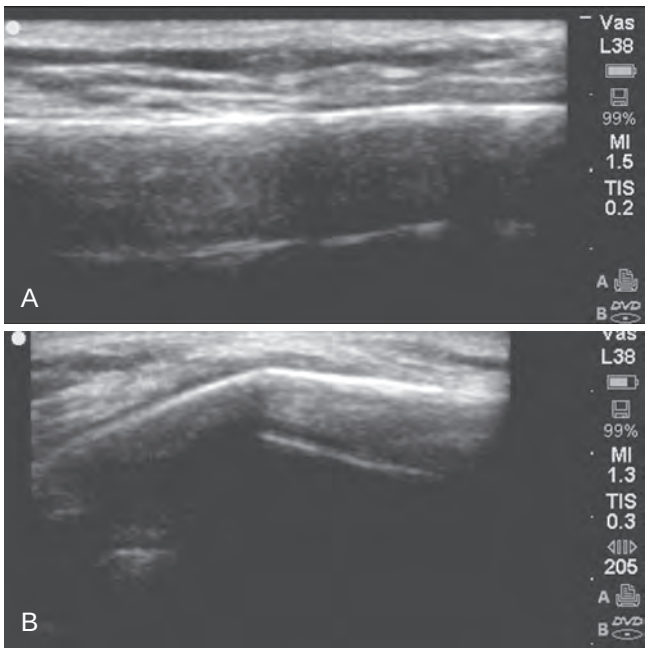

Fig. 46.8. Ultrasound images of the clavicle. **A,** Normal. **B,** Midclavicular fracture. (Courtesy Keith Cross, MD.)

Disposition. Most fractures of the clavicle heal uneventfully, and follow-up can be provided by a primary care physician. A sling should be worn until the patient is comfortable, which may precede radiographic evidence of callous formation. Early passive shoulder range-of-motion exercises (Figs. 46.9 and 46.10) are encouraged to reduce the risk of adhesive capsulitis (so-called "frozen shoulder"). Adolescents and adults generally require 4 to 8 weeks of immobilization. Contact sports should be avoided until the bone healing is solid (6 to 8 weeks). Full range of motion of the shoulder and an absence of pain are two reliable clinical signs that the fracture has healed.

Complications. The most common complications are delayed union, nonunion, and symptomatic malunion.[3] Displaced middle third fractures have a 15% to 20% rate of nonunion and up to 25% rate of symptomatic malunion.[14] Vascular complications after fractures of the medial third resemble those associated with posterior sternoclavicular dislocations. Type III lateral clavicle fractures can lead to subsequent ACJ osteoarthritis.

Fig. 46.9. Greenstick fracture of the clavicle *(arrow)*.

Scapula

Principles. Fractures of the scapula are rare accounting for approximately 1% of all shoulder fractures and are caused by high-energy trauma, such as high-speed MVCs and falls from significant height.[16] Scapular fractures rarely require management but are associated with major injury (75% to 98%) specifically, injuries to the ipsilateral lung, chest wall, and shoulder girdle complex.[5] The most common associated orthopedic injuries are fractures of the ribs, proximal humerus, and clavicle. Associated lung injuries, including pneumothorax, hemothorax, and pulmonary contusion, usually occur acutely but may manifest up to 2 to 3 days after the initial injury. Associated injuries of the head, spinal cord, brachial plexus, and subclavian or axillary vessels are less common.[5]

The Orthopaedic Trauma Association classification system is based on the severity and prognosis associated with these fractures. Fractures are divided into two main types: extra-articular (neck [Fig. 46.11], body, acromion process, coracoid process, spine) and intra-articular (with partial or total glenoid involvement).[17]

Clinical Features. In a conscious patient, the shoulder is held in a position of most comfort; adducted with the arm held close to the body, and any attempts at movement will result in significant pain. Tenderness, crepitus, or hematoma may be noted over the fracture site. The clinical findings occasionally mimic those with a rotator cuff tear.

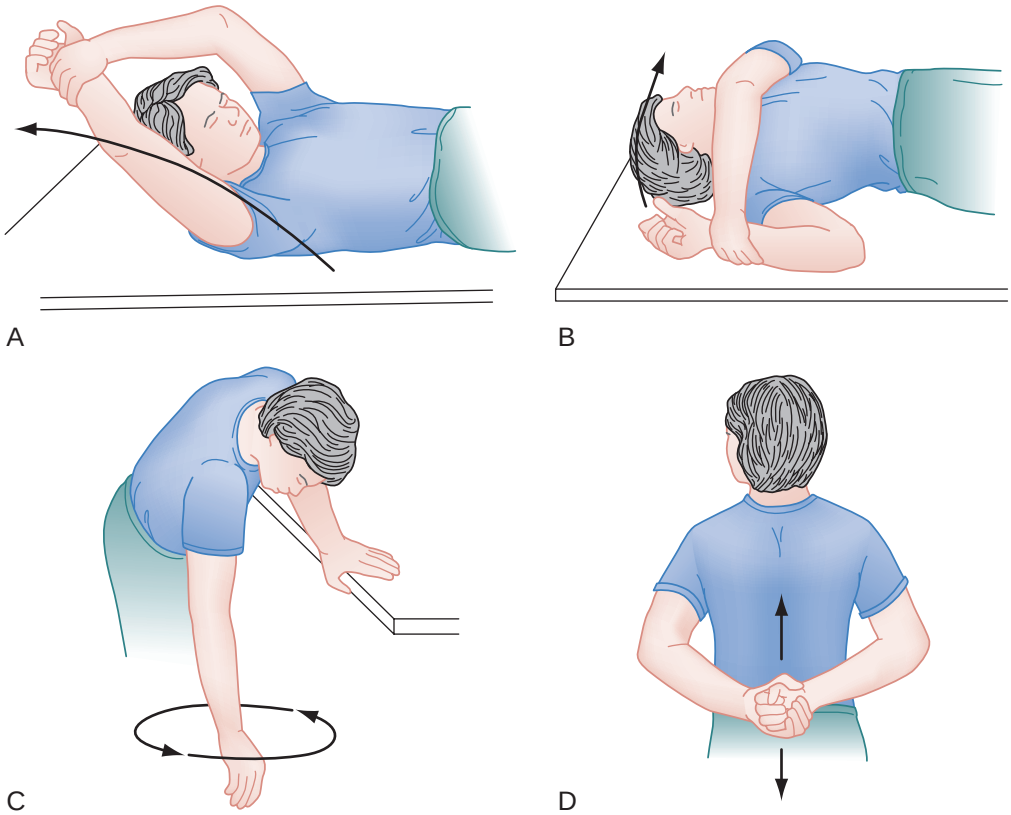

Fig. 46.10. Types of active and passive shoulder exercises. **A,** Active flexion. **B,** Active external rotation. **C,** Pendular. **D,** Active internal rotation.

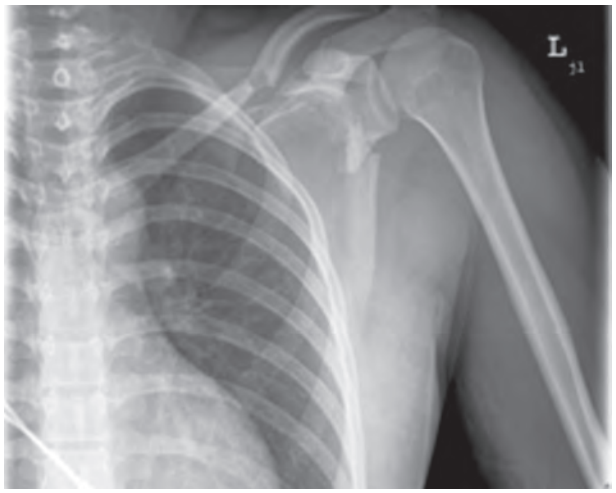

Fig. 46.11. Type II scapular fracture involving the neck of the scapula. Note the associated midclavicular fracture.

Fig. 46.12. Three-part minimally displaced fracture of the proximal humerus involving the greater and lesser tuberosities.

Diagnostic Testing

Radiology. The three-view trauma shoulder series will reveal most scapular fractures, as will careful examination of the scapula on the trauma chest radiograph.[5,16] An os acromiale (unfused acromial process epiphysis) is present in 3% of the population, will not be tender to examination, and should not be confused with a fracture of the acromion.[18] A comparison film can be useful, because the abnormality is present bilaterally in 60% of cases. Although additional dedicated scapula views can be obtained in the ED, the presence and the extent of scapular injury is best determined by CT. In the event that a trauma chest CT scan has been obtained to search for associated injuries, a three-dimensional reconstruction of the scapula should be requested to define the nature and extent of the injury.[16]

Management. Presence of a scapular fracture should prompt a thorough search for associated thoracic, intracranial, orthopedic, and neurovascular injuries. Most fractures, including fractures with severe comminution heal rapidly with nonoperative therapy.[17] Initial therapy consists of analgesia, immobilization in a sling for comfort to support the ipsilateral upper extremity, and passive range-of-motion exercises (see Fig. 46.10). Most patients require a sling for 2 to 4 weeks, physical therapy, and follow-up assessment for delayed displacement.[5,16]

Nondisplaced fractures of the body, spine, and acromion process usually require no further therapy. Displaced acromial fractures that impinge on the GHJ require surgical management. Rarely, the acromion is fractured as part of a superior dislocation of the humeral head. In these instances, an accompanying tear of the rotator cuff is invariably present, which may require surgical repair. If the coracoclavicular ligaments remain intact, fractures of the coracoid process respond well to conservative therapy. Severely displaced coracoid fractures with ruptured coracoclavicular ligaments usually require open reduction and internal fixation. Scapular neck and glenoid fossa fractures present the most difficult management issues. Although most of these injuries also do well with conservative therapy, open reduction and internal fixation may be recommended for fractures with glenoid involvement, or displaced or angulated fractures.[5,16]

Complications. Associated injuries of the ipsilateral lung, chest wall, and shoulder girdle account for most complications. Neurovascular (eg, brachial plexus, axillary artery, suprascapular nerve) injuries also have been reported with fractures of the acromial process, coracoid process, scapular neck, body, or spine fractures that extend into the suprascapular notch. Delayed complications include adhesive capsulitis and rotator cuff dysfunction.

Proximal Humerus

Principles. Fractures of the proximal humerus occur primarily in the older population, in whom structural changes (osteoporosis) weaken the proximal humerus, predisposing it to injury from low-energy falls. Although most of these injuries involve minimal displacement and are adequately managed with conservative therapy, significantly displaced fractures may require operative intervention. Displacements encountered with fractures of the humerus usually reflect the pull of the attached muscle group.

Fractures of the proximal humerus separate along old epiphyseal lines, producing four distinct segments consisting of the articular surface (anatomic neck), greater tuberosity, lesser tuberosity, and humeral shaft (surgical neck). Neer's classification system is based on the relationship of these fracture fragments.[15] In this system, a segment is considered displaced if it is angled more than 45 degrees or separated more than 1 cm from the neighboring segment. Because this classification system considers only displacement, the number of fracture lines is irrelevant. There are four major categories of fracture: (1) minimal displacement (Fig. 46.12), (2) two-part displacement (Fig. 46.13), (3) three-part displacement, and (4) four-part displacement. When present, anterior and posterior dislocations are included as part of the classification. Impaction and head-splitting fractures are classified separately.

The classic mechanism of injury involves a fall on an outstretched abducted arm. Concurrent pronation limits further abduction and levers the humerus against the acromial process; this produces a fracture or dislocation, depending on the tensile strengths of the bone and surrounding ligaments. Older patients are prone to fracture, whereas younger persons are apt to have dislocations. The combined injury (fracture and dislocation) may be seen in middle-aged patients. Proximal humerus fractures also may result from a direct blow to the lateral side of the arm or from

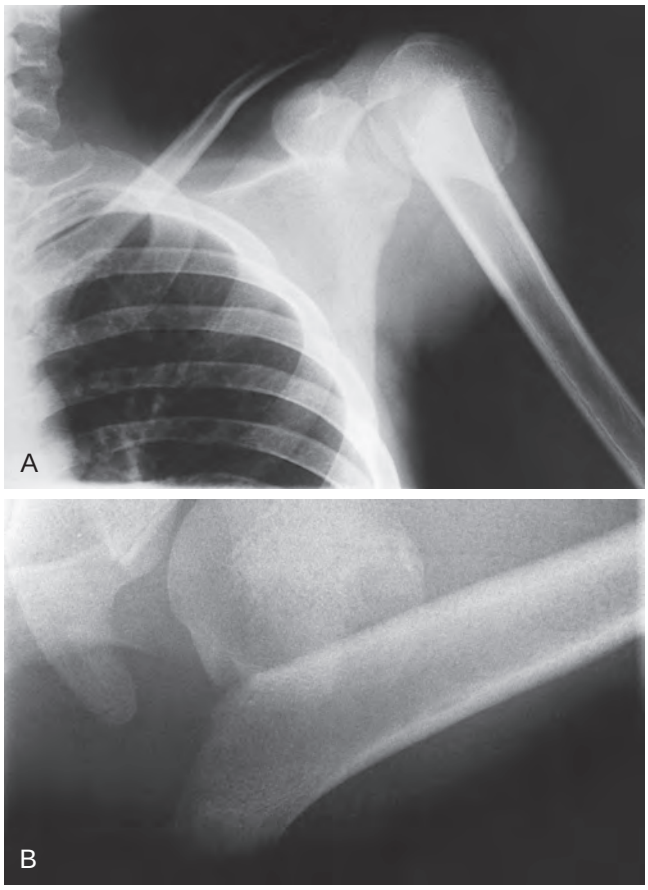

Fig. 46.13. Anteroposterior **(A)** and axillary **(B)** radiographic views of a two-part displaced fracture of the proximal humerus. The degree of displacement often is better visualized on the axillary view. (Courtesy David Nelson, MD.)

an axial load transmitted through the elbow. High-energy mechanisms and polytrauma are more common in younger persons.

Clinical Features. The affected arm is held close to the body, and movement is restricted by pain. Tenderness, hematoma, ecchymosis, deformity, or crepitus may be noted over the fracture site. A thorough neurovascular examination is essential to identify associated injuries of the axillary nerve, brachial plexus, or axillary artery (see Table 46.1). The three-view trauma series allows for assessment of the number of fracture fragments and degree of displacement or angulation.

Management. Minimally displaced fractures (see Fig. 46.12) constitute up to 80% to 85% of all cases.[7] In these instances, limited displacement or angulation is present, and the fracture segments are held together by the capsule, periosteum, and surrounding muscles. Initial treatment consists of adequate analgesia and immobilization with a sling.[19] A Cochrane review noted that rapid commencement of physiotherapy (within 1 week) resulted in less pain without compromising long-term outcomes.[19] Initial passive exercises (see Fig. 46.10) are gradually replaced by more active and resistive exercises. Most nondisplaced fractures heal over 4 to 6 weeks.

Displaced two-part, three-part, and four-part fractures often require surgical fixation and an orthopedist should be consulted.[15] Prospective and retrospective observational studies, however, have failed to show a significant functional difference between operative and nonoperative treatment of displaced two-part and three-part fractures in elderly patients. Current literature continues to support operative treatment of four-part fractures in the elderly; the procedure of choice is hemiarthroplasty.[7,15,19]

Fracture-dislocation injuries are best managed in consultation with an orthopedic surgeon before attempts at reduction (except in cases of neurovascular compromise or unavailability of an orthopedic surgeon). Of note, reductions of these injuries in the ED may be unsuccessful, and manipulation can cause separation of previously non-displaced segments. Closed reduction under fluoroscopic control and general anesthesia is preferable.

Complications. The most common complication of proximal humeral fractures is adhesive capsulitis. This complication can be prevented by the early initiation of pendular shoulder exercises, along with a thorough rehabilitation program. One of the most devastating complications is avascular necrosis (AVN), which is more common in multi-part fractures, and fracture-dislocations due to the disruption of the blood supply to the humeral head.[15] Repeated forceful attempts at reduction of fracture-dislocations may be associated with subsequent heterotopic bone formation (myositis ossificans). Neurovascular injuries (axillary nerve, brachial plexus, and axillary artery) may be encountered with displaced surgical neck fractures and fracture dislocations.

Proximal Humeral Epiphysis

Principles. Fractures of the proximal humeral epiphysis are uncommon and account for a small proportion of pediatric fractures.[20] The injury can occur at any age while the epiphysis remains open but is most common in adolescent boys. The most common mechanism of injury involves a fall onto the outstretched hand, and the fracture typically occurs through the zone of hypertrophy in the epiphyseal plate. Injuries can be classified according to their location (Salter system), stability, and degree of displacement.[20]

Clinical Features. The patient holds the injured arm tightly against the body, using the opposite hand. The area over the proximal humerus is swollen and tender to palpation. Radiographs obtained at 90 degrees to each other confirm the diagnosis. Comparison views may be helpful with minimally displaced fractures. Point of care ultrasound has also been demonstrated to accurately identify these injuries, with a sensitivity of approximately 90%.[9]

Management. Fractures of the proximal humeral epiphysis can result in significant permanent injury and disability as the physis accounts for 80% of the longitudinal growth of the bone. Urgent orthopedic consultation should be obtained for all such injuries.

Complications. Complications are rare and include malunion, growth plate disturbances, and injuries to the neurovascular bundle. Markedly displaced or angulated fractures are more likely to result in a residual loss of mobility.

Dislocations

Sternoclavicular

Principles. SCJ dislocations are infrequent and account for less than 1% of all dislocations.[21] Significant forces are required to disrupt the strong ligamentous stabilizers of this joint. The most common causes are MVCs and injuries sustained in high impact contact sports. The vast majority of dislocations are anterior. Posterior dislocations, although less common, can be associated with life-threatening injuries within the superior

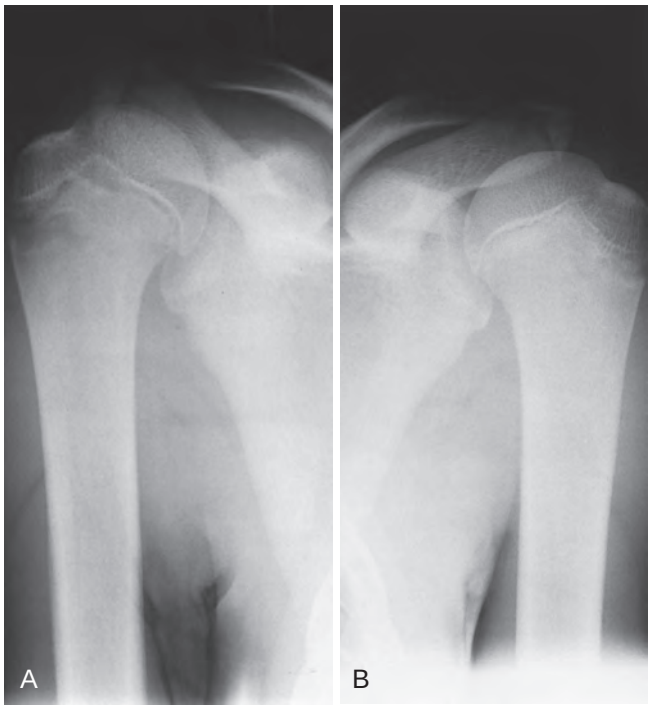

Fig. 46.14. A, Salter I injury of the right proximal humeral epiphysis. **B,** Normal left side is included for comparison.

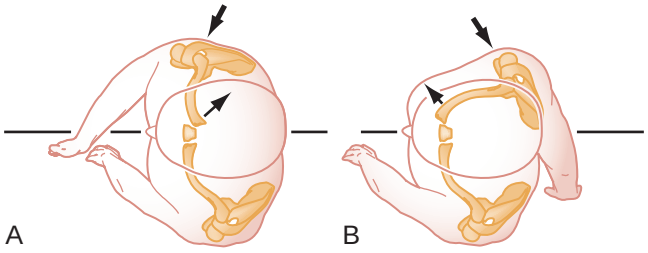

Fig. 46.15. Mechanisms that produce posterior and anterior displacements of the sternoclavicular joint (SCJ). **A,** When a compression force *(upper arrow)* is applied to the posterolateral aspect of the shoulder, the medial end of the clavicle is displaced posteriorly *(lower arrow)*. **B,** When the lateral compression force *(upper arrow)* is directed from the anterior position, the medial end of the clavicle is dislocated anteriorly *(lower arrow)*. The same mechanism could apply with any type of lateral compression injury of the shoulder. (From Neer CS, Rockwood CA: Fractures and dislocations of the shoulder. In Rockwood CA, Green DP, editors: Fractures in adults, ed 4, Philadelphia, 1984, JB Lippincott.)

mediastinum.[21,22] The usual mechanism of injury for anterior and posterior dislocations are pictured in Figures 46.14 and 46.15. Posterior dislocations can also result from a direct blow to the medial clavicle.

Injuries to the SCJ can be graded into three types.[21] A grade I injury is a mild sprain of the sternoclavicular and costoclavicular ligaments. A grade II injury is associated with subluxation of the joint (anterior or posterior) secondary to disruption of the sternoclavicular ligament and capsule. Complete rupture of the sternoclavicular and costoclavicular ligaments results in a grade III injury (dislocation). In patients younger than 25 years old, these may represent Salter type I injuries if the medial clavicle epiphysis is unfused.[21,23]

Clinical Features. Clinical suspicion based on mechanism and physical examination is the single most important factor in diagnosing these injuries. The injured extremity is flexed at the

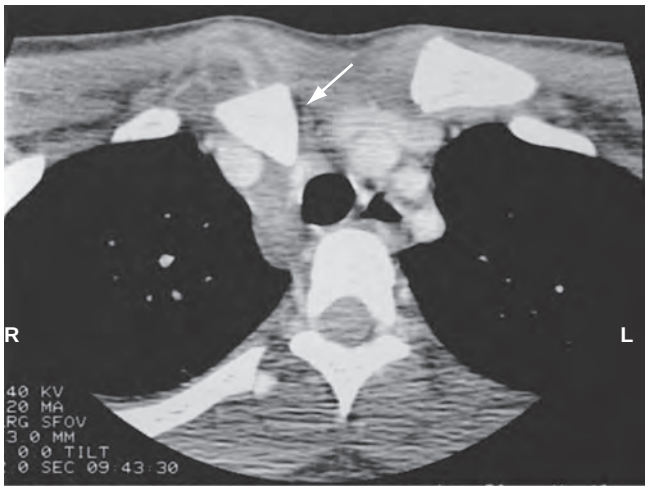

Fig. 46.16. This computed tomography (CT) scan shows posterior dislocation of the right sternoclavicular joint (SCJ; *arrow*) with compression of the superior mediastinum. (Courtesy Donald Sauser, MD.)

elbow and supported across the trunk by the opposite arm and pain results from any movement of the upper extremity or lateral compression of the shoulders. The SCJ may be mildly swollen and tender to palpation. With an anterior dislocation, the displaced medial end of the clavicle may be palpable. Posterior dislocations are associated with more severe pain, are caused by higher intensity direct force and may be associated with and may accompany complaints of hoarseness, dysphagia, dyspnea, and weakness or paresthesias in the ipsilateral upper extremity. The patient's neck is often flexed toward the injured side at rest and the clavicular notch of the sternum may be palpable along. Hoarseness may be related to tracheal injury. Damage to the innominate vein may present as cyanosis and venous congestion of the neck and should prompt vascular imaging and consultation.[21,23]

Diagnostic Testing. Although diagnosed clinically, sternoclavicular dislocation requires radiological confirmation. Findings on standard anteroposterior, oblique, and specialized (40-degree cephalic tilt) SCJ views are difficult to interpret. These dislocations and associated injuries are best visualized by CT (Fig. 46.16). Ultrasound imaging may be a useful adjunct.[24]

Management. Treatment of grade I injuries includes sling immobilization for comfort and primary care follow-up. Immobilization generally is maintained until symptoms improve and full painless motion is restored. Grade II injuries should be immobilized with a sling and the patient referred for orthopedic follow-up care. Grade II injuries require a longer course of immobilization (4 to 6 weeks) and are more likely to be associated with persistent pain.[21] Grade III injuries should be managed by closed reduction and rarely open reduction.

Anterior dislocations may be reduced in the ED with proper analgesia and on occasion may require general anesthesia (Fig. 46.17). Stable reductions should be maintained in a sling and referred for orthopedic follow-up care.[23] Most reductions are unstable; and because the deformity is primarily cosmetic and not functional, the treatment of choice for recurrent anterior dislocations is benign neglect.

Posterior dislocations constitute true orthopedic emergencies and should be reduced expeditiously.[23] Ideally, reduction of posterior dislocations should be attempted under general anesthesia, although when not feasible or in the setting of airway or vascular compromise can be attempted in the ED with use of procedural sedation. Emergency reduction may be required for patients with

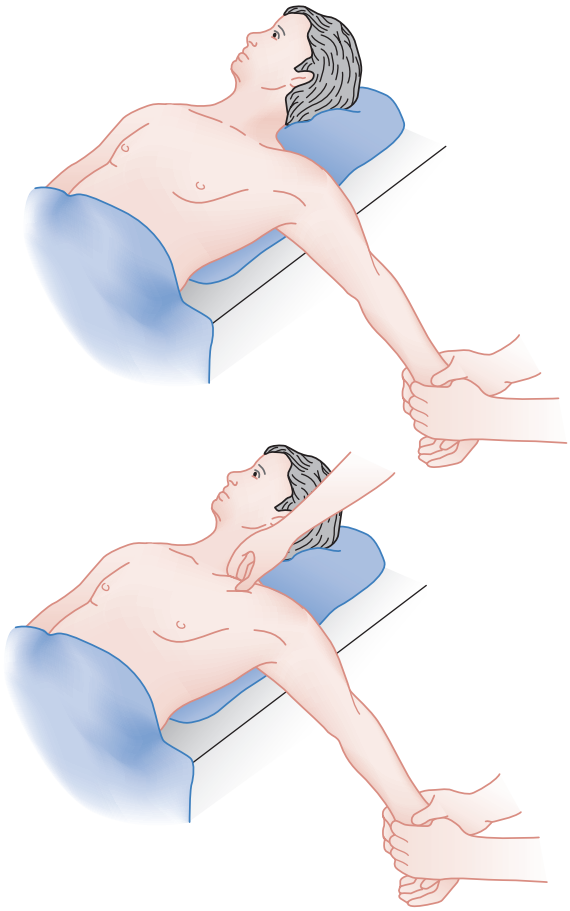

Fig. 46.17. Reduction of dislocated sternoclavicular joints (SCJs). A rolled sheet is placed posteriorly between the shoulder blades to elevate both shoulders approximately 5 cm above the table. Traction is applied to the arm in an extended (10- to 15-degree) and abducted (90-degree) position. If reduction does not occur, an assistant can add inward pressure on the medial end of the clavicle. (From Simon RR: Emergency orthopedics: the extremities, ed 7, Norwalk, CT, 2015, McGraw-Hill.)

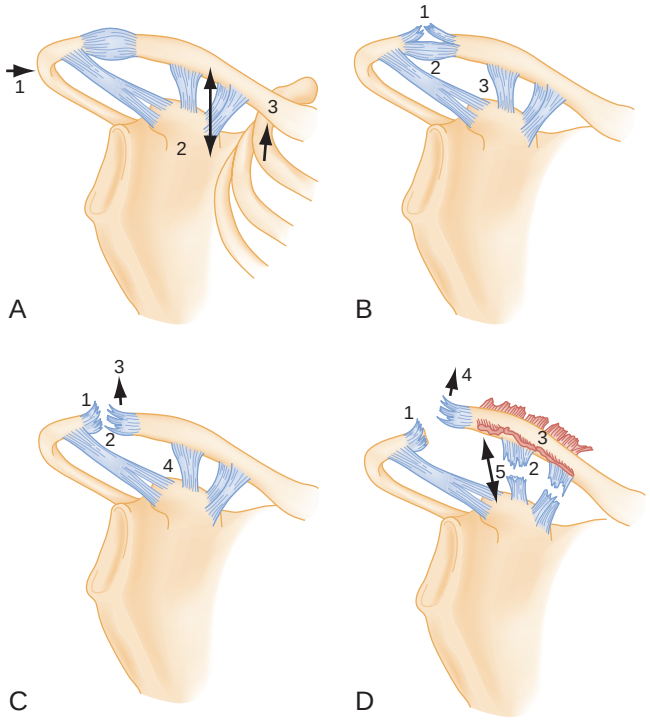

Fig. 46.18. Mechanism of injury and classification of acromioclavicular joint (ACJ) injuries. *Arrows indicate direction of applied force and relevant movement.* **A,** The direct force is applied to the point of the shoulder *(1);* the scapula and attached clavicle are forced downward and medially; the clavicle approaches the first rib *(2).* If the force continues, the first rib abuts the clavicle, producing a counterforce *(3).* Depending on the magnitude of the force, a grade I, II, or III sprain may occur. **B,** Grade I sprain. A few fibers of the acromioclavicular ligament stretch, and a few tear *(1);* the ACJ is stable *(2);* the coracoclavicular ligament is intact *(3).* **C,** Grade II sprain (subluxation). The joint space widens but the coracoclavicular distance is maintained. The capsule and the acromioclavicular ligament rupture *(1);* the joint is lax and unstable *(2);* the end of the clavicle rides upward, with displacement usually less than half of the width of the end of the clavicle *(3);* the coracoclavicular ligament remains intact *(4);* the attachments to the trapezius and deltoid remain intact. **D,** Grade III sprain (dislocation). The capsule and acromioclavicular ligaments rupture *(1);* the coracoclavicular ligament ruptures *(2);* the insertions of the trapezius and deltoid tear away *(3);* the clavicle rides upward *(4);* the interval between the clavicle and the coracoid process is greatly increased *(5). Not pictured:* In type IV and V injuries, the ligamentous and muscle disruptions are similar to the disruptions encountered in type III injuries, but the clavicle is displaced either posteriorly into the trapezius (type IV) or superiorly in an exaggerated fashion (coracoclavicular distance increased 100% to 300%; type V). In the rare type VI injury, the clavicle is displaced inferiorly. (From DePalma AF: Surgery of the shoulder, ed 3, Philadelphia, 1983, JB Lippincott; Stucken C, Cohen, SB: Management of acromioclavicular joint injuries. Orthop Clin North Am 46:57, 2015.)

airway obstruction or vascular compromise. The patient is positioned as described previously (see Fig. 46.17). If traction alone does not reduce the dislocation, concurrent clavicular manipulation may be helpful. After sterile preparation of the skin and administration of local anesthesia, the clavicle shaft is grasped with a sterile towel clip and pulled out anterolaterally. Once reduced, these injuries generally are stable and can be immobilized with a sling. An alternate method of reduction involves traction to the adducted injured arm while both shoulders simultaneously are forced posteriorly with direct pressure.[25] This technique levers the clavicle into place and requires less force than the traditional abduction-extension method.

Complications. Complications of anterior injuries are primarily cosmetic. By contrast, 30% of posterior dislocations may be complicated by life-threatening injuries to intrathoracic and superior mediastinal structures.[21] These include compression or laceration of the great vessels, tracheoesophageal fistula, tracheal compression, pneumothorax, thoracic outlet syndrome, and brachial plexus injuries. These injuries are best visualized though a chest CT angiogram.

Acromioclavicular Joint

Principles. Injuries of the ACJ occur primarily in young men as a result of MVC, bicycle accidents, or participation in high impact contact sports. The most common mechanism of injury involves a fall or direct blow to the point of the shoulder with the arm adducted. The weak acromioclavicular ligaments rupture first. With increasing force, the coracoclavicular ligament ruptures, and the attachments of the deltoid and trapezius muscles are torn from the distal clavicle. The ACJ also can be injured after a fall onto the outstretched hand.

Classification is based on the degree of damage sustained by the acromioclavicular and coracoclavicular ligaments (Fig. 46.18) and classified according to the Rockwood 6-class grading system.[26]

Clinical Features. Patients should be examined while they are upright, because the supine position can mask ACJ instability, and it is helpful to visualize both shoulders simultaneously to assess for symmetry. Type I and type II injuries are associated with

mild tenderness and swelling over the ACJ margin, with minimal deformity and full range of motion (although painful). Patients with type III, IV, V, and VI injuries are characterized by severe pain and patients hold the arm tightly adducted to reduce traction stress across the joint. In type III injuries, the shoulder hangs downward and the clavicle rides high, producing a characteristic clinical deformity that can be reduced by an upward force under the elbow. In type IV injuries, the clavicle may be palpable posteriorly, and in type V injuries, the clavicle may be palpable subcutaneously above the acromion, and unlike type III is not reducible by elbow pressure. In type VI injuries, the shoulder assumes a flattened clinical appearance as seen from the side.

Diagnostic Testing

Radiology. The recommended projections include routine anteroposterior and an axillary lateral view to evaluate for vertical migration of the clavicle and anteroposterior displacement, respectively. A Zanca view (an anteroposterior with 15-degree cephalic tilt view) can improve visualization by removing the scapula from behind the joint. Anteroposterior and Zanca views are ideally obtained with a view of both joints on a single-wide film.[26] Standing radiographs can help unmask a higher-grade injury. The normal coracoclavicular distance ranges from 11 to 13 mm. A difference of more than 5 mm between the injured and uninjured sides is diagnostic of a complete coracoclavicular disruption. With type I injuries, the radiographic appearance is essentially normal. With type II injuries, radiographs show upward or posterior displacement of the clavicle so that the lower margin of the clavicle is clearly cephalad to the lower margin of the acromion, and normal coracoclavicular distance is preserved. With type III, IV, and V injuries, radiographic features include a widened joint, an increased coracoclavicular distance, and either superior or posterior displacement of the clavicle (Fig. 46.19) with the lower margin of the clavicle cephalad to the upper margin of the acromion. Stress views of the ACJ are no longer recommended, because they are uncomfortable for patients and are not clinically necessary.[26]

Management. Type I and II injuries should be immobilized in a sling for comfort and to remove stress on injured ligaments. Patients with these injuries can be referred for follow-up with their primary care physician. When pain has subsided (1 to 2 weeks), gradual range-of-motion and strengthening exercises can begin, with a return to sports when pain-free function has been achieved (usually 2 to 6 weeks).

The management of type III injuries is variable, although most favor initial nonoperative management.[4] Selected patients who are young, are serious athletes, have severe displacement (more than 2 cm), and perform repetitive overhead activities may be candidates for surgical intervention. Treatment of type III injuries in the ED should consist of sling immobilization and sports medicine or orthopedic referral. Type IV, V, and VI injuries require early surgical treatment.[26]

Fig. 46.19. Third-degree sprain of the left acromioclavicular joint (ACJ). The coracoclavicular distance is increased. Bilateral clavicle view (patient is standing) can assist in comparison to the unaffected side. (Courtesy Erik Foss, MD.)

Complications. The most common concurrent injuries are associated fractures of the clavicle and coracoid process. The most common complications of ACJ injuries are residual symptomatic instability and joint tenderness due to secondary degenerative changes.[26]

Glenohumeral Dislocations

Principles. The GHJ is the most commonly dislocated major joint in the body. There are two distinct age peaks, the first in men 20 to 30 years old and the second in women in their 60s. The GHJ can dislocate anteriorly, posteriorly, inferiorly, or superiorly. Anterior dislocations account for 96% to 98% of all glenohumeral dislocations.[27] Posterior dislocations account for most of the remainder, whereas inferior (luxatio erecta) and superior dislocations are rare.

Anterior Dislocations

Pathophysiology. Anterior dislocations can result from indirect or direct forces. In younger persons, the injury usually is sustained during athletic activities involving rapid movements with the arm elevated, abducted and externally rotated, or rarely by a direct force applied posterolaterally.[27] A characteristic pathologic feature is avulsion of the anteroinferior glenohumeral ligament with capsulolabral detachment (Bankart's lesion).[6] In older patients, a fall onto the palm of an outstretched arm is the more common mechanism of injury.

Anterior dislocations can be classified according to their cause (traumatic or nontraumatic), frequency (primary or recurrent), and the anatomic position of the dislocated humeral head (Figs. 46.20 and 46.21). In most dislocations (99%) the humeral head will assume a subcoracoid or subglenoid position. Of these, the subcoracoid is more common, and the head is displaced anteriorly and rests inferior to the coracoid process. Subclavicular and intrathoracic dislocations are extremely rare and involve the addition of strong lateral to medial forces that push the humeral head medially.

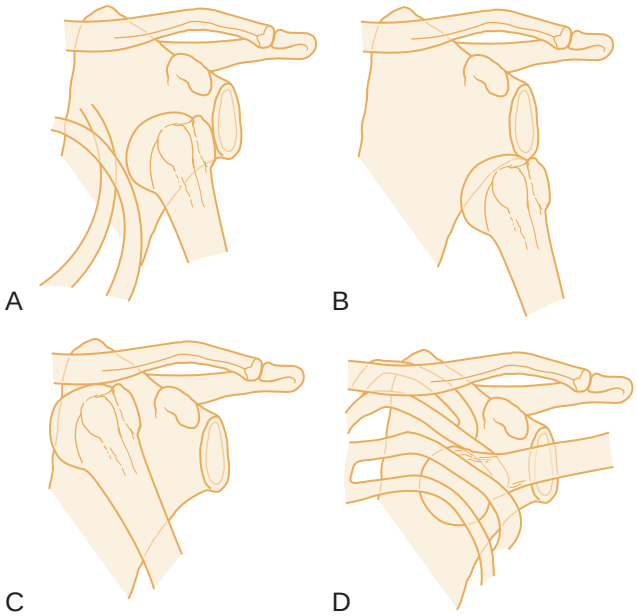

Fig. 46.20. Types of anterior dislocation. **A,** Subcoracoid. **B,** Subglenoid. **C,** Subclavicular. **D,** Intrathoracic. (From DePalma AF: Surgery of the shoulder, ed 3, Philadelphia, 1983, JB Lippincott.)

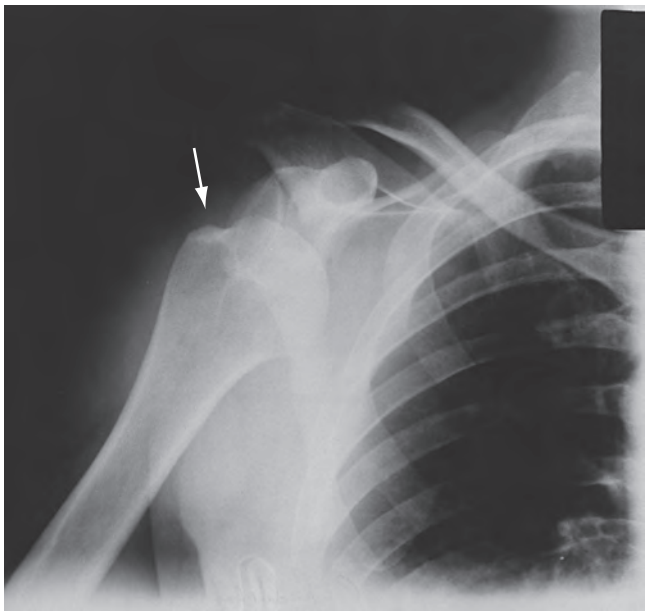

Fig. 46.21. Recurrent anterior subcoracoid dislocation with Hill-Sachs deformity of the humeral head *(arrow)*.

Clinical Features. The patient presents in severe pain often supporting the dislocated shoulder with the opposite extremity. The lateral edge of the acromion process is prominent, and the normally rounded shoulder assumes a "squared-off" appearance. The coracoid process is indistinct, and the anterior shoulder appears full. The patient leans away from the injured side and cannot adduct the shoulder even slightly without severe pain. Dislocations can be associated with injuries of the brachial plexus, axillary nerve or artery. Almost half of patients will have some degree of nerve injury, although most of these are clinically inconsequential and are more frequent in patients older than 50 years old.[27,28]

Diagnostic Testing

Radiology. Radiographs will confirm the clinical diagnosis and identify the position of the humeral head, although they are not required before relocation in otherwise healthy patients with a recurrent dislocation and without significant concomitant injury or diagnostic uncertainty. Point of care ultrasound may be useful as a diagnostic adjunct.[8] Some patients with a dislocation will have an associated fracture—most commonly, a compression fracture of the posterolateral aspect of the humeral head (Hill-Sachs deformity) caused by forceful impingement against the anterior rim of the glenoid fossa. Hill-Sachs fractures are not clinically significant unless they are large enough to cause recurrent shoulder instability or painful clicking or catching, in which case surgical repair may be necessary.

Management. Reduction of the dislocation should be accomplished expeditiously, because the incidence of neurovascular complications increases with time as does the difficulty with which the fracture can be reduced due to muscle spasm. For most patients, reduction may be attempted before imaging after a discussion with the patient. A postreduction film remains advisable to aid in the identification of glenoid rim fractures, as well as Hill-Sachs deformities, which when large can be associated with subsequent shoulder instability.

Bedside ultrasound can also be used to diagnose dislocations and assess for successful relocation after reduction attempts. In a study that added ultrasound to usual ED care, the assessment diagnosed 100% of dislocations and had a sensitivity of 100% for assessing complete reduction. Clinicians can consider using it to confirm reduction prior to obtaining postreduction radiographs.[8]

Procedural sedation is often used to facilitate reduction in the ED. Adequate analgesia often can also be provided through intra-articular injection of a local anesthetic agent. This technique is especially useful when procedural sedation is contraindicated. Longer acting local anesthetic agents (such as, bupivacaine) may also offer continued postreduction analgesia. Multiple studies have found intra-articular lidocaine achieved a similar reduction effectiveness (RR 0.92) when compared with procedural sedation with fewer complications.[29] Depending on the duration of the dislocation, nature (primary vs. recurrent) and technique, reduction can also be attempted and accomplished successfully without the use of any analgesia or sedation, provided the examiner is prepared to abandon the procedure if the patient experiences pain.[30]

Reduction can be accomplished with various techniques, most of which involve traction, leverage, or scapular manipulation principles.[1] The ideal method should be simple, quick, and effective; require little assistance; and cause no additional injury to the shoulder. It is important to be familiar with several techniques of reduction because none are uniformly successful. Several common techniques are described in Table 46.2. Clues to a successful reduction include feeling of a "clunk," relief of pain, normalization of anatomy, and improvement in range of motion. The neurovascular examination should be repeated and recorded after any reduction attempt. Most of these techniques are usually effective; however, approximately 5% to 10% of dislocations cannot be reduced in the ED and require reduction under anesthesia.[1] After reduction, the affected extremity is immobilized with a sling and swathe bandage for comfort. Patients should be discharged with adequate analgesia and follow-up. Primary dislocations and complicated cases (associated fracture, rotator cuff tear, axillary nerve injury) should follow up with an orthopedist. Immobilization duration can be individualized depending on age, if a first time or recurrent dislocator, or if there are associated Bankart's fractures. General recommendation from the ED is sling immobilization for 1 to 2 weeks until orthopedic follow-up.[31] The most important postreduction therapy is a rehabilitation program aimed at restoring the static and dynamic stabilizers of the GHJ, which follows the period of immobilization.[6]

Complications. Complications include fractures and neurovascular injuries. Most axillary nerve injuries are neurapraxic, management is expectant, and the prognosis for recovery of function is good.[27] Rotator cuff tears are especially common in primary dislocations in patients older than 40 years old, increasing to 80% in patients over 60 years old.[27,30] In this setting, failure to abduct the arm is commonly confused with an axillary nerve injury. Most of these patients require tendon and capsular repair to restore shoulder stability. Recurrence also is a common complication after anterior dislocation, and patients younger than 30 years old have recurrence rates of 79% to 100%. A Hill-Sachs deformity, Bankart's lesion, or a glenoid rim fracture are associated with increased risk of recurrence.[6] The traditional method of treatment (immobilization followed by physical therapy) is ineffective in preventing redislocation in young athletic patients. Arthroscopic studies of primary anterior dislocations in such patients have detected a high incidence of anterior-inferior capsulolabral avulsions (Bankart's lesion) from the glenoid rim. This avulsion is believed to be the primary predisposing factor for recurrence, and affected patients seem to benefit from early arthroscopic repair of the lesion.[30] Recurrence rates decline with increasing age and in the presence of a greater tuberosity fracture.[27,31]

TABLE 46.2

Techniques to Reduce Anterior Shoulder Dislocations

REDUCTION TECHNIQUE	DESCRIPTION
Stimson (hanging weight)[a]	Patient placed prone with the dislocated shoulder hanging over the edge of the examining table. Attach a 10- or 15-pound weight to the wrist or lower forearm provides traction in forward flexion. Reduction usually occurs over 20 to 30 minutes (Fig. 46.22).[b,d]
Traction/countertraction	Apply traction along the abducted arm while an assistant using a folded sheet wrapped across the chest applies countertraction. Although commonly used it requires more force than other techniques (Fig. 46.23).[b]
External rotation method	No traction involved. Patient seated or in supine, the involved arm is slowly and gently adducted to the side. The elbow is flexed to 90 degrees, and slow, gentle external rotation is applied to achieve reduction (Fig. 46.24).[b,e] Success rates with this method range from 80% to 97%.[b,c,e]
Cunningham[a]	Patient sits without slouching in a hard backed chair. Adduct the affected arm to the body and place elbow in full flexion resting against operator's shoulder. Operator then provides traction by placing their wrist on patient's forearm while asking the patient to shrug shoulders superiorly and posteriorly. The operator adds massage down through the trapezius, deltoid, and the biceps muscles. This technique is targeted to relax muscles causing a dynamic obstruction.
Milch technique[a]	Patient is placed supine and the head of the bed is elevated 20 to 30 degrees. The affected arm is held by the wrist and slowly abducted and externally rotated. The operator stops whenever resistance to motion is encountered and continues when the patient is relaxed. If the humerus has not reduced by the time 90 degrees of abduction and 90 degrees of external rotation have been reached, gentle longitudinal traction is applied along the humerus while the free hand is used to exert lateral and superior pressure on the humeral head to complete the maneuver. The effectiveness of this method has been attributed in part to more conical symmetry of the muscle forces acting across the glenohumeral joint (GHJ).[d]
FARES[a]	A variation of the Milch technique called *FARES* (FAst, REliable, and Safe). FARES adds oscillation in a vertical direction while the affected arm is abducted. It is more effective, faster, and less painful than the traction/countertraction and Kocher methods.
Scapular manipulation[a]	Reduction is accomplished by repositioning the glenoid fossa rather than the humeral head. Manipulation can be combined with the other techniques, particularly Stimson or traction/countertraction. Apply traction (manual or hanging weights), and then manipulate the scapula by rotating the inferior tip medially and stabilizing the superior and medial edges with the opposite hand. This technique can also be used in a seated position in which a second operator applies traction in the forward horizontal position.[b,c] Scapular manipulation can be difficult in obese patients, in whom it is difficult to palpate and grasp the inferior tip of the scapula (Fig. 46.25).
Not recommended	Hippocratic method (traction with the foot in the axilla) and the Kocher maneuver (leverage, adduction, and internal rotation), are no longer recommended because of a high incidence of associated complications (axillary nerve injury, humeral shaft and neck fractures, capsular damage).

[a]May also be attempted with minimal to no analgesia or sedation.
[b]Bonz J, Tinloy B: Emergency department evaluation and treatment of the shoulder and humerus. Emerg Med Clin North Am 33(2):297, 2015.
[c]Malik S, Chiampas G, Leonard H: Emergent evaluation of injuries to the shoulder, clavicle and humerus. Emerg Med Clin North Am 28:739, 2010.
[d]Catalano LW 3rd, Glickel SZ, Barron OA, et al: Effect of local corticosteroid injection of the hand and wrist on blood glucose in patients with diabetes mellitus. Orthopedics 35:e1754, 2012.
[e]Amar E, Maman E, Khashan M, et al: Milch versus Stimson technique for nonsedated reduction of anterior shoulder dislocation: a prospective randomized trial and analysis of factors affecting success. J Shoulder Elbow Surg 21:1443, 2012.

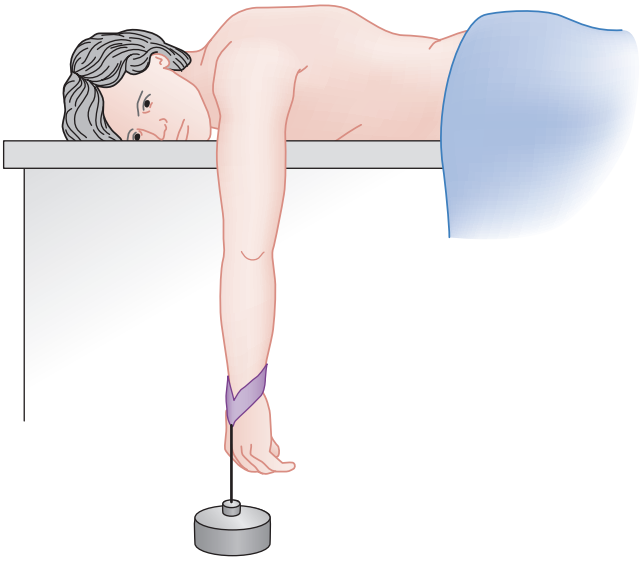

Fig. 46.22. Stimson or hanging weight method of reduction for anterior shoulder dislocations.

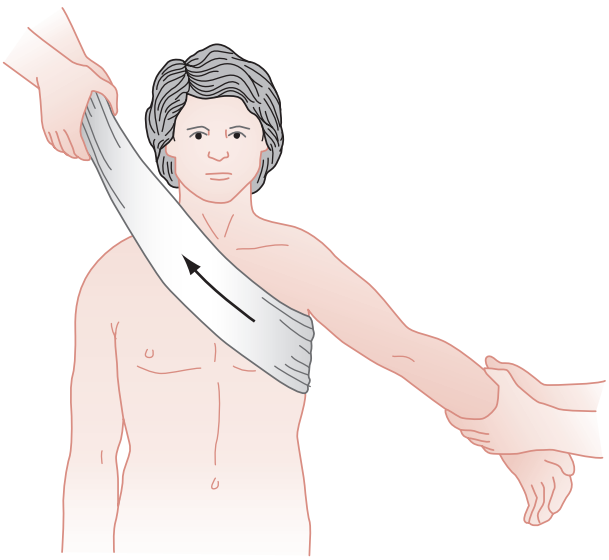

Fig. 46.23. Traction/countertraction method for reducing anterior shoulder dislocations.

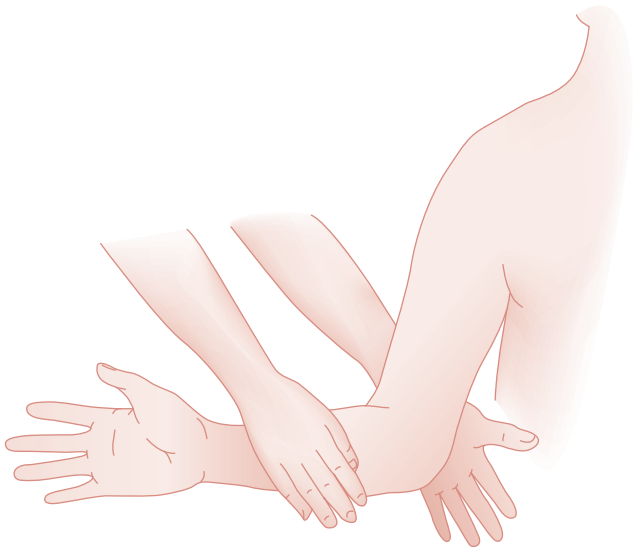

Fig. 46.24. External rotation technique for reducing anterior shoulder dislocations. The involved arm is slowly adducted to the patient's side, and the elbow is flexed 90 degrees. Gentle external rotation is applied to the forearm to achieve reduction. (From Simon RR, Koenigsknecht SJ: Emergency orthopedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

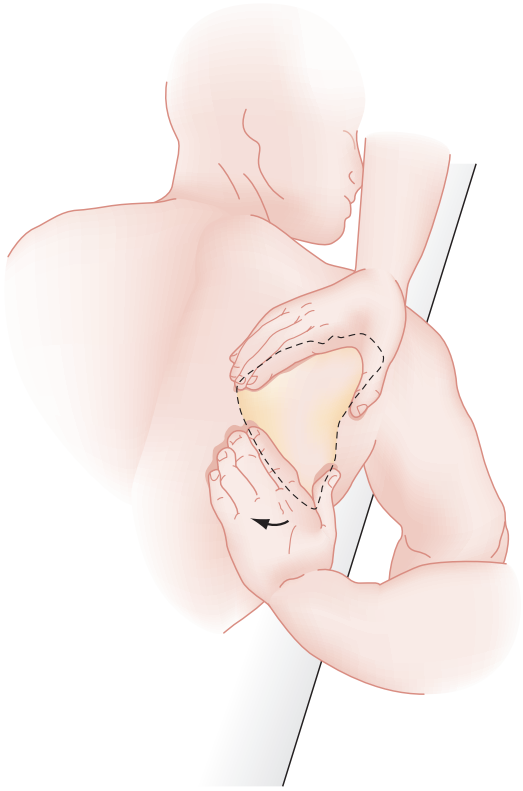

Fig. 46.25. Proper hand position and direction of rotation during shoulder relocation via the scapular manipulation technique. *Arrow indicates direction of applied force.* (From Kothari RU, Dronen SC: The scapular manipulation technique for the reduction of acute anterior shoulder dislocations. J Emerg Med 8:625, 1990.)

Anterior Subluxation

Transient anterior subluxation of the shoulder is encountered often in young athletic adults. The patient reports sudden sharp shoulder pain and weakness ("dead arm syndrome") that occurred while performing an abduction and external rotation maneuver. The patient also may relate a sensation of the shoulder's slipping in and out. The radiographic appearance usually is normal, and presence of an apprehension sign confirms the diagnosis. For this sign to be elicited, the injury motion (abduction and external rotation of the arm) is gently reproduced while an anterior force is applied to the posterior shoulder. This maneuver increases the pain and may cause anterior displacement of the humeral head. With a positive test result, the patient will actively resist further external rotation and appear apprehensive. A lax or redundant anterior capsule is thought to be responsible for this syndrome, and recurrent episodes are common. These patients can be placed in a sling for comfort with instructions on pendulum exercises, and they should be referred for orthopedic follow-up care because definitive therapy (capsulorrhaphy) is surgical.

Posterior Dislocation

Pathophysiology. Posterior dislocations are uncommon, accounting for fewer than 5% of all glenohumeral dislocations.[32,33] The glenoid fossa acts as a partial buttress protecting against posterior dislocations. Posterior dislocations are easily missed on initial evaluation unless x-rays are obtained in two planes and carefully reviewed and, if missed, may remain unrecognized ("locked posterior dislocations") for weeks or months.

A posterior dislocation can result from several distinct mechanisms of injury. A posterior dislocation can occur after a fall onto the outstretched hand with the arm held in flexion, adduction, and internal rotation or after a direct blow to the anterior aspect of the shoulder. Convulsive seizures (epileptic or after electrical shock) have been associated with unilateral or bilateral posterior dislocations. A seizure disorder should be suspected in cases of unexplained nocturnal posterior dislocations. Acute posterior dislocations are anatomically classified into three types—subacromial (most common), subglenoid, and subspinous—based on the final resting position of the humeral head.[32,33]

Clinical Features. Early diagnosis is essential to prevent long-term complications. Obtaining true orthogonal images (axillary or scapular view) can prevent misdiagnosis. The affected arm is held across the chest in adduction and internal rotation. The normal shoulder contour is replaced by a flat, squared-off appearance, and the coracoid process is prominent and easily palpated. The humeral head may be palpable posteriorly beneath the acromion process. Abduction is severely limited, external rotation is completely blocked, and restricted forearm supination may be present.

Diagnostic Testing

Radiology. True or standard anteroposterior radiographs can appear deceptively normal with posterior dislocations. Radiographic features include loss of the half-moon elliptic overlap of the humeral head and glenoid fossa on a standard anteroposterior film. In addition, the distance between the anterior glenoid rim and the articular surface of the humeral head is increased (the rim sign). The humeral head is profiled in internal rotation and takes on a "lightbulb" or "drumstick" appearance (Fig. 46.26A). A true anteroposterior film shows abnormal overlap of the glenoid fossa with the humeral head (see Fig. 46.26B) and can be useful in visualizing an impaction fracture of the anteromedial humeral head (reverse Hill-Sachs deformity). This fracture may produce a curvilinear density on the frontal projection parallel to the articular cortex of the humeral head (the trough sign). An orthogonal view, such as a transscapular Y (see Fig. 46.26C), axillary lateral (see Fig. 46.26D), or apical oblique view, confirms the diagnosis. The axillary lateral view or apical oblique view also identifies associated fractures of the humeral head and posterior glenoid

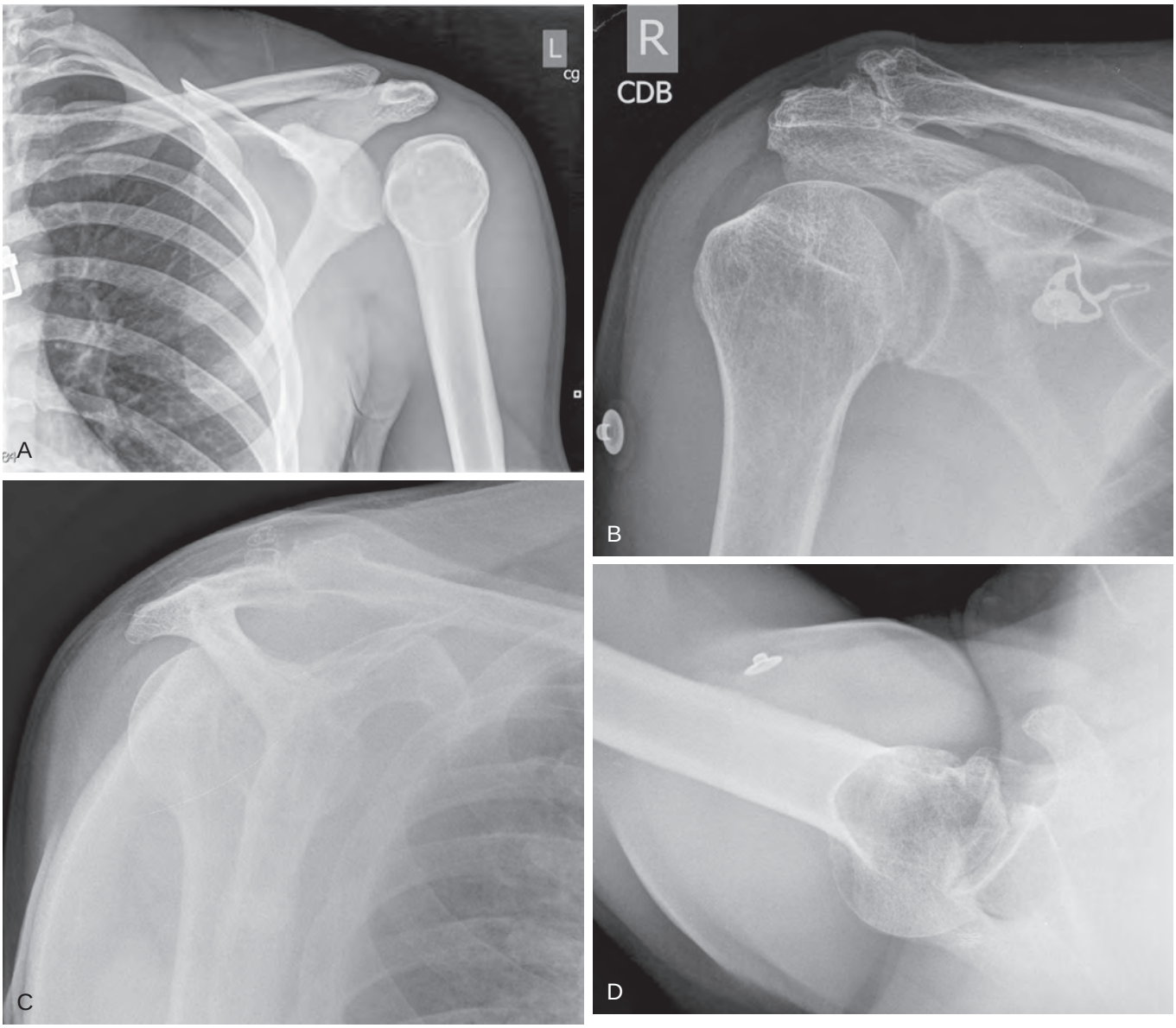

Fig. 46.26. Routine anteroposterior **(A)** radiograph of a posterior dislocation. Note the "lightbulb" or "drumstick" appearance of the humeral head while in internal rotation. True anteroposterior **(B),** transscapular **(C),** and axillary **(D)** radiographic views of a posterior glenohumeral dislocation. Note the abnormal overlap of the glenoid rim and humeral head.

rim. If an adequate orthogonal view cannot be obtained, shoulder CT should be considered.[33,34] Bedside ultrasound has also been used to diagnose posterior shoulder dislocations in the ED.[35]

Management. Closed reduction may be attempted in the ED with procedural sedation. The technique incorporates internal rotation and lateral traction to disimpact the humeral head from the glenoid rim. In the absence of humeral neck fracture or significantly engaged reverse Hill-Sachs lesion, the Stimson technique can also be used (see Table 46.2). If unsuccessful, reduction with the patient under general anesthesia is indicated. After reduction the shoulder should be immobilized in a sling, or if available in an external rotation sling with slight abduction (can use towel roll) until orthopedic follow-up in 1 to 2 weeks.[33] Cases that were missed initially and manifest as chronic or "locked" posterior dislocations should be discussed with the orthopedist, because they often require semielective open reduction and internal fixation or arthroplasty.[34]

Complications. Posterior glenohumeral dislocations usually are associated with anteromedial impression fractures of the articular surface. A similar fracture of the posterolateral aspect of the humeral head is present with anterior dislocations (Hill-Sachs deformity). Impression fractures involving more than 20% of the articular surface usually are unstable and require surgical repair post reduction.

Fractures of the glenoid rim, greater tuberosity, lesser tuberosity, and humeral head account for most associated injuries. The subscapularis muscle rarely may be avulsed from its insertion site on the lesser tuberosity. Neurovascular injuries are uncommon because the anterior location of the neurovascular bundle protects it from injury.

Inferior Glenohumeral Dislocation (Luxatio Erecta)

Pathophysiology. Luxatio erecta is a rare type (<0.5%) of glenohumeral dislocation in which the superior aspect of the

humeral head is forced below the inferior rim of the glenoid fossa (Fig. 46.27).[36] Application of a direct axial load to an abducted shoulder also can disrupt the weak inferior glenohumeral ligament and drive the humeral head downward.

Clinical Features. Clinically, the patient has the arm locked overhead in 110 to 160 degrees of abduction. The elbow usually is flexed, and the forearm typically rests on top of the head. The shoulder is fixed in this position. The inferiorly displaced humeral head may be palpable along the lateral chest wall. A thorough neurovascular examination is essential to evaluate for associated injuries.

Diagnostic Testing

Radiology. Luxatio erecta are easily mistaken and diagnosed and treated as subglenoid anterior dislocations, because the radiographic features are remarkably similar. Standard anteroposterior radiographs show the superior articular surface inferior to the glenoid fossa (Fig. 46.28). In addition, the humeral shaft characteristically lies parallel to the spine of the scapula on the anteroposterior view. This radiographic feature is useful in distinguishing luxatio erecta from a subglenoid anterior dislocation; in the latter, the humeral shaft lies parallel to the chest wall. Associated fractures of the acromion, coracoid, clavicle, greater tuberosity, humeral head, and glenoid rim are common.

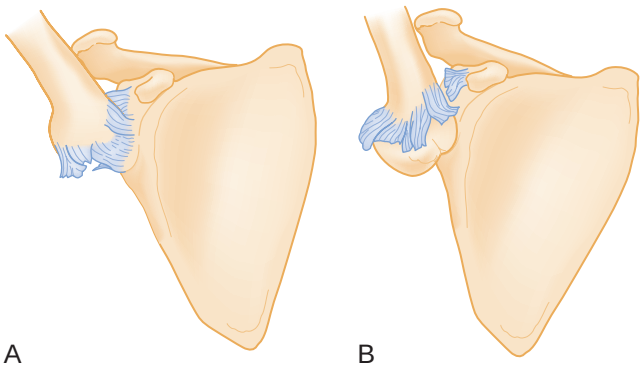

Fig. 46.27. Inferior dislocation (Luxatio erecta). **A,** The mechanism by which this injury occurs in hyperabduction. **B,** Leverage from impingement of the humeral shaft against the acromion ruptures the capsule and dislocates the head inferiorly. (From Simon RR, Koenigsknecht SJ: Emergency orthopedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

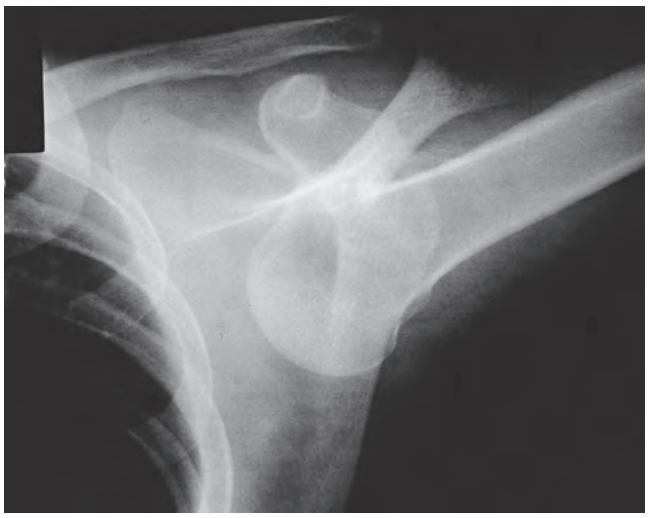

Fig. 46.28. Anteroposterior radiographic view of an inferior glenohumeral dislocation. The humeral shaft lies parallel to the spine of the scapula.

Management. Reduction usually can be accomplished by traction/countertraction maneuvers (Fig. 46.29) under procedural sedation. Regional anesthesia in the form of an ultrasound guided interscalene block has also been reported to be an effective for facilitating reduction.[37] Multiple attempts may be necessary; occasionally, "buttonholing" of the capsule will prevent closed reduction, necessitating an orthopedic consultation for open reduction. An alternative approach is the two-step closed reduction maneuver in which the inferior dislocation is first converted into an anterior dislocation before being reduced. The two-step maneuver requires a single operator, fewer attempts, minimal force, and only local analgesia or minimal procedural sedation.[38]

Complications. Neurapraxic lesions of the brachial plexus are common, and thrombosis of the axillary artery has also been associated with luxatio erecta.[36,38] Other associated injuries include tears of the rotator cuff, damage to the glenoid labrum, and avulsion fractures of the greater tuberosity.

Scapulothoracic Dissociation

Scapulothoracic dissociation is a rare and severe injury characterized by complete disruption of the scapulothoracic articulation and may be thought of as a partial or complete closed internal forequarter amputation of the upper extremity.[39,40] Mechanism of injury involves a high energy force directed over the shoulder with severe traction applied to the ipsilateral upper extremity. Approximately half of the reported cases involve motorcycle accidents, with the injury occurring when the motorcyclist hangs onto the handlebars while the body is forced away.[39,40] Because most patients present with significant concomitant trauma, the

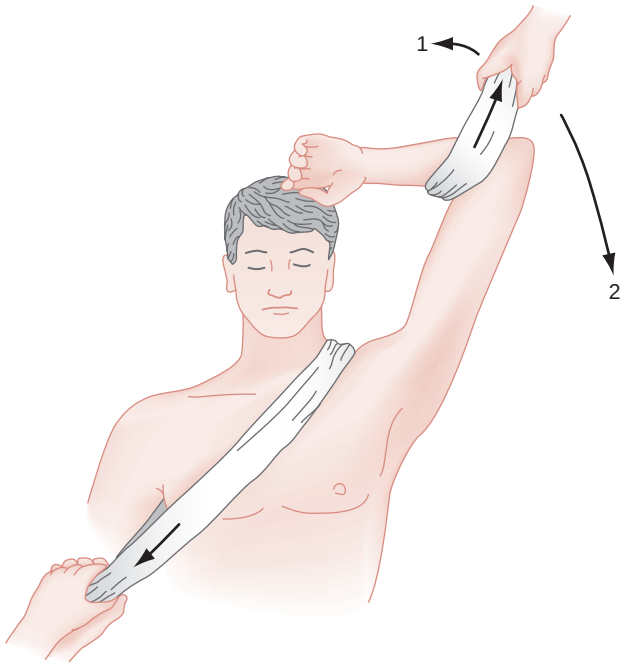

Fig. 46.29. Traction/countertraction method for reduction of luxatio erecta humeri. *Arrows indicate direction of applied force and relevant movement.* The initial maneuver *(1)* includes steady axial traction in line with the humeral shaft position, followed by gentle abduction. This reduces the glenohumeral dislocation. At this point *(2),* the arm is brought down to a position of adduction and internal rotation. (Redrawn from Davids JR, Talbott RD: Luxatio erecta humeri: a case report. Clin Orthop Relat Res 252:144, 1990.)

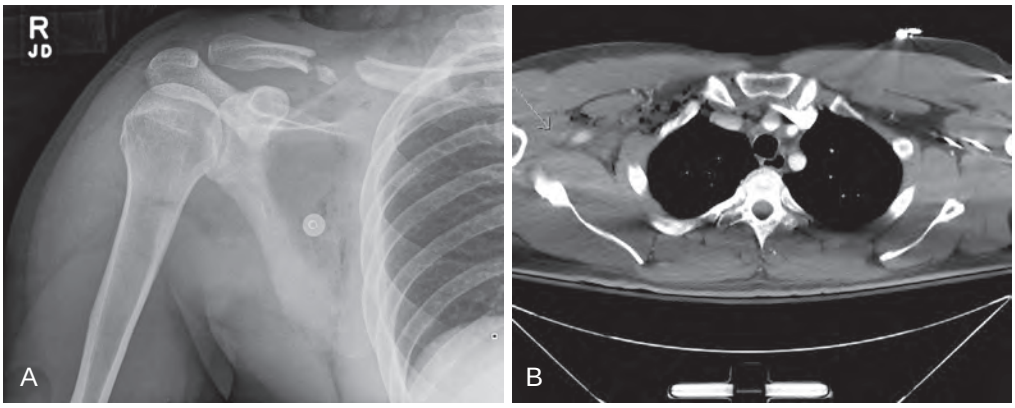

Fig. 46.30. Scapulothoracic dissociation with associated clavicle fracture **(A),** and computed tomography (CT) scan of associated axillary artery injury **(B).**

dislocation may not be initially recognized. Massive local soft tissue swelling of the shoulder, along with more than 1 cm of lateral displacement of the scapula on the anteroposterior chest radiograph, is pathognomonic for scapulothoracic dissociation (Fig. 46.30). Associated osseous injuries include acromioclavicular separation, displaced fractures of the clavicle, and dislocations of the SCJ. Vascular lesions (subclavian, axillary, or brachial vessels) have been reported in 64% to 100% of patients and severe neurologic injuries in 94%.[39] Acute limb ischemia is rare because of the extensive collateral network in the shoulder. Vascular and neurologic injuries can be confirmed through emergent angiography and MRI. Outcomes generally are poor, with death in 11% of cases and a flail anesthetic upper extremity in complete brachial plexus injuries leading to above-elbow amputation.[39]

Soft Tissue Conditions

Impingement Syndromes

Principles. The differential diagnosis of impingement syndrome is extensive and includes intrinsic and extrinsic causes of shoulder pain. Extrinsic sources include the cervical spine, lung, heart, and diaphragm. Intrinsic conditions include acromioclavicular arthritis, adhesive capsulitis, calcific tendinitis, traumatic anterior subluxation, as well as a pathophysiologic continuum from rotator cuff tendinitis or tendinopathy and subacromial bursitis to the endpoint of rotator cuff rupture.[41]

The subacromial space is the area between the coracoacromial arch and the greater tuberosity of the humerus. This space, which is only a few millimeters wide, contains the long head of the biceps, the rotator cuff, and the subacromial bursa. The bursa provides the gliding mechanism between the musculotendinous cuff and the coracoacromial arch. Impingement can occur during shoulder forward flexion, between 60 to 120 degrees of abduction and in the extremes of adduction. The critical wear from impingement is centered on the supraspinatus tendon, near its insertion on the greater tuberosity. Narrowing of the subacromial space (anatomic variants of anterior acromion) and occupations that require excessive overhead activity accelerate the entire process resulting in rotator cuff tendinitis. With time, the inflammatory reaction spreads to involve the adjacent bursa. This inflammation leads to edema, thickening, and fibrosis, further narrowing the subacromial space (secondary impingement) eventually followed by attritional changes within the rotator cuff. Because the rotator cuff is a primary humeral head depressor, loss of function adds to the secondary impingement process.[41]

The impingement process also may involve the long head of the biceps. In such cases, bicipital tendinitis, degeneration, or rupture may be present. If osteoarthritis of the ACJ has narrowed the subacromial space, the pathologic process can be accelerated. Impingement in this context occurs at 120 to 180 degrees of abduction (Fig. 46.31).

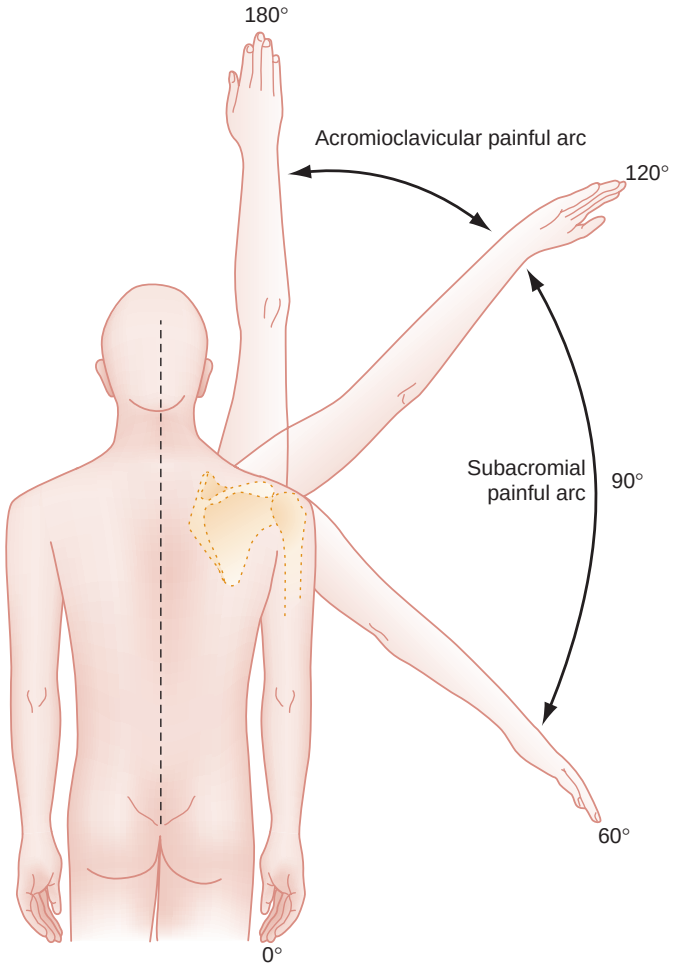

Fig. 46.31. Arcs of painful abduction: subacromial painful arc, 60 to 120 degrees; acromioclavicular painful arc, 120 to 180 degrees. (From DePalma AF: Surgery of the shoulder, ed 3, Philadelphia, 1983, JB Lippincott.)

Clinical Features. The spectrum of illness is marked by a progression of symptoms.[25] Initially patients report a dull ache around the deltoid area after strenuous activity. The inflammatory

process within the bursa and tendons then leads to the formation of minor adhesions. Disruption of these adhesions is thought to account for the pain becoming more persistent and particularly severe at night. Significant tendon degeneration after a prolonged history of tendinitis and bursitis, can lead to tears in the rotator cuff.

On examination, tenderness can be elicited over the supraspinatus and anterior acromion. A painful arc of abduction at 60 to 120 degrees (see Fig. 46.31) has a sensitivity and specificity of 53% and 76%, respectively. The Hawkins-Kennedy impingement sign (arm placed into 90 degrees of flexion followed by internal rotation), has a sensitivity and specificity of 79% and 59%, respectively.[42]

Management. Initial treatment in impingement syndrome is conservative and consists of rest, simple analgesia using acetaminophen or analgesic doses of nonsteroidal antiinflammatory drugs (NSAIDs), and modification of activities that produce impingement. Patients should be advised to seek primary care follow-up if not better within 1 to 2 weeks for consideration of physical therapy to maintain range of motion and strengthen the rotator cuff. Treatment-refractory disease may eventually require decompression surgery to control pain.

Rotator Cuff Tears

Principles. The rotator cuff acts as a dynamic stabilizer of the GHJ. Its primary function is to hold the humeral head in place throughout the full range of rotational motion (see Fig. 46.5). The infraspinatus and teres minor act as external rotators, whereas the subscapularis is an internal rotator. The supraspinatus is essential for the first 30 degrees of shoulder abduction.

The tenuous blood supply of the rotator cuff, abusive tensile overload, and chronic wear under the coracoacromial arch predispose it to age-related degenerative changes and impingement. The advanced stage of this process is characterized by complete rupture.

Rotator cuff tears typically involve the dominant arm and occur in men older than 40 years old. The occupational history is significant for strenuous work requiring overhead activity. Tears can be classified according to their chronicity, size, completeness, pattern location, or duration. Acute tears (10%) usually are associated with a specific traumatic event. Often, no history of previous shoulder problems can be identified. The most common mechanism of injury is forced abduction associated with significant resistance; this usually occurs when the patient attempts to break a fall with an outstretched hand.

Clinical Features. With acute tears, patients report a sudden tearing sensation in the shoulder followed by severe pain that radiates into the arm. Pain and muscle spasm limit shoulder motion. Physical findings depend on the completeness, size, and location of the tear. Point tenderness is usually present over the site of rupture (greater tuberosity). Patients with large tears cannot initiate shoulder abduction. A discrepancy between active and passive range of motion is highly suggestive of a rotator cuff tear. The drop-arm test, performed by passively abducting the arm to 90 degrees and asking the patient to hold the arm in this position, is positive with significant tears. Slight pressure on the distal forearm or wrist causes the patient to drop the arm suddenly. The acute pain resulting from hemorrhage and spasm subsides over a few days. Repeat examination at this point confirms the loss of function in significant tears.

Chronic tears account for approximately 90% of all lesions. Chronic tears are attritional and more insidious in their presentation. Early findings include the painful arc sign as a result of secondary impingement. The pain is worse at night and interferes with sleep. Worsening pain is followed by the gradual onset of weakness in the arm. Flexion and abduction are affected with involvement of the supraspinatus. The patient attempts to initiate abduction with scapulothoracic movement. A tear in the subscapularis tendon weakens internal rotation. A tear in the teres minor or infraspinatus compromises external rotation.

Diagnostic Testing

Radiology. Plain radiographs likely will be normal in acute and chronic tears and are not generally indicated. If they are obtained, there may be evidence of nonspecific degenerative changes within the GHJ and subacromial space. The hallmark of a complete tear is superior displacement of the humeral head best seen on an external rotation view. The normal distance from the superior aspect of the humerus to the undersurface of the acromion ranges from 7 to 14 mm. A distance of less than 6 mm is highly suggestive of a complete tear. Outpatient ultrasound examination, MRI, or an MRI arthrogram can confirm the diagnosis. Point-of-care ultrasound appears to be an excellent initial screening test for the detection of partial- and full-thickness rotator cuff tears (Fig. 46.32). When compared to MRI, ultrasound evaluation had a sensitivity of 91% and a specificity of 86%.[43]

Management. Acute tears should be immobilized in a sling for comfort and the patient referred for orthopedic follow-up. Early surgical repair (before 3 weeks) for certain lesions is preferred in young or active individuals. The management of chronic tears includes pain control and a shoulder rehabilitation program. Orthopedic follow-up care may be needed as patients with persistent pain and weakness may require surgical repair.

Lesions of the Biceps Muscle

The biceps is composed of two heads. The long head originates from the supraglenoid tubercle and glenoid labrum and ascends over the humeral head to enter the arm by way of the bicipital groove. The long head is covered by a synovial sheath and is held in place within the groove by the coracohumeral and transverse humeral ligaments. The short head of the biceps originates from the coracoid process and inserts with the long head onto the radial tuberosity. The biceps is responsible for flexion as well as supination at the elbow and serves as a stabilizer for the GHJ.

Bicipital Tendinitis

Pathophysiology. Anatomically, the long head of the biceps is subject to the same stresses as those incurred by the rotator cuff within the subacromial space. Irritation and microtrauma as a

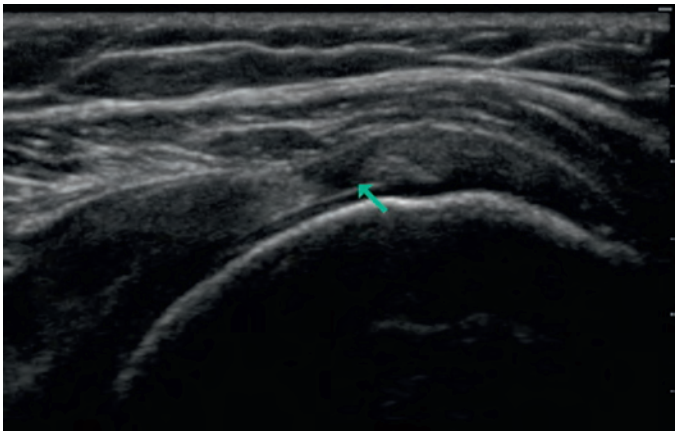

Fig. 46.32. Bedside ultrasound image of a rotator cuff tendon tear. (Courtesy Ryan Petering, MD.)

result of repetitive elevation or abduction of the shoulder produce an inflammatory reaction within the synovial sheath. Bicipital tendinitis is often associated with other acromial arch impingement conditions. Primary bicipital tendinitis (inflammation without other underlying pathology) is rare (approximately 5% of cases) and affects younger individuals.

The typical patient is middle-aged and involved in an occupation or recreational activity that requires repetitive overhead movement. The pain localizes to the anterior part of the shoulder along the bicipital groove. There is usually no history of trauma. Abduction and external rotation in particular are painful. Pain is worse at night and may interfere with sleep.

Clinical Features. On examination, point tenderness can be elicited over the biceps tendon as it passes through the bicipital groove. This is best shown with the arm in 10 degrees of internal rotation. Active range of motion is limited by pain, but the passive range remains intact. Supination against resistance—the Yergason test—with the arm adducted and the elbow flexed to 90 degrees reproduces the pain in 50% of cases. Another proactive test is the biceps resistance test (Speed test), in which forward flexion of the shoulder (elbow extended and forearm supinated) carried out against resistance produces pain in the bicipital groove. The specificity of these tests is limited in the presence of impingement and rotator cuff disease.

Diagnostic Testing

Radiology. Radiographs are usually normal and not indicated unless fracture or dislocation is suspected. When obtained, they may show evidence of subacromial space impingement by associated acromioclavicular arthritis and osteophytic spurs. The preferred imaging modality is ultrasound or MRI. Ultrasound has been found to be excellent in diagnosing complete rupture, subluxation or dislocation, but is less sensitive for partial tears.[44]

Management. Emergency treatment consists of rest (sling for comfort), ice, and acetaminophen or analgesic doses of an NSAID. Gentle exercises are encouraged as symptoms subside. Although the bicipital sheath can be injected by landmarks with a corticosteroid preparation, the procedure is technically difficult, and inadvertent direct tendon injection can lead to tendon rupture. We do not recommend injection treatment of bicipital tendinitis in the ED. Surgery may be necessary in patients who fail to respond to conservative therapy.

Ruptures of the Biceps Tendon

Principles. Ruptures of the biceps tendon can be classified into proximal and distal types. Distal ruptures are rare and are not discussed here. Proximally, microtears and other age-related attritional changes within the long head predispose it to rupture. The rupture can be spontaneous or follow a traumatic event involving either forced extension or resisted supination and flexion.

Clinical Features. The classic history of an acute rupture is that of a sudden snap or pop, followed by pain and ecchymosis along the arm. Recent fluoroquinolone and oral steroid use increases risk of tendon rupture.[45] With a complete rupture, distal retraction of the muscle results in a "Popeye" appearance of the arm. A difference in muscle contour (Ludington sign) also may be seen when both arms are placed behind the head and the biceps muscles are contracted. Functionally, forearm supination is weakened, but elbow flexion stays strong because the coracobrachialis and short head of the biceps remain intact. Most bicep tendon ruptures are associated with the impingement syndrome and a rotator cuff tear.

Diagnostic Testing

Radiology. Radiographic findings usually are unremarkable, and the confirmatory test of choice is MRI. ED point of care ultrasound can be used to identify presence or absence of tendon in bicipital groove, and fluid within the sheath.[10]

Management. The injured arm should be immobilized in a sling with the elbow in 90 degrees of flexion. The patient should be referred to an orthopedic surgeon for further evaluation and treatment within 72 hours. Surgical repair is a consideration in young, active persons. In older patients, conservative therapy (range-of-motion and strengthening exercise) is preferred because the cosmetic deformity is minimal and the mild functional loss usually is acceptable.

Subluxations and Dislocations of the Biceps Tendon

Subluxations and dislocations of the biceps tendon usually are associated with a congenitally shallow bicipital groove or atraumatic (attritional) tears of the coracohumeral and transverse humeral ligaments. The patient reports a snapping sensation in the upper arm with abduction and external rotation. External and internal rotation of the abducted shoulder shows dislocation and relocation of the tendon. With complete dislocation, the arm may reflexively drop to relocate the tendon. These conditions may require operative repair and should be referred to an orthopedist.

Calcific Tendinitis

Pathophysiology. Shoulder calcific tendinitis affects up to 10% of the population and frequently is encountered in the ED. The condition affects people aged 40 to 60 years old and is painful in 65% of patients.[46] Calcific deposits occur primarily in the supraspinatus tendon near its attachment to the greater tuberosity. Women are more often affected than men, and 10% of the patients have bilateral deposits.[47]

Clinical Features. The clinical presentation can be divided into silent, subacute, and acute phases based on the physical characteristics of the calcific deposits and the nature of the inflammatory response within the tendon and subacromial bursa. The painful arc syndrome (see Fig. 46.31) is a hallmark of the subacute phase of calcific tendinitis. Enlargement and softening of the deposit lead to narrowing of the subacromial space, resulting in impingement under the acromial arch.

A severe inflammatory reaction within and around the deposit produces the acute phase of calcific tendinitis. Often there is a precipitating history of atraumatic repetitive motion (eg, swinging a tennis racket or moving bales of hay). The patient is in severe pain and holds the arm close to the chest. Active and passive range of motion is severely limited. The shoulder is warm and extremely tender to the touch. Severe pain is related to increased intratendinous pressure, and spontaneous rupture of the deposit into the subacromial bursa can be associated with dramatic relief of symptoms.

Diagnostic Testing

Radiology. Radiographs show calcific deposits in the involved tendon (Fig. 46.33). Bedside ultrasound can also identify location of calcific deposits (Fig. 46.34).

Management. The acute phase should be treated with sling for comfort, an antiinflammatory dose of an NSAID, and avoiding offending activities. Refer patients to primary care or sports medicine clinic, because they may benefit from subacromial bursa steroid injections, or needle lavage procedures to maximize conservative therapy before considering surgical removal.[46] Early

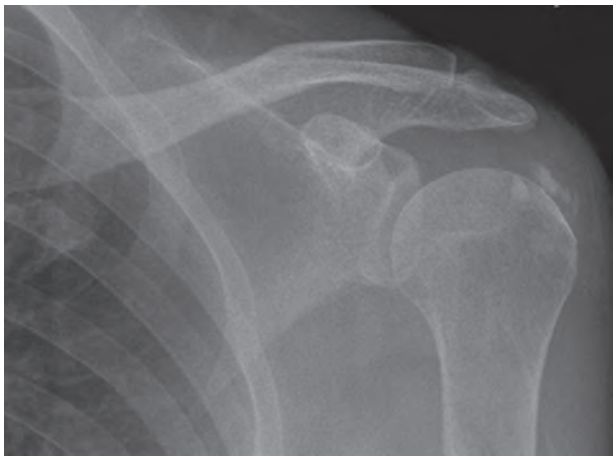

Fig. 46.33. Radiograph with rotator cuff calcific tendinitis.

Fig. 46.34. Ultrasound image of rotator cuff calcific tendinitis within subscapularis tendon. (Courtesy Ryan Petering, MD.)

shoulder range-of-motion exercises are encouraged in all patients to minimize the risk of adhesive capsulitis. All symptomatic patients should be referred for sports medicine or orthopedic follow-up care. The subacromial injection of anesthetic with corticosteroids for impingement symptoms in patients with an atraumatic shoulder injury that is due to calcific tendonitis may give targeted relief (steroids take 1 to 3 days to take effect). With an experienced outpatient provider, patients may be candidates for needle lavage (puncturing of the calcific deposits multiple times to decrease intratendinous pressure) under ultrasound or fluoroscopy guidance also has been described as an effective treatment during the acute phase.[46] Patients with chronic or refractory symptoms may need surgical removal.[46] Early shoulder range-of-motion exercises are encouraged in all patients to minimize the risk of adhesive capsulitis. All symptomatic patients should be referred for sports medicine or orthopedic follow-up care.

Adhesive Capsulitis

Principles. Adhesive capsulitis ("frozen shoulder") is a specific diagnostic entity characterized by an idiopathic inflammatory reaction within the capsule and synovium of the GHJ. The inflammatory reaction results in the formation of adhesions within the capsule and inferior axillary fold, leading to restricted active and passive range of motion. Adhesive capsulitis should be differentiated from other, more common causes of the painful stiff shoulder (eg, calcific tendinitis, rotator cuff tear, osteoarthritis, or trauma), which may be associated with decreased range of motion.[48] Any condition associated with prolonged disuse of the arm can result in capsular contraction, including immobilization for painful intrinsic shoulder conditions use of a sling or in healthy shoulders such as after a mastectomy or a distal upper extremity injury (eg, Colles' fracture).

Clinical Features. The typical patient is a woman 40 to 60 years old. The nondominant arm usually is affected, and the patient has trouble with the activities of daily living. The pain often is severe at night and localized over the deltoid area. As the condition progresses, there is uniform limitation of all glenohumeral movement. On passive testing of external rotation, a sense of mechanical restriction of joint motion can often be appreciated. Shoulder radiographs usually are normal in appearance if no associated pathologic condition is present.

Management. The best form of therapy is preventive in nature. Prolonged shoulder immobilization is to be avoided, and early motion encouraged in all instances (see Fig. 46.10). Treatment of adhesive capsulitis in the ED consists of anti-inflammatories and referral to a sports medicine provider or orthopedic surgeon. Initial therapy is conservative and consists of a gentle assisted exercise program along with an intra-articular steroid injection. Surgical treatment, including manipulation under anesthesia and arthroscopic capsular release, is reserved for patients who fail to improve with nonoperative treatment for at least 6 months.[48]

Injection Therapy

The local injection of corticosteroid preparations has long been used in many painful conditions that affect the shoulder, including rotator cuff tendinitis, subacromial bursitis, calcific tendonitis and adhesive capsulitis. Ultrasound guidance is improving accuracy but unclear of a clinical improvement compared to landmark based treatment for subacromial injections.[49] Although advocated for relieving the inflammatory reaction, corticosteroid injections in general do not alter the underlying disease process, and there is no evidence that they are superior to short courses of anti-inflammatory doses of NSAIDs. Systemic complications are rare after local injection therapy, although diabetics may experience elevated glucose levels.[50] Site-specific complications include articular cartilage damage, tendon weakening or rupture, and subcutaneous atrophy. Direct tendon injection is particular hazardous, and there is a high failure rate for rotator cuff repairs when patients have received more than three preoperative subacromial injections. Corticosteroid injection treatments generally are deferred to outpatient providers (primary care, sports medicine, or orthopedic practitioners).

KEY CONCEPTS

- Axillary nerve function is best evaluated by testing the motor function of the deltoid muscle.
- The three-view trauma series of the shoulder (true anteroposterior, scapular Y, and axillary views) leads to an accurate radiographic diagnosis of most fractures and dislocations, although specialized views are sometimes necessary. Consider the presence of unfused epiphyses in adolescents and young adults.
- Most fractures can be treated with simple immobilization with good functional outcomes.
- The most important aspect of scapular fractures, scapulothoracic dissociation and posterior sternoclavicular joint (SCJ) dislocations is the high incidence of associated injuries to the ipsilateral lung, chest wall, mediastinum, or shoulder girdle complex.
- Most studies have concluded that conservative treatment is best for type III acromioclavicular joint (ACJ) dislocations.
- Recurrence is a common complication after anterior dislocation, especially in male patients younger than 30 years old, and such patients may benefit from surgical repair.
- Posterior dislocation should be included in the differential diagnosis of any shoulder injury, particularly in patients who reports shoulder pain after a convulsive episode.
- Ultrasound can be a useful technique for diagnosing tendon tears, selected soft tissue conditions, fractures, dislocation, as well as confirming reduction.
- Early initiation of passive shoulder range-of-motion exercises reduces the risk of adhesive capsulitis when the shoulder is immobilized for any reason.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 46: QUESTIONS & ANSWERS

46.1. Which of the following represents a true orthopedic emergency?

A. Anterior glenohumeral dislocation
B. Anterior sternoclavicular dislocation
C. Biceps rupture
D. Posterior glenohumeral dislocation
E. Posterior sternoclavicular dislocation

Answer: E. Posterior sternoclavicular dislocations can be associated with life-threatening injuries within the superior mediastinum and intrathoracic cavity; therefore, they are considered true orthopedic emergencies and should be reduced expeditiously. Reported complications associated with posterior sternoclavicular dislocations include compression or lacerations of the great vessels, tracheal compression, pneumothorax, thoracic outlet syndrome, tracheoesophageal fistula, and injury to the brachial plexus.

46.2. A 30-year-old patient presents complaining of right shoulder pain and limited range of motion. On physical examination, you note that the shoulder has a "squared off" appearance and is held in abduction and external rotation. The patient is unable to adduct the arm or

internally rotate without severe pain. What is the best way to manage this patient without the aid of other emergency department (ED) personnel?
A. Anderson method
B. Hippocratic method
C. Kocher maneuver
D. Milch technique
E. Traction/countertraction method

Answer: D. The ideal method for reduction of an anterior shoulder dislocation should be simple, quick, and effective; require little assistance; and cause no additional injury to the shoulder. It is wise to be familiar with several techniques of reduction because none is uniformly successful. The Milch technique allows for reduction by a single practitioner, and it can be attempted without procedural sedation. More traditional techniques, such as the Hippocratic method (traction with the foot in the axilla) and the Kocher maneuver (leverage, adduction, and internal rotation), are no longer recommended because of a high incidence of associated complications (axillary nerve injury, humeral shaft and neck fractures, and capsular damage). Traction/countertraction requires two people to reduce the shoulder, and there is no reduction technique called the Anderson method.

46.3. Urgent orthopedic consultation is recommended for which type of clavicle fracture?
A. Greenstick fracture
B. Minimally displaced midclavicular fracture
C. Type I lateral clavicle fracture
D. Type II lateral clavicle fracture
E. Type III lateral clavicle fracture

Answer: D. Type I lateral clavicle fractures are stable and minimally displaced because the coracoclavicular ligaments are intact. Type II fractures are associated with a torn coracoclavicular ligament and have a tendency to displace because the proximal fragment lacks any stabilizing forces. Type III injuries involve the articular surface. More urgent orthopedic consultation (before 72 hours) is recommended for type II lateral clavicle fractures, because these fractures have up to a 30% incidence of nonunion and may benefit from surgical repair.

CHAPTER 47

Musculoskeletal Back Pain

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PRINCIPLES

Background

Back pain is one of the most common patient complaints encountered in emergency departments (EDs). Approximately two-thirds of adults are affected by back pain at some point in their lives, making it the second most common complaint in ambulatory medicine and the third most expensive medical disorder following cancer and heart disease. Most cases of musculoskeletal back pain are related to physical motion of the vertebrae and musculature of the back, including muscle strain, ligamentous injury, vertebral misalignment, and intervertebral disk disease, although a precise pathoanatomic diagnosis can be found only about 15% of the time.

Back pain complaints are the most prevalent and expensive cause of work-related disability in the United States. Back pain has been reported at least once in 85% of adults, and 15% to 20% of Americans complained of at least one episode of back pain yearly. Chronic back pain and low back pain syndromes can lead to significant loss of work productivity.[1]

Back pain presents the emergency clinician with a challenging diagnostic dilemma. Although most causes of acute or acute-on-chronic back pain are not precisely identifiable, certain causes of back pain require timely diagnosis and intervention.

Epidemiology

Back pain is a common complaint among men and women and most frequently occurs in people from 30 to 50 years old.[2-4] Smokers have increased incidence of back pain, although no causative link has been identified, and the association is higher in the adolescent age range.[5]

Anatomy and Physiology

Musculoskeletal back pain derives from pathology in the thoracic or lumbar spine and its associated muscles, nerves, and soft tissue structures. The thoracic spine consists of twelve thoracic vertebrae. The lumbar spine consists of five lumbar vertebrae and the sacrum and ends in the coccyx. The sacrum and coccyx are each composed of five small fused vertebrae. The vertebrae are connected by the anterior longitudinal ligament (ALL), the posterior longitudinal ligament (PLL), and the ligamentum flavum. The vertebrae articulate with each other at facet joints, where an inferior articular process from each vertebral body pairs with a superior articular process from the vertebral body below it bilaterally, creating four facet joints at each level. The thoracic vertebral bodies also have bilateral rib facets, which articulate with 12 pairs of ribs, whereas the lumbar vertebral bodies do not. Additionally, each vertebral body has bilateral transverse processes and a spinous process. Between the spinous process and the transverse processes are the lamina, and between the transverse processes and the posterior aspect of the vertebral body are the pedicles. Together, the pedicles and lamina form the neural arch, which, along with the posterior aspect of the vertebral body, forms the confines of the vertebral canal that contains the spinal cord and nerve roots. At each level, there are intervertebral (neural) foramina, bounded by pedicles superior and inferiorly, facet joints posteriorly, and the vertebral body anteriorly. These provide a route for the exit of spinal nerves.

Between the vertebral bodies are the intervertebral discs, which provide elasticity and stability to the spine. Each disc is comprised of the outer annulus fibrosis, a ring of fibrous tissue, and the inner nucleus pulposus, a collagenous substance. The vertebral bodies and discs are connected by the PLL and the ALL. The ALL prevents hyperextension of the spine, whereas the PLL limits flexion of the spine. The spinous processes are connected by the supraspinous and interspinous ligaments. The ligamentum flavum connects the lamina posteriorly and helps maintain disc tension. The intertransverse ligament connects transverse processes on either side of the spine and limits lateral movement. Finally, the iliolumbar ligament stabilizes the lumbosacral joint.

Movements of the spine are governed by extensor muscles, found in the back—forward flexors, which are the abdominal wall muscles and the psoas and iliacus; lateral flexors, which are the quadratus lumborum assisted by abdominal wall muscles; and rotators, which are really the extensors and lateral flexors used unilaterally.

The spinal cord runs continuously from the foramen magnum to the L1 to L2 interspace. The spinal cord may sometimes be as low as L3. At this point, it splits into the cauda equina. It is surrounded by three membranes—the tough dura mater, and the more delicate arachnoid and pia mater (the leptomeninges). The epidural space, between the bony vertebral canal and the dura, contains connective tissue padding and the spinal venous plexus. The dural sac ends between S1 and S3. The dura also protects the spinal nerve roots as the nerves exit the spine. Between the arachnoid and pia mater cerebrospinal fluid bathes the spinal cord. At each level of the spine, nerves exit the cord and the cauda equina just below the correspondingly numbered vertebral body, for example L1 nerves exit bilaterally just below the L1 vertebral body. There are twelve thoracic nerve pairs, five lumbar nerve pairs, and five sacral nerve pairs. The spinal nerves give rise to sinuvertebral nerves, which provide sensory innervation to the meninges, the periosteum, and the PLL and ALL. The discs themselves have little innervation.

Pathophysiology

Uncomplicated Back Pain

In as many as 85% of patients, no pathologic cause for back pain can be identified. In these patients, pain is presumed to be from the soft tissue structures supporting the spine, primarily muscles and ligaments. Sprains and strains of the thoracic and lumbar paraspinous muscles can occur, as can ligamentous strain. These patients typically have localized pain and no radiation of pain or paresthesias to the lower extremities.[6]

Nerve Root Syndromes

Nerve root syndromes occur when there is compression or irritation of the nerve root, leading to pain, which often radiates down a leg, and paresthesias. There are multiple possible etiologies for nerve root syndromes.

As one ages, intervertebral discs desiccate and degenerate and the nucleus pulposus herniates outward, compressing the nerve root as the nerve exits the foramen.

Herniations tend to occur mainly at the L4 to L5 and L5 to S1 levels. This is because most flexion and extension of the spine occurs at the lumbosacral joint and to a lesser degree at L4 to L5. Additionally, the PLL is weak at this level of the spine. Disc herniation accounts for only 4% of acute back pain cases. Approximately 95% of patients with disk herniation have sciatica. Thus, only about 1 out of 500 patients with acute back pain but without sciatica symptoms will have a herniated disc as the cause.

The annulus fibrosis may tear without a true herniation of the nucleus pulposus. This can result in nerve root irritation rather than a true compression syndrome, and pain may radiate down the leg but not below the knee.

Although most disc herniations are posterolateral, discs sometimes herniate centrally, at the level of the cauda equina, causing severe compression of multiple nerve roots, resulting in cauda equina syndrome (CES). This results in spinal cord compression below the termination at the conus medullaris and loss of function of the lumbar plexus. This presents symptomatically as back pain that radiates to both legs, saddle anesthesia, and loss of bowel or bladder function. Saddle anesthesia involves the S3, S4, and S5 dermatomes, and it manifests clinically by numbness or tingling to the perineum, anus, and genitalia.[7] Decreased rectal muscle tone causes loss of bowel function. Bladder dysfunction generally takes the form of inability to urinate, which may manifest as overflow incontinence as a result of urinary retention. CES may also be caused by compressive lesions other than a herniated disc, including severe spinal stenosis, malignancy, infection, hemorrhage, or fracture.

Nerve compression can also be caused by spinal stenosis. Aging causes the disc space to narrow but also deteriorates the joints in the spine. Osteophytes form at the facet joints, and the ligamentum flavum calcifies. These changes lead to narrowing of the neural foramina and the central canal with nerve root compression from osteophytes and increased intrathecal pressure in the narrowing canal. Pain is often bilateral, unlike impingement from a herniated disc. It also results in leg pain that typically worsens with walking that can be temporarily relieved if the person flexes forward slightly at the waist, relieving pressure on the nerve root, allowing further ambulation for a short period of time. This is known as the *pseudoclaudication sign*.

Spinal epidural abscess causing CES or other nerve root symptoms is a rare but an important emergency. An abscess develops in the epidural space, usually from hematogenous spread of bacteria (often staphylococcal species), related to intravenous (IV) drug use or a recent tattoo. Patients can also develop epidural abscess from direct inoculation, such as an epidural steroid injection or recent spinal surgery. An epidural hematoma may present similarly, usually resulting from instrumentation of the epidural space or recent surgery, although it can occur spontaneously in a patient taking anticoagulants.

Skeletal Causes

Fractures may occur in any part of the spine secondary to trauma (see Chapter 36). Although a significant amount of force, either direct, axial loading, or flexion/distraction injury, is required to fracture a normal spine, patients with osteopenia secondary to age or chronic steroid use may sustain a fracture with little to no trauma. The incidence of vertebral compression fractures increases with advancing age. Even with the advancing age of general population, vertebral fracture accounts for less than 5% of acute back pain. In patients older than 50 years old, compression fracture may be the cause of sudden onset of acute back pain. Compression fracture may occur without trauma or injury. Spontaneous fractures generally present as compression fractures of the thoracic or lumbar vertebral bodies, whereas traumatic fractures may occur in any bony part of the vertebral column. Fractures may present with or without radicular symptoms, depending on the location of the injury and impingement on the spinal canal or nerve roots by a fracture fragment.[8]

Like epidural abscess, osteomyelitis of the spine can be caused by hematogenous spread by bacteria. Pain is caused by inflammation of bone and periosteum and may or may not be associated with other manifestations of infection, such as fever. Again, IV drug use is a risk factor, as is direct bacterial infection from spinal surgery. Tuberculosis can also be a cause of osteomyelitis of the spine (Pott's disease).

Cancer in the spine is usually a metastatic lesion from another source, but primary bone tumors in the spine can also occur. Primary tumors are usually found in patients younger than 30 years old and involve the posterior vertebral elements. Primary spinal tumors include multiple myeloma, Ewing's sarcoma, and osteosarcoma, but primary lesions are 25 times less common than metastatic disease. Metastatic tumors more typically involve the vertebral body. Unlike many other causes of back pain, metastatic spinal lesions are more likely to be found in the thoracic spine (about 70%) than in the lumbar vertebrae. Metastasis is usually by the hematogenous route, and multiple levels are often involved. Lung and breast cancers make up over 50% of metastatic spinal lesions. Lymphoma, melanoma, cancers of the gastrointestinal (GI) tract, prostate, and kidney, and multiple myeloma may also present as metastatic spinal lesions. Of note, intramedullary and extramedullary metastases may also occur but are less common than bony metastases.

Skeletal back pain may also be caused by nontraumatic congenital or acquired abnormalities of the spine. Spondylolisthesis, or slippage of one vertebral body on another, causes back pain when the displacement is backward (retrolisthesis) but not when it is forward (anterolisthesis). Spondylolisthesis is usually the result of degenerative changes but may follow a traumatic event. Facet arthropathy, also a result of aging, may also be a cause of back pain. Inflammatory arthropathies, such as ankylosing spondylitis and rheumatoid arthritis, may cause the same changes in the spine as osteoarthritis and may also results in pathologic fractures.

CLINICAL FEATURES

History

A thorough history and a directed physical examination will, in most cases, guide the clinician to the correct diagnosis and will allow differentiation between simple musculoskeletal pain and more sinister diagnoses. The patient is asked to describe the current episode: onset; duration; severity; character of the pain (burning, shooting, dull or sharp, constant or intermittent); location, including presence of any abdominal or flank pain; and radiation. Radiation of the pain to the lower extremity is another important feature of the history. Pain that radiates below the knee is more likely to be radicular. Pain that does not radiate is more likely muscular in origin. Pain that radiates, but not below the knee, may suggest an annular ligament tear.

Aggravating factors are also important. Pain that increases with increasing intrathecal pressure (such as, coughing, sneezing, or bearing down with bowel movements) increases the likelihood of

a radicular or spinal cause. Pain that is worse with walking or prolonged standing, or pseudoclaudication, particularly if relieved by bending forward, suggests spinal stenosis. Pain that is worse in the mornings and improves through the day suggests a rheumatic etiology.

The patient is asked about neurologic findings (such as, numbness or weakness), pain in other parts of the spine, and whether there is bowel or bladder dysfunction. Next, seek the nature and timing of any prior episodes of back pain and any history of back trauma, malignancy, systemic symptoms (fever, chills, malaise, nausea, generalized myalgia), spinal surgery or procedures (eg, epidural injection), and anticoagulant use. Medications are reviewed, particularly corticosteroid use, which may point to an underlying inflammatory cause, and also can cause osteopenia with increased likelihood of fracture. Family history is rarely contributory, but history of autoimmune inflammatory diseases and malignancy may be helpful.

Physical Examination

The patient is undressed and placed in a gown. Inspection of the overlying skin for changes such as erythema, warmth, or swelling is supplemented by a general observation of the patient's wellness, degree of discomfort, and presence of any generalized skin changes, such as jaundice, rash, or multiple bruises. The patient ambulates and the gait should is observed. Range of motion includes flexion and extension at the waist (entire spine), lateral flexion (mostly thoracic spine), and rotation (exclusively thoracic spine). This is also a good time to examine for scoliosis, which may be longstanding or acute secondary to muscle spasm.

Next, palpation in the location of the pain may identify areas of maximal tenderness or the presence of muscle spasm. Strength testing of the lower extremities is best done with the patient standing. The patient is instructed to flex both hips and knees, assuming a partial sitting position, then to lift one leg briefly, then the other. Walking on heels and on toes (while holding the examiner's hands) requires full plantar and dorsiflexion strength, because the entire body weight is carried on a single extremity. If the patient is not able to comply with this testing because of pain, strength testing can be performed with the patient lying down, but it is not as reliable. Sensory testing is done with the patient lying down or sitting. Testing should include the upper extremities, because some conditions, such as spinal stenosis, may occur at multiple levels of the spine and may involve the cervical spine as well. A thorough neurologic examination can help the clinician determine if multiple levels of the spine need to be imaged.

Straight leg raise and crossed leg raise tests are important in determining if the pain is radicular. The straight leg raise test is more sensitive but less specific than the contralateral straight leg raise test for the diagnosis of radiculopathy due to disc herniation.[9,10] The straight leg raise test is performed as follows:

- With the patient supine and legs extended, the examiner raises the each leg, flexing at the hip with the knee in extension.
- The patient is completely passive for this examination, and the quadriceps should not be engaged.
- This can be determined by noting that the patella can be moved freely move side to side.
- A positive result is pain radiating from the back to a point below the knee of the raised leg at 30 to 40 degrees of elevation. A positive result predicts L5 or S1 radiculopathy with a sensitivity of approximately 90% and a specificity of 30% or lower.[11]

Because these two discs are implicated in 95% of disc herniations, this is a highly useful test, and a negative result is reassuring in ruling out disc pathology. Radiation of pain from the back to the area of the posterior knee or above is a nonspecific finding of no clinical value.

The contralateral leg raise test is performed in an identical manner. A positive finding is pain that radiates below the knee of the contralateral leg (the leg that is not being raised). The sensitivity of this test for disc herniation is poor, below 25%, but specificity approaches 100%.[11] This makes a positive test result strongly suggestive of disc pathology at the L5 or S1 levels. If one has a positive straight leg raise test, a positive contralateral straight leg raise test can be considered confirmatory of the presence of a ruptured disc. If the contralateral straight leg raise is positive with a negative straight leg raise test, disc herniation is still highly likely due to the high specificity of the contralateral test.

Patellar and Achilles deep tendon reflexes should be elicited and the plantar reflex assessed. Hyperreflexia, clonus, or a Babinski sign (positive plantar reflex) suggests upper motor neuron pathology, such as a cord impingement or malignancy.

Perineal sensation and anal sphincter tone are assessed in patients with bilateral symptoms or findings, gait disturbance, severe pain, complaints of saddle anesthesia, or bowel or bladder dysfunction. Bladder dysfunction is evaluated by post-void ultrasonographic measurement of bladder volume. A completely normal bladder should have about 20 cc of residual urine after voiding, and anything over 100 cc is considered abnormal. If bedside ultrasound is not available, post-void residual is measured by in-and-out urinary catheterization.

Because pain from abdominal or pelvic pathology often radiates to the back, a thorough abdominal examination, including assessing for costovertebral angle tenderness and, where indicated, a prostate or gynecologic examination should be performed to rule out non-musculoskeletal causes of low back pain.

DIFFERENTIAL DIAGNOSES

Table 47.1 lists the various causes of low back pain along with findings on the history that point toward the specific cause of back pain. In constructing a differential diagnosis, the clinician incorporates history and physical examination finding, particularly whether there is evidence of a nerve root cause for the pain, or findings to suggest infection or malignancy. Radicular pain is most often due to true herniated discs. Classic presentation includes decreased sensation in a dermatomal distribution corresponding to the level of the involved disc along with motor weakness and reflex loss (Table 47.2). However, herniated discs can present with only a positive straight leg raise test (see earlier discussion).

DIAGNOSTIC TESTING

Laboratory Testing

Laboratory testing is rarely indicated for low back pain. When spinal epidural abscess is suspected, prompt imaging is required, although a white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be obtained in parallel with the imaging plan. The WBC count is often obtained when infection is suspected but is neither sufficiently sensitive nor specific to confirm or exclude any particular diagnosis. The presence of an elevated ESR significantly increases the suspicion for a spinal epidural abscess, osteomyelitis, or discitis. Marked elevations in the ESR are more often due to infection than other causes, but noninfectious disorders such as malignancy, chronic diseases, inflammation, trauma, and tissue ischemia are also common etiologies. ESR values of over 100 mm/hour are most likely due to infection, whereas lower values suggest myriad causes, of which infection is just one. CRP is both less sensitive and specific than ESR, but it may add some diagnostic information when elevated. Markedly elevated levels of CRP are strongly associated with infections with values in above 10 mg/dL (100 mg/L).

TABLE 47.1

Historical Clues to the Cause of Low Back Pain

QUESTIONS FOR PATIENT	POTENTIAL DIAGNOSIS
Does the back pain radiate down past the knees?	Radiculopathy and likely a herniated disk
Is the pain worse with walking and better with bending forward and sitting?	Spinal stenosis
Do you have morning back stiffness that improves with exercise?	Ankylosing spondylitis
Are you older than 50 years old?	Osteoporotic fracture, spinal malignancy
Has there been any recent history of blunt trauma?	Fracture
Do you take long-term corticosteroids?	Fracture, spinal infection
Do you have a history of cancer?	Spinal metastatic malignancy
Does your pain persist at rest?	Spinal malignancy, spinal infection
Has there been persistent pain for longer than 6 weeks?	Spinal malignancy
Has there been unexplained weight loss?	Spinal malignancy
Is the pain worse at night?	Spinal malignancy, spinal infection
Are you immunocompromised (eg, HIV infection, alcoholism, diabetes)?	Spinal infection
Have you had fevers or chills?	Spinal infection
Do you have pain, weakness, or numbness in both legs?	CES
Do you have bladder or bowel control problems?	CES

CES, Cauda equina syndrome; *HIV,* human immunodeficiency virus.

TABLE 47.2

Physical Findings Corresponding to Herniated Disc Location

LEVEL	PAIN LOCATION	MOTOR LOSS	SENSORY LOSS	REFLEX LOSS
L3	Front of leg	Hip flexion and knee extension	Anterior thigh, medial calf	Loss of knee jerk
L4	Front of leg	Leg extension at knee	Around knee	Loss of knee jerk
L5	Side of leg	Foot dorsiflexion	Web of big toe	No reflexes lost
S1	Back of leg	Foot plantar flexion	Lateral foot	Loss of ankle jerk

Coagulation testing is indicated for patient taking long-term anticoagulants. If the prothrombin time (PT) or international normalized ratio (INR) is excessively elevated in the setting of low back pain complaints, one should consider a spontaneous epidural or retroperitoneal bleed.[12]

Urinalysis may also be helpful when the problem is not clearly musculoskeletal, because low back pain in women can be of pelvic origin. A urine pregnancy test should be obtained when imaging is indicated in a woman of childbearing age or if back pain is felt to be of pelvic origin.

BOX 47.1

Indications for Advanced Imaging Studies

History of malignancy
Fever with localized back pain
Back pain with history of intravenous (IV) drug use, recent tattoo, or bacterial source
New neurologic deficit (especially loss of bowel or bladder function or saddle anesthesia)
Direct trauma
Worsening pain after spinal surgery
Sudden onset of back pain in patients on anticoagulants
Recent spinal procedure, such as epidural injection

Imaging Studies

Most patients with back pain require neither plain radiographs nor advanced imaging. Routine imaging for low back pain is not associated with an improvement in patient outcomes. Even when abnormalities are found, they are often incidental and not the cause of presenting symptoms.[13,14] Imaging in the setting of acute pain should be reserved for patients with suspected diagnoses that would necessitate emergency management.[12] Signs, symptoms, and historical features that should lead the clinician to consider imaging studies are provided in Box 47.1.

Plain Radiographs

In general patients with nontraumatic low back pain with a normal neurological examination do not need plain radiographs in the ED. Clinicians may obtain plain radiographs when there is concern for occult spontaneous compression fractures in patients with nontraumatic back pain who have osteopenia or are taking chronic steroids. If ESR or CRP tests are elevated, plain films should not be obtained, and one should proceed directly to advanced imaging. In cases where there is a history of low energy traumatic injury (such as, ground level fall or low speed motor vehicle collision), plain radiographs of the affected area of the spine are sufficient to identify or exclude significant fractures. Elderly patients are at particular risk for occult fractures with minor trauma, and the clinician should obtain plain films in the ED when localized pain or tenderness is present, even with low energy mechanisms. Anteroposterior and lateral views of the thoracic and lumbar spine are usually sufficient in the ED to evaluate for acute factures. Oblique views show the pars interarticularis in profile and may help in the diagnosis of spondylolysis. In general, oblique views do not add additional information and significantly increase the dose of radiation. These views, therefore, are not recommended for routine evaluation. Flexion/extension views may be helpful in patients who have had surgical fusion procedures to evaluate for slippage or fracture of hardware. Plain radiographs of the chest may also be helpful, particular in the setting of thoracic back pain, because rib fractures can be detected and may be the cause of pain referred to the back. The sensitivity, specificity, and diagnostic accuracy of plain films and advanced imaging techniques for spine trauma are discussed in Chapter 36. In nontrauma cases, advanced neuroimaging is indicated when localizing signs and symptoms suggest possible epidural abscess, mass, or hematoma, osteomyelitis or discitis, or CES, or when

there are new significant neurological deficits or unexplained neurological findings. Computed tomography (CT), magnetic resonance imaging (MRI), and CT myelogram are the most commonly used modalities, and each is further discussed in the following sections.

Computed Tomography

CT is preferable to MRI for bony anatomy abnormalities. If a fracture is present on plain films, CT can better delineate the nature and extent of the fracture. In patients with higher pre-test probability of fracture (ie, those with a significant injury mechanism, on chronic steroid therapy, or with point tenderness directly on a thoracic or lumbar vertebra), the clinician should omit plain radiographs and proceed directly to CT scan. In a multi-trauma patient undergoing CT scans of the chest and abdomen, views of the thoracic and lumbar spine can be reconstructed from these studies, and dedicated plain films are not necessary. CT has superior sensitivity for detecting abnormalities of cortical bone over MRI, which cannot directly visualize cortical bone. Therefore, when bony injury or lesions are suspected, CT is preferable over MRI. The converse is true when soft tissue pathology, including spine and nerve roots, is suspected.

Magnetic Resonance Imaging

MRI is the test of choice for evaluating the spinal cord and the spinal structures, including the canal, intervertebral discs, and soft tissue, including ligaments and epidural space. MRI defines the bony anatomy and visualizes soft tissues and neural structures, such as the conus medullaris and spinal nerve roots within the canal and neural foramina. It provides axial as well as sagittal views, which can demonstrate pathologic discs, ligaments, nerve roots, and epidural fat, as well as the shape and size of the spinal canal. MRI is both more sensitive and specific than plain radiographs for the detection of spinal infection and malignancy, and it is the modality of choice in back pain patients with elevated ESR or CRP. Emergent MRI is indicated for suspected CES, epidural hemorrhage, or history of malignancy with sudden onset or worsening of pain accompanied by new neurological findings. MRI helps delineate many etiologies of back pain, including epidural hematoma or abscess, herniated disc, ligamentous injury, and spinal stenosis, and it is the test of choice for diagnosing osteomyelitis. MRI may also help to determine the chronicity of a fracture. For example, if a plain film, or even CT, demonstrates a compression fracture but there was no inciting trauma or the history is unclear, MRI may help delineate whether the fracture is acute. However, for acute fractures, CT is still the imaging modality of choice. Contrast administration provides little additional information to the MRI and is unnecessary unless either new spinal symptoms arise postoperatively or there is a question of intraspinal infection or metastasis.

In evaluating for spinal cord lesions, the clinician must make a decision about which spinal levels to include. A thorough neurologic examination that includes upper extremities may be used to exclude the C spine from imaging, but it is important to remember that spinal processes (such as, malignancy or stenosis) can occur simultaneously in several levels, and the region of pain may not always correspond to the lesion causing a neurologic deficit. Cervical or thoracic spine lesions may cause lower extremity deficits. For this reason, consideration should be given to imaging the entire spine.

Computed Tomography Myelogram

Myelography is rarely performed in current practice and generally used in patients who need advanced imaging but are not able to have an MRI, such as those with implanted hardware (pacemaker, spinal hardware, deep brain stimulator) or retained metal fragments from previous surgery or injuries. Because of the theoretical increased risk of seizure during this procedure, emergency clinicians should be aware of medications the patient is taking that lower seizure threshold, such as tramadol. If on these medications, some centers require that they be held for 24 to 72 hours before the test can be performed. Clinicians should discuss medications with their consulting radiologist before ordering this test.

MANAGEMENT

Figure 47.1 presents and algorithmic approach to ED management of patients with low back pain based on physical and/or ancillary test findings.

Uncomplicated Back Pain

Initial therapy for uncomplicated back pain focuses on pain control to maximizing return to function.[1] Treatment in the ED is directed at supportive care and symptomatic relief. In patients with mild to moderate pain and adequate function (can get up and down off the bed and walk unaided), initial therapy is an oral nonsteroidal antiinflammatory drug (NSAID) in analgesic doses (eg, ibuprofen 400 to 600 mg every 4 hours), or acetaminophen 1000 mg every 4 to 6 hours, if the patient is NSAID intolerant.[15] For patients with severe pain or muscle spasm that significantly affects normal daily function and with a normal neurologic examination, oral analgesia with an NSAID, as mentioned earlier, is supplemented by an oral opioid medication, such as oxycodone 5 to 10 mg, with observation for improvement over a 2-hour period. There is no proven benefit of ongoing opioid analgesic therapy, and opioid prescriptions at discharge should provide coverage only for 24 to 72 hours to mitigate the acute pain and improve sleep, movement, and ambulation. Combination therapy with NSAIDs and opioids, as compared to NSAIDs alone, does not appear to improve functional outcomes or pain at 1-week follow-up.[16,17] Similarly, there is no proven benefit of "muscle relaxant" medications, such as cyclobenzaprine or carisoprodol, and these agents have very significant side effect profiles. We do not recommend their use, either in the ED or as a discharge prescription. A benzodiazepine may be prescribed to supplement the analgesic regimen when the patient has failed an appropriate regimen or when the pain is causing substantial anxiety or sleep disturbance. Once the patient's symptoms are improving, the patient is discharged on an appropriate pain regimen, guided by the results in the ED. Wherever possible, outpatient management should be achieved with NSAID medication alone, although some patients with severe pain may require a short course (3 days) of opioid medication as well.[18]

Bed rest is not recommended. Patients without sciatic symptoms benefit from staying active, and patients with sciatic symptoms are likely to experience no difference in pain from bed rest versus staying active.[19]

Early return to work, with or without activity restrictions, is associated with better long-term outcomes. Patients may also experience benefit from gentle stretching exercises. Physical therapy, although not associated with improved outcomes for uncomplicated back pain, is associated with improved patient satisfaction. A referral to physical therapy may be made in the ED or by the patient's primary care physician.[20] Seventy percent of patients achieve improvement within 1 week.[21,22] Only about 10% of all patients have long-term issues, often because of functional overlay. Chronic back pain is more likely to develop in patients with psychiatric disorders, poor overall health status, and nonorganic signs. Development is not associated with demographic variables, prior episodes of back pain, or baseline pain levels.[23]

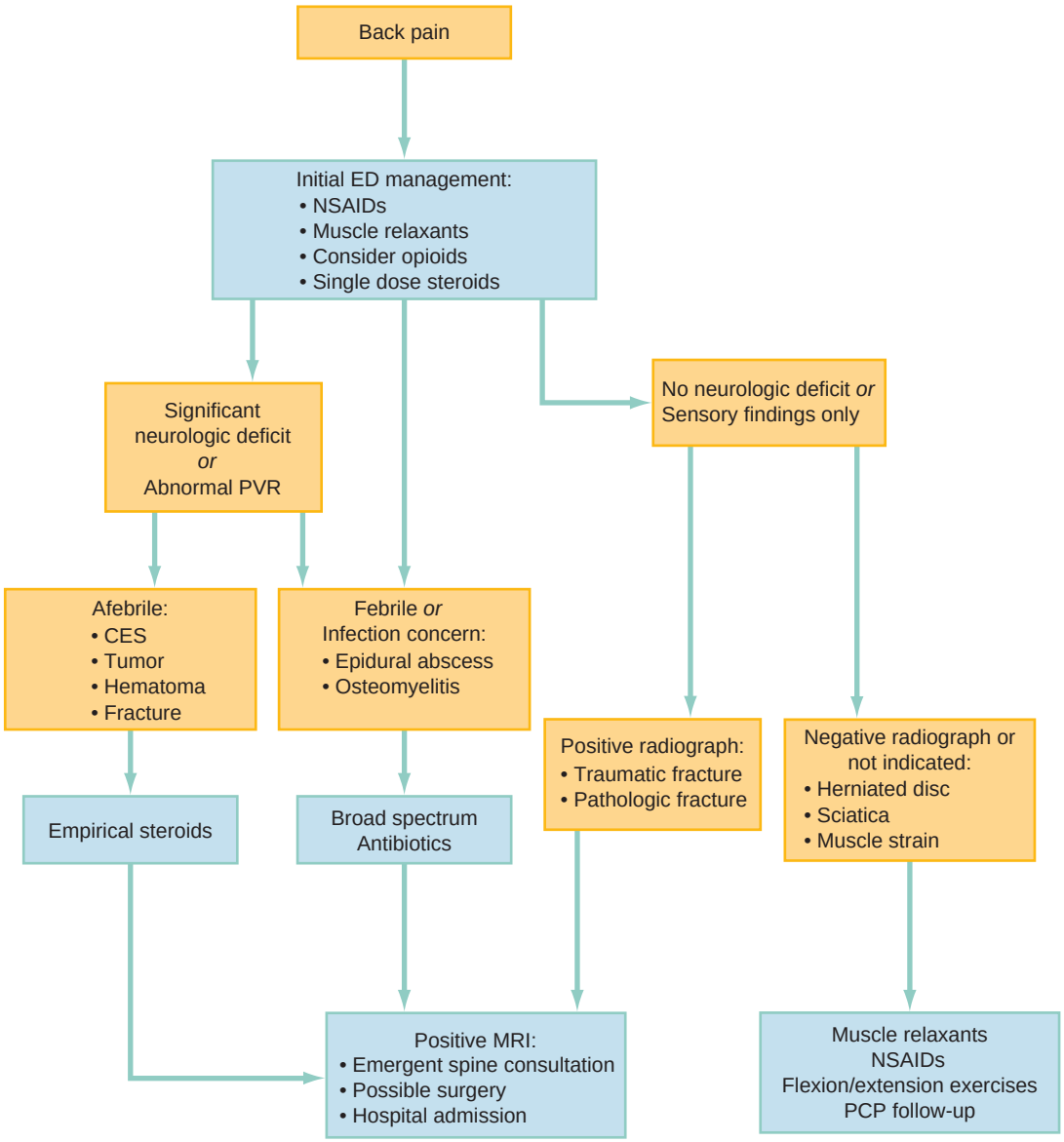

Fig. 47.1. Algorithmic approach to emergency department *(ED)* management of low back pain. *CES,* Cauda equina syndrome; *MRI,* magnetic resonance imaging; *NSAID,* nonsteroidal antiinflammatory drug; *PCP,* primary care physician; *PVR,* post-void residual.

Disk Herniation

Herniated disks are commonly managed initially like lumbosacral strain with no imaging indicated and symptomatic treatment provided. Signs and symptoms that indicate the need for advanced imaging include new bowel or bladder dysfunction, new localized motor weakness, progressive leg weakness, or acute and substantial worsening of symptoms or findings in patients with known herniated discs or chronic back problems. Indications for emergent spine service consultation include rapidly progressive neurological symptoms or signs of acute cord compression, including CES.

Nerve Root Pain

Patients with nerve root or sciatic pain and no neurologic deficits should be treated similarly to those with uncomplicated back pain. Oral steroids do not improve recovery for unselected patients with acute back pain.[24] However, there is evidence that the subset of patients with nerve root pain and acute radiculopathy benefit from a single pulse dose of 6 to 10 mg of IV dexamethasone in the ED.[25] Alternatively, a 15-day course of a tapering dose of prednisone (60 mg, 40 mg, 20 mg daily for 5 days each) improves function but without improvement in pain.[23]

Epidural Abscess and Spinal Osteomyelitis

Epidural abscess is a surgical emergency. Emergent spine surgery consultation should be obtained; or if not possible at the treating hospital, the patient should be transferred to a facility with spine surgery available. Empirical antibiotics should also be administered to cover suspected pathogens, usually *Staphylococcus, Streptococcus,* and gram-negative species. Because of increasing rates of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, vancomycin should be included in the antibiotic regiment. Pseudomonal coverage should be considered when the infection is felt to be due to hematologic spread, particularly in diabetic patients and those with sickle cell disease. Antibiotics should be directed against the known pathogen if the culture or

Gram stain of the aspirate is positive. Appropriate empirical parenteral regimens include:

- Vancomycin (30 to 60 mg/kg IV per day in two equally divided doses adjusted for renal function) for empirical coverage of MRSA
  plus
- Metronidazole (500 mg IV every 8 hours)
  plus
- Either cefotaxime (2 g IV every 6 hours), ceftriaxone (2 g IV every 12 hours), or ceftazidime (2 g IV every 8 hours): Ceftazidime is preferable when *Pseudomonas aeruginosa* is considered a possible or likely pathogen.

In some cases, especially where MRI shows minimal cord impingement, conservative management with antibiotics alone and no surgery may be considered.

Osteomyelitis also requires antibiotics with coverage for similar bacterial pathogens, along with surgical consultation. The need for surgery may be less emergent than with epidural abscess if there is no mass effect on the cord or purulent fluid collection. Whenever possible, antibiotic therapy should be delayed in stable patients until tissue cultures can be obtained. If tissue culture is not obtainable and in advance of tissue culture results, broad-spectrum empirical therapy should be administered. Empirical inpatient antibiotics commonly include:

- Inpatient treatment:
  - Nafcillin (2 g every 4 hours) for methicillin-sensitive *Staphylococcus aureus* (MSSA) coverage
  or
  - Vancomycin (30 to 60 mg/kg IV per day in two equally divided doses adjusted for renal function) for empirical coverage of MRSA
  or
  - Cefepime (2 g IV every 8 to 12 hours) for gram-negative and *Pseudomonas* coverage
- Outpatient treatment:
  - Ciprofloxacin (750 mg by mouth BID)
  or
  - Trimethoprim-sulfamethoxazole (1 double-strength tablet twice daily)

Epidural Hematoma

Although rare, the diagnosis of epidural hematoma should result in emergent spinal surgical consultation. Additionally, patients on anticoagulant should have their anticoagulation reversed as described in Chapter 114. Because of the danger of hematoma expansion, consultation should be obtained rapidly and all necessary steps taken to facilitate rapid operative intervention.

Cauda Equina Syndrome

CES, when suspected, requires rapid confirmation and, if confirmed, emergency decompression, usually by surgery, is the usual course of action. Emergency medicine and radiology departments should collaborate on the development of a CES imaging protocol that gives immediate priority to patients clinically suspected of CES and ensures the most rapid possible completion of MRI imaging and expert interpretation. Whenever possible, the emergency spine surgery consultation should be obtained in parallel with the ordering of the imaging study so that plans can be established in the event the diagnosis is confirmed by imaging. Although prompt surgery provides the best opportunity for a good outcome, some patients may not recover function even after decompressive surgery; and in patients with longstanding or chronic symptoms of CES, surgery may be deferred. Planning with respect to emergency surgical intervention occurs in consultation with spine surgery. Some clinicians initiate IV corticosteroid therapy when the diagnosis of CES is strongly suspected or confirmed; however, multiple clinical trials have failed to identify convincing evidence of greater or more rapid recovery of function with this practice. The risk of a single dose of corticosteroids is very low. We recommend that corticosteroids not be used in CES unless ordered by the treating spine surgeon.

Malignancy

If malignancy is diagnosed on plain film or advanced imaging but the patient is neurologically intact and pain can be well controlled, management may be continued as an outpatient. However, patients with compressive malignant lesions of the spine or spinal cord may benefit from emergent corticosteroids to reduce the severity of mass effect. A single dose of 10 mg IV dexamethasone is the steroid of choice, and it is administered when new neurologic findings suggest an acute compressive malignant lesion.[26] However, the effects are transient, and surgical decompression may be required. Additionally, radiation oncology consultation is sought to determine whether emergency decompressive radiation therapy is indicated. This can be done in conjunction with oncology or surgical consultation.

Fracture

The management of acute traumatic spinal fractures is discussed in Chapter 36.

DISPOSITION

The vast majority of patients presenting to the ED with acute back pain will be discharged with symptomatic treatment and an appropriate follow-up plan. For most, follow-up with a primary care physician is adequate. If the patient has no radicular findings, then that the clinician should explain to the patient why imaging is not helpful and that the pain will likely resolve with conservative measures. Work notes may help patients limit heavy lifting or significant time on their feet. Patients should also be counseled that despite being provided medications, acute back pain is unlikely to resolve quickly and may take days or weeks to significantly improve. Setting an expectation for the time frame for improvement may reduce the likelihood of a quick return to the ED for unchanged symptoms. Patients with suspected radiculopathy should also be given clear return precautions, including the development of weakness, inability to stand or ambulate, saddle anesthesia, or bowel or bladder dysfunction.

For those with back pain thought to be secondary to a compressive lesion (such as, a herniated disc) and non-emergent sensory or motor findings (see earlier discussion), follow-up should occur in 3 to 7 days with the primary care physician or a spine surgeon. This is the case for patients who did not have imaging, or imaging was performed but did not identify an urgent surgical lesion. When imaging is not obtained, the patient is counseled that imaging will not likely be required in future unless symptoms persist or worsen over several weeks. Studies of the benefits of interventions (such as, epidural steroid injection) have provided mixed results, but discussion of such therapy is the domain of the spine consultant on an outpatient basis.

Patients who require emergent surgical intervention for spinal epidural abscess, neoplasm, osteomyelitis, fracture, or other compressive spine lesions should be transferred to the care of a spine surgeon emergently, which may involve transfer to a tertiary care center.

Transfer may also be necessitated by the non-availability of MRI or CT myelography in patients in whom an emergent infectious or compressive etiology is strongly suspected. Patients

believed to have an epidural abscess or osteomyelitis should receive empirical parenteral antibiotics as detailed in Epidural Abscess and Spinal Osteomyelitis section earlier. Patients with findings consistent with CES or other compressive lesions due to malignancy should receive parenteral steroids prior to transfer if ordered by the receiving physician or the onsite consultant.

KEY CONCEPTS

- Most back pain presenting to the emergency department (ED) is benign, self-resolving with conservative therapy, and does not require imaging.
- Indications for emergent imaging include history of malignancy, new significant neurologic deficit, bowel or bladder dysfunction or saddle anesthesia, intravenous (IV) drug use, fever, immunocompromised state, chronic steroid use, and anticoagulant use.
- Metastatic disease is more common than primary tumors in the spine, and thoracic metastases are more common than lumbar metastases.
- Epidural abscess or hematoma, cauda equina syndrome (CES), spinal malignancy with compressive symptoms, and spinal osteomyelitis are indication for emergent surgical consultation or transfer to a center where emergent surgical consultation is available.
- Empirical parenteral antibiotics active against staphylococci, streptococci, and gram-negative bacilli should be administered for suspected epidural abscess. Antibiotics should be directed against the known pathogen if the culture or Gram stain of the aspirate is positive.
- Corticosteroids given as a single dose in the ED (10 mg dexamethasone) or as a 15-day tapering course after discharge (prednisone 60 mg, 40 mg, 20 mg daily for 5 days) may improve functional ability but do not improve pain for patients with nerve root findings related to disc herniation.
- Corticosteroids are of no proven benefit for patients with CES. We recommend that corticosteroids not be used for patients with suspected or known CES unless desired by the treating spine surgeon.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 47: QUESTIONS & ANSWERS

47.1. A 55-year-old man presents with the complaint of low back pain for 1 month. The pain is worse at night and is associated with a 10-pound weight loss. He denies any radicular symptoms. Which of the following is the most likely cause of this man's back pain?

A. Chordoma
B. Lymphoma
C. Multiple mieloma
D. Osteosarcoma
E. Sciatica

Answer: B. The patient's subacute time course of back pain and worrisome finding of weight loss suggest a malignancy. Primary and metastatic bone neoplasms can cause back pain from tumor infiltration into the bone. Primary bone tumors, such as multiple myeloma, chordoma, Ewing's sarcoma, and osteosarcoma, are 25 times less frequent than metastatic disease. Of the neoplasms, breast, lung, prostate, thyroid, lymphoma, and kidney are the most likely to metastasize to bone.

47.2. Which one of the following indicates a benign presentation of back pain?

A. Low back pain and fever
B. Low back pain and saddle anesthesia
C. Low back pain in a 6-year-old child
D. Low back pain with a negative sitting but a positive supine straight leg raise (SLR) test
E. Low back pain with post-void residual of 500 mL

Answer: D. A positive supine SLR test but a negative sitting SLR test suggests a nonphysiologic cause for the pain. Low back pain and fever suggest an epidural abscess or spondylitis. Saddle anesthesia and post-void residual greater than 100 mL are indicative of cauda equina syndrome (CES). Children complaining of back pain must be investigated. They may have spondylolysis with varying degrees of spondylolisthesis, Scheuermann's disease (kyphosis and osteochondritis of the vertebral end plates), infectious diseases, or neoplastic etiologies.

47.3. The adult spinal cord usually ends at which level?

A. L1 to L2
B. L3 to L4
C. L5 to S1
D. S2 to S3
E. Coccyx

Answer: A. The spinal cord ends at around L2 in adults, lower in children. Remember that between individuals, there may be significant anatomic variance.

47.4. A 55-year-old man complains of low back pain when walking downhill that is relieved with walking uphill. His neurovascular examination is unremarkable except for decreased bilateral Achilles reflexes. What is the appropriate management of this patient?

A. Lumbosacral radiographs
B. Magnetic resonance imaging (MRI)
C. Pain management and bed rest
D. Pain management and emergent surgical consultation
E. Pain management and surgical referral for pseudoclaudication

Answer: E. This patient presents with typical complaints of spinal stenosis. Patients with spinal stenosis should be managed conservatively with pain medications. In the absence of alarming red flag findings, these patients do not require laboratory or radiographic studies in the emergency department (ED). These patients may be candidates for surgery if they show any of the following conditions: progressive neurologic deficit, progressive reduction in ability to walk secondary to pseudoclaudication, evidence of cauda equina syndrome (CES), or intractable pain.

47.5. Which of the following statements regarding cauda equina syndrome (CES) is false?
- **A.** Hallmarks are saddle anesthesia and urinary retention
- **B.** Is often caused by a central disk herniation
- **C.** Is most often associated with a post-void urinary residual of 75 mL or less
- **D.** Requires emergency surgical decompression
- **E.** Usually compresses bilateral nerve roots

Answer: C. The most consistent examination finding in CES is urinary retention. With a high sensitivity of 90%, the patient is unlikely to have this disease process if his or her post-void residual urine volume is less than 100 to 200 mL. Saddle anesthesia (sensory deficit over the buttocks, upper posterior thighs, and perineal area) is frequently an associated finding, with a sensitivity of 75%. In 60% to 80% of cases, the rectal examination reveals a decreased sphincter tone.

47.6. A 42-year-old man presents to the emergency department (ED) with a 12-day history of low back pain after an episode of heavy lifting at work. He reports bilateral low back pain at the level of the iliac crests. He denies sensory or motor symptoms. He also denies bowel or bladder dysfunction. His neurologic examination is normal. For this patient, which are the most important treatments and recommendations?
- **A.** Lumbar MRI
- **B.** Lumbar MRI, complete blood count (CBC), and erythrocyte sedimentation rate (ESR)
- **C.** Obtaining lumbar radiographs with anteroposterior, lateral, and oblique views
- **D.** Placement on strict bed rest for 4 weeks
- **E.** Treatment with symptomatic medication and return to light activity

Answer: E. The patient most likely suffers from idiopathic low back pain. This is also commonly called *acute lumbosacral strain.* Most patients with this injury should not be placed on bed rest and should be allowed to return to normal activity, possibly with some restrictions. The patient has a relatively short history of low back pain with clear onset around an episode of lifting. Given a lack of concerning historical or examination findings, the patient does not require imaging at this time. Blood work would not be of help in evaluating the patient, because he lacks history or examination findings consistent with spinal infection.

47.7. A 35-year-old woman presents with a 3-day history of severe right lower extremity pain associated with mild low back pain. Her neurologic examination is normal except for a positive straight leg raise (SLR) test on the right and a negative cross straight leg raise (CSLR) test on the left. What is the most likely source of this patient's symptoms?
- **A.** Acute lumbosacral strain
- **B.** Ankylosing spondylitis
- **C.** Lumbar disk herniation with radiculopathy
- **D.** Spinal epidural abscess
- **E.** Spinal malignancy

Answer: C. Patients with herniated lumbar disks often present with radicular leg pain that overshadows the complaint of back pain. It is very common for a patient with lumbar radiculopathy to have no clear motor or sensory deficit but have exacerbation of leg pain with SLR testing. The SLR has high sensitivity but low specificity. In contrast, the CSLR test has high specificity but low sensitivity. Given this, it is common for the patient with lumbar disk herniation to have a positive SLR but negative CSLR. The reverse is very uncommon. Diagnoses (such as, spinal epidural abscess and spinal malignancy) usually present with prominent low back pain that is more significant than extremity pain.

47.8. A 68-year-old man presents with a 5-week history of worsening low back pain. He reports mostly midline spinal pain with occasional radiation into both lower extremities. Two weeks before the onset of his pain, he was discharged from the hospital after an inpatient stay for pneumonia. On examination, he has intact lower extremity motor and sensory function but tenderness to percussion over the lumbar spine. Initial evaluation of the patient is most likely to reveal which of the following?
- **A.** Lumbar computed tomography (CT) showing degenerative spondylolisthesis at L4 to L5
- **B.** Lumbar magnetic resonance imaging (MRI) showing unilateral L4 to L5 disk herniation
- **C.** Lumbar MRI showing very large central disk herniation at L4 to L5 with compression of the cauda equina
- **D.** White blood cell (WBC) count of 9000 and erythrocyte sedimentation rate (ESR) of 58
- **E.** WBC count of 22,000 and ESR of 4

Answer: D. The patient's history is suspicious for spinal epidural abscess. He is at higher risk because of his age and recent infection. In addition, the patient has tenderness with percussion of his spine. Patients with epidural abscess usually have an ESR elevated above 20 mm/hr. However, it is not uncommon for them to have a normal or only mildly elevated WBC count. It would be uncommon for the patient to have an elevated WBC count but normal ESR. Lumbar disk herniation is rarely associated with spinal tenderness to percussion. A large central disk herniation with bilateral nerve root compression would likely present with lower extremity symptoms. Degenerative spondylolisthesis at L4 to L5 would likely be an asymptomatic problem.

47.9. A 63-year-old man presents with a 9-month history of progressive low back pain with ambulation. He reports significant pain in his buttocks and posterior thighs when he walks distances greater than 25 meters. He says the pain is partially relieved when he flexes forward and completely relieved by recumbency. He reports the pain is not relieved if he stops walking but remains standing. On neurologic examination, he has intact lower extremity strength but diminished Achilles reflexes bilaterally. Other likely findings include which of the following?
- **A.** Diminished posterior tibial and dorsalis pedis pulses
- **B.** Lumbar magnetic resonance imaging (MRI) revealing right L5 to S1 disk herniation
- **C.** Lumbar MRI revealing spinal stenosis at L4 to L5 and L5 to S1
- **D.** Normal lumbar MRI
- **E.** Thoracic MRI revealing significant T5 to T6 disk herniation with spinal cord compression

Answer: C. The patient presents with classic findings of spinal stenosis and neurogenic claudication or "pseudoclaudication," including relief with flexing forward and recumbency. Persistence of pain with standing despite having stopped ambulating is also indicative of neurogenic claudication, as are diminished Achilles reflexes. Diminished pulses are indicative of vascular claudication. Pain from vascular claudication is generally relieved if a patient stops walking but remains standing. Unilateral disk herniation does not usually present with bilateral lower extremity symptoms. Spinal cord compression from T5 to T6 disk herniation would cause myelopathy and generally present with gait unsteadiness and hyperreflexia but not pain.

CHAPTER 48

Pelvic Trauma

Michael C. Bond | Michael K. Abraham

PERSPECTIVE

Background

Patients with traumatic pelvic ring injury are immensely challenging for the emergency care provider. Pelvic ring fractures present significant risk for exsanguinating pelvic hemorrhage because the extreme magnitude of force required to disrupt the pelvic ring frequently causes severe injuries to other organs.[1] Prompt stabilization of pelvic fractures, rapid identification of other major injuries and sites of blood loss, and the coordination of definitive angiographic and surgical treatments are the necessary steps to help avoid the development of hemorrhagic shock.

Epidemiology

The majority of high-energy pelvic ring injuries are caused by motor vehicle collisions (MVCs), motorcycle crashes, pedestrians being struck by motor vehicles, and falls from height. Mortality of patients with pelvic fracture ranges to over 20%; in studies of large cohorts of trauma patients, the presence of pelvic fracture has been consistently shown to be an independent risk factor for death.[1] Patients with pelvic fractures who present with shock on arrival to the hospital have mortality rates of up to 50%. Increased age, the presence of shock at the time of arrival, presence of multisystem injuries, and the need for transfusion increase the risk of death.

Despite advances in motor vehicle safety design, MVCs continue to be a major cause of pelvic fracture, with lateral impact collisions remaining the most prevalent mechanism. The widespread use of front impact airbags has had little protective effect on these lateral collisions. However, side-impact airbags have been shown to reduce the risk of death in lateral impact MVC by 30% to 40%. Current research suggests that side impact airbags reduce the risk of head injuries by 30%, but they have minimal protective effect on thoracic or pelvic injuries.[2] Newer technology knee bolster airbags are claimed to reduce the risk of knee-thigh-hip injuries; however, there is not enough evidence to date to know whether they are effective or not.[3,4]

Anatomy

Detailed descriptions of pelvic anatomy can be found in standard anatomy texts. This section focuses on the relevant anatomy essential to understanding pelvic injuries.

Bony and Ligamentous Anatomy

The pelvic ring is made up of right and left innominate bones and the sacrum. The innominate bones consist of the pubis, ischium, and ilium (Fig. 48.1). The bony pelvis provides protection for its visceral contents, serves as attachment points for muscles, and transmits weight from the trunk to the lower limbs. The main weight-bearing forces are transmitted through the posterior wall of the pelvis, called the *posterior arch,* which is composed of thick bone and ligaments. The rich network of major arteries, veins, and nerves that course in front of the posterior arch can be injured concomitantly with forces responsible for bony injuries.

Knowledge of the ligamentous attachments of the pelvic ring is crucial to understanding how stability is maintained or disrupted in pelvic injuries. Pelvic stability is maintained by ligaments as well as the muscles and fascia that make up the pelvic floor. Anteriorly, the symphysis pubis provides the major mechanical stability. Posteriorly, a composite of strong ligaments—the sacrospinous, sacrotuberous, iliolumbar, and anterior and posterior sacroiliac ligaments—maintains the integrity of the posterior arch (Fig. 48.2). These ligaments are the primary stabilizing force of the posterior pelvis. Disruption of these ligaments is the primary cause of a mechanically unstable pelvic fracture.

Vascular Anatomy

Most of the blood supply to the pelvis comes from the left and right internal iliac arteries. The internal iliac arteries course at the level of the sacroiliac joints. The various arteries that derive from the internal iliac arteries initially run in close proximity to the posterior pelvic arch and eventually anastomose extensively with one another, forming a rich collateral network (Fig. 48.3). The superior gluteal artery is the largest branch and is commonly injured in fractures of the posterior pelvic arch. The obturator and internal pudendal branches are often injured in fractures involving the pubic rami.

The venous system also has many collateral branches but does not have valves, which allows bidirectional flow. The veins are arranged in a plexus that adheres closely to the pelvic walls. Because these veins are thin-walled, they do not have the ability to constrict in response to damage. This anatomic arrangement of the arteries and veins accounts for the hemorrhage often associated with pelvic fractures.

Neurologic Anatomy

The cauda equina travels through the sacral spinal canal and exits through the sacral neural foramina to form the lumbar and sacral plexus. Injury to the posterior bony pelvis and sacrum can result in neurologic deficits in the lower extremities and autonomic dysfunction involving the bowel, bladder, and genitalia.

Pathophysiology and Key Patterns of Pelvic Fracture

Numerous classification schemes for pelvic fractures have been created. Two widely used schemes for pelvic injury are presented here. The Tile classification stresses the biomechanical stability of the pelvic ring (Box 48.1). The Young-Burgess classification emphasizes the mechanisms of injury (Box 48.2). From a practical viewpoint, it is highly useful to consider both of these elements in the assessment of a pelvic ring fracture. Both classification systems delineate numerous subtypes of injuries, the interobserver reliability of which has been questioned. For the emergency clinician,

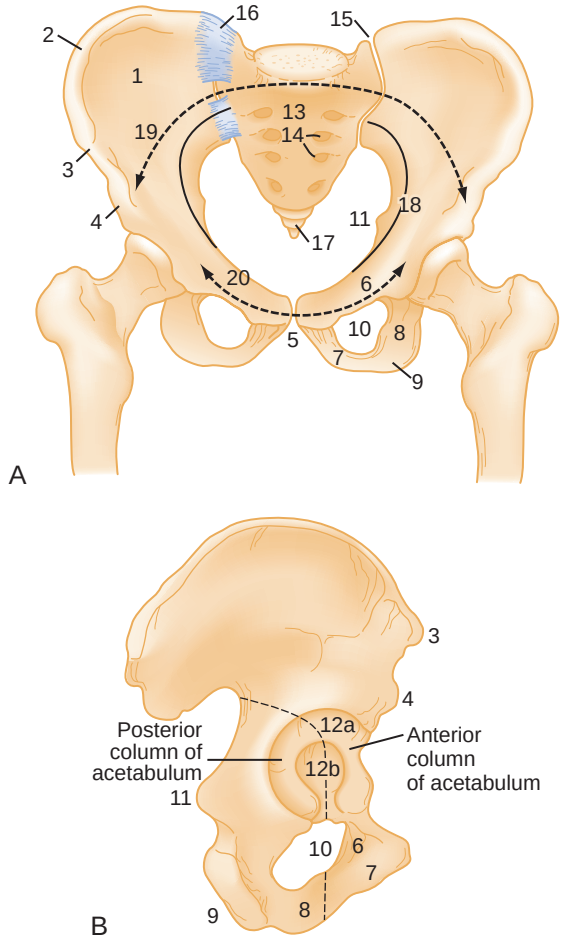

Fig. 48.1. Bony pelvic anatomy. **A,** Anterior view of pelvis. **B,** Lateral view of right innominate bone. *1,* Iliac fossa; *2,* iliac crest; *3,* anterior superior iliac spine; *4,* anterior inferior iliac spine; *5,* symphysis pubis; *6,* superior ramus of pubis; *7,* inferior ramus of pubis; *8,* ramus of ischium; *9,* ischial tuberosity; *10,* obturator foramen; *11,* ischial spine; *12,* acetabulum (*12a,* articular surface; *12b,* fossa); *13,* sacrum; *14,* anterior sacral foramina; *15,* sacroiliac joint; *16,* anterior sacroiliac ligament; *17,* coccyx; *18,* arcuate line; *19,* posterior or femorosacral arch, through which main weight-bearing forces are transmitted; *20,* anterior arch.

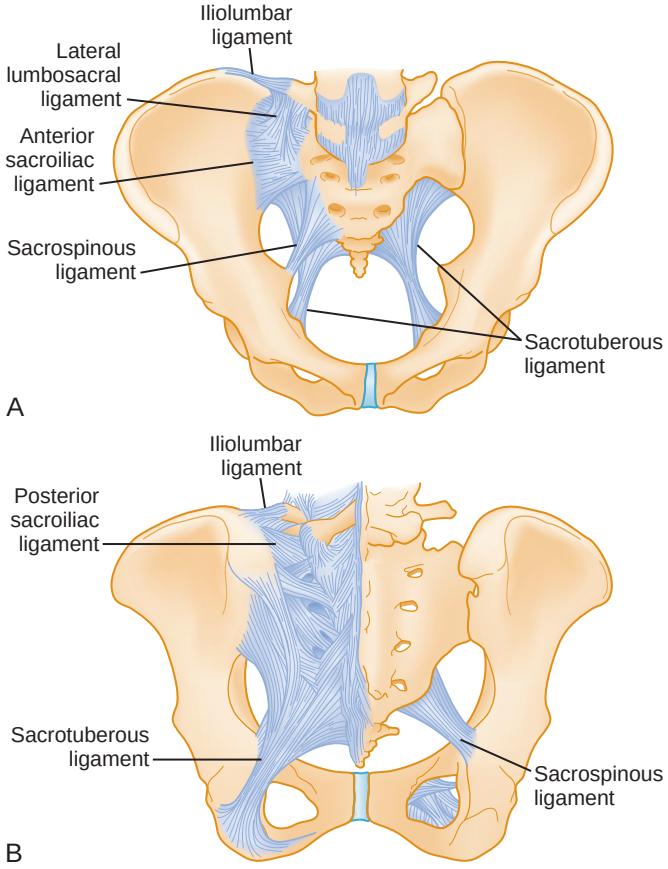

Fig. 48.2. **A,** Anteroposterior view of the pelvis indicates that the sacrospinous ligament is a triangular strong ligament lying anterior to the sacrotuberous ligament, which is a strong broad band extending from the lateral portion of the dorsum of the sacrum to the ischial tuberosity. **B,** The major posterior stabilizing structures of the pelvic ring, that is, the posterior tension band of the pelvis, include the iliolumbar ligament, posterior sacroiliac ligaments, sacrospinous ligaments, and sacrotuberous ligaments.

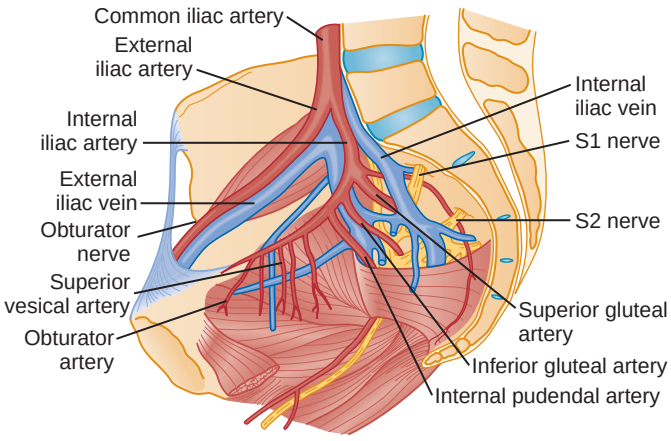

Fig. 48.3. The internal iliac plexus of arteries and veins. (From Tile M: Fractures of the pelvis and acetabulum, ed 3, Philadelphia, 2003, Lippincott, Williams & Wilkins.)

a good understanding of the principles of pelvic stability and the mechanism of injury is far more important than a detailed knowledge of injury subtypes. The broad distinction between mechanically stable and unstable fractures of the pelvic ring is clinically useful in assessing patients, because it has been demonstrated consistently that those with unstable injuries have a higher mortality rate and greater transfusion requirements.[5]

Stable Injuries (Tile Type A)

Fractures of individual bones without involvement of the pelvic ring represent one-third of all pelvic fractures. Most stable pelvic fractures heal well with rest and analgesia (Fig. 48.4).

Undisplaced or Minimally Displaced Fractures of the Pelvic Ring. The normal pelvis is not totally rigid because of the slight mobility at the sacroiliac joints and symphysis pubis and the inherent elasticity of bone. It is possible to sustain a single break in the ring but the pelvis is not totally forgiving, so identification of a single break in the ring should prompt a thorough search for a second disruption.

The most common pelvic ring fracture is an isolated fracture of the superior or inferior pubic ramus. These fractures are stable. They are common in elderly people after a fall and should be considered in the evaluation of an acutely painful hip. Fracture of the body of the ischium is a rare injury that can result from a fall into the sitting position. Fractures around the obturator foramen are treated conservatively with bed rest, analgesia, and early mobilization.

BOX 48.1

Tile's Classification of Pelvic Fractures

Type A: Stable, posterior arch intact; includes avulsion fractures, isolated iliac wing fracture, pubic rami fractures, minimally displaced ring fracture, and transverse fractures of the sacrum or coccyx.

Type B: Partially stable, incomplete disruption of the posterior arch; includes anteroposterior injuries ("open-book" fracture) and lateral compression injuries; may be unilateral or bilateral; these injuries are rotationally unstable but vertically stable.

Type C: Unstable, complete disruption of the posterior arch; includes iliac, sacroiliac, and vertical sacral injuries that result from vertical shearing forces; may be unilateral or bilateral. These injuries are both rotationally and vertically unstable.

BOX 48.2

Young-Burgess Classification of Pelvic Fractures

ANTEROPOSTERIOR COMPRESSION

I. Symphysis diastasis <2.5 cm
II. Symphysis diastasis >2.5 cm, sacrospinous and anterior sacroiliac ligament disruption, results in rotational instability
III. Symphysis diastasis >2.5 cm, with complete disruption of the anterior and posterior sacroiliac ligament, results in complete rotational and vertical instability

LATERAL COMPRESSION

I. Sacral crush injury on ipsilateral side
II. Sacral crush injury with disruption of posterior sacroiliac ligaments; iliac wing fracture may be present (crescent fracture); rotationally unstable
III. Severe internal rotation of ipsilateral hemipelvis with external rotation of contralateral side ("windswept" pelvis), rotationally unstable

VERTICAL SHEAR

Vertical displacement of symphysis and sacroiliac joints resulting in complete rotational and vertical instability

COMBINED MECHANISMS

Any combination of the aforementioned mechanisms

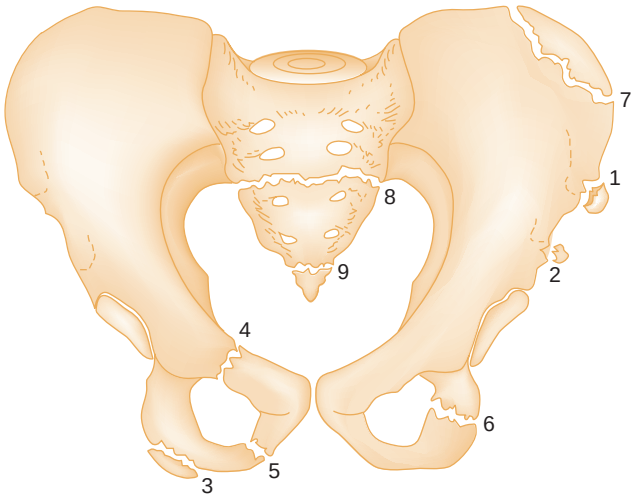

Fig. 48.4. Fractures of individual pelvic bones. *1,* Avulsion of anterosuperior iliac spine; *2,* avulsion of anteroinferior iliac spine; *3,* avulsion of ischial tuberosity; *4,* fracture of superior pubic ramus; *5,* fracture of inferior pubic ramus; *6,* fracture of ischial ramus; *7,* fracture of iliac wing; *8,* transverse fracture of sacrum; *9,* fracture of coccyx. (From Tile M: Fractures of the pelvis and acetabulum, ed 3, Philadelphia, 2003, Lippincott, Williams & Wilkins.)

Fracture of the superior and inferior pubic rami on the same side is a commonly encountered injury after a fall or MVC. These are generally stable fractures and are treated conservatively. However, the presence of significant displacement at the fracture site indicates a second disruption elsewhere in the pelvic ring. Alternatively, fractures of both rami on the same side can be associated with an unrecognized impaction fracture of the posterior pelvis.

If the patient with a ramus fracture reports posterior pelvic pain and if plain radiographs do not reveal a posterior injury, further investigations could reveal posterior fractures, such as occult bony or ligamentous injury of the acetabulum or sacroiliac joint. Up to 95% of elderly patients with isolated ramus fractures on plain films will have a sacral fracture detected by magnetic resonance imaging (MRI). This finding does not alter treatment, however, and an MRI is not indicated for most elderly patients with ramus fractures. Among the mechanically stable pelvic fractures, the lateral compression type I fracture described by Young and Burgess (Fig. 48.5), characterized by a pubic ramus fracture with ipsilateral sacral compression, bears special consideration. This fracture has a mortality rate of nearly 10% and a high incidence of associated injuries.[5]

A *straddle fracture* is a four-pillar injury involving fractures of both pubic rami on both sides of the symphysis pubis, creating a "butterfly segment" (Fig. 48.6) and is produced by a direct blow with a straddle mechanism. Although these fractures can occur without posterior arch disruption, four-pillar injuries are commonly associated with lateral compression or vertical shear forces, which can cause concomitant injuries to the posterior pelvic arch. Computed tomography (CT) of the pelvis is required in four-pillar injuries to precisely detect and classify the posterior arch injury and to plan orthopedic treatment. The genitourinary tract is often injured with this type of pelvic fracture and should be evaluated carefully (see Fig. 48.6).

An isolated fracture of the iliac wing was first described by Duverney in 1751 and now bears his name. It is caused by direct trauma to the iliac crest, usually by lateral compression forces. Although there is usually minimal displacement because of the arrangement of the muscle attachments of the abdominal wall, orthopedic consultation is recommended. Extension of the fracture into the acetabulum alters treatment and prognosis. Severely displaced fractures of the iliac wing require open reduction and internal fixation (ORIF). A high incidence of major associated non-pelvic injuries has been reported among patients with isolated iliac wing fracture.

Transverse Fractures of the Sacrum. Transverse fractures of the sacrum do not compromise the pelvic ring. Transverse fractures at or below the S4 level are unlikely to be accompanied by neurologic injury. An upper sacral transverse fracture is the result of a flexion injury, such as being struck on the lower back by a heavy load while bending over, or by direct forces to the sacrum, as in a fall from a great height. The patient often reports pain in the buttocks, perirectal area, and posterior thighs. There may be local pain, swelling, and bruising overlying the sacrum. Gentle bimanual rectal examination might elicit severe pain and abnormal motion and allow detection of a palpable hematoma. Radiographically, the fracture may be difficult to visualize on anteroposterior and lateral projections, in which case a pelvic outlet view may be helpful. Simple transverse fractures at or below

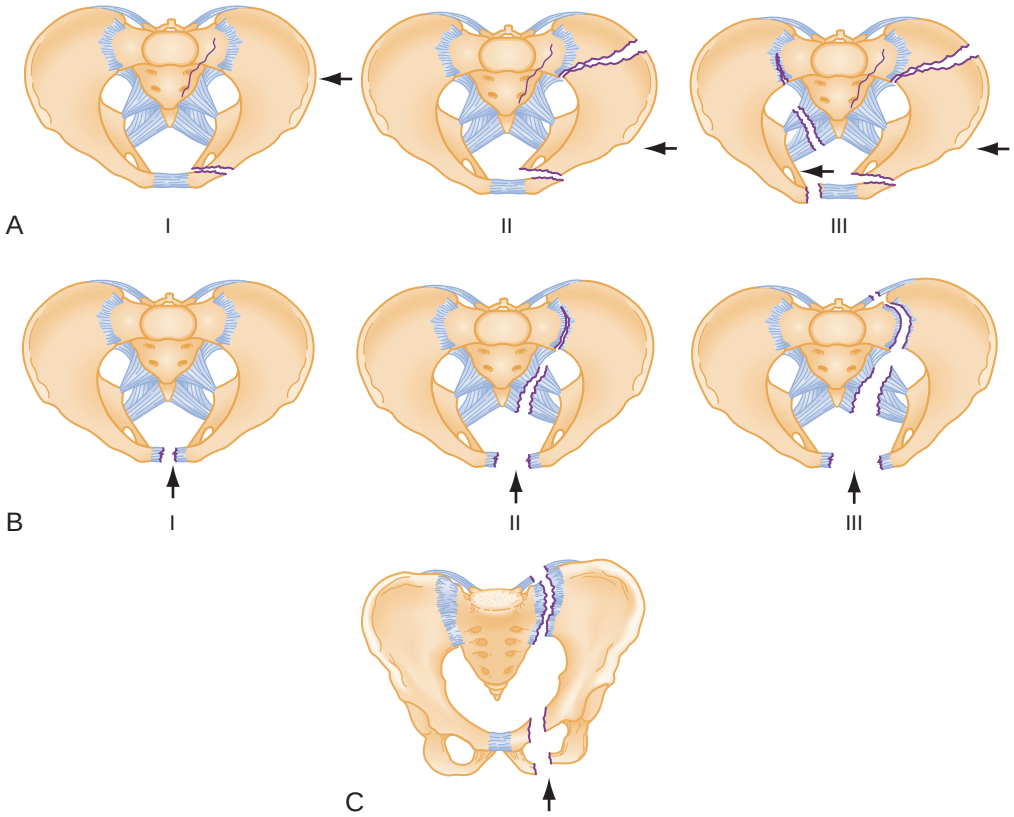

Fig. 48.5. Young-Burgess classification. **A,** Lateral compression. *Type I,* A posteriorly directed force causing a sacral crushing injury and horizontal pubic ramus fractures ipsilaterally. *Type II,* A more anteriorly directed force causing horizontal pubic ramus fractures with an anterior sacral crushing injury and either disruption of the posterior sacroiliac joints or fractures through the iliac wing. *Type III,* An anteriorly directed force that is continued, causing external rotation of the contralateral side; the sacroiliac joint is opened posteriorly, and the sacrotuberous and spinous ligaments are disrupted. **B,** Anteroposterior compression. *Type I,* Symphysis disrupted but with intact posterior ligamentous structures. *Type II,* Continuation of a type I fracture with disruption of the sacrospinous and potentially the sacrotuberous ligaments and an anterior sacroiliac joint opening. *Type III,* Continuation force disrupts the sacroiliac ligaments. **C,** Vertical shear. Vertical fractures in the rami and disruption of all posterior ligaments. This injury is equivalent to an anteroposterior type III or a completely unstable and rotationally unstable fracture. *Arrow indicates the direction of force.* (Redrawn from Young JWR, Burgess AR: Radiologic management of pelvic ring fractures, Baltimore, 1987, Urban & Schwarzenberg. Browner BD: Skeletal trauma: basic science, management, and reconstruction, ed 3, St Louis, 2003, Saunders/Elsevier.)

S4 are treated conservatively. Above S4, neurologic injuries are common, necessitating careful clinical evaluation and surgery when neurologic compromise is present.

Avulsion Fractures. These usually occur during athletic activities and are the result of a sudden, forceful muscular contraction or excessive muscle stretch. They are seen more commonly in older children and teenagers before the corresponding physis closes; adults can have the same symptoms from ligamentous injury at these sites, which would not be evident on a plain film or CT scan. The sites of ligamentous attachments on the pelvis are highlighted in Figure 48.7.[6]

The ischial tuberosity can be avulsed during strenuous contraction of the hamstrings. The result is pain on palpation of the involved tuberosity, which is increased by flexion of the hip with the knee in extension (hamstrings stretched), but not with the knee flexed (hamstrings relaxed). Ischial tuberosity avulsion can also cause chronic discomfort without a history of acute injury.

A portion of the iliac crest epiphysis can be avulsed by contraction of the abdominal muscles. Similarly, the anterior superior iliac spine can be avulsed by forcible contraction of the sartorius muscle. Forceful contraction of the rectus femoris (as in kicking a ball) can result in the less common injury of anterior inferior iliac spine avulsion; however, this radiographic finding should be distinguished from a normal variant, the os acetabuli, which is a secondary center of ossification at the superolateral margin of the acetabulum.[7] The physical examination is similar in these injuries and reveals local pain, swelling, and limitation in the motion of the hip.

Conservative treatment, including analgesia and bed rest in a position that avoids tension on the affected muscles, is generally all that is required for avulsion injuries; surgical treatment is rarely necessary. Orthopedic consultation is advised for follow-up care.

Stress Fractures. Stress fractures can occur with vigorous athletic or military training and in the last trimester of pregnancy. The diagnosis of stress fractures is based on the clinical evaluation and can be confirmed, if required, by radionuclide bone scan, although MRI has been shown to be a superior method for detecting these injuries.[8]

Pathologic and Insufficiency Fractures. Pathologic fracture related to neoplasm, Paget's disease, or dietary osteomalacia should be included in the differential diagnosis of any pelvic fracture. Radiation therapy increases the risk of pelvic fracture.

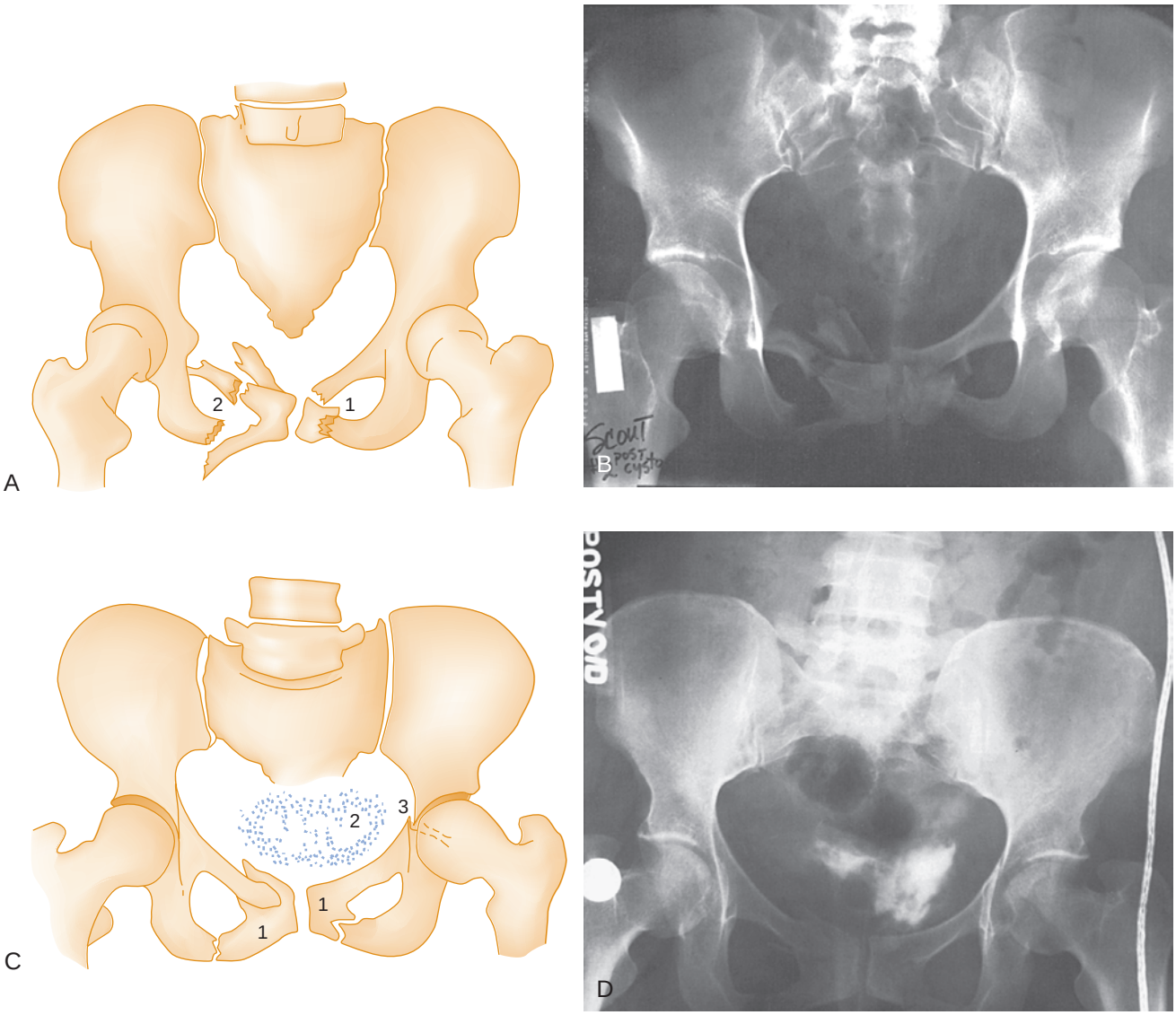

Fig. 48.6. Four-pillar (straddle) fracture. **A** and **B,** Partial inlet view of pelvis shows straddle fracture. *1* and *2,* Marked comminution of left pubic bone and comminuted right superior and inferior rami. This partial inlet projection shows displacement of fragments into the pelvis, which is not evident on the anteroposterior view of the same patient in **C** and **D.** A true inlet projection and computed tomography (CT) scan (not available) would provide further information about the posterior arch, which is injured frequently in straddle fractures and should be imaged (see text). **C** and **D,** Post-void cystogram of the same patient with anteroposterior pelvis. *1,* Fractures of pubic rami are seen again but do not appear to be as displaced compared with **A** and **B**, because this projection is an anteroposterior view. Even minor degrees of angulation of the x-ray beam can change the appearance of pelvic fracture displacement. *2,* Extravascular contrast indicates bladder rupture. *3,* Left acetabular fracture is seen in this projection but not in **B** because of the difference in projection. The acetabular fracture disrupts the ilioischial line (see also Fig. 48.13) and is a posterior column fracture.

Partially Stable and Unstable Injuries (Tile Types B and C)

Partially stable and unstable injuries are caused by high-energy impact. The forces applied to the pelvis determine the types of injuries that occur. Broadly, forces can be applied to the pelvic ring in anteroposterior, lateral, or vertical directions, resulting in characteristic injury patterns; combinations of forces result in more complex injuries. The terms *unstable fracture* (referring to mechanical stability) and *unstable patient* (referring to hemodynamic status) should not be confused, although a cause-and-effect relationship often exists.

Anteroposterior Compression. Severe anteroposterior compression forces cause disruption at or near the symphysis pubis. Symphysis widening of less than 2.5 cm is considered a stable injury (the symphysis is normally ≤0.5 cm in an adult but can increase 2 to 3 mm during or after pregnancy); however, with continued force in the anteroposterior direction, the hemipelvis externally rotates, tearing the sacrospinous, sacrotuberous, and anterior sacroiliac ligaments. The sacroiliac joint opens and hinges on the intact posterior sacroiliac ligaments. The resulting injury is aptly described as an "open-book" fracture. The pelvis is rotationally unstable in the horizontal plane, but the intact posterior sacroiliac ligaments maintain vertical stability.

When diastasis of the pubic symphysis is greater than 2.5 cm on an anteroposterior radiograph, the posterior injury is usually seen as widening of the sacroiliac joint and occasionally as a sacral or iliac fracture (see Fig. 48.5). If the injurious forces continue,

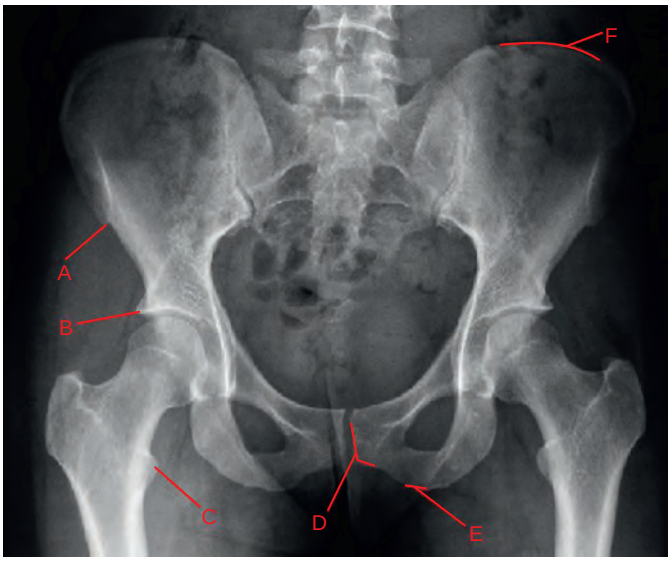

Fig. 48.7. Site of tendon insertion for muscles originating from the pelvis. *A,* Sartorius (origin on the anterior superior iliac spine). *B,* Rectus femoris (origin on the anterior inferior iliac spine). *C,* Iliopsoas (inserts on lesser trochanter). *D,* Adductors and gracilis (origin on body of pubis or inferior pubic rami). *E,* Hamstrings (origin on the ischial tuberosity). *F,* Abdominal muscles (origin on the iliac crest).

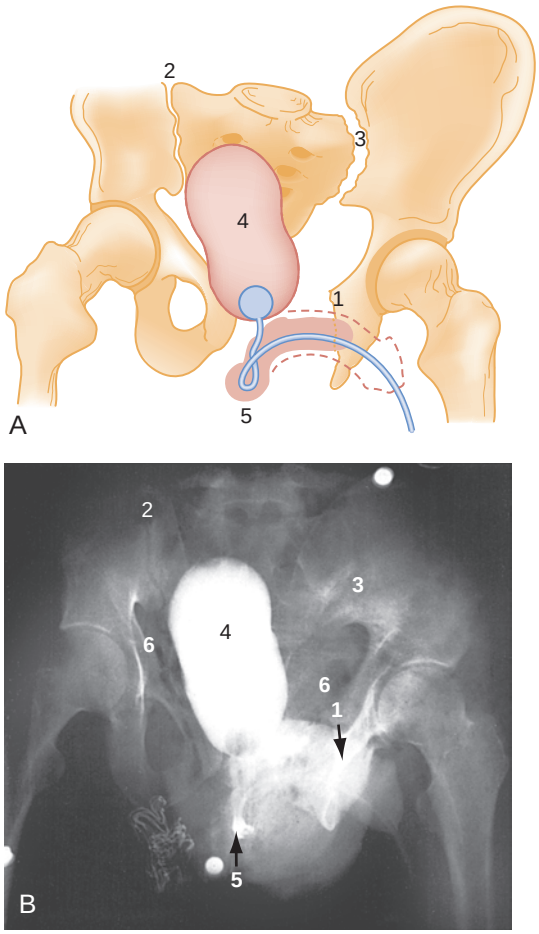

Fig. 48.8. Interpretive drawing **(A)** and radiograph **(B).** Severe unilateral "open-book" fracture from anteroposterior compression forces, which is also open (compound). *1,* Separated pubic symphysis with asymmetry of hemipelvis; *2,* normal sacroiliac joint; *3,* separated sacroiliac joint; *4,* cystogram with displacement and abnormally elongated shape of bladder caused by retroperitoneal hematoma associated with separated left sacroiliac joint, which has pushed the bladder to the right; *5,* extravasated contrast into perineum from urethral rupture; *6,* soft tissue air indicating an open fracture.

they can separate the hemipelvis, and the sacroiliac joint is seen as widely separated on a plain anteroposterior radiograph (Fig. 48.8) and on CT. The anteroposterior radiograph can be misleading in suggesting a pure open-book fracture in cases with symphysis disruptions greater than 2.5 cm. These cases commonly are associated with vertical shear fractures, so careful clinical and CT assessment for vertical instability is essential to classify the fracture properly and plan treatment accordingly.

These same forces can also injure the neurologic and vascular structures at the posterior arch; the overall volume of the pelvis is increased in the open-book injury, facilitating the expansion of a retroperitoneal hematoma. Several studies have demonstrated that patients with severe grades of anteroposterior compression injuries have the highest crystalloid and blood requirements. In addition, these injuries can be associated with non-pelvic injuries that contribute to significant blood loss.

Lateral Compression. Lateral compression of the pelvic ring results in varying degrees of internal rotation of the affected hemipelvis. Initially, this causes buckling of the sacrum and horizontal pubic rami fractures. Rami fractures can occur on the ipsilateral or contralateral side, the latter being referred to as a "bucket-handle" fracture (Fig. 48.9).

As the magnitude of force increases, the symphysis can be disrupted, causing overlapping of the pubic bones. On plain radiographs, evidence of injury to the sacrum might be subtle; overlapping pubic bones with any significant displacement should prompt a search for a posterior injury.

Similar to the anteroposterior injury, as disruption of the posterior ligaments increases, so does rotational instability. In the most severe lateral compression trauma, the ipsilateral pelvis rotates internally to such a degree that the contralateral pelvis might externally rotate. This is referred to as a "windswept" pelvis. Lateral compressive injuries result in varying degrees of horizontal rotational instability; however, the vertical stability of the pelvis is maintained (see Fig. 48.9).

Because internal rotation causes the pelvic volume to decrease, lateral compressive injuries are generally associated with lesser degrees of blood loss than are anteroposterior injuries.

Vertical Shear. Vertical shear injuries are the most unstable injuries affecting the pelvic ring and are associated with violent axial loading of the hemipelvis (eg, a fall from a height or "submarining" under a dashboard) that causes fractures in vertical planes. Anteriorly, the symphysis and rami could be disrupted. Posteriorly, gross displacement and instability in the rotational and vertical planes may be present through the sacrum, the sacroiliac joint, or the ilium such that the hemipelvis is displaced posteriorly and cephalad (see Fig. 48.10).

Avulsion of the ischial spine, the lower lateral lip of the sacrum, and the transverse process of the fifth lumbar vertebra (sites of insertion of ligaments) (Fig. 48.10 and Box 48.3) are important clues to the presence of vertical shear fractures. The vertical shearing forces transmitted through the bony pelvis are also transmitted through the rich vascular network and nerve plexus directly adjacent to the bone. This accounts for the major hemorrhage and neurologic injuries associated with vertical shear fractures.

Vertical Sacral Fractures. A crucial distinction in considering sacral fractures is that transverse fractures do not involve the pelvic ring, but vertical fractures do. Vertical sacral fractures are caused by high-energy injuries and were classified by Denis into three groups according to whether the fracture line extends (1)

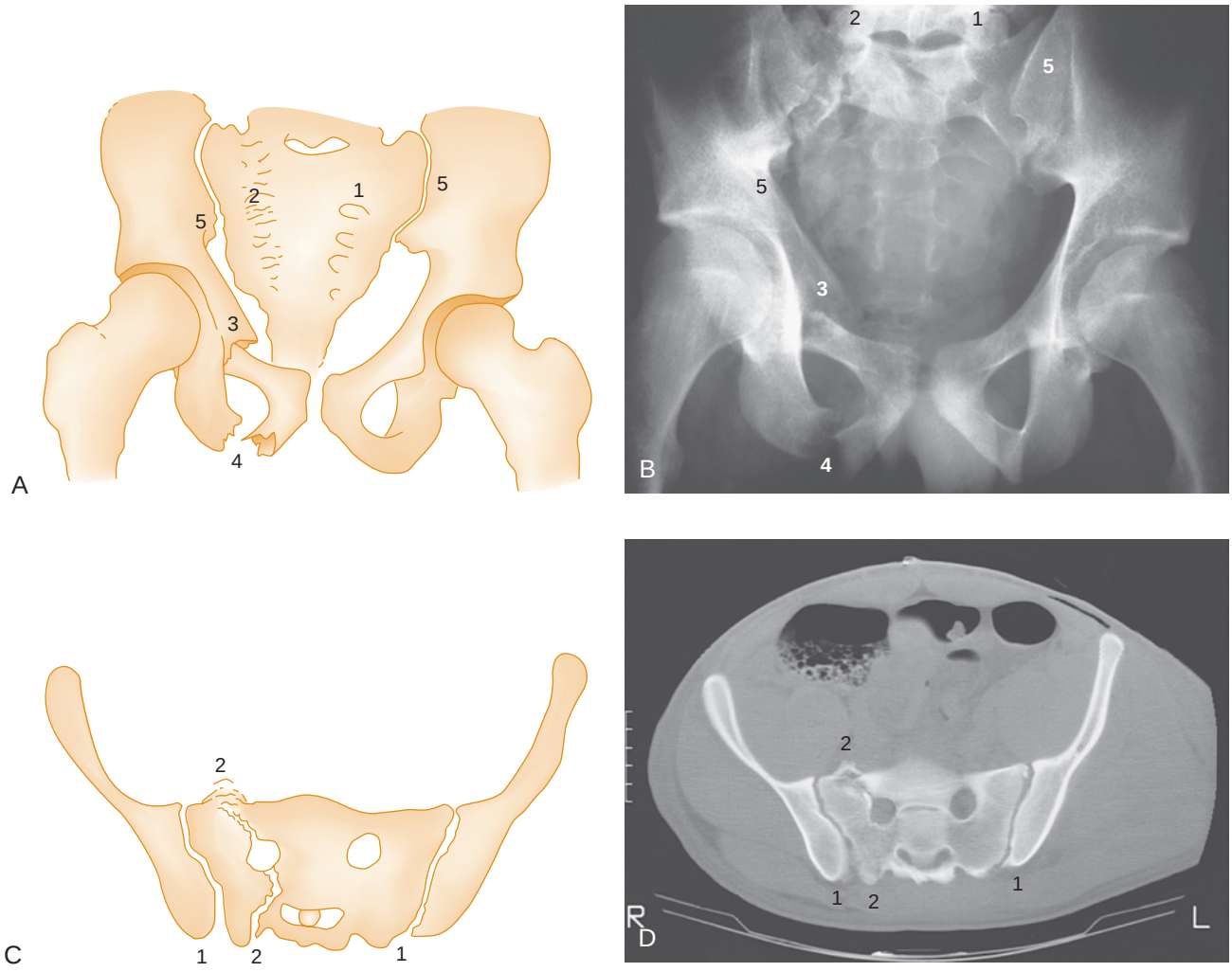

Fig. 48.9. Lateral compression fracture. **A** and **B,** Anteroposterior view of the pelvis. *1,* Normal sacral foraminal lines on the left; *2,* sacral foraminal lines on the right are indistinct and do not mirror the normal side, indicating the subtle second break in the pelvic ring; *3* and *4,* fractures of the superior and inferior pubic rami are overriding and displaced, indicating the lateral compression forces (there must be a second break in the pelvic ring); *4,* the "bucket-handle" fracture; *5,* normal sacroiliac joints. **C** and **D,** Computed tomography (CT) scan of the same pelvis. *1,* Normal sacroiliac joints; *2,* compression fracture of the sacrum through the foramen corresponding to the loss of definition of the foraminal lines in **A** and **B.**

BOX 48.3

Radiographic Clues to Posterior Arch Fractures

Avulsion of L5 transverse process*
Avulsion of ischial spine*
Avulsion of lower lateral lip of the sacrum (sacrotuberous ligament)*
Displacement at the site of a pubic ramus fracture
Asymmetry or lack of definition of bone cortex at superior aspect of the sacral foramina

*Indicates mechanical instability.

laterally to the sacral foramina, (2) through the foramina, or (3) medially to the foramina, involving the central spinal canal (Fig. 48.11). The radiographic diagnosis of this fracture hinges on careful examination of the symmetric cortical lines that are normally present at the superior margins of the sacral foramina on the anteroposterior view. Disruption, distortion, or asymmetry of these lines is an important marker of sacral fractures.[7]

These injuries carry a high risk of neurologic complications: 6% when lateral to the foramina, 28% when through the foramina, and 58% when medial to the foramina. Neurologic dysfunction correlates to the nerve roots involved but can also manifest as bowel, bladder, or sexual dysfunction. Surgery is commonly performed for fractures associated with neurologic dysfunction, with the goals of bony fixation of the sacrum and decompression of the affected nerve roots.

Open Pelvic Fractures

An open pelvic fracture is present when there is direct communication between the fracture site and a skin, rectal, or vaginal wound. These are potentially lethal injuries, especially if not recognized early: hemorrhage accounts for early mortality, and infection, sepsis, acute respiratory distress syndrome, and multisystem organ failure are causes of delayed death. The majority of older case series reported mortality rates greater than 50%; rates reported from more recent studies are generally less than 30%. A 2015 study of more than 30,000 patients reported in-hospital mortality of 2.7%, but this rate doubled for patients ages 55 to 70

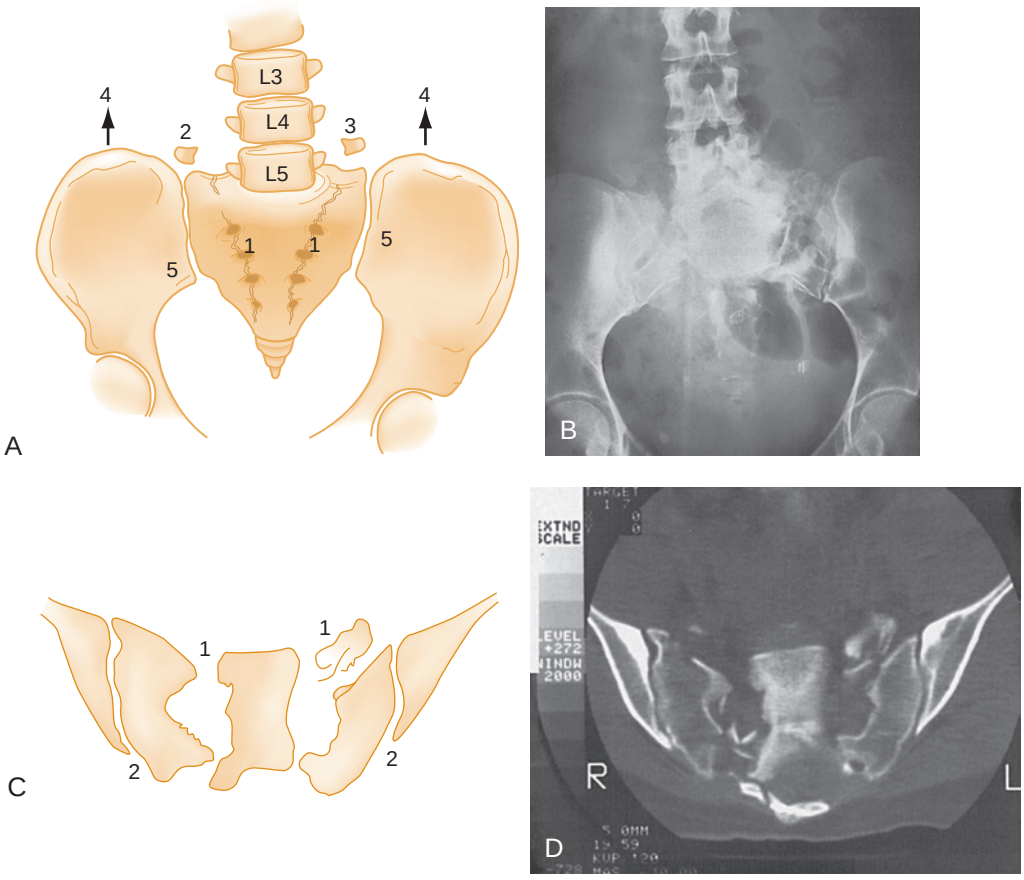

Fig. 48.10. **A** and **B,** Vertical shear fractures bilaterally. At first glance the pelvis appears normal because of the smooth, uninterrupted arcuate line, but careful interpretation reveals the extremely critical nature of the injuries. *1,* Fractures through the sacrum—note loss of definition and symmetry of sacral foramina, indicating vertical fractures through both sides of the sacrum (see computed tomography [CT] scan in **D**). *2,* Transverse process fragment from right L5 (iliolumbar ligament attachment) is pathognomonic for a vertical shear fracture through the right sacrum. *3,* Transverse process fragment from left L5, pathognomonic for a vertical shear fracture through the left sacrum. *4,* Both hemipelves are dislocated cephalad because of the double-ring fractures through each side of the sacrum. This dislocation explains why the L5 transverse processes appear so close to the iliac crests. (The body of L5 is obscured because of rotational dislocation of the central free sacral fragment posteriorly and because of technique.) *5,* Normal sacroiliac joints. **C** and **D,** CT scan of same pelvis. *1,* Bilateral comminuted fractures of sacrum with lateral displacement of both hemipelves; *2,* normal sacroiliac joints.

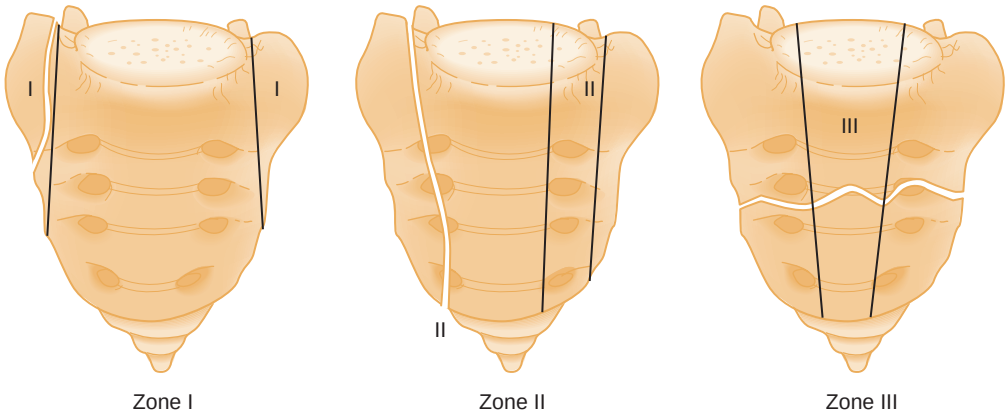

Fig. 48.11. The Denis classification of vertical sacral fracture. *Zone I* is lateral to the sacral foramina (known as the *sacral ala*). *Zone II* is transforaminal. *Zone III* is the central sacrum medial to the foramina.

years old and quadrupled for patients older than 70 years old.[9] Other predictors of mortality included injury severity, mental status, prolonged mechanical ventilation, or need for blood product administration.[9]

The skin over the posterior pelvis and gluteal area and perineum must be inspected carefully for wounds. Some fractures are open only by virtue of a bone spicule penetrating the vagina or rectum, which can be identified by careful digital rectal examination (DRE) and vaginal examination. Hemorrhage from a large open laceration should be treated with direct manual pressure or pressure dressing. Traditionally, pelvic fractures communicating with the rectum have mandated a diverting colostomy; however, a systematic review of the literature on this topic found no difference in infection rates between patients treated with or without colostomy.

Penetrating Pelvic Trauma

Because of the complex anatomy of the viscera, blood vessels, and nerves within the pelvis, penetrating trauma to this area presents a major diagnostic challenge. Overall mortality in this group of patients is about 10%, but the mortality rate of patients who present in shock is as high as 50%. Vascular injuries can involve the aorta; common iliac artery; and external, internal, and common iliac veins or a combination of vessels. Genitourinary structures and hollow viscera could be injured; fecal contamination from colorectal injury is a serious complication. The finding of blood on DRE is an important clue that a rectal injury has occurred. Emergent surgical consultation is recommended for all cases of penetrating pelvic trauma.

Associated Pelvic Injuries

Urologic Injury

The overall incidence of bladder or urethral disruption associated with any pelvic fracture is approximately 5%, with increased risk among those with severe pelvic injuries.[10] Because the urethra is far less exposed in women than in men, injury to the urethra in women with pelvic fracture is rare.

Patients with fractures of the anterior arch of the pelvis were at greatest risk for bladder injury. Diastasis of the symphysis more than 1 cm and fracture around the obturator ring with displacement more than 1 cm are associated with a tenfold and threefold increased risk of bladder rupture, respectively.

The presence of gross hematuria indicates injury of the lower urinary tract. Bladder rupture is diagnosed in about 25% of patients with gross hematuria and pelvic fracture.[10] Patients with blood at the urethral meatus in the context of pelvic fracture have an incidence of up to 90% of urethral injury, and indicate the need for a retrograde urethrogram followed by a cystogram (see Chapter 40). Gross hematuria is variably investigated with a combination of urethrography, intravenous pyelography, cystography, and CT. The sequence and types of examinations are individualized for each patient. Fracture of the inferomedial pubic ramus and widened symphyseal diastasis have both been shown to be predictive of a urethral injury. Retrograde urethrocystography done before CT of the pelvis might impair the ability of CT to detect extravasation of contrast, which would indicate active pelvic bleeding. Therefore, if CT is to be performed, it ideally is performed before retrograde urethrocystography.

Sexual dysfunction is a recognized complication of pelvic trauma, occurring in 44% of females and 50% of males.[11] Even in the absence of a urethral injury, sexual dysfunction in men can occur secondary to neurovascular disruption associated with the pelvic fracture.

Neurologic Injury

The risk of neurologic injury correlates with instability of the pelvic injury, with a reported incidence of neurologic dysfunction of 2%, 4%, and 14% in Tile type A, B, and C fractures, respectively. Up to 10% of patients with acetabular fractures experience neurologic dysfunction.[12] Neurologic injury occurs commonly in patients with vertical sacral fractures or transverse fractures above the S4 level. Up to 30% of patients with vertical fractures that involve the foramina have associated neurologic deficits. In patients with fractures medial to the foramina involving the spinal canal, almost two-thirds have neurologic deficits.

Pelvic injury can cause various plexopathies and radiculopathies, depending on the nerve root level at which the injury occurs (Table 48.1). In patients with sacral fractures, cauda equina syndrome may be fully or partially present. Hyperesthesia and subsequent anesthesia occur in a saddle-shaped distribution in the groin, as well as weakness of ankle plantar flexion, hamstrings, and gluteus muscles and decreased or absent ankle jerk. If the lower sacral roots are affected, the patient might experience neurogenic bladder with overflow incontinence, motor and sensory deficits in the lower extremities, anal sphincter dysfunction, or sexual dysfunction. Patients with neurologic deficits from sacral fractures require orthopedic or neurosurgical consultation.

Gynecologic Injury

Blood at the introitus may indicate a urethral injury, open pelvic fracture, or local laceration without communication with the bony pelvis. Delayed urologic or sexual dysfunction and complications with pregnancy are common after pelvic injury. Gynecologic consultation is recommended for any female who sustains an injury to the reproductive tract in association with a pelvic fracture and for all pregnant women who sustain a pelvic fracture of any kind.

Associated Non-Pelvic Injuries

The magnitude of force required to disrupt the pelvis commonly results in severe injuries to other organ systems. Among those patients who die as a result of pelvic fracture, it is rare that the fracture is an isolated injury.[13] Associated injuries in trauma patients with pelvic fracture can contribute more to the mortality risk than the pelvic injury itself.

Although patterns of non-pelvic injuries associated with certain patterns of pelvic fracture have been described, these findings have not been reproduced consistently in the literature. Severe injuries to the head, spine, thorax, aorta, and abdomen can occur in patients with both stable and unstable pelvic fractures,

TABLE 48.1

Neurologic Deficits of Pelvic Fractures as Expected by Nerve Root Level

NERVE ROOT	EXPECTED DEFICIT
L5	Weakness—anterior tibial compartment Sensory deficit—dorsum of foot and lateral calf
S1 and S2	Weakness—hip extension, knee flexion, and plantar flexion Sensory deficit—posterior aspect of the leg, sole and lateral foot, genitalia
S2 to S5	Sensory deficit to perineum, sexual dysfunction, bowel and bladder dysfunction

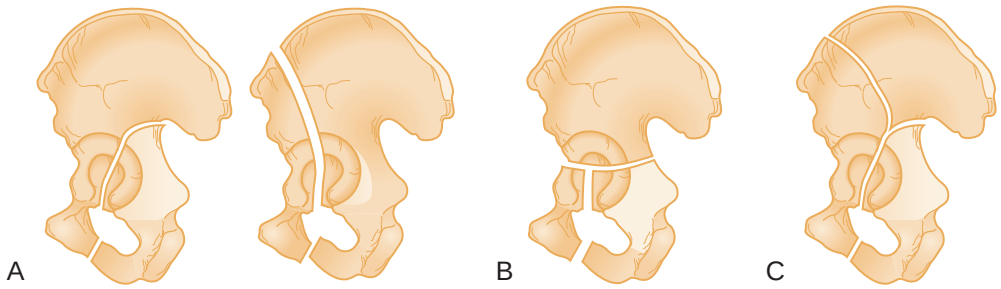

Fig. 48.12. Universal classification of acetabular fractures. **A,** Type A: Fractures of one column or one wall, for example, posterior column *(left)* and anterior *(right)* column. **B,** Transverse (T-type) fractures involving both columns but, by definition, leaving a fragment of articular cartilage attached to the proximal ilium and thus to the axial skeleton. **C,** Type C: Two-column fracture of the acetabulum. No portion of the articular surface remains attached to the axial skeleton because fracture of both columns of the ilium is proximal to the joint. (From Tile M: Fractures of the pelvis and acetabulum, ed 3, Philadelphia, 2003, Lippincott, Williams & Wilkins.)

BOX 48.4

Classification of Acetabular Fractures

Type A: Fractures of one column of the acetabulum (anterior or posterior column).
Type B: Transverse (T-type) fractures through both anterior and posterior columns; a portion of the acetabulum remains attached to the proximal ilium.
Type C: Transverse (T-type) fractures through both anterior and posterior columns; no portion of the acetabulum remains attached to the axial skeleton.

and are associated with all major mechanisms of pelvic injury. Because of the forces involved, the diagnosis of a pelvic fracture should prompt a careful evaluation for other system injuries.

Acetabular Fractures

Pain and inability to bear weight are the hallmark complaints associated with acetabular fractures. On clinical examination, pain in the hip area with percussion of the heel of the foot or with medial pressure applied to the greater trochanter may indicate the presence of an acetabular fracture. The sciatic nerve is commonly injured suggested by the presence of a neurologic injury. A common mechanism of acetabular injury is the so-called "dashboard injury," caused by the knee striking the dashboard during sudden deceleration, driving the head of the femur into the acetabulum. As a result, concurrent fracture or dislocation of the patella (or both) are common.

Acetabular fractures are broadly classified into three types (Fig. 48.12 and Box 48.4).

Type A fractures are subdivided into anterior and posterior column injuries. Posterior wall fractures are the most common acetabular injuries and are generally caused by a forceful impact to a flexed knee (eg, dashboard injury)—the force is transmitted up through the femur through the posterior acetabulum. An associated posterior dislocation of the hip is frequently associated with posterior rim fracture of the acetabulum, which may result in an unstable hip joint, leading to recurrent dislocation. Posterior hip dislocation is commonly associated with secondary sciatic nerve injury. The anterior column of the acetabulum is commonly injured when a superior ramus fracture extends into the low anterior column.

Type B fractures involve both anterior and posterior columns, but a portion of the acetabulum remains attached to the ilium.

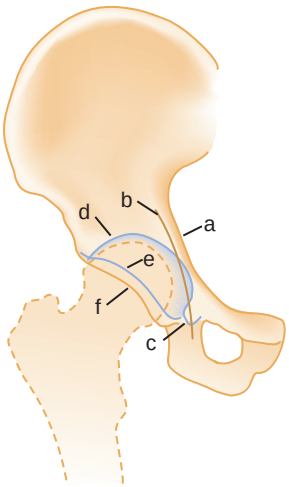

Fig. 48.13. Schematic drawing of radiographic anatomy of acetabulum in anteroposterior pelvis projection. *a,* Arcuate (iliopubic) line; *b,* ilioischial line; *c,* radiographic U, or teardrop, caused by superimposition of parasagittal surface of ilium onto anteroinferior portion of acetabulum; *d,* acetabular roof; *e,* anterior lip of acetabulum; *f,* posterior lip of acetabulum. (Redrawn from Rogers LF, Novy SB, Harris NF: Occult central fractures of the acetabulum. Am J Roentgenol 124:98, 1975.)

When the columns are split, the injury is referred to as a *transverse (T-type) fracture.* The T-type fracture is associated with the worst prognosis, due to the difficulty in obtaining open anatomic reduction.

Type C fractures are two-column fractures of the acetabulum, with none of the articular surface remaining attached to the axial skeleton. These fractures are readily apparent on plain radiographs as a result of disruption of the ilium.

Assessment of an anteroposterior pelvic radiograph should focus on disruption of the ilioischial and iliopectineal lines, as well as the anterior and posterior lips of the acetabulum (Fig. 48.13). Ramus fractures should be evaluated for possible extension into the acetabulum. When plain films are used, oblique views of the acetabulum (Judet views) can aid in visualizing the anterior and posterior columns. CT is the imaging test of choice for visualizing acetabular fractures and, when deemed necessary, planning surgical repair. Because a fracture of the acetabulum often results from a high-energy mechanism, patients with isolated acetabular fractures could have significant hemorrhage necessitating blood transfusion. Patients with acetabular fractures require orthopedic consultation in the emergency department.

Coccyx Fractures

Fractures of the coccyx are caused by a fall into the sitting position or being kicked in that area of the body. The bone can also be fractured during the birthing process. Physical examination reveals local tenderness to palpation in the gluteal crease cephalad to the anus. DRE may elicit pain and allow detection of abnormal motion of the coccyx. Normally, the tip of the coccyx moves 30 degrees anteriorly and 1 cm laterally. If displacement is detected during rectal examination, attempts at reduction are not recommended.

Radiographic confirmation of a coccygeal fracture is generally not necessary. Displaced fractures often are seen on the lateral view, but the diagnosis is evident on physical examination. Nondisplaced fractures can be difficult to identify radiographically. Rarely does the knowledge gleaned from radiographic studies alter the therapy to a degree that warrants radiation exposure to the pelvis, especially in women.

Treatment of coccygeal fracture consists of limited activity (activity limited by pain), stool softeners, non-opioid analgesia, and hot baths, if they are symptomatically helpful. As activity is increased, maneuvers that minimize discomfort include the use of an inflatable rubber donut cushion while sitting, alternately sitting on the side of each buttock, slouching to displace body weight more proximally, and sitting on a hard chair rather than a soft one, as sinking into a soft chair distributes weight onto the coccyx. Because of ongoing muscle forces on the bony fragment, healing is slow, and patients should be told that discomfort will persist for 4 to 8 weeks. If severe disability persists, an orthopedic consultation is indicated for consideration of local steroid injection or possible coccygectomy. Coccydynia also can occur without fracture and is caused by trauma during parturition; faulty posture; midline disk herniation (caused by non-segmental referral of pain from irritation of the dura); lumbar facet arthropathy; compression of the first, fourth, and fifth sacral roots; neuralgia from sacral plexopathy or sacrococcygeal neuropathy; infections; and local tumors.

CLINICAL FEATURES

History

Understanding the mechanism of injury is an important means of determining a patient's risk of having a pelvic fracture and, if present, its pattern and severity. Low-energy injuries (eg, ground-level falls) typically cause stable injuries to the pelvis; patients who have sustained high-energy injuries (eg, MVCs, falls from heights) are at risk for unstable fracture patterns of the pelvis, as well as associated injuries to other organ systems.

Determining the direction of forces applied to the pelvis can also give important clues to the types of injury sustained. Anteroposterior forces (eg, head-on MVCs) can cause open-book injuries to the pelvis. Lateral forces (eg, side-impact collisions) can disrupt the posterior ligaments; however, the pelvic floor generally remains intact. Vertical shear injuries (eg, falls from height) can disrupt the posterior ligaments and pelvic floor, causing gross instability of the pelvis.

Age is an important consideration in patients with pelvic fracture. When compared with their younger counterparts, elder patients have lower density bone, which fractures more easily, increased likelihood of hemorrhage, higher morbidity and mortality with pelvic fracture, greater comorbidity, and worse outcomes after acute resuscitation from hypotension.

Physical Examination

On inspection, rotation of the iliac crests indicates a serious pelvic fracture. Leg-length discrepancy suggests a hip injury or cephalad migration of an unstable hemipelvis. Careful inspection of the skin and skin folds is necessary to identify open fractures. Perineal or genital ecchymosis or hematoma might be observed, and if many hours have elapsed since the injury, ecchymosis in the periumbilical area (Cullen's sign), in the flanks (Grey Turner's sign), or over the inguinal ligament (Fox's sign) from retroperitoneal hemorrhage could be present. Careful palpation of the pelvic ring, seeking the presence of point tenderness, is imperative; palpation starts at the symphysis anteriorly and proceeds to both pubic rami, the iliac spines and crests, and finally to the sacrum and sacroiliac joints posteriorly. The presence of tenderness in any of these locations is an important indicator of pelvic ring injury in alert patients without distracting injury.

Manipulation of the pelvis during physical examination is essential to help determine stability, but pressure should initially be applied gently and progressively increased, as long as the patient does not report pain. "Spring boarding" (ie, vigorous downward pressure on the anterior superior iliac spines) to assess the rotational stability of the pelvic ring should be strictly avoided, because this maneuver has the potential to disrupt any tenuous blood clotting that may have occurred around a fracture site and can therefore worsen hemorrhage. Inward stability should be checked by bilateral compression of the iliac wings before outward stability to minimize the risk of opening the pelvis and causing more internal bleeding.

The penis should be milked to examine for blood at the meatus. DRE, once a fixture in assessment of pelvic trauma, is not sufficiently sensitive or specific to guide diagnosis of urethral or bladder injury (see Chapter 40).[14] The DRE allows evaluation of sensation and sphincter tone for spinal cord injury, and the presence of frank blood, indicating possible mucosal disruption. A vaginal speculum examination should be performed to assess for an open fracture in women identified with fracture on imaging. If operative intervention is planned, this examination, which can be uncomfortable and distressing, is deferred to the operating room. Because it is possible to create an open fracture iatrogenically through the vaginal or rectal wall, the DRE and vaginal examination must be performed carefully, especially in unconscious patients who cannot localize pain. The examiner should be mindful when performing these examinations that bony spicules can lacerate the examining finger. Extravasated urine might be detected in the scrotum or the subcutaneous tissues of the penis, vulva, or abdominal wall. The presence and quality of pulses in the lower limb should be assessed, as should sensation, strength, and deep tendon reflexes.

DIFFERENTIAL DIAGNOSIS

Pain can be referred from a multitude of areas. A detailed history and physical examination will often elicit the cause of a patient's pain. The causes of pelvic pain after trauma are outlined in Table 48.2. Thorough examinations of the back, abdomen, and lower extremities are necessary to exclude referred pain and associated injuries.

DIAGNOSTIC TESTING

Radiology

Plain Radiography

Routine radiographs of the pelvis are not necessary after blunt trauma if the patient is asymptomatic, awake, and alert and has normal findings on physical examination of the pelvis, including lack of tenderness to lateral and anteroposterior compression and to direct pressure applied to the symphysis pubis.[15] However, routine anteroposterior plain radiography is indicated for patients

TABLE 48.2

Causes of Pelvic Pain

NONTRAUMATIC CAUSES	TRAUMATIC CAUSES
• Appendicitis • Colon cancer • Constipation • Cystitis • Diverticulitis • Ectopic pregnancy • Endometriosis • Fibroids • Inflammatory bowel disease • Intestinal obstruction • Miscarriage • Nephrolithiasis • Pelvic inflammatory disease • Prostatitis • Ruptured ovarian cyst • Testicular/ovarian torsion	• Acetabular fracture • Back pain • Femur fracture • Herniated disk • Hip fracture • Muscle strain/sprain • Pelvic fracture • Tendon/ligamentous strain • Vertebral fracture

with severe mechanisms of injury, such as MVC, pedestrian struck by motor vehicle, or fall greater than 10 feet, who are symptomatic or whose examination is compromised by either a decreased level of consciousness or distracting injuries.

On the anteroposterior radiograph, the symphysis pubis is normally no more than 0.5 cm wide, and a small (1- or 2-mm) vertical offset of the left and right pubic rami is normal.[7] Overlapping at the symphysis pubis is abnormal and is the result of a severe crushing injury. Normally the sacroiliac joint is approximately 2 to 4 mm wide.[7]

On the anteroposterior view, the degree of pelvic rotation caused by technique and positioning can be judged by the presence of asymmetry in the size and shape of the left and right obturator foramina and iliac wings. Diastasis of the sacroiliac joint also causes an asymmetric appearance of the obturator foramina and the iliac wings. If there is displacement into external rotation, the affected iliac wing appears broader and the anterior iliac spine appears more prominent.[7] Avulsion fracture of the fifth lumbar transverse process by the iliolumbar ligament often accompanies an sacroiliac joint disruption or a vertical sacral fracture and is a valuable clue to posterior arch injuries (see Fig. 48.10 and Box 48.3).[7]

Several studies have shown that plain pelvic radiography has insufficient sensitivity and specificity to definitively identify or exclude pelvic fractures, and plain radiography is not generally necessary when abdominopelvic CT evaluation is planned.[16,17] In particular, sacral fractures and sacroiliac joint disruptions are not well visualized on the anteroposterior view. However, the addition of inlet and outlet views of the pelvis increases the sensitivity and specificity of plain radiographs in detecting significant pelvic fracture (Fig. 48.14) and sacroiliac joint disruption and should be considered in all patients with presumed stable anterior pelvic ring injuries with any complaints of posterior pelvic pain for whom CT scanning is not anticipated.

When patients are too unstable to undergo CT investigation, or when significant hemorrhagic shock is present in the context of clinically suspected pelvic fracture, the anteroposterior pelvic radiograph is useful to screen for the pelvic injuries that are most often associated with major blood loss and that might require urgent intervention.[18] Findings that predict the need for transfusion include an open-book fracture or displacement of 0.5 cm or more at any fracture site in the pelvic ring in combination with a displaced symphysis pubis, a displaced obturator ring fracture, or obvious vertical displacement in the posterior pelvis. Any of these signs could be associated with posterior pelvic injury. Therefore, plain radiography can be a vital test for patients who are unstable, those who are suspected to have unstable pelvic fracture on clinical examination, or those for whom CT cannot be immediately performed and may alert the clinician of the need for surgery, angiography, or other definitive management of pelvic hemorrhage.

Computed Tomography

CT is the imaging test of choice for evaluating the injured pelvis. CT provides detailed information about the posterior arch and rotational deformities that indicate the relative stability of the pelvic ring; furthermore, the acetabulum, which can be difficult to assess with plain radiographs, is well visualized with CT. Furthermore, abdominopelvic CT provides detailed information about concomitant injury to abdominal organs, which aids in the planning of laparotomy, external fixation of the pelvis, angiography, and definitive orthopedic management. Controversy exists regarding whether all high risk patients should undergo "pan-scan," which is CT scanning of the head, neck, chest, abdomen, and pelvis, or whether a selective approach is better, using clinical indications to guide CT scanning. Proponents of pan-scanning argue that selective scanning of high-energy trauma patients leads to a high miss rate for important diagnoses that alter treatment plans.[19] However, although selective CT scanning misses some injuries, fewer than 5% of those missed injuries require a change in the treatment plan.[20] Scan ordering should be based on the evaluation of the patient in the resuscitation bay, accounting for mechanism of injury, hemodynamic status, and suspicion of injury on physical examination. Some patients will require a pan-scan, but doing this amount of imaging on all patients meeting certain global criteria results in unnecessary radiation exposure, resource use, and expense. In general, CT scanning protocols are based on institutional preferences, somewhat guided by the literature. Imaging of the multiple-trauma patient is discussed in Chapter 33.

Unless a patient requires an immediate lifesaving surgical intervention, it is recommended that CT be used to evaluate all patients with high-energy mechanisms of injury if pelvic fracture is suspected or has been confirmed by plain radiography; this will help delineate the injury.

Evaluation of Hemorrhage

Hemorrhage is the most devastating direct complication of pelvic fracture. In the original series of high-energy pelvic injuries used to formulate their classification system, Burgess and colleagues found that an average of 14.8 units of blood were transfused in the anteroposterior compression group, 9.2 units in the vertical shear group, and 3.6 units in the lateral compression group. The correlation between transfusion requirements and type of pelvic fracture has been confirmed in other studies that demonstrate that unstable fracture patterns increase the need for transfusion and risk of mortality.

Major pelvic hemorrhage results from lacerations of the rich vascular network supplying the pelvis in the retroperitoneal space. Pelvic hemorrhage is commonly venous in origin; an intact peritoneum may help contain or tamponade a retroperitoneal hematoma. However, it is possible for bleeding to extend beyond the retroperitoneum and dissect into the anterior abdominal wall or through the peritoneum into the abdominal cavity. Bleeding can also occur from the marrow at the fracture sites.[21] Finally, coagulopathy can lead to persistent retroperitoneal bleeding and should be considered when the patient does not respond to fluid and blood replacement.

The combination of pelvic and intra-abdominal bleeding is associated with devastating outcomes. Major pelvic injury is

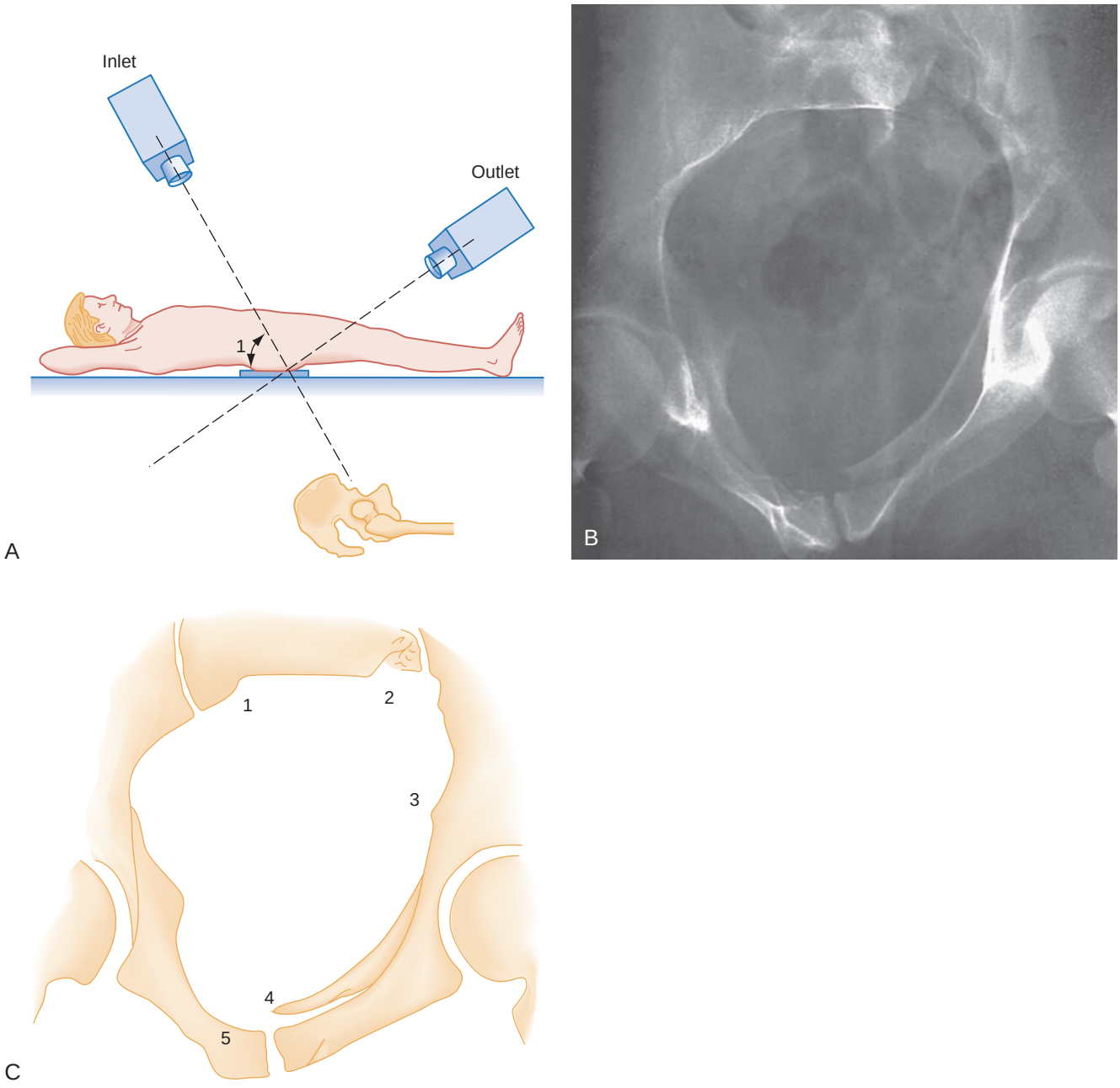

Fig. 48.14. A, The inlet and outlet views. The inlet view is angled 60 degrees to the plate from head to feet; the outlet view is angled 30 degrees in the opposite direction. Both views can be obtained with a portable machine if necessary. Injuries to the sacrum and sacroiliac joint are commonly difficult to visualize with the anteroposterior view only. The combination of all three views allows the identification of virtually all significant injuries to the bony pelvis. **B,** Inlet of pelvis is well demonstrated in this radiograph of a unilateral vertical shear fracture with cephalad and posterior displacement of the left hemipelvis. **C,** Schematic of unilateral vertical shear fracture. *1,* Normal sacral ala on the right side; *2,* left sacral ala is indistinct because of a vertical fracture, and the cephalad and posterior displacement of this hemipelvis is shown by this inlet projection; *3,* ischial spine on the left is partially obscured by bowel gas, but it is located more cephalad compared with the right spine because of cephalad displacement of the left hemipelvis; *4,* fractured left superior pubic ramus with displacement cephalad; *5,* the inlet view is taken looking through the superior and inferior pubic rami, which are superimposed so that the obturator foramina are not seen.

associated with intra-abdominal injuries in up to one-third of cases, particularly the liver and spleen. In the patient with pelvic fracture who is in shock, it is important to establish early whether hemorrhage is occurring within the abdominal cavity and thus necessitating laparotomy. Diagnostic strategies for evaluation of hemorrhage resulting from pelvic fracture include diagnostic peritoneal lavage (DPL), ultrasound, and CT. Regardless of which is chosen, unnecessary laparotomy should be avoided at all costs, because a negative abdominal exploration is associated with a higher mortality rate for hemodynamically unstable patients with pelvic fractures.

Diagnostic Peritoneal Lavage

DPL, once widely accepted as an accurate means of establishing the presence of intra-abdominal hemorrhage, has been largely

supplanted by ultrasound and CT scanning. When DPL is used, a supra-umbilical peritoneal aspirate that is negative for blood indicates that the peritoneal cavity is not a major source of bleeding or a significant contributor to hemorrhagic shock. In the absence of another identified source of blood loss, a negative peritoneal aspirate in a patient with a major pelvic fracture and hypotension indicates pelvic hemorrhage.

Gross aspiration of blood suggests major intra-abdominal hemorrhage, and pelvic stabilization, as indicated, with urgent laparotomy is recommended for hemodynamically unstable patients.

Ultrasound

Focused assessment with sonography in trauma (FAST) is the standard approach used to identify free intraperitoneal fluid in the trauma patient. An important caveat is that FAST is not helpful for evaluating the retroperitoneal space, where pelvic hemorrhage commonly occurs, but FAST has essentially completely replaced DPL to identify whether intraperitoneal bleeding is the cause of the hypotension, leaving the pelvis as the culprit when FAST is negative. Although a positive FAST study is widely used to decide whether to perform laparotomy in a hemodynamically unstable patient, its reliability in patients with major pelvic injury has been questioned. Sensitivity is about 80% and specificity 95% for the detection of hemoperitoneum in patients with pelvic fracture.[22]

The use of FAST in the evaluation of blunt abdominal trauma is discussed in Chapter 39.

Computed Tomography

CT is the diagnostic test of choice for detecting pelvic and intra-abdominal injuries. It reveals bleeding in the peritoneal and the retroperitoneal spaces. In many cases, CT with intravenous contrast can distinguish a stable hematoma from ongoing bleeding from pelvic arteries. The presence or absence of extravasated intravenous contrast material on CT of the pelvis is useful in predicting which patients will require therapeutic angiography. However, absence of extravasation does not exclude the possibility of ongoing pelvic bleeding. Pelvic computed tomography angiography (CTA) can localize active pelvic bleeding and also distinguish bleeding from arterial and venous sources.[23,24] This distinction can have great impact on the decision to perform therapeutic angiography for active arterial bleeding.

MANAGEMENT

Resuscitation

Blunt trauma patients who have the combination of pelvic ring fractures and hemorrhagic shock have a mortality rate of approaching 50% and may require massive quantities of blood products. For patients in shock, resuscitation is as described in Chapter 33.

For patients with pelvic fracture, achieving a normal pulse and blood pressure with fluid resuscitation alone in the ED may be an unrealistic goal. Such attempts may contribute to ongoing bleeding and may delay definitive treatment that can halt the hemorrhagic process.

Intravenous access in the lower limbs should be avoided in patients with severe pelvic fractures, because infused fluids and blood products might be lost through venous bleeding into the retroperitoneal space.

Box 48.5 details methods for controlling hemorrhage during the ED management of patients with pelvic fractures.

BOX 48.5

Pelvic Fracture–Related Hemorrhage: Goals in the Emergency Department

1. Resuscitation: Recognize the patient who is in hemorrhagic shock and initiate blood transfusion early in the resuscitation.
2. Recognition: Realize that patients with posterior arch injuries are at higher risk for pelvic hemorrhage.
3. Evaluation: Identify associated non-pelvic injuries (especially head, chest, and intra-abdominal) that contribute immensely to an increase in mortality in patients with pelvic fracture.
4. Stabilization: Wrapping the pelvis in a sheet and towel clamps is the easiest way to immobilize the pelvis in the emergency department. Stabilization by external fixation or pelvic C-clamp should be performed by orthopedic surgeons.
5. Control of pelvic bleeding: Angiography is highly effective in treating pelvic arterial hemorrhage. Pelvic packing during laparotomy is another way of controlling bleeding. Institutional practices determine if one or both techniques are used.

Control of Hemorrhage

In addition to blood transfusion, two important therapeutic modalities for control of hemorrhage are mechanical stabilization of the pelvis and angiographic embolization. There has been some debate as to which of these modalities should take precedence, and this has been predicated on institutional availability. As a general rule, angiography with therapeutic embolization of bleeding arteries is more effective than and takes precedence over invasive external fixation.

Stabilizing the Pelvis

Noninvasive Techniques. The most readily available means to stabilize the pelvis quickly in the ED is a sheet and towel clamps. Wrapping the pelvis tightly with a sheet and securing it with towel clamps can reduce an open-book pelvic injury (Fig. 48.15) and the potential volume in the pelvis for blood loss.

Other commercial circumferential compression devices have been developed to facilitate noninvasive stabilization of the pelvis. Cadaveric studies suggest that these devices are effective at reducing an open-book pelvis.[25] Patients with exsanguinating pelvic hemorrhage treated with a noninvasive splinting device appear to fare as well as those for whom formal external fixation was performed emergently.

Patients with open-book pelvic injuries are most likely to derive benefit from tight wrapping of the pelvis. This maneuver might not be desirable when lateral compression forces have already internally rotated the hemipelvis—indiscriminately forceful wrapping could, in fact, worsen the degree of displacement. Therefore, some judgment is required to discern whether one is wrapping the pelvis to *reduce* the volume of an externally rotated pelvis or *splinting* a pelvis to minimize movement, especially when the patient is repositioned.

Formal External Fixation. External fixation of the pelvis is performed by orthopedic surgeons to prevent movement at fracture sites and to control attendant bleeding. Application of an external fixator does not appear to decrease morbidity or mortality rates but may improve clinical outcome by limiting hemorrhage and restoring mechanical integrity.[26] Application of a fixator is a time-consuming process; it should not be attempted if it will delay more definitive treatment of pelvic bleeding by angiography or the treatment of other sources of severe blood loss. The timing

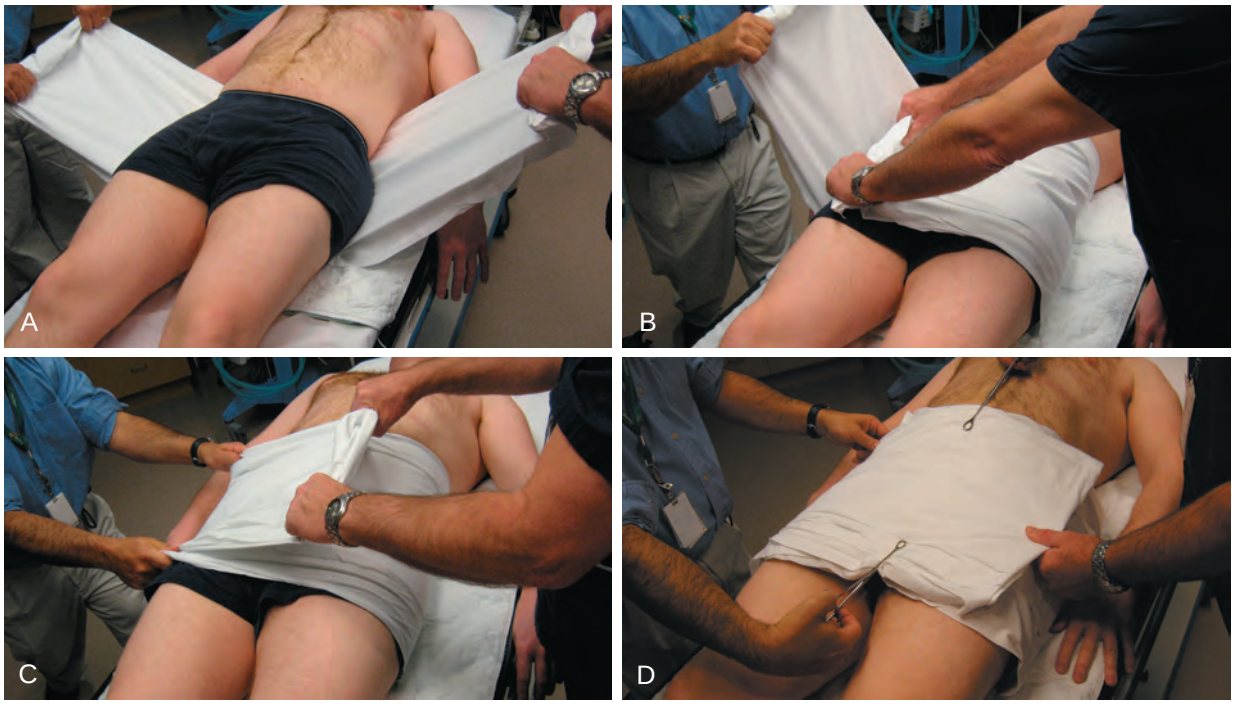

Fig. 48.15. A, Circumferential pelvic antishock sheeting is applied in this example patient. The patient's clothing should be removed before application. The sheet is positioned beneath the patient's pelvis smoothly. The ends of the sheet are crossed in an overlapping manner anteriorly **(B)** and are pulled taut **(C). D,** Clamps secure the smooth and snug sheet.

of the application of the external fixator requires coordination among the emergency medicine trauma captain, trauma surgeon, orthopedic surgeon, and interventional radiologist. Early surgical consultation is needed for efficient planning and prioritization of surgical management.

Many stable anteroposterior and lateral compression fractures can be treated definitively with an external fixator. When the pelvis is vertically displaced, traction combined with external fixation is necessary to reduce the pelvis, pending definitive open surgical repair. Most fixators can be constructed to allow convenient surgical access to the abdomen and groin.

The specific mode of invasive fixation is specific to the institution and the orthopedic or trauma consultant.

Angiography and Embolization

Arteriography and venography have been evaluated for their utility in managing hemorrhage associated with pelvic fractures. Although pelvic bleeding is commonly venous in origin, venography is not useful in management; extensive anastomoses and valveless bidirectional collateral flow make embolization impractical. In contrast, arteriography is excellent at both diagnosing and managing arterial bleeding.

Angiography is indicated when hypovolemia persists in a patient with a major pelvic fracture despite control of hemorrhage by other means. Although it is impossible to determine whether bleeding is venous or arterial in origin until angiography is performed, an inadequate response to initial resuscitation (defined as failure to maintain a systolic blood pressure above 90 mm Hg after the administration of 2 or more units of packed red cells or less) and the presence of contrast extravasation on admission CT are indicative of active arterial bleeding. Although the presence of contrast extravasation on CT is an indication for angiography, the absence of contrast blush on CT is not sufficient to rule out serious pelvic bleeding. Sacroiliac joint disruption, persistent systolic blood pressure below 100 mm Hg, and female gender have been shown to be predictors of the need for embolization at the time of angiography.

The timing of angiography is individualized for each patient, depending on priorities for the treatment of concomitant injuries. Posterior arch disruptions are associated with the most severe hemorrhage; angiography should be considered at an early stage for patients with this injury. Whether patients undergo angiography immediately from the ED or immediately preceding laparotomy, it is important to be mindful of the logistical delay that often occurs in mobilizing the angiography team, so this intervention should be anticipated as early as possible. Transfer to the angiography suite requires orchestrating the necessary personnel and equipment to care for a critically injured patient. The use of mobile angiography equipment in the ED to control pelvic hemorrhage has been reported; this option removes the logistic delays while ensuring a greater degree of safety in monitoring patients during the procedure.[27]

The contrast material for arteriography is injected through the femoral artery on the less-injured side or via the upper extremity. The examination starts above the level of the aortic bifurcation and proceeds to selective branches of the internal iliac (hypogastric) artery. Transcatheter embolization with thrombogenic coils, foam, or spherules is used to stop hemorrhage from the branches of the internal iliac artery.

Embolization is highly effective for controlling arterial bleeding, with fewer than 10% of patients requiring a repeat procedure because of ongoing bleeding. The complications that can result from embolization include gluteal muscle necrosis, surgical wound breakdown, infections, impotence, and bladder necrosis.[28]

Hemodynamically Unstable Patients With Pelvic and Intra-Abdominal Hemorrhage

Patients who hemorrhage from both the pelvis and the abdomen have mortality rates above 40% and deserve special consideration. These patients may be too unstable to undergo CT imaging.

Prioritizing the need for laparotomy versus angiography in these patients becomes challenging when the need for laparotomy is based on the detection of intra-abdominal fluid by FAST (or DPL). Unnecessary laparotomy performed in patients who are hemodynamically unstable with pelvic fracture further exacerbates their high mortality rate. In these cases, it is crucial that the general or trauma surgeon, orthopedic surgeon, and interventional radiologist coordinate their efforts to optimize the timing of necessary procedures.

If DPL is performed, gross aspiration of blood is a strong indicator for prompt laparotomy. FAST examination is used similarly. A positive FAST examination indicates hemoperitoneum, and it is generally accepted that laparotomy should be pursued before angiography in such cases. Given the significant rate of false-negative FAST examinations in patients with pelvic trauma, a single negative FAST examination should not be considered to exclude significant intraperitoneal hemorrhage. However, patients with hemorrhagic shock and a negative FAST examination with adequate windows likely are bleeding from the pelvis injury. When concurrent pelvic bleeding is highly suspected (eg, in patients with severe open-book pelvis), it is advisable that angiography promptly follows the laparotomy.

At the time of laparotomy, the orthopedic surgeon will determine if it is appropriate to place an external fixator. Packing of the pelvis at the time of laparotomy is a means of achieving hemostasis in pelvic hemorrhage.[29,30] This procedure has been a mainstay of treating pelvic hemorrhages in selected centers, mostly in Europe; it has become much more widely accepted as studies have documented improved mortality rates with its use.[31] Part of the rationale for packing rather than angiography is the fact that pelvic bleeding is commonly venous in origin, for which arteriography and embolization are useless. In contrast, packing might provide tamponade of bleeding from the posterior venous plexus. It is recommended that the pelvis be stabilized before packing to provide solid structural support. Intraperitoneal, retroperitoneal, and extraperitoneal techniques of packing have been described; the retroperitoneal and extraperitoneal approaches have been used rapidly, even in the ED. A systematic review of pelvic packing concluded that, for patients with hemodynamic instability caused by pelvic hemorrhage, packing can be used as a temporizing measure for control of bleeding until more specific treatment can be initiated.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is another option for control of bleeding from pelvic fractures whose use has been growing.[32,33] Similar to cross clamping the aorta, this endovascular balloon can be placed in the infrarenal position using the seldinger technique to occlude the aorta and prevent blood from entering the pelvis. This technique is amendable to out of hospital or bedside placement in the ED with ultrasound guidance of the final position of the balloon.[34] Several studies have shown improved mortality in patient with hemorrhagic shock from non-compressible torso and pelvic injuries.[35-38] This technique is associated with risk of vascular injury and limb ischemia, so it is restricited to patients in extremis, similar to what is seen with cross clamping.[32,37] With appropriate training, REBOA can be a safe bridge to obtain hemodynamic stability until more definitive hemorrhage control can be obtained in the the operating room or angiography suite.[39]

DISPOSITION

Disposition of the patient depends on whether or not the fracture is considered stable, and whether there are other injuries or significant comorbidities. Most patients who have stable fractures (eg, pubic ramus fracture, minor iliac wing fracture) can be discharged to home with adequate analgesics and with crutches or canes, as needed, to aid in weight bearing. Patients with stable coccyx and sacral fractures might benefit from a donut pillow that distributes their weight onto their buttocks and away from the fracture site when seated.

Patients with unstable fractures, hemodynamic compromise, or significant associated injuries require admission to the hospital for definitive care. Management in the emergency department consists of temporarily stabilizing the fracture, addressing any life-threatening injuries, and arranging admission or transfer to a hospital or service that can provide definitive care.

KEY CONCEPTS

- The most serious pelvic ring injuries caused by high-energy impact are (1) anteroposterior compression fractures ("open-book" fracture), (2) vertical shear fractures, and (3) fractures involving significant displacement. These injuries are associated with major blood loss and transfusion requirements.
- Pelvic injury is a marker for serious injury to other organ systems. The vast majority of patients who die after sustaining a pelvic fracture have multiple trauma.
- Careful examination of the perineum and buttocks, as well as digital rectal and vaginal examinations, are necessary to diagnose open fractures.
- Computed tomography (CT) is the imaging test of choice to diagnose pelvic fracture and concurrent intra-abdominal injuries for patients stable enough to undergo the scan. CT aids in establishing surgical priorities and planning of definitive orthopedic care. The significance of contrast extravasation during CT imaging is a subject of ongoing research regarding the ability to distinguish between arterial and venous sources of pelvic bleeding.
- In the hemodynamically unstable patient who cannot undergo CT imaging, the anteroposterior radiograph usually reveals serious pelvic fractures that cause major pelvic bleeding, which is sufficient information to undertake pelvic stabilization if indicated.
- The combination of posterior arch fracture plus hypotension is associated with a mortality rate of approximately 50%.
- Early fluid resuscitation with blood products is recommended for patients suspected of having active pelvic bleeding.
- Trauma hospitals should have institutional guidelines and mechanisms to facilitate early decisions regarding the treatment for pelvic hemorrhage. Treatment options include angiography and embolization, pelvic packing, invasive fixation, or any combination of these therapies.
- Unstable patients with a positive FAST and a pelvic fracture should be treated with laparotomy with pelvic stabilization and possible pelvic packing, and then angiography.
- Unstable patients with a negative FAST and a pelvic fracture should be treated with pelvic stabilization (eg, a pelvic binder) and angiography, and then a repeat FAST and laparotomy if they remain unstable.
- "Open-book" pelvis fractures should be internally compressed with a pelvic binder or sheet to reduce the size of the pelvis, unless the fracture forces have already internally rotated the hemi-pelvis as this could cause an increase in the pelvic diameter.

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The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 48: QUESTIONS & ANSWERS

48.1. While examining a patient with blunt abdominal trauma, you note blood at the urethral meatus. What is the most appropriate next step in the patient's management?

A. Order a cystography
B. Order a retrograde urethrogram
C. Order a urinalysis
D. Order an anterograde urethrogram
E. Order an intravenous pyelography

Answer: B. Blood at the urethral meatus necessitates a retrograde urethrogram followed by a cystogram. Gross hematuria is investigated by a combination of urethrography, intravenous pyelography, cystography, and computed tomography (CT).

48.2. An avulsion fracture caused by the rectus femoris muscle most likely involves which of the following structures?

A. Anterior inferior iliac spine
B. Anterior superior iliac spine
C. Iliac crest
D. Ischial tuberosity
E. Sacrum

Answer: A. Forceful contraction of the rectus femoris (as in kicking a ball) can result in an injury of anterior inferior iliac spine avulsion. The ischial tuberosity may be avulsed during strenuous contraction of the hamstrings. A portion of the iliac crest epiphysis may be avulsed by contraction of the abdominal muscles. The anterior superior iliac spine may be avulsed by forcible contraction of the sartorius muscle.

48.3. A 25-year-old patient involved in a motor vehicle collision (MVC) presents with a suspected unstable pelvic fracture. Vital signs are: blood pressure, 90/50 mm Hg; heart rate, 120 beats per minute; and respiratory rate, 22 breaths per minute. What is the most appropriate next step in this patient's management?

A. Call trauma service for immediate laparotomy
B. Call orthopedics for fixation
C. Chest, abdominal, and pelvis radiographs
D. Computed tomography (CT) scan of the abdomen and pelvis
E. Perform serial abdominal and focused assessment with sonography in trauma (FAST) examinations

Answer: C. The addition of inlet and outlet views of the pelvis has been shown to increase the sensitivity and specificity of plain radiographs in detecting significant pelvic fracture. When patients are too unstable to undergo CT investigation, the anterior/posterior portable radiograph is useful in screening for pelvic injuries that are most associated with major blood loss. Findings with this technique that have been reported to predict the need for transfusion include "open-book" fracture or displacement of 0.5 cm or more at any fracture site in the pelvic ring, and displaced symphysis pubis or obturator ring fracture.

48.4. Which of the following treatments can provide definitive control of hemorrhage from severe pelvic fracture?
- **A.** Blood transfusion
- **B.** Commercial circumferential pelvic compression devices
- **C.** External fixation
- **D.** Transfusion of concentrated clotting factors
- **E.** Wrapping pelvis with sheet

Answer: C. External fixation is an invasive strategy aimed at cessation of pelvic hemorrhage. Options A and E are important for the emergency clinician to quickly stabilize a mechanically unstable pelvic fracture and hopefully minimize bleeding, but these options, per se, are not definitive treatments. Transfusion of blood products is important in overall resuscitation of the patient but does not stop bleeding from pelvic fractures.

48.5. Which of the following radiographic findings necessitates further evaluation of the pelvic ring?
- **A.** Asymmetry of the pelvis caused by rotation
- **B.** Duverney fracture
- **C.** Sacroiliac joint 4 mm wide on pelvic radiograph
- **D.** Symphysis pubis 7 mm wide
- **E.** Transverse fracture of the sacrum

Answer: D. On the anteroposterior radiograph, the symphysis pubis is normally no more than 5 mm wide, and a small (1 or 2 mm) vertical offset of the left and right pubic rami may be normal. Normally, the sacroiliac joint is approximately 2 to 4 mm wide. On the anteroposterior view, the physician may judge the degree of pelvic rotation caused by technique and positioning by the presence of asymmetry.

CHAPTER 49

Femur and Hip

Michael K. Abraham | Michael C. Bond

PRINCIPLES

Fractures of the femur are notable for their associated morbidity and mortality. Women are at increased risk for both femoral neck fractures and intertrochanteric fractures. Femoral neck fractures have a female-to-male ratio of 4:1 and typically occur in elderly patients with osteoporosis. The incidence of intertrochanteric fractures increases with age, and women are affected six times more often than men.[1] More than three-quarters of all hip fractures occur in postmenopausal women older than 50 years old.

In the emergency care setting, nontraumatic hip pathology is also very common among the elderly segment of society. Osteoarthritis of the hip can severely limit one's ability to perform activities of daily living.

The elderly are not the only population affected by hip and femur pathology. Perthes' disease, or avascular necrosis (AVN) of the femoral head, occurs in children from 2 to 14 years old, with a peak age of onset of 5 years old. It is five times more common in boys than in girls.[2-5] The incidence of slipped capital femoral epiphysis (SCFE) peaks at 13½ years old among boys and 12 years old among girls, in association with the onset of puberty. This condition is nearly twice as common in boys.[6]

Anatomy of the Hip and Femur

Skeletal Anatomy

The femur is the longest and strongest bone in the human body and is routinely subjected to substantial forces during powerful muscle contraction and weight transmission. It consists of the femoral head, neck, and shaft. The femoral head is firmly seated in the acetabulum, reinforced by the labral cartilage. The well-developed capsule, overlying ligaments, and proximal musculature of the lower extremity add strength to the joint (Fig. 49.1). Structurally, the femoral neck serves as an oblique strut between the pelvis (the horizontal beam) and the shaft of the femur (the vertical beam) (Fig. 49.2). The length, angle, and narrow circumference of the femoral neck permit substantial range of motion at the hip, but these same characteristics subject the neck to incredible shearing forces.

The type of bone in the femur changes depending on location, which affects fracture patterns. The bone in the femoral head, neck, and intertrochanteric region is predominantly cancellous, which is less resistant to torsional forces. Distal to the intertrochanteric region, including the subtrochanteric region and femoral shaft, the bone is cortical, requiring great forces to break. At the distal metaphysis, the femur widens and the cortical bone thins, lessening its resistance to stress.

Musculature

The musculature of the hip and thigh is the largest and most powerful in the human body. The muscles in this region of the body are located within three compartments, each containing associated nerves and vessels (Table 49.1). The muscles are grouped according to their primary action at the hip. Knowledge of the major muscle actions offers insight into common injury patterns and deformities (Fig. 49.3).

Arterial Supply

The arterial supply of the femoral head, neck, and shaft arises from different sources. The major arterial supply to the femoral head and neck comes from the medial and lateral circumflex arteries, which are branches off the femoral artery (Fig. 49.4). These branches form an extracapsular arterial ring around the femoral neck. Another source to the femoral head typically arises from the obturator artery and courses through the ligamentum teres.

As the external iliac artery passes beneath the inguinal ligament, it becomes the common femoral artery. At this point, the artery is located midway between the anterior superior iliac spine (ASIS) and the symphysis pubis. Approximately 3 to 4 cm distal to the inguinal ligament, the deep femoral artery branches off. The deep femoral artery is predominantly responsible for the vascular supply of the femur. It runs posterolaterally to the superficial femoral artery, supplies the hamstrings, and terminates in the distal third of the thigh as small branches pierce the belly of the adductor magnus. The superficial femoral artery continues to pass along the anteromedial aspect of the thigh and terminates at the junction of the middle and lower thirds of the thigh. Here, the superficial femoral artery passes through the adductor hiatus and becomes the popliteal artery.

Venous System

In the proximal two-thirds of the thigh, the common and superficial femoral veins lie adjacent to the common and superficial femoral arteries. At the inguinal ligament, the common femoral vein is posterior and medial to the common femoral artery and moves to the lateral position as it passes distally. The deep femoral vein and the greater saphenous vein are the two main tributaries to the common and superficial femoral veins. The deep femoral vein and artery run in parallel as the vein joins the superficial femoral vein just distal to the inguinal ligament. The greater saphenous vein arises in the dorsum of the foot and ascends anterior to the medial malleolus. This vein is relatively superficial as it passes up the medial aspect of the leg to join the common femoral vein distal to the inguinal ligament.

Nerves

The femoral and sciatic nerves are the major nerves within the thigh. The femoral nerve is the largest branch of the lumbar plexus; it passes under the inguinal ligament lateral to the femoral artery and divides into anterior and posterior branches soon after entering the thigh. The sensory divisions of the anterior branch, the intermediate and medial cutaneous nerves, supply sensation to the anteromedial aspect of the thigh. The motor division of the anterior branch innervates the pectineus and sartorius muscles.

TABLE 49.1

Structures Within Compartments of the Thigh

COMPARTMENT	MUSCLES	NERVES	VESSELS
Anterior	Quadriceps femoris, sartorius, iliacus, psoas, pectineus	Lateral femoral cutaneous	Femoral artery and vein
Medial	Gracilis, adductor longus and magnus, obturator externus	Obturator	Profundus femoris artery, obturator artery and vein
Posterior	Biceps femoris, semitendinosus, semimembranosus, adductor magnus	Sciatic, posterior femoral cutaneous	Profundus femoris artery branches

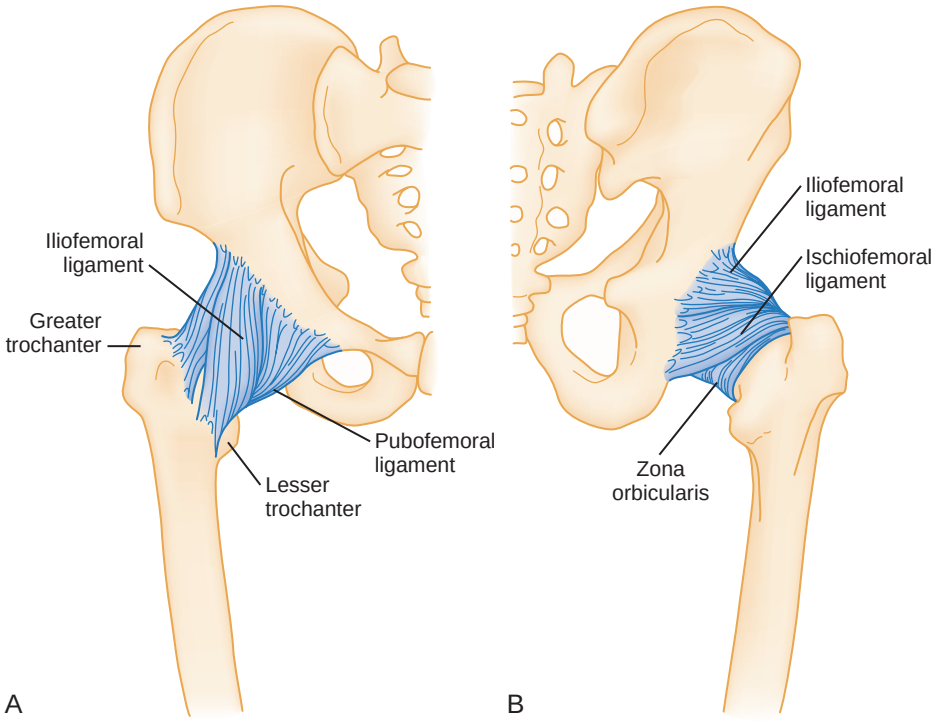

Fig. 49.1. The ligaments of the hip combine to form a tough joint capsule, as seen on both anterior **(A)** and posterior **(B)** views.

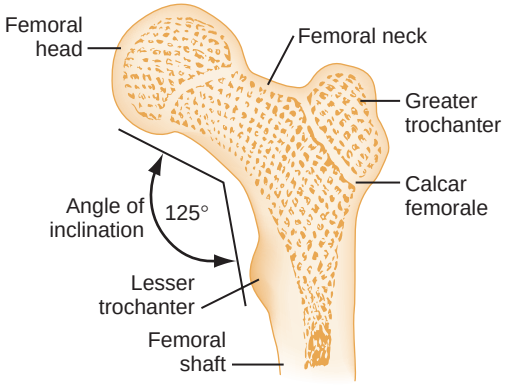

Fig. 49.2. Bony architecture of the proximal end of the femur.

The posterior femoral branch gives off the saphenous nerve, which supplies sensation to the skin along the medial aspect of the lower part of the leg. The posterior branch also supplies motor function to the muscles of the quadriceps femoris group.

The sciatic nerve is the largest peripheral nerve in the body. It arises from the sacral plexus. The sciatic nerve exits the pelvis through the greater sciatic foramen and travels through the posterior thigh; it extends from the inferior border of the pyriformis muscle to the distal third of the thigh. The sciatic nerve gives off articular branches that supply the hip joint. In the thigh, muscular branches innervate the adductor magnus and hamstring muscles. Just proximal to the popliteal fossa, the sciatic nerve divides to form the tibial and common peroneal nerves.

Pathophysiology

Osteoporosis of the Femur

Osteoporosis is the leading cause of hip fracture. The pathophysiology of osteoporosis is not completely understood, but strong associations with hormonal changes related to aging, genetic predisposition, vitamin D deficiency, lack of physical activity, and smoking have been recognized. Severe osteoporosis and hip fractures are most common in elderly white women; however, a decrease in bone density after age 30 is seen across all demographic groups. The trabeculae of the femoral head and neck strengthen the bone and support the large mechanical forces produced across the hip joint. As osteoporosis begins and then progresses, these trabeculae disappear. This loss of trabeculae weakens the bone and increases the risk of fracture. Osteoporosis currently affects

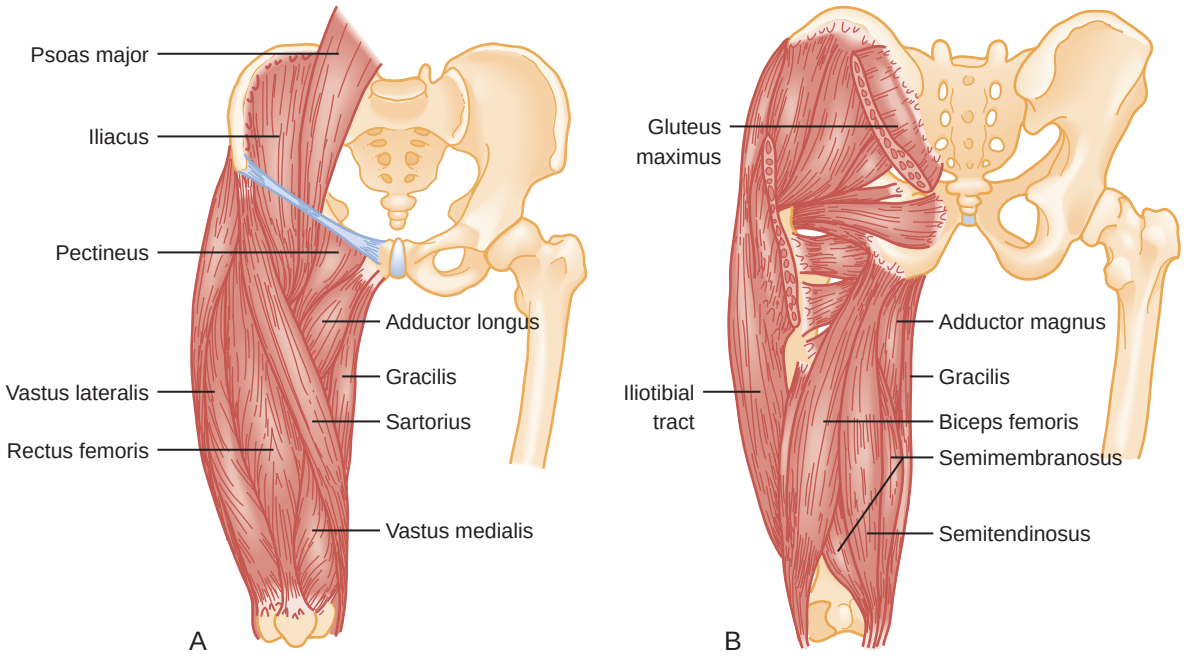

Fig. 49.3. **A** and **B,** The major muscles acting about the hip and thigh.

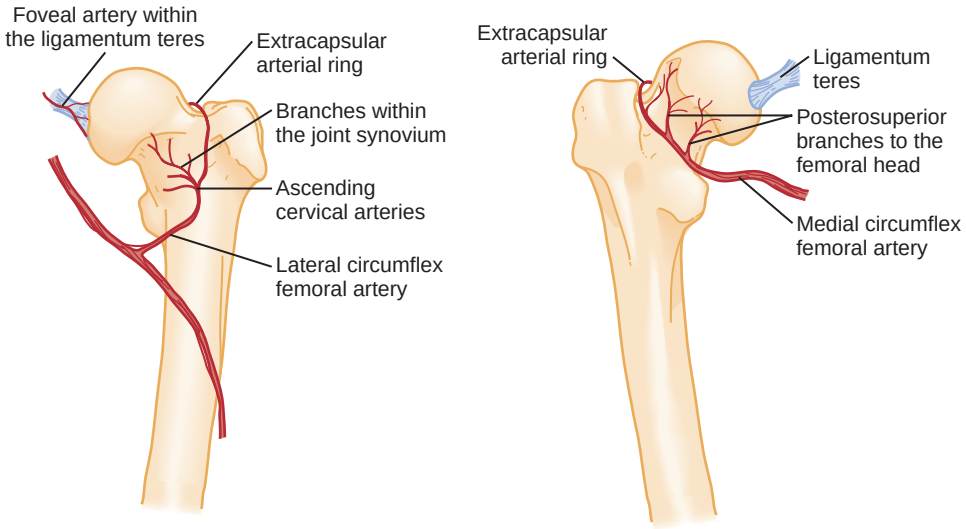

Fig. 49.4. The arterial blood supply of the femoral neck and head is provided to varying degrees by three sources: the ascending cervical arteries, the arterial branches within the marrow *(not illustrated),* and the foveal artery within the ligamentum teres.

more than 10 million people in the United States and is projected to affect approximately 14 million adults older than 50 years by the year 2020. The number of hip fractures attributable to osteoporosis is expected to be 6.3 million by the year 2050, although the incidence in women has been decreasing in recent years.[3]

Fractures and Trauma of the Femur and Hip

The vast majority of hip fractures occur in elderly patients with preexisting bone disease who sustain low-energy trauma, usually a ground-level fall. In young healthy individuals, major trauma, such as a motor vehicle collision (MVC) or a fall from a significant height, is responsible for most fractures.

Twenty percent of patients with hip fracture die during the first year after the injury, mostly from sequelae of the fracture rather than the fracture itself. One-third of patients require nursing home placement, and less than one-third regain their pre-fracture level of physical function. The economic impact of these fractures is enormous.

Osteoarthritis of the Hip.

A large percentage of the American population experiences chronic pain from degenerative osteoarthritis of the hip due to the significant weight-bearing responsibility. Osteoarthritis ranks fifth in health impact (measured in years lost to disability) in high-income countries and ninth in low- and middle-income countries. Disability often results from persistent pain and limited physical mobility. The progression of osteoarthritis can be demonstrated with serial radiographs of the affected hip (Fig. 49.5); however, radiographic findings do not necessarily correlate with symptoms.

Fig. 49.5. Radiographic evidence of the development of osteoarthritis or degenerative joint disease of the hip is demonstrated with serial radiographs in the same patient over several years. **A,** The symptoms initially are more dramatic than would be expected with the radiographic findings of increased sclerosis along the weight-bearing surface of the superior acetabulum. **B,** The joint space is lost. **C,** Erosion of the head and acetabular surfaces and reactive bony cystic changes are now evident.

Fig. 49.6. Avascular necrosis (AVN) of the left femoral head. Note the asymmetry of the joint and the collapse of the femoral head.

Avascular Necrosis

When a patient has an increasingly painful hip, buttock, thigh, or knee and no history of recent trauma, AVN of the femoral head should be considered. AVN has been referred to as *aseptic necrosis, ischemic necrosis,* and *osteonecrosis.* It is the result of ischemic bone death of the femoral head after compromise of its blood supply (Fig. 49.6). AVN is bilateral in 40% to 80% of patients. It is common in relatively young patients, the mean age at diagnosis being 38 years old. Although a specific causative disorder is not identified in 20% of cases, known atraumatic causes include chronic corticosteroid therapy, chronic alcoholism, hemoglobinopathy (eg, sickle cell anemia), dysbarism, and chronic pancreatitis. AVN is an emerging complication associated with human immunodeficiency virus (HIV) infection. It is unclear whether the pathologic agent is the virus itself or the treatment.

Traumatic AVN, a subacute manifestation after hip dislocation or femoral neck fracture, is a direct result of disruption of the blood supply to the femoral head. It is more common in males and African Americans. The incidence of AVN as a subacute complication is clearly related to both the initial degree of trauma and the amount of time the femoral head remains dislocated. Multiple studies have demonstrated a relationship between the length of time the hip is dislocated and the rates of AVN: it develops in about 5% of patients if reduction is performed within 6 hours and as many as 60% when reduction occurs after 12 hours. For this reason, hip dislocation is an orthopedic emergency. The emergency clinician should perform reduction of the hip if orthopedic consultation will be delayed.

Even with optimal treatment, femoral neck fractures are complicated by AVN in up to 20% of cases. They are essentially intra-articular fractures. Immediately after fracture, bleeding from the site may cause high intracapsular pressure and a tamponade effect on the femoral head, thereby impairing the blood supply. If the bone fragments are not impacted, synovial fluid will lyse the blood clot, which prevents the development of capillary buds and the scaffolding needed for osseous repair. In contrast, intertrochanteric and subtrochanteric fractures are located in an area with a rich extracapsular arterial supply; therefore, AVN rarely complicates these fractures.

Myositis Ossificans

Myositis ossificans (heterotrophic ossification) is pathologic bone formation at a site where bone is not normally found. Traumatic myositis ossificans results most commonly from a direct blow to muscle. Bleeding into the muscle after trauma produces a local hematoma with subsequent new bone formation within it. The thigh and hip muscles are often involved. This inappropriate response can also result from repeated minor trauma. The ossific mass might be palpable and might limit motion, depending on its location.

Myositis occurs in up to 20% of patients undergoing medical evaluation for thigh contusions, likely related to the severity of the injury.[4] The incidence of myositis ossificans after hip surgery is approximately 2%, and these lesions are clinically significant in 10% to 20% of cases. Increased susceptibility to myositis ossificans has been described in persons with hemophilia and other bleeding disorders in conjunction with soft tissue injury. Radiographically, myositis ossificans appears as irregularly shaped masses of heterogeneous bone in the soft tissues around the joint or along fascial planes (Fig. 49.7). It can be seen as early as 10 to 21 days after injury, but radiographic evidence typically lags behind the onset of symptoms by weeks. Its appearance might simulate primary bone neoplasm, especially when the periosteum is involved. Osteosarcoma and periosteal osteogenic sarcoma should be considered in the differential diagnosis. Computed tomography (CT) can sometimes be helpful in distinguishing between neoplasm and myositis ossificans, because the lesions of myositis ossificans begin to calcify at the periphery and progress toward the center,

and those of osteosarcoma begin to calcify at the center first. Orthopedic follow-up should be arranged for these patients.

Calcific Bursitis and Calcifying Peritendinitis

Calcification surrounding tendons and bursae or occurring in the joint capsule is referred to as *calcific bursitis* or *calcifying peritendinitis.* The cause of these lesions is unknown. No relationship has been documented between the radiographic findings and acute symptoms. Calcific bursitis of the hip is uncommon, but when it does occur, it most frequently affects the trochanteric bursa (Fig. 49.8). Other possible affected areas include the gluteal muscles and the hip flexors and adductors. The bursal calcification is seen on radiographs as an amorphous, poorly marginated line that is clearly separate from the cortex of the femur.

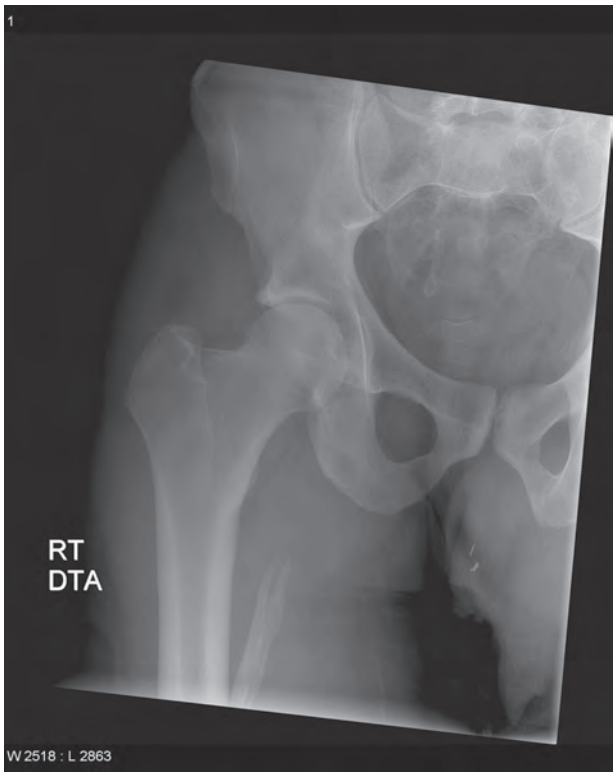

Fig. 49.7. Myositis ossificans of the proximal end of the femur. Lesions can be immature or mature such as this one, with well-organized calcifications.

Neoplastic Disease in the Hip

The most common neoplastic disease of bone is metastatic, generally from breast, kidney, lung, thyroid, or prostate tumors.[5] Primary bone lesions also occur, the most common being osteoid osteoma (Fig. 49.9). Bone lesions can be osteoblastic or osteolytic. Patients come to the ED with significant bone pain or a large mass,

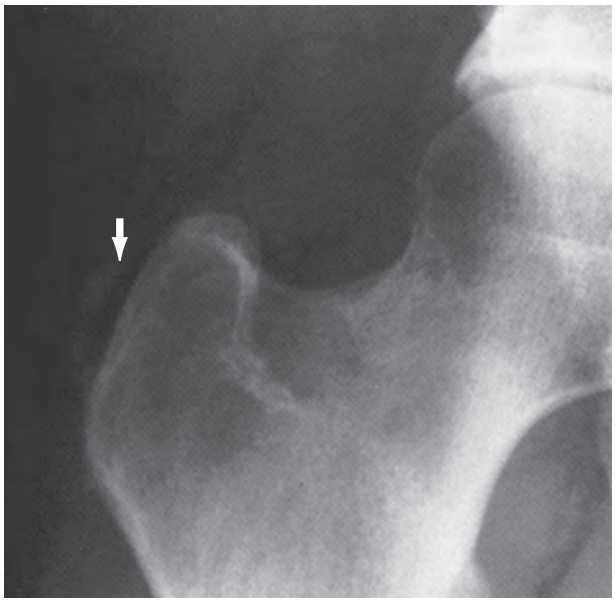

Fig. 49.8. Calcific trochanteric bursitis. Faint calcification *(arrow)* in the region of the trochanteric bursa is visible along the lateral cortex of the greater trochanter. (From Harris JH, Harris WH, Novelline RA: The radiology of emergency medicine, ed 3, Baltimore, 1993, Williams & Wilkins.)

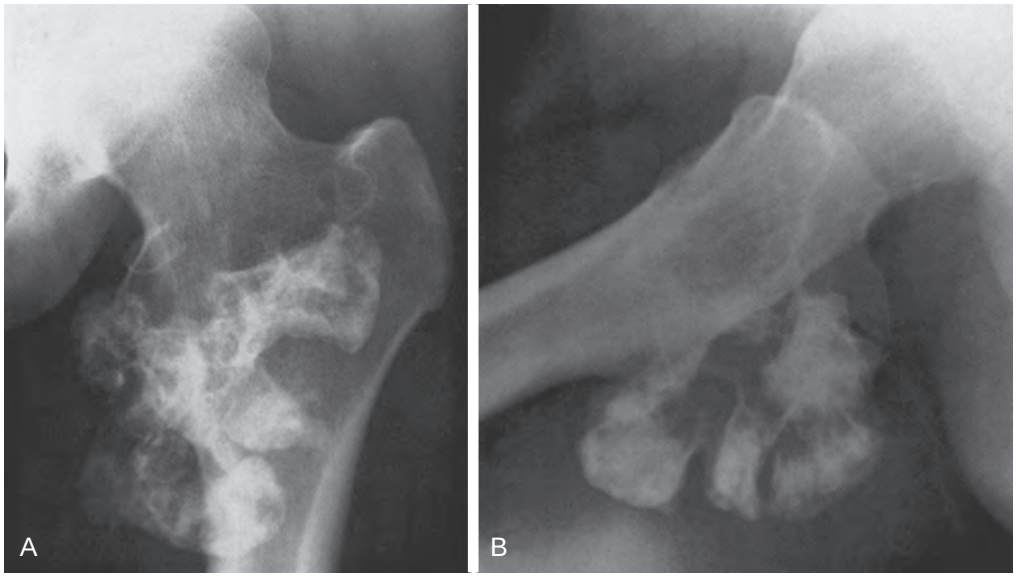

Fig. 49.9. Classic radiographic appearance of a solitary osteochondroma of the femur as seen in the anteroposterior **(A)** and frog leg lateral **(B)** views. This lesion is a cartilage-capped bony excrescence, typically arising from the cortex of long tubular bones. (From Harris JH, Harris WH, Novelline RA: The radiology of emergency medicine, ed 3, Baltimore, 1993, Williams & Wilkins.)

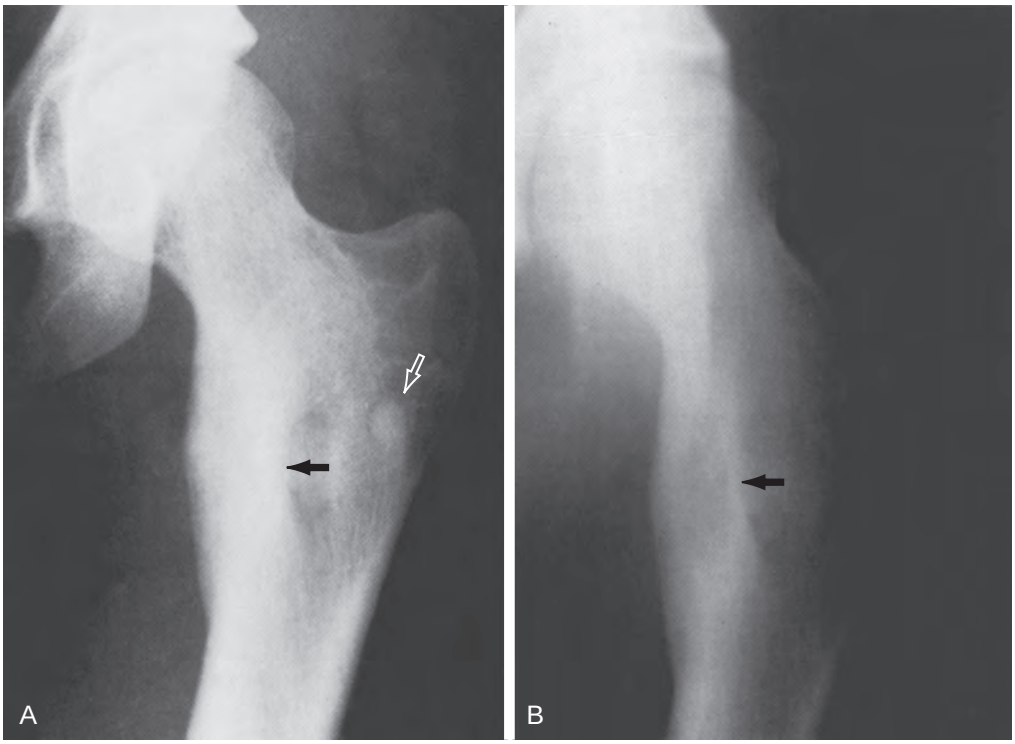

Fig. 49.10. Osteoid osteoma of the femur *(solid black arrow)*. **A,** A large focal area of greater density than that of the surrounding femur represents both cortical and endosteal proliferation. The new cortical bone is smooth and sharply delineated, indicative of a nonaggressive process. The open arrow represents a bone island. **B,** A frontal-view tomogram demonstrates an oval central radiolucent nidus *(solid black arrow)*. (From Harris JH, Harris WH, Novelline RA: The radiology of emergency medicine, ed 3, Baltimore, 1993, Williams & Wilkins.)

such as a solitary osteochondroma that has become irritated or painful (Fig. 49.10). Neoplasms place the patient at higher risk for pathologic fracture, especially if the lesions are large or lytic or have eroded the cortex.

CLINICAL FEATURES

History

Injuries and pathologic conditions involving the femur are commonly dictated by age and gender. Because the femur is strong and can withstand the normal "bumps" of everyday life, the complaint is commonly related to a traumatic incident. A detailed description of antecedent trauma or other precipitating events is often helpful, because details of the mechanism of injury can aid in predicting injury patterns. Although direct trauma is a common cause of injuries, a thorough past medical history should be obtained, because it might provide meaningful clues. Patients who recently altered their level of physical activity or exercise routine could have a stress fracture. Information about systemic illnesses or metabolic disorders should be elicited. A previous cancer diagnosis and its treatment with irradiation or chemotherapy could be a predisposing factor, providing clues about pathologic fractures. Any past steroid use, including inhaled steroids, is important to identify because it places patients at higher risk for AVN of the femoral head. A linear relationship has been recognized between cumulative steroid dose and the incidence and severity of osteoporosis and hip fracture.

Determination of the location of the patient's pain is paramount, because true hip joint pain can be perceived as groin pain. Children with hip pathology often have knee pain as the sole presenting complaint. The review of systems should include information that can help distinguish hip or femur pathology from another cause of the pain. Atypical causes of hip or groin pain include nephrolithiasis, pelvic inflammation, infection, malignancies, inguinal and femoral hernias, and lymphadenopathy. A history of low back pain suggests radiculopathy as the cause of the patient's pain. The differential diagnosis of hip pain without obvious fracture on radiographs is listed in Box 49.1.

The history should also focus on comorbid conditions and injuries. Elderly patients with a hip fracture sustained in a fall at home might be unable to summon help for hours to days. They often have concomitant dehydration, electrolyte abnormalities, rhabdomyolysis, and renal insufficiency. They require a thorough evaluation and resuscitation before surgery is considered. In addition, the reason for the fall should be determined, because it may reveal other comorbid conditions (eg, syncope, cardiac dysrhythmias, polypharmacy, and/or alcoholism). Sedative and antihypertensive medications predispose elderly patients to falling and should be prescribed carefully. With a fall, elderly patients might sustain additional injuries, most commonly, the fracture of a vertebral body or wrist. Cervical spine and intracranial injuries should also be considered. Forty percent to 75% of young patients with a hip fracture resulting from high-energy mechanisms have concomitant injuries.

Physical Examination

Management principles for injuries of the hip and femur are the same as those for traumatic injuries elsewhere in the body.

Because patients with femoral pathology can have a multitude of presentations, a thorough physical examination is important. Due to the major forces that are sustained in multisystem trauma, hypotension is a problem commonly encountered during the

BOX 49.1

Differential Diagnosis of a Painful Hip Without Obvious Fracture

Referred pain (lumbar spine, hip, or knee)
Avascular necrosis (AVN) of the femoral head
Degenerative joint disease or osteoarthritis
Herniation of a lumbar disk
Diskitis
Transient synovitis of the hip
Septic arthritis
Bursitis
Tendonitis
Ligamentous injuries of the knee or hip
Occult fracture
Slipped capital femoral epiphysis (SCFE)
Perthes' disease
Tumor (lymphoma)
Deep venous thrombosis
Arterial insufficiency
Osteomyelitis
Iliopsoas abscess
Retroperitoneal hematoma
Inguinal hernia
Inguinal lymphadenopathy
Genitourinary complaints
Sports-related hernia

initial resuscitation. Although hypotension might result from the loss of up to 3 units of blood into the thigh of a patient with a femoral fracture, other conditions (cardiac, pulmonary, intra-abdominal, and pelvic trauma) must be considered. Hemorrhagic shock from an isolated femoral fracture should be a diagnosis of exclusion. Hypotension, neurovascular compromise, or suspicion for multiple injuries are indications for transfer to a specialized trauma center.

After life-threatening conditions have been addressed, the injured extremity should be evaluated carefully. The position of the leg offers a clue to radiographic findings. External rotation, abduction, and shortening suggest a displaced femoral neck fracture. External rotation with shortening suggests an intertrochanteric fracture. Visual inspection might reveal pallor, ecchymosis, asymmetry, or deformity. The presence of abrasions, lacerations, and open wounds alters the management of concomitant fractures. Nondisplaced fractures, including stress fractures, should not produce limb shortening or rotation deformities but will be painful on passive range of motion, particularly internal and external rotation. In patients with obvious deformities, range of motion should be deferred until after radiographs have been obtained.

Systematic examination of the injured extremity will reveal focal tenderness or warmth suggesting injury or infection. Active and passive range of motion and assessment of muscle strength, though offering important information, are frequently limited by pain. A detailed neurovascular assessment is vital, as femoral nerve and arterial injuries often occur in conjunction with subtrochanteric and femoral shaft fractures or anterior hip dislocations. The sciatic nerve can be injured with a hip fracture or posterior hip dislocation. Neurologic examination includes evaluation of light touch and pinprick sensation. The examination should also assess for any signs of arterial injury indicating a rapidly expanding hematoma. Femoral, popliteal, dorsalis pedis, and posterior tibial pulses should all be assessed. Comparative blood pressures obtained by Doppler examination in the injured and uninjured extremities (arterial pressure index) could be useful in diagnosing occult femoral arterial injuries. If the systolic pressure in the affected extremity is 90% or less (ratio less than 0.9) than that in the unaffected extremity, additional diagnostic studies should be performed. Those studies include Doppler flow ultrasound imaging, computed tomography angiography (CTA), or angiography alone. The ankle-brachial index (ABI) also can be determined by comparing the systolic pressures of the affected extremity and the ipsilateral arm. An index less than 0.9 necessitates further diagnostic studies.[6] Although compartment syndrome of the thigh is rare, consideration should be given to this diagnosis if the patient sustained a severe mechanism of injury and has tense swelling in the thigh.

DIFFERENTIAL DIAGNOSIS

A detailed history and physical examination often elicit the cause of the pain. Patients with hip and thigh pain can have pain referred from a multitude of other areas. If a fracture is not apparent, emergency clinicians should consider the causes outlined in Table 49.1 in patients who are experiencing hip or thigh pain. In the setting of trauma, it is imperative that a thorough physical examination be done to exclude referred pain and associated injuries. Most patients who arrive in the emergency department (ED) with hip or thigh pain provide a clear history of a traumatic event. Hip or knee pain in the young, in athletes, and in the elderly deserves investigation, even when minimal or no trauma has been reported. This diverse patient population commonly has an occult hip disruption, occasionally involving the femur. Senile osteoporosis is the leading cause of femoral neck fractures after minor trauma; pathologic fractures of the femur can result from metastatic, metabolic, or endocrine disease.

DIAGNOSTIC TESTING

Radiographic Evaluation

Plain radiographs, including true anteroposterior and lateral views of the femur, are usually adequate for the evaluation of potential fractures (Fig. 49.11). The femur should be in as much internal rotation as possible. Fracture lines can be very subtle, particularly in the femoral neck. Three methods are useful for identifying inconspicuous fractures:

- First is the use of Shenton's line, which is described in a subsequent section on hip dislocations.
- Second is a search for the normal S and reverse S curves seen on radiographs of non-fractured hips. In normal anatomic position, the convex outline of a normal femoral head smoothly joins the concave outline of the femoral neck. This produces an S curve and a reverse S curve, regardless of the orientation of the radiographic projection. In searching for a fracture of the femoral neck, the medial and lateral cortical margins of the femoral head and neck should be carefully examined for those curves (Fig. 49.12). A fracture produces a tangential or sharp angle, indicating disruption of the normal anatomic relationship.
- The third method, useful in the evaluation of seemingly unremarkable hip radiographs, is tracing the trabecular lines as they pass from the femoral shaft to the femoral head. Disruption of these lines as they pass through the fracture site is often the only, albeit subtle, clue.

In impacted femoral neck fractures, the neck cortex is driven into the cancellous femoral head. Bone impaction lends a certain inherent stability (Fig. 49.13). If a fracture is found, radiographs of the knee should be obtained as well. It is a basic orthopedic principle to image the joint above and below any fracture, because concomitant injuries are common.

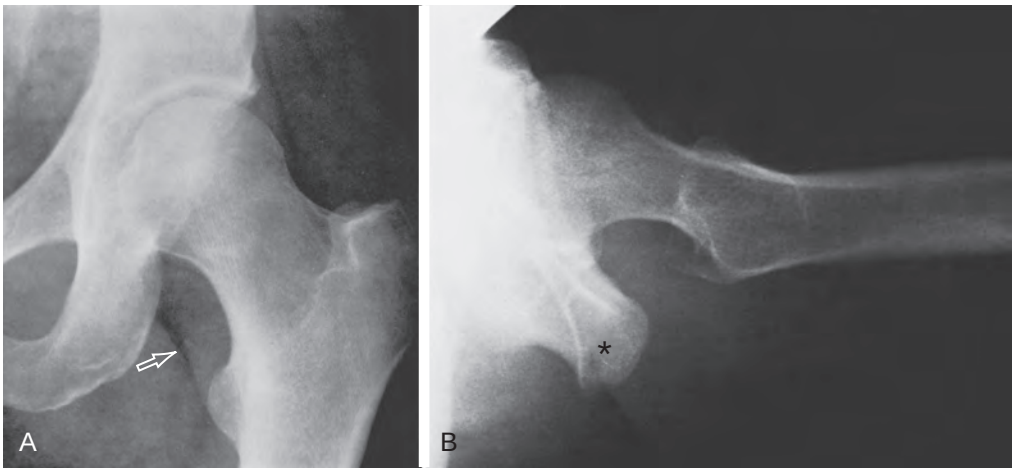

Fig. 49.11. Normal radiographic anatomy of the hip. **A,** Anteroposterior view of the normal adult hip. The open arrow indicates the edge of the iliopsoas muscle shadow. This muscle lies immediately on the capsule of the hip joint. The small concavity in the center of the femoral head is for the attachment of the ligamentum teres. **B,** Cross-table lateral view of the hip demonstrating the normal relationship of the femoral head to the neck. *The asterisk indicates the ischial tuberosity.* (From Harris JH, Harris WH, Novelline RA: The radiology of emergency medicine, ed 3, Baltimore, 1993, Williams & Wilkins.)

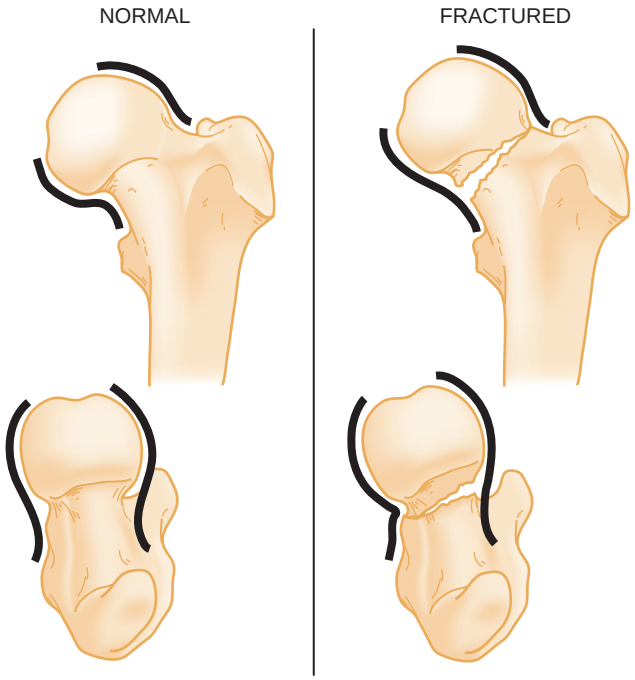

Fig. 49.12. The normal anatomic appearance of the femoral head as smooth S and reversed S lines is drawn above. The concave outline of the femoral neck meets the convex outline of the femoral head as shown here in various views. Any tangential angle suggests a fracture.

Occult Hip Fracture

If radiographs do not show an overt fracture or injury, the care provider should assess gait. Inability to ambulate or difficulty in weight bearing suggests an occult fracture. Up to 10% of all hip fractures are radiographically "occult" on plain films. Failure to detect these injuries increases the risk of death, the risk of subsequent displacement of the fracture, and the incidence of AVN. When a painful hip prevents ambulation and plain radiographs do not reveal a fracture, advanced imaging (CT or magnetic resonance imaging [MRI]) is necessary (Fig. 49.14). Elderly patients with unexplained hip pain lasting more than 3 weeks might be harboring an occult fracture even if they continue to walk. T1-weighted MRI will reveal a fracture that was imperceptible at the time of injury with 100% accuracy and has been found to be cost-effective compared with other strategies. MRI is superior to CT and remains the "gold standard" for diagnosing occult hip fractures and helps guide treatment decisions (see Fig. 49.12).

Bone scans have been useful in these patients, but they lack adequate sensitivity. To identify most occult fractures, this type of scan should be delayed for 72 hours after the injury, which limits its use in the emergency care setting.

MANAGEMENT

Patients with femoral pathology need hemodynamic stabilization. Because of the risk of blood loss—from both the injury and its operative repair—patients with traumatic fracture of the hip or femur should be typed and crossmatched for at least 2 units of blood. Hemodynamic instability can result from dehydration and the loss of up to 3 units of blood into the fracture site. Operative repair should be performed after the patient is resuscitated and in optimal preoperative condition. The preoperative stabilization of an elderly patient with a hip fracture may require a multidisciplinary approach from emergency medicine, orthopedics, internal medicine, cardiology, and anesthesiology. Comprehensive programs co-managed by geriatricians and orthopedic surgeons have been shown to improve short-term outcomes for the elderly with hip fractures and might even lower the mortality rate, highlighting the importance of the medical management of these complex patients.[7]

Traction and Immobilization

If prehospital personnel suspect a femoral fracture, they often place a Hare splint, Sager splint, or similar device that applies traction to the leg before transporting the patient. This management strategy is popular, because it provides pain relief, immobilization, and limits blood loss. However, great care should be taken to ensure the proper use of these devices. Prolonged traction while other injuries are being assessed and managed can cause or worsen serious neurologic injury in the thigh. Traction used in the field for transport can cause skin breakdown at pressure points and might produce potentially damaging tension on the nerve. The

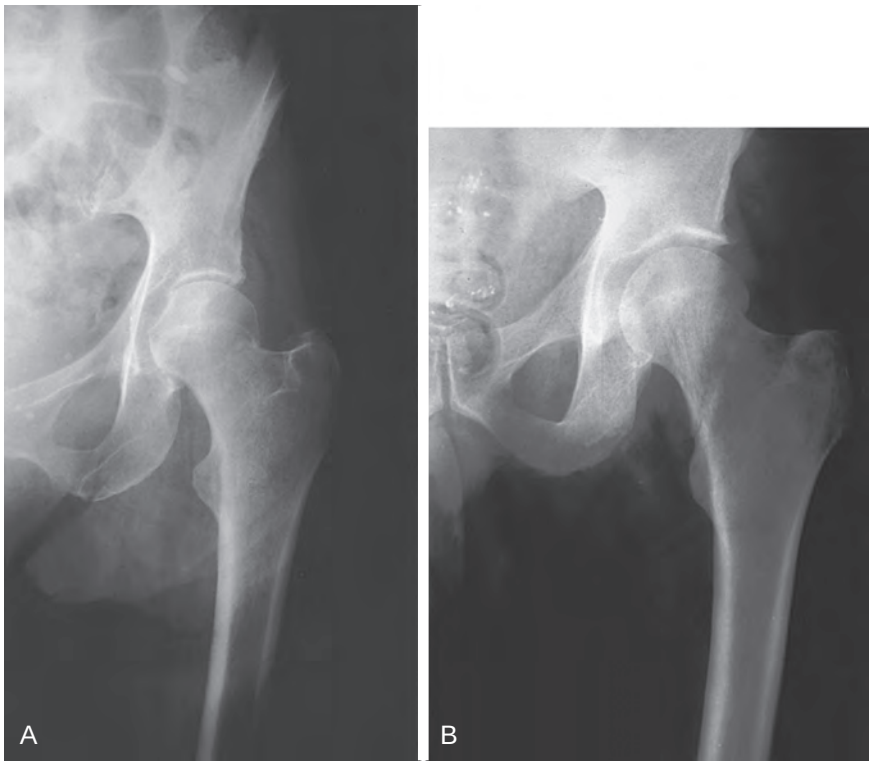

Fig. 49.13. **A,** Subtle nondisplaced impacted femoral neck fracture. Use of S curves aids in identification. **B,** A nondisplaced femoral neck fracture possesses no stability without impaction.

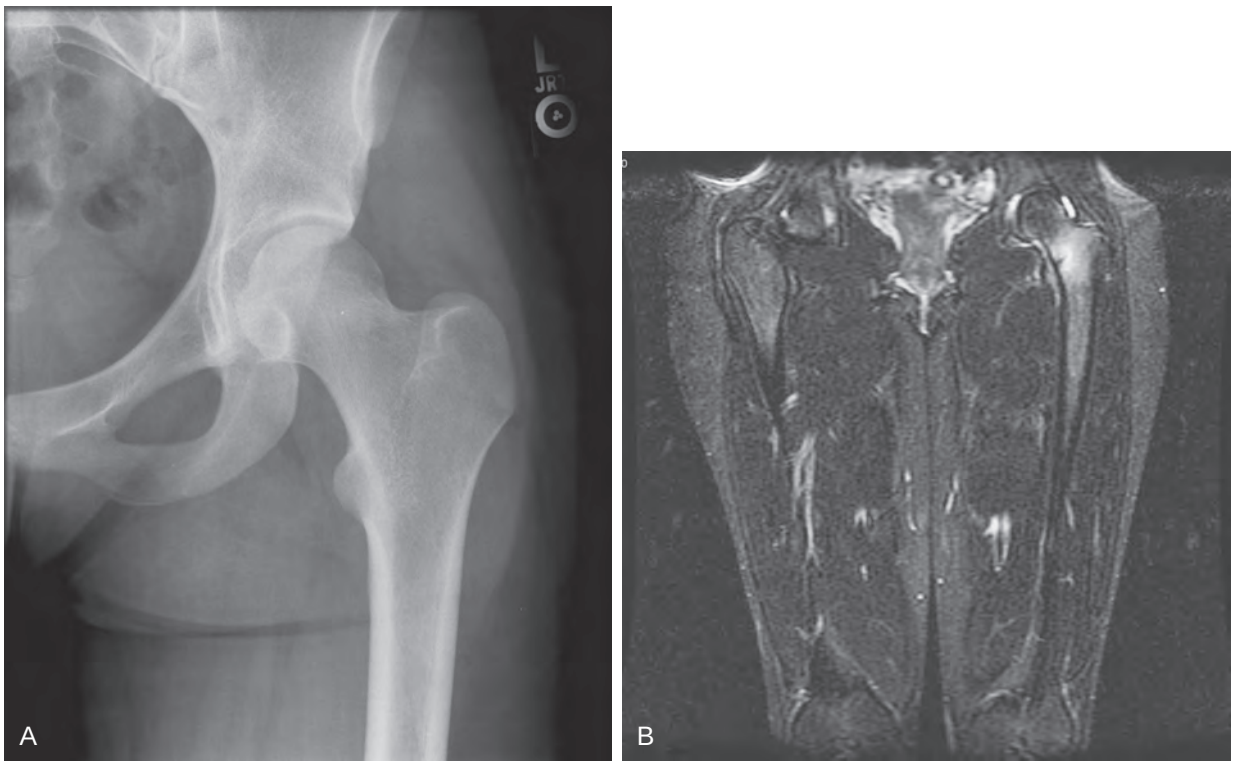

Fig. 49.14. The patient reported hip pain and could not ambulate. **A,** Initial radiographs failed to demonstrate a fracture. **B,** A magnetic resonance image (MRI) revealed a femoral neck fracture through the compressive trabecular fibers.

femoral and sciatic nerves are more likely to be injured from traction or during surgery than from a femoral fracture.

Contraindications to the use of traction splints include pelvic fractures, patellar fractures, ligamentous knee injuries, and tibia or fibula fractures. In the prehospital setting, traction should not be applied to any open fracture that has exposed bone. Such reduction pulls grossly contaminated bone fragments back into the wound before adequate débridement. A study that evaluated patients with multisystem trauma in whom traction splints were placed in the field for femur fractures showed that up to 38% had contraindications to the splints that were placed.

With or without traction, the injured extremity should be immobilized when the patient is moved, to prevent further damage from mobile bone fragments. In the prehospital setting, this can be achieved with simple splinting. In the ED, maintaining the leg in slight flexion at the hip reduces intracapsular pressure, whereas extension of the leg increases pressure and the potential for ischemic necrosis of the femoral head. Therefore, traction for proximal femur fractures should be discontinued once the patient has arrived in the ED. The leg can be supported in a position of comfort with a pillow placed under the thigh. The theoretic advantages for continuation of traction in the ED are pain control and fracture reduction, making operations easier to perform. This is likely true for patients with femoral shaft fractures; however, a Cochrane systematic review that looked at preoperative traction for fractures of the proximal femur in adults found no evidence to support these proposed advantages.

Open Fracture Care

By definition, an *open fracture* is any fracture in which a break in the integrity of the skin and soft tissue allows communication with the fracture and its hematoma. Any nearby wound or break in the skin must be considered to communicate with the fracture. The three categories of open fractures are described in Table 49.2. A bone piercing from the inside outward often causes only a small wound, after which the contaminated bone tip slips deceptively back into the soft tissue. Open wounds should be irrigated and then covered with sterile saline-moistened gauze.

For all type I open fractures, a first-generation cephalosporin (such as, cefazolin, 1 g) should be administered intravenously. Types II and III might require additional gram-negative coverage depending on the amount of devitalized tissue and the extent of involvement of the groin and its gram-negative skin flora. This additional coverage could be provided by an aminoglycoside (such as, tobramycin, 1.5 mg/kg). The use of perioperative first-generation cephalosporins reduces the risk of postoperative infection even in patients with closed fractures. Great care should be taken to identify tetanus-prone wounds so that appropriate prophylaxis can be provided with tetanus immune globulin when indicated. Immunization status should be verified in all patients and updated as needed.

TABLE 49.2

Classification of Open Fractures

CRITERION	TYPE I	TYPE II	TYPE III
Wound size	<1 cm	1 to 10 cm	>10 cm
Soft tissue damage	Minimal, if any	Moderate, without nerve, arterial, or periosteal stripping	Extensive muscle devitalization; nerve and arterial involvement often classified as type IIIb
Mechanism of injury	Bone edge pierces outward	Variable	High-energy shotgun blast, high-velocity gunshots

From Hoff WS, et al: East Practice Management Guidelines Work Group: update to practice management guidelines for prophylactic antibiotic use in open fractures. J Trauma 70:751-754, 2011.

Compartment Syndrome

Because of the thigh's larger volume, compartment syndrome within the thigh is far less common than in the lower part of the leg. A large amount of bleeding into the thigh compartment is required before the pressure rises above capillary perfusion pressure. When compartment syndrome does occur in the thigh, only 50% of the cases are associated with a femur fracture. It is difficult to clinically differentiate the expected swelling after an injury from early compartment syndrome. Clinical examination and the use of direct pressure measurements can detect the development of compartment syndrome at an early stage.

Pain Management

Systemic Analgesia

Pain control in EDs is often inadequate. For patients with femoral fractures, opioid analgesia is often indicated in combination with other pain-relief strategies. In addition to parenteral medications, other pain-relieving strategies include immobilization of the injured extremity, placement of the injured extremity in a position of comfort, and the consideration of local analgesia in the form of nerve blocks.

Pharmacologic Approaches

The classic pharmacologic treatment for pain management in patients with traumatic femoral injuries is opioid analgesics. Morphine, fentanyl, and hydromorphone are all acceptable options. Meperidine should not be used because of unacceptable side effects. Pentazocine is contraindicated in the elderly because of its central nervous system (CNS) effects (eg, lowered seizure threshold). Nonsteroidal antiinflammatory drugs (NSAIDs) can also be difficult to titrate, especially in the elderly, due to their renal and gastrointestinal side effects.

Femoral Nerve Block

The femoral nerve block is an excellent option as an adjunct or alternative to systemic analgesics in patients at risk for hypotension. Femoral nerve blocks significantly decrease the time to the lowest pain score compared with intravenous narcotics, and patients require significantly lower doses of narcotics. The block can be created with the assistance of a peripheral nerve stimulator to localize the nerve or bedside ultrasound to directly visualize the nerve before the anesthetic is injected.[8] The procedure can also be performed by emergency clinicians without the assistance of peripheral nerve stimulators or ultrasound. If a long-acting anesthetic such as bupivacaine is used, the expected onset of analgesia is within 30 minutes and its duration is 6 to 8 hours.[9]

Careful neurovascular examination should be performed and documented before the femoral nerve block is performed. After the nerve block procedure, continued assessment of the femoral muscular compartments is advisable to check for the development of compartment syndrome. If an injury is considered at especially high risk for compartment syndrome, orthopedic surgery consultation should be obtained before the block, and measurement of compartment pressures after the block should be considered. Because the sciatic nerve innervates the compartments of the

lower limb, a femoral nerve block will not mask the clinical presentation of compartment syndrome in the lower leg.

Hip Arthroplasty

The most common indication for total hip arthroplasty (THA) is joint failure resulting from severe osteoarthritis. Other indications include rheumatoid arthritis, some types of hip fracture, AVN, and certain tumors. Arthritis associated with Paget's disease, trauma, ankylosing spondylitis, and juvenile rheumatoid arthritis is also relative indications for total or partial hip arthroplasty.

THA provides an immediate, substantial reduction of pain and improvement in functional ability and overall quality of life. A 10-year follow-up study of patient outcomes, including gait, perception of pain, physical mobility, sleep patterns, and energy scores, showed positive results in more than 90% of cases. Despite the tremendous success of THA, numerous complications have been reported. The most common is aseptic loosening of the prosthesis. Others include component wear, infection, adjacent femoral fractures, deep vein thrombosis, and postoperative dislocation of the femoral component. In general, flexion past 90 degrees, adduction, and internal rotation place the hip at risk for dislocation. This combination can occur when patients bend at the waist (eg, to sit on a low toilet or to get out of a chair) or cross their legs (Fig. 49.15).

Fractures of the Hip and Femur

Avulsion Fractures

The incidence of avulsion fractures is increasing as a result of the growth of competitive sports participation, especially in teenage athletes. The muscular origin of this type of injury commonly involves the pelvic apophyses, which might not fully ossify until age 25. Avulsion at the site of the growth plate is the result of sudden maximal muscular exertion. It can occur with rapid acceleration or sudden changes in speed or direction. The athlete classically experiences a sudden piercing pain at the site of injury, along with a "snapping" or "popping," and frequently falls to the ground because of the intensity of this pain. The pain of avulsion injuries of the hip can manifest as referred pain to the thigh; these fractures are most common in adolescents and young adult athletes. As depicted in Figure 49.16, avulsion at the ASIS involves the separation of a thin piece of bone as the sartorius muscle suddenly contracts (see Fig. 49.16A). The anterior inferior iliac spine (AIIS) is avulsed by the rectus femoris, and the hamstring group can displace the ischial tuberosity (see Fig. 49.16B). Avulsion fractures of the ASIS and AIIS are managed nonoperatively. Treatment of avulsion fractures of the ischial tuberosity is more controversial. Most experts recommend conservative treatment for avulsion injuries with less than 2 cm of displacement. Fractures with more than 2 cm of displacement might benefit from operative fixation to prevent nonunion, as well as union achieved by exuberant callus formation.

Proximal Femoral Fractures

Fractures of the proximal end of the femur are classified on the basis of their relationship to the hip capsule (intracapsular or

Fig. 49.15. Dislocation of the femoral prosthesis in a patient who had undergone total hip arthroplasty (THA). The femoral head often becomes caught on the rim of the acetabular cup, thereby preventing reduction. Reduction can disrupt or dislocate the acetabular cup.

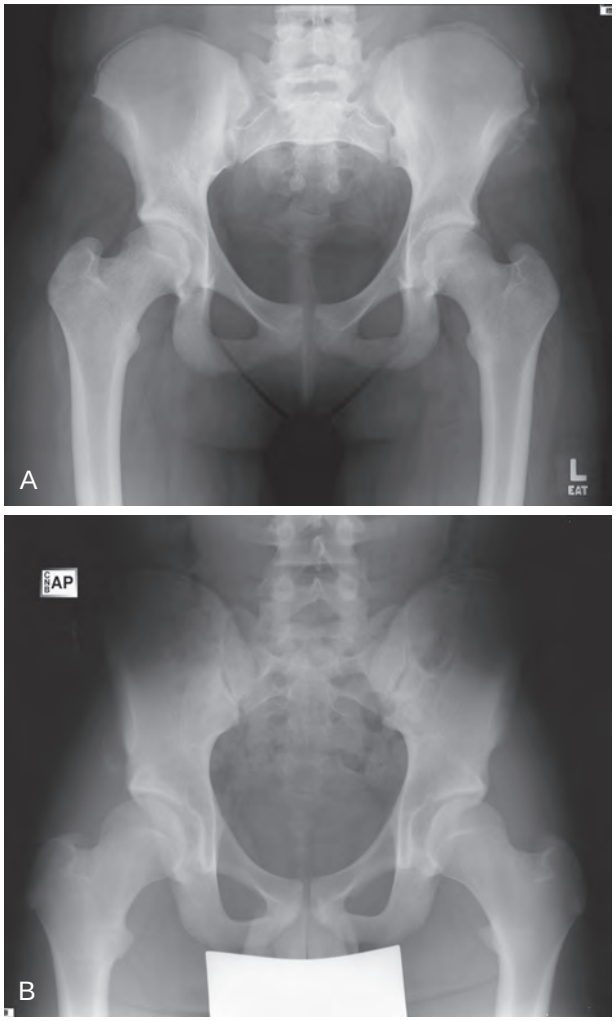

Fig. 49.16. **A,** Avulsion fracture of the anterior superior iliac spine (ASIS) by the sartorius muscle. **B,** Avulsion fracture of the anterior inferior iliac spine (AIIS) by the rectus femoris.

extracapsular), anatomic location (neck, trochanteric, intertrochanteric, subtrochanteric, and shaft fractures), and degree of displacement.

Femoral Neck Fractures

Classification. Although several classification systems have been used to describe these fractures, they have been abandoned because of poor inter-rater reliability and limited clinical utility. Currently, femoral neck fractures should be classified as either nondisplaced or displaced.

Between 15% and 20% of all femoral neck fractures are *nondisplaced fractures*. The fracture line is often very subtle. Techniques that allow detection of subtle fracture lines are useful for this reason. Evaluation of the continuity of the subcapital cortical lines, search for an indistinct broad band of increased subcapital density, and identification of the S and reverse S radiographic curves (see Fig. 49.12) leads to the correct diagnosis in most cases. In impacted femoral neck fractures, the neck cortex is driven into the cancellous femoral head. Bone impaction lends a certain inherent stability (see Fig. 49.13). Because of this stability, two management approaches have been advocated: internal fixation and early ambulation. Internal fixation reduces the length of hospital stay and improved rehabilitation and has become the preferred treatment modality. Without impaction, a nondisplaced femoral neck fracture is unstable and will become displaced without internal fixation.

On initial evaluation, a patient with a *displaced fracture* of the femoral neck lies with the limb externally rotated, abducted, and slightly shortened. The diagnosis is easily confirmed with plain hip films. To avoid further disruption of the blood supply to the femoral head, range-of-motion assessment should be deferred. Treatment of these displaced fractures consists of open reduction and internal fixation (ORIF), hemiarthroplasty, or THA. In all displaced femoral neck fractures, the femoral head is rendered largely avascular, and signs of AVN and collapse might develop over the ensuing several years. The mortality rate during the first year after a femoral neck fracture is 14%, compared with 9% for the control population. Factors affecting the mortality rate include age, male sex, psychiatric illness, end-stage renal disease, and congestive heart failure. Institutionalized patients have a death rate up to three times higher than noninstitutionalized patients. Complications can be minimized by early reduction, stable internal fixation, early ambulation, and close attention to medical comorbidities.

The two major complications of femoral neck fractures are AVN and nonunion. AVN is the most common complication, despite optimal treatment, because of the complex arterial anatomy. Deep infection in the form of osteomyelitis or septic arthritis is more common with femoral neck fractures, because the fracture line extends into the joint. The use of perioperative antibiotics dramatically reduces the rate of infection. Pulmonary embolism is another significant complication and is the leading cause of death 7 days after fracture. Anticoagulation is recommended for at least 10 days after any hip surgery in patients without significant contraindications. Fondaparinux is an effective anticoagulant in this setting.

Intertrochanteric Fractures

The fracture line of intertrochanteric fractures extends between the greater and lesser trochanters of the femur. These injuries are considered extracapsular fractures. The fracture line extends through cancellous bone, which has an excellent blood supply. The hip's short external rotators remain attached to the distal fracture fragment, and the internal rotators are attached to the proximal fracture fragment. The strong action of the iliopsoas muscle causes the leg to be shortened and externally rotated.

A large number of classification systems for intertrochanteric fractures have been proposed to predict the possibility of achieving and maintaining stable reduction. A useful system designates the fracture according to the number of bone fragments (Fig. 49.17).

Intertrochanteric fractures often are associated with other, distant, fractures caused by the same trauma, such as a fall. Associated fractures of the distal radius, proximal humerus, ribs, and lumbar and thoracic spine are often overlooked because the femoral fracture distracts the attention of both patient and

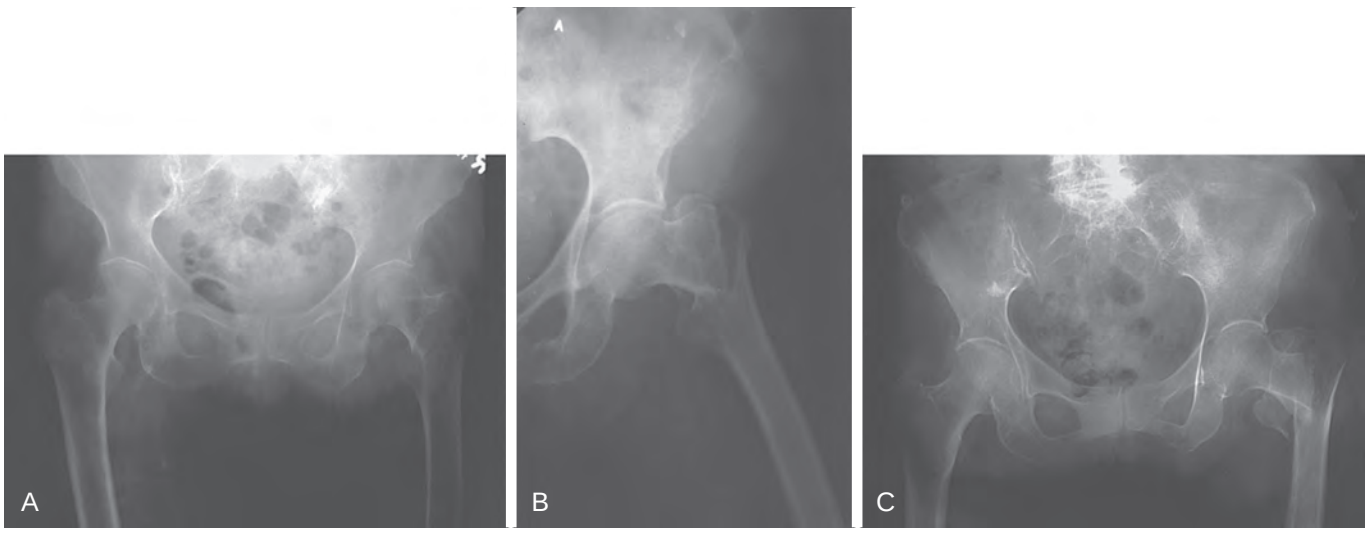

Fig. 49.17. The number of parts produced by the fracture classifies intertrochanteric fractures. **A,** Two-part fractures have one part connected to the femoral head and a second part attached to the shaft. **B,** The greater or lesser trochanter also is fractured with three-part fractures. A greater degree of instability is produced because the attached muscles continue to act on the fractured trochanter. **C,** Four-part intertrochanteric fractures involve both trochanters.

clinician. Nutrition, chronic diuretic use, and decreased oral intake prior to the injury contribute to dehydration, and greater need for resuscitative fluids.

A substantial majority of intertrochanteric fractures require internal fixation. Such fixation brings rapid mobilization, decreased hospital length of stay, reduced mortality, and improved function. The procedure should be performed on an urgent rather than an emergent basis, because the patient should be fully resuscitated prior to operative repair. The risk of death increases when the patient is taken to the operating room on the day of injury; however, early repair within 24 to 48 hours improves the 1-year mortality rate. Preoperative medical optimization by multidisciplinary medical teams can decrease the 1-year mortality rate in these patients.[7]

Patients with intertrochanteric fractures have a mortality rate of up to 30% in the first year.[7] Life expectancy returns to normal among patients who survive that year. Survival is most commonly related to the patient's age and preexisting medical conditions. Additional risks associated with operative treatment include mechanical failure, implant migration, and infection. Mechanical failures and nonunion are much more common in patients with unstable fractures and those whose fractures were not reduced adequately. Approximately half of patients who sustain these fractures are eventually able to regain their original level of ambulation. Yearly infusion of zoledronic acid (a bisphosphonate) beginning within 90 days after hip fracture repair reduces the incidence of new fractures and decreases the mortality rate.

Isolated Fractures of the Greater or Lesser Trochanter

Fractures of the greater or lesser trochanter are rare. They occur in women more often than in men and are the result of a fall directly onto the trochanter or avulsion by the iliopsoas muscle. There may be a comminuted fracture involving only part of the greater trochanter or more subtle impaction of the lateral cortex. If an avulsion is present, the fragments are displaced superiorly and posteriorly (Fig. 49.18).

Fig. 49.18. Isolated fracture of the greater trochanter. Note that the trochanter is displaced in the typical posterior and superior direction.

Treatment consists of pain control and early mobilization with crutches; weight bearing is allowed as tolerated. Satisfactory outpatient management of this injury is possible, because the prognosis is good and healing generally is excellent.

Subtrochanteric Fractures

Subtrochanteric fractures occur between the lesser trochanter and the proximal 5 cm of the femoral shaft. They may accompany intertrochanteric fractures. The subtrochanteric region is composed almost entirely of cortical bone, which lacks the vascularity important to new bone growth and repair. When fractured, it is more likely to be comminuted than bone with a higher cancellous content. In addition, the greater portion of the biomechanical forces of the femur is transmitted down the curved medial cortex of the femoral shaft. If this cortex is disrupted, the metal hardware undergoes the majority of the stress. This mechanism accounts for the increased incidence of hardware failure when the medial cortex is largely involved.

These fractures characteristically are deformed because of the unbalanced muscle forces. In displaced fractures, the attachments of the iliopsoas, gluteal, and external rotator muscles consistently produce flexion, abduction, and external rotation of the proximal fragment.

Subtrochanteric fractures account for 11% of all fractures of the proximal end of the femur. Although a small percentage of these fractures is caused by gunshot wounds, the usual mechanism of injury is direct blunt trauma. There is a bimodal distribution of injuries. The first group comprises victims of extreme high-energy trauma. In these patients, the subtrochanteric fracture is rarely an isolated injury because of the tremendous force required to produce it. Thirty percent to 50% of patients with subtrochanteric fractures have associated fractures of the pelvis, spine, or other long bones. The second group consists of elderly patients who experience a fall, in whom the fracture occurs through an area of weakened cortical bone. Pathologic fractures from metastatic lesions, Paget's disease, renal osteodystrophy, osteogenesis imperfecta, and osteomalacia are well-recognized clinical entities in these patients. Stress fractures can occur in this region but are extremely uncommon. Various classification systems for these fractures have been proposed, although none is widely accepted. From a practical standpoint, it is best to define and describe these fractures by location (proximal or distal), angle (transverse or oblique), and the presence of comminution (Fig. 49.19).

Hemodynamic instability can result from blood loss at the fracture site. Although such blood loss can lead to hypovolemic shock, other causes of hypotension in a trauma patient need to be considered due to the forces required to obtain these injuries. Open fractures are rare and, when present, are accompanied by significant soft tissue injury. Vascular and neurologic injuries are also uncommon.

Definitive management of subtrochanteric fractures is a complex issue. Maintaining limb length and controlling rotation are difficult. ORIF is the treatment of choice. However, in the rare case of a severely comminuted or an open, grossly contaminated fracture, nonoperative management might be preferable. Children younger than 10 years old also can be managed nonoperatively. The amount of remodeling and growth stimulation occurring in children of this age usually ensures good results without internal fixation.

The bone in the subtrochanteric region is largely cortical and relatively avascular compared with the cancellous intertrochanteric region. It logically follows that healing is comparatively slow. Comminuted and distal subtrochanteric fractures carry a worse prognosis.

Complications include fat embolism in patients of all ages and the adverse effects of prolonged immobilization in the elderly. The

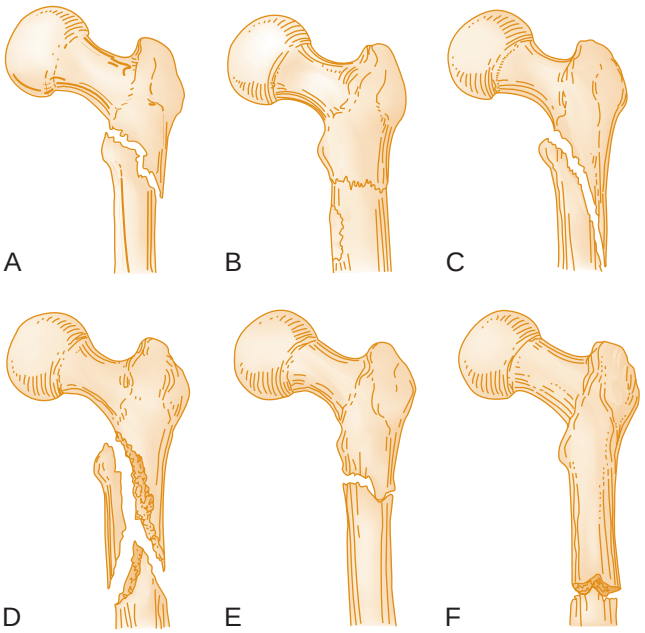

Fig. 49.19. Variants of subtrochanteric fractures. **A,** Short oblique fracture. **B,** Short oblique fracture with comminution. **C,** Long oblique fracture. **D,** Long oblique fracture with comminution. **E,** High transverse fracture. **F,** Low transverse fracture.

mortality rate from subtrochanteric fractures is approximately 10%. The violent force and common associated injuries contribute to the high mortality among patients who sustain these fractures.

Femoral Shaft Fractures

Femoral shaft fractures are common injuries in young adults after high-energy trauma. As is the case with other femoral cortical fractures, considerable force is required to produce a fracture in a normal shaft. Automobile and motorcycle crashes, falls, and pedestrian incidents account for a majority of femoral shaft fractures. The femoral shaft usually fails under tensile strain, resulting in a transverse fracture. Higher forces produce varying degrees of segmentation. Open fractures of the femoral shaft are less frequent and are often the result of a gunshot wound. Pathologic fractures occur from a low-mechanism force that produces torsion and spiral fractures.

If seemingly trivial trauma has resulted in a spiral femoral shaft fracture in a child, non-accidental trauma and pathologic fracture should be considered. Common causes of pathologic fracture include unicameral bone cysts, fibrous dysplasia, osteogenesis imperfecta, and malignancy.

There is no commonly accepted or easily remembered classification for femoral shaft fractures. The location and geometry of the fracture line should be used to describe them. Useful terms include *transverse*, *oblique*, *spiral*, *wedge*, and *comminuted*.

Patients often arrive with the injured extremity immobilized by traction devices, which should be removed while immobilization of the limb is maintained. Neurovascular injuries are rarely associated with closed femoral shaft fractures. Significant hemorrhage into the thigh can occur with a femoral shaft fracture, just as with intertrochanteric and subtrochanteric fractures. Common concomitant injuries in patients with femoral shaft fractures include hip fractures, fracture-dislocations, femoral neck fractures, supracondylar femoral fractures, and patellar fractures. Almost half of femoral shaft fractures have associated ligamentous damage in the knee. If the patient has a femoral fracture, pain often prevents adequate evaluation of knee stability. Any attempt to evaluate the stability of the knee acutely will cause additional pain and hemorrhage without providing useful, reliable information.

Internal fixation with intramedullary rods has been demonstrated to shorten both hospitalization and total disability time after most femoral shaft fractures. The vast majority of femoral shaft fractures heal well in time, regardless of the mode of treatment. Severely comminuted fractures are more likely to be treated by closed reduction.

Femoral shaft fractures have a union rate close to 100%, and most patients are able to return to work after approximately 6 months. Even a minor degree of limb shortening or misalignment can result in arthritis of the hip or knee or chronic back pain. Refracture is a rare occurrence that is most likely to occur during early healing and callus formation or during the brief period after the hardware is removed. After the hardware is removed, the unsupported bone is required to bear the entire weight of axial loading and is at risk for refracture.

Stress Fractures

Pathophysiology. Stress fracture of the femoral neck was first reported in 1905 by Blecher. Stress fractures or reactions occur when normal bone is subjected repeatedly to submaximal forces. This recurring stress stimulates the bones to remodel and strengthen. In a stress fracture, osteoblasts are unable to lay down new bone and remodel fast enough, so the bone fails. Stress fractures can also occur in diseased bone when it is subjected to repeated minimal stress.

The symptoms of a stress fracture of the femoral neck often are so subtle that they can be mistaken for muscle strain or an overuse injury. Early symptoms frequently include morning stiffness and aching in the hip on the first steps after a period of rest. The pain gradually increases during prolonged exercise and may reach the point at which weight bearing becomes impossible. Patients complain of pain in the groin or along the medial aspect of the thigh toward the knee.

Patients with these fractures usually limp because of pain. Their antalgic gait is characterized by shortening of the stance phase of the injured extremity. No obvious external rotation or shortening of the leg is seen; the patient experiences only minor discomfort with active or passive motion, except at the extremes of flexion and internal rotation. Tenderness is minimal because of the large amount of soft tissue coverage at the femoral neck.

Radiographs are helpful if they demonstrate a fracture, but findings often are negative until 10 to 14 days after the injury. Endosteal or subperiosteal callus develops at the fracture site during this period. In addition to the standard anteroposterior and lateral views of the hip, oblique views may delineate the fracture line. Close attention should be paid to the trabecular fibers of the femoral neck. A stress fracture is often identified as an isolated disruption of either the tensile (lateral aspect of the femoral neck) (Fig. 49.20A) or the compressive (medial aspect of the femoral neck) (see Fig. 49.20B) trabecular fibers. If a fracture is suspected clinically but radiographic findings are negative, the next step is MRI. If a fracture is found, the contralateral hip should be evaluated extensively because of the significant incidence of bilateral stress fractures.

Treatment of stress fractures of the femoral neck is based on involvement of the compressive or tensile aspect. Compressive-side fractures involving less than half of the cortex are inherently stable and can be treated conservatively with partial weight bearing with crutches. Tension-side fractures and compressive-side fractures involving more than half the cortex are considered unstable and at risk for displacement. These fractures should be treated operatively with screw fixation.[10]

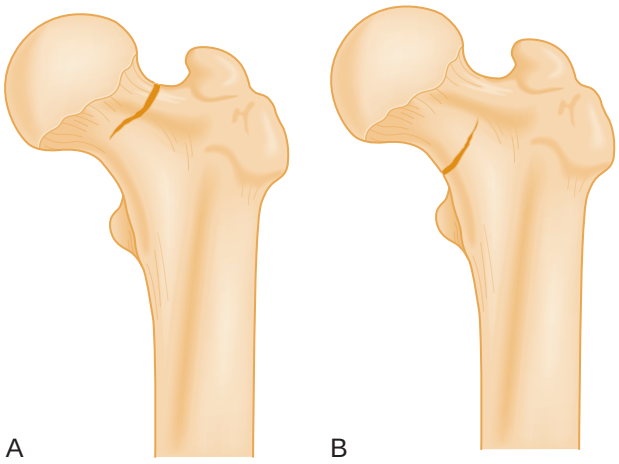

Fig. 49.20. Femoral neck fractures through the tensile **(A)** and compressive **(B)** trabecular fibers.

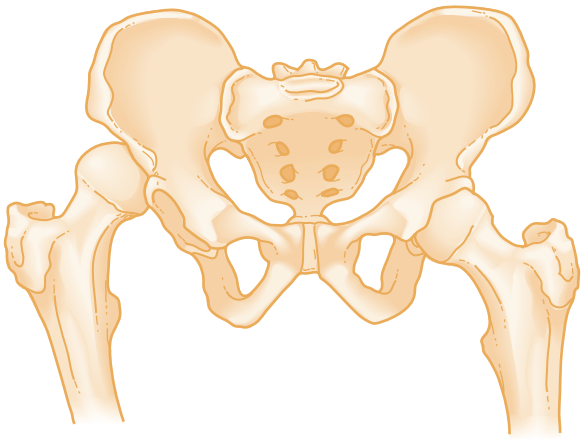

Fig. 49.21. In a posterior dislocation, the hip is internally rotated and the lesser trochanter is superimposed on the femoral shaft. Failure to visualize the lesser trochanter on the anteroposterior projection identifies a posterior dislocation.

Dislocations and Fracture-Dislocations of the Hip and Femur

Hip Dislocations

Dislocations and fracture-dislocations of the hip are true orthopedic emergencies. The hip joint possesses impressive inherent strength and stability; therefore, considerable force is required to produce these injuries. With this understanding, a hip dislocation serves as a "red flag" for multisystem injury and should prompt a diligent search for other injuries. As many as 70% of patients with a dislocation have an associated acetabular fracture. Knee fractures, ligamentous injuries, and dislocations are present in up to 30% of patients who have sustained a hip dislocation. It is highly recommended that, in the presence of this type of injury, patients be managed as major trauma victims. The incidence of hip fractures and dislocations is increasing in young patients, often as a result of high-energy trauma. Up to 50% of children with a hip dislocation have fractures elsewhere. In small children, dislocation of the hip is more common than femoral neck fractures. The force required to dislocate a pediatric hip is much less than that required in an adult because the acetabulum is less completely developed. Seemingly negligible trauma, such as tripping or a minor fall, can dislocate the femoral head in a young child. In a school-age child, athletic injuries are the major cause of traumatic hip dislocation. In the teenage years, MVCs predominate as the cause of hip dislocations.

Traumatic hip dislocations occur primarily in patients sustaining severe multisystem trauma, most often as a result of a high-speed MVC. Failure to use seat belts is a significant risk factor. Less common mechanisms include falls, sports injuries, and pedestrians struck by automobiles.

Posterior dislocations are almost always the result of MVCs. A seated vehicle occupant typically has the hip adducted, flexed, and internally rotated at the time of impact. As the knee strikes the dashboard, the force is transmitted through the femoral shaft to the femoral head. With sufficient force, the femoral head dislocates posteriorly. Anterior dislocations result from forceful extension, abduction, and external rotation of the femoral head. These forces lever the head up out of the acetabular cup.

The relationship of the femoral head to the acetabulum is used to classify dislocations into anterior, posterior, central, and inferior types. A fracture-dislocation includes an associated fracture of the acetabulum or femoral head. Posterior dislocations (Fig. 49.21) account for 80% to 90% of dislocations. Anterior dislocations (Fig. 49.22) are seen in 10% to 15% of patients. In anterior

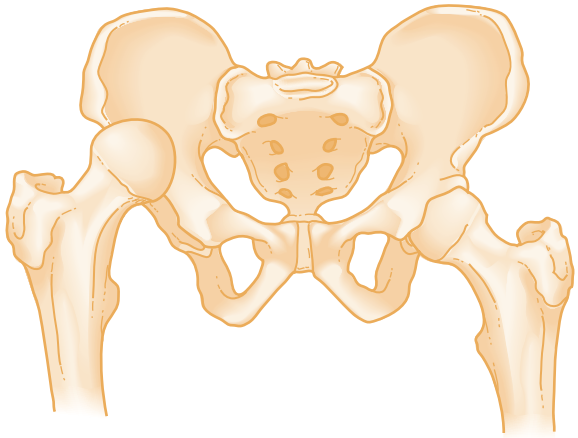

Fig. 49.22. In an anterior dislocation, the hip is externally rotated and the lesser trochanter appears in profile. The hip is farther from the x-ray cassette than the unaffected side and may appear larger because of the beam's projection.

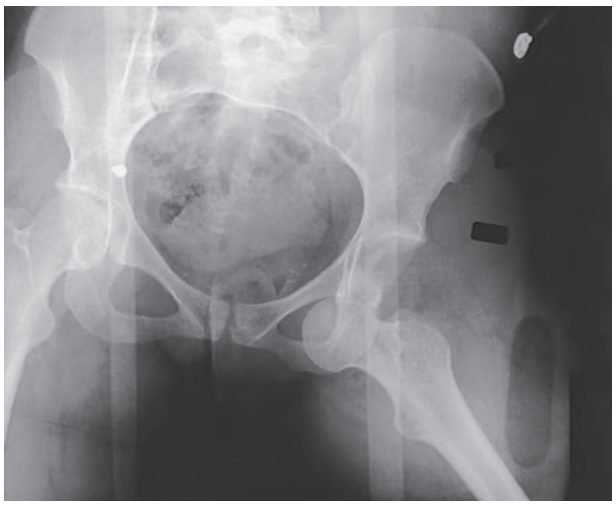

Fig. 49.23. Obturator dislocation.

dislocations, the femoral head can dislocate medially toward the obturator foramen (obturator dislocation) (Fig. 49.23) or laterally toward the pubis (pubic dislocation) or the iliac crest. Central dislocations, which occur in 2% to 4% of cases, are not true dislocations, because the entire femoral head is forced centrally

through a comminuted fracture of the acetabulum. Inferior dislocation of the hip associated with inversion of the femoral shaft (luxatio erecta femoris) is a very rare condition that occurs with or without associated trochanteric fracture.[11]

The position of the injured extremity might provide valuable clues in the evaluation of a hip dislocation. A patient with a posterior dislocation typically holds the hip flexed, adducted, and internally rotated. The knee of the affected extremity rests on the opposite thigh. The extremity generally is shortened, and the greater trochanter and buttock may be unusually prominent. In contrast, a patient with an anterior dislocation holds the hip in abduction, slight flexion, and external rotation, and the leg could appear lengthened. These physical findings might be absent in patients with an associated ipsilateral femoral shaft fracture.

The neurovascular examination should focus on the sciatic nerve and femoral vessels. Sciatic palsy is present in approximately 10% of patients with hip dislocation and most commonly involves the peroneal nerve branch. The most sensitive clinical sign of peroneal nerve palsy is weakness of the extensor hallucis longus; other signs include weakness of dorsiflexion and numbness or tingling over the dorsum of the foot. The femoral vessels and nerve are particularly prone to injury after an anterior dislocation.

Radiologic investigation begins with an anteroposterior view of the pelvis. This view alone will identify a majority of hip dislocations. An anteroposterior pelvis film should be obtained in all trauma patients with the aforementioned deformities. The anteroposterior radiograph should include the entire pelvis and the proximal third of the femur to allow comparison of both hips. When a dislocation is found or suspected, a lateral view of the hip will provide additional definition of the injury.

Although most hip dislocations are seen clearly with these two views, several more subtle radiographic signs can assist emergency clinicians in making a diagnosis. The first indicator involves the position of the lesser trochanter. Because a posteriorly dislocated hip is internally rotated, the lesser trochanter is superimposed on the femoral shaft and is not seen on the anteroposterior projection. By contrast, an anteriorly dislocated hip is externally rotated, and the lesser trochanter appears in profile. The second clue is found in the size of the femoral head. Because a posteriorly dislocated hip is closer than the unaffected side to the x-ray cassette, it appears smaller. The converse is true in anterior dislocations, in which the hip is farther from the x-ray cassette than the contralateral side is and thus appears larger. The third finding relates to the integrity of Shenton's line (Fig. 49.24), a smooth, curved line drawn on the radiograph along the superior border of the obturator foramen and medial aspect of the femoral metaphysis. Disruption of this line should raise suspicion for a femoral neck fracture or hip dislocation.

An obvious dislocation might distract the clinician from a search for concomitant fractures. Examination of the trabecular pattern can identify associated fractures of the acetabulum and femoral head, neck, or shaft. It is important to identify acetabular fractures before closed reduction is attempted because intra-articular bone fragments could interfere with effective reduction. Although these fractures might make the reduction more difficult, their presence is not a contraindication to the procedure.

Hip dislocations constitute a true orthopedic emergency, and reduction should be performed within 6 hours. The incidence of AVN, traumatic arthritis, permanent sciatic nerve palsy, and joint instability increases logarithmically with the length of time the hip remains dislocated.

The timing and method of reduction depend on the overall condition of the patient, the type of dislocation, and the presence or absence of associated fractures. In cases of simple dislocation, closed reduction should be attempted first. Although some clinicians recommend that this procedure be performed with the patient under general anesthesia, this delay, with its associated increase in the rate of AVN, is not warranted when procedural sedation in the ED is available. If the emergency clinician chooses to attempt closed reduction, the principles of procedural sedation and monitoring should be followed. The primary relative contraindication to closed reduction is the presence of a femoral neck fracture. Another relative contraindication is the presence of fractures in the dislocated extremity, because such fractures preclude application of traction to the limb. Techniques of closed reduction are described next.

Stimson's technique and the Allis technique have been used most commonly for reduction of posterior hip dislocations (Fig. 49.25). The Allis technique usually is effective for both posterior and obturator dislocations (Fig. 49.26). It is the most commonly

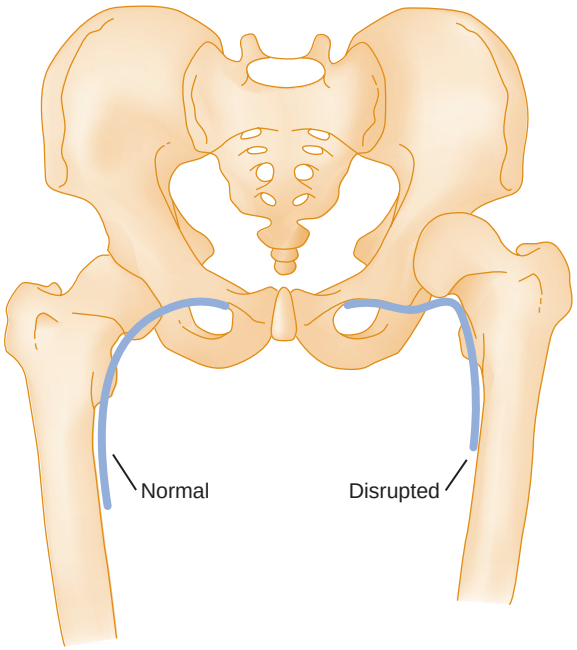

Fig. 49.24. Shenton's line is a smooth curved line drawn along the superior border of the obturator foramen and medial aspect of the femoral metaphysis. Disruption of this line should raise suspicion of a femoral neck fracture or hip dislocation.

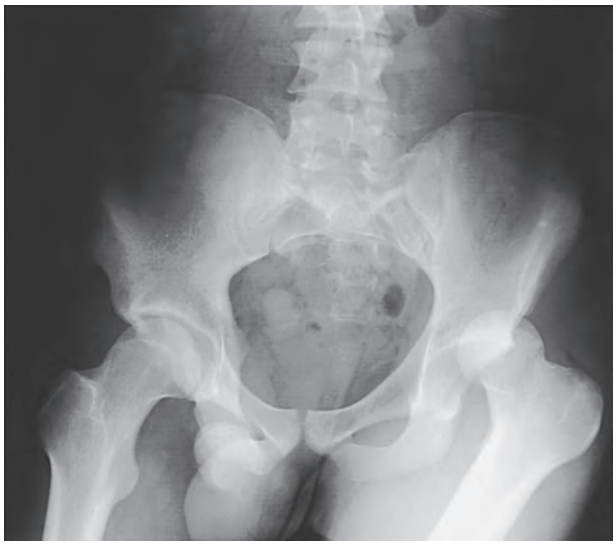

Fig. 49.25. Radiograph of posterior dislocation identified by loss of the lesser trochanter on the anteroposterior view.

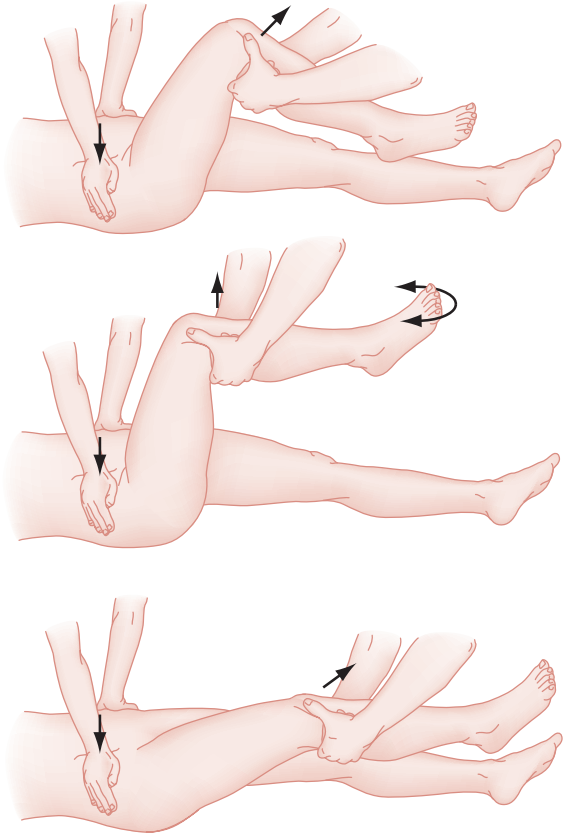

Fig. 49.26. The Allis technique for hip reduction.

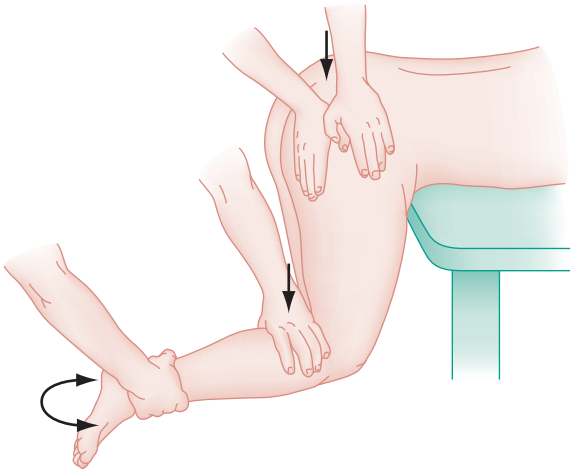

Fig. 49.27. Stimson's technique for hip reduction.

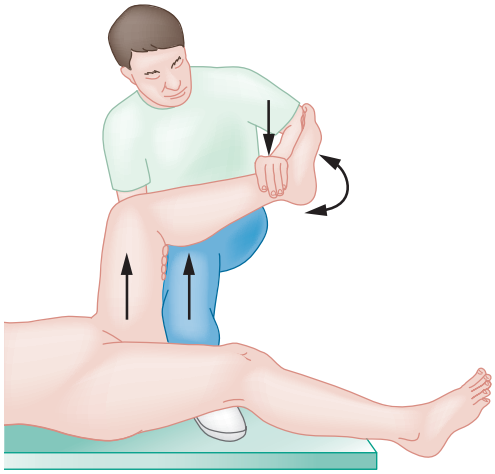

Fig. 49.28. Captain Morgan technique for hip reduction. (Redrawn from Hendey GW, Avila A: The Captain Morgan technique for the reduction of the dislocated hip. Ann Emerg Med 58:536–540, 2011.)

used method for hip reductions in the ED. Unfortunately, it places the clinician at risk of slipping and falling off the bed, places strain on the lower back, and can be extremely difficult for smaller practitioners.

To perform the Allis technique for reduction of posterior hip dislocation:

1. Place the patient in the supine position, with the pelvis stabilized by an assistant.
2. With the knee flexed, apply steady traction in line with the deformity.
3. Slowly bring the hip to 90 degrees of flexion while applying steady upward traction and gentle rotation.
4. Ask the assistant to push the greater trochanter forward toward the acetabulum.
5. Once reduction has been achieved, bring the hip to the extended position while maintaining traction.

Stimson's technique (Fig. 49.27) uses the weight of the limb and the force of gravity to reduce the dislocation and is relatively atraumatic. Although Stimson's technique generally is effective, placing an acutely and often multiply injured trauma patient in the required prone position could be a challenge. Adequate radiographic clearance of the spine usually has not yet been accomplished, and the administration of sedatives and analgesics to a prone patient has inherent risks.

To perform Stimson's technique for reduction of posterior hip dislocation:

1. Place the patient in a prone position, with the leg hanging over the edge of the bed. The hip and knee are flexed at 90 degrees.
2. Ask an assistant to stabilize the pelvis.
3. Apply steady downward traction in line with the femur.
4. Gently rotate the femoral head while the assistant pushes the greater trochanter anteriorly toward the acetabulum.
5. Once reduction has been achieved, bring the hip to the extended position while maintaining traction.

These two techniques are being replaced by new methods that are safer and just as effective: the Whistler and Captain Morgan methods.[12] These techniques use the power of the provider's leg muscles to reduce the hip, instead of relying on lower back and arm strength. The Captain Morgan and Whistler techniques use the provider's knee and arm, respectively, as a fulcrum to apply force and reduce the hip. The Captain Morgan technique has a success rate of 95%, but there are reports that excessive downward force on the ankle has caused ligamentous injuries in the knee.[12,13]

To perform the Captain Morgan technique for reduction of posterior hip dislocation (Fig. 49.28)[12]:

1. With the patient supine on the stretcher in its lowest position, secure the pelvis to the stretcher with a bed sheet or strap. Place the strap over the ischial wings and pubic symphysis. This prevents you from lifting the patient off the bed and is more effective than having an assistant try to secure the pelvis.
2. Stand at the side of the bed and place one foot up on the bed (like Captain Morgan standing on a rum barrel). If you need additional height, consider using a stable cardiopulmonary resuscitation (CPR) stool.
3. Place the patient's ipsilateral leg over your leg so that your knee is resting in his or her popliteal fossa.

Fig. 49.29. Whistler technique for hip reduction. (From Walden PD, Hamer JR: Whistler technique used to reduce traumatic dislocation of the hip in the emergency department setting. J Emerg Med 17:441–444, 1999. Used with permission.)

4. While holding the ankle in position with slight downward pressure, lift up with both legs to apply traction on the femur and reduce the hip.
5. If traction alone does not work, use your hands to internally and externally rotate the leg to achieve the reduction.

The Whistler technique often works better for practitioners who are of shorter stature and have difficulty getting their leg in proper position for the Captain Morgan technique. In this method, the clinician uses his or her stabilized arm under the ipsilateral knee to lift the leg using the leg muscles.

To perform the Whistler technique for reduction of posterior hip dislocation (Fig. 49.29):

1. Start with the patient lying supine on the bed, and secure the patient's hips to the bed, as for the Captain Morgan technique.
2. Bend the contralateral leg so that the patient's knee is flexed 90 degrees and the foot is on the bed.
3. Bend the ipsilateral leg to the same position.
4. Place your arm under the ipsilateral knee and rest it on top of the contralateral knee.
5. Now rotate your body so that you are perpendicular to the patient and looking at his or her feet. This should cause you to squat a little.
6. While holding the patient's ipsilateral ankle with your other hand, slowly lift up with your legs, while keeping your arm straight and strong. This puts traction on the femur and should reduce the dislocation.
7. If reduction is not achieved with traction alone, use your hand that is on the ankle to internally or externally rotate the leg to achieve the reduction.

Other techniques for closed reduction of posterior hip dislocations include the Rochester method and the traction-countertraction technique.

Closed reduction of a pubic dislocation can be quite difficult. The anterior position of the femoral head will resist flexion, making the Allis technique impossible. The following sequence of maneuvers is recommended.

To perform the technique for reduction of pubic dislocation:

1. Place the patient in the supine position.
2. Apply longitudinal traction in line with the deformity.
3. Hyperextend and internally rotate the hip while an assistant applies downward pressure on the femoral head.

Although prompt anatomic reduction is clearly desirable, multiple attempts at reduction in the ED should be avoided because of potential damage to the articular surface and because the incidence of osteonecrosis increases with the number of attempts at reduction, as well as the duration of the dislocation. Difficulty with reduction is usually the result of incarceration of a tendon, a capsular structure, or an osteochondral fragment that is blocking reduction. In the case of a non-reducible dislocation, closed reduction with the patient under general anesthesia or an open reduction procedure often is required.

After closed reduction, the hip should be tested for stability, which is accomplished by gently taking it through its full range of motion to see whether it will redislocate. After testing has ensured stability, the injured extremity should be placed in a knee immobilizer and an abduction pillow should be applied to prevent repeat dislocation. An anteroposterior radiograph of the pelvis should be obtained to verify the adequacy of reduction. The radiograph should be inspected carefully to verify that the femoral head is in the acetabulum, the shaft of the femur is in neutral position, Shenton's line is intact, and the profile of the lesser trochanter is well visualized. The intra-articular space should be symmetrical and, when measured, of the same depth as in the unaffected joint. Asymmetry signals an entrapped intra-articular fragment and is an indication for CT imaging.

The precarious blood supply to the femoral head is particularly important with regard to the long-term consequence of hip dislocations. The development of AVN of the femoral head has been reported in 1% to 17% of dislocations. Other risk factors for the development of AVN include the total dislocation time, the severity of the injury, the number of reduction attempts, and the presence of comorbid conditions.

Fracture-Dislocation of the Femoral Head

Hip dislocations can be associated with fractures of the femoral head (Fig. 49.30A). Femoral head fracture occurs in 35% to 55% of anterior hip dislocations and in 10% to 16% of posterior hip dislocations. These injuries are almost always the result of high-speed vehicular trauma. Because of the tremendous force required to produce this injury pattern, coexistent multisystem trauma is the rule.

When a femoral head fracture and hip dislocation coexist, patients assume the position typical for the dislocation. Hip mobility is markedly reduced, and pain usually is severe. After initial stabilization, the involved extremity should be examined carefully for associated fractures of the femoral shaft and knee. The neurovascular examination should assess for femoral or sciatic nerve injury. Radiographs should be evaluated carefully for any femoral head fracture in all patients with hip dislocations. Evidence for fracture of the femoral head can be subtle. These fractures can be detected on radiographs by following the curve of the dislocated head and the acetabular cup to search for a small fragment that could otherwise be overlooked. Known or suspected injuries can be further defined by CT or MRI.

In most cases, satisfactory results can be obtained with closed reduction (see Fig. 49.30B). Several experts recommend obtaining a CT scan of the hip before closed reduction to further define the injury and locate fracture fragments. If the hip cannot be reduced by manipulation or if reduction of the femoral head fragment is unsatisfactory, open reduction will be required.

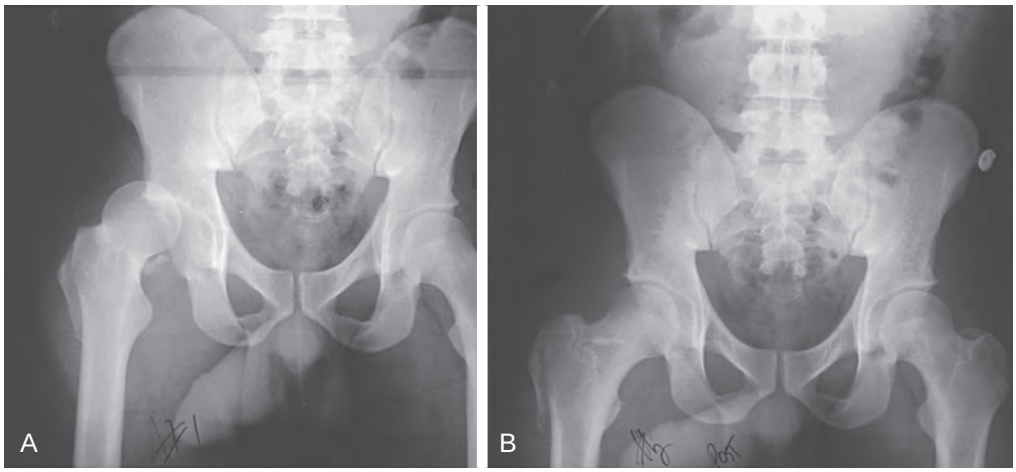

Fig. 49.30. **A,** Anterior hip dislocation is identified as the lesser trochanter is brought into profile. Note the fracture of the lateral aspect of the greater trochanter. **B,** A postreduction radiograph demonstrates adequate reduction with symmetrical joint spaces.

Dislocation of Hip Prosthetics

An increasing number of patients have undergone hip arthroplasty. In addition to those procedures performed for treatment of femoral neck fractures, more than 230,000 patients undergo elective primary THA each year. Postoperative dislocation occurs in 0.5% to 3% of patients with primary THA and in 5% to 27% of patients with a revised THA.[14] Although most dislocations take place within 3 months of surgery, "late dislocations" have been reported up to 10 years after the operative procedure; such dislocations can result from major trauma or from trivial events (eg, rising from a seated position). Posterior dislocations account for 75% to 90% of cases (see Fig. 49.15). Reduction techniques for prosthetic hip dislocations are identical to those described earlier. Consultation with an orthopedic surgeon is essential for safe reduction and development of a long-term treatment plan for the patient. Reduction of the prosthesis does not carry the same urgency as for reduction of a dislocated native hip, because there is no risk for the development of AVN once the femoral head has been replaced. Traction on the sciatic nerve can occur, however, making early reduction more compelling. In addition, the reduction itself carries the unique dangers of loosening of the components, fracturing of the surrounding bone, and movement of the acetabular cup. Reduction is best performed either by or in consultation with an orthopedic specialist.

Soft Tissue Injuries

Soft tissues can be subject to muscle or tendon strain or contusions from misuse, overuse, or trauma. Rupture, hemorrhage, or myositis ossificans can develop in muscles.

Muscular Injuries

Strenuous exercise by a poorly conditioned person, sudden exertion, and direct trauma all can injure soft tissues. Cold temperature, vascular or infectious disease, fatigue, and poor training are predisposing conditions for muscular injury.

Classification of complete and partial tears is reasonable and of clinical utility. Partial tears are reversible injuries that are aggravated by movement or tension. Mild spasm, swelling, ecchymosis, and tenderness cause minor loss of function and strength. Complete tears produce a palpable depression, and the torn muscle edge is often palpable. Other possible findings include severe spasm, swelling, ecchymosis, tenderness, and loss of muscle function. In significant muscle strains, radiographs are needed to evaluate for the possibility of an accompanying bone avulsion injury.

Initial management of incomplete tears traditionally includes the local application of ice for the first 48 hours, followed by heat.

Compressive wraps can exacerbate distal venostasis, with the potential for distal venous clot formation, and do not significantly decrease recovery time. A regimen of nonsteroidal anti-inflammatory agents to achieve sufficient analgesia is important for recovery and patient satisfaction. Muscle relaxants may be useful when the injury is accompanied by muscular spasm. In general, complete rest of the affected muscle should be maintained, with the recommendation of "weight bearing as tolerated." This progressive muscle loading can be started within 3 to 5 days once sufficient scar has formed. To prevent reinjury, muscle loading should be limited by the patient's pain. Any patient with significant injury should be referred for physical therapy.

A complete muscle tear is a serious condition. Consultation plus follow-up care with an orthopedic surgeon or sports medicine specialist is vital for these patients.

Athletes commonly experience muscular injury from accidents and overtraining. The two most common injuries involve the hamstrings and the quadriceps.

The Hamstrings. Hamstring muscle strains are common in sports involving running and sudden acceleration. The injury is accompanied by sudden intense pain in the posterior aspect of the thigh. Any active or passive motion at the hip is poorly tolerated because of the intense pain that movement causes. Ischial avulsion fractures can occur, and pelvic radiographs should be obtained if the examination reveals bony tenderness. Crutches and toe-touch weight bearing are recommended until the patient is evaluated by a physician trained in sports medicine. *Toe-touch weight bearing* refers to walking with crutches while the toes of the injured extremity rest on the ground without placing any weight on it. Appropriate weight-training programs speed rehabilitation of this injury. Complete recovery from a hamstring muscle strain can take weeks to months.

The Quadriceps. The quadriceps is the most common muscular group to sustain complete tears. This injury occurs when the muscles are contracted suddenly against the body's weight, as may occur when an athlete slips or stumbles and

attempts to avoid a fall. Ambulation is significantly affected. There is pain with active and passive knee extension. In significant tears, the patient might be unable to actively extend the knee or maintain its extension against gravity. A palpable depression just proximal to the superior pole of the patella suggests a complete tear. It is imperative to document an intact patellar mechanism on examination because a complete tear of the quadriceps often requires surgical repair and extensive rehabilitation.

Iliopsoas Strain. Gymnasts and dancers are the athletes most likely to experience an injury to the iliopsoas as a result of sudden forceful hip flexion against resistance. Severe pain often is experienced in the groin, thigh, or low back. Severe intra-abdominal pain is common at the muscle origin and might dominate the clinical picture. Examination reveals groin tenderness and pain with active hip flexion. Radiographs of the femur should be obtained to identify an avulsion fracture of the lesser trochanter. CT frequently demonstrates a large hematoma. Bed rest with partial flexion at the knee and hip generally is required for 7 to 10 days. With severe strains, symptoms could persist for 2 to 3 months.

Hip Adductor Strain. Injury to the hip adductors occurs as the thigh is forcefully abducted, as in a straddle injury. The patient reports pain in the groin, the pubic region, and the medial proximal aspect of the thigh. Abduction and adduction often are limited because of pain. Swelling and skin discoloration may confirm presence of the tear. If the tear is complete, a defect in the muscle can be felt by the examiner along the medial aspect of the thigh near the groin. Treatment is conservative, with patients initially benefiting from rest, with gradual progression in a stretching and strengthening program.

Gluteus Muscle Strain. The gluteus muscles can be injured with vigorous or forced hip extension, as seen in track-and-field jumping events. The pain typically is less severe than that associated with injuries to other muscle groups. The hip is tender when extended or abducted.

Tendon Injuries

Clinically, tendon strains tend to have a more insidious onset than that typical for muscle strains. These strains occur at the attachment of the muscles to the superior or inferior pubic ramus, the pubic symphysis, the ischium, and the femur.

One study found adductor strains to be the most common groin injury in athletes, with 62% of the cases involving the adductor longus muscle. The adductor magnus and brevis and the pectineus often are involved as well. This injury commonly occurs in skaters and cross-country skiers when an accidental stress abducts the thigh during a powerful contraction of the adductors. These muscles also can be injured from overuse in an unconditioned patient. Local pain is noted at the inferior pubic ramus and the ischial tuberosity. Extension, abduction, and adduction of the hip are painful. The pain might radiate to the back of the thigh.

Pain over the greater trochanter could represent tendon strain of the attachments of the gluteus medius, gluteus minimus, tensor fasciae latae, or piriformis. The pain is aggravated by resisted abduction. Tenderness in the groin and painful hip movement suggest a strain of the iliopsoas tendon at its attachment to the lesser trochanter. Trochanteric bursitis, peritendinitis, AVN, neoplasm, and other possible causes should be considered.

Treatment of a tendon strain is similar to that for other soft tissue injuries. The use of crutches with weight bearing as tolerated is helpful for the first 2 weeks. Opioid analgesics and a short course of antiinflammatory agents should be given. Complete tendon disruption might require surgical repair.

Osteitis Pubis

Osteitis pubis is a poorly understood disorder. It is characterized by pubic symphysis pain and joint disruption and is most common in distance runners and soccer players. The adductor muscles act as a "compression strut," displacing forces across the hip. The most likely mechanism is repetitive pulling of the adductor muscles, causing increased shearing at the pubic symphysis.

Clinically, patients have groin pain of insidious onset, with most reporting pain at the symphysis and adductor muscles. Pain usually can be elicited on palpation of the symphysis and also can be provoked by adduction of the hip or by sit-ups. Plain radiographs show widening of the symphysis, irregular contour of the articular surfaces, or periarticular sclerosis (a late finding) (Fig. 49.31). These features are not specific and in one study were seen in 76% of asymptomatic soccer players. MRI is the imaging study of choice and will show marrow edema on T2 images early in disease. Osteitis pubis has been associated with spontaneous cases of pubic symphysis osteomyelitis and should be considered in the differential diagnosis.

Treatment is conservative, and in most cases the process is self-limited. Patients benefit from activity modification, wearing supportive shoes, and from therapy addressing flexibility and strength of the pelvic and hip musculature. Average time to heal has been reported to be 9 months. Owing to the length of healing associated with these injuries, follow-up care should be arranged at the time of initial injury to prevent unnecessary ED visits.

Vascular Injuries

Hip dislocations and femoral fractures may have associated arterial injury. The vessel can be partially lacerated, dissected, completely severed, or thrombosed. Lack of distal arterial flow might also represent a stretched vessel in spasm. The superficial femoral artery is most commonly injured with trauma to the hip and thigh. The common and the deep femoral arteries are less frequently injured. In the acute setting, penetrating trauma is the usual mechanism of injury. Arterial injury with a femoral shaft

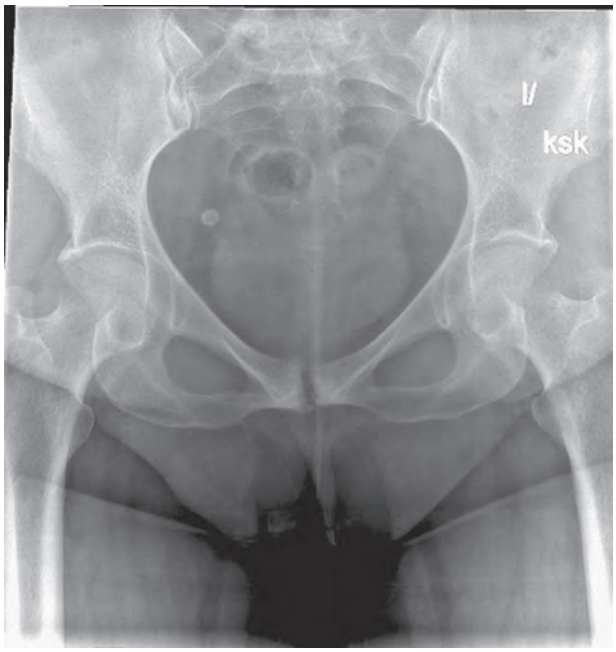

Fig. 49.31. Plain radiograph showing irregular articular surfaces and periarticular sclerosis consistent with osteitis pubis.

fracture is rare. Anterior and superior dislocations can produce femoral artery injury.

Neurologic Injuries

Peripheral nerve injury can be caused by trauma, infectious agents, and degenerative disease. In trauma, nerves can be injured by a blunt object that causes a contusion, by a sharp penetrating object that produces a partial or complete tear, or by stretch. Nerves are particularly vulnerable to prolonged ischemia, which can lead to necrosis. Compression of the nerve from a hematoma or a dislocated femoral head may also appear as a neurapraxia manifested by transient loss of conductivity. The femoral and sciatic nerves are rarely injured with femoral shaft fractures, because they are encased in muscle throughout the length of the thigh.

Treatment of neurovascular compromise from a hip dislocation or a displaced femoral fracture consists of immediate reduction to ensure limb viability. Whenever possible, reduction should be accomplished before the patient is transferred to another treatment center.

When the femoral nerve is injured, the iliac and femoral arteries are commonly involved because of their anatomic proximity. The femoral nerve is most often traumatized in penetrating trauma of the pelvis, groin, or thigh. Femoral neuropathy occasionally results from compression by a hematoma within the abdominal wall or the iliopsoas as a complication of hemophilia, anticoagulant therapy, or severe trauma.

The motor deficit in complete femoral neuropathy manifests as marked weakness of knee extension. The patient is able to walk on level ground yet has extreme difficulty walking up stairs or an incline. Patients cannot rise from a sitting position because of significant proximal muscle weakness. The sensory deficit varies but is localized along the anterior aspect of the thigh and medial lower aspect of the leg. The most reliable spot for testing for a sensory deficit is just superior and medial to the patella. The deep tendon reflex of the knee is diminished or absent with such deficits.

If traumatic neuropathy is suspected, immediate orthopedic consultation should be obtained. Nerve exploration and repair generally are preferred for penetrating trauma and when direct impingement on the nerve by bone fragments or hematoma is suspected. Surgical exploration and drainage of a hematoma that is impinging on the femoral nerve are appropriate.

Progressive nontraumatic neuropathies warrant urgent neurology consultation. With chronic neuropathy, atrophy of the anterior aspect of the thigh already has developed. The motor deficits were discussed previously.

Sciatic injury is rare with femur fractures, but occasionally it may be the result of traction used to stabilize the fracture during the initial management period. Complete traumatic injury can result from a deep penetrating wound in the hip, thigh, or buttock. Posterior hip dislocations and fracture-dislocations produce sciatic neurapraxia in 10% to 14% of patients with these injuries. Patients with complete sciatic neuropathy have paralysis of the hamstring muscles and all muscles below the knee. With partial injury, a peroneal palsy with weakness of the extensor hallucis longus muscle is the most sensitive clinical sign. There is sensory loss below the knee and along the posterior aspect of the thigh. The deep tendon reflex at the ankle is absent or diminished. Sciatic nerve palsy from inadvertent injection into the nerve or secondary to intraneural or extraneural hemorrhage in patients taking anticoagulants has been described.

Sciatic injury from posterior dislocations often consists of only transient loss of conductivity, particularly in motor fibers. Unfortunately, the other patterns of injury to the sciatic nerve carry the worst prognosis of all peripheral nerve injuries. The prognosis is poorest when the injury is proximal and complete. Even with optimal repair, recovery often is inadequate. Sciatic neuropathy is a disabling problem. Obvious atrophy of the lower part of the leg and foot develops, followed by ulceration of the sole of the foot and infection. A below-the-knee amputation frequently is necessary in these cases.

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KEY CONCEPTS

- Hip dislocation is an orthopedic emergency. The likelihood of avascular necrosis (AVN) is related to both the initial degree of trauma and the amount of time the femoral head remains out of joint. Reduction of the hip within 6 hours after dislocation significantly decreases the incidence of AVN.
- When a painful hip makes ambulation difficult and plain radiographs do not reveal a fracture, computed tomography (CT) or magnetic resonance imaging (MRI) should be performed. MRI is the gold standard for diagnosis.
- In patients with intertrochanteric fractures, hemodynamic instability can result from dehydration and blood loss. Up to 70% of patients with these injuries are under-resuscitated.
- It is important to identify acetabular fractures before closed reduction is attempted, because intra-articular bone fragments can interfere with effective reduction.
- In elderly patients, the use of femoral nerve blocks should be considered due to the adverse effects of parenteral opioids.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 49: QUESTIONS & ANSWERS

49.1. Which of the following fractures has the best outcome and lowest rate of complications?

A. Femoral neck fracture
B. Insufficiency fracture
C. Intertrochanteric fracture
D. Lesser trochanteric fracture
E. Subtrochanteric fracture

Answer: D. Treatment of a lesser or greater trochanteric fracture consists of pain control and early mobilization with crutches; weight bearing is allowed as tolerated by pain. Outpatient management of this injury is possible with a satisfactory social situation. The prognosis is good, and healing is generally excellent. The mortality rate during the first year after a femoral neck (also known as an *insufficiency fracture*) fracture is 14%. Intertrochanteric fractures have an associated mortality rate of 10% to 30% in the first year. The reported mortality rate from subtrochanteric fractures ranges from 9.6% to 13.3%.

49.2. A 40-year-old man complains of persistent thigh pain that worsens over 2 weeks after an assault with a baseball bat. His pain is worse with knee extension. On physical examination, you note that there is a small palpable mass at the midanterior thigh. What should be your next confirmatory test?

A. Bone scan for fracture
B. Bone scan for stress fracture
C. Computed tomography (CT) scan for tumor
D. Magnetic resonance imaging (MRI) for evaluation of torn muscle
E. Radiograph for heterotropic calcification

Answer: E. Myositis ossificans (heterotrophic ossification) is pathologic bone formation at a site where bone is not normally found. Traumatic myositis ossificans results most commonly from a direct blow to muscle. It should be suspected when symptoms persist past 10 to 14 days or if symptoms intensify several weeks after the trauma. The ossific mass is often palpable and may limit motion, depending on its location.

49.3. An 80-year-old woman presents complaining of pain in her right leg after a motor vehicle collision (MVC). Emergency medical services (EMS) noted a swelling and a deformity to her thigh, so they placed a traction device on her leg. Her vital signs are: blood pressure, 80/40 mm Hg; heart rate, 110 beats per minute; and respiratory rate, 18 breaths per minute. What is the most appropriate next step in the management of the patient's fracture?

A. Femoral nerve block and leave the traction device in place
B. Femoral nerve block and remove the traction device
C. Intravenous morphine and leave the traction device in place
D. Intravenous narcotic pain medication and remove the traction device
E. Immediate orthopedic consult to take the patient to the operating room for an open reduction and internal fixation (ORIF)

Answer: B. Although the patient may ultimately need to go to the operating room, the patient is currently unstable and requires resuscitation and evaluation for other injuries. A femoral nerve block is invaluable as an adjunct or alternative to systemic analgesics in a patient at risk for hypotension and has been underused by emergency clinicians. Prolonged traction during the assessment and management of other injuries can cause or worsen serious neurologic injury in the thigh by producing potentially damaging tension on the sciatic and/or femoral nerves.

49.4. What is the most common complication of a proximal femur fracture?

A. Avascular necrosis (AVN)
B. Myositis ossificans
C. Osteomyelitis
D. Pulmonary embolism
E. Septic arthritis

Answer: A. AVN is the most common complication of proximal femur fractures (despite optimal treatment) because of the complex arterial anatomy. Deep infection in the form of osteomyelitis or septic arthritis is more common with femoral neck fractures because the fracture line extends into the joint. Pulmonary embolism is another significant complication and is the leading cause of death 7 days after fracture in all orthopedic patients.

49.5. A 60-year-old woman presents complaining of right hip pain after a trip and fall at home. The patient denies loss of consciousness or other symptoms. You note that the patient's right leg is internally rotated, and the thigh is adducted and flexed at the hip joint so that the ipsilateral knee is resting on the opposite thigh. Which is the correct maneuver?

A. Apply traction and splint the leg in full extension.
B. Apply traction to an extended knee and flexed hip at 90 degrees with a gentle rotational component.
C. Consult orthopedics immediately to take the patient to the operating room.
D. Provide analgesia and Holter monitor for discharge when ambulatory.
E. Use the Allis maneuver and place the patient in a knee immobilizer.

Answer: E. A patient with a posterior dislocation typically holds the hip flexed, adducted, and internally rotated. The knee of the affected extremity rests on the opposite thigh. The Allis technique is usually effective for both posterior and obturator dislocations. With the knee flexed, the operator applies steady traction in line with the deformity. The hip is slowly brought to 90 degrees of flexion while steady upward traction and gentle rotation are applied.

49.6. A mother brings her 11-year-old boy for evaluation of left knee pain that is worse after physical activity. Radiographs of the knee were negative. What is the most appropriate next step in the patient's management?
- **A.** Hip radiograph with frog-leg views
- **B.** Joint aspiration for evaluation of transient synovitis
- **C.** Place a knee immobilizer and ensure follow-up in 1 week
- **D.** Radiograph of right knee for comparison
- **E.** Rest, ice, compression, elevation, and orthopedic follow-up urgently

Answer: A. This patient may have a slipped capital femoral epiphysis (SCFE), which most commonly develops in boys 10 to 17 years old during their period of rapid growth. Referred pain to the knee is a classic manifestation, and patients frequently present with groin, thigh, or knee pain rather than hip pain. Initially, anteroposterior, lateral, and frog-leg lateral radiographs of the hip should be obtained. The frog-leg lateral projection shows the hip in a plane midway between the anteroposterior and lateral views.

49.7. A 75-year-old woman presents after a fall from standing. She has right hip pain and tenderness to palpation but no obvious deformity. Right knee and ankle examinations are normal, without tenderness, deformity, or external signs of trauma. Hip and pelvis radiographs are negative for fracture, but the patient is unable to bear weight on her right leg. The next appropriate step in management is:
- **A.** Admit to the hospital for bed rest.
- **B.** Discharge patient home with analgesia and a walker.
- **C.** Obtain magnetic resonance imaging (MRI) of the hip to assess for fracture not identified by radiographs.
- **D.** Obtain radiographs of the rest of her right leg to ensure no occult fracture is present.

Answer: C. With hip injury, if radiographs do not show a fracture or suggestion of injury and the patient is unable to ambulate, further imaging studies should be obtained to evaluate for occult fracture. Two percent to 10% of all hip fractures are radiographically occult. Failure to detect these fractures results in increased morbidity and mortality.

49.8. Which of the following injuries is appropriate for traction splinting by prehospital providers?
- **A.** Femoral fracture with bone protrusion through skin
- **B.** Posterior hip dislocation
- **C.** Severe crush injury of leg with obvious deformity of the knee
- **D.** Suspected closed mid shaft femoral fracture

Answer: D. Traction splints can provide pain relief, immobilization, and limit blood loss when applied correctly to a femoral fracture. However, contraindications to the use of traction splints include pelvic fractures, patellar fractures, ligamentous knee injuries, and tibia or fibula fractures. Traction in the prehospital setting should not be applied to any open fracture that has exposed bone. Such reduction pulls grossly contaminated bone fragments back into the wound before adequate débridement can be undertaken in the operating room.

49.9. A 15-year-old female gymnast presents after experiencing the sudden onset of severe groin pain during a dismount when she landed in a flexed hip position. The pain radiates into her abdomen, and flexion of the hip produces pain, but there is no deformity noted. What is the most likely radiographic finding?
- **A.** Avascular necrosis (AVN) of the femoral head noted on magnetic resonance imaging (MRI) scan
- **B.** Diastasis of the pubic symphysis on anteroposterior pelvis radiographs
- **C.** Femoral neck fracture on dedicated anteroposterior hip radiograph
- **D.** Iliopsoas muscle with some associated hemorrhage on computed tomography (CT) scan

Answer: D. Gymnasts and dancers are the group of athletes most likely to experience an injury to the iliopsoas as a result of sudden forceful hip flexion against resistance. Severe pain often is experienced in the groin, thigh, or low back region. Severe intra-abdominal pain is common at the muscle origin and may dominate the clinical picture. Examination reveals groin tenderness and pain with active hip flexion. Radiographs of the femur should be obtained to identify an avulsion fracture of the lesser trochanter. CT scan frequently will demonstrate a large hematoma. Bed rest with partial flexion at the knee and hip generally is required for 7 to 10 days. With severe strains, symptoms may persist for 2 to 3 months. Referral to a sports medicine specialist is appropriate.

49.10. A 45-year-old male presents with a posterior hip dislocation after a motor vehicle crash (MVC) noted on radiographs. After sedation of the patient and reduction of the dislocated hip, what is the most appropriate next step in the patient's management?
- **A.** Have the patient ambulate to assess the stability of the joint.
- **B.** Measure the femoral compartment pressure.
- **C.** Obtain postreduction hip radiographs to assess for additional injuries and adequate reduction.
- **D.** Place a traction splint.

Answer: C. Obtaining postreduction radiographs to ensure adequate reduction and evaluate for associated injuries is essential. After closed reduction, the hip should be tested for stability, which is accomplished by gently taking it through a full range of motion to see whether it will re-dislocate. After testing has ensured stability, the injured extremity should be placed in a knee immobilizer, and an abduction pillow should be applied to prevent repeat dislocation.

CHAPTER 50

Knee and Lower Leg

Daniel J. Pallin

KNEE

PRINCIPLES

Background and Importance

Knee injuries range in severity from minor contusions to limb-threatening injuries to the popliteal artery. The knee joins the longest mechanical levers in the body, the femur and tibia, and is therefore subject to high forces. It is the largest and most complex joint in the body and functions through a complicated interaction of flexion, extension, rotation, gliding, and rolling. Its large synovial space frequently is involved in infections and other inflammatory conditions.

The main goal in emergency evaluation of the traumatized knee is to prevent further damage by identifying reparable vascular injuries, reducing dislocations, stabilizing fractures, and administering antibiotics when indicated. Definitive treatment of less urgent problems is deferred to other settings, such as primary care offices for chronic knee pain and orthopedic clinics for ligamentous injuries.

ANATOMY AND PHYSIOLOGY

The knee is a modified hinge, diarthrodial synovial joint that consists of the tibiofemoral and patellofemoral joints. The head of the fibula, although not part of this articulation, is closely approximated laterally and provides a site for the attachment of muscles and ligaments. Joint stability is provided by ligaments, although surrounding muscles and the joint capsule contribute as well (Fig. 50.1).

The distal femur terminates in the medial and lateral condyles. A condyle is a rounded prominence at the end of a bone, where it interfaces with another bone. An epicondyle is a prominence on a condyle, where a ligament or tendon attaches. The femoral condyles protrude anteriorly, leaving a vertical groove between them, forming the femoral trochlea. *Trochlea* is the term for an anatomic structure that resembles a pulley. The patella slides up and down in the groove during knee extension and flexion.

The femoral condyles articulate with the superior surface of the tibia and tibial condyles. The medial and lateral menisci are cushions between the femoral and tibial condyles. The tibia is anchored to the femur by four strong ligaments, the anterior and posterior cruciate ligaments (ACL and PCL) and medial and lateral collateral ligaments (MCL and LCL). The ACL and PCL are located deep within the knee. The ACL arises from the posterior aspect of the femoral intercondylar notch and inserts on the anterior surface of the tibial plateau within the tibial intercondylar notch. It prevents anterior displacement of the tibia relative to the femur. The PCL arises from the anterior aspect of the femoral intercondylar notch and inserts on the posterior surface of the tibial plateau within the tibial intercondylar notch. It prevents posterior displacement of the tibia relative to the femur. The cruciate ligaments have a rich blood supply, and injury typically results in a hemorrhagic knee effusion.

The MCL and LCL connect the femoral epicondyles to the tibial condyle and head of the fibula, respectively. The MCL prevents valgus deviation. Valgus deviation refers to angulation with the apex pointing medially. The LCL prevents varus deviation, angulation of the tibia relative to the femur with the apex pointing laterally.

Functionally, the knee joint can be divided into three compartments—patellofemoral, medial tibiofemoral, and lateral tibiofemoral. These compartments, defined anatomically by the articulation of the bones, are contained within the same joint capsule. The patellofemoral compartment, located anteriorly, contains the quadriceps tendon, which envelops the patella, continues inferiorly as the patellar tendon, and inserts on the tibial tubercle. The fibers of the medial and lateral retinacula are found on either side of the patella, originating from the vastus medialis and vastus lateralis. The patella increases the mechanical advantage of the quadriceps tendon. The quadriceps tendon is a continuation of the quadriceps femoris muscle, which consists of the rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius, which extend the knee.

The medial tibiofemoral compartment is located on the medial aspect of the knee and consists of the medial femoral condyle, concave medial tibial condyle (plateau), medial meniscus, MCL, adductor tubercle, and pes anserinus. The pes anserinus (literally, goose foot) is a three-pronged tendinous structure that is the conjoined insertion of the sartorius, semitendinosus, and gracilis muscles, located on the proximal medial tibia.

The lateral tibiofemoral compartment encompasses the lateral half of the knee joint and includes the lateral femoral condyle and epicondyle, lateral tibial condyle (plateau), LCL, lateral meniscus, and popliteus tendon. The fibular head can be palpated posterolaterally and inferiorly to the joint line but is not usually considered a structure of the lateral tibiofemoral compartment. The fabella, present in some patients, is a sesamoid bone located in the lateral head of the gastrocnemius muscle and should not be mistaken for an intraarticular loose body or fracture fragment. The knee is surrounded by a thick ligamentous sheath composed largely of tendons and their expansions. The capsule of the knee joint is reinforced at multiple sites—anteriorly, by the ligamentum patellae; medially and laterally, by the medial and lateral patellar retinacula; and posterolaterally, by a combination of structures termed the *posterolateral corner.* The tibiofemoral joint communicates with the suprapatellar bursa, which expands in conditions that cause knee effusion. The prepatellar bursa is anterior to the patella and does not communicate with the tibiofemoral joint. It is important not to confuse prepatellar bursitis with knee arthritis.

The popliteal fossa is a hollow in the posterior aspect of the knee. It is bounded laterally by the biceps femoris tendon, medially by the semimembranosus and semitendinosus muscles, and inferiorly by the two heads of the gastrocnemius muscle. Found within the popliteal space are the popliteal artery, popliteal vein, and peroneal and tibial nerves.

The popliteal artery is the continuation of the femoral artery beyond the adductor hiatus. It descends across the posterior

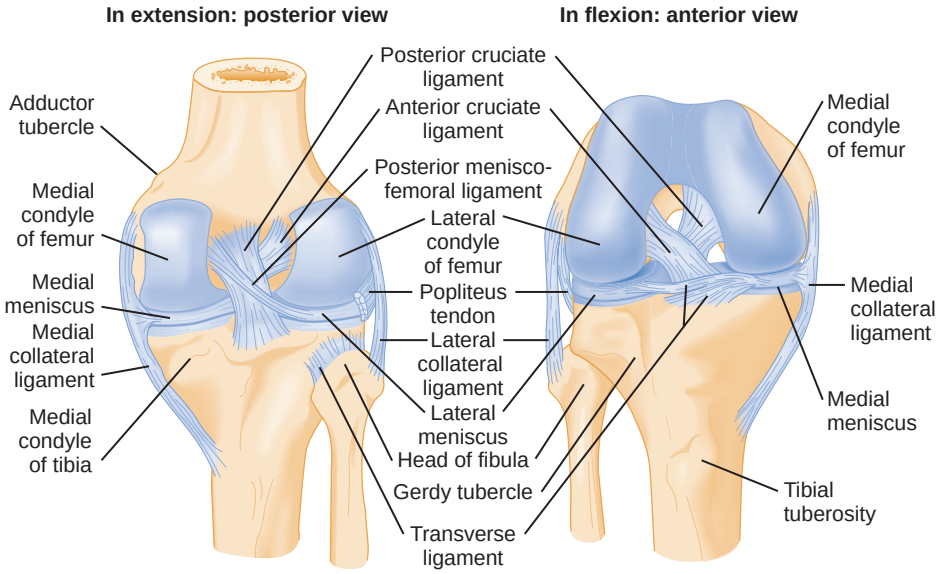

Fig. 50.1. Posterior and anterior views of the right knee.

aspect of the knee joint and terminates at the level of the tibial tubercle, where it divides into the anterior and posterior tibial arteries. The peroneal artery then branches from the posterior tibial artery. Together the three arteries are termedas the *trifurcation of the popliteal artery.* The popliteal artery is anchored firmly at the proximal and distal ends of the popliteal fossa, which explains the high incidence of arterial injury with knee dislocations. Blood supply to the knee joint comes from the popliteal artery by way of the geniculate arteries.

The tibial nerve, along with one of its branches, the common peroneal nerve, is responsible for innervation of the knee. The tibial nerve joins the artery and vein in the popliteal fossa. The common peroneal nerve wraps around the head of the fibula and continues inferiorly as the deep and superficial peroneal nerves. Common peroneal nerve injury may occur in association with tibiofemoral dislocation or injury to the head of the fibula or may be caused by prolonged compression, as when the flexed knee hangs over the edge of a hard surface, such as an operating room table. This causes footdrop, in which dorsiflexion strength at the ankle is reduced.

Depending on the population studied, management of knee and leg fractures commonly requires immobilization, which can result in deep vein thrombosis in up to 19% of patients. Prophylactic treatment with low-molecular-weight heparin reduces this risk.

CLINICAL FEATURES

Patients with knee injuries may have pain, tenderness, deformity, limited range of motion (ROM), effusion, warmth, or redness. Knee pain without an immediately apparent knee abnormality should prompt a careful evaluation of the entire femur and hip, injuries of which frequently manifest with pain referred to the knee. Patients with radiculopathy of the third, fourth, or fifth lumbar roots also may report knee pain. Children with a slipped capital femoral epiphysis, toxic tenosynovitis, or septic hip frequently complain of knee pain.

A knee effusion may result from infection, hemarthrosis, lipohemarthrosis, or inflammatory arthritis. Arthrocentesis may be used for diagnosis when the mechanism is not clear and there is suspicion of infection.

High-energy trauma without knee swelling should raise suspicion for disruption of the joint capsule, with expulsion of synovial fluid and blood into the thigh or lower leg. Lower energy injuries are more commonly associated with meniscal tears, patella dislocations, and less severe ligament injuries. Activities with twisting and turning are associated with anterior cruciate and meniscal tears. Immediate deformity, hemarthrosis, or instability suggests an intraarticular fracture, cruciate ligament injury, or vascular injury. By contrast, a torn meniscus more commonly is associated with delayed onset of swelling over 12 to 24 hours, intermittent locking associated with joint line pain, and eventually arthritis and recurrent effusion later in life.

Locking of the knee manifests clinically with inability to extend the joint fully. It typically results from a meniscal tear or trapping of a loose body within the joint, thereby preventing full extension. A complaint of giving way may indicate instability or involuntary muscle inhibition secondary to pain. This is a nonspecific symptom and may be reported in association with arthritis or patellofemoral disorders when inhibition of quadriceps function occurs in association with episodic pain. Although pain remains a helpful indicator of injury, its absence should not be interpreted as proof that only minor injury is present. Complete ligament tears may be less painful than partial tears because the completely disrupted ligament has no tension across injured fibers.

Physical Examination

Proper examination of the knee requires the patient to be supine, with both legs exposed. The question of whether knee pain may be the result of hip or spine pathology should be raised early, and the neurovascular integrity of the foot should be assessed. Examination of the knee begins with visual inspection (Box 50.1), followed by palpation (Fig. 50.2). Any obvious deformity, swelling, effusion, or ecchymosis is noted. Localized swelling should be distinguished from the presence of a joint effusion, which may obliterate the normal contour of the knee. If a large effusion is present, the patella is elevated from the femur by fluid, and the patella can be ballotted against the femur. Loss of the medial peripatellar concavity may be the only sign of a small knee effusion. An effusion in the prepatellar bursa is found just beneath the skin anterior to the patella; this should not be confused with a knee effusion.

Palpate areas of suspected tenderness last to avoid causing anxiety and muscle spasm during the examination. The insertion of the patellar tendon onto the tibial tubercle should be palpated.

BOX 50.1

Examination of the Knee

1. Assess neurovascular integrity of the foot.
2. Determine whether a knee effusion is present, and assess for gross deformity.
3. Identify signs of infection—redness, warmth, and effusion out of proportion to mechanism of injury.
4. Localize tenderness.
5. Assess range of motion and perform stability testing and meniscal evaluation when feasible.

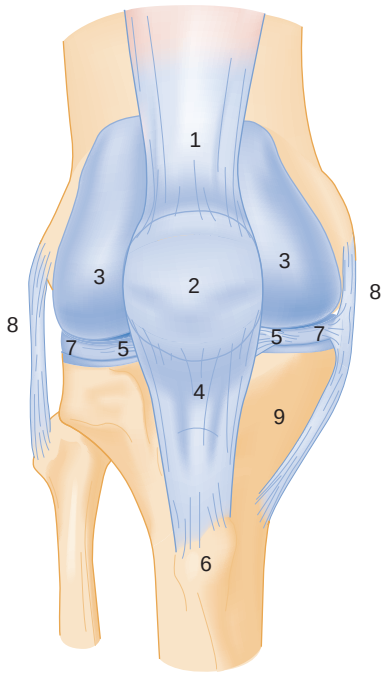

Fig. 50.2. Sites for palpation of tenderness in the knee. *1,* Quadriceps tendinitis; *2,* prepatellar bursitis, patella pain; *3,* retinacular pain after patella subluxation; *4,* patella tendinitis; *5,* fat pad tenderness; *6,* tibial tubercle pain caused by Osgood-Schlatter disease; *7,* meniscus pain; *8,* collateral ligament pain; *9,* pes anserine tendinitis-bursitis. (Adapted from Cailliet R: Knee pain. In soft tissue pain and disability, ed 3, Philadelphia, 1976, FA Davis, p 411.)

Pain at this location in an adolescent is the hallmark of Osgood-Schlatter disease. In an adolescent, pain along the femoral or tibial epiphysis after trauma may represent a Salter-Harris type I fracture (ie, a nondisplaced fracture through the physis). The joint line should be palpated carefully. Pain along the joint line may also indicate meniscal pathology. The posterior aspect of the knee should be examined for fullness, which may indicate a Baker's cyst or popliteal artery pseudoaneurysm.

Accurate diagnosis of soft tissue knee injuries often is impossible in the acute phase because of pain and swelling. In the acute setting, the main goals are to relieve pain, stabilize the joint, rule out vascular injury, determine the need for radiography, and identify infections and inflammatory conditions hidden by a history of minor trauma. Loss of active extension of the knee and inability to maintain the passively extended knee against gravity are the hallmarks of quadriceps and patellar tendon rupture, which otherwise may be clinically occult.

A number of maneuvers have been developed to aid the emergency clinician in diagnosing ligamentous and meniscal injuries using only the physical examination. However, interpretation of these maneuvers is limited by pain, splinting, or effusion so they are not particularly useful in the acute injury phase and have been found variably accurate, at best, when compared with magnetic resonance imaging (MRI) or arthroscopy findings. Accuracy of the findings of these maneuvers likely is improved if they are used after pain and swelling have resolved. The primary initial goals in emergency care are to identify whether fracture or vascular injury is present, ensure necessary nonweightbearing or decreased weightbearing, and refer for reevaluation by a primary care provider or orthopedist. With this caveat, we present a brief overview of the more common stability tests.

Tests for Specific Injuries and Disturbances

Anterior Drawer Test. The anterior drawer test seeks to identify tears of the ACL. A positive test result is defined as greater anterior movement of the tibia as compared with the other knee. The test is performed with the patient in a supine position, hip flexed at 45 degrees, and knee flexed at 90 degrees. The test is poorly sensitive but fairly specific. Lachman's test is a more accurate way to diagnose ACL injuries, with a sensitivity of 80% when performed acutely and 100% when performed with the patient under general anesthesia. Lachman's test is done with the knee flexed 20 to 30 degrees while the examiner uses one hand to grasp the thigh and stabilize it. The tibia is pulled anteriorly, and the examiner notes tibial excursion. The examiner records "firmness" or a "soft endpoint." The endpoint can be graded as 1+ (0–5 mm more displacement than on the normal side), 2+ (5–10 mm), or 3+ (>10 mm). The PCL must be intact for the test results to be valid. Arthrometers are devices that quantitate anterior displacement of the tibia relative to the femur and are far more accurate in diagnosing ACL tears than the anterior drawer and Lachman's tests, although these devices are rarely used in the ED setting.

The pivot shift test, also termed *subluxation provocation* or the *jerk test,* is performed to detect anterolateral rotatory instability associated with an injury to the ACL or lateral capsular structure. This sensitive but nonspecific test should be done carefully, if at all, in the acutely injured knee because the test maneuvers can exacerbate the initial injury.

The pivot shift test is performed with the patient supine. The knee is examined in full extension. The tibia is internally rotated while the examiner grasps the foot with one hand and applies a mild valgus stress at the level of the knee joint with the other hand. Then, with flexion of the knee to approximately 20 to 30 degrees, a jerk is suddenly felt by the examiner at the anterolateral corner of the proximal tibia. With a positive result, the tibia subluxates when the knee is extended and relocates when it is flexed to 20 to 30 degrees. Grading of the relocation event is as follows: absent (0), rolling (1+), moderate (2+), or momentary locking (3+). Because of pain or spasm, the pivot shift test is unreliable without the use of anesthesia.

Posterior Drawer Test. The posterior drawer test assesses for PCL injury. The posterior drawer test can be accomplished with the patient's knee flexed at 90 degrees and the foot stabilized by the examiner's thigh. A smooth backward force is applied to the tibia. Posterior displacement of the tibia more than 5 mm, or a soft endpoint, indicates injury to the PCL. A normal knee should exhibit no significant posterior excursion. The posterior drawer test result may be positive in only 85% of patients with PCL insufficiency documented operatively.

Posterior Sag Sign Test. The posterior sag sign test is a second method of determining PCL integrity. Sensitivity in the acute phase is 79%. The test is done as follows. The patient is placed in a supine position, and a pillow is placed under the distal thigh for support while the heel rests on the stretcher. The knee

is flexed to 45 or 90 degrees, depending on which position provides the greater muscle relaxation. If the tibia sags backward, the test result is considered to be positive, indicating PCL insufficiency. If the posterior sag sign is not appreciated before the different drawer tests are performed, a false-positive result on the anterior drawer test is misinterpreted as an ACL injury. Posterior sag also may be shown by passive elevation of the leg in a fully extended position, with the examiner applying the elevating force at the ankle. As the leg is elevated, the tibia may fall back on the femur if the PCL is ruptured.

Collateral Ligament Stress Test. The collateral ligament stress test is used to test the integrity of the MCL and LCL. With the patient lying supine, the examiner applies varus and valgus stress with the knee at 0 and 30 degrees of flexion. Joint line opening is the amount of movement (ie, hinging) produced between the tibia and femur; this can be palpated and estimated in millimeters. The normal knee should be subjected to the same amount of valgus and varus stress; the joint line opening is then compared with that in the injured knee. Isolated collateral ligament tears are detected only with the knee in slight flexion because, in extension, the cruciate ligaments, capsule, and lesser ligaments of the knee provide significant lateral stability. Laxity in full extension implies complete collateral ligament tear and also injury to the cruciate ligaments or other structures. Laxity may be graded as grade I, some laxity, grade II, marked laxity, and grade III, total laxity.

Assessing for Meniscal Tears. Meniscal tears are difficult to diagnose in the acute setting; these assessments are best reserved for the convalescent phase. Even then, small meniscal tears can cause significant symptoms but may not be detected on physical examination, and arthroscopic evaluation may be required for diagnosis.

Mcmurray's Test. McMurray's test is used to help identify meniscal tears. The patient is placed in a supine position with the knee hyperflexed. The examiner grasps the foot with one hand and the knee with the other. The examiner flexes and extends the knee while simultaneously internally and externally rotating the tibia on the femur and providing slight varus and valgus stress. A positive test result is the occurrence of clicking palpable along the joint line, or locking of the knee.

Apley's Test. This test also aids in diagnosing meniscal tears. With the patient prone, the knee is flexed 90 degrees, and the leg is internally and externally rotated with pressure applied to the heel. Pain elicited by downward pressure suggests meniscal pathology. The pain should be relieved with distraction of the knee and rotation of the leg back to a neutral position. Although relatively specific, Apley's test is not sensitive.

DIAGNOSTIC TESTING

Radiologic Evaluation

Because the sensitivity of radiographs for acute knee injuries is approximately 50%, we recommend computed tomography (CT) or knee immobilization and orthopedic referral for reevaluation when fracture is suspected and plain films are negative. MRI is slightly more sensitive than CT for fracture and is the imaging gold standard (comparable to arthroscopy findings) for soft tissue injury, but is rarely indicated in the evaluation of knee and leg trauma in the emergency department (ED).

Plain films are useful for diagnosing fracture, effusion, foreign bodies and, to a limited extent, joint space narrowing and lipohemarthrosis. Any disruption of the continuous line of the cortex should raise suspicion for fracture. Subtle cortical disruptions indicate nondisplaced fractures or draining cortical veins. The next step is to evaluate for the presence of an effusion, seen as a radiolucent area (with density similar to that of fat) distending the joint capsule. The presence of a linear interface between two different densities within an effusion suggests lipohemarthrosis (Fig. 50.3), in which the effusion contains not only blood but also fat. This feature results from the entry of marrow fat into the joint cavity and is diagnostic of fracture.

Clinical decision rules help decrease unnecessary radiography. According to the Ottawa Knee Rule, radiography is necessary only if any one of five conditions is present: (1) age older than 55 years; (2) inability to transfer weight from one foot to the next four times at the time of injury and in the ED; (3) inability to flex the knee to 90 degrees; (4) patellar tenderness with no other bone tenderness; and (5) tenderness of the fibular head. This rule detects nearly 100% of fractures while allowing significantly fewer radiographs to be done. The Pittsburgh Knee Rule states that radiography is necessary only if the patient fell or sustained blunt trauma to the knee and if either of two conditions is present: (1) age younger than 12 or older than 50 years; and (2) inability to walk four full weight-bearing steps in the ED. This decision rule

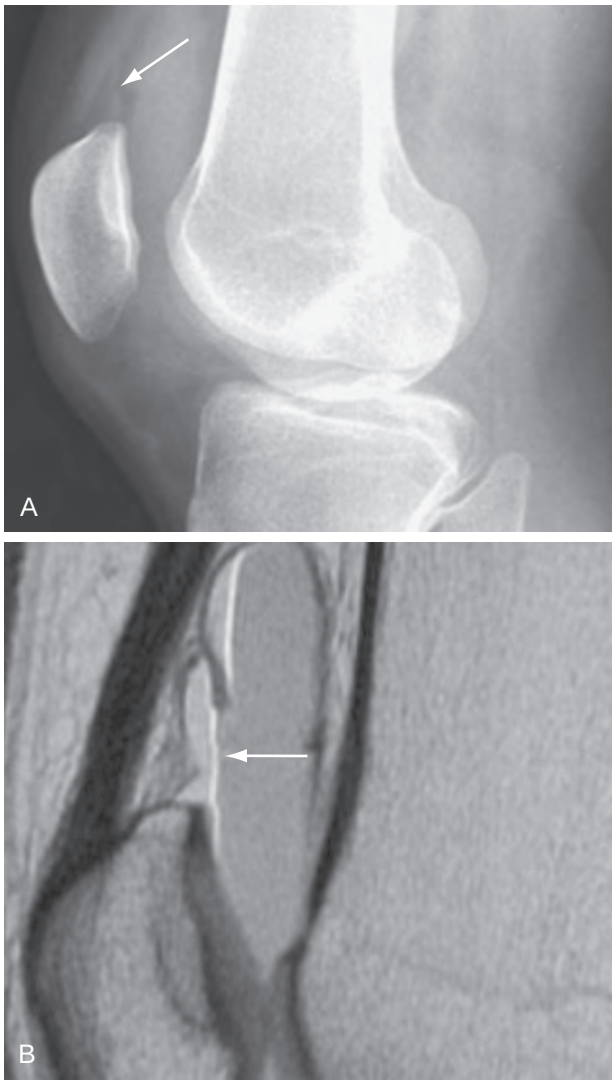

Fig. 50.3. Lipohemarthrosis. **A,** Lateral plain film of the knee of a young woman with a nondisplaced patella fracture. The only radiographic abnormality is an effusion that contains a linear interface (*arrow*) between two soft tissue densities, suggesting lipohemarthrosis. **B,** MRI scan from the same patient shows plainly the presence of blood and fat in the effusion (*arrow*). The nondisplaced patella fracture is not seen.

has been validated for use in children older than 5 years, with similar sensitivity to the Ottawa Rule.

When the two rules are compared, both have a sensitivity over 95%, but the Pittsburgh rule may be more specific, allowing fewer radiographs to be done without sacrificing sensitivity. We recommend use of a decision rule—the Ottawa or Pittsburgh Rule—as decision support when considering plain knee radiographs. Either rule may be adopted as a clinical decision rule and, if applied to all patients, will miss fewer than 1% of significant fractures. Regardless of which rule is applied, the patient should be reevaluated at follow-up for persistent or progressive symptoms.

Tunnel views, which image the intercondylar notch, are used to detect tibial spine fractures and loose bodies within the notch. Although most ligamentous injuries cannot be diagnosed by plain radiography, avulsion of the attachment site can be seen occasionally and provides indirect evidence of ligament disruption.

CT is most useful for detecting and classifying tibial plateau fractures and usually is done when the diagnosis is unclear or if operative intervention is being considered. CT angiography (CTA) is an effective tool for detecting injury to the popliteal artery and has been replacing traditional angiography, although its sensitivity relative to traditional angiography has not been quantified in large high-quality studies.

Angiography

In the ED evaluation of trauma to the knee and leg, angiography is indicated for evaluation of popliteal artery injury after knee dislocation. Conventional angiography, with its complication rate of about 2%, largely has been supplanted by CTA, which does not require arterial puncture. False-positive results can lead to unnecessary surgical exploration. From a practical standpoint, the patient must be moved from the ED to a radiology suite, where other injuries cannot be addressed, and the angiography team must be mobilized, often resulting in delays in care.

Duplex Ultrasonography

Duplex ultrasonography refers to the combination of two-dimensional ultrasound imaging plus color Doppler examination. This method is used for evaluation of the popliteal artery after tibiofemoral dislocation (discussed later). Color Doppler imaging is used to compare the velocity of blood in a narrowed area with the velocity just proximal to the narrowed area. As the lumen narrows, flow accelerates, and the ratio of velocities is an accurate predictor of the degree of stenosis.

Radionuclide Bone Scan

Almost never indicated as an emergency study, a radionuclide bone scan can be used to detect osteomyelitis or occult bony injuries, such as stress fractures, osteochondritis dissecans, and avascular necrosis. It is generally used only for patients who cannot undergo MRI or have ambiguous MRI results.

Arthroscopy

Arthroscopy of the knee is the most commonly performed orthopedic surgical procedure in the United States. This nonemergent procedure is useful in the diagnosis and treatment of knee injuries, including injuries of the meniscus, cruciate ligaments, articular cartilage, capsule, and synovium. Arthroscopy is superior to MRI for the diagnosis of meniscal tears and other soft tissue injuries, and the diagnosed problem can be repaired immediately. The need for arthroscopy is established in the convalescent phase of injury and need not be determined in the emergent setting as long as appropriate referral to an orthopedist is made.

Joint Injection

An open joint is considered a surgical emergency. When violation of the joint capsule is suspected but not obvious, 200 mL of sterile normal saline can be injected into the joint capsule and the laceration observed to see if the saline emerges from the laceration. Methylene blue had been used in the past but should not be used because it has not been shown to be more accurate, can interfere with arthroscopy, and may cause an inflammatory reaction.

Arthrocentesis

Aspiration of fluid from the knee joint can be diagnostic as well as therapeutic by reducing pressure from a effusion. Arthrocentesis should be performed if the injured knee is greatly distended with a tight effusion or when the cause of the joint effusion is unknown. Aspiration of the joint and subsequent analysis can differentiate simple effusion, hemarthrosis, lipohemarthrosis, and septic arthritis and often provides significant relief of pain for the patient.

KNEE INJURIES

Dislocation

Anatomy and Pathophysiology

Knee dislocation refers to tibiofemoral dislocation and should not be confused with patellofemoral dislocation, a relatively minor injury. Knee dislocation is a limb-threatening emergency because a popliteal artery injury occurs frequently. Knee dislocation is uncommon but should be considered in the setting of an appropriate injury mechanism because 50% of all knee dislocations are reduced spontaneously before the patient arrives at the ED. Reduction before ED arrival does not lessen the likelihood of vascular injury, however, and these patients should be evaluated for vascular injury, particularly when associated with ligamentous injuries and high-energy mechanisms.

By definition, knee dislocations are associated with significant ligamentous injury. The joint capsule is disrupted, with accompanying trauma to the muscles and tendons. Injury to the popliteal artery is the most severe complication and is the primary cause of morbidity and limb loss.

The neurovascular bundle, which is composed of the popliteal artery, popliteal vein, and common peroneal nerve, runs posteriorly behind all bony and ligamentous structures in the popliteal fossa. The popliteal artery is fixed in the fibrous tunnel of the adductor magnus hiatus proximally and traverses the fibrous arch of the soleus and interosseous membrane distally. In essence, it is tethered to the femur and tibia, and its inherent immobility renders it susceptible to injury during dislocation. Because of the parallel course of the popliteal vein and peroneal nerve, they are often injured simultaneously.

Anatomically, dislocations are described according to the displacement of the tibia relative to the femur. They are classified into five types—anterior, posterior, medial, lateral, and rotary. More than half of all dislocations are anterior and result from hyperextension. Posterior dislocations are the second most common type and usually result from high-velocity direct trauma to the flexed knee, often in association with vehicular trauma (eg, dashboard impact).

Clinical Features and Differential Diagnosis

The diagnosis of knee dislocation is based on the mechanism of injury and clinical and radiographic findings. When a dislocation is present and has not reduced spontaneously, it is usually obvious.

However, there may be no effusion after reduction because the ruptured capsule allows blood and joint fluid to escape into the thigh and leg.

Popliteal artery injury is reported in up to two-thirds of these patients. The collateral geniculate arteries around the knee also may be damaged directly or may be secondarily compressed by hematoma formation after the dislocation. Direct arterial injury, decreased collateral circulation, and elevated compartment pressures all may compromise limb perfusion. In addition to being clinically occult, vascular injury in blunt trauma is more difficult to manage because of associated soft tissue injury and edema.

Findings associated with peripheral vascular injury and management approaches are described in Chapter 41. The posterior tibial and dorsal pedal pulses should be evaluated, but popliteal artery injury may still be present in up to 15% of patients with these pulses present.

Isolated intimal tears are usually managed without surgery, but a vascular surgeon should be consulted when such a tear is identified. Isolated intimal tears are not detectable on physical examination and are seen only angiographically or with duplex ultrasound. These injuries are treated nonoperatively with observation, with or without anticoagulation. Injuries to small branches of the popliteal artery can be managed by observation and serial examinations, and all such examinations must also include evaluation for possible development of compartment syndrome.

As with all limb injuries, neurologic integrity should be assessed and documented. The peroneal is the most commonly injured nerve with knee dislocation; some degree of dysfunction occurs in 20% to 40% of patients and is permanent in approximately 80% of them. Peroneal nerve function is evaluated by determining sensation of the dorsum of the foot and by having the patient dorsiflex the ankle. Less commonly, the posterior tibial nerve may be injured, which causes diminished plantar sensation and flexion of the foot. Complete nerve palsy in the acute setting is associated with a poor prognosis for recovery.

Diagnostic Testing

The diagnostic evaluation begins with an understanding of two crucial facts. First, half of all tibiofemoral dislocations are reduced before presentation, and injury to the popliteal artery should be assumed with tibiofemoral dislocation regardless, of spontaneous reduction. Therefore, the diagnostic strategy is applied to all patients with known knee dislocation, multiligament knee injury, or known or possible high-force trauma to the knee. The intubated multitrauma patient with ecchymosis around the knee may harbor an occult popliteal injury.

Popliteal artery injury is assessed by measurement of the ankle-brachial index (ABI) with serial physical examinations, CTA, and duplex ultrasonography. Formal angiography is rarely used.

Serial physical examinations—palpation of the pedal pulses—is not sufficiently sensitive for an injury with such potentially devastating consequences. Adding measurement of the ABI improves sensitivity. The ABI is is the ratio of the systolic blood pressure measured in the standard humeral location to the systolic pressure measured at the ankle. An ABI more than 0.9 has a negative predictive value for popliteal artery injury, approaching 100% in knee dislocation. Duplex ultrasonography and CTA are highly reliable options for diagnosis in this setting.

The choice of diagnostic strategy depends on the patient's presentation. At one extreme is the patient with obviously impaired leg perfusion. In this case, emergency angiography or surgical exploration are indicated. At the other extreme is the patient with knee trauma but no clear indication that a dislocation even occurred. Fig. 50.4 depicts a safe and efficient algorithm.[1] During the secondary survey, the dislocation is reduced, if present on presentation. The feet are examined and, if both are warm and well-perfused, dorsalis pedis and posterior tibial pulses are palpable and symmetric and, in the awake patient, sensation is intact, the ABI can be determined. If the ABI is above 0.9, the physical examination, including ABI determination, is repeated every 3 to 4 hours for 24 hours. If no abnormalities attributable to popliteal artery disruption are detected, no further emergent evaluation is indicated. Before surgery to repair associated injuries, the surgeon may choose to perform duplex ultrasonography to evaluate for an isolated intimal tear, which, although not important to detect in the ED setting, can lead to complications during surgery. If the pedal pulses are asymmetric or the ABI is below 0.9, urgent CTA is indicated. If pedal pulses are absent, the foot is cool or otherwise appears poorly perfused, or there is an expansile popliteal hematoma, immediate surgical exploration is indicated, with or without arteriography.

Management

The dislocated knee should be reduced at the earliest opportunity if isolated and during the secondary survey if the patient is multiply injured. Unless there is diagnostic uncertainty, reduction should occur prior to obtaining imaging, with the neurovascular status documented before and after reduction. For patients being transferred from a nontrauma to trauma center, reduction should be attempted prior to transfer. Reduction usually can be accomplished with simple traction-countertraction, almost always requiring procedural sedation. Lateral pressure may be required—for example, for an anterior dislocation, the femur can be pushed posteriorly while the tibia is pulled anteriorly, with special care taken not to apply undue pressure to the popliteal fossa. Posterolateral dislocations may not be reducible because the medial femoral condyle and MCL secure the dislocated joint in place, in which case emergent open reduction in the operating room is indicated. Because many reductions are unstable, the limb should be immobilized in a long leg posterior splint with the knee in 15 to 20 degrees of flexion, and popliteal artery injury sought, according to the algorithm shown in Fig. 50.4.

Disability is minimized by expedient revascularization and primary arterial repair, heparinization when not contraindicated, repair of popliteal venous injury, and thorough wound débridement. Open joints require prophylactic antibiotics, such as cefazolin, 2 g IV qid. If the neurovascular structures remain intact after dislocation, the knee joint is reduced and allowed to rest for 2 to 3 days before reconstruction of the torn ligaments is considered.

Delayed complications associated with traumatic knee dislocations include deep vein thrombosis, compartment syndrome, pseudoaneurysm, and arterial thrombosis. Compartment syndrome generally develops within 24 to 48 hours of the initial injury. Pseudoaneurysms are rare but may form several hours to months after popliteal artery injury. Heterotopic ossification is a poorly understood syndrome of calcification of the soft tissues of the knee. It has been observed in uninjured knees of patients who have sustained major trauma. In its most severe form, heterotopic ossification can cause dramatic decrease in knee mobility. Almost half of dislocated knees are found to have subsequent heterotopic ossification, although the most function-limiting form may be limited to patients with a history of severe trauma.

Distal Femur Fractures

Anatomy and Pathophysiology

Distal femur fractures are uncommon, constituting approximately 4% of femur fractures. Fractures of the distal femur are essentially knee injuries. See Chapter 49 for more detailed discussion of femoral shaft and proximal femur fractures. A high-energy mechanism of injury is required. An isolated fracture of the

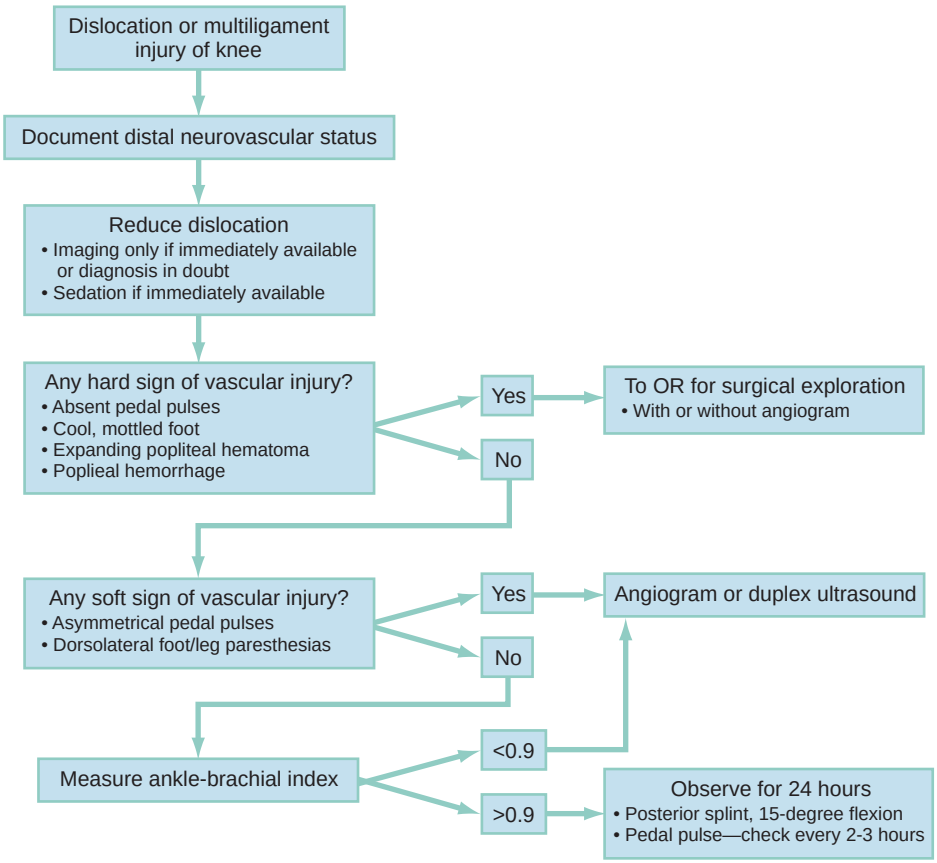

Fig. 50.4. Algorithm for the management of knee dislocation. (From Nicandri GT, Dunbar RP, Wahl CJ: Are evidence-based protocols which identify vascular injury associated with knee dislocation underutilized? Knee Surg Sports Traumatol Arthrosc 18:1005–1012, 2010.)

femoral condyle may occur, or the fracture may extend in a T or Y pattern to include the intercondylar or supracondylar region of the femur. Condylar fractures are intraarticular and may result in disruption of the articular surface, with subsequent arthritis.

Clinical Features

Patients with condylar or intercondylar fractures have pain and swelling in the distal femur and suprapatellar region and often are unable to bear weight. Examination may reveal shortening, rotation, and angulation of the extremity and tenderness to palpation along the medial or lateral joint line. Acute hemarthrosis is common and may be caused by intraarticular extension of the fracture or associated ligamentous injury. Distal neurovascular status should be documented. Any laceration in the region of the fracture represents an open fracture until proven otherwise.

Diagnostic Testing

Routine anteroposterior (AP) and lateral views should be obtained and usually show the fracture pattern and any significant displacement of fragments. In high-energy injuries, radiographs of the ipsilateral hip and tibia are required to exclude associated fractures. Occasionally, CT or MRI may be required to diagnose a nondisplaced fracture. If signs of vascular impairment are present, consultation for angiography or surgical exploration should be obtained emergently.

Management and Disposition

Femur fractures are painful, and IV opioid analgesia is indicated, titrated to pain relief. Ultrasound-guided femoral nerve blocks are also extremely effective. After the initial examination, the leg should be splinted to prevent excessive motion of the fracture site, which also is helpful in reducing pain. Emergent orthopedic consultation is advised. In a stable patient with an uncomplicated fracture, reduction may be done with skeletal traction, followed by immobilization. Intraarticular fractures generally are treated with open reduction and internal fixation. Distal femur fractures may be associated with thrombophlebitis, fat embolus syndrome, delayed union or malunion if reduction is incomplete or not maintained, intraarticular or quadriceps adhesions if the fracture is intraarticular, angulation deformities, and osteoarthritis, particularly affecting the patellofemoral articulation. Virtually all patients with distal femur fracture require admission to an inpatient orthopedic service.

Tibial Plateau Fractures

Anatomy and Pathophysiology

The proximal end of the tibia is expanded into the medial and lateral condyles. Together they make up approximately three-quarters of the proximal tibial surface, and their integrity is important for normal knee alignment, stability, and motion. The plateau normally slopes 10 degrees from anterior to posterior; on a straight AP view, the anterior and posterior portions of the plateau may not appear to be at the same level.

Tibial plateau fractures often are intraarticular. The forces that normally act on the tibial condyles include axial compression and rotation. The most common mechanism of injury is a strong valgus force with axial loading. Severe high-energy tibial plateau fractures occur primarily in younger patients and are often the result of motor vehicle collisions (MVCs) or falls from heights.

These fractures occur in concert with many other injuries and may be open. Fatigue stress fractures of the tibial plateau occur mostly in older adults. These low-energy fractures are the result of compression forces in osteoporotic bones.

The Segond fracture represents a bone avulsion of the lateral tibial plateau (Fig. 50.5). The avulsion occurs at the site of attachment of the lateral capsular ligament. On radiographs, an oval-shaped fragment can be seen adjacent to the lateral tibial plateau, which can be confused with an avulsion from the adjacent fibular styloid. Segond fractures are usually accompanied by ACL disruption and anterolateral rotatory instability. Most Segond fractures are caused by sports injuries; the mechanism is almost always knee flexion with excessive internal rotation and varus stress.

Clinical Features

Knee fractures cause pain, tenderness, ecchymosis, soft tissue swelling, and hemarthrosis when intraarticular. A valgus or varus limb deformity may be present and usually indicates a depressed fracture or concomitant leg fracture. The most important aspect of the initial examination is assessment of neurovascular status. Many tibial plateau fractures cause vascular complications. The popliteal artery may be injured by fragments from bicondylar or comminuted fractures involving the subcondylar area. Displaced fractures of the lateral condyle may produce peroneal nerve paralysis in addition to injury to the anterior tibial artery. Stretch of the peroneal nerve is the usual cause of injury.

Soft tissue injuries also may involve the capsuloligamentous structures of the knee. Ligamentous injuries accompany tibial plateau fractures in up to 66% of cases, most often involving the ACL and MCL.

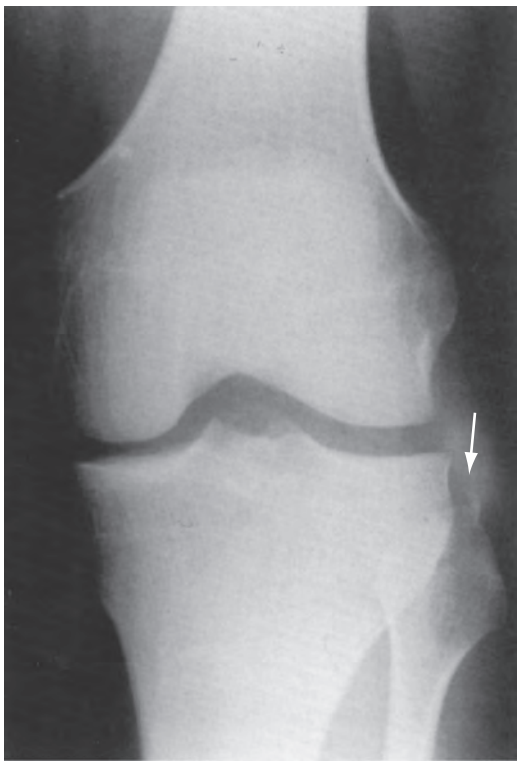

Fig. 50.5. Segond fracture. Anteroposterior view of the left knee shows lateral curvilinear avulsion fracture (*arrow*) and joint effusion. (From Kerr HD: Segond fracture, hemarthrosis, and anterior cruciate ligament disruption. J Emerg Med 8:29–33, 1990.)

Diagnostic Testing

Lipohemarthrosis, seen as a fat-fluid level on a plain film, suggests an occult fracture and is caused by entry of marrow fat into the joint space (see Fig. 50.3). Lipohemarthrosis also is detected when fat globules are found on aspiration of a hemarthrosis. All knee radiographs should be examined closely for bone avulsion fragments from the fibular head, femoral condyles, and intercondylar eminence because these may indicate ligamentous injury. Widened joint spaces associated with a fracture of the opposite condyle also may indicate concomitant ligamentous injury.

CT and MRI are more sensitive than plain radiography, help localize occult lesions, and help quantify the amount of depression in displaced fractures and extent of articular surface involvement in comminuted fractures. In the emergency setting, when clinical suspicion of a fracture is high, CT may be performed or this can be done in the outpatient setting, with the patient discharged with crutches and non–weight-bearing instructions.

Management and Disposition

All patients with a tibial plateau fracture should be referred for evaluation by an orthopedist, which usually will occur in the ED. In the acute phase, if orthopedic consultation is not obtained in the ED, the fracture should be immobilized in a noncircumferential splint, and the patient should not bear weight on the limb until seen by an orthopedist. Weightbearing generally is delayed until healing is complete, usually 6 to 8 weeks. Stable nondisplaced fractures may be treated with immobilization alone, but instability or significant depression or disruption of the joint surface require surgical management. CT scanning is often required for surgical planning, even when indications for surgery are evident based on the clinical examination and x-ray.

Fractures of the Intercondylar Eminence (Tibial Spine)

Anatomy and Pathophysiology

The intercondylar eminence, or tibial spine, is the central portion of the proximal tibial surface. The spine has two prominences, the medial tubercle and lateral tubercle. The medial tubercle is larger and more anterior. Two intercondylar fossae are present on the proximal tibial surface, one anterior to the intercondylar eminence and one posterior to it. The ACL and anterior horns of the medial and lateral menisci attach in the anterior intercondylar fossa. The PCL and posterior horns of the menisci attach in the posterior intercondylar fossa. A fracture of the anterior tibial spine usually is associated with an ACL rupture. Tibial spine fractures are more common in children than in adults because the ligaments are stronger than the adjacent physeal plates in the immature skeleton; this fracture may be an isolated injury in the presence of open physes.

Most tibial spine fractures occur as a result of violent knee twisting, hyperflexion, hyperextension, or valgus-varus forces generated during MVCs or athletic activities. The tibial spines are fractured by twisting knee movements, whereas hyperextension or hyperflexion forces may cause avulsion of the intercondylar eminence or cruciate ligaments from their tibial attachments.

Clinical Features

After a tibial spine fracture, the patient reports pain and swelling of the knee and may be unable to bear weight on the affected extremity. The examination confirms acute hemarthrosis and may reveal a block to full knee extension. Tense effusion may limit

ROM, hinder physical examination, and mask ligament disruption. ACL laxity is expected.

Diagnostic Testing

Radiographic evaluation should include standard AP and lateral views; a tunnel view provides a clearer look at the intercondylar area and may reveal the diagnosis. Joint margins should be examined closely for evidence of collateral ligament or capsular bone avulsions. CT sometimes is required to show the location and displacement of the fracture.

Management and Disposition

The knee should be immobilized, and the patient should be given non–weight-bearing instructions and referred to an orthopedist within 3 to 7 days. Most patients are managed conservatively with good results, although some, particularly when reduction cannot be achieved, or there is significant ligamentous disruption, require surgical repair.

Osteochondritis Dissecans

Osteochondritis dissecans is a rare orthopedic disorder of unknown cause (Fig. 50.6). The disorder is found mainly in adolescents and results in partial or total separation of a segment of articular cartilage and subchondral bone from the underlying bone. It is commonly unilateral, involving the non–weight-bearing lateral aspect of the medial femoral condyle, and is thought to be related to acute or chronic trauma. Occasionally, the lateral femoral condyle or inferior patella pole is involved. Patients often have pain, swelling, and giving-way episodes without a history of trauma. Localized tenderness of the condyle often is the only physical finding. Routine radiographic views usually are diagnostic; a subcortical lucency (see Fig. 50.6) can be appreciated, and an osteochondral fragment may be seen separated from the underlying bone. Rarely indicated in the ED, MRI or CT may aid in determining the exact location and extent of the osteochondrotic lesion. ED patients with suspected osteochondritis dissecans should not bear weight until seen by an orthopedist.

Extensor Mechanism Injuries

Anatomy and Pathophysiology

The extensor mechanism consists of the quadriceps muscles, quadriceps tendon, medial and lateral retinacula, patella, patellar tendon, and tibial tubercle (Fig. 50.7). Passive and dynamic stabilization of the patella are aided by the surrounding soft tissue. Although this anatomic complex encompasses the most superficial aspect of the knee, ruptures of the extensor mechanism are infrequent injuries relative to other types of injuries of the knee joint. Disruptions of the extensor mechanism may occur at any level, from the quadriceps muscle to the insertion on the tibial tubercle. Injury generally occurs as a result of sudden vigorous contraction of the quadriceps muscle with the knee in a flexed position, laceration, or direct blow. Rupture of the quadriceps tendon usually occurs at or just proximal to the patellar insertion. Occasionally, the rupture may extend into the vastus intermedius tendon or transversely into the retinaculum. Most patellar tendon ruptures occur at the site of origin on the inferior pole of the patella.

Chronic systemic conditions, including rheumatoid arthritis, gout, systemic lupus erythematosus, hyperparathyroidism, and iatrogenic immunosuppression in organ transplant recipients, may render the tendon vulnerable to rupture. Several studies have implicated the use of steroids or fluoroquinolones in tendon rupture. In children, quadriceps and patellar tendon ruptures are rare, and muscle tears seem to predominate. In adolescents, patellofemoral dysplasia, chronic tendinitis, and use of steroids are predisposing factors. Dysplasia may cause extensor mechanism injury by repetitive tensile overloading; corticosteroids seem to weaken collagen ultrastructure and impair the reparative process.

Clinical Features

Clinical evaluation can elicit the correct diagnosis in most cases of complete disruption of the extensor mechanism. Patients with extensor disruption may have the following signs and symptoms: (1) acute onset of pain, swelling, and ecchymoses over the anterior aspect of the knee and a palpable defect in the patella, quadriceps tendon, or patella tendon; (2) loss or limitation of ability for active

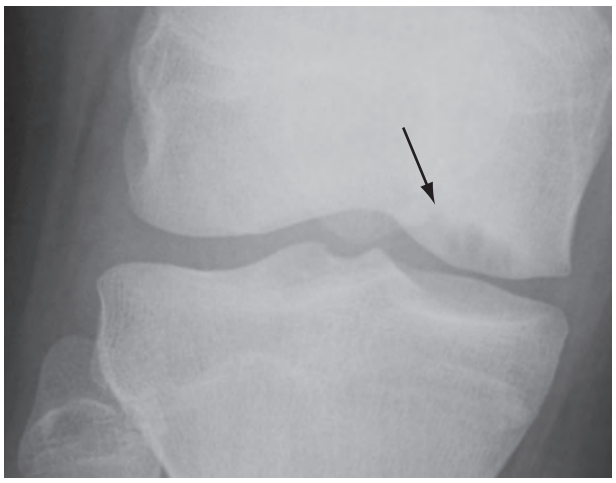

Fig. 50.6. Osteochondritis dissecans. A subcortical radiolucency (*arrow*) is seen in the knee of an adolescent female with chronic medial knee pain.

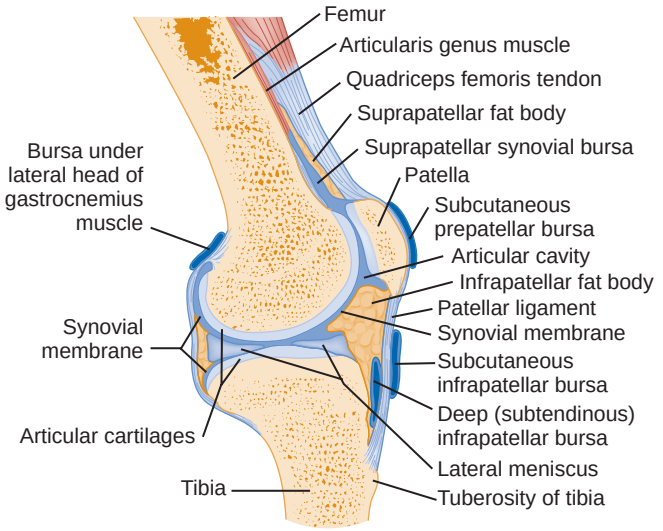

Fig. 50.7. Parasagittal section (lateral to midline) of the knee showing extensor mechanisms and relevant structures.

leg extension—extension lag usually is seen when extension for the last 10 degrees is performed haltingly or with difficulty; (3) high-riding patella (patella alta), with patellar tendon rupture and superior retraction; and (4) low-riding patella (patella baja), with quadriceps tendon rupture and inferior retraction. Partial disruptions may be difficult to diagnose on clinical examination and may require MRI for confirmation.

Diagnostic Testing

Standard AP and lateral radiographs should be obtained and may reveal characteristic findings, possibly including obliteration of the quadriceps or patella tendon, poorly defined suprapatellar or infrapatellar soft tissue mass, soft tissue calcific densities, or displaced patella (Fig. 50.8). Patella alta may be sought on the lateral radiograph with use of a ratio of patellar length to patellar tendon length (Insall-Salvati ratio). If this ratio is less than 0.8, patella alta is present. The degree of flexion should not affect this ratio, which relies on the inelasticity of the patellar tendon. Obliteration of the extensor tendons may be caused by a frayed tendon and surrounding hematoma. A soft tissue mass represents proximal or distal retraction of the torn tendon. Calcific densities may represent avulsed bone fragments of the patella or tibial tubercle or dystrophic calcifications in the substance of the tendons. Despite these multiple radiographic signs, the correct diagnosis is infrequently made by plain radiography in cases of incomplete quadriceps tendon rupture. MRI shows the entire extensor mechanism and is the best imaging modality. MRI usually is reserved for patients with possible incomplete disruption or with a complication of intraarticular derangements.

Management

Treatment of acute extensor mechanism injuries produces a much better clinical outcome if instituted early, within 2 to 6 weeks of the initial injury. All patients with partial or complete tears of the extensor mechanism should be referred for orthopedic care.

Patients with delayed diagnosis of patellar tendon rupture may experience significant retraction of the patella proximally and subsequent development of quadriceps contractures or adhesions. If the tear is only partial, immobilization with the knee in full extension for 4 to 6 weeks is the treatment of choice. Surgical intervention is required for reattachment of complete tendon ruptures, and repair should be performed as soon as possible after injury for the best results to be achieved.

Patellar Fractures

Anatomy and Pathophysiology

The patella is the largest sesamoid bone in the body. It is held in place by the quadriceps tendon, patellar ligament, and medial and lateral retinacula. As an integral part of the extensor mechanism, the patella increases the effective lever arm of the quadriceps by providing anterior displacement of the quadriceps tendon. All fractures of the patella, except for small avulsion fractures of the rim, are considered intraarticular.

Patellar fractures are classified as transverse, stellate, or comminuted, longitudinal or marginal, proximal pole or distal pole and, rarely, osteochondral. They may be displaced or nondisplaced and occur from direct or indirect forces or from dislocation. The most common fracture pattern is the transverse fracture (accounting for 50%–80% of cases). This type often is seen in young adults and usually results from a powerful contractile force transmitted from the quadriceps tendon. This force may pull the superior portion of the patella upward, leading to wide displacement. In such cases the medial and lateral retinacula are usually disrupted, resulting in significant functional disability; active extension is impossible. Nondisplaced transverse patellar fractures usually are caused by a direct blow to the anterior aspect of the patella (eg, a fall on the knee or a direct blow sustained in vehicular trauma). The retinaculum and extensor mechanism usually remain intact, and the patient retains limited functional ability for active extension. Stellate and comminuted fractures account for 30% to 35% of all patellar fractures and commonly result from a direct impact. The fracture elements often appear as separated fragments on plain radiographs but are held in place and supported by the medial and lateral retinacula and the overlying soft tissues. Small

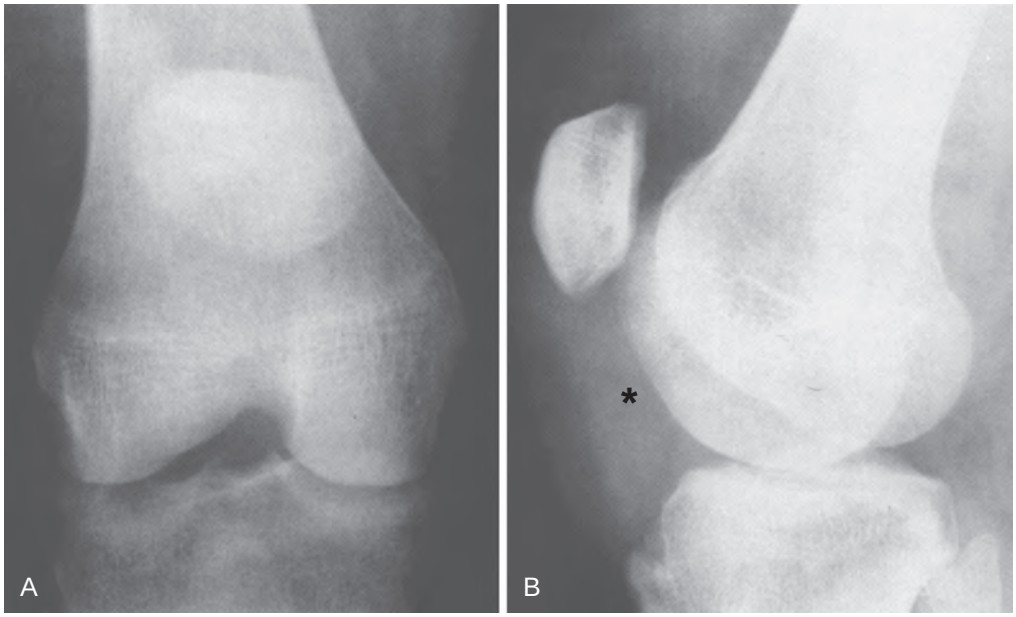

Fig. 50.8. Rupture of the patellar tendon, resulting in the high-riding patella in frontal (**A**) and lateral (**B**) projections. **B,** The normally lucent infrapatellar portion of the joint space is dense (*asterisk*), representing blood within the anterior compartment. (From Harris JH Jr, Harris WH: The radiology of emergency medicine, ed 3, Baltimore, 1993, Williams & Wilkins.)

proximal fragments are at risk for avascular necrosis because the patellar blood supply is central and inferior. Longitudinal or marginal vertical patellar fractures are less common, are usually the result of direct injury, and involve the lateral facet.

Clinical Features

On physical examination, tenderness, swelling, and ecchymosis over the patella and prepatellar bursa are noted. Active extension may be limited or absent, depending on the fracture pattern and amount of fragment displacement. Associated injuries may include fractures of the femoral neck, dislocation of the hip, and acetabulum fractures.

Diagnostic Testing

Radiologic evaluation of patellar fractures should include standard AP, lateral, and sunrise views. Most patellar fractures are obvious on plain radiographs, but vertical marginal fractures may be difficult to identify; they are obscured by the femur on the AP view and not seen at all on the lateral view. Close examination of sunrise (or equivalent) views may reveal an osteochondral avulsion fragment or marginal fracture (Fig. 50.9). Bipartite and multipartite patellae are common normal variants and should not be confused with fractures. Ossification centers are found at the upper outer quadrant of the patella and have smooth cortical margins, but differentiating physeal lines from fractures can be difficult. Comparison radiographs may be helpful because these anatomic anomalies often are bilateral. In some cases, MRI or arthroscopy may be needed to identify occult marginal fractures or free osteochondral fragments.

Management

For initial management, a knee immobilizer may be used. Patients should be instructed to use crutches, with partial weightbearing as tolerated, and should be referred for orthopedic evaluation within 1 week.

For widely displaced transverse fractures, open reduction and internal fixation are necessary for optimal results. Although operative techniques vary among surgeons, tension band wire and suturing of the retinaculum often are used. A knee immobilizer or long leg posterior splint can be used initially to immobilize the extremity before definitive care is provided. Treatment options for displaced comminuted fractures include open reduction, internal fixation, and partial or complete patellectomy.

Persistent patellofemoral pain and osteoarthritic symptoms are reported as late sequelae of patellar fractures in approximately 50% of patients.

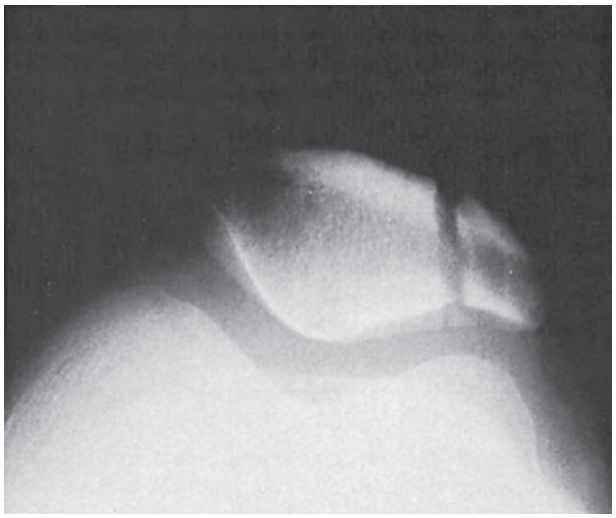

Fig. 50.9. Patellar fracture, sunrise view. The sharp nonsclerotic margins identify this as an acute fracture and not a congenital finding. (From Rosen P, et al: Diagnostic radiology in emergency medicine, St. Louis, 1992, Mosby, p 196.)

Patellar Dislocation

Anatomy and Pathophysiology

Traumatic patellar dislocation is a relatively common knee injury, with a high frequency of recurrence. It is more common in children than in adults. Most cases are lateral, and the mechanism of injury usually is a direct blow to the anterior or medial surface of the patella. It may occur from an athletic injury caused by a valgus stress combined with flexion and external rotation. In nearly all cases, disruption or sprain in the medial patellar retinaculum results from stretching of this structure as the patella subluxes laterally; subluxation usually indicates a stretched medial retinaculum, and dislocation suggests a tear.

Clinical Features

Patients with lateral patellar dislocation may complain of the knee giving out, accompanied by pain and swelling. Inability to bear weight and inability to flex the knee are common complaints. There may be a history of previous dislocation. Examination reveals a defect anteriorly, with the patella deviated laterally. Tenderness along the medial joint line usually can be elicited by palpation, and an effusion may be present. Acute hemarthrosis is usually seen if there is an associated osteochondral fracture. Osteochondral fractures typically occur on the articular surface of the patella and may involve only cartilage (chondral fractures) or may include a piece of underlying cortical bone. Patellar dislocations may reduce spontaneously, or the patient may self-reduce the dislocation, usually followed by formation of a large effusion.

The patellar apprehension test is used to aid the clinical identification of patients at risk for patellar dislocation or subluxation. The apprehension sign refers to the combination of manifestations of anxiety and anticipatory reactions observed in the patient when the examiner attempts to slide the nondisplaced patella laterally. A positive result on the apprehension test indicates a tendency for patellar subluxation or dislocation. This test has no proven value and is not necessary in a patient with acute patellar dislocation, but it may be useful in establishing the diagnosis in patients who report an event that resolved spontaneously.

Diagnostic Strategies

Standard AP and lateral radiographic views generally are adequate for diagnosis. Obtaining a sunrise (skyline) view usually is not possible because of pain and inability to flex the knee. Radiographic findings include lateral deviation of the patella out of the trochlear groove, usually with an effusion. Radiographs should be examined for evidence of avulsion fractures.

Management and Disposition

After dislocation is diagnosed, closed reduction should be attempted. Usually, the procedure is very straightforward, involving simple, slow, gentle, passive extension of the knee, with inferomedial pressure on the patella. If done with appropriate care,

patient discomfort often is minimal, and the patient does not require procedural sedation. If the procedure is painful, or the patient is excessively anxious, appropriate sedation and analgesia are used. Application of downward pressure to the lateral aspect of the patella can help in reduction by unlocking the medial patellar facet. Postreduction radiographs are recommended and should reveal the patella in the trochlear grove. Osteochondral avulsion fragments may be visualized radiographically, and postreduction radiographs should be examined carefully for their presence. Radiologically evident intraarticular loose bodies may require arthroscopic removal.

Typically, traumatic patellar dislocations occur with disruption of the medial retinaculum but an intact lateral retinaculum, preventing internal rotation. Dislocations irreducible by conventional methods may be associated with significant internal rotation and lateral retinaculum pathology.

After successful reduction, the knee should be immobilized in full extension, and the patient may be discharged with referral for orthopedic or primary care follow-up within 2 weeks. Ice, elevation, non–weight-bearing status, and analgesia are helpful. Although the incidence of recurrence may be decreased with appropriate therapy and proper patient selection, up to 44% will experience a recurrent dislocation, and more than 50% of all patients with a primary patellar dislocation will continue to have symptoms of instability or anterior knee pain and may require surgery.

Cruciate and Collateral Ligament Injuries

Ligament injuries to the knee may involve any or all of the ligaments and may range in severity from a mild sprain to complete tears. Collateral ligament injury usually causes tenderness and pain along the joint line. Cruciate injuries pose more of a diagnostic dilemma because they are intraarticular.

Clinical Features

Cruciate Ligament Injuries. The cruciate ligaments are so named (Latin *crus,* meaning "cross") because they cross each other between their attachments. They are the primary stabilizers for anterior and posterior displacement of the tibia on the femur. The ACL extends obliquely upward, medially, and posteriorly from the anterior intercondylar area of the tibia to the medial aspect of the lateral femoral condyle. The ACL prevents excessive anterior displacement of the tibia on the femur and helps control rotation and hyperextension of the knee during twisting and turning activities. It is the most commonly injured major ligament of the knee, with more than 100,000 new ACL tears occurring in the United States annually. The PCL passes upward, laterally, and forward medially to the ACL from the posterior intercondylar area of the tibia to the lateral aspect of the medial condyle of the femur. The PCL prevents excessive posterior displacement of the tibia on the femur, especially during flexion. The PCL is extremely strong, and injuries are relatively uncommon. Cruciate ligament injury is uncommon in children with open physes.

The ACL is commonly injured in sports. Numerous mechanisms of injury produce ACL disruption. Although ACL injuries can be caused by contact, they are more common in noncontact sports, with the plant and pivot and stop and jump mechanisms predominating. A direct blow to the flexed knee, as may occur in MVCs (from the dashboard), and turf injuries with the knee flexed and the ankle plantar-flexed also can result in an ACL injury.

Half of ACL injuries are associated with meniscal tears. The lateral meniscus is torn more commonly than the medial meniscus in acute ACL injuries but, in chronic ACL tears, the medial meniscus is more commonly involved. The classic so-called unhappy triad of ACL, MCL, and medial meniscus injury may actually be less common than the association of torn ACL, torn MCL, and torn lateral meniscus.

The diagnosis of ACL injury often can be made from the history alone. Pain is the most common complaint with ACL rupture and usually is immediate. An audible pop at the time of injury is an important clue and is reported by approximately 70% of patients with an ACL rupture. Patients also may report buckling, locking, or collapse of the knee and its inability to bear weight. The anterior drawer test is used to diagnose ACL injuries (see earlier).

Isolated PCL injuries are comparatively rare. Mechanisms include a fall onto the ground with the foot plantar-flexed (striking the tibial tubercle), direct posterior blow to a flexed knee (eg, a dashboard injury), hyperflexion, hyperextension, severe varus or valgus loads after failure of the collaterals, and knee dislocations. Nearly all PCL injuries are associated with other ligament injuries, including concurrent injuries of the MCL, ACL, or posterolateral complex. Pain and swelling are common complaints, with isolated PCL tears and PCL tears having combined capsuloligamentous disruption. Popping or tearing sensations are infrequently noted, and instability usually is not immediately appreciated. Later, the patient may complain of feeling the femur "fall off" the tibia. The posterior drawer test (see earlier) is commonly done to assess the integrity of the PCL.

Collateral Ligament Injuries. The medial stabilizers of the knee are the joint capsule and MCL. The semimembranosus and pes anserinus contribute as well. These structures resist valgus laxity and medial rotary instability. The MCL is a two-part structure with a long superficial and deep capsular component; the latter attaches to the medial meniscus and acts as a stabilizer for this structure. The MCL usually is injured by a direct blow or impact to the lateral aspect of the knee, which imposes a valgus stress. MCL injury is the most common isolated knee ligament injury and is the injury most commonly associated with ACL injury. MCL injury usually does not require surgical treatment.

The lateral stabilizers of the knee are the LCL and lateral joint capsule. Secondary contributors to lateral stability are supplied by the iliotibial (IT) band, biceps tendon, and popliteal arcuate complex in the posterolateral corner of the knee. Resistance to varus stress is provided mainly by the LCL. Fibers descend from the lateral femoral condyle and insert at the fibular head. The lateral ligaments are under tension during standing and walking, when they are at or near maximal extension. The LCL usually is injured by a mechanism of hyperextension with varus stress, commonly accompanied by a direct blow or rotation. Injuries to the LCL are less common but more disabling than injuries of the MCL. The lower incidence of injury is attributed to the greater mobility of the LCL and overall greater stability of the lateral compartment. Varus injury is uncommon because the inner aspect of the knee is protected by the opposite leg. The forces necessary to produce LCL injury usually are greater than the forces required for medial injury, which partially explains the high frequency of associated injuries accompanying LCL injury. The tendon of the biceps femoris muscle attaches to the head of the fibula; the peroneal nerve passes just inferior to this. Because of this relationship, common peroneal nerve injury and biceps femoris tendon injury are possible although uncommon in patients with LCL injury.

The accuracy of the knee examination for ligamentous damage is enhanced if done soon after injury and before the onset of swelling and pain, but the patient may not tolerate the examination anyway, and muscle spasm can obscure findings. In any case, ligamentous injuries are not emergencies and can be diagnosed definitively after the acute phase has passed. Focal tenderness at

the origin or insertion sites suggests collateral ligament trauma but also can occur with muscular injury, osseous pathology, or meniscal tear.

Diagnostic Testing

The goal of radiographic investigation is to identify associated fractures. The initial radiographic evaluation should include AP, lateral, intercondylar notch, and sunrise views. Each radiograph should be evaluated for possible osteochondral injuries, loose bodies, or avulsion injuries at the attachment sites of ligaments. The lateral capsular sign, associated with the Segond fracture (see Fig. 50.5) and fracture of the posterior aspect of the lateral tibial plateau, commonly is associated with a ACL tear.

Arthroscopy is the gold standard for the diagnosis of soft tissue injuries of the knee (ligaments or menisci). MRI is useful but may miss small tears and anatomic abnormalities and, even if findings are normal, arthroscopy may still be necessary if symptoms persist. Moreover, abnormalities discovered at arthroscopy can be repaired. Therefore, many orthopedic surgeons recommend arthroscopy rather than MRI for diagnostic evaluation of knee pain when the causative disorder is not apparent on physical examination.

Management and Disposition

ED management consists compressive dressing from the foot to thigh, ice, simple analgesia with acetaminophen or a nonsteroidal antiinflammatory drug (NSAID) and no or minimal weight bearing. Orthopedic evaluation should take place within 1 week, when feasible. In the orthopedic surgeon's office, isolated collateral ligament injuries usually are managed nonoperatively, provided that the ACL is intact. Patients may be placed on a regimen of partial weightbearing or non–weight-bearing status with the use of crutches. A rehabilitative exercise program for quadriceps and hamstring strengthening may be instituted when the acute injury has resolved.

There is controversy among orthopedists regarding management of ACL tears because short-term disability and long-term arthritic sequelae are difficult to predict. Most young patients with a complete ACL tear who are active in sports will have reconstructive surgery to stabilize the knee. Surgical repair usually is performed arthroscopically after a delay of 2 to 3 weeks to allow swelling to subside. Older patients and patients who do not participate in active sports may be managed conservatively with muscle strength training.

Isolated PCL injuries are unusual and are generally managed nonoperatively. These injuries often are painful but usually do not lead to instability. Rehabilitation involves quadriceps strengthening and functional bracing. Over 10 to 20 years, degenerative changes of the articular surface may result in stiffness and pain.

Meniscal Injuries

Anatomy and Pathophysiology

The medial and lateral menisci are crescent-shaped fibrocartilaginous cushions that sit on the superior articular surface of the tibia and provide a gliding surface for the femoral condyles. They function as shock absorbers and aid in the distribution of stress across the joint surface by providing a larger area of contact. They also act as secondary stabilizers by deepening the tibial plateau. Normal tibiofemoral articulation and function depend on meniscal integrity; damage or loss leads to osteoarthritis. The medial meniscus is firmly attached anteriorly and posteriorly to the joint capsule. The lateral meniscus is less firmly attached to the capsule and more mobile. The menisci move slightly forward with extension and backward with flexion. Because of its greater mobility, the lateral meniscus is less vulnerable to injury. The meniscus is avascular except at the peripheral third, which has the greatest potential to heal after injury.

Meniscal injury classically manifests with pain and tenderness at the joint line, effusion, and clicking or locking of the knee. Because the menisci are much less vascular than the cruciate ligaments, significant hemarthrosis is usually not seen with isolated meniscal injury. Locking results from a meniscal fragment blocking joint movement. Injury to the menisci may be from a single traumatic episode, degenerative process, or combination. The mechanism usually involves a twisting maneuver on a weight-bearing knee. The force required sometimes can be as slight as arising from a chair while turning. Most meniscal tears are posterior.

Clinical Features

An isolated meniscal tear should be suspected in a patient with a history of intermittent locking, effusion, giving way, and pain and physical examination findings of joint line tenderness.

The cardinal sign of a meniscal tear is local pain and tenderness along the joint line. Joint line pain and tenderness are especially apparent with extremes of flexion and extension. Not all tears of the menisci are symptomatic. Degenerative lesions of the posterior horn are relatively common in middle age and later and may be asymptomatic. The differential diagnosis for a torn meniscus is extensive and includes loose bodies, osteochondrotic lesions, tibial spine fractures, patellofemoral pain syndrome, popliteal tendinitis, plica syndromes, inflammatory arthritis, and discoid menisci, with or without tears. Meniscal tears commonly accompany ACL tears.

Diagnostic Testing

Diagnosis of acute meniscal injury is difficult, more so in the presence of another acute knee injury, especially an ACL tear. Meniscal injury cannot be diagnosed by plain radiography or CT scanning. Arthroscopy is the gold standard for diagnosis; MRI is an alternative but may miss some meniscal tears.

Management and Disposition

Definitive treatment of a meniscal injury is not urgent. Unless the knee is locked and cannot be extended or flexed, a patient with a meniscal tear should be managed with analgesics, immobilization, ice, non–weight-bearing status, and referral for orthopedic or primary care follow-up. The locked knee requires acute orthopedic consultation if a knee immobilizer cannot be applied. Surgery is reserved for patients with persistent symptoms that limit activity, because research has suggested that surgical repair is no better than conservative management.[2]

Overuse Syndromes

Overuse syndromes result from repetitive trauma and inflammation. The typical complaint is knee pain, often localized to one of three particular areas—the medial aspect, lateral aspect, or peripatellar region. Medial knee pain may be caused by a subluxation of the patella, stress fracture of the upper third of the tibia, anserine bursitis or tendinitis, and MCL strain related to excessive foot pronation. Lateral knee pain may be caused by IT or popliteal tendinitis, LCL strain, or stress fracture of the fibula. Anterior pain is typical of lateral patellar compression syndrome, peripatellar tendinitis, and patellofemoral syndrome, the most common cause of knee pain.

Patellofemoral Pain Syndrome

Anatomy and Pathophysiology

The patellofemoral pain syndrome refers to the clinical presentation of anterior knee pain related to changes in the patellofemoral articulation. Chondromalacia patellae describes softening of the articular cartilage. Correlating pathologic changes on the surface of the patella and clinical symptoms has been difficult, and the pain mechanism has not been precisely defined.

Clinical Features

Patellofemoral pain syndrome is the most common cause of knee pain. Affected patients generally are 10 to 20 years of age and often have difficulty describing their symptoms clearly. The pain usually begins gradually and commonly is not related to trauma. One knee usually is more affected than the other. The knee is more painful with prolonged flexion (eg, from sitting in a movie theater), and the discomfort typically is accentuated by stair climbing and kneeling. The patient may have instability related to patellar subluxation or dislocation. The syndrome occurs in athletes and in older patients who have arthritis affecting the patellofemoral joint. Considerations in the differential diagnosis include tears of the menisci, plica syndrome, inflammatory or degenerative arthritis, ligament injuries, and overuse syndromes (eg, prepatellar bursitis, patella tendinitis).

The physical examination should begin with observation. The patient may ambulate with an antalgic gait. A tibiofemoral joint effusion may be present. The patellar facets may be tender. Classically, compression of the patella against the femur with the knee extended causes pain. There may also be apprehension regarding medial or lateral subluxation.

Diagnostic Testing

Patellofemoral pain syndrome is a clinical diagnosis; radiography is usually not required and, when performed, images are usually normal. More advanced studies are not indicated unless alternative diagnoses are being considered.

Management

Most patients, regardless of the cause of their condition, respond to a rehabilitation program. Conservative treatment for patellofemoral pain usually is effective, with most patients responding to one or more of four types of treatment: (1) exercises to strengthen the quadriceps; (2) brace support of the patellofemoral mechanism; (3) activity modification limiting flexion; and (4) medications such as NSAIDs for pain. The initial goal is to reduce pain and improve function, with emphasis placed on strengthening the vastus medialis oblique muscle. The patient should receive appropriate referral to ensure that an optimal rehabilitative scheme is designed.

Iliotibial Band Syndrome

Clinical Features

The IT band is a strip of fascia lata that extends from the iliac crest to the lateral tibial tubercle. It connects the lateral femoral condyle and lateral tibia and stabilizes the knee joint in extension. Irritation from overuse can cause inflammation of a bursa underlying the IT band at the lateral femoral epicondyle, resulting in lateral knee pain. The syndrome is most common in distance runners and is more likely in hyperpronators. Physical findings include localized tenderness of the lateral femoral epicondyle and IT tightness or pain, elicited by Ober's test or a related test. In Ober's test, the patient lies on his or her side with the unaffected leg down, flexed to 90 degrees at the hip and knee. The affected hip is abducted, the knee is extended, and then the hip is allowed to return to neutral adduction with gravity. Failure of the hip to adduct fully with gravity or reproduction of pain at the lateral knee indicates IT tightness or inflammation, respectively. Radiographs are not indicated. Considerations in the differential diagnosis include early degenerative joint disease, cystic or torn lateral meniscus, lateral capsular strain, lateral tibial or femoral condyle osteonecrosis, stress reactions, chondromalacia, and popliteus tendinitis.

Management and Disposition

Treatment involves rest, ice, and NSAIDs during the acute phase, followed by an IT band stretching regimen, improved footwear and orthotics when indicated, and gradual return to previous levels of activity. Steroid injections are helpful for refractory cases, and surgical release is uncommonly required.

Peripatellar Tendinitis

Peripatellar tendinitis, or jumper's knee, refers to a spectrum of patellar tendon and extensor mechanism abnormalities that result from chronic repetitive stress from jumping, running, or cutting. Microscopic tears occur in the tendon. Treatment includes NSAIDs, rest, and activity modification. Local steroid injections are not recommended. For highly competitive athletes and patients for whom conservative treatment is ineffective, surgery with débridement of abnormal tissue may be performed.

Plica Syndrome

Plicae, or redundant folds of synovium, are normal embryologic structures that persist in the adult knee. Repetitive bouts of synovitis within the plica may result in a tight inelastic band that interferes with knee motion. Patients typically complain of pain over the region of the medial femoral condyle brought on by activity but also occurring after sitting for prolonged periods. A snapping sensation is another commonly reported symptom as the plica sweeps across the femoral condyle. Other nonspecific symptoms include intermittent swelling, locking, weakness, and stiffness. The physical examination often elicits tenderness over the medial femoral condyle but not the medial joint line; the latter finding would be more typical of a medial meniscal lesion. An effusion, crepitus, loss of motion, quadriceps atrophy, and positive result on McMurray's test may be noted as well.

Plain radiography may be necessary to exclude other causes of knee pain but is of no value in diagnosing plica syndrome, for which arthroscopy usually is required. Most plicae are incidental arthroscopic findings unrelated to underlying knee pathology. Medial patella pain is more likely to be related to patellofemoral maltracking than to plica syndrome. Likewise, anteromedial joint line tenderness is more likely to be related to a meniscal tear than to a pathologic plica.

Treatment involves rest and NSAIDs. When the acute symptoms have resolved, a rehabilitation program is instituted to emphasize quadriceps strengthening and stretching. Arthroscopic excision of pathologic plica may be necessary if conservative treatment fails.

Popliteus Tendinitis

The popliteus is a small flat muscle that originates on the lateral femoral condyle and inserts on the posteromedial tibia, capsule, and lateral meniscus. It passes beneath the lateral head of the

gastrocnemius. Its tendon is surrounded by a bursa that separates it from the fibular collateral ligament, femoral condyle, and capsule. Functionally, it prevents external rotation of the tibia and withdraws the lateral meniscus during flexion to prevent impingement between the femur and tibia. A third function, along with the quadriceps and PCL, is to stabilize the knee by preventing forward displacement of the femur on the tibia. Popliteal tendinitis usually occurs in athletes and often causes localized pain over the posterior or posterolateral aspect of the knee. Running and walking downhill exacerbate symptoms. Usually, there is no history of effusion, locking, or giving way.

On physical examination, tenderness is noted at the insertion point of the muscle, medial to the insertion of the lateral head of the gastrocnemius. Because of the close relationship of the popliteus to other soft tissue structures, diagnosis may be difficult. The Webb test is performed with the patient supine and knee flexed to 90 degrees. The leg is rotated internally, and the patient is asked to resist the examiner's attempt to rotate the leg externally. Reproduction of symptoms suggests the diagnosis. Considerations in the differential diagnosis for popliteus tendinitis include injury of the biceps femoris insertion, lateral meniscus, lateral gastrocnemius, and IT band.

Treatment involves rest, ice, NSAIDs, and quadriceps strengthening and stretching. Most athletes can gradually return to activity in 10 to 14 days.

Bursitis

The knee has several bursae, which decrease friction between moving structures. They usually are thin but, with repeated stress, may become thickened and fluid-filled. The prepatellar bursa is located between the patella and skin. The superficial infrapatellar bursa is located between the tibial tubercle and skin. The deep infrapatellar bursa is located between the posterior margin of the distal part of the patellar tendon and anterior aspect of the tibia. The suprapatellar bursa is not a true bursa but rather is an extension of the tibiofemoral joint capsule. The anserine bursa separates the pes anserinus from the distal portion of the MCL and medial tibial condyle. As noted previously, pes anserinus means "goose foot" and anserine means "related to the pes anserinus." The term *pes anserinus* derives from the fact that the bursa underlies the anserine tendon, a three-forked structure constituting the insertion of the gracilis, sartorius, and semitendinosus muscles.

Bursitis is caused by repeated stress, infection, local trauma, crystal deposition, or systemic inflammatory arthropathy. It is important to differentiate bursitis from a joint effusion. Prepatellar bursitis is characterized by swelling, with effusion of the superficial bursa overlying the lower pole of the patella. Usually, passive motion is fully preserved, and the pain is mild. The disorder usually is caused by pressure from repetitive kneeling on a firm surface (so-called housemaid's knee). The prepatellar bursa also is a common site of septic bursitis, and a common error is to confuse this entity with a septic knee (involving the tibiofemoral joint).

Anserine bursitis involves pain and tenderness at the proximal medial tibia, a few centimeters inferior to the medial joint line. It usually occurs in obese women in association with osteoarthritis of the knee but also may occur from overuse, especially in runners. It is characterized by a relatively abrupt onset of knee pain, with localized tenderness and puffiness at the pes anserinus. It can be confused with a medial meniscal or MCL tear.

Radiographic studies are not required but, when obtained, may reveal soft tissue swelling. Ultrasound imaging also may detect the fluid collection. MRI may be helpful but is not required on an urgent basis. With any uncertainty regarding the possibility of infection, the bursa fluid should be aspirated, and Gram staining, culture, cell count, and crystal analysis of the aspirate should be performed.

Septic (bacterial) bursitis requires antibiotic treatment, with operative drainage in refractory cases. Aseptic (inflammatory) bursitis is treated with ice, rest, antiinflammatories, injection of bupivacaine and, when infection is not suspected, corticosteroids. All the bursae of the knee may be injected with steroids; in the ED, steroid injection of the anserine and prepatellar bursae is most common.

Septic Arthritis

The knee is the most common joint affected by septic arthritis. Hematogenous seeding is the most common route of spread, but joint trauma also is a frequent cause. Bacterial spread usually affects the vascular synovial membrane and then extends into the joint. *Staphylococcus aureus* is the most common pathogen in the setting of trauma. For prevention of septic arthritis in the ED setting, all open joint injuries should be treated by operative washout and antibiotics; emergency clinicians should avoid performing arthrocentesis through infected skin, which can seed the joint.

Baker's Cyst

Baker's cyst (popliteal cyst) is a herniation of the synovial membrane through the posterior aspect of the capsule of the knee (Fig. 50.10). It results from an enlarging knee effusion of any cause. A mass is palpable in the posteromedial corner of the knee and often produces pressure, pain, and limitation of ROM. Rupture of the bursa, with resultant escape of fluid into the calf, may produce a clinical picture similar to that of deep vein thrombosis or compartment syndrome. In this circumstance, ruptured

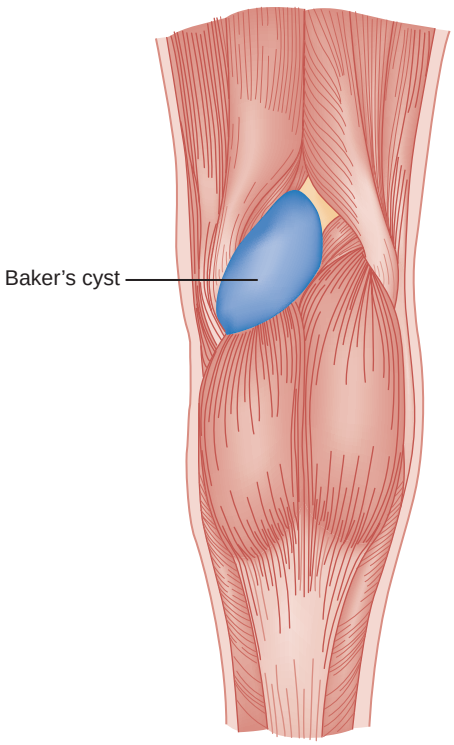

Fig. 50.10. Baker's cyst is an extension of the semimembranosus bursa posteriorly. This bursa often is connected with a joint cavity.

Baker's cyst is a diagnosis of exclusion (ie, thrombosis should be ruled out). Treatment is directed at the underlying intraarticular pathology.

LEG

PRINCIPLES

Anatomically, the leg is comprised of the tibia, fibula, and associated soft tissues, whereas the thigh is comprised of the femur and its soft tissues. Bearing the full weight of the body, the leg is subject to enormous stress, and the tibia is the most commonly fractured long bone. Moreover, the tibia is poorly covered by soft tissue anteriorly, making infection and delayed healing common.

ANATOMY AND PATHOPHYSIOLOGY

The bony structure of the lower leg is relatively simple, consisting of the tibia and fibula. The fibula does not bear weight. The shaft of the tibia is triangular in cross section and poorly covered with soft tissue over its anteromedial aspect. It is the most common long bone to be fractured and sustain open fracture. The lack of overlying soft tissue results in a tenuous blood supply, which increases the rate of osteomyelitis and contributes to delayed union and nonunion, which are common in tibial fracture.

The distal end of the tibia is expanded and bears an additional surface feature, the fibular notch, for the lower tibiofibular joint. The medial malleolus projects from the distal medial aspect of the tibia and has a posterior groove for the tibialis posterior tendon. The inferior surface of the distal tibia is covered with articular cartilage and forms the tibial plafond, the upper anterior surface of the ankle joint. The fibula, in contrast to the tibia, is covered by soft tissue except at the ankle, where it is subcutaneous and easily palpable. The fibula is composed of the head with its styloid process, neck, shaft, and lateral malleolus of the ankle.

The tibia and fibula are connected by superior and inferior tibiofibular joints and a strong interosseous membrane or syndesmotic ligament. The latter is a fibrous band that has particular importance at the distal portion of the lower leg, where it is responsible for keeping the tibia and fibula closely approximated to provide a stable ankle mortise.

The vascular supply of the lower leg is derived from the popliteal artery, which trifurcates to form three branches—the anterior tibial artery, posterior tibial artery, and peroneal artery. The anterior tibial artery can be assessed by palpating the dorsalis pedis artery pulse over the dorsum of the foot, and the posterior tibial artery pulse can be palpated posterior to the medial malleolus.

The lower leg is divided into compartments by deep partitions of the investing crural fascia. Each compartment has a sensory nerve running through it, an anatomic feature that can be used to help diagnose compartment syndrome. The compartments are anterior, lateral, superficial posterior, and deep posterior. The anterior compartment contains the tibialis anterior, long toe extensor muscles, anterior tibial artery, and deep peroneal nerve, which supplies sensation to the first web space of the foot. The lateral compartment contains two muscles that evert the foot, the peroneus longus and brevis, and the superficial peroneal nerve, which supplies sensation to the dorsum of the foot. The superficial posterior compartment contains the gastrocnemius, plantaris, and soleus muscles and sural nerve, which supplies the lateral side of the foot and distal calf. The deep posterior compartment contains the tibialis posterior muscle, long toe flexor muscles, posterior tibial and peroneal arteries, and tibial nerve, which supplies sensation to the plantar aspect of the foot.

CLINICAL FEATURES

Proximal Extraarticular Tibial Fractures

Subcondylar Tibial Fractures

Subcondylar tibial fractures usually are associated with tibial plateau fractures, especially bicondylar fractures. Subcondylar fractures involve the proximal tibial metaphysis and typically are transverse or oblique. The mechanism of injury involves a rotational or angular stress accompanied by vertical compression. Examination reveals tenderness and swelling of the involved area. A hemarthrosis may indicate extension of the fracture into the joint or associated ligamentous injury. Routine radiographic views usually are adequate in showing the fracture line. ED management includes ice and immobilization with a long leg posterior splint. Stable extraarticular nondisplaced transverse fractures usually are treated conservatively with a long leg splint, followed by delayed casting on an outpatient basis because of the risk of swelling and compartment syndrome. In children, casting (with adequate padding) is sometimes performed acutely. Comminuted fractures or fractures associated with an intraarticular component require open reduction and internal fixation, which may be undertaken acutely.

Tibial Tubercle Fractures

Anatomy and Pathophysiology. The tibial tubercle is located at the proximal anterior border of the tibial shaft and is the insertion point of the patellar ligament. The proximal tibial epiphysis and tibial tuberosity develop from two separate ossification centers that coalesce during adolescence. Epiphyseal ossification terminates in late adolescence.

Avulsion fractures of the tibial tubercle are uncommon. They occur predominantly in adolescent boys. The injury typically occurs near the end of growth, when endochondral ossification of the physeal cartilage of the tibial tubercle occurs. Avulsion fractures mainly occur as an indirect injury during activity. The mechanism of injury has been described as a violent flexion of the knee against a tightly contracted quadriceps muscle, which also can cause patellar tendon rupture. The Watson-Jones classification describes three grades of injury depending on the extent of displacement (Fig. 50.11):

- In type I injuries, the tubercle is hinged upward, without displacement from the proximal base.
- The type II injury has a small portion of the tubercle avulsed but it is retracted proximally; the articular surface is not involved.
- Type III fractures are more severe and extend across the articular surface; displacement of the fragment and often comminution are features.

Clinical Features. Physical examination reveals acute tenderness and swelling at the anterior aspect of the knee and proximal tibia. Depending on the type of injury, functional disability may range in severity from extensor lag to complete loss of active extension. Hemarthrosis is evident with type III injury because of intraarticular fracture extension across the proximal epiphysis.

Diagnostic Testing. Plain radiographs usually are adequate for diagnosis. The lateral view shows the avulsion fracture, number of fragments, and amount of displacement. Swelling of the overlying soft tissue is evident. Comparison views may be necessary when a type I injury is suspected.

Management. Treatment depends on the degree of displacement and presence of joint involvement. Nondisplaced type

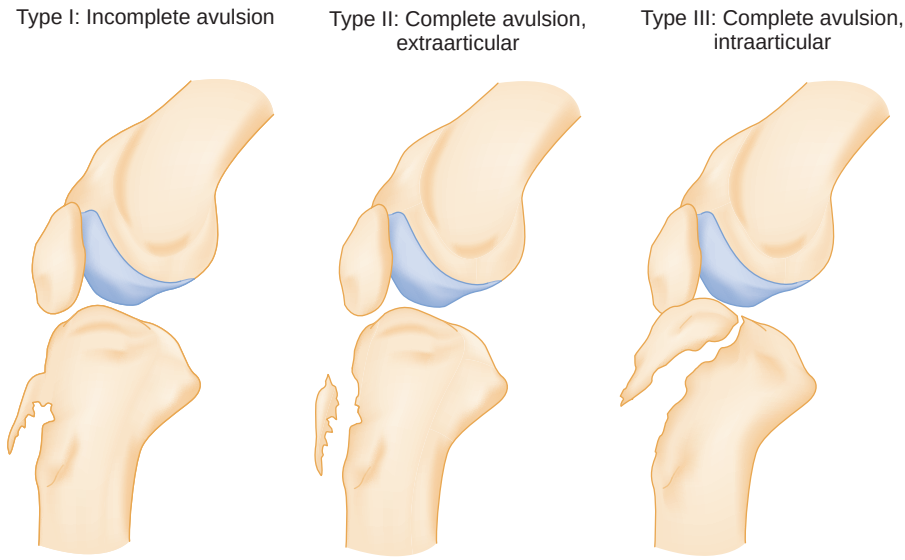

Fig. 50.11. Tibial tuberosity fractures.

I avulsions are treated with cast immobilization, with the knee in extension, until healing results. Minimally displaced type II avulsions may be treated similarly if the displacement can be reduced by external manual maneuvers. Displaced type III fractures are treated by open reduction and internal fixation to restore proper biomechanics and joint congruity. Fixation screw and tension band wiring techniques have yielded excellent results. After a period of immobilization and progressive rehabilitation, most patients are able to return to full activity.

Complications of tibial tubercle fractures are rare and include genu recurvatum (backward curvature of the knee), patella alta, meniscal tears, failure of surgical fixation, and subsequent heterotopic ossification and osteonecrosis of the tubercle. If the involved growth plates are closing at the time of injury, premature physeal closure can result in a significant recurvatum deformity, but this rarely occurs.

Tibial Shaft Fractures

Anatomy and Pathophysiology

The tibia and fibula are tightly bound to each other by the syndesmotic ligament. This strong band of tissue can transmit energy so that the tibia and fibula may be fractured at nonadjacent sites. The fibula remains intact in only 15% to 25% of tibial shaft fractures. Tibial shaft factures are associated with a high incidence of infection, delayed union, nonunion, and malunion, in part because of the poor soft tissue coverage of the anterior tibia.

Transverse tibial diaphyseal fractures typically result from high-energy direct trauma. Low-energy rotatory and compressive forces often result in spiral or oblique fractures.

Tibial fractures also may occur without trauma. Stress fractures usually occur in the tibial shaft. Pathologic fractures may be caused by metabolic bone disease, osteomalacia, or neoplasm.

Clinical Features

Tibial shaft fractures cause pain, swelling, and localized deformity, usually angulation or rotation of the foot. Determination of vascular integrity is the priority. Distal dorsalis pedis and posterior tibial pulses should be assessed; however, vascular injury is a rare complication of these fractures. Neurologic injury, by contrast, is common, particularly injury of the peroneal nerve. Motor function of the peroneal nerve is checked by testing active ankle and toe dorsiflexion (deep peroneal nerve) and active foot eversion (superficial peroneal nerve). Sensory function of the peroneal nerve is documented by testing sensation in the first dorsal web space in the foot (deep peroneal nerve distribution) and sensation of the dorsal lateral foot (superficial peroneal nerve distribution). Integrity of the posterior tibial nerve is assessed by checking for the presence or absence of plantar sensation. Significant soft tissue damage also may accompany tibial shaft fractures. Compartment syndrome may be a complication of tibial fractures that usually develops within the first 24 to 48 hours.

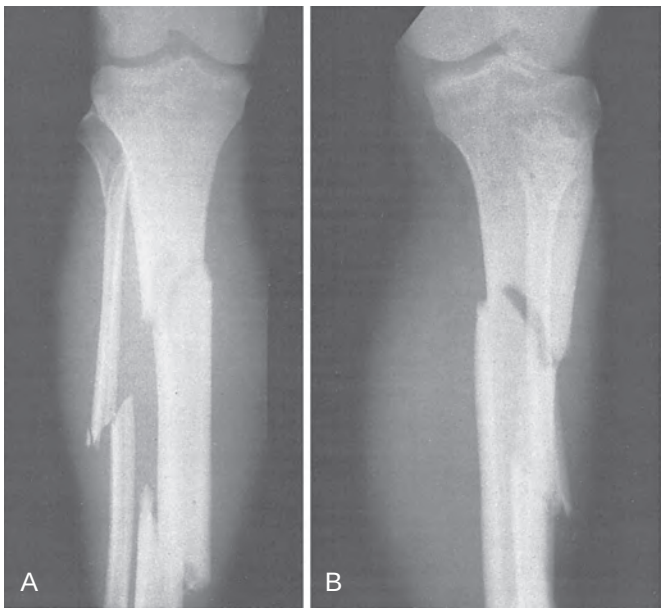

Fig. 50.12. Tibiofibular fracture. **A,** Anteroposterior view. Comminuted fractures of the tibial and fibular shafts are present. Note the obliteration of the normal soft tissue planes secondary to edema or hemorrhage. **B,** Lateral view. (From Rosen P, et al: Diagnostic radiology in emergency medicine, St Louis, 1992, Mosby, p 198.)

Diagnostic Testing

AP and lateral radiographic studies document the fracture, define the fracture pattern, and identify any associated bone loss (Fig. 50.12). The knee and ankle should be included in both views, and

radiographs of the pelvis and ipsilateral femur may be required to assess for associated injuries. Postreduction views should be taken after any manipulation of the extremity and should include the knee and ankle joints so that alignment of the proximal and distal joint surfaces can be determined.

Management and Disposition

The initial management of closed tibial shaft fractures consists of immobilization in a long leg posterior splint applied with the knee in 10 to 20 degrees of flexion. The splinting procedure may require analgesia and sedation. In general, after fractures have been immobilized, pain decreases. If the patient reports continued severe pain after immobilization, a complication such as compartment syndrome, nerve root compression, or limb ischemia should be considered. Circumferential casts generally are avoided in the acute setting because of the risk of compartment syndrome, although some orthopedists will cast pediatric fractures in the acute phase. Initial hospitalization is indicated for most patients with significant tibial shaft fractures to allow adequate pain control and observation for compartment syndrome.

Open fractures should be covered by a sterile dressing. Antistaphylococcal antibiotics (typically, cefazolin, 1 to 2.5 mg/kg/dose every 8 to 12 hours) should be given. Gentamicin (2 mg/kg tid) may be added for severely contaminated wounds. Tetanus vaccination status should be updated as indicated. A long leg posterior splint should be applied. This applies to all open fractures.

Emergency operative débridement with external or internal fixation is recommended as soon as possible for open tibial fractures with significant soft tissue disruption. Osteomyelitis is more likely with open fracture, significant soft tissue disruption, and longer time from contamination to definitive surgical management.

In general, tibial fractures are slow to heal. The average time to union is approximately 20 weeks for stable tibial shaft fractures caused by a low-energy mechanism and more than 30 weeks for unstable fractures caused by a high-energy mechanism. Delayed union describes fracture segments that have not united after 24 weeks or that show no radiographic evidence of callus formation for 3 consecutive months. Nonunion is a radiographic diagnosis, with a finding of rounded, well-corticated edges of the major fracture fragments. It is much more common in adult long bone fractures than in childhood fractures, which generally heal rapidly. Delayed vascular injuries, including pseudoaneurysm, arteriovenous fistula, and deep vein thrombosis, also may occur as a complication of tibial shaft fractures. Fat embolism also may occur acutely, especially after reamed nailing. Additional late complications include malrotation of the leg, refracture, and reflex sympathetic dystrophy.

Proximal Fibula Fractures

Anatomy and Pathophysiology

Isolated fibular fractures are relatively unimportant because the fibula is a non–weight-bearing bone. The mechanism of injury usually is a direct blow to the lateral aspect of the leg or an indirect varus stress to the knee. An important exception is the Maisonneuve fracture (Fig. 50.13). This injury involves a medial ankle disruption (deltoid ligament tear or medial malleolar fracture), with complete tearing of the syndesmotic ligament joining the tibia and fibula and fracture of the proximal fibula. Consequently, the fibula floats free relative to the tibia, resulting in an unstable ankle mortise, for which surgical fixation is required. The possibility of this injury indicates the need for examination of the proximal fibula in all medial ankle injuries.

Fig. 50.13. Maisonneuve fracture, anteroposterior view. The rotatory force involved in this injury has caused fractures of the distal tibia and the proximal fibula (*arrows*). (From Rosen P, et al: Diagnostic radiology in emergency medicine, St Louis, 1992, Mosby, p 197.)

Clinical Features

Isolated fibular shaft fractures cause lateral leg pain that is exacerbated by walking. Local pain, swelling, and tenderness at the fracture site may be elicited, although signs and symptoms can be subtle. A thorough evaluation should be done to exclude serious associated occult neurovascular or ligamentous injuries. The common peroneal nerve courses around the neck of the fibula and may be contused or lacerated at the time of injury. The LCL of the knee may be ruptured or strained in association with the fracture, and anterior tibial artery injury with thrombosis may occur.

Diagnostic Testing

AP and lateral radiographic views should include the knee and ankle joints.

Management and Disposition

Isolated fibular shaft fractures are treated symptomatically with ice, analgesia, and non–weight-bearing status. Immobilization in a long leg cast is rarely done but may provide symptomatic relief beginning 2 days after the acute injury. Weightbearing may be advanced progressively as tolerated; pain should be avoided. Patients with nondisplaced or minimally displaced fractures may have little pain and tolerate crutch walking without casting. In general, isolated fibula shaft fractures can be managed on an outpatient basis and heal without complication.

For severely displaced fibular shaft fractures or fractures with associated peroneal nerve deficit (ie, footdrop), orthopedic consultation is indicated. Cast immobilization is not recommended in cases with concomitant nerve damage, and follow-up is scheduled at a shorter interval from injury. Elective surgical repair may

be indicated if function does not return. A Maisonneuve fracture results in an unstable ankle, and open reduction and internal fixation usually are required.

Proximal Tibiofibular Joint Dislocations

Anatomy and Pathophysiology

The proximal tibiofibular joint is a small synovial joint between a circular or oval facet on the head of the fibula and a similar facet on the inferior aspect of the lateral tibial condyle. The proximal tibiofibular joint is stabilized by the joint capsule and anterior and posterior tibiofibular ligaments. Dislocation of the proximal tibiofibular joint is rare, occurring most commonly in adolescents and young adults because of its association with MVCs and sports injuries. Several types of dislocations of the joint have been described; anterolateral dislocation is the most common and usually is caused by a fall on a flexed abducted leg. Posterior medial dislocation generally is caused by a direct blow to the flexed knee and is more often associated with peroneal nerve injury. Superior dislocation is associated with ankle diastasis and typically occurs simultaneously with an ankle fracture.

Clinical Features

The patient may complain that the knee feels out of joint or, if the problem is intermittent, the knee may lock or give way periodically. Physical examination reveals tenderness and swelling over the proximal fibula and tibiofibular joint. In the absence of associated injury, findings on knee examination are otherwise normal, with full ROM and no joint line tenderness or effusion.

Diagnostic Testing

Plain radiography may confirm the diagnosis, although CT may be required. On the AP view, the fibular head is displaced laterally, and the interosseous space is widened. Comparison views of the uninjured knee may be necessary to appreciate these findings.

Management

Traumatic proximal tibiofibular dislocation is treated initially with closed reduction. If the patient seeks treatment within a few days of injury, reduction of an anterolateral dislocation can be accomplished in the ED by flexing the knee to 90 degrees, everting the ankle, and applying direct pressure to the head of the fibula. Orthopedic referral and immobilization of the knee for a minimum of 3 to 6 weeks are necessary after reduction. If closed reduction fails, the patient may require open reduction, with repair of the torn capsule ligaments and pinning. For recurrent dislocations or injuries that do not respond to initial treatment, resection of the proximal fibula or arthrodesis may be effective.

Stress Fractures

Anatomy and Pathophysiology

The tibia is a common site of stress fracture. Usually, the stress fracture occurs on the tibial shaft. Fractures typically are horizontal or oblique and uncommonly longitudinal. Other sites of stress fracture include the femur, fibula, tarsals (especially navicular), and metatarsals. Stress fractures result from overuse. Stress fractures, which occur as a result of excessive repetitive force to normal bone, are distinguished from pathologic fractures, which occur as a result of normal forces acting on abnormal bone (eg, because of osteoporosis or tumor).

Clinical Features

Bone pain and tenderness without a history of direct trauma are characteristic. The most important historical information includes a recent increase in physical activity, training on hard surfaces, and inadequate footwear. The pain usually is insidious in onset and progressive but may be sudden. Pain is usually relieved with rest. The differential diagnosis for lower leg pain also includes shin splints (see later), exercise-induced compartment syndrome, contusion, muscle strains, tendinitis, periostitis, and interosseous membrane strains. The physical examination may reveal localized bone tenderness and swelling of the overlying soft tissues. Usually, there is no muscle atrophy, weakness, or restriction of joint ROM range of motion and unsuitable.

Diagnostic Testing

The radiographic findings vary, depending on the location of the fracture and stage of healing. Approximately one-third of stress fractures are evident radiographically at the time of initial diagnosis, compared with 50% after 2 to 6 weeks. The radiographic findings often are subtle and may include periosteal new bone, sclerosis, and a lucent line perpendicular to the cortex. MRI can diagnose the condition earlier and more accurately than plain film radiography.

If a stress fracture of the lower extremity is suspected and findings on initial plain radiography are unremarkable, follow-up evaluation at 10 days to 2 weeks may detect radiographic signs of fracture after a period of inactivity. Evidence of healing (periosteal reaction) in response to treatment usually is sufficient to confirm the diagnosis.

Management

Most tibial and fibula stress fractures can be treated nonoperatively. Activity should be decreased for 3 to 6 weeks to allow for healing, and serial radiographs should be obtained. In those rare cases in which walking causes pain, a cast and non–weight-bearing status may be required. Serial radiographs are used to evaluate healing. Rare cases of nonunion require surgery.

Compartment Syndrome

Compartment syndrome is caused by increased pressure within a fascial compartment, leading to necrosis of muscle and nerve, and is discussed in Chapter 49.

Soft Tissue Injuries Involving the Lower Leg

Strains

Gastrocnemius Strain. The medial head of the gastrocnemius muscle often is strained in sports activities and sometimes ruptures. On physical examination, a palpable gap may be identified in the substance of the muscle, and point tenderness may be elicited in the medial and inferior borders of the muscle belly. Any attempted active or passive ankle dorsiflexion elicits pain.

Gastrocnemius strain or rupture may be confused with the following: rupture of the plantaris tendon, which causes tenderness, swelling, and ecchymosis in the proximal calf; rupture of a Baker's cyst, which may result in the escape of fluid into the calf; thrombophlebitis; deep venous thrombosis; and Achilles tendon rupture, which typically results in a palpable gap just proximal to the calcaneus. The diagnosis is made clinically, although a soft tissue defect may be seen on plain radiographs of large ruptures. MRI can confirm the diagnosis but is rarely necessary.

A mild partial rupture of the medial head of the gastrocnemius can be treated with rest and non–weight-bearing status for several days. Treatment for more extensive incomplete ruptures involves casting for 8 weeks, with the ankle plantar-flexed. For a complete tear, most orthopedists recommend surgical repair to restore normal length and tensile strength. Acute compartment syndrome can complicate gastrocnemius strain.

Plantaris Strain and Rupture. The plantaris is a small variable muscle that originates at the lateral condyle of the femur and passes beneath the soleus to insert on the Achilles tendon. It is a feeble flexor of the knee and plantar flexor of the ankle joint, with little functional significance. Rupture may occur at the myotendinous junction, with or without an associated partial tear of the medial head of the gastrocnemius muscle. A strain of the more proximal plantaris muscle also may occur as an isolated injury or in conjunction with injury to the ACL of the knee. With rupture, the patient often describes a sudden sharp snap sensation—"like I was shot with a ping pong ball"—in the proximal posterior calf, followed by a duller deep ache, which may be disabling. Tenderness is greatest just lateral to the midline of the posterior calf. Examination will show intact strength, but pain, with plantar flexion. Treatment is symptomatic, with a posterior splint in partial equinus position for the first few days if pain is severe or assisted walking with a cane in milder cases. The patient should be cautioned that significant posterior calf and posterior ankle ecchymosis often appears over the first few days.

Shin Splints

The term *shin splints* refers to anterior tibial pain occurring during or after exercise. The most common causes are a tibial stress reaction or periostitis. Tibial stress reactions are microfractures caused by stress placed on the tibia and are distinct from gross stress fractures, which predispose the affected bone to complete fracture.

The physical examination reveals localized tenderness over the tibia, usually at the junction of the middle and lower thirds. Radiographic studies are not helpful in the diagnosis of shin splints and also cannot exclude a tibial stress fracture with certainty. Treatment is symptomatic—rest, NSAIDs, ice, and supportive footwear. The patient should be referred for outpatient evaluation, during which conservative therapy can be continued or further diagnostic evaluation can be pursued.

Foreign Bodies

Foreign bodies such as plant matter (eg, thorns) are commonly encountered in the leg. Missed retained foreign bodies in the lower leg can be the cause of cellulitis, abscess, necrotizing fasciitis, and gangrene. Plain films are a necessary part of evaluation but will be unhelpful when the foreign body is radiolucent. Ultrasound imaging is superior for diagnosis and localization; fluoroscopy and MRI are alternatives. Surgical exploration is sometimes necessary. Extraction is difficult, and deep foreign bodies should be removed by a surgeon, often in the operating room.

KEY CONCEPTS

- Knee dislocation often causes vascular injury to the popliteal artery. Early revascularization is crucial. Hard signs of vascular injury include absent pedal pulses, cool mottled foot, expanding popliteal hematoma, or popliteal hemorrhage. When any of these are present, angiography or surgical exploration is indicated.
- Soft signs of popliteal artery injury include asymmetric pedal pulses and dorsolateral foot or leg paresthesias. CT angiography or duplex ultrasound study is indicated when these are present.
- In the absence of signs of popliteal injury, the knee dislocation patient can be observed for 24 hours, with measurement of the ankle-brachial index (ABI) every 3 hours. An ABI persistently over 0.9 for 24 hours effectively excludes significant popliteal artery injury.
- Patella dislocation is common, examination reveals the dislocated patella fixed in a position superolateral to its normal position, and reduction is by gentle knee extension with medial pressure on the displaced patella. In contrast, in patellar tendon rupture, the patella rides high (patella alta), is not laterally displaced, and is mobile, and the patient is unable to extend the knee.
- Injuries to the cruciate and collateral ligaments may not be detectable on initial examination because of effusion and splinting. Emergent diagnosis is not necessary, but the patient should undergo a follow-up examination by an orthopedist.
- Lipohemarthrosis is an uncommon and subtle sign of occult fracture and should be sought on radiographs of traumatized knees.
- Compartment syndrome is a serious complication of tibial shaft fracture, usually occurring 24 to 48 hours after injury. Orthopedic consultation or measurement of compartment pressure should be undertaken when the patient's pain is increasing, despite immobilization and support of the fracture.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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1. Nicandri GT, Dunbar RP, Wahl CJ: Are evidence-based protocols which identify vascular injury associated with knee dislocation underutilized? Knee Surg Sports Traumatol Arthrosc 18:1005–1012, 2010.

2. Sihvonen R, Paavola M, Malmivaara A, et al: Finnish Degenerative Meniscal Lesion Study (FIDELITY) Group: Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N Engl J Med 369:2515–2524, 2013.

CHAPTER 50: QUESTIONS & ANSWERS

50.1. A 45-year-old woman presents after a high-impact motor vehicle collision with pain in the left knee. The distal neurovascular examination is intact. What is the most appropriate management?
A. Compression wrap and early range-of-motion exercises
B. Discharge if radiographs are negative with partial weightbearing
C. Knee immobilizer with orthopedic follow-up
D. Measure ankle-brachial index and perform duplex ultrasonography if less than 0.9
E. Orthopedic consultation

Answer: D. This patient had a knee dislocation. Knee dislocation is uncommon but should be considered in the setting of an appropriate injury mechanism because 50% of all knee dislocations are reduced spontaneously before emergency department (ED) arrival. Reduction before ED arrival does not lessen the likelihood of vascular injury, and vascular injury should be considered in patients with severe ligamentous injuries and injuries caused by high-energy mechanisms. Vascular injury to the popliteal artery is the most severe complication and is the major cause of morbidity and limb loss. Management of suspected knee dislocation involves an algorithm designed to be noninvasive but sensitive for arterial injury.

50.2. A 42-year-old man was at the gym performing squatting exercises. As he was coming to a stand, he had an immediate onset of pain in his right thigh. He presents with an inability to extend his knee. What is the most likely physical finding?
A. High-riding patella
B. Midquadriceps muscle tenderness and deformity
C. Popliteal swelling and tenderness
D. Positive Lachman's test
E. Suprapatellar tenderness with patella baja

Answer: E. This is a quadriceps tendon rupture. Patients with extensor disruption may have signs and symptoms that include an acute onset of pain, swelling, ecchymoses over the anterior aspect of the knee, a palpable defect in the patella, quadriceps tendon, or patella tendon loss or limited ability for active leg extension; extension lag usually is seen when the last 10 degrees of extension are performed haltingly or with difficulty. With quadriceps rupture, a low-riding patella (patella baja) and inferior retraction may be seen.

50.3. A college football lineman presents complaining of left knee pain and inability to bear weight. He was on the scrimmage line when the ball was placed in motion and, as he lunged forward, he twisted his leg and heard an audible pop in his knee. He was immediately unable to bear weight. On physical examination, you find the left knee swollen, with moderate joint line tenderness and a positive pivot shift test. What is the most sensitive way to diagnose the injury accurately?
A. Arthroscopy of the knee
B. Computed tomography (CT) scan of the knee
C. History and physical examination
D. Magnetic resonance imaging (MRI) of the knee
E. Plain radiography of the knee

Answer: A. Clinical evaluation is moderately sensitive for ACL tears but, in the acute phase, is often inaccurate because of swelling and splinting. Acutely, only plain films are indicated as long as dislocation is not suspected. Tibial plateau fractures detected on plain film may require CT to determine the need for admission for early operative repair. Arthroscopy is the gold standard for diagnosis of soft tissue injuries of the knee. MRI is useful but may miss small tears and anatomic abnormalities, and a normal study may still lead to arthroscopy if symptoms persist. MRI scanning of the knee is rarely indicated in the acute setting.

50.4. A man presents with severe pain of his right lower leg. He was in the ED the previous night for splint placement for a tibial fracture. After removal of the splint, you see a lower leg with mild ecchymosis, healing abrasions, and palpable posterior tibial and dorsalis pedis pulses. He has severe pain on passive movement of his first toe and decreased sensation of the first toe web space. Which of the following should be the next step?
A. Admit for IV antibiotics and pain control.
B. Obtain venous Doppler scans.
C. Resplint the patient.
D. Test the anterior compartment pressures.
E. Test the superficial posterior compartment pressures.

Answer: D. The lower leg is divided into the following compartments by deep partitions of the investing crural fascia—anterior, lateral, superficial posterior, and deep posterior. The anterior compartment contains the tibialis anterior, long toe extensor muscles, anterior tibial artery, and deep peroneal nerve, which supplies sensation to the first web space of the foot.

50.5. A severe medial ankle sprain with no ankle fracture necessitates evaluation of which of the following?
A. Cervical spine
B. Femoral nerve
C. Lumbar spine
D. Popliteal artery
E. Proximal fibula

Answer: E. An important exception to fibular fractures being stable is a Maisonneuve fracture (see Fig. 50.13). This involves a medial ankle disruption (deltoid ligament tear or medial malleolar fracture), with complete tearing of the syndesmotic ligament joining the tibia and fibula and fracture of the proximal fibula. This results in an unstable ankle mortise because the fibula now floats free relative to the tibia, and surgical fixation is required.

50.6. A 14-year-old boy presents with right knee pain that is worse with physical activity. He has swelling of the inferior aspect of the knee, with point tenderness below the patella, along the patellar tendon, and on the tubercle. Radiographs do not demonstrate a fracture. What is your next step in managing this patient?
A. Admission for repeat serology and physical examinations
B. Discharge if complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level are normal

C. Emergent orthopedic consultation
D. Knee brace and crutches
E. Rest, ice, and pain management

Answer: E. This patient has Osgood-Schlatter disease. Treatment varies according to the acuteness of the symptoms and skeletal age of the patient. Initially, rest, ice, and analgesics are the mainstays of therapy. As symptoms subside, a rehabilitation program that stretches and strengthens the quadriceps should be instituted. Knee orthoses are used to dampen the pull of the extensor mechanism on the weakened tibial apophysis. Immobilization is reserved for the unreliable patient who will not or cannot comply with the program of relative rest in which aggravating activities are avoided.

CHAPTER 51

Ankle and Foot

Nicholas G.W. Rose | Thomas J. Green

The ankle and foot are highly evolved structures designed to support the body's weight and facilitate locomotion over varied terrain. Findings related to ankle and foot injuries are often subtle, and diagnoses may be delayed or missed, particularly in cases of multiple trauma.

The ankle and foot are best approached clinically as a single functional unit. Although they are discussed sequentially in this chapter, mechanisms of injury overlap, and a pathologic condition in one location may accompany an associated pathologic condition in another.

ANKLE

PRINCIPLES

Anatomy

The ankle joint is the articulation of the tibia and fibula with the talus. The dome of the talus fits into the mortise formed by the medial malleolus, horizontal articular surface of the tibia (plafond), and lateral malleolus. Fundamentally, the stability of the ankle depends on the bony and ligamentous integrity of the mortise. The calcaneus is also important for the motion and stability of the ankle (Figs. 51.1 and 51.2).

The ankle is composed of three primary articulations—the inner surface of the medial malleolus with the medial surface of the talus, distal tibial plafond with the talar dome, and medial surface of the lateral malleolus with the lateral process of the talus. These three articular surfaces are contiguous, lined with cartilage, and enclosed by a single joint capsule. The distal tibia also articulates with the distal fibula just proximal to the talus, forming the distal tibiofibular joint. Collectively, these articulations are termed the *talocrural joints.*

Three sets of ligaments—the syndesmotic ligaments, lateral collateral ligaments, and medial collateral ligaments—support the ankle joint and are essential to its stability.

Tendons course through the ankle in four geographic groups. The flexor retinaculum tethers the tendons of the tibialis posterior, digitorum longus, and flexor hallucis muscles behind the medial malleolus. The peroneal retinaculum and tendon sheath tether the peroneus longus and brevis tendons behind the lateral malleolus. The extensor retinaculum tethers the tendons of the tibialis anterior, extensor digitorum longus, extensor hallucis longus, and peroneus tertius over the anterior aspect of the ankle. Posteriorly, in the midline, lie the Achilles and plantaris tendons.

Pathophysiology

Ankle movements are complex and often involve more than one joint. The ankle joint complex is made up of the talocrural joints and talocalcaneal (subtalar) joints, which allow movements along several axes of motion. Dorsiflexion (ankle flexed so the toes point toward the head) and plantar flexion (ankle extended so the toes point toward the floor) of the ankle joint complex occur primarily at the talocrural joints. Motions of the ankle joint complex in conjunction with the midtarsal joints include inversion (sole of the foot points to the midline), eversion (sole of the foot points away from the midline), abduction (external rotation of the foot), and adduction (internal rotation of the foot), which are rotational movements about the longitudinal axis of the tibia.

The components providing stability to the ankle are best conceptualized as a ringlike structure surrounding the talus[1] (Fig. 51.3). Disruption of one element of this ring does not, by itself, induce instability. Injury to one ring element, however, should prompt careful scrutiny for a second injury. Any disruption of two or more elements causes ankle instability and can significantly affect joint function.[1]

Clinical Features

Carefully eliciting the mechanism of injury can often provide clues as to the injuries sustained. The presence of sudden swelling and severe pain in the ankle region suggests serious ligament disruption, hemarthrosis, or fracture, and rapid progression of symptoms may represent more severe injury. Inability to bear weight immediately after an injury often implies a significant pathologic condition. Patient recollection of a popping sound should prompt consideration of ligament, tendon, or retinacular rupture but does not necessarily increase the probability of a fracture. Finally, the inciting event causing the ankle injury should be determined and, when necessary, investigated further.

Patients with a subacute or chronic ankle problem may be unable to correlate symptom onset with a particular traumatic event. Inquiry should elicit the type and extent of physical activities and whether the ankle gave way. In older patients, ankle injuries or fractures may manifest as subacute problems reflecting misdiagnosis of a serious condition as a simple sprain or neglect by the patient or caregiver.

Physical Examination

The examination of the ankle starts with an assessment of deformity, ecchymosis, edema, and perfusion, followed by active and passive range of motion. Assessment of point tenderness may localize ligament, bone, or tendon injuries, particularly when the patient is seen soon after injury. Palpation should include the medial and lateral collateral ligaments, syndesmotic ligaments, inferior and posterior edges of the medial and lateral malleoli, entire length of the fibula and tibia, anterior plafond, medial and lateral dome of the talus (palpable with the ankle in plantar flexion), base of the fifth metatarsal, calcaneus, Achilles tendon, and tendons behind the medial and lateral malleoli. Stress testing of the ankle joint, discussed later, should not be performed until a fracture has been excluded. An evaluation of weight-bearing ability should proceed only if clinical suspicion of a fracture is low, the location of tenderness does not indicate the need for plain radiography, or radiographs have ruled out a fracture. Specific clinical examination tests are discussed elsewhere in the appropriate sections.

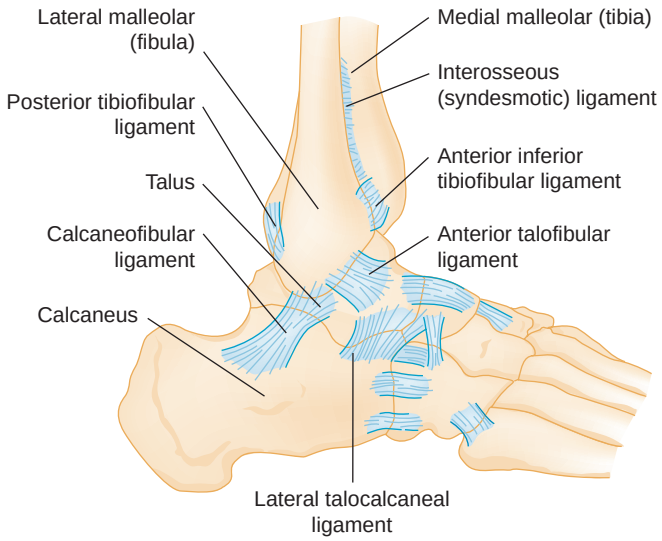

Fig. 51.1. Anatomy of the lateral collateral and syndesmotic ligaments of the ankle. (From Nicholas JA, Hershman EB, editors: The lower extremity and spine in sports medicine, ed 2, St. Louis, 1994, Mosby.)

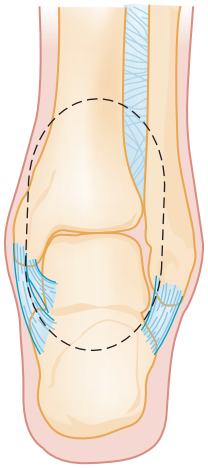

Fig. 51.3. The ring structure surrounding the talus is made up of the tibial plafond, medial malleolus, deltoid ligaments, calcaneus, lateral collateral ligaments, and syndesmotic ligaments. The integrity of this ring determines the stability of the ankle, and the degree of disruption determines the need for operative intervention. (From Simon RR, Koenigsknecht SJ: Emergency orthopedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

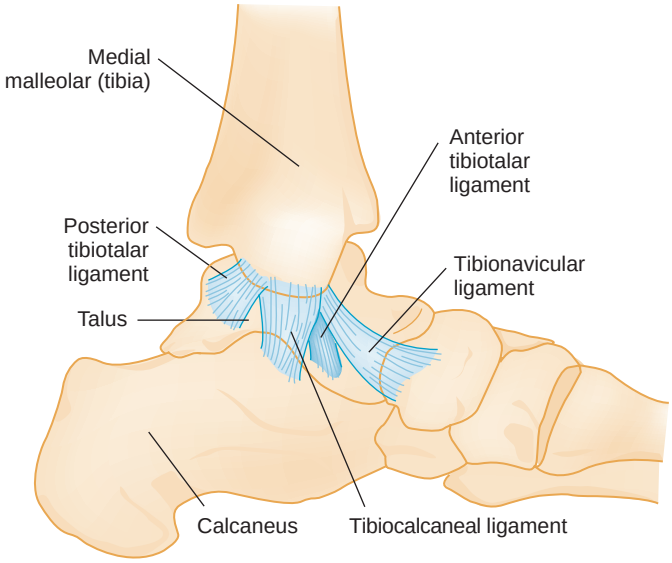

Fig. 51.2. Anatomy of the medial collateral ligaments of the ankle. (Adapted from Nicholas JA, Hershman EB, editors: The lower extremity and spine in sports medicine, ed 2, St. Louis, 1994, Mosby.)

DIAGNOSTIC TESTING

Radiology

The anteroposterior, lateral, and mortise views constitute the standard three-view radiographic series of the ankle. Subtle fractures can be easily missed on ankle radiographs, and a standardized approach to radiographic interpretation can reduce the likelihood of missing ankle fractures (Fig. 51.4).[2] The lateral view is useful in identifying an ankle effusion, which appears as a teardrop-shaped density displacing the normal fat adjacent to the anterior or posterior margin of the joint capsule. The presence of an effusion suggests the possibility of a subtle intraarticular injury, such as an osteochondral lesion of the talar dome.[3]

The lateral and mortise views, taken with the ankle in 15 to 25 degrees of internal rotation, are the most important for evaluating the congruity of the articular surface between the dome of the talus and mortise. On the lateral view, any incongruity of the articular space between the talar dome and distal tibia suggests ankle instability, particularly if narrowing of the anterior joint space is present. In the mortise view, the lines formed between the articular surfaces should be parallel, the joint space should appear uniform throughout the tibiotalar and talofibular components of the joint, and the medial clear space should not exceed 4 mm[3] (Fig. 51.5).

In most cases of isolated blunt ankle trauma evaluated within 48 hours of injury, the Ottawa Ankle Rules (OAR) should be used to determine whether ankle or foot radiographs are necessary. The OAR state that an ankle radiographic series is required if there is pain in the malleolar region with any of the following findings:

- Bone tenderness at the posterior edge of the distal 6 cm or tip of the lateral malleolus
- Bone tenderness at the posterior edge of the distal 6 cm or tip of the medial malleolus
- Inability to bear weight (defined as the ability to transfer weight onto each leg regardless of limping) for at least four steps immediately after the injury and at the time of evaluation

The OAR further state that a foot radiographic series is required if there is pain in the midfoot region with any of the following findings:

- Bone tenderness at the navicular bone
- Bone tenderness at the base of the fifth metatarsal
- Inability to bear weight for at least four steps immediately after the injury and at the time of evaluation

The OAR have a sensitivity approaching 100% in detecting malleolar zone ankle fractures and midfoot zone fractures. They were derived in an adult population and are not applicable in subacute or chronic injuries. The OAR appear to perform well in pediatric patients older than 5 years, for whom the guidelines can be applied as for adults. In children younger than 5 years, alternative approaches can be used (see Chapter 175).[4]

The decision rules for foot radiography, although applicable to blunt ankle trauma, apply only to the midfoot zone. The OAR were not designed to be general guidelines for foot radiography and certainly do not apply to the hindfoot or forefoot. Finally, the OAR are not applicable to intoxicated patients or those who are difficult to assess because of head injuries, multiple injuries, or diminished sensation related to neurologic deficits.

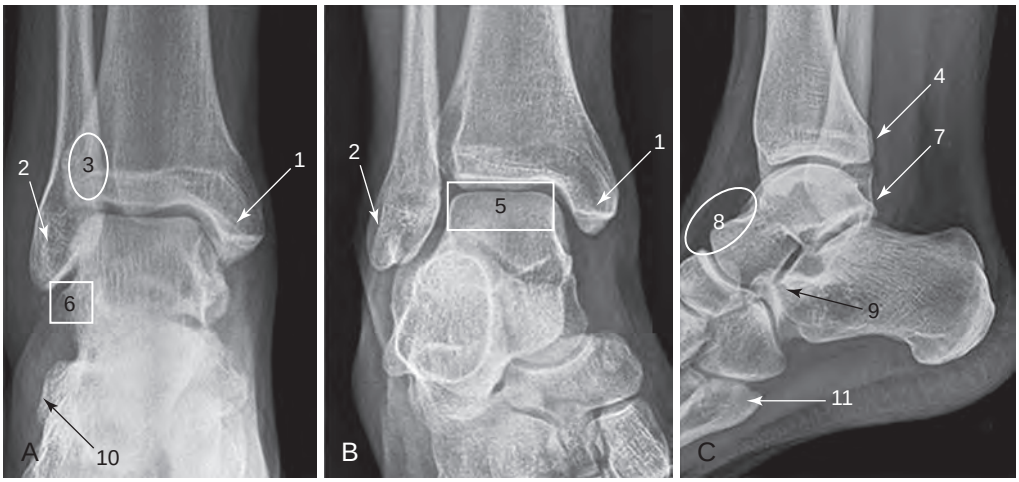

Fig. 51.4. Approach to reviewing ankle radiographs. **A–C,** A standard radiographic series of the ankle has three views—an anteroposterior view (**A**), an internal rotation or mortise view (**B**), and a lateral view (**C**). The following 11 locations should be carefully scrutinized because they are areas where fractures frequently occur: medial (1) and lateral (2) malleoli, anterior tibial tubercle (3) and posterior tibial malleolus (4), talar dome (5), lateral talar process (6), tubercles of the posterior talus process (7), dorsal to the talonavicular joint (8), anterior calcaneus process (9), calcaneal insertion of the extensor digitorum brevis (10), and base of the fifth metatarsal bone (11). (From Yu JS, Cody ME: A template approach for detecting fractures in adults sustaining low-energy ankle trauma. Emerg Radiol 16:309, 2009.)

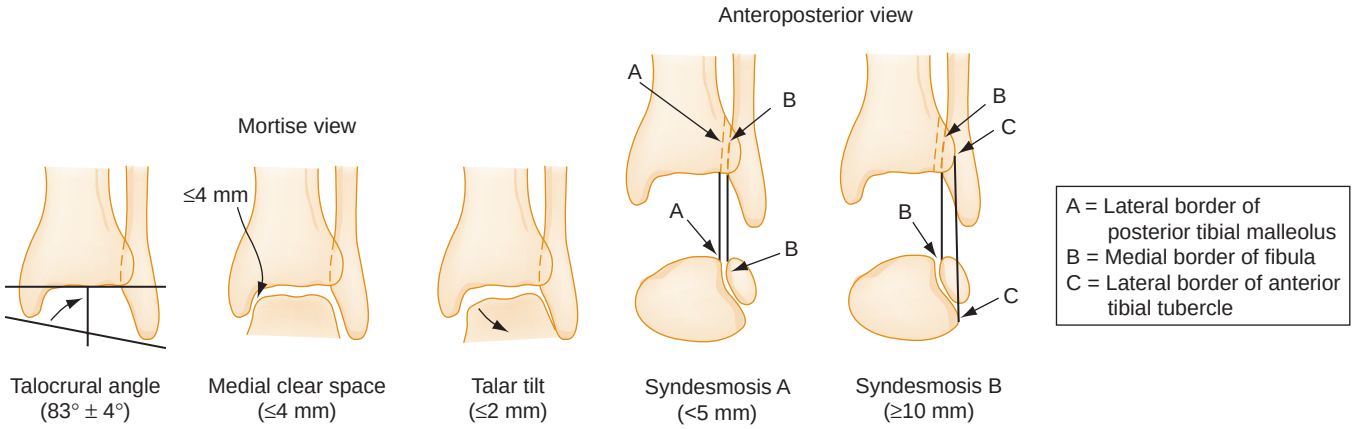

Fig. 51.5. Radiologic criteria for evaluating the syndesmosis. (From Stiehl JB: Ankle fractures with diastasis. Instr Course Lect 39:79, 1990.)

Other Imaging Techniques

Although plain radiography is the initial imaging modality of choice for ankle injuries, it can miss subtle ankle fractures, osteochondral lesions, stress fractures, or ligamentous injuries. When unexplained symptoms persist after negative or inconclusive findings on plain radiographs, other imaging modalities or orthopedic consultation may be advisable. In situations where these are unobtainable, the ankle should be immobilized, the patient discharged with instructions to be nonweightbearing, given clear instructions that a fracture may be present despite the lack of conclusive evidence of it on x-ray, and instructed that repeat x-rays or additional imaging may be required on follow-up.

Computed tomography (CT) scanning provides superior bone imaging and is an excellent modality to delineate abnormalities not identified or incompletely characterized by other imaging techniques. This is particularly relevant in the foot and ankle, where x-rays are complicated by overlying structures and complex articulations. In acute injuries, CT imaging of the foot or ankle is indicated, despite apparently normal radiographs when a fracture is highly suspected.[5] The emergency clinician can perform CT in the emergency department (ED) or as part of outpatient follow-up, with the ankle immobilized and nonweightbearing in the interim. CT can detect small fractures, subtle stress fractures, and intraarticular fractures and can facilitate surgical planning. Radionuclide imaging (bone scanning) can detect soft tissue injuries such as distal syndesmotic disruptions, stress fractures, and osteochondral lesions. Bone scan abnormalities are present once a patient is symptomatic; they typically appear 1 to 2 weeks before radiographic evidence of a stress fracture. Because of its high sensitivity, a negative bone scan effectively rules out the diagnosis. Bone scan abnormalities are nonspecific, however, because infections and tumors also can lead to positive results (see later discussion on stress fracture imaging—"Foot"). Bone scanning is not useful for follow-up because abnormalities can persist for up to 1 year after recovery. Radionuclide imaging is virtually always ordered on an outpatient basis and has been largely supplanted by CT and magnetic resonance imaging (MRI).

MRI, although not typically performed emergently, provides unprecedented clarity in depicting soft tissue structures such as ligaments and tendons and can also delineate bone marrow changes associated with stress fractures before radiographic abnormalities appear. MRI can be helpful in guiding management decisions and following the patient's response to therapy.

MRI or CT arthrography can be useful in the evaluation of chronic ankle pain to detect loose bodies, ligamentous injuries, cartilaginous abnormalities, or osteochondral lesions. CT plus single-photon emission computed tomography (SPECT), which combines CT and radionuclide scanning, has been shown to increase the diagnostic ability of imaging significantly in osteochondral lesions, stress fractures, impingement syndromes, and osteomyelitis.[6] The decision to perform specialized imaging of this nature is typically made through orthopedic or radiologic consultation; such studies are not routinely performed in the ED.

SPECIFIC PATHOLOGIC CONDITIONS

Ankle Fractures: General Considerations

Pathophysiology

Fractures occur when a deforming force is sufficient to overcome the structural strength of a bone. A bone under tension breaks along the axis of the deforming force. Alternatively, ligamentous rupture or an avulsion fracture can occur at either end of a stressed ligament or tendon, and the mechanism of injury generally causes predictable fracture patterns (Fig. 51.6).

Management

The management of ankle fractures consists of identification and classification, assessment of stability, emergent reduction of fracture-dislocations that threaten soft tissues or neurovascular status, and specific treatment and disposition.

To date, no ideal system has been developed for the classification of ankle fractures. The Lauge-Hansen classification and Danis-Weber systems are based on mechanism of injury and fracture location, respectively. The Lauge-Hansen classification was intended to characterize ligamentous injury patterns based on the radiographic appearance of ankle fractures but is complex and has been shown to have limitations in broad applicability. The Danis-Weber system (Fig. 51.7) has predictive value for operative repair in isolated lateral malleolar fractures because the location of the fibular fracture is related to the integrity of the syndesmosis. As such, it is more useful to emergency clinicians than the Lauge-Hansen classification. Both systems have limitations, however, and neither accurately predicts management or clinical outcome in all situations. Further details regarding how and when to apply the Danis-Weber system are provided below with the discussion of specific fractures.

The injured ankle should be promptly immobilized, elevated, and iced to minimize swelling and further soft tissue damage. The presence of gross deformity with neurovascular compromise or skin tenting necessitates prompt intervention. Plain radiography before reduction can be helpful but should not delay reduction in injuries with obvious vascular compromise.

In most cases, appropriate procedural sedation and analgesia techniques are required for reduction. The notion that some reductions are accomplished relatively quickly and easily (from the clinician's vantage point) is not an excuse for failing to adequately manage the often extreme pain that these orthopedic manipulations cause for the patient. The fundamental principle of closed reduction is to reverse the deforming forces. For example, reduction of a fracture-dislocation caused by an adduction injury would require an abduction force. The initial application of a distracting force, sometimes combined with slightly increasing the deformity, is often helpful in achieving reduction. After reduction, neurovascular status should be reassessed, the leg immobilized and elevated, and postreduction radiographs obtained. The overarching goal in the definitive treatment of ankle fractures is to achieve anatomic reduction.

Disposition

The outcome of ankle fractures depends on the extent of injuries, number of malleoli fractured, ankle stability, and patient age. In general, all displaced or potentially unstable ankle fractures require orthopedic consultation in the ED (Box 51.1).

Extraarticular nondisplaced fractures that disrupt only one ring element generally can be treated with casting for 6 to 8 weeks and involve nonweightbearing with the use of crutches. Orthopedic follow-up on an outpatient basis within 1 to 2 weeks of the injury is ideal if operative intervention is required. The presence of any abnormal measurement on the mortise view (see Fig. 51.5) suggests instability and the need for orthopedic consultation, typically on an urgent outpatient basis. Avulsion fractures, in which the avulsed fragment is smaller than 3 mm in diameter and minimally displaced, can be treated in an identical manner to an ankle sprain.

For ankle fractures that require surgery, the outcome is better in unimalleolar fractures over trimalleolar fractures, in isolated lateral malleolar fracture over isolated medial malleolar fractures, in multimalleolar fractures without medial malleolar fracture over those with malleolar fractures, and in cases with posterior fragments involving less than one-third of the articular surface over larger fragments.

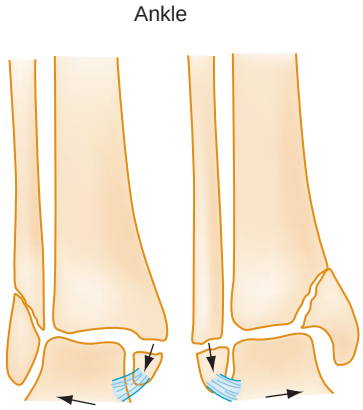

Fig. 51.6. The mechanics of bone failure in rotational tension and types of tension ankle fractures. *Arrows* indicate the direction of distracting forces. (From Dahners LE: The pathogenesis and treatment of bimalleolar ankle fractures. Instr Course Lect 39:85, 1990.)

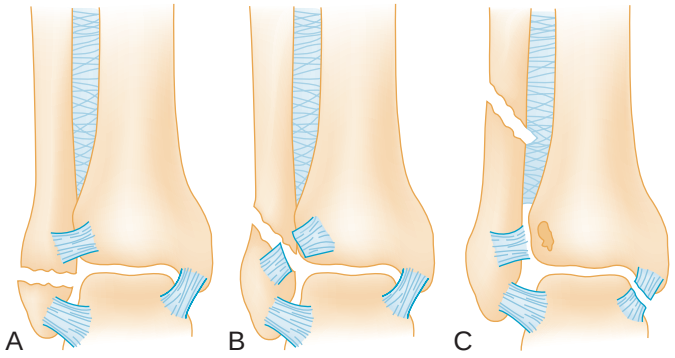

Fig. 51.7. The Danis-Weber classification of ankle fractures focuses on the location of the fibular fracture in relation to the tibiotalar joint and syndesmosis. Weber A fractures involve inversion-adduction forces. Weber B fractures involve abduction forces. Weber C fractures involve eversion-abduction forces. See text for further explanation. (From Wilson FC: The pathogenesis and treatment of ankle fractures: classification. Instr Course Lect 39:79, 1990.)

BOX 51.1

Ankle Fractures for Which Orthopedic Consultation in the Emergency Department Is Recommended

- Unimalleolar fractures
  - Displaced medial malleolar fracture
  - Medial malleolar fracture with lateral collateral ligament rupture
  - Displaced lateral malleolar fracture
  - Lateral malleolar fracture with deltoid ligament rupture
  - Lateral malleolar fracture with widened medial clear space
  - Unimalleolar fracture with syndesmotic diastasis
  - Fibula fracture at or proximal to the tibiotalar joint line
  - Displaced posterior malleolar fracture
  - Posterior malleolar fracture involving >25% of articular surface
- All intraarticular fractures with an articular surface step deformity
- All bimalleolar fractures
- All trimalleolar fractures
- All intraarticular fractures with step deformity
- All open fractures
- All pilon fractures

Unimalleolar Fractures

Lateral Malleolar Fractures

Lateral malleolar fractures are the most common ankle fracture. Stability of the ankle joint depends on the location of the fracture in relation to the level of the tibiotalar joint, which defines the distal portion of the syndesmotic ligament. The Danis-Weber classification (see Fig. 51.7) is useful and predictive of outcome in these types of unimalleolar fractures. This classification groups fractures into three types—A, B, and C. Subgroups exist but do not assist the emergency clinician in prognosticating the necessity of operative repair and are beyond the scope of this text. Lateral malleolar fractures below the tibiotalar joint (Danis-Weber type A) rarely disrupt other bony or ligamentous structures and, in the absence of injury to medial structures, such fractures are unlikely to affect the dynamic congruity of the ankle joint.[7] The management of uncomplicated lateral malleolar fractures involves casting for 6 to 8 weeks, with no weightbearing for at least the first 3 weeks and ongoing follow-up with orthopedics to ensure proper union. Concomitant tenderness over the deltoid ligament may suggest a biomechanical disruption of both malleoli, an associated fracture of the medial malleolus, or an associated fracture of the posterior malleolus, and warrants orthopedic consultation, especially if the medial clear space on the mortise view is widened (see Fig. 51.5). CT imaging can be useful in such situations because it may identify occult medial or posterior malleolar fractures.

Fibular fractures proximal to the tibiotalar joint line (Danis-Weber type C injury; see Fig. 51.7) frequently, but not always, disrupt the distal tibiotalar syndesmosis and medial structures. These commonly require orthopedic consultation in the ED and operative intervention.

Treatment of an isolated fibular fracture at the level of the tibiotalar joint (Danis-Weber type B injury; see Fig. 51.7) is controversial because 50% of these injuries are accompanied by an injury to the distal tibiofibular syndesmosis that may require operative intervention.[7,8] Tenderness on palpation of the syndesmotic ligament or widening of the medial joint space on the mortise x-ray view adds further support to the need for emergency orthopedic consultation. Stress x-ray views of the ankle to identify ligamentous instability can clarify the need for operative intervention but are generally requested by the orthopedic consultant.

Medial Malleolar Fractures

Medial malleolar fractures are usually the result of eversion or external rotation. These two forces exert tension on the deltoid ligament, causing an avulsion of the tip of the medial malleolus or a rupture of the deltoid ligament. Although they can occur in isolation, medial malleolar fractures are commonly associated with lateral or posterior malleolar disruption. Because of this, identification of a medial malleolar fracture warrants a careful examination of the entire length of the fibula for tenderness, the presence of which warrants radiographic evaluation to rule out a proximal fibular fracture (Fig. 51.8).

An isolated nondisplaced medial malleolar fracture can be treated with casting for 6 to 8 weeks, with no weightbearing for at least the first 3 weeks and close orthopedic follow-up. Any displacement or concurrent disruption of the lateral components of the ankle warrants orthopedic consultation in the ED for consideration of operative management.

Posterior Malleolar Fractures

Isolated fractures of the posterior malleolus are rare and imply an avulsion of the posterior tibiofibular ligament. These injuries can be associated with proximal fibular fractures and medial and lateral collateral ligament sprains. Treatment usually consists of casting for 6 weeks for nondisplaced fractures in which no associated injury or ankle instability is present.[9] CT is generally used to ensure anatomic reduction prior to conservative management. Fractures involving more than 25% of the tibial surface usually require open reduction and internal fixation (ORIF); however, this is an area of controversy, and displaced posterior malleolar fractures require orthopedics consultation.[10]

Bimalleolar Fractures

Bimalleolar fractures involve the disruption of at least two elements of the ankle ring and are therefore unstable. These fractures result from adduction or abduction forces, with the latter being more common. Rotational injuries also can cause bimalleolar fractures, as well as trimalleolar fractures, if the posterior malleolus is involved. Associated damage to other soft tissue structures (eg, the syndesmosis) is common with bimalleolar fractures.

Controversy exists about whether nondisplaced bimalleolar fractures should be treated with surgical or closed reduction, and orthopedic consultation in the ED is warranted. Rarely, stress fractures of the medial malleolus or distal fibula can be seen, particularly in athletes and runners. Plain radiographs may be nondiagnostic, but radionuclide bone scanning, CT, or MRI—the choice is often influenced by local availability—can establish the diagnosis. These injuries can be treated nonoperatively with outpatient orthopedic consultation and follow-up.

Trimalleolar Fractures

Trimalleolar fractures involve fractures of the medial, lateral, and posterior malleoli and almost always require surgical fixation.

Open Fractures

Open ankle fractures are usually caused by severe isolated ankle injuries or multiple trauma and require emergent orthopedic consultation.

Management

After documentation of the neurovascular status and extent of soft tissue trauma, gross contaminants should be removed from

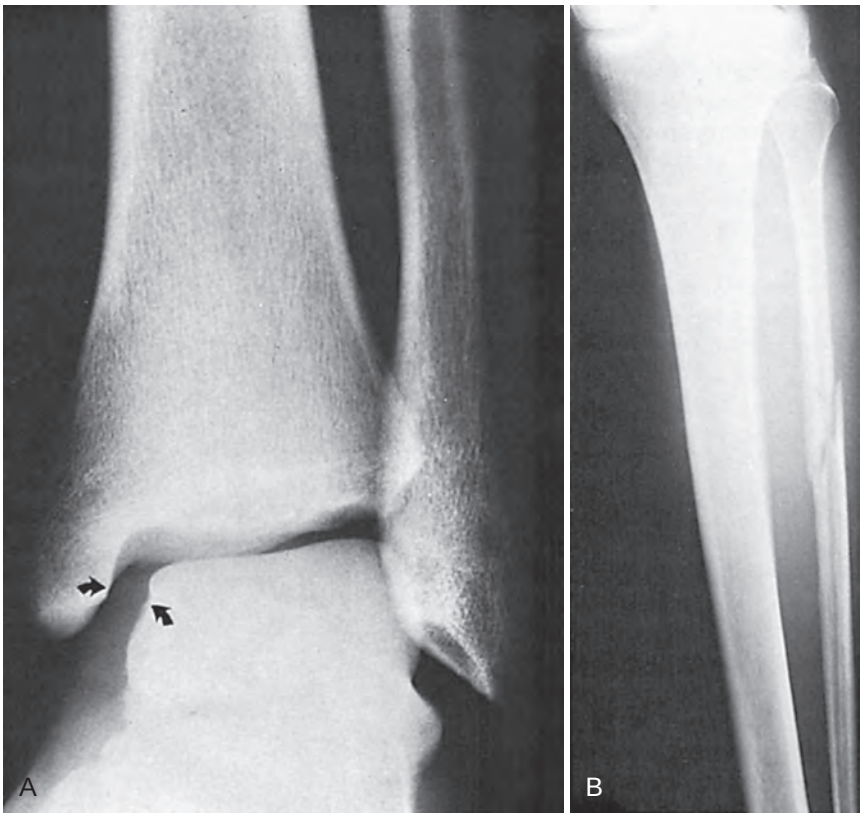

Fig. 51.8. Maisonneuve fracture. **A,** Anteroposterior view shows a slight widening *(arrows)* of the ankle mortise and the medial clear space. **B,** Anteroposterior view shows an oblique fracture at the proximal shaft of the fibula. (From Nicholas JA, Hershman EB, editors: The lower extremity and spine in sports medicine, ed 2, St. Louis, 1994, Mosby.)

the wound, saline-soaked sterile gauze should be applied, and the injured leg should be splinted.[11] Swabbing an open wound for bacterial culture and sensitivity testing is unnecessary. If significant deformity is present, immediate reduction before splinting is indicated. Tetanus immunoprophylaxis should be administered, as appropriate. Because open fractures are invariably contaminated with bacteria, patients with these injuries should receive intravenous (IV) antibiotics. For low-energy injuries with mild to moderate contamination, a first-generation cephalosporin is usually sufficient.[11] Heavily contaminated wounds require the addition of gram-negative bacterial coverage, typically an aminoglycoside. Adding penicillin G or clindamycin (if the patient is penicillin-allergic) as a third antibiotic is necessary for farm- or soil-related crush injuries, in which contamination with *Clostridium perfringens* can be present.

Most open fractures benefit from early surgical intervention for débridement and irrigation. They require emergent orthopedic consultation.[11]

Complications

Early operative complications of closed and open ankle fractures include pin site infection, delayed skin necrosis, skin graft rejection, and osteomyelitis. Delayed complications of operative and nonoperative treatment include malunion, nonunion, osteopenia, traumatic arthritis, chronic instability, ossification of the interosseous membrane, avascular necrosis, and complex regional pain syndrome.

Pilon Fractures

Pilon fractures involve the distal tibial metaphysis and usually are the result of high-energy mechanisms with axial loading of the ankle joint, such as falls from a significant height. These injuries often are comminuted and associated with significant soft tissue trauma, devastation of joint architecture, and leg shortening. Due to the high-energy mechanism of injury, patients with pilon fractures frequently have other significant injuries.

Pathophysiology

Destot first coined the term *hammer fracture* to describe how the head of the talus drives itself into the tibial plafond and causes a pilon fracture. The primary deforming force is one of axial compression, and the position of the foot at the time of injury determines the fracture location and pattern[12] (Fig. 51.9). Secondary rotational or shear forces may cause increased comminution and fragment displacement with more extensive soft tissue injuries. One-fourth of pilon fractures are open; associated injuries include fractures of the calcaneus, tibial plateau, femoral neck, acetabulum, and lumbar vertebrae, as well as trauma to other major systems.

Management

Radiographic examination should include the entire tibia and fibula, as well as the ankle. Emergency management principles for open fractures, as outlined previously, should be applied. Treatment involves restoration of the articular surface and fibular length, combined with meticulous management of soft tissue injuries.[12] Because surgical management is required, emergent orthopedic consultation is necessary. Pilon fractures with low-grade soft tissue damage are managed with primary ORIF.[12] In severe pilon fractures with extensive soft tissue damage, however, results are better with a two-stage approach involving initial length restoration and external fixation, followed by anatomic

reduction and internal fixation after soft tissue swelling has subsided.[12,13]

Complications

Complications of pilon fractures are common, particularly in more severe cases. Early complications include wound infection, skin sloughing, pin site infection, and wound dehiscence. Delayed and late complications include malunion, nonunion, leg shortening, posttraumatic arthritis, avascular necrosis, and protracted pain. Some patients with severe pilon fractures ultimately require arthrodesis.

Soft Tissue Injuries

Ligament Injuries

Ankle sprains are commonly seen in EDs and are one of the most common injuries in an active population. Proper diagnosis and rehabilitation are important because 40% of patients experience dysfunction for up to 6 months postinjury. The term *ankle sprain* refers to a potpourri of ligamentous and nonligamentous injuries. Even when ligamentous injury is certain, the ideal treatment approach is controversial, and there is significant variation in clinical practice.[14,15]

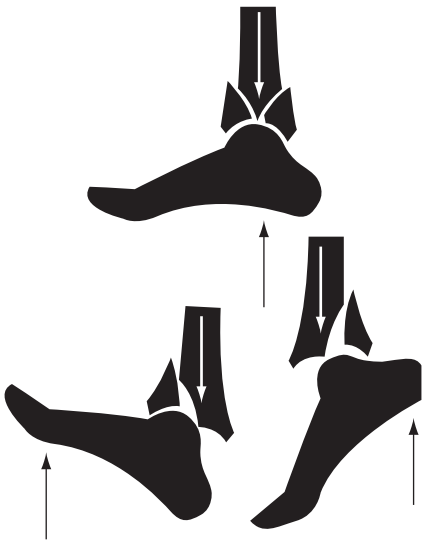

Fig. 51.9. Schematic diagram of the pathophysiology of pilon fractures. The position of the foot at the time of impact determines the fracture pattern. (From Gustilo RB, Kyle RF, Templeman DC, editors: Fractures and dislocations, St. Louis, 1993, Mosby.)

Pathophysiology. Most ankle sprains occur from extreme inversion and plantar flexion that produce symptoms on the lateral aspect of the ankle. Usually, the anterior talofibular ligament is injured first, followed by the calcaneofibular ligament if the deforming forces are sufficiently strong (see Fig. 51.1). Approximately two-thirds of ankle sprains are isolated anterior talofibular ligament injuries, whereas 20% involve anterior talofibular and calcaneofibular ligament injuries. In addition, the lateral talocalcaneal ligament may be strained with an inversion injury, leading to avulsion fractures at either end of the attachment sites. Isolated calcaneofibular or posterior talofibular ligament injuries are rare.

Isolated injury of the medially located deltoid ligament occurs in less than 5% of ankle sprains. Rupture of this ligament usually occurs in conjunction with lateral malleolar fractures, especially when an external rotational force is involved.

Injuries of the distal tibiofibular syndesmotic ligaments are uncommon in the general population because of the degree of force required, but represent 10% to 20% of ankle sprain injuries in competitive athletes. Dorsiflexion and external rotation forces are usually responsible for this injury; their presence may significantly prolong the recovery time from concomitant lateral collateral ligament sprains.

Ligamentous injuries are classified into three grades based on functional and presumed pathologic findings, as outlined in Table 51.1. This classification system, although commonly used, fails to characterize ankle injuries involving two or more ligaments and does not address nonligamentous injuries.

Clinical Features. Although desirable, an accurate history of ankle position and injury mechanism is often unavailable. Inversion followed by external rotation of the ankle suggests the potential for deltoid or syndesmotic injury. Forced dorsiflexion with snapping may indicate peroneal tendon displacement. On physical examination, the presence of edema, ecchymosis, and point tenderness over the medial or lateral collateral ligaments or syndesmotic ligaments suggests a ligamentous injury. Inability to

TABLE 51.1

Ligamentous Injury Classification According to Functional and Presumed Pathologic Findings

CLASSIFICATION (GRADE)	PHYSICAL EXAMINATION	PATHOPHYSIOLOGY	TREATMENT
1	• Minimal lateral ATFL tenderness • Small effusion or no effusion • Weightbearing immediately or within 24 hr	• Microscopic tearing of ligamentous complex fibers	• PRICE • Weightbearing as tolerated • ROM, proprioceptive, and other functional exercises, as tolerated
2	• Moderate lateral ATFL tenderness and hematoma • Small to moderate effusion • Unable to bear weight for >24 hr	• Complete tear of some ligamentous fibers	• PRICE • Immobilization with air cast • ROM, proprioceptive, and other functional exercises, as tolerated
3	• Significant lateral ATFL tenderness ad hematoma • Large effusion • Unable to bear weight for >24 hr • Positive anterior draw, talar tilt test	• Complete tear of all ligamentous fibers within the ligamentous complex	• PRICE • Immobilization • Delayed ROM, proprioceptive, and other functional exercises, as tolerated • Prolonged rehabilitation phase ± delayed surgery

ATFL, Anterior talofibular ligament; *PRICE, **p**rotection, **r**est, **i**ce, **c**ompression, **e**levation; ROM,* range of motion.

bear weight in the absence of a fracture suggests the presence of a grade II or III ankle sprain. Deltoid ligament tenderness necessitates palpation of the full length of the fibula to rule out a proximal fibular fracture—type C Danis-Weber or Maisonneuve fracture (see Figs. 51.7 and 51.8). Tenderness should prompt imaging of the entire tibia and fibula.

Diagnostic Tests and Differential Diagnosis. The fibular compression test, or squeeze test can be used to diagnose fibular and syndesmotic injuries.[16] To perform this test, the examiner places the fingers over the fibula and the thumb over the tibia at midcalf and squeezes the two bones. Pain anywhere along the length of the fibula suggests a fibular fracture or interosseous membrane or syndesmotic ligament disruption at that location.[16] Finally, the Achilles tendon should be assessed for rupture.

Stress testing is the application of a deforming force to assess joint motion beyond the physiologic range; its presence suggests ligament disruption or mechanical instability. Common ankle stress tests include the anterior drawer test, inversion stress test, and external rotation test. The anterior drawer test primarily assesses the integrity of the anterior talofibular ligament. To perform this test, the patient is seated with the knee in 90 degrees of flexion and the ankle in a neutral position or 10 degrees of plantar flexion, which is best achieved by allowing the foot to rest along the examiner's wrist and distal forearm, as the examiner cups the heel in his or her hand and gently flexes the ankle to the 90-degree position. The examiner then applies slow but firm traction on the heel with that hand and places the other hand on the anterior tibia to prevent the leg from moving anteriorly. Anterior displacement of the talus, the perception of a "clunk," and the induction of a sulcus anteromedially over the joint indicate partial or complete tear of the anterior talofibular ligament.

The inversion stress test, or talar tilt test, evaluates the anterior talofibular ligament and calcaneofibular ligament. It is performed by inverting the heel with the knee in 90 degrees of flexion and the ankle in neutral position. Palpation of the head of the talus laterally or a finding of increased laxity compared with the uninjured side suggests partial or complete tear of these ligaments.

The external rotation stress test is indicated when injury to the distal tibiofibular syndesmotic ligaments is suspected. It is performed by externally rotating the foot with the knee in 90 degrees of flexion and the ankle in a neutral position. Pain at the syndesmosis or the sensation of lateral talar motion suggests partial or complete tear of the ligaments.

Stress testing in the ED to identify acute ligamentous disruption is often limited by pain and, to be performed properly, the joint must be anesthetized with local anesthetic. Furthermore, a positive stress test suggesting ligamentous instability rarely alters management in the ED. If needed, this test can be deferred to follow-up.

Standard ankle radiographic views exclude fractures and detect ligamentous instability by allowing the measurement of joint spaces (see earlier discussion and Fig. 51.5).[3] The presence of avulsion fractures constitutes an important clue to the location of ligamentous injuries. Common locations for avulsion fractures include the bases of the malleoli, lateral process of the talus, lateral aspect of the calcaneus, posterior malleolus, lateral aspect of the distal tibia, and base of the fifth metatarsal.

In addition to the standard mortise measurements previously discussed, two measurements on the anteroposterior radiograph further evaluate the distal tibiofibular syndesmosis (see Fig. 51.5). At the distal overlap between the fibula and tibia, the distance between the posterior edge of the lateral tibial groove and medial fibular cortex (syndesmosis A) should not exceed 5 mm. Furthermore, the amount of tibiofibular bony overlap (syndesmosis B) should be at least 10 mm. Measurements outside these values suggest a syndesmotic diastasis. Stress radiographs, accomplished by taking radiographs during stress testing of the ankle, generally do not influence the emergency management of ankle sprains and are not recommended.

BOX 51.2

Differential Diagnosis for Presumed Ankle Sprain

Lateral collateral ligament sprain
Peroneal tendon dislocation
Osteochondral lesion of the talar dome
Fracture of the posterior process of the talus
Fracture of the lateral process of the talus
Fracture of the anterior process of the calcaneus
Midtarsal joint injury
Fracture of the base of the fifth metatarsal

Many injuries can masquerade as ankle sprains. Box 51.2 lists conditions to be considered in the differential diagnosis.

Management. Most ligament sprains, regardless of severity, heal well and result in a satisfactory outcome. To date, compelling evidence for a significant difference in outcomes between surgical and functional (nonsurgical) treatment is lacking. Most patients with acute sprains of the ankle should start with functional treatment.[15] For the minority who fail to respond, delayed operative repair of ruptured ligaments, sometimes years after the injury, has been shown to yield results equivalent to those with primary repair.[17]

Functional treatment, a form of therapy in which the ankle is not fully immobilized, allowing complete or partial joint function, starts in the ED with PRICE therapy (***p***rotection, ***r***est, ***i***ce, ***c***ompression, and ***e***levation). However, significant variability exists in how this combination is applied, and optimal methods for the rehabilitation of ankle sprains remain unclear.[15] The evidence to date suggests that lace-up ankle support is more effective in short-term edema reduction than semirigid ankle support, elastic bandaging, and taping.[15]

For grade I or II injuries, short-term protection with a compression bandage, taping, laced-up support, or commercial brace, with the optional use of crutches for a few days, is appropriate. For patients with first-time ankle sprains, treatment with a lace-up brace combined with elastic wrapping results in an earlier return to function compared with the use of a brace alone, elastic wrap alone, or walking cast.[14,15]

For severe grade II or grade III injuries, there has been equipoise regarding the merits of immobilization compared with functional rehabilitation, with little high-quality evidence to guide therapy. There is little evidence for a more favorable outcome with complete immobilization over functional treatment incorporating a removable brace, so use of a lace-up support or air cast that permits some ankle motion is preferred.[14,15] These patients should also use crutches to avoid weightbearing until they can stand and walk a few steps on the injured ankle without pain. Crutch use varies significantly, ranging from a few days to 2 or 3 weeks. Functional therapy allows for the incorporation of earlier physical therapy rehabilitation and quicker recovery.

Discharge instructions are important in ankle sprains. According to evidence-based guidelines, the expected time for return to activity is generally 2 to 4 weeks, depending on the grade of the injury, with more severe injuries requiring a longer return to activity. Patients who have not returned to a normal activity level beyond this time frame should be reevaluated for talar dome

osteochondral lesions, syndesmotic injury, or occult fracture with advanced imaging.[15,18] Follow-up with the patient's primary care physician or sports medicine physician is appropriate.

Pain improves with immobilization, but analgesia is usually required. Appropriate analgesia can be provided by systemic nonsteroidal antiinflammatory drugs (NSAIDs), in analgesic doses, or acetaminophen. A short course (2–3 days) of oral opioids is added when pain is severe.[19]

Disposition. Acute ankle ligament sprain rarely, if ever, requires orthopedic consultation in the ED. Primary surgical repair of acute ligament rupture is controversial; possible indications include sprains with displaced osteochondral lesions, complete tears of the anterior talofibular and calcaneofibular ligaments in a young athlete, a ligament sprain associated with a fracture causing instability (eg, a deltoid ligament rupture with a lateral malleolar fracture), and an acute severe sprain in a patient with a history of recurrent and severe sprains.[17] Failure of nonoperative treatment also constitutes an indication for surgical repair; however, an orthopedic referral on an outpatient basis is adequate ED management.[17]

Small avulsion fractures of the fibula or tibia with minimal or no displacement can be treated in the same manner as an ankle sprain. If the avulsed fragment is larger than 3 mm or significantly displaced, splinting and referral for orthopedic follow-up on an outpatient basis are justified.

Tendon Injuries

The tendons of the ankle and foot (see Fig. 51.1) are important for facilitating the complex motions of the foot. In general, chronic causes of tendinopathy are more common than acute injuries and occur with overuse type patterns of injury. These may present to the ED with sudden worsening or debilitating pain causing an inability to bear weight. Acute injuries tend to occur in the sports settings or with sudden and forced motion, often against an opposing force. Table 51.2 outlines many of the tendinous injuries located around the ankle joint. Some of the more significant tendon injuries are discussed below in further detail.

Achilles Tendon Rupture. Achilles tendon rupture is most common in middle-aged men, and its causes are multifactorial. This condition is easily misdiagnosed, leading to a delay in therapy, worse prognosis, and increased morbidity, including chronic weakness and loss of function. In the great majority of cases, a complete transection of the tendon is present; however, partial tears of the Achilles tendon can occur and may be more prone to misdiagnosis.

Achilles tendon rupture results from direct trauma or indirectly transmitted forces, including sudden unexpected dorsiflexion, forced dorsiflexion of a plantar-flexed foot, and strong push-off of the foot with simultaneous knee extension and calf contraction,

TABLE 51.2

Tendon Injuries to the Ankle and Foot

TENDON AND FUNCTION	INJURY AND MECHANISM	CLINICAL PRESENTATION	MANAGEMENT
Achilles • Ankle plantar flexion	Chronic tendinopathy > acute injury Tendon rupture • Direct trauma • Sudden or forced ankle hyperdorsiflexion	Rupture • Sudden pain, snap or pop, posterior ankle • Ankle plantar flexion weakness, inability • Palpable defect in Achilles tendon • Positive Thompson test	• Orthopedic referral for conservative vs. operative management • Heel lift with slight plantar flexion while in walking boot, posterior slab
Peroneal longus, brevis • Ankle plantar flexion • Ankle eversion	Chronic tendinopathy > acute injury (rupture vs dislocation) Tendon rupture • Forced dorsiflexion while forced inversion	• With dislocation, snapping sensation while everting ankle ± dorsiflexion • Sudden pain, swelling, lateral (posterior groove) malleolus • Weakness with eversion	• Orthopedic referral for tendon rupture or dislocation • PRICE, physical therapy for tendinopathy
Tibialis posterior • Ankle plantar flexion • Ankle inversion	Chronic tendinopathy > acute injury Tendon rupture • Forced eversion • Disruption of flexor retinaculum, 2 degrees closed anterior ankle dislocation	• Medial ankle pain • Unopposed peroneal brevis action; therefore exaggerated eversion causing pes planus • Inability to perform single leg heel raise	• Orthopedic referral for tendon rupture • PRICE, physical therapy for tendinopathy
Tibialis anterior • Ankle dorsiflexion	Traumatic laceration > acute rupture > chronic overuse injury	• Anterior mass 2 degrees tendon retraction with laceration • Visible recruitment of EDL, EHL to assist in dorsiflexion causes dorsiflexion of hallux	• Orthopedic referral for tendon rupture • PRICE, physical therapy for tendinopathy
Flexor hallucis longus • Ankle and hallux plantar flexion	Chronic tendinopathy > acute injury	• Pain posteromedial ankle • Pain with ankle and hallux plantar flexion	• Orthopedic referral for tendon rupture • PRICE, physical therapy for tendinopathy
Extensor hallucis longus • Ankle and hallux dorsiflexion	Chronic tendinopathy > acute injury	• Pain anterior ankle • Pain with ankle and hallux dorsiflexion	• Orthopedic referral for tendon rupture • PRICE, physical therapy for tendinopathy

EDL, Extensor digitorum longus; *EHL,* extensor hallucis longus; *PRICE,* ***p****rotection,* ***r****est,* ***i****ce,* ***c****ompression,* ***e****levation;* *ROM,* range of motion.

as in a runner accelerating from the starting position. Factors predisposing to Achilles tendon rupture include preexisting disease such as rheumatoid arthritis, systemic lupus erythematosus, gout, hyperparathyroidism, chronic renal failure, steroid use or injection, fluoroquinolone antibiotic therapy, and previous Achilles tendon rupture. The vast majority of ruptures, however, occur spontaneously during activity or trauma, without risk factors other than being male and advancing age.

The diagnosis of Achilles tendon rupture is primarily clinical. Patients usually describe a sudden onset of pain at the back of the ankle associated with an audible pop or snap. Although the pain can resolve rapidly, weakness in plantar flexion persists. On examination, a visible and palpable tendon defect may be noted 2 to 6 cm proximal to the calcaneal insertion in acute presentations but will be less apparent in delayed presentations because of hematoma or edema. Even in cases of complete Achilles tendon rupture, weak plantar flexion may still be possible because of the actions of the tibialis posterior, toe flexors, and peroneal muscles. This retained ability for plantar flexion leads to the misdiagnosis of complete ruptures as ankle strains or partial tears in as many as 25% of cases.

The classic maneuver to assess the integrity of the Achilles tendon is the Thompson test. This is performed with the patient prone and the knee flexed at 90 degrees or the feet hanging over the end of the stretcher. Alternatively, the patient kneels on a chair with both knees flexed at 90 degrees and the feet hanging over the edge. With an intact Achilles, squeezing the calf muscles in these two positions should cause passive plantar flexion of the foot. Absence of this motion, or a markedly weakened response compared with the uninjured side, suggests complete rupture. Lateral radiographic views of the ankle may suggest rupture by showing opacification of the fatty tissue–filled space anterior to the Achilles tendon (Kager's triangle) or an irregular contour and thickening of the tendon. Ultrasonography or MRI can demonstrate partial or complete tendon ruptures, but these studies are indicated only when diagnostic uncertainty exists.

A lack of consensus exists between operative and nonoperative management in the treatment of Achilles tendon rupture.[20-22] Surgical repair is routinely performed in active individuals owing to its lower incidence of rerupture. However, surgery carries higher rates of other complications, such as superficial or deep wound infections, in comparison with nonoperative management.[20] In both types of management, early mobilization improves functional recovery without increasing rerupture rates.[20,21] Achilles tendon rerupture after initial nonoperative treatment usually necessitates surgical repair. Orthopedic referral of patients with Achilles tendon rupture is necessary to determine the appropriate management. Regardless, on discharge from the ED, for surgical or conservative management, the patient is placed in a walking boot with maximal heel lift or posterior slab with the foot plantarflexed in full equinus.[22]

Peroneal Tendon Dislocation or Rupture. The peroneal muscles are the primary evertors and pronators of the foot and also participate in plantar flexion. The peroneus longus and brevis tendons use the posterior peroneal sulcus (the fibular groove), located behind and underneath the lateral malleolus, as a pulley for their midfoot insertions. The peroneus brevis tendon inserts onto the tuberosity of the fifth metatarsal, and the peroneus longus tendon courses beneath the cuboid to insert onto the medial cuneiform and base of the first metatarsal. The superior peroneal retinaculum (Fig. 51.10), a fibrous structure running from the distal fibula to the posterolateral aspect of the calcaneus, maintains the peroneal tendons against the fibular groove and, when ruptured, causes dislocation of the peroneal tendons. Injuries of the peroneal tendons include chronic overuse tendinopathy, tendon rupture, and tendon dislocation.

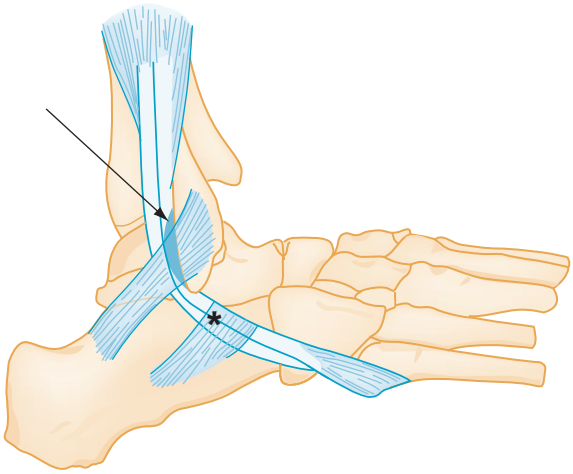

Fig. 51.10. Locations of the superior (*arrow*) and inferior peroneal retinaculum (*star*) in relation to the fibula and peroneal tendons. (From Arrowsmith SR, et al: Traumatic dislocations of the peroneal tendons. Am J Sports Med 11:142, 1983.)

Tibialis Posterior Tendon Rupture. The tibialis posterior is primarily responsible for plantar flexion and inversion along the subtalar joint. Its tendon uses the posteroinferior surface of the medial malleolus as a pulley and inserts onto the navicular, medial cuneiforms, and bases of the second through fifth metatarsals. The peroneus brevis opposes the action of the tibialis posterior. With rupture of the tibialis posterior tendon, the peroneus brevis becomes unopposed, and the medial longitudinal arch loses its muscular support, leading to valgus deformity of the hindfoot and a unilateral flatfoot.

The mechanism of traumatic tibialis posterior rupture involves forced eversion. In addition to a unilateral flatfoot, pain and swelling on the medial aspect of the ankle are seen. Tenderness is present over the navicular, and the patient cannot perform a toe raise on the affected side. The patient with a tibialis posterior tendon rupture is also unable to invert the foot when it is in plantar flexion and eversion. With a unilateral flatfoot, an observer standing behind the patient can see more toes on the lateral aspect of the affected side—a classic sign of tibial posterior rupture. Plain radiography can exclude other bony abnormalities. Outpatient orthopedic consultation is indicated for tibialis posterior tendon ruptures because surgical repair often is necessary.

Other Tendon Injuries. Injuries to the other tendons of the ankle are relatively rare and are outlined in Table 51.2. The tibialis anterior tendon is the primary dorsiflexor of the foot. It courses under the superior extensor retinaculum anterior to the medial malleolus and inserts onto the navicular, medial cuneiform, and base of the first metatarsal. The flexor hallucis longus tendon is responsible for flexion of the great toe and participates in plantar flexion of the foot. It courses behind the medial malleolus through a fibro-osseous canal and travels along the undersurface of the foot to insert onto the distal phalanx of the great toe. The extensor hallucis longus tendon travels anteriorly through the superior extensor retinaculum and inserts on the dorsal surface of the base of the distal phalanx of the hallux.

Ankle Dislocations

Ankle dislocations are described based on the direction of displacement of the talus and foot in relation to the tibia. Dislocation may be upward, posterior, medial, lateral, posteromedial, or anterior. Medial dislocation is the most common. Most dislocations involve associated ankle fractures; rarely, however,

dislocations can occur without fracture. The mechanism in all dislocations begins with axial loading of a plantar-flexed foot, which forces the talus anteriorly or posteriorly from the ankle mortise. The eventual position of the dislocation depends on the position of the foot at the time of injury and direction of the displacing force. Ankle dislocations can be closed or open and usually result from significant falls, motor vehicle collisions (MVCs), or high-speed sports. The neurovascular supply to the foot usually is intact but may be compromised in open dislocations.

ED management involves the assessment of neurovascular status and tendon function, followed by rapid reduction. Radiographs are helpful but should not delay reduction when vascular compromise or skin tenting is present. After appropriate procedural sedation or hematoma block,[23] the patient is placed supine, and the knee is flexed to 90 degrees. Distraction of the foot, followed by a gentle force to reverse the direction of the dislocation, usually accomplishes the reduction. Reassessment of the neurovascular status, splint immobilization, ankle elevation, and post-reduction radiography should follow. Open dislocations require the same management as previously discussed for open fractures. The prognosis for an ankle dislocation is usually good, although open fractures are associated with an increased incidence of complications.

FOOT

PRINCIPLES OF DISEASE

Anatomy

The foot is composed of 28 bones and 57 articulations (Fig. 51.11), which can be divided into three anatomic and functional regions—the hindfoot, containing the talus and calcaneus; the midfoot, consisting of the navicular, cuboid, and cuneiforms; and the forefoot, which includes the metatarsals, phalanges, and sesamoids. The midtarsal, or Chopart's joint, connects the hindfoot to the midfoot, and the tarsometatarsal, or Lisfranc's joint, connects the midfoot and forefoot. The subtalar joint, comprised of three articulations between the talus and calcaneus, is another clinically important joint. Inversion and eversion of the hindfoot occur primarily through the subtalar joint, adduction and abduction of the forefoot through the midtarsal joints, and flexion and extension through the metatarsophalangeal (MTP) and interphalangeal (IP) joints.

The bones of the foot interlock to form a complex system of arches and beams tethered by ligaments and intrinsic muscles. Extrinsic muscles originating in the lower leg are responsible for most of the foot's movements. The course and insertion of these extrinsic muscles are important in their actions and association with specific avulsions and injuries. The arterial supply to the foot is from the anterior and posterior tibial arteries and peroneal artery, a proximal branch of the posterior tibial artery. Motor and sensory innervation comes from branches of the deep and superficial peroneal, posterior tibial, saphenous, and sural nerves.

Clinical Features

In the setting of foot injury, an accurate history is essential, paying particular attention to the mechanism of injury, timing, and duration of symptoms. The location of pain, along with a description of its quality, duration, and precipitants, focuses the differential diagnosis. A history of underlying medical conditions, medications, and previous foot problems is important in certain clinic contexts.

A directed examination specific for the patient's complaint is most useful in the ED.[24,25] The physical examination of the foot begins, if possible, with observation of gait and proceeds with assessment of the foot in its position of rest, normally one of slight plantar flexion and inversion. Swelling, deformity, ecchymosis, open wounds, color, and temperature should be noted. Precise localization of pain or crepitus, when not precluded by swelling, is extremely valuable and facilitates appropriate use of further diagnostic tools. The entire foot should be methodically palpated, paying particular attention to commonly injured areas. Complete assessment includes a detailed neurovascular examination.

In some situations, an evaluation of active and passive range of motion is indicated. Subtalar motion is evaluated by holding the lower leg with one hand and the heel with the other. Then, with the foot in a neutral position, the heel is inverted and everted. There is a substantial variability in range, with normal being 5 to

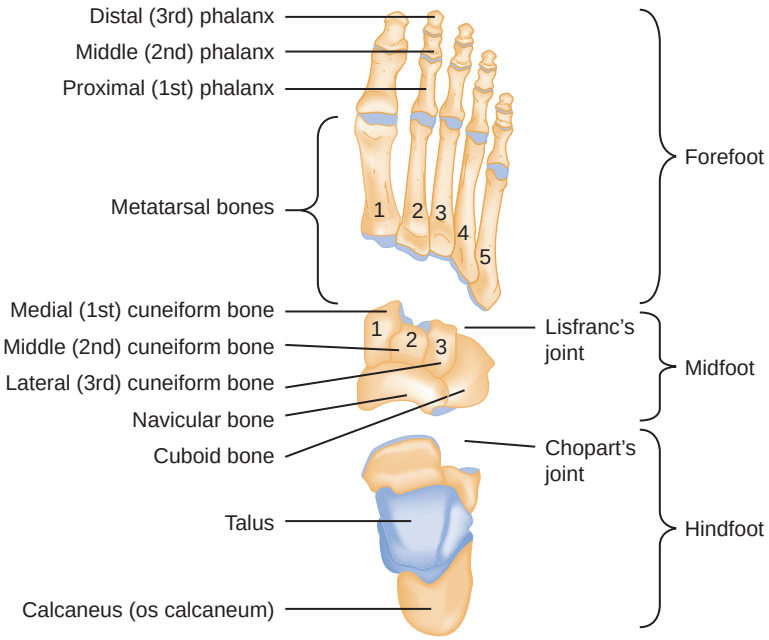

Fig. 51.11. Bones and joints of the foot. (From Rockwood CA, Green DP, Bucholz RW, editors: Rockwood and Green's fractures in adults, ed 3, New York, 1991, JB Lippincott.)

20 degrees of eversion and 5 to 40 degrees of inversion.[24,25] Midtarsal motion is evaluated by stabilizing the heel while the other hand grasps the forefoot. There should be at least 20 degrees of adduction and 10 degrees of abduction.

Forefoot motion is evaluated by flexing and extending the MTP and IP joints individually. The first MTP joint has a particularly wide passive range of motion, with 45 degrees of flexion and 70 to 90 degrees of extension. Throughout the physical examination, findings can be compared with those of the opposite foot.

Diagnostic Testing: Radiology

Standard three-view radiographs of the foot consist of anteroposterior, lateral, and oblique projections. The lateral gives the best imaging of the hindfoot and soft tissues, whereas the anteroposterior and oblique projections give the best imaging of the midfoot and forefoot. The overlapping bones of the foot demand this complete radiographic series when radiographic examination is indicated. Injuries to the hindfoot may warrant the addition of ankle projections and, when indicated, calcaneus views.

Foot radiographs can be difficult to interpret. Moreover, foot fractures are often minimally displaced or nondisplaced, increasing the challenge of radiographic diagnosis. In certain cases, specialized views may improve the imaging of specific areas of the foot. Although largely supplanted by the use of CT, certain views may be of particular clinical value. This is the case for stress or weight-bearing views in suspected Lisfranc injuries.

Accessory ossification centers, found in 30% of the population, can complicate interpretation of plain radiographs. These accessory bones are differentiated from fractures by their smooth corticated surfaces and with comparison radiographs of the opposite foot, although such variants are not inevitably bilateral. The most commonly seen accessory bones are the os trigonum, os tibiale externum (also called an accessory navicular bone), os peroneum, and os vesalianum.[26] Accessory bones themselves can also fracture or cause pain syndromes.

Plain radiography has limitations in the assessment of foot and ankle injuries. In the foot, overlapping bones and complex articulations can make plain radiography difficult to interpret. CT is valuable for imaging the midfoot, calcaneus, subtalar joint and tarsometatarsal (Lisfranc) joint complex.

Advanced imaging, including MRI, ultrasound, and bone scanning, are useful for the diagnosis of foot injuries. However, these tests are rarely indicated in the ED and are often best arranged following consultation with orthopedic, sports medicine, or radiology specialists.

MRI is useful for the diagnosis of ligamentous injury and soft tissue injury but also has value for identifying stress fractures and cartilaginous injury, such as talar dome osteochrondral lesions.[27,28] A common indication for MRI in foot injury would be the diagnosis of a low-energy, or ligamentous, Lisfranc injury. In the case of stress fractures, MRI has comparable sensitivity and better specificity than bone scanning and has emerged as the imaging modality of choice for this diagnosis.[29]

Radionuclide imaging (bone scanning) can be useful for evaluating unexplained foot pain or pain in athletic injuries. CT-SPECT overlays bone scanning with more detailed anatomic information provided by CT imaging to improve localization of lesions. This specialized technique is useful in the diagnostic algorithm for a number of foot disorders, including osteochondral lesions, stress fractures, and osteomyelitis.[30,31]

SPECIFIC PATHOLOGIC CONDITIONS

This section covers the major fractures and dislocations seen in the foot, progressing anatomically from the hindfoot through to the forefoot.

Hindfoot Injuries

The hindfoot is commonly involved in foot injuries and is a difficult area to image. Fractures or dislocations in this region can masquerade as ankle sprains and can be easily missed.

Talar Fractures

Principles of Disease: Anatomy. The talus is divided into three regions—the head, which articulates with the navicular and calcaneus; the body, which articulates with the tibia, fibula, and calcaneus; and the neck, which connects the head and body. The neck is the only region that is predominantly extraarticular. The talus has seven articulations making up 60% of its surface, has no muscular attachments, and is held in position by the malleoli and ligamentous attachment. The anterior width of the talus is greater than the posterior, causing it to be less stable and more prone to dislocation when the foot is plantar-flexed.

The blood supply to the talus is from a vascular ring formed by branches of the anterior and posterior tibial arteries and perforating branch of the peroneal artery. Vessels enter from three sites, all of which can be disrupted by fractures or dislocations, putting the talus at risk of avascular necrosis.

Pathophysiology. Talar fractures are described by anatomic region and are grouped into minor and major fractures, with minor fractures being the more common.

Minor Talar Fractures. These include avulsion fractures of the superior neck and head and lateral, medial, and posterior aspects of the body. These fractures often involve the same mechanism as ankle sprains (see Box 51.2), a combination of plantar flexion or dorsiflexion and an inversion force. Lateral process fractures result from forced dorsiflexion. These fractures, which can be occult on plain radiographs, have been most commonly described in snowboarding, but do occur in other sports, as well as MVCs.[32-34] Osteochondral lesions of the talar dome, which also fall into the minor fracture category, can cause significant morbidity.

Major Talar Fractures. These are high-energy fractures that occur in the head, neck, or body. Talar head fractures make up 5% to 10% of all talar fractures.[35] Their mechanism is a compressive force applied on a plantar-flexed foot and transmitted up through the talonavicular joint. Comminution is common, and associated navicular fractures can occur, further disrupting the talonavicular articulation.

Talar neck fractures account for 50% of major talar injuries.[35] Their mechanism usually is an extreme dorsiflexion force, as generated in falls or MVCs. Associated fractures are common, usually an oblique or vertical fracture of the medial malleolus. Other associated injuries include calcaneal fractures and vertebral compression fractures.

The Hawkins classification grades talar neck fractures by displacement and associated subluxations (Fig. 51.12):

- Type 1 fractures are nondisplaced.
- Type 2 fractures are displaced vertical fractures, with subtalar joint subluxation.
- Type 3 fractures, 50% of which are open, involve a vertical talar neck fracture, with subluxation of the subtalar and tibiotalar joints.
- Type 4 fractures, which are uncommon, involve distraction of the subtalar, tibiotalar, and talonavicular joints.

This classification system guides treatment and correlates with the incidence of avascular necrosis (AVN) which can approach 50% for type 3 fractures. Posttraumatic arthritis has been reported in up to 75% of patients following talar neck fractures.[36,37]

Talar body fractures include many of the minor talar fractures previously listed. Major talar body fractures are uncommon and

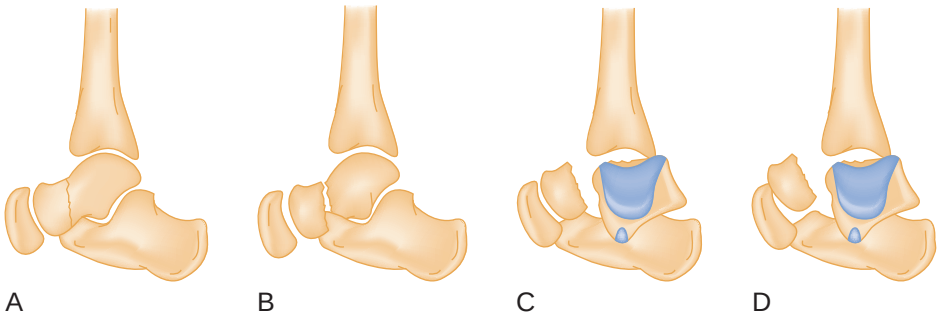

Fig. 51.12. Hawkins classification of talar neck fractures. **A–D,** Hawkins tendons. *Shading* indicates the articular surface of the talar dome. (From Gustilo RB, Kyle RF, Templeman DC, editors: Fractures and dislocations, St. Louis, 1993, Mosby.)

Fig. 51.13. Comminuted fracture of the talar body (*arrows*). (From Rosen P et al, editors: Diagnostic radiology in emergency medicine, St. Louis, 1992, Mosby.)

Fig. 51.14. Fracture of the talar neck (*arrow*). (Courtesy Dr. Thomas J. Green.)

usually result from falls with axial compression of the talus between the tibial plafond and calcaneus. These fractures are typically intraarticular, involving the ankle and subtalar joints.[35]

Clinical Features. Talar fractures range from obvious open fractures to subtle injuries requiring special imaging for diagnosis. Typically, a history of a twisting injury, fall, or high-energy impact can be elicited. Dorsal swelling and tenderness over the talus are characteristic findings. Although ankle motion may be preserved, inversion and eversion of the hindfoot often are painful.

Diagnostic Testing: Radiology. With minor talar fractures, plain radiographs can be misinterpreted as normal, and CT may be required when clinical suspicion is high. Standard foot and ankle radiographs usually demonstrate major talar fractures (Figs. 51.13 and 51.14), with anterior and oblique projections showing talar alignment within the mortise and the lateral projection showing the talar neck and alignment of the posterior aspect of the subtalar joint. In the case of major talar fractures and intraarticular fractures, routine CT scanning is recommended.[38] Plain radiographs have a sensitivity of only 74% and may underestimate fracture severity, particularly with respect to the degree of articular involvement. CT improves the reliability of classification[39] and provides additional information in 93% of talar fractures.[38]

Management. Nondisplaced minor talar fractures are treated with casting. Depending on the degree of swelling and follow-up plans, patients should be nonweightbearing, with a below-knee cast or posterior plaster slab. Displaced or comminuted lateral process fractures require operative fixation because of their articular involvement. Minor fractures with fragments larger than 5 mm in diameter may require excision.

Talar neck fractures carry a significant risk of long-term morbidity and require precise reduction. Type 1 fractures, which are nondisplaced, are the only talar neck fractures amenable to nonoperative treatment, which initially consists of 6 weeks of nonweightbearing in a cast. Close outpatient orthopedic follow-up is essential.[40] Hawkins types 2 to 4 fractures or talar neck fractures with any displacement are managed surgically. Significantly displaced fractures, particularly if associated with neurovascular or cutaneous compromise, require an emergent attempt at closed reduction in the ED.

The treatment of talar head and body fractures is controversial and requires emergent orthopedic consultation. Displaced fractures, or those involving a significant degree of articular surface, should be managed surgically. Nondisplaced fractures of the talar body may require surgical management due to the large articular surface requiring precise anatomic alignment. However, some

have advocated for the treatment of nondisplaced talar body fractures with a cast and nonweightbearing.[35,40]

Disposition. All patients with talar fractures should be followed by orthopedics. Minor fractures that are nondisplaced are suitable for outpatient referral. Displaced or comminuted minor fractures such as lateral process fractures can be splinted for urgent orthopedic evaluation in 1 to 2 days.

Patients with major talus fractures should have an emergent orthopedic evaluation. These fractures have a high incidence of complications, the most significant of which is avascular necrosis.[36,37] The outcome depends on the degree of anatomic reduction attained and preservation of the vascular supply. Other potential complications include skin infection, skin necrosis, posttraumatic arthritis, malunion, delayed union, nonunion, and predisposition to peroneal tendon dislocation.

Osteochondral Lesions

Osteochondral lesions of the talar dome warrant special mention. These talar body injuries describe defects of the articular cartilage and often include subchondral bone.[35] The mechanisms of injury are identical to those causing ankle sprains and fractures. Although limited data exist, osteochondral lesions may complicate up to 50% of ankle sprains and 70% of ankle fractures.[41,42] Osteochondral lesions are graded from 1 to 4, according to the progressive depth of the lesion.

An osteochondral lesion should be considered in any patient with acute ligamentous ankle injury accompanied by gross edema and an effusion visible on plain radiographs. However, most osteochondral lesions are not diagnosed at the time of injury but present as persistent pain and effusions (see Box 51.2). Physical findings usually are nonspecific, although tenderness over the posteromedial talus and increasing pain with exertion, weightbearing, or passive plantar flexion may be noted. Standard view radiographs are commonly normal in appearance or show subtle and easily overlooked abnormalities (Fig 51.15). Bone scanning has historically been advocated as a screening modality, but its role has been supplanted by MRI, CT-SPECT, or CT. MRI has emerged as the imaging modality of choice for osteochondral lesions owing to its ability to detect bone marrow edema and cartilaginous defects.

The natural history of osteochondral lesions is poorly defined and variable; however, chronic ankle discomfort and osteoarthritis are potential sequelae. When an osteochondral lesion is confirmed or suspected, patients should be referred for outpatient consultation with an orthopedic specialist. Low-grade and minimally symptomatic lesions are amenable to a trial of conservative therapy in a protective boot. Although there are many management options, higher grade lesions are often managed surgically. Patients with higher grade symptomatic lesions should be made nonweightbearing and can be placed in a splint for comfort.

This discussion underscores the importance of detailed discharge instructions following diagnosis of an ankle sprain. Patients with persistent swelling and pain or inability to return to function beyond the expected 2 to 4 weeks should be advised to seek follow-up with a primary care physician.

Subtalar Dislocations

Principles of Disease: Pathophysiology. Subtalar dislocation, also called peritalar dislocation, is the simultaneous

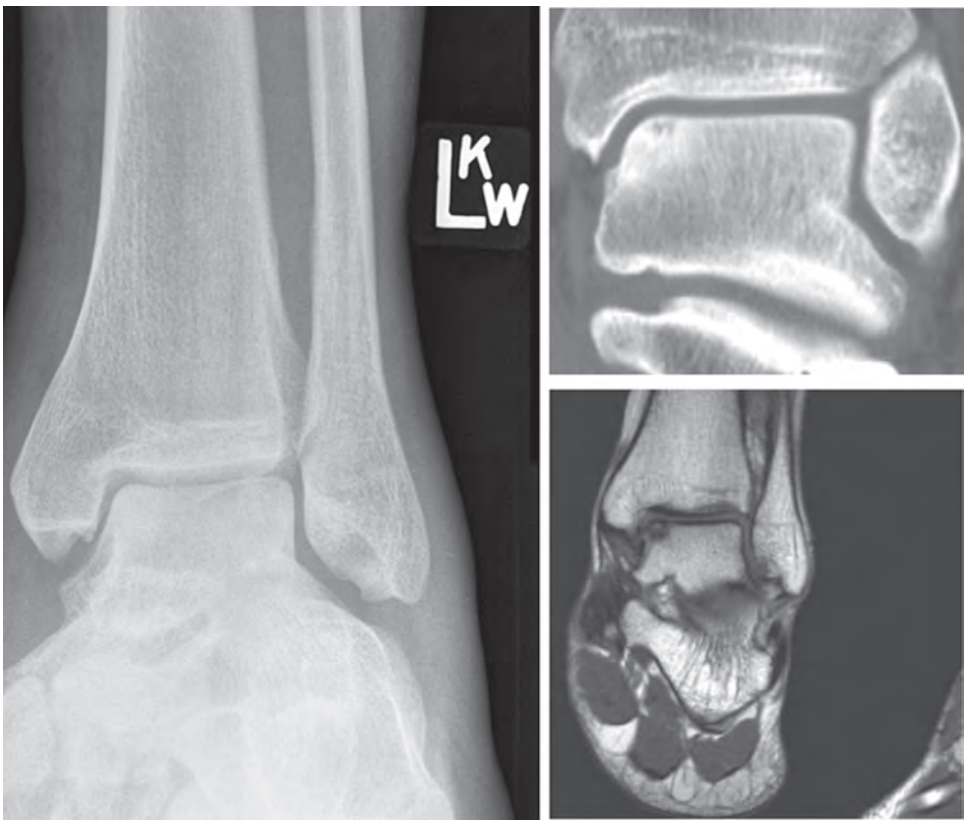

Fig. 51.15. **A,** Mortise view of an ankle fails to identify an osteochondral lesion in a patient with recurrent effusions and ongoing pain following a sprain. **B,** CT scanning identifies the suspected lesion. **C,** Similar lesion in a different patient demonstrates the value of MRI in making the diagnosis. (**A, B** courtesy Dr. Thomas J. Green; **C** adapted from Frost A, Roach R: Osteochondral injuries of the foot and ankle. Sports Med Arthrosc Rev 17:187, 2009.)

disruption of the talocalcaneal and talonavicular joints, without disruption of the tibiotalar joint. This occurs when the talonavicular and talocalcaneal ligaments rupture while the stronger calcaneonavicular ligament remains intact. Subtalar dislocations are rare and are classified by the direction that the foot takes in relation to the talus. Medial dislocations are most common, with lateral, anterior or posterior occurring rarely. Of subtalar dislocations, 10% are open, and associated fractures are present in 50% of cases, particularly those with lateral dislocations. Dislocation of the calcaneus is an exceptionally rare event distinct from subtalar dislocation; it involves disruption of the talocalcaneal and calcaneocuboid articulations.

Clinical Features. Obvious deformity typically is present, often with skin tension on the side opposite the direction of dislocation. Neurovascular status should be carefully assessed, although it is rarely compromised. Swelling can mask the extent of the injury; thus, diagnosis can be delayed or missed if only ankle radiographs are obtained.

Diagnostic Testing: Radiology. Although standard foot radiographic views are diagnostic, properly positioning the patient for them may be difficult. The single most helpful radiograph is an anteroposterior view of the foot, which will demonstrate the talonavicular dislocation.

Management. Subtalar dislocations require expeditious reduction. Most closed subtalar dislocations can be treated with closed reduction, with procedural sedation in the ED or general anesthesia. Closed reduction is performed by flexing the knee and applying longitudinal traction to the foot with initial accentuation, followed by reversal of the deformity, using eversion for medial dislocations and inversion for lateral dislocations. Sometimes, direct pressure over the head of the talus aids in reduction. Closed reduction may be impossible because of buttonholing of the talus through the extensor retinaculum, entrapment in the peroneal tendons, or associated fractures. After reduction, immobilization in a below-knee cast for 4 to 6 weeks is indicated.

Disposition. Emergent orthopedic consultation is indicated for subtalar dislocations. Although serious complications, such as AVN, are uncommon in cases of closed subtalar dislocation, most patients have long-term limitation of subtalar motion, a sequela that can affect gait.

Total Talar Dislocation

Total talar dislocation is an extremely rare and devastating injury requiring orthopedic consultation in the ED. In these injuries, which are the end result of the same forces that produce subtalar dislocation, the entire talus is distracted from all its articulations. Most are open, and infection and AVN are common complications.[43]

Calcaneal Fractures

Principles of Disease: Anatomy. The calcaneus is the largest and most commonly fractured tarsal bone. It articulates superiorly with the talus (forming the subtalar joint) and anterolaterally with the cuboid.

Pathophysiology. Calcaneus fractures are often high-energy injuries with serious short- and long-term consequences. They are most common in younger males, occurring frequently as a result of a fall from a height. Multisystem injury has been noted in 5% and spinal injury in approximately 6% of patients with calcaneus fractures.[44] Up to 5% are open fractures, and compartment syndrome occurs in up to 10% of calcaneus fractures.[44,45] Frequently, the diagnosis of compartment syndrome is made late, only after the development of complications.[45] Other common complications include infection, chronic heel pain, posttraumatic arthritis, and hindfoot deformity. Inability to return to work or wear normal shoes are also common complications.[46] Despite the association with high-energy injuries, other mechanisms may cause calcaneal fractures, including simple falls from standing height, particularly in older women.[44] Calcaneus fractures are classified as intraarticular, which involve the subtalar joint, or extraarticular.

Intraarticular Calcaneal Fractures. These are more common and more serious, accounting for up to 75% of calcaneal fractures. Classification systems used to describe intraarticular fractures are complex and more relevant to surgical consultants for planning and prognosis. The commonly used classification systems have suffered poor interobserver reliability although, with CT scanning, reliability has improved.[47]

Extraarticular Calcaneal Fractures. These do not involve the posterior articular surface. They include fractures of the anterior process, sustentaculum tali, lateral and medial calcaneal processes, peroneal tubercle, and tuberosity and extraarticular fractures of the calcaneal body. Isolated calcaneal tuberosity fractures occur as a result of avulsion by the Achilles tendons and are rare. These fractures can be serious in that displacement can compromise the skin overlying the Achilles tendon.[48]

Clinical Features. Physical examination reveals pain, swelling, and tenderness over the heel. Weightbearing on the hindfoot is usually impossible. Ecchymosis may extend over the entire sole, and the heel may appear deformed, shortened, widened, or tilted. Particular attention should be given to the assessment of compartment syndrome, as well as to tension in overlying skin.

Diagnostic Testing: Radiology. In the case of a suspected calcaneus fracture, initial radiographic imaging should include a foot series with the addition of a Harris, or axial calcaneal, view. The anteroposterior view shows the calcaneocuboid joint and anterosuperior calcaneus, whereas the lateral view shows the posterior facet and can demonstrate compression of the calcaneal body. The Harris view is an additional axial projection of the calcaneal tuberosity, subtalar, and sustentaculotalar joints (Fig. 51.16).

Two assessments are critical to the management of calcaneal fractures—determining whether the fracture involves the subtalar joint and the degree of depression of the posterior facet. Compression fractures are not always obvious, and measurement of Boehler's angle (Fig. 51.17) can be helpful in making the diagnosis. However, the prognostic value of Boehler's angle is controversial. Recent evidence has suggested that determining the preoperative Boehler's angle is predictive of injury severity, but only the postoperative angle is predictive of functional outcome.[49]

Findings on x-ray can be subtle. CT scanning can be provide valuable information for prognosis and treatment planning.[47] When an intraarticular fracture is identified on plain film, or is clinically suspected, a CT scan should be performed.

Management. The decision to manage intraarticular or displaced calcaneal fractures operatively or conservatively must be made in consultation with an orthopedic surgeon. Recent reviews have provided conflicting results regarding the functional outcome of operatively and nonoperatively managed calcaneal fractures.[50-53] Operative repair is indicated for open fractures, as well as those with neurovascular, skin, and soft tissue compromise. The treatment of nondisplaced extraarticular fractures usually involves casting for 6 to 8 weeks.

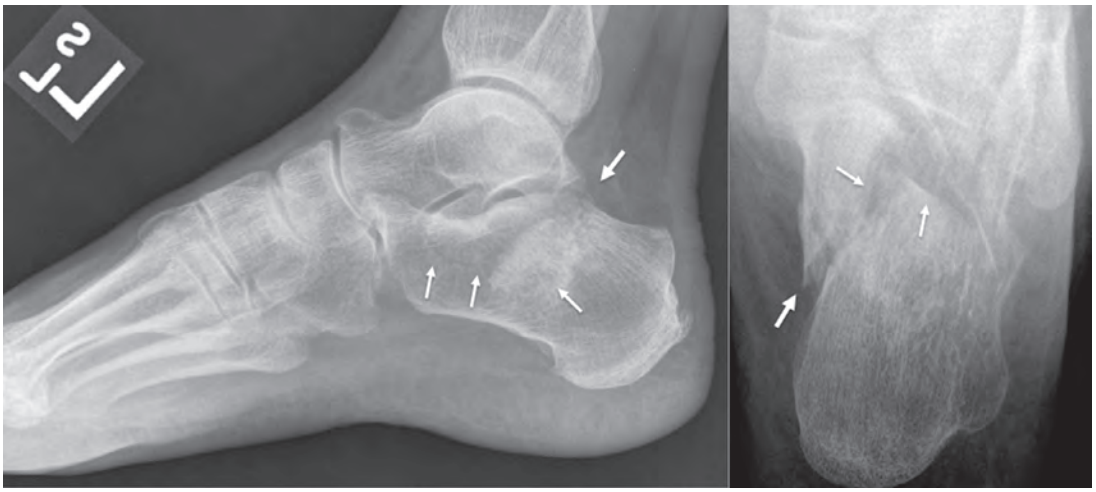

Fig. 51.16. A, Lateral view of a comminuted fracture of the body of the calcaneus (*arrows*). **B,** Axial or Harris view of the same fracture. (Courtesy Dr. Thomas J. Green.)

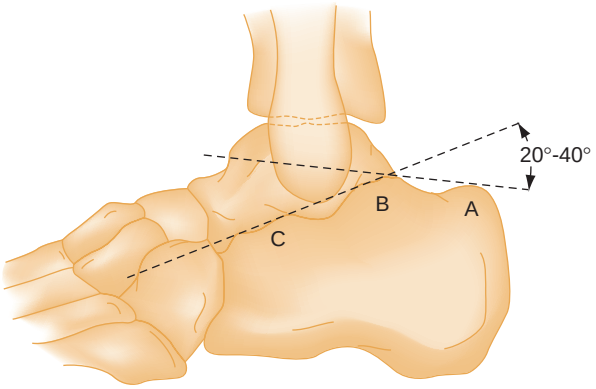

Fig. 51.17. Boehler's angle is obtained by measuring the angle formed by two lines, one between the posterior tuberosity (A) and apex of the posterior facet (B) and the other between the apex of the posterior facet (B) and apex of the anterior process (C). Although several ranges for this measurement have been cited, an angle of 20 to 40 degrees gives the best diagnostic performance for fracture detection. An angle of less than 20 degrees suggests a compression fracture; comparison measurement of the uninjured side is helpful in questionable cases. (From Rosen P et al, editors: Diagnostic radiology in emergency medicine, St. Louis, Mosby, 1992.)

Disposition. Intraarticular or displaced calcaneal fractures require emergent orthopedic consultation and detailed evaluation for associated injuries. Calcaneus fractures are often high-energy, extremely painful injuries that can be at high risk of acute complications, including compartment syndrome.[45] These fractures also have a high incidence of long-term functional limitation, arthritis, and chronic pain.[46] Operative management may occur emergently or may be delayed to allow soft tissue swelling to decrease. Patients can be placed in a padded loose dressing, with the foot elevated.

In general, nondisplaced extraarticular fractures have lower morbidity and benefit from symptomatic or conservative therapy. Outpatient orthopedic follow-up should be arranged for these fractures, and patients can be discharged with a compressive soft dressing or splint. In the case of tuberosity fractures, which result from avulsion of the Achilles tendon, particular attention should be paid to tension of overlying skin, which can be at risk of necrosis.[48] If the tension cannot be relieved, orthopedic consultation in the ED is indicated.

Midtarsal Joint Injuries

The midtarsal joint (Chopart's joint) is composed of the talonavicular and calcaneocuboid joints. Injury in this area can occur with any ankle, hindfoot, or midfoot trauma. Midtarsal joint injuries usually result from forced dorsiflexion and often are associated with other fractures. Sprains, fracture-subluxations and fracture-dislocations, and an isolated so-called swivel dislocation (a variant of a subtalar dislocation) all can occur at the midtarsal joint. Pain, swelling, inability to bear weight, and tenderness over the midtarsal joint are usual findings. Although standard radiographs often are abnormal in appearance, the diagnosis frequently is overlooked or delayed, with symptoms ascribed to an ankle sprain (see Box 51.2). The possibility of a midtarsal joint injury should be considered with any isolated midfoot fracture, particularly those of the navicular tuberosity. MRI can be helpful in the evaluation of midfoot tendon and ligamentous injuries, although rarely indicated in the ED. Nondisplaced injuries may heal with casting, but operative fixation is often required, and management can be difficult. Complications are common and include persistent pain, arthritis, and long-term disability. Patients with a clinically suspected midtarsal joint injury should be made nonweightbearing, with specialist follow-up for repeat assessment and arrangements made for advanced imaging, if indicated.

Midfoot Injuries

The midfoot is an inherently stable region of the foot and is not commonly injured. Fractures and relationships of the midfoot tarsals are difficult to visualize on standard radiographic views. A compounding factor is that pain associated with midfoot injuries may be ill-defined and poorly localized. Although isolated fractures of the midfoot tarsals occur, associated injuries, including metatarsal fractures, subluxations, and spontaneously reduced tarsometatarsal dislocations, may be present.

Navicular Fractures

Principles of Disease: Anatomy. The navicular forms the supporting structure for the medial arch of the foot and bears most of the load within the tarsal complex during weightbearing. Because of the navicular's extensive articular surface, its blood supply enters only through a small waist of cortex, leaving the middle third relatively avascular and therefore at risk for avascular necrosis.

Pathophysiology. Navicular fractures are classified as dorsal avulsion fractures, tuberosity fractures, and body fractures. Stress fractures of the navicular, although uncommon, carry a high risk of morbidity related to misdiagnosis and subsequent fracture with nonunion.

Clinical Features. Navicular fractures cause localized tenderness over the dorsal and medial aspects of the midfoot. The navicular tuberosity is palpated anterior to the sustentaculum tali, a shelf of bone on the medial ankle approximately 2.5 cm below the tip of the medial malleolus. In the case of tuberosity fractures, pain may be exacerbated by passive eversion or active inversion of the foot.

Diagnostic Testing: Radiology. Although standard foot radiographs usually identify navicular fractures, advanced imaging with CT may be necessary. This is particularly the case for patients with high-energy or complex foot injuries, for which the sensitivity of plain radiography is poor. It is not uncommon to confuse the os tibiale externum, also called an accessory navicular bone, with an acute fracture.

Management. Nondisplaced dorsal avulsion, tuberosity, and body fractures are treated in a walking cast for 4 to 6 weeks. Decisions regarding treatment of displaced body fractures, as well as dorsal avulsion fractures involving more than 25% of the talonavicular joint, should be made in consultation with orthopedics. These fractures may be operatively managed and can carry a significant risk of long-term complications and functional limitation.[54]

Disposition. Most navicular fractures are suitable for outpatient orthopedic referral. Unless a significant amount of articular surface is involved, dorsal avulsion fractures can be treated with a compressive dressing and symptomatic management. Significant fractures, particularly if intraarticular, warrant orthopedic consultation in the ED. Navicular tuberosity fractures can be complicated by nonunion. AVN and arthritis are potential late sequelae.

Cuboid Fractures

Cuboid fractures usually occur with other midfoot fractures, including Lisfranc injuries.[55] Fractures are generally the result of avulsion or crush injury. The latter, known as a nutcracker fracture, results from compression of the cuboid between the bases of the fourth and fifth metatarsals and calcaneus. They are also associated with fractures of the posterior malleolus.

The cuboid is best evaluated by the oblique view of a standard foot radiographic series because this demonstrates the calcaneocuboid and cuboid-metatarsal relationship. The possibility of Lisfranc's injury should be considered with any cuboid fracture. Treatment of isolated injuries ranges from casting for minor nondisplaced fractures to operative fixation. Nondisplaced cuboid fractures are suitable for urgent outpatient orthopedic follow-up. A compressive dressing and splint are reasonable in the interim prior to consultation. Cuboid fractures associated with more significant injury or other fractures should have orthopedic consultation in the ED. Extraarticular cuboid fractures can be complicated by disruption of the peroneus longus tendon at the level of the peroneal groove.

Cuneiform Fractures

Fractures of the cuneiforms are extremely uncommon and usually result from direct trauma. As with cuboid fractures, the patient should be assessed carefully for the presence of Lisfranc's injury. Treatment usually is by casting; however, displaced fractures require orthopedic assessment.

Dislocations of the Navicular, Cuboid, and Cuneiforms

Isolated dislocations of each of the midfoot bones have been described. These uncommon injuries often require open reduction. Emergent orthopedic consultation is required for these injuries.

Lisfranc (Tarsometatarsal) Fractures and Dislocations

Principles of Disease: Anatomy. Lisfranc injuries refer to any fracture, dislocation, or ligamentous injury at the tarsometatarsal joint (Lisfranc's joint). This joint is composed of the articulations of the bases of the first three metatarsals with their respective cuneiforms and the fourth and fifth metatarsals with the cuboid. In concert, the tarsometatarsal joints act to allow supination and pronation of the forefoot. The intrinsic stability of Lisfranc's joint is provided by the bony architecture and associated ligaments. The metatarsal bases form an arch, with the second metatarsal acting as the keystone. Lisfranc's ligament itself joins the medial cuneiform with the base of the second metatarsal and provides crucial structural support. Strong transverse intermetatarsal ligaments join the bases of the second through fifth metatarsals. The joint is further supported by dorsal and plantar ligaments, plantar fascia, and insertions of the tibialis anterior and peroneus longus tendons at the first metatarsal base.

Pathophysiology. Lisfranc injuries carry a significant risk of long-term disability. They can be thought of as high-energy injuries, such as occurring in MVCs, or low-energy injuries, such as those occurring in sports activities. High-energy injury usually results in fractures or fracture-dislocations, whereas low-energy injuries can result in more subtle, isolated ligamentous injuries. Lisfranc injuries arise from three mechanisms—rotational forces, whereby the body twists around a fixed forefoot; axial loads, whereby the weight of the body drives the hindfoot into the bases of the metatarsals; and crush injuries. The most intuitive classification categorizes the direction of the dislocation in the horizontal plane (Fig. 51.18).[56] In type A, or homolateral, injuries, all five metatarsals are displaced in the same direction. In type B, or isolated, injuries, one or more metatarsals are displaced away from the others. In type C, or divergent, injuries, the metatarsals are splayed outward in the medial and lateral directions. A component of dorsal displacement also is commonly present in displaced Lisfranc injuries, whereas plantar displacement is uncommon because of the joint's bone architecture and strength of the plantar ligaments and fascia.

Low-energy Lisfranc injuries have been previously classified as stage 1 injuries, which are nondisplaced with low-grade strain, stage 2 injuries, in which a 2- to 5-mm diastasis exists between the first cuneiform and base of the second metatarsal, and stage 3 injuries, in which more than 5 mm of diastasis exists, and there is loss of metatarsal arch height. Because of ligamentous attachments, Lisfranc injuries are frequently associated with metatarsal fractures, usually of the second metatarsal base. Fractures of the cuboid, cuneiforms, and navicular also are common, occurring in more than one-third of cases. Lisfranc injuries may be complicated by vascular injury because a critical branch of the dorsalis pedis artery dives between the first and second metatarsals to form the plantar arch. Trauma to this vessel can cause significant hemorrhage and, uncommonly, vascular compromise.

Clinical Features. Most Lisfranc injuries are clinically obvious; however, findings may be subtle, and the true extent of the pathologic condition can easily be missed or misdiagnosed.

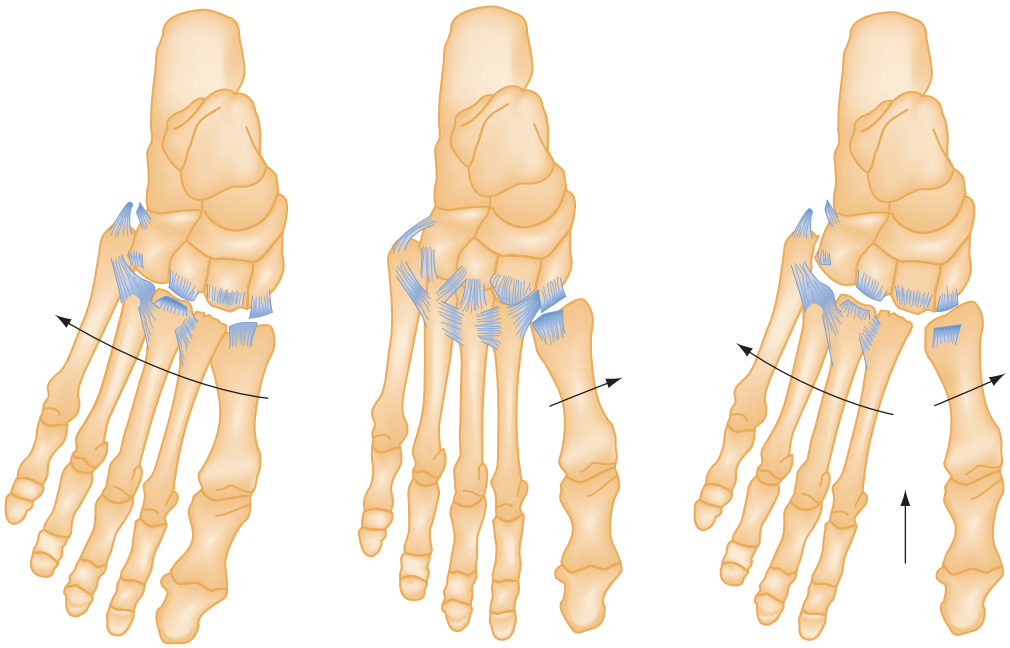

Fig. 51.18. Classification of Lisfranc injuries by direction of displacement of metatarsals with respect to the midfoot. Direction of displacement is indicated by arrows. The ligamentous anatomy of the Lisfranc complex also is depicted. (From Hardcastle PH, Reschauer R, Kutscha-Lissberg E, Schoffmann W: Injuries to the tarsometatarsal joint: incidence, classification and treatment. J Bone Joint Surg Br 64:349, 1982.)

Seemingly trivial fractures, if viewed in isolation, may fail to reflect the serious soft tissue disruption that can be present. Some have estimated that the diagnosis is missed on initial ED presentation in up to 20% of cases.[57]

The clinical presentation varies with the extent of injury and displacement. Severe pain in the midfoot and inability to bear weight, particularly on the toes, are usual features. Paresthesias are occasionally present, and examination may reveal edema and ecchymosis. The dorsalis pedis pulse can be absent, or evidence of vascular compromise of the forefoot may be present. Typically, tenderness along the affected tarsometatarsal joints and pain with passive abduction and pronation of the forefoot are present, sometimes with pathologic mobility. It should be kept in mind that low-energy injuries may present with subtle findings, such as chronic pain and limitation in activity, with few other clinical signs.

Diagnostic Testing: Radiology. Standard radiographic views of the foot often are sufficient to diagnose injuries to the Lisfranc complex, although findings may be subtle (Fig. 51.19). The anteroposterior view allows assessment of the first and second metatarsals with their cuneiforms, whereas the oblique view assesses alignment of the third and fourth metatarsals with the lateral cuneiform and cuboid. The lateral foot radiograph allows assessment of metatarsal alignment with the cuneiforms in the saggital plane. Typical radiographic findings are outlined in Box 51.3.

When Lisfranc injury is clinically suspected, and initial radiographs are normal, one should obtain additional imaging in the ED or in outpatient follow-up. CT scanning has been shown to detect Lisfranc injuries missed on plain film. In one study, using CT as a reference standard, plain films identified only 31 of 45 injuries.[58] Despite diagnostic improvement, CT scanning does not image ligamentous structures and may miss low-energy or isolated ligamentous injuries which can still carry a burden of disability. MRI accurately images the Lisfranc joint and has been shown to predict instability, although studies have not proven its clinical value.[59] Although often difficult to obtain because of pain, weight-bearing plain radiographs continue to have clinical value by demonstrating isolated ligamentous injury when plain radiographs fail to do so.[59]

Initial assessment of the Lisfranc joint should include plain radiography. When plain radiographs are normal, and clinical suspicion of a Lisfranc injury is high, CT scanning is indicated. A further diagnostic option would be to obtain weight-bearing plain radiographs in the ED if pain can be adequately controlled. The American College of Radiology, in their guidelines on appropriate imaging, have suggested that CT scanning or MRI are appropriate

BOX 51.3

Radiographic Findings Consistent With Lisfranc Injuries

ANTEROPOSTERIOR VIEW

Loss of alignment of the medial border of the second metatarsal with the medial cuneiform
Presence of a fleck sign from avulsion of the Lisfranc ligament
Diastasis > 2 mm between base of the first and second metatarsals
Compared to the uninjured foot: difference > 1 mm between base of the first and second metatarsals

OBLIQUE VIEW

Loss of alignment between the medial border of the fourth metatarsal and medial border of the cuboid

LATERAL VIEW

Loss of alignment between the plantar aspect of the fifth metatarsal and the medial cuneiform
Loss of dorsal alignment of tarsals with their respective metatarsals

Adapted from Eleftheriou KI, Peter F. Rosenfeld PF: Lisfranc injury in the athlete: evidence supporting management from sprain to fracture dislocation, Foot Ankle Clin 18:219, 2013.

Fig. 51.19. A, Anteroposterior radiograph showing a Lisfranc injury with fractures of the bases of the second through fourth metatarsals, including a fragment suspicious for an avulsion from the Lisfranc ligament at the second metatarsal base. **B,** Lateral radiograph showing a step-off at the tarsometatarsal joints (*arrow*). **C,** Computed tomography scan of the same patient showing increased detail, including lateral displacement of the first metatarsal relative to the first cuneiform (*arrow*). (From Gupta RT, Wadhwa RP, Learch TJ, Herwick SM: Lisfranc injury: imaging findings for this important but often-missed diagnosis. Curr Probl Diagn Radiol 37:115, 2008.)

second tests, followed by weight-bearing or stress views, when indicated.[60]

Management. Displaced or high-energy Lisfranc injuries are usually treated surgically, followed by non–weight-bearing casting for 12 weeks and wearing an orthotic for 1 year. Low-energy ligamentous injury without displacement can be treated with immobilization in a below-knee cast for 6 weeks.

Disposition. Any high energy or displaced Lisfranc injury requires emergency orthopedic consultation. Patients with a proven or suspected ligamentous Lisfranc injury should have orthopedic consultation in the ED or be immobilized in a below-knee cast or splint pending orthopedic follow-up as an outpatient.

The diagnosis of Lisfranc injury can be difficult, with subtle radiologic and clinical findings. Delayed treatment or misdiagnosis can result in significant complications and a poor functional outcome for which management is challenging. When radiographs in the ED are nondiagnostic, clinical suspicion of Lisfranc injury warrants further investigation and referral to an orthopedic surgeon for further assessment. This is particularly important for ligamentous injuries, in which the diagnosis is more challenging.

Forefoot Injuries

Traumatic forefoot conditions are commonly underdiagnosed and often consist of more than one fracture or dislocation occurring simultaneously. As occurs elsewhere in the foot, forefoot trauma may lead to prolonged disability and dysfunction.

Metatarsal Fractures

Metatarsal fractures are common and account for one-third of foot fractures. Injuries should be classified anatomically as occurring in the shaft, head and neck, or base. Treatment is then dictated by the metatarsal involved, specific location and type of fracture, and nature of any associated injuries.[61]

Metatarsal Shaft Fractures

Principles: Pathophysiology. Metatarsal shaft fractures arise from direct trauma (eg, a crush injury from a heavy object) or indirect trauma (eg, a twisting force applied to a fixed forefoot). Because of the nature of the mechanism of injury, associated phalangeal fractures often occur. Direct trauma may be highly disruptive, resulting in multiple metatarsal fractures and severe complications. The third metatarsal is the most commonly fractured, and metatarsal shaft stress fractures are common.

Biomechanics is an important consideration in the approach to metatarsal shaft fractures. During stance, weight is distributed between the heel and forefoot, where it is spread across the metatarsals, with the first metatarsal carrying twice its share of the load. Great toe metatarsal fractures, although uncommon, require aggressive management because of their load-bearing function. Alignment of fractured metatarsals is important because dorsal or plantar displacement can lead to pain or functional disability by altering the transverse arch and load distribution. Dorsal angulation commonly occurs at the site of metatarsal fractures from the action of intrinsic muscles and toe flexors. This can contribute to metatarsalgia as a long-term consequence. Medial or lateral displacement, although less critical, can lead to the development of painful bony prominences or neuromas.

Clinical Features. Metatarsal shaft fractures cause weight-bearing difficulty and tenderness, which usually is maximal on the plantar surface. Axial compression of the involved toe is often painful, and ecchymosis usually appears within 12 hours of injury. Rotational alignment should be assessed by evaluating the position and plane of the involved digit.

Diagnostic Testing: Radiology. Standard radiographs are usually sufficient to diagnose metatarsal shaft fractures. Attention should be paid to displacement and angulation in the sagittal and mediolateral planes.

Management. Although local practice may vary, most undisplaced metatarsal shaft fractures of the second through fifth metatarsals are treated with a below-knee walking cast or boot for 2 to 4 weeks. Although not strictly necessary, pain may necessitate a period of nonweightbearing.

The great toe metatarsal needs more aggressive management because of its biomechanical role and the stresses imposed on it during gait. Nondisplaced first metatarsal fractures should be treated with casting for 4 to 6 weeks.[61] The patient should be nonweightbearing for at least the first 3 weeks, if not the entire period.

Reduction should be considered in any metatarsal shaft fracture with more than 3 mm of displacement or 10 degrees of angulation. Closed reduction, with toe traps and countertraction at the ankle, is often successful. Non–weight-bearing casting for 4 to 6 weeks should follow. The indications for open reduction are controversial but generally include the presence of compartment syndrome, unstable fractures, open fractures, fractures that have failed closed reduction, and multiple fractures. These are treated with fixation with Kirschner wires or plates.[61] In particular, displaced first and fifth metatarsal shaft fractures are commonly treated operatively. Major forefoot trauma, with crushing and multiple open metatarsal fractures, necessitates an aggressive approach, with staged operative management.

Disposition. Although nonurgent orthopedic follow-up is reasonable, most nondisplaced metatarsal shaft fractures are suitable for management without orthopedic referral. More urgent orthopedic consultation should be obtained for patients with multiple or displaced fractures. Complications are rare in nondisplaced or minimally displaced metatarsal shaft fractures. Complex regional pain syndrome can occur and may be related to the unnecessary use of non–weight-bearing casting.[62] Inadequate reduction, particularly in the sagittal plane, can lead to biomechanical problems and the formation of painful callosities or metatarsalgia. Malunion in the mediolateral plane, particularly if involving the first or fifth metatarsal, can lead to the development of pressure points, neuromas, or biomechanical problems. Delayed union, nonunion, compartment syndrome, and soft tissue complications occur uncommonly.

Metatarsal Head and Neck Fractures

Metatarsal head and neck fractures, although similar in pathophysiology and assessment to shaft fractures, are commonly multiple and often result from direct trauma. Nondisplaced fractures may be treated with a walking cast for 4 to 6 weeks. These fractures, however, are frequently displaced, with the distal fragment pulled in a plantar and lateral direction by the flexor tendons. Precise realignment of neck and head fractures is important to maintain the transverse arch. Although reduction may be successful with toe traps, instability is common, and operative fixation is required more commonly than with shaft fractures. Displaced fractures require consultation with an orthopedist or urgent outpatient follow-up. Nondisplaced fractures can be followed by orthopedics, sports medicine, or primary care. Complications are similar to those seen with shaft fractures.

Metatarsal Base Fractures

Pathophysiology. Isolated fractures of the first through fourth metatarsal bases are uncommon. Most are nondisplaced transverse fractures within 1 cm of the tarsometatarsal articulation and arise as a result of direct trauma. An indirect mechanism may suggest an occult Lisfranc injury. The most commonly encountered metatarsal base fractures occur at the fifth metatarsal.

Fifth Metatarsal. Fractures of the base of the fifth metatarsal are commonly divided into three types according to anatomic location (Fig. 51.20). Zone 1 fractures are tuberosity avulsion fractures. Zone 2 fractures occur at the level of the fourth-fifth intermetatarsal articulation. Zone 3 fractures are proximal diaphyseal stress fractures. The term *Jones fracture* is commonly understood to describe zone 2 injuries.

Zone 1, or tuberosity fractures, are the more common and benign of the fifth metatarsal fractures. The tuberosity, which is easily palpated over the lateral edge of the foot, is fractured by a sudden inversion of a plantar-flexed foot. The mechanism of fracture is an avulsion by the lateral band of the plantar aponeurosis, although it is commonly thought to result from avulsion by the peroneus brevis.[63]

Tuberosity fractures range from tiny flecks to lesions involving the entire tuberosity. They are usually extraarticular, although they may extend into the cubometatarsal joint. Often, these injuries masquerade as ankle sprains (see Box 51.2), making the fifth metatarsal base an important area to palpate in any twisting injury.

Zone 2, or Jones fractures, and zone 3 are more serious fractures, with a higher incidence of nonunion than in zone 1 fractures.[64,65] Jones fractures occur at least 15 mm distal to the proximal end of the bone and involve the fourth and fifth intermetatarsal joint. Diaphyseal fractures result from a combination of forces generated when a load is applied to the lateral forefoot in the absence of inversion. Zone 3 injuries commonly are the result of stress fractures.

Clinical Features. The assessment of metatarsal base fractures is similar to that described for fractures of the metatarsal shaft. Pain often is diffuse and difficult to localize in these injuries, with the exception of the easily palpable fifth metatarsal tuberosity. Passive inversion also may be painful with a fifth metatarsal base fracture.

Diagnostic Testing: Radiology. Standard radiographic views easily demonstrate most metatarsal base fractures. Radiographs should be carefully assessed for fracture angulation, displacement, and articular extension. If the fracture is intraarticular, an estimation of the percentage of articular surface involved is essential for determining management. In difficult cases, CT may be helpful.

With fractures of the first through fourth metatarsal bases, it is important to recognize the potential for a Lisfranc injury. A fracture of the second metatarsal base is virtually pathognomonic for occult tarsometatarsal joint disruption. In assessment for a fifth metatarsal base fracture, differentiation between the tuberosity and diaphysis is important (Fig. 51.20).[64] Standard ankle

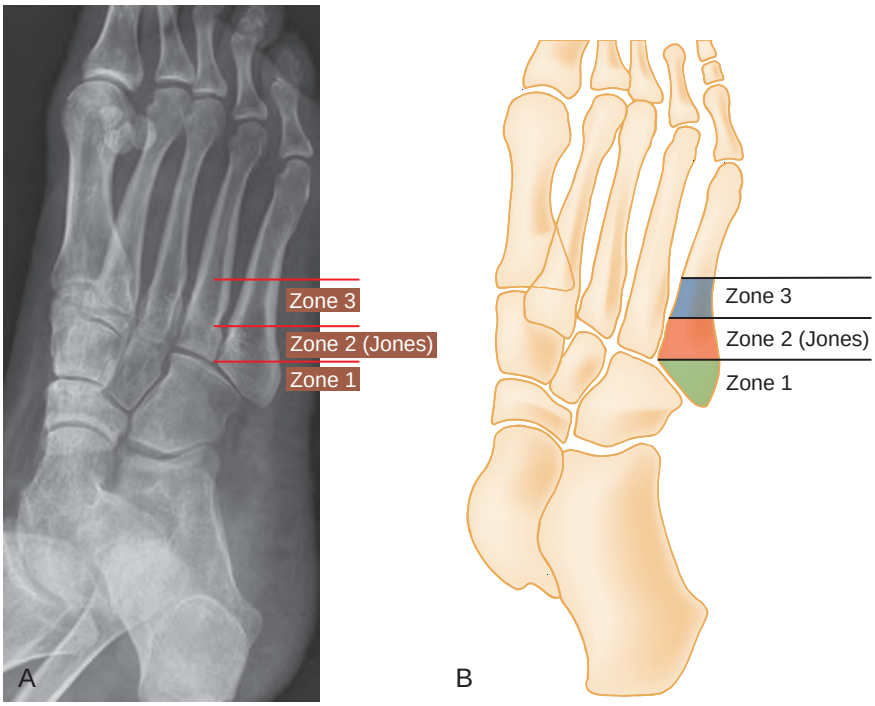

Fig. 51.20. Classification of fractures of the base of the fifth metatarsal. Zone 1 is a tuberosity avulsion fracture. Zone 2 (Jones fracture) occur through the fourth and fifth intermetatarsal articulation. Zone 3 fractures are distal to the articulation.

radiographs also demonstrate the fifth metatarsal base, and this area should be evaluated routinely.

Management. Nondisplaced extraarticular fractures of the first through fourth metatarsal bases usually are managed with a below-knee cast. Displaced fractures should be reduced and often require fixation. Intraarticular fractures, especially those of the first metatarsal, often lead to complications. Operative fixation may be required, even in nondisplaced, intraarticular, first metatarsal base fractures, if more than 25% of the articular surface is involved.

The management of fifth metatarsal base fractures depends on the type of fracture. Extraarticular tuberosity, or zone 1, fractures, regardless of their size or degree of displacement, heal well and are managed symptomatically with a walking cast for 2 to 3 weeks or stiff shoes.[63] Historically, intraarticular tuberosity fractures involving more than 30% of the articular surface or with more than 2 mm of displacement required fixation, although this is controversial.[63-66] Nondisplaced intraarticular fractures usually are treated initially with non–weight-bearing casting for 6 to 8 weeks, followed by radiographic reassessment.[63]

The management of zone 2 and 3 fractures remains controversial. Zone 2 fractures are usually treated with immobilization for up to 3 months, with operative consideration given to some fracture patterns and patient populations.[67] Others have recommended that zone 2 fractures be treated functionally, similar to zone 1 fractures.[65,66] Zone 3 fractures (progression of a stress fracture) may be treated with prolonged immobilization but often require operative management.[68] Displaced fifth metatarsal diaphyseal fractures usually are managed operatively.

Disposition. Because they are rare, and treatment varies, most first through fourth metatarsal base fractures require orthopedic assessment. Nondisplaced extraarticular fractures of the first through fourth metatarsal bases are suitable for orthopedic follow-up on an outpatient basis. Orthopedic consultation in the ED should be obtained in any other first through fourth metatarsal base fracture or if a Lisfranc injury is suspected.

All fifth metatarsal diaphyseal fractures (zones 2 and 3) should have outpatient orthopedic referral. Extraarticular and nondisplaced tuberosity (zone 1) fractures are suitable for primary care follow-up. Significant or displaced intraarticular, fifth metatarsal tuberosity fractures require orthopedic follow-up for consideration of operative repair.

Although fifth metatarsal fractures are seemingly minor injuries, approximately 30% of patients report pain, and 10% have persistent functional limitation at 1 year. Complications are rare in cases of fifth metatarsal tuberosity fractures, although fibrous nonunion of the fracture fragment can occur. Fifth metatarsal diaphyseal fractures are often complicated by delayed union, nonunion, or fracture recurrence because of poor healing subsequent to disruption of the metatarsal vascular supply. These complications occur in more than 50% of patients treated conservatively, often require aggressive surgical therapy, and have prolonged healing times.

Phalangeal Fractures

Pathophysiology. Phalangeal fractures are the most common forefoot fracture. The proximal phalanges are more commonly fractured than middle or distal phalanges. The proximal phalanx of the fifth toe is the most commonly injured. Fractures of the hallux often are displaced, whereas those of the lesser phalanges are often comminuted but are less commonly displaced.

Clinical Features. Although phalangeal fractures generally are considered minor injuries, they can lead to disabling sequelae. Patients present with acute pain and swelling of the affected toe, often with difficulty ambulating or wearing shoes. Examination may reveal tenderness, crepitus, and reduced range of motion. A subungual hematoma often is present if the distal phalanx is involved, and open fractures are common.

Diagnostic Testing: Radiology. As with metatarsal fractures, carefully assessed standard radiographic views are sufficient to demonstrate phalangeal fractures.

Management. Most phalangeal fractures are easily managed and heal well. Large and symptomatic subungual hematomas should be trephinated and, on rare occasions, nail bed repair may be required. Nondisplaced lesser phalangeal fractures should be stabilized by buddy taping, with placement of gauze between the splinted toes to prevent skin maceration. Phalangeal fractures often remain painful for 2 to 3 weeks until stabilized by callus. Use of a stiff shoe may be beneficial.

If significant displacement or angulation is present, reduction should be performed with manual traction or toe traps after digital block anesthesia. Moderate persistent angulation or displacement is acceptable if the clinical appearance and function of the toe remain satisfactory. Rarely, operative fixation of lesser phalangeal fractures is indicated, particularly in cases with severe rotatory deformity or open fractures requiring débridement.

Nondisplaced phalangeal fractures involving the hallux are treated by buddy taping, with a walking cast worn for 2 to 3 weeks if the toe is painful. Alternatives to standard casting techniques, such as the slipper cast, have also been described for phalangeal fractures. Displaced phalangeal fractures of the hallux require reduction. If the reduction is inadequate or unstable, operative fixation may be indicated. Unless completely nondisplaced, most intraarticular fractures involving the hallux are treated with operative fixation, although this has been controversial.

Disposition. In general, primary care follow-up is appropriate for phalangeal fractures. If displacement persists or causes cosmetic or functional concern, outpatient orthopedic referral is advised. Poorly reduced, or intraarticular hallux fractures should be splinted for urgent outpatient orthopedic follow-up. Complications of phalangeal fractures are uncommon. With intraarticular phalangeal fractures, particularly those involving the hallux, arthritis may be a late sequela. Symptomatic angular malunion and osseous deformity can occur with phalangeal fractures, and exostectomy is sometimes required.

Sesamoid Fractures

The sesamoids are two flat oval bones found in the tendon of the flexor hallucis brevis, under the head of the first metatarsal and, rarely, under the second to fifth metatarsal heads. Sesamoid fractures are uncommon, usually are caused by direct trauma or hyperextension of the great toe, and have been described in association with MTP joint dislocations. Stress fractures of the sesamoids also occur. A fracture should be differentiated from a bipartite sesamoid, which occurs in up to one-third of the population and also is more common on the medial aspect. Most sesamoid fractures heal without complication, with a below-knee walking cast for 3 to 4 weeks. Orthopedic consultation is suggested only for patients with nonunion or chronic pain.[69,70] This can be arranged by the primary care physician.

Metatarsophalangeal Dislocations

Pathophysiology. MTP joint dislocations can occur in any joint and in any direction but are uncommon injuries because of the protection most footwear provides and inherent stability of the MTP and IP joints. First MTP joint dislocations require large forces and usually result from MVCs. These injuries, which are frequently open, are usually dorsal dislocations of the distal component caused by hyperextension of the MTP joint. Associated sesamoid fractures may be present. Complex dislocations, in which the sesamoids or local tendons prevent closed reduction, can occur. Second through fifth MTP dislocations usually are medial or lateral displacements that occur when the toe strikes or hooks an object. The most common is a lateral dislocation of the fifth MTP joint.

Clinical Features. First MTP joint dislocations usually are obvious because the toe is angled upward, with dorsal and proximal displacement of the proximal phalanx. Rarely, the sesamoids are palpable dorsal to the metatarsal, indicating a complex dislocation. Dislocations of the lesser toes may be more subtle in presentation, and comparison with the uninjured foot may be helpful. Neurovascular compromise is rare.

Diagnostic Testing: Radiology. Dislocations of the MTP joint are well-visualized on standard radiographic views of the foot. Radiographs should be scrutinized for signs suggestive of a complex dislocation, such as the sesamoids lying between the two articular surfaces or dorsal to the metatarsal head.

Management. Most MTP joint dislocations, particularly of the lesser toes, are easily reduced with longitudinal traction after appropriate analgesia or local anesthesia. Dorsal dislocations of the first MTP joint can be more challenging and may require initial accentuation of the deformity, in addition to longitudinal traction, for reduction. Joint stability should be assessed and repeat radiographs obtained after reduction of an MTP joint dislocation. After reduction, a walking cast with a toe plate is worn for 3 weeks, followed by physiotherapy to ensure adequate range of motion. Alternatively, buddy taping and an aluminum splint can be used for immobilization.

Disposition. Most MTP joint dislocations can be managed without orthopedic consultation. If crepitus or obvious instability is present, or postreduction radiographs show joint incongruity or an intraarticular fracture, orthopedic consultation should be obtained for possible fixation. First MTP joint dislocations that are open, show radiographic evidence of complexity, or do not easily reduce require emergent orthopedic consultation. Very rarely, MTP joint dislocations of the lesser toes require open reduction.

Complications are rare after MTP dislocation. Arthritis and reduced range of motion, particularly of the hallux, may occur. Dislocations for which the diagnosis is delayed for more than 3 weeks often are not amenable to closed reduction and may require metatarsal head excision.

Interphalangeal Joint Dislocations

IP joint dislocations are much less common than MTP joint dislocations and are sometimes overlooked. Most IP joint dislocations occur in the great toe and are a result of axial loading. IP joint dislocations usually involve dorsal displacement of the distal component. Reduction is performed with longitudinal traction after digital block anesthesia. Initial accentuation of the deformity may be necessary if reduction is unsuccessful with traction. If the dislocation involves the great toe, a walking cast with a toe plate for 3 weeks is indicated after reduction. Lesser toes require only buddy taping. As with the MTP joint, complex dislocations involving the first IP joint can occur, and orthopedic consultation in the ED for open reduction may be necessary. Very rarely, lesser toe IP joint dislocations are not reducible with closed methods and will require open reduction.

Foot Pain

Perspective. Foot pain, particularly in the absence of obvious trauma, poses a diagnostic and therapeutic challenge. Although a definitive diagnosis is often difficult to obtain in the ED, a structured approach, with a thorough history and physical examination, aids in management and disposition. Although consultation in the ED is rarely required, orthopedic or sports medicine follow-up on an outpatient basis is indicated for select cases.

The history should elicit prior injury, with attention paid to patterns of activity and overuse, as well as reviewing relevant medical history. Pain, which may occur on a spectrum from acute to chronic, is best approached anatomically by localizing symptoms to the hindfoot, midfoot, or forefoot.

Hindfoot Pain. Hindfoot pain is a common complaint that usually is the result of overuse rather than trauma.[71] Bone pain in the hindfoot necessitates consideration of calcaneal or talar stress fractures. A calcaneal stress fracture may be suspected when pain is elicited on squeezing the calcaneus mediolaterally.

Most patients with hindfoot pain describe subcalcaneal heel pain, with plantar fasciitis being the most common diagnosis. The differential diagnosis includes fat pad atrophy, acute rupture of the plantar fascia, lateral plantar nerve compression, and tarsal tunnel syndrome.[71]

Plantar fasciitis is a common and painful diagnosis in which patients may present to the ED having difficulty ambulating. The plantar fascia is a tough layer of the sole that is functionally significant during foot strike and the early stance phase of walking. Plantar fasciitis is an overuse injury of insidious onset. Pain is classically felt on first weightbearing in the morning or after prolonged sitting. This progresses to persistent pain during activity. Tenderness is noted at the calcaneal insertion. The diagnosis of plantar fasciitis is clinical, and primary care follow-up is sufficient. Although there are many options, the mainstays of management of plantar fasciitis include activity and footwear modification, stretching, NSAIDs, and physiotherapy.[72]

Plantar fascial rupture is a tear of the origin of the plantar fascia at the calcaneus. This injury usually occurs during the push-off phase of gait. Swelling may be noted, and typically pain is elicited by passive dorsiflexion of the hallux. Treatment is nonsurgical, often with a period of cast immobilization for symptomatic relief.

Many tendons course through the hindfoot, particularly anteromedially, and tendinitis can occur (see Table 51.2). Other tendon pathologic conditions (eg, ruptures, dislocations, retinacular injuries) should be considered because they can result in significant functional disability.

Midfoot Pain. Isolated midfoot pain is less common than forefoot or hindfoot pain. Midfoot stress fractures, although uncommon, usually involve the navicular. A careful history and consideration of a low-energy ligamentous Lisfranc injury is important in patients with midfoot pain. Other causes of midfoot pain include symptomatic accessory bones, particularly the accessory navicular, os tibiale externum, and os peroneum.

Forefoot Pain. The forefoot is the site for a myriad of painful problems. Bunions, painful bursae, blisters, corns, calluses, hammertoes, and ingrown toenails all are diagnostically obvious but can pose therapeutic challenges. Many are the result of poor footwear or a biomechanical problem with the foot and respond to appropriate padding, avoidance of precipitants and, occasionally, surgical intervention.

Metatarsalgia is an often used, although loosely defined, term referring to pain in the region of the metatarsal heads.[73] This is a common presenting complaint, with many potential causes relating to biomechanics of the forefoot. Metatarsal stress fractures should be considered in the differential diagnosis for any unexplained forefoot pain. Flexor or extensor tendinitis also can produce metatarsal area pain. Arthritis, sesamoiditis, or a sesamoid stress fracture should be considered when pain occurs in the plantar area of the hallux. The term *turf toe* refers to MTP joint inflammation of the hallux resulting from repeated hyperextension. It usually responds to symptomatic measures but can be a debilitating injury in some athletes.

An important cause of unilateral metatarsalgia is a perineural fibrosis of the intermetatarsal plantar digital nerve, more commonly known as Morton's neuroma. This neuropathy usually involves the second-third or third-fourth intermetatarsal space, causing lancinating pain with weightbearing that can radiate to the toes and may be associated with paresthesias. Pain is reproduced when structures of the affected interspace are pinched or when the metatarsal heads are compressed together. Hence, pain may occur with tight-fitting footwear. Crepitus or a nodule may be palpable. Treatment ranges from footwear modification and physiotherapy to steroid injections and surgery for chronic and severe cases.[74]

Freiberg's disease is an osteochondrosis of the metatarsal head, usually involving the second metatarsal, and is another cause of pain in this area. Ingrown toenails are a common affliction that can occur in any toe, usually the hallux. Often, the abnormality is perpetuated by short nail trimming, which affords the opportunity for a spicule of nail to grow under the nail fold. Allowing the nail to grow out and providing local care usually will lead to resolution, although chronic or recurring ingrowth necessitates partial or complete excision of the nail and germinal ablation. Antibiotics are indicated if infection is present.

SPECIAL CONSIDERATIONS

Complex Regional Pain Syndrome

Complex regional pain syndrome is a condition involving pain in the presence of trophic changes and vasomotor instability from inappropriate sympathetic nervous system activity; it was previously termed *reflex sympathetic dystrophy*.[62,75] Complex regional pain syndrome occurs months after trauma, which may be major, as in a Lisfranc injury, or relatively innocuous. It produces pain of a diffuse burning, aching, or searing nature, together with evidence of vasomotor instability. Complex regional pain syndrome should always be considered in the differential diagnosis for chronic foot pain after trauma. Management is multifaceted, and usually is directed by a pain specialist.

Stress Fractures

Pathophysiology

Stress fractures can occur anywhere in the appendicular skeleton but are particularly common in the lower extremity. They are thought to occur as a result of extrinsic factors (eg, training volume, footwear, training surface) and intrinsic factors (eg, metabolic state, fitness, muscle endurance, anatomic alignment).[76] The so-called female athlete triad of disordered eating, menstrual disturbances, and low bone mineral density is known to be associated with stress fractures.[77]

It is useful to categorize stress fractures as being high risk and low risk based on the rate of complications, including delayed union, nonunion, and persistent functional limitation. High-risk stress fractures often occur in bones with a vulnerable vascular supply. In the lower extremity, high-risk stress fractures include the femoral neck, anterior tibia, medial malleolus, navicular, proximal fifth metatarsal, and sesamoid bones.[77]

Clinical Features

Although the history is variable, most stress fractures produce localized pain of insidious onset, usually with aching over a period of weeks. Initially, symptoms occur after athletic activities, but later they limit such activities. Often, a predisposing factor, such as a training regimen change, is present. A menstrual history

should be obtained in female patients because amenorrhea, often a result of overtraining, can predispose to stress fractures.

Physical examination may reveal swelling, point tenderness, or percussion tenderness. However, in most patients, these findings are absent, and the diagnosis is suspected by history alone.

Diagnostic Testing: Radiology

Initial plain radiographs are commonly normal because bone reaction in stress fractures depends on the length of time from symptom onset. Radiographic abnormalities in the metaphyses can take up to 4 weeks to develop, and those in the diaphyses can take 6 weeks. Although plain radiographs have low sensitivity for stress fractures, their specificity is high. The three important findings are periosteal new bone formation, endosteal thickening, and a radiolucent line.

Because only 50% of patients develop plain radiographic abnormalities, the diagnosis of a stress fracture can be easily missed. Traditionally, plain radionuclide bone scanning was the imaging modality of choice for stress fractures. Bone scans are nonspecific but extremely sensitive, usually showing abnormal uptake within 24 hours of injury. More advanced imaging techniques such as CT-SPECT and MRI have gained value in diagnosing stress fractures.[30]

Management

Athletic stress fractures are overuse injuries and necessitate an evaluation of training habits, equipment, and techniques. Most low-risk foot and ankle stress fractures resolve in 4 to 6 weeks with limitation of impact activities as guided by pain; most can remain weight-bearing and do not require immobilization unless symptoms are severe. High-risk stress fractures, including the anterior tibia, medial malleolus, navicular, base of fifth metatarsal, and sesamoids, require more aggressive management.

High-risk stress fractures of the foot and ankle should be treated with immobilization and nonweightbearing under the guidance of a sports medicine or orthopedic surgery specialist. High-risk stress fractures frequently are managed surgically, particularly those of the anterior tibia.

Disposition

Patients with confirmed low-risk stress fractures can be managed by primary care and can be weight-bearing as tolerated, with activity modification. If required by symptoms, these patients can be placed in a short walker boot for comfort. Patients with clinically suspected but unconfirmed stress fractures can be referred to sports medicine or orthopedic consultants to arrange further diagnostics, as indicated. All patients with high-risk stress fractures should be made nonweightbearing and immobilized, with arrangements made for outpatient orthopedic or sports medicine consultation.

Tendon Injuries

Acute tendon ruptures in the foot, apart from the Achilles and posterior tibial tendons, are rare. Although isolated ruptures of the flexor hallucis longus and anterior tibial tendons have been described, most tendon transections are the result of lacerations (see Table 51.2).

Orthopedic or plastic surgery consultation is indicated for any patient known or suspected to have a tendon injury in the foot. It is clear that flexor and extensor hallucis longus tendons should be repaired primarily; however, the need to repair other tendons is controversial. In general, an attempt should be made to repair any tendon transection, because apparently minor injuries can lead to complications, such as claw deformity. Tendon injuries associated with innocuous lacerations are easily missed if not carefully sought. Splinting for 2 to 6 weeks is required after tendon repair.

Crush Injuries, Amputations, and Major Vascular Injuries

Rapid assessment, stabilization, and emergent consultation are priorities in the ED management of a major crush injury, amputation, or vascular injury of the foot. The injured limb is handled gently and can be irrigated with sterile saline solution to remove debris. The use of other irrigating solutions, exploration, or débridement, even if done carefully, is contraindicated. Antibiotics should be administered, as for any open fracture. The injured extremity can be dressed with well-padded, saline-soaked gauze, and the patient should receive appropriate analgesia. Compartment syndrome should be considered in all crush injuries.

Compartment Syndrome

Principles of Disease: Pathophysiology

Compartment syndrome is defined as an increase in pressure within a confined osseofascial space that impedes neurovascular function, resulting in tissue damage; it is discussed in detail in Chapter 42. By convention, four compartments—medial, central, lateral, and interosseous—are described in the foot, although as many as nine have been identified.[78] Foot compartment syndrome is relatively rare, accounting only for an estimated 5% of limb compartment syndrome cases.[79] As elsewhere, compartment syndrome in the foot constitutes a surgical emergency.

Pedal compartment syndrome is most commonly caused by high-energy injuries, such as crush injuries, Lisfranc fractures, calcaneus fractures, and midfoot or forefoot trauma. Pedal compartment syndrome after an ankle sprain has also been reported. Damage is related to the duration and magnitude of compartment pressure increase and the arteriovenous gradient. Compartment syndrome can develop anywhere from 2 hours to 6 days after an insult, although the peak incidence is at 15 to 30 hours.

Clinical Features

Compartment syndrome typically causes pain out of proportion to that expected for the injury. The pain is not decreased by immobilization and can be described as a feeling of tautness within the foot. Physical examination may reveal tense swelling and sensory deficits. Pain is exacerbated by any movement (active or passive) that stretches the muscles of the involved compartment. Peripheral pulses and capillary refill usually are initially normal in compartment syndrome and thus offer no reassurance when present. The presence of an open wound does not guarantee that all compartments are decompressed.

Diagnostic Testing: Special Procedures

Definitive diagnosis of compartment syndrome is by measurement of intracompartmental pressure. Pressure greater than 30 mm Hg is generally considered an indication for emergent decompression. Compartment syndrome can occur at lower pressures in hypotensive patients.[78] More details on the pathophysiology, diagnosis, and treatment of this condition can be found in Chapter 42. Needle localization and distinguishing foot compartments is challenging. For this reason, and because of its importance in surgical decision making, measurement of pedal compartment pressures usually should be left to an orthopedic surgeon.

Management

Early identification and prevention of further tissue damage are important considerations in any patient with a mechanism consistent with the development of compartment syndrome. Circumferential bandages and casts should be avoided during early management. In diagnosed or suspected cases of compartment syndrome, the limb should be positioned at the level of the heart. Limb elevation beyond this point is contraindicated because it would decrease arterial flow, thereby narrowing the arteriovenous pressure gradient.

Disposition

If compartment syndrome is suspected, emergent orthopedic consultation is indicated for consideration of decompressive fasciotomy.

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KEY CONCEPTS

- The Ottawa Ankle and Foot Rules should be used to evaluate for the need for x-rays in ankle and foot injuries.
- CT scans are indicated for negative x-rays of the ankle and foot when a high clinical concern of fracture exists.
- Ankle dislocations with obvious vascular compromise should be reduced promptly, before radiographs are obtained.
- The entire fibula should be examined if an isolated medial malleolar fracture is present to rule out a proximal fibular (Danis-Weber type C or Maisonneuve) fracture.
- Osteochondral lesions of the talar dome, nondisplaced fractures of the lateral posterior process of the talus, and fracture of the anterior process of the calcaneus are important to include in the differential diagnosis of presumed ankle sprains.
- Patients discharged with a diagnosis of ankle sprain should be encouraged to seek outpatient follow-up should ankle pain and swelling persist for longer than 2 weeks.
- Patients with Achilles tendon rupture are still capable of weak plantar flexion. Ultrasound may be used to confirm the diagnosis if clinical uncertainty exists.
- A Lisfranc injury should be considered with any fracture or dislocation in the tarsometatarsal region, particularly with fractures of the second metatarsal base. When suspicion for a Lisfranc injury is high, and plain radiographs and CT scans are negative, immobilization and orthopedic referral are indicated.
- Fifth metatarsal tuberosity (zone 1) fractures should be carefully differentiated from diaphyseal fractures. Orthopedic referral is indicated for zones 2 and 3 fractures.
- Stress fracture should be considered in patients with long-standing foot pain, particularly if symptoms are in the metatarsal region. This may be diagnosed by plain radiography, CT scanning, or radionuclide bone scanning.
- Compartment syndrome may occur in any of the four major compartments of the foot. Diagnosis is by measurement of the intracompartment pressure.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 51: QUESTIONS & ANSWERS

51.1. A middle-aged farmer presents after an accident with a plow with a crushed open distal tibia fracture. What is the appropriate antibiotic choice?
A. Cefazolin
B. Cefazolin and gentamycin
C. Cefazolin, gentamycin, and penicillin G
D. Ciprofloxacin
E. Pen VK and cephalexin

Answer: C. Because the patient has a probable soil contaminant in his open fracture, he will need the addition of penicillin G to cover *Clostridium perfringens*. For low-energy injuries with mild to moderate contamination, a broad-spectrum cephalosporin is usually sufficient. Heavily contaminated wounds require the addition of gram-negative bacterial coverage, typically with an aminoglycoside. Adding penicillin G as a third antibiotic is necessary for farm- or soil-related crush injuries.

51.2. A 30-year-old woman complains of pain in the ankle and difficulty walking after attempting a jump shot while playing basketball. Her past medical history includes a recent urinary tract infection, for which she is taking ciprofloxacin. On physical examination, her ankle joint is not swollen, there is a palpable defect 4 cm proximal to the posterior ankle, and she has weakened plantar flexion. Which of the following is true concerning her condition?
A. Boehler's angle should be less than 20 degrees.
B. In a seated position, squeezing the calf causes foot dorsiflexion.
C. It requires a stress radiograph view.
D. On the radiograph, there may be an opacification at Kager's triangle.
E. Talofibular ligament laxity is present.

Answer: D. The patient has a ruptured Achilles tendon. On examination, a visible and palpable tendon defect 2 to 6 cm proximal to the calcaneal insertion may be present. In some cases of complete Achilles tendon rupture, weak plantar flexion may still be present because of the actions of the tibialis posterior, toe flexors, and peroneal muscles. When the Achilles tendon is intact, squeezing the calf muscles should cause passive plantar flexion of the foot (Thompson test). Lateral radiographs of the ankle may confirm rupture by showing opacification of the triangular fatty tissue–filled space anterior to the Achilles tendon (Kager's triangle) or an irregular contour and thickening of the tendon.

51.3. A 24-year-old patient presents with pain in the left foot after a twisting injury. On physical examination, you find no point tenderness on the medial or lateral distal 6 cm of the malleoli, no proximal fibular tenderness, and no navicular tenderness. Which of the following physical findings would necessitate radiographs being taken in the emergency department?
A. Inability to ambulate to the car
B. Laxity on anterior drawer testing
C. Moderate swelling with ecchymosis
D. Tenderness at the base of the fifth metatarsal
E. Tenderness over the deltoid ligament

Answer: D. The Ottawa Ankle Rules advise ankle radiographs when any of the following are present: tenderness at the posterior edge of the distal 6 cm or tip of the lateral malleolus, tenderness at the posterior edge of the distal 6 cm or tip of the medial malleolus, or inability to bear weight for at least four steps immediately after the injury and at the time of evaluation. Foot radiographs in the setting of blunt ankle trauma are advised when any of the following are present: tenderness over the navicular, tenderness at the base of the fifth metatarsal, or inability to bear weight for at least four steps immediately after the injury and at the time of evaluation.

51.4. In what order are ligaments injured with inversion ankle injuries?
A. Anterior talofibular, calcaneofibular, and lateral talocalcaneal ligaments
B. Anterior talofibular, posterior talofibular, and tibiofibular syndesmotic ligaments
C. Calcaneofibular, tibiofibular syndesmotic, and deltoid ligaments
D. Posterior talofibular, anterior talofibular, and calcaneofibular ligaments
E. Posterior talofibular, calcaneofibular, and deltoid ligaments

Answer: A. Usually, the anterior talofibular ligament is injured first, followed by the calcaneofibular ligament if the deforming forces are sufficiently great. In addition, the lateral talocalcaneal ligament may be stressed with an inversion injury, leading to avulsion fractures at either of its attachment sites. Isolated calcaneofibular or posterior talofibular ligament injuries are rare.

51.5. A 20-year-old man presents complaining of foot pain after a motor vehicle collision. Radiographs show a fracture of the base of the second metatarsal. What is the most appropriate next step in the patient's management?
A. Apply a hard-soled shoe.
B. Buddy tape second toe and arrange primary care follow-up.
C. Discharge on crutches with progressive weightbearing.
D. Obtain stress radiographs.
E. Splinting and orthopedic referral should be instituted if not the foot is improved in 2 weeks.

Answer: D. Findings suggestive of a Lisfranc injury include widening between the first and second or second and third metatarsal bases or any fracture around the Lisfranc joint. A fracture of the second metatarsal base is virtually pathognomonic of occult tarsometatarsal joint disruption. Significant Lisfranc injuries are usually treated with closed reduction and internal fixation with percutaneous Kirschner wires. This is followed by a non–weightbearing cast for 12 weeks and an orthotic for 1 year. Treatment of a Lisfranc sprain usually involves immobilization for 6 weeks in a below-knee walking cast.

51.6. Pain on the medial aspect of the heel that is worse in the morning is suspicious for which of the following disorders?
A. Compartment syndrome
B. Foot sprain
C. Osteoarthritis of the ankle
D. Plantar fasciitis
E. Septic arthritis

Answer: D. Plantar fasciitis, an overuse injury of insidious onset, usually begins with pain on first weightbearing in the morning or after prolonged sitting. This progresses to persistent pain during gait. Pain and tenderness are localized to the medial aspect of the heel.

51.7. A 28-year-old man was working on a roof when he slipped and fell to the ground feet first. He presents with his right leg shortened and significant ankle swelling. Ankle radiographs show a comminuted distal tibial metaphysis fracture. Which of the following statements regarding this injury is false?
A. Arthrodesis may be required.
B. It has a high association with concomitant injuries.
C. It has a low rate of complications.
D. Orthopedic consultation for open reduction and internal fixation (ORIF) is necessary.
E. Shear forces increase fracture comminution.

Answer: C. The primary deforming force of a pilon fracture is one of axial compression, and the position of the foot at the time of injury determines the fracture location and pattern. Shear forces may cause increased comminution and fragment displacement with more extensive soft tissue injuries. Complications are common with pilon fractures, particularly in more severe injuries. Some patients with pilon fractures ultimately require arthrodesis.

CHAPTER 52

Wound Management Principles

Barry C. Simon | H. Gene Hern, Jr.

PRINCIPLES

The goals of emergency wound treatment are to restore function, repair tissue integrity with strength and optimal cosmetic appearance, and minimize risk of infection. Risk of infection depends on the location, mechanism, host, and care. The risk for a clean facial wound produced by incision is less than 1%, whereas a dirty crush injury to the lower extremity may have more than a 20% risk. Wound infection generally results in delayed healing, decreased strength, and a poor cosmetic result. These facts highlight the need for high-quality wound care. Understanding the biology of wound healing and the technical aspects of wound treatment facilitates emergency management of these patients.

Emergency clinicians must also be aware of the medicolegal risk associated with soft tissue injuries. Including injuries to the hand, wound-related complaints are the fourth most common cause of malpractice claims against emergency clinicians. Missed foreign body, wound infection, and missed tendon or nerve injury are the most common complications leading to these claims.

Anatomy of Skin and Fascia

An understanding of skin anatomy leads to better appreciation of wound closure concepts and techniques. The skin is a complex organ that protects the body against bacterial invasion and ensures thermoregulation. The skin also helps to regulate water content and register sensory stimuli.

The skin and fascia vary in thickness from 1 to 4 mm, depending on the part of the body. The epidermis, the outermost layer, is several cell layers thick. The most important parts of the epidermis are the stratum germinativum (basal layer), where new cells originate, and the stratum corneum, the outermost cell layer that gives the skin its cosmetic appearance. The layer of skin directly beneath the epidermis is the dermis. The much thicker dermis is primarily composed of connective tissue. The dermis is the key layer for the ultimate healing of skin wounds. Optimal healing and minimal scar formation depend on the removal of debris and devitalized tissue from the dermis. The dermis also functions to anchor sutures placed percutaneously or subcutaneously.

The superficial fascia lies directly beneath the dermis and encloses the subcutaneous fat. This space must be irrigated and débrided to decrease the risk of infection. The deep fascia lies beneath the fat and is a strong, off-white sheath that covers and protects the underlying muscles and helps prevent superficial infection from spreading to deeper tissues. The deep fascia must be closed to maintain its protective and functional roles.

Wound Biology

Normal wound healing is a well-choreographed sequence of biologic events. It is described as an orderly process, but it actually represents multiple phenomena that occur simultaneously. These events include coagulation, inflammation, collagen metabolism, wound contraction, and epithelialization. Maintaining the balance of these events is crucial for normal healing. Delaying any of the stages may result in a weak closure and dehiscence. Prolonging segments of the process may affect the ultimate scar appearance.

Soon after tissue integrity is altered, the process of coagulation begins. Platelet release factors initiate and enhance a response from inflammatory cells. Capillary permeability increases to allow white blood cells to migrate into the wound. Neutrophils and monocytes act as scavengers to rid the wound of debris and bacteria. Monocytes transform into macrophages, which seem to have a major role in subsequent healing phenomena. In addition to providing wound defense, macrophages release chemotactic substances, signaling other monocytes to stimulate fibroblast replication and trigger neovascularization.

Collagen is the principal structural protein of most tissues of the body. Normal tissue repair depends on collagen synthesis, deposition, and cross-linking. Fibroblasts synthesize and deposit collagen compounds 48 hours after injury. Immature collagen is highly disorganized because it has a gel-like consistency.

After a series of enzymatic processes, characteristic fibrils are produced. Subsequent intermolecular cross-links are responsible for a major portion of the strength of the collagen fibril. The entire process depends on tissue lactate and ascorbic acid and is directly related to tissue arterial carbon dioxide partial pressure. In the absence of vitamin C, prolyl and lysyl hydroxylase do not activate, and oxygen is not transferred to proline or lysine. Underhydroxylated collagen is produced, and characteristic collagen fibers are unable to form. Wound healing is poor, and capillaries are fragile. Without oxygen to hydroxylate proline and lysine, a local condition resembling scurvy tends to occur.

Under normal conditions, collagen synthesis peaks by day 7, coincident with rapid increases in tensile strength. The healing wound has the greatest mass at 3 weeks but remodels itself during the next 6 to 12 months. However, the wound achieves less than 15% to 20% of its ultimate strength by 3 weeks and only 60% by 4 months.

Wound contraction is the movement of whole-thickness skin toward the center of the skin defect. Immediately after injury, the wound edges retract and increase the size of the defect. Normal skin tension along the lines of minimal tension produces this

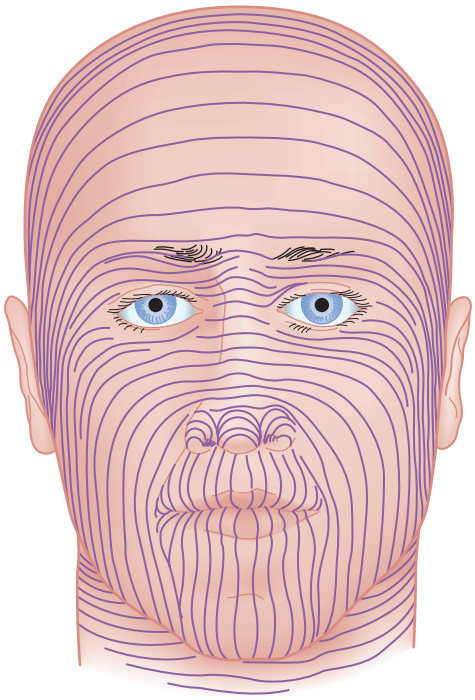

Fig. 52.1. Skin tension lines of the face. Incisions or lacerations parallel to these lines are less likely to create widened scars than those that are perpendicular to these lines. (Adapted from Simon R, Brenner B: Procedures and techniques in emergency medicine, Baltimore, 1982, Williams & Wilkins; as published in Trott A: Wounds and lacerations: emergency care and closure, ed 2, St Louis, 1997, Mosby.)

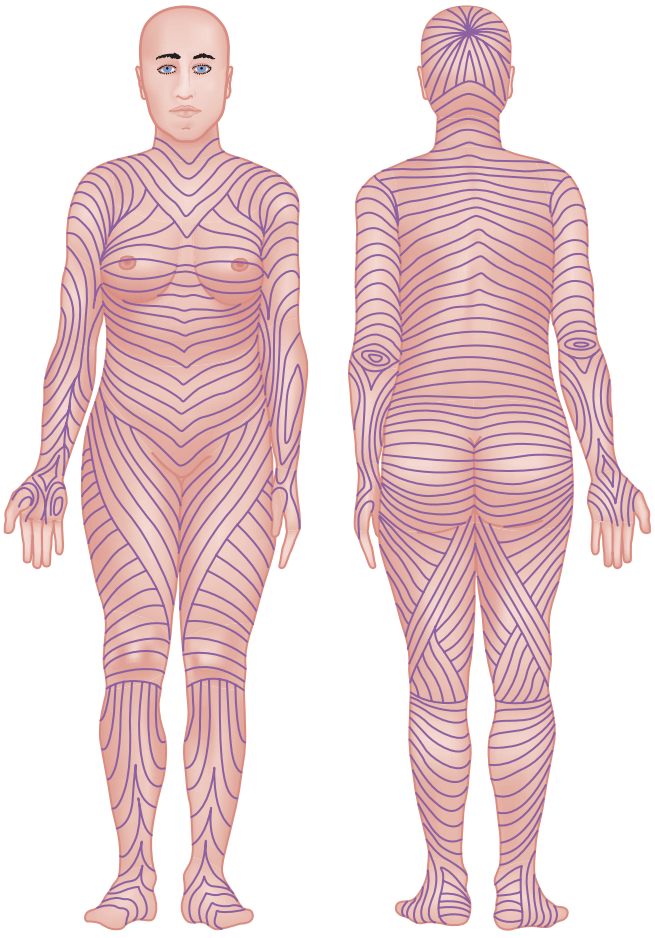

Fig. 52.2. Skin tension lines of the body surface. (Adapted from Simon R, Brenner B: Procedures and techniques in emergency medicine. Baltimore, 1982, Williams & Wilkins; as published in Trott A: Wounds and lacerations: emergency care and closure, ed 2, St Louis, 1997, Mosby.)

retraction (Figs. 52.1 and 52.2). Wounds perpendicular to these lines are under greater tension and result in a larger scar.

During the next 3 or 4 days, the wound size shrinks as its edges move toward the center. This phenomenon is independent of epithelialization, and the presence of collagen is not necessary for it to occur. This process is considered beneficial to healing and should not be confused with contracture that results from scar shortening.

Contracture becomes more apparent when the normal healing process is prolonged. The effect is a disfiguring hypertrophic scar. Optimizing the duration of the inflammatory phase and minimizing wound tension help to produce a more "appealing" scar.

Epithelialization is a mechanism in the healing process whereby epithelial cells migrate across the wound. Mitosis appears at the wound edge near the basal cell layer within hours of injury. Eschar or other debris impedes this process. When a wound is properly cleansed and débrided and kept moist and protected, epithelialization proceeds at a maximum rate.

In a surgically repaired laceration, epithelialization bridges the defect by 48 hours. The new tissue proceeds to thicken and grow downward, beginning to resemble the layered structural characteristics of uninjured epidermis within 5 days. Simultaneously, keratin formation loosens the overlying scab.

Biomechanical Properties of Skin

Various forces (lines of tension) exist as a result of skin elasticity from collagen fibers. These static forces may vary more than fivefold with the respective area of body skin surface, but the static tension of a given area of skin remains constant. These static forces are shown clinically by the gaping of wounds after incision. The magnitude of static skin tension is directly related to ultimate scar width.

Uneven, jagged wounds have greater surface area than do linear lacerations. The skin tension is distributed over a greater area and is less per unit length of tissue. Meticulous reapproximation of the jagged edges results in a more appealing scar. Sharp débridement, converting a jagged wound to a linear laceration, is often unwise because it may cause too much tissue loss and produce a wider, more visible scar. Skin forces produced by muscular contraction and movements of flexion and extension influence healing and scar size.[1] These dynamic forces are greatest where skin elasticity is necessary for function. Lacerations parallel to skin folds, lines of expression, and joints do not impair function or produce unattractive scars. Wounds that traverse the skin lines heal with conspicuous scars and may impair function. Knowledge of these lines and forces is necessary for optimal wound repair. In addition, the patient should be educated about wound healing and scarring potential.

CLINICAL FEATURES

History

A detailed history should be obtained as part of routine wound evaluation. Serious complications can result when basic information is not obtained. If the patient has significant peripheral vascular disease, is immunocompromised, or has a high risk of a retained foreign body, wound care decisions may be changed. Essential historical information includes past medical history, mechanism and setting of injury, and tetanus status.

BOX 52.1

Risk Factors for Wound Infection

1. Location: Leg and thigh, then arms, then feet, then chest, then back, then face, then scalp
2. Contamination with devitalized tissue, foreign matter, saliva, or stool
3. Blunt (crush) mechanism
4. Presence of subcutaneous sutures
5. Type of repair: Risk greatest with sutures > staples > tape
6. Anesthesia with epinephrine
7. High-velocity missile injuries
8. Diabetes

Risk Factors

Risk factors for wound morbidity include prolonged time since injury; crush mechanism; deep wounds longer than 5 cm; age of the patient; high-velocity missiles; location on lower extremities; and contamination with saliva, feces, soil, or other foreign matter (Box 52.1).Three hours after acute trauma, bacteria proliferate to a level that may result in infection. Standard wound care guidelines for routine wound care recommend closure within 8 to 12 hours of injury yet new data suggests that timing is less important than the other risk factors.[1] All risk factors must be considered to optimize wound care, and flexibility is required. Lacerations produced by fine cutting forces resist infection better than crush injuries. Reduction of blood flow to wound edges in the latter may increase the infective concentration of bacteria by a hundredfold. High-velocity missile injuries produce damage remote from the missile tract. The extent of injury may not be apparent for several days. Clean, finely cut lacerations on the face may be safely closed in some patients 24 or more hours after injury, whereas blunt lacerations to the leg or thigh may be treated with delayed primary closure as early as 4 to 6 hours after injury. For sutured wounds, location appears to have the strongest association with infection. Lacerations repaired on the leg and thigh may have an infection rate greater than 20%, those on the torso and other extremities greater than 10%, and those on the face and scalp less than 4%.

Optimal physical assessment of wounds requires patience, diligence, and an organized approach. Wound closure decisions are individualized for each laceration and each patient. In addition to the acute history, host specific data will influence management decisions: (1) immunocompetence of the host, (2) physical characteristics of the host (eg, peripheral vascular disease), and (3) structural defects that invite bacterial seeding (eg, damaged or prosthetic heart valves).

Physical Examination

Physical examination errors are minimized with optimal visualization and anesthesia. When the injury occurs on an extremity, use of a sphygmomanometer may help to ensure a bloodless field. The blood pressure cuff is placed proximal to the injury, and the extremity is elevated above the heart for at least 1 minute. Exsanguinating the extremity may be hastened by wrapping the limb tightly with an Ace bandage, beginning distally and ending at the base of the cuff. The sphygmomanometer is inflated to a pressure greater than the systolic pressure of the patient. Although this process causes the patient significant discomfort after 1 minute, the cuff can safely remain inflated for 2 hours. Alternatively, a peripheral nerve block or Bier block should be used if inflation longer than several minutes is contemplated.

A thorough examination of the wound requires that the tissues be adequately anesthetized. Subcutaneous tissues quickly reapproximate after injury, giving the appearance of a shallow wound. In addition, significant subcutaneous swelling lends to this appearance and renders examination of the laceration more difficult, as in wounds of the scalp and face. Careful probing and examination are needed to avoid missing damage to structures deep to the skin and subcutaneous tissue. This warning is more crucial for wounds on the distal aspects of upper and lower extremities. Finger lacerations are rarely gaping, but crucial structures (eg, tendons, nerves, and vessels) are often damaged. The examiner must pry the wound margins apart, ensure a blood-free field, and examine the tissues as the digit or extremity is placed through range of motion. The injured section of tendon may have been in a different state of tension and in a more proximal or distal location at the time of injury. Wounds that cannot be explored adequately and wounds with probable trauma to underlying tissues or with foreign matter require additional studies. It may be appropriate to extend the laceration to enable improved visualization of wound depth and extent.

Sterile gloves may not be a necessary part of wound closure. Although data are limited, one study found that the use of sterile gloves makes no difference with respect to the incidence of infection. However, clean nonsterile gloves should be worn to offer some protection for both the patient and the provider.[2]

No single method can guarantee the identification and removal of all foreign matter from wounds. The key is to document all efforts and to explain to the patient the possibility of a foreign body. Physical examination with wound exploration will discover about 78% of foreign bodies; plain radiography will detect glass foreign bodies in about 75% of cases, metal in 99%, and wood in 7%.[3] Good follow-up can protect the patient as well as the health care provider.

DIAGNOSTIC TESTING

As noted earlier, attempts to visualize foreign matter by standard radiography are not as helpful as might be expected. The radiodensity of an object depends on the relative density of the matter and the adjacent tissue. Pieces of glass more than 1 mm thick are visible when appropriate views are ordered. Many organic substances, such as wood, are not visible on plain films, but specifically requested soft tissue views may increase the yield. A radiolucent shadow may be seen on close inspection, because the foreign substance displaces tissue in its path. Xerograms are better than plain radiography but still miss some plastics and organic matter. A computed tomography (CT) scan is excellent for identifying all foreign substances but is expensive and results in exposure to radiation. Ultrasonography is a good technique, but the small size of many foreign bodies and pockets of air, edema, pus, and some calcifications may produce confusing echoes, limiting its clinical usefulness. When simpler, standard methods fail to locate a foreign body that is likely or definitely present, we recommend that ultrasonography or a CT scan should be considered.[3]

MANAGEMENT

Anesthesia

After an appropriate neurovascular examination is documented, the involved tissue should be anesthetized. Careful physical examination and thorough cleansing, irrigation, and débridement require that the patient be free of pain. Regional anesthesia may be preferable for wounds innervated by one superficial nerve. Injections at the wound site produce swelling and further distortion of landmarks. With a regional block, more than one laceration may be repaired in the same nerve distribution without

additional anesthesia. Lacerations on the face, hands, fingers, feet, and toes and in the mouth are often well suited for regional anesthesia.

Anesthetic Agents

Lidocaine (Xylocaine) is the most common agent used for local and regional anesthesia. It is safe and fast acting. Onset of action for direct infiltration occurs within seconds, and the effects last 20 to 60 minutes. When lidocaine is administered as a regional nerve block, onset occurs in 4 to 6 minutes and the effects generally last 75 minutes, although the block may remain effective for 120 minutes. A 1% lidocaine solution contains 10 mg/mL. It is safe to use 3 to 5 mg/kg, not exceeding 300 mg at a single injection. More volume can be added safely every 30 minutes. When epinephrine is added, the resulting vasoconstriction prolongs the effect for 2 to 6 hours, and the safe dose is increased to 5 to 7 mg/kg. However, the addition of epinephrine has been shown to delay healing and lower resistance to infection. Lidocaine with epinephrine should be avoided in wounds with higher risks of infection and when tissue viability is of concern. Traditional teaching has been to avoid epinephrine in the fingers and toes because of the risk of vasoconstriction in small arterioles. However, recent literature suggests that with careful screening, epinephrine can be safely used in digital blocks. Digital artery vasospasm, accidentally induced by local injection of epinephrine, can be reversed successfully with a local injection of 0.5 to 2 mg of subcutaneous phentolamine or application of topical nitroglycerin.

Bupivacaine (Marcaine) provides anesthesia that is equal to that of lidocaine. Onset of action is slightly slower than that of lidocaine, but the duration of anesthesia is four to eight times longer.[4] These benefits suggest that bupivacaine is the preferred local anesthetic agent for the care of most wounds. In adults, the maximal reported safe dose is approximately 2.5 mg/kg without epinephrine and 3.5 mg/kg with epinephrine. The dose can be repeated every 3 hours, not exceeding a total of more than 400 mg in a 24-hour period. The maximal intraoral dose is 90 mg.

Local injection of lidocaine should be done with a 27-gauge needle; the slower the injection, the less pain produced. The rate of injection through a 30-gauge needle is far too slow, and the thin needle is difficult to control. A 25-gauge needle is acceptable, but the more rapid injection can result in greater patient discomfort. The needle should be introduced through the cut margin to minimize the pain of the injection. Concerns of spreading bacteria into the adjacent uninvolved tissue and increasing the frequency and severity of wound infections are unfounded. The pain of injecting lidocaine can be ameliorated with the addition of bicarbonate to buffer the solution. The shelf life of the lidocaine-bicarbonate mixture decreases, but it remains effective for 1 week at room temperature and for 2 weeks if refrigerated. Adding sodium bicarbonate in a 1:10 volume ratio to lidocaine (1 mL bicarbonate and 10 mL lidocaine) decreases the pain of injection without compromising the quality of anesthesia. A much smaller dose of bicarbonate is added to bupivacaine because the alkalinization results in precipitation. A 1:100 volume ratio (0.1 mL of bicarbonate and 10 mL of bupivacaine) has been found to be effective. Warming the anesthetic solution is also an effective means of decreasing the pain of injection.

Topical anesthesia may be an effective painless alternative. Studies show that a combination of lidocaine (4%), epinephrine (0.1%), and tetracaine (0.5%) (LET) can function effectively on skin lacerations, especially on the face and scalp.[20,21] LET may be administered by soaking a cotton ball with 3 mL of the combined solution and applying it to the wound for 20 minutes. A gel formulation is available and may be preferred, because it's easier to control and to limit run off and inadvertent contact with mucous membranes. The duration of action is 45 to 60 minutes following the removal of the gel from the wound. Toxicity is rare when the dose administered is no more than 3 cc and mucous membranes are avoided. Potential toxic effects of lidocaine and tetracaine are related to the cardiovascular and central nervous systems. Cardiovascular effects may include arrhythmia, ectopy, decreased contractility, and cardiac arrest. Central nervous system toxicity may include headache, irritability, restlessness, blurred vision, and seizures. With use of a topical anesthetic, time to repair is reduced, patient acceptance improves, and landmarks are left undisturbed. If additional anesthesia is required, the pain of the subsequent injection is lessened by the topical anesthesia.[5]

Although LET has been found to be very safe, weight-based dosing has been recommended for children weighing less than 17 kg. Adminstering a maximum of 0.175 mL/kg of LET will prevent the application of more than 5 mg/kg of lidocaine. No cases of methemoglobinemia have been reported, but given the small risk associated with tetracaine extra caution is advised in neonates.

Tetracaine, adrenaline (epinephrine), and cocaine (TAC) was the original topical anesthetic solution. This combination is as effective as LET on the face and scalp and more effective elsewhere on the body. However, the risk of complications is greater, and the complexities tied to the handling of cocaine limits its utility.

Eutectic mixture of local anesthetics (EMLA) is a cream used to produce anesthesia of wounds and intact skin. The active ingredients are lidocaine (2.5%) and prilocaine (2.5%). The micron-sized particles of the cream are designed to penetrate layers of the skin to lessen the pain of needle penetration. Studies have demonstrated efficacy in venipuncture, immunization administration, lumbar puncture, and laceration repair. Peak effect requires about 1 hour and continues for 30 to 60 minutes after removal of the cream.

Allergy

Allergy to local anesthetics is uncommon. Two distinct groups of "caine" anesthetics exist. The esters include procaine, tetracaine, and benzocaine. The second group, including lidocaine and bupivacaine, belong to the amide family. Allergy to the esters is uncommon. True allergy to agents in the amide family is rare.

The subject of allergy is complicated further, because multidose vials contain the preservative methylparaben, an ester related structurally to anesthetics in the ester family. Apparent allergic reaction to lidocaine or bupivacaine may be a reaction to the methylparaben. Single dose, preservative free, vials of lidocaine and bupivacaine should be standard stock in every emergency department (ED).

When allergy to a local anesthetic is known or strongly suspected, alternatives are available. No cross-reactivity occurs between the amide and ester families, so an agent from a different group may be chosen. A test dose of 0.1 mL may be administered intradermally before proceeding. The patient should be observed for 30 minutes, and as with any allergy testing, the emergency clinician should be prepared to treat all complications. Aqueous diphenhydramine (1%) has also been shown to provide effective local anesthesia.

Skin Preparation

Disinfection of the skin (not the wound itself) may be accomplished with several different agents. The ideal agent is fast acting, has a broad spectrum of antimicrobial activity, and has a long shelf life. Povidone-iodine (Betadine) and chlorhexidine (Hibiclens) have all three characteristics. Although excellent as skin disinfectants, both products are toxic to wound defenses and may increase the incidence of wound infection. Povidone-iodine is effective against gram-positive and gram-negative bacteria, fungi,

and viruses. Chlorhexidine is less effective against gram-negative bacteria, and its efficacy against viruses is unknown. Care must be taken to avoid spilling these substances into the wound. Exposure of the eye to these agents can be detrimental. Chlorhexidine has been shown experimentally and in case reports to produce serious permanent corneal opacification. Current data suggests that chlorhexidine-alcohol preparations are safe and more effective at limiting infection compared with povidone-iodine solutions.[6,7]

Body, facial, and head hair is usually removed to clean and examine the wound, although this is not necessary to diminish the risk of wound infection. Removal of the hair makes it easier for the patient to keep the area clean and ultimately facilitates accurate suture placement and removal. Exceptions are parts of the body where hairlines provide important landmarks for the accurate reapproximation of tissue margins, most notably the eyebrow. Reports of inconsistent or absent eyebrow hair regrowth suggest that eyebrow hair should not be shaved.

Surgical studies show that hair removal with a razor is three to nine times more likely to result in a wound infection than clipping the hair. It seems that the razor damages the infundibulum of the hair follicle. The wounded follicle provides access for bacterial invasion and ultimately infection. For wounds considered to be at high risk of infection, clipping may be done with electronic shears or scissors. Another option is to apply a petroleum-based product to the hair adjacent to the wound margins, allowing the provider to keep the hair away from the surgical field.

Wound Preparation

Débridement

Débridement is the removal of foreign matter and devitalized tissue from the wound. With respect to ultimate wound healing and risk of infection, débridement is the most important consideration in wound care. The presence of any devitalized tissue in the wound delays healing and significantly increases the risk of infection. However, the benefits of débridement have to be weighed against the consequences of producing a larger tissue defect. The resultant closure is exposed to higher tension and may result in a wider scar. Skin edges that are clearly devitalized are débrided before wound closure. On the trunk, where there is little concern for specialized tissue, wide excision and débridement are feasible. On the face and hands, where all tissue must be saved if possible, the process is more difficult. Meticulous sharp excision of small fragments of nonviable tissue should be performed only by experienced physicians. When the viability of large areas of skin or muscle is a significant concern, the wound should be prepared for delayed primary closure.

Wound Cleansing

An ideal wound cleanser has broad antimicrobial activity with a rapid onset. It is nontoxic to the tissue and does not reduce tissue resistance to infection, delay healing, or decrease the tensile strength of the healing wound. Many antiseptic solutions have been used clinically and studied in great detail. Much debate exists regarding which agent comes closest to possessing these qualities. Povidone-iodine in various concentrations, saline, and, more recently, tap water have received the most attention.

Evidence suggests that a 0.9% normal saline solution or tap water are effective irrigants when used with high-pressure syringe irrigation. Saline is the traditional wound-irrigating fluid of choice. However, tap water has consistently produced equivalent rates of infection and cosmetic outcomes. Tap water irrigation allows a large volume of irrigation rapidly and inexpensively and is especially suited to upper extremity and scalp injuries.[8]

Free iodine, although possessing broad, rapid antimicrobial activity, is too toxic to tissue and its defenses to have therapeutic value in the open wound. Iodophor is a complex of iodine with a carrier to increase its solubility and decrease the availability of free iodine. The most widely used iodophor is povidone-iodine, in which the carrier molecule is povidone (formerly polyvinylpyrrolidone). It is generally available in a 10% solution, which is 1% free iodine. It is well documented that even a 5% povidone-iodine solution is toxic to polymorphonuclear neutrophil leukocyte activity and may increase the infection rate. A 1% solution is safe and effective with little or no toxicity. Detergent-containing cleansers, such as povidone-iodine scrub, may be excellent for skin preparation but are toxic to tissue defenses and should never be allowed to contaminate open wounds.

Although many different irrigation solutions may be beneficial, it seems that the key to cleansing is high-pressure irrigation rather than the type of solution used. Tap water irrigation soon may become the preferred method of irrigation, because it is safe, is effective, requires no preparation, and is less expensive.

Irrigation

The quality of mechanical cleansing is one of the most important determinants of wound prognosis. The most effective form of wound cleansing is high-pressure irrigation. Irrigating with pressures greater than 7 pounds per square inch (psi) significantly decreases the number of bacteria and the incidence of infection. Although several commercial devices are available, attaching an 18-gauge needle to a 35-mL syringe yields a force of 7 or 8 psi. High pressures of 50 to 70 psi may be obtained with a commercial water pick. These pressures may cause some tissue damage, but the beneficial effect of ridding the wound of bacteria and debris outweighs this risk. Simply soaking the wound in an antiseptic solution is not beneficial and may be harmful. Scrubbing the wound with a sponge with large-pore cells inflicts tissue trauma and impairs the ability to resist infection. Tissue damage can be decreased by use of a sponge with a fine size of pore cell. Adding a surfactant further minimizes the mechanical trauma inflicted by the sponge. Flooding the wound under low pressure via a bulb syringe or gravity alone does not reduce the incidence of infection, regardless of the agent used.

At least one study has shown little benefit to any irrigation in facial and scalp lacerations. This study prospectively compared outcomes of almost 2000 immunocompetent patients. Infection rates and cosmetic outcomes were similar in the irrigation and the non-irrigation groups. We recommend irrigation only for scalp wounds more than 5 cm long and those with other high risk features.

Wound Closure

Decision-Making

The first determination required is whether the wound should be treated open or closed. Each wound, patient, and clinical circumstance must be handled individually. As discussed in the Risk Factors section, most wounds have a low risk of infection and can safely be closed primarily. A small study from Europe failed to show a difference in infection risk for wounds sutured more than 6 hours after injury.[9] At the other end of the spectrum, some wounds must never be closed at the time of their initial ED visit. A large stellate laceration to the foot produced by blunt force and contaminated with dirt and grease must be cleaned and left open to be closed later. Human and animal bites to the hand are additional examples of wound that should not be closed primarily. Physician judgment is often the best method for deciding when it is safe to close a wound. In one study in which hand wounds were

described as dirty, 22% became infected. When the injury was documented to be clean, the incidence of infection was 7.1%.

Three wound closure options are available. The wound may be (1) closed primarily in traditional fashion, (2) closed in 4 or 5 days (delayed primary closure), or (3) left open and allowed to heal on its own. Delayed primary closure is a safe alternative to traditional primary closure. Overall healing time is not affected, and the risk of infection is greatly decreased if proper technique is used. When a wound is slated for delayed primary closure, it is prepared, débrided, and irrigated in the same manner as for immediate closure. The wound should be packed to prevent it from closing on its own. If the wound is on an extremity, the injury should be splinted and dressed, and appropriate wound care instructions should be given. The patient should return for a wound check and packing change in 24 hours and should be instructed to follow up in another 72 hours for definitive repair, with wound closure undertaken 96 to 120 hours after injury. No studies offer guidelines for prophylactic antibiotic use when delayed primary closure is the treatment option. Extrapolation from other wound studies strongly suggests that antibiotics offer no benefit.

Individuals who do not seek medical care after an injury select the option of leaving a wound open to heal on its own. Most patients who visit an ED with a laceration undergo some form of wound closure. Yet one study that examined unsutured hand lacerations less than 2 cm long followed patients for 3 months and found that there was no significant difference in cosmetic appearance, and there was no difference in time to resumption of activities of daily living.

Closing a wound loosely is occasionally discussed as an option in the treatment of contaminated wounds. This choice should rarely be considered. The loosely closed wound approximates the tissue margins enough to allow the wound to seal itself completely within 48 hours. The infection risk when this method is used is the same as when the wound is closed traditionally.

Wound Tension

The goal of wound closure is optimal anatomic and functional reapproximation of tissue with minimal risk of complication. Consideration must be given to the wound's size, shape, location, depth, and degree of tension. Wounds with high static and dynamic tension that require meticulous closure cannot be closed with tape or staples. Delicate approximation of wound edges under tension can be accomplished only with suture.

Several techniques may be used to reduce wound tension. Deep sutures may be placed in subcutaneous tissue to help bring the wound margins closer together. In this manner, forces on the skin are reduced, and potential dead space can be closed. Care should be taken to avoid suturing adipose tissue, because it may become necrotic, increasing the likelihood of infection. The number of dermal sutures depends on the characteristics of the wound. In general, the number should be kept to a minimum, because suture material acts as foreign matter in the wound and can increase the risk of infection. Subcutaneous sutures should never be placed in the hand or foot because of the major structures that reside near the surface. Another method of ameliorating static tension from cut edges of the wound is to undermine at the lacerated margin. Undermining helps free the dermis from its deeper attachments, allowing the skin edges to be approximated with less force. Care must be taken to preserve the blood supply to the wound margins and not increase dead space in the process.

Suture Technique

Careful surgical technique is important to optimize the ultimate repair. If possible, pickups, hemostats, or forceps should not be used, especially on wound margins. Blind clamping in a wound can damage a nerve, artery, or tendon. Wound margins should be everted and the sutures tied just tightly enough to allow the edges to approximate lightly. The edges can be everted by ensuring that the needle enters and exits perpendicular to the skin. Wounds with opposing margins of different thickness can be difficult to close. If this difference is not considered and corrected, the ultimate scar has uneven margins that cast a shadow on the skin and is unsightly. In closing these wounds, the needle should be pulled through the cut margin of one side before entering the opposite edge. This method gives the emergency clinician the best opportunity to take an equivalent amount of tissue on both sides of the wound. Viable edges of a jagged wound must be meticulously reapproximated. Because of the greater surface area and the ultimate contraction of the wound, preserving the jagged edges results in a more "natural" scar.

Most lacerations are closed with running or interrupted percutaneous suture. The running technique is appropriate for linear lacerations under minimal tension when there is a low risk of infection. This technique is more rapid, requires less suture material, and yields equivalent cosmetic results. Curvilinear or jagged wounds are best closed with interrupted sutures to distribute tension properly. Because tensile strength of interrupted sutures may be superior, wound edges subjected to higher levels of tension should be closed with interrupted sutures.

Basic and Advanced Techniques

Simple Sutures. Wound closure with simple interrupted sutures is the most common method of laceration repair in the ED. The placement of simple sutures yields excellent cosmesis and a low infection rate.

Procedure. The needle is placed to one side of the laceration margin and enters the skin at approximately 90 degrees. To pass the needle through the tissue, the clinician supinates his or her wrist and guides the needle deep but parallel to the skin surface. Wrist supination is extended as the needle exits the skin on the opposite side perpendicular to the surface. Proper technique produces wound edges that are slightly everted and are lightly touching. The art of the process takes into consideration swelling while being careful not to secure the suture too tightly, because necrosis of the wound margin tissue can seriously compromise healing.

Intradermal (Buried) Sutures. Placing cutaneous sutures in wounds under tension can lead to ischemia of the wound margin and an unsightly scar. Proper placement of buried intradermal sutures helps to approximate dermal margins and reduce wound edge tension. Buried sutures should not be used in contaminated wounds, because they increase the risk of wound infection. Sutures through adipose tissue also increase infection and do not relieve skin tension.

Procedure. Placement of buried sutures differs from traditional suturing because of the need to bury the knot deep to the skin. Failure to do this can interfere with dermal healing and can leave a small lump under the surface of the skin. The needle is introduced deep in the wound in the subcutaneous tissue and emerges from the dermis below the skin surface. The needle is reintroduced in the dermis on the opposite wound margin and emerges from the subcutaneous tissue at the same level on the opposite side. The knot is secured and remains buried deep below the skin surface.

Scalp Laceration Repair. In contrast to small lacerations elsewhere on the body, most scalp lacerations require repair because of the propensity to bleed profusely. The dense connective tissue beneath the skin tends to hold vessels open and delay hemostasis. Frontal scalp lacerations in young men should be considered to be a cosmetically significant wound. Although the scalp

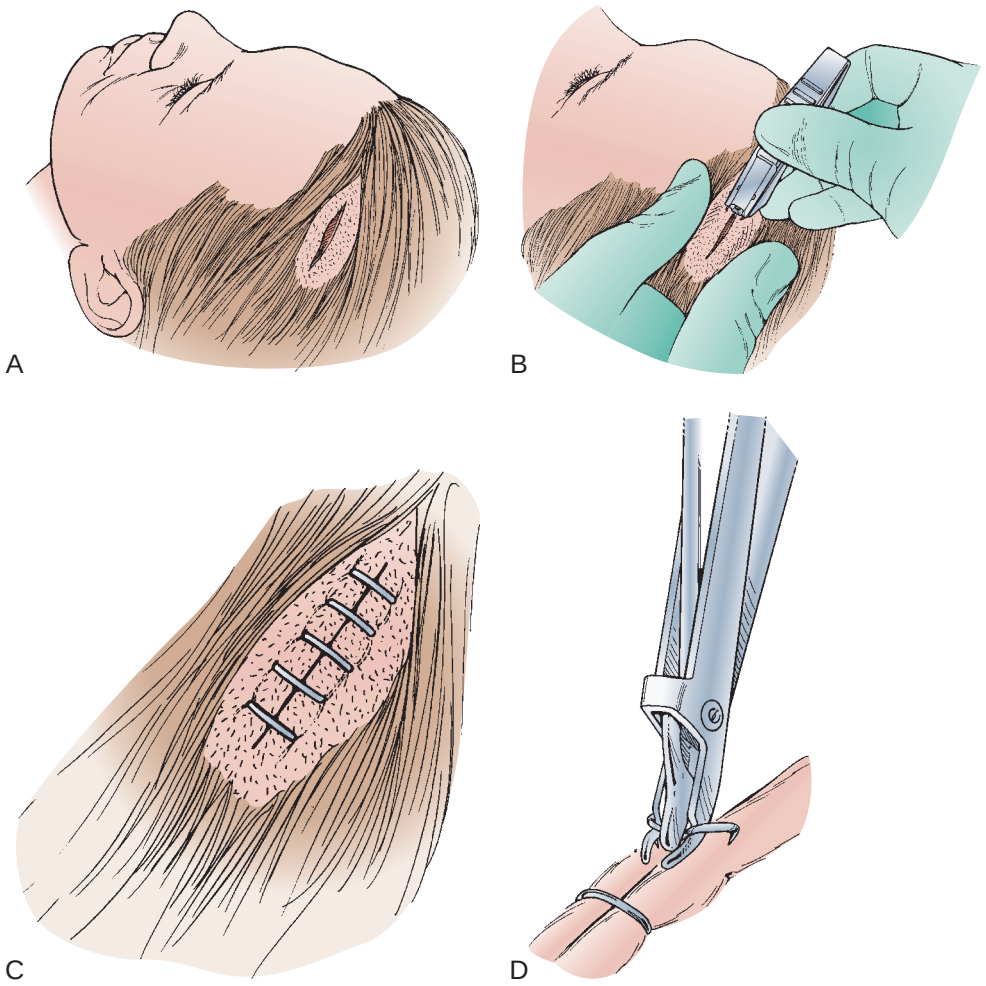

Fig. 52.3. A to **D,** Scalp laceration repair. (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al, editors: Atlas of emergency procedures, St Louis, 2001, Mosby.)

laceration currently may be well hidden by hair, most men experience some balding. Care must be taken to explore the laceration thoroughly to look for a defect in the galea, an injury that requires repair with deep sutures. Staples may be ideal for the skin closure of simple linear scalp lacerations. Hair is less of a problem in placing staples, staples can be placed more quickly than traditional suture, and staples are easier to see and can be removed 1 to 3 days earlier than traditional sutures (Fig. 52.3). Staples may produce artifact on CT scans, but useful information may still be obtained if CT is necessary. Staples may move during magnetic resonance imaging (MRI) and should not be placed if this imaging modality is being considered. Lightweight stapling devices are available. Most devices come preloaded with five or more staples and are easy to use. Hair apposition may also be an option for the closure of many scalp wounds. The technique involves grabbing a bundle of hair on both sides of the wound and then twisting the hair bundles with a hemostat. A small dab of cyanoacrylate glue is applied to the twisted hair to prevent unraveling. Patient satisfaction is high with this approach.[10]

Traditional sutures are used to repair most scalp lacerations, usually with standard nylon suture. Absorbable chromic gut can be used in children and in adults who may not return for suture removal.

Procedure. Anesthesia with epinephrine is recommended to help control bleeding. Hair removal is necessary only if the hair makes closure difficult. A defect in the galea is closed with 3-0 or 4-0 absorbable suture. Failure to repair the galea can lead to a cosmetic deformity related to frontalis muscle function. Linear superficial scalp lacerations that do not require deep sutures can be closed with staples or with monofilament nylon sutures applied with a simple interrupted or running technique. Jagged or macerated lacerations may require some débridement and horizontal mattress sutures. When one chooses to staple a scalp laceration, the adjacent skin margins are pinched together with forceps to evert wound margins. The "mouth" of the stapler is placed gently on the skin surface, taking care not to indent the skin. The handle of the stapler is squeezed carefully to eject the staple into the tissue. Ideally, the staple closely approximates the wound margins without indenting the surface of the skin. For release of the staple, the wrist is pulled back to disengage itself from the last staple.

Vigorously bleeding scalp lacerations often need temporizing measures to control bleeding while the patient is being evaluated and resuscitated. An anesthetic agent with epinephrine should be used and may be helpful to control some bleeding. Blindly clamping in an attempt to control bleeding is unwise and not likely to be successful. Raney scalp clips can be rapidly applied to the wound margins to quickly gain control of the bleeding. An applicator is used to apply and remove the clips so that they can be replaced with sutures once the patient has been stabilized. The clips are plastic and will not interfere with CT or MRI.

Staple removal is simple, especially if the patient has kept the wound clean and free of dried secretions. The dual prongs on the

disposable staple remover slide under the staple crossbar. As the handle is squeezed and the horizontal aspect of the staple is depressed, the sharp edges are eased out of the tissue for removal.

Skin Tears. Most commonly seen in the elderly and chronically ill, skin tears can be a treatment dilemma for emergency clinicians. These tears are a result of shearing forces that separate the epidermis from the underlying dermal layer of the skin. Often the result of minor trauma, these injuries may be minor tears or as large gaping wounds with extensive loss of tissue. Approximating the wound margins by aligning thin fragile tissue can be very difficult. Studies have confirmed that the use of Steri-Strips and or topical skin adhesives (cyanoacrylate-based derivatives; see later) is currently the preferred option. Either material may be used alone; however, when tension exists, placing the Steri-Strips first, then the adhesive, may be the optimal approach. Care must be taken in deciding what type of dressing to use. Transparent films can cause fluid to collect and delay healing. Adhesives are difficult to remove and can cause additional tearing. If the wound must be covered, then hydrogel sheets, hydrocolloid dressings, or both are recommended.[11]

Vertical Mattress Sutures. Vertical mattress sutures improve wound edge eversion. They are also used for the closure of gaping wounds and deep lacerations that may need more than simple sutures to close potential dead space. Areas of lax skin tension, generally where maximal skin mobility is needed (such as, over joint surfaces), may need assistance to ensure eversion of the wound margins. Vertical mattress sutures may be ideal to accomplish both tasks.

Procedure. A vertical mattress suture is a combination of deep and superficial components. The needle is introduced at a 90-degree angle approximately 1 cm from the wound margin. The needle courses through the depth of the wound and emerges on the opposite side, 1 cm from the laceration margin at a 90-degree angle. The needle is reintroduced 1 or 2 mm from the epidermal edge for final approximation of the wound.

Horizontal Mattress Sutures. Horizontal mattress sutures are useful to help disperse excess skin tension and to evert wound edges. The scalp, which has minimal skin mobility, is one area where gaping lacerations may benefit from this tension-reduction method. Horizontal mattress sutures may also be beneficial in thin, fragile skin of elderly people and for lacerations that have lost tissue from the injury or débridement.

Procedure. The initial step is to pass the needle as for a simple interrupted stitch (Fig. 52.4). On exiting the skin, however, the needle is reintroduced approximately 0.5 cm adjacent to the exit point. This second "bite" reemerges 0.5 cm adjacent to the initial insertion point and is tied. Unlike with vertical mattress sutures, each bite is always the same distance from the wound margin.

Dog-Ear Deformity Repair. Some redundant tissue may result on one side of the repair as the closure nears completion,

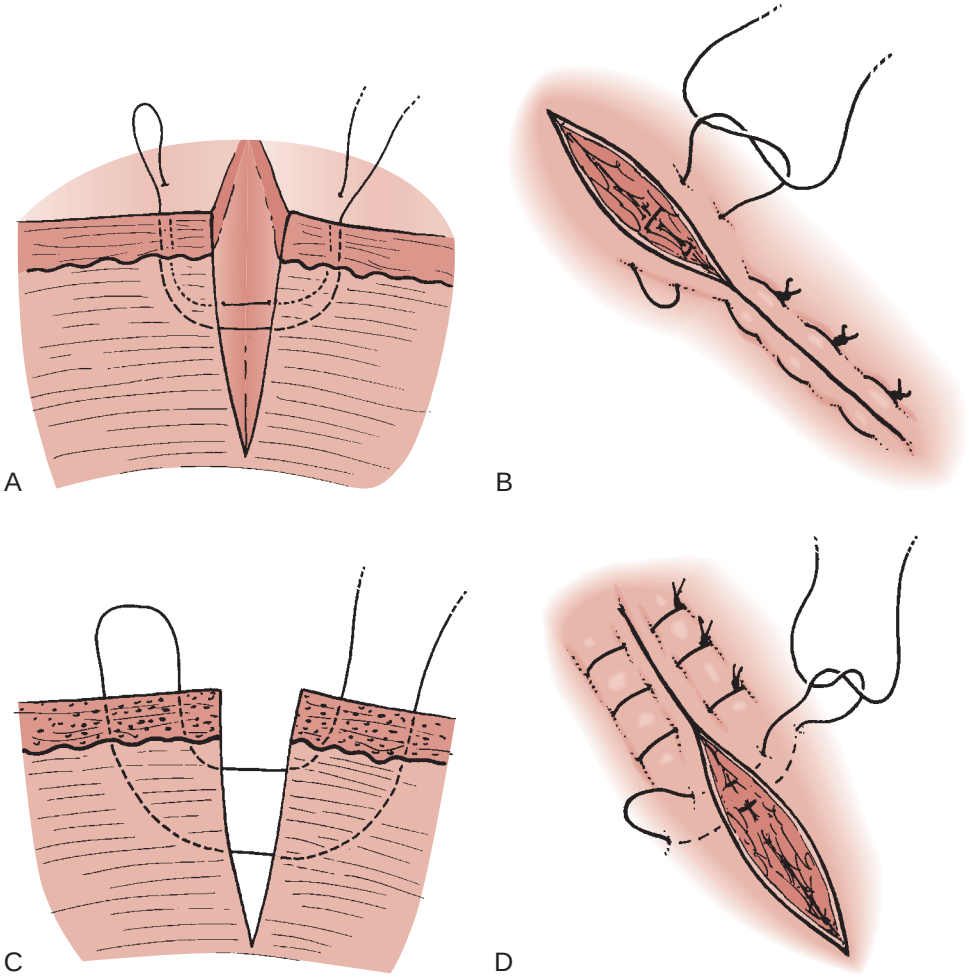

Fig. 52.4. A to **D,** Mattress suture. (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al, editors: Atlas of emergency procedures, St Louis, 2001, Mosby.)

especially in the closure of curvilinear lacerations. This redundant tissue generally can be avoided by placing the initial suture in the middle of a curvilinear wound. If the clinician has limited experience, excision and undermining of tissue are likely to result in complications and should not be attempted.

Procedure. The laceration repair begins in a traditional manner and continues to approximately the final 1 cm of the wound (Fig. 52.5). A short incision (approximately 1 cm) is made from the end of the laceration at a 45-degree angle. The angle is cut toward the side of the redundant, bunched tissue. In most cases, the subcutaneous tissue from the start of the dog-ear defect to the newly created end of the wound must be gently undermined to mobilize the skin. The next step, the final step before suturing, is the most important. The work that has just been completed leaves a small triangular piece of excess tissue. The redundant piece is gently lifted with the tissue forceps and excised in a line parallel to the incision made above. The wound can now be closed with simple interrupted suture technique.

Corner Stitch (Half-Buried Horizontal Mattress Sutures). Jagged and triangular wounds create corners that can be difficult to repair. The clinician must avoid placing the suture directly in the tip of the flap. This practice may "stretch" the tissue and further compromise blood flow to the wound margin. The corner stitch allows optimal tissue approximation with minimal tension.

Procedure. The needle is introduced percutaneously through the non-flap side of the wound a few millimeters from the corner of the wound (Fig. 52.6). The needle is passed horizontally through the dermis of the flap. The final step is to pass the needle into the dermis of the non-flap aspect of the wound a few millimeters from the opposite side of the corner. The suture is led out

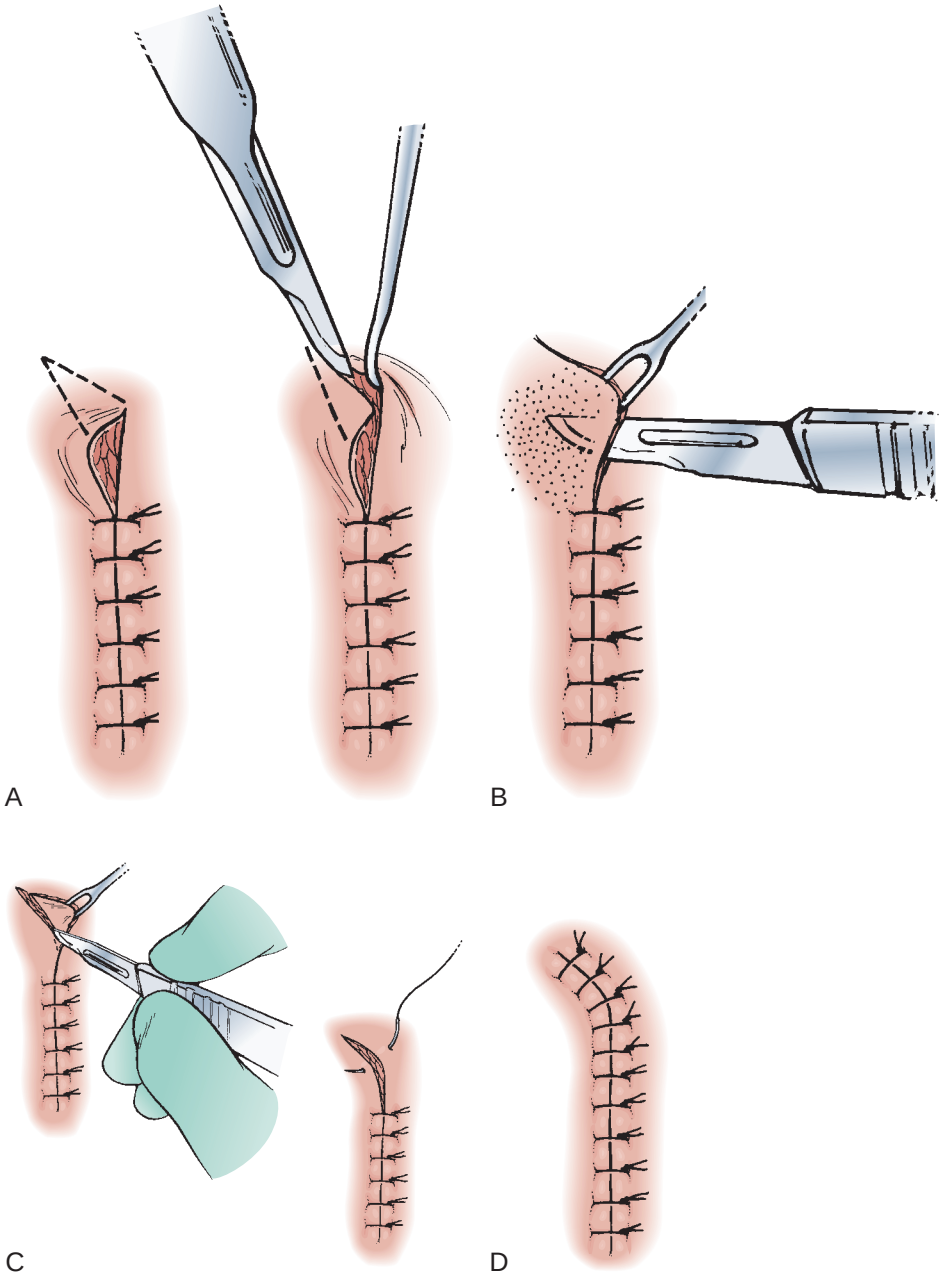

Fig. 52.5. A to **D,** Dog-ear repair. (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al, editors: Atlas of emergency procedures, St Louis, 2001, Mosby.)

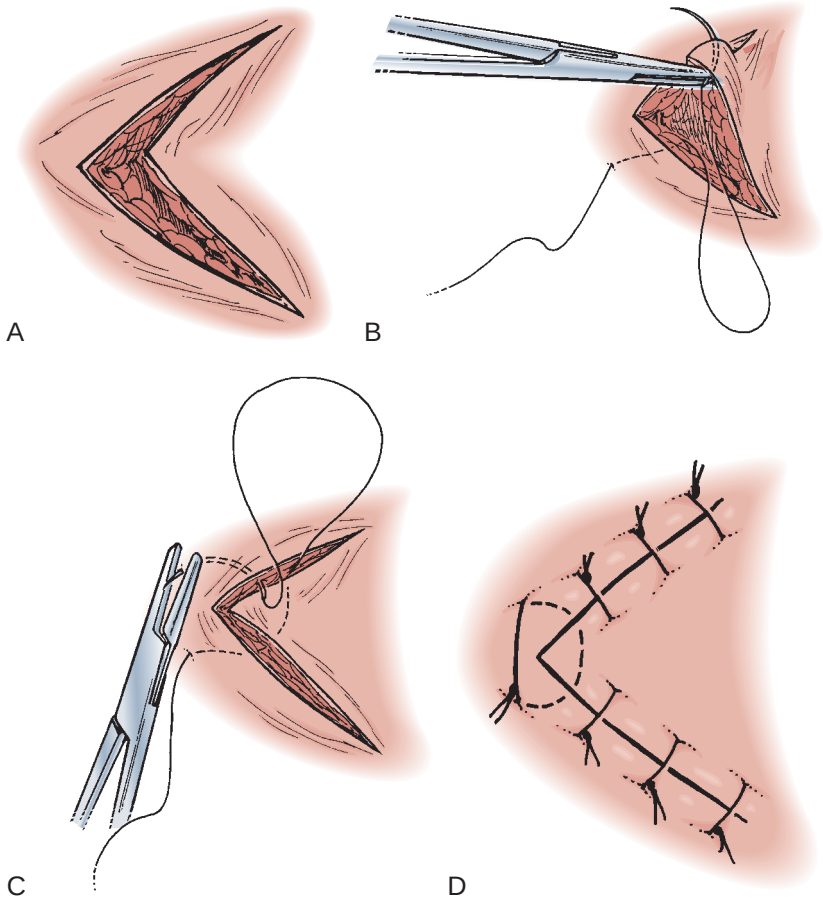

Fig. 52.6. A to **D,** Corner stitch (half-buried horizontal mattress). (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al, editors: Atlas of emergency procedures, St Louis, 2001, Mosby.)

through the epidermis and tied. This technique can also be used to encompass multiple flaps either individually or simultaneously if the tips are adjacent to one another. The most difficult but important aspect of the corner stitch is to take bites of equal depth with each pass of the needle. Failure to take equal bites of tissue results in a wound with opposing sides that do not lie flat; this leads to a more obvious scar. When the corner has been repaired, the remaining two sides of the wound may be closed with simple interrupted or running suture technique.

V-Y Wound Closure. The V-Y closure is indicated for the repair of V-shaped wounds with tissue loss or with nonviable margins that must be trimmed. The tissue loss is such that the adjacent mobile tissue is not sufficient to close the remaining defect.

Procedure. Nonviable tissue is trimmed with fine iris scissors (Fig. 52.7). The long V-shaped portion of the wound is sutured with simple interrupted percutaneous stitches. This first step brings the tip of the flap closer to the newly created corner of the wound. A corner stitch is used to secure the tip of the flap. The remaining limbs of the Y can be repaired with simple interrupted stitches. Some degree of undermining is likely to be needed to mobilize tissue to close the defect. Débridement of too much tissue can make the final repair more difficult and can distort adjacent anatomy.

Materials

In the Middle Ages and earlier, materials used to close wounds included flax, hemp, fascia, hair, linen strips, pigs' bristles, reeds, grasses, and even the mouth parts of the pincher ant. In the early 1900s, natural organic protein products, including silk, cotton, and catgut, were the only available substances. Polyester (Dacron) and nylon were the first synthetic materials, available in the 1940s. Since then, a host of other synthetic materials have become available.

Suture. The ideal suture is inert to metabolism, is resistant to infection, has great tensile strength, does not tear tissue, is easy to work with and tie, and is available in convenient colors with a variety of cutting and noncutting needles. A common classification of suture material relies on relative *absorbability.* In general, the materials that maintain their tensile strength for more than 60 days after implantation have been defined as *nonabsorbable.* Materials that undergo rapid degradation in tissue and lose their strength in less than 60 days are considered *absorbable.* A second classification considers the source and nature of the material. *Biologic* substances, which include catgut, collagen, silk, linen, and cotton, generally produce the greatest tissue reaction and have the lowest relative tensile strength but have good knot security. These characteristics are in contrast to *synthetic* materials, such as polyester (Dacron), polyamide (nylon), polypropylene (Prolene), polyglycolide and polylactide polymers (Dexon and Vicryl), polydioxanone (PDS), and steel, which usually have less tissue reactivity, greater strength, and less knot security.

Knotting properties and handling characteristics tend to vary inversely. Knot security is of particular importance in maintaining wound closure and the patient's confidence in the physician. Sutures with smooth or slippery surfaces produce little friction and glide effortlessly through tissue and are easy to tie. Smoother

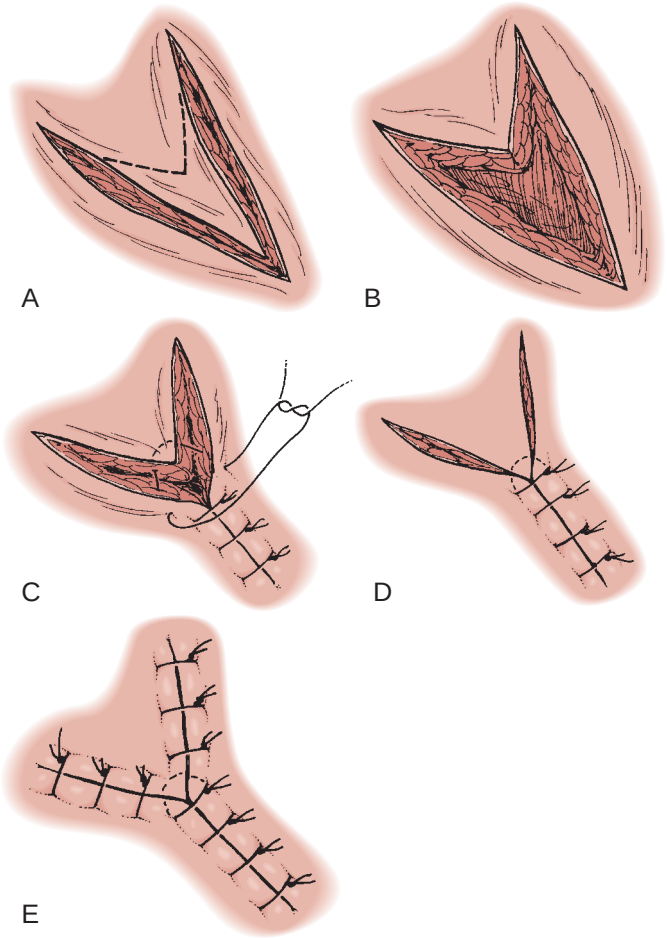

Fig. 52.7. A to **E,** V-Y closure. (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al, editors: Atlas of emergency procedures, St Louis, 2001, Mosby.)

materials are more difficult to handle and more likely to untie spontaneously. Certain monofilament synthetic materials tend to return or spring back to their original shape. To overcome this suture memory, the first part of the tie should be a "double throw" pulled tightly enough to approximate the tissue, with care taken not to strangulate the margins. The second throw locks the tension of the first part into position. A third throw is used for added security. If this is done properly, additional knotting is not needed after the third throw.

The presence of any suture material in a wound increases the likelihood of infection. Subcutaneous sutures bear the greatest risk. The degree of risk depends on characteristics of the substances used. Braided multifilament materials, such as the polyesters, polyamides, polyglycolides, and silk, yield the highest infection rates, whereas monofilament synthetic substances have the lowest risk of infection. There are several nonabsorbable monofilament synthetic sutures and one absorbable monofilament (PDS). The degree of infectivity of PDS compares well with the low rates of infectivity of similar materials.

Consideration of patient comfort in suture selection is important. Although silk is highly reactive, it ties well, is easy to handle, and is comfortable for the patient. It is an excellent choice for use in and around the lips, where comfort is a major concern. PDS is a comfortable absorbable suture and can be left in intraoral mucosa to be absorbed, with apparently low risks of infection, or it can be removed in 5 to 7 days. Staples or metallic sutures are excellent when strength is needed, but they may be uncomfortable for the patient. Nylon and polypropylene, which are the most common sutures used on skin, produce little tissue reaction and offer good tensile strength. They tend to be stiff, produce discomfort near the lips, have poor knot security, and may be difficult to work with. A braided, coated polyester nonabsorbable material, such as Ethibond, is easier to work with and has better knot stability. Although Ethibond is more expensive than nylon, its characteristics and added patient comfort suggest that it may be preferable. Absorbable suture materials, such as polyglycolide and polylactide polymers (Dexon and Vicryl), have been used strictly for subcutaneous and mucosal closures. Their highly reactive nature allows them to be broken down and absorbed over weeks. Chromic catgut, another absorbable material, has been shown to be safe and effective for the closure of scalp wounds in children.

Needles. Surgical needles are available in a variety of sizes and shapes with myriad other characteristics. Cutting needles may be reverse cutting, conventional cutting, taper cut, or precision point. Most emergency wounds may be closed with a conventional cutting needle. In addition to its sharp point, it has two opposing cutting edges, with a third on the inside curve. Precision point needles are similarly shaped but are honed 24 extra times and maintain their added sharpness longer. These needles are used for delicate plastic or cosmetic surgery. Noncutting needles are reserved for organ repair and subcutaneous suturing. Cutting needles may also be used to repair subcutaneous tissue. Needle nomenclature is confusing and varies by manufacturer.

Tape. Tape closure may be superior to closure with sutures and staples if applied in the appropriate circumstances. In general, the laceration should be linear and subjected to weak static and dynamic forces. Tape is not considered for wounds requiring meticulous tissue approximation. Compared with other closure materials, tape is associated with lower risk of infection, less expense, and less physician time. In addition, a painful injection of local anesthetic is not needed.

The ideal wound closure tape allows water and gas exchange and possesses elasticity, strength, and optimal adhesiveness. For adhesive properties to be maximized, tincture of benzoin should be painted on the skin adjacent to the wound. Care must be taken to avoid introducing benzoin compound in the wound. A nonwoven, microporous tape, which is not reinforced, has been found to best meet these requirements.

Staples. Staples offer several advantages over sutures. Monofilament stainless steel staples offer less risk of infection than even the least reactive suture.[49] The time necessary to accomplish closure may be significantly lessened. Acceptable wounds must be linear and subjected to weak skin forces. Wounds requiring accurate approximation of tissue are not candidates for staple closure. Staples are also uncomfortable while in situ and on removal. Stapled wounds gain tensile strength sooner, and the staples can be removed 1 to 3 days earlier than sutures. After removal, the staples should be replaced with wound closure tape for continued reinforcement.

Various stapling devices are available. The device must allow good visual access and flexible positioning for difficult angles. A pre-cocking mechanism is necessary to allow the physician to hold the staple securely during its placement. The angle of staple delivery is important. One brand releases the staple perpendicular to the wound with its crossbar flush with the skin; this can result in cross-hatching on the skin or tissue strangulation if placed too deeply. The device needs an ejector spring for smooth staple release and must be able to be handled without producing fatigue.

Tissue Adhesives. European and Canadian physicians have used tissue adhesives (butyl-2-cyanoacrylates) for many years. In 1998, octyl-2-cyanoacrylates were approved for use in the United

States. Tissue adhesives offer many advantages over traditional sutures. The emergency clinician can apply the adhesive quickly and easily with a minimum of patient discomfort. In addition, suture removal in 7 to 10 days is unnecessary, because the adhesive sloughs off the skin in approximately the same amount of time. Evidence indicates that adhesives not only provide their own dressing but also have antibacterial properties and may decrease the rate of wound infections. Closing wounds with adhesives is less expensive than traditional suturing and carries no risk of needle-stick injuries.

Tissue adhesives achieved cosmetic results similar to those of traditional sutures in randomized trials. Tissue adhesive may be applied in high-tension areas, but only if used in conjunction with subcutaneous or subcuticular sutures. If used alone, tissue adhesives are not recommended for lacerations longer than 4 cm or in areas of higher tension or frequent repetitive movements, such as joints or hands.

Other disadvantages of tissue adhesives include the inability to use antibacterial or other petroleum-based products on the wound; the recommendation not to swim, to limit forces that may prematurely remove the adhesive; and the greater risk of dehiscence. The tensile strength of tissue adhesives is significantly less than that of sutures. Despite these disadvantages, tissue adhesives represent a tremendous advance in the management of routine uncomplicated lacerations in non-tension areas. Patients routinely prefer tissue adhesives over traditional sutures.

Application of tissue adhesive begins with routine skin and wound preparation. The area must be dried and adequate hemostasis achieved before application of the adhesive. The wound margins are approximated as meticulously as possible, and care should be taken to prevent adhesive from getting between the wound margins. Applying tape (Steri-Strips) before application will facilitate wound margin approximation and make it easier to apply with similar results. Adhesive between the wound margins delays healing and increases the likelihood of wound dehiscence. The adhesive is applied to the entire length of the wound sufficient to cover 5 to 10 mm of skin adjacent to the margins. A single layer of adhesive is adequate if the current formulation is used. The adhesive sets in roughly 95 seconds.[12] Special care is taken to ensure that the adhesive does not run off and disturb adjacent tissues. Having the patient lie on the affected side will help prevent contamination of the eye near the wound and the opposing eye. Newer, high-viscosity formulations are now available that help limit this risk. Wounds may get wet but should not be immersed in water and should be blotted dry and not vigorously rubbed. An additional dressing may be desired by the patient but is not necessary.

Antibiotic Prophylaxis

Routine antibiotic prophylaxis for simple wounds has no scientific basis. A meta-analysis compared the rates of infection in patients with simple non-bite wounds receiving antibiotics with those in control groups. Of 1734 patients enrolled in the seven studies, patients treated with antibiotics had a slightly greater incidence of infection. The authors concluded that prophylactic antibiotics had no role in simple non-bite lacerations. Routine antibiotic use has obvious known complications, such as increasing resistance to antibiotics, gastrointestinal side effects (nausea, vomiting, *Clostridium difficile* colitis), and allergic reactions that are common and may result in significant morbidity and unnecessary cost.

Although irrigation and débridement are the most important means of preventing wound infections, antibiotic prophylaxis is recommended in some very limited circumstances. Prophylaxis must be tailored to each patient. Some recommendations are supported by scientific data, whereas others have few data to support their use and are based on established practice standards.

Contamination, Crush, and Host Factors

Antibiotic prophylaxis is often provided for patients with wounds with gross contamination, patients with severe crush injuries, and immunocompromised patients. Some authors recommend not closing these wounds and instead using delayed primary closure. If circumstances require wound closure despite the infection risk, many emergency clinicians recommend prophylaxis despite scarce data.[13]

Some authors believe that a patient with significant crush injury requires antibiotics. Crush injuries are high-risk wounds because they produce more devitalized tissue. A definitive answer may not be forthcoming, because it would be difficult to complete a well-controlled prospective, blinded study.

Patients with certain risk factors have increased wound infection rates. Large prospective studies of patients with surgical wounds showed an increased rate of wound infection in patients with diabetes, obesity, malnutrition, chronic renal failure, advanced age, and chronic steroid use. Because of higher rates of infection, some authors suggest the use of antibiotics in these patients, again based on individual circumstances. No controlled studies of antibiotic prophylaxis in these patients exist, however. Finally, some authors advocate prophylaxis for other host factors, such as prosthetic joints or risk for endocarditis. Little evidence exists to support either recommendation.

Open Fractures, Joint Wounds, and Gunshot Wounds

Wounds that involve joints or open fractures necessitate use of prophylactic antibiotics. Prospective randomized controlled studies have documented decreased infection rates in patients receiving antibiotics compared with placebo. Indeed, the time to antibiotic administration in these wounds was found to be the most important factor in decreasing wound infection rates.[14] Open fractures without evidence of significant soft tissue damage (avulsions and crushed or devitalized tissue) necessitate use of antibiotics for 24 hours. Open comminuted fractures or fractures with significant tissue damage necessitate 72 hours of antibiotics. For gunshot wounds, which are classified as a type of open fracture, the recommendations vary with the type of missile wound. Low-velocity missile wounds not treated with antibiotics showed no increased infection rate in a randomized controlled trial of 67 patients with fractures treated with a closed technique. High-velocity wounds with fracture, on the other hand, are associated with an increased risk of infection, and antibiotic therapy should be initiated early and maintained for 48 to 72 hours. In addition, patients with shotgun wounds with fracture should receive prophylaxis as well. Appropriate antibiotic therapy would be a cephalosporin with or without an aminoglycoside plus penicillin (to cover *Clostridia* species). Use of cefazolin (Ancef) 1 g every 8 hours and clindamycin 600 mg intravenously (IV) every 8 hours may be considered. For the severely contaminated wounds, tobramycin 1 mg/kg every 8 hours is added. Some recent data has proposed limiting aminoglycoside use altogether and only using cefazolin for Gustilo grade I/II open fractures and ceftriaxone for grade III open fractures. A single institution study showed little difference in infection rates after limiting aminoglycoside administration for open fractures.[13,14]

Bites and Puncture Wounds

Antibiotics are indicated for through-and-through intraoral lacerations, cat bites, some dog bites, some human bites, and some puncture injuries to the foot. Of all mammalian bites, school age children account for almost half of all patients in this category, and 70% of animal bites are from pets or animals known to the victim (also see Chapter 54).[15]

Cat Bites. Prophylaxis is required for patients with cat bites, especially bites to the hand. These bites tend to be deep puncture wounds that are difficult to irrigate adequately. These wounds also tend to become infected at a much higher rate than other types of bites. Cat bites have been reported to cause infections in 10% to 40% of all wounds. In one study, 13% of patients had signs of infection when they visited the ED, and 16% eventually developed infection. Other authors report that 80% of these bites become infected, although obvious selection bias limits this interpretation. Antibiotics seem to decrease the incidence of infection but a Cochrane review on mammalian bites suggested the limited literature on cat bites did prove antibiotic efficacy, except in hand bites. At this time, we still advocate for antibiotic prophylaxis in cat bites.

The organisms found in cat bites include *Staphylococcus* species, *Streptococcus* species, and, most often, *Pasteurella multocida*. *P. multocida* is usually found in infected cat bite wounds and is present in the normal oral flora of 70% of all cats. *P. multocida* is sensitive to penicillin, but the infection is often polymicrobial. *P. multocida* is resistant to dicloxacillin, cephalexin, and clindamycin, and there are many erythromycin-resistant strains. Amoxicillin with clavulanate (875 mg bid for 7 days) is the current recommendation for antibiotic prophylaxis for cat bites.

Dog Bites. Antibiotic prophylaxis for dog bites is more controversial. The infection rate has been reported as 6% to 16% for patients not receiving antibiotics. Dog bites tend to involve more crush injuries with tearing and avulsions rather than puncture wounds. As such, dog bites are usually more amenable to irrigation and débridement. Seven of eight randomized trials of dog bite wounds showed no benefit with antibiotics. However, pooled data for meta-analysis did show a small but statistically significant benefit from antibiotics. It may be logical to limit the use of antibiotics to high-risk wounds, such as hand injuries, deep puncture wounds, and wounds in older or immunocompromised patients.

Hand Bites. In addition to the previous bite wound recommendations, antibiotic prophylaxis of injuries to the metacarpophalangeal joints is advised. These wounds are assumed to be human bites until proved otherwise. Also known as "fight bites," these wounds have a high incidence of infection. Patients without signs of infection may be managed as outpatients. Close inspection after anesthesia has been applied is necessary to thoroughly evaluate the area for tendon involvement and/or penetration of the joint. If the joint is involved, irrigation is required. In some institutions, all these patients are taken to the operating room for a thorough washout. Patients with early signs of infection are admitted for intravenous antibiotics and débridement and irrigation. The choice of antibiotics reflects the predominant organisms of hand bite infections. *Streptococcus* and *Staphylococcus* species are common, but *Eikenella corrodens* and *Bacteroides* species are also typical pathogens. Because *Eikenella* is often resistant to clindamycin, first-generation cephalosporins, and erythromycin, patients with early infection are treated with amoxicillin with clavulanate. Patients with later infection are treated with intravenous extended-spectrum antibiotics (eg, ampicillin with sulbactam).

Intraoral Lacerations. Lacerations of the oral mucosa involve bacteria-rich oral secretions and may become infected slightly more often (6% to 12%) than other wounds. Rates of infection for through-and-through lacerations may be twice the rates for simple mucosal lacerations. Although few data suggest a clear indication for prophylactic antibiotics, one study showed that patients benefit from antibiotics if they are compliant with their regimen. Another study looked at all the literature (four studies) on antibiotics in intraoral lacerations and found the studies do not conclusively show a benefit to giving antibiotics in these types of wounds. It may be reasonable to limit antibiotic use to high-risk patients with through-and-through wounds. Penicillin 500 mg bid for 5 days is an appropriate choice of antibiotic.

Puncture Wounds of the Foot. Puncture wounds of the foot are seen frequently in the ED. These wounds are often caused by common carpentry nails, although other objects (eg, glass, metal, and wood) must be considered. Despite their simple appearance, these wounds may produce significant morbidity. The infection rate for puncture wounds has been reported to be 15%. Most wounds occur on the plantar surface, from the neck of the metatarsal to the toes. Simple cellulitis accounts for half of these infections. More significant infections include septic arthritis, abscesses, and osteomyelitis. *Pseudomonas* organisms cause 90% of osteomyelitis cases from puncture wounds. No data suggest a benefit from prophylactic antibiotics, but given the high risk of infection and serious complications, their use may be considered in select puncture wounds. *Pseudomonas* organisms should be suspected when the puncture went through a rubber-soled shoe is essential. Patients with puncture wounds to the foot require early follow-up. Ciprofloxacin is the drug of choice to treat outpatients with suspected wound infection when *Pseudomonas* is of concern. Cephalexin (Keflex) or dicloxacillin is adequate for staphylococcal and streptococcal coverage unless methicillin-resistant *Staphylococcus aureus* (MRSA) is likely. In cases suspicious for MRSA, sulfamethoxazole-trimethoprim or doxycycline is recommended.

Drains, Dressings, and Immobilization

Drains

Drains probably have no role in ED wound care. In general, drains are placed when a collection of fluid exists or may develop. The presence of a drain reduces the wound's resistance to infection, regardless of the materials used in its construction, and the use of drains should be avoided. In wounds likely to collect fluid (eg, around the elbow or knee), it is preferable to place the extremity at rest with a plaster splint or perform delayed primary closure.

Dressings

Various dressing materials are available. The microenvironment created by a dressing affects the biology of healing. The optimal wound climate must not interfere with the activity of fibroblasts and macrophages. The production of granulation tissue and migration of epithelial cells across the wound must be optimized.

Several factors should be considered in choosing the appropriate dressing. Dressings that prevent evaporation of water and keep tissues moist are helpful. A drying wound produces a thick, hardened scab that impedes the process of epithelialization. Excess fluid can lead to maceration of tissue and may be a potential culture medium for bacterial proliferation. Gaseous permeability is essential because epithelialization is accelerated greatly in the presence of oxygen. The wound-covering product should be impermeable to bacteria and other particulate matter that can contaminate the wound. It is important not to traumatize newly established tissue during dressing changes. The optimal dressing should have a nonadherent surface, be permeable to gases, and have a capacity to absorb some fluid but not allow desiccation. The outer barrier of the product should be impermeable to bacteria but permeable to water vapor. These products include films, hydrocolloids, foams, and hydrogels. The choice of dressing for ED wounds is primarily based on the amount of drainage that is expected.

Film dressings are thin membranes that are transparent, adhesive, and waterproof but are not absorptive. They are best reserved for wounds with low levels of drainage. Film dressings may be left in place for up to 7 days, as long as they do not leak or separate from the wound bed. For wounds with a moderate amount of drainage, moderately absorptive hydrocolloid dressings may be indicated. These dressings are thicker than films, semiocclusive, waterproof, and very comfortable for the patient. Like films, they can be left on for up to 7 days. Foam dressings are more absorptive and made of a soft cushion sponge-like material. Some may require a secondary dressing for adhesion and need to be removed every 3 days. Hydrogel dressings are moisture-donating water-based gels that are available in sheets attached to a semipermeable film. These dressings do not absorb fluids, so they must be used on relatively dry wounds. Patients often find these dressings to be the most comfortable, but they need to be changed every 1 to 3 days. The least expensive and simplest method of dressing a straightforward, uncomplicated laceration is to use Vaseline-impregnated gauze or gauze on top of a thick layer of antibiotic ointment. These should be changed daily to prevent desiccation.

Immobilization

Wounds in proximity to joints must be immobilized as part of routine care. Splinting the injured body part places the injury at rest and hastens healing. Failure to splint appropriately exposes the healing tissue to the dynamic forces of muscular contractions, ultimately slowing the healing process and increasing scar size. In addition, immobilization decreases lymphatic flow and minimizes spread of microflora from the wound.

DISPOSITION

Wound Care Instructions

It is difficult for patients to identify and recognize the signs of infection (Box 52.2). Discharge instructions must be clear, understandable, and reasonably comprehensive. Instructions should include daily care, observation for signs of infection, suture removal dates, and a follow-up source. It should be recommended to the patient that injured extremities be elevated during the first 24 to 48 post-traumatic hours and explained that elevation lessens edema, hastens healing, and mollifies pain. The wound should be protected as described previously or cleaned daily to remove crust formations. It is safe for patients to bathe and get the wound wet 24 hours after injury. Daily swabbing with half-strength hydrogen peroxide rids the wound of debris and any blood clot that forms between the sutured edges. Hydrogen peroxide should not be used after separation of the scab, because it is toxic to the epithelium and may produce bullae.

Wound infection is difficult for the untrained observer to distinguish from the inflammatory response of injury and subsequent healing. Patient education in this regard should be cautious and straightforward (eg, return or seek follow-up for redness, swelling, increased pain, fever, pus, or red lines progressing up an extremity). An injury classified as high risk must be reexamined 48 hours after the trauma, regardless of its appearance. Discharge instructions should include highlighting the possibility that a foreign body may be present despite efforts to remove it. Return precautions outlining signs of wound infection are essential.

Suture removal times vary, but generally they are approximately 4 days for the face and 7 to 14 days for other body parts (see Box 52.2). Considerations include cosmetics, dynamic forces in proximity to the injury, static skin tension, blood supply, and anticipated healing rates.

BOX 52.2

Wound Care Instructions

I. Elevate the injured extremity above the level of the heart. Wear a sling when appropriate.
II. Cleanse daily in a gentle manner to remove debris and crusting that develops. Use dilute hydrogen peroxide.
III. Immobilization should be maintained at least until suture removal.
IV. Signs of infection
  A. Redness
  B. Increasing pain
  C. Swelling
  D. Fever
  E. Red streaks progressing up an extremity
V. Wound check
  A. As needed to check signs of infection
  B. Routine at 48 hours for high-risk wounds
VI. Suture removal (*Note:* Suture may be removed earlier if Steri-Strips reinforce the wound.)
  A. Face: 3 to 5 days (always replace with Steri-Strips)
  B. Scalp: 7 to 10 days
  C. Trunk: 7 to 10 days
  D. Arms and legs: 10 to 14 days
  E. Joints: 14 days

Tetanus Immunization

The incidence of tetanus in the United States is rare with only 233 cases reported during the 2001 to 2008 surveillance period with a case fatality rate of 13.2%.[16] Most tetanus patients in the United States are older than 50 years old. Immunization status needs to be considered in all patients with wounds, regardless of severity. Forty percent of all cases of tetanus occur in individuals who have either minor wounds or no recollection of injury. These numbers raise serious questions regarding the validity of separating immunization recommendations according to clean and tetanus-prone wounds. Studies show that many people are inadequately immunized, especially patients older than 70 years, immigrants, and people with no education beyond grade school.[4,17] Also, patient immunization histories are often unreliable. Given the inability to predict which wounds are at high risk, all wounds are approached with suspicion.

The usual incubation period for tetanus is 7 to 21 days (range, 3 to 56 days). Immunization is given as soon as possible but can be given days or weeks after the injury. The dose of tetanus toxoid (T) or diphtheria, pertussis, and tetanus toxoids (DTaP) is 0.5 mL intramuscularly, regardless of the patient's age. Inadequately immunized patients need a dose of DTaP and tetanus immune globulin (TIG). The TIG dose is 250 IU for all ages 7 years old or older and 4 IU/kg IM up to 250 IU for ages younger than 7 years old (Table 52.1). A single injection of TIG provides protective levels of passive antibodies for at least 4 weeks. The immune globulin and toxoid may be given during the same visit but should be administered with a different syringe at separate sites. The literature suggests that emergency clinicians need to be more diligent administering TIG, because it is often not provided when indicated.

Because studies suggest that 10% to 40% of the population in the United States is inadequately immunized against pertussis, pertussis vaccination is recommended along with tetanus toxoid.[17] Immunity to pertussis wanes approximately 5 to 10 years after vaccination. Since the 1980s, the number of reported pertussis cases has steadily increased, especially among adolescents and adults. Children younger than 11 years old should receive the DTaP immunization. In 2005, a tetanus toxoid, reduced

TABLE 52.1

Tetanus Prophylaxis for All Patients With All Wounds[a,b]

IMMUNIZATION HISTORY	DTAP (0.5 mL)	TIG (250 IU)
Fully immunized, <10 years since booster	No	No
Fully immunized, >10 years since booster	Yes	No
Incomplete series (<3 injections)	Yes[c]	Yes

[a]All injections are intramuscular.
[b]Consider more frequent immunization for elderly patients. Tdap recommended for ages 11 to 64 years old (Adacel, Sanofi Pasteur) and 65 years old and older (Boostrix, GalaxoSmithKlineBiologicals), although both products likely effective in the older than 65 age group.
[c]Refer these patients to complete their series; DTaP in 6 weeks and 12 months.
DTaP, Diphtheria, pertussis, tetanus toxoids; *TIG,* tetanus immune globulin.

diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Tdap) product formulated for use in adults and adolescents was licensed in the United States for people 11 to 64 years old. Updated recommendations allow for Tdap (Boostrix, GlaxoSmithKline Biologicals) to given to patients 65 years old and older, although it is likely that either Adacel or Boostrix vaccine will provide protection.[17] When possible, it is recommended that this triple combined formulation be used in the ED for tetanus prophylaxis of adolescents and adults. Although all four injections (T, diphtheria and tetanus toxoids [DT], TIG, and DTaP) are considered safe and effective in pregnancy, because of limited experience during pregnancy the recommendation is to use DT. However, DTaP is recommended immediately postpartum, including for breast-feeding women.

Box 52.3 summarizes the principles of wound care management.

BOX 52.3

Summary of Wound Care

I. Stabilize patient
II. History (include tetanus immunization and allergies)
III. Physical examination
  A. Neurovascular examination
  B. Anesthesia: Bupivacaine 0.5% without epinephrine, regional or local
  C. Bloodless field: Tourniquet or sphygmomanometer for extremities
  D. Thorough examination of anatomic structures, skin, nerves, tendons, blood vessels, bones, muscles, fascia, other (ducts, cartilage)
  E. Consultation if indicated
IV. X-ray films to detect injury to bone or the presence of foreign bodies (plain films, CT or ultrasound)
V. Wound preparation
  A. Cut—do not shave—surrounding hair
  B. Prepare surrounding skin with a chlorhexidine-alcohol solution
  C. Sharp débridement of foreign matter and devitalized tissue
  D. High-pressure irrigation with saline or a 1% povidone-iodine (Betadine) solution
VI. Wound closure
  A. Tape, staples, or suture
  B. Do not use subcutaneous sutures unless the wound is under high tension
VII. Antibiotics
  A. Apply topical antibiotics
  B. No systemic antibiotics unless wound is very high risk
VIII. Dress and immobilize: Consider a transparent gas-permeable dressing
  A. Wound care instructions (see Box 52.2)
    1. Signs of infection
    2. Elevation
    3. Wound check if necessary
    4. Suture removal as soon as possible

KEY CONCEPTS

- Risk factors for wound infection include crush mechanism; long (>5 cm) deep penetrating wounds; high-velocity missiles; diabetes; and contamination with saliva, feces, soil, or other foreign matter.
- The most effective intervention to decrease infection is thorough cleansing, with use of saline or tap water irrigation at approximately 8 psi. Attaching an 18-gauge needle to a 35-mL syringe creates an irrigant force of 7 or 8 psi, which decreases bacterial counts.
- Soaking wounds in povidone-iodine (Betadine) is more toxic than beneficial to healthy tissue. Prepare the skin with a chlorhexidine-alcohol solution.
- Antibiotics are indicated for through-and-through intraoral lacerations, cat bites, some dog bites, some human bites, puncture injuries to the foot in high-risk individuals, open fractures, and wounds involving exposed tendons or joints.
- High-risk wounds should not be sutured primarily but may be repaired in 4 or 5 days (ie, delayed primary closure).
- Tetanus immunization should be provided soon after injury but can be given days or weeks later. The usual incubation period for tetanus is 7 to 21 days (range, 3 to 56 days).
- Tdap is recommended for patients 65 years old or older requiring tetanus prophylaxis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 52: QUESTIONS & ANSWERS

52.1. Which of the following is associated with an increased risk of infection?
- **A.** Avoidance of epinephrine use in wound anesthesia
- **B.** High-pressure irrigation
- **C.** Use of clippers instead of razors for hair management near wound
- **D.** Use of silk suture material
- **E.** Use of tape over sutures for wound closure

Answer: D. Silk yields the highest infection rates, whereas monofilament synthetic substances have the lowest risk of infection.

Risk Factors for Wound Infection

1. Injury more than 8-12 hours old (varies depending on the following factors)
2. Location: leg and thigh, then arms, then feet, then chest, then back, then face, then scalp
3. Contamination with devitalized tissue, foreign matter, saliva, or stool
4. Blunt (crush) mechanism
5. Presence of subcutaneous sutures
6. Type of repair: risk greatest with sutures > staples > tape
7. Anesthesia with epinephrine
8. High-velocity missile injuries

52.2. A 32-year-old man presents with 20 stab wounds to his arms and legs after sustaining an assault. He weighs 80 kg. Which of the following is an appropriate dosage of wound anesthesia?
- **A.** 240 mg of 1% lidocaine
- **B.** 320 mg of 0.5% bupivacaine
- **C.** 400 mg of 0.5% bupivacaine with epinephrine
- **D.** 700 mg of 1% lidocaine with epinephrine

Answer: A. In adults, the maximal reported safe dose of bupivacaine is approximately 2.5 mg/kg without epinephrine and 3.5 mg/kg with epinephrine, assuming the injection is a wound infiltration technique and not one in a highly vascular area. General dose guidelines for lidocaine are 3 and 5 mg/kg without and 5 to 7 mg/kg with epinephrine, respectively. A 1% lidocaine solution contains 10 mg/mL. The actual percent solution does not matter; the total milligram dose does.

52.3. A 23-year-old female presents with a laceration to her thigh. As you begin to apply anesthetic, she tells you that when she went to the dentist she had an allergic reaction to procaine. Which of the following should you use?
- **A.** Benzocaine
- **B.** Benzocaine with epinephrine
- **C.** Bupivacaine
- **D.** Lidocaine from a multidose vial
- **E.** Tetracaine

Answer: C. Allergy to local anesthetics is uncommon. Two distinct groups of "caine" anesthetics exist. The esters include procaine, tetracaine, and benzocaine. The second group, including lidocaine and bupivacaine, belongs to the amide family. Allergy to the esters is uncommon. True allergy to agents in the amide family is rare. No cross-reactivity occurs between the amide and ester families, so an agent from a different group may be chosen. A "preservative-free" preparation should ideally be used because the para-aminobenzoic acid in multidose vials may cause an amine-like reaction that may be confused with an allergy to the primary agent.

52.4. Which of the following is most likely to require no antibiotic prophylaxis?
- **A.** Cat bite
- **B.** Diabetic with contaminated wound
- **C.** Dog bite
- **D.** Human bite
- **E.** Puncture wound through rubber sole

Answer: C. Antibiotic prophylaxis is often provided for patients with wounds with gross contamination, patients with severe crush injuries, and immunocompromised patients. Prophylaxis is also required for patients with cat bites. Seven of eight randomized trials of dog bite wounds showed no benefit with antibiotics. Human bites or lacerations to the metacarpophalangeal (MCP) joint are termed "fight bites," and these wounds have a high incidence of infection. Thus, of the choices given, dog bites have the lowest incidence of infection and therefore are the least likely to require prophylactic antibiotics.

52.5. Antibiotic coverage of a cat bite must target which of the following pathogens?
A. *Bacteroides* species
B. *Clostridium perfringens*
C. *Eikenella corrodens*
D. *Pasteurella multocida*
E. *Pseudomonas* species

Answer: D. The organisms found in cat bites include *Staphylococcus* species, *Streptococcus* species, and, most often, *P. multocida. P. multocida* is usually found in infected cat bite wounds and is present in the normal oral flora of 70% of all cats. *P. multocida* is sensitive to penicillin, but the infection is often polymicrobial. *P. multocida* is resistant to dicloxacillin, cephalexin, and clindamycin, and there are many erythromycin-resistant strains. Amoxicillin with clavulanate is the current recommendation for antibiotic prophylaxis for cat bites.

52.6. A 74-year-old patient presents with a gaping wound from a dog bite, complaining of pain at the site. The dog belongs to a friend, has reportedly had "all his shots," and is in custody. The patient is from Central America but has lived in the United States for more than 50 years; he does not recall his immunization history. Besides copious irrigation and wound dressing, which of the following should be included in the treatment of this patient?
A. Diphtheria, pertussis, tetanus toxoids (DTaP) and tetanus immunoglobulin (TIG)
B. Rabies immunization
C. Tetanus toxoid
D. Tetanus toxoid and immunoglobulin
E. B and D

Answer: A. Studies show that many people are inadequately immunized, especially patients older than 70 years old, immigrants, and people with no education beyond grade school. Patient immunization histories are often unreliable. Given the inability to predict which wounds are high risk, all wounds should be approached with suspicion. Inadequately immunized patients need a dose of DTaP and TIG. Because studies suggest that 10% to 40% of the population in the United States is inadequately immunized against diphtheria, diphtheria vaccination should be given along with tetanus toxoid. Many adults are not immunized against pertussis, and the incidence of disease has been rising since the 1980s. In 2005, a new acellular form of the pertussis vaccine became available and is recommended for all adults.

CHAPTER 53

Foreign Bodies

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PRINCIPLES

Patients often present to the emergency department (ED) with a complaint of a retained foreign body. The anatomical locations vary and may determine the management, emergent removal, and need for subspecialty referral or surgical removal under general anesthesia. Patients may be forthright with a complaint of a foreign body, but in some cases information may be withheld due to embarrassment.

Clinical Features

When people ingest or insert foreign bodies, often a brief history may be sufficient to establish the diagnosis, guide initial management decisions, and predict the process required for definitive removal. Those at higher risk of having a foreign body include neurologically impaired patients, edentulous individuals, patients with certain psychiatric diagnoses, incarcerated individuals, and individuals at the extremes of age. In these same groups, definitive history is often elusive, and the emergency clinician has to rely upon situational clues.

Depending on the location of the foreign body, the physical examination can provide direct or indirect evidence of the object. Specifics are described in the following sections, but there is a recurring theme, which is meticulous examination frequently establishes the correct diagnosis, as well as suggesting a successful extraction method.

Differential Diagnoses

Even when patients are fully cooperative, the diagnosis of foreign body can be complicated by the fact that patients can be unaware of the object's presence. Although foreign body cases are usually not diagnostic dilemmas, the emergency clinician should keep in mind the possibility of "foreign body mimics" such as angioedema.[1]

Diagnostic Testing

Plain radiography is classically the primary imaging modality that yields foreign body detection and characteristics of location, size, and number. Even when objects are not visualized, radiographs may show secondary changes (eg, pulmonary air trapping) providing clues to foreign body presence.[2] To assist in the localization, two views—anteroposterior and lateral—are usually necessary. Metallic objects are usually easy to visualize on plain radiography. For non-metallic (eg, organic) material with density similar to that of human tissue, visualization requires alternative imaging, such as ultrasound, magnetic resonance imaging (MRI), or computed tomography (CT).[3-5]

Management

Extraction is indicated in most cases. A discussion with the patient (or appropriate surrogates) should outline the benefits and risks of the anticipated course for foreign body removal. Sometimes a foreign body represents an immediate life threat, as is the case with an airway obstructing foreign body, and the need for urgent extraction action takes precedence. Even without overt life threats, some foreign bodies require expeditious removal. For instance, illicit drug leakage can kill a body packer, an impacted button battery can cause fatal tissue perforation and hemorrhage, or an otic insect can cause intense pain and damage sensitive ear structures.[6-8] Foreign bodies may serve as a nidus for infection that is recurrent or refractory to antibiotic therapy; definitive resolution only occurs with identification and removal. Specific recommendations for foreign body removal are presented in the following sections outlining management considerations by anatomic location.

Disposition

Most patients can be safely discharged home following uncomplicated foreign body removal. Retained foreign bodies may need surgical specialty follow-up, such as in an outpatient setting. Depending on anatomic location and patient ability to cooperate, some retained foreign bodies require surgical intervention under general anesthesia.

EYE

Principles

The diagnosis usually is self-evident. Ocular trauma without proper eye protection is the most common history.[9,10] Foreign bodies are occasionally identified by abnormal ocular examination findings without a stated history of trauma. For example, the cause of reduced vision in an intoxicated patient may be a foreign body (Fig. 53.1). Early diagnosis, care, and follow-up minimize risks, such as endophthalmitis or sight-threatening siderosis bulbi.[9,11]

Clinical Features

Most patients report a foreign body sensation, even though they cannot see the foreign body. The patient may complain of frequent lacrimation and conjunctival reddening. Foreign bodies that have created corneal injury and are no longer present may account for symptoms identical to those noted with a retained foreign body. Occasionally, patients with retained foreign bodies (such as, malpositioned contact lenses) can present with recurrent conjunctivitis.[12]

An important component of the history is whether radial keratotomy or similar ocular surgery has been performed. Historically, ophthalmologic procedures (such as, radial keratotomy) have been reported to be associated with increased potential for delayed-diagnosis foreign body entrapment.[13] Although more current literature contains little or no mention of these procedures as foreign body risk factors, the potential for situational

Fig. 53.1. Computed tomography (CT) scan shows right intraocular foreign body (BB pellet) in intoxicated patient without known trauma history.

relevance (eg, management of corneal foreign bodies) dictates a need for the emergency clinician to obtain a complete ocular surgical history.

The initial survey includes standard elements of the ED eye examination. Visual acuity at the time of presentation is a consistently reported predictor of ultimate visual outcome.[9,14,15] Slit-lamp examination allows the emergency clinician to detect a corneal foreign body by the shadow that it casts on the iris. The slit-lamp may also facilitate identification of rust rings. Fluorescein can aid in detecting abraded corneal epithelium.

The inner aspects of both lids should be examined. The lower lid is often successfully exposed with gentle manual retraction outward and downward as the patient looks upward. The upper lid can be successfully exposed through eversion, instructing the patient to look downward while upward eyelash traction is applied. During this procedure an applicator stick can be used to act as a fulcrum on the proximal edge of the tarsal plate. After location and removal of one foreign body, re-examination should occur to evaluate for other ocular foreign objects.

Differential Diagnoses

Selected differential diagnoses of ocular foreign bodies include corneal abrasions, conjunctivitis, iritis, glaucoma, allergic chemosis, and globe perforation.

Diagnostic Testing

If the history and mechanism of injury are compatible with ocular penetration by radiopaque material, or if a small wound of the globe is noted, anteroposterior and lateral radiography of the orbit is a reasonable initial step to evaluate for deeper penetration into the globe (see Fig. 53.1). Given its advantages in depicting small ocular foreign bodies and complications such as globe rupture, CT is the best initial approach, especially when there is strong suspicion of intraocular penetration.[16,17] CT has the additional utility of imaging of the intracranial compartment, which is often indicated in cases in which ocular trauma has occurred.

When globe penetration is strongly suspected, fluorescein is best avoided because its application can obscure findings in subsequent physical examination. Fortunately, the incidence of intraocular perforation in the setting of low-velocity (non-explosive) exposures is low. One case series of 288 patients reported a near-zero incidence of intraocular foreign body in patients with corneal metal foreign bodies after low-velocity exposures.[10] When perforation is judged unlikely and fluorescein is administered, identification of rivulets of fluorescein tracking from a puncture (ie, positive Seidel test) is helpful in identifying intraocular penetration.

Ultrasound is a useful adjunct to CT scanning in patients with foreign bodies that are difficult to localize.[18,19] For patients in whom a foreign body is suspected despite negative ED evaluation, outpatient referral to ophthalmology should be executed because CT, ultrasound, and even MRI have all missed ocular foreign bodies in patients who subsequently developed complications.[20] Given the paucity of reported case series and justifiable concerns about eye damage from mobilization of ferromagnetic foreign objects, use of MRI for ophthalmologic foreign body imaging remains controversial. When there is any chance of metallic object presence in the eye, the emergency clinician should not order MRI without consulting both ophthalmology and radiology specialists.[17]

Management

In nearly all cases, therapy is removal of the ocular foreign body. If the object is located on the bulbar or palpebral conjunctiva (*not* the cornea), it often can be removed easily by sweeping the site with a moist cotton-tipped applicator. For small corneal foreign bodies, after application of topical ocular anesthesia, it is often necessary to use an eye spur or small-gauge tuberculin syringe needle to move gently underneath one end of the object and flick it out. It is prudent for the emergency clinician to avoid significant corneal procedures in patients who have had corneal surgery, such as laser-assisted in situ keratomileusis (LASIK).

After the removal of a corneal foreign body that leaves no rust ring, treatment is essentially the same as for corneal abrasion. When there is a rust ring, ED management should be dictated by standing protocol (designed in collaboration with ophthalmologists) or referred to ophthalmology for removal.

Disposition

If attempts at foreign body removal are not indicated or are unsuccessful, the patient should be referred to ophthalmology for object removal within 24 to 48 hours. Ophthalmology referral should be initiated after removal of metallic foreign bodies because there may be subtle retained fragments or rust rings requiring removal.

EAR

Principles

Otic foreign body extraction can prove problematic, and the difficulty is rarely diagnosis. Instead, with otic foreign bodies the challenge usually lies in working in a sensitive anatomical region in a patient population that is often uncooperative.

Clinical Features

If the foreign body is an insect, the patient may report feeling motion or hearing buzzing. As compared to insect foreign bodies

in the nose or throat, those in the ear are far more likely to be living (and moving).[6] Less specific complaints include itching, discharge, or otalgia. Similar secondary symptoms may be present when non-insect foreign bodies are within the ear canal. Nonspecific presentations are common in children, who can be fearful of reporting a foreign body. The child presents only when there are secondary problems (such as, purulent discharge) from the affected ear.

If the ear canal foreign body erodes into the middle or inner ear, complications may range from malocclusion to eustachian tube dysfunction and serious infections (such as, mastoiditis and meningitis).[21] Although these situations are infrequent, recent literature outlines risk entailed with impression material (eg, silicone) used for indications, such as molding of hearing aids.[22,23]

History should include home attempts at foreign body removal. Such efforts may have caused problems, such as ear canal trauma or tympanic membrane perforation.

The cylindrical external auditory canal has two anatomic points of narrowing (and, thus, foreign object lodging). The first point is near the inner end of the cartilaginous portion of the canal and the second is at the point of bony narrowing called the *isthmus.*

Adequate lighting and an appropriately sized otoscope are essential to optimizing the visual search for otic foreign bodies. With any examination involving the external auditory canal, grasp the pinna of the ear and retract it in a posterosuperior direction to straighten the canal. This maneuver affords a more complete view of both the canal and the tympanic membrane.

If the tympanic membrane has been ruptured by the foreign object or by prior removal attempts, documentation should indicate the presence of rupture before ED attempts at foreign object removal. As in other body locations, the risk of multiple foreign objects warrants consideration.

Differential Diagnoses

The selected differential diagnoses of ear foreign bodies include otitis media, otitis externa, ear canal trauma, tympanic membrane perforation, Ménière's disease, and otologic tumors.

Diagnostic Testing

Diagnostic imaging is rarely required in otic foreign bodies. CT or MRI may be performed to characterize infectious or erosive sequelae.

Management

The treatment for otic foreign bodies is their removal, which should usually occur in the ED. Success rates for ED removal of ear canal foreign bodies vary with patient population and constituent foreign body types.

Even in a very young patient, presence of a foreign body for more than 1 or 2 days does not constitute an independent risk factor for foreign body removal failure or complication. In the absence of clear contraindications (eg, obvious tympanic membrane rupture), the emergency clinician should proceed with otic foreign body removal efforts, even in children with objects in the ear canal for a few days.

The patient should be informed about the extreme sensitivity of the auditory passage and the likely discomfort and potential for minor bleeding. Lidocaine instillation may aid in topical anesthesia; liquid 1% or 2% solution is preferred to gel preparations, which impair subsequent visualization.

Infrequently, foreign body removal requires local anesthesia of the external ear canal. The anesthesia instillation procedure may cause patient discomfort and iatrogenic injury if not performed with care (and patient control). The procedure entails injecting all four quadrants of the canal with lidocaine via a tuberculin syringe inserted through an otic speculum. Given complexity of local anesthesia to the canal, systemic procedural sedation and analgesia may be preferable.

When the ear canal is inhabited by an insect, it is important to kill or immobilize the creature to facilitate its removal. Any of a number of agents can be used to kill the insect. Topical anesthetics are recommended, and hydrogen peroxide should be avoided because of risk of injury to inner ear if there is tympanic membrane perforation. Efficacious formulations include lidocaine as a 10% spray or less concentrated liquid, 2% lidocaine gel, mineral oil with 2% or 4% lidocaine, and alcohol.

Immobilization reduces the chance of patient discomfort or ear damage caused by an insect attempting to evade forceps introduced into the ear canal. Patient comfort may also be optimized by minimization of shining light into an ear canal inhabited by light-avoiding insects (such as, cockroaches).

Several extrication methods may prove effective and various instruments may be useful. With soft or irregularly shaped objects, it is often possible to grasp the foreign body with forceps (alligator forceps are usually best) and remove it either in one piece or in fragments. If the object cannot be grasped, it may be possible to remove it by passing a blunt-tipped right-angle hook beyond the foreign body and gently coaxing it out. Alternatively, a balloon-tipped catheter can be passed distal to the object, with subsequent attempts to withdraw the (inflated) balloon, extracting the object. Any balloon-tipped catheter design may be used, as long as its caliber is small enough (about 18-gauge or smaller) to allow comfortable introduction into the ear canal.

Irrigation techniques take advantage of the elliptic shape of the external ear canal. A stream of lukewarm or room-temperature water or saline should be directed at the foreign body's periphery via a 20-mL syringe and a 14- or 16-gauge catheter; this arrangement has been studied in the laboratory and demonstrated to generate pressures that are well below those required to perforate the tympanic membrane.[24] Irrigation should not be used if there is known history, clinical suspicion, or physical examination evidence of tympanic membrane perforation.

Removal of objects from the middle ear with cyanoacrylate adhesive-tipped swabs is not recommended and carries the risk of contaminating the ear canal with a substance that is difficult to remove and has been associated with ear canal and tympanic membrane injury. When cyanoacrylate has been instilled into the ear, acetone instillation is recommended to facilitate its safe removal.[25]

Removal of otic foreign bodies must be undertaken with care and steadiness. Patient apprehension and sudden movements can risk untoward foreign body movement and avoidable damage to the ear canal.

Otic foreign body sequelae are usually not serious. There are sporadic reports, usually related to missed diagnoses and persistent ear canal objects, of serious complications ranging from chronic otitis to hearing loss, facial palsy, and deep-seated infections, such as mastoiditis.[21,22,26] The most common complications include external ear canal bleeding (10%), otitis externa, and (in about 2% of patients) tympanic membrane perforation.[27] Complications are more likely when the otic foreign body has been in place for prolonged periods, when patients are unable to be cooperative with removal attempts, and when practitioners are less experienced.[27]

After removal of the foreign body, the canal examination is repeated to ensure the lack of retained material and to evaluate otic anatomy. In cases in which the tympanic membrane is ruptured and the middle ear is at risk for infection, appropriate oral and topical antibiotics are recommended.

Disposition

If ED methods of removal are unsuccessful, the patient should be referred to an otolaryngologist within a week. More urgent referral is recommended for cases in which the tympanic membrane is ruptured, or in cases where foreign body removal proves particularly traumatic (in such cases the follow-up is aimed at assessing for external otitis).

NOSE

Principles

Although seen less frequently than otic foreign bodies, objects in the nasal passages are still commonly encountered in the ED. Compared with patients with otic foreign bodies, children with nasal foreign bodies tend to be younger (most commonly younger than 5 years old).[27]

ED removal is nearly always successful, and with proper technique (eg, care to avoid aspiration), serious sequelae are rare. Sedation with agents (such as, ketamine) is often necessary. Although evidence is sparse, the overall risk of nasal foreign bodies' entering the bronchial tree is low. Cases of intranasal magnets or alkaline button batteries, which may cause electrical or chemical burns and tissue necrosis, are exceptions and could cause more serious complications.[28-30]

Clinical Features

Most patients seek medical attention within 24 hours. Presentation delays are directly associated with increased likelihood of presentation with secondary complications, such as infection.[27]

Patients seen in the ED with nasal foreign bodies usually have one of two histories. More commonly, the patient admits to having, or was seen placing, an intranasal object. The less common history is one of purulent or bloody discharge (usually unilaterally) suggestive of an unreported foreign object. Unresolving rhinitis or sinusitis despite appropriate antibiotic therapy should raise suspicion for a nasal foreign body.

Preparing the patient for examination and subsequent removal attempts is advised. Because of risks of iatrogenic movement of the foreign body further posteriorly, children may need to be restrained to permit the examination. The nasal mucosa is normally quite sensitive, and this sensitivity is increased by any infection or irritation. Examination is facilitated by provision of topical anesthesia and vasoconstriction to the nasal mucosa. Examination should include both nares, with adequate lighting and visualization facilitated by use of a nasal speculum. The presence of the foreign body and any secondary tissue damage should be documented. Necrosis of the nasal mucosa and septum may accompany button battery impaction.[31,32]

Differential Diagnoses

The select differential diagnoses of nasal foreign bodies include nasal polyps, septal hematomas, nasal tumors, infectious and allergic rhinitis, and anterior and posterior epistaxis.

Diagnostic Testing

Diagnostic imaging does not usually play a major role, although plain radiography is important when there is suspicion for a metallic foreign body, such as a button battery.[32] When intrasinus foreign bodies are suspected, CT can be helpful. The potential risk of MRI for detection of foreign bodies may become more relevant with increasing frequency of foreign bodies related to magnetic jewelry (ie, nose rings and studs).[30]

Management

The emergency clinician is highly successful at removal of nasal foreign bodies and is only rarely a need for subspecialty consultation and operating room removal.[6,33,34] Foreign bodies that have eroded into the sinus space are an obvious exception to the rule of ED removal; admission for endoscopy in the operating room is recommended in such cases.[35]

Occasionally, positive pressure applied to the patient's mouth by a parent or relative achieves rapid foreign body dislodgment while obviating the need for restraint, sedation, and other requirements attendant to more invasive removal techniques. The underlying principle is that a short burst of air blown into the mouth of a child, with finger occlusion of the nonobstructed naris, may force the foreign object out of the nose. Insufflation, preferably applied a mouth-to-mouth maneuver from a parent, can also be provided by a manual ventilation bag (with a pop-off valve to prevent pressure rising above 30 mm Hg) or similar positive-pressure device.

Insufflation may be self-applied. Children can be instructed to take a deep breath and blow hard through their nose, as a parent closes the unaffected naris.

When insufflation is not warranted or is unsuccessful, ear, nose, and throat instruments and removal techniques may be required. Regardless of the method, the patient (usually a child) may benefit from some combination of restraint, sedation, and pretreatment with vasoconstrictive agents (eg, nebulized racemic epinephrine) and anesthetic (eg, benzocaine spray).[6] Adequate illumination is essential. Depending on the nature of the foreign object, necessary instruments include a blunt-tipped right-angle probe, suction catheter, and alligator forceps. The forceps are used when the foreign body is to be directly grasped, and the right-angle probe is used in an attempt to reach behind the foreign object and displace it forward.

Other useful instruments include Fogarty (vascular) and Foley catheters; commercially available "specialized" balloon-tipped catheters can also be used. Magnets may be useful when the intranasal foreign body is metallic and appropriately constituted.[29] In some cases, suction can be used to withdraw foreign bodies directly. Cyanoacrylate-tipped swabs may be useful in certain circumstances, although there are obvious risks of inadvertent contact between the glue and nasal mucosa.

Disposition

Patients with a simple foreign body presentation for whom the object is easily removed, do not require special follow-up. In cases where the nasal foreign body was in place for an extended period of time, or in cases for which removal was difficult or traumatic, otolaryngology follow-up in 24 to 48 hours should occur to assess for postextraction complications.

AIRWAY

Principles

Background and Importance

Children and the elderly are at high risk for foreign body aspiration. Most airway foreign body patients are younger than 9 years old, and there is a decline in incidence as mastication is facilitated by emergence of permanent teeth.[36] In adults, the elderly are at significant risk because of the presence of comorbidities such as neurological and dental conditions.[37]

The most common airway foreign bodies vary with the particular case series, and the case report literature includes an array of respiratory tract objects ranging from dental appliances to turban pins and wall plugs.[38-40] In most series, food items are commonly aspirated as are medications.[36,41]

Diagnostic delay is associated with increased complications in all patient age groups.[42,43] One pediatric study identified a doubling of complication rates with presentations delayed beyond 48 hours.[44] Patients with altered mental status from a variety of causes are at heightened risk for occult aspiration. Even in large-series reports of aspiration, the elusive nature of specific and reliable indicators of airway foreign body presence means that a concerning history should prompt a diligent foreign body search.[42,43,45]

Anatomy and Pathophysiology

Foreign bodies can be located as proximally as the oropharynx, with retained objects having been found in the palatal and pharyngeal mucosal regions.[46,47] Foreign body impaction at the laryngeal or subglottic level often is caused by inappropriately executed attempts to finger-sweep an oropharyngeal foreign body.

Airway foreign bodies that pass beyond the laryngeal inlet may cause complete obstruction. Foreign bodies passing beyond the carina are less likely to cause acute hypoxia because there is an unobstructed contralateral airway. Right-sided bronchial aspiration is the more common location because the carina is positioned right of the midtrachea in 40% of infants, and the proximal right bronchus is both wider and more steeply angled than the left.[47]

Foreign objects can be bilateral, and the rule for airway foreign bodies mirrors that for other foreign bodies: when one object is identified, there should be a search for a second.

Clinical Features

Clinical presentation can range from chronic nonspecific respiratory complaints to acute airway obstruction.[48] In one series of ambulance-transported airway foreign body patients 50% suffered cardiopulmonary arrest prior to ED arrival.[48] In most aspiration cases, foreign body presence can be suspected after a thorough history. Patients with airway foreign bodies may have noisy breathing, inspiratory stridor, vomiting, and hemoptysis.[49]

Some patients may give a history, known as the *penetration syndrome,* including a choking sensation accompanied by wheezing and coughing.[50] Coughing may not eject the foreign body completely but rather results in its impaction in the subglottic region. Therefore, coughing after suspected aspiration should prompt a search for a foreign body even if the symptoms improve.

In pediatric patients with suspected foreign body aspiration, sudden onset of choking or intractable cough associated with wheezing and respiratory distress is present in over 63% of cases.[36] In addition to coughing and choking, stridor is frequent.[51] Absence of early cough and choking is correlated with delayed diagnosis and chronic presentations (eg, recurrent pneumonia).[44,52,53]

With sudden onset of dyspnea and odynophagia, an impacted subglottic object may be present. If the object is known to be sharp and thin, the emergency clinician should suspect embedding between the vocal cords or in the subglottic region with resultant partial obstruction.

Other components of the history can help diagnose and characterize foreign bodies in patients with aspiration of nonfood objects. Many types of items may be aspirated by children who are exploring their environment. Another at-risk population comprises individuals who normally "store" small items in their mouths for quick access; examples of the latter include construction workers (nails) and seamstresses (pins).

Trauma patients with injured and loose teeth may have aspirated in the field or during emergency laryngoscopy for oral intubation. The incidence of airway aspiration of avulsed teeth or prosthetic dental appliances is low (0.5% of 1411 facial trauma patients), but both the initial trauma and subsequent airway management pose risks.[54] In some cases (such as, penetrating or blast trauma), the patient may be unaware of the potential for aspiration and not attribute symptoms to this entity. Patients aspirating objects that are long and thin (eg, needles, hatpins) may have minimal or no symptoms other than mild cough or chronic hemoptysis or odynophagia.[39]

The child with respiratory difficulty after eating can represent a diagnostic dilemma. Children with stridor or other respiratory symptoms may have airway foreign body aspiration or esophageal bolus impaction with external compression of the trachea. The pediatric trachea is soft, especially posteriorly, and may be compressed by a large esophageal body pressing anteriorly on the trachea. In addition, the trachea itself may be displaced anteriorly and kinked, causing a partial obstruction. Fever and localized infection may indicate bony aspiration (eg, into the piriform fossa) that may occur when bone-containing foods are fed to very young children.[55] Unfortunately, missed esophageal foreign bodies in children can result in wheezing and stridor from fistula formation; the result is long-term, yet mistaken, diagnosis and treatment for asthma.[56]

The presentation of patients with a retained airway foreign object may include only infectious complications. A foreign object may cause retropharyngeal abscess. A patient with atypical or recurrent pneumonia may have pulmonary infection secondary to persistence of a foreign object serving as a nidus of infection.

Physical findings depend on degree of airway obstruction and duration of the object's presence. Depending on size and location of the foreign body, the examination may show a normal patient, one with cyanosis and respiratory arrest, or anything in the range between these two extremes.[57,58] There are some useful findings. Unilateral diminution of breath sounds, present in over a third of cases in one large pediatric series, may help diagnose an aspirated foreign body.[36] Patients may be stridorous or hoarse with upper airway foreign objects, and intercostal or sternal retractions may be noted in patients with high-grade obstruction from tracheal foreign bodies. Hypoxemia may be present. Patients with secondary infection may have fever.

Oropharyngeal examination may reveal a foreign body posteriorly or "donor sites" of fractured teeth. The examination should include a search for fractured or missing dental prostheses. Oropharyngeal examination frequently can be augmented by indirect or direct laryngoscopy or nasopharyngoscopy, but these procedures should be performed only if the procedural stress does not pose undue risk of airway compromise.

Coughing may result from local irritation caused by bronchial foreign bodies. Localized or apparently generalized wheezing is frequently auscultated in patients with lower respiratory tract foreign bodies.[2] Complete obstruction of a mainstem bronchus may be associated with absent ipsilateral breath sounds; however, breath sounds can be transmitted across the thorax and the only physical abnormality may be asymmetric chest rise. Occasionally a foreign body acts as a one-way valve, allowing air into the lung during inspiration but permitting none to exit during expiration. The involved lung becomes hyperexpanded, and this finding may be detected as hyper-resonance to percussion.

Differential Diagnoses

The selected differential diagnoses of airway foreign bodies include anaphylactic reactions, acute pharyngitis, acute epiglottitis, retropharyngeal abscess, neck tumors, pulmonary carcinomas, pneumonia, bronchitis, bronchiolitis, and tuberculosis.

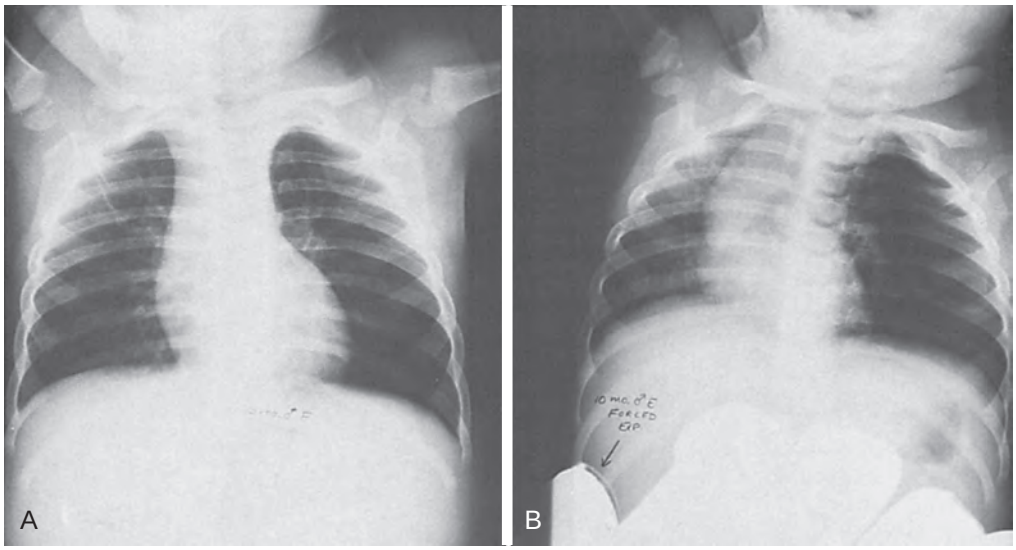

Fig. 53.2. A, "Normal" inspiratory chest film in child with left mainstem bronchus foreign body. **B,** Forced expiratory view shows expanded lung on the left with shift of mediastinum to uninvolved right side.

Diagnostic Testing

The main reason to characterize the type of airway foreign object is to determine the likelihood of radiopacity. Imaging decisions are informed by understanding whether a foreign body's constituent material is likely to be radiopaque.

Most airway foreign bodies are not visible with plain films. In 3149 aspirated foreign body cases, 84% of airway foreign bodies consisted of organic material (usually nuts) difficult to see on x-rays.[59] Nearly half of fatal choking cases in children are a result of radiolucent food aspiration. In the stable patient, plain radiography of the neck and chest remains the mainstay of initial airway foreign body imaging. Air trapping may be visible when inspiratory and expiratory films are compared but more recent literature casts doubt on the clinical necessity for adding expiratory views to plain radiography.[60] Decubitus chest x-ray positioning does not offer significant benefits to standard radiographs of the chest.[60]

A normal radiograph cannot rule out an aspirated foreign body in a patient with a suggestive history. Studies of series of patients who underwent endoscopy with confirmed foreign body aspiration demonstrate both low sensitivity and poor specificity.[60,61]

Specific findings on plain radiography are categorized as direct (ie, identification of the foreign body itself) or indirect (eg, hyperinflation). Radiographic findings are indirect in most cases, with hyperinflation and emphysema being far more common than pneumothorax.[61]

If doubt exists as to the radiopacity of the suspected foreign body, and if the patient has brought a piece of the object, it may be tested for radiodensity by placing it over the shoulder during taking of the radiographs. When subglottic foreign body impaction is suspected, plain soft tissue radiographs of the neck are the best initial step, provided that they are performed under the close supervision of a physician trained in airway management. Negative plain radiographs are not diagnostic, but clear identification of an airway foreign body can provide a rapid diagnosis leading to admission for endoscopy.

Indirect or secondary signs, such as subglottic space narrowing (from an embedded foreign object), are an important aid in foreign body radiography. Air trapping and atelectasis are the most common early clues to airway foreign body presence, with bronchiectasis and pneumonia developing later. In air trapping, a comparison of inspiratory and expiratory films shows a flat, fixed diaphragm on the involved side, and the heart and mediastinum shift to the uninvolved side during expiration (Fig. 53.2). In one classic pediatric series, air trapping was found in 90% of patients with lower airway foreign bodies, but subsequent years' clinical experiences confirm that the indirect signs of airway foreign body are easily missed on initial x-ray readings. If obstruction becomes complete, the involved lung becomes atelectatic and pneumonia can develop; patients with persistent atelectasis or pneumonia should have foreign objects considered as the explanation. An additional indirect radiographic sign of more proximal foreign bodies is prevertebral swelling or soft tissue emphysema seen on neck films.

In a stable patient when a foreign body is seen on the chest radiograph but its airway-versus-esophageal location is in doubt, the anteroposterior orientation of the object may help (Fig. 53.3). Esophageal foreign bodies usually are oriented in the coronal plane, and airway objects are oriented in the sagittal plane (Fig. 53.4). X-ray films also can provide useful information by showing whether the object is within or outside of the tracheal air column (Fig. 53.5).

Advanced imaging with CT or MRI is indicated when there is high clinical suspicion and plain radiography does not provide definitive results. These imaging modalities usually require a more extended period outside of the ED, so patients must be sufficiently stable for movement to the CT or MRI suite.[58]

CT or MRI benefits include characterization of extra-airway anatomical complications, such as perforation or bleeding. Visualization of a foreign body by advanced imaging can also eliminate a step in foreign body evaluation, allowing elimination of diagnostic flexible bronchoscopy in favor of movement directly to therapeutic rigid bronchoscopy for foreign object retrieval.

In usual practice, CT tends to be more rapidly accessible in most EDs, so CT is the advanced imaging modality that is most useful for foreign body searches. The role for MRI tends to be in diagnosis of foreign objects that are radiolucent (eg, nuts with high fat content).

CT (and less commonly, MRI) offers an additional utility—virtual bronchoscopy. Multidetector imaging provides a three-dimensional view of the tracheobronchial airway with proven utility in respiratory foreign body cases. One of the largest series

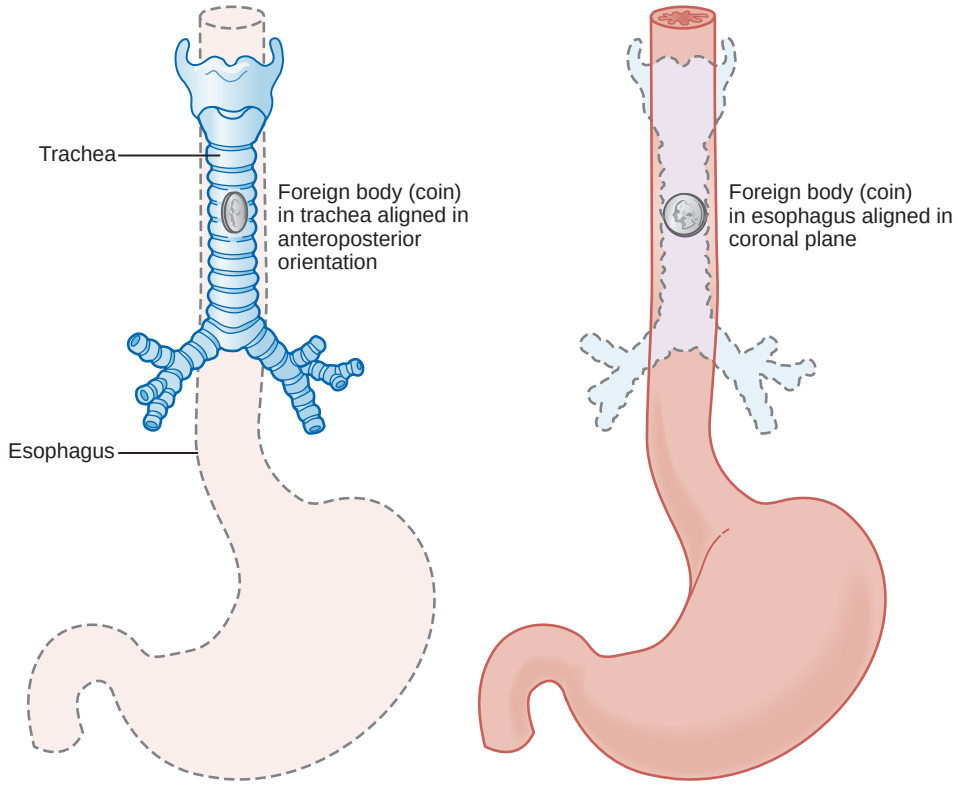

Fig. 53.3. Coronal orientation of esophageal foreign object *(left)* and sagittal orientation of tracheal foreign object *(right)*.

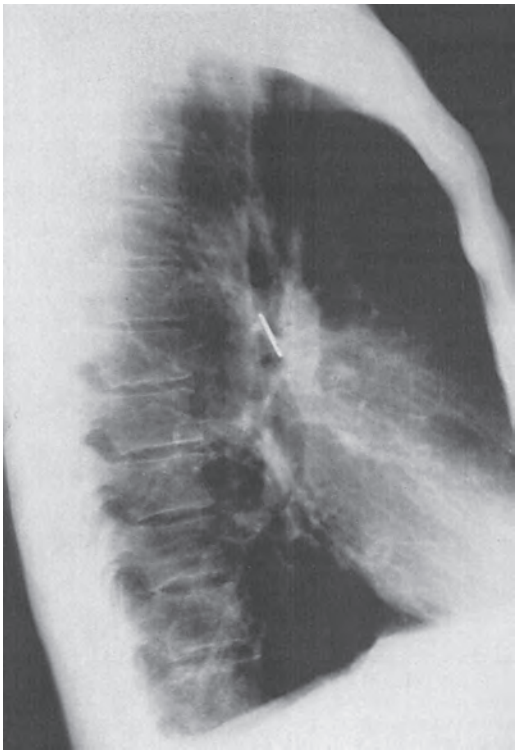

Fig. 53.4. Lateral x-ray study of chest shows aspirated coin in tracheal air column.

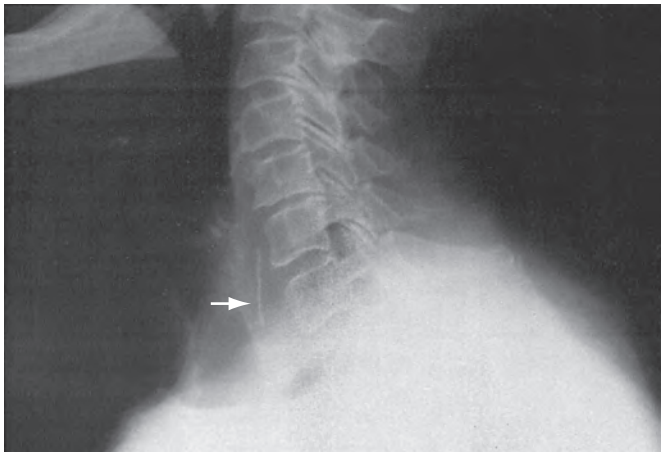

Fig. 53.5. Lateral x-ray study of neck shows foreign body (chicken bone) in esophageal soft tissue shadow *(arrow)*.

assessing utility of CT virtual bronchoscopy compared the new imaging technique with findings from rigid bronchoscopy in 60 pediatric patients with vegetable foreign bodies. In only one of the 60 cases was CT virtual bronchoscopy incorrect—identifying a thick mucus plug as a foreign body—thus yielding an overall positive-predictive value of 98%.[62] CT virtual bronchoscopy should be considered when clinical suspicion is high and initial radiography is nondiagnostic.

Fluoroscopy was historically useful in airway foreign body evaluation. This modality has been supplanted by other advanced imaging techniques (eg, CT, bronchoscopy).

Management

Management of an airway tract foreign body is removal, which generally leads to rapid recovery of the patient. When the foreign object is distal to the oropharynx, subspecialty consultation is the safest means for foreign body removal. In rare cases, even oropharyngeal foreign bodies (such as, small needles) may necessitate subspecialist consultation and operative removal.[63] As a general

rule, early consultation with an otolaryngologist to perform bronchoscopy in any patient with a suspected foreign body is key to reducing morbidity and mortality; the role of endoscopic management remains important given limitations of other diagnostic methods.[59]

In a patient with critical airway obstruction and impending or actual respiratory arrest, the emergency clinician must act quickly to identify and remove the foreign body. There are generally three options: (1) attempt to extract the foreign body with maneuvers, (2) perform laryngoscopy or fiberoptic nasopharyngoscopy with attempts at removal under direct visualization, or (3) control the patient's airway. If at all possible, emergent consultation with other specialties who can assist in advanced airway management is imperative (eg, otolaryngology, anesthesiology, surgery).

Oropharyngeal foreign bodies may be removed with use of pediatric or adult Magill forceps after visualizing the foreign body in the mouth. Blind finger sweeps should never be performed to remove a foreign body.

The basic life support management of a choking infant includes up to five back blows with the patient in a head-down position, followed by chest thrusts. In children, the Heimlich maneuver may be considered in the choking but conscious patient. In children who are unconscious, chest compressions are begun in cycles of five and the oropharynx visualized between cycles to see if the foreign body has been expelled into the mouth. If basic maneuvers fail to dislodge the foreign body allowing removal from the mouth, direct laryngoscopic visualization followed by removal of the object with Magill forceps should be performed.[64] When a foreign body is not visualized on laryngoscopy, the foreign body lies below the level of the vocal cords or is in the esophagus. The emergency clinician may choose to attempt to intubate the patient to establish an airway, but this is not without significant risk.

Intubation may force the foreign body distally, especially if the endotracheal tube tip is passed beyond the carina. Placement of the endotracheal tube into the right mainstem bronchus may displace the foreign body into the right bronchus, allowing oxygenation and ventilation through the left-sided pulmonary tree when the endotracheal tube is withdrawn back to normal position proximal to the carina. If the foreign body is in the esophagus, endotracheal intubation may provide necessary stenting of the trachea to keep the airway open.

In cases in which intubation fails because of positioning of the proximal foreign object, surgical cricothyrotomy (needle cricothyrotomy in young children) is indicated. Cricothyrotomy may bypass such proximal obstruction and provide sufficient oxygenation to bridge the time gap to further definitive care by surgical subspecialists.

Patients who do not require immediate intubation or cricothyrotomy for complete airway obstruction may require airway management for other indications. These patients may have poor oxygenation, severe respiratory distress, and or hypoventilation. Especially in pediatric patients requiring bronchoscopy, the laryngeal mask airway may be an appropriate approach if ED airway management is necessary.[65]

In noncritical situations, the only airway foreign objects generally amenable to emergency clinician removal are those in the oropharynx, which is best removed by forceps under direct laryngoscopic (including fiberoptic-facilitated) visualization performed after administration of topical anesthesia.[66] Care should be taken when nonobstructing foreign objects appear to be impaled in the oropharynx because postremoval hemorrhage can occur. These should be removed in the operating room under general anesthesia. Removal of a laryngeal foreign object, even with general anesthesia, can be dangerous. Risks include hemorrhage, laryngeal trauma, and airway obstruction from the mobilized foreign object. Also, special care should be taken to prevent posterior displacement of oropharyngeal foreign objects or dropping of incompletely grasped proximal foreign bodies into the more distal airway.

The management decisions for endoscopic evaluation and treatment depend on the clinical presentation. When there is time-critical airway obstruction, rigid bronchoscopy is employed with flexible instrumentation used for diagnostic purposes in less acute patients.

Disposition

Pediatric data suggest that performance of bronchoscopy within 24 hours of initial ED presentation reduces complications by half.[44] Even after foreign body removal, sequelae may occur and can range from bleeding to infectious complications. Patients with a lower airway foreign body should be admitted for foreign body removal and observed for development of sequelae with postdischarge follow-up within a few days of removal of the foreign body.

GASTROINTESTINAL TRACT

Principles

Most cases of gastrointestinal foreign bodies occur in pediatric patients, but adults are also at risk particularly if they are edentulous or if there are psychiatric conditions.[67,68] Higher risk is present in cases in which chemical or electrical mucosal injury is likely (eg, button battery or magnet ingestions).[69] Perforation occurs in approximately 3% of cases and most frequently involves the esophagus or the ileocecal region.[70]

Pharynx and Esophagus

Clinical Features

Foreign bodies lodged in the pharynx and esophagus are usually a sharp object (eg, fishbone) that is impaled in the wall of the pharynx, hypopharynx, or esophagus or a larger bolus, usually a coin or food, that cannot pass beyond the anatomic points of esophageal constriction. Pediatric series report that coins are the most common culprit, comprising well over half of ingested foreign bodies.[71]

Esophageal constriction locations, where foreign objects tend to lodge, are (1) the proximal esophagus at the level of the cricopharyngeus muscle and thoracic inlet or, radiographically, the clavicular level; (2) the midesophagus at the level of the aortic arch and carina; and (3) the distal esophagus just proximal to the esophagogastric junction or, radiographically, a level two to four vertebral bodies cephalad to the gastric bubble. In one 15-year pediatric series, 92% of esophageal foreign bodies were impacted at the cricopharyngeal level.[71] Foreign bodies may lodge at any level of the esophagus (or remainder of the gastrointestinal tract) with abnormal anatomy.

The complication rate for esophageal foreign body ingestion depends on the nature of the foreign body, the presence of impaction, and the duration of impaction. Overall, complications are rare, but there are important exceptions for perforating foreign bodies or those (eg, button batteries) that mediate chemical damage.[72,73] Complications become more likely with increasing impaction time and include esophageal erosion or perforation, tracheal compression, mediastinitis, esophagus-to-airway or esophagus-to-vascular fistulae, spondylodiskitis, extraluminal migration, abscess development, and formation of strictures or false esophageal diverticula.[74,75]

In addition to coins, other common objects impacting the esophagus include but are not limited to food, toys, bones, batteries, wood, and glass. Esophageal rupture is a particular risk from

the button (disk) battery. These batteries cause pathologic changes through pressure, electrical current, leakage of corrosives, or heavy metal poisoning.[76] The identification of button batteries has both prognostic and therapeutic ramifications. Esophageal button battery impaction is considered an indication for prompt endoscopic intervention and removal.[73,76] Although not as likely as button batteries or sharp foreign bodies to cause esophageal rupture, practically any ingested foreign body (eg, meat) can cause rupture if patients vomit repeatedly after impaction.

Children usually are brought to the ED within 6 hours of foreign object ingestion. The most frequent presenting symptoms are dysphagia, drooling, retching, and vomiting. Pain, usually odynophagia, may be the major complaint. Anorexia, wheezing, or chest or neck pain also may be present.

Patients may complain that they can feel the object in the throat or chest, are unable to pass it, and are often able to localize the foreign body accurately. This presentation is particularly common if the foreign object is lodged in the upper esophagus. Drooling is consistent with high-grade obstruction.

Patients with suspected esophageal foreign body impaction rarely have complaints of shortness of breath or air hunger. When these findings are present, the emergency clinician should suspect a large esophageal foreign body impinging anteriorly and compressing the trachea. Infants and children may experience coughing, choking, croup-like symptoms, or significant respiratory compromise from foreign bodies lodged in the upper esophagus.[73]

Patients may manifest late sequelae. Foreign bodies serving as a nidus for infection can result in complaints, such as fever. Signs of mediastinitis indicate esophageal perforation. Perforation of the esophagus with erosion into the vasculature or pulmonary tree can result in presentations ranging from hemoptysis to pulmonary abscess or life-threatening hemorrhage.

The history should include any known esophageal anatomic abnormality or prior instrumentation. A patient with a history of esophageal stenting should be considered to have stent migration when the history is dysphagia. Migration typically occurs within the first week of placement.

Examination begins with a careful inspection of the pharynx and hypopharynx. This search may reveal the foreign body or identify an oropharyngeal mucosal scratch that can cause foreign body symptoms even in the absence of an impacted object. Oropharyngeal examination also may provide indirect clues; for example, a missing dental plate on examination should lead the emergency clinician to suspect this item as a possible gastrointestinal tract foreign object. The base of the tongue, vallecula, supraglottic area, epiglottis, and piriform sinus should be examined. Topical anesthesia facilitates the examination. If adequate visualization is not obtained with the indirect laryngoscopy mirror, fiberoptic nasopharyngoscopy or direct laryngoscopy may be performed.

Subcutaneous emphysema found by neck palpation indicates probable esophageal perforation.

Differential Diagnoses

The selected differential diagnoses pharyngeal and esophageal foreign bodies include acute pharyngitis, acute epiglottitis, retropharyngeal abscess, esophagitis, strictures, esophageal webs, and oral cancers. When the history is unclear, the emergency clinician should consider an ingested foreign body in the differential diagnosis of atypical chest pain, wheezing, stridor, or signs of respiratory distress.

Diagnostic Testing

The fact that most foreign bodies (eg, coins) are radiopaque accounts for reports that radiography contributes to diagnosis and management in most cases of esophageal impaction.[77] The initial step is generally a posteroanterior and lateral chest radiograph and lateral cervical spine x-ray study using soft tissue technique. The primary utility of plain radiography lies in detection of radiopaque objects, with indirect findings (eg, soft tissue swelling) more likely of utility in cases where there are chronic foreign bodies with complications.

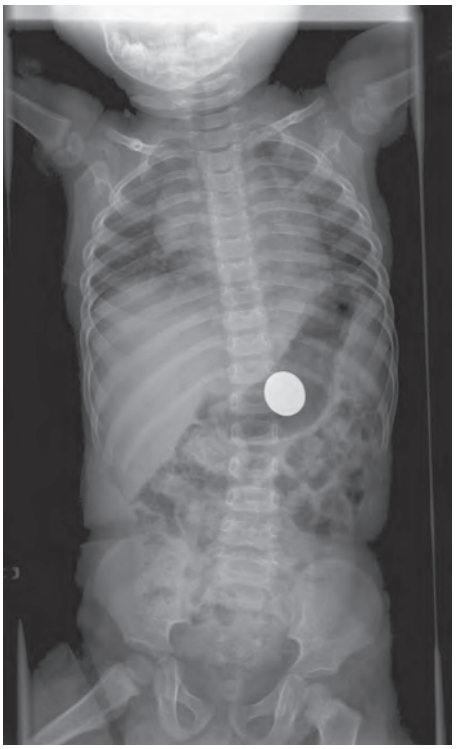

Fig. 53.6. Radiograph of a child after ingestion of a coin, located in the stomach.

Overall, the sensitivity of plain radiography for detection of esophageal foreign bodies depends on the nature of the foreign body. In patients who are transferred to the ED from an outlying hospital, repeat radiography may be useful to assess whether the foreign object has passed into the stomach in the interval since prior films (Fig. 53.6).

Esophageal foreign objects usually align themselves in the coronal plane and are posterior to the tracheal air column on lateral view. Coins in the esophagus lie in the coronal position in virtually all cases because the opening into the esophagus is much wider in this orientation (see Fig. 53.3).

Certain common foreign bodies are not radiopaque. Fish and chicken bones are frequently ingested, are difficult to visualize directly or radiographically, and often scratch the esophageal mucosa. Although some studies suggest that technique variation improves fish bone detection, plain x-ray examination remains insufficiently sensitive as a means to rule out these foreign bodies and CT is recommended when initial imaging is negative.

When plain films fail to visualize foreign bodies and suspicion remains high, one option is contrast esophagography, which can be useful with radiopaque and sometimes with radiolucent foreign bodies. If perforation is not a concern, barium may be used as the contrast medium because it provides higher-quality images. If an esophageal leak is suspected, water-soluble contrast solution should be used. When initial contrast films are not definitive, patients may be asked to swallow a contrast-soaked cotton ball, which may localize the foreign body by lodging proximal to the object.

Contrast studies, even performed with barium, have limitations when the suspected object is an impacted bone. Barium swallow yields better results but risks aspiration and coats the object and esophagus, reducing effectiveness of subsequent endoscopy.

CT scans with coronal and sagittal reconstructions are useful in identifying foreign bodies or more completely characterizing objects that are only vaguely appreciated on plain films. For some suspected foreign bodies that tend to be radiolucent, CT may be the primary diagnostic modality because it can give information about foreign body size, type, location, and orientation with respect to other anatomic structures. CT also can assist with identification of complications, because it can assess extra-esophageal anatomy.

One interesting modality reported in detection of metal foreign bodies is the handheld metal detector. This modality does not involve risk or ionizing radiation, has no complications, and is quite useful with reported sensitivity approaching 90%.[78] Especially when results are positive and indicate a foreign body below the diaphragm, or when the metal detector is used to track foreign body progress (eg, coin passage) over time, this modality can obviate the need for radiography.[78,79]

Management

Pharyngeal foreign bodies visualized by direct or indirect laryngoscopy usually can be removed with forceps or a clamp. The emergency clinician should guard against the possibility of inducing trauma or airway obstruction during extraction attempts.

With an esophageal food bolus or coin, the emergency clinician may be able to provide definitive management. With sharp objects, displaced esophageal stents, or impacted button batteries, more invasive and specialty specific management is necessary. Treatment strategy depends on the nature of the foreign body, the length of time the object has been lodged, and the expertise of the clinicians managing the case. In addition, the patient's age and prior medical and surgical history may be relevant. The overall success rate for endoscopic (ie, nonsurgical) removal of esophageal objects is very high.[71]

When the esophageal impaction is food, pharmacologic maneuvers are the first basic strategy for foreign body management. These steps are appropriate only if the object is known to be an impacted food bolus. The first medication that may be administered in an attempt to move a distal esophageal food bolus into the stomach is intravenous glucagon (0.5 to 2 mg). The drug appears to act by lowering the smooth muscle tone at the lower esophageal sphincter without inhibiting normal esophageal peristalsis. Glucagon's historical efficacy of relieving esophageal food impaction in about a third of cases has been confirmed in more recent series.[80] It should be noted that glucagon is less effective in esophageal eosinophilic infiltration, which diagnosis may be increasingly reported by food-impaction patients presenting to the ED.[80,81]

Although it remains reasonable to try glucagon, the drug should be given slowly. If glucagon is given rapidly, there is theoretical risk that the induced vomiting could cause rupture of an obstructed esophagus.

Gas-forming agents have been historically used for ED treatment of impacted esophageal food bolus, and this approach has little or no recent evidentiary support. These medications also incur a known risk of mucosal injury and are not recommended.

Two other agents, nitroglycerin and nifedipine, have been historically used for distal food bolus impaction but are not as useful as glucagon and thus not recommended for use in the ED. Both of these agents have a relaxing action on the lower esophageal sphincter, yet they appear only marginally effective as therapy for impacted food bolus. A last approach, enzymatic degradation of an impacted meat bolus by use of the proteolytic enzyme papain, has fallen into disfavor because of risks of esophageal perforation.

The preferred strategy for impacted esophageal foreign body removal is, in most cases, early endoscopy.[82] Flexible endoscopy is the optimal early course for a variety of esophageal foreign bodies, including coins. The procedure does not require general anesthesia, can be performed in a sedated (nonintubated) patient, and may be diagnostic and therapeutic.[81]

The final strategy for foreign body removal, bougienage, involves pushing the foreign object into the stomach. The emergency clinician is generally not responsible for patient selection or actual performance of this procedure.

Expectant management, hoping for spontaneous foreign object passage into the stomach, is often successful. This approach is best suited for patients seen within 24 hours of ingestion who have a radiographically identified "safe" object (eg, small coin) in the distal esophagus.

Disposition

If a disk battery or magnetic object has been ingested, the location must be ascertained. If lodged in the esophagus, ED consultation should be directed toward emergent removal by endoscopy. If the object has passed distal to the esophagus, observation may be appropriate but the high risk of these cases dictates involvement of appropriate gastrointestinal consultants in management decisions.[69]

Regardless of the method used for esophageal foreign body therapy, there should be a follow-up evaluation of esophageal anatomy and patency after the removal of any esophageal object. Referral for such evaluation should be made by the emergency clinician.

Stomach and Bowel

Principles

Foreign bodies that reach the stomach (Fig. 53.7) rarely cause major difficulties, although problems may occur, such as perforation and infection (eg, after occult fish bone ingestion).[83] Objects may still become impacted, most often at the gastric outlet or the ileocecal valve, although complications can arise at any point throughout the intestinal portion of the gastrointestinal tract. The increasing frequency of pediatric magnet ingestions is contributing to an increasing complication rate seen with gastrointestinal foreign objects.[8]

Clinical Features

Symptoms of intraluminal objects range from none to vague abdominal pain to obstruction or perforation-associated peritonitis. Most patients have a specific history of ingested items.

Hiding of illicit drugs is a relatively frequent motivation for foreign body ingestion. Rupture of these drug-containing packages, especially when cocaine is involved, can result in rapid, lethal consequences.[84] Less often, such packages can cause bowel obstruction. Even when obstruction is not present, vomiting may be reported. *Body packing,* which entails systematic gastrointestinal tract placement of previously prepared drug packages (Fig. 53.8), should be clinically differentiated from *body stuffing,* which denotes hurried ingestion of hastily prepared packages in the face of imminent police presence. Due to the poorly organized wrapping of illicit drugs, body stuffers are more likely to experience toxicity and less likely to have well-delineated findings on plain radiography. Drugs most often seen with body packing or body stuffing are cocaine and heroin.

Fig. 53.7. Radiograph of a child after ingestion of a fishing lure without hooks.

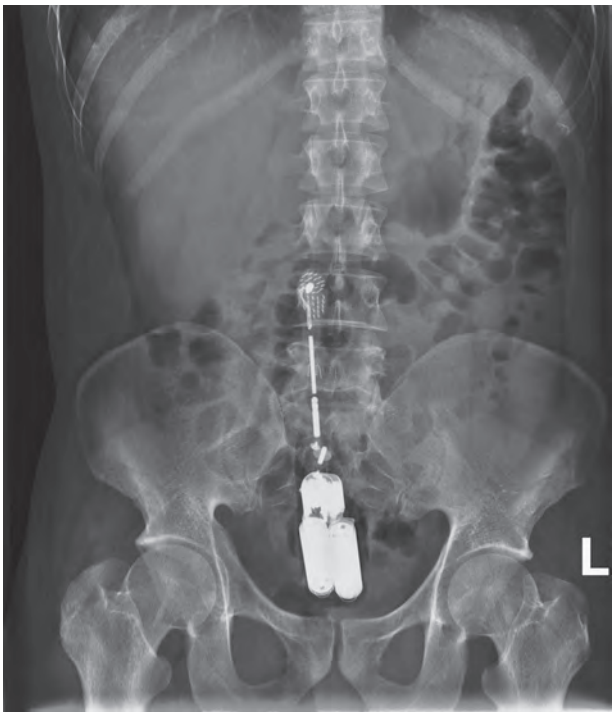

Fig. 53.9. Radiograph of a patient who inserted an electronic toothbrush into the rectum. The toothbrush was removed during proctoscopy.

Fig. 53.8. Radiograph of a patient after body packing. Note the appearance of previously prepared drug packages.

Another important component of the history is medical implants in the gastrointestinal tract. Dental hardware and biliary stents are among the implants that can migrate and cause complications in the distal gastrointestinal tract.[85,86]

Patients with gastrointestinal tract foreign bodies should be asked about history possibly related to bezoar presence. A habit of chewing hairs can result in trichobezoars, which infrequently extend from the stomach into the small intestine as a "tail" (Rapunzel syndrome). Phytobezoars (composed of vegetable matter) and lactobezoars (from milk curds) also have caused complications, usually in the stomach. Other bezoars may be composed of infectious material (eg, fungal bezoars) or inorganic substances (eg, lithobezoars). Ingested toothpicks can lodge in the bowel wall, causing gastrointestinal complications and erosions or compression of nearby structures.[87]

If the foreign body is a bezoar (a mass of indigestible food or nonfood material), there may be a palpable mass on abdominal examination. Physical findings may also include abdominal examination abnormalities typical of bowel obstruction or peritonitis.

Differential Diagnoses

The selected differential diagnoses of stomach and bowel foreign bodies include peptic ulcer disease, gastroesophageal reflux disease (GERD), gastric outlet obstruction, gastric tumors, bowel obstruction, intestina polyps, and small and large bowel carcinomas.

Diagnostic Testing

Because most ingested foreign bodies are radiopaque, the initial imaging modality of plain radiography is often diagnostic (Figs. 53.9 and 53.10; see Fig. 53.6).[88] Even when suspicion is low, radiography can identify foreign bodies as the explanation for symptoms. Two-view plain radiography has proved useful for situations ranging from coin ingestion to body packing (see Figs. 53.6 and 53.8).

The sensitivity of plain radiography varies widely, depending on the nature of the foreign material. When plain films are nondiagnostic, follow-up contrast radiography or CT is recommended. Contrast administration for some CT-delineated foreign bodies can identify the objects and assess for complications, such as perforation.[89]

In the setting of body packing or body stuffing, the preferred CT imaging approach is avoidance of oral contrast, but even this approach has been reported to have sensitivity of well under 50%

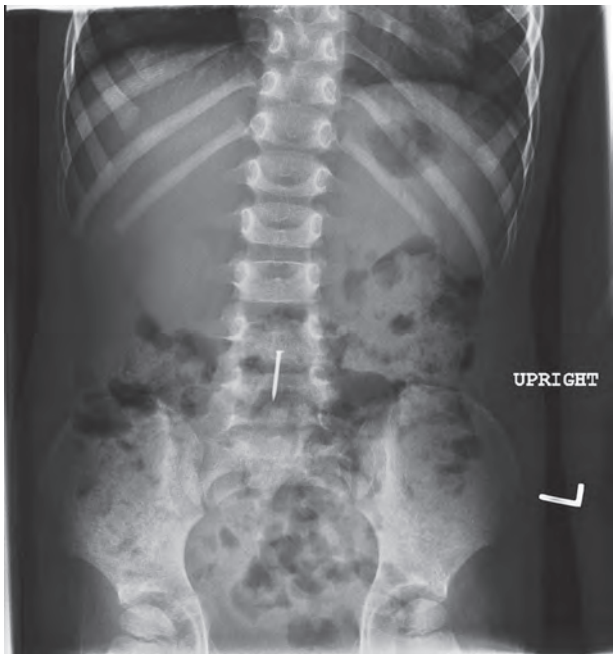

Fig. 53.10. Radiograph of a child after ingestion of a nail (which ultimately passed after observation).

for either detection or enumeration of packs.[90] Ultrasound is useful in drug packet cases in which plain radiography is nondiagnostic, when there is need for an initial screening test, or when previously identified packets need to be tracked without ionizing radiation.[91] Negative ultrasound results are nondiagnostic.

Management

The general rule for the management of gastric or intestinal foreign bodies is observation, with radiographic and stool follow-up to confirm passage. As is the case with esophageal impactions, more referral centers are reporting early endoscopy as a useful approach due to the modality's low risk and high efficacy.[92] However, for the routine cases (eg, coin ingestions) encountered by emergency clinicians, most ingested objects are expected to pass spontaneously if patients have normal anatomy.

Management decisions are based in part on the nature of the ingested object. Blunt objects can be expected to pass through the bowel with expulsion verifiable by stool collection and examination. If there is particular concern, serial radiographs may be obtained after a week. Sharp objects (such as, needles) may be recovered via endoscopy, but consultants (with whom all sharp gastrointestinal foreign bodies should be discussed) may decide to manage these cases expectantly.[93,94] Early removal generally is required for objects wider than 2 cm because they do not pass the pylorus or longer than 5 to 6 cm because they do not clear the duodenal sweep.[94,95] Overall, surgery is rarely required in intestinal foreign body cases, but there will be cases (eg, bowel obstruction) in which clinical circumstances prompt early operative intervention.

When chosen, observation should be continued until (1) the object is found in the patient's stool; (2) the object becomes associated with bowel obstruction or perforation, necessitating immediate surgical intervention; or (3) the object shows no evidence of progression through the gastrointestinal tract on two radiographic examinations performed 24 hours apart, indicating impaction and need for active removal.

In a body packer or body stuffer (see Chapters 149 and 156), regardless of law enforcement pressures, the emergency clinician should perform only interventions justified medically as reasonable steps to prevent injury from the ingested object or substance. If emergent drug package retrieval is medically unwarranted, the patient should be admitted for close observation for package passage or signs of toxicity. Monitoring drug metabolites in the urine may be helpful. Usually the package passes through the gastrointestinal tract spontaneously. This passage can be facilitated with polyethylene glycol solution, laxatives, or both.[96] Immediate removal of drug-containing packages should be considered if the patient develops intestinal obstruction or drug intoxication. Endoscopic removal of drug-containing packages is associated with theoretical risk due to package rupture and drug intoxication, but endoscopy remains a therapeutic mainstay in patients who are not passing ingested packets spontaneously.[96]

Button batteries and magnets represent an additional group of foreign body types with specific management implications. Intact objects of this category that are ingested and pass into the stomach can be observed without the immediate removal necessary in cases of esophageal impaction. Administration of polyethylene glycol solution may speed distal movement. If the foreign body has not been passed after the first few clear-liquid stools, repeat radiography may identify objects in the rectum, where they may be digitally evacuated. The emergency clinician should obtain early consultation (for endoscopy or surgery) when button batteries or magnets are encountered in the gastrointestinal tract, because the complication rates with these objects are higher than for other foreign bodies.[97-100] Available evidence is insufficient to confirm usefulness of adjuvant medications (eg, steroids, antireflux agents, prophylactic antibiotics) in cases of button battery ingestion.[76]

Disposition

For button battery or magnet ingestions that are managed expectantly, repeat radiographs should be taken the next day to ensure movement of the object into the intestinal tract. X-rays should be repeated at least every 3 to 4 days thereafter to confirm continued distal movement. Management of other foreign bodies and bezoars depends on type and location. Infants with lactobezoars should be changed to elemental diets with close follow-up; most cases resolve without surgery.

Rectum

Principles

Most anorectal foreign bodies result from retrograde introduction, typically as a result of sexual practices.[101,102] Prompt diagnosis is crucial because delay in definitive treatment is strongly associated with complications.

Clinical Features

Patients with anorectal foreign bodies are often hesitant to provide accurate histories. Studies have found that many patients with self-introduced anorectal foreign bodies do not freely admit to insertion but rather report anal pain or simply constipation. Other complaints include rectal pain, bleeding, or inability to void when large objects impinge on the urethra.[102]

It is possible for ingested food or objects (eg, fish bones) to lodge in the rectum after passing through the proximal gastrointestinal tract. The duration for which the object has been in the anorectum has implications for mucosal failure and rupture.

Patients with anorectal perforation may have findings of peritonitis or abdominal tenderness. On digital rectal examination, the foreign body might be directly palpated; this is the method of diagnosis in a large number of cases. In the absence of direct

foreign body palpation, digital rectal examination may reveal findings (eg, bloody discharge, loose sphincter tone) that raise suspicion for anorectal foreign body.[102]

When the digital rectal examination findings are negative or when better visualization is required, anoscopy is the next step. Although the anoscope's diameter limits the size of foreign bodies that may be extracted through the instrument, anoscopy affords an improved view of the object's nature and positioning. Rigid sigmoidoscopy may be performed, with special care taken to minimize pressure on possibly ischemic anorectal mucosa.

In many patients, especially patients in whom multiple examinations or removal attempts have been made, sedation and analgesia may be required to enable invasive examination techniques. When there is any doubt about the integrity of the anorectal mucosa, invasive examination is best done in the operating room with use of general anesthesia.[102,103]

Differential Diagnoses

The selected differential diagnoses of rectal foreign bodies include internal and external hemorrhoids, anal fissures, rectal and anal tumors, perirectal and anal abscess, and rectal vault stool impaction.

Diagnostic Testing

With rectal foreign bodies, the history usually renders imaging unnecessary unless there is a need to assess for complications, such as perforation or abscess. When diagnostic radiography is needed, plain films are recommended as the initial step and will often demonstrate the foreign body (Fig. 53.11, see Fig. 53.9). An important secondary finding on plain films is free intra-abdominal air secondary to anorectal perforation. If the object is not visualized on plain x-ray studies, a contrast study can be performed, with care taken to minimize hydrostatic pressures on potentially compromised mucosa. Water-soluble contrast should be used if perforation is suspected. CT should be employed to provide defining detail when plain films are nondiagnostic or if complications (eg, perforation) are suspected.[104]

Fig. 53.11. Radiograph of a patient who inserted an aerosol can into the rectum.

Management

With patience and judiciously administered procedural sedation and analgesia, the emergency clinician often can remove rectal foreign bodies. Surgical intervention may be necessary on occasion. Depending on the nature of the foreign body and the presence of damage or perforation of the rectal wall, transanal removal (with or without sedation and local anesthesia) is successful in roughly half of patients.[105] Some advocate early triage of patients for operating room removal if ED foreign body extraction carries undue risk of anal sphincter injury.[106] The emergency clinician should not attempt to retrieve objects that pose high risk for rectal injury (eg, light bulbs).

Initial efforts at foreign body removal in the ED should begin with the examiner's digit. Small rectal objects occasionally can be hooked by the finger and withdrawn. The digits should be lubricated with lidocaine jelly, and gentle abdominal pressure may be applied posteriorly and inferiorly in an attempt to mobilize foreign objects distally.

When digital extraction fails, the emergency clinician should attempt to use an anoscope or small vaginal speculum to visualize the foreign body. Ring forceps are placed through the visualizing apparatus to grasp and remove small objects. Sometimes the mucosa may become tightly adherent to the distal end of the foreign body, creating a vacuum that prevents object withdrawal. Passage of a Foley catheter beyond the foreign object (sometimes via a rigid sigmoidoscope) with proximal air inflation of the catheter balloon usually breaks the vacuum and permits retrieval. When the emergency clinician possesses the appropriate expertise and equipment or if consultants are available, the next step may be removal with a vacuum device that is well-suited for some foreign bodies or forceps; sigmoidoscopy may be a necessary adjunct to such an approach. As with other removal means, the physician should be careful to minimize risk of anorectal perforation. Caution should be used when enemas or cathartics are administered to patients with known rectal foreign bodies, especially foreign bodies with sharp edges.

An assessment for rectal injury is indicated after removal of the foreign object. When foreign body retrieval has been simple and the patient does not show increased pain, tenderness, or rectal bleeding, further imaging or direct visual evaluation for rectal trauma is unnecessary. Appropriate antibiotics are indicated in all cases of suspected bowel wall perforation and peritonitis.

Disposition

If any signs or symptoms of pain or rectal bleeding are present, postremoval sigmoidoscopy may identify small abrasions requiring close follow-up with a gastrointestinal or colorectal specialist. In general, hospitalization is indicated if emergent surgery is needed or if a rectal laceration or perforation is found.

GENITOURINARY TRACT

Principles

The literature describes a wide variety of genitourinary tract foreign objects, ranging from easily extracted tampons and condoms to penile rings removed with great difficulty. As is the case with other foreign body locations, the genitourinary tract has also been the site at which a variety of odd foreign objects have been reported (eg, radio antennae, electric cables).[107,108]

Clinical Features

The patient history has major value in diagnosis of most genitourinary objects, because these are often placed by the patient or

the patient is aware of their placement (eg, body piercing).[107-112] However, in children who fear parental disapproval of foreign object placement, secondary signs are the more common presentation. They are brought to medical attention when parents note foul-smelling, purulent discharge or bleeding from the urethra, the vagina, or both. Another common presentation in infants is penile constriction caused by inadvertent wrapping of hairs around the shaft, usually just proximal to the corona.

In adolescents and adults, metal objects may be placed for autoerotic stimulation.[111] Constricting bands may be placed proximal to the scrotum or more often on the penile shaft. These patients frequently have presentations delayed by 12 hours or more.[111] The swelling that renders these constricting bands so difficult to remove also hinders the physical examination, emphasizing the need for an accurate history.

Occasionally, an object (eg, tampon) is forgotten until it causes purulent discharge. Secondary symptoms also can bring foreign bodies to physicians' attention. Migration of both physician-placed intrauterine devices and patient-placed wires into the bladder has occurred with diagnosis made due to symptoms of cystitis.[113]

Genitourinary tract foreign bodies may be infectious. The term *bezoar,* traditionally considered to delineate indigestible material in the gastrointestinal tract, also has been used (along with *urobezoar*) to describe foreign material collections throughout the urinary tract.[114-116] One common urinary tract bezoar is the *Candida* bezoar. Fungal bezoars are usually, but not always, seen in immunosuppressed patients or in patients with diabetes mellitus, neurogenic bladder, antibiotic use, or an indwelling urinary catheter.[116,117]

Patients of all ages require a careful, gentle examination due to frequent anxiety about the anatomic region being examined. In a pediatric patient, a nasal speculum may be used to help visualize a vaginal foreign body. Thorough vaginal examination is indicated in patients with symptoms of vaginitis, with the search directed for infectious agents and foreign bodies. A vaginal foreign body may be palpated during digital rectal examination.

In children and adults, the presence of blood or discharge at the urethral meatus or vagina should be noted. Patients with intraurethral foreign objects also may have perineal induration and a high incidence of associated infection, which may progress to sepsis. In males with penile shaft swelling, the emergency clinician should perform careful inspection for constricting objects. In any child (including an infant) with penile or labial swelling, a coronal constricting hair should be sought.[118,119]

In patients with retained penile rings, especially in those cases presenting after some hours' delay, examination often will reveal a swollen penis with mottling, duskiness, and excoriation. The interruption of venous and lymphatic outflow results in increasing penile enlargement with risks of tissue damage. Damage is especially likely if there have been previous attempts—as is usually the case—by the patient at self-removal of the constricting device. Examination may reveal indirect evidence of other genitourinary objects as well (eg, multiple abscesses from embedded metal objects).[120]

Differential Diagnoses

The selected differential diagnoses of genital urinary tract foreign bodies include urethritis, urethral strictures, penile tumors, penile hematomas and priapism, vaginitis, cervicitis, Bartholin cysts, and retained products of conception.

Diagnostic Testing

Often, no imaging is necessary and the foreign body's contours and extent are evident on examination. Plain films may be used when urethral or bladder radiopaque foreign bodies are suspected. Plain radiography also has proved useful in unusual cases of embedded metallic objects that may be difficult to palpate due to regional swelling and tenderness on palpation.

Ultrasound is useful to investigate for hydronephrosis. Acoustic shadowing may not be seen, depending on the nature of the foreign body; *Candida* bezoars lack acoustic shadowing. These bezoars and other genitourinary tract objects are generally identifiable on CT.[121] Urethrocystography and cystourethroscopy may be useful tools for the urologist identifying and locating genitourinary tract foreign objects.

Management

Vaginal foreign bodies usually are removed easily. If the object has been present for some time, there may be associated bacterial or fungal infection. This should be treated with appropriate antimicrobials (eg, metronidazole 500 mg three times daily for a week for bacterial infection; fluconazole 150 mg in a single oral dose for candidal vaginitis).

In males or females, foreign bodies located just inside the urethral meatus usually can be grasped with a clamp and removed. After failure of one or two attempts at removal by the emergency clinician, the best course is early urology consultation. Objects located in the proximal urethra or bladder usually require cystoscopy for extrication. One exception is the *Candida* bezoar, which generally is treated with antifungal agents. Penile urethral foreign bodies may be associated with urinary retention and secondary infection; in these cases, early urology consultation for endoscopic intervention is necessary.

Constricting penile foreign bodies are removed as early as possible because progressive swelling makes removal more difficult. Sedation and analgesia may be necessary. Also, care should be taken when removing constricting objects with instruments such as ring cutters, because penile shaft lacerations may be easily caused due to tautness of the thin underlying skin. Hair and string foreign bodies are removed relatively easily with forceps and scissors or scalpel.

Disposition

After penile ring removal and confirmation of ability to void, patients usually can be discharged with close follow-up. Consultation with a urological specialist should be obtained for patients with penile trauma. Vaginal tears secondary to foreign body insertion or extraction may require admission and emergent gynecological surgery.

SOFT TISSUES

Principles

Soft tissue foreign bodies present unique diagnostic and management dilemmas. Foreign bodies may be present not only in patients with known wounds but also in patients with secondary symptoms who are unaware or uncertain of foreign body entry.

Clinical Features

All patients with wounds should be considered for soft tissue foreign body contamination. In straightforward cases, patients have symptoms such as pain or foreign body sensation and may specifically report a foreign body. Meticulous examination and use of diagnostic aids are in order when the patient is certain of a foreign body not readily seen by the emergency clinician. Particularly for radiolucent objects, such as wood splinters, the history and patient sensation are used as a guide to exploration.

In more difficult cases, patients have symptoms related to complications. Soft tissue infections, especially if recurrent, should suggest a foreign body serving as a nidus. A careful history in patients with soft tissue complaints should include a search for antecedent trauma, no matter how remote, that may have resulted in foreign body entry.

The diagnosis is frequently obvious on visual inspection or standard wound evaluation. For smaller objects, use of magnification may be a significant aid in foreign body identification and removal. In addition to location of the foreign body, the examination should address injuries collateral to the object's presence. Distal neurovascular function should be tested.

Differential Diagnoses

The selected differential diagnoses of soft tissue foreign bodies include skin infections, arthropod bites, lipomas, ganglion cysts, melanoma, and basal and squamous cell carcinomas.

Diagnostic Testing

Depending on the nature of the foreign object, anteroposterior and lateral radiographs of the involved area of the body can be diagnostic. Plain radiography has been shown to be more than 98% sensitive when the foreign body is metal or other radiopaque material, such as gravel. If silver nitrate sticks were used to achieve hemostasis before imaging, the deposited metal can be expected to appear on plain radiography.

One common foreign body is glass, which is usually radiopaque.[122-124] The size glass that will be seen on x-rays depends on composition and alignment, but it appears that about 0.5 mm is the cross-section above which glass should be visualized on plain films.[125] Not seen easily on plain radiographs are items such as vegetable material (eg, wood) and plastic.

Xeroradiography, recommended in the past, has fallen out of favor. This technique has no clearly demonstrated advantage over plain films and has been discarded in favor of other modalities (eg, CT) when plain films are negative and suspicion remains.[125]

Fluoroscopy has received attention as a diagnostic and therapeutic tool. Against the risks attendant to higher doses of ionizing radiation (especially when compared to ultrasound), fluoroscopy offers long-proven ability to facilitate identification and complete removal of foreign objects.[122]

When plain radiographs are negative and suspicion for a foreign body remains, ultrasound or CT is the next step. Ultrasound is readily available in many EDs and has been the subject of intensive study and the technique continues to evolve. With use of a 10-MHz or 7.5-MHz probe for shallow depths and a 5-MHz probe for deeper searching, ultrasound is clearly useful when positive. The main imaging findings in a series of sonographic imaging of non-radiopaque foreign materials in 47 patients were hyperechoic foci (96% of cases) and posterior acoustic shadowing (77% of cases); a halo sign indicating infection (fluid around the foreign body) was seen in 11%.[126]

Overall, given the availability of ultrasound in the ED and the multiple case reports of its occasional utility in foreign body localization and removal, it is reasonable to employ this technique with the understanding that a positive test result is much more useful than a negative one.[127-129] In specific situations, ultrasound may even be the best available imaging modality. For example, B-scan ultrasound as performed by ophthalmologists is better than both CT and MRI for identification of wooden foreign bodies in the posterior segment of the eye.[130]

In addition to characterizing objects seen on plain films, CT may prove useful for items (eg, plastic, wood) missed on plain radiographs.[125,131] CT may also prove valuable in localizing small or deep objects. CT also is useful for identifying foreign body sequelae (eg, abscess). For objects such as gravel, glass, and metals, MRI streaking can hamper image interpretation and CT is preferred.[132]

MRI can assist in identifying foreign body presence and complications in a variety of anatomical areas.[133-135] Soft tissue objects can induce a chronic inflammatory reaction and lytic or blastic osseous changes that allow MRI to locate foreign bodies. In other cases, MRI is less optimal. Wood, especially if rich in water (as is the case with chronic foreign bodies), is better imaged with CT than MRI.[131,132]

Management

The most important determinant of successful foreign body removal is knowledge of the object's precise location. Standard radiopaque markers can aid in wound localization. Fluoroscopy or ultrasound may allow simultaneous visualization and removal. When objects are not radiopaque, judicious probing of wounds with fine-gauge needles or forceps may allow tactile detection of the foreign body. For metallic foreign bodies, magnets may facilitate removal.[136]

For removal of a foreign body, it may be necessary to extend the original wound or, if it is located away from the entrance site, to make a separate incision. The emergency clinician can perform limited wound extension or make separate incisions in regions where adequate analgesia and a relatively bloodless field can be achieved. Retrieval of foreign bodies, especially those linear in shape, is best achieved if the orientation of the foreign body is understood. The proximal end of the foreign body is grasped, and the object is gently removed following the plane of orientation.

When inorganic objects are deeply embedded, it may be better to leave them in place than to create large surgical wounds to effect removal. Depending on foreign body location, operative intervention may be necessary for safe foreign body extraction. After foreign body removal, the emergency clinician should consider tetanus prophylaxis and empiric antibiotic treatment.

Disposition

Patients with suspected vascular or neurologic injuries require early evaluation by appropriate subspecialists. Soft tissue foreign bodies that are not suspected or undetected can lead to infectious sequelae. Therefore, careful discharge instructions and timely follow-up are crucial in these patients.

KEY CONCEPTS

- If the history and mechanism of injury are compatible with ocular penetration or if a small puncture wound of the globe is noted, anteroposterior and lateral radiographs of the orbit are an appropriate initial step when the foreign body is thought to be radiopaque. CT and ultrasound are complementary diagnostic studies.
- Although most otic and nasal foreign bodies are amenable to ED removal, instrumentation of these anatomical areas must be effected with great care because removal attempts can cause more injury than the foreign body itself.
- Most airway foreign bodies are seen in pediatric patients and may not be visible on plain films. A normal radiograph does not rule out an aspirated foreign body.
- The patient with critical airway obstruction and impending or actual respiratory arrest requires one of three options: (1) forced expulsion

KEY CONCEPTS—cont'd

of the foreign body; (2) direct laryngoscopy with attempted manual removal with Magill forceps; or (3) cricothyroidotomy, other transtracheal ventilation, or intubation, while pushing the foreign body distally.

- Esophageal foreign bodies typically are found at one of the three constriction locations: (1) proximal esophagus at the level of the cricopharyngeal muscle and thoracic inlet—radiographically, the clavicular level; (2) midesophagus at the level of the aortic arch and carina; and (3) distal esophagus just proximal to the esophageal-gastric junction—radiographically, a level two to four vertebral bodies cephalad to the gastric bubble.
- Esophageal foreign bodies (eg, coins) usually are oriented in the coronal plane, and airway objects usually are oriented in the sagittal plane.
- Foreign bodies in the stomach and bowel are increasingly managed with a conservative approach with watchful waiting and tracking of the object's progression through the gastrointestinal tract.
- In the perineal region, foreign body removal tends to be more difficult than anticipated by physicians and physically and psychologically traumatic for patients. Consultation with appropriate specialists (eg, urology or general surgery) is indicated.
- The most important determinant of successful soft tissue foreign body removal is an understanding of the object's precise location.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 53: QUESTIONS & ANSWERS

53.1. A 33-year-old construction worker presents with left eye pain. On gross inspection, you note a watery discharge and moderate erythema. The patient tells you she was working with her coworker when she felt something hit her eye. She admits to not wearing protective goggles. Fluorescein examination of the eye reveals rivulets of dye tracking from a corneal defect. What is the next appropriate step in the patient's management?

A. Attempt ultrasound to find a foreign body
B. Check intraocular pressures
C. Obtain orbital computed tomography (CT) scan and consult ophthalmology
D. Obtain plain radiographs of the orbits
E. Topical antibiotics and ophthalmology follow-up in 24 hours

Answer: C. Rivulets of fluorescein tracking from the puncture (ie, positive Seidel test) are helpful in identifying the fact that intraocular penetration has occurred. Ultrasound is, as always, operator dependent, and the pressure of the probe on the orbit may risk further injury to an open globe. Checking for intraocular pressures with an open globe is contraindicated. Compared with plain radiographs, CT delivers less radiation to the lens. Multiplanar reconstruction minimizes streak artifacts, affording better localization of intraorbital objects.

53.2. A 2-year-old presents with purulent drainage from the right naris, brought to the ED by a parent concerned about sinusitis. The patient's vital signs are heart rate 110 beats/min, respiratory rate 15 breaths/min, and temperature 37.7° C. On physical examination, you see a small plastic ball in the naris surrounded by swelling and purulent discharge. What should be the next step?

A. Attempt to displace the foreign body posteriorly
B. Blow air into the contralateral naris to help dislodge the foreign body
C. Consult the otolaryngologist for removal under anesthesia
D. Make sure you have a right-angle probe, suction, and alligator forceps
E. Treatment with topical vasodilators to facilitate removal

Answer: D. The emergency clinician can remove most nasal foreign bodies. Posterior movement of a nasal foreign body risks aspiration; objects should be removed anteriorly via suction or traction. In some circumstances, it may be prudent to place patients in lateral decubitus, perhaps with additional Trendelenburg positioning, to help prevent aspiration of objects. Foreign bodies can sometimes be easily removed via positive pressure applied to the patient's mouth (not the contralateral naris, which should instead be clamped closed to increase pressure on the involved-side naris). Pretreatment with vasoconstrictive spray may improve chances of success. If positive-pressure techniques are not indicated or do not work, it is important to have necessary instruments close at hand to proceed with foreign body removal attempts. These instruments include a blunt-tipped right-angle probe (to maneuver posterior to the foreign body), suction equipment, and alligator forceps.

53.3. A 14-month-old girl presents in respiratory distress after eating a hot dog for lunch. Her mother states that she had stepped out of the kitchen, and when she came back, her daughter was sitting forward with noisy breathing and obvious distress. Which of the following management interventions is contraindicated?

A. Back blows
B. Blind finger sweep as the first step
C. Chest thrusts
D. Direct laryngoscopic visualization
E. Intubate for respiratory distress

Answer: B. Blind finger sweeping has resulted in conversion of partial to complete airway obstruction when objects are displaced into the subglottic space. For this reason, the technique has lost favor as an initial maneuver in pediatric and adult patients. It is recommended that up to five back blows be delivered (with the patient in a head-down position), followed by chest thrusts. Intubation or needle cricothyroidotomy may be performed if other maneuvers fail and circumstances dictate their need.

53.4. A 45-year-old man was at dinner when he had a choking episode. When he recovered, he experienced new-onset wheezing and presents with the following vital signs: blood pressure 140/90 mm Hg, heart rate 110 beats/min, respiratory rate 20 breaths/min, and arterial oxygen saturation (Sao_2) 92%. On chest radiograph, you see a flat, fixed diaphragm on the right with a mediastinal shift to the left and inadequate left-sided expansion. What is the next step in the management of this patient?

A. Albuterol nebulizers and steroids intravenously
B. Consult pulmonary for bronchoscopy
C. CT scan of the chest with intravenous contrast
D. Needle decompression of the left side
E. Needle decompression of the right side

Answer: B. Air trapping and atelectasis are the most common early clues to airway foreign body presence, with bronchiectasis and bronchial stenosis developing later. In air trapping, a comparison of inspiratory and expiratory films shows a flat, fixed diaphragm on the involved side, and the heart and mediastinum shift to the uninvolved side during expiration. When the foreign object is distal to the oropharynx, however, subspecialty consultation is the safest and most expeditious means for foreign body removal. As a general rule, early bronchoscopy in any patient with a suspected foreign body is key to reducing morbidity and mortality.

53.5. A concerned father brings in his toddler, who has swallowed a button battery. Which of the following management strategies is most appropriate for this patient?

A. Endoscopy is indicated if it is above the lower esophageal sphincter.
B. Endoscopy is not indicated if it is found in the esophagus.
C. Expectant management is appropriate.
D. If it is in the small bowel, further surveillance is not indicated.
E. Nifedipine may aid in the movement of the battery through the esophagus.

Answer: A. If a disk battery has been ingested, its location must be ascertained with immediate removal if it has lodged in the esophagus. If the button battery has passed distal to the esophagus, the patient can be observed, with follow-up radiography to confirm spontaneous passage through the gastrointestinal tract. Nifedipine is occasionally effective in managing food boluses but should not be used to manage nonorganic foreign bodies.

53.6. Which of the following is an initial management option for esophageal food bolus impactions in the ED?
A. Glucagon
B. Nifedipine
C. Papain
D. Sublingual nitroglycerine

Answer: A. Two agents used for distal food bolus impaction, which are probably not as useful as glucagon, are nitroglycerine and nifedipine. A last approach, enzymatic degradation of an impacted meat bolus using the proteolytic enzyme papain, has fallen into disfavor because of risks of esophageal perforation. The gold standard intervention strategy for esophageal foreign body removal is endoscopy.

53.7. What do you expect to see on the chest radiograph of a child who has swallowed a coin?
A. Foreign body anterior to tracheal air column
B. Foreign body causing air trapping on the left side
C. Visualized flat foreign body in the coronal plane
D. Visualized round foreign body in the coronal plane
E. Visualized round foreign body in the transverse plane

Answer: D. Esophageal foreign objects usually align themselves in the coronal plane and are posterior to the tracheal air column on lateral view. Coins in the esophagus lie in the coronal position in virtually all cases because the opening into the esophagus is much wider in this orientation.

CHAPTER 54

Mammalian Bites

Wesley P. Eilbert

PRINCIPLES

Background

It is estimated that 50% of individuals will suffer a domestic animal bite during their lifetime, with many of these bites being unreported.[1] Dogs are responsible for over 80% of animal bites in the United States, with cats accounting for 5% to 10%. Although few studies exist that have examined the incidence of wild mammalian bites, rodents are probably the most common offender in this group. Bites from other species including monkeys, ferrets, raccoons, foxes, bears, cougars, bats, livestock, and other wild mammals make up only a small percentage of reported bites.

Bites cause damage to the skin and underlying structures including muscle, blood vessels, nerves, tendons, joint spaces, and bony structures. A secondary consideration with all bite wounds is contamination with the oral flora of the biting animal resulting in infection. The potential for tetanus and rabies exposure must also be considered. Tetanus is discussed in Chapter 52, and rabies is covered in Chapter 123.

DOG BITES

Principles

Of the nearly 4.5 million Americans bitten by dogs every year, half are children and one in five will require medical attention.[2] Rates of dog bite are highest among children 5 to 9 years old, with males more likely to be bitten than females.[2] The arm and hand is the body region most often bitten. Compared with adults, children are much more likely to be bitten on the face, head, or neck.[3] In the majority of dog bite cases, the dog is known to the victim either as a family pet or a neighbor's dog.[4]

Dog biting pressures exert forces of 200 to 400 pounds per square inch, and dogs often shake the victim vigorously. This causes a "hole and tear" effect resulting in complex lacerations and avulsions. On average, 10 to 20 dog bite related fatalities occur in the United States each year. The majority of victims are younger than 10 years old. Pit bulls and Rottweilers are the breeds responsible for the majority of these fatalities.[5]

Clinical Features

Dog bite wounds may be contusions or ecchymoses without a break in the skin, but more commonly are abrasions, lacerations, avulsions, or gaping crush wounds. Most dog bite injuries are superficial, and the majority of patients are treated with simple medication, dressings, or suturing. Larger breeds cause more severe crush injuries due to the higher pressures exerted by their jaws and pose a greater risk of major organ or vessel injury than smaller breeds. Dogs used in law enforcement exert greater bite forces than civilian dogs and are trained to use a bite-and-hold technique to apprehend suspected felons. These factors result in a higher overall incidence of bite complications including vascular, nerve and tendon injuries, fractures, and infections compared with bites from civilian dogs.

Dog bites to the hand are often of an occlusive nature, with the crush injury component increasing the risk of infection. Because of the several bones and joints adjacent to the skin surface, the number of small enclosed compartments and fascial planes, and numerous small nerves, hands are the most common bite site to develop infection and long-term morbidity.[6] Tenosynovitis, septic arthritis, abscess formation, and traumatic digit amputation from dog bites have been reported.[7]

Dog bites to the head and neck are of cosmetic concern and are at greater risk of life-threatening injury. The lips, cheek, nose, and ears are the facial structures most likely to be bitten. Young children are at greatest risk for mortality from a dog bite, with exsanguination after carotid trauma as the major cause of death. In children up to 2 years old, there are case reports of dog bites that have perforated the skull, resulting in open depressed fractures, brain laceration, intracranial abscess, and meningitis.

Dog bites have reported infection rates ranging from 2% to 30%, with hand bites at higher risk for infection.[6,8] Bites to the face and scalp are at lower risk for infection, presumably due to their rich blood supply. The type of wound appears to influence infection rates, with puncture wounds at higher risk for infection than avulsions and lacerations.[9] Of infected dog bite wounds, 60% are punctures, 10% lacerations, and 30% a combination of these two. Thirty percent of dog bite infections are nonpurulent wounds, 58% are purulent, and 12% present as abscesses.

Dog bite wound infections are usually polymicrobial, with an average of five bacterial isolates per wound culture. The responsible bacteria are often a mixture of canine oral flora, environmental organisms, and the victim's skin flora. Approximately half of dog bite–related infections contain a mixture of aerobic and anaerobic bacteria, with anaerobes more likely to be present in abscesses and purulent wounds. In contrast to older studies, more recent studies have found *Pasteurella* species to be the predominant organism, present in approximately half of infected dog bites. Other common aerobic bacteria include streptococci, staphylococci, *Neisseria* species, *Corynebacterium* species, and *Moraxella* species. Common anaerobic isolates from infected dog bites include *Fusobacterium, Bacteroides, Porphyromonas, Prevotella,* and *Propionibacterium* species.

Capnocytophaga Canimorsus

C. canimorsus was first identified in 1976 as a cause of systemic infection following dog bites. It is a slow-growing gram-negative rod found in the normal oral flora of both cats and dogs.[10] *C. canimorsus* is a rare, though well-described cause of systemic illness. Transmission is related to a bite in the majority of cases, although has been documented from licks, scratches, or close animal contact.[11] An animal is responsible for the infection in approximately 90% of cases, with 91% from dogs and 8% cats. In approximately 10% of cases, the source of infection is unknown. The disease tends to strike middle-aged men, with the majority of

affected individuals having underlying medical problems, most commonly alcoholism, splenectomy, or immunosuppression.[11]

The illness usually begins within 3 days of exposure (range 1 to 10 days). The most common initial symptom is fever, present in the majority of cases, followed by vomiting, diarrhea, abdominal pain, headache, and confusion. Cutaneous signs are common with purpuric lesions present in approximately one third of cases. These skin lesions may progress to peripheral gangrene in up to 15% of patients, with cutaneous gangrene at the site of the bite strongly suggestive of *C. canimorsus*. Although a minority of patients present with findings consistent with only cellulitis, the clinical picture on presentation is often that of sepsis with hypotension, renal insufficiency, respiratory distress, and disseminated intravascular coagulopathy (DIC). The few case series published have noted a mortality rate of approximately 30%. Endocarditis and meningitis from *C. canimorsus* has also been described.

Differential Diagnoses

The differential diagnosis of dog bites in general includes other domestic pets, such as cats and wild canines, including coyotes and wolves. The differential diagnosis for the patient with symptoms suggestive of *C. canimorsus* infection is extensive. Given its relative rarity and various initial symptoms, *C. canimorsus* infections are likely to be misdiagnosed and treated as other more common infections initially. Those patients with primarily cutaneous manifestations may be diagnosed with cellulitis or necrotizing fasciitis if systemic symptoms are also present. Invasive gastroenteritis would be an obvious consideration in those patients with primarily gastrointestinal symptoms, as would meningitis in patients presenting with fever, headache, and confusion. Bacteremia with another organism, especially *Neisseria meningitides,* should be considered in patients presenting with fever, hypotension, and purpuric skin lesions.

Diagnostic Testing

Radiographs should be obtained if there is a likelihood of damage to underlying bones and joints, such as with the hand. Bite penetration of joint capsules may be seen as air in the joint on plain radiographs. Scalp bites in children younger than 2 years old may require computed tomography (CT) imaging, because intracranial penetration and injury may occur.[12] Preemptive wound cultures sent from fresh bites are rarely of value and are not generally indicated.

C. canimorsus grows slowly and requires special media and growth conditions. In cases of sepsis without an obvious source following a dog or cat bite, *C. canimorsus* should be considered and the laboratory should be notified to arrange for appropriate testing. Polymerase chain reaction (PCR) has recently proven valuable in the rapid identification of *C. canimorsis.*[11,13]

Management

Key elements of the history can be divided into three main parts: (1) the circumstances of the attack, (2) information about the biting animal, and (3) information about the bite victim. The timing of the bite should be determined. As a general rule, untreated bites more than 6 hours old are at higher risk for infectious complications. When possible, it should be determined whether the bite was provoked or unprovoked, because this may influence the decision to administer rabies prophylaxis. Information about the biting animal should include ownership and immunization status, as well as current location of the animal. With dog bites, inquiring about the specific breed is important, because certain breeds (eg, German shepherds, Rottweilers, and pit bulls) notoriously cause severe bites with damage to underlying structures. Information about the bite victim should include their medical history, current medications, and tetanus status.

The general principles of wound management apply to bite wound patients (see Chapter 52). Adequate analgesia is vital to allow for appropriate examination and wound care. Washing the wound with soap and water, ideally with gentle scrubbing with a fine pore sponge to minimize additional tissue trauma, should be performed. A virucidal agent such as povidone-iodine solution should be used, specifically if there is a concern for rabies exposure.

Examination of bite wounds should ideally take place in a bloodless field to allow for adequate visualization of deep structures. A blood pressure cuff inflated above the systolic pressure for up to 20 minutes can be used for this purpose. The wound should be examined specifically for damage to tendons and possible joint capsule violations. Any retained teeth fragments should be removed. It is often helpful to extend the margins of puncture wounds in high risk areas (eg, overlying joints and tendons) to allow for better visualization. Assessment of the neurovascular status distal to all extremity bites should be performed. As with other traumatic wounds, appropriate high pressure irrigation with normal saline or sterile water and débridement of devitalized tissue is necessary.

Primary closure of mammalian bites is controversial with conflicting data having been reported. Ultimately, the benefit of improved cosmesis of primary closure must be weighed against the increased risk of infection. Studies have found no significant difference in rates of infection between repaired dog bite wounds and those left open. Carefully selected dog, cat, and human bites closed primarily have an overall infection rate of 5.5%, which is an infection rate similar to sutured non-bite wounds. When closing bite wounds, the use of subcutaneous sutures should be kept to a minimum, because the presence of foreign material increases the risk of infection. To optimize cosmetic outcome in those wounds deemed too high risk for infection for primary closure, loosely approximating the wound edges using adhesive strips may be performed. Another option is to reevaluate the wound in 48 to 72 hours and if no evidence of infection is present, perform a delayed primary closure.

Given the available data, we recommend the following guidelines (Table 54.1). Bite wounds of the face and scalp from any

TABLE 54.1

Recommendations for Bite Wound Closure and Prophylactic Antibiotics

SPECIES	SUTURING	PROPHYLACTIC ANTIBIOTICS
Dogs, coyotes, wolves	The majority except hands and feet	Hand and foot wounds High-risk wounds*
Cat	Face only	All wounds extending through the epidermis
Human	Face only (up to 24 hours after the bite)	All wounds extending through the epidermis
Monkey	Face only (up to 24 hours after the bite)	All wounds extending through the epidermis
Rodent	All (but rarely needed)	No
Ferret, pig, horse, camel, bear, big cats	Face only	All wounds extending through the epidermis

*High-risk wounds: Deep puncture wounds, crush injury or damage to deep structures, delayed presentation (>6 hours), wounds closed primarily, and high-risk patients (see Table 54.2).

species that are less than 6 hours old may be sutured after appropriate wound preparation. It is probably safe to suture most other uncomplicated dog bites. Bites of the hands and feet are at high risk for infection and should rarely be sutured. Puncture wounds, wounds more than 12 hours old, and wounds infected at presentation should not be sutured. Prophylactic antibiotic should be given for the majority of bite wounds closed primarily.

Prophylactic Antibiotics

The value of prophylactic antibiotics given for mammalian bites is secondary to the value of proper cleaning, débridement, and irrigation of the wounds. Antibiotics should ideally be given within 3 hours of the bite to achieve a prophylactic effect and then continued for 3 to 5 days. A Cochrane review including eight randomized controlled trials of prophylactic antibiotics for dog, cat, and human bites concluded that antibiotics did not reduce infection risk after dog and cat bites.[9] The analysis also established that the type of wound (eg, laceration versus puncture) did not appear to influence the effectiveness of the prophylactic antibiotic. Sub-analysis of hand bites showed infection rates were significantly reduced by antibiotics.[9]

A meta-analysis of eight published studies using prophylactic antibiotics for dog bites estimated approximately 14 patients would have to be treated to prevent one infection.[14] A sub-analysis of the data found a protective effect specifically with hand bites. A recent study of prophylactic antibiotics after dog bites with cost model analysis of treatment suggested treating only those dog bites at high risk for infection.[8] We advise giving prophylactic antibiotics to high-risk patients and to those with dog bite wounds of the hand or other high risk wounds (Table 54.2).

TABLE 54.2

Risk Factors for Bite Wound Infections

FACTOR	HIGH RISK	LOW RISK
Species	Cat (domestic and wild) Human Monkey Pig Camel Bear	Dog (excluding hands and feet) Rodent
Location of wound	Hand (especially clenched fist injuries [CFIs]) Foot	Face Scalp
Wound type	Puncture Crush injury or damage to deep structures Presence of devitalized tissue Delayed presentation (more than 6 hours) Closed primarily	Laceration Superficial
Patient characteristics	Age over 50 Diabetes Renal failure Liver disease Alcoholism Immune disorder Malnutrition Use of corticosteroids or other immunosuppressive medications Peripheral vascular disease Chronic edema of the bitten area	

No clinical trials have reliably demonstrated the superiority of one antibiotic regimen over another. With a significant percentage of dog bite infections caused by *Pasteurella* species, coverage of these pathogens is recommended. Treatment failure of *Pasteurella* infections caused by dog and cat bites using monotherapy with erythromycin, clindamycin, penicillinase-resistant penicillins, and first-generation cephalosporins has been described. We recommend amoxicillin-clavulanate (Augmentin) for dog bite prophylaxis because this combination is active against most of the pathogens that can be isolated from these wounds in vitro, and studies have demonstrated it is effective in vivo.[15] Clindamycin combined with either trimethoprim-sulfamethoxazole or ciprofloxacin may be used in penicillin-allergic patients (Table 54.3). Empirical antibiotic options for those patients with established dog bite wound infections are the same as those used for prophylaxis. Parenteral antibiotic options for those patients requiring admission are listed in Table 54.3.

Although no clinical trials have evaluated antibiotic selection in *C. canimorsus* infections, penicillin G, ampicillin/sulbactam, third-generation cephalosporins, and fluoroquinolones have all been effective for in vitro studies.

Disposition

Indications for admission after an animal bite are listed in Box 54.1. Those patients deemed appropriate for outpatient therapy should be reevaluated in 24 to 48 hours.

TABLE 54.3

Suggested Antibiotic Regimens for Bite Wound Prophylaxis and Inpatient Treatment of Establishing Infections

SPECIES	PROPHYLAXIS	INPATIENT TREATMENT OF ESTABLISHING INFECTION
Dog and cat	Augmentin Moxifloxacin Clindamycin plus trimethoprim-sulfamethoxazole or ciprofloxacin	Unasyn (ampicillin/sulbactam) Timentin (ticarcillin/clavulanate) Zosyn (piperacillin/tazobactam) Clindamycin plus trimethoprim-sulfamethoxazole or ciprofloxacin
Human and monkey	Augmentin amoxicillin-clavulanate Moxifloxacin Cefoxitin Clindamycin plus penicillin or ciprofloxacin	Unasyn (ampicillin/sulbactam) Timentin (Ticarcillin/clavulanate) Zosyn (piperacillin/tazobactam) Imipenem Meropenem Ertapenem Clindamycin plus penicillin or ciprofloxacin
Rodent	Not recommended	
Ferret, pig, horse, bear, big cats, coyotes, wolves	Same as for cats and dogs	Same as for cats and dogs
Camel	Ciprofloxacin Ofloxacin	Same as for cats and dogs

BOX 54.1

Indications for Admission After an Animal Bite

STRUCTURAL
Injury to deep structures (bones, joints, tendons, arteries, or nerves)
Injuries requiring reconstructive surgery
Injuries requiring general anesthesia for appropriate wound care

INFECTIOUS
Rapidly spreading cellulitis
Significant lymphangitis or lymphadenitis
Evidence of sepsis
Infection in patients at high risk for complications (see Table 54.2)
Infections involving bones, joints, tendons
Infection with failed outpatient therapy

CAT BITES

Principles

Although victims of dog bites are more likely to be male, females are twice as likely as males to be the victim of a cat bite, with a peak age incidence in the third decade.[2,16] The majority of cat bites are to the upper extremity, particularly the hands and fingers.[17] More than 80% of cat bites are caused by a domestic pet that is owned by the victim.[17] Cats possess narrow sharp teeth that easily penetrate skin and the underlying soft tissues like a needle. This mechanism creates a small break in the skin that heals quickly, trapping the bacteria in the deeper structures, often resulting in invasive infection.[18]

Clinical Features

Cat bites are more likely to become infected than dog bites, with reported infection rates of up to 80%.[18] This increased rate of infection is multifactorial: The higher incidence of puncture wounds, a higher proportion of hand bites, an older average age for cat bite victims, and a higher likelihood of *Pasteurella* species in the feline flora. Although not as likely to cause damage by crush injury as dog bites, cat bites are more likely to cause infection in deeper structures, including osteomyelitis and soft tissue abscesses. Of infected cat bite wounds, 52% present with cellulitis, 22% with tenosynovitis, 15% with osteomyelitis or septic arthritis, and 11% with an abscess.

Bacteriology

There is a median of five bacterial isolates per culture of infected cat bites, with mixed aerobic and anaerobic bacteria present in 63%. Thirty-two percent of cat bite infections are due to only aerobic bacteria. *Pasteurella* species are the most common pathogens, present in 70% to 75% of infected cat bites, with streptococci, staphylococci, *Moraxella,* and *Bacteroides* also common aerobic pathogens. Common anaerobes include *Bacteroides*, *Fusobacterium, Porphyromonas,* and *Prevotella*.

Pasteurella Multocida. An important factor contributing to the risk of infection after cat bites is the presence of *P. multocida,* a highly virulent, facultative anaerobic, gram-negative rod found in the normal oral flora of up to 90% of cats. It can also be found in the oral flora of the majority of dogs and several wild animals. Most human infections with *P. multocida* are caused by cat bites or scratches, dog bites, or open wounds that have been licked by a dog or cat.

The most common initial manifestation of *P. multocida* infection is a rapidly spreading cellulitis, usually presenting within 12 to 24 hours of the exposure. A low-grade fever and serosanguineous or purulent discharge at the site may be present. Regional lymphadenopathy is often present. Left untreated, local complications, most commonly subcutaneous abscesses and tenosynovitis, may occur.[19] Other local complications include septic arthritis and osteomyelitis. Systemic illnesses from *P. multocida* including bacteremia, pneumonia, endocarditis, and meningitis have been well described in case series. The majority of patients with systemic illness had an underlying medical condition, with liver disease, malignancy, and chronic obstructive pulmonary disease being the most frequent comorbidities. There is a 31% mortality rate from *P. multocida* bacteremia.

Differential Diagnoses

The cellulitis associated with *P. multocida* is typically of more rapid onset after the initial traumatic injury and more rapidly progressive than the cellulitides caused by more common pathogens. Cat scratch disease, an infection caused by *Bartonella henselae* associated with a cat scratch or bite, presents with a regional lymphadenopathy often with an associated fever. A preceding cat or dog bite may be the only initial clue that indicates *P. multocida* as the cause of a systemic illness, such as bacteremia.

Diagnostic Testing

As with dog bites, radiographs should be obtained if there is a likelihood of damage to underlying bones and joints, such as with the hand. Bite penetration of joint capsules may be seen as air in the joint on plain radiographs. Preemptive wound cultures sent from fresh bites are rarely of value and are not generally indicated.

Management

P. multocida is not susceptible to many oral antibiotics typically given for skin and soft tissue infections, including dicloxacillin, cephalexin, and clindamycin. In most cases, treatment with a beta-lactam antibiotic (such as, ampicillin), amoxicillin-clavulanate, or a second or third generation cephalosporin is effective.[20] Fluoroquinolones, tetracyclines, and trimethoprim sulfamethoxazole may be used in penicillin allergic patients.

There is only one published randomized controlled study of prophylactic antibiotics in cat bites; although small, it demonstrated reduced infection.[21] A Cochrane review concluded there was no evidence that antibiotic prophylaxis was effective for cat bites, although the authors also concluded that animal bites on the hands (where most cat bites occur) benefit from prophylaxis.[9] We advise giving prophylactic antibiotics to all cat bites that penetrate through the epidermis regardless of location, given the high risk nature of these bites for infection. With similar common pathogens as dog bites, we recommend amoxicillin-clavulanate (Augmentin) be used for prophylaxis (see Table 54.3).

Disposition

Indications for admission after an animal bite are listed in Box 54.1. Those patients deemed appropriate for outpatient therapy should be reevaluated in 24 to 48 hours.

OTHER MAMMALS

Monkeys

Principles

Monkey bites are rare in the United States, occurring primarily in laboratory workers because these animals are widely used in

biomedical research. Monkey bites are more prevalent in other countries including India, where they are the second most commonly reported animal bite. Although not well studied, monkey bites are reported to have a high rate of infection and complications, such as osteomyelitis.

Clinical Features

The major concern with monkey bites is B virus exposure. Other terms for this virus include *herpesvirus simiae, herpesvirus B,* and *monkey B virus*. This virus has serologic cross-reactivity with herpes simplex virus (HSV) type 1 and type 2, which cause herpetic lesions in humans. Seventy-three percent to 100% of monkeys of the genus *Macaca* (macaques) used for biomedical research are seropositive for the B virus. The virus causes disease in monkeys resembling that of human herpes viruses. Asymptomatic infected monkeys harbor the virus in their conjunctiva, buccal mucosa, and genital areas and may shed the virus, being more likely to do so when ill, under stress, immunocompromised, or breeding.

More than 50 cases of B virus infection in humans have been reported, with the vast majority of these in the United States being in laboratory workers. Of those investigated, the majority were due to monkey bites, although transmission via scratches, exposure to animal tissue, and needlestick injuries has been reported.

B virus disease in humans has an incubation period as short as 2 days but more commonly 2 to 5 weeks. The disease often starts with vesicular lesions at the site of exposure with concomitant influenza-like symptoms. Paresthesias and muscle weakness may develop and proceed proximally along the affected extremity. Signs of central nervous system dysfunction develop when the virus enters the brain and include altered mental status, cranial nerve palsies, ataxia, coma, and respiratory failure. Left untreated, the mortality rate of B virus infection is estimated to be 80%.

Differential Diagnoses

The bacteria isolated from infected monkey bites is similar to that from infected human bites, with a predominance of *Staphylococcus* and *Streptococcus* species, *Eikenella corrodens,* and anaerobes including *Bacteroides* and *Fusobacterium* species.

Management

The most critical period for the prevention of B virus infection is during the first few minutes after the exposure. The area should be scrubbed with soap, concentrated solution of detergent, povidone-iodine or chlorhexidine, and then irrigated with running water for 15 to 20 minutes.[22] Prophylaxis of high risk bites with valacyclovir is recommended (Box 54.2). Postexposure prophylaxis should be offered for up to 5 days after the bite, although it should be started as soon as possible. Treatment of suspected B virus infection is with intravenous acyclovir or ganciclovir.[22]

Disposition

The majority of monkey bites can be safely discharged home from the emergency department (ED) following local wound care, appropriate antibiotics, and reassurance of outpatient follow-up. Those patients with systemic symptoms of infection may require admission for intravenous antibiotics.

BOX 54.2

Prophylaxis for Monkey Virus B Exposure

PROPHYLAXIS RECOMMENDED

Skin exposure (with loss of skin integrity) or mucosal exposure to a high-risk source (eg, a macaque that is ill, immunocompromised, known to be shedding virus, or has lesions compatible with B virus disease)
Inadequately cleaned skin exposure (with loss of skin integrity) or mucosal exposure to any macaque
Deep puncture bite
Laceration of the head, neck, or torso
Needlestick associated with tissue or fluid from the nervous system, eyelids, mucosa, or lesions suspicious for B virus
Puncture or laceration after exposure to objects contaminated with either fluid from monkey oral, genital, or nervous system tissues or any object known to be contaminated with B virus
A post cleaning wound culture is positive for B virus

PROPHYLAXIS CONSIDERED

Mucosal splash that has been adequately cleaned
Laceration (with loss of skin integrity) that has been adequately cleaned
Needlestick involving blood from an ill or immunocompromised macaque
Puncture or laceration occurring after exposure to either objects contaminated with body fluid (other than from a lesion) or potentially infected cell culture
Drug of first choice: Valacyclovir 1 g by mouth every 8 hours for 14 days
Alternative drug: Acyclovir 800 mg by mouth five times/day for 14 days

PROPHYLAXIS NOT RECOMMENDED

Skin exposure in which the skin remains intact
Exposure associated with non-macaque species of nonhuman primates

Rodents

Principles

As with monkey bites, laboratory workers are frequent rodent bite victims because these animals are commonly used in biomedical research. Rat bites tend to occur in urban areas, in patients of low socioeconomic class, and are more common in children. The majority of these bites occur while the victim is asleep, with the face and upper extremity being the areas most often bitten.

Clinical Features

Rat bite fever is a disease syndrome caused by *Streptobacillus moniliformis* or *Spirillum minus,* both found in the nasopharyngeal flora of healthy rats. Over 200 cases of rat bite fever have been documented in the United States, but this is likely a significant underrepresentation because rat bite fever is not a reportable public health disease.[23] Disease transmission may occur by bite, scratch, or simply handling a rat.[23] The incubation period ranges from 3 days to over 3 weeks but typically is less than 7 days. At disease onset, fever is prominent, followed by a migratory polyarthralgia. Nearly 75% of patients develop a maculopapular, petechial, or purpuric rash. Untreated, rat bite fever has a mortality rate of approximately 10%.

Differential Diagnoses

A number of systemic diseases may be transmitted by rodent bites including rat bite fever, leptospirosis, tularemia, sporotrichosis, murine typhus, and plague.

Management

Rodent bites are at low risk for local wound infection and require only appropriate wound care without antibiotic prophylaxis.

Intravenous penicillin is the treatment of choice for proven or highly suspected cases of rat bite fever, with streptomycin and tetracycline reasonable options for penicillin allergic patients. Antibiotic prophylaxis for rat bite fever is not recommended given the low risk for infection after a bite.

Disposition

The vast majority of rodent bites can be safely discharged home from the ED with wound care instructions and outpatient follow-up.

Ferrets

Ferrets *(Mustela putorius furo)* are in the same family as badgers, weasels, and skunks, and became increasingly popular as pets in the United States in the 1980s. Initially bred to hunt rats and rabbits, ferrets are known for their exceptionally vicious attacks, with infants and small children often their victims. Unlike dog and cat bites, many ferret bites are unprovoked and will frequently require plastic and reconstructive surgery. Although the oral flora of ferrets is known to contain *Pasteurella* and other aerobic species and *Fusobacterium* and other anaerobic species, no reports exist that have examined the rates of infection or common pathogens with ferret bites.

DOMESTIC HERBIVORES

Sheep, Cattle, and Pigs

Bites from sheep and cattle are rarely reported in the medical literature. Pig bites are a common occupational hazard among farmers and slaughterhouse workers and most commonly occur on the posterior aspect of the thigh. Males have large, sharp tusks capable of deep penetrating wounds with injury to deeper structures. Bites from females are less damaging. Pig bites have a high incidence of infection that is often polymicrobial with organisms including *Staphylococcus* and *Streptococcus* species, *Haemophilus influenzae, Pasteurella, Actinobacillus,* and *Flavobacterium* species.

Horses

Of all horse-related injuries, most are from falls and less than 5% are due to bites.[24] Horse bite injuries range from superficial trauma to amputation of digits. Horse bite infections are typically polymicrobial with a mix of aerobic and anaerobic species. *Actinobacillus* species are gram-negative coccobacilli that are part of the normal oral flora of horses and common pathogens in infected bites. Other common pathogens include *Staphylococcus* and *Streptococcus* species, *Pasteurella* species, as well as *Fusobacterium* and *Bacteroides* species.

Camels

Camel bites are commonly reported in Africa, the Middle East, and the Indian subcontinent. Camel bites are more likely to occur during their mating season from November through March, with most injuries occurring to the upper extremities.[25] Camels have a strong jaw and canine teeth that may reach up to 4 cm in length, which result in serious injury and even death from their bites. A recent study found 48% of upper extremity bites had associated fractures, and bites to the head have been associated with skull fractures and intracranial injury.[25,26] Camel bites have a high infection rate with *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa,* and *Bacteroides* and *Fusobacterium* species as common pathogens.

WILD ANIMALS

Bears

Bear attacks are rare in North America, occurring at a rate of 10 or fewer per year, with most occurring in the western United States and Canada. Bear attacks are more common in the warm weather months and have a reported mortality rate of up to 21%. Grizzly bears are responsible for an inordinate number of serious and fatal injuries caused by bears in North America. Most bear bites are to the head and face, often with underlying bony injury.[27] Although not well studied, bear bites have a reported infection rate of 44%. The bacteriology of bear bite infections has also not been well described.

Wild Cats

Most attacks by big cats (lions, tigers, leopards, jaguars, cougars, and cheetahs) now occur in captive conditions, such as zoos, animal farms, and circuses, although attacks in the wild are still reported with some frequency in Asia and Africa.[28] Large cats target the neck of their prey, causing damage to the spine, trachea, and large blood vessels.[29,30] Cougars are responsible for the majority of big cat attacks in North America, with children the most common victims and the nape of the neck being the most commonly bitten area. Common injuries from these attacks include neck lacerations and internal carotid and cervical spine injuries. As is true for domestic cats, *Pasteurella multocida* is the most frequently isolated pathogen in wounds from large cats. Hyenas, which are related to cats, have been known to attack humans in the wild in Africa and Asia. Unlike the big cats, hyenas tend to bite the central face of their victims, causing damage to the cheeks, nose, and lips.[31]

Coyotes and Wolves

Bites from coyotes and wolves are similar to dog bites and should be treated as such.

Management

As with non-bite lacerations, location, type of wound, time to treatment, and patient factors all contribute to the risk of wound infection. Delay in wound cleaning and inappropriate cleaning techniques will increase infection risk. The animal responsible for the bite also is a factor in determining the risk of infection (see Table 54.2).

Although there are no studies to support the practice, antimicrobial prophylaxis for bites from other mammals is often provided. Ferrets, pigs, horses, bears, big cats, coyotes, and wolves have bite wound pathogens similar to those of dogs and cats, so in the absence of other data, prophylactic antibiotics given for these bites should also be similar. A unique mixture of camel bite wound pathogens is most adequately covered by fluoroquinolone antibiotics (see Table 54.3).

Other Prophylaxis

Tetanus prophylaxis should be considered for all bite wounds. Rabies immunization should be considered following bites from bats, coyotes, foxes, raccoons, skunks, and stray dogs outside of the United States.

Disposition

Indications for admission after an animal bite are listed in Box 54.1. Those patients deemed appropriate for outpatient therapy should be reevaluated in 24 to 48 hours.

HUMAN BITES

Principles

Males are more likely to be the victims of human bites, with a peak incidence in the 10- to 34-year-old age group. Human bites tend to occur during summer months, typically on weekends, and most often involve acts of aggression. Sporting events and rough sexual activity are less common causes. The hands and upper extremities are the most commonly bitten location, followed by the head and neck. With victims of sexual crimes, the breast is the most commonly bitten area, and the arm is the most frequently bitten site in victims of child abuse. For various reasons, including embarrassing circumstances and possible legal repercussions, many adult human bite victims delay seeking medical care until a complication ensues. This is especially true for human bites of the hand.

Human bites can be divided into two categories: occlusive bites and clenched fist injuries (CFIs). Occlusive bites are those caused by closure of the perpetrator's teeth onto the victim's skin. CFIs, or "fight bites," are injuries to the dorsum of the metacarpophalangeal joints of the fist as it strikes the teeth of an adversary. The overwhelming majority of CFIs occur in young adult males and frequently involve alcohol.[32] Human bites have reported infection rates ranging from 2% to 50%, with hand bites and specifically CFIs having the highest rates of infection. Children, in whom human bites are usually superficial, tend to have lower rates of infection (less than 10%) as compared with adults.

Clinical Features

Fight Bites (Clenched Fist Injury)

Acute CFIs typically present as an innocuous-appearing 3 to 8 mm laceration over the dorsal aspect of the second, third, fourth, or fifth metacarpophalangeal (MCP) joint (Fig. 54.1). Despite their initial benign appearance, CFIs often have extensive deep structure damage. Damage to underlying bones occurs in approximately half CFIs, and approximately half will have violation of a joint capsule. Up to 20% of CFIs will have an associated tendon injury. Injury to the extensor tendons occurs with the fist clenched. When the fist is relaxed, the tendons retract, carrying bacteria deeper into the hand, extending infection to other spaces. Retained teeth or tooth fragments in the wound may also occur. Given these facts, it is not surprising that CFIs have high rates of osteomyelitis (16%), septic arthritis (12%), and tenosynovitis (22%). Further confounding this issue is the fact that many patients will be reticent to discuss the details of their injury, and approximately one third of CFI patients will initially offer an alternative explanation for their hand laceration.

Fig. 54.1. Acute clenched fist injury (CFI). (Courtesy Jeffrey E. Keller, MD.)

Other Human Bites

Human occlusive bites generally cause less tearing and crush injury than dog bites, and do not penetrate soft tissues as readily as cat bites. Occlusive human bites that are superficial, do not involve the hands or feet, and are not over joints or cartilaginous structures have a very low rate of infection and do not benefit from prophylactic antibiotics.

Intraoral and oral-cutaneous wounds caused by the patient's own teeth are usually a result of blunt facial trauma. These bite wounds are typically small and confined to the oral mucosa, requiring no specific intervention. Larger wounds of the mucosa and those that communicate with the overlying facial skin ("through and through" wounds) may require closure for functional or cosmetic reasons. Infection rates of these wounds range from 4% to 33%. Organisms cultured from these infected wounds include *Staphylococcus* and *Streptococcus* species, *Bacteroides* and *Corynebacterium*. In the absence of any current clear evidence-based recommendation regarding the use of prophylactic antibiotics for these wounds, we advise prophylactic penicillin be used in those lacerations requiring primary closure and those that result in mucocutaneous communication.

Bacteriology. Human saliva can contain up to 10^9 organisms per mL, and may contain as many as 190 different species of bacteria. As with other mammalian bites, cultures sent from fresh, uninfected human bite wounds do not predict which patients will become infected, nor do they reveal the responsible pathogens in those who do. Information on the bacteriology of infected human bite wounds has come primarily from hand bites, with the majority being CFIs. Polymicrobial infections are the rule with human bites, with an average of four isolates per wound culture. Approximately half contain a mixture of aerobic and anaerobic species, with less than 5% containing only anaerobes. *Staphylococcus* and *Streptococcus* species, as well as *Corynebacterium* and *Fusobacterium* species, are common pathogens. *Eikenella corrodens,* a fastidious facultative anaerobe, is present in up to 30% of infected human bites. It is resistant to multiple antibiotics including clindamycin, erythromycin, antistaphylococcal penicillins, and first-generation cephalosporins.

Differential Diagnoses

Human bites have resulted in transmission of tetanus, syphilis, actinomycosis, and herpes. Herpetic whitlow, an infection of the finger by HSV types 1 and 2, is an occupational hazard of nurses, physicians, dentists, and oral hygienists (Fig. 54.2). Although the presence of human immunodeficiency virus (HIV) inhibitors in saliva render the virus non-infective in most cases, there are

Fig. 54.2. Herpetic whitlow. (Courtesy Gary M. White, MD.)

several case reports of HIV transmission by human bites.[33,34] Several people have become infected with hepatitis B virus (HBV) from human bites, and the risk of HBV transmission from a bite appears greater than that of HIV. The infectivity of the hepatitis C virus (HCV) from a bite is believed to be midway between that of HIV and HBV, and there are case reports of its transmission by human bites.

Diagnostic Testing

Due to their high incidence of deep structure injury and the possibility of retained tooth fragments, we advise obtaining radiographs in the majority of hand bites. A "skyline" view of the distal metacarpals may aid in the identification of vertical articular fractures of the metacarpal heads caused by CFIs.

Management

History should focus on the mechanism of the bite (occlusive or CFI), the health of the bite victim including medical history and tetanus status, and the potential for transmission of viral hepatitis or HIV. If the biter is available for testing, local law may permit testing even without consent depending on the particular circumstances.

Treatment of occlusive human bites is generally similar to that of other mammalian bites. Although some authors have advocated surgical exploration of all CFIs in the operating room, we recommend nonoperative management in the ED for selected patients.[35] Such an approach is predicated on thorough wound exploration in a bloodless field. The hand should be examined through its entire range of motion, including in the closed fist position when the fingers are flexed, because extensor tendon injuries and cartilage damage may not be evident in any other position. Patients in whom exploration shows injury to the joint or joint capsule, tendons, or bones should be admitted for open débridement and irrigation in the operating room. It is typical for patients with CFIs to present several days after the injury with evidence of an infected wound. These patients will also require surgical exploration and irrigation in the operating room.

Given their propensity for infection, only human bites to the face should be closed primarily. Case series of human facial bites closed primarily have reported infection rates of 0% to 10%, although all of these studies reported delays of treatment of up to several days. We recommend primary closure of human bites to the face for up to 24 hours after the bite has occurred (see Table 54.1). Those CFIs not requiring operative intervention should be cleaned, débrided, and irrigated, then left open with the hand splinted in a position of comfort.

HIV postexposure prophylaxis is recommended for both the bite victim and the bite source if either party is known to be HIV-positive or at high risk and blood exposure has occurred.[36] Postexposure prophylaxis is also indicated in all bites if either party is known to be HBV-positive or at high risk and blood or saliva exposure has occurred.[36] No current postexposure prophylaxis is available for HCV, so serologic testing with appropriate follow-up and counseling should be offered if the bite resulted in blood exposure, and either party is known HCV positive or at high risk.[36]

Prophylactic Antibiotics

The only randomized, placebo-controlled study of patients with human bites found no infections in patients who received timely antibiotics, and a 47% infection rate in those patients that received placebo. Of significance is that this study only included hand bites.[37] A Cochrane review concluded that prophylactic antibiotics do reduce infection risk after human bites.[9] We advise the use of prophylactic antibiotics for any human bite that penetrates deeper than the epidermis regardless of body location, with the exception of those bites greater than 72 hours old without evidence of infection. We recommend beta-lactam/beta-lactamase inhibitor combination antibiotics, such as amoxicillin-clavulanate (Augmentin), or fluoroquinolones with enhanced anaerobic activity, such as moxifloxacin, for human bite prophylaxis. Other prophylactic antibiotic options are listed in Table 54.3. As with other prophylactic antibiotics, the first dose should be given ideally within 3 hours of the injury and continued for 5 days.

BOX 54.3

Indications for Admission for Human Bites of the Hand

Infection present at the time of presentation
Deep structure violation (tendon or tendon sheath, joint, or bone)
Wounds requiring operative intervention for débridement of devitalized tissue or foreign body removal
Patients at high risk for wound infection (see Table 54.2)
Patients with likely social support or compliance issues

Disposition

Delay in presentation with human bites to the hand is strongly correlated with infection related complications, and these patients should be admitted for parenteral antibiotics. Other indications for admission with human bites of the hand are listed in Box 54.3. Localized infections of human bites elsewhere on the body in immunocompetent patients can usually be treated as an outpatient. All patients with human bites discharged from the ED should have their wounds reevaluated in 24 to 48 hours. Patients with CFIs have notoriously high rates of noncompliance with follow-up care.[32] It is reasonable to admit patients who might predictably fall into this category.

KEY CONCEPTS

- Mammalian bites require evaluation not only as traumatic injuries but also for their risk of infection.
- Cat and human bites are at higher risk for infection than dog bites.
- Most mammalian bite wound infections are polymicrobial. *Pasteurella* species are the most common pathogens in dog and cat bites.
- The value of prophylactic antibiotics for mammalian bites is secondary to the value of proper cleaning, débridement, and irrigation of the wounds.
- Prophylactic antibiotics should ideally be given within 3 hours of the bite and continued for 5 days.
- Amoxicillin-clavulanate (Augmentin) is the prophylactic antibiotic of choice for dog, cat, and human bites. Moxifloxacin is an alternative for those patients that are penicillin-allergic.
- The decision to close mammalian bite wounds must weigh the benefit of improved cosmesis against the increased risk of wound infection.
- Given their propensity for infection, mammalian bites to the hand should not be closed primarily. Most facial bites can safely be closed if done so within 24 hours of the bite.
- Due to the anatomy of the hand, clenched fist injuries (CFIs) or "fight bites" have exceptionally high rates of damage to deep structures and infection.
- Mammalian bites to the hand should receive prophylactic antibiotics. Any infected human bite to the hand should be treated on an inpatient basis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 54: QUESTIONS & ANSWERS

54.1. A 75-year-old woman presents with a puncture mark on her hand. She reports being bitten by her cat the previous night. Which of the following statements regarding this patient's injury is *true?*

A. *Capnocytophaga canimorsus* is the organism of concern.
B. Cats are very clean animals and do not carry any virulent strains.
C. Cats produce superficial infections because their teeth are not long enough to inoculate past the dermis.
D. Concern exists for a virulent gram-negative bacterium, which can produce a rapid cellulitis.
E. Irrigation and topical antibiotics are indicated.

Answer: D. Cats have long, slender, pointed teeth that can penetrate tendons, joints, and bone, inoculating bacteria deep into these tissues. Cat bites have a substantially higher risk of infection than dog bites do. Another important factor in the development of wound infection after cat bites involves the presence of *Pasteurella multocida,* a highly virulent, gram-negative, facultatively anaerobic rod found in the oral cavity or nasopharynx of 70% to 90% of healthy cats.

54.2. What is the most appropriate antibiotic prophylaxis for a cat bite?

A. Amoxicillin-clavulanate
B. Clindamycin
C. Erythromycin
D. First-generation cephalosporins
E. Vancomycin

Answer: A. In vitro, *P. multocida* is sensitive to penicillin, ampicillin, tetracycline, fluoroquinolones, amoxicillin-clavulanate, second- and third-generation cephalosporins, and trimethoprim-sulfamethoxazole.

54.3. A 19-year-old man presents 10 hours after sustaining a dog attack. He has multiple lacerations on his head and right hand. What is the appropriate management of this patient?

A. Repair the hand and the head lacerations
B. Repair the hand laceration but not the head laceration
C. Repair the head laceration but not the hand laceration
D. Use Steri-Strips on all and give him a prescription for amoxicillin-clavulanate (Augmentin)
E. Wound cleansing and bandaging

Answer: C. For dog bites, the infection rate of hand wounds is as high as 30%, regardless of suturing, whereas the infection rate of dog bites elsewhere averages 9%. Similarly, dog bites of the face and neck (including punctures) have an infection rate of only 0% to 5% even when they are sutured. Bite wounds of the face and scalp from any species that are less than 12 hours old may be cleansed well and sutured. Most other bite wounds that are going to be closed should have this done within 6 hours.

54.4. Selected monkey bites require postexposure prophylaxis with which of the following medications?

A. Amoxicillin clavulanate
B. Clindamycin
C. Flagyl
D. Tetracycline
E. Valacyclovir

Answer: E. Valacyclovir to prevent herpes B virus infection. Other terms for this virus include *herpesvirus simiae, herpesvirus B,* and *monkey B virus*. This virus has serologic cross-reactivity with herpes simplex virus (HSV) type 1 and type 2, which cause herpetic lesions in humans. Seventy-three percent to 100% of monkeys of the genus *Macaca* (macaques) used for biomedical research are seropositive for the B virus. Other antibacterials may be needed if cellulitis infection ensues.

CHAPTER 55

Venomous Animal Injuries

Edward Joseph Otten

PRINCIPLES

Epidemiology

Venomous animals account for considerable morbidity and mortality worldwide. Southeast Asia, India, Brazil, and areas of Africa lead the world in snakebite mortality.[1] Snakes alone are estimated to inflict 2.5 million venomous bites annually, with approximately 125,000 deaths. It is impossible to estimate the worldwide morbidity and mortality resulting from other venomous animals, such as bees, wasps, ants, and spiders.

Approximately 45,000 snakebites occur annually in the United States; 7000 to 8000 are inflicted by venomous snakes, and fewer than 10 result in death. Insects are responsible for 52% of deaths, snakes for 30%, and spiders for 13%. Specifically, bees are responsible for the most fatalities, followed by rattlesnakes, wasps, and spiders.

The American Association of Poison Control Centers began collecting data in 1983 on deaths caused by venomous animals. Their 30-year experience shows a significant number of exposures by bite or sting but relatively few deaths (Table 55-1).[2] Although these data include most of the United States, there is no requirement that hospitals, emergency departments (EDs), coroners, or public health agencies report deaths or exposures to regional drug and poison information centers. This decline in deaths may be caused by an actual decrease in mortality or may be a result of inadequate reporting. Meaningful morbidity data, such as the number of amputations, hospitalizations, and disabilities, do not exist. The number of exposures and deaths from nonnative snakes seems to be increasing, possibly because of interest in collecting "exotic" or venomous varieties, such as cobras, mambas, and vipers.[3-5] The morbidity from marine animal injuries is increasing in proportion to the number of people exposed to the ocean and the number of private collectors, but the mortality has not increased dramatically. An increase in outdoor recreational activities, such as camping, scuba diving, wilderness trekking, and travel to endemic areas puts more people in proximity to venomous animals and increases the risk of envenomation.[6] Most exposures occur from April to October, which is when animals are most active and potential victims are outdoors and involved in activities that might increase their risk for envenomation. Many spider bites and exotic animal envenomations that occur indoors can take place at any time. Most deaths seem to occur in very young, elderly, or inappropriately treated patients.

Venom Delivery

Animals that have developed specific venom glands and venom delivery systems can be found in every class, including birds. The toxin and toxic apparatus vary from class to class. For example, the rattlesnake has modified salivary glands and maxillary teeth and uses this system primarily to obtain food. The bee has a modified ovipositor that is used mainly for defense. Poisonous and venomous animals are not the same and should be differentiated. Animals can be considered *poisonous* because of various toxins distributed in their tissues. For example, certain shellfish, toads, and barracuda have been known to cause death after ingestion. However, only animals with specific glands for producing venom connected to an apparatus for delivering that venom to another animal can be considered *venomous.*

VENOMOUS REPTILES

Snakes

Of the 3000 species of snakes, approximately 10% to 15% are venomous. Of the 14 families of snakes, four contain venomous species. Snakes are distributed throughout most of the earth's surface, including fresh and salt water. The major exceptions are the Arctic and Antarctic zones, New Zealand, Malagasy, and many small islands. Most snakebites occur in tropical and subtropical climates, especially in agricultural settings where the inhabitants go barefoot. Sea snakes are found only in the Pacific and Indian Oceans. Snakes are poikilotherms, which accounts for their distribution and activity. Their inability to raise their body temperature above ambient levels restricts their activity to a fairly narrow temperature range, approximately 25° to 35°C. All snakes are carnivorous, and their venom apparatus evolved for the purpose of obtaining food.

Epidemiology

The incidence of reported venomous snakebites in the United States is greatest in the South. States having the highest death rates are North Carolina, Arkansas, Texas, and Georgia. Of all snakebites, 97% occur on the extremities, with two-thirds on the upper extremities and one-third on the lower extremities. This reversal of historical distribution may reflect bites being provoked rather than accidental. Bites that occur accidentally are considered "legitimate," whereas bites that occur during attempts to handle or disturb a snake are considered "illegitimate." Men are bitten nine times more frequently than women.

Imported venomous snakes have recently been an increasing problem throughout the United States. In the past, only zoos, research centers, and herpetologists kept exotic venomous snakes. Today, hundreds of people are raising deadly venomous snakes without the necessary precautions, such as specialized cages, safe handling techniques, and rapid access to specific antivenom. They place not only themselves, but also their families and the general public, in danger.

Classification and Characteristics

The four venomous families of snakes are the Colubridae, Elapidae, Viperidae, and Atractaspididae. The Colubridae, although representing 70% of all species of snakes, have very few venomous members dangerous to humans; these include the boomslang and bird snake. They are rear-fanged snakes, and although many possess venom, they generally do not envenomate humans. The Elapidae are more common and include the cobras, kraits,

TABLE 55.1

Venomous Animal Injuries and Deaths, 1983–2011

ANIMAL	ENVENOMATIONS	DEATHS
Coelenterates	16,657	1
Fish	28,403	0
Ants	51,810	0
Bees, wasps, hornets	361,507	24
Caterpillars, centipedes	53,615	0
Other arthropods	279,580	3
Copperheads	18,125	1
Rattlesnakes	26,618	31
Water moccasins	2,988	0
Coral snakes	1,494	0
Exotic snakes	2,387	4
Nonvenomous snakes	38,877	0
Unknown snakes	44,881	4
Black widow spiders	62,370	0
Brown recluse spiders	45,199	7
Other or unknown spiders	272,886	2
Scorpions	297,757	5

Data compiled from Watson WA, Litovitz TL, et al: American Association of Poison Control Centers data. Am J Emerg Med 2:1984–2005; Lai et al: Clin Toxicol 44, 2006; and Bronstein et al: Clin Toxicol 45, 2007; Clin Toxicol 46, 2008; Clin Toxicol 47, 2009; Clin Toxicol 48, 2010; Mowry et al, Clin Toxicol, 51, 2013; Mowry et al, Clin Toxicol 52, 2014.

Fig. 55.1. The nose of the coral snake is black, with adjacent red and yellow body bands.

Fig. 55.2. Body bands are separated by a black band on the scarlet king snake.

mambas, and coral snakes. The Hydrophiidae are sea snakes and a subfamily of the Elapidae. The Viperidae, or true vipers, are represented by Russell's viper, the puff adder, the Gaboon viper, the saw-scaled viper, and the European viper. The Crotalidae, or pit vipers, are sometimes considered a separate family and sometimes a subfamily (Crotalinae) of the Viperidae. Among the pit vipers are the most common American venomous snakes, such as rattlesnakes, water moccasins, copperheads, the bushmaster, and the fer-de-lance. Several species of Asian pit vipers are responsible for bites in Okinawa and bites by imported snakes in the United States. The Atractaspididae are the mole vipers, which have side-positioned fangs; they rarely envenomate humans and are found only in Africa and the Middle East.

Pit vipers, the most prevalent venomous snakes in the United States, are native to every state except Maine, Alaska, and Hawaii. They are classified into three main groups: true rattlesnakes (genus *Crotalus*), copperheads and water moccasins (genus *Agkistrodon*), and pygmy or Massasauga rattlesnakes (genus *Sistrurus*). Pit vipers account for 98% of all venomous snakebites in the United States.[7]

The Colubridae and Hydrophiidae have few venomous encounters with humans and are responsible for even fewer injuries. Some colubrid species found in the United States that were previously thought to be harmless may indeed be venomous. Examples are the lyre snake, the hognose snake, and the wandering garter snake. No deaths have been reported, but the problem has generated much interest among herpetologists and toxicologists. The yellow-bellied sea snake (*Pelamis platurus;* subfamily Hydrophiidae) has been found off the coast of southern California and western Mexico, but bites by this snake are rare.

The other major group of venomous snakes in the United States is the coral snakes. The eastern coral snake *(Micrurus fulvius)* is found in North Carolina, South Carolina, Florida, Louisiana, Mississippi, Georgia, and Texas. There are two subspecies that have similar clinical presentations and will be discussed together. The western or Sonoran *(Micruroides euryxanthus)* coral snake is native to Arizona and New Mexico. Although both species are generally quite shy unless handled, the eastern coral snake is considered deadly. There are no records of fatalities caused by the western species.

Coral snakes can be readily identified by their color pattern. At first glance, they resemble one of several varieties of king snake found in the southern United States. The coral snake can be differentiated from the king snake by two characteristics: The nose of the coral snake is black, and the red and yellow bands are adjacent on the coral snake but separated by a black band on the king snake (Figs. 55.1 and 55.2). The popular rhyme is as follows:

Red next to yellow, kill a fellow.
Red next to black, venom lack.

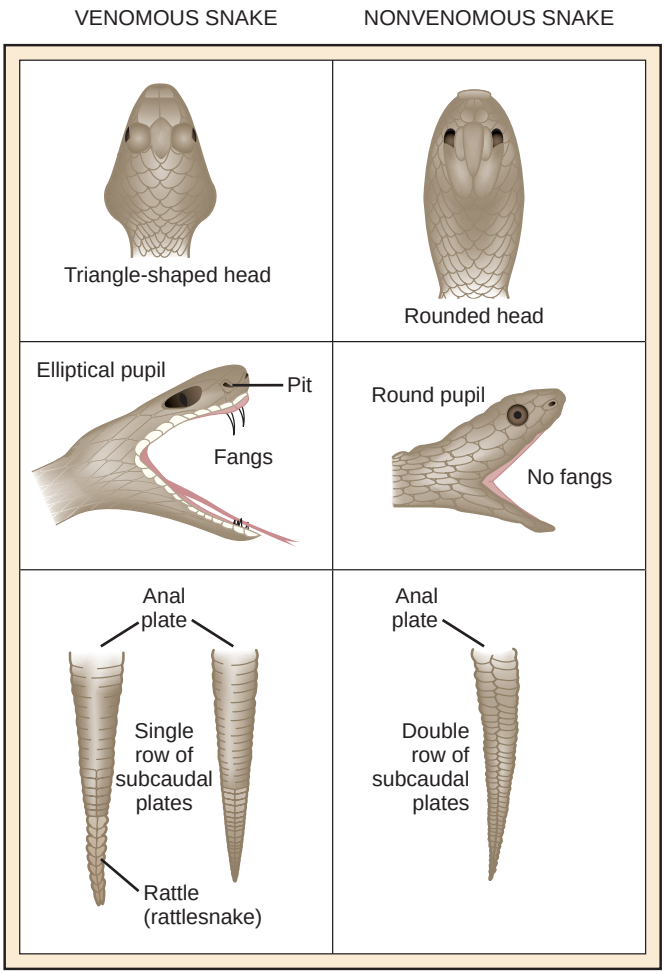
This rhyme can be used only in the United States; venomous Brazilian coral snakes have red next to black bands, and some coral snakes have no red bands.

Identification

There are two key principles for identifying venomous snakes: Only experts should handle live snakes, and even dead snakes can envenomate careless handlers. It is not difficult to differentiate between pit vipers and harmless snakes found in the United States (Fig. 55.3). Pit vipers, as their name implies, have a characteristic pit midway between the eye and the nostril on both sides of the head. This pit is a heat-sensitive organ that enables the snake to locate warm-blooded prey. Pit vipers may be identified through other methods, but this characteristic is very consistent. The triangular shape of the head, the presence of an elliptical pupil, the tail structure, and the presence of fangs are useful characteristics but are inconsistent. The arrangement of subcaudal plates may be used for Crotalinae if the head has been damaged or is unavailable. An individual specimen may not fit the classic description, depending on the age of the snake, the time of the year, and the condition of the tail and mouthparts. Neither color nor skin pattern is a reliable method of identifying pit vipers (Fig. 55.4).[7]

Size is not an important factor in identifying various reptiles. Venomous snakes range in length from several inches to several feet. Although a 6-foot eastern diamondback rattlesnake is much more dangerous than a 10-inch copperhead, all venomous snakes are able to envenomate from birth and should be treated as though they are dangerous.

Exotic snakes that are *not* pit vipers are not as easily identified. If possible, they should be safely transported to an expert for positive identification. Local zoos, herpetologists, poison control centers, and universities often have individuals who can identify unknown snakes.[5,6]



A

Fig. 55.3. **A** and **B,** Identification of venomous and nonvenomous North American snakes.

Other Reptiles

Only two venomous lizards are found in the world, both in the southwestern United States and Mexico. They are the Gila monster *(Heloderma suspectum)* and the Mexican beaded lizard *(Heloderma horridum)*. Fortunately, both these lizards are nonaggressive and rarely encountered. Bites usually result from handling the animals in captivity. The Gila monster and the Mexican beaded lizard are easily identifiable. Both have thick bodies, beaded scales, and either white and black or pink and black coloration (Fig. 55.5).

Toxins

The two main factors influencing the pathophysiology of any venomous animal injury are the toxic properties of the venom and the victim's response to these toxins. In the past, snake venoms were classified as either neurotoxic or hematotoxic, depending on the observed response of the victim to the various venoms. Modern toxicologic investigation has shown that this classification is inadequate because most snake venoms studied contain

Fig. 55.4. Western diamondback rattlesnake *(Crotalus atrox)*.

Fig. 55.5. Gila monster *(Heloderma suspectum).*

compounds that have many toxic properties. It is true, however, that the venom of a particular species of snake may cause a clinical response that is predominantly neurotoxic or hematotoxic.

The toxic components of snake venom can be classified into four broad categories: enzymes, polypeptides, glycoproteins, and low-molecular-weight compounds. They can also be classified as protein and nonprotein compounds. Proteins, which account for most of the toxic manifestations, make up 90% to 95% of venom. Symptoms can generally be classified as local or systemic. Local effects are usually caused by enzymatic action on the various cellular and noncellular structures in the victim's tissues. These enzymes can cause coagulation, anticoagulation, cell lysis, hemorrhage, hemolysis, and the destruction of nucleic acid, mitochondria, and other organelles.

Polypeptides are structurally smaller and more rapidly absorbed than proteins and may account for the venom's effects on presynaptic and postsynaptic membranes and other organ systems.

Phospholipase A can inhibit electron transfer at the level of cytochrome c and render mitochondrial-bound enzymes soluble. It can hydrolyze phospholipids in nerve axons, break down acetylcholine vesicles at the myoneural junction, cause myonecrosis, and induce lysis of red cell membranes. This single enzyme has been identified in all venoms of Hydrophiidae, Elapidae, Viperidae, and Crotalinae thus far investigated.

Elapidae and Hydrophiidae venoms have predominantly systemic effects, whereas Colubridae, Viperidae, and Crotalinae venoms have mainly local effects. There are many exceptions to this general division. For example, the venom of the Mojave rattlesnake *(Crotalus scutulatus)* may show minimal local effects and significant systemic effects, whereas the venom of the cobra *(Naja naja)* may cause extensive local tissue destruction.

Venom Delivery

The mechanism for delivering venom is fairly standard among snakes. It consists of two venom glands, hollow or grooved fangs, and ducts connecting the glands to the fangs. The glands, which evolved from salivary glands, are located on each side of the head above the maxillae and behind the eyes. Each gland has an individual muscle and a separate nerve supply that allow the snake to vary the amount of venom injected. The venom duct leads from the anterior portion of the gland along the maxilla to the fangs. Pit vipers have fangs that are large anterior maxillary teeth. These teeth are hollow and rotate outward from a resting position to a striking position. The coral snake has fixed, hollow maxillary teeth that are much smaller than those of pit vipers. The fangs in most snakes are shed and replaced regularly, and it is not unusual to see a snake with double fangs on one or both sides of its mouth.

The snake can control the amount of venom injected. In biting a human, a prey much too large to swallow, the snake may inject little or no venom (a "dry" bite), especially if injured or surprised. However, the snake may inject more than 90% of the contents of the gland for the same reasons.

Clinical Features

The signs and symptoms of a venomous snakebite vary considerably and depend on many factors. Up to 50% of venomous snakebites result in little or no envenomation. A person with impaired cardiovascular, renal, or pulmonary function is less able to cope with even a moderately severe envenomation. Because of these multiple variables, the individual clinical response is the only way to judge the severity of a venomous snakebite. Factors that influence the effects of a snakebite are the age, health, and size of the snake; the relative toxicity of the venom; the condition of the fangs; whether the snake has recently fed or is injured; the size, age, and medical problems of the victim; and the anatomic location of the bite.

Local envenomation, if left untreated, can cause serious systemic problems (eg, disseminated intravascular coagulation, pulmonary edema, and shock) as the toxic products are absorbed. The victim's autopharmacologic response to the envenomation must also be taken into account. An immunoglobulin E (IgE)–mediated anaphylactic-type reaction may develop in victims of a previous snakebite when reexposed to the venom. Many venoms contain enzymes that trigger the release of bradykinin, histamine, and serotonin from the patient's cells, which may cause fatal anaphylactoid reactions. A wave of effects ranging from minimal pain to multisystem failure and death can occur over a period of several days.

Pit Vipers

The most consistent symptom associated with pit viper bites is immediate burning pain in the area of the bite, whereas pain may be minimal with bites of Elapidae and other exotic snakes. With pit vipers, the severity of pain is probably related to the amount of venom injected or the degree of swelling. Edema surrounding the bite that gradually spreads proximally is a common finding. This edema is usually subcutaneous, begins early, and may involve the entire extremity. Compartment syndrome has been described; however, a true compartment syndrome is unusual even with severe edema. It has been reported more frequently in models involving intracompartmental venom injection.[8-10] Most fangs do not penetrate into the fascial compartments but subcutaneously, although muscle destruction may result from direct toxicity. Mortality is less frequent with distal bites to the toe and finger and is greatly increased with intravenous bites. An intravenous bite from any venomous snake is likely to be fatal. Petechiae, ecchymosis, and serous or hemorrhagic bullae are other local signs, which tend to be more pronounced with patients on anticoagulant therapy.[11] Necrosis of skin and subcutaneous tissue is noted later and may result from inadequate doses of antivenom. Many systemic symptoms, such as weakness, nausea, fever, vomiting, sweating, numbness and tingling around the mouth, metallic taste in the mouth, muscle fasciculations, and hypotension, often occur after pit viper envenomation.

Death from pit viper bites is associated with disruption of the coagulation mechanism and increased capillary membrane permeability. Ultimately, these two processes lead to massive pulmonary edema, shock, and death. Heart and kidney damage occur secondary to these mechanisms. Specific toxins in certain species

may act directly on specific organs, such as the heart or skeletal muscle. An allergic type of reaction may add to this process through release of histamine and bradykinin.[12]

Coral Snakes

Signs and symptoms can vary considerably with bites of coral snakes, Mojave rattlesnakes, and many exotic snakes, especially cobras and Australian elapids. Little pain and swelling may occur. Many of these species' venoms contain compounds that block neuromuscular transmission at acetylcholine receptor sites and have direct inhibitory effects on cardiac and skeletal muscle. Ptosis is common and often the first outward sign of envenomation. Other signs and symptoms include vertigo, paresthesias, fasciculations, slurred speech, drowsiness, dysphagia, restlessness, increased salivation, nausea, and proximal muscle weakness. The usual cause of death is respiratory failure.

Gila Monster

Gila monster bites are generally associated with pain, edema, and weakness. Hypotension is common with severe bites. Envenomation involves secretion of the venom from glands along the lower jaws. The venom is introduced into the victim through grooved teeth and a chewing mechanism. There are no reported deaths from Gila monster bites, although myocardial infarctions have been reported.

Infection

Although snakebite envenomation has been stressed here, any bite or puncture wound carries a risk for bacterial contamination. Gram-negative organisms predominate when snake venom and mouthparts are cultured. Although several studies have shown that prophylactic antibiotics are not indicated for snakebite, tetanus, osteomyelitis, cellulitis, or gas gangrene may occur in cases of snakebite with or without envenomation. This is especially true when a large amount of local tissue destruction has occurred, treatment has been delayed, or inappropriate first aid was attempted.

Differential Diagnoses

The differential diagnosis of venomous snake bites include dry bites, bites from nonpoisonous snakes, spider and tick bites, scorpion and hymenoptera stings, dermatological disorders such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, and methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Diagnostic Testing

Ultrasonography can be used to assess the extent of the dermatologic involvement and depth of the snakebite.[13] An electrocardiogram, complete blood count, urinalysis, prothrombin time, and levels of fibrinogen, fibrin split products, electrolytes, blood urea nitrogen, and creatinine are recommended; blood should be typed and cross-matched for 4 units of packed red blood cells. Enzyme-linked immunosorbent assay (ELISA) testing can be performed for the specific species of rattlesnakes, but the turnaround time is too delayed to have any clinical impact in the ED.[14]

Management

Out-of-Hospital Care

All snakebites are considered an emergency, and any victim should be medically evaluated. The initial 6- to 8-hour period after a snakebite is critical. During this time, medical therapy can help prevent the morbidity associated with severe envenomation. Effective out-of-hospital care can be important.[15]

Out-of-hospital care is relatively simple if guided by four basic concepts. First, the estimated time until arrival at a medical facility, as well as the skill of the on-scene assistants, must be considered when first aid is instituted. Separate the victim from the snake if possible to prevent further bites. A stick, pole, or other object longer than the snake can be used to move the snake away from the victim or, if necessary, to kill the snake by striking it behind the head. Rapid transportation to a medical facility is the best first aid for a snakebite. Any constricting jewelry or clothing should be removed from an extremity to prevent a tourniquet effect proximal to the swelling.

Second, spread of the venom should be slowed if possible; several methods are known. The patient's excitement and physical activity, movement of the bitten area, alcohol consumption, and greater depth of the bite may increase the spread of venom. Except for the last factor, these issues can be addressed by calming the victim, immobilizing the bitten area with a sling or splint, and not giving anything by mouth. A method of first aid for venomous snakebites that was developed in Australia—the *immobilization and compression technique* (also called the *Commonwealth Serum Laboratory technique*)—slows uptake of Elapidae venom and mock venom in humans. The bitten extremity is either wrapped in an elastic bandage or placed in an air splint. In another technique from Australia called the *Monash method,* a thick pad and bandage are placed over the bite wound and extremity. Both of these techniques have similar postulated mechanisms of action: The lymphatic vessels and superficial veins are collapsed, and the proximal spread of venom is slowed. Although this method is successful as first-aid therapy for Elapidae and coral snakebites, its use for pit vipers has not been demonstrated.[16] If less than 30 minutes has elapsed since the bite, a constricting band applied tightly enough to impede superficial venous and lymph flow, but not arterial blood flow, may be used. The band is applied loosely enough to admit a finger between the band and the skin after application. It is used with caution to prevent the development of a tourniquet effect under swollen tissue, which may cause more local tissue destruction than the snakebite. Incision of bite wounds has no proven efficacy and poses potential danger to underlying structures and therefore is not recommended. The use of ice is not helpful in slowing the spread of venom, but an ice bag wrapped in a towel and applied to the bite area helps relieve pain. Ice water immersion or cryotherapy and packing of the extremity in ice are not recommended and only contribute to tissue destruction. The use of commercial suction devices has not been shown to be beneficial.[17]

Third, when feasible, snakes should be identified when possible, although this should not delay transport of the patient to definitive medical care. Identification of the snake must be done safely—usually only by someone expert in handling snakes. If the snake is indigenous to the area, identification is usually not necessary because the treatment protocol is the same, particularly with pit vipers. A photo may be useful in identifying the snake if a close-up of the head and tail are included. Dead snakes can be placed in a hard container, such as a bucket or ice chest. Care should be taken to not touch the head of the snake because envenomation can occur even after death.

Fourth, additional medical interventions, if available, should be initiated, including cardiac monitoring, intravenous fluids, and analgesics.

Emergency Department Care

Many snakes do not envenomate the victim when they bite, which has provided false support for the historical folk lore use of

whiskey, clam juice, or chickens in the treatment of snakebite. The only proven therapy is antivenom. Emergency care of a snakebite focuses on supportive care and rapid treatment with the appropriate antivenom. Rapid decision-making is required to determine the optimal type, amount, and route of administration of the antivenom. By the time the emergency clinician examines a snakebite victim, the venom may have already caused much damage, both locally and systemically. In this case, the emergency clinician must be prepared to support the victim's cardiovascular and respiratory systems.

Patient History. Specific historical information includes time elapsed since the bite, the number of bites, whether first aid was administered and what type, location of the bite, and symptoms (eg, pain, numbness, nausea, tingling around the mouth, metallic taste in the mouth, muscle cramps, dyspnea, and dizziness). A brief medical history includes the last tetanus immunization, medications, and cardiovascular, hematologic, renal, and respiratory problems. An allergy history with emphasis on symptoms after exposure to horse or sheep products, previous injection of horse or sheep serum, and a history of asthma, hay fever, urticaria, or allergy to wool, papain, chymopapain, papaya, or pineapple should be obtained if antivenom treatment is being considered.

Patient Examination. The bite area is examined for signs of fang marks or scratches and local envenomation (eg, edema, petechiae, ecchymosis, and bullae). The area distal to the bite is checked for pulses. A general physical examination is performed, with emphasis on the cardiorespiratory system and the neurologic examination, especially if a Mojave rattlesnake, coral snake, or exotic snake is suspected. If the bite involves an extremity, the circumference of the extremity at the site of the bite and approximately 5 inches proximal to the bite should be measured and recorded. These data aid in objectively estimating both spread of the venom and the effect of antivenom (Fig. 55.6).

Initial Medical Care. If the bite occurred less than 30 minutes before arrival in the ED, first-aid measures can be instituted, including a constricting band until antivenom can be obtained. Snakebite victims with clinical evidence of envenomation should have an intravenous line with normal saline placed

Fig. 55.6. A and **B,** Northern copperhead *(Agkistrodon contortrix mokasen)* bite on right hand with normal left hand for comparison. **C,** Northern Copperhead bite to upper extremity showing diffuse swelling, and hemorrhagic bullae formation.

in an unaffected extremity. The patient's vital signs are monitored closely. Snakebite victims may be hypotensive because of third-space losses and hemorrhage. In an edematous extremity, the distal pulse may have to be examined with a Doppler instrument. If a compartment syndrome is suspected, insert a pressure monitor and obtain surgical consultation. If signs and symptoms of true compartment syndrome are present, pressure greater than 30 mm Hg may indicate the need for a fasciotomy; however, there is evidence that administration of antivenom is much more efficacious in lowering compartment pressures.[10,12]

Once stabilization is initiated, the severity of the bite must be determined and a decision made regarding whether to administer antivenom. The more distal the bite on the extremity, the less toxicity associated with the bite. Intravenous bites may be rapidly fatal. Bites occurring on the trunk, neck, and face have increased risk because of rapid transit of the venom.

Antivenom. The emergency clinician must determine the type of antivenom to administer, how much, and over what period. If the bite is from a pit viper, the problem is not too difficult. Bites from copperheads usually cause a moderate amount of edema but generally do not require antivenom, although it may be indicated in selected cases.[18] Envenomation may be classified according to severity into five grades, from grade 0 (no sign of envenomation) to grade IV (very severe envenomation). The amount of antivenom can be correlated with the grade of envenomation:

- Grade 0 (minimal): There is no evidence of envenomation, but snakebite is suspected. A fang wound may be present. Pain is minimal, with less than 1 inch of surrounding edema and erythema. No systemic manifestations are present during the first 12 hours after the bite. No laboratory changes occur.
- Grade I (minimal): There is minimal envenomation, and snakebite is suspected. A fang wound is usually present. Pain is moderate or throbbing and localized to the fang wound, surrounded by 1 to 5 inches of edema and erythema. No evidence of systemic involvement is present after 12 hours of observation. No laboratory changes occur.
- Grade II (moderate): There is moderate envenomation, more severe and widely distributed pain, edema spreading toward the trunk, and petechiae and ecchymoses limited to the area of edema. Nausea, vomiting, and a mild elevation in temperature are usually present.
- Grade III (severe): The envenomation is severe. The case may initially resemble a grade I or II envenomation, but the course is rapidly progressive. Within 12 hours, edema spreads up the extremity and may involve part of the trunk. Petechiae and ecchymoses may be generalized. Systemic manifestations may include tachycardia and hypotension. Laboratory abnormalities may include an elevated white blood cell count, creatine phosphokinase, prothrombin time, and partial thromboplastin time, as well as elevated fibrin degradation products and D-dimer. Decreased platelets and fibrinogen are common. Hematuria, myoglobinuria, increased bleeding time, and renal or hepatic abnormalities may also occur.
- Grade IV (very severe): The envenomation is very severe and is seen most frequently after the bite of a large rattlesnake. It is characterized by sudden pain, rapidly progressive swelling that may reach and involve the trunk within a few hours, ecchymoses, bleb formation, and necrosis. Systemic manifestations, often commencing within 15 minutes of the bite, usually include weakness, nausea, vomiting, vertigo, and numbness or tingling of the lips or face. Muscle fasciculations, painful muscular cramping, pallor, sweating, cold and clammy skin, rapid and weak pulse, incontinence, convulsions, and coma may also be observed. An intravenous bite may result in cardiopulmonary arrest soon after the bite.

Dart and colleagues have advocated slightly different grading systems and higher doses of antivenom: Grades 0 and I correspond to *minimal* envenomation, grade II represents *moderate* envenomation, and grades III and IV correspond to *severe* envenomation.[19,20] Either system can be used interchangeably.

Onset of symptoms after a pit viper bite may be delayed and may involve a variety of neurologic symptoms, including weakness, ptosis, stupor, bulbar paralysis, and other cranial nerve dysfunction, as well as nausea, abdominal pain, and headache.[21,22]

Administration of Antivenom. Any victim of a venomous snakebite with moderate or severe envenomation is a candidate for antivenom. The choice of antivenom depends on the species of snake, and the antivenom may be horse serum- or sheep-derived Fab fragments. Wyeth Laboratories, producer of the polyvalent horse serum–derived antivenom for Western Hemisphere pit vipers, no longer manufactures that antivenom. Many zoos and hospitals still maintain vials of this antivenom, but most have replaced this with the ovine-derived Fab antivenom (FabAV). This antivenom is derived from four species of pit vipers in the United States and has not been clinically studied with regard to bites from Mexican, Central American, or South American pit vipers.[20,23] There is a reported case of a patient bitten by a South American rattlesnake who was successfully treated with FabAV.[24]

Most antivenom for exotic snakes and the eastern coral snake is derived from horse serum. A recent polyvalent Fab(2) antivenom derived from horse serum and produced in Mexico has been shown to be effective against both North and South American crotalid species.[25] Skin testing was commonly performed before administration of horse serum–derived antivenom, but it is not medically indicated because of the inaccuracy of the test. Moreover, testing with normal horse serum may precipitate an allergic reaction, and even a positive test result may not preclude treatment if a patient has sustained severe envenomation. The incidence of allergic reactions with FabAVs has been much less than previously seen with whole immunoglobulin G (IgG). The incidence of allergic reactions was 17% for early reactions and 12% for late reactions in postmarketing analysis. This was thought to be a result of incomplete purification of one lot contaminated by Fc fragments. Most of these reactions were minor and did not require stopping the infusion of the antivenom. The true incidence is unknown.[26-29]

Dosage and Precautions. Current treatment of pit viper envenomation in the United States is to use a FabAV polyvalent antivenom rather than the horse serum product.[30] This is designed to limit the allergic reactions associated with horse serum antivenom by use of antigen-binding fragments (Fabs) of sheep (ovine) immunized against four species of venomous snake found in the United States. CroFab has been shown to be as effective as the Wyeth antivenom with fewer allergic reactions. Because of more rapid clearance of smaller Fab fragments by the kidney, however, a repeat-dose regimen must be used to prevent the recurrence of coagulopathy. Reported adverse side effects of FabAV polyvalent antivenom include subacute coagulopathy, thrombocytopenia, and ischemic stroke.[31-33] The duration of action of the venom may be longer than the therapeutic effect of the antivenom. Initial studies have shown promise for a new affinity-purified, mixed monospecific ovine FabAV that has been tested with favorable results in humans after minimal to moderate crotalid envenomation.[20] Its efficacy in pit vipers from South America or Asia has not been proved. Purification of antivenom by separation of active fractions may lead to safer administration of horse serum–derived antivenom. An algorithm has been developed that can aid in decision-making after a crotalid bite (Table 55.2 and Fig. 55.7).[30] In the next decade, snakebite management will probably change radically throughout the world. Phytotherapy (botanical therapy)

and other non-antivenom drug therapies for snakebite have shown promise in experimental animal studies, and some centers have successfully treated snakebite with medical support only. Hyperbaric oxygen therapy has also been used as an adjunct to antivenom in the treatment of venomous snakebite; however, there is insufficient evidence to recommend its use.[34]

The following are general guidelines to maximize patient care when antivenom is used:

1. Because anaphylaxis may occur whenever antivenom is administered, appropriate therapeutic agents (eg, oxygen supply, airway support, epinephrine, corticosteroids, and other pressors) must be ready for immediate use. Any patient requiring antivenom should have two intravenous lines inserted. If an allergic reaction occurs, the line with the antivenom can be clamped and the other line used for resuscitation. Administration of 0.3 mg of 1:1000 epinephrine subcutaneously before administration of antivenom may prevent allergic reactions to horse serum–derived antivenom and, if not contraindicated, should be used. If an allergic reaction occurs, then the epinephrine can be given intramuscularly as needed.
2. The initial dose of antivenom is prepared. The smaller the body of the patient, the larger the relative initial dose that may be required. A bitten child usually receives more venom in proportion to body weight and thus requires more antivenom to neutralize it. Because children seem to have less resistance and less body fluid with which to dilute the venom, they may require twice the adult dose of antivenom. The total fluid requirements of children are lower, however, so the antivenom is given in a more concentrated solution. All antivenom is administered intravenously.[35]
3. Pregnancy is not a contraindication to antivenom therapy.
4. Administration of antivenom at or around the site of the bite is not recommended.
5. The need for subsequent doses is based on the patient's clinical response. The patient is monitored closely after the initial dose, and local and systemic symptoms, as well as laboratory findings, are determinants of the need for further antivenom. Additional injections of one to five vials of antivenom are administered every 1 or 2 hours if symptoms progress. Most pharmacies do not stock large amounts of antivenom, and the pharmacy should be notified to obtain additional antivenom for treating a severe bite. Continuous infusions of Crotalidae polyvalent Immune Fab (ovine) FabAV has been used in selected North American rattlesnakes.[36]
6. Even with a history or signs of allergy, patients with severe envenomation are treated with a dilute form of antivenom and epinephrine to maximize antivenom administration but minimize allergic symptoms.

TABLE 55.2

Antivenom Dosage for Pit Viper Envenomation*

	FabAV†	FabAV
ENVENOMATION	INITIAL DOSAGE TOTAL	MAINTENANCE DOSAGE
Moderate	4 to 6 vials	2 vials
Severe	8 to 12 vials	2 to 4 vials
Very severe	12 to 18 vials	4 to 10 vials

*Dosage based on initial findings and clinical response to antivenom (see also Fig. 55.7).
†If this dose elicits a clinical response, it is recommended that an additional two vials be given at 6, 12, and 18 hours. The patient's coagulation studies should be followed to determine additional amounts.
FabAV, Fab antivenom.

Coral and Exotic Snakes. It is recommended that all victims of bites by the eastern coral snake *(Micrurus fulvius)* be

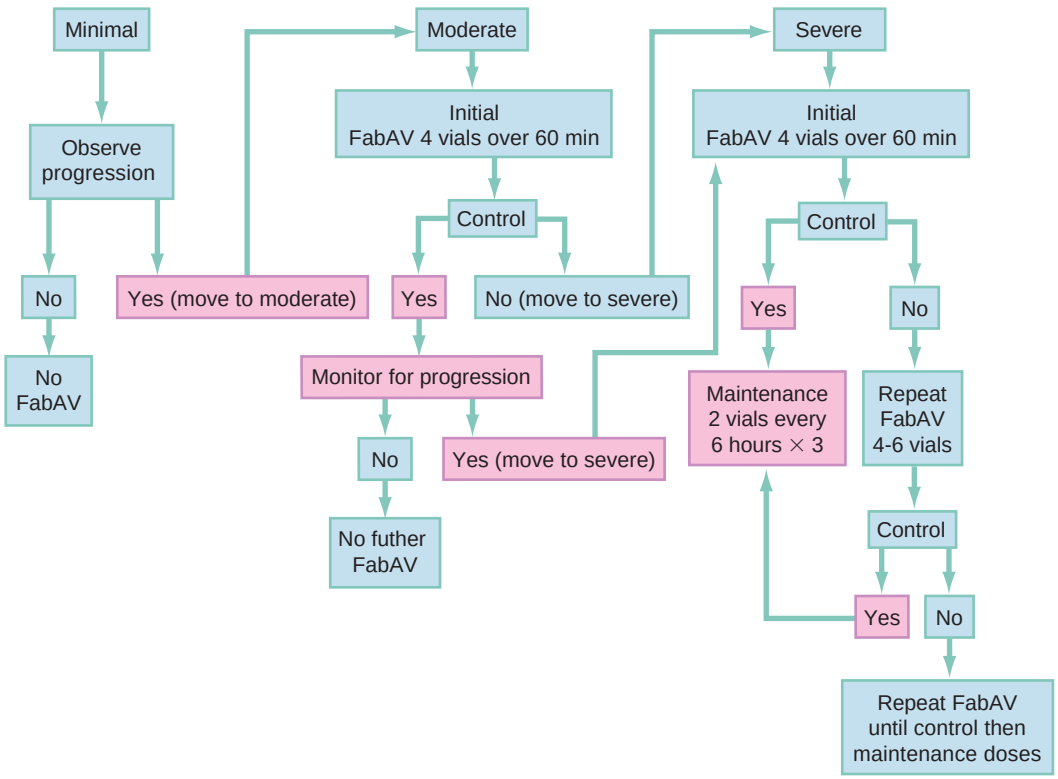


Fig. 55.7. Algorithm for use of Fab antivenom *(FabAV)* (antivenom).

given antivenom even before any symptoms develop. Unfortunately, this antivenom is no longer manufactured by Wyeth, and existing stocks are slowly being depleted. The toxicity of this venom has a rapid onset, and once symptoms develop, it may be too late to reverse the effects with antivenom. The recommended dosage is 3 to 5 vials in 300 to 500 mL of normal saline. Antivenom is given based on the clinical response. If no antivenom is available, management is based on meticulous supportive care emphasizing the respiratory and neurologic status. No antivenom exists for the venom of the Arizona (Sonoran) coral snake, which fortunately is less dangerous. Treatment of this type of snakebite is supportive.

The problems with bites of exotic snakes are threefold: Positive identification of the specimen is sometimes difficult, even for experts; specific antivenom is not always readily available; and even if the antivenom is available, the instructions for reconstitution and dosage may not be written in English. Many zoos maintain a supply of antivenom for their venomous snakes, and this may be the best source of antivenom for an exotic species.[3-5] Some collectors keep appropriate antivenom on hand for the species that they collect. The Antivenom Index at the Arizona Poison Center (602-626-6016) can assist in identifying sources of exotic antivenom or in obtaining more pit viper antivenom. As with coral snakes, many patients do not show any early signs after envenomation by exotic snakes. The antivenom should be administered before neurologic symptoms develop. An alternative regimen is clindamycin plus metronidazole plus a fluoroquinolone.

Wound Care. The snakebite wound is cleaned and examined for foreign bodies (such as, retained fangs or teeth), the area is immobilized, and analgesia is addressed. Elevation at or above heart level may relieve some of the pain. Excision of the bitten area is no longer recommended. As with any puncture wound, one should ensure that tetanus immunization is up-to-date. Broad-spectrum antibiotics have not been shown to be useful in uncomplicated snakebites. If signs of secondary infection develop, ampicillin-clavulanate is recommended.

Patients admitted to the hospital require serial determinations of platelets, fibrinogen, prothrombin time, and urinalysis every 4 hours to check for myoglobin and hemoglobin. Blood products, including packed red blood cells, fresh frozen plasma, and other coagulation factors, are administered as needed. Usually, it is best to wait until antivenom therapy has been started, or the use of the blood products may be futile. Awake patients who have no nausea or abdominal pain can be given oral fluids. Local wound care includes daily cleansing with soap and water and the application of a sterile dressing to open wounds.

Surgical consultation is may be required for débridement or skin grafting. Débridement should probably not be performed earlier than 3 days after the bite, until the coagulopathy has resolved. Surgical exploration of the bite wound is not necessary and may be harmful. Skin grafts are occasionally necessary after bites by pit vipers that produce large necrotic areas. Fasciotomy is rarely indicated unless compartment pressures are elevated above 30 mm Hg and signs of true compartment syndrome are present. We recommend adequate doses of antivenom to lower intracompartment pressures prior to any consideration of fasciotomy. Physical therapy is often needed and should begin soon after the acute phase of the envenomation is complete.[10,12]

Serum Sickness. In most patients who receive more than 10 vials of horse serum–derived antivenom and in approximately 15% of those who receive FabAV, serum sickness develops up to a week later. The administration of diphenhydramine plus cimetidine, and in severe cases a tapering dose of corticosteroids, can be used to treat this problem. Serum sickness is the only indication for the use of steroids with snakebite.[37]

Other Envenomation. Gila monster and Mexican beaded lizard bites are treated similarly to pit viper bites with regard to first aid. No definitive medical treatment exists. Antivenom is currently not available. Local wound care, tetanus prophylaxis, the use of antibiotics and analgesics, and supportive care are the extent of ED treatment available for this type of envenomation.

Envenomation by the yellow-bellied sea snake causes severe muscle necrosis with the release of large amounts of myoglobin and neurologic symptoms. Although a polyvalent antivenom is available from Australia, airway control, maintenance of adequate urine output, alkalinization of urine, and general supportive care are usually sufficient.

Disposition

If no envenomation is evident after clinical examination and the snake was either nonvenomous or a pit viper, the victim can be observed for 6 to 8 hours. With some snakebites, however, toxicity may be delayed by up to 8 hours. If no sign of envenomation is seen after 8 hours, the patient may be discharged. These patients require tetanus immunization when indicated, wound care instructions, and referral for follow-up within 24 to 48 hours. They require instructions on the types of delayed symptoms that may occur and when to return to the ED.

If only local pain and minimal edema have occurred, the patient is closely watched for 12 hours in the ED. If the pain and swelling decrease and no systemic symptoms or laboratory abnormalities develop, the patient may be treated with the same precautions as a patient with no signs of envenomation. Any patient with moderate or severe envenomation should be admitted to an intensive care unit for monitoring during antivenom therapy. Depending on the severity of the bite, blood products, vasopressors, and invasive monitoring may be necessary.

Any patient bitten by a coral snake, a Mojave rattlesnake, or an exotic snake is at risk for severe neurologic sequelae that may not become evident for many hours.[38] As a result, these patients require hospital admission, preferably to an intensive care unit where they can be monitored closely for up to 24 hours. Arrangements should be made to have a ventilator, invasive monitoring, and dialysis equipment available if necessary. Appropriate antivenom should be obtained and treatment initiated at the earliest onset of symptoms. Some experienced clinicians may wait until symptoms develop before administering antivenom. All patients receiving antivenom require close monitoring for recurrence of coagulopathy, which may occur several days after initial envenomation.[39] The overall disability of patients surviving snake envenomation is low including chronic pain at the bite site, extremity paresthesias, and focal weakness.[40]

VENOMOUS ARTHROPODS

Arthropods are animals with segmented bodies and jointed appendages. This phylum (Arthropoda) contains approximately 80% of all known animals. The living members of this phylum are categorized into 12 classes. Two classes, the Insecta and the Arachnida, are of particular interest because numerous venomous species have evolved that are harmful to humans. Many species have developed venom glands and an apparatus for delivering the venom to obtain food. Others have developed venom delivery systems used solely for defense; most of these species are found in the orders Hymenoptera and Lepidoptera.

Arthropods account for a higher percentage of deaths from envenomation than do snakes. They are found inside dwellings, as well as in deserts, forests, and lakes. Although most arthropods are more active during the warmer months, many are active throughout the winter. Arthropods are also active 24 hours a day, and many can fly, thus increasing their range. This high level of

contact results in millions of cases of envenomation annually. Most fatalities result from an autopharmacologic response by the victim rather than the toxicity of the venom. An individual stung by a bee may have a small amount of pain and local swelling or, in severe cases, an anaphylactic reaction and death.

Arthropods use three main methods of delivering venom: stinging, biting, and secreting venom through pores or hairs. Some arthropods combine two systems, one for offense and the other for defense. In general, venom systems found on the oral pole of an animal are used for offensive purposes or food acquisition, whereas systems found on the caudal pole are used for defense. Humans are not considered prey for any venomous arthropod, and therefore bites from them are defensive, accidental, or reflexive. Many venomous arthropods are omitted from this discussion because of their infrequent contact with humans or the relative impotence of their venom.

Hymenoptera

Hymenoptera is a familiar order of arthropods that is composed of the families of bees, wasps, hornets, yellow jackets, and ants. Many of these species are social insects, and their defense response is related to protection of the group rather than the individual organism. Although most members of this order are stinging insects, several species of ant can bite and sting simultaneously.

Bees and wasps have similar mechanisms of delivering venom. Female insects of this type have modified ovipositors that protrude from the abdomen and act as hypodermic needles to administer the venom. The barbed stinging apparatus of the bee is quite prominent. The stinging action pulls the stinger from the bee, thereby eviscerating the insect and killing it.

The wasp, which has an unbarbed stinger, may inflict many stings without damaging itself or its stinging apparatus. The venom is produced in one or two tubular glands that empty into a venom reservoir. The venom reservoir has a duct that connects to the stinger. The venom is composed of several classes of substances varying in composition among different species. Proteins, as in snake venom, make up most of the venom by dry weight. Peptides, amino acids, carbohydrates, lipids, and other low-molecular-weight substances are also found. The most common enzymes are phospholipase A and hyaluronidase. Peptides are common in some species and constitute up to 50% of the dry weight. Most of the toxicity of the venom results from substances of low molecular weight (eg, bradykinin, acetylcholine, dopamine, histamine, and serotonin). Many other antigenic substances have been identified in bee and wasp venom, and they account for the induction of hypersensitivity and anaphylaxis in humans. In the United States, 10% of all cases of anaphylaxis are attributed to stinging insects or hymenoptera.[41]

Clinical Features

The signs and symptoms of bee and wasp stings vary, depending on the degree, type, and location of envenomation, as well as the characteristics of the victim. Bee and wasp venom can cause serious injury other than allergic types of reactions, depending on the number of stings, the species of insect, the size and previous health of the victim, and the anatomic area stung. For example, a stinger in the tongue or throat may quickly compromise the airway. Honeybee venom causes a much greater release of histamine per gram than does other hymenoptera venom and thus is more dangerous. Certain species of honeybee release a pheromone, isoamyl acetate, when the ovipositor is pulled from the abdomen after stinging a victim. This pheromone attracts other bees to the victim and thus incites multiple stings.

There is little antigenic overlap among species, which may explain the variability in reaction to stings reported by victims. Victims who are allergic to honeybees and who mistakenly identify a yellow jacket as a honeybee may not have a systemic reaction and thus may think that they are no longer allergic to honeybees.

The most consistent finding is immediate pain at the site of the sting, followed by local swelling, redness, and itching. A sensitive victim may experience swelling, urticaria, coughing, wheezing, coma, and respiratory arrest. Some large and especially venomous hornets have been known to cause muscle necrosis, rhabdomyolysis, and renal damage. Additionally, cerebrovascular accidents, intracranial bleeds, and myocardial infarction have been described.[42] Most serious reactions to bee stings occur in the first 30 minutes; however, the local effects of a sting may persist for 2 or 3 days. Delayed hypersensitivity may occur 7 to 10 days after the sting.[43-45]

"Killer Bees." Health officials have been concerned about a particularly aggressive species of bee imported from Africa to Brazil in 1956 to increase honey production that has been known to attack humans and cattle with fatal results. This bee has managed to compete with native species and is gradually replacing some of these species while still retaining its aggressive behavior. Envenomation from these aggressive arthropods is a public health issue and most dangerous to very young or elderly patients and those with concomitant medical conditions.[46] Killer bees have colonized northern Mexico and have moved into the southern United States, including California, Arizona, and Texas, where the mean high temperature is at least 60° F. This type of bee is not more toxic, only more aggressive (Fig. 55.8).

Fire Ants. Another unwelcome import to the United States is the fire ant. This insect is a member of the family Formicidae and is another of the Hymenoptera that is harmful to humans. Several species of fire ant are known, some native to North America and some imported. The species responsible for 95% of clinical cases, *Solenopsis invicta,* was imported from Brazil to Alabama in the 1930s. This ant is now found in nine southern states and is replacing many native species and inhabiting new niches. The only limiting factor keeping the fire ant from progressive migration seems to be cold winters. This ant is small and light reddish brown to dark brown. Its venom is unique to the animal kingdom in that it is 99% alkaloid. The remaining 1% is quite immunogenic and can sensitize an individual to the venom. Properties of this venom include hemolysis, depolarization of membranes, activation of the alternative complement pathway, and general tissue destruction. The sting is produced when the ant bites the victim with its jaws and, while holding tight, pivots around and stings the victim with its ovipositor. The sting usually produces a sterile pustule within 24 hours. Other symptoms include local burning, redness, and itching. With multiple stings and in sensitive individuals, urticaria, angioedema, dyspnea,

Fig. 55.8. African "killer bee."

nausea, vomiting, wheezing, dizziness, and respiratory arrest may occur. Approximately 10% of victims have some degree of hypersensitivity reaction.[44]

Differential Diagnoses

The differential diagnosis of hymenoptera envenomation include stings from honeybees, wasps, hornets, yellow jackets, fire ants, scorpions, centipedes, millipedes, caterpillars, spider bites, infectious causes such as cellulitis, and other allergic reactions, including anaphylaxis and contact dermatitis.

Diagnostic Testing

Most cases of hymenoptera stings with localized reactions require no diagnostic studies. Severe reactions, infections, and anaphylaxis should have a complete blood count, serum electrolytes, and an acid-base status assessed. Those demonstrating severe allergic reactions should be referred for more comprehensive allergy skin testing.

Management

Prehospital Care. First aid for Hymenoptera envenomation depends on the degree of reaction to the sting. For simple stings, an ice bag wrapped in a towel and applied to the sting area usually relieves the pain and swelling. In the event of an anaphylactic reaction, basic life support is administered until further medical help arrives. Many people allergic to Hymenoptera envenomation carry an emergency insect sting kit containing a tourniquet, epinephrine in a 1:1000 dilution, and an antihistamine. These kits are readily available, and both the patient and the patient's family should be instructed in the treatment of a severe allergic reaction.

Emergency Department Care. No specific antivenom exists for Hymenoptera stings. Treatment consists of local wound care and general supportive measures. A history of any previous allergic reactions to bee stings, hay fever, asthma, or drug reactions is obtained. The circumstances surrounding the sting and the number and location of stings are noted. In patients with a single sting and only a local reaction, the sting area is inspected for evidence of a venom apparatus, which, if present, can be removed by scraping the edge of a scalpel blade parallel to the skin and lifting the apparatus away from the skin. An ice bag wrapped in a towel may then be applied and the patient given an oral antihistamine (eg, 50 mg of diphenhydramine). Adults in whom a severe urticarial reaction, dyspnea, or hypotension develops are treated with 0.3 mL of epinephrine in a 1:1000 dilution intramuscularly, 50 mg of diphenhydramine intravenously, and 50 mg of ranitidine intravenously. There is no evidence that diphenhydramine or steroids will prevent recurrence or biphasic reactions, but they may lessen the itching and skin symptoms. It is recommended that patients with severe hypertension or cerebrovascular disease or those taking monoamine oxidase inhibitors be given epinephrine cautiously because of the potential for adverse reactions. Patients who are taking beta-blockers may not respond to epinephrine and should be given glucagon 1 to 2 mg intravenously. Based on their body weight, children are treated with 0.01 mL of a 1:1000 dilution of epinephrine per kilogram intramuscularly and 1 mg of diphenhydramine per kilogram intravenously.[43] These patients must be watched closely for signs of respiratory problems and treated accordingly. After 1 hour, these individuals should be totally free of symptoms (except for some itching around the sting site). A biphasic allergic reaction can occur in up to 20% of patients. A general rule is urticaria plus involvement of any other organ system constitutes anaphylaxis.[43] Epinephrine is the treatment of anaphylaxis or anaphylactoid reaction and is given if these types of reactions are suspected. Patients who are wheezing after an insect sting are demonstrating a systemic reaction; they require intravenous access, inhaled beta$_2$-agonist therapy, intravenous steroids, and H_1 and H_2 blockers. Patients who have life-threatening reactions (hypotension, respiratory arrest, and cardiac arrest) may be given 0.1 mg of epinephrine in at least a 1:10,000 dilution, very slowly intravenously. The intramuscular route is preferred for all but the most extreme reactions.[44,45]

Treatment of allergic reactions to fire ant stings is the same. The skin lesions should be kept clean with soap and water. Ice bags may be applied initially to relieve burning and pain. Prophylactic antibiotics are not needed.

Of patients who have a systemic reaction to an insect sting, 60% can have a future allergic reaction if they have a positive skin test result. These patients should be desensitized to any specific venom to which they are allergic. Purified insect venom is currently available for most Hymenoptera, including fire ants.

Disposition

The patient is monitored, and if no further reaction is observed, he or she may be discharged with instructions to return to the ED if wheezing, dyspnea, hives, dizziness, or dysphagia occurs. Any patient requiring epinephrine should be watched for at least 6 hours and may require 23-hour observation if symptoms recur. There is a possibility of recurrence of the reaction up to 72 hours, and patients should be warned of this in their discharge instructions. Patients with allergic reactions to a single sting should be given an emergency insect sting kit and instructed in its use and referred to an allergist for desensitization. Patients seen in the ED with systemic reactions to stings should be referred for skin testing and immunotherapy and desensitization.[41]

Spiders and Scorpions

The class Arachnida contains the largest number of venomous species known, with approximately 34,000 species of venomous spiders and 1400 species of venomous scorpions. Virtually all known species are venomous, but most are not harmful to humans. Only approximately 50 species of arachnids in the United States cause human illness, because most species do not have fangs or stingers sufficiently long to penetrate human skin. Humans fear spiders and scorpions, for good reason in certain cases. Ticks, which also belong to this class, are less feared but probably cause more morbidity because of transmission of infectious diseases, such as Rocky Mountain spotted fever and Lyme disease. Some spider bites are never diagnosed because of lack of significant symptoms and the fact that they occur while the victim is sleeping. Many non-spider bites are incorrectly diagnosed as spider bites, and unfortunately there is no gold standard for making the diagnosis.

Black Widow Spider

The black widow spider, *Latrodectus mactans,* may be the most recognized venomous spider in the world. Several other closely related species of *Latrodectus,* or widow spiders, are found throughout the United States, including *Latrodectus hesperus,* which is common in Arizona and other western states. The diagnosis and treatment of the bites of all species are the same.

The black widow is found throughout the United States (except Alaska) and in southern Canada. The female is approximately twice as large as the male, and although both are venomous, only the female is able to envenomate humans. The black widow is glossy black, occasionally with red stripes, and has a bright red marking on the abdomen (Fig. 55.9). This marking may have an hourglass shape or may appear only as two spots. Abdominal

Fig. 55.9. Female black widow spider *(Latrodectus mactans)* with a red hour-glass marking.

markings may vary, and related *Latrodectus* species may be similar in appearance and toxicity. The combined length of the black widow's head and abdomen is approximately ½ inch, and the spider is approximately 1½ inches long, including the legs. It is found in dark, protected places, such as under rocks, in woodpiles, and in outhouses and stables. The female is not aggressive except when guarding her eggs.

The venom apparatus of the black widow is a modified first appendage of the head known as the *chelicera.* The spider is able to control the amount of venom injected into its prey. The venom of the black widow is complex and contains both protein and nonprotein compounds.

Spiders normally use the venom to paralyze their prey and also to liquefy the tissues of the prey for digestion. The venom probably evolved from digestive glands analogous to the salivary glands in snakes. The ingredient most toxic to humans is thought to be a neurotoxin. This toxin destabilizes neuronal membranes by opening ionic channels, causing depletion of acetylcholine from presynaptic nerve terminals and increasing the frequency of spontaneous miniature endplate potentials at neuromuscular junctions.[47]

Clinical Features. The classic symptomatology of the black widow bite is initially a pinprick sensation that may be followed by minimal local swelling and redness. If the area is examined closely, two small fang marks may be noticed. Sometimes the bite is not felt, especially if the victim is working when the bite occurs. From 15 minutes to 1 hour later, dull crampy pain develops in the area of the bite and gradually spreads to include the entire body. Usually, the pain is concentrated in the chest after upper extremity bites or in the abdomen after lower extremity bites. The abdomen may become boardlike, and the patient may complain of severe crampy pain. The abdominal manifestation may mimic pancreatitis, a peptic ulcer, or acute appendicitis. Pregnant women may go into premature labor and precipitous delivery. Associated symptoms include dizziness, restlessness, ptosis, nausea, vomiting, headache, pruritus, dyspnea, conjunctivitis, facial swelling, sweating, weakness, difficulty speaking, anxiety, and cramping pain in all muscle groups. Priapism has been reported in children.[48,49] The patient is usually hypertensive, and cerebrospinal fluid pressure is sometimes elevated.[50]

In adults, the signs and symptoms begin to abate after several hours and usually disappear in 2 or 3 days. A small child bitten by a black widow spider, however, may not survive. As with snake envenomation, the volume of distribution of black widow venom is much smaller in children than in adults. A dose that may cause only a few hours of pain in an adult may lead to complete cardiac decompensation and respiratory arrest in a child. Adult patients with preexisting hypertension, cerebrovascular disease, or cardiovascular disease are also at greater risk for complications. Symptoms usually persist for 8 to 12 hours and then subside, although in severe cases muscle cramps may continue for several days.

Differential Diagnoses. The abdominal manifestation following a black widow spider bite may mimic pancreatitis, a peptic ulcer, renal colic, acute appendicitis, or scorpion stings.

Diagnostic Testing. Patients with symptoms of moderate envenomation, pregnant women, children, and those with preexisting cardiovascular disease or hypertension should have a complete blood count, electrolytes, blood urea nitrogen, creatinine, coagulation studies, urinalysis, and an electrocardiogram. There may be electrocardiographic changes similar to those produced by digitalis.

Management. First aid for a black widow spider bite consists of applying an ice pack to the bite area for relief of pain and transporting the victim to a hospital where supportive, symptomatic, and definitive treatment can be administered. The rescuer should obtain the specimen if possible because many dangerous spiders resemble harmless species and vice versa. The patient is monitored en route to the hospital, and basic life support is initiated if necessary. Bites in the neck or mouth area may cause airway compromise through muscle spasm. ED care consists of obtaining a history of the circumstances surrounding the bite, a description of the appearance of the spider, any significant past medical history, current medications, and allergies to insect bites, horses, or horse serum.

The wound site is inspected for fang marks and cleansed with soap and water. As with any puncture wound, the patient's tetanus immunization status is assessed.

Symptomatic treatment involves controlling the muscle cramps responsible for most of the discomfort associated with the bite. Diazepam or other benzodiazepines given intravenously are useful for relieving muscle spasms.[50] There is one preliminary report in the literature supporting the benefit of dantrolene sodium both orally and intravenously to provide muscle relaxation for *Latrodectus* envenomation. However, dantrolene administration has not been shown to be clinically efficacious in more recent studies. Parenteral analgesics may be necessary to control pain; these drugs may affect an already compromised respiratory condition, and therefore their use must be closely monitored.

Latrodectus *Antivenom.* In general, pediatric patients, pregnant women, and the elderly may need to be given *Latrodectus* antivenom (Lyovac), which is derived from horse serum.[50] A highly purified equine F(ab)2 antibody black widow spider antivenom has been recently investigated.[51] Clinical judgment is used to adjust for the age and category of patients needing antivenom. Candidates for antivenom include patients with severe envenomation manifesting as seizures, respiratory failure, or uncontrolled hypertension, and patients not responding to other therapy. The dose of the antivenom is one vial diluted in 50 mL of normal saline and administered intravenously over a period of 15 minutes. Precautions for allergic reactions should be taken before antivenom is administered. A dose of subcutaneous 1 : 1000 epinephrine may prevent allergic reactions when given before horse serum antivenom. This antivenom is also useful with other species of the *Latrodectus* genus.

Disposition

The patient is observed for approximately 6 hours. If symptoms do not develop and the spider was not positively identified as a

Fig. 55.10. Brown recluse spider *(Loxosceles reclusa)* with characteristic violin shape on its dorsal cephalothorax.

black widow, the patient may be discharged with instructions to return to the ED if any symptoms develop. Patients with moderate symptoms are admitted to the hospital and monitored until symptoms subside; usually within 24 hours. Hypertensive patients may require antihypertensive medications to control severe elevated blood pressure or related symptoms. Fetal monitoring is initiated for pregnant women, and patients with severe symptoms are admitted to the intensive care unit for cardiovascular monitoring.

Brown Recluse Spider

Several deaths were attributed to the brown recluse spider, *Loxosceles reclusa,* in the 1950s, primarily in the south-central United States, thus drawing the attention of the medical community. Many species of *Loxosceles* are venomous to humans, and at least five are found in the United States. These spiders are approximately 1 inch long, including leg span, and range in color from tan to dark brown. The most distinguishing mark is a violin-shaped darker area found on the cephalothorax (Fig. 55.10). Close examination may reveal that the brown recluse has three pairs of eyes rather than the usual four.

These spiders, as their name implies, are not aggressive and are usually found under rocks, in woodpiles, and occasionally in attics and closets. Their range is concentrated in the south-central United States, especially Missouri, Kansas, Arkansas, Louisiana, eastern Texas, and Oklahoma. However, they have been reported in several large cities outside this range.

The venom apparatus is similar to that of most spiders, including the black widow. The composition of brown recluse venom has not been completely determined, but sphingomyelinase D is a primary component. The local tissue destructive effects are thought to be primarily caused by hemolytic enzymes and a levarterenol-like substance that induces severe vasoconstriction. The systemic symptoms seem to be an allergic phenomenon and vary according to the individual's immune response to the venom.[52]

Clinical Features. The symptoms of a brown recluse spider bite are both local and systemic. Initially they are similar to those caused by bites of many other spiders and other conditions. The victim may notice some burning pain in the area of the bite. Some victims do not notice the initial bite at all. Pain usually develops within 3 or 4 hours, and a white area of vasoconstriction begins to surround the bite. A bleb then forms in the center of this area, and an erythematous ring arises on the periphery. The lesion at this stage resembles a bull's-eye. The bleb darkens, necroses over the next several hours to days, and continues to spread slowly and gravitationally, with involvement of skin and subcutaneous fat. Systemic symptoms include fever, chills, rash, petechiae, nausea, vomiting, malaise, and weakness. Hemolysis, thrombocytopenia, shock, jaundice, renal failure, hemorrhage, and pulmonary edema are the usual signs of severe envenomation.[53,54] Although rare, fatalities are more common in children, which are most often the result of severe intravascular hemolysis.[55]

Differential Diagnoses. Differential diagnosis of a brown recluse spider bite includes pyoderma gangrenosum, furuncles, viral and fungal infections, and foreign body reactions. The most common mimic of *Loxosceles* or other necrotic spider bite is a MRSA skin infection.[55,56]

Diagnostic Testing. With significant wounds and systemic symptoms, a complete blood count, metabolic and coagulation profile, and urinalysis are performed. Patients with delayed presentation with a necrotic lesion wound cultures for MRSA. A reduced red blood cell surface glycophorin analysis has been investigated as a potential biomarker for brown recluse spider exposure.[53]

Management. First aid for a brown recluse spider bite is simple. The specimen is secured if possible and the victim transported to a medical facility. Because the lesion develops over a period of days, there may not be any local treatment of the lesion that is effective. The emergency evaluation involves a history of the circumstances surrounding the bite; the time elapsed since the bite; past history of allergic reactions, medications, or medical problems; and an assessment for systemic toxicity. If a specimen is available, identification may be facilitated by recruiting the help of a local entomologist. If signs of systemic toxicity develop, an intravenous line is placed in an unaffected extremity. Vital signs and urine output are closely monitored. Excision of the lesion has not been shown to aid healing and may be detrimental. Lesions have been known to cause extensive scarring, infection, and necrosis. Bites that are in fatty areas, such as the thigh or buttocks, may cause more extensive necrosis.

Historically, dapsone, 50 to 200 mg/day, was thought to be helpful in preventing local effects of the venom.[51] If used within 48 hours, it may limit the size of the lesion that develops. However, dapsone may cause methemoglobinemia and hemolysis in young children and patients with glucose-6-phosphate dehydrogenase deficiency. As a result, we do not recommend routine use of dapsone in patients suffering brown recluse spider bites. Hyperbaric oxygen has been shown to decrease lesion size in animal models. Analgesics and antibiotics should be used as indicated during the course of the disease, but are generally limited to secondary infections. Hemodialysis may be necessary if acute renal failure develops. Plasma exchange for refractory hemolysis after brown recluse spider envenomation may be required.[54] Surgical consultation should be obtained for evaluation of the wound. In a normal host, allow the wound to run its course before wide excision or skin grafting is performed.

The Instituto Butantan in Sao Paulo, Brazil, and Instituto Bioclon, Mexico, both produce an antivenom for *Loxosceles* bites, but they are not available in the United States.

Disposition. Patients with signs of systemic envenomation require hospital admission for monitoring.

Other Spiders

Several other spiders can cause envenomation but are uncommon in the United States. Some of these spiders are large and can be quite aggressive. Most are imported either intentionally or as

stowaways on cargo ships. Tarantulas, wandering spiders, funnel-web spiders, pallid spiders, and crab spiders are a few of the imported venomous spiders. Many of these species can cause envenomation similar to that of the brown recluse spider, and some produce neurotoxins.

An outbreak of bites by a species of *Tegenaria,* known as the *hobo* or *aggressive house spider,* has been reported. This species was imported from Europe to the Pacific Northwest. This spider is a small brown spider with a herringbone pattern on its abdomen. The lesions are similar to those caused by the brown recluse spider, but systemic symptoms include headache and weakness. Treatment is largely supportive.

Tarantulas are popular pets in the United States, and most native species are relatively nontoxic. Tarantulas are unusual in that the abdominal hairs can be thrown by the spider and embedded in human skin and the eye. These hairs can cause allergic reactions and severe conjunctivitis and must generally be removed under a slit lamp or by an ophthalmologist.

Antivenom is produced for some of these groups (eg, Brazilian *Phoneutria* and Australian *Atrax* species) but is usually available only in the country in which the species is generally found.[57] Emergency care therefore involves symptomatic and supportive treatment. A recent import from Thailand, the cobalt blue tarantula, *Haplopelma lividum,* is a very aggressive spider with toxic venom.[58]

Scorpions

Scorpions are arachnids that resemble crustaceans and are among the oldest terrestrial animals. Scorpions are found throughout the world, and several species are located in the southwestern United States. Only one species, *Centruroides sculpturatus* (formerly *Centruroides exilicauda*), which is found in Arizona, is particularly dangerous. Scorpions are nocturnal predatory animals that usually spend the day under rocks, logs, or floors and in crevices. *C. sculpturatus,* or the bark scorpion, is found on or near trees (Fig. 55.11).

The scorpion has a tail-like structure that is actually the last six segments of its abdomen. The last segment, or the *telson,* contains the two venom glands and stinger. The toxicity of scorpion venom varies greatly from species to species. In general, the less dangerous species produce more local reactions, and the more dangerous species cause more systemic reactions. Several proteins have been identified in their venom; some cause hemolysis, local tissue destruction, and hemorrhage. The venom of *C. sculpturatus* is predominantly a neurotoxin that causes or enhances repetitive firing of axons by activation of sodium channels.[47]

Fig. 55.11. Arizona bark scorpion (*Centruroides sculpturatus,* formerly *Centruroides exilicauda*).

Clinical Features. Envenomation causes severe and immediate pain at the sting site. Local edema and erythema may or may not be present, depending on the species. After envenomation by *C. sculpturatus,* the victim may have heightened sensitivity to touch in the area of the sting along with local numbness and weakness. The diagnosis is often made by tapping on the site of the sting and causing an increase in pain at the site. Systemic symptoms may then develop, including anxiety, restlessness, muscle spasms, nausea, vomiting, excessive salivation, sweating, itching of the nose and throat, hyperthermia, blurred vision, roving eye movement or nystagmus, myoclonus, priapism, hypertension, hemiplegia, syncope, cardiac dysrhythmias, and respiratory arrest.[59] Various systemic complications may occur, depending on the species of scorpion. *Tityus trinitatis* scorpion stings from Trinidad cause pancreatitis to develop in 80% of victims. A wave of symptoms sometimes occurs over a 24-hour period, or respiratory failure may develop in the first 30 minutes. As with most envenomations, children are at a greater risk for severe reactions. A grading system has been developed to guide management of bark scorpion stings.[60]

Differential Diagnoses. The differential diagnosis of scorpion stings includes black widow spider bites, centipede stings, and hymenoptera stings, such a bees, wasps, and fire ants.

Diagnostic Testing. Laboratory testing for symptomatic patients includes a complete blood count, renal function test, serum electrolytes, creatine phosphokinase, lipase, and an electrocardiogram if a potentially cardiotoxic scorpion. A serum Western blot test has been developed that can differentiate various scorpion venoms and thus help with diagnosis of *Centruroides* species, but it is not commercially available.[60]

Management. First aid for a scorpion sting consists of applying an ice bag to the area of the sting and transporting the victim to the hospital. A history of the circumstances surrounding the sting, any previous medical problems, and a description of the scorpion if no specimen is present should be obtained. It is relatively difficult for a layperson to differentiate the various scorpions. Anascorp (*Centruroides* [scorpion] immune F[ab]2 equine injection) is horse serum derived and has been shown to be effective and safe in both blinded and open studies of patients. It was effective in children if given within 4 hours of the sting.[59] However, most patients will not require antivenom therapy for bark scorpion *(Centruroides)* stings. Epinephrine 1:1000 can be given before Anascorp to prevent allergic reactions, although the incidence should be less than with whole immunoglobulin. Opioids and benzodiazepines have been shown to be clinically beneficial in controlling pain.[59,61]

Approved antivenom is recommended in all cases of severe envenomation. Intravenous diazepam or another benzodiazepine may be used for myoclonus and muscle spasms. Phenobarbital, previously used in large doses in children, may be more dangerous than efficacious and may have contributed to deaths in the past. Atropine may be administered to control hypersalivation and bradycardia. Nitroprusside and prazosin have been used to control hypertension. Ventilatory assistance may be necessary, especially in children.[59]

Disposition

It is recommended that victims with systemic symptoms be observed for 24 hours, and children should be admitted to the

hospital for monitoring. Patients with localized pain at the site of the sting can be given pain medications and discharged home with wound care instructions.

Other Arthropods

Ticks are vectors of human disease, and certain pregnant female ticks also secrete a toxin that causes a progressive ascending paralysis in humans and animals. The precise mechanism and structure of the toxin are unclear. The two species responsible in the United States are *Dermacentor andersoni* (wood tick) and *Dermacentor variabilis* (dog tick). The bite of the tick is usually painless, but the victim later has difficulty walking, weakness, flaccid paralysis, slurred speech, and visual disturbances.[62] The victim is usually a child, often with a history of recent outdoor activity. Treatment is removal of the offending tick before the paralysis has progressed too far. Any patient with ascending paralysis should be closely examined for the presence of a tick, especially on the head and back. Patients with a dermatologic erythema migrans rash or "target lesion" following a tick bite should be evaluated for Lyme disease and treated with doxycycline. *Borrelia* species known to cause Lyme disease are collectively known as *Borrelia burgdorferi* (see Chapter 126 for more details regarding tick bites and Lyme disease).

Several species of beetle, millipede, and caterpillar secrete irritating substances that cause severe burning pain, numbness, pustular contact dermatitis, edema, nausea, vomiting, and headache. Oropharyngeal exposure can cause mucosal edema and irritation.[63] Deaths have rarely been reported. Treatment consists of washing the area thoroughly with soap and water and removing any spines or hairs present. Spines can be removed with adhesive tape or by applying white glue or facial peel. Locally applied ice bags and a paste of baking soda and water may be of benefit. Analgesics should be used as needed, and supportive therapy may be necessary for severe envenomation.[64]

Centipedes can inflict bites that cause erythema and edema. Treatment is usually local soaks and the use of analgesics. Conenose bugs, or "kissing bugs," may cause severe local and systemic allergic reactions. Treatment with antihistamines and supportive care, depending on the degree of reaction, are all that is necessary. Many other arthropods can cause local skin reactions and severe allergic reactions, depending on the individual's sensitivity. Patients are treated symptomatically with local steroid creams, antihistamines, and other symptomatic supportive measures.

VENOMOUS MARINE ANIMALS

Principles

Almost 2000 species of animals found in the ocean are either venomous or poisonous to humans, and many can produce severe illness or fatalities. An estimated 40,000 to 50,000 marine envenomations occur annually. In recent years, the number of injuries caused by these animals has increased dramatically because of the greater number of scuba divers, snorkelers, surfers, and others engaging in water sports. These animals are not usually aggressive, and many are completely immobile. Most of the venomous marine animals injure humans with defensive or food-procuring devices. Most venomous marine animals in the United States are found along the California, Gulf of Mexico, and southern Atlantic coasts. These animals range in complexity from sponges to bony fishes and contain some of the most complex and toxic venoms known. Recently, populations of lionfish have been increasing in American coastal waters due to release of these predatory fish in nonindigenous waters.[65]

Venom Delivery

In general, venomous marine animals are divided into three main classes according to the mechanism of venom delivery: bites, nematocysts, and stings.

Bites

Biting animals include several species of cephalopods, most often octopi. Although popular media portray a giant deadly creature that squeezes its victims to death, the most dangerous octopi are seldom larger than 20 cm. Several fatalities have been reported after a bite by the blue-ringed octopus, *Hapalochlaena maculosa*. Most victims are bitten on the upper extremity because they disturb this normally nonaggressive creature. The octopus has a pair of modified salivary glands that secrete venom into the wound produced by the animal's beak. The venom contains a potent vasodilator and an inhibitor of neuromuscular transmission similar to tetrodotoxin. No known antivenom exists, and treatment is largely supportive, with respiratory support being the most important lifesaving intervention.

Nematocysts

The second type of venom mechanism is the nematocyst found in coelenterates *(Cnidaria)*. This group of animals includes the Portuguese man-of-war,[66] true jellyfish, fire corals, stinging hydroids, sea wasps, sea nettle, and anemones. Most of these organisms are sessile, but some are free floating. Because of their large numbers, this group accounts for the greatest number of envenomations by marine animals.

Many different types of nematocysts are known, but the basic mechanism is a "spring-loaded" venom gland that can, on mechanical or chemical stimulation, suddenly evert and discharge a structure that penetrates the prey and delivers the venom through a connecting tube. These nematocysts, found on the animal's tentacles, can number in the hundreds of thousands. Tentacles can be up to 100 feet long in some giant species. Nematocysts can still function even if the animal is dead or if the tentacles are separated from the animal's body. These stinging cells can remain active for weeks after an animal becomes beached. Often, not all nematocysts fire on initial contact but may discharge later during attempted rescue and treatment. Certain marine species have evolved methods of using ingested nematocysts for their own defense.

Toxicity. Nematocyst venom contains various peptides, phospholipase A, proteolytic enzymes, hemolytic enzymes, quaternary ammonium compounds, serotonin, and other toxic compounds. The venom of the coelenterates is antigenic, and allergic reactions are often seen. The severity of the envenomation is related to several factors. First, the severity of the injury is directly proportional to the number of nematocysts discharged. Second, the toxicity varies from species to species. It is unlikely that the victim or the treating physician will be able to identify the species from the appearance of the wound.

Clinical Features

Symptoms may range from simple isolated stinging to respiratory paralysis, cardiovascular collapse, and death. Therefore, the diagnosis must be made according to the clinical findings. The victim's autopharmacologic response to the venom may turn a relatively minor envenomation into a fatal anaphylactic reaction. Any clinician who regularly treats this type of injury should become acquainted with the common species indigenous to their region.

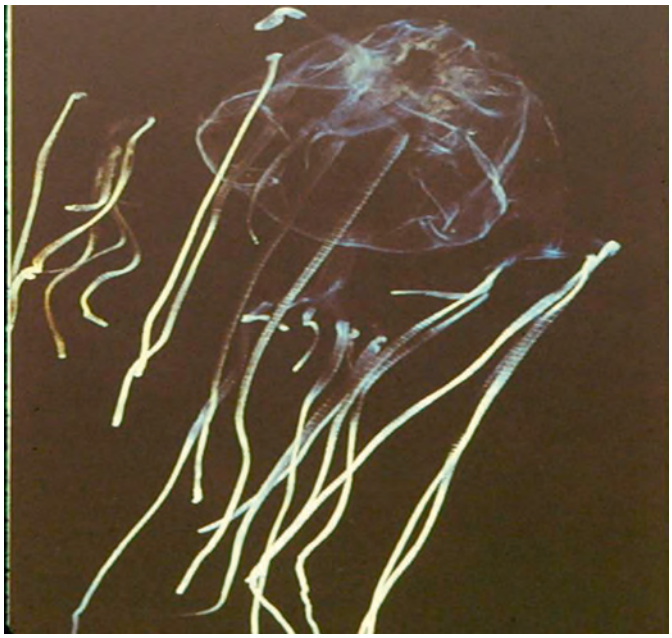


Fig. 55.12. Box jellyfish or sea wasp *(Chironex fleckeri).*

Although lethal and potentially lethal jellyfish exist worldwide, the extremely toxic specimens are found off the coast of Australia and in other Indo-Pacific waters. Probably the most notable and most toxic coelenterate is the box jellyfish, also known as the "sea wasp" (Fig. 55.12). More dangerous than the famed great white shark, this small animal causes several deaths along the Australian coast annually. Cardiac arrest may occur within minutes. Another north Australian jellyfish, *Carukia barnesi,* also produces a devastating envenomation known as *Irukandji syndrome.*[67] This causes major catecholamine release, hypertensive crisis, and passive death.[67]

The Portuguese man-of-war *(Physalia physalis)* is found along the southern coastline of the United States.[66] This organism is not a true jellyfish but a hydroid colony. Envenomation is usually limited to local pain, scarring, and paresthesias, but it may progress systemically to nausea, headache, chills, and even cardiopulmonary collapse. This organism has also been responsible for several deaths.

Most other envenomations are minimal, and the danger is either drowning after being stung or an allergic reaction to the venom. The symptoms resulting from coelenterate envenomation usually consist of a severe burning sensation accompanied by raised erythematous lesions where nematocysts have discharged into the skin. The symptoms may progress, depending on the species and the number of nematocysts, to include nausea, vomiting, chest pain, muscle cramps, dyspnea, diarrhea, cough, convulsions, angioedema, and respiratory arrest. The initial pain and redness may last from a few hours to 2 or 3 days, depending on the therapy.

A related type of envenomation is caused by various species of coral, particularly fire coral *(Millepora).* These injuries combine nematocyst envenomation with wound contamination. Animal protein and calcareous material left behind in these wounds cause infection and chronic inflammation.

Stings

Some marine animals cause a "sting" that is produced by a specialized apparatus that punctures the victim's skin and then introduces venom. Common examples of this type of animal are sea urchins, cone shells, bristle worms, crown-of-thorns starfish, stingrays, lionfish fish, weever fish, catfish, stonefish, rabbit fish, and zebra fish. Sea urchins, cone shells *(Conus californicus),* catfish, scorpion fish, and stingrays account for most of the venomous marine animal injuries in the United States.[65]

Sea Urchins. Sea urchins belong to the Echinodermata phylum along with starfish and sea cucumbers. These animals produce injury and envenomation mostly through toxin-coated spines. These spines often break off and introduce calcareous material and debris into the wound, thereby potentiating infection. Symptoms most often include severe local burning, pain, and discoloration, but they may progress systemically in some patients. The degree of envenomation is usually related to the number of spines involved and the species of animal encountered.

Cone Shells. Cone shells are much more toxic than sea urchins, and some species have been responsible for fatalities in the Indo-Pacific region. The venom apparatus is a tubular gland that connects to several teeth at the end of a retractable proboscis. All envenomations reported have occurred in persons handling the shells. The venom contains several proteins, protein-carbohydrate complexes, and 3-indolyl derivatives that act mainly on skeletal muscle and cause variably spastic and flaccid paralysis. Symptoms may or may not include pain, depending on the species. Severe envenomation may cause diplopia, slurred speech, numbness, weakness, paralysis, and respiratory arrest. Onset and regression of symptoms may vary from minutes to days. No antivenom is available for cone shell envenomation. Airway control and supportive care are the mainstays of therapy for severe envenomations.

Stingray. The stingray is a member of the shark family. It is a broad, flat fish with a long, whiplike tail that may have one or more stingers with barbed ends. Stingrays vary in size from a few inches to several feet, and the stingers are proportional to the size of the fish. The stinger is encased in an integumentary sheath and contains venom glands. Stingrays bury themselves in the sand of shallow water, where they can be easily stepped on inadvertently.[68] The sheath and stinger are often broken or left in the wound. The victim experiences an immediate, intense pain in the area of the wound, which may spread to the entire extremity. Systemic symptoms include salivation, nausea, vomiting, diarrhea, syncope, muscle cramps, fasciculations, dyspnea, cardiac dysrhythmias, and convulsions. The exact composition of the venom is unknown. Enzymes, proteins, serotonin, and a cholinergic substance have been identified, but the exact toxin responsible for most of the severe symptoms is yet to be isolated. The presence of foreign material may also impair healing and cause infection.

Bony Fishes. Bony fishes inflict their wounds through spines located on their fins. The spines and venom glands are encased in a sheath, and grooves along the spines act as channels for the venom. These fish injuries are typically encountered when the fish are stepped on in shallow water or handled by fishermen. The venom is made up of several classes of proteins, most of which are heat labile. The family Scorpaenidae includes three groups of species categorized by venom apparatus: zebra fish, scorpion fish, and stonefish. Zebra fish include the popular aquarium resident, the lionfish. Scorpion fish produce intense pain that can spread to the entire affected extremity within minutes. Stonefish envenomation may cause serious and even life-threatening systemic illness, but manifestations such as cardiac and respiratory symptoms can be prevented by early administration of the appropriate antivenom. Saltwater and freshwater catfish produce envenomation through contact with dorsal and pectoral spines.

Management

Much of the venom from marine animals can be neutralized at the scene, and most fatalities can be prevented. The most important step is to remove the victim from the water. Drownings after minimal envenomation may account for more fatalities than the end effects of severe envenomation. The patient should be questioned about the circumstances of the bite, allergies, and systemic symptoms. If a severe allergic reaction has occurred, the victim is treated for this emergency before the wound is addressed. The type of wound care largely varies according to the type of venom apparatus involved. All marine stings from either bony fish or stingrays are treated with immersion in hot (110° F) water for 30 to 90 minutes.[69] This therapy usually improves pain within minutes, but supplemental analgesics may be needed. As with all wounds encountered in the ED, appropriate cleansing, débridement, and tetanus prophylaxis are paramount. Prophylactic antibiotics, such as ciprofloxacin, are recommended when residual foreign body is suspected. Specific antivenoms are available for some species, such as the box jellyfish and stonefish.

Bite injuries are treated with basic life-support measures and general wound care consisting of cleansing, débridement, and irrigation. Systemic signs and symptoms are treated as appropriate, with aggressive attention paid to the cardiac and respiratory systems.

Nematocysts

Nematocyst injuries are treated by first removing the nematocysts without allowing them to discharge. Tentacles are removed with a gloved hand or forceps. The remaining nematocysts are fixed by pouring vinegar (dilute acetic acid) over the wound area.[67,70,71] For *Physalia* (man-of-war) stings, hot water may be useful or hot vinegar may be even better.[72] Baking soda and alcohol have also been shown to be effective, and deactivation of nematocysts may be species specific. Fresh water is not used, because it may stimulate continued nematocyst discharge. Other methods include scraping off residual material with the use of a shaving cream or baking soda slurry. The affected area is then débrided and cleansed. Hot water immersion may relieve pain. Most lifeguard stations in areas where coelenterate stings are common have the necessary materials for this regimen. Supportive pharmacologic therapy (eg, analgesics, antihistamines, and steroid creams) is indicated for all but the most trivial envenomation. Delayed cutaneous reactions may persist despite optimal therapy.

Early aggressive resuscitation offers the best chance of recovery from *(Chironex fleckeri)* stings. Box jellyfish antivenom is available in limited supply and may be life-saving.[73,74] Delayed neutralizing effects of the antivenom may take up to 60 to 70 minutes to take full effect justifying prolonged cardiopulmonary resuscitation (CPR) and other resuscitation attempts in these patients.

Fish

Puncture injuries are treated by removing the spine or sting if possible. An x-ray film of the involved area is obtained because many spines and sheaths are radiopaque.[75] Sea urchin spines usually break off in the wound; they are so fragile that removing them is difficult without the proper instruments. The stinger of the stingray should be removed with forceps, although these stingers with their sheaths have been known to penetrate body cavities and require surgery for removal. Although not usually present in the wound, the fish spines of bony fish should be removed with forceps. In all cases, the wound should be copiously irrigated. Most venoms injected through puncture wounds are heat labile. Significant analgesia can be achieved by submersion of the wound in hot (110° F) water for 30 to 90 minutes or until symptoms improve.[69] A specific antivenom for stonefish envenomation is available in Australia.

Disposition

Patients envenomated by unknown or unfamiliar organisms should be observed for systemic signs and symptoms. Careful discharge instructions are provided to the patient, warning him or her to return for increasing pain, numbness, difficulty breathing, and signs of infection.

KEY CONCEPTS

- Snake venom causes neurotoxicity and hematotoxicity, but one usually predominates, depending on the species of snake.
- The amount of crotalid antivenom given depends on the grade of envenomation, from 0 (minimal or no sign of envenomation) to IV (severe envenomation). Antivenom recommended for grade II to IV snakebites. Children require the same amount of antivenom as adults.
- Pit vipers have a characteristic pit found midway between the eye and the nostril on both sides of the head.
- Arthropods such as hymenoptera account for more deaths from envenomation than snakes, usually as a result of allergic reactions.
- Black widow spider bites are neurotoxic causing severe pain and muscle spasms; brown recluse spider bites cause necrotizing skin wounds.
- Nematocyst (jellyfish) stings should be immediately neutralized with vinegar or hot water, and fish stings with hot water. Stings from venomous fish (such as, lionfish and sting rays) are treated with circulating hot water to denature the toxin.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 55: QUESTIONS & ANSWERS

55.1. Which of the following venomous snakes in the United States is a member of the neurotoxic Elapidae family?
- **A.** Copperhead
- **B.** Coral snake
- **C.** Rattlesnake
- **D.** Water moccasin

Answer: B. Pit vipers from the family Viperidae are the most prevalent venomous snakes in the United States. They are native to every state except Maine, Alaska, and Hawaii. They are classified into three main groups: true rattlesnakes (genus *Crotalus*), copperheads and water moccasins (genus *Agkistrodon*), and pygmy and Massasauga rattlesnakes (genus *Sistrurus*). Pit vipers account for 98% of all venomous snakebites in the United States. Other families include Colubridae, Hydrophiidae, Elapidae (to which the neurotoxic coral snake belongs), and Crotalidae.

55.2. A 30-year-old man complains of pain, burning, and swelling of his hand after gardening. Physical examination shows two puncture marks on his thenar eminence, as well as moderate localized swelling. When you inquire about it, he said that he did have some burning pain briefly while digging around in the ground by a bush, but he dismissed it as abrasions from sharp sticks. That was 2 hours ago. What should you do next?
- **A.** Apply a constricting band to impede venous and arterial flow.
- **B.** Discharge with instructions for rest, ice, immobilization, and use of oral antibiotics.
- **C.** Give tetanus and clindamycin for prophylaxis.
- **D.** Obtain baseline laboratory studies and observe the patient for increasing symptoms.
- **E.** Test compartment pressure and prepare for fasciotomy.

Answer: D. The symptoms are typical for a pit viper snakebite. The most consistent symptom associated with pit viper bites is immediate burning pain in the area of the bite, whereas pain may be minimal with bites of Elapidae and other exotic snakes. Tetanus prophylaxis may be indicated, but antibiotics are not. Fasciotomy is rarely if ever indicated for snakebite. A constricting band may be useful for first aid in the field with certain neurotoxic snakes, but not in the emergency department (ED). Immobilization may be helpful, but ice and antibiotics are not.

55.3. A 43-year-old woman sustained a snakebite while in her garden. She was not able to secure the snake, but she remembered it to be colorful. She presents with ptosis, slurred speech, and nausea. What is true about the type of snake most likely involved in this case?
- **A.** Death usually occurs from coagulopathies.
- **B.** Eastern species are the most deadly.
- **C.** The snake has a heat-sensitive organ between eyes and nostrils on both sides of the head.
- **D.** The snake has a triangle-shaped head.
- **E.** The snake has elliptical pupils.

Answer: B. This woman sustained a bite from a coral snake. All of the above except B are related to pit vipers. The coral snake can be differentiated from the king snake by two characteristics: the nose of the coral snake is black, and the red and yellow bands are adjacent on the coral snake. Eastern coral snake is considered deadly as opposed to its western relative. There are no records of fatalities caused by the western species. Ptosis is common and often the first outward sign of envenomation. Other signs and symptoms include vertigo, paresthesias, fasciculations, slurred speech, drowsiness, dysphagia, increased salivation, nausea, and proximal muscle weakness.

55.4. Which of the following is true about antivenom?
- **A.** Antivenom may reverse all the symptoms of envenomation.
- **B.** Antivenom should be administered around the wound.
- **C.** Even mild envenomations require antivenom.
- **D.** Exotic snakebites require only antivenom if neurologic symptoms are present.
- **E.** Pregnancy is a contraindication to receive antivenom.

Answer: A. Pregnancy is not a contraindication to antivenom therapy. Any victim of a venomous snakebite with moderate or severe envenomation is a candidate for antivenom. Antivenom may reverse the local signs, systemic symptoms, and laboratory abnormalities associated with envenomation. As with coral snakes, many patients do not show any early signs after envenomation by exotic snakes. The antivenom should be administered before neurologic changes develop. All antivenom should be administered intravenously.

55.5. A 28-year-old man presents with a copperhead snakebite that occurred 1 hour ago. He complains of pain and moderate swelling of his right hand and wrist. He has no systemic symptoms and has a pulse of 92. His initial coagulation studies are normal. What should be done?
- **A.** Admit for observation and antivenom
- **B.** Discharge with elevation, ice, and pain medications
- **C.** Give antivenom if swelling spreads to forearm
- **D.** Immediate antivenom 4 vials intravenously
- **E.** Observe 12 hours for signs of increasing envenomation

Answer: E. Most copperhead bites do not require antivenom. Some toxicologists will administer antivenom if swelling is severe and may cause long-term disability. Copperhead bites generally cause a moderate amount of swelling that may peak 24 to 36 hours after the bite. All venomous snakebites should be observed for at least 12 hours if signs of envenomation are present. If systemic signs develop or the patient develops a coagulopathy, antivenom may be indicated.

55.6. Which of the following patients is most likely to be the first discharged home safely?
- **A.** A pregnant woman with black widow envenomation
- **B.** A 5-year-old child with a scorpion sting 1 hour before arrival
- **C.** A 55-year-old man with hypertension and coronary artery disease with black widow envenomation
- **D.** An 8-year-old with a coral snake bite
- **E.** An 18-year-old with an unknown snake bite 8 hours before arrival

Answer: E. A scorpion sting in a child should be observed for at least 6 hours. Symptomatic children with stings should be admitted. Most venomous snakes will show signs of envenomation with 6 hours. If this patient is asymptomatic, it is likely that the snake was nonvenomous or this was a "dry bite." All children with envenomation and coral snake bites should be admitted for observation. Pregnant patients and those with coexisting medical problems should be admitted after black widow envenomations.

55.7. While walking in shallow water, a patient accidentally steps on a stonefish. Which of the following is not indicated?
- **A.** Irrigating the wound with vinegar
- **B.** Obtaining radiographs for retained foreign body
- **C.** Observing for cardiovascular and respiratory symptoms

D. Removing the spine with forceps
E. Using hot water to relieve the pain

Answer: A. Stonefish, a type of bony fish, may cause serious cardiac and respiratory symptoms, which can be prevented by early administration of the appropriate antivenom. The fish spines of bony fish should be removed with forceps because they are thick and less likely to break off at the skin (like a bee stinger). In all cases, the wound should be copiously irrigated. Vinegar has been shown to be useful for some types of nematocyst injuries from jellyfish. Significant analgesia is achieved by submersion of the wound in hot water for 30 to 90 minutes or until improvement.

55.8. A patient presents with a necrotic lesion on her midthigh that started as a bleb while she was working in her garden 3 days ago. The wound has grown gravitationally. Her blood pressure is 110/80 mm Hg, respiratory rate 16 rpm, heart rate 110 bpm, and temperature 38.3°C. You suspect an envenomation of which of the following?
A. *Centruroides exilicauda*
B. *Hapalochlaena maculosa*
C. *Haplopelma lividum*
D. *Latrodectus mactans*
E. *Loxosceles reclusa*

Answer: E. The cobalt blue tarantula, *Haplopelma lividum,* is an aggressive spider with toxic venom. The black widow spider is *Latrodectus mactans*. *Centruroides exilicauda,* which is found in Arizona, is a particularly dangerous kind of scorpion. The blue-ringed octopus is *Hapalochlaena maculosa.* The brown recluse spider, *Loxosceles reclusa,* causes an initial white area of vasoconstriction at the site of the bite within 3 or 4 hours. A bleb then forms in the center of this area, and an erythematous ring arises on the periphery. The lesion at this stage resembles a bull's-eye. The bleb darkens, necroses during the next several hours to days, and continues to spread slowly and gravitationally.

CHAPTER 56

Thermal Burns

Adam J. Singer | Christopher C. Lee

PRINCIPLES

Background

Thermal burns are common injuries seen and managed in the emergency department (ED). In most cases, burns are relatively small in size and superficial in depth and can be managed entirely by the emergency clinician without the need for emergent consultation or admission. Accurate assessment of burn size and depth followed by meticulous local wound care is all that is needed in most cases. On the other hand, early management of the airway, breathing, and circulation are essential in the treatment of major burns. Emergency escharotomy may also be required sometimes, especially with circumferential burns of the extremities, thorax, and neck.

The ability of the skin to regenerate is largely dependent on the depth of injury because regeneration occurs mostly from underlying dermal skin appendages, such as the hair follicles and sebaceous glands. Cooling of the burns as well as prevention of wound desiccation and infection will help prevent conversion of the burns from partial (second degree) to full thickness (third degree). Unlike mechanical injuries, in which the maximal extent of damage occurs immediately after injury, thermal burns are dynamic and tend to progress over time. As a result, it may be difficult to accurately assess burn depth and be able to predict the potential for spontaneous healing without the need for burn eschar excision and skin grafting during the initial ED assessment. Although burn depth may be obvious in very superficial and very deep burns respectfully, in many cases close follow-up and frequent reassessments may be required to determine the appropriate therapeutic plan. Consultation with a burn specialist is recommended with obviously deep burns and when burn depth is indeterminate.

Epidemiology

Although the number of burns in the United States has appeared to be decreasing, a recent study from England suggests that this trend may be reversing with an increase in total number of burns.[1,2] The overall survival rate from burns in the United States is over 96% with 3400 deaths per year. Between the years 2003 to 2012 the case fatality rate from burns decreased 25% to 35%.[3] Most burns occur in men in the working years of life. Although scalds are the most common etiology of burns in children younger than 5 years old, burns due to exposure to fire or flame predominate in all other age groups.[3] Most burns are relatively small in size with only 2% covering 40% total body surface area (TBSA) or more. Currently, the burn size associated with a 50% case fatality (LA-50) is between 60% and 70% TBSA.[4] The hospital length of stay can be estimated and is roughly 1 day per percent TBSA burned.[3]

Anatomy and Physiology

The skin is the largest organ of the body and is composed of three main layers: the epidermis, the dermis, and the subcutaneous layers. The epidermis provides a waterproofing and bacteria-proofing layer, whereas the dermis (along with the subcutaneous layer) gives the skin its toughness and durability. The dermis and subcutaneous layers are also important sources of stem cells that help regenerate the epidermis after thermal injury.

The main function of the skin is to serve as a barrier between the internal and external environments minimizing fluid losses and microbial invasion. Other important functions of the skin include thermoregulation, sensory detection, and immune surveillance. When large portions of the skin are lost or damaged, there is a risk of hypovolemic shock and sepsis, and complete loss of the skin is incompatible with life.

Pathophysiology of Burns

Burns are the result of exposure of the skin, to energy in the form of heat. The degree of injury is dependent on the temperature and duration of exposure as well as the structure of the skin. The skin in the very young and elderly is relatively thin; therefore, they are more prone to the development of deep burns. Temperatures below 44°C are generally well tolerated and do not cause cell death or injury even after prolonged periods of exposure. When the temperature rises, there is damage to the cells ultimately leading to cell death. Exposure of cells to supra-physiological temperatures results in progressive denaturation or unfolding of protein molecules with most proteins denatured at 60°C.[5] The lipid bilayer and membrane-bound adenosine triphosphates are especially vulnerable to thermal denaturation leading to disruption of the cellular membrane and subsequent cellular necrosis.[6] In addition to classical cellular necrosis, cell death may also occur as a result of apoptosis and necroptosis. Cellular necrosis (also known as *oncosis*) is a result of depletion of the cell's energy stores and loss of integrity of the cellular membrane with subsequent cellular swelling leading to bursting of the cell with significant associated inflammation. In contrast, *apoptosis* is a highly programmed active process characterized by shrinking of the cell and its organelles, DNA fragmentation, and budding without cellular swelling ultimately leading to cell death with minimal inflammation. Apoptosis is the result of activation of caspase proteases that ultimately are the executors of cell death. A third mechanism of cell death that has recently been reported is *necroptosis* in which the cells also swell and burst.[7,8] However, unlike classical necrosis, necroptosis is an active programmed process that requires the formation of an intracellular complex, which includes receptor-interacting protein 3 (RIP-3). *Autophagy* (a pathway that conserves energy by recycling intracellular macromolecular waste) may also play a role in burn injury progression.[9] The importance of these findings is that it paves the way for the development of potential therapies aimed at preventing necroptosis or apoptosis.

The pathophysiology of burns in many ways resembles that of myocardial infarction, stroke, and traumatic brain injury. In all of these cases, a large number of cells are irreversibly damaged by exposure to the most extreme injury conditions, whereas the cells in the surrounding area are exposed to lesser insults putting them at risk of death due to stasis or a reduction in blood flow. The

classical three zones of burn injury originally described by Jackson include the central zone of irreversible necrosis, the intermediate and potentially reversible zone of stasis, and the outermost reversible zone of inflammation.[10] Thermal injury sets into motion a cascade of events, which includes inflammation, compromised perfusion, oxidative stress, and recurring cycles of ischemia reperfusion.[11] These processes result in the release of a large number of toxic cytokines and mediators, as well as free oxygen and nitrogen radicals leading to additional injury. For example, free radicals damage vital proteins, lipids, and DNA leading to lipid peroxidation and disruption of the cellular membrane. Occlusion of the dermal microcirculation by red and white blood cells followed by the formation of microthrombi further reduces perfusion to the injured skin. Additionally increases in capillary permeability lead to edema formation, which further compromises local blood flow.

Burn injuries are also characterized by a catabolic state with up to a threefold increase in the metabolic rate often necessitating enteral or parenteral nutrition. In addition to adrenergic stress, burn hypermetabolism may be due in part to uncoupling of oxidative phosphorylation in the mitochondria.[12] Nonspecific down regulation of the immune system also occurs due to defects in both cell mediated and humoral pathways possibly as a result of the release of mediators, such as interleukin-12 (IL-12) and IL-17.[13]

Smoke inhalation-associated lung injury occurs in approximately 2% of burn victims with <20% TBSA burns and in 14% of burns with 80% to 99% TBSA and contributes greatly to mortality.[14] Although more common with large burns, inhalation injury can exist with or without cutaneous burns; however, its presence is associated with a more than threefold increase in mortality.[14] Anatomically, injuries from smoke inhalation may involve direct heat injury to the upper airway, chemical injury to the lower airway, and systemic toxicity such as with inhalation of carbon monoxide or cyanide. Unless exposed to steam, the heat dissipating properties of the upper airway generally restrict direct thermal injury to the supraglottic structures. Lower airway and intrathoracic injury is generally the result of exposure to various chemicals contained in the smoke.

A large variety of toxic substances may be released with burning materials, such as rubber and plastic including sulfur dioxide, cyanide, nitrogen dioxide, ammonia, and chlorine, as well as toxic aldehydes. These substance damage epithelial and endothelial cells of the airways and their blood vessels leading to the formation of pseudomembranes or airway casts consisting of cellular debris, fibrin, and mucin that obstruct the airways and cause significant mismatches in ventilation and perfusion (V/Q). Increases in inflammatory mediators and reactive oxygen and nitrogen species lead to further impairments in blood flow worsening V/Q mismatch. Air trapping from the formation of ball valve obstructions of the airway may also lead to regional barotrauma further injuring the lungs. Mucociliary transport is also impaired leading to a reduction in bacterial clearance and risk of infection. Loss of surfactant can lead to alveolar collapse and atelectasis resulting in further impairment in ventilation and oxygenation. The toxic effects of carbon monoxide and cyanide are discussed in Chapter 153.

CLINICAL FEATURES

Classification and Diagnosis of Burns

The prognosis and management of thermal burns are dependent on the depth and surface area of the burn, emphasizing the need for accurate estimates of burn depth and size. Unfortunately, both estimations can be difficult and inaccurate. Although clinical examination is most commonly used to determine burn depth (even when performed by a burn specialist), its accuracy is only 50% to 75%.[15] A large number of modalities have been evaluated to improve the accuracy of clinical estimation of which only laser Doppler imaging of dermal perfusion is used.[16] However, its use has been limited mostly to burn centers and research facilities. The dynamic nature of burn injuries and their tendency to progress over time reemphasizes the need for close monitoring and follow-up.

The depth of burns has traditionally been classified as first, second, or third degree based on the degree of involvement of the dermis (none, partial, and complete, respectively). Although first-degree burns almost always heal within 1 week without any scarring or sequelae, third degree burns generally require more than 3 weeks to heal and result in significant scarring (although this dogma has recently been challenged).[17] As a result, most third degree burns (unless very small, usually less than 1 cm^2) will require surgical excision and skin grafting. Because the dermis is relatively thick (up to 1 to 3 mm) and the ability of second degree burns to heal spontaneously without much scarring is dependent on how many dermal appendages survive, second degree burns have been further classified as *superficial partial* (limited to the upper or papillary dermis) and *deep partial thickness* burns (including the deeper reticular dermis). In contrast, third degree burns that involve the entire thickness of the dermis are called *full thickness.* Clinical findings that help with estimating the burn depth include color, presence of blisters, skin pliability, capillary refill, and sensitivity to touch or needle prick (Table 56.1). Typical examples of the appearance of different burn depths are presented in Figures 56.1 to 56.3.

The percentage TBSA burned predicts mortality and helps determine the amount of fluid resuscitation required. The Baux score is the sum of the patient's age and the percentage of TBSA burned.[18] In the original article, the Baux score that predicted 100% mortality was 100. A more recent study found that a Baux score of 160 predicted 100% mortality, and a Baux score of 109.6 predicted 50% mortality (95% confidence interval), which is a

TABLE 56.1

Clinical Estimation of Burn Depth

DEPTH	APPEARANCE	BLANCHES WITH PRESSURE	SENSITIVITY TO PINPRICK	PLIABILITY	TIME TO HEALING	NEED FOR EXCISION AND GRAFTING
Superficial (first degree)	Red, no blisters	+	++	Soft	1 week	–
Superficial partial thickness (second degree)	Red, blisters	+	++	Soft	1 to 2 weeks	–
Deep partial thickness (second degree	Red or white, no blisters	±	+	Slightly tense	2 to 3 weeks	+
Full thickness (third degree)	Leather like, charred	–	–	Stiff, leather like	>3 weeks	+

Fig. 56.1. Superficial partial thickness burn, which is pink and glistening. Some of the blisters have sloughed off.

Fig. 56.2. Deep partial thickness burn. The white appearing area over the dorsum of the hand is a deep partial thickness burn.

Fig. 56.3. Full thickness burn over both feet. The central area is depressed and has a yellowish color indicating it is a full thickness burn.

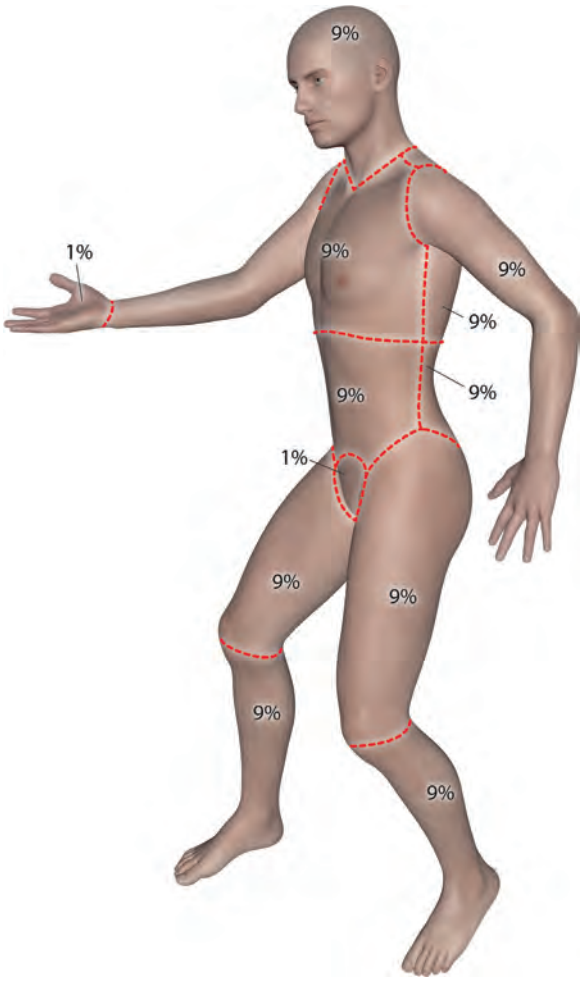


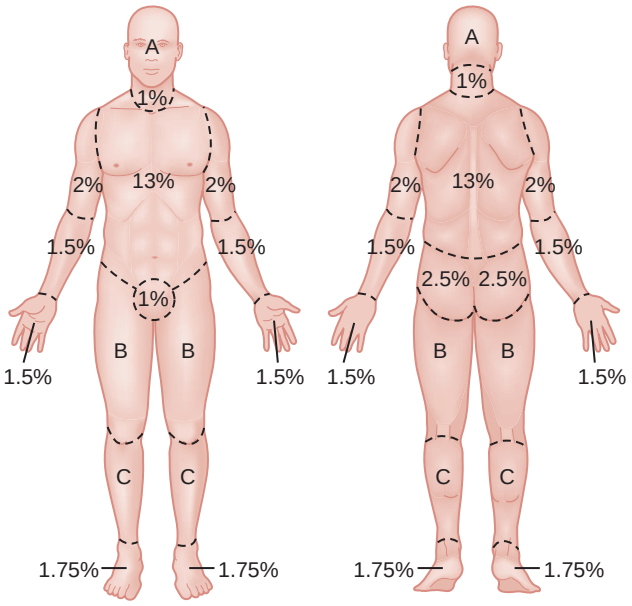
Fig. 56.4. The "rule of nines" for estimating burn area in adults.

testament to improved therapy and outcomes.[19] Estimation of percentage of TBSA burned is often inaccurate. A retrospective study of burns transferred to the Danish National burn center found that 30% of the referrals were unnecessary due to overestimation of burn size.[20] Air transports to another burn center based on burn size estimation were significantly reduced when the patients were evaluated by a burn specialist via telemedicine again, suggesting that emergency clinicians tend to overestimate burn size.[21] Other than over-triage, over estimation of burn size may lead to excessive intravenous fluid administration that can result in compartment syndromes and acute respiratory distress syndrome (ARDS).[22]

For large burns, Wallace's "rule of nines" is often used to estimate burn size. The "rule of nines" method divides the body into areas that approximate 9% of the TBSA—the head and neck, each upper extremity, the anterior or posterior surfaces of each of the lower extremities, and half of the anterior or posterior surfaces of the trunk (Figure 56.4). With children, the Lund-Browder chart should be used that adjusts for age related differences in the distribution of body parts and sizes (Figure 56.5).[23] For small burns, the surface of the *patient's* palm (including the palmer surface of the fingers) can be used to estimate 1% of the TBSA.[24] A number of methods have been developed to increase the accuracy of burn size estimation. Mobile applications and computer software help improve burn size estimation.[25,26] Burn severity has also been classified as mild, moderate, and severe based on a combination of age, depth, and size (Table 56.2).

DIFFERENTIAL DIAGNOSES

The diagnosis and etiology of burns is generally straightforward. A number of other diseases may sometimes masquerade as burns, such as epidermal necrolysis and pemphigus.[27-30] Epidermal necrolysis is a spectrum of life-threatening mucocutaneous eruptions, including Steven-Johnson syndrome and toxic epidermal necrolysis characterized by diffuse erythema and sloughing of large areas of the skin, usually caused by a medication or infection.



Relative percentages of areas affected by growth

Age	Half of head (A)	Half of one thigh (B)	Half of one leg (C)
Infant	9.5	2.75	2.5
1 yr	8.5	3.25	2.5
5 yr	6.5	4	2.75
10 yr	5.5	4.25	3
15 yr	4.5	4.25	3.25
Adult	3.5	4.75	3.5

Fig. 56.5. Lund-Browder chart.

TABLE 56.2

Classification of Burn Severity

	MILD	MODERATE	SEVERE
Children	<5% TBSA	5% to 10% TBSA	>10% TBSA
Adult	<10% TBSA	10% to 20% TBSA	>20% TBSA
Elderly	<5% TBSA	5% to 10% TBSA	>10% TBSA
All	<2% full thickness	2% to 5% full thickness, high voltage, inhalation, circumferential, comorbid disease	>5% full thickness, high voltage, significant burn to face, eyes, ears, genitalia, or joints, significant associated trauma
Disposition	Outpatient	Admission	Burn unit

TBSA, Total body surface area.

The consequences and management of epidermal necrolysis are very similar to those of large burns. Pemphigus includes a spectrum of autoimmune bullous diseases characterized by the formation of multiple blisters in the skin and mucous membranes. The blisters generally appear in the mucous membranes first followed by the skin. When left untreated, they may become generalized. Inciting factors, such as medications, infections, and stress, may be identified. Child or elderly abuse must always be considered, especially when the history and pattern of burns are inconsistent with the physical findings.

DIAGNOSTIC TESTING

Routine laboratory testing is generally of little value in evaluating and managing patients with burns in the ED. Patients with suspected inhalation injury should have a chest radiograph and blood gas determination, including carbon monoxide levels. In patients with little or minimal symptoms or signs of inhalation injury pulse oximetry and noninvasive determinations of carbon monoxide may be used. Patients with large burns requiring an admission should have baseline laboratory testing, including a complete blood count, basic metabolic panel, blood type and cross, and coagulation studies, which may all become impaired in patients with large burns.

MANAGEMENT

Initial First Aid

Patients should be removed from the source of injury and any garments and jewelry removed from the affected areas. Burns should be cooled with room temperature water.[31] Direct exposure to ice or iced water should be avoided because it may result in frostbite. In patients with large burns careful monitoring of core body temperature is recommended to avoid hypothermia.[32] Although the subject of debate, in general blisters should be left intact.[33] In the ED most blisters should be left intact; however, very large or tense blisters, as well as those located over joints, should probably be ruptured to ease local wound care. The burns should be covered with a clean dressing to minimize further trauma and reduce pain associated with air currents.

During transport to the ED patients with large burns (greater than 20% in adults and greater than 10% in children) should have two large bore intravenous catheters placed and fluid resuscitation should be initiated (see later for more details on fluid resuscitation). Patients should be placed on supplemental oxygen to maintain oxygen saturation greater than 92%. Pain management using intravenous doses of an opioid is also recommended as per local emergency medical service (EMS) protocols in hemodynamically stable patients (see later for more details on pain management).

Airway Management

One of the most critical decisions in managing burn victims is the need for and optimal timing of endotracheal intubation because injury to the upper airway may result in massive swelling of the tongue, epiglottis, and aryepiglottic folds. In some cases (such as, in the presence of significant oropharyngeal swelling, stridor, and respiratory distress), the decision to intubate is obvious and straightforward. In other cases, airway swelling may develop more gradually over several hours as fluid resuscitation proceeds. Clinical signs such as facial burns, hoarseness, drooling, carbonaceous sputum, and singed nasal hairs certainly should raise the probability of inhalation injury. However, they are often unreliable and poor predictors of injury. A recent prospective study of 100 burn patients with suspected inhalation injury that were evaluated by fiberoptic bronchoscopy found that 21% had no evidence of upper airway involvement and 39% had no lower airway pathology. In contrast, 38% of patients with documented inhalation injury did not have singed nasal hair.[34] Traditionally emergency clinicians have been encouraged to secure the airway as early as possible, even prophylactically, prior to the onset of airway obstruction. When in doubt, early intubation is encouraged; however, the presence of neck or facial burns alone should not be an indication for intubation. Recently there have been concerns that overly aggressive airway management may be detrimental to patients.[35-37] Inappropriate intubation and mechanical ventilation may lead to the ARDS possibly due to the release of inflammatory

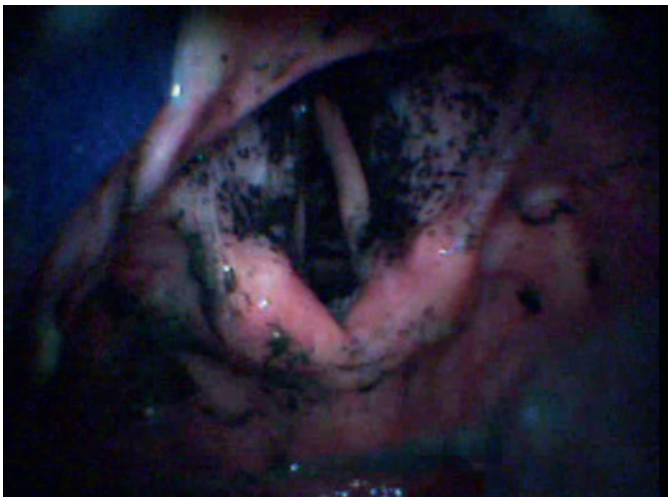


Fig. 56.6. Fiberoptic view of inhalation injury. (Courtesy Dr. Marvin Wayne.)

mediators. Ventilator-associated pneumonia is also seen in up to 30% of ventilated burn patients. A study of 1029 intubated burn patients found that 17% underwent extubation within hours and another 49% within 1 day of admission without the need for reintubation, suggesting that tracheal intubation was unnecessary.[35] Another study found that inhalation injury could not be confirmed in more than half of the burned patients that were intubated.[37] The best way to confirm inhalation injury and the need for endotracheal intubation is by directly visualizing the upper airways with fiberoptic, video, or direct laryngoscopy using topical anesthesia supplanted with mild to moderate sedation when necessary. The presence of significant edema or soot in the supraglottic region necessitates immediate intubation (Figure 56.6). When necessary, small doses (10 to 20 mg) of intravenous ketamine can be used to sedate the patient without compromising their ability to control the airway. An intravenous dose of glycopyrrolate (0.1 to 0.2 mg) may also be considered prior to laryngoscopy to reduce secretions. Laryngoscopy may also be repeated if the clinical condition changes. Rapid sequence induction should be avoided unless direct visualization confirms that tracheal intubation will be relatively easy. Rarely, a surgical airway is required when it is not possible to endotracheally intubate the patient. Awake intubation with generous amounts of topical anesthetics with or without supplemental sedation should be used when a difficult airway is suspected.

Breathing Management: Recognition and Management of Inhalation Injury

A history of exposure to smoke in a closed space should always raise the suspicion for smoke inhalation. Physical findings may include facial burns, singed nasal hair, hoarseness, drooling, stridor, and carbonaceous sputum. However, clinical signs may be unreliable. Although the chest radiograph and CT scans of the thorax may be helpful in some cases, direct visualization of the upper airways remains the best method for confirming the presence of inhalation injury.

All patients with suspected inhalation injury should receive supplemental humidified oxygen to maintain oxygen saturation above 92%. Inhaled beta-agonists should be administered to reduce bronchoconstriction associated with inhalation injury.[38] Carbon monoxide levels should be measured using CO-oximetry or noninvasive bedside devices. Cyanide toxicity should be suspected in patients injured in a closed space, especially with combustion of plastics and in the presence of lactic acidosis.

BOX 56.1

Indications for Endotracheal Intubation and Mechanical Ventilation

Upper airway obstruction
Inability to handle secretions
Hypoxemia despite 100% O_2
Patient obtundation
Muscle fatigue suggested by a high or low respiratory rate
Hypoventilation (P_{CO_2} >50 mm Hg and a pH <7.2)

O_2, Oxygen; *P_{CO_2}*, partial pressure of carbon dioxide.

TABLE 56.3

Recommended Initial Ventilator Settings

Tidal volume	6–8 mL/kg
Respiratory rate	8–12 in adults 12–45 in children
Plateau pressures	<35 cm H_2O
I/E ratio	1:1 to 1:3
Flow rates	40–100 L/min
PEEP	8 cm H_2O

I/E, Inspiratory-expiratory; *PEEP*, positive end-expiratory pressure.

Endotracheal intubation and mechanical ventilation are indicated with persistent hypoxemia despite supplemental oxygen. Other indications for intubation and mechanical ventilation are included in Box 56.1. The best method of ventilation in patients with inhalation injury is subject to debate.[39] A large randomized trial of patients requiring mechanical ventilation demonstrated lower mortality with lower tidal volumes (6 mL/kg of predicted weight).[40] Maintaining airway plateau pressures below 35 mm Hg is also desirable to avoid further injury from overinflation of the poorly aerated lungs. This may lead to hypercapnia (permissive hypercapnia), which should be tolerated as long as the PCO_2 remains below 60 mm Hg and the pH remains above 7.2 and there is no hemodynamic instability. Addition of positive end-expiratory pressure (PEEP) may increase residual capacity and improve oxygenation. Suggested initial ventilator settings are presented in Table 56.3. Some studies suggest that high frequency percussive ventilation (HFPV) may improve oxygenation in patients with inhalation injury when traditional methods (such as, assist control) are ineffective.[41] Prone positioning of the patient may also be considered in hypoxic patients.[42] Noninvasive ventilation may be considered in awake, cooperative, spontaneously breathing, hemodynamically stable patients who can maintain their airway.[43]

Patients with smoke inhalation are at risk of developing pneumonia. Simple strategies such as elevating the head of the bed, frequent position changes, and good oral care should be used. However, prophylactic antibiotics do not reduce the risk of ventilator-associated pneumonia.

A number of strategies have been used to help reduce the copious secretions that tend to obstruct the airways. Bronchoscopic lavage may be used to remove airway debris and secretions that impede ventilation and enhance the inflammatory response. Because intra-airway coagulation and fibrin deposition play a significant role in the pathology of inhalation injury, anticoagulants have also been evaluated. A recent systematic review of preclinical

and clinical studies concluded that inhaled anticoagulant regimens improved survival and decreased mortality without altering systemic markers of clotting and anticoagulation.[44] An aerosolized combination of an oxygen free radical scavenger and mucolytic, N-acetylcysteine (the antidote for acetaminophen toxicity), with heparin has been shown to improve outcomes in some but not all studies.[45,46] Its use, as well as bronchial lavage, should probably be limited to the burn unit.

Circulation Management and Fluid Resuscitation

Burn injuries result in significant fluids losses and fluid shifts due to loss of the epidermal barrier and an increase in capillary permeability respectively. Leakage of plasma proteins into the interstitial space during the early phases of a burn increases its oncotic pressure, further contributing to fluid shifts and tissue edema.[11] As a result, a major focus of burn care is fluid resuscitation to restore tissue perfusion and prevent hypovolemic shock. Intravenous fluid resuscitation through large bore intravenous cannulas should be instituted for most burns greater than 20% in adults and greater than 10% in children.[47] A number of formulas have been proposed for estimating the fluid requirements of burn patients (Table 56.4). Although these formulas are used as a general starting point, frequent readjustments based on patient response (vital signs, mental status, and hourly urine output) are required to avoid both over and under resuscitation. Of all parameters, urine output is most accurate in assessing the clinical response to fluid resuscitation with limited evidence of increased benefit with utilization of more invasive hemodynamic monitoring.[48] Overly aggressive fluid resuscitation has been coined "fluid creep" and can have devastating results, including worsening local tissue edema with burn conversion, extremity compartment syndrome, abdominal compartment syndrome, and pulmonary edema.[49] The Parkland formula is the most common method used to calculate fluid requirements over the first 24 hours after injury and is based entirely on lactated Ringer solution (see Table 56.4). Half of the fluids are given within the first 8 hours *from injury,* whereas the other half is giver over the next 16 hours. This formula was based on a small number of animal and human studies. However, a recent study found that patients managed with the Parkland formula received on average 6.3 mL/kg per percentage of TBSA over the first 24 hours instead of the recommended 4 mL/kg per percentage of TBSA, increasing the risk of over resuscitation.[50] The Modified Brooke formula, which calls for 2 mL/kg per percentage of TBSA, may be a better starting point. The United States Armed Forces Institute of Surgical Research has recently proposed a simplified formula, the "rule of tens" in which patients are administered 10 mL lactated Ringer solution for every percentage of TBSA burned per hour, with hourly adjustments based on clinical response and urine output with a target of 0.5 mL/kg per hour in adults and 0.5 to 1.0 mL/kg per hour in children.[51] With patients weighing more than 80 kg, an additional 100 mL/hour should be given for each additional 10 kg. The "rule of tens" may lead to overestimation of fluid requirements in patients weighing less than 40 kg and an underestimation in those weighing more than 140 kg. Another method that has been shown to improve the accuracy of estimated fluid requirements is the Burn Resuscitation Index (BRI) that uses tables to assign a score that is based on weight and estimated burn size.[52] Colloids have not been shown to be of benefit in burn patients, especially during the first 12 hours, when capillary leakage is greatest.[53] Recent guidelines issued by the American Burn Association recommend either the Parkland or Modified Brooke formulas with addition of a colloid (such as, albumin) after the first 12 to 24 hours, especially in difficult to manage patients.[47] The use of hypertonic solutions has been studied with contradictory results; its use should be limited to centers with considerable experience in use of hypertonic saline.[47]

Escharotomy

With deep burns a leather-like necrotic eschar, which is stiff and inelastic, covers the wound. When the eschar surrounds an extremity or the neck, it may compress the underlying tissues

TABLE 56.4

Burn Resuscitation Formulas

FORMULA	FIRST 24 HOURS	NEXT 24 HOURS
Parkland	Lactated Ringer solution 4 mL/kg per percentage of burn; ½ within first 8 hours	Colloids (5% albumin) in amount of 20% to 60% of plasma volume; glucose in water added to maintain urine output 0.5 to 1.0 mL/kg per hour in adults and 1 mL/kg/hr in children
Modified Parkland	Lactated Ringer solution (mL) = 4 × kg × percentage of burn in adults	Colloid infusion of 5% albumin at the amount 0.3 to 1.0 mL/kg per percentage of burn every 16 hours
Evans	Crystalloids in the amount of 1 mL/kg per percentage of burn, plus colloids at 1 mL/kg per percentage of burn, plus 2000 mL glucose in water	Crystalloids at 0.5 mL/kg per percentage of burn, colloids at 0.5 mL/kg per percentage of burn, and the same amount of glucose in water as the first 24 hours
Brooke	Lactated Ringer solution 1.5 mL/kg per percentage of burn, plus colloids at 0.5 mL/kg per percentage of burn, plus 2000 mL glucose in water	Lactated Ringer solution 0.5 mL/kg per percentage of burn, colloids at 0.25 mL/kg per percentage of burn, and the same amount of glucose in water as the first 24 hours
Modified Brooke	Lactated Ringer solution 2 mL/kg per percentage of burn in adults and 3 mL/kg per percentage of burn in children	Colloids 0.3 to 0.5 mL/kg per percentage of burn, glucose in water to maintain urine output
Monafo	Solution containing 250 mEq Na, 150 mEq lactate, 100 mEq Cl; amount adjusted to urine output	Solution titrated with ⅓ NS according to urine output
Galveston	Lactated Ringer solution at 5000 mL/m^2 TBSA burned plus 2000 mL/m^2 TBSA, ½ within 8 hours	3750 mL/m^2 TBSA burned plus 1500 mL/m^2 TBSA
Rule of ten	Lactated Ringer solution at 10 mL per percentage of burn per hour for every 10 kg above 80 kg, 100 mL is added to this hourly rate	Not applicable

Cl, Chloride; *Na,* sodium; *NS,* normal saline; *TBSA,* total body surface area.

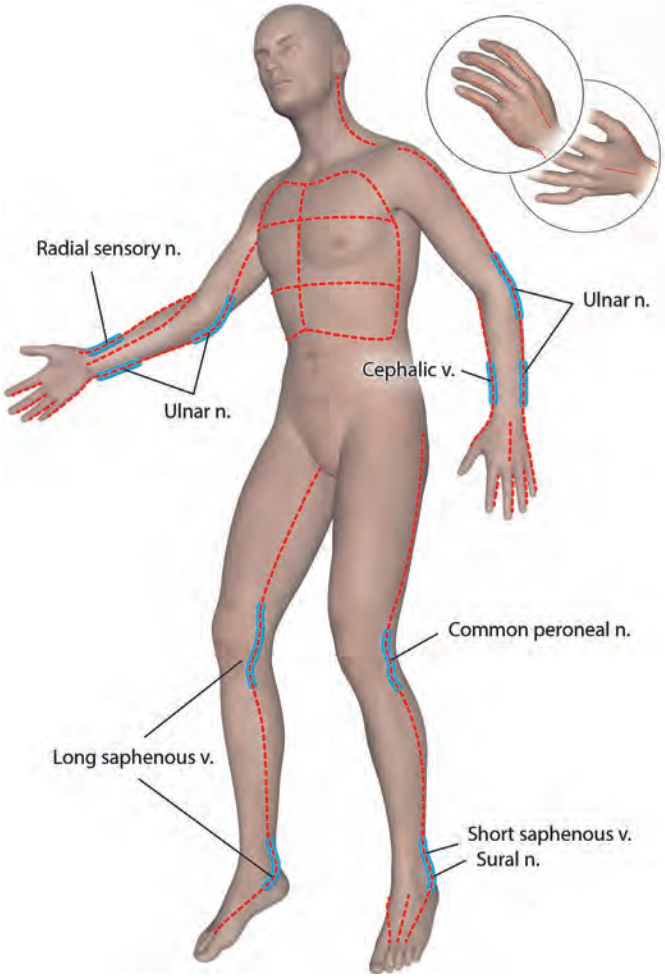


Fig. 56.7. Location of escharotomy incisions.

(vessels, nerves, muscle) leading to a compartment syndrome.[54] Similarly, an eschar involving the thorax may impede ventilation. When this occurs, emergent release of the tissue pressure by making an incision through the eschar (escharotomy) is required to prevent tissue necrosis and hypoventilation respectively. Because the eschar is composed of necrotic tissue, escharotomy is generally associated with little pain or blood loss. The amount of blood loss can be further minimized by using electric cautery. To be effective, the incisions should be down to the subcutaneous level, allowing the stiff eschar shell to split open. The incisions should also be slightly extended into normal tissue both proximally and distally. Along the extremities, the incisions are made over the medial and lateral aspects to avoid damage to underlying vital structures. With hand burns the incisions may need to be extended into the fingers. The proper placement of escharotomy incisions over the chest are displayed in Figure 56.7. The absence of distal pulses as well as distal Doppler and pulse oximetry signals indicate that an escharotomy is required. However, their presence should not be used to exclude the need for emergent escharotomy. Increased pain (especially with passive motion), pallor, weakness, and sensory loss all may be signs of impending compartment syndrome.

Local Wound Therapies

With most burn victims, care focuses on local wound therapies aimed at protecting the burn from further injury and infection and maintaining a moist wound environment that is most conducive to healing. First-degree burns do not require any local treatment. However, topical application of a nonsteroidal anti-inflammatory agent or aloe vera may reduce pain. In addition, systemic administration of an analgesic, such as acetaminophen or a nonsteroidal anti-inflammatory drugs (NSAIDs), should be considered.

After cleaning the burn with soap and water, large or tense blisters should either be aspirated with a needle or de-roofed and any nonadherent necrotic tissue should be gently removed.[33] If the burn is very deep or involves a large area, the patient will require admission, preferably to a burn unit. In this case, local wound therapy should generally be performed in the burn unit. If the patient is to be transferred, the burns should be covered with a clean, nonadherent dressing. Small (<1% TBSA) full-thickness burns that are being referred to a burn specialist within 48 hours can be covered with an antimicrobial agent (such as, a triple antibiotic) and an outer absorptive dressing.

Management of partial thickness burns is subject to considerable debate as evidenced by the large number of natural and synthetic agents and dressings available (Table 56.5). The two methods of local treatment include a topical antibiotic ointment or cream together with a nonadherent yet absorptive dressings or one of many occlusive wound dressings (see Table 56.5). Ointments are preferred over creams because they are better tolerated, maintain a moist wound environment, and do not adhere to overlying dressings. With facial burns or over areas that are difficult to dress, application of a topical antibacterial ointment is recommended. Silver sulfadiazine cream has a wide antibacterial and antifungal spectrum and should be considered in heavily contaminated or infected burns. A systematic review of 30 randomized controlled trials found that silver sulfadiazine was consistently associated with poorer healing outcomes than biosynthetic (skin substitute) dressings, silver-containing dressings, and silicon-coated dressings.[53] Therefore, silver sulfadiazine is no longer recommended for most burns. A recent randomized controlled trial found that even burns treated with a petrolatum-impregnated gauze without an antibacterial agent healed slightly faster that silver sulfadiazine treated wounds.[55] Use of topical agents is also generally preferred for heavily exudating burns. When topical agents are used, they should be applied once or twice daily after washing the burn wound with mild soap and water while removing any nonadherent debris.

An alternative to topical antimicrobials, especially in burns without heavy exudation, is one of a number of commercially available occlusive dressings (see Table 56.5). Although generally more expensive than topical agents, occlusive dressings require less frequent dressing changes and are associated with less pain. Therefore, occlusive dressings may also be cost effective when compared to less expensive topical agents.[56] A large number of materials such as foams, alginates, silicones, hydrocolloids, and hydrogels (with or without antimicrobial agents, such as very low concentrations of silver) have been studied. A systematic review of burn dressings in children with partial thickness burns found that membranous dressings, such as Biobrane and amnion membrane, improved healing, shortened hospital stay, and reduced pain compared with an antibacterial impregnated gauze.[57] However, the use of these biological dressings is best limited to a burn specialist. Our recommendation is a silicone-coated foam dressing impregnated with silver (Mepilex Ag) that is absorptive, conforms to bodily contours, and is easy to remove without causing additional injury to the tissues.[58] With most of the occlusive dressings, the dressing may be left in place for approximately 1 week unless obviously saturated or malodorous. Burns on the extremities should be elevated to reduce swelling and care should be taken to avoid tight compressive dressings.

A number of novel burn therapies have been investigated in preclinical and clinical studies but are not yet recommended in emergency settings. A systematic review of preclinical studies

TABLE 56.5

Representative Topical Agents and Dressings for Burns

CATEGORY	EXAMPLES	ADVANTAGES	DISADVANTAGES
NON-OCCLUSIVE, ABSORPTIVE			
Gauze, nonadherent	Telfa (Kendall, Mansfield, MA)	Nonadherent, inexpensive	Requires daily dressing changes
OCCLUSIVE			
Foams	Mepilex (Mölnlycke Health Care AB, Göteborg, Sweden); Curafoam (Kendall, Dublin, Ireland); Allevyn foam (Smith & Nephew, London, United Kingdom)	Absorbs exudate, conforms to body site, prevents surrounding maceration	Opaque, may dehydrate wounds with minimal exudate
Hydrocolloid	DuoDERM (ConvaTec, Skillman, NJ); Tegasorb (3M, St. Paul, MN)	Absorbs exudates, protective cushioning of wound	Opaque, no antimicrobial properties
Alginate	SeaSorb (Coloplast, Humlebaek, Denmark); Algiderm (Bard, Murray Hill, NJ); Melgisorb (Mölnlycke Health Care AB, Göteborg, Sweden)	Absorptive	Frequent dressing changes
Nanocrystalline silver	Acticoat (Smith & Nephew, Largo, FL); Aquacel Ag (ConvaTec, Skillman, NJ)	Antimicrobial, creates a moist environment, less frequent dressing changes	Need to keep dressing moist
Hydrogel	Curagel (Kendall, Mansfield, MA); Flexigel (Smith & Nephew, Largo, FL); Nu-Gel (Johnson & Johnson, Arlington, TX)	Rehydrates dry wounds	Non-absorptive
Transparent films	Tegaderm (3M, St. Paul, MN); OpSite (Smith & Nephew, Largo, FL)	Transparent, inexpensive	Non-absorptive

suggested that warm water, simvastatin, erythropoietin, or cerium nitrate may represent particularly promising approaches for translation into clinical use in the near future to reduce the conversion of superficial to deep burns.[59] Another recent systematic review and meta-analysis of growth factor therapy for partial thickness burns concluded that this therapy (fibroblast growth factor, epidermal growth factor, and granulocyte macrophage-colony stimulating factor) might be an effective and safe add-on to standard wound care for partial-thickness burns.[60]

Pain Management

Due to the direct stimulation of nociceptors in the skin and the transmission of painful neural impulses via A-delta and C-fibers, most burns are very painful. However, the pain in burn victims is often undertreated.[61] Routine monitoring of pain severity and the use of pain management protocols have been shown to improve pain management.[62] Although pharmacological agents are the cornerstones of burn pain management, non-pharmacological methods (such as, cooling of the burn, covering the burn with a dressing) and cognitive-behavioral therapy (such as, relaxation and distraction) should be considered.[63] Most national guidelines for the management of burn-associated pain include acetaminophen (500 mg every 6 hours) or NSAIDs (such as ibuprofen 400 mg every 8 hours) for mild to moderate pain and opioids (such as, fentanyl at 1 to 2 mcg/kg or morphine at 0.1 mg/kg) for more severe pain.[64] The addition of an anxiolytic, such as midazolam or lorazepam, may be more effective than an opioid alone. A systematic review of four experimental trials involving 67 patients found that intravenous ketamine (0.1 to 0.2 mg/kg) showed some efficacy as an analgesic for burn injuries, with a reduction in secondary hyperalgesia when compared with opioid analgesia alone. Combination therapy with ketamine and morphine also resulted in the abolishment of the wind-up pain phenomena (the perceived increase in pain over time).[65] Furthermore, the side-effect profile seemed to be similar to opioids alone. Despite initial studies suggesting that intravenous lidocaine may be effective in treating severe burn pain, the current literature does not support its use.[66] The anticonvulsants gabapentin and pregabalin (which inhibit presynaptic *N*-methyl-d-aspartate [NMDA] receptors) may also be considered in burn patients with severe pain despite traditional therapies.[67] However, these therapies are not useful in the immediate post burn period.

BOX 56.2

Criteria for Referral to a Burn Center

Partial thickness burns greater than 10% TBSA
Burns that involve the face, hands, genitalia, perineum, or major joints
Third degree burns in any age group
Electrical burns, including lightning injury (see Chapter 134)
Chemical burns
Inhalation injury
Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality
Any patient with burns and concomitant trauma (such as, fractures) in which the burn injury poses the greatest risk of morbidity or mortality
Burned children in hospitals without qualified personnel or equipment for the care of children
Burn injury in patients who will require special social, emotional, or rehabilitative intervention

TBSA, Total body surface area.

DISPOSITION

Most superficial and small burns can be managed in the ED by an emergency clinician with close follow-up by a physician comfortable handling burns (usually a burn specialist) within the next 3 to 5 days. Patients with large or deep burns, burns involving sensitive areas, and those with significant comorbidities and trauma should be admitted. Criteria for referral to a burn center are presented in Box 56.2.[68]

KEY CONCEPTS

- After carefully removing the patient from the source of injury, burns should be cooled with room temperature water while avoiding hypothermia in patients with very large burns.
- Clinical signs such as facial burns, hoarseness, drooling, carbonaceous sputum, and singed nasal hairs certainly should raise the probability of inhalation injury; however, they are often unreliable and poor predictors of injury severity.
- The best way to confirm inhalation injury and the need for endotracheal intubation is by directly visualizing the upper airways with fiberoptic, video or direct laryngoscopy using topical anesthesia supplanted with mild to moderate sedation when necessary. The presence of significant edema or soot in the supraglottic region necessitates immediate intubation.
- Supplemental oxygen should be given in patients with suspected inhalation injury and determination of carbon monoxide levels should be performed.
- Fluid management to support vital organ perfusion and adequate urine output using crystalloids by the Parkland formula or modified Brooke formula should be administered as recommended by the American Burn Association.
- Adequate pain relief for larger burns may be accomplished using frequent intravenous titration with opioids supplemented with sub-dissociative doses of ketamine.
- While patients with large (>20% for adults and >10% for children and the elderly) or deep burns will require admission to a burn center, most patients presenting to the ED will have small and superficial burns that can be managed by over-the-counter topical antibiotic ointments (silver sulfadiazine is no longer recommended except for highly contaminated or infected wounds), or with one of many commercially available burn dressings.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 56: QUESTIONS & ANSWERS

56.1. A 30-year-old man presents with a burn to both anterior aspects of his forearms after being burned by a radiator. He has severe pain and has deep (reticular) dermis extension of the burn. You call the consultant and describe the burn as which of the following?
- **A.** First-degree burn of 4.5% body surface area
- **B.** Second-degree superficial burn of 9% body surface area
- **C.** Second-degree deep burn of 4.5% body surface area
- **D.** Third-degree burn of 2.5% body surface area
- **E.** Fourth-degree burn of 9% body surface area

Answer: C. Deep second-degree burns extend through the epidermis into the deep (reticular) dermis. Body surface area is determined by the rule of nines. Nine percent for each upper extremity means that the forearm is approximately one fourth of 9%. Two forearms burns are half of 9%. Second-degree burns are often more painful than third-degree burns, in which all of the nerve endings are destroyed.

56.2. A 3-year-old boy presents with circumferential burns involving both upper extremities, including his hands, from pulling a boiling pot of water off the stove. The burns are mixed second-degree and third-degree burns. Which of the following best describes the body surface area burned and the most appropriate disposition?
- **A.** 9% and admit to pediatrics with surgery consultation
- **B.** 9% and transfer to burn unit
- **C.** 18% and transfer to burn unit
- **D.** 18% and admit to pediatric surgery
- **E.** 20% and admit to pediatric intensive care unit

Answer: C. Children with burns over 10% total body surface area (TBSA) should be transferred to a burn unit. In addition, hand burns should be treated at a burn unit. Circumferential burns are not consistent with a splash injury, and child abuse should be suspected and reported.

56.3. A 55-year-old, 80-kg man presents with second-degree burns of both his legs, front torso, and groin. What is the initial fluid resuscitation according to the Parkland formula?
- **A.** 500 mL lactated Ringer solution in the first 4 hours
- **B.** 1100 mL normal saline in the first hour
- **C.** 1100 mL of lactated Ringer solution in the first hour
- **D.** 2400 mL normal saline in the first hour
- **E.** 4200 mL lactated Ringer solution in the first 4 hours

Answer: C. The amount of lactated Ringer solution required for the first hour can be rapidly estimated with the Parkland formula by multiplying the estimated total body surface area (TBSA) of the second- and third-degree burn (55%) by body weight in kilograms (80 kg) and dividing by 4.

56.4. A 25-year-old woman presents with a second-degree burn to her right forearm after a grilling accident. You note areas of gray discoloration with decreased blanching in the erythematous region of the burn. In addition to irrigation, débridement, and dressing with a nonadherent dressing, which of the following would be the most appropriate treatment?
- **A.** Apply silver sulfadiazine and follow-up with plastic surgery in 1 week
- **B.** Calculate the Parkland formula and administer fluids before discharge
- **C.** Educate the patient about daily dressing changes and have her follow-up with plastic surgery in 24 to 48 hours
- **D.** Immerse her forearm in ice water for pain control
- **E.** Unroof soft blisters and have the patient follow-up with her primary care physician in 1 week

Answer: C. The distinction between superficial and deep second-degree burns is important in that deep second-degree burns often do not heal within 2 or 3 weeks and may result in severe scarring and contractures, especially in children. As a result, deep second-degree burns that do not heal within 21 days may require excision and skin grafting to minimize scarring. Deep second-degree burns may also progress to third-degree burns during the course of several days after injury. Burns over less than 20% TBSA can be treated with oral hydration. Blisters are generally left intact initially if possible. They may later require débridement.

56.5. Which of the following is an indication for intubating a patient who was found in a burning house?
- **A.** Facial edema
- **B.** Fire occurred in a closed space
- **C.** Patient unable to handle own secretions
- **D.** Singed eyebrows
- **E.** Soot in the airway and singed nasal hair

Answer: C. See Box 56.1. Traditionally, inhalation injury was diagnosed on the basis of clinical findings, such as facial burns, singed nasal vibrissae, carbonaceous sputum, and a history of injury within a closed space. However, these findings are neither highly sensitive nor highly specific. Nonetheless, these patients must be closely observed for potential delayed airway compromise.

56.6. What is the most appropriate management for a superficial partial thickness burn on the forearm?
- **A.** A clean dry dressing, such as gauze
- **B.** A commercially available silver containing dressing
- **C.** Systemic antibiotics and silver sulfadiazine
- **D.** Topical antibiotic ointment
- **E.** B and D

Answer: E. Superficial partial thickness burns may be treated with a topical antibiotic ointment or one of several commercially available silver releasing dressings. Silver sulfadiazine, as well as dry dressings, will slow reepithelialization. Silver sulfadiazine is appropriate for infected or heavily contaminated burns. Systemic antibiotics are *not* indicated for non-infected burns.

CHAPTER 57

Chemical Injuries

Michael D. Levine

PRINCIPLES

During the past century, there has been a dramatic increase in the number of chemicals produced. Worldwide, there are more than 5 million known chemicals, with new chemicals developed annually. Although large incidents, such as the methyl isocyanate release from a pesticide plant in Bhopal India or the release of 4-methylcyclohexanemethanol in the Elk River in West Virginia draw large-scale media attention, many smaller chemical spills occur daily.

It is estimated that 25,000 to 35,000 chemical incidents occur annually in the United States, with the majority resulting from either equipment failure or human error.[1] Approximately 5000 individuals will suffer injuries as a result of these spills. Among those patients injured, nearly half occur among the general public.[1] Individuals living close to an industrial complex may be exposed to a chemical following inadvertent release from the industrial site. However, other individuals living far from any stored chemicals may be exposed due to accidents during transport. It is estimated that half of all pesticide or agricultural chemical spills occur during transport.[2] The transport of hazardous materials occurs daily throughout the United States. These chemicals, which include acids, alkalis, and other highly reactive substances, not only are found throughout industry but also are ingredients in many household products. Exposure to these substances can result in injuries to many organ systems, including the eyes, skin, and lungs.

A hazardous material (HazMat) is defined as any substance, including gases, solids, or liquids, that has the potential to cause harm to people or the environment. Previously, the Hazardous Substances Emergency Events Surveillance (HSEES) system collected information on chemical exposures. In 2010, the National Toxic Substances Incidents Program (NTSIP) was established. It compiles data from multiple sources to perform chemical surveillance.[1] The most commonly released hazardous substances are volatile organic compounds, herbicides, acids, and ammonia. Various other products, such as cement, drain cleaners, and gasoline, are also potentially quite hazardous, and exposure can result in severe disability or death.

Community Preparedness and HazMat Response

Hazardous materials are found in residential, urban (eg, manufacturing), and rural (eg, agricultural) settings. Furthermore, because these substances are often transported on highways and railroads, a HazMat exposure could potentially occur in virtually any community. First responders, paramedics, and members of the HazMat response team must work together to identify toxic chemicals and assess hazardous environments. Placards, shipping papers, United Nations chemical identification numbers, and markings on shipping containers help identify the offending agent. The Chemical Transportation Emergency Center (CHEMTREC) in Arlington, Virginia, maintains a 24-hour telephone hotline (Box 57.1) to assist in the rapid identification and management of chemical agents. Standardized placards have been developed by the National Fire Protection Association (NFPA). This placard uses four diamonds to identify specific hazards associated with this project. In addition, regional poison control centers (see Box 57.1) provide specific health information regarding individual chemicals.

Although placards can identify chemicals in the case of an industrial chemical, occasionally it is not known that there is a chemical exposure. These challenges in identification of a HazMat scene are highlighted in Japan, where there has been an epidemic of chemical suicides inside locked cars from hydrogen sulfide gas. Following widespread Internet awareness of this situation, there has become a subsequent increase of similar fatalities in the United States.[3] Such exposures put first responders on particularly high risk of chemical injury, because they may be unaware of any exposure to chemicals by history.

Contingency Plan

The contingency plan for HazMat management is divided into two parts: initiation of the site plan and evacuation. *Initiation of the site plan* begins after the specific offending agent has been identified and the surrounding environment has been assessed. Only after the substance has been identified can the risks to the public and the environment accurately be identified. First responders should be trained to recognize the potential for a HazMat incident and should establish a perimeter. For the *evacuation* phase, the HazMat technicians are specifically trained in the use of personal protective equipment (PPE), establishing entry into a HazMat scene, victim rescue, and determining the type and extent of a HazMat emergency. A central command post should be used to coordinate the activities of the HazMat team with those of the emergency medical services personnel, firefighters, police officers, and other relevant personnel.

CLINICAL FEATURES

Most chemical agents cause skin damage by producing a chemical reaction rather than a hyperthermic injury. However, certain chemicals can generate significant heat production via an exothermic reaction after exposure to moisture. Nonetheless, the majority of dermal injuries result from direct damage to the skin rather than from a hyperthermic injury. The type of chemical reaction produced depends on the properties of the individual agent. In general, the degree of damage is directly correlated with the toxic agent's concentration and duration of exposure. Several other factors also contribute to the degree of injury—for example, areas of the body where the skin is particularly thin are more at risk than areas of the body where the skin is thicker. Skin that is thin or broken is at risk for more severe injury.

DIFFERENTIAL DIAGNOSES

Exposure to acidic compounds can produce protein denaturation and subsequent *coagulative necrosis*. This eschar limits the depth by which an acid can penetrate. Various acids produce eschars with characteristic colors. For example, nitric acid burns result in a yellow eschar, whereas sulfuric acid burns result in a black or

BOX 57.1

Important Phone Numbers to Assist in the Identification and Management of Chemicals and Chemical Injuries

CHEMTREC: 1-800-424-9300
Poison Control: 1-800-222-1222

brown eschar. Hydrochloric acid and phenol burns produce a white to gray-brown eschar. Despite the eschar formation, profound chemical burns can occur following exposure to an acid. Alkali agents, in contrast, produce a saponification and reactive *liquefactive necrosis*. Because there is no eschar to limit penetration, alkali burns tend to penetrate deeper into the tissues, which results in significant tissue damage.

Other infections (eg, cutaneous anthrax), injury (eg, full thickness burn), or envenomations (eg, arthropod envenomation) that result in eschar formation can be confused with chemical injury. However, history and physical findings differ, allowing for distinction from chemical injury. For example, a splash pattern may be seen following exposure to liquid chemicals. Ocular injection may be seen following exposure to chemical fumes that affect mucosal membranes. Wheezing may be heard following various inhalational injuries.

DIAGNOSTIC TESTING

Those patients with significant burns or systemic toxicity should have a complete blood count, metabolic profile, including serum electrolytes, with hepatic and renal function tests measured. If infection or sepsis is a consideration, an arterial or venous blood gas and serum lactic acid level is recommended.

MANAGEMENT

In dealing with a HazMat incident, two distinct processes occur simultaneously. First, the scene is secured, which involves containing the substance, extinguishing fires, and controlling other environmental hazards. The second process involves treatment, which begins with decontamination. The exact decontamination depends on the specific agent and route of exposure. In general, all decontamination should be performed before arrival in the emergency department (ED). Individuals who are not exposed to the hazardous material are kept away from the scene to prevent subsequent exposure.

At the outset of any contamination event, the offending agent may not be known. Therefore first responders and those having direct contact with ill patients must wear appropriate PPE. Once the first responder is dressed appropriately, decontamination begins by removing the patient's contaminated clothes. Dry (anhydrous) chemicals can be brushed off the patient's skin, followed by copious irrigation with water delivered under low pressure. Ideally, the contaminated water will be contained on the scene for appropriate disposal. Liquid chemicals can be copiously irrigated directly. If decontamination was indicated and not performed on the scene, the patient should be decontaminated before entering the ED. The primary and secondary survey can occur simultaneously with decontamination.

Although the exact requirements for PPE among hospital personnel are somewhat controversial, at a minimum all personnel involved with decontamination should wear chemical-resistant clothing with a hood, boots, eyewear, at least two layers of gloves, and some form of respiratory protection.

The initial management of the chemically burned patient involves removing the individual from the hostile environment. Because various chemicals will continue to destroy tissue until it is removed from the skin, clothing should be removed, and prompt decontamination measures should be initiated.

Hydrotherapy involves the gentile irrigation of a large volume of water under low pressure for a prolonged time. Such therapy dilutes the toxic agent and washes it out of the skin. High-pressure irrigation should not be used, because it theoretically can drive the chemical deeper into the tissues, as well as produce splattering of the chemical into the eyes of the patient or rescuer.

At present, water is the agent of acidic or alkali substances.[4] The deleterious effects of attempting to neutralize acid and alkali burns were first noted in experimental models in the 1920s. In those studies, animals with acid or alkali burns that underwent initial irrigation with water survived longer than animals treated with chemical neutralizers. It was hypothesized that neutralizing agents produced additional heat, thereby augmenting the burn. Although the same effect may occur when certain chemicals come in contact with water, large volumes of water tend to limit the exothermic reaction. More recently, scientists are beginning to question the belief that neutralization of an alkaline burn of the skin with an acid does increase tissue damage because of the exothermic nature of acid-base reactions. However, these data are preliminary and limited, and therefore we recommend irrigation with water alone as the best method for decontamination.[4]

Not all agents are best decontaminated with irrigation or hydrotherapy. Dry chemical agents, such as lye, should be brushed away before hydrotherapy is instituted. Elemental metals (eg, sodium or potassium) may produce exothermic reactions when combined with water. To minimize the exothermic reaction from such compounds, mineral oil is applied to the skin first. However, copious irrigation should not be delayed while waiting for mineral oil. In addition to lye and elemental metals, some have argued that phenol (carbolic acid) should not be irrigated with water owing to concern for enhanced skin penetration after exposure to water. However, the use of a substance that has both hydrophobic and hydrophilic properties (ie, polyethylene glycol [PEG]) has not been proven to exhibit clear benefit over water alone; therefore if hydrotherapy is to be initiated, hydrotherapy should not be delayed while waiting for PEG. If PEG solution is used for decontamination, the molecular weight of the preferred solution should be 200 to 400 daltons, which is different from the molecular weight of the PEG solution used for colonoscopy preparations and gastric decontamination.

DISPOSITION

Patients should be treated in a similar manner as with thermal burns. Those meeting referral for burn center criteria should be transferred to a burn center (see Chapter 56). Those with minor symptoms, in whom pain is controlled, and who lack systemic symptoms can be referred home. In contrast, those patients with systemic toxicity, significant opioid analgesic requirements, and those requiring systemic administration of an antidote (eg, intra-arterial calcium for hydrofluoric acid) should be admitted.

OCULAR INJURIES

Principles

Chemical burns to the eye require emergent management. Alkali burns are more common than acidic burns.[5] Unilateral involvement is more common than bilateral involvement. Common causes include inadvertent handling of chemicals with resultant splash injury, exploding batteries, airbag deployment, and intentional assaults.

Clinical Features

Alkali burns can initially appear trivial, but because of an interaction with lipids in the corneal epithelial cells, a liquefaction necrosis results, and deep penetration through the corneal stroma can ensue. The injury can occur rapidly; for example, anhydrous ammonia can penetrate into the anterior chamber in less than 1 minute, resulting in complete blindness.

There are numerous grading systems that have been developed to describe ocular burns.[6] Historically, the Roper-Hill classification has been used, which divides burns into four grades. However, because anyone with more than 50% limb ischemia is classified together, this classification has been criticized.[6] Due to changes in surgical treatment and improved outcomes, a different classification scheme has been developed in an attempt to overcome the deficiencies of the Roper Hill classification (Table 57.1). When comparing the Dua and Roper-Hill classifications in a prospective trial, the Dua classification was found to yield superior prognostic characteristics.[7]

Differential Diagnoses

The differential diagnosis for a red eye or vision loss is broad and is more fully discussed in Chapter 19. In the setting of trauma, the differential diagnosis includes subconjunctival hemorrhage, perforation, foreign body, and corneal abrasions. In the absence of trauma, the differential diagnosis includes benign etiologies (such as, subconjunctival hemorrhage or conjunctivitis) to more concerning etiologies (such as, iritis, uveitis, episcleritis, glaucoma, optic neuropathy, central retinal artery occlusion, or central retinal vein occlusion).

Diagnostic Testing

Visual acuities should be performed in all patients with ocular complaints. The pH of the eye should be checked with litmus paper, ideally before and after irrigation. If the patient can tolerate the procedure, a comprehensive slit-lamp examination is advised.

Management

When a chemical injury to the eye is suspected, copious irrigation is started immediately. At the scene, it is recommended that the victim submerge the eyes in running tap water and continuously open and close the eyes with the head turned such that the affected eye is lower than the unaffected eye to minimize any contamination into the unaffected eye. In the ED, tap water irrigation can be continued during preparation for a more definitive irrigation system. The repeated application of topical anesthetics (such as, proparacaine) can decrease pain and facilitate irrigation. Hydrotherapy can also be accomplished by connecting intravenous tubing to a bag containing normal saline or lactated Ringer's solution. The initial therapy consists of continual irrigation of the eye with 2 L of normal saline during the first 30 minutes. A Morgan lens can be used for irrigation, although there is a theoretic risk of trapping the chemical between the conjunctiva and the Morgan lens, thereby increasing the burn. If a Morgan lens is used, we recommend replacing the lens between saline applications. After 2 L has been infused, as described earlier, litmus paper is inserted into the conjunctiva to determine the pH; irrigation is continued until the pH is at a near-physiologic level (pH of 7.4). Alkali burns are likely to require more irrigation than acidic burns. For very severe acid or alkali burns, prolonged irrigation may be needed regardless of a normal ocular pH. It is important to also evert the upper eyelid and visually inspect the area for any lodged or hidden particulate matter. A slit-lamp examination with fluorescence staining should be performed to assess for any corneal abrasion. Although of undetermined benefit, ocular antibiotics are recommended after decontamination if a corneal abrasion is present.

The use of topical or subconjunctival corticosteroids following alkali burns has been associated with reduced corneal opacity, vascularization, and inflammation.[6,8] Ascorbate has been hypothesized to promote new collagen deposition. In addition, there is some data on the use of vitamin C for the treatment of corneal burns.[6]

TABLE 57.1

Roper Hill Classification

GRADE	PROGNOSIS	CLINICAL FINDINGS	CONJUNCTIVAL INVOLVEMENT
I	Very good	0 clock hours of limbal involvement	0
II	Good	<3 clock hours of limbal involvement	<30%
III	Good	3 to 6 clock hours of limbal involvement	30% to 50%
IV	Good to guarded	6 to 9 clock hours of limbal involvement	50% to 75%
V	Guarded to poor	9 to 12 clock hours of limbal involvement	75% to 100%
VI	Very poor	Complete limbal involvement	100%

Disposition

Immediate ophthalmologic consultation and close follow-up are indicated for all significant exposures. All but the mildest burns should be treated with a long-acting cycloplegic and a mydriatic. After consultation with an ophthalmologist, a carbonic anhydrase inhibitor may be used for 2 weeks (or until the pain disappears). These medications decrease the potential for pupillary constriction, increased intraocular pressure, and early glaucoma. Procedures such as amniotic membrane patching, anterior chamber paracentesis, and corneal transplant have been used for chemical injuries to the eye but should be performed by the ophthalmologic consultant.

Patients with lower grade ocular injuries can often be managed as outpatients, but patients with higher-grade injuries should be admitted to the hospital.

SPECIFIC TOXINS

Hydrofluoric Acid

Principles

Hydrofluoric acid is an acidic aqueous solution made from the element fluorine. It is used in the petroleum industry to manufacture high-octane gasoline. It is also used in the production of microelectronics and for etching glass, removing rust, and cleaning cement and bricks. It is available in many over-the-counter products in concentrations ranging from 6% to 12% but can be used in the industrial setting in concentrations exceeding 70%.[9]

Absorption of hydrofluoric acid can occur after exposure to the lung, skin, and eyes. In a 20-year review of all hydrofluoric acid deaths reported to the Taiwan Poison Control Center, dermal exposure accounted for 84% of all exposures, and the majority

occurred in an occupational setting.[10] Of these 324 subjects, the majority of subjects had mild toxicity. However, approximately 40% of subjects had moderate toxicity and 1% had severe toxicity. Two subjects died strictly from hydrofluoric acid related dysrhythmias and shock.[10] Hydrofluoric acid solutions with a concentration exceeding 50% will produce near immediate pain, whereas burns from more dilute concentrations can be delayed for hours.

Hydrofluoric acid is unique in its mechanism of action. Despite being an acid, it is capable of causing a liquefactive necrosis, similar to alkalis. The free fluoride ion is responsible for most of the damage associated with hydrofluoric acid exposure. The free fluoride ion scavenges cations, such as calcium and magnesium, thereby resulting in systemic hypocalcemia and hypomagnesemia. In addition, free fluoride ions can inhibit sodium, potassium–ATPase (Na^+,K^+-ATPase) and the Krebs cycle. The combination of cellular destruction and inhibition of Na^+,K^+-ATPase can also result in hyperkalemia as a preterminal finding. As a result of the numerous electrolyte disturbances, QT prolongation, hypotension, and ventricular arrhythmias can occur. The severity of injury depends on the concentration of the substance and the duration of exposure.

Clinical Features

Inhalational Exposure

Inhalation of hydrofluoric acid is rare, and it almost always occurs in the industrial setting. Patient outcomes vary considerably depending on the concentration and duration of exposure to hydrofluoric acid. Inhalation and skin exposure to 70% hydrofluoric acid can result in pulmonary edema and death within 2 hours. However, delayed pneumonitis and adult respiratory distress syndrome can also occur, and they can be present for months. Pneumonitis can be severe and require ventilatory support.

Gastrointestinal Exposure

Unless it is an intentional ingestion, gastrointestinal exposure is rare; it can produce symptoms ranging from nausea, vomiting, and abdominal pain and with larger ingestions, life-threatening fluoride toxicity.

Ocular Exposure

Despite the fact that hydrofluoric acid is an acid, exposure of the eye to hydrofluoric acid can result in a severe burn with penetration and necrosis of the structures throughout the anterior chamber. As with other ocular injuries, immediate and copious irrigation of the eye is indicated. Systemic absorption is possible.

Dermal Exposure

Dermal exposure is perhaps the most common route of hydrofluoric acid injury. During handling of containers in which hydrofluoric acid is stored, contamination of inadequately protected fingers and hands often results in a chemical burn injury. The hydrofluoric acid skin burn has a distinct characteristic: the exposure causes progressive tissue destruction. Intense pain can occur quickly or be delayed for several hours, and it can persist for days if untreated. The degree of pain may seem out of proportion the examination.[9] With larger exposures, the involved skin may develop a tough, coagulated appearance. If untreated, the burn can progress to an indurated, whitish appearance with vesicle formation. Within the digits, hydrofluoric acid has a predilection for subungual tissue. Severe untreated burns can progress to full-thickness burns and can even result in loss of digits.

Differential Diagnoses

Because pain may seem out of proportion to examination findings, shingles, neuropathy, and other chemical injuries should be within the differential diagnosis. In the presence of apparent burns, the differential diagnosis includes blistering disorders, toxic epidermal necrolysis, and infectious etiologies.

Diagnostic Testing

Patients with hydrofluoric acid burns should have serum potassium and ionized calcium levels checked. With electrolyte abnormalities, an electrocardiogram (ECG) should be assessed for dysrhythmias or changes in the QTc or QRS intervals. A chest radiograph should be obtained in individuals with inhalant or pulmonary symptoms. A detailed eye examination, including a slit-lamp examination, fluorescein staining, and visual acuities should be performed on individuals with ocular exposure.

Management

The initial treatment of hydrofluoric acid skin exposure is immediate irrigation with copious amounts of water for at least 15 to 30 minutes. Most exposures to dilute solutions of hydrofluoric acid respond favorably to immediate irrigation. Severe pain or any pain that persists after irrigation denotes a more severe burn that requires detoxification of the fluoride ion. Detoxification is accomplished when an insoluble calcium salt is formed.

Unlike most thermal burns, blisters are removed because necrotic tissue may harbor fluoride ions. The fluoride ions can then be detoxified through topical treatment, local infiltrative therapy, or intra-arterial infusion of calcium. Calcium gluconate (2.5%) gel can be administered topically. (Calcium chloride is irritating to the dermis.) Calcium gluconate gel is often not available in hospital pharmacies, but it can be made by mixing 3.5 g of calcium gluconate powder in 150 mL of a water-soluble lubricant (eg, glycerin-hydroxyethyl cellulose lubricant [K-Y Jelly]). This gel is secured by an occlusive cover (eg, powder-free latex glove). Because the skin is impermeable to calcium, topical treatment is effective only for mild, superficial burns.

Infiltration Therapy

Subcutaneous. Infiltrative therapy is necessary for treatment of deep, painful hydrofluoric acid burns. Calcium gluconate is the agent of choice and can be administered by either direct infiltration or intra-arterial injection. A common technique involves injecting 0.5 mL/cm^2 of 10% calcium gluconate subcutaneously through a 27- or 30-gauge needle. The use of an equal volume mixture of 5% calcium gluconate and 0.9% normal saline has been shown to reduce irritation of tissues and decrease subsequent scarring.

Despite its wide acceptance, the infiltration technique has disadvantages, especially in treating digits. A regional nerve block is recommended because the injections may be very painful. Removal of the nail to expose the nail bed is required if subungual tissue is involved. Vascular compromise can occur if excessive fluid is injected into the skin exposure sites, and unbound calcium ions have a direct toxic effect on tissue. Because of these disadvantages with subcutaneous infiltration in the hand, we recommend intra-arterial infusion of in most instances.

Intravenous and Intra-Arterial. Patients with pain refractory to local or subcutaneous calcium administration may benefit from regional anesthesia, either in the form of an intravenous infusion (eg, Bier block), or intra-arterially. Various dilute solutions of calcium have been used. One approach is to place an

intravenous catheter in the hand or foot involving the affected burn. The extremity is elevated for 1 minute, and a double-cuffed tourniquet is inflated to 40 kPa. An elastic bandage is then placed at 8 kPa. Subsequently, 15 mL of calcium gluconate gel, diluted with 35 mL of 0.9% normal saline, was infused over 2 minutes. The tourniquet is then deflated over 20 minutes.[11] Another approach involves the administration of a mixture of 10 mL of solution of 10% calcium gluconate in 40 to 50 mL of normal saline infused over 4 hours. Because of ease of administration, we recommend starting with this approach, although other approaches can be used in conjunction with this approach if pain persists. If more than 6 hours has elapsed since the time of hydrofluoric acid exposure, tissue necrosis cannot be prevented, even though pain relief can be achieved up to 24 hours after exposure. There is a direct correlation between the speed by which arterial infusion of calcium administration occurred and both the time of wound healing and the need for surgical intervention.[12]

The intra-arterial infusion technique has potential disadvantages. Arterial spasm or thrombosis may result in significant skin loss. The intra-arterial procedure is more costly, because it requires hospitalization for the use of the infusion pump and the monitoring of serum calcium concentrations if repeated infusions are used. Recently, the use of epidermal growth factor was found to be superior to saline, calcium gluconate, or magnesium sulfate.[11]

Ocular Exposures

The ocular use of calcium gluconate is somewhat controversial, because it has the potential to cause further damage to the eye. The use of ocular calcium gluconate is not routinely recommended.

In the ocular setting, use of Hexafluorine may be considered after copious irrigation of the eye.[13]

Systemic Toxicity

Hydrofluoric acid binds calcium and magnesium ions with strong affinity. Systemic manifestations of fluoride toxicity are related to hypocalcemia and include abdominal pain, muscle fasciculations, nausea, seizures, ventricular dysrhythmias, and cardiovascular collapse. Burns as small as 2.5% of the total body surface area have proven fatal in concentrated hydrofluoric acid exposure. Hypocalcemia can occur after significant exposure to hydrofluoric acid and is corrected with the intravenous administration of a 10% calcium gluconate infusion. Calcium chloride can be used, but its administration requires central access. In addition, fluoride ion accumulation has cardiac and neurotoxic effects.

Disposition

Patients treated with calcium therapy with continued refractory pain should be hospitalized for observation and toxicological consultation. Patients with significant hydrofluoric acid exposure with systemic toxicity require hospitalization to monitor for cardiac dysrhythmias for 24 to 48 hours.

Formic Acid

Principles

Formic acid is a caustic organic acid used in the rubber, paper, tanning, and electroplating industry, along with the manufacturing of disinfectants.[14] It is also used agriculturally.

Clinical Features

Formic acid causes cutaneous injury by inducing a coagulative necrosis. Systemic toxicity occurs after absorption and is manifested by metabolic acidosis, gastrointestinal bleeding, bowel perforation, and aspiration. Because of its ability to induce oxidant stress, hemolysis may occur.[14]

Differential Diagnoses

Similar to hydrofluoric acid, the differential diagnosis includes various other chemical burns, infectious etiologies, toxic epidermal necrolysis, and blistering disorders.

Diagnostic Testing

No specific diagnostic testing is indicated. If the patient shows any signs of systemic toxicity, in addition to a complete blood count and serum electrolytes, the acid-base status should be measured with an arterial or venous blood gas.

Management

Copious wound lavage should be instituted immediately. Acidosis (pH <7.30) should be treated with sodium bicarbonate. Mannitol may be used to expand plasma volume and promote osmotic diuresis in patients with hemolysis. Folinic acid, which enhances formate degradation, can be administered for severe toxicity. Hemodialysis may be required for patients with systemic toxicity, renal failure, and metabolic acidosis.[14] Exchange transfusion may be required for patients refractory to the medical management, including hemodialysis.

Disposition

Patients should be treated according to local burn center referral guidelines. Those who meet criteria for evaluation in a burn center should be referred. Other patients, including those without systemic manifestations and those who are not requiring significant doses of parenteral analgesics, can be discharged home with close out patient follow-up. Specific treatment recommendations and disposition decisions can be discussed with a regional poison control center (see Box 57.1).

Anhydrous Ammonia

Principles

Anhydrous ammonia is a colorless, pungent gas used extensively as a fertilizer in the agricultural setting. It can also be used in the manufacture of explosives, petroleum, plastics, and synthetic fibers. In addition, the "dry cook" method of methamphetamine production uses anhydrous ammonia as an amphetamine precursor. This method was associated with numerous burns due to anhydrate ammonia. In recent years, due to changes in legislation, the use of anhydrous ammonia has often been substituted with ammonium nitrate or ammonium sulfate based products in a so-called "one pot" method.[15] Nonetheless, its use continues in methamphetamine production. Anhydrous ammonia can be transported as a pressurized liquid. The sudden release of liquid ammonia can cause injury through two distinct mechanisms.

Clinical Features

Anhydrous ammonia is generally stored at an extremely low temperature (−33° C). Consequently, exposure to liquid at this temperature can result in tissue necrosis and frost bite. Second, the ammonia vapors readily dissolve in the moisture in skin, eyes, oropharynx, and lungs to form hydroxyl ions that cause chemical burns by liquefaction necrosis, which can result in full-tissue skin loss. The severity of injury is directly related to the concentration

and duration of ammonia exposure. In general, acute exposure to anhydrous ammonia produces the greatest injury to the proximal airway rather than the distal airway.

Differential Diagnoses

The differential diagnosis includes chemical burns from any other chemical (eg, Freon), blistering disorder, infectious etiologies, and environmental exposures, such as frostbite and cold-related injuries.

Diagnostic Testing

Patients with pulmonary complaints should have a chest radiograph performed. Most patients with exposure to anhydrous ammonia should have electrolytes checked.

Management

Treatment consists of prompt irrigation of the eyes and skin with water and management of inhalation injury. If necessary, the airway should be secured through standard intubation methods with a large-diameter tube to prevent distal airway obstruction from sloughing of mucosa. After intubation, lower airway injury is managed with positive end-expiratory pressure ventilation.

Disposition

Patients with minor burns, and not otherwise requiring admission or referral to a burn center, as per local guidelines can be discharged home, as long as there is no evidence of systemic toxicity or significant analgesic requirements.

Cement

Cement is primarily composed of calcium oxide that combines with water to form calcium hydroxide. This compound is alkaline. Most cases of cement toxicity involve a contact dermatitis from dermal exposure among lay persons.[16]

There are three types of cement burns. The most common burn is a chemically abrasive form, and heat-related or blast-induced burns can also occur. Heat-related and blast-induced burns are more common in the industrial setting and are associated with severe burns, often involving the respiratory tract.

The treatment of a cement burn attempts to eliminate the toxic component via copious irrigation after all clothes have been removed. Early excision and grafting are often necessary, and referral to plastic surgery may be required for patients with extensive injury.

Phenol and Derivatives

Principles

Phenols are used industrially as starting materials for many organic polymers and plastics. They are widely used in the agricultural, cosmetic, and medical fields. Because of their antiseptic properties, they are also used in many commercial germicidal solutions. A number of phenol derivatives (eg, hexylresorcinol and resorcinol) are more bactericidal than phenol.

Phenol (carbolic acid) is an aromatic acidic alcohol with a characteristic odor. The concentration of phenol is inversely related to its depth of burn, because highly concentrated solutions result in coagulation of the keratin, thereby preventing deeper penetration. Histologic studies have demonstrated that 100% concentrations of phenol produce 35% to 50% less penetration than a 50% solution.

Both phenol and its derivatives are highly reactive, corrosive poisons that damage cells by inducing cell wall disruption, protein denaturation, and coagulative necrosis. After penetrating the dermis, phenol produces necrosis of the papillary dermis. This necrotic tissue may temporarily delay its absorption.

Clinical Features

When skin comes in contact with phenol, treatment should be instituted immediately. The exposed area is irrigated with large volumes of water delivered under low pressure. Because dilute phenol solutions are more rapidly absorbed through skin than concentrated solutions, gentle swabbing of the skin surface with sponges soaked in water should be avoided. Any hair, including a beard or mustache, that has come in contact with a phenol is removed as soon as possible, because the phenol can become trapped in hair. Because of its lipophilic nature, it can easily penetrate the dermis, producing not only local findings, but systemic manifestation.[9]

In animal studies, exposure to as little as 0.6 mg of phenol per kilogram can be lethal. Systemic toxicity of phenol primarily affects the central nervous system (CNS) and cardiovascular system. In the CNS, toxicity can manifest as stimulation, lethargy, seizures, or coma. Conduction disturbances can be either tachycardic or bradycardic in nature. Marked hypotension may occur as a result of central vasomotor depression, in addition to a direct toxic effect on the myocardial cells and small blood vessels. Hypothermia and metabolic acidosis can also occur.

Differential Diagnoses

The differential diagnosis includes burns from any other chemical or heat, blistering disorders, dermal infections, hydrofluoric acid exposure, methyl salicylate toxicity, and toxic epidermal necrolysis.

Diagnostic Testing

Patients with phenol exposure should have an ECG performed. In addition, serum electrolytes and an arterial or venous blood gas should be measured.

Management

Dilute solutions of phenol have been used historically by plastic surgeons for chemical face peels. Phenols are usually mixed with water, soap, and croton oil. This solution can produce a partial-thickness burn of a predictable depth in a controlled manner. The concentration is kept sufficiently low to reduce the occurrence of systemic complications. The physician performing phenol chemical peels should be concerned about the possibility of rapid phenol absorption. Even in a controlled setting, ventricular dysrhythmias occur as a result of the phenol application.

Polyethylene Glycol Therapy

Experimental studies indicate that water alone is effective in reducing the severity of burns and preventing death in animals with skin exposed to phenol and its derivatives. The most effective treatment is undiluted PEG (molecular weight 200 to 400 Daltons) or isopropanol (isopropyl alcohol). Adequate supplies of either PEG or isopropanol should be stocked in hospitals located near areas of phenol use and can often be found in the chemical section of hospital pharmacies. A quick wipe of the skin with PEG solutions reduces mortality and burn severity in experimental animals. These solutions can be used for phenol burns of the face, because they are not irritating to the eyes. Decontamination with water

should be performed until a PEG solution is obtained. Large amounts of water must be used, however, because small amounts are detrimental, enhancing dermal absorption of phenol. Removal of phenol should be undertaken in a well-ventilated room so that hospital personnel are not exposed to high concentrations of phenol fumes.

Treatment of Systemic Toxicity

The treatment of systemic symptoms is primarily supportive. Respiratory depression may require ventilatory support. Hypotension is best treated with an initial fluid bolus of 20 cc/kg of 0.9% normal saline or lactated Ringer's solution. If fluids administration is inadequate, vasopressors should be used. Metabolic acidosis can be treated with sodium bicarbonate until the pH is near 7.40. The alkalinization can also help prevent hemoglobin precipitation in the nephron as a result of hemolysis. Benzodiazepines (lorazepam or diazepam) may be required to treat seizures caused by CNS stimulation. Intravenous lidocaine may be effective in treating ventricular dysrhythmia.

Disposition

Patients without systemic manifestations and not otherwise meeting local criteria for a burn center can be discharged after a period of 6 to 8 hours of cardiac monitoring, providing there are no arrhythmias or other manifestations of systemic toxicity. Those with significant pain requirements should be admitted.

Phosphorus

Principles

Phosphorus is a nonmetallic element that exists in three forms: elemental phosphorus, white phosphorus, and red phosphorus. White phosphorus, which is also referred to as *yellow phosphorus,* is widely used in munitions manufacturing, in fireworks, as an ingredient in methamphetamine production, and in fertilizers. Historically, it has also been used as a rodenticide. The autoignition temperature (the temperature at which spontaneous combustion can occur) is 30°C (86°F). When white phosphorus comes in contact with air at temperatures above the autoignition point, the phosphorus spontaneously oxidizes, forming phosphorus pentoxide. Phosphorus pentoxide can combine with small amounts of moisture in the air, forming phosphoric acid. In wounds, oxidation of phosphorus pentoxide will continue until it is removed through débridement, neutralized, or consumed.

Clinical Features

Tissue injury from white phosphorus appears to have both thermal and chemical causes. The corrosive action of the phosphoric acid results in an exothermic reaction, thereby liberating heat and causing a thermal burn. The hygroscopic action of the phosphorus pentoxide is also responsible for causing a chemical burn, which frequently results in a partial-thickness or full-thickness burn.

After oral ingestion of white phosphorus, three stages of toxicity are described, although it is uncommon that all three stages occur. The first stage, which can last 8 to 24 hours, is characterized by gastrointestinal tract irritation, including vomiting, abdominal pain, diarrhea, and gastrointestinal bleeding. The stool is occasionally described as being luminescent or "smoking." Hypovolemic shock can result. Up to one third of patients who ingest significant quantities of white phosphorus will die during this stage. The second stage is a latent phase. During this period, which can last 1 to 3 days, symptoms appear to be improving. However, the third stage is characterized by multisystem organ failure, including hepatic failure, renal failure, and CNS depression. Renal failure is usually present at days 1 to 4, whereas jaundice typically manifests at days 3 to 5.

Red phosphorus can cause some gastrointestinal illness if consumed orally but is less toxic than white phosphorus.

Differential Diagnoses

The differential diagnosis depends on the type of phosphorous exposure. For isolated burns, the differential diagnosis includes thermal or chemical burns (acids or alkali), infectious etiologies, and blistering disorders. For those with significant gastrointestinal illness, heavy metal toxicity (eg, lead, mercury, thallium, arsenic, and iron), as well as ischemic bowel and causes of gastrointestinal bleeding should be considered

Diagnostic Testing

Metabolic derangements can also occur after white phosphorus exposure, including hypocalcemia and hyperphosphatemia. Conduction system disturbances, including bradycardia, QT prolongation, and ST and T wave abnormalities, can occur and are partially explained by electrolyte derangements. These ECG changes may explain the sudden early death that may occur in patients with relatively minor white phosphorus burns.

Management

The out-of-hospital management involves the immediate removal of contaminated clothing, followed by submersion of the injured skin in cool water. Warm or hot water is avoided because white phosphorus becomes liquid at 44°C (111°F). Phosphorus particles are removed from the victim's skin and submerged in water. The burned skin is covered with towels soaked in cool water during transport to the ED.

After the patient arrives at the ED, the burned skin is washed copiously with normal saline. In the past, some advocated use of a suspension of 5% sodium bicarbonate, 3% copper sulfate, and 1% hydroxyethyl cellulose. Other, similar solutions containing copper sulfate have also been described. The use of 0.9% normal saline solution, however, has demonstrated better effects than copper-containing solutions. Although there are some conflicting recommendations in the literature, given that saline is as efficacious as copper sulfate solutions and has less associated toxicity, we recommend saline irrigation as the preferred irrigating solution.

Phosphorus particles can be identified with either ultraviolet light or copper-containing solutions. When a Wood's lamp is used, the phosphorus will fluoresce under an ultraviolet light. Unlike copper-containing solutions, the use of a Wood's lamp is not associated with any adverse or detrimental effects. The use of the copper-containing solutions causes the phosphorus particles to become coated with black cupric phosphide. These black particles are more easily identified and thus more easily removed. Copper sulfate also decreases the rate of oxidation of the phosphorus particles, thus limiting their damage to the underlying tissue. However, because the blackened particles can still cause tissue damage, they should be removed. If a copper solution is used, after 30 minutes of exposure to the burned skin the copper-containing solution must be thoroughly washed from the skin, thereby limiting the development of systemic copper toxicity.

After copious irrigation with saline solution decontamination, and treatment of associated electrolyte disturbances, definitive management of the skin burns is accomplished as with any other burn wound. Serum calcium and phosphate levels should be monitored for 24 to 48 hours.

Disposition

Patients with significant phosphorus exposures should be admitted to a monitored setting. Those with burns that would otherwise meet criteria for referral to a burn center should be transferred as per local guidelines.

Nitrates and Nitrites

Principles

Both nitrates (NO_3^-) and nitrites (NO_2^-) are abundant in rural and industrial settings. Both sodium nitrate and sodium nitrite are used in food preservatives. Nitrites also have many medicinal uses secondary to their vasodilatory properties. Nitrates are commonly used in electroplating, engraving, and metal casting and as fertilizing agents. Exposure to either nitrates or nitrites has been associated with methemoglobinemia.

Reduced hemoglobin contains four heme groups, each with a ferrous (Fe^{2+}) ion. Methemoglobinemia results when the ferrous ion becomes oxidized to the ferric (Fe^{3+}) state. Under routine physiologic conditions, the body reduces the ferric valence back to the ferrous valence via cytochrome b5 reductase. At any given time, methemoglobin accounts for 1% to 2% of circulating hemoglobin. Cyanosis from methemoglobin occurs when methemoglobin concentrations exceeded 1.5 g/dL.

Clinical Features

Methemoglobin toxicity exists along a spectrum. Many patients with low levels are asymptomatic. When methemoglobin concentrations in nonanemic individuals exceed 20%, headache, anxiety, dyspnea, and tachycardia can occur, although some individuals may be asymptomatic with levels exceeding 30%.[17] Confusion, lethargy, and acidosis typically occur with methemoglobin levels approaching 40% to 50%. Coma, seizures, hypotension, dysrhythmias, and death occur when levels exceed 70%.[17] Patients with anemia can develop symptoms at lower methemoglobin percentages and in the setting of profound anemia, cyanosis may not be apparent.

Differential Diagnoses

The differential diagnosis includes exposure to any agent that can cause oxidant stress, including local anesthetics, phenazopyridine, dapsone, and arsine gas. In addition, hemolysis from non-oxidant stress should be included on the differential diagnosis.

Diagnostic Testing

The diagnosis of methemoglobinemia should be sought in any cyanotic patient whose pulse oximetry displays a saturation of 85% to 88% that is unresponsive to oxygen therapy and whose arterial blood appears "chocolate brown" in color. The methemoglobin level can be measured on an arterial blood gas analyzed with standard co-oximetry.

Management

Asymptomatic patients are treated by rapidly removing the offending agent. For symptomatic patients without glucose-6-phosphate dehydrogenase (G6PD) deficiency, 1 to 2 mg/kg of a 1% methylene blue solution can be administered over 3 to 5 minutes. A repeat dose may be needed in cases of severe toxicity. Methylene blue acts via the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase, in which NADPH converts methylene blue to leukomethylene blue, which in turn donates an electron to reduce methemoglobin.[17] For those patients who fail to respond to methylene blue, or those with severe G6PD deficiency with concurrent severe toxicity from methemoglobinemia, exchange transfusion may be required.

Disposition

Patients without systemic toxicity and no evidence of methemoglobinemia can be discharged home after 6 hours, as long as the cutaneous burn is not too severe to warrant referral to a burn center as per local guidelines. Patients who develop methemoglobinemia should be observed on a monitored setting for 24 hours, even if the methemoglobinemia resolves after treatment with methylene blue.

Hydrocarbons

Principles

Hydrocarbons are a heterogeneous group of organic compounds that are derived from carbon and hydrogen molecules. They are found in fuels, solvents, paints, paint and spot removers, dry cleaning solutions, lamp oil, rubber cement, and lubricants.

Hydrocarbons are classified as aromatic, in which the carbon moieties are arranged in a ring, or aliphatic, in which the carbon moieties are arranged in a linear or branched chain. Halogenated hydrocarbons are a subgroup of aromatic hydrocarbons in which one of the hydrogen molecules is substituted with a halogen.

Clinical Features

The toxicity from hydrocarbons can affect many different organs, but the lungs are the most commonly affected. The toxicity of hydrocarbons is directly related to their volatility and inversely related to the viscosity and surface tension. The primary toxicity from hydrocarbons occurs from pulmonary aspiration. Thus substances with high volatility, low viscosity, and low surface tension are most likely to be aspirated.

Systemic toxicity from dermal exposure to a hydrocarbon is relatively rare. Significant dermal exposures can occasionally cause local tissue irritation.

Differential Diagnoses

The differential diagnosis includes exposure to any agent that can cause a chemical pneumonitis, as well as infectious pneumonia, acute exacerbation of a reactive airway disease, or pulmonary edema.

Diagnostic Testing

We recommend obtaining a chest radiograph 6 hours after ingestion, although no randomized study has demonstrated this approach to be superior to observing the patient for clinical manifestations of aspiration (eg, coughing gagging vomiting, wheezing, tachypnea, or hypoxia). If the patient is persistently hypoxic on pulse oximetry, an arterial blood gas measurement is recommended.

Management

Treatment involves removal of the patient from the source of exposure and removal of any contaminated clothing. Copious irrigation with warm water should be performed and burns managed as are other thermal injuries.

Chronic dermal exposure can result in perioral or perinasal dermatitis with pyoderma. This so-called "huffer's rash" is

primarily seen with recreational abuse. The hydrocarbon inhalant can dry the skin, thereby causing microscopic cracks and allowing bacteria to enter, causing a bacterial superinfection.

Significant toxicity from inhaled (nonaspiration) exposure to hydrocarbons is also unlikely to produce serious effects. Some patients may develop mild headache, dizziness, nausea, or wheezing. These symptoms resolve after removal of the patient from the source of exposure.

Ingestion of hydrocarbons can result in aspiration and systemic toxicity. After ingestion of hydrocarbons, it is recommended that patients be monitored for 6 hours. There is no role for gastric decontamination. Beta-agonists can be administered for bronchospasm, and supplemental oxygen administered as needed. Endotracheal intubation is occasionally required for severe hypoxia and aspiration pneumonitis. Neither corticosteroids nor empirical antibiotic administration are indicated. Antibiotics may be warranted, however, if a superimposed bacterial infection develops, which will typically occur several days after the chemical pneumonitis develops.

Disposition

A patient can be discharged home after a 6-hour observation period, assuming no symptoms develop during the observation period and a chest radiograph (if obtained) is negative. All other patients warrant admission to observe for progression of symptoms and treatment of hydrocarbon-induced pneumonitis.

Tar

Principles

There are two types of hot tar: coal tar pitches and petroleum-derived asphalts. Both products are heated to maintain a liquid form. Roofing tar needs to be heated to temperatures of at least 232°C to achieve desirable viscosities.[18] Deeper burn injuries are associated with burns from roofing asphalt.

Clinical Features

When hot, liquefied tar comes in contact with skin, heat is transferred, and thermal injury results. The tar cools and solidifies on the skin, making removal difficult.

Management

Burns from hot tar present a treatment challenge. When hot tar touches skin, it rapidly cools, solidifies, and becomes enmeshed in the hair. It is important to facilitate this cooling process by adding cold water to the tar at the scene of the accident. Cooling tar with cold water limits the amount of tissue damage and prevents the spread. The tar is continually washed with water until it has cooled and hardened. After cooling, the skin is dried with towels to prevent systemic hypothermia.

Adherent tar should not be removed at the scene of the accident. In the ED, definitive care of the burn injury involves early removal of tar, because it occludes injured skin and encourages bacterial growth. Tar adheres to skin because it is enmeshed in the hair, not because of a direct bond between epidermis and tar.

Solvents used to remove tar ideally should have a close structural affinity to tar. Both petroleum-based aromatic hydrocarbon solvents and surface-active agents, such as polyoxyethylene sorbitan (Tween 80) and petroleum-based (De-Solv-it), have been used to facilitate tar removal. In addition, the use of topical neomycin can enhance removal.[18] Use of these surface-active agents is an effective, safe, and inexpensive means of removing tar from skin. Sunflower oil, NISA baby oil, mayonnaise, and butter have also been used to remove adherent tar from skin, requiring 30 to 90 minutes for complete removal. Sunflower oil has proved effective and safe in removing tar without causing further skin damage.

Asphalts are susceptible to both aromatic (eg, naphthalene) and aliphatic (eg, hexade) hydrocarbon solvents, whereas coal tars are susceptible only to aromatic hydrocarbons. Broad-spectrum antibiotic ointments can be used both to help with removal and to help prevent infection. If used, they should be removed and a new coating applied every hour until all the tar has been removed. This process typically takes 12 to 48 hours. Commonly used antibiotic ointments include bacitracin (400 μg/g), polymyxin B (5000 U/kg), and neomycin (5 mg/g). Antibiotic ointment can be used to remove tar layered over the cornea and conjunctiva.

Disposition

Patients with significant burns requiring multiple doses of parenteral analgesics should be admitted. Those who meet criteria for referral to a burn center should be transferred as per local guidelines. Other individuals can be discharged home with close, expedited out-patient follow-up and detailed wound care instructions.

Elemental Metals

The elemental metals, such as lithium, sodium, and potassium, are harmless unless they come in contact with water. When this happens, a violent exothermic reaction occurs that produces heat, hydrogen gas, and hydroxide. Explosions are possible.[18] The evolved heat is sufficient to ignite the hydrogen gas, which results in further heat production and thermal burns. The formation of the hydroxide compound may also result in significant chemical injury to tissue. The reaction occurs more rapidly with elemental potassium than with sodium. These deleterious effects of potassium have been attributed to trace amounts of potassium superoxide released on exposure to room air. Water lavage is therefore contraindicated in these circumstances.

Chromium

Chromium burns can produce systemic toxicity. Death may occur with burn surface areas exceeding 10%.[19] In addition to local wound effects, systemic toxicity can result including hemolysis and renal failure. It has been suggested that early excision may reduce systemic complications, although there is no experimental evidence to support such a practice. Medical management of chromium toxicity remains the mainstay of therapy. Chelation therapy with ethylenediaminetetraacetic acid (EDTA) has not been proven to be of clinical benefit.

Miscellaneous Gases

Chlorine

Chlorine gas was used in World War I as part of chemical warfare. Today, exposure to chlorine most commonly results from accidental industrial exposure. As was demonstrated when a recent chlorine leaked from a train car and spread over the city of Festus, Missouri, individuals not directly involved with industry can be exposed.

Chlorine is a heavy greenish-yellow gas or liquid with a characteristic odor. The combination of bleach (sodium hypochlorite) with an acid produces chlorine gas, and the combination of bleach and ammonia produces chloramine gas.[20] Both chlorine and chloramine gas produce similar toxicities. The clinical effects observed after chlorine or chloramine exposure are directly related to the time and concentration of the gas. Mild exposure may simply

cause mucosal membrane irritation, whereas more severe exposure will induce edema of both the upper airway and the lung parenchyma. Large acute exposure can induce wheezing, cough, and dyspnea. Acute lung injury and/or adult respiratory distress syndrome can result in severe cases. Because these gases are primarily reactive only at a local level, absorbed systemic effects are not commonly observed. Following large exposure, fatalities can occur.[20]

Phosgene

Similar to chlorine, phosgene was also used in World War I as a weapon, but it remains widely used today in industry.[21] Phosgene reacts with water to form carbon dioxide and hydrochloric acid. Given that phosgene is relatively water insoluble, high concentrations are needed before enough hydrochloric acid can be produced to cause mucosal membrane irritation. Phosgene undergoes acetylation to produce lung injury, which can manifest as delayed pulmonary edema. The timing of the pulmonary edema is inversely related to the degree of exposure.

The first step in treating an exposure to chlorine, chloramine, or phosgene gas is removal of the individual from the environment. After significant exposure to these agents, the patient's cardiopulmonary status should be assessed. Endotracheal intubation may be required. Bronchospasm is treated with beta-agonists, such as albuterol. Irritation of the eyes is managed with copious irrigation with water or saline, followed by an assessment for corneal abrasions if persistent eye irritation is noted. Nebulized 4% sodium bicarbonate can be used for treatment of chlorine or chloramine gas exposure. There is limited evidence of the use of nebulized acetylcysteine (1 to 2 g; 5 to 10 mL of a 20% solution) following phosgene exposure.[21] The use of corticosteroids has not been proven to be beneficial in the treatment of chlorine, chloramine, or phosgene toxicity. A study of mice exposed to chlorine gas demonstrated improved outcomes following systemic administration of nitrites.[22] However, we do not recommend the use of systemic nitrites to treat chlorine exposure.

Nitrogen Oxides

Nitrogen oxides include nitrogen dioxide (NO_2), nitric oxide (NO), and nitrous oxide (N_2O). NO_2 toxicity can occur from the burning of nitrocellulose, from use of Zamboni machines in poorly ventilated areas, and from silo filler's disease, in which the gas accumulates within a silo of decomposing grain. NO_2 fumes can often be easily recognized because of their reddish-brown color. The nitrogen oxides can cause respiratory tract irritation. Toxicity varies somewhat depending on the oxide, but severe toxicity can result in delayed pulmonary edema, hypotension, hemoptysis, and methemoglobinemia.

Zinc or aluminum phosphide pellets are often used as rodenticides. When the phosphide pellets come in contact with water, phosphine (PH_3) gas is formed. In addition, PH_3 gas can also be formed during the production of methamphetamine from red phosphorus. Inhalation of PH_3 gas produces near instantaneous symptoms. Toxicity occurs via several mechanisms, including free radical formation, inhibition of cytochrome oxidase, and increased lipid peroxidation. Both pulmonary toxicity and gastrointestinal toxicity can result after exposure to PH_3 gas. Common pulmonary symptoms include cough, chest tightness, and dyspnea, followed later by pulmonary edema and acute lung injury. Vomiting, diarrhea, and abdominal pain are also commonly encountered. Coma, hypotension, renal failure, and various dysrhythmias have been described.[23,24] Treatment is largely supportive. However, there is limited evidence suggesting beneficial effects of intravenous *N*-acetylcysteine and magnesium.[25-27] Given the potential toxicity of aluminum or zinc phosphide and the relatively minimal harm and cost associated with these therapies, the risk/benefit ratio probably favors treatment with these agents.

Phosgene, phosphene, NO_2, nickel carbonyl, diborane, and zinc smoke bombs can cause delayed-onset pulmonary edema. Therefore, patients exposed to these chemicals are best admitted for 24 hours of observation to the hospital of observation unit, even if asymptomatic early on in the clinical course. In addition, chlorine gas, chloramine gas, cadmium, and polymer fume fever can cause delayed pulmonary edema. However, unlike the former group of gases, with which patients can be asymptomatic for hours and then develop pulmonary edema, delayed pulmonary edema is unlikely with chlorine, chloramine, cadmium, and polymer fume fever in the absence of earlier pulmonary symptoms, and asymptomatic individuals who have been exposed to these chemicals therefore do not require prolonged observation.

Chemical Terrorism

Principles

After the terrorist attack on September 11, 2001, the public has become increasingly aware of chemical terrorism. Despite being banned by the 1925 Geneva Convention, chemical weapons have been used in both the military and the civilian arenas for many years, including the decades preceding the September 11 attack. In the 1980s, chemical weapons were employed against Iraqi civilians. In 1995, Aum Shinrikyo, a Japanese cult, released sarin nerve gas in the Tokyo subway, causing 12 deaths and more than 5000 casualties. In 2013, sarin nerve gas was used by military forces in the Syrian civil war. A more complete discussion of chemical and biological weapons are in Chapter 193.

As terrorist organizations continue to use unconventional weapons such as chemical and biologic agents, the civilian medical community needs to better understand their characteristics and pathophysiology.

Response

The United States government recognizes the emerging threat of terrorism and the potential for terrorist organizations to use nonconventional weapons. Appropriate casualty triage remains a critical component of dealing with unconventional weapons. Triage should be performed by specially trained emergency medical personnel who are familiar with these agents and with the use of PPE. The ED could be quickly overwhelmed with masses of noncritically injured survivors. Ideally, triage would be conducted both at the scene of the attack and again at a second point before ED arrival. The greatest challenge for EDs in caring for these individuals is the sudden increase in patients requiring treatment in addition to the day-to-day surge capacity of the hospital.

Chemical Agents

Chemical agents are classified as (1) nerve agents, (2) vesicants, (3) choking agents, or (4) cyanide and related toxins (Table 57.2). The first nerve agent documented was tabun, which was synthesized by German chemist Gerhard Schrader in 1937. Schrader developed tabun (military symbol: GA) while researching new insecticides. The following year, sarin (GB) was created. Other popular nerve agents include soman (GD) and VX. Although nerve agents were stockpiled for use during prior military conflicts, the first documented use in a war was in the 1980s during the Iran-Iraq War. The largest use of nerve agents by terrorists was by the Aum Shinrikyo cult of Japan, which produced both VX and sarin.

Vesicants, also known as *blistering agents,* are a class of drugs that produce blisters at the site of contact. Despite their discovery

TABLE 57.2

Common Gases That Can Be Encountered as Weapons of Mass Destruction

CLASS	EXAMPLE*	TREATMENT
Nerve agents	Tabun (GA) Sarin (GB) Soman (GD) Cyclosarin (GF) VX	Atropine and pralidoxime
Vesicants	Mustard agents Mustard, sulfur mustard (H) Distilled mustard, sulfur mustard (HD) Nitrogen mustard (HN1, HN2, HN3) Organic arsenical agents (eg, lewisite; L) Halogenated oxime agents (eg, phosgene oxime; CX)	Hydrotherapy Moist dressing on blisters Supportive care
Choking agents	Phosgene (CG) Chlorine (CL) Military smoke (HC) Chloropicrin (PS)	Supportive care
Cyanide agents	Hydrogen cyanide	Cyanide kit Amyl nitrite Sodium nitrite Sodium thiosulfate Hydroxocobalamin

*Chemical or common name (military chemical symbol).

in the 1800s, their introduction to warfare did not occur until the 20th century. Since World War I, however, sulfur mustard (also known as *mustard gas, mustard,* or *CAS No. 505-60-2*) has remained a constant threat in modern warfare. Other vesicants include lewisite (dichloro-2-chlorovinylarsine), which is an organic arsenical, and phosgene (dichloroformoxime), which is a halogenated oxime. Although phosgene is often considered a vesicant, it technically is not, as the urticarial lesions that develop following contact are not fluid-filled.

Choking agents have been used in both military and civilian settings. Although there are many different agents and uses, the collective term *choking agent* refers to a chemical that can potentially induce pulmonary edema. Phosgene and chlorine are two agents that were used in World War I. Although chlorine is no longer used as a warfare agent, it is still used widely in the industrial setting. Zinc-containing smoke is another choking agent that is used in conventional warfare. Other agents are used for riot control. These agents were discussed earlier in the Miscellaneous Gases section.

Cyanide agents, such as hydrogen cyanide or sodium azide, are cellular toxins. Cyanide was discovered in the 18th century by the Swedish chemist Carl Wilhelm Scheele. Today, hydrogen cyanide is one of the most toxic chemicals known.

Nerve Agents

Principles

The nerve agents are classified as either "G" agents or "V" agents. The nerve agents are all derived from phosphoric acid and are volatile liquids at room temperature. As such, they must be aerosolized or evaporated to be used as inhalational weapons. Because the vapors are heavier than air, they tend to remain close to the ground and will travel downwind and downhill.

The nerve agents function by affecting acetylcholine (ACh). ACh receptors are found on the postsynaptic receptor of cholinergic synapses. These receptors can be either nicotinic or muscarinic. Activation of the nicotinic receptors results in depolarization of the postsynaptic neuron or skeletal muscle cell, whereas muscarinic activation affects exocrine glands and smooth muscle, primarily in the CNS. Under normal conditions, the enzyme acetylcholinesterase hydrolyzes ACh in the synapse, thereby inactivating ACh. The primary mechanism of action of the nerve agents is to prevent acetylcholinesterase from hydrolyzing ACh. As a result, excess ACh accumulates in the synapse. The effects at the muscarinic receptors include excess secretions and smooth muscle contractions.

Clinical Features

The mnemonics *DUMBELS* (diarrhea, urination, miosis, bronchoconstriction or bronchorrhea, emesis, lacrimation, and salivation) and *SLUDGE* (salivation, lacrimation, urination, defecation, and gastrointestinal emesis) are often used to describe these effects. The nicotinic manifestations include muscle fasciculations and weakness. The primary lethal clinical effects are respiratory and treatment should be aimed at correcting these effects.

Differential Diagnoses

The differential diagnosis of a nerve gas exposure includes gastroenteritis, ischemic bowel, ketoacidosis, pulmonary edema, and reactive airway disease. Other cholinergic agents such as carbamate insecticides and herbicides (eg, paraquat and diquat) are differential diagnosis considerations.

Diagnostic Testing

Plasma and red blood cell cholinesterase levels should be obtained, although they may not return in a timely manner in the ED setting. Patients should also have a chest radiograph, ECG, arterial blood gas, and electrolytes obtained.

Management

Victims of dermal exposure are undressed and thoroughly decontaminated with large-volume, low-pressure irrigation with water. After decontamination, the initial treatment is aimed at maintaining an airway and restoring adequate oxygenation and ventilation. If rapid sequence intubation is desired for airway management, the paralytic succinylcholine should be used with caution because the duration of action will be significantly prolonged as normal degradation will be inhibited by the nerve agent. Atropine is a direct-acting antagonist of the muscarinic receptor. Because atropine does not bind to the nicotinic receptors, all nicotinic effects, including weakness or paralysis, will not be reversed. The initial recommended dose is 2 mg of atropine for adults, although much larger doses will likely be required (2 mg every 5 minutes until desired clinical effect). The endpoint for stopping atropine administration is not improvement in heart rate but, rather, drying of bronchial secretions. Pralidoxime is also administered to patients with suspected or known ingestion with significant symptoms. The traditional dosage of pralidoxime is 30 mg/kg (2 g maximum) intravenously over 30 minutes, followed by a maintenance infusion of 8 to 10 mg/kg/hr (650 mg maximum). Standard doses of benzodiazepines (diazepam 5 to 10 mg intravenous push [IVP] or lorazepam 1 to 2 mg IVP) are recommended to prevent and to treat seizure activity.

For pediatric patients, if accurate weight-based dosage cannot be achieved, children younger than 1 year old can receive 0.5 mg

atropine, whereas children older than 1 year can receive the standard adult dose of 2 mg atropine as a starting dose. As with adults, the subsequent doses should double (eg, 0.5 mg followed by 1 mg, followed by 2 mg) until respiratory secretions are dried.

Disposition

Patients who do not develop any sign of toxicity after a 6-hour observation period can be discharged home. Those with any signs of cholinergic toxicity, respiratory distress, or seizures should be admitted to an intensive care unit.

Vesicants

Principles

At temperatures below 14°C, mustard exists in the solid form. Once in the liquid or gaseous form, mustard gas can be recognized by its unique garlic or fishlike odor. Mustard vapor is also much heavier than air and, as a result, tends to remain close to the ground. When stored as an oil-based liquid, it can be readily aerosolized and attached to a bomb device or shell. Because vaporization occurs slowly, the risk of injury is much greater in cool environments and closed spaces. Several minutes of exposure can result in skin and eye injury, and exposure for more than 30 minutes can lead to respiratory injury and death.

Mustard gas can enter the body after inhalational, dermal, or oral exposures. After entering the body, it functions as an alkylating agent. The altered molecules then interact with proteins and nucleic acids, forming covalent bonds. Mustard is the only vesicant that does not cause immediate pain.

Clinical Features

Several hours after exposure, manifestations of exposure occur. After exposure to aerosolized mustard gas, cutaneous manifestations appear after a latent period of up to 24 hours. Initial dermal symptoms include burning, itching, and erythema, followed by hyperpigmentation, vesicle formation, and, later, bullae. Electrolyte depletion and secondary bacterial infection can occur if the affected body surface area is large. In addition, inhaled mustard gas can lead to vomiting and diarrhea. Myelosuppression can occur within 3 to 5 days of exposure, resulting in leukopenia and thrombocytopenia. Direct mucosal damage in the respiratory tract can occur, resulting in bronchiolar damage and hemorrhage. The systemic manifestations can occur with any route of exposure.

Differential Diagnoses

The primary differential diagnosis includes blistering diseases and cutaneous infections, such as toxic epidermal necrolysis. Burns from any chemical or thermal agent may present with similar dermatological findings.

Diagnostic Testing

A complete blood count should be obtained and reassessed daily for several days to assess for the development of myelosuppression. Those with pulmonary exposure should have a chest radiograph performed. Individuals with gastrointestinal illness should have serum electrolytes measured.

Management

Treatment consists first and foremost of removing the patient from the environment and decontaminating the vesicant. If available, water can be used for decontamination but may not be the preferred agent. Currently, the United States military recommends using an alkaline hypochlorite solution (pH 10 or 11) as the decontamination method of choice; a 0.5% hypochlorite solution (diluted household bleach [1:9]) is another alternative. However, these solutions should not be used on open abdominal or chest wounds. No specific antidote exists. British antilewisite (BAL; 2,3-dimercapto-1-propanol; dimercaprol) was originally developed as an antidote for lewisite. Although BAL is currently available as a chelator for other heavy-metal poisonings (eg, mercury, arsenic), we do not recommend its use for mustard gas poisonings.

Disposition

Patients with extensive exposure to mustard gas should be admitted to the hospital for monitoring, dermal care, fluid resuscitation, and serial assessment for pancytopenia.

Cyanide

Principles

Cyanide salts and hydrocyanic acid are commonly used for metal cleaning, precious metal extraction, photographic processes, electroplating, laboratory assays, and jewelry cleaning. In addition, cyanide gas is often liberated from the combustion of plastic-containing compounds. Iatrogenic cyanide toxicity can result from exposure to cyanogens, including plant or herbal cyanogenic glycosides, nitriles, and nitroprusside. There is growing concern that cyanide may be used as terrorist weapon of mass destruction.

Pathophysiology

Cyanide is a cellular toxin. It binds to both Fe^{3+} and cobalt. By binding and inactivating the enzyme cytochrome oxidase, which is part of cytochrome a3 on the electron transport chain, cyanide inhibits oxidative phosphorylation. This inhibition results in profound cellular hypoxia and death.

Clinical Features

After ingestion of cyanide, patients experience sudden cardiovascular collapse coma and profound metabolic acidosis. A characteristic odor of bitter almonds is frequently discussed but only rarely clinically noted.

Differential Diagnoses

The primary differential diagnosis is hydrogen sulfide and azide gas exposure. Carbon monoxide should be included on the differential diagnosis, and these two conditions may occur simultaneously particularly in house or industrial fires.

Diagnostic Testing

Although cyanide levels are confirmatory, they are rarely immediately available. However, most patients with significant cyanide exposure will have a profound lactic acidosis. In addition, because the cellular utilization of oxygen is blocked, venous blood is highly oxygenated. Therefore, an elevated mixed venous oxygen saturation, or an elevated peripheral venous partial pressure of oxygen (Po_2) may be observed. Cyanide toxicity commonly results in shortening of the QT interval, with subsequent "T-on-R" phenomena. The pulse oximeter reading may be near normal in cyanide toxicity, despite significant cellular hypoxia.

Management

The initial treatment focuses on maintaining adequate oxygenation and vascular perfusion. Standard antiarrhythmic medications are appropriate for the treatment of cyanide-induced cardiac arrhythmias. Vasopressors such as norepinephrine may be required.

First responders should wear PPE when rescuing a patient unresponsive after cyanide gas exposure. Patients with cyanide salts on their skin must have the particulate matter brushed off, followed by topical irrigation; decontamination from other routes of exposure is rarely indicated. Currently, two specific types of antidotes can be used to treat known or suspected cyanide intoxication. One method of treatment involves the administration of amyl nitrite, sodium nitrite, and sodium thiosulfate. With this combination of medications, amyl nitrite pearls are broken open, and the patient is allowed to breathe a pearl for 30 seconds of each minute. A new pearl is needed every 3 or 4 minutes. Once intravenous access has been established, 300 mg of sodium nitrite (one 10-mL ampule of 3% solution for adults and 0.12 to 0.33 mL/kg for children) can be administered. Because sodium nitrite is a potent vasodilator, hypotension can ensue. Therefore the sodium nitrite is administered over a minimum of 5 minutes. After sodium nitrite administration, sodium thiosulfate is administered at a dose of 12.5 g (one 50-mL ampule of a 25% solution for adults and 1.65 mL/kg for children). The function of the nitrites is to induce methemoglobinemia. Thiosulfate enhances transulfuration of hydrogen cyanide to thiocyanate via rhodanese, which is renally excreted. If coexisting carbon monoxide toxicity is suspected, as can occur with smoke inhalation, nitrites should be avoided.

Hydroxocobalamin (Cyanokit) is the most recently introduced antidote for cyanide intoxication. Hydroxocobalamin binds to cyanide to form cyanocobalamin, which subsequently undergoes renal excretion. Hydroxocobalamin appears to be safe for use in both the hospital and the out-of-hospital settings. Emergency clinicians should be made aware that administration may result in a red discoloration of the skin, which is not a true allergic reaction. Its use is also associated with alteration in laboratory measurements of magnesium, iron, aspartate aminotransferase, total bilirubin, and creatinine. In treating a patient for known or suspected cyanide toxicity (even if in combination with carbon monoxide poisoning), sodium thiosulfate and hydroxocobalamin can be safely administered.

Disposition

Patients with a brief exposure without any manifestations of toxicity can be discharged home after an observation period of 6 hours. One notable exception includes those with exposure to agents that get metabolized to cyanide (eg, acetonitrile); individuals with exposure to these agents should be admitted to an intensive care unit for 24 hours. Any patient with metabolic acidosis, coma, or seizures should be admitted to an intensive care unit.

KEY CONCEPTS

- For chemical injury, the degree of skin destruction is determined mainly by the properties of the toxic agent, its concentration, and the duration of its contact.
- Chemical injuries are commonly encountered after exposures to acids and alkalis.
- HazMats are substances that can cause physical injury and can damage the environment if improperly handled.
- In dealing with HazMat incidents, two distinct goals must be achieved: (1) The HazMat must be contained, fire and explosions should eventually be extinguished, and the site must eventually be cleaned, and (2) people exposed to the HazMat must be decontaminated and treated.
- Decontamination consists of removal of contaminated clothing and hydrotherapy (ie, wash the skin) for the majority of exposures. For lithium, potassium, and sodium exposure, hydrotherapy is contraindicated because of the exothermic reaction with contact with water.
- Alkali burns tend to penetrate deeper than acidic burns; as a result, alkali burns tend to be associated with greater morbidity.
- Hydrofluoric acid burns can be associated with significant hypocalcemia.
- Exposure to various toxic gases can occur from routine industrial settings, and knowledge of these agents is necessary for proper treatment by the emergency clinician.
- Unconventional chemical weapons may be categorized into four major classifications: nerve agents, vesicants, choking agents, and cyanide agents.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 57: QUESTIONS & ANSWERS

57.1. A 34-year-old man presents with burning, erythema, and blurred vision after cleaning liquid is splashed in his eye. Which of the following should you do?

A. Be concerned about acidic burn.
B. Be concerned about alkali burn.
C. Postpone irrigation until confirmation of the type of cleaning liquid.
D. Use a miotic agent.
E. Use copious irrigation until a pH of 7.4.

Answer: E. When a chemical injury to the eye is suspected, regardless of the offending agent, copious irrigation should be started immediately. Irrigation with water or normal saline should continue until the pH is at a physiologic level (approximate pH of 7.4). All but the mildest burns should be treated with a long-acting cycloplegic, a mydriatic.

57.2. A patient presents to the emergency department (ED) complaining of severe burning of both hands since leaving her building this morning. In her history, you find out that the metal doors of her housing complex had just been cleaned of all rust. She has small blisters on her palms and a white appearance to the skin. What is the next step?

A. Consult plastics for an alkali burn.
B. Leave blisters, cover with bacitracin and gauze.
C. Mix calcium gluconate with KY jelly, apply to hands and cover with gloves.
D. Obtain pain control and prescribe oral clindamycin.
E. Treat as a second-degree burn.

Answer: C. The rust cleaning and physical findings are descriptive of a hydrofluoric acid burn. It is also commonly used in the production of microelectronics, etching glass, for removing rust, and for cleaning cement and bricks. Calcium gluconate (2.5%) gel is the preferred topical agent. However, this gel is often not available in hospital pharmacies, but it can be made by mixing 3.5 g calcium gluconate powder in 150 mL of a water-soluble lubricant. The gel should be secured by an occlusive cover, such as a latex glove.

57.3. In a hydrofluoric burn, what electrolyte abnormality causes systemic manifestations contributing to this chemical's significant morbidity and mortality?

A. Hypercalcemia
B. Hypermagnesemia
C. Hypocalcemia
D. Hypokalemia
E. Hyponatremia

Answer: C. Hydrofluoric acid binds calcium and magnesium ions with strong affinity. Systemic manifestations of fluoride toxicity are at least partly related to hypocalcemia and include abdominal pain, muscle fasciculations, nausea, seizures, ventricular dysrhythmias, and cardiovascular collapse. Of note, hyperkalemia is often a terminal finding in fatal cases.

57.4. A 29-year-old man presents by emergency medical services confused and hypoxic. Vitals signs are blood pressure 100/70 mm Hg, heart rate 120 beats/min, respiratory rate 22 breaths per minute, and an oxygen saturation of 83% despite 100% oxygen via non–rebreathing mask. The arterial blood gas is reported as venous. You see the syringe and note that the color is a chocolate brown. Which of the following should be the next step?

A. Determine the methemoglobin level and prepare methylene blue
B. Methylene blue intravenously
C. Sodium thiosulfate intravenously
D. Urine assessment for "vin rose" coloration
E. Wood's lamp to aid in the diagnosis

Answer: A. The patient is suffering from methemoglobinemia. For those symptomatic patients without glucose-6-phosphate dehydrogenase (G6PD) deficiency, 2 mL/kg of 1% methylene blue can be administered over 3 to 5 minutes. Symptoms typically improve within 20 minutes. Severe cases can be treated with exchange transfusion. Candidates for exchange transfusion include those with G6PD with significant toxicity from methemoglobinemia or those patients who fail to respond to methylene blue.

57.5. A 21-year-old man presents to the emergency department (ED) with chronic shortness of breath and a "huffer's rash." The patient has dry, cracked skin with perioral pyoderma. The cause of these symptoms is most likely which of the following?
A. Anhydrous ammonia
B. Cyanide
C. Hydrocarbons
D. Nitrites
E. White phosphorous

Answer: C. The toxicity from hydrocarbons can affect many different organs, but the lungs are the most commonly affected organ. The toxicity is directly related to the volatility and inversely related to the viscosity and surface tension. Chronic dermal exposure to hydrocarbons can result in perioral or perinasal dermatitis with pyoderma. This so-called "huffer's rash" is primarily seen with recreational abuse.

57.6. Nerve agent poisoning may be rapidly fatal. Beside appropriate decontamination, which of the following should be administered?
A. British anti-Lewisite 2 mg/kg intramuscularly
B. Methylene blue 2 mg/kg intravenously
C. *N*-acetylcysteine 140 mg/kg orally
D. Pralidoxime 600 mg intramuscularly
E. Pyridostigmine 1 mg intravenously

Answer: D. Nerve agents work by affecting acetylcholine (ACh) levels via inhibition of acetylcholinesterase. ACh receptors are found on the postsynaptic receptor of cholinergic synapses. These receptors can be either nicotinic or muscarinic. The effects at the muscarinic receptors include excess secretions and smooth muscle contractions. The initial recommended treatment is 2 mg of atropine for adults, although much larger doses will likely be required. Pralidoxime should also be administered to patients with suspected or known ingestion with significant symptoms. This agent potentially helps prevent irreversible inhibition of the acetylcholinesterase enzyme.

57.7. A 31-year-old man was found in his apartment after an apparent suicide attempt. He smells of bitter almonds. He is obtunded with hypotension, tachypnea, and normal oxygen saturation. After decontamination and resuscitation, what is the next step?
A. Atropine
B. Hydroxocobalamin
C. Methylene blue
D. Naloxone
E. Sodium thiosulfate

Answer: B. This patient likely has cyanide poisoning. One method of treatment involves the administration of amyl nitrite, sodium nitrite, and sodium thiosulfate. The U.S. Food and Drug Administration (FDA) approved hydroxocobalamin (Cyanokit) for treatment of cyanide intoxication. Hydroxocobalamin binds to cyanide to form cyanocobalamin, which subsequently undergoes renal excretion.

CHAPTER 58

Sexual Assault

Judith A. Linden | Ralph J. Riviello

PRINCIPLES

The term *sexual violence* includes rape and sexual assault. Depending on state statutes, rape is generally defined by three characteristics: (1) penetration of an orifice (mouth, vagina, or anus) however slight; (2) by a penis, body part, or object; and (3) with the threat or use of force or incapacitation. *Sexual assault* is a broader term and includes unwanted touching or fondling of sexual or genital anatomy or forced involvement in or viewing of pornography. According to the 2010 Centers for Disease Control and Prevention (CDC) National Intimate Partner and Sexual Violence Survey (NISVS), 1 in 5 women and 1 in 71 men have been victims of actual or attempted sexual assault in their lifetimes, with 1.3 million women in the United States reporting having been raped in the previous year.[1] Nationally representative data on nonfatal injury-related emergency department (ED) visits has revealed that 4.2% of all assault-related visits to the ED were for sexual assault. Most of these victims were women. The lifetime prevalence of sexual assault for women presenting to the ED for any reason has been shown to be 39%.[3] Male victims are often younger than 9 years; female victims are most likely to be ages 10 to 19 years. Given the prevalence and role that emergency clinicians play in evaluating victims of sexual assault, emergency clinicians should be comfortable evaluating, treating, and coordinating their care. In many areas, specialized sexual assault teams or forensic examiners are available to assist with care and forensic evidence collection. The care team often includes an emergency nurse, rape crisis advocate, and/or social worker and may involve the local police, sexual assault detective(s), and forensic examiner. The emergency clinician's responsibilities include responding in a compassionate and nonjudgmental manner, diagnosing and treating acute injuries and administering medications to prevent pregnancy and sexually transmitted infections (STIs), offering forensic evidence and comprehensive toxicology testing when appropriate, and providing linkages to support and follow-up services.[4]

The ED evaluation and treatment of the rape victim can take hours and requires the coordination of multiple resources. Evaluation and treatment of the rape victim has medical, legal, and forensic aspects. Medical stabilization and evaluation should always take priority over forensic evaluation. It is not the emergency clinician's responsibility to determine if a rape occurred; this is the role of a jury at trial. The role of the emergency clinician is to record objectively information heard, observed, examined, or photographed. In many cases, a trained forensic examiner will be available to complete the forensic evidence collection process. Even years after the event, the emergency clinician may be called to testify in the event of a trial, necessitating thorough and accurate documentation.

CLINICAL FEATURES

Many sexual assaults are never reported to police or health care providers.[5] Victims who report to the police and who sustain injuries are more likely to present to the ED for evaluation.[5] Many victims present with concerns about injuries, risk of pregnancy, or contracting STIs (including human immunodeficiency virus [HIV]). Victims may present with mental health concerns, including depression, anxiety, and suicidal ideation. Acquaintance and intimate partner rape is less commonly reported to police and health care providers.[3,1] When these victims do present to the ED, they are more likely to present in a delayed manner, when medications to decrease pregnancy rates and STI transmission are less likely to be effective. Most patients who present to the ED with the complaint of sexual assault are women.[2,6] Although some studies have reported a similar age distribution for males and females, others have noted that males are assaulted at a younger age (<12 years).[7] Populations at increased risk for sexual assault include the homeless, those with severe disabilities (eg, serious injury, chronic disease, chronic mental health problems), incarcerated men and women, and the young.[1,8,9] Other populations at increased risk include college-aged women (especially freshman), nonheterosexuals, those who use drugs and alcohol, and sex workers.[8,10-13]

Patients who come to the ED with the complaint of sexual assault or rape may present with injuries related to the assault, with general body injuries in up to 67%.[7,14] It is not uncommon to have minimal or no genital injury from a rape. Genital findings depend on time to presentation, victim's age, virginal status and parity, and methods used to evaluate for genital injury (see later, "Medical Forensic Examination").[14-18] Nonfatal strangulation, associated with rape, carries a risk of immediate and delayed psychological and medical sequelae, including airway obstruction, pulmonary edema, and vascular dissection leading to stroke. Nonfatal strangulation has also been associated with an increased risk of future lethality (eg, in intimate partner rape).[19]

Rape can occur in the context of force or coercion (forcible rape) or in the context of drug or alcohol ingestion (alcohol or drug-facilitated rape [AOD-FR]). About 50% of all rapes are in the context of alcohol or drug ingestion, especially in the adolescent or college-aged population. Alcohol or drugs may have been ingested voluntarily by the victim or administered surreptitiously by the assailant. Comprehensive toxicology testing should be considered in those presenting within the specific jurisdiction's time limits (usually within 72–96 hours).

Acute reactions to the experience of sexual assault vary and are influenced by prior sexual assaults or trauma, events surrounding the assault, and preexisting mental health conditions. Victims may appear calm and collected, detached, or be agitated, angry,

depressed, tearful, or anxious. Anger may be directed outwardly toward health care providers, making interactions between the patient and provider challenging. Rape crisis advocates are helpful in supporting the patient and in helping victims understand that their reaction is a normal reaction to a very abnormal and traumatizing event.

The neurochemical changes in the brain that occur in response to trauma can make recall of details surrounding the assault difficult.[20] Recall may be sporadic and disorganized but may become clearer with time and should not be construed as fabrication. Recent research has focused on the concept of tonic immobility, whereby the victim experiences paralysis, increased muscular rigidity, eye closing, and suppressed vocal cord activity in response to an extremely traumatic event. This phenomenon has been well documented in many nonhuman species. Increasing evidence has suggested that humans may respond this way to a life-threatening event when coupled with inescapability.[21] Although tonic immobility may occur in any traumatic event, it is more common in victims of childhood sexual assault. Victims who report tonic immobility often experience increased feelings of guilt and are at increased risk of developing posttraumatic stress disorder (PTSD).[22,23] These victims are also less likely to respond to pharmacologic therapy.[24,25]

DIAGNOSTIC CONSIDERATIONS

Differential Diagnosis

The purpose of the medical forensic sexual assault examination is to document history and physical findings and collect evidentiary material; it is not to determine whether or not a rape occurred. Final diagnosis and discharge instructions should avoid the words "rule out" and "alleged." Options may include "evaluation following sexual assault," "sexual assault," and "reported sexual assault." According to published studies, approximately 53% to 71% of sexual assault victims sustain nongenital injuries.[7,26-28] Fortunately, injuries are usually minor and rarely require emergent medical or surgical intervention. Most injuries are from blunt trauma and include contusion, laceration, incised wound, bruise, hematoma, sprain or strain, fracture, closed head injury, intracerebral injury, and intra-abdominal injury. Treatment of life-threatening injuries should follow advanced trauma life support (ATLS) and trauma protocols and takes precedence over evidence collection.

Diagnostic Testing

There are no specific diagnostic tests for sexual assault. Traumatic injuries should be evaluated as per standard protocols. There is no test that can determine if a rape occurred; even visualization of sperm on wet mount by emergency clinicians is notoriously inaccurate[7,29]

Sexually Transmitted Infections

Testing for STIs is controversial in adult sexual assault patients.[30] Despite rape shield laws prohibiting the use of a victim's past sexual behavior in court cases, there remains concern that the presence of a preexisting STI may be used to discredit the victim's claim. Furthermore, STI prophylaxis is provided to rape victims and will treat any preexisting STIs. Proponents for testing cite public health concerns; identifying preexisting disease allows for notification of contacts.[31] In children, the presence of an STI can be conclusive proof of a sexual assault, and STI testing is recommended. We recommend testing adults for STIs if the patient complains of STI signs or symptoms or when the patient requests testing. We recommend routinely testing children and young adolescents.

Alcohol- or Drug-Facilitated Rape

Comprehensive toxicology testing, often performed in specialized forensic laboratories, is recommended in cases of suspected AOD-FR and can test for over 150 illicit and over-the-counter substances. The most commonly detected substances include ethanol, cannabinoids, cocaine, amphetamines, and benzodiazepines.[32] Box 58.1 lists symptoms and conditions suspicious for AOD-FR. Because many substances have a short half-life, toxicologic testing should be performed expeditiously; most protocols obtain specimens up to 72 to 96 hours postassault or after ingestion. Many jurisdictions have specific collection requirements and kits that are sent to comprehensive crime laboratories. At least 100 mL of urine and 12 mL of blood (sodium fluoride tube) should be collected and specimens refrigerated, with chain of custody carefully maintained (Fig. 58.1).

Evaluating the Victim of Attempted Strangulation

Strangulation is a serious and potentially life-threatening method used to gain power and control over another person. In intimate

BOX 58.1

Indications for Comprehensive Toxicology Screening

- Period of unconsciousness
- Period of loss of motor control
- Amnesia or confused state with suspicion of sexual assault
- Patient suspicion or belief that she or he was drugged prior to or during sexual assault
  And
- Less than 72–96 hours since assault (depending on jurisdictional protocol)

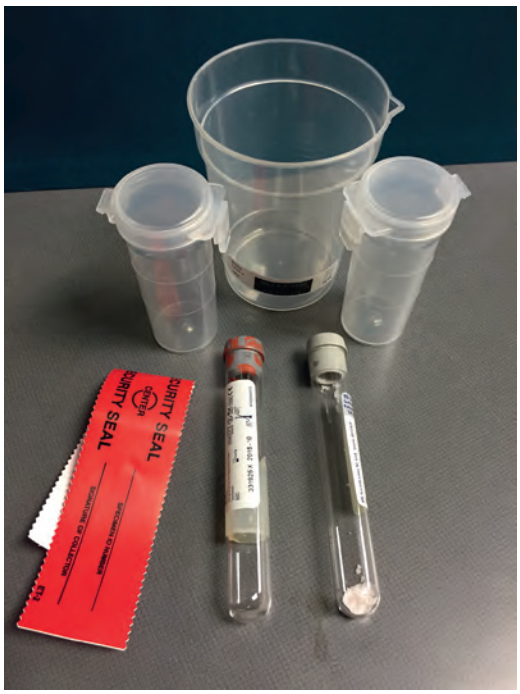


Fig. 58.1. Example of a forensic toxicology test kit for urine and serum specimens.

partner violence survivors, nonfatal strangulation has a sevenfold increased risk of future attempted and completed homicide.[19] Hypoxia is the final common pathway in strangulation and can occur by three main mechanisms—jugular vein occlusion, carotid artery occlusion, or laryngeal occlusion. Symptoms of dysphagia and odynophagia may accompany physical findings, including facial, neck, and periorbital petechiae (Fig. 58.2) and subconjunctival hemorrhages, the result of venous occlusion causing increased intravessel pressure and rupture. Other possible findings include bruising on the neck in the shape of fingerprints (Fig. 58.3) and defensive scratch marks on the neck from the victim attempting to pry off the assailant's fingers (Fig. 58.4). Alteration in consciousness, neurologic complaints, and urinary and fecal incontinence may result from restricted blood flow to the brain. Direct laryngeal injury may lead to vocal cord injury and laryngeal or hyoid fractures. Carotid artery injury, dissection, or intraluminal thrombosis may cause stoke symptoms, which may not present until months or years after the assault.[33,34]

Imaging should be considered for patients with facial petechiae, loss of consciousness, incontinence, stroke symptoms, or voice changes. Imaging modalities and strategies for patient evaluation are listed in Tables 58.1 and 58.2.[35-37] We recommend a number of diagnostics tests, including a chest x-ray to evaluate for early pulmonary edema and aspiration pneumonitis, flexible laryngoscopy to evaluate the glottic and supraglottic airways, and computed tomography angiography (CTA) or magnetic resonance

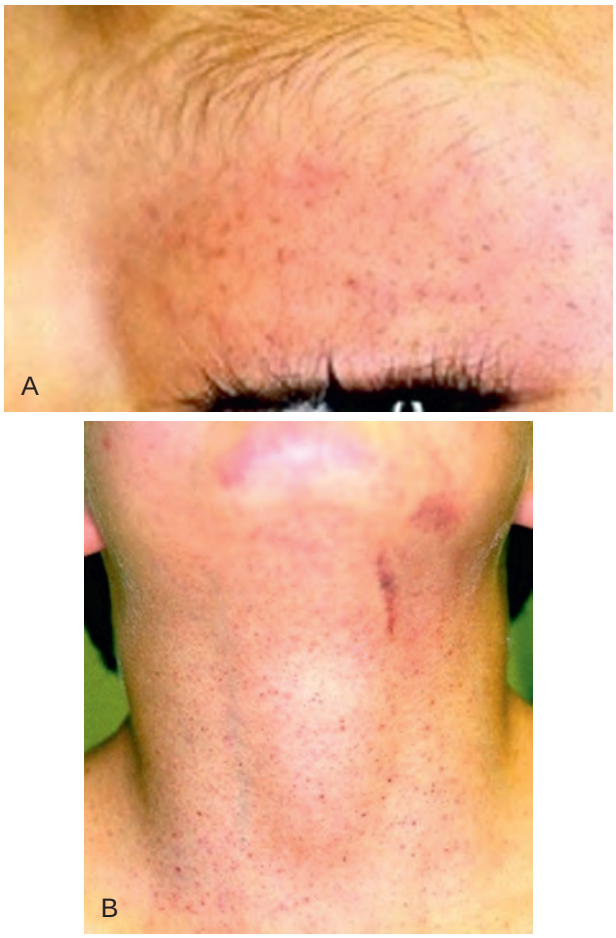


Fig. 58.2. Petechiae in nonfatal strangulation. **A,** Eyelid petechiae following the nonfatal strangulation of a child. **B,** Neck petechiae seen in the same patient in **A**. There is also an abrasion present on the left side of the neck and ecchymosis of the left and right mandibles. (Courtesy Training Institute on Strangulation Prevention, San Diego, CA; used with permission.)

Fig. 58.3. Neck bruising in nonfatal strangulation. **A,** Circular neck bruising following manual strangulation. This injury is referred to as a fingertip bruise. **B,** Other bruises of the neck in the same patient, most likely made by the assailant's fingers.

Fig. 58.4. Claw marks in nonfatal strangulation. The patient caused these injuries as she attempted to pry the assailant's hands off of her neck. (Courtesy Training Institute on Strangulation Prevention, San Diego, CA; used with permission.)

TABLE 58.1

Imaging Modalities in Nonfatal Strangulation

MODALITY	INDICATIONS	ADVANTAGES	DISADVANTAGES
Plain radiograph (bone technique)	Visualize cervical vertebral fracture	Readily available in the emergency department (ED)	Limited information provided because C-spine fractures are rare
Plain radiograph (soft tissue technique)	Tracheal injury (subcutaneous emphysema, edema, tracheal deviation) Hyoid fractures	Readily available in the ED	Low sensitivity in detecting these rare signs of deep soft tissue and laryngeal injury Hyoid bone fracture is rare.
Computed tomography (CT)	Soft tissue and laryngeal injuries Neuroimaging (brain)	Readily available in the ED High sensitivity Easy to perform	May need IV contrast
CT angiography (CTA)	Carotid artery injury, dissection, or thrombosis	Readily available in the ED High sensitivity	Requires IV contrast
Magnetic resonance imaging (MRI)	Soft tissue injuries of the neck and airway	Highest sensitivity	Not readily available Expense
Doppler US	Visualize intimal injury (dissection) or thrombosis of carotid artery	Readily available in the ED Portable for unstable patients	Less sensitive for carotid injury and/or thrombosis
Fiberoptic laryngoscopy	Visualize vocal cords and adjacent structures	Sensitive for vocal cord and laryngeal injury	Availability depends on institution

TABLE 58.2

Imaging Strategy for Nonfatal Strangulation*

SCENARIO AND FINDINGS	RECOMMENDED MODALITY	ALTERNATIVE MODALITY
No loss of consciousness, no physical complaints	None	None
No loss of consciousness but voice changes	Four-vessel cervicocranial CT angiography with fiberoptic laryngoscopy	Magnetic resonance imaging (MRI) with contrast
Loss of consciousness and physical findings of force to the neck (eg, bruising, petechiae)	Four-vessel cervicocranial CT angiography	MRI without contrast
Persistent unconsciousness	Four-vessel cervicocranial CT angiography	MRI without contrast
Intact consciousness with unilateral neurologic findings	Four-vessel cervicocranial CT angiography	Doppler ultrasound of the carotid artery—four-vessel angiography

*Imaging modality chosen will vary based on institution-specific protocols and availability of imaging modalities.

imaging (MRI) to evaluate for arterial dissection (most commonly, carotid).[35,36] Patients with persistent unconsciousness, laryngeal fracture, carotid injury, or neurologic symptoms should be admitted to the intensive care unit for close monitoring. Patients with reported loss of consciousness, incontinence, facial or conjunctival petechiae, or signs and symptoms of soft tissue neck injury, or who are under the influence of drugs or alcohol, should be admitted to the hospital or observed for 12 to 24 hours and monitored for delayed symptoms of injury. Patients with no loss of consciousness, minimal to no physical findings, no intoxication, and a safe discharge environment can be discharged home with instructions to watch for late development of complications.

MANAGEMENT

Management of the sexually assaulted patient requires an organized victim-centered and trauma-informed approach, defined by institutional protocols and available support resources. In most cases, a sexual assault forensic examiner (SAFE) or sexual assault nurse examiner (SANE) will perform the evidentiary examination. Hospitals should have a protocol concerning the activation of the SAFE team. If there is no SAFE team available at the hospital, the American College of Emergency Physicians supports the triage of medically stable sexual assault victims to designated examination facilities for evidence collection by specially educated and clinically trained personnel.[38]

On arrival to the ED, the sexual assault patient should be rapidly triaged and placed in a private area or examination room. Other sexual assault response team (SART) members should be mobilized—SANE, social worker, and rape crisis medical advocate. Depending on department protocol, the patient may or may not be evaluated by the emergency clinician. If the emergency clinician sees the patient, it is important to keep the history brief. The goal of the history is to rule out potentially serious injury, determine which medications are needed for prophylaxis, and decide if the patient is in the time limit for evidence collection. Some questions include the following:

- When did it happen?
- What types of assault occurred?
- Where did penetration occur?
- Were any objects used during the assault?
- Have there been symptoms since the assault?
- Was there loss of memory, incoordination, or suspicion for drug-facilitated sexual assault?

As with any ED patient, providers should elicit the patient's medical problems, medications, past medical history, and last menstrual period.

Medical Forensic Examination

The medical forensic examination should proceed in an organized and coordinated fashion, and the patient should be informed of all steps of the process. The examination can be conducted up to 7 days following assault, depending on jurisdiction policy, with most using 5 days as a cutoff.[39] In cases of oral and anal assault, evidence is usually not collected more than 24 hours after the assault. In vaginal assaults, DNA and sperm can be recovered from the cervix up to 120 hours later. Evidence is collected using a jurisdictionally specific sexual assault evidence kit or physical evidence recovery kit (rape kit). This kit contains all the supplies necessary to collect and properly store recovered evidence (Fig. 58.5).

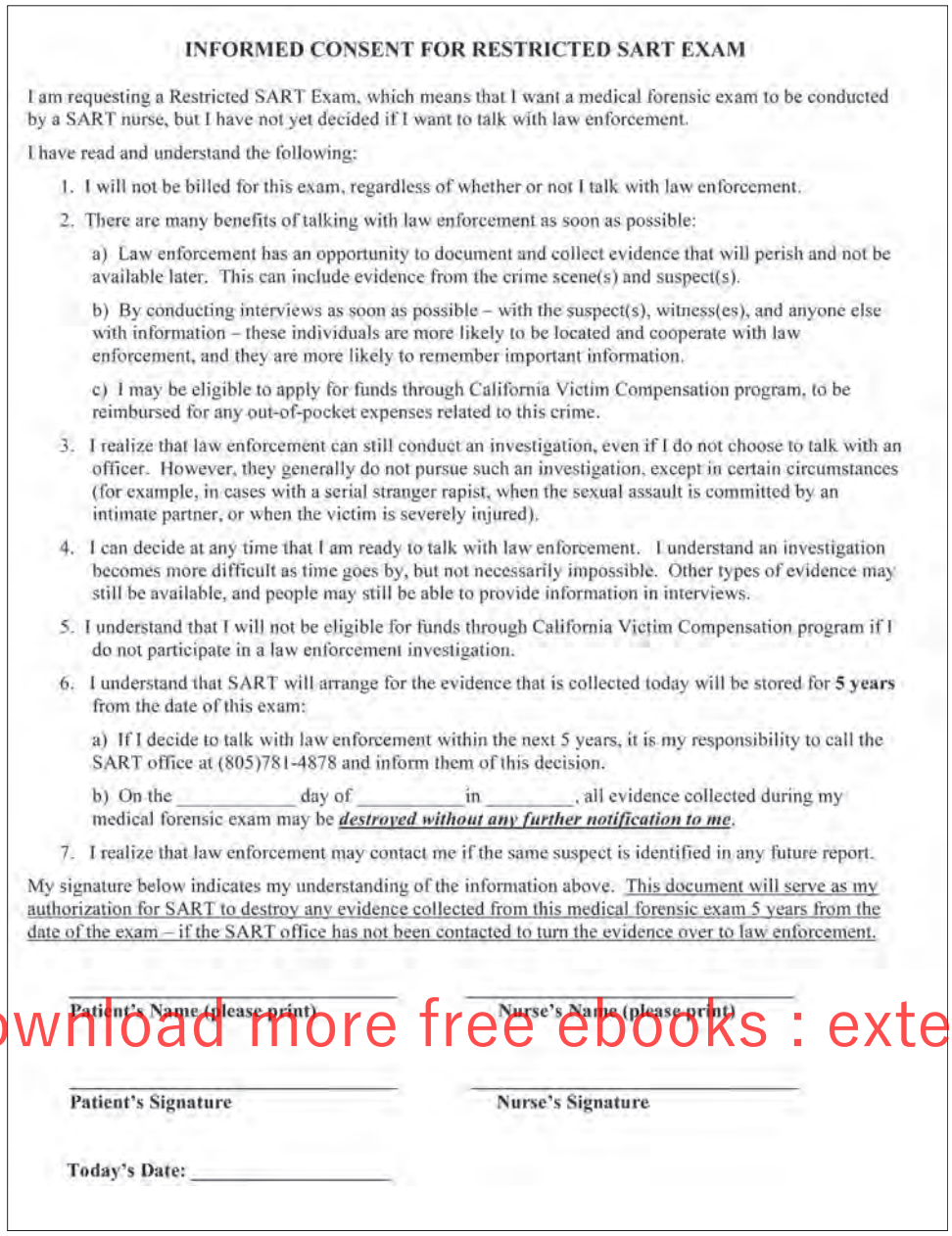
The patient should consent to the examination and collection of evidence and for evidence (and photographs) to be turned over to law enforcement (Fig. 58.6). The patient has the right to decline any or all parts of the examination and can revoke or change that consent at any time during the process. This is his or her decision and right; this should be reinforced to the victim who may have a sense of powerlessness after a sexual assault. The consent process begins with the forensic examiner explaining the purpose of the examination, steps, and process involved. The forensic examination process should proceed only after the patient has a thorough understanding of the examination process and has consented. The Violence Against Women Act (VAWA) of 1994 created and supports comprehensive, cost-effective responses to sexual, domestic, and dating violence. This act provides financial support for state, tribal, and territory service provision, as well as a grants program. Any state that receives VAWA funding is required to provide a rape examination while not requiring the patient to report to the police. Many jurisdictions have policies that allow the victim to have evidence collected and stored for a given amount of time, leaving the victim the option to report to the police at a later date. Also, the VAWA program ensures that patients are not required to pay for the services provided; with its most recent reauthorization, it improved services for all victims, especially immigrants, lesbian, gay, bisexual, and transgender (LGBT) victims, Native American women, college students and youth, and public housing residents.

Questions regarding consent are often complex, especially when the victim is a minor, intellectually disabled, or incapacitated by drugs or alcohol. In the case of the minor who is unable to legally consent (due to age), the doctrine of the mature minor (one who has been supporting himself or herself, is a parent, or is in the armed forces, depending on state statutes) may allow the minor to consent without guardian notification. In many states, the minor who is in danger of having been exposed to pregnancy or an STI can also consent. If the minor does not assent to examination, SAFE programs should not force the patient to undergo the examination because the minor has the right to determine what happens to her or his body. Additionally, an examination cannot be forced at the request of a parent or guardian. A discussion with the guardian regarding the detrimental effects of forcing an examination on the child, and the inability of the examination to determine if an assault occurred, will often help assuage the situation. For the person unable to give consent due to mental health, psychological, or neurologic conditions, consent should be obtained from a guardian or legally authorized representative. In the case of the patient who is temporarily incapacitated due to drugs or alcohol, the examination can be delayed until the effects of the intoxicants have worn off and the patient is able to consent. In patients unable to give consent for a prolonged period of time (eg, severe head injury or requiring intubation), the decision to proceed with a medical forensic examination is complicated because lack of patient consent may be perceived as a further violation. Because many patients would desire evidence collection if incapacitated, and because there is a limited window of time for collection, institutional protocols should be crafted to address these specific scenarios.[40] At some institutions, the physician or family member or guardian can consent to evidence collection on behalf of the patient. In these situations, evidence is collected (as an anonymous kit) and held until the patient is competent to decide on reporting. Institutional legal counsel and ethics consults should be used when protocols have not been established.

Documentation of the forensic examination should occur on jurisdiction-specific forms that have preprinted questions often included in the rape kit and kept separate from the patient's medical record (Fig. 58.7). The medical forensic examination begins with the forensic history, followed by physical examination, documentation of injuries, and evidence collection (including photographs). Key features of the forensic history are detailed in Box 58.2. The examination should proceed in a head to toe fashion, with the more intrusive parts (eg, pelvic and rectal areas) examined at the end. Each part of the body is uncovered, one area at a time, to maintain as much modesty as possible. Each jurisdiction has a standard protocol for the sequence of evidentiary collection, modified by elements of the history. Table 58.3 highlights potential steps during the forensic examination and describes the technique for each step. Some jurisdictions may require additional steps (eg, a wet mount to look for motile sperm and for slides to be made in addition to swabs). For victims who were unconscious or cannot remember specifics of the assault, oral, external genital, vaginal, cervical, anal and rectal, neck, and breast swabs should be obtained because these areas have a higher likelihood of DNA recovery.

A recent study of over 2000 victims found that 27% sustained an anogenital injury[26]; historically, the literature reports a rate of 16% to 81%.[14-18,27] Anogenital injuries are usually seen at the posterior fourchette, fossa navicularis, and hymen (see Fig. 58.8 for diagrams and terminology of female genitalia). Injuries are documented using the face of a clock, with 12:00 representing anterior and 6:00 representing posterior injuries. Although genital injury can occur in up to 10% to 52% of women after consensual intercourse, sexual assault victims are more likely to have multiple injuries, abrasions, and a higher frequency of lesions beyond the posterior genital area.[16-18,41,42] The mnemonic TEARS (***t***ears/cuts, ***e***cchymosis, ***a***brasions, ***r***edness, and ***s***welling) can been used to describe specific findings (Figs. 58.9 to 58.12).[15] The Genital

Fig. 58.5. Physical evidence recovery kit. This is an example of a commercially available physical evidence recovery kit (rape kit) used to collect, package, and store evidence. The kit can be customized to each jurisdiction's protocols and needs. (Courtesy Massachusetts Sexual Assault Nurse Examiner Program.)



INFORMED CONSENT FOR RESTRICTED SART EXAM

I am requesting a Restricted SART Exam, which means that I want a medical forensic exam to be conducted by a SART nurse, but I have not yet decided if I want to talk with law enforcement.

I have read and understand the following:

1. I will not be billed for this exam, regardless of whether or not I talk with law enforcement.
2. There are many benefits of talking with law enforcement as soon as possible:
   a) Law enforcement has an opportunity to document and collect evidence that will perish and not be available later. This can include evidence from the crime scene(s) and suspect(s).
   b) By conducting interviews as soon as possible – with the suspect(s), witness(es), and anyone else with information – these individuals are more likely to be located and cooperate with law enforcement, and they are more likely to remember important information.
   c) I may be eligible to apply for funds through California Victim Compensation program, to be reimbursed for any out-of-pocket expenses related to this crime.
3. I realize that law enforcement can still conduct an investigation, even if I do not choose to talk with an officer. However, they generally do not pursue such an investigation, except in certain circumstances (for example, in cases with a serial stranger rapist, when the sexual assault is committed by an intimate partner, or when the victim is severely injured).
4. I can decide at any time that I am ready to talk with law enforcement. I understand an investigation becomes more difficult as time goes by, but not necessarily impossible. Other types of evidence may still be available, and people may still be able to provide information in interviews.
5. I understand that I will not be eligible for funds through California Victim Compensation program if I do not participate in a law enforcement investigation.
6. I understand that SART will arrange for the evidence that is collected today will be stored for **5 years** from the date of this exam:
   a) If I decide to talk with law enforcement within the next 5 years, it is my responsibility to call the SART office at (805)781-4878 and inform them of this decision.
   b) On the _____ day of _____ in _____, all evidence collected during my medical forensic exam may be ***destroyed without any further notification to me***.
7. I realize that law enforcement may contact me if the same suspect is identified in any future report.

My signature below indicates my understanding of the information above. This document will serve as my authorization for SART to destroy any evidence collected from this medical forensic exam 5 years from the date of the exam – if the SART office has not been contacted to turn the evidence over to law enforcement.

Patient's Name (please print) **Nurse's Name (please print)**

Patient's Signature **Nurse's Signature**

Today's Date: _____

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Fig. 58.6. Sample consent form for a medical forensic examination. *SART,* Sexual assault response team.

Injury Severity Scale (GISS) is another available instrument that uses gross visualization, colposcopy, and toluidine blue staining. Variables include five types of injuries—swelling, color change, tissue break, hymen and introitus injury, toluidine blue dye uptake—and two classes of severity—tissue integrity intact and disrupted.[43,44] The GISS can help distinguish sexual assault patients from consensual intercourse subjects based on type and class of injury. In a cohort of sexual assault victims, 40% had class B or tissue-disrupted injuries versus 10% in the consensual group. Although not commonly used in clinical practice by emergency clinicians, the GISS has been validated in defining and measuring external genital injury after sexual intercourse and is most commonly used by sexual assault experts.[44]

General Principles of Evidence Collection

Gloves should be worn during collection, processing, and packaging of evidence and should be changed in between each step of evidence collection to avoid cross-contamination of evidence. Clothing that has been ripped or torn or shows other signs of force should be collected, taking care not to cut through existing holes or tears. Areas of clothing with possible DNA (including underwear not worn at the time of assault, but put on later) should also be collected. Clothing and other evidence should be placed in paper bags because plastic promotes mold and bacteria growth and can destroy DNA evidence. If a piece of evidence is wet when collected, the package should be labeled as such, and the police or crime laboratory be made aware of this so that they can dry and repackage the evidence. A minimum of two swabs should be taken when swabbing an area, allowing the crime laboratory to save one swab for future analysis by the defense's laboratory. In general, wet stains should be collected with a dry swab or cotton tipped applicator; dry stains are collected with a swab moistened with sterile or distilled water. For dried specimens and bite marks, a double-swab technique is performed. First, the area is swabbed in a rolling fashion with a moistened swab, and then a dry one is rolled over the area. All swabs should be allowed to dry by air, using a

Text continued on p. 748

FORENSIC MEDICAL REPORT: ACUTE (<72 HOURS)
ADULT/ADOLESCENT SEXUAL ASSAULT EXAMINATION

STATE OF CALIFORNIA
California Emergency Management Agency

CalEMA 2-923

Confidential Document **Patient Identification**

A. GENERAL INFORMATION (print or type)

Name of Medical Facility:

1. Name of patient — Patient ID number

2. Address — City — County — State — Telephone (W) (H)

3. Age	DOB	Gender M F	Ethnicity	Arrival Date	Arrival Time	Discharge Date	Discharge Time

B. REPORTING AND AUTHORIZATION

Jurisdiction (☐city ☐county ☐other):

1. Telephone report made to law enforcement agency — Name of Officer — Agency — ID Number — Telephone — Reported by: Name — Date — Time

2. Responding Officer — Agency — ID Number — Telephone

3. I request a forensic medical examination for suspected sexual assault at public expense.

Law enforcement officer — ID number — Agency

Telephone — Date — Time — Case Number

Telephone Authorization
Agency:
Authorizing party:
ID number:
Date/time:

C. PATIENT INFORMATION

- I understand that hospitals and health care professionals are required by Penal Code Sections 11160-11161 to report to law enforcement authorities cases in which medical care is sought when injuries have been inflicted upon any person in violation of any state penal law. The report must state the name of the injured person, current whereabouts, and the type and extent of injuries. _____ (Initial)
- I have been informed that victims of crime are eligible to submit crime victim compensation claims to the State Victims of Crime (VOC) Restitution Fund for out-of-pocket medical expenses, psychological counseling, loss of wages, and job retraining and rehabilitation. _____ (Initial)

D. PATIENT CONSENT

Minors: Family Code Section 6927 permits minors (12 to 17 years of age) to consent to medical examination, treatment, and evidence collection for sexual assault without parental consent. See instructions for parental notification requirements for minors.

- I understand that a forensic medical examination for evidence of sexual assault at public expense can, with my consent, be conducted by a health care professional to discover and preserve evidence of the assault. If conducted, the report of the examination and any evidence obtained will be released to law enforcement authorities. I understand that the examination may include the collection of reference specimens at the time of the examination or at a later date. I understand that I may withdraw consent at any time for any portion of the examination. _____ (Initial)
- I understand that collection of evidence may include photographing injuries and that these photographs may include the genital area. _____ (Initial)
- I hereby consent to a forensic medical examination for evidence of sexual assault. _____ (Initial)
- I understand that data without patient identity may be collected from this report for health and forensic purposes and provided to health authorities and other qualified persons with a valid educational or scientific interest for demographic and/or epidemiological studies. _____ (Initial)

Signature _____ ☐ Patient ☐ Parent ☐ Guardian

DISTRIBUTION OF CalEMA 2-923

☐ Original - Law Enforcement ☐ Copy within evidence kit - Crime Lab ☐ Copy - Child Protective Services (if patient is a minor) ☐ Copy - Medical Facility Records

CalEMA 2-923 (Rev 7/02) 1

E. PATIENT HISTORY

1. Name of person providing history: — Relationship to patient: — Date — Time

2. Pertinent medical history:
- Last menstrual period _____
- Any recent (60 days) anal-genital injuries, surgeries, diagnostic procedures, or medical treatment that may affect the interpretation of current physical findings? ☐ No ☐ Yes
  If yes, describe: _____
- Any other pertinent medical condition(s) that may affect the interpretation of current physical findings? ☐ No ☐ Yes
  If yes, describe: _____
- Any pre-existing physical injuries? ☐ No ☐ Yes
  If yes, describe: _____

3. Pertinent pre- and post-assault related history:

	No	Yes	Unsure
• Other intercourse within past 5 days?	☐	☐	
If yes,			
anal (within past 5 days)? When _____	☐	☐	
vaginal (within past 5 days)? When _____	☐	☐	
oral (within past 24 hours)? When _____	☐	☐	
If yes, did ejaculation occur?	☐	☐	☐
If yes, where? _____			
If yes, was a condom used?	☐	☐	☐
• Any voluntary alcohol use within 12 hours prior to assault?	☐	☐*	
• Any voluntary drug use within 96 hours prior to assault ?	☐	☐*	
• Any voluntary drug or alcohol use between the time of the assault and the forensic exam?	☐	☐*	

* If yes, collection of toxicology samples is recommended according to local policy. ☐ Blood ☐ Urine

4. Post-assault hygiene/activity: ☐ Not applicable if over 72 hours

	No	Yes
Urinated	☐	☐
Defecated	☐	☐
Genital or body wipes	☐	☐
If yes, describe: _____		
Douched	☐	☐
If yes, with what _____		
Removed/inserted tampon☐ diaphragm☐	☐	☐
Oral gargle/rinse	☐	☐
Bath/shower/wash	☐	☐
Brushed teeth	☐	☐
Ate or drank	☐	☐
Changed clothing	☐	☐
If yes, describe: _____		

5. Assault-related history:	No	Yes
Loss of memory? If yes, describe:	☐	☐*
Lapse of consciousness? If yes, describe:	☐	☐*
*If yes, collection of toxicology samples is recommended according to local policy. ☐Blood ☐Urine		
Vomited? If yes, describe:	☐	☐
Non-genital injury, pain and/or bleeding? If yes, describe:	☐	☐
Anal-genital injury, pain, and/or bleeding? If yes, describe:	☐	☐

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Patient Identification

F. ASSAULT HISTORY

1. Date of assault(s): — Time of assault(s):

2. Pertinent physical surroundings of assault(s):

3. Alleged assailant(s) name(s)	Age	Gender	Ethnicity	Relationship to patient: Known	Relationship to patient: Unknown
#1.		M F			
#2.		M F			
#3.		M F			
#4.		M F			

4. Methods employed by assailant(s):

	No	Yes	If yes, describe:
Weapons	☐	☐	
Threatened?	☐	☐	
Injuries inflicted?	☐	☐	
Type(s) of weapons?	☐	☐	
Physical blows	☐	☐	
Grabbing/holding/pinching	☐	☐	
Physical restraints	☐	☐	
Choking/strangulation	☐	☐	
Burns (thermal and/or chemical)	☐	☐	
Threat(s) of harm	☐	☐	
Target(s) of threat(s)	☐	☐	
Other methods	☐	☐	

Involuntary ingestion of alcohol/drugs ☐No ☐Yes ☐Unsure

If yes, ☐ Alcohol ☐ Drugs

If yes, ☐ Forced ☐ Coerced ☐ Suspected

If yes, toxicology samples collected: ☐ Blood ☐ Urine ☐ None

5. **Injuries inflicted upon the assailant(s) during assault?** ☐No ☐Yes
If yes, describe injuries, possible locations on the body, and how they were inflicted.

Fig. 58.7. A-D, Sample chart to document the medical forensic examination. (From www.caloes.ca.gov/GrantsManagementSite/Documents/2-923%20Form%20Forensic%20Medical%20Report,%20Acute-Adolescent%20Sexual%20Assault%20Examination.pdf.)

Continued

G. ACTS DESCRIBED BY PATIENT

- **Any penetration of the genital or anal opening, however slight, constitutes the act.**
- **Oral copulation requires only contact**
- **If more than one assailant, identify by number.**

Patient Identification

	No	Yes	Attempted	Unsure
1. Penetration of vagina by:				
Penis	☐	☐	☐	☐
Finger	☐	☐	☐	☐
Object	☐	☐	☐	☐
If yes, describe the object:				
2. Penetration of anus by:				
Penis	☐	☐	☐	☐
Finger	☐	☐	☐	☐
Object	☐	☐	☐	☐
If yes, describe the object:				
3. Oral copulation of genitals:				
Of patient by assailant	☐	☐	☐	☐
Of assailant by patient	☐	☐	☐	☐
4. Oral copulation of anus:				
Of patient by assailant	☐	☐	☐	☐
Of assailant by patient	☐	☐	☐	☐
5. Non-genital act(s):				
Licking	☐	☐	☐	☐
Kissing	☐	☐	☐	☐
Suction injury	☐	☐	☐	☐
Biting	☐	☐	☐	☐
6. Other act(s):	☐	☐	☐	☐

Describe:

	No	Yes	Unsure
7. Did ejaculation occur?	☐	☐	☐

If yes, note location(s):
- ☐ Mouth
- ☐ Vagina
- ☐ Anus/Rectum
- ☐ Body surface
- ☐ On clothing
- ☐ On bedding
- ☐ Other

Describe:

	No	Yes	Unsure
8. Contraceptive or lubricant products:			
Foam used?	☐	☐	☐
Jelly used?	☐	☐	☐
Lubricant used?	☐	☐	☐
Condom used?	☐	☐	☐

Describe Type/Brand, if known:

H. GENERAL PHYSICAL EXAMINATION

Record all findings using diagrams, legend, and a consecutive numbering system.

1. Blood Pressure	Pulse	Resp	Temp	2. Exam Started Date	2. Exam Started Time	Exam Completed Date	Exam Completed Time

3. Describe general physical appearance	4. Describe general demeanor

Patient Identification

5. Describe condition of clothing upon arrival.

6. Collect outer and underclothing if indicated. ☐ Not Indicated

7. Conduct a physical examination. ☐ Findings ☐ No Findings

8. Collect dried and moist secretions, stains, and foreign materials from the body. Scan the entire body with a Wood's Lamp.
☐ Findings ☐ No Findings

9. Collect fingernail scrapings or cuttings according to local policy.

Diagram A

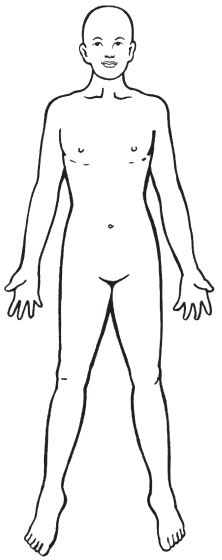
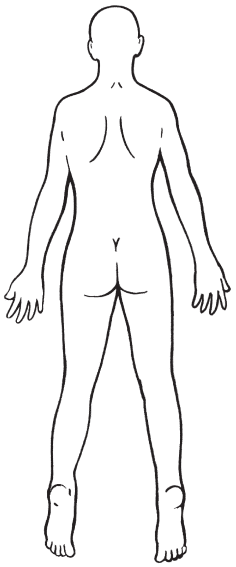


Diagram B



LEGEND: Types of Findings

AB	Abrasion	**DF**	Deformity	**FB**	Foreign Body	**MS**	Moist Secretion	**PE**	Petechiae	**TB**	Toluidine Blue ⊕
BI	Bite	**DS**	Dry Secretion	**IN**	Induration	**OF**	Other Foreign Materials (describe)	**PS**	Potential Saliva	**TE**	Tenderness
BU	Burn	**EC**	Ecchymosis (bruise)	**IW**	Incised Wound			**SHX**	Sample Per History	**V/S**	Vegetation/Soil
CS	Control Swab	**ER**	Erythema (redness)	**LA**	Laceration	**OI**	Other Injury (describe)	**SI**	Suction Injury	**WL**	Wood's Lamp ⊕
DE	Debris	**F/H**	Fiber/Hair					**SW**	Swelling		

Locator #	Type	Description	Locator #	Type	Description

RECORD ALL CLOTHING AND SPECIMENS COLLECTED ON PAGE 8

Fig. 58.7, cont'd.

I. HEAD, NECK, AND ORAL EXAMINATION

Record all findings using diagrams, legend, and a consecutive numbering system.

1. **Examine the face, head, hair, scalp, and neck for injury and foreign materials** ☐ Findings ☐ No Findings
2. **Collect dried and moist secretions, stains, and foreign materials from the face, head, hair, scalp, and neck.** ☐ Findings ☐ No Findings
3. **Examine the oral cavity for injury and foreign materials (if indicated by assault history). Collect foreign materials.** **Exam done:** ☐ Not applicable ☐ Yes ☐ Findings ☐ No Findings
4. **Collect 2 swabs from the oral cavity up to 12 hours post assault and prepare one dry mount slide from one of the swabs.**
5. **Collect head hair reference samples according to local policy.**

Patient Identification

Diagram C

Diagram D

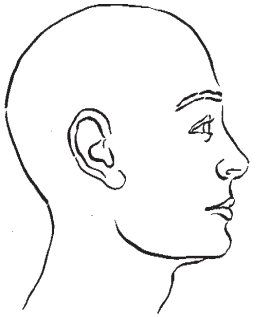


Diagram E

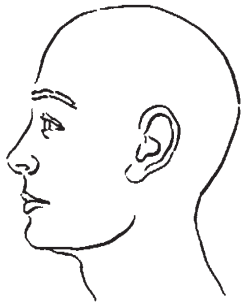
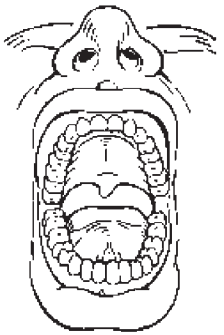


Diagram F



LEGEND: Types of Findings

AB Abrasion	**DF** Deformity	**FB** Foreign Body	**MS** Moist Secretion	**PE** Petechiae	**TB** Toluidine Blue ⊕
BI Bite	**DS** Dry Secretion	**IN** Induration	**OF** Other Foreign Materials (describe)	PS Potential Saliva	**TE** Tenderness
BU Burn	**EC** Ecchymosis (bruise)	**IW** Incised Wound		**SHX** Sample Per History	**V/S** Vegetation/Soil
CS Control Swab	**ER** Erythema (redness)	**LA** Laceration	**OI** Other Injury (describe)	**SI** Suction Injury	**WL** Wood's Lamp ⊕
DE Debris	**F/H** Fiber/Hair			**SW** Swelling	

Locator #	Type	Description	Locator #	Type	Description

RECORD ALL SPECIMENS COLLECTED ON PAGE 8

J. GENITAL EXAMINATION - FEMALES

Record all findings using diagrams, legend, and a consecutive numbering system.

1. **Examine the inner thighs, external genitalia, and perineal area. Check the box(es) if there are assault related findings:**
   ☐ No Findings
   ☐ Inner thighs ☐ Periurethral tissue/urethral meatus
   ☐ Perineum ☐ Perihymenal tissue (vestibule)
   ☐ Labia majora ☐ Hymen
   ☐ Labia minora ☐ Fossa navicularis
   ☐ Clitoris/surrounding area ☐ Posterior fourchette
2. **Collect dried and moist secretions, stains, and foreign materials. Scan the area with a Wood's Lamp.** ☐ Findings ☐ No Findings
3. **Collect pubic hair combing or brushing.**
4. **Collect pubic hair reference samples according to local policy.**
5. **Examine the vagina and cervix. Check the box(es) if there are assault related findings.** ☐ No Findings ☐ Vagina ☐ Cervix
6. **Collect 4 swabs from the vaginal pool. Prepare one wet mount slide and one dry mount slide.**
7. **Collect 2 cervical swabs (if over 48 hours post assault).**
8. **Examine the buttocks, anus, and rectum (if indicated by history).** **Exam done:** ☐ **Yes** ☐ **Not applicable**
   Check the box(es) if there are assault related findings:
   ☐ No Findings
   ☐ Buttocks ☐ Anal verge/folds/rugae
   ☐ Perianal skin ☐ Rectum
9. **Collect dried and moist secretions, stains, and foreign materials.** ☐ Findings ☐ No Findings
10. **Collect 2 anal and/or rectal swabs and prepare one dry mount slide.**
11. **Conduct an anoscopic exam if rectal injury is suspected or if there is any sign of rectal bleeding.**
    Rectal bleeding ☐ No ☐ Yes
    If yes, describe:_____
12. **Exam position used:**
    ☐ Supine ☐ Other Describe:

LEGEND: Types of Findings

AB Abrasion	**EC** Ecchymosis (bruise)	**MS** Moist Secretion	**SI** Suction Injury
BI Bite	**ER** Erythema (redness)	**OF** Other Foreign Materials (describe)	**SW** Swelling
BU Burn	**F/H** Fiber/Hair		**TB** ToluidineBlue⊕
CS Control Swab	**FB** Foreign Body	**OI** Other Injury (describe)	**TE** Tenderness
DE Debris	**IN** Induration	**PE** Petechiae	**V/S** Vegetation/Soil
DF Deformity	**IW** Incised Wound	**PS** Potential Saliva	**WL** Wood's Lamp⊕
DS Dry Secretion	**LA** Laceration	**SHX** Sample Per History	

Locator #	Type	Description

RECORD ALL SPECIMENS COLLECTED ON PAGE 8

Patient Identification

Diagram G

Diagram H

Diagram I

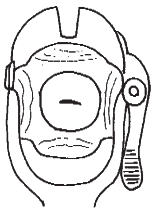


Diagram J

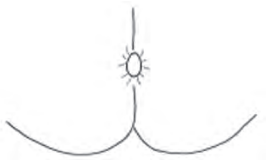


Fig. 58.7, cont'd.

Continued

K. GENITAL EXAMINATION – MALES

Record all findings using diagrams, legend, and a consecutive numbering system.

1. **Examine the inner thighs, external genitalia, and perineal area. Check the box(es) if there are assault related findings:**
   ☐ No Findings
   ☐ Inner thighs ☐ Glans penis ☐ Scrotum
   ☐ Perineum ☐ Penile shaft ☐ Testes
   ☐ Foreskin ☐ Urethral meatus
2. **Circumcised:** ☐ No ☐ Yes
3. **Collect dried and moist secretions, stains, and foreign materials. Scan the area with a Wood's Lamp.** ☐ Findings ☐ No Findings
4. **Collect pubic hair combing or brushing.**
5. **Collect pubic hair reference samples according to local policy.**
6. **Collect 2 penile swabs, if indicated by assault history.** ☐ N/A
7. **Collect 2 scrotal swabs, if indicated by assault history.** ☐ N/A
8. **Examine the buttocks, anus, and rectum (if indicated by history)**
   Exam done: ☐ **Yes** ☐ **Not applicable**
   Check the box(es) if there are assault related findings:
   ☐ No Findings
   ☐ Buttocks ☐ Anal verge/folds/rugae
   ☐ Perianal skin ☐ Rectum
9. **Collect dried and moist secretions, stains, and foreign materials.**
   ☐ Findings ☐ No Findings
10. **Collect 2 anal and/or rectal swabs and prepare one dry mount slide.**
11. **Conduct an anoscopic exam if rectal injury is suspected or if there is any sign of rectal bleeding.**
    Rectal bleeding: ☐ No ☐ Yes
    If yes, describe: _____
12. **Exam position used:**
    ☐ Supine ☐ Other Describe:

LEGEND: Types of Findings

AB Abrasion	**EC** Ecchymosis (bruise)	**MS** Moist Secretion		**SI** Suction Injury	
BI Bite	**ER** Erythema (redness)	**OF** Other Foreign Materials (describe)		**SW** Swelling	
BU Burn	**F/H** Fiber/Hair			**TB** ToluidineBlue⊕	
CS Control Swab	**FB** Foreign Body	**OI** Other Injury (describe)		**TE** Tenderness	
DE Debris	**IN** Induration	**PE** Petechiae		**V/S** Vegetation/Soil	
DF Deformity	**IW** Incised Wound	**PS** Potential Saliva		**WL** Wood's Lamp⊕	
DS Dry Secretion	**LA** Laceration	**SHX** Sample Per History			

Locator #	Type	Description

RECORD ALL SPECIMENS COLLECTED ON PAGE 8

Patient Identification

Diagram K

Diagram L

Diagram M

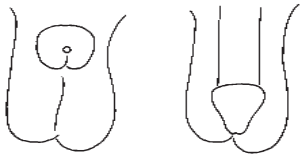
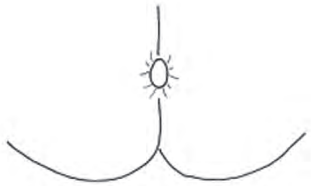


Diagram N



L. EVIDENCE COLLECTED AND SUBMITTED TO CRIME LAB

1. Clothing placed in evidence kit	Other clothing placed in bags

2. Foreign materials collected

	No	Yes	Collected by:
Swabs/suspected blood	☐	☐	
Dried secretions	☐	☐	
Fiber/loose hairs	☐	☐	
Vegetation	☐	☐	
Soil/debris	☐	☐	
Swabs/suspected semen	☐	☐	
Swabs/suspected saliva	☐	☐	
Swabs/Wood's Lamp⊕ area(s)	☐	☐	
Control swabs	☐	☐	
Fingernail scrapings/cuttings	☐	☐	
Matted hair cuttings	☐	☐	
Pubic hair combings/brushings	☐	☐	
Intravaginal foreign body	☐	☐	
If yes, describe: _____			
Other types	☐	☐	
If yes, describe:			

3. Oral/genital/anal/rectal samples

	# Swabs	# Slides	Time collected	Collected by:
Oral				
Vaginal				
Cervical				
Anal				
Rectal				
Penile				
Scrotal				

Aspirate/washings (optional) ☐ No ☐ Yes

4. Vaginal wet mount slide

	No	Yes	Time	Examiner:
Slide prepared				
Motile sperm observed				
Non-motile sperm observed				

M. TOXICOLOGY SAMPLES

	No	Yes	Time	Collected by:
Blood alcohol/toxicology (gray top tube)				
Urine toxicology				

N. REFERENCE SAMPLES

	No	Yes	Collected by:
Blood (lavender top tube)			
Blood (yellow top tube)			
Blood card (optional)			
Buccal swabs (optional)			
Saliva swabs			
Head hair			
Pubic hair			

O. PHOTO DOCUMENTATION METHODS

	No	Yes	Colposcope/ 35mm	Macrolens/ 35mm	Colposcope/ Videocamera	Other Optics
Body	☐	☐	☐	☐	☐	☐ _____
Genitals	☐	☐	☐	☐	☐	☐ _____

Photographed by:

Patient Identification

P. RECORD EXAM METHODS

	No	Yes		No	Yes
Direct visualization only	☐	☐	Toluidine Blue Dye	☐	☐
Colposcopy	☐	☐	Anoscopic exam	☐	☐
Other magnifier	☐	☐	Anal speculum exam	☐	☐
Other	☐	☐			

If yes, describe: _____

Q. RECORD EXAM FINDINGS

☐ **Physical Findings** ☐ **No Physical Findings**

R. RECORD ASSESSMENT OF FINDINGS

☐ Exam consistent with history
☐ Exam inconsistent with history

S. SUMMARIZE FINDINGS

T. PRINT NAMES OF PERSONNEL INVOLVED

History taken by:	Telephone:
Exam performed by:	
Specimens labeled and sealed by:	
Assisted by: ☐ N/A	
Signature of examiner	License No.

U. EVIDENCE DISTRIBUTION

	GIVEN TO:
Clothing (item[s] not placed in evidence kit)	
Evidence kit	
Reference blood samples	
Toxicology samples	

V. SIGNATURE OF OFFICER RECEIVING EVIDENCE

Signature: _____

Print name and ID #: _____

Agency: _____

Date: Phone:

Fig. 58.7, cont'd.

BOX 58.2

Important Historical Information for the Medical Forensic Examination[a]

PATIENT HISTORY
- Pertinent past medical history
- Last consensual intercourse[b]—when? with whom? areas penetrated? ejaculation?
- Voluntary drug or alcohol use

ASSAULT HISTORY
- Date?
- Time?
- Surroundings?
- Assailant(s)?
- Involuntary drug or alcohol ingestion
- Genital and nongenital injury, pain, bleeding?
- Loss of memory?
- Loss of consciousness?
- Vomiting?
- Injury inflicted on assailant? consumption?

METHODS USED BY ASSAILANT
- Weapons—type? use? injury?
- Physical blows—slapping? hitting? punching?
- Grabbing, holding, pinching
- Threats of harm
- Physical restraints
- Choking/strangulation
- Burns
- Targets of threat

VICTIM POSTASSAULT HYGIENE, ACTIVITY
- Urinated
- Defecated
- Genital, body wipes
- Douched
- Removed, inserted tampon
- Removed, inserted diaphragm
- Ate
- Drank
- Gargled
- Brushed teeth
- Changed clothes
- Washed clothes

ASSAULT ACTS[c]
- Vaginal penetration—penis? object? finger?
- Oral penetration—penis? object? finger?
- Anal penetration—penis? object? finger?
- Oral copulation of genitals—of patient by assailant? of assailant by patient?
- Oral copulation of anus—of patient by assailant? of assailant by patient?
- Nongenital acts—biting? sucking? licking? kissing? locations?
- Did ejaculation occur? location?
- Contraception or lubricant used—foam? jelly? lubricant? condom?

[a]These questions should only be asked by emergency clinician if they are performing the entire medical forensic examination, including evidence collection.
[b]This information is needed for uploading the DNA profile into CODIS, so as not to confuse DNA from a consensual partner.
[c]Yes, no, attempted, or unsure answer choices.

TABLE 58.3

Steps in Sexual Assault Evidence Collection Kit

STEP	TECHNIQUE
Clothing collection	Collect clothing the patient wore during the assault. • Have the patient disrobe on a sheet laid on the floor. Keep clothing articles separate. • Place each item of clothing in a paper bag; label and seal. • Fold the sheet and package the same way.
Debris collection	Scan the body from head to toe looking for potential evidentiary materials • Document findings and collect objects using tweezers, tape, or lint roller. • Package each piece separately in an envelope; label and seal.
Biologic evidence	Scan the body for potential biologic material and fluids and bite or suck marks. • Use an alternate light source, location guided by patient history. • Use swab to collect evidence, air-dry, package, label, and seal.
Fingernail evidence	Obtain evidence from the fingernails if applicable. • Use rosewood stick, broken tongue blade, or moistened swab to scrape beneath the nails. • Nail clippers can be used to cut the nails. • Package, label, and seal.
Pubic hair combings	Obtain foreign material from pubic hair. • Place collection sheet under the buttocks. • Use plastic comb to comb through hair toward the sheet. • If pubic hair is absent or trimmed, a lint roller may be used. • Package sheet and comb, label, and seal.
Pubic hair pulling (painful, abandoned by most protocols)	To obtain reference DNA on patient: • Pull pubic hairs, trying to obtain the root. • Package, label, and seal.

Continued

TABLE 58.3

Steps in Sexual Assault Evidence Collection Kit—cont'd

STEP	TECHNIQUE
Head hair pulling (painful, abandoned by most protocols)	To obtain patient reference DNA • Pull head hair strands from different parts of the scalp to try to obtain the root. • Package, label, and seal.
External genital examination and swabs	Obtain biologic evidence from the external GU sites—vulva and perineum— while inspecting for injury. • Use retraction and separation technique to look for evidence of genital injury. • Use moistened swabs to swab the areas. • If matted pubic is hair present, use scissors to cut the matted section. • Package, label, and seal.
Internal genital swabs	Obtain biologic evidence from internal GU sites—vagina and cervix—to assess for genital injury. • Use swabs to collect fluid and evidence from the posterior fornices. • Collect any foreign object, such as a tampon or condom. • Insert swab into cervix and gently twirl. • Obtaining STI cultures is done at this time. • Package, label, and seal.
Anal examination and swabs	Obtain biological evidence from the anus/rectum and to assess for injury • Gently retract the anus with slow steady pressure to allow natural dilation, and inspect for injury. • Gently insert swabs and twirl. • An anoscope can be used to assess for injury. • Package, label, and seal.
DNA reference sample	Obtain a DNA reference sample. • As per protocol, collect a blood or buccal swab sample.
General principles	• Two sterile cotton-tipped swabs are used simultaneously to collect samples. One will be used for the crime laboratory, and one is available for the defense, if requested. • Dry swabs are used to collect evidence from moist areas; swabs moistened with control sterile water are used to collect evidence from dry areas. • Swabs are air-dried, placed back in the sleeves, and then placed in an envelope. • All evidence is placed in paper (not plastic) because moisture may cause mold growth and destroy DNA.

GU, Genitourinary; *STI,* sexually transmitted infection.

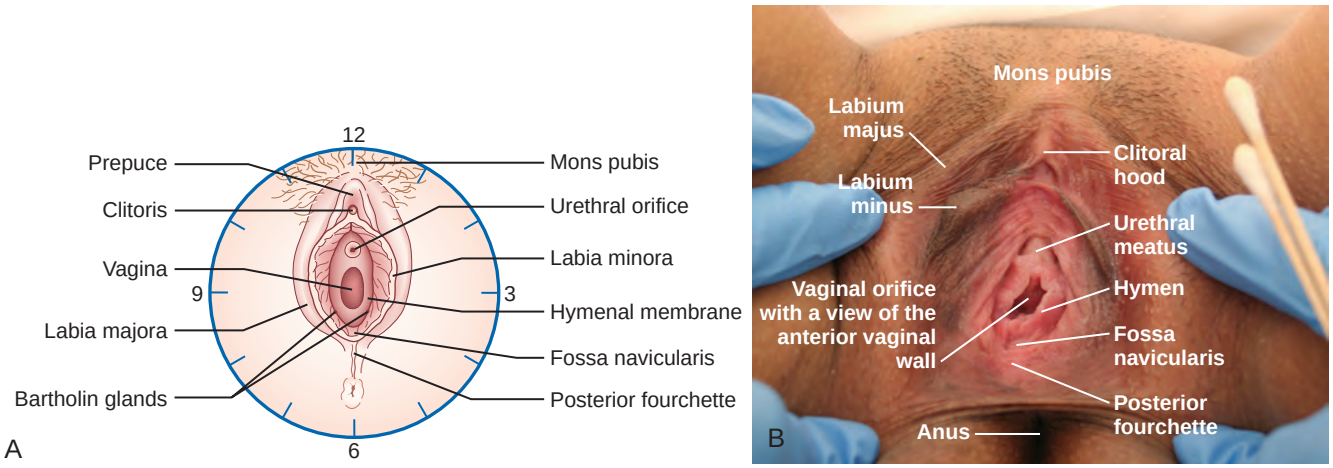


Fig. 58.8. Female genitalia. **A,** Anatomy of the female external genitalia with the clock positions used in documentation. **B,** Actual photograph highlighting the relative anatomy of the female external genitalia important in a medical forensic examination. (From Roberts JR, Custalow CB, Thompsen TW: Roberts and Hedges' clinical procedures in emergency medicine, ed 6, Philadelphia, 2013, Elsevier Saunders.)

desiccant pack, or in a swab dryer. The evidence is packaged into envelopes once the examination is completed, and all swabs have dried. The completed evidentiary collection kit is labeled and sealed and, while maintaining chain of custody, stored according to departmental policy or turned over to law enforcement.

The chain of custody describes the path that the evidence takes once it is collected from the body and ensures that the evidence was not tampered with or mishandled. Failure to maintain the chain of custody calls into question validity of the evidence and may make it inadmissible in court. Chain of custody documentation should describe how the evidence was handled and include a log of those who have had contact with it. The medical forensic examination form or rape kit will typically contain chain of custody forms (Fig. 58.13).

Special Techniques

Colposcopy. This is a diagnostic procedure to illuminate, magnify, and photograph or digitally record external and internal genital structures. Having widespread application in gynecology, the colposcope microscopically improves gross visualization. The colposcope has a 4× to 30× magnification and can be equipped with a still or video camera. Colposcopy is superior to gross visualization for detecting anogenital injuries. Most SAFE programs routinely use colposcopy in their evaluations. Limitations of colposcopy include the cost and size of the instrument, as well as the technical training required for its use. Because of this, several programs use digital photography alone to detect and document genital injury. Although no study has directly compared

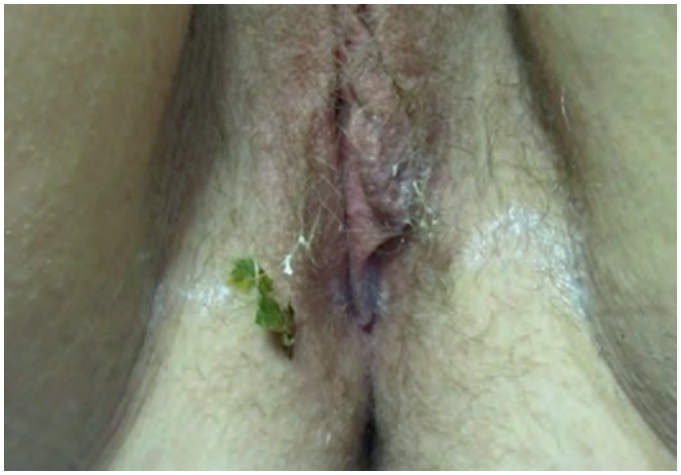
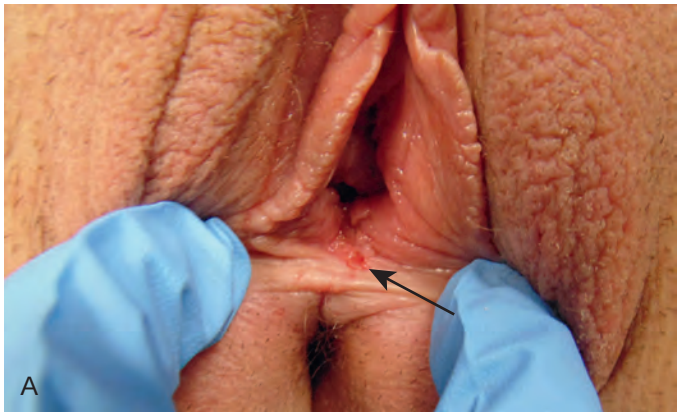


Fig. 58.9. Examination of the external genitalia. This illustrates foreign debris (presumed semen and piece of paper) on the external genitalia of a rape victim.

Fig. 58.10. External genitalia injury. Shown are marked swelling and ecchymosis of the right labia major, inguinal area, and buttocks in a middle-aged woman following sexual assault by a single perpetrator.



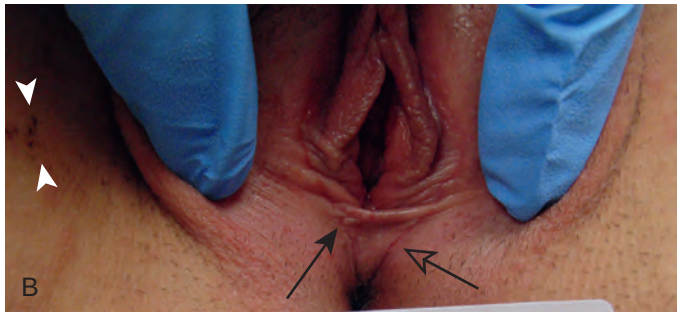


Fig. 58.11. External genitalia injury. **A,** Tear and abrasion at the 6 o'clock position of the fossa navicularis. **B,** *Closed arrow* is abrasion to the posterior fourchette at 6:30. *Open arrow* is abrasion of the perineum (anterior to the rectum). *Arrowheads* are abrasion and ecchymosis of right medial thigh. **C,** The patient in this picture sustained multiple tears and abrasions. There is a large linear tear extending from the fossa navicularis through the posterior fourchette and onto the perineum all in the midline. There are also tears bilaterally on the labia minora, three at the 7 o'clock position and two at the 5 o'clock position.

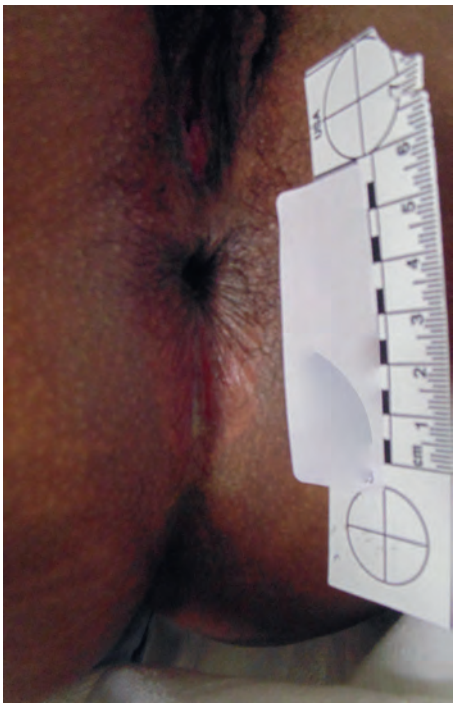


Fig. 58.12. Anal injury. There is a linear anal abrasion and tear at the 6 o'clock position with the patient in the lithotomy position.

colposcopy to digital photography for detecting injury, we recommend colposcopy when available.

Toluidine Blue Dye. Toluidine blue dye (TBD) is a stain that adheres to nuclei in damaged epithelial cells and has not been shown to interfere with DNA testing. Zink and colleagues have demonstrated that more tears were identified with TBD enhancement by direct visualization and colposcopy.[45] The dye should be applied prior to speculum insertion because the speculum may introduce genital injury.[46] The dye is applied to the external genitalia and then gently wiped with surgical lubricant, 1% acetic acid solution, or baby wipes to remove excess solution (Figs. 58.14 and 58.15), which can lead to false-positive findings.

Alternate Light Source. An alternate light source (ALS) uses ultraviolet light to fluoresce biologic material. In sexual assault examinations, the ALS is used to scan the body and genitalia for areas of fluorescence that can be swabbed and submitted for potential DNA identification. Semen and saliva fluoresce under an ultraviolet (UV) light wavelength of 450 nm (range, 390–500 nm). Although the ALS is sensitive for semen, it is not specific. False-positive ALS results may be seen with hand cream, powder, body gel, laundry detergent, fabric softeners, soaps, and other ointments and creams. However, physician training can improve the ability to distinguish semen from other substances (eg, hand cream, soap, bacitracin). A Wood's lamp, which emits UV light at wavelengths less than 390 nm, is a poor substitute for an ALS device and is thus not recommended for routine use in detecting biologic evidence.[47,48]

SPECIAL POPULATIONS

Older Adult Sexual Assault

From 2005 to 2010, the National Crime Victimization Survey reported 0.2/1000 cases of rape or sexual assault occurred in women aged 65 years and older.[49] Older persons may be at risk for sexual assault due to neurologic or cognitive disease, physical disabilities, frailty, and institutionalized living arrangements. In one study, older victims reported verbal threats more frequently.[27] Postmenopausal women are thought to be at particular risk for genital injury due to atrophy of connective tissue, loss of tissue elasticity, and atrophy of vaginal epithelium.

Studies have shown mixed results regarding the severity of genital injury. A recent study of 122 postmenopausal women found that 37% suffered a genital injury compared to 17% of premenopausal women; although postmenopausal women had similar rates of extragenital injury, they were more likely to have sustained large bruises.[27] The locations of the genital injuries are similar to those of younger victims, but older victims tend to have more anogenital lacerations and abrasions.[26,27] The medical forensic examination of the older victim should proceed in the same manner as for other victims. The history may be difficult due to neurologic or cognitive impairment in the victim. Patient positioning may be more challenging due to physical disabilities; the typical dorsal lithotomy position may not be possible, and other positions (left lateral Sim's, lateral recumbent, and dorsal recumbent) may be needed for victim comfort (Fig. 58.16). Prophylaxis against STIs and HIV infection should be offered while considering potential medication interactions. Older victims can also suffer major psychological trauma, including PTSD and rape trauma syndrome and should be referred to rape crisis center services.

Male Sexual Assault

Male sexual assaults occur in straight, homosexual, and bisexual individuals, college students, prisoners, military personnel, gang members, and institutionalized individuals. According to the 2010 NISVS, 40% of gay men, 47% of bisexual men, and 21% of heterosexual men in the United States have experienced sexual violence other than rape at some point in their lives.[1] Males are raped by men or women, tend to underreport their rape, and seek medical services much less frequently than females.[50] Compared to women, males tend to be of a similar age (20–30 years), report more forcible penetration (52% anal, 15% oral, and 33% both), have more anal trauma and injury, suffer more object and digital penetration, have multiple assailants, have more weapons used, and know their assailant(s) less often. Male sexual assault includes forced oral copulation or vaginal and anal penetration of the victim or assailant. Male victims may ejaculate during the assault due to fear and physical stimulation.[50] This can cause increased feelings of guilt and shame and can often be used to argue in a court of law that the victim was a willing participant.

The forensic history and physical examination proceed in a similar fashion to that for a female victim. During the physical examination, attention is paid to the oral cavity, penis and scrotum, and anus and rectum. See Fig. 58.17 for a diagram of the terminology for male genitalia. Swabs should be taken from the oral cavity, external genitals, and anus. When swabbing the genitals, attention should be paid to all parts of the penis, including the base of the penis and anterior scrotum. The anal and rectal examination should include visualization to look for potential foreign bodies and gross injury, such as tears, abrasions, bleeding, erythema, hematoma, fissures, engorgement, and friability. Anal swabs should be inserted approximately 2 cm into the rectum. Visualization can be enhanced using TBD and anoscopy. Anoscopy has been shown to detect more injuries than colposcopy or an unassisted examination. Significant pain and an inability to tolerate anoscopy may warrant an examination under anesthesia, with some victims requiring surgical evaluation and treatment.

Male victims should be offered similar STI prophylaxis. HIV prophylaxis should be considered given the high risk of transmission from anal receptive and anal insertive intercourse. Victims should also be referred for rape crisis counseling services.

PHILADELPHIA SEXUAL ASSAULT RESPONSE CENTER

EVIDENCE COLLECTED

CLOTHING	RAPE KIT
□None	□None
□Shirt/blouse, describe:	□DNA Reference Sample
□Pants/slacks, describe:	□Oral Swab
□Dress/skirt, describe:	□Vulvar Swab
□Bra/undershirt, describe:	□Vaginal Swab
□Jacket/coat, describe:	□Cervix Swab
□Nightgown/pajamas, describe:	□Rectal Swab
□Underwear, describe:	□Perineum Swab
□Other, describe:	□Penile Swab
□Other, describe:	□Pubic Hair Combings
□Other, describe:	□Debris, source:
	□Debris, source:
TOXICOLOGY	□Bite/suck mark:
□None	□Bite/suck mark:
□Blood and Urine Specimens	□Other, describe:
	□Other, describe:

PHOTOGRAPHS

Photos Taken: □ YES □ NO Number:_____

Type: □ Camera □ Colposcope

Photographer:_____

_____ _____

Patient Name **Examiner's Initials**

Fig. 58.13. Sample chain of custody form. **A,** Evidence collection inventory form.

Continued

PHILADELPHIA SEXUAL ASSAULT RESPONSE CENTER

CHAIN OF CUSTODY

□ All items listed in Evidence Collected labeled and sealed and secured in locked room.

□ Check and list items:

- o Bagged Evidence (number of bags): _____
- o Rape Kit:_____
- o Drug Scan Kit:_____
- o Other:_____

Evidence was collected and secured by:

Name:_____ Signature:_____

Date:_____ Time:_____

****

All evidence/items transferred:

To:_____(print name/badge #)

Agency:_____

Signature:_____

Date:_____ Time:_____

By:_____

Signature:_____

_____ _____

Patient Name **Examiner's Initials**

Fig. 58.13, cont'd. **B,** Chain of custody form including in forensic report.

CITY OF PHILADELPHIA

SEXUAL ASSAULT EVIDENCE COLLECTION KIT

MEDICAL PERSONNEL

PLEASE PRINT

AFFIX BIOHAZARD SEAL HERE

VICTIM'S NAME: _____

CASE NUMBER: _____

ATTENDING PHYSICIAN/NURSE: _____

HOSPITAL/CLINIC: _____

KIT SEALED BY: _____

PLACE SEALED KIT AND CLOTHING BAGS IN SECURE AND REFRIGERATED STORAGE AREA AFTER EVIDENCE COLLECTION

PLACED BY: _____

DATE: _____ TIME: _____ am pm

POLICE PERSONNEL

CHAIN OF POSSESSION

RECEIVED FROM: _____

DATE: _____ TIME: _____ am pm

RECEIVED FROM: _____

DATE: _____ TIME: _____ am pm

RECEIVED FROM: _____

DATE: _____ TIME: _____ am pm

RECEIVED FROM: _____

DATE: _____ TIME: _____ am pm

DELIVER SEALED KIT AND CLOTHING BAGS TO THE CRIME LABORATORY IMMEDIATELY

FORENSIC LABORATORY PERSONNEL

LABORATORY NUMBER: _____

POLICE CASE NUMBER: _____

Fig. 58.13, cont'd. **C,** Chain of custody form included on the front of the rape kit box.

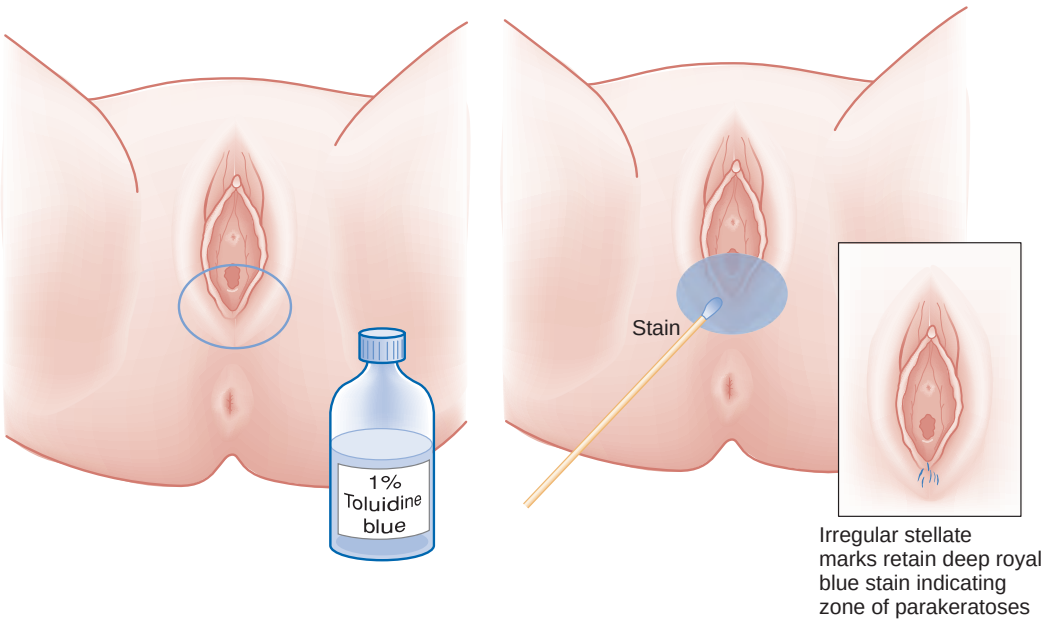


Fig. 58.14. Toluidine blue dye (TBD) application. This figure illustrates the application and removal of TBD during a forensic medical examination.

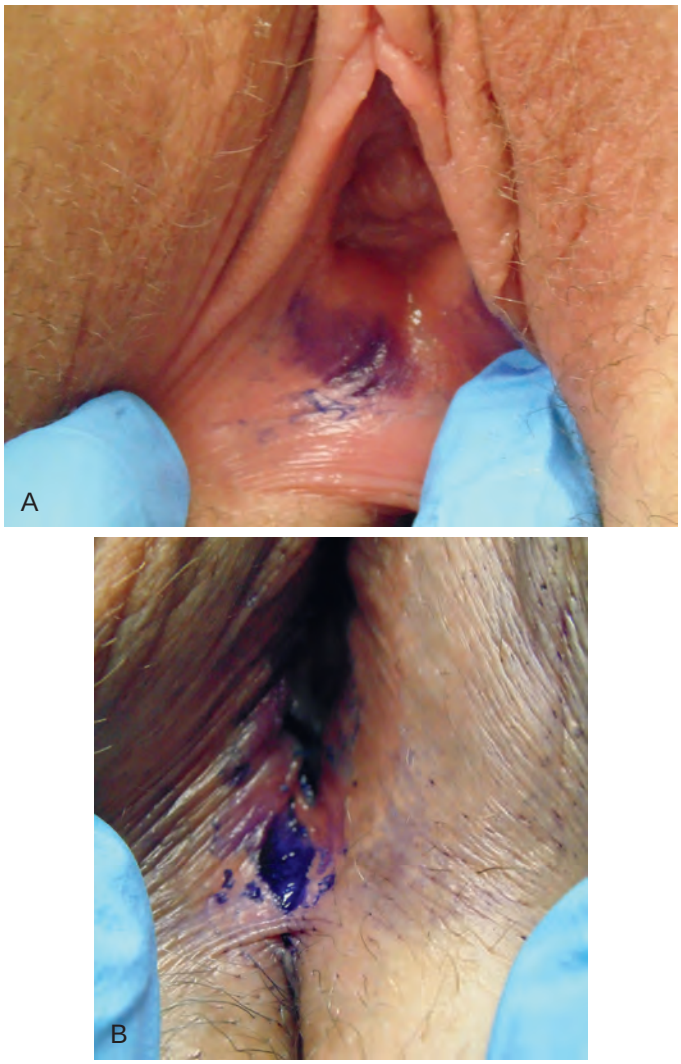


Fig. 58.15. External genitalia examination after toluidine blue dye (TBD) application. **A,** After the TBD was applied, two tears of the fossa navicularis were seen between the 6 and 7 o'clock positions. **B,** TBD application highlighting a large tear and abrasion of the fossa navicularis at the 6 o'clock position. There are also other scattered, smaller injuries present.

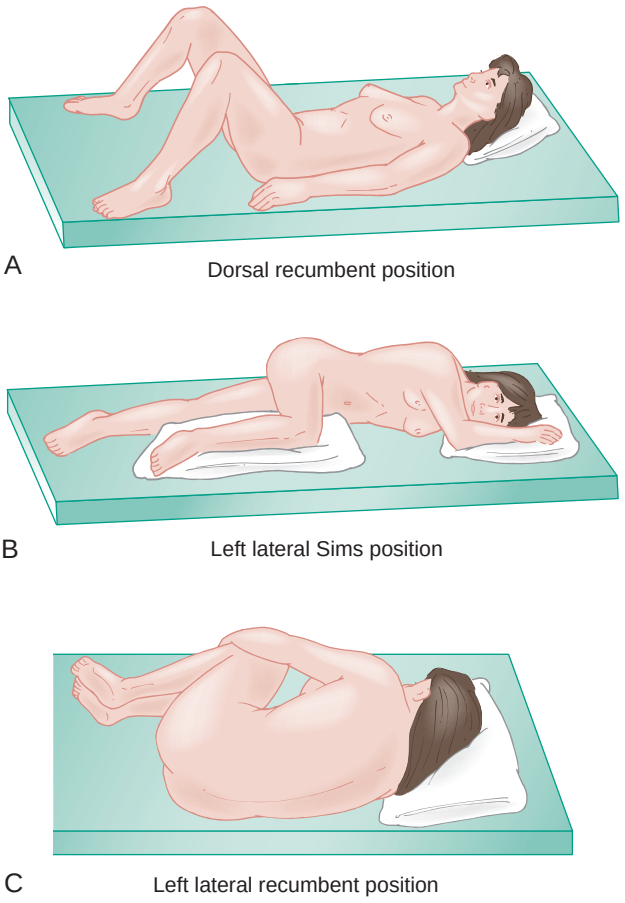


Fig. 58.16. **A,** Dorsal recumbent position. **B,** Left lateral Sims position. **C,** Left lateral recumbent position.

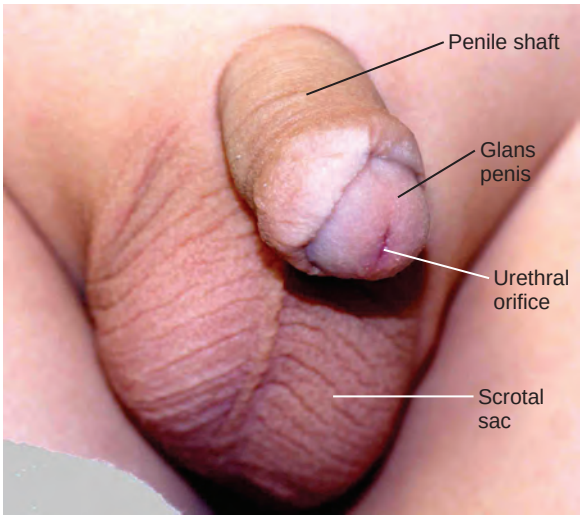


Fig. 58.17. Male genitalia. This picture highlights the relative anatomy of the male genitalia important in a medical forensic examination. (From Roberts JR, Custalow CB, Thompsen TW: Roberts and Hedges' clinical procedures in emergency medicine, ed 6, Philadelphia, 2013, Elsevier Saunders.)

FURTHER CONSIDERATIONS

Definitive Treatment to Prevent Sexually Transmitted Infections and Pregnancy

One of the most common concerns of survivors who present to the ED is that of becoming pregnant and acquiring STIs, including HIV. The risk of becoming pregnant after rape has been estimated at 5% but depends on the age of the patient, use of birth control by the patient and condoms in the assailant, and timing in the menstrual cycle. The risk of acquiring STIs after a rape depends on the local prevalence of the infections. Prior research has shown the risk is greatest for acquiring bacterial vaginosis (19%), trichomonas (12%), *Neisseria gonorrhea* (4%), and chlamydia (2%).[31] The risk of acquiring HIV is very low, estimated to be 0.1% to 0.3% for receptive vaginal intercourse and 0.5% to 3.0% for receptive anal intercourse (Table 58.4).[51,52] However, estimates do not take into account the increased risks associated with sexual violence and injuries.[53] The risk of HIV transmission is also related to viral load in the assailant (highest in very early and very late HIV disease), route of assault, and presence of STIs in the victim.

According to CDC recommendations, all sexual assault victims presenting to the ED should be offered medications to prevent pregnancy (women of childbearing potential), STIs, hepatitis B, and HIV (Table 58.5). Many states mandate that emergency clinicians offer pregnancy prevention to sexual assault victims (www.ncsl.org/research/health/emergency-contraception-state-laws.aspx). See Table 58.6 for emergency contraception options. All victims should also be given a tetanus booster, if indicated. HIV postexposure prophylaxis (PEP) should be offered to sexual

assault patients who have been assaulted by multiple assailants, a known HIV-positive assailant, or high-risk assailant. Unfortunately, because the HIV status of the assailant is usually unknown, the CDC recommends offering prophylaxis on a case by case basis, taking into account patient preferences and ability to comply with the 1-month course of medications and follow-up. See Fig. 58.18 for the CDC algorithm on the decision to treat for possible HIV body fluid exposure. When the decision is made to treat with HIV PEP, the current recommendation is to treat all exposures with three-drug therapy, not differentiating between high- and low-risk exposure. HIV PEP medication regimens change frequently, and the emergency clinician should consult the local HIV expert for the most up to date regimen. The National HIV Clinician's

TABLE 58.4

Calculated Risks of Acquiring HIV from Isolated Sexual Contact With Known HIV-Positive Individual

TYPE OF CONTACT	RISK[a]
Oral	Negligible
Anal	0.5%–3.0%
Vaginal	0.08%–0.3%
Health care worker percutaneous needlestick	0.3%

[a]Risk is higher in early or late HIV infection, higher viral load in assailant, presence of trauma or genital ulcers, and sexually transmitted infection in victim.
Data from Dosekun O, Fox J: An overview of the relative risks of different sexual behaviours on HIV transmission. Curr Opin HIV AIDS 5:291–297, 2010; and Boily MC, Baggaley RF, Wang L, et al: Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis 9:118–129. 2009.

TABLE 58.5

Recommended Treatment to Prevent Sexually Transmitted Infection and Pregnancy

INFECTION OR CONDITION	MEDICATION
Gonorrhea[a]	Ceftriaxone, 250 mg IM
Chlamydia	Azithromycin, 1 g PO *or* Doxycycline, 100 mg PO bid × 10 days
Trichomoniasis	Metronidazole, 2 g PO (recommended to take at home later)
HIV	See most recent CDC guidelines[b] and Fig. 58.17 (decisions made on a case by case basis)
Hepatitis B	First dose of hepatitis vaccine if not already vaccinated
Tetanus	Tdap, 0.5 mL IM
Pregnancy	Levonorgestrel, 1.5 g PO *or* Ulipristal acetate, 30 mg PO
Antiemetic	Practitioner's discretion

[a]If patient reports a severe penicillin allergy (anaphylaxis, TEN, or Stephens-Johnson syndrome), treat with azithromycin. There has been an increase in N. Gonorrhea resistance to azithromycin, so follow-up testing is recommended in this scenario.
[b]Centers for Disease Control and Prevention: 2015 sexually transmitted diseases treatment guidelines. www.cdc.gov/std/tg2015/tg-2015-print.pdf.

TABLE 58.6

Emergency Contraception

METHOD	BRAND NAME	DOSE	TIMING AFTER INTERCOURSE	EFFICACY	ADVERSE EFFECTS	RELATIVE CONTRAINDICATIONS[a]	NOTES
Copper IUD	Paragard	Single IUD	0–120 h	>99%	Pain, bleeding	Infection, copper allergy, uterine anomalies	Consider in IPV where recurrent assault more likely (effective up to 10 yr) Most effective, but often not feasible or desirable from the ED after assault
Levonorgestrel[b]	Plan B, Plan B One-Step, Next Choice	1.5 mg	0–72 h (may be used with decreased efficacy up to 120 h)	85%	Nausea, vomiting, headache, menstrual changes		Less effective if >72 h or BMI > 26
Ulipristal acetate[c]	Ella, Ella One	30 mg	0–120 h	85%	Nausea, vomiting, headache, menstrual changes	Renal, hepatic impairment, uncontrolled asthma, breast-feeding	More effective than LNG at 72–120 h More effective for BMI 26–35 (less effective in BMI > 35)

BMI, Body mass index; *ED,* emergency department; *IUD,* intrauterine device; *IPV,* intimate partner violence; *LNG,* levonorgestrel.
[a]There are no absolute contraindications to ED, except for an established pregnancy, because they will not be effective.
[b]Levonorgestrel is not an abortifacient and is not teratogenic.
[c]Ulipristal acetate is not an abortifacient. It has not been tested adequately in human studies in pregnancy or breast-feeding; animal studies showed increased pregnancy loss.
Adapted from Glasier AF, Cameron ST, Fine PM, et al: Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 375:555–562, 2010; and Glasier A, Cameron ST, Blithe D, et al: Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. Contraception 84:363–367, 2011.

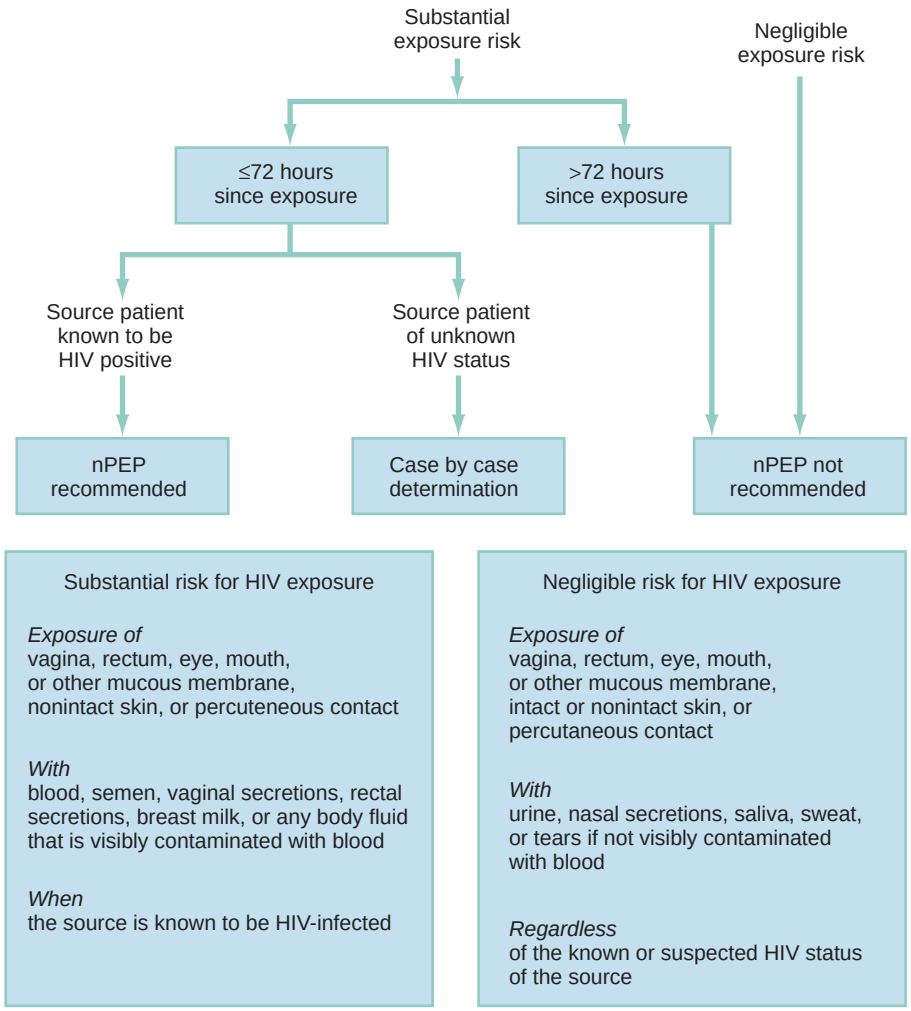


Fig. 58.18. CDC algorithm for HIV prophylaxis and for the evaluation and treatment of possible nonoccupational HIV exposure. *nPEP,* Nonoccupational postexposure prophylaxis.

Consultation Center offers online information and telephone consultation for providers who do not have access to a local HIV expert (nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/).

Disposition

Most sexual assault patients will be discharged from the ED. There are myriad websites that can assist the emergency clinician who is caring for the sexual assault patient (Box 58.3). If available in the ED, social services and a rape crisis advocate can help formulate a safe discharge plan. Victims of attempted strangulation, especially those with loss of consciousness, bowel or bladder incontinence, or persistent shortness of breath or voice changes, should be admitted for observation. If safe house resources are unavailable, consider admitting patients who do not have a safe place to go. The discharge instructions should include the number of the forensic kit when the examination is performed. Patients should be encouraged to follow up with their local rape crisis center, primary care provider (or other medical provider), and mental health provider, as needed. Medical follow-up should include any needed completion of the hepatitis B series, repeat pregnancy testing, STI testing (if they did not get treated), and repeat HIV testing (at 6 weeks). If they received HIV prophylaxis, they should follow up with the local HIV expert or clinic to have follow-up laboratory testing, monitoring for side effects, and compliance with medications.

BOX 58.3

Useful Websites for Sexual Assault

- Tonic Immobility: Neurobiology of sexual assault. nij.gov/multimedia/presenter/presenter-campbell/pages/welcome.aspx.
- Centers for Disease Control and Prevention: 2015 STD treatment guidelines—sexual assault and abuse STD guidelines. www.cdc.gov/std/tg2015/sexual-assault.htm.
- Clinician Consult Center: PEP: post-exposure prophylaxis. nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis.
- U.S. Department of Justice, Office on Violence Against Women: A national protocol for sexual assault medical forensic examinations. www.ncjrs.gov/pdffiles1/ovw/241903.pdf.
- American College of Emergency Physicians: Evaluation and management of the sexually assaulted or sexually abused patient. www.acep.org/forensicsection.
- Training Institute on Strangulation Prevention: www.strangulationtraininginstitute.com.
- National Sexual Violence Resource Center: www.nsvrc.org.
- Rape, Abuse, and Incest National Network (RAINN): www.rainn.org. (Hotline: 1-800-656-HOPE [4673])

BOX 58.4

Steps in Court Testimony

PREPARATION FOR TRIAL

1. Respond to the subpoena in a timely fashion; a delay can result in criminal charges for you.
2. Notify and consult with the institutional legal counsel.
3. Update your CV and be able to recite dates of education and certification.
4. Ask to meet with the prosecutor to review the medical records, evidence collection kit, and a list of questions the prosecutor plans to ask the emergency clinician.

DAY OF THE TRIAL

1. The day of the trial may change due to motions and order of witnesses.
2. Arrive early and dress in professional attire—a suit is preferred, rather than a white coat.
3. Before testifying, the emergency clinician will be sworn in and seated in the witness box. There are three parts to the testimony—questioning by the prosecution (testimony), cross-examination by the defense attorney, and redirect by the prosecution.
4. In general, the emergency clinician should look at the prosecution or defense attorney when being questioned and the jury when answering questions; this is the provider's opportunity to educate the judge and jury.
5. Responses to questions should be brief and answer only the question; do not add information and explanations unless asked, and resist using medical jargon such as *ecchymosis* in favor of clearly understood terms such as *bruising*.
6. All answers should be verbal, taking care not to nod in response. The line of questioning will often start with asking the provider to state her or his name and then describe training and certification, including how long he or she has been practicing emergency medicine.
7. Do not refer to the patient as the "victim."
8. If an answer cannot be recalled, then just simply state, "I cannot recall."
9. Documents can be reviewed in court (eg, medical or evidentiary kit records) on request.
10. If the question is not understood, the emergency clinician can ask the attorney to repeat the question or clarify it prior to answering.

Patients may experience subsequent symptoms of PTSD or rape trauma syndrome (RTS). Symptoms may include depression, anxiety, flashbacks, and difficulty sleeping and interacting with friends and loved ones. Acute pain after sexual assault is common and often undertreated, sometimes involving areas that were not traumatized.[54,55] Delayed or worsening pain in many regions of the body has been shown to occur in up to 60% of sexual assault survivors at 6 weeks and 3 months postassault.[54]

Testifying in Court

Although good medical care is the primary goal of ED treatment, the emergency clinician may at times be responsible for collecting sexual assault evidence. In this case, the emergency clinician may be called on to testify in court. The key to competent testimony is preparation and knowledge of the court process.

In most cases, the emergency clinician will be called on as a fact witness or as someone who testifies to what the patient said or did, as well as findings on physical examination. Occasionally, the emergency clinician may be called on as an expert witness. An expert witness has specific training and may be called on to provide an explanation or educate the jury, even if he or she did not actually care for the patient. Box 58.4 outlines the steps in court testimony and includes some helpful suggestions for the emergency clinician in preparation for such a trial.

Although testifying is anxiety-provoking, being prepared, appearing professional, remaining calm, and taking the opportunity to educate the judge and jury will help the emergency clinician feel more confident in his or her testimony.

KEY CONCEPTS

- Sexual assault is more common in women, but can happen in gay and heterosexual men, and in lesbian, gay, bisexual, transgender, and gender-nonconforming individuals.
- Sexual assault often results in no physical signs of injury.
- Optimal care includes creating a safe confidential environment while incorporating the principles of trauma-informed care. The patient should be included in decision making and ultimately decide treatment. Options include injury evaluation, treatment to prevent pregnancy and STIs, support and trauma counseling, evidence collection, and comprehensive toxicology testing if within jurisdictional time limits.
- The sexual assault evidence collection examination is an intensive, protocol-driven, multistep process, best performed by a certified sexual assault examiner.
- Adult sexual assault patients should be treated empirically according to CDC guidelines to prevent STIs (including gonorrhea, syphilis, chlamydia, trichomonas, HIV, and hepatitis B), where appropriate. Children and adolescents should be tested and, if symptoms develop, treated for STIs.
- All adolescent and adult female sexual assault patients should be offered pregnancy prophylaxis.
- HIV postexposure prophylaxis should be offered if the assailant is known to be HIV-positive or if multiple assailants are involved or, if the HIV status of the assailant is unknown, offered on a case by case basis.
- Alcohol and drugs may have been ingested voluntarily or involuntarily by the patient. If the patient consents, comprehensive toxicology testing may be appropriate.
- A strangulation attempt with loss of consciousness, bowel and bladder incontinence, persistent voice changes, difficulty swallowing, or shortness of breath should be comprehensively evaluated in the ED. Evaluation options include a chest x-ray, flexible laryngoscopy, and CTA or MRI of the neck. Admission should be considered for persistent symptoms.
- Many victims will not have obvious physical injuries; this does not imply consent or refute a sexual assault.
- The emergency clinician should not determine if a sexual assault happened but should record observations, statements, and findings objectively that were gathered during the course of ED treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 58: QUESTIONS & ANSWERS

58.1. Which of the following statements best describes hepatitis B infection prevention for victims of sexual assault?

A. Give HBIG and hepatitis B vaccine if the patient has not been immunized.
B. Give HBIG only if the patient has not been immunized.
C. Give hepatitis B vaccination if patient is unimmunized or uncertain.
D. Give hepatitis B vaccine only if serologic testing shows that the patient is not adequately immunized.
E. Serologic testing is always required, followed by hepatitis B immunoglobulin (HBIG).

Answer: C. Give hepatitis B vaccination if the patient is unimmunized or uncertain. Follow-up doses should be given at 1 to 2 months and 4 to 6 months (total of three doses). This strategy, which avoids the need for serologic testing, has been shown to be effective. HBIG is not recommended by the CDC after sexual assault (although it is recommended in body fluid exposures in unimmunized health care workers).

58.2. Which of the following empirical antibiotic regimen is indicated for sexual assault patients to prevent sexually transmitted infections?

A. Cefixime, 400 mg PO
B. Cefixime, 400 mg PO once, plus doxycycline, 100 mg PO bid for 10 days
C. Ceftriaxone, 1 g IM (intramuscularly)
D. Ceftriaxone, 1 g IM, plus azithromycin, 2 g orally (PO)
E. Ceftriaxone, 250 mg IM, plus metronidazole, 2 g PO, plus azithromycin, 1 g PO

Answer: E. Ceftriaxone is given to cover gonorrhea, azithromycin to cover chlamydia, and metronidazole (Flagyl) to cover *Trichomonas.* Ceftriaxone is preferred over oral cefixime to cover incubating syphilis and due to increasing gonorrhea resistance. Many providers opt to give the metronidazole to take at home because it increases the risk of nausea and vomiting, a common side effect of many of the medications (including emergency contraception and HIV postexposure prophylaxis).

58.3. Which of the following statements best describes sexual assault in males?
- **A.** Ejaculation should not occur in the victim during male sexual assault.
- **B.** Males are more likely to overreport sexual assault.
- **C.** Males are more likely to require sexually transmitted infection (STI) prophylaxis.
- **D.** Males do not require referral to rape crisis centers.
- **E.** Males may require anoscopy to detect anogenital injuries.

Answer: E. Males may actually suffer more anogenital injuries than woman; injury detection can be aided or enhanced by using an anoscope. Males underreport the crime, do not seek medical attention, and absolutely need referral to rape crisis centers for post-rape care and counseling. Males are not more likely to require STI prophylaxis because the risk of transmission per act does not change based on gender. Ejaculation may occur during sexual assault due to prostatic stimulation and fear arousal. This should not be taken to infer that the assault was consensual.

58.4. Sexual assault often leads to injury. Which of the following statements best describes the rate of sexual assault injury in females?
- **A.** Genital injury can be seen following consensual and nonconsensual intercourse.
- **B.** Nongenital injury is uncommon and rarely seen.
- **C.** Resistance of the victim and force used do not influence the risk of genital injury.
- **D.** The precise location of genital injury can be used to confirm sexual assault.
- **E.** The presence of genital injury confirms that a sexual assault occurred.

Answer: A. Genital injury can be seen following consensual and nonconsensual intercourse; its presence or location of injury does not confirm that a rape occurred. Nonconsensual intercourse (sexual assault) is more likely to result in more injuries that can be more severe. Other bodily injury can be commonly seen and may be more common than genital injury. Injury can be influenced by age, virginal status, resistance, force, number of assailants, and relationship of the assailant to the victim.

58.5. Which of the following factors reduces the likelihood of finding genital injury during the sexual assault examination?
- **A.** Digital penetration
- **B.** Increased time since sexual assault occurred
- **C.** Penile penetration
- **D.** Use of foreign object during the assault
- **E.** Victim sexual immaturity

Answer: B. The genital structures heal quickly, so the longer the time since the sexual assault occurred, the less likelihood of finding evidence of injury on examination. All the other factors increase the likelihood of finding genital injury at the time of the sexual assault examination.

58.6. A 25-year-old woman presents 4 days after vaginal penetration. Her body mass index (BMI) is 35. Which of the following is true about emergency contraception (EC)?
- **A.** A pregnancy test is mandatory prior to offering EC.
- **B.** She should be offered levonorgestrel because it is more effective in this situation.
- **C.** She should be offered ulipristal.
- **D.** She should have an intrauterine device (IUD) inserted because this is the most effective form of EC for her.
- **E.** She should not receive EC because it will likely be less effective due to her BMI.

Answer: C. Emergency contraception should be offered up to 5 days after vaginal assault. Ulipristal, levonorgestrel, and high-dose birth control pills are options. Ulipristal is more effective after 72 hours and in women with a BMI greater than 26. At a BMI above 35, both forms of oral EC are less effective, but should still be administered if there is no alternative. IUD placement is the most effective form of EC; it can be placed up to 5 days after assault. IUD placement allows for ongoing birth control in situations where there is likely to be loss of reproductive control (intimate partner assault), but is often less desirable after assault. IUD placement is most often not available in a timely manner. A pregnancy test is not mandatory prior to giving EC because it will not harm an existing pregnancy. A pregnancy test is suggested prior to ulipristal administration, given the lack of large studies in pregnant women.

58.7. A 28-year-old woman presents following sexual assault, during which the assailant strangled her, and she passed out. Which of the following is true concerning this patient's injury?
- **A.** Nonfatal strangulation has little impact on the risk of future injury in the domestic violence victim.
- **B.** Regardless of her symptoms, no additional imaging is needed.
- **C.** The hyoid bone is commonly fractured during an attempted strangulation.
- **D.** The signs and symptoms of nonfatal strangulation are usually caused by arterial or venous blood flow occlusion or blockage of air entry through the trachea.
- **E.** There must be physical evidence of injury for it to be a proven case of nonfatal strangulation.

Answer: D. Strangulation leads to hypoxia by jugular vein occlusion, carotid artery occlusion, or blockage of the airway. The hyoid bone is rarely injured. A large percentage of patients may have no physical findings and may require imaging, depending on the signs and symptoms present. In intimate partner violence (IPV) relationships, nonfatal strangulation increases the risk of future homicide sevenfold.

CHAPTER 59

Intimate Partner Violence and Abuse

Esther K. Choo | Judith A. Linden

PRINCIPLES

Background and Importance

Intimate partner violence (IPV)[1] has been defined by the Centers for Disease Control and Prevention (CDC) as the threat or infliction of physical, psychological, or sexual harm by a current or former intimate partner or spouse.[1] Physical violence includes aggressive behaviors, such as pushing, hitting, slapping, punching, kicking, biting, burning, strangulation, and using objects and weapons with the potential to cause death, disability, injury, or other harm. Psychological or emotional violence includes words and behaviors meant to intimidate, degrade, humiliate, or isolate the victim from family and friends, threats, controlling access to clothing, transportation, money, and other basic needs, and limiting professional and social activities. Sexual violence includes using physical force to attempt sexual acts or sexual contact against the victim's will, or on a victim not able to consent, whether or not the sexual act is completed. Although not explicitly included in the CDC definition, sexual abuse may also include prevention of or interference with the use of birth control (so-called reproductive coercion)[2] and refusal to use condoms to prevent the transmission of sexually transmitted infections (STIs) and human immunodeficiency virus (HIV).[3] Threats of physical or sexual harm are also considered IPV.

According to the CDC's 2010 National Intimate Partner and Sexual Violence Survey (NISVS), 35.6% of women will experience IPV over their lifetimes, only considering physical violence, rape, and stalking. One in three victimized women experiences multiple forms of IPV.[4] Obtaining accurate national estimates of IPV prevalence among emergency department (ED) patients or even of ED visits directly related to IPV injuries is hampered by poor documentation and coding practices. In the National Hospital Ambulatory Medical Care Survey (NHAMCS), IPV is a recorded diagnosis in less than 0.25% of visits. However, in individual ED studies, observed IPV prevalence in women is disproportionately high compared to the general population, with estimates of recent (6–12 month) prevalence ranging from 12% to 19% (≈8–12 times that of the general population) and of lifetime prevalence from 44% to 54% (≈1.4–1.7 times that of the general population).

IPV commonly occurs against men as well as women. In the CDC's 2010 NISVS, one in four men reported lifetime physical abuse, stalking, or rape by an intimate partner, and 35% of them reported associated physical or psychological sequelae of abuse.[4] Data from the Behavioral Risk Factor Surveillance System, another nationally representative CDC survey, have reinforced that men experience all forms of IPV and its mental and physical health sequelae.[5] The high prevalence of abuse among men may be partly understood by the fact that IPV is frequently bidirectional. IPV researchers have described two distinct forms of IPV, intimate terrorism and situational couple violence.[6] The two forms are differentiated based on the use of power to control. Intimate terrorism is defined as "the attempt to dominate one's partner and to exert general control over the relationship," whereas situational couple violence is "violence that is not connected to a general pattern of control." Situational couple violence is usually less injurious or severe and more likely to be engaged in by either member of the couple. Intimate terrorism is characterized as more injurious, more frequent, and more often perpetrated by men against women. Overall, women continue to be the primary targets of violence and to experience high rates of health sequelae. Therefore, health care responses to IPV, as well as community resources for survivors, are largely directed toward women.

IPV affects other aspects of health and is associated with risky health behaviors, such as cigarette smoking, heavy alcohol and drug use, and physical inactivity, as well as mental illness (eg, depression, anxiety, posttraumatic stress disorder [PTSD], suicidality).[4,7-11] IPV is associated with increased rates of cervical cancer.[12] IPV patients often have poor maintenance of chronic medical conditions such as asthma, diabetes, and chronic pain syndromes.[4] Pregnant IPV victims tend to seek prenatal care late and are at risk for termination of pregnancy, placental abruption, preterm delivery, and low infant birth weight.[13-16]

IPV is responsible for most intentional injuries experienced by women, accounting for 38% of all female homicides globally.[17-19] IPV fatalities do not usually occur as a freak event in an otherwise happy family; IPV is a precursor to the homicide in 65% to 75% of cases.[19] Many IPV homicide victims see a health care provider within the year before their death. ED visits represent an opportunity to identify IPV and those at high risk for future severe injury or death.

The annual economic cost in the United States has been estimated at more than $4.8 billion dollars for direct medical and mental health services and an additional $1.8 billion in lost earnings and productivity,[20] above and beyond those without IPV. Encouragingly, health care use has been observed to return to normal rates several years after the cessation of IPV,[21] suggesting that interventions against IPV may have a positive overall effect on health.

Causes and Natural History of Intimate Partner Violence

IPV is a complex multifactorial phenomenon, influenced by multiple, interconnected societal, community, relationship, and individual factors (Fig. 59.1). Individual-level risk factors include childhood exposure to IPV, presence of a physical or mental disability, and use of alcohol or drugs.[22-27] Relationship factors that may influence IPV occurrence include the couple's communication and conflict resolution skills[28] and socioeconomic stressors; IPV appears to occur at increased rates in relationships among those with lower income, job or housing instability, and male unemployment. Housing instability also increases the risk of sequelae, such as PTSD, depression, and increased ED use in IPV victims.[29] Lack of social support for women and delinquent peer associations for men have been associated with victimization and perpetration, respectively, whereas bolstering social supports can decrease violence.[30]

Finally, the individual, family, and community all function within an overarching society or culture with its laws, attitudes,

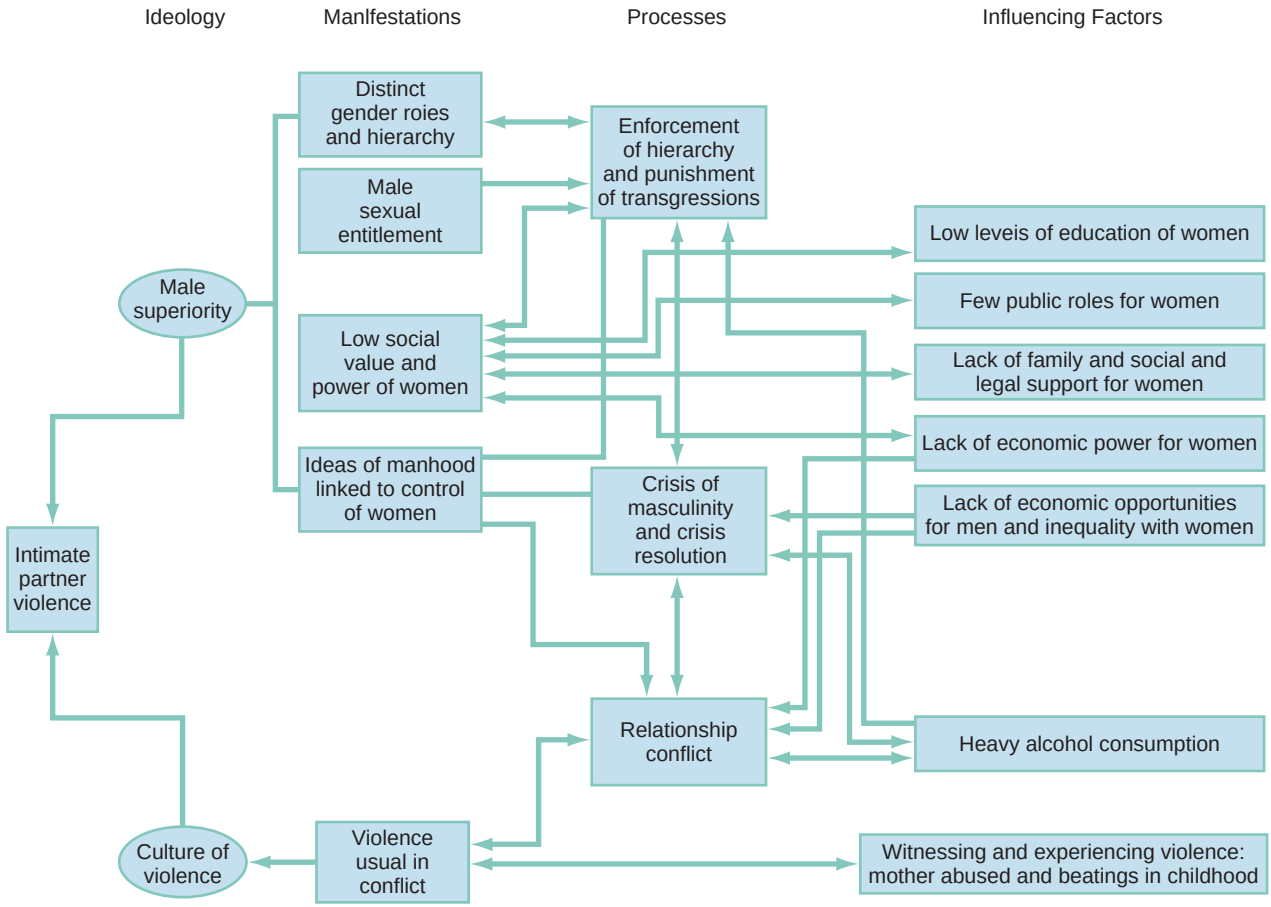

Fig. 59.1. Multifactorial causes of intimate partner violence.

norms, and biases, including overall societal tolerance toward violence. The predominant cultural theory regarding the cause of IPV is so-called feminist theory, which states that violence against women results from gender inequity, both ideologic (belief, norms, values) and structural (access to and positions within social institutions).

In some ways, IPV fits a chronic disease model because it tends be a lifelong condition that recurs in cyclic patterns within a relationship. Additionally, children who have experienced family violence tend to enter future violent relationships. Care for IPV requires systematic screening and multidisciplinary care, with the need for long-term physical and mental health care, counseling and advocacy, legal aid, and long-term strategies for financial and social independence. Approaching IPV as a chronic disease underscores the importance of population-wide screening efforts. In addition to providing acute medical care, emergency clinicians should connect patients who screen positive with primary care physicians and/or domestic violence community agencies to ensure continuity of care for what is typically a long-term, recurring problem.

This chronic disease model is in contrast to traditional clinical thinking about IPV, which is focused around a crisis event, such as injury. A significant body of older literature was dedicated to patterns of injury that might be considered classic signs of IPV. However, physical findings have demonstrated poor sensitivity and specificity for IPV and thus are not amenable to clinical decision rules. IPV can present with any number of symptoms, usually without any injury at all.[31] For this reason, the US Preventive Services Taskforce (USPSTF) has recommended routine screening for IPV in women of childbearing age, even in the absence of overt injuries.[32]

Despite USPSTF recommendations and Joint Commission requirements for robust health system responses to IPV, there are a number of barriers to its identification and management. Emergency clinicians generally receive little training and thus have low confidence in their ability to respond effectively to revelations of abuse. In busy clinical settings such as the ED, the high volume of patients and acuity of disease may preclude screening and more in-depth discussions of partner abuse. Given the complex psychosocial issues that may accompany IPV, emergency clinicians may also fear opening a Pandora's box, uncovering a range of needs. Staff may be uncertain about whose responsibility it is to screen for IPV, discuss positive screens with the patient, and provide necessary counseling and referrals. Overall, current screening and intervention practices fail to identify women who are at risk for future IPV. Incorporating screening into triage processes, including into electronic medical record documentation, routine training of clinical staff, and use of newer modalities, such as self-administered, computer-based screening, may aid EDs and emergency clinicians in improving the detection of IPV.

CLINICAL FEATURES

Classic injury patterns (eg, maxillofacial injuries, multiple injuries, extremity fractures) have demonstrated limited predictive value in screening for IPV. Most IPV victims present to the ED with noninjury visits, including gynecology-related complaints, mental health and substance abuse complaints, pain syndromes, and uncontrolled medical illnesses. Elements of the history that may suggest IPV include a delay in seeking medical care, noncompliance with medications, and/or missed medical appointments; all these may reflect the fact that an abuser is controlling the patient's

access to care. Unless probed about the presence of IPV, these patients may not be identified. If the injury is a result of IPV, the patient may be reluctant to divulge the information. Additional historical clues that an injury may be a result of IPV are a vague or changing history, a history that is inconsistent with the injuries, a statement by the patient that he or she is accident-prone, and a past history of injuries.

IPV is often considered in women who present with injuries or assault, but should also be considered in male victims of assault. Although men do report being victims of IPV, reported injuries are commonly abrasions, and the mechanism is often scratching, punching, or being hit with a blunt object.[33]

Injury Presentations

Emergency clinicians should ask patients presenting with injuries if they were intentionally inflicted and specifically if injuries were caused by IPV. If the patient attributes the injuries to IPV, the identity of the other person, as well as that person's relationship to the patient, should be ascertained and documented. Not only is noting the nature of the relationship important for ensuring the accuracy of diagnostic coding, but a victim who is living with an assailant requires different resources compared to a victim of a stranger assault.

IPV patients may come to the ED with acute injuries, or injuries may be an incidental finding discovered during the physical examination for medical complaints. The emergency clinician should look for clues that an injury may be intentional in nature—a central location (eg, trunk, breasts), bilateral injuries (both arms or both legs), defensive injuries (eg, ecchymoses on the back of the hand from protecting the face), and patterned injuries (having the markings of an object such as the sole of a shoe or a burn with the imprint of an iron). Common locations for IPV injuries are the head, face, mouth, and neck. Types of injuries may include facial contusions, lacerations, fractures, traumatic alopecia, concussion, skull fractures, intracranial hemorrhages, and strangulation. Extremity injuries with grab marks (fingertip contusions) to the upper arms are suggestive of IPV. Emergency clinicians should document injury location, size, swelling, tenderness, coloration, evidence of healing, and presence of a pattern.

Certain traumatic injuries are more commonly associated with IPV, such as injuries to the face, head, neck, thorax, and abdomen.[34] Some studies have considered differentiating IPV versus non–IPV-related assaults presenting to the ED. Assaults that occur in the home are more likely to be IPV-related in men and women, and assaults involving a head injury were more likely to be IPV-related in women.[35] While inquiring about who assaulted the patient is important, discovering where the assault occurred can give clues for IPV. Patients given an e-code of IPV are likely to have traumatic diagnoses such as contusion and facial fractures and are also more likely to present with complications of pregnancy.[36]

Gynecologic-Related Presentations

IPV victims commonly present to the ED with obstetric and gynecologic complaints.[37] Presentations related to IPV may include unintended pregnancy, requests for emergency contraception and termination of pregnancy, and frequent sexually transmitted infections.[38-40] IPV survivors report increased rates of STIs and other gynecologic disorders, such as cervicitis and vulvovaginitis.[40-42] Unintended pregnancy and STIs may be a consequence of loss of reproductive control and/or sexual assault. Sexual violence is a common tactic used for intimidation and control in IPV; 46% to 68% of abused women admit to sexual assault in the context of abuse.

The sequelae of intimate partner sexual abuse are at least as serious as those of stranger sexual assault. Victims of intimate partner sexual abuse are more likely to sustain more serious nongenital injuries than victims of stranger assault. Many validated IPV screening tools (Table 59.1) omit questions about sexual abuse or reproductive coercion.[2] Women who are sexually assaulted by an intimate partner or family member are more likely to present in a delayed manner or not present to the ED at all for evaluation. Emergency clinicians should ask all sexual assault victims about IPV and safety at home. IPV patients may not consider themselves raped or sexually assaulted if the perpetrator was their partner, husband, or boyfriend. Thus, emergency clinicians should ask whether the patient has been forced to perform sexual activities rather than having been "raped."

Mental Health Presentations

IPV victims frequently experience depression, suicidal ideation, homicidal ideation, PTSD, insomnia, eating disorders, and alcohol and drug misuse.[4,9-11,43,44] Mental health presentations including substance abuse, therefore, should prompt suspicion for possible IPV. IPV survivors are also more likely to report depression, anxiety, and PTSD and use mental health resources.[20]

TABLE 59.1

Sample of Brief Intimate Partner Violence and Abuse Screening Tools

TOOL	QUESTIONS	SENSITIVITY	SPECIFICITY
HITS	How often does your partner: • Physically hurt you? • Insult you or talk you down? • Threaten or harm you? • Scream or curse at you?	30%–98%	83%–97%
PVS	• Have you been hit, kicked, punched, or otherwise hurt by someone in the past year? If so, by whom? • Do you feel safe in your current relationship? • Is there a partner from a previous relationship who is making you feel unsafe now?	65%–71%	80%–84%
STaT	Have you ever been in a relationship where your partner has: • Slapped or pushed you? • Thrown, broken, or punched things? • Threatened you with violence?	96% (cutoff >1%) 89% (>2%) 64% (>3%)	75% (cutoff >1%) 100% (>2%, >3%)

Alcohol and Drug Use and Intimate Partner Violence

Whether in the perpetrator or recipient of abuse, alcohol and drug misuse place women at greater risk for physical and sexual intimate partner victimization.[44] Alcohol and drug use may be a coping response to the emotional and physical sequelae of IPV, but can also lead to abuse.[22,44] Explanations for this include conflicts over substance use—women who misuse alcohol or drugs are more likely to choose partners who use alcohol and drugs—or that alcohol or drugs impedes the victim's ability to recognize escalating aggressive behavior, navigate tensions, and resolve conflict within a relationship. Overall, alcohol and drug misuse increase women's vulnerability to IPV victimization and reduces the likelihood that they will be screened for these problems.[45] Those with coexisting problems not only face mental and physical health problems of greater complexity,[26,44,46] but must contend with additional challenges to recovery; for example, few substance use treatment programs address violence, and few domestic violence agencies are equipped to address active substance misuse.[26]

Chronic Medical Conditions

IPV patients may seek care for chronic conditions that are a result of previous injuries or are comorbid medical conditions of the abuse.[4,47] These include psychosocial disorders (substance abuse, depression, anxiety, tobacco use), musculoskeletal disorders (degenerative joint disease, low back pain, joint trauma, cervical pain, acute sprains), reproductive complaints (menstrual disorders, vulvovaginitis, sexually transmitted infections), and others (confusion, headaches, urinary tract infections, abdominal pain, chest pain, respiratory infections, reflux disease, and lacerations). Other common medical presentations of IPV patients include cardiorespiratory illnesses (palpitations, chest pain, asthma exacerbations, shortness of breath), gastrointestinal disorders (functional bowel disease), and general constitutional complaints (weakness, fatigue, dizziness, chronic pain).

Pain Syndromes

IPV should be in the differential diagnosis as a co-occurring condition and possible contributing factor in patients who present with chronic pain.[48,49] Chronic pain, including headache, abdominal pain, back pain, and bone and joint pain are common in IPV survivors, and disability and pain symptoms may persist for years after being separated from the abuser. Those with a history of more severe abuse, sexual abuse, and childhood abuse report more symptoms. Asking about and identifying past abuse may decrease unnecessary testing and inappropriate medication administration and facilitate referral to critical resources.

DIAGNOSTIC CONSIDERATIONS

Differential Diagnosis

Human Trafficking

A victim of human trafficking (HT) can be mistaken for a victim of IPV. HT is a form of modern slavery and can present in a similar manner as IPV. HT, however, entails very different dynamics, challenges, and approaches to intervention and resources. The World Health Organization has defined human trafficking as "the recruitment, transportation, transfer, harboring or receipt of persons, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability, or of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for the purpose of exploitation." Exploitation includes, at a minimum, "the exploitation of the prostitution of others or other forms of sexual exploitation, forced labor or services, slavery or practices similar to slavery, servitude, or the removal of organs."[50] Trafficking of victims can occur across or within national borders. HT victims can be of any age or gender, but are usually women and children, who are often from a poverty situation and are previous victims of sexual or physical abuse. Victims are lured by promises of money, love, or opportunities for success. HT victims are often held in bondage and required to pay large amounts of money in return for transportation, favors, or food and shelter. They are paid little or nothing, and thus are unable to pay back this debt. Trafficking victims often have no autonomy, and access to health care or reproductive control and may be forced to sleep behind locked doors or not allowed to leave their place of employment. They may present to the ED with STIs, pregnancy, injuries, and medical and mental health conditions. HT victims often experience the initiation and forced use of drugs or alcohol, as well as physical, emotional, and sexual violence. They are often controlled with addiction to alcohol or drugs and may present as victims of an overdose or in alcohol and drug withdrawal. Trafficking victims can also present with medical complaints, such as headaches, stomach pain, memory problems, back pain, loss of appetite, and tooth pain.[51] Many victims report fatigue, headaches, back pain, weight loss, mental health symptoms such as depression and anxiety, and sexual and reproductive health problems.[52] The severity of symptoms appears to increase with the duration of trafficking. To date, there has been very little research on the health effects and presentations of HT, and most studies have concentrated on young female HT victims. Clues in a patient's presentation that may suggest trafficking rather than IPV are included in Box 59.1.

Although the emergency clinician may suspect HT, most victims will not be identified in the ED. There are many reasons why a victim of HT might not disclose in the ED which are similar to IPV—shame, embarrassment and self-blame, lack of trust or familiarity with the provider, isolation with lack of economic and

BOX 59.1

Presentations Prompting Consideration of Human Trafficking

- Delay in seeking medical care
- Stated age older than visual appearance
- Evidence of lack of care for previously identified or obviously existing medical conditions
- Discrepancy between stated history and clinical presentation or observed pattern of injury
- Scripted, memorized, or mechanically recited history
- A patient who is overly concerned with the time, contacting their "partner," leaving the ED
- Subordinate, hypervigilant, or fearful demeanor
- Reluctance or inability to speak on one's own behalf
- Companion who refuses to leave
- Lack of identification documents, or documents in possession of another party
- Accompanied by individual who answers questions for patient and attempts to control encounter, including insisting on providing interpretation (may be "grandmotherly" type)
- Has tattoos or other marks or insignias that may indicate a claim of "ownership" by another, unwilling or uncomfortable talking about the tattoo
- Evidence of any type of physical violence, including torture
- Frequent relocations

BOX 59.2

Questions to Identify Human Trafficking

- Do you get paid for the work you do?
- Are you able to leave when you want to?
- Are there locks on the outside of your doors and windows?
- Can you come and go as you want?
- Have you been threatened if you leave your job?

social supports, fear of reprisal from the captor, lack of recognition of being trafficked, constant surveillance with intimidation, and confiscation of documents or identification (often under the guise of "keeping them in a safe place"). There may be a language or cultural barrier, fear of deportation, and distrust of authorities for those brought in from other countries. Victims of sex trafficking may be relocated frequently, often to areas where there are large sports or entertainment venues, such as the Super Bowl and other national sporting events.

When an emergency clinician suspects that his or her patient is a HT victim, it is important to interview the patient in private, using a medical interpreter when appropriate. HT victims may be accompanied by a "grandmotherly" figure who is actually a captor. As with IPV, HT survivors note that they are more likely to disclose their situation if they perceive that the emergency clinician is knowledgeable and nonjudgmental about HT and when there is a trusting relationship. An advocate or social worker who is knowledgeable about the dynamics of HT can be helpful. Box 59.2 provides helpful questions for the patient who is willing to make a disclosure. Even if the patient does not disclose, the emergency clinician can send an important message that the hospital is a safe place to come to for help. Institutions should institute safe, culturally sensitive, and responsive resources through staff training and community partnerships. Community resources may include law enforcement task forces, safe houses, and legal remedies for undocumented immigrants (eg, special visas). Many state medical societies have developed educational materials for physicians.[50]

Diagnostic Testing

Diagnostic testing for specific injuries and illnesses related to IPV follows general medical, trauma, and injury guidelines.

Screening

IPV survivors use the ED at high rates. One study of law enforcement–involved survivors has found that 64% had used the ED in the year prior to police identification, and 82% used the ED in the 2 years surrounding law enforcement involvement.[53] Many of these were not identified on review of the ED records, and most of the ED visits (71%) were non–injury-related. Directed screening for IPV involves questioning patients who present with illnesses and conditions that are more frequently associated with IPV (eg, chronic pain, multiple ED visits, STIs, unintended pregnancy, mental health issues such as depression, anxiety, PTSD, and suicide, alcohol and drug presentations). Universal screening includes screening those who are asymptomatic.

The Institute of Medicine has recommended screening for IPV as a preventive health measure,[54] the USPSTF has recommended routine screening of asymptomatic women of childbearing age for IPV in the health care setting, with referral to intervention services,[32] and the American College of Emergency Physicians has endorsed assessing for family violence in all forms.[53] The USPSTF's recommendation has a B grade, indicating that there is high certainty that the net benefit is moderate to substantial and there is little evidence of harm, based on a systematic review. Although studies have shown an increase in identification, proving a decrease in violence and increase in quality of life is challenging. A systematic review has found evidence of benefit from screening in certain populations.[55] The task force does not indicate where this screening should happen, but given that survivors use the ED at high rates, and IPV is often missed, the ED seems an appropriate place to screen. Screening in the ED has been found to be safe. When surveyed in the ED, 26% of women in a past-year relationship screened positive and, at follow-up at 1 week and 3 months, there was no report of increased violence or harm as a result of screening.

Although many authorities have recommended screening for IPV, and screening has been found to be acceptable to patients, barriers to screening have been identified, such as time constraints, lack of institutional protocols, policies, and procedures for screening, and negative attitudes and perceptions.[56] Screening is often included in the triage section of the medical record and is often performed by a nurse in a hectic and sometimes public triage area. This approach puts privacy and security at risk because IPV survivors may be accompanied by their abusive partner. This approach also precludes developing a rapport with the provider, an important catalyst for disclosure. Providers should further question intoxicated patients after they are sober, because patients who present with alcohol and drug misuse are less likely to be screened on presentation due to their altered level of consciousness.[45]

Some examples of validated IPV screening tools are presented in Table 59.1. Triage screening should be followed up privately, after all visitors have been asked to step out of the room. When asking about IPV, framing statements are helpful to normalize and destigmatize IPV. Such statements may include the following:

- "Because violence is so common in the lives of my patients, I ask all patients if they are being hurt or threatened by a current or ex-partner."
  or
- "I have found that many of my patients experience violence at home, so I like to ask my patients if they feel stress, or feel threatened at home."

The word "stress" may prompt recall of abuse that may not be perceived as IPV by the patient, but that may represent psychological or sexual abuse. Using inclusive terms such as *partner* will make those in a same sex or gender nonconforming relationships feel more comfortable about disclosing their situation. The emergency clinician should ask open-ended questions to give patients a chance to tell their story. Data have shown that when emergency clinicians asked at least one additional related question, patients were more likely to disclose abuse. Other methods of screening for IPV include electronic and paper surveys filled out by the patient while in the waiting room. Patient should be informed about state-specific reporting requirements that may accompany disclosure of IPV.

MANAGEMENT

An overview of management and documentation considerations is provided in Table 59.2. ED screening for IPV should be combined with a strong, coordinated, institutional response.[57,58] This should include ED staff training, development of institution-wide written and easily accessible policies and protocols, and in-person resources, including a social worker with IPV expertise or a domestic violence advocate. Components associated with high provider efficacy in screening include screening protocols, institutional support, initial and ongoing training, and access to IPV expert referrals.[57,59] A strong, hospital-based IPV response includes systems for screening, provider training and maintenance of skills in identification and immediate response, social services, mental

TABLE 59.2

Intervention Strategies Based on Intimate Partner Violence (IPV) Exposure and Risk Level

PATIENT TYPE BASED ON ASSESSMENT	INITIAL INTERVENTION STEPS	CRITICAL DOCUMENTATION FOR THE ENCOUNTER
No history of IPV or suspicion of abuse	Provide basic message that IPV is a health problem.	"No history of IPV; no suspicion of IPV"
Prior history of IPV but no current exposure	Assess for sequelae of prior abuse; provide educational message that patient is at risk of future IPV relationship.	Add history of IPV to problem list (can be coded as a V code); describe medical and mental health impact and any referrals made.
Recent or current abuse but no injuries and no elements on danger assessment	Assess for sequelae of abuse; provide referrals to IPV resources.	Add IPV to problem list; describe health sequelae from abuse; note referral for urgent follow-up provided to patient.
Recent or current abuse with injuries or positive findings on danger assessment	Crisis bedside consultation by social services or IPV advocate; discuss possibility of an order for protection; notify police if required by law.	Add IPV to problem list; describe health sequelae; summarize follow-up plan as outlined by social services or IPV advocate; complete mandatory reports; describe injury findings using narration, diagrams, and photographs.
Suspicion of current abuse but patient denies IPV	Provide basic message that IPV is a health problem; request bedside consultation by social services or IPV advocate; provide referrals to IPV resources.	Document IPV as a suspected health problem; note that bedside consultation was done and resources were provided; if injured, describe injury findings using narration, diagrams, and photographs.

health and substance abuse staff knowledgeable about IPV, and specialized IPV intervention programs. For institutions that lack a hospital-based IPV program, partnering with a local domestic violence agency or shelter increases resources and facilitates coordination of care. A tool developed by the Agency for Healthcare Research and Quality is available to assess system readiness.[59a] This assesses hospital policies and procedures, physical environment, cultural environment, emergency clinician education, screening and safety assessment, program evaluation and quality improvement, and collaborative agreements.

A trauma-informed approach is critical when working with survivors of IPV. This approach recognizes the effect of past and present trauma on an individual and how this influences her or his care. It emphasizes the strengths of the survivor, rather than emphasizing the traumatic effects, recognizes the unique expertise that the individual has regarding the situation, and determines which interventions are most helpful at a given point in time.

BOX 59.3

Simple Steps for Discussing Intimate Partner Violence After Patient Has Identified

1. Acknowledge abuse and thank the patient for sharing.
2. Validate the patient. Explain that no one deserves to be treated in an emotionally, physically, or sexually abusive manner.
3. Explain that you would like to help them today. Ask permission to get an advocate or social worker involved. Ask how else staff can help today.
4. Safety and danger assessment—assess immediate safety concerns; have further discussion and planning with the social worker or advocate.
5. Make a plan for follow up. Reinforce that IPV is a health care problem and that the patient can return for assistance.

Intervention

Once a patient has disclosed IPV, the emergency clinician only needs to follow a few simple steps (Box 59.3). The emergency clinician should do the following: (1) acknowledge the abuse experience, commend the patient for disclosing, and explain how this information will facilitate good medical care; (2) validate the patient's experience and emphasize that no one deserves to suffer physical, psychological, or sexual abuse; and (3) address the risk of acute danger to the patient or their children, determine readiness to take steps to increase safety, and provide specific means to increase safety. Individualized safety planning is complex and time-consuming and is best done by an experienced social worker or advocate in the ED or at follow up. See Fig. 59.2 for a sample template safety plan that can be used when a social worker or advocate is not immediately available.

Possible management options for patients experiencing IPV may include support groups, legal remedies (eg, orders for protection, custody, pressing charges), shelter placement, or ongoing plans for follow-up with community advocates. A discussion about past strategies and what has been successful can help guide future management. Discussing the scope and consequences of abuse on the patient and his or her children can help the patient decide which actions are most appropriate. Orders for protection have been shown to be effective in decreasing future violence, but also have the potential to increase violence.[60] Abusers who do not have respect for the law or act in public are less likely to respect protection orders. Although survivors may make undesirable decisions, the provider should support the survivor and encourage her or him to continue to speak with health care providers and contact IPV agencies in the future.

If children are present in the home, have experienced violence, or are at risk for becoming targets of violence, the emergency clinician may be mandated by law to report this to child protective services. Reporting to child protective services should be done in collaboration with the patient, explaining that this is done to increase resources to help keep the children safe; such a discussion may mitigate the fears of victims that disclosures of violence in the home would risk loss of custody of the child. A brief discussion about the long-term health effects of violence on children may be helpful.

If the patient has not disclosed, but the emergency clinician suspects IPV, a disclosure should not be forced. It is more

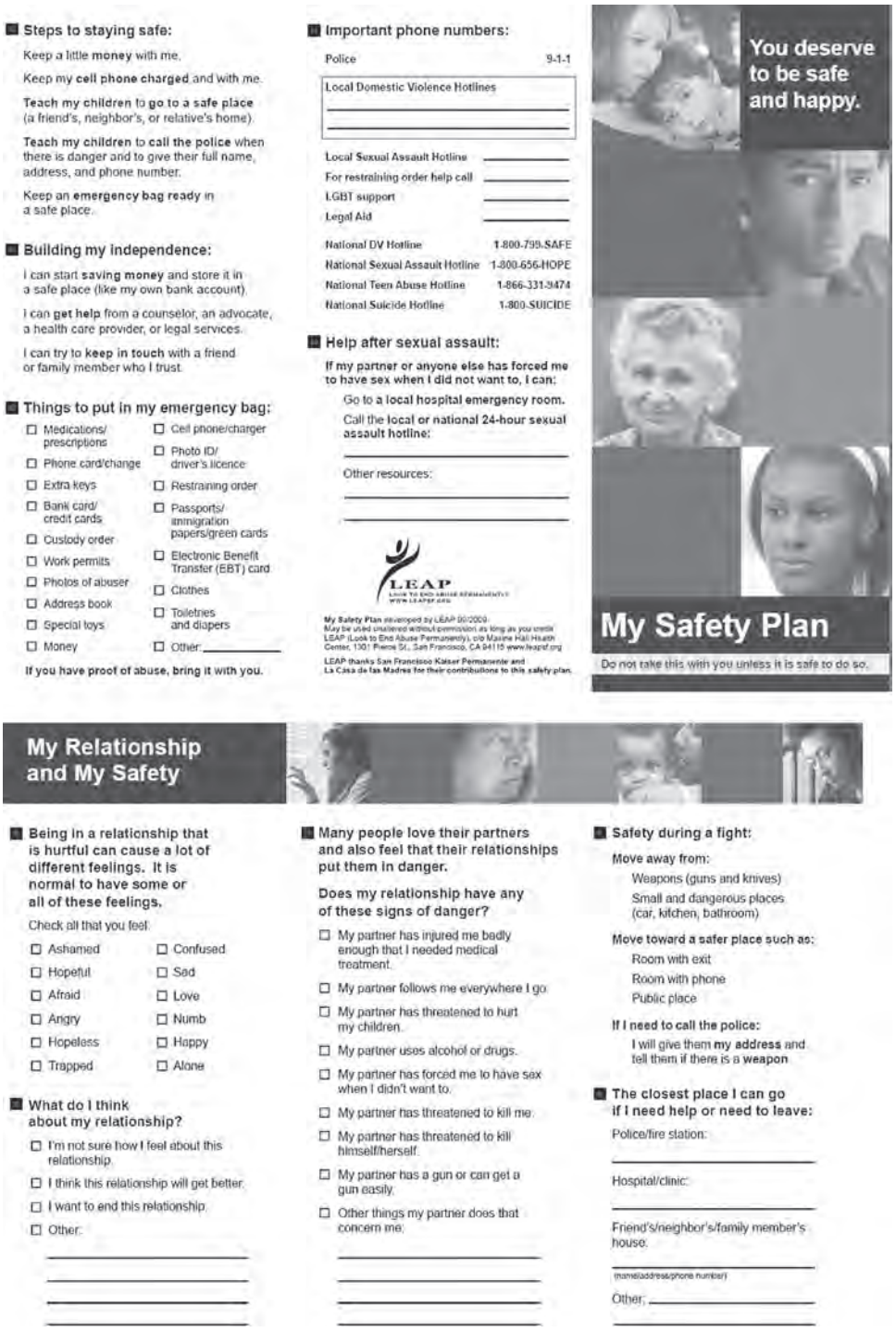

Fig. 59.2. Sample safety planning brochure. (From Look to End Abuse Permanently (LEAP): Safety plan. www.leapsf.org/pdf/LEAP-Safety-Plan-bro-10_05_09_ENG-OUTSF-B&W-low-res-for-web.pdf.)

important to express concern for the patient, explain how the condition may be related to stress (if this is true), and offer support, community domestic violence resources, and the opportunity to return for assistance.

Danger Assessment

Campbell and colleagues have developed a 20-item danger assessment tool (Fig. 59.3) that was developed and validated based on reviews of IPV-related homicides across 11 cities.[61] This study identified factors that were more often correlated with IPV violence leading to homicide and can be used to assess immediate risk for future severe violence and lethality in IPV survivors. The tool is somewhat complex to score and requires familiarity. A self-administered version of this tool is available as a downloadable application on iTunes (Fig. 59.4). A brief, five-item version of this tool (Box 59.4) has been evaluated in an ED population of identified IPV survivors at risk for severe or potentially lethal assault, with a "yes" answer to at least three of the questions as the threshold for high risk (sensitivity, 83%). This five-item tool is

DANGER ASSESSMENT

Jacquelyn C. Campbell, Ph.D., R.N.
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Several risk factors have been associated with increased risk of homicides (murders) of women and men in violent relationships. We cannot predict what will happen in your case, but we would like you to be aware of the danger of homicide in situations of abuse and for you to see how many of the risk factors apply to your situation.

Using the calendar, please mark the approximate dates during the past year when you were abused by your partner or ex partner. Write on that date how bad the incident was according to the following scale:

1. Slapping, pushing; no injuries and/or lasting pain
2. Punching, kicking; bruises, cuts, and/or continuing pain
3. "Beating up"; severe contusions, burns, broken bones
4. Threat to use weapon; head injury, internal injury, permanent injury
5. Use of weapon; wounds from weapon

(If **any** of the descriptions for the higher number apply, use the higher number.)

Mark **Yes** or **No** for each of the following. ("He" refers to your husband, partner, ex-husband, ex-partner, or whoever is currently physically hurting you.)

___ 1. Has the physical violence increased in severity or frequency over the past year?
___ 2. Does he own a gun?
___ 3. Have you left him after living together during the past year?
3a. (If have *never* lived with him, check here___)
___ 4. Is he unemployed?
___ 5. Has he ever used a weapon against you or threatened you with a lethal weapon?
(If yes, was the weapon a gun?___)
___ 6. Does he threaten to kill you?
___ 7. Has he avoided being arrested for domestic violence?
___ 8. Do you have a child that is not his?
___ 9. Has he ever forced you to have sex when you did not wish to do so?
___ 10. Does he ever try to choke you?
___ 11. Does he use illegal drugs? By drugs, I mean "uppers" or amphetamines, "meth", speed, angel dust, cocaine, "crack", street drugs or mixtures.
___ 12. Is he an alcoholic or problem drinker?
___ 13. Does he control most or all of your daily activities? For instance: does he tell you who you can be friends with, when you can see your family, how much money you can use, or when you can take the car? (If he tries, but you do not let him, check here: ___)
___ 14. Is he violently and constantly jealous of you? (For instance, does he say "If I can't have you, no one can.")
___ 15. Have you ever been beaten by him while you were pregnant? (If you have never been pregnant by him, check here: ___)
___ 16. Has he ever threatened or tried to commit suicide?
___ 17. Does he threaten to harm your children?
___ 18. Do you believe he is capable of killing you?
___ 19. Does he follow or spy on you, leave threatening notes or messages, destroy your property, or call you when you don't want him to?
___ 20. Have you ever threatened or tried to commit suicide?
___ Total "Yes" Answers

Thank you. Please talk to your nurse, advocate or counselor about what the Danger Assessment means in terms of your situation.

Fig. 59.3. Danger assessment tool.

more rapidly and easily administered, but has not been externally validated.

Mental Health Screening

Given the increased prevalence of mental health disorders, including depression, anxiety, and suicide in IPV survivors, providers should conduct a brief mental health evaluation. Houry and associates have devised and validated a brief screening tool for use in this population (Fig. 59.5).[62] A score of 4 or higher has a positive predictive value (PPV) of 96% for depression, 84% for PTSD symptoms, and 54% for suicidal ideation.

BOX 59.4

Brief Danger Assessment

1. Has the physical violence increased in frequency or severity over the past 6 months?
2. Has he ever used a weapon or threatened you with a weapon?
3. Do you believe he is capable of killing you?
4. Have you ever been beaten by him while you were pregnant?
5. Is he violently and constantly jealous of you?

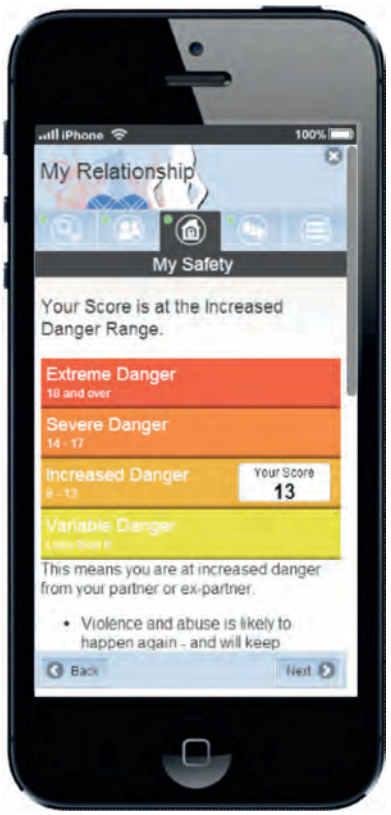

Fig. 59.4. Downloadable SmartPhone application with danger assessment.

Privacy and Confidentiality Considerations

Privacy is a concern for many IPV survivors. Any referrals or records should be released only after permission is obtained from the survivor. IPV should not be reported to police without the consent of the survivor unless mandated by law in cases of coexisting child, elder, or disabled abuse or based on state-specific reporting statutes (eg, burns or injuries inflicted by weapons). If reporting is mandated, the provider should make every effort to involve the patient. However, concerns for Health Insurance Portability and Accountability Act (HIPAA) violations do not apply in this circumstance; the privacy rule contains a provision allowing disclosure of protected health information to law enforcement in the case of reporting required by law.

Documentation

When a patient does disclose IPV, documentation in the medical record can help other health care providers and the survivor when seeking legal remedies, such as custody or restraining orders. Medical records are often admitted into a court of law as an exception to the hearsay rule, which states that someone cannot testify about something that someone else said. These statements are accepted because they are often made in the usual course of medical care or when the patient is upset and may have less impetus to fabricate. Patient statements should be documented with quotes whenever possible, or with a preceding statement—"patient states. …" Injuries should be described, recording the size or length, type of injury (eg, bruise, incised wound, abrasion), and location. EDs should have protocols for digitally photographing injuries and wounds so that they are obtained consistently, with

Brief Mental Health Screen

Feel sad?
- 0 I do not feel sad.
- 1 I feel sad.
- 2 I am sad all of the time and can't snap out of it.
- 3 I am so sad or unhappy that I can't stand it.

Have you experienced a traumatic event (rape, car accident, domestic violence, death in the family, et cetera) in the past year?
- 0 No
- 1 Yes

Wish to live
- 0 I have a medium to strong wish to live.
- 1 I have a weak wish to live.
- 2 I have no wish to live.

Wish to die
- 0 I have no wish to die.
- 1 I have a weak wish to die.
- 2 I have a medium to strong wish to die.

Total Score: _____

(A score of 4 or higher considered positive, with the need for further mental health referral.)

Fig. 59.5. Brief mental health screen. (From Houry D, Kemball RS, Click LA, Kaslow NJ: Development of a brief mental health screen for intimate partner violence victims in the emergency department. Acad Emerg Med 14:202–209, 2007.)

adequate quality for legal use. Photographs should follow the rule of 4:1 long-range picture, which includes the face for identification, one medium range, and two close range, and one with and one without a ruler (or an object for comparison, such as a coin). All photographs should be stored in tamper-resistant CDs and labeled with the name of the patient, medical record, date, and signature of the person taking the photograph. The presence of photographs should be documented in the medical record. Referrals should also be recorded in the medical record. The diagnosis of IPV or suspected IPV should be documented for the medical record for possible use in legal proceedings, as well as for purposes of research and epidemiology.

Intimate Partner Violence Coding and Diagnosis

International Classification of Diseases (ICD)–10 coding provides increased specificity for the coding of IPV (Table 59.3). New codes added to the primary category allow the provider to include adult maltreatment and neglect. Other codes added include suspected IPV (T codes) and past IPV and counseling (V codes). Similar to ICD-9, ICD-10 also includes E codes, which are used to describe the nature of the cause of the injury—for example, "Who committed the act of violence" (E967.0–E967.9), the nature of the abuse (E960–E968), the intent of the abuse or neglect (E904.0–E968.4), and the intentionality of the abuse (E980–E989).

TABLE 59.3

ICD-10 Coding Categories Used for Intimate Partner Violence

ICD-10 CODE	DESCRIPTION
995.8_	Maltreatment (abuse)
995.81	Physically abused adult
995.82	Adult emotional and psychological
995.83	Adult sexual
995.84	Adult neglect
995.85	Other, multiple forms
E	Who, intentionality, nature of abuse
T4	Suspected abuse
T7	Confirmed abuse
V	Past history of abuse

ICD, International Classification of Diseases.

DISPOSITION

Most ED patients with IPV will be treated and discharged. Patients who are victims of potentially life-threatening injuries, particularly attempted strangulation, are at great danger of future violence and should have safe plans for discharge or be offered temporary admission for safety.[63] Although shelters are one option, they are an extreme solution, typically removing the survivor from friends and family and sometimes requiring them to leave their place of employment and their children's school. Furthermore, shelters are not always an available option; they are often full and may not accept patients with substance abuse issues, teenage male children of survivors, or male or transgender survivors.

All survivors who are being discharged should receive resources for domestic violence, mental health, substance abuse, and social services. The emergency clinician may not agree with the choices made by the survivor but should always respect these decisions and offer encouragement and validation. This approach will increase the chances of a positive interaction and increase the likelihood of further help-seeking behavior.

KEY CONCEPTS

- Intimate partner violence encompasses a pattern of controlling behaviors, including intentional physical assault, sexual assault, psychological violence, and financial control.
- Treatment and intervention in intimate partner violence may be compared to a chronic disease model, whereby intervention happens over time, and relapses may be a part of the cycle. It is also critical to remember that although intervention is often offered to the survivor, responsibility for the behavior should be placed on the abusive partner.
- Treatment and intervention in IPV requires a coordinated approach, including physician training, an integrated system that includes social work and IPV counselor availability, and a close relationship with area IPV service provider groups.
- Routine screening for IPV in women of childbearing age is recommended by the USPSTF; screening methods may include paper-based, computer-based, face to face (by nurse or physician), or combination of screening methods.
- Sequelae of IPV include chronic pain, mental health issues (eg, depression, PTSD, substance abuse), STIs and unintended pregnancy, and worsening of medical problems (eg, diabetes, asthma).
- Attempted strangulation in IPV is associated with a sevenfold increased risk of an attempted or completed lethal attack, and patients should be encouraged to seek protection from further incidents.
- Some cases of IPV presenting to the ED may actually be cases of human trafficking. Cases of human trafficking have a very different dynamic and require specialized interventions.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 59: QUESTIONS & ANSWERS

59.1. By state law, you are a mandated reporter for intimate partner violence (IPV). You are concerned about violating the Health Insurance Portability and Accountability Act (HIPAA). Which of the following is correct?
- **A.** Patients are always free to act of their own free will.
- **B.** Reporting should be done without telling the patient, because you cannot report if the patient objects.
- **C.** When reporting is required by law, it does not require patient consent.
- **D.** You need a signed consent to make the report.
- **E.** You should call the legal department before reporting.

Answer: C. IPV patients are not always free to act of their own will in health care decision making. Some states have laws that require reporting to local authorities. Reporting of health conditions required by local laws are exempted from HIPAA regulations. Fear may be so profound in the IPV survivor that decision making is impaired, thus jeopardizing informed consent.

59.2. Which of the following is not suspicious for intentional injury from IPV?
- **A.** Bilateral injuries
- **B.** Ecchymosis of lower extremity
- **C.** Injuries to the breasts or abdomen
- **D.** Injuries to the hands and extensor surface of the forearms
- **E.** Pattern injuries

Answer: B. Signs of an intentional injury include a central location (ie, trunk and breasts), bilateral injuries (both arms or both legs), defensive injuries (ie, ecchymoses on the back of the hand as a result of protecting the face), and patterned injuries (having the markings of an object, such as the sole of a shoe or a burn with the imprint of an iron).

59.3. Which of the following about a woman should alert the provider that the patient may be a victim of human trafficking, rather than IPV?
- **A.** Appears much younger than her stated age and does have not identification with her
- **B.** Is accompanied by her partner who will not leave her side
- **C.** Is easily startled
- **D.** Is evasive in answering questions about her injuries
- **E.** Presents with a traumatic injury at night

Answer: A. Most of these situations apply to the IPV survivor and victim of human trafficking. Presentations that should alert the provider that the patient may be a victim of human trafficking rather than IPV include a person who looks much younger than her stated age (she often is younger). Other clues include a victim that does not have identification papers (the "employer" often takes these from the victims under the guise of "keeping the documents safe"), but this also prevents the victim from leaving without these documents. Untreated sexually transmitted infections (STIs, including pelvic inflammatory disease), malnourishment, and addiction to drugs and alcohol. It is important for the provider to consider the presentations of human trafficking, because although the victim may not be identified in the ED—for a number of reasons, including lack of trust and familiarity with the ED provider, the resources that may be helpful are somewhat different than those used by IPV survivors.

59.4. Key management steps after identifying a patient experiencing IPV include which of the following?
- **A.** Creating a detailed and comprehensive safety plan
- **B.** Emphasizing the importance of leaving the abuser immediately
- **C.** Keeping the patient in the ED until she agrees to contact police and have a restraining order issued
- **D.** Providing validation about disclosing the abuse
- **E.** Reinforcing the importance of secrecy about the abuse until the woman has left the home

Answer: D. Emergency clinicians should validate the disclosure of abuse, emphasize that the victim is not at fault, and encourage future discussions with IPV community agencies or other health care providers. Immediate safety should be assessed, but most patients will not want to leave the abuser immediately; however, a positive initial conversation may begin the process of ending the abusive relationship. A templated list will allow the ED staff to create a basic safety plan with the patient; an individualized plan is best done in conjunction with trained domestic violence advocates, typically in follow-up.

CHAPTER 60

Oral Medicine

Ryan Anthony Pedigo | James T. Amsterdam

INTRODUCTION

Dental concerns are a common chief complaint in the emergency department (ED). The spectrum of oral disease ranges from bothersome to emergently life-threatening. This chapter covers disorders of the tooth, gingiva and periodontium, dental procedure-related issues, odontogenic and deep infections of the head and neck, traumatic dental emergencies, as well as temporomandibular joint disorder (TMD) and dislocation.

DISORDERS OF THE TOOTH

Principles

Anatomy

Humans have 20 deciduous (primary) teeth and 32 permanent (secondary) teeth, which are supported and maintained in the maxilla (upper teeth) and mandible (lower teeth) by the periodontium. The tooth that is normally visible in the mouth is considered the crown, whereas the tooth that is under the gingival line is the root (Fig. 60.1).

The crown of the tooth has three layers; from outside to inside they are the enamel, dentin, and pulp. The enamel is the only part of the tooth that is visible in the absence of pathology (eg, fractures, caries) and is a hard coating that protects the tooth. The next layer deep to the enamel is the dentin, which is an intermediate layer between the enamel and the pulp (for the crown) and between the cementum and the pulp (for the root). Yellow in appearance, dentin is comprised of porous microtubules, supports the enamel, and acts as a cushion during mastication. If dentin is exposed from caries or trauma, the patient will have tooth sensitivity and/or pain. The deepest layer is the pulp cavity, which houses its neurovascular supply.

The normal primary, or deciduous, dentition ("baby teeth") consists of 10 mandibular and 10 maxillary teeth (Fig. 60.2). The lower central incisor is the first tooth to erupt at approximately 6 months of age; all primary teeth should be present by 3 years of age. The permanent dentition begins to erupt at approximately 5 to 6 years of age with the appearance of the first molar.

The permanent dentition consists of 32 teeth; there are 8 teeth per quadrant (eg, right upper, right lower, left upper, left lower). From medial to lateral, the names of the teeth in each quadrant are: the central incisor, lateral incisor, canine, two premolars (also called *bicuspids*), and three molars (also called *tricuspids*). The third molars ("wisdom teeth") are the last to erupt, appearing at approximately 16 to 18 years of age. The permanent dentition are numbered from 1 to 32, starting with the upper right third molar (1) and moving to the upper left third molar (16), to the lower left third molar (17), and to the lower right third molar (32). The starting point for this numbering system can be recalled by the mnemonic "upright." It is often easier to name the tooth or teeth involved; for instance, if tooth 8 is injured, the clinician could describe the tooth as the "right maxillary central incisor" or the "right upper central incisor." If multiple teeth are involved, numbering is more concise.

Specific terminology is also used to describe the various surfaces in the mouth. The *facial* (also referred to as *labial* or *buccal*) surface faces outside the oral cavity; the *oral* (also referred to as *palatal* for upper teeth, or *lingual* for lower teeth) surface faces the tongue; the *mesial* surface is toward the midline; and the *distal* surface is toward the ramus of the mandible. The *interproximal* surface refers to the contacting area of adjacent teeth, and the *occlusal* surface refers to the biting area. Finally, *apical* is in the direction of the root, whereas *coronal* is toward the crown of the tooth.

Pathophysiology

Dental caries are caused by breakdown of the teeth secondary to bacterial activity. Bacteria generate acid as a byproduct from cellular metabolism of food left on the tooth surface, subsequently demineralizing the enamel. Once the enamel is breached, the microporous dentin is able to transmit saliva, byproducts of the bacteria, and the bacteria to the pulp. The pulp initially reacts with a hyperemic response, which continues to an inflammatory state termed *pulpitis*, which can be reversed. Untreated, pulpitis can further progress to total degeneration and necrosis *(irreversible pulpitis)*.

Cracked tooth syndrome (CTS) is a condition that generally affects adults 30 to 60 years old and is defined as "a fracture plane of unknown depth and direction passing through tooth structure that may progress to communicate with the pulp and/or periodontal ligament."[1] These fractures can occur due to either excessive forces on a normal tooth (eg, accidentally biting on a hard object, such as metal or bone), or normal forces on a weakened tooth (eg, a carious tooth or one that has undergone dental procedures previously). Because of the mechanism of injury, teeth subjected to larger forces (such as the mandibular molars) are most commonly affected. If misdiagnosed, the fracture may propagate into the pulp or periodontal ligament and compromise viability of the tooth.

Clinical Features

Dental caries is the most common cause of odontogenic pain. The patient may give a variable history of a sudden or gradual onset of a sharp to dull, throbbing pain. In most cases, the patient can

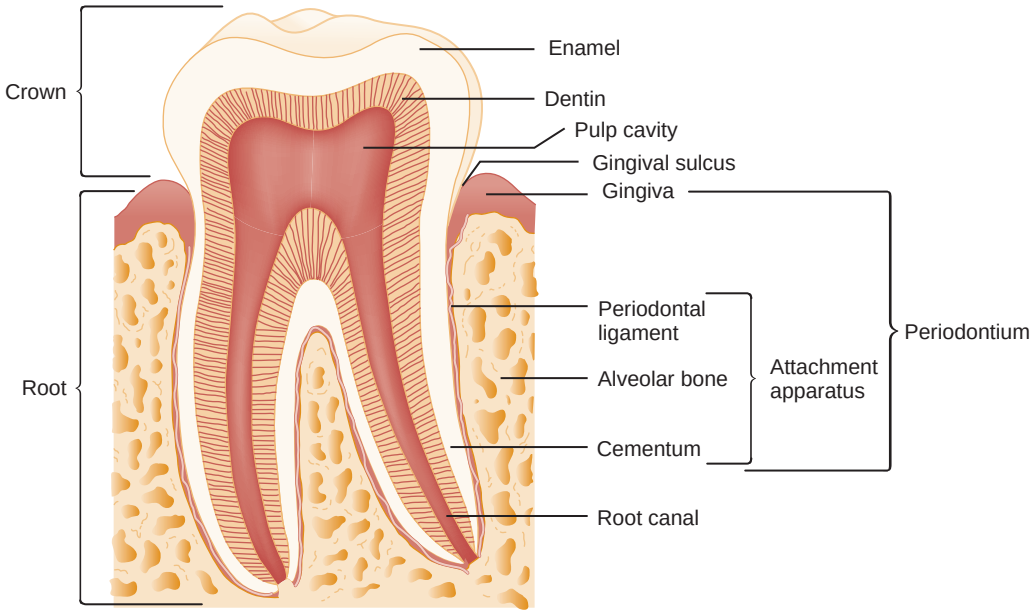

Fig. 60.1. The anatomy of the tooth and associated attachment apparatus.

indicate the specific tooth involved, but pain may be generalized. Early (reversible) pulpitis is sensitive to changes in temperature and pressure; irreversible pulpitis can have pain without any stimulus.

CTS patients may provide a history of preexisting dental procedures or disease, or they may have a history of occlusive trauma. Presenting symptoms are similar to those of dental caries.

Physical Examination

The physical examination described here is applicable to all sections of this chapter. Ideally the patient should be placed in a dental or ear, nose, and throat chair or on a bed at a 45-degree angle with adequate lighting. Pediatric patients often are examined while sitting in the parent's lap.

Pediatric patients may require anxiolysis or sedation to permit adequate oral assessment and treatment of a painful condition. Pediatric procedural sedation is described in Chapter 162.

A complete examination includes inspection of the oral cavity, gingiva, teeth, and surrounding structures (eg, throat, neck, sinuses) if indicated. Assess teeth for caries or cracks. Localization of the involved tooth may be accomplished by percussing the teeth or by having the patient bite on a tongue blade. Exquisite pain to percussion suggests an underlying periapical abscess (discussed in the section Odontogenic and Deep Neck Infections).

Examine the nares and sinuses for discharge and pain, respectively, to evaluate for sinusitis. Palpate the temporomandibular joint (TMJ) with opening and closing of the jaw to assess for "clicks" or "pops," which may indicate the etiology of pain as TMJ disorder. In older individuals, palpate the temporal artery for tenderness and prominence.

Differential Diagnoses

Most dental pain in the ED is odontogenic, the most common being pulpitis due to caries. Tooth pain is not always odontogenic, however. Unilateral upper tooth pain (usually the posterior teeth) can be related to maxillary sinus dysbarism or inflammation. Trigeminal neuralgia can present as tooth pain, but it is usually lancinating and may not be related to temperature changes or mastication (see Chapter 95). Atypical odontalgia is a centralized trigeminal neuropathy localized in a tooth or teeth. Frequently-misdiagnosed, patients will often undergo multiple dental procedures with worsening of their pain.[2] Atypical odontalgia causes persistent throbbing or burning pain that does not fulfill diagnostic criteria for another disorder and therefore is a diagnosis of exclusion.

Older patients with temporal (giant cell) arteritis may have pain with mastication because of jaw claudication.

Diagnostic Testing

No laboratory or radiographic testing is routinely indicated.

Management

Management of dental caries with pulpitis and CTS is aimed at treating the patient's pain and referring to a dentist for definitive care.

Severe pain can be treated with supraperiosteal infiltration of local anesthetic to provide temporary relief (Fig. 60.3). To perform this, dry the area with gauze, apply a topical anesthetic to the gingiva (eg, 20% benzocaine or 5% lidocaine) and allow it to sit for 5 minutes. Inject 1 to 2 mL of local anesthetic (eg, 2% lidocaine) through the mucobuccal fold of the affected tooth with the bevel facing the tooth. Alternatively, an inferior alveolar nerve block may be used when multiple lower teeth are affected on one side.

The patient can be discharged with ibuprofen 400 to 600 mg tablets every 4 to 6 hours. Nonsteroidal antiinflammatory drugs (NSAIDs) given at scheduled times (rather than as needed) are more effective than opioid analgesics for these conditions.[3] However, for severe odontalgia, a short course of opioid analgesics *in addition to* scheduled NSAID administration is reasonable. Opioid analgesics should not be prescribed for long-standing dental problems, such as well-established caries.

Disposition

The patient with odontalgia from dental caries or CTS should follow-up with a dentist within the week. Those with CTS should be instructed to avoid chewing on the affected side to avoid further trauma and fracture propagation.

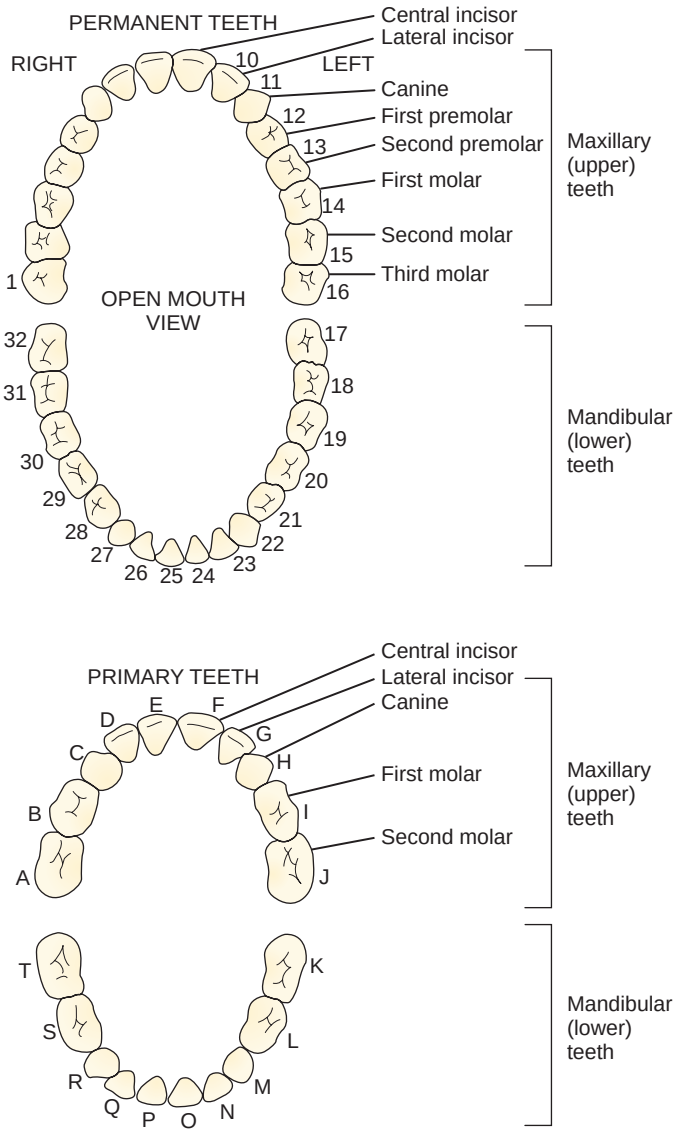

Fig. 60.2. Identification of teeth, adult and child. Conventional numbering starts with the upper right third molar 1 to the upper left third molar 16; lower left third molar 17 to the lower right third molar 32. For the primary dentition, A to J and K to T. (Modified from Roberts J: Roberts & Hedges' clinical procedures in emergency medicine, ed 6, Philadelphia, 2014, Elsevier, Fig. 64.2, p 1344.)

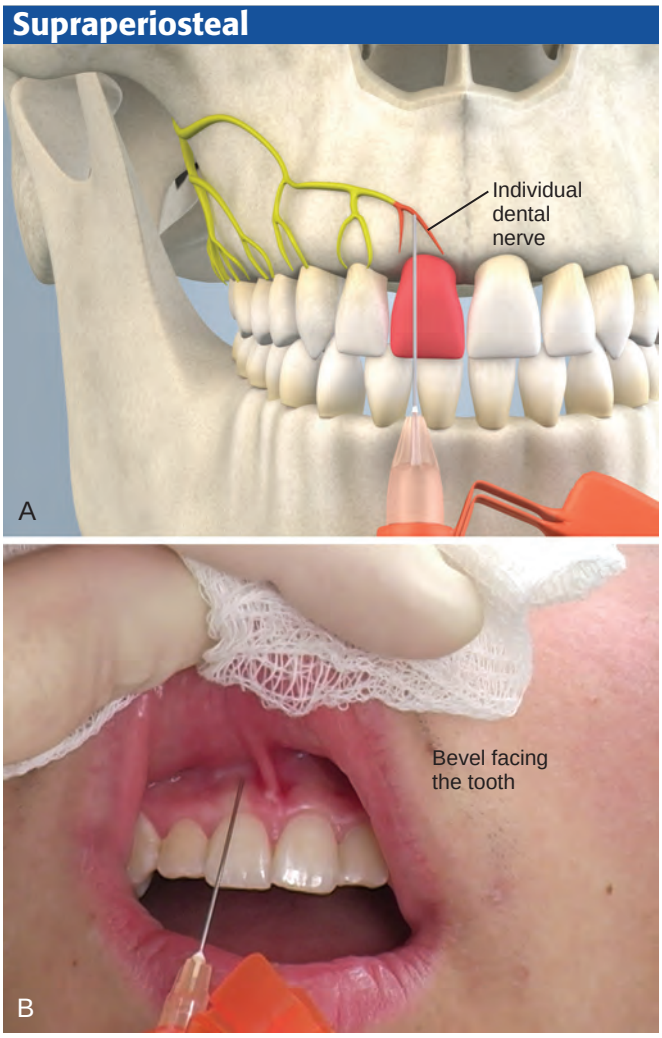

Fig. 60.3. **A** and **B,** Supraperiosteal nerve block for anesthesia of individual teeth. (From Roberts J: Roberts and Hedges' clinical procedures in emergency medicine, ed 6, Philadelphia, 2014, Elsevier, Fig. 30.5.)

DISORDERS OF THE GINGIVA AND PERIODONTIUM

Principles

Anatomy

The periodontium serves to hold the teeth in place, as well as protect the root from bacteria. Surrounding the root of the tooth instead of enamel is cementum, which helps fix the tooth to the alveolar bone by attaching to the periodontal ligaments. Collectively, the periodontal ligament, alveolar bone, and cementum comprise the attachment apparatus. The attachment apparatus plus the gingiva ("gums") is referred to as the *periodontium*. The gingiva consists of the mucosal tissue that overlies the mandible and maxilla inside the mouth and, in the normal state, acts as a barrier to infection and injury.

Pathophysiology

Gingivitis and Periodontitis. Periodontitis is inflammation of the supporting structures of the teeth (gingiva, alveolar bone, cementum, periodontal ligament). Degradation of the support structure leads to loss of alveolar bone and subsequent loosening or loss of teeth.

In necrotizing periodontal diseases, polymicrobial bacteria (with a predominance of *Fusobacterium* and spirochetes) invade the tissue and cause pain, bleeding, and destruction. These diseases include necrotizing gingivitis (acute necrotizing ulcerative gingivitis [ANUG], or "trench mouth") if only the gingiva are involved, necrotizing periodontitis if the attachment apparatus in addition to the gingiva is involved, and necrotizing stomatitis if the disease further extends into the surrounding oral mucosa (Fig. 60.4). Infection of the tonsils and pharynx is termed *Vincent's angina*. The most diffuse necrotizing disease is termed *noma* (cancrum oris, fusospirochetal gangrene) where the entire mouth is involved and is often fatal; this disease is most commonly encountered in young children in developing countries (Fig. 60.5).

Pericoronitis. The gingiva and surrounding tissue can also become inflamed due to a condition known as *pericoronitis*. As teeth start to erupt, debris and bacteria can accumulate between

Fig. 60.4. Necrotizing stomatitis. The gingiva has classic papilla necrosis but the oral mucosa is also involved, making this condition necrotizing stomatitis and not simply necrotizing gingivitis. (From Smith J: HIV and AIDS in the adolescent and adult: an updated for the oral and maxillofacial surgeon. Oral Maxillofac Surg Clin North Am 20(4):535–565, 2008, Fig. 8.)

Fig. 60.5. Noma (cancrum oris, fusospirochetal gangrene) is usually found in children in developing countries and can be disfiguring or even fatal. Noma represents the most severe end of the necrotizing periodontal disease spectrum. (From Farrar J, Hotez PJ, Junghanss T, et al, editors: Manson's tropical diseases, ed 23, London, 2014, Saunders/Elsevier, Fig. 29.1.)

the tooth and the surrounding soft tissue (this "gum flap" overlying the tooth is called the *operculum;* Fig. 60.6). The third molar ("wisdom tooth") is most commonly implicated, and symptoms typically occur in the second or third decade of life. This condition is more common with teeth that are malerupted or impacted. As the tissue becomes enlarged due to inflammation, the problem is worsened by trauma to the area during mastication.

Gingival Hyperplasia. Gingival hyperplasia can occur secondary to medications. The most commonly-associated drug classes are anticonvulsants, calcium channel blockers, and immunosuppressants (Table 60.1).

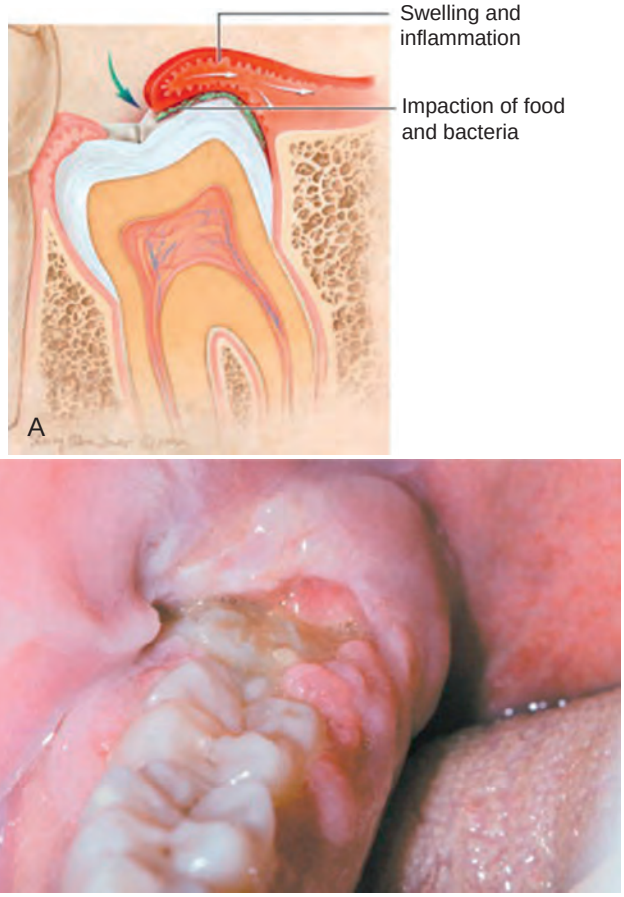

Fig. 60.6. Pericoronitis. **A,** Illustration of pericoronitis with swollen and inflamed operculum. **B,** Picture of pericoronitis of the third molar with erythema and inflammation of the surrounding tissue. (**A,** From Buttaravoli P, Leffler SM: Minor emergencies, ed 3, St Louis, 2012, Elsevier, Fig. 46.1; **B,** From Neville BW, Damm DD, Allen CM, et al: Oral and maxillofacial pathology, ed 4, St Louis, 2016, Elsevier.)

TABLE 60.1

Medication Classes and Their Risk of Drug-Induced Gingival Overgrowth

CATEGORY	PHARMACOLOGIC AGENT	PREVALENCE
Anticonvulsants	Phenytoin	50%
	Sodium valproate (valproic acid)	Rare
	Carbamazepine	None
Immunosuppressants	Cyclosporine	25% to 30% (adults) 70% (children)
Calcium channel blockers	Nifedipine	6% to 15%
	Felodipine	Rare
	Amlodipine	Rare
	Verapamil	<5%
	Diltiazem	5% to 20%

From Song HJ: Periodontal considerations for children. Dent Clin North Am 57(1):17–37, Table 1.

Clinical Features

Historical Features

The presentation of periodontitis is variable, depending on the severity of the disease. Simple gingivitis presents with complaints

of swollen gingiva that are tender, gingival bleeding after manipulation (eg, brushing teeth, flossing), and halitosis from bacterial overgrowth. Periodontitis involves the attachment apparatus as well; therefore, patients often will have the aforementioned symptoms but in addition may have gingival recession from loss of alveolar bone and concomitant teeth loosening. Individuals with more severe periodontitis may also report fevers and malaise. A medication history should be obtained to assess for drug-induced gingival overgrowth.

Physical Examination

The gingiva should be inspected for erythema, edema, and hyperplasia. Gingivitis is typically painless but will show inflammation, edema, and bleeding with probing. The interdental papillae should normally be pointed but, in necrotizing disease, the interdental papillae become blunted, "punched out," ulcerated, and covered with a whitish-yellow pseudomembrane of necrotic tissue and bacteria. The triad for necrotizing periodontal diseases includes papillary necrosis, gingival bleeding, and pain.[4] More severe infection (eg, necrotizing stomatitis) may also have associated submandibular lymphadenopathy.

Mobile teeth suggest alveolar bone loss, where the disease has progressed deeper than the gingiva. Partially-erupted teeth should be examined for evidence of pericoronitis. The overlying tissue (operculum) should be assessed for bleeding and inflammation.

Differential Diagnosis

Ulceration of the mucosa can be caused by necrotizing stomatitis but also by aphthous ulcers and other oral lesions. Aphthous ulcers are 2 to 3 mm in diameter and have a whitish center and are tender, but they usually do not become infected. The neighboring gingiva should not be affected and appear healthy. Recurrent aphthous lesions can occur with Behçet disease and human immunodeficiency virus (HIV). Treatment is symptomatic with hydrogen peroxide rinses and topical anesthetics. Another consideration is acute herpetic gingivostomatitis, which is the most common manifestation of primary herpes simplex virus infection in children. For patients with gingival hyperplasia, an infiltrative process (such as, leukemia) should be considered, especially if the patient is not on any medications associated with hyperplasia.

Diagnostic Testing

Necrotizing periodontal disease occurs most often in patients with diabetes, and those who are immunocompromised, such as patients with HIV or long-term immunosuppressive therapy. Blood glucose and HIV testing may be initiated in the ED or as part of follow-up.

Management

Gingivitis and Periodontitis

Gingivitis will respond to proper oral hygiene, and the patient should be instructed on twice daily flossing and brushing. Antibacterial mouth rinses should be prescribed if the gingivitis is severe: either chlorhexidine rinses (preferred agent, 0.12% to 0.2%) or 3% hydrogen peroxide (diluted 1:1 with warm water) should be performed twice daily. Necrotizing periodontal disease should be treated by a dentist, who will need to débride the necrotic tissue. Oral antimicrobials should be prescribed for patients with extensive disease or systemic effects; see Table 60.2 for suggestions.

All patients who smoke should be counseled on smoking cessation; this is the most common risk factor in HIV-negative patients. Analgesia with an NSAID or acetaminophen relieves pain and facilitates appropriate oral hygiene, because periodontal conditions are painful. Opioid analgesics rarely are needed. Topical analgesics (eg, viscous lidocaine) can also be effective, but should be applied only to small areas; patients must be cautioned about targeted use to avoid local anesthetic toxicity.

Pericoronitis

Patients with pericoronitis should receive rinses as described for periodontal disease; systemic antibiotics are not necessary unless the pericoronitis is severe. In such cases, antibiotics are as described for periodontal disease. Patients with pericoronitis should be referred to dentist or oral surgeon for local treatment of the operculum or, if impacted or malerupting, removal of the tooth.

Disposition

Patients with gingivitis are discharged with dental follow-up in 1 to 2 weeks. Those with necrotizing gingivitis or mild necrotizing stomatitis should see a dentist within 24 to 72 hours, because they require frequent débridement until the infection is controlled. Patients with severe necrotizing stomatitis or gingivitis should have emergency dental consultation (within 24 hours). Patients with significant systemic symptoms (especially fever), those who are immunocompromised with severe oral disease, and those who are unable to adequately hydrate because of mouth pain are admitted to hospital or placed in an observation unit for intravenous (IV) hydration, analgesia, and dental or oral medicine consultation.

TABLE 60.2

Recommended Antibiotics for Severe Periodontal Disease, Severe Pericoronitis, and Simple Odontogenic Infections

ANTIBIOTIC	DOSAGE	DURATION	NOTES
Penicillin V	500 mg by mouth qid	10 days	
Amoxicillin/clavulanate	500 mg/125 mg by mouth tid	10 days	
Metronidazole	500 mg by mouth bid	10 days	If allergic to penicillin
Clindamycin	300 mg by mouth qid	10 days	If allergic to penicillin
Nystatin	100,000 units/mL 5 mL swish/spit qid	10 days	If immunocompromised or suspect candidal infection

DISORDERS INVOLVING DENTAL PROCEDURES

Principles

Anatomy

The most common dental procedures include fillings, crowns, root canals, and extractions. Fillings cover caries and protect the underlying tooth from further decay and infection. Crowns (or "caps") cover the portion of the tooth exposed above the gingiva and require an intact root for attachment. Root canals involve opening the pulp chamber, removing pulp tissue and root, sterilizing the canal, and sealing it to prevent ingress of saliva and contamination. Extractions are performed for non-salvageable teeth and involve removal of the entire tooth. All of these procedures can have complications that may bring a patient to the ED.

Pathophysiology

Dislodgement of a filling or crown can expose the highly-innervated pulp and lead to significant odontalgia. Similarly, the pulp can be irritated during procedures that involve the pulp (eg, root canal) because of residual gas bubbles that are inadvertently sealed into the cavity. In addition, any swelling that may elevate the tooth even minimally post-procedurally will cause premature and painful contact during mastication.

After an extraction, the patient will have an adherent clot in the fossa where the root of the tooth previously was. If this clot becomes dislodged (typically 3 to 4 days post-extraction) a condition called *alveolar osteitis* ("dry socket") can occur (Fig. 60.7). The incidence of alveolar osteitis is 2% after routine extraction but as high as 20% to 30% after removal of impacted mandibular third molars. The pain is secondary to localized inflammation of the now-exposed surrounding alveolar bone.

Clinical Features

Historical Features

Patients usually can provide the history of their dental procedures; dislodgement of a filling or crown can happen at any time but is more common early or with trauma. Post-root canal pain due to retained gas bubbles typically occurs immediately after the initial nerve block wears off.

Fig. 60.7. Alveolar osteitis ("dry socket") with extraction site devoid of clot. (From Krakowiak PA: Alveolar osteitis and osteomyelitis of the jaws. Oral Maxillofac Surg Clin North Am 23[3]:401–413, 2011, Fig. 1.)

Alveolar osteitis characteristically presents 3 to 4 days after an extraction with severe dull, aching pain at the site of extraction, which is often associated with halitosis and a foul taste in the mouth. They may have an antecedent history of sucking through a straw or other activity that dislodged the clot.

Those with continued bleeding after an extraction should have their medical history and medications reviewed with specific attention to coagulopathies, such as hemophilia, as well as medications, such as anticoagulants, including anti-platelet agents.

Physical Examination

Patients with dislodged fillings or crowns will have exposed dentin or pulp over the affected teeth. Post-extraction pain secondary to inflammation or retained gas bubbles may have a normal examination. Those with alveolar osteitis will have a tooth socket that has at least partial loss of the blood clot with exposed bone.

Diagnostic Testing

An international normalized ratio (INR) is indicated for patients who are on warfarin and have post-extraction bleeding.

Management

For teeth with exposed pulp, calcium hydroxide cement (Dycal) application to cover the exposed surface may provide symptomatic relief. If the patient has a loose or displaced crown, the crown itself can be reimplanted if the tooth surface is clean; place the calcium hydroxide cement and ask the patient to bite down.

Analgesia with NSAIDs is generally sufficient. For those with severe pain and objective findings, a short course (2 to 3 days) of an opioid can be prescribed. Patients with retained gas bubbles after a root canal have intense pressure-like pain, often refractory to analgesics and even nerve blocks, and they should be referred to an endodontist, preferably the clinician who performed the initial procedure.[5]

Patients with alveolar osteitis should receive NSAID analgesia and have prompt (next working day) consultation by their treating oral surgeon. If follow-up will be delayed, nerve block followed by gentle irrigation of the socket with sterile saline can be performed. The socket should not be curetted and the clot should not be removed if residual clot exists, because this will expose more bone and lead to higher risk of continued pain and osteomyelitis. Medicated iodoform gauze with eugenol (an anesthetic) can be placed in the cavity and changed by the patient's surgeon within 24 to 48 hours with repeat irrigation. No other treatment for alveolar osteitis has enough evidence to recommend use.[6]

Extraction site bleeding should first be managed with direct pressure with the patient biting on dry gauze. If this fails, perform a supraperiosteal nerve block with lidocaine *with epinephrine*, because this will decrease blood supply as well as anesthetize the area so that more firm direct pressure can be applied. Repeat the direct pressure. If bleeding continues after a second trial of pressure, the socket should be packed with absorbable gelatin sponge (Gelfoam) with or without topical thrombin. The gingiva can also be loosely closed with a 3-0 absorbable suture in a figure-of-eight fashion. If there is significant ongoing hemorrhage that will not respond to local measures, reversal of anticoagulation may be undertaken in consultation with the patient's cardiologist (see Chapter 114).

Disposition

In the absence of infection and with control of bleeding, patients with dental procedure-related complications can be discharged

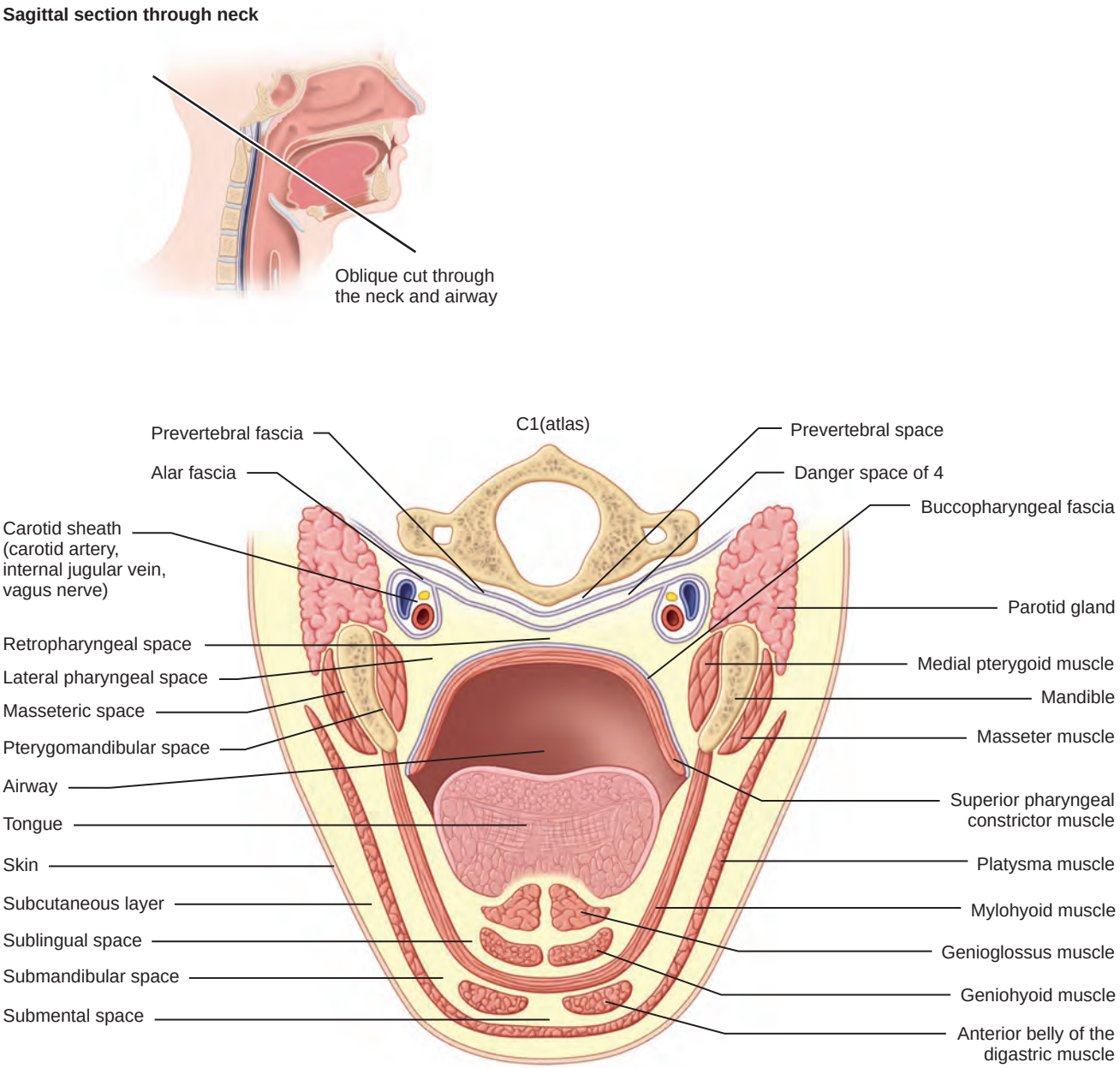

Fig. 60.8. Anatomy of maxillofacial space infections. (From Bagheri SC: Clinical review of oral and maxillofacial surgery, ed 2, St Louis, 2013, Elsevier/Mosby, Fig. 4.4.)

home with follow-up with the provider who performed the procedure.

ODONTOGENIC AND DEEP NECK INFECTIONS

Principles

Anatomy

The anatomy of the neck is complex and comprises multiple true and potential spaces. There are fascial planes that normally act to contain infection; with aggressive organisms, an immunocompromised state, or surgical breech of these planes, further extension can occur. For odontogenic infections, these spaces can be divided into those involved with maxillary infections and those involved with mandibular infections. More severe infections of the head and neck (such as, those involving these spaces) are called deep neck infections. An overview of the anatomy relevant to the discussion is presented in Fig. 60.8.

There are two primary spaces that can be involved with maxillary deep neck infections: the canine and buccal space. Infections of the root of the maxillary canine can lead to a *canine* space infection and often present with flattening of the ipsilateral nasolabial fold (Fig. 60.9). The major complication of this type of infection is cavernous sinus thrombosis. The *buccal* (buccinator) space can be involved with maxillary molars but also with mandibular molars (Fig. 60.10). Occasionally, the maxillary sinus itself can be involved.

The mandible has three associated primary spaces: submental, sublingual, and submandibular. The *submental* space is bound laterally by the digastric muscles and therefore causes a very discrete midline swelling when involved in a deep neck infection (Fig. 60.11); the mandibular incisors are the main culprits, because other teeth do not overly this space. The *sublingual* space is

between the floor of the mouth and the mylohyoid muscle, but it does not have a posterior border and therefore communicates with the submandibular space. Characteristically, infection of this space causes elevation of the tongue and firmness of the floor of the mouth (Fig. 60.12). Lastly, the *submandibular* space is usually involved as an extension of infection from a mandibular molar (Fig. 60.13). Although submandibular space infections have their medial border at the anterior belly of the digastric muscle, it can easily bypass this and enter the submental space and move to the contralateral submandibular space, as well as the sublingual space (because there is no posterior boundary); this leads to infection of all three spaces and causes *Ludwig angina.*

Fig. 60.9. Left canine space infection. (From Lypka M, Hammoudeh J: Dentoalveolar infections. Oral Maxillofac Surg Clin North Am 23[3]:415–424, 2011.)

These primary space infections can progress to secondary spaces and lead to more wide-spread infection into the neck and mediastinum. A discussion of these spaces (eg, retropharyngeal, parapharyngeal, prevertebral, and "danger" spaces) can be found in Chapter 65.

Pathophysiology

Oropharyngeal infections are the most common cause of deep neck infections in children (Fig. 60.14, Scenario 1 and 2). Acute tonsillitis can lead to peritonsillar abscesses and, if further invasion of the parapharyngeal space occurs, can spread into either the retropharyngeal (leading to a retropharyngeal abscess) or submandibular space (potentially leading to Ludwig angina). Children can have retropharyngeal lymphadenopathy with pharyngeal and/or sinus infections, which can lead to retropharyngeal cellulitis, lymphadenitis, or abscess. By age 4, there is spontaneous atrophy of these nodes; therefore, a retropharyngeal abscess in the absence of trauma (esophagogastroduodenoscopy [EGD], bone stuck in

Fig. 60.11. Submental space infection with characteristic discrete midline swelling. (From Flynn TR: Complex odontogenic infections. In Hupp JR, Ellis E, Tucker MR: Contemporary oral and maxillofacial surgery, ed 6, St Louis, 2014, Elsevier/Mosby, pp 319–338.)

Fig. 60.10. Left buccal space infection. **A,** Schematic. **B,** Photograph. (From Lypka M, Hammoudeh J: Dentoalveolar infections. Oral Maxillofac Surg Clin North Am 23[3]:415–424, 2011.)

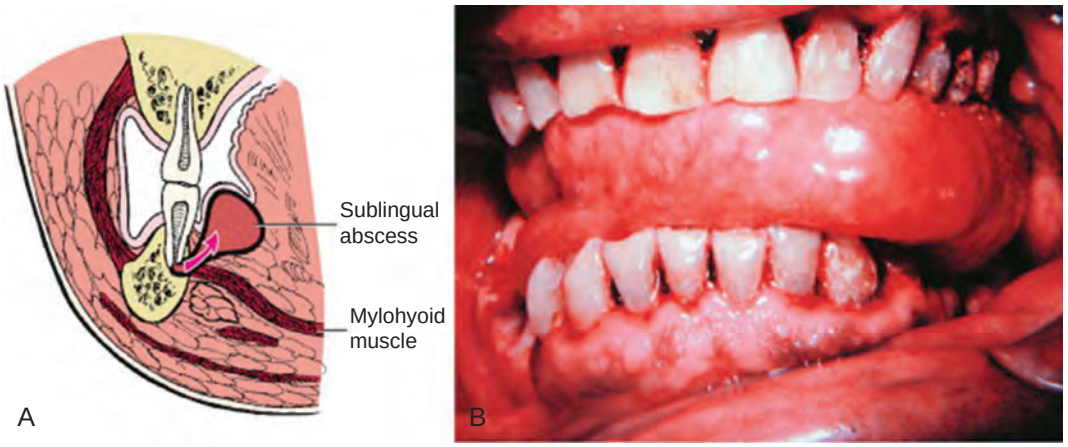

Fig. 60.12. **A,** The sublingual space lies between the oral mucosa and the mylohyoid muscle. The space is primarily involved by infection from mandibular premolars and first molar. **B,** Significant swelling causing elevation of the tongue. (From Flynn TR: Complex odontogenic infections. In Hupp JR, Ellis E, Tucker MR: Contemporary oral and maxillofacial surgery, ed 6, St Louis, 2014, Elsevier/Mosby, pp 319–338.)

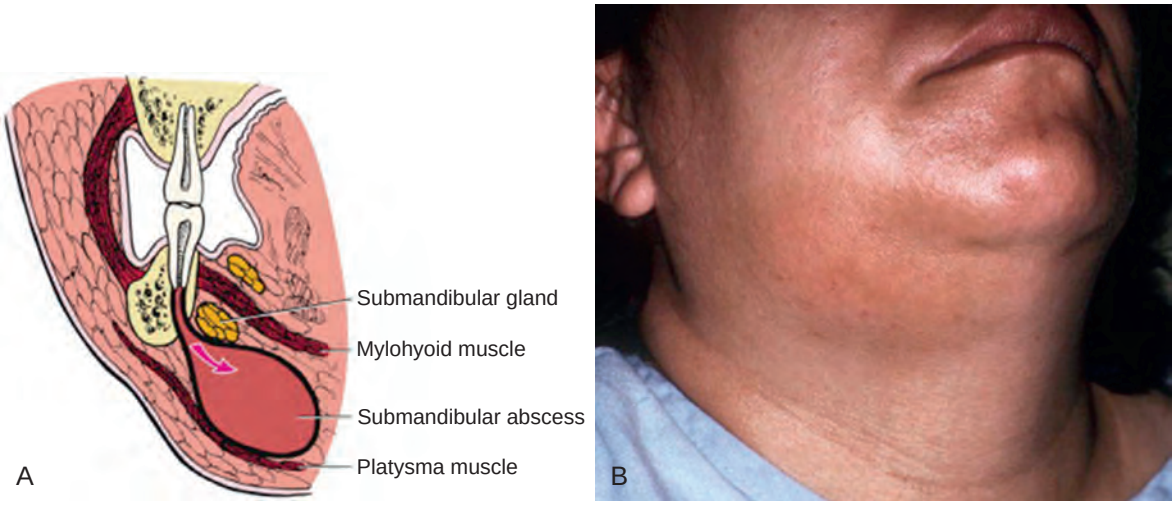

Fig. 60.13. **A,** Schematic of the submandibular space. **B,** Significant swelling that is bound medially by the digastric muscle. (From Flynn TR: Complex odontogenic infections. In Hupp JR, Ellis E, Tucker MR: Contemporary oral and maxillofacial surgery, ed 6, St Louis, 2014, Elsevier/Mosby, Figs. 17.15 and 17.16.)

throat, and so on) in older children or adults is rare.[7] Another complication of oropharyngeal infections is septic thrombophlebitis of the internal jugular vein, termed *Lemierre syndrome,* and is most frequently secondary to *Fusobacterium necrophorum.* Septic emboli dislodge from the internal jugular vein and lead to necrotic pleuropulmonary emboli, abscesses, and empyema. More distant embolic events can occur, leading to brain abscesses, meningitis, and septic joints.

Dental infections are the most common cause of deep neck infections in adults (see Fig. 60.14, Scenario 3). Pus can leak from the apex of an infected tooth root and form a periapical abscess, confined within the alveolar bone (Fig. 60.15). The abscess may break through the cortical plate of either the mandible or the maxilla and spread subperiosteally, extending into the previously-described spaces. When the submental, submandibular, and sublingual spaces are involved with cellulitis with or without abscess, Ludwig angina occurs. Ludwig angina is a bilateral, boardlike swelling involving the submandibular, submental, and sublingual spaces with elevation of the tongue (Fig. 60.16). The most serious immediate sequelae is airway obstruction. A characteristic brawny induration is present; there is no fluctuance for incision and drainage. Hemolytic Streptococcus is most commonly responsible for the infection, although a mixed staphylococcal-streptococcal flora is common, and both may lead to an overgrowth of anaerobic gas-producing organisms, including *Bacteroides fragilis.*

Facial cellulitis is typically polymicrobial with a predominance of anaerobes, which reflects typical oropharyngeal flora.[8] However, atypical organisms can also be present: Actinomyces can cause cervicofacial actinomycosis with draining sinus tracts, tuberculosis can cause cervical lymphadenopathy (scrofula) with secondary infection, and *Bartonella henselae* (the causative organism for cat scratch disease) can cause cervical lymphadenitis.

Clinical Features

Historical Features

Facial cellulitis and deep neck infections have many common historical features: in children, an antecedent sinus or pharyngeal infection is common; in adults, a history of poor dentition is common. Frequently-reported symptoms include pain at the affected site, fever, and malaise.

Recent dental work or trauma, recent upper airway manipulation or surgery, intravenous (IV) drug abuse, sinusitis, and

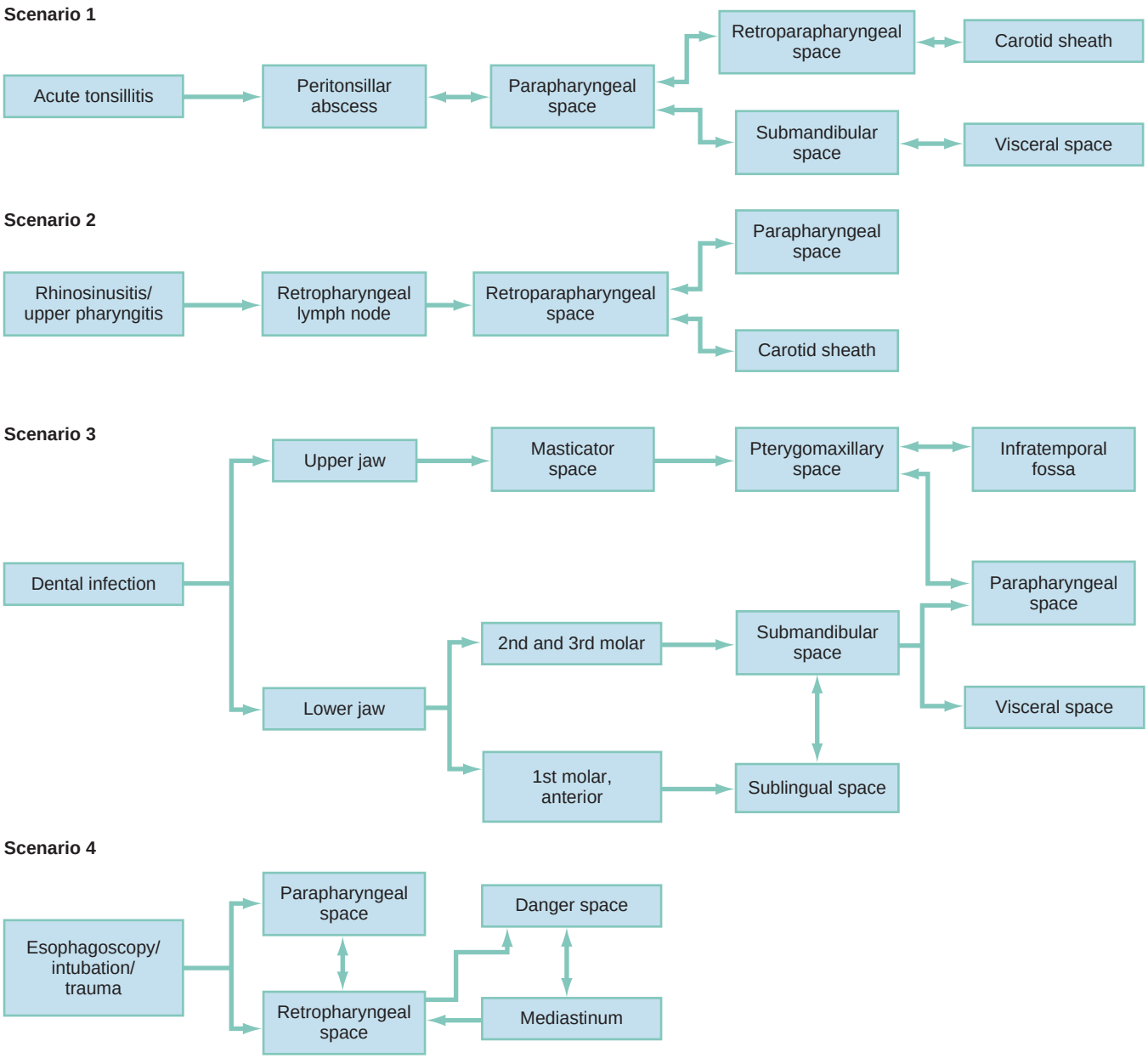

Fig. 60.14. Common routes of spread in deep neck infections. (Modified from Cummings CW, Flint PW, Harker LA: Cummings otolaryngology head & neck surgery, ed 4, St Louis, 2004, Elsevier/Mosby, Fig. 10.2.)

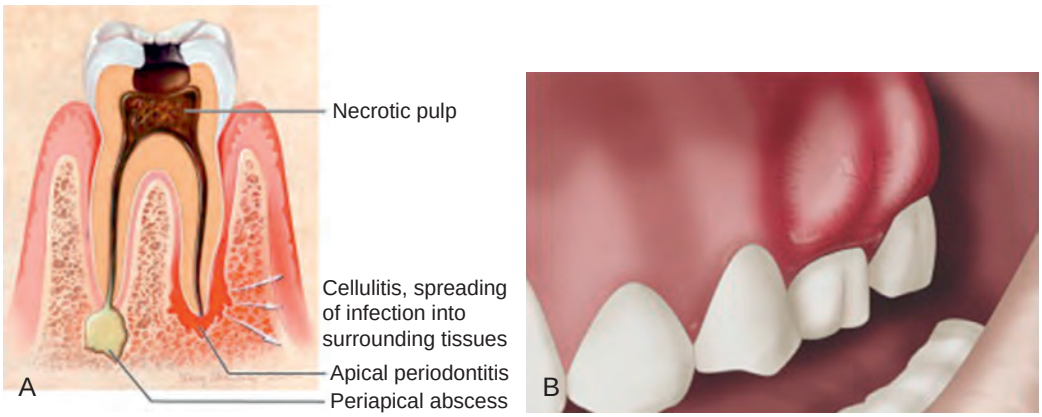

Fig. 60.15. **A,** Periapical abscess diagram. **B,** Physical examination findings of a periapical abscess. (From Buttaravoli P, Leffler SM: Minor emergencies, ed 3, St Louis, 2012, Elsevier, pp 178–180, Figs. 45.3 and 45.4.)

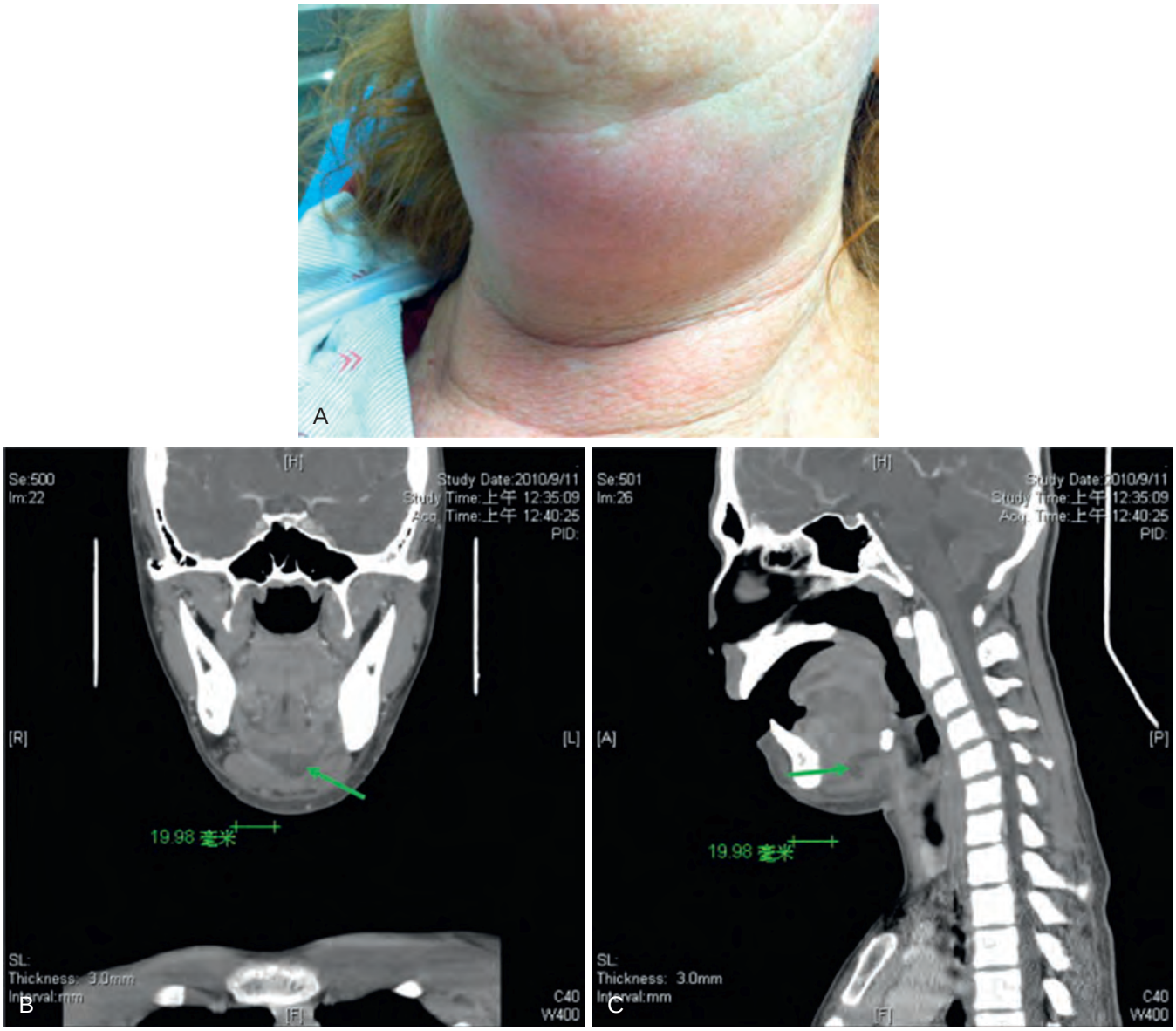

Fig. 60.16. Ludwig angina. **A,** Photograph. **B,** Coronal computed tomography (CT) scan. **C,** Sagittal CT scan. (**A,** From Hughes D, Holt S, Kman NE: Ludwig's angina triaged as an allergic reaction. J Emerg Med 45[5]:e175–176, 2013, Fig. 2. **B** and **C,** From Kao, et al: Ludwig's angina in children. J Acute Med 1[1]:23–26, 2011, Fig. 3 [coronal] and 4 [sagittal].)

otitis media are all risk factors for infection. Patients who are immunosuppressed from HIV/acquired immunodeficiency syndrome (AIDS), cirrhosis, diabetes, chemotherapy, and/or steroid use are all at higher risk and should raise suspicion.

Physical Examination

A complete head and neck examination is required, keeping in mind the aforementioned anatomy. Extraoral palpation can help assess whether there is deep space involvement; presence or absence of tenderness, warmth, fluctuance, and crepitus should be evaluated. The quality of dentition should be assessed and any concerning areas should be percussed for tenderness, which may indicate a periapical abscess. The floor of the mouth should be evaluated to see if the sublingual space is involved.

Irritation of the internal pterygoid or masseter muscles causes trismus, which is the inability to open the mouth because of involuntary muscle spasm. Trismus limits the ability to perform a complete oral examination; it will also make intubation difficult because it is not relieved with neuromuscular blockade. Difficulty swallowing or handling secretions suggests the possibility of retropharyngeal or parapharyngeal infection. Respiratory distress may be apparent, or the airway may occlude rapidly after a period of minimal signs of impending obstruction.

Diagnostic Testing

A complete blood count usually shows leukocytosis, but the absence of such does not rule out a deep neck infection or significant cellulitis. The imaging modality of choice is a computed tomography (CT) of the face (and, if clinically indicated, the neck as well) with IV contrast (if not contraindicated). The physical examination may be inaccurate in correctly determining the extent of an infection, and CT is required to delineate the infection and to ascertain its effects on adjacent structures (eg, the airway). Patients with HIV have an increased risk of deep neck infections, and HIV testing may be helpful for patients not known to have HIV and not recently tested.[9]

TABLE 60.3

Recommended Antibiotics for Deep Neck Infections

ANTIBIOTIC	DOSAGE	NOTES
Ampicillin/sulbactam **plus** vancomycin	3 g IV every 6 hours 20 mg/kg (2 g maximum)	
Clindamycin	600 mg IV every 8 hours	If allergic to penicillin
Meropenem **plus** vancomycin	1 g IV every 8 hours	If immunocompromised

IV, Intravenous.

Management

Well-appearing patients with simple odontogenic infections (localized infection, no recent antibiotics, and an immunocompetent patient) can be managed with antibiotics as shown in Table 60.2. Simple tooth abscess can be drained with local incision under local anesthesia if the clinician is skilled in the procedure. A 3-day course of antibiotics is as effective as a 5- or 7-day course of antibiotics after drainage of a localized dentoalveolar abscess if the patient has systemic symptoms. In the absence of systemic symptoms, routine antibiotics are unnecessary after successful drainage of a periapical abscess.[10]

Most abscesses are drained by dentists or oral surgeons and tooth extraction may be required. Oral or oral maxillofacial surgery consultation is advisable before drainage of suspected deeply-seated abscesses.

All serious deep neck infections should have broad-spectrum IV antibiotics administered. We recommend ampicillin-sulbactam with vancomycin or, if allergic to penicillin, clindamycin monotherapy in the immunocompetent host. See Table 60.3 for further details regarding antibiotic therapy in deep neck infection.

Ludwig angina management consists of antibiotics and airway management. Oral intubation may be difficult because of inability to displace the tongue with a laryngoscope. Intubation is not generally emergent and can be done in the operating room. Examination of the glottis and supraglottic airway by flexible endoscopy will ascertain the degree of airway compromise and, hence, the urgency of airway management. When emergent intubation is indicated, or a patient requires intubation before a prolonged transfer for care, we recommend use of a videolaryngoscope or flexible intubating endoscope (see Chapter 1). Consultation with an oral maxillofacial surgeon or otolaryngologist is indicated.

Disposition

Those with simple odontogenic infections can be discharged with close outpatient follow-up; more severe odontogenic infections, systemic toxicity, or immunocompromised patients should be admitted. Deep neck infections should be admitted. Those with concern for airway compromise (eg, Ludwig angina) or with extension into the neck or mediastinum should be admitted to the intensive care unit (ICU) after thorough evaluation of the airway by CT, flexible endoscopy, or both.

DENTOALVEOLAR TRAUMA

Principles

Anatomy

Dentoalveolar trauma is common complaint and can involve any tooth. The maxillary central incisors are commonly-involved because many children have an anterior overbite, predisposing these teeth to injury. When teeth are subject to trauma, they can become concussed (with pain to percussion), subluxed (whereby teeth become more mobile, but are in their normal anatomic position), luxed (moved from their anatomic position), avulsed (out of the socket), or fractured. Refer to the first section of this chapter to review the relevant dental anatomy.

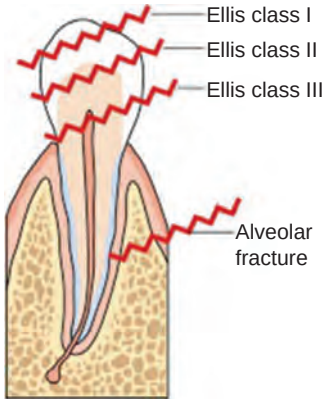

Fig. 60.17. Ellis fracture classification. *Ellis class I* fractures involve the enamel only; *Ellis class II* fractures involve the enamel and dentin; *Ellis class III* fractures involve the enamel, dentin, and pulp. (From Fowler GC: Management of dental injuries. Pfenninger JL, Fowler GC, editors: Pfenniger and Fowler's procedures for primary care, Philadelphia, 2011, Elsevier/Mosby, pp 511–515, Fig. 81.2.)

Pathophysiology

Dental Fractures. Forces that are applied to a tooth can lead to fractures. Fracture classification is important, because it guides management. When a fracture only involves the enamel, it is termed an *Ellis class I;* when a fracture involves the enamel and dentin, it is termed an *Ellis class II;* when a fracture involves the enamel, dentin, and pulp, it is termed an *Ellis class III* (Fig. 60.17). It is appropriate to name the fracture either anatomically (eg, a fracture of the right maxillary central incisor involving the enamel and dentin) or by Ellis classification (eg, an Ellis class II fracture of the right maxillary central incisor). Some practitioners are unfamiliar with the Ellis classification, but an anatomic description is always understood and is therefore probably preferred. The presence of dentin can be ascertained by seeing the yellow tint of the dentin through the fracture. Fractures involving the pulp have a pinkish tinge or have a small amount of visible blood.

Concussion, Subluxation, Luxation, and Avulsion. Concussion occurs when the periodontal ligament sustains a mild injury, causing tooth pain but no mobility. More severe injuries include subluxation or luxation. If a tooth is mobile but is in the correct anatomic position, it is subluxed and will heal as long as no further trauma occurs. Luxation is where the tooth itself is moved in any direction that is no longer anatomic, and it can be further divided into four types: (1) extrusive luxation is where the tooth is forced partially out of the socket in an axial direction, (2) intrusive luxation occurs when a tooth moves apically (and can be mistaken for an avulsion if completely intrusively luxated), (3) laterally luxed, where the tooth is displaced laterally with potential surrounding alveolar bone injury, and (4) avulsion where the tooth is completely out of the socket (Fig. 60.18). A long-term sequela of blunt trauma or reimplantation of teeth is resorption of the root.

Dental trauma can also involve the surrounding alveolar bone. The alveolar bone usually breaks in segments, leading to malocclusion, pain, and a segment of teeth that are misaligned with respect to their uninvolved neighbors (Fig. 60.19). These injuries usually present in conjunction with injury to the tooth itself.

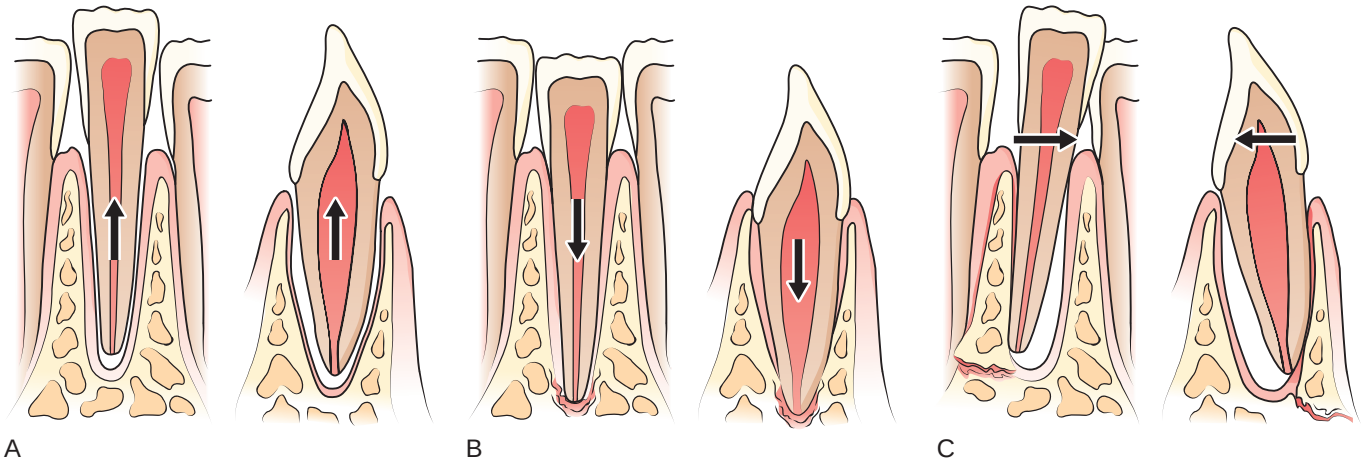

Fig. 60.18. Luxation of teeth. **A,** Extrusive luxation occurs when the tooth is forced partially out of the socket in an axial direction. **B,** Intrusive luxation of a tooth compresses the periodontal ligament and vascular supply of the pulp. It may even crush the apical bone. **C,** Lateral luxation occurs when the tooth is displaced in a lingual, mesial, distal, or facial direction. Fractures of the alveolar bone frequently accompany lateral luxation injuries. (From Roberts J: Roberts and Hedges' clinical procedures in emergency medicine, ed 6, Philadelphia, 2014, Elsevier, Fig. 64.9.)

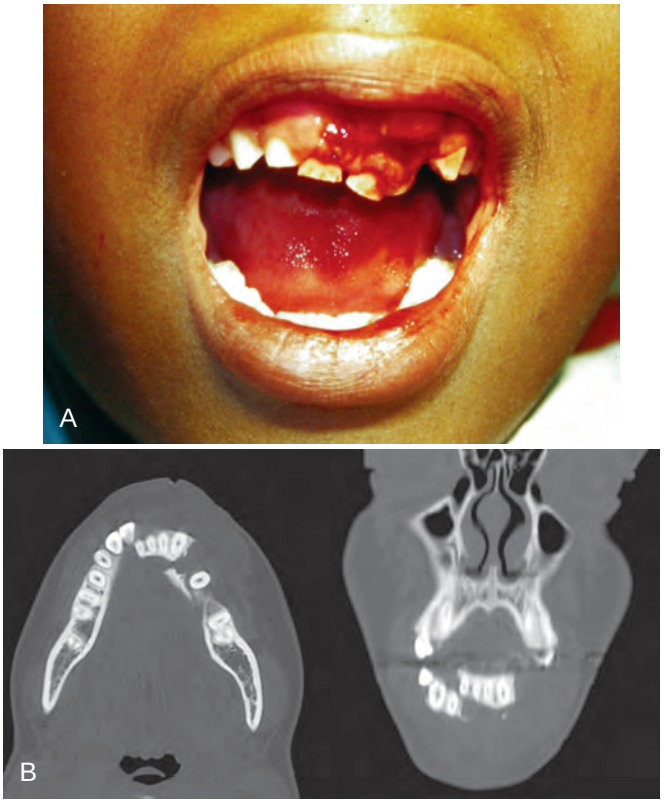

Fig. 60.19. **A,** Alveolar ridge fracture involving the maxillary incisors with a segment of teeth misaligned with respect to their neighboring teeth. **B,** Computed tomography (CT) demonstrating an alveolar ridge fracture in the axial and coronal planes, respectively. (From Roberts J: Roberts and Hedges' clinical procedures in emergency medicine, ed 6, Philadelphia, 2014, Elsevier, Figs. 64.14 and 64.15.)

Clinical Features

Historical Features

Patients invariably will have a history of dentoalveolar trauma. Replantation of a pediatric tooth depends on whether the tooth is primary or secondary. Fig. 60.20 can be used as a general guideline; primary dentition should never be reimplanted. Reimplanted primary teeth ankylose or fuse to the bone, potentially leading to interference with the eruption of the permanent tooth. Assessing the storage medium and timing of avulsion of a permanent tooth is important as it predicts success of reimplantation.

Physical Examination

Missing teeth should be accounted for. If a tooth appears to be missing, ask if there were teeth recovered at the scene. If no tooth is visualized, examine the socket to see if the tooth has been intrusively luxated. The surrounding soft tissue should be evaluated, because parts of teeth and even entire teeth can be embedded in a deep mucosal laceration. If no tooth is found, a chest x-ray should be obtained to exclude aspiration.

The teeth should be inspected to evaluate for fractures, tenderness, and mobility. The diagnosis of subluxation can be made by gently tapping a tooth with two tongue blades: any perceptible mobility is evidence of subluxation.

The oral mucosa and tongue should be evaluated for trauma. Small lacerations can usually be managed expectantly, but larger lacerations may require repair. Evaluate injuries for foreign bodies and to ensure injuries are not full-thickness.

Diagnostic Testing

Diagnosis of a tooth fracture or luxation is clinical, but CT of the face or an orthopantomogram (Panorex) x-ray can be ordered if CT is not available. Specialized views (eg, maxillary anterior, periapical views) are used by dental professionals but are not regularly available in the ED.

Management

Prior to any manipulation of teeth, appropriate analgesia should be administered. Nerve blocks such as supraperiosteal nerve blocks (for isolated teeth) or inferior alveolar nerve blocks (for multiple traumatized mandibular teeth) are highly effective and easy to perform.

The status of tetanus immunization should be checked, and the patient should be treated according to the standard for a non-tetanus-prone wound (10-year immunization update). All patients with dentoalveolar trauma (especially those who have splinting or

Upper teeth	Primary erupt	Permanent erupt
Central incisor	8-12 months	7-8 years
Lateral incisor	9-13 months	8-9 years
Canine (cuspid)	16-22 months	11-12 years
First premolar		10-11 years
Second premolar		10-12 years
First molar	13-19 months	6-7 years
Second premolar	25-33 months	12-13 years
Third molar		17-21 years

Lower teeth	Primary erupt	Permanent erupt
Third molar		17-21 years
Second molar	23-31 months	11-13 years
First molar	14-18 months	6-7 years
Second premolar		11-12 years
First premolar		10-12 years
Canine (cuspid)	17-23 months	9-10 years
Lateral incisor	10-16 months	7-8 years
Central incisor	6-10 months	6-7 years

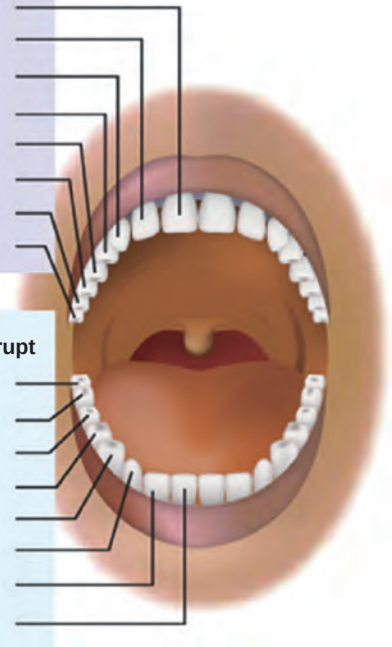

Fig. 60.20. Age of primary dentition and secondary (permanent) dentition of various teeth. (From Olynik CR, Gray A, Sinada GG: Dentoalveolar trauma. Otolaryngol Clin North Am 46[5]:807–823, 2013, Fig. 2.)

calcium hydroxide paste applied) should be placed on a liquid diet for several days and advanced to a soft diet for 1 week.

Dental Fractures

Fractures of teeth involving the enamel only (Ellis I) need no emergent treatment. If available, an emery board can be used to file down any sharp edges to prevent intraoral trauma. Deeper fractures involving the dentin only (Ellis II) or both dentin and pulp (Ellis III) need to be covered with a calcium hydroxide paste to protect the underlying structures from infection. ED pulpotomy to remove exposed pulp has been described, but it has a high complication rate and should not be attempted. The main difference in management between an Ellis II and III fracture is immediacy of follow-up: Ellis III needs immediate consultation, whereas Ellis II needs follow-up within 24 hours. We recommend follow within 24 hours for all dental fractures that do not receive dental consultation in the ED.

To cover the tooth, dry the affected tooth. Mix the catalyst and base of the calcium hydroxide product and directly apply to the exposed tooth surface (Fig. 60.21). To keep the tooth dry, gauze rolls in the mucobuccal fold and a nasal cannula with air or oxygen directed at the anesthetized tooth surface is often helpful.

Tooth Avulsion

Avulsed *permanent* teeth should be reimplanted at the earliest opportunity. Permanent teeth should be handled only by the crown to avoid injury to the periodontal ligament at the root. In the prehospital setting, the tooth can be reimplanted or stored in an appropriate medium. Ideally, the tooth should be stored in either a commercially-available solution, such as Hank's balanced salt solution (eg, Save-A-Tooth, EMT Toothsaver) or milk. Oral rehydration solution can also be used as a storage medium.[11] A 2013 literature review of all storage solutions found that milk performed better than even saliva; therefore, if a commercially-available storage solution is not available and immediate reimplantation is not undertaken, milk is the preferred storage medium.[12] See Table 60.4 for the approximate length of viability of a tooth based on the solution in which it is stored.

TABLE 60.4

Periodontal Ligament Cell Viability by Storage Medium

SOLUTION	LENGTH OF PRESERVATION OF PERIODONTAL LIGAMENT
None (dry)	Less than 60 minutes
Milk	3 to 8 hours
HBSS	12 to 24 hours
Oral rehydration solution	Similar to HBSS

HBSS, Hank's balanced salt solution.

Some texts recommend soaking the tooth in a 5% doxycycline solution for 5 minutes prior to reimplantation based on experimental data with periodontal cells, but a 2015 study demonstrated no clinical benefit and obtaining the solution and completing the soaking simply delays reimplantation. Therefore, we do not recommend this practice.[13] The 2012 International Association of Dental Traumatology guidelines list doxycycline soaking as only a consideration.[14]

In the awake patient not at risk for aspiration, provide analgesia (eg, supraperiosteal nerve block), rinse the permanent tooth with saline, irrigate the socket to remove debris, and reimplant the tooth into the socket. Do not remove debris from the tooth that does not come off with saline, because manual removal can damage the periodontal ligament cells. After replantation, a dental consultant can provide immobilization for the reimplanted tooth. If dental consultation is not available, use periodontal dressing material (Coe-Pak) to splint the tooth to the adjacent normal

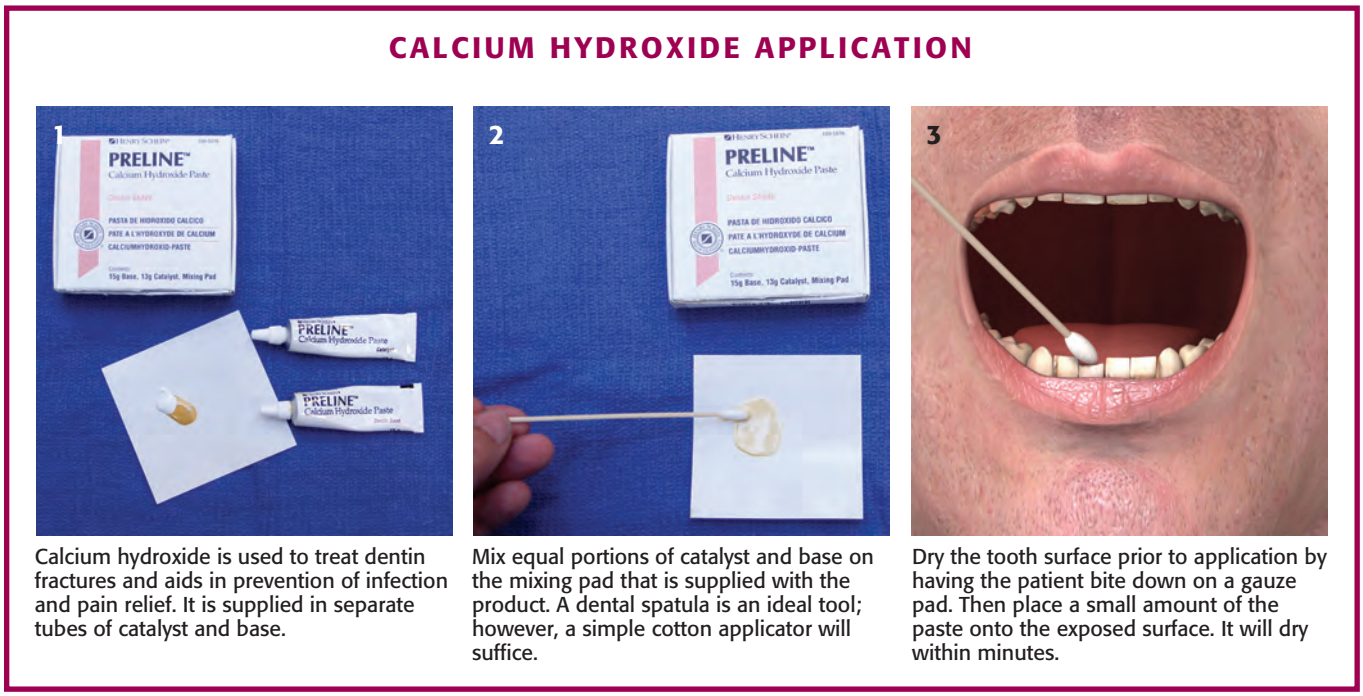

Fig. 60.21. Calcium hydroxide application for the treatment of fractures involving the dentin (Ellis class II) and pulp (Ellis class III). (From Roberts J: Roberts and Hedges' clinical procedures in emergency medicine, ed 6, Philadelphia, 2014, Elsevier, Fig. 64.7.)

teeth to provide a 24 to 48 hour temporary splint. A resin and catalyst paste are mixed together in equal quantities to a firm consistency and molded over the anterior and posterior aspects of the involved tooth and two or three adjacent teeth on each side (Fig. 60.22). The gingiva and enamel must be completely dry; the provider's gloves should be wet or covered in lubricating jelly to allow for ease of handling of the paste. The positioning of the tooth does not need to be anatomically perfect, just approximate. Avoid getting the paste on the occlusal surface of the tooth. Advise the patient to have a soft diet (but avoid hot liquids that may soften the packing) and follow up with a dentist within 24 hours. Doxycycline 100 mg by mouth bid for 7 days should be prescribed in adults; in children younger than 12 years old (in whom doxycycline is contraindicated), penicillin 50 mg/kg/day divided qid (maximum 500 mg qid) for 7 days is an alternative. Patients should be further counseled on brushing gently with a soft toothbrush after each meal and utilizing chlorhexidine mouth rinses twice a day for 1 week.

Luxation and Alveolar Fractures

Teeth that are concussed or subluxed usually do not need specific treatment. Teeth that have undergone extrusive or lateral luxation should be gently placed into anatomic position and splinted in place. Intrusive luxation does not have any ED-specific interventions except referral to a specialist, because the tooth cannot be easily retrieved.

Alveolar fractures may be apparent clinically from exposed pieces of bone or diagnosed radiographically. In massive facial trauma, care should be taken to conserve as much of the alveolar bone as possible, unless there is a great danger of aspiration. Indiscriminate loss of alveolar bone results in tremendous cosmetic deformity that is difficult to restore with prosthetic devices or leaves no foundation for a dental implant, thus necessitating autologous bone grafting procedures. An alveolar fracture will eventually require 4 to 6 weeks of stabilization for adequate healing; if there is an associated subluxed or avulsed tooth, stabilization is maintained at the expense of possible ankylosis of the tooth.

Soft Tissue Injuries

Generally, lacerations to the buccal mucosa do not require repair if under 1 cm. A common rule is that if food can get stuck in the laceration, it should be considered for repair. Lacerations to the gingiva that expose the base of the teeth should be repaired; this is a complex repair, however, and consultation or referral is indicated if the clinician is not experienced with the procedure. Frenulum injuries generally are not repaired. However, frenulum injuries in neonates and infants should raise suspicion of child abuse (see Chapter 177).

Tongue lacerations usually heal well without intervention unless they are gaping, have a flap, involve the muscle, cause a bifid or grooved tongue, or if hemostasis cannot be achieved otherwise. After a lingual block or direct infiltration of anesthetic and irrigation, absorbable sutures such as 4-0 chromic, Vicryl, Dexon, or Vicryl Rapide can be used. Lacerations involving the muscular layer of the tongue should be closed with one set of deep sutures that involve both the muscle and mucosa; a two-layer repair is not necessary. Full-thickness tongue lacerations can be closed either in three layers (eg, mucosa inferiorly, muscle, mucosa superiorly) or one side of the mucosa can be repaired followed by a set of deep sutures that closes the muscular layer and opposing mucosa.

Disposition

Patients with dentoalveolar trauma usually do not need to be admitted, unless they have other concomitant trauma, uncontrolled pain, or have severe trismus preventing oral intake. All patients should have appropriate follow-up. Discharge with appropriate analgesia, antibiotics if indicated, and dental hygiene instructions.

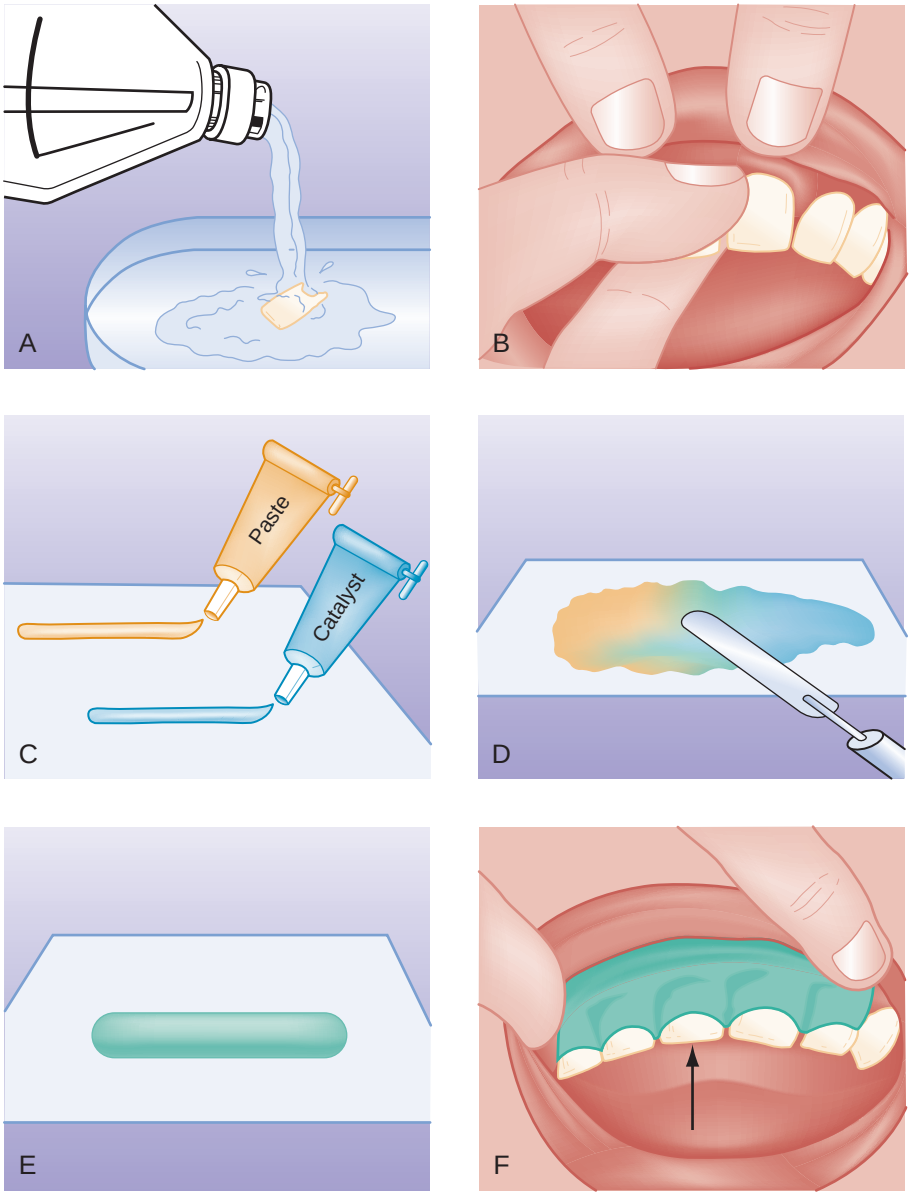

Fig. 60.22. Reimplantation and stabilization of an avulsed tooth. **A,** Tooth is rinsed. **B,** Tooth is placed back into socket. **C** and **D,** Periodontal pack is mixed. **E,** Splint material is ready for application. **F,** Packing is molded over reimplanted tooth and two adjacent teeth to either side.

TEMPOROMANDIBULAR JOINT DISORDER AND DISLOCATION

Principles

Anatomy

The TMJ is the articulation between the squamous portion of the temporal bone and the condyle of the mandible. It is comprised of two types of synovial joints: hinge and sliding. The hinge joint action dominates during normal mouth opening, but with wide opening, translational movement occurs and the articular disc and condyle complex slide inferiorly (Fig. 60.23). When the condyle moves anterior to the articular eminence, dislocation occurs.

Pathophysiology

Temporomandibular Joint Disorder. The cause of TMD is debated, but jaw clenching and grinding associated with stress is thought to contribute. Tooth malocclusion was previously thought to be a common etiology, but this is rare unless there is an inciting event (eg, if symptoms began after dental work with resultant malocclusion).

Temporomandibular Joint Dislocation. TMJ dislocation occurs when the condyle travels anteriorly along the eminence and becomes locked in the anterosuperior aspect of the eminence. The masseter, internal pterygoid, and temporalis go into spasm attempting to close the mandible; trismus results and the condyle cannot return to the temporal fossa. Mandibular dislocation is painful and frightening for the patient. Patients prone to mandibular dislocation include individuals with anatomic disharmonies between the fossa and articular eminence, weakness of the capsule and the temporomandibular ligaments, or torn ligaments. Dystonic reaction to drugs may result in mandibular dislocation. Patients who have had one episode of mandibular dislocation are predisposed to further dislocations. If a unilateral dislocation has occurred, the jaw deviates to the opposite side. More commonly, a symmetrical dislocation occurs.

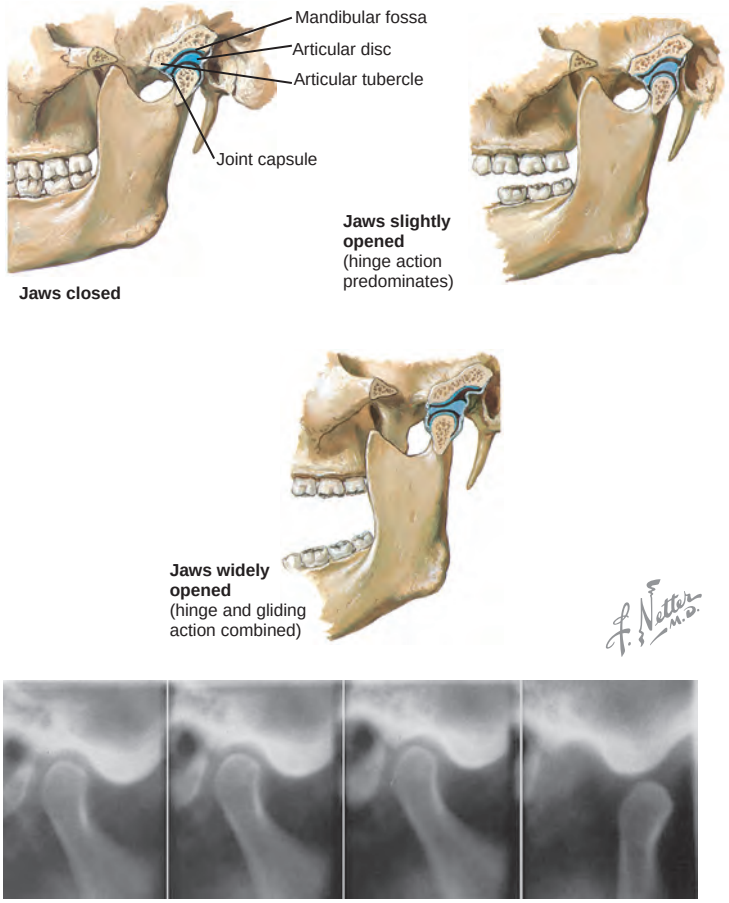

Fig. 60.23. The temporomandibular joint (TMJ). With slight opening, the joint's function as a hinge predominates. With greater jaw opening, there is translational movement. (From Norton NS: Temporomandibular joint. In: Netter's head and neck anatomy for dentistry, ed 2, Philadelphia, 2012, Elsevier/Saunders 2011.)

Clinical Features

Historical Features

Temporomandibular Joint Disorder. TMD is defined as "aching in the muscles of mastication, sometimes with occasional brief severe pain on chewing, often associated with restricted jaw movement and clicking or popping sounds." Therefore, history should focus on elucidating whether or not the patient has those features. Patients may complain of a headache, facial pain, or even an earache. Pain is often precipitated by use of the muscles of mastication (eg, chewing) or with increased ranging of the TMJ (eg, laughing, yawning).

Temporomandibular Joint Dislocation. The mandibular condyles may dislocate from trauma, but more often, dislocation follows extreme opening of the mandible, such as the case with yawning. Patients may have had prolonged jaw opening, such as in the case of dental procedures. They will complain of not being able to close the mouth. Recurrent dislocations are common, and patients may present knowing they have an anterior dislocation. Verbalization of their complaint is often difficult because their mouth is stuck open.

Physical Examination

Temporomandibular Joint Disorder. For TMDs, the main physical signs are related to three items: joint sounds, such as crepitus or a joint click upon range of motion; limitations of joint movements with pain during assisted maximum mouth opening; and muscle and joint pain and pain just anterior to the auricular canal. None of these findings alone has sufficient testing characteristics to rule TMD in or out, however.[15] The diagnostic criteria of TMJ is outside the scope of this text, because there are many subtypes; the criteria were most recently updated in 2014 and the included reference can be used.[16]

Temporomandibular Joint Dislocation. On examination, jaw dislocations are usually readily apparent. The jaw will not be able to be closed, and a depression can be felt and seen in the preauricular area; there may be the appearance of an underbite as the mandible is anteriorly displaced. Symmetry should be evaluated, because occasionally a jaw dislocation will be unilateral. If a traumatic mechanism is suspected, a secondary survey for trauma should be initiated.

Differential Diagnoses

The diagnosis of a TMJ dislocation is straightforward. However, TMD has many presenting complaints and therefore consideration for other etiologies is warranted. Pain can be secondary to pulpitis, an odontogenic infection, headache, otitis media (as ear pain is a presenting complaint of TMD), sinusitis, and trigeminal neuralgia.

Diagnostic Testing

Radiographs are not indicated for straight-forward nontraumatic dislocation, unless the diagnosis is not certain. In cases of traumatic dislocation, a panoramic view of the mandible (Panorex)

or CT scan of the facial bones should be considered to exclude the possibility of a fracture.

Management

Temporomandibular Joint Disorder

Patients with TMD often have symptoms that fluctuate over time, and therefore initial therapy should be conservative. NSAIDs, application of heat or cooling, and consideration of bite guards if the patient has bruxism are all reasonable first-line therapies. Heat therapy is typically 15 minutes at a time, four to six times daily. Refractory cases can also benefit from diazepam (2 to 5 mg by mouth tid or qid).[17] If the symptoms are more severe, referral to a specialist is warranted because a multidisciplinary approach is often necessary to manage symptoms; there are even studies investigating transcutaneous electrical nerve stimulation therapy, and refractory cases may benefit from surgical intervention.[18-19]

Temporomandibular Joint Dislocation

Reduction of a dislocated mandible is often difficult, because masseter muscle contraction must be overcome. To relax the masseter, procedural sedation and analgesia is almost invariably necessary. Either facing the patient or from behind, the emergency clinician grasps the mandible with both hands; the thumbs rest on the ridge of the mandible intraorally, posterior to the molars, and the fingers wrap around the outside of the jaw. It is best to have the patient sitting up, with a firm surface behind the head, so that posterior and inferior pressure can be exerted without accompanying movement of the patient's entire head. Some physicians prefer to place the thumbs on the occlusal surfaces of the teeth; in this case, the thumbs are wrapped with gauze and fortified with a piece of wooden tongue blade to protect them when reduction is accomplished, because the masseter muscles can contract with tremendous force.

Firm, progressive, downward pressure is applied on the mandible to free the condyles from the anterior aspect of the eminence; the mandible is guided caudally, then posteriorly and superiorly back into the temporal fossae (Fig. 60.24). If this maneuver is unsuccessful, both hands can be used on the affected side of the mandible.[20] The patient is advised to avoid extreme opening of the mandible, such as occurs during laughing and yawning, to begin a soft diet for 1 week, and to apply warm compresses in the TMJ area. NSAIDs and muscle relaxants may be helpful. Patients with chronic dislocation may be helped initially with the application of a Barton bandage (elastic fabricated bandage that wraps around the top of the head and mandible).

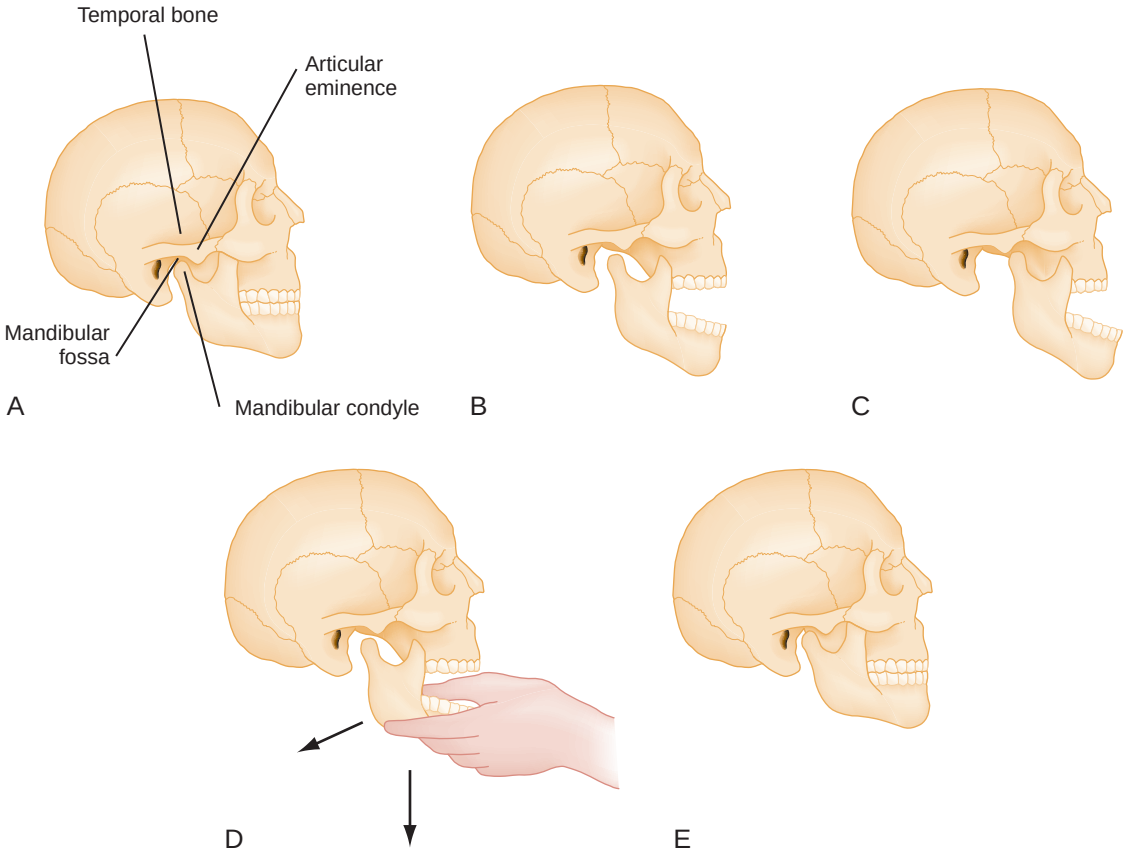

Fig. 60.24. Reduction of temporomandibular joint (TMJ) dislocation. The TMJ is illustrated in normal and dislocated positions. **A,** Closed position, with the mandibular condyle resting in the mandibular fossa behind the articular eminence. **B,** In maximally open position, the mandibular condyle is just under and slightly behind the articular eminence. **C,** In dislocated position, the mandibular condyle moves forward and upward slightly above the articular eminence; muscle spasm then occurs. **D,** For reduction of dislocation, the thumbs are placed intraorally and lateral to the lower molars, and pressure is applied to the lower molar ridge area near the jaw angle in a downward and backward direction. **E,** When the mandibular condyle has cleared the articular eminence, muscle contraction returns the jaw to a normal closed position. (Adapted from Rose LF, Hendler BH, Amsterdam JT: Temporomandibular disorders and odontic infections. Consultant 22:125, 1982.)

More recently (2014) a new technique was described for a hands-free approach for reduction of acute nontraumatic TMJ dislocation using a "syringe" technique.[21] With this technique, a 5- or 10-mL syringe is placed between the posterior upper and lower molars (or gums if edentulous) on the affected side. The patient then gently bites down and rolls the syringe back and forth; the syringe is a rolling fulcrum that helps the anteriorly-displaced condyle slip back into its normal position.

Disposition

Patients with TMD and with TMJ dislocation who have been relocated can be discharged home. Those with irreducible TMJ dislocation or those with TMJ dislocation in conjunction with a fracture should have specialty consultation and may require admission for surgical reduction and fixation.

KEY CONCEPTS

- Assessment of airway patency, either by CT or flexible endoscopy, is important during assessment of deep space infections of dental origin. Patients with significant airway compromise should be intubated.
- Tissue infections are treated for 10 days with simple penicillin or ampicillin/sulbactam. For penicillin-allergic patients, use metronidazole or clindamycin.
- Fractures of teeth are managed differently depending on which structures are involved—enamel, dentin, or pulp exposure.
- Avulsed *permanent* teeth are reimplanted as quickly as possible and are best preserved in Hank's solution; primary teeth should not be reimplanted.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 60: QUESTIONS & ANSWERS

60.1. A 27-year-old previously healthy man presents with dental pain and facial swelling. Physical examination is remarkable for trismus, poor dentition with diffuse periodontal disease, and inability to manage secretions. You determine endotracheal intubation is necessary. Which of the following statements regarding the patient's management is *true?*

A. An awake intubation technique is indicated.
B. Pre-induction methocarbamol will decrease the trismus.
C. Rapid sequence induction with rocuronium is indicated.
D. Succinylcholine will worsen the trismus.
E. Transtracheal retrograde wire intubation is indicated.

Answer: A. The trismus is "mechanical," or muscular. Neuromuscular blockade, regardless of the choice between depolarizing or non-depolarizing agents, is not likely to help. Awake intubation, using a videolaryngoscope or flexible endoscope is indicated. Transtracheal retrograde wire intubation is rarely, if ever, indicated in modern emergency practice. Traditional "muscle relaxants" are sedatives and have no direct muscle-relaxing properties.

60.2. A 21-year-old man presents with tooth pain. He underwent a left mandibular premolar extraction 3 days ago. Examination is remarkable for a painful but nonbleeding tooth socket. The face and mandible are not swollen. Which of the following statements regarding this patient's condition is *true?*

A. Analgesia is the main goal of emergency department (ED) therapy.
B. Antibiotics are indicated.
C. Dental consultation in the ED is indicated.
D. Opioids are the treatment of choice.
E. Provocation of socket bleeding is encouraged to form new clot.

Answer: A. A dry socket is an exquisitely painful post-extraction syndrome that typically occurs 3 or 4 days later. The pathophysiology is loss of the healing blood clot and localized bone infection. Treatment consists of pain control. Optionally, gentle irrigation, and packing with gauze soaked in eugenol can be performed. Opioids may be used, but this would be in addition to nonsteroidal antiinflammatory drugs (NSAIDs), which are excellent analgesics for dental pain and are preferred due to the inflammatory component.

60.3. A 2-year-old previously healthy toddler presents with an avulsed tooth after hitting his mouth on the ground after a trip and fall. Physical examination is remarkable for a non-toxic appearing child who is crying and has an open slightly oozing pocket at the maxillary central incisor. Which of the following statements regarding the patient's management is *true?*

A. Set-up for conscious sedation should be arranged, because the replacement of the avulsed tooth may be painful.
B. The mother should have the patient place the tooth in the patient's mouth.
C. The tooth should be placed in milk or Hank's balanced salt solution.
D. The tooth should be replaced in the socket as soon as possible.
E. The tooth should not be reimplanted.

Answer: E. Management of recovered avulsed teeth depends on the age of the patient and the length of time for which the tooth has been displaced. Avulsed primary teeth in a pediatric patient 6 months old to 6 years old are *not* replaced in the socket. Reimplanted primary teeth ankylose or fuse to the bone, so although the dentofacial complex grows downward and forward, the reimplantation site does not. There also may be interference with the eruption of the permanent tooth. Cosmetic deformity results in either case. Thus, this patient should be referred to a pedodontist for consideration of a space maintainer or cosmetic appliance.

60.4. A 25-year-old previously healthy woman presents with recurrent pain from her temporomandibular joint disorder (TMD). The pain is described as being dull, and it worsens during the course of the day. Physical examination is remarkable for a non-toxic appearing female with normal dentition without any deformities but mild tenderness to palpation over the temporomandibular

joint (TMJ) and some spasm noted over the masseter and internal pterygoid. Which of the following statements regarding the patient's management is *true?*

A. A computed tomography (CT) scan of the face would be helpful.
B. A Panorex should be obtained.
C. Patient should be prescribed narcotic agents.
D. Treatment consists of external application of heat for 15 minutes four to six times per day, soft diet, analgesics including nonsteroidal antiinflammatory drugs (NSAIDs), and a muscle relaxant, such as diazepam (2 to 10 mg up to four times per day).
E. Ultrasound of the joint should be obtained.

Answer: D. TMJ radiographs are not helpful. Treatment consists of the external application of heat for 15 minutes four to six times per day, soft diet, analgesics including NSAIDs, and a muscle relaxant, such as diazepam (2 to 10 mg up to four times per day). Patients should be referred to a dentist specializing in TMD, such as a periodontist or a periodontal prosthodontist.

60.5. A 32-year-old previously healthy man presents with a fractured maxillary lateral incisor after a mechanical trip and fall. Physical examination is remarkable for a portion of the tooth that has an ivory-yellow appearance. You determine that he has a fractured tooth. Which of the following statements regarding the patient's management is *true?*

A. A calcium hydroxide paste should be used to cover the exposed dentin.
B. A dressing can be placed for comfort.
C. An urgent pulpotomy is indicated.
D. If this were a pediatric patient or an adolescent, it would be considered less serious, because children have more dentin than adults.
E. The patient will likely need a subsequent root canal.

Answer: A. This patient has a fracture involving the dentin, which has an ivory-yellow appearance. The pulp continually lays down dentin throughout the life of the tooth. In a child, the pulp is relatively large in size, and there is less dentin; the inverse is true in the adult. Because dentin is a microtubular tissue capable of preventing bacteria to percolate into the pulp chamber, fractures involving dentin are more serious in children and adolescents. In younger patients, the management of dentin fractures involves the immediate placement of a dressing of calcium hydroxide paste over the exposed dentin. Early intervention may prevent contamination of the pulp and avoid the need for subsequent root canal. In an adult, who has a greater thickness of dentin compared with pulpal tissue, there is less need for urgent referral to a dentist. A dressing can be placed on the tooth for comfort. Referral should be made to a dentist for the next working day. Fractures involving pulp exposures are true dental emergencies.

CHAPTER 61

Ophthalmology

Kama Guluma | Jeffrey E. Lee

The emergent conditions that affect the eye, its surrounding tissues, and the act of seeing itself are myriad and broad in scope and include trauma, inflammatory conditions, infections, hydrostatic issues (such as, glaucoma), vascular events, structural issues, optical derangements, and neurological developments (such as, visual field cuts, anisocoria, nystagmus, diplopia). The evaluation of a chief complaint of "eye problem" may take the clinician in any of a variety of directions. Figure 61.1 represents a general orientation to non-neurological and nontraumatic ophthalmological emergencies, insofar as they incorporate four key symptoms of pain, redness, disordered vision, and swelling.

TRAUMATIC CONDITIONS

Principles

The evaluation of a traumatic injury to the eye should be anatomically methodical, considered from superficial (eyelids, conjunctival, corneal, and anterior segment) structures to deep (including ocular, retrobulbar, and periorbital) structures, keeping in mind that deep injuries may be present with minimal superficial manifestations. Many extraocular structures are found in close proximity, and concomitant, non-ocular injury is common (traumatic facial injury is discussed in more detail in Chapter 35). A detailed examination for additional injury is therefore important.

Periorbital Contusions and Eyelid Lacerations

Clinical Features and Differential Diagnosis

Periorbital contusions and eyelid lacerations present very evidently, but it is important to determine whether additional ocular injury such as a globe perforation, an orbital septal injury (suggested by prolapsed fat), a canalicular laceration (suggested by a laterally displaced puncta) (Fig. 61.2), a levator or canthal tendon laceration, or an intraorbital foreign body is present, because all require consultation in the emergency department (ED) with an ophthalmic surgeon. An eyelid or periorbital injury should not be a distraction from less visible underlying injuries to the eye itself (see sections on deeper injuries later for clinical features).

Diagnostic Testing

The emergency clinician should undertake best attempts to thoroughly examine all ocular structures, even those hidden by swollen eyelids and periorbital tissue, and evaluate visual function. With delay, swelling can increase and limit visualization. Early examination, gentle pressure to displace fluid, or use of ice can improve ability to open the eyelids, whereupon an assessment for deeper injuries can be made. Use of eyelid retractors, such as the Desmarres, can help avoid increasing intraocular pressure (IOP). However, if there is concern for a ruptured or perforated globe (with or without a foreign body present) and the globe cannot be safely and properly examined, computed tomography (CT) imaging, with or without consultation with an ophthalmologist, is advised (see Intraocular Foreign Bodies and Globe Rupture later).

Management and Disposition

Isolated soft tissue injury to the eyelids and the surrounding area is treated with symptomatic management such as head elevation and cool compresses, as most will resolve. Patients should be instructed to seek follow-up care for any increase in pain or swelling, decreased vision, double vision, or significant flashing lights or floaters as these may be indications of retinal injury (see Posterior Segment/Ocular Injuries: Commotio Retinae, Retinal Detachment, Intraocular Foreign Body, and Perforated Globe later). If there are no additional complications, one can manage simple lid lacerations that are parallel to relaxed skin tension lines (exceptions for damage to important structures noted earlier) with primary closure with 6-0 or 7-0 nylon or Prolene interrupted sutures, removed within a week.

Conjunctival and Scleral Injuries: Subconjunctival Hemorrhage, Conjunctival Laceration, and Scleral Laceration

Clinical Features and Differential Diagnosis

Injuries to the conjunctiva include a subconjunctival hemorrhage (very common with blunt or penetrating injury) and conjunctival laceration. A subconjunctival hemorrhage develops when subconjunctival blood vessels bleed, either spontaneously or after a sudden acute venous congestion of the head, such as from a Valsalva maneuver or vigorous coughing. The hemorrhage smoothly and minimally raises the overlying conjunctiva, with no vessels visible behind the blood, and is often incidentally discovered by the patient upon looking in the mirror (Fig. 61.3). Symptoms, if any are present, may include a very mild, diffuse foreign body sensation (from the size and location of the hemorrhage), with no change in visual acuity.[1] Subconjunctival hemorrhages from minor instigations (such as, coughing) are typically self-limited, but those from more direct trauma may be complicated by underlying injury. A 360-degree area of involvement associated with chemosis or pain, decreased visual acuity, or sensitivity to light, should prompt an evaluation for globe perforation. A conjunctival laceration will present with significantly more discomfort than a subconjunctival hemorrhage, and if present, should prompt an evaluation for globe perforation—and retained foreign body if indicated. A globe perforation from a related foreign body may present in an occult fashion, with only a mild-appearing conjunctival laceration or scleral "bruise," and should be screened for if the mechanism of injury (such as, in an injury from a compressed air tool or gun, a nail or object deflected by a hammer, or a significant impact directly on the eye) suggests energy sufficient for globe penetration. A patient may also present with a scleral laceration, a laceration of the thick white envelope that provides the structural integrity of the globe, which should also prompt consideration of globe perforation.

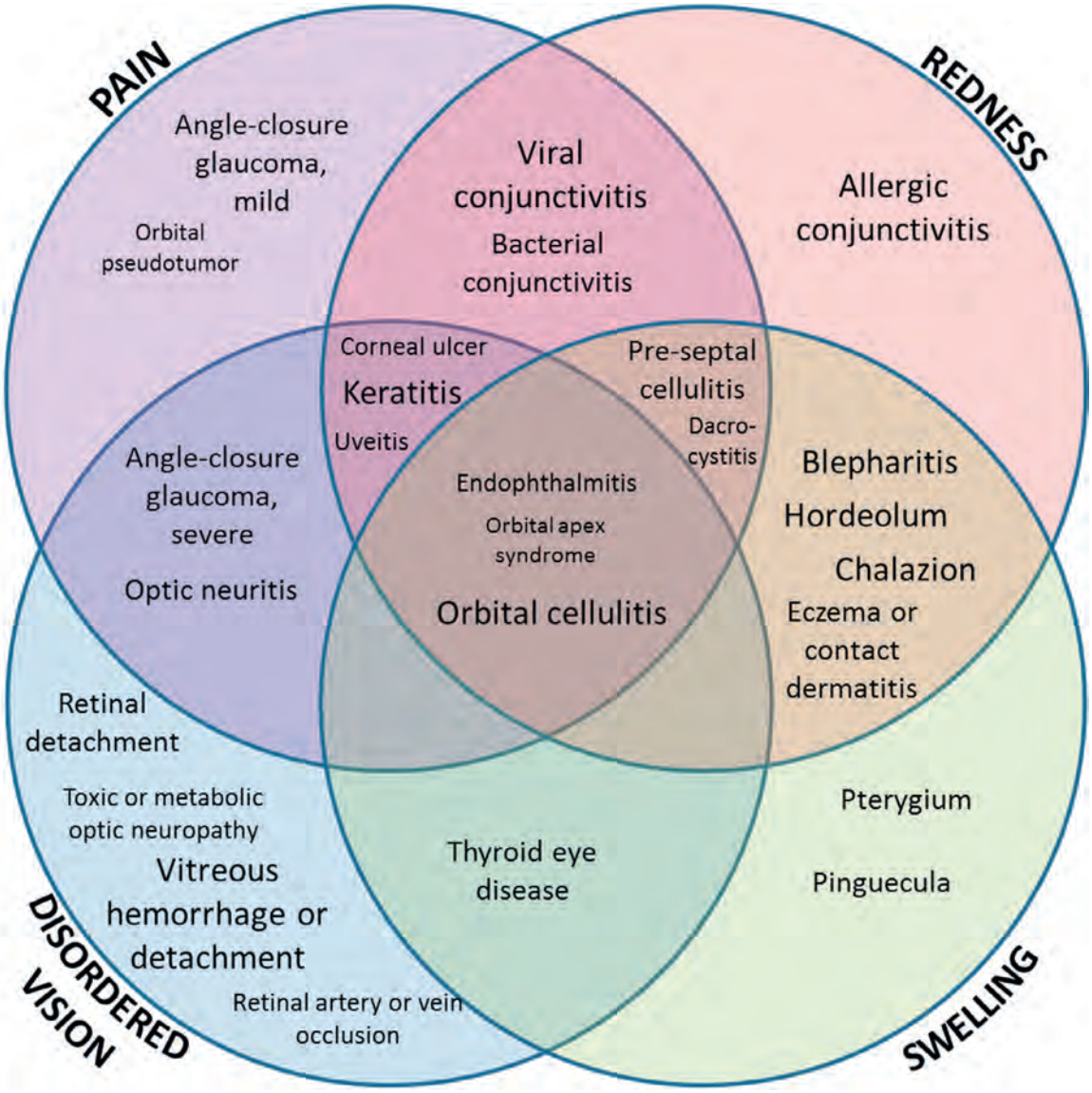

Fig. 61.1. An overview of nontraumatic, non-neurological ophthalmological conditions, arranged by primary presentation in the emergency department (ED). Relative text size is a general representation of the incidence or relatively likelihood of that entity in relation to others. (Note: The actual incidence or likelihood of the entity in any one ED will vary with the local disease patterns and patient population being treated in the department.)

Fig. 61.2. Canalicular laceration. **A,** This patient experienced a laceration of the upper canaliculus. **B,** Canalicular laceration extending from forehead and brow. (**A,** From Zitelli BJ, Davis HW, editors: Atlas of pediatric physical diagnosis, ed 5, St Louis, 2002, Mosby. **B,** Courtesy Jeffrey Lee, MD, University of California San Diego.)

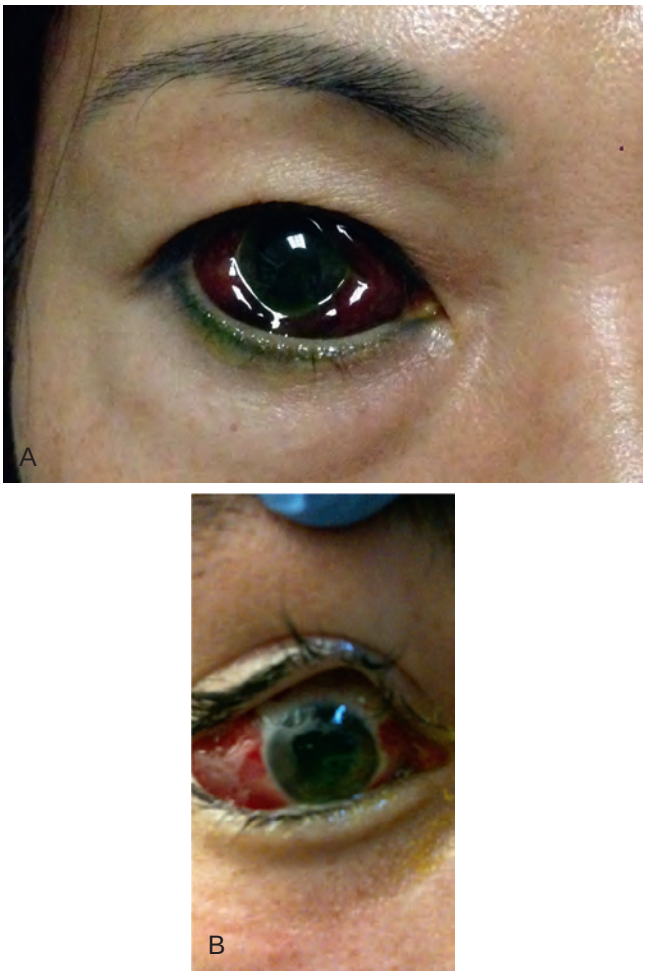

Fig. 61.3. **A** and **B,** Subconjunctival hemorrhage. (Courtesy Jeffrey Lee, MD, University of Calfornia San Diego.)

Diagnostic Testing

An important aspect of the examination for subconjunctival hemorrhage, conjunctival laceration, or scleral laceration (or any injury to the eye for that matter) is examination of the conjunctiva, sclera, cornea, and underlying anterior chamber with a slit lamp, and application of fluorescein dye. This is especially helpful in three ways: (1) identification of corneal abrasions, (2) screening for evidence of a globe perforation, and (3) identification of tarsal foreign bodies. In using fluorescein, the conjunctival and corneal surface is painted with a 10% fluorescein strip (with anesthetic or saline solution). Fluorescein is not taken up by intact corneal epithelium but will stain areas of injured or lost epithelium bright green. If the fluorescein staining has a pattern of repeated lines (Fig. 61.4), this suggests the possibility of a retained tarsal foreign body hidden under the upper or lower lid. If the fluorescein dye on the conjunctival surface is focally displaced by leakage of nonfluorescent aqueous fluid (called a *positive Seidel's test*), or if there is brownish black uveal tissue visible in the scleral wound (Fig. 61.5), a globe perforation is present (see Intraocular Foreign Bodies and Globe Rupture). If no globe perforation is suspected, the eyelids should be everted and the conjunctival fornices inspected for a hidden foreign body.

Management and Disposition

Subconjunctival hemorrhages typically resolve spontaneously without treatment. Cool compresses are often recommended, but there is no evidence that they hasten recovery or improve outcome.

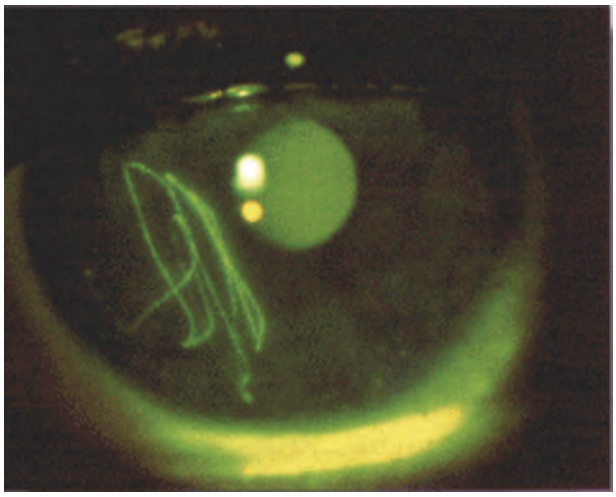

Fig. 61.4. Corneal abrasion demonstrated by slit-lamp examination. (Courtesy www.perret-optic.ch/optometrie/symptomes_diagnostiques/symptomes/opto_symfor_gb.htm#abrasion.)

Fig. 61.5. Scleral laceration with penetrating globe injury. Note care being taken not to increase intraocular pressure (IOP) with examiner's fingers.

There is no evidence to support the use of artificial tears or lubricants. Patients with simple subconjunctival hemorrhage are advised regarding the gradual resolution of their hemorrhage over 10 to 14 days, with the typical colorations associated with resolving hemorrhage. No follow-up is required unless the patient develops recurrent hemorrhages or new symptoms. Although most conjunctival lacerations do not require repair, lacerations that are more than 1 cm should be evaluated by an ophthalmologist in the ED for possible repair. Although there is no evidence to support the practice, topical antibiotic prophylaxis for 3 to 5 days (usually in ointment form; Table 61.1) is common practice. A deeper scleral laceration requires emergent consultation with an ophthalmologist, and may predispose to endophthalmitis. A full-thickness scleral laceration should be treated as a globe perforation.

Corneal Injuries: Corneal Abrasions, Foreign Bodies, and Lacerations

Clinical Features and Differential Diagnosis

Traumatic corneal injuries come in three varieties: (1) abrasions, (2) foreign bodies, and (3) lacerations (which may also go into

TABLE 61.1

Useful Topical Ophthalmic Medications and Their Dosages

MEDICATION	DOSAGE
TOPICAL ANTIBIOTICS	
Erythromycin 0.5% ointment	½-inch ribbon, four times per day for 7 days
Polymyxin B/trimethoprim solution	1 drop, four times per day for 7 days
Sulfacetamide 10% solution	1 to 2 drops, four times per day for 7 days
Azithromycin ophthalmic 1% solution	1 drop twice a day for 2 days, then daily for 5 days
ANTI-PSEUDOMONAL TOPICAL ANTIBIOTICS	
Ciprofloxacin 0.3% ointment	½-inch ribbon, four times per day for 7 days
Ciprofloxacin 0.3% solution	1 to 2 drops, four times per day for 7 days
Moxifloxacin 0.5% solution	1 to 2 drops, three times per day for 7 days
Gentamicin 0.3% ointment	½-inch ribbon, two to three times per day for 7 days
Gentamicin 0.3% solution	1 to 2 drops, four times per day for 7 days
Ofloxacin 0.3% solution	1 to 2 drops, four times per day for 7 days
TOPICAL CYCLOPLEGICS	
Cyclopentolate 1%	1 drop (may repeat in 5 minutes if needed), three times a day, for up to 4 days
Homatropine 5%	1 drop, four times per day, for up to 4 days
TOPICAL ANESTHETICS[a]	
Tetracaine hydrochloride 0.5% or 1%	1 drop, every 30 minutes as needed, for 24 hours only
Proparacaine 0.05% (10 times dilution[b])	2 to 4 drops, every 30 minutes as needed, for 48 hours only
TOPICAL NONSTEROIDAL ANTIINFLAMMATORY DRUGS	
Diclofenac 0.1%	1 drop, four times per day for 2 to 3 days
Ketorolac 0.4%	1 drop, four times per day for 2 to 3 days
TOPICAL ANTIHISTAMINES (ALLERGY)	
Azelastine 0.05%	1 drop twice a day
Emedastine 0.05%	1 drop up to four times per day
TOPICAL STEROIDS	
Prednisolone acetate 1%	2 drops every 15 to 30 minutes four times, then four times per day for 2 to 3 days

[a]For corneal abrasions—use only in reliable patients who have been educated on use.
[b]Can use undiluted 0.5% for diagnostic purposes in emergency department (ED).
Azari AA, Barney NP: Conjunctivitis: a systematic review of diagnosis and treatment. JAMA 310(16):1721-1729, 2013; Wipperman JL, Dorsch JN: Evaluation and management of corneal abrasions. Am Fam Physician 87(2):114–120, 2013.

the sclera). A corneal abrasion is typically sustained when an object or part of an object is dragged across the eye, such as seen with a fingernail injury to the eye or an attempt to pull off an adherent contact lens. A corneal foreign body is typically sustained when a small dense object travelling at high velocity impacts the cornea and becomes embedded, such as seen with debris impact from a grinding tool. A corneal laceration is typically sustained from a direct lancinating injury to the surface of the eye, such as by an infant's fingernail sweeping by the eye of its mother. All of these injuries present with more intensity than a conjunctival or isolated scleral injury, with significant foreign body sensation, pain, tearing, and a decrease in visual acuity if the abrasion, object, or laceration infringes upon the visual axis. A foreign body may actually be conjunctival and not imbedded in the cornea, presenting with more diffuse irritation, or sensation reported by the patient as "something under the eyelid," but may cause a corneal abrasion and more intense, localized foreign body symptoms upon subsequently being moved across the surface of the eye by blinking or rubbing the eye. As with a conjunctival and scleral injury, a perforated globe should be considered in the differential diagnosis of a corneal injury, suggested by symptoms and signs (such as, chemosis, deep eye pain, decreased visual acuity, and/or photophobia) and injury mechanism.

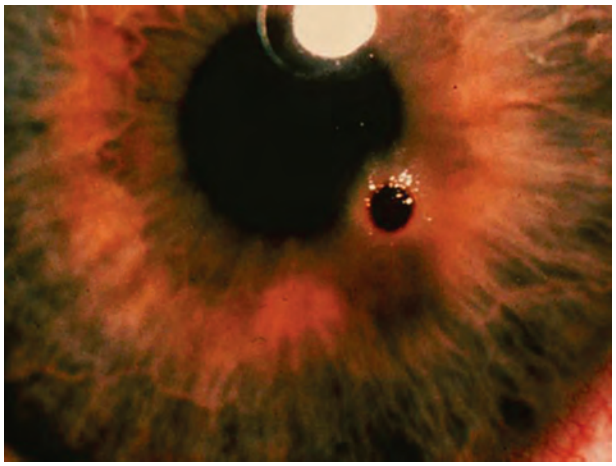

Fig. 61.6. Corneal foreign body seen on slit-lamp examination. (Courtesy www.tedmontgomery.com.)

Diagnostic Testing

With corneal abrasions and foreign bodies, topical anesthesia (see Table 61.1) can not only facilitate patient cooperation, but it help localize the extent of injury; focal pain that is completely abolished by topical anesthesia, with no signs of deeper injury present, suggests an injury confined to the superficial layers of the cornea. This does not obviate the need for a detailed examination with a slit lamp and fluorescein staining, with diagnostic goals as outlined with conjunctival injuries earlier. A corneal foreign body should be readily evident on slit-lamp evaluation (Fig. 61.6). If the foreign body spans the full-thickness of the cornea, it is considered a globe perforation until proven otherwise and should trigger emergent consultation with an ophthalmologist.

A corneal laceration may be difficult to characterize (or may even be hidden) on slit-lamp examination, and the primary diagnostic goal is identifying it, and determining whether or not it is through-and-through (ie, representing an open globe). Signs suggesting the latter are loss of anterior chamber depth, prolapsed iris (Fig. 61.7A), an irregular or teardrop-shaped pupil (see Fig. 61.7B), blood in the anterior chamber (Fig. 61.8), and a 360-degree subconjunctival hemorrhage. Testing for a positive Seidel's test with fluorescein, as described for conjunctival injuries earlier, can be used to confirm (but not exclude) an open globe. A critical point is that corneal perforation is a form of open globe, and once this is found, the examination ends (so as to prevent the additional extrusion of globe contents, worsening visual outcome) until the

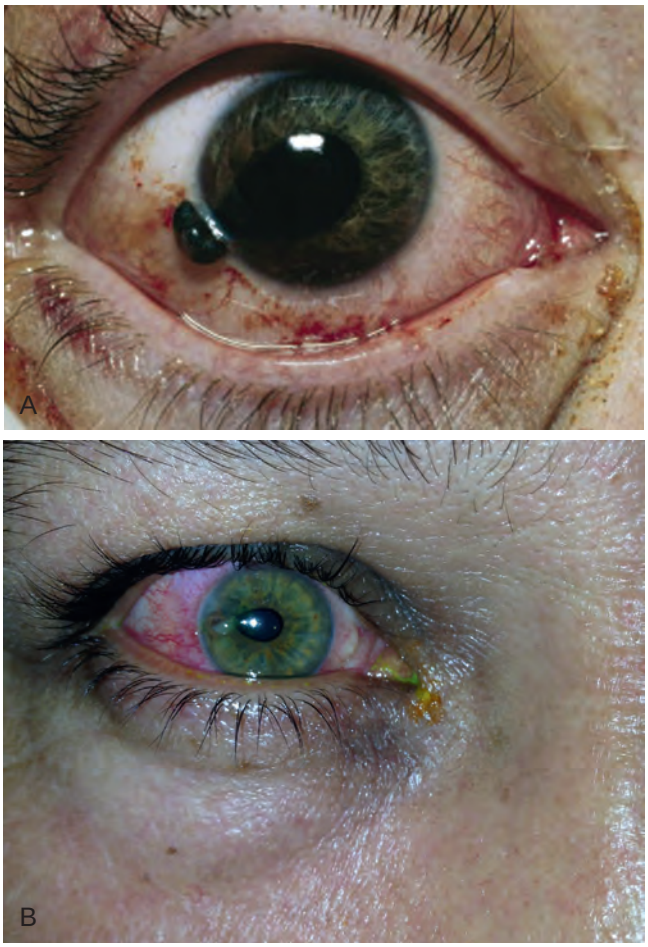

Fig. 61.7. Corneal laceration with prolapse of the iris. **A,** The pupil is irregular and teardrop shaped, pointing toward the laceration. **B,** Corneal laceration with tear drop teardrop pupil, pointing toward the laceration. (**A,** From Roberts JR, Hedges JR, editors: Clinical procedures in emergency medicine, ed 5, Philadelphia, 2010, Saunders. **B,** Courtesy Jeffrey Lee MD, University of California San Diego.)

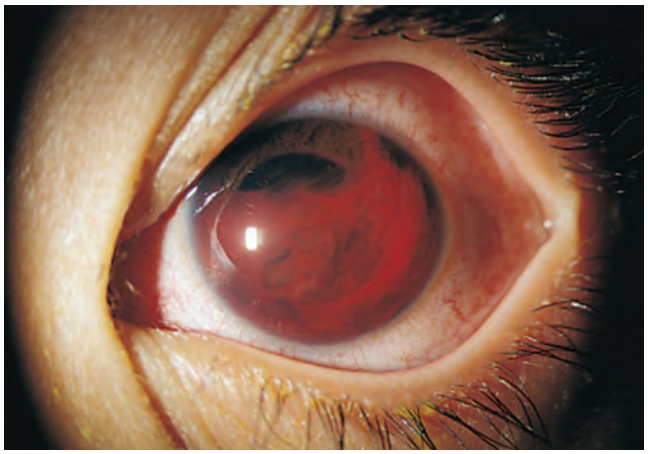

Fig. 61.8. Hyphema in the anterior chamber. (Courtesy Steve Chalfin, MD, University of Texas Health Science Center, San Antonio, TX.)

patient can be further examined under controlled conditions by an ophthalmologist (see Intraocular Foreign Bodies and Globe Rupture later).

If the mechanism of injury involves a high-velocity projectile and no foreign body is seen on slit-lamp examination but is suspected, then an evaluation for an intraocular foreign body as outlined in Intraocular Foreign Bodies and Globe Rupture later should be initiated.

Management and Disposition

Corneal Abrasions. There is no evidence that treatment of corneal abrasions with topical antibiotics, as often recommended, has any beneficial effect. Furthermore, the infection rate of untreated corneal abrasions is low—at 0.7%—and prophylactic antibiotic use is not warranted. We recommend that antibiotics not be used for uncomplicated corneal abrasions (that are not deep, not imparted by a heavily contaminated object, and not in high-risk patients), especially because the indiscriminate prescribing of these agents introduces the risk of toxic and allergic medication reactions in the eye. It is reasonable, however, to empirically treat a corneal abrasion in a contact lens wearer or immunocompromised patient with an anti-pseudomonal agent such as tobramycin, ciprofloxacin, or ofloxacin, as outlined in Table 61.1 (although for a shorter course than would be prescribed for an already established infection; ie, 3 to 5 days).[2]

A major goal in the treatment of a corneal abrasion is managing the pain. Topical nonsteroidal antiinflammatory drugs (NSAIDs), such as ketorolac or diclofenac (see Table 61.1) are options.[3] Prospective trials have revealed that topical anesthetics self-administered as needed for a short duration of time by ED patients for corneal abrasion pain results in significant pain relief without complications.[4,5] Meta-analyses incorporating these trials as well as postoperative ophthalmology literature support this finding.[6,7] A patient with a corneal abrasion can therefore be provided a limited 24- to 48-hour course of a topical anesthetic (see Table 61.1), because the most intense pain occurs in the first 24 hours. This being said, uninformed patients using over-the-counter topical anesthetics for otherwise simple corneal injuries can develop an erosive keratopathy.[8] Regardless of whether this association is due to masking the pain of an emerging infection or due to a direct toxic effect from a misused anesthetic, it is important to counsel patients on the correct and limited use of these agents. Eye patches are not recommended, because they can mask a worsening infection. Urgent ophthalmologic consultation is warranted with signs of active infection, such as a corneal infiltrate (whitening of the cornea) or ulceration (see Corneal Ulcers and Infiltrates later); otherwise, the patient can follow up with an ophthalmologist in 24 to 48 hours.

Corneal Foreign Bodies. Foreign bodies of the cornea and conjunctiva—especially those containing iron (given the propensity for worsening rust deposition over time)—should be removed in the ED if possible, using a topical anesthetic (see Table 61.1) for comfort. Corneal foreign bodies can be removed by moist cotton-tipped applicator or, if needed, by using a 25-gauge or 27-gauge needle carefully applied in a plane tangential to the surface of the cornea, under slit-lamp visualization. Non-corneal conjunctival foreign bodies can be removed by irrigation, a wet cotton-tipped applicator, or fine forceps if needed. For metallic foreign bodies, residual rust rings can be removed 24 to 48 hours later, because the rust will migrate toward the corneal surface and be more accessible. Ophthalmologic consultation is recommended for deep and large corneal foreign bodies or if the central area of the visual axis is involved. Considerations for topical antibiotic prophylaxis are the same as for corneal abrasions (see earlier).

Corneal Lacerations. Large but partial corneal lacerations should be evaluated by ophthalmology for potential closure in the operating room versus observation with medical therapy (topical cycloplegics and antibiotics; see Table 61.1), pressure patch, and possible tissue grafts. Smaller corneal lacerations can be evaluated and treated as corneal abrasions (with the only modification being

they should be empirically treated with topical antibiotic prophylaxis given their depth). A complication of a corneal laceration or abrasion is an infected corneal ulcer (see Corneal Ulcers and Infiltrates), which may develop days to weeks later.

Anterior Segment Injuries: Traumatic Hyphema, Iritis, Cyclodialysis, and Lens Dislocation

Clinical Features and Differential Diagnosis

Any blunt or penetrating injury of the eye may result in injury to the underlying anterior chamber, the iris, lens, and associated anterior segment structures of the eye. A traumatic hyphema (blood in the anterior chamber from ruptured vessels in the ciliary body or iris) can present with a spectrum of severity, from microhyphema (where red blood cells only visible by slit-lamp examination are suspended in the anterior chamber aqueous), to a layered hyphema (where a layer of blood may be observed grossly in the lower anterior chamber), or to a full or total hyphema (in which the entire anterior chamber is filled with blood). A microhyphema may not be visible to the naked eye but will be associated with suggestive clinical features that include peri-limbal conjunctival injection (ciliary flush), abnormal pupil size (larger, smaller, or irregular), and dilated pupils (traumatic mydriasis) (Fig. 61.9). Symptomatically, patients may experience blurry vision and photophobia (from ciliary spasms) from a simultaneous traumatic iritis (iridocyclitis). A traumatic hyphema from a blunt injury may also be associated with a cyclodialysis, a tear in which the ciliary muscle is avulsed from a scleral spur.[9,10]

A blunt injury to the eye can also weaken the lens zonule complex and result in a lens dislocation (Fig. 61.10A). Predisposing factors for lens dislocation include Marfan's syndrome, homocystinuria, and high degrees of myopia. Patients may complain of monocular diplopia, distorted images, and blurred vision, and have other signs related to the trauma, such as traumatic mydriasis, iridocyclitis, and hyphema.

Diagnostic Testing

A diagnosis of a traumatic hyphema can often be missed without the illumination and magnification with a slit lamp. One sequela is increased IOP, and therefore the pressure should be measured (assuming there are no signs of globe rupture). An elevated IOP occurs up to 3 days after the initial injury in approximately one-fourth of patients; it is typically self-limited, but in certain instances can be high and persist and can lead to optic nerve injury and vision loss. Photophobia in the injured eye, especially if occurring on illumination of the opposite eye, strongly suggests a traumatic iritis. A cyclodialysis will be evident on slit-lamp examination as a separation of the edge of the iris away from the limbal margin.

A lens dislocation may be evident on slit-lamp examination; one may see the edge of the natural lens (which is normally not visible whether or not the patient is dilated) (see Fig. 61.10B), phacodonesis (shimmering of the lens with eye movement), and iridodonesis (shimmering of the iris with eye movements), which are evidence that the lens zonules have been compromised. A displaced crystalline lens may also be visible on ultrasound (using a large amount of gel to minimize any pressure from the ultrasound probe on the eye).[11] Depending on the lens location, additional findings including increased IOP (secondary to angle closure glaucoma), corneal swelling, and intraocular inflammation may be present.

Management and Disposition

Traumatic Iritis, Hyphema, and Cyclodialysis. With isolated traumatic iritis, the primary goals of treatment are minimizing scarring, decreasing inflammation, and pain relief. This is often best achieved with a paralytic agent for the iris and ciliary body (eg, homatropine or cyclopentolate; see Table 61.1). Topical ophthalmic steroid drops (eg, prednisolone acetate; see Table 61.1) are considered in cases where significant post traumatic inflammation is present; however, caution should be applied in cases of corneal abrasions. Close follow-up with ophthalmology within 48 hours is warranted to ensure injury does not result in other ocular issues, such as glaucoma, corneal damage, and hypotony.

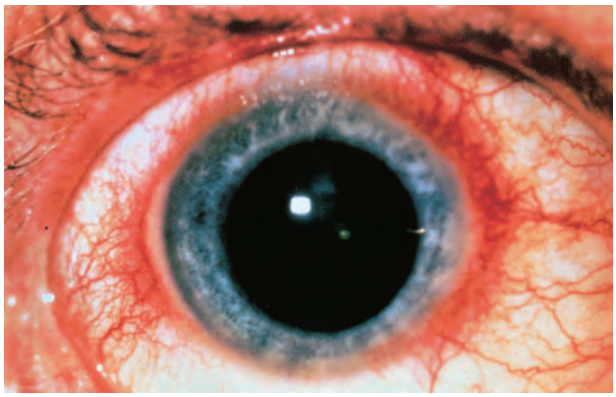

Fig. 61.9. Ciliary flush. Note that conjunctival injection is most prominent immediately around the limbus. (Courtesy Douglas Brunette, MD.)

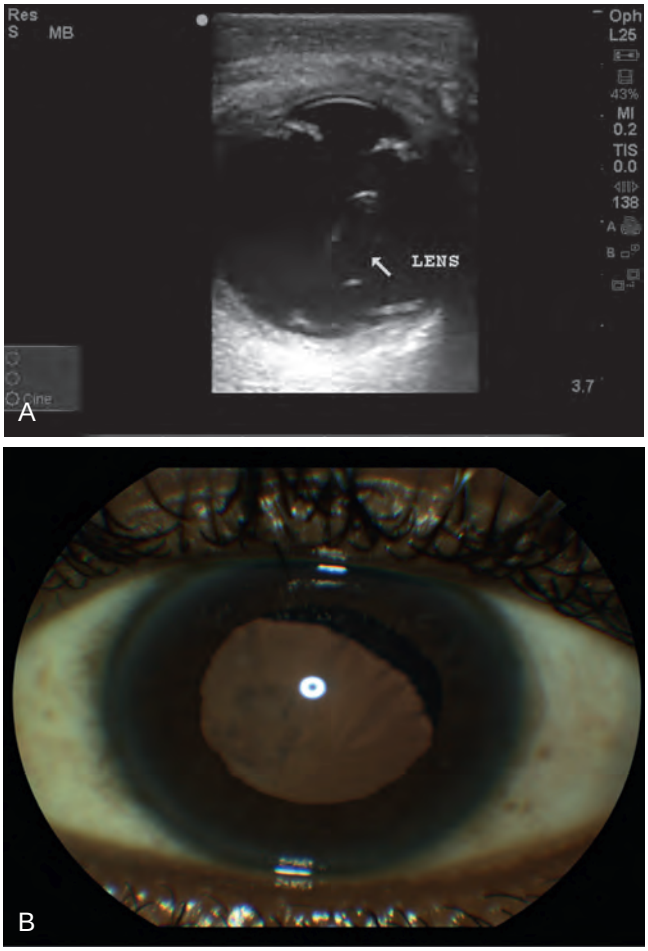

Fig. 61.10. **A,** Ocular ultrasound showing lens dislocation. **B,** Dislocated lens with edge visible. (**A,** Courtesy Douglas Brunette, MD. **B,** Courtesy Jeffrey Lee, MD, University of California San Diego.)

Both easily visible (see Fig. 61.8) and subtle traumatic hyphema deserves attention in follow-up to help minimize the likelihood of long-term complications. These complications include corneal staining and elevated IOP, which should be monitored and followed up to ensure proper resolution. In the past, recommended treatments for hyphema included strict bedrest with the head of bed elevated at least 30 degrees (presumably to allow blood to settle and filter out inferiorly) and restriction of work requiring near-vision (since accommodation may stress injured blood vessels). However there is no evidence that strict bedrest has any effect on outcome or that head of bed position affects resorption rate in a consistent manner, so a patient with an uncomplicated hyphema can be discharged home with gentle ambulation allowed, with head of bed elevation simply to keep hyphema that is larger from clotting in the visual axis.[12,13] The recommendations for pediatric patients with uncomplicated traumatic hyphema are identical; admission to hospital is not warranted, because it results in no discernable benefit.[14,15]

Admission is recommended, however, for patients with hyphema of greater than 50% (in which the large volumes of blood can lead to severely high IOP and permanent corneal damage), sickle cell trait (in whom sickling of red cells in the naturally hypoxic and acidotic anterior chamber prevents egress of aqueous humor and blood products), uncontrolled IOPs, and anticoagulated patients (in whom there is concern for re-bleed). Topical and oral agents to lower IOP are appropriate, but carbonic anhydrase inhibitors should be avoided in sickle cell patients. Antifibrinolytics, such as systemic or topical aminocaproic acid, may also be considered, because they have been shown to reduce the rate of recurrent bleeding even if they do not affect final visual acuity.[12] Initiation of these treatments are best deferred to an ophthalmologist.

For patients discharged with a traumatic hyphema, next-day follow-up with an ophthalmologist is recommended to assess IOP and to evaluate for indications for urgent paracentesis of the anterior chamber or an emergent trabeculotomy, such as inability to clear the hyphema, uncontrolled IOP, or rebleeding (which occurs in 6% to 33% of patients within 2 to 5 days).[12,16] Patients—particularly those with 20/200 vision or less in whom a rebleed might go unnoticed—should be followed for 3 days to identify these developments. Patents with underlying traumatic iritis may be prescribed cycloplegics (homatropine; see Table 61.1), but there is little evidence to support their use for hyphema without iritis; there is also no evidence that eye patching—postulated to prevent photosensitization of the corneal endothelium by protoporphyrin, a blood product—has any effect.[12]

The patient with a cyclodialysis can be treated with topical cycloplegics (see Table 61.1) to relax the iris and ciliary body and be referred to an ophthalmologist for routine outpatient follow-up; small tears tend to resolve spontaneously and can be managed conservatively, whereas large ones may be permanent and—especially if causing visual issues due to hypotony—may require surgery to re-attach.[10]

Lens Subluxation and Dislocation. Lens subluxations or dislocations can be vision-threatening emergencies and should be evaluated by an ophthalmologist in the ED for potential treatment, both medical and surgical.

Posterior Segment/Ocular Injuries: Commotio Retinae, Retinal Detachment, Intraocular Foreign Body, and Perforated Globe

Clinical Features and Differential Diagnosis

A more significant mechanism increases the possibility of a deeper ocular injury, and the spectrum of injury includes commotio retinae, a retinal or vitreous hemorrhage, a retinal detachment, an intraocular foreign body and a perforated globe.

Three main sequelae of a blunt injury to the retina are commotio retinae, retinal or vitreous hemorrhage, and retinal detachment or tear. Commotio retinae, also known as *Berlin's edema,* can occur after ocular trauma. One study showed that it was present in approximately 6% of patients who had surgically treated orbital blowout fractures.[17] With a retinal or vitreous hemorrhage, patients can experience vision compromise ranging widely from dark floaters to vision blackout. A retinal detachment can present with floaters and/or flashes of light (photopsia) and eventually cause a curtain-like blocking of the patient's vision as it evolves into a retinal detachment. Because the retina has no pain receptors, patients are usually pain-free.

An important evaluation after blunt trauma to the orbit is to determine if a globe perforation (ruptured globe) or intraocular foreign body are present. Besides pain and decrease in vision, other signs as previously mentioned (loss of anterior chamber depth, irregular or tear drop-shaped pupil, blood in the anterior chamber, 360 degree subconjunctival hemorrhage, and/or prolapse of uveal tissue) should be noted. When vector forces of the trauma are not enough to blow out the orbit, the forces are directed on the globe itself. Muscle insertion sites and the limbus are the most common sites of scleral rupture because these are the thinnest areas (see Fig. 61.5). Significant collateral damage of the adjacent tissue structures such as the lens, retina, uvea, and optic nerve can also occur. The patient with a globe injury may develop sympathetic ophthalmia, a vision-threatening autoimmune response to the remaining healthy eye triggered by the exposure of the previously naïve immune system to intraocular contents from the ruptured eye.

Diagnostic Evaluation

In some cases of retinal injury, visual acuity testing can even be normal. Commotio retinae may appear as whitening of the retina on funduscopy. The diagnostic approach to retinal detachment is discussed in more detail in the Primary Disorders of Vision section later in this chapter. In instances of a penetrating injury to the globe or orbit, careful evaluation for a retained foreign body is important. Initially, it may not be clear if a foreign body is intraocular or just intraorbital. If the suspicion for an intraocular foreign body or ruptured globe is high but the examination cannot be performed without minimal manipulation, the examination should be deferred to one performed under anesthesia and tonometry avoided. Prior to this, a CT can be performed to provide structural integrity of the globe and orbit (and location of foreign bodies); however, because it has a sensitivity of between 56% to 75% for open globe injury, it cannot be relied upon alone, and formal surgical exploration may be needed.

Management and Disposition

Retinal Injuries. A traumatic retinal detachment, if detected and treated early before the macula is involved, carries a good prognosis. About 10% of all retinal detachments are from blunt trauma. The management of retinal detachment and vitreous hemorrhage is discussed in more detail in the Primary Disorders of Vision section later in this chapter. The decreased visual acuity from commotio retinae is self-limited and resolves in a few weeks.[18] Evaluation by an ophthalmologist in the ED is recommended, however, because the commotio can mask a retinal tear.

Intraocular Foreign Bodies and Globe Rupture. For a globe perforation (open globe) with or without an intraocular foreign body, an ophthalmologist should be consulted emergently, and the examination stops until the patient can be taken to the

operating room. In anticipation of potential surgery, a protective shield should be placed (so that nothing touches the eye), tetanus vaccine administered, the patient kept *nil per os* (nothing by mouth) (NPO), and pain and nausea controlled. The incidence of endophthalmitis (an infection of the globe; see Infectious Conditions later) following open-globe injury ranges from 2.6% to 30%, and systemic antibiotics (cefazolin or vancomycin and a fourth-generation fluoroquinolone—due to its vitreal penetration) to cover common culprits of traumatic endophthalmitis (*Bacillus* species, *Staphylococcus aureus, Pseudomonas* species, gram-negative organisms, and anaerobes) should be administered.[19] Foreign bodies, especially non-metallic foreign bodies, pose the highest risk of infection.

In general, almost all intraocular foreign bodies need to be removed. For intraorbital foreign bodies, the type and location of the material influences the necessity to remove them. Removal of inert plastic, glass, and metals may cause more damage than their permanent presence, whereas organic foreign bodies typically need to be removed because of their propensity to cause infection. Siderous oxidation of ocular tissues is a late complication of iron-containing intraocular foreign bodies and can lead to visual loss. Chalcosis, a sterile inflammatory reaction to copper-containing compounds, may occur, necessitating removal of the offending object.

It is controversial whether it is necessary to avoid the use of succinylcholine for rapid sequence intubation in open globe injury because of the very theoretical possibility of a rise in IOP from succinylcholine causing further extrusion of globe contents.[20] Where time and circumstances permit, we recommend rocuronium for intubation of patients with open globe injuries, but there is no hard evidence that succinylcholine will cause harm.

Retrobulbar and Peribulbar Injuries: Orbital Wall Fracture, Retrobulbar Hemorrhage, and Optic Nerve Injury

Clinical Features and Differential Diagnosis

Trauma to the eye can result in disruption to tissue around the globe and should be suspected based on the mechanism and recognition of specific clinical features. Clinical signs that could indicate an acute orbital wall fracture include ecchymoses, tissue swelling, hypesthesia of the trigeminal nerve, double vision, blurry vision, enophthalmos (posterior displacement of the eyeball within the orbit), and ptosis. In an orbital floor fracture, a medially-hinged bony "trapdoor" fragment may have transiently displaced inferiorly, allowing herniation of orbital contents into the maxillary sinus. Associated globe injuries occur in 10% to 25% of patients with orbital floor fractures. A patient can develop a vision-threatening injury without an orbital wall fracture, specifically a retrobulbar hemorrhage. The orbit is essentially a continuous cone-shaped fascial envelope with rigid bony walls on all sides (except anteriorly where the orbital septum forms an inflexible boundary), in which there is little room to accommodate an increase in volume.[21] A retrobulbar hemorrhage from a ruptured infraorbital or ethmoidal artery occurring with intact orbit walls will increase intraorbital pressure and can cause an orbital compartment syndrome, resulting in ischemia to the optic nerve and retina. The triad of proptosis, ophthalmoplegia, and vision suggests this process. Blunt trauma can also cause a direct optic nerve injury, causing decreased visual acuity, if not vision loss. A rare complication of an orbital fracture or retrobulbar injury is an oculocardiac reflex from periorbital soft tissues that—through an afferent signal via the trigeminal nerve and efferent signal via the vagus nerve—can trigger bradycardia, junctional rhythm or even asystole, with nausea and vomiting, and is potentially fatal if unresolved.

Diagnostic Testing

A thorough examination paying particular attention to extraocular eye movements, assessing for an afferent pupillary defect (APD; Fig. 61.11) and checking facial sensation is imperative in the diagnostic evaluation of a possible retrobulbar or orbital injury. An orbital wall fracture is most readily diagnosed with an orbital CT scan with axial and coronal fine (minimum 1.5 mm) cuts (Fig. 61.12). Less sensitive diagnostic screening tools include plain x-ray, in which suggestive signs are a bulge extending from the orbit into the maxillary sinus ("teardrop" sign) and an air-fluid level in the maxillary sinus, and bedside ultrasound (sensitivity 56% to 92%) in which a suggestive sign is bright acoustic shadowing from subcutaneous or orbital air.

Clinical signs strongly suggesting a retrobulbar hematoma include the presence of three or more of the following: pain, decreased vision, proptosis with resistance to retropulsion, chemosis, limited extraocular motility, diplopia, diffuse subconjunctival hemorrhage, increased IOP, and an APD.[21] Funduscopy may reveal edema of the optic disc or retina or retinal venous congestion. A CT scan of the orbit can provide additional evidence if clinical findings are inconclusive. However, if there is significant suspicion, treatment (see the following Management and Disposition section) should not be delayed because vision loss can be permanent.

An optic nerve injury may or may not be coincidental with a retrobulbar hematoma, and clinical findings may not necessarily differentiate whether there is compression or transection. An optic nerve injury may manifest as a decrease in visual acuity, visual field deficit, a relative APD (Marcus-Gunn pupil), or a change in optic nerve appearance. The optic disc can appear normal or swollen. CT can help determine the nature and degree of optic nerve injury.

Management and Disposition

Orbital Wall Fractures. Prophylactic antibiotics are frequently recommended by consultants for orbital wall fractures, but there is no literature evidence to support their use outside of intra-operative administration.[22,23] Antibiotic prophylaxis may be warranted, however, in patients with coincident sinusitis seen on CT scan, because it increases the risk of developing orbital cellulitis.[23] The patient should be instructed to avoid exerting Valsalva maneuvers, and nose blowing and should be prescribed nasal decongestants, such as pseudoephedrine 30 mg every 6 hours, so as to decrease the risk of orbital emphysema. Lastly, to improve healing and decrease swelling, ice packs to the orbit for at least 48 hours is recommended. Some ophthalmologists use steroids to reduce swelling, however, this is a case by case decision. Clinical findings that warrant urgent surgical exploration (ie, within 24 or 48 hours) include early enophthalmos greater than 2 mm; large (>2 cm^2) defects of the orbital floor/medial wall; pediatric trapdoor fractures; and when CT evidence of entrapment is associated with symptomatic diplopia, gaze restriction, or a non-resolving oculocardiac reflex.[24] Outside of these indications, persistent diplopia and cosmetic concerns (such as, enophthalmos) are generally not addressed until swelling subsides after 7 to 10 days. Patients can be discharged for reevaluation by an ophthalmologist in 1 to 2 weeks. Children with orbital wall fractures are a special consideration, because they are more predisposed to "green-stick" fractures of the orbital wall and develop fibrosis and shortening of the affected muscle within a couple of days, affecting ocular function; thus, children with orbital wall fractures should be seen by an ophthalmologist in 1 to 2 days.[23]

Retrobulbar Hemorrhage. The loss of vision associated with a retrobulbar hematoma is irreversible within 60 to 100

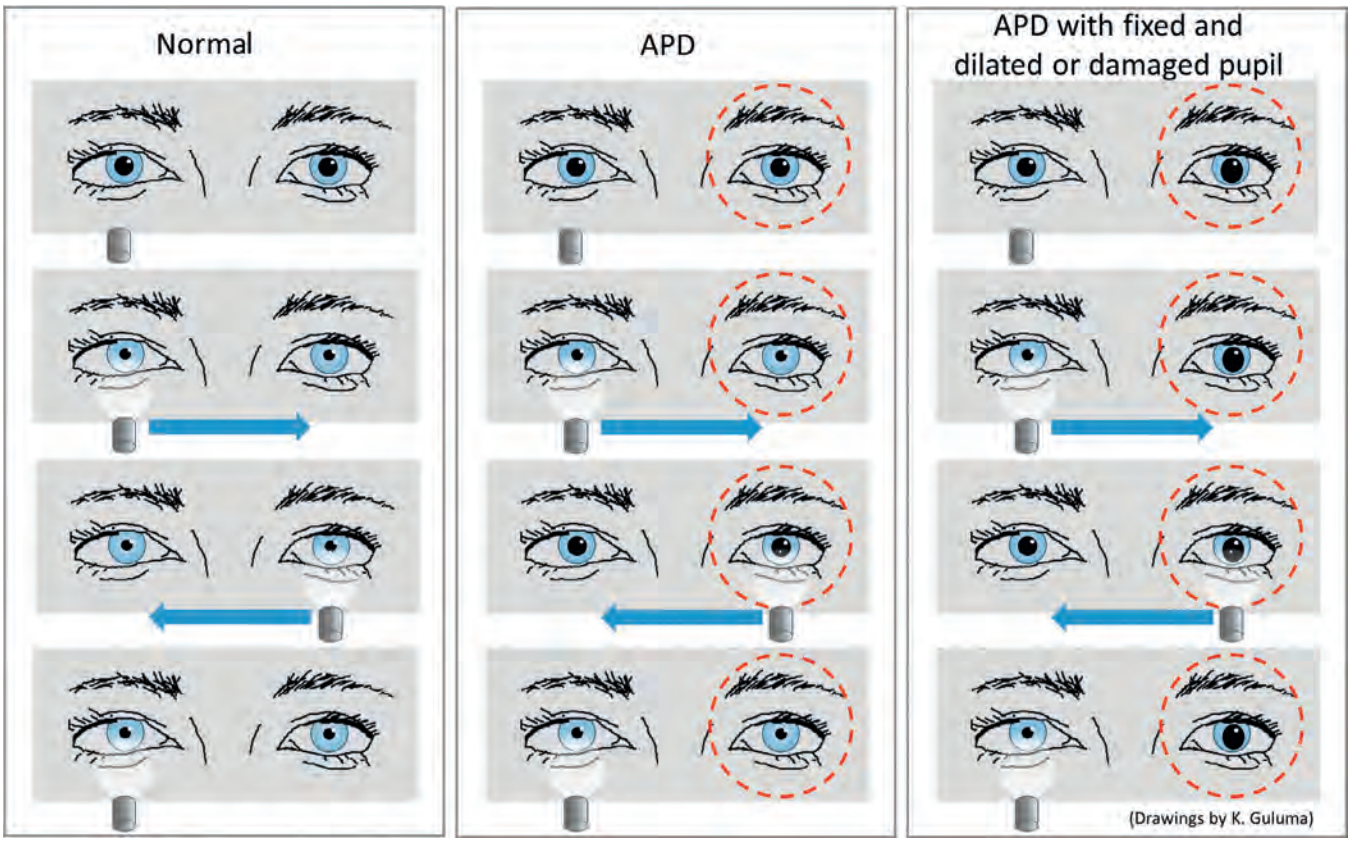

Fig. 61.11. The "swinging flashlight test" for an afferent pupillary defect *(APD),* which is otherwise known as a *Marcus Gunn pupil*. Normally *(panel on left),* both pupils constrict regardless of which eye is illuminated, due to intact afferent stimulus into the direct and consensual pupillary light reflexes. With an APD *(panel in the middle),* the pupils dilate upon "swinging" the flashlight to the pathological eye with dysfunction in the retina or optic nerve (dashed circle), because of a sudden loss of afferent stimulus into light reflexes. With a fixed and dilated or damaged pupil *(panel on the right),* the same will hold true, except that the damaged pupil may not react due to an intrinsic problem, regardless of the presence of an APD. In each condition, whether normal or with an APD, the pupillary findings will reverse on swinging the flashlight back across to the other eye. The flashlight should be held over each eye for at least 3 seconds to ensure time for a response.

Fig. 61.12. Facial computed tomography (CT) scan showing left inferior orbital fracture with blood in maxillary sinus. (Courtesy University of Iowa Department of Ophthalmology, http://webeye.ophth.uiowa.edu/eyeforum/Images/floorfx_08232004.jpg.)

minutes after the onset of ischemia. Emergent ophthalmologic consultation for decompression is therefore indicated, keeping in mind that the clock does not start with the injury but at the time at which the intraorbital compartment pressure from the hematoma reached a pressure critical enough to start to cause vision loss. In the meantime, IOP-lowering agents (such as, intravenous [IV] carbonic anhydrase inhibitors, topical beta-blocker, alpha agonists, and in some cases 1 to 2 g of IV mannitol per kilogram) can be used. However, once ischemia and vision loss sets in, time is of the essence, and—depending upon the availability of an ophthalmologist in this time frame—a lateral canthotomy may need to be performed by the emergency clinician as a temporizing, vision-saving measure before definitive decompression (Fig. 61.13).[25]

Optic Nerve Injury. Once the determination of the type and degree of optic neuropathy is determined, treatment options can be considered. Surgical decompression of orbital canal fractures that impinge the nerve is not clearly beneficial, and steroids for traumatic optic neuropathy in general do not provide any additional benefit over observation.[26] In both cases, an ophthalmologist should be consulted in the ED for potential therapy options.

Chemical Exposures and Glues

Clinical Features

In addition to blunt or penetrating trauma, the eye can also be injured by chemical exposures. Chemical burns can lead to devastating vision loss. Acids burns precipitate and do not penetrate as deeply into tissue (due to coagulative necrosis, in which the

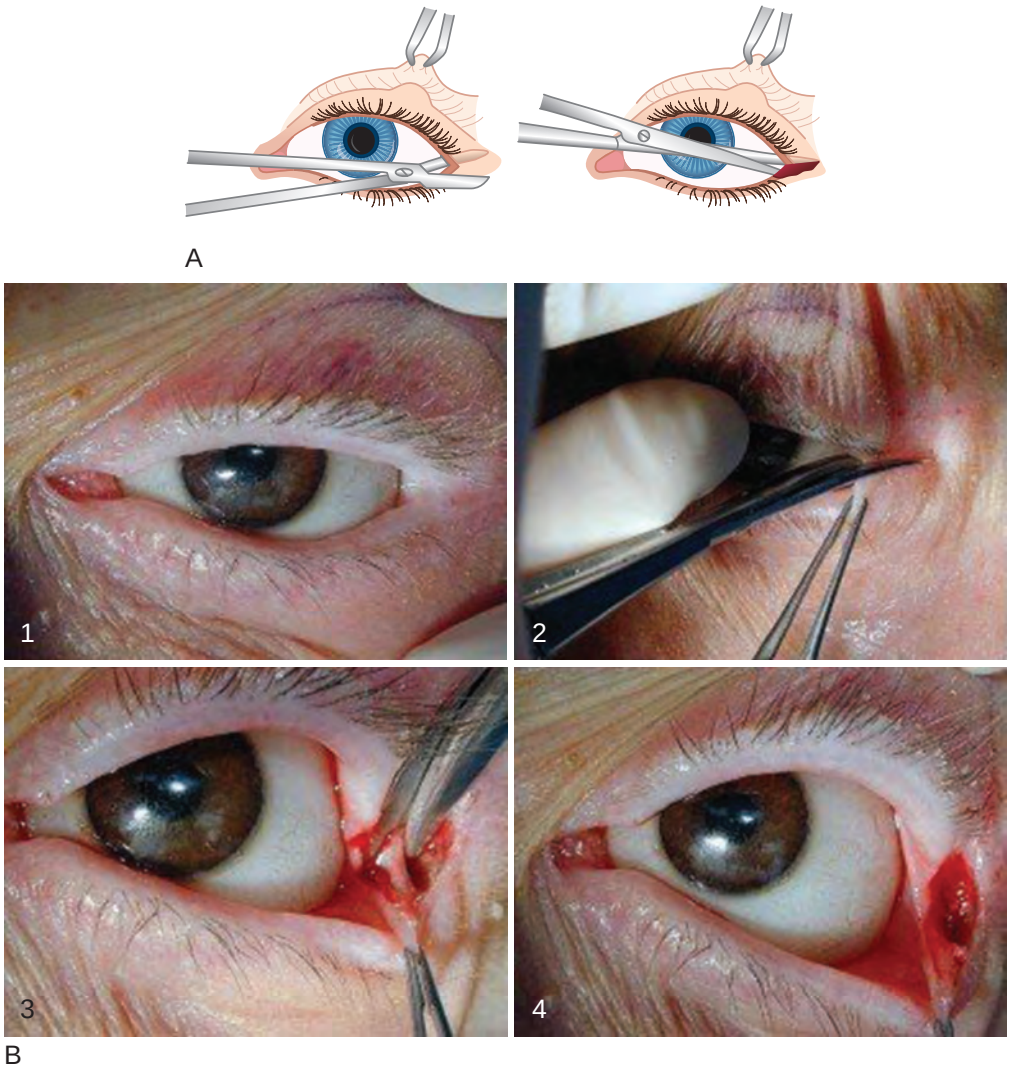

Fig. 61.13. A, Lateral canthotomy. **B,** *1,* Preoperative view of orbit. *2,* Incision for lateral canthotomy. *3,* Identification and incision of inferior canthal tendon, completing cantholysis. *4,* View after lateral canthotomy and inferior cantholysis, creating maximal immediate decompression by allowing eyeball and orbital contents to move anteriorly. (**B,** From Ramakrishnan VR, Palmer JN: Prevention and management of orbital hematoma. Otolaryngol Clin North Am 43:789–800, 2010.)

precipitation of tissue proteins limits the depth of the injury). The one exception to this is hydrofluoric acid, which may rapidly pass through cell membranes and enter the anterior chamber.[27] Alkaline burns are more severe because they produce a liquefactive necrosis (because damaged tissues then secrete proteolytic enzymes as part of an inflammatory response), leading to cataract formation, damage to the ciliary body and trabecular meshwork, and irreversible intraocular damage in as little as 5 to 15 minutes.[27] Another chemical exposure that may present in the ED is superglue to the eye. Cyanoacrylate is often used in ophthalmological surgical procedures and is relatively nontoxic to the eye. The main issues arising from superglue exposure are adhesion of eyelashes, which is difficult to reverse, and concurrent conjunctival and corneal abrasion.[28]

Differential Diagnosis

It is important to treat all unknown chemical exposures as an acidic or alkali exposure until proven otherwise. Certain substances, such as detergents and solvents, can lead to epithelial injury and anterior chamber inflammation, which then should be treated based on their particular findings (abrasion/iritis). Signs of a potent chemical exposure include periorbital edema and erythema, de-epithelialized skin, and loss of eyelashes and eyebrows, corneal and conjunctival epithelial defects, chemosis, corneal cloudiness, sterile ulceration, edema, and perforation. Elevated IOP may result from damage and/or inflammation of the trabecular meshwork. Although a determination of the pH of the solution involved is the most important consideration, other factors in the exposure (such as, temperature, amount, impact force, concentration, osmolarity, and redox potential) can greatly influence the pathophysiology of chemical tissue damage.[28a] Accessing the material safety data sheet (MSDS) of the agent involved or consulting with a Poison Center can greatly facilitate identification of the offending agent and guide the appropriate treatment. If the exposure occurred as a result of explosion, penetrating globe injury may also be present.

Diagnostic Testing

Treatment of a chemical exposure should begin as soon as possible with copious irrigation, even prior to arrival to the ED. The initial basic ophthalmic examination should pay attention to an inspection of the fornices, to ensure that there is no remaining chemical

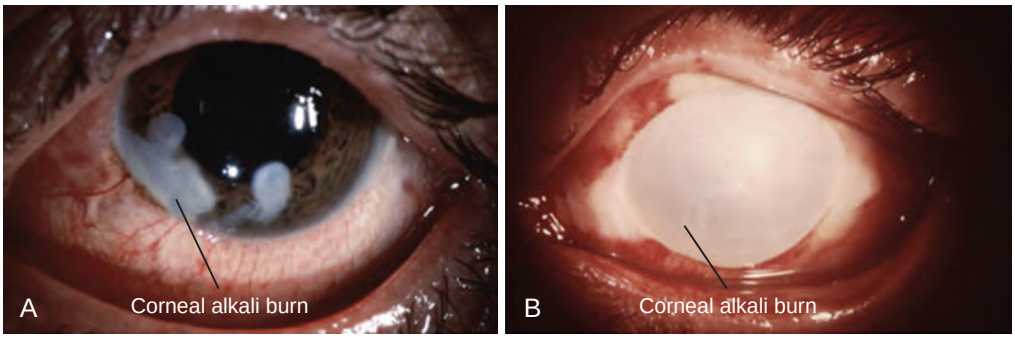

Fig. 61.14. A, Alkali burn demonstrating corneal burns and conjunctival injection on the day of the accident. **B,** Complete corneal tissue destruction 7 days after alkali burn. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary illustrated manual of ophthalmology, ed 2, Philadelphia, 2004, WB Saunders.)

gel or solid material (such as, alkaline lime or plaster), as well as screening for ocular trauma, facilitated with the use of a topical anesthetic for patient comfort.[27] With known chemical exposures, irrigation should be continued for a minimum of 10 minutes until a quick evaluation can be performed. This should include a pH measurement (Nitrazine paper dipped in lower lid fornix) to evaluate for acidity or alkalinity. If the pH is not in the neutral 7 to 7.5 range, irrigation should be continued. Superglue exposure represents a special circumstance, and there are two main principles in the evaluation: (1) to separate the lids so that a detailed eye examination can be performed and to remove visible superglue, and (2) to identify any corneal abrasion with fluorescein staining.[28]

Management and Disposition

For acid or alkaline burns, irrigation of the eye should be performed immediately. The longer irrigation is delayed, more irrigation volume will likely be required because the chemical can deposit within the tissue.[27] It may take up 20 L or more to change the pH to a physiologic level (a goal pH of 7 to 7.5). Based on animal studies, traditional isotonic saline irrigation solutions may be relatively ineffective at neutralizing a significant exposure to an alkaline agent (such as, sodium hydroxide) within the 20 minute time frame required to reduce injury and that buffered irrigation products specially designed for the task are significantly more effective.[29,30] This being said, initiation of irrigation with whatever solution is most readily available should not be delayed while such a solution is being obtained. Surprisingly, tap water is more effective than saline at normalizing pH, specifically for alkali burns.[29] It is also better tolerated than saline and is therefore recommended in situations in which a buffered product is not available. Use of topical anesthesia (see Table 61.1) and assistive devices, such as a Morgan lens and an eyelid retractor, can aid in delivering the irrigation more effectively. Emergent ophthalmological consultation is warranted in significant acid burns, and all alkaline burns, especially those in which irrigation to a pH of 7 required copious irrigation.[29] In chemical exposures deemed to have a low risk of significant injury (an assessment of facilitated by contact with a local poison center) with no signs of immediate ocular injury (such as, corneal burns), the patient can be treated and referred for follow-up with an ophthalmologist in 24 to 48 hours.

For more significant chemical injuries, cycloplegics, antibiotics (ointments are usually preferred because they also provide comfort), and occasionally steroid drops are indicated (see Table 61.1 for agents and dosing). After the acute treatment has been completed, obtaining additional history (such as, the nature of the substance) can be useful in determining prognosis; substances with pH ranging from 2 to 12 with limited contact time tend to have a better prognosis. However, at the time of presentation, the severity and complications of the injury may not be completely assessed because the full extent of the injury has not yet occurred. These complications can include permanent corneal injury (Fig. 61.14), glaucoma, palpebral and conjunctival adhesions, cataracts, and retinal injury.

In the case of superglue, cyanoacrylate does not bond well to wet surfaces, and an exposure into the eye typically results in a forceful blink and extrusion of the glue onto the dry surfaces of the lid margins.[28] Gentle traction will often separate glued eyelashes; if not, trimming with Westcott scissors can help. Examination by slit lamp can help determine which lashes can be more readily separated. Time will help loosen the adhesions and allow for removal of the glue. If there is eyelid malposition, cutting the lashes can often allow for normalization of the eyelid position. Attempts to dissolve the glue with other substances (especially acetone) should be avoided, because they may cause ocular damage. Ophthalmology consultation in the ED is recommended for cases in which the above measures fail to separate the lids to enable an examination, if there is residual eyelid mal-positioning, or if there is a suspected corneal abrasion from the hardened glue. If separating eyelids reveals no evidence of subsequent lid malpositioning and no sign of conjunctival involvement or injury, the patient can be referred to an ophthalmologist for follow-up as an outpatient in the next day.

INFLAMMATORY CONDITIONS

Principles

Inflammatory conditions of the eye tend to present as a "red eye," which is a general term that encompasses a variety possible etiologies in the conjunctiva, cornea, globe and surrounding orbit. The clinical approach to the red eye in general (which includes not just inflammatory processes but also infectious processes) is described in detail in Chapter 19.

The Conjunctiva and Cornea: Keratitis, Pterygium and Pinguecula

Clinical Features and Differential Diagnosis

Conjunctival and corneal inflammatory conditions present in a somewhat stereotyped fashion and include allergic conjunctivitis, superficial punctate keratitis, ultraviolet (UV) keratitis (radiation keratitis), and pterygium and pinguecula. Allergic conjunctivitis, although technically an inflammatory process, is similar enough in presentation to infectious conjunctivitides that it is considered together with the infectious processes outlined later this chapter.

Superficial punctate keratitis presents with pain or foreign body sensation, photophobia, and redness due to poor lubrication of the corneal surface from any one of several etiologies, including dry eyes, drug toxicity, and contact lens overuse. UV keratitis is a specific form of keratitis that presents when prolonged exposure to UV light (from a source such as a tanning booth, reflection from snow or water, or a welder's arc) causes a direct injury to the corneal epithelium, at times severe enough to cause ulceration. There is a latency of 6 to 10 hours before symptoms arise, at which point patients have a significant degree of pain and discomfort, photophobia, and mild conjunctival injection.

Another set of conjunctival inflammatory conditions, somewhat similar in appearance to one another, are pterygium and pinguecula. A *pterygium* is a chronic fibrovascular growth of conjunctiva triggered by chronic exposure to UV light that grows temporally from the nasal side of the eye (or vice versa), eventually covering the cornea. A pterygium can get acutely inflamed, whereupon patients experience foreign body sensation, dry eyes, and redness, but they should not have loss of vision unless the process has started to infringe upon the visual axis (a very gradual and chronic process). A *pinguecula* is of similar pathology and pathophysiology to a pterygium, resulting in similar symptoms, except that it stops at the limbus and does not enter the cornea or visual axis.

Diagnostic Evaluation

Examination with a slit lamp is an integral part of the diagnostic evaluation of conjunctival and corneal inflammatory conditions. With superficial punctate keratitis and UV keratitis, multiple punctate epithelial erosions are seen upon fluorescein staining. A patient with a pterygium or pinguecula will have a visible, opaque conjunctival overgrowth on the conjunctiva of one or both eyes, typically triangular or pie-shaped, with the apex of the triangle pointing towards the pupil.

Management and Disposition

Superficial Punctate Keratitis and Radiation Keratitis. Determination of etiology of the keratitis is important for definitive treatment. In general, however, care is supportive. The treatment considerations for superficial punctate keratitis and UV keratitis are the same as with corneal abrasion (because both entail an injury to the corneal epithelium and superficial cornea, see Corneal Abrasions) and include limited use of topical anesthetics and topical antibiotics administered for 3 to 5 days only if infection is a concern (see Table 61.1). UV keratitis will typically resolve in about 24 hours or so, and given the nature of the injury, patients should be instructed to avoid damaging UV rays.[31] Ophthalmologic follow-up in 24 hours is recommended if symptoms have not resolved.

Pterygium and Pinguecula. Treatment of pterygium and pinguecula are similar, and it includes UV protection, lubrication, and treatment of acute inflammation with topical NSAIDs (see Table 61.1). The inflammation of a pterygium or pinguecula is usually self-limited, and encroachment into the visual axis from a pterygium is typically very gradual; non-emergent referral to an ophthalmologist is recommended for surgical treatment of severe cases, and for evaluation of the rare coexistence of an ocular surface squamous neoplasia.

The Globe: Uveitis, Scleritis, and Episcleritis

Clinical Features and Differential Diagnosis

The globe itself can on rare occasion be afflicted by a variety of autoimmune conditions, typically involving the uvea as an autoimmune uveitis, or the sclera, as a scleritis. Three noninfectious, inflammatory considerations causing a painful red globe are uveitis, scleritis, and episcleritis.

Uveitis is an autoimmune inflammation of the uvea, the part of the middle layer of eye that includes the highly vascularized and pigmented iris, ciliary body, and choroid.[32] The iris and ciliary body are most commonly involved, a condition called *iritis* or *anterior uveitis,* but uveitis may rarely involve the intermediate and posterior chambers as a rare panuveitis. No cause is identified in 60% to 80% of people, although uveitis is one of the most frequent extra-articular features in seronegative arthritides (including ankylosing spondylitis, psoriatic arthropathy, arthritis from inflammatory bowel disease [ie, Crohn's], and reactive arthritis [ie, Reiter's syndrome]). The typical patient with an acute anterior uveitis will present with a very painful red eye, often with photophobia, and occasionally with decreased visual acuity.[33]

Scleritis is a similar autoimmune inflammatory process, but involving the sclera (the tough connective tissue layer that begins at the limbus and surrounds the eye) instead of the uvea.[34] It is divided into anterior scleritis and the less frequent posterior scleritis (inflammation of the sclera posterior to the insertion of the rectus muscles). Scleritis can also be infectious, treated much in the same way an endophthalmitis would be (see The Globe: Endophthalmitis).

Episcleritis, which can be confused with scleritis, is caused by inflammation in the episcleral layer of the eye rather than the deeper scleral layer. Episcleritis, unlike scleritis, is not vision-threatening and is not associated with as much discomfort.

Diagnostic Evaluation

On slit-lamp examination, uveitis will typically reveal conjunctival injection, ciliary flush in the peri-limbal area, and cells and flare in the anterior chamber. Episcleritis can be distinguished from scleritis in that it is associated with more peri-limbal injection and has a redness that described as salmon pink as opposed to the deeper purple hue seen in scleritis; instillation of 10% phenylephrine drops will constrict and blanch injected superficial episcleral vessels in episcleritis but will not do so to the injected deeper vessels involved in scleritis.[34] Scleritis is often more severe than episcleritis and has a much higher association with systemic diseases, such as Wegener granulomatosis, rheumatoid arthritis, and connective tissue disease (an evaluation that can be deferred to outpatient follow-up).

Management and Disposition

Treatment of both uveitis and scleritis typically involves topical corticosteroid drops (and cycloplegics for symptoms of iridospasm; see Table 61.1), with a transition to systemic corticosteroids and immunosuppressants if these treatments fail. NSAIDs are helpful for scleritis, although systemic steroids may be more useful in severe cases.[35,36] Decisions about treatment are typically made in concert with an ophthalmologist, and patients should be referred to an ophthalmologist for close follow-up in the next day or so; scleritis has a higher association with ocular complications, including keratitis, increased IOP, and vision loss.[35]

The Orbit: Orbital Pseudotumor, Orbital Apex Syndrome, and Thyroid Orbitopathy

Clinical Features, Differential Diagnosis, and Diagnostic Evaluation

The orbit may be affected by typically idiopathic, noninfectious inflammatory processes that lead to diffuse eye pain, redness,

swelling, and potentially disordered vision. Considerations include orbital inflammatory pseudotumor and orbital apex syndrome (which are unilateral), as well as thyroid myopathy (which is usually bilateral).

Orbital inflammatory pseudotumor (also known as *idiopathic orbital inflammation syndrome, orbital pseudotumor,* or *orbital inflammatory syndrome*) presents as an acute to subacute tumor-like inflammation consisting of a pleomorphic cellular response and a fibrovascular tissue reaction, and it is associated with various rheumatologic disorders, including Wegener's granulomatosis, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, and rheumatoid arthritis.[37] In orbital apex syndrome, the apex of the orbit (through which the cavernous sinus drains the eye and orbit, and cranial nerves [CNs] III, IV, and VI travel) may be selectively affected by a cavernous sinus mass or vasculitis. Etiologies include infection, carotid-cavernous fistula, inflammatory vasculitides (such as, giant cell arteritis), Tolosa-Hunt syndrome (a rare idiopathic vasculitis), or tumor or infiltration (eg, sarcoidosis). Both orbital inflammatory pseudotumor and orbital apex syndrome may result in proptosis, chemosis, and/or conjunctival injection; and with orbital apex syndrome, there may be palsies of CNs III, IV, and VI (see Chapter 18).

Inflammatory thyroid orbitopathy from Grave's disease is the most common cause of ocular myopathy in older adults, and it presents with oculomotor muscle swelling and restriction that may be bilateral in 85% of cases. It classically affects the inferior and medial recti muscles first, leading to restriction of elevation and abduction of the eye with orbital muscle dysfunction and misalignment of the visual axes.[38] The examination may reveal stigmata of the underlying disease process, such as lid lag or periorbital swelling or proptosis, as well as diffuse conjunctival edema, and vascular injection near the insertions of the rectus muscles.

The diagnostic evaluation of a suspected orbital inflammatory process primarily involves imaging of the orbit. Options include a magnetic resonance imaging (MRI) scan of the orbits with gadolinium, which can allow an assessment for enlargement or enhancement in extraocular muscles and orbital structures, or—as a likely more readily available second-line option—a contrast-enhanced orbital CT (with fine cuts through the orbit).[39]

Management and Disposition

The mainstay of therapy (assuming infection is excluded) for orbital pseudotumor and orbital apex syndrome is systemic corticosteroid therapy, although there is increasing use of antimetabolites, cytotoxic agents, and other immunosuppressive agents.[37] Treatment choices will typically be made in concert with an ophthalmologist. For thyroid orbitopathy, the treatment of the underlying Graves' disease will address the ophthalmological issues but may involve immunosuppressive medications, radiation, or surgery.

INFECTIOUS CONDITIONS

Principles

A critical clinical distinction that comes into play in a patient with a red, irritated, or painful eye is whether or not there is an infectious process in play. This is based on clinical features, keeping in mind that the globe of eye and the encompassing tissues of the orbit represent a pristinely organized and functional arrangement of tissue planes and glandular structures, and that any disruption to these structures, whether from minor trauma, prior surgery, or inflammation, can predispose to an infectious process.

The Conjunctiva: Allergic, Viral and Bacterial Conjunctivitis, and Ophthalmia Neonatorum

Clinical Features, Differential Diagnosis, and Diagnostic Testing

Symptoms of conjunctivitis—which may be allergic, toxic, or infectious—include redness, discharge, foreign body sensation, photophobia, and blurry vision.

The most common form of conjunctivitis is thought to be allergic conjunctivitis. This is not infectious per se, but it is considered in the differential diagnosis here because it is sometimes a challenge to distinguish from a viral conjunctivitis. Allergic conjunctivitis is a type 1 histaminergic hypersensitivity reaction with red itchy eyes, clear discharge, and is classically bilateral, associated with pollen and dust. In more severe cases, moderate to severe injection with glassy chemosis is observed. A toxic conjunctivitis (from topical ocular medications) may appear similar to allergic conjunctivitis; a contact dermatitis (from a trigger like eye makeup) should be suspected if there is an associated lichenified, eczematous periorbital dermatitis and edema.

Of the infectious etiologies, viral causes are most common. Viral conjunctivitis is classically preceded by a viral infection with upper respiratory symptoms, with sequential involvement of both eyes, but many viral conjunctivitis episodes have no preceding upper respiratory infection (URI) syndrome. It is most commonly by adenovirus, easily spread by contact with fomites. The conjunctival discharge with viral infections tends to be more watery and less purulent than that in bacterial conjunctivitis, with signs such as preauricular lymphadenopathy and follicular changes of the conjunctiva (Fig. 61.15). Viral conjunctivitis, and keratoconjunctivitis, however, can present with impressive purulence, including having the eyelids stuck shut when awakening from sleep. Such findings do not distinguish bacterial from viral causes. Viral infections typically last 1 to 3 weeks. Epidemic keratoconjunctivitis is a highly contagious and more virulent viral conjunctivitis often presenting in epidemics, with which the patient may also complain of foreign body sensation and have a mild keratitis.

Bacterial conjunctivitis is significantly less common than viral. The organisms involved include Staphylococcus organisms, as well as *Moraxella catarrhalis, Streptococcus pneumoniae, Haemophilus influenzae* and rarely *Neisseria gonorrhoeae,* with an increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) conjunctivitis over the last decade.[40] Conjunctivitis from gonorrhea classically presents with copious purulent discharge (Fig. 61.16) and carries a high risk for corneal involvement and

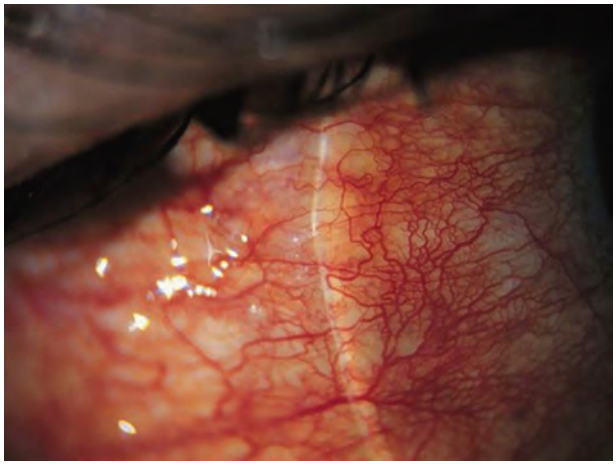

Fig. 61.15. Conjunctival injection resulting from viral conjunctivitis. (Courtesy www.tedmontgomery.com.)

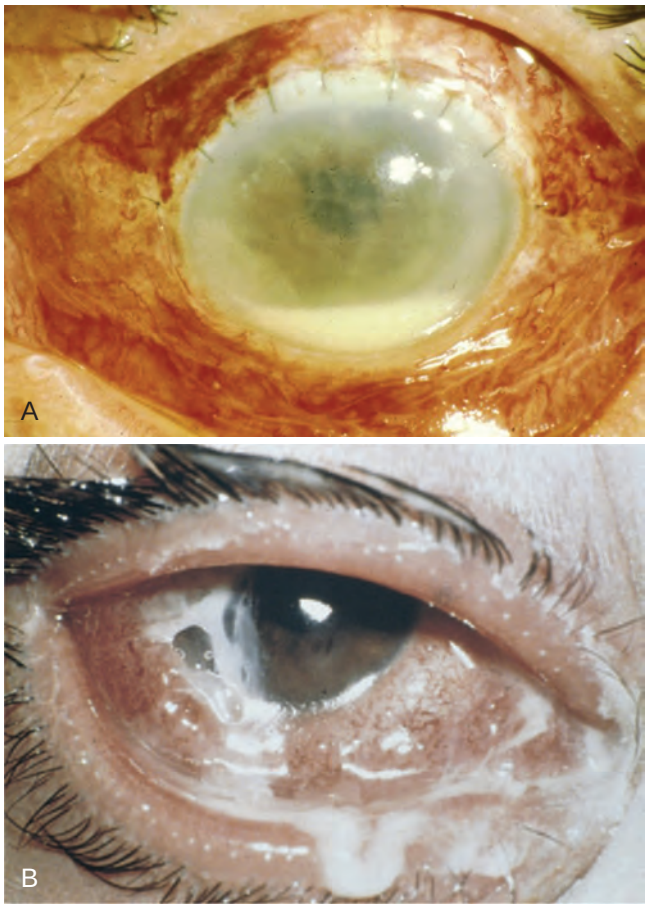

Fig. 61.16. Purulent discharge and conjunctival hyperemia suggest bacterial conjunctivitis. (From Goldman L, Schaefer AI, editors: Goldman's Cecil medicine, ed 24, Philadelphia, 2012, Saunders.)

subsequent corneal perforation.[40] A gram stain and culture (or a polymerase chain reaction [PCR] test as done for genital samples) can aid in the diagnosis.[41]

Distinguishing a viral from a bacterial conjunctivitis can sometimes be a challenge in the ED. A systematic review found that redness of the conjunctival membrane that is intense enough to obscure the tarsal vessels (likelihood ratio [LR], 4.6; 95% confidence interval [CI], 1.2 to 17.1), physician-observed purulent discharge (LR, 3.9; 95% CI, 1.7 to 9.1), and matting of both eyes in the morning (LR, 3.6; 95% CI, 1.9 to 6.5) increase the probability of a bacterial cause, whereas inability to discern that the patient's eye is red from 20 feet away (LR, 0.2; 95% CI, 0 to 0.8) and absence of morning matting of either eye (LR, 0.3; 95% CI, 0.1 to 0.8) decrease the probability of a bacterial cause.[42]

What appears to be an infection of the conjunctiva may actually represent an infection of the cornea, and therefore a slit-lamp examination is important; if signs of corneal involvement are present, a keratitis is in play (see Diagnostic Evaluation in The Conjunctiva and Cornea: Keratitis). Epidemic keratoconjunctivitis may have some mild punctate keratitis on fluorescein staining.

A consideration specific to neonates is ophthalmia neonatorum, which is a neonatal conjunctivitis developing the first 30 days of life. It can be from allergic or chemical causes but most concerning are bacterial and viral causes, presenting with tearing and discharge followed by scarring and blindness. The evaluation involves gram stain and cultures geared to infections such as *N. gonorrhoeae*, *Chlamydia,* and herpes simplex virus (HSV) that are transmitted from mother to infant through the birth canal. HSV may have associated corneal microdendrites and lid edema. Infection with *N. gonorrhoeae* manifests within 2 to 4 days after birth (but may take up to 20 days). The infant should be carefully examined for any evidence of a systemic gonococcal infection.

Management and Disposition

Allergic and Viral Conjunctivitis. Allergic conjunctivitis and viral conjunctivitis are usually self-limited, and can be treated with supportive measures, such as cool compresses (nature's anti-inflammatory). Topical antibiotics should be avoided unless there is concern for a bacterial superinfection. For allergic conjunctivitis, the patient should be counseled to avoid the offending agent and can be prescribed topical and systemic anti-allergy medications (see Table 61.1 for choices and dosing of topical options). Medications with preservatives in them should be avoided, because they may exacerbate symptoms. Presumed viral conjunctivitis rarely requires a culture. If symptoms and findings of either allergic or viral conjunctivitis worsen after 2 to 3 days, other etiologies should be considered. If inflammation is severe (with pseudomembranes, bleeding), then an ophthalmology evaluation in the ED for steroid treatment is recommended, otherwise patients can be discharged with a referral to an ophthalmologist if they worsen or if they do not improve by 7 to 10 days. Children with viral conjunctivitis should usually be kept out of school until symptoms have resolved, which will be 3 to 5 days, keeping in mind that communicability is estimated to last up to 10 to 14 days.

Bacterial Conjunctivitis. Although bacterial conjunctivitis is typically self-limited, most resolving in 1 to 2 weeks without treatment, topical antibiotics shorten the time to resolution.[43] Ointment is preferred given the smoothing effect on the eye and ease of instillation (patients know if ointment was applied or not and have to do it less frequently). The prescribed antibiotics (see Table 61.1 for options) should cover the organisms mentioned previously and be taken for at least 1 week; those with the highest level of evidence for the treatment of bacterial conjunctivitis are tobramycin, ciprofloxacin, moxifloxacin, ofloxacin, azithromycin, and trimethoprim/polymixin B.[40] Gentamicin and neomycin should be avoided due to toxicity. Contact lens wearers should have coverage for *Pseudomonas* (see Table 61.1). Treatment of a bacterial conjunctivitis suspected to involve *N. gonorrhoeae* consists of ceftriaxone 1 g intramuscularly once, and saline irrigation of the affected eye(s), with concomitant empirical treatment for *Chlamydia trachomatis* infection (either 1 mg of azithromycin orally once, or doxycycline 100 mg orally bid for 7 days).

Ophthalmia Neonatorum. Hospitalization of neonates with blood and cerebrospinal fluid examination may be indicated for ophthalmia neonatorum. *N. gonorrhoeae* conjunctivitis in a neonate is typically treated with single dose of ceftriaxone 25 to 50 mg/kg up to a total dose of 125 mg intramuscularly, topical erythromycin or polymyxin B–bacitracin ointment, and saline washes of the affected eye. Potential ocular chlamydial infection is often simultaneously treated with topical erythromycin ointment and oral erythromycin syrup 50 mg/kg/day divided into four doses per day for 14 days. HSV should be treated with acyclovir IV 45 mg/kg/day plus vidarabine 3% ointment five times per day for 14 to 21 days. Evaluation for systemic involvement is indicated and ophthalmology consultation in the ED is warranted.

The Cornea: Corneal Ulcers, Herpes Simplex Keratitis, and Herpes Zoster Keratitis

Clinical Features and Differential Diagnosis

What appears to be conjunctivitis may actually represent an infection of the cornea. A *corneal ulcer* (Fig. 61.17) is an infectious and/

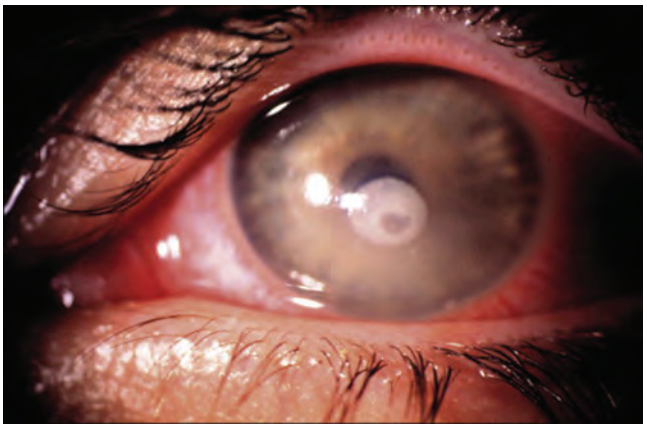

Fig. 61.17. This corneal ulcer caused by *Pseudomonas aeruginosa* occurred in a young man who wore decorative contact lenses without professional supervision. (From Yanoff M, Duker JS, editors: Ophthalmology, ed 3, Philadelphia, 2008, Mosby.)

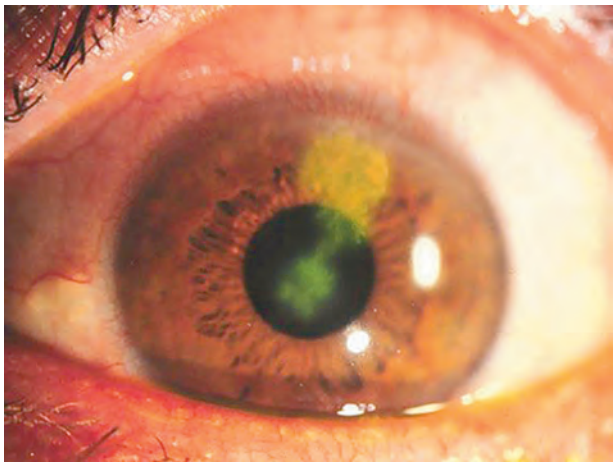

Fig. 61.18. Herpes simplex keratitis infection. Note typical dendritic pattern on cornea. (Courtesy www.tedmontgomery.com.)

or inflammatory erosion, "ulcerative keratitis," of both the outer epithelial cell layer and the underlying stromal layer (which is the bulk of the cornea). Corneal ulcers present with pain and redness of the eye, tearing, sensitivity to light, and blurred, hazy, or otherwise decreased vision. There can also be discharge or a foreign body sensation. A corneal abrasion can become an ulcer if secondarily infected, which in turn lead to corneal perforation if severe and untreated. Although corneal ulcers are due to infection, most of the resulting corneal injury is due to the secondary inflammation. The most common bacterial pathogens are *Staphylococcus, Streptococcus, Mycobacterium,* and *Pseudomonas*, which is associated with contact lens wear. Fungal pathogens are typically seen in users of corticosteroid drops, and in agricultural workers and others who may have contamination of the eye with vegetable matter or soil.

The cornea can also be infected by viruses. Herpes simplex keratitis, one of the most common causes of viral keratitis, can produce recurrent corneal ulcers similar to recurrent herpes labialis or herpes genitalis. Herpes simplex may be either primary or reactivation of preexisting disease. Symptoms are similar to corneal ulcers. Herpes zoster keratitis can occur in the setting of herpes zoster ophthalmicus. Herpes zoster is re-activated along the ophthalmic division of the trigeminal nerve, and eye involvement is possible. Patients will typically present with a dermatomal rash over the forehead and upper eyelid and sometimes along the nose (branch of the nasociliary nerve—called *Hutchinson's sign*), or even have a local Horner's syndrome.

Diagnostic Testing

The foundation of the diagnostic evaluation of corneal lesions is a careful examination and biomicroscopy with the slit lamp and fluorescein staining to evaluate corneal epithelial surface disruptions. On slit-lamp examination, a corneal ulcer may appear to have more "heaped up" edges (seen with tangential lighting) than those seen with a corneal abrasion; this finding, combined with stromal edema or infiltration (whitening of the underlying or surrounding cornea), helps red-flag the process as an ulcer instead of an uncomplicated abrasion.

A corneal ulcer from herpes simplex keratitis may present with classic "dendritic" lesions on slit-lamp examination (Fig. 61.18), or with an amoeba-shaped ulceration, or have nonspecific findings such as punctate epithelial erosions, stromal whitening, and thinning of the cornea, possibly with classic herpetic vesicles located on the lids or conjunctiva. Herpes zoster keratitis may appear somewhat similar but will have signs of a dermatomal vesicular rash, and it is frequently associated with iritis, uveitis, and choroiditis.[44] Viral cultures of tissue can help direct therapy.

Management and Disposition

Corneal Ulcers and Infiltrates. Topical anti-microbial therapy for corneal ulcers and infiltrates is appropriate, although in some severe cases, systemic antibiotics may be warranted. The fluoroquinolones (see Table 61.1) have particularly good ocular penetration; doxycycline and other tetracyclines have good anti-collagenase properties that help preserve corneal integrity. Steroids may be used to decrease inflammation but must be used with caution, because they may exacerbate the clinical situation (and if a herpetic process is suspected, steroids may have to be avoided, or antivirals concurrently used). Ophthalmology consultation in the ED is important for management of corneal ulcers, because they can rapidly progress.

Herpes Simplex Keratitis. Herpes simplex keratitis is the most common cause for corneal transplants in the United States. Emergent ophthalmologic consultation is advised, because the severity of disease will dictate treatment. Herpes simplex keratitis is treated with topical antiviral agents, such as topical acyclovir trifluridine 1% nine times a day for 14 days. Topical prophylactic antibiotics, such erythromycin ointment, and a cycloplegic agent if there are symptoms of iritis can be considered (see Table 61.1). Topical steroids should be avoided because they worsen infection.[40] Systemic therapy should be considered (acyclovir 400 mg five times daily or valacyclovir 500 mg three times daily for 7 to 10 days) if topical treatment is not available or if the process is severe; admission will typically not be needed, but close follow-up with an ophthalmologist within 1 to 3 days is important.

Herpes Zoster Keratitis. Herpes zoster ophthalmicus accounts for approximately 10% to 20% of all zoster cases and necessitates emergent ophthalmologic consultation. If not treated and recognized immediately, herpes zoster ophthalmicus may result in permanent vision loss. Systemic therapy is the standard of care (unlike HSV, topical antivirals have little effect). If retinal involvement occurs or the patient is immunocompromised, inpatient treatment is recommended. Higher dose antiviral agents (acyclovir 800 mg five times daily, valacyclovir 1000 mg three times daily, or famciclovir 500 mg three times daily, all for 7 to 10 days[40]) are used, and occasionally topical steroid agents and systemic antibiotics may be added. Topical antibiotics are used to prevent bacterial superinfection of skin and lid lesions.

Early treatment with antiviral therapy within 72 hours of the onset of the rash has been shown to reduce acute pain and ocular complications. Additional consideration for therapy includes pain management and aggressive lubrication to maintain a healthy ocular surface.

The Eyelids and Periorbital Area: Hordeolum, Chalazion, Dacryocystitis, Blepharitis, and Cellulitis

Clinical Features and Differential Diagnosis

The tissues of the eyelids and periorbital area are susceptible to any of a number of types of infections, which include those related to glandular or ductal structures, such as a hordeolum, chalazion, or dacryocystitis, or more diffuse involvement of tissue, such as blepharitis or periorbital cellulitis. Hordeola and chalazia, also known as *styes of the eyelid,* are inflamed oil glands of the eye. A *hordeolum* is caused by acute inflammation of a gland of Zeis or hair follicle. It is typically painfully tender, erythematous, associated with swelling, and can be infected. On the other hand, a *chalazion* is a chronic sterile, granulomatous inflammation of a meibomian gland (and may evolve from a hordeolum), which results in localized swelling that is usually not acutely painful (Fig. 61.19).

Dacryocystitis is an infection of the lacrimal sac, usually resulting from a nasolacrimal duct obstruction. It is more common in females. Symptoms and signs include pain, tenderness, swelling, and erythema over the lacrimal sac medial to the eye (Fig. 61.20). Pressure over the sac may express purulent material from the puncta. The lacrimal gland itself can also become infected, appearing as a focal area of periorbital erythema, swelling and tenderness lateral to and above the upper eyelid.

Patients with blepharitis typically describe itching and burning of the eyelids with associated tearing and crusting of the eyelids. The eyelids become diffusely inflamed and thickened, with erythematous margins, and telangiectasias surrounding the eyelid margin. Blepharitis can be distinguished from a pre-septal cellulitis in that it is isolated to just the eyelid margin. Blepharitis has an association with atopic dermatitis, rosacea, and eczema.

Any one of the aforementioned focal infections, but especially dacryocystitis and blepharitis, may be complicated by a more diffuse, associated cellulitis. Cellulitis frequently presents, however, as an individual entity, and it has to be carefully distinguished as either pre-septal (also called *periorbital*) or post-septal (also called *orbital*). *Pre-septal* and *post-septal* are the most useful terms because (1) they incorporate the most impactful clinical distinction in the ED and (2) remove any chance of confusion as to what is being referred to in communications with consultants. Pre-septal cellulitis is limited to the tissue anterior to the orbital septum, whereas a post-septal cellulitis implies spread of the infection beyond the septum, which is concerning because it can lead to involvement of valuable orbital structures. Pre-septal cellulitis will present with lid erythema, warmth, tenderness, swelling, and even a low-grade fever. Post-septal cellulitis will present with the same but may also have more alarming symptoms including proptosis, ophthalmoplegia, pain with eye movement, chemosis, and systemic signs of infection. In very severe cases, visual loss can occur. In children, pre-septal cellulitis is often more difficult to differentiate from a post-septal cellulitis because of an incomplete orbital septum.

Diagnostic Testing

For hordeolum, chalazion, dacryocystitis, blepharitis, and a cellulitis that is clearly pre-septal, the diagnosis is established on the clinical examination alone, and no additional diagnostics are needed. CT imaging is, however, indicated in cases concerning for an orbital abscess or in which localization of an infection (pre-septal or post-septal) is difficult. In such cases, a complete blood count (CBC) may also be helpful. The primary diagnostic decision for the ED patient with a cellulitis around the eye is deciding who needs further evaluation with a CT scan. Symptoms and signs of proptosis, ophthalmoplegia, pain with eye movement, and chemosis easily suggest the possibility that a cellulitis is post-septal,

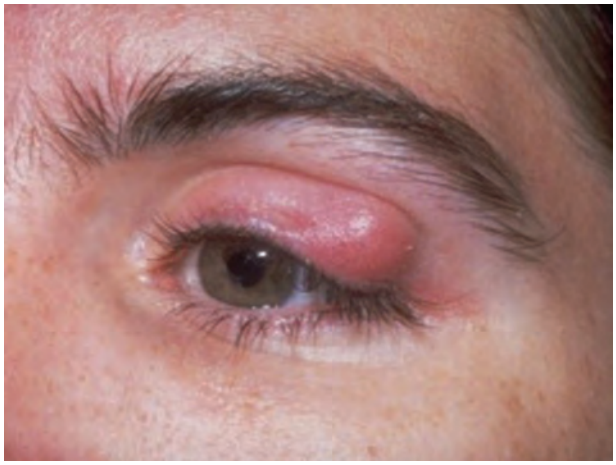

Fig. 61.19. Chalazion of the upper eyelid. (Courtesy www.tedmontgomery.com.)

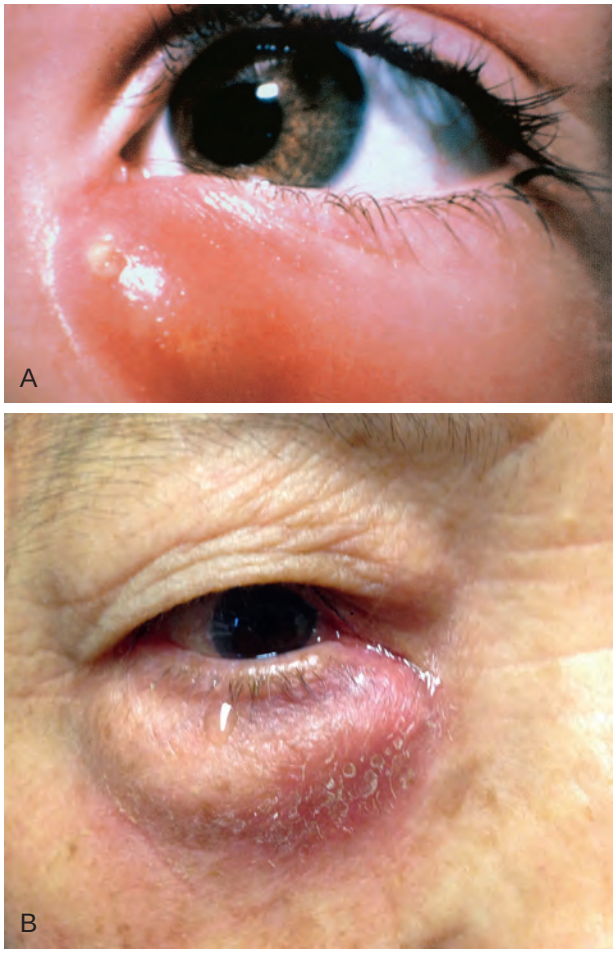

Fig. 61.20. **A** and **B,** Dacryocystitis. (Courtesy Jeffrey Lee, MD, University of California San Diego.)

but upward of 50% of confirmed cases may not have these symptoms.[45,47] In these "no orbital symptom" cases, a peripheral absolute neutrophil count (ANC) of >10 000 cells/μL, moderate-to-severe periorbital edema (extending beyond the eyelid margins), absence of conjunctivitis as the presenting symptom, older than 3 years old, and recent antibiotic use have been shown to be predictors of an orbital abscess—specifically in the pediatric population.[45] In addition, a sudden onset is more typical of a post-septal orbital cellulitis.[47] The absence or presence of a fever has little discriminatory utility. Cultures obtained from swabs of the eyes are discouraged due to the risk of misleading results from inoculation with commensal organisms, and blood cultures have little diagnostic utility.[46]

Management and Disposition

Hordeolum and Chalazion. Often, hordeola and chalazia are self-limited and can resolve on their own when the glands become unobstructed. Conservative treatment to normalize flow of the obstructed oil glands is the primary goal. This includes warm compresses for 10 to 15 minutes, 3 to 5 times a day. Treatment of an underlying blepharitis may be indicated. Referral to an ophthalmologist is recommended for incision and drainage or additional management and evaluation in nonresponsive cases. Progression to an infected oil gland may indicate need for antibiotics, depending whether the process takes the form of a blepharitis or a cellulitis (see treatment of each in the following sections).

Dacryocystitis. The most common causative organisms in dacryocystitis are *S. aureus, S. pneumoniae*, *H. influenzae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*, with an emerging prevalence of MRSA.[47] Treatment consists of massage, warm compresses, and systemic antibiotics selected so as to include coverage of MRSA. An attempt should be made to obtain a culture by applying gentle pressure to the nasal lacrimal duct and expressing fluid. In infants, acute dacryocystitis represents a medical emergency, because it can lead to complications including post-septal orbital cellulitis. Admission is warranted for severe cases. Occasionally, drainage of the sac is required; however, this can lead to fistula formation. Dacryocystorhinostomy is the definitive treatment, but the optimal time for surgery is when the infection is controlled. Discharged patients should follow-up with an ophthalmologist in 24 to 48 hours.

Blepharitis. The initial treatment of blepharitis is conservative, designed to remove residual oils and scurf, and entails warm massage with a moist washcloth about for 10 to 15 minutes, three to five times a day, and cleaning the lid margins twice a day with a cotton swab soaked in mild baby shampoo. Because blepharitis arises as a result of an inflammatory process, there is potential for bacterial overgrowth and superinfection (*Staphylococcus epidermidis* primarily, but also *Propionibacterium acnes,* and corynebacteria), and—if there is a concern for infection—topical azithromycin, erythromycin, or levofloxacin (see Table 61.1) can be considered.[47,47a] Uncomplicated cases can be discharged to follow-up with an ophthalmologist within a week or so, or within 1 to 3 days if there is concern for infection.

Periorbital Cellulitis. If pre-septal cellulitis with no other underlying medical conditions is diagnosed with certainty, the patient can be discharged on an oral antibiotics directed toward the most common organisms, *Streptococcus* and *Staphylococcus,* keeping in mind that orbital cellulitis tends to be polymicrobial.[47] Although many practitioners empirically cover for MRSA, this organism is actually very rare when it comes to orbital cellulitis (at least in published series involving primarily children).[48] An option is a beta-lactam antibiotic, such as oral amoxicillin-clavulanate, 875 mg two times daily for 10 to 14 days for adults (or 20 to 40 mg/kg divided into three doses for 10 to 14 days for children). Close follow-up, with a re-examination within a day at a primary care provider's office or with an ophthalmologist is important to assure response to treatment.

In more severe cases of pre-septal cellulitis, or with any concern of post-septal cellulitis, hospitalization with IV antibiotics is indicated to avoid complications, such as subperiosteal abscess, orbital abscess, meningitis, osteomyelitis, and cavernous sinus thrombosis. In children, the difficulty in localizing the spread of the infection dictates more aggressive management of any periorbital infection. An IV second- or third-generation cephalosporin, such as cefuroxime or ceftriaxone, is recommended. Other IV antibiotic options include ampicillin/sulbactam (Unasyn), or a combination of a first-generation cephalosporin with metronidazole.[47]

The Globe: Endophthalmitis

Clinical Features, Differential Diagnosis, and Diagnostic Testing

Endophthalmitis is an infection involving the globe itself. Pain and decreased vision are the primary symptoms. Examination findings include decreased visual acuity, chemosis, and hyperemia of the conjunctiva, intraocular inflammation (evidenced by hypopyon) (Fig. 61.21). The most common etiology of endophthalmitis is recent intraocular surgery. Other etiologies include previous perforated globe and endogenous infection. Early diagnosis and management is imperative for improved prognosis. The diagnosis is primarily clinical, and will typically have to be done in consultation with an ophthalmologist, because endophthalmitis can be difficult to distinguish from a uveitis, and the two have vastly different treatments and acuity.[49] An ultrasound of the eye (done in much the same way as to evaluate for retinal detachment) can be used to augment the evaluation; and with endophthalmitis, it may reveal numerous stands and membranes in a vitreous that would otherwise be uniformly hypoechoic.[49]

Management and Disposition

Endophthalmitis is a medical emergency that must be promptly treated. Systemic antibiotics are not effective, and therefore—although IV antibiotics can be considered (their effect is unknown)—intravitreal antibiotics must always be given.[50] The evaluation and treatment should be done in consultation with an ophthalmologist who can administer the intravitreal antibiotics at the bedside and perform a vitrectomy (removal of infected vitreous akin to draining an abscess) in the operating room if

Fig. 61.21. Eye with endophthalmitis, illustrating a hypopyon (pus in the anterior chamber). (Courtesy Kama Guluma, MD, University of California San Diego.)

needed. The typical bacterial pathogen varies with the likely cause; coagulase-negative staphylococci are most common in post-cataract endophthalmitis, *Bacillus cereus* is a major cause of post-traumatic endophthalmitis, and *S. aureus* and streptococci are important causes of endogenous endophthalmitis associated with endocarditis.[50]

ACUTE ANGLE-CLOSURE GLAUCOMA

Principles

Aqueous humor provides structural support to the eye and delivers oxygen and nutrients to the avascular lens and cornea. It is produced by the ciliary processes, passes from the posterior chamber to the anterior chamber through the pupillary aperture, and then is transported into the trabecular meshwork located at the anterior chamber angle formed by the junction of the root of the iris and the peripheral cornea. This trabecular meshwork serves as a one-way valve and filter for the aqueous humor into the canal of Schlemm, which in turn drains into episcleral veins. IOP is determined by the rate of aqueous humor production relative to its outflow and removal, and it is normally between 10 to 20 mm Hg.

Clinical Features, Differential Diagnosis, and Diagnostic Testing

Glaucoma is an acquired chronic optic neuropathy. It is characterized by an enlarged ratio of the diameter of the optic cup to the diameter of the optic disc (termed *cupping*) and visual field loss. Glaucoma usually but not always is associated with elevated IOP. The two most common and important forms of glaucoma are primary open-angle glaucoma and acute angle-closure glaucoma.

Primary open-angle glaucoma is a chronic condition characterized by asymptomatic elevated IOP (but IOP may not always be elevated), and an enlarged ratio of the diameter of the optic cup to the diameter of the optic disc (termed *cupping*) and peripheral visual field loss. Patients may be on chronic topical ophthalmic medications designed to improve aqueous outflow. It is not typically a cause for an urgent visit to the ED (and therefore not discussed further), although it can lead to complete blindness over time.

Acute angle-closure glaucoma is the entity that typically precipitates an acute ED visit, at times in a patient with no prior knowledge or history of chronic glaucoma. A variety of rare conditions (such as, tumors, neovascular processes) can predispose a patient to this, but the more common predisposed patient has an anatomically shallow anterior chamber that further narrows with aging as the lens enlarges. Acute symptoms are often precipitated by pupillary dilation from being in a low-light environment (eg, movie theater) or taking an anticholinergic or sympathomimetic medication. This transient contraction of the iris crowds the angle ("pupillary block"), and continued formation of aqueous leads to an increased IOP, causing the iris to bulge forward, further inhibiting outflow, and eventually compromising arterial flow into the eye. The patient with acute angle-closure glaucoma typically presents with severe unilateral eye pain, redness, and blurred vision with "halos," as well as nausea and vomiting. On examination, the pupil may be moderately dilated and unreactive to light, the anterior chamber shallow when illuminated from the side with a penlight, the conjunctiva injected, and the cornea cloudy (steamy) (Fig. 61.22). The IOP is significantly elevated, and ischemia to intraocular structures, particularly the optic nerve, retinal nerve fiber layer, and the avascular anterior portion of the lens (which is sustained by aqueous humor) may occur. Sustained elevation in IOP can cause permanent corneal and optic nerve damage, and cause the peripheral iris to adhere to the trabecular meshwork, forming anterior synechiae and an irreversible occlusion that only can be corrected by surgery.

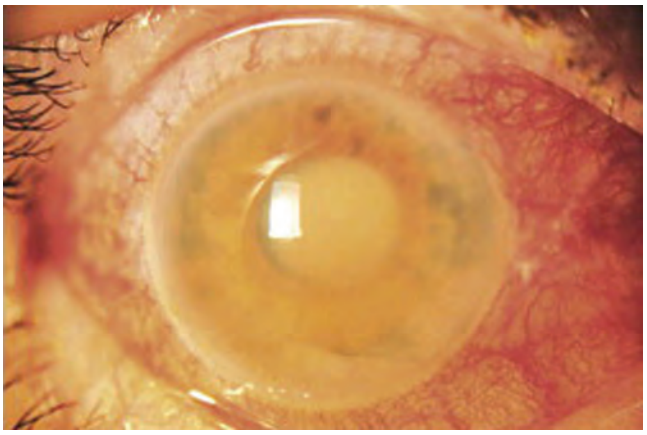

Fig. 61.22. Acute angle-closure glaucoma. (From Yanoff M, Duker JS, editors: Ophthalmology, ed 3, Philadelphia, 2008, Mosby.)

Management and Disposition

Treatment of acute angle-closure glaucoma begins with medications used to lower the IOP and then proceeds to definitive treatment of the anatomical abnormality that led to the elevated pressure in the first place.[51] Emergent ophthalmology consultation is necessary, and the treatment paradigm in the ED is as follows:

- Drugs that may be used to reduce production of aqueous humor:
  - Topical beta-blocker (timolol 0.5%—1 to 2 gtt)
  - Carbonic anhydrase inhibitor (acetazolamide 500 mg IV or orally)
  - Systemic osmotic agent (mannitol 1 to 2 g/kg IV over 45 minutes, to minimize cerebral effects, and typically reserved if topical medications and acetazolamide do not work within 1 hour)
- Drugs that may be used to increase outflow:
  - Topical alpha-agonist (phenylephrine 1 gtt)
  - Miotics (pilocarpine 1% to 2%)
  - Topical steroid (prednisolone acetate 1%—1 gtt every 15 to 30 minutes four times, then every hour)
- Definitive treatment—laser peripheral iridotomy within 24 to 48 hours

PRIMARY DISORDERS OF VISION

Principles

The process of visual perception is an orchestration of light refraction by the cornea and lens, signal transduction by the retina to generate electrical impulses, and transmission of those impulses through the optic nerve to be processed in each occipital cortex, being split and crossed at the chiasm along the way (Fig. 61.23). Primary disorders of vision can be caused by a derangement in any component in this process and may present as blurred vision, a focal disturbance somewhere in the visual field (in the form of dark objects or floaters, flashing lights (photopsia), or a visual field cut), or frank vision loss. Double vision has a very distinct presentation and is comprehensively addressed in Chapter 18.

The history enables a tailored approach to the evaluation of a patient with an atraumatic visual disturbance but may be fraught with challenges. One is the potential for a patient to use the term *blurred vision* to actually describe double vision, and vice versa. Another is that the patient with a cortical visual field cut may not

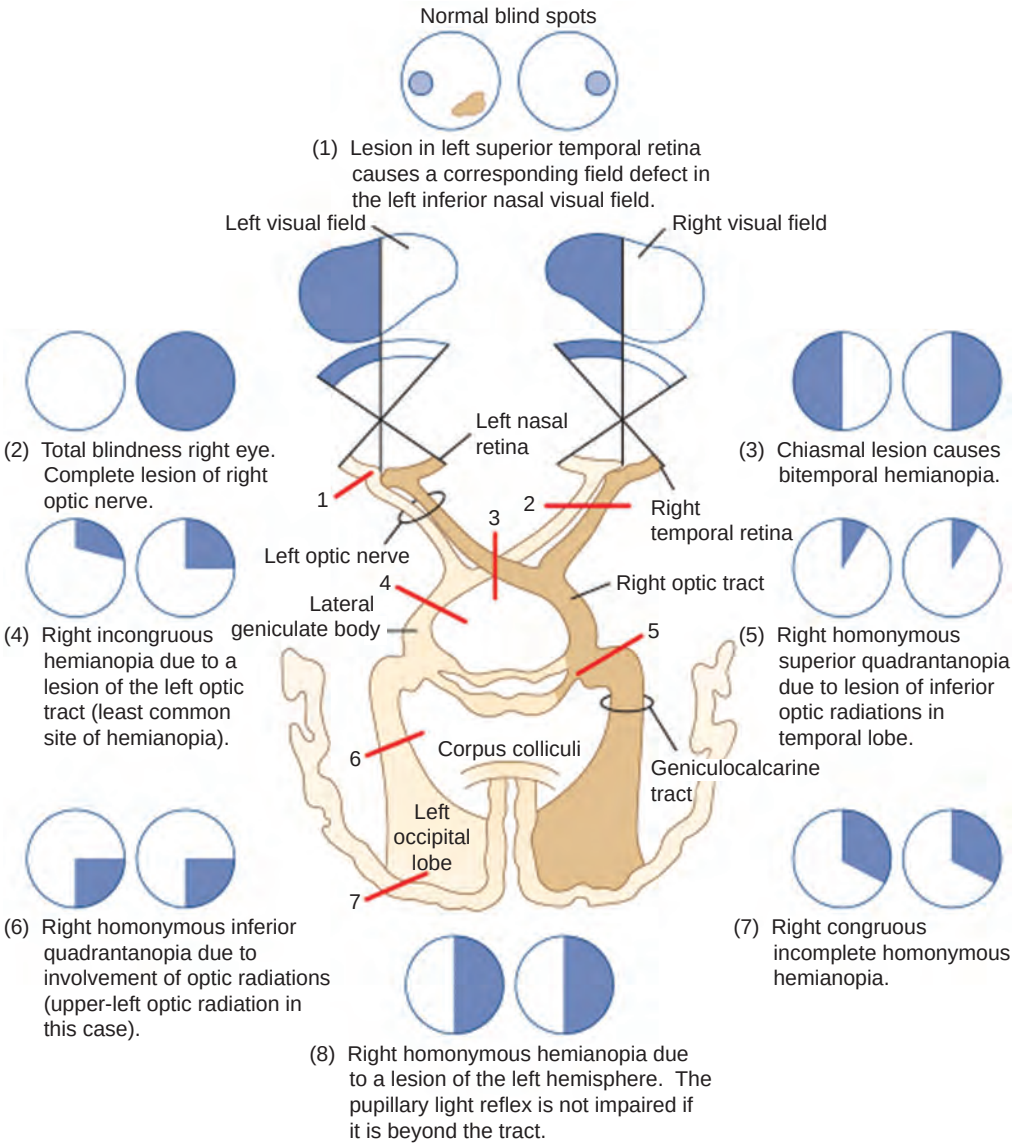

Fig. 61.23. Topographic diagnosis of visual field defects. (From Bradley WG, Duroff RB, Fenichel GM, et al: Neurology in clinical practice, ed 5, Oxford, 2007, Butterworth-Heinemann.)

even be aware there is a visual field deficit, being "blind to the blind spot." In addition, a patient may not notice a chronic problem in one eye until a problem finally develops in the remaining functioning eye. Finally, a patient may report what was actually a binocular defect of both visual fields on one side as a monocular issue involving a single eye on that side (a discrimination of which will be lost if the visual disturbance was transient and the patient did not check if the problem persisted with one eye or the other closed).

The elements of a screening ED ophthalmological examination are described in detail in Chapter 19 and should carefully incorporate a visual field and a neurological examination, in addition to the elements of visual acuity, pupillary examination, extraocular muscle movement, and examinations of the anterior and posterior segment (with a slit-lamp examination and a funduscopic examination). It should be kept in mind that a patient with a visual field defect or a retinal detachment may have a normal visual acuity, due to sparing of the macula.

An etiology of the visual loss occurring beyond the retina can be considered *neuro-ophthalmologic* and can be further divided into prechiasmal, chiasmal, and post-chiasmal (see Fig. 61.23). Patients with prechiasmal visual loss have monocular decreased visual acuity or visual field loss, typically from dysfunction of the optic nerve on that side, with an APD on the side involved on swinging flashlight test (see Fig. 61.11), and a visual field defect that does not respect the vertical midline and is often localized to the center of the visual field. Patients with chiasmal and post-chiasmal visual loss will typically have preserved visual acuity, and a visual field loss in both eyes that respects the midline (see Fig. 61.23).

Blurred Vision: Optic Neuritis, Toxic and Metabolic Disturbances, and Papilledema

Clinical Features and Differential Diagnosis

Any disturbance in the refraction of light may cause the symptom of blurred vision. Considerations include corneal infiltrates (from infections), significant pupillary dilation (which results in an increase in the scattered of light rays reaching the lens), and changes in the refractive properties of the lens or vitreous (due to edema from rapid osmotic changes). Blurred vision may also result from transductive dysfunction from retinal or optic nerve inflammation or edema. Considerations in the differential diagnosis of blurred vision include optic neuritis (which is usually

monocular) and toxic and metabolic visual disturbances (usually binocular), and papilledema from raised intracranial pressure (also usually binocular).

Optic neuritis is a primary, autoimmune inflammatory process of the optic nerve, affecting mostly young patients (range, 15 to 45 years old), has an association with multiple sclerosis, and is the presenting symptom of multiple sclerosis in 25% of cases.[52] The patient with optic neuritis typically presents with monocular blurring or fogginess of vision evolving over hours or days, mild pain with movement of the involved eye if the lesion is within the orbit, and at times bright, fleeting flashes of light with eye movement, as well as worsening of vision with small increases in body temperature (from exercise, hot baths, or hot weather).[52] The natural history of optic neuritis is for visual acuity to reach its poorest within 1 week and then slowly improve over the next several weeks. Approximately 30% of patients with acute optic neuritis develop multiple sclerosis within 5 years. Approximately 30% of patients with optic neuritis have a recurrence within 10 years of initial presentation.

With regards to toxic visual disturbances, perhaps the most characterized toxidrome presenting with acute visual change is methanol toxicity.[53] Orally ingested methanol (the toxicity of which is described in entries dedicated to it elsewhere in this text) is metabolized to formic acid, which accumulates in the optic nerve and leads to edema and compromised axoplasmic flow; in addition, it leads to widespread electrophysiological dysfunction that also affects photoreceptors in the retina, leading to visual loss. Other potential causes of a toxic visual disturbance are barbiturates, chloramphenicol, emetine, ethambutol, ethylene glycol, isoniazid, and heavy metals.

In terms of metabolic visual disturbances, any rapid osmolar shift in the cornea, lens, or even retina has the potential to cause visual changes. A representative scenario is acute hyperglycemia. A rapid elevation in blood glucose (or a rapid correction of severe hyperglycemia), as seen in poorly controlled diabetics, may cause an acute hyperopia (far-sightedness), presumably due to changes in refraction in the lens.[54] It may alternatively cause acute myopia when the rise in intracellular glucose levels in the lens overwhelms the normal glucose metabolic pathway such that it is converted to less absorbable sorbitol and fructose, generating an acute hyperosmolar state and stromal swelling. This may be followed by acute bilateral cataract formation within a matter of hours to days. Metabolic visual disturbances can also be from a nutrition-related optic neuropathy from causes such as thiamine deficiency and pernicious anemia.

Papilledema may be seen on examination and refers to the changes in the optic disc from increased intracranial pressure. The subarachnoid space of the brain is continuous with the optic nerve sheath. Any increase in the cerebrospinal fluid pressure (such as, from pseudotumor cerebri syndrome [otherwise known as *idiopathic intracranial hypertension*], cryptococcal meningitis in HIV/AIDS patients, or hydrocephalus or intracranial mass) can be transmitted to the optic nerve, resulting in swelling of the optic nerve head. Although visual symptoms may be isolated on rare occasion, patients with these entities will typically present with headache, which will provoke their consideration. That being said, a small percentage of patients with pseudotumor cerebri present with isolated subjective visual loss, blurred vision, or enlargement of the physiologic blind spot as the initial presenting symptom of the disease, and rapid deterioration may occur over days in severe cases.[55] Swelling of the optic disc and blurring of the disc margins, hyperemia, and loss of physiologic cupping are present (Fig. 61.24A). There may be obliteration of spontaneous venous pulsations. Flame-shaped hemorrhages and yellow exudates may appear near the disc margins as the edema progresses (see Fig. 61.24B). Visual acuity may be affected as the swelling becomes severe. Papilledema is typically bilateral but may be asymmetrical. There are conditions with optic nerve swelling (such as, ischemic optic neuropathy [ION], optic disk vasculitis, and diabetic papillitis) that may mimic papilledema.

Diagnostic Testing, Management, and Disposition

In the diagnostic evaluation of blurred vision, a standard ophthalmological assessment including visual acuity and a slit-lamp examination is important, but funduscopy (so as to screen for retinal or optic nerve edema or pathology) and an assessment of visual fields (to screen for associated sectoral abnormalities in retinal or optic nerve transduction) are critical.

Optic Neuritis. With optic neuritis, visual acuity will usually be abnormal (with the primary complaint of blurred vision), and the patient may have variable visual field defects (central, altitudinal, arcuate, hemianopic), with central defects being more common than peripheral ones.[52] An APD is usually present, and direct ophthalmoscopic examination reveals a normal or swollen disk (Fig. 61.25). An orbital MRI of the optic nerves with gadolinium is the mainstay of diagnosis, revealing optic nerve lesions in 95% of cases. A lumbar puncture can be done, which may show CSF pleocytosis and a raised protein concentration.[52] For treatment, steroids for optic neuritis has a long track record of investigation but with no demonstrated long-term effect on visual outcome.[55a] Some still recommend high-dose methylprednisolone (either 500 mg per day orally for 5 days or 1 g per day IV for 3 days), due to mild short-term benefits; plasmapheresis and IV immunoglobulins are also options.[52]

Toxic and Metabolic Visual Disturbances. A key component in the diagnostic approach to blurred vision from toxic and metabolic disturbances is recognizing the existence of a cause. These processes are bilateral, progressive, and symmetrical and may manifest with a drop in visual acuity, evident haziness in the lenses, or retinal edema on funduscopy. Visual loss can be severe and visual field testing reveals central defects. In each case, the treatment is aimed at the underlying toxin, metabolite, or deficiency involved (described in entries dedicated to them elsewhere in this text). Blurred vision due to hyperglycemia typically reverses when hyperglycemia is treated, although cataracts may sometimes be permanent.

Papilledema. The diagnostic evaluation and management of specific disease processes that result in bilateral papilledema can be found in entries specifically dedicated to them elsewhere in this text. An important part of the assessment is a funduscopic eye examination, with an assessment of the optic disc. Early or mild papilledema may be difficult to detect with the direct ophthalmoscope, and if the suspicion of such a process is high, consultation with ophthalmologist in the ED for stereoscopic viewing of the optic discs with indirect ophthalmoscopy is recommended, and patients should undergo neuroimaging (either with MRI or contrast-enhanced CT).[55]

Visual Field Disturbances: Floaters, Flashes, and Field Deficits

Clinical Features and Differential Diagnosis

Visual field disturbances may take the form of floaters (seeing objects in the field of vision, caused by material obstructing the light path), photopsia (flashing lights, caused by aberrant stimulation of the retina), or field deficits (focal areas of visual loss, caused by dysfunction in the transport or processing of impulses sent by the retina). Photopsia may be unilateral or bilateral, depending on the cause. The most common causes of unilateral

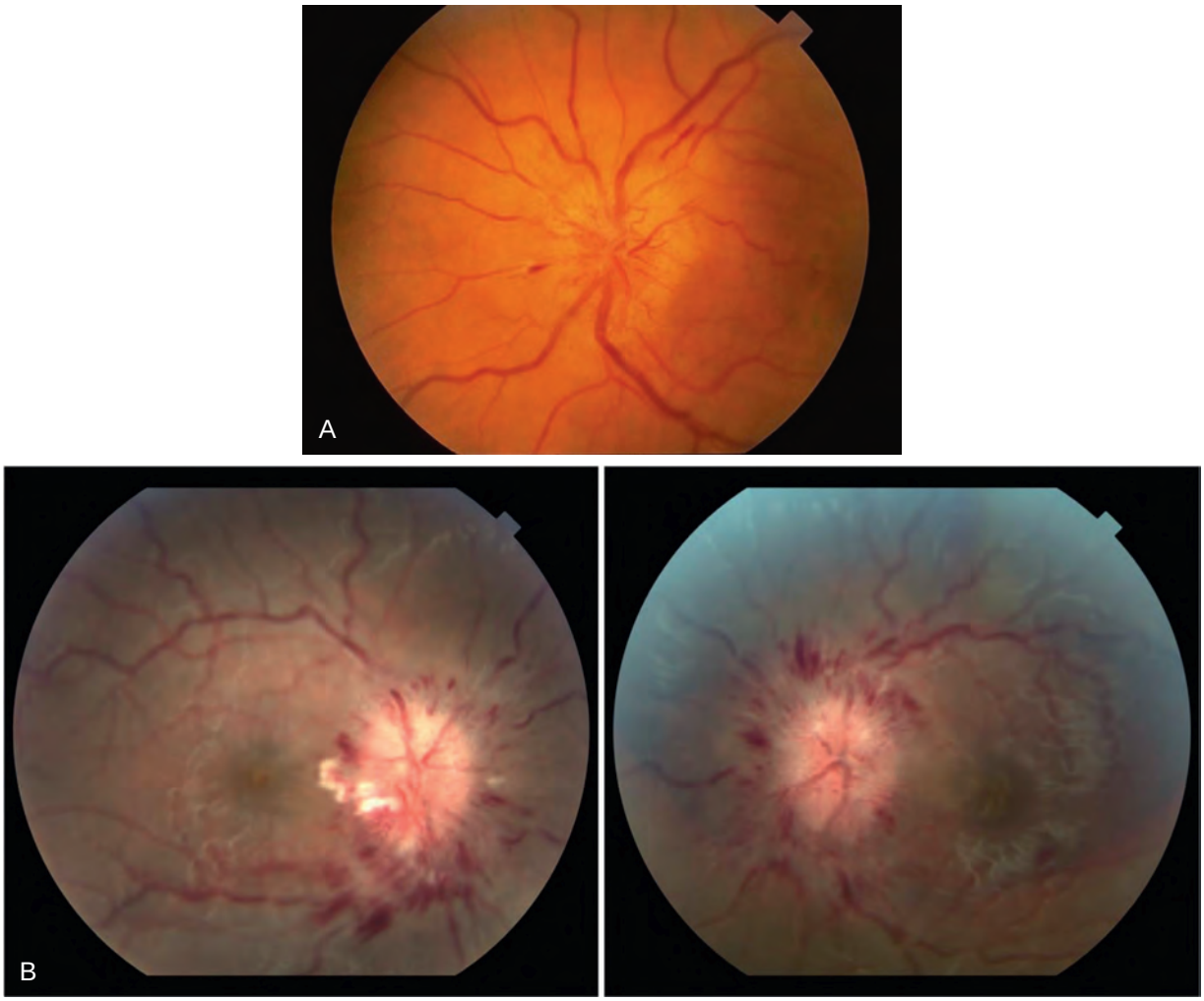

Fig. 61.24. A, Papilledema. Note the blurred disk margins. **B,** Papilledema. Note the blurred disk margins, exudates, and hemorrhages.

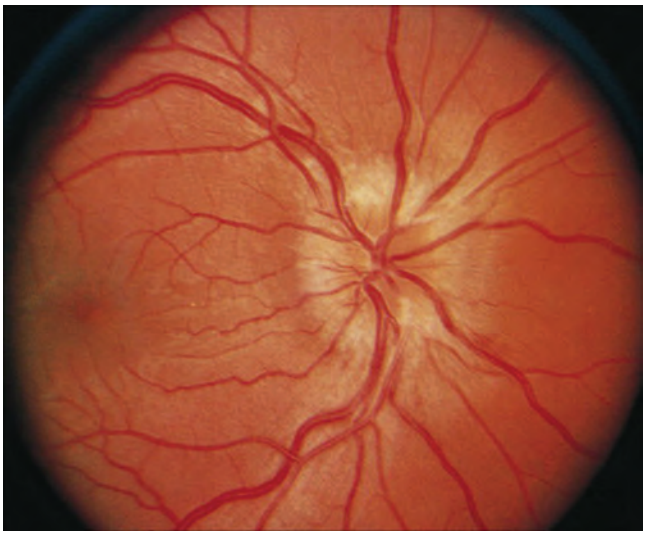

Fig. 61.25. Optic disk swelling (papillitis) associated with acute optic neuritis. (From Yanoff M, Duker JS, editors: Ophthalmology, ed 3, Philadelphia, 2008, Mosby.)

photopsia are vitreous or retinal detachment (see later), with which abnormal mechanical stimulation of the retinal photoreceptors leads to a cascade of action potentials that the visual system interprets as flashes of light. A less common cause of unilateral photopsia is uveitis involving the choroid. The most common cause of bilateral (and homonymous) photopsia is migraines, although scintillating scotomata is much more frequent. Less common causes of bilateral homonymous photopsia include lesions of the visual cortex with release hallucinations or epileptic seizures.

Considerations in the differential diagnosis of these visual field disturbances include intraocular (monocular) entities such as vitreous hemorrhage, vitreous and retinal detachment, and extraocular (binocular) entities at the optic chiasm and beyond.

Vitreous hemorrhage results from bleeding into the pre-retinal space or into the vitreous cavity. The most common causes are diabetic retinopathy and retinal tears. Additional causes include neovascularization associated with branch vein occlusion, sickle cell disease, retinal detachment, posterior vitreous detachment, trauma, age-related macular degeneration, retinal artery microaneurysms, trauma, and intraocular tumor. Symptoms begin with dark floaters or "cobwebs" in the vision and may progress over a few hours to painless visual loss. Floaters, described by the patient as dark or black dots or strands moving in the visual field in the direction of the preceding eye movement, are caused by vitreous blood.

Vitreous detachment is a common occurrence in patients older than 60 years old. With aging, the vitreous gel desiccates, shrinks, and pulls away from the retina, leading to symptoms similar to those of vitreous hemorrhage and retinal detachment.

Retinal detachment can occur by three mechanisms: (1) rhegmatogenous, (2) exudative, and (3) tractional. The retina has two layers—the inner neuronal retina layer and the outer retinal pigment epithelial layer—that can be separated by fluid accumulation. A retinal tear in the retinal membranes may or may not lead to a retinal detachment. A rhegmatogenous retinal detachment occurs as a result of a tear in the neuronal layer, allowing fluid from the vitreous cavity to leak between and separate the two retinal layers. It occurs in patients older than 45 years old, is more common in men, and is associated with degenerative myopia. Trauma can cause this type of detachment at any age, with patients with severe myopia being at greater risk. An exudative retinal detachment occurs as a result of fluid or blood leakage from vessels within the retina and is associated with hypertension, pre-eclampsia, central retinal venous occlusion, glomerulonephritis, papilledema, vasculitis, and choroidal tumor. Finally, a tractional retinal detachment is a consequence of contraction of a fibrous band that has formed in the vitreous. With retinal detachment, patients typically note flashes of light related to the traction on the retina, floaters related to vitreal blood or pigmented debris, and visual loss. The visual loss is commonly described as filmy, cloudy, or curtain-like in appearance, and is painless.

If a visual field disturbance is binocular, then a chiasmal or cortical disorder should be considered. Chiasmal disease is most commonly caused by chiasmal compression from pituitary tumors, craniopharyngiomas, or meningiomas. Visual loss is gradual and progressive. Beyond the optic chiasm, the most common causes of visual disturbances are infarctions, tumors, arteriovenous malformations, and migraine disorders. Patients report difficulty in performing a certain task, such as reading. Lesions can be located from the immediate post-chiasmal optic tract to the occipital cortex.

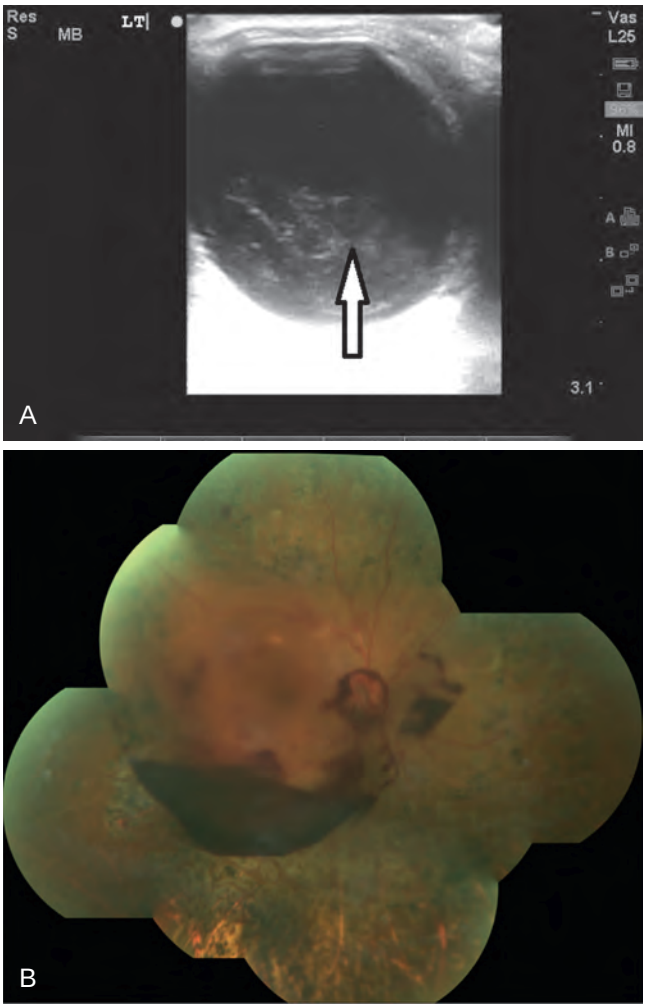

Fig. 61.26. **A,** Ocular ultrasound showing vitreous hemorrhage *(white arrow).* **B,** Boat shaped pre-retinal vitreous hemorrhage (**A,** Courtesy Douglas Brunette, MD. **B,** Courtesy Jeffrey Lee, MD.)

Diagnostic Testing, Management, and Disposition

In the diagnostic evaluation of visual field disturbances, the history should be specific enough to ascertain if the problem is an issue of an absence of vision (ie, a "blind spot," or visual field deficit, as seen in chiasmic or cortical etiologies), or of an obstruction of vision (ie, "floater," as seen in vitreous detachment or hemorrhage, or retinal detachment). In addition, a visual field examination should be detailed enough to determine if the disturbance is monocular or binocular and whether it respects the midline. Funduscopy is especially important to enable an assessment of the vitreous and retina, and ocular ultrasound is a helpful adjunct. With this approach, the considerations outlined earlier can be differentiated and addressed.

Vitreous Hemorrhage and Detachment. With a vitreous hemorrhage, direct ophthalmoscopy reveals a reddish haze in mild cases and a black reflex in severe cases. Details of the fundus are usually difficult to visualize. There is a diminished red reflex and an inability to visualize the fundus clearly with the direct ophthalmoscope. Ocular ultrasound, which will reveal echogenic debris in the vitreous, can be an effective diagnostic screening tool (Fig. 61.26A). A vitreous hemorrhage or detachment usually does not cause an APD by itself, and if an APD is present, an occult retinal detachment may be present. A hemorrhage may be evenly distributed throughout the vitreous, or—if trapped in the subhyaloid space as a pre-retinal hemorrhage—may be focal, with a boat shape (see Fig. 61.26B).

Ophthalmologic consultation in the ED, or a same-day evaluation by an ophthalmologist, will typically be needed to characterize the extent and complications of any suspected vitreous hemorrhage or detachment and manage vision-threatening complications. The management of a vitreous hemorrhage is otherwise largely expectant, with limitation of activity, avoidance of anticoagulants, and sleeping with the head of bed elevated to allow blood to settle and optimize visualization of the retina on subsequent examinations. Surgery is typically required if there is an associated retinal detachment. The same consideration applies for a posterior vitreous detachment, for which no specific emergent treatment is indicated unless accompanied by a retinal tear, vitreous hemorrhage, or retinal detachment.

Retinal Detachment. With a retinal detachment, visual acuity can range from minimally changed to severely decreased. Visual field deficits relate to the location of the retinal detachment, and an APD occurs if the detachment is large enough. When the detachment is visible on ophthalmoscopy, the retina appears out of focus at the site of the detachment. In large retinal detachments with large fluid accumulation, a bullous detachment with retinal folds can be seen (Fig. 61.27A). Retinal detachment cannot be ruled out by direct funduscopy. Indirect ophthalmoscopy is needed to visualize the more anterior portions of the retina. Bedside ED ultrasonography can be a useful tool in screening for a retinal detachment (see Fig. 61.27B).[56] It will reveal a billowing hyperechoic line that may undulate with side-to-side movements of the eye.

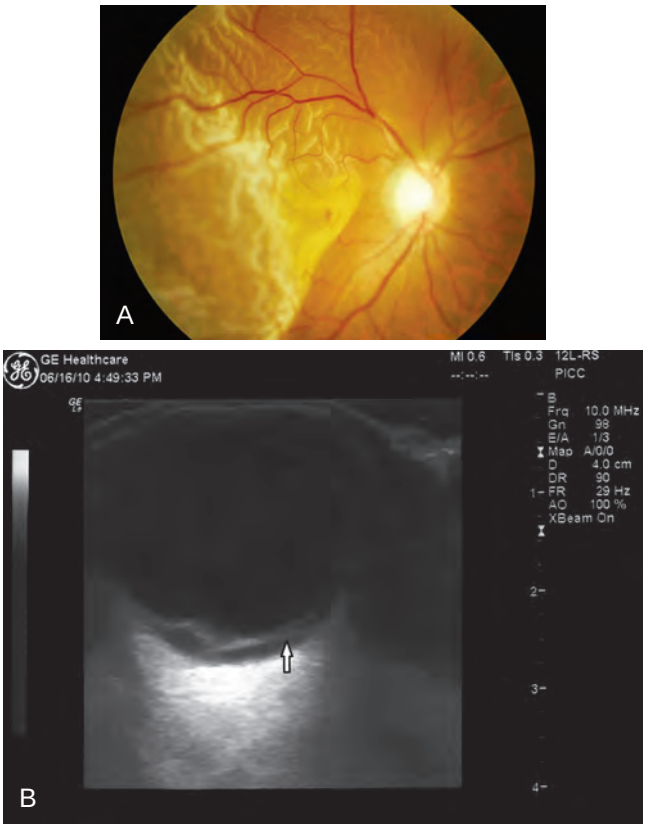

Fig. 61.27. A, Retinal detachment. Note large portion of retina billowing forward. **B,** Bedside emergency department (ED) ultrasound showing retinal detachment *(white arrow)*. (**A,** Courtesy www.tedmontgomery.com. **B,** Courtesy Nicholas Connors, MD, and Sophia Lin, MD, New York Presbyterian-Weill Cornell Medical Center.)

Any patient suspected of having a retinal tear or detachment requires immediate ophthalmologic consultation, because treatment with tamponade or retinopexy can prevent a retinal detachment that does not involve the macula (a "macula-on" retinal detachment) from progressing to involve the macula ("macula-off") and significantly degrade visual acuity. The duration of macular detachment, measured from the reported time of the loss of central visual acuity, is inversely related to final visual acuity. Even though the literature suggests that there is almost a day's-worth of leeway in the timing of repair of a "macula-on" detachment, and a fair amount of visual acuity is recoverable if a "macula-off" detachment is repaired early enough, a "macula-on" detachment that is close to the macula is at risk of converting to "macula-off" with even a few hours delay.[56-59]

Chiasmal and Cortical Disturbances. Although formal visual field testing may be necessary to stage the condition, the diagnosis of a chiasmic or cortical etiology to a visual field disturbance can usually be made by confrontation visual field testing. The classic defect for a lesion in or compression of the optic chiasm (chiasmal) is a bitemporal hemianopsia; however, tumors often compress the chiasm and optic nerves asymmetrically, resulting in combined central and temporal defects. When a visual field defect respects the vertical midline, the lesion is out of the globe and likely either chiasmal or post-chiasmal (see Fig. 61.23).

The classic visual field defect in post-chiasmal (cerebral or cortical) disease is a homonymous hemianopsia, a visual field loss on the same side of both eyes (see Fig. 61.23). Patients with such lesions have a focal neurologic deficit and need to be evaluated and treated based on the primary neurological diagnostic considerations, which include occipital infarction, neoplasm, an inflammatory process, or an infectious process (such as, encephalitis).

Sudden Vision Loss: Retinal Artery and Vein Occlusion, and Ischemic Optic Neuropathy

Clinical Features and Differential Diagnosis

Sudden onset of atraumatic, vision loss is usually due to a vascular process, such as infarction (although nonvascular processes, such as from retinal detachments and hemorrhages affecting the macula, are possible). Binocular processes include a sudden homonymous hemianopia from an infarction of the visual pathways in the temporal, parietal, or occipital lobes; and sudden total blindness in both eyes due to a basilar artery territory infarction of both occipital lobes. Central nervous system (CNS) processes (such as, ischemic stroke) that underlie these binocular events are discussed in entries specific to them elsewhere in this text. This section is, therefore, dedicated to sudden onset of painless monocular vision loss, which is ophthalmological and is usually due to a vascular process, such as infarction in either the retina or the optic nerve; the differential diagnosis primarily includes central retinal artery occlusion (CRAO), central retinal vein occlusion (CRVO), and ischemic optic neuropathy (ION). These typically present with sudden vision loss that is painless, severe, and develops over seconds, and may be permanent, or transient (amaurosis fugax).

In a CRAO, acute retinal ischemia develops from a sudden embolic, thrombotic, vasculitic or vasospastic occlusion of a branch of the retinal artery (a branch retinal artery occlusion [BRAO]) or the central retinal artery itself (a CRAO). A CRAO may be (1) non-arteritic and permanent (over two-thirds of all CRAO cases, due to platelet fibrin thrombi and emboli from atherosclerotic disease), (2) non-arteritic and transient (with transient monocular blindness, a transient ischemic attack [TIA] of the retina, related to transient vasospasm due to serotonin release from platelets on atherosclerotic plaques), or (3) arteritic (due to temporal arteritis and rare).[60] It generally has a poor visual prognosis with spontaneous resolution occurring in 1% to 8% of cases. Most commonly occurring in patients 50 to 70 years old, CRAO risk factors include hypertension, carotid artery disease, cardiac disease, diabetes, collagen vascular disease, vasculitis, cardiac valvular abnormality, and sickle cell disease. Patients with increased orbital pressure from acute glaucoma, retrobulbar hemorrhage, and endocrine exophthalmos are also at risk.

A CRVO leads to congestion of venous blood and fluid in the intraretinal space that may lead to secondary retinal ischemia. It is typically characterized as either non-ischemic or ischemic; a non-ischemic CRVO is associated with dilatation of retinal vessels and edema only, whereas an ischemic CRVO presents with the sudden onset of painless vision loss in one eye. Predisposing factors include hypertension, hyperlipidemia, diabetes mellitus, vasculitides, hyperviscosity, and smoking.

ION falls into two primary types, anterior ischemic optic neuropathy (AION; involving the optic nerve head) and posterior ischemic optic neuropathy (PION; involving the rest of the optic nerve). AION can further be divided into arteritic anterior ischemic optic neuropathy (A-AION; due to temporal arteritis) and—more commonly—non-arteritic anterior ischemic optic neuropathy (NA-AION; due to noninflammatory causes).[61]

Patients with A-AION may have concurrent symptoms of temporal arteritis (giant cell arteritis), such as weight loss, malaise, jaw pain, headache, scalp tenderness, polymyalgia rheumatica, and low-grade fever; in up to 25%, however, the acute vision loss is the only symptom.[60] Vision loss can be preceded by episodes of amaurosis fugax. Untreated it may progress to involve both eyes. Temporal arteritis is extremely rare in people younger than 50

years old, and the incidence rises with each subsequent decade. Vision loss has been shown to be unilateral in 46%, sequential in 37%, and simultaneously bilateral in 17%.

Patients with the much more common NA-AION lack the classic symptoms of temporal arteritis and tend to be younger with systemic vascular disease, diabetes, or hypertension. This is an acute ischemic event affecting the anterior optic nerve that typically occurs in patients over the age of 50 (typically 60 to 70 years old), at times associated with precipitant anemia, hypovolemia, dehydration, systemic hypotension, or fluctuations in blood pressure (especially that associated dialysis).[61]

A sudden complete loss of vision due to a vascular cause can be transient, whereupon it is called *amaurosis fugax,* and can be a manifestation of any of the aforementioned processes. It has been found in 2% of CRAO, 14% of BRAO, 5% of CRVO, just over 3% in NA-AION, and in 32% of patients with temporal arteritis who have ocular involvement.[62] Amaurosis fugax may also implicate proximal cerebrovascular disease and be a form of transient ischemic attack.

Diagnostic Testing, Management, and Disposition

Central Retinal Artery Occlusion. With CRAO, the examination reveals a markedly reduced visual acuity with a prominent APD, and an edematous with a pale gray-white retina with a cherry-red spot representing the fovea seen on funduscopy (Fig. 61.28). Patients younger than 50 years old should have a hypercoagulability evaluation, whereas older patients at risk for temporal arteritis should have an evaluation appropriate for that consideration.[60]

A number of interventions geared toward dislodgement of the embolus (via direct digital pressure through closed eyelids for 10 to 15 seconds and followed by a sudden release), dilation of the artery to promote forward blood flow (by increasing intra-arterial carbon dioxide level [pCO_2] with an inhaled mixture of 95% oxygen/5% carbon dioxide [carbogen]), and reduction of IOP (such as, with glaucoma, even using anterior chamber paracentesis) to increase in perfusion gradient have been recommended, but there is little evidence to support the benefit of any of these treatments.[62a] Other options in include hyperbaric oxygen. Overall, the efficacy of the above therapies varies between 6% and 49%, with a mean visual improvement rate of 15% to 21%.[60]

A CRAO may be amenable to the use of thrombolytic agents, with the caveat that it is usually an atheromatous embolic event, and thrombolysis is designed to lyse the fibrinoplatelet occlusion in a non-arteritic CRAO.[59] Studies are heterogenous, using different agents, dosing regimens, and time-windows in largely retrospective case series with different findings, but it appears that intra-arterial thrombolytic therapy might be effective if given less than 6 hours from onset.[60,63] IV thrombolysis might be effective if given less than 4.5 hours from onset, with a post-thrombolysis major hemorrhage rate significantly lower than that seen with ischemic stroke (none documented with tissue-plasminogen activator or urokinase).[64] Until a large randomized controlled trial of the safety and efficacy of thrombolysis for CRAO is performed, management should be tailored to individual patient circumstances in consultation with an ophthalmologist.

Central Retinal Vein Occlusion. A CRVO is differentiated from CRAO based on findings on funduscopic examination. Appearance can vary but classically includes dilated and tortuous veins, retinal hemorrhages, and disk edema (Fig. 61.29). Branch retinal vein occlusion is an incomplete CRVO and carries about better prognosis. Neovascular glaucoma and macular edema are the major complications of ischemic CRVO.

Over 80% of patients with a non-ischemic CRVO will have an ultimate visual acuity that is better than 20/200, whereas less than 10% of patients with ischemic CRVO will have an ultimate visual acuity better than 20/200. Treatment of CRVO includes treating the underlying etiology and monitoring for potential sequelae. Ophthalmology should be consulted in the ED to secure timely initiation of therapy, which largely centers around treating the macular edema associated with the occlusion. Treatment involves anti-vascular endothelial growth factor (anti-VEGF) pharmacotherapies, intravitreal corticosteroid injection with a dexamethasone intravitreal implant or triamcinolone, as well as retinal photocoagulation, normalization of IOP, and cyclocryotherapy.[65] The use of antithrombotic therapy, in particular the use of low–molecular-weight heparin, has also shown recent promise.[65a] Underlying medical disease should be managed;

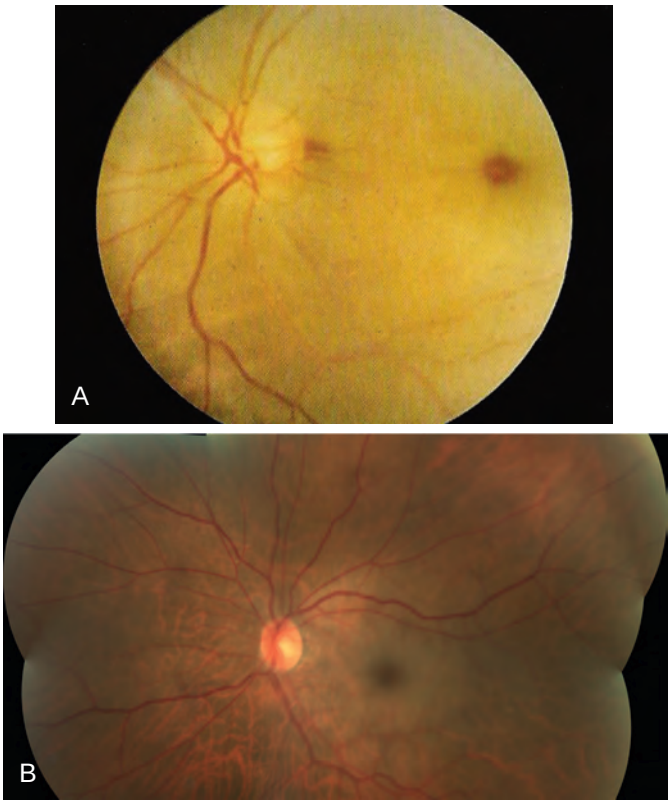

Fig. 61.28. Central retinal artery occlusion (CRAO). **A,** Note the cherry-red spot representing the fovea. **B,** Note whitening of the retina, with a less prominent cherry red spot. (**B,** Courtesy Jeffrey Lee, MD, University of California San Diego.)

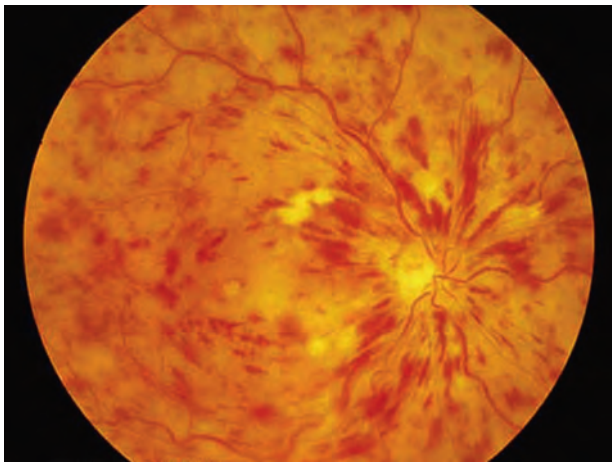

Fig. 61.29. Central retinal vein occlusion (CRVO). Note the "blood and thunder" appearance. (Courtesy www.tedmontgomery.com.)

the prognosis depends on the degree of obstruction and resultant complications.

Ischemic Optic Neuropathy. Examination findings are similar in A-AION and NA-AION, and include a large APD, visual loss, and a visual field defect that may respect the horizontal (as opposed to vertical) midline, with a pale and swollen optic disc on funduscopy.

The diagnosis of a temporal arteritis underlying an A-AION is outlined in entries specific to it elsewhere in this text, and it may include an erythrocyte sedimentation rate (ESR). Patients with NA-AION, on the other hand, do not have an elevated ESR, and an MRI may reveal abnormalities to the optic nerve head.

Temporal arteritis with evolving vision loss or amaurosis fugax from A-AION—as opposed to just headache alone—represents a distinct clinical emergency. Untreated, vision loss becomes bilateral in days to weeks in at least 50% of cases.[61] Patients should therefore be admitted for high-dose IV methylprednisolone (typically 500 mg to 1 g daily for 3 days) before transition to oral medications.[66] Patients treated with high-dose IV methylprednisolone are more likely to have visual improvement (a 34% chance of improvement) and are less likely to develop fellow eye involvement than those receiving oral prednisone.

The visual loss in NA-AION is less severe than with temporal arteritis, and improvement occurs in one-third of patients. There is no known treatment (intravitreal and systemic steroids have been tried without success, as have anti-VEGFs). Emergent ophthalmological consultation in the ED is warranted for any apparent ION to aid with differentiation of the type and extent of the process and management.

Functional Vision Loss

Clinical Features, Differential Diagnosis, Diagnostic Testing, Management, and Disposition

Functional (or factitious) vision loss may be a hysterical conversion reaction (a non-deliberate, imagined visual loss in a patient with a relatively flat affect) or malingering (a vision loss for secondary gain in a patient who somewhat dramatically demonstrates blindness). Although the evaluation may require collaborative consultation with an ophthalmologist, neurologist, and a psychiatrist, some tests can be performed in the ED that will suggest a functional overlay, given that the most common presentation of functional vision loss is a decreased visual acuity.[67,68] They include (1) rotating an optokinetic drum or rocking a mirror slowly back and forth in front of the patient (which will induce nystagmus or eye movements in the functional patient, but not in the truly blind patient), (2) rapidly moving the examiners hand toward the eye in question (which will induce a blink to a visual threat in the functional patient, but not in the truly blind patient), (3) checking for an APD as in Figure 61.11 (which will be absent in the functional patient but not in the truly blind patient with an optic nerve problem), (4) having the patient raise his or her arms and touch both index fingers together (which a functional patient will feign inability to do, but a truly blind patient will be able to do, given that the test is actually one of proprioception and not vision). The other presentation of functional visual loss is a defect in the visual field, typically with a central scotoma.[67,68] This can be identified as functional by having the patient sit in front of a picture (or grid) and describe the extent of a visual field defect vis-à-vis what is missing, and then moving him or her further away and asking for another description of what is missing. The functional patient may describe same missing elements in the picture (in an effort to convince the examiner that the defect is stable), whereas the patient will a real visual field deficit will notice that more elements in the picture (or grid) are missing.

DIPLOPIA

Chapter 18 provides a comprehensive overview of the approach to diplopia in the ED expounding on a methodological consideration of whether a binocular diplopia is due to an due to (1) a simple restrictive, mechanical orbitopathy from inflammatory or infectious mass-effect directly restricting of the movement of the eye, (2) a palsy of one or more of the oculomotor CNs, (3) a more proximal neuro-axial process involving the brainstem and related CNs, or (4) a systemic neuromuscular process.

ANISOCORIA

Principles

Dilation (mydriasis) of the pupil is controlled by the dilator muscle, innervated by sympathetics that exit spinal cord at the level of C8, T1, and T2, and then come back up under the subclavian artery and over apices of the lungs, enter the superior cervical ganglion, then the internal carotid plexus, and finally the ophthalmic division of CN V (the trigeminal nerve), whereupon they reach the eye through the superior orbital fissure. This sympathetic innervation serves a largely inhibitory role, facilitating pupillary dilation in darkness.

Constriction (or miosis) of the pupil is controlled by the pupillary sphincter muscle, innervated by parasympathetics that originate in the nuclei of CN III. This parasympathetic innervation is the primary means of regulating pupillary size in response to different intensities of light. Afferent input from the retina of each eye bifurcates to innervate the Edinger Westphal nuclei of each CN III, and each nucleus in turn provides efferent output to its pupillary constrictor muscle, underlying the direct and consensual pupillary light reflexes. Anisocoria, or a difference in pupillary size, can result from a process affecting the nuclei or the innervation pathways or from pharmacological interference at the neural endplates in the pupillary muscles.

Clinical Features and Differential Diagnosis

The differential diagnosis of anisocoria include an Adie's or Argyll Robertson pupil, pharmacologic mydriasis and miosis, a third-nerve palsy, Horner's syndrome, and a physiologic or headache-associated anisocoria.

Adie's and Argyll Robertson Pupils

An Adie's tonic pupil results from dysfunction or lesion of the ciliary ganglion or short ciliary nerves, and may be idiopathic (seen more frequently in women than men), for from local ocular or orbital damage from surgery, trauma, procedures, infection, inflammation, or ischemia. An Adie's tonic pupil may also be part of a condition causing systemic autonomic dysfunction, such as diabetes, dysautonomia, neurosyphilis, amyloidosis, or sarcoidosis. These patients present with a large pupil, sensitivity to light in that eye, and blurred vision when looking at things near them (but may be asymptomatic, with the pupil noticed incidentally). The Argyll Robertson pupil is typically smaller than an Adie's and similarly constricts poorly to direct light, but it briskly constricts when a target within reading distance is viewed. It is attributable to a dorsal midbrain lesion (such as from neurosyphilis) that interrupts the pupillary light reflex pathway but spares the more ventral pupillary near reflex pathway.

Pharmacologic Mydriasis and Miosis

Anisocoria can be caused by a variety of accidental medication and plant exposures. Parasympathomimetic miosis may be

induced by exposures to organophosphate esters, pilocarpine drops, or dust containing cholinesterase inhibitor from a dog's flea collar. Parasympatholytic mydriasis may be seen with anticholinergic medications (such as, transdermal scopolamine), aerosolized ipratropium administered through ventilator masks, cycloplegics (such as, homatropine, cyclopentolate, or tropicamide), and plants containing anticholinergic agents, such as Jimsonweed *(Datura stramonium)* and Angel's trumpet *(Datura suaveolens)*.[69-70] *Sympathomimetic mydriasis* may occur from sprays containing phenylephrine (Neo-Synephrine) and from apraclonidine (a glaucoma medication).

Third-Nerve Palsy

CN III innervates the medial, inferior, and superior recti muscles, the inferior oblique muscle, and the levator palpebrae superioris muscle, which lifts the upper eyelid. It also provides parasympathetic innervation to two intrinsic ocular muscles, the ciliary and constrictor pupillae muscles, which constrict the pupil. A CN III palsy, therefore, results an eye that appears deviated "down and out" with a dilated pupil and ptosis. The parasympathetic fibers that affect pupillomotor constriction are located peripherally and on the superomedial surface of CN III, where compression from an aneurysm or other source may cause pupillary involvement before other oculomotor signs, such as ptosis or diplopia, develop.

Horner's Syndrome

Horner's syndrome presents with ptosis, miosis, and facial anhidrosis resulting from a disruption of sympathetic innervation anywhere along the chain of sympathetic innervation.[71] The presence of associated symptoms may help localize etiology, as outlined in Table 61.2.[72] In children, the most common cause of acquired Horner's syndrome is a neuroblastoma of the paravertebral sympathetic chain, although it may be from a mediastinal tumor. Horner's syndrome can also be congenital, suggested by heterochromia or hypopigmentation of the ipsilateral iris.[71]

Physiologic and Headache-Associated Anisocoria

In physiological anisocoria, the difference in pupil size will typically be 1 mm or less. A more prominent transient mydriasis (benign episodic unilateral mydriasis) may occasionally accompany a migraine headache, either from sympathetic hyperactivity, or—with an ophthalmoplegic migraine—parasympathetic hypoactivity from CN III dysfunction.[73,74] A non-migrainous benign episodic unilateral mydriasis can occur without headache, ptosis, or ocular motility disorder, in episodes lasting minutes, hours, or even days and is also thought to be caused by over-activity of sympathetic innervation to the pupil. Patients are typically female, relatively young, and episodes last a median duration of 12 hours.

Patients can also present with a "tadpole pupil," in which the pupil becomes distorted and pulled in one direction like the tail of a tadpole, possibly occurring several times a day for several days and then resolving. This is likely the result of a sectoral spasm of the dilator muscle, thought to be benign, and has been associated with strenuous exercise. If, on the other hand, the patient has a baseline anisocoria and the tadpole pupil manifests in the smaller of the pupils, testing for Horner's syndrome is recommended.

Diagnostic Testing, Management, and Disposition

Determination of the potential etiology of an anisocoria can be facilitated by the approach outlined in the explanatory algorithm in Figure 61.30. Assuming no damage to the iris (implying a purely structural problem) is evident on slit-lamp examination, the strategy is to differentiate a benign cause of anisocoria (eg, physiological or pharmacological) from one that requires additional neuro-ophthalmological consultation (eg, Horner's syndrome) or emergent neuro imaging (eg, CN III compression potentially due to an aneurysm). The first step is to determine which pupil—the larger or the smaller—is the pathological one, keeping in mind that that parasympathetic innervation constricts a pupil in bright light, whereas sympathetic stimulation helps dilate a pupil in the dark. The subsequent steps incorporate the principles that an abnormally large pupil may be due to either a decrease in parasympathetic stimulation or an augmentation of sympathetic stimulation, and an abnormally small pupil may be due to either a decrease in sympathetic stimulation or an augmentation of parasympathetic stimulation.

The type of response to a topical application of cocaine (which specifically blocks norepinephrine uptake) can be diagnostic of Horner's syndrome, in that with no norepinephrine available to block the re-uptake, the Horner's pupil will typically not dilate. Other medications, such as hydroxyamphetamine (an

TABLE 61.2

Potential Locations of Lesion Causing a Horner's Syndrome, Based on Symptoms and Signs

SYMPTOMS AND SIGNS	POTENTIAL LESION LOCATION	POTENTIAL LESION TYPE
Brainstem symptoms (vertigo, ataxia, diplopia, and focal sensory and motor deficits)	Pontine or midbrain	Infarction or neoplasm
Myelopathic symptoms (paraparesis, sensory deficit, bowel or bladder symptoms, or hyperreflexia)	High spinal cord	Neoplastic or demyelinating process
Arm pain, weakness or numbness, neck lymphadenopathy (especially with hoarseness from recurrent laryngeal nerve compression)	Brachial plexus or cupula of the lung	Neoplastic process, such as a Pancoast tumor
Ipsilateral ear or neck pain (especially with symptoms of phrenic or vagus nerve involvement)	Carotid sheath	Carotid dissection; inadvertent injection of an anesthetic into the sheath during dental or line-placement procedures
Hearing loss and ear pain; trigeminal nerve dysautonomia (ipsilateral facial pain, rhinorrhea, conjunctival injection, and tearing)	Skull base	Neoplasm; inflammatory or infectious mass effect

Flaherty PM, Flynn JM: Horner syndrome due to carotid dissection. J Emerg Med 41(1):43-46, 2011. Davagnanam I, Fraser CL, Miszkiel K, et al: Adult Horner's syndrome: a combined clinical, pharmacological, and imaging algorithm. Eye (Lond) 27(3):291-298, 2013.

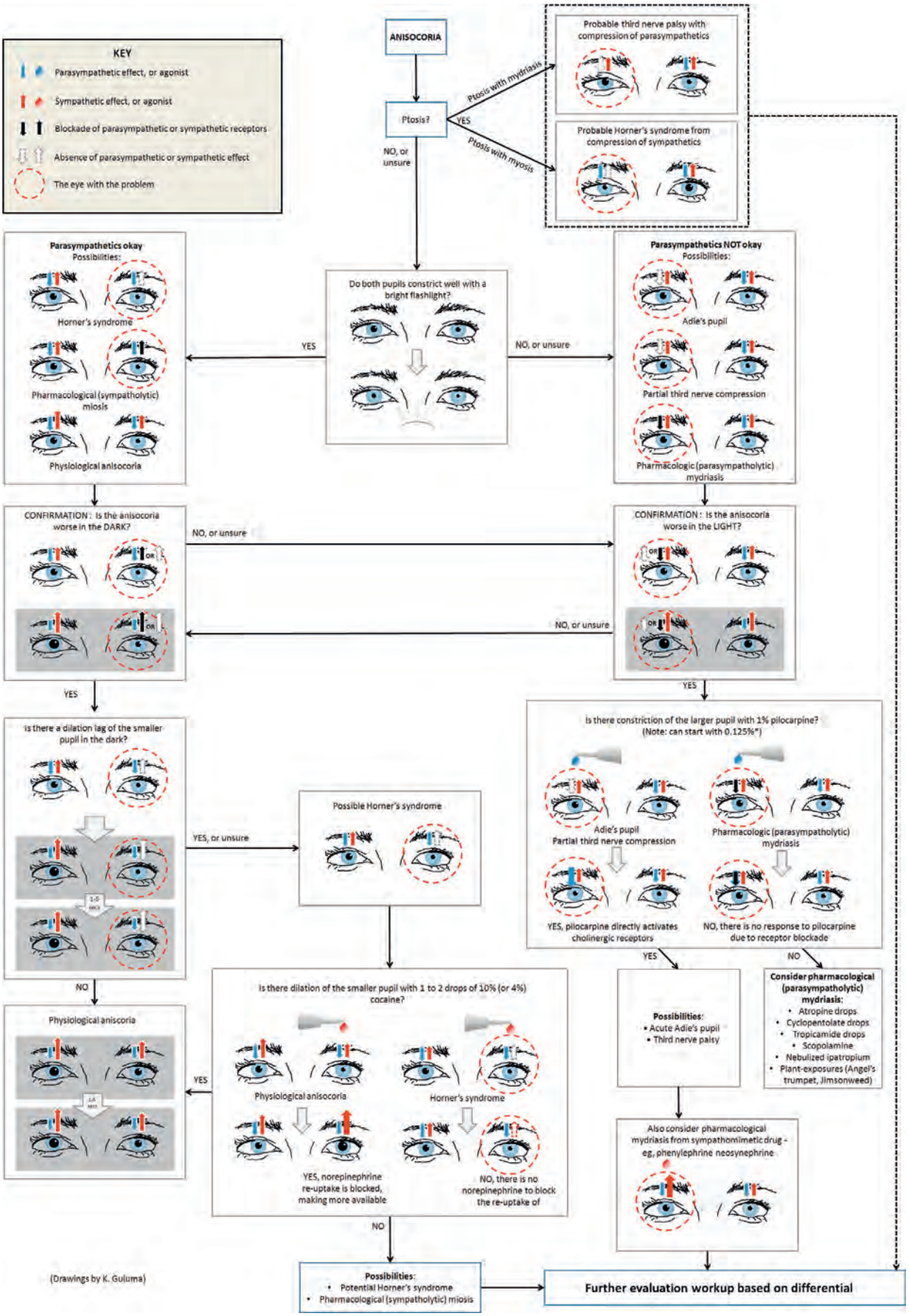

Fig. 61.30. The approach to anisocoria in the emergency department (ED), an explanatory algorithm. *Some authors advocate that a marked response to low concentration (0.1% or 0.125%) pilocarpine is more consistent with an Adie's pupil and can be used to differentiate it from an acute third nerve palsy (which may require the more concentrated 1% to elicit a reaction). This approach may be impractical, however, as a sole means to rule out a third nerve palsy from something like an aneurysm.

indirect-acting adrenergic mydriatic that causes endogenous norepinephrine to be released from sympathetic nerve endings without directly stimulating the effector cells[75]), as well as direct adrenergic agonists, such as a phenylephrine or 1% apraclonidine, can be used with ophthalmological consultation to perform a secondary evaluation of a Horner's pupil. Pilocarpine is a direct is a cholinergic receptor agonist and is used to differentiate hypo-parasympathetic conditions (see Fig. 61.30).

Once one of the typical presentations of anisocoria is identified, the evaluation progresses based on the clinical indications. Examination of an Adie's pupil typically reveals poor reaction to light with sectoral palsy of the iris sphincter, and a lack of (or slow) constriction with near accommodation (at least in the acute phase; later on, with re-innervation, the pupil will constrict strongly, and will thus be a "tonic" pupil).[76] Slit-lamp examination may reveal sectoral palsies of the iris, and a weak cholinergic agent (pilocarpine 0.1%) causes an intense pupillary constriction (compared to the patient's normal pupil) as a result of the cholinergic supersensitivity in the affected pupil. These patients should be referred non-emergently to an ophthalmologist for further evaluation. The Argyll Robertson pupil, like the Adie's pupil, will demonstrate segmental, slow, or little iris sphincter constriction with light, but normal constriction with near accommodation ("light-near dissociation," which distinguishes it from an acute Adie's pupil). A patient with bilateral Argyll Robertson pupils should be screened for neurosyphilis as per standard (please refer to entries dedicated to syphilis elsewhere in this text). The patient with a new-onset Horner's syndrome should undergo an evaluation to determine the cause and will typically require targeting imaging based on the diagnostic considerations outlined in Table 61.2, with MRI for brain, skull-base, and spinal cord lesions, and computed tomography angiography (CTA) for chest and neck/carotid pathology.[72] The cadence of the evaluation (and which components are done in the ED) will be dictated by the acuity of the primary considerations in the differential diagnosis, with aneurysm, dissection, brainstem stroke, and a rapidly progressive myelopathic process evaluated emergently in the ED and a more subacute or chronic process (such as, a tumor) being worked up urgently as an outpatient. The diagnostic evaluation and management of a third nerve palsy is covered in Chapter 18 and Chapter 95. With regards to pharmacologic mydriasis and miosis, most of the exposures and their effects will be self-limited and transient, and the specific management will dictated by the toxicological sequelae expected. The first-time clinical presentation of physiological and headache-associated anisocoria (mydriasis) may provoke a neuro-imaging evaluation for the presence of aneurysmal or mass compression of CN III; although this is being excluded, treatment can be rendered along lines that are standard for migraine headache. Physiological and headache-associated anisocoria is otherwise self-limited and will not typically require urgent ophthalmology referral unless persistent.

NYSTAGMUS

Principles

Three specific mechanisms keep an object of visual interest on the fovea: (1) fixation, wherein the visual system detects retinal drifts and programs corrective eye movements; (2) the vestibulo-ocular reflex (VOR), which keeps the eyes on target despite head movements; and (3) eccentric gaze-holding, which requires ongoing signals from the brainstem and cerebellum to overcome the natural elastic pull of orbital tissues when the eyes are deviated away from the mid-position to fixate on a target.[76] Dysfunction in any of these three mechanisms removes the visual target from the fovea and may result in nystagmus and oscillopsia (a subjective sense of movement of the visual field).

Nystagmus is a repetitive horizontal, vertical, or torsional back and forth movement of the eyes that may appear as an equal "to and fro" motion (pendular nystagmus), or demonstrate an alternating, slow phase followed by a corrective fast phase (jerk nystagmus). In jerk nystagmus, although the slow phase is the abnormal one, the directionality of the nystagmus is described as that of the fast phase. Gaze-evoked nystagmus (GEN) is an ability to hold the eyes in a fixed position at the eccentric extremes of gaze.

Nystagmus can be physiologic or pathologic and congenital or acquired. Patients may have an incidental nonspecific physiological nystagmus with a very small amplitude and a very fast velocity, non-sustained (less than three beats), only elicited in extreme eccentric gaze, only horizontal and symmetric, and without other signs or symptoms of cerebellar system dysfunction.[77] A patient may also have congenital nystagmus, typically identified as chronic or present since birth, which requires no acute intervention in the ED. The focus in the ED is therefore on acquired pathological nystagmus, of which the etiologies can be classified as either (1) peripheral (such as, seen with benign peripheral vertigo or vestibular neuronitis), (2) central (such as, seen with ischemic stroke or CNS mass lesions), or (3) toxic and metabolic (such as, that induced by medications, alcohol or illicit drugs). The clinical priority is to distinguish a peripheral (which is relatively benign and can be treated as an outpatient) from central (which may imply focal CNS pathology and require targeted neuro-imaging) from toxic or metabolic etiologies (which may imply toxic levels of a medication, or an underlying illicit drug intoxication).

Clinical Features, Differential Diagnosis, Diagnostic Evaluation, Management, and Disposition

Peripheral Nystagmus and Central Nystagmus

Because peripheral and central nystagmus from lesional processes (eg, from otoconia, vestibular neuronitis, posterior circulation stroke, brain tumor, and so on) present with prominent vertigo, a detailed discussion of these entities is deferred to the entries on vertigo and dizziness in Chapter 16. Table 61.3 highlights the specific features of the nystagmus associated with these conditions. The key clinical goal in the ED with regards to nystagmus caused by a lesion somewhere is differentiating more subtle presentations of a central cause from benign peripheral one. This can achieved along the lines of (1) the direction of the nystagmus, (2) how its intensity changes with extremes of gaze, and (3) how it is affected by visual fixation, as outlined in Table 61.3.

Toxic and Metabolic Nystagmus

Nystagmus from drug or medication toxicity may be suggested by a concurrent toxidrome and, depending on the agent and the degree of toxicity, a lack of prominent vertigo or ataxia (keeping in mind that the specificity of nystagmus findings as an indicator of toxicity is unknown). Drug-induced GEN, although symmetric, is different from physiological nystagmus in that it has a larger amplitude and slower velocity and beats in the direction of the gaze (ie, upbeat nystagmus with the patient looking up, rightward nystagmus with the patient looking to the right, and so on). GEN from a focal cerebellar or brainstem lesion may look similar to that which is drug-induced, but it is characterized by a sustained asymmetric and rebound nystagmus in which, although the slow phase is directed toward primary position where the eyes are deviated, a few slow phases may be directed toward the prior gaze direction after the eyes return to the primary position.[77,78] The management is targeted toward the overall toxicological profile of the specific offending agent.

TABLE 61.3

Forms and Causes of Nystagmus

TYPE OF NYSTAGMUS	PRESUMED AREA OF DYSFUNCTION	CHARACTER/ PRIMARY DIRECTION	TRIGGERED BY HEAD MOVEMENTS?	SUPPRESSES ON VISUAL FIXATION ON AN OBJECT?	CHANGES DIRECTION WITH GAZE?	SUSTAINED?
PERIPHERAL NYSTAGMUS						
Labyrinthitis or vestibular neuronitis	Labyrinthine dysfunction or viral infection of the superior portion of the vestibular nerve trunk	Horizonto-rotatory, one direction only, slow phase towards dysfunctional nerve	Yes	Yes	No, just gets more pronounced the further the patient looks away from dysfunctional nerve	Yes
Benign paroxysmal positional vertigo (BPPV)	Otolithic, posterior canal (most common)	Torsional combined with vertical, one direction only	Yes, raising the head from horizontal to vertical	Yes	No	No
Benign paroxysmal positional vertigo (BPPV)	Otolithic, other canals	Horizonto-rotatory, one direction only, slow phase toward dysfunctional canal	Yes, turning head side-to-side	Yes	No, just gets more pronounced the further the patient looks away from dysfunctional canal	No
CENTRAL NYSTAGMUS						
Downbeat nystagmus	Vestibulocerebellum Drugs: Lithium, phenytoin, carbamazepine, alcohol, toluene, felbamate, lamotrigine, phencyclidine (PCP), ketamine Nutritional deficiencies: magnesium, vitamin B_{12} or thiamine	Pure vertical, with fast component downward	No	No	No, just more pronounced on looking down	Yes
Upbeat nystagmus	Pontomesencephalic or pontomedullary junction, or the superior vestibular nucleus and tracts Nutritional deficiencies: Thiamine (Wernicke's)	Pure vertical, with fast component upward	No	No	No, just more pronounced on looking up	Yes
Torsional	Cerebellum or brainstem Drugs: PCP, ketamine	Pure rotary, with bidirectional fast component	No	No	Yes	Yes
Horizontal	Cerebellum or brainstem Drugs: PCP, ketamine	Bi-directional	No	No	Yes, fast component beats in direction of gaze, and gets worse with more extreme deviation	Yes
Gaze-evoked nystagmus (GEN)	Cerebellum or brainstem Drugs: Phenytoin, alchohol	Multi-directional, but asymmetric intensity	No	No; in fact worsens on eccentric fixation	Yes, fast component beats in direction of gaze, and gets worse with more extreme deviation	Yes, specifically if vision is eccentrically fixated on an object

TABLE 61.3

Forms and Causes of Nystagmus—cont'd

TYPE OF NYSTAGMUS	PRESUMED AREA OF DYSFUNCTION	CHARACTER/ PRIMARY DIRECTION	TRIGGERED BY HEAD MOVEMENTS?	SUPPRESSES ON VISUAL FIXATION ON AN OBJECT?	CHANGES DIRECTION WITH GAZE?	SUSTAINED?
OTHER MISCELLANEOUS CENTRAL NYSTAGMUS PRESENTATIONS						
Acquired pendular nystagmus	Paramedian pontine tract (seen in multiple sclerosis) Drugs: Phenytoin	Oblique or elliptical movements, can even be monocular	No	No	No	Yes
Periodic alternating nystagmus	Nodulus and ventral uvula of the vestibulocerebellum Drugs: Phenytoin	Horizontal nystagmus with a slow phase that changes direction every 1 to 2 min	No	No	No	Yes
Superior oblique myokymia	Possible cranial nerve (CN) disorder	Torsional oscillopsia, in one eye	No	No	No	Yes
See-saw nystagmus	Parasellar mass, or stroke to mesodiencephalic regions	Elevation with intorsion of one eye, with simultaneous depression and extorsion of the other eye	No	No	No	Yes
Oculopalatal myoclonus	Dentate, red, and inferior olivary nuclei in brainstem	Vertical-torsional or pure vertical (with one eye being more prominent), associated with palatal myoclonus	No	No	No	Yes

From Baier B, Dieterich M: Incidence and anatomy of gaze-evoked nystagmus in patients with cerebellar lesions. Neurology 76:361-365, 2011; Ehrhardt D, Eggenberger E: Medical treatment of acquired nystagmus. Curr Opin Ophthalmol 23(6):510–516, 2012; Shaikh AG: Fosphenytoin induced transient pendular nystagmus. J Neurol Sci 330 (1-2):121-122, 2013.

KEY CONCEPTS

- Routine prophylactic topical antibiotics are not indicated for the treatment of corneal abrasions, and eye patches are not recommended because they can mask a worsening infection.
- Eyelid lacerations that may require referral to a plastic or ophthalmic surgeon include those with lid margin lacerations, a canalicular laceration, or levator or canthal tendon injuries.
- Alkaline burns to the cornea and conjunctiva need to be copiously irrigated until a neutral pH is attained, because they produce a liquefactive necrosis that penetrates and dissolves tissue.
- Admission should be considered for traumatic hyphema patients with sickle cell trait, uncontrolled elevations in intraocular pressures (IOPs), hyphema of greater than 50%, and concern for re-bleeding.
- Any manipulation, palpation, or tonometry on a suspected globe rupture should be avoided, pending ophthalmological consultation and further examination.
- Scleritis, an autoimmune inflammatory process involving the sclera, can be confused with episcleritis, caused by inflammation in the more superficial episcleral layer of the eye. Episcleritis, unlike scleritis, is associated with much less discomfort, a pinker and more pronounced peri-limbal injection, and has injected superficial episcleral vessels that—unlike the deeper injected scleral vessels in scleritis—will vasoconstrict and blanch with 10% phenylephrine. Treatment of both involves topical corticosteroid drops.
- Endophthalmitis is an infection of the eye itself, and the most common etiology is recent intraocular surgery. Intravitreal antibiotics are indicated for endophthalmitis.
- Herpes zoster keratoconjunctivitis can complicate herpes zoster ophthalmicus, and necessitates emergent ophthalmologic consultation and treatment with systemic antiviral agents.
- The acute treatment of acute angle-closure glaucoma uses a two-armed approach: (1) reducing the production of aqueous humor with a topical beta-blocker (timolol 0.5%—1 to 2 gtt), a carbonic anhydrase inhibitor (acetazolamide 500 mg IV or PO), and a systemic osmotic agent (mannitol 1 to 2 g/kg IV); and (2) increasing the outflow of aqueous humor with a topical alpha-agonist (phenylephrine 1 gtt), miotic drops (pilocarpine 1% to 2%), and topical steroids (prednisolone acetate 1%, 1 gtt every 15 to 30 minutes four times, then every hour).
- With anisocoria, the following considerations help in the determination of which pupil—the larger or the smaller—is the pathological one: (1) parasympathetic innervation constricts a pupil in bright light, whereas sympathetic stimulation helps dilate a pupil in the dark; (2) an abnormally small pupil may therefore be due to a either a decrease in sympathetic stimulation or an augmentation of parasympathetic stimulation—but likely the former (eg, Horner's syndrome); (3) an abnormally large pupil may therefore be due to a either a decrease in parasympathetic stimulation or an augmentation of sympathetic stimulation—but likely the former (eg, partial third-nerve palsy from compression, Adie's pupil, pharmacological mydriasis); or (4) the abnormally small pupil will usually look worse in the dark, whereas the abnormally large pupil will usually look worse in the light.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 61: QUESTIONS & ANSWERS

61.1. A 23-year-old male presents with left periorbital pain after being struck with a fist. On examination, there are no globe injuries but marked periorbital swelling is noted. Computed tomography (CT) of the face reveals an orbital floor fracture. Which of the following would be the most likely physical findings?

A. Cheek anesthesia, enophthalmos, and limitation of upward gaze
B. Cheek anesthesia, ptosis, and limitation of inferior gaze
C. Forehead anesthesia and afferent papillary defect
D. Forehead anesthesia, diplopia, and limitation of lateral gaze
E. Ptosis, miosis, and ipsilateral anhydrosis

Answer: A. An orbital floor fracture may entrap the inferior rectus and inferior oblique muscles, resulting in diminished upward gaze. Other findings may include ptosis, enophthalmos, ipsilateral cheek/lip anesthesia, and orbital emphysema. Ten percent to 25% of such patients have associated globe injuries. Option E describes Horner's syndrome, which is not a typical finding.

61.2. A 20-year-old male presents with periorbital pain and swelling after a blow to the eye by a softball. Physical examination reveals proptosis with blurred vision and limitation of ocular motion in all planes. Tonometry reveals an intraocular pressure (IOP) of 35 mm Hg. Which of the following should be the first indicated maneuver?

A. Acetazolamide 500 mg IV, mannitol 20 g IV, and topical timolol
B. Computed tomography (CT) scan of the head and face
C. Endotracheal intubation and hyperventilation
D. Immediate lateral canthotomy and cantholysis
E. Ophthalmologic consultation

Answer: D. These findings should make one suspect retrobulbar hemorrhage. All of these interventions are likely indicated. Intraocular hypertension may compromise central retinal artery flow. Although immediate ophthalmologic consultation and pressure-lowering maneuvers are indicated, lateral canthotomy and cantholysis will provide the most rapid temporizing measure to preserve vision.

61.3. A 43-year-old male presents with acute ocular pain after a splash injury from drain cleaner. What should be the sequence of interventions?

A. Copious irrigation for 10 minutes, pH testing, cyclopentolate cycloplegia, topical antibiotics/intraocular pressure (IOP) measurement
B. Intravenous (IV) analgesia, cyclopentolate cycloplegia, IOP measurement, isotonic irrigation
C. IOP measurement, analgesia, head-up position, cycloplegia
D. Phenylephrine cycloplegia, isotonic irrigation for 10 minutes, pH testing, slit-lamp examination for foreign bodies
E. Phenylephrine cycloplegia, slit-lamp examination for foreign bodies, isotonic irrigation for 10 minutes, pH testing

Answer: A. Copious irrigation, ideally beginning at the scene, is the cornerstone of management. Nitrazine pH testing after 10 minutes should guide the need for continued irrigation. Cycloplegia, IOP measurement, and topical antibiotics come after pH normalization. Phenylephrine is contraindicated for cycloplegia in these cases because of its vasoconstrictive properties.

61.4. A 17-year-old girl who wears contact lenses presents with a 24-hour history of right eye pain. Physical examination reveals a right corneal abrasion at the six-o'clock position of the limbus. Appropriate treatment consists of which of the following?

A. Cessation of contact lens wear, eye irrigation (qid) with isotonic saline solution, followed by instillation of undiluted topical tetracaine for 5 days
B. Emergent ophthalmology consultation
C. Tetanus prophylaxis, eye patching for 48 hours, antibiotic ointment, and a 24-hour recheck
D. Tetanus prophylaxis, topical nonsteroidal anti-inflammatory drugs (NSAIDs), cessation of contact lens wear, and a 24-hour recheck
E. Topical nonsteroidal medications, topical antipseudomonal antibiotic, and a 24-hour recheck

Answer: E. Tetanus prophylaxis is not indicated for corneal abrasion unless there is corneal perforation or contamination with organic material. Topical NSAIDs reduce corneal abrasion pain. Antipseudomonas coverage with cessation of contact lens wear is appropriate. Eye patching is not indicated. Administration of undiluted topical anesthetics for more than 24 hours is untested and may be dangerous. Oral analgesics may be needed.

61.5. How do patients with subconjunctival hemorrhage most commonly present?

A. Asymptomatic blood in the eye, noticed in the mirror or by a friend
B. Decreased visual acuity
C. Foreign body sensation
D. Modest pain
E. Photophobia

Answer: A. Any significant symptoms, such as pain, decreased vision, foreign body sensation, or photophobia, should spark the search for more serious pathology. Bilateral hemorrhage in the absence of a clear cause (eg, severe vomiting) should raise suspicion for coagulation issues.

61.6. A 38-year-old man presents with unilateral left-sided visual loss after a motor vehicle collision (MVC). The only clinical finding is a left-sided hyphema rising to 50% of the height of the anterior chamber. Intraocular pressure (IOP) is 17 mm Hg in the unaffected eye and 29 mm Hg in the affected eye. Appropriate management should include which of the following?

A. Cycloplegia, intravenous (IV) mannitol, ophthalmology consultation
B. IV analgesia and antibiotic, immediate ophthalmologic consultation for decompression resulting from intraocular hypertension
C. Oral acetazolamide, patch and shield, antiemetics, 24-hour recheck
D. Topical beta-blocker, patch and shield, modest analgesia, admission
E. Topical beta-blocker, topical nonsteroidal anti-inflammatory drugs (NSAIDs) for pain, patch and shield, 24-hour recheck

Answer: D. Significant hyphema is an indication for admission. The presence of elevated IOP requires urgent treatment (which might also include topical alpha-agonists or IV acetazolamide,

and so on), patch and shield, elevation of the head, and cautious use of systemic analgesics. Any form of platelet inhibition would be contraindicated (ie, NSAIDs).

61.7. What is the major complication of hyphema?
A. Detached retina
B. Glaucoma
C. Horner's syndrome
D. Rebleeding
E. Vitreous hemorrhage

Answer: D. Rebleeding typically occurs 2 to 5 days later as the clot retracts. It is most common in patients with elevated intraocular pressures (IOPs), hyphema greater than 30% of the anterior chamber, and with delayed presentation. Rebleeding may lead to glaucoma and synechia formation.

61.8. A 48-year-old woman presents with right eye pain, photophobia, and decreased vision after a motor vehicle collision (MVC). Physical examination reveals an irregularly shaped pupil and a small hyphema. Photophobia, decreased acuity, minimal pupil reactivity, and bloody chemosis are seen on examination. What is the most likely diagnosis?
A. Acute angle–closure glaucoma
B. Blunt ciliary injury
C. Iridodialysis
D. Scleral rupture
E. Traumatic miosis

Answer: D. Scleral rupture occurs either at the insertion of the extraocular muscles or at the limbus, where the sclera is the thinnest. A "teardrop" pupil is often seen and may be accompanied by bloody chemosis or severe subconjunctival hemorrhage. Brownish black pigment prolapse may also be seen. Intraocular pressure (IOP) may be low, but tonometry is generally contraindicated in cases of suspected globe injury.

61.9. A 26-year-old man presents with a 3-day history of right eye pain, decreased vision, and photophobia. He reports a history of left eye trauma 6 weeks prior, with hyphema, traumatic iritis, and persistent decreased vision. He is otherwise healthy. Physical examination reveals photophobia in the right eye with bilateral decreased vision. Before the past 3 days, the vision in the right eye had been perfect. What is the most likely explanation for his right eye symptom?
A. Collagen vascular disease
B. Post-traumatic conjunctivitis
C. Post-traumatic retinal tear
D. Spontaneous vitreal hemorrhage
E. Sympathetic ophthalmia

Answer: E. Sympathetic ophthalmia is an autoimmune inflammatory response in the unaffected eye, days to months after uveal trauma in the opposite eye. Pain, photophobia, and decreased vision are common. This patient had no findings consistent with conjunctivitis or collagen vascular disease, and a retinal tear would not typically be painful.

61.10. Oral antibiotics are indicated for which of the following?
A. Blepharitis
B. Chalazion
C. Dacryocystitis
D. Endophthalmitis
E. Hordeolum

Answer: C. Dacryocystitis is an infection of the lacrimal sac from nasociliary duct obstruction. Warm compresses are also recommended and may be helpful, although evidence is lacking. Warm compresses and topical antibiotics are appropriate for the other conditions. Intravitreal antibiotics are indicated for endophthalmitis.

61.11. Emergency department (ED) bedside ocular ultrasonography can provide useful information for which of the following conditions?
A. Lens dislocation
B. Retinal detachment
C. Vitreous hemorrhage
D. All of the above

Answer: D. A displaced lens can be seen in the relatively hypoechoic vitreous. Vitreous hemorrhage and retinal detachment can both be diagnosed with ED bedside ultrasonography.

CHAPTER 62

Otolaryngology*

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OTITIS MEDIA

Principles

Otitis media is broadly defined as inflammation of the inner ear and is a continuum of disease. Acute otitis media is defined as the signs and symptoms of an acute infection, with evidence of effusion; this has also been called acute suppurative or purulent otitis media. Otitis media with effusion (OME) includes effusion without signs or symptoms of an acute infection; additional descriptive terms include serous, mucoid, nonsuppurative, and secretory otitis media. Chronic otitis media or chronic suppurative otitis media refers to chronic discharge from the ear through perforation of an intact membrane. Recurrent otitis media is defined by three or more episodes over 6 months or four episodes in 1 year.

Acute otitis media (AOM) is one of the most common diseases affecting preschool children in the United States and represents the most common indication for antibiotic usage and pediatric outpatient visits.[1] More than 80% of children will have at least one episode of AOM during their lifetime and, by 3 years of age, up to 40% will have had at least three episodes. In 2011, there were 6.21 million patient visits with a diagnosis of otitis media.[2] The financial repercussions are enormous, with one estimate that it adds $2.88 billion to annual health care expenses.[1]

Male gender, daycare attendance, parental smoking, pacifier use, family history of middle ear disease, premature birth, and lower socioeconomic status have been implicated as risk factors. Children with anatomic abnormalities, such as cleft palate and Down syndrome, have a higher rate of OM, probably because of eustachian tube abnormalities. Some immunocompromised patients, including patients with human immunodeficiency virus (HIV) infection, may have recurrent OM as an initial symptom of their underlying disease. OM and upper respiratory infections occur primarily in the winter. Breast-feeding seems to be protective. Immunizations for pneumococcus and influenza provide some protection but the decrease in overall episodes of otitis media is multifactorial. These factors include improved diagnosis, public education campaigns, and decreasing exposure to secondhand smoke. AOM is much less common in adults and is treated with the same antibiotics as for younger populations. OME is also less common in adults and is frequently associated with sinus disease, smoking-induced nasopharyngeal lymphoid hyperplasia, adult-onset adenoidal hypertrophy, and head and neck tumors such as nasopharyngeal carcinomas.[3]

Anatomy and Pathophysiology

Eustachian tube dysfunction is the central theme of most theories of AOM pathogenesis. The eustachian tube, between the middle ear cavity and nasopharynx, ventilates the middle ear to equilibrate pressure, allows for middle ear drainage, and provides protection from nasopharyngeal secretions. In young children, the eustachian tube is short and horizontal. As individuals age, the eustachian tube widens, doubles in length, becomes more vertically oriented, and stiffens, which may explain the decreased incidence of AOM in adults. Normally, the tube is collapsed, but it opens during yawning, chewing, and swallowing.

The eustachian tube may become mechanically or functionally obstructed, decreasing middle ear ventilation. Examples of mechanical obstruction include inflammation from an upper respiratory infection, hypertrophied adenoids, and a cleft palate. Functional obstruction from persistent tubal collapse occurs primarily in young children, who have less fibrocartilage support of the medial eustachian tube than older children or adults. There is general consensus that AOM occurs as a consequence of an upper respiratory infection resulting in eustachian tube dysfunction and subsequent negative middle ear cavity pressure, causing a transudate of fluid that combines with the reflux of nasopharyngeal secretions and bacteria. As such, there is a proliferation of bacteria and viruses.

The advent of reverse transcriptase polymerase chain reaction technology and other techniques for viral identification has led to improvements in diagnosis, and thus the number of viral agents identified in the middle ear has increased. In pediatric patients, middle ear cultures have been positive for viruses 48% to 70% of the time, with viral and bacterial coinfection occurring between 45% and 66% of the time. Respiratory syncytial virus is the most common virus, but parainfluenza virus, influenza virus, rhinovirus, and adenovirus have also been found in the middle ear aspirates of children. Viruses contribute to a poor treatment outcome by increasing middle ear inflammation, decreasing neutrophil function, and decreasing antibiotic penetration into the middle ear. The most common causes of bacterial infection in children are *Streptococcus pneumoniae, Haemophilus influenzae* (primarily nontypeable), and *Moraxella (Branhamella) catarrhalis. Streptococcus pyogenes, Staphylococcus aureus,* and gram-negative bacteria are much less common. The widespread use of the pneumococcal seven-valent conjugate vaccine (PCV-7) and subsequent pneumococcal 13-valent conjugate vaccine (PCV-13) have changed the frequency of these common organisms, with *H. influenzae* increasing in frequency, particularly in persistent AOM and treatment failures.

In young children, it was previously believed that gram-negative organisms and *S. aureus* were the causative organisms. Although these bacteria may be the causes in intubated patients or patients in the neonatal intensive care unit, healthy newborns tend to be infected by the same pathogens as healthy older children. Bullous myringitis produces bullae on the tympanic membrane (TM) in up to 5% of cases of OM in children younger than 2 years. Although it was previously thought to be caused by *Mycoplasma pneumoniae, M. pneumoniae* is uncommon; a culture of middle ear aspirates in this condition generally grow the usual organisms that cause AOM in all age groups. Bullous myringitis is therefore treated with the same antibiotics.

More than 70% of children with purulent conjunctivitis may have OM, a symptom complex described as the otitis-conjunctivitis syndrome, which is predominantly caused by *H. influenza.* Other

*The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

less likely organisms that can cause AOM include *Mycobacterium tuberculosis* (primarily in children) and *Chlamydia trachomatis* (most commonly seen in children <6 months).

Up to 10% of the general pediatric population may be at risk for developing four or more episodes of OM in the first year of life; these children are generally said to be otitis-prone. They may have subtle immunologic abnormalities or a greater baseline colonization of viruses and bacteria than the general population.

Clinical Features

Ear pain, unilateral or bilateral, is the most important symptom for making the diagnosis of AOM. Patients with AOM may present with a multitude of symptoms, such as cough, upper respiratory tract symptoms, poor appetite, diarrhea, vomiting, fever, and pulling at the ears, all of which are nonspecific. In fact, there is no constellation of symptoms or scoring systems that predict AOM, and examination of the tympanic membrane is essential to make the diagnosis.[4]

During the physical examination, the auricle and external canal are inspected for signs of erythema, discharge, and/or tenderness. If the canal is occluded with cerumen, curettage may clear the canal to improve visibility. In the cooperative child, the placement of 3% hydrogen peroxide or emulsifying drops, followed by gentle irrigation, may cleanse the canal if curettage is unsuccessful. The normal TM may be red, pink, yellow, or a normal pearly gray or translucent. The presence of erythema in itself does not indicate infection because crying or fever may cause hyperemia; however, a TM that is distinctly red (defined as hemorrhagic, strongly or moderately red) suggests AOM. Landmarks on the TM that should be visible include the pars flaccida, malleolus, and light reflex below the umbo. The presence of opacification, bubbles, air fluid levels, or retraction of the TM are suggestive of middle ear effusion. AOM is a visual diagnosis. A bulging tympanic membrane in a patient with signs and symptoms of acute infection is diagnostic of acute infection.[5] Demonstration of tympanic membrane immobility by pneumatic otoscopy is useful in distinguishing the presence of effusion in cases in which the provider is uncertain, but this is difficult, even with experienced providers.[6] A comparison examination of the other ear may help in confirming suspected infection.

In neonates, the TM is in a highly oblique position and normally appears thickened and opaque in the first few weeks of life. With tympanostomy tubes, even in the absence of infection, the TM may have decreased mobility, altered landmarks, opacity, or dullness. If the tube is patent, erythema and discharge indicate infection. If the tube is not patent, typical erythema, bulging of the TM, and immobility indicate AOM.

Before the use of antibiotics, there was a 20% incidence of complications from AOM, with mastoiditis and otic meningitis being relatively common. Complications are intratemporal or intracranial, occurring in adults and children. The development of either complication of OM occurs by one of three mechanisms: (1) direct extension of infection through bone weakened by osteomyelitis or cholesteatoma; (2) retrograde spread of infection by thrombophlebitis; or (3) extension of infection along preformed pathways, such as the round or oval windows or through dehiscences that are the result of congenital malformations. The use of antibiotics has led to a reduction of all complications to less than 1%.[7]

Usually, TM perforation occurs at the pars tensa and resolves spontaneously. It may persist for a longer period, resulting in a chronic perforation, chronic OM, or both. Chronic otitis media refers to inflammation of the middle ear that persists for 6 weeks or longer, accompanied by discharge through perforation of an intact membrane. Cholesteatoma is an accumulation of keratin-producing squamous epithelium in the middle ear and may result in erosion of bone within the middle ear cavity. It is seen most often in OME, in which retraction of the TM is a common problem, and its presence may alter the course of some treatment modalities.

The facial nerve courses through the middle ear, and facial paralysis is a known complication in OM. The exact mechanism is unknown, but the paralysis may be a result of infection, surrounding osteitis, facial nerve swelling, demyelination of the facial nerve from bacterial toxins, or facial nerve ischemia. Bony destruction as a result of mastoiditis can result in a defect over the semicircular canals, resulting in a labyrinth fistula. The patient may present with vertigo and some degree of hearing loss.

Meningitis is the most common intracranial complication of AOM,[8] resulting from hematogenous spread and direct invasion. Brain abscesses are usually caused by chronic otitis and are the second most common intracranial complication. Extradural abscesses, subdural empyema, and lateral venous sinus thrombosis have all been identified as complications of OM.

Differential Diagnoses

AOM is not common in children younger than 6 months as a result of the protection of maternal antibodies acquired transplacentally. Other sources of infection should be investigated in a febrile, ill-appearing infant (see Chapter 166). In addition to OM, other causes of otalgia include OME, trauma, foreign bodies, and complications of OM, such as mastoiditis and referred pain from the teeth, sinuses, throat, or temporomandibular joint.

Diagnostic Testing

Pneumatic otoscopy to confirm bulging and immobility of the TM is the primary diagnostic modality for AOM.

Management

Physicians in the Netherlands in the early 1990s had suggested that OM is a self-limited disease and recommended observation as an initial treatment option, followed by the use of antibiotics if the patient's condition did not improve within 72 hours. The American Academy of Pediatrics (AAP) and the American Academy of Family Physicians developed guidelines in 2004 for the diagnosis and management of AOM and updated them in 2013.[9] The guidelines cover diagnosis, pain management, observation, and antibiotic recommendations and apply to healthy children and not those with anatomic conditions that put them at risk for infections. Given the multidisciplinary approach, we recommend adherence to these guidelines.

The 2013 guidelines recommend these diagnostic criteria[10]:

1. Moderate to severe bulging of the TM or new onset of otorrhea not due to otitis externa *or*
2. Children who present with mild bulging of the TM and recent (<48 hours) ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM.

AOM can cause substantial pain, which should be appropriately addressed. Acetaminophen and ibuprofen are safe, over-the-counter, first-line analgesics. The use of opioid analgesia has not been well studied. Benzocaine-antipyrine, a local anesthetic, may be helpful in some patients with an intact TM. It has been shown to be more effective than placebo and is an additional option that we recommend for pain relief.

Children younger than 2 years, those with bilateral OM, or those with otorrhea gain the greatest benefit from antibiotic treatment but, because more than 80% of cases of AOM resolve spontaneously, the use of observation versus antibiotics has been advocated. This approach of watchful waiting for 48 hours has resulted in lower rates of antibiotic-resistant bacteria. The delay

TABLE 62.1

Recommendations for Initial Management for Uncomplicated Acute Otitis Media (AOM)

AGE	OTORRHEA WITH AOM[a]	UNILATERAL OR BILATERAL AOM[a] WITH SEVERE SYMPTOMS[b]	BILATERAL AOM[a] WITHOUT OTORRHEA	UNILATERAL AOM[a] WITHOUT OTORRHEA
6 mo–2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation[c]

[a]Applies only to children with well-documented AOM with high certainty of diagnosis.
[b]A toxic-appearing child, persistent otalgia >48 hr, temperature >39°C (102.2°F) in the past 48 hr, or if there is uncertain access to follow-up after the visit.
[c]This plan is initial management and provides an opportunity for shared decision making with the child's family for those categories appropriate for additional observation, if offered; a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48–72 hr of AOM onset.
Adapted from Lieberthal AS, Carroll AE, Chonmaitree T, et al: Clinical Practice Guideline: the diagnosis and management of acute otitis media. Pediatrics 131:e964–e999, 2013.

does not worsen recovery but may be associated with transient worsening of a child's condition.[10] The observation option has been restricted to healthy children older than 6 months. In children between 6 months to 2 years of age, treatment recommendations are based on the certainty of the diagnosis and severity of illness. In patients with unilateral AOM without otorrhea, observation is an option if the diagnosis is uncertain. In children older than 2 years, treatment is necessary only for patients with severe illness, defined as severe otalgia or temperature higher than 39°C (102°F) or patients with otorrhea. Children older than 2 years can be treated or clinically observed. Table 62.1 summarizes the AAP recommendations.

Observation recommendations are also based on the reliability of the caregivers and ability for close follow-up. Providers should involve the parents in the discussion, with shared decision making. If there is concern about the ability to get follow-up, give parents a safety net prescription to be filled if the patient's condition does not improve within 48 hours. Several studies in the emergency department (ED) have shown success with use of this approach. An analysis from the National Ambulatory Medical Care Survey has revealed that management without antibiotics has not increased since the guidelines were published, although children who did not receive antibiotics were more likely to have mild infections.[11] There are no data on the use of observation in adult patients, so they should be treated with amoxicillin, 500 mg tid for 10 days.

The decision to treat is balanced against the medication's adverse effects, which may include allergic reactions, gastric upset, accelerated bacterial resistance, and unfavorable changes in the bacterial flora. Several large systematic reviews have revealed that antibiotics are modestly more effective than no treatment, but 4% to 10% of children experience adverse effects from the treatment itself.[12] Two randomized controlled trials comparing amoxicillin-clavulanate versus placebo in a total of 610 patients have reported modestly improved time to resolution of symptoms and otoscopic findings but with more side effects, with diarrhea being the most common.[13,14] Although some authorities believe that these studies settled the treatment controversy, the studies were far from conclusive. Observation in children from 6 months to 2 year of age with unilateral AOM without otorrhea, or children older than 2 years with a nondraining ear or lacking severe symptoms, remains an acceptable and recommended treatment.

Amoxicillin's cost, efficacy, safety profile, and palatability justify its recommendation as the first-line agent in the non–penicillin-allergic patient. It can be given at a dose of 90 mg/kg bid. This higher dose is preferred because it is effective against susceptible and intermediately resistant strains of *S. pneumonia*, and because 15% to 20% of children have poor gastrointestinal absorption of amoxicillin.

In patients with reported allergies, a distinction should be made between types I and II hypersensitivity. There is only minimal cross-reactivity to cephalosporins for patients with penicillin allergy, and the use of a second- or third-generation cephalosporin is generally considered safe, unless the child has a previous adverse reaction to cephalosporins. In patients with type II hypersensitivity, alternate treatment options include cefdinir (14 mg/kg per day in one or two doses), cefuroxime (30 mg/kg per day in two divided doses), cefpodoxime (10 mg/kg once daily), and intramuscular ceftriaxone (50 mg/kg per day) IV or IM for 1 to 3 days. Patients with type I sensitivity are problematic in that macrolides have poor sensitivity against *S. pneumoniae* and *H. influenzae*, and clindamycin has poor sensitivity against *H. influenzae*. In patients with severe allergy, we recommend azithromycin, 10 mg/kg, as a first dose, followed by 5 mg/kg for days 2 through 5 or clindamycin, 30 to 40 mg/kg per day tid.

Children who have taken amoxicillin in the previous 30 days, those with concurrent conjunctivitis, or those for whom coverage with β-lactamase–positive *H. influenzae* and *M. catarrhalis* is desired should be initially treated with high-dose amoxicillin-clavulanic acid (90 mg/kg per day amoxicillin and 6.4 mg/kg/day clavulanate) tid.[12]

Patients should be reevaluated in 3 days if there is no improvement. Treatment failure is defined by lack of clinical improvement in signs and symptoms, such as ear pain, fever, and TM findings of redness, bulging, or otorrhea. The reasons for treatment failure may include the wrong initial diagnosis or antibiotic resistance.[15] In these cases, treatment includes agents effective against the β-lactamase–producing organisms *H. influenzae* and *M. catarrhalis*. Recommended agents include amoxicillin-clavulanate (80–90 mg of the amoxicillin component/kg per day) and intramuscular ceftriaxone (50 mg/kg for 1–3 days). Table 62.2 summarizes the AAP guidelines for antibiotic treatment.

Patients with AOM for whom treatment with a conventional β-lactam antibiotic has failed and β-lactam–allergic patients for whom macrolide therapy has failed should be referred to a pediatric infectious disease specialist or otolaryngologist. These patients may need a myringotomy and treatment with a fluoroquinolone, which is not US Food and Drug Administration (FDA)–approved for children. Response to antibiotics is only one of a number of factors that affect clinical outcome. Other factors include eustachian tube function, coinfection with nonbacterial pathogens, and host immune response. Local practice patterns and antimicrobial sensitivities may also play a role in the type of treatment given. Treatment historically involved a 10-day course. Numerous studies have compared traditional treatment courses with shorter therapy, which is most appropriate for uncomplicated AOM. Patients younger than 2 years, those with TM perforations, or those with chronic or recurrent infections should be treated with a 10-day course. Children older than 2 years with a first-time infection and an intact TM can be treated with a 5- to 7-day course. The antibiotic treatment of AOM in adults is the same as for children. There is no indication for the use of

TABLE 62.2

Recommended Antibiotics for Initial or Delayed Treatment and for Patients Who Have Failed Initial Antibiotic Treatment

INITIAL IMMEDIATE OR DELAYED ANTIBIOTIC TREATMENT		ANTIBIOTIC TREATMENT AFTER 48–72 H OF FAILURE OF INITIAL ANTIBIOTIC TREATMENT	
Recommended First-Line Treatment	**Alternative Treatment (if Penicillin-Allergic)**	**Recommended First-Line Treatment**	**Alternative Treatment**
Amoxicillin (80–90 mg/kg/day in two divided doses)	Cefdinir (14 mg/kg/day in one or two doses)	Amoxicillin-clavulanate[a] (90 mg/kg/day of amoxicillin, with 64 mg/kg/day of clavulanate in two divided doses)	Ceftriaxone, 3 days Clindamycin (30–40 mg/kg/day in three divided doses), with or without third-generation cephalosporin
or	Cefuroxime (30 mg/kg/day in two divided doses)	or	Failure of second antibiotic
Amoxicillin-clavulanate[a] (90 mg/kg/day of amoxicillin, with 64 mg/kg/day of clavulanate [amoxicillin to clavulanate ratio, 14 : 1] in two divided doses)	Cefpodoxime (10 mg/kg/day in two divided doses)	Ceftriaxone (50 mg IM or IV for 3 days)	Clindamycin (30–40 mg/kg/day in three divided doses) plus third-generation cephalosporin
	Ceftriaxone (50 mg IM or IV/day for 1 or 3 days)		Tympanocentesis[b] Consult specialist[b]

[a]May be considered for patients who have received amoxicillin in the previous 30 days or who have otitis-conjunctivitis syndrome.
[b]Perform tympanocentesis and drainage if skilled in the procedure or seek a consultation from an otolaryngologist for tympanocentesis and drainage. If the tympanocentesis reveals multidrug-resistant bacteria, seek and infectious disease specialist consultation.
[c]Cefdinir, cefuroxime, and ceftriaxone are highly unlikely to be associated with cross-reactivity with penicillin allergy on the basis of their distinct chemical structures.
Adapted from Lieberthal AS, Carroll AE, Chonmaitree T, et al: Clinical Practice Guideline: the diagnosis and management of acute otitis media. Pediatrics 131:e964–e999, 2013.

antihistamines, decongestants, steroids, or tympanostomy tubes for an acute episode of AOM.

After a 10-day treatment with antibiotics, 50% of children may exhibit OME, but 90% of OME cases resolve within 3 months. However, about 30% to 40% of children have recurrent OME, and 5% to 10% of cases last 12 months or longer. The treatment of OME is controversial, with one large systematic review suggesting that tympanostomy tubes decrease effusion and improve hearing over a short period without affecting speech, language, or other functional outcomes.[16] There is little benefit from antibiotics, and they should not be used. Antihistamines, decongestants, steroids, or surgical procedures are not beneficial for patients with OME. Myringotomy and tympanostomy tubes may be beneficial in children who have had OME for more than 4 months with persistent hearing loss, those with hearing loss greater than 40 dB, children with structural damage to the TM or middle ear, and children with persistent OM who are at risk for speech, language, or hearing problems. Tonsillectomy is not beneficial, but adenoidectomy may be helpful for older children who have a specific indication, such as nasal obstruction or chronic adenoiditis.

Emergency clinicians may encounter three types of otitis media associated with a perforation of the TM:

1. Acute otitis media complicated by perforation of the tympanic membrane, presenting as otorrhea
2. Otitis media in patients with tympanostomy tubes
3. Chronic suppurative otitis media defined as tympanic membrane perforation with chronic inflammation of the middle ear and persistent otorrhea for 2 weeks to 3 months.

As noted earlier, tympanic membrane perforation is a known complication of AOM and, in most cases, will heal spontaneously. Patients presenting with AOM and otorrhea should be treated with oral high-dose amoxicillin, as if the TM were not ruptured. There is no advantage to adding topical therapy.

Tympanostomy tubes have also been used in recurrent AOM unresponsive to prophylactic antibiotics, for complications of AOM, and for complications of eustachian tube dysfunction, including TM retraction with hearing loss, ossicular erosions, and retraction pocket formation. Thus, tympanostomy tube insertion is one of the most common operative procedures for children in the United States, and emergency clinicians will frequently encounter patients with drainage from these tubes. In general, increased drainage from these tubes is as a result of an acute infection. The organisms involved are the same ones that cause AOM, particularly in children younger than 2 years, but *Pseudomonas aeruginosa, S. aureus, and Staphylococcus epidermidis* are also implicated. Fluoroquinolone drops are the only medications FDA-approved for use in patients with a nonintact tympanic membrane. In the acute setting, topical antibiotic administration with 5 ofloxacin drops to the affected ear bid or 4 drops of ciprofloxacin-dexamethasone bid for 7 days is an effective treatment. Systemic treatment (usually with amoxicillin-clavulanate, 45 mg/kg bid) should be reserved for patients showing signs of complicated or invasive infections or signs of systemic disease.

Chronic suppurative otitis media (CSOM) is one of the most common childhood infectious disease worldwide and is the most common cause of hearing impairment in the developing world, although it is infrequently seen in the developed world.[1] Again, *P. aeruginosa and S. aureus* are the most common organisms. Because of the tympanic membrane perforation, we recommend topical treatment with quinolone antibiotics.

Disposition

Patients should be seen in 48 to 72 hours if there is no improvement. Children who improve can be followed up in 8 to 12 weeks to ensure resolution of any residual effusion. Patients with complications need ear, nose, and throat (ENT) referral. Adults who have persistent OME warrant ENT referral to rule out nasopharyngeal carcinoma.

OTITIS EXTERNA

Principles

External otitis is an inflammation of the external auditory canal. The external auditory canal is lined with squamous epithelial cells

and cerumen glands that provide a protective lipid layer. This protective layer may be disrupted by high humidity, increased temperature, maceration of the skin after prolonged exposure to moisture, and local trauma (eg, cotton swabs or the use of hearing aids), resulting in the introduction of bacteria. Otitis externa (OE) is usually caused by *P. aeruginosa* and *S. aureus* but can also be polymicrobial. Occurring most often in the summer and in tropical climates, it is also known as swimmer's ear or tropical ear.

Clinical Features

The diagnosis is made clinically. The external auditory canal may be initially pruritic and may become erythematous and increasingly swollen. Symptoms include otalgia and ear fullness, as well as possible hearing loss or jaw pain. Physical findings include erythema or edema of the canal; pulling on the auricle or tragus classically reproduces the discomfort. There may be associated lymphadenitis, TM erythema, or local cellulitis. The disease may progress to a chronic form, with itching, eczema, and flaking of the epithelium, which may be from a bacterial, fungal, or dermatologic condition. In children, it is usually secondary to chronic OM.

Differential Diagnoses

It may be difficult to distinguish OE from OM with drainage from a ruptured TM, particularly in children. The TM may be erythematous in both conditions, and the edema may preclude diagnosis. The discharge may be from OE or a perforated TM and, in equivocal cases, it is prudent to treat for both conditions.

Otomycosis or fungal infection can occur as a primary or secondary infection and accounts for 10% of cases of OE. Itching is the prominent symptom, often with minimal pain or otorrhea. Aspergillosis is the cause in most cases. Otomycosis usually appears in individuals in tropical climates, diabetics, and immunocompromised patients. Treatment involves cleansing and the use of acidifying and antifungal ear drops, such as acetic acid, or a topical antifungal such as clotrimazole.

Furunculosis is a small, erythematous, and well-circumscribed infection of the cartilaginous portions of the external canal, usually caused by *S. aureus.* There is usually no drainage; treatment involves incision, drainage, and oral antibiotics effective for cellulitis based on local sensitivity. Cellulitis of the auricle and canal may cause erythema, induration, and other systemic signs. Clindamycin, 450 mg qid, will cover *S. aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA). Skin conditions such as eczema, seborrhea, and contact dermatitis can all mimic otitis externa. A careful history about possible skin diseases, as well as medication and exposure history, should be elicited. Exposure to reactive metals such as nickel from devices such as hearing aids and chemicals from cosmetics and shampoos are also possible culprits.

Herpes zoster oticus, also known as the Ramsay Hunt syndrome, is a viral manifestation of disease affecting the auricle, with resulting facial paralysis that may involve multiple cranial nerves. It initially causes pain, erythema, and swelling, with vesicles developing approximately 3 to 7 days later. Treatment consists of analgesia and antivirals (acyclovir, 800 mg five times/day, famciclovir, 500 mg, or valacyclovir, 1000 mg tid), but there is little evidence supporting its efficacy.

Diagnostic Testing

OE is a clinical diagnosis. No additional testing is indicated.

Management

Treating OE involves cleaning the canal and treating the infection. The external canal may be cleaned with a small cotton swab or combination of gentle suctioning and irrigation, depending on the amount of obstructing exudates and whether there is an intact TM. Cleansing solutions include tap water, sterile saline, 2% acetic acid, and Burow's solution.

Topical antibiotics are highly effective for OE treatment, with clinical cure rates of 65% to 80% within 10 days. A combination of polymyxin B, neomycin, and hydrocortisone (Cortisporin) can be given at a dose of 3 or 4 drops to the affected ear qid, although occasionally patients develop cutaneous sensitivity to the neomycin. Ofloxacin (5 drops) or ciprofloxacin with hydrocortisone (3 drops) bid may result in improved patient compliance. The addition of steroid drops may decrease inflammation and the formation of granulation tissue in the canal, but this has not been proven.

Care should be taken if there is a concern for TM perforation. As noted, quinolone drops have a better safety profile than neomycin-containing drops, which are ototoxic, especially after prolonged or repeated use.[17,18] Having the patient lie down for 5 minutes after the solution has been placed may obviate the need for packing. Commercially available wicks made of compressed cotton or hydroxycellulose facilitate medication delivery. The wick is placed 10 to 12 mm into the canal, moistened with antibiotic drops, and left in place for 2 to 3 days. The wick generally falls out or, if left in place, may become a foreign body in the ear. Therefore, a patient should follow up with her or his primary care physician. There is no evidence that systemic antibiotics alone or in combination with topical preparations improve treatment outcome compared with topical antibiotics alone, but systemic medication, such as ciprofloxacin (500 mg bid), are indicated for immunocompromised patients with diabetes or HIV infection or for those with infections involving the skin and periauricular areas.[17] OE can be extremely painful, and severe symptoms may require opiate analgesia. Topical anesthesia, such as benzocaine with or without antipyrine, may also be used for pain relief.

Disposition

Patients with otitis externa rarely require admission. If it does not respond to therapy in 2 to 3 days, other conditions such as necrotizing external otitis should be considered. Patients who have a wick placed should be evaluated in 2 to 3 days to ensure improvement of the condition and that the wick is removed.

NECROTIZING (MALIGNANT) EXTERNAL OTITIS

Principles

Previously known as malignant otitis externa because of its associated high mortality rate, necrotizing external otitis (NEO) is an extremely form of OE. Patients affected include older diabetics, those with acquired immunodeficiency syndrome (AIDS) and, rarely, immunocompromised children. *Pseudomonas* is the predominant pathogen, but *S. aureus, S. epidermidis, Proteus mirabilis, Klebsiella, Aspergillus,* and *Salmonella* have all been described as causative organisms. The infection begins in the external canal and progresses through the periauricular tissue and cartilaginous bony junction of the external auditory meatus. It then spreads into the adjacent tissues along clefts in the floor of the meatus known as the fissures of Santorini. It may spread to the base of the skull at the temporal bone, with a resultant *skull-base osteomyelitis,* another term often used to describe this entity. The facial nerve is the first cranial nerve affected, but other nerves may also be involved. The pathogenesis is uncertain but may be related to vascular insufficiency or immune dysfunction.

Clinical Features

Patients may have persistent otorrhea unresponsive to topical medications, severe otalgia, headache, and periauricular pain and swelling. The diagnosis should be considered in patients at risk who have a prolonged course of OE. The characteristic clinical finding is granulation tissue on the floor of the ear canal at the bony cartilaginous junction. Cranial nerve VII is most commonly involved; involvement manifests with facial paralysis, which occurs when the stylomastoid foramen is involved. Further extension can result in involvement of the glossopharyngeal, vagal, spinal accessory, hypoglossal, trigeminal, and abducens nerves. Cranial nerve involvement is not associated with increased mortality rates. Additional complications include meningitis, brain abscess, and thrombosis of the sigmoid sinus.

Differential Diagnoses

Patients with necrotizing otitis will present with severe ear pain. Other differential considerations include severe otitis externa, otitis media, otitis media complications, trauma, and referred pain from the teeth, sinuses, throat or temporal mandibular joint.

Diagnostic Testing

There is no single diagnostic criterion for necrotizing external otitis. The diagnosis is made from a range of clinical, laboratory, and radiographic findings. The C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) may be elevated, but they are nonspecific markers. In the ED, computed tomography (CT) is the initial study of choice and, in most cases, will identify bony erosion and soft tissue abnormalities. Magnetic resonance imaging (MRI) is better at delineating responses to therapy. This disease should be considered in all patients with risk factors who have failed to respond to antimicrobial therapy for temporal bone inflammation and otalgia.[19]

Management

If NOE is suspected, consultation should be made with an otolaryngologist. The patient presentation will determine disposition. Patients who appear ill require admission for IV fluoroquinolones, such as ciprofloxacin, 400 mg IV q8h, to ensure that there is an adequate clinical response. The patient can then be switched to oral ciprofloxacin, given its bioavailability and penetration to bone. Treatment may be required for 6 to 8 weeks. Although extensive surgical treatment was previously required, its use is now limited to diagnostic confirmation or débridement of granulation tissue. Although some have recommended hyperbaric treatment for advanced disease with significant skull base or intracranial involvement, there is little evidence of its effectiveness.

Disposition

The decision for admission versus outpatient management should be made in consultation with an otolaryngologist.

MASTOIDITIS

Principles

Mastoiditis is the most frequent suppurative complication of OM, although the incidence of acute and chronic mastoiditis has decreased significantly since the advent of antibiotics. Although it is still associated primarily with AOM, some patients have not had a preceding episode of OM. Mastoiditis also has been described as a complication of leukemia, mononucleosis, sarcoma of the temporal bone, and Kawasaki disease.

Acute mastoiditis is a natural extension of middle ear infections because the mastoid air cells are generally inflamed during an episode of AOM. The aditus ad antrum is a narrow connection between the middle ear and mastoid air cells. If this connection becomes blocked, a closed space is formed, with the potential for abscess development and bone destruction. The infection may spread from the mastoid air cells by venous channels, resulting in inflammation of the overlying periosteum. Progression results in the destruction of the mastoid bone trabeculae and coalescence of the cells, resulting in acute mastoid osteitis or coalescent mastoiditis. The resulting pus may track through many routes: (1) through the aditus ad antrum, with resultant spontaneous resolution; (2) laterally to the surface of the mastoid process, resulting in a subperiosteal abscess; (3) anteriorly, forming an abscess below the pinna or behind the sternocleidomastoid muscle of the neck (often called a Bezold abscess); (4) medially to the petrous air cells of the temporal bone, resulting in a rare condition known *as petrositis*; and (5) posterior to the occipital bone, resulting in osteomyelitis of the calvaria or a Citelli abscess.

Chronic mastoiditis is generally a complication of chronic OM. There may be extensive invasion of granulation tissue from the middle ear into the mastoid air cells. Another entity, latent or masked mastoiditis, also has been described. It is indolent in nature, with minimal signs and symptoms, little or no fever, and a history of otalgia. The TM may be intact or perforated. Suspicion should be raised by the presence of intracranial complications without an apparent source. Patients at risk include newborns and immunosuppressed patients (eg, those who have undergone recent chemotherapy or steroid administration, diabetic or geriatric patients).

S. pneumoniae continues to be the leading cause of acute mastoiditis in the post–heptavalent pneumococcal vaccine era.[20] The introduction of the pneumococcal conjugate vaccine has resulted in an increase of a particularly virulent strain, serotype 19A, although the PCV-13 included this serotype. Other organisms include group A streptococci, *S. aureus, H. influenzae, and P. aeruginosa.*[21] Chronic mastoiditis also often has mixed cultures, with *P. aeruginosa* being the predominant organism.

Clinical Features

Clinical findings in acute mastoiditis include fever, headache, otalgia, and erythema. Pain is universally present. There are no specific diagnostic criteria, but the most common physical findings are postauricular erythema and tenderness, protrusion of the auricle, and an abnormal TM. The TM is similar to that in AOM—erythema, bulging, and decreased mobility—but may be normal in 10% of cases. Suspicion should be heightened if symptoms of AOM have lasted longer than 2 weeks. In chronic mastoiditis, symptoms include persistent drainage through the perforated TM, redness, edema, and retroauricular sensitivity.

Differential Diagnoses

The differential diagnosis includes severe otitis media, external otitis, skull fracture, lymphadenopathy or lymphadenitis, and deep space neck infections.

Diagnostic Testing

Although the diagnosis of mastoiditis can be made clinically in patients with typical findings, a CT scan is indicated in patients with neurologic symptoms, when an intracranial complication is suspected, or there is failure to improve with conservative therapy.[22] Fig. 62.1 is a CT scan of acute mastoiditis.

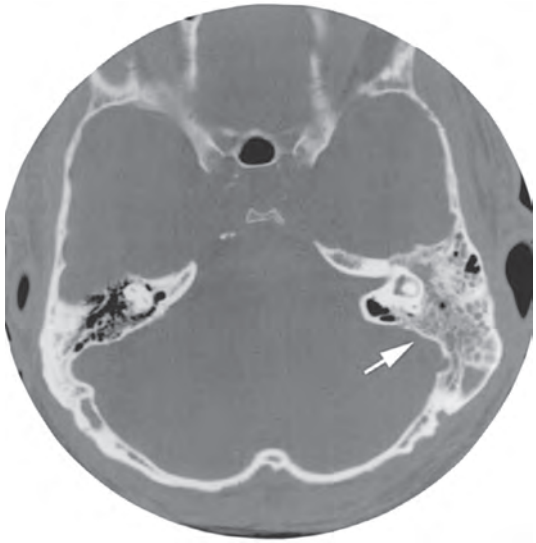


Fig. 62.1. CT scan of mastoiditis. (From McWhorter AJ, Limb CJ, Niparko JK: Otologic and skull base emergencies. In Eisele DW, McQuone SJ, editors: Emergencies of the head and neck, St. Louis, 2000, Mosby, p 384.)

Management

The initial treatment of choice in the emergency department is the administration of antibiotics, such as vancomycin, 15 to 20 mg IV bid, and a third-generation cephalosporin such as ceftriaxone (50 mg/kg per day). Surgical procedures may range from myringotomy and tympanostomy tube placement (for drainage and identification of the offending organism) to mastoidectomy and drainage for more extensive disease progression.

Disposition

Hospitalization is usually necessary for the administration of IV antibiotics. Early otolaryngologic referral is also recommended for possible aspiration and drainage of the middle ear, as well as the management of any potential complications.

SUDDEN HEARING LOSS

Principles

Sudden sensorineural hearing loss (SSNHL), defined as the idiopathic loss of hearing of 30 dB over at least three test frequencies occurring over a period of less than 3 days, is considered an otolaryngologic emergency. Any age group can be affected, but the peak incidence occurs in the fifth or sixth decade of life, with an equal gender distribution. The overall incidence ranges from 5 to 20/100,000 people/year. Its severity ranges from difficulty with conversation to complete hearing loss.

SSNHL is idiopathic in 70% of cases, infectious in 13%, and related to otologic disease, trauma, vascular disease, hematologic disorders, or neoplasm in the vast majority of other cases.[23] A delay in diagnosis is common because the patient may report ear fullness that is often attributed to cerumen impaction or congestion from upper respiratory infections. Tinnitus is a common finding. The likelihood of recovery is related to the severity of the hearing loss, age of the patient, and associated vestibular symptoms. A history should include the time of onset, history of trauma or recent illnesses, medications, and presence of otologic and neurologic symptoms.

Clinical Features

The physical examination includes a thorough inspection of the external canal and TM integrity.

Differential Diagnoses

The differential for hearing loss is broad and can be differentiated into causes that involve the outer, middle, or inner ear. Outer ear causes include cerumen impaction and OE. Middle ear causes include otitis media and tympanic membrane perforation. Inner ear causes include medications, barotrauma, and autoimmune disease.

Diagnostic Testing

Weber's test for hearing and Rinne's test may help in distinguishing conductive versus sensorineural deficits. A comprehensive neurologic examination, including cranial nerve and cerebellar testing, may localize brainstem involvement. Laboratory testing and CT scanning are not indicated in the ED evaluation unless the physical examination points to a space-occupying lesion (ie, focal neurologic deficits not referable to the ear). MRI of the brain with gadolinium is the study of choice to identify retrocochlear pathology but should be performed in consultation with an otolaryngologist.

Management

A tapered dose of oral steroids is the most common treatment, although their efficacy is unproven. The dose is 1 mg/kg, up to 60 mg, tapered over 10 to 14 days.[24] Additional treatments have included intratympanic steroids, hyperbaric oxygen, antiviral therapy, zinc,[25] vasoactive and hemodilution therapies, dextran, and magnesium, all with mixed results. Given the lack of treatment options for this condition, we recommend that a steroid taper be offered.

Disposition

Patients should get expeditious ENT referral on discharge from the ED.

EPISTAXIS

Principles

Epistaxis is a common otolaryngologic problem, with 60% of people experiencing it in their lifetime, although only 6% require medical treatment.[26] It accounts for about 1 in 200 emergency room visits,[27] with less than 0.2% ultimately requiring hospitalization.[28] There is a bimodal distribution of children younger than 10 years and adults older than 50 years. Epistaxis is more common in colder seasons and in northern climates because of decreased humidity and subsequent drying of the nasal mucosa.[29] Nasal bleeding is a frightening condition for patients but is seldom life-threatening. A solid understanding of physiology and treatment allows for prompt and efficient management of the disorder.

Anterior epistaxis accounts for 90% of all nosebleeds and usually involves Kiesselbach's plexus on the anteroinferior nasal septum. Epistaxis is unilateral and can be controlled with anterior packing. Accounting for 10% of nosebleeds, and usually arising from a posterior branch of the sphenopalatine artery, posterior epistaxis differs from anterior bleeding in that it is more severe and occurs mostly in older adults with multiple comorbidities.[30]

Three arteries with anastomoses between them supply the nasal area. The sphenopalatine artery supplies the turbinates and

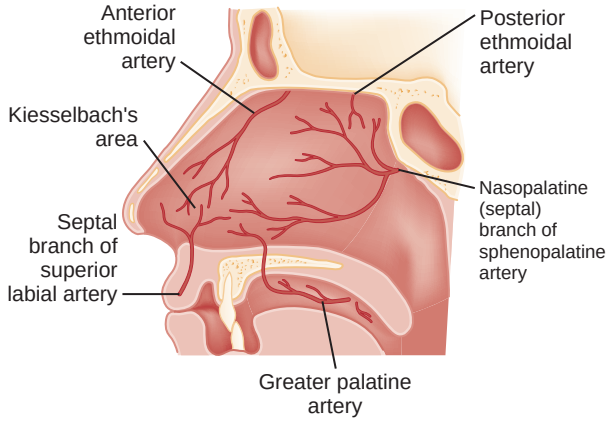


Fig. 62.2. Arterial supply to the medial wall of the nose.

meatus laterally and the posterior and inferior septum medially. The anterior and posterior ethmoidal arteries from the ophthalmic branch of the internal carotid artery supply the superior mucosa medially and laterally. The superior labial branch of the facial artery provides circulation to the anterior mucosal septum and anterior lateral mucosa (Fig. 62.2).

There are many reasons for epistaxis, but the most common are an upper respiratory infection with concomitant mucosal congestion and vasodilation and trauma, either accidental or iatrogenic (ie, nose picking; Box 62.1).

Clinical Features

A past medical history with particular emphasis on trauma, medical conditions, and medications that could cause epistaxis should be elicited. Patients often are anxious and hypertensive. An elevated blood pressure is usually from stress and anxiety and resolves with treatment. Hypertension has never been shown to cause epistaxis, although it can worsen the bleeding when present.[31] Sedation with a benzodiazepine or narcotic may help these patients.

Differential Diagnosis

The differential diagnosis includes nasal trauma, infections, nasal foreign bodies, and bleeding disorders.

Diagnostic Testing

Identifying the source of the bleeding is often difficult. If the nose is actively bleeding, the patient should clear clots by blowing the nose and then applying bilateral pressure on the nasal septum by compressing the cartilaginous part of the nose for 10 to 15 minutes. Spraying oxymetazoline into each nare twice before applying pressure will optimize hemostasis and facilitate inspection after the pressure is released. This simple maneuver also educates the patient on how to self-manage further episodes. It is important to optimize the examination. The floor of the nose should be parallel to the room floor. If the head is tilted, only the anterior and upper aspect of the nares can be visualized. The nasal speculum should be opened in a vertical direction rather than side to side in the nares, so as not to obscure the septum, which is the area of greatest interest. During this time, materials for illumination, suction, visualization, and treatment should be assembled. Discharge without identification and treatment of the bleeding site often results in recurrences. Anterior clots may give the appearance of posterior epistaxis if the blood runs posteriorly. Persistent bleeding should be controlled with pledgets soaked in cocaine, lidocaine-epinephrine, or oxymetazoline to promote vasoconstriction and anesthesia. Routine laboratory testing is usually unnecessary unless the patient is anticoagulated or has an underlying condition.

BOX 62.1

Causes of Epistaxis

LOCAL CAUSES
Nasal or facial trauma
Upper respiratory tract infections
Nose picking
Allergies
Low home humidity
Nasal polyps
Foreign body in the nose
Environmental irritants
Nasopharyngeal mucormycosis
Traumatic internal carotid artery aneurysm
Chlamydial rhinitis neonatorum
Neoplasms
Septal deviation
Surgery (postoperative epistaxis)

IDIOPATHIC EPISTAXIS
Habitual
Familial

SYSTEMIC CAUSES
Atherosclerosis of nasal blood vessels
Anticoagulant therapy
Pregnancy
Barotrauma
Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)
Blood dyscrasias (eg, hemophilia, leukemia, lymphoma, polycythemia vera, anemias, idiopathic thrombocytopenic purpura, granulocytosis, inherited platelet disorders, acquired platelet disorders [ie, aspirin use])
Hepatic disease
Rupture of internal carotid artery aneurysm
Diabetes mellitus
Alcoholism
Vitamin K deficiency
Folic acid deficiency
Chronic nephritis
Chemotherapy
Blood transfusion reactions
Migraine headache
Chronic use of nasal vasoconstrictors
Cocaine use
Drug induced thrombocytopenia

Management

Identify and treat the source of bleeding, because the most significant risk factor for recurrent bleeding is not identifying the bleeding point.[32] Application of silver nitrate chemically cauterizes the area but is often unsuccessful during active bleeding, so hemostasis should be secured first. With 4 to 5 seconds of application, nitric acid is formed and coagulates tissue. Coagulation should never be maintained longer than 15 seconds because septal damage may occur. The area should be cauterized from the periphery to the center and superiorly to inferiorly to avoid blood, which renders the silver nitrate sticks ineffectual. Bilateral application of silver nitrate to the septum is not advised because it may deprive the septum of a blood supply and theoretically could lead to necrosis.

If cautery is unsuccessful, topical thrombogenic agents, such as absorbable gelatin sponge (Gelfoam) and absorbable knitted fabric (Surgicel), can be tried. Tranexamic acid may be an option if bleeding continues. Tranexamic acid works by irreversibly binding and blocking the lysine binding sites on plasminogen molecules, resulting in inhibition of plasminogen activator and fibrinolysis. It has also been successfully used in 109 patients and resulted in much quicker resolution of bleeding and faster ED discharge when compared to nasal packing.[33] The injectable solution (500 mg in 5 mL) is applied to a 15-cm nasal pledget and applied to the anterior nares.[33]

If bleeding persists, the next step is the use of a nasal tampon. Nasal tampons work by three mechanisms: direct pressure, decreased bleeding from mucosal irritation from the foreign body, and indirect pressure from further surrounding clot formation. Cutting them to fit the contour of the nares and lubricating them with an antibiotic ointment makes the application easier. For large noses, a second tampon may be required. Occasionally, for uncontrolled bleeding despite the presence of a tampon, a second tampon should be inserted into the opposite nare. If bleeding still continues, a nasal balloon catheter with fibrin colloid material, such as Rapid Rhino (Smith & Nephew, Austin, TX), may be used. These devices are moistened with saline, so lubricants are unnecessary. They are placed in the floor of the nose and inflated with air. The fibrin colloid forms a hemostatic dressing. A second balloon in the opposite nose may be required if one side is unsuccessful.

Toxic shock syndrome (TSS) due to *S. aureus* has been reported in patients with nasal packing. Although many providers prophylactically give antibiotics after nasal packing, no study has shown that antibiotics are preventive for TSS or sinusitis, and the incidence of TSS is rare (16/100,000 population). We do not recommend routine antibiotic prophylaxis after nasal packing. Packing is uncomfortable and the patient may require opioids in the ED and on discharge. The packs are left in for 48 hours to minimize rebleeding and removed at 48 hours to avoid tissue necrosis associated with prolonged placement.

Posterior epistaxis is suggested when bleeding occurs with a properly placed anterior nasal pack. In this case, a posterior pack is necessary with a Foley catheter or commercially available balloon. A standard Foley catheter may be inserted into the nasopharynx, partially inflated with 5 to 7 mL of water, and then pulled anteriorly, creating pressure posteriorly with an additional 5 to 7 mL of water added to the balloon, but caution should be exercised to avoid pressure necrosis. Water, rather than saline, should be used because saline can crystallize and cause problems with balloon deflation. Vaseline gauze should be packed firmly around the catheter anteriorly. Fig. 62.3 shows how the Foley catheter is placed.

The commercially available devices have anterior and posterior balloons. Similar to Foley placement, the device is placed into the nose, inflated, and pulled anteriorly. Once seated, the anterior balloon should be slowly inflated to the point that the patient can tolerate.

If these techniques do not provide successful control, otolaryngologic consultation is necessary. Surgical ligation has been the treatment of choice for intractable bleeding but endovascular embolization has emerged as a treatment alternative. The decision to choose surgery over embolization is influenced by factors such as patient comorbidity, presence of anticoagulation, institutional experience, patient preference, and health care costs.[27,34,35] Transnasal endoscopic surgery has advantages in that it visualizes bleeding location, improves the diagnosis of other causes, and is associated with lower health care costs and complications such as blindness. The advantages of embolization include avoiding general anesthesia, improving the diagnosis of vascular pathology, and causing less trauma to the nasal mucosa.[30] In one national survey, patients who underwent endovascular embolization had higher rates of head and neck cancer, hereditary hemorrhagic telangiectasia, and arteriovenous malformation compared with patients who underwent surgical ligation.[34]

Disposition

There has been concern that patients with posterior nasal packs may develop hypoxia as a result of a nasopulmonary reflex. However, there is little evidence to support this theory.[36] Adverse respiratory events are due to a combination of factors such as sedation, underlying cardiovascular or pulmonary disease, and severe obstructive sleep apnea.[37] Most patients with posterior nasal packing can be admitted to a setting with continuous pulse oximetry, but patients with serious comorbidities such as heart disease or obstructive sleep apnea may require a higher level of care.[38]

SIALOLITHIASIS

Stones of the salivary glands occur in 1% of the population. They are usually found in those between 30 and 50 years of age. The most common gland affected is the submandibular (submaxillary) gland, accounting for 80% to 95% of cases. Stones are found less commonly in the sublingual and parotid glands. Sialolithiasis is uncommon in children, occurring in only 3% to 5% of the population.[37]

The exact causative mechanism is unclear, but sialolithiasis is thought to be due to increased viscosity of the saliva and the long upward curvature of the submandibular (Wharton's) duct. Stasis and inflammation result in precipitation of calcified stones after a nidus of a complex glycoprotein combines with calcium and phosphate. Risk factors include dehydration, diuretic or anticholinergic medications, trauma, gout, and a history of smoking.[39]

Clinical Features

Leading to swelling and pain, obstruction by a sialolith is usually associated with mealtime, when salivary secretion is enhanced.[40] Patients generally present with pain, swelling, and tenderness of the gland. If the gland is infected, the patient may have systemic symptoms, such as fever or chills. The area may be erythematous, with purulence coming from the duct, a condition termed *sialadenitis*.[41] *S. aureus, Streptococcus viridans, S. pneumoniae,* and *H. influenzae* predominate in bacterial infections. Children differ in that they have a shorter duration of symptoms, and their stones present more distally in ducts than those found in adults.[37]

Differential Diagnosis

The differential diagnosis includes salivary gland pathology, lymph node disease, granulomatous process, soft tissue mass, and neoplastic lesion.

Diagnostic Testing

CT without contrast is very sensitive for calculi of all sizes and remains the gold standard, although there is the associated risk of ionizing radiation. Although there have been reports of ultrasonography recognizing up to 90% of stones larger than 2 mm, it does not allow reliable exclusion of small salivary calculi.[42] Both modalities may help identify other causes of inflammation, such as an abscess or cellulitis.

Management

If the stone is palpable, gently massage the gland in an attempt to extract the stone. Additional measures include sialogogues (tart

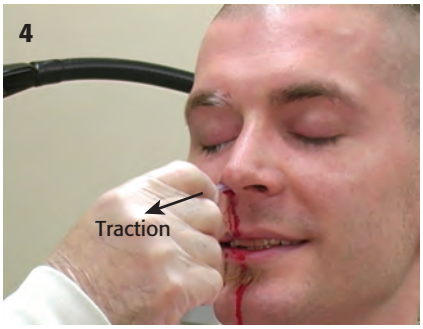
EPISTAXIS MANAGEMENT: POSTERIOR PACKING WITH INFLATABLE DEVICES

A

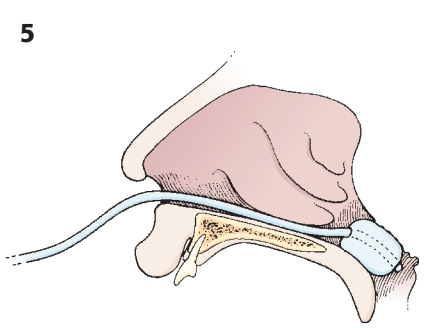
Insert a 12-Fr Foley catheter through the naris and into the posterior pharynx.

Look into the mouth to confirm that the catheter is properly positioned.

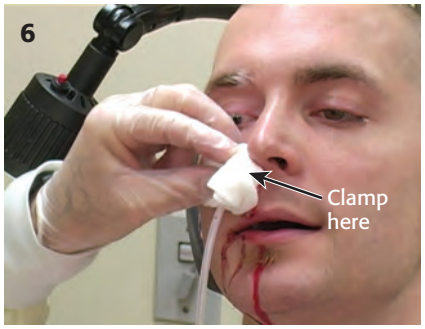
Inflate the balloon halfway with about 5–7 mL of water.



Slowly pull the catheter into the posterior nasopharynx up against the posterior aspect of the middle turbinate.

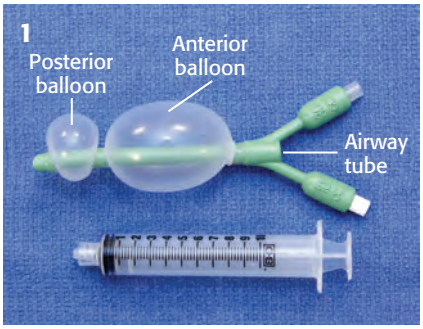


Foley catheter in proper position in the posterior nasopharynx. Inflate the balloon with another 5–7 mL of water.

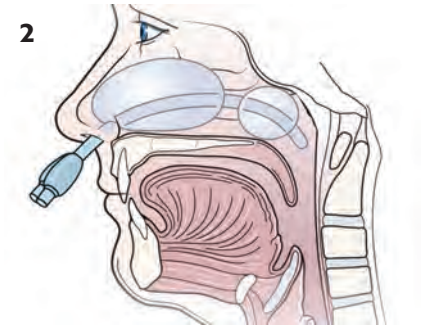


While maintaining traction, place anterior packing with layered gauze. Packing of the opposite side may be required to prevent septal deviation. Place a piece of gauze on the exposed catheter and secure with an umbilical clamp.

B



Double-balloon epistaxis catheters have both an anterior and posterior balloon, and some have an integral airway tube. These devices serve as an anterior and posterior pack. They are easily inserted and are often successful in the temporary control of posterior epistaxis in the ED.



Insert the lubricated device along the nasal floor as far back as possible. Inflate the posterior balloon halfway with air, apply traction to pull the balloon up against the middle turbinate, and then complete the inflation. Maintain the position of the balloon and then inflate the anterior balloon with 30 mL of air.

This patient with posterior epistaxis was successfully treated in the ED and discharged. Historically, most patients with posterior packs were admitted to the hospital; however, the ease and safety of balloon devices allow selected patients to be treated as outpatients. Consider admission for older adults and those with pulmonary or cardiovascular disease.

Fig. 62.3. Management of epistaxis—posterior packing with inflatable devices. **A,** Foley catheter technique. **B,** Dual-balloon tamponade catheter. (Adapted from Riviello RJ: Otolaryngologic procedures. In Roberts JR: Roberts and Hedges' clinical procedures in emergency medicine, Philadelphia, 2013, Elsevier/Saunders, p 1330.)

hard candies to promote glandular secretions), analgesia with antiinflammatory medications, or opioids. When infection is present, antibiotics covering the affected organisms, such as cephalexin, 500 mg qid, or clindamycin, 450 mg tid (in the penicillin-allergic patient), are appropriate.

Disposition

Stones larger than 5 mm or stones located within the gland or in the proximal duct are often resistant to conservative measures. These may require surgical or minimal invasive treatment by an otolaryngologist or oral surgeon.[43]

NECK MASSES

Principles

Neck masses are a relatively common clinical finding, with a multitude of causes. The differential diagnosis can generally be broken down into three categories—inflammatory, congenital, or neoplastic. Children and young adults are more likely to have benign disorders, such as inflammatory or congenital abnormalities, including thyroglossal or branchial cleft cysts. Adult neck masses are more likely to be neoplastic. In general, 80% of nonthyroid neck masses in adults are neoplastic, of which 80% are malignant. In children, however, more than 80% of neck masses are benign. This is often referred to as the rule of 80, or the 80% rule. Risk factors that may predispose patients to ENT malignancies include alcohol and tobacco use, viruses such as herpes, genetics, diet, and excessive exposures to ultraviolet sunlight, dust, or chemicals.

Identifying the parotid and submandibular glands, thyroid cartilage, thyroid gland, and lymph nodes can help distinguish normal structures from other masses (Fig. 62.4). The neck is divided into cervical triangles, with the sternocleidomastoid muscle as the common boundary. The anterior portion is bordered by the midline of the neck, inferior aspect of the mandible superiorly, and anterior border of the neck posteriorly. Lesions of the skin, scalp, oral cavity, oropharynx, hypopharynx, larynx, and tongue may manifest here. The posterior triangle is bordered by the sternocleidomastoid anteriorly, posteriorly by the trapezius muscle, and inferiorly by the clavicle. Lesions in this area may include those from the nasopharynx and metastatic lesions from the lung and gastrointestinal and genitourinary tracts.

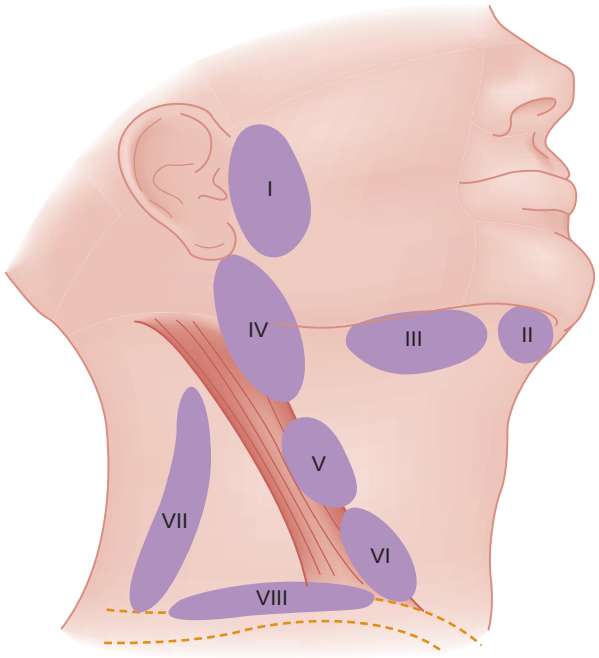


Fig. 62.4. Major lymph node groups in the head and neck. *I,* Parotid nodes; *II,* submental nodes; *III,* submandibular nodes; *IV,* jugulodigastric nodes (superior jugular nodes); *V,* midjugular nodes; *VI,* lower jugular nodes; *VII,* spinal accessory nodes; *VIII,* subclavian nodes. Groups VI and VII are often termed *scalene nodes*. (Adapted from Moloy PJ: How to [and how not to] manage the patient with lump in the neck. In American Academy of Otolaryngology–Head and Neck Surgery Foundation: Common problems of the head and neck region, Philadelphia, 1995, WB Saunders, p 134.)

Clinical Features

Important associated symptoms include dysphagia, odynophagia, otalgia, stridor, speech disorders, and globus phenomena. Dysphagia, or difficulty swallowing, may be caused by physical obstruction or neurologic disorders. Odynophagia is pain on swallowing and can have a number of causes, such as tonsillitis or carcinoma of the pharynx. In an adult, a sore throat that lasts for several weeks should raise the suspicion of a neoplastic process. Otalgia is pain felt in the ear that may be referred from the larynx, pharynx, or cranial nerves V, IX, or X. Referred ear pain is an ominous sign in adults and should be presumed to be cancer until proved otherwise. Similarly, unilateral OME in adults should be considered nasopharyngeal carcinoma until proven otherwise.

Stridor, specifically inspiratory stridor, is diagnostic of upper airway obstruction. It localizes a lesion to above or at the level of the larynx. In adults, the presence of stridor with a neck mass increases the possibility of carcinoma. Speech disorders, particularly so-called hot potato speech, are suggestive of space-occupying lesions above the oropharynx, such as a peritonsillar abscess. Globus is the symptom of having a lump in the throat. It has occurred in almost everyone at one time or another, is localized to the pharynx, and is often a functional complaint. Hoarseness is a fairly common complaint, with a myriad of causes ranging from viral pharyngitis to laryngeal cancer. Also, similar to the term *dizziness,* the term *hoarseness* has many descriptions, including breathiness, muffling, harshness, scratchiness, and unnatural deepening of the voice. Hoarseness lasting longer than 2 weeks should be investigated further. Additional history about the location of the mass, rate of growth, presence of pain, and constitutional symptoms, such as fever, night sweats, and weight loss, are also helpful.

The head and neck examination may identify masses, lesions, mucosal ulcerations or discolorations, and cranial nerve abnormalities. The mass itself should be palpated for location, size, and consistency. Benign lymph nodes are generally mobile, soft, fleshy, and smaller than 1 to 1.5 cm, so any hard nodes larger than 1.5 cm with decreased mobility should be considered abnormal and as warning signs of malignancy.

Differential Diagnoses

Box 62.2 lists common possibilities for the differential diagnosis of neck masses.

Diagnostic Testing

The diagnostic strategy is tailored to results of the history and physical examination. Patients with hoarseness lasting longer than 2 weeks should be referred to an otolaryngologist for a flexible endoscopic examination unless they have developed acute stridor, dyspnea, or sense of acute deterioration. These patients should have otolaryngologic consultation in the ED, and most will need flexible endoscopic examination of the upper airway. In the ED, chest radiography is an initial test to identify possible lung pathology as a source. CT of the neck with contrast is the initial study of choice to delineate significant neck masses better.

BOX 62.2

Differential Diagnosis of Neck Masses

INFLAMMATORY
Adenitis
Bacterial (*Streptococcus, Staphylococcus*)
Viral (HIV, EBV, HSV)
Fungal (coccidioidomycosis)
Parasitic (toxoplasmosis)
Cat scratch disease
Tularemia
Local cutaneous infections
Sialoadenitis (parotid and submaxillary glands)
Thyroiditis
Mycobacterium avium-intracellulare
Mycobacterium tuberculosis

CONGENITAL OR DEVELOPMENTAL
Brachial cleft cyst
Thyroglossal duct cyst
Dermoid cyst
Cystic hydromas
Torticollis
Thymic masses
Teratomas
Ranula
Lymphangioma
Laryngocele

NEOPLASTIC
Benign
Mesenchymal tumors (eg, lipoma, fibroma, neural tumor)
Salivary gland masses
Vascular abnormalities (eg, hemangioma, AVM, lymphangioma, aneurysm)

Malignant
Primary tumors
Sarcoma
Salivary gland tumor
Thyroid or parathyroid tumors
Lymphoma

Metastasis
From primary head and neck tumors
From infraclavicular primary tumors (eg, lung or esophageal cancer)

AVM, Arteriovenous malformation; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus.

Management and Disposition

Most masses in children are inflammatory. Thus, it is a reasonable strategy to start the patient on antibiotics, with a 2-week follow-up. If inflammation is thought to be the cause of the neck mass in an adult, a similar strategy can be used. However, adults need ENT referral if the mass does not resolve in 2 weeks, is enlarging or fixed, or is associated with matted cervical lymph nodes, or if the masses are noted in the parotid or thyroid gland.

KEY CONCEPTS

- Most cases of AOM resolve spontaneously. Nontoxic children from 6 months to 2 years of age with unilateral AOM and those older than 2 years with unilateral or bilateral AOM may be observed for 3 days to determine whether antibiotics are required. When indicated, amoxicillin is the initial choice for treatment of AOM, 80 to 90 mg/kg per day.
- Otitis externa is treated with topical antibiotic drops. Only fluoroquinolone drops are FDA-approved for use when a tympanic perforation may be present. Necrotizing OE should be considered in immunocompromised patients who have persistent otitis externa.
- Patients with epistaxis with posterior nasal packing should be admitted to the hospital.
- Bullous myringitis is caused by the usual organisms that cause otitis media.
- Adult patients with AOM should be treated with amoxicillin, 500 mg tid.
- The diagnosis of AOM is made by a bulging TM and signs and symptoms of acute infection.
- Acute hearing loss is most often idiopathic. A 10- to 14-day steroid taper is usually prescribed but is not known to provide benefit.
- Hoarseness or an unexplained neck mass that persists for longer than 2 weeks requires ENT referral.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 62: QUESTIONS & ANSWERS

62.1. Which of the following clinical symptoms is most useful in diagnosing acute otitis media (OM)?
- **A.** Cough
- **B.** Decreased appetite
- **C.** Ear pain
- **D.** Fever
- **E.** Vomiting

Answer: C. Although all the symptoms of acute OM are nonspecific, ear pain appears to be the most useful.

62.2. A 56-year-old man presents with sudden onset of hearing loss in his left ear. He also complains of tinnitus. His neurologic examination is otherwise unremarkable. What should be the next step in the patient's management?
- **A.** Consult a neurologist.
- **B.** Consult an otolaryngologist.
- **C.** Obtain a head computed tomography (CT) scan.
- **D.** Obtain a magnetic resonance imaging (MRI) scan with gadolinium.
- **E.** Start a steroid taper.

Answer: B. Sudden sensorineural hearing within 72 hours is considered an otolaryngologic emergency. The evaluation and potential treatment options, including steroids, hyperbaric oxygen, and antiviral agents, are best performed in consultation with an otolaryngologist.

62.3. A 30-year-old woman presents with onset of a severe right posterior occipital headache and low-grade fever. Her physical examination reveals an area of erythema and swelling posterior to the right ear and a nonmobile tympanic membrane in that ear. What is the most appropriate next diagnostic step?
- **A.** ENT referral STAT to the operating room (OR)
- **B.** CT scan
- **C.** Lumbar puncture
- **D.** MRI with gadolinium
- **E.** No further diagnostic evaluation necessary

Answer: B. Clinical findings in acute mastoiditis may include fever, headache, otalgia, and posterior auricular erythema and tenderness. Although there are no specific diagnostic criteria, an initial step would be a CT scan to identify mastoid inflammation and possible bony erosion. MRI would be indicated if there is concern for intracranial extension.

62.4. All the following are implicated as risk factors in OM except:
- **A.** Children with cleft palate
- **B.** Daycare attendance
- **C.** Female gender
- **D.** Immunocompromised patient
- **E.** Parental smoking

Answer: C. Male gender appears to be a risk factor for middle ear disease, as well as daycare attendance, parental smoking, immunocompromised patients, and children with anatomic abnormalities such as cleft palate or Down syndrome. Breast-feeding appears to be protective.

62.5. An 18-month-old boy returns to the emergency department (ED) 4 days after being diagnosed with left OM. He was prescribed amoxicillin, 90 mg/kg/day, and the parents reported compliance. He has continued ear tugging, fever, and irritability. He is tolerating PO nutrition with no vomiting or diarrhea. Physical examination reveals an alert crying male with oral temperature 101.5°F, heart rate 136 beats/min, and respiratory rate 24 breaths/min. His physical examination is otherwise negative except for severe erythema of the left tympanic membrane, with obscure landmarks and loss of mobility. What is the most appropriate next step in this patient's management?

A. Admit for intravenous antibiotics.
B. Change therapy to an oral cephalosporin.
C. Draw blood cultures and continue current amoxicillin regimen.
D. Intramuscular ceftriaxone is given.
E. Lumbar puncture is performed.

Answer: D. Otitis media treatment failures at 3 days should receive intramuscular ceftriaxone. Continued use of a failing regimen would not be indicated. The child exhibits no signs or symptoms warranting a lumbar puncture and no immediate criteria for hospital admission.

62.6. A 13-year-old diabetic girl presents with left otalgia, left facial palsy, and fever. Physical examination reveals a left peripheral seventh nerve palsy, intense left otitis externa, diffuse tenderness of the pinna, and mild weakness of the left trapezius muscle. What is the most likely diagnosis?

A. Acute mastoiditis
B. Left temporal brain abscess resulting from left-sided otitis
C. Malignant otitis externa
D. Meningitis
E. Sigmoid sinus thrombosis

Answer: C. Necrotizing (malignant) otitis externa is a result of chronic otitis externa often seen in immunocompromised patients. The facial nerve is the cranial nerve usually affected, but the glossopharyngeal, vagal, accessory, abducens, and trigeminal nerves may also be involved. When otoscopic view permits, granulation tissue in the floor of the external canal at the bone–cartilage junction is characteristic. CT is the imaging technique of choice and is able to indicate bony erosions and abscess formation. Ciprofloxacin is the antibiotic of choice. All the other choices are recognized complications.

62.7. The management of anterior and posterior epistaxis is similar regarding which of the following?

A. Antibiotic requirements after packing
B. Duration of packing
C. Indications for hospitalization
D. Surveillance for secondary complications
E. Value of topical cauterization

Answer: C. Strong evidence for postpacking of antibiotics are lacking in both situations. Anterior packs are left in place for approximately 48 hours, whereas posterior packs may require 3 to 5 days. Patients requiring posterior nasal packs for epistaxis typically need hospitalization for supplemental oxygen and surveillance for pack expulsion with rebleeding, dysrhythmias, bradycardia, aspiration, and stroke.

62.8. Which of the following statements is true regarding inspiratory stridor?

A. It implies a palatal or uveal obstruction.
B. It is diagnostic of tracheal pathology.
C. It is typically accompanied by hoarseness.
D. It localizes a lesion at or above the vocal cord.
E. It may be seen with extremely severe asthma exacerbations.

Answer: D. Inspiratory respiratory distress (stridor) implies an extrathoracic flow obstruction. This may be laryngeal, epiglottis, or pharyngeal. Asthma, emphysema, and aspirated foreign bodies all have expiratory airflow limitations. Inspiratory stridor may or may not directly involve the larynx and may not be accompanied by hoarseness.

CHAPTER 63

Asthma

Richard M. Nowak | Glenn F. Tokarski

PRINCIPLES

Background and Importance

The word *asthma*, derived from the Greek ασυμα, signifies panting and was used initially as a synonym for "breathlessness." In 1698, Floyer published *A Treatise of the Asthma,* in which he attempted to differentiate asthma more clearly from other pulmonary disorders. Subsequent definitions of asthma highlight concepts of airway hyperresponsiveness, bronchospasm, reversible airway obstruction, and inflammation, emphasizing the many facets of this complex disease.

Asthma is a chronic respiratory disease characterized by periods of variable and recurring symptoms, airflow obstruction, and bronchial hyperresponsiveness that manifests clinically as attacks of impaired breathing.[1,2] Asthma is an inflammatory disease; repetitive episodes of acute superimposed on chronic airway inflammation are responsible for alterations in airway function and result in irreversible structural airway changes. Control of asthma symptoms ultimately depends on ameliorating airway inflammation. Genetic, social, physiologic, and environmental factors influence the expression and control of asthma symptoms. Asthma is thus a complex interaction of the immune system, the environment, and genetic predispositions, which combine to alter airway structure and function. Successful emergency department (ED) management of asthma must address the multiple factors that result in airway dysfunction.

In 2013, it was estimated that 39.5 million Americans had been diagnosed with asthma by a health professional within their lifetime.[3] Asthma is more prevalent in children than adults, in females than males, and in African Americans than whites or Hispanics (Fig. 63.1).[4] In the United States, asthma is more prevalent in impoverished and obese persons, cigarette smokers, and those residing in nonmetropolitan locales (Fig. 63.2).[5] The northeastern states have the highest asthma prevalence.[6]

African American adults had an ED visit rate nearly twice that of whites and a hospitalization rate 2.3 times greater (Fig. 63.3). Over 3500 deaths due to asthma were reported in 2013 in the United States.[7] The female death rate from asthma was 1.03 times higher than males. African Americans were two to three times more likely to die from asthma than whites, Hispanics, and other races. Decreases in asthma death rates have been noted from 1999 to 2010 (Fig. 63.4). The highest death rate is reported among adults 65 years old and older and the lowest among children 0 to 4 years old.

The estimated financial burden of asthma totaled $56 billion in the United States in 2013 with approximately 89% attributable to direct costs (hospital care and physician services).[5] In 2008, asthma accounted for an estimated 14.2 million lost work days and 10.5 million lost school days.[3]

Developed nations have higher rates of asthma, which suggests that urbanization and westernization are correlated with increased asthma prevalence. Migrants who move from an area of low asthma prevalence to an area of high asthma prevalence assume increased asthma prevalence, suggesting that environmental factors play a role. Urban areas in the United States (New York City, Los Angeles, and Chicago) have high mortality rates associated with asthma, indicating that poverty and lack of access to medical care may also be major determinants of asthma complications.

Factors that contribute to asthma morbidity and mortality include under-treatment; of acute episodes by emergency clinicians; overuse of prescribed or over-the-counter medications leading to delays in seeking treatment; failure of emergency clinicians to consider previous ED visits, hospitalizations, or life-threatening episodes of asthma; and failure to initiate corticosteroid therapy early in the course of an exacerbation. Cost of asthma care is a barrier to asthma management; African American and Hispanic adults identify costs related to seeking asthma care with a primary care physician and/or an asthma specialist and the cost of asthma medications are significant impediments.[8] Over-reliance on emergency facilities for all asthma care and lack of access or compliance with ongoing asthma care are other important factors contributing to morbidity and mortality from asthma.

Anatomy and Physiology

Asthma is a complex immunologically mediated condition involving a variety of cellular and airway alterations; airway inflammation and remodeling are the final common pathways that result in bronchospasm and limitation of airflow.

Compared with healthy individuals, patients with asthma show bronchial hyperreactivity (hyperresponsiveness) in response to various environmental and infectious stimuli (eg, methacholine). Allergens (eg, environmental, viruses, occupational) and non-allergic stimuli (eg, exercise, aspirin-induced and menstrual-related asthma) induce bronchoconstriction via release of mediators and metabolic products from inflammatory cells. Edema, inflammation, mucus production, and airway smooth muscle hypertrophy result in bronchoconstriction, airway obstruction, and airflow limitation. Recurrent episodes of airway inflammation result in permanent structural airway remodeling that also contributes to airway obstruction and hyperresponsiveness and decreases in the response to therapy.

Necropsies of patients with fatal asthma reveal grossly inflated lungs that may fail to collapse on opening of the pleural cavities. Histologic examination reveals luminal plugs consisting of inflammatory cells, desquamated epithelial cells, and mucus. Marked thickening of the airway basement membrane, submucosal inflammatory cells, increased deposition of connective tissue,

mucous gland hyperplasia, and hypertrophy of airway smooth muscle are also observed. Reports of slow-onset asthma fatalities reveal greater bronchial eosinophilia and basement membrane thickening when compared with rapid-onset fatal asthma. Reports of rapid-onset fatal asthma describe a greater number of degranulated mast cells and less mucus in the airway lumens, suggesting that terminal events may be dominated by bronchoconstriction without excessive luminal plugging.

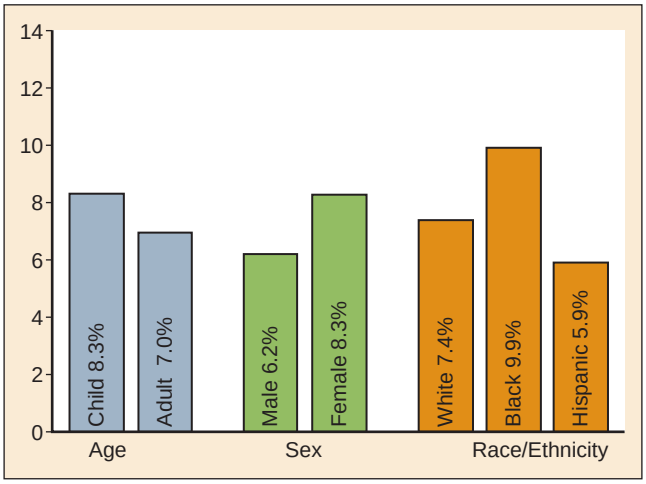

Fig. 63.1. Asthma prevalence percentages in 2013 by age, sex, and race/ethnicity in the United States. (From Centers for Disease Control and Prevention: Asthma: data, statistics, and surveillance. Available at www.cdc.gov/asthma/asthmadata.htm.)

Pathophysiology

Evidence that inflammation is a component of asthma physiology was initially derived from autopsy findings in patients with fatal asthma. The airways revealed infiltration by neutrophils, eosinophils, and mast cells and the presence of subbasement membrane thickening, loss of epithelial cell integrity, goblet cell hyperplasia, and mucous plugs. Ante mortem bronchial biopsy findings in patients with even mild degrees of asthma also demonstrate inflammatory changes in the central and peripheral airways that correlate with disease severity. Inflammatory and chemotactic cytokines produced by both resident airway and recruited inflammatory cells are identified in bronchoalveolar lavage washings and pulmonary secretions.

Asthma has been divided into allergic and non-allergic types based on the presence or absence of immunoglobulin E (IgE) antibodies to common environmental antigens (pollen, dander, mites) and microbiologic antigens (bacteria, viruses). Exposure to microbes and allergens during childbirth, infancy, and childhood may confer a protective effect against atopy and suppress expression of the asthma phenotype later in life (known as the *hygiene hypothesis*).[9] Regardless of the asthma type, a common feature is the presence of airway T-helper cells that release cytokines (eg, interleukin [IL]-4, IL-5, and IL-13) that stimulate basophil, eosinophil, mast cell, and leukocyte migration to the airways and enhance IgE production. The result is amplification of the airway

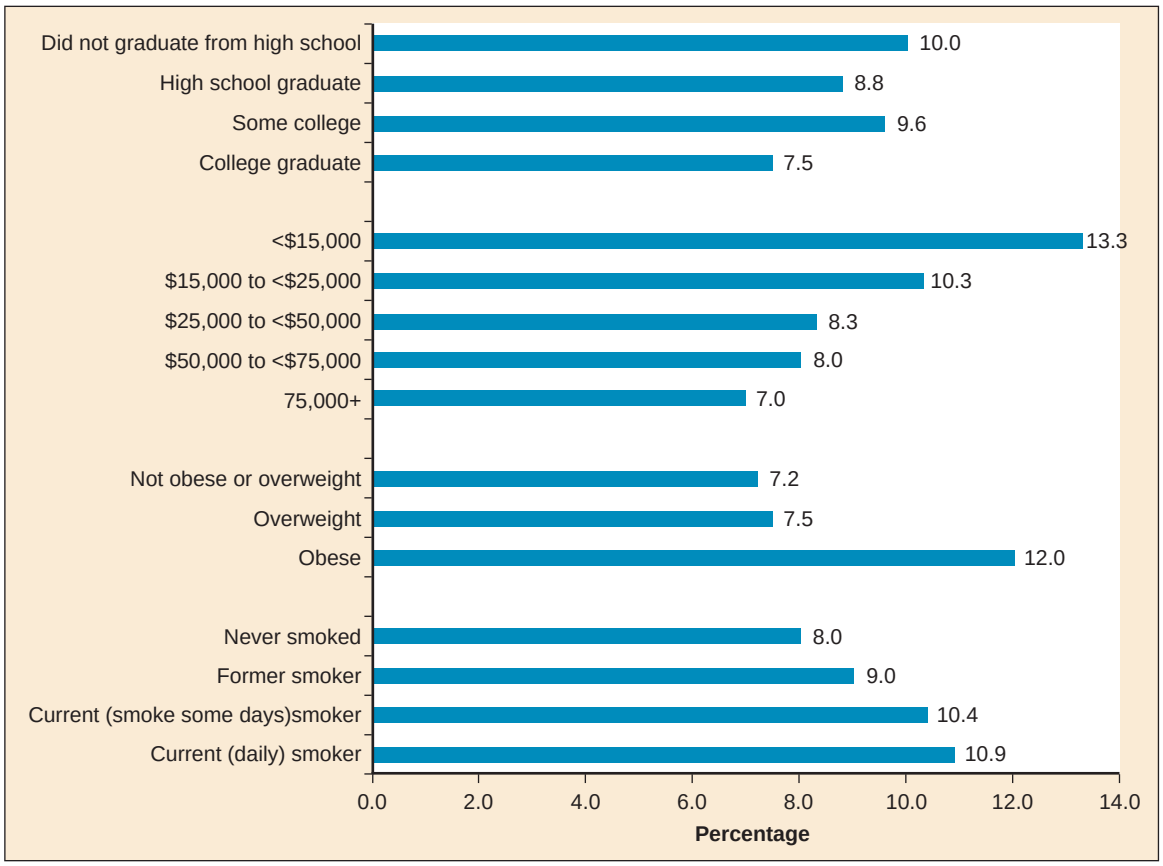

Fig. 63.2. Adult asthma prevalence percent in 2010 by education, income, and behavioral risk factors. (From Centers for Disease Control and Prevention: Asthma facts: CDC's National Asthma Control Program Grantees. Available at www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf.)

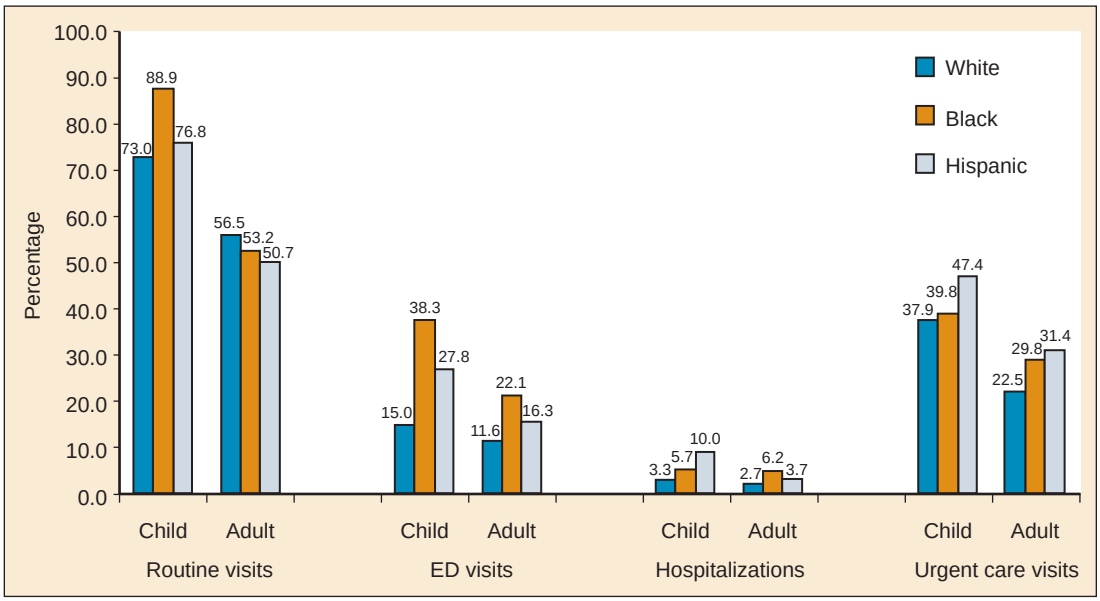

Fig. 63.3. Asthma health care utilization among children and adults with current asthma by race and ethnicity in 2010. White and black categories are non-Hispanic. Thirty-three National Asthma Control Program (NACP) grantees completed Asthma Call-Back Survey (ACBS) for adults and 16 NACP grantees completed the ACBS for children. *ED,* Emergency department. (From Centers for Disease Control and Prevention: Asthma facts: CDC's National Asthma Control Program Grantees. Available at www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf.)

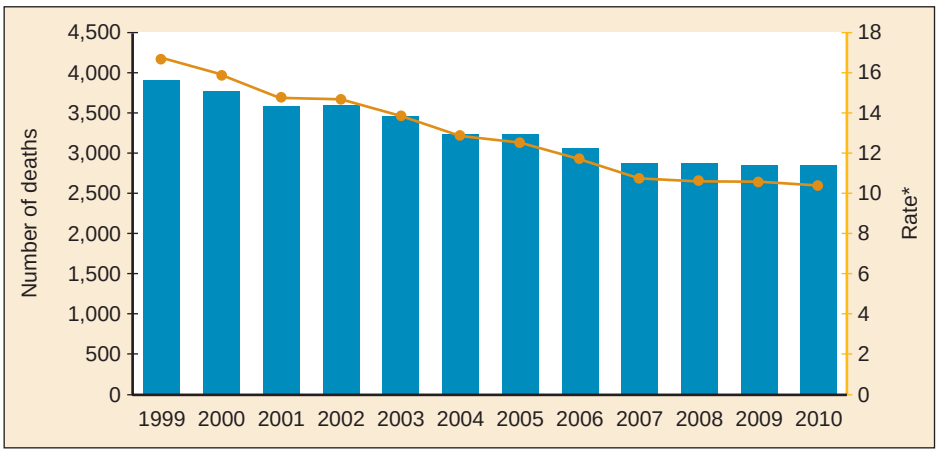

Fig. 63.4. Asthma death rates and number of deaths from 1999 to 2010. Thirty-five National Asthma Control Program (NACP) grantees. (Puerto Rico is excluded.) *Age-adjusted rate per million population. (From Centers for Disease Control and Prevention: Asthma facts: CDC's National Asthma Control Program Grantees. Available at www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf.)

inflammatory response and over time irreversible airway remodeling. These complex cellular interactions clinically manifest as bronchospasm, mucus production, airway edema, and limitation of airflow.

Mast cells and eosinophils contain and release intracellular mediators and cytokines (histamine, prostaglandins, leukotrienes, tumor necrosis factor alpha [TNF-α]) that contribute to prolonged bronchial smooth muscle spasm, edema, and mucus production (Fig. 63.5).[9] Airway epithelial cells are more than a passive barrier and produce pro-inflammatory mediators. Abnormal repair processes may further airway obstruction and contribute to airway remodeling. Nitric oxide produced by airway epithelial cells in the large and small airways and alveoli is a reflection of ongoing airway inflammation. Measurements of fractional exhaled nitric oxide (FENO) are useful for monitoring the response to asthma therapy.[10,11]

Airway remodeling refers to the persistent structural changes in airways caused by repetitive or chronic airway inflammation. Microscopic remodeling features include epithelial thickening, subepithelial fibrosis, mucous gland metaplasia, increases in airway smooth muscle, angiogenesis, and loss of cartilage integrity. Airway remodeling occurs very early in asthma (childhood) and may precede clinical symptoms. Remodeling features are prominent in patients with severe asthma.[12] Basement membrane thickening may be protective by preventing inflammatory cells and proteins from entering the airway submucosa through

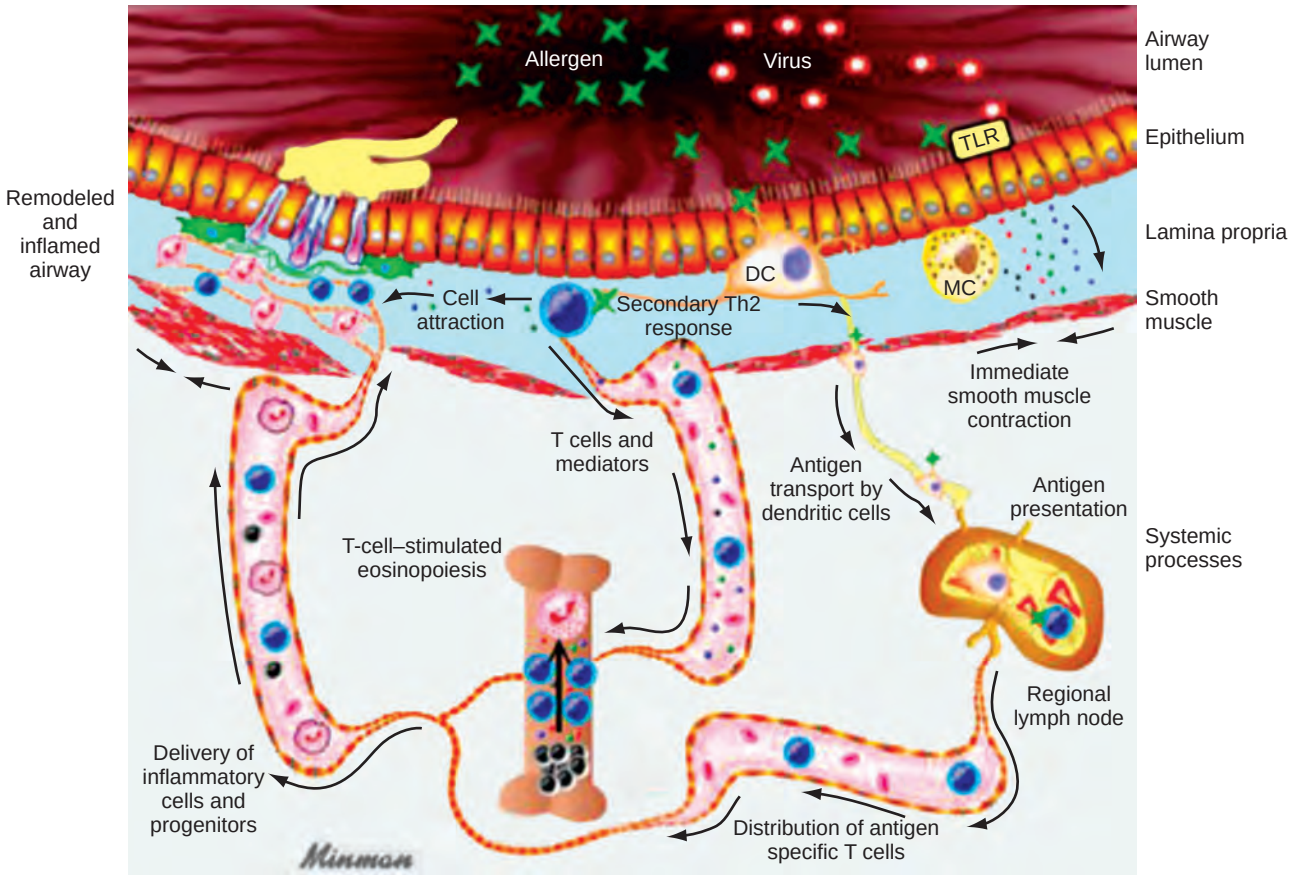

Fig. 63.5. The physiologic mechanism of asthma. *DC,* Dendritic cell; *MC,* mast cell; *Th2,* T-helper 2; *TLR,* toll-like receptor. (From Murphy DM, O'Byrne PM: Recent advances in the pathophysiology of asthma. Chest 137:1417, 2010.)

a damaged epithelium; simultaneously, this process may be counterproductive by reducing the elasticity of the small airways. Airway remodeling induced by chronic inflammation may lead to the development of chronic irreversible airflow limitation and increased asthma mortality.

Genetics is playing an ever-increasing emerging role in the understanding of asthma pathophysiology. Heritability estimates vary between 35% to 95% for asthma and 30% to 66% for bronchial hyperresponsiveness. The first Genome Wide Association Study (GWAS) identified a novel asthma susceptibility locus on chromosome 17p21 and two large meta-analyses of asthma GWASs identified four gene loci considered robustly associated asthma susceptibility genes.[12] Environmental influences (eg, allergens, pollutants, tobacco, and occupational exposures) are associated with asthma, and the interaction of genetic variability and environmental factors may allow prediction of future disease risk, expression, and severity and response to therapies.[13]

CLINICAL FEATURES

Symptoms

Most patients with acute asthma have a constellation of symptoms, including cough, dyspnea, and wheezing. Cough often begins early in the attack, may be the sole manifestation of the disease in cough-variant asthma and elder patients, and can be associated with sputum production. Although increased airway resistance, diminished flow rates, and increased bronchial hyperactivity are contributing factors, asthmatic patients who come to the ED with nocturnal asthma attacks have disease severity similar to that of other asthmatics. Up to 40% of asthmatic women experience premenstrual worsening of symptoms, which peak 2 to 3 days before menses and are associated with more severe disease; ED visits increase during the preovulatory and perimenstrual intervals.

There are inter-individual differences in the dyspnea perceived by asthmatic subjects for the same level of airway narrowing. Patients with a blunted perception of dyspnea ("poor perceivers") have more ED visits, hospitalizations, and near-fatal and fatal asthma attacks.

Approximately 80% of patients with asthma have symptoms of rhinitis, whereas 5% to 15% of patients with perennial rhinitis have asthma, and control of sinonasal inflammation can lead to asthma improvement. Overweight (body mass index [BMI] of 25 kg/m^2 or more) asthmatics have poorer asthma control, higher admission rates, and a greater risk of complications, possibly secondary to a difference in the perception of dyspnea or in response to asthma controller agents. However obesity does not adversely influence the severity or the resolution of an acute exacerbation.[14]

One-third of patients who come to the ED with acute asthma are current cigarette smokers, and these patients (who may have a coexisting chronic obstruction pulmonary disease [COPD]-asthma phenotype) have poorer asthma control and greater acute care needs than lifelong nonsmokers or former smokers.[15] African Americans with acute asthma have lower flow rates and more potentially life-threatening episodes than whites, but they respond equally well to albuterol. There are no racial disparities in inpatient asthma care when comparing whites, blacks, and Hispanics.

Asthma can appear at any age, including the ninth decade, and so wheezing and dyspnea may be mis-ascribed by patients and physicians to heart failure, bronchitis, COPD, occupational lung disease, or poor exercise capacity. Older asthmatics (>55 years old) have higher morbidity and mortality).[16]

The frequent ED asthma patient tends to be male with social, financial, and addiction problems.[17] Also barriers to urgent care and not recognizing the need for provider attention until the need is urgent may contribute to the ED use for asthma.[18]

Slow-onset asthma with progressive deterioration over a period of at least 6 hours (usually days) occurs in over 80% of cases. This type has a female predominance, is triggered by upper respiratory tract infections, and has an airflow inflammation mechanism that results in a slower response to treatment. Sudden-onset asthma with rapid deterioration in less than 6 hours occurs in less than 20% of cases. This type has a male predominance, is triggered by respiratory allergens, exercise, and psychosocial stress, and has a bronchospastic cause resulting in more severe airway obstruction with a faster response to therapy.

Risk factors for death from asthma are important to determine and are listed in Box 63.1.[1] In urban areas, heroin and cocaine abuse are commonly associated with life-threatening asthma requiring noninvasive positive-pressure ventilation (NPPV) or intubation in the ED.[19]

The brief history pertinent to the current exacerbation should include onset and possible triggers (generally the more triggers the worse the clinical status, severity of symptoms especially as compared with previous exacerbations, and other comorbidities—especially those that may be worsened by systemic corticosteroids, such as diabetes, peptic ulcer, hypertension, and psychosis).[20,21] All current asthma medications should be noted, including times and amounts recently used, and any potential asthma aggravators, such as aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), beta-blockers (including topical agents used for glaucoma), and angiotensin-converting enzyme inhibitors. Cardioselective and nonselective beta-blocker use increases hospitalizations and ED visits.

Patients with mild acute asthma usually speak in sentences, with moderate asthma they usually speak in phrases, and with severe asthma they usually speak in words. Although alterations in mentation indicate severe asthma, restlessness and agitation do not reliably indicate hypoxia or hypercapnia. Patients who sit upright have severe airway obstruction; cyanosis is uncommon because of the left shift of the oxyhemoglobin dissociation curve produced by respiratory alkalosis.

Tachypnea and tachycardia are associated with severe obstruction, but lower rates do not rule out severe asthma. The respiratory rate correlates poorly with pulmonary function tests (PFTs) and indicates severe obstruction if it is higher than 40 breaths/min. A pulsus paradoxus or inspiratory fall in systolic blood pressure less than 10 mm Hg usually signifies severe disease, but its absence does not exclude it. When present, pulsus paradoxus may disappear with minimal improvement in airflow. Similarly, use of accessory muscles of respiration is not prognostic.

Wheezing does not designate the presence, severity, or duration of asthma. It correlates poorly with the degree of functional derangement and may be absent when maximal effort produces minimal airflow. Physical examination may help to identify such complications of asthma as pneumonia, pneumothorax, or pneumomediastinum.

DIFFERENTIAL DIAGNOSES

See Box 63.2. Of note, vocal cord dysfunction may mimic or coexist with asthma and is gaining recognition as a common cause of respiratory symptoms often misdiagnosed as steroid-refractory asthma.

BOX 63.1

Risk Factors for Death From Asthma

ASTHMA HISTORY

Previous severe exacerbation (intubation or ICU admission for asthma)
Two or more hospitalizations for asthma in the past year
Three or more ED visits for asthma in the past year
Hospitalization or an ED visit for asthma in the past month
Use of more than two MDI short-acting beta-2 agonist canisters per month
Requiring three or more classes of asthmatic medication
Current use of or recent withdrawal from systemic corticosteroids
Difficulty perceiving asthma symptoms or severity of exacerbations

SOCIAL HISTORY

Low socioeconomic status or inner-city residence
Serious psychosocial problems
Alcohol or illicit drug use, especially inhaled cocaine and heroin

COMORBIDITIES

Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

ED, Emergency department; *ICU,* intensive care unit; *MDI,* metered-dose inhaler.

BOX 63.2

The Differential Diagnosis of Asthma

Cardiac conditions
- Valvular heart disease
- Congestive heart failure

COPD exacerbation

Pulmonary infection
- Pneumonia
- Allergic bronchopulmonary aspergillosis
- Löffler's syndrome
- Chronic eosinophilic pneumonia

Upper airway obstruction
- Laryngeal edema
- Laryngeal neoplasm
- Foreign body
- Vocal cord dysfunction

Endobronchial disease
- Neoplasm
- Foreign body
- Bronchial stenosis

Pulmonary embolus

Cystic fibrosis

Carcinoid tumor

Allergic/anaphylactic reaction

Adverse drug reaction (ACE inhibitors)

Miscellaneous conditions
- Churg-Strauss syndrome
- GERD
- Hyperventilation with panic attack
- Noncardiogenic pulmonary edema
- Addison's disease
- Invasive worm infection

ACE, Angiotensin-converting enzyme; *COPD,* chronic obstructive pulmonary disease; *GERD,* gastroesophageal reflux disease.

DIAGNOSTIC TESTING

Pulmonary Function Studies

The severity of airflow obstruction cannot be accurately assessed from symptoms and physical examination alone. Because physicians initially tend to underestimate the degree of airway obstruction in acute asthma, routine PFTs should be part of ED assessment and monitoring. The forced expiratory volume in 1 second (FEV_1) from maximal inspiration or the peak expiratory flow rate (PEFR) in liters per second, starting with fully inflated lungs and sustained for at least 10 msec, may be used. Any patient not able to perform PFTs should be considered to have severe airway obstruction.

Although FEV_1 can be adequately measured in most acute asthmatics to meet modified American Thoracic Society performance goals, most assessments in the ED use single-patient-use portable peak flow meters because PEFR is easier to measure. The identical device should be used to assess then reassess an individual patient, and different portable meters should not be used interchangeably. The FEV_1 and PEFR measurements are not interchangeable in assessing acute airway obstruction. Although absolute PFT measurements can be used, the percentage of personal best (optimal) or predicted values are preferable to account for age (now to age 85), sex, and height.

Blood Gas Analysis

Equilibration of oxyhemoglobin saturation occurs within 3 to 4 minutes of initiation or alteration of supplemental oxygen, and oxygenation status can quickly be monitored using pulse oximetry. Stimulated hyperventilation leads to a fall in the partial pressure of carbon dioxide in arterial blood ($PaCO_2$). Because airway obstruction increases with resulting hypoventilation, the $PaCO_2$ normalizes (PFTs 15% to 25% predicted) and then increases (PFTs <15% predicted) with resulting respiratory acidosis. Capnography or a venous blood gas (VBG) will reliably indicate these changes, and an arterial blood gas (ABG) is rarely indicated (unless pulse oximetry cannot be obtained or the clinician has reason to question the capnography or VBG results).

Occasionally, despite improvement in PFT values with bronchodilator therapy, some patients have a transient fall in the partial pressure of oxygen in arterial blood (Pao_2) secondary to pulmonary vasodilatation and worsening ventilation-perfusion mismatch. Also, capnographic waveform analysis can indicate improvements in airway diameter in acute asthma and has the advantages of being effort independent and providing continuous monitoring.[22]

Other Blood Testing

Leukocytosis is common with acute asthma exacerbation but is not of discriminatory value in detecting acute superimposed pulmonary infection. Corticosteroids and catecholamines demarginate polymorphonuclear leukocytes after 1 to 2 hours, and patients on chronic steroid therapy may have normal or significantly elevated white blood cell counts.

Serum electrolytes are not altered unless the patient is taking corticosteroids or diuretics or has cardiovascular disease and is receiving beta-2 agonist therapy. Frequent albuterol treatments can cause transient hypokalemia, hypomagnesemia, and hypophosphatemia, but this is rarely of clinical significance. The rare asthmatic on chronic theophylline therapy should have a level measured for possible toxicity. In the older asthmatic with cardiovascular comorbidities, measurement of the B-type natriuretic peptide (BNP) level may reveal unrecognized congestive heart failure.

Hyperlactatemia is common in acute asthma and is thought to be secondary to albuterol therapy or the increased work of breathing. However it is not associated with lower PFTs or more hospitalizations or relapse at 1 week.[23] Overall routine testing of the blood in an acute asthma exacerbation is not recommended.

A chest radiograph is of little value in most acute asthma exacerbations and should be restricted to patients with a suspected complicating cardiopulmonary process, such as pneumonia, pneumothorax, pneumomediastinum, subcutaneous emphysema, or congestive heart failure.[24,25] Also, patients who do not respond to optimal therapy and require hospital admission have a higher likelihood of radiographically identifiable, unsuspected, clinically significant pulmonary complications of asthma (15% of cases). The finding of an ultrasound comet-tail sign has high diagnostic accuracy in differentiating acute heart failure-related from COPD/asthma-related causes of acute dyspnea.[26]

The electrocardiogram (ECG) is selectively helpful in assessing patients with chest pain or a history of significant cardiovascular disease, in whom the asthma attack may be a physiologic stress test. In patients with severe asthma, the ECG may show a right ventricular strain pattern that reverses with improvement in airflow. All patients with severe hypoxemia, and those for whom intubation is contemplated, should also receive cardiac monitoring.

In summary, the severity of airflow obstruction cannot be accurately judged by patients' symptoms, physical examination findings, and laboratory test results. Serial measurements of airflow obstruction (FEV_1 or PEFR) are key components of disease assessment and response to therapy (Table 63.1).

Future Monitoring Strategies

Noninvasive monitoring of bronchial inflammation may customize the ED assessment of acute asthma. This may include measurement of biologic biomarkers, such as cytokine profiles and total

TABLE 63.1

Objective Findings in Asthma Assessment

FACTOR	SEVERE ASTHMA (FEV_1)
Pulse rate (beats/min)	≥120 but may be less with equally severe asthma
Respiratory rate (breaths/min)	≥40 but most are >20, therefore non-discriminating
Pulsus paradoxus (mm Hg)	≥10 but may be absent with equally severe asthma in 50% of cases
Pulse rate ≥120, respiratory rate ≥20, pulsus paradoxus ≥10	If all three abnormal, 90% with severe asthma, but only 40% with FEV_1 <1.0 L have all three abnormal
Use of accessory muscles of respiration	If present, may indicate severe asthma; if absent, may have equally severe asthma in 50% of cases
ABG analysis (mm Hg)	Pao_2 ≤60 or $Paco_2$ ≥42 indicates severe asthma; all other values difficult to interpret unless PEFR or FEV_1 known
Pulmonary function studies	PEFR and FEV_1 measure directly the degree of airflow obstruction; most useful in assessing severity and guiding treatment decisions

ABG, Arterial blood gas; *FEV_1,* forced expiratory volume in 1 second; *$Paco_2$,* partial pressure of carbon dioxide in arterial blood; *Pao_2,* partial pressure of oxygen in arterial blood; *PEFR,* peak expiratory flow rate.

antioxidants in the blood, evaluation of leukotriene E_4 in the urine, and the monitoring of exhaled pentane, hydrogen peroxide, nitric oxide, or carbon monoxide levels. Of these measurements, exhaled nitric oxide, a marker of airway inflammation, shows the most promise, because studies show that forced expired nitric oxide can be measured in the ED with good reproducibility, and levels measured after 6 hours of care are associated with better asthma control after discharge.[26a]

MANAGEMENT

Subacute lack of asthma control (more than four outpatient visits or more than five short-acting beta-2 agonist prescriptions per year) is associated with increased risk of acute asthma exacerbation. Home management includes increased use of inhaled beta-2 agonists, early administration of systemic corticosteroids (not simply doubling the dose of current inhaled corticosteroids [ICSs]), and specific instructions regarding emergency care.[1] The ability to gauge the severity of an attack with use of the ED in a timely manner is important, because patients who wait longer have worse asthma on presentation, more functional limitations, and are more likely to be admitted.[27] Emergency medical services providers should provide albuterol inhalation therapy by protocol, and basic emergency medical technicians can be authorized to administer the patient's own inhaler. Further studies are needed to determine whether paramedics should be trained to administer continuous positive airway pressure ventilation in asthmatics with severe respiratory failure in efforts to decrease tracheal intubation and mortality rates.

The rapidity of reversal of the acute airflow obstruction is directly predictive of the outcome. Effective bronchodilation often results in a decreased need for hospitalization with significant cost savings. As outlined in Table 63.2, the severity of attack as measured by PFTs determines the aggressiveness of the therapy.

Oxygen Administration

All patients should receive supplemental oxygen titrated to maintain arterial oxygen saturation more than 90% (>95% in pregnant women and with coexistent heart disease) rather than at predetermined flow rates, because high concentrations of oxygen therapy causes significant increase in $PaCO_2$ in severe acute asthma.[28] Humidification of the inspired air-oxygen mixture is not essential, although studies suggest that active airway rehydration should be revisited.

Adrenergic Medication

Epidemiologic studies report an association between death and near death from asthma and the frequent use of inhaled beta-2 agonists. The use of more than one canister per month doubles the risk for each additional monthly canister used. Guidelines for chronic use of inhaled beta-2 agonists, however, recommend limited daily use in a rescue-only mode.[1]

One form of albuterol is a racemic mixture of equal amounts of *R* and *S* isomers. Data from animal and human studies suggest that the *S* isomer with no bronchodilator activity, proinflammatory, is spasmogenic, and induces bronchial hyperreactivity. This

TABLE 63.2

Initial Severity Assessments and Therapies in the Emergency Department

	MILD TO MODERATE	SEVERE
FEV_1 or PEFR (percentage predicted/personal best)	≥40%	Unable or <40%
Oxygen therapy	Maintain Sao_2 ≥90%	Maintain Sao_2 ≥90%
NEBULIZED ALBUTEROL SOLUTION		
Levalbuterol (optimal)	1.25 mg every 20 minutes for up to three doses	1.25 mg every 20 min for three doses Continuous for 1 hour if severe
Racemic albuterol	2.5 mg every 20 minutes for up to three doses	5.0 mg every 20 minutes for three doses Continuous for 1 hour if severe
ALBUTEROL METERED-DOSE INHALER WITH VALVED HOLDING CHAMBER		
Levalbuterol (45 μg/puff) (optimal)	6 to 12 puffs every 20 minutes for up to three doses with supervision	Same for three doses (if able to do) with supervision
Racemic albuterol (90 μg/puff)	6 to 12 puffs every 20 minutes for up to three doses with supervision	Same for three doses (if able to do) with supervision
IPRATROPIUM THERAPY		
Nebulized solution	If previous response (same dose as for severe)	0.5 mg every 20 minutes for three doses (may mix with albuterol solution)
MDI (18 μg/puff) with VHC	If previous response (same dose as for severe)	8 puffs every 20 minutes for three doses
SYSTEMIC CORTICOSTEROIDS		
Oral (preferred)	40 to 80 mg of prednisone or prednisolone per day if no immediate response to albuterol	40 to 80 mg of prednisone or prednisolone per day
IV (unable to take orally or absorb)	40 to 80 mg of methylprednisolone per day	40 to 80 mg of methylprednisolone per day
IV magnesium sulfate	Not indicated	2 to 3 g over 20 minutes (or at rates of up to 1 g/min) if FEV_1 ≤25% predicted

FEV_1, Forced expiratory volume in 1 second; *IV,* intravenous; *MDI,* metered-dose inhaler; *PEFR,* peak expiratory flow rate; *Sao_2,* oxygen saturation in arterial blood: *VHC,* valved holding chamber.

could explain the increased morbidity and mortality rates associated with its regular or excessive use.

Some patients may use at home nonprescription racemic epinephrine (Asthmanefirn, marketed as an alternative to Primatine mist metered-dose inhaler [MDI]) delivered by a handheld electronic ultrasound nebulizer. It may be less effective than albuterol and the U.S. Food and Drug Administration (FDA) has issued a safety alert secondary to adverse reports associated with its use.[29]

Levalbuterol, the *R* isomer of racemic albuterol, is available as a preservative-free nebulizer solution (unit doses of 0.31, 0.63, or 1.25 mg) and in a MDI for prevention and treatment of bronchospasm. In chronic asthma, levalbuterol provides a better therapeutic index than the standard dose of racemic albuterol, further fueling the debate on the potential adverse effects of the *S* isomer of beta-agonists. Clinical studies in acute disease report that levalbuterol on a milligram for milligram basis is a better bronchodilator than similar amounts of *R*-albuterol delivered with the *S* isomer in racemic albuterol. The amount and frequency of delivery of levalbuterol and albuterol depend on the initial severity and response to therapy, as shown in Tables 63.2 and 63.3. Patients with more severe obstruction with a poor response to initial therapy should receive higher dosage schedules and continuous administration.[30] When patients are stable but require admission to the hospital, it may be possible to administer nebulized levalbuterol at 1.25 mg every 8 hours as opposed to racemic albuterol at 2.5 mg every 4 to 6 hours.

The PFT response to the initial bronchodilator therapy over the initial 15 to 60 minutes is a better predictor of the need for hospitalization than is the severity of an exacerbation. A PEFR variation over baseline of more than 50 L/min and a rate that exceeds 40% of predicted measured at 15 to 60 minutes suggest a good outcome.

Nebulizer Versus Metered-Dose Inhaler and Valved Holding Chamber. An MDI plus a valved holding chamber ("spacer") provides similar bronchodilation and side effects, even in severe asthma, when compared with nebulization (see Table 63.2). It requires more supervision because some patients have difficulty firing the canister before inhalation, breathing slowly, and holding their breath for 5 seconds, which may explain their infrequent ED use. The MDI with a spacer, however, uses less treatment time and may be more economical.

Intravenous Adrenergic Agonists. Some international asthma guidelines (not United States guidelines) recommend use of intravenous (IV) beta-agonists for severe nonresponsive acute asthma.[21] IV albuterol (not available in the United States) is given as a loading dose of 4 µg/kg for 2 to 5 minutes followed by an infusion of 0.1 to 0.2 µg/kg/min, with close monitoring. Evidence to support the use of IV beta-agonists in patients with severe acute asthma is lacking; the potential risks are warranted only when inhaled therapy is not feasible.[1] Epinephrine is used cautiously in patients older than 40 years old or those with suspected cardiovascular disease. IV epinephrine titrated to effect (average 1.5 µg/min with a range of 0.5 to 13.3 µg/min) is associated with a low rate of major (3.6% of cases) and moderate or minor adverse events.

Subcutaneous Adrenergic Agents. Subcutaneous use of adrenergic agents does not have an advantage over aerosol delivery. It may be considered in patients who cannot adequately inhale albuterol or who experience severe bronchospasm.

Epinephrine, a mainstay for almost 100 years, has both alpha and beta effects. It can produce tachycardia, hypertension, dysrhythmias, and vasoconstriction. It can be given subcutaneously or intramuscularly (1:1000 solution 0.2 to 0.5 mL every 20 to 30 minutes as needed for three doses).

Terbutaline is a longer-acting beta-2 agonist with bronchodilating properties equivalent to those of epinephrine in acute asthma. It can cause skeletal muscle tremor and tachycardia. A 0.25-mg dose can be given subcutaneously every 20 minutes for three doses.

Long-Acting Beta-2 Agonists. Salmeterol is a long-acting (12 hours) beta-2 agonist (LABA) that is an effective additional medication for management of symptoms that are not adequately controlled by regular and adequate doses of effective controller medications, such as ICSs. Its onset of action is 20 minutes and thus is not a rescue medication. Regular use of this drug without concomitant use of ICSs results in greater hospitalizations and asthma-related deaths, resulting in a black box warning on the package insert.[31]

Racemic formoterol dry powder and both racemic and single-isomer formoterol solution for nebulization are also LABAs that have onset of action within minutes (similar to albuterol) and maximal effect within 2 hours. These drugs could evolve as acute rescue medications with extended length of action (12 hours) and similar safety profiles.[32] The FDA has changed the labeling for LABAs to contraindicate their chronic use in patients of all ages without concomitant use of an asthma controller medication, such as an ICS.[33]

Corticosteroids

Despite decades of corticosteroid use, controversy persists regarding the types and quantities required to induce a rapid remission, the time needed for drug action, the route of administration, the

TABLE 63.3

Response After 1 Hour of Initial Treatment

	MODERATE EXACERBATION	SEVERE EXACERBATION
FEV_1 or PEFR (percentage predicted)	40% to 69%	<40%
Oxygen therapy	Unnecessary	Maintain Sao_2 ≥90%
ALBUTEROL THERAPY		
Levalbuterol (optimal)	Reassess as may need less than with racemic dosing	Reassess as may need less than with racemic dosing
Racemic albuterol	Every 1 to 3 hours, admit decision in less than 4 hours	Every 1 hour or continuous
Ipratropium therapy	Unnecessary	Every 1 hour or continuous
Corticosteroids	Every 6 to 8 hours	Every 6 to 8 hours

FEV_1, Forced expiratory volume in 1 second; *PEFR*, peak expiratory flow rate; *Sao_2*, oxygen saturation in arterial blood.

existence of dose response effects, and the determination of which patient populations respond to this therapy.

Systemic Corticosteroids. Corticosteroids are indicated for all patients with moderate to severe attacks or those experiencing an incomplete response to initial beta-agonist therapy. In addition, early systemic corticosteroids should be considered for patients who are taking oral corticosteroids or ICSs, have relapsed after a recent exacerbation, or have prolonged symptoms. Steroid effects begin within hours in acute asthma and peak at about 24 hours. Use of systemic steroids speeds the resolution of airflow obstruction, reduces the rate of relapse, and may decrease admissions in severe but not in mild to moderate attacks.[1] The PEFR may improve within 2 hours of steroid therapy in those not responding to initial albuterol inhalation.

Studies demonstrate that oral corticosteroids are as beneficial as IV therapy. The initial oral dose is usually 60 mg of prednisone. If IV methylprednisolone is used, the dose is 40 to 80 mg/day in one or two divided doses until the switch to oral therapy or until PEFR reaches 70% of predicted or personal best.

Continuing therapy with oral prednisone or prednisolone is given in an adult dose of 40 to 80 mg/day. Oral dexamethasone can alternatively be prescribed at a dose of 16 mg per day for 2 days.[34] Oral steroid therapy is preferred unless the patient is very ill, is unable to swallow or is vomiting, or is thought to have impaired gastrointestinal transit or absorption.

Side effects of short-term (hours or days) steroid use include reversible increases in glucose (important in diabetics) and decreases in potassium, fluid retention with weight gain, mood alterations including rare psychosis, hypertension, peptic ulcers, aseptic necrosis of the femur, and rare allergic reactions.

Inhaled Corticosteroids. Use of ICSs, either alone or in addition to systemic steroids, to treat acute asthma has the potential benefits of reducing systemic side effects, directly delivering medication to the airway, and reducing airway reactivity and edema more effectively. Patients treated with ICSs are less likely to be admitted whether they received systemic steroids or not, and no increased cough or bronchospasm is seen with the use of ICSs. Patients treated with these agents have early improvement in outcomes (<3 hours) because of the topical effects. High doses of ICSs given over hours may be necessary. Evidence suggests that treating both systemically and via airway with corticosteroids in acute disease is more effective than either treatment method alone.

Corticosteroids and Discharged Patients. Discharged patients who receive systemic corticosteroids should continue oral outpatient therapy to control disease and prevent relapse. Any need for additional steroids should be determined at follow-up. An acceptable regimen is 40 to 60 mg of prednisone (or equivalent) in single daily dose for a total of 5 to 10 days. Dose tapering to prevent asthma rebound or out of concern for adrenal suppression is unnecessary unless the patient was already receiving systemic steroids or unless a prolonged course of therapy (more than 2 weeks) is deemed necessary. An alternative approach, if compliance or inability to obtain oral corticosteroids is an issue, is to give a single depot dose of dexamethasone 10 mg, triamcinolone diacetate 40 mg, or methylprednisolone 160 mg before discharge.

Patients with acute exacerbations of asthma may be taking insufficient amounts of chronic controller medications based on their symptoms and excessive use of beta-2 agonists.[1] If the patient is not taking oral corticosteroids or ICSs, the addition of inhaled high-dose budesonide (400 μg, two puffs twice per day) to the patient's regular asthma medications on discharge improves symptoms and decreases relapse by approximately 50% in the ensuing 3 weeks. Thus patients with a history compatible with persistent asthma but not taking any ICS should be given a prescription for one (1- to 2-month supply). Patients already on ICS therapy should continue.

Corticosteroid-Resistant Asthma. A small proportion of asthmatics do not respond to high doses of oral and inhaled glucocorticoids. The mechanism of this steroid resistance may be related to abnormalities in the glucocorticoid receptor number or binding properties or may suggest an alternative diagnosis, such as vocal cord dysfunction. These patients are usually receiving alternative therapies, such as cyclosporine, methotrexate, troleandomycin, hydroxychloroquine, azathioprine, gold, intravenous immune globulin (IVIG), or (in the patient with severe allergic asthma) omalizumab.

Anticholinergic drugs available for inhalation therapy include atropine sulfate or methylnitrate, glycopyrrolate, and ipratropium bromide. They are all bronchodilators that override the smooth muscle constrictor and secretory consequences of the parasympathetic nervous system, blocking reflex bronchoconstriction and reversing acute airway obstruction. Ipratropium bromide (Atrovent), a quaternary derivative of atropine, is preferable to atropine or glycopyrrolate.

The maximum effect with inhaled ipratropium is in 30 to 120 minutes, lasting up to 6 hours. Its bronchodilating potency is lower and onset of action slower than those of the beta-2 agonists and should not be used alone for acute attacks. Trials assessing the role of this agent in combination therapy with beta-2 agonists for acute disease have found that ipratropium provides a modest improvement in PFT results and a reduction in hospitalization. These benefits are higher in patients with more severe disease. Treatment recommendations (see Table 63.2) include adding ipratropium (0.5 mg) with the first three albuterol treatments in severe acute asthma ($PEFR/FEV_1$ <40% predicted). The equivalent MDI dose is approximately eight puffs (18 μg/puff) every 20 minutes three times. Ipratropium can be given to anyone, both acutely and at discharge, who has improved with its past use. Ipratropium may be more effective in patients older than 40 years old, should be used in reversing bronchospasm secondary to beta-blocking agents, and might help those in whom psychological factors contribute to their disease.

Inhaled tiotropium bromide is a long-acting (>24 hours) anticholinergic agent (FDA approved for treatment of COPD) that improves symptoms and lung function when added to ICSs with inadequately controlled asthma.[35]

Magnesium relaxes bronchial smooth muscle and dilates asthmatic airways in vitro. Mechanisms include calcium channel–blocking properties, inhibition of cholinergic neuromuscular transmission, stabilization of mast cells and T lymphocytes, and stimulation of nitric oxide and prostacyclin. Intracellular magnesium levels are lower in acute asthma and the level correlates with airway reactivity in chronic disease.

There is evidence that IV magnesium therapy for severe attacks can obviate the need for intubation. Magnesium adjunctive administration in severe asthma attacks (FEV_1 <25% predicted) improves airflow obstruction and decreases the need for hospital admission. The optimal dose and rates of infusion are unclear, but it is reasonable to administer to adults 2 to 3 g of IV magnesium sulfate over 20 minutes or at rates of up to 1 g/min to patients with severe refractory asthma while continuing aggressive inhalation therapy. IV magnesium therapy is widely used in those with acute severe asthma and life-threatening exacerbations.

Side effects of magnesium infusion are dose related and include warmth, flushing, sweating, nausea and emesis, muscle weakness and loss of deep tendon reflexes, hypotension, and respiratory depression. Inhalation magnesium in acute asthma may also have a role as an isotonic vehicle for nebulized bronchodilator therapy

in improving the PFT response or it may be nebulized alone for bronchodilation (investigational).

Methylxanthines

Theophylline is the main oral methylxanthine used to treat asthma, and a small subset of ambulatory patients may benefit from its chronic administration. The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report- 3 (EPR-3) does not recommend the use of methylxanthines for acute disease because of lack of demonstrated efficacy and increased adverse events.[1] However the British guidelines state that IV aminophylline may benefit a small subset of patients not responding to initial therapy.[21]

Leukotriene Modifiers

The cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) are highly potent mediators of inflammation that play a large role in the pathogenesis of asthma. Zafirlukast (20 mg twice a day) and montelukast (10 mg daily) are rapid-acting, safe, oral asthma controller drugs that are potent and highly selective antagonists of type 1 cysteinyl leukotriene receptors.

Asthmatics generally have elevated levels of leukotrienes, and in acute attacks the amounts in the urine can be markedly increased. The addition of either 7 or 14 mg of IV montelukast (not available in the United States) to standard therapy for acute asthma causes a 15% non–beta-2 mediated increase in FEV_1 over placebo. The onset of action is as early as 10 minutes, persisting for 2 hours.[36] Oral zafirlukast, when given as adjunctive therapy (20 or 160 mg) for acute asthma, improves PFT results and dyspnea but does not decrease admission rates. Oral montelukast (10 mg) given during acute asthma results in significantly increased PEFR the morning after admission when compared with standard treatment.[37] The rapid onset and sustained non–beta-mediated bronchodilating effects of these medications may help manage acute disease.

Other and Future Therapies

In patients without dehydration or hypovolemia, vigorous administration of fluids does not clear airway secretions. Mucolytics may worsen cough or airflow obstruction, and chest physical therapy is not beneficial. Sedatives are contraindicated in acute disease because of their respiratory depression.

Bacterial, chlamydial, and mycoplasmal respiratory tract infections infrequently contribute to acute asthma. Antibiotics should generally be reserved for patients with fever, purulent sputum, pneumonia, or evidence of bacterial sinusitis, to prevent inappropriate prescription of antibiotics for acute asthma.

Neurokinin antagonists, inhaled loop diuretics (furosemide in acute attacks), and lidocaine may inhibit neurogenic inflammation, and heparin may have a role in the inhibition of mast cell products. Infused BNP and enoximone (a phosphodiesterase III inhibitor) can cause significant bronchodilation.[38] Specific cytokine antagonists, agonists, inhibitors of T-cell function, selective inducible nitric oxide synthetase inhibitors, and possibly gene-directed therapies may become novel treatments.

There are currently biologic therapies available for the management of chronic asthma. Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, is indicated for the treatment of severe allergic asthma.[39] It has been shown to control symptoms in severe chronic asthmatic and may be an alternative for patients with poor compliance to ICS therapy.[40-42] Benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, when given in the ED to severe nonresponding patients decreases future hospitalizations.[42]

The use of percutaneous vagal nerve stimulation for acute asthma has been reported.[43] Lastly, the use of rescue therapy with an inhaled combination of a rapid-onset beta-agonist and a corticosteroid might provide both bronchodilation and self-titrated antiinflammatory therapy.

SPECIAL SITUATIONS

Pregnancy

Asthma complicates 4% to 8% of pregnancies, and 27% of pregnant women with asthma have at least one ED visit or hospitalization during pregnancy.[44] The effect of pregnancy on asthma is unpredictable. Knowledge of a pregnant patient's baseline asthma severity is important to predict the risk of severe exacerbation during pregnancy. Asthma exacerbation rates and hospitalizations are directly proportional to the degree of asthma control (NAEPP guidelines[1]) and pregnant patients with severe asthma have an exacerbation rate of 52% and a hospitalization of 27%.[45] Obesity and female fetal sex are associated with an increased risk of exacerbation.[46] Maternal and neonatal outcome are excellent in patients with mild or moderate asthma; severe asthma during pregnancy is associated with gestational diabetes and delivery before 37 weeks.[44]

The hyperventilation of pregnancy is compensated for by a metabolic acidosis. Typical pregnant patients have ABGs with a pH of 7.40 to 7.45, Po_2 of 106 to 110 mm Hg, and partial pressure of carbon dioxide (Pco_2) of 28 to 32 mm Hg; therefore a normal Pco_2 actually represents hypercarbia. Maternal hypoxia quickly results in fetal hypoxemia. PEFR remains unchanged during pregnancy, and monitoring in the ED is strongly recommended. Monitoring of FENO has also been demonstrated to reduce asthma exacerbations in pregnant women.[47]

The smallest amount of medication needed to maintain the pregnant asthmatic in the mild severity range is recommended. Acute exacerbations should be treated as in any nonpregnant patient. Pregnant asthmatics have been observed to be less likely to receive systemic corticosteroids than non-pregnant asthmatics in the ED.[48] However, oral and IV steroids are safe during pregnancy and should be administered in a manner similar to nonpregnant patients. ICSs are not associated with adverse perinatal outcomes and are recommended for all pregnant patients with asthma (budesonide is preferred). Inhaled beta-2 agonists, ipratropium, magnesium sulfate, cromolyn, theophylline, and leukotriene antagonists are safe.[45] Heliox and use of NPPV have been reported in pregnant women with critical asthma syndromes (CASs) without negative effect. Oxygen saturation should be maintained at 95% or more. Intensive care unit (ICU) admission and mechanical ventilation are recommended as in any other patient, with the caveat that a Pco_2 of 40 to 45 mm Hg represents early respiratory failure in the pregnant patient. Refractory severe or uncontrolled asthma may be improved by delivery. Fetal monitoring is recommended for third-trimester ED patients with moderate or severe asthma exacerbations. Acute asthma attacks are rare in labor likely due to endogenous steroid production. There are no contraindications to any asthma medication in the breast-feeding patient.

Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease (AERD) was first described more than 100 years ago. Clinically, AERD includes the tetrad of nasal polyps, eosinophilic sinusitis, asthma, and sensitivity to cyclooxygenase (COX)-1 inhibitor drugs (eg, aspirin).[49] NSAIDs also precipitate AERD. AERD is a common precipitant of life-threatening asthma; one survey notes that 25% of asthmatics who require mechanical ventilation have AERD.

Clinically, most patients with AERD are females who develop symptoms in the third decade (average age of onset is 34 years old), frequently after a viral respiratory illness. A previous history of asthma or allergic rhinitis may be noted, but many patients have no prior respiratory disease. The initial phase manifests as nasal congestion that progresses to eosinophilic rhinosinusitis and nasal polyposis; bronchial asthma and sensitivity to aspirin (acetylsalicylic acid [ASA]) and NSAIDs then results.[50] After ingestion of aspirin or a nonsteroidal drug, acute asthma symptoms occur within 3 hours, usually accompanied by profuse rhinorrhea, conjunctival injection, periorbital edema, and occasionally a scarlet flushing of the head and neck.

The pathogenesis of AERD is detailed in Figure 63.6. ASA inhibits COX, of which two isoforms have been identified. COX-1 produces prostaglandins that are involved in normal physiologic maintenance of renal function, gastric mucosal integrity and hemostasis, and inflammatory states. COX-2 is not expressed in normal physiologic circumstances but produces prostaglandins only in response to inflammatory stimuli. COX is necessary for the production of prostaglandin E_2 (PGE_2) in mast cells and eosinophils. PGE_2 has a stabilizing effect on these cells via blockade of the enzyme 5-lipoxygenase. AERD occurs as a result of ASA inhibition of COX, a decrease in the production of PGE_2 and decreased inhibition of 5-lipoxygenase. The end results are an increase in production of leukotrienes, some of which are potent bronchoconstrictors (IL-4 and IL-5) and inflammatory mediator release from mast cells and eosinophils. Cytokines and staphylococcus, super-antigens in the airways, amplify the inflammatory response. Nasal topical and systemic corticosteroids remain the cornerstone of therapy for AERD, and many patients benefit from agents that block synthesis of leukotrienes (eg, zileuton) or specific leukotriene receptors (eg, zafirlukast, montelukast). Desensitization with slowly increased doses of oral aspirin may be used when aspirin avoidance is not possible (eg, in patients with cardiovascular disease).

COX-2 inhibitors have the advantage of inhibiting inflammation without renal, gastrointestinal, or hematologic side effects. AERD is not reported after administration of COX-2 inhibitors. These agents provide a potentially safe alternative for treatment of inflammatory conditions in patients with AERD.

Acetaminophen is a poor COX inhibitor. Most patients with AERD can tolerate up to 500 mg of acetaminophen safely, but 28% to 34% experience mild respiratory reactions when administered 1000 to 1500 mg. Reactions to acetaminophen tend to be milder than those to NSAIDs.

Exercise-Induced Asthma

Exercise-induced bronchoconstriction has been recognized since the first Olympic Games. It occurs in 5% to 20% of the general population, 30% to 70% of elite winter and summer endurance athletes, and up to 90% of patients with persistent asthma. Atopy is strongly associated with exercise-induced asthma (EIA), and up to 40% of patients with allergic rhinitis have EIA. Clinically, EIA is usually preceded by 3 to 8 minutes of exercise. Peak symptoms usually occur 8 to 15 minutes after exercise is complete and

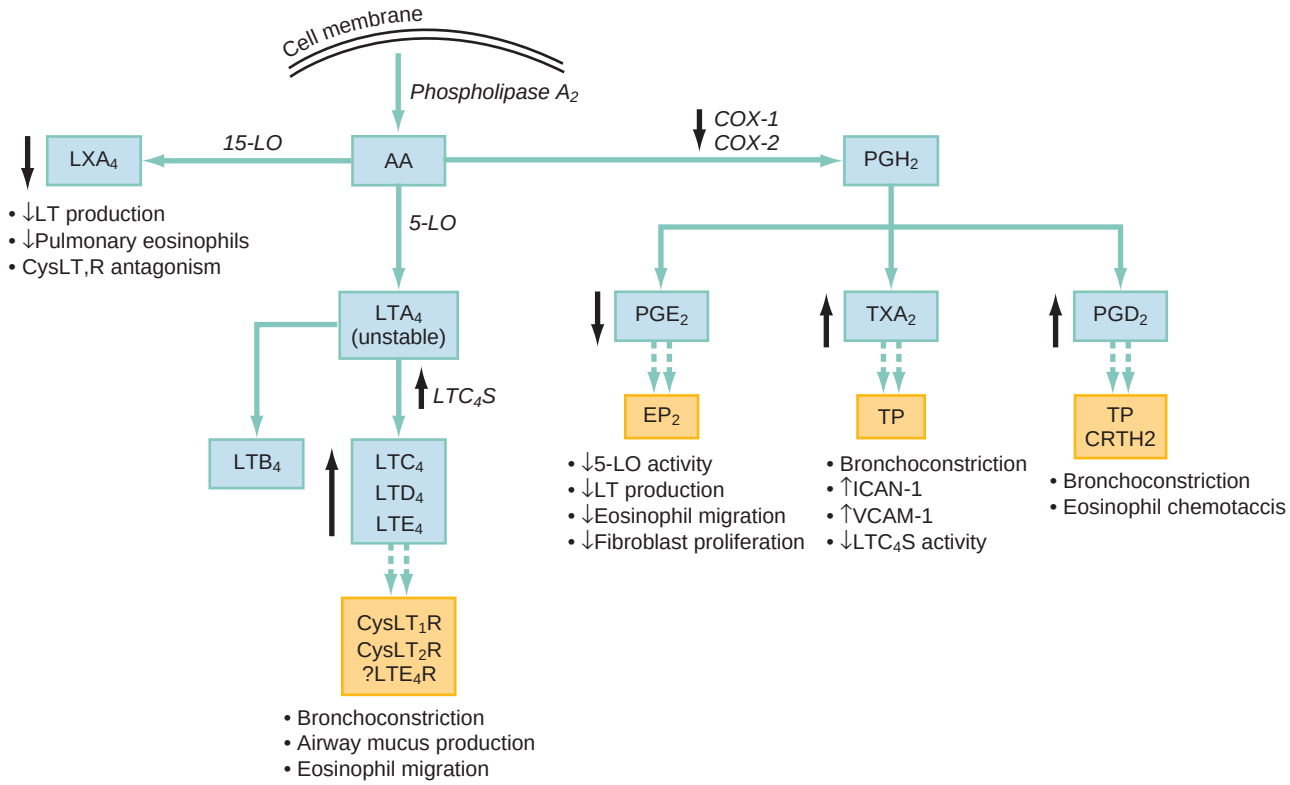

Fig. 63.6. Mechanism of aspirin-exacerbated respiratory disease (AERD). Inhibition of the enzyme cyclooxygenase *(COX)* decreases production of prostaglandin E_2 *(PGE_2)*. PGE_2's inhibitory effect on 5-lipoxygenase *(5-LO)* is diminished resulting in increased production of leukotrienes (*LTC_4, LTD_4,* and *LTE_4)* causing bronchoconstriction, mucus production, and airway eosinophil migration. *5-LO,* 5 Lipoxygenase; *15-LO,* 15 lipoxygenase; *AA,* arachidonic acid; *COX-1,* cyclooxygenase 1; *COX-2,* cyclooxygenase 2; *CRTH2,* chemokine receptor-homologous Th2 lymphocytes; *$CysLT_1R$,* cysteinyl leukotriene T1R; *$CysLT_2R$,* cysteinyl leukotriene T2R; *EP_2,* E prostanoid 2 receptor; *LTA_4,* leukotriene A4; *LTB_4,* leukotriene B4; *LTC_4S,* leukotriene C4 synthetase; *LTC_4,* leukotriene C4; *LTD_4,* leukotriene D4; *LTE_4,* leukotriene E4; *LTE_4R,* leukotriene E4R; LXA_4, lipoxin A4; *PGD_2,* prostaglandin D2; *PGE_2,* prostaglandin E2; *PGH_2*, prostaglandin H2; *TP,* T prostanoid receptor; *TXA_2,* thromboxane A2. (From Laidlaw TM, Boyce JA: Pathogenesis of aspirin-exacerbated respiratory disease and reactions. Immunol Allergy Clin North Am 33(2):195, 2013.)

then begin to remit spontaneously; recovery occurs within 60 minutes.

The key stimulus is felt to be airway dehydration resulting from increased ventilation, resulting in an increase in the osmolarity of the airway lining fluid. The increased osmolarity is felt to trigger release of mediators (histamine, leukotrienes, prostaglandins) from airway inflammatory cells, resulting in smooth muscle contraction and airway edema.[51] Another exercise-specific factor is autonomic deregulation associated with prolonged high-intensity physical training. The predominantly parasympathetic drive of athletes (evidenced by low heart rates) may also increase bronchomotor tone and increase the risk of EIA.

Prophylaxis for EIA includes environmental measures (face mask or nasal breathing to allow warming and humidification of cool dry air, pre-exercise warm-up, and avoidance of known allergens) and medications. Inhaled glucocorticoids are strongly recommended and a short-acting inhaled beta-2 agonist used 5 to 10 minutes before exercise is effective in preventing exercise induced bronchoconstriction (however the regular use of inhaled beta-2 agonist may lead to tolerance and a decrease in their effects during exercise).[51] LABAs in combination with inhaled glucocorticoids are useful when low doses of inhaled glucocorticoids are ineffective. Pretreatment with cromolyn, leukotriene antagonists (montelukast), and inhaled parasympatholytics is also effective.

Perimenstrual Asthma

Perimenstrual asthma affects up to 40% of asthmatic women yet receives little emphasis in asthma treatment guidelines.[1] The ratio of female-to-male asthma prevalence increases dramatically after puberty, and health care for asthma increases in the perimenstrual phase. Perimenstrual asthma is associated with high BMI, low forced vital capacity (FVC) percentage predicted, and higher rates of gastroesophageal reflux disease and is common in women with severe and poorly controlled asthma.[52] Perimenstrual reductions in PEFRs of 35% to 80% are reported. Fluctuations in estrogen and progesterone levels are postulated as causal factors.[53] Estradiol inhibits eosinophil degranulation and suppresses leukotriene activity; estrogen withdrawal in the luteal phase may enhance these actions. Progesterone may also have bronchodilator and antiinflammatory activity, and the rapid decline in progesterone levels before menstruation may contribute to increased bronchospasm. Beneficial therapies for perimenstrual asthma include leukotriene antagonists, LABAs, and oral contraceptives.

Critical Asthma Syndromes

Patients with severe asthma represent about 5% to 10% of all asthmatics yet consume excessive health care resources. The European Respiratory Society/American Thoracic Society guidelines define *severe asthma* as that requiring treatment with high dose ICS and LABA or leukotriene modifier/theophylline for the previous year or systemic corticosteroids for 50% or more of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy. *Uncontrolled asthma* is defined if one of the four criteria in Box 63.3 is present.[54]

Clinical features of severe asthma include a lesser prevalence of atopy, a history of aspirin sensitivity, and a higher incidence of sinusitis and use of nasal corticosteroids (suggesting involvement of the upper, as well as the lower, respiratory tract). Exacerbations may be associated with menses.

Critical asthma syndrome (CAS) has been proposed to replace terms that previously have been used to describe acute, poorly responsive, and life-threatening asthma (eg, *status asthmaticus, refractory asthma, brittle asthma,* and *near-fatal asthma*). CAS does not require the patient to have severe asthma; rather it refers acute episodes requiring immediate multimodal therapies to prevent progression to irreversible hypoxia and cardiopulmonary arrest. The terms *status asthmaticus* and *near-fatal asthma* are part of the spectrum of CASs; the former is defined as bronchospasm that does not respond to aggressive therapies within 30 to 60 minutes, the latter as asthma that is refractory to treatment and progresses to acute respiratory failure requiring ventilatory support.

Two types of CASs that may progress to fatal asthma are recognized. Slow-onset CAS typically reflects a gradual deterioration of asthma symptoms over several days, usually superimposed on chronic poorly controlled asthma. Slow-onset CAS is associated with a greater frequency of health care usage. Deaths associated with the slow-onset mechanism are preventable in many cases because of the gradual progression of symptoms. Rapid-onset CAS is characterized by symptom onset and progression to life-threatening status in 3 hours or less. Clinically, rapid-onset CASs are characterized by greater hypercapnia than occurs in the slow-onset type. The hypercapnia in rapid-onset CAS is more responsive to therapy than that in the slow-onset type, and these patients require shorter durations of mechanical ventilation.

Risk factors for death from asthma have been identified (see Box 63.1). Other risk factors linked to near-fatal CAS and fatal asthma include a decreased use of corticosteroids, hospital admission for asthma treatment within the previous 12 months, low socioeconomic status, environmental exposures (air pollution, cigarette smoking), and psychosocial problems. Patients with near-fatal CAS are likely to depend on EDs for asthma management. Patients with fatal asthma commonly tend to be African American, live in inner-city areas, and are 15 to 34 years old. Less than 1% of asthmatics in the ICU die from their disease. Most deaths occur outside or on the way to the hospital, at night, and within 24 hours of the onset of symptoms.

BOX 63.3

European Respiratory Society/American Thoracic Society Definitions of Severe and Uncontrolled Asthma

Severe asthma for patients 6 years old and older is defined as:
Asthma which requires treatment with guidelines suggested medications for Global Initiative for Asthma steps 4 to 5 asthma (high-dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids for ≥50% of the previous year to preventing it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy

Uncontrolled asthma is defined as one of the following:

1. Poor symptom control (ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/Global Initiative for Asthma guidelines)
2. Frequent severe exacerbations: Two or more bursts of systemic corticosteroids (>3 days each) in previous year
3. Serious exacerbations: At least one hospitalization, ICU stay, or mechanical ventilation in the previous year
4. Airflow limitation: After appropriate bronchodilator, withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)
5. Controlled asthma that worsens on tapering of these high doses of ICS or systemic corticosteroids (or additional biologics)

ACQ, Asthma Control Questionnaire; *ACT,* Asthma Control Test; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *ICS,* inhaled corticosteroid; *ICU,* intensive care unit; *LABA,* long-acting beta-2 agonist; *NAEPP,* National Asthma Education and Prevention Program.

From Chung KF, Wenzel SE, Brozek JL, et al: International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 43(2):343–373, 2014.

Clinical Approach to the Critically Ill Asthmatic

The critically ill asthmatic appears agitated (hypoxemic), assumes an upright position, and appears to be in severe respiratory distress. Tachypnea, diaphoresis, and accessory muscle use are evident. Speech is fragmented into single or short bursts of syllables or words. Absence of wheezing indicates severe expiratory obstruction and minimal air movement. Peak expiratory testing is difficult for the patient to perform but when possible indicates severe expiratory obstruction. Alterations in consciousness and bradypnea indicate hypercarbia and impending respiratory arrest.

No laboratory markers identify critically ill asthmatics. Measurement of lactic acid is not recommended in the critically ill asthmatic. Elevated lactic acid levels are common in patients receiving beta-2 agonist therapy and are not commonly associated with metabolic acidosis.[55] Hyperlactemia occurs even in ventilated and paralyzed asthmatics thus does not necessarily represent respiratory muscle fatigue.[56] An elevated lactic acid level is not predictive of respiratory failure in critically ill asthmatics and should not be interpreted as a poor prognostic indicator.[57] Serial peak flow measurements are the best indicator of severity and response to therapy.

Attempts to abort the episode include continuously nebulized beta-2 and anticholinergic agents (see Table 63.2). If parenteral adrenergic therapy is desired, terbutaline is preferred because of its beta-2 selectivity. IV magnesium sulfate or $beta_a$-agonists (where available) may be of benefit. Oral prednisone 60 mg or IV methylprednisolone 125 mg should be administered. The potential role of cytokine and TNF-α antagonists, such as etanercept and infliximab, is unclear.[58,59] Golimumab, a monoclonal antibody to TNF-α possesses an unfavorable risk-benefit profile and has not been found to be clinically useful.[14] Studies using monoclonal antibodies against IL-5, IL-4, and IL-13 are ongoing, but definitive benefit is lacking.

Helium is an inert gas with one-eighth the density of nitrogen. When 60% to 80% helium is blended with 20% to 40% oxygen, the resulting gas mixture (heliox) has a threefold reduction in density compared with air. Heliox reduces the resistance associated with gas flow through airways with non-laminar flow and reduces respiratory muscle work; it also increases the diffusion of carbon dioxide and may improve alveolar ventilation.[60] Although heliox is not intrinsically therapeutic, it may decrease the work of breathing long enough to abort intubation by carrying bronchodilators to the distal airways and allowing antiinflammatory agents time to achieve their effects. When heliox was compared to oxygen to drive nebulized delivery of $beta_a$-agonist therapies, a 17% increase in PEFR and a lower rate of hospitalization was observed.[61] Patients with severe asthma receiving heliox nebulization of beta-2 agonists have significant increases in PEFR and other PFTs compared to those mild-moderate asthma.[62] Heliox has not been demonstrated to decrease the need for intubation in severe and resistant asthma. It is administered by nonrebreather mask and can be used with mechanical ventilation. Considerations for heliox include cases of severe airflow obstruction (PEFR <30% predicted and a rapid onset of symptoms within 24 hours), a history of labile asthma or previous intubation, and inability to be adequately mechanically ventilated.

NPPV may benefit carefully selected patients with severe and resistant asthma (see Chapter 2). Continuous positive airway pressure improves oxygenation and reduces respiratory muscle fatigue by increasing functional residual capacity and lung compliance and supplying some of the inflating pressure required during inspiration. Biphasic positive airway pressure (BiPAP) provides continuous positive airway pressure but delivers higher pressure during inspiration than expiration. BiPAP allows speech and reduces the need for sedation. Nebulized bronchodilators can be delivered through the BiPAP circuitry. BiPAP is well tolerated by children with status asthmaticus and may decrease the need for intubation and mechanical ventilation. BiPAP may decrease the need for hospitalization, intubation, and ICU/hospital length of stay in adults with status asthmaticus.[63,64] However, there is limited evidence to routinely recommend NPPV in patients with respiratory failure from severe asthma exacerbations.[65]

BiPAP is not a substitute for endotracheal intubation and mechanical ventilation. Recommendations for BiPAP are conditional—a trial of BiPAP before intubation and mechanical ventilation should be considered in select patients. Patient considerations include alert mental status and intact airway reflexes. Providers should be familiar with BiPAP use in other medical conditions (eg, COPD, congestive heart failure), and ICU admission is mandatory. Intermittent ABG monitoring during BiPAP identifies nonresponders.

Ketamine is an IV dissociative anesthetic with potent bronchodilator effects. Case reports suggest benefit when used in acute asthma, but only a single randomized controlled trial evaluating its use in children with acute asthma exacerbations has been performed and no significant benefit was reported.[66] At present, ketamine is not recommended for therapy of acute asthma in the nonintubated patient.

Endotracheal intubation and mechanical ventilation is required in 2% of all asthma exacerbations and 10% to 30% requiring ICU admission.[67] Indications for intubation include coma, altered consciousness, cardiac or respiratory arrest, paradoxical breathing pattern, refractory hypoxemia, and failure of NPPV. Some authors recommend threshold levels for intubation based on ABG results, but there is no evidence that ABG results provide better guidance regarding need for intubation than does overall clinical assessment.

Orotracheal rapid sequence intubation (RSI) with induction agents and muscle paralysis is preferred (see Chapter 1). A large endotracheal tube (≥8.0 mm for adults) will facilitate airway suctioning, mucous plug removal, and bronchoscopy. Ketamine (1 to 2 mg/kg) is the preferred agent for induction in RSI of the asthmatic patient because of its bronchodilatory and sympathetic stimulatory properties. Succinylcholine (1.5 mg/kg) or a competitive neuromuscular blocking agent, such as rocuronium (1 mg/kg), can be used for intubation paralysis. Alternatively, propofol (1.5 to 2 mg/kg) offers rapid-onset deep sedation and also possesses bronchodilating properties, but its vasodilatory effects may cause hypotension, especially in the volume depleted asthmatic. Continued deep sedation with propofol, a long-acting benzodiazepine (eg, lorazepam) or an opioid that does not release histamine, (eg, fentanyl) usually avoids the need for muscle paralysis and can improve patient comfort. After emergent intubation has been accomplished, care must be taken to avoid hyperventilation.

A ventilator strategy providing adequate oxygenation and ventilation while minimizing hyperinflation, high airway pressure, barotrauma, and systemic hypotension must be instituted. Priority must first be given to decreasing hyperinflation—not correcting hypercarbia and respiratory acidosis. The technique of permissive hypercapnia is common (see Chapter 2). Airway pressure is kept low by providing low tidal volumes (6 to 8 mL/kg), thus preventing excessive increases of intrinsic positive end-expiratory pressure ("auto-PEEP"), stacking of ventilations, and barotrauma. Low ventilation rates (below 10 breaths/min) and high inspiratory flow rates (above 60 L/min) provide prolonged time for expiration. Oxygenation is maintained by use of a high fraction of inspired oxygen (Fio_2). Hypercarbia and respiratory acidosis (pH maintained at 7.15 to 7.2 with sodium bicarbonate) is tolerated. Adjunctive therapies (IV hydration, inline beta-2 agonists and anticholinergics, IV corticosteroids, and possibly magnesium) to decrease airway pressure and airway obstruction are delivered simultaneously.

Continuous capnography is advisable. Moderate levels of hypercapnia are well tolerated and have few deleterious effects. Elevated carbon dioxide levels have vasodilatory effects on cerebral vessels. Cerebral blood flow reaches its maximum at a $Paco_2$ level of 120 mm Hg, which may increase intracranial pressure. Although there is no consensus on what constitutes a safe level of hypercapnia, $Paco_2$ levels above 100 mm Hg should be avoided. Hypercapnia can decrease cardiac contractility and produce cardiovascular collapse; thus permissive hypercapnia should be supplemented by generous repletion of intravascular volume through IV fluids.

Neuromuscular blocking agents should be used only in cases in which deep sedation with adequate analgesia fails to provide sufficient relaxation for successful mechanical ventilation (see Chapter 1). Myopathy attributed to the use of neuromuscular blocking agents (and corticosteroids) is correlated with the dose and duration of administration of these agents. Because corticosteroids are an essential element of therapy for the critically ill asthmatic, the use of neuromuscular blocking agents should be avoided.[68] Complications of mechanical ventilation in the asthmatic patient include hypoxemia, hypotension, nosocomial infections, and barotrauma. Hypotension is almost uniformly secondary to increased intrathoracic pressure with a subsequent decrease in venous return and cardiac output. Slowing the rate of mechanical ventilation or removing the patient from the ventilator for a short time (20 to 30 seconds) allows more time for expiration, thereby decreasing intrathoracic pressure. Volume depletion and medication effects (eg, narcotic sedative agents) are other potential explanations for hypotension. Pneumothorax should be considered whenever sudden deterioration occurs or when hypotension is accompanied by a significant rise in peak inspiratory ventilator pressures. Although complications may occur, the use of mechanical ventilation in critically ill asthmatics is associated with low morbidity and mortality.

If the intensively treated, intubated critically ill asthmatic continues to have elevated airway pressures, persistent hypoxemia, and continued bronchospasm, general anesthetic agents should be considered. IV anesthetic agents are more practical to use in the ED. Data supporting the use of IV ketamine and propofol is sparse, but these agents have bronchodilatory effects and may be of benefit in this situation.

The American Heart Association recommendations for CPR in asthmatics indicate no difference from other cardiac arrest situations.[69] However, the technique of external lateral chest compression may be of benefit. Chest compression is delivered by bilateral squeezing of the lower chest walls immediately after end inspiration occurs. Compressions delivered too early (ie, during inspiration) may increase airway pressure and result in barotrauma. Allowing more time for exhalation during CPR ventilation is paramount.

Unrecognized barotrauma may cause cardiac arrest. Rapid bedside ultrasound should be used to identify occult pneumothorax and reveal nonpalpable cardiac contractions. Empirical bilateral tube thoracostomy should be performed if unexplained cardiac arrest occurs, especially in the context of dramatic increases in peak inspiratory pressure. IV epinephrine is a logical agent in the setting of cardiopulmonary arrest, because it has inotropic, chronotropic, and bronchodilatory properties. Isoproterenol, a pure beta-agonist, may increase heart rate and provide bronchodilation but decreases coronary perfusion pressure. Extracorporeal membrane oxygenation (ECMO) may be indicated for severe asthma refractory to conventional therapies.[70]

DISPOSITION

Asthmatic patients discharged from the ED have rates of relapse that vary from 11% over 3 days to 45% at 8 weeks. The relapse risk increases in those with numerous asthma-related ED visits within the previous year, with more outpatient medications, and with longer duration of symptoms before the ED visit. Other studies find similar out-of-control indices predicting relapse but have also included insufficient improvement in PFTs with hospital-based treatment for an attack.

Patients requiring extended care who are without life-threatening exacerbations, pregnancy, or complications of asthma can generally be treated in an observation unit with 8-week outcomes equal to those admitted and with significant cost savings. The ability to predict discharge from the observation unit can be assessed by the PEFR response to the third beta-2 agonist treatment (PEFR >40% predicted is often associated with successful observation unit discharge). Patients prefer observation unit treatment of acute attacks over routine inpatient care. Table 63.4 summarizes disposition guidelines.

Asthma exacerbation does not end on discharge; airway inflammation and peripheral obstruction may take hours to days to resolve. Patients are likely to need continued beta-2 agonist rescue therapy, and they should demonstrate the correct use of their inhalers. If the patient is having difficulty coordinating the canister activation with inhalation, a breath-activated inhaler or spacer device can be prescribed or the need for a home nebulizer discussed. A patient using a portable, preloaded, multidose dry powder inhaler must be able to inhale from the mouthpiece in a rapid and forceful inhalation to total lung capacity.

Patients receiving ED systemic corticosteroids should continue these orally for 5 to 10 days. If the patient was not using controller medications before the acute visit and has characteristics of persistent asthma (symptoms or rescue therapy more than twice per week, interference with sleep more than twice per month, activity limitation caused by asthma or exacerbations requiring oral corticosteroids more than once in the past year), moderate-dose ICSs or a combination ICS and LABA should be started. A less preferred option is to prescribe a leukotriene modifier (eg, zafirlukast 20 mg twice a day or montelukast 10 mg daily) to decrease relapse and improve asthma control.

Patients should contact their physician for asthma-related problems within the following 3 to 5 days and should make a

TABLE 63.4

Emergency Department Disposition Decision-Making Guidelines

	GOOD RESPONSE	INCOMPLETE RESPONSE	POOR RESPONSE
FEV_1 or PEFR (% predicted/ personal best)	≥70%	≥40% but <69%	<40%
DISPOSITION SITE			
Home	Yes	Individualized decision (see text)	No, continue therapy
CDU	No	Yes, if available	Yes, if available and appropriate
Hospital ward	No	Yes, if no CDU	Yes, if appropriate and available
Critical care unit	No	No	Yes, if with respiratory insufficiency or failure

CDU, Clinical decision unit; *FEV_1*, forced expiratory volume in 1 second; *PEFR*, peak expiratory flow rate.

follow-up medical appointment (ideally done while the patient is still in the ED) within 1 to 4 weeks. Interventions that include free medications, transportation vouchers, and appointment assistance significantly increase the likelihood that discharged asthma patients will obtain primary care follow-up. These assistances, however, may not affect long-term outcomes.

Patients that follow-up and are managed by asthma specialists have fewer symptoms, less beta-agonist use, improved quality of life, and reduced ED visits and hospitalizations than those managed by generalists. Patients with severe persistent asthma or prior severe exacerbations should be referred to an asthma specialist.

The asthma patient can be provided written education about discharge medications, medication adjustment if the condition is not improving (such action plans are not often created and when done are often inadequate) and a peak flow meter for daily measurements, especially for those who have difficulty perceiving airflow obstruction or who have symptoms of worsening asthma. At a minimum, focused education should address the need for follow-up and for understanding the difference between controller and rescue medications and their use. Smoking asthmatics have more respiratory symptoms, lower lung function, and more parenchymal abnormalities noted on chest computed tomography, so smoking cessation should be discussed.

KEY CONCEPTS

- Inhaled and systemic steroid medications are effective in controlling airway inflammation and have important roles in management of asthma exacerbations.
- Inhaled bronchodilators and systemic corticosteroids remain as the mainstays of management for most acute asthma exacerbations.
- Theophylline is the main oral methylxanthine used to treat asthma, and we do not recommend its use for acute disease because of lack of demonstrated efficacy and increased adverse events.
- Critical asthma syndromes (CASs) require rapid identification. Treatment must be aggressive and may use strategies not used in mild to moderate exacerbations, such as infusion of magnesium sulfate, use of noninvasive ventilation, and endotracheal intubation.
- Ventilator management in the intubated asthmatic is critical and includes lower tidal volumes (6 to 8 mL/kg) and low respiratory rates, often less than 10 per minute.
- A normal partial pressure of carbon dioxide (Pco_2) in a pregnant patient represents hypercarbia.
- Elevated lactic acid levels are common in critically ill asthmatics and do not reflect deterioration or a poor prognosis.
- ED management of acute asthma is expanding (up to 24 hours) as more non-critically ill asthmatics are treated in observation units.
- Integration of discharged patients with acute asthma into chronic management strategies to prevent relapse requires that asthma patients' physicians be familiar with controlling medications, such as ICSs and leukotriene modifiers.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 63: QUESTIONS & ANSWERS

63.1. A 33-year-old woman presents with a first-ever episode of shortness of breath, nonproductive cough, and wheezing. She had been previously healthy but experienced a mild upper respiratory infection 1 month ago, followed by chronic nasal congestion, conjunctival infection, rhinorrhea, and decreased sense of smell. This episode of cough and wheezing started 2 days ago. Inspection reveals a healthy appearing woman with mild respiratory distress: temperature, 97.5°F (36.4°C) oral; blood pressure, 110/70 mm Hg; respiratory rate, 24 breaths per minute; and oxygen saturation, 95%. Physical examination is remarkable for diffuse moderate expiratory wheezes. Chest radiograph is negative. What is the most likely diagnosis?
A. Aspirin-exacerbated respiratory disease (AERD)
B. Atypical pneumonia
C. Bronchitis
D. Maxillary sinusitis
E. Pulmonary aspergillosis

Answer: A. This is a classic adult-onset sequence presentation for AERD. Aspirin sensitivity and periodic asthma flares typically follow this apparent upper respiratory infection–induced cycle. Clinically significant sinusitis might be expected to show facial pain/tenderness with fever. Bronchitis may present with bronchospasm, but the nasal and ocular symptoms do not fit. Pulmonary aspergillosis would likely occur in an immunosuppressed patient or very chronic asthmatic.

63.2. Periodic asthma flares may be precipitated by which of the following?
A. Increased production of prostaglandin E_2 (PGE_2)
B. Falling leukotriene levels
C. Falling progesterone levels
D. Rising estrogen levels
E. Thyroid hormone fluctuations

Answer: C. Menstrual-induced asthma is likely triggered by falling progesterone levels just prior to menstruation. Estrogen may likewise exert a salutary bronchodilating effect. Elevated levels of the inflammatory mediator leukotriene are the hallmark of chronic asthma. Cyclo-oxygenase inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) and falling PGE_2 levels may explain part of the aspirin-induced asthma syndrome.

63.3. A 30-year-old woman with a history of asthma presents with a typical asthma flare that has progressed slowly over 16 hours. Which of the following is true?
A. Airway obstruction is probably more predominant than airway inflammation.
B. Most cases of asthma exacerbations in adults have a much more rapid and abrupt onset.
C. Response to treatment would be expected to be rapid.
D. Steroids are less likely to be helpful.
E. The episode was likely triggered by an upper respiratory infection.

Answer: E. Slow-onset asthma typically occurs in females. This phenotype represents 80% of cases. There is a primary inflammatory mechanism, and response to treatment is slower. Abrupt-onset asthma more typically occurs in males and is bronchospastic, exercise or stress induced, and more rapidly responsive to treatment.

63.4. Which of the following is a risk factor for sudden death from asthma?
A. A hospitalization for asthma in the past year but not within the past 30 days
B. An emergency department (ED) visit for asthma in the past year but not within the past 30 days
C. Current use of systemic corticosteroids
D. Patient perception that the current exacerbation is very severe
E. Use of over-the-counter medications

Answer: C. Risk factors for sudden death are current or recent corticosteroid use, ED or hospitalization within the past 30 days, more than two hospitalizations for asthma in the past year, more than three ED visits for asthma in the past year, using more than two beta-agonist canisters per month, previous intubation or intensive care unit (ICU) visit, and difficulty perceiving symptoms or their severity.

63.5. A 23-year-old man with known severe asthma presents with an acute asthma flare over 2 hours. Physical examination reveals a well-developed man in marked respiratory distress. Heart rate is 120 beats per minute, oxygen saturation is 90%, respiratory rate is 26 breaths per minute, blood pressure is 140/92 mm Hg, and oral temperature is 98.7°F (37.2°C). Current medications are albuterol metered-dose inhaler (MDI) and fluticasone inhaler 500 μg twice daily. What therapy is recommended for this acute flare?
A. Albuterol 2.5 mg nebulized, methylprednisolone 125 mg intravenously, and magnesium sulfate 3 g intravenously
B. Epinephrine infusion at 5 μg per minute
C. Ipratropium 500 μg nebulized × three doses with methylprednisolone 125 mg intravenously
D. Methylprednisolone 125 mg intravenously with salmeterol nebulized via continuous nebulization
E. Terbutaline 0.25 mg subcutaneously, ipratropium 500 μg nebulized, and methylprednisolone 125 mg intravenously

Answer: A. Short-acting inhaled beta-agonists, with or without anticholinergics (ie, ipratropium), are the cornerstone of acute asthma management. Corticosteroids are indicated in any moderate or severe flare. Oral steroids are as efficacious as intravenous (IV) steroids if the patient can take oral medications. Magnesium sulfate may obviate the need for intubation in severe cases. Salmeterol is a slow-onset, long-acting beta-2 agonist (LABA) not indicated in acute asthma management.

63.6. What is the medication combination of choice for the rapid sequence induction of an asthmatic?
A. Etomidate/succinylcholine
B. Ketamine/succinylcholine

C. Midazolam/pancuronium
D. Propofol/rocuronium
E. Thiopental/succinylcholine

Answer: B. No choice is contraindicated. Ketamine is the sedative of choice because of its bronchodilatory effect. Propofol may have this same benefit, although less profound. Thiopental releases histamine, and etomidate does not bronchodilate. Succinylcholine releases trace amounts of histamine, but this is not known to cause any adverse effect. Rocuronium has an onset time similar to that of succinylcholine, no histamine release, and a prolonged duration of action. Either succinylcholine or rocuronium is acceptable for rapid sequence intubation (RSI) in acute asthma.

63.7. Which of the following is a risk factor for death in patients presenting with an asthma attack?
A. Currently taking theophylline
B. Family history of asthma
C. Presence of symptoms for 1 week
D. Recently ran out of inhaled corticosteroid (ICS)
E. Use of three albuterol metered-dose inhalers (MDIs) per month

Answer: E. The following are risk factors for death from asthma:
- Past history of sudden severe exacerbations
- Prior intubation for asthma
- Prior asthma admission to an intensive care unit (ICU)
- Two or more hospitalizations for asthma in the past year
- Three or more emergency department (ED) care visits for asthma in the past year
- Hospitalization or an ED care visit for asthma within the past month
- Use of more than two MDI short-acting beta-2 agonist canisters per month
- Current use of or recent withdrawal from systemic corticosteroids
- Difficulty perceiving severity of airflow obstruction
- Comorbidities such as cardiovascular diseases or other systemic problems
- Serious psychiatric disease or psychosocial problems
- Illicit drug use, especially inhaled cocaine and heroin

63.8. A 25-year-old woman presents with wheezing and shortness of breath from asthma. She was recently exposed to cigarette smoke. She denies cough and fever. You cannot get much more of a history from her at this time because she finds it difficult to speak in complete sentences. Her vital signs are: blood pressure, 136/85 mm Hg; heart rate, 110 beats per minute; respiratory rate, 32 breaths per minute; and temperature, 99° F (37.2° C). Her oxygen saturation is 92%. Her peak expiratory velocity-1 is 50% of predicted percentage. On physical examination, you note bilateral wheezing, regular tachycardia, and accessory muscle use. The remainder of her examination is normal. Over the course of 1 hour, she receives supplemental oxygen, three doses of nebulized albuterol (5 mg) mixed with ipratropium (0.5 mg), and oral prednisone 60 mg. She now reports feeling somewhat better. She speaks in longer sentences but still cannot speak in complete sentences. A repeat peak flow measurement is now 60% of predicted. Otherwise, there are no changes on a repeat physical examination. You plan to admit her to your ED observation unit. What is an appropriate next step in the management of this patient?
A. Additional nebulized albuterol
B. Intravenous (IV) magnesium sulfate
C. IV methylprednisolone (Solu-Medrol)
D. Oral montelukast
E. Subcutaneous terbutaline

Answer: A. This patient presents with a moderate-to-severe asthma exacerbation. She has responded to initial therapy but continues to have moderate symptoms. Additional adrenergic medications are indicated. Because she is tolerating nebulized medications and is responding, there is no need for IV or subcutaneous adrenergics, such as terbutaline. IV magnesium sulfate is a smooth muscle relaxant, but it is generally reserved for more severe asthma exacerbations. Oral and IV steroids have the same efficacy, and regardless of the route, only need to be administered every 6 to 8 hours. Montelukast is a leukotriene-modifying drug that is used in chronic management. Studies are ongoing with the use of these medications in acute exacerbations of asthma. They may improve pulmonary function tests (PFTs), but they do not change rates of admission or adverse outcomes.

CHAPTER 64

Chronic Obstructive Pulmonary Disease

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PRINCIPLES

Background

Chronic obstructive pulmonary disease (COPD) is one of the most common causes of death worldwide. Although prevalence estimates vary by measurement methods and by population studied, there is general agreement that COPD is underdiagnosed and under-reported. In patients older than 65 years old, the percentage of all hospitalizations related to COPD approaches 20%.[1] COPD in the United States also accounts for a large financial burden, approximately 54 billion dollars annually, in large part due to hospitalizations and treatment of acute exacerbations.[2] Cigarette smoking remains the most important cause for developing COPD, although other factors, such as genetic syndromes and noxious exposures, contribute significantly to the worldwide burden of COPD. Other important risk factors include occupational exposure, passive smoke inhalation, biomass heating fuels in poorly ventilated areas, and air pollution.[3]

In response to the impact of COPD, large multinational collaborations, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD), sponsored jointly by the National Heart, Lung, and Blood Institutes and the World Health Organization (WHO), have developed guidelines and worldwide strategies to improve prevention and treatment of this debilitating lung disease. In their executive summary, the GOLD collaborators have updated their definition of COPD as "a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gas." The definition specifically avoids mention of chronic bronchitis and emphysema, two entities that have been traditionally included in the definition of COPD.[4]

Rather than using traditional definitions of COPD, the GOLD collaborators focus on airflow limitation as the principle feature of the disease. Airflow limitation is a direct result of a combination of parenchymal destruction and small airways disease. Both processes are a consequence of chronic inflammatory changes and present clinically in varying degrees amongst patients with COPD.

An exacerbation of COPD is characterized by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations, requiring a change in medication. As the severity of the underlying disease progresses, so does the frequency of exacerbations.[5] Moreover, in a subset of patients, incomplete recovery from acute exacerbations may reflect a contribution of exacerbations to the pathophysiology of disease progression.

Pathophysiology

Chronic airway inflammation is at the center of the pathophysiology for both COPD and asthma, but the inflammatory process differs in these two diseases. In asthma, the cellular response is largely eosinophil-mediated, whereas in COPD, neutrophils, CD8+ lymphocytes, and macrophages predominate in bronchial washings. Multiple inflammatory mediators are associated with lung parenchymal destruction in COPD, including tumor necrosis factor, leukotriene B4, and interleukin-8. These differences in the nature of the inflammatory response in COPD may account for its relatively poor response to anti-inflammatory treatment.

Progressive inflammation in COPD leads to airway limitation and obstruction. However, not all patients who smoke or have exposure to noxious stimuli develop COPD, raising the possibility that other contributory factors such as genetics and environmental factors make some patients more susceptible to this disease.[6] In COPD, evidence of airway inflammation is found from the trachea down to the smallest peripheral airways. In the larger, more proximal airways, an increase in both the number and size of mucous-secreting goblet cells can result in the formation of mucous plugs, which further contributes to airflow obstruction. Damage to the endothelium impairs the mucociliary response that clears bacteria and mucous. Airway resistance and flow limitation are mainly due to damage to the distal, smaller airways where the diameter is 2 mm or less. Smaller airways are further compromised by damage to surrounding connective tissue, resulting in a loss of the radial support that normally maintains their patency during expiration.

Apart from the inflammatory changes that occur in the airways, COPD patients also experience damage to the lung parenchyma. Damage to these zones of air exchange ultimately results in the pathologic state known as *emphysema.* In cigarette smokers, the parenchymal damage will typically present in a centriacinar pattern, especially in the early stages of the disease. Emphysema is no longer routinely used in the definition of COPD, because it is a pathologic and anatomically defined condition. Chronic bronchitis on the other hand is a clinical condition defined by the presence of chronic productive cough for 3 months in each of 2 successive years, where other causes of chronic cough have been excluded. Most patients with COPD will have mixed features of both conditions.

There is compelling evidence that protease/anti-protease imbalance plays a role in the modification of the inflammatory cascade and resultant parenchymal destruction seen in COPD. Protease-mediated destruction of connective tissues, including elastin results in lung parenchymal damage and resultant emphysema. Anti-proteases protect against connective tissue destruction and are an integral component in the pathogenesis of patients with congenital α1-antitrypsin deficiency. Congenital α1-antitrypsin deficiency accounts for a small percentage of COPD patients and is recognized by the lack of the anti-protease enzyme that inhibits the protease enzyme, neutrophil elastase.[7] The deficiency of this anti-protease results in uninhibited protease action, parenchymal destruction, and severe panacinar emphysema. Oxidative stress also plays a role in the inflammation associated with COPD. Oxidants are released after cigarette smoke and other noxious particles stimulate inflammatory cells, such as neutrophils and macrophages. The end result of this oxidative and inflammatory stress is airflow limitation from both parenchymal destruction and airway narrowing.

The combination of airway obstruction, parenchymal destruction, and obliteration of the pulmonary vascular bed results in failure of gas exchange. Blood gas analysis may reveal both hypoxemia and hypercapnia. As the overall size of the pulmonary

vascular bed decreases with time, chronic hypoxia induces a thickening of the vessel walls, which contributes to the development of pulmonary hypertension, polycythemia and, eventually, right-sided heart failure (cor pulmonale).

Although the precise mechanisms are ill-defined, the pathologic processes of COPD extend beyond the cardiac and pulmonary systems. The effects of circulating inflammatory mediators, oxidative stress, and protease/anti-protease imbalance may be responsible for the non-pulmonary complaints of weight loss, muscular wasting, metabolic derangements, and depression often seen in the later stages of disease. COPD influences a variety of management decisions in the emergency department (ED), ranging from the choice of agents for procedural sedation and rapid sequence intubation to the appropriate disposition of patients with non-pulmonary diagnoses.

CLINICAL FEATURES

Symptoms and Natural History

A clinical diagnosis of COPD should be considered in any patient with dyspnea, chronic cough or sputum production, and a history of risk factors for the disease. COPD patients have a long premorbid course during which decreases in airflow indices can be measured in the absence of significant symptoms. Airflow limitation can be measured via spirometry in the outpatient setting, which may be the earliest indicator and best predictor of early onset COPD. Intermittent cough or shortness of breath on exertion may be easily misattributed to poor physical conditioning. Moreover, patients may remain asymptomatic for many years by gradually limiting their activities in proportion to their pulmonary reserve. After several years, a daily productive cough frequently develops, and periods of dyspnea, the cardinal symptom of airflow limitation, increase. Note that the absence of wheezing does not exclude the diagnosis of COPD; nor does the presence of wheezing confirm the diagnosis. The clinical progression of COPD is slow and insidious, with gradual decreases in airflow punctuated by increasingly frequent and debilitating exacerbations. Eventually the patient becomes truly incapacitated by dyspnea on minimal or no exertion. Profound muscle wasting and weight loss and the emergence of cor pulmonale or chronic ventilatory failure are characteristic of end-stage disease. Figure 64.1 depicts the progression of COPD over time.

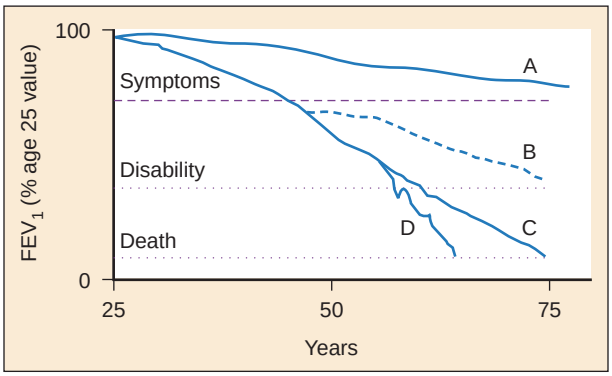

Fig. 64.1. The progression of chronic obstructive pulmonary disease (COPD) over time. Natural history of COPD as measured by forced expiratory volume in 1 second *(FEV_1)* as a percentage of the baseline value at age 25. Normal nonsmoking individuals *(A)* have a progressive loss of FEV_1 but never become symptomatic with airway obstruction. Patients with COPD who quit smoking *(B)* experience an FEV_1 decline that parallels a nonsmoking, age-matched person. Patients with progressive COPD *(C)* can develop a loss of FEV_1 that may eventually produce symptoms, disability, and death. Some COPD patients *(D)* have steep declines in lung function during discrete clinical episodes. (From Heffner JE: Chronic obstructive pulmonary disease on an exponential curve of progress. Respir Care 47:586, 2002.)

TABLE 64.1

The GOLD Grading of Severity of Airflow Limitation in Chronic Obstructive Pulmonary Disease Based on Post-Bronchodilator FEV_1/FVC Less Than 70%

GRADE	CHARACTERISTICS
I: Mild COPD	FEV_1 ≥80% of predicted
II: Moderate COPD	50% ≤FEV_1 <80% predicted
III: Severe COPD	30% ≤FEV_1 <50% predicted
IV: Very severe COPD	FEV_1 <30% of predicted

COPD, Chronic obstructive pulmonary disease; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *GOLD,* Global Initiative for Chronic Obstructive Lung Disease.

Adapted from Vestbo J, Hurd S, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187:351, 2013.

Severity of Airflow Limitation

Indicative of persistent airflow limitation, a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) less than 0.70, measured by spirometry, is now required to make the diagnosis of COPD. Although spirometry is important for outpatient evaluation of COPD, there is currently no role for spirometry in the ED. Once the diagnosis is made, the GOLD collaborators define four grades based on the patient's FEV_1. The grades are divided beginning with a GOLD I grade (mild COPD) where spirometry is abnormal but symptoms may not yet be apparent, and ending in GOLD IV grade (very severe COPD), when FEV_1 is less than 30% of predicted (Table 64.1). These grades can be predictive of an increased frequency of exacerbations as well as an increased risk of death.[8,9] Despite the GOLD classification of airflow limitation, the best predictor of exacerbations continues to be a history of previous exacerbations.[10]

Physical Examination

The division of patients with COPD into two phenotypes, the "blue bloater" (for the patient with chronic obstructive bronchitis) and the "pink puffer" (for the patient with emphysema), is outdated because many patients with COPD do not conform to these descriptions. Nonetheless, these classic images do highlight some of the important clinical features that may be encountered in the patient with COPD and have implications for management. Most patients have some combination of chronic obstructive bronchitis and emphysema and appear with a mixture of the syndromes described later. The precise identification of which process is predominant is less important than the evaluation of each patient and formulation of a specific treatment plan. In particular, the degree of chronic hypoxemia and dependence on home oxygen therapy, the presence of cor pulmonale, and evidence of comorbid illness (such as, ischemic heart disease) should be determined.

In patients in whom chronic bronchitis predominates, the findings are those of chronic respiratory failure and cor pulmonale. Little air hunger or anxiety is present, and the combination of polycythemia and hypoxemia creates a plethoric, cyanotic appearance. Cough, as the clinical hallmark of bronchitis, is prominent and, when vigorous, causes expectoration. If acute ventilatory failure is present, the patient's consciousness is clouded. This often is described as "irritable somnolence," and asterixis may

be present. Chronic ventilatory failure and cor pulmonale lead to prominent peripheral edema and jugular venous distention. If there is relatively little emphysema, the thoracic anteroposterior diameter is normal, and the diaphragm is not abnormally low. The presence of severe bronchopulmonary secretions is evidenced by scattered rhonchi and rales, especially at both lung bases posterolaterally. These patients often have chronic carbon dioxide retention, requiring close monitoring of oxygen therapy because of their relative dependency on hypoxemic drive for ventilation.

When emphysema predominates, the patient is often thin, anxious, alert and oriented, dyspneic, and tachypneic and uses accessory muscles of breathing. The patient often self-administers positive end-expiratory pressure (PEEP) by using a pursed lip exhalation pattern to increase intraluminal bronchial pressure and provide internal support for bronchial walls that have lost their external support. Such patients usually assume a sedentary existence, chronically hunched forward. Gross lung over-inflation occurs, with a low immobile diaphragm and an increased anteroposterior diameter of the thorax. Percussion of the chest reveals hyper-resonance, and auscultation demonstrates diminished breath sounds with faint end-expiratory rhonchi. Despite air hunger caused by the extensive lung parenchyma destruction, the patient maintains adequate oxygen saturation and often has near-normal arterial blood gas (ABG) levels. The heart is small and hypodynamic, and the blood pressure is usually low.

DIFFERENTIAL DIAGNOSES

The differential diagnosis of the acutely dyspneic and hypoxic patient is broad. The condition that is most commonly mistaken for COPD is cardiogenic pulmonary edema, which may manifest with dyspnea and wheezing ("cardiac asthma"). Other serious cardiac causes include myocardial ischemia and pericardial effusion. Important pulmonary diagnoses include pneumothorax, pulmonary embolism (PE), pneumonia, asthma, acute respiratory distress syndrome, bronchiectasis, pulmonary fibrosis, pleural effusions, and tuberculosis. In addition, metabolic acidosis and shock may manifest as dyspnea and ventilatory failure.

In most cases, a COPD exacerbation can be differentiated from acute congestive heart failure (CHF) on clinical grounds. Nonetheless, a significant percentage of patients who come to the ED with acute dyspnea and an established diagnosis of COPD are ultimately diagnosed with acute CHF despite having no prior history of heart failure.[11] The addition of a B-type natriuretic peptide (BNP) assay to the ED evaluation of such patients identifies some in whom a new diagnosis of CHF is not suspected.

Because BNP can be elevated in association with right ventricular stretch, incautious interpretation of an elevated BNP may lead the emergency clinician to favor the diagnosis of acute left-sided CHF and overlook cor pulmonale and PE, both critical considerations in the patient with COPD. Moreover, acute CHF and COPD often coexist, and even severe elevations in BNP do not obviate the identification and treatment of acute pulmonary pathology. Thus, although BNP measurement may be helpful in the evaluation of the acutely dyspneic patient, it cannot be interpreted in isolation and must not supplant clinical judgment.

Acute pneumothorax can occur with COPD secondary to ruptured bullae.[12] This diagnosis should be actively pursued in patients with worsening respiratory status, especially when its onset is abrupt. In older patients with COPD, chest pain is often absent. A small pneumothorax cannot be excluded by physical examination and can be very difficult to detect on inspiratory chest films, especially in patients with bullous emphysema. Bedside ultrasound is a useful modality for diagnosing pneumothorax in the ED.[13] In assessing for pneumothorax, however, the presence of COPD may result in false-positive results. Ultimately, a chest computed tomography (CT) should be performed when clinical suggestion of a pneumothorax is high and plain films and ultrasound are nondiagnostic.

Patients with COPD are often sedentary and may consequently be at increased risk for venous thromboembolic disease.[14,15] The patient with cor pulmonale is at even higher risk because of increased blood viscosity, high peripheral venous pressure, and venous stasis. PE should be considered when an acute exacerbation is more severe than prior episodes, particularly if deterioration occurs quickly with no other apparent cause.

Unfortunately, because there is significant overlap in presentation, differentiating PE from a COPD exacerbation can be extremely difficult, and PE should remain in the differential diagnosis especially when the patient does not respond to standard treatments.

Lobar atelectasis occurs as a result of mucous plugging of bronchi and can be lethal. Similar to pneumothorax and PE, it may manifest abruptly. The chest film may show linear horizontal streaking or small flare-like shadows; more often, it is normal. Hypoxemic reactive airway patients with a protracted course unresponsive to bronchodilators should be presumed to have either PE or atelectasis. If PE is excluded, such patients often require endotracheal intubation and aggressive interventional pulmonary toilet.

Pneumonia is a common, devastating complication of COPD that leads to mortality. In COPD patients, older age, higher COPD severity, comorbidities, and previous episodes of pneumonia are risk factors for pneumonia.[16] Classic symptoms of cough, fever, and toxicity are seen less often than the more nonspecific and subtle symptoms of malaise, weakness, decreased activity, and anorexia. Leukocytosis may or may not be present, and its presence is not necessarily indicative of infection because of its low specificity. Radiographic infiltrates may be subtle or absent, especially in patients whose lung parenchyma has been distorted or obliterated by emphysema, and comparison to previous radiographic studies may be necessary. Patients with radiographic signs of pneumonia have a higher mortality and hospital length of stay when compared to those without radiographic findings.[17]

Rib fractures occur in patients with COPD secondary to trauma, but in patients receiving steroids, they can be caused by vigorous cough alone. COPD has also been shown to have an association with osteoporosis, putting them at even higher risk of fractures.[18] When rib fractures are identified, secondary pulmonary contusion and pneumothorax also should be considered.

Lung malignancy is always a consideration in COPD, because these patients have a twofold to fivefold increase in lung cancer risk even when compared to other smokers without COPD.[19] Patients presenting with COPD and radiographic abnormalities should have these findings noted in the chart and follow-up arranged.

There are other treatable chronic, nonobstructive pulmonary diseases. For example, bronchiectasis is an often overlooked cause of purulent expectoration. It may accompany and contribute to COPD exacerbations. Although its pathologic characteristic is dilation, not constriction, of airways, the secretions that accompany it may result in an obstructive component. Active tuberculosis is considered in patients with infiltrates (not only apical), a chronic wasting course, and risk factors for active disease, such as human immunodeficiency virus (HIV) disease and homelessness. Sarcoidosis, which can manifest with chronic cough and constitutional symptoms, usually causes a dry cough and may be suggested on the basis of the radiographic appearance.

Finally, there are some iatrogenic causes of acute decompensation in COPD. Many agents, such as beta-blockers and cholinergic agents, may directly or indirectly produce bronchospasm. A second group of potentially deleterious drugs is sedatives. It is important not to confuse hypoxic agitation with anxiety because patients with chronic respiratory failure are abnormally

BOX 64.1

Causes of Acute Decompensation in the Patient With Chronic Obstructive Pulmonary Disease

ACUTE EXACERBATIONS

Infectious

Viral
- Rhinovirus, respiratory syncytial virus, coronavirus, influenza virus

Bacterial
- *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella (Branhamella) catarrhalis, Pseudomonas aeruginosa*

Atypical bacteria
- *Chlamydia pneumoniae, Legionella*

Air Pollution

Nitrogen dioxide
Ozone
Particulates, dust

OTHER CRITICAL EVENTS

Pneumothorax
Pulmonary embolism (PE)
Lobar atelectasis
Congestive heart failure (CHF)
Pneumonia
Pulmonary compression (eg, obesity, ascites, gastric distention, pleural effusion)
Trauma (eg, rib fractures, pulmonary contusion)
Neuromuscular and metabolic disorders
Unrelated treatable chronic pulmonary disease (bronchiectasis, tuberculosis, sarcoidosis)
Noncompliance with prescribed treatment regimens
Iatrogenic
- Inadequate therapy
- Inappropriate therapy (eg, deleterious drugs)

sensitive to the respiratory depressant effect of sedatives, and even small doses may significantly worsen hypoventilation. Box 64.1 summarizes the causes of acute decompensation in the patient with COPD.

DIAGNOSTIC TESTING

Currently, the diagnosis of an acute COPD exacerbation is clinical and based on an increase in dyspnea, cough, or sputum production that is beyond normal day-to-day variation. Other diagnostic modalities can help guide management but should not be a substitute for the patient's clinical presentation.

Pulse Oximetry, Blood Gas Analysis, and Capnography

Pulse oximetry is a core element of the evaluation and monitoring of the acutely exacerbated COPD patient. Comparison with prior values, both in crisis and in baseline state, helps to interpret measurements obtained during an acute exacerbation. The change in pulse oximetry from baseline or in response to emergency therapy is generally more important than absolute levels.

The stages of COPD severity correlate with arterial gas tensions. Abnormal ventilation-perfusion relationships of COPD produce only modest decreases in arterial partial pressure of oxygen (PaO_2) in its early stages (80 to 100 mm Hg). Later in the course of the disease, hypoxemia below 60 mm Hg stimulates respiratory centers, producing hyperventilation (partial pressure of carbon dioxide [PCO_2] over 35) and acute respiratory alkalosis. As pulmonary dysfunction progresses, the work of hyperventilation becomes cost-ineffective—that is, more carbon dioxide is produced by the effort than is cleared by the increased ventilation. Eventually, alveolar hypoventilation impairs gas exchange, leading to carbon dioxide retention and acute respiratory acidosis. With renal compensation through bicarbonate retention, the pH normalizes. Finally, when acute ventilatory failure is superimposed at this late stage of the disease, an elevated PCO_2, lowered pH, and elevated bicarbonate are found.

Although measurement of ABGs was once a mainstay of ED evaluation of COPD patients, we do not recommend their routine use. Response to therapy can often be monitored sufficiently by the patient's clinical status and noninvasively by capnography and pulse oximetry. The decision to intubate a patient or initiate bi-level positive airway pressure (BiPAP) should be guided by the overall state of the patient, progression of fatigue, comorbid illness, and response to therapy. Patients with very poor blood gas values may do well without intubation or BiPAP, whereas others with mildly disturbed values may require urgent airway intervention.

If an ABG is performed, the presence of respiratory failure that is unresponsive to therapy (defined as PaO_2 <60 mm Hg with or without a $PaCO_2$ >50 mm Hg, and pH <7.25 mm Hg) warrants consideration of admission to an intensive care unit, but clinical evaluation is much more important than any particular blood gas values. The GOLD guidelines recommend obtaining ABGs prior to intubating a COPD patient. Although it may be useful for post intubation management to know the patient's serum pH, the authors do not support any delay in care for obtaining a blood gas.

The correlation of venous blood gases (VBGs) and ABGs has been studied in both COPD patients and in patients receiving noninvasive mechanical ventilation. They yield similar results with regard to serum pH and bicarbonate levels, whereas PCO_2 levels demonstrate less agreement.[20,21]

Waveform capnography, which represents the continuous quantitative measurement of exhaled carbon dioxide, has emerged as a useful monitoring tool in patients with respiratory distress or undergoing procedural sedation. Unfortunately, in patients with COPD, the actual end-tidal carbon dioxide ($ETCO_2$) measurement obtained from capnography does not correlate well with the arterial PCO_2, especially in more severe disease. Therefore, capnography and $ETCO_2$ measurement should not be considered as a part of the decision-making process to predict $PaCO_2$ level in COPD patients.[22]

Chest Radiography

In patients who are known to have COPD, the primary role of the chest radiograph is to evaluate for the presence of other alternative diagnoses. A chest x-ray can determine whether there is an acute, treatable cause for clinical deterioration, especially pneumothorax or parenchymal consolidation (atelectasis secondary to mucous plugging, pneumonia, or obstruction by tumor). Otherwise, the chest radiograph is of limited use and may exhibit a range of chronic changes, depending on disease severity and the relative degree of the various pathologic processes. Findings may include hyperinflated lung fields, decreased vascular markings, and a small cardiac silhouette or, in contrast, normal inflation with increased vascular markings and an enlarged heart.[23] In cor pulmonale, impingement on the retrosternal airspace by the enlarged right ventricle can be seen on the lateral film.

Bullae may also be present and may mimic or mask a pneumothorax. In addition, chest radiography may reveal important coexistent pathology, including CHF, effusions, and tumors. Routine chest radiography is recommended for evaluation of the patient with an acute COPD exacerbation.

Spirometry

Although spirometry plays a key role in making a diagnosis of COPD in the outpatient setting, there is no role for pulmonary function testing in the ED because it is difficult to perform and inaccurate in patients with acute exacerbations. Measurement of forced expiratory volume is simple to perform but is less useful in COPD than in asthma, where airway obstruction is more acutely reversible.

Sputum Examination

Although a clinical history of changes in sputum production and purulence can support a diagnosis of COPD exacerbation, diagnostic testing of sputum does not provide clinical value in the ED setting.

As with asthma, viral infection appears to be a frequent inciting agent in COPD exacerbations. Commonly implicated viruses include rhinovirus, respiratory syncytial virus, coronavirus, and influenza virus.[24] Although rapid influenza tests during epidemics may prompt antiviral therapy in patients with severe COPD, other viral tests are not useful.

Controversy remains regarding the role of bacterial pathogens in acute exacerbations of COPD. Almost half of all exacerbations are associated with negative cultures for the typical respiratory pathogens, such as *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella (Branhamella) catarrhalis,* and *Pseudomonas aeruginosa.* In addition, these organisms are recovered from the tracheobronchial tree of patients in their chronic, steady state, suggesting that bacteria may play a more important role in the pathogenesis of chronic COPD than in acute exacerbations.

Electrocardiogram and Cardiac Monitoring

The classic descriptions of P pulmonale (peaked P waves in leads V_2, V_3, and aV_F), low QRS voltage, clockwise rotation, and poor R wave progression in the precordial leads are interesting correlates of COPD but are both insensitive and nonspecific. The presence of electrocardiogram (ECG) criteria for right ventricular hypertrophy (RVH) suggests established cor pulmonale. These findings, however, can be easily obscured on the ECG by other processes, and the absence of criteria for RVH cannot be relied on to rule out cor pulmonale.

In severely ill patients or those with concomitant chest pain, continuous ECG monitoring may be helpful, at least for the initial phase of the patient's evaluation and treatment. ECG monitoring can detect dysrhythmias associated with COPD exacerbations and changes of rate and rhythm in response to therapy. The most common dysrhythmias associated with COPD are atrial tachydysrhythmias, such as atrial fibrillation and multifocal atrial tachycardia. Although atrial fibrillation may require treatment with rate control or conversion, multifocal atrial tachycardia often resolves with the treatment of the COPD exacerbation itself.

Blood Tests

Routine hematologic evaluation adds little to the treatment of the patient with COPD and acute exacerbation. A complete blood count (CBC) may reveal polycythemia associated with chronic hypoxia. An elevated white blood cell (WBC) count is nonspecific and should not be interpreted as indicative of coexistent infection, nor should a normal-range WBC count support a contention that infection is not present. Therefore, obtaining a CBC is not recommended for an acute exacerbation responsive to initial therapy.

The measurement of BNP, released by myocardial tissue in response to stretch and a critical part of volume homeostasis, may be useful as a diagnostic adjunct in patients with acute dyspnea. BNP values above 500 pg/mL are suggestive of decompensated heart failure, and levels below 100 pg/mL are very suggestive of the absence of CHF.[25,26]

Despite the sensitivity of BNP in detecting the physiologic presence of heart failure, its utility as a routine test in the assessment of dyspneic patients is debated. Additionally, the interpretation of a BNP is of limited value in certain patient populations. For example, we do not recommend routine BNP studies in patient with renal failure on hemodialysis, because these numbers are often elevated regardless of whether the patient has heart failure.[27] We do recommend BNP testing in the patient who has both COPD and CHF who presents with dyspnea to help discern whether the patient is primarily presenting with a CHF exacerbation or a COPD exacerbation. Although we do not recommend the routine use of BNP in all acutely dyspneic patients in the ED, a BNP may be useful in the appropriate clinical setting in assessing for CHF versus COPD in the undifferentiated patient with dyspnea and/or wheezing.

Troponins are often ordered in the ED evaluation of the acutely dyspneic patient. In the presence of an abnormal ECG or when the patient's dyspnea is more severe than expected, we do recommend ordering a troponin in the acute exacerbation COPD patient. Although they rarely identify acute cardiac pathology missed by ECG, elevated troponins in patients with COPD exacerbation are associated with increased in-hospital and 30-day mortality, and should be considered in the decision to admit.

MANAGEMENT

The three classes of medications most often used in the management of acute COPD exacerbations are short-acting bronchodilators, steroids, and antibiotics, and each will be reviewed in further detail. An overview of the emergency assessment and management of COPD exacerbations is provided in Table 64.2.

Oxygenation and Ventilation

All COPD patients in acute respiratory distress require continuous ECG and pulse oximetry monitoring. Patients who are hypoxemic should receive controlled oxygen therapy, with a goal

TABLE 64.2

General Therapeutic Guidelines for Chronic Obstructive Pulmonary Disease Exacerbations*

LIFE-THREATENING	MODERATE OR SEVERE	MILD
Address ABCs	Oxygen to maintain oxygen saturation near 90%	Oxygen to maintain oxygen saturation near 90%
Bag-valve ventilation, preoxygenation	Nebulized beta-agonist, anticholinergic	MDI or nebulized beta-agonist, anticholinergic
Intubation with or without rapid sequence technique	Noninvasive ventilation if severe	Consider oral or IV corticosteroid
Inline beta-agonist, anticholinergic	IV corticosteroid	Consider oral antibiotic on discharge
IV corticosteroid	IV antibiotic	
IV antibiotic		

ABC, Airway, breathing, and circulation; *IV,* intravenous; *MDI,* metered-dose inhaler.
*It is important to consider an inciting or aggravating factor and provide specific therapy as discussed in text.

of oxygen saturation as measured by pulse oximetry (SpO_2) of 88% to 92% or PaO_2 above 60 mm Hg.[28] The method of administration should be tailored to the clinical circumstances. Nasal cannulae are well tolerated but are less useful for patients who are markedly tachypneic or mouth-breathing. Venturi masks are excellent for delivering a more reliable, high-flow, and adjustable concentration of supplemental oxygen but may be difficult for a distressed patient to tolerate.

Some patients with moderate to severe COPD and other chronic pulmonary diseases will respond to high-flow supplemental oxygen by developing hypercapnic respiratory failure. The mechanism for this response is debated but may be a result of several factors, including the suppression of hypoxic respiratory drive in patients accustomed to hypercapnia and the release of hypoxic vasoconstriction in poorly oxygenated areas of the lung, worsening ventilation/perfusion mismatch. We recommend setting a specific SpO_2 target of 88% to 92% and avoiding uncontrolled high-flow oxygen in dyspneic COPD patients, including in the prehospital environment.[29]

The patient in terminal ventilatory failure may be cyanotic, speechless, lethargic, or confused and has gasping, ineffective respirations. Such patients require immediate endotracheal intubation and mechanical ventilation. Because these patients have exhausted all pulmonary reserve, rapid sequence intubation should be performed with the goal of rapid paralysis and unconsciousness (see Chapter 1). For induction and paralysis, a combination of a hemodynamically stable sedative-hypnotic (such as, etomidate or ketamine) and a rapidly acting paralytic (such as, succinylcholine) is an appropriate regimen.

Initial ventilator settings should include a fraction of inspired oxygen (FiO_2) of 100%, tidal volume in the 6- to 8-mL/kg range, and respiratory rate of 8 to 10 breaths/minute in an assist-control mode, with an inspiratory flow rate of 80 to 100 L/minute. Sedation and analgesia are indicated to facilitate ventilation. Ongoing neuromuscular blockade post intubation is not routinely required and should be avoided when possible (see Chapter 1). Increased air trapping and resultant high intra-alveolar pressures induce intrinsic positive end-expiratory pressure (iPEEP) that can cause barotrauma. In addition, increased intrathoracic pressure decreases cardiac filling and output; therefore, peak flow pressures and systemic blood pressures must be carefully monitored. If continuous capnography is not available, ABGs should be drawn after 15 to 20 minutes to ensure that ventilation is appropriate. After intubation, permissive hypercapnia is essential to the ventilatory treatment of these patients, and subsequent normalization of pH and PCO_2 should be gradual over many hours. Low volume and rate settings will result in hypercapnia and respiratory acidosis, but this approach helps prevent associated barotrauma often seen in treating these patients. Moreover, hyperventilation alkalosis must be scrupulously avoided, particularly because patients may have preexisting chronic metabolic alkalosis. This alkalosis can result in seizures and dysrhythmias, especially with coexisting hypokalemia.

Noninvasive ventilator support/BiPAP is an accepted and effective alternative to invasive ventilation in many patients with ventilatory failure (see Chapter 2). BiPAP can be highly beneficial in avoiding intubation by decreasing respiratory rate and work of breathing, improving respiratory acidosis, and reducing mortality rates.[30,31] Additional benefits of avoiding invasive ventilation include lower rates of ventilator-associated pneumonia and shorter hospital stays.[32] If the patient does require intubation, BiPAP optimizes preoxygenation for the intubation. Patients likely to benefit from BiPAP are those with moderate to severe ventilatory failure and elevated PCO_2 but without marked hypoxemia or altered mental status.[33,34] BiPAP cannot substitute for invasive ventilation in patients who are hemodynamically unstable, markedly agitated and uncooperative, or in whom respiratory arrest appears inevitable. On the opposite end of the spectrum, it remains unclear whether BiPAP should be instituted in patients with mild to moderate exacerbations. Although the Cochrane systematic review stresses early BiPAP therapy to prevent the development of worsening acidosis and need for intubation, there is insufficient evidence to recommend the routine use of BiPAP in mild exacerbations.[35] Table 64.3 outlines inclusion and exclusion criteria for the use of BiPAP.

TABLE 64.3

Suggested Selection and Exclusion Criteria for the Use of Noninvasive Ventilatory Support

SELECTION CRITERIA (ONE OR MORE MAY BE PRESENT)	EXCLUSION CRITERIA (ANY MAY BE PRESENT)
Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion	Respiratory arrest
Respiratory rate 25 breaths/min	Cardiovascular instability
Moderate to severe acidosis (pH <7.35) and hypercapnia ($Paco_2$ >45 mm Hg)	Uncooperative patient (agitated or severely somnolent)
	Upper airway obstruction
	High aspiration risk
	Recent facial or gastroesophageal surgery
	Craniofacial trauma, fixed nasopharyngeal abnormalities
	Non-fitting mask

$Paco_2$, Arterial partial pressure of carbon dioxide.
Adapted from Vestbo J, Hurd S, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187:351, 2013; Soto F, Varkey B: Evidence-based approach to acute exacerbations of COPD. Curr Opin Pulm Med 9:117, 2003.

BiPAP can be delivered by either nasal or full-face mask. It is not uncommon for patients to experience claustrophobia and panic with either type of mask. Coaching and reassurance may help some of these patients tolerate BiPAP long enough to feel some relief of their dyspnea and anxiety. Moreover, some patients who do not tolerate nasal masks will tolerate full-face masks and vice versa. Repeated and prolonged attempts at BiPAP, however, in a patient who is panicked and in obvious respiratory failure should not delay definitive airway intervention if necessary.

Although nasal CPAP with pressure support of 5 to 10 cm H_2O pressure is a simple technique that can help stent obstructed airways open, we recommend BiPAP in order to decrease the work of breathing. Expiratory positive airway pressures are typically set at 2.5 to 5 cm H_2O, whereas inspiratory pressures range from 7.5 to 15 cm H_2O.

If the patient experiences relief of dyspnea, has stronger respirations, and becomes more alert, intubation may be averted. Improvement of pH within 1 hour of BiPAP administration can be predictive of survival to hospital discharge.[36] Increasing respiratory rate, lethargy, exhaustion, speechlessness, paradoxical abdominal breathing movements, and worsening hypoxia necessitate invasive ventilation.

The most important factor in the decision to intubate is the patient's clinical status, not ABG measurements. Even in the face of a significant rise in PCO_2 with oxygen administration, intubation may be unnecessary if the patient's clinical status has stabilized. Similarly, improving ABG values should not overrule the clinical impression of deterioration. Temporary improvement may be followed by exhaustion and respiratory failure. Box 64.2 outlines indications for invasive mechanical ventilation. Several of these criteria, adapted from the GOLD collaborators, are subject to interpretation, underscoring the critical role of clinical judgment in airway management decisions.

BOX 64.2

Proposed Indications for Mechanical Ventilation

Respiratory arrest
Worsening level of consciousness despite maximal therapy*
Cardiovascular instability (shock, heart failure)*
NIPPV failure or exclusion criteria (see Table 64.3)
Severe dyspnea with use of accessory muscles and paradoxical abdominal motion*
Severe tachypnea*
Life-threatening hypoxia
Severe acidosis and hypercapnia*
Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism [PE], barotraumas, massive pleural effusion)*

Adapted from Vestbo J, Hurd S, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187:351, 2013.
NIPPV, Nasal intermittent positive-pressure ventilation.
*For several of these parameters, criteria are deliberately imprecise; clinical decisions must be individualized in each case.

General Drug Therapy

Bronchodilators

Although bronchospasm is not the primary inciting event in acute COPD exacerbation, both short-acting beta-agonists and anticholinergic agents are considered first-line agents. The choice of agent for treating a given patient may depend on the respective side effect profiles of these two classes of drugs, although the combination of both medications is safe in most patients.

Although many choices are available, inhaled albuterol, which is short acting with selective beta-2 receptor action, is the beta-agonist of choice. The nebulization dose of albuterol is 2.5 to 5.0 mg (0.5 to 1.0 mL of 0.5% solution). Most patients tolerate two to three rapid successive doses of oxygen-nebulized beta-agonist with little difficulty. Therapy must occasionally be titrated if the side effects of tremor, tachycardia, or ventricular ectopy are significant.

Anticholinergic agents block muscarinic receptors and prevent smooth muscle contraction while decreasing the release of secretions from submucosal glands. Inhaled anticholinergic agents are as effective as beta-2 agonists in COPD and can be used alone or in conjunction with beta-2 agonists as first-line therapy in acute exacerbations. Although evidence regarding the efficacy of their coadministration is controversial, for moderate to severe exacerbations in the ED, these drugs should be given together for their possible synergistic effects. Anticholinergics can be administered by nebulization or metered-dose inhaler (MDI) and are also effective for intubated patients. Ipratropium bromide, a quaternary ammonium compound, has been extensively studied in COPD. The nebulization dose is 0.5 mg, which may be repeated every half hour for a total of three doses and subsequently every 4 hours. Although anticholinergics have powerful bronchodilating properties, caution should be exercised in patients with preexisting arrhythmias and cardiac disease, because these medications may put the patient at higher risk of adverse cardiac events.[37]

Long-acting bronchodilator agents, such as salmeterol (beta-2 agonist) and tiotropium (anticholinergic), are used for chronic stable COPD. Although these agents may reduce the frequency of COPD exacerbations, they have no role in ED management of acute exacerbation.

The COPD patient with a mild to moderate exacerbation may be able to self-administer bronchodilator agents through use of an MDI with a spacer device, which is as effective as nebulized treatment. Studies also demonstrate the efficacy and cost benefit of MDI therapy over nebulization in acutely hospitalized patients. Because of the smaller dose delivered with single MDI puffs, MDI protocols often involve multiple puffs at each administration interval. This mode of therapy should only be considered for stable, cooperative patients. The intubated patient should receive bronchodilator therapy via inline nebulization.

Methylxanthines, principally aminophylline, were once commonly used in COPD exacerbations. Evidence is not supportive of their use, however, because they do not improve outcomes, even when combined with beta-agonists and anticholinergic agents. Recommendations that include methylxanthines as a second-line therapy when other modalities have failed are tempered by concerns about toxicity, which may outweigh the positive effects of these agents. If a rare patient is encountered who is taking methylxanthines on a chronic, ambulatory basis, additional methylxanthines should not be used in the course of treatment in the ED.

In addition to beta agonists and anticholinergics, magnesium sulfate may also demonstrate a bronchodilatory effect that is thought to occur through bronchial smooth muscle relaxation. Current guidelines make no recommendations for the use of magnesium in acute exacerbation COPD. Although there is some evidence that IV magnesium sulfate may play a role in potentiating the bronchodilatory effects of beta-agonists, there is currently insufficient high quality evidence to recommend routine administration of IV or inhaled magnesium in the treatment of COPD in the ED.[38,39]

Corticosteroids

The anti-inflammatory effects of steroids provide a strong rationale for their use in acutely ill patients with COPD. Although steroids may not alter the immediate ED course, their use does result in a modest decrease in the relapse rate of acute exacerbations and improvement of dyspnea. When initiating steroid therapy in the acute exacerbation COPD patient, the emergency clinician must decide on the optimal dose and route of administration. Recommended doses and routes of corticosteroids have varied widely in published studies. There is some evidence that shorter courses of systemic steroids (less than 7 days) are likely to be as effective as longer 10 to 14 day courses.[40,41]

Regarding the route of administration, guidelines continue to recommend oral systemic corticosteroids over IV corticosteroids because they generally provide similar efficacy but have the advantage of reduced cost and higher ease of administration.[42] Current evidence supports the use of oral prednisone for both admitted and discharged patients though less evidence exists for the critically ill COPD patient admitted to the ICU.[43] Systemic IV glucocorticoids should be administered to patients who are unable to tolerate oral steroids due to severity of illness or other causes of *per os* (by mouth; PO) intolerance. For COPD exacerbation patients, prednisone 40 mg PO or methylprednisolone 1 to 2 mg/kg intravenous (IV) are acceptable initial steroid doses. We recommend use of lowest effective dose and shortest effective duration of therapy to minimize common adverse effects, such as hyperglycemia, myopathy, and immunosuppression.

Antibiotics

In contrast to asthma exacerbation and acute bronchitis in the setting of normal lung function, in which antibiotics are of no benefit, some COPD patients with an acute exacerbation appear to benefit from antibiotic therapy.[44,45] Despite a large body of literature on the topic, the exact role of antibiotics in COPD continues to remain controversial. The GOLD collaborators recommend administering antibiotics to patients with an increase in sputum purulence and either increased dyspnea or increased

sputum volume, as well as to any patients requiring invasive or noninvasive ventilation. The GOLD collaborators further recommend that antibiotics be continued for 5 to 10 days based on Level D evidence. A 2012 Cochrane review examined the role of antibiotics in COPD exacerbations and stratified their results into ICU, inpatient, and discharged patients.[46] Amongst ICU patients, the authors found that antibiotic use resulted in large and consistent beneficial effects and an additional mortality benefit. For non-ICU admitted patients, patients receiving antibiotics improved clinically but without any definitive mortality benefit. For discharged patients, there is less clear benefit and evidence for the use of antibiotics in this patient population remains inconsistent and controversial.

Many of the randomized, controlled trials suggesting a treatment benefit with antibiotics were conducted before the emergence of widespread resistance. The GOLD collaborators recommend use of antibiotics that reflect local patterns of antibiotic sensitivity to *S. pneumoniae, H. influenzae,* and *M. catarrhalis.* Currently, antibiotic therapy in COPD patients typically involves the use of aminopenicillins with or without clavulanic acid, macrolides, or tetracyclines. Patients with frequent exacerbations, severe airflow limitation, or mechanical ventilation may have pseudomonal involvement or other resistance patterns requiring expanded spectrum antibiotics, such as fluoroquinolones.[4] Although antibiotics with broader-spectrum coverage, such as the fluoroquinolones and third-generation cephalosporins, are commonly prescribed, the evidence for the superiority of these newer agents is indirect. Studies suggest that short (3- to 5-day) courses of antibiotics, such as respiratory fluoroquinolones or macrolides, may be as effective as more traditional, longer (7- to 14-day) courses of beta-lactams and tetracyclines.[47] There is limited data, however, on the optimal antibiotic regimen in these patients. The authors recommend prescribing a short course of macrolides or a standard course of tetracycline for uncomplicated outpatient and inpatient COPD exacerbations requiring antibiotics. For more complicated inpatient COPD admissions, consideration of fluoroquinolones or extended spectrum beta-lactams is appropriate in patients at risk for antibiotic resistance, such as mechanical ventilation or those with multiple and frequent hospitalizations.

Based on the GOLD recommendations and Cochrane review findings, the authors recommend antibiotic administration to all patients admitted for acute exacerbation COPD. Because the literature is less clear on routine antibiotic administration for discharged patients, the emergency clinician can use his or her clinical judgment in deciding to prescribe antibiotics. In general, the emergency clinician should be more likely to consider antibiotics if the patient has an increase in sputum purulence and either increased dyspnea or increased sputum volume.

Other Therapeutic Agents

Mucokinetic Medications and Mucus Clearance Strategies. Mucus production and cough are cardinal symptoms of COPD. Unfortunately, little evidence exists that mucokinetic agents are successful, and they are not recommended. Nebulized saline, oral expectorants, and chest physiotherapy also fail to demonstrate benefit.

Heliox. Helium-oxygen mixtures decrease the work of breathing and improve airflow by virtue of their low density. Such mixtures, however, fail to demonstrate clinical benefit in patients with COPD exacerbations.[48]

Respiratory Stimulants. Several respiratory stimulants have been studied in patients with COPD, including opioid antagonists, progesterone, acetazolamide, doxapram, and almitrine. Doxapram appears to be the most effective of these agents and works by stimulating chemoreceptors in the carotid bodies, stimulating the brainstem respiratory center. Although doxapram can effect small, temporary improvements in blood gas exchange in the first hours of treatment, it is less effective than other techniques, such as BiPAP. Respiratory stimulants are therefore not recommended for routine use in the ED.

Prevention of Chronic Obstructive Pulmonary Disease Exacerbations via Anti-Inflammatory Therapy. Preliminary evidence points to the possibility that other therapeutic strategies may reduce exacerbation frequency via immunomodulatory effects. Roflumilast, a selective phosphodiesterase 4 inhibitor, may be of benefit in the outpatient setting in the prevention of COPD exacerbations.[49,50] However, there does not appear to be any current role for the ED use of roflumilast in the management of acute exacerbations.

Macrolide antibiotics, such as erythromycin and azithromycin, also exhibit immunomodulatory and anti-inflammatory properties in addition to their antibiotic effects and have therefore also been suggested in the prevention of COPD exacerbation. Although studies have shown some promise in reduction of exacerbations, GOLD does not currently recommend the use of daily macrolides for this purpose given its potential to increase antibiotic resistance and QT intervals, resulting in cardiac toxicity.[51]

Future Therapies for Chronic Obstructive Pulmonary Disease Exacerbations. Bedoradrine is a highly selective beta-adrenergic agent for management of exacerbations. A phase II study in patients with an exacerbation, this agent was given by slow IV injection and resulted in prolonged bronchodilatation without an increase in adrenergic adverse events.[52] We do not currently recommend the use of this medication until further studies are completed.

In summary, current ED management of COPD exacerbations involves supplemental oxygen to prevent severe hypoxia and noninvasive or invasive ventilatory support when necessary. Every patient should receive short-acting bronchodilator therapy and oral systemic steroids. Finally, supplemental antibiotics should be considered depending on the individual patient presentation.

DISPOSITION

Significant deterioration from baseline is the general guideline for admission of patients with COPD. Important factors in the decision include the presence of coexisting conditions, failed outpatient management for the current exacerbation, and lack of improvement while in the ED.[53] The GOLD collaborators propose guidelines for admission, and these are adapted in Box 64.3. If the

BOX 64.3

General Guidelines for Admission of the Patient With Chronic Obstructive Pulmonary Disease

- Significant worsening of symptoms from baseline
- Inadequate response of symptoms to emergency department (ED) management
- Significant comorbid condition (eg, pneumonia, heart failure)
- Worsening hypoxia or hypercarbia (from baseline)
- Inability to cope at home or insufficient home resources

Adapted from Vestbo J, Hurd SS, Agusti AG, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187:351, 2013.

decision is made to discharge the patient, attention should also be directed to the patient's vaccination status, proper technique of inhaler use, evaluation of outpatient support systems, appropriate referrals, and, perhaps most important, smoking cessation.

KEY CONCEPTS

- Acute exacerbation of chronic obstructive pulmonary disease (COPD) is defined by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations, requiring a change in medication.
- Cigarette smoking remains the most important single cause for developing COPD. However, genetic syndromes, occupational exposures, passive smoke inhalation, biomass heating fuels in poorly ventilated areas, and air pollution are also important contributory risk factors worldwide.
- Consider other life-threatening diagnoses in the acute exacerbation COPD patient who does not respond to standard treatments. Such diagnoses include acute heart failure, pulmonary embolism (PE), pneumonia, mucous plugs, and pneumothorax. Emergency clinicians should maintain a high index of suspicion for lung malignancy in COPD patients.
- The most common dysrhythmias associated with COPD are atrial fibrillation and multifocal atrial tachycardia. Classic electrocardiogram (ECG) findings for COPD include P pulmonale, low QRS voltage, and poor R wave progression but none of these findings are sufficiently sensitive or specific for COPD and should not be relied upon to make the diagnosis.
- Noninvasive ventilator support/bi-level positive airway pressure (BiPAP) is an accepted and effective alternative to invasive ventilation in COPD patients with moderate to severe COPD exacerbation. However, BiPAP cannot substitute for invasive ventilation in patients who are hemodynamically unstable, markedly agitated, and uncooperative or in whom respiratory arrest appears inevitable.
- The most important factor in the decision to intubate is the patient's clinical status, not arterial blood gas (ABG) measurements. Even in the face of a significant rise in partial pressure of carbon dioxide (PCO_2) with oxygen administration, intubation may be unnecessary if the patient's clinical status has stabilized.
- The three classes of medications most often used in the management of acute COPD exacerbations are bronchodilators, steroids, and antibiotics.
- Bronchodilators, such as albuterol (short-acting beta-2 receptor agonist) and ipratropium bromide (anticholinergic), are considered first-line agents in the treatment of acute exacerbation COPD and may provide a synergistic treatment effect.
- Acute exacerbation COPD patients should receive systemic corticosteroids. Oral and intravenous (IV) forms demonstrate similar efficacy, but patients who are unable to tolerate the oral form due to respiratory failure or *per os* (by mouth; PO) intolerance should receive the IV form.
- Antibiotics should be administered to all acute exacerbation COPD patients requiring both intensive care unit (ICU) and non-ICU admission. In discharged patients, the emergency clinician should consider antibiotics if the patient has an increase in sputum purulence and either increased dyspnea or increased sputum volume.
- Although there is some evidence that IV magnesium sulfate may play a role in potentiating the bronchodilatory effects of beta-agonists, there is currently insufficient high quality evidence to recommend routine administration of IV or inhaled magnesium in the treatment of COPD in the emergency department (ED).
- Currently there is no role for methylxanthines, heliox, or respiratory stimulants in the management of COPD patients in the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 64: QUESTIONS & ANSWERS

64.1. Which of the following statements regarding smoking and chronic obstructive pulmonary disease (COPD) is true?

A. Approximately 50% of COPD patients have a significant smoking history.

B. Progression can be reliably predicted in percentages per year.

C. Smoking cessation fairly reliably halts progression of COPD.

D. Smoking results in a destructive inflammatory cascade very similar to that seen in asthmatics.

E. The minority of smokers eventually develop airflow limitation.

Answer: E. Most smokers do not get airflow limitations. Genetic and environmental factors play important roles. The destructive inflammatory process, once initiated, continues to some degree despite smoking cessation. This cascade, as compared with asthma, involves neutrophils rather than eosinophils, different leukotrienes, and tumor necrosis factor expression. Progression cannot be precisely predicted.

64.2. Frequent chronic obstructive pulmonary disease (COPD) exacerbations can be anticipated when a patient's baseline forced expiratory volume in one second (FEV_1) falls below which of the following?
- **A.** 75%
- **B.** 50%
- **C.** 25%
- **D.** 10%
- **E.** There is no correlation.

Answer: B. This corresponds to stage 3/stage 4 COPD.

64.3. What is the most frequent etiology for chronic obstructive pulmonary disease (COPD) exacerbation?
- **A.** Bacterial
- **B.** Environmental
- **C.** IdiopathicD. Viral
- **E.** Other systemic illnesses

Answer: D. Idiopathic accounts for approximately 30%. The role of bacterial pathogens is unclear, with chronic colonization suggesting a greater role in the chronic progression rather than acute flares. Environmental causes play a role, but this is difficult to define.

64.4. A 69-year-old man with known chronic obstructive pulmonary disease (COPD) presents with an acute 2-day flare of his disease. Current medications are albuterol inhaler, amlodipine 10 mg/day for hypertension, and furosemide 40 mg/day. His primary symptoms are exertional dyspnea and cough with a change to yellow sputum production from clear. Vital signs are: blood pressure, 160/100 mm Hg; respiratory rate, 24 breaths per minute; heart rate, 120 beats per minute; oral temperature, 98.4°F (36.9°C); and oxygen saturation, 91%. Chest radiograph shows hyperinflation with no infiltrate. Electrocardiography (ECG) shows multifocal atrial tachycardia (MAT). Which of the following is true?
- **A.** As for acute bronchitis, antibiotics are of no benefit for acute COPD exacerbation.
- **B.** Beta-agonist and corticosteroid treatment mirror recommendations for acute asthma flares.
- **C.** If endotracheal intubation is required, ventilatory settings to maintain a partial pressure of oxygen (Po_2) greater than 60 mm Hg and a partial pressure of carbon dioxide (Pco_2) 40 mm Hg or less are recommended.
- **D.** Outpatient management is indicated.
- **E.** Pharmacologic intervention should be initiated early for rate control of MAT.

Answer: B. The dosing of beta-agonists and corticosteroids is very similar to guidelines for asthma. Unlike acute bronchitis, COPD patients who have experienced a change in sputum production often benefit from empirical antibiotics. MAT does not typically require treatment and often resolves as the COPD flare is ameliorated. Mechanical ventilation of COPD patients is aimed acutely at maximizing oxygenation, with as low a forced inspiratory oxygen (Fio_2) as possible while slowly normalizing Pco_2 levels over many hours via permissive hyper-apnea to allow acid-base normalization and avoidance of generation of excessive intrathoracic pressures by high ventilating rates. Hypoxemia and abnormal heart rhythm mandate inpatient care.

64.5. The addition of B-type natriuretic peptide (BNP) to the initial evaluation of patients with acute dyspnea will do which of the following?
- **A.** Be normal in cases of acute pulmonary embolus
- **B.** Help differentiate right from left heart failure in chronic obstructive pulmonary disease (COPD) patients with some degree of heart failure
- **C.** Rarely be helpful
- **D.** Reliably help identify patients whose symptoms are caused by exacerbation of congestive heart failure (CHF)
- **E.** Result in a smaller number of patients being treated for CHF regardless of the cutoff value used

Answer: D. The addition of a BNP level to the evaluation of COPD patients may benefit when taken in the context of the clinical impression. By establishing a cutoff value, the majority of CHF patients will be identified, but at any cutoff, there will be false positives. The BNP cannot differentiate left versus right ventricular stretch and strain and may not be normal in cases of pulmonary embolus because of the right ventricular stretch.

64.6. A 34-year-old man presents with 3 days of severe sore throat and painful swallowing. He reports his symptoms are worsening. His vital signs are: blood pressure, 127/85 mm Hg; heart rate, 132 beats per minute; respiratory rate, 22 breaths per minute; and temperature, 100. 8°F (38.2°C). On physical examination, he is sitting upright and is noted to be spitting his saliva into a cup. On lung examination, you note good air movement but inspiratory stridor. The remainder of his physical examination is within normal limits. As you begin preparations for airway management, which antibiotic is appropriate?
- **A.** Amoxicillin
- **B.** Azithromycin
- **C.** Ceftriaxone
- **D.** Doxycycline
- **E.** Rifampin

Answer: C. This patient has epiglottitis by history and physical examination. Adult patients with epiglottitis have higher mortality than pediatric patients, secondary to delayed diagnosis. The most important and time-sensitive intervention is airway management. Once a decision has been made about airway management, it is important to initiate prompt treatment of the infection. *Haemophilus influenzae* is the most commonly isolated bacterial pathogen, and thus treatment should be aimed at this pathogen. Staphylococci, streptococci, and viruses have also been implicated. Ceftriaxone and cefotaxime are commonly used first-line agents. Another option would be medications from the fluoroquinolone class. Up to 50% of *H. influenzae* isolates are resistant to amoxicillin (because of beta-lactamase production). Resistance is also a problem with both azithromycin and doxycycline, so they are not appropriate first-line agents. Although rifampin has activity against *H. influenzae*, resistance develops, and this agent should not be used as monotherapy. After initial coverage, culture and sensitivity results should be used to guide therapy.

CHAPTER 65

Upper Respiratory Tract Infections

Frantz R. Melio

PHARYNGITIS (TONSILLOPHARYNGITIS)

Principles

Tonsillopharyngitis—pharyngitis—is an inflammatory syndrome of the oropharynx. Transmission is mainly through contact with respiratory secretions but can also occur through food and fomite contact. Although most cases of pharyngitis are uncomplicated and self-limited, the associated swelling may threaten airway patency or preclude the ingestion of adequate liquids, leading to dehydration. Furthermore, a few causes of pharyngitis can also lead to systemic complications.

Viruses are responsible for most cases of pharyngitis in children and adults. Bacterial causes of pharyngitis include group A beta-hemolytic *Streptococcus* (GAS), non–group A streptococci, *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and sexually transmitted diseases. *Fusobacterium necrophorum* has been increasing recognized as a cause of pharyngitis in adolescents and young adults.[1-3] Whereas immunization has led to a decline in diphtheria as a cause of pharyngitis, it can result in serious complications and needs to remain in any differential diagnosis.

Mixed aerobic and anaerobic bacteria often cause chronic or recurrent pharyngitis, especially those that produce β-lactamase. Epstein-Barr virus (EBV) and *Actinomyces* are also implicated in chronic or recurrent pharyngitis. Rare causes of bacterial pharyngitis include *Francisella tularensis, Yersinia pestis,* and *Yersinia enterocolitica.*[2]

Clinical Features

Table 65.1 outlines the various causes of pharyngitis and their associated signs, symptoms, and treatment. The most common symptom is pharyngeal pain aggravated by swallowing that may radiate to the ears. Examination usually reveals fever, pharyngeal erythema, pharyngeal or tonsillar exudate, and tonsillar enlargement (Fig. 65.1). The infection tends to localize to lymphatic tissue and produces suppuration and swelling of the tonsils, along with tender cervical adenopathy. Occlusion of the eustachian tubes may result in secondary otitis media. Clinical differentiation of the causative organisms is virtually impossible.[2]

Viral pharyngitis usually occurs in conjunction with cough, rhinorrhea, myalgia, hoarseness, headache, stomatitis, conjunctivitis, exanthem, and odynophagia. Low-grade fever, diarrhea, oral ulcers, and pharyngeal edema, erythema and exudates may be present. Cervical lymphadenopathy is generally absent.[2] Systemic viral infections, including measles, cytomegalovirus (CMV), rubella, and human immunodeficiency virus (HIV), may initially manifest as mild pharyngitis.[2] HIV and CMV pharyngitis may be clinically indistinguishable from infectious mononucleosis.

Influenza occurs in epidemics and is associated with high fever, myalgia, and headache. Although 50% to 80% of patients with influenza experience pharyngeal discomfort, pharyngeal exudate and cervical lymphadenopathy are rare. Adenovirus may cause severe exudative pharyngitis with cervical adenitis similar to that in streptococcal pharyngitis. Of cases of adenoviral pharyngitis, 30% to 50% are associated with a follicular, usually unilateral, conjunctivitis and preauricular lymphadenopathy. Coxsackieviruses are the most frequent causes of hand-foot-and-mouth disease and herpangina.

Pharyngitis is a common manifestation of infectious mononucleosis (caused by EBV) in young adults.[2] Symptoms develop after an incubation period of 4 to 7 weeks. Fever and a tonsillar exudate or a cheesy or creamy white membrane is often present. Cervical as well as generalized lymphadenopathy (90%–100%) and splenomegaly (50%) are usually noted, and palatal petechiae may be present. Hepatomegaly is present in 10% to 15% of cases. Periorbital edema and rash are rare findings. In up to 90% of patients with mononucleosis who are given ampicillin or amoxicillin, a diffuse macular rash develops that may be misdiagnosed as an allergic reaction.

Patients with early (days to weeks) HIV infection can develop an acute retroviral syndrome. This is manifested by fever, sore throat, generalized nontender lymphadenopathy, diffuse maculopapular rash, arthralgias, mucocutaneous ulcerations and, commonly, diarrhea. Nonexudative pharyngitis is present in 50% to 70% of patients. Oral thrush and ulcers may be present. Acute HIV infection can be differentiated from infectious mononucleosis by a more acute presentation, absence of tonsillar hypertrophy or exudates, frequent occurrence of rash, and presence of oral ulcerations.

Herpes simplex pharyngitis, which typically affect young adults, manifests with the presence of painful vesicles with erythematous bases. Ulcers may be present on the pharynx, lips, tongue, gums, and buccal mucosa. Pharyngeal erythema and exudate, fever, and tender lymphadenopathy are common for 1 to 2 weeks. In an immunocompromised host, large painful ulcers may be present. Herpes pharyngitis can be caused by primary infection or reactivation. Concomitant bacterial superinfection may occur.

GAS pharyngitis is primarily a disease of children 5 to 15 years old and, in temperate climates, occurs in winter and early spring. It is responsible for 5% to 15% of cases of pharyngitis in patients older than 15 years and is rare in patients younger than 3 years. In epidemics, amongst persons in semiclosed communities and within families of index cases, the incidence may double. GAS pharyngitis is associated with sudden-onset sore throat, temperature over 38.3°C (101°F), tonsillar erythema and exudates, palatal and uvular petechiae (Fig. 65.2), uvular edema and erythema, and tender anterior cervical lymphadenopathy. Headache, nausea, vomiting, and abdominal pain may be present. GAS pharyngitis associated with a fine sandpaper erythematous rash that subsequently desquamates is termed *scarlet fever.* These findings, however, cannot be used to diagnose or exclude streptococcal pharyngitis reliably. Patients with recent exposure to others at risk for GAS pharyngitis or in whom it has been diagnosed are more likely to become infected.[2] Non-GAS species can cause pharyngitis indistinguishable from GAS. Groups C and G streptococci can cause epidemic foodborne pharyngitis.

Diphtheria is a potentially lethal cause of pharyngitis that is uncommon where adequate vaccinations are administered. US serologic surveys have indicated that a large percentage of adults

TABLE 65.1

Clinical Signs and Treatment of Various Causes of Pharyngitis

ORGANISM OR CONDITION	CHARACTERISTIC PRESENTATIONS AND FEATURES	TREATMENT
Group A beta-hemolytic *Streptococcus* (GAS)	Fever, pain, pharyngeal erythema and exudate, tender anterior cervical lymphadenopathy, nausea, vomiting, abdominal pain, fine sandpaper rash = scarlet fever; systemic complications possible	Penicillin, steroids may be beneficial
Epstein-Barr virus	Fever, exudate, lymphadenopathy, splenomegaly	Steroids may be beneficial.
Influenza	Fever, myalgia, headache; cervical lymphadenopathy rare	Supportive treatment
Herpesvirus	Gingivostomatitis, mucosal ulcers, lymphadenopathy	Acyclovir, valacyclovir, or famciclovir
Human immunodeficiency virus	Fever, generalized nontender lymphadenopathy, rash, arthralgia, diarrhea	Antiretrovirals
Diphtheria	Fever, malaise, dysphagia, grayish membrane on mucosal surfaces, respiratory distress; systemic toxin can lead to vascular collapse.	Antitoxin plus penicillin G, followed by penicillin VK once patient can tolerate oral medication, for a total of 14 days
Arcanobacterium haemolyticum	Rash, similar presentation as GAS; at times, membranous pharyngitis	Erythromycin, 250 mg PO qid for 10 days
Anaerobic (Vincent's angina)	Superficial ulcerations and necrosis, foul breath, poor oral hygiene, submandibular lymphadenopathy	Penicillin plus metronidazole *or* Clindamycin plus hydrogen peroxide rinses
Gonococcus (*Neisseria gonorrhoeae*)	Exudative or nonexudative	Ceftriaxone, 250 mg IM, plus Azithromycin, 1 g PO
Chlamydia	Lower respiratory tract infections, sinusitis, recurrent and persistent, tender deep cervical lymph nodes	Doxycycline, trimethoprim-sulfamethoxazole, or macrolide
Tuberculosis	Hoarseness, dysphagia, ulcerations, late disease	
Mycoplasma pneumoniae	Mild symptoms, lower respiratory tract infections, hoarseness	Macrolide or doxycycline, 7–14 days

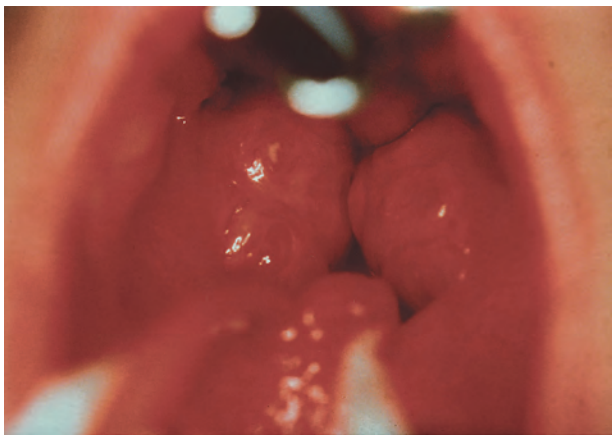

Fig. 65.1. Bilateral tonsillopharyngitis.

Fig. 65.2. Palatal petechiae. (Courtesy Centers for Disease Control and Prevention and Dr. Heinz F. Eichenwald.)

and adolescents lack immunity to diphtheria toxin. After a 2- to 4-day incubation period, patients develop malaise, sore throat, fever, and dysphagia. Examination early in the disease process may reveal pharyngeal erythema and isolated spots of gray or white exudate that later coalesce to form a pseudomembrane. This gray-green pseudomembrane is usually well demarcated and covers the nares, tonsils, soft palate, pharyngeal mucosa and, occasionally, the uvula. The membrane may extend to involve the larynx and tracheobronchial tree, leading to hoarseness, cough, stridor, and airway obstruction. Painful cervical lymphadenopathy may be found. Severe inflammation and edema can produce dysphonia and a characteristic so-called bull neck appearance. Some strains of *Corynebacterium diphtheriae* produce a systemic toxin that may cause myocarditis, polyneuritis (at first autonomic and then peripheral), vascular collapse, diffuse focal organ necrosis, and death. Asymptomatic carriers may transmit the disease. *Corynebacterium ulcerans* is an animal pathogen transmitted by the consumption of raw milk that can produce infection indistinguishable from that caused by *C. diphtheriae.*

Arcanobacterium haemolyticum typically affects the 10- to 30-year-old age group and can be indistinguishable from streptococcal pharyngitis. Most patients have an associated rash that may be scarlatiniform, urticarial, or erythema multiforme; occasionally, skin manifestations may be the only complaint. Patients report a moderately severe sore throat and are usually nontoxic and afebrile. *A. haemolyticum* may cause a membranous pharyngitis

that strongly mimics diphtheria; it is also associated with chronic tonsillitis.[2]

Anaerobic pharyngitis, or Vincent's angina, is characterized by superficial ulceration and necrosis that often results in the formation of a pseudomembrane. Foul-smelling breath, odynophagia, submandibular lymphadenopathy, and exudate are often present. Patients typically have poor oral hygiene.[2]

Gonococcal pharyngitis is a sexually transmitted disease that may occur independently of genital infection. Those at highest risk are persons who practice receptive oral sex, especially men who have sex with men. Its severity is variable and may result in an exudative or nonexudative pharyngitis. These differing manifestations occur after a latent period of infection. Asymptomatic carriers are described, as is chronic and recurrent pharyngitis. Gonococcal pharyngitis is an important source of gonococcemia.[2] Syphilitic pharyngitis is a manifestation of primary or tertiary syphilis and manifests with painless mucosal lesions. *Chlamydia trachomatis* pharyngitis is a sexually transmitted disease that manifests similarly to gonococcal pharyngitis and is associated with orogenital sex. Urogenital culturing is necessary, along with treatment of sexual contacts. Patients are usually asymptomatic or may have only mild symptoms.

Tuberculous pharyngitis usually occurs in patients with advanced disease. Symptoms and signs include hoarseness and dysphagia with pharyngeal ulcerations. Candidal pharyngitis is usually found in immunocompromised adults. Patients have dysphagia, odynophagia, and adherent white plaques with focal bleeding points.

Mycoplasma pneumoniae infection usually causes a mild pharyngitis. *Mycoplasma* infection occurs in epidemics and in crowded conditions and can be responsible for approximately 10% of cases of adult pharyngitis. Pharyngeal and tonsillar exudates, cervical lymphadenopathy, and hoarseness are common. Lower respiratory tract infection may also be present.[2]

C. pneumoniae pharyngitis resembles *M. pneumoniae* pharyngitis. It also occurs in epidemics or crowded conditions. Severe pharyngitis with laryngitis is suggestive of *C. pneumoniae* infection. Swelling and pain in the deep cervical lymph nodes may be prominent. Lower respiratory tract and concomitant sinusitis occur. The hallmarks of chlamydial pharyngitis are recurrence and persistence.[2] *Fusobacterium* pharyngitis presents in a manner similar to GAS, primarily in patients aged 10 to 49 years.[3]

Although most cases of pharyngitis follow a benign course, life-threatening complications can occur. Airway compromise from tonsillar enlargement, local and distant spread of infection, deep neck abscesses, necrotizing fasciitis, sleep apnea, bacteremia, sepsis, and death have been reported but are very rare.[2]

Infectious mononucleosis may lead to hepatic dysfunction, splenic injury, neurologic disorders, pneumonitis, pericarditis, and hematologic disorders, including thrombocytopenia and hemolytic anemia. Complications of GAS pharyngitis are suppurative and nonsuppurative. Suppurative complications include peritonsillar abscess, deep space abscesses, cervical lymphadenitis, otitis media, sinusitis, mastoiditis, bacteremia, sepsis, osteomyelitis, empyema, meningitis, and soft tissue infections. Nonsuppurative complications include scarlet fever, rheumatic fever, poststreptococcal glomerulonephritis, nonrheumatic perimyocarditis, erythema nodosum, and streptococcal toxic shock syndrome. In contrast to rheumatic fever, other complications of GAS pharyngitis have been increasing in incidence and severity. A chronic carrier state of streptococcal infection exists and can persist for several months, despite treatment. Affected patients are asymptomatic, at low risk for rheumatic fever, and not considered highly contagious. Non–group A streptococcal pharyngitis may be complicated by the same suppurative complications as group A infections. Scarlet fever and acute glomerulonephritis, but not rheumatic fever, are linked to groups C and G pharyngitis.[1,2]

Diagnostic Considerations

Differential Diagnosis

The differential diagnosis of pharyngitis includes epiglottitis, tracheitis, lingual tonsillitis, parapharyngeal abscess, retropharyngeal and other deep space abscesses and cellulitis of the neck, tumors, allergic reactions, Stevens-Johnson syndrome, drug reactions, angioneuropathic edema, chemical and thermal burns, esophagitis, gastroesophageal reflux disease, thyroiditis, cricoarytenoid arthritis, and foreign bodies.

Diagnostic Testing

The Monospot test has a sensitivity of approximately 85% and a specificity of almost 100%; however, results may be falsely negative in up to 10% of patients with infectious mononucleosis in the early stages of the illness. Immunoglobulin M (IgM) antibodies to EBV capsid antigen develop in 100% of cases. EBV nuclear antigens develop within 3 to 6 weeks and are useful if an initially negative test result becomes positive at a later date. Peripheral blood smears demonstrate atypical mononuclear cells in 75% of patients, with the peak incidence occurring in the second to third weeks of illness. The test may be ordered when the patient has failed treatment for GAS pharyngitis or when posterior cervical lymphadenopathy predominates.

Herpes pharyngitis may be diagnosed by culture, cytopathologic tests on scrapings of lesions, and serologic tests. Enzyme-linked immunosorbent assay testing for HIV can be falsely negative during the first 3 to 4 weeks of illness. During this period, quantitative assays for plasma RNA should be performed.[2,4]

Several authors have proposed scoring systems for diagnosing GAS pharyngitis based on clinical findings. Clinical scoring is most accurate in identifying patients at low risk for GAS pharyngitis.[2,4] Antistreptolysin O titers are not recommended for the diagnosis of routine GAS pharyngitis. A single throat culture has a sensitivity of 90% to 95% in detecting *Streptococcus pyogenes* in the pharynx. Variables that affect the accuracy of throat cultures include collection and culturing techniques and the recent use of antibiotics.[2,4]

Rapid diagnostic tests for GAS detect streptococcal antigens. Rapid streptococcal tests (RSTs) have a reported specificity and sensitivity of up to 95%. Sensitivity and specificity in actual practice are lower than in controlled trials. Using RSTs in patients without clinical findings consistent with GAS increases false-positive results. A positive RST result seems to indicate the presence of *S. pyogenes* in the pharynx reliably and does not require backup culture. Patients with positive cultures or RSTs may actually be carriers (5%–15% of cases) who may not need treatment and are at low risk for transmission and complications. In contrast, RST results are often negative in the setting of pharyngitis with a low bacterial count. Although it is recommended that a negative RST result in a child be followed by a confirmatory culture, adults with negative RST results do not require confirmatory cultures because of the lower incidence of GAS infection and extremely low risk for complications. Neither testing nor antibiotic treatment should be used in adults who are clinically at low risk for GAS infection, especially patients who have symptoms associated with a viral pharyngitis, including cough, rhinorrhea, hoarseness, oral ulcers, stomatitis, and conjunctivitis.[2,4]

We recommend the use of clinical criteria in conjunction with RSTs for the diagnosis of GAS pharyngitis. The Centor criteria (Box 65.1) is a useful, validated clinical tool for adults but is not useful for diagnosing GAS pharyngitis in children. Adults who present with none or only one Centor criterion should not be tested or treated; patients with all four criteria should be treated without testing. Patients with two or three criteria should undergo

BOX 65.1

Centor Criteria for Determining Group A Beta-Hemolytic Streptococcal Pharyngitis

- Tonsillar exudates
- Tender anterior lymphadenopathy or lymphadenitis
- Absence of cough
- History of fever

TABLE 65.2

Centor Criteria Scoring for Determining Testing and Treatment for Group A Beta-Hemolytic Streptococcal Pharyngitis

CENTOR SCORE	TESTING AND TREATMENT
0 or 1	None
2 or 3	Treatment based on results of rapid streptococcal test results
4	Treat without testing

RSTs and be treated only if they have positive results (Table 65.2). This approach may lead to some overtreatment with antibiotics.[2,4]

These recommendations apply only to immunocompetent patients without comorbidities or a history of rheumatic fever. They do not apply in settings of outbreaks of GAS infection or rheumatic fever, nor are they appropriate where the endemic rate of rheumatic fever is higher than that in the United States.

Pharyngitis caused by other treatable organisms should also be considered.[4] Non–group A streptococcal pharyngitis should also be treated because the same suppurative complications occur as with group A streptococcal pharyngitis. Confirmation of diphtheria requires culturing on the proper media and immunologic testing (polymerase chain reaction assay), and toxigenicity testing should also be performed.[1] The diagnosis of *A. haemolyticum* infection should be considered if a rash, including erythema multiforme, accompanies pharyngitis. The diagnosis of Vincent's angina is based on clinical findings and Gram staining. In cases of possible gonococcal infection, a sample should be plated on Thayer-Martin agar. Tuberculous pharyngitis is diagnosed by acid-fast staining. Syphilitic pharyngitis is diagnosed with dark-field microscopy, direct immunofluorescence, and serologic testing. Candidal pharyngitis is diagnosed by noting yeast on potassium hydroxide preparations of throat swabs or Sabouraud's agar.[2] The diagnosis of mycoplasmal pharyngitis can be confirmed serologically or by culture. Rapid antigen tests for *Mycoplasma* are available. Chlamydial pharyngitis can be diagnosed by serologic testing, culture, or antigen detection tests.

Management

Patients with pharyngitis should be treated symptomatically with topical anesthetic rinses or lozenges and acetaminophen or ibuprofen. Oral hydration and saltwater gargles are helpful. Most cases of pharyngitis are self-limited and follow a benign course.[3-5] Antibiotics are not indicated in the vast majority of cases of pharyngitis diagnosed in the United States.

Treatment of infectious mononucleosis is supportive (see Chapter 130). Patients should avoid contact sports for 6 to 8 weeks to minimize the small risk of splenic rupture. Corticosteroids are indicated for patients with tonsillar hypertrophy that threatens airway patency, severe thrombocytopenia, or hemolytic anemia. Steroids should be used cautiously in children and in only those with documented GAS infections. GAS pharyngitis is primarily a disease of children 5 to 15 years of age. In adults, GAS is a self-limited illness that lasts 3 to 4 days. The rationale for treating streptococcal pharyngitis is that antibiotics decrease suppurative and nonsuppurative complications, shorten the course of illness by about 1 day, and decrease transmission. Patients are no longer infectious after 24 hours of antibiotic treatment, and persistent symptoms lasting beyond a few days are suggestive of suppurative complications.[2,5] GAS pharyngitis should be treated adequately (within 9 days) to prevent rheumatic fever, which is rare in the United States and complicates 0.3% of cases of GAS pharyngitis but, in epidemics, the incidence increases to 3%. The incidence and course of poststreptococcal glomerulonephritis caused by nephritogenic strains are unaffected by antibiotic therapy.[2]

The antibiotic regimen of choice for adults with GAS pharyngitis is a single intramuscular (IM) injection of 1.2 million units of benzathine penicillin or a 10-day course of penicillin V, 500 mg orally bid.[2] IM penicillin may be more effective than oral penicillin and ensures compliance, but allergic reactions are more severe as a result of procaine allergy, and treatment is more expensive. Penicillin failure usually reflects noncompliance, reinfection, or the presence of β-lactamase–producing organisms. Clarithromycin, cephalosporins, or clindamycin for 10 days, or a 5-day course of azithromycin, is recommended for patients who are allergic to penicillin.[2,6] Adjunctive therapy with corticosteroids has been shown to shorten the duration and severity of symptoms somewhat in patients with GAS. Single-dose dexamethasone has been shown to be helpful in adults and children.

Patients whose symptoms return within a few weeks of treatment may have been noncompliant, acquired a new infection (at times from asymptomatic close contacts), or could be chronic carriers of GAS who are experiencing repeat viral infections. With actual recurrent GAS infections, treatment should be with IM penicillin. Alternative antibiotics for recurrent infections include cefdinir, cefpodoxime, amoxicillin-clavulanate, and clindamycin. Further recurrences require more extensive evaluation, and pharyngeal cultures should be obtained and consideration given to evaluating and treating close contacts for GAS infection.[2,6]

The successful treatment of diphtheria is inversely related to disease duration. When diphtheria is strongly suspected based on clinical findings, patients should be placed in respiratory droplet isolation and antitoxin (a horse serum product) treatment begun empirically. The dose of antitoxin varies widely and depends on the site of infection and duration of symptoms. Antibiotics have little effect on the resolution of systemic toxicity but are useful in eradicating *C. diphtheriae* infection and preventing transmission. The antibiotic of choice is penicillin G followed by penicillin VK, when able to tolerate oral antibiotics, for a total of 14 days, or erythromycin 500 mg (IV or orally) qid for 14 days. A small percentage of patients require an additional 10-day course of erythromycin for persistent infection. Rifampin, 600 mg/day for 10 days, is also effective in eradicating the carrier state of *C. diphtheriae* and treating erythromycin-resistant diphtheria. Close contacts should be cultured and treated with penicillin G or erythromycin 500 mg qid a day for 7 to 10 days. Diphtheria toxoid should be administered during convalescence and to unvaccinated close contacts.[6]

Candidal pharyngitis is treated with systemic fluconazole or itraconazole. Alternative therapy includes nystatin (suspension or tablets) or oral clotrimazole for 14 days. Chronic suppression therapy with fluconazole may be required for HIV pharyngitis.[6]

Treatment of recurrent or chronic tonsillitis should include β-lactamase–resistant antibiotics active against aerobic and anaerobic organisms. Choices include oral cephalosporins, amoxicillin-clavulanic acid, penicillin with rifampin or metronidazole, and clindamycin.[2,6]

Steroids given in conjunction with oral antibiotics in adults with acute pharyngitis may significantly shorten the duration of symptoms and provide a greater degree of pain relief without increasing complications. Oral (40–60 mg of prednisone/day for 1–5 days) or IM (single dose of 10 mg of dexamethasone) administration is equally effective.[7]

Disposition

The vast majority cases of pharyngitis follow an uncomplicated course, and patients can be treated on an outpatient basis. The presence of local (airway) and systemic complications should prompt consultation with an otolaryngologist, and possibly an infectious disease specialist, and will often lead to hospital admission.

LINGUAL TONSILLITIS

Principles

Lingual tonsillitis is a rarely diagnosed cause of pharyngitis that predominantly occurs in patients who have had their palatine tonsils removed. The lingual tonsils are usually (size and location are highly variable) located symmetrically on either side of the midline, just below the inferior pole of the palatine tonsils and anterior to the vallecula at the base of the tongue. This lymphoid tissue may enlarge after puberty, repeated infection, and tonsillectomy.

Clinical Features

Patients with lingual tonsillitis have a sore throat that worsens with movement of the tongue (including tongue depression) and phonation. The patient may have a classic so-called hot potato voice—the muffled voice one has when eating very hot food—and report feeling a swelling in the throat. Dysphagia, fever, respiratory distress, and stridor may be present. Chronic or recurrent lingual tonsillitis may also cause a chronic cough or sleep apnea. Physical findings often include a normal-appearing pharynx with mild hyperemia.

Diagnostic Considerations

Differential Diagnosis

The differential diagnosis is similar to that mentioned for adult pharyngitis.

Diagnostic Testing

Plain lateral radiographs of the neck are helpful in the diagnosis of lingual tonsillitis (Fig. 65.3). Computed tomography (CT) scanning and direct visualization with laryngoscopy may also help clarify the diagnosis.

Management

Management includes maintenance of airway patency, antibiotics, and supportive therapy. Rarely, acute lingual tonsillitis may be a life-threatening condition. Airway management includes warmed humidified oxygen, hydration, and corticosteroids. Nebulized epinephrine can relieve the acute respiratory distress and stridor. Antibiotics are similar to those used for the treatment of pharyngitis.

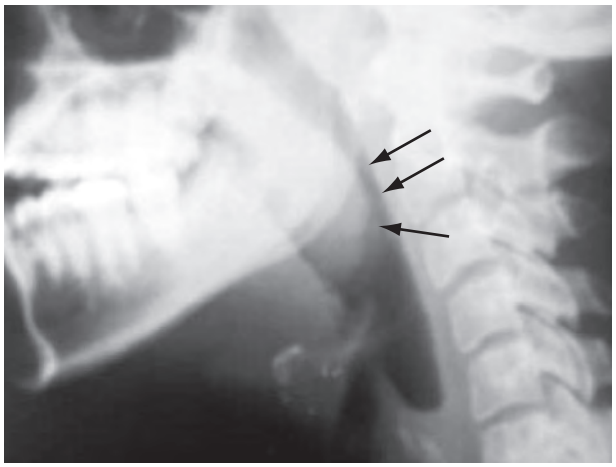

Fig. 65.3. Lingual tonsillitis. Note the scalloped appearance of the lingual tonsil on the anterior surface of the vallecula (*arrows*), with a normal epiglottis and aryepiglottic fold.

Disposition

Unless there is evidence of airway compromise, patients with lingual tonsillitis can be safely discharged home.

LARYNGITIS

Principles

Laryngitis is a common inflammatory condition which, when infectious, is almost always caused by a viral infection. There are numerous causes of noninfectious laryngitis, including acid reflux disease, trauma, chemical and thermal burns, overuse of the vocal cords, and allergies.

Clinical Features

Laryngitis generally is a benign viral illness, with peak symptoms lasting 3 to 4 days. Patients present with dysphonia. Fever, throat pain, dysphagia, coughing, and myalgia may also be present. Patients may develop chronic laryngitis.

Diagnostic Considerations

Differential Diagnoses

The differential diagnosis is similar to that mentioned for pharyngitis.

Management

Although voice rest is recommended, there is no evidence that this is of any benefit in terms of duration or severity of symptoms. Proton pump inhibitors are useful in treating laryngitis and chronic laryngitis due to esophageal reflux disease. Antibiotics are not indicated unless signs of bacterial infection are present.[8] Steroids may hasten the resolution of symptoms.[9]

Disposition

Laryngitis is a self-limiting disease treated on an outpatient basis.

ADULT EPIGLOTTIS

Principles

Adult epiglottitis can lead to rapid, unpredictable airway obstruction. Although the incidence of pediatric epiglottitis has diminished since the introduction of *Haemophilus influenzae* vaccine, there has been an increase in cases of adult epiglottitis.[10,11] Adult epiglottitis is a localized cellulitis involving the supraglottic structures, including the base of the tongue, vallecula, aryepiglottic folds, arytenoid soft tissues, lingual tonsils, and epiglottis. Inflammation does not extend to the infraglottic regions. Some adults have a normal epiglottis in the setting of severe supraglottic involvement; thus, the term *supraglottitis* may be a more accurate description. Adults with epiglottic involvement are prone to epiglottic abscesses.[10]

Adult epiglottitis can be caused by many viral, bacterial or, rarely, fungal pathogens, but the most commonly isolated bacterial pathogen is *H. influenzae* type b, which is associated with a more aggressive disease course. The predominant organisms isolated from epiglottic abscesses are *Streptococcus* and *Staphylococcus* spp. Adult epiglottitis may also result from thermal injury.[10]

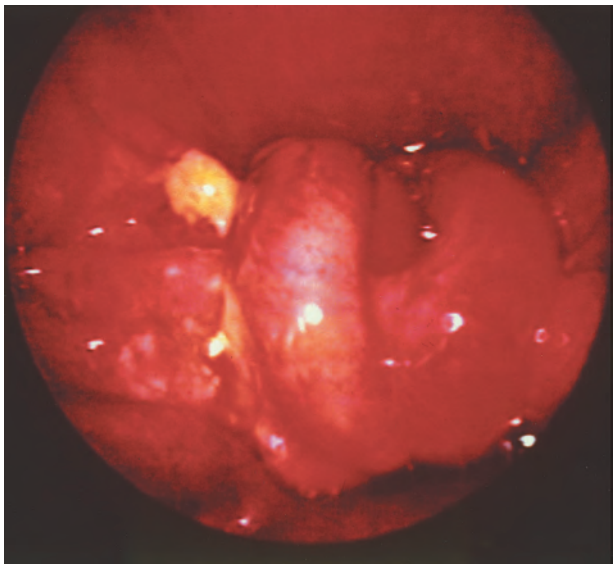

Fig. 65.4. Epiglottitis.

Clinical Features

Adult epiglottitis has no age or seasonal prevalence. Males and smokers are more commonly affected. Adults with epiglottitis typically experience a prodrome resembling that of a benign upper respiratory tract infection. The duration of the prodrome is usually 1 to 2 days but may be as long as 7 days or as short as several hours. Patients who have a rapid onset of the disease, as well as those with comorbid conditions (especially diabetes), are more likely to require airway intervention.[10]

Patients typically have dysphagia, odynophagia, and a sore throat. Pain may be severe, and the suspicion of epiglottitis is raised when the patient reports severe symptoms of pharyngitis and has obvious odynophagia or dysphagia but examination of the oral pharynx and tonsils shows only minimal or no signs of inflammation or exudate. Dysphonia and a muffled voice are common, whereas hoarseness is unusual. Fever is absent in up to 50% of cases and may develop only in the later stages of the disease. Concomitant uvulitis, pharyngitis, tonsillitis, Ludwig's angina, peritonsillar abscess, and parotitis can occur. Tenderness to palpation of the anterior aspect of the neck in the region of the hyoid and when the larynx is moved side to side is a suggestive finding in epiglottitis.

Diagnostic Considerations

Differential Diagnosis

The differential diagnostic considerations are similar to those listed for pharyngitis.

Diagnostic Testing

When epiglottitis is suspected, visualization of the epiglottis is indicated. Necessary equipment to provide bag-mask ventilation, intubation, or cricothyrotomy must be immediately available. In patients with respiratory distress, drooling, aphonia, or stridor, it is important that the patient be maintained in a position of comfort. Airway examination is undertaken as soon as equipment has been obtained and requires a double setup, with the ability to proceed immediately to cricothyrotomy.[10] Depending on the perceived urgency of the airway examination, preparations should include a drying agent, preferably glycopyrrolate, 0.2 mg intravenously (IV), topical anesthesia (eg, 4% lidocaine by atomizer, after the glycopyrrolate has reduced secretions), and light sedation (eg, midazolam in 1-mg increments, often with small doses [50-μg increments] of fentanyl). Laryngospasm and complete obstruction can occur during instrumentation of the inflamed airway. Flexible laryngoscopy is the preferred approach because it provides direct, minimally invasive examination of the upper airway and intubation, if planned in advance, can be completed over the laryngosope. Laryngoscopy reveals a swollen epiglottis and surrounding structures (Fig. 65.4). The epiglottis may appear cherry red but is often pale and edematous.

Although lateral cervical soft tissue radiographic films have a sensitivity of up to 90% when compared with the gold standard of laryngoscopy, radiographs are not a substitute for visualization of the upper airway structures by flexible or rigid laryngoscopy. Patients with severe pain, altered voice, complaints of dyspnea, or inability to swallow secretions are at risk for sudden airway obstruction; they should undergo prompt upper airway examination and should not be sent to radiology for x-ray examination. Radiologic findings, when present, include obliteration of the vallecula, swelling of the arytenoids and aryepiglottic folds, edema of the prevertebral and retropharyngeal soft tissues, and ballooning of the hypopharynx and mesopharynx. The edematous epiglottis appears enlarged and thumb-shaped (Fig. 65.5). An epiglottic width greater than 8 mm or aryepiglottic fold width greater than 7 mm is suggestive of epiglottitis. Adults with suspected epiglottitis and normal soft tissue radiographic films should undergo laryngoscopy. Similarly, patients determined to have epiglottitis by radiography also require upper airway examination by laryngoscopy to determine the extent of airway compromise and the need for intubation.

Management

Unlike in the pediatric population, most cases of adult epiglottitis can be managed without intubation or tracheostomy. Antibiotic therapy and intensive care support until symptoms resolve is the cornerstone of therapy in these patients. Airway management is indicated for less than 15% of patients and should be considered for those with symptoms and signs of imminent airway obstruction. Symptoms of severe disease that may require rapid airway intervention include tachycardia disproportionate to fever, tachypnea, stridor, shortness of breath, and rapid onset of symptoms. Patients who are spiting, drooling, or unable to swallow their own saliva, and patients who assume a classic sniffing position, should

Fig. 65.5. Radiograph of epiglottitis.

be considered to be at imminent risk for rapid airway obstruction. These patients should not be laid flat, and immediate preparations should be made to secure the airway rapidly (see Chapter 1).[10] In patients with a rapidly progressive course, such as those whose symptoms have increased greatly in severity over 4 to 6 hours, even with only moderate laryngoscopic findings, preventive intubation is indicated because progression of swelling and airway compromise can occur rapidly and with little warning. Intubation also is undertaken, despite only moderate findings on laryngoscopy, for patients who are immunocompromised or diabetic or have an epiglottic abscess.[10]

All patients with epiglottitis should be treated with extreme care because of the possibility of unpredictable sudden airway obstruction. Endotracheal intubation should be performed under direct visualization. Awake flexible endoscopic intubation is the optimal method, but awake orotracheal intubation by direct laryngoscopy or videolaryngoscopy also can be done.[10] Blind nasotracheal intubation can lead to airway obstruction and is contraindicated in the setting of epiglottitis.

Antibiotics should be initiated against *H. influenzae* and other likely bacterial pathogens. First-line agents pending culture and sensitivity results are cefotaxime and ceftriaxone plus vancomycin. Alternative antibiotics include levofloxacin plus clindamycin.[6] The role of steroids is unresolved, but racemic epinephrine is used only as a temporizing measure while preparations are made to secure the airway because short-term use can produce improvement, only to be followed by a rebound effect, in which the symptoms and signs revert to their pretreatment level of severity or become even worse.[10] For patients admitted to the hospital, consultation with an otolaryngologist should be arranged.

Disposition

If upper airway endoscopy shows mild or moderate disease, with preservation of a widely patent airway, and the patient's symptoms have developed gradually over a longer period of time (ie, 24 hours), treatment with IV antibiotics, parenteral opioid analgesia, and humidified oxygen in a monitored inpatient unit (often the intensive care unit [ICU]) or an emergency department (ED) observation unit is appropriate, providing the patient is without dyspnea and can handle his or her secretions. Laryngoscopy is repeated in 6 to 12 hours to ensure that the patient's condition is improving and to determine readiness for discharge.

PERITONSILLITIS (PERITONSILLAR CELLULITIS AND PERITONSILLAR ABSCESS)

Principles

Peritonsillitis may occur as a result of acute tonsillitis. Infection in Weber's glands or the tonsillar crypts invades the peritonsillar tissues and thereby leads to cellulitis and abscess formation. Fibrous fascial septae divide the peritonsillar space into compartments and direct the infection anteriorly and superiorly.

Dental infections, chronic tonsillitis, infectious mononucleosis, smoking, chronic lymphocytic leukemia, and tonsilloliths are predisposing factors. Peritonsillar abscess occurs in patients who have undergone complete tonsillectomy and is seen in all age groups. Peritonsillitis recurs in up to 50% of patients, with the incidence of recurrent peritonsillar abscess approximately 10%. The highest incidence of recurrence is seen in patients younger than 40 years and in those with a history of chronic tonsillitis.

Most peritonsillar abscesses are polymicrobial. *Fusobacterium necrophorum* is common. β-Lactamase–producing organisms are isolated more commonly in patients who have received prior antibiotics.[12]

Clinical Features

There is often a delay of 2 to 5 days between abscess formation and local and systemic symptoms. Symptoms and signs include odynophagia, dysphagia, drooling, trismus, and referred otalgia. Patients may have a characteristic muffled, hot potato voice, and rancid breath. Systemic manifestations include fever, malaise, and dehydration. Patients may relate a history of recurrent tonsillitis.

The examination of the pharynx can be limited by trismus. Physical findings of peritonsillitis include inflamed and erythematous oral mucosa, purulent tonsillar exudates that obscure the tonsil, and tender cervical lymphadenopathy. Peritonsillar cellulitis may be a precursor of and mimics peritonsillar abscess. Peritonsillar abscess is characterized by a greater frequency of drooling, trismus, and dysphagia, whereas peritonsillar cellulitis is usually bilateral. The distinguishing feature of peritonsillar abscess is inferior medial displacement of the infected tonsil (at times involving the soft palate), with contralateral deviation of the uvula (Fig. 65.6). The abscess is generally unilateral and located in the superior pole of the tonsil. Bilateral peritonsillar abscesses occur occasionally.

Diagnostic Considerations

Differential Diagnosis

The differential diagnosis of peritonsillitis includes hypertrophic tonsillitis, infectious mononucleosis, tubercular granuloma, diphtheria, other deep space infections of the neck, cervical adenitis, carotid artery aneurysms, foreign bodies, and neoplasms.

Diagnostic Testing

Aspiration of pus establishes the diagnosis of peritonsillar abscess. Because patients with peritonsillar abscess have a 20% incidence

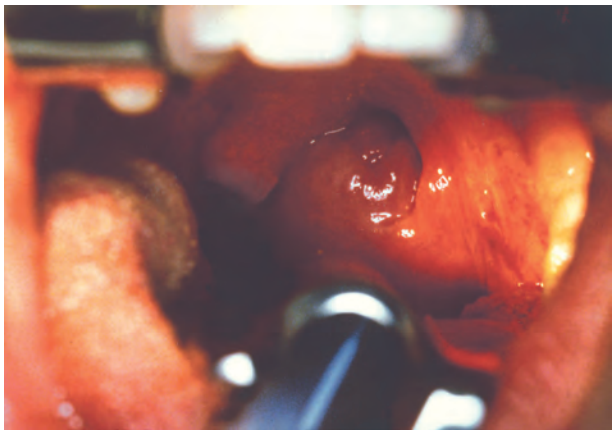

Fig. 65.6. Peritonsillar abscess with uvular displacement to the right.

of mononucleosis, laboratory testing for mononucleosis should be considered when systemic symptoms or findings of mononucleosis are present (see Chapter 122.)

Radiographs are of no value when the clinical examination identifies peritonsillar abscess. Although contrast-enhanced CT and ultrasonography (intraoral and transcutaneous) aid in differentiating peritonsillar abscess from cellulitis, especially when patients are unable to cooperate with needle aspiration, these rarely, if ever, are required.[13]

Management

Needle aspiration is indicated when an abscess is present or suspected. Antibiotics alone may suffice with peritonsillar cellulitis. Regimens include piperacillin-tazobactam or high-dose ceftriaxone plus metronidazole. Alternative antimicrobial agents include clindamycin, cefoxitin, ampicillin-sulbactam, a carbapenem, high-dose penicillin and rifampin, or ticarcillin-clavulanate. The use of steroids are also beneficial.[6]

Drainage of an abscess is usually curative. Needle aspiration of abscesses by emergency clinicians and otolaryngologists is diagnostic, although false-negative aspirations occur in approximately 10% of cases, and another 10% may require repeated aspirations, and therapeutic. This immediately relieves symptoms and is more cost-effective, less painful, and easier to perform than incision and drainage. Intraoral ultrasound-guided needle aspiration is a useful adjunct in the presence of trismus.[13]

Disposition

Hospital admission rarely is indicated but is considered for patients who have significant comorbidity, appear toxic, or are unable to tolerate oral fluids or whose pain is not managed by oral analgesics. Most patients can be observed for 4 to 6 hours after aspiration in the ED observation unit or ED who are receiving antibiotics, IV hydration, and analgesia. The most dangerous immediate complication of peritonsillitis is pharyngeal obstruction with upper airway compromise. Other very rare complications include sepsis, abscess rupture, and pulmonary aspiration leading to pneumonia, empyema, and pulmonary abscess formation. Infection can spread contiguously to the parapharyngeal and retropharyngeal spaces. Ludwig's angina, mediastinal involvement (including mediastinitis, pneumonia, empyema, and pericarditis), myocarditis, carotid artery erosion, jugular vein thrombophlebitis, septic embolization, abscess formation, Lemierre's syndrome (see later, "Parapharyngeal Abscess"), and cervicothoracic necrotizing fasciitis can complicate peritonsillitis. The intracranial extension of peritonsillitis may result in meningitis, cavernous sinus thrombosis, and cerebral abscess.

LUDWIG'S ANGINA

Principles

Ludwig's angina is a potentially fulminant disease process that can lead to death within hours. This is a progressive cellulitis of the connective tissues of the floor of the mouth and neck that begins in the submandibular space, comprised of the sublingual and submaxillary spaces. Dental disease is the most common cause of Ludwig's angina. An infected or recently extracted lower molar is noted in most affected patients. Other causes of Ludwig's angina include a fractured mandible, foreign body or laceration in the floor of the mouth, tongue piercing, traumatic intubation and bronchoscopy, secondary infections of an oral malignancy, osteomyelitis, submandibular sialadenitis, peritonsillar abscess, furuncles, infected thyroglossal cysts, and sepsis.

Clinical Features

Infection of the sublingual and submaxillary spaces leads to edema and soft tissue displacement, which may result in airway obstruction. The most common presentation in patients with Ludwig's angina includes dysphagia, odynophagia, neck swelling, and neck pain. Other symptoms and signs include dysphonia, hot potato voice, dysarthria, drooling, tongue swelling, pain in the floor of the mouth, restricted neck movement, and sore throat. Patients should be questioned regarding recent dental extraction and disease. The rapid development of crepitus and unilateral pharyngitis in patients with a recent dental extraction should suggest the diagnosis of Ludwig's angina.

The most common physical findings in Ludwig's angina are bilateral submandibular swelling and elevation or protrusion of the tongue. Other findings include elevation of the floor of the mouth, posterior displacement of the tongue, and a woody consistency of the floor of the mouth. The combination of tense edema and brawny induration of the neck above the hyoid may be present, described as a bull neck. Marked tenderness to palpation of the neck and subcutaneous emphysema may be noted. Usually, trismus and fever are present, but there is no palpable fluctuance or cervical lymphadenopathy. Tenderness to percussion may be elicited over the involved teeth.

Diagnostic Considerations

Differential Diagnosis

The differential diagnosis includes deep cervical node suppuration, peritonsillar and other deep neck space abscess, parotid and submandibular gland abscess, oral carcinoma, angioedema, submandibular hematoma, and laryngeal diphtheria.

Diagnostic Testing

The diagnosis is made clinically. Soft tissue plain films of the neck may confirm the diagnosis by identifying swelling of the affected area and airway narrowing and gas collections but, in general, are not of value. CT and magnetic resonance imaging (MRI) can identify deep space neck infections and airway compromise. Ultrasonography is also useful in diagnosing abscesses and edema in the setting of Ludwig's angina.

Management

Sudden asphyxiation is the most common cause of death in patients with Ludwig's angina. Stridor, tachypnea, dyspnea, inability to handle secretions, and agitation all suggest impending airway compromise. Flexible endoscope–guided oral or nasal

intubation under sedation with topical anesthesia is the preferred method of airway control. Direct laryngoscopy can be particularly difficult because of the inability to retract the tongue into the submandibular space and posterior and cephalad displacement of the tongue by the infection. There have been no reports reporting the use of videolaryngoscopes in this condition. Emergent tracheostomy may be necessary in patients with Ludwig's angina if flexible endoscopic intubation cannot be accomplished. Cricothyrotomy may be technically difficult due to anatomic distortion and opens tissue planes that increase the risk of spreading infection into the mediastinum.[14]

Emergent high-dose IV antibiotic regimens include piperacillin-tazobactam, ticarcillin-clavulanate, and high-dose penicillin plus metronidazole. Clindamycin can be used in penicillin- allergic patients. Vancomycin should be added if the initial Gram stain reveals gram-positive cocci.[6] With the exception of dental extractions, surgery is reserved for patients who do not respond to medical therapy and those with crepitus and purulent collections.

Disposition

All patients with Ludwig's angina require admission to the ICU and parenteral antibiotics. The mortality rate associated with Ludwig's angina is less than 10% with early aggressive antibiotic therapy and adequate protection of the airway.

RETROPHARYNGEAL ABSCESS

Principles

The retropharyngeal space lies in the midline and extends from the base of the skull to the superior mediastinum (at about the level of T2). Retropharyngeal abscesses tend to occur laterally to the midline. Posterior to the retropharyngeal space lies the so-called danger space, which extends from the base of the skull to the diaphragm. The prevertebral space extends from the base of the skull to the coccyx. Danger space and prevertebral abscesses are located in the midline. Infections in the retropharyngeal, danger, and prevertebral spaces easily access the mediastinum, which allows the rapid spread of infection and life-threatening complications (Fig. 65.7). Infection may spread from one deep space to another, and patients may present with concomitant deep space infections.[15] Retropharyngeal swelling reflects expansion of the retropharyngeal, danger, or prevertebral space. This discussion refers to infections in these spaces collectively as retropharyngeal abscesses.

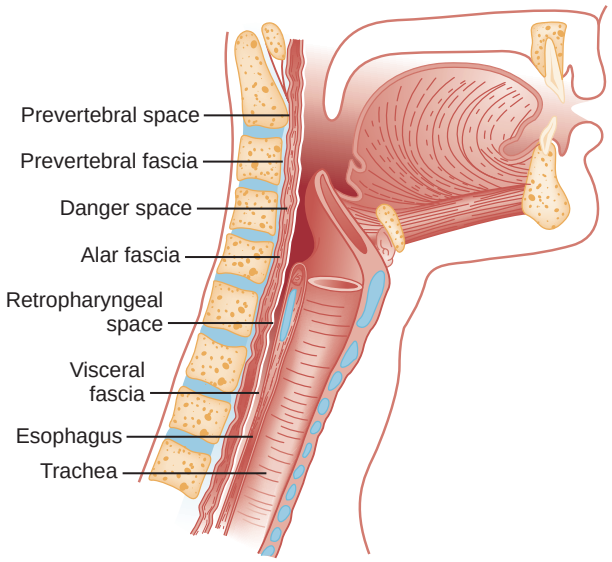

Fig. 65.7. Lateral view of the neck showing the relationship of fascia to the prevertebral danger area and retropharyngeal and submandibular spaces.

Retropharyngeal abscess is an uncommon condition that previously was a disease of childhood, with 96% of cases occurring in patients younger than 6 years. In adult patients, who are now increasingly affected, cellulitis develops in the retropharyngeal area. Once the retropharyngeal space is involved, the infection spreads rapidly and an abscess forms. Nasopharyngitis, otitis media, parotitis, tonsillitis, peritonsillar abscess, dental infections and procedures, upper airway instrumentation, endoscopy, lateral pharyngeal space infection, and Ludwig's angina are all implicated in the development of retropharyngeal abscess.[6,15] Other causes include blunt and penetrating trauma (usually from foreign bodies, commonly fish bones), ingestion of caustic substances, vertebral fractures, and hematologic spread from distant infection. Vertebral osteomyelitis and diskitis may also lead to infection of the prevertebral space.

Retropharyngeal abscesses are usually polymicrobial, with a mixture of aerobes and anaerobes. β-Lactamase–producing organisms are present in two-thirds of the cases. Tuberculosis is rarely reported in the United States as a cause of retropharyngeal abscess. *Staphylococcus* is the most common cause of pyogenic vertebral osteomyelitis, leading to the formation of retropharyngeal abscess. Disseminated coccidioidomycosis may also cause retropharyngeal abscess.[15]

Clinical Features

Patients typically have a sore throat, dysphagia, odynophagia, drooling, muffled voice, neck stiffness, pain, and fever. Dysphonia is usually present and is described as a duck quack (*cri du canard*). Patients may report feeling a lump in the throat; those with a retropharyngeal abscess may appear quite ill and generally prefer to hold their necks extended and remain in the supine position. This position keeps the swollen posterior pharynx from compressing the upper airway. Forcing the patient to sit may lead to increased dyspnea.[15]

Physical examination may reveal tender cervical lymphadenopathy and cervical musculature, neck swelling, torticollis, and igh fever. Trismus may be present and makes visualization of the pharynx difficult. With retropharyngeal cellulitis, diffuse edema and erythema of the posterior pharynx are present. Once an abscess has developed, palpation may demonstrate a unilateral mass if the retropharyngeal space is affected and a midline mass if the abscess is in the prevertebral or danger space. Palpation of a fluctuant mass is unreliable and carries a risk of inadvertent rupture. Tenderness on moving the larynx and trachea side to side (tracheal so-called rock sign) is commonly present. A retropharyngeal abscess may also cause pain in the back of the neck or shoulder, precipitated by swallowing. Cold abscesses (caused by tuberculosis) are characterized by insidious onset, chronicity, constitutional symptoms, and a lower fever. Symptoms disproportionate to the findings should prompt further evaluation.

Diagnostic Considerations

Differential Diagnosis

The differential diagnosis includes retropharyngeal tumors, foreign bodies, inflammation, hematoma, aneurysms, hemorrhage, lymphadenopathy, and edema. Other considerations include tendinitis of the longus colli muscle and retropharyngeal thyroid tissue.[16]

Diagnostic Testing

Diagnosis rests on the clinical findings and particularly on lateral cervical radiographs and CT and MRI scans. The anteroposterior (AP) diameter of the soft tissue along the anterior bodies of C1-4 should be less than 40% of the AP diameter of the vertebral body just behind it; an increase in this tissue thickness suggests infection or abscess. Soft tissue swelling may be diffuse in the case of cellulitis or more focal if an abscess cavity is present. A pathologic process is suggested if the retropharyngeal space on lateral neck films (measured from the anteroinferior aspect of the second vertebral body to the posterior pharyngeal wall) is wider than 7 mm in children and adults or the retrotracheal space (measured from the anteroinferior aspect of the sixth vertebral body to the posterior pharyngeal wall) is more than 14 mm in children and 22 mm in adults. True lateral films with the neck fully extended during deep inspiration are the most reliable. Other radiographic findings include reversal of the normal lordosis of the cervical spine, air-fluid levels in the abscess cavity, foreign bodies, and vertebral body destruction.

Plain films may not be sufficiently sensitive to diagnose retropharyngeal abscess. CT or MRI should be performed when doubt persists after plain x-ray examination. These studies not only aid in the diagnosis and differentiation between cellulitis and abscess but also determine the extent of the disease process and presence of complications (Figs. 65.8 and 65.9). Ultrasonography is useful for differentiating retropharyngeal cellulitis from retropharyngeal abscess.

Management

Patients with retropharyngeal cellulitis are treated with high-dose IV antibiotics. Appropriate regimens include clindamycin, high-dose penicillin plus metronidazole, piperacillin-tazobactam, and ampicillin-sulbactam. The resolution of retropharyngeal cellulitis is possible without surgical intervention.[6,15]

In general, retropharyngeal abscesses are treated with antibiotics in conjunction with operative incision and drainage by an otolaryngologist. In select cases, retropharyngeal abscesses can be treated successfully with antibiotics alone or in combination with needle aspiration. Tuberculous (cold) abscesses should be drained only extraorally unless the patient is in acute respiratory distress. Consultation with an infectious disease specialist and otolaryngologist is advised when tuberculosis or a fungal infection is suspected as the causative agent.[15,17]

Neck immobilization may be necessary in patients with vertebral body destruction caused by osteomyelitis or atlantoaxial separation. Atraumatic atlantoaxial separation is caused by damage to the transverse ligament of the atlas from the abscess. These patients may have neurologic symptoms and a widened predental space on plain films or CT or MRI scans. These patients need neurosurgical or orthopedic evaluation and may require fixation.

Disposition

Patients with retropharyngeal abscess are admitted to the ICU, and emergent consultation with an otolaryngologist is obtained.

PARAPHARYNGEAL ABSCESS

Principles

The parapharyngeal space is divided into two compartments by the styloid process. The anterior compartment contains connective tissue, muscle, and lymph nodes. The carotid sheath, which contains the carotid artery, internal jugular vein, vagus nerve, cranial nerves IX through XII, and the sympathetic chain, runs in the posterior compartment. Parapharyngeal abscesses are usually polymicrobial, emanating from an odontogenic or pharyngotonsillar infections. Parapharyngeal space infections can also arise from contiguous spread from deep neck space infections, parotitis, sinusitis, infected neck tumors, infected branchial cleft cysts, suppurative lymphadenitis, chronic otitis with cholesteatoma, mastoiditis, and iatrogenic introduction of organisms during a mandibular nerve block or anesthesia for tonsillectomy, nasal intubation, or dental extraction.

Clinical Features

Odynophagia, pain, and swelling of the neck are the most common complaints. A history of an antecedent sore throat may be elicited; torticollis caused by irritation of the sternocleidomastoid muscle is also reported.

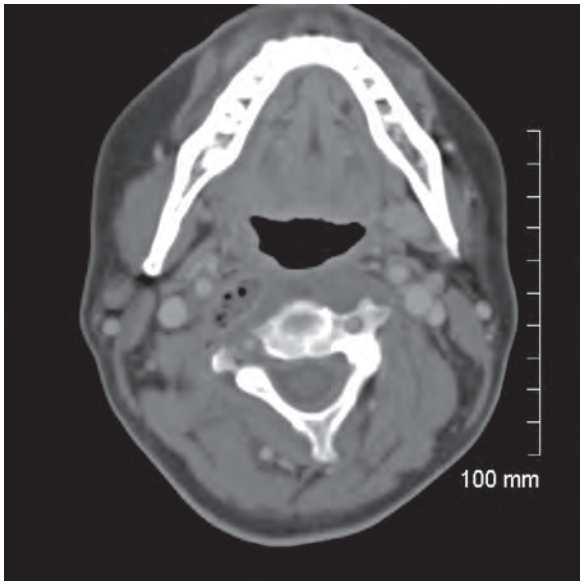

Fig. 65.8. CT scan demonstrating a right-sided retropharyngeal abscess.

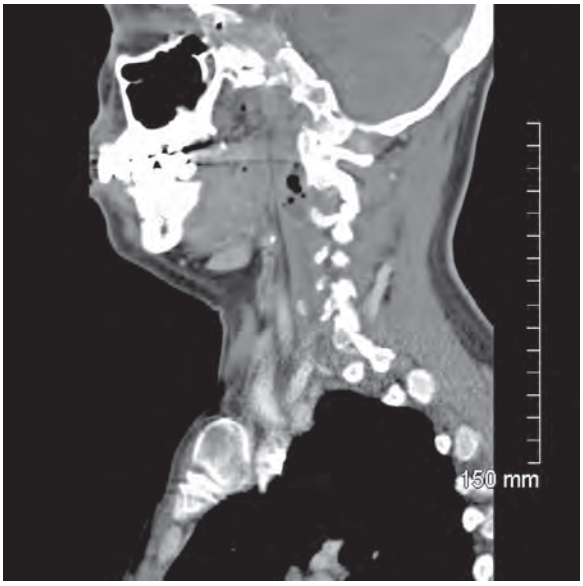

Fig. 65.9. Sagittal CT scan demonstrating a right-sided retropharyngeal abscess.

The classic physical findings of infection involving the anterior compartment of the parapharyngeal space are medial tonsillar displacement and posterolateral pharyngeal wall bulging. Other findings include fever, trismus, caused by irritation of the muscles of mastication, edema, and swelling at the angle of the mandible, often seen in patients with an anterior parapharyngeal abscess.

Involvement of the posterior space is associated with many of these same signs. If the anterior compartment is spared, however, little or no trismus occurs. Instead, posterior displacement of the tonsillar pillar and retropharyngeal swelling may be present.

Complications of a parapharyngeal abscess include airway obstruction and abscess rupture, with subsequent aspiration, pneumonia, and empyema. Infection can spread to surrounding spaces and into the mediastinum and pericardium. This spread may lead to mediastinitis, mediastinal abscess, pericarditis, myocardial abscess, and/or empyema. Other complications include osteomyelitis of the mandible, cervicothoracic necrotizing fasciitis, parotid abscess, cavernous sinus thrombosis, and meningitis.

Posterior parapharyngeal space infections are particularly dangerous. These may affect the cervical sympathetic chain, carotid artery, or internal jugular vein. Ipsilateral Horner's syndrome and neuropathies of cranial nerves IX through XII may occur. Carotid artery erosion may lead to hemorrhage and the formation of aneurysms. Oral, nasal, and aural warning bleeding is common with carotid artery erosion, with aural bleeding being particularly ominous. Any unexplained bleeding associated with parapharyngeal or other deep neck space infection should be investigated thoroughly. Persistent peritonsillar swelling, despite resolution of the parapharyngeal abscess or a tender unilateral pulsatile mass, may indicate an arterial aneurysm. Aspiration or incision of a carotid artery aneurysm thought to be a parapharyngeal abscess may have disastrous complications.

Involvement of the internal jugular vein may lead to septic thrombosis and Lemierre's syndrome.[18] This entity, also termed *postanginal septicemia,* affects primarily young healthy patients and is easily confused with right-sided endocarditis or aspiration pneumonia. The manifestation is one of a pharyngitis that initially improves but is then followed by severe sepsis. It is thought that the pharyngeal infection spreads to the parapharyngeal space and causes septic thrombophlebitis of the jugular vein. Patients usually appear ill and are febrile. Metastatic infections involve primarily the lung and are manifested by bilateral nodular infiltrates, pleural effusion, and pneumothorax. Septic embolization may also lead to arthritis, osteomyelitis, cellulitis and abscesses, meningitis, and a vesiculopustular rash. Positive blood cultures, leukocytosis, and elevated bilirubin levels and liver function tests, with and without hepatomegaly and jaundice, are often present. Albuminuria, hematuria, and elevations in serum creatinine and blood urea nitrogen levels are reported. Septic shock rarely develops, although acute respiratory distress syndrome, transient coagulopathies, and hypotension commonly occur. The most frequent cause of this entity is *Fusobacterium* (primarily *Fusobacterium necrophorum*), although *Staphylococcus aureus* is the most common pathogen in IV drug users. Treatment consists of parenteral antibiotics and incision and drainage of abscesses. Antibiotic regimens include piperacillin-tazobactam, imipenem-cilastatin, high-dose ceftriaxone plus metronidazole, and clindamycin. Jugular vein ligation and resection are necessary in patients with uncontrolled sepsis and respiratory failure caused by repeated septic pulmonary emboli. The value of anticoagulation is unknown.[18]

Diagnostic Considerations

Differential Diagnosis

The differential diagnosis includes infections of other deep spaces of the neck, tumors and metastatic lymph nodes, thyroiditis, branchial cleft cyst, and carotid artery aneurysms.

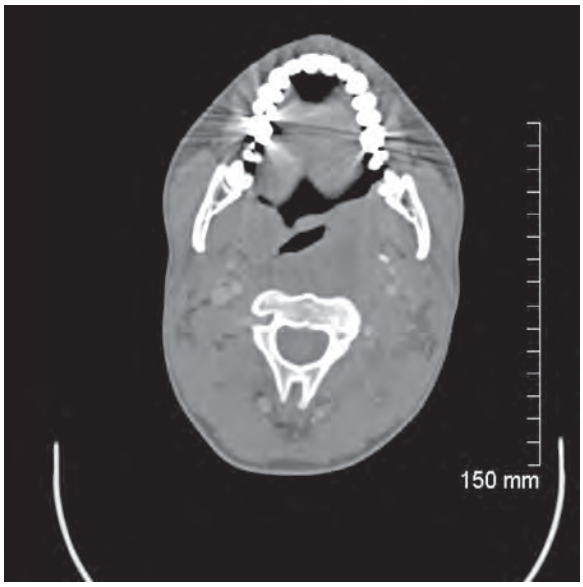

Fig. 65.10. CT scan demonstrating a left-sided parapharyngeal abscess.

Diagnostic Strategies

Ultrasonography, CT, and MRI are more useful than lateral radiography in diagnosing parapharyngeal abscess and its complications (Fig. 65.10). Angiography, Doppler flow studies, and magnetic resonance angiography may also be helpful in evaluating vascular complications.

Management

Treatment includes high-dose IV antibiotics and consultation with an otolaryngologist for surgical drainage. Appropriate antibiotic regimens are those used for retropharyngeal abscess. IV antibiotics alone will cure parapharyngeal space infections in patients without abscess.[6,15,17] The successful resolution of parapharyngeal abscesses with IV antibiotics and needle aspiration has been reported.[15,17]

Disposition

Patients with parapharyngeal infections require emergent consultation with an otolaryngologist and admission to the ICU. These patients may require emergent surgical intervention.

RHINOSINUSITIS

Principles

Because sinusitis usually involves the nasal cavity, the term *rhinosinusitis* is preferred. These terms will be used interchangeably in this section.[19]

The paranasal sinuses—frontal, maxillary, ethmoid, and sphenoid—are named for the facial bones with which they are associated. Pneumatization may involve other bones but represents extension from the main sinus. The maxillary, anterior ethmoid, and frontal sinuses drain into the medial meatus, located between the inferior and middle nasal turbinates. This area is termed the *ostiomeatal complex* and is the focal point of sinus disease. The posterior ethmoid sinus drains into the superior meatus and phenoid sinus just above the superior turbinate.[19]

A healthy sinus is sterile, depends on a patent ostium with free air exchange, and is reliant on appropriate mucus drainage. Many different processes can result in ostial obstruction and

rhinosinusitis, but the most common are viral upper respiratory tract infections and allergic rhinitis. Ciliary abnormality or immobility also inhibits drainage, resulting in sinusitis. Bacteria are introduced into the sinus by coughing and vigorous nose blowing, leading to increased inflammation, decreased oxygen tension in the sinus, and bacterial overgrowth. Other factors predisposing to rhinosinusitis include immunocompromise, nasal septal deviation and other structural abnormalities, nasal polyps, tumors, trauma and fractures, rhinitis medicamentosa, rhinitis secondary to toxic mucosal exposure, barotrauma, foreign bodies, nasal cocaine abuse, and instrumentation, including nasogastric and nasotracheal intubation.[19]

Sinusitis can be classified into acute viral, acute bacterial, chronic, and recurrent acute variations. Approximately 90% of patients with colds have an element of the acute viral form. Acute viral sinusitis may lead to the development of the acute bacterial variety. *Streptococcus pneumoniae*, nontypable *H. influenzae*, and *Moraxella catarrhalis* are the primary pathogens responsible for acute bacterial and recurrent acute sinusitis. *Pseudomonas aeruginosa* is associated with sinusitis in the setting of HIV infection and cystic fibrosis. Anaerobic bacteria, streptococcal species, and *S. aureus* are more prominent causes of chronic sinusitis. Fungi also have a role in chronic sinusitis. *Rhizopus, Aspergillus, Candida, Histoplasma, Blastomyces, Coccidioides,* and *Cryptococcus* spp., as well as other fungi, may cause sinusitis, primarily in immunocompromised hosts. It is important to distinguish infectious from allergic sinusitis. Allergic sinusitis is associated with sneezing, itchy eyes, allergen exposure, and previous episodes.[19]

Clinical Features

Frontal sinusitis can cause severe headache localized to the forehead and orbit. Sphenoid sinusitis may cause vague headaches and focal pain almost anywhere in the head. Maxillary sinusitis may be seen with pain over the zygoma, in the canine or bicuspid teeth, or periorbitally. Ethmoid sinusitis can cause medial canthal pain and periorbital or temporal headaches.[19]

The cardinal findings of acute rhinosinusitis are mucopurulent nasal discharge, nasal obstruction or congestion, and facial pain, fullness, or pressure lasting less than 4 weeks. Other symptoms and signs include postnasal drip (which may lead to coughing), pressure over the involved sinus, malaise, hyposmia, anosmia, fever, maxillary dental pain, and ear fullness or pressure. Acute sinusitis typically progresses over a period of 7 to 10 days and resolves spontaneously. During the first 3 to 5 days of illness, it may be difficult to differentiate acute viral from acute bacterial sinusitis; antibiotics are not indicated in this phase because most cases are viral and will resolve without treatment. Bacterial sinusitis is more likely, and antibiotics are warranted when symptoms persist beyond 10 days, or with severe onset of disease (fever > 39° C [102.2° F] with severe facial pain or purulent nasal discharge) for at least 3 or 4 consecutive days. Bacterial origin also is suggested by so-called double sickening, which refers to patients who improve initially, only to have worsening sinus congestion and discomfort. In addition, the diagnosis of sinusitis is made in the pediatric population when a child with an upper respiratory infection presents with persistent illness (daytime cough or nasal discharge) longer than 10 days without improvement, a worsening course (worsening or new nasal discharge, daytime cough, or fever after initial improvement), or severe onset of symptoms (concurrent fever and purulent nasal discharge for at least 3 days).[19,20]

Chronic sinusitis is slow in onset, prolonged in duration (>12 weeks), and recurrent. Symptoms can be nonspecific but are generally similar to those of acute disease. Symptoms of chronic disease may include chronic cough, fetid breath, laryngitis, bronchitis, and worsening asthma. Recurrent acute sinusitis is diagnosed when four or more episodes of acute bacterial infection, without its symptoms or signs between episodes, occur annually. The presentation and treatment of recurrent acute disease is similar to that for acute bacterial sinusitis.[19] Invasive fungal sinusitis (mucormycosis) is an aggressive opportunistic rhinocerebral infection that affects immunocompromised hosts. Mucormycosis (*Rhizopus*) is generally associated with fever, localized nasal pain, and cloudy rhinorrhea. On examination, the affected tissue (usually the turbinates) appears gray, friable, anesthetic, and nonbleeding because of infarction caused by mucormycotic angioinvasion. In advanced cases, the affected tissues are necrotic and black, and the infection spreads beyond the sinus.[19]

Diagnostic Considerations

Differential Diagnosis

Rhinitis can be differentiated from sinusitis by the increased response of nasal obstruction to treatment, clear nasal discharge, and absence of pain or fever. Rhinitis does not lead to ostial obstruction, and patients do not complain of facial pain. Malignancy, tension headache, vascular headache, foreign body, dental disease, brain abscess, epidural abscess, meningitis, and subdural empyema may also manifest in a manner similar to that of sinusitis.

Diagnostic Testing

Physical examination is best performed after the application of a topical decongestant. Mucosal erythema and edema are usually present. Purulent discharge from the nasal meatus may be observed if the sinus ostia are not completely obstructed. In the setting of acute sinusitis, nasal and nasopharyngeal cultures do not differentiate between acute viral and acute bacterial infections and are not indicated. Culture and biopsy are indicated in suggested chronic, recurrent acute, and fungal sinusitis.[19]

For suspected acute sinusitis, routine radiographic examination is not recommended and should be limited to the diagnosis of chronic or recurrent acute sinusitis, cases of questionable diagnoses, patients with unresponsive disease, or investigation of complications. Axial and coronal CT is the imaging modality of choice. CT findings suggestive of sinusitis include air-fluid levels, sinus opacification, sinus wall displacement, and mucosal thickening (Fig. 65.11). CT is sensitive, although not specific. Incidental sinus mucosal thickening is seen in 40% of asymptomatic patients, and abnormal CT findings can also be noted in just 50% of patients with seasonal allergies. CT with IV contrast or MRI may be required to evaluate complications of rhinosinusitis and are helpful in determining alternative diagnoses. In children, CT or MRI with IV contrast should be performed if there is suspicion of orbital or central nervous system complications. Sinus endoscopy is an optional diagnostic modality for the evaluation of sinusitis.[19,20]

Management

Most cases of acute sinusitis are self-limited and resolve spontaneously; therefore, management should focus on symptomatic treatment and patient education. The goal of symptomatic treatment should be to reduce patient discomfort; it includes appropriate pain management and local decongestant therapy. When allergic symptoms are prominent or the patient has a history of allergic rhinosinusitis, antihistamines, such as loratadine, 10 mg daily, are helpful, but antihistamines otherwise are of no value.[19]

Decongestant therapy, available in topical and systemic preparations, can be used to reduce tissue edema, facilitate drainage, and maintain patency of the sinus ostia.[19] Topical agents provide more relief than systemic decongestants. Longer acting agents,

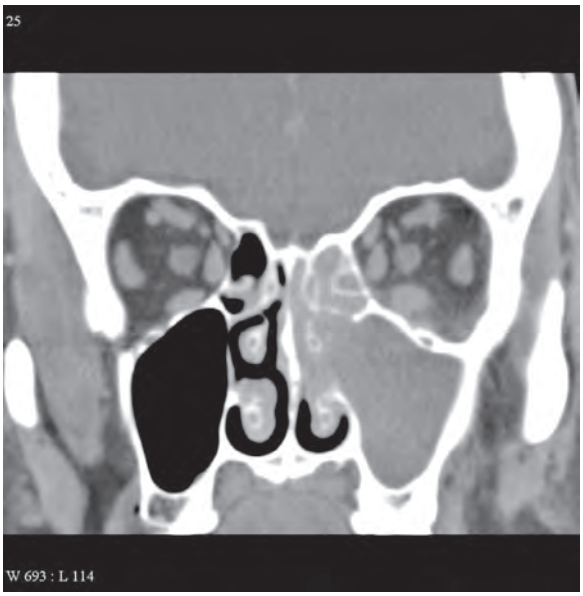

Fig. 65.11. CT scan demonstrating left maxillary sinus opacification in the setting of acute sinusitis.

such as 0.05% oxymetazoline hydrochloride, are easy to use and highly effective. Topical agents should be used for up to 5 days because extended use results in rebound vasodilation and nasal obstruction, a condition termed *rhinitis medicamentosa.* Systemic oral adrenergic agonists (eg, phenylpropanolamine, pseudoephedrine) offer no advantage over topical agents and have significant systemic effects, so they should not be used unless the patient is unwilling to use topical decongestants. They should not be used in patients with poorly controlled hypertension or patients who are taking tricyclic antidepressants, monoamine oxidase inhibitors, or nonselective β-adrenergic blockers.[19] Topical and systemic steroids offer modest benefit when used in conjunction with antibiotics for the treatment of bacterial sinusitis. Topical but not systemic steroids are indicated for chronic and allergic sinusitis. Systemic steroids may be indicated in allergic and chronic sinusitis with nasal polyps.[21,22]

Sinus self-irrigation with a Neti pot or powered commercial irrigator can be helpful for patients with chronic low-grade symptoms or frequently recurring acute episodes. Saline nasal irrigation is beneficial for the treatment of acute bacterial, recurrent acute, and chronic sinusitis and even may be efficacious for the prevention of sinusitis. Hypertonic saline preparations have superior antiinflammatory properties and may be more effective than normal saline.[19]

Antibiotic therapy should be initiated when the diagnosis of acute bacterial sinusitis is established. In children, those with severe onset or worsening symptoms should be treated with antibiotics. Children with persistent symptoms and one of the following should also be treated with antibiotics: (1) antibiotic therapy in the last 4 weeks; (2) concurrent bacterial infections; (3) actual or suspected complications of sinusitis; or (4) underlying conditions (eg, asthma, cystic fibrosis, anatomic abnormalities of the upper respiratory tract, immunodeficiency). Children with persistent stable symptoms may be managed with antibiotics or an additional short (usually up to 3-day) period of observation because there is low risk for complications in these patients, and the symptoms may resolve on their own. Patients who do not improve within 72 hours should be treated with antibiotics. The choice of antibiotics should consider β-lactamase production and multidrug-resistant pneumococci. Amoxicillin-clavulanate for 5 to 7 days in adults and 10 days in children is the first-line agent for uncomplicated bacterial sinusitis. High-dose amoxicillin-clavulanate is recommended as empirical treatment for patients from areas in which there are high endemic rates of invasive *S. pneumoniae*, severe infections, and those at risk for suppurative complications, such as patients who have recently been hospitalized, used antibiotics within the past 4 to 6 weeks, are older than 65 years, or are immunocompromised. Penicillin-allergic patients may be treated with levofloxacin, or doxycycline may be used in adults and, in children, a combination of clindamycin plus cefixime or cefpodoxime may be used in those with non–type I penicillin allergy. Children who are vomiting, unable to tolerate oral medications, or are at risk for nonadherence to oral therapy can be treated with an initial dose of 50 mg/kg of ceftriaxone (IV or IM) until they are able to tolerate oral antibiotics. Trimethoprim-sulfamethoxazole, macrolides, and second- and third-generation cephalosporin antibiotics are no longer recommended as empirical therapy due to bacterial resistance.[6,19,20]

Failure of symptoms to resolve after 3 to 5 days of antibiotic therapy, or patients who worsen after 48 to 72 hours of empirical antibiotics, necessitate reassessment to confirm the diagnosis of acute bacterial sinusitis, a change to an alternate antibiotic regimen for 5 to 10 days, and referral to an otolaryngologist. Appropriate management for patients with mild to moderate disease includes amoxicillin-clavulanate, cefpodoxime, and cefdinir. Patients with severe disease should be treated with a respiratory fluoroquinolone. Treatment of life-threatening complications requires consultation and high-dose IV antibiotics. Patients with chronic sinusitis should be referred to an otolaryngologist. Antibiotics may be helpful in the setting of chronic sinusitis and should be effective against anaerobic and β-lactamase–producing bacteria. Amoxicillin-clavulanate or clindamycin for 3 to 10 weeks may be used. Antifungals may be beneficial in the treatment of chronic sinusitis.[6,19]

Disposition

Most patients with rhinosinusitis can be treated on an outpatient basis. Frontal or sphenoid sinusitis with air-fluid levels may necessitate hospitalization. A previously healthy, nontoxic patient with good home support can be treated as an outpatient but should return immediately for any symptoms or signs of complications, including severe headache, neurologic changes, and visual changes. Patients who appear toxic, are immunocompromised, or have poor home resources require hospital admission and IV antibiotics.

KEY CONCEPTS

- Most cases of pharyngitis have a viral causes. CENTOR clinical criteria in conjunction with RST can be used to determine the likelihood of GAS pharyngitis.
- Rheumatic fever is rare in developed countries, where it may occur in epidemics.
- Although rare, local (airway) and systemic life-threatening complications of bacterial pharyngitis do occur.
- A severe sore throat with surprisingly minimal findings on examination of the oropharynx suggests serious soft tissue infection, such as epiglottitis or retropharyngeal abscess.
- Deep space cellulitis is difficult to differentiate from deep space abscess and may require needle aspiration after CT or MRI.
- Patients with upper airway infections should be kept in a position of comfort. Patients with epiglottitis prefer the classic sniffing position, whereas those with a retropharyngeal abscess prefer to lie supine.
- Posterior to the retropharyngeal space lies the danger space, which extends from the base of the skull to the superior mediastinum at about the level of T2.
- Resolving pharyngitis followed by severe sepsis, right-sided endocarditis, or aspiration pneumonia should suggest septic thrombosis of the internal jugular vein and Lemierre's syndrome.
- Imaging is rarely indicated in the setting of sinusitis and should be reserved for complex presentations or if there is a suspicion of complications.
- In children with persistent and stable sinusitis, a 3-day period of observation prior to the initiation of antibiotics is effective.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 65: QUESTIONS & ANSWERS

65.1. Which of the following associations regarding pharyngitis is true?

A. Appears clinically well—diphtheria
B. Cervical adenopathy—influenza
C. Conjunctivitis—coxsackievirus
D. No pharyngeal exudates—infectious mononucleosis
C. Pharyngeal exudates—adenovirus

Answer: E. Adenovirus often mimics streptococcal pharyngitis regarding the appearance of the exudate. It is also associated with conjunctivitis, rather than coxsackievirus, which is associated with hand-foot-and-mouth disease. Influenza rarely shows cervical adenopathy or pharyngeal exudates. Infectious mononucleosis typically exhibits a tonsillar exudate or membrane. Diphtheria cases are usually toxic-appearing.

65.2. A 9-year-old boy presents with fever, neck tenderness, and painful swallowing. The physical examination reveals a well-developed boy in no distress with oral temperature, 39.2° C (102.6° F), heart rate, 125 beats/min, respiratory rate, 22 breaths/min, blood pressure, 100/60 mm Hg, and O_2 saturation, 99%. Examination reveals whitish bilateral tonsillar exudates, tender bilateral cervical adenopathy, clear lungs, and normal tympanic membranes. Appropriate treatment measures include which of the following?

A. Admission for intravenous antibiotics
B. Amoxicillin daily for 10 days
C. Discussion with the family that antibiotic treatment prevents rheumatic fever but does not shorten illness duration
D. Symptomatic treatment only
E. Symptomatic treatment, throat culture, and return visit within 3 to 4 days for culture review and antibiotics as indicated

Answer: B. A 10-day course of penicillin or cephalosporin is the treatment of choice. The antibiotic regimen of choice for adults with group A beta-hemolytic *Streptococcus* (GAS) pharyngitis is a single intramuscular injection of 1.2 million units of benzathine penicillin. Culture and follow-up visits are acceptable practice but time-consuming and expensive. Symptomatic treatment is only indicated when GAS) has been ruled out. Antibiotic treatment prevents rheumatic fever and modestly shortens illness duration.

65.3. A 10-year-old boy, who recently immigrated to the United States from Honduras, complains of 3 days of sore throat, fever, and trouble swallowing. Examination reveals a healthy boy in mild distress with a grayish membrane covering the soft palate, pharynx, and uvula. The airway is patent. The child is slightly hoarse. He has bilateral tender anterior cervical adenopathy; his lungs are clear. Vital signs are temperature, 102.5° F (39° C) oral, heart rate, 130 beats/min, blood pressure, 105/65 mm Hg, respiratory rate, 28 breaths/min, and O_2 saturationm 100%. Which of the following treatments is most appropriate?

A. Antitoxin
B. High-dose corticosteroids
C. High-dose intravenous penicillin
D. Nebulized racemic epinephrine treatments
E. Urgent endotracheal intubation

Answer: A. This is diphtheria. Urgent antitoxin is necessary. The toxin may produce airway collapse, vocal cord necrosis, neuritis, and carditis. Antibiotics eradicate only the carrier state. Corticosteroids do not affect the toxin-induced damage. The status of the child does not warrant emergent endotracheal intubation because his hoarseness is only mild and he has a patent airway, although he must be closely monitored.

65.4. A 14-year-old girl returns to the ED 1 week after completing a 10-day course of penicillin for rapid strep test–confirmed GAS pharyngitis. She reports identical symptom return 1 week after completion of her antibiotics. Examination is again consistent with an exudative pharyngitis. Which of the following is indicated?

A. Admission for intravenous antibiotics
B. Cephalosporin, 10-day course
C. Counseling the family that this is likely infectious mononucleosis and symptomatic treatment is warranted
D. Intramuscular benzathine penicillin, 1.2 million units
E. Repeat rapid strep testing

Answer: D. Such patients may have been noncompliant or reinfected by asymptomatic contacts. Throat culture, surveillance of contacts, and intramuscular penicillin are indicated.

CHAPTER 66

Pneumonia

Gregory J. Moran | Matthew A. Waxman

PRINCIPLES

Background and Importance

Pneumonia is the leading infectious cause of death worldwide, with over 3.1 million deaths annually.[1] In the United States, there are over 4 million adult cases of community-acquired pneumonia (CAP) annually.[2] The economic burden associated with CAP annually in the United States is over $17 billion dollars. Most cases of CAP are managed in the outpatient setting, and the mortality is low (≈1%). Pneumonia necessitating hospitalization is associated with a mortality rate as high as 20%. Pneumonia remains challenging because of an expanding spectrum of pathogens, changing antibiotic resistance patterns, continued introduction of newer antimicrobial agents, and increasing emphasis on cost-effectiveness and outpatient management.

The epidemiology of CAP is changing. As the percentage of the population older than 65 years continues to increase, the incidence of pneumonia is expected to increase. An increasing number of patients are taking immunosuppressive drugs related to the treatment of malignancy, transplantation, or autoimmune disease, resulting in more cases of pneumonia from opportunistic pathogens. *Streptococcus pneumoniae* is the most frequently identified pathogen and is also associated with increasing antimicrobial resistance. In addition, the threat exists of respiratory infections caused by biologic terrorism or newly recognized pathogens such as Middle East respiratory syndrome that have the potential to spread globally through international travel.

Anatomy and Physiology

Despite the constant presence of potential pathogens in the respiratory tract, the lungs are remarkably resistant to infection. The alveolar surface of the lungs covers an area of approximately 140 m^2, about 10,000 L of air passes through the respiratory tract each day, and typical ambient air can contain hundreds to thousands of microorganisms per cubic meter. Although the cough and laryngeal reflexes prevent most large particulate matter from entering the lower respiratory tract, aspiration of oropharyngeal contents may be a common occurrence during normal sleep. Despite these hazards, the lower airway tract is a virtually sterile environment.

Pathophysiology

The development of clinical pneumonia requires a defect in host defenses, presence of a particularly virulent organism, or introduction of a large inoculum of organisms. Pneumonia commonly results from microaspiration of upper respiratory pathogens into the sterile lower respiratory tract. If the challenge of invading organisms overwhelms host defenses, microbial proliferation leads to inflammation, an immune response, and clinical pneumonia. If host defenses are weak, a minimal challenge may lead to the development of pneumonia. The challenge with pneumonia is identifying the causative agent rather than making the diagnosis in general. It is unlikely that a specific pathogen can be identified in the emergency department (ED), but a careful history, including foreign travel, recent antibiotic use, and exposure to the health care system, can help inform empirical therapy. Empirical therapy should be chosen with activity against the spectrum of likely pathogens based on the patient's overall clinical presentation.

There is difficulty in determining the specific cause of pneumonia because advanced microbiologic and serologic testing is generally not available during an ED evaluation. In CAP, a microbial cause cannot be determined in more than 50% of cases, even after a thorough inpatient investigation. Among hospitalized adults in whom a pathogen can be identified, organisms such as *S. pneumoniae* and *Haemophilus influenzae,* referred to as typical pathogens, account for approximately 50% of cases. *Legionella, Mycoplasma,* and *Chlamydophila* (previously known as *Chlamydia*) spp., referred to as atypical pathogens, are also common.[3] Testing for common viral agents reveals a viral cause in approximately 18% of cases, with influenza and parainfluenza viruses being the most common.[4]

Among adults requiring intensive care unit (ICU) admission, *S. pneumoniae* is the most common pathogen, with even higher prevalence among fatal cases. *Legionella* spp., *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), and aerobic gram-negative bacilli also appear to be relatively more common among adults with severe CAP.[5] Atypical organisms, such as *Mycoplasma* species or viruses, account for a relatively higher proportion of pneumonia in patients who have milder illness amenable to outpatient therapy.[6] Atypical organisms can also occur with significant frequency in patients with severe illness requiring hospitalization, particularly because of *Legionella* infection. Coinfection, such as with *Chlamydophila pneumoniae* and *S. pneumoniae,* is also well recognized.

S. pneumoniae is a gram-positive coccus that is the most common cause of CAP in adults requiring hospitalization. It colonizes the nasopharynx in 40% of healthy adults. Although this organism can cause pneumonia in healthy people, patients with a history of diabetes, cardiovascular disease, alcoholism, sickle cell disease, splenectomy, and malignancy or other immunosuppressive illness are at increased risk. A vaccine containing the 23 capsular polysaccharides of pneumococcal types most commonly associated with pneumonia reduces the likelihood of serious pneumococcal infection. It is recommended for adults at increased risk because of underlying illness or age older than 65 years.[7] Despite this recommendation, many ED patients have not received the pneumococcal vaccine, and vaccinating eligible patients in this setting seems to be feasible and effective.[8] A 13-valent protein-conjugate pneumococcal vaccine effectively reduces invasive pneumococcal disease and pneumonia in infants and young children.[9] Although underused in the adult population, the vaccine has resulted in a marked decrease in the incidence of pneumococcal pneumonia.[8]

H. influenzae, the second most frequently isolated organism in CAP among adults, is a pleomorphic gram-negative rod. It is

a common pathogen in adults with chronic obstructive pulmonary disease (COPD), alcoholism, malnutrition, malignancy, or diabetes.

S. aureus may be emerging as a more common cause of CAP and has been found more frequently than *H. influenzae* in some recent series. Community-associated strains of methicillin-resistant *S. aureus* (CA-MRSA) are uncommon in CAP but are more likely to cause severe disease.[10] Often associated with influenza, staphylococcal pneumonias are often necrotizing, with cavitation and pneumatocele formation. Intravenous (IV) drug users may develop hematogenous spread of *S. aureus* that involves both lungs, with multiple small infiltrates or abscesses (eg, tricuspid endocarditis resulting in septic pulmonary emboli).

Klebsiella pneumoniae is a gram-negative rod that rarely causes disease in a normal host and accounts for a small percentage of cases of CAP. It may cause severe pneumonia in debilitated patients with alcoholism, diabetes, or other chronic illness. There is a high incidence of antibiotic resistance because the organism is often hospital-acquired.

Mycoplasma pneumoniae is one of the most common causes of CAP in previously healthy patients younger than age 40 years. Another important organism in CAP is *C. pneumoniae,* an intracellular parasite that is transmitted between humans by respiratory secretions or aerosols. Seroprevalence studies have indicated that virtually everyone is infected with *C. pneumoniae* at some time and that reinfection is common, particularly in older adults. It accounts for at least 10% of CAP cases treated as outpatients, although this is an underestimate owing to difficulty in diagnosing infection with this organism.

At least 30 species of *Legionella* have been isolated since the 1976 convention-related outbreak in Philadelphia, from which the organism derives its name. At least 19 are known human pathogens. *Legionella* is an intracellular organism that lives in aquatic environments. There is no person to person transmission. Although it is implicated in point outbreaks related to cooling towers and similar aquatic sources, the organism also lives in ordinary tap water and is underdiagnosed as a cause of CAP. *Legionella* prevalence seems to vary greatly by region.

Lower respiratory infections caused by anaerobic organisms generally result from the aspiration of oropharyngeal contents with large amounts of bacteria. These infections are typically polymicrobial, including *Peptostreptococcus, Bacteroides, Fusobacterium,* and *Prevotella* spp. Presentation is often subacute or chronic and may be difficult to distinguish clinically from other causes of pneumonia. Clinical factors that suggest an anaerobic infection include risk factors for aspiration, such as central nervous system depression or swallowing dysfunction, severe periodontal disease, fetid sputum, and presence of a pulmonary abscess or empyema.

Viral pneumonias are common in infants and young children and are recognized as an important cause of pneumonia in adults. Respiratory syncytial virus and parainfluenza viruses are the most common causes of pneumonia in infants and small children, occurring mostly during autumn and winter. Influenza viruses are the most common cause of viral pneumonia in adults. Winter influenza outbreaks, usually of influenza type A, may cause up to 40,000 deaths annually in the United States. More than 90% occur in people aged 65 years or older. Metapneumovirus is a paramyxovirus that is an important cause of viral pneumonia in children and adults.[11]

Fungal infections caused by organisms such as *Histoplasma capsulatum, Blastomyces dermatitidis,* and *Coccidioides immitis* commonly manifest as pulmonary disease. These organisms are present in the soil in various US geographic areas—*H. capsulatum* in the Mississippi and Ohio River valleys, *C. immitis* in desert areas of the Southwest, and *B. dermatitidis* in a poorly defined area extending beyond that of *H. capsulatum.* These infections should be considered in people in appropriate geographic areas, especially in those who are near activities that disturb the soil, such as construction or dirt bike riding, and in patients who do not respond to antibacterial antibiotics. The clinical presentation varies from an acute or chronic pneumonia to asymptomatic granulomas and hilar adenopathy.

Pneumocystis pneumonia (PCP) occurs in immunocompromised hosts, principally those with acquired immunodeficiency syndrome (AIDS) or malignancy. *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*) is one of the most common infections leading to a diagnosis of HIV infection and AIDS. Patients with pulmonary complaints should be questioned about HIV risk factors, and emergency clinicians should search for signs of HIV-related immunosuppression, such as weight loss, lymphadenopathy, and oral thrush. PCP typically manifests subacutely with fatigue, exertional dyspnea, nonproductive cough, pleuritic chest pain, and fever.

Mycobacterium tuberculosis is a slow-growing bacterium transmitted between people by droplet nuclei produced from coughing and sneezing. *M. tuberculosis* survives within macrophages as a facultative intracellular parasite and may remain dormant in the body for many years. Active tuberculosis (TB) develops within 2 years of infection in approximately 5% of patients, and another 5% develop reactivation disease at some later time. Reactivation is more likely to occur in people with impaired cell-mediated immunity, such as patients with diabetes, renal failure, immunosuppressive therapy, malnutrition, or AIDS. Approximately one-third of the world's population is infected with *M. tuberculosis*; about 9 million new cases of active disease develop annually, resulting in 1.5 million deaths worldwide. Approximate 10,000 patients/year in the United States develop tuberculosis. Multidrug-resistant strains of *M. tuberculosis* have been found in increasing numbers, especially among patients with HIV and in immigrants from Southeast Asia.

Clinical Features

The ED evaluation should focus on establishing the diagnosis of pneumonia and determining the presence of epidemiologic and clinical features that would influence decisions regarding hospitalization and antibiotics. Key components of the history include character of symptoms, setting in which the pneumonia is acquired, recent contact with the health care system, geographic or animal exposures, and host factors that predispose to certain types of infections and are associated with outcome.

Pneumonia generally manifests as a cough productive of purulent sputum, shortness of breath, and fever. In most healthy older children and adults, the diagnosis can be reasonably excluded on the basis of history and physical examination, with suspected cases confirmed by chest radiography. The absence of any abnormalities in vital signs or chest auscultation substantially reduces the likelihood of pneumonia as demonstrated by radiography. No single isolated clinical finding, however, is highly reliable in establishing or excluding a diagnosis of pneumonia.[12]

Older or debilitated patients with pneumonia often have nonspecific complaints, such as acute confusion or a deterioration of baseline function, without classic symptoms. Similarly, older patients may not present with a well-defined infiltrate on radiography. Older patients are more likely to have advanced illness at the time of presentation and may have sepsis in the absence of a previous syndrome suggestive of pneumonia. Occasionally, patients with lower lobe pneumonia have abdominal or back pain as a presenting symptom.

Classic teaching divides pneumonia based on clinical patterns into typical pneumonia caused by pyogenic bacteria, such as *S. pneumoniae* or *H. influenzae,* and atypical pneumonia caused by organisms such as *Mycoplasma* and *Chlamydophila* spp. This

classic teaching is artificial, and a clear differentiation between these two types of pneumonia on clinical grounds alone is impossible. Certain clinical factors may be suggestive of atypical organisms. Factors studied prospectively and found not to help differentiate atypical pneumonias from those with pyogenic bacterial causes include gradual onset, viral prodrome, absence of rigors, nonproductive cough, lower degree of fever, absence of pleurisy or consolidation, normal leukocyte count, and an ill-defined infiltrate on a chest radiograph. Although it is impossible to determine the specific cause of pneumonia with a high degree of certainty without the results of microbiologic or serologic tests, certain clinical factors suggest that a specific pathogen should be considered.

Clinical factors suggesting pneumococcal pneumonia include the abrupt onset of a single shaking chill, followed by fever, cough productive of rust-colored sputum, and pleuritic chest pain. Patients with a history of asplenia, sickle cell disease, AIDS, multiple myeloma, or agammaglobulinemia are at increased risk of pneumococcal bacteremia and sepsis, with high mortality rates. Adults with chronic lung disease who develop pneumonia caused by *H. influenzae* typically demonstrate an insidious worsening of baseline cough and sputum production, and bacteremia is rare. *K. pneumoniae* may cause severe pneumonia in older or debilitated patients with so-called currant jelly sputum from the necrotizing nature of the infection. Abscess formation, empyema, and bacteremia are common with this organism, and mortality is high.

Atypical pneumonia is caused by organisms such as *M. pneumoniae, C. pneumoniae,* viruses, *Legionella* spp., or rickettsiae such as *Coxiella burnetii.* Mycoplasmal infection usually begins as a flulike illness with headache, malaise, fever, and nonproductive cough. Skin lesions, including maculopapular, vesicular, urticarial, or erythema multiforme–type rashes, are common, especially in younger patients. Although bullous myringitis is described as a classic finding, it is not specific for mycoplasmal infection and is seldom encountered. Patients generally do not have a toxic appearance, and most can be treated on an outpatient basis. Although mucopurulent sputum generally indicates the presence of pyogenic bacterial pneumonia or bronchitis, it may also be present with mycoplasmal or viral pneumonia. Viral pneumonia in adults is often preceded by symptoms of upper respiratory infection, such as rhinitis or sore throat. Most *C. pneumoniae* infections in young adults cause a minor, self-limited, upper respiratory illness that is subacute in onset. This organism is also associated with bronchitis, wheezing, sinusitis, and pharyngitis. Development of radiographically evident pneumonia is more common in older adults with C. *pneumoniae*. Some patients with *Legionella* infection have a mild, self-limited atypical pneumonia presentation. Older patients, smokers, and those with chronic disease or immunosuppression are more prone to develop the more acute and severe systemic illness of Legionnaires' disease. Gastrointestinal symptoms, such as diarrhea and abdominal cramping, confusion, and muscle aches are sometimes prominent.

In addition to age, the presence of underlying illness, and presenting symptoms, the setting of acquisition of pneumonia may provide clues to likely causes. CAP that occurs in otherwise healthy individuals is likely to be caused by viruses, *Mycoplasma* spp., or *S. pneumoniae. S. aureus,* including MRSA, can cause severe pneumonia associated with influenza. Recently hospitalized and long-term care patients may develop pneumonia from agents that are uncommon in CAP, such as Enterobacteriaceae, *Pseudomonas aeruginosa,* and *S. aureus.* Healthy patients in an institutional setting, such as a dormitory or military barracks, are likely to have pneumonia caused by *Mycoplasma* spp. or viruses.

Patients with underlying lung disease, especially COPD, constitute an important group likely to develop pneumonia. The lower respiratory tract of these patients is commonly colonized with organisms such as *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis.* Cystic fibrosis patients are prone to pneumonia caused by *P. aeruginosa* or *S. aureus*. Defective mucociliary clearance in both these groups makes them highly susceptible to repeated episodes of pneumonia.

Patients with immunosuppression as a result of hematologic malignancy, patients receiving chemotherapy for malignancy, and transplant recipients are prone to pulmonary infections with a wide variety of organisms. In addition to the usual pathogens, these patients may develop pneumonia secondary to viruses such as cytomegalovirus (CMV), varicella, or herpes simplex virus. They are also more likely to develop pneumonia caused by aerobic gram-negative bacilli, *Aspergillus* and geographic fungi, and *P. jiroveci*.

Although the use of highly active antiretroviral therapy (HAART) has decreased the incidence of opportunistic infections among HIV-infected patients, individuals who are not under regular care often come to the ED. In addition to *P. jiroveci*, there is also an increased incidence of *M. tuberculosis* and common bacterial pathogens such as *S. pneumoniae.* Bacterial pneumonia remains the most common pneumonia in HIV-infected patients. Other less common causes of pneumonia in HIV-infected patients include *Mycobacterium avium* complex, CMV, aerobic gram-negative bacilli, and *Cryptococcus neoformans.* PCP usually has a subacute presentation characterized by nonproductive cough, exertional dyspnea, and weight loss. Hypoxemia, hypocapnia, and an increased arterial-alveolar oxygenation gradient are usually present. A clinical clue suggesting PCP pneumonia in the ED is a significantly decreased oxygen saturation with ambulation in the setting of HIV disease or risk factors.

The potential for opportunistic pulmonary infection can be predicted by a recent absolute CD4 lymphocyte count less than 200/mm^3. This count is often known by patients with recognized HIV infection or may be surmised by a peripheral total lymphocyte count less than 1000/mm^3. In patients who do not know their HIV status, the presence of findings such as weight loss, hairy leukoplakia, and oral candidiasis strongly suggests immunosuppression.

Patients in nursing homes and extended-care facilities are at increased risk for infection with resistant organisms such as *P. aeruginosa, K. pneumoniae* (including strains producing extended-spectrum β-lactamases), *Acinetobacter* spp., and hospital-associated strains of MRSA. In 2005, the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) issued guidelines for the management of patients who may be at risk for multidrug resistance based on recent exposure to the health care system. See Box 66.1 for definitions of hospital-acquired, ventilator-associated, and health care–associated pneumonia (HCAP). An important part of the initial evaluation of the patient with pneumonia is a careful history and review of the medical record for recent exposure to the health care system. HCAP is associated with a greater likelihood of resistant pathogens such as *Pseudomonas* and MRSA, and mortality is higher than that for CAP.[13]

Diagnostic Considerations

Differential Diagnoses

Differentiation between upper and lower respiratory tract infections may be difficult. A chest radiograph helps differentiate between upper respiratory tract infection or bronchitis and pneumonia.

Many noninfectious conditions may result in inflammatory lung processes, including exposure to mineral dusts (eg, silicosis), chemical fumes (eg, chlorine and ammonia), toxic drugs (eg, bleomycin), radiation, thermal injury, or oxygen toxicity. Immunologic disease (eg, sarcoidosis, Goodpasture's syndrome, and

collagen vascular disease) or hypersensitivity to environmental agents (eg, farmer's lung disease) may also result in pneumonia. Tumors may be confused radiographically with pneumonia or may appear initially as a postobstructive infection or adenopathy with peripheral infiltrates. The lymphangitic spread of lung malignancy may resemble that of interstitial pneumonia.

It is important to distinguish between the acute aspiration of gastric contents or other liquids and bacterial pneumonia that may develop later as a complication of aspiration. Aspiration of liquids into the lung disrupts surfactant and causes an inflammatory response that may lead to hypoxia and respiratory failure. The aspiration of acidic gastric contents is particularly damaging to the lungs and is common in patients who are unconscious from intoxication or anesthesia or who have neurologic deficits. Patients may initially have coughing or shortness of breath or may appear well initially and then develop respiratory dysfunction during the next several hours.

Acute aspiration of acidic fluid into the lungs causes a chemical pneumonitis. This may produce fever, leukocytosis, purulent sputum, and radiographic infiltrates that mimic those of bacterial pneumonia. Although some patients go on to develop bacterial pneumonia, prophylactic administration of antibiotics is controversial.[14] Antibiotics should be initiated if the patient develops signs of bacterial pneumonia, including new fever, expanding infiltrate appearing more than 36 hours after aspiration, or unexplained deterioration.

BOX 66.1

American Thoracic Society/Infectious Disease Society of America Definitions of Hospital-Acquired, Ventilator-Associated, and Health Care–Associated Pneumonia

Hospital-acquired pneumonia (HAP)—occurs ≥48 hr after admission and does not appear to be incubating at the time of admission

Ventilator-associated pneumonia (VAP)—occurs >48–72 hr after endotracheal intubation

Health care–associated pneumonia (HCAP)—occurs in a nonhospitalized patient with extensive health care contact defined by one or more of the following exposures:

- IV therapy, wound care, or IV chemotherapy within the prior 30 days
- Residence in a nursing home or other long-term care facility
- Hospitalization in an acute care hospital for 2 or more days within the past 90 days
- Received hemodialysis within the prior 30 day.

American Thoracic Society; Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare associated pneumonia. Am J Respir Crit Care Med 171:388–416, 2005.

Diagnostic Testing

Although many chest radiographs are obtained unnecessarily for patients with upper respiratory tract infections or bronchitis, it is difficult to identify a set of specific criteria to direct test ordering that is better than the clinical judgment of an experienced physician. A routine chest radiograph for all patients with cough is not necessary. Computed tomography (CT) of the chest is more sensitive than plain radiography for detecting the presence of pulmonary consolidation, although the natural history of CT-positive, plain radiograph–negative pneumonia is not clear. CT of the chest should be considered in patients such as older adults or those with significant comorbidities, for whom identification of a subtle infiltrate would change management. Young healthy adults with a presumptive diagnosis of pneumonia who will be treated as outpatients may have a chest radiograph deferred unless there is a suspicion of immunocompromise or other unusual features of disease.[15] A chest radiograph should be obtained subsequently if there is a poor initial response to treatment. Routine performance of chest radiography for patients with exacerbation of chronic bronchitis or COPD is of low yield and may be limited to patients with other signs of infection or congestive heart failure.

Although the causative agent cannot be determined solely by the results of chest radiography, certain radiographic patterns may suggest the possibility of specific pathogens. In pyogenic bacterial pneumonias, radiographs usually show an area of segmental or subsegmental infiltration and air bronchograms (Fig. 66.1). Lobar

Fig. 66.1. Posteroanterior chest radiograph reveals left upper lobe pneumonia. A variety of organisms can produce this pattern, usually *Streptococcus pneumoniae*, *Haemophilus influenzae*, or gram-negative bacilli, but also *Chlamydophila pneumoniae, Mycoplasma,* or *Legionella* spp.

consolidation is present in a few cases of bacterial pneumonia, often caused by pneumococci or *Klebsiella*. A dense lobar infiltrate with a bulging fissure appearance on a chest radiograph is often described with pneumonia caused by *Klebsiella,* but this finding is nonspecific, and most cases manifest as a more subtle bronchopneumonia. Pneumonia resulting from the spread of infection along the intralobular airway results in fluffy or patchy infiltrates in the involved areas of the lung. A wide variety of bacteria and agents such as *Chlamydophila*, *Mycoplasma*, and *Legionella* spp., viruses, and fungi may cause this pattern.

An interstitial pattern on a chest radiograph (Fig. 66.2) typically is caused by *Mycoplasma* spp., viruses, or *P. jiroveci*. The classic radiographic findings in PCP are bilateral interstitial infiltrates that begin in the perihilar region (Fig. 66.3). Radiographic manifestations of PCP can vary considerably, including normal appearance and lobar infiltrates, pleural effusions, hilar adenopathy, parenchymal nodules, and cavitary disease. Tiny nodules disseminated throughout both lungs represent a miliary pattern typical of granulomatous pneumonias, such as TB or fungal disease. The location of infiltrates may also suggest the cause. Aspiration pneumonia occurs in dependent areas of the lung, usually the superior segments of the lower lobes or posterior segments of the upper lobes. Infiltrates from pneumonias produced by hematogenous spread (eg, *S. aureus*) tend to be multiple and peripheral. Apical infiltrates suggest TB.

The presence of additional radiographic features in association with infiltrates may suggest a specific cause. An infiltrate associated with hilar or mediastinal adenopathy suggests the presence of TB or fungal disease or may indicate pneumonia associated with a neoplasm. Bacteria most likely associated with cavitation (Fig. 66.4) are anaerobes, aerobic gram-negative bacilli, and *S. aureus.* Cavitation also may be present in fungal disease or TB and with noninfectious processes (eg, malignancy and pulmonary vascular disease). Pneumatoceles or spontaneous pneumothorax may be seen in AIDS patients with PCP. Pleural effusions occur

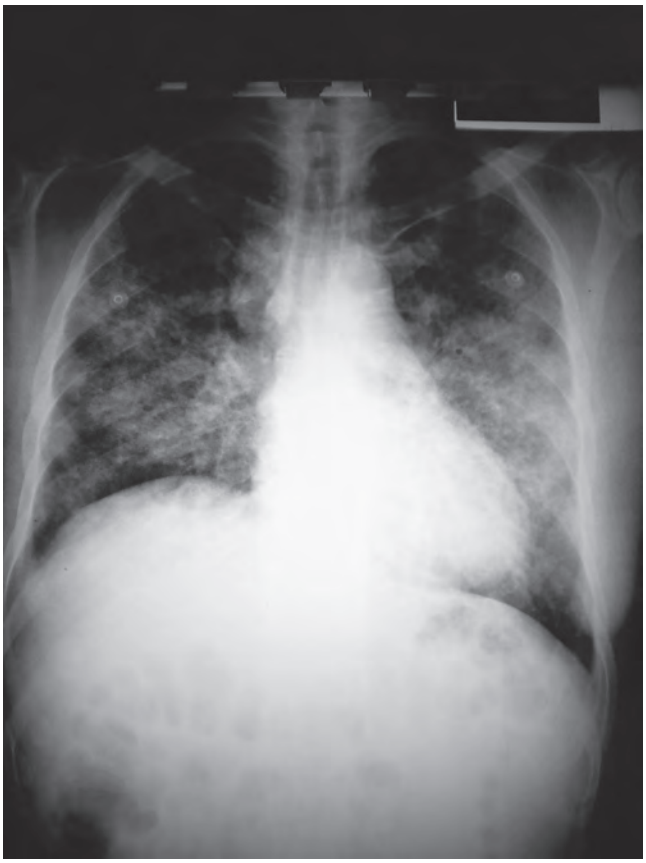

Fig. 66.2. Posteroanterior chest radiograph reveals patchy interstitial infiltrates. Viruses and *Mycoplasma* are the most likely causes in an otherwise healthy patient, but many bacterial organisms may also produce this pattern.

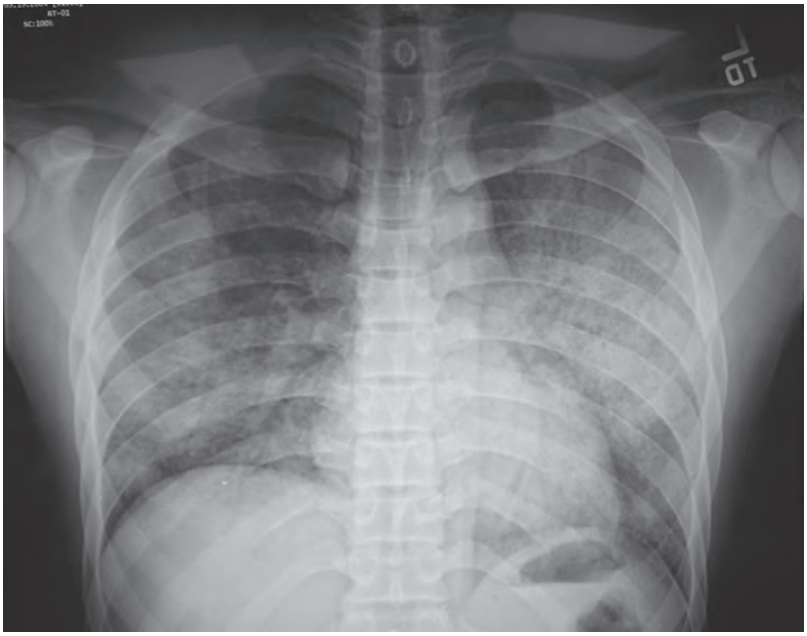

Fig. 66.3. Posteroanterior chest radiograph of a human immunodeficiency virus (HIV)–infected patient reveals interstitial disease mixed with patchy alveolar infiltrates. *Pneumocystis jiroveci* is the most common cause, but bacterial pathogens and tuberculosis also are considered.

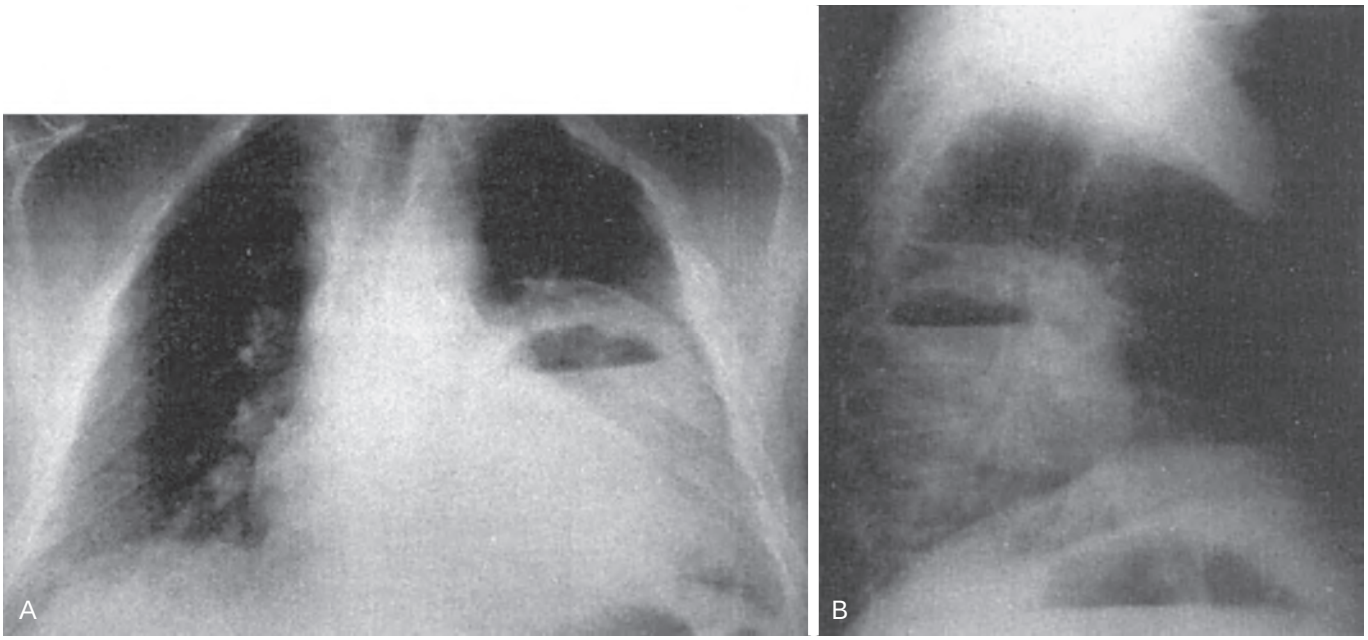

Fig. 66.4. Posteroanterior (**A**) and lateral (**B**) chest radiographs reveal a lung abscess in the left lower lobe, with a distinct air-fluid level.

with a wide variety of organisms, including many types of pyogenic bacterial pneumonias, *Chlamydophila* and *Legionella* spp., and TB. Anaerobic infections associated with an effusion are especially prone to the development of empyema. The diagnosis and aspiration of pleural effusions can be aided by the use of bedside ultrasonography in the ED.

Radiographic findings are nonspecific for predicting a particular infectious cause. *Mycoplasma* pneumonia may manifest as a dense infiltrate, or pneumococcal pneumonia may manifest as a diffuse interstitial infiltrate. Immunocompromised patients are particularly prone to having atypical radiographic appearances. Rarely, patients with a clinical picture strongly suggestive of pneumonia have a normal chest radiograph, and some are found to have an infiltrate within the next 24 to 48 hours. The absence of findings on a chest radiograph should not preclude the use of antimicrobial therapy in appropriate patients with a clinical diagnosis of pneumonia. Immunocompromised patients, older adults, and patients with significant comorbidities may be treated with empirical antibiotics in the setting of signs and symptoms indicating pneumonia, even with a negative chest radiograph.

Laboratory studies also are nonspecific for identifying the cause of pneumonia. Although the finding of a white blood cell (WBC) count greater than 15,000/mm^3 increases the probability of the patient having a pyogenic bacterial cause rather than a viral or atypical cause, the predictive value of this finding depends on the stage of the illness and likely prevalences of various causes. This is neither sensitive nor specific enough to aid decisions regarding therapy in an individual patient. A WBC count may be helpful if it yields evidence of immunosuppression, such as neutropenia, or if it reveals lymphopenia that may indicate immunosuppression from AIDS. Basic metabolic panels may help identify patients with renal or hepatic dysfunction or metabolic acidosis associated with sepsis. These findings predict a complicated course and influence decisions regarding disposition, choice of antimicrobial agents, and dosages. The serum lactate dehydrogenase level is significantly elevated in AIDS patients with PCP compared with patients with non-PCP pneumonia. Inflammatory markers such as the erythrocyte sedimentation rate, and procalcitonin and C-reactive protein levels are not helpful in clinical decision making regarding pneumonia. The procalcitonin level has been suggested as a means to assess the likelihood of a bacterial cause, response to antimicrobial therapy, and prognosis. A procalcitonin strategy can slightly reduce antibiotic use without increased morbidity, but is only moderately sensitive for identifying bacterial pneumonia and has not been shown to add prognostic information beyond other risk stratification systems.[16] Assessment of respiratory function with pulse oximetry is important in the evaluation of patients with pneumonia because the clinical assessment of oxygenation can be inaccurate. Pulse oximetry should be performed in any patient suspected to have pneumonia, and pneumonia should be considered in patients with low oxygen saturation.

Sputum Gram staining rarely results in a change in therapy or outcome. Correlation between the identification of pneumococcus on Gram staining and sputum culture results is poor, even when commonly used criteria for an adequate sputum specimen are applied (<five squamous epithelial cells and >25 WBCs/high-power field). Gram staining is even less likely to show gram-negative pathogens, such as *H. influenzae,* and should not be relied on to rule out a gram-negative cause. Empirical antimicrobial agents are usually highly clinically effective if chosen based on clinical information without sputum analysis. ATS/IDSA guidelines for the management of CAP support limiting sputum Gram staining and culture to patients with more severe disease or risk factors for unusual pathogens.[12] Confirmation of the diagnosis of PCP requires sputum induction and staining and, in some cases, further invasive procedures, such as bronchoscopy with bronchoalveolar lavage or biopsy.

Routine blood cultures are of essentially no value in nonimmunocompromised adults with pneumonia, in whom there is a very low prevalence of bacteremia, and management is rarely changed based on the results. Follow-up of false-positive blood cultures is costly and labor-intensive and may lead to the unnecessary use of antibiotics, such as vancomycin or linezolid, when contaminant growth is initially reported as gram-positive cocci. Blood samples for culturing should be obtained from immunocompromised patients, those with severe sepsis or shock, or those with risk factors for endovascular infection (eg, prosthetic valves, IV drug use, cavitary infiltrates).[17,18] When culture specimens are drawn, they should be obtained before the initiation of antibiotics, although antibiotics should not be delayed for this reason.

Patients with a pleural effusion larger than 5 cm on an lateral, upright, posterior-anterior chest radiograph should undergo diagnostic thoracentesis, with fluid sent for cell count, differential, pH (pH < 7.2 predicts the need for a thoracostomy tube), Gram staining, and culture. For most patients, thoracentesis can be safely deferred until after hospital admission. Patients in significant respiratory distress, however, or with evidence of tension and mediastinal shift, require emergent diagnostic and therapeutic thoracentesis.

Serologic tests are available for the diagnosis of many organisms, including *C. pneumoniae, Legionella* spp., and fungi. The use of serologic tests to determine the cause of pneumonia may be helpful retrospectively, but these usually require acute and convalescent serum titers and are of little use in the ED. Urine antigen tests for *S. pneumoniae* and *Legionella* are available and, in some facilities, results can be obtained within the time frame of an ED evaluation. It is not clear, however, that a positive result should prompt a change in empirical treatment. Rapid diagnostic tests for viral antigens are available for several viruses, including respiratory syncytial virus (RSV) and influenza. The test results may be useful for infection control decisions in hospitalized patients and may provide an indication for influenza therapy and family prophylaxis. Some commercially available rapid influenza tests are insensitive for certain strains. Rapid testing for respiratory viruses (ie, RSV, influenza, metapneumovirus, adenovirus, enterorhinovirus) with a polymerase chain reaction assay is increasingly available to emergency clinicians to determine the specific cause of pneumonia and is more accurate than antigen tests.

MANAGEMENT

The possibility of communicable disease should prompt consideration for early isolation. Patients with a history of TB exposure or suggestive symptoms (eg, persistent cough, weight loss, night sweats, hemoptysis) or who belong to a group at high risk for TB (eg, homeless, IV drug user, alcoholic, HIV risk, immigrant from high-risk area) should be given a mask and placed in respiratory isolation before evaluation, including chest radiography.[18] Because AIDS patients with pulmonary TB cannot be distinguished reliably from AIDS patients with other pulmonary infections at presentation, TB should be considered in all HIV-infected patients with respiratory complaints, and respiratory isolation should be initiated. EDs that frequently care for patients at risk for TB should consider triage protocols to identify these individuals rapidly before patients, visitors, or staff are unnecessarily exposed. Suspected infection with organisms transmitted by respiratory droplet (eg, influenza) should prompt infection control precautions, such as a mask being placed on the patient.

Antimicrobials should be administered in the ED for patients who are being admitted to the hospital. The timely administration of antimicrobials is associated with improved outcomes for hospitalized pneumonia patients, although confounding factors limit a full understanding of this relationship. Any presumed benefit of early antibiotic administration should be weighed against the risk of inappropriate use for patients in which the diagnosis is unclear. The antibiotics selected should cover the likely causes based on clinical, laboratory, radiologic, and epidemiologic information. The regimen should also be as selective as possible to avoid drug toxicity, emergence of resistance to broad-spectrum agents, and excessive cost.

The prevalence of drug-resistant *S. pneumoniae* (DRSP) has been increasing. In most areas of the United States, high-level penicillin resistance occurs in approximately 15% to 20% of outpatient pneumococcal sputum isolates.[19] DRSP that is resistant to penicillin is usually resistant to other β-lactams, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMX). Extended-spectrum (or respiratory) fluoroquinolones, such as levofloxacin, are active against DRSP and other typical and atypical bacterial pathogens. Because the oral bioavailability of fluoroquinolones is high, oral therapy provides serum and tissue levels essentially equivalent to parenteral therapy. It is not clear, however, the extent to which in vitro resistance is related to adverse clinical outcome. Most cephalosporins and macrolides achieve adequate levels in serum and tissues to treat *S. pneumoniae* respiratory tract infections successfully, even if the laboratory reports that the organism is resistant.

CA-MRSA is the most common pathogen isolated in community-acquired skin and soft tissue infections. It causes severe, rapidly progressing pneumonia with sepsis, often in children or healthy young adults with influenza.[20] CA-MRSA remains an uncommon cause of CAP[11] but empirical coverage of MRSA should be strongly considered for patients with severe pneumonia associated with sepsis,[21] especially those with likely influenza, contact with someone infected with MRSA, or radiographic evidence of necrotizing pneumonia. Antimicrobials with consistent in vitro activity against CA-MRSA isolates include vancomycin, TMP-SMX, tigecycline, linezolid, and ceftaroline. Although vancomycin is used most often for documented MRSA infections, vancomycin may be losing efficacy in light of increasing minimum inhibitory concentrations.

Appropriate agents for the outpatient treatment of adults with CAP include macrolides, doxycycline, and fluoroquinolones with enhanced activity against *S. pneumoniae* (Table 66.1).[12] In patients properly identified as being at low risk for complications with careful outpatient follow-up, use of a macrolide such as azithromycin, 500 mg orally (PO) once, followed by 250 mg PO daily for

TABLE 66.1

Community-Acquired Pneumonia in Adolescents and Adults: Outpatient Treatment

CLINICAL SETTING	ANTIBIOTIC REGIMEN[a]	COMMENTS
Previously healthy, no antimicrobials in last 3 mo	Doxycycline, 100 mg PO bid	Preferred for adolescent or young adult when likelihood of *Mycoplasma* is high; variable activity vs. *Streptococcus pneumoniae*
	Azithromycin. 500 mg once, followed by 250 mg daily for 4 days	Treats common typical bacterial and atypical pathogens; clarithromycin can be substituted.
Comorbidities or antimicrobials in last 3 mo	Levofloxacin, 750 mg PO daily for 5 days	Can substitute moxifloxacin, 400 mg daily for 7–14 days; treats common typical and atypical bacterial pathogens; active against DRSP; use fluoroquinolone if recently received β-lactam or macrolide
	Cefpodoxime, 200 mg PO bid, + azithromycin, 500 mg PO daily	Use if fluoroquinolones recently received; can substitute cefdinir, cefprozil, or amoxicillin-clavulanate for cefpodoxime; variable activity against DRSP

[a]Doses are for 70-kg adult with normal renal and hepatic function.
DRSP, Drug-resistant *S. pneumoniae*; *PO,* orally.

4 days, is preferred. Doxycycline is an alternative choice that has activity against some uncommon causes of pneumonia such as MRSA, but it has more side effects. For patients at higher risk of DRSP because of recent antibiotic use or comorbidities such as chronic heart, lung, liver, or renal disease, a respiratory fluoroquinolone should be considered. For patients who have received a fluoroquinolone within the previous few months, a combination of a macrolide plus a β-lactam agent (eg, high-dose amoxicillin [1 g tid], amoxicillin-clavulanate [2 g PO bid], or cefpodoxime) is appropriate. Levofloxacin, 750 mg daily for 5 days, doxycycline, 100 mg bid for 7 days, or a 5-day course of azithromycin is indicated for CAP. Patients admitted to the ICU for respiratory failure or pneumonia should be treated with oseltamivir during influenza season.

For patients whose illness is severe enough to necessitate hospital admission and parenteral antibiotics, a combination of a β-lactam agent, such as ceftriaxone, 1 g (IV) q24h (or ceftaroline, cefotaxime, ampicillin-sulbactam, or ertapenem), plus a macrolide (eg, azithromycin, 500 mg IV or PO daily) is the regimen recommended in ATS/IDSA guidelines.[12] Alternatively, an extended-spectrum fluoroquinolone (eg, levofloxacin, moxifloxacin) can be given as monotherapy, but this regimen may be more likely to promote antimicrobial resistance. These regimens treat the most common bacterial pathogens, such as *S. pneumoniae*, and *H. influenzae*, and atypical pathogens, such as *Mycoplasma, Chlamydophila,* and *Legionella* spp. β-Lactam monotherapy has been found to be noninferior to β-lactam–macrolide combination therapy or fluoroquinolone monotherapy in nonsevere CAP; it is a reasonable choice for patients without a specific reason to suspect atypical organisms.

Fluoroquinolones have some activity against TB and should be avoided in patients for whom TB is a possible cause because of the risk of obscuring the correct diagnosis and selection of resistant TB. IV azithromycin alone may be an option for patients with milder illness who are unlikely to be bacteremic; it does not achieve significant serum levels and lacks significant activity against many aerobic gram-negative bacilli and DRSP. If anaerobic organisms are suspected (eg, aspiration), clindamycin or metronidazole could be added to the regimen, or the regimen could include an antibiotic with anaerobic activity, such as ertapenem, ampicillin-sulbactam, piperacillin-tazobactam, tigecycline, or moxifloxacin (Table 66.2).

Seriously ill patients with severe sepsis or septic shock require aggressive fluid resuscitation and may benefit from more intensive management with vasopressors, transfusion, and inotropic agents. Severely ill and compromised patients are at relatively greater risk of infection with *S. pneumoniae,* aerobic gram-negative bacilli, *S. aureus* (including MRSA) and, in some areas, *Legionella* spp. For pneumonia patients admitted to an ICU, adequate activity against DRSP may be more important. Outcomes with severe pneumonia may be better with combination therapy.[22] A third-generation cephalosporin or β-lactam or β-lactamase inhibitor can be combined with a macrolide or fluoroquinolone, and addition of vancomycin or linezolid should be considered for MRSA activity.

Patients with recent hospitalization, neutropenia, or underlying bronchiectasis are at increased risk of infection with *P. aeruginosa.* Empirical therapy should include two agents with extended gram-negative activity, including *P. aeruginosa.* Empirical regimens include cefepime, imipenem, meropenem, doripenem, or piperacillin-tazobactam, plus ciprofloxacin (high dose) or an aminoglycoside and macrolide. For life-threatening pneumonia in populations at risk for MRSA, the addition of vancomycin or linezolid may be considered.

Because HCAP is associated with higher mortality and a greater likelihood of unusual pathogens, the use of broader spectrum empirical therapy is often appropriate, usually with a combination of antimicrobials to increase the chance that at least one antibiotic will be active against the causative pathogen. The reflex broadening of empirical therapy for patients with risk factors for HCAP (see Box 66.1) has been called into question. Automatic application of the criteria for HCAP may result in the unnecessary overuse of antibiotics. It is recommended that the emergency clinician individualize the decision to initiate multidrug resistant empirical coverage in patients who are sufficiently ill or with multiple risk factors for HCAP. Such appropriate combinations include an antipseudomonal β-lactam agent (eg, piperacillin-tazobactam, cefepime, imipenem, meropenem) with an aminoglycoside or fluoroquinolone and vancomycin or linezolid for MRSA.[22]

For patients with AIDS, it is important to treat *P. jiroveci* and bacterial pathogens such as *S. pneumoniae.* TMP-SMX is the treatment of choice; the usual regimen is 15 mg/kg of TMP and 75 mg/kg of SMX daily qid, to be continued for 21 days, in addition to a regimen to cover CAP organisms.[23] For most adult patients a

TABLE 66.2

Community-Acquired Pneumonia in Older Children and Adults: Inpatient Antimicrobial Treatment

CLINICAL SETTING	ANTIBIOTIC REGIMEN*	COMMENTS
Community-acquired, nonimmunocompromised	Ceftriaxone 1 g q24h ± azithromycin, 500 mg q24h IV or PO Respiratory fluoroquinolone (levofloxacin, 750 mg IV q24h, or moxifloxacin, 400 mg IV q24h)	Can substitute cefotaxime, ceftaroline, ampicillin-sulbactam, or ertapenem for ceftriaxone Treats most common bacterial and atypical pathogens; active against DRSP
Severe pneumonia (ICU)	Ceftriaxone, 1 g IV q24h + levofloxacin, 750 mg IV q24h + vancomycin, 1 g IV q12h	Can substitute cefotaxime, cefepime, ceftaroline, ertapenem, or β-lactam or β-lactamase inhibitor for ceftriaxone; can substitute moxifloxacin for levofloxacin; can substitute linezolid for vancomycin
Health care–associated pneumonia or severe pneumonia with neutropenia, bronchiectasis (risk for *Pseudomonas*)	Cefepime, 2g IV q12h + ciprofloxacin, 500 mg IV q12h + vancomycin, 1 g IV q12h	Can substitute other antipseudomonal β-lactams, such as piperacillin-tazobactam, imipenem, meropenem, or doripenem, for cefepime; can substitute aminoglycoside plus macrolide for ciprofloxacin
Presumed PCP	TMP-SMX, 240/1200 mg IV q6h	Add ceftriaxone to TMP-SMX if severe, until PCP confirmed; alternatives for sulfa allergy include clindamycin + primaquine

*Doses are for a 70-kg adult with normal renal and hepatic function.
DRSP, Drug-resistant *S. pneumoniae*; *ICU,* intensive care unit; *IV,* intravenously; *PCP, Pneumocystis* pneumonia; *PO,* orally; *TMP-SMX,* trimethoprim-sulfamethoxazole.

regimen of three ampules (80 mg of TMP–400 mg of SMX/ampule) qid is appropriate. For patients allergic to sulfa, options include clindamycin, 600 mg IV tid, plus primaquine, 30 mg PO daily. The addition of corticosteroids (prednisone, 40 mg PO bid) reduces mortality and clinical deterioration in patients with hypoxemia. Traditionally, this has been defined as a Pao_2 less than 70 mm Hg or alveolar-arterial gradient greater than 35 mm Hg. In practice, pulse oximetry with an $Sao_2 \leq 92\%$ on room air or desaturation with exercise should warrant the initiation of corticosteroids. *Mycoplasma, Legionella,* and *Chlamydophila* spp. are uncommon causes of severe pneumonia in AIDS patients, so empirical therapy with erythromycin or doxycycline is not routinely recommended.

DISPOSITION

There is tremendous variability among emergency clinicians in deciding whom to admit for pneumonia.[24] The more common tendency is the overestimation of disease severity, leading to hospitalization of patients at low risk for death or serious complications. The decision to hospitalize a patient with pneumonia does not necessarily mean that a prolonged inpatient stay is required. Observation for 12 to 24 hours in the ED observation unit or hospital may allow the early discharge of certain moderate-risk patients. Inpatient treatment of pneumonia is 15 to 20 times more expensive per patient than outpatient treatment, and most patients are more comfortable in a home environment.

Although no firm guidelines exist regarding hospital admission, scoring systems may assist with hospitalization decisions. One commonly used system is based on the Pneumonia Patient Outcomes Research Team study, a prospectively validated predictive rule for mortality among immunocompetent adults with CAP. This model (also known as the pneumonia severity index [PSI]) suggests a two-step approach to assess risk. Patients in the lowest risk class appropriate for outpatient management are those younger than 50 years, without significant comorbid conditions (eg, neoplasm, congestive heart failure, cerebrovascular disease, renal disease, liver disease, HIV), and without findings that include altered mental status, pulse rate 125 beats/min or greater, respiratory rate, 30 breaths/min or greater, systolic blood pressure less than 90 mm Hg, or temperature less than 35°C (95°F) or 40°C (104°F) or higher. Patients who do not fit the lowest risk category are classified into categories based on a scoring system that accounts for age, comorbid illness, physical examination findings, and laboratory abnormalities (Table 66.3). Hospitalization is recommended for patients with a score greater than 91, and brief admission or observation may be considered for patients with a score of 71 to 90. Although this method of assessing the likelihood of successful outpatient management is helpful, it can be cumbersome, is not modeled to predict acute life-threatening events, does not take into account dynamic evaluation over time, and has many important exceptions (eg, an otherwise low-risk patient with severe hypoxia would be discharged by strict interpretation of this rule). Clinical judgment should supersede a strict interpretation of this scoring system. When emergency clinicians are educated, and provided with the patient's risk score, use of the decision rule results in a significantly lower overall admission rate, cost savings, and similar quality of life scores compared with those for patients conventionally managed by their physicians.[25] Additional discharge criteria include improving and stable vital signs over a several-hour observation period, ability to take oral medications, ambulatory pulse oximetry greater than 90%, home support, and access to follow-up.[12]

A simpler tool is the CURB-65 rule. This mnemonic uses five simple criteria to determine patients at lower risk for adverse events—***c***onfusion, ***u***remia (blood urea nitrogen > 20 mg/dL), ***r***espiratory rate greater than 30 breaths/min, ***b***lood pressure less than 90 systolic or less than 60 mm Hg diastolic, and age ***65*** years or older. The risk of 30-day mortality increases with more of these factors present: 0.7% with zero factors, 9.2% with two factors, and 57% with five factors. Patients with zero or one feature can receive outpatient care, those with two should be admitted, and ICU care should be considered for those with three or more factors. No randomized trials of hospital admission strategies have directly compared the PSI with the CURB-65 score. In a comparison of scores in the same population of CAP patients, the PSI yields a slightly higher percentage of patients in the low-risk category, with a similar low mortality rate.

The decision to admit a patient to the ICU is straightforward when patients are intubated or require vasopressors. It is more difficult to identify patients who do not require these interventions initially but may be at greater risk for deterioration and require a level of monitoring that may be beyond that available on the typical hospital ward. Objective criteria using the PSI (class V) and CURB-65 have been proposed but have not been prospectively validated for the ICU admission decision. When similar criteria were retrospectively studied in a cohort of CAP patients, they did not perform better than actual emergency clinician decisions. ATS/IDSA guidelines include criteria for defining severe CAP (Box 66.2), but these have not been validated.[12] An ICU risk stratification score is abbreviated as SMART COP; intensive

TABLE 66.3

Scoring System for Pneumonia Mortality Prediction

PATIENT CHARACTERISTICS	POINTS
DEMOGRAPHIC FACTOR	
Age • Male • Female	 Age (yr) Age (yr) – 10
Nursing home resident	10
COMORBID ILLNESS	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
PHYSICAL EXAMINATION FINDINGS	
Altered mental status	20
Respiratory rate > 30 breaths/min	20
Systolic blood pressure < 90 mm Hg	20
Temperature < 35°C (95°F) or > 40°C (104°F)	15
Pulse > 125 beats/min	10
LABORATORY OR RADIOGRAPHIC FINDINGS	
Arterial pH < 7.35	30
Blood urea nitrogen > 30 mg/dL	20
Sodium < 130 mEq/L	20
Glucose > 250 mg/dL	10
Hematocrit < 30%	10
Arterial Po_2 < 60 mm Hg	10
Pleural effusion	10

BOX 66.2

Criteria for Severe Community-Acquired Pneumonia

MINOR CRITERIA[a]

Respiratory rate > 30 breaths/min[†]
Pao_2/Fio_2 ratio < 250[b]
Multilobar infiltrates
Confusion, disorientation
Uremia (BUN level > 20 mg/dL)
Leukopenia[c] (WBC count < 4000 cells/mm^3)
Thrombocytopenia (platelet count < 100,000 cells/mm^3)
Hypothermia (core temperature < 36° C [96.8° F)
Hypotension requiring aggressive fluid resuscitation

MAJOR CRITERIA

Invasive mechanical ventilation
Septic shock with the need for vasopressors

BUN, Blood urea nitrogen; *Pao_2/Fio_2,* arterial oxygen pressure/fraction of inspired oxygen; *WBC,* white blood cell.
[a]Other criteria to consider include hypoglycemia (in patients who do not have diabetes), acute alcoholism or alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.
[b]A need for noninvasive ventilation can substitute for a respiratory rate higher than 30 breaths/min or a Pao2/Fio2 ratio below 250.
[c]As a result of infection alone.
Adapted from Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44:S27–S72, 2007.

respiratory or vasodepressor support is predicted by low systolic blood pressure (2 points), multilobar chest radiography involvement (1 point), low albumin level (1 point), high respiratory rate (1 point), tachycardia (1 point), confusion (1 point), poor oxygenation (2 points), and low arterial pH (2 points). A SMART-COP score above 3 points has identified 92% of patients who received intensive respiratory or vasodepressor support, including 84% of patients who did not need immediate admission to the ICU.[26] The decision to admit a patient to the hospital largely reflects the potential for acute deterioration, and some rate of floor to ICU transfer is inevitable.

Most patients with CAP do not need respiratory isolation. Patients who could pose a threat of transmission to other patients (eg, influenza, varicella, TB, plague) should be isolated. Neutropenic patients generally are placed in reverse isolation. HIV-infected patients with pneumonia should be isolated until their TB status can be evaluated via sputum acid-fast bacilli smears; this is particularly true for patients with other risk factors for TB. The chest radiograph cannot exclude TB in AIDS patients because it often does not have the typical appearance of TB. Isolation should be strongly considered for others at high risk for TB, such as inner city homeless people and IV drug users.

KEY CONCEPTS

- Empirical antimicrobial therapy should be started in the ED for patients admitted with pneumonia.
- Empirical therapy should treat the most likely pathogens for the clinical situation, such as *S. pneumoniae, H. influenzae, M. pneumoniae,* and *C. pneumoniae,* and should be consistent with current national treatment guidelines, such as those from the ATS/IDSA.
- HIV or other immunosuppressive conditions should be considered for all patients in whom pneumonia is suspected.
- Disposition is dictated by the patient's underlying medical conditions, severity of illness, likelihood of clinical deterioration, and feasibility of home care and outpatient follow-up.
- No characteristic radiographic pattern is pathognomonic for a specific pneumonia pathogen.
- *Legionella* should be suspected in patients with gastrointestinal or neurologic symptoms presenting with pneumonia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 66: QUESTIONS & ANSWERS

66.1. Which of the following statements regarding community-acquired pneumonia (CAP) is true?

A. Among hospitalized adults with CAP, *Streptococcus pneumoniae* and *Haemophilus influenzae* account for most cases.
B. *Chlamydophila* is the most common atypical agent causing severe pneumonia.
C. Clinical history and prodrome often lead to organism identification.
D. *S. pneumoniae* is the most common pathogen among those requiring intensive care unit (ICU) admission.
E. Viral causes are seen in approximately 40% of cases.

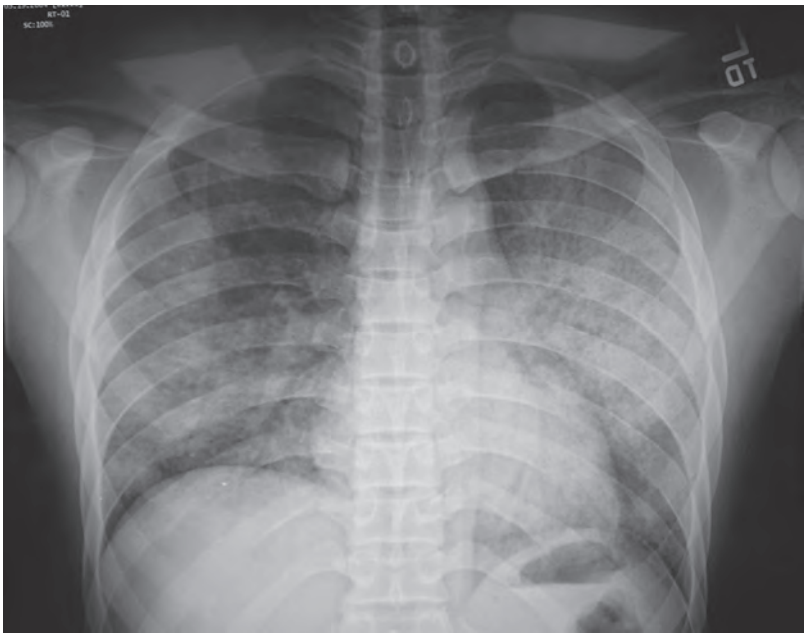
Answer: D. *Pneumococcus* and *H. influenzae* account for 25% of cases of hospitalized CAP. Viral causes are seen in approximately 18% of cases, although there is uncertainty about this figure because most patients are not tested for specific viruses. *Legionella*, rather than *Chlamydia*, causes the most severe pneumonia among the atypicals. There is no clinical history or symptom complex that reliably allows organism identification.

66.2. Which of the following associations is correct?

A. Cytomegalovirus (CMV) pneumonia—immunosuppression, adults
B. Influenza pneumonia—summer, adults
C. *Mycoplasma* pneumonia—winter, infants
D. Parainfluenza pneumonia—spring, infants
E. Varicella zoster pneumonia—winter, military recruits

Answer: A. CMV pneumonia rarely occurs in healthy people and is typically seen in the immunosuppressed patient, such as a transplant patient. Varicella pneumonia is associated with smoking and pregnancy in adults. Influenza and parainfluenza typically occur in winter months. *Mycoplasma* pneumonia is typically a disease of adolescents and adults.

66.3. A 26-year-old landscaper presents with chronic cough with intermittent fevers. He has no other past medical history. The symptoms began 2 months ago after a 7- to 10-day prodrome of cough with productive sputum, for which he received a macrolide without improvement. Physical examination and vital signs are normal. The chest radiograph is shown here. What is the most likely cause for this process?



A. *Histoplasma capsulatum*
B. *Klebsiella pneumonia*
C. *Pneumocystis jiroveci*
D. Sarcoidosis
E. *Streptococcus pneumoniae*

Answer: C. *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis* are fungi present in the soil in various geographic areas. They are most common in people engaged in soil-disturbing activities, such as construction or dirt bike racing trials, and should be considered when patients fail to respond to antibacterial treatment. The chest radiograph shows asymmetric hilar adenopathy and left-sided cavitation with fibrotic changes. Sarcoidosis would clinically show symmetrical adenopathy. *Klebsiella* is rarely seen in healthy adults. *Pneumocystis jiroveci* would be a possibility if the patient were known or suspected to be infected with human immunodeficiency virus (HIV), but a 2-month history would be uncommon.

66.4. The potential for opportunistic pulmonary infection can be predicted by an absolute CD4 lymphocyte count less than which of the following?
A. 50/mm^3
B. 100/mm^3
C. 150/mm^3
D. 200/mm^3
E. 250/mm^3

Answer: D. This count is often found in patients with HIV infection or may be estimated by a peripheral total lymphocyte count less than 1000/mm^3.

66.5. A 60-year-old man with a past medical history of adult-onset diabetes controlled with glyburide presents with cough, weakness, and purulent sputum production. Vital signs are temperature 38.3°C (101°F) oral, heart rate, 130 beats/min, blood pressure, 85/50 mm Hg, respiratory rate, 30 breaths/min, and oxygen saturation, 91%. The chest radiograph reveals a consolidated left lower lung (LLL) pneumonia. What is the most appropriate antibiotic therapy?
A. Ceftriaxone plus levofloxacin plus vancomycin
B. Ceftriaxone with a macrolide
C. Fluoroquinolone only
D. Trimethoprim-sulfamethoxazole (TMP-SMX)
E. Vancomycin only

Answer: A. In patients requiring hospitalization for CAP, coverage for CAP would typically be with a fluoroquinolone or combination of a macrolide with a β-lactam. Because this patient has signs of severe sepsis, consideration should be given to the addition of an agent for methicillin-resistant *Staphylococcus aureus* (MRSA; vancomycin) in addition to CAP coverage.

66.6. Which of the following causative agents of pneumonia would be an indication for respiratory isolation when suspected?
A. *Histoplasma capsulatum*
B. *Mycobacterium tuberculosis*
C. *Pneumocystis jiroveci*
D. *Staphylococcus aureus*
E. *Streptococcus pneumoniae*

Answer: B. Any patient for whom tuberculosis is a suspected possibility should be placed in respiratory isolation in a negative-pressure room until it can be ruled out by acid-fast bacilli (AFB) smears. The other listed organisms do not require respiratory isolation.

CHAPTER 67

Pleural Disease

Joshua M. Kosowsky | Heidi Harbison Kimberly

Pleural disease emergency presentations range in severity from asymptomatic pleural effusion to tension pneumothorax. This chapter reviews the two most common nontraumatic pleural problems, spontaneous pneumothorax and pleural inflammation with effusion.

SPONTANEOUS PNEUMOTHORAX

Principles

Background and Importance

Pneumothorax is defined as the presence of air in the intrapleural space and can range from a benign to a life-threatening process. A spontaneous pneumothorax occurs in the absence of any external precipitating factor, traumatic or iatrogenic. Primary spontaneous pneumothorax occurs in individuals without clinically apparent lung disease. Secondary spontaneous pneumothorax arises in the context of an underlying pulmonary disease process. Tension pneumothorax is a life-threatening complication resulting from pressure in the pleural cavity causing hemodynamic compromise.

Primary spontaneous pneumothorax typically occurs in healthy young men of taller than average height and is approximately three times more common in men than women.[1] Factors associated with primary spontaneous pneumothorax include smoking cigarettes and cannabis, as well as changes in ambient atmospheric pressure. Familial patterns suggest an inherited propensity in some cases of primary spontaneous pneumothorax. Mitral valve prolapse and Marfan syndrome are also associated with spontaneous pneumothorax.

Secondary spontaneous pneumothorax can occur in the context of many underlying pulmonary diseases (Box 67.1). The incidence of secondary spontaneous pneumothorax is three times higher in men. The most common condition associated with secondary spontaneous pneumothorax is chronic obstructive pulmonary disease (COPD), and patients with severe COPD are at highest risk. Spontaneous pneumothorax is relatively common in patients with cystic fibrosis and is also a known complication of *Pneumocystis jiroveci* pneumonia in patients with acquired immunodeficiency syndrome. Malignancy, especially in patients with lung metastases, is a condition associated with secondary spontaneous pneumothorax. In developing countries, tuberculosis and lung abscess remain leading causes of secondary spontaneous pneumothorax.

Catamenial pneumothorax is a rare condition in which recurrent spontaneous pneumothorax occurs in association with menses, typically within 72 hours of onset. Although it is termed *thoracic endometriosis syndrome* and often responds to ovulation-suppressing medications, the exact cause of catamenial pneumothorax is uncertain.

Spontaneous pneumothorax is rare in children. There is a male predominance in the pediatric population. Common causes of secondary spontaneous pneumothorax in children include asthma, cystic fibrosis, foreign body aspiration, and connective tissue disease, such as that seen with juvenile idiopathic arthritis. The principles of diagnosis, imaging, treatment, and surgical management for pediatric primary spontaneous pneumothorax are similar to those for adult pneumothorax.[2]

Anatomy and Physiology

Under normal conditions, the visceral and parietal pleurae lie in close apposition, with only a potential space between them. Normally, intrapleural pressure is negative (less than atmospheric) during expiration. Intrabronchial and intraalveolar pressures are negative during inspiration and positive during expiration. The alveolar walls and visceral pleura form a barrier that separates the intrapleural and intraalveolar spaces and maintains the pressure gradient. If a defect occurs in this barrier, air enters the pleural space until the pressures equalize or the communication seals. In spontaneous pneumothorax, disruption of the alveolar-pleural barrier can occur when a subpleural bulla (or bleb) ruptures into the pleural space. Underlying lung disease and chronic inflammation also weaken the alveolar-pleural barrier. Other factors, including increased intrabronchial and intraalveolar pressures generated by bronchospasm and coughing, also play a role.

With the loss of negative intrapleural pressure in the unilateral hemithorax, the ipsilateral lung collapses. A large pneumothorax results in restrictive ventilation impairment, with reduced vital capacity, functional residual capacity, and total lung capacity. Shunting of blood through nonventilated lung tissue may result in acute hypoxemia although, over time, this effect is mitigated by compensatory vasoconstriction in the collapsed lung.

In tension pneumothorax, the alveolar-pleural defect acts as a one-way valve, allowing air to pass into the pleural space during inspiration and trapping it there during expiration (Fig. 67.1). This trapping leads to progressive accumulation of intrapleural air and increasingly positive intrapleural pressure, causing compression of the contralateral lung, with asphyxia and worsening hypoxia. Increasing intrapleural pressure impairs venous return to the heart and, if allowed to progress, cardiovascular collapse and death ensue.

Clinical Features

Symptoms of primary spontaneous pneumothorax typically begin suddenly while the individual is at rest. Ipsilateral chest pain and dyspnea are the most common symptoms. At the outset, the pain is typically pleuritic in nature (ie, often described as sharp and made worse with deep inspiration), but it often evolves over time into a dull steady ache. Although patients frequently describe shortness of breath, extreme dyspnea is uncommon in the absence of underlying lung disease or tension pneumothorax. Symptoms are often mild and patients may wait several days before they seek medical attention. Without treatment, symptoms often resolve spontaneously within 24 to 72 hours, although the pneumothorax is still present.

Physical findings tend to correlate with the degree of symptoms. Sinus tachycardia is the most common early physical

BOX 67.1

Causes of Secondary Spontaneous Pneumothorax

AIRWAY DISEASE
Chronic obstructive pulmonary disease
Asthma
Cystic fibrosis

INFECTIONS
Necrotizing bacterial pneumonia, lung abscess
Pneumocystis jiroveci pneumonia
Tuberculosis

INTERSTITIAL LUNG DISEASE
Sarcoidosis
Idiopathic pulmonary fibrosis
Lymphangiomyomatosis
Tuberous sclerosis
Pneumoconioses

NEOPLASMS
Primary lung cancers
Pulmonary or pleural metastases

MISCELLANEOUS
Connective tissue diseases
Pulmonary infarction
Endometriosis, catamenial pneumothorax

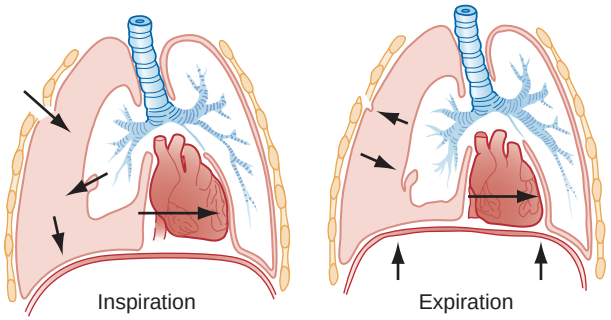


Fig. 67.1. Tension pneumothorax with total collapse of the right lung and shift of mediastinal structures to the left. Air is forced into the pleural space during inspiration and cannot escape during expiration.

finding. With a large pneumothorax, hypoxia and decreased or absent breath sounds with hyperresonance to percussion may be present. In children, breath sounds are distributed throughout the thorax, which makes hearing a decrease in breath sounds on the affected side more challenging. Other classic signs of a large pneumothorax include unilateral enlargement of the hemithorax, decreased excursion with respirations, absent tactile fremitus, and inferior displacement of the liver or spleen. Absence of any or all of these findings does not exclude pneumothorax, however, and a chest radiograph should be obtained when pneumothorax is suspected.

With tension pneumothorax, signs of asphyxia and decreased cardiac output develop. Tachycardia and hypoxia are common. Hypotension is a late and ominous finding. Distention of the jugular veins is common but may be difficult to detect. Displacement of the trachea to the contralateral side is classically described but is an uncommon finding, usually occurring only in the immediately preterminal phase of the pneumothorax, if at all. Its absence should not be considered evidence that a tension phenomenon is not present.

In patients with significant underlying lung disease, pneumothorax manifests differently. Because of poor pulmonary reserve, dyspnea is nearly universal, even when the pneumothorax is small, and symptoms tend not to resolve on their own. Physical findings, such as hyperexpansion and distant breath sounds, often overlap considerably with the underlying lung disease, making the clinical diagnosis difficult. The diagnosis of pneumothorax should be considered whenever a patient with COPD or significant underlying lung pathology experiences an exacerbation of dyspnea, and we recommend obtaining a chest radiograph in most cases of COPD exacerbations. In children, because spontaneous pneumothorax is relatively rare, routine chest radiography is not recommended but should be performed if signs and symptoms warrant further investigation.

Differential Diagnoses

The differential diagnosis of pneumothorax includes numerous conditions associated with chest pain and dyspnea. Among the most important is pulmonary embolism (PE), which may manifest in a similar fashion, with unilateral pleuritic chest pain. Most pleural-based processes (eg, pneumonia, embolism, tumor) have characteristic radiographic findings. Rarely, pneumothorax may mimic an acute myocardial infarction with electrocardiographic changes simulating an acute injury pattern or pericarditis. Pericardial effusion with or without tamponade can present with dyspnea, chest pain, and tachycardia but can be readily distinguished from pneumothorax with bedside cardiac ultrasound.

Spontaneous pneumomediastinum is a closely related clinical entity, diagnosed by the presence of subcutaneous emphysema and the finding of mediastinal air on the chest x-ray. In contrast to spontaneous pneumothorax, spontaneous pneumomediastinum typically occurs during exertion, particularly after a strenuous Valsalva maneuver. Most cases of spontaneous pneumomediastinum occur in the absence of known underlying disease and have a benign course. Secondary causes of pneumomediastinum (eg, Boerhaave's syndrome) are more serious, and treatment is aimed at the underlying disorder.

Spontaneous hemopneumothorax is a rare but potentially serious condition that occurs when collapse of the lung is associated with the rupture of a vessel in a parietopleural adhesion. The clinical presentation is similar to that of spontaneous pneumothorax but may be accompanied by symptoms and signs of hemorrhagic shock. Treatment entails large-caliber tube thoracostomy to evacuate the pleural space, reexpand the lung, and tamponade of bleeding.

Diagnostic Testing

Although suggested by the patient's history and physical examination, the diagnosis of pneumothorax is generally made with imaging, including chest radiography, ultrasound, and chest computed tomography (CT).[3,4] The classic radiographic appearance is that of a thin, visceral pleural line lying parallel to the chest wall, separated by a radiolucent band devoid of lung markings. The average width of this band can be used to estimate the size of the pneumothorax, such as with the Rhea method (Fig. 67.2). However, precise quantification is often inaccurate and, in general, it is more reasonable simply to characterize the pneumothorax as small, moderate, large, or total. British Thoracic Society guidelines define size based on measurement of the interpleural distance at the level of the hilum: small, less than 1 cm; moderate, 1 to 2 cm; and large, more than 2 cm. The American College of Chest Physicians measures from the apex to the cupola—small is less than 3 cm, and large is more than 3 cm.[5] The estimated size of the

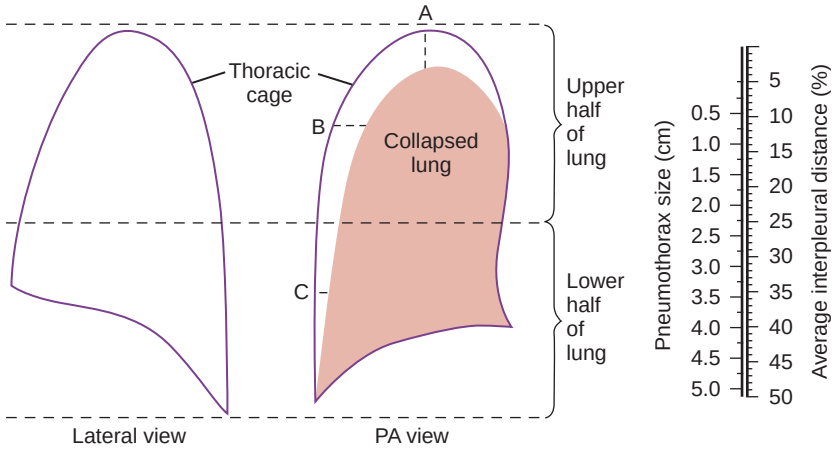


Fig. 67.2. Determining the size of a pneumothorax by calculating the average interpleural distance to predict pneumothorax size. *PA,* Posteroanterior.

pneumothorax and the patient's clinical status can be useful in guiding management decisions.

Tension pneumothorax is a clinical diagnosis, and delay in treatment to obtain radiographic confirmation is inadvisable. When the diagnosis of tension pneumothorax is not apparent clinically and a chest radiograph is obtained, the classic appearance is one of complete lung collapse, with gross distention of the thoracic cavity on the affected side and shift of mediastinal structures across the midline (Fig. 67.3A). In patients with underlying pulmonary disease, however, pleural adhesions and lack of lung elasticity may mask the fact that a pneumothorax is under significant positive pressure. In critically ill patients for whom only a supine chest radiograph can be obtained, the finding of a deep sulcus (ie, a deep lateral costophrenic angle) can suggest the presence of pneumothorax on that side (see Fig. 67.3A).

Special care should be taken in viewing the chest radiographs of patients with underlying lung disease. In patients with COPD, the relative paucity of lung markings makes pneumothorax more difficult to detect. At the same time, giant bullae may simulate the radiographic appearance of pneumothorax. A clue to differentiating a pneumothorax from a giant bulla is that the former tends to run parallel to the chest wall, whereas the latter tends to have a more concave appearance. When the diagnosis is unclear, CT can differentiate between the two entities, as well as evaluate underlying pulmonary pathology. We recommend obtaining a chest CT in patients with significant underlying pulmonary disease who present with new dyspnea or hypoxia and nondiagnostic chest radiography. Chest CT with contrast is necessary to rule out PE but a noncontrast chest CT can identify occult pneumonia, pneumothorax, or progression of underlying disease. CT can also be used in primary spontaneous pneumothorax to detect emphysematous changes, predict the likelihood of recurrence, and guide intervention decisions. Occult pneumothorax, a pneumothorax identified only on a chest CT scan, is an increasingly common phenomenon, given the increase in the use of CT. Typically, small occult pneumothoraces can by managed expectantly in stable patients. Ventilated patients with an occult pneumothorax require close monitoring with serial radiographs.

Point of care thoracic ultrasound is increasingly used in the diagnosis of pneumothorax.[3,4] Bedside thoracic ultrasound is more sensitive than chest radiography for the diagnosis of pneumothorax.[6,7] In addition to routine use for the diagnosis of spontaneous pneumothorax, thoracic ultrasound can be used to evaluate for postprocedural pneumothorax and the diagnosis of occult pneumothorax in critically ill patients. In a normal lung, the closely opposed visceral and parietal pleura create the appearance of shimmering or sliding of the pleural interface during respiration. Visualization of lung sliding at the pleural line effectively rules out pneumothorax in the area being scanned. Absence of pleural sliding is suggestive of pneumothorax. Identification of the lung point, or the boundary between normal lung and pneumothorax, is highly specific for the detection of pneumothorax.[7] See Video 67.1. Caution should be used in patients with underlying pleural disease because false-positive results can occur in patients with pleural pathology, including blebs, fibrosis, or history of pleurodesis or pneumonectomy. In addition, absence of lung sliding is seen over the nonaerated hemithorax after mainstem bronchus intubation. Assessment of lung sliding is optimally performed with a high-frequency linear transducer or curvilinear transducer set to a shallow depth (see Fig. 67.3B). Further information regarding performing and interpreting bedside thoracic ultrasound can be found in Chapter e5.

Management

If the clinical circumstances suggest tension pneumothorax, treatment should be initiated prior to definitive diagnosis by chest radiography. As soon as tension pneumothorax is suspected clinically or based on the absence of lung sliding on ultrasound, the pleural space should be decompressed. This decompression may be accomplished by insertion of an intravenous catheter followed by tube thoracostomy or immediate tube thoracostomy, depending on the availability of equipment and expertise of the provider. The diagnosis is confirmed by the hiss of air escaping under positive pressure as the needle or chest tube enters the pleural space. Needle decompression is only a temporizing procedure, and definitive management requires prompt tube thoracostomy. In obese patients, the needle and catheter may be of insufficient length to reach the pleural space, and a longer needle may be required. If needed, measurement of the depth from the skin surface to the pleural line can be obtained via ultrasound.

The management of spontaneous pneumothorax has two goals: (1) to evacuate air from the pleural space; and (2) to prevent recurrence. Pursuit of the latter goal extends beyond the realm of the emergency department (ED) but may influence the initial approach to management. Therapeutic options for the treatment of pneumothorax range from simple observation or aspiration with a catheter to video-assisted thoracoscopic surgery or thoracotomy.[5] Decisions should be individualized, with consideration of several factors, including size of the pneumothorax, severity of signs, presence of underlying pulmonary disease, other comorbidities, history of previous pneumothoraces, patient reliability, degree and persistence of the air leak, and available follow-up monitoring.

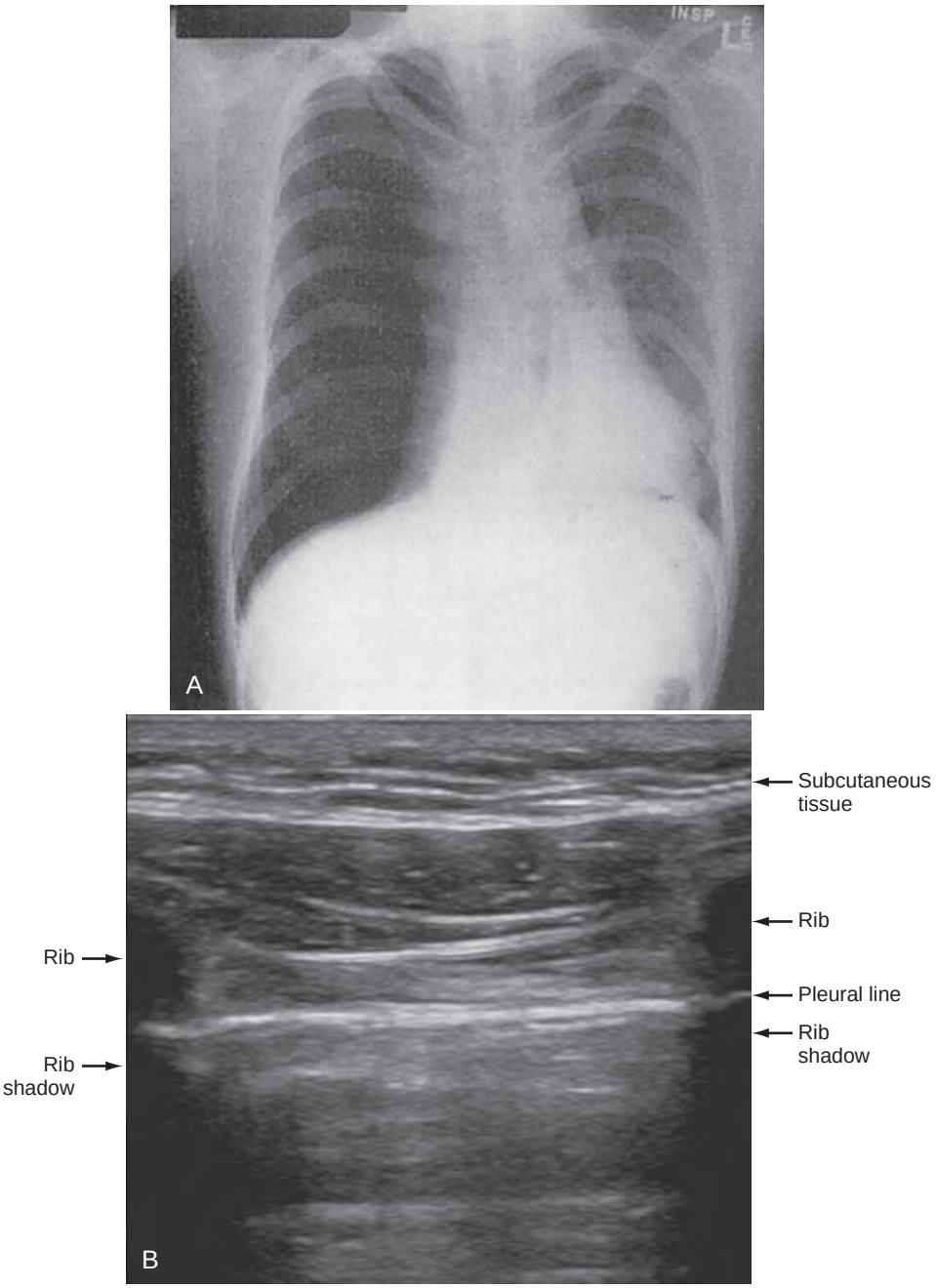


Fig. 67.3. A, Radiograph of tension pneumothorax, with mediastinal shift to the left. **B,** Ultrasound demonstrating location of pleural line. Lung sliding is dynamic and visualized in real time as shimmering or sliding of the pleural line.

For otherwise healthy young patients with a small primary spontaneous pneumothorax (ie, pleural line 1–2 cm from the chest wall as measured on chest x-ray) and minimal symptoms, supplemental oxygen and observation alone may be appropriate. The intrinsic reabsorption rate ranges from 1% to 2%/day, a rate that is accelerated significantly with the administration of 100% oxygen. Although there are no evidence-based guidelines, we recommend observing these patients in the ED for a 4- to 6-hour period. This observation period also can occur in an ED-based observation unit.[8] A repeat chest radiograph obtained before discharge should confirm that there is no interval worsening in the size of the pneumothorax.

For primary spontaneous pneumothoraces that are larger in size (ie, >2–3 cm) therapeutic options include needle aspiration or placement of a small bore (8–14 Fr) chest tube or chest catheter (eg, pigtail). In patients with a first episode of spontaneous pneumothorax without underlying lung disease, we recommend initial needle aspiration with an intravenous catheter. Aspiration is typically performed with a 16- or 18- gauge needle and three-way stopcock; the catheter may be left in during a 4- to 6-hour period of observation or removed after aspiration.[9] If 6 hours after aspiration the chest radiograph shows no reaccumulation of the pneumothorax, the patient can be discharged home, with the same caveats that apply to patients managed with observation alone. Alternatively, patients with large, primary spontaneous pneumothoraces can be initially managed by placement of a small-bore chest tube or catheter. Limited data have suggested that pigtail chest catheters, which are placed using a Seldinger technique over a guidewire, have similar outcomes to the use of small-bore chest tubes. Traditionally, patients with indwelling chest tubes or

catheters have been managed in the hospital. However, recent studies have suggested that with access to close outpatient follow-up, patients with large primary spontaneous pneumothoraces can be discharged home after placement of a pigtail catheter with a one-way Heimlich valve.[10]

Although there is no universal agreement on the optimal treatment of patients with a first episode of primary spontaneous pneumothorax, evidence has suggested that aspiration may be equally effective as chest tube drainage and, clearly, causes much less patient discomfort. Advantages of simple aspiration include low morbidity, lack of invasiveness, and overall cost savings, with reported rates of successful outcome ranging from 45% to 71%.[11] Success is less likely when the patient is older than 50 years or the volume of air aspirated exceeds 2.5 L, suggesting a continuing air leak. If aspiration fails to reexpand the lung fully, a small-bore chest tube or chest catheter should be placed. Alternatively, if the catheter was left in place after needle aspiration, it can be attached to a water seal device or to a one-way Heimlich valve and managed like a small-caliber chest tube.

Most recurrent and secondary spontaneous pneumothoraces should be managed with tube thoracostomy or pigtail catheter placement and hospital admission because less invasive approaches (ie, observation, simple aspiration) are associated with significantly lower success rates. Similarly, patients who have respiratory distress, have tension physiology, or are likely to require mechanical ventilation should undergo tube thoracostomy to reexpand the lung definitively. Also, if there is significant pleural fluid (hemothorax or hydrothorax), tube thoracostomy is required. Finally, tube thoracostomy may be considered in uncomplicated cases of primary spontaneous pneumothorax as a first-line intervention or after a less invasive approach (ie, observation, simple aspiration) fails.

For most primary spontaneous pneumothoraces, placement of a small-caliber (8–14 Fr) tube or pigtail catheter is generally sufficient because air leakage tends to be minimal. Small-caliber tubes are easy to insert, are well tolerated by patients, and leave only a small scar after removal. Complications associated with small-caliber tubes include kinking, malposition, inadvertent removal, occlusion by pleural fluid or clotted blood, and large persistent air leaks. For secondary spontaneous pneumothorax, a standard size (20–28 Fr) thoracostomy tube is recommended. When there is detectable pleural fluid or an anticipated need for mechanical ventilation, a larger tube size (≥28 Fr) is required.

After insertion, the tube is attached to a water seal device and left in place until the lung has reexpanded fully and the air leak has ceased. A Heimlich valve, which consists of a one-way flutter valve covered in transparent plastic, can be used in place of a water seal device and allows unhindered ambulation. Specific complications associated with the use of a Heimlich valve include accidental disconnection and occlusion by fluid.

Routine application of suction neither increases the rate at which the lung reexpands nor improves patient outcome and is no longer recommended. The use of suction (with a pressure of 20 cm H_2O) is reserved for situations in which the lung fails to reexpand after drainage through a water seal device or Heimlich valve for 24 to 48 hours.

Disposition

Disposition decisions should take into account the type and size of pneumothorax, underlying comorbidities, hemodynamic stability, and availability of close follow-up.

Admission to the hospital generally is not required for a young, otherwise healthy patient with a small pneumothorax and no hemodynamic disturbance or hypoxia. After a period of observation, typically 6 hours, she or he can be discharged home. Discharged patients should be able to return to an ED if their condition worsens and should undergo telephone or in-person follow-up with a primary care provider in 24 to 48 hours. Air travel and underwater diving must be avoided until the pneumothorax has completely resolved. Patients who are not able to follow up with a primary care physician in the desired interval are advised to return to the ED for follow-up evaluation.

In most cases, chest tube management requires hospital admission, although outpatient management of spontaneous pneumothorax with a small-caliber tube and Heimlich device is also reasonable in a stable responsible patient with good follow-up availability.[12] Common complications of chest tube placement include incorrect placement, pleural infection, and prolonged pain. Reexpansion pulmonary edema and reexpansion hypotension are rare occurrences after rapid evacuation of large pneumothoraces.

Most spontaneous pneumothoraces resolve within 7 days of tube thoracostomy. Air leaks that persist for longer than 2 days are less likely to resolve on their own. If an air leak persists beyond 4 to 7 days, tube thoracostomy is considered to have failed, and surgical intervention is generally recommended. Failure of tube thoracostomy is more common with secondary spontaneous and recurrent pneumothoraces because these tend to be associated with larger and more persistent air leaks.

Recurrences of spontaneous pneumothorax are common. The risk of recurrence after a primary spontaneous pneumothorax is approximately one in three. Younger age, lower weight-height ratio, and ongoing smoking are associated with increased rates of recurrence. Recurrence rates after a secondary spontaneous pneumothorax are slightly higher and are improved by thoracic surgery.[13]

Recurrences may be life-threatening for patients with serious underlying lung disease, and intervention is advocated to prevent recurrence as part of the initial approach to secondary spontaneous pneumothorax. In contrast, for patients with primary spontaneous pneumothorax, interventions typically are not considered until after a second ipsilateral pneumothorax. Preventive treatment also is recommended for patients who plan to continue activities such as flying or diving that increase the risk of serious complications if a pneumothorax recurs.

A variety of operative and nonoperative interventions decrease the rate of recurrence; these involves improving adherence of the parietal and visceral pleura, which obliterates the pleural space. Pleurodesis can be accomplished by mechanical pleural abrasion or by instillation of sclerosing agents.

Another strategy involves resection of apical bullae or other lesions at risk for causing recurrences. Often the two strategies are combined. Minimally invasive procedures, such as video-assisted thoracoscopic surgery (VATS), allow for resection of bullae and pleurodesis. Patients with extensive bullae may require thoracotomy for wider visualization of lesions.

PLEURAL INFLAMMATION AND EFFUSION

Principles

Background and Importance

Pleural effusion implies the presence of an abnormal collection of fluid in the pleural space. The most common cause of pleural effusions in the West countries is congestive heart failure, followed by malignancy, bacterial pneumonia, and PE.[14] Tuberculosis remains the leading cause of pleural effusions in most of the developing world. Other conditions commonly associated with pleural effusions include viral infections, cirrhosis, nephrotic syndrome, uremia, ovarian hyperstimulation syndrome, collagen vascular diseases, myxedema, and intra-abdominal processes. Esophageal perforation is a rare but uniquely morbid cause of a pleural effusion.

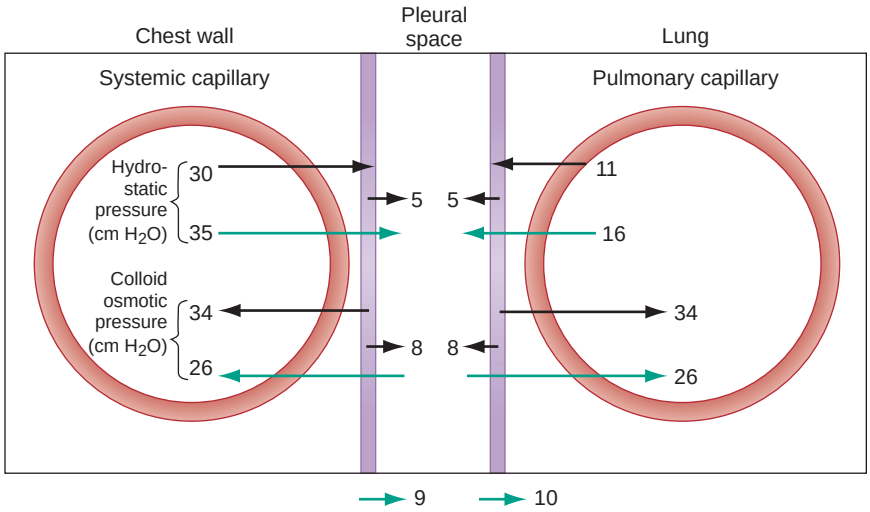


Fig. 67.4. Diagrammatic representation of the pressures involved in the formation and absorption of pleural fluid. (Adapted from Robert G, Fraser GA, Paré PD, et al: Diagnosis of diseases of the chest, ed 3, Philadelphia, 1989, WB Saunders.)

Pleuritis (also referred to as pleurisy) is a nonspecific term denoting inflammation of the pleurae. Pleuritis is a common presentation for a range of infectious and inflammatory disease processes, ranging from self-limited viral syndromes to chronic illnesses, such as systemic lupus erythematosus. Pleuritis can occur with or without significant accumulation of fluid in the pleural space.

A pleural effusion associated with bacterial pneumonia or lung abscess is termed a *parapneumonic effusion.* The term *pleural empyema* (or *pyothorax*) implies the presence of actual pus in the pleural space. Fluid that is anatomically confined and not freely flowing within the pleural space is termed a *loculated effusion.* Loculated effusions occur when there are adhesions between the visceral and parietal pleurae. Traumatic hemothorax as a distinct type of pleural effusion is approached separately.

Anatomy and Physiology

Under normal circumstances, a thin layer of fluid lies between the visceral and parietal pleurae. Pleural fluid is produced from systemic capillaries at the parietal pleural surface and absorbed into pulmonary capillaries at the visceral pleural surface. Although lymphatics also play an important role in removing pleural fluid the direction of pleural fluid flow is normally governed by the difference in hydrostatic pressure between the systemic and pulmonary circulations (Fig. 67.4). Under normal circumstances, pleural fluid exists in a dynamic equilibrium, with approximately 1 L of fluid traversing the pleural space over 24 hours, but the net accumulation of fluid in the pleural space is small (≈0.1–0.2 mL/kg body weight) and clinically insignificant. Pleural effusion develops when the influx of fluid into the pleural space exceeds the efflux.

Pathophysiology

Pleural effusions classically are divided into two groups—transudates and exudates—according to the composition of the pleural fluid (Box 67.2) Transudates are essentially ultrafiltrates of plasma, containing very little protein. A transudative effusion develops due to an increase in hydrostatic pressure or decrease in oncotic pressure within the pleural microvessels. The most common cause of transudative effusion is congestive heart failure, with its associated increase in hydrostatic pressure. Patients with severe malnutrition develop transudative effusions because of

BOX 67.2

Causes of Pleural Effusion

TRANSUDATES
Congestive heart failure
Cirrhosis with ascites
Nephrotic syndrome
Hypoalbuminemia
Myxedema
Peritoneal dialysis
Glomerulonephritis
Superior vena cava obstruction
Pulmonary embolism

EXUDATES

Infections
Bacterial pneumonia
Bronchiectasis
Lung abscess
Tuberculosis
Viral illness

Neoplasms
Primary lung cancer
Mesothelioma
Pulmonary or pleural metastases
Lymphoma

Connective Tissue Disease
Rheumatoid arthritis
Systemic lupus erythematosus

Abdominal or Gastrointestinal Disorders
Pancreatitis
Subphrenic abscess
Esophageal rupture
Abdominal surgery

Miscellaneous Conditions
Pulmonary infarction
Uremia
Drug reactions
Postpartum
Chylothorax

profound hypoalbuminemia and loss of plasma oncotic pressure. Certain conditions, such as hepatic cirrhosis and nephrotic syndrome, may be associated with an increase in hydrostatic pressure and a loss of plasma oncotic pressure.

Exudates, in contrast, contain relatively high amounts of protein, reflecting an intrinsic abnormality of the pleurae. Any pulmonary or pleural process associated with inflammation can result in an exudative effusion. The most common exudative effusion is a parapneumonic effusion, in which infection of the adjacent lung elicits an intense pleural inflammatory response. Malignant effusions are the second most common form of exudative effusion and often reflect alterations in pleural permeability and problems with lymphatic drainage. Exudative effusions also may arise in response to inflammatory processes in the abdomen, such as pancreatitis or subphrenic abscess. As an exudative effusion is reabsorbed, the fibrinous tissue left behind gives rise to in pleural adhesions.

Some pleural effusions can have exudative and transudative characteristics. For example, in the case of PE, the pathogenesis of a pleural effusion may be multifactorial, reflecting increased pulmonary vascular pressure (a transudative process) and ischemia and inflammation of the pleural membrane (an exudative process).

Massive effusions (>1.5–2 L) are usually associated with malignancy but also can arise in the setting of heart failure and other conditions of volume overload. Massive effusions restrict respiratory movement, compress the lung parenchyma, and result in intrapulmonary shunting. In extremely rare cases, tension hydrothorax can develop, with a mediastinal shift and circulatory collapse.

Clinical Features

Small pleural effusions often are entirely asymptomatic. Pleural inflammation, with or without effusion, is heralded by typically pleuritic pain (ie, worse with deep breathing) or pain referred to the shoulder. It is generally not until the volume of pleural fluid in an adult reaches at least 500 mL that dyspnea becomes apparent.

Physical findings also depend on the size of the effusion. A pleural friction rub may be the only finding in a patient with isolated pleurisy, whereas with massive effusions, signs of cardiopulmonary compromise may be present. Classic physical signs of pleural effusion include diminished breath sounds, dullness to percussion, and decreased tactile fremitus. The simple technique of auscultatory percussion (ie, percussing the chest while listening for dullness with the stethoscope) may be even more sensitive and specific for the physical diagnosis of pleural effusion. Egophony and enhanced breath sounds are often appreciated at the superior border of the effusion because of underlying atelectatic lung tissue.

Differential Diagnosis

The differential diagnosis of pleural effusion includes a wide variety disease processes characterized by dyspnea and/or chest pain, ranging from congestive heart failure and volume overload to pneumonia, PE, and pericardial effusion. Of note, many of these conditions are associated with and may coexist with pleural effusion. In any case, the presence of pleural effusion requires thoughtful consideration of the underlying disease process. Specifically, an unexplained pleural effusion should raise concern for malignancy and requires follow-up.

Diagnostic Testing

When clinically suspected, the diagnosis of pleural effusion should be confirmed by chest radiography. A volume of approximately 200 mL is required before pleural effusion can be reliably demonstrated on an upright, frontal chest radiograph; a lesser amount of fluid may be visible in the posterior costophrenic gutter on a lateral projection. The classic radiographic appearance of a pleural effusion is blunting of the costophrenic angle. With larger effusions, the hemidiaphragm may be completely obscured, typically with an upwardly concave pattern, because pleural fluid tends to layer higher laterally than centrally. Pleural fluid can also extend up a major fissure and appear as a homogeneous density in the lower portion of the lung field. Massive pleural effusions can completely opacify the hemithorax (so-called white-out).

In the recumbent patient, free pleural fluid gravitates superiorly, laterally, and posteriorly and thus may not be clearly discernible on a supine radiograph. If the effusion is large enough, diffuse haziness or partial opacification of a hemithorax may be seen. Other findings on the supine radiograph may include apical capping, obscuring of the hemidiaphragm, and/or a widened minor fissure. Some pleural effusions can be challenging to diagnose on plain radiographs. Clues to the presence of a subpulmonic effusion include an apparent shift of diaphragmatic dome toward the lateral chest wall and, when located on the left side, a radiodense gap between the gastric bubble and aerated lung. Loculated fluid in a pleural fissure may assume a fusiform appearance and can simulate a mass (Fig. 67.5A and B). The lateral recumbent view, although historically useful for demonstrating small loculated effusions, has been largely replaced by ultrasound or CT.

Thoracic ultrasound is more sensitive than chest radiography in diagnosing and estimating the size of pleural effusions.[15] Sonographically, pleural effusions typically appear as hypoechoic fluid above the diaphragm and are best visualized with a curvilinear probe in the midaxillary line (see Fig. 67.5C). Not all pleural fluid is hypoechoic; hemothorax and pyothorax may appear heterogeneous. Often, compressed lung or pleural adhesions can be visualized within the effusion, and careful observation of these findings, as well as the location of the diaphragm, liver, or spleen, can aid in the correct localization for thoracentesis or tube thoracostomy. If available in the ED, ultrasound-guided thoracentesis should be performed to decrease the risk of complications such as pneumothorax.[16]

CT can detect as little as 3 to 5 mL of pleural fluid and is the gold standard for the diagnosis of small pleural effusions. CT is particularly useful in distinguishing between pleural and parenchymal disease to help identify an underlying cause (eg, PE, malignancy), quantify the volume of pleural effusion, and guide thoracentesis.[17]

Most patients with pleural effusion should undergo diagnostic thoracentesis at some point to determine the nature of the effusion (ie, transudate, exudate) and identify an underlying cause (eg, malignancy).[18] The exception to this rule would be an effusion associated with an obvious diagnosis such as heart failure or a known underlying condition such as connective tissue disease. In the ED, the clearest indication for diagnostic thoracentesis is to evaluate a life-threatening condition immediately, such as empyema or esophageal rupture in a toxic patient; in most other cases, diagnostic thoracentesis to distinguish between transudative and exudative processes can be deferred.

Although numerous classification schemes have been proposed, Light's criteria remain the most widely accepted means of differentiating transudates and exudates (Box 67.3).[19] A pleural fluid pH less than 7.3 is associated with parapneumonic effusions, malignancies, rheumatoid effusions, tuberculosis, and systemic acidosis. A pH less than 7.0 strongly suggests empyema or esophageal rupture and is generally taken to be an indication for tube thoracostomy. In the case of a parapneumonic effusion, Gram staining and culture of pleural fluid are routinely performed but rarely change management.

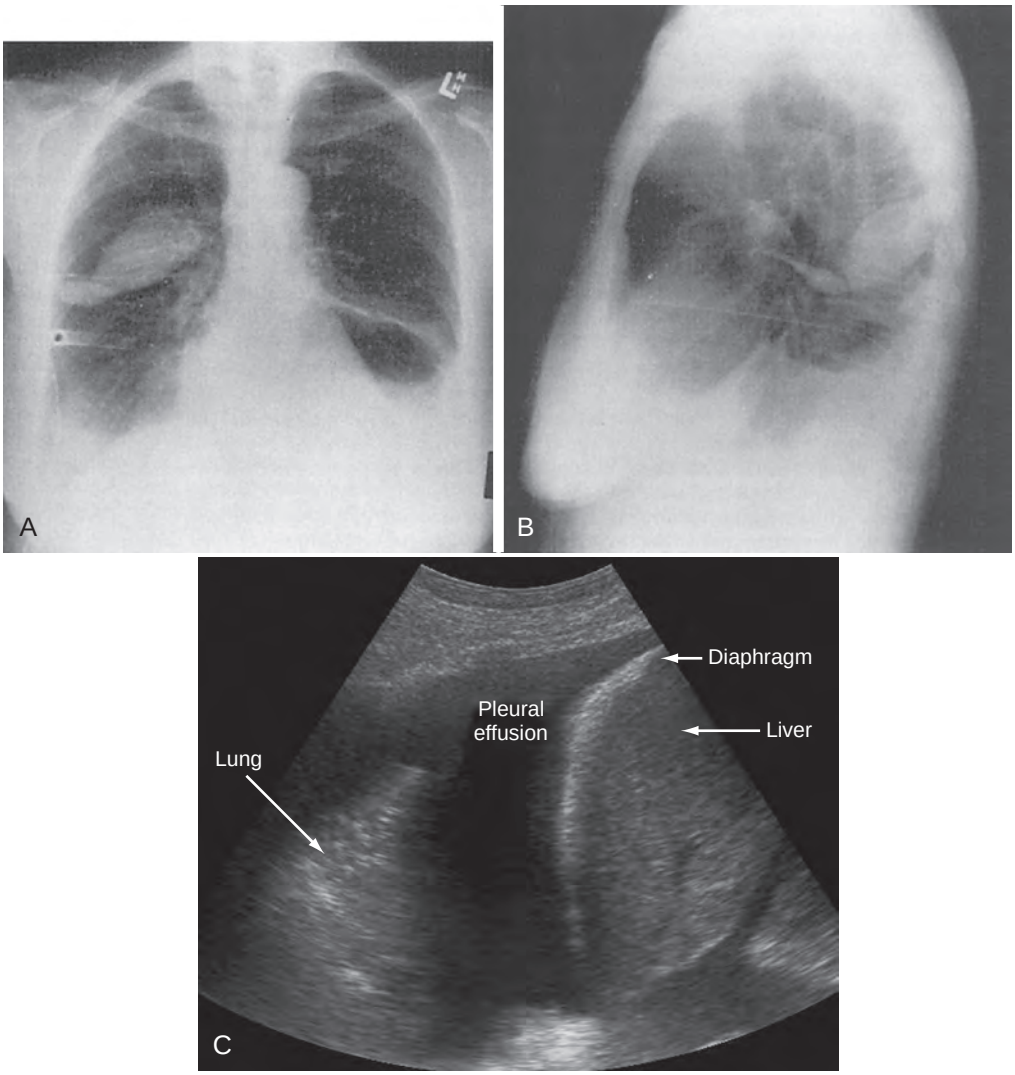


Fig. 67.5. **A** and **B,** Radiographs of pleural effusion along major and minor fissures. **C,** Ultrasound image of the right upper quadrant demonstrating the typical hypoechoic appearance of a pleural effusion.

BOX 67.3

Light's Criteria for Differentiating Transudates From Exudates

Pleural fluid is considered an exudate if one or more of the following conditions are met:

1. Pleural fluid protein level/serum protein level exceeds 0.5.
2. Pleural fluid lactate dehydrogenase (LDH) level/serum LDH level exceeds 0.6.
3. Pleural fluid LDH level exceeds two-thirds of the upper limit of normal for the serum LDH level.

From Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr: Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 77:507–513, 1972.

In the absence of a traumatic tap, bloody fluid suggests trauma, neoplasm, or pulmonary infarction. If the hematocrit of the pleural fluid exceeds that of the peripheral blood by 50%, the effusion is, by definition, a hemothorax. Atraumatic hemothorax is relatively rare but can occur with spontaneous rupture of a tumor or blood vessel.

If the diagnosis of a malignant pleural effusion is being considered, pleural fluid should be submitted for cytologic examination. Contrary to popular belief, the sensitivity for diagnosis of pleural malignancy does not depend on the volume of pleural fluid extracted during thoracentesis.[20]

Management

Most pleural effusions do not require emergent drainage, and there are few indications for therapeutic thoracentesis in the ED. For patients with massive effusions (ie, >1.5–2 L), urgent thoracentesis may stabilize respiratory or circulatory status. Patients with empyema require timely chest tube drainage in the ED or operating room to prevent complications. In most other cases, the timing of therapeutic thoracentesis can be individualized. For example, therapeutic thoracentesis would be reasonable to perform in the ED for an oncology patient with a recurrent effusion if symptomatic relief will allow the patient to be discharged.

Relative contraindications to thoracentesis include coagulopathy and other bleeding disorders. Consider the risks and benefits of a procedure prior to initiating in the ED. Pleural adhesions are also a relative contraindication to thoracentesis because of the

potential for pneumothorax, but this risk can be minimized with use of ultrasound guidance.

Following a diagnostic or therapeutic thoracentesis, a chest radiograph should be obtained to evaluate for iatrogenic pneumothorax. Other potential complications of thoracentesis include hemothorax, lung laceration, shearing of the catheter tip, infection, and transient hypoxia due to ventilation-perfusion mismatch. Postexpansion pulmonary edema is a rare occurrence, except when large volumes (>1500 mL) are drained in one session. Hypotension can occur after the removal of a large volume of fluid, particularly in patients who are already intravascularly volume-depleted.

Disposition

The natural history of pleural disease is determined largely by the underlying diagnosis, and the decision to admit a patient with pleural disease to the hospital must be individualized, taking into account the patient's respiratory and hemodynamic status and predicted clinical course. For example, small pleural effusions are common after abdominal surgery and in the postpartum state, but they almost always resolve spontaneously within a few days. Viral pleuritis, with or without effusion, is generally self-limited and resolves without specific treatment. In patients with congestive heart failure, pleural effusions generally respond well to diuretic therapy, but may persist in patients with poorly compensated disease. In nearly 20% of pleural effusions, no definitive diagnosis can be established, even after extensive investigation. A sizable percentage of these effusions are probably caused by viral infections, and most of these resolve spontaneously without sequelae.

Parapneumonic effusions contribute significantly to morbidity and mortality. For this reason, the presence of a parapneumonic effusion is an indication to hospitalize a patient with community-acquired pneumonia.[21] Empyema will develop in 5% to 10% of patients with a parapneumonic effusion, and early surgical drainage results in better outcomes than conservative management.[22]

Pleural effusions associated with malignancy are a marker of significant morbidity. The presence of a malignant effusion indicates disseminated disease, and most of the malignancies that cause pleural effusions—such as lymphoma and carcinoma of the lung, breast, or ovary—are not curable at this stage. Therapeutic thoracentesis can relieve dyspnea in the short term, but malignant effusions tend to be recurrent, often rapidly so. That said, control of pleural effusions can improve quality of life in these patients. Strategies for managing recurrence include chemical or mechanical pleurodesis to obliterate the pleural space and placement of a permanent catheter or pleuroperitoneal shunt to provide continual drainage.

KEY CONCEPTS

- Point of care thoracic ultrasound can be used to rule out pneumothorax with greater sensitivity than a portable supine chest x-ray examination. Chest CT is the gold standard for diagnosis of pneumothorax but is reserved for cases in which pneumothorax is highly suspected and the chest x-ray is negative.
- For healthy young patients with a small (<20%) primary spontaneous pneumothorax, observation alone (with administration of 100% oxygen) is an appropriate treatment option; for larger symptomatic pneumothoraces, simple aspiration with an intravenous catheter is often successful.
- In most cases of secondary spontaneous pneumothorax, tube thoracostomy should be considered because less invasive approaches are associated with lower rates of success.
- The routine application of suction after tube thoracostomy is no longer recommended and does not accelerate lung reexpansion.
- The most common cause of pleural effusions in the West is congestive heart failure, followed by malignancy and bacterial pneumonia; however, the diagnosis of PE should not be overlooked in a patient with pleural effusion of unknown cause.
- Therapeutic thoracentesis is indicated for the relief of acute respiratory or cardiovascular compromise and should be performed under ultrasound guidance, if possible.
- The clearest indication for diagnostic thoracentesis in the ED is to diagnose immediately life-threatening conditions, such as empyema or esophageal rupture in a toxic patient. In most other cases, diagnostic thoracentesis to distinguish between transudative and exudative processes can be deferred.
- On a frontal (anteroposterior or posteroanterior) projection, a volume of at least 200 mL of pleural fluid is required before radiographic demonstration is possible. However, ultrasound can detect as little as 50 mL of pleural fluid and can be easily performed at the bedside.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 67: QUESTIONS & ANSWERS

67.1. What is the most common condition associated with secondary spontaneous pneumothorax in adults?
- **A.** Chronic obstructive pulmonary disease
- **B.** Collagen vascular disease
- **C.** *Pneumocystis* pneumonia
- **D.** Pulmonary malignancy
- **E.** Severe asthma exacerbation

Answer: A. Chronic obstructive pulmonary disease is the most common condition associated with secondary spontaneous pneumothorax, although all the conditions listed may also be causes.

67.2. Which of the following describes intrapleural pressure in relation to atmospheric pressure during normal spontaneous ventilation?
- **A.** Inspiration, positive; expiration, negative
- **B.** Inspiration, positive; expiration, positive
- **C.** Inspiration, negative; expiration, negative
- **D.** Inspiration, negative; expiration, positive
- **E.** The relationship is variable and altitude-dependent.

Answer: C. In relation to atmospheric pressure, normal intrapleural pressure is approximately −10 mm Hg during inspiration and −2 mm Hg during expiration. Intrabronchial pressures are similarly negative during inspiration but rise to slightly positive during expiration. This largely negative intrapleural force maintains lung expansion and promotes venous return to the heart, which is greater during inspiration.

67.3. Which of the following may differentiate spontaneous pneumomediastinum from spontaneous pneumothorax?
- **A.** Cough
- **B.** Occurrence during exertion
- **C.** Pain
- **D.** Tachycardia
- **E.** Tachypnea

Answer: B. Spontaneous pneumomediastinum, unlike pneumothorax, often occurs with exertion, particularly after a strenuous Valsalva maneuver. Signs and symptoms—pain, cough, tachycardia, and tachypnea—are similar in the two conditions.

67.4. A 29-year-old, otherwise healthy man presents with acute onset of right pleuritic chest pain and modest cough. The symptoms occurred at rest. Physical examination is remarkable only for a tachycardia of 108 beats/min. Chest radiography reveals an estimated 30% right pneumothorax. Review of symptoms and past history are negative. Which of the following would be suitable management?
- **A.** Admission for 100% face mask oxygen and repeat radiography in 1 day
- **B.** Endotracheal intubation
- **C.** One-time air aspiration and repeat radiography in 6 hours
- **D.** Reassurance and observation
- **E.** Tube thoracostomy

Answer: C. Observation is typically indicated for primary spontaneous pneumothoraces less than 20%. Larger primary spontaneous cases may be treated with aspiration and repeat chest radiography. Advantages include lower cost and morbidity and lack of invasiveness. Success rates range from 45% to 71%. Tube thoracostomy is indicated for most cases of secondary spontaneous pneumothorax and if any pleural fluid is present.

67.5. Which of the following statements is true regarding the routine application of suction after tube thoracostomy?
- **A.** It improves the rate of lung expansion.
- **B.** It increases the risk of reexpansion pulmonary edema.
- **C.** It is associated with increased rates of empyema.
- **D.** It is not routinely indicated.
- **E.** When indicated, it should be applied with a pressure of at least 10 cm H_2O.

Answer: D. Suction neither accelerates lung reexpansion nor improves outcomes. It is indicated when reexpansion with a Heimlich or water seal device does not occur after 24 to 48 hours. A pressure of at least 20 cm H_2O should be used.

67.6. A 68-year-old man with a history of esophageal cancer presents with progressive fever, chest pain, and shortness

of breath over 24 hours. Chest radiography demonstrates a possible left lower lobe pneumonia and large left pleural effusion. Pleural fluid analysis reveals pH of 6.95, glucose level of 47 mg/dL, 11,500 white blood cells (WBCs)/mm^3 (82% neutrophils), and protein level 75% of plasma levels. What are the indicated next steps in management?

A. Antibiotics and fluid resuscitation
B. Antibiotics and tube thoracostomy
C. Antibiotics, tube thoracostomy, and esophageal Gastrografin study
D. One-time pleural aspiration for fluid analysis
E. Pleural Gram staining and culture and tube thoracostomy if infection is confirmed

Answer: C. This is an exudative pleural effusion as defined by Light's criteria (see Box 67.3). A pH less than 7.0 suggests emphysema or esophageal rupture. This patient is at risk for both; hence, the need to assess esophageal integrity. A pH less than 7.0 with glucose level less than 50 mg/dL are indications for tube thoracostomy. Normal pleural fluid has a WBC count of less than 1,000/mm^3.

CHAPTER 68

Acute Coronary Syndrome

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PRINCIPLES

Acute coronary syndrome (ACS) refers to the constellation of clinical diseases occurring as a result of acute myocardial ischemia. ACS includes a spectrum of clinical presentations ranging from unstable angina (UA) to acute myocardial infarction (AMI), including two AMI subtypes, non–ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). Sudden cardiac death (SCD) is the most extreme form of ACS. ACS, particularly AMI and its sequelae, remain the leading causes of death in much of the developed world.

Several advances in the mid-20th century have drastically changed the approach to acute coronary care. The first developments of significance—external defibrillators, cardiac pacemakers, and new pharmacologic agents—have provided emergency clinicians with effective approaches for treating life-threatening dysrhythmias occurring as a result of AMI. The introduction of selective coronary arteriography by Sones revolutionized the management of patients with coronary artery disease (CAD). In 1960, Kouwenhoven inaugurated the era of cardiopulmonary resuscitation (CPR), providing an important tool in the management of SCD.

These developments led to the recognition that the time between onset of symptoms and initiation of therapy is critical. Management priorities were directed at complications of AMI. Day organized a cardiac arrest team in 1960 and established the first coronary care unit 2 years later, reducing AMI mortality by half. In the 1980s, DeWood performed coronary angiography early in the course of AMI and demonstrated coronary occlusion in the infarct-related artery. Later in that decade, the experience of Rentrop with the intracoronary administration of streptokinase for AMI ushered in the era of thrombolysis, now termed *fibrinolytic therapy.* This accomplishment, the use of fibrinolytic therapy, allowed the emergency clinician to interrupt the actual infarction, restoring perfusion to the infarct-related artery and anatomic segment that were experiencing AMI. Acute cardiac care was then revolutionized, and the reperfusion era was born.

Recognition that most sudden deaths from ischemic heart disease occur outside the hospital led to numerous advances for prehospital ACS care. In 1969, advanced prehospital cardiac care was initiated in Belfast with Pantridge's mobile cardiac care units. In 1970, Nagel reported the benefits of prehospital telemetry for field providers of advanced cardiac life support in patients experiencing dysrhythmias or sudden cardiac death. In the 1980s, portable 12-lead electrocardiograms (ECGs) were introduced into the emergency medical services (EMS) environment, enabling the diagnosis of STEMI prior to hospital arrival.

Fibrinolytic therapy and interventional, catheter-based techniques revolutionized the treatment of patients with STEMI during the late 1980s. Combination therapies with antiplatelet, antithrombotic, and fibrinolytic agents continue to be studied for STEMI patients, further optimizing reperfusion and adjunctive therapies. Interventional success has been improving with the use of newer stenting devices and various platelet and coagulation system inhibitors. STEMI systems of care address the management of STEMI from a systems-based perspective, starting with EMS in the prehospital setting through the emergency department (ED) to the cardiac catheterization laboratory (CCL) and coronary care unit. This systems-based approach stresses a number of factors crucial in the management of STEMI, including the time sensitivity of treatment, e multidisciplinary composition of the management team, and multistep nature of the overall process. In addition to further development of the STEMI systems of care approach, current efforts focus on the establishment of regional cardiac centers and expansion of interventional capabilities to smaller hospitals. Furthermore, appropriate methods of evaluation of potential ACS patients without obvious STEMI or other diagnostic findings continue to mature. The observation unit–based rule-out myocardial infarction (MI) strategy has been shortened in total time, rendered more efficient in process, and made safer with respect to medical management and detection of ACS events. Although this strategy of chest pain evaluation is more efficient than previous approaches, further improvements in reducing the missed MI in the ED are under development.

EPIDEMIOLOGY

Ischemic heart disease and CAD, the immediate effects and sequelae, continue to be the leading causes of death among adults in many developed countries, including the United States and Canada.[1] Ischemic heart disease accounts for nearly 1 million deaths in the United States annually, of which approximately 160,000 occur in persons 65 years of age or younger. More than half of all deaths from cardiovascular disease occur in women, and CAD remains a major cause of morbidity and mortality in women beyond their middle to late 50s. The incidence of cardiovascular disease is expected to continue to increase owing to lifestyle and behavioral changes that promote heart disease.[2]

A significant reduction in age-adjusted mortality from CAD has occurred in the United States and Canada over the past 5 decades; this decline continues while the incidence of ACS is increasing.[1,3] In large part, the decline has been accompanied by diminished mortality from AMI. This decrease is a result of a reduction in the incidence of AMI by 25% and a sharp drop in the case-fatality rate. Reduction in cigarette smoking, management of lipids, and improved management of hypertension and diabetes mellitus undoubtedly play a role, along with significant advances in medical treatment.

In 2005, 5.8 million patients were evaluated for chest pain or related complaints in EDs in the United States, constituting 5% of all ED visits. In 2004, 4.1 million visits to the ED had a primary diagnosis of cardiovascular disease, and over 1.5 million patients were hospitalized for a primary or secondary diagnosis of ACS. In addition, approximately 2% of patients with ACS are inappropriately discharged from the ED. In the United States, approximately 900,000 persons experience an AMI every year, of whom 20% die before reaching the hospital, and 30% die within 30 days. The majority of fatalities from CAD occur outside the hospital, usually from an ACS-related dysrhythmia within 2 hours of onset of symptoms. For many patients who experience a nonfatal AMI, their lives are limited by impaired functional status, anginal symptoms, and diminished quality of life. The economic cost of ACS is estimated to be $120 to $140 billion annually.[1]

Spectrum of Illness: Coronary Artery Disease and Acute Coronary Syndrome

Coronary heart disease includes the spectrum from asymptomatic CAD and stable angina to UA, AMI, and sudden cardiac death. ACS includes the acute subtypes of coronary heart disease, including UA, AMI, and sudden cardiac death; AMI is further subdivided into NSTEMI and STEMI.

Stable Angina

Stable angina pectoris, not considered a form of ACS, is transient, episodic chest discomfort resulting from myocardial ischemia. This discomfort is typically predictable and reproducible, with the frequency of attacks constant over time. Physical or psychological stress (eg, physical exertion, emotional stress, anemia, dysrhythmias, environmental exposures) may provoke an attack of angina that resolves spontaneously over a constant, predictable period of time with rest or nitroglycerin (NTG).

The Canadian Cardiovascular Society (CCS) classification for angina is defined as follows:

Class I—no angina with ordinary physical activity
Class II—minimal limitation of normal activity as angina occurs with exertion or emotional stress
Class III—severe limitation of ordinary physical activity as angina occurs with exertion under normal physical conditions
Class IV—inability to perform any physical activity without discomfort as anginal symptoms occur at rest or with minimal physical exertion

Unstable Angina

Unstable angina should be considered from a semantic perspective and pathophysiologic perspective; when considered together, unstable angina is best defined from its description as well as the results of the clinical evaluation. From the semantic perspective, unstable angina is broadly defined as angina that is new onset or occurring at rest or with minimal exertion. It is further defined as angina that is worsening from a previously stable pattern of pain occurrence in terms of frequency or duration of attacks, resistance to previously effective medications, or provocation with decreasing levels of exertion or stress.

Rest angina is defined as angina occurring at rest, lasting longer than 20 minutes, and occurring within 1 week of presentation. New-onset angina is angina of at least CCS classification class II severity, with onset within the previous 2 months. Increasing or progressive angina is diagnosed when a previously known angina becomes more frequent, longer in duration, or increased by one class within the previous 2 months of at least class III severity. Symptoms that last longer than 20 minutes, despite cessation of activity, are consistent with angina at rest; in the appropriate clinical setting, such a presentation could be considered UA.

UA is often referred to as preinfarction angina, accelerating or crescendo angina, intermediate coronary syndrome, and preocclusive syndrome, underscoring its difference from stable angina. In its more severe forms, UA should be considered a possible harbinger of AMI and, hence, should be treated aggressively.

UA can also be defined from a pathophysiologic perspective. Plaque rupture accompanied by thrombus formation and vasospasm illustrate the intracoronary events of UA. This is frequently characterized by an electrocardiographic abnormality, including T wave and ST segment changes.

Variant angina—also known as Prinzmetal's angina—is caused by coronary artery vasospasm at rest with minimal fixed coronary artery lesions; it may be relieved by exercise or NTG. The ECG reveals ST segment elevation that is impossible to discern from STEMI clinically and electrocardiographically.

Acute Myocardial Infarction

Acute myocardial infarction is defined as myocardial cell death with necrosis of the myocardium. The 4-decade-old World Health Organization (WHO) definition for AMI has been replaced by clinical criteria developed jointly by the European Society for Cardiology and American College of Cardiology (ACC) that focus on defining infarction as any evidence of myocardial necrosis. This definition for an acute, evolving, or recent MI requires a typical rise and fall of a cardiac biochemical marker, currently troponin, with clinical symptoms, electrocardiographic changes, or coronary artery abnormalities based on interventional evaluation.[4] The actual definition, referred to as the universal definition of myocardial infarction, includes the following; either one of these criteria satisfies the diagnosis for an acute, evolving, or recent MI[4]:

1. Typical rise and gradual fall or more rapid rise and fall of biochemical markers of myocardial necrosis, with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following clinical parameters:
   - Ischemic symptoms
   - Electrocardiographic changes indicative of ischemia (T wave changes or ST segment deviation)
   - Development of pathologic Q waves on the ECG and/or
   - Imaging evidence of presumably new findings, such as a loss of viable myocardium or a regional wall motion abnormality
2. Pathologic findings of an AMI

Furthermore, regarding an established MI, any one of the following criteria satisfies this diagnosis[4]:

- Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms; biochemical markers of myocardial necrosis may have normalized, depending on the length of time since the infarct developed.
- Imaging study findings consistent with MI—imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a nonischemic cause
- Pathologic findings of a healed or healing MI

Considering the myriad clinical situations in which AMI is encountered, the five primary types of infarction are described by the following classification[4]:

Type 1—spontaneous MI related to ischemia resulting from a primary coronary event, such as plaque erosion rupture, erosion, fissuring, or dissection with accompanying thrombus

formation and vasospasm. Type 1 infarctions represent the true ACS event.

Type 2—MI secondary to ischemia caused by increased oxygen demand or decreased supply, as seen in coronary artery spasm, coronary embolism, severe anemia, compromising arrhythmias, or significant systemic hypotension related to a range of causes.

Type 3—sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST segment elevation or new left bundle branch block (LBBB) pattern. Fresh coronary thrombus is noted via angiography or autopsy; death occurs before appropriate sampling of the blood to detect the abnormal cardiac biomarker.

Type 4—MI associated with coronary instrumentation, such as occurring after percutaneous coronary intervention (PCI). For PCIs in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than three times the 99th percentile URL are designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is similarly recognized.

Type 5—MI associated with coronary artery bypass grafting (CABG). For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than five times the 99th percentile URL, plus any of the following, are designated as defining CABG-related MI:

- New pathologic Q waves or new LLLB
- Angiographically documented new graft or native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium

This categorization is more than a simple semantic description of AMI. Diagnostic and management issues clearly are different, depending on the subtype of MI encountered. For example, the type 1 event should be approached with attention to platelet, coagulation system, and vasospasm considerations, whereas the type 2 infarction should have attention paid to the inciting pathophysiologic situation causing imbalance in oxygen delivery and myocyte requirements.

AMI is further classified by findings on the ECG and serum markers at presentation as NSTEMI or STEMI. Previous descriptors, such as transmural, nontransmural, Q wave, and non–Q wave MI fail to describe the coronary event and its related pathophysiology, electrocardiographic presentation, and pathologic outcome adequately. The differentiation between STEMI and NSTEMI has important implications in terms of management, outcome, and prognosis for patients with AMI. In fact, the ACC and American Heart Association (AHA) have separate clinical guidelines for the management of patients with UA-NSTEMI and those with STEMI.[5-7]

PATHOPHYSIOLOGY

The underlying pathophysiology of ACS is myocardial ischemia as a result of inadequate perfusion to meet myocardial oxygen demand. Myocardial oxygen consumption is determined by heart rate, afterload, contractility, and wall tension. Inadequate perfusion usually results from coronary arterial vessel stenosis as a result of atherosclerotic CAD. Usually, the reduction of coronary blood flow does not cause ischemic symptoms at rest until the vessel stenosis exceeds 95% obstruction to flow. Myocardial ischemia, however, may occur with exercise and increased myocardial oxygen consumption with as little as 60% vessel stenosis.

CAD is characterized by thickening and obstruction of the coronary vessel arterial lumen by atherosclerotic plaques. Although atherosclerosis is usually diffuse and multifocal, individual plaques vary greatly in composition. Fibrous plaques are considered stable but can produce anginal symptoms with exercise and increased myocardial oxygen consumption because of the reduction in coronary artery blood flow through the fixed stenotic lesions. Vulnerable, or unstable, fibrolipid plaques consist of a lipid-rich core separated from the arterial lumen by a fibromuscular cap. These lesions are likely to rupture, resulting in a cascade of inflammatory events, thrombus formation, and platelet aggregation that can cause acute obstruction of the arterial lumen and myocardial necrosis; this rupture initiates the pathophysiologic process of ACS.

Thrombus formation is considered an integral factor in ACS, including all subtypes ranging from UA to AMI. These syndromes are initiated by endothelial damage and atherosclerotic plaque disruption, which leads to platelet activation and thrombus formation. Platelets play a major role in the thrombotic response to rupture of coronary artery plaque and subsequent ACS. Platelet-rich thrombi are also more resistant to fibrinolysis than fibrin- and erythrocyte-rich thrombi. The resulting thrombus can occlude the vessel lumen, leading to myocardial ischemia, hypoxia, acidosis, and eventually infarction. The consequences of the occlusion depend on the extent of the thrombotic process, characteristics of the preexisting plaque, extent of the vessel obstruction, and availability of collateral circulation.

In the setting of UA, acute stenosis of the vessel is noted; complete obstruction, however, is encountered in only 20% of cases. In these cases, it is likely that extensive collateral vessel circulation prevents total cessation of blood flow, averting frank infarction.[8] With AMI, the occlusive, fibrin-rich thrombus is fixed and persistent, resulting in myonecrosis of the cardiac tissue supplied by the affected artery. Angiographic studies have demonstrated that the preceding coronary plaque lesion is often less than 50% stenotic, indicating that the most important factors in the infarction are the acute events of plaque rupture, platelet activation, and thrombus formation rather than the severity of the underlying coronary artery stenosis.

Another important aspect of ACS is vasospasm. After significant coronary vessel occlusion, local mediators and vasoactive substances are released, inducing vasospasm, which further compromises blood flow. Central and sympathetic nervous system input increases within minutes of the occlusion, resulting in vasomotor hyperreactivity and coronary vasospasm. Sympathetic stimulation by endogenous hormones, such as epinephrine and serotonin, may also result in increased platelet aggregation and neutrophil-mediated vasoconstriction. Approximately 10% of MIs occur as a result of coronary artery spasm and subsequent thrombus formation without significant underlying CAD. This mechanism may be more prevalent during UA and other coronary syndromes that do not result in infarction.

Further myocardial injury occurs at the cellular level as inflammatory, thrombotic, and other debris from the occlusive plaque lesion is released and embolizes into the distal vessel. Such embolization can result in obstruction at the microvasculature, leading to hypoperfusion and ischemia of the distal myocardial tissue, even after reopening of the more proximal, initial obstructing lesion. In particular, the introduction of calcium, oxygen, and cellular elements into ischemic myocardium can lead to irreversible myocardial damage that causes reperfusion injury, prolonged ventricular dysfunction (known as myocardial stunning), or reperfusion dysrhythmias. Neutrophils probably play an important role in reperfusion injury, occluding capillary lumens, decreasing blood flow, accelerating the inflammatory response, and resulting in the production of chemoattractants, proteolytic enzymes, and reactive oxygen species.

CLINICAL FEATURES

Clinical features associated with ACS vary based on the patient type, including gender, comorbid conditions, and age considerations. Women, patients with diabetes mellitus, and older adults, among other populations, can exhibit differing presentations of ACS. Women can demonstrate less remarkable ACS presentations. Diabetic patients frequently exhibit nontraditional symptoms of ACS, such as dyspnea. Older adults commonly note only weakness, confusion, or other nonclassic symptoms as the primary manifestation of ACS.

Prehospital Evaluation

Appropriate pharmacotherapy for suspected ACS in the prehospital setting includes sublingual NTG, oral aspirin (acetylsalicylic acid [ASA]) that is preferably chewed, and intravenous (IV) opioid analgesic agents, such as morphine sulfate or fentanyl. Of these three agents, only ASA is associated with a documented improvement in outcome related to AMI; NTG and opioid analgesics can reduce chest discomfort, dyspnea, and anxiety associated with the current situation, although neither class of medications has been demonstrated to improve outcome in the ACS patient. Thus, their administration is not mandatory nor required in any fashion.

Establishment of the diagnosis of ACS in this setting is difficult, however, because chest pain is a poor predictor of the diagnosis of AMI, and adjunctive tools are limited. A prehospital 12-lead ECG offers high specificity (99%) and positive predictive value (93%) for STEMI in patients with atraumatic chest pain while increasing the paramedic scene time by an average of only 3 minutes. This approach offers many advantages, including the following: (1) earlier detection of STEMI; (2) ability to base the destination on the availability of PCI; (3) hospital-based preparation for patient arrival; and (4) more rapid initiation of hospital-based reperfusion therapy, either fibrinolysis or PCI.[9,10]

Emergency Department Evaluation

History

The character of the chest discomfort, as well as the onset, location, radiation, duration, prior presence, and any exacerbating or alleviating factors, should be sought. Associated symptoms, especially of a cardiac, pulmonary, gastrointestinal, and/or neurologic nature, should be elicited. Results from any prior cardiac testing should be obtained, if logistically and practically possible.

Traditionally, a history of risk factors for CAD is sought; these include male gender, age, tobacco smoking, hypertension, diabetes mellitus, hyperlipidemia, and family history of AMI at an early age (usually <50 years); additional risk factors to consider include artificial or early menopause and chronic cocaine abuse. Approximately 80% of a population of more than 122,000 patients with known CAD had at least one of the four conventional risk factors—diabetes mellitus, cigarette smoking, hypertension, or hyperlipidemia. However, cardiac risk factor burden has little impact on the ED diagnosis of ACS but, in older patients, ACS is significantly more likely if four of the five major risk factors—diabetes mellitus, smoking, hypertension, hyperlipidemia, and family history—are present (compared with none). Nevertheless, Bayesian analysis indicates that risk factors are a population phenomenon and do not increase or decrease the likelihood of any condition in any one patient. Thus, the presence of an individual risk factor or collection of risk factors is far less important in diagnosing ACS in the ED than the history of presenting illness, prior diagnosis of ischemic cardiac disease in the patient, presence of ST segment or T wave changes, or cardiac marker abnormalities, or all these clinical features considered as a whole.

Risk assessment tools, such as the PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk model, GRACE (Global Registry of Acute Coronary Events) risk model, and TIMI (Thrombolysis in Myocardial Infarction) risk score, can be used to determine the risk of death and ischemia in NSTEMI and STEMI. However, these and similar clinical decision tools should not be used solely to determine disposition from the ED.[11]

The TIMI risk score assigns a point each for seven factors based on history, cardiac markers, and ECG (it can be accessed at www.timi.org). Although these tools may aid in decision making and risk stratification for patients to determine their inpatient disposition properly (telemetry bed vs. intensive care unit), none of them, when used as the sole determinant, are designed to identify patients who may safely be discharged home. Recent investigations of the TIMI risk score in the ED has confirmed that it can be used as one of several consideration to assist in determining disposition in ED patients; yet, again, it should not be used as the sole means of this determination.[8,12,13]

There are several nontraditional risk factors for coronary disease that should be considered in the appropriate patient. Antiphospholipid syndrome, rheumatoid arthritis, human immunodeficiency virus (HIV), and particularly systemic lupus erythematosus (SLE) are associated with a higher risk of cardiovascular disease. Women with SLE who are 35 to 44 years of age are more than 50 times more likely to have an MI than a similar age- and gender-matched Framingham population.

Classic History. The term *angina* refers to tightening, not pain. Classic angina pectoris may not be pain at all but rather described as a discomfort, with a squeezing, pressure, tightness, fullness, heaviness, or burning sensation. Classically, it is substernal or precordial in location and may radiate to the neck, jaw, shoulders, or arms. If the discomfort does extend down the arm, it typically involves the ulnar aspect. Discomfort in the left chest and radiation to left-sided structures is usual, but location and radiation to both sides or only to the right side can be consistent with angina. Radiation of the discomfort to the right arm or shoulder, or to both arms or shoulders, are also presentations of ACS and are consistent with the diagnosis.[14] Refer to Table 68.1 for characteristics of angina chest pain.

TABLE 68.1

Clinical Characteristics of Classic Anginal Chest Discomfort

CHARACTERISTIC	MORE LIKELY TO BE ANGINA	LESS LIKELY TO BE ANGINA
Type of pain	Dull, pressure	Sharp, stabbing
Duration	2–5 min, often 15–20 min	Seconds or hours
Onset	Gradual	Rapid
Location	Substernal	Lateral chest wall, back
Reproducible	With exertion	With inspiration
Associated symptoms	Present	Absent
Palpation of chest wall	Not painful	Painful, exactly reproduces pain complaint

Adapted from Zink BJ: Angina and unstable angina. In Gibler WB, Aufderheide TP, editors: Emergency cardiac care, St. Louis, 1994, Mosby.

Symptoms characteristically associated with angina pectoris, or other entities of ACS, include dyspnea, nausea, vomiting, diaphoresis, weakness, dizziness, excessive fatigue, and anxiety. These symptoms can be considered as associated symptoms and anginal equivalent symptoms. If these symptoms arise without chest discomfort, alone or in combination, as a presenting pattern of known ischemic coronary disease, they are termed *anginal equivalent symptoms.* Recognition that coronary ischemia may arise with an anginal equivalent rather than a classic symptom is the key to understanding the atypical presentation of ACS. Dyspnea is the most common angina equivalent symptom presentation. Isolated diaphoresis, nausea, and emesis are very uncommon sole presenting symptoms in ACS; weakness, dizziness, excessive fatigue, and anxiety likely do not occur as the single presenting complaint, or manifestation, in the ACS patient except, perhaps in the extreme older patient population.

If there are complaints of gas, indigestion, or heartburn in the absence of a known history of gastroesophageal reflux disease, the heartburn is different from the patient's usual gastroesophageal reflux, or there is a lack of reproducible pain on abdominal palpation, this should raise suspicion of ACS. However, these presenting complaints do not indicate ACS in most cases. Nonetheless, gastroesophageal and upper gastrointestinal (GI) maladies are common misdiagnoses in cases of missed AMI.

Nontraditional (or Atypical) History. A description of typical symptoms is at times lacking in ACS; this nontraditional presentation may be a result of atypical features of the pain (eg, character, location, duration, exacerbating and alleviating factors) or the presence of anginal equivalent symptoms (eg, dyspnea). Patients with an ultimate diagnosis of ACS can have pain that is pleuritic, positional, or reproduced by palpation. Some patients describe their pain as burning or indigestion, sharp, or stabbing.[14] Of course, a single historical point or combination of points does not rule in nor rule out ACS. Rather, the emergency clinician evaluating the patient must consider the chief and related complaints as well as the other features of the presentation—in other words, the entire diagnostic picture.

Previous studies have shown that of the ED patients ultimately diagnosed with AMI, one-third did not have chest pain on presentation. Multiple studies have identified risk factors for an atypical presentation of ACS, including diabetes mellitus, older age, female gender, nonwhite ethnicity, dementia, no prior history of MI or hypercholesterolemia, no family history of coronary disease, and previous history of congestive heart failure (CHF) or stroke.

Atypical features of ACS are present with increasing frequency in sequentially older populations. Before age 85, chest pain is found in most patients with AMI, although dyspnea, stroke, weakness, and altered mental status are notably present. In those older than 85 years, however, atypical symptoms are more common than chest pain, with 60% to 70% of patients older than 85 years having an anginal equivalent complaint, especially dyspnea. Coincident ACS is more likely to occur in older adults; patients with another acute condition (eg, trauma, infection) should be scrutinized for concurrent ACS.

Patients with diabetes mellitus are at heightened risk for ACS and an atypical presentation. Medically unrecognized AMI can occur in 40% of patients with diabetes mellitus compared with 25% of a nondiabetic population, and a myocardial scar unaccompanied by an antemortem diagnosis of MI is three times more likely in diabetics. As with age and diabetes, female gender is an important risk factor for AMI without a classic chest pain presentation. In some series, less than 60% of women reported typical chest discomfort at the time of their AMI, with others reporting dyspnea, indigestion, or vague symptoms, such as weakness, unusual fatigue, cold sweats, sleep disturbance, anxiety, and dizziness.

Finally, nonwhite racial and ethnic populations may have atypical symptoms in ACS. Compelling data have demonstrated a disparity in treatment approach related to race and ethnicity in patients with acute manifestations of coronary heart disease. Whether this is related to the atypical nature of presenting symptoms in different racial and ethnic groups is not clear. Although certain features of the chest pain history serve to increase or decrease the likelihood of ACS, none of them is strong enough to endorse discharge of the patient based on the history alone.

Outcomes in Nontraditional Presentations

Not surprisingly, atypical presentation of patients with ACS is associated with poorer outcomes; this worsened outcome is a function of a prolongation in the time to ACS treatment and, unfortunately, is understandable. If the diagnosis is not suspected, appropriate treatment cannot be started. It has been demonstrated that patients with an AMI without chest pain were significantly more likely to die in the hospital (two- to threefold increased mortality when comparted to patients with chest pain) and were more likely to experience stroke, hypotension, or heart failure that required intervention, possibly reflecting the older age and greater comorbidity in this group. Patients with atypical symptomatology seek medical care later and are less likely to receive appropriate treatment. Patients 65 years of age or younger with NSTEMI have a 1% chance of dying during their hospitalization, but this risk is increased to 10% for patients aged 85 years and older.

Physical Examination

The physical examination focuses on the cardiac, pulmonary, abdominal, and neurologic examinations, looking for complications of ACS as well as alternative diagnoses for chest pain (Table 68.2). In general, the physical examination in the ACS patient will demonstrate few findings suggestive of ACS; pale appearance, anxiety, and diaphoresis are frequent findings in patients with severe forms of UA and AMI. Bradycardia, tachycardia, hypotension, and pulmonary edema, not infrequent in the AMI patient, are manifestations of ACS complication; these findings also are ominous signs in patients with known or suspected ACS.

Historical studies, using untrained physicians (ie, not emergency clinicians), identified chest wall tenderness or reproducible chest wall tenderness in up to 15% of patients ultimately diagnosed with AMI, but these data are highly suspect. The real

TABLE 68.2

Key Entities in the Differential Diagnosis of Chest Pain

Acute myocardial infarction	Unstable angina
Stable angina	Prinzmetal's angina
Pericarditis	Myocardial or pulmonary contusion
Pneumonia	Pulmonary embolism
Pneumothorax	Pulmonary hypertension
Pleurisy	Aortic dissection
Boerhaave's syndrome	Gastroesophageal reflux
Peptic ulcer disease	Gastritis or esophagitis
Esophageal spasm	Mallory-Weiss syndrome
Cholecystitis or biliary colic	Pancreatitis
Herpes zoster	Musculoskeletal pain

incidence of truly reproducible chest wall tenderness (ie, when the patient reliably identifies to the examiner that the pain produced on palpation is identical to the pain causing the patient's presentation) in ACS is probably extremely rare. It is suggested that patients with chest pain that is significantly ***p***leuritic, ***p***ositional, or reproducible by ***p***alpation (the three Ps) are at extremely low risk (but not no risk) for ACS.

Missed Diagnosis of Acute Coronary Syndrome

Approximately 2% to 4% of patients with AMI in the ED are discharged without diagnosis. Missed ACS is the misdiagnosis that accounts for the largest amount of payments by emergency clinicians in medical malpractice claims. Atypical presenting symptoms are an obvious causative consideration. Patients with undiagnosed ACS discharged from the ED are younger, more likely to be women or nonwhite, more likely to have atypical complaints, and less likely to have electrocardiographic evidence of acute ischemia. Among all patients with cardiac ischemia, women younger than 55 years seem to be at highest risk for inappropriate discharge. With respect to electrocardiographic findings, it has been shown that 53% of patients with missed AMI and 62% of patients with missed UA have normal or nondiagnostic ECGs. Finally, the risk-adjusted mortality ratio for all patients with acute cardiac ischemia is 1.9 times higher among nonhospitalized patients. Factors associated with misdiagnosis of ACS in medical malpractice closed claims analysis include emergency clinicians with less experience who document histories less clearly, admit fewer patients, and misinterpret the ECG.

Early Complications of Acute Myocardial Infarction

Bradydysrhythmia and atrioventricular (AV) conduction block occur in 25% to 30% of patients with AMI; sinus bradycardia is usually seen. Symptomatic bradydysrhythmias in the first few hours after inferior STEMI tend to be atropine-responsive; conduction abnormalities that appear beyond 24 hours of AMI tend not to respond to atropine. Patients with AV block in the setting of anterior STEMI tend to respond poorly to therapy and have a poor prognosis.

Tachydysrhythmias are common in the setting of AMI and may be atrial in origin (eg, sinus tachycardia and atrial fibrillation) or ventricular (eg, ventricular tachycardia and fibrillation). Not all require treatment, such as a compensatory sinus tachycardia in patients with AMI complicated by CHF. Primary ventricular fibrillation occurs in an estimated 4% to 5% of patients with AMI, with 60% of those cases occurring in the first 4 hours and 80% within 12 hours.

Cardiogenic shock is defined as hypotension with end-organ hypoperfusion resulting from decreased cardiac output unresponsive to restoration of adequate preload. Patients at risk include those with large infarctions, prior MI, low ejection fraction on presentation (<35%), older age, and diabetes mellitus. Adjunctive diagnostic measures include bedside echocardiography and invasive hemodynamic monitoring, with the latter demonstrating systemic hypotension, low cardiac output, elevated filling pressures, and increased systemic vascular resistance. Therapeutic measures include vasopressor and inotropic support, intraaortic balloon counterpulsation, and early revascularization; fibrinolytic therapy does not decrease mortality in cardiogenic shock.

Left ventricular free wall rupture is uncommon. Approximately one-third of cases occur in the first 24 hours, and the remainder occur 3 to 5 days after large MIs, typically anterior wall STEMIs. Clinically, free wall rupture may occur with sudden death, pulseless electrical activity, or precipitous deterioration in the presence of STEMI. Signs of pericardial effusion on the ECG or echocardiogram are suggestive of the diagnosis in the setting of an acute or recent MI. This diagnosis is significantly challenging and difficult to establish. Free wall rupture is almost universally fatal, although prompt diagnosis followed by emergent surgical intervention may rarely be lifesaving; pericardiocentesis is indicated as an immediate temporizing intervention if the diagnosis is suspected.

Rupture of the interventricular septum may also occur; regarding the time of presentation and AMI type, rupture of the interventricular septum is similar to that of rupture of the free wall of the left ventricle. The clue to this diagnosis on physical examination is the development of a new, harsh, loud holosystolic murmur heard best at the left lower sternal border. The diagnosis can be confirmed by echocardiography with color flow Doppler imaging. The presentation of acute catastrophic deterioration with a new, harsh systolic murmur should prompt immediate cardiac surgery consultation for repair of a septal defect or ruptured papillary muscle of the mitral valve. Medical therapy, including vasopressor and inotropic support, as well as intraaortic balloon counterpulsation, is an important bridge to the definitive surgical treatments of valve repair or replacement. As with free wall rupture, this diagnosis is significantly challenging and difficult to establish.

Pericarditis, when associated with AMI, can occur early or in a delayed fashion; the former is termed *infarct-related pericarditis,* and the latter is known as post-MI or Dressler's syndrome. Infarct-related, or infarct, pericarditis is associated with transmural insult and thus principally involves the pinnacle of the infarct zone near the epicardium. Although the characteristic ST segment changes may be obscured by ST segment abnormalities related to the infarction itself, they are localized if they are evident. Infarct pericarditis is a common cause of new chest pain in the first week after MI. This pain is characteristically pleuritic and worse in the supine position, likely quite different from the chest discomfort experienced resulting from the AMI. Embolic complications are more common in patients with infarct pericarditis; linked to this is the higher rate of ventricular aneurysm development in this population.

Dressler's syndrome, unlike infarct pericarditis, does not require transmural involvement. It is a relatively uncommon late complication occurring from 1 week to several months after the MI. Clinical features include fever, malaise, pleuropericardial pain and, at times, the presence of a rub on cardiac auscultation. Laboratory findings are highly nonspecific and include an elevated erythrocyte sedimentation rate and leukocyte count. The ECG may show ST segment–T wave findings of pericarditis although, as with infarct pericarditis, these changes may be overshadowed by the evolving changes of the recent MI. PR segment depression is a telltale clue. Pericardial or pleural effusions may be evident and can be serous or bloody. Echocardiography assesses pericardial fluid and risk of tamponade. The pericardial reaction is believed to be immune-mediated; treatment includes antiinflammatory agents.

Stroke may also complicate AMI, usually ischemic or thromboembolic. The major predisposing mechanisms with a recent MI are embolization from a left ventricular mural thrombus with decreased ejection fraction, embolization from the left atrial appendage with atrial fibrillation, and hypercoagulability with concomitant carotid arterial disease. It is known that the rate of stroke is higher in the setting of MI (0.9%, tapering to 0.1% at day 28 after MI) than in similar non-AMI patients (0.014%).

Hemorrhagic stroke is an obvious concern in the patient undergoing fibrinolytic therapy. The rate of hemorrhagic stroke with varying fibrinolytic agents is less than 1%; the rate is marginally higher in older patients. PCI lowers the overall risk of stroke compared with fibrinolytic therapy. Analysis of only fibrinolytic-eligible patients from the NRMI-2 database indicates more than 24,000 patients treated with alteplase and more than 4000 who

received primary PCI (termed *angioplasty* in this study). The difference in stroke rate is highly significant (1.6% in the fibrinolytic group vs. 0.7% in the PCI group). Considering hemorrhagic strokes, we have seen that the difference is again dramatic (1.0% in the fibrinolytic group vs. 0.1% in the PCI group).

Adverse events of ACS therapy should also be considered as potential complications, including hemorrhage associated with medications resulting from invasive procedures. The various antiplatelet, anticoagulant, and fibrinolytic therapies (as noted earlier) are all associated with hemorrhage as a major complicating issue. Within a single class of medications, many of these agents are so similar in efficacy that superiority is determined by the rate of occurrence of adverse effects; this trend in an adverse reaction profile with anticoagulant-antiplatelet medication is most important to understand for agent selection. Aggressive supportive care coupled with so-called antidote therapy is the most appropriate approach to patients with hemorrhagic complications from medication. Protamine can be helpful in the reversal of the heparins. Fresh-frozen plasma (FFP) and platelet infusions are of value in certain anticoagulant and antiplatelet scenarios. The low-molecular-weight heparins (LMWHs) cannot be reversed. Fibrinolytic agents also cannot be reversed; rather, therapy including FFP and packed red blood cell transfusions is most appropriate. These various antidotal agents should be considered only with life-threatening hemorrhage. The emergency clinician at the bedside, who can evaluate the risks and benefits of these treatments in the setting of a complicated ACS event, is in the best position to determine management strategies.

Procedural complications include arterial injury with hemorrhage related to percutaneous interventions; the most typical is a pseudoaneurysm of the femoral artery with hemorrhage into the thigh compartment or retroperitoneal area. The diagnosis is made based on a high degree of clinical suspicion in a patient with recent femoral artery cannulization. Physical examination findings, including extensive bruising in the thigh and bruits over the femoral artery, are suggestive; ultrasonography or CT of the thigh or retroperitoneal area can confirm the diagnosis.

DIAGNOSTIC CONSIDERATIONS

Differential Diagnoses

The differential diagnosis of chest pain in the adult patient is broad and includes life-threatening and non–life-threatening causes. The nontraumatic potential life threats include AMI, unstable angina, aortic dissection, aortic aneurysm with perforation, pulmonary embolus, spontaneous pneumothorax, esophageal perforation, myopericarditis, and pneumonia; traumatic life threats include pulmonary contusion or laceration, traumatic pneumothorax, and penetrating chest wounds. Non–life-threatening causes are numerous and include costochondritis, musculoskeletal chest pain, herpes zoster infection, and various gastrointestinal maladies; although these entities are usually non–life-threatening, significant morbidity can occur (Tables 68.2 and 68.3)

TABLE 68.3

Differential Diagnosis of Electrocardiographic ST Segment Elevation in the Adult Chest Pain Patient

Acute myocardial infarction	Acute pericarditis
Left ventricular hypertrophy	Left ventricular aneurysm
Ventricular paced rhythm	Benign early repolarization
Normal variant	Osborn wave of hypothermia
Hyperkalemia	Brugada's syndrome
Pulmonary embolism	Acute cerebral hemorrhage
Prinzmetal's angina	Postelectrical cardioversion

Diagnostic Testing

Electrocardiography

In the patient with chest discomfort or other symptoms suggestive of ACS, the 12-lead ECG can assist in a number of important applications, including establishing the diagnosis, determining candidacy for various therapies, and performing risk assessment. In the setting of STEMI, the ECG provides crucial data regarding the diagnosis—anatomically arrayed ST segment elevation of at least 1 to 2 mV in at least two leads. Furthermore, the ECG provides pivotal information regarding therapeutic intervention; ST segment elevation establishes candidacy for emergent reperfusion therapy, fibrinolysis or PCI. Regarding risk assessment, a number of electrocardiographic findings, such as total ST segment deviation, LBBB, left ventricular hypertrophy (LVH), and QT interval prolongation, indicate an increased cardiovascular hazard. Other 12-lead ECG determinations include cardiac rhythm, evolution of the ACS event, response to therapy, and clinical information suggesting an alternative diagnosis. Rhythm determination is quite important, particularly if a compromising dysrhythmia is present. Finally, an alternative diagnosis, such as pulmonary embolism (PE) or acute myopericarditis, can be suggested by the ECG.

In ACS, morphologic changes may occur in the T wave, ST segment, and QRS complex; the PR segment (eg, ST segment depression in atrial infarction or infarct-related pericarditis) can also demonstrate abnormalities, yet the current clinical use of this information is uncertain. The ECG may be normal or nonspecifically abnormal in the presence of an early ACS event, including AMI. The diagnostic abilities of the ECG is further limited by individual variations in coronary anatomy and preexisting coronary disease (eg, previous MI, LBBB, collateral circulation, coronary bypass surgery) and because it does not view the posterior, lateral, and apical left ventricular walls well. Importantly, a single ECG, by itself, is neither 100% sensitive nor 100% specific for AMI and reflects a single point in time of cardiac electrical imaging.

Overreliance on a normal or nonspecifically abnormal ECG in a sensation-free patient with a concerning presentation of anginal chest pain should be avoided. Patients with an initial nondiagnostic ECG who later develop AMI during that hospitalization are often sensation-free or minimally uncomfortable on presentation. Furthermore, the total elapsed time from chest pain onset in patients with normal ECGs does not assist in ruling out the possibility of AMI in patients with chest pain with a single ECG. Although the negative predictive value is high, it is not 100%, even up to 12 hours after the onset of the patient's chest symptoms. The patient's history of the event, and the emergency clinician's interpretation of the history, is the most important diagnostic study and is considered within the context of the interpretation of the ECG.

Electrocardiographic Abnormalities in Acute Coronary Syndromes. The earliest electrocardiographic finding in STEMI is the hyperacute T wave (Fig. 68.1), a tall and peaked structure that can appear within minutes of the interruption of blood flow and initiation of acute infarction. It is usually broad-based and asymmetric in structure; the ST segment can be elevated at the J (or junction between the QRS complex and ST segment) point. The hyperacute T wave progresses to ST segment elevation in typical STEMI. This hyperacuity may not be appreciated on the

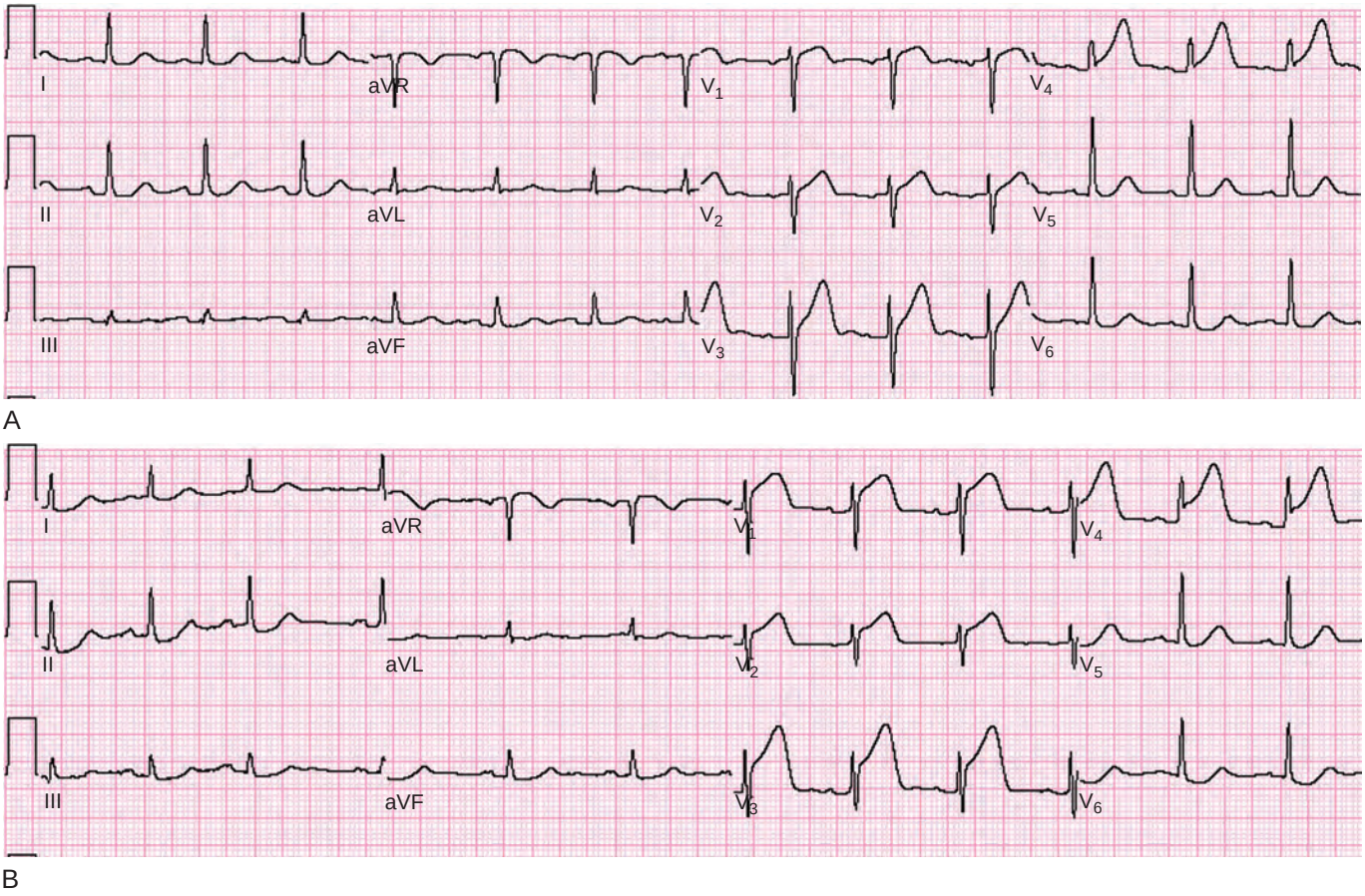


Fig. 68.1. Hyperacute T wave of acute myocardial infarction. **A,** Note the broad, tall T waves in leads V_3 and V_4 in this patient with chest pain and diaphoresis. These are the hyperacute T waves of early ST segment elevation myocardial infarction. The ST segment is just beginning to rise in leads V_3 and V_4; leads V_1 and V_2 are also suspicious. **B,** This tracing is from the same patient taken about 30 minutes after the electrocardiogram in **A**. Note the prominent ST segment elevation in leads V_1 to V_4.

initial ECG in that the finding occurs early in the course of acute infarction and is transient with rapid progression to obvious ST segment elevation. The differential diagnosis of the tall T wave includes hyperacute T waves of STEMI, hyperkalemia, benign early repolarization (BER), LVH, LBBB, and acute pericarditis.

As the STEMI progresses, ST segment elevation may become evident, allowing for the diagnosis. Morphologic variations of ST segment elevation (Fig. 68.2) can be seen from the J point at the end of the QRS complex to the apex of the T wave. This upsloping portion of the ST segment usually progresses as it elevates from flat to convex, domed or tombstoned; if flat, it is characteristically horizontal or oblique. At times, the ST segment may be concave or scooped in its elevation with STEMI.[15] This morphology may progress to a convex shape or may stay the same throughout the infarction. The concave morphology, if noted in all elevated ST segments, is atypical for STEMI and is more commonly seen with other ST segment elevation syndromes. ST segment elevation is measured in millimeters; one block on the electrocardiographic tracing is equivalent to 1 mm in height. The baseline is usually considered to be the TP segment, although some advocate use of the terminal point of the PR segment. In general, the most definable, constant baseline evident on the ECG should be used.

ST segment elevation, benign and pathologic, is a common finding on the ECG in adults with chest pain (Table 68.3). Most normal ECGs, especially those of men, may have some degree of ST segment elevation—indeed, upward of 90%. This elevation is seen in the precordial leads and is usually 1 mm or more in men and 1 mm or less in women. The ST segment elevation is concave and is more prominent as the corresponding S wave (or negative deflection of the QRS complex) becomes deeper. Because of the common occurrence of this finding, it is not a normal variant but rather a normal finding. A helpful point in differentiating normal ST segment elevation from the pathologic ST segment elevation of STEMI is that the latter is a dynamic phenomenon; ECGs recorded sequentially over time, with waxing and waning symptoms, should demonstrate some fluctuation in the degree of ST segment deviation in the presence of ACS.

ST segment depression generally represents subendocardial ischemia. Ischemic ST segment depression is typically horizontal or downsloping; an upsloping contour may be seen but is less frequently associated with ischemia. Subendocardial ischemic ST segment depression may be diffuse, spanning anterior and inferior leads. This finding can be seen in unstable angina or NSTEMI; the distinction is made considering the clinical presentation as well as the results of serial serum markers. The differential diagnosis of ST segment depression includes myocardial ischemia or infarction, repolarization abnormality of left ventricular hypertrophy (the so-called strain pattern), bundle branch block, ventricular paced rhythm (VPR), digoxin effect, hyperkalemia, hypokalemia, PE, intracranial hemorrhage, myocarditis, rate-related ST segment depression, postcardioversion of tachydysrhythmias, and pneumothorax (Fig. 68.3).

ST segment depression in ACS (1) may be seen in NSTEMI, (2) may precede ST segment elevation in STEMI, (3) may reflect

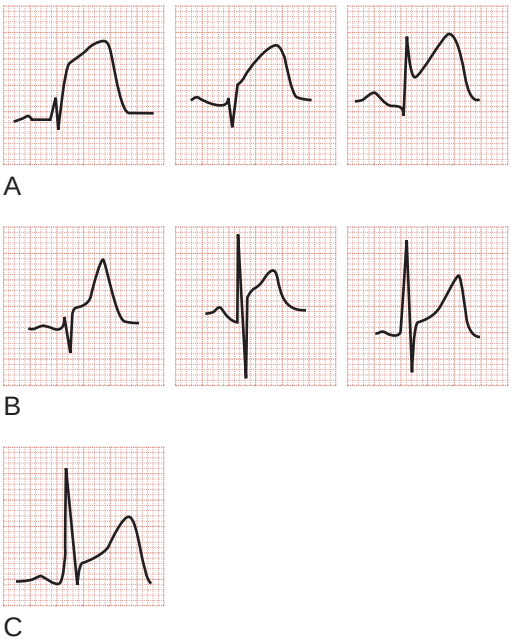


Fig. 68.2. Analysis of ST segment–T wave morphology in acute myocardial infarction (AMI), benign early repolarization (BER), and acute pericarditis. An analysis of the ST segment–T wave morphology (from the beginning at the J point to the end at the apex of the T wave) may be particularly helpful in distinguishing among the various causes of ST segment elevation (STE) and identifying the STE case. **A,** The initial upsloping portion of the ST segment is usually flat (horizontally or obliquely) or convex in the patient with STEMI. This morphologic observation, however, should be used only as a guideline; it is not infallible. **B,** Non-AMI causes of STE are seen here with concavity of the ST segment–T wave (*left,* BER; *middle,* pericarditis; *right,* BER). **C,** Patients with STE related to STEMII may demonstrate concavity of this portion of the waveform.

a mirror image of ST segment elevation from posterior MI when found in the right-sided precordial leads (ie, ST segment depression in V_1 to V_3 in posterior MI), and (4) may represent reciprocal ST segment depression seen with STEMI. With reciprocal ST segment depression, such changes are seen in leads on the opposite side of the heart from simultaneous ST segment elevation. For example, the ST segment depression seen in leads V_1 to V_3 with a posterior MI is actually a reciprocal finding resulting from the ST segment elevation that would be recorded in posterior leads V_8 and V_9. An inferior MI with ST segment elevation more frequently manifests reciprocal ST segment depression than the anterior STEMI. The reciprocal ST segment depression in inferior MI is best seen in lead aVL, which is 150 degrees removed from lead III when the positive poles of these leads in the frontal plane are considered. Anterior STEMI may feature reciprocal ST segment depression in at least one of the inferior leads (II, III, or aVF). Reciprocal changes in the setting of STEMI increase the specificity and positive predictive value of the ECG in AMI and also identify a patient with a larger infarction, greater chance of cardiovascular adverse events, and more frequent death. Fig. 68.3 depicts the various forms of ST segment depression.

T wave inversions, although frequently nonspecific, are a possible suggestion of chronic ischemic change or ACS; if ACS, they can represent unstable angina with myocardial ischemia or NSTEMI. Normally, the T wave is upright in the left-sided leads I, II, and V_3 to V_6 and inverted in the right-sided lead aVR. T wave vectors are variable in leads III, aVL, and aVF. They are usually normally inverted in V_1 and are occasionally normally inverted in lead V_2. The T wave inversions of ACS are classically narrow and symmetrically inverted (Fig. 68.4). The preceding ST segment is typically isoelectric and may be bowed slightly upward or concave. Associated ST segment depression may occur. T wave inversions are best evaluated in comparison with the most recent prior ECG, given the multitude of normal variations.

A notable subgroup of ischemic T wave inversions is associated with Wellens syndrome, which classically manifests with deep

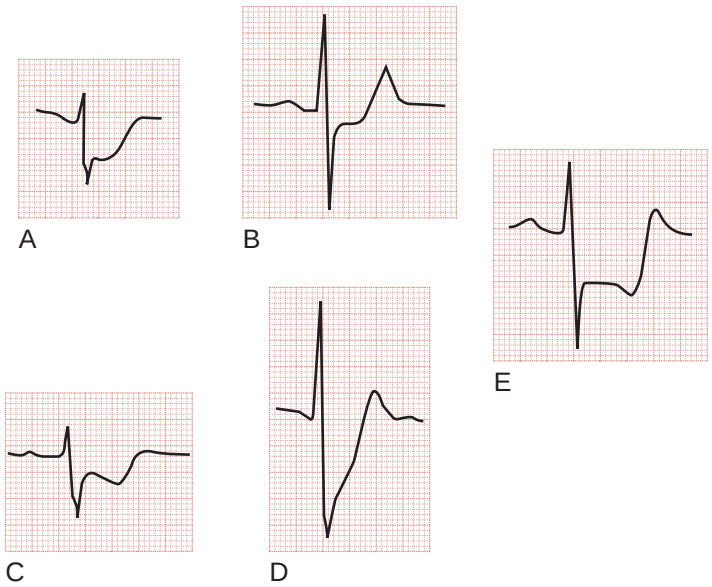


Fig. 68.3. ST segment depression (STD) in acute coronary syndrome. **A,** Horizontal STD unstable angina pectoris (USAP). **B,** Horizontal STD (non–ST segment elevation [STE] acute myocardial infarction). **C,** Downsloping STD (USAP). **D,** Upsloping STD (USAP). **E,** Horizontal STD as seen in lead III in a patient with anterior wall acute myocardial infarction, an example of reciprocal STD, also known as reciprocal change.

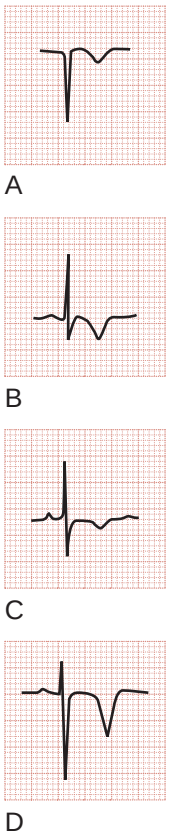


Fig. 68.4. T wave inversions of acute coronary syndrome (ACS). **A, B,** T wave inversions in patients with ACS. **C,** T wave inversion in a patient with non-–ST segment elevation (STE) acute myocardial infarction. **D,** Deeply inverted T waves in a patient with proximal left anterior descending artery stenosis—Wellens syndrome.

symmetric T wave inversions (type I) or biphasic T wave changes (type II) in the anterior precordial leads. The presence of biphasic T waves is suggestive of ischemic heart disease. Other electrocardiographic features include isoelectric or minimally elevated (<1 mm) ST segments and no precordial Q waves. This finding may manifest in the anginal or pain-free state and may or may not be accompanied by cardiac marker elevations, which is indicative of a lesion of the left anterior descending artery. The natural history of this presentation is anterior wall STEMI.

Although T wave inversion is sought as a harbinger of ACS, it can also occur as an evolutionary change after MI. In MI without culprit artery reperfusion, the T waves may invert as the ST segments return to baseline, although not particularly deeply. In hearts that are reperfused, T wave inversion may follow ST segment elevation in a biphasic or deeply inverted morphology, an appearance much like the T wave changes of Wellens syndrome. The differential diagnosis of T wave inversion is broad and includes ACS, ventricular hypertrophy, bundle branch block, VPR, myocarditis, pericarditis, PE, pneumothorax, Wolff-Parkinson-White syndrome, cerebrovascular accident, hypokalemia, GI disorders, hyperventilation, persistent juvenile T wave pattern, and normal variants.

The emergency clinician must also consider pseudonormalization of the T wave as a potential electrocardiographic indicator of ACS. Pseudonormalization occurs when, during an acute episode of chest discomfort or anginal equivalent, an apparently normal-appearing T wave on the ECG replaces the normally inverted T wave that existed prior to the development of symptoms. The T wave assumes a normal appearance and may indicate ACS at this presentation.

TABLE 68.4

Regional ST Segment Changes in Acute Myocardial Infarction (AMI)

LOCATION	LEADS	ST SEGMENT
Anterior wall STEMI	V_1 - V_4	Elevation
Lateral wall STEMI	I, aVL, V_5, V_6	Elevation
Inferior wall STEMI	II, III, aVF	Elevation
Right ventricular wall AMI	V_4R	Elevation
Posterior wall AMI	V_8, V_9 V_1 - V_3	Elevation Depression

STEMI, ST segment elevation myocardial infarction.
Adapted from Aufderheide TP, Brady WJ: Electrocardiography in the patient with myocardial ischemia or infarction. In Gibler WB, Aufderheide TP, editors: Emergency cardiac care, St. Louis, 1994, Mosby.

Q waves are generally representative of irreversible myocardial necrosis but are rarely the sole manifestation of AMI. Pathologic Q waves may emerge within the first hour of infarction but most commonly develop 8 to 12 hours into the infarction. It follows that ST segment elevation with concomitant Q waves does not preclude consideration of emergent reperfusion therapy; a consideration of the patient's history is vital here with respect to the time of onset of continuous chest discomfort. Q waves may persist after MI as enduring markers of previous infarction on the ECG; in some cases, however, Q waves disappear with time, regardless of whether the infarcted territory was reperfused.

Anatomic Location of Acute Myocardial Infarction. The regional distribution of an AMI can be derived from noting the pattern of the various morphologic changes that are described (Table 68.4). Anterior infarctions are primarily evidenced by changes in the precordial leads V_1 to V_4 (Fig. 68.5). Septal involvement is reflected by changes in V_1 and V_2. Extension to the lateral wall (ie, anterolateral MI) is evident if the pathologic changes extend beyond leads V_1 to V_4 to include leads V_5, V_6, I, and aVL. In anterior STEMI, reciprocal ST segment depression may occur in leads III and aVF. The anterior wall is served by the left anterior descending artery. The first diagonal branch of the left anterior descending artery is likely to be involved when the ST segment elevation extends to leads I and aVL. Isolated occlusion of the diagonal branch of the left anterior descending artery displays similar findings, but of smaller amplitude, as those seen with left anterior descending artery occlusion (ST segment elevation in leads V_2 and V_3, and possibly leads V_1 and V_4, or both, along with ST segment depression in lead II and III, aVF, or both).

Anterior or anterolateral STEMI resulting from left main coronary artery occlusion is a high-risk presentation; the ability to identify this high-risk STEMI subtype further enables the emergency clinician to adjust therapy appropriately. In a patient with symptoms of ACS, ST segment elevation in lead aVR should prompt consideration of occlusion of the left main coronary artery. Pooled data have demonstrated that ST segment elevation in lead aVR (>0.5 mV) is approximately 78% sensitive and 83% specific for left main coronary artery disease; alternatively, this finding in lead aVR may represent multivessel disease, acute proximal left anterior descending occlusion or, less commonly, left circumflex or right coronary occlusion. If ST segment elevation occurs in leads aVR and V_1, greater elevation in the former lead favors left main disease, whereas if it is greater in the latter lead, occlusion in the left anterior descending artery is more likely.

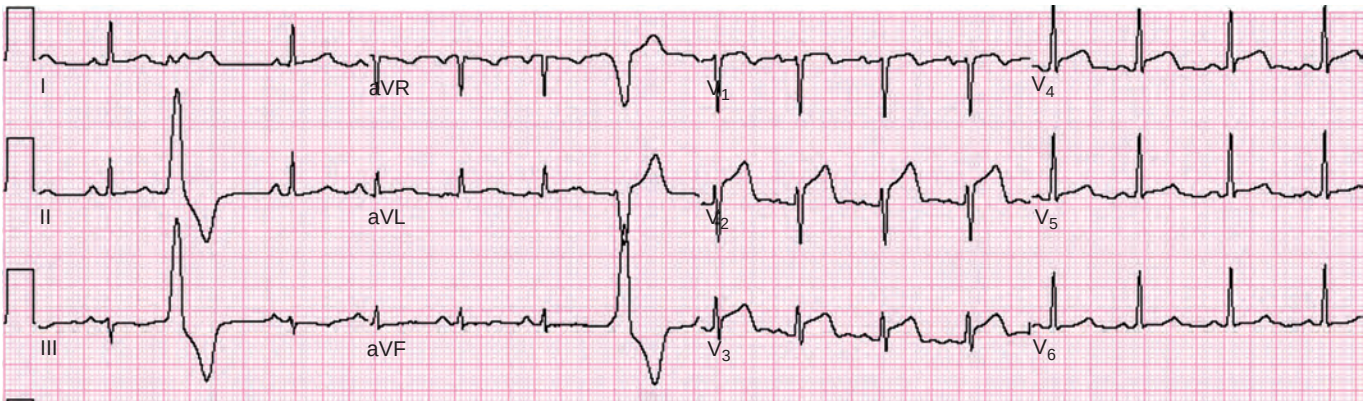


Fig. 68.5. Anterior wall acute ST segment elevation myocardial infarction (STEMI). ST segment elevation is evident in leads V_1 to V_4. The morphology seems obliquely straight. Emergency cardiac catheterization revealed a 90% stenotic lesion in the left anterior descending artery; the patient did well after placement of a coronary stent but showed serum marker evidence of acute myocardial infarction (AMI).

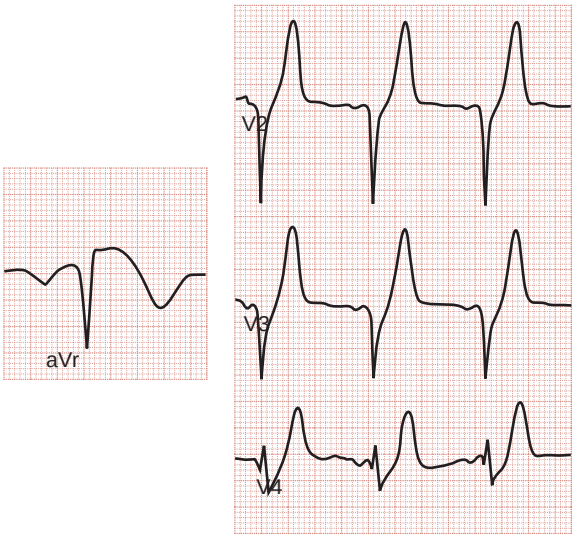


Fig. 68.6. The de Winter electrocardiographic finding, a pattern associated with proximal left anterior descending coronary artery obstruction. In the anterior leads, ST segment depression with depression of the J point is noted along with prominent, hyperacute T wave. In addition, segment elevation is also seen in lead aVR.

In addition to Wellens syndrome as a predictor of proximal left anterior descending artery occlusion, the so-called de Winter presentation is ACS syndrome with proximal occlusion of the left anterior descending artery. The electrocardiographic findings associated with this presentation include prominent T waves with J point depression producing ST segment depression seen in the precordial leads, coupled with ST segment elevation in lead aVR (Fig. 68.6).[16] Like Wellens syndrome, this presentation is associated with a high-risk coronary obstruction pattern, proximal left anterior descending artery occlusions; in addition, these patients are usually ill-appearing, with ongoing chest discomfort. Certain authorities consider this presentation a so-called STEMI-equivalent pattern.[16]

Lateral infarctions are frequently seen in concert with anterior infarction (anterolateral), inferior infarctions (inferolateral), or inferior infarctions with posterior extension (inferoposterolateral). This is because the lateral wall of the heart is variably served by the left anterior descending, right coronary, and left circumflex coronary arteries. Thus, lateral involvement is manifested by changes in some or all of the lateral leads I, aVL, V_5, and V_6. So-called high lateral infarctions are restricted to leads I and aVL (Fig. 68.7) and are suggestive of occlusion of the left circumflex coronary artery. ST segment elevation in these leads may be accompanied by reciprocal ST segment depression in leads III, aVF, and V_1. Based on cardiac magnetic resonance imaging (MRI) localization of some of these lesions, new Q waves appearing in leads I and aVL (but not V_6) indicate a mid–anterior wall MI, previously referred to as a high lateral MI.

Inferior infarctions are characterized by morphologic changes in limb leads II, III, and aVF. The inferior wall of the heart and AV node are served by the right coronary artery in about 90% of cases (right dominant); in the remainder, the left circumflex artery serves that function (left dominant). An inferior STEMI is present if two or more contiguous inferior leads (III, aVF, II) are involved; reciprocal ST segment depression is frequently seen in lead aVL, lead I, or both (Fig. 68.8) and perhaps in the anterior precordial leads, V_1 less than V_2 and V_3. ST segment depression in leads V_1 to V_3 in the presence of an inferior MI can be caused by reciprocal change, posterior extension, or simultaneous anterior ischemia during inferior infarction. ST segment elevation inferiorly that is greater in lead III than in lead II, accompanied by ST segment depression in lead aVL, I, or both, is 90% sensitive and 71% specific for right coronary artery occlusion. ST segment elevation in lead V_1 in the presence of an ST segment elevation inferior MI (with elevation greater in lead III than in lead II) suggests concomitant right ventricular infarction. Coexistent reciprocal change with inferior STEMI is associated with larger infarct size and increased mortality. Occlusion of the left circumflex artery may be occult on the 12-lead ECG. If it is responsible for inferior ST segment elevation, the ST segment elevation in lead III would not be expected to exceed that seen in lead II, and lead aVL may display an isoelectric or elevated ST segment.

Posterior infarctions are estimated to contribute to 15% to 20% of all AMIs and usually are seen with inferior or inferolateral infarctions. Posterior infarctions occur in isolation in approximately 5% of AMI cases (demonstrating elevated ST segments only in accessory leads, posterior leads V_7 through V_9). The culprit lesion may be in the right coronary artery, its posterior descending branch, or left circumflex artery. In that the 12-lead ECG features no electrodes placed directly over the posterior wall of the heart, one has only the reciprocal ST segment changes in the right precordial leads (V_1 to V_3) with which to infer AMI of the posterior wall. Findings seen in leads V_1 to V_3 suggestive of acute posterior myocardial infarction include the following: (1) horizontal ST segment depression; (2) an upright T wave; (3) tall, wide R wave; and (4) R wave amplitude-to-S wave amplitude ratio greater than

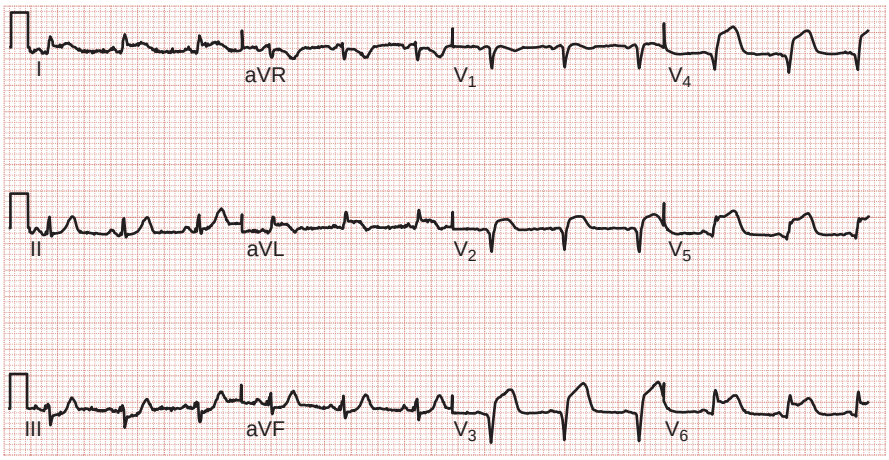


Fig. 68.7. Anterolateral acute myocardial infarction. ST segment elevation is seen in leads I, aVL, V_5, and V_6. A proximal left anterior descending artery lesion with thrombus was noted at emergent percutaneous coronary intervention.

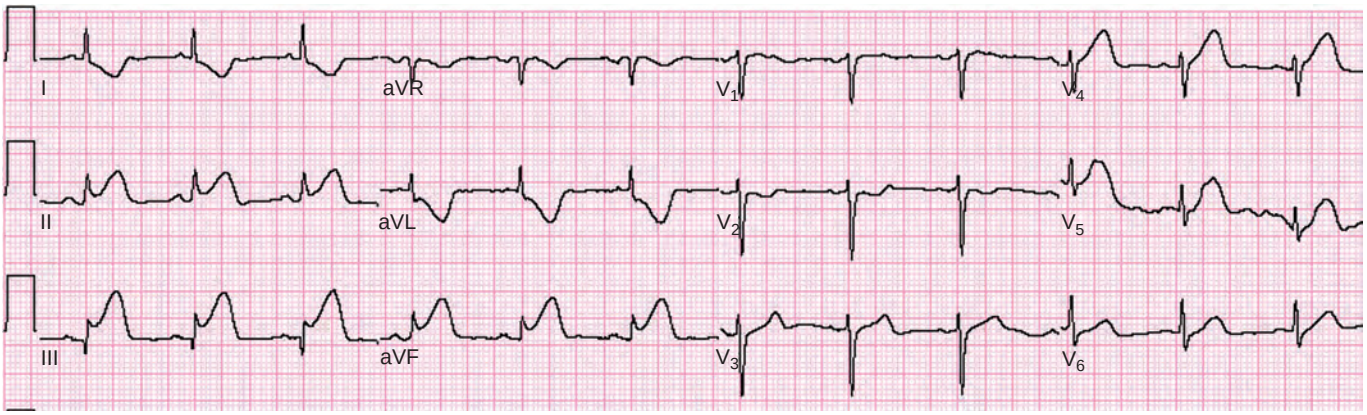


Fig. 68.8. Inferior acute myocardial infarction with reciprocal changes. Marked ST segment elevation is seen inferiorly (leads II, III, and aVF). Classic reciprocal ST segment depression is evident in leads I and aVL.

1 (Fig. 68.9). The combination of horizontal ST segment depression with an upright T wave increases the diagnostic accuracy of the 12-lead ECG for acute posterior MI. Furthermore, in that the tall R wave in the right precordial leads is actually the mirror image of a posterior Q wave, its emergence may be delayed in posterior infarction. Additional leads (posterior leads V_8 and V_9) increase the sensitivity for detection of acute posterior MI. Patients with inferior MI who have ST segment depression in leads V_1 to V_3 or ST segment elevation in the posterior leads V_8 and V_9 generally have larger infarction zones, lower resultant ejection fractions, and higher rates of cardiovascular morbidity and mortality than patients with isolated inferior MI. Cardiac MRI suggests that these so-called posterior infarctions producing tall R waves in leads V_1 and V_2 are actually lateral left ventricular wall MIs. A consensus document has suggested reclassifying posterior infarctions as inferobasal infarctions.

Right ventricular infarctions rarely occur in isolation and are usually associated with inferior or inferoposterior MI, although only about one-third of inferior infarctions have associated infarction of the right ventricle. At times, an anterior MI involves some (but <50%) of the right ventricular wall. It follows that occlusion in any of the major coronary arteries may lead to right ventricular infarction, although the right coronary is most commonly involved. Clinically, right ventricular infarction features include elevated jugular venous pressure and hypotension in the

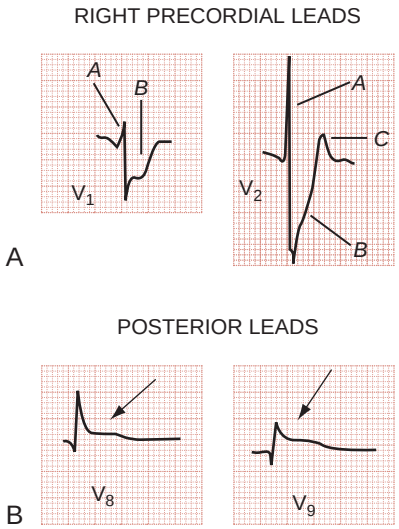


Fig. 68.9. Isolated posterior wall acute myocardial infarction (PMI)—complexes from right precordial leads and posterior leads. The right precordial leads V_1 and V_2 reveal typical findings of PMI with prominent R wave (**A**), ST segment depression (STD; **B**), and upright T wave (**C**). The posterior leads V_8 and V_9 in the same case demonstrate ST segment elevation (STE) (*arrows*), confirming isolated PMI.

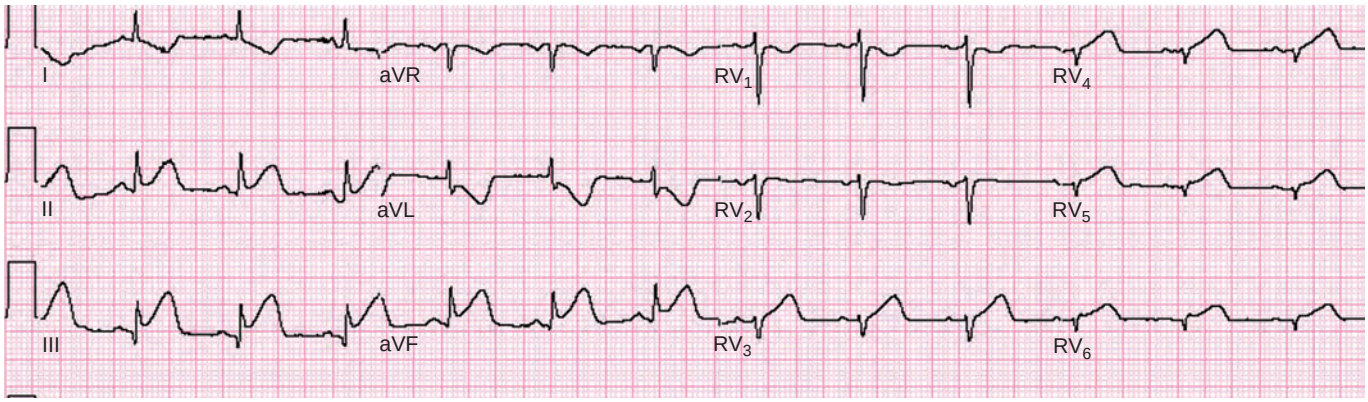


Fig. 68.10. Right ventricular infarction demonstrated with right-sided precordial leads (RV_1 to RV_6). This tracing is taken from the same patient as in Fig. 68.8. The ST segment elevation of inferior acute myocardial infarction is still present, as is the reciprocal ST segment depression in leads I and aVL. The precordial leads are right-sided chest leads, as might be inferred from the relatively low voltage. ST segment elevation is noted in leads RV_3 to RV_6 (V_3R to V_6R), consistent with right ventricular infarction.

setting of inferior wall MI. These findings, however, are also suggestive of pericardial tamponade. Nitrate-induced hypotension is also suggestive of right ventricular infarction and of tamponade. Initial therapy for both would include volume loading and avoidance of vasodilators or other agents that may lower the blood pressure.

ST segment elevation in lead V_1 in the setting of inferior STEMI (ie, ST segment elevation in leads II, III, and aVF rather than in the setting of concomitant ST segment elevation in all anterior precordial leads) is suggestive of right ventricular infarction. This is not surprising in that lead V_1 is the most rightward, or right ventricular–oriented, of the precordial leads. These changes occasionally extend into lead V_2 with right ventricular infarction. ST segment elevation is usually greater in lead III than in leads II and aVF when right ventricular infarction coexists with inferior STEMI. This logically follows in that the positive vector of lead III (in the frontal plane) is more rightward than that of leads II and aVF. Application of so-called right-sided precordial leads is the best means to diagnose right ventricular infarction with the ECG. These leads, as a mirror image of the left precordial leads, demonstrate ST segment elevation with right ventricular infarction in leads V_3R to V_6R, with V_4R having the highest sensitivity. Electrocardiographic changes in the right-sided precordial leads with right ventricular infarction may be subtle because of the smaller muscle mass of the right ventricle and resulting diminution in QRS complex size (Fig. 68.10). Patients with inferior STEMI with concomitant right ventricular infarction have larger infarcts and experience more in-hospital complications and higher mortality rates.

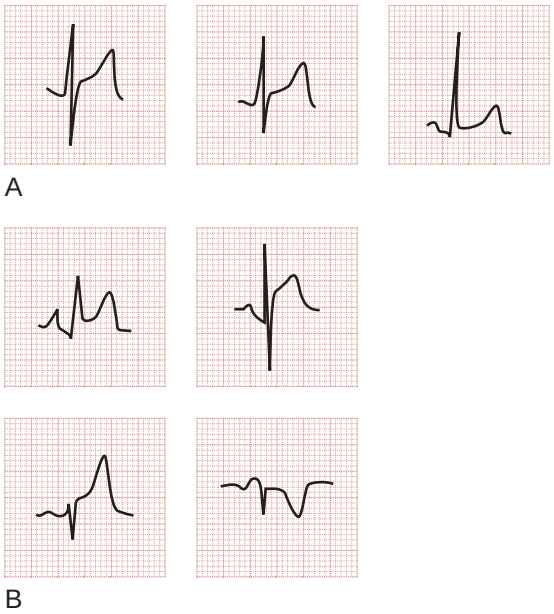


Fig. 68.11. Noninfarctional ST segment elevation (STE). **A,** Benign early repolarization (BER) with concave STE. **B,** Acute pericarditis with concave STE and PR segment depression (*upper two panels*); concave STE without PR segment abnormalities (*lower left panel*); and reciprocal STE and PR segment elevation in lead aVR (*lower right panel*).

Electrocardiographic Differential Diagnosis of ST Segment Elevation. ST segment elevation on the ECG in the context of a presentation compatible with ACS is considered to represent STEMI until proven otherwise. Several other conditions, particularly LBBB and LVH, also feature ST segment elevation that mimics infarction (see Table 68.3). ST segment elevation resulting from STEMI is not the most common cause of ST segment deviation in adults with chest pain who are suspected of AMI. Caution is required when interpreting ST segment elevation in regard to the decision to initiate reperfusion treatment, whether it be PCI or fibrinolytic therapy.

Benign early repolarization is a normal electrocardiographic variant that does not imply, nor exclude, ACS or CAD. BER includes the following electrocardiographic characteristics: (1) ST segment elevation; (2) upward concavity of the initial portion of the ST segment; (3) notching of the terminal portion of the QRS complex at the J point (ie, junction of the QRS complex with the ST segment); (4) symmetric concordant T waves of large amplitude; (5) diffuse ST segment elevation on the ECG; and (6) relative temporal stability over the short term, although these changes may regress with advancing age. J point elevation is usually less than 3.5 mm, and the concave ST segment is usually elevated less than 2 mm in the precordial leads (although it may be elevated as much as 5 mm in some cases) and 0.5 mm in the limb leads. Maximal ST segment elevation in BER is typically seen in leads V_2 to V_5. Isolated BER in the limb leads is rare and should prompt reconsideration of STEMI (Fig. 68.11A and 68.12).

Pericarditis, in the acute phase, also features diffuse ST segment elevation. In pericarditis, the ST segments are concave, with an initial upsloping contour, and are usually less than 5 mm in

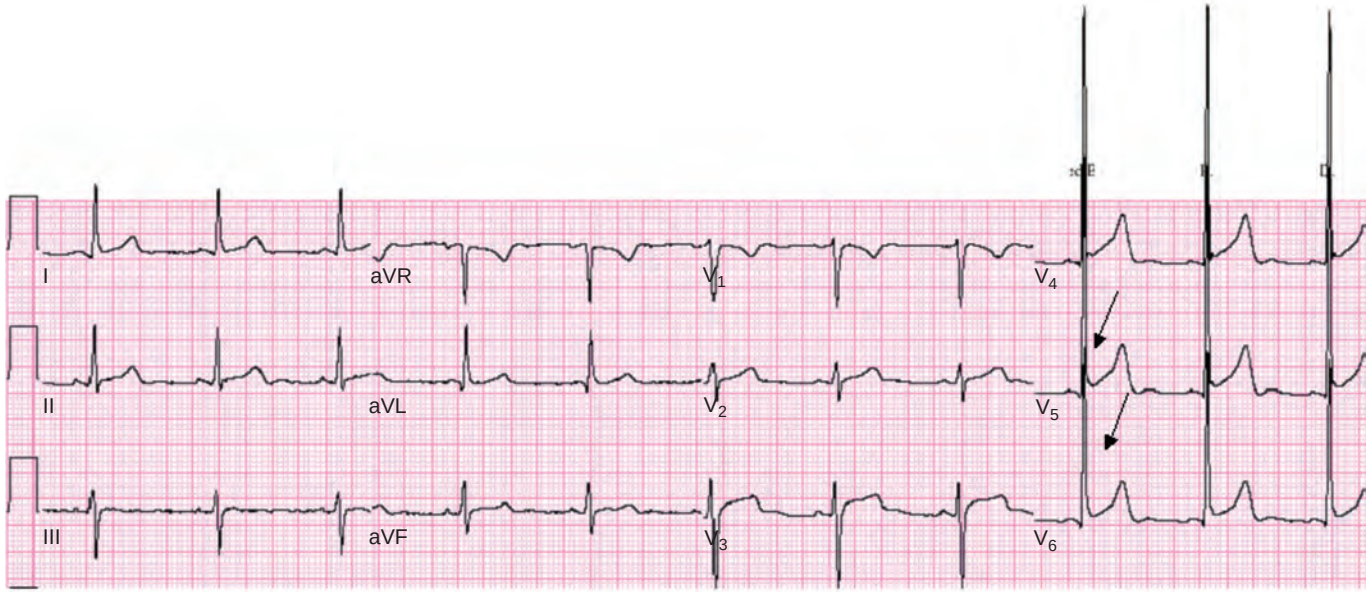


Fig. 68.12. Benign early repolarization. Note the upwardly concave ST segment elevation, best seen in leads V_4 to V_6. The T waves are relatively large in the same leads. Subtle notching is also seen at the J point in leads V_4 and V_5. Prior electrocardiograms of this patient were unchanged.

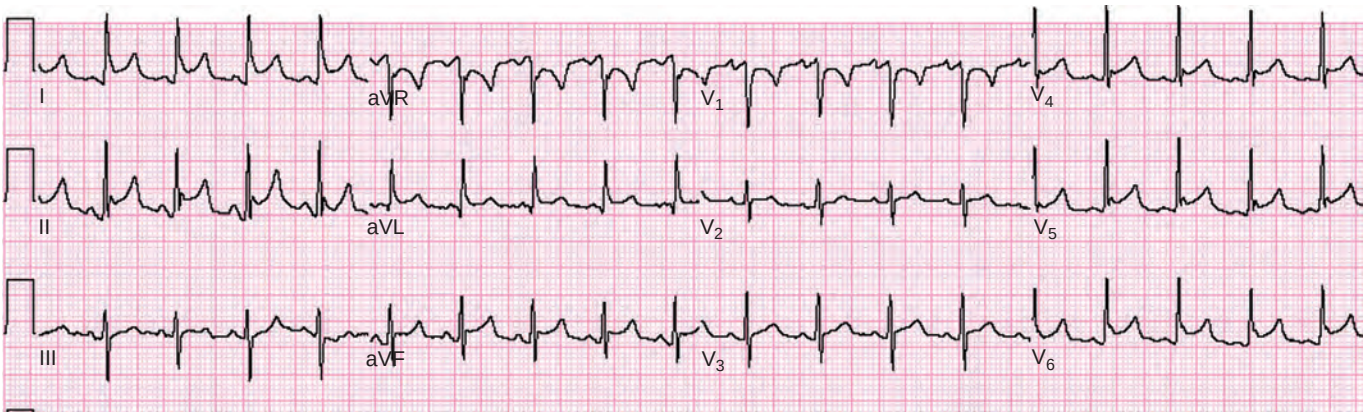


Fig. 68.13. Pericarditis. This tracing demonstrates several classic signs of pericarditis: (1) sinus tachycardia; (2) diffuse, concave upward ST segment elevation; (3) PR segment depression, best seen in lead II; and (4) PR segment elevation in lead aVR.

height. Occasionally, the initial contour is obliquely flat, but convex or domed ST segment morphology is strongly suggestive of STEMI. The ST segment elevation is usually seen in all leads with the exception of aVR (where it is depressed); V_1 is variable. Focal pericardial inflammation manifests as a more accentuated change in the leads reflecting the affected region. PR segment depression is an insensitive yet specific associated electrocardiographic finding in pericarditis, which is typically best seen in the inferior leads and lead V_6; correspondingly, PR segment elevation may be evident in lead aVR (Fig. 68.13; see Fig. 68.11B). In that ST segment changes are encountered in these patients, the most appropriate term applied is myopericarditis, rather than *pericarditis*. Recall that the pericardium is electrically silent; thus, electrocardiographic changes result from epicardial irritation and ST segment elevation—hence, the term *myopericarditis*.

Left ventricular aneurysm (LVA), wherein a focal area of myocardium paradoxically bulges outward during systole, has characteristic electrocardiographic changes that can be difficult to differentiate from those of STEMI. Considerable overlap exists between populations of patients with potential for STEMI and LVA, and the electrocardiographic changes of LVA tend to be regional rather than diffuse. Anatomically, LVA is usually found anteriorly, and changes are most often seen in leads V_1 to V_6 and leads I and aVL. ST segment elevation may be of any morphology (eg, convex or concave), and Q waves may be present (Fig. 68.14). The calculation of the ratio of the amplitude of the T wave to the QRS complex may help distinguish acute anterior MI from LVA. It has been shown that if the ratio of the amplitude of the T wave to the QRS complex exceeds 0.36 in any single lead, the ECG probably reflects STEMI. If the ratio is less than 0.36 in all leads, however, the findings are probably the result of a ventricular aneurysm.

LBBB is a confounding pattern that reduces the ECG's ability to detect ACS. Furthermore, in a clinical situation strongly suggestive of ACS, a new LBBB is consistent with AMI in a number of case. Its sole presence, however, should not prompt AMI management. LBBB, whether new or preexisting, shares many similarities to various electrocardiographic findings of ACS. In the right precordial leads (leads V_1 to V_3), ST segment elevation and tall, vaulted, upright T waves mimic those seen in anterior STEMI. The QS pattern of LBBB in these leads resembles the Q waves seen in infarction. Depressed ST segments with T wave inversions are seen

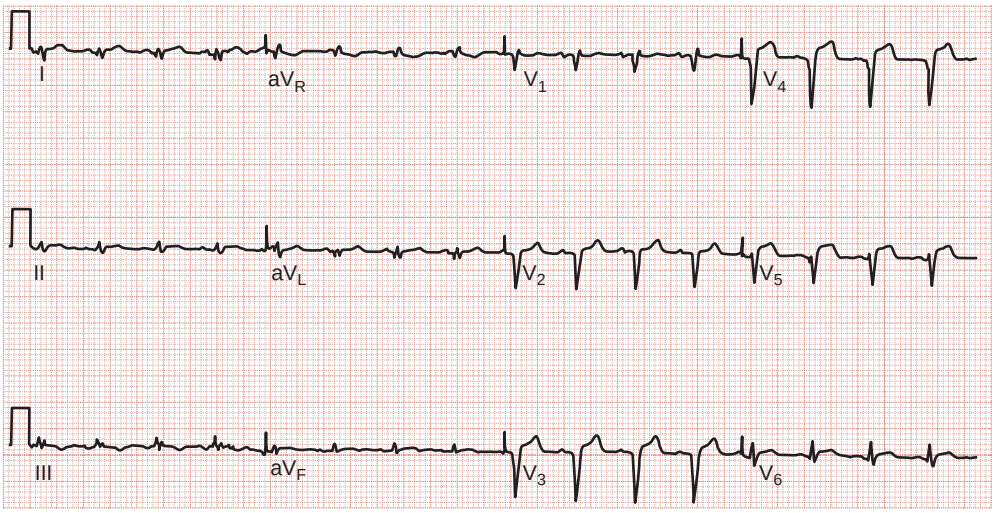


Fig. 68.14. Left ventricular aneurysm. This is a representative example of a 12-lead electrocardiogram from a patient with an anterior left ventricular aneurysm. Note the well-developed, completed Q waves in leads V_2 through V_5 and absence of reciprocal changes in contralateral leads. (Adapted from Aufderheide TP, Brady WJ: Electrocardiography in the patient with myocardial ischemia or infarction. In Gibler WB, Aufderheide TP, editors: Emergency cardiac care, St. Louis, 1994, Mosby, pp 196–216.)

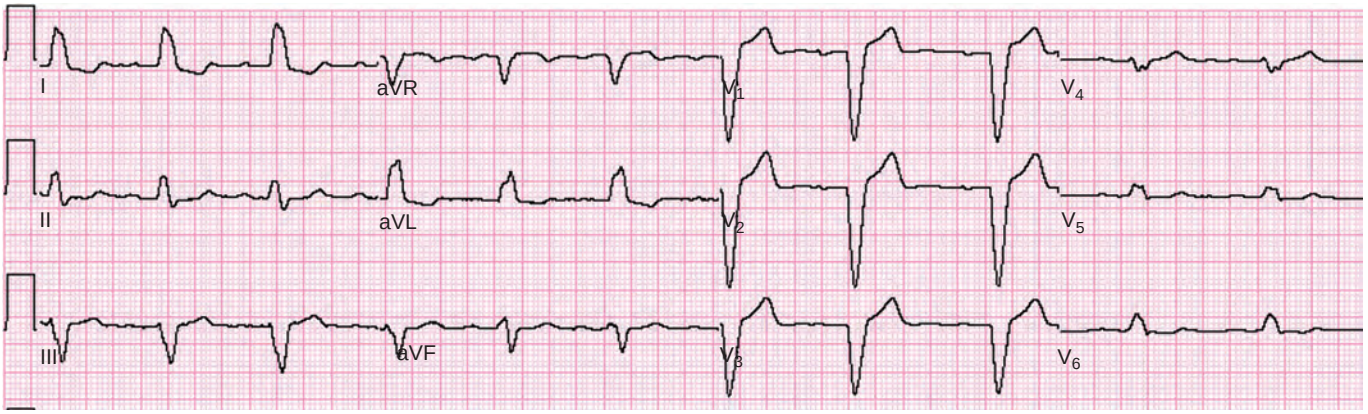
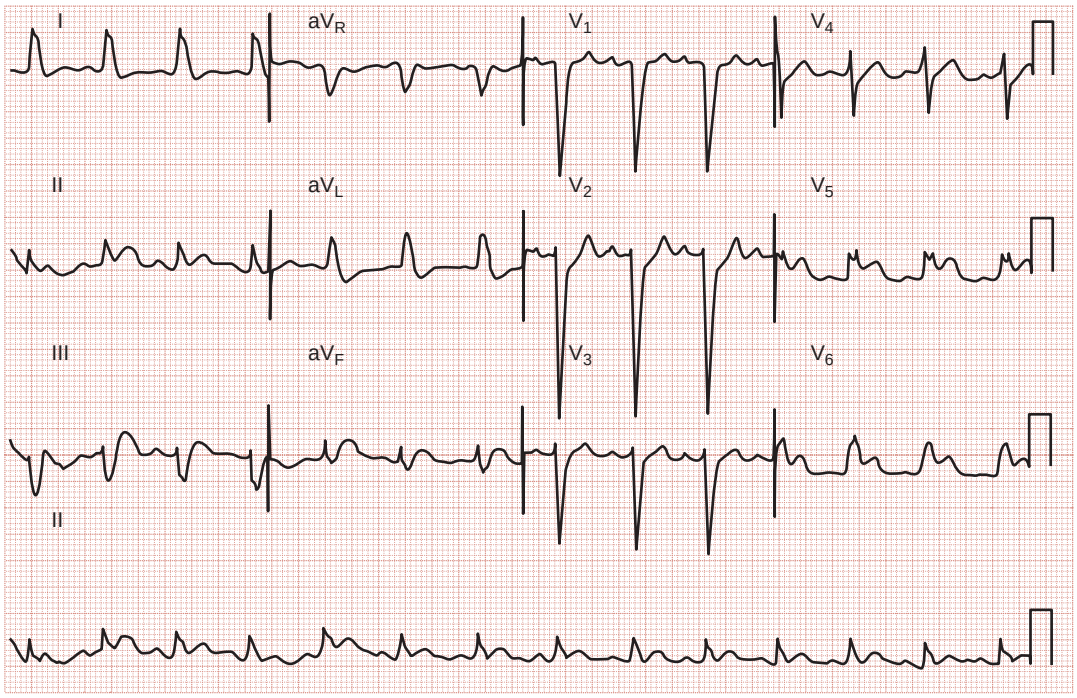


Fig. 68.15. Left bundle branch block (LBBB; normal). This tracing demonstrates the classic findings of LBBB: (1) QRS complex width > 0.12 sec; (2) absence of Q wave in lead V_6; (3) broad monophasic R wave in leads V_5, V_6, I, and aVL; (4) discordant ST segment–T wave changes in leads V_1 to V_3 (simulating acute myocardial infarction), I, and aVL. A first-degree atrioventricular block is also apparent.

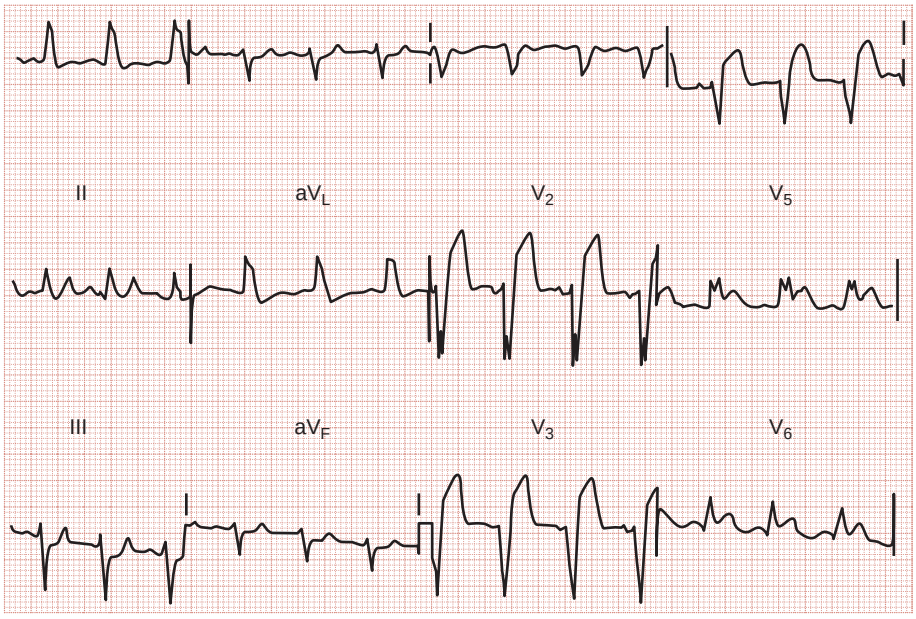
in some or all of the lateral leads (leads V_5, V_6, I, and aVL) in LBBB; both of these resemble ischemic changes seen in ACS. However, these findings in LBBB are merely expressions of the so-called rule of appropriate discordance. The ST segment and T wave vectors are expectedly discordant, or opposite in direction, to the major vector of the QRS complex in those leads. Because LBBB is a frequent finding on the ECG of a patient at risk for CAD, the normal findings in LBBB (Fig. 68.15) and presentation of AMI in a patient with LBBB must be distinguished.

Sgarbossa and colleagues used a large AMI database to obtain a population of patients with LBBB and serum marker confirmation of AMI. Three independent electrocardiographic predictors of AMI in the presence of LBBB were identified: (1) ST segment elevation of at least 1 mm that is concordant with the QRS complex (Fig. 68.16); (2) ST segment depression of at least 1 mm in lead V_1, V_2, or V_3 (see Fig. 68.16A): and (3) ST segment elevation of at least 5 mm that is discordant with the QRS complex (see Fig. 68.16B). These findings were assigned weighted scores of 5, 3, and 2, respectively. For accuracy in diagnosis, a specificity of 90% requires a score of at least 3. Thus, if an ECG features only discordant ST segment elevation of 5 mm or more but neither of the other two criteria, further testing is recommended before one can conclude that the ECG is indicative of AMI. Subsequent literature reports have yielded mixed reviews of the Sgarbossa criteria for the diagnosis of AMI in the presence of LBBB. Ultimately, the approach to the patient with LBBB and possible AMI remains complicated. If the clinical presentation is consistent with AMI, diagnostic adjuncts to the history and physical examination (eg, serial ECGs, comparison with prior ECGs, echocardiography, serum cardiac marker measurement) should be liberally used when the ECG is not diagnostic for acute infarction as noted by the Sgarbossa criteria. A newly noted LBBB, occurring in patient with a very convincing clinical impression of AMI, should be considered a high-risk presentation; AMI in this situation is likely.

VPRs can mimic and mask the manifestations of AMI. VPRs originating in the right ventricular apex create a wide QRS complex, with a pseudo-LBBB pattern. As with LBBB, the right precordial leads in VPR typically feature predominantly negative QRS complexes with discordant ST segments and T waves that are elevated and tall or vaulted, respectively. Unlike LBBB, however, VPR originating in the right ventricular apex often yields a predominantly negative QRS complex in leads V_5 and V_6 as well; this



A



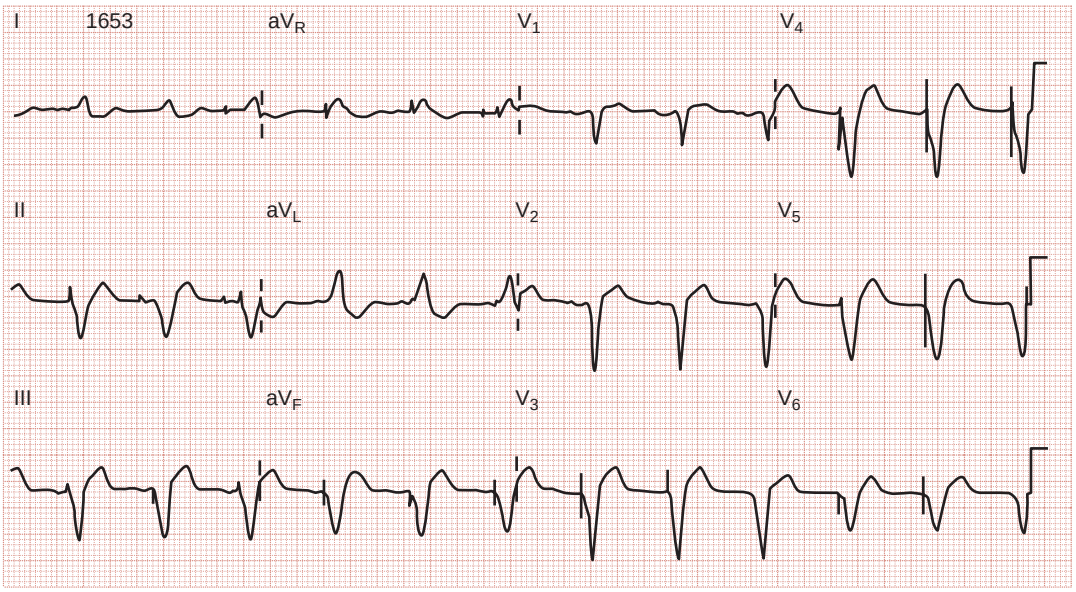
B

Fig. 68.16. Acute myocardial infarction (AMI) in left bundle branch block (LBBB). **A,** Using the Sgarbossa criteria, there is strong evidence of AMI because of the concordant ST segment elevation greater than 1 mm in leads II, V_5, and V_6. Also suggestive is the ST segment depression seen in V_2. **B,** Again, applying the Sgarbossa criteria to this tracing with underlying LBB. **B,** AMI is strongly suggested. There is concordant ST segment elevation in leads V_5 and V_6 that appears to exceed 1 mm; furthermore, there is excessively discordant ST segment elevation in leads V_2 and V_3, probably greater than 5 mm.

is oriented leftward and slightly downward, whereas the impulse generated from the pacemaker wire is oriented superiorly. Furthermore, small vertical pacemaker spikes immediately preceding the QRS complex should be a clue to VPR although, at times, these deflections are hard to detect on the 12-lead ECG.

Limited data exist to guide the emergency clinician in interpreting the 12-lead ECG in this setting. As with the LBBB scenario, the VPR pattern represents a significant confounding variable in the evaluation of the patient with chest pain suspected of having ACS. Sgarbossa and associates have advanced criteria for the detection of AMI in the presence of VPR that were derived from the same database of patients and are essentially the same as the LBBB criteria: (1) ST segment elevation of at least 5 mm discordant with the QRS complex; (2) ST segment elevation of at least 1 mm concordant with the QRS complex; and (3) ST segment depression of at least 1 mm in lead V_1, V_2, or V_3 (Fig. 68.17).

LVH may mimic or obscure ACS on the ECG. LVH may feature prominent left-sided forces, manifesting as large rS or QS



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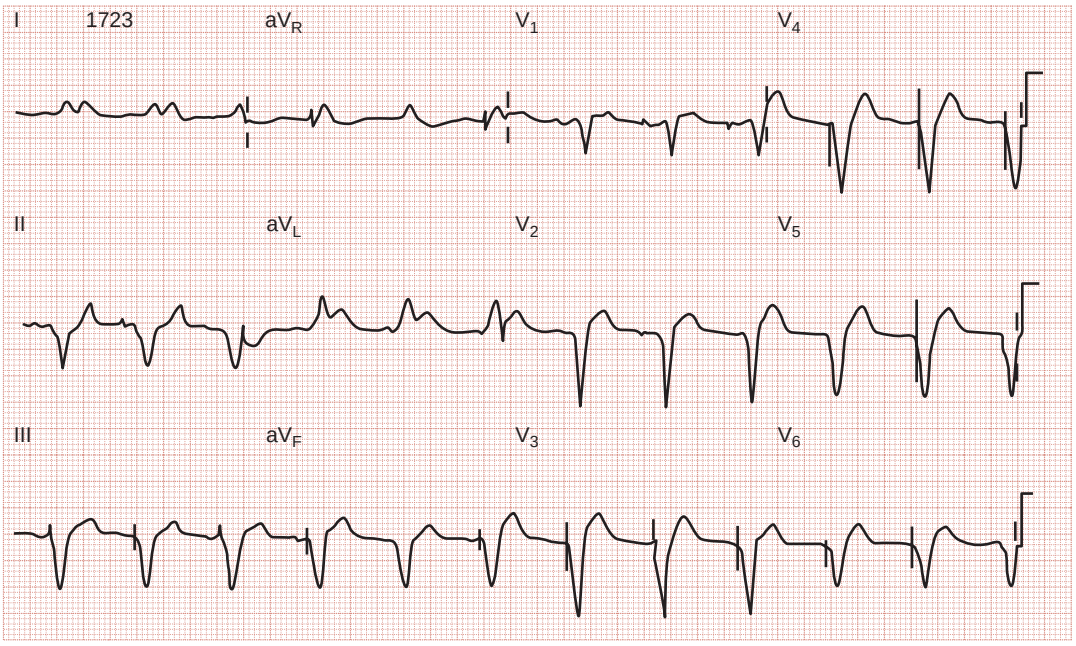


B

Fig. 68.17. Permanent right ventricular paced pattern with acute myocardial infarction (AMI)—ventricular paced rhythm. **A,** Appropriate ST segment–T wave findings in the patient with a paced rhythm. **B,** Serial electrocardiogram from the patient in **A,** revealing evolution of changes worrisome for ST segment elevation myocardial infarction (STEMI), including concordant ST segment elevation in leads I and aVL consistent with lateral wall STEMI.

complexes in the right precordial leads, yet these changes seldom extend beyond V_1 and V_2 in the case of LVH. Consistent with the rule of appropriate discordance, the leads demonstrating such a pattern feature discordant ST segment elevation and tall vaulted T waves, paralleling the changes of AMI. The initial portion of the elevated ST segment in LVH is generally concave, as opposed to the obliquely straight or convex pattern that usually (but not always) is seen with ST segment elevation in AMI. In LVH, the left precordial leads (and, at times, leads I and aVL) may show evidence of a repolarization abnormality (or strain pattern), with ST segment depression and asymmetrically inverted T waves. The presence of this strain pattern in the left precordial leads is reassuring when ST segment elevation and tall T waves in the right precordial leads are being attributed to LVH rather than to AMI because one is essentially the mirror image of the other. The changes in LVH should be static over time (Fig. 68.18).

Takotsubo cardiomyopathy is referred to as left apical ballooning or so-called broken heart syndrome. It features ST segment elevation (or deep T wave inversions) without evidence of obstructive CAD. Positive serum markers for cardiac ischemia may be present, as well as hemodynamic compromise. It occurs principally in postmenopausal women and characteristically is triggered by intense emotional stress. Ballooning of the left ventricular apex is seen on ventriculography or echocardiography. Prognosis is excellent, typically with recovery of normal wall motion within 1 month or less.

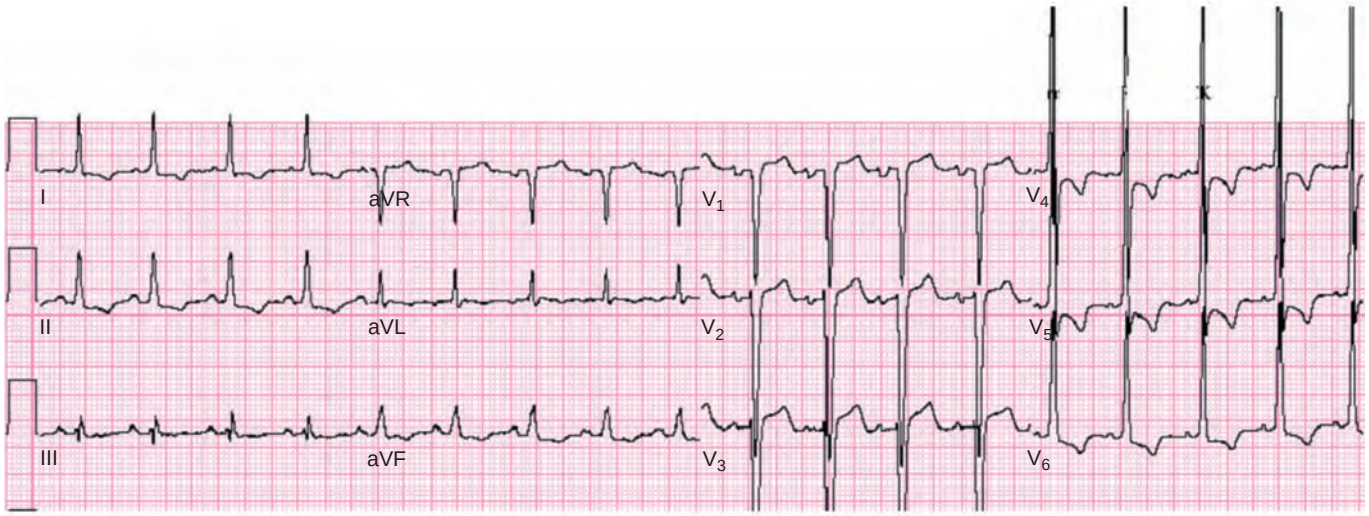


Fig. 68.18. Left ventricular hypertrophy (LVH) with repolarization abnormality. This tracing demonstrates classic repolarization abnormality, with ST segment depression in the left-sided precordial leads following large-amplitude R waves. The T waves in these leads are asymmetrically inverted. The right precordial leads (V_1 and V_2) show a mirror image of the changes seen in V_3 to V_6, with slight ST segment elevation (contour initially concave) and asymmetric tall T waves. See Fig. 68.20B for evidence of evolving acute myocardial infarction in a patient with LVH and repolarization abnormality.

Non–ST Segment Elevation Myocardial Infarction. Non–ST segment elevation myocardial infarction, or NSTEMI, supplants non–Q wave MI, previously termed *subendocardial infarction.* Precise terminology is difficult because Q waves may disappear with time and the criteria for significant Q waves vary. Moreover, transient ST segment elevation may simply be missed on the ECG. Nonetheless, it is useful to describe the entity wherein there is serum marker evidence of MI in the appropriate clinical scenario but no documented ST segment elevation.

Pathophysiologically, total occlusion of the diseased artery may not have occurred, or the infarct zone may have been partially spared by collateral circulation or therapeutic intervention. Electrocardiographic manifestations of NSTEMI include ST segment depression and T wave inversion, which may be deep and symmetric; nonspecific ST segment and/or T wave abnormalities may also be seen in the NSTEMI presentation. Absence of STEMI, however, does not necessarily translate to better outcomes. Previous studies have demonstrated that patients with ST segment depression on the initial ECG have an in-hospital mortality rate similar to that of patients with ST segment elevation or LBBB (15%–16%). Furthermore, ST segment depression in leads V_1 to V_3 or V_4 may herald true posterior infarction on the 12-lead ECG. Acute posterior (inferobasal) MI is one entity wherein emergent fibrinolysis or PCI is potentially indicated in the absence of ST segment elevation on the 12-lead ECG.

Electrocardiographic Adjuncts in the Diagnosis of Acute Coronary Syndrome. Additional lead ECGs can increase sensitivity for AMI by evaluating regions of the heart prone to electrical silence on the 12-lead tracing. Usually, additional lead ECGs use posterior (leads V_8 and V_9) and right ventricular (V_4R) electrodes, thus constituting the 15-lead ECG (Fig. 68.19). Posterior leads V_8 and V_9 are placed under the tip of the left scapula and at the left paraspinal area at the same level as leads V_4 to V_6. Morphologic changes in the posterior leads may be subtle, mainly because of the increased distance between these electrodes and posterior wall of the heart.

Electrocardiographic imaging of the right ventricle is enhanced with the use of the right-sided chest leads V_1R to V_6R (also termed RV_1 to RV_6). These leads are placed in mirror image fashion across the right precordium. Of the right precordial leads, V_4R has the highest sensitivity for right ventricular infarction and is the lead of choice to include in the 15-lead tracing. Morphologically, less pronounced changes can be expected in the right-sided chest leads because of the relatively thinner wall of the right ventricle.

Use of the 15-lead ECG may improve diagnostic precision but does not appear to affect the rate of AMI diagnosis, use of reperfusion therapy, disposition, or outcome in all ED patients with chest pain evaluated for ACS. It has been shown that in the subset of ED ACS patients identified as candidates for admission to the cardiac care unit (ie, high-risk patients), the 15-lead ECG increased the sensitivity of ACS detection by 12%. Possible applications for additional lead ECGs include the following: (1) ST segment changes (depression or elevation) in leads V_1 to V_3, in an isolated lead or in more than one; (2) equivocal ST segment elevation in the inferior (II, III, aVF) or lateral (I, aVL) limb leads, or both; (3) all inferior STEMI; and (4) hypotension in the setting of ACS. Additional lead applications can be used, including the 18- and 24-lead ECG; electrocardiographic body mapping with use of multiple electrocardiographic leads, such as the 80-lead ECG, can also be used. In general, the emergency clinician can image larger segments of the heart with more electrocardiographic leads in use. It is suggested that these additional lead ECGs, including body mapping, can increase the rate of STEMI diagnosis and thus the number of patients who are candidates for emergent reperfusion therapy.

Body surface mapping increases the amount of electrocardiographic data for processing and decision-making. Whereas serial ECGs and ST segment trend monitoring increase the period of time over which data are collected on a 12-lead ECG, body surface mapping increases the number of electrodes used to gather data and increases the vantage points from which the heart is evaluated. Various devices use 40 to 120 leads. With an 80-electrode device, 64 chest and 16 back electrodes are applied in a vestlike fashion with self-adhering strips. Recording from all electrodes simultaneously, the body surface map enters ST segment elevation and depression data into a computer, which transforms the data into a color-coded torso image. With red representing ST segment elevation, blue signifying ST segment depression, and green reflecting normal, the degree of disease is also expressed in terms

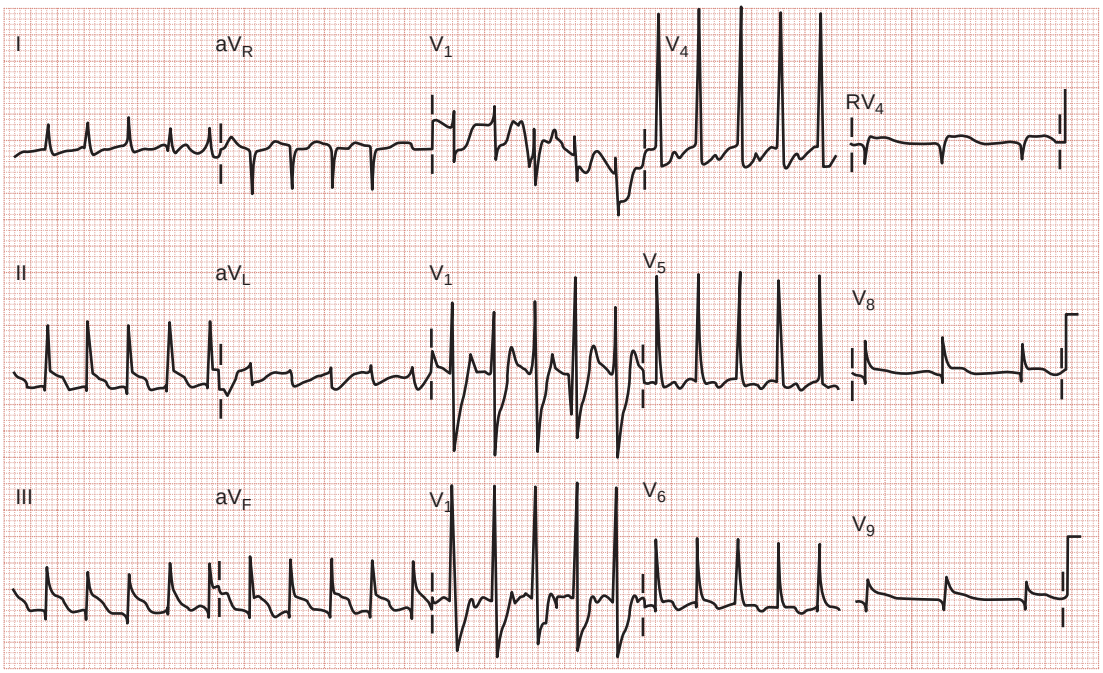


Fig. 68.19. Fifteen-lead electrocardiogram (ECG) with inferior, lateral, posterior, and right ventricular acute myocardial infarction (AMI). The standard 12-lead ECG reveals the typical ST segment elevation (STE) in the inferior and lateral leads, as well as ST segment depression (STD) with prominent R wave in the right precordial leads. Posterior AMI is indicated by the right precordial STD with a prominent R wave and the STE in posterior leads V_8 and V_9. Note that the degree of STE is less pronounced than that seen in the inferior leads because of a relatively longer distance from the posterior epicardium to surface leads. The right ventricular infarction is noted in this case, using the simplified approach with only RV_4, which demonstrates STE of relatively small magnitude.

of color intensity. Body surface mapping may increase the sensitivity for MI, especially in areas that are relatively electrically silent on the 12-lead ECG (eg, posterior and lateral walls of the left ventricle and right ventricle) and in patients with underlying LBBB. In prior studies, the 80-lead ECG provided an incremental 27.5% increase in STEMI detection as compared with the 12-lead ECG. Patients with 80-lead, ECG-only STEMI had adverse outcomes similar to those encountered in the 12-lead STEMI patients, yet these individuals were treated much less aggressively.

Serial ECGs and ST segment trend monitoring overcome the limitations of the single snapshot of a 12-lead ECG. The use of increased electrocardiographic surveillance demonstrates diagnostic benefit in patients with recurrent or continuous chest pain, particularly patients with an initially normal nondiagnostic or possible ST segment mimicking syndrome ECG (eg, ST segment elevation potentially resulting from BER) in whom there is a high clinical suspicion for ACS. We know that the examination of ST segment trends (measured every 20 seconds for at least the first hour) and automated serial ECGs (at least every 20 minutes) in ED patients with chest pain can significantly increase the sensitivity and specificity for detection of STEMI (16%) and ACS compared with just the initial ECG (Fig. 68.20). Previous studies have demonstrated that in patients admitted with nondiagnostic initial ECGs and symptoms consistent with ACS, 12 hours of continuous 12-lead electrocardiographic monitoring in a coronary care unit setting revealed that only serum cardiac marker elevation and presence of ST segment episodes (defined as ST segment elevation or depression > 1 mm different from baseline that endured for at least 1 minute) predict cardiac death or MI.

Limitations of Electrocardiography in Acute Coronary Syndrome. The sensitivity and specificity of a single ECG for AMI are approximately 60% and 90%, respectively. Serial ECGs in the setting of continued or recurrent pain in a patient with a higher clinical suspicion for ACS and an initially nondiagnostic ECG increase the diagnostic value. The initial ECG is nondiagnostic in approximately 50% of patients in the ED who are ultimately diagnosed with STEMI. Moreover, nondiagnostic and even normal ECGs do not exclude the diagnosis for AMI in that about 20% of patients ultimately diagnosed with AMI have nondiagnostic ECGs earlier in their course. As time elapses from symptom onset to electrocardiographic recording, the ability of the ECG to exclude AMI does not markedly increase. Thus, in a patient with higher clinical suspicion for ACS, a single normal or nondiagnostic ECG does not ensure the absence of ACS, even if the ECG was recorded well after the onset of symptoms. In patients being evaluated for ACS, only serial electrocardiography, combined with serial cardiac marker determinations, can exclude AMI and, even then, UA without actual myocardial necrosis may be present.

Chest Radiography

The chest radiograph provides information concerning the application of therapies (eg, an evaluation of mediastinal width in the consideration of fibrinolytic agent use and determination of pulmonary congestion in the consideration of acute parenteral β-adrenergic blocking therapy). Furthermore, the presence of CHF on the chest radiograph increases risk in AMI patients who may benefit from an aggressive therapeutic approach.

There is radiographic evidence of pulmonary congestion in approximately one-third of AMI patients. AMI patients who develop CHF have increased mortality, as reported by the Killip classification. The chronicity of the CHF syndrome may also be suggested by heart size. Patients with AMI complicated by pulmonary edema who have a normal heart size usually have no past

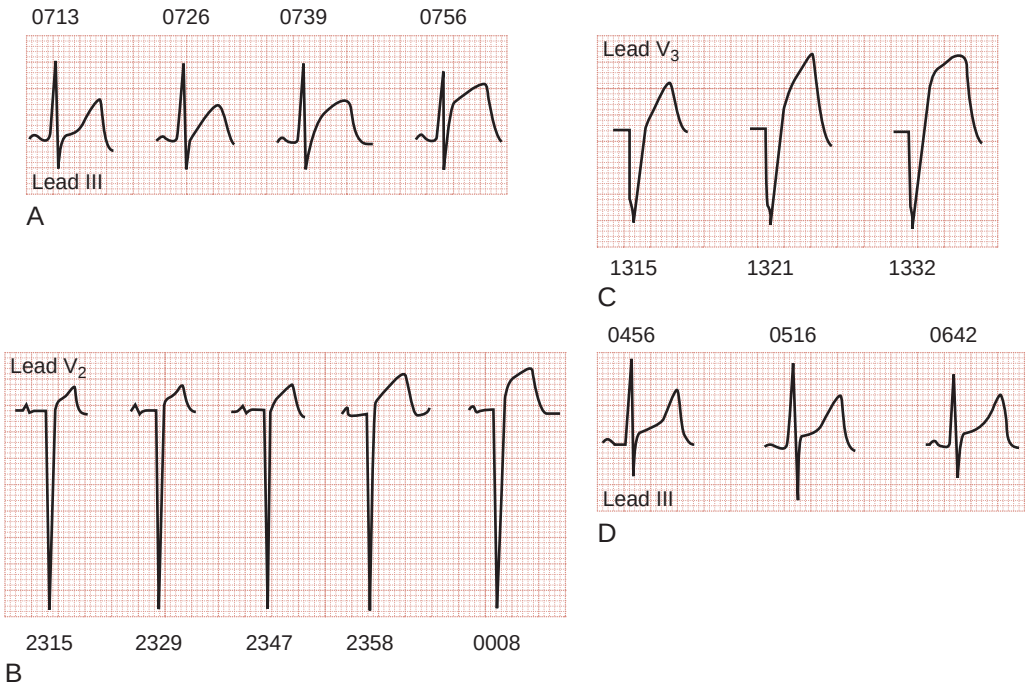


Fig. 68.20. Serial electrocardiography. **A,** Representative example of lead III in a patient with chest pain and an initially nondiagnostic electrocardiogram depicting the evolution of ST segment elevation myocardial infarction (STEMI). **B,** Representative example of lead V_2 in a patient with the left ventricular hypertrophy pattern. Serial sampling of this patient with ongoing chest pain and a confounding electrocardiographic pattern reveals the progression to STEMI. **C,** Representative example of lead V_3 in a patient with left bundle branch block and evolving acute myocardial infarction (AMI). D, Representative examples of lead III in a patient with chest pain and noninfarctional ST segment elevation (STE). Note the lack of change (degree of elevation as well as morphology of elevation) over time in this patient with benign early repolarization.

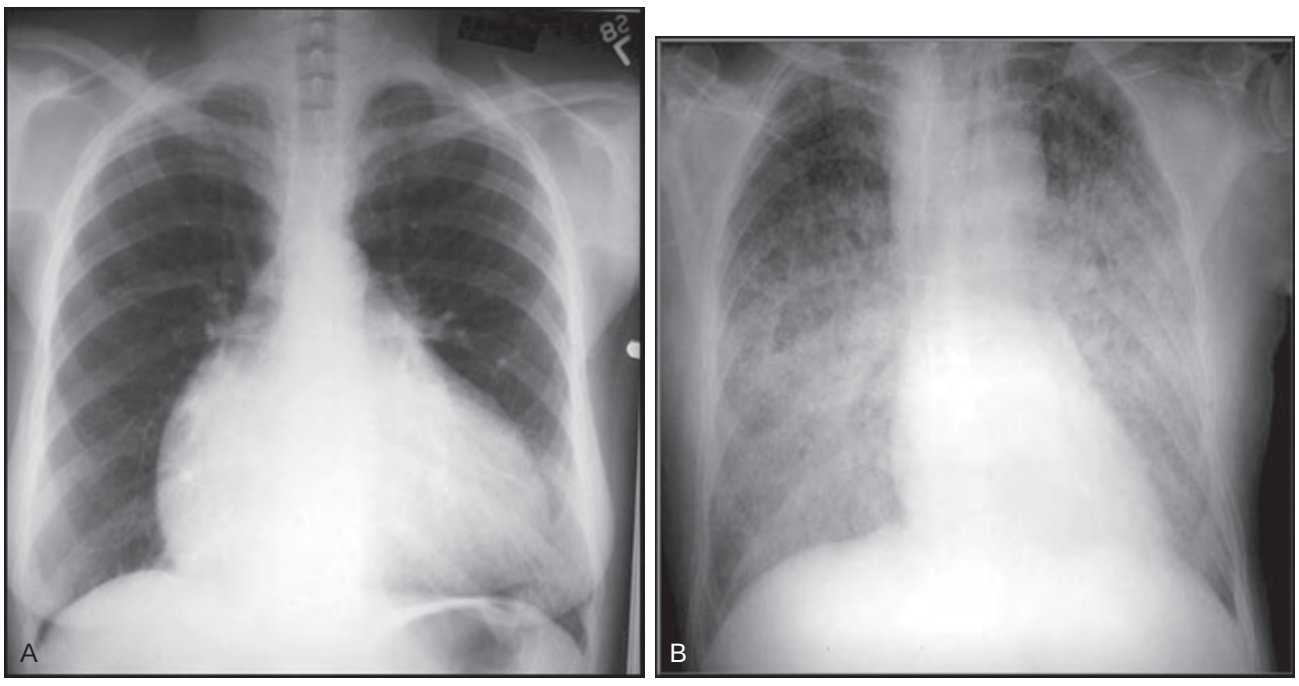


Fig. 68.21. Chest radiographs in patients with acute coronary syndrome. **A,** Cardiomegaly. **B,** Borderline cardiomegaly with pulmonary edema.

history of CHF. AMI is the most frequent cause of pulmonary edema with a normal cardiac size. In other cases, patients with AMI and cardiomegaly, with or without pulmonary edema, frequently have a preexisting history of CHF, anterior wall infarct, and multiple-vessel CAD (Fig. 68.21).

Serum Markers

Biochemical markers play a pivotal role in the diagnosis, risk stratification, and guidance of treatment of ACS. The European Society of Cardiology and ACC have defined the criteria for AMI

TABLE 68.5

Summary of Test Performance Studies of Diagnostic Technologies for Acute Coronary Syndrome in the Emergency Department

TEST	DISEASE STUDIED	NO. OF STUDIES (SUBJECTS)	PREVALENCE RANGE OF STUDIES, %	DISEASE SENSITIVITY, % (95% CI)[a]	DISEASE SPECIFICITY,* % (95% CI)[a]
Creatine kinase (single)	AMI	12 (3195)	7–41	37 (31–44)	87 (80–91)
Creatine kinase (serial)	AMI	2 (786)	26–43	69–99	68.84
CK-MB (presentation)	ACS AMI	1 (1042) 19 (6425)	20 6–42	23 42 (36–48)	96 97 (95–98)
CK-MB (serial)	ACS AMI	1 (1042) 14 (11,625)	20 1–43	31 79 (71–86)	95 96 (95–97)
Myoglobin (presentation)	AMI	18 (4172)	6–62	49 (43–55)	91 (87–94)
Myoglobin (serial)	AMI	10 (1277)	11–41	89 (80–94)	87 (80–92)
Troponin I (presentation)	AMI	4 (1149)	6–39	39 (10–78)	93 (88–97)
Troponin I (serial)	AMI	2 (1393)	6–9	90–100	83–96
Troponin T (presentation)	AMI	6 (1348)	6–78	39 (26–53)	93 (90–96)
Troponin T (serial)	AMI	3 (904)	5–78	93 (85–97)	85 (76–91)
CK-MB and myoglobin combination (presentation)	AMI	3 (2283)	9–28	83 (51–96)	82 (68–90)
CK-MB and myoglobin combination (serial)	AMI	2 (291)	11–20	100	75–91
Exercise stress ECG	ACS	2 (312)	6–10	70–100	82–93
Rest echocardiography	ACS AMI	2 (228) 3 (397)	3–30 3–30	70 (43–88) 93 (81–91)	87 (72–94) 66 (43–83)
Stress echocardiography	AMI	1 (139)	4	90	89
Sestamibi (rest)	ACS AMI	3 (702) 3 (702)	9–17 92 (78–98)	81 (74–87) 67 (52–79)	73 (56–85)

[a]Point estimate from a single study or a range of reported values; meta-analysis not performed.
ACS, Acute coronary syndrome; *AMI,* acute myocardial infarction; *CI,* confidence interval; *CK-MB,* creatine phosphokinase MB fraction; *ECG,* electrocardiogram.
Adapted from Pope JH, Selker HP: Diagnosis of acute cardiac ischemia. Emerg Med Clin North Am 21:27–59, 2003.

diagnosis on biochemical grounds because specific markers, particularly troponins, indicate irreversible cell damage.[4] In the past, detection of AMI by characteristic enzyme level elevations over days within the hospital was sufficient to establish the diagnosis of AMI because there was no specific therapy to reverse or prevent the developing myocardial necrosis. The advancement in diagnostic tests, as well as medical and interventional therapies for AMI, has made the diagnosis and intervention of AMI in the first minutes to hours of the ED visit not only possible, but essential.

For patients with a nondiagnostic ECG, early elevation of serum markers specific for of myocardial necrosis (troponin I or T) confirms a presumptive diagnosis of NSTEMI. Caution is advised, however, when a single initial serum marker level is not elevated. This single test, in the first hours following symptom onset, is too insensitive to be used to support a decision that the patient can be discharged or determine that no acute coronary event has occurred.[17-19] The patient's history remains the most vital portion of the diagnostic evaluation of potential ACS. Serial testing substantially improves the sensitivity of these tests for AMI (Table 68.5 and Fig. 68.22), but if the patient's presentation is consistent with unstable angina, no marker can be used to rule out that diagnosis. A sensitive and specific marker to identify myocardial ischemia without myocardial necrosis is not yet available.

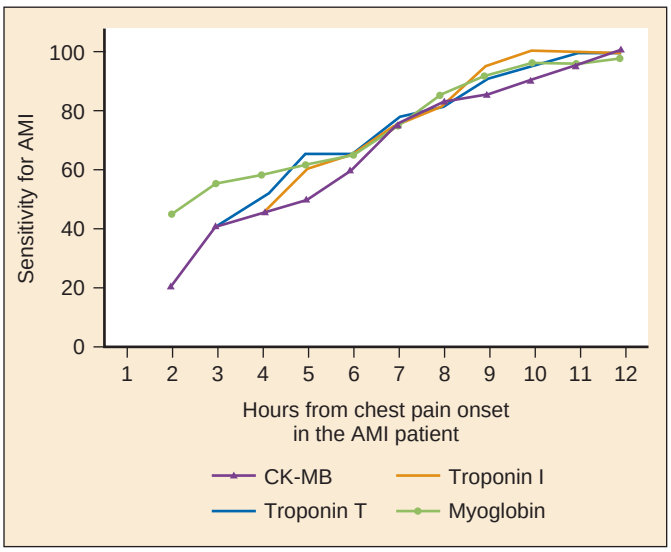


Fig. 68.22. Serum marker sensitivity relative to the time of onset of chest pain in the patient with acute myocardial infarction (AMI). ACS, Acute coronary syndrome; CAD, coronary artery disease; *CK-MB,* creatine phosphokinase MB fraction; STEMI, ST segment elevation myocardial infarction.

Troponins. Because of their superior sensitivity and specificity compared with other biochemical markers, cardiac troponins are the best markers for the identification of myocardial cell injury. Because of this, cardiac troponin (cTn) is the only cardiac marker referenced in the universal definition of MI[4] and is used in isolation in the most recent validated standardized decision rules for the evaluation of ACS.[20,21] Two myocardium-specific proteins, myocardial troponin I (TnI) and troponin T (TnT), precede the release of creatine kinase (CK-MB) into the serum. The cardiac troponins are genetically distinct from troponin forms found in other muscle tissue. TnI and TnT are very similar in their diagnostic and prognostic value and their serum kinetics and rates of increase and decrease associated with myocardial ischemia, infarction, and ACS.

The biokinetics of troponin release relate to the location of the protein within the cell. Normally, small quantities of troponins are free in the cytosol, and most is entwined in the muscle fiber. After injury, a biphasic rise in serum troponin levels corresponds to early release of the free cytoplasmic proteins, followed by a slower and greatly prolonged rise, with breakdown of the actual muscle fiber. The slow destruction of the myocardial cell contractile proteins provides a sustained release of the troponins for 5 to 7 days. Serum troponin levels begin to rise measurably in the serum at about the same time as CK-MB level elevations become detectable, as early as 2 to 3 hours after onset, but troponin levels remain elevated for 7 days or more.

The cardiac-specific troponins, determined serially, are highly sensitive for the early detection of myocardial injury. A positive test result is associated with significant risk, and serial negative results predict low risk. A single troponin measurement on presentation, however, has limited value in excluding AMI in the first hours of symptom onset and no ability to detect UA without infarction because cell injury is required. Serial measurements, particularly when performed at least 6 hours after symptom onset (as early as 2–3 hours when using newer, high-sensitivity assays),[17-19] markedly improve the sensitivity of the cardiac troponins for AMI, and the pattern of rise may assist in determining the acuity of the event. These serial measurements of troponin levels are to assess for a change in serum concentration over time (delta). Responding to the absolute change in serum concentration, rather than the relative change, has been shown to be more accurate in the diagnosis of AMI. The highly sensitive troponin assays produce positive results after AMI reliably within several hours. These newer assays, however, seem to yield more false-positive results and are still limited in sensitivity because they do not detect UA.[22] As with most tests, as the new generation of highly sensitive troponin assays become more sensitive, they lose specificity for ACS evaluation and diagnosis. Recent evidence has indicated that we may have reached a point of maximum diagnostic return with regard to troponin assay sensitivity, in which increased sensitivity may only complicate the evaluation for ACS.[23]

Because cardiac troponins are not found in the serum of healthy individuals, an abnormally elevated level is defined as that exceeding the 99th percentile in a healthy population. Sensitivity to detect abnormal low troponin levels, however, varies among the multiplicity of existing assays, particularly with respect to TnI. Emergency clinicians, therefore, must be familiar with the sensitivity and limitations of the particular assay used at their institution and cutoff concentrations for clinical decisions.

Data indicate that even very low values of troponin level elevations are associated with a significantly adverse clinical prognosis. This is true not only in patients with chest pain, but also in asymptomatic individuals in the general population for whom data have shown that detectable serum troponin levels, using a high-sensitivity troponin assay, are associated with the presence of structural heart disease and all-cause mortality.[24-26]

In a number of studies, up to 33% of patients diagnosed with UA with normal CK-MB levels had elevated troponin levels, indicating the marker's improved sensitivity for myocardial cell injury. The risk of these patients for cardiac events and mortality is similar to that of patients diagnosed with AMI by traditional World Health Organization (WHO) criteria and has led to the redefinition of AMI on the basis of biochemical markers. It has been shown that there is almost a linear correlation between increasing troponin levels and risk of cardiac events and mortality, even in patients with a nondiagnostic ECG and normal CK-MB levels. Small elevations of troponin levels may be used as an objective measure of preinfarcts that characterize UA and are associated with increased risk of infarction in the near term. Marked elevations in troponin levels consistent with AMI represent further progression along the continuum of ACS toward so-called traditional AMI. Cardiac troponin levels may also guide ACS treatment. Data from earlier studies have suggested that patients with elevated troponin levels who are treated with an early invasive interventional strategy within 48 hours have a marked improvement in recurrent ischemia, infarction, and mortality in the short term and at 6 months. These studies included patients without major electrocardiographic criteria for immediate interventional reperfusion strategies.

It is likely that the improved sensitivity of troponin as a marker has captured a high-risk ACS population not previously diagnosed or treated. It is important to note that elevated troponin levels identify patients with UA or NSTEMI who stand to gain the greatest benefit from an early invasive strategy with coronary angiography and revascularization.

Elevated troponin levels occur in a variety of cardiac and noncardiac conditions unrelated to the typical ACS pathophysiology. Cardiac conditions that can result in significant increased troponin levels in patients without evidence of ACS include myocarditis, pericarditis, CHF, LVH, and nonpenetrating cardiac trauma. Although the presence of elevated troponin levels in these conditions might be considered false-positive results, studies have supported the contention that the source of these levels is underlying noninfarction myocyte injury that occurs with these conditions. Moreover, elevated troponin levels in many of these non-ACS cardiac conditions have prognostic significance.[27]

Troponin level elevations can also be seen in noncardiac conditions, including PE, sepsis, extreme physical exertion, renal insufficiency, and even essential hypertension.[28] Troponin level elevation may result from right ventricular dysfunction and myocyte injury in the case of submassive and massive PE and is a significant predictor of an adverse outcome. Similar elevated troponin levels have been reported in patients with sepsis and critically ill patients with multiple organ system failure.[27] In each of these subsets of patients, troponin level elevations are associated with increased morbidity and mortality.

Elevated troponin levels are commonly seen in asymptomatic patients with end-stage renal disease. Earlier studies in asymptomatic hemodialysis patients using a high-sensitivity troponin assay has shown that as many as 100% of the serum samples taken will have measurable troponin levels exceeding the 99th percentile value. This finding may relate to the high prevalence of cardiac disease in this population rather than any reduced renal clearance and may still represent evidence of subclinical myocardial damage. The TnT isoform is associated with elevated levels in renal failure more often than TnI, particularly in patients undergoing hemodialysis. Elevated troponin levels in the setting of renal failure are associated with increased risk of death and major cardiac and vascular morbidity and should not be ascribed to chronic renal failure unless old records are available to corroborate that the elevated troponin level is actually the patient's normal baseline level.

Other Serum Markers. Creatinine phosphokinase (CK) is found in large quantities, not only in cardiac muscle but also in skeletal muscle, brain, kidney, lung, and GI tract. Myocardial cells are the most abundant potential sources of CK-MB; thus, the appearance of CK-MB in the serum is highly suggestive of MI. The CK-MB fraction remains the best alternative to troponin levels as a cardiac marker. In the setting of AMI, CK-MB is released and is detectable in the serum as early as 3 hours after onset of the necrosis, peaks at 20 to 24 hours, and becomes normal within 2 to 3 days after injury. Unfortunately, skeletal muscle does contain small amounts of CK-MB, particularly the pelvic musculature. Abnormal CK-MB level elevations may be seen in patients with trauma, muscular dystrophies, myositis, and rhabdomyolysis and after extremely vigorous exercise. Because of this lack of specificity, CK and CK-MB have seen a gradual decrease in clinical use in recent years. As troponin level assays have become more sensitive, with detectable levels in the serum even preceding CK and CK-MB changes, CK-MB has been virtually eliminated from the modern clinical decision rules targeting ACS evaluation in the ED.

The diagnostic value of CK-MB is improved by requiring that the serum level not only be elevated but also be at least 5% of the total CK level (the CK-MB fraction or ratio). False-positive elevations can occur with noncoronary conditions, such as pericarditis, myocarditis, skeletal muscle disease, rhabdomyolysis, trauma, and exercise. In presentations in which dual biomarkers are obtained, the presence of nominal elevations in the CK-MB level with a simultaneous normal serum troponin level is of less clinical concern.

Myoglobin, a small protein (17 kDa) found in muscle tissue, is rapidly released into the circulation after cellular injury. In cases of myocardial injury, the myoglobin level rises in the initial 1 to 2 hours, peaks at 5 to 7 hours, and returns to baseline by 24 hours. Because of its rapid rise, myoglobin is attractive as an early indicator of myocardial injury. Myocardial myoglobin, however, is not currently distinguishable immunologically from skeletal muscle myoglobin. Thus, the myoglobin level is elevated in any clinical situation involving the skeletal muscle, such as trauma, exercise, and significant systemic illness. In addition, myoglobin level increases are seen in patients with renal failure because of reduced clearance. Despite its high sensitivity for AMI, particularly early in the course of ACS, myoglobin has largely fallen out of favor due to its extreme lack of specificity for ACS or myocardial injury in general.

Troponin, CK, and myoglobin levels are all measures of myonecrosis. Biochemical assays for potential new cardiac markers for necrosis are being developed in the hope of finding those with improved sensitivity, risk determination capability, and prognostic power. One such new cardiac-specific myonecrosis marker is heart-type, fatty acid–binding protein. Other potential markers with usefulness in ACS include those that may detect ischemia before actual necrosis and plaque instability or inflammation.

Episodes of ischemia and inflammation can result in biochemical changes before actual irreversible cell necrosis. Ischemia-modified albumin (so-called cardiac albumin) is a potentially useful ACS biomarker that reportedly detects early myocardial ischemia rather than the later myocyte necrosis and its level may be elevated even earlier than myoglobin. Other potential ischemia markers include unbound free fatty acid and whole blood choline levels. A variety of biochemical markers for inflammation and plaque instability may have value in evaluating the risk of a cardiac event. Chief among these are the inflammatory markers C-reactive protein (CRP) and high-sensitivity CRP (hsCRP), which have long-term prognostic value for cardiac events in healthy individuals and potential short-term prognostic value when combined with other markers for ACS. Other inflammatory markers include interleukin-6 and tumor necrosis factor alpha. Elevated plasma levels of myeloperoxidase, an abundant leukocyte enzyme found in vulnerable coronary plaques that have ruptured, predict the short-term risk of adverse cardiac events, even with negative cardiac troponin levels and no evidence of myocardial necrosis. None of the biochemical markers of ischemia (without necrosis) or inflammation have yet shown significant diagnostic value for ACS in the ED setting.

Markers of hemodynamic status, including the natriuretic peptides, may also be useful in the evaluation of ACS patients. These markers have shown value in determining future prognosis, rather than in making the diagnosis of ACS in the ED. These markers, such as B-type natriuretic peptide (BNP) and NT-proBNP (N-terminal pro-BNP), are released from cardiac myocytes in response to increases in ventricular wall stress. BNP is generally used as a marker for CHF but is a useful adjunct to the standard cardiac markers and has good predictive power for recurrent ACS events and cardiac-related deaths, as well as CHF exacerbations, in patients with AMI. Moreover, the natriuretic peptides are excellent predictors of short- and long-term mortality in patients with UA, NSTEMI, and STEMI.

Multiple Marker Strategies. Traditionally, multimarker approaches to ACS evaluation have been standard practice in the ED. However, with the advent of highly sensitive troponin assays, multiple studies have shown limited benefit to additional markers in the ED evaluation of ACS.[29,30] In addition to simplifying the evaluation, it has been shown that there is significant potential cost savings to the hospital by limiting excess cardiac biomarker testing.[31] The multimarker approach does not appear to offer benefit over individual troponin level evaluations for ACS and is therefore no longer recommended.

Exercise Testing

Exercise stress testing for ED patients is feasible. Previous studies in ED patients with low-risk chest pain (5% incidence of CAD), who underwent exercise testing after negative serial markers and 9 hours of electrocardiographic monitoring in the ED, showed that stress testing had a negative predictive value of 98.7% for the diagnosis of ACS or cardiac event within 30 days. An abbreviated ED-based, so-called rule-out MI protocol, followed by mandatory stress testing, appears to be an effective diagnostic method for the detection of symptomatic CAD in low- to moderate-risk patients. Appropriate patient selection is vital, as is true in all diagnostic situations, to the correct application of this evaluation strategy. Current guidelines on exercise testing state that such testing can be performed when patients are free of active ischemic or heart failure symptoms for a minimum of 8 to 12 hours.[32]

Immediate stress testing without the rule-out MI evaluation, however, may be safe and cost-effective in patients with chest pain thought possibly to be of cardiac origin but with low suspicion of ACS. For determination of the safety and value of immediate exercise testing in the ED, previous studies were able to identify low-risk patients who underwent immediate exercise testing, with no adverse effects. Negative exercise test results were found in 64% of patients, all of whom were discharged home from the ED. The rate of CAD diagnosis or cardiac event within 30 days was 29% for the positive stress group, 13% for the nondiagnostic group, and 0.3% for the negative stress group. In this low-risk group of ED chest pain patients, 30-day follow-up revealed no mortality in any of the three groups.

Graded exercise testing in the ED at most institutions is not available continuously. The mortality rate is extremely low (1/2500), but absolute contraindications include recent AMI (within 2 days), high-risk UA, uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise, symptomatic

severe aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary embolus or infarction, acute myocarditis or pericarditis, and acute aortic dissection.

Patients with a high pretest probability of CAD have a significant rate of false-negative results, and patients with a low pretest probability have a significant rate of false-positive stress test results. The specificity of the test is decreased in the presence of underlying electrocardiographic abnormalities secondary to medications, electrolyte abnormalities, LVH, or artifact. A false-positive test outcome may result from aortic stenosis or insufficiency, hypertrophic cardiomyopathy, hypertension, arteriovenous fistula, anemia, hemoglobinopathies, low cardiac output states, chronic obstructive pulmonary disease, digitalis toxic states, LVH, hyperventilation, mitral valve prolapse, and BBBs. An increase in the rate of false-positive test results in women tends to decrease the usefulness of graded exercise testing in this population.

TABLE 68.6

Emergency Department Bedside Echocardiography in Acute Coronary Syndrome—Pros and Cons

PROS	CONS
• Readily accessible, portable • Inexpensive • Safe, noninvasive • Detection of wall motion abnormalities, useful for early diagnosis and presentations involving diagnostic uncertainty • Identification of nonischemic causes of symptoms	• Skill level—operator- and interpreter-dependent • Limited sensitivity, particularly in small areas of myocardial injury • Limited visual windows in ≈10% of patients • Inability to distinguish acute wall motion abnormalities from chronic

Echocardiography

Two-dimensional echocardiography detects regional wall motion abnormalities associated with ACS due to the close correlation between wall motion and myocardial blood flow. Impaired myocardial contractility can range from hypokinesis to akinesis, with associated impaired myocardial relaxation during diastole. After AMI, paradoxical wall motion and decreased ejection fraction observed during systole indicate the subsequent loss of muscle tone from necrosis.

Particularly in individuals with nondiagnostic ECGs, the presence of regional systolic wall motion abnormalities in a patient without known CAD is a moderately accurate indicator of AMI or infarction, with a positive predictive accuracy of about 50%. When echocardiography is performed shortly after ED arrival, during an episode of chest pain, wall motion abnormalities have been detected in up to 90% of patients with ACS. The age of wall motion abnormalities, however, often cannot be determined without prior echocardiograms.

The absence of segmental abnormalities (presence of normal wall motion or diffuse abnormalities) has a significant high negative predictive value, as high as 98% for cases of suspected MI. Moreover, segmental wall motion abnormalities can be seen not only in the zone of acute infarction, but also in regions of ischemic stunning. Resting echocardiography provides an assessment of global and regional function, an important predictor of complications and mortality in patients with ACS. Prior studies have indicated that patients with mild and localized, as opposed to extensive, wall motion abnormalities have a low risk of ACS complications. In addition, echocardiography can help evaluate other causes of clinical presentations mimicking ACS, including valvular heart disease, aortic dissection, pericarditis, mitral valve prolapse, and pulmonary embolus. Finally, echocardiography is an important tool to assess for various complications of AMI, including acute mitral regurgitation, pericardial effusion, ventricular septal and free wall rupture, and intracardiac thrombus formation.

Technical limitations restrict the use of echocardiography in the ED. These include the quality of the study and xpertise of the reader interpreting the study at the patient's bedside. Injury involving more than 20% of the myocardial wall is required before segmental wall motion abnormalities can be detected echocardiographically.[4] In addition, the inability of the two-dimensional echocardiogram to distinguish among ischemia, AMI, or old infarction and potential absence of wall motion abnormality in nontransmural infarctions can further limit the usefulness of two-dimensional echocardiography (Table 68.6).

Stress echocardiography, as opposed to resting echocardiography, can detect CAD and assess cardiac function early after an AMI. This can be performed with graded increases in cardiac workload by standardized exercise or pharmacologic adrenergic-stimulating agents, such as dobutamine. In addition, vasodilating agents, such as dipyridamole and adenosine, induce heterogeneous myocardial perfusion and reveal functional myocardial ischemia in susceptible patients. Stress echocardiography is superior to conventional treadmill testing for CAD in women. Graded dobutamine stress echocardiography assesses myocardial viability and ventricular function within the first few days after an AMI. Clinical studies of patients with nondiagnostic ECGs, negative markers, and negative rest echocardiography have suggested a role for emergency pharmacologic stress echocardiography as a provocative test after a period of observation with at least two marker and ECG assessments in a chest pain or ED observation unit.

Myocardial contrast echocardiography (MCE) uses microbubble ultrasonic contrast agents to assess microvascular perfusion and regional function with echocardiography. MCE evaluation of perfusion and regional function allows accurate risk stratification of ED patients with chest pain and nondiagnostic ECGs, even before serum markers are available. Smaller studies have reported low rates of adverse cardiac events in chest pain patients with normal MCE findings after a nondiagnostic ECG and negative serum markers. The clinical value of MCE in the ED, like that of resting and stress echocardiography, remains uncertain.

Myocardial Scintigraphy (Nuclear Imaging)

Radionuclide tracer injection and scintigraphy, such as with single-photon emission computed tomography (SPECT), allows real-time assessment of myocardial perfusion and function. Technetium-99 sestamibi has a slow redistribution to ischemic myocardium. This property allows immediate injection and imaging, which detects altered distribution consistent with some form of ischemic heart disease, followed by subsequent scanning, which provides more definitive data regarding the particular subtype of ACS. In patients with a normal initial study, the likelihood of ACS is extremely low. In patients with an initial study revealing abnormal distribution (ie, reduced uptake) of the tracer, some form of ischemic heart disease is likely. Subsequent imaging then reveals one of two patterns—normal redistribution (normal uptake) or continued reduced uptake. The redistribution pattern is consistent with active coronary ischemia, and continued reduced uptake is found in patients with MI, remote or recent. Myocardial scintigraphy has promising positive and negative predictive values for cardiac events, with high sensitivity and good specificity for CAD.

Immediate myocardial scintigraphy is useful for detecting ACS and the risk of cardiac events in patients in the ED with atypical chest pain, nondiagnostic ECGs, and low to moderate risk of AMI.

Multiple studies have found a relatively high incidence of cardiac events, presence of AMI, and need for revascularization in patients with a positive nuclear scan. The probability of a cardiac event is tenfold higher in patients with abnormal scans than in patients with a normal scan. The incidence of cardiac events with a normal scan is lower than 1% for the 30-day period after the index study. Myocardial scintigraphy, if available, can reduce the number of patients admitted from the ED with chest pain who are ultimately determined not to have ACS, without reducing appropriate admissions for patients with ACS.

Myocardial scintigraphy, although accurate in establishing the diagnosis and useful in guiding therapeutic and further evaluation strategies, is not always available nor appropriate for use following the ED process of care for many reasons. Radioisotopes and the personnel to administer them may not be immediately available. Emergency clinician interpretation ability is not universal; particular expertise is required. Finally, myocardial scintigraphy of ED perfusion imaging are resting studies, rather than more provocative stress (exercise or pharmacologically induced) perfusion studies.

Coronary Computed Tomography Angiography

Coronary CT angiography (CCTA) imaging is a noninvasive modality to assess for coronary artery disease in the setting of the patient who has been ruled out for AMI and other active forms of ACS. This test has rapidly been gaining popularity as a valuable imaging study in this patient group. In a noninvasive fashion, CCTA provides information similar to that obtained from cardiac catheterization; cardiac catheterization, of course, is still considered the gold standard of cardiac imaging, but its position is being challenged by CCTA.[33,34]

The emergency clinician must, however, understand the two basic applications of CT scanning in the patient with possible CAD, cardiac CT scanning and CCTA. Cardiac CT was introduced over 2 decades ago to screen for coronary calcium as a marker of underlying atherosclerotic heart disease and risk of ACS, largely in asymptomatic individuals. Whereas there are calcium scoring systems that assess cardiovascular disease risk, few studies have examined the role of standard cardiac CT in the assessment of patients with acute chest pain suspected of having experienced an ACS. Currently, standard cardiac CT is, at best, a screening tool for the presence of CAD and likely has little applicability in the ED.

The other modality of CT scanning in the patient suspected of CAD is coronary CT angiography, or CCTA. CCTA is used primarily in the evaluation of patients with acute chest pain and those with chronic chest pain; in both settings, the study is performed to assess for CAD.[35] This imaging modality has potential application in the ED population for the patient with acute chest pain, most appropriately after some form of rule-out MI process, including serial assessments using examination, electrocardiography, and biomarkers. When considering the presence or absence of CAD, CCTA is accurate in the detection of coronary artery obstructive lesions. For example, in a large meta-analysis of appropriate studies, the accuracy for significant coronary artery obstructive lesions was very high, assuming that high-resolution, newer generation CT is used.[36] Figs. 68.23A and B illustrate representative CCTA images demonstrating normal coronary anatomy; see Figs. 68.23C to E, which illustrate CCTA images with proximal left anterior descending (LAD) artery occlusion.

In symptomatic stable patients with low to intermediate pretest probability of CAD, CCTA is a very appropriate imaging study. CCTA is accurate, not only for the detection of significant coronary obstructive lesions but also the prediction of outcome. For example, a negative CCTA shows a very high negative predictive value of significant CAD and very low rate of a subsequent adverse event.[37] In a multicenter study of patients seen in the ED with symptoms suggestive of ACS, the addition of CCTA into the evaluation strategy improved ED throughput, with a reduction in length of stay and reduced rate of admission.[37] In this same study, an increase in outpatient testing was noted, ultimately resulting in no reduction in overall costs. A meta-analysis of four randomized controlled trials demonstrated similar findings, with reduced ED length of stay balanced by an increase in the use of invasive coronary angiography and revascularization.[38]

The issue of radiation must also be considered in this study application. Newer testing CCTA modalities are associated with markedly lower doses of radiation. CCTA can be used with relatively smaller exposures to radiation, ranging from 2.0 to 5 mSv. For reference purposes, standard CT scanning and cardiac catheterization are associated with the following approximate radiation doses—9 mSv and 12 mSv, respectively.

Thus, in the ED population suspected of ACS, CCTA can be used in patients with low to intermediate suspicion for CAD after some form of ACS evaluation. This testing modality is accurate with respect to the identification of significant CAD and prediction of adverse events related to ischemic heart disease. The test requires significant expertise with respect to interpretation, whether by a radiologist or cardiologist. When used with newer testing modalities, it is associated with much lower radiation exposure. Although calcium scoring is not considered a useful testing modality in the ED population, calcium scoring may be considered when CCTA is performed. In general, a higher calcium presence in the coronary arteries is associated with less accuracy with the use of CCTA for the demonstration of significant CAD. CCTA can reduce ED evaluation time and admission rate at the expense of slightly greater use of additional, outpatient cardiac testing, such as cardiac catheterization.

Observation Unit Evaluation

The process of evaluation of the chest pain patient suspected of ACS occurs through three distinct phases of care (Fig. 68.24), including the STEMI recognition, rule-out ACS, and consideration of significant CAD. In the first phase, STEMI is the primary consideration; rapid performance of the 12-lead ECG is important so that STEMI is recognized with activation of appropriate ED- and hospital-based resources. The second phase is the traditional rule-out MI period, in which the patient is monitored clinically along with serial ECGs and serum markers. The evolution of STEMI as well as the diagnosis of NSTEMI and significant ACS will be made here. In the final phase of evaluation, the consideration of significant CAD, is applied. Multiple appropriate pathways exist for this last goal. In fact, it can be accomplished in the ED or after ED discharge with outpatient follow-up. This last task can be accomplished during the initial ED presentation or later at follow-up; most appropriately, the stable patient is further evaluated after ED discharge by the primary care physician or consulting cardiologist on an outpatient basis. Unstable patients or patients with concerning findings during the ED evaluation should be considered for admission to the hospital for further care.

This process of care can occur in the ED or an ED-based observation unit. The concept of an observation unit can be a physical location with a specified area of the ED or a virtual concept with its abilities applied anywhere in the ED with appropriate monitoring and treatment capability.

Specialized units for the lower risk population are used in one-third of EDs in the United States. The goal of the chest pain center (CPC) is to provide an integrated approach to patients with chest pain or potential ACS that includes rapid triage, early identification, evaluation, and treatment of low-risk ACS patients. Guidelines and clinical pathways play an essential role in the CPC

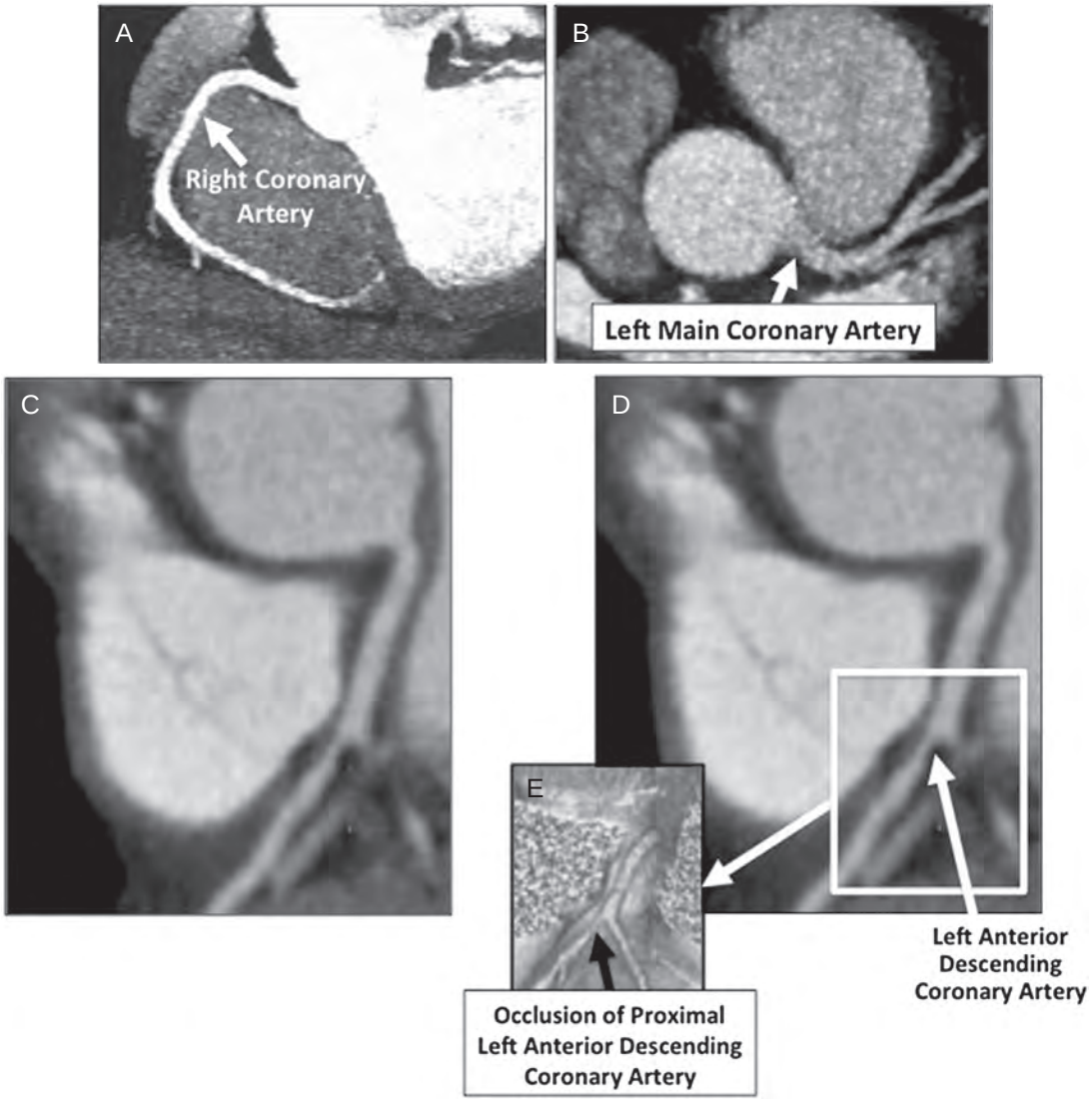
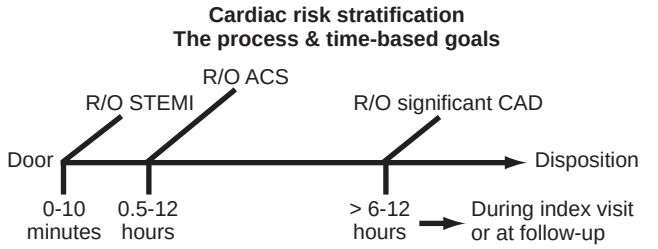


Fig. 68.23. Coronary CT angiography. **A,** Normal right coronary artery. **B,** Normal left main coronary artery. **C,** Left anterior descending coronary artery (LAD) with proximal obstruction. **D,** Labeling of LAD obstruction. **E,** Three-dimensional image of LAD obstruction.



Time period	Goal	Tools
0 to 10 min	STEMI identification	Focused exam & ECG
0.5 to ~6-12 hrs	ACS identification	Serial exam, ECG, & biomarkers
>~6-12 hrs	CAD identification	Potential cardiac imaging

Fig. 68.24. The process of evaluation of the chest pain patient suspected of acute coronary syndrome (ACS) occurs through three distinct phases of care, including ST segment elevation myocardial infarction (STEMI) recognition, rule-out (R/O) acute coronary syndrome (ACS), and consideration of significant coronary artery disease (CAD) phases.

process. Staff, resources, and space are often dedicated for a CPC, but the unit can be part of an ED observation unit or a virtual decision unit located near or within the ED. By virtual, it is meant that the process of a rule-out MI can be performed in an appropriate ED bed location and not require a specific geographic location in the ED.

A CPC protocol should rapidly direct patients with possible ACS into an appropriate treatment area where electrocardiography and a clinical examination can be performed within the first 10 minutes. Patients with STEMI who require immediate reperfusion therapy, with UA who need further intervention, or are experiencing other cardiorespiratory complications of ACS can be identified quickly. This goal can be combined with an efficient ED evaluation of patients with a low to moderate risk of ACS. The greatest medical benefit from the CPC is the early identification of patients with ACS, particularly STEMI; the most significant financial impact is the reduction of low-yield hospital admissions.

There are multiple CPC models, but all emphasize expedited assessment and initiation of ACS care. The benefit of this standardization is magnified when we look at time-sensitive care, such as a target door to drug time of less than 30 minutes or a door to balloon time of less than 90 minutes (where percutaneous

procedures are available) for patients with typical and uncomplicated presentations of STEMI. The CPC may have assigned nursing personnel who rapidly evaluate the patient with chest pain with a 12-lead ECG, as well as screening vital signs and cardiac monitoring, and deliver the ECG directly to an emergency clinician capable of making a decision about activation of the catheterization laboratory or administration of fibrinolytic therapy.

The CPC may also be used as an observation and evaluation unit where patients with chest pain and a low to intermediate clinical likelihood of ACS can be monitored with electrocardiography, ST segment trending, serial 12-lead ECGs, and sequential serum markers. In addition, many CPCs now use further ACS evaluation with stress testing, echocardiography, or myocardial scintigraphy before disposition. Significant cost savings occur through the expedited evaluations and avoidance of unnecessary admissions, with typical charges and actual costs ranging from 20% to 50% of the costs for the usual inpatient approach. Previous studies have prospectively compared a CPC with the traditional hospital admission to rule out MI and showed a reduction in hospital admissions by almost 50%, with no adverse events in CPC patients with a negative stress test.

A chest pain–accelerated diagnostic protocol approach to low- to intermediate-risk patients can be feasible, safe, and effective. Many accelerated diagnostic protocols have been validated to shorten the length of ED evaluation needed in the lower risk patient populations and, as troponin assays have increased in sensitivity, the length of time of serial testing has decreased dramatically in these protocols. The HEART Pathway Randomized Trial has demonstrated that the use of a clinical decision tool—the HEART score—plus troponin measurements at 0 and 3 hours was safe and effective in ACS evaluation in patients presenting to the ED with ACS-associated symptoms without ST elevation on the ECG. The HEART Pathway has demonstrated shorten length of stays, increased early discharges, a trend toward decreased objective cardiac testing at 30 days, and no adverse cardiac events in the early discharge group at 30 days of follow-up.[39]

Approximately 80% of patients with chest pain can be safely evaluated in the ED with ultimate discharge to home. The resources required for a successful CPC-based operation, in which patients undergo rapid exclusion of ACS through serial testing, continuous monitoring, and immediate provocative stress testing, are considerable. Although studies have suggested that CPCs decrease the number of admissions, they may increase the number of patients seen in the ED for chest pain, and emergency clinicians may overuse the CPC-accelerated diagnostic protocol approach in patients whom they would otherwise have discharged.

MANAGEMENT

An understanding of the pathophysiology of ACS allows the emergency clinician to select the most appropriate therapies for the ACS patient. ACS pathophysiology includes the following: (1) endothelial damage through plaque disruption, irregular luminal lesions, and shear injury; (2) platelet aggregation; (3) thrombus formation causing partial or total lumen occlusion; (4) coronary artery vasospasm; and (5) reperfusion injury caused by oxygen free radicals, calcium, and neutrophils. In patients with noninfarction ACS, spontaneous fibrinolysis of the thrombus occurs rapidly, minimizing ischemic insult; persistence of the occlusive thrombus, however, often results in more serious forms of ACS, including NSTEMI and STEMI.

Time-Sensitive Nature of Acute Coronary Syndrome Therapy

Early patency resulting in myocardial salvage is the key benefit of emergent reperfusion therapy, using fibrinolysis or PCI. Timely treatment within the first hours after symptom onset may result in substantial, if not complete, myocardial salvage. Delivered later, from 2 to 12 hours after STEMI onset, treatment may result in a more modest, but significant, benefit. The opening of the occluded artery causes less adverse ventricular modeling, reduces occurrence of ventricular aneurysm, increases blood flow to the myocardium, and improves electrophysiologic stability. It has been well established that preserved left ventricular function and mortality at the 24-hour and 30-day endpoints are directly related to angiographic patency at 90 minutes. The relationship between rapid revascularization and mortality has been clearly demonstrated, and it has been shown that with each additional 30 minutes of delay to PCI, the relative 12-month mortality risk increases by 7.5%. Fig. 68.25 depicts the relationship between time to reperfusion and benefit in STEMI.

Prehospital delay factors occur from the time the patient decides to seek medical attention until the patient arrives at the ED. It is not uncommon for patients to delay treatment significantly by calling their primary care physician, attempting to transport themselves or waiting for transport by other nonmedical professionals. For slightly less than 50% of patients with suspected AMI, the EMS system is the point of first medical contact.[40] Wide variations in the availability of EMS systems and their varied levels of integration into their local ED and hospital ACS identification and evaluation processes can further complicate and delay care. EMS system resource is related to patient care ability; in systems with advanced and robust local resource, very comprehensive state of the art care is possible.[41]

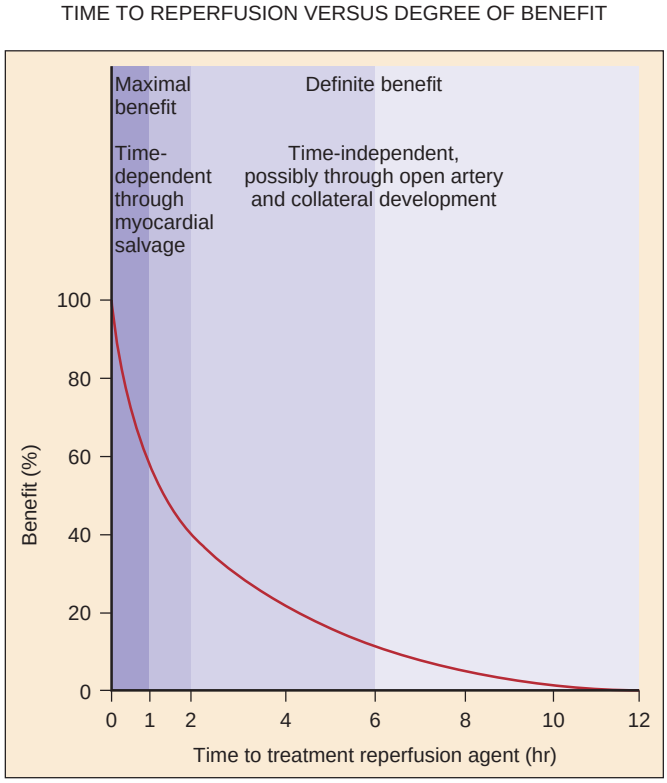


Fig. 68.25. Relationship between time to reperfusion and benefit STEMI This figure depicts combined human and animal data and represents the time-dependent benefit anticipated, depending on the length of the interval between coronary artery occlusion and reperfusion. (Adapted from Tiefenbrunn AJ, Sobel BE: Timing of coronary recanalization. Paradigms, paradoxes, and pertinence. Circulation 85:2311, 1992; and from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute [NIH Publication No. 93-3278], September 1993, p 8. Copyright ©1992 American Heart Association.)

Further delays can occur between the time a patient arrives at the hospital and initiation of acute revascularization therapy. Although studies have shown that the average time to fibrinolysis ranges from 45 to 90 minutes, the AHA recommends that all patients with STEMI receive fibrinolytic therapy within 30 minutes of arrival or undergo primary PCI (ie, device across the culprit artery) no later than 90 minutes after arrival.[6]

STEMI patients who receive hospital-based reperfusion therapies (eg, fibrinolytic agent, PCI) progress through a sequence of steps that can define process time points. Within each interval, various impediments to timely care can occur. Reducing delay times is applicable to all time points in the ED by addressing the four Ds: ***d***oor (events before arrival at the ED), ***d***ata (obtaining the ECG), ***d***ecision (arriving at the STEMI diagnosis and deciding on therapy), and ***d***rug (administering the fibrinolytic agent or passing the angioplasty catheter across the culprit lesion for PCI candidates).[42]

Prehospital notification to the ED of the impending arrival of a patient with a suspected STEMI, particularly when ST segment elevation is suspected, has become standard practice in many established EMS systems. A field 12-lead ECG may assist in diagnosis and decrease the reperfusion time by initiating the hospital-based sequence of necessary events to occur in parallel, as opposed to serially. Some systems have been able to bypass the ED in selected prehospital notifications of STEMI, and these patients go directly from the ambulance to the CCL for PCI. Although these systems have shown significant decreases in door to reperfusion times, however, they were unable to demonstrate any improvement in clinical outcomes, including mortality.[43]

Self-transported patients with possible ACS should be evaluated by the triage nurse immediately and an ECG acquired within 5 to 10 minutes of arrival. The development of hospital-based protocols and system response plans for identifying and rapidly treating patients reduces the amount of time to treatment. When using fibrinolysis in uncomplicated cases, the emergency clinician should activate the hospital-based system for reperfusion. Checklists of inclusion and exclusion criteria for fibrinolytic therapy should be available, and those fibrinolytic agents should be stored and administered in the ED. In a system in which fibrinolysis is the sole reperfusion therapy, the decision to administer that therapy rests solely with the emergency clinician. Nonconsultative communications with family physicians, internists, or cardiologists before administration of the agent may result in unnecessary delays. Consultative discussions should only be required in complicated situations before the administration of therapy.

If the hospital offers primary PCI, many hospitals activate so-called STEMI alert responses when an STEMI patient is identified prehospital or in the ED. Analogous to the trauma alert, the cardiologist and catheterization laboratory personnel are immediately mobilized. Prehospital or emergency clinician activation of the catheterization laboratory demonstrates very high rates of accurate STEMI diagnosis, with very low rates of false activation (ie, the STEMI mimicker) while markedly reducing the time to definitive therapy.[43-45] Interhospital transfer of STEMI patients for PCI when they are also candidates for fibrinolysis should be discouraged if definitive therapy (ie, catheter placement across the culprit lesion) is likely to be delayed beyond 120 minutes, except in cases of hemodynamic shock (see later) or in patients for whom fibrinolysis is contraindicated.[7]

Pharmacologic Intervention

A range of medications can be used in the patient with ACS (Table 68.7). These agents range from the basic to the complex, including oxygen, IV fluids, antiplatelet and anticoagulant agents, nitroglycerin, opioid analgesics, β-adrenergic blocking agents, and fibrinolytic agents.

TABLE 68.7

Medications Used in Emergency Department Management of Acute Coronary Syndrome (ACS)

MEDICATION AND MEDICATION CLASS	EXAMPLES	INDICATIONS	RISK ISSUES
Nitroglycerin	Nitroglycerin (sublingual, topical, IV)	Chest pain, pulmonaryedema medication, blood pressure medication	Hypotension
Opiates	Morphine, fentanyl	Chest pain	Hypotension, respiratory suppression
β-ADRENERGIC BLOCKERS			
• IV	Metoprolol, labetalol, esmolol	Blood pressure agent, dysrhythmia agent	Hypotension, bradycardia, cardiogenic shock
• Oral	Metoprolol	None; inpatient use	
ACE inhibitors	Captopril, enalapril, lisinopril, ramipril	None; inpatient use	
Statins	Lovastatin, atorvastatin, simvastatin, pravastatin	None; inpatient use	
Calcium channel blockers	Diltiazem	None; inpatient use	
Aspirin	Aspirin	Chest pain	Hemorrhage, gastric irritation
Other antiplatelet agents	Clopidogrel, ticagrelor, prasugrel, ticlopidine	ACS (with objective confirmation)	Hemorrhage
Antithrombin agents	Heparin, enoxaparin, bivaliruden	ACS (with objective confirmation)	Hemorrhage, heparin-induced thrombocytopenia (for heparins)
Fibrinolytic agents	Streptokinase t-PA r-PA Tenecteplase	STEMI	Hemorrhage

Oxygen

Oxygen is considered a medication, a medication with significant potential to benefit and harm the patient with ACS. A brief mention of the most appropriate strategy for oxygen treatment in the ACS patient is warranted. Respiratory compromise can occur during ACS, usually as a result of acute pulmonary edema or chronic pulmonary disease. Suspected ACS patients with respiratory distress, demonstrated by physical examination and/or oxygen saturations, should receive supplemental oxygen as standard therapy. The rationale for this standard oxygen therapy is that maximization of oxygen saturation may improve the delivery of oxygen to the tissues and thus reduce the ischemic process and related negative outcomes.

There is limited evidence regarding the use of supplemental oxygen therapy in the suspected ACS patient with normal oxygen saturation and no other evidence of respiratory compromise. The practice of administering oxygen to all patients, regardless of their oxygen saturation, is based on rational conjecture and research performed prior to the current reperfusion era in acute coronary care. More recent studies of this issue are limited[46] but have suggested that excessive oxygen therapy can increase the rate of adverse outcome in the ACS patient, particularly involving STEMI. Hyperoxia, developing as a result of excessive supplemental oxygen therapy, can potentiate coronary vasoconstriction and increase oxidative stress, worsening outcome in these patients.[47] Recently, the AVOID trial demonstrated that oxygen therapy, delivered to patients suspected of STEMI who also had normal oxygen saturations and no other evidence of respiratory compromise, likely increased early myocardial injury and was associated with a larger size of the infarction. Furthermore, re-infarction and cardiac dysrhythmia were also increased in the oxygen therapy group.[47] In other patient groups, such as resuscitated cardiac arrest patients, hyperoxia has been associated with worse outcomes as compared with normoxia.

Thus, in suspected or confirmed ACS patients, supplemental oxygen therapy is appropriate for patients demonstrating respiratory compromise, noted by physical examination or oxygen saturations less than 94%. Conversely, in patients without respiratory compromise, oxygen therapy can be withheld.

Nitroglycerin

Nitrates decrease myocardial preload and, to a lesser extent, afterload. Nitrates increase venous capacitance and induce venous pooling, which decreases preload and myocardial oxygen demand. Direct vasodilation of coronary arteries may increase collateral blood flow to the ischemic myocardium.

Nitroglycerin has been used for decades in patients with suspected or known ACS. Most studies of IV NTG in the setting of ACS, however, are from the prefibrinolytic era. Although the data from multiple trials originally noted a 35% mortality reduction with IV NTG in the setting of AMI, this study preceded the modern era of aggressive reperfusion therapies coupled with potent anticoagulant and antiplatelet agents. No contemporary evidence (ie, in the reperfusion era of acute cardiac care) has shown improved outcomes with the routine use of any form of nitrate therapy in patients with AMI. In the ACS patient, it must be noted that the use of NTG in any formulation is another management option, yet its use is not mandatory. In situations in which hypoperfusion is present or is anticipated to occur, it is very appropriate to withhold NTG in all formulations.

Patients with possible ACS and a systolic blood pressure greater than 90 mm Hg can receive a sublingual NTG tablet (0.4 mg [400 μg]) on presentation. If symptoms and pain are not fully relieved with three sublingual tablets, IV NTG can be considered. With bradycardia, hypotension, inferior wall STEMI, and right ventricular infarction, a sudden decrease in preload associated with NTG can result in profound hypotension. An initial infusion rate of 10 μg/min is titrated to pain symptoms. The emergency clinician can increase the infusion at regular intervals, allowing a 10% reduction in the mean arterial pressure if the patient is normotensive and a 20% to 30% reduction if hypertensive.

Morphine and Other Opioid Analgesic Agents

Morphine is a potent opioid analgesic with weak sympathetic blockade, systemic histamine release, and anxiolysis. If a patient with possible ACS is unresponsive to NTG or has recurrent symptoms despite maximal antiischemic therapy, administration of morphine sulfate is a reasonable analgesic. The relief of pain and anxiety decreases oxygen consumption and myocardial work. Some vasodilatory effects are also noted with preload reduction. Standard doses of morphine sulfate are 2 to 4 mg IV, repeated every 5 to 30 minutes as necessary. Caution is advised with morphine use in this setting. Although appropriate, it must be remembered that morphine is a potent medication with significant vasodilatory effects and profound sedation, with respiratory depression. In addition to allergic reactions, the most significant adverse effect of morphine sulfate administration is hypotension, which is managed with IV crystalloid as a bolus. Its use in modest amounts is reasonable. In addition to its analgesic properties, it is also an anxiolytic agent, a valuable feature in certain ACS patients. Withholding morphine and other analgesic agents is not inappropriate if the emergency clinician is concerned about the potential for iatrogenic hypoperfusion, sedation, or respiratory depression.

Other opioid agents, such as fentanyl, are reasonable for use in the ACS patient. The same caveats and general recommendations apply with other opioid agent administration in the ACS patient.

β-Adrenergic Blockers

Historically, β-adrenergic blocking agents have been effective in ameliorating catecholamine-induced tachycardia, including ventricular fibrillation, increased contractility, and heightened myocardial oxygen demand during the infarction period. Although beta blockade was shown to decrease mortality for patients with AMI, these observations occurred when adjunctive therapies were few and β-adrenergic blockade was essentially monotherapy in AMI. Contemporary management strategies include highly effective reperfusion therapies coupled with potent anticoagulant and antiplatelet agents; thus, their widespread use must be reconsidered.

Multiple studies have suggested that the widespread intravenous use of β-adrenergic blockade should be reconsidered. The use of the early IV β-adrenergic blocking agents in these studies was associated with higher rates of death, heart failure, cardiogenic shock, recurrent ischemia, and pacemaker use as compared to patients who received early oral administration. These increases occurred despite the exclusion of patients with obvious contraindications, including preexisting hypotension, bradycardia, or heart failure. Large studies followed that evaluated patients with suspected STEMI, comparing early IV β-adrenergic blocking agent use followed by continued oral therapy versus placebo. These studies found no significant difference between the two groups in terms of mortality; however, the group receiving β-adrenergic blockers demonstrated a minimal reduction of re-infarction and ventricular fibrillation. This was at the expense of a significantly higher rate of cardiogenic shock and increased rates of development of heart failure requiring treatment, persistent hypotension, and bradycardia..

The early IV use of β-adrenergic blocking agents, when coupled with contemporary therapy in the setting of ACS, does not appear

to offer significant benefit and is associated with an increased rate of adverse events. Therefore, their IVs use in the ED in the ACS patient is discouraged. Conversely, oral administration to ACS patients without contraindications during the first 24 hours of management is a class I recommendation from the ACC/AHA and can be accomplished after admission has occurred. This strategy allows for stabilization of the patient while additional clinical data are obtained to determine appropriateness of this therapy.[5] Empirical therapy in the ED, however, should be reserved for only those patients who have adverse effects from significantly elevated blood pressure or significant tachydysrhythmia, despite application of other appropriate medications.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitor agents benefit patients with CHF. ACE inhibitors may also reduce morbidity and mortality after AMI. In particular, patients treated with ACE inhibitors experience a reduction in cardiovascular mortality, decreased rates of significant CHF, and fewer recurrent AMIs. These benefits increase when ACE inhibitors are used in conjunction with other agents, such as aspirin and fibrinolytic agents. The mechanism of action regarding a reduction in recurrent AMI is unknown but may involve a reduction in plaque rupture related to decreased intracoronary shear force or neurohumoral influences. Therapy should be initiated within the first 24 hours following an ACS event, although ED administration is not indicated.[5]

HMG–Coenzyme A Reductase Inhibitors (Statins)

A number of investigations have demonstrated a reduction in inflammation and reinfarction, angina, and lethal arrhythmia with the administration of statin drugs in the first few days after an ACS event. Although there is no indication for statin therapy in the ED management of ACS, initiation of this therapy should occur within the first 24 hours[5] or should continue if patients are already undergoing statin therapy, because discontinuation during hospitalization is associated with an increase in near-term mortality and adverse events. The administration of statin therapy before elective or urgent PCI for ACS is reasonable to decrease the incidence of a periprocedural AMI; however, there are no specific risk or safety data regarding its use in this setting.

Calcium Channel Blockade

As with beta blockade, the primary benefit of calcium channel blockers appears to be in regard to symptom resolution. Unfortunately, these agents may be accompanied by a significant vasodilatory effect, resulting in hypotension and potentiation of the coronary ischemic process. Like beta blockers, calcium channel blockers have a substantial negative inotropic effect. AV nodal blockade is also a significant side effect that may be exacerbated in patients previously treated with beta blockers or with ischemia-related conduction disturbance. Unless specifically used for rate control of supraventricular dysrhythmia in a patient who cannot tolerate beta blockade, calcium channel blocker agents have no role in the ED management of ACS.

Antiplatelet Therapy

In non-AMI ACS patients (ie, unstable angina), dramatic reductions in the progression to acute infarction are noted with appropriate antiplatelet therapy. The administration of antiplatelet therapy, particularly aspirin, is indicated in the ED for most ACS patients. For AMI, the administration of aspirin and other antiplatelet agents is associated with significant reductions in mortality, ranging from 25% to 50%.

Aspirin. Aspirin, the prototypical antiplatelet agent, is the most cost-effective treatment in ACS care. It irreversibly acetylates platelet cyclooxygenase, thereby removing all activity for the life span of the platelet (8–10 days). Thus, aspirin stops the production of proaggregatory thromboxane A2 and is an indirect antithrombotic agent. Aspirin also has important nonplatelet effects because it inactivates cyclooxygenase in the vascular endothelium, thereby diminishing the formation of antiaggregatory prostacyclin.

It is well established and accepted that aspirin independently reduces the mortality of patients with AMI without fibrinolytic therapy (overall 23% reduction) and is synergistic when used with fibrinolytic therapy (42% reduction in mortality). The usual dose is 324 mg of non–enteric-coated aspirin, chewed and swallowed. Enteric-coated aspirin should be avoided in the acute setting of ACS due to delays in the onset of antiplatelet activity.[48] The administration of aspirin in the ED is strongly recommended immediately on identification of any patient with suspected ACS, either UA or AMI. It should be administered to all such patients unless significant allergy, hemorrhage, or other issues, such as a potential aortic dissection, contraindicates its use. More recent studies have established that lower dose aspirin (<162 mg) appears to be as effective as higher dose aspirin (>162 mg) at preventing adverse cardiac events, with fewer bleeding risks. These findings were consistent when given alone or with other antiplatelet agents (eg, clopidogrel).

Glycoprotein IIb/IIIa Receptor Inhibitors. Glycoprotein IIb/IIIa receptor inhibitors (GPIs) are potent antiplatelet agents; they include abciximab, eptifibatide, and tirofiban. GPIs, however, demonstrate clinical usefulness in only a subset of ACS patients, those undergoing PCI as a reperfusion strategy. Therefore, the primary indication regarding GPI administration is planned mechanical coronary intervention. Furthermore, the largest studies on GPI administration timing have not shown outcome benefit to upstream use in the ED when compared to catheterization laboratory administration. Currently, there is no clear indication for the ED administration of GPIs unless other antiplatelet agents are not tolerated or unavailable. This class of medications is not standardly given in the ED setting, and other antiplatelet agents (PSY_{12} receptor inhibitors) are preferred for upstream administration in the care of ACS.[5]

Numerous trials have demonstrated the effectiveness of these agents in the subset of ACS patients who are managed with PCI, with or without an intracoronary stent. These trials have consistently shown reduced mortality, need for subsequent revascularization, and recurrent ischemia, although at the cost of an increase in hemorrhagic complications.

Multiple studies evaluating GPI use in ACS patients have concluded that patients who undergo PCI benefit markedly from GPI administration. In ACS patients managed medically, without mechanical revascularization, consistent benefit with GPI therapy is not found with the use of direct outcome measures or secondary markers of successful reperfusion, and hemorrhagic complications are increased.

The benefits of GPI therapy were established mainly before the development of contemporary invasive strategies, raising questions about the timing (ie, upstream initiation in the ED) when combined with other antiplatelet therapies. Although initially small preliminary studies have shown promise for upstream GPI administration, larger trials have not supported their routine use in the ED. Evidence supports a highly selective strategy for the use of GPIs that balances ACS risk in the treatment of a patient with dual-agent platelet inhibition and planned PCI versus the potential bleeding risk. GPIs consistently demonstrate benefit in ACS patients treated with urgent mechanical revascularization; in other groups of ACS patients, such as medically managed patients,

patients receiving a combination fibrinolytic agent, or transferred patients, an invariable positive effect has not been established.

PSY_{12} Receptor Inhibitor Agents. The thienopyridines ticlopidine, clopidogrel, and prasugrel are more potent platelet inhibitors than aspirin. They inhibit the transformation of the PSY_{12} receptor into its high-affinity ligand-binding state, irreversibly inhibiting platelet aggregation for the duration of the life of the platelet. Ticlopidine has nonlinear kinetics and, with repeated administration, reaches a maximal effect after 8 to 11 days of use. Clopidogrel, a ticlopidine analogue, and prasugrel have the advantage of a rapid onset of action.

Clopidogrel has traditionally been the preferred ED agent of this class due to its relatively rapid onset of action, improved safety profile, and proven efficacy when given upstream and in association with thrombolytic therapy. Prasugrel incurs a higher bleeding risk than clopidogrel, in patients older than 75 years, those who weigh more than 60 kg, those who have had a previous transient ischemic attack (TIA) or stroke, and those at high risk for bleeding. The ACCOAST trial showed no improvement in outcomes for patients treated with prasugrel in the ED versus dosing at the time of PCI. Because of this and other similar studies, prasugrel is not recommended for upstream use in the ED in ACS patients.[49] Ticlopidine is associated with a risk of neutropenia, thrombotic thrombocytopenic purpura, and agranulocytosis; furthermore, it demonstrates a much slower onset of platelet inhibition. With clopidogrel, maximal platelet inhibition occurs after 3 to 5 days of clopidogrel therapy with 75 mg daily; an earlier onset of platelet inhibition is seen when a higher loading dose is used (300–600 mg). For example, there is clear benefit to clopidogrel administration (300 mg loading dose) at least 6 hours before PCI in patients with STEMI; higher doses (eg, 600 mg) demonstrate a trend toward improvement at slightly earlier time periods (ie, 3–4 hours).

Ticagrelor, a nucleoside analogue, also acts as a PSY_{12} receptor inhibitor, however, via a different mechanism not requiring hepatic activation. It is rapidly absorbed, reaching peak serum concentration at 2.5 hours. Clinical data have demonstrated that ACS patients given ticagrelor were less likely to die from cardiovascular causes, but these improved outcomes are tempered by higher rates of nonprocedure-related bleeding, including more frequent fatal intercranial hemorrhage when compared with clopidogrel administration. Further analysis of the PLATO study has assessed the increased cost of ticagrelor versus clopidogrel when combined with aspirin and determined that with the increased life expectancy, ticagrelor plus aspirin is a "good value for the money."[50]

Cangrelor, an IV PSY_{12} receptor inhibitor, has potential for significant therapeutic advantages over the other drugs in this class due to its immediate onset of antiplatelet activity and very short half-life. It is administered IV in its active form (unlike clopidogrel), not as a prodrug requiring metabolism prior to its onset of action. Unlike the oral drugs in this class, which that require 2 to 6 hours to reach active levels, cangrelor is active immediately on injection. This has potential benefits in patients who are undergoing rapid PCI—specifically, the STEMI population with an invasive management plan. Cangrelor also has a very short half-life (4–6 minutes), which makes the treatment of potential CABG patients with a PSY_{12} receptor inhibitor possible up until the time of surgery. Initial studies have shown the ability to maintain low levels of platelet activity in the presurgery time period on cangrelor, compared to the recommended 5 days off of medication with the oral PSY_{12} receptor inhibitors, without an increase in major bleeding in CABG patients.[51] Cangrelor also appears to have the potential for improved outcomes in patients undergoing PCI when compared to current antiplatelet therapy.[52] The drug is currently seeking US Food and Drug Administration (FDA) approval, after rejection in 2014 due to mixed results in previous clinical trials. Cangrelor received a favorable vote for limited indications from the FDA in April 2015 and may be available for clinical use in the near future.

In accordance with the 2013 AHA Guidelines for STEMI management, patients should receive a loading dose of clopidogrel or ticagrelor in addition to standard ACS care (ASA, anticoagulants, and reperfusion therapy), assuming there are no contraindications to its use, prior to PCI (upstream).[6] For patients with definite or likely NSTEMI, in accordance with the 2014 AHA guidelines for NSTEMI management, the administration of a PSY_{12} receptor inhibitor should also be initiated upstream in the ED prior to PCI.[5]

Another indication for the ED administration of clopidogrel is the patient with a high-risk ACS presentation who is truly allergic to ASA (ACC/AHA class I indication).[5] This high-risk presentation would be characterized by objective clinical abnormality, including a significantly abnormal serum marker or 12-lead ECG. Considerations include the ultimate treatment strategy chosen (ie, medical vs. invasive) and the time to angiography if an invasive plan is selected. ACS patients managed medically (ie, noninvasively) or invasively with coronary angiography deferred to a later time are the most appropriate potential candidates for clopidogrel. In the patient selected for invasive management, the time to the procedure is a primary issue in considering clopidogrel; patients undergoing early angiography, within 6 hours, are less likely to derive significant benefit, whereas deferred catheterization likely will gain advantage.

In the patient with UA or NSTEMI, clinical benefit is confirmed in UA patients when treated with clopidogrel in a noninvasive strategy scenario, with an increase in the incidence of major hemorrhage. As noted, invasively managed patients receiving the drug with less time to procedure performance do not benefit from such treatment. The NSTEMI patient demonstrates improved outcome with clopidogrel therapy when a conservative treatment scenario is initially followed. Of note, a large portion of these patients will undergo PCI within the first 24 hours after admission; however, this so-called delayed PCI allows for benefit to occur from clopidogrel administered earlier in the course of management.

The STEMI patient who is managed medically (ie, with a fibrinolytic agent) will also benefit from clopidogrel use. Clopidogrel therapy in conjunction with fibrinolysis, followed by deferred cardiac catheterization occurring at least 2 days after AMI—clearly beyond the 6-hour window—decreases the rates of death, recurrent ACS, and urgent coronary revascularization. This improvement occurs without a significant increase in hemorrhage.

The potential need for urgent CABG should also be strongly considered. The higher risk ACS patient will more likely benefit from PSY_{12} receptor inhibitor therapy, but that same patient is also more likely to need urgent CABG. It is not possible, however, to identify ACS patients requiring urgent CABG reliably. Previous registries have shown that as many as 14% of ACS patients will undergo CABG, a reasonably frequent rate of surgical intervention; most centers, however, report a 2% to 5% incidence of coronary surgery. Reviews of ED ACS patients have been unable to demonstrate one or a combination of clinical features apparent in the ED that reliably identify patients not requiring CABG. It is interesting and important to note that although these CABG patients had a greater incidence of bleeding perioperatively, outcomes were not statistically different in clopidogrel versus placebo groups in this surgical subset. It is likely that as the cardiovascular surgeon gains more experience with PSY_{12} receptor inhibitor administration, and as other alternatives such as cangrelor become available for perioperative therapy in the CABG patient, this concern will continue to decrease.[53]

The ACC and AHA have suggested, in the form of a class I recommendation, that clopidogrel or ticagrelor should be

withheld for at least 24 hours before urgent on-pump CABG, if possible.[5] If CABG is performed within 5 days of clopidogrel use, patients have increases in the following: incidence of operative and postoperative hemorrhage; need for transfusions; need for reoperation for hemostasis; and postoperative mortality. Nevertheless, the recommendation suggests that early PSY_{12} receptor inhibitor therapy be considered in patients who likely will not require CABG.[5] In that it does not appear possible for the emergency clinician to predict reliably which patients will require urgent CABG, collaborative multidisciplinary pathways should be developed, with emergency clinicians,, cardiologists, and cardiovascular surgeons providing input.[54]

Antithrombins

As with antiplatelet therapies in ACS patients, significant reductions in the progression to acute, recurrent, or extensive infarction and death are noted in individuals treated with aggressive antithrombin therapy. There are currently four options for antithrombin therapy in the setting of ACS, including unfractionated heparin (UFH), LMWH, direct thrombin inhibitors (bivalirudin), and factor Xa inhibitors (fondaparinux). Antithrombotic therapy is indicated for ACS patients with recurrent anginal pain, AMI (NSTEMI and STEMI), a significantly positive serum marker, and a dynamic 12-lead ECG.

Heparins. The term *heparin* refers not to a single structure but to a family of mucopolysaccharide chains of varying lengths and composition—hence, unfractionated—with pronounced antithrombotic properties. At standard doses, UFH binds to antithrombin III, forming a complex that is able to inactivate factor II (thrombin) and activate factor X. This prevents the conversion of fibrinogen to fibrin, thus preventing clot formation. Heparin by itself has no anticoagulant property. This indirect effect on thrombin inhibits clot propagation; it prevents heparin, however, from having any effect on bound thrombin in a thrombus. UFH also assists in the inactivation of factors XIa and IXa through antithrombin and interacts with platelets.

UFH has a profound synergistic effect with aspirin in preventing death, AMI, and refractory angina in ACS patients, particularly those with AMI and, to a lesser extent, high-risk UA. UFH should be administered early in patients with the following ACS features: recurrent or persistent chest pain, AMI, positive serum marker, and a dynamic ECG. In patients receiving thrombolytic therapy and UFH, it has been shown that bleeding and mortality were higher in patients receiving an 80-unit/kg bolus and 18-unit/kg infusion compared with patients with a lower bolus amount and infusion rate. Therefore, the weight-adjusted regimen recommended for UFH in the setting of a STEMI receiving thrombolytic therapy or non-ST elevation ACS patients is an initial bolus of 60 units/kg (maximum, 4000 units) and an initial infusion of 12 units/kg/hr with an activated partial thromboplastin time goal of 1.5 to 2.5 times the control value.[5,6] The weight-adjusted regimen UFH in STEMI patients receiving PCI is dependent on the planned use of a GPI during PCI. If GPI use is planned during PCI, the bolus dose should be 50 to 70 units/kg (no maximum dose) and, if no GPI use is planned, the bolus dose should be 70 to 100 units/kg (no maximum dose).[5,6] LMWHs constitute approximately one-third of the molecular weight of heparin and are less heterogeneous in size. LMWHs inhibit the coagulation system in a fashion similar to that of UFH. Approximately one-third of the heparin molecules bind to antithrombin III and thrombin. The remaining molecules bind only to factor Xa. The variable efficacy found among the LMWHs is attributed to different ratios of antifactor Xa to antifactor IIa. High-ratio preparations have a clear advantage over standard heparin; enoxaparin has the highest ratio of available LMWHs. LMWH was designed on the basis of the hypothesis that the inhibition of earlier steps in the blood coagulation system would be associated with a more potent antithrombotic effect than inhibition of subsequent steps. This results from the amplification process inherent in the coagulation cascade—that is, a single factor Xa molecule can lead to the generation of multiple thrombin molecules.

Potential advantages of LMWH over UFH include easier administration, greater bioavailability, more consistent therapeutic response among patients, and longer serum half-life, producing a more manageable administration schedule, albeit at a higher cost. The combination of aspirin, beta blocker, and LMWH significantly decreases the rate of nonfatal AMI or death at 1 in the first several weeks after treatment but has much less pronounced impact out to multiple months. Studies comparing outcomes between LMWH and UFH have shown mixed results; some show better outcomes with LMWH, but others do not. In summary, the LMWH enoxaparin demonstrates some degree of benefit compared with UFH in patients at higher risk for non–ST segment elevation ACS who are treated conservatively without immediate PCI (ie, beyond 24 hours). For STEMI patients managed aggressively with rapid PCI, UHF is preferred over enoxaparin.[5]

Enoxaparin is administered in a twice-daily regimen subcutaneously at a dose of 1 mg/kg for all ACS patients. If patients have renal dysfunction, with an estimated glomerular filtration rate of less than 30 mL/min, the dose should be reduced to 1 mg/kg in a single daily administration. Few safety data are available for enoxaparin in ACS patients with renal insufficiency, and UFH may be preferable.

Contraindications to heparin therapy include known allergy, active ongoing hemorrhage, and predisposition to such hemorrhage. Furthermore, patients who have their heparin therapy changed (UFH to LMWH and vice versa) during the active treatment phase of their ACS care experience higher rates of bleeding.

Most patients with AMI require therapy with heparin, whether it is fractionated or unfractionated. Non-AMI ACS, however, is an entirely different issue because UA is a heterogeneous condition. Only high-risk UA patients (recurrent or continued pain, or new ischemic electrocardiographic changes) should be considered for heparin therapy. For example, the stable patient with a classic description of new-onset angina, who is sensation-free with a negative serum marker and normal ECG, is still correctly diagnosed with UA. In contrast, an individual with ongoing pain, intermittent or constant, with a dynamic ECG clearly is experiencing an active, unstable coronary event. The latter patient, who is at higher risk, can benefit from heparin therapy more than the former. Heparin therapy, however, can be a major contributor to morbidity and mortality among hospitalized patients. Major bleeding develops in 1 of every 90 patients treated, and heparin-induced thrombocytopenia in 1 of 34 patients. LMWH is as effective as UFH in patients with non–ST segment elevation ACS and does not greatly increase the bleeding risk while decreasing the risk of thrombocytopenia.

Other Antithrombins: Bivalirudin, Fondaparinux, and Hirudin. The direct thrombin inhibitor bivalirudin is a potent antithrombin anticoagulant providing significant theoretical advantages compared with heparin. Bivalirudin is a bifunctional 20–amino acid peptide designed on the basis of the structure of hirudin. It has properties similar to those of hirudin but also interacts with the catalytic site of thrombin. Bivalirudin, however, is more effective than heparin in reducing death or reinfarction in patients with ACS, particularly those patients undergoing very early PCI.

Bivalirudin, compared with heparin, produces similar rates of ischemia and major bleeding at 1 month. Bivalirudin when used with clopidogrel is comparable to the combination of

heparin and GPI before coronary angiography or PCI. When used alone, it is inferior to the combination of heparin and GPI. Bivalirudin should be considered an acceptable alternative anticoagulant agent compared with the UFH in the STEMI patient undergoing PCI.[5]

Fondaparinux is a synthetic oligosaccharide with a structure similar to the heparins. It is the first widely used selective factor Xa inhibitor. With the increased emphasis on the reduction of hemorrhagic complications in ACS care, this drug may be considered as a reasonable alternative to UFH in the care of NSTEMI patient receiving non-invasive management; however, the increased risk of catheter-associated thrombi during PCI prevents its use without additional UFH administration when an invasive strategy is chosen.

In previous comparison studies, fondaparinux was found to be similar to enoxaparin in the short-term reduction of ischemic events, yet substantially reduced major bleeding and improved long-term outcome. When the use of fondaparinux was reviewed in STEMI patients managed medically with streptokinase, it was found that fondaparinux significantly reduced hemorrhage as well as death and MI when compared to UFH and LMWH. As a result, fondaparinux has a class 1 AHA recommendation as an alternative to UFH and LMWH in NSTEMI and STEMI patients that are not undergoing PCI.[5,6]

Hirudin is a peptide derived from the leech salivary gland but was also synthesized as recombinant hirudin. It binds directly with high affinity to thrombin and can inactivate thrombin already bound to fibrin (clot-bound thrombin) more effectively than UFH. Hirudin does not require endogenous cofactors, such as antithrombin III, for its activity. Also, unlike heparin, hirudin can inhibit thrombin-induced platelet aggregation. Hirudin has demonstrated little significant benefit over other anticoagulants in ACS, with a possibly increased rate of hemorrhage; thus, its pharmaceutical production was discontinued in 2012.

Reperfusion Therapies

Rapidly reestablishing perfusion in the infarct-related coronary artery with the use of fibrinolytic therapy or PCI increases the opportunity for myocardial salvage, with resultant reductions in mortality and improvements in quality of life post-MI. Pharmacologic and mechanical methods of reperfusion are both effective under specific clinical conditions. More than 2 decades ago, the importance of early coronary artery patency was recognized, and it was demonstrated that 90-minute patency predicts improved rates of survival and preserves left ventricular function.

Fibrinolytic therapy unequivocally improves survival in patients with STEMI and is an ACC/AHA class I recommendation.[5-7] Although fibrinolysis has widespread availability and proven ability to improve coronary flow, limit infarct size, and improve survival in STEMI patients, many individuals with acute infarction are not suitable candidates. Patients with absolute contraindications to fibrinolytic therapy, certain relative contraindications, cardiogenic shock, and UA, and most NSTEMI cases, may not be eligible. The limitations of fibrinolytic therapy, as well as the benefits of percutaneous coronary intervention, suggest that rapidly performed PCI is often the treatment of choice in the STEMI patient. To provide the most significant benefit, PCI must be performed as soon as possible after the initial presentation. In certain other settings, PCI that is delayed is inferior to rapidly administered fibrinolytic agents, assuming that the patient has no contraindications to this therapy.

Fibrinolytic Therapy

Fibrinolytic Agent Selection. Options for fibrinolytic therapy include streptokinase (the original fibrinolytic agent) and three types of plasminogen activator: tissue-type plasminogen activator (t-PA) and two recombinant tissue-type plasminogen activators, r-PA (reteplase) and tenecteplase (TNK). Initial studies comparing streptokinase with slower administration of t-PA have shown no difference in outcomes in the setting of AMI. Subsequent studies, however, have shown improved outcomes with the use of t-PA compared to streptokinase in the setting of AMI, due to so-called accelerated administration of the former agent. Due to more effective options for fibrinolytic therapy, and easier to administer alternatives, streptokinase is no longer marketed in the United States. It is still used in many areas of the world due to of its low cost when compared to the other fibrinolytic options.

Fibrinolytic practice remains highly affected by early studies testing the hypothesis that early and sustained infarct vessel patency is associated with better survival rates in patients with AMI. Investigators have studied multiple different fibrinolytic strategies and found that accelerated t-PA given over 90 minutes, plus IV heparin, shows improved results when compared to streptokinase in combination with multiple forms of anticoagulation. Unlike in previous trials, t-PA was given in a more aggressive, front-loaded, 90-minute infusion (referred to as accelerated t-PA). In addition to mortality, coronary artery patency and degree of normalization of flow were found to be directly affected by this accelerated t-PA administration. This was the first proven association of the relationship between early coronary artery patency and improved clinical outcome. The accelerated t-PA patients showed significant mortality benefit following treatment (15%), and the benefit out to 1-year follow-up was highly consistent across virtually all subgroups, including older patients, AMI location, and time since symptom onset. Also, the angiographic evaluation demonstrated a strong relationship between TIMI flow and outcome. Patients with strong forward flow (ie, TIMI grade 3 flow) at 90 minutes had significantly lower mortality rates than patients with little to no flow. The mechanism for this benefit was found to be earlier, more complete infarct vessel patency with accelerated t-PA; this early t-PA patency advantage over other agents was lost by 180 minutes after symptom onset. As would be expected, patients with the higher risk derived the most substantial benefit with accelerated t-PA compared with streptokinase in this large study. Accelerated t-PA is associated with increased risk of hemorrhagic strokes compared to streptokinase, but the combined endpoint of death and disabling stroke still favors the accelerated t-PA regimen.

Other large studies have compared accelerated t-PA with r-PA; r-PA can be administered in a fixed, double-bolus dose with no adjustment required for weight, which simplifies administration. r-PA has been found to be equivalent to accelerated t-PA, and results have been nearly identical for the two drugs. The one exception was the patient with presentation more than 4 hours after onset of symptoms, a significant number of patients in many institutions. In this group, accelerated t-PA may be superior to r-PA because of its greater fibrin specificity.

In the setting of STEMI, TNK has been found to have several potential benefits: (1) its longer half-life allows it to be administered as a single bolus; (2) it is 14 times more fibrin-specific than t-PA and even more so than r-PA; and (3) it is 80 times more resistant to plasminogen activator inhibitor type 1 than t-PA. In comparisons of single-bolus TNK (30–50 mg on the basis of body weight) or accelerated t-PA (100 mg total infusion) in the setting of AMI, there were no differences in mortality or intracranial hemorrhage. However, there may be benefit in 30-day mortality among patients with presentation more than 4 hours after onset of symptoms in those treated with TNK, as well as fewer nonintracranial major bleeding episodes in this group. On the basis of these results, it is concluded that TNK is equally or minimally more effective, particularly in late presenters. Concerning adverse reactions, TNK also appears modestly safer than accelerated t-PA. Finally, because of its single-bolus administration, TNK is

markedly easier to use in prehospital environments and the ED. At present, it appears that TNK is marginally more effective, minimally safer, and easier to administer than t-PA, and thus is recommended. Furthermore, cost differences are minimal and likely will not affect medical decision making in the ED.

Eligibility Criteria for Fibrinolytic Agent Therapy. In the absence of contraindications, fibrinolytic therapy should be considered in patients with STEMI and the onset of ischemic symptoms within the previous 12 hours when it has been anticipated that primary PCI cannot be performed within 120 minutes of first medical contact.[5-7] The following section discusses the specific issues regarding fibrinolytic agent eligibility.

12-Lead Electrocardiogram. Combined with the patient's history and physical examination, the 12-lead ECG is the key determinant of eligibility for fibrinolysis. The electrocardiographic findings should be consistent with STEMI based on the European Society of Cardiology (ESC)/American College of Cardiology Foundation (ACCF)/AHA/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction. These findings include diagnostic ST elevation in the absence of LVH or LBBB, including ST elevation at the J point in at least two contiguous leads more than 2 mm in men or more than 1.5 mm in women in leads V_2 and V_3 and/or more than 1 mm in other contiguous chest or limb leads.[4] Other electrocardiographic findings that should be considered for fibrinolytic therapy include the following: (1) ST elevation in aVR with coexistent multilead ST depression, concerning for proximal LAD or left main coronary artery occlusion; and (2) evidence of posterior transmural injury (posterior STEMI) indicated by ST segment depression in two or more precordial leads (V_1–V_4).[6]

Patients with new LBBB and AMI are at increased risk for a poor outcome and benefit significantly from the administration of rapid reperfusion therapy if they are experiencing an AMI. Tthe new development of LBBB in the setting of AMI suggests proximal occlusion of the LAD artery, placing a significant portion of the left ventricle in ischemic jeopardy. However, new or presumably new LBBB at presentation should not be considered diagnostic of AMI in isolation.[55] The finding of a new or presumably new LBBB at presentation of AMI occurs infrequently and, because of this poor diagnostic accuracy, an isolated new LBBB is no longer considered a STEMI equivalent. Rather, one of the more specific electrocardiographic findings to identify STEMI in the setting of LBBB, as defined by Sgarbossa, should be present before an LBBB is considered for STEMI treatment.[6] A new or presumably new LBBB in a patient with a classic presentation of AMI who is very ill from an ACS perspective should be expeditiously evaluated with prompt cardiology consultation, if possible, to expedite cardiac-focused care.

Patients with STEMI in anterior, inferior, or lateral anatomic locations benefit from fibrinolytic therapy. Acute, isolated posterior wall MI, diagnosed by posterior leads, may be another electrocardiographic indication for fibrinolysis. Although unproven in large fibrinolytic agent trials, patients with isolated posterior AMI may be considered for reperfusion therapy; the emergency clinician at the bedside is in most appropriate position to make these treatment decisions.

Fibrinolytic therapy should not be used routinely in patients with only ST segment depression on the 12-lead ECG; in fact, the mortality rate may actually be increased. Multiple studies have demonstrated a significant increase in mortality in fibrinolytic-treated patients who presented only with ST segment depression. Acute posterior wall AMI presenting with anterior ST segment depression, as noted, can be considered an exception to this general statement.

Patient Age. Past trials do not provide evidence to support withholding fibrinolytic therapy or choosing one particular agent over another on the basis of the patient's age. It is general consensus at this point that age alone should no longer be considered a contraindication to fibrinolytic therapy. It must be noted, however, that patients older than 75 years do have a higher incidence of hemorrhagic stroke than younger patients.

Time From Symptom Onset. The generally accepted therapeutic time window for administration of a fibrinolytic agent after the onset of STEMI is 12 hours. Patients treated within the first 6 hours of STEMI have the best outcome. Later administrations, from 6 to 12 hours after STEMI onset, also confer benefit, although of a lesser magnitude. The Late Assessment of Fibrinolytic Efficiency (LATE) trial, which compared fibrinolytic therapy with placebo, found a significant 26% decrease in 35-day mortality in patients treated with t-PA, heparin, and aspirin 6 to 12 hours after the onset of symptoms. There was no significant decrease in mortality among patients treated 12 to 24 hours after symptom onset.

Blood Pressure Extremes. Patients with a history of chronic hypertension should not be excluded from fibrinolytic therapy if their blood pressure is adequately controlled or can be lowered to acceptable levels with standard therapy for ischemic chest pain. The admission blood pressure is also an important indicator of risk of intracerebral hemorrhage. It has been shown that the risk of cerebral hemorrhage increases with systolic blood pressure higher than 150 mm Hg on admission and further increases when systolic blood pressure is 175 mm Hg or higher. Despite an increased mortality rate during the acute setting, fibrinolytic therapy in the setting of hypertension has shown an overall long-term benefit for patients with systolic blood pressure higher than 150 to 175 mm Hg. Although the literature appears to indicate an acceptable risk-benefit ratio for patients with substantially increased systolic blood pressure, a persistently elevated blood pressure—during the ED presentation—that is higher than 200/120 mm Hg is generally considered to be an absolute contraindication to fibrinolytic therapy.

The benefit of fibrinolytic therapy in patients with hypotension is unclear. Multiple trials have shown no apparent reduction in mortality rate with fibrinolytic therapy among patients classified as Killip class III or IV. However, reviews of data on STEMI patients have demonstrated that patients with an initial systolic blood pressure below 100 mm Hg who were not treated with fibrinolytic therapy had a very high risk of death (35.1%), and those who were treated with fibrinolytic therapy had the largest absolute benefit (60 lives saved/1000 patients). Although cardiogenic shock and CHF are not contraindications to fibrinolysis, PCI is the preferred method of reperfusion if it can be accomplished on site.

Retinopathy. Active diabetic hemorrhagic retinopathy is a strong relative contraindication to fibrinolytic therapy because of the potential for permanent blindness caused by intraocular bleeding. There is no reason, however, to withhold the use of a fibrinolytic agent in a diabetic patient with evidence of simple background retinopathy. Patients with diabetes mellitus who sustain a STEMI have an almost doubled incidence of mortality. It is impossible to determine the presence or absence of active retinal hemorrhage in the ED during the care of STEMI; thus, the emergency clinician should consider the risk-benefit analysis with respect to the presentation and involve the patient in the decision making.

Cardiac Arrest Requiring Cardiopulmonary Resuscitation. CPR is not a contraindication to fibrinolytic therapy unless CPR is prolonged—more than about 10 minutes—or extensive chest trauma from manual compression is evident. Although the in-hospital mortality rate is higher in AMI patients who experience cardiac arrest and then receive fibrinolytic agents in the ED, no difference has been found in the rates of bleeding complications. Specifically, hemothorax and cardiac tamponade were not diagnosed in cardiac arrest patients receiving CPR and

fibrinolytics who survived to admission. Even CPR prolonged beyond 10 minutes does not appear to be associated with higher rates of complication. Again, the emergency clinician should consider the risk-benefit analysis with respect to the presentation in this high-acuity, complex medical situation.

Previous Stroke or Transient Ischemic Attack. A history of a previous stroke or TIA is a major risk factor for hemorrhagic stroke after treatment with fibrinolytic therapy. A history of previous ischemic stroke should remain a strong relative contraindication to fibrinolytic therapy, and previous hemorrhagic stroke is an absolute contraindication.

Previous Myocardial Infarction or Coronary Artery Bypass Graft. In the setting of STEMI, a previous MI should not preclude consideration for treatment with fibrinolytic agents. Without treatment, there is a potential for greater loss of function in the newly infarcting region of the myocardium. In patients with a previous MI, studies of fibrinolysis have demonstrated a 26% relative mortality rate reduction, and patients with a history of past MI who received fibrinolytic therapy for recurrent acute infarction have a decreased mortality rate compared to control patients without fibrinolytic therapy.

Many studies have reported successful fibrinolysis in STEMI patients with a prior CABG, but these patients should be preferentially considered for direct angioplasty, if immediately available, or combined fibrinolysis and rescue angioplasty. Complete thrombotic occlusion of the bypass graft is the cause of AMI in approximately 75% of cases as opposed to native vessel occlusion. Because of the large mass of thrombus and absent flow in the graft, conventional fibrinolytic therapy may be inadequate to restore flow.

Recent Surgery or Trauma. Recent surgery or trauma is considered a relative contraindication to fibrinolytic therapy. The term *recent* has been subject to variable interpretation in fibrinolytic trials. The ACCF/AHA guidelines list significant head or facial trauma in the past 3 months and intracranial or intraspinal surgery within the past 2 months as absolute contraindications to fibrinolytic therapy in STEMI. Major surgery within the past 3 weeks and recent internal bleeding (2–4 weeks) are also listed as relative contraindications to fibrinolytic therapy in the setting of STEMI.[5,6]

Menstruation. Because natural estrogen is partially cardioprotective, there is very little clinical experience with fibrinolysis in premenopausal women. Gynecologists have indicated that any excessive vaginal bleeding that may occur after undergoing fibrinolytic therapy should be readily controllable by vaginal packing and therefore can be considered as a compressible site of bleeding.

Percutaneous Coronary Intervention. Although fibrinolysis has widespread availability and a proven ability to improve coronary flow, limit infarct size, and improve survival in STEMI patients, many individuals with acute infarction are not suitable candidates. PCI has many theoretic advantages over fibrinolysis, including an increased number of eligible patients, lower risk of intracranial bleeding, significantly higher initial reperfusion rate, earlier definition of coronary anatomy with rapid triage to surgical intervention, and risk stratification allowing safe, early hospital discharge. Potential disadvantages include lack of operator expertise and numerous catheterization laboratory logistic issues, including limited geographic availability and delays to therapy application. However, it must be stated that PCI is superior when applied early and rapidly in the STEMI patient, yet it loses its treatment advantage over fibrinolysis if time to procedure is prolonged.

Several trials of varying sizes comparing primary PCI with fibrinolysis have been reported. Interventions in the early trials were performed before the widespread adoption of coronary stents with GPI. Despite a clear and consistent benefit of PCI in restoring patency of the infarct-related artery, differences in mortality in the individual trials were difficult to evaluate because of the smaller sample sizes. It has been shown that compared with standard-dose t-PA, PCI reduces the combined occurrence of nonfatal reinfarction or death, is associated with a lower rate of intracranial hemorrhage, and results in similar left ventricular function. Other studies have indicated that primary angioplasty is associated with a higher rate of patency of the infarct-related artery, less severe residual stenotic lesion, better left ventricular function, and less recurrent myocardial ischemia and infarction than in patients receiving streptokinase.

Multiple studies comparing PCI versus t-PA have now shown a decrease in death, reinfarction, and nonfatal disabling stroke in patients with STEMI when treated with PCI. These results even held true in the setting of accelerated t-PA administration and patients requiring transfer for PCI when the transfer can occur within 3 hours. Multiple studies continue to support the findings that PCI is superior to fibrinolytic therapy in the setting of STEMI, even where rapid transfer for PCI is necessary.

The combination of dual-antiplatelet therapy in addition to PCI with stenting has been shown to reduce the risk of death, recurrent MI, stroke, or need for urgent revascularization by about 50% compared to PCI with angioplasty alone. This dramatic reduction in death and cardiovascular events has led to PCI with stenting to replace simple angioplasty as the treatment of choice for STEMI.

The longer term results with PCI, however, are less well established. Much of the earlier literature comparing acute reperfusion therapies in STEMI did not include the use of coronary stenting during PCI or contemporary dual-agent platelet therapy. Previous large studies showed no overall mortality advantage of PCI at 6 months. The issue of long-term outcome in PCI-managed STEMI patients is further complicated by drug-eluting stents (DESs). Early studies used bare metal stents, which, in the setting of an acute thrombotic event such as STEMI, raised concern regarding stent thrombosis with obstruction and recurrent AMI. PCI with stenting is superior to standard angioplasty. The addition of DESs to the equation has produced less favorable results, however, with similar rates of MI and death coupled with a lower rate of revascularization in the DES patients at several years postintervention.

Rescue Percutaneous Coronary Intervention. Historically, rescue PCI was considered advantageous in patients whose infarct-related arteries failed to reperfuse after fibrinolytic therapy. These patients are profoundly ill, with a markedly worse outcome. Some centers routinely catheterize patients after fibrinolytic therapy to determine whether successful reperfusion has occurred and to perform PCI if feasible. Other centers catheterize patients after fibrinolytic therapy only if there is clinical evidence that the infarct-related artery fails to open, as suggested by continued chest pain or persistent ST segment elevation.

Large trials have compared outcomes after rescue PCI with a conservative management strategy in STEMI patients in whom fibrinolysis has failed. Rescue PCI has not been associated with improved short-term or long-term survival; furthermore, increased rates of stroke and transfusion were noted in this group. In a meta-analysis of STEMI patients who did not achieve satisfactory reperfusion after fibrinolysis, rescue PCI was not associated with mortality reductions. In this very ill group, however, the incidence of heart failure and recurrent infarction was reduced. Repeat fibrinolysis was not associated with significant improvements in mortality or recurrent infarction. Although the decision to offer rescue PCI to the patient in whom fibrinolytic therapy has failed remains controversial, evidence favors rescue PCI (class IIa recommendation)[5,6] and does not support the use of repeat fibrinolysis.

Facilitated Percutaneous Coronary Intervention. Facilitated percutaneous coronary intervention refers to combination

therapy involving fibrinolysis coupled with emergent PCI. This concept originally was developed to maximize therapy in STEMI patients who would be transferred urgently for PCI. The patient would receive the additive benefit of medical therapy (a fibrinolytic agent) before transfer, optimizing perfusion in the culprit artery before arrival at the PCI-capable institution. Unfortunately, outcomes from this facilitated approach are less optimal than fibrinolysis or standard PCI alone.[56] In light of these results, the continued use of a facilitated PCI approach should not be used at this time outside of a scientific investigation.

Choice of Reperfusion Therapy. As noted, the two primary choices for reperfusion therapy in the STEMI patient include fibrinolysis and PCI. Important issues to consider in this treatment choice include the selected form of reperfusion therapy, total elapsed time of infarction, patient's candidacy for fibrinolysis (ie, presence or absence of contraindications), type of hospital facility (ie, PCI-capable), and anticipated time to transfer to the PCI-capable facility. Regardless of the strategy selected, the system's reperfusion goal should be a first medical contact to therapy time that is within 120 minutes—a 30-minute goal for the initiation of fibrinolysis and 120-minute goal for PCI performance. These time periods include transfer for PCI; in other words, if a transfer from one hospital to another is part of an individual patient's care plan, the first medical contact is the initial hospital.[5-7]

With respect to treatment benefit, there are important time-based differences when one considers PCI and fibrinolysis. First, PCI is the preferred strategy for STEMI reperfusion therapy, assuming that it can be performed in timely fashion. Second, the changing impact on mortality, as total infarction time increases, is much more pronounced with fibrinolysis as compared to PCI. The success of PCI in reestablishing perfusion in the early hours after STEMI does not change significantly with time; conversely, the ability of fibrinolytic therapy to restore coronary perfusion decreases significantly with increasing time of infarction, reaching a significant reduction at approximately 6 hours of total STEMI time.

The following discussion considers the preferred reperfusion strategy for the STEMI patient arriving at non–PCI-capable hospital. The patient should be considered for immediate transfer without fibrinolysis to a PCI-capable facility within an appropriate time period (AHA class I recommendation).[5-7] If the patient is a candidate for fibrinolysis and cannot be transferred to a PCI-capable hospital within an appropriate time period, immediate fibrinolytic therapy should be administered, with consideration of subsequent transfer for cardiac catheterization within the next 24 hours; at this time, PCI can be performed, if indicated. If the patient is not a fibrinolytic candidate, transfer should be arranged as soon as possible.[5-7] In this series of recommendations, "appropriate time period" is a key phrase and must be considered from the perspective of two important variables—the total time duration of acute infarction at the time of presentation and anticipated time to performance of PCI.

From these two perspectives, the following general statements regarding reperfusion management of the STEMI patient who arrives at a non–PCI-capable hospital can be made:

- If presentation is within 2 hours or less of symptom onset, consider immediate fibrinolysis unless transfer time for PCI is anticipated to be no more than 60 minutes (AHA class IIB recommendation).
- If presentation is within 2 to 3 hours of symptom onset, consider immediate fibrinolysis or PCI if time to transfer time for PCI is anticipated to be no more than 60 to 120 minutes (AHA class IIB recommendation).
- If presentation is within 3 to 12 hours of symptom onset, consider PCI as opposed to initial fibrinolysis if time to transfer time for PCI is anticipated to be no more than 120 minutes (AHA class IIB recommendation).

As the total STEMI time increases, the overall effectiveness of fibrinolysis decreases significantly; at 6 hours of STEMI time, a longer delay allowing for transfer for PCI is a reasonable management option.[7]

If the STEMI patient arrives at a PCI-capable hospital, PCI remains the reperfusion therapy of choice, with the same time constraints as noted above. The STEMI patient should arrive in the catheterization laboratory with initiation of procedure within 120 minutes of initial medical contact.[5-7] If PCI is not possible at the PCI-capable hospital and the patient is a fibrinolytic candidate, fibrinolytic therapy should be administered if a delay beyond 120 minutes is anticipated. Other candidates for PCI include high-risk STEMI patients, so-called late presenters (ie, >3 hours since the onset of STEMI symptoms), patients in cardiogenic shock, and individuals with contraindication to fibrinolysis. Furthermore, when the diagnosis of STEMI is in doubt, PCI is the most appropriate diagnostic and therapeutic strategy.

Hospitals should have a fibrinolytic therapy plan in place for the treatment of STEMI patients in the event of PCI delay or unavailability. If the time required to mobilize staff and arrange for PCI is prolonged, or if delays in transfer are anticipated, fibrinolysis is preferred within the first several hours of STEMI occurrence. Prior agreement between the ED and cardiovascular physicians at institutions with invasive capability must be obtained and a transfer pathway should be in place so that PCI consideration does not introduce further delays in fibrinolytic drug administration. Consensus clinical pathways limit additional delays in the administration of fibrinolytic agents for patients who are considered for PCI in STEMI.

It has been well established that delays to reperfusion therapy have negative consequences. Delays in reperfusion are associated with increased mortality for PCI and fibrinolysis treatment strategies and appear to be more pronounced in patients undergoing fibrinolysis.

A cooperative effort among all providers and units can markedly reduce the door to therapy time in STEMI patients.[42] A so-called STEMI alert system, analogous to the trauma alert approach, mobilizes hospital-based resources, optimizing the approach to the AMI patient. This system, whether activated by data gathered in the ED or in the field, has the potential to offer time-sensitive therapies in a rapid fashion. Emergency clinician activation of the catheterization laboratory has demonstrated very high rates of accurate STEMI diagnosis while markedly reducing the time to definitive therapy, with very low rates of inappropriate activation (ie, the STEMI mimicker). The ACC and AHA recognize the numerous challenges and potential difficulties in achieving these reperfusion therapy time goals.[6]

Reperfusion Therapy in Cardiogenic Shock. Patients with STEMI experiencing cardiogenic shock, which occurs in up to 10% of cases, demand special consideration because of a mortality rate approaching 80%. Fibrinolysis is not effective in these patients, likely owing to a significantly lower coronary perfusion pressure. In circulatory shock states, the occlusive thrombus is not exposed to the fibrinolytic agent, resulting in clinical failure of the drug. In large fibrinolytic trials, STEMI patients in cardiogenic shock were not found to benefit from fibrinolysis. Conversely, primary PCI has been investigated in more than 600 patients in several small studies. A cumulative analysis has revealed a significantly lower mortality rate (45%) compared with placebo or historical controls.

In previous studies that compared the outcomes of STEMI patients in cardiogenic shock, patients were randomly assigned to emergency revascularization (PCI or emergent CABG) or initial medical stabilization, including fibrinolysis. Overall mortality at

30 days did not differ significantly between the revascularization and medical therapy groups, but the 6-month mortality was lower in the revascularization group. This finding—of reduced mortality in PCI compared to fibrinolytic therapy for patients with cardiogenic shock in the setting of STEMI—has been repeated in multiple studies. Thus, emergency revascularization with PCI or CABG is preferred for patients with STEMI complicated by cardiogenic shock, irrespective of the delay to treatment.[6] Fibrinolytic therapy should be considered in eligible patients who are otherwise unsuitable candidates for PCI or CABG.[6]

Resuscitated Cardiac Arrest With Suspected Acute Coronary Syndrome

In the patient who has been resuscitated from out-of-hospital cardiac arrest (OHCA), postresuscitation care in the ED includes many important areas of management. Beyond the basic critical care interventions, urgent coronary reperfusion should be considered in the resuscitated OHCA patient who has experienced a cardiogenic cardiac arrest. More than 50% of these resuscitated, cardiogenic, OHCA patients who have undergone urgent coronary reperfusion survive to hospital discharge, a survival rate higher than the approximate 10% survival rate of all patients experiencing OHCA cardiac arrest in the out-of-hospital arena. Most of these patients have satisfactory neurologic function at the time of hospital discharge.[57] The literature base considering this issue is heterogeneous, addressing a broad range of resuscitated patient types, including important differences in the various initial cardiac arrest rhythms, range of subsequent mental status after the return of spontaneous circulation (ROSC), and cardiopulmonary status in the ED. Thus, the most appropriate candidate types for urgent coronary reperfusion have not been conclusively identified.[58-63]

Most OHCA patients have a cardiogenic cause responsible for the cardiac arrest. ACS is considered to be the most frequent cause, including STEMI and NSTEMI; not surprisingly, the ECG demonstrates ST segment deviation in many of these patients. For example, the alert patient with ventricular tachycardia or ventricular fibrillation who has been resuscitated and demonstrates STEMI on the ECG likely will benefit significantly from emergent PCI.[7] Although STEMI patients are the most likely group to achieve benefit from emergent cardiac catheterization with PCI, if indicated, electrocardiographic findings should not be considered as strict selection criteria for performing urgent PCI. It has been noted that patients with electrocardiographic presentations other than STEMI derive benefit from this intervention.[58,63]

Importantly, a clinical presentation of coma after cardiac arrest should not be considered a contraindication to reperfusion therapy because this finding is commonly present. Multiple investigations have followed patients with resuscitated cardiac arrest complicated by STEMI. Among those patients who were conscious at the time of PCI, invasive therapy restored coronary perfusion in more than 90%of cases, and all these patients survived without neurologic deficit. The outcome in the comatose patient subgroup was less favorable, with approximately a 50% survival rate and good neurologic outcome, yet still markedly better than the average OHCA victim who has achieved ROSC.[1] Therapeutic hypothermia used in the resuscitated, unresponsive OHCA patient with presumed cardiogenic cause and, when combined with PCI, demonstrates an impressive rate of survival, with good neurologic outcome. Based on previous case series therapeutic hypothermia coupled with PCI demonstrates a significantly improved rate of survival.

The AHA, in their 2015 guidelines, have suggested that urgent cardiac catheterization with PCI, if indicated, should be considered in the resuscitated OHCA patient, regardless of the presence or absence of ST segment elevation.[7] These guidelines noted that "…coronary angiography with PCI, if indicated, should be performed emergently in those resuscitated patients with suspected cardiogenic cardiac arrest who demonstrate electrocardiographic ST segment elevation…"[7]; this recommendation is a class I indication. Furthermore, addressing two specific presentation types, emergent coronary angiography "…is a reasonable intervention in the resuscitated cardiogenic cardiac arrest …[in patients who are comatose and do not demonstrate ST segment elevation on the ECG]"[7] (class IIA indication). It is reasonable to consider including PCI as part of a standard postresuscitation care program because almost 50% of cardiogenic cardiac arrest survivors have an acute occlusion or culprit lesion amenable to intervention.[58] For a range of issues, PCI is the preferred reperfusion strategy in the post-ROSC patient; in this patient presentation with STEMI, in which PCI is not available in timely fashion, fibrinolysis can be considered, assuming that there are no contraindications.

Cardiac catheterization with the possibility of PCI, if warranted, can offer survival and functional benefits to selected patients. Patient selection for emergent PCI after resuscitation from OHCA, however, is a challenging, difficult to answer question. What is clear in this situation is that a subset of these patients, with and without ST segment elevation, alert or comatose, do benefit significantly from emergent reperfusion therapy, delivered along with other appropriate postresuscitation management. With the significant benefit derived by some individuals, emergent reperfusion should be considered in the OHCA patient who has achieved ROSC. In this consideration, the most appropriate discussion should include the emergency clinician and cardiologist. It must be noted that the emergency clinician can suggest and advocate for such and intervention but the invasive cardiologist ultimately makes this decision, as is appropriate in the turnover of care that is occurring.

Management Summary: Potential Pharmacologic Management Approach

The patient with stable or resolved chest pain, with a normal to minimally abnormal ECG and a negative serum marker, is best managed initially with NTG sublingually or topically in combination with aspirin. Resolution of the discomfort with continued stability probably does not warrant further ED pharmacologic management. Continued or recurrent pain in the ED may be treated with parenteral morphine sulfate. Continued pain may ultimately require IV NTG, heparinization with UFH or LMWH, and additional antiplatelet therapy with a thienopyridine (eg, clopidogrel, ticagrelor). The patient with stable UA (ie, new-onset or altered pattern but now symptom-free and lacking abnormal serum markers and an abnormal ECG) does not require heparin or other more aggressive platelet inhibition therapy in most cases.

The ACS patient with an abnormal ECG, particularly ST segment and T wave abnormalities, or elevated serum marker levels may warrant numerous therapies, including ASA, heparin, and other antiplatelet agents (typically a thienopyridine). NTG may be administered by the topical or IV route. The patient with recurrent angina may also benefit from such an approach. Heparin therapy is generally indicated in this case.

The AMI patient without ST segment elevation—the NSTEMI patient—requires aspirin, NTG, heparin, a thienopyridine, or an alternative second antiplatelet agent, and morphine sulfate. The patient with STEMI is treated with the preceding medications noted and should be considered for urgent revascularization, achieved by fibrinolytic agents, PCI, or, in the rare case, CABG.

DISPOSITION

Just as coronary artery disease and ACS represent a spectrum of disease, there is a similar spectrum of disposition options for

patients presenting to the ED with chest pain or other complaints concerning for ACS. These options include rapid transport to the cardiac CCL within minutes of arrival for emergent intervention, ICU admission, acute care admission with cardiac monitoring, observation unit admission (actual or virtual), and discharge to home after evaluation. Patients with evidence of an acute or ongoing ACS event will require admission to the hospital. The final location of these admissions will depend on the patient's clinical presentation, electrocardiographic findings, results of the troponin assay, and cardiorespiratory status.

If the patient's presentation and ECG are consistent with STEMI, the disposition is determined by the reperfusion options available at the facility. In a facility where interventional cardiology and PCI are available, the patient can be urgently transported to the CCL for reperfusion via PCI, as long as this can be accomplished without delay. If PCI is not available as a timely option, fibrinolytic therapy should be initiated rapidly. Regardless of the reperfusion strategy of choice, patients with STEMI will require ICU admission due to the significant risk of adverse events during the first 24 hours of hospitalization. All hospitals, regardless of their size or resources, should have a clear care pathway for STEMI patients that may include CCL activation or fibrinolysis, followed by admission to the ICU; an expedited transfer should also be considered for the appropriate patient, dependent on the initial facility's capabilities.

In patients who have evidence of ACS without STEMI, their disposition is based on the emergency clinician's risk assessment of the patient and his or her clinical presentation. Patients with high-risk presentations, including dynamic electrocardiographic changes, uncontrolled ischemic pain, or rising troponin levels (consistent with NSTEMI or unstable angina) will likely benefit from ICU-level care and monitoring due to their significant risk of adverse events.

If the patient has no evidence of active ischemia, most risk stratification tools recommend separating patients into categories based on the risk of ACS and adverse events. High-risk patients without dynamic electrocardiographic changes or elevated troponin levels often benefit from hospitalization in a monitored bed, with further diagnostic testing and management. Intermediate-risk patients often benefit from abbreviated stays in an observation unit (structural or virtual unit) for repeat troponin level tests and possible provocative testing or anatomic imaging, if indicated. Patients at low risk of ACS can often receive evaluation in the ED setting, followed by discharge with primary care follow-up and possible outpatient testing, as indicated.

Transfer of a Patient With Acute Coronary Syndrome

There are several indications for the transfer of a patient with ACS to a facility with PCI capability. These include rapid access to PCI, persistent hemodynamic instability or ventricular dysrhythmias, and postinfarction or postreperfusion ischemia. Hospital transfer for PCI is also suggested for patients with fibrinolytic contraindications who may benefit from PCI or CABG.

The urgent transfer of a fibrinolytic-eligible STEMI patient to another institution for PCI is not recommended until fibrinolytic therapy has been initiated if a delay in PCI application is anticipated. The ACC/AHA guidelines have noted that in hospitals without PCI capability, immediate transfer for primary PCI is a treatment option when it can be accomplished within 60 to 120 minutes of first medical contact, depending on the duration of STEMI at the time of presentation.[7] If delays in PCI performance are anticipated, and the patient is an acceptable candidate for fibrinolysis, the fibrinolytic should be started before or during transport to the receiving hospital. This decision is made in conjunction with the receiving cardiologist.

Many institutions are not PCI-capable. Thus, the decision for the emergency clinician involves not only the relatively simple fibrinolysis versus PCI issue but also the potential need for urgent transfer to a larger center. Previous studies have explored the potential benefit of PCI over fibrinolysis and the all-important impact of transfer of the STEMI patient in a noninterventional hospital, These studies revealed about a 25% reduction in the composite endpoints of death, recurrent infarction, stroke, and/or revascularization in fibrinolytic patients compared to those in the PCI group. The conclusion was that the early benefit from a transfer-related invasive strategy was sustained over long-term follow-up, but the benefit was largely a result of a lower event rate in the PCI patients in the first 30 days after presentation.

The potential need to transfer the STEMI patient over long distances can also affect reperfusion therapy decisions. This is usually seen in rural areas with long transport times to the nearest PCI facility. In this setting, organized processes for rapid transfer should be in place to address the expected delays, including a rapid initiation of transfer by the emergency clinician, an agreed-on expedited transfer process to the PCI center, and rapid access to a transport vehicle (ground or air) that will be needed for safe transport. Multiple investigations have suggested that rapid transfer for PCI in the STEMI patient can occur in the rural setting with acceptable time to therapy.

KEY CONCEPTS

- Angina-equivalent symptoms that are not characteristically associated with ACS vary widely and often distract from the diagnosis. The patient's age, diabetes status, ethnicity, and gender are considered with an atypical history.
- Limitations of the 12-lead ECG in ACS include initial nondiagnostic findings, evolving fluctuations with ongoing symptoms, anatomic myocardial blind spots, and confounding or obscuring patterns, such as LBBB.
- Patients with proximal left anterior descending artery stenosis (Wellens syndrome) may have deeply inverted or biphasic T waves in the anterior precordial leads.
- ST segment elevation in lead aVR more than 0.5 mV suggests left main coronary artery disease.
- Functional testing strategies for ACS include graded exercise testing, echocardiography, and myocardial scintigraphy. Graded exercise testing, with or without nuclear scintigraphy, can be used in the patient with low to moderate likelihood of CAD who is able to exercise. Myocardial scintigraphy with pharmacologic stress can be used in the debilitated or older patient (ie, unable to exercise). Echocardiography with pharmacologic stress is appropriate for the woman older than 45 years, the patient with diabetes mellitus, and the patient with other forms of organic heart disease (eg, valvular dysfunction, low cardiac output states).
- The use of coronary CT angiography is most appropriate in the younger patient; excessive coronary calcification can reduce the ability of CCTA to evaluate the patient for significant CAD reliably.
- Fibrinolysis is not effective in patients with STEMI who are in cardiogenic shock.
- Unless used for rate control of supraventricular dysrhythmia in a patient who cannot tolerate beta blockade, calcium channel blockade is not recommended for those with ACS.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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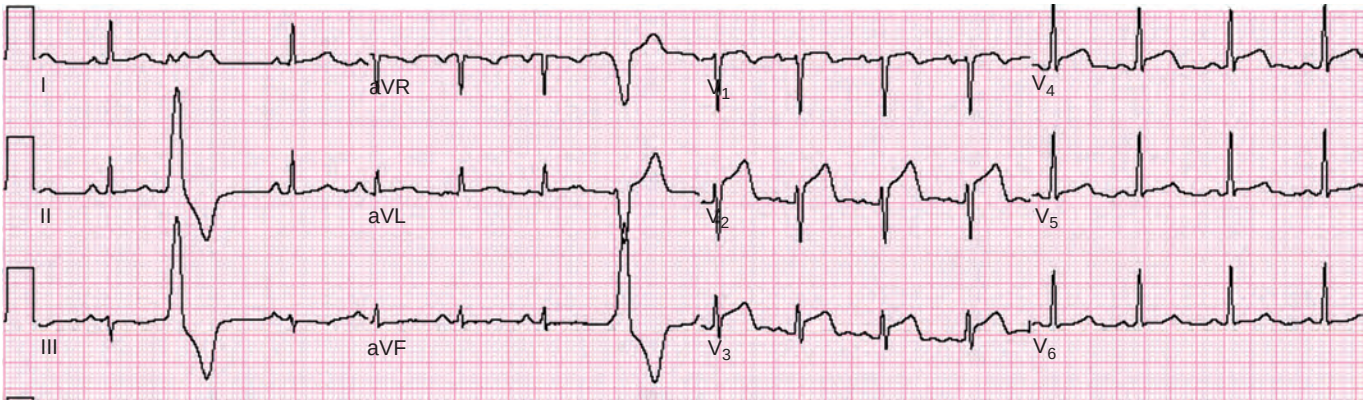
CHAPTER 68: QUESTIONS & ANSWERS

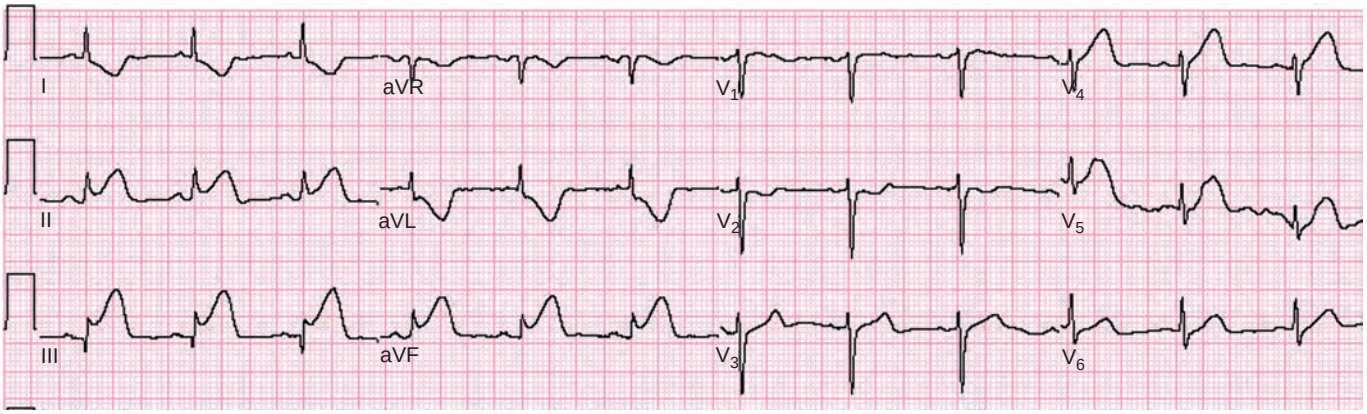
68.1. A 40-year-old man presents with a 3-hour history of left-sided chest pain, slightly worse in the supine position, associated with mild dyspnea and diaphoresis. He is 2 weeks status post–left anterior/lateral subendocardial myocardial infection (MI), with acute stenting of the left anterior descending and circumflex arteries. He is unable to discern if this pain is the same as his original cardiac pain. His current medications are aspirin, 81 mg/day, lovastatin, 80 mg/day, amlodipine 10 mg/day, and clopidogrel 75 mg/day. His electrocardiogram (ECG) is shown here. Cardiac troponin I is within normal limits. Vital signs are temperature, 38°C oral, heart rate (HR), 110 beats/min, blood pressure (BP), 153/96 mm Hg, respiratory rate (RR), 22 breaths/min, and O_2 saturation, 96%. What is the most likely diagnosis?



A. Coronary ischemia
B. Dressler's syndrome
C. Infarct pericarditis
D. Pleuritic chest wall pain
E. Ventricular aneurysm formation

Answer: B. Dressler's syndrome is a late sequela of typically nontransmural MI. It may occur 1 week to several months post MI. It is an immune-mediated process sometimes associated with pleural or pericardial effusion. Infarct pericarditis is usually seen within the first week after a transmural infarct, and the classic pericarditis electrocardiographic finding may be overshadowed by the MI changes. PR segment depression is seen in both entities. The characteristic ECG, presence of fever, and pain with recumbency argue for this diagnosis. A ventricular aneurysm would be expected after transmural MI; the ECG will demonstrate ST segment elevation, usually with prominent Q waves and T waves of diminished amplitude. Myocardial ischemia is a possibility, but troponin is negative and ECG is noncontributory.

68.2. A 37-year-old male renal dialysis patient presents with a 6-hour history of intermittent left-sided chest pain. He missed his last dialysis session due to feeling ill. His past history is significant for hypertension with secondary renal failure, tobacco use, and hypercholesterolemia. His current medications are amlodipine, 10 mg/day, a statin, and his renal failure medications. Vital signs are temperature, 36.7°C oral, HR, 92 beats/min, BP, 170/110 mm Hg, RR, 22 breaths/min, and O_2 saturation, 95%. His ECG is shown below. The serum potassium level is 5.8 mEq/L. What is the most important intervention?



A. Calcium gluconate, 1 g IV, followed by dextrose, 100 g, and regular insulin, 10 units IV
B. Emergent dialysis
C. IV enoxaparin
D. IV metoprolol
E. Nitroglycerin, aspirin, 325 mg orally, and cardiology consultation

Answer: E. The ECG shows asymmetric hyperacute T waves, possibly consistent with coronary ischemia. This is clinically the early electrocardiographic manifestation of AMI. The differential diagnosis of hyperacute T waves is ischemia, hyperkalemia, benign early repolarization, left ventricular hypertrophy, left bundle branch block, and pericarditis. The asymmetry of the T waves argues for ischemia, as does the relatively modest rise in the serum potassium. Enoxaparin might be indicated, but only as part of an acute coronary regimen with appropriate renal dosing. Beta blockers would worsen his hyperkalemia and would have to be carefully considered before administration.

68.3. A 63-year-old woman with a past medical history of diabetes presents with altered mental status, diaphoresis, and substernal chest pain for 4 hours. Vital signs are HR, 96 beats/min, BP, 80/50 mm Hg, RR, 26 breaths/min, temperature, 37° C, and O_2 saturation, 94%. The ECG clearly demonstrates a large, anterior, ST segment elevation MI. Your institution does not have a cardiac catheterization laboratory. The closest hospital with a cardiac catheterization laboratory is 2 hours by ground, and no aircraft is available due to weather. After normal saline boluses, what is the most appropriate treatment?
A. Administer aspirin, PSY_{12} inhibitor, intravenous (IV) unfractionated heparin (UFH), vasopressor therapy as needed, and admit to your institution.
B. Administer aspirin, PSY_{12} inhibitor, IV UFH, and immediate transfer to primary percutaneous coronary intervention (PCI) center by ground emergency medical services (EMS).
C. Administer aspirin, PSY_{12} inhibitor, IV UFH, IV fibrinolysis, and immediate transfer to the PCI center.
D. Administer aspirin, PSY_{12} inhibitor, IV UFH, and transfer to the primary PCI center when helicopter becomes available in 4 hours.

Answer: B. Patients who present with ST segment elevation myocardial infarction (STEMI) and cardiogenic shock should be preferentially treated with percutaneous coronary intervention (PCI) if there are no contraindications to mechanical reperfusion. Because PCI is the preferred therapy, a delay of beyond the usual threshold of 60 to 120 minutes from first medical contact to PCI for the administration of fibrinolytics is tolerated. Although a delay beyond 120 minutes is tolerable, it should be as small as possible.

68.4. A 48-year-old man with history of hypertension and hypercholesteremia presents with chest pain and hyperacute T waves in an anterior distribution on the initial ECG. During your initial history and physical examination. the patient experiences ventricular fibrillation that responds to cardiopulmonary resuscitation (CPR) and defibrillation after being pulseless for a period of 3 minutes. Following cardiac arrest, the patient is comatose, with the following vital signs: HR, 110 beats/min, BP, 160/98 mm Hg, RR, 12 breaths/min (intubated), temperature, 36.5° C, and O_2 saturation, 96%. A repeat ECG demonstrates a large, evolving anterior STEMI. Which of the following treatment plans is most appropriate?
A. Administer aspirin, PSY_{12} inhibitor, IV UFH, IV fibrinolysis, and admission to intensive care unit (ICU)
B. Administer aspirin, PSY_{12} inhibitor, IV UFH, IV fibrinolysis, initiation of therapeutic hypothermia, and admission to ICU
C. Neurologic examination for brain death and admission to palliative care because outcome almost universally fatal
D. Rapid revascularization with percutaneous coronary intervention (PCI), initiation of therapeutic hypothermia, and admission to ICU for comprehensive postresuscitation care
E. Supportive care, and admission to ICU

Answer: D. A neurologic examination immediately following cardiac arrest is poorly prognostic of a favorable neurologic outcome with modern postresuscitation care. The sharp increase in survival with a favorable neurologic outcome has elevated rapid revascularization with percutaneous coronary intervention (PCI) and immediate application of therapeutic hypothermia as part of comprehensive postresuscitation care as a class I ACC/AHA recommendation. Although not contraindicated, fibrinolysis is inferior to PCI following cardiac arrest and should only be used when a patient is not a candidate for PCI.

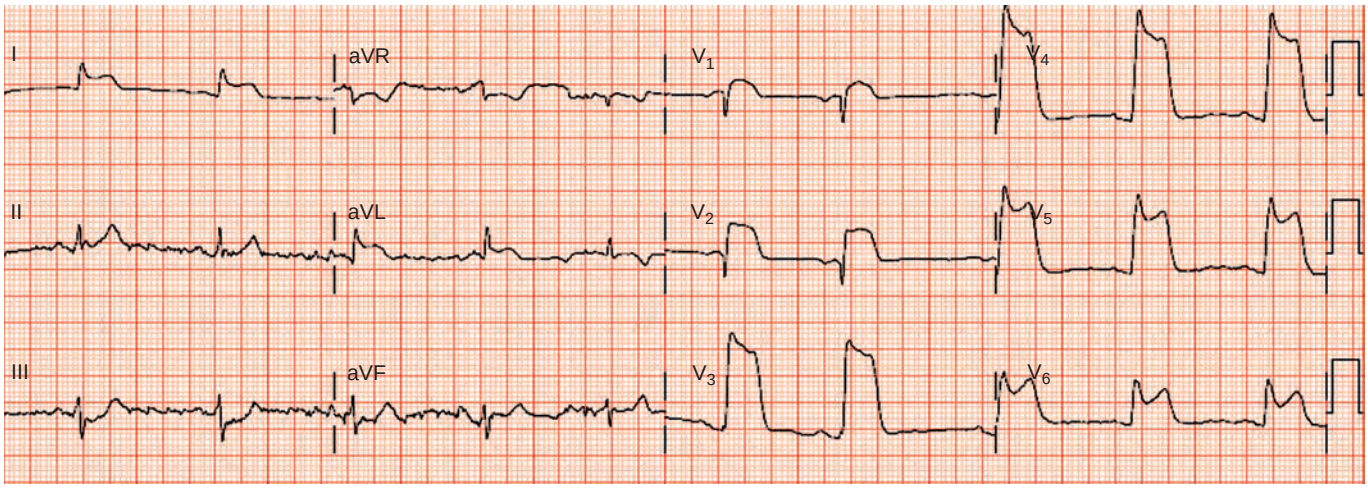
68.5. Which of the following is an absolute contraindication to fibrinolytic therapy?
A. Age older than 75 years
B. Appendectomy performed 2 months ago
C. Previous coronary artery bypass grafting (CABG)
D. Previous hemorrhagic stroke
E. Systolic blood pressure of 175/90 mm Hg following administration of vasoactive agents

Answer: D. Although patients older than 75 years have a higher risk of intercerebral hemorrhage, age should not be considered a contraindication to fibrinolysis. Although prior CABG patients should be preferentially considered for PCI, there is no contraindication to fibrinolytic use in these patients if PCI is not available. Systolic blood pressure above 150 mm Hg is a risk factor for intracerebral hemorrhage. Only hypertension persistently above 200/120 mm Hg, despite reasonable efforts, should be considered an absolute contraindication. Recent major surgery or trauma is a relative contraindication for fibrinolysis; however, the term *recent* is variably defined in the fibrinolytic literature and never as more than 6 weeks.

68.6. Which of the following drugs provides mortality benefit in the setting of AMI?
A. Aspirin
B. Intravenous beta blocker
C. Intravenous morphine
D. Nitroglycerin
E. Oxygen

Answer: A. The ISIS-2 trial has demonstrated that aspirin independently reduces mortality by 23% in the setting of AMI. Intravenous morphine has not been shown to improve mortality and has been associated with mortality. Although nitroglycerin does improve symptoms and cause vasodilation, it has never been proven to improve mortality. Oxygen beyond that needed to maintain an oxygen saturation of 94% has been associated with additional mortality. The use of intravenous beta blockers does not offer significant benefit and is associated with an increased rate of adverse events.

68.7. A 42-year-old male patient presents with 45 minutes of chest pain. The ECG is depicted below. You are working at a noninvasive (ie, no PCI capability) hospital; transfer time to the closest major medical center with PCI capability is 4.5 hours considering weather and logistics. The patient has no contraindications for fibrinolysis. Which of the following statements is most appropriate?



A. The patient must be transferred rapidly to the closest PCI center, with initiation of appropriate β-adrenergic blocking agents and antiplatelet and anticoagulant therapies before transfer.

B. The patient should receive a fibrinolytic agent followed by appropriate antiplatelet and anticoagulant therapies with admission to your hospital's ICU.

C. The patient should receive a fibrinolytic agent followed by appropriate antiplatelet and anticoagulant therapies, with transfer to the closest PCI center for immediate PCI.

D. The patient should receive a fibrinolytic agent followed by appropriate antiplatelet and anticoagulant therapies, with transfer to the closest PCI center within 24 hours for reevaluation and consideration of immediate PCI.

Answer: D. The ECG demonstrates an extensive anterolateral STEMI. The patient is young and has presented early in the STEMI evolution. This patient is at extreme risk due to the extensive nature of the STEMI and yet can benefit significantly from early reperfusion therapies. A delay of more than 60 to 120 minutes in this patient is not appropriate for the initiation of reperfusion therapies; furthermore, he is a candidate for a fibrinolytic agent. The early initiation of reperfusion therapy (fibrinolysis or PCI) is vital to reduce morbidity and mortality. Such a significant delay in this case for PCI is not justified, so a fibrinolytic agent is preferred. On arrival at the closest PCI center, the patient can be evaluated for PCI if he has not demonstrated successful reperfusion with resolution of chest discomfort and normalization of the ST segment elevation.

CHAPTER 69

Dysrhythmias

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PRINCIPLES

The term *dysrhythmia* denotes any abnormality in cardiac rhythm. In this chapter we review the electrophysiology of normal and abnormal cardiac impulse formation and conduction and then provide a general approach to dysrhythmia recognition and management, along with an overview of antidysrhythmic agents. Finally, we discuss the evaluation and treatment of specific dysrhythmias in the prehospital and emergency department (ED) settings.

Cardiac Cellular Electrophysiology

The electrophysiologic function of cardiac cells depend on an intact resting membrane potential. Membrane potential is largely the result of differential concentrations of Na^+ and K^+ on either side of the cell membrane, measuring approximately −90 mV in normal resting nonpacemaker cells. This gradient exists because of the Na^+-K^+ exchange pump and concentration-dependent flow of K^+ out of the cell. The influx of Ca^{2+} through passive exchange with Na^{2+} also allows for conduction and myofibril contraction (Fig. 69.1).

In normal nonpacemaker cells, an electrical stimulus causes the membrane potential to become less negative, termed *depolarization*. When the membrane potential reaches −70 mV, specialized Na^{2+} channels open, causing a rapid influx of positive charge into the cell. This so-called fast channel activity further decreases the membrane potential and is augmented at 30 to 40 mV by a second slow channel that allows Ca^{2+} influx. When these channels close, resting potential is restored by the sodium-potassium pump, an event termed *repolarization* (Fig. 69.2).

In nonpacemaker cells, depolarization from a second electrical stimulus is not possible when the membrane potential remains more positive than −60 mV, called the effective refractory period (Fig. 69.3). When the membrane potential reaches −60 to −70 mV, some fast channels are capable of responding but impulse propagation is not normal; this is known as the relative refractory period. At a membrane potential of −70 mV or less, fast channels are ready for activity (see Fig. 69.3).

Pacemaker cells differ from non–impulse-generating cells in that they can spontaneously depolarize via slow Na^+ influx. Dominant pacemaker cells are present in the sinoatrial (SA) node, but other pacemaker cells exist in the atrioventricular (AV) node, within the His-Purkinje system, and elsewhere. With a failure of normal pacemaking cells, or other pathologic conditions such as metabolic derangement or myocardial ischemia, nonpacemaker cells undergo spontaneous depolarization.

Anatomy and Conduction

The SA node is an area of specialized impulse-generating tissue at the junction of the right atrium and the superior vena cava. Its blood supply is from the right coronary artery (RCA) in 55% of patients and left circumflex artery (LCA) in 45%. The normal SA node produces spontaneous depolarization at a faster rate than other pacemakers and is usually the dominant pacemaker. In healthy adults, the SA node normally maintains a rate of 60 to 90 beats/min. Hypothermia and vagal stimulation slow the sinus rate, whereas hyperthermia and sympathetic stimulation increase the rate. Low or absent parasympathetic tone—for example, with certain drugs or after heart transplantation—creates a faster sinus rate.

In the absence of normal SA node impulses, other myocardial tissues may assume the role of pacemaker. The AV node has an intrinsic impulse-generating rate of 45 to 60 beats/min. Infranodal pacemakers within the His bundle, Purkinje system, and bundle branches maintain intrinsic rates ranging from 30 to 45 beats/min. Under pathologic conditions, other atrial and ventricular tissues may pace the heart at varying rates. Impulses from the SA node are propagated through the atrial tissue to the AV node. Atrial depolarization is characterized by the P wave on the surface electrocardiogram (ECG; Fig. 69.4).

The AV node is an area of conduction tissue separating the atria and the ventricles, located in the posterior-inferior region of the interatrial septum. Its blood supply is from a branch of the RCA in 90% of patients (right dominant) and from the LCA in the remaining 10% (left dominant). Transmission of impulses within the AV node is slower than in other parts of the conducting system (Table 69.1) because of a dependence on slow-channel ion influx for membrane depolarization. An accessory pathway refers to conduction tissue outside the AV node that forms an alternative, or bypass, tract between the atria and ventricles. The term *preexcitation* refers to early ventricular depolarization via an accessory pathway.

On the surface ECG, the time it takes for conduction of an impulse through the atria to the ventricles is represented by the PR interval, normally ranging from 0.10 to 0.20 second (see Fig. 69.4). Impulses originating in lower atrial tissues or accessory pathways often have a shortened PR interval. PR prolongation is usually a result of nodal or supranodal conduction system disease.

After passing through the AV node, impulses propagate to the His bundle onto the three main bundle branch fascicles—the right bundle branch (RBB), left anterior-superior bundle (LASB), and left posterior-inferior bundle (LPIB). The RBB and LASB are typically supplied by the left anterior descending (LAD) artery, whereas the LPIB may be supplied by the RCA or LCA. After conduction down the three main bundle branches, impulses are delivered to the Purkinje fibers, which propagate impulses to myocardial tissues in a swift and orderly fashion, allowing for coordinated ventricular contraction. If an impulse arrives prematurely, it may be conducted abnormally (termed *aberrant*, associated with bundles that are relatively refractory) or blocked (if the bundles are completely refractory).

On the surface ECG, the QRS complex represents ventricular depolarization (see Fig. 69.4), normally 0.09 second or less; a duration of 0.12 second or longer is abnormal. The T wave corresponds to ventricular repolarization and its duration depends, among other things, on the length of the cardiac cycle. The QT

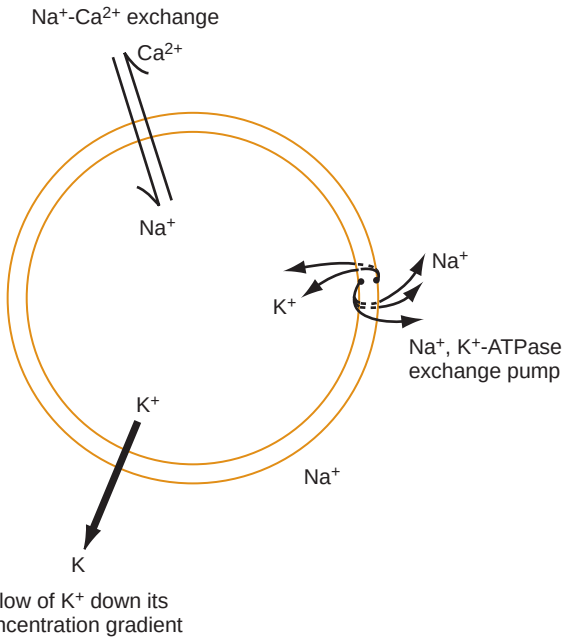


Fig. 69.1. Flow of various ions across the myocardial cell membrane. The Na^+-K^+ pump exchanges three Na^+ ions for each two K^{2+} ions, generating a net negative flow of 10 mV. The flow of K down the concentration gradient (*dark arrow*) generates another 80 mV of current. The Na^+-Ca^{2+} exchange adds little to the resting potential. *ATPase,* Adenosine triphosphatase. (From Marriott HJL, Conover MB: Advanced concepts in dysrhythmias, ed 2, St. Louis, 1989, Mosby.)

TABLE 69.1

Conduction Velocities in Various Heart Tissues

TISSUE	VELOCITY (M/S)
Atrium	1000
Atrioventricular node	200
His-Purkinje system	4000
Ventricles	400

interval represents the total time of ventricular depolarization and repolarization and is altered by inherent physiologic abnormalities, metabolic changes, drugs, or structural changes. This interval is key to assess for QT prolongation in any patient with syncope or ventricular dysrhythmia, given the link to ventricular dysrhythmia recurrence.[1]

Mechanisms of Dysrhythmia Formation

Enhanced automaticity refers to spontaneous depolarization in nonpacemaker cells or depolarization at an abnormally low threshold in pacemaker cells (Fig. 69.5). Classic examples of enhanced automaticity include the idioventricular rhythms of severe hyperkalemia or myocardial ischemia and the atrial and junctional tachycardias (JTs) associated with digitalis toxicity.

Triggered activity refers to abnormal impulse(s) resulting from afterdepolarizations. Afterdepolarizations are fluctuations in membrane potential that occur as the resting potential is restored. These fluctuations may precipitate another depolarization just before full resting potential is reached (early afterdepolarizations) or after full resting potential is reached (delayed afterdepolarizations). The classic dysrhythmia associated with early afterdepolarization is acquired torsades de pointes, which typically arises in the setting of a prolonged QT interval and a new metabolic or drug trigger. Delayed afterdepolarizations classically arise in the setting of rapid heart rates and intracellular Ca^{2+} overload, as seen with digitalis toxicity or reperfusion therapy for acute myocardial infarction.

Reentry dysrhythmias arise from repetitive conduction of impulses through a self-sustaining circuit (Fig. 69.6). To maintain a reentry circuit, one conduction pathway must have a longer refractory period than the other, so that when an impulse exits one limb of the circuit, it may then reenter the other in retrograde fashion. The cycle is then repeated, creating a self-sustaining dysrhythmia. Reentry mechanisms are responsible for most narrow-complex tachycardias and many ventricular tachycardias (VTs). Treatment is predicated on altering conduction in one or both limbs of the circuit.

CLASSIFICATION OF ANTIDYSRHYTHMIC DRUGS

The four classes of antidysrhythmic medications are categorized according to their electrophysiologic effects (Box 69.1). Class I agents exert their major effects on the fast Na^+ channels, resulting in membrane stabilization. The subclasses IA, IB, and IC have differing effects on depolarization, repolarization, and conduction. Class II agents are the β-adrenergic antagonists, which depress SA node automaticity, slow AV node conduction, and suppress conduction in ischemic myocardial tissue. Class III agents prolong repolarization and refractory period duration, predominantly via their effects on K^+ channels. Class IV agents are the Ca^{2+} channel blockers, which slow conduction through the AV node and suppress other calcium-dependent dysrhythmias. Other agents important in the emergency treatment of dysrhythmias include magnesium sulfate, digitalis, and adenosine.

Class IA Agents

Class IA agents slow conduction through the atria, AV node, and His-Purkinje system and suppress conduction in accessory pathways. Class IA agents also exhibit anticholinergic and mild negative inotropic effects.

Procainamide

Procainamide is the most commonly used class IA agent in the emergency treatment of ventricular and supraventricular dysrhythmias, and it can alter normal and accessory pathway conduction. In stable patients, the recommended administration is a rate of 20 to 30 mg/min until the dysrhythmia is terminated, hypotension occurs, or the QRS complex widens (to 50% of the pretreatment width), up to a total dose of 18 to 20 mg/kg (12 mg/kg if congestive heart failure is present). Procainamide triggers hypotension from vasodilatory effects in 5% to 10% of patients. Other class IA agents are not currently in use for acute care.

Class IB Agents

Class IB agents slow conduction and depolarization less than other class I agents, and they shorten repolarization rather than prolonging it. Class IB agents have little effect on accessory pathway conduction.

Lidocaine

Lidocaine is the sole class IB agent used in emergency rhythm management. Lidocaine can suppress dysrhythmias from enhanced automaticity, such as VT. Lidocaine also suppresses SA and AV node function and is associated with asystole in the setting

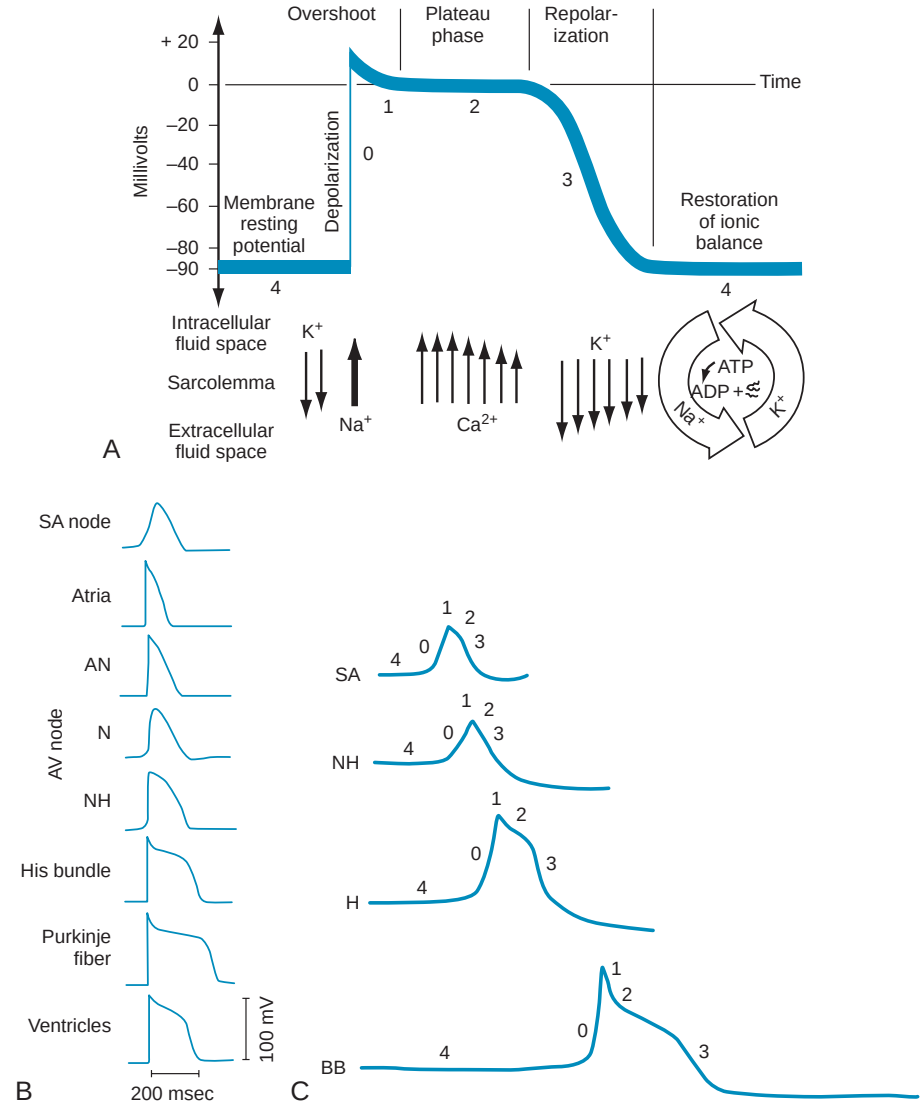


Fig. 69.2. **A,** Action potential of a myocardial cell and its relation to ion flow. **B,** Action potentials of various myocardial tissues. **C,** Action potentials of various pacemaker cells. Note that phase 4 becomes flatter as its location becomes more distal. *AN,* Atrial-nodal; *AV,* atrioventricular; *BB,* bundle branch fascicles; *H,* His bundle; *N,* nodal; *NH,* nodal-His; *SA,* sinoatrial. (**A**, **B,** from Calcium in cardiac metabolism, Whippany, NJ, 1980, Knoll Pharmaceutical; and **C,** from Conover M: Understanding electrocardiography, ed 5, St Louis, 1988, Mosby.)

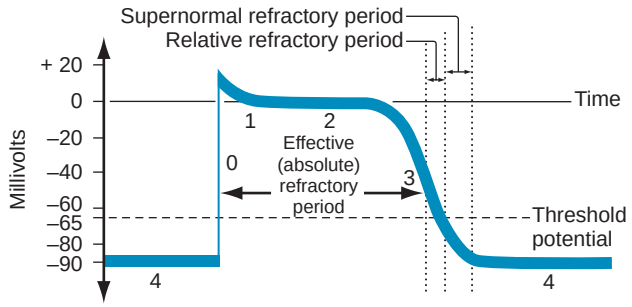


Fig. 69.3. Action potential showing various refractory periods. (From Calcium in cardiac metabolism, Whippany, NJ, 1980, Knoll Pharmaceutical.)

of acute myocardial ischemia. Currently, lidocaine is a second-line agent in ventricular tachycardia due to lower conversion rates compared to other agents. It also may have a role in prophylaxis from recurrent dysrhythmias in those surviving out-of-hospital ventricular fibrillation,[2] although experimental data are limited.

Class IC Agents

The class IC agents profoundly slow depolarization and conduction. More than any other class, these agents are associated with prodysrhythmia, the creation of a new ventricular dysrhythmia[3]; this potential exists with class IA agents albeit much less. Class IC agents are approved only for oral use in the United States.

Flecainide

Flecainide is a class 1C antidysrhythmic agent used for paroxysmal supraventricular tachycardia and certain forms of VT. Flecainide has high oral bioavailability, variable half-life, and narrow therapeutic index, all hampering its use. Flecainide is not recommended for patients with ischemic or structural heart disease.

Propafenone

Propafenone shares electrophysiologic properties with classes IA and IC agents and possesses some β-adrenergic and calcium channel–blocking properties. Oral propafenone is used to prevent

atrial fibrillation and ventricular dysrhythmias. Like flecainide, this is used with caution in patients who have ischemic and/or structural heart disease.

Class II Agents

Class II agents—β-adrenergic blockers—suppress SA node automaticity and slow conduction through the AV node. Because of their effect on AV node conduction, class II agents are well suited to control the ventricular rate in patients with atrial tachydysrhythmias and can be useful to terminate AV nodal reentrant tachycardias (AVNRTs). In the setting of acute myocardial ischemia, beta blockers play a role in preventing ventricular dysrhythmias.

All beta blockers are active at β_1 and β_2 receptors (Table 69.2) to varying degrees. Those with more prominent β_1 effects are called cardioselective. Relative contraindications to the use of beta blockers include asthma or chronic obstructive lung disease, advanced congestive heart failure, and third-trimester pregnancy. Beta blockers should not be used in patients with preexisting bradycardia or heart block beyond first-degree. Acute side effects of beta blockers include bronchospasm, heart failure, excessive bradycardia, and hypotension. Intravenous (IV) beta blockers can trigger additive side effects when used in conjunction with calcium channel blockers, notably hypotension or bradycardia.

Esmolol

Esmolol is a β_1-selective agent useful in the emergency setting because of its rapid onset of action and short elimination half-life (minutes). Common dosing of esmolol is an IV bolus of 500 μg/kg followed by a continuous infusion beginning at 50 μg/kg/min and titrating to need and effect.

Metoprolol

Metoprolol is available in oral and IV preparations. Although not approved for dysrhythmia treatment in the United States, metoprolol (5–10 mg IV every 10–15 minutes in an adult, titrated to response) will slow atrial and nodal tachycardias.

Class III Agents

All class III agents prolong the refractory period primarily by blocking K^+ channels, with variable effects on the QT interval. In

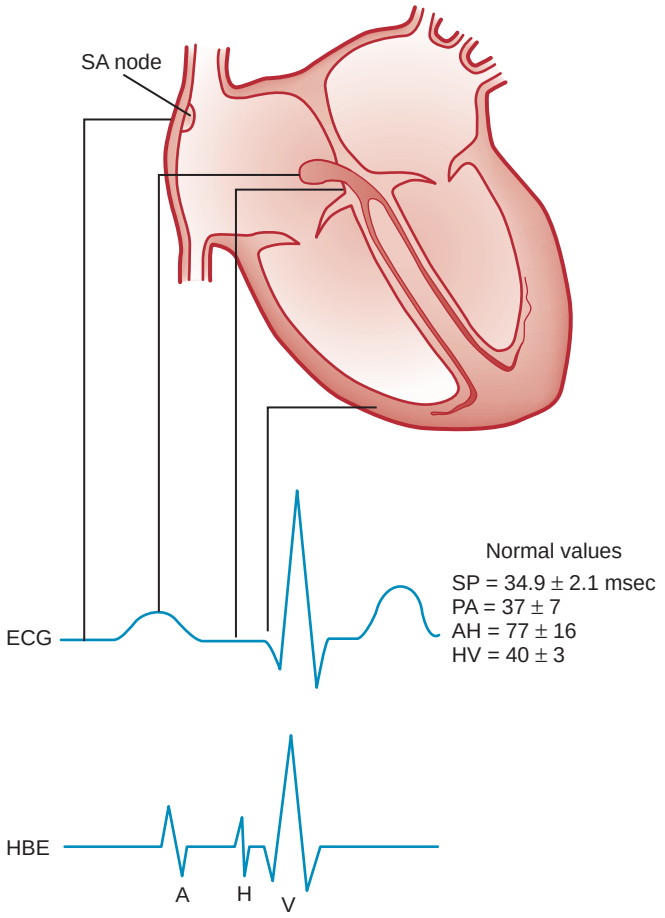


Fig. 69.4. Electrical events in the heart related to surface electrocardiogram (ECG) and His bundle electrogram (HBE). The approximate relationship of sinus node discharge is also related to the surface ECG. *AH,* Atrioventricular nodal conduction time; *HV,* His-Purkinje conduction; *PA,* intraatrial conduction time; *SA,* sinoatrial; *SP,* SA conduction time. (From Marriott HJL, Conover MB: Advanced concepts in dysrhythmias, ed 2, St. Louis, 1989, Mosby.)

TABLE 69.2

Cardiac and Respiratory β-Adrenergic Receptors and Responses to Pharmacologic Manipulation

RESPONSE TO RECEPTORS	LOCATION	STIMULATION	ANTAGONISM
β_1-Adrenergic	Heart	Increased heart rate and ectopy Increased contractility	Decreased heart rate and ectopy Decreased contractility
β_2-Adrenergic	Airway (smooth muscle) Peripheral vasculature	Decreased tone (relaxation) Decreased tone (relaxation)	Increased tone (contraction) Increased tone (contraction)

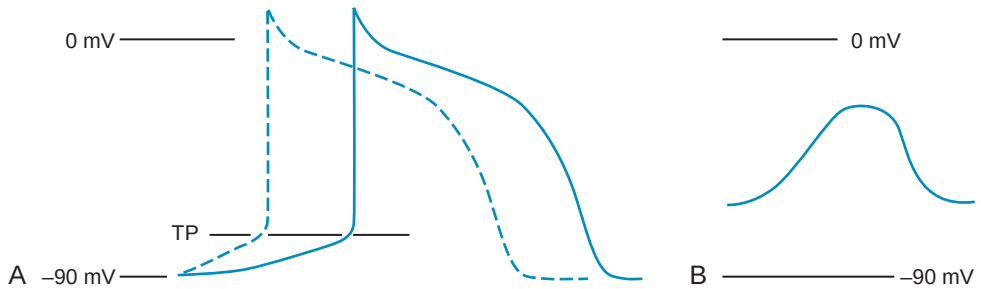


Fig. 69.5. **A,** Enhanced normal automaticity (*dashed line*). **B,** Abnormal automaticity. *TP,* Threshold point. (From Marriott HJL, Conover MB: Advanced concepts in dysrhythmias, ed 2, St. Louis, 1989, Mosby.)

general, class III agents are alternatives to class I agents for the treatment of many ventricular and atrial dysrhythmias.

Bretylium

Bretylium was once the most commonly used class III agent. Due to its frequent hemodynamic side effects and limited effectiveness, bretylium is no longer available in the United States.

Amiodarone

Amiodarone is approved for the treatment of ventricular and supraventricular dysrhythmias and is the preferred choice for drug treatment of acute ventricular tachycardia. In addition to features in common with all class III agents, amiodarone has other effects, including actions that are similar to those of class IA, II, and IV agents.

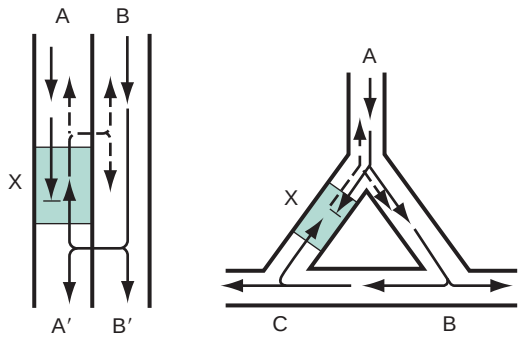


Fig. 69.6. Mechanism of reentry.

The serum half-life of amiodarone is 25 hours after a single IV dose and up to 50 days during long-term oral use. Because of its unusual pharmacokinetics, oral regimens vary widely. The acute side effects of amiodarone include hypotension, bradycardia, and heart failure (Box 69.2). There is an additive risk of bradycardia and hypotension when amiodarone is used in conjunction with calcium channel or β-adrenergic blockers. Rates of prodysrhythmia are relatively low. Long-term amiodarone use is associated with extracardiac side effects, including irreversible lung and thyroid disease. Amiodarone alters the pharmacokinetics of numerous other drugs, including digoxin and warfarin.

Ibutilide

Ibutilide has a unique mechanism of action characterized by the induction of a slow inward Na^{2+} current, thereby prolonging the refractory period. IV ibutilide is approved for cardioversion of atrial fibrillation and atrial flutter. Because of QT prolongation and the risk of polymorphic VT, most health care providers choose to start ibutilide only in a monitored setting.

Sotalol

Sotalol is a β-adrenergic receptor blocker with type III antidysrhythmic properties. It is used orally for the suppression of supraventricular and ventricular dysrhythmias. Like ibutilide, start sotalol should be started in a monitored setting, watching for QT prolongation; it has a very limited role in emergency care.

Dofetilide

Dofetilide is a powerful class III agent approved for chemical cardioversion and maintenance of sinus rhythm in patients with

BOX 69.1

Classification of Antidysrhythmic Drugs

CLASS I
Sodium (fast) channel blockers—slow depolarization with varying effects on repolarization. These drugs have membrane-stabilizing effects.

Class IA
Moderate slowing of depolarization and conduction; prolong repolarization and action potential duration.
Procainamide
Quinidine
Disopyramide

Class IB
Minimally slow depolarization and conduction; shorten repolarization and action potential duration.
Lidocaine
Phenytoin
Tocainide
Mexiletine

Class IC
Markedly slow depolarization and conduction; prolong repolarization and action potential duration.
Flecainide
Encainide
Lorcainide
Propafenone (shares properties with class IA agents)
Vernakalant (atrial-specific, investigational)

CLASS II
β-Adrenergic blockers
Propranolol
Esmolol
Metoprolol
Atenolol

CLASS III
Antifibrillatory agents—prolong action potential duration and refractory period duration with antifibrillatory properties.
Bretylium (historical significance)
Amiodarone
Dofetilide
Ibutilide[a]
Sotalol[b]
Dronedarone
Azimilide

CLASS IV
Calcium (slow) channel blockers
Verapamil
Diltiazem

MISCELLANEOUS
Digitalis
Magnesium sulfate
Adenosine

[a]Shares activity with class I agents.
[b]Shares activity with class II agents.

BOX 69.2

Adverse Effects of Amiodarone

ACUTE EFFECTS
Hypotension
Slowing of heart rate
Decreased contractility

LONG-TERM EFFECTS
Common Effects
Corneal deposits
Photosensitivity
Gastrointestinal intolerance

Less Common Effects
Hyperthyroidism
Heart failure
Pulmonary toxicity, fibrosis
Hypothyroidism
Bradycardia
Prodysrhythmic effect

DRUG INTERACTIONS
Increased Levels
Phenytoin
Procainamide
Warfarin
Digoxin
Flecainide

atrial fibrillation or flutter. However, because of its high risk for prodysrhythmia, it can only be prescribed by physicians with specialized training.[1] It has no current role in emergency care.

Dronedarone

Structurally related to amiodarone, dronedarone displays class III properties in addition to those of other antidysrhythmic classes. Dronedarone is approved for oral use to maintain sinus rhythm in patients with atrial fibrillation or flutter but is contraindicated in patients with severe or recent heart failure. It has no current role in emergency care.

Class IV Agents

Class IV agents block slow Ca^{2+} channels, slowing conduction within the AV node and suppressing the SA node to a lesser degree. Like beta blockers, these are used in patients with supraventricular tachycardia.

All class IV agents are associated with peripheral vasodilation. Verapamil has the least effect on peripheral vascular tone, and diltiazem has an effect between that of verapamil and purely peripherally acting calcium channel blockers (eg, nifedipine). In the acute setting, IV calcium salts (1 g, slow IV delivery) attenuate these peripheral vasodilatory effects. Class IV drugs should not be administered to patients with second- or third-degree AV block unless a functional pacemaker is in place and should be avoided in patients with first-degree block.

Diltiazem

IV diltiazem dosing is a 0.25- to 0.35-mg/kg bolus over 2 minutes. For longer term rate control, a continuous infusion (5–15 mg/hr initially, then titrated to need) or an oral dose (60–90 mg immediate-release formulation initially) will sustain the response.

BOX 69.3

Adverse Effects of Digitalis

COMMON EFFECTS
Gastrointestinal intolerance (eg, nausea, vomiting, abdominal pain, diarrhea, anorexia)
Fatigue
Drowsiness
Visual color disturbances
Headache
Depression
Apathy

LESS COMMON EFFECTS
Psychosis
Cardiac symptoms
Heart block
Increased ectopy
Combined block and ectopy (multifocal atrial tachycardia with block or complete atrioventricular block with accelerated junctional rhythm, usually in overdose setting)
Ventricular tachycardia

Verapamil

IV verapamil is rarely used today given the advent of diltiazem, although still effective. If used, start at a dose of 0.1 mg/kg over 1 to 2 minutes; for the average healthy adult, this translates to a dose of 5 to 10 mg, which can be repeated or increased by 50% if unsuccessful and there is no hypotension 10 minutes after administration. In older adults or those with borderline hypotension (systolic blood pressure of 90–110 mm Hg), use a smaller dose (0.05 mg/kg or 2.5-mg increments).

Miscellaneous Agents

Digoxin

Digitalis compounds have a variety of effects on myocardial cells. Digoxin inhibits the adenosine triphosphate (ATP)–dependent Na^+-K^+ exchange pump, increasing intracellular Na^+ concentrations and decreasing intracellular K^+ concentrations. The resultant increase in intracellular Ca^{2+} concentration accounts for the positive inotropic effects of digitalis. The prodysrhythmic effects of digoxin are enhanced automaticity and triggered activity, particularly at high therapeutic or toxic doses. At the same time, digoxin slows AV node conduction via lengthening of the refractory period.

Digoxin (0.25–0.5 mg IV) can control the ventricular rate in patients with supraventricular tachycardia, notably atrial fibrillation and atrial flutter. Because of its delayed onset of action (often not therapeutic for 30 minutes or longer and peaking at 6 hours) and narrow therapeutic window, digitalis is not a first-line agent for emergency therapy.

Side effects of digoxin are listed in Box 69.3 and are aggravated by hypokalemia, hypercalcemia, hypomagnesemia, increased catecholamine levels, and acid-base disturbances. Digoxin toxicity is discussed in Chapter 147.

Magnesium

Magnesium can abort ventricular dysrhythmias via its membrane-stabilizing properties. Magnesium (1–2 g IV) may terminate torsades de pointes and is an adjunct in VT therapy.

Adenosine

Adenosine is a naturally occurring purine nucleoside that is the best choice for the termination of regular, nonatrial, narrow-complex tachydysrhythmias, notably junctional reentry. Administered as an IV bolus, adenosine causes an abrupt slowing of AV conduction in anterograde and retrograde pathways. Adenosine has an onset of action of 5 to 20 seconds and a duration of effect of 30 to 40 seconds. Except in rare cases, adenosine has little or no effect on infranodal conduction pathways. For this reason, adenosine is an option as a diagnostic (and sometimes therapeutic) agent in patients with wide-complex tachydysrhythmia when the cause is unclear.

Start adenosine by using a 6-mg rapid IV bolus (large, non–distal vein followed by a rapid flush) in for adults (≥50 kg body mass); key is the rapid bolus technique, with higher success noted after training to adhere to that tenet of delivery.[4] If no response is seen within 1 to 2 minutes, increase the dose to a 12-mg IV bolus. If no effect is seen after a second 12-mg dose, then reassess the rhythm and use another therapy. There is no benefit to repeating adenosine when transient lowering is seen after a dose is given, followed by a return to the previous rhythm. Pediatric doses are 0.05 mg/kg initially, with doubling at similar intervals, up to a total dose of 0.25 mg/kg.

Side effects occur in up to one-third of patients given adenosine and are usually minor and self-limited. These include flushing, dyspnea, chest pressure, nausea, headache, dizziness, transient bradycardia or heart block, and hypotension. Asystole is possible but generally transient.

Because of its short duration of action, adenosine is not an effective rate control agent for atrial fibrillation or flutter, although it can help unmask these rhythms when not apparent on the initial surface ECG.

APPROACH TO DYSRHYTHMIA: RECOGNITION AND MANAGEMENT

Clinical Features

Dysrhythmias are classified according to their electrophysiologic origin, appearance on the ECG, and underlying ventricular rate. Although overlap exists, the following categorization is useful:

- Bradycardias
- Extrasystoles
- Narrow-complex (QRS < 0.12 second) tachycardias (regular and irregular)
- Wide-complex (QRS ≥ 0.12 second) tachycardias (regular and irregular)

Classically, the approach to any specific dysrhythmias is broadly defined based on clinical stability, which is driven by the effect on perfusion. Clearly unstable patients have severe or multiple end-organ features of hypoperfusion, such as altered sensorium, respiratory distress, hypotension, syncope, and/or chest pain suggestive of myocardial ischemia. Stable patients may be asymptomatic or have mild symptoms, such as lightheadedness, dyspnea on exertion, palpitations, and/or mild anxiety. In practice, clinical stability is a continuum; in the absence of profound altered sensorium or hypotension, a clear line distinguishing stable and unstable patients is often not present. One simple axiom is important:

- Clearly unstable patients with a primary dysrhythmia outside of a clear external trigger (eg, bradycardia for hypothermia or tachycardia for hypovolemic or distributive shock) need prompt electrical therapy—a countershock if there is a fast rate with a pulse and cutaneous pacing if there is a slow rate with a pulse.

Care of patients with cardiac arrest (those with no pulse) is covered elsewhere in this text (see Chapter 8).

A key consideration is whether a dysrhythmia is the cause or effect of a clinical presentation; for example, rapid atrial fibrillation may cause hypotension or may be a response to volume depletion or ischemia. Failure to consider the clinical situation can lead to an inappropriate treating of the rhythm to the detriment of the patient (eg, giving a rate-slowing agent when the tachycardia is a response to volume depletion). Recognizing this potential, treatment of patients who are clearly unstable and with a dysrhythmia is best done assuming that the rhythm is the cause. In a stable patient, a more systematic approach should be used to identify the cause and choose the most appropriate therapy.

Initial Assessment of Stable Patients

The approach begins with gathering evidence from the history, physical examination, and 12-lead ECG with a rhythm strip. The nature of any symptom is important, including the timing, velocity of onset (gradual vs. abrupt, with the latter often re-entrant based), and duration. For the patient with palpitations, questions about the rate and regularity of the heartbeat are often asked, and having the patient tap out the rhythm with a finger can aid. Other important questions are about precipitating events and associated symptoms, such as dizziness, chest pain, dyspnea, and/or syncope. The past history—notably of rhythm disturbances, ischemic or structural heart disease—and a medication history may raise a concern for specific rhythms. For example, a new and symptomatic wide-complex tachycardia in a patient with known ischemic heart disease is much more often VT than a supraventricular dysrhythmia. Occasionally, the family history helps, particularly if there are first-degree relatives with a history of dysrhythmia, unexplained syncope, or sudden death—all of which suggest an inherited disorder, such as an accessory pathway or Brugada's syndrome.

Aside from palpating the pulse and listening to the heart sounds, the physical examination should be focused on detecting evidence of end-organ hypoperfusion (eg, agitation or confusion) or clues to an underlying cause of the dysrhythmia (eg, left ventricular failure). Observing the patient's rhythm on a continuous cardiac monitor while he or she reports symptoms can add valuable information.

DIAGNOSTIC CONSIDERATIONS

Differential Diagnosis

Loose leads, muscle contraction, shivering, tremors, and other patient movement can produce artifactual findings on a monitor, rhythm strip, or 12-lead ECG (Fig. 69.7). Such pseudodysrhythmias mimic and are often mistaken for serious dysrhythmias, including ventricular fibrillation. The important point is avoiding decisions based solely on the ECG without incorporating the clinical context.

Diagnostic Testing

The 12-lead ECG is essential to evaluating any patient with a suspected dysrhythmia. Use of a single ECG lead is often adequate for diagnosis, especially in unstable patients; multiple leads are optimal in stable patients. The latter helps detect as the presence or absence of P waves (often best seen in inferior leads or $V_{1\text{-}2}$; Fig. 69.8), the relationship between P waves and QRS complexes, prolongation of the QRS and QT interval, and evidence of ischemia or prior myocardial infarction (Box 69.4). For certain conditions, such as Brugada's syndrome, the 12-lead ECG, together with a history of syncope, is diagnostic. Because useful information

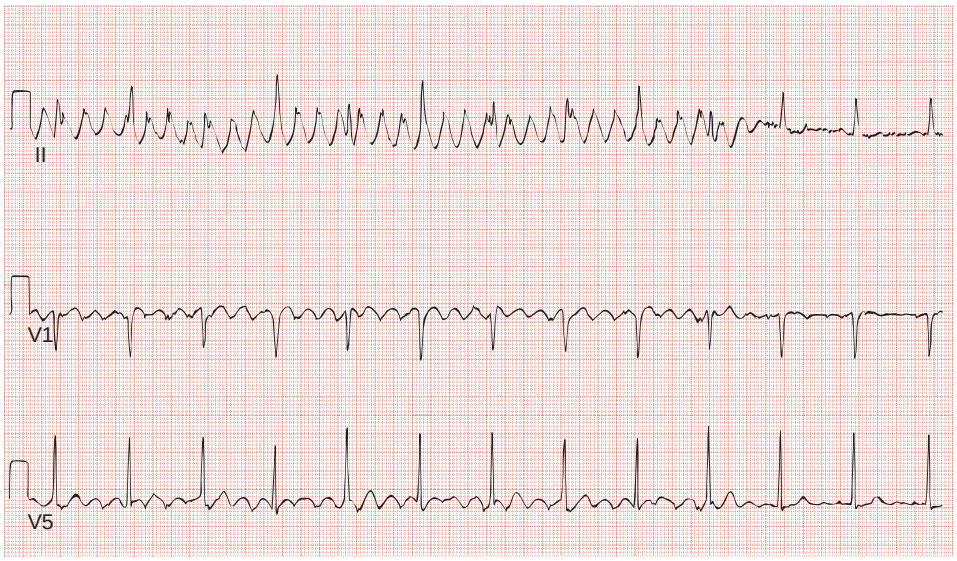


Fig. 69.7. Pseudodysrhythmia. In this case, atrial flutter waves appear to be present but are recognized as an artifact when the patient and right side of the electrocardiogram are examined.

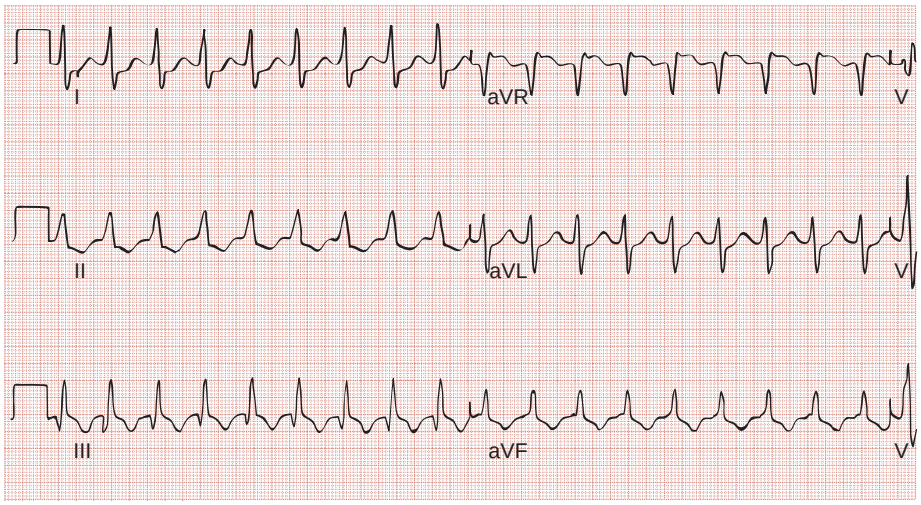


Fig. 69.8. Note the P waves before the QRS complexes in lead aVF.

BOX 69.4

Basic Electrocardiographic Observations During Dysrhythmia Analysis

1. Ventricular rate—fast (>100 complexes/min), slow (<60 complexes/min), or normal (60–100 complexes/min).
2. Rhythm—regular, completely irregular (irregularly irregular or chaotic), regular with occasional irregularity, or grouped impulses; calipers, long strips help detect subtle irregularities
3. QRS width—prolonged (>0.12 s), borderline (0.09–0.12 s), or normal. If determined without electrocardiogram being physically present (eg, prehospital radio medical command), ask for QRS duration in "number of small boxes" from printed rhythm strip (each box = 0.04 s) to ensure accuracy.
4. P wave presence and relationship to QRS complexes—May require mapping of P waves with calipers to detect those falling within QRS complex or T wave.
5. Rhythm changes—examine these areas closely for clues.
6. Multiple leads, especially chest leads or esophageal lead if difficulties with P wave visualization are experienced.
7. Comparison with previous tracings (if available) is often valuable.

about paroxysmal dysrhythmias is at the onset or termination of the rhythm, inspect those areas carefully and save the strip(s) for future reference.

Maneuvers that alter autonomic tone target relative increases in parasympathetic tone through the vagus nerve to help expose certain dysrhythmias and terminate others. In the ED, these maneuvers often fail, likely from a selection bias (easy responders terminate before arrival) or poor clinical technique. Vagal maneuvers, such as carotid sinus massage and the Valsalva maneuver, transiently slow AV conduction, which may help terminate or uncover a supraventricular rhythm disturbance. The key to using physical methods of enhancing parasympathetic tone is to optimize technique—have the patient lie flat, lift the legs, and ask for a Valsalva effort, with or without massage, to enhance success.[5,6] A nodal reentrant tachycardia may terminate abruptly with vagal maneuvers, whereas it often temporarily slows the ventricular rate in those with atrial fibrillation or atrial flutter; VT patients rarely have any change after vagal maneuvers. Auscultate the neck for bruits before carotid sinus massage, particularly in older patients, and avoid the maneuver if any are found or previous carotid disease is likely. Vagal maneuvers are frequently unsuccessful in the ED, but will rarely result in clinical deterioration. Poor technique often impairs massage-based maneuvers—for example, not

having the patient supine or incorrect massage of the carotid artery instead of the carotid body. Other vagotonic maneuvers, such as rectal or ocular massage and ice water head dunking, are impractical and less effective.

MANAGEMENT

Sinus Bradycardia and Sinoatrial and Atrioventricular Block

Bradycardia is defined as a ventricular rate of less than 60 beats/min, although in practice rates above 50 beats/min are not usually a concern. Bradycardia occurs because of depression of the sinus node or because of a conduction system block; when the rate falls below a particular threshold, a subsidiary pacemaker elsewhere in the atrium, AV junction, or ventricle may assume the dominant role, resulting in an escape rhythm.

Sinus Bradycardia

Sinus bradycardia is characterized by a P wave with normal morphology, a fixed P-P interval equal to the R-R interval, and a ventricular rate below 60 beats/min (Fig. 69.9). This pattern may be found in healthy individuals, particularly well-conditioned athletes or young adults with a high resting vagal tone. Sinus bradycardia occurs in a variety of pathologic conditions associated with vagal stimulation, ranging from autonomic-mediated syncope to hemoperitoneum or acute inferior wall myocardial infarction. Other pathologic causes of sinus bradycardia include hypothermia, hypoxia, drug effects (especially β-adrenergic blockers and calcium channel blockers), and intrinsic sinus node disease (ie, sick sinus syndrome; see later). When sinus bradycardia drops below 40 beats/min, a junctional escape rhythm often emerges.

Sinus bradycardia is often asymptomatic and requires no specific treatment. If needed, first-line treatment for symptomatic sinus bradycardia in adults is atropine, a 0.5-mg IV bolus, repeated as needed every 3 to 5 minutes, to a total dose of 3 mg. Occasionally, a second-line agent such as dopamine or epinephrine infusion is needed. Emergency cutaneous pacing for sinus bradycardia is rarely indicated.

Sinus Dysrhythmia

Sinus dysrhythmia is a manifestation of the natural variation in heart rate that occurs during the respiratory cycle, manifested on the surface ECG as normally conducted P waves with a variable P-P interval (Fig. 69.10). It is a normal variant and is seen frequently in children and young adults.

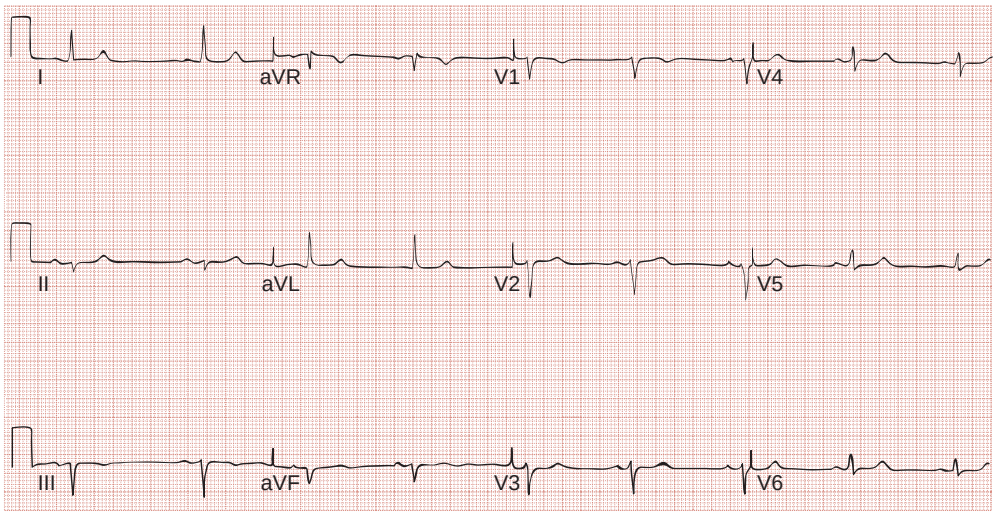


Fig. 69.9. Sinus bradycardia.

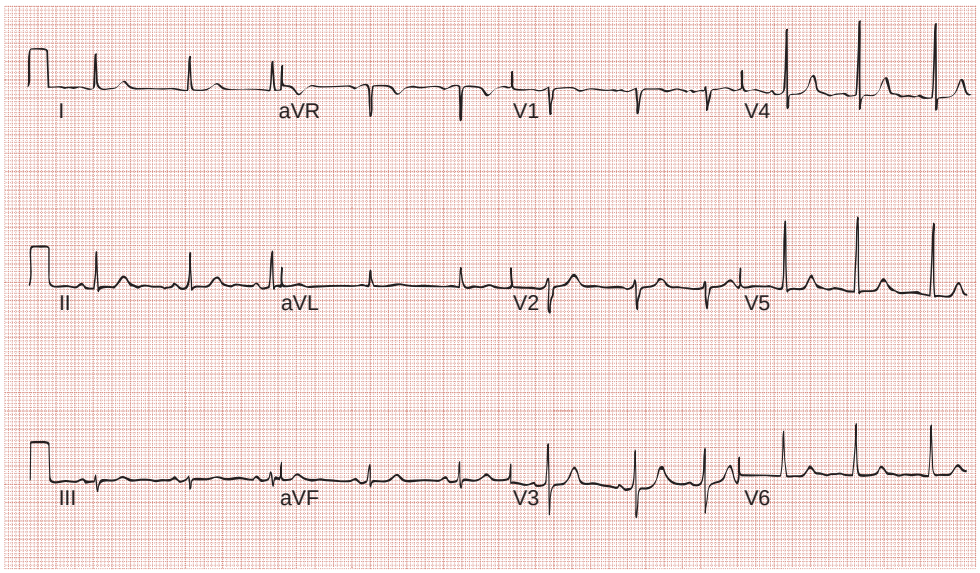


Fig. 69.10. Sinus dysrhythmia (note slight irregularity).

Sinus Arrest and Sinoatrial Exit Block

A lack of atrial depolarization can occur because of failure of the sinus node to generate an impulse (sinus arrest) or failure of impulse conduction out of the SA node (SA exit block; Fig. 69.11). With SA exit block, it is not uncommon to see dropped P waves in regularly occurring patterns, representing 2:1, 3:1, or 4:1 block. Sinus arrest and SA exit block may be manifestations of intrinsic SA node disease, but can also be seen under conditions of increased vagal tone, whether benign or pathologic. When symptomatic, the approach to treatment is similar to that for sinus bradycardia.

Sick Sinus Syndrome

Sick sinus syndrome (SSS) is a group of dysrhythmias caused by disease of the sinus node and its surrounding tissues, creating sinus bradycardia, sinus arrest, or SA exit block. A variant of SSS known as bradycardia-tachycardia syndrome is characterized by one or more of these bradydysrhythmias alternating with a tachydysrhythmia, typically atrial fibrillation. SSS is most common in older adults, a result of fibrotic degeneration. It is also associated with cardiomyopathies, connective tissue diseases, and certain drugs. In the acute setting, treat the specific rhythm, although be wary about a profound subsequent bradycardia that could require temporary pacing following the use of a nodal blocking agent (especially a calcium channel blocker) for the tachycardic presentation. Long-term management requires permanent pacemaker placement for symptomatic bradycardia to allow for pharmacologic therapy for atrial fibrillation.

Atrioventricular Block

AV block results from impaired conduction through the atria, AV node, or proximal His-Purkinje system. First- and second-degree AV blocks represent partial impairment of conduction, whereas third-degree block indicates complete interruption. Advanced or high-grade AV block refers to AV block resulting in a ventricular rate that is pathologically slow.

First-Degree Atrioventricular Block

First-degree AV block is from prolonged conduction at the level of the atria, AV node (most common), or His-Purkinje system. On the ECG, first-degree AV block shows a prolonged PR interval (>0.20 second), typically with a narrow QRS complex (Fig. 69.12). First-degree AV block is a normal variant in up to 2% of healthy young adults. First-degree AV block requires no specific treatment other than avoiding any prolonged nodal blocking agents.

Second-Degree Atrioventricular Block

Second-degree AV block is when one or more (but not all) atrial impulses fail to reach the ventricles. The conduction ratio is the number of P waves to the number of QRS complexes over a period of time (eg, 3:2, 2:1). In circumstance in which the atrial rate is unusually fast—atrial flutter, for example—a conduction ratio of 2:1 may be physiologic, reflecting the normal refractory period of the AV node. However, in most other cases, a conduction ratio more than 1:1 is pathologic. Second-degree AV block is classified

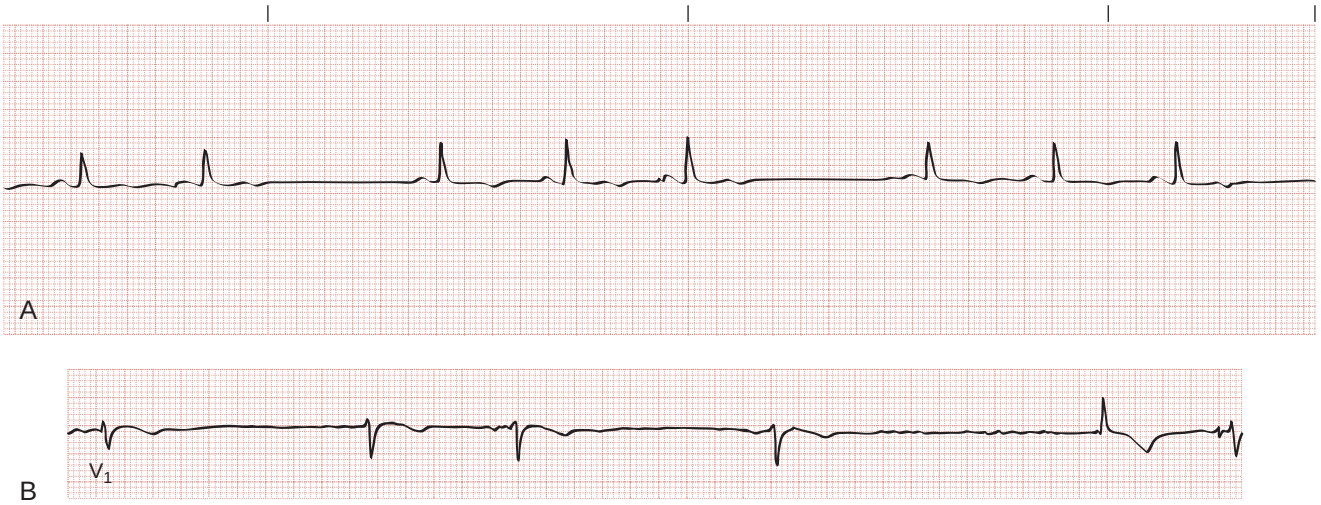


Fig. 69.11. A, Incomplete sinus block. **B,** Complete sinus block (sinus arrest) with ventricular escape rhythm.

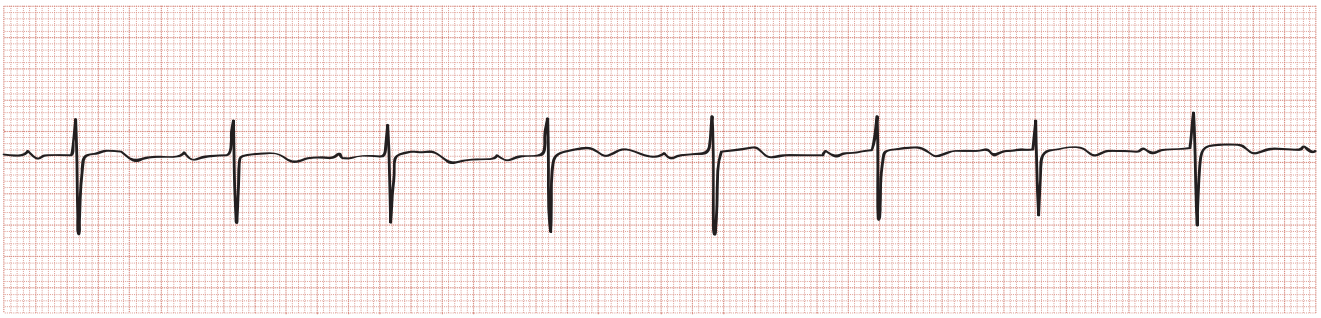


Fig. 69.12. First-degree atrioventricular block.

into two types on the basis of the underlying pathophysiology and appearance of the ECG (Table 69.3).

Type I Second-Degree Atrioventricular Block. Type I second-degree AV block, also called Wenckebach or Mobitz I AV block, is associated with progressive impairment of conduction within the AV node. The surface ECG shows a lengthening of the PR interval from beat to beat until a P wave is entirely blocked (so-called dropped beat). This pattern gives the appearance of successive P waves retreating into the preceding QRS complexes (Fig. 69.13). Grouped beating (eg, pairs, trios) occurs and is not unique to type I second-degree AV block (Box 69.5).

Type I second-degree AV block occur in a variety of conditions, benign and pathologic; often, these are associated with increased vagal tone and do not require specific treatment. In the setting of an acute myocardial infarction, type I second-degree AV block is generally transient and associated with a good outcome.

TABLE 69.3

Features of Types I and II Second-Degree Atrioventricular Block

FEATURE	TYPE I	TYPE II
Clinical	Usually acute Inferior myocardial infarction Rheumatic fever Digitalis or beta blockers	Often chronic Anteroseptal Lenègre disease (Lev disease) Cardiomyopathy
Anatomic	Usually AV node	Infranodal
Electrophysiology	Increased relative refractory period Decremental conduction	No relative refractory period All or none conduction
Electrocardiographic features	RP/PR reciprocity Prolonged PR interval QRS duration normal	PR interval stable PR interval usually normal QRS duration prolonged
Response to atropine and exercise	Improves	Worsens
Response to carotid massage	Worsens	Improves[a]

[a]Primarily refers to conduction ratio.
AV, Atrioventricular.

Type II Second-Degree Atrioventricular Block. Type II second-degree AV block, or Mobitz II block, is a conduction block just below the level of the AV node. On the surface ECG, conduction of atrial impulses is sporadic and typically periodic, but the PR interval does not widen from beat to beat (Fig. 69.14). The QRS complex is usually narrow, but concomitant infranodal conduction disturbances (ie, bundle branch blocks) can be seen in those with type II second-degree AV block.

Type II second-degree AV block can occur at conduction ratios similar to those seen with type I second-degree block but can also occur at higher conduction ratios (eg, 3:1, 4:1, or higher). When the conduction ratio is exactly 2:1, it is hard to distinguish type I from type II second-degree AV block on the surface ECG. In general, the presence of a prolonged PR interval makes type I block more likely, whereas the presence of wide QRS complexes makes type II block more likely.

Type II second-degree AV block arises as a result of senescent degeneration, drug toxicity, ischemia, or other pathologic conditions; it generally carries a worse prognosis than type I second-degree AV block. In acute myocardial infarction, type II second-degree AV block is associated with anterior wall injury and is often a precursor to complete AV block. No specific therapy is needed, aside from ensuring that pacemaking capability is immediately available.

Third-Degree Atrioventricular Block

Third-degree AV block, also known as complete heart block, is absent conduction of any atrial impulses (Fig. 69.15). Complete heart block is typically accompanied by a slow escape rhythm, with the width and frequency of QRS complexes depending on the site of the escape rhythm pacemaker. Pacemakers above the His bundle are associated with a narrow-complex QRS at a rate of 45 to 60 beats/min, whereas pacemakers at or below the His bundle produce a wide-complex QRS at a rate of 30 to 45 beats/min.

BOX 69.5

Causes of Grouped Impulses

Wenckebach mechanism (usually at atrioventricular node, but can occur elsewhere)
Sinoatrial exit block
Atrial tachycardia or flutter with alternating conduction
Frequent extrasystoles
Nonconducted atrial trigemini
Concealed or interpolated extrasystoles

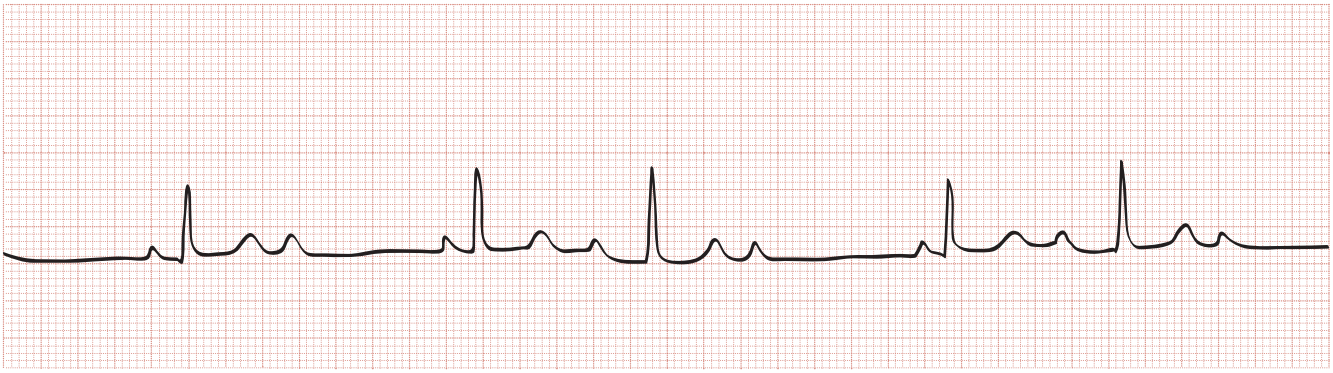


Fig. 69.13. Second-degree atrioventricular block, type I (Wenckebach). Note the prolongation of the PR interval between the second and third beats, followed by a nonconducted atrial impulse.

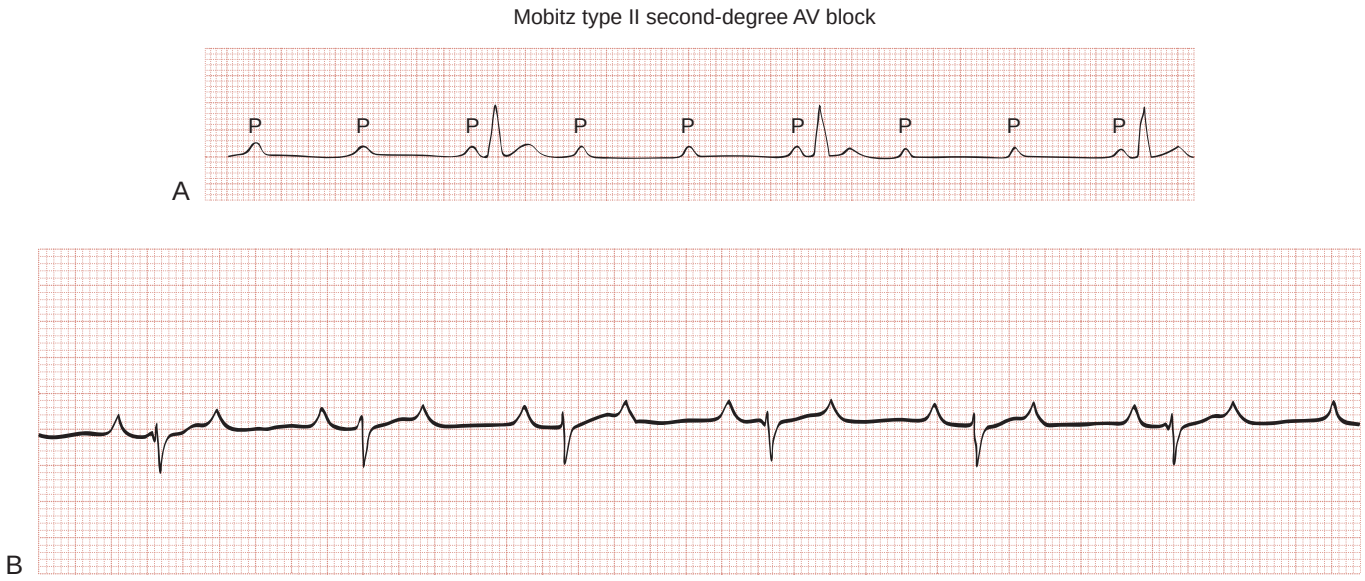


Fig. 69.14. A, Second-degree atrioventricular (AV) block, type II. In this example, 3:1 conduction is shown. **B,** Second-degree AV block with 2:1 conduction. From the rhythm strip alone, it is difficult to categorize this as a type I or II block. (**A** from Goldberger AL, Goldberger E: Clinical electrocardiography, ed 2, St Louis, 1981, Mosby.)

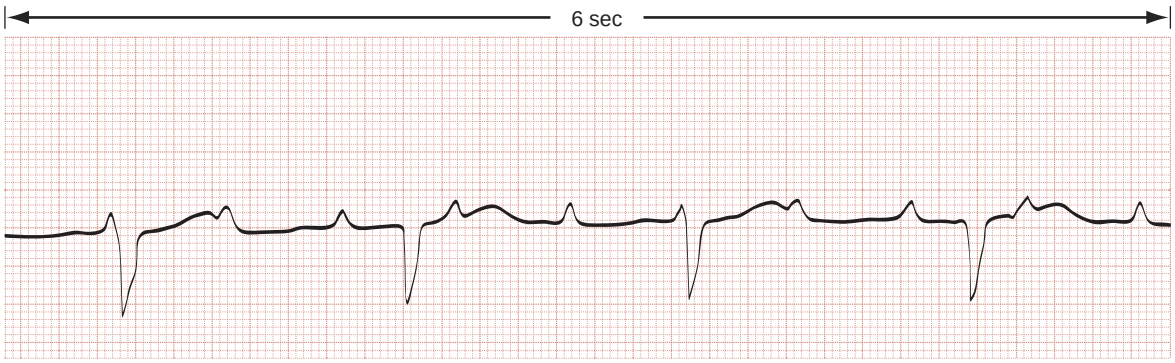


Fig. 69.15. Complete (third-degree) atrioventricular block. Note that there is no constant relationship of P waves to QRS complexes, even though some are noted in close proximity.

The hallmark of complete heart block is AV dissociation (ie, no electrocardiographic relationship between P waves and QRS complexes), with an R-R interval longer than the P-P interval. Conversely, the presence of AV dissociation with an R-R interval shorter than the P-P interval (eg, as occurs with accelerated junctional rhythms and VTs) does not imply third-degree heart block. When the atrial rate and the escape rates are similar (termed *isorhythmic*), detecting AV dissociation may require a long rhythm strip to track the P waves and QRS complexes. When complete heart block occurs in the presence of atrial fibrillation, the fibrillatory atrial waves are accompanied by a slow and regular ventricular response (so-called regularized atrial fibrillation). This specific dysrhythmia is classically associated with digitalis toxicity.

Third-degree AV block can be congenital but is usually acquired because of senescent degeneration of the electrical conduction system or as a result of acute ischemia, drug therapy, or other pathologic conditions (eg, Lyme or Chagas' disease).

In the ED setting, management of type II second-degree or complete AV block depends on the cause and presence of symptoms. Patients with newly acquired or symptomatic advanced AV block should be admitted to the hospital; in those who are markedly symptomatic (ie, signs of hypoperfusion at rest), temporary transcutaneous or transvenous pacing should be started until the reversible cause can be treated (eg, ST elevation myocardial infarction, beta blocker overdose) or a permanent pacemaker is placed. Atropine is usually ineffective.

Extrasystoles

An extrasystole is an electrical impulse originating from an ectopic atrial or ventricular focus. Depending on the site of origin and timing of the impulse, there may not be an associated mechanical contraction. The terms *premature atrial contraction* and *premature ventricular contraction* are widely used but are misleading, because contraction may not occur with the extra electrical activity seen on the ECG. The extrasystole and its preceding impulse are the couplet, and the coupling interval is the period between these two beats. Bigeminy (Fig. 69.16) occurs when there is an extrasystole after every native beat, so that every other impulse is extrasystolic; trigeminy (every third beat) and quadrigeminy (every fourth beat) are similar. Most extrasystoles are the result of enhanced automaticity from the atria, AV node, His-Purkinje system, or ventricles.

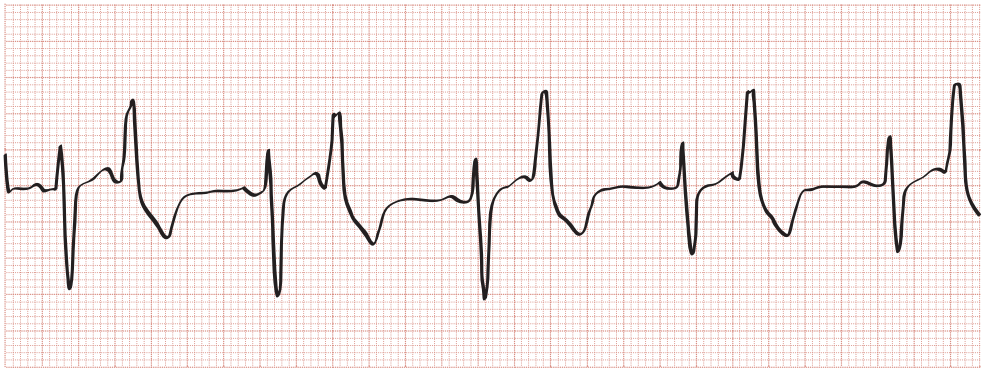


Fig. 69.16. Ventricular bigeminy.

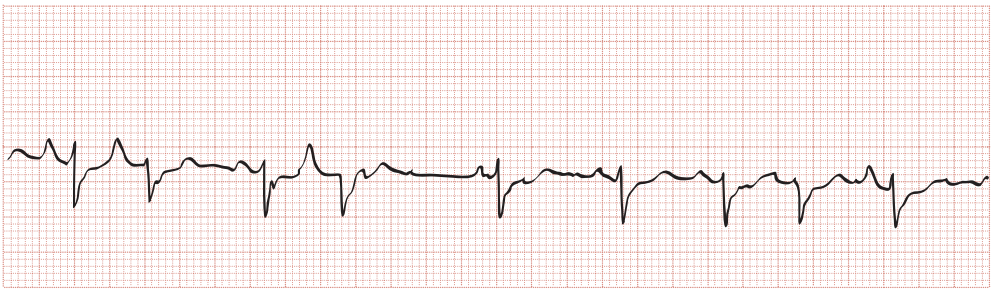


Fig. 69.17. Premature atrial contractions.

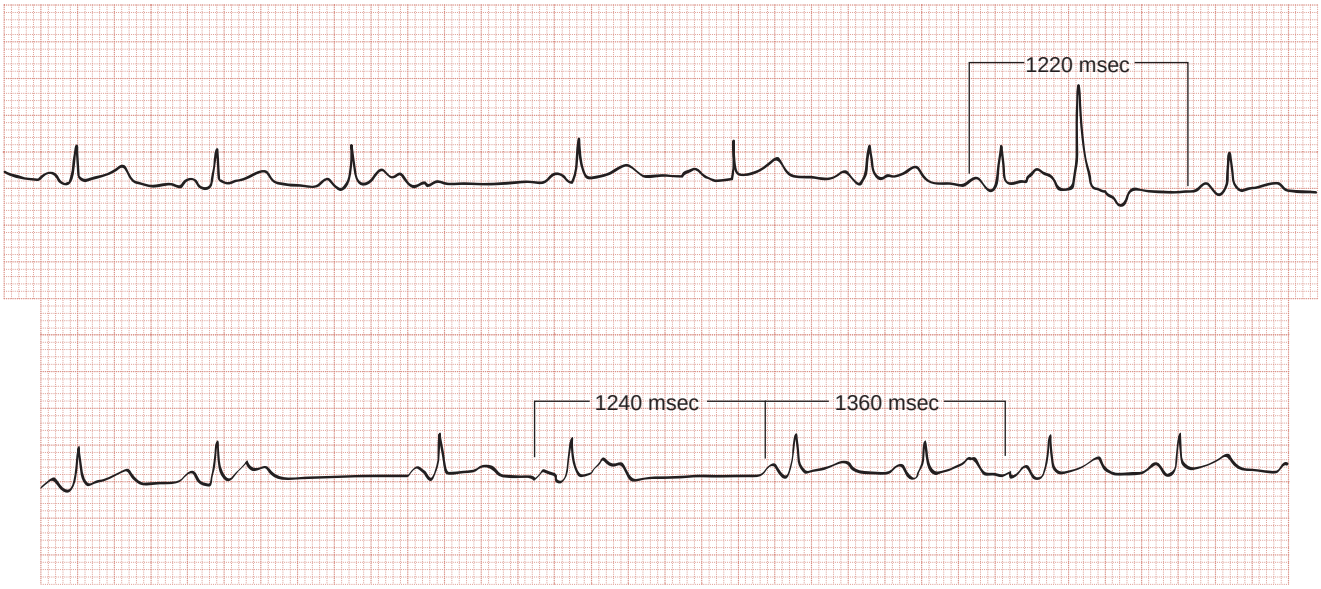


Fig. 69.18. Premature atrial contractions (PACs) with noncompensatory pauses and one aberrantly conducted impulse (*upper strip*). Note that conducted and nonconducted PACs reset the sinus node, with the latter creating a pause.

Premature Atrial Contractions

Premature atrial contractions (PACs; Fig. 69.17) are common and usually have little clinical significance. PACs on the ECG are an abnormal P wave early within a cardiac cycle, although sometimes the P wave may be difficult to detect if it is buried within the preceding T wave.

Most PACs will depolarize the sinus node, resetting its refractory period. Because of this, the P-P interval between two sinus beats surrounding a PAC will be less than twice the intrinsic P-P cycle length (see Fig. 69.17). If a PAC reaches the AV node or infranodal conducting system during its absolute refractory period, there will be no ventricular depolarization. A nonconducted (or blocked) PAC typically results in a noncompensatory pause (ie, R-R interval less than twice the intrinsic R-R cycle; Fig. 69.18) because the sinus node is reset. Blocked PACs are a common cause of electrocardiographic pauses and can be easily overlooked. On occasion, a PAC can be the precipitant of a more important dysrhythmia, such as atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachycardia (PSVT).

If a PAC reaches the infranodal conducting system during its relative refractory period, the QRS complex is widened (or aberrant), typically with an RBBB pattern. Because the refractory period depends on the previous cycle length, an early arriving PAC

TABLE 69.4

Features Distinguishing Premature Atrial Contractions With Abnormal Conduction From Premature Ventricular Contractions

PREMATURE ATRIAL CONTRACTIONS	PREMATURE VENTRICULAR CONTRACTIONS
No compensatory pause	Fully compensatory pause (unless interpolated)
Preceding P wave (different from sinus P wave; occasionally buried in T wave)	No preceding P waves (although retrograde atrial conduction can cause inverted P wave after QRS)
Usually classic right bundle branch block pattern (especially if long-short cycle sequence appears) identical to sinus QRS	Left bundle branch block, right bundle branch block, or hybrid pattern
QRS axis normal or near-normal	Frequently bizarre QRS axis
QRS rarely > 0.14 s	QRS often > 0.14 s

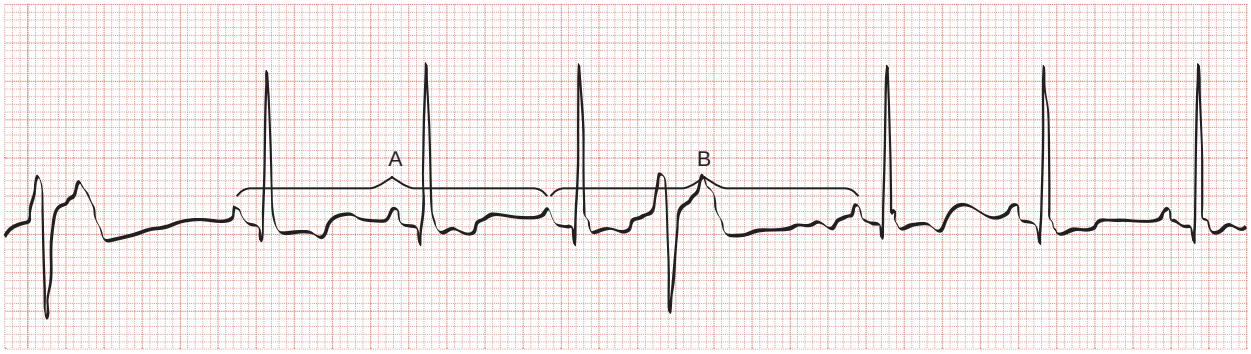


Fig. 69.19. Premature ventricular contractions with compensatory pause. Note that a sinus P wave can be seen in the T wave of the extrasystolic beat. Also note the secondary T wave changes in beats 1 and 4 (the T wave is opposite the main deflection of the QRS complex).

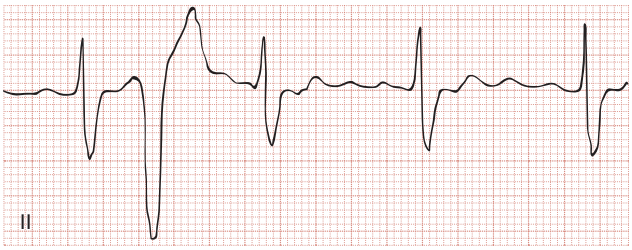


Fig. 69.20. Interpolated premature ventricular contraction.

that follows a long cardiac cycle is more likely to be aberrantly conducted. PACs are benign and require no specific treatment, but they may accompany catecholamine excess, myocardial ischemia, heart failure, hyperthyroidism, or a metabolic abnormality.

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) occur in a wide variety of states. Occasional PVCs are common in healthy adults or conditions associated with catecholamine excess, such as pain, anxiety, and use of stimulants (eg, caffeine, nicotine, cocaine, amphetamines). Pathologic conditions associated with frequent PVCs include myocardial infarction, potassium or magnesium disturbances, and medication toxicity (notably any with sodium channel–blocking or sympathetic enhancing activity). Although usually not requiring intervention, frequent PVCs may herald the onset of VT, especially in the setting of ST elevation myocardial infarction or in patients with a prolonged QT interval.

A PVC appears as a wide–QRS complex extrasystole without a preceding P wave (Fig. 69.19). Because retrograde conduction of a PVC rarely extends far enough to capture and reset the SA node, atrial impulses continue to arrive at the AV node at the intrinsic sinus rate. As a result, the R-R interval surrounding a PVC ends up being equal to exactly twice the intrinsic R-R interval length (see Fig. 69.19), a phenomenon termed a *compensatory pause.* Rarely, a PVC will capture the SA node, resulting in a noncompensatory pause, or will fail to capture the AV node, leaving the underlying rhythm completely unaffected (a so-called interpolated PVC; Fig. 69.20).

The morphology of a PVC depends on the origin of the impulse, with a left bundle branch block (LBBB) appearance resulting from an extrasystolic focus in the right ventricle, and vice versa. Multiform (or multifocal) PVCs come from more than one source and have variable morphologies. When a PVC occurs at or around the time that a supraventricular impulse is set to depolarize the ventricle, the result is a fusion QRS complex (Fig. 69.21). Table 69.4 lists common features of PACs and PVCs.

Direct therapy for PVCs toward correcting any precipitating condition whether it is catecholamine excess, drug effect, electrolyte imbalance, or cardiac ischemia (Box 69.6). Often, PVCs do not require treatment in the ED. When occurring in isolation, treat symptomatic PVCs with a beta blocker (metoprolol, 5–10 mg IV or 25–50 mg PO), although this is rarely an emergent need. Although lidocaine suppresses PVCs, do not use it routinely in the absence of VT because of limited clinical benefit and the risk of asystole.

Narrow-Complex Tachycardia

Narrow-complex tachycardias have a QRS complex duration of 0.12 second or less on the surface ECG and a ventricular rate more than 100 beats//min. The term *supraventricular tachycardia* may

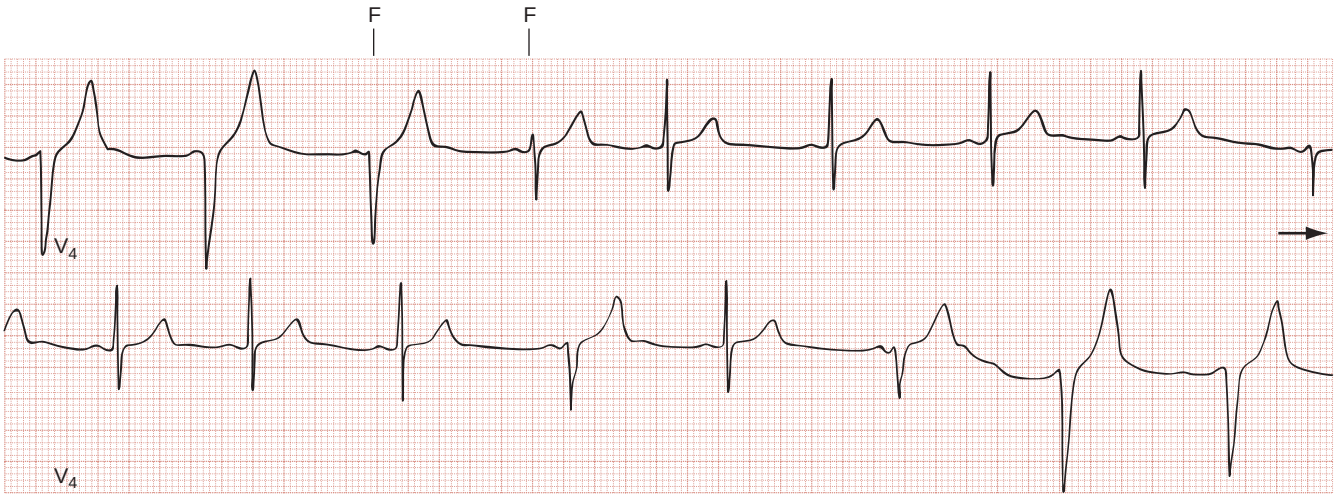


Fig. 69.21. Sinus rhythm with premature ventricular contraction and run of accelerated idioventricular rhythm. Note fusion beats (F) displaying a hybrid appearance of both morphologies.

BOX 69.6

Causes of Premature Ventricular Contractions and Ventricular Tachycardia

Acute or previous myocardial infarction or ischemia
Hypokalemia
Hypoxemia
Ischemic heart disease
Valvular disease
Catecholamine excess[a]
Other drug intoxications (especially cyclic antidepressants)
Idiopathic causes[b]
Digitalis toxicity
Hypomagnesemia
Hypercapnia
Class I antidysrhythmic agents
Ethanol
Myocardial contusion
Cardiomyopathy
Acidosis
Alkalosis
Methylxanthine toxicity

[a]Relative increase in sympathetic tone from drugs (direct or indirect) or conditions that augment catecholamine release or decrease parasympathetic tone.
[b]Isolated premature ventricular contractions (PVCs) can occur in up to 50% of young subjects without obvious cardiac or noncardiac disease; however, multiform and repetitive PVCs and ventricular tachycardia are rarely seen in this population.

be confusing; sometimes it is used specifically to note AV reentry tachycardia, but it can denote any tachycardia originating at or above the AV node.

ECG features that help distinguish between different narrow-complex tachycardias include the appearance of P waves and the regularity or irregularity of the R-R interval. For example, a narrow-complex tachycardia, an irregular R-R interval, and no clear P waves is almost certainly atrial fibrillation. With rapid tachycardias, evidence of atrial depolarization is often obscured by ventricular repolarization; for example, with a regular, narrow-complex tachycardia at a rate of 150 beats/min, it can be difficult to distinguish sinus tachycardia from atrial flutter or a JT. Vagal maneuvers or adenosine may transiently slow AV nodal conduction and expose evidence of atrial depolarization and aid diagnosis. Alternatively, the patient may convert to sinus rhythm, in which case AVNRT can be diagnosed and treated.

Sinus Tachycardia

Sinus tachycardia displays a regular, usually narrow-complex tachycardia, with normal P waves preceding each QRS complex (Fig. 69.22) on the ECG. In adults, sinus tachycardia rarely exceeds a rate of 170 beats/min; in infants and young children, it is not unusual to see rates above 200 to 225 beats/min. Sinus tachycardia tends to speed up or slow down in a graded and continuous manner over time, relayed by history or observed under care.

Sinus tachycardia is often a response to physiologic stress or is a compensation for a relative lack of perfusion or oxygen delivery (to increase cardiac output). Usually, the effect is salutary, as seen with hypovolemia, anemia, or hypoxemia; efforts to slow the heart rate without addressing the underlying pathophysiology are likely to make things worse. At other times, sinus tachycardia is a counterproductive response, as in acute decompensated heart failure or aortic stenosis, in which a decrease in filling time further compromises cardiac output. Even in these settings, therapy is aimed first at the underlying problem rather than the tachycardia.

Sinus tachycardia can be seen with any sympathetic excess, whether endogenous (eg, pain, anxiety, fever, hyperthyroidism) or exogenous (eg, stimulants, other drugs). The approach to the patient with sinus tachycardia centers on identifying and addressing the cause(s).

Atrial Tachycardia

Atrial tachycardia (AT) is an atrial rhythm with more than 100 QRS complexes/min arising from a non–sinus node site(s) within the left or right atrium. The electrocardiographic hallmark of AT is morphologically abnormal P waves on the surface ECG, all or mostly related to each QRS wave (Fig. 69.23). If the site of origin is close to the sinus node, atrial depolarization waves may look like a normal P wave. Depending on the atrial rate, the AV conduction ratio may be 1:1, 2:1, or higher.

AT is common in children and young adults with structural heart disease, often precipitated by the occurrence of a PAC. The rhythm is usually transient and does not require specific therapy. AT can occur in patients with structural heart disease, hypoxemia, metabolic disturbances, and/or drug toxicity. In patients taking

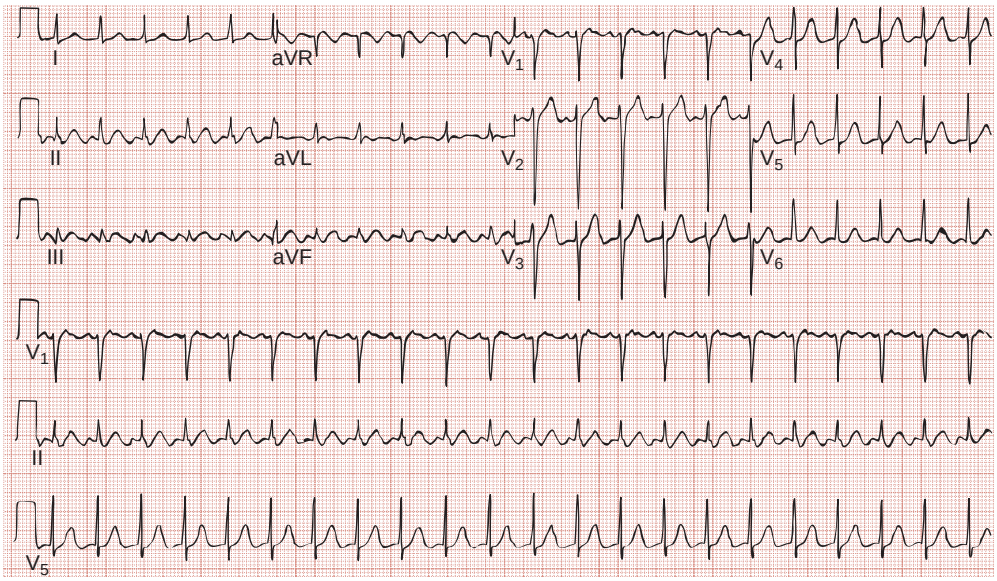


Fig. 69.22. Sinus tachycardia.

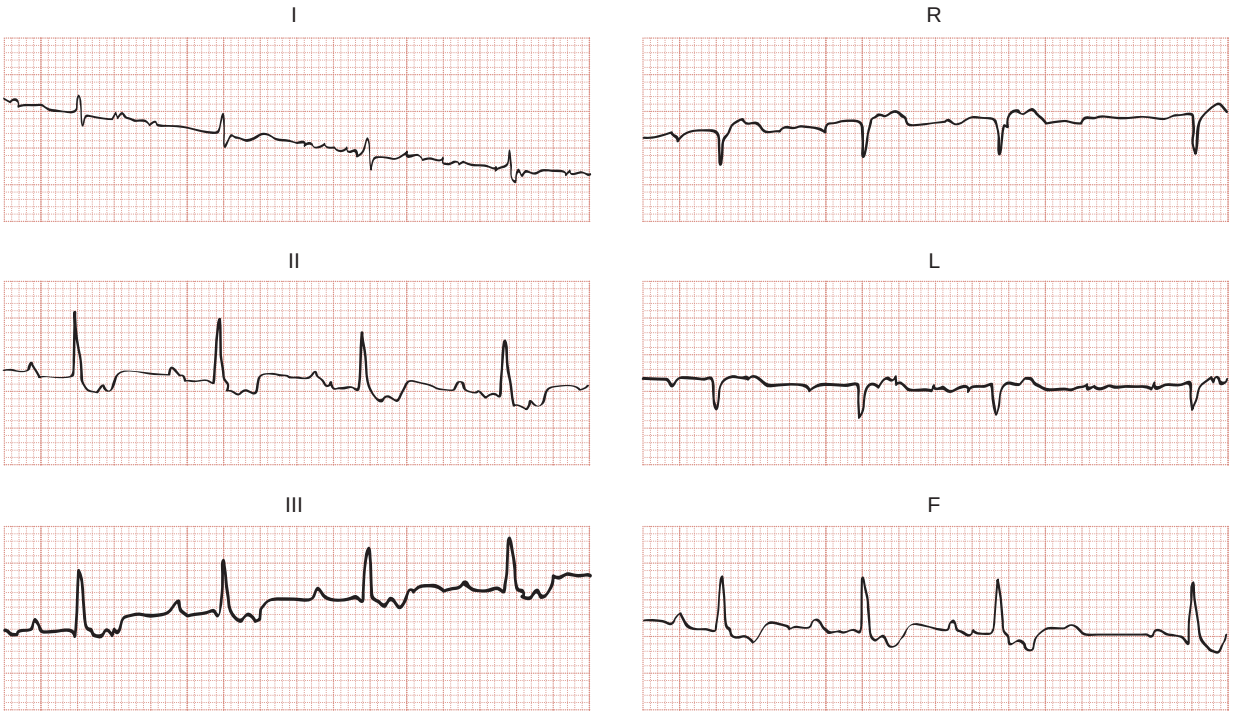


Fig. 69.23. Atrial tachycardia (with 2:1 conduction) in a patient with digitalis toxicity. (From Marriott HJL, Conover MB: Advanced concepts in dysrhythmias, ed 2, St. Louis, 1989, Mosby.)

digitalis, suspect toxicity if AT exists, particularly in the presence of 2:1 or higher grade AV block.

Multifocal atrial tachycardia (MAT) is a form of AT with three or more distinct P wave morphologies, and varying PR and P-P intervals from the multiple ectopic atrial foci (Fig. 69.24). MAT is associated with pulmonary disease (usually chronic obstructive pulmonary disease [COPD]) in up to 60% of cases, but can also be seen in the presence of primary cardiac pathology. On the surface ECG, MAT is often mistaken for atrial fibrillation because of the nonuniform atrial activity and irregular R-R intervals.

The approach to patients with AT is to identify and treat any precipitating factors, such as hypoxia or hypoxemia, electrolyte abnormalities, and drug toxicity. In patients with suspected hypomagnesemia, give supplemental magnesium (2 g IV over 5 minutes). Vagal maneuvers and adenosine are unlikely to be effective in AT or MAT, although these may help unmask the atrial activity. Pharmacologic therapy to slow AV conduction with a beta blocker or calcium channel blocker aids in the symptomatic but stable patient. Because AT and MAT are often precipitated by underlying illnesses, electrical cardioversion often fails or the rhythm recurs.

Atrial Fibrillation

Atrial fibrillation is identified by electrical chaos; it starts from unpatterned depolarization of atrial tissues caused by multiple

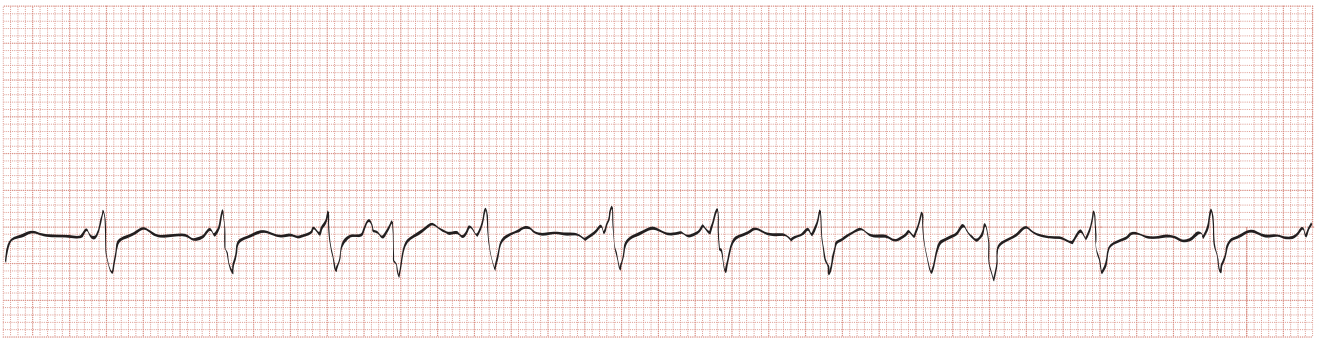


Fig. 69.24. Multifocal atrial tachycardia. Note that although the rhythm is irregular, at least three distinct P wave morphologies are present.

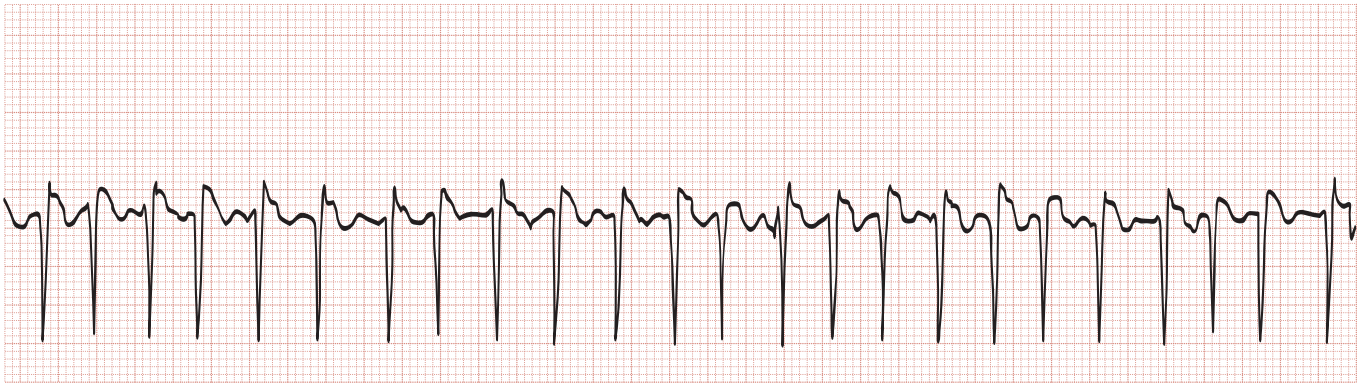


Fig. 69.25. Atrial fibrillation with rapid ventricular response. Note that the irregularity could be easily overlooked.

microreentry circuits, generating 300 to 600 atrial impulses/min. This chaotic activity reduces cardiac output from a loss of coordinated atrial contractions and from a rapid ventricular rate, both of which may limit the diastolic filling and stroke volume of the ventricles.

Atrial fibrillation is the most common sustained dysrhythmia, increasing with age; it affects 1% of the population older than 60 years and 5% of those 69 years old or more. Patients with atrial fibrillation can develop left atrial thrombi, especially in the left atrial appendage, and consequent embolic events. The risk of stroke is three to five times greater than in those without atrial fibrillation. Appendageal sequestration through transcatheter approaches may alter the need for long-term, clot-directed therapy to mitigate embolic risks, but empirical long-term data are absent. Also, ablation therapies may restore sinus rhythm without the need for ongoing drug therapy.

Atrial fibrillation may be paroxysmal (spontaneously converts), persistent (requires cardioversion to convert), or permanent (when no further efforts to restore sinus rhythm are planned). Long-term approaches to management depend on many factors, including chronicity, symptomatology, underlying heart disease, and other comorbidities.

The electrocardiographic hallmark of atrial fibrillation is a so-called irregularly irregular QRS pattern (Fig. 69.25). Although atrial fibrillation is not the sole cause of an irregular ventricular rhythm, it is the most common (Box 69.7). Atrial fibrillatory waves appear coarse or fine on the basis of their amplitude and are often best appreciated in the inferior leads or lead V_1.

Typically, the ventricular rate in adults with atrial fibrillation does not exceed 150 to 170 beats/min and often is slower, particularly in the presence of nodal blocking agents. Atrial fibrillation in an adult with a ventricular rate exceeding 200 beats/min strongly suggests the presence of an accessory conduction pathway and has important implications for management (see later). Frequently, rapid atrial fibrillation with an accessory path will have a wide QRS complex, but not always; if the irregularity of ventricular depolarization is not sought by the careful use of a caliper or similar measurement, it is easy to mistake this wide but chaotic rhythm for VT. When a wide QRS complex is seen at rates below 200 beats/min but with ventricular chaos, an existing or acquired bundle branch block with atrial fibrillation is likely present.

BOX 69.7

Causes of Completely Irregular (Chaotic) Rhythms

Atrial fibrillation
Atrial tachycardia or flutter with varying conduction
Multifocal atrial tachycardia
Multiple extrasystoles
Wandering pacemaker (usually atrial)
Parasystole

The Ashman phenomenon refers to aberrant ventricular conduction of an early-arriving atrial impulse following a relatively long R-R interval, the result of a partially refractory His bundle. Such aberrantly conducted impulses are commonly seen in atrial fibrillation but can occur in any irregular rhythm in which long-short cycle sequences occur; they typically assume an RBBB pattern (Fig. 69.26). Ashman beats can be mistaken for PVCs or paroxysmal VT, if sustained.

Atrial fibrillation is usually associated with underlying heart disease (myopathic or valvular) or hypertension (Box 69.8), but can also occur in isolation (so-called lone atrial fibrillation) or as

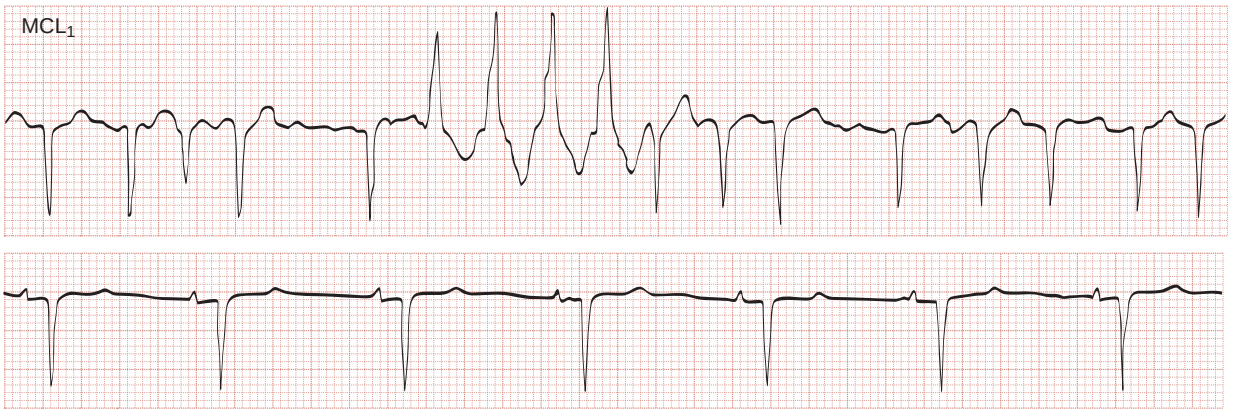


Fig. 69.26. Atrial fibrillation with classic Ashman phenomenon series of beats. Note the long-short cycle before aberrantly conducted impulses are sustained for four beats. (From Marriott HJL, Conover MB: Advanced concepts in dysrhythmias, ed 2, St. Louis, 1989, Mosby.)

BOX 69.8

Causes of Atrial Fibrillation

Hypertensive heart disease
Cardiomyopathy
Ischemic heart disease
Valvular disease (especially mitral)
Congestive heart failure
Pericarditis
Hyperthyroidism
Sick sinus syndrome
Myocardial contusion
Acute ethanol intoxication (holiday heart syndrome)
Idiopathic
Cardiac surgery
Catecholamine excess
Pulmonary embolism
Accessory pathway (Wolff-Parkinson-White) syndrome

a manifestation of hyperthyroidism. As many as one-third of patients with congestive heart failure also have atrial fibrillation.

The presentation of patients with atrial fibrillation is variable. For example, patients without underlying cardiopulmonary disease may tolerate atrial fibrillation with ventricular rates of 150 to 170 beats/min, noting only palpitations or exercise intolerance. Conversely, a patient with left ventricular dysfunction and new or worsened rate control may experience dyspnea at rest. In a stable patient with preexisting atrial fibrillation and a new rapid ventricular rate, direct the initial evaluation at determining if the tachycardia is a response to some other hemodynamic stress, such as decompensated heart failure, sepsis, hypovolemia, massive pulmonary embolism, or cardiac tamponade. Failure to recognize the underlying cause of a new tachycardia may result in counterproductive attempts at rate control or cardioversion. Measuring the thyroid-stimulating hormone level is prudent in those with new or recurrent atrial fibrillation, because this can trigger the condition and be easily treated.

For stable patients with persistent or recurrent rapid atrial fibrillation, administration of a nodal blocking agent with a goal of achieving a target ventricular rate of 120 beats/min or less is a first step.[7,8] IV calcium channel blockers (eg, diltiazem, verapamil) or beta blockers (eg, metoprolol) are easily titrated and can be followed by an oral agent. Nodal agents should not be used for rate control in the setting of accessory pathway conduction because AV conduction—with retrograde conduction into the accessory pathway—may be the only thing preventing the ventricular rate from accelerating and degenerating into ventricular fibrillation.

The debate as to whether asymptomatic patients with persistent atrial fibrillation benefit additionally from rhythm control via cardioversion or by other means (eg, ablation) is ongoing without a definitive answer. In older adults, those with recurrence despite rhythm-directed therapy, or with valvular disease, rate control is a wise choice; 40% to 60% of all patients placed on antidysrhythmics to sustain sinus rhythm fail. For patients younger than 50 years and without valve disease, attempts to maintain sinus rhythm to avoid cardiomyopathy or stroke are reasonable. In choosing rate control for the long term, the ideal target rate is unclear, with some advocating less than 80 beats/min at rest instead of the common goal of 110 beats/min or less; there is as yet no clear evidence of either target being superior.

For stable patients with new-onset or newly recurrent atrial fibrillation—defined as having a duration of 48 hours or less—or in those with therapeutic anticoagulation, ED cardioversion is an option unless valve disease, hypokalemia, or digitalis toxicity exist; the latter two conditions increase the risk of ventricular fibrillation with any type of conversion therapy.[7-11] If atrial fibrillation has been present longer than 2 days or for an uncertain interval in the absence of ongoing anticoagulation, do not attempt cardioversion to avoid the increased risk of systemic embolization (1%–4% at 30 days).

The choice of electrical versus pharmacologic cardioversion is dependent on institutional factors and patient preference, although success rates are higher with electrical conversion (80%–95%).[9,10] Among patients with new or recurrent atrial fibrillation of less than 48 to 72 hours duration, up to 50% will convert spontaneously to sinus rhythm within 24 hours. Patients with valvular disease fail cardioversion or recur frequently, limiting the ED options to rate control.

Various agents are available for the pharmacologic cardioversion of patients with stable atrial fibrillation in the ED, including the class IA, IC, and III antidysrhythmics (Box 69.9). In practice, IV procainamide, amiodarone, and ibutilide are the agents most commonly used in the ED setting. Amiodarone is commonly used because it initially slows the ventricular response without the need for an antecedent rate-controlling agent. Although there are differences in success rates among various agents, the overall response is 40% to 65% for drug-based ED cardioversion, although it may require up to 6 hours to occur. Do not use class IC antidysrhythmics in patients with structural or ischemic heart disease. For atrial fibrillation with accessory pathway conduction, use

BOX 69.9

Pharmacologic Approach to Atrial Fibrillation and Flutter Conversion

IV procainamide, 30–50 mg/min, up to a total dose of 18–20 mg/kg (12 mg/kg in patients with congestive heart failure) or until conversion or side effects occur
or
Amiodarone, 3–5 mg/kg IV, over 15–20 min
or
Ibutilide, 0.015–0.02 mg/kg IV, over 10–15 min (conversion usually occurs within 20 min if successful)
or
Oral propafenone, 600 mg (contraindicated in setting of structural heart disease or ischemia)
or
Oral flecainide, 300 mg (contraindicated in setting of structural heart disease or ischemia)

NOTE: If needed, a calcium channel blocker can be given before the type IA agent (if no contraindications are present) to lower the ventricular response rate to below 120 beats/min and to attenuate further tachycardia from the vagolytic effects of these agents.

BOX 69.10

CHA_2DS_2VASC Scoring for Guiding Clot-Directed Therapy in Atrial Fibrillation

CLINICAL FEATURE	POINTS
Congestive heart failure	1
Hypertension	1
Age ≥ 75 yr	2
Diabetes mellitus	1
Any previous stroke, transient ischemic attack, embolism	2
Gender—female	1
Age, 65–74 yr	1

Vascular disease—myocardial infarction, peripheral vascular disease, aortic plaque

Actions:

- Score 0—no clot-directed therapy
- Score 1—no therapy, aspirin, or oral anticoagulation; all reasonable
- Score 2 or higher—oral anticoagulation

Warfarin or newer oral anticoagulants chosen based on patient factors

Adapted from Fuster V, Rydén LE, Cannom DS, et al: 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 57:e101–e198, 2011.

procainamide as a first-line agent because it has no effect on AV conduction.

If choosing electrical cardioversion, obtain consent for the procedure and systemic sedation or analgesia needed. Rate-controlling agents before countershock are not required and may impair success.[12] While closely monitoring the airway and cardiac responses, place the pads on the front and back of the chest and use 100 J, biphasic and unsynchronized preferred; occasionally, a second attempt at 100 to 200 J is required.

Many patients with atrial fibrillation, whether paroxysmal or permanent, benefit from long-term anticoagulation as prophylaxis against stroke. The American Heart Association (AHA) and European Society of Cardiology recommend using the CHA_2DS_2-VAS_2 score to guide clot prevention therapy in those with atrial fibrillation (Box 69.10).[7,8] The choices include no therapy for the lowest risk strata (by definition those <65 years and without other features); aspirin (325 mg daily) for the next strata of patients who are still lower risk, and warfarin or one of the new oral direct thrombin inhibitors (eg, dabigatran, rivaroxaban, apixaban) for the remaining higher risk patients.[13,14] Although long-term anticoagulation typically falls beyond the scope of the ED, starting therapy early can enhance compliance. Start outpatient anticoagulation therapy in the ED only after confirming close and timely follow-up.

Atrial fibrillation alone is not an indication for hospital admission. Observation or admission is best in symptomatic patients with atrial fibrillation complicated by underlying acute or exacerbated cardiopulmonary disease, for those where duration is unknown and follow-up uncertain, for those who fail cardioversion or the dysrhythmia returns, and in all patients with concomitant new noncardiac illnesses.

Atrial Flutter

Atrial flutter is characterized by atrial depolarization occurring at a regular rate of 250 to 350 beats/min (300 beats/min is typical) caused by an atrial reentry mechanism (Fig. 69.27). Flutter waves on the ECG are broad, sawtooth-appearing, regular depolarizations prior to QRS complexes, with the latter occurring at some fraction of the atrial rate. The ventricular rate in atrial flutter is often rapid, but in the absence of a bypass tract (in which 1:1 conduction is possible), the conduction ratio is limited by the refractory period of the AV node. With 2:1 conduction, the ventricular rate is approximately 150 beats/min, often making flutter waves difficult to appreciate and allowing the rhythm to be mistaken for sinus tachycardia. Because the atrial rate can vary, the classic ventricular rate of 150/min is not always present with atrial flutter. When the conduction ratio changes from beat to beat, this is termed *atrial flutter with variable conduction,* with a resultant irregular ventricular rate making it difficult to distinguish from atrial fibrillation.

Atrial flutter often accompanies pulmonary disease, structural heart disease, particularly valvular heart disease, and cardiomyopathies. The acute management of atrial flutter is similar to that of atrial fibrillation, with a few special considerations. Because AV conduction occurs at fixed ratios in atrial flutter, the administration of beta blocker or calcium channel blocker therapy can result in an abrupt rate change, making it more challenging to titrate therapy to a desired target rate.

Atrial flutter is more sensitive to DC cardioversion (up to 90% conversion rate) than atrial fibrillation, and usually requires lower energy (20–50 J) for conversion to sinus rhythm.[15] Atrial flutter is more resistant to chemical cardioversion (<50% success) than new-onset, nonvalvular atrial fibrillation.

Atrioventricular Nodal Reentrant Tachycardia

Also known by the less precise term *paroxysmal supraventricular tachycardia* (PSVT, or just SVT), AVNRT is a regular, narrow-complex rhythm with a ventricular rate of 130 beats/min or greater, commonly more than 160 beats/min (Fig. 69.28). It is the most common non–sinus tachydysrhythmia in young adults. AVNRT is the result of a reentry circuit within the AV node, with normal conduction (narrow QRS) down the bundles of His and with retrograde conduction (inverted P waves typically buried within the QRS) up into the atria (Fig. 69.29).

The onset and spontaneous end of AVNRT is typically abrupt, and it frequently arises in the context of strenuous exercise or

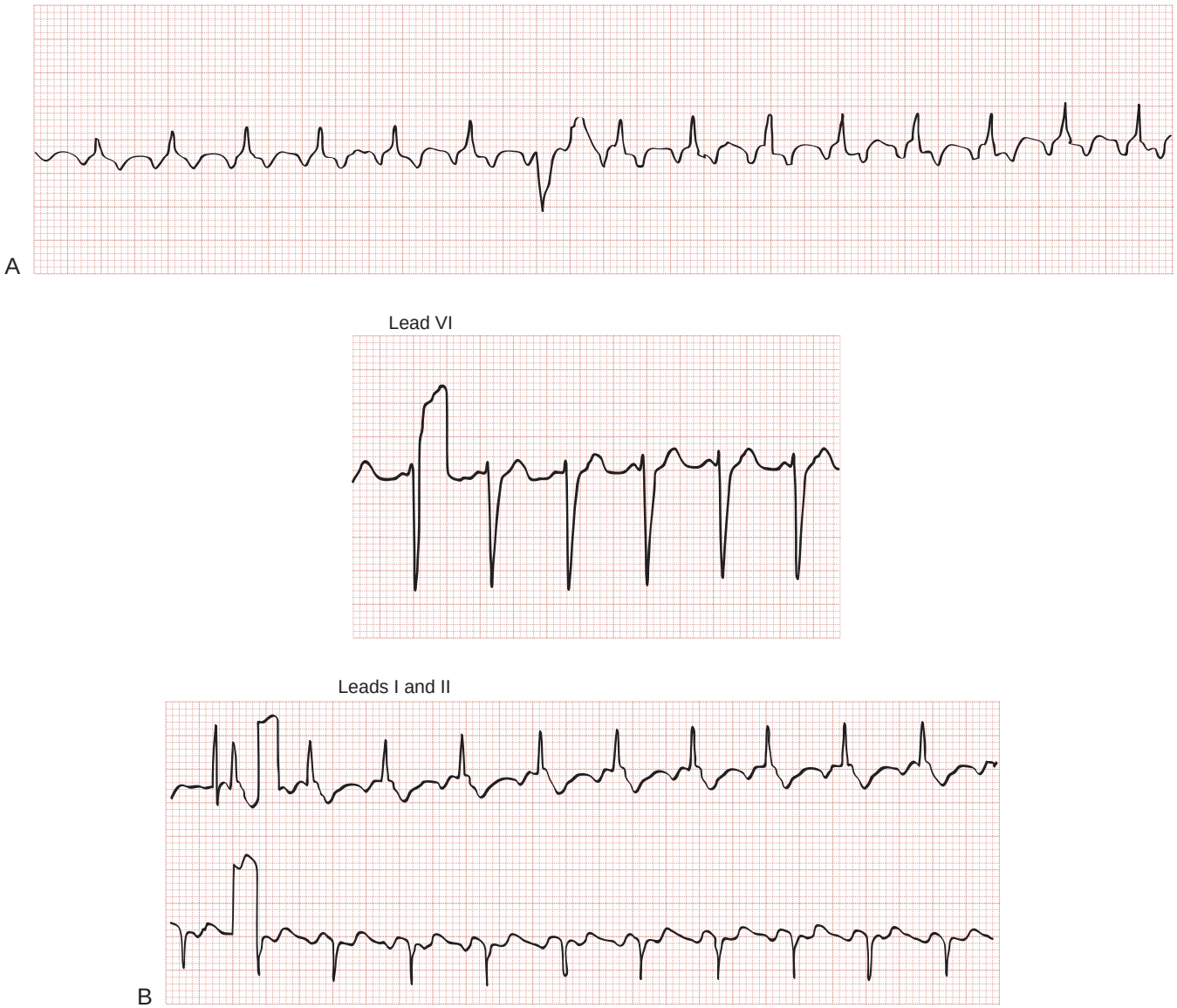


Fig. 69.27. **A,** Atrial flutter with 2 : 1 conduction and isolated premature ventricular contraction. **B,** Atrial flutter with 2 : 1 conduction. Lead II helps identify characteristic flutter waves.

emotional stress. Most patients with AVNRT are symptomatic, but hemodynamic instability is unusual in the absence of underlying cardiopulmonary disease.

If vagal maneuvers fail to restore sinus rhythm, first-line field or ED therapy for AVNRT is adenosine[16] (6 mg rapid, large-bore IV bolus followed by a flush; repeat with 12 mg if no effect on rate). This approach is successful in 85% to 90% of cases and is safe.[17] In refractory cases, diltiazem, esmolol, or metoprolol are options. Rarely needed, synchronized cardioversion (at 100–200 J, synchronized and biphasic preferred) can terminate AVNRT refractory to pharmacologic therapy or in a patient with hemodynamic instability.

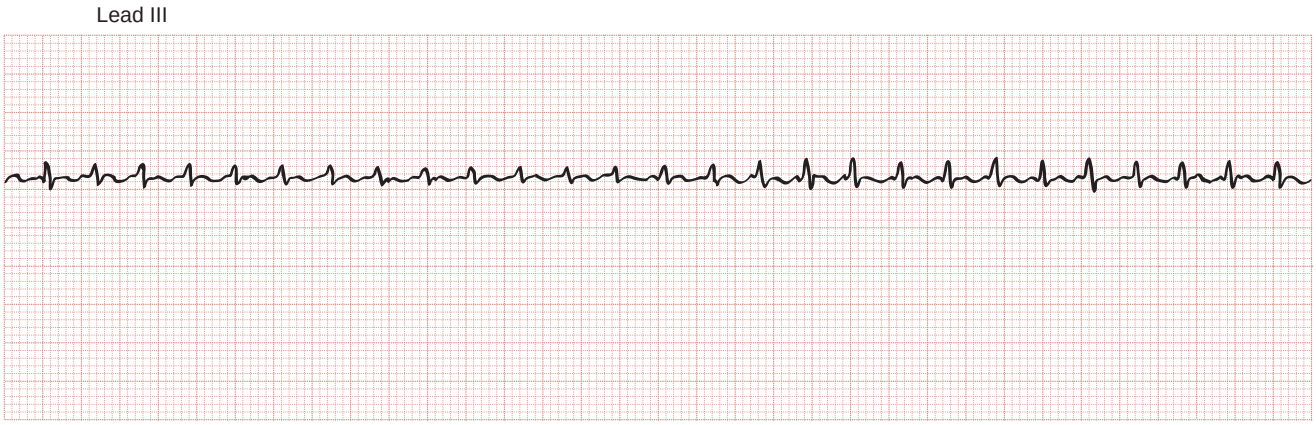
No specific laboratory testing is needed, although mild troponin level elevations occur but are of uncertain significance aside from other concerns for myocardial ischemia.[18] Most patients can be discharged after terminating AVNRT with adenosine or vagal maneuvers and typically require no testing beyond an ECG, including in the field setting.[19] Patients with frequent recurrences are candidates for prophylaxis (primarily with a beta blocker or calcium channel blocker) or ablation therapy. Starting rhythm control therapy from the ED is best only for those patients who have a secure follow-up plan known by their primary care provider.

Junctional Tachycardia

In contrast to the bursts seen in AVNRT, JTs (also known as nonparoxysmal or sustained JTs) show sustained ventricular rates but rarely exceed 130 beats/min. JTs are associated with structural heart disease, metabolic disturbances, or drug toxicity. Treatment is aimed at addressing underlying conditions, although a trial of nodal blockade with calcium or beta blockers is an option.

Preexcitation and Accessory Pathway Syndromes

The term *preexcitation* is depolarization of the ventricular myocardium via an accessory pathway (or bypass tract) linking the atria to the ventricles, circumventing the normal AV node. Accessory pathways do not have the so-called brakes or rate limits of the AV node, lending themselves to reentry tachycardia and



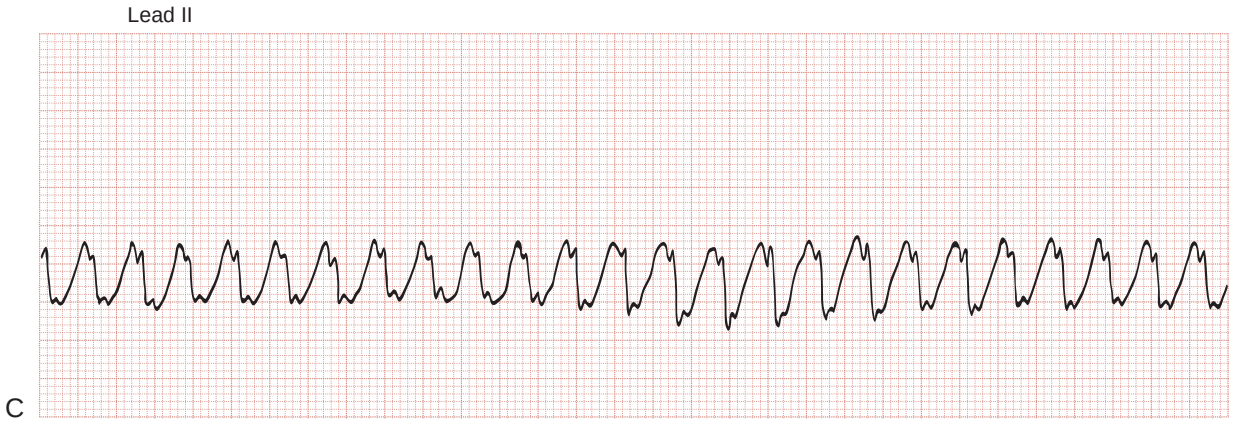


Fig. 39.27, cont'd. C, Atrial flutter with 1 : 1 conduction. This is rare and can be mistaken for ventricular tachycardia (lead II).

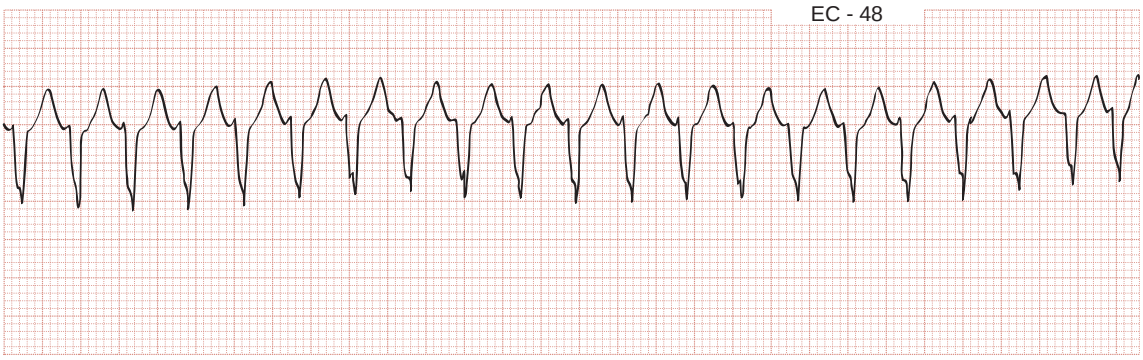


Fig. 69.28. Paroxysmal supraventricular tachycardia. Note the narrow, regular QRS complexes.

rapid ventricular rates. Wolff-Parkinson-White (WPW) syndrome is the classic accessory pathway syndrome, characterized by paroxysmal tachycardia and three resting electrocardiographic features (Fig. 69.30):

- Short PR interval (<0.12 second)
- QRS duration longer than 0.10 second
- Slurred upstroke to the QRS complex, referred to as a delta wave

Not all patients with WPW or other preexcitation syndromes have all the classic features on their surface ECG. Conversely, some patients with WPW-like patterns on their resting ECG never develop reentry tachycardia. Although some with WPW syndrome have structural disease, most patients have no other underlying cardiac abnormality (Box 69.11). Patients with WPW can develop atrial fibrillation, seen in up to 30% of patients with WPW.

BOX 69.11

Diseases Associated With Wolff-Parkinson-White Syndrome

Idiopathic[a]
Cardiomyopathy (especially hypertrophic)
Transposition of great vessels
Endocardial fibroelastosis
Mitral valve prolapse
Tricuspid atresia
Ebstein's disease

[a]Most common.

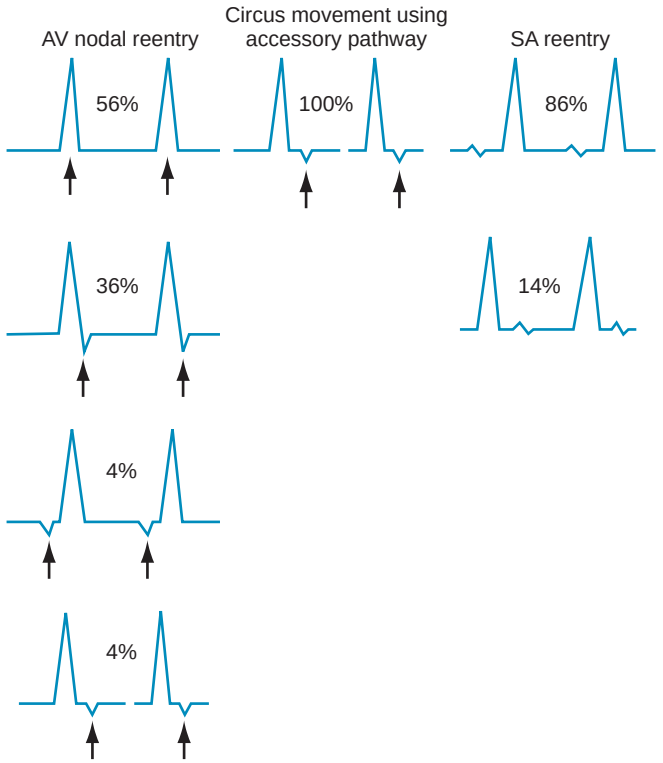


Fig. 69.29. Location of P waves in common causes of regular narrow-complex tachycardia. *AV,* Atrioventricular; *SA,* sinoatrial. (From Marriott HJL, Conover MB: Advanced concepts in dysrhythmias, ed 2, St. Louis, 1989, Mosby.)

The presence of an accessory pathway can form a reentry circuit together with an AV nodal pathway to produce and sustain a rapid ventricular rate (Fig. 69.31). When the AV node is being used for anterograde conduction to the ventricles, and the accessory path is used for retrograde conduction, it is called an orthodromic AV-reentrant tachycardia—the QRS complex is typically narrow, and the ventricular rate is constrained by the refractory period of the AV node. Conversely, when the accessory pathway is being used as the anterograde limb and the AV node as the retrograde limb of the reentry circuit, it is called an antidromic AV-reentrant tachycardia—the QRS complex is wide and ventricular rates can be extremely rapid.

Orthodromic AV reentrant tachycardia is the most common presenting dysrhythmia in WPW syndrome and is indistinguishable clinically from AVNRT. Like AVNRT, treat orthodromic AV reentrant tachycardia with vagal maneuvers and adenosine as first-line therapy, followed by calcium channel blockers and beta blockers as second-line agents.

In contrast, antidromic AV reentrant tachycardia, with its characteristic wide QRS complexes, can have ventricular rates of 200 beats/min or more and clinical instability. When the typical QRS antidromic changes are coupled with tachycardia, AV nodal blocking agents are contraindicated to avoid degeneration into ventricular fibrillation.[17] Similarly, in patients with a very rapid (>220/min) irregular tachycardia accompanied by a wide-complex QRS, do not use nodal blockade because of the risk of rapid deterioration to ventricular fibrillation from unbridled conduction down the accessory pathway. Procainamide is first-line therapy for tachycardia whenever the presence of wide QRS complexes suggests conduction down an accessory pathway; amiodarone is an alternative. Use prompt electrical cardioversion (100–200 J) if there is any clinical deterioration, failure of pharmacologic therapy, or extreme tachycardia (>250 beats/min).

The Lown-Ganong-Levine syndrome is an uncommon accessory pathway syndrome associated with paroxysmal narrow-complex tachycardia, short PR interval, and normal QRS complex without a delta wave. The treatment parallels that for the WPW syndrome.

Wide-Complex Tachycardia

Wide-complex tachycardia refers to any tachydysrhythmia accompanied by a QRS duration of 0.12 second or more. Wide-complex tachycardia can start in the ventricles (ie, ventricular tachycardia, VT) or can originate from above the AV node but be accompanied by aberrant AV conduction. The aberrant conduction is caused by an accessory pathway or a bundle branch block. The presence of AV dissociation or fusion beats on the 12-lead ECG clearly points to VT; older age and a prior history of myocardial infarction make VT more likely than a supraventricular tachycardia with aberrancy. On the other hand, an irregular tachycardia with a wide QRS approximating a bundle branch morphology is most likely atrial fibrillation with aberrant conduction. For stable patients, there are decision tools that can be used to distinguish VT with relatively good accuracy (Table 69.5; Fig. 69.32). Although new-onset VT patients are usually unstable, the presence of hemodynamic stability does not exclude VT.

It can be difficult to make the distinction between VT and an SVT and abnormal conduction when confronted with a patient displaying a wide-complex tachycardia. Many of the decision rules rely on an ability to discern subtleties of the QRS morphology, and none has perfect discriminatory power. As a general rule:

- Consider any new wide-complex tachycardia to be VT until proven otherwise.

The classic Wellens criteria are an example of time-honored but hard to use criteria because of their complexity and lack of order or weighting of findings.

The Brugada ECG criteria describe four features of VT from among those described in the original Wellens criteria, any one of which makes the diagnosis of VT. The rhythm needs to be regular for these to be used, because irregularity suggests atrial fibrillation with altered conduction. The sequential criteria are as follows (Fig. 69.33; see Fig. 69.32):

1. Absence of any RS complexes in the precordial leads
2. RS duration (measured from beginning of R to deepest part of S wave) greater than 100 msec
3. AV dissociation (often present but overlooked; may be best appreciated in inferior limb leads and $V_{1\text{-}2}$; Fig. 69.34)
4. Specific VT morphologic criteria (see Fig. 69.33)

Only the absence of all the Brugada criteria allows the diagnosis of SVT. Although the original investigators found excellent sensitivity (98.7%) and specificity (96.5%) in detecting VT, follow-up investigations have shown a lower but still helpful level of accuracy in ED patients (sensitivity of 92%–94%). Often, emergency clinicians are not able to complete the assessment or agree on the findings. In patients receiving class I agents, the Brugada criteria are less reliable.

The Griffith criteria use a three-step approach to identify aberrancy, first through classic RBBB or LBBB morphologies in V_1 and V_6 to identify an SVT and then seeking AV dissociation in the remainder to identify VT (see Figs. 69.32 and 69.34). This approach has a sensitivity of 92% with a lower specificity than that seen with the Brugada approach. There are no direct, in-practice comparative data between these two approaches. Finally, the Vereckei criteria (Fig. 69.35) examine lead aVR to differentiate between VT and SVT; however, in practice, these have not been shown to be more effective or accurate, limiting their use.[20-23]

Treat unstable patients with a wide-complex tachycardia with electrical cardioversion (100 J, synchronized and biphasic, if possible). For borderline patients, electrical cardioversion with

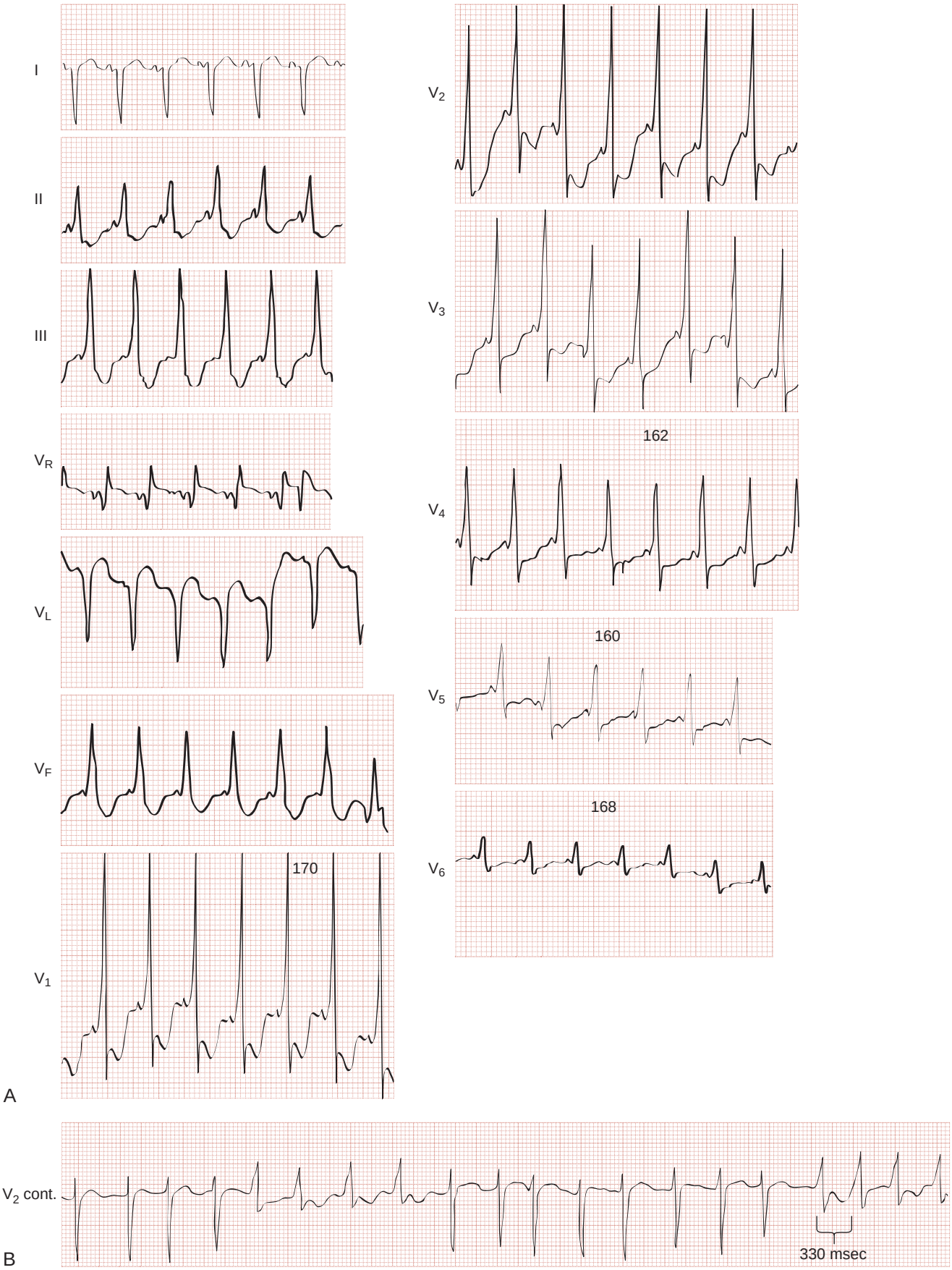


Fig. 69.30. **A,** Wolff-Parkinson-White (WPW) syndrome. **B,** WPW syndrome with atrial fibrillation. Note the short refractory period (330 ms). (**A** from Watanabe Y, Dreifus LS: Cardiac dysrhythmias, New York, 1977, Grune & Stratton.)

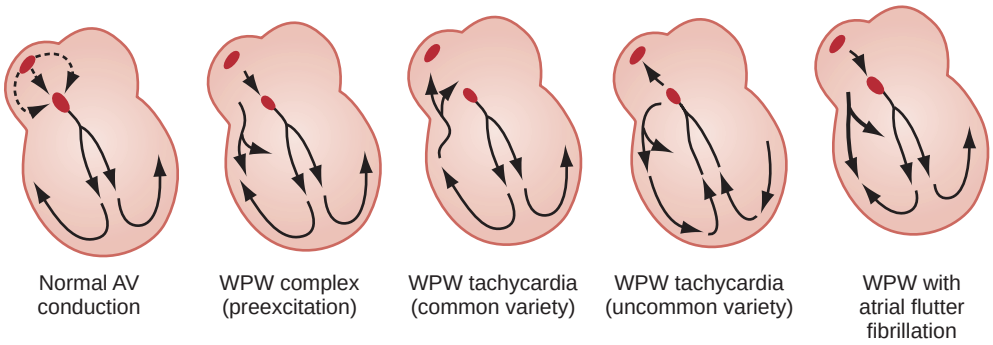


Fig. 69.31. Wolff-Parkinson-White (WPW) paths and associated rhythms. *AV,* Atrioventricular. (**A** from Watanabe Y, Dreifus LS: Cardiac dysrhythmias, New York, 1977, Grune & Stratton.)

TABLE 69.5

Features Distinguishing Ventricular Tachycardia From Supraventricular Tachycardia With Abnormal Conduction

PARAMETER	VENTRICULAR TACHYCARDIA	SUPRAVENTRICULAR TACHYCARDIA PLUS ABERRANCY
Clinical features	Age ≥ 50 yr History of myocardial infarction, congestive heart failure, CABG, or ASHD Previous history of ventricular tachycardia	Age ≤ 35 yr None Previous history of supraventricular tachycardia
Physical examination	Cannon A waves Variation in arterial pulse Variable first heart sound	Absent Absence of variability Absence of variability
Electrocardiogram	Fusion beats AV dissociation QRS >0.14 s Extreme LAD artery (30 degrees) No response to vagal maneuvers	None Preceding P waves with QRS complexes QRS usually <0.14 s Axis normal or near normal Slow or terminate with vagal maneuvers
Specific QRS patterns	V_1: R, qR, or RS V_6: S, rS, or qR Identical to previous ventricular tachycardia tracing[a] Concordance of positivity or negativity[b]	V_1: rSR′ V_6: qRs Identical to previous supraventricular tachycardia tracing[a]

[a]If proven by electrophysiologic studies or by a preponderance of evidence.
[b]Main deflection of QRS complex either positive or negative in every precordial lead.
ASHD, Arteriosclerotic heart disease; *AV,* atrioventricular; *CABG,* coronary artery bypass graft; *LAD,* left anterior descending.

systemic sedation or analgesia or pharmacologic treatment with procainamide or amiodarone are options.

Adenosine is an option after a careful search of the ECG does not suggest VT. Do not use adenosine if you suspect VT or if there is an irregular or very rapid ventricular rate (≥250 beats/min). Most SVTs will slow or terminate with adenosine, and only rare VT forms respond; any ill effects of adenosine are usually fleeting. Other pharmacologic therapies for stable VT are discussed later. If pharmacologic treatment fails, synchronized cardioversion is an option.

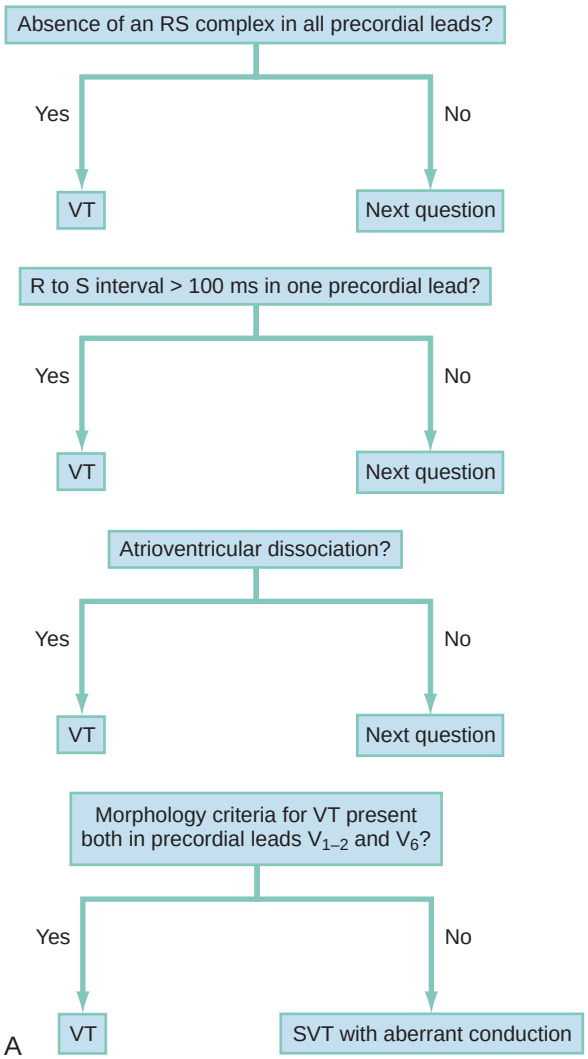
Ventricular Tachycardia

VT originates within or below the His bundle. Nonsustained VT refers to short episodes (<30 seconds) reverting spontaneously, whereas sustained VT is more prolonged. Reentry mechanisms are the most common cause of VT, although automatic and triggered mechanisms occur. Most patients with VT have underlying heart disease.

Monomorphic ventricular tachycardia is the most common form of VT and is characterized by morphologically consistent QRS complexes, usually in a regular pattern and at a rate of 150 to 200 beats/min (Fig. 69.36). Polymorphic ventricular tachycardia is seen with varying QRS morphologies and suggests more severe underlying disease (Figs. 69.37 and 69.38). VT is prevalent in patients with ischemic and nonischemic cardiomyopathy.

For stable patients with VT, amiodarone (3–5 mg/kg IV over minutes, often 250–350 mg) is the best choice, with reported successful termination of up to 90%.[23] Procainamide (30–50 mg/min IV, up to a total of 18 mg/kg or until VT is terminated) is a second-line agent. Lidocaine (1.0- to 1.5-mg/kg IV bolus, up to 3 mg/kg maximum, and followed by an infusion) was the preferred choice in the past and is easy to deliver, but it was hampered by lower success rates and is now relegated to an alternative role. Unstable patients or those with VT refractory to pharmacotherapy should undergo synchronized cardioversion with 100 J (biphasic preferred), with procedural sedation; escalating doses (up to 200 J biphasic or 360 J monophasic) are occasionally needed.

Seek expert consultation and admit all patients with new or symptomatic VT, with the exception of potential discharge after consult for those who have properly functioning implanted defibrillators (see Chapter 80).



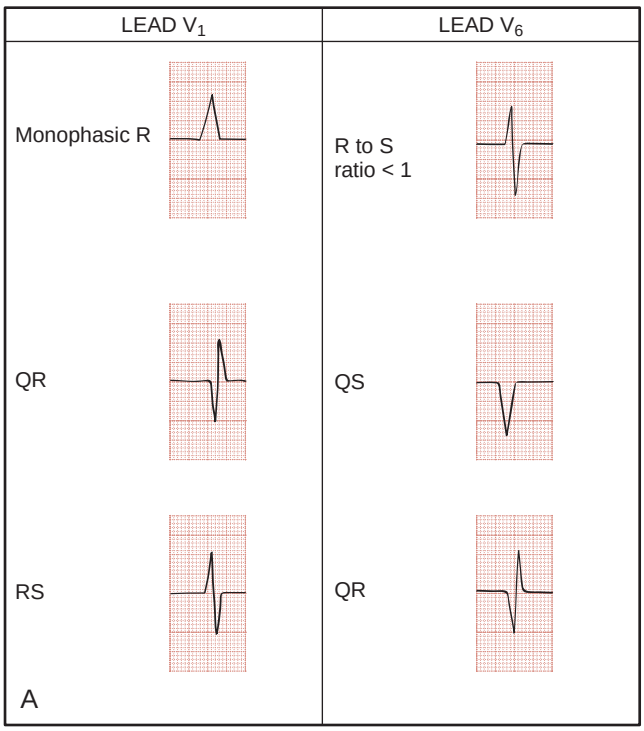
	BBB pattern
Right	
V_1	rSR′ pattern with R > rRS (RS) pattern with R > S; Q wave
V_6	<40 msec and <2 mm (0.2 mV) were allowed
Left	
V_1	rS or QS pattern with time to 5 wave nadir <70 msec
V_6	R wave with no Q wave

BBB = bundle branch block.

If no classic BBB pattern as noted above that would define SVT with aberrancy, search for AV dissociation; if present, VT is diagnosed and if absent, SVT is diagnosed by default.

B

Fig. 69.32. A, Brugada four-step approach for differentiating ventricular tachycardia (VT) and wide-QRS supraventricular tachycardia. Only when the response to all four questions is negative is a supraventricular rhythm with abnormal conduction diagnosed. As soon as a single "yes" answer is noted, VT is diagnosed. **B,** Griffith approach, in which aberrant conduction is sought in leads V_1 and V_6 (right bundle branch block [RBBB] or left bundle branch block [LBBB], classic appearances), followed by a search for atrioventricular (AV) dissociation. If classic RBBB and LBBB patterns are absent, or if the remainder of the leads have no AV dissociation, VT is diagnosed. (**A** from Brugada P, Brugada J, Mont L, et al: A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. Circulation 83:1649–1659, 1991; **B** adapted from Griffith MJ, Garratt CJ, Mounsey P, Camm AJ: Ventricular tachycardia as default diagnosis in broad complex tachycardia. Lancet 343:386–388, 1994.)



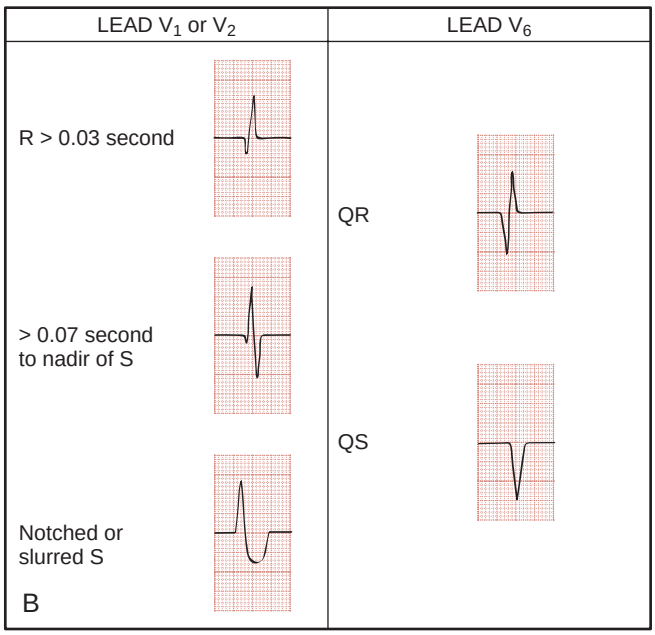
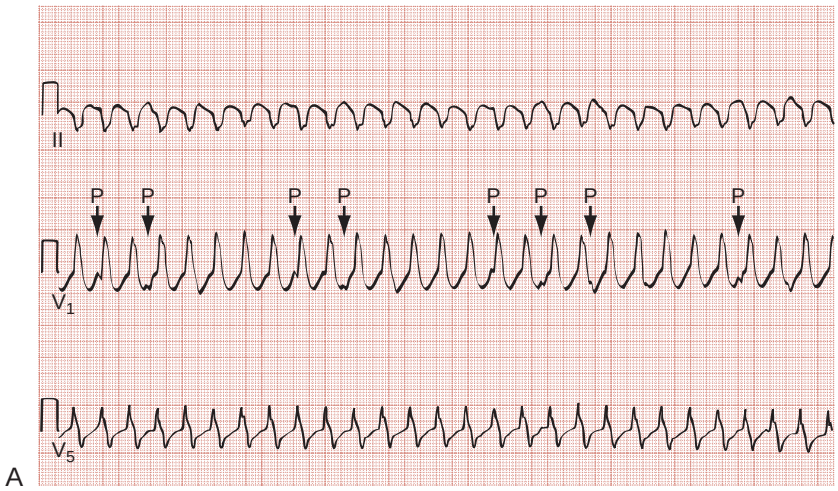


Fig. 69.33. Morphology associated with the fourth criterion in the Brugada system. **A,** In patients with a right bundle branch–appearing complex. **B,** In patients with a left bundle branch–appearing complex.



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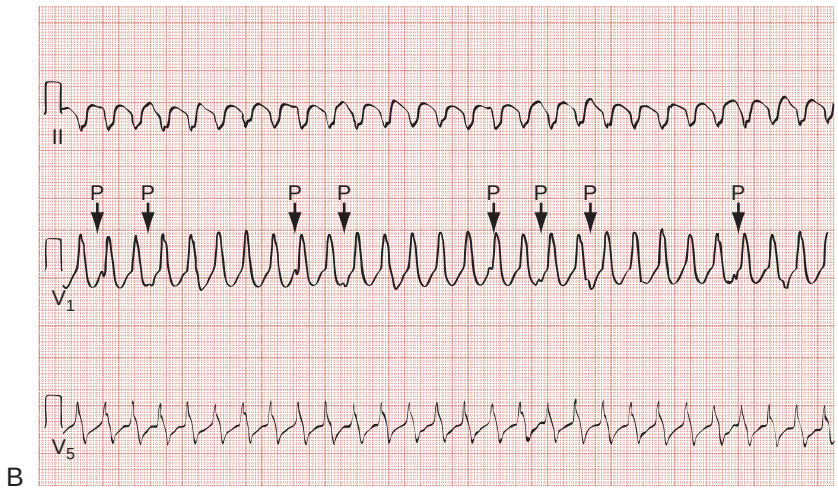

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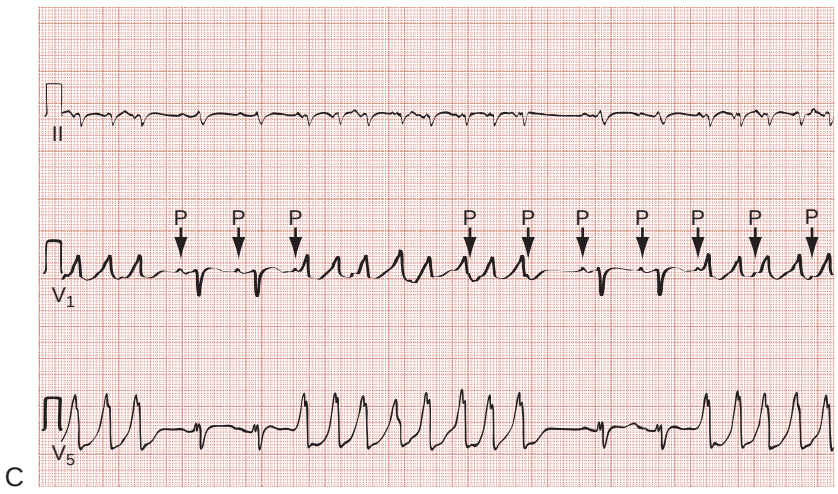


C

Fig. 69.34. **A, B,** Ventricular tachycardia. Note atrioventricular dissociation. **C,** Intermittent, nonsustained ventricular tachycardia. Atrioventricular dissociation is evident. (Courtesy Dr. Edward Curtis.)

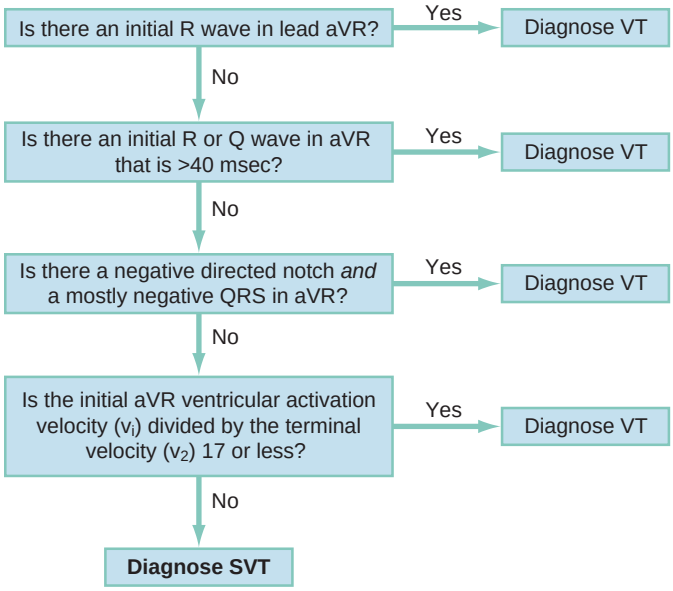


Fig. 69.35. Vereckei criteria for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia (SVT).

BOX 69.12

Classification and Causes of Prolonged QT Syndromes That Produce Torsades de Pointes

PAUSE-DEPENDENT (ACQUIRED)

Drug-induced—class IA and IC antidysrhythmics; many phenothiazines and butyrophenones (notably haloperidol and droperidol), cyclic antidepressants, antibiotics (especially macrolides), organophosphates, antihistamines, antifungals, antiseizure and antiemetic agents
Electrolyte abnormalities—hypokalemia, hypomagnesemia, hypocalcemia (rarely)
Diet-related—starvation, low protein
Severe bradycardia or atrioventricular block
Hypothyroidism
Contrast injection
Cerebrovascular accident (especially intraparenchymal)
Myocardial ischemia

ADRENERGIC-DEPENDENT (TACHYCARDIA-PROMPTED)

Congenital

Jervell and Lange-Nielsen syndrome (deafness, autosomal recessive)
Romano-Ward syndrome (normal hearing, autosomal dominant)
Sporadic (normal hearing, no familial tendency)
Mitral valve prolapse

Acquired (Rare)

Cerebrovascular disease (especially subarachnoid hemorrhage)
Autonomic surgery: radical neck dissection, carotid endarterectomy, truncal vagotomy

Torsades de Pointes

Torsades de pointes is literally translated as "twisting of the points" and is a paroxysmal form of polymorphic VT that meets the following clinical criteria (see Fig. 69.38):

1. Ventricular rate greater than 200 beats/min
2. Undulating QRS axis, with the polarity of the complexes appearing to shift about the baseline
3. Paroxysms of less than 90 seconds

Torsades de pointes occurs in the setting of a prolonged QT interval, a reflection of abnormal ventricular repolarization. A prolonged QT interval can be congenital or acquired. Women are at a greater risk for Torsades de pointes. Acquired Torsades de pointes is much more common than congenital and is pause-dependent, triggered by a slow heart rate.

Acquired QT prolongation is the most common form seen outside a specialized pediatric setting and usually has multifactorial causes (Box 69.12). Common triggers include electrolyte disturbances (eg, hypokalemia, hypomagnesemia) and many different drugs (notably class IA and IC agents but also many others; see Box 69.12), especially when used in combination.

Treatment of torsades de pointes in stable adult patients involves correcting any underlying metabolic or electrolyte abnormalities and increasing the heart rate to shorten ventricular repolarization. In patients with torsades de pointes, do not use class IA and IC antidysrhythmics. Empirical IV magnesium sulfate is effective in treating torsades de pointes, even in the absence of hypomagnesemia, and may prevent recurrence if electrical cardioversion succeeds.

A baseline ventricular rate of 100 to 120 beats/min is usually enough to prevent acquired torsades de pointes, achieved by overdrive pacing (ie, external pacing at a rate greater than the patient's intrinsic rate) or via β-adrenergic infusion. Use electrical cardioversion for unstable patients, as outlined in the discussion of VT with sustained torsades de pointes, without any attempt to synchronize.

Congenital torsades de pointes is rare and is triggered by sympathetic excess or tachycardia; it is usually seen in children and young adults. Patients often have syncope during exertion and a prolonged QT interval on the ECG. In contrast to acquired forms, treat congenital torsades de pointes with beta blockers.

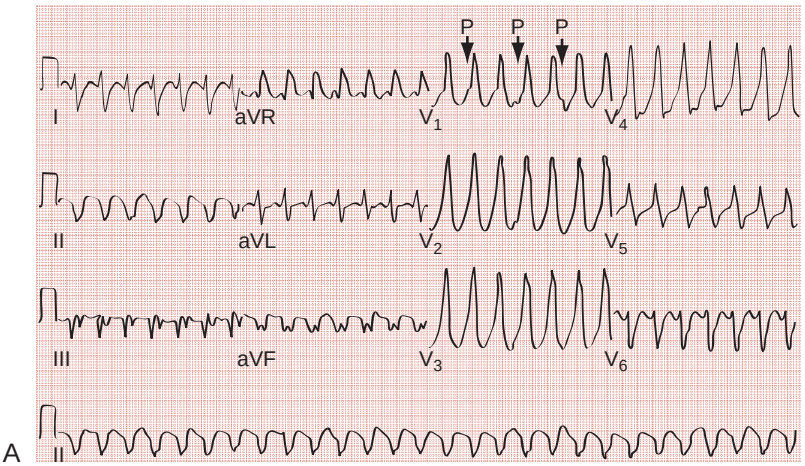
Brugada's Syndrome

Brugada's syndrome is characterized by ventricular dysrhythmias triggering syncope or sudden cardiac death in the absence of structural heart disease. This syndrome is caused by an inherited disorder of sodium channels and is commonly diagnosed in men during young adulthood. The Brugada electrocardiographic pattern shows a downward coved or humped (saddleback) ST segment elevation in leads V_1 to V_3 (Fig. 69.39), sometimes simulating an RBBB appearance. The ST segment findings may be transient or elicited only with pharmacologic stimulation.

Any patient with unexplained syncope and a Brugada pattern ECG requires admission for consideration of an implanted defibrillator. For patients in whom a Brugada pattern ECG is noted incidentally, there is no consensus on treatment, but we recommend referral to a cardiologist.

DISPOSITION

Patients with dysrhythmias that are markedly symptomatic and nonresponsive to ED therapy require admission; in those without symptoms or only palpitations, and who resolve, with no evidence of structural heart disease, outpatient ambulatory monitoring and close contact with a cardiologist is an option.[24] When evaluating anyone with symptomatic rhythm changes, we recommend a cardiology consultation. Those with VT or torsades de pointes, and most symptomatic patients with type II second-degree or complete heart block, require admission.



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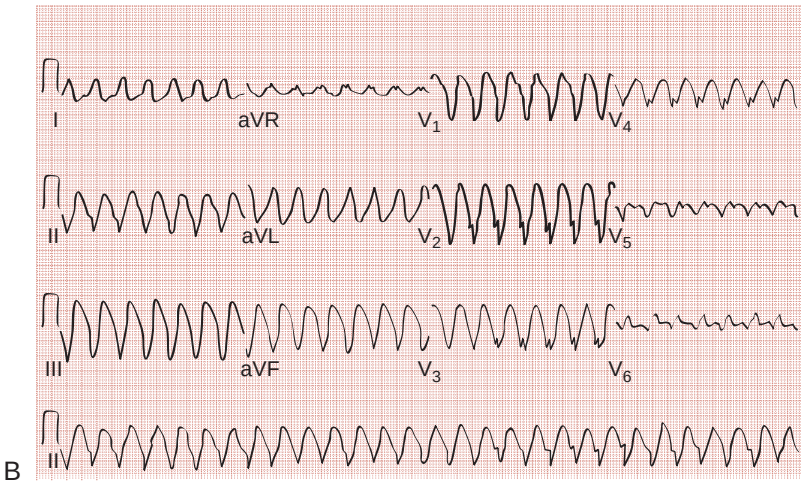

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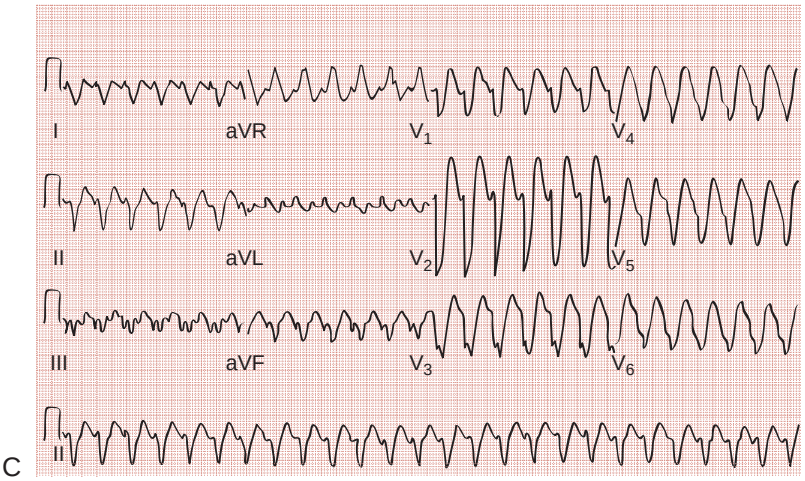

C

Fig. 69.36. Ventricular tachycardia. **A,** RS complexes are present in chest leads, but RS duration is greater than 100 ms. Although the Brugada criteria indicate that no further analysis is necessary, atrioventricular dissociation is also evident, and QRS morphology in lead V_6 is consistent with ventricular tachycardia. **B,** Some RS complexes are present, RS duration is no longer than 100 msec, and atrioventricular dissociation is difficult to appreciate. The morphologic criteria for ventricular tachycardia are fulfilled because S is notched in V_1 and QR is present in V_6. **C,** Diagnosis is based on morphologic criteria because S is notched in V_1 and V_2 and QS is present in V_6. (Courtesy Dr. Edward Curtis.)

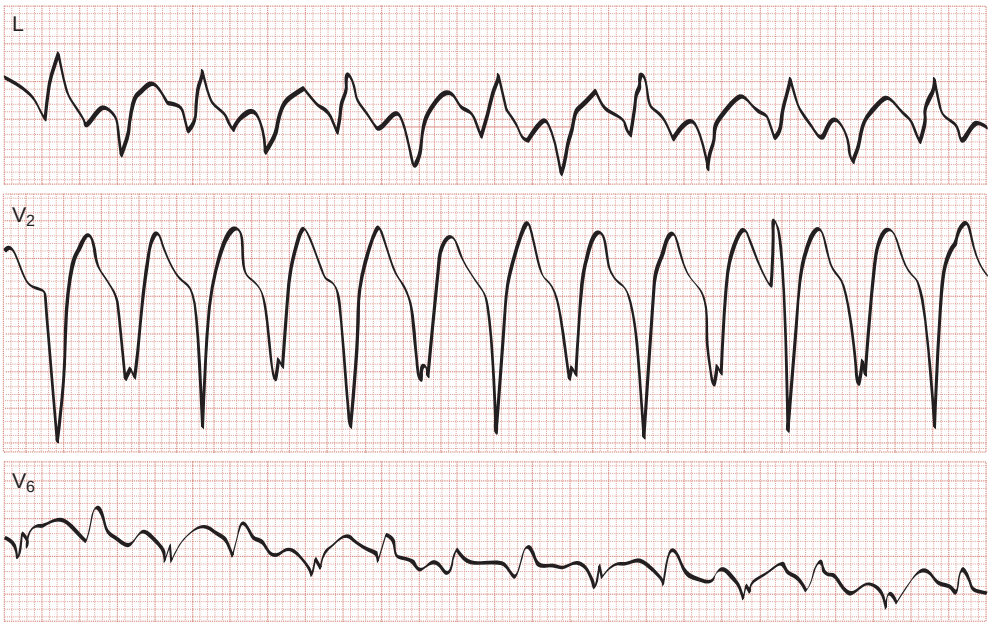

Fig. 69.37. Bidirectional ventricular tachycardia in a patient with digitalis toxicity. (From Marriott HJL, Conover MB: Advanced concepts in dysrhythmias, ed 2, St. Louis, 1989, Mosby.)

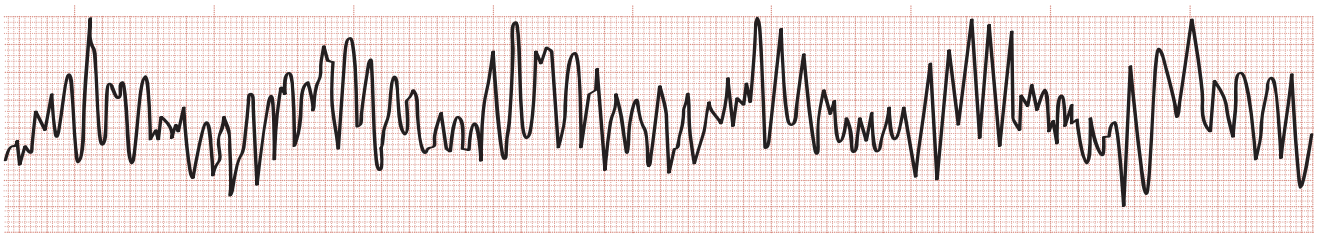

Fig. 69.38. Torsades de pointes with classic spiraling of QRS complexes around the baseline.

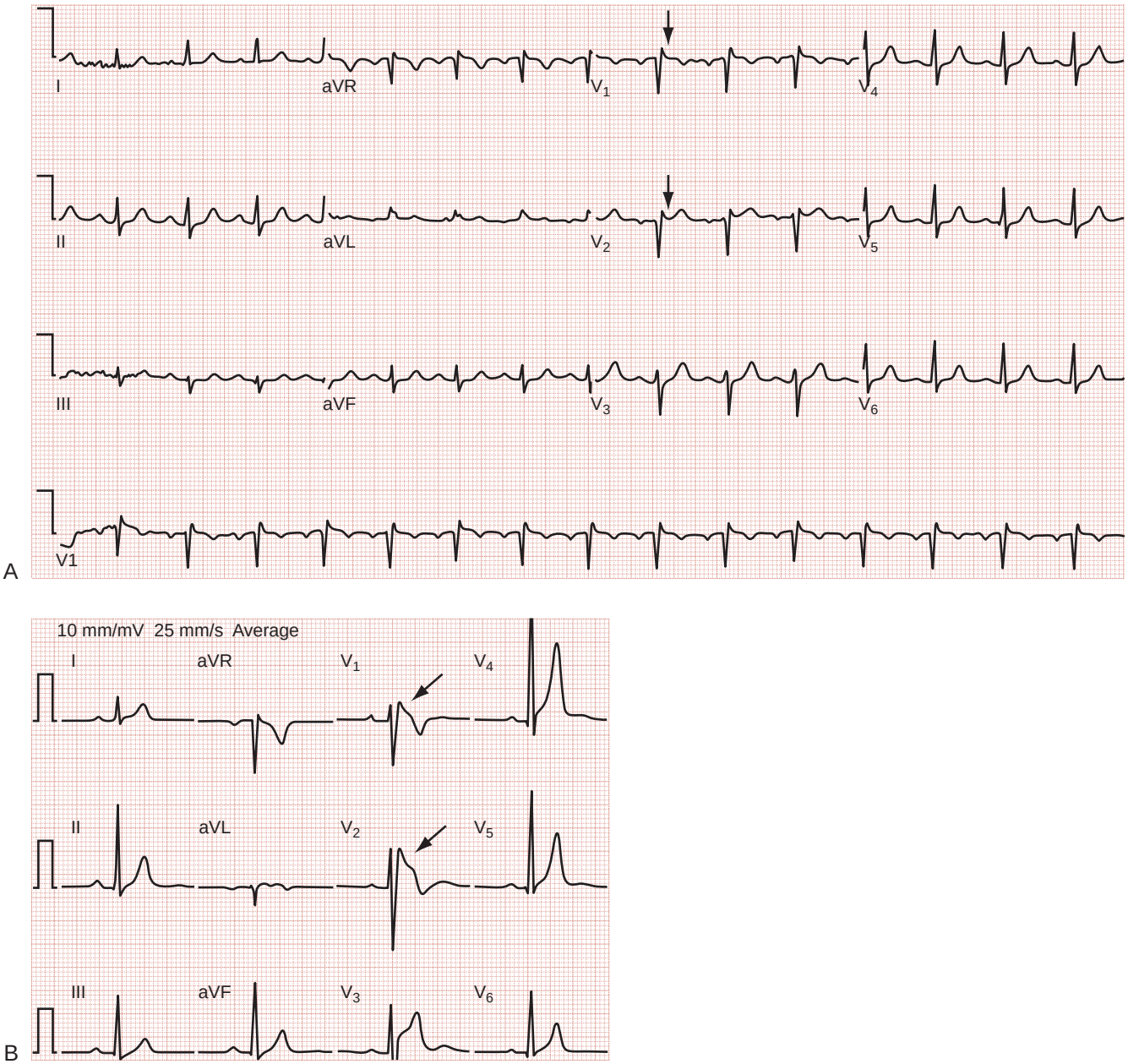

Fig. 69.39. Brugada's syndrome, with ST elevation in V_{1S}. The ST elevation is coved (*upper,* **A**) or saddleback (*lower,* **B**) and may be transient.

KEY CONCEPTS

- Electrical therapy is used for any unstable patient in whom a dysrhythmia is the cause of symptoms—pacing if the heart rate is slow, countershock with sedation if fast.
- Assume that any regular, new-onset, symptomatic, wide-complex tachycardia is VT until proven otherwise.
- Type II second-degree AV block is never a normal variant and implies a conduction block below the AV node. When the conduction ratio is 2:1, assume that type II block exists until proven otherwise and have pacing readily accessible.
- Consider an accessory pathway syndrome in anyone with tachycardia exceeding a rate of 225 to 250 beats/min, regardless of the QRS complex morphology, and avoid nodal blocking agents.
- Look closely for irregularity in tachycardia over 200 beats/min; this and underlying atrial fibrillation can be missed if R-R intervals at fast rates are not carefully tracked.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 69: QUESTIONS & ANSWERS

69.1. What is the primary electrochemical difference between pacemaker and nonpacemaker cells?

A. Lack of a plateau phase 3 in nonpacemaker cells
B. Rapid phase 0 upstroke in nonpacemaker cells after stimulus
C. Slow calcium ion influx during phase 2 for pacemaker cells
D. Slow phase 4 spontaneous depolarization in pacemaker cells
E. Transient membrane repolarization by potassium channel closure during phase 1 for pacemaker cells

Answer: D. The spontaneous return to a depolarization threshold during phase 4 (diastole) characterizes pacemaker cells. Both cell types then exhibit a rapid phase 0 upstroke resulting from sodium ion (Na^+) influx, brief repolarization resulting from potassium ion (K^+) efflux (phase 1), plateau phase resulting from balanced calcium ion (Ca^{2+}) entry and K^+ efflux (phase 2), and then repolarization resulting from Ca^{2+} channel closure and K^+ efflux (phase 3).

69.2. For a reentrant tachydysrhythmia to occur, what three conditions exist?

A. Electrolyte disturbance, ischemia, and altered conduction in an endogenous atrioventricular pathway
B. Electrolyte disturbance, two conduction pathways, with one of the pathways being slower
C. Ischemia, two conduction pathways, with one of the pathways being slower
D. Two conduction pathways, one path being slower, and differing responsiveness
E. Two conduction pathways with equal responsiveness

Answer: D. Remember that a conducting pathway is bidirectional. In a typical scenario, the alpha pathway of the atrioventricular (AV) node is the anterograde conducting limb, and the beta pathway is the retrograde conducting limb. Reentrant dysrhythmias are almost always AV nodal and narrow complexes that start and end abruptly.

69.3. Classic antifibrillatory effects are seen with which class of antidysrhythmic?

A. IA
B. IB
C. IC
D. II
E. III

Answer: E. Class III agents, of which amiodarone is the prototype, prolong the action potential and refractory period duration. Class I agents have variable effects on depolarization rate and repolarization duration.

69.4. The most frequent proarrhythmic effects are seen with which class of antidysrhythmic?

A. IA
B. IB
C. IC
D. II
E. III

Answer: C. Class IC agents, such as flecainide, encainide, and propafenone, markedly slow depolarization and conduction and prolong repolarization and action potential duration. Class IB agents generally have the least proarrhythmic effect.

69.5. A 49-year-old woman presents with a sudden onset of palpitations and shortness of breath. This has happened once before. She has no past history and takes no medications. Vital signs are temperature, 36.0°C (96.8°F)

oral, blood pressure, 115/69 mm Hg, heart rate 156 beats/min, respiratory rate 24 breaths/min, and oxygen (O_2) saturation, 98%. Her electrocardiogram (ECG) is shown in Fig. 69.28. What is the most appropriate intervention?

A. Adenosine, 6 mg IV
B. Digitalis, 0.25 mg IV
C. Diltiazem, 0.4 mg/kg IV
D. Propranolol, 1 mg IV
E. Synchronized electrical cardioversion after IV sedation with midazolam

Answer: A. Adenosine causes slowing of conduction in the anterograde and retrograde pathways, with no effect on ventricular contractility. It converts a high percentage of narrow-complex tachycardias to sinus rhythm, but with a 25% recurrence rate. Diltiazem would not be unreasonable, but the quoted dose is too high. Calcium channel blockers also exert their effects only on the anterograde pathway, with little direct effect on accessory pathways. Contractility may be diminished. Digitalis use has been largely supplanted by adenosine and class IV agents. Its onset of action after IV use is 1.5 to 2 hours. Cardioversion would not be indicated unless the patient exhibited hemodynamic instability.

CHAPTER 70

Implantable Cardiac Devices

Benjamin Squire | James T. Niemann

PRINCIPLES

Electrical cardiac pacing for the management of bradyarrhythmias was first described in 1952, and permanent transvenous pacing devices were introduced into clinical practice in the early 1960s.[1] The first devices for endocardial defibrillation were implanted in surviving victims of sudden cardiac death in 1980.[2] Implanted electrical devices for the management of cardiac dysrhythmias have changed rapidly over the years, with both increasing complexity and miniaturization. Between 1993 and 2009, 2.9 million new permanent pacemakers were implanted in the United States.[3] Indications for the use of permanent pacemakers in the management of congenital and acquired heart disease has expanded beyond treatment of dysrhythmias to include cardiac resynchronization therapy for heart failure.[4-6]

A number of large clinical trials comparing implantable cardioverter-defibrillators (ICDs) with antiarrhythmic drugs for the prevention of sudden cardiac death resulting from ventricular dysrhythmias have indicated that ICDs significantly improve survival.[7,8] Such studies have led to a dramatic increase in ICD implantations, and it is estimated that there are more than 125,000 new ICD implants annually in the United States.[9] The widespread use of these devices assures that emergency clinicians will encounter patients, often with symptoms that may be related to the normal function or malfunction of the pacemaker or ICD.

CLINICAL FEATURES

Guidelines for the implantation of these devices have been developed by a joint task force of the American Heart Association (AHA) and the American College of Cardiology (ACC) and are periodically updated.[10,11] Similar to categorization of evidence for other recommendations or guidelines, recommendations are categorized as class I, II, or III. Class I includes conditions for which there is general agreement that a device should be implanted. A class II recommendation includes conditions for which these devices are frequently used but for which there is disagreement about their need or benefit. Class III is reserved for conditions for which there is general agreement that a device is not needed.

Class I indications for a permanent pacemaker or ICD are listed in Boxes 70.1 and 70.2. In general, pacing is recommended for patients with symptomatic heart block, symptomatic sinus bradycardia, and atrial fibrillation with a symptomatic bradycardia (low ventricular response rate) in the absence of medications that affect atrioventricular (AV) conduction. Biventricular pacing (cardiac resynchronization therapy) is indicated for systolic heart failure patients with left ventricular ejection fracture under 35% and left bundle branch block.[5,11-13]

Pacemaker Terminology

A letter code, initially established in 1974 and revised as technology advances, standardizes nomenclature for pacemakers. Table 70.1 includes an explanation of the five-letter code scheme and the standard abbreviations in each category. The first three code letters are used most commonly. Using this table, one should be able to understand the features of any pacing mode. For example, a VDD (Ventricle, Dual, Dual) pacemaker is capable of pacing only the ventricle, sensing both atrial and ventricular intrinsic depolarization, and responding by dual inhibition of both atrial and ventricular pacing if intrinsic ventricular depolarization occurs; a paced ventricular beat is triggered in response to a sensed intrinsic atrial depolarization. The codes of a permanent pacemaker that are used most frequently and the indications, advantages, and disadvantages of each are listed in Table 70.2. Detailed algorithms for matching a patient with the appropriate pacemaker exist.[10] The majority of permanent pacemakers are dual chamber and most often rate adaptive.

Pacemaker Components

All pacemaker systems have three basic components: the pulse generator, which houses the power source (battery); the electronic circuitry; and the lead system, which connects the pulse generator to the endocardium.

Nearly all implanted pacemakers are lithium powered. Lithium-powered pulse generators function normally for 4 to 10 or more years, depending on the pacemaker features, such as single versus dual chamber, pacing threshold, and rate adaptiveness. This long "battery life" and the fact that the output voltage of the lithium-iodine cell decreases gradually rather than abruptly, as occurred with the early mercury-zinc cell, make sudden pulse generator failure an unlikely cause of pacemaker malfunction.

Permanent pacemakers have endocardial leads that are positioned in contact with the endocardium of the right ventricle and, in the case of a dual-chamber device, the right atrium, with a subclavian or cephalic vein approach used for insertion. Occasionally, an epicardial lead may be implanted during open-heart surgery performed for another indication, such as prosthetic valve insertion or correction of a congenital cardiac defect. Pacemaker leads may be either bipolar or unipolar in configuration. A bipolar endocardial lead has both the negative (distal) and the positive (proximal) electrodes, separated by approximately 1 cm, within the heart. A unipolar lead has the negative electrode in contact with the endocardial surface, and the positive pole is the metallic casing of the pulse generator. Each lead system has potential advantages and disadvantages.[1] The unipolar configuration is not compatible with ICD systems and is prone to oversensing of myopotentials and electromagnetic interference but is of smaller diameter and less susceptible to fracture. The bipolar configuration is compatible with ICD systems but is larger and more prone to lead fractures. Oversensing, however, is rarely a problem. The selection of lead configuration usually depends on patient characteristics, as well as the experience and preference of the operator.

History

The patient should be asked for the pacemaker identification card. The information on the card explains why a pacemaker was placed

TABLE 70.1

Five-Letter Pacemaker Code

LETTER 1: CHAMBER PACED	LETTER 2: CHAMBER SENSED	LETTER 3: SENSING RESPONSE	LETTER 4: PROGRAMMABILITY	LETTER 5: ANTITACHYCARDIA FUNCTIONS
A = Atrium	A = Atrium	T = Triggered*	P = Simple	P = Pacing
V = Ventricle	V = Ventricle	I = Inhibited	M = Multiprogrammable	S = Shock
D = Dual	D = Dual	D = Dual (A and V inhibited)	R = Rate adaptive	D = Dual (shock pace)
0 = None	0 = None	0 = None	C = Communicating	
			0 = None	

*In the triggered response mode, the pacemaker discharges or fires when it recognizes an intrinsic depolarization. As a result, pacemaker spikes occur during inscription of the QRS complex. Because this mode results in high energy consumption and a shortened battery life and because the sensing response can be misinterpreted as pacemaker malfunction, this sensing mode is not used with modern pacemakers.

TABLE 70.2

Common Permanent Pacemakers

CODE	INDICATION	ADVANTAGES	DISADVANTAGES
VVI	Intermittent backup pacing; inactive patient	Simplicity; low cost	Fixed rate; risk of pacemaker syndrome
VVIR	Atrial fibrillation	Rate responsive	Requires advanced programming
DDD	Complete heart block	Atrial tracking restores normal physiology	No rate responsiveness; requires two leads and advanced programming
DDDR	Sinus node dysfunction; for rate responsiveness atrioventricular (AV) block and need	Universal pacer; all options available by programming	Complexity, cost, programming, and follow-up evaluation

BOX 70.1

Class I Indications for Permanent Pacing in Adults

1. Third-degree and advanced second-degree AV block at any anatomic level associated with any of the following:
   - Symptomatic bradycardia (including heart failure) or ventricular dysrhythmia presumed to be a result of AV block
   - Symptomatic bradycardia secondary to drugs required for dysrhythmia management or other medical condition
   - Documented periods of asystole lasting more than 3 seconds or an escape rate of less than 40 beats/min or an escape rhythm originating below the AV node in an awake, asymptomatic patient in sinus rhythm
   - Awake, asymptomatic patients with atrial fibrillation and bradycardia a documented pause of 5 seconds or longer
   - After catheter ablation of the AV node
   - Postoperative AV block that is not expected to resolve
   - Neuromuscular disease with AV block (eg, the muscular dystrophies)
2. Symptomatic bradycardia resulting from second-degree AV block regardless of type or site of block
3. Asymptomatic, persistent third-degree AV block with awake ventricular rate over 40 beats/min with cardiomegaly or left ventricular dysfunction or if block is below AV node
4. Chronic bifascicular or trifascicular block with intermittent third-degree AV block or type II second-degree AV block
5. Second or third-degree AV block with exercise in the absence of myocardial ischemia

AV, Atrioventricular.

BOX 70.2

Class I Indications for Implantable Cardioverter-Defibrillator Therapy

1. Cardiac arrest resulting from VF or VT not caused by a transient or reversible event
2. Spontaneous sustained VT
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred
4. Nonsustained VT with coronary artery disease, prior myocardial infarction, left ventricular dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressible by a class I antiarrhythmic drug

VF, Ventricular fibrillation; *VT,* ventricular tachycardia.

and the pacing modality used. If the card is not available, information may be obtained by calling the device manufacturer. If the manufacturer is unknown, calls can be made to the most common manufacturers until the patient is found in one of the registries. All manufacturers provide support including representatives on call to respond to the hospital to interrogate a device.

Most patients with pacemaker malfunction have symptoms reminiscent of those that prompted pacemaker therapy: syncope, near-syncope, orthostatic dizziness, lightheadedness, dyspnea, or palpitations.

The majority of pacemaker complications and most instances of pacemaker malfunction occur within the first few weeks or months of pacemaker implantation. After wound healing, palpation of the pulse generator site should not elicit tenderness. A wound infection or pocket infection typically arises with localized pain. Bacteremia secondary to infection of the pacing catheter, however, may arise only with fever and without other manifestations of the systemic inflammatory response syndrome. Pain in the arm ipsilateral to the site of insertion should suggest acute thrombophlebitis.

Patients who develop the pacemaker syndrome secondary to the loss of AV synchrony may have nonspecific complaints of easy fatigability, generalized weakness, dyspnea, or an uncomfortable fluttering or "pounding" sensation in the neck or abdomen. Syncope or near-syncope may also occur, but these complaints should prompt an evaluation for true pacemaker malfunction. The pacemaker syndrome should be a diagnosis of exclusion.

Physical Examination

A pacemaker infection should be suspected in the presence of fever, even if another potential source of infection can be identified. Extremely low (<60 beats/min) or high (>100 beats/min in the resting patient) pulse rates are suggestive of altered pacing parameters (battery depletion or pacemaker-mediated tachycardias). Hypotension may be present in either instance. Cannon "A" waves on inspection of the jugular venous pulse wave indicate AV asynchrony. Auscultation of lungs may reveal bibasilar rales if congestive heart failure is present.

During pacing, the first heart sound may vary in intensity as a result of AV dissociation (VVI mode), and the second heart sound may be paradoxically split when ventricular pacing occurs (the right ventricle is activated first). A pericardial friction rub may also be heard if the tip of the pacing catheter has perforated the wall of the right ventricle. Perforation, however, usually occurs at the time of pacemaker implantation and is usually recognized at that time. Although the pacing catheter traverses the tricuspid valve, tricuspid regurgitation is rarely heard unless there is myocardial disease such as right ventricular dilation, which is common in the cardiomyopathies. Pedal edema may be present and is important if it is a new symptom or if chronic edema has recently worsened.

DIFFERENTIAL DIAGNOSIS

Complications of Implantation

Infection

Pacemaker implantation is a surgical procedure and, like all surgery, carries a risk of infection; the presence of a foreign body enhances this risk. The incidence of infection is small—approximately 2% for wound and subcutaneous pacemaker "pocket" infection and approximately 1% for bacteremia with sepsis. The presence of a foreign body complicates management, and few cases of bacteremia that develop after implantation can be managed with antibiotics alone. In most instances, reimplantation and replacement of the lead system is necessary.[14]

Pain and local inflammation at the site of the pacemaker are the first manifestations of a wound infection, cellulitis, or pocket infection. Approximately 20% to 25% of patients with a local infection have positive blood cultures. Bacteremia may occur in the absence of a focal infection and may arise with the typical manifestations of the systemic inflammatory response syndrome or sepsis. A hematoma of the pacemaker pocket may mimic a wound or pocket infection. Needle aspiration of the pocket should be done only under fluoroscopy, because the needle may cut the insulation surrounding the pulse generator or the portion of the pacemaker lead that lies within the pacemaker pocket.

When a local infection or bacteremia is suspected, blood cultures should be obtained and intravenous antibiotic therapy initiated. *Staphylococcus aureus* and *Staphylococcus epidermidis* are isolated in approximately 60% to 70% of cases. Gram negative infection is rare.[15] Empirical antibiotic therapy should include vancomycin pending culture and sensitivity data. If blood cultures are positive, the pulse generator and pacemaker leads are usually removed, temporary transvenous pacing is performed, and intravenous antibiotic therapy is continued for 4 to 6 weeks. The permanent pacemaker and lead are subsequently reimplanted.[14]

Thrombophlebitis

The incidence of venous obstruction associated with permanent transvenous pacemakers ranges from 30% to 50%, with approximately one-third of patients having complete venous occlusion.[16] Thrombosis of varying degrees can involve the axillary, subclavian, and innominate veins or the superior vena cava (SVC). The site of insertion does not appear to affect the incidence of this complication. Chronic thrombosis of the veins of the upper arm is common and usually asymptomatic owing to extensive venous collateral circulation.

Because of extensive collateralization, approximately 0.5% to 3.5% of patients develop symptoms indicative of acute thrombosis. These patients will commonly have edema, pain, and venous engorgement of the arm ipsilateral to the site of lead insertion. Although rare, SVC syndrome resulting from pacemaker lead-induced thrombosis occurs. The signs and symptoms of lead-induced SVC syndrome are identical to those described in patients with SVC syndrome and malignancy.

Although symptoms might suggest thrombosis, definitive diagnosis of acute thrombosis usually requires duplex sonography of the jugular venous system or contrast-enhanced computed tomography. The symptoms usually respond to systemic anticoagulation therapy followed by long-term anticoagulation. Treatment of these clots is controversial as they are rarely associated with pulmonary embolism. There are no studies comparing treatments for deep vein thrombus (DVT) related to pacemakers. Most commonly, anticoagulation is achieved using low–molecular-weight heparin followed by warfarin for 3 to 6 months.

The "Pacemaker Syndrome"

After pacemaker implantation, a patient may develop new complaints or report a worsening of the symptoms that prompted evaluation and eventual pacemaker therapy. Such complaints often include syncope or near-syncope, orthostatic dizziness, fatigue, exercise intolerance, weakness, lethargy, chest fullness or pain, cough, uncomfortable pulsations in the neck or abdomen, right upper quadrant pain, and other nonspecific symptoms.

These symptoms, termed the *pacemaker syndrome,* are caused by loss of AV synchrony and by the presence of ventriculoatrial conduction. This syndrome is most commonly encountered in the setting of VVI pacing but is also described with the DDI mode. With VVI pacing, the ventricle is electrically stimulated and depolarized, resulting in ventricular systole. If sinus node function is intact, the atria can be depolarized by a sinus impulse and contract when the tricuspid and mitral valves are closed. This contractile asynchrony results in an increase in jugular and pulmonary venous pressures and may produce symptoms of congestive heart failure.

Atrial distention can result in reflex vasodepressor effects mediated by the central nervous system. Elevated levels of B-type natriuretic peptide (BNP) and diuresis are considered markers for the syndrome in its more severe form. If the contribution of atrial

contraction to late diastolic ventricular filling is important in maintaining an adequate cardiac output, basal and orthostatic hypotension may occur. DDI pacing in a patient with AV block may result in this syndrome if the sinus node discharge rate exceeds the programmed rate of the pacemaker.

Approximately 20% of patients report symptoms suggesting the pacemaker syndrome after pacemaker insertion. In most instances, symptoms are mild and patients adapt to them. In approximately one-third of these patients, symptoms are severe. Treatment usually requires replacing a VVI pacemaker with a dual-chamber pacemaker or lowering the pacing rate of the VVI unit. If symptoms occur in a patient paced in the DDI mode, optimizing the timing of atrial and ventricular pacing is usually required. Patients appear to prefer dual-chamber pacing to the VVI modality.[17]

Pacemaker Malfunction

The term *pacemaker malfunction* refers specifically to problems with the circuitry or power source of the pulse generator, the pacemaker lead (most commonly displacement or fracture), or the interface between the pacing electrode and the myocardium (pacing or sensing threshold). In addition, environmental factors, such as extracardiac or extracorporeal electrical signals, may interfere with normal pacemaker function.[18,19] With use of the standard electrocardiogram (ECG), pacemaker malfunction can be separated into three broad categories: (1) failure to capture (no pacemaker spikes or spikes not followed by an atrial or ventricular complex), (2) inappropriate sensing (oversensing or undersensing spikes occur prematurely or do not occur even though the programmed interval is exceeded), or (3) inappropriate pacemaker rate. Symptomatic pacemaker malfunction after implantation occurs in less than 5% of patients and is rarely immediately life-threatening. Malfunction is most commonly a result of inappropriate sensing, followed by failure to capture. Typical presentations and causes of pacemaker malfunction are listed in Box 70.3.

In the context of suspected pacemaker malfunction, knowledge of the pacing modalities (see Table 70.1) and what is normal for a given pacing modality are critical when the ECG is reviewed. Fortunately, patients are provided with important identifying information, usually in the form of a wallet card, after pacemaker implantation. The most important information is provided in the five-letter code. Many patients will carry a card with the specifics of their pacemaker. If that is not available and the pacer type is not described in the medical records, a standard posteroanterior chest radiograph can provide clues based on number and placement of leads. A single lead in the apex of the right ventricle indicates a VVI pacemaker. With VVI pacing, only one stimulus artifact or spike is seen with each stimulated ventricular depolarization (Fig. 70.1). If sinus node activity is present, the paced QRS complex is dissociated from the intrinsic P waves. If separate leads are identified in the right atrium and right ventricle, the pacing modality is most often DDD or DVI, and paced P waves and QRS complexes (two spikes for each QRS complex) are seen (Fig. 70.2). Although DDD and DVI units are capable of pacing both the right atrium and the right ventricle, only one spike may be seen (Fig. 70.3). Failure to identify two spikes with a DDD or DVI unit can represent normal pacemaker function.

A magnet placed externally over the pulse generator is occasionally used in the assessment of pacemaker function. Magnet application causes closure of a reed switch, turning off sensing function, thus converting the pacemaker to fixed-rate pacing. The technique is most commonly used when the patient's intrinsic heart rate exceeds the pacemaker's set rate and pacemaker function is inhibited. Magnet application then allows pacing to occur, despite the patient's native cardiac activity, and pacing rate and the presence of capture can be determined. Magnets are made by each manufacturer, but any cardiac pacemaker magnet will typically activate the reed switch in any device.

Failure to Capture

Failure to capture may range from the complete absence of pacemaker spikes to spikes not followed by a stimulus-induced

BOX 70.3

Causes of Pacemaker Malfunction

FAILURE TO CAPTURE
- Lead disconnection, break, or displacement
- Exit block
- Battery depletion

UNDERSENSING
- Lead displacement
- Inadequate endocardial lead contact
- Low-voltage intracardiac P waves and QRS complexes
- Lead fracture

OVERSENSING
- Sensing extracardiac signals: myopotentials
- T wave sensing

INAPPROPRIATE RATE
- Battery depletion
- Ventriculoatrial conduction with pacemaker-mediated tachycardia
- 1:1 response to atrial dysrhythmias

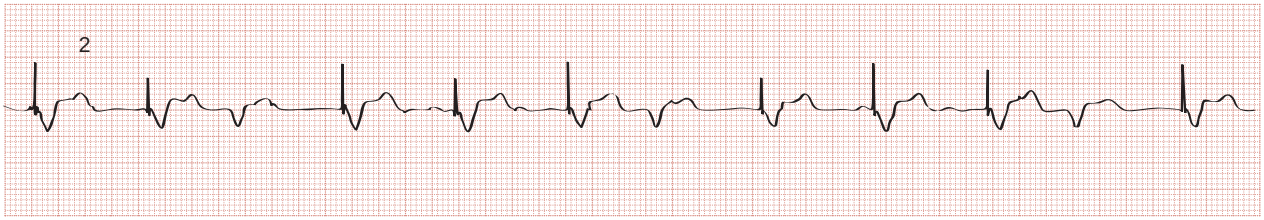

Fig. 70.1. Normal VVI pacemaker (rhythm strip). This rhythm strip was recorded in a patient with a VVI pacemaker implanted for the treatment of symptomatic complete heart block. The pacing rate is approximately 75 beats/min (determined by measuring the time between consecutive pacemaker spikes). Each pacemaker spike is followed by a paced QRS complex. The third QRS from the left has a slightly different morphology than the paced QRS complexes. It is an intrinsic QRS complex that is sensed by the pacemaker, and a paced beat does not occur again until the programmed rate of the pacemaker is exceeded. The time interval between the spontaneous QRS and the next paced beat is approximately the same as the interval between consecutive pacemaker spikes. This sequence is subsequently repeated twice on this strip.

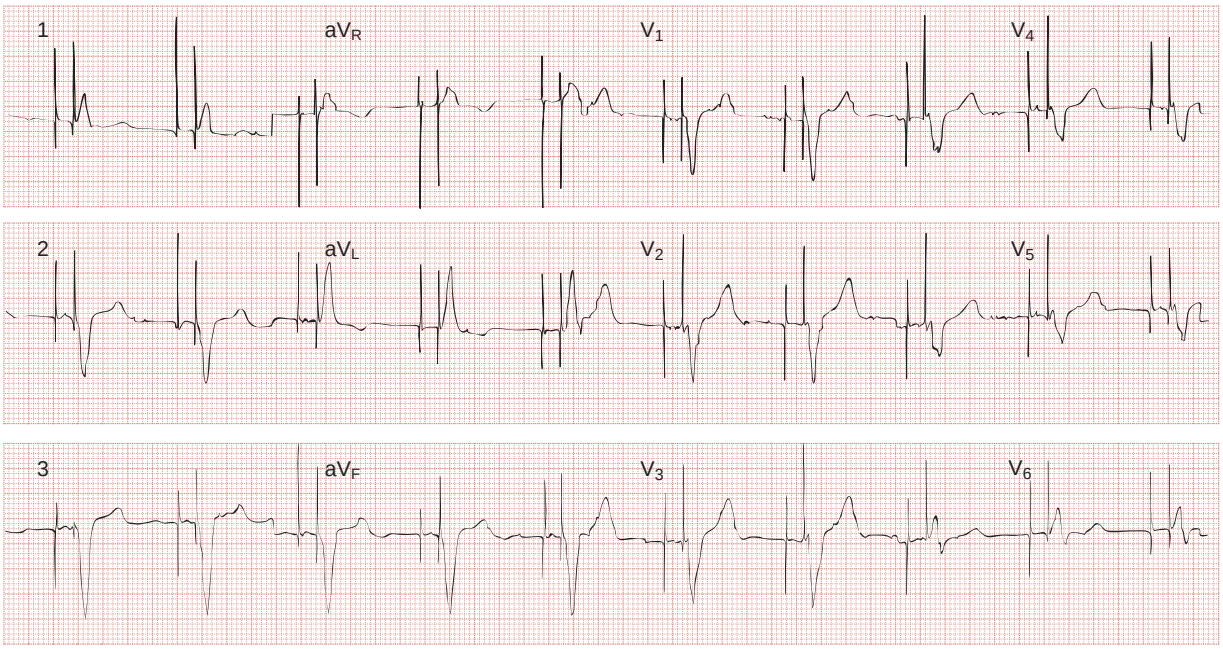

Fig. 70.2. Normal DDD pacemaker (12-lead electrocardiogram [ECG]). Each QRS complex is preceded by two pacemaker spikes. The first spike results in atrial depolarization, and the second produces a wide QRS complex. The QRS complex is conducted with a left bundle branch morphology, which is expected with endocardial pacing at the right ventricular apex.

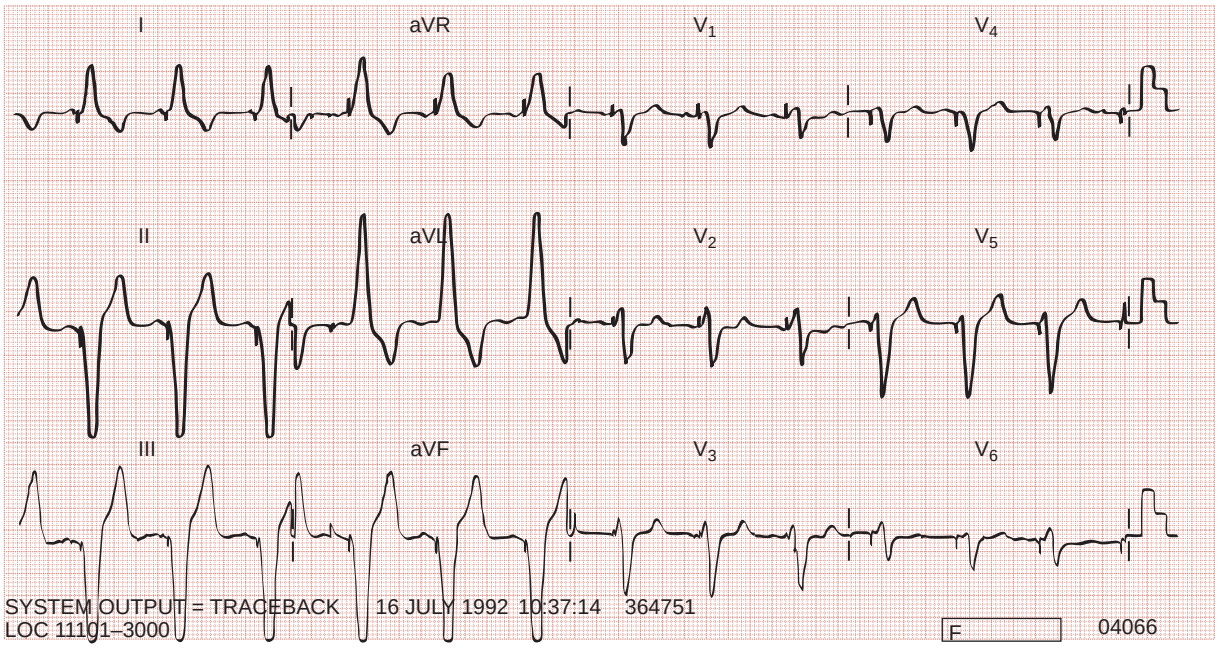

Fig. 70.3. Normal DDD pacemaker (half-standard 12-lead electrocardiogram [ECG]). Three paced QRS complexes preceded by a stimulus artifact or spike are evident in leads I, II, and III. Paced QRS complexes occur after spontaneous or intrinsic P waves are sensed and atrioventricular (AV) conduction delay exceeds the pacemaker's programmed AV interval. The first QRS complex in the augmented leads, best seen in lead aV_F, demonstrates both a paced P wave and a paced QRS complex. Although the pacemaker is a dual-chamber device, two spikes may not always be seen preceding every QRS complex, and the presence of only one spike, or no spikes, should not be interpreted as evidence of pacemaker malfunction. Also evident on this ECG are the different amplitudes of the pacemaker spikes from lead to lead. When a single-lead rhythm strip is recorded, the selected lead should be the one in which the pacemaker spikes are most easily identified.

complex (Fig. 70.4). A complete absence of pacemaker spikes may result from battery depletion, fracture of the pacemaker lead, or disconnection of the lead from the pulse generator unit.

Current lithium-iodine batteries are not subject to sudden power failure, and they display typical end-of-life functional changes over a period of months to a year before complete depletion.[1] Usually the first sign of voltage depletion is a decrease in the programmed pacing rate. This change is gradual and should be detected during the regular follow-up evaluations that pacemaker patients receive. When voltage output falls to a critical level,

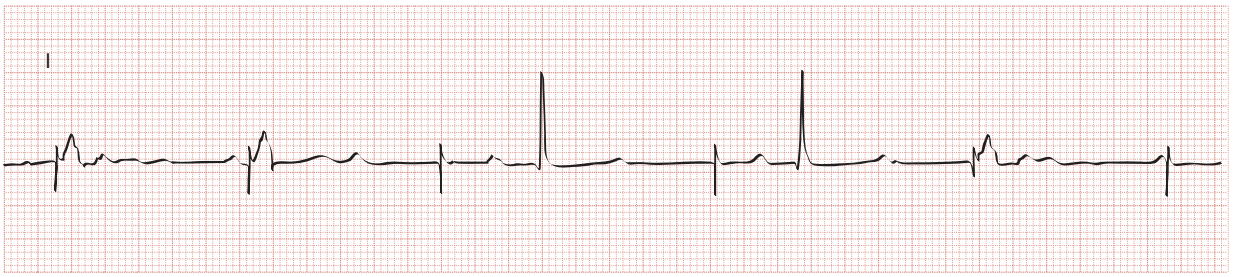

Fig. 70.4. Intermittent failure to capture and slow pacing rate (lead I). This lead I rhythm strip demonstrates intermittent failure to capture of a VVI pacemaker. The first and second pacemaker spikes are followed by wide-paced QRS complexes; the third and fourth spikes are not. The pacemaker spikes occur at a rate of approximately 50 beats/min. The device was programmed to pace at a rate of 75 beats/min. This is a typical example of "end-of-life" pacing characteristics of a depleted battery.

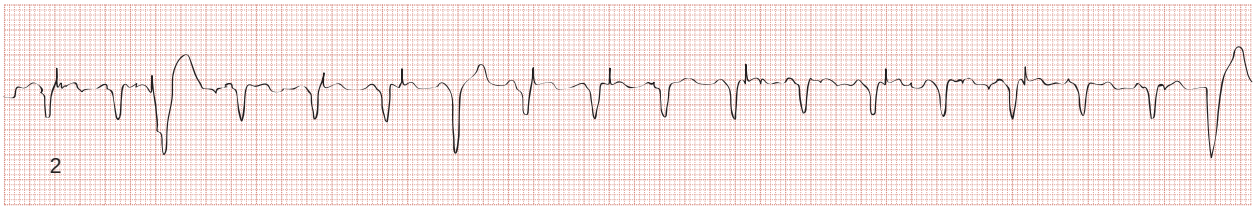

Fig. 70.5. Failure to sense or undersensing (lead II). Pacemaker spikes are evident during inscription of the ST segment on this rhythm strip. These spikes do not produce QRS complexes because they occur during the ventricular refractory period of the preceding spontaneous QRS complex. The third QRS complex on the strip is a paced QRS complex. The device is capable of capture but is undersensing the spontaneous rhythm.

stimulus strength falls below the required threshold, and failure to capture or intermittent failure to capture may be observed late in battery life. As a result, urgent or emergent battery replacement is rare.

Failure to capture, which may be complete or intermittent, is most commonly a lead problem. Lead displacement is the most common cause and is most likely to occur within the first month of pacemaker insertion. The chest radiograph may demonstrate the tip of the pacing catheter displaced from the right ventricular apex. The catheter tip is commonly found in the pulmonary outflow tract, where it may have intermittent contact with endocardium, resulting in intermittent failure to pace and sense. The atrial leads of dual-chamber devices are commonly displaced into the body of the right atrium, resulting in loss of contact between the pacing lead and the atrial endocardium.

Lead fracture, which is uncommon with the current polyurethane lead coating,[1] produces an insulation break, resulting in failure to capture as a result of current leakage. It can be detected as a change in pacing threshold during pacemaker interrogation. Lead fractures occur at predictable locations, usually at the site of attachment to the pulse generator or at abrupt angulations that serve as stress points. Inadequate contact of the lead with the pulse generator can mimic a lead fracture. Occasionally, when a lead fracture is complete or nearly complete, a break in the catheter or its insulation can be detected on an over-penetrated posteroanterior chest radiograph. Loss of lead-pulse generator contact can be detected on the chest radiograph with close inspection of the pulse generator.

Exit block (the failure of an adequate stimulus to depolarize the paced chamber) can also result in failure to pace. Exit block should be considered when the preprogrammed pacing stimulus output fails to result in capture in the presence of a normally functioning pulse generator and an intact lead system. Most commonly this problem is a result of changes in the endocardium in contact with the pacing system. Causes include ischemia or infarction of the endocardium in contact with the electrodes, systemic hyperkalemia, and the use of class III antiarrhythmic drugs (such as, amiodarone), which affect ventricular depolarization. Although other drugs alter pacemaker threshold, the effect is small and is rarely clinically important.

Inappropriate Sensing

For a pacemaker to function in a noncompetitive mode, it must be capable of sensing the intrinsic or "native" electrical activity of the heart. The electrical activity that is sensed is determined by the pacing modality (see Table 70.1). Sensing parameters are determined at the time of pacemaker insertion on the basis of the signal size of the intracardiac ECG and can be changed or fine-tuned externally at a later time if needed.

Undersensing

Failure to sense may be complete or intermittent. It may result from a change in the sensing parameters selected at the time of insertion. This is most commonly encountered after acute right ventricular infarction or during the progressive fibrosis that accompanies many cardiomyopathies, causing intracardiac signals to decrease in amplitude. Lead displacement, fracture, and poor contact with the endocardium may also cause undersensing.

Undersensing is typically recognized electrocardiographically as the appearance of pacemaker spikes occurring earlier than the programmed rate. The spike may or may not be followed by a paced complex, depending on when it occurs during the cardiac refractory period (Fig. 70.5). Failure of a stimulus spike to produce a complex when it occurs during the atrial or ventricular refractory period should not be interpreted as failure to pace.

Oversensing

In rare instances, the pacemaker may detect electrical activity that is not of cardiac origin. The result may be intermittent, irregular

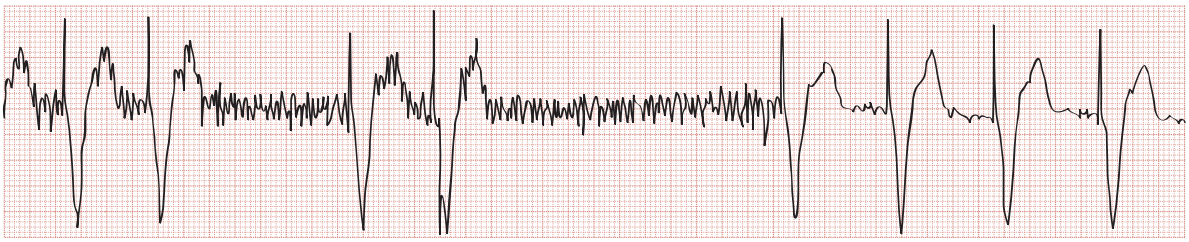

Fig. 70.6. Oversensing (lead II). This VVI unipolar lead pacemaker is oversensing myopotentials produced by contraction of the pectoralis major. Myopotentials result in the undulating and irregular baseline seen in the middle of the strip. After muscular contraction ceases, normal pacing resumes (last four complexes on the strip).

pacing or an apparent complete absence of pacemaker function. Myopotentials produced by the pectoralis muscle (Fig. 70.6) and extracorporeal electrical signals are frequently oversensed when a unipolar lead system is used. T waves that follow an intrinsic ventricular depolarization are the most common oversensed cardiac signals. Common medical sources of electrical interference include electrocautery, which can cause temporary pacemaker inhibition, and magnetic resonance imaging (MRI), which can alter pacemaker circuitry and result in fixed-rate or asynchronous pacing. Electromagnetic interference resulting from close proximity to a microwave oven should not cause problems with currently implanted pacemaker units. The current generation of digital cellular phones do not interfere with implanted pacemakers.[18]

Inappropriate Pacemaker Rate

A pacing rate below the programmed rate is a typical finding in pulse generator depletion and does not occur abruptly with lithium-iodine batteries. An extreme increase in pacing rate, the so-called "runaway pacemaker," is rarely, if ever, encountered with current pacemaker technology and circuitry in which upper rate limits are set (typically 140 beats/min). An "endless loop" tachycardia may develop during dual-chamber pacing when ventriculoatrial conduction occurs, and the resulting retrograde atrial depolarization results in a stimulated or paced ventricular depolarization.[19] If atrial flutter develops during dual-chamber pacing, flutter waves may be sensed and tracked, resulting in a rapid, paced ventricular rate. In both instances, the ventricular rate does not exceed its set upper limit. Patients with such rhythms may complain only of palpitations or symptoms of hemodynamic compromise. When such rhythms are detected, magnet application converts the pacemaker to a fixed rate and terminates the tachyarrhythmia.

DIAGNOSTIC TESTING

Chest Radiograph

A chest radiograph should be obtained to define pacing catheter tip position and to determine the number of pacing leads, unless this information is available from another source. A ventricular pacing catheter tip in the right ventricular outflow tract or an atrial catheter tip in the SVC or right ventricle is abnormal. The pulse generator site should also be examined on the radiograph.

12-Lead Electrocardiogram

A standard ECG and a long rhythm strip should be obtained in all patients. With bipolar pacing systems, the stimulus artifact may be extremely small and difficult to recognize in some leads (see Fig. 70.3). Inspection of the rhythm strip may reveal failure to sense or pace, a low pacing rate, or an abnormally rapid rhythm, suggesting a pacemaker-mediated tachycardia.

The modern pacemaker has two basic functions: (1) to stimulate the heart electrically and (2) to sense intrinsic cardiac electrical activity. Additional functions are available and are noted in the pacemaker code system (see Table 70.1, letters 4 and 5). The pacemaker delivers an electrical stimulus to either the atrium or the ventricle if it does not recognize (sense) any intrinsic electrical activity from that chamber after a selected time interval. This interval is usually programmed at the time of implantation and can be changed noninvasively at a later time, if necessary, with use of a programming and an "interrogating" device provided by the pacemaker manufacturer. If the pacemaker recognizes or senses an intrinsic atrial depolarization (P wave) or ventricular depolarization (QRS complex), it inhibits or resets its output to prevent competition with the underlying intrinsic rhythm. The stimulus intensity and sensing threshold (amplitude of electrical activity that is detected as being intrinsic) are typically set at the time of implantation but can also be reprogrammed later.

The two basic functions of a pacemaker can be easily recognized and confirmed on a standard 12-lead ECG or rhythm strip. The normal function of a single-chamber VVI pacemaker is most easily recognized (see Fig. 70.1). After a programmed interval is surpassed during which intrinsic ventricular activity does not occur, a pacer "spike" or stimulus artifact appears. The pacer spike is a narrow deflection that is usually less than 5 mm in amplitude with a bipolar lead configuration and usually 20 mm or more in amplitude with a unipolar lead. A wide QRS complex appears immediately after the stimulus artifact. Depolarization begins in the right ventricular apex, and the spread of excitation does not follow normal conduction pathways. Characteristically, a left bundle branch block conduction pattern is seen. A right bundle branch pattern is abnormal and may represent lead displacement through a patent foramen ovale, placement of the lead in the coronary sinus, septal perforation, or may be seen with safe right ventricular apical position. In VVI pacing the paced QRS complexes are independent of intrinsic atrial depolarization if present (AV dissociation).

The recognition of normal dual-chamber pacing is more complex owing to the interactive sensing and pacing of the right atrium and ventricle (see Fig. 70.2). Dual-chamber devices are typically used in patients with non-fibrillating atria coupled with intact AV conduction. A normal-appearing QRS complex may follow an intrinsic P wave as a result of normal sinoatrial node discharge if the intrinsic atrial depolarization is conducted to the ventricles. The intrinsic P wave and QRS complex inhibit the atrial and ventricular circuitry. A normal QRS complex follows a paced P wave if the paced atrial beat is conducted through the AV node and the programmed AV delay period is not exceeded. If it is not conducted to the ventricles (AV delay period exceeded), the pacemaker stimulates the ventricle, resulting in a paced P wave and a wide, paced QRS complex with left bundle branch block configuration.

Recognition of the interactivity of the paced chambers is important. A paced P wave may be mistaken for failure to sense

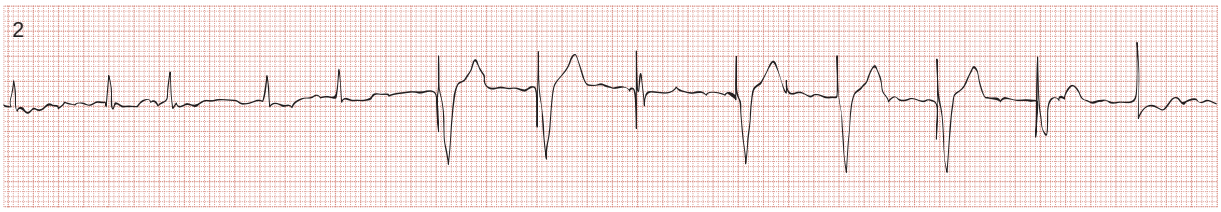

Fig. 70.7. VVI pacemaker with fusion beats (pseudomalfunction). This VVI pacemaker was implanted in a patient with atrial fibrillation and intermittent symptomatic complete heart block. In the lead II rhythm strip, the first five QRS complexes are normal in morphology and irregular, as would be expected in atrial fibrillation. The next two QRS complexes are wide and preceded by a pacemaker spike. This represents normal sensing and pacing. The eighth QRS complex is narrow but preceded by a pacemaker spike. The spikes occur at a fixed and regular interval. In this instance, spontaneous ventricular depolarization had begun at approximately the time the pacemaker discharged. The 12th QRS complex in the sequence represents a fusion beat. Within the QRS complex of the 13th beat, a pacemaker spike is visible. Again, this represents nearly simultaneous conduction of a supraventricular beat and pacemaker electrical discharge. At first glance, this may appear to be failure to sense; however, the pacemaker is functioning normally and competing with the underlying rhythm.

or pace, and malfunction may be diagnosed when it is not present (pseudomalfunction). In addition, if the programmed rate of the pacemaker approximates the patient's intrinsic heart rate, fusion of paced and native beats may occur and represents another common type of pseudomalfunction (Fig. 70.7).

MANAGEMENT

Advanced Cardiac Life Support Interventions

Electrical defibrillation at recommended shock strengths (200, 300, and 360 J) can be safely performed in the patient with a pacemaker. If the sternal defibrillation pad is placed adjacent to the sternum, it is at a safe distance (>10 cm) from the pulse generator. Alternatively, defibrillation electrodes can be placed in an anteroposterior configuration. All pacemakers should be interrogated after successful resuscitation, as well as placement. A chest radiograph should also be obtained to ensure that the pacing catheter was not displaced during chest compression.

Immediate return of pacing (capture) may not occur after defibrillation; this is commonly the result of global myocardial ischemia and increased pacing threshold and is not an indication of pacemaker malfunction. Temporary transcutaneous pacing may be needed if the pacemaker cannot be reprogrammed or normal pacing does not resume spontaneously. Transcutaneous pacing can also be safely used because the anterior and posterior pacing electrodes, if properly positioned, are distant from the pulse generator. Attempting temporary transvenous pacing is usually not necessary and is unlikely to be successful without fluoroscopic guidance and may also dislodge the permanent catheter.

Chronic venous thrombosis, which is common and most often asymptomatic after pacemaker insertion, may preclude temporary catheter insertion through the neck veins. Insertion through the femoral vein is also difficult because the permanently implanted catheter may prevent entry into the right ventricle.

DISPOSITION

As a result of the current design of modern pacemakers and the frequent follow-up evaluation of patients with pacemakers, life-threatening emergencies resulting from pacemaker malfunction requiring emergent intervention are rare. Most instances of malfunction are subtle and difficult to recognize without interrogation of the pacemaker with manufacturer-specific devices by an individual trained in pacer interrogation. In all instances of suspected pacemaker malfunction, the patient's cardiologist should be consulted.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

PRINCIPLES

The ICD was first used clinically in 1980. Technical refinements to this modality for treating ventricular dysrhythmias have progressed even more rapidly than refinements to the less complex standard pacemaker. A surge in the use of ICDs is reflective of improved survival with ICDs versus antiarrhythmic therapy in patients at risk for sudden cardiac death. Generally accepted indications for ICD implantation are noted in Box 70.2. Many patients still require drug therapy after ICD implantation to suppress ventricular dysrhythmias, minimize the frequency of ICD shocks, improve patients' tolerance, and decrease energy use, which prolongs ICD life.

CLINICAL FEATURES

Terminology and Components

The majority of ICDs are now placed percutaneously in a manner similar to that of the standard pacemaker. A transvenous electrode system has largely replaced epicardial lead placement, which required thoracotomy. An epicardial defibrillation lead may occasionally be placed during coronary artery bypass surgery or in a few patients who cannot be defibrillated with use of existing transvenous electrode systems.

The typical modern ICD consists of components similar to those in the standard permanent pacemaker, namely, a power source, electronic circuitry, and lead system. In addition, the standard ICD has a high-voltage capacitor and complex microprocessor memory.[20] The power source is lithium chemistry based with a battery life of 5 to 10 years. The longevity is largely determined by the frequency of shocks. All ICDs are also ventricular pacemakers. The right ventricular lead is used for sensing and pacing, and shocks are typically delivered between a coil in the right ventricular lead and the pulse generator. If dual-chamber pacing is required, a second lead is placed in contact with the endocardium of the right atrium. A biphasic waveform is currently the preferred waveform for internal defibrillation. The biphasic waveform is more effective at lower energies than earlier monophasic waveforms and allows a smaller capacitor to be used, thereby reducing the size and increasing the comfort of the ICD unit.

The diagnostic and treatment functions of the ICD are determined at the time of implantation. In most instances, the cardioversion and defibrillation thresholds are determined at the time

of ICD insertion by inducing ventricular tachycardia (VT) and ventricular fibrillation (VF) and adjusting the shock strength at a level above the minimum required to terminate the induced rhythm. Optimally, the required shock strength for defibrillation is less than half the maximum output (approximately 30 J) of the device. VT is typically managed with use of either low-energy shocks or antitachycardia pacing that interrupts the VT reentrant circuit. Antitachycardia pacing is less likely to have proarrhythmic effects and requires less energy, thereby extending battery life. In the setting of VF, ICDs are capable of delivering up to five additional shocks if the first shock fails.

DIFFERENTIAL DIAGNOSIS

Complications of Implantation

Complications of ICD implantation are nearly identical in type and frequency to those of permanent pacemaker implantation and management as well.

Malfunction

Patients with ICD malfunction usually come to the emergency department (ED) with a limited number of specific symptoms (Box 70.4).

In contrast to patients with a permanent pacemaker, ICD patients are usually aware of when the ICD delivers a discharge or shock. The most common complaint of ICD patients is the occurrence of frequent shocks.[20] An increasing shock rate may be appropriate and not indicative of ICD malfunction if the patient is experiencing an increase in the frequency of VT or VF episodes. An increase in the frequency of episodes may occur in the setting of hypokalemia, hypomagnesemia, ischemia (with or without infarction) related to underlying coronary artery disease, or the proarrhythmic effect of drugs administered to decrease the frequency of ventricular tachyarrhythmias. Many ICD patients, particularly those with newly implanted devices, report that their device has discharged, but subsequent device interrogation reveals that no discharge occurred.

An increase in the shock frequency is a manifestation of ICD sensing malfunction if (1) a supraventricular tachyarrhythmia is inappropriately sensed as VT, (2) shocks are delivered for nonsustained VT, or (3) intracardiac T waves detected by the ICD system are sensed as QRS complexes and the ICD interprets this as an increased heart rate. Temporary ICD deactivation with magnet application may be necessary if oversensing is the problem. Syncope, near-syncope, dizziness, or lightheadedness in the patient with an ICD may indicate undersensing of sustained VT or inappropriately low shock strength to terminate the rhythm. An approach to the evaluation of ICD malfunction is shown in Fig. 70.8.

BOX 70.4

Causes of Implantable Cardioverter-Defibrillator Malfunction

Increase or abrupt change in shock frequency
- Increased frequency of VF or VT (consider ischemia, electrolyte disorder, or drug effect)
- Displacement or break in ventricular lead
- Recurrent nonsustained VT
- Sensing and shock of supraventricular tachyarrhythmias
- Oversensing of T waves
- Sensing noncardiac signals
  Syncope, near-syncope, dizziness
- Recurrent VT with low shock strength (lead problem, change in defibrillation threshold)
- Hemodynamically significant supraventricular tachyarrhythmias
- Inadequate backup pacing for bradyarrhythmias (spontaneous or drug induced)
  Cardiac arrest
- Assume malfunction, but probably caused by VF that failed to respond to programmed shock parameters

VF, Ventricular fibrillation; *VT,* ventricular tachycardia.

DIAGNOSTIC TESTING

Diagnostic testing depends on presenting symptoms. As with pacemakers, chest radiograph can identify lead placement. ECG is indicated to evaluate for arrhythmias. Patients who present with history of more than one ICD shock should have the ICD interrogated while in the ED.

MANAGEMENT

Advanced Cardiac Life Support Interventions

An ICD does not prevent sudden death in all patients at risk, and a patient with an ICD may arrive in cardiac arrest (2% annual incidence in patients with implanted devices). Cardiac arrest is not necessarily an indication of ICD malfunction. Appropriate repeated shocks may have been delivered but were ineffective. Alternatively, the ICD may not have sensed VF or the ventricular ectopic activity that typically precedes VF. Resuscitation efforts in the patient with an ICD should be undertaken in accordance with current recommendations. Transthoracic defibrillation can be performed in the standard manner with a monophasic or biphasic

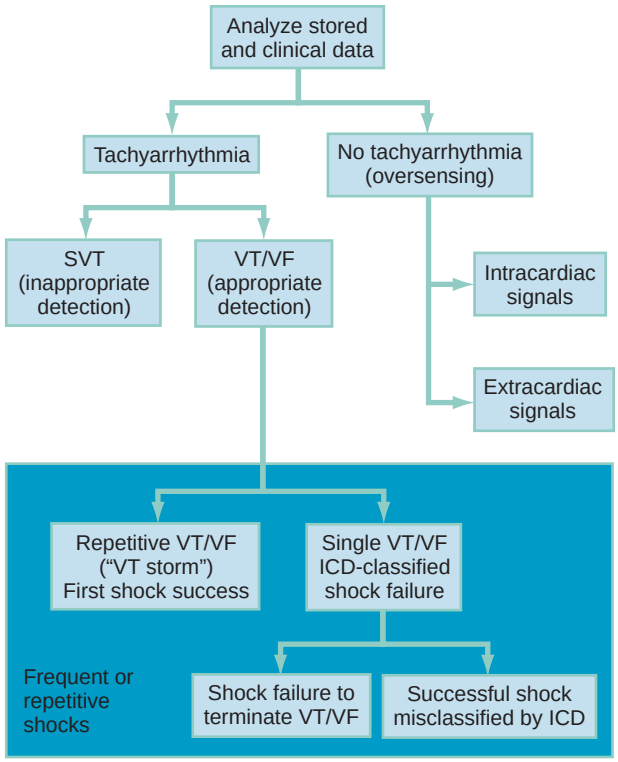

Fig. 70.8. Approach to the patient with shocks. *Top,* Flow diagram for one or infrequent shocks. *Bottom,* Diagram for multiple or repetitive shocks. *ICD,* Implantable cardioverter-defibrillator; *SVT,* supraventricular tachycardia; *VT/VF,* ventricular tachycardia/ventricular fibrillation. (Redrawn from Swerdlow CD, Zhang J: Implantable cardioverter defibrillator shocks: a troubleshooting guide. Rev Cardiovasc Med 2:61, 2001.)

defibrillator if VF is the arrest rhythm. The sternal electrode or paddle should be placed in a parasternal location approximately 10 cm from the ICD subcutaneous pouch if the device has been implanted in the right deltopectoral area. If it has been implanted in the left deltopectoral region, this recommended safety distance is usually exceeded.

ICD discharge during manual chest compressions poses no risk to providers, although the rescuer may feel a weak shock. Although generally not indicated, the device can be deactivated with magnet application during resuscitation. Deactivation is probably more important in the immediate post-resuscitation period. Ventricular dysrhythmias are common at this time due to prolonged global myocardial ischemia during the arrest period, reperfusion, and the hyperadrenergic state, which is worsened by the use of intravenous epinephrine during resuscitation. ICD malfunction should be assumed, and these post-resuscitation rhythms treated with standard pharmacologic agents (lidocaine and amiodarone). Although class 1 antidysrhythmic agents may raise the defibrillation threshold of the ICD, their impact on the defibrillation threshold during transthoracic countershock, due to the high energy, is clinically inconsequential.

DISPOSITION

As a result of the difficulty in documenting or excluding ICD function or malfunction in the patient with transient symptoms, the device should be interrogated to guide further evaluation and therapy. In cases in which the patient reports a single ICD shock, an assessment for acute cardiac ischemia, worsening of chronic congestive heart failure, symptoms of new-onset heart failure, and electrolyte abnormalities should be performed. In the absence of a change in clinical status, such patients can be discharged in consultation with the managing or consulting cardiologist after timely follow-up is ensured. For patients reporting multiple shocks, interrogation is essential, because in many of these cases the defibrillator has not discharged and the patient is experiencing hiccoughs, diaphragmatic twitching, or other nonelectrical phenomena. In such cases, discharge home is the rule. When multiple defibrillator discharges are confirmed by interrogation, emergent consultation is required along with admission to a monitored setting for extended telemetric observation. If frequent ventricular ectopy is noted, intravenous amiodarone is indicated.[20] ICD interrogation allows assessment of ICD function and preceding dysrhythmia episodes.[20] Based on the findings, reprogramming may be necessary; and if a lead problem is detected, reimplantation is required. Similar to a pacemaker, a magnet can be placed over the ICD to inactivate the defibrillator. This should be done only if the emergency clinician is confident that the ICD is delivering inappropriate shocks, such as a supraventricular tachycardia.

BIVENTRICULAR PACING

PRINCIPLES

Biventricular pacing, also known as *cardiac resynchronization therapy,* is a therapy for patients with left-sided heart failure and ventricular dyssynchrony. Indications for biventricular pacing have expanded to include patients with New York Heart Association (NYHA) class II, III or IV heart failure, left ventricular dysfunction, and left bundle branch block, *or* patients with AV block and ventricular systolic dysfunction with NYHA class I, II, or III heart failure.[5,11-13]

CLINICAL FEATURES

Left bundle branch block causes an altered sequence of depolarization of the left ventricle such that the interventricular septum contracts before the left ventricular free wall, leading to inefficient mechanical pumping. Biventricular pacing "resynchronizes" the ventricles by simultaneously pacing the left and right ventricles, eliminating the delay in left ventricular free wall contraction and improving systolic function. Right atrial and right ventricular leads are positioned as for conventional atrial and univentricular pacing. The left ventricular lead is positioned in a left ventricular epicardial location via the coronary sinus and veins, preferably in a posterolateral or lateral location. The QRS duration of paced ventricular complexes is often but not always less than the QRS duration measured before resynchronization therapy.[5] Cardiac resynchronization therapy has not been shown to be beneficial in heart failure with narrow QRS.[21]

DIFFERENTIAL DIAGNOSIS

The complications and malfunctions inherent with conventional cardiac pacing are also observed with biventricular pacing. In addition, biventricular pacing has unique complications related to placement of the left ventricular pacing lead through the coronary sinus. In large clinical trials, coronary sinus dissection occurred in 0.3% to 4.0% of patients and coronary vein or coronary sinus perforation in 0.8% to 2.0% of patients. Cardiac tamponade caused by perforation of the coronary venous system is seen in less than 1% of patients. Dislodgement of the left ventricular electrode with resultant loss of pacing occurs as an early complication in approximately 10% of patients. Patients with malfunction of a biventricular pacing system frequently report palpations or acute decompensation of chronic heart failure.

DIAGNOSTIC TESTING

Biventricular pacing can usually be recognized on the standard ECG (Fig. 70.9). Two stimulus artifacts or "spikes" may be seen preceding a paced QRS complex. With biventricular pacing, a predominantly negative QRS complex is seen in lead I, in contrast to the typical upright complex seen with right ventricular pacing (see Fig. 70.2). A predominantly positive QRS complex is seen in lead V_1 with biventricular pacing.[5]

MANAGEMENT

Patients with biventricular pacemakers have advanced heart failure and may be treated using all current heart failure treatments (see Chapter 71). As with standard pacemakers, transvenous pacing is rarely needed and may be difficult due to preexisting leads blocking passage of the transvenous pacing wire. Cardiac tamponade due to pacemaker placement is treated using usual technique. Treatment of lead misplacement or dislodgement requires cardiology consultation.

DISPOSITION

Disposition of patients with biventricular pacemakers will depend on presenting symptoms and or complications.

CARDIAC ASSIST DEVICES

PRINCIPLES

Mechanical ventricular assistance devices have been used as a "bridge" to transplantation since the 1960s.[22] Newer devices, such as the Jarvik 2000 and HeartMate II, are continuous flow pumps that are portable and powered with long lasting, wearable battery packs allowing patients to live in their community. With advancing technology, infectious complications and postoperative mortality have decreased, significantly with 2 year survival in over half

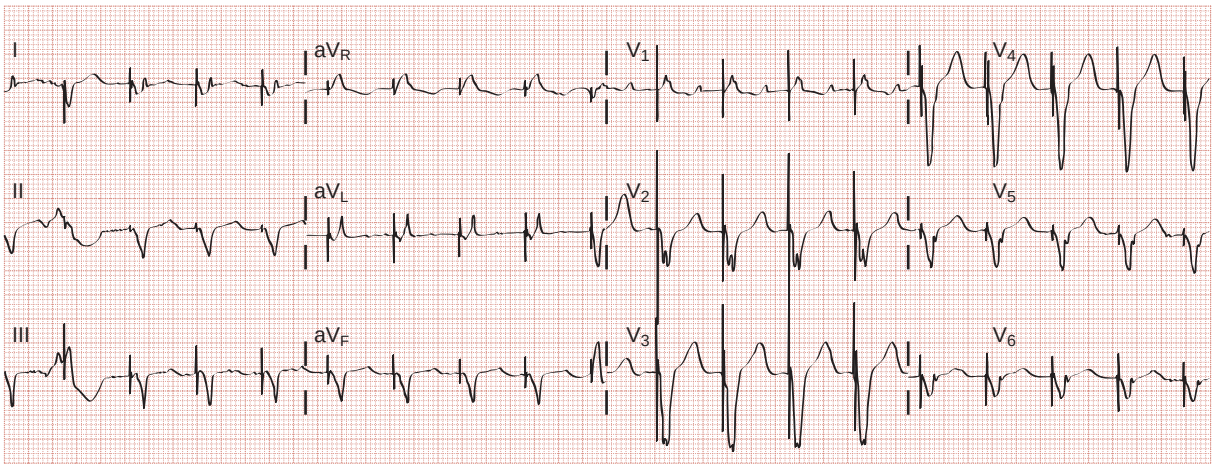

Fig. 70.9. Biventricular pacemaker. This 12-lead electrocardiogram (ECG) demonstrates an atrial sensed, biventricular pacemaker in a patient with cardiac synchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) system (CRT-D). The PR interval is 350 msec and represents the programmed atrioventricular (AV) delay for this patient. The paced QRS complexes have an S wave in lead I and an R wave in lead V_1 that are distinctly different from the morphology and axes seen with right ventricular apical pacing. The second beat from the left is a premature ventricular contraction (PVC). There is a pacemaker "spike" superimposed on this complex, likely representing safety pacing in CRT-D.

of patients.[23] The greatest mortality is noted within the first 30 days after implantation and during hospitalization. These mechanical assist devices may be used as a bridge to cardiac transplant or as "destination" therapy in patients who do not qualify for cardiac transplantation.[22,24] Three types of implanted heart assist devices now exist. These include the left ventricular assist device (LVAD), the biventricular assist device (BiVAD) and the total artificial heart (TAH).

Mechanical options for patients with biventricular heart failure include the BiVAD and the TAH. The BiVAD is similar to the LVAD, but it consists of two pumps—one assisting the right ventricle, one assisting the left ventricle. The failing heart is left in place while the pumps are attached to it. The mechanism, as well as complications and precautions for the BiVAD are similar to those for the LVAD.

CLINICAL FEATURES

The LVAD supports the patients cardiac output via a mechanical pump that draws blood from an inflow cannula in the left ventricle and pumps it into the ascending aorta via an outflow cannula. The pump at the left apex is connected via a driveline exiting the patient at the epigastrium to the external controller box. The controller box and batteries are worn by the patient on a belt and shoulder harness, allowing freedom of movement. The controller displays battery life and alarms. Patients with LVADs require lifelong anticoagulation to prevent the graft from clotting. Most patients also have a pacemaker or automatic implanted cardiac defibrillator (AICD) placed.

The most common LVADs produce a non-pulsative flow, therefore patients are essentially pulseless making traditional hemodynamic vital sign interpretation impossible. Adequate perfusion can be assessed by evaluating mental status and alertness, oxygenation, and renal function. Blood pressure may be measured using a manual cuff with a Doppler probe over the radial or brachial artery. The cuff pressure is reduced until a constant sound is heard. The pressure at this point represents the mean arterial pressure. Blood pressure can also be measured invasively using an arterial catheter.

Assessing the LVAD for device malfunction can be challenging, but assistance is available by calling the patient's LVAD coordinator by phone, as well as enlisting the help of the patient's family members who receive extensive training when the device is implanted. The screen on the control panel can help determine if the problem may be due to battery level, flow, or other malfunction. Listening to the epicardium should reveal a continuous noise if the pump is operating.

DIFFERENTIAL DIAGNOSIS

Like any other patient with indwelling catheters, the driveline can become a conduit for infection and patients with LVADs are prone to infections that may be localized around the LVAD device, as well as systemic including bacteremia. These infections are treated with broad-spectrum antibiotics, including methicillin-resistant *Staphylococcus aureus* (MRSA) coverage with device removal rarely necessary.

Most LVAD patients are anticoagulated and are at increased risk for bleeding. This most frequently presents as intracranial or gastrointestinal hemorrhage. In addition to pharmacologic anticoagulation, patients with LVAD can develop acquired von Willebrand's factor (vWF) platelet dysfunction. Reversal of anticoagulation should be approached with caution due to risk of graft failure due to obstructing thrombus, and patients who are inadequately anticoagulated are at risk for pump failure due to thrombus. A patient with hemodynamic collapse due to clot on inflow or outflow cannulas can be treated with intravenous heparin or in extreme cases, thrombolysis.

Patients with an LVAD experiencing signs of shock or poor perfusion may be due to right ventricular failure, because the device does not support the right ventricle. This can be evaluated with a bedside echocardiogram showing a small right ventricle with poor contraction. In these cases, preload augmentation with titrated fluid boluses may improve hemodynamics. Inotropes such as dopamine, dobutamine, or a combination of these drugs have also proven beneficial in these situations.

Dysrhythmias are frequent with LVAD patients. Because the pump can maintain forward flow despite dysrhythmias, the patient may remain awake and conscious despite persistent VF. Most patients have an AICD place, which should respond to tachydysrhythmias. If there is no AICD or the AICD is not functioning, LVAD patients may be cardioverted using standard

TABLE 70.3

Comparison of Common Ventricular Assist Devices

	THORATEC VAD	HEARTMATE II	HEARTMATE I OR XVE
Flow type	Pulsatile: Patient will have a pulse and BP	Axial: Patient will not have a pulse or BP Use Doppler to confirm flow	Pulsatile: Patient will have a pulse and BP
Backup method	Hand pump	No external method	Hand pump
Battery life	Up to 3 hours	Up to 10 hours	Up to 10 hours
Defibrillation or cardioversion	No precautions	No precautions	Use hand pump during procedure
Cardiac arrest	Use hand pump	No external method	Use hand pump

BP, Blood pressure.

external pads, taking care not to place pads directly over mechanical parts. Patients may also be treated with any antidysrhythmic medication.

DIAGNOSTIC TESTING

ECG is useful in LVAD patients to identify arrhythmias. Ultrasound or echocardiogram may be used for LVAD patients to confirm blood flow. Electrocardiography and echocardiography are not useful in patients with the TAH, because there is no native heart and no electrical activity.

MANAGEMENT

Chest compressions risk dislodging the device, resulting in massive hemorrhage, although a recent case series of eight patients with LVAD who received chest compressions showed no cannula dislodgements with four patients surviving the initial arrest.[25] Prior to considering chest compressions, multiple methods should be used to confirm absence of circulation, and attempts should be made to correct mechanical pump malfunction. In some devices, the hand pump can be used to provide backup circulation, and early transition to cardiopulmonary bypass should be considered (Table 70.3).

In contrast to the BiVAD, with the TAH, the failing heart is removed and the TAH implanted. The currently available TAH (SynCardia) produces pulsatile flow. Because the native heart has been removed, patients with a TAH have no cardiac electrical activity (asystole); therefore defibrillation and pacing are never indicated. Chest compressions are not effective with the TAH and could be harmful due to traumatic disruption of the heart or drive lines. Epinephrine and vasopressin are generally not recommended for TAH patients, because there is no native heart to respond.

DISPOSITION

Although patients with an LVAD or TAH typically require care at cardiac transplant centers, they often present to their local community or closest ED. In such cases, telephone consultation with an expert at a transplant center can assist in management and help facilitate transfer. Emergency clinicians need to be familiar with management of LVAD and TAH complications and be able to stabilize these patients to the extent possible prior to transfer.

KEY CONCEPTS

- Pacemaker malfunction soon after implantation (within 6 to 8 weeks) is usually a result of a lead problem, such as a lead displacement, or a pacemaker programming failure, such as a pacing rate too slow for the patient's needs.
- Pacemaker malfunction arises in a limited number of ways: failure to pace, oversensing, undersensing, and pacing at an inappropriate rate (too fast or too slow).
- With lithium-iodine batteries, abrupt failure is an unlikely cause of pacemaker malfunction.
- If a patient with a pacemaker has a fever of unclear cause, pacemaker lead infection and endocarditis should be considered.
- Because paced ventricular complexes are conducted with a left bundle branch block pattern, a paced rhythm obscures the electrocardiographic diagnosis of acute myocardial infarction. A right bundle branch pattern is abnormal and suggests lead displacement.
- Magnet application does not turn off a pacemaker, it turns off the sensing or inhibition function. Fixed-rate pacing that is independent of or in competition with the underlying native rhythm will ensue. Removal of the magnet restores the inhibitory activity of the pacemaker and returns it to demand pacing mode.
- Defibrillation is safe in patients with a pacemaker or implantable cardioverter-defibrillator (ICD). Paddles should be placed at least 10 cm from the subcutaneous implant site of the device. Alternatively, anteroposterior defibrillation with adhesive defibrillation electrodes can be performed. There are no reports of injury to rescuers from ICD discharges during manual chest compressions.
- Most left ventricular assist device (LVADs) do not produce pulsatile flow; therefore, these patients will not have a palpable pulse. Because chest compressions may be harmful, multiple methods should be used to confirm absence of circulation and attempts should be made to correct mechanical pump malfunction.
- Patients with a total artificial heart (TAH) have no native heart and no cardiac electrical activity. Electrocardiogram (ECG) for the TAH will read asystole. Defibrillation and pacing will not be effective. Chest compressions will not be effective and may be harmful.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 70: QUESTIONS & ANSWERS

70.1. Which of the following conditions is an indication for permanent pacemaker placement after acute myocardial infarction?

A. Asymptomatic persistent third-degree atrioventricular (AV) block
B. New-onset left bundle branch block
C. Symptomatic persistent second-degree infranodal AV block
D. Transient symptomatic third-degree AV block

Answer: C. Symptomatic persistent *symptomatic* second- or third-degree AV block and bilateral bundle branch block with persistent second-degree AV block at the His-Purkinje level are also indications.

70.2. Which of the following technical characteristics is applicable for most permanent pacemakers?

A. A unipolar pacemaker configuration is less prone to oversensing of myopotentials.
B. Bipolar systems are implantable cardioverter-defibrillator (ICD) compatible.
C. Lithium battery life is 10 to 20 years.
D. Most leads are implanted within the myocardium.
E. Optimal ventricular lead placement is at the right ventricular outflow tract.

Answer: B. Bipolar systems have the proximal (positive) and distal (negative) leads in close proximity to each other on the surface of the endocardium. Bipolar leads are more fracture prone but less likely to oversense myopotentials and are also ICD compatible. In unipolar systems, the proximal lead is enclosed in the pulse generator. Typical lithium battery life is 4 to 10 years. Unipolar lead amplitude is approximately four times longer than typical bipolar spikes (20 mm vs. 5 mm). Lead placement should not be in the outflow tract.

70.3. A 72-year-old man presents with dyspnea. He has a history of symptomatic bradycardia that required pacemaker placement and a history of hypertension and peripheral vascular disease. In the course of your evaluation, an electrocardiogram (ECG) is obtained showing a ventricular-paced rhythm with a right bundle branch morphology, rate 72. Vital signs are normal. This likely indicates which of the following?

A. A nonfunctioning atrioventricular (AV) sequential system
B. A ventricular demand pacemaker
C. Electrolyte disturbance
D. Lead displacement
E. Right ventricular apex depolarization by a unipolar endocardial lead

Answer: D. The typical depolarization begins in the right ventricular apex, and a left bundle branch pattern is the norm. The presence of a right bundle branch block (RBBB) pattern should raise suspicion of lead displacement. Electrolyte disturbance does not typically cause a morphology change.

70.4. A 60-year-old man presents with swelling and tenderness around his left subclavian pacemaker. It was implanted 2 years previously for heart block. It was last interrogated 8 weeks prior by his cardiologist, with good function documented. Physical examination is unremarkable except for mild tenderness with minimal swelling and erythema at the pulse generation site. Vital signs are unremarkable.

Which of the following interventions should be performed next?

A. A course of oral antibiotics with *Staphylococcus aureus* coverage should be initiated.
B. Blood cultures should be sent.
C. Local aspiration should be considered to rule out hematoma.
D. Serial examinations would be acceptable management.

Answer: B. The incidence of wound/pocket infection is 1% or 2%. With infection, however, the incidence of bacteremia is 20% to 25%. Local signs may be minimal. If pacemaker site infection is suspected, blood cultures, admission for intravenous (IV) antibiotics, and cardiology consultation with the potential need for pacemaker explantation should be undertaken.

70.5. What is the incidence of venous obstruction after permanent transvenous pacemaker placement?

A. <15%
B. 15% to 30%
C. 30% to 50%
D. 50% to 70%

Answer: C. This may be partial or complete and involve the axillary, subclavian, innominate veins, or the superior vena cava (SVC). Because of collateralization, only approximately 4% of patients develop symptoms consistent with acute thrombosis. Thrombolytic therapy is most useful within the first 2 weeks.

70.6. Which of the following statements best describes risk of pacemaker syndrome in patients receiving a permanent pacemaker?

A. It is most common with VVI pacemakers.
B. It is not seen with dual-chamber pacing systems.
C. It occurs in less than 5% of patients after pacemaker placement.
D. It occurs in the setting of preexisting congestive heart failure (CHF).

Answer: A. Pacemaker syndrome occurs in approximately 20% of pacemaker recipients. It is due to poor atrioventricular (AV) synchrony occurring when the ventricle is paced, but an intact sinus node stimulates the atria to fire against closed tricuspid and mitral valves. CHF symptoms and elevated B-type natriuretic peptide (BNP) may be seen. It occurs less commonly with DDI systems, but when it does occur, it may require reprogramming for better AV synchrony. It is most common after VVI placement.

70.7. A 72-year-old woman presents in cardiac arrest. Her history is remarkable for automatic implanted cardiac defibrillator (AICD) implantation 6 months ago for recurrent ventricular tachycardia (VT). No other history is available. The rhythm is ventricular fibrillation (VF). Which of the following is next best steps?

A. Her cardiac arrest is indicative of implanted cardiac defibrillator (ICD) failure.
B. ICD should not be inactivated because of the high incidence of post resuscitation ventricular dysrhythmias.
C. Rescuers should be warned of potential painful shocks while performing cardiopulmonary resuscitation (CPR).
D. Transthoracic defibrillation may be performed in the standard manner for VF.

Answer: D. ICD does not prevent sudden death, as evidenced by the 2% annual incidence. Cardiac arrest is not an indication of ICD failure, because shocks may have been ineffective or there may have been a failure to sense. Transthoracic defibrillation may be done in the standard manner, but with attempts to keep the paddle 10 cm from the generator, very mild shocks may be felt by the person performing CPR, but these are not painful or dangerous. Immediate deactivation is not a priority but should be considered in the post resuscitation period, when the ICD may not function well.

CHAPTER 71

Heart Failure

John F. O'Brien | Christopher L. Hunter

PRINCIPLES

Background

Heart failure is a debilitating cardiac condition characterized by dyspnea, poor exercise tolerance, and chronic fatigue, along with high morbidity and mortality. *Heart failure* may be defined as the pathophysiologic state in which the heart is incapable of pumping a sufficient supply of blood to meet the metabolic requirements of the body, or requires elevated ventricular filling pressures to accomplish this goal. The caveat about high filling pressures acknowledges that a failing heart may continue to maintain systemic perfusion via the compensatory Frank-Starling mechanism, resulting in the maintenance of normal stroke volume (SV) despite reduced ejection fraction (EF). Conversely, low filling pressure with hypoperfusion indicates a pump-priming problem distinct from cardiac disease.

Heart failure is conceptually separated into two clinical subtypes: systolic heart failure and diastolic heart failure, with much overlap between the two. The American Heart Association (AHA) and American College of Cardiology (ACC) guidelines define heart failure related to systolic dysfunction (also known as heart failure with reduced ejection fraction [HFrEF]) as a left ventricular ejection fraction (LVEF) less than 40%.[1] Diastolic heart failure (also known as heart failure with preserved ejection fraction [HFpEF]) is a pathologic condition involving normal or near-normal systolic function with failure of ventricular relaxation and consequent high filling pressures, which may exist in over half of older individuals with heart failure.[2,3] HFpEF carries a prognosis similar to HFrEF.[4,5]

Heart failure is a progressive and multifaceted disease that begins long before symptoms and signs are evident. Guidelines approved by the AHA and ACC reflect a new classification system for heart failure that includes four categories: (1) patients at risk, (2) patients with asymptomatic left ventricular (LV) dysfunction, (3) patients with symptomatic heart failure, and (4) those with refractory heart failure.[6] The number of patients with asymptomatic LV dysfunction is approximately fourfold greater than those with symptomatic heart failure.[7] The main predisposing factors for heart failure in the United States include atherosclerotic coronary artery disease, hypertension, diabetes mellitus, dyslipidemia, obesity, along with cocaine, ethanol, and tobacco abuse. Hypertension precedes heart failure in up to 75%, particularly in African-Americans. Approximately two-thirds of patients with systolic heart failure have significant coronary artery disease. Those with diabetes mellitus have an increased risk of cardiac ischemic events and heart failure.[8] High dietary sodium is associated with heart failure.[9] Treatment should ideally be initiated in patients at risk to prevent disease progression. Control of hypertension greatly reduces the risk of development of heart failure, as does improvement of dyslipidemias in patients with atherosclerosis.[10,11] Appropriate lifestyle changes, including substance abuse cessation, weight reduction, restriction of salt intake, and modest exercise programs reduce symptoms in heart failure and may delay progression. In particular, obesity leads to excessive lipid accumulation within the myocardium, is directly cardiotoxic, and causes LV remodeling with dilated cardiomyopathy.[12] Substantial weight loss in patients with heart failure associated with obesity produces a reversal of many of the clinical manifestations and improves cardiac function.[13] However, moderately overweight and obese patients have lower cardiovascular mortality in chronic heart failure, termed the *obesity paradox*, which is perhaps partly explained by cardiorespiratory fitness.[14]

Epidemiology

Heart failure is a leading cause of mortality of Western society and represents the fastest growing type of cardiovascular disease.[15] About 6,100,000 individuals (approximately 2% of the population) in the United States have manifest heart failure, and almost 650,000 new cases are diagnosed annually.[16] The incidence exceeds 10 per 1000 in people older than 65 years old, and the elderly comprise about 80% of the 1 million or so patients hospitalized with heart failure each year.[17,18] Decompensated heart failure is a common reason for hospital admission in this age group and also for readmission within 30 days of discharge, with the emergency department (ED) a main portal of entry. Hospitalization for acute heart failure predicts a poor prognosis, with postdischarge mortality or rehospitalization rates reaching 45% within 60 to 90 days.[19] Heart failure results in an annual estimated health care cost of approximately $40 billion.[20] The aging population, coupled with improvements in the therapy of heart failure, will result in increased prevalence of this disease.[21]

Heart failure carries an approximate 50% mortality at 5 years after symptom onset, and one-third of patients with the most severe disease die within the first year after diagnosis.[22] Heart failure disproportionately affects blacks when compared to white Americans, both in incidence and mortality, whereas all females have a survival advantage over males. Progressive hemodynamic deterioration accounts for approximately 50% of heart failure mortality, but sudden death resulting from malignant ventricular dysrhythmias occurs in up to half. Multiple medical therapies decrease the morbidity and mortality in heart failure by improving functional status and slowing progression of pump dysfunction. Implantable cardioverter-defibrillator (ICD) devices most reliably reduce the frequency of sudden death.[23]

The prognosis in heart failure is related to a number of factors, including age, LVEF, exercise tolerance, plasma norepinephrine and natriuretic peptide levels, cardiothoracic ratio on chest radiograph, anemia, hemoglobin A_{1c} level, and renal function, as well as resting heart rate (HR), electrocardiogram (ECG) evidence of LV hypertrophy, atrial fibrillation, or presence of ventricular dysrhythmias.[24-29] Renal dysfunction is a particularly important comorbidity in heart failure, with our understanding of the bidirectional interactions between the heart and kidney still limited.[30] One-third to one-half of patients with heart failure have some degree of renal insufficiency, which is one of the strongest predictors of mortality.[31] Treatment of comorbid conditions in heart failure may have a huge impact on the primary disease.[32]

Anatomy and Physiology

A complex neurohormonal regulatory relationship exists between the heart and multiple organ systems. Feedback loops mediated through a variety of vasoactive substances secreted by the heart, autonomic nervous system, kidneys, adrenals, lungs, and vascular endothelium are most important. Perturbations of function in any of these organs affect the others (Fig. 71.1). Accordingly, the cardiovascular system should be viewed as a dynamic one, continually adapting to optimize organ perfusion. Dysfunction of the heart or any component of the cardiopulmonary system initiates adaptive neurohormonal activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), natriuretic peptides, endothelin (ET), vasopressin, and other regulatory mechanisms. Neurohormonal activation initially compensates for circulatory system dysfunction. These mechanisms eventually lead to increased mechanical stress on the failing heart, however, causing maladaptive electrical and structural events, progressive cardiac fibrosis with apoptosis, and further impairment of systolic and diastolic function. This creates a vicious cycle of increasing myocardial dysfunction causing further neurohormonal modulation, leading to a progressive downward spiral. The degree of myocardial dysfunction depends on both the amount of primary myocardial disease and other pathologic conditions, particularly in the pulmonary, renal, and peripheral vascular systems. Understanding these underlying compensatory mechanisms is leading to progressive improvement in the management of heart failure, with a shift from a hemodynamic to a neurohormonal model.

Cellular Mechanisms

The heart is composed of a mass of individual striated muscle cells (myocytes) that form a branching syncytium. Each myocyte contains an intracellular tubular system termed the *sarcoplasmic reticulum* and numerous cross-banded strands termed *myofibrils* that traverse the length of the myocyte. Myofibrils, in turn, contain multiple subunits called *sarcomeres,* which form the basic functional unit of myocardial contraction. Sarcomeres occupy approximately 50% of myocardial cell mass and are composed of contractile proteins actin and myosin along with regulatory proteins troponin and tropomyosin. These proteins are surrounded by invaginations of the myocardial cell membrane (sarcolemma) and sarcoplasmic reticulum.

The sarcomere ranges in length from 1.6 to 2.2 μm, depending in part on the tension exerted on the muscle before contraction (preload). Sarcomere contraction occurs when thin, double-helix actin is exposed to thick myofilament myosin. Contraction, as well as relaxation, is controlled by calcium ion (Ca^{2+}) release from the sarcoplasmic reticulum. When intracellular Ca^{2+} is increased, it binds to the contraction regulatory protein troponin, which

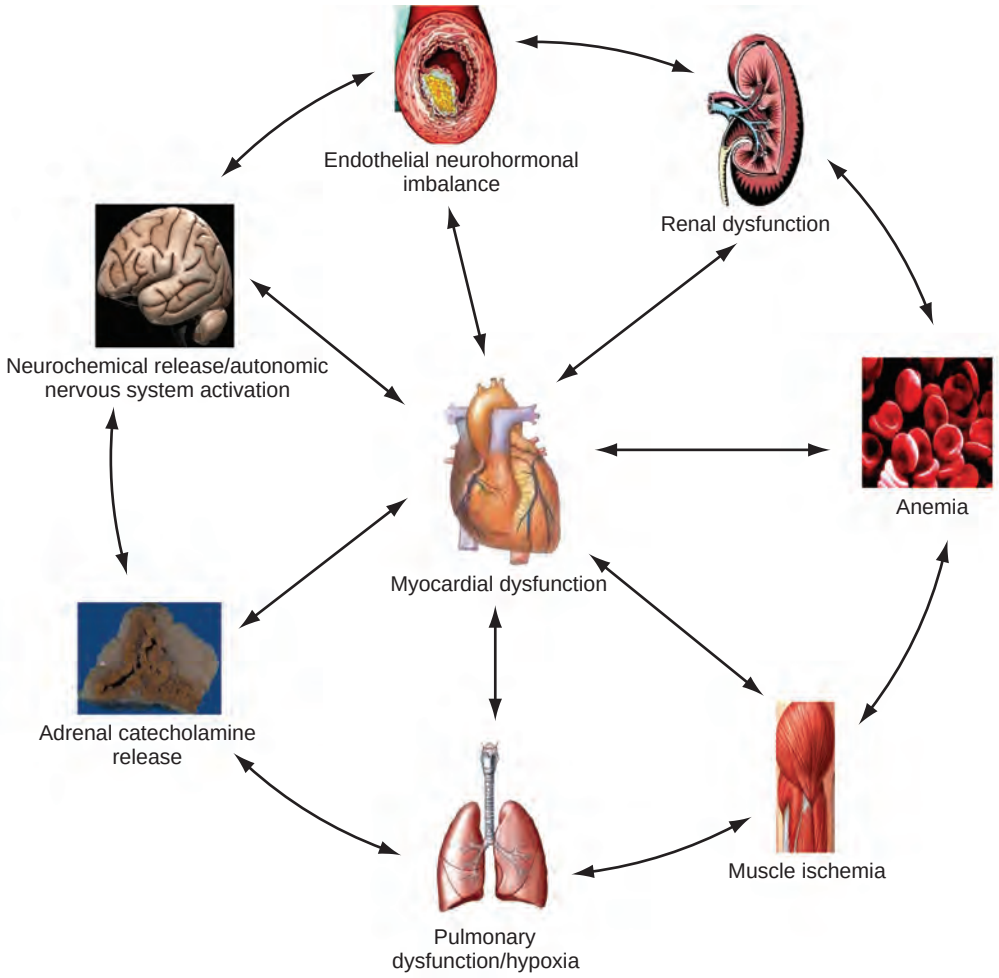

Fig. 71.1. The neurohormonal model of heart failure describes a complex interdependence among many organ systems in which a functional disturbance in any component causes complex compensatory changes in the others that are eventually maladaptive. Correction of organ system dysfunction by medications and other interventions may result in correction of these perturbations.

causes a conformational change in tropomyosin that exposes actin to myosin. In the presence of adenosine triphosphate (ATP), linkages between actin and myosin are rapidly made and broken, causing the actin to slide along the myosin filaments. This process generates muscle tension and ultimately myocyte contraction. A decrease in intracellular Ca^{2+} by sarcoplasmic reticulum reaccumulation reconforms the troponin-tropomyosin complex in such a way that myosin and actin linkages are broken, allowing sarcomere relaxation. Intracellular ionic calcium is thus the principal mediator of the heart's inotropic state and is mainly stored and regulated by the sarcoplasmic reticulum. Most positive inotropic agents, including digitalis and catecholamines, act by increasing availability of intracellular calcium. On the downside, increased intracellular calcium reduces diastolic relaxation.

Cardiac Physiology

The normal cardiac index is 2.5 to 4.0 L/min/m^2 at rest and is determined by contractility, preload, afterload, and HR. In normal hearts, the collective force of contraction of the cardiac chamber is the sum of forces generated by individual myocytes. Myocyte force is in turn a function of the ability of contractile proteins to generate power (inotropic state or contractility), as well as degree of sarcomere stretch at the start of contraction (preload). Stretching the sarcomere progressively toward its optimal length of 2.2 µm increases the force of contraction by allowing the maximum number of actin-myosin myofilament interactions. This forms the basis of the Frank-Starling relationship, which states that within physiologic limits, force of ventricular contraction is directly related to end-diastolic length of the myofibril. Contractility can be affected by multiple physiologic depressants (eg, hypoxia, hypercarbia, acidosis, ischemia) and pharmacologic agents (eg, antidysrhythmic agents, calcium channel blockers, beta-blockers, alcohol) that decrease myocardial function. Correcting physiologic myocardial depressant factors and discontinuing unnecessary medications with negative inotropic properties are important first steps in managing heart failure. Inotropic agents enhance contractility and may improve hemodynamics both acutely (such as with catecholamines) and chronically (such as with cardiac glycosides).

Preload is the amount of force stretching the myofibril before contraction. In the intact ventricle, preload is produced by venous return into the chamber, resulting in stretch of the myofibrils constituting the chamber walls. The volume filling the chamber also results in development of pressure that can be measured in either ventricle. The pressure measured inside a chamber is determined by both the volume stretching the wall and compliance characteristics of the muscle. For this reason, ventricular pressure is only an indirect reflection of preload. Changes in compliance occur acutely with ischemia or chronically with hypertrophy, and may substantially alter the relationship between chamber volume, pressure, and preload (Fig. 71.2).

Optimal preload is the filling pressure that stretches ventricular myofibrils maximally and leads to greatest stroke output per contraction. The actual optimal preload is unique for each patient because it is affected by LV loading conditions and compliance characteristics. For example, patients with acute myocardial infarction (AMI) tend to have a stiffer, less compliant left ventricle. In these patients, optimal LV pressure ranges are higher. No matter the inotropic state of the ventricle, optimizing preload results in maximum stroke output for that ventricle (Fig. 71.3). Ventricles with normal compliance accommodate larger volumes before the chamber pressure rises. Accordingly, if pressure is used to estimate preload, the normal ventricle has more dramatic increases in stroke output for similar increases in filling pressure (steeper Starling curve). The risk of pulmonary edema increases when LV end-diastolic pressure rises significantly above normal ranges (6 to 12 mm Hg). In patients with low colloid osmotic pressures secondary to hypoalbuminemia, pulmonary edema may occur at even lower filling pressures.

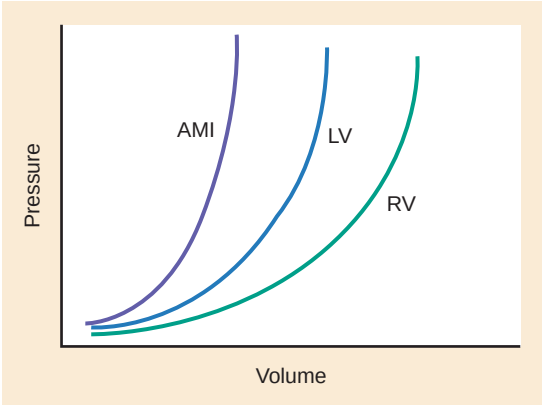

Fig. 71.2. The end-diastolic pressure of a chamber is determined by its filling volume and compliance characteristics. The right ventricle *(RV)* is more compliant than the more muscular left ventricle *(LV),* which becomes stiffer still under conditions of ischemia or acute myocardial infarction *(AMI).*

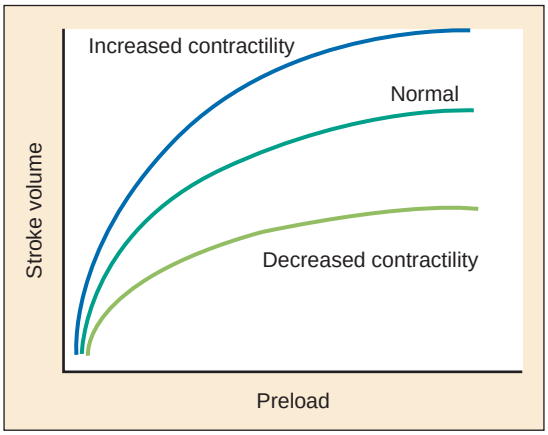

Fig. 71.3. Increased preload improves stroke volume (SV) irrespective of the contractile state of the ventricle. At any level of contractility, an optimal preload is reached beyond which further increases in chamber pressure may result in increased risk of pulmonary edema, with minimal incremental increase in SV.

Afterload, for clinical purposes, can be thought of as the pressure against which the heart must pump to eject blood. Blood pressure (BP) is determined by the product of cardiac output (CO) and systemic vascular resistance (SVR) (BP = CO × SVR). Hypertension is a major contributor to heart failure. Patients with heart failure and low cardiac output tend to maintain BP through peripheral vasoconstriction mediated mainly by endogenous catecholamines and the RAAS. Afterload represents the mural tension on myocardial cells during contraction and is determined by the total peripheral vascular resistance and the cardiac chamber size. Peripheral resistance is affected by the total cross-sectional area of the circulation, blood viscosity, and other factors. The arterioles are the major resistance vessels in the circulation. Flow is directly proportional to the fourth power of the vessel radius (Poiseuille's law). The larger the ventricular cavity, the more mural tension and thus myocardial work is required during contraction (law of Laplace).

Failing ventricles have difficulty overcoming increases in peripheral resistance, instead dilating further, increasing end-diastolic volume to maintain SV, even with decreasing EF (preload

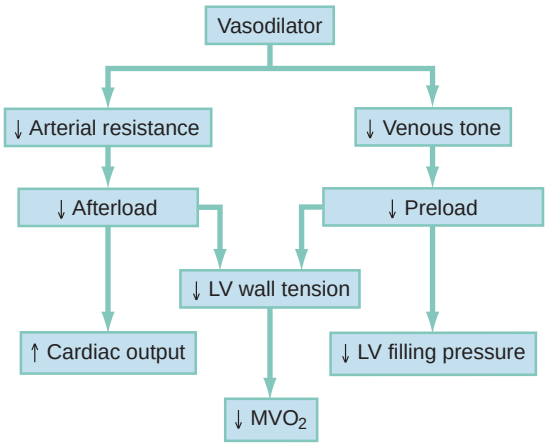

Fig. 71.4. Arterial vasodilators decrease resistance to flow and result in increased cardiac output. Venodilators decrease venous return to the heart and relieve pulmonary congestion. Balanced agents (eg, nitrates) do both. Decreased mural tension reduces myocardial oxygen demand *(MVO_2)* and may relieve ischemia. *LV,* Left ventricular.

reserve). Failing hearts are, therefore, extremely afterload sensitive, and modest vasodilation can dramatically increase cardiac output, particularly in those most compromised (Fig. 71.4). Afterload reduction may be beneficial because it allows conversion of pressure work into flow work. When BP is decreased, cardiac output increases, as long as preload is maintained. Because flow work is proportionally less oxygen demanding, afterload reduction therapy has the additional benefit of decreasing myocardial oxygen demand.

HR and rhythmic contraction are important determinants of optimal cardiac output (CO = HR × SV). As HR increases to the range of 150 to 160 beats/min in the adult, cardiac output increases progressively. Tachycardia much above this rate compromises diastolic filling time and may lead to decreased cardiac output. Coronary perfusion, which occurs only during diastole, also becomes impaired by severe tachycardia. SV is maximized when atrial contraction "primes" the ventricular pumps before they contract. Therefore, any derangement of intracardiac conduction or dysrhythmia can reduce SV. Loss of atrial priming (eg, atrial fibrillation) can lead to marked deterioration in cardiac output, especially in diseased, stiffer hearts that need high filling pressures to optimize preload. Synchronized contraction of myocardial tissue and chambers is now a focus of therapeutic intervention.

Physiologic Mechanisms

Increase in Stroke Volume

Increased SV occurs in response to increase in preload (Frank-Starling mechanism). This compensatory mechanism is prompt and effective in improving cardiac output in response to acute systemic demands. It is a limited response, however, because myofibril stretch to a sarcomere length beyond 2.2 µm does not further increase stroke output and may actually reduce it. Also, this mechanism greatly increases myocardial energy demand, which may lead to dysfunction in the setting of significant coronary artery disease.

Increased Systemic Vascular Resistance

Increased SVR results in redistribution of a subnormal cardiac output away from skin, skeletal muscles, and kidneys to maintain normal blood flow to the brain and heart. This elevated afterload also greatly increases myocardial work.

Development of Cardiac Hypertrophy

LV remodeling describes the changes in ventricular mass, volume, shape, and composition in response to mechanical stress and systemic neurohormonal activation. Development of cardiac hypertrophy is the primary chronic adaptation of the heart to compensate for pump failure. This hypertrophy occurs mainly by increasing the number of myofibrils per cell, because the heart has very limited ability to produce new cells (hyperplasia). New myofibrils arrange in series in response to an increase in chamber volume (leading to dilation over time) and in parallel when responding to higher pressure loads (leading to increased chamber wall thickness). LV hypertrophy leads to a less efficient round LV chamber compared to the normal elliptical shape.[33] In addition to myofibril hypertrophy, mitochondrial mass expands, leading to additional ATP provision for the expanded myofibril mass. However, impaired mitochondrial function is recognized in heart failure, with reduced energy production and higher oxidative stress.[34]

Initially, hypertrophy leads to improved function of each myocardial cell but at a higher energy cost. Hypertrophy is associated with myosin and other sarcomere protein isoform shifts, with related slowing of contraction, prolongation of time to peak tension, and reduced rate of relaxation.[35] With the continued influence of volume overload, myofibril mass expands more than mitochondrial mass. Relative capillary blood flow is also reduced, leading to progressive myocyte death with fibrosis and increased stress on the remaining myocytes. This leads to extracellular matrix expansion, which is one of the negative effects of pathological LV remodeling. Thus the remodeling response, if allowed to continue, eventually becomes maladaptive, accelerating myocyte death, reducing microvascular perfusion, increasing extracellular collagen, and reducing pump function.[36,37] This process gradually occurs as a normal part of aging.[38]

Neurohormonal Modulation

Neurohormonal mechanisms maintain BP, as well as vital organ perfusion, and are activated by LV dysfunction. Regrettably, these neurohormonal mechanisms also increase the hemodynamic burden and oxygen consumption of the failing ventricle and are counterproductive on a chronic basis.

Cardiac Neurohormonal Response

Increases in myocardial wall stretch activate release of cardiac natriuretic peptides, which are structurally related proteins important in volume and sodium homeostasis. They include atrial, C-type, and brain (also known as B-type) natriuretic peptide (BNP). All are elevated in patients with LV dysfunction and heart failure. A variety of natriuretic peptide receptors exist on endothelial cells, vascular smooth muscle cells, renal epithelial cells, and in the myocardium. Natriuretic peptides promote water and sodium excretion, increase peripheral vasodilation, and inhibit the RAAS. In early heart failure, they play a key role in compensation for LV dysfunction. Attenuation of renal response to natriuretic peptides occurs as heart failure progresses.

Central and Autonomic Nervous System Neurohormonal Response

The heart and great vessels contain sensory receptors that detect changes in perfusion. Metabolic receptors in muscles also exert inhibitory and excitatory influences on brainstem vasomotor neurons. Arginine vasopressin (antidiuretic hormone [ADH]) is released from the pituitary gland in response to decreases in perfusion. Elevated vasopressin levels in heart failure increase

intravascular volume and decrease osmolality. This potentiates effects of angiotensin II and norepinephrine.[39]

Heart failure results in a generalized stimulation of sympathetic activity and inhibition of parasympathetic tone. Increased sympathetic outflow results in release of epinephrine and norepinephrine from the adrenal glands, as well as norepinephrine at peripheral sympathetic nerve endings. These elevated catecholamine levels stimulate surface receptors in the heart and blood vessels, increasing cardiac contractility, HR, and vascular tone. The resulting increased vascular tone augments preload through venous contraction, as well as afterload by arterial vasoconstriction. Acutely, arterial BP is improved and cardiac output increased by catecholamines. Chronically, a decrease in the number and affinity of surface catecholamine receptors occurs in myocardial tissue, reducing responsiveness to epinephrine and norepinephrine. Elevated catecholamines adversely affect myocardial perfusion, leading to progressive cardiac cell death and fibrosis.

Renal Neurohormonal Response

Decreased glomerular perfusion results in reduced renal excretion of sodium, causing renal arteriolar and adrenergic receptors to stimulate renin release by the juxtaglomerular apparatus. Renin facilitates the conversion of angiotensinogen to angiotensin I, which is further converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor and an important stimulus for aldosterone release by the adrenal cortex. Aldosterone increases renal sodium retention and potassium excretion. Renal adaptation to hypoperfusion occurs mainly through production of vasodilatory hormones, such as prostacyclin, along with prostaglandin I_2 (PGI_2) and prostaglandin E_2 (PGE_2). Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) interfere with prostaglandin synthesis by inhibiting cyclooxygenase. Therefore, except for the useful antiplatelet effect of aspirin, NSAIDs optimally should be avoided in patients with chronic heart failure, because they may contribute to acute renal insufficiency, with concomitant salt and water retention.

Vascular Endothelial Neurohormonal Response

Endothelial function locally regulates vasomotor tone. A family of endothelins are produced by endothelial and smooth muscle cells, as well as neural, renal, pulmonary, and inflammatory cells. This occurs in response to hemodynamic stress, hypoxia, catecholamines, angiotensin II, and many inflammatory cytokines. ET-1 is the most important ET and the most potent vasoconstrictor known.[40] ET-1 plasma levels are elevated in heart failure, correlate with symptoms as well as hemodynamic stress, and are associated with adverse prognosis.

Nitric oxide (NO) is synthesized from L-arginine and one of three subforms of NO synthase. NO is produced in almost all tissues, and plays a critical role in homeostasis of cardiac function.[41] NO exerts its biologic signaling through production of cyclic guanosine monophosphate (cGMP), which is broken down by cyclic nucleotide phosphodiesterases (PDEs).[42,43] PDE inhibitors like sildenafil (Viagra) reduce NO degradation. Reduced synthesis or increased degradation of NO at the endothelial level is detrimental in heart failure.[44] NO-mediated endothelial dysfunction may represent the earliest stage of target organ damage, which ultimately leads to hypertensive heart disease and heart failure.[45]

Pathophysiology

Maladaptive Changes in Heart Failure

Ventricular remodeling includes cardiac dilation, reactive hypertrophy, progressive fibrosis, and changes in wall conformation, all of which correlates with poor clinical outcomes in heart failure.[46] Serial measurements of various biomarkers may serve as surrogate markers of ventricular remodeling.[47] Reverse remodeling is a concept in which progressive LV dysfunction is not simply arrested but also partially reversed.[48] Various antihypertensive therapies, including beta-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists allow regression of LV hypertrophy and reduce the rate of sudden cardiac death.[49] Targeting the myocardial interstitium, mitochondrial dysfunction, and improving metabolic impairment in heart failure are other areas of intense interest.[50-52]

Primary Disease Processes Resulting in Heart Failure

Heart failure can result from primary diseases of coronary arteries, myocardium, cardiac valves, pericardium, peripheral vessels, or lungs. Heart failure frequently has multifactorial causes. Often, determination of the causes of heart failure is simpler early in its course than during later stages.

Coronary Artery Disease. In developed countries, atherosclerotic coronary artery disease remains the leading cause of heart failure, which is present in almost 70% of patients in multicenter heart failure trials.[53] Acute coronary thrombosis leads to focal myocardial necrosis, with resultant fibrosis and scarring. This process leads to areas of dyskinesis that result in decreased EF. Aneurysmal dilation of infarcted areas with paradoxical wall motion during systole may disproportionately decrease EF. When approximately 40% of the LV muscle mass is acutely infarcted, cardiogenic shock ensues. Transient loss of contractile function may result from episodes of myocardial ischemia that do not cause frank necrosis, or from an ischemic zone surrounding the infarct. This "myocardial stunning" may persist for several days. Owing to improved treatment of acute coronary syndromes, the rates of secondary death and heart failure are decreasing.

Chronic coronary insufficiency leads to a more diffuse myocardial fibrosis termed *ischemic cardiomyopathy.* The role of late coronary revascularization in reducing heart failure–associated morbidity and mortality remains controversial. Diseases affecting the coronary microcirculation, such as vaso-occlusive sickle cell anemia and diabetes mellitus, result in similar pathology.

Cardiomyopathy and Myocarditis. Cardiomyopathies are a group of disease processes that primarily affect myocardium. Myocardial diseases resulting from coronary, valvular, and pericardial pathologies are excluded. Cardiomyopathy is categorized as primary if cause is unknown, or secondary if some etiology is identified. Clinically, patients with cardiomyopathy tend to have three forms—dilated, hypertrophic, or restrictive—each associated with heart failure. Dilated cardiomyopathy is much more common than the other two and is the second most common cause of heart failure. The specific cardiomyopathies and myocarditis, which may cause heart failure, are discussed in Chapter 72.

Valvular Heart Disease. Cardiac valvular disease is the third leading cause of heart failure, after ischemic heart disease and dilated cardiomyopathy. Most acute valvular dysfunction involves either the mitral or aortic valve and usually results in severe regurgitation. Acutely stenotic lesions are predominantly restricted to mechanical catastrophes of prosthetic valves. These patients may be in extremis with fulminant pulmonary edema.

Mitral insufficiency and aortic stenosis are most commonly associated with chronic heart failure. Knowledge of the precise valvular pathology may have important implications for emergent heart failure therapy. For example, patients with decompensated aortic stenosis should generally not receive vasodilator agents, because flow cannot increase across a fixed obstruction. These

patients may become hypotensive owing to reduced preload, with resultant decreased systemic and coronary perfusion. On the other hand, patients with mitral regurgitation benefit greatly from vasodilators, which improve antegrade flow by reducing afterload. Valvular disease is discussed in Chapter 73.

Pericardial Diseases. Pericardial diseases may significantly affect ventricular function by decreasing cardiac output and increasing intracardiac pressures. In particular, cardiac tamponade may cause dyspnea and hypoperfusion not easily distinguished clinically from heart failure. ED use of bedside ultrasound has great usefulness in quickly identifying this problem. Pericardial diseases are fully discussed in Chapter 72.

Pulmonary Disease. Chronic obstructive pulmonary disease (COPD) has a prevalence of 20% to 30% in heart failure and may obscure recognition.[54] Pulmonary dysfunction reduces myocardial oxygen supply, while cardiac output increases because tissue is being perfused with suboptimally oxygenated blood. Hypoxia leads to pulmonary arteriolar vasoconstriction, reducing lung vascular bed area and elevating pulmonary artery pressures. Chronic increases in pulmonary arterial pressure lead to right ventricular (RV) hypertrophy and dilation. When compensatory mechanisms fail, the patient develops right-sided heart failure (cor pulmonale), usually with LV output preserved, at least at rest. Causes of acute pulmonary hypertension, such as a large pulmonary embolus, may precipitate sudden systemic hypotension and death, in part due to decreased LV priming.

Distinguishing primary pulmonary disease causing predominantly right-sided heart failure from LV failure with secondary right-sided dysfunction is clinically challenging. Wheezing or rhonchi may be present in both entities. The chest radiograph may be difficult to interpret because both presentations cause interstitial changes. Hyperinflation depresses the diaphragm, which elongates the cardiac silhouette and may mask cardiomegaly. Competition for intrathoracic space reduces lung capacity in patients with chronic heart failure.[55] Natriuretic peptide levels are only slightly elevated in primary pulmonary disease compared with much higher levels in LV failure.[56,57]

Classification of Heart Failure

Many different methods of classifying heart failure exist, including acute versus chronic, systolic versus diastolic, right versus left sided, and high versus low output. Early in heart failure, these may be useful clinical descriptors suggesting particular causes and treatment strategies.

Acute Versus Chronic Heart Failure. The prototypical case of acute heart failure involves a healthy person who develops a large myocardial infarction (MI) or acute valvular dysfunction. Chronic heart failure is best characterized by a disease state, such as dilated cardiomyopathy, with gradual deterioration of cardiac function. In acute heart failure, early presentation may be a result of systolic dysfunction and hypoperfusion, often with acute cardiogenic pulmonary edema (ACPE) resulting from sudden reduction in chamber compliance. Chronic heart failure usually arises with symptoms related to gradual fluid retention, with compensatory mechanisms adjusted so that normal perfusion exists, at least in the resting state. In clinical practice, approximately 80% of heart failure cases seen the ED involve acute decompensation of chronic heart disease.[58,59]

Systolic Versus Diastolic Dysfunction. *Systolic heart failure,* or *HFrEF,* refers to contractility impairment, with stroke output reduced and forward flow compromised. Systolic dysfunction is typically caused by myocyte damage from etiologies, such as MI or myocarditis. Asymptomatic LV systolic dysfunction is much more common than symptomatic systolic heart failure. Almost all cases of systolic dysfunction also involve some degree of diastolic dysfunction.

Diastolic heart failure, or HFpEF, indicates a primary problem with ability of the ventricles to relax and fill normally.[60] In some cases, normal or even supernormal systolic function is preserved. Echocardiographic and nuclear imaging techniques demonstrate that up to half of patients with congestive heart failure have EFs more than 50% and experience primarily diastolic dysfunction, and this proportion increases with age.[61,62] Asymptomatic diastolic dysfunction is much more common than asymptomatic systolic dysfunction. Diastolic dysfunction is the predominant pathophysiology in hypertrophic and restrictive cardiomyopathies, valvular aortic stenosis, and, most important, hypertension.

Diastolic dysfunction occurs predominantly as a result of one of three mechanisms: (1) impaired ventricular relaxation, (2) increased ventricular wall thickness, or (3) accumulation of myocardial interstitial collagen. Impaired lusitropic (relaxation) capacity of the myocardium leads to higher ventricular filling pressure, resulting in congestive symptoms. Myocardial relaxation is an active, energy-requiring process. Failure of myocytes to relax may be secondary to low intracellular energy stores. Physiologic stresses causing increased cardiac demands can precipitate lusitropic abnormalities. In chronic renal disease, mortality is higher in diastolic than systolic heart failure.[63] In addition, systolic contractile dyssynchrony occurs in one-third of diastolic heart failure patients, whereas diastolic dyssynchrony is present in more than half, with therapeutic implications.[64]

As with the other classification schemes, most patients with heart failure have components of both systolic and diastolic dysfunction, with the predominant type allowing specific treatment strategies. For example, patients with predominantly diastolic dysfunction have the advantage of intact myocardial contractile function. Stiffer hearts, however, have steep pressure-volume curves. Therefore, small reductions in diastolic filling volume, as may occur with vasodilator or diuretic therapy, may markedly decrease ventricular filling and compromise stroke output (see Fig. 71.3).

Right-Sided Versus Left-Sided Heart Failure. The notion that one cardiac chamber can fail independently of the others is somewhat artificial. The right and left circulations are connected and output from the two sides must be equal. Furthermore, the right and left ventricles share an interventricular septum, and dysfunction in one chamber may have an impact on the other. For example, acute right-sided heart failure from pulmonary hypertension secondary to acute respiratory failure causes bulging of the interventricular septum into the LV chamber. This so-called "septal shift" results in decreased LV preload and low cardiac output that is volume responsive. Chronic left-sided heart failure leads to pulmonary hypertension with resultant right-sided heart failure.[65,66] In addition, cardiac biochemical changes, including abnormal catecholamine response, affect all chambers.

The terms have usefulness in identifying the predominant clinical presentation. Fluid accumulation "behind" the involved ventricle is responsible for many of the clinical manifestations of heart failure. For example, LV failure leads primarily to pulmonary congestion with symptoms mostly of dyspnea and orthopnea. Patients with right-sided heart failure have symptoms of systemic venous congestion, such as pedal edema and hepatomegaly.

When previously healthy patients have acute pathology, the concept of left- versus right-sided heart failure may be clinically useful. Patients with acute MI may have ACPE; yet unlike patients with chronic heart failure, they may not have jugular venous distention or pedal edema because central venous pressure may remain within normal limits. A chest radiograph reveals evidence

of pulmonary venous congestion, interstitial edema, and, in fulminant cases, alveolar edema. The cardiac shadow is often of normal size, because there has not yet been time for cardiac dilation.

Acute RV infarction may manifest as hypoperfusion with jugular venous distention and absent pulmonary congestion. There is often evidence of ST segment elevation or depression in the V_1 lead, and right-sided leads may provide further evidence of RV infarction. Approximately one-third of patients with acute inferior infarction have significant RV involvement, leading to inadequate pulmonary perfusion and low LV priming (decreased preload). These patients have right-sided heart failure with hypotension that is often symptomatic. High volume, rapid crystalloid resuscitation, followed by inotropic support with norepinephrine, may be necessary for adequate LV preload and restoration of BP.

High-Output Versus Low-Output Failure. *High-output failure* refers to a hyperdynamic state with supranormal cardiac output and low arteriovenous oxygen difference (decreased oxygen extraction ratio). The hyperdynamic state may result from increased preload (eg, renal retention of salt and water, or excess mineralocorticoids), decreased SVR (eg, arteriovenous fistulas, pregnancy, cirrhosis, severe anemia, beriberi, thyrotoxicosis, Paget's disease, or vasodilator medications), increased beta-sympathetic activity, or persistent tachycardia. A persistent hyperdynamic state results in myocardial damage over time. Early recognition of the hyperdynamic state may allow effective therapy of the underlying condition, thus avoiding development of heart failure. As the condition progresses, myocardial dysfunction with circulatory overload is superimposed, resulting in symptom progression. At some point, cardiac output becomes normal or even low, and is indistinguishable from classic heart failure.

Low-output failure is the more typical variety of heart failure and occurs as a result of entities such as ischemic heart disease, dilated cardiomyopathy, valvular disease, and chronic hypertension. Low cardiac output (systolic dysfunction), high filling pressures (diastolic dysfunction), and an increased systemic oxygen extraction ratio (widened arteriovenous oxygen difference) characterize this more commonly encountered form of heart failure.

Precipitating Causes of Heart Failure and Exacerbating Factors

When cardiac decompensation occurs due to an acute precipitating cause, intervention can be directed at the specific precipitating factor(s). Prognosis for patients who present due to a specific cause is much better when compared to intrinsic progression of cardiac failure. Causes of acute cardiac decompensation are in Box 71.1. In chronic heart failure, the most common cause of decompensation is iatrogenic or relative decrease in intensity of treatment, including drug therapy, dietary sodium increase, limited physical activity, or a combination of these factors.

Sodium and Volume Excesses

Decompensation may be precipitated by plasma volume expansion due to increased sodium ingestion, most often a result of dietary noncompliance, as well as by excessive crystalloid infusion or transfusion. Noncompliance with renal dialysis, in particular, is a very common cause of heart failure in ED patients.

Systemic Hypertension

Sudden elevation of arterial pressure acutely increases afterload, which may precipitate abrupt onset of heart failure. This is particularly common when antihypertensive therapy is discontinued. Emotional upset can dramatically increase afterload as well as precipitate coronary vasospasm, with the extreme example being acute stress cardiomyopathy (Takotsubo syndrome; see Chapter 68).

BOX 71.1

Common Precipitating Causes of Acute Heart Failure

Sodium and volume excess
Systemic hypertension
Myocardial infarction (MI) or ischemia
Systemic infection
Dysrhythmias
Acute hypoxia or respiratory problems
Anemia
Pregnancy
Thyroid disorders
Acute myocarditis
Acute valvular dysfunction
Pulmonary embolus
Sympathomimetic or alcohol excess
Excessive exertion or trauma
Pharmacologic complications

Myocardial Infarction and Ischemia

A new ischemic event may precipitate heart failure by impairing contractility and decreasing LV compliance. Pulmonary edema may occur quickly in this setting, especially when large areas of myocardium are involved. In the compromised heart, even local ischemia may precipitate heart failure. Occult acute coronary syndrome is common, particularly in the elderly, and should be considered in any heart failure exacerbation. The presence of heart failure on admission in patients with acute coronary syndromes is associated with increased short- and long-term rates of death and MI.

Systemic Infection

Infection results in increased systemic metabolic demands. The sepsis syndrome is associated with a reversible form of myocardial depression, mediated by various cytokines, including interleukin (IL)-1, and IL-6, as well as tumor necrosis factor.[67] Proinflammatory cytokines, such as tumor necrosis factor alpha and IL-6, also play an important pathogenic role in chronic heart failure.[68]

Dysrhythmias

Both tachydysrhythmias and bradydysrhythmias can severely affect cardiac output, especially when acute. Tachydysrhythmias compromise diastolic filling time, reduce cardiac output, and impair coronary perfusion. The tachycardia also results in increased myocardial oxygen demand. These factors may precipitate ischemia, which may further impair contractility and exacerbate heart failure.

The prevalence of atrial fibrillation in patients with heart failure increases from less than 10% in New York Heart Association (NYHA) functional class I to approximately 50% in NYHA functional class IV.[69] Neurohormonal alterations, electrophysiologic changes, and mechanical factors create an environment in which heart failure predisposes to atrial fibrillation and atrial fibrillation exacerbates heart failure. New-onset atrial fibrillation or other dysrhythmias may affect coordinated atrial priming of the ventricular pump and reduce preload, especially in disease states with reduced ventricular compliance. Significant bradydysrhythmias

may also reduce cardiac output simply by reducing the number of systolic ejections per minute (CO = SV × HR).

Acute Hypoxia and Respiratory Problems

COPD exacerbations, increased air pollution, and respiratory tract infections are very important precipitating factors for heart failure exacerbation.[70,71] Pulmonary infection, which is more common in patients with pulmonary vascular congestion, may add hypoxia to the metabolic stressors of fever, tachycardia, and increased tissue perfusion requirements.

Anemia

With chronic anemia, increased cardiac output maintains tissue oxygen delivery. Anemia increases in prevalence with increasing severity of heart failure, especially with declining renal function and increasing age. Anemia is associated with poorer survival in heart failure, with greater disease severity, greater LV mass index, and higher hospitalization rates.[72] Abrupt exacerbations of anemia increase systemic perfusion demands and, especially if coupled with reduced coronary oxygen delivery, may prompt onset or exacerbation of heart failure.

Pregnancy

Cardiac output is normally increased significantly during pregnancy, which may lead to decompensation with underlying valvular disease or other cardiac pathology. Peripartum cardiomyopathy is a type of dilated cardiomyopathy that may occur late in pregnancy or more commonly in the early postpartum period.

Thyroid Disorders

Heart failure may be a clinical manifestation in patients with previously compensated cardiac disease who develop hyperthyroidism. Hypothyroidism also adversely affects myocardial pump function. Restoration of normal thyroid function may reverse abnormal cardiovascular hemodynamics.[73,74]

Acute Myocarditis

A variety of infectious and inflammatory myocardial diseases, including viral agents and acute rheumatic fever, may precipitously impair cardiac contractility.

Acute Valvular Dysfunction

Almost all causes of acute heart failure resulting from cardiac valve dysfunction are secondary to aortic or mitral insufficiency. Mitral valve papillary muscle dysfunction or rupture may result from acute MI, whereas acute aortic insufficiency, although uncommon, can be precipitated by acute bacterial endocarditis or aortic dissection. Rarely, acute valvular stenosis may occur, usually as a consequence of acute dysfunction of a prosthetic valve.

Pulmonary Embolus

The pulmonary hypertension and hypoxia that accompany pulmonary embolus may cause acute heart failure. This diagnosis should be entertained in patients who have unexplained heart failure and risk factors for pulmonary embolism.

Sympathomimetic or Alcohol Excess

Pheochromocytoma and other states associated with high sympathetic outflow may precipitate heart failure, as may cocaine and other sympathomimetic drugs of abuse, by a similar mechanism. Although 1 to 2 ounces of alcohol a day reduces risk of heart failure and other cardiovascular mortality, heavy consumption greatly increases risk of cardiac arrhythmias, dilated cardiomyopathy, heart failure, stroke, and overall mortality.[75] Binge alcohol use can cause sudden decompensation. Modest coffee consumption conversely, may actually reduce risk of heart failure.[76]

Excessive Exertion or Trauma

Increased physical activity may lead to cardiac decompensation, particularly in patients with significant heart failure. Trauma as well as critical illness and injury in general also increase demand on the heart, precipitating acute heart failure, although the mechanisms are multifactorial.

Pharmacologic Complications

Beta-blockers and calcium channel blockers have negative inotropic effects that may precipitate overt heart failure with excessive administration. Many antidysrhythmic agents have similar effects. Glucocorticoids, NSAIDs, vasodilator medications, and others may result in sodium retention with substantial increases in plasma volume that may precipitate heart failure.[77] NSAIDs in particular interfere with prostaglandin synthesis through cyclooxygenase inhibition, thereby impairing renal homeostasis in patients with heart failure. They also interfere with the effects of diuretics and ACE inhibitors. Nonadherence to medication regimens for hypertension, heart failure, or ischemia is the most common pharmacologic cause of cardiac decompensation.

CLINICAL FEATURES

History

The presence and character of dyspnea, chest pain, previous heart disease, cardiac catheterization, surgery, current medications (plus adherence), and possible intercurrent illness should be explored. Paroxysmal nocturnal dyspnea results from pulmonary congestion precipitated by plasma volume expansion that occurs during recumbency, because interstitial edema is reabsorbed into the circulation. Orthopnea occurs through the same mechanism, with the supine position causing significant increases in diastolic filling pressure. Symptoms abate after the patient stands or props up the trunk and venous return decreases. Nocturia results from the same pathophysiologic process. Many historical features increase the likelihood of heart failure. Most predictive is a past history of heart failure or paroxysmal nocturnal dyspnea, and absence of dyspnea on exertion reduces the likelihood of chronic heart failure.[78]

Physical Examination

Most heart failure patients are hypertensive, which is prognostically preferable to normal or low BP. Clammy, vasoconstricted patients with a thready pulse and delayed capillary refill may have systemic hypoperfusion despite adequate BP, which is maintained by intense vasoconstriction. Noninvasive assessment of BP in the vasoconstricted patient with low cardiac output can be inaccurate.[79] If available, intra-arterial pressure monitoring may more accurately reflect the systemic hemodynamic state and guide the choice of therapy in hypotensive heart failure patients.

Most patients with ACPE are diaphoretic because of intense sympathetic activation. Patients with pulmonary congestion secondary to heart failure develop interstitial and alveolar pulmonary edema, causing reduced pulmonary compliance and decreased functional residual capacity. Clinical findings include diffuse rales,

which may be absent with decreased ventilation in more agonal patients. Peribronchial edema may cause wheezing or rhonchi, which can mimic bronchospastic disease ("cardiac asthma"). A positive response to bronchodilator therapy does not exclude heart failure. Jugular venous distention is present in approximately 50% of cases of heart failure, and one-third of patients have peripheral edema. An S_3 gallop may be present in up to 25% but is often difficult to hear. Physical examination of patients with ACPE resulting from acute MI may identify surgically correctable lesions, such as acute mitral regurgitation or ventricular septal defect.

These common clinical findings of chronic heart failure are prevalent among patients with ACPE, because most patients have acute exacerbations superimposed on chronic underlying disease. Jugular venous distention, pedal edema, and cardiomegaly may be absent in previously healthy individuals with pulmonary edema resulting from an initial episode of acute heart failure. The presence of a third heart sound significantly increases the likelihood of heart failure, whereas absence of rales decreases the likelihood.[78]

DIFFERENTIAL DIAGNOSES

Careful consideration of the differential diagnosis of heart failure is symptom based. The most common manifestation of acute heart failure is respiratory distress caused by pulmonary edema. The differential diagnosis, therefore, includes non-cardiogenic pulmonary edema, exacerbation of COPD or asthma, pulmonary embolus, pneumonia, tension pneumothorax, cardiac tamponade, anaphylaxis, and other causes of acute respiratory distress. These etiologies may cause hypoperfusion, as can sepsis syndrome, hypovolemia, and hemorrhage. The NYHA classification system is a time-honored categorization for patients with chronic heart failure based on degree of activity causing symptoms (Box 71.2).

DIAGNOSTIC TESTING

An upright chest radiograph helps distinguish cardiogenic pulmonary edema from other causes of dyspnea. An enlarged cardiac silhouette is seen in 70% of cases. A normal heart size suggests ACPE in a patient without prior heart failure, diastolic dysfunction, COPD, or noncardiogenic pulmonary edema. An early ECG for arrhythmia recognition and management is important, as well as for identification of acute coronary syndrome. Absence of cardiomegaly on chest radiography and a normal ECG greatly decrease the likelihood that heart failure is causing the presentation.[78] Obtaining a complete blood count (CBC) to evaluate for anemia and a basic metabolic panel to determine electrolyte status as well as renal function is generally useful. Cardiac troponins help evaluate for ongoing myocyte injury, which may be clinically silent.

In most cases, and particularly when the diagnosis of heart failure is unclear, natriuretic peptide levels are helpful. Pre-proBNP is synthesized in the ventricles in response to myocyte stretch, with release and enzymatic cleavage to NH_2-terminal–proBNP (NT-proBNP) and BNP. NT-proBNP and BNP levels help identify patients with heart failure and may improve evaluation of patients in the ED with undifferentiated dyspnea.[80] The "breathing not properly" BNP Multinational Study was a prospective evaluation of patients who came to the ED with acute dyspnea. BNP levels above 500 pg/mL were highly associated with heart failure (likelihood ratio [LR] = 8.1), but levels of 100 to 500 pg/mL were generally indeterminate (LR = 1.8). A low BNP level (<100 pg/mL) indicated that heart failure was highly unlikely (LR = 0.13).[81] ED use of BNP or NT-proBNP assays aids diagnosis of heart failure and can reduce admission rates, as well as length of hospitalization in acute dyspnea.[82,83]

Natriuretic peptide levels correlate with ventricular function, NYHA classification, and prognosis, with BNP probably the most useful.[84] There is often a disconnect between the perceived severity of heart failure by clinicians and the degree of BNP elevation, yet BNP levels are better predictors of 90-day outcome than physician judgment.[85] Natriuretic peptide level guided therapy reduces all-cause mortality, as well as heart failure rehospitalization, and provides a strong measure of therapeutic response in chronic heart failure compared with usual care.[86] Mildly elevated BNP levels may also be seen in right-sided heart failure related to cor pulmonale or pulmonary embolism. BNP and troponin levels are only slightly elevated in patients with end-stage renal disease, and in this setting marked elevation reflects ventricular dysfunction.[87] Admission BNP and troponin levels are independent predictors of in-hospital mortality and other adverse outcomes in acute decompensated heart failure.[88,89]

Pulmonary artery catheterization in severe symptomatic heart failure increases anticipated adverse effects but does not affect overall mortality or duration of hospitalization.[90] Noninvasive impedance cardiography appears to be an effective and developing technology to measure cardiac output and other hemodynamic variables in heart failure, although it cannot reliably measure LV filling pressures.[91-92] Bedside ultrasound can be an important ED screening tool in heart failure, with attention to wall motion abnormalities, EF, and valvular function, as well as exclusion of cardiac tamponade.[93-94] Echocardiography is similarly useful and can provide detailed measures of LV function and determine structural heart disease.[95] Point-of-care ultrasound is also superb in recognizing pulmonary edema on lung examination, with very high sensitivity and specificity to diagnose ACPE. Lung ultrasonography has higher accuracy for diagnosis of acute decompensated heart failure in undifferentiated dyspneic patients than clinical evaluation, chest x-ray, or natriuretic peptides.[96] It can also recognize pneumonia, pleural effusion, and decompensated COPD or asthma.[97] Multidetector computed tomography coronary angiography can distinguish ischemic from other forms of cardiomyopathy but is rarely useful in acute heart failure. Cardiac magnetic resonance and radionuclide imaging have an expanding role in evaluating chronic heart failure but no utility in the acute setting.

MANAGEMENT

Of patients with heart failure in the ED, about 20% are experiencing their first episode of heart failure, and 80% have had prior hospital visits for the same condition. The approach to acute heart failure focuses on (1) determining the underlying cardiac pathology, (2) identifying the precipitant(s), and (3) mitigating the decompensation. The primary therapeutic goals are to improve respiratory gas exchange, maintain adequate arterial saturation, and decrease LV diastolic pressure while maintaining adequate cardiac and systemic perfusion.

The acute congestive state can be controlled by (1) reducing cardiac workload through decreased preload and afterload, (2)

BOX 71.2

Classification System for Chronic Heart Failure

NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSES

I. Asymptomatic on ordinary physical activity
II. Symptomatic on ordinary physical activity
III. Symptomatic on less than ordinary physical activity
IV. Symptomatic at rest

reducing excessive retention of salt and water, and (3) improving cardiac contractility. Patients with acute heart failure may have a wide spectrum of symptoms and signs ranging from mild dyspnea on exertion to full-blown cardiogenic shock with hypotension and concomitant respiratory failure.

Acute Heart Failure

Pulmonary edema is classified clinically into cardiogenic and noncardiogenic forms. Most patients in the emergency setting with pulmonary edema have the acute cardiogenic variety, resulting mainly from elevated LV end-diastolic pressure, forcing a protein-sparse plasma ultrafiltrate across the pulmonary capillary membrane into the pulmonary interstitium. Large amounts of edema accumulate, leading to alveolar flooding. Up to 1 to 2 L may leave the plasma over a short time and create respiratory compromise. Most commonly, ACPE occurs with acute myocardial ischemia or infarction, cardiomyopathy, valvular heart disease, or hypertensive emergencies.

Patients with ACPE have substantially lower plasma volumes than control patients. These changes are reflected by initial hemoconcentration as evidenced by higher hematocrits and colloid osmotic pressures. Despite the presence of pulmonary congestion, concomitant hypotension might need a fluid challenge to restore preload, cardiac output, systemic perfusion, and BP. Thus careful volume infusion with aliquots of normal saline is appropriate initial resuscitation for the hypoperfusing patient with ACPE.

In contrast, noncardiogenic pulmonary edema generally results from an alteration in the permeability characteristics of the pulmonary capillary membrane. The alteration may have such diverse causes as septic shock, inhalation injuries, drugs or toxins, aspiration syndromes, fat emboli syndrome, neurogenic causes, and high altitude.

Acute Heart Failure With Adequate Perfusion

Many patients with acute heart failure demonstrate adequate systemic perfusion with elevated BP because of activation of various compensatory mechanisms. The ability of the left ventricle to generate normal or elevated systolic pressures indicates the presence of considerable myocardial reserve and is associated with lower mortality in both acute and chronic heart failure.[98] These patients should be quickly distinguished from those with pulmonary edema and evidence of hypoperfusion. Hypertensive pulmonary edema is easier to manage because afterload reduction with vasodilators is extremely effective.

Therapeutic interventions should decrease both preload and afterload. Excessive preload reduction may result in an abrupt decrease in cardiac output, however, which could cause hypotension. This occurs more readily in patients with less compliant hearts. Fluid challenge generally restores BP. Therapy for ACPE with adequate perfusion should begin with upright positioning, supplemental oxygen, nitrates, morphine sulfate, and loop diuretics (Fig. 71.5). This allows prompt improvement in most of these patients.

Oxygen and Ventilation

Most patients with significant pulmonary edema have hypoxemia and need high-flow oxygen by face mask if they are spontaneously

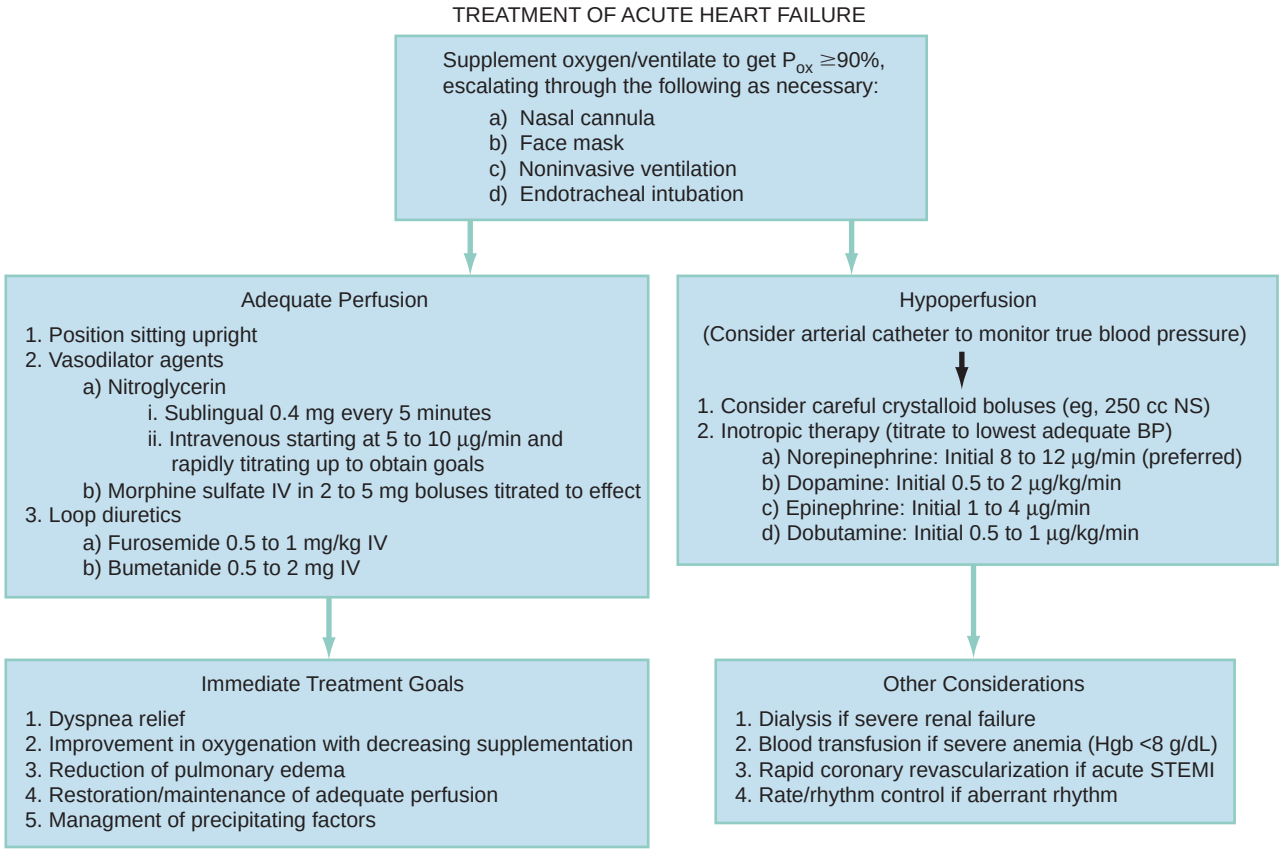

Fig. 71.5. A general therapeutic strategy for acute heart failure involves thoughtful application of interventions to achieve a reasonable improvement in early clinical treatment goals. Appropriate interpretation of the perfusion state with use of clinical criteria and occasionally arterial pressure monitoring is central to the strategy. *BP,* Blood pressure; *Hgb,* hemoglobin; *IV,* intravenous; *NS,* normal saline; P_{ox}, pulse oximetry; *STEMI,* ST segment elevation myocardial infarction.

breathing and if oxygen saturation as measured by pulse oximetry (Spo_2) is below 90%. Excessive oxygen therapy, however, may significantly increase afterload and worsen cardiac function in decompensated heart failure.[99] The typical acid-base disturbance of acute heart failure is mixed. Patients with fulminant ACPE may have lactic acidosis, and many also have concomitant respiratory alkalosis resulting from the tachypnea stimulated by metabolic acidosis, hypoxemia, and decreased pulmonary compliance. In more severe cases, respiratory acidosis ensues as the patient fatigues and respirations fail. The ratio of dead space to total ventilation (V_D/V_T) may be significantly increased owing to alveolar flooding. Patients with inadequate ventilation or with severe hypoxia that does not respond to supplemental oxygen will need ventilatory support. Noninvasive ventilation (NIV) techniques are effective in treating severely compromised, but not agonal, ACPE patients (see Chapter 2). Continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BiPAP) applied by an adjustable, snugly fitting face mask increases functional residual capacity, improves oxygenation, reduces work of breathing, and results in decreased LV preload and afterload by raising intrathoracic pressure (Fig. 71.6). NIV provides earlier improvement in respiratory disease and related metabolic abnormalities than supplemental oxygen alone in ACPE and improves short-term mortality.[100] Prehospital studies using CPAP in ACPE also demonstrate reduced intubation rates and mortality, reinforcing greater use in this arena.[101,102] The addition of inspiratory pressure support (BiPAP) further reduces the work of breathing and more rapidly improves hypercarbia than CPAP alone.[103] Most spontaneously breathing patients benefit greatly from these techniques when appropriately applied in conjunction with pharmacotherapy, and the majority of alert hypercarbic patients can be managed without mechanical ventilation.

Patients too ill for NIV are supported with bag-valve-mask assisted oxygenation in preparation for endotracheal intubation. Intubation is indicated for apneic patients and those with respiratory distress, agitation, or hypoxemia not responsive to high-flow oxygen or NIV. Mechanical ventilation with moderate levels of positive-end-expiratory pressure is safe in acute heart failure and may provide hemodynamic benefit through afterload reduction.[104] Extracorporeal membrane oxygenation may have a rescue role in severe heart failure unresponsive to other therapies.[105,106]

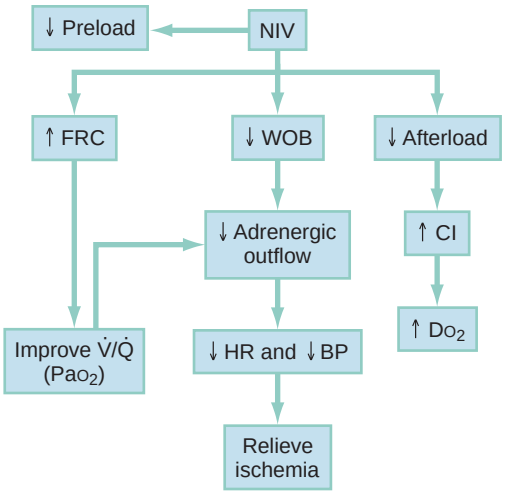

Fig. 71.6. Noninvasive ventilation *(NIV)* techniques recruit collapsed alveoli and increase functional residual capacity *(FRC),* which improves oxygenation and reduces work of breathing *(WOB).* These factors tend to reduce sympathetic tone, heart rate *(HR),* and blood pressure *(BP),* relieving myocardial ischemia. NIV also acts as an afterload-reducing agent, which tends to directly improve cardiac index *(CI),* systemic oxygen delivery *(Do_2),* partial pressure of oxygen in arterial blood *(Pao_2),* and ventilation-perfusion ratio *($\dot{V}/\dot{Q}$).* Preload is also reduced by NIV.

Vasodilator Agents

Nitrates

Organic nitrates activate the enzyme guanylate cyclase, leading to accumulation of cGMP, which relaxes vascular smooth muscle by sequestering calcium in the sarcoplasmic reticulum. At lower doses, nitrates are primarily venodilators. They effectively decrease preload and are therefore very effective in the initial therapy of ACPE. At higher doses, intravenous nitroglycerin also causes arteriolar dilation that decreases BP and afterload. Thus pump function is improved while myocardial oxygen demand is decreased. Nitroglycerin may further reduce myocardial ischemia by its direct coronary vasodilator effect and is particularly effective when myocardial ischemia is contributing to acute decompensation. Prolonged nitrate therapy over hours to days leads to tachyphylaxis secondary to depletion of intracellular sulfhydryl groups.

Nitroglycerin may be initiated by the sublingual route, followed by titrated intravenous administration. Intravenous nitroglycerin has rapid onset and offset of action. Hypotension from excessive preload reduction or vagally mediated idiosyncratic reactions may occur. Nitroglycerin should be avoided in patients who have taken medications for erectile dysfunction (PDE type 5 inhibitors) within the previous 24 hours (up to 48 hours for tadalafil [Cialis]), because the combination may precipitate refractory hypotension. Transcutaneous absorption may be erratic because of diaphoresis and poor skin perfusion, so ointment should not be used as a delivery mechanism until the patient's condition has stabilized. Sodium nitroprusside works similarly to nitroglycerin, acting as a balanced vasodilator to reduce both preload and afterload. However, patients with renal failure may experience thiocyanate toxicity from high-dose nitroprusside infusions. Cyanide toxicity, recognized clinically by the presence of agitation and lactic acidosis, may occur in individuals with a genetic predisposition. Nitroglycerin also has less hypoperfusion and coronary steal than nitroprusside, and it is the preferred vasodilator in heart failure. Nesiritide, a recombinant human BNP, is not more effective than intravenous nitroglycerin in heart failure. Meta-analyses of studies using nesiritide in acute heart failure suggest no special benefit and the possibility of increased drug-related mortality.[107,108] It is not indicated in ED treatment of acute heart failure.

Morphine Sulfate

Morphine sulfate, an opioid analgesic, reduces pulmonary congestion through a central sympatholytic effect and release of vasoactive histamine, causing peripheral vasodilation and reduced preload. In addition, through reduced systemic catecholamines, morphine decreases HR, BP, cardiac contractility, and myocardial oxygen consumption. In addition, patients with ACPE tend to be agitated as a result of air hunger, and the calming effect of morphine is advantageous in this setting. Morphine is administered in repetitive 2- to 5-mg intravenous doses carefully titrated to effect. If oversedation results in hypoventilation, gentle stimulation usually restores ventilatory effort. In ACPE, mild carbon dioxide (CO_2) retention does not contraindicate morphine use, because it results from acute alveolar flooding that is improved by the mechanisms just delineated. Airway support should be considered, however, before morphine use in obtunded heart failure patients.

Loop Diuretics

Loop diuretics inhibit sodium resorption from renal filtrate, resulting in significant increases in salt and water excretion. In

patients with volume overload, this diuretic action lowers plasma volume, decreasing preload and pulmonary congestion. Although the renal effects of intravenously administered loop diuretics begin within 10 minutes, symptom relief in patients with ACPE often occurs much faster, as a result of diuretic-induced neurohumoral changes; acting both as a vasodilator, promoting renal PGE_2 and natriuretic peptide secretion, and as a vasoconstrictor, stimulating renin release. Loop diuretics (furosemide or bumetanide) should be administered to patients with hypertensive ACPE. The half-life of furosemide in patients with ACPE is prolonged when compared to healthy volunteers. Continuous infusion of furosemide is not superior to bolus therapy.[109]

Patients with abrupt onset of ACPE who do not have underlying chronic heart failure may have low plasma volumes at presentation, and diuresis in this group of patients may be unnecessary. Patients who fail to respond to loop diuretic administration may have compromised renal function.[110-112] In this situation, invasive hemodynamic monitoring may be beneficial. Diuretic therapy causes depletion of the important cations K^+ and Mg^{2+}, which may be significant in patients already on chronic diuretics or other agents. High-dose diuretic therapy in ACPE is associated with deterioration in renal function and increased mortality.[113]

Other Therapies

Most patients with ACPE and adequate systemic perfusion respond promptly to oxygen with ventilatory support, nitrates, morphine, and diuretics. Hemodialysis may be required in patients with renal insufficiency. Blood transfusion candidates in acute heart failure have worse clinical features but derive some benefit from red blood cell (RBC) repletion for hemoglobin levels below 8 g/dL.[114,115] The last decade of acute heart failure research for therapies (such as, ET receptor antagonists, vasopressin receptor antagonists, adenosine receptor antagonists, renal natriuretic peptides, calcium-sensitizing drugs, tumor necrosis factor antagonists, and renin inhibitors) has been disappointing.[116-123] Early trials of serelaxin, a vasodilating hormone, actually show promise in effectively improving heart failure symptoms, length of hospital stay, and mortality in acute heart failure.[124] Historical therapies (eg, rotating tourniquets, phlebotomy, and theophylline) have no demonstrated efficacy in ACPE. Endotracheal intubation should be reconsidered if the patient develops severe respiratory deterioration unresponsive to NIV, significant cardiac dysrhythmias, low cardiac output, or has ongoing chest pain.

Treatment of Acute Heart Failure in Hypotensive Patients

Patients with ACPE and apparent systemic hypotension present a therapeutic dilemma. Coronary perfusion in patients depends on the pressure gradient between the aorta and LV chamber in diastole. The combination of hypotension and elevated left-sided filling pressure dramatically decreases coronary perfusion, particularly with coronary artery disease, leading to further impairment of contractility from increased ischemia. Vasopressor administration to maintain coronary perfusion pressure may be necessary if this set of conditions truly exists. Vasopressors, however, can increase afterload, decrease cardiac output, increase myocardial oxygen demand, exacerbate ischemia, and precipitate dysrhythmias. As previously discussed, an intra-arterial catheter provides more accurate and sustained BP monitoring and is helpful in guiding therapy in these patients.

Of patients admitted with heart failure, 15% to 25% have low systolic BP with or without signs or symptoms of hypoperfusion.[125] If the patient truly has evidence of hypoperfusion, initial measures should be directed at restoring adequate perfusion pressure. In this setting, the patient is either in true cardiogenic shock (pulmonary edema, hypotension, and decreased peripheral perfusion) or is volume depleted. Patients in true cardiogenic shock have lost as much as 40% of their ventricular muscle function. Nearly 25% of patients with acute MI and clinical evidence of systemic hypoperfusion, however, have low preload, indicating the presence of hypovolemia. Fluid challenge alone in these patients restores hemodynamic stability in half. ACPE patients with hypoperfusion might benefit from a judicious fluid challenge, such as a 250-mL crystalloid bolus over 5 to 10 minutes. If respiratory status is not deteriorating, repeated aliquots may be administered. If hypovolemia is contributing to hypotension, this intervention could restore BP and systemic perfusion without need for vasopressors. If the patient has true cardiogenic shock, more intensive interventions, including vasopressor therapy, intra-aortic balloon pump, and endotracheal intubation with mechanical ventilation, may be needed.[126] ACPE with systemic hypoperfusion in the setting of acute coronary syndrome represents ischemic cardiogenic shock. Emergency coronary revascularization is the treatment of choice.[127]

Inotropic or Vasopressor Therapy

Inotropic agent use in heart failure increases myocardial oxygen demand, cardiac arrhythmias, and mortality.[128] Intravenous inotropic agents with vasoactive properties should be reserved for temporary use in hypoperfused patients with low cardiac output despite a high LV filling pressure.[129,130] In patients with acute MI or ischemia and severe LV dysfunction, the use of a catecholamine may be counterproductive, because all increase myocardial cell work and exacerbate ischemia myocardial cell damage. Revascularization to reperfuse stunned or hibernating myocardium is preferable.

In hypotensive patients who are adequately volume repleted (true cardiogenic shock), norepinephrine is the pressor of choice.[131] It raises BP and coronary perfusion pressure (alpha-vasoconstrictor effect) with a modest beta effect for inotropy, and the least overall increase in HR and contractility, limiting the increase in myocardial oxygen demand. In cardiogenic shock, norepinephrine administration is a temporizing maneuver to maintain coronary perfusion pending rescue strategies, such as angioplasty, intra-aortic balloon pumping, or cardiac surgery.

Dopamine is a naturally occurring catecholamine and a norepinephrine precursor. It has a dose-dependent effect on peripheral vascular tone and is a positive inotropic and chronotropic agent. Despite previous recommendations, dopamine in heart failure has no clinically significant perfusion-sparing effect on the kidneys at any dose.[132] Epinephrine is a potent alpha- and beta-agonist that maintains BP and increases cardiac output. In cardiac surgery patients, it combats myocardial stunning after cardiopulmonary bypass. Dobutamine is a synthetic catecholamine that is mainly a $beta_2$-receptor agonist with some $beta_1$- and alpha-agonist activity. It is an inotropic vasodilator at therapeutic doses and should be used with caution in patients with borderline hypotension, because it occasionally reduces BP further. Isoproterenol is a potent beta-agonist that causes profound tachycardia with vasodilation and is contraindicated in heart failure.

Amrinone and milrinone are PDE type III inhibitors that increase cyclic adenosine monophosphate (cAMP) in the myocardium and peripheral smooth muscle. These intravenous vasodilating inotropic agents increase cardiac output and reduce LV pressures without producing significant changes in HR and BP. The positive inotropic effects of amrinone and dobutamine are additive, and concomitant use of both drugs appears to be better tolerated than high doses of dobutamine alone, with lower metabolic consequence. Amrinone and milrinone may be useful on a short-term basis in patients awaiting heart transplantation. They should be used with caution in selected patients, usually in the

context of invasive hemodynamic monitoring. These agents are prodysrhythmic, and long-term use of PDE type III inhibitors reduces survival in heart failure.[133]

Rate and Rhythm Controllers

Rate and rhythm control is occasionally necessary in heart failure. Compensatory tachycardia is the rule in heart failure, unless the patient is taking beta-blocking agents. Noncompensatory tachycardia increases myocardial oxygen consumption while reducing coronary perfusion and is a particular problem with atrial flutter or fibrillation with rapid ventricular response. Diltiazem is effective and a safe choice in this situation in normotensive patients.[134] Various other medical therapies are available in acute atrial fibrillation.[135] Electrical cardioversion is indicated when a new-onset tachydysrhythmia is causing or exacerbating heart failure, especially with hypoperfusion or ongoing evidence of myocardial ischemia. Transcutaneous pacing may be necessary in severe bradycardia with hypotension.

Chronic Heart Failure

Chronic heart failure involves a more gradual onset of symptoms, with a slow increase in dyspnea on exertion, progressive orthopnea, fatigue, and other symptoms. Patients with chronic heart failure often have complex multiorgan dysfunction, several comorbidities, and use polydrug medical regimens. In this clinical setting, the potential impact of any therapeutic intervention on the entire spectrum of disease and compensatory mechanisms should be considered. For example, adding an NSAID to the medical regimen of a patient with chronic heart failure may negatively affect renovascular function and precipitate increased fluid retention and pulmonary edema.

Neurohormonal modulation is the cornerstone of therapy for chronic HFrEF but is much less effective in HFpEF.[136,137] The mainstay of treatment for both chronic heart failure and asymptomatic LV dysfunction is vasodilator therapy, which benefits pump function by reducing both afterload and preload. The most important vasodilators for chronic heart failure are ACE inhibitors, angiotensin II receptor antagonists, and nitrates.

Common Therapeutic Agents in Chronic Heart Failure

Renin Angiotensin System Blocking Drugs. ACE inhibitors are natriuretic vasodilators that block production of angiotensin II and aldosterone secretion, reducing diuretic and potassium supplement requirements. Additional ACE inhibitor effects include inhibition of bradykinin degradation and reduction of intrinsic ET-dependent vasoconstriction. ACE inhibitors provide the most effective therapy for LV dysfunction, increasing survival in all classes of chronic heart failure, as well as reducing development of heart failure in patients with MI and asymptomatic LV dysfunction.[138] Unlike most other vasodilators, they do not induce reflex tachycardia. Main side effects of ACE inhibitors are hypotension, deterioration of renal function, chronic cough, and upper airway angioedema. ACE inhibitors should be initiated at low doses with careful attention to the potential for hypotension, with concomitant reduction in diuretic and potassium supplementation. Optimization of ACE inhibitor dosage appears to be neglected in many patients with heart failure, particularly the elderly.[139]

Angiotensin type I (AT_1) receptor blockers are most useful in patients intolerant of ACE inhibitors, and cause less cough and bradykinin accumulation.[140] Both ACE inhibitors and ARBs allowed reverse remodeling in heart failure and reduce risk of development of atrial fibrillation.[141-143] ARBs are not superior to ACE inhibitors in reducing mortality or hospitalization for heart failure.[144] The combination of an ARB and an ACE inhibitor (dual renin-angiotensin blockade) provides minimal additional benefit, but increases hyperkalemia and hypotension while worsening renal function, and is no longer recommended in heart failure.[145]

Beta-Blocker and Combined Alpha- and Beta-Blocker Therapy. Despite the apparent paradox of using agents that reduce myocardial contractility, beta-adrenergic blocking agents have significant efficacy in chronic heart failure. Long-term activation of the sympathetic nervous system in heart failure, direct cardiotoxicity because of elevated norepinephrine levels, activation of the RAAS, and myocardial beta-adrenergic receptor downregulation are associated with adverse effects.[146] An extensive meta-analysis shows that beta-blockers in chronic heart failure significantly increase EF and decrease mortality.[147] HR reduction with use of beta-blockers correlates with improvement in LVEF and lowers death rate in heart failure.[148] AHA/ACC guidelines recommend beta-blockers for all patients with symptomatic LV systolic dysfunction.[149,150]

Beta-blockers should not normally be initiated in acute heart failure. They are most useful in chronic heart failure associated with conditions having indications for beta-blocker therapy, including hypertension, angina pectoris, and significant dysrhythmias. Slow upward titration of beta-blocker therapy facilitates maximal tolerability. This is particularly important in COPD, where beta-1 selective agents are effective and preferred in heart failure.[151] Usually, it is not necessary to discontinue beta-blocker therapy in the setting of acute decompensation of chronic heart failure, but dose reduction may be appropriate if there is hemodynamic instability.[152] Carvedilol, a third-generation alpha- and beta-blocker with vasodilating and antioxidant properties, may be a particularly effective agent in chronic heart failure. Although direct comparisons show carvedilol superior to other beta-blockers in heart failure, the benefits of beta-blockers in HFrEF appears to be mainly a class effect, because no clear evidence supports superiority of any single agent.[153-154]

Diuretics. Patients with chronic heart failure exhibit a reduced ability to excrete a sodium and water load, with abnormal cardiac and hemodynamic adaptations to salt excess.[155] Low-dose diuretics are used to prevent recurrence of heart failure, but there is limited evidence from randomized trials to guide their use.[156,157] Loop diuretics, although commonly used, are associated with significant side effects, including hypovolemia, electrolyte disturbances (low K^+, Mg^{2+}, and Na^+), hyperuricemia, worsening renal function, and metabolic alkalosis. Torsemide, unlike furosemide, inhibits aldosterone secretion and has other effects that may make it a more effective loop diuretic in chronic heart failure.[158] The addition of thiazide diuretic therapy to loop diuretics greatly increases sodium and fluid excretion but increases side effects.[159]

The hypokalemia and hypomagnesemia secondary to diuretic therapy are prodysrhythmic. The use of potassium-sparing diuretics in heart failure is associated with a reduced risk of death. Spironolactone and eplerenone directly antagonize aldosterone and are equally effective.[160] They significantly reduce mortality while improving LV function in patients with severe heart failure (EF below 35%) already being treated with an ACE inhibitor and a loop diuretic, with or without digoxin.[161,162] Spironolactone reverses remodeling in patients with mild to moderate chronic systolic heart failure.[163] Aldosterone antagonists may lead to serious hyperkalemia in the presence of significant renal insufficiency or in patients taking supplemental potassium.

Hyponatremia is common in heart failure and may be exacerbated by diuretics. Low serum sodium is an independent predictor of mortality, hospitalization for heart failure, and death or rehospitalization, despite clinical and hemodynamic improvements similar to those in patients without hyponatremia.[164-165]

Nitrates. Nitrate therapy, by virtue of a direct vasodilator effect, improves exercise tolerance in chronic heart failure and offers potential hemodynamic improvement. The main problem with nitrate therapy appears to be rapid drug tolerance, which can be partially addressed by daily nitrate drug-free intervals. Isosorbide used in combination with the arteriolar dilator hydralazine prolongs survival in patients with heart failure but less so than ACE inhibitors. ACE inhibitors, however, are less effective in African Americans. A fixed-dose isosorbide dinitrate/hydralazine regimen is particularly effective in chronic heart failure in African Americans,[166] reducing hospitalization and mortality significantly, with these positive effects sustained over time.[167-168]

Cardiac Glycosides. The cardiac glycosides inhibit the ATP-dependent sodium/potassium pump in the cell membrane of the cardiac myocyte. This inhibition increases the availability of intracellular calcium to contractile proteins in myocardial cells, with modest positive inotropic effect. Low dose digoxin may be of benefit in chronic heart failure by reducing symptoms and improving quality of life and exercise tolerance. Digoxin reduces the rate of hospitalization in chronic heart failure and lowers mortality when added to an ACE inhibitor and diuretic therapy.[169] Digoxin should be used in low doses for persistently symptomatic heart failure patients whose treatment already includes ACE inhibitors, diuretics, and beta-blocker therapy.[170] Digoxin toxicity is a considerable risk in heart failure, particularly with renal insufficiency, and cardiac glycosides have limited efficacy in HFpEF.[171]

Other Considerations in Chronic Heart Failure

Electrical Therapy. ICDs have a substantial mortality advantage over antiarrhythmics in chronic heart failure, particularly in patients with previous MI and low LVEF.[172] Prophylactic placement in appropriate patients undergoing coronary artery bypass grafting (CABG), however, has been found to be ineffective in reducing mortality in the first 6 months after surgery.[173] Although a meta-analysis of ICD therapy continues to show benefit in MI patients with low EF,[174] the economic impact is unclear. Newer subcutaneous ICDs require no venous electrodes, are easily implanted with minimal complications, have efficacy and inappropriate shock rates similar to conventional ICDs, and may be a game changer in treating recurrent malignant arrhythmias.[175-176]

Patients with severe heart failure and significant LV dyssynchrony benefit from atrioventricular sequential pacing.[177] RV apical pacing is often used in chronic heart failure but creates abnormal LV contraction, hypertrophy, and reduced pump function.[178] Cardiac resynchronization therapy (CRT) via LV or biventricular pacing attempts to coordinate the activation of the interventricular septum and left ventricle free wall in heart failure. LV or biventricular pacing allows more physiologic LV contraction, and both are equally effective.[179-180] CRT improves heart failure symptoms and exercise capacity and can reverse chronic cardiac dilation.[181-183] CRT combined with ICD use greatly reduces risk of sudden cardiac death and other cardiac events.[184-186] Cardiac resynchronization in patients with atrial fibrillation has some efficacy in improving EF, as well as functional outcome, and appears more effective than pharmacologic therapy.[187] CRT also reduces functional mitral regurgitation.[188] Intrathoracic impedance monitoring is available on some devices to continuously monitor hemodynamic status in heart failure.[189] Potential roles for telemonitoring in chronic heart failure are evolving.[190]

Antidysrhythmic Therapy. Seventy percent to 95% of patients with cardiomyopathy and heart failure have frequent premature ventricular beats, and 40% to 80% develop nonsustained ventricular tachycardia with an associated increased risk of sudden death.[191] Amiodarone and classmate dronedarone are useful in acute management of sustained ventricular tachyarrhythmias. Unfortunately, amiodarone and other antidysrhythmic agents have significant toxicities and may be prodysrhythmic, and none demonstrates decreased mortality in heart failure.[192] In patients with post-MI LV systolic dysfunction with or without heart failure, amiodarone is associated with increased early and late all-cause cardiovascular mortality.[193] Dronedarone has been found to similarly increase mortality and worsen heart failure in patients with LV systolic dysfunction.[194] ICD therapy is superior to antiarrhythmics in preventing sudden death in selected patients with heart failure.[24]

Atrial fibrillation is a marker of worse prognosis in heart failure, and new atrial fibrillation increases morbidity and mortality in chronic heart failure.[195] In chronic heart failure, amiodarone prevents the development of atrial fibrillation and converts significantly more patients with atrial fibrillation to sinus rhythm.[196] In patients with atrial fibrillation and chronic heart failure, however, medical rhythm control does not reduce the cardiovascular death rate compared with rate control.[197] The role of nonpharmacological strategies like catheter ablation is evolving in atrial fibrillation and heart failure.[198]

Rate control of sinus rhythm is recognized as an avenue for therapeutic intervention in heart failure.[199] In patients with LV dysfunction and stable coronary artery disease, elevated HR above 70 beats/min is associated with higher cardiovascular mortality and admission for MI or heart failure.[200] In particular, for every increase of 5 beats/min above 70 beats/min, there are increases in cardiovascular death, admission for heart failure or MI, and coronary revascularization. Ivabradine, a selective sinus node inhibitor, demonstrates reduced hospitalization and death rates in chronic heart failure with resting HR over 70 beats/min and EF below 35%.[201-202]

Calcium Channel Blockers. First-generation calcium channel blockers (verapamil, diltiazem, and nifedipine) do not improve survival in chronic heart failure and may precipitate clinical deterioration.[203] Second-generation dihydropyridines (nicardipine and amlodipine) have more moderate negative inotropic effects. Calcium channel blockers used to treat hypertension increase the incidence of heart failure compared with other regimens.[203] Although used to treat hypertension, angina, and dysrhythmias, benefits may be reduced in patients with associated chronic heart failure. There is no compelling evidence for the use of calcium channel blockers in chronic heart failure, although they may be needed in patients intolerant of beta-blockers, ACE inhibitors, ARBs, and combined nitrates plus hydralazine.

Ultrafiltration and Renal Dialysis. Ultrafiltration reduces volume overload when diuretic therapy is inadequate.[204] In decompensated heart failure, ultrafiltration may be more effective than intravenous diuretics in volume overloaded states but does not reduce rehospitalization rate or mortality.[205] Renal dialysis is important for heart failure treatment in end-stage renal disease. Potential complications of renal disease that may need special consideration include fluid overload, severe hyperkalemia, iatrogenic hypermagnesemia, uremic pericardial effusion, and drug toxicity (eg, digitalis). Missed or inadequate dialysis is a frequent cause of chronic heart failure decompensation.

Coronary Artery Bypass Grafting and Angioplasty. In patients with coronary artery disease amenable to CABG and EF below 35%, CABG combined with medical therapy, compared with medical therapy alone, reduces death from cardiovascular causes but not all-cause mortality.[206] Another study shows vessel opening gave no advantage in preventing heart failure, death, or reinfarction in stable patients with occlusion of the infarct-related

artery 3 to 28 days after MI.[207] Assessing for myocardial viability in ischemic LV dysfunction does not identify a survival benefit from CABG.[208-209] However, early revascularization in non–ST elevation acute coronary syndrome and heart failure reduces mortality.[210]

Phosphodiesterase Inhibitors. There are limited indications for use of long-term PDE type 3 inhibitors (amrinone or milrinone), which increase morbidity and mortality in patients with severe chronic heart failure.[211] Use should be limited to hypoperfusion states unresponsive to other therapies. PDE type 5 inhibition with sildenafil, used commonly for erectile dysfunction, is safe in heart failure, and may have other beneficial effects, including better cardiac output and exercise capacity.[212-214] Long-term use of sildenafil in chronic heart failure and severe pulmonary hypertension improves hemodynamic and clinical status.[215]

Statins and Polyunsaturated Fatty Acids. Statins improve endothelial function and have antiinflammatory, antioxidative, and immunomodulatory effects that may be beneficial in patients with chronic heart failure.[216] Early use of statin therapy after acute MI reduces risk of heart failure.[217] Use in nonischemic heart failure improves LVEF and NYHA classification and reduces serum levels of multiple inflammatory markers. A statin reduces risk of heart failure substantially in high-risk populations and also decreases risk of major vascular effects. Statin therapy lowers hospitalizations, reduces inflammatory markers, improves EF, and decreases mortality among patients with severe heart failure.[218] Utility in mild heart failure is less obvious.[219] High-dose statin therapy adds benefit to lower doses in heart failure.[220] Omega-3 polyunsaturated fatty acids show improved LV systolic function, functional capacity, and reduced hospitalizations in patients with dilated cardiomyopathy.[221] In patients with heart failure from any cause, omega-3 polyunsaturated fatty acids use leads to a small decrease in mortality and admissions for cardiovascular reasons.[222-223] The Mediterranean-style diet, with a focus on vegetables, fruit, fish, whole grains and olive oil, is particularly effective in reducing cardiovascular events, including heart failure.[224]

Anemia. Anemia is present in about one-third of chronic heart failure patients and is associated with increased mortality in both systolic and diastolic heart failure. Iron deficiency occurs with a similar frequency in heart failure. Improving anemia in chronic heart failure by using iron supplements improves LV systolic function, LV remodeling, BNP levels, NYHA class, sleep-related breathing disorders, and renal function, as well as need for hospitalization.[225] A higher transfusion threshold does not seem helpful in heart failure,[226] whereas erythropoiesis-stimulating agents can provide clinical benefits, but may cause harm.[227]

Sleep Apnea-Related Respiratory Support. Hypoxemia and related hemodynamic stress underlies the impact of sleep disorders in heart failure.[228] Obstructive sleep apnea is more prevalent in chronic heart failure than previously recognized, and treatment improves nocturnal oxygenation, EF, and exercise capacity, but is not proven to increase survival.[229,230] Effective treatments for obstructive sleep apnea include CPAP, BiPAP, and adaptive servoventilation, with the latter most effective and involving variable ventilatory pressure support synchronization based on respiratory rate and airflow.[231] Other therapies include dental devices, surgery, and weight loss.[232]

Exercise Programs. Cardiopulmonary exercise testing provides prognostic information in patients with heart failure.[233] Various exercise programs in chronic heart failure show benefits in terms of functional status and quality of life, and reduce rehospitalization rates, but do not reduce mortality.[234-236] Testosterone and growth hormone replacement in heart failure increase exercise capacity and quality of life.[237-238]

Advanced Surgical Therapies. Management of severe left-sided valvular failure, when appropriately timed, may be very helpful in both preventing and treating heart failure.[239] Transcatheter valve replacement is developing as an effective, minimally invasive surgical technique.[240]

After a promising beginning, left ventriculoplasty has largely been abandoned because of failure to demonstrate long-term efficacy in heart failure. A study of ventriculoplasty during coronary artery bypass surgery also failed to show functional improvement or reduced mortality in heart failure.[241] In contrast, LV aneurysm repair is useful in severe heart failure.[242]

Multiple implantable left ventricular assist devices (LVADs) are in use for chronic heart failure as a bridge to transplantation and as a surgical alternative to chronic medical management.[243] Treatment of end-stage heart failure with LVADs has been shown to improve cardiorespiratory performance during exercise testing, as well as overall quality of life.[244-245] LVAD technology has advanced greatly, and there is potential for this as a long-term alternative to transplantation.[246-247] Familiarity with proper LVAD function and potential complications is a new arena of learning for emergency clinicians.[248]

Heart transplantation is still the most effective therapy for end-stage heart failure, with median survival exceeding 10 years.[249] The limited availability of donors (2500 heart transplants per year in the United States) and need for lifelong immunosuppression makes alternative surgical techniques of interest in end-stage heart failure. There is increasing evidence that stem cell therapy may offer promise in chronic heart failure, but it remains at the research level at present.[250-251] Autologous stem cell transplantation significantly improved cardiac function in a small number of patients undergoing CABG for ischemic cardiomyopathy.[252] However, multiple challenges need to be overcome before stem cell therapy can advance beyond the experimental level for heart failure therapy.[253]

Psychosocial Factors. Significant depression is common in patients with heart failure and increases cardiovascular mortality.[254] Treatment is challenging, but exercise programs, improved social support, and appropriate pharmacotherapy are helpful.[255]

A discussion of end-of-life preferences and palliative care is important in advanced heart failure.[256-257] Hospice services may be particularly useful in that setting.[258]

DISPOSITION

Admission Criteria, Observation Units, and Predictors of Readmission

Appropriate disposition of patients presenting with decompensated heart failure depends upon clinical stability, comorbidities, precipitating events, and the availability of resources that may determine hospital admission versus an alternate pathway. In general, exacerbations of chronic heart failure need admission if the cause of the exacerbation cannot be readily recognized and corrected, if the disease process is unstable, or if clinical deterioration appears likely. Precipitating events, including acute coronary syndrome, concomitant pneumonia, or worsening renal function increase hospital mortality and should prompt admission. Additionally, several risk factors predict poor post-discharge outcome, including ischemic ECG changes, elevated troponin or natriuretic peptide levels, hyponatremia, elevated blood urea nitrogen (BUN) or creatinine, and low systolic BP.[259-260] In-hospital mortality for acute decompensated heart failure is about 4%, but higher with increased age, elevated HR, hyponatremia, hypotension, LV

systolic dysfunction, increased BUN, creatinine, troponin, or natriuretic peptides, or if heart failure is the primary cause for admission.[261-262]

In comparison, patients presenting to the ED with rectifiable dietary or medication noncompliance issues may be safely discharged with close follow-up. However, many of these patients are admitted because of the inability to identify those at low risk for poor outpatient outcomes, or difficulty providing proper bedside heart failure education and close follow-up. In fact, re-hospitalization occurs at higher rates when patients are directly discharged from the ED.[263] Observation units may have a substantial role in avoiding heart failure admission, reducing costs, and providing a bridge to appropriate outpatient care.[264-265] Reporting of preventable readmissions, changing financial incentives, and an emphasis on education and post-discharge care help drive the discussion of short-stay observation units for patients with heart failure. Evidence suggests that certain patients need only minimal medical management and that symptoms are often relieved within 24 hours.[266-267] The question remains if low risk patients that quickly respond to therapy can be safely discharged after observation with close outpatient follow-up.[268] More evidence is needed to determine which heart failure patients may benefit from observation units.

The difficulties of outpatient heart failure management range from compliance and understanding of the multifactorial therapeutic strategies to optimization of care after hospital discharge, including diet, medications, and weight monitoring. Patients with heart failure are frequently readmitted for both cardiac and unrelated causes.[269] Several studies have demonstrated reduced readmission rates with individualized, comprehensive discharge planning, structured post-discharge follow-up, telemonitoring, and directed home self-management.[270-275] Readmission rates are lower for those with comprehensive discharge planning and post-discharge support versus standard therapy.[276-277] There is significant variability in the adherence to heart failure quality-of-care issues in the United States. Prompt initiation of optimal therapeutic modalities leads to early benefits, including decreased risks of mortality and rehospitalization for heart failure.[278]

KEY CONCEPTS

- Heart failure is among the most frequent conditions resulting in emergency department (ED) visits and hospital admissions, with high morbidity and mortality.
- Heart failure can be divided into heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF), which have similar incidences, morbidities, and mortalities, but different pathophysiologies and response to therapies.
- Neurohormonal mechanisms provide initial compensation for cardiac dysfunction but are ultimately deleterious in heart failure. Chronic therapy to negate these effects is important even in asymptomatic myocardial dysfunction.
- The most common manifestation of acute heart failure is respiratory distress, triggering a differential diagnosis primarily including non-cardiogenic pulmonary edema, exacerbation of chronic obstructive pulmonary disease (COPD) or asthma, pulmonary embolus, pneumonia, tension pneumothorax, cardiac tamponade, and anaphylaxis.
- Recognition of precipitating causes in heart failure allows early understanding of appropriate management issues.
- Biomarkers such as B-type natriuretic peptide (BNP) may improve recognition of heart failure in dyspnea of unclear cause, correlate with severity, help stratify risk, and monitor therapeutic response.
- Distinguishing primary pulmonary disease causing predominantly right-sided heart failure from left ventricular (LV) failure with secondary right-sided dysfunction is clinically challenging, because the physical examination findings and chest radiograph may be similar. Natriuretic peptide levels are much higher in LV failure.
- Most acute heart failure can be managed with upright positioning, supplemental oxygen, non-invasive ventilation, vasodilators, and loop diuretics.
- Hypoperfusing patients with acute cardiogenic pulmonary edema (ACPE) often have unreliable cuff blood pressure (BP) readings and may benefit from invasive arterial monitoring.
- Patients with true poor perfusion may benefit from fluid challenge to restore preload, cardiac output, systemic perfusion, and BP. Careful volume infusion with aliquots of normal saline is appropriate initial resuscitation for the hypoperfusing patient with acute-onset cardiogenic pulmonary edema.
- In hypoperfusing patients who are adequately volume repleted (true cardiogenic shock), norepinephrine is the pressor of choice.
- In chronic heart failure, routine use of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), diuretics including spironolactone, and occasionally digoxin has resulted in sustained symptomatic improvement and reduced 5-year mortality in HFrEF.
- Various electrical therapies, particularly cardiac resynchronization therapy (CRT) and implantable defibrillators, as well as mechanical techniques like implantable left ventricular assist devices (LVADs) and cardiac transplantation add complexity to chronic heart failure management, but improve morbidity and mortality.
- Observation medicine plays an increasing role in reducing costs and admissions in heart failure.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 71: QUESTIONS & ANSWERS

71.1. In developed countries, what is the most common cause of heart failure?
- **A.** Acute myocarditis
- **B.** Atherosclerotic coronary artery disease
- **C.** Chronic obstructive pulmonary disease (COPD)
- **D.** Dilated cardiomyopathy
- **E.** Valvular heart disease

Answer: B. In developed countries, atherosclerotic coronary artery disease is the leading cause of heart failure, present in almost 70% of patients in multicenter heart failure trials. Dilated cardiomyopathy is much more common than hypertropic or restrictive types and is the second most common cause of heart failure. Valvular heart diseases and myocarditis are less common causes of heart failure. COPD, with a prevalence of 20% to 30% in heart failure, frequently obscures its recognition.

71.2. A 54-year-old male with a history of hypertension and diabetes mellitus presents with sudden onset of dyspnea and severe chest pain. His electrocardiogram (ECG) shows 2 to 3 mm of ST-segment elevation in leads V_1 to V_4. A portable chest radiograph demonstrates evidence of pulmonary edema. He is placed on oxygen and a nitroglycerin drip, and his chest pain resolves while his ECG changes improve. His blood pressure (BP) suddenly drops to 80/54 and his heart rate (HR) increases to 112 beats per minute. Besides stopping the nitroglycerin drip and contacting interventional cardiology, what is the next appropriate therapeutic intervention?
- **A.** Crystalloid boluses to restore perfusion
- **B.** Intra-arterial pressure monitoring to confirm hypotension
- **C.** Lopressor to reduce HR
- **D.** Norepinephrine for cardiogenic shock
- **E.** Thrombolytic therapy for ST-elevation myocardial infarction (STEMI)

Answer: A. Understanding the pathophysiology here is important. Presumably, this is acute coronary syndrome, probably resulting from left anterior descending coronary artery occlusion. The resultant acute diastolic dysfunction increases left ventricular (LV) filling pressure greatly and leads to flash pulmonary edema with alveolar flooding. This pulmonary edema came from acute displacement of intravascular volume, which is now significantly reduced. Because coronary ischemia often has a stuttering course and nitroglycerin may also improve coronary perfusion through vasodilatory properties, the ischemia and diastolic dysfunction can acutely resolve. Hypotension, if it occurs, is related to intravascular volume depletion, and crystalloid volume replacement, done judiciously, is the most appropriate intervention. Lopressor, a beta-blocking agent, would be less helpful here, because cardiac inotropic function needs to be maintained. Norepinephrine is the vasopressor of choice for cardiogenic shock, but in this particular setting, volume resuscitation should be tried first. Although intra-arterial pressure monitoring is appropriate to best understand the true perfusion situation, volume resuscitation is needed promptly. Percutaneous coronary intervention has a survival advantage over thrombolytic therapy in cardiogenic shock resulting from acute myocardial infarction (AMI). With resolution of myocardial ischemia and related improvement in cardiac function, the pulmonary edema will eventually return to the intravascular space. Noninvasive ventilation (NIV) may accelerate this process.

71.3. Which of the following is *not* a common precipitating factor for heart failure?
- **A.** Acute atrial fibrillation
- **B.** Acute hypertension
- **C.** Adrenal insufficiency
- **D.** Iatrogenic volume overload
- **E.** Pneumonia

Answer: C. Infection, particularly pneumonia resulting from its associated hypoxia and increased work of breathing, is a common precipitating factor for heart failure. Acute atrial fibrillation may reduce ventricular priming (a particular problem with diastolic dysfunction) and also increase heart rate (HR), contributing to heart failure. Volume overload, either because of dietary noncompliance or excessive crystalloid infusion during patient care, can rapidly cause heart failure. Uncontrolled blood pressure (BP) elevations, often resulting from medication noncompliance, may contribute to heart failure exacerbations. Adrenal insufficiency is associated with intravascular volume depletion and more likely to cause hypoperfusion.

71.4. A 63-year-old male presents with an acute exacerbation of chronic heart failure. He admits to moderate alcohol and occasional cocaine use. He is presently intoxicated and slightly agitated. His blood pressure (BP) is 234/124 mm Hg with a heart rate (HR) of 128, respiratory rate of 28, and temperature at 100.4° F (38.0° C), along with oxygen saturation measured by pulse oximetry (SpO_2) of 95% on room air. He has jugular venous distention; bibasilar rales; a rapid, regular S1 and S2; and 3+ edema in both lower extremities. Which of the following interventions is likely to provide the most benefit?
- **A.** 100% oxygen by face mask
- **B.** Biphasic positive airway pressure (BiPAP)
- **C.** Furosemide
- **D.** Lopressor
- **E.** Nitroglycerin

Answer: E. Lopressor, a beta-blocking agent, is not usually a drug of choice in *acute* heart failure and may indeed lead to unopposed alpha-agonist effect if cocaine has been recently used, with possible deterioration. The patient's pulse oximetry suggests adequate oxygenation, and supplemental oxygen would provide minimal benefit, whereas hyperoxemia may theoretically increase afterload by its vasoconstrictive effect. Similarly, noninvasive ventilatory support using BiPAP may not be well tolerated in this agitated patient, and although it may help by reducing both preload and afterload, better options exist. Furosemide may be a reasonable intervention, but prompt afterload reduction with nitroglycerin, preferably intravenously, is likely to be the most beneficial treatment for this very hypertensive heart failure patient.

71.5. Each of the following classes of medications has a significant role in the management of chronic heart failure, except:
- **A.** Angiotensin-converting enzyme (ACE) inhibitors
- **B.** Beta-blockers
- **C.** Calcium channel blockers
- **D.** Diuretics
- **E.** Nitrates

Answer: C. Beta-blocker therapy increases survival in heart failure, probably through modulation of multiple neurohormonal responses. ACE inhibitors provide the most effective therapy for left ventricular (LV) dysfunction. Diuretics help deal with the decreased ability to excrete excess salt and water in heart failure. Nitrates, by direct vasodilatory effects, improve exercise tolerance and hemodynamics in chronic heart failure. Calcium channel blockers, particularly first-generation ones (verapamil, diltiazem, and nifedipine), do not improve survival in this disease, and there

is no compelling evidence that they are useful in chronic heart failure.

71.6. A 47-year-old female presents with severe shortness of breath and palpitations. She has bilateral proptosis; a symmetrically enlarged thyroid gland; inspiratory crackles bilaterally on pulmonary examination; rapid, irregular heart sounds on cardiac examination; and bipedal edema. Her blood pressure (BP) is 220/100 mm Hg with an irregular pulse at 156 beats per minute. What is the initial therapy of choice?

A. Dexamethasone
B. Diltiazem
C. Esmolol
D. Nesiritide
E. Nitroglycerin

Answer: C. This patient has acute pulmonary edema and probable atrial fibrillation, with a high output type of heart failure likely due to thyrotoxicosis, presumably caused by Graves' disease. Beta-blockade, here with esmolol, which has a short half-life and can be titrated, is in this particular clinical situation the therapy of choice among these options. Beta-blockade will reduce the elevated thyroid hormone effects on cardiac function, which probably precipitated high output heart failure and atrial fibrillation. Vasodilator therapy with nitroglycerin will not improve the cardiac effects of thyrotoxicosis, and nesiritide has minimal role in the present treatment of heart failure. Diltiazem may reduce ventricular rate but is not the most effective treatment in this clinical situation. Dexamethasone plays a minor role in the treatment of thyrotoxicosis.

CHAPTER 72

Pericardial and Myocardial Disease

Nicholas J. Jouriles

PERICARDIAL DISEASE (PERICARDITIS)

Principles

Pericardial Anatomy Physiology and Pathophysiology

The pericardium envelops the heart and attaches to the great vessels. It consists of parietal and visceral layers, with a narrow potential space between. Each layer is 1 or 2 mm thick and is composed of elastic fibers. Its blood supply comes from the internal mammary artery; its nerve supply comes from the phrenic nerve. An ultrafiltrate of plasma, 15 to 35 mL of fluid, is normally contained in the pericardial space. The pericardium serves several functions: It maintains the heart's position, lubricates the heart's surface, prevents the spread of infection, prevents cardiac overdilation, augments atrial filling, and maintains the normal pressure-volume relationships of the cardiac chambers. Patients with congenital absence (or surgical removal) of the pericardium, however, show few, if any, problems. Pericardial absence may be associated with other, genetic based problems.[1]

The inflammation of pericarditis is characterized by a granulocytic and lymphocytic infiltration of the pericardium. There is an increase in the number of antibodies in the pericardial fluid.

SPECIFIC DISORDERS: IDIOPATHIC PERICARDITIS

Principles and Clinical Features

The classic symptoms of pericarditis include chest pain, pericardial friction rub, and electrocardiogram (ECG) abnormalities. A history of fever and myalgias is common. Pericarditis chest pain is sharp, pleuritic, and varies with position. It is relieved by sitting forward and worsened by lying down, deep inspiration, or swallowing. Pericarditis pain is retrosternal, can radiate to the trapezius muscles, or can present as isolated shoulder pain.

The classic physical examination finding is a pericardial friction rub. The rub may be caused by friction between inflamed or scarred visceral and parietal pericardium or may result from friction between the parietal pericardium and adjacent pleura. It may be audible anywhere over the anterior chest wall and is best heard with the stethoscope diaphragm positioned at the lower left sternal border with the patient leaning forward in full expiration. The rub also can be accentuated by a full inspiration, followed by a breath hold. The rub tends to be intermittent, migratory, and difficult to hear in a loud emergency department (ED).

Differential Diagnosis

In patients with pericardial disease, the differential diagnosis would include inflammatory or infectious disease of the chest wall (costochondritis), pleura (pleurisy or pleuritis), or other infections, such as pneumonia. Rarely pulmonary embolism can mimic pericarditis and must be considered in the differential diagnosis and ruled out based on history, physical findings, risk stratification, and diagnostic testing.

Acute coronary syndromes may also mimic pericarditis; and a thorough history and physical examination, as well as diagnostic testing, rarely only consultation with cardiology and/or coronary angiography can distinguish these entities.

Diagnostic Testing

There is no single test that is diagnostic for pericarditis. The ECG is the most reliable diagnostic tool. It evolves through stages over time. The first stage occurs in the first hours to days of illness and includes diffuse ST segment elevation and reciprocal ST segment depression. Most patients with acute pericarditis have concurrent PR segment depression (Fig. 72.1). In the next stages, the ST and PR segments normalize, but the T waves flatten followed by deep, symmetrical T wave inversion. At the last stage, the ECG reverts to normal, although the T wave inversions may become permanent.[2-3]

The classic chest pain and ECG patterns are seen in only two-thirds of patients with pericarditis, making the diagnosis difficult.[4]

The early ECG findings of acute pericarditis may be difficult to distinguish from acute myocardial infarction (AMI), coronary artery spasm, or benign early repolarization. In contrast to the ECG in AMI, the ST segment elevations in stage 1 acute pericarditis are concave rather than convex upward, simultaneous T wave inversions are not seen, and the findings are not bound to a single coronary artery distribution. Subsequent tracings do not evolve through a typical myocardial infarction (MI) pattern, and Q waves do not appear. When the ECG pattern suggests acute coronary syndrome and the pain is not clearly pericardial in nature, the best course after observation is diagnostic coronary angiography. Ventricular dysrhythmias are rare in pericardial disease. Patients with pericarditis who have ventricular dysrhythmias should be presumed to have concomitant myocarditis, another cardiac disease, or to have been misdiagnosed.

Echocardiography facilitates the definitive diagnosis of pericarditis with effusion. A normal echocardiogram does not exclude pericarditis. Cardiac tamponade, increased pericardial thickness, pericardial tumors, cysts, constrictive pericarditis, and the congenital absence of the pericardium can all be diagnosed by echocardiography.[5]

Some patients with acute pericarditis have elevated cardiac markers caused by myopericarditis, myocarditis, or MI. The white blood cell (WBC) count and erythrocyte sedimentation rate (ESR) may be elevated or normal and are not sensitive or specific. Other laboratory studies should be directed at determining non-idiopathic causes of pericarditis.

It is at times difficult to distinguish acute coronary syndrome from pericarditis. In those cases, acute coronary syndrome should be ruled out.

Management and Disposition

If a specific etiology of pericarditis is found, therapy should be directed at that cause. Otherwise, therapy for acute pericarditis is

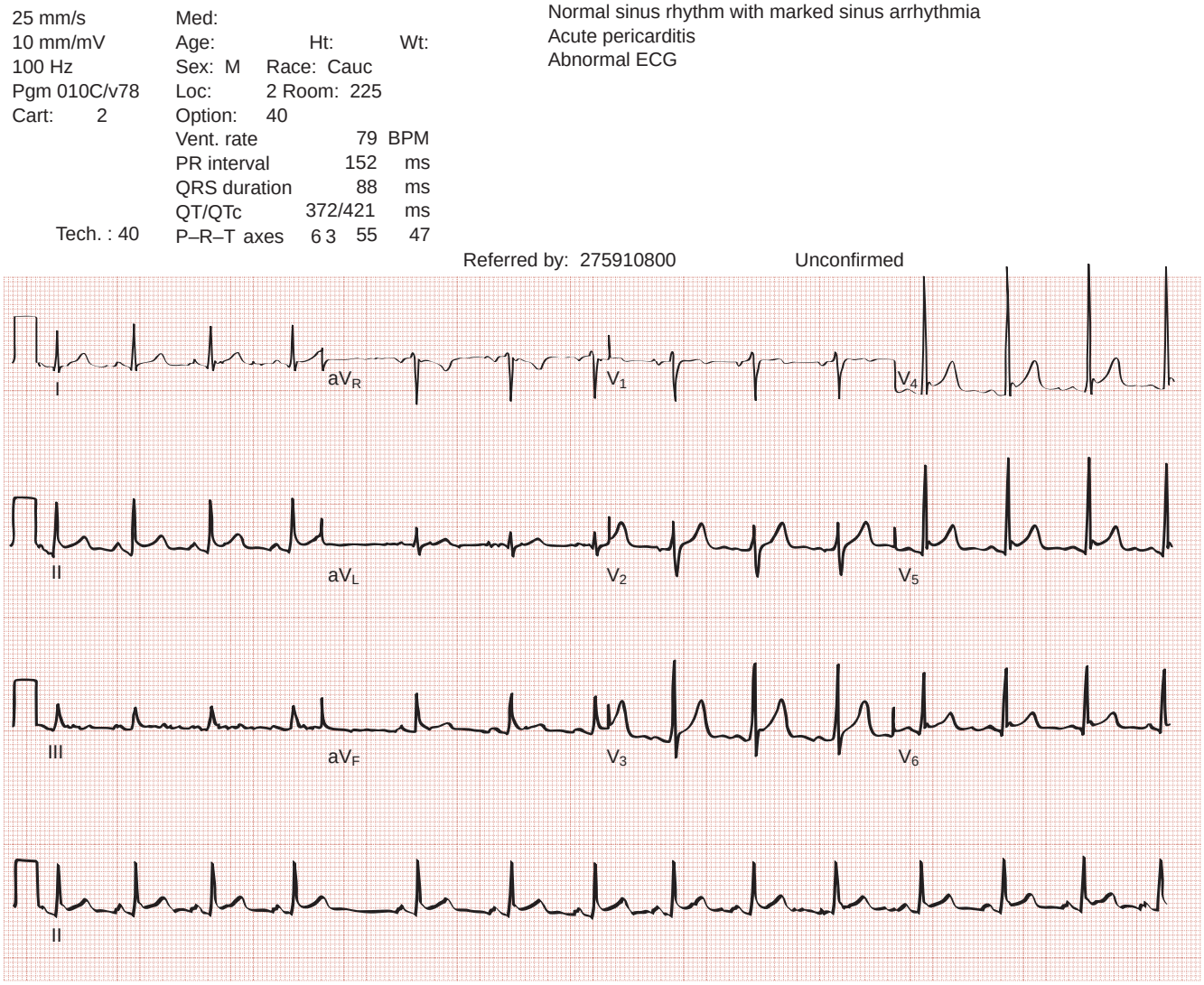

Fig. 72.1. Electrocardiogram (ECG) showing acute pericarditis. (Courtesy Ohio Chapter of the American College of Emergency Physicians.)

symptomatic. Nonsteroidal antiinflammatory drugs (NSAIDs) are the first choice. The patient will often report significant pain relief from the analgesic effect even before onset of the anti-inflammatory effect. Ibuprofen has the best side effect profile, but other NSAIDs are equally effective. If the chosen NSAID is not effective within 1 week, a different class of NSAIDs should be tried. Colchicine should be added to reduce the risk of recurrent pericarditis.[6-9] Colchicine is also the treatment of choice for recurrent pericarditis, where steroid therapy has shown mixed results.[10-11] Recurrent pericarditis is often due to an immune or rheumatologic etiology, and surgery is an option if medical therapy fails.[12-13] Most patients can be managed as an outpatient unless significant pericardial effusion, diagnostic uncertainty with acute coronary syndrome, or patient has hemodynamic abnormalities that preclude outpatient management (Box 72.1).

Complications

The clinical course of pericarditis is variable: 60% of patients have complete recovery within 1 week, and almost 80% have complete recovery within 3 weeks. Patients with fever, pericardial effusion, a subacute course, or failure of initial NSAID treatment have a worse prognosis.[14] Eighteen percent of patients will have recurrent pericarditis that requires serial echocardiography to exclude effusion or tumor.

UREMIC PERICARDIAL DISEASE

Principles

Uremic pericarditis occurs secondary to renal failure or dialysis. The etiology of dialysis-associated pericarditis is unknown and may be associated with both hemodialysis and peritoneal dialysis; although for unclear reasons, it occurs more frequently with hemodialysis. Uremic pericarditis is associated with occult infection and the evaluation of a chronic renal disease patient with pericarditis requires a diligent search for infectious causes.

Clinical Features and Diagnostic Testing

Patients with uremic pericarditis have typical symptoms and physical examination findings. The ECG in uremic pericarditis is often normal because little epicardial inflammation occurs. In a dialysis patient, cardiac enlargement on chest radiograph in the

BOX 72.1

Etiology of Pericarditis

- Infectious
  - Viral
  - Bacterial
  - Fungal
  - Parasite
  - *Rickettsia*
- Postinjury
  - Penetrating trauma
  - Blunt trauma
  - Surgery
  - Myocardial infarction (MI)
  - Radiation
  - Medication
- Systemic diseases
  - Uremia
  - Metastatic cancer
  - Rheumatoid arthritis
  - Systemic lupus erythematosus (SLE)
  - Sarcoidosis
  - Scleroderma
  - Dermatomyositis
  - Amyloidosis
- Primary tumors
- Aortic dissection

absence of signs of volume overload or congestive heart failure (CHF) should prompt consideration of pericardial effusion. Ultrasound will provide the definitive answer. Uremic pericarditis is one of the most common causes of cardiac tamponade.

Management and Disposition

Uremic pericarditis is initially treated with intensive dialysis. NSAIDs are ineffective and often are contraindicated. Systemic steroids should be used in the few patients who do not respond to dialysis.

POST–MYOCARDIAL INFARCTION PERICARDITIS

Approximately 20% of patients with transmural MI experience a different quality of chest pain 2 to 4 days after infarction. This pain may represent early post-MI pericarditis. There is frequently low-grade fever and a transient pericardial friction rub. Early post-MI pericarditis is generally short-lived and is treated with aspirin therapy. The ECG changes of pericarditis usually are masked by the AMI changes, making the diagnosis difficult.[15] Patients with early post-MI pericarditis have more dysrhythmias and heart failure. Pericarditis in AMI may be an indicator of greater myocardial damage and a worse outcome.

In contrast to early post-MI pericarditis, Dressler reported a syndrome of fever, pleuritis, leukocytosis, friction rub, and chest radiograph evidence of new pericardial or pleural effusions in post-MI patients. Frequent relapses led Dressler to describe this syndrome as a delayed complication of MI. The cause of late post-MI pericarditis (Dressler's syndrome) may be immunologic. The syndrome may also occur with pulmonary embolus and after pericardiotomy. Anticoagulants should be discontinued to reduce the risk of hemorrhage. Delayed post-MI pericarditis is treated with NSAIDs.

POSTINJURY PERICARDITIS

Principles

Postcardiac injury syndrome is defined as pericarditis after MI, cardiac surgery, or trauma. The incidence ranges from approximately 5% after MI to 30% after thoracic surgery or trauma. It can also occur after chest trauma that does not involve the heart or pericardium.[16]

Injury to the pericardium in blunt trauma may range from contusion to laceration or rupture. Some degree of traumatic pericarditis is found during surgery or at autopsy in many patients sustaining severe blunt trauma of the chest. Penetrating wounds to the heart usually cause laceration of the pericardium and the myocardium, with secondary pericarditis and pericardial infections. Although the exact incidence is unknown, infection, tamponade, myocarditis, and inflammatory pericarditis may occur. An immune pathogenesis is suggested by the development of cardiac autoantibodies, although these autoantibodies are common after injury, even in patients who do not develop pericarditis.

Clinical Features, Diagnostic Testing, Management, and Disposition

Symptoms and signs of postcardiac injury syndrome include pericardial rub, fever, and chest pain. Although the diagnosis is usually established clinically, confirmation by echocardiography is helpful. The interval between injury and the onset of pericarditis ranges from 4 to 12 days. During hospitalization, purulent pericarditis should be considered as a possible source of febrile illness in a trauma patient with multisystem organ failure.

Most patients respond to aspirin or NSAIDs. Uncomplicated pericarditis secondary to blunt trauma usually resolves.

NEOPLASTIC PERICARDIAL DISEASE

Principles

Malignant pericardial tumors typically manifest late, which complicates diagnosis and treatment. Malignant involvement of the pericardium is observed in up to 31% of cancer autopsies. The most common associated cancers are lung (30%), breast (23%), lymphoma (17%), and leukemia (9%). Primary malignancies of the pericardium are rare.[17]

The pattern of cardiac involvement by a malignant tumor is determined by the heart's lymphatic drainage system. Malignant pericardial effusions contribute directly to the patient's death—in most cases from cardiac tamponade. Although the underlying disease process is often advanced when tamponade develops, the patient's quality of life can usually be improved if tamponade is treated promptly.

Clinical Features and Diagnostic Strategies

Primary cardiac neoplasms initially cause symptoms consistent with pericarditis.[18] The typical course is that of an acute pericarditis that resolves then recurs. Malignant pericardial disease is difficult to diagnose. Most patients are asymptomatic or have nonspecific symptoms, such as shortness of breath, cough, palpitations, ill-defined chest pain, weakness, dizziness, hiccups, or fatigue.

The diagnostic evaluation includes an echocardiogram, computed tomography (CT), or magnetic resonance imaging (MRI). Pericardial fluid cytology is recommended if the underlying malignancy is undiagnosed.

Management and Disposition

Treatment may include pericardiocentesis, local instillation of sclerosing or chemotherapeutic agents, systemic chemotherapy, cardiac radiation, and pericardial window.[19] The method chosen depends on the primary tumor and the patient's expected length of survival. Prognosis is poor and directly related to the type and extent of the primary cancer.

RADIATION-INDUCED PERICARDITIS

Fewer than 5% of patients treated with radiation therapy develop pericarditis. The incidence has decreased with improved radiation therapy techniques and is seen most commonly in patients with lymphoma or breast cancer. The percentage of pericardial volume irradiated and the dosage determine which patients develop pericarditis. Tumor recurrence should be considered.

PERICARDIAL DISEASE RELATED TO CONNECTIVE TISSUE DISORDERS

Pericarditis occurs in approximately one-third of patients with rheumatoid arthritis, usually within 3 years of the initial diagnosis, and is rarely clinically significant. Occasional patients develop effusions, constrictive pericarditis, or cardiac tamponade. Prednisone is the initial treatment.

Pericarditis, usually with effusion, is found at autopsy in more than 50% of patients with systemic lupus erythematosus (SLE). The effusion is usually thick and fibrinous. Either cardiac tamponade or constrictive pericarditis may develop. Lupus erythematosus cells may be identified in pericardial fluid specimens. Corticosteroid or NSAID therapy is indicated.[20]

Other connective tissue diseases that may cause pericarditis include Sjögren's syndrome, giant cell arteritis, ankylosing spondylitis, Reiter's syndrome, Behçet's disease, systemic sclerosis, and polyarteritis nodosa.

MISCELLANEOUS INFECTIOUS CAUSES OF PERICARDITIS

Other causes of pericarditis include *Rickettsia conorii,* which causes Mediterranean spotted fever (treated with doxycycline), *Mycoplasma pneumoniae* (treated with a macrolide), *Nocardia asteroides* (treated with pericardiectomy and long-term use of antibiotics, such as sulfisoxazole), *Chlamydia trachomatis,* Epstein-Barr virus, cytomegalovirus infection, *Haemophilus actinomycetemcomitans* (treated with chloramphenicol), and coccidioidomycosis (endemic in the southwestern United States). Viral and bacterial causes of pericarditis can coexist, such as varicella-zoster infection superinfected with *Staphylococcus aureus.* Varicella associated superinfections are more common in children.

TUBERCULOUS PERICARDITIS

Tuberculous pericarditis is estimated to occur in 1% or 2% of patients with pulmonary tuberculosis and is associated with high mortality. In Africa, it is the most common cause of pericarditis. Pericardial fluid aspirates reveal acid-fast bacilli by smear or culture (which may require 4 to 6 weeks to become positive) in approximately 50% of cases. Diagnostic evaluation should include assessment for human immunodeficiency virus (HIV). Triple-drug therapy should be started and continued for at least 9 months. Patients do not benefit from oral prednisolone therapy.[21]

OTHER CAUSES OF PERICARDITIS

Amyloid deposition can cause either restrictive cardiomyopathy (RCM) or constrictive pericarditis. Pericarditis can occur rarely as an extra-intestinal complication of inflammatory bowel disease and is independent of the clinical course of the gut disorder. Iatrogenic pericarditis can also occur as a complication of an implantable defibrillator or pacemaker. Bacterial pericarditis can occur after transbronchial needle aspiration or as a complication of endoscopic variceal sclerotherapy. Rarely, pericarditis can also be caused by erosion of a foreign body, such as a sewing needle or toothpick, through the esophagus into the pericardium. Less than 1% of patients with HIV develop acute pericarditis, but 40% have asymptomatic pericardial effusion. This is more frequent in patients in the more advanced stages of HIV infection.

PERICARDIAL EFFUSION

Principles and Clinical Features

The most common causes of pericardial effusion are viral or idiopathic pericarditis, malignancy, uremia, trauma, and radiation therapy. Drug reactions and autoimmune diseases are less common.

Pericardial effusion is often asymptomatic. Patients with known associated conditions (eg, cancer or renal failure) with cough, fever, chest pain, or dyspnea should be considered to have an effusion until proven otherwise.

Diagnostic Testing

A minimum of 200 to 250 mL of pericardial fluid is necessary to produce cardiomegaly on a chest radiograph. Ultrasound is the diagnostic modality of choice (Fig. 72.2). It easily differentiates pericardial fluid from cardiac chamber enlargement and provides information about myocardial wall motion. CT or MRI may be useful when the echocardiogram is technically unsatisfactory. Nuclear scans may be useful to detect purulent pericardial effusions.

Management and Disposition

Pericardiocentesis may be performed for either diagnostic or therapeutic purposes. Common complications include dysrhythmias, pneumothorax, myocardial perforation, coronary or internal mammary artery laceration, and liver laceration. Ultrasound-guided pericardiocentesis is the procedure of choice.[22] Patients requiring pericardial aspiration with pericardiocentesis should be admitted to observation unit or to the hospital for serial examinations and determination of the cause of the pericardial effusion.

CARDIAC TAMPONADE

Principles

Ten percent of all patients with cancer develop cardiac tamponade. Cardiac tamponade should be suspected in patients with penetrating chest wounds. It is also common in patients with uremic pericarditis.

Cardiac tamponade is the result of compression of the myocardium by the contents of the pericardium. This compression is usually caused by fluid. It may be caused by gas, pus, blood, or a combination of substances.

Cardiac tamponade occurs in a physiologic continuum reflecting the amount of fluid, the rate of accumulation, and the nature of the heart. The most important factor in the development of tamponade is the rate of fluid accumulation. The three stages

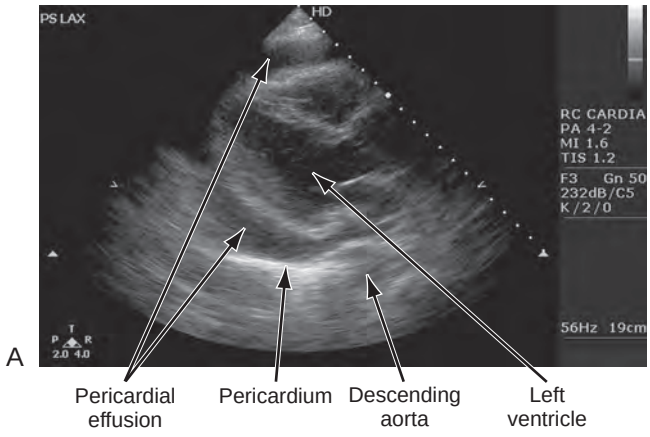

Fig. 72.2. A, Bedside ultrasound showing a pericardial effusion. The effusion is best seen superior to the left ventricle at the top of the image. **B,** The proper technique for emergency department (ED) ultrasound of pericardial effusion. (Courtesy Jessica Resnick, MD.)

necessary for tamponade to develop are (1) fluid filling the recesses of the parietal pericardium, (2) fluid accumulating faster than the rate of the parietal pericardium's ability to stretch, and (3) fluid accumulation that exceeds the body's ability to increase blood volume to support right ventricle filling pressure. The result is increased pericardial pressure, which causes decreased ventricle compliance and decreased flow of blood into the heart. The reduction of blood inflow into the right ventricle results in decreased stroke volume that leads to decreased cardiac output.

The heart initially responds to tamponade by increasing heart rate to maintain cardiac output. This compensatory mechanism is maintained until late in the clinical course, followed by rapid decompensation.

Clinical Features and Diagnostic Testing

Cardiac tamponade symptoms, though often nonspecific, include chest pain, cough, or dyspnea, any of which may be progressive and severe. Dyspnea is the most common.[23] The classic triad described by Beck is hypotension, distended neck veins, and muffled heart sounds. These signs may not be present if tamponade develops quickly.

The chest radiograph may show cardiomegaly but only if there is a large accumulation of fluid (250 mL). The ECG classically shows decreased voltage or electrical alternans (Fig. 72.3). The latter is rare. Ultrasound confirms the diagnosis when effusion and chamber collapse are seen.[24] Cardiac catheterization demonstrates equalization of right and left ventricle pressures.

Management and Disposition

Initial treatment is intravenous fluids to increase right sided filling pressure to overcome pericardial constriction. Pericardiocentesis or pericardial window is the treatment of choice. If tamponade recurs, pericardiocentesis may be repeated, or a drainage catheter may be left in the pericardial space. A pericardiectomy ultimately may be necessary. Cardiac tamponade has a high mortality depending on the severity and nature of the underlying disease, the time course of onset, and the rapidity of diagnosis and

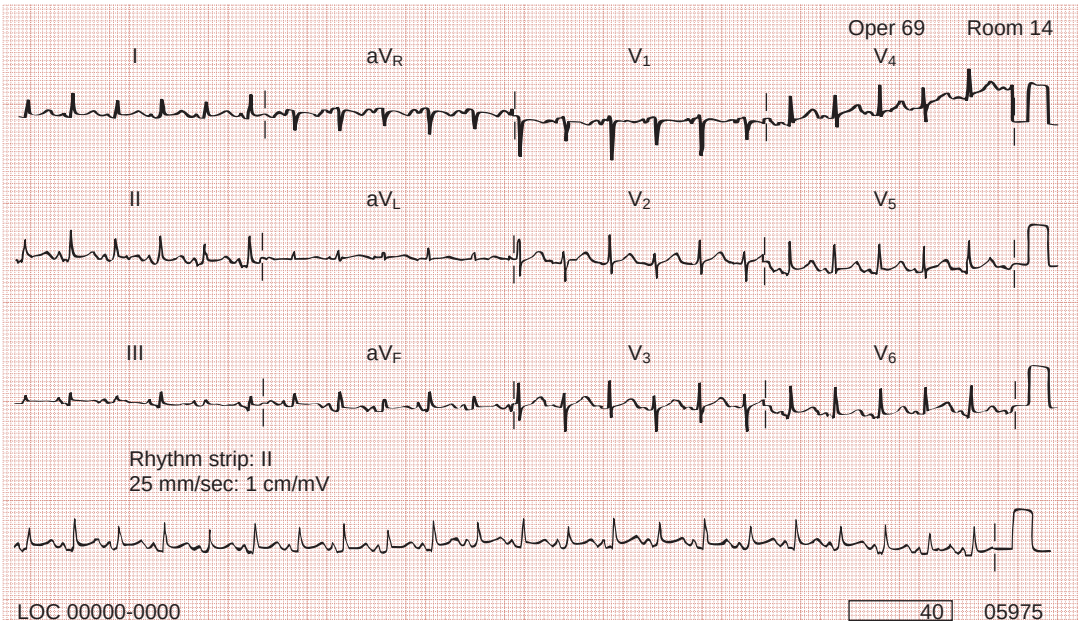

Fig. 72.3. Electrocardiogram (ECG) showing electrical alternans.

intervention. All patients with cardiac tamponade require inpatient management in an intensive care unit (ICU) setting.

PURULENT PERICARDITIS

Principles

Purulent pericarditis is a life-threatening process most commonly seen in a hospitalized patient with systemic illnesses who develops sepsis. It can occur in any age group and can be caused by any type of infectious agent. *Streptococcus* and *Staphylococcus* are the most common. *Candida* pericarditis is found after cardiac surgery and in patients with impaired host defenses or severe debilitating underlying diseases. *Histoplasma* infection occurs in endemic areas, including the Ohio and Mississippi River valleys.

Pathophysiology

Purulent pericarditis occurs by several mechanisms: (1) spread from an adjacent infection, such as pneumonia or empyema; (2) hematogenous spread from a distant site; (3) direct inoculation of bacteria (trauma or procedure); and (4) spread from an intracardiac source. The most common mechanism is spread from a distant site.

Clinical Features and Diagnostic Testing

Purulent pericarditis usually manifests as a febrile illness lasting 2 or 3 days. Common presenting signs include tachycardia, dyspnea, hepatomegaly, elevated central venous pressure, chest pain, friction rub, and leukocytosis. The most common presentation is a hospitalized patient with a serious underlying disease who initially improves after treatment of the primary process but later develops fever, dyspnea, chest pain and a pericardial effusion. The search for a fever source is usually not successful, and the patient gets worse until a pericardial source is considered. Pericardiocentesis is necessary to establish the diagnosis, obtain fluid for microbiologic studies, and relieve cardiac tamponade.

Management and Disposition

Pericardiectomy is the traditional treatment of choice. Indwelling catheters, coupled with lavage, antibiotics, and fibrinolytics, may avoid the need for surgery. Patients require admission for intravenous antibiotics or antifungals and cardiorespiratory monitoring. Fibrinolytic therapy may reduce the rate of constrictive pericarditis when surgery is not an option.[25]

The overall survival rate for purulent pericarditis is approximately 30% with antibiotic therapy alone and 50% when combined with early surgical drainage. In addition to complications related to sepsis and tamponade, long-term sequelae include constrictive pericarditis.

PNEUMOPERICARDIUM

Principles

Pneumopericardium and pyopneumopericardium are rare. Pneumopericardium may be caused by diseases that can lead to formation of fistulae between the pericardial and pleural space, bronchial tree, or upper gastrointestinal tract. It may result from bronchial carcinoma or infection with gas-producing microorganisms, or it can be idiopathic. Pyopneumopericardium may result from trauma, foreign body, ingestion of caustic substances, or invasive procedures.

Spontaneous pneumopericardium is caused by an increase in intra-alveolar pressure above atmospheric pressure, resulting in rupture of alveoli and is associated with myriad causes including asthma, labor, barotrauma from positive-pressure ventilation, or Valsalva maneuvers, including weightlifting, and even recreational drug inhalation from positive-pressure devices (huffing).

Clinical Features and Diagnostic Testing

Physical findings depend on the quantity of fluid and gas in the pericardial space. Heart sounds can be of variable intensity, change depending on body position, and have a metallic quality that may be accompanied by splashing sounds. *Hamman's sign* and *mediastinal crunch* are the terms used for a loud, crunching sound associated with pneumopericardium or pneumomediastinum and is diagnostic for the presence of mediastinal air. The diagnosis of pneumopericardium is confirmed by chest radiograph, CT scan, or ultrasound. Clinical sequelae of tension pneumopericardium are similar to acute cardiac tamponade.

Management and Disposition

Stable patients with uncomplicated spontaneous pneumopericardium may be observed. After all other life-threatening injuries and complications have been excluded, no long-term sequelae are expected. Tension pneumopericardium should be treated with emergency pericardiocentesis.

CONSTRICTIVE PERICARDITIS

Principles and Pathophysiology

Constrictive pericarditis may be a late consequence of acute pericarditis of virtually any cause. The incidence has increased as a result of improved survival in patients with chronic renal disease.

Constrictive pericarditis results from fibrous reaction of the pericardium. The key pathophysiologic feature is impaired diastolic filling from external cardiac compression caused by the thickened pericardium. In advanced cases, the visceral and parietal pericardial layers may be adherent.

Because the pericardium limits volume, ventricular filling is rapid and completed within the first third of diastole, after which left ventricular volume and pressure remain unchanged.

Clinical Features

The symptoms and signs of constrictive pericarditis are identical to those of CHF. Dyspnea, fatigue, and weight gain are the most common complaints. Hepatomegaly, marked pitting lower extremity edema, and ascites can be seen on physical examination. The characteristic auscultatory finding of constrictive pericarditis is a pericardial knock in early diastole. A friction rub may also be heard.

Diagnostic Testing and Management

The diagnosis is considered in a patient with right-sided heart failure symptoms. Heart size on the chest radiograph is typically normal. Pericardial calcification is suggestive when present. Liver function tests are consistent with passive congestion. ECG findings include low QRS voltage, nonspecific ST-T wave abnormalities, and atrial dysrhythmias.

Doppler echocardiography may help differentiate constrictive pericarditis from RCM or cardiac tamponade. There is a quick uptake in chamber filling and a shift in the ventricular septum that are diagnostic.[26] Cardiac catheterization and simultaneous measurement of right ventricular and left ventricular end-diastolic pressures or endomyocardial biopsy may be necessary.

Pericardiectomy is the therapy of choice, although is associated with a mortality as high as 10%.[27]

MYOCARDIAL DISEASES

MYOCARDITIS

Principles

The term *myocarditis* was coined initially by Sobernheim in 1837. Romberg reported the association with scarlet fever and typhus in 1891, and "isolated idiopathic interstitial myocarditis" was described by Fiedler in 1899.

Pathophysiology

Some degree of myocarditis is detected in almost 10% of routine autopsies but is often not recognized clinically. The overall incidence is unknown and probably underdiagnosed. The coxsackie B virus was originally named as the causative organism. The predominant agents in the 1990s were the adenoviruses, followed by parvovirus 19 and human herpesvirus 6 in the 2000s. Any infectious agent can cause myocarditis (Box 72.2). The etiology varies by patient age and region. Worldwide, Chagas' disease is a leading cause, especially in South America.

Myocarditis occurs by (1) necrosis from direct invasion of an offending infectious agent and its replication within or near myocytes, (2) destruction of cardiac tissue from infiltration of host cellular immune components or from cytotoxic effects of host immunity activated by the infectious agent, or (3) the toxic effect of exogenous or endogenous chemicals produced by a systemic pathogen. Three stages of disease have been proposed: (1) acute (early after infection), with viral cytotoxicity and focal necrosis; (2) subacute, in which there is an increase in humoral factors leading to autoimmune injury; and (3) chronic, in which there is diffuse myocardial fibrosis and cardiac dysfunction that may lead to dilated cardiomyopathy (DCM). Traditionally, in children the pathologic changes are more often related to direct viral damage, whereas immunologic changes are more often related to direct viral damage in adults.

Our current understanding of the disease builds on this foundation.[28-29] In the first stage, the type of virus matters. For example, enterovirus enters cells and a single strand RNA is reversely transcribed into positive strand for virus replication. This causes direct myocyte lysis followed by inflammatory changes. Other viruses infect the endothelial cells and cause inflammation. Host injury response, apoptosis and cell remodeling all contribute to the pathophysiology. This heterogeneity of virus and host response partially explains the variable clinical presentations.[30]

The activation T cells and B cells and antibody production begins the second phase. Inflammatory proteins are activated and cardiac autoantibodies develop. There is a higher concentration of anti–β-myosin antibodies in patients with myocarditis and DCM than in controls. Because myocarditis is linked to the development of DCM (up to 16% of cases in adult and 46% in children), idiopathic DCM after myocarditis may be predominantly autoimmune in origin, resulting from either shared antigens or molecular mimicry.[31] The amino acid sequences of the coxsackie B virus and β-myosin heavy chain protein are similar. An immune response to the former yields damage to the latter (molecular mimicry).

BOX 72.2

Infectious Causes of Myocarditis

Adenovirus
Chagas' disease
Coxsackie B virus
Chlamydia
Cytomegalovirus
H1N1 virus
Hepatitis A
Hepatitis B
Hepatitis C
Human herpesvirus 6
Influenza A
Influenza B
Lymphocytic choriomeningitis virus
Mononucleosis
Mumps
Mycoplasma
Parainfluenza
Parvovirus 19
Rabies
Rubeola
Rubella
Streptococcus
Toxoplasma gondii
Varicella zoster
Legionella

Clinical Features

Flulike signs and symptoms, including fever, fatigue, myalgias, vomiting, and diarrhea, are usually the first manifestations of myocarditis. The most common presentation in children is dyspnea. In adults, it is dyspnea, chest pain, and dysrhythmias. Altered vital signs include fever, tachycardia, tachypnea, and, uncommonly, hypotension. Toxic appearance or tachycardia disproportionate to the temperature may be the only physical findings. No symptom or sign is sensitive or specific and cardiac examination is often unremarkable. When chest pain or CHF occurs at initial presentation, the prognosis is worse.

In children, prominent physical findings include grunting respirations and intercostal retractions. Approximately 10% to 15% have rhonchi. Infants often have a fulminant syndrome characterized by fever, cyanosis, respiratory distress, tachycardia, and cardiac failure. When children have ventricular dysrhythmias, myocarditis and idiopathic DCM are commonly seen on endomyocardial biopsy, despite findings of a structurally normal heart by noninvasive studies. Long-term prognosis in children correlates with the severity of their initial presentation.

Diagnostic Testing

Common ECG changes include sinus tachycardia, a widened QRS, and low voltages. There may be a prolonged corrected QT interval, atrioventricular (AV) block, or AMI pattern.

Cardiac troponin may be elevated, although when in the course of the disease is unknown. The prognostic significance of elevation is not known, although one can assume that a higher level correlates with more myocardial damage and a negative troponin does not rule out the diagnosis. The WBC count, C-reactive protein (CRP), and ESR may be elevated or normal and so are not of diagnostic value. The echocardiographic features of myocarditis, although nonspecific, include reduced left ventricular ejection fraction, global hypokinesis, and regional wall motion abnormalities. Contrast-enhanced MRI or nuclear studies may be diagnostic. Acute and convalescent viral titers are positive in less than 40% of cases.

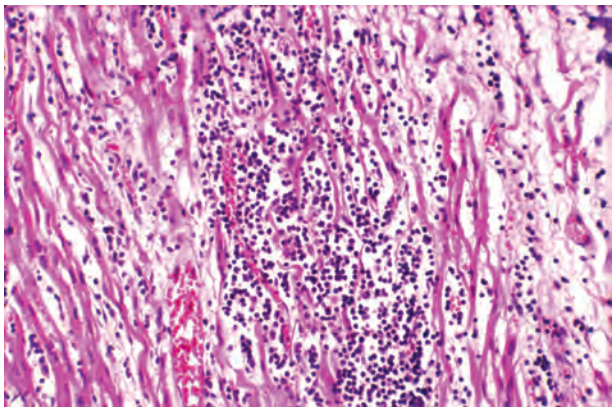

Fig. 72.4. Myocardial biopsy specimen showing myocarditis. Note the lymphocytic infiltrate.

Endocardial biopsy, the historical gold standard, has variable sensitivity and specificity owing to sampling error (Fig. 72.4). Histologic criteria for myocarditis are present in only 5% to 30% of patients with clinically suspected myocarditis and up to half of patients with DCM. Molecular genetic probes, such as polymerase chain reaction assays, are used to supplement standard histologic analysis. In addition, polymerase chain reaction analysis of tracheal aspirates of intubated patients with myocarditis shows a correlation with endocardial biopsy. Because of the limitations of biopsy, magnetic imaging may become the diagnostic test of choice and the next gold standard.[31]

Differential Diagnosis

Myocarditis can masquerade as AMI with severe chest pain, ECG changes, elevated cardiac markers, and heart failure. Patients with myocarditis are usually young and have few risk factors for coronary artery disease. ECG abnormalities may extend beyond the distribution of a single coronary artery. There may be global, rather than segmental, wall motion abnormalities on echocardiography. In myocarditis, chest pain continues, but there are no further ischemic ECG changes. The diagnosis of myocarditis should also be considered in an otherwise healthy patient with symptoms and signs of new CHF or dysrhythmias. Coronary angiography is usually normal in myocarditis, which should prompt consideration of endomyocardial biopsy.

Management

Treatment is supportive and aimed at preserving left ventricular function. This may extend from simple limitation of activity to rhythm and CHF treatment, extracorporeal membrane oxygenation, ventricular assist devices, and eventual cardiac transplantation.

Therapy is stage specific. In the first phase, demonstration of replicating virus suggests that early antiviral agents, such as beta-interferon or ribavirin, may be effective.[32] Unfortunately, the diagnosis is often made after the initial viral phase. Agents active at the coxsackievirus/adenovirus receptor present an intriguing theoretic approach.

Multicenter trials of immunosuppressive therapy for the subacute phases have shown no benefit.[33] Efforts to identify patient and treatment subsets in which immunosuppressive therapy may be beneficial are ongoing. Many researchers believe that there is a place for immunotherapy despite the evidence to date.[32] High-dose immunoglobulin therapy may be associated with improved recovery of left ventricular function and better survival during the first year after presentation in a pediatric population.

In the chronic stage, CHF symptoms predominate and standard pharmacologic treatment for CHF is indicated. In some cases, the deterioration of cardiac function is reversible with the aid of a ventricular assist device. These devices have been used successfully over extended periods, including up to 70 days. Their use should be considered before transplantation, because some patients recover enough function to avoid transplantation.

Disposition

All patients should be admitted to the hospital to a monitored bed, and those with persistent hemodynamic instability require intensive care. Complications of myocarditis include ventricular dysrhythmias, left ventricular aneurysm, CHF, and DCM.

The mortality rate is 20% at 1 year and 50% at 5 years, despite optimal medical management and has not changed in over 25 years. Ejection fraction and right ventricular function 1 year after initial presentation may be the best predictors of subsequent survival. The long-term prognosis in survivors is variable.

Patients who undergo transplantation because of myocarditis have decreased 1-year survival compared with patients who undergo transplantation for other reasons including a higher allograft rejection rates. The overall 5-year survival rate for children is 70%.

CHAGAS' DISEASE

Principles and Clinical Features

Chagas' disease is one of the leading causes of myocardial disease in many countries, particularly Central and South America. Chagas' disease is caused by the protozoan *Trypanosoma cruzi* with transmission by insect vectors.

Most seropositive patients never develop symptoms. Acute infection presents as a nonspecific viral-like illness, then latent phase, then cardiac phase with conduction abnormalities, and then DCM. Systemic symptoms include fever, hepatic or splenic enlargement, and unilateral periorbital edema. Cardiac manifestations include angina-like chest pain, dysrhythmias, embolic episodes, heart failure, conduction abnormalities, multifocal ventricular premature contractions, and abnormal ST segment and T wave abnormalities. Ventricular tachycardia is common and considered by some to be a hallmark of disease.[34] Syncopal or near-syncopal episodes occur in nearly two-thirds of patients.

Diagnostic Testing

Serum testing for parasites establish the diagnosis, as does measuring anti-IgG for *T. cruzi.* Chagas' disease should be considered in patients with new cardiac symptoms and a Latin American travel or immigration history. Echocardiography may show a left ventricular apical aneurysm or scar, which is a reliable marker of the disease.

Management

Chagas' disease is treated with variable success by the antitrypanosomal drugs benznidazole and nifurtimox. These are available from the Centers for Disease Control and Prevention (CDC). Amiodarone may be useful to treat ventricular tachycardia. An angiotensin-converting enzyme (ACE) inhibitor may be useful for CHF. Up to 30% of patients develop CHF from 5 to 30 years after initial infection.[35] Increased world attention, with elimination of the vector and improved blood donation screening, especially for platelet transfusions, is decreasing the incidence of this disease.

TRICHINOSIS

Trichinosis is caused by ingestion of the cysts of *Trichinella spiralis* in undercooked meat. Historically, pork was the most commonly implicated meat, but *Trichinella* has been eradicated for many decades from commercial domestic pork in the United States. It is most likely caused by wild game in the United States. The acute illness consists of fever, myalgias, muscle tenderness, neck stiffness, and a characteristic periorbital edema. Laboratory studies reveal an eosinophilia and often elevated creatine phosphokinase.

Myocardial involvement is present in approximately 20% of clinically diagnosed cases and appears in the second or third week of illness, when other symptoms are declining. Cardiac manifestations include chest pain, dyspnea, cardiomegaly, dysrhythmias, and CHF. ECG findings, such as nonspecific ST-T wave abnormalities and conduction blocks, may appear transiently, even in the absence of cardiac symptoms.

The diagnosis is usually established with serologic studies or biopsy of any symptomatic muscle group. Treatment usually involves corticosteroids together with anthelminthic drugs, such as albendazole and mebendazole.

DIPHTHERIA

Myocardial involvement is clinically evident in 10% to 25% of cases and is the major cause of death. Early signs of myocarditis are tachycardia and faint heart sounds. Cardiac enzymes are often elevated. Prolongation of the PR interval and ST-T wave abnormalities occur early in the course of the disease. Bundle branch block or complete heart block, when they occur, precede total circulatory collapse and are associated with a poor prognosis. Treatment with oral carnitine is associated with a lower incidence of mortality, heart failure, and severe conduction blocks. Diphtheria is rare in the United States.

LYME DISEASE

Epidemiology and Clinical Features

Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi*. Lyme disease–related carditis occurs weeks to months after the onset of erythema migrans. Cardiac complications occur in 4% to 10% of patients, most commonly a conduction delay, caused by a reversible effect on the AV node. Pericarditis and CHF also occur.[36]

Lyme disease–related carditis should be suspected in otherwise healthy persons with unexplained heart block and potential exposure to ticks in an endemic area. Lyme disease is diagnosed by identification of the spirochete with serologic testing. A screening ECG should be performed whenever the diagnosis of Lyme disease is suspected.

Temporary pacemaker placement is often required in unstable patients. Antibiotic therapy with intravenous penicillin or oral doxycycline is effective and can reverse AV block. Erythromycin should be prescribed in place of tetracycline in young children. Ceftriaxone is also effective. Most patients recover completely, and a permanent pacemaker is rarely needed.

OTHER CAUSES OF MYOCARDITIS

The cardiac manifestations of acquired immunodeficiency syndrome (AIDS) are diverse and cause death in at least 6% of patients with HIV. The prevalence of left ventricular dysfunction in adult AIDS patients is approximately 20%. Myocarditis is described in approximately 46% of AIDS patients undergoing postmortem examination. HIV treatment may also lead to cardiac toxicity. Pentamidine can cause torsades de pointes ventricular tachycardia. Zidovudine and dideoxyinosine also can lead to cardiac dysfunction.

Cardiac involvement with *Legionella pneumophila* is uncommon, although the heart may be the only affected organ. Clinical symptoms resemble pericarditis and myocarditis, including dysrhythmias and conduction blocks. After treatment with erythromycin, normal cardiac function may return.

Cardiac *Toxoplasma* infection may lead to clinically significant disease. Infection is well described in recipients of bone marrow and cardiac transplantation. Immunocompromised patients with toxoplasmic myocarditis may have bundle branch block, CHF, pericarditis, and dysrhythmias as a result of lesions in the conducting system. Untreated toxoplasmic myocarditis is fatal.

Myocarditis associated with *M. pneumoniae* may be caused by direct invasion of the myocardium, an autoimmune mechanism, or intravascular coagulation. Miliary tuberculosis, including tuberculosis myocarditis, can produce granulomas within the myocardial conduction system that can precipitate fatal dysrhythmias. Sudden death can occur secondary to *Chlamydia pneumoniae* myocarditis. Myocarditis, presumably mediated by exotoxin, is associated with *Shigella* infection. Cardiac involvement of the conduction system and the pericardium also may occur in dermatomyositis and polymyositis. Patients are usually asymptomatic, but pericarditis, myocarditis, and dysrhythmias can occur.

Myocarditis can also occur with chemotherapeutics, most notably doxorubicin, which can cause both acute and chronic cardiotoxicity. Manifestations of acute cardiotoxicity include dysrhythmias, pericarditis, myocarditis, and left ventricular dysfunction.

COCAINE CARDIOTOXICITY

Cocaine causes ischemia, myocarditis, and DCM. Myocarditis is a common autopsy finding in patients with cocaine abuse. The mechanism is largely unknown. Theories include increased sympathomimetic effect, severe oxidative stress, and metabolite interaction with ion channels.[37] Cocaine has a direct, negative inotropic effect on cardiac muscle. It is the cause of many deaths. Patients who die with detectable cocaine levels have myocarditis and myocardial contraction bands more often than controls. The severity correlates with the serum and urine concentrations of cocaine. This may supply the anatomic substrate for ventricular dysrhythmias.

CARDIOMYOPATHIES AND SPECIFIC HEART MUSCLE DISEASE

Principles

Cardiomyopathies are a heterogeneous group of diseases associated with mechanical or electrical dysfunction.[38] They usually exhibit inappropriate ventricular hypertrophy or dilation and have a variety of causes. Many of these diseases result from genetic mutations.

Pathophysiology

A variety of pathologic processes may initiate myocyte injury. When injury occurs, common pathophysiologic pathways are activated. These pathways involve neurohumoral factors, immune factors, and cytokines that cause myocyte dysfunction with subsequent remodeling, either hypertrophy or dilation. There is an increase in interstitial fibrosis that impairs ventricular filling and leads to increased metabolic demand. At a cellular level, the pathophysiologic derangement may be the troponin complex, intracellular concentration of calcium, myocardial subproteins, or the sarcomere. These lead to alteration in the myocytes ability to

contract, which causes clinical pathology. The cardiac microvascular circulation also changes and is an independent predictor of morbidity and mortality. Although traditionally defined by organ level pathology, the classification of cardiomyopathies may evolve into a unified theory that shows all types of cardiomyopathy to be variations of a common genetic, anatomic, and humoral pathophysiologic processes. The exact correlation between genotype, phenotype, and clinical presentation is unknown, as is the point when changes at the molecular level transition from compensatory to pathologic.

DILATED CARDIOMYOPATHY

Principles

DCM is a spectrum of disorders that have in common a dilated and failing heart. The incidence of DCM is estimated to be 5 to 8 cases per 100,000 adults and 0.57 cases per 100,000 children.[39] Many cases previously thought to be of unknown cause may be genetic or secondary to infection. Myocarditis is the most common cause of DCM in children. The true incidence is probably underestimated because many asymptomatic cases remain undiagnosed. Thirty percent to 40% of cases have a genetic cause. More than 35 gene mutations have been discovered, primarily coding for cytoskeleton or sarcomere proteins.[40]

DCM affects men more than women, African Americans more than whites, and may occur in any age group, with 40 to 65 years old being the most common. Risk factors include ethanol and tobacco abuse, pregnancy, hypertension, and infection.

Pathophysiology

There are both primary and secondary causes. Possible pathophysiologic causes include myocardial inflammation mediated by cytokines, macrophages, and natural killer cells; local inflammation caused by the release of cytokines by infiltrating lymphocytes; direct reaction of antibodies with receptors on myocardial muscle; toxins, such as ethanol, impairing myocardial biochemical processes; and loss or dysfunction of myocardial matrix proteins. The result is impaired myocardial force generation, which initiates a vicious cycle that increases the burden on the remaining cells that leads to increased stress, more work, and more cell death. There may also be a genetic predisposition to the pathology involved.[41]

Clinical Features

Symptoms have an insidious onset. Left-sided heart failure occurs as the initial manifestation in 75% of adults, with dyspnea (usually with exertion or while supine) being the major symptom. Exacerbation of coronary artery or renal disease, dietary indiscretion, and medication noncompliance are key contributors. CHF symptoms are the most common presentation in children. Chest pain on exertion is the initial symptom in 10% of adults, and systemic or pulmonary emboli are the initial manifestation in 4%. Right-sided heart failure is a late and ominous sign.

Diagnostic Testing

ECG findings are nonspecific and may include poor R wave progression, intraventricular conduction delay, or a left bundle branch block. Holter monitoring may show frequent premature ventricular contractions and occasional ventricular tachycardia. Sudden death is uncommon. The chest radiograph reveals cardiomegaly.

Echocardiography shows left ventricular dilation, reduced systolic function, and variable wall motion abnormalities. Abnormal ventricular contractility defines DCM, and an ejection fraction less than 45% is required for diagnosis. End-diastolic and systolic volumes are increased, as are pulmonary capillary wedge pressure and central venous pressure.

Endomyocardial biopsy may also be necessary, although histologic abnormalities are nonspecific. New histochemical, immunologic, and molecular biologic techniques improve the diagnostic yield, especially for infectious causes. MRI may help. Right-side failure should have occult atrial septal defect ruled out. Because many patients may have a genetic defect, obtain a family history and consider genetic counseling.[42]

Management and Disposition

Therapy includes supportive measures, such as adequate rest, weight control, abstinence from tobacco, moderate salt and ethanol consumption, and structured physical activity. Medical treatment includes standard measures for CHF.

ACE inhibitors reduce morbidity and mortality. Isosorbide dinitrate and hydralazine, spironolactone, and the angiotensin receptor-blocking agents also prolong survival. Beta-blockers can reduce symptoms and improve left ventricular function, functional capacity, and survival. In addition, the improvement in cardiac function associated with beta-blockers is associated with changes in expression of genes encoding for alpha- and beta-myosin heavy chain and sarcoplasmic reticulum calcium adenosine triphosphate.

Implantable defibrillators improve survival and should be considered in patients with an ejection fraction less than 30% or symptoms for more than 9 months. Antidysrhythmics are not usually effective. There is encouraging research indicating that stem cell transplant may improve survival.[42]

Outcome

Patients with DCM show progressive deterioration. Because medical therapy usually fails, DCM is the leading indication for cardiac transplantation. Mortality is 18% by 1 year, 35% by 5 years, and 50% by 10 years. The clinical course for children is variable, with a better prognosis in young children. Some children show delayed, spontaneous, and unexplained improvement.

HYPERTROPHIC CARDIOMYOPATHY

Principles

Hypertrophic cardiomyopathy (HCM) is a complex disorder with variable clinical manifestations. The prevalence is estimated to be 1 in 500 persons in the general population. It affects all races, men and women equally, and can manifest at any age. It is the most commonly inherited cardiac disease.[42]

Pathophysiology

HCM is a disease involving abnormalities of heart muscle at the anatomic, cellular, and genetic levels. Specifically, it is a genetic disease of sarcomere proteins.[43] The defining anatomic feature of HCM is a hypertrophied left ventricle in the absence of another cause. The dimensions of both ventricles are small or normal. Atrial dilation is common. Ventricle thickening is usually asymmetrical and varied. It involves the septum more than the free wall. The extent of hypertrophy correlates with the manifestation of the disease. Histologically, individual muscle cells are hypertrophied, with a disorganized, characteristic whorled pattern and fibrous scar tissue. Sarcomere disarray is the histologic hallmark.

HCM is an autosomal dominant disease caused by mutations in genes that encode for sarcomere contractile proteins.

Twenty-three genes and more than 470 different mutations have been identified. More than 18 of these genes code for sarcomere proteins, including a mis-sense mutation for β-myosin heavy chain (which constitutes 30% of myocardial protein), as well as myosin-binding protein C and troponin T. Because many genes are involved, there are many clinical expressions of the disease.[39,44]

The hypertrophy in HCM may be a compensatory response to the cardiac protein abnormalities. In vitro studies show that mutant β-myosin heavy chain protein exhibits impaired contractility and disrupts the normal sarcomere. The usual cardiac response to physiologic stress is hypertrophy, dilation, or both. Gene mutations lead to abnormal proteins, changed cellular structure and impaired function owing to fibrous changes in the sarcomere. This compensatory tissue hypertrophy manifests as HCM.

Patients with HCM have an abnormal echocardiogram or cardiac MRI that shows asymmetric left ventricular hypertrophy and hyperdynamic ventricles. There may be outflow obstruction, which usually occurs with exertion. The thickness of the ventricles and degree of outflow obstruction reflect the amount of fibrous changes and correlate with disease severity.[41] The pathophysiology involves impaired ventricular filling during diastole.

Genetic studies of families with HCM identify specific mutations that correlate with sudden cardiac death. In families with Arg403Gln mutation, less than half of affected family members survive past 45 years old. Genetics alone does not account for the clinical manifestation of HCM, because patients with the same genotype differ in phenotypic expression and clinical course.

Clinical Features

Although HCM occurs at all ages, the average age at diagnosis is between the ages of 30 and 40 years old. Approximately 2% of cases are diagnosed in children younger than 5 years old, 7% are diagnosed before 10 years old, and presentations vary widely. It may be found in relatives of patients who have HCM.

Often, the first presentation of disease is sudden death, which most commonly occurs during periods of exertion, and HCM gained notoriety after the press coverage of the sudden deaths of several young athletes. For patients who do not initially experience sudden death, 90% will have a presenting complaint of shortness of breath. Other symptoms include chest pain, syncope, near-syncope, and palpitations. Large-scale ECG screening of young athletes occurs in Italy, although it is controversial and most likely would not be cost-effective in the United States.[45-47]

Physical examination may reveal a loud S_4 gallop and a harsh crescendo-decrescendo midsystolic murmur. This murmur is accentuated by the Valsalva maneuver or changing from a standing to a squatting position. Other physical findings may include a bifid arterial pulse, paradoxical splitting of the second heart sound, and, rarely, a mitral leaflet septal contact sound, which are all difficult to hear in a busy ED. Many dysrhythmias are seen in HCM, including premature atrial and ventricular contractions, multifocal ventricular ectopy, and ventricular tachydysrhythmias with atrial fibrillation being the most common. In the ED, the diagnosis should be considered in anyone with a family history, characteristic murmur, and cardiopulmonary symptoms not explained by other life-threatening conditions.

Diagnostic Testing

Patients with suspected HCM should have an ECG, chest radiograph, and echocardiogram. The ECG is abnormal in approximately 90% of patients. The most common abnormalities are left ventricular hypertrophy, ST segment alterations, T wave inversion, left atrial enlargement, abnormal Q waves, and diminished or absent R waves in the lateral leads. The chest radiograph may be normal or may show left ventricular or atrial enlargement.

Echocardiography is the most important clinical diagnostic strategy. Findings include asymmetrical left ventricular hypertrophy, left ventricular outflow tract narrowing, a small left ventricular cavity, and reduced septal motion. The dynamic characteristic of HCM distinguishes it from the discrete forms of obstruction to ventricular flow. Doppler techniques help assess the severity of this obstruction at rest and with provocative maneuvers. Left ventricle obstruction at rest is an independent predictor of heart failure. Magnetic resonance is helpful when the echocardiogram is not, including assessing risk for sudden death.[48-49] Electrophysiologic studies may show dysrhythmias but are not more predictive of sudden death than clinical factors. Cardiac catheterization may be necessary to confirm the diagnosis. Genetic screening may be helpful to predict other family members at risk.

Differential Diagnosis

HCM mimics many disorders. In individuals with murmurs, HCM may be confused with valvular diseases or a ventricular septal defect. In the absence of a murmur, symptoms may suggest mitral valve prolapse, primary pulmonary hypertension, or coronary artery disease. ECG changes, without a history of preceding MI, may also suggest HCM.

Management

Beta-blocker therapy is the mainstay of therapy. They modulate the effect of catecholamines on the outflow gradient which prolongs diastole, increases ventricular filling, and results in symptomatic improvement and exercise tolerance. Calcium channel blockers are also useful. Verapamil reduces obstruction, decreases contractility, and improves diastolic relaxation and filling. Verapamil is contraindicated when conduction blocks are present. Disopyramide may be added if beta-blockers fail.

Nitroglycerin, the traditional initial ED management for chest pain, should be avoided in HCM-associated chest pain because it decreases ventricular volume. Amiodarone is the drug of choice for treatment of ventricular dysrhythmias and atrial fibrillation. Phenylephrine and intravenous fluids are the choices for hypotension. Implantable cardioverter defibrillators are indicated for patients with sudden death or a risk factor for it.

Surgical treatment is reserved for patients with large (>50 mm Hg) systolic gradients, severe symptoms, and poor quality of life who do not respond to medical therapy. The most common procedure is septal myomectomy. Dual-chamber pacing decreases outflow gradient and improves symptoms, but it does not improve outcome.

Disposition

The natural history of HCM is variable and probably reflects the many different genetic causes. The annual mortality rate is 0.7%. The clinical course is either heart failure, atrial fibrillation, or sudden death.[50]

The onset of atrial fibrillation in patients with HCM may precipitate marked hemodynamic compromise and severe CHF. Cardioversion and rate control should be attempted. The risk of stroke is high and anticoagulation is indicated.

Risk factors for sudden death include malignant genotype, unexplained syncope, sudden death in first-degree relatives, abnormal blood pressure response to exercise, greater than 30-mm ventricular thickening and non-sustained ventricular tachycardia.[42] These factors all reflect the extent of interstitial fibrosis.

Patients with HCM initially diagnosed in the ED should have strenuous physical activity specifically proscribed until the patient

has been evaluated by a cardiologist. Patients with HCM who have angina, syncope, near-syncope, dysrhythmias, and abrupt hemodynamic changes should be hospitalized.

RESTRICTIVE CARDIOMYOPATHY

Principles

RCM is a gradual and progressive limitation of ventricular filling secondary to myocardial infiltration. RCM is the least common type of cardiomyopathy, accounting for less than 5% of all cases. The most common cause in the United States is amyloidosis. Other causes include sarcoidosis, hemochromatosis, scleroderma, neoplastic cardiac infiltration, glycogen storage disorders, Fabry's disease, Gaucher's disease, and mutations related to myocardial muscle proteins.

Pathophysiology

Restriction of ventricular filling results in low ventricular volumes, high end-diastolic ventricular pressures, and decreased cardiac output. Systolic function is maintained. Grossly, there is atrial enlargement and small ventricles. As the disease progresses the ventricular cavities may become obliterated by fibrous tissue, scarring, or thrombus.

Clinical Features and Diagnostic Testing

Symptoms are those of worsening diastolic dysfunction and include exercise intolerance (cardiac output cannot be increased because ventricular filling is compromised), elevated central venous pressure, peripheral edema, pulmonary edema, and S_3 and S_4 gallops. Children demonstrate failure to thrive.

Differentiation from constrictive pericarditis requires CT, MRI, or Doppler echocardiography. Pericardial calcification favors a diagnosis of constrictive pericarditis over the diagnosis of RCM. Myocardial biopsy may be necessary.

Management and Disposition

Most of the underlying causes of RCM are untreatable. The exception is hemochromatosis. Symptomatic treatment with vasodilators and diuretics may help. Patients with RCM should be maintained in sinus rhythm, because loss of the atrial contribution to cardiac output results in hypotension. Transplantation is a possibility in some patients with better survival than controls. RCM is relentless, with 90% of patients dying within 10 years of diagnosis.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic disease with ventricle scarring. Myocytes are replaced by fibrous or fatty tissue. Up to 75% of the time the left ventricle is also involved. ARVC is autosomal dominant with incomplete penetrance and variable expression. The genes responsible for ARVC code for the proteins of the intercalated discs of cardiac myocytes. ARVC is clinically characterized by dysrhythmias, palpitations, syncope, sudden death, and heart failure. ECG shows wide QRS, left bundle branch pattern, and inverted T waves. MRI may show scarring and direct confirmatory biopsy. Treatment is exercise avoidance. Dysrhythmias should be treated with amiodarone and sotalol. An implantable cardioverter-defibrillator (ICD) should be used. Evidence shows that outcomes are not improved by cardiac ablation. Patients and relatives should be sent for genetic counselling.[41,51]

PERIPARTUM CARDIOMYOPATHY

Principles

Peripartum cardiomyopathy (PPCM) is uncommon and represents less than 1% of the cardiovascular problems associated with pregnancy. PPCM is defined as an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricle systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found.[52] The cause of PPCM is unknown. Risk factors include myocarditis, excessive use of tocolytics, preeclampsia, advanced maternal age, multiparity, twins, obesity, cocaine use, and genetic predisposition.[53] The incidence is estimated to be 1 case of PPCM per 13,000 to 15,000 live births.

Clinical Features and Diagnostic Testing

PPCM is clinically identical to DCM. Patients usually have symptoms of CHF but may also have chest pain, palpitations, or thromboembolism. Physical examination often reveals tachycardia, tachypnea, pulmonary rales, an enlarged heart, and an S_3 heart sound.

The ECG may show left ventricular hypertrophy or nonspecific ST-T wave changes. On echocardiography, all four chambers are enlarged with reduction in left ventricular systolic function.

Management and Disposition

Treatment of PPCM includes limitation of physical activity, beta-blockers, alteration of preload with nitrates and diuretics, increase in ventricular contractility, and afterload reduction. ACE inhibitors and angiotensin receptor blockers should be avoided, if possible, in pregnancy and during breast-feeding. Hydralazine and labetalol are effective choices.

Subsequent pregnancies have a 33% to 50% recurrence and high mortality rate. Mortality for PPCM in the United States is approximately 2%. Half of the survivors have complete or near-complete recovery of cardiac function within the first 6 months. Patients who do not recover completely show either continuous clinical deterioration or persistent left ventricular dysfunction. Factors associated with favorable prognosis include small left ventricle diastolic dimension (<5.5 to 6.0 cm), elevated systolic function (ejection fraction >30% to 35% and fractional shortening >20%) at the time of diagnosis, absence of troponin elevation and absence of left ventricular thrombus.[52] In the ED, patients with signs of hemodynamic instability or failure to maintain oxygenation should be admitted for treatment and fetal monitoring.

TAKOTSUBO CARDIOMYOPATHY

Principles

Takotsubo cardiomyopathy (TCM), also known as *stress cardiomyopathy, broken heart syndrome,* or *tako-tsubo cardiomyopathy,* was first reported from Japan in 1991 (Box 72.3). In Japanese, *tako-tsubo* means octopus trap. The term was used because the cardiac abnormality observed in this disease resembles that of the device used to catch octopi.[54] There have been hundreds of cases reported in the medical literature since that time. The pathophysiology of TCM is a sudden temporary myocardial weakening. The exact mechanism is unknown. Speculated causes include stress hormones, microvascular spasm, focal myocarditis, and cellular level muscle changes. It may not be correct to think of TCM as a cardiomyopathy, because the triggers lie elsewhere and the cardiac effect is the outcome.[55]

BOX 72.3

Published Causes of Takotsubo Cardiomyopathy

Achalasia
Addison's disease
Anaphylaxis
Anesthesia
Asthma
Chemotherapy
Closed head injury
Depression
Diarrhea
Diving
Emotional stress
Foley catheter insertion
Hanging
Hypoglycemia
Inferior vena cava clot
Lightning strike
Multiple traumas
Myocardial infarction (MI)
Near drowning
Opioid withdrawal
Pancreatitis
Pheochromocytoma
Pneumopericardium
Pregnancy
Seizures
Sepsis
Sexual intercourse
Stress testing
Subarachnoid hemorrhage
Surgery or medical procedures
Abdominal aneurysm repair
Bronchoscopy
Carotid endarterectomy
Colonoscopy
Esophagogastroduodenoscopy (EGD)
Electroconvulsive therapy
Epidural anesthesia
Mitral valve replacement
Radiofrequency ablation
Sclerotherapy
Thrombotic thrombocytic purpura
Thyrotoxicosis
Transient ischemic attack
Tricyclic overdose
Vomiting

Clinical Features and Diagnostic Testing

TCM presents in menopausal females after an emotional stress. Symptoms include chest pain and dyspnea on exertion. Almost 90% of cases involve women.[56] ECG is often consistent with an anterior MI. There are transient Q waves and ST elevation. Later, the ECG shows T wave inversion and a prolonged QT interval. Cardiac enzymes are elevated slightly and resolve to normal quickly. Coronary artery angiography shows no—or very little—disease. It is assumed that coronary artery spasm plays a role on some level. The diagnosis is made by left ventricular angiography or echocardiography that shows a ballooning of the apex during the acute phase of the disease. The involved area does not match a coronary artery anatomic distribution. MRI can also help establish a diagnosis.[57]

Management and Disposition

In the ED, TCM is not distinguishable from AMI. Patients should be treated the same as any patient with acute coronary syndrome. Long-term treatment includes beta-blockers and ACE inhibitors. Most patients show complete resolution of symptoms and reversal to normal of their left ventricular apex ballooning and contractile function.

ION CHANNELOPATHIES

Principles

Several uncommon dysrhythmic diseases are caused by mutations of genes for ionic channel proteins, which are cell membrane transport proteins for sodium and potassium. These include long QT syndrome, short QT syndrome, and Brugada syndrome. In patients with normal heart anatomy and sudden death, 10% may be caused by a channelopathy, many of which are genetic based. Treatment is medication for rhythm control and referral for an ICD and genetic testing.[58-59]

Sudden Death

Approximately 25% of sudden deaths in patients younger than 21 years old can be attributed to disease of the myocardium. Cardiac causes include myocarditis, HCM, and anomalous coronary artery circulation. Prodromal symptoms are reported in more than half of the patients with cardiac causes, most commonly chest pain (25%) in patients older than 20 years old and dizziness (16%) in patients younger than 20 years old. The distribution of sudden death causes by age is as follows:

- Younger than 20 years old: Myocarditis 22% and HCM 22%
- 20 to 29 years old: Myocarditis 22% and HCM 13%
- 30 to 39 years old: Myocarditis 11% and HCM 2%

Coronary artery disease becomes the leading cardiac cause (58%) of sudden death in people older than 30 years old. HCM and anomalous coronary arteries are seen more often in sports-related deaths.

KEY CONCEPTS

- Pericarditis and myocarditis should be differentiated from acute myocardial infarction (AMI). Acute treatment is with nonsteroidal antiinflammatory drugs (NSAIDs) supplemented with colchicine.
- Cardiac tamponade is suspected in patients with dyspnea, distended neck veins, hypotension, and muffled heart sounds. Diagnosis is by ultrasound. Pericardiocentesis is both diagnostic and therapeutic.
- Myocarditis should be considered in *any* patient with the combination of viral illness symptoms and a new presentation of cardiac disease.
- Patients with newly diagnosed hypertrophic cardiomyopathy (HCM) should avoid strenuous exertion until evaluated by a cardiologist. Beta-blockers are the mainstay of therapy for HCM; nitrates should be avoided.
- Many of the cardiomyopathies have genetic origins. Send patients for cardiology evaluation and genetic testing.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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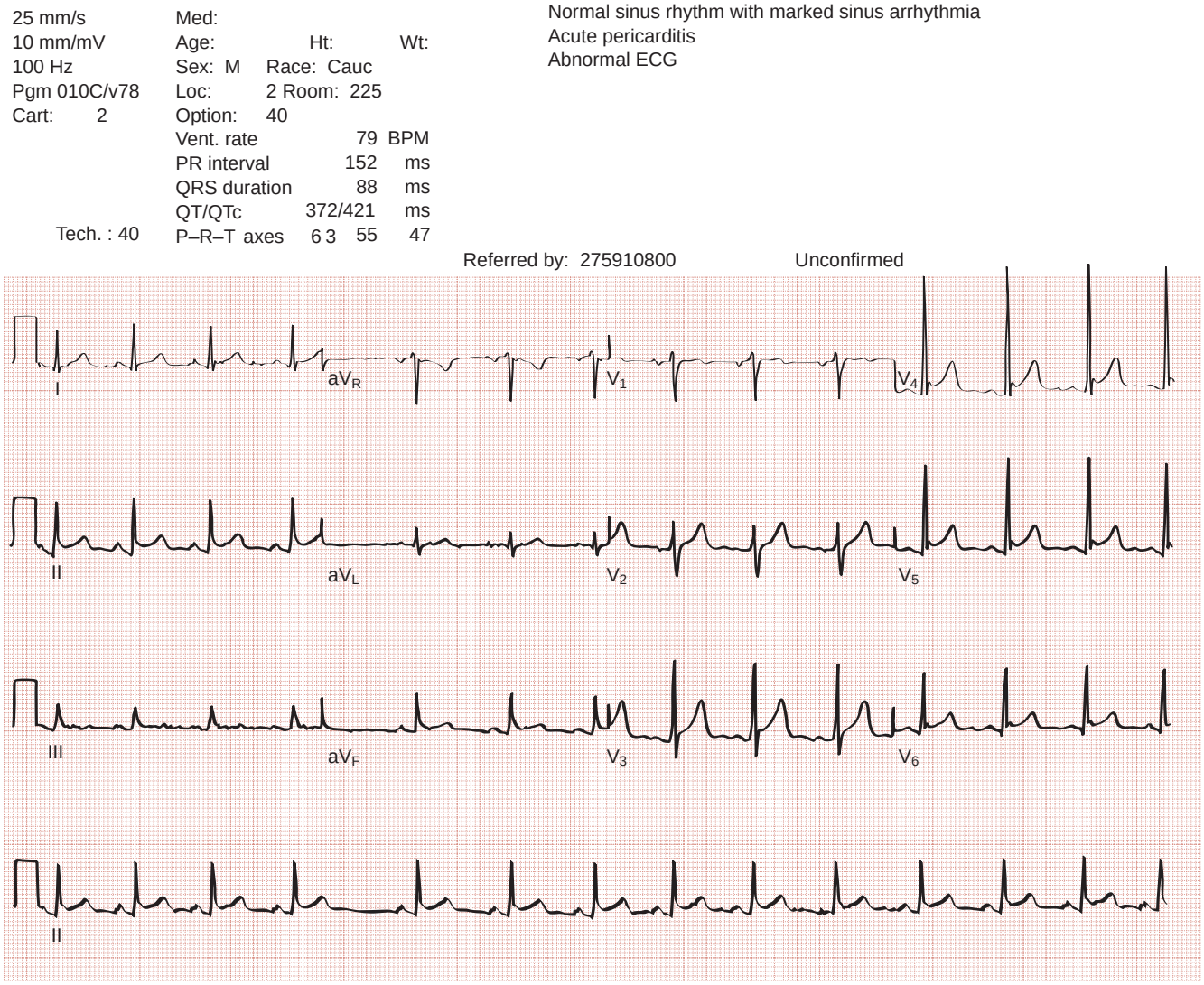
CHAPTER 72: QUESTIONS & ANSWERS

72.1. A 33-year-old man presents with a 4-hour history of left anterior chest pain associated with mild shortness of breath. He is otherwise healthy except for chronic tobacco use. Vital signs are: blood pressure, 142/92 mm Hg; heart rate, 120 beats per minute; respiratory rate, 24 breaths per minute; temperature, 100.4° F (38.0° C) oral; and oxygen saturation, 97%. Physical examination is remarkable only for tachycardia. The patient's electrocardiogram (ECG) is shown below. Which of the following would be the most appropriate therapy?



A. Further decision making after initial troponin evaluation
B. Nitroglycerin, aspirin 325 mg *per os* (by mouth) (PO), cardiology consultation
C. Nonsteroidal antiinflammatory drugs (NSAIDs) and reassurance
D. Reassurance and ibuprofen 800 mg tid for 7 days
E. Thrombolysis

Answer: A. The ECG shows findings consistent with acute pericarditis. Clinically, diffuse ST elevation is seen in leads I, II, II, aV_L, aV_F, and V_2 to V_6. In contrast to finding an acute myocardial infarction (AMI), ST elevations are concave upward in acute pericarditis rather than convex upward as seen with a myocardial infarction (MI). PR depression is also a frequent finding. As the acute pericarditis resolves, ST changes revert to normal, followed by T wave flattening and later deep symmetrical inversion, which may persist. NSAIDs are the mainstay therapy for uncomplicated pericarditis.

72.2. Which of the following statements regarding post–myocardial infarction (MI) pericarditis is true?
A. Classic pericarditis electrocardiogram (ECG) findings are reliably seen.
B. It indicates a greater degree of myocardial damage than those without pericarditis.
C. Large pericardial effusions are common.
D. The incidence of congestive heart failure (CHF) is unchanged.
E. The incidence of dysrhythmias is unchanged.

Answer: B. Both dysrhythmias and CHF are more common in patients who experience post-MI pericarditis. Large effusions are uncommon, and classic pericarditis ECG findings are often overshadowed by the changes of the recent or evolving MI.

72.3. Which of the following disorders is *least* likely to be associated with pericarditis?
A. Giant cell arteritis
B. Rheumatoid arthritis
C. Sjögren's syndrome
D. Systemic lupus erythematosus (SLE)
E. Takayasu's arteritis

Answer: E. Fifty percent of SLE patients have pericarditis discovered at autopsy. Approximately one-third of patients with rheumatoid arthritis and Sjögren's syndrome develop evidence of pericarditis, with the former typically also having rheumatoid

nodules and valvular disease. Giant cell arteritis typically demonstrates a granulomatous myocarditis. Takayasu's arteritis is a large cell vasculitis, typically affecting the aorta and/or its major branches. Pericarditis is very uncommon.

72.4. A 35-year-old woman presents with progressive dyspnea, chest pain, and cough over 5 days. She has a past history of Hodgkin's lymphoma and is 2 years status postchemotherapy and mediastinal irradiation for malignant adenopathy. She is currently on no medications and does not smoke. Vital signs are: temperature, 100.2° F (37.9° C) oral; heart rate, 120 beats per minute; respiratory rate, 26 breaths per minute; blood pressure, 100/60 mm Hg; and oxygen saturation, 96% on room air. Physical examination is remarkable for 3-cm jugular venous distention at 45 degrees, clear lung fields on auscultation, tachycardia without a friction rub, trace pretibial edema, and weak peripheral pulses that disappear during expiration. Chest radiograph shows an enlarged cardiac silhouette and clear lung fields. What would be the most appropriate initial intervention?

A. Endotracheal intubation with rapid sequence induction
B. Enoxaparin 1 mg/kg intravenously
C. Helical computed tomography (CT) scan of the chest
D. Isotonic fluid bolus and emergent cardiac ultrasonography
E. Methylprednisolone 125 mg intravenously

Answer: D. This patient is presenting with pericardial tamponade, presumably malignant because of her history of lymphoma. Radiation pericarditis is also possible, and effusion would be possible in this circumstance. Pulmonary embolus is a consideration but less likely, given the picture of normal oxygen saturation and an enlarged heart. The initial intervention should be fluid loading to maintain venous return and cardiac output, followed by ultrasound confirmation and likely pericardiocentesis. Tracheal intubation is not currently indicated because improvement would be expected after effusion aspiration.

72.5. A 44-year-old man complains of swollen legs. He just finished two courses of prednisone for wheezing related to asthma. The first course was prescribed 6 weeks ago in the emergency department (ED), where he was diagnosed with new onset asthma and normal chest radiograph. The second course was prescribed by his family physician 2 weeks ago. The patient denies fever and chest pain and is still mildly short of breath, which is worse at night or with exertion. Examination shows bibasilar rales in his lungs, normal heart sounds, and 1+ edema in both legs up to his knees. What is his diagnosis?

A. Asthma exacerbation
B. Idiopathic dilated cardiomyopathy (DCM)
C. Prednisone-induced edema
D. Prednisone-induced liver failure
E. Renal failure

Answer: B. The patient is unlikely to have a new diagnosis of asthma. He most likely had a viral process leading to reactive airway disease initially and a viral myocarditis later. He unfortunately now has a DCM and symptoms of congestive heart failure (CHF). Treatment is supportive.

72.6. A 16-year-old male presents in cardiac arrest suffered during a high school football game. He is successfully resuscitated in the emergency department (ED) and admitted to the intensive care unit (ICU). What is the most likely cause of his arrest and what should you tell the family?

A. Cocaine-induced dysrhythmia: Stop using drugs
B. Familial dysrhythmia: Seek cardiology evaluation
C. Hypertrophic cardiomyopathy (HCM): Seek genetic testing
D. Steroid-induced cardiac damage: Stop steroids and consult cardiology
E. Traumatic arrest: Wear more padding

Answer: C. HCM is a common cause of cardiac arrest in patients thought to be too young for coronary artery disease. It is a genetic disease with many different clinical expressions. Both the patient and all family members should be screened for HCM. Although screening may not predict future risk of sudden death, treatment and prevention could be considered.

CHAPTER 73

Infective Endocarditis, Rheumatic Fever, and Valvular Heart Disease

Joshua M. Kosowsky | Sukhjit S. Takhar

INFECTIVE ENDOCARDITIS

PRINCIPLES

Background and Importance

The natural history of infective endocarditis (IE) has undergone considerable changes in the antibiotic era. The older classifications of acute, subacute, and chronic have become less meaningful, immunologic phenomena, such as Osler's nodes and glomerulonephritis, are rarely seen, and nosocomial infections from indwelling catheters and devices are increasing. Early diagnosis and treatment play a significant role in the clinical outcome because IE remains a disease that causes considerable morbidity and mortality.

Estimates of the incidence of IE in the United States vary widely, in part because of changing case definitions throughout the years but also because of differences in predisposing conditions among studied populations. Currently, the annual incidence of endocarditis in industrialized countries range between 3 to 10 cases/100,000.[1,2] IE is increasingly a disease of older adults, with more than 35% of cases occurring in individuals older than 70 years.[3] This reflects the pervasiveness of degenerative valve disease in older adults and the increased prevalence of prosthetic heart valves. Nosocomial endocarditis is increasingly common; the source is often infected intravascular devices, pacemakers, and hemodialysis catheters.

Most patients with bacterial endocarditis have a predisposing valvular abnormality. Among older patients, calcific or degenerative disease of the aortic and mitral valves is the most common predisposing factor. Rheumatic heart disease (RHD), although less prevalent than in prior decades, remains an important predisposing factor for IE among individuals from developing countries. Congenital cardiac lesions involving high-pressure gradients (eg, ventricular septal defects, pulmonary stenosis, tetralogy of Fallot) also increase the risk of IE. A history of previous endocarditis is a major risk factor for recurrence because infected valves heal with irregularities that become a nidus for future vegetations. Mitral valve prolapse (MVP) is now the most common predisposing abnormality for IE in developed countries.

The incidence of IE associated with injection drug use is estimated at 150 to 2000/100,000 person-years. Although any valve can be affected, injection drug use is typically associated with right-sided endocarditis.

Prosthetic valve endocarditis (PVE) is a unique and potentially devastating complication of valve replacement. The incidence of endocarditis in prosthetic valve recipients ranges from 0.5% to 4%/year. PVE can arise early or late after surgery, and the timing of infection reflects different portals of entry and microbiology.

The hospital mortality rate for IE is high, with many centers reporting a mortality rate of around 20% and with rates varying according to the proportion of causative microorganism and presence of complications.[1-5] Viridans streptococci and *Streptococcus bovis* carry a mortality of less than 10%, but the mortality is more than 40% in patients with prosthetic valve IE due to *Staphylococcus aureus.* The mortality for right-sided endocarditis resulting from injection drug use is approximately 10%.

Pathophysiology

The classic lesion of endocarditis is the vegetation, originating as a sterile thrombus on which microorganisms adhere and colonize. The target is usually the cardiac valve; however, chordae tendineae, septal defects, and the endocardium can be involved. The initial thrombus may form at a site of mechanical damage induced by inflammation, degenerative changes, or abnormal turbulence. In injection drug users, contaminants such as talc can injure the previously normal valve leaflets and encourage bacterial implantation. Theoretically, the onset of bacterial endocarditis is preceded by a period of subclinical bacteremia. Dental procedures, cystoscopy, endoscopy, and other invasive procedures result in transient bacteremia, but usually there is no clear precipitant for community-acquired IE.

A number of microorganisms cause IE, with staphylococci and streptococci accounting for most cases (Table 73.1). Although many organisms cause IE, a few have such a predilection that they count as a major criterion in the modified Duke score (Box 73.1). A blood culture positive for community-acquired enterococcus and *Streptococcus bovis* should suggest IE. Also, the HACEK group—*Haemophilus* spp., *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*—a collection of fastidious gram-negative bacilli, is commonly reported in large studies of IE. Finally, a positive blood culture or positive antibody titer to *Coxiella burnetii* (Q fever) is also included in the modified Duke score.

The microbiology of PVE relates to the time of onset. *S. aureus* is now the most prevalent pathogen in the first 2 months after valve replacement, followed by coagulase-negative staphylococci. One year after surgery, the microbiology mirrors native valve endocarditis. Among injection drug users, the most common infecting organism is *S. aureus,* often causing right-sided infections.

Candida and *Aspergillus* spp. cause most cases of fungal endocarditis. Predisposing factors include indwelling intravenous (IV) catheters, immunocompromise, and injection drug use. Large fungal vegetations can embolize, and analysis of these emboli may be the only clue suggesting fungal endocarditis. *Bartonella* spp. is another group of fastidious organisms associated with IE in immunocompromised patients.

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

Symptoms associated with IE are nonspecific and diverse. The most common symptoms are intermittent fever (85%) and

TABLE 73.1

Epidemiology of Infective Endocarditis

MICROORGANISM	%
Staphylococcus aureus	32
Viridans group streptococci	18
Enterococci	11
Coagulase-negative staphylococci	11
Streptococcus bovis	7
Other streptococci	5
Non-HACEK,[a] gram-negative bacteria	2
Fungi	2
HACEK	2
Other organisms	3
Polymicrobial	1
Culture negative	8

[a]HACEK group—*Haemophilus* spp., *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.*

BOX 73.1

Duke Criteria (Clinical) for Diagnosis of Infective Endocarditis

DEFINITE ENDOCARDITIS

Endocarditis is considered definitely present if any one of the following combinations of clinical findings is present:

- Two major clinical criteria
- One major and any three minor clinical criteria
- Five minor clinical criteria

POSSIBLE ENDOCARDITIS

Possible endocarditis is defined as the presence of any one of the following combinations of clinical findings:

- One major and one or two minor clinical criteria
- Three minor clinical criteria

REJECTED ENDOCARDITIS

The diagnosis of endocarditis is considered rejected if any of the following occurs:

- A firm alternate diagnosis is made.
- Resolution of clinical manifestations occurs after 4 days or less of antibiotic therapy.
- Clinical criteria for possible or definite infective endocarditis not met.

MAJOR CRITERIA

Positive blood cultures (of typical pathogens) from at least two separate cultures

Evidence of endocardial involvement by echocardiography, such as the following:

- Endocardial vegetation
- Paravalvular abscess
- New partial dehiscence of prosthetic valve
- New valvular regurgitation

MINOR CRITERIA

Predisposition—predisposing heart condition or intravenous drug use

Fever—temperature > 38° C (100.4° F)

Vascular phenomena—arterial emboli, septic pulmonary infarcts, mycotic aneurysm, conjunctival hemorrhages, or Janeway lesions

Immunologic phenomena—Osler's nodes, Roth's spots, and rheumatoid factor

Microbiologic evidence—single positive blood culture (except for coagulase-negative *Staphylococcus* or an organism that does not cause endocarditis)

Echocardiographic findings—consistent with endocarditis but do not meet major criteria

malaise (80%). Other nonspecific symptoms (eg, weakness, myalgias, back pain, dyspnea, chest pain, cough, headaches, anorexia) vary widely in their incidence. Many patients seen early during the bacteremic phase of the illness do not have a cardiac murmur and are indistinguishable from the large population of patients who come to the emergency department (ED) with a febrile viral illness. During the initial assessment, a careful history should be taken, with attention to any preexisting cardiac pathology or clues suggesting a recent source of bacteremia, such as IV drug use, indwelling intravascular catheters, or invasive procedures. In the absence of specific risk factors, the diagnosis of IE may be suspected when infectious symptoms persist or do not follow a typical course for viremia. The classic triad of fever, anemia, and heart murmur is rare.

Some patients will have complications of IE as presenting complaints. The most common and severe are congestive heart failure and neurologic events. Heart failure results from valvular destruction. A patient with strokelike symptoms and fever should alert one to the possibility of IE. Strokes can be the result of septic emboli or ruptured mycotic aneurysms.

Almost all patients with IE have a cardiac murmur at some time during the course of their illness. A murmur, however, may be absent at presentation. In this population, unexplained fever alone is sufficient to raise concern about possible endocarditis. A substantial minority of patients exhibit some form of vasculitic lesion, including petechiae, splinter hemorrhages, Osler's nodes, and Janeway lesions. Approximately 30% of patients have splenomegaly. Ocular findings include conjunctival or retinal hemorrhages, the latter of which may have a characteristic pale center surrounded by a red halo (Roth's spots).

DIAGNOSTIC TESTING

Laboratory findings in bacterial endocarditis are nonspecific. As with other infectious conditions, leukocytosis is insensitive (occurring in ≈50% of patients diagnosed with IE) and nonspecific. An elevated erythrocyte sedimentation rate or C-reactive protein level may be present, but these are also nonspecific. Most patients have a mild anemia, and up to 50% have microscopic hematuria as a result of embolic lesions of the kidney. A chest radiograph may show signs of heart failure or embolic disease, and an electrocardiogram (ECG) may display conduction abnormalities if an abscess has formed in the myocardium.

Although not always practical, three blood cultures from three separate venipuncture sites are recommended for patients with a presumptive diagnosis of possible endocarditis, with the first and last cultures preferably drawn 1 hour apart. If the patient appears septic, cultures may be obtained more rapidly to permit initiation of early empirical therapy. Cultures need not be timed to the presence of chills or fever because patients with IE typically have a continuous bacteremia.

Echocardiography should be performed in all patients for whom the suspicion of endocarditis is moderate to high. Although transthoracic echocardiography (TTE) is highly specific for vegetations in IE, it may be nondiagnostic because of obesity, chronic obstructive pulmonary disease, and chest wall deformities. Overall

sensitivity of TTE is at most 60%.Transesophageal echocardiography (TEE), on the other hand, although more invasive and time-consuming, is far superior to TTE in its sensitivity and specificity.

Explicit criteria for the diagnosis of IE are important because underdiagnosis can lead to serious morbidity and death, whereas overdiagnosis can result in weeks of unnecessary antimicrobial therapy. The modified Duke criteria are the most widely accepted and validated, stratifying patients with suspected bacterial endocarditis into three distinct categories—definite, possible, and rejected (Box 73.1).[6]

MANAGEMENT

Once the diagnosis of IE is established, whether by clinical, echocardiographic, or microbiologic methods, antimicrobial therapy should be administered. The choice of antibiotics depends on the likely (or known) causative organism but is usually empirical. In the ED, however, usually without results of an echocardiogram (TTE or TEE), the diagnosis of endocarditis is not confirmed. In addition, there is increasing concern regarding community-acquired, methicillin-resistant *S. aureus* (MRSA), even in native valve endocarditis. Thus, a combination of 15 mg/kg of vancomycin and 2 g of ceftriaxone is a reasonable empirical antibiotic choice in someone with undifferentiated sepsis and suspected endocarditis.

Endocarditis is a heterogeneous disease. Although initial treatment is medical, early consultation with a cardiac surgeon is advisable when mechanical complications are observed or expected (eg, in patients with acute heart failure or those with infections involving prosthetic valves; Box 73.2). Consultation with an infectious diseases specialist or cardiologist is also useful. Early valve replacement for more severe disease may decrease the risk of embolic events.[7] If possible, most patients with left-sided endocarditis should be initially managed in facilities with access to cardiac surgery.

With appropriate antibiotic therapy, most patients with IE will defervesce within 1 week. The duration of antibiotic therapy needs to be sufficient to eradicate microorganisms present within the valvular vegetations. This may require 6 weeks, or more, depending on the organism and type of vegetation.[8]

DISPOSITION

Historically, most patients with IE received the entire course of antimicrobial therapy while in the hospital. The development of home health care, however, allows selected patients with endocarditis to be treated as outpatients during much or all of their therapy. Patients selected for outpatient therapy should be hemodynamically stable, compliant, and capable of managing the technical aspects of IV therapy.

BOX 73.2

Conditions Requiring Surgical Therapy for Infective Endocarditis

Infective endocarditis with acute heart failure
Fungal endocarditis
Periannular extension of infection
Recurrent emboli
Large mobile vegetations
Persistent bacteremia

PROPHYLAXIS

The American Heart Association guidelines limit prophylaxis to conditions with the highest risk of adverse outcome from IE (Box 73.3).[9] Virtually all the procedures that are routinely performed in the ED, including suturing of lacerations, endotracheal intubation, placement of central venous catheters, vaginal deliveries, and placement of Foley catheters (in the absence of infection), do not require prophylactic antibiotics.

BOX 73.3

High-Risk Conditions for Bacterial Endocarditis

Prosthetic heart valve
History of endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
Completely repaired congenital heart defects with prosthesis during the first 6 mo after the procedure
Repaired congenital heart disease with residual defect at or adjacent to the site of the prosthetic device
Cardiac valvulopathy in a transplanted heart

RHEUMATIC FEVER

PRINCIPLES

Background and Importance

From 1920 to 1950, acute rheumatic fever (ARF) was the leading cause of death in US children and the most common cause of heart disease in individuals younger than age 40 years. During the 1960s and 1970s, the incidence of ARF in the United States and other developed countries declined dramatically because of widespread antibiotic treatment of streptococcal infections, declining prevalence of the more virulent strains of group A streptococci, and improved living conditions. Children 4 to 9 years of age remain at greatest risk, with an incidence of ARF of 2 to 14 cases/100,000. In many developing nations, however, ARF continues to be a leading cause of childhood mortality. RHD peaks in adults between the ages of 25 and 34 years and continues to be a leading cause of morbidity and mortality in impoverished areas.[10]

Pathophysiology

ARF is a delayed nonsuppurative complication of streptococcal pharyngitis. Although the pathogenesis remains obscure, ARF results from an exaggerated immunologic response to group A beta-hemolytic streptococci that results in antibodies cross-reacting with tissues in the heart, joints, skin, and central nervous system. Patients with a history of ARF are predisposed to recurrent infections, and repeated infections lead to progressive heart damage.

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

Acute rheumatic fever occurs approximately 3 weeks after the initial bout of pharyngitis (ranging from 1–5 weeks). Up to one-third of patients with documented ARF do not remember having had pharyngitis in the preceding month. Fever is generally present during the acute phase of rheumatic fever, rarely lasting more

than 2 weeks without a characteristic pattern. Along with fever, manifestations of ARF may include arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum.

Migratory polyarthritis is the most common manifestation of ARF. Arthritis tends to occur early in the course of ARF and often coincides with a rising titer of streptococcal antibodies. The polyarthritis classically affects larger joints, such as the knees, ankles, elbows, and wrists, and the pain can be more severe than physical findings suggest. Analysis of the synovial fluid generally reveals a sterile inflammatory fluid.

Cardiac manifestations of ARF may be subtle and can include symptoms and signs of pericarditis, myocarditis, and endocarditis. The mitral valve is the most common valve affected in ARF, causing mitral regurgitation. Inflammation of the valvular endocardium can result in permanent deformity and impairment of one or more cardiac valves over the course of decades. Stenotic lesions of the mitral or aortic valves are unusual at presentation, but are common late manifestations of RHD (Fig. 73.1).

Chorea is manifested by random, rapid, purposeless movements, usually of the upper extremities and face. Chorea is relatively rare in ARF and tends to emerge after a longer latency period than some of the other manifestations. Erythema marginatum and subcutaneous nodules are found in fewer than 10% of cases of ARF. Their presence, however, should suggest the diagnosis. Erythema marginatum is a nonpruritic, painless, evanescent so-called smoke ring of erythema that commonly appears on the trunk and proximal extremities (Fig. 73.2). Subcutaneous nodules are pea-sized and nontender. They typically appear over the extensor surfaces of the wrists, elbows, knees and, occasionally, the spine.

DIAGNOSTIC TESTING

In 1944, Jones formulated major and minor criteria for the diagnosis of ARF. After multiple revisions, the Jones criteria remain the diagnostic basis for this disease (Box 73.4).[11] The diagnosis of ARF necessitates evidence of an antecedent streptococcal infection plus at least two major, or one major and two minor, manifestations from the Jones criteria. Although throat cultures are usually negative at the time of clinical onset of ARF, antistreptolysin

BOX 73.4

Jones Criteria (Revised) for the Diagnosis of Acute Rheumatic Fever

MAJOR MANIFESTATIONS
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules

MINOR MANIFESTATIONS
Arthralgias
Fever
Increased erythrocyte sedimentation rate or C-reactive protein level
Prolonged PR interval

EVIDENCE OF PRECEDING STREPTOCOCCAL INFECTION
Positive throat culture for group A beta-hemolytic streptococci or positive rapid streptococcal antigen test
Elevated or rising streptococcal antibody titer, usually antistreptolysin O

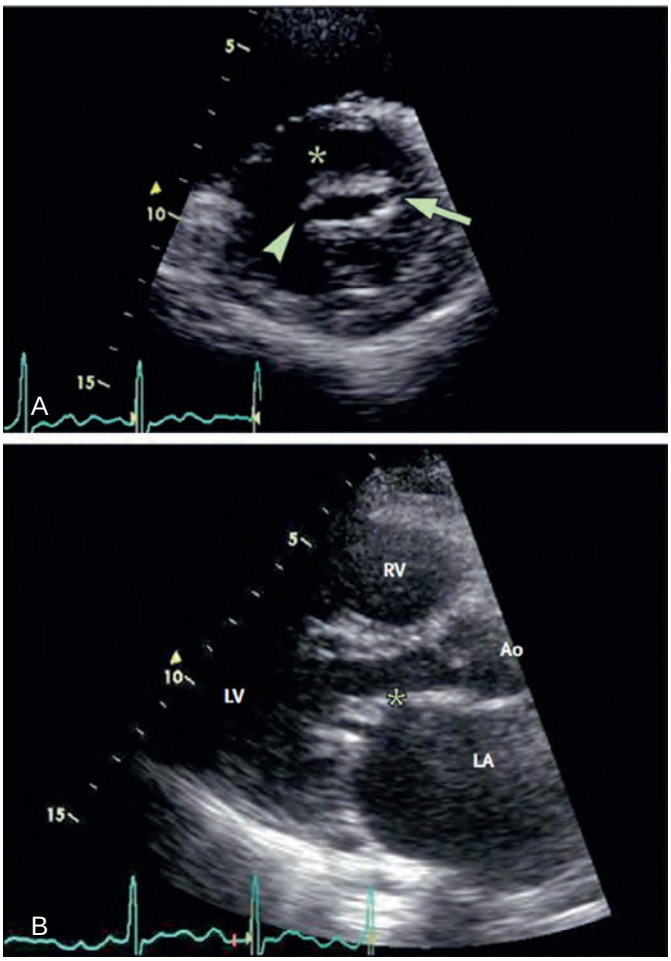


Fig. 73.1. Transthoracic echocardiography of symptomatic rheumatic mitral stenosis (* represents a thickened anterior mitral leaflet). *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle. (From Marijon E, et al: Rheumatic heart disease. Lancet 379:953–964, 2012.)

Fig. 73.2. Erythema marginatum. This is one form of annular erythema seen in 10% of cases of children with acute rheumatic fever but is rare in adults with the disease. (From Cohen J, Powderly WG: Infectious diseases, ed 2, New York, 2004,Mosby.)

antibody titers remain positive for 4 to 6 weeks from the time of infection. The erythrocyte sedimentation rate and C-reactive protein levels are typically elevated, and a prolonged PR interval is common and suggestive in ARF.

MANAGEMENT AND DISPOSITION

All patients with ARF should receive antibiotic therapy, regardless of the clinical history of pharyngitis. Penicillin can be administered orally (250 mg for children, 500 mg for adults, bid or tid for 10 days) or intramuscularly (600,000 units of benzathine penicillin in patients weighing <27 kg and 1.2 million units in patients >27 kg as a one-time dose).

Treatment for arthritis consists of antiinflammatory agents, usually aspirin, administered until symptoms are absent and the erythrocyte sedimentation rate and C-reactive protein concentration normalize. Patients with severe carditis are often treated with corticosteroids, but no evidence supports this treatment.[10,12] Patients with congestive heart failure should be managed accordingly. Treatment of patients with ARF involves only symptom relief and does not decrease the likelihood of progression to RHD. Primary prevention involves treating those with group A streptococcal pharyngitis within 9 days of the onset of symptoms because this greatly decreases the risk of ARF. Patients with a history of ARF should receive ongoing prophylactic antibiotics (generally, penicillin) to prevent recurrences. The recommended duration of secondary prophylaxis varies, depending on the presence and severity of cardiac involvement.

VALVULAR HEART DISEASE

PRINCIPLES

Anatomy and Physiology

Of the four heart valves, three (tricuspid, pulmonic, and aortic) are composed of three cusps, whereas the mitral valve has only two cusps. Each cusp is a double layer of endocardium attached at its base to the fibrous skeleton of the heart. The margins of the cusps are attached to muscular projections from the ventricles (papillary muscles) via tendinous cords (chordae tendineae). Contraction of the ventricle, and consequently the papillary muscle, results in the opening or closing of the valve, depending on its location.

Mitral Stenosis

The most common cause of mitral stenosis is RHD. Symptoms of valvular dysfunction typically develop after a latency period of 1 to 3 decades. Many patients will not recall a history of ARF. Less common causes of mitral stenosis include congenital mitral stenosis and mitral annular calcification.

Pathophysiology

The normal cross-sectional area of the mitral valve orifice is 4 to 6 cm^2. Stenosis becomes clinically significant when the area decreases to below 2 cm^2. Impeded flow from the left atrium to the left ventricle results in left atrial hypertension, restricted cardiac output and, ultimately, pulmonary congestion. As the disease progresses, patients may develop pulmonary hypertension and right ventricular failure.

The most common complication of mitral stenosis is atrial fibrillation, which, in the absence of rate control, is not well tolerated. Patients with underlying mitral stenosis will decompensate under other conditions associated with increased cardiac demand and reduced ventricular filling, such as pregnancy, anemia, infection, and hyperthyroidism.

Clinical Features

Early symptoms of mitral stenosis include reduced exercise tolerance and dyspnea on exertion. Patients with more advanced disease may have orthopnea and, if right ventricular failure is present, peripheral edema. Hemoptysis, caused by the rupture of a bronchial vein, and hoarseness, caused by compression of the recurrent laryngeal nerve, are classic but uncommon presentations. Aside from the typical signs of heart failure, findings that suggest the presence of mitral stenosis include a loud S_1 and an opening snap in early diastole, accompanied by a low-pitched, rumbling diastolic apical murmur.

Although the chest radiograph may be normal, left atrial enlargement may be suggested by straightening of the left heart border in more advanced cases. Common electrocardiographic abnormalities, in addition to atrial fibrillation, include left atrial enlargement and, ultimately, right ventricular hypertrophy. Echocardiography confirms the diagnosis and assesses the severity of disease.

Management

Medical treatment for patients with mitral stenosis is comprised of diuresis for symptoms of vascular congestion and anticoagulation for atrial fibrillation. Once symptoms have developed, however, median survival without intervention is 7 years.[13] Several surgical options exist, ranging from balloon valvulotomy or open commissurotomy to valve reconstruction or replacement. Management of the patient with mitral stenosis in the ED centers on identification and treatment of underlying precipitants, such as atrial fibrillation or anemia, diuresis, and referral for definitive intervention.

Mitral Regurgitation

Acute and chronic mitral regurgitation are two distinct disease entities. Acute mitral regurgitation is a true emergency. It can result from idiopathic rupture of the chordae tendineae, papillary muscle dysfunction in the setting of acute ischemia, papillary muscle rupture 2 to 7 days postinfarction, or perforation of a valve leaflet in the setting of infectious endocarditis or trauma. Chronic mitral regurgitation, on the other hand, usually occurs in the setting of dilated cardiomyopathy (due to enlargement of the mitral annular ring) or RHD, often coexisting with mitral stenosis. Other causes of chronic mitral regurgitation include MVP and connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome.

Pathophysiology

Acute mitral regurgitation is associated with low left atrial compliance and thus sharply elevated left atrial pressure, which results in acute pulmonary congestion. In contrast, chronic mitral regurgitation is characterized by high left atrial compliance and near-normal left atrial pressures, with reduced forward output. Patients with chronic mitral regurgitation typically decompensate in the setting of volume overload.

Clinical Features

The characteristic presentation of acute mitral regurgitation is one of fulminant pulmonary edema. This is accompanied by a unique, harsh, midsystolic murmur that radiates to the base rather than the axilla. Patients typically have no prior history of heart failure. The ECG may display signs of ischemia or infarction.

The presentation of chronic mitral regurgitation is similar to that of chronic systolic heart failure, with clinical symptoms and

signs of decompensated congestion. The murmur is classically described as holosystolic, heard best at the apex and radiating to the axilla. The ECG often reflects left atrial and ventricular hypertrophy. Atrial fibrillation is common, and left atrial enlargement may be suggested by the chest radiograph. Echocardiography may demonstrate a normal or above-normal ejection fraction, but some portion of systolic flow is retrograde.

Management

When the diagnosis of acute mitral regurgitation is suspected, emergency echocardiography and cardiac catheterization will assess the degree of regurgitation and urgency for surgery. Initial stabilization should include treatment of pulmonary edema with nitrates and diuretics. In a hypotensive patient, a counterpulsation intraaortic balloon pump may provide temporary stabilization as a bridge to surgery.

The natural history of chronic mitral regurgitation is generally a very slow progression, with 15-year survival approaching 70% with medical therapy, including diuretics and afterload-reducing agents. However, once the ejection fraction falls below 60%, valve repair or replacement is recommended to avoid irreversible left ventricular dysfunction.[13]

Aortic Stenosis

The most common cause of aortic stenosis is calcific degeneration, which is prevalent in older adults with coronary artery disease. This also occurs in younger individuals with a bicuspid aortic valve. Aortic stenosis can also coexist with mitral stenosis in patients with RHD.

Pathophysiology

The normal aortic valve area is larger than 3 cm^2. Significant obstruction occurs when the valve area is reduced by more than 50%. Critical aortic stenosis is defined by a valve area of less than 0.8 cm^2 or a pressure gradient across the valve that exceeds 50 mm Hg. Compensatory left ventricular hypertrophy can maintain cardiac output until the stenosis becomes severe. Further progression of disease is associated with left ventricular dysfunction, left atrial enlargement, and atrial fibrillation. Individuals with severe or critical aortic stenosis are preload-dependent and have very little cardiovascular reserve. Any disruption of the delicate balance between myocardial oxygen supply and demand (eg, rapid atrial fibrillation, dehydration, acute blood loss) can result in precipitous decompensation.

Clinical Features

Classic symptoms of aortic stenosis progress from angina (increased demand resulting from wall stress and decreased supply resulting from reduction in perfusion pressure) to exertional syncope (fixed cardiac output and vasodepressor response), to congestive heart failure (diastolic and ultimately systolic dysfunction). In an older patient with chest pain, particularly if seemingly preload-dependent, the possibility of aortic stenosis, with or without coronary artery disease, should be considered.

The classic auscultatory finding in aortic stenosis is a crescendo-decrescendo systolic murmur heard best at the base (right second intercostal space) that radiates into the carotids and is associated with the presence of an S_4 gallop and a soft aortic component of S_2. Although counterintuitive, as the severity of disease increases, the murmur peaks later and becomes less apparent. Carotid pulses may be delayed (tardus) and diminished in intensity (parvus). The ECG typically reveals left ventricular hypertrophy. Echocardiography is required for the assessment of the severity of stenosis and presence of left ventricular dysfunction.

Management

The natural history of aortic stenosis is one of slow progression, without symptoms for years. Once symptoms develop, medical management has a limited role, and survival is markedly reduced unless the valve is replaced. In high-risk patients, balloon valvuloplasty is feasible and safe as a bridge to percutaneous or surgical valve replacement, but long-term survival is poor with valvuloplasty alone.[14] In the acute setting, management of decompensated aortic stenosis centers on judicious fluid resuscitation, blood transfusion, restoration of sinus rhythm, and avoidance of vasodilators and diuretics and inotropic agents, if possible. When there is no response to medical therapy and the patient is a candidate for valve replacement, an intraaortic balloon pump may provide a bridge to surgery.

Aortic Insufficiency

Aortic insufficiency can occur as a consequence of RHD, infectious endocarditis, or the presence of a bicuspid valve. Aortic root abnormalities, such as ectasia, aneurysm, or dissection, can also lead to aortic insufficiency.

Pathophysiology

In acute aortic insufficiency, left ventricular compliance is low, and left ventricular pressure increases rapidly during diastole, leading to acute pulmonary congestion. In chronic aortic insufficiency, the left ventricle dilates, allowing the heart to maintain normal or near-normal cardiac output, despite significant regurgitation. The enhanced stroke volume results in a wide pulse pressure and the clinical signs that are commonly associated with aortic insufficiency. Pulmonary congestion, when present, is generally a consequence of volume overload.

Clinical Features

Patients with acute aortic insufficiency can present with severe respiratory distress and/or frank cardiogenic shock. At the same time, the physical findings specific to acute aortic insufficiency can be quite subtle. The pulse pressure will be widened only slightly, if at all, and the short, soft, diastolic murmur may be difficult to detect. Emergent echocardiography is required to confirm the diagnosis.

In contrast, chronic aortic insufficiency is characterized by a widened pulse pressure, which may be accompanied by a number of classic physical findings, such as a rapidly rising and falling carotid pulse (water hammer,or Corrigan's, pulse), spontaneous nail bed pulsations (Quincke's sign), or a to and fro murmur over the femoral artery (Duroziez's sign). A high-pitched, blowing, diastolic murmur at the left sternal border is characteristic of chronic aortic insufficiency. An Austin-Flint murmur—the soft diastolic rumble caused by a regurgitant stream against the mitral valve—may also be present.

Management

In contrast to chronic aortic insufficiency, acute aortic insufficiency is a surgical emergency necessitating urgent valve replacement, along with repair of any underlying aortic root pathology. Medical stabilization entails the cautious use of vasodilators and diuretics. For obvious reasons, intraaortic balloon counterpulsation is contraindicated in the presence of an incompetent aortic valve. Chronic aortic insufficiency is managed like other types of decompensated heart failure, with emphasis on diuresis, as well as preload and afterload reduction. Ideally, however, valve repair or replacement should be performed before the development of left ventricular systolic dysfunction.[13]

Mitral Valve Prolapse

MVP is defined pathophysiologically as an abnormal movement of one or both of the mitral valve leaflets during systole. Although generally a benign condition, it is infrequently associated with more serious cardiac pathology such as mitral regurgitation, endocarditis, and arrhythmias. Echocardiographic studies report a true prevalence of less than 1% in h men and women versus the previously reported 5%, with a female predominance.[15]

Pathophysiology

Structurally, MVP is characterized by myxomatous proliferation of the spongiosa layer within the mitral valve that results in abnormal billowing of the leaflet during systole. MVP usually occurs in isolation but, like other valvular diseases, may be associated with other connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome.

Clinical Features

MVP is associated with a wide variety of clinical symptoms, including chest pain, palpitations, dyspnea, lightheadedness, and fatigue. Appropriately controlled clinical studies, however, such as the Framingham Heart Study, have suggested that patients with MVP and control subjects may be equally symptomatic. The classic auscultatory feature of MVP is a midsystolic click caused by snapping of the chordae tendineae with prolapse of the valve. Occasionally a mid to late systolic murmur can be appreciated over the mitral area. Confirmation of the diagnosis is made by echocardiography.

Management

Cardioselective beta blockers may control symptoms such as palpitations, chest pain, and anxiety. Lifestyle modifications, such as exercise, relaxation techniques, and avoidance of ethanol or caffeine and other stimulants, may also be helpful. Often, simple reassurance about the generally benign nature of the disease will suffice.

Complications of Prosthetic Valves

Prosthetic heart valves are classified as mechanical or biologic. The latter category includes whole valve transplants (human or porcine) as well as bioprosthetic valves, which are typically manufactured from bovine pericardium. All prosthetic heart valves are associated with complications, ranging from structural failure and thrombosis to systemic embolization, hemolysis, and endocarditis. In the acute setting, the diagnosis of a prosthetic valve complication can be challenging because symptoms and signs are often subtle.

Primary structural failure is extremely uncommon with modern mechanical valves. When it does occur, the presentation is one of acute severe regurgitation and shock, and emergent valve replacement is required. With biologic valves, in contrast, structural failure is relatively more common, but less dramatic. At 10 years, 20% to 30% of bioprosthetic valves exhibit some evidence of structural failure, and most are replaced electively. Symptoms are characteristically insidious in onset and are similar to those of native valvular disease.

Prosthetic valve thrombosis occurs with mechanical and biologic valves. When adequately anticoagulated, mechanical valves have thrombotic complications at a similar rate (≈2%/year) as biologic valves.[16] Symptoms of prosthetic valve thrombosis are generally subacute and may have characteristics of stenotic disease, regurgitant disease, or both. On physical examination, the diagnosis is suggested by a decreased or absent valve click, new regurgitant murmur, or louder than expected stenotic murmur. Echocardiography may demonstrate the thrombus or restricted leaflet motion. Treatment options include fibrinolytic therapy and surgery.

The incidence of systemic embolization from a prosthetic valve is approximately 1%/year. Compared with aortic valve prostheses, mitral valve prostheses are associated with twice the risk of systemic embolization, with rates roughly equal for a biologic mitral valve or appropriately anticoagulated mechanical mitral valve. The vast majority of diagnosed embolic events (85%) involve the central nervous system, and roughly 50% of these result in permanent impairment.[16]

A mild hemolytic anemia resulting from sheer forces through the prosthetic valve aperture is common but usually subclinical. In more severe case, presenting features can include dyspnea, fatigue, and even jaundice. Iron replacement is effective therapy for most patients but transfusion may be required in severe cases. If hemolysis is the result of a periprosthetic leak or other structural failure, scheduled reoperation is commonly required.

The incidence of PVE is highest during the initial months after surgery and is similar for mechanical and bioprosthetic valves. Early PVE, within 60 days of surgery, is presumed to be caused by a pathogen acquired perioperatively and is associated with higher morbidity and mortality, whereas late PVE is more likely related to transient bacteremia and is generally associated with a more benign course. As with other forms of endocarditis, fever is the most common presenting symptom, whereas other manifestations are variable. Echocardiography can identify vegetations, but a normal study does not rule out endocarditis. In the ED, the diagnosis of PVE is generally presumptive because definitive diagnosis requires blood cultures or biopsy.

Disposition

Patients with acute symptoms related to valvular heart disease should be admitted to the hospital until their condition has stabilized and the cause for their decompensation has been addressed. For patients with stable valvular disease, outpatient cardiology follow-up is recommended.

KEY CONCEPTS

- Many patients seen early in the bacteremic phase of IE lack a murmur and are indistinguishable from those with viremia.
- Patients for whom suspicion of endocarditis is moderate to high require blood cultures, echocardiography, and admission for definitive diagnosis and initiation of empirical therapy.
- Prophylaxis for IE is rarely, if ever, indicated for procedures performed in the ED.
- Acute rheumatic fever is a delayed nonsuppurative complication of streptococcal pharyngitis characterized by arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum.
- In a patient with severe mitral stenosis, hypovolemia and tachycardia are poorly tolerated. Slow and full are appropriate goals.
- In patients with critical aortic stenosis, excessive preload reduction with vasodilators and diuretics is to be avoided.
- In patients with acute aortic insufficiency, classic physical findings may be absent. Medical stabilization entails the cautious use of vasodilators and diuretics. Intraaortic balloon counterpulsation is contraindicated.
- Complications of prosthetic heart valves range from structural failure and thrombosis to systemic embolization, hemolysis, and endocarditis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 73: QUESTIONS & ANSWERS

73.1. What is the most common manifestation of acute rheumatic fever (ARF)?

A. Carditis
B. Chorea
C. Erythema marginatum
D. Polyarthritis
E. Subcutaneous nodules

Answer: D. Arthritis occurs early in the course of ARF. The knees, ankles, elbows, and wrists are commonly affected, and pain can be out of proportion to physical findings. Cardiac manifestations are subtle and may reflect endocarditis, myocarditis, or pericarditis. Chorea, nodules, and erythema marginatum are rare. Chorea is typically a late finding.

73.2. A 49-year-old woman presents with progressive dyspnea on exertion and orthopnea. Vital signs are temperature 36.7° C (98.1° F; oral), heart rate, 110 beats/min, blood pressure, 135/80 mm Hg, respiratory rate, 22 breaths/min, and oxygen (O_2) saturation, 97% on room air. The physical examination is remarkable for clear lung fields and an irregularly irregular rhythm with a 4/6 diastolic murmur in the left anterior axillary line. She has no peripheral edema. Which of the following would be appropriate hemodynamic management of her cardiac pathophysiology?

A. Aggressive diuresis
B. β_1-Agonist to increase chronotropy
C. Beta blockade
D. Selective arterial vasodilator
E. Selective venodilator

Answer: C. This patient has a picture consistent with atrial fibrillation and mitral stenosis. The apical diastolic murmur and left atrial enlargement, along with progressive dyspnea, all support the diagnosis. Tachycardia is poorly tolerated because of the need for higher left atrial pressures and a longer time during diastole to perfuse across the stenotic valve. Slow and full would be appropriate guidelines. Both diuresis and a venodilator might decrease venous return. Any agent producing tachycardia would decrease diastole time and left ventricular preload. An arterial vasodilator would have little effect, given the normal blood pressure and the fact that systemic vascular dilation would not be seen at the mitral valve level as long as the aortic valve was competent.

CHAPTER 74

Hypertension

Phillip D. Levy | Aaron Brody

PRINCIPLES

Background

Hypertension (HTN) is an important but largely treatable risk factor for cardiovascular disease that affects almost one-third of Americans and approximately 1 billion people worldwide.[1,2] Although more than 80% of those with HTN are aware of their condition and most (~75%) are receiving at least some form of antihypertensive therapy, blood pressure (BP) remains uncontrolled in nearly 50% of patients.[3,4] The implications of this on the practice of emergency medicine are clear. According to data from a nationwide emergency department (ED) sample between 2006 and 2010, one of every five ED visits included HTN as a diagnosis.[5] Moreover, as shown in the most recent analysis of the National Hospital Ambulatory Medical Care Survey,[6] moderate (ie, >140–159/90–99 mm Hg) to severely elevated (ie, ≥160/100 mm Hg) BP is present in over 40% of ED patients.[7]

Despite this understanding, there is a critical divide between what constitutes emergency and medicine when it comes to elevated BP in the ED. When associated with acute target organ damage (TOD), HTN represents a true emergency that warrants emergent intervention. However, this is relatively rare and, for the vast majority, acute TOD will be not be present, even in the setting of markedly elevated BP. Although such patients have a low likelihood of near-term adverse events and are thus not emergencies per se, they would undoubtedly benefit from measures to decrease their overall cardiovascular risk through better BP control. This distinction is thus a key aspect of the approach to HTN in the ED and a core feature of emergency medicine practice.

Importance

Hypertension is a major modifiable risk factor for the development of cardiovascular, cerebrovascular, and renovascular disease. Uncontrolled BP is strongly associated with heart failure, myocardial infarction, stroke, vascular dementia, and chronic kidney disease. The risk of developing these conditions increases with the degree of BP elevation, and it has been estimated that the risk of cardiovascular disease doubles for each elevation of 20 mm Hg systolic and 10 mm Hg diastolic BP, starting at 115/75 mm Hg. Conversely, BP treatment can lower the risk for stroke by 40%, myocardial infarction by 25%, and heart failure by 50%.

The distribution of HTN is not uniform. African Americans have higher rates of disease (40.4% vs. 27.1% for whites) and poorer BP control, leading to an increased risk of adverse outcome,[8-10] whereas people of Hispanic ethnicity have lower rates (26%). This disparity, in combination with other economic, social, and lifestyle determinants, leads to dramatically increased morbidity of cardiovascular disease in the African American population.[11] HTN is the single most important contributor to racial differences in life-years lost from cardiovascular disease, accounting for 50% of the excess risk within the African American community.[12]

Definition of Hypertension and Relevant Terminology

Although BP below 120/80 mm Hg is considered normal, an understanding of what constitutes HTN has been evolving. Present definitions are based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), which set a BP level of 120 to 139/80 to 89 mm Hg as pre-HTN, 140 to 159/90 to 99 mm Hg as stage I HTN, and 160/100 mm Hg or higher as stage II HTN.[13] In the JNC 8, a much anticipated update to this pivotal guideline, no changes to these categorical definitions were proposed.[14] However, greater emphasis was placed on age-based treatment thresholds, with antihypertensive therapy recommended when the systolic BP exceeds 140 mm Hg for those younger than 60 years and 150 mm Hg for those 60 years of age or older. As with other guidelines, a diastolic BP of 90 mm Hg or higher remains an indication for treatment, regardless of age.[15]

Historically, the approach to BP measurement has been office-based, with a diagnosis of HTN considered to be present when BP of 140/90 mm Hg or higher is detected on properly measured, seated readings on two or more occasions. Recent data have suggested that 24-hour ambulatory BP measurement may be a better method for establishing a diagnosis of HTN.[16] Ambulatory BP measurement enables the evaluation of BP over a range of conditions, minimizing the potential for so-called white coat effects while increasing the likelihood of detecting masked HTN. The increased reliability of the ambulatory BP measurement has prompted recent guidelines to recommend that the threshold for HTN be set at 135/85 mm Hg when the BP is determined via this approach.[17,18]

How ED-measured BPs fit into this paradigm is not clear. Many ED patients with elevated BP will have an established history of HTN, but a sizeable proportion will not, presenting an opportunity to establish the diagnosis. Although this should be approached with caution on the basis of a single ED measurement, demonstration of persistently elevated BP over several prior ED visits may be a reasonable indicator of true underlying HTN. Prior studies have shown that as many as 70% of patients with elevated BP in the ED will also have an abnormal BP at primary care follow-up, and this proportion increases with the ED BP value. Newer automated BP devices that perform serial measurements, discarding the first reading and averaging subsequent

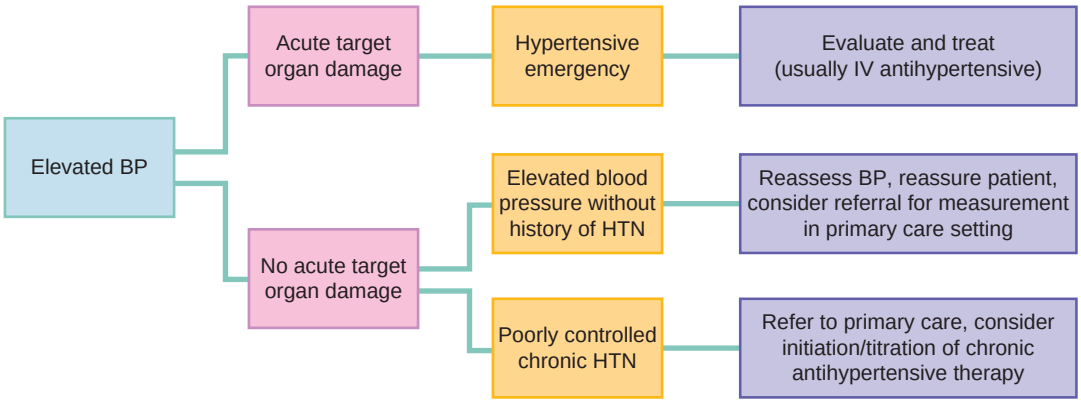

Fig. 74.1. Schematic for the approach to elevated blood pressure (BP) in the emergency department. *HTN,* Hypertension.

values, have been shown to improve the accuracy of office-based methods and may be a useful adjunct in the ED for such patients.[19]

Perhaps more important in the ED setting than making the diagnosis of chronic HTN is understanding the need for acute intervention among patients who have marked BP elevations (ie, ≥180/100 mm Hg). Although terms such as *hypertensive crisis*, *hypertensive urgency*, and *accelerated* or *malignant* HTN, are liberally applied to such patients, they are poorly defined and are often used interchangeably and incorrectly by emergency clinicians. A better approach focuses on the presence (or absence) of signs or symptoms attributable to acute TOD within the context of established or potentially new-onset HTN, thus distinguishing patients with active vasculopathy from those without.

Based on this conceptual model, there are three distinct subgroups of patients with elevated BP that are relevant to emergency medicine practice:

1. Hypertensive emergency—a disease state defined by acute TOD, manifest by newly developed clinical sequelae or diagnostic test abnormalities. A hypertensive emergency can exist in patients with or without underlying chronic HTN. Although it has been estimated that 1% to 2% of patients with chronic HTN will experience a hypertensive emergency in their lifetime, hospitalization for this condition is relatively rare, occurring in only 110 of every 100,000 admissions in the United States.[20]
2. Poorly controlled chronic HTN—a presentation in which patients with established HTN are found to have elevated BP without specific attributable symptoms or evidence of acute TOD. Such presentations often result from nonadherence to treatment regimens or inadequate medical management, but may also reflect refractory disease. Concurrent use of seemingly innocuous medications, including nonsteroidal antiinflammatory drugs (NSAIDs), steroids, decongestants, appetite suppressants, over-the-counter stimulants, oral contraceptives, and tricyclic antidepressants or rebound from short-acting antihypertensives, such as clonidine, may be contributory.
3. Elevated BP without prior history of HTN—a relatively frequent occurrence in which routine ED vital signs identify an elevated BP. Such individuals also may visit the ED after an outpatient physical examination, community health screening event, or self-performed, automated BP measurement identifies elevated BP. Whether or not this truly represents HTN can be difficult to determine in the ED, and all such patients should have repeat measurement of BP, ideally 1 hour or more after arrival, and after analgesic treatment for those with acute pain. Depending on the circumstance, an evaluation for potential TOD may be warranted, along with referral for subsequent follow-up in an outpatient setting.

An approach to elevated BP in the ED based on this understanding is presented in Fig. 74.1.

Physiology of Hypertension

Whereas BP is known to rise with increasing age, onset of HTN in the non–older adults represents a complex interplay of multiple inciting factors, including neurohormonal dysregulation, vascular modulation, sodium intake, psychosocial stress, and obesity. Alterations in cardiac and renal function are also important, serving as contributors to and consequences of ongoing BP elevation. Despite an advanced understanding of the pathophysiology of HTN, the definitive cause of elevated BP remains unknown in more than 90% of patients. These individuals are labeled as having primary or essential HTN, and the cause is considered idiopathic. In the subset of patients for whom an identifiable cause can be ascertained, the term *secondary HTN* applies (Table 74.1). Although it may not be possible to diagnose and treat such causes of secondary HTN in the ED, when suspected, early referral for outpatient evaluation or, in some cases, hospital admission to expedite evaluation, may be warranted.

Neurohormonal Dysregulation

The sympathetic nervous system (SNS) has a pivotal role in the development of HTN.[21] Norepinephrine, the principal sympathetic neurotransmitter, is a potent stimulator of vasoconstriction. This effect is mediated through peripheral α_1-adrenergic receptor activation in vascular smooth muscle cells and occurs predominantly in small-diameter arterioles. Although individually these vessels contribute a miniscule amount to BP, in aggregate they serve as the primary driver of systemic vascular resistance (SVR) and constitute the main force that amplifies afterload in HTN.[22] The SNS also stimulates β_1-adrenergic receptors in the heart, leading to an increase in cardiac output (CO) through augmentation of stroke volume and heart rate, but these are considered lesser contributors to the pathologic process of high BP. Sympathoactivation exerts additional direct effects on the kidney that promote sodium reabsorption, leading to an increase in circulating blood volume, and trigger renin release, resulting in angiotensin II production and further vasoconstriction.[23]

In addition to activation by the SNS, the renin-angiotensin-aldosterone system exerts critical independent effects on BP.[24,25] Renin is an enzyme produced by juxtaglomerular cells in the kidney in response to several factors beyond adrenergic stimulation, including sodium load in the distal tubule and renal perfusion status. Renin cleaves angiotensin I from its plasma globulin precursor, angiotensinogen. Angiotensin I is then converted to

TABLE 74.1

Secondary Causes of Hypertension

CAUSE	DIAGNOSTIC TEST	CLINICAL CLUES
ENDOCRINE		
Cushing's syndrome and other glucocorticoid excess states	History; dexamethasone suppression test	Glucose intolerance; purple striae
Hyperaldosteronism and other mineralocorticoid excess states	24-hr urinary aldosterone level or other mineralocorticoids	Unexplained hypokalemia
Oral contraceptive use	History	
Pheochromocytoma	24-hr urinary metanephrine and normetanephrine	Labile or paroxysmal HTN with palpitations, pallor, perspiration
Thyroid disease Parathyroid disease	Serum TSH Serum PTH	Temperature intolerance, weight loss, tachycardia; hypercalcemia
PULMONARY		
Obstructive sleep apnea	Sleep study with O_2 saturation	Obesity; narcolepsy
RENAL		
Chronic pyelonephritis	History; urinalysis, urine culture	
Diabetic nephropathy and other chronic kidney disease	Estimated GFR; urine albumin/creatinine ratio	
Nephritic and nephrotic syndromes	Urinalysis; renal biopsy	
Polycystic kidney disease	Renal ultrasound	
Renovascular conditions (eg, renal artery stenosis)	Doppler flow study; magnetic resonance angiography	HTN onset before the age of 30 yr or after 55 yr; abdominal bruit; refractory HTN control; recurrent pulmonary edema; unexplained renal failure
TOXIC OR METABOLIC		
Chronic alcohol abuse	History; ETOH level	
Sympathomimetic drug use	History; drug screen	
Tyramine-containing foods	History	Paroxysms of HTN, especially in those taking monoamine oxidase inhibitors
VASCULAR		
Atherosclerosis		
Coarctation of the aorta	CT angiography	Decreased lower extremity pulses

CT, Computed tomography; *ETOH,* ethyl alcohol; *GFR,* glomerular filtration rate; *HTN,* hypertension; *O_2,* oxygen; *PTH,* parathyroid hormone; *TSH,* thyroid-stimulating hormone.

angiotensin II by circulating and tissue-bound (especially in the lung), angiotensin-converting enzyme (ACE). Angiotensin II exerts systemic and renal effects by binding to angiotensin II type I (AT_1) receptors, which results in arterial vasoconstriction, sodium reabsorption, and modulation of the glomerular filtration rate (GFR). Through AT_1 receptor binding in the adrenal gland, angiotensin II also serves as a potent stimulator of aldosterone release, which promotes further sodium reabsorption and potassium excretion.

Vascular Modulation

Continued vascular stimulation by the SNS and renin-angiotensin-aldosterone system, coupled with an increase in wall tension caused by HTN itself, leads to ongoing remodeling throughout the arterial tree.[26,27] In large vessels such as the aorta or carotid arteries, this results in increasing intima-media thickness, with minimal luminal narrowing—unless there is unrelated plaque buildup. In contrast, small-vessel and arteriolar remodeling reduce the lumen diameter.[28] Although both forms of remodeling work to normalize wall stress associated with HTN, they reduce vasodilatory capacity and enhance the vasoconstrictor response when faced with a hypertensive stimulus.

Sodium Intake

The average American has a daily sodium intake of close to 3500 mg (150 mEq)—more than double the recommended level of 1500 mg (≈65 mEq) recommended by the American Heart Association (AHA) in its 2011 guidelines.[29] Randomized trials have demonstrated a reduction in systolic BP with diminished daily sodium intake (up to 7 mm Hg/1200 mg, or a 52-mEq decrease in hypertensive individuals)[30]; however, the impact of this intervention on long-term cardiovascular outcomes is unclear.[31] Salt sensitivity is defined by an increase in BP with intake of a high-sodium diet. It is linked to obesity but may be more directly related to defects in renal ion transport mechanisms that lead to ongoing sodium retention and potassium depletion.[32] Although not fully defined, the latter plays a critical role, because the entire effect of salt sensitivity on BP can be mitigated with high-dose (≈4000 mg, or 100 mEq/day) potassium supplementation.[33-35]

Psychosocial Stress

Life stressors, especially socioeconomic status, are known to affect health and wellness adversely. Through its effects on SNS function and the hypothalamic-pituitary axis, stress modulates BP and is a

specific contributor to disparities in HTN.[36,37] Although episodic stress reactions can lead to transient sympathetic surges, sustained stimulation related to ongoing concern over life circumstances (eg, financial security, crime and safety, racism) triggers a chronic adaptive response and has been emerging as an important consideration in patients with seemingly idiopathic HTN.[38,39]

Obesity

Obesity is a known risk factor for the development of HTN. For every increase of body mass index by 5 kg/m^2, the risk of hypertension increases by 1.4 (95% confidence interval [CI], 1.38–1.49).[4] Elevated BP in obese individuals correlates with high circulating aldosterone and cortisol levels, which in turn may be related to salt sensitivity.[40] Obesity, especially truncal, is also strongly associated with diabetes and obstructive sleep apnea, both of which contribute to poor BP control.[41]

Pathophysiology of Target-Organ Damage

Uninterrupted by treatment, continued vasoconstriction in chronic HTN leads to a number of deleterious consequences that culminate in TOD. On a macrocirculatory level, the central components of the cardiovascular system (ie, heart, large blood vessels) are most affected. Sustained elevations in SVR cause significant augmentation of the pressure wave reflected from the periphery back to the central circulation (termed the *augmentation index*), thus driving up left ventricular (LV) afterload; the increase manifests with a rise in the central aortic pressure and change in the morphology of its waveform.[22,42] This results in increasing impedance to forward flow from the heart, which in turn necessitates greater contractile force to maintain aortic valve opening and the duration of ventricular ejection.[43] Active contraction against this resistance also increases intraventricular wall tension, which, together with ongoing stimulation from, among other things, the SNS and renin-angiotensin-aldosterone system, triggers cardiomyocyte hypertrophy and myocardial fibrosis. Initially, this leads to an increase in LV mass, which enhances the heart's pumping against excessive afterload. However, when progressive, the net result is LV stiffening and impaired diastolic function, with an increase in LV filling pressure and diminished flow from the left atrium to the left ventricle. If the increase in afterload is sudden, an abrupt decrease in stroke volume occurs, precipitating backflow of fluid into the lungs and rapid onset of so-called flash pulmonary edema. If excess afterload is more gradual or even chronic, a subacute rise in LV end-diastolic pressure may cause increased wall tension, with compression of the subendocardial microvasculature and myocardial ischemia. Over time, this contributes to LV wall thinning, chamber dilation, and eventually systolic dysfunction.

On a microcirculatory level, the initial beneficial effect of vascular remodeling gradually gives way to critical luminal narrowing and the potential for regional ischemia from occlusion or loss of vessel wall integrity with leakage or rupture. Autoregulation, the intrinsic capacity of resistance vessels to dilate or constrict rapidly in response to dynamic perfusion pressure changes, works to maintain relatively constant blood flow and is protective with moderate fluctuations. Small-vessel ischemic episodes, many of which are silent, are the primary cause of chronic TOD, including progressive white matter (ie, multi-infarct) disease in the brain and hypertensive nephropathy.[44,45] Cerebral microbleeds, which are identified by imaging of hemosiderin deposits on brain magnetic resonance imaging (MRI) scans, are a relatively new class of subclinical brain injury associated with chronic HTN and portend more rapid cognitive decline in older adults.[46-48]

Unlike the pattern of TOD that occurs with poorly controlled chronic HTN, a hypertensive emergency results from acute endothelial injury triggered by an abrupt rise in vascular pressure that overwhelms autoregulatory mechanisms. A subsequent drop in nitric oxide (NO)–mediated vascular smooth muscle relaxation and excess release of endothelin further increase SVR, which functionally maintains BP at severely elevated levels. Unchecked wall tension ensues, and terminal arterioles dilate and eventually rupture, leading to a proinflammatory hypercoagulable state, with fibrin deposition and diffuse ischemia.[49] Rising pressure in the proximal capillary beds causes fluid leakage and tissue edema, which, combined with the process of fibrinoid necrosis, produces acute TOD along with microangiopathic hemolytic anemia and other signs of small vessel injury.

CLINICAL FEATURES

Although BP elevation alone does not define any particular clinical syndrome, acute TOD does not occur in the absence of moderate to severe HTN (ie, ≥180/110 mm Hg). Conversely, in the absence of symptoms, the mere presence of an excessively high BP in the ED (regardless of the level) does not herald imminent development of TOD.

Hypertensive Emergency

Most hypertensive emergencies occur in patients with chronic HTN.[50] Organ system involvement is relatively consistent and is dominated by injury to the heart, brain, or kidneys (Table 74.2). True hypertensive emergencies are defined by the target organ acutely involved. Focal neurologic deficit or altered mentation point to brain injury, whereas chest pain or shortness of breath may be indicative of cardiac or vascular involvement. Although frequently accompanied by an elevated BP, symptoms such as headache, epistaxis, and dizziness are not, in and of themselves, evidence of acute TOD and, in isolation, do not constitute a hypertensive emergency nor do they indicate the need for acute BP reduction.

TABLE 74.2

Hypertensive Emergencies by Organ System

INJURY PATTERN BY TARGET ORGAN	APPROXIMATE INCIDENCE[a] (%)
Heart (cumulative)	27–49
• Acute heart failure	14–37
• Acute coronary syndrome	11–12
Brain (cumulative)	37–45
• Acute ischemic stroke	6–25
• Spontaneous intracranial hemorrhage	5–23
• Hypertensive encephalopathy	8–16
Kidney	
• Acute renal risk	15
• Acute kidney injury	8
Vascular	
• Aortic dissection	1–2
Other	
• Eclampsia	2
• Acute hypertensive retinopathy	1

[a]Adapted from Levy P: Hypertensive emergencies: on the cutting edge. Advancing the standard of care: cardiovascular and neurovascular emergencies. www.emcreg.org.

Hypertensive Encephalopathy

Hypertensive encephalopathy is the essential factor in hypertensive emergencies. Resulting from diffuse, vasogenic cerebral edema, it is caused by a failure of autoregulation in the brain, with vasospasm, ischemia, increased vascular permeability, punctate hemorrhages, and interstitial edema. Severe headache, vomiting, and altered mental status are common features, which may progress to seizures or coma. Retinal involvement may cause blurred vision progressing to complete blindness. When present, focal neurologic deficits do not follow a singular anatomic pattern and may occur on opposite sides of the body, indicating diffuse cerebral dysfunction rather than an anatomically localized stroke syndrome or space-occupying lesions. Papilledema, although difficult to recognize, is often present, along with significant hypertensive retinopathy. Computed tomography (CT) may not show acute hemorrhage or other acute pathology. Diffuse or regional cerebral edema and small hemorrhages have been reported. The combination of diffuse cerebral dysfunction on clinical examination, normal or nonspecific CT scan, and markedly elevated systemic BP, particularly if supported by objective findings such as papilledema or retinal hemorrhage, is sufficient to make a presumptive diagnosis of hypertensive emergency and necessitates the initiation of acute antihypertensive therapy. Hypertensive encephalopathy is fully reversible with early, prompt BP reduction (30%–40% decrease); recently published data from the Nationwide Inpatient Sample have suggested that the overall in-hospital mortality rate is less than 1%.[51]

First defined in 1996, posterior reversible encephalopathy syndrome (PRES) has a neurologic presentation similar to that of hypertensive encephalopathy, albeit with less global and more region-specific features. Also caused by increased vascular permeability secondary to endothelial damage with vasogenic edema, PRES is characterized by a constellation of symptoms related to posterior cerebral impairment, including visual changes, headache, altered mental status, and seizures.[52] It is diagnosed by the visualization of white matter edema in the posterior parietal-temporal-occipital regions on MRI. As the name suggests, PRES is reversible by treating the underlying cause. HTN is the most common condition associated with PRES, although it may also be seen with kidney disease, malignancies, cytotoxic therapy, and autoimmune disease.

Other Hypertension-Related Emergencies

The clinical features of other hypertension-related emergencies cross over with nonhypertensive manifestations, and they are described in greater detail elsewhere in this text. Moreover, these conditions are defined by more than just HTN and, in many cases, their onset is incidental to, not caused by, elevated BP. However, long-standing HTN is often a contributor to the underlying problem and, when elevated BP is causal, effective treatment can have a dramatic impact on the clinical course. Elevated BP frequently accompanies acute intracranial hemorrhage, and the rapid initiation of antihypertensive therapy is a routine component of ED care (see Chapter 91). HTN is the primary population-attributable risk factor for the development of chronic cardiac dysfunction, and more than 50% of ED patients with acute heart failure have elevated BP on presentation (see Chapter 71). Patients with acute heart failure and HTN respond well to vasodilatory agents and afterload reduction. Nitroglycerin has long been used in the setting of acute coronary syndrome and demand ischemia (see Chapter 68), and antihypertensive therapy is a key component of ED management for acute aortic dissection (see Chapter 75). Acute kidney injury in the setting of elevated BP may be a consequence of associated TOD, especially acute heart failure, particularly when these patients are on baseline diuretic or calcium channel blocker therapy. Recent or chronic NSAID or newly initiated ACE inhibitor therapy may also contribute, but the effect of these agents are usually transient (see Chapter 87).[44] Pre-eclampsia and eclampsia are discussed in Chapter 178.

Blood Pressure Elevation

Acute Target Organ Damage in the Context of Systemic Illness

Any medical condition that leads to a hypermetabolic state can impair electrolyte homeostasis and trigger an intrinsic vasomotor response, causing BP to rise acutely. Depending on the circumstance, this may also be associated with clinical or diagnostic evidence of acute TOD. Distinguishing this from a true hypertensive emergency necessitates demonstration that the elevated BP does not contribute directly to the pathologic condition. Treatment of the underlying disorder will often resolve the BP elevation, although BP reduction may play a role in supportive management.

Absence of Target Organ Dysfunction

Most patients who are found to have significant HTN on intake vital signs measurement or who come to the ED because BP was found to be elevated in an outpatient setting or by self-measurement do not have an acute hypertensive emergency. For such patients, acute reduction of BP is not indicated and offers no tangible outcome benefit. Although many patients who fall into this group have poorly controlled chronic HTN, some will lack such a history. To connote an absence of acute TOD, these patients are often described by the term *asymptomatic*, but this is potentially misleading because nonspecific symptoms (eg, low-grade or recurrent headache, atypical chest pain, dyspnea, dizziness, generalized weakness, focal but anatomically uncorrelated weakness or numbness, vague visual disturbances) are frequently present. However, with the exception of dyspnea, the occurrence of these symptoms appears to be unrelated to the degree of BP elevation. In addition, despite widespread belief among the lay community and some members of the health care profession that acute severe HTN contributes to epistaxis, there is no evidence to support a causal relationship.[53]

As a general rule, acute BP reduction is not indicated in patients with elevated BP who lack acute TOD, even when vague symptoms are present. In many cases, BP will spontaneously improve with time, and there is no need to hasten this with antihypertensive therapy. If chronic oral medications have been missed, as is often the case, these should be restarted, perhaps with the first dose administered in the ED to reinforce the importance of future compliance, although this is in no way required and will not change any outcome. However, there are no data supporting a threshold BP that warrants such treatment or a target BP to be achieved before discharge. Importantly, the administration of a short-acting, potent antihypertensive agent such as clonidine or hydralazine simply to improve BP values lacks rationale or evidence of benefit and, according to a retrospective cohort study, may be associated with an increased likelihood of subsequent ED visit for issues related to HTN.[54] As previous experience with sublingual nifedipine has shown, BP reduction in the absence of acute TOD is also potentially dangerous, inducing relative cerebral hypoperfusion and increasing the likelihood of related morbidity and mortality, and should not be administered in the ED.

DIAGNOSTIC CONSIDERATIONS

Differential Diagnoses

Differential considerations are based on patient subtype. For those with a suspected hypertensive emergency, the decision point

centers on the potential causal relationship between patient presentation and acutely elevated BP. Clinical entities within this broader heading, such as stroke syndromes and acute heart failure, carry their own differentials, but a full discussion of each is beyond the scope of this chapter. Depending on the clinical scenario, ancillary testing may be needed to rule out alternatives to a hypertensive cause, particularly in patients with systemic illness. For those with poorly controlled chronic HTN, a consideration of cause (ie, primary vs. secondary) may be warranted. A related diagnostic evaluation (see Table 74.1) can usually be pursued on an outpatient basis, but for some (ie, individuals with multiple episodes of flash pulmonary edema, symptomatic paroxysmal episodes of labile BP, or suspected poor follow-up), initiation of treatment from the ED or admission to the hospital is needed. The final factor to consider is whether a newly detected BP elevation is caused by true HTN. Although the diagnostic accuracy of BP can be enhanced by a second repeat measurement in the ED, the ideal approach may be to average several measurements taken over a brief period of observation. For those without a previous history of HTN, definitive diagnosis will typically require reassessment in an outpatient setting.

Diagnostic Testing

The diagnostic evaluation of hypertensive emergency is guided by symptoms and signs identified on clinical examination but will often involve a number of tests. In nearly all cases, laboratory testing to look for acute or worsening renal dysfunction (ie, basic metabolic panel, urinalysis) and microangiopathic hemolytic anemia (ie, complete blood count with manual differential, peripheral smear) may be needed. Individuals with chest pain or shortness of breath may require a chest radiograph, electrocardiogram, and cardiac biomarker (ie, troponin, natriuretic peptide [NP]) measurement. Advanced cardiovascular imaging by CT, transesophageal echocardiography, or MRI should be considered if there is clinical suspicion for aortic dissection. When focal neurologic deficits or altered mentation is present, nonenhanced brain imaging by CT and, in many cases, MRI, will be needed, along with laboratory tests to evaluate for potential toxic, metabolic, or infectious causes.

Hypertensive retinopathy identified on funduscopy signifies underlying TOD and, when present, is strongly associated with an enhanced risk of stroke in patients with HTN.[55] Findings of acute hypertensive retinopathy include focal intraretinal periarteriolar transudates (whitish ovoid lesions deep in the retina), focal retinal pigment epithelial lesions (evidence of choroidal injury), macular and optic disk edema, and cotton wool spots (fluffy white lesions that consist of swollen ischemic axons caused by small vessel occlusion). Hard exudates, which consist of lipid deposits located deep in the retina, are also a common but late occurrence. When identified, such funduscopic abnormalities are considered diagnostic; however, they may be absent in more than 30% of patients with a clinically evident hypertensive emergency.[56] Lesions of acute retinopathy are distinct from more chronic changes, which include arterial narrowing, copper or silver wiring of the arterioles, arteriovenous nicking, and retinal hemorrhages. The spectrum of retinal findings in HTN can be graded on a five-point scale (Box 74.1). Despite such value, funduscopy is infrequently performed in the evaluation of severely elevated BP in ED patients. Technical challenges and a lack of experience likely contribute to this. Nonmydriatic digital fundus photography can help overcome these issues and has shown promise as an adjunct to detect chronic and acute changes associated with hypertensive retinopathy in the ED setting.[57]

Although funduscopy provides useful information, whether this or any other form of diagnostic evaluation is needed in the ED for those without overt TOD is a matter of debate. Although the JNC 7 has provided recommendations on routine testing in the primary care setting, there is no specific guidance for the ED.[13] In the only prospective multicenter study of JNC 7–recommended routine tests (ie, basic metabolic panel, urinalysis, electrocardiography, chest x-ray) performed in the ED, clinically meaningful abnormalities were detected in only 6% of patients, none of which were definitively attributable to HTN. However, in settings where HTN-related kidney disease is prevalent (eg, predominantly African American communities),[58] evaluation of renal function by a basic metabolic panel may be a reasonable consideration. Although such information is highly unlikely to affect emergent management, there is value in knowing baseline renal function and electrolyte levels, particularly if the initiation of chronic antihypertensive therapy is planned. Urine testing, especially spot measurement of the urine albumin-to-creatinine (Cr) ratio, is a reasonable alternative to detect subclinical kidney disease, although it does not provide information on electrolyte levels.[59] Newer markers of renal dysfunction, including cystatin C, neutrophil gelatinase-associated lipocalin, and kidney injury molecule–1, may also be considered, but their availability in most medical centers is limited,[60] and they are not indicated for an emergent evaluation.

Unlike renal function, there is no simple, efficient test for detecting subclinical cardiac disease in the ED, and evaluation in this setting is guided by symptoms. Although chest x-ray and electrocardiography are often used, they have poor sensitivity for TOD (especially LV hypertrophy), and abnormalities, when identified, are unlikely to alter clinical management.[61] Serum NP levels (ie, B-type NP [BNP] and N-terminal pro-BNP [NT-proBNP]) have yielded conflicting results and are not optimal screening tests, nor are they indicated for the emergent evaluation of HTN unless there is suspected cardiac TOD. Based on findings from a recent study, in which echocardiography was used as the criterion standard, the prevalence of subclinical hypertensive heart disease in select populations appears to be substantial (≈90%), suggesting the need for development of a more effective screening strategy.[62] Bedside cardiac ultrasound in the ED focused on the identification of LV hypertrophy and perhaps diastolic dysfunction has shown potential for this purpose[63-65]; however, validation of such an approach in large prospective trials will be needed before widespread adoption can be endorsed.

BOX 74.1

Funduscopic Grading of Suspected Hypertensive Retinopathy

Grade 0—normal
Grade 1—minimal arterial narrowing
Grade 2—obvious arterial narrowing with focal irregularities
Grade 3—arterial narrowing with retinal hemorrhages and/or exudate
Grade 4—grade 3 plus disk swelling

MANAGEMENT

Acute Blood Pressure Control

Antihypertensive Therapy

Antihypertensive therapy is indicated in treatment of acute hypertensive encephalopathy and in the presence of specific target organ injury (see earlier). The goal of acute antihypertensive therapy is to lower BP safely and effectively in a relatively rapid fashion while maintaining peripheral perfusion. Although some oral (ie, clonidine) or sublingual (ie, captopril, nitroglycerin)

medications are capable of this, patients who truly require acute lowering of BP benefit from the predictable controlled effects of a parenteral agent by titrated intravenous (IV) boluses or by adjustable infusion.

Mean arterial pressure (MAP), a summary measure that represents the average arterial pressure during one cardiac cycle, is a composite of circulatory inputs. The relationship is defined by the following equation:

$$MAP = (CO \times SVR) + CVP$$

where SVR reflects vasogenic tone in the arterioles (ie, afterload), CO reflects the pumping force of the heart, and central venous pressure (CVP) represents intravascular volume (ie, preload) and the effective hydrostatic force in the circulatory system. The hemodynamic response to a specific medication or class of medications is a function of how they interact with this equation and, as shown in Table 74.3, effects can differ substantially. Existing IV antihypertensive agents exert their effects directly through receptor-mediated actions (largely agonist or antagonist properties) or indirectly through a decrease in the production or release of endogenous vasoconstrictors. The magnitude of BP reduction reflects the mechanism of action as well as the pharmacokinetic and pharmacodynamic activity, with some variability in the latter based on aging.

According to the STAT (Studying the Treatment of Acute hyperTension) registry, labetalol and nitroglycerin are the most common IV antihypertensive medications used in the ED,[66] but outcome data related to different agents are lacking. Thus, although studies such as CLUE (Evaluation of IV Ni***c***ardipine and ***L***abetalol ***U***se in the ***E***mergency Department)[67] have suggested more favorable effects on BP reduction with nicardipine, a dihydropyridine calcium channel blocker, clear superiority of one drug over another has yet to be demonstrated. A general guide to IV antihypertensive therapy is provided in Table 74.4. However, depending on the desired response profile, certain agents may be more appealing than others for a specific indication.

Blood Pressure Goals

Optimal treatment of a true hypertensive emergency involves therapy that is directed toward the precipitant of specific TOD and the acute consequences of elevated BP rather than the BP itself. Based on recommendations in JNC 7, the long-standing approach to acute antihypertensive therapy has been to target a maximal reduction in MAP of 20% to 25% within the first hour and a goal BP of 160/100 mm Hg by 2 to 6 hours.[13] This arises from an understanding of the cerebral autoregulation curve, which maintains stable blood flow within a range of pressures (MAP of 60–160 mm Hg) under normal circumstances, but resets in chronic HTN with a shift of the lower limit toward the right. This shift tends to settle at a point approximately 25% below baseline MAP, resulting in concern for a decrease cerebral blood flow with BP reduction beyond this. Although such a consideration is relevant for patients who have poorly controlled chronic HTN, BP is often markedly elevated compared with baseline and well above the lower limit of the individual patient's autoregulation curve in the setting of a hypertensive emergency. Consequently, a margin of safety exists in this case, with antihypertensive therapy serving to bring BP down to (rather than along) the perfusion plateau from the ascending portion of the autoregulation curve (Fig. 74.2). Use of a single BP goal for all hypertensive emergencies fails to account for this and may preclude the ability to interrupt the pathophysiology causing acute TOD effectively. Therefore, the best approach is to focus on condition-specific targets. An overview of respective treatment goals and relevant caveats for differing indications is found in Table 74.5.

Acute Coronary Syndrome and Acute Heart Failure

In acute coronary syndrome complicated by HTN, the primary goal (beyond expeditious reperfusion) is a decrease in cardiac work and improved coronary artery perfusion, each of which can be dramatically affected by changes in afterload. Similarly, in

TABLE 74.3

Hemodynamic Effect Profile of Common Intravenous Antihypertensive Medications

		HEMODYNAMIC EFFECT		
CLASSIFICATION	AGENT(S)	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE	CENTRAL VENOUS PRESSURE
Adrenergic inhibitors				
• α_1-Blockers	Phentolamine, urapidil[a]	↑	↓	↑
• β_1-Blockers	Esmolol, metoprolol	↓	↑↓	↑↓
• Mixed α_1–β_1 blockers	Labetalol	↓	↓	↑↓
Angiotensin-converting enzyme inhibitors	Enalaprilat	↑↓	↓	↑↓
Calcium channel blockers				
Dihydropyridine	Clevidipine, nicardipine	↑	↓	↑↓
Nondihydropyridine	Diltiazem, verapamil	↓	↓	↑↓
Direct-acting vasodilators	Hydralazine	↑	↓	↑↓
Dopamine-1 receptor agonists	Fenoldopam	↑↓	↓	↑↓
Loop diuretics	Furosemide, bumetanide, torsemide	↑↓	↓	↓
Natriuretic peptide receptor agonists	Nesiritide	↑	↓	↓
Nitric oxide donors	Sodium nitroprusside, nitroglycerin, isosorbide dinitrate	↑	↓	↓

[a]Also has serotonin-1A (5-HT1A) agonist properties.
Adapted from Levy P: Hypertensive emergencies: on the cutting edge. Advancing the standard of care: cardiovascular and neurovascular emergencies. www.emcreg.org.

TABLE 74.4

Guide to Intravenous Antihypertensive Therapy

MEDICATION BY CLASS	BOLUS OR LOADING DOSE	INFUSION RATE	TIME TO ONSET	DURATION OF ACTION	COMMENTS
ADRENERGIC INHIBITORS					
Phentolamine	5–15 mg q5min	0.2–0.5 mg/min	1–2 min	10–30 min	Avoid with coronary artery disease
Urapidil	12.5–50 mg q5min	9–30 mg/hr	1–2 min	2.5 hr	Not FDA approved
Esmolol	0.5–1 mg/kg × 1	50–300 μg/kg/min	1–2 min	20 min	
Metoprolol	5 mg q5min	None	10–30 min	5–8 hr	
Labetalol	20–80 mg q10min	1–2 mg/min	2–5 min	3–6 hr	Beta blocker effects predominate (1:7)
ACE INHIBITOR					
Enalaprilat	0.625–1.25 mg q15min	1–2 mg/hr	15–30 min	6–12 hr	May produce prolonged hypotension; avoid in pregnancy
CALCIUM CHANNEL BLOCKERS					
Clevidipine	None	2–32 μg/hr	1–2 min	1–5 min	
Nicardipine	None	5–15 mg/hr	5–15 min	4–6 hr	Avoid with aortic stenosis and liver failure (hepatic metabolism)
Diltiazem	0.25–0.35 mg/kg q15min	5–15 mg/hr	5–15 min	6 hr	Will decrease blood pressure but not often used for this indication
Verapamil	2.5–5 mg IV q15min	None	5–15 min	6 hr	
DIRECT-ACTING VASODILATOR					
Hydralazine	5–20 mg q30min	1.5–5 μg/kg/min	10–20 min	2–4 hr	Causes reflex activation of the sympathetic nervous system
DOPAMINE ANTAGONIST					
Fenoldopam	None	0.1–0.3 μg/kg/min; titrate by 0.1 μg/kg	<5 min	30 min	Increases intraocular pressure; contains sodium metabisulfate—avoid in patient with sulfa allergy
LOOP DIURETICS					
Furosemide	40–240 mg q12hr	10–40 mg/hr	30–60 min	2–4 hr	Limited antihypertensive effect compared with other agents listed
Bumetanide	0.5–4 mg q12hr	None	30–60 min	2–4 hr	
Torsemide	10–20 mg q12hr	None	30–60 min	2–4 hr	
NATRIURETIC PEPTIDE					
Nesiritide	2 μg/kg × 1	0.01 μg/kg/min	15 min	18 min	Indicated only for use in acute heart failure
NITRIC OXIDE DONORS					
Sodium nitroprusside Nitroglycerin Isosorbide dinitrate	None 1–2 mg q5min 3–4 mg q5min	0.25–10 μg/kg/min 5–200 μg/min 1–10 mg/hr	Immediate 2–5 min 2–5 min	1–2 min 5–10 min 5–10 min	May cause precipitous drop in blood pressure with right ventricular ischemia or renal artery stenosis; bolus administration controversial; risk of cyanide toxicity with nitroprusside; avoid entire class in patients taking phosphodiesterase–5 inhibitors (eg, sildenafil)

ACE, Angiotensin-converting enzyme; *FDA*, US Food and Drug Administration; *IV*, intravenously.

patients with acute hypertensive heart failure, in which a rise in SVR—more specifically the augmentation index—impedes forward flow and exacerbates ventricular stiffness, intervention aimed at reducing afterload can offset resistive forces, enabling more effective contraction. Nitric oxide (NO) donors (medications that exert their effect by providing an exogenous source of NO), such as nitroglycerin, can be highly beneficial in both circumstances because they produce small-vessel dilation, which yields a dose-dependent decrease in overall vascular resistance, and diminish the intensity of arterial waveform reflection, thus improving systolic ejection time and diastolic coronary artery filling.

Rapid reduction in MAP has been associated with profound symptom resolution and improved short-term outcomes among patients with severe, acute hypertensive heart failure.[68] As shown in Fig. 74.3, this may be due to improved coronary perfusion and a decrease in subendocardial ischemia. Achieving this may require higher doses of nitroglycerin than most emergency clinicians are accustomed to (ie, 1–2 mg by bolus or infusion rates greater than 250 μg/min), but this approach appears to be well tolerated, with

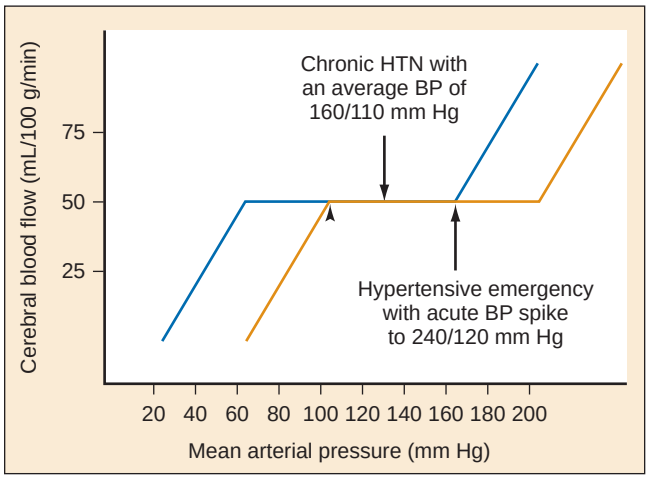

Fig. 74.2. Cerebral blood pressure (BP) autoregulation curve *(black line)* and its right shift response to chronic hypertension (HTN; *red line*). Data shown are for a hypothetical patient with chronic hypertension and poor blood pressure control at baseline *(blue arrow)* with a hypertensive emergency *(black arrow)*. As indicated by the *arrowhead*, the lower limit of the shifted autoregulation curve in this scenario sits well beyond a 25% reduction in mean arterial pressure.

no adverse effects, even at MAP reductions of 30% to 40%. Moreover, using nitroglycerin in this manner avoids the challenges associated with alternatives such as sodium nitroprusside, including the need for arterial line monitoring, risk of cyanide toxicity, and potential for compound photodegradation. Perhaps the only caveat is that NO donors should be used with caution in patients who have taken a phosphodiesterase-5 (PDE5) inhibitor such as sildenafil (Viagra) or tadalafil (Cialis) within the preceding 24 to 48 hours because this can result in more a profound BP decrease and persistent hypotension.

ACE inhibitors are also well tolerated and have been associated with rapid symptom improvement in patients with hypertensive heart failure. Enalaprilat can be administered by IV bolus or infusion and is the preferred ACE inhibitor in the setting of acute heart failure, but cautious dosages (0.625–1.25 mg/dose, up to a maximum of 2.5 mg over 30 minutes) are recommended because the drug is long-acting and can precipitate a sustained drop in BP. Given their short half-life, third- and fourth-generation IV dihydropyridine calcium channel blockers (eg, nicardipine, clevidipine) have been emerging as potential alternatives, with at least one prospective trial suggesting that this class can safely and effectively reduce BP while improving dyspnea more rapidly than standard therapy in those with acute hypertensive heart failure.[69] Labetalol and other IV agents with inhibitory β-adrenergic effects, such as metoprolol, should be avoided in the early stages of treatment because they produce a decrease in CO and, in acute coronary syndrome, may increase the risk of developing cardiogenic shock.[70]

Although BP reduction drives symptom improvement in acute hypertensive heart failure, adverse events are more likely to occur when BP is rapidly normalized (ie, decreased to ≤120/80 mm Hg), particularly in the setting of compromised cardiac function.[71] Therefore, antihypertensive therapy for acute coronary syndrome or acute heart failure should be titrated to symptom resolution rather than a specific MAP, with short-term tolerance of persistently elevated BP in a clinically improving patient.

Aortic Dissection

With aortic dissection, unlike for other hypertensive emergencies,, BP control to a specific target (systolic BP < 110 mm Hg) is essential because it decreases ongoing injury and reduces the likelihood of perioperative adverse events.[72] The immediate goal is to reduce intimal shear forces by driving down the pressure that results from LV ejection with each cardiac cycle (termed *dP/dt*). This is best accomplished by decreasing heart rate and stroke volume through administration of a rapid-acting IV beta blocker, such as esmolol. Although a direct reduction in BP is also critical, it is important that beta blocker therapy be initiated before vasodilation because the latter can lead to reflex tachycardia and worsening of dP/dt. Once beta blockers have been initiated, and a heart rate of less than 60 beats/min has been achieved, agents such as sodium nitroprusside, nicardipine, or clevidipine can be rapidly titrated to reduce systolic BP as low as can be tolerated (and, ideally, to <120 mm Hg) within 30 minutes. Because labetalol has both alpha and beta blocker properties, it may be an acceptable alternative, particularly if used as a continuous infusion. Diltiazem and verapamil, which are both mixed calcium channel blockers (ie, agents with cardiac and vascular effects), may also be used, although neither is ideal as monotherapy. For patients with persistently elevated BP, despite initial therapy, the use of multiple agents from different classes may be needed.

Acute Ischemic Stroke

Understanding the nuances of elevated BP in acute ischemic stroke is critical. A U-shaped relationship exists between mortality and BP, with worse outcomes at the high and low extremes. The optimal range appears to lie between 120 and 200 mm Hg systolic, and 81 to 110 mm Hg diastolic, but consensus on a specific target or threshold for treatment is lacking. Current American Heart Association/American Stroke Association (AHA/ASA) guidelines call for a BP reduction to below 185/110 mm Hg only when thrombolysis is planned, with maintenance of BP at below 180/110 in such cases. Otherwise, antihypertensive therapy is not indicated unless BP is higher than 220/120 mm Hg and, even in such cases, the goal is to decrease BP by approximately 15% gradually, over the first 24 hours after symptom onset.[73] The AHA/ASA guidelines are supported by a metaregression of BP control trials in stroke that suggest the following: (1) an association between large rises or falls in BP and worse outcome; and (2) a decrease in death and/or dependency with more modest BP reduction.

Based on these recommendations, and considering data from two large randomized studies (Scandinavian Candesartan Acute Stroke Trial [SCAST]; $N = 2029$[74] and China Antihypertensive Trial in Acute Ischemic Stroke [CATIS]; $N = 4071$])[75] that showed no benefit with BP reduction over the first 24 hours, there appears to be a limited role for ED management of elevated BP in patients with acute ischemic stroke who will not undergo thrombolysis. However, a subanalysis of SCAST also showed a trend toward reduced vascular events (but not functional outcomes) among those treated within 6 hours of symptom onset,[74] suggesting a possible time-dependent component, with increased susceptibility to the adverse effects of sustained BP elevation earlier in the disease course.

For patients who need IV antihypertensive therapy, labetalol and nicardipine have emerged as the agents of choice because they maintain adequate cerebral perfusion while producing generalized reductions in vascular resistance. Nicardipine may offer some advantage over labetalol because it results in a more rapid and sustained achievement of BP goals with reduced BP variability, a potentially important determinant of patient outcome.[76,77] Esmolol may also be used, although its BP effects depend more on a reduction in CO than systemic vascular resistance. Although sodium nitroprusside is a highly effective antihypertensive option, it and other NO donors should be avoided because they can cause an increase in intracranial pressure.

TABLE 74.5

Indication-Specific Approach to Management of Hypertensive Emergencies

INDICATION	GOALS OF TREATMENT	OPTIMAL AGENTS	ALTERNATIVE THERAPY	CAVEATS
Acute coronary syndromes	Diminish cardiac workload and improve coronary artery perfusion	*Primary*—nitroglycerin *Secondary*—metoprolol, labetalol	Esmolol, nicardipine	Routine use of intravenous beta blocker therapy is controversial.
Acute heart failure syndromes	Reduce impedance to forward flow and diminish cardiac workload	*Primary*—nitroglycerin, furosemide *Secondary*—enalaprilat	Clevidipine, nicardipine, sodium nitroprusside	Intubation or noninvasive ventilatory support decreases preload and may drop BP. Enalaprilat may cause sustained hypotension. Although FDA-approved, use of nesiritide is controversial.
Aortic dissection	Reduce shear force and dP/dt	*Primary*—esmolol plus sodium nitroprusside *Secondary*—labetalol	Esmolol plus (clevidipine or nicardipine), diltiazem, verapamil	Avoid beta blockers if aortic regurgitation is present.
Acute ischemic stroke[a]	Reduce hemorrhagic conversion and edema while avoiding regional hypoperfusion	*Primary*—nicardipine *Secondary*—labetalol	Esmolol	Acute BP reduction is indicated only with planned fibrinolytic administration or when secondary target organ dysfunction is involved.
Acute intracerebral hemorrhage[a]	Reduce hematoma expansion and perihematomal edema	*Primary*—nicardipine *Secondary*—labetalol	Esmolol	BP may decrease with pain management alone. Clevidipine is currently under investigation.
Hypertensive encephalopathy[a]	Decrease brain edema, reduce intracranial pressure, improve autoregulatory control	*Primary*—nicardipine *Secondary*—labetalol	Esmolol, enalaprilat	Other causes of altered mental status should be considered in the evaluation.
Acute kidney injury	Decrease pressure in renal parenchyma and glomerular apparatus	*Primary—Secondary*—clevidipine, nicardipine	Labetalol, sodium nitroprusside	Angiotensin-converting enzyme inhibitors and diuretics should be avoided.
Preeclampsia and eclampsia	Decrease intracranial pressure while maintaining placental perfusion	*Primary*—hydralazine *Secondary*—labetalol	Nicardipine	Intravenous magnesium (6 g initially) is administered in all cases. Emergent cesarean section is definitive treatment.
Sympathetic crisis	Reduce alpha$_1$-adrenergic receptor–mediated vasoconstriction	*Primary*—phentolamine *Secondary*—nitroglycerin	Fenoldopam, clevidipine, nicardipine, sodium nitroprusside	Benzodiazepines are first-line therapy when sympathetic crisis is caused by cocaine or amphetamines. Beta blocker monotherapy (including labetalol) is contraindicated.

[a]Nitric oxide donors and hydralazine should be avoided with these indications.
BP, Blood pressure; *dP/dt,* change in pressure/change in time; *FDA,* US Food and Drug Administration.
Adapted from Levy P: Hypertensive emergencies: on the cutting edge. Advancing the standard of care: cardiovascular and neurovascular emergencies. www.emcreg.org.

Spontaneous Intracranial Hemorrhage

Spontaneous intracranial hemorrhage (ICH) is strongly associated with HTN, and persistently elevated BP contributes to hematoma expansion, vasogenic edema, and rebleeding. A large systematic review[78] and several multicenter trials have shown improved outcomes with BP reductions to 140 to 150 mm Hg.[79-82] In contrast to ischemic stroke, there is little evidence to suggest adverse outcomes from hypotension in ICH. The 2010 AHA/ASA guidelines recommended rapid reduction when the systolic BP exceeds 200 mm Hg or MAP exceeds 150 mm Hg and stated that a target systolic BP of 140 mm Hg is safe for such patients.[83] When more modest elevations are present (systolic BP > 180 mm Hg or MAP > 130 mm Hg), lower targets are indicated (BP, 160/90 mm Hg, or MAP, 110 mm Hg).

Although reasonably informative, these guidelines were developed based on incomplete efficacy data that included limited information on the ideal time to achieve BP targets. Results from the recent Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2; $N = 2829$) augment the AHA/ASA guidelines and indicated the following: (1) an association between intensive antihypertensive therapy targeting a systolic BP of 140 mm Hg within 1 hour; and (2) improved functional outcome at 90 days for patients with a baseline systolic BP between 150 and 220 mm Hg, although no difference in mortality or major disability was found.[84] However, in a recent post hoc analysis of INTERACT2, patients who achieved a reduction in systolic BP of 20 mm Hg or more within the first hour of treatment ($N = 1092$) were 35% less likely to experience a poor outcome, suggesting that optimal recovery from acute ICH requires early, intensive antihypertensive therapy.[85] Data from the Antihypertensive Treatment of Cerebral Hemorrhage (ATACH II) study (NCT01176565), which has enrolled 1280 patients and has included an intervention arm of target systolic BP lower than 140 mm Hg within 4.5 hours

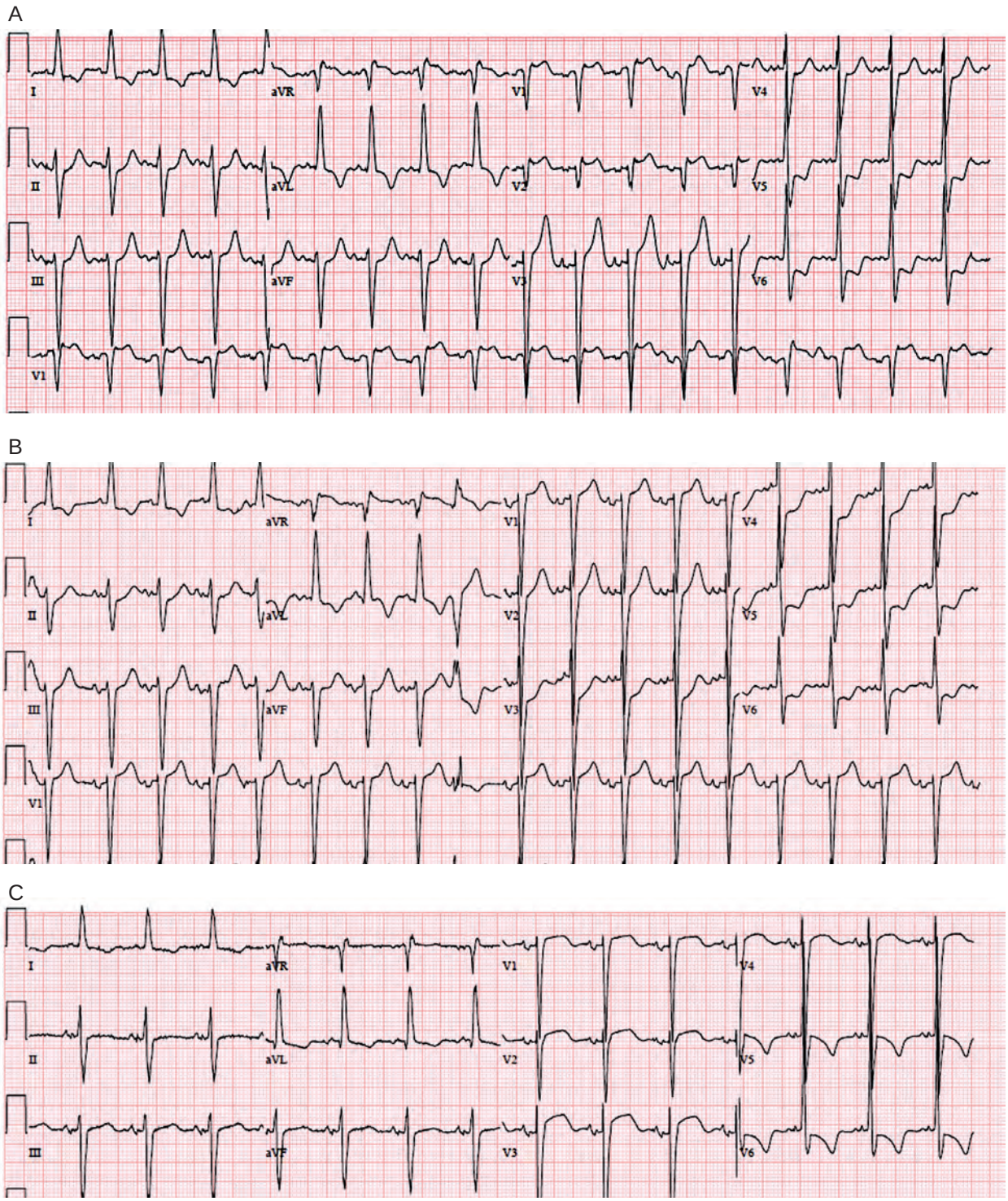

Fig. 74.3. Serial electrocardiograms demonstrating resolution of relative myocardial ischemia in a profoundly hypertensive patient with acute heart failure after treatment with high-dose intravenous nitroglycerin. **A,** BP, 241/122 mm Hg. Anterior leads (V1–3) show ST segment elevation and lateral leads (V5–6) show ST depression. **B,** BP, 192/103 mm Hg. Anterior lead ST elevation has resolved, but lateral lead ST depressions persist. **C,** BP, 150/92 mm Hg. ST segment deviations have largely resolved.

of ICH onset, will have provided much needed additional insight into the timing and intensity of BP control in this patient population.[86]

As with ischemic stroke, labetalol and nicardipine are the preferred agents for acute BP reduction. However, in INTERACT2, the choice of antihypertensive therapy was at emergency clinician discretion and urapidil, an α-adrenergic antagonist, was the most commonly used agent (32.5%) in the intensive treatment arm, followed by nitroglycerin or nitroprusside (27.0%), nicardipine (16.2%), and labetalol (14.4%). Whether such heterogeneity in antihypertensive therapy may have influenced outcomes is not known, making the pending ATACH-II study, in which nicardipine

is being used exclusively, all the more important. Nimodipine, an oral dihydropyridine calcium channel blocker, is specifically indicated for patients with subarachnoid hemorrhage, although its benefit appears to be related more to a reduction in intracranial arterial vasospasm than to an effect on SVR.

Hypertensive Encephalopathy

Unlike acute stroke syndromes, in which HTN may be reactive rather than causative, a direct association exists between the degree of BP elevation and neurologic symptoms in patients with hypertensive encephalopathy. Once alternative causes of altered mentation have been ruled out, therapy should be directed toward the initiation of rapid BP reduction. The goal is to return BP to a point at which autoregulation can regain control of cerebral blood flow and the process leading to cerebral edema can be reversed—a circumstance that necessitates MAP to be brought back down to the pressure curve plateau. To achieve this, reductions in MAP of 30% to 40% may be needed. Whereas MAP targets should still be kept in mind, symptom resolution is the best gauge of therapeutic effectiveness, with treatment directed specifically toward improvement of encephalopathy.

The agents of choice for BP reduction in hypertensive encephalopathy are labetalol and nicardipine because they produce an even decrease in resistance across vascular beds in different organ systems. In contrast, NO donors (nitroglycerin and nitroprusside), although widely used for this indication, have a differential effect on the cerebral and systemic circulations, resulting in a relative increase in cerebral BP and a shunt effect to the peripheral circulation. This serves to decrease cerebral blood flow and may produce a greater than anticipated reduction in cerebral perfusion, thereby increasing the risk of ischemia in watershed areas of the brain. This may be worsened by the relative increase in intracranial pressure known to occur with sodium nitroprusside therapy. Several case reports have described neurologic deterioration with administration of nitroglycerin in posterior reversible encephalopathy syndrome (PRES), a subtype of hypertensive encephalopathy, supporting this as an actual rather than theoretical concern.[87] Similar differential circulatory effects may also occur with hydralazine (a direct-acting vasodilator that inhibits calcium release from the sarcoplasmic reticulum) and, unless BP is completely refractory to other therapy, it is best to avoid use of these agents.

Acute Kidney Injury

Defined by an increase in serum creatinine level of 0.3 mg/dL or more in 48 hours, 1.5 or more times baseline in 7 days, or a urine volume of less than 0.5 ml/kg/hr over 6 hours,[88] acute kidney injury (AKI) represents an abrupt worsening of renal function. Although often a manifestation of ongoing glomerular injury from chronic poor BP control, deterioration of kidney function in the setting of severe HTN may be precipitated by prerenal causes, including volume depletion (often related to concurrent diuretic therapy), extrinsic alterations in the GFR (often triggered by drug-mediated, afferent arteriolar vasoconstriction and ACE inhibitor–induced autoregulatory modulation) or intrinsic nephron destruction caused by acute pressure overload. Consequently, some patients require fluid administration to augment volume, whereas others need antihypertensive therapy to mitigate pressure-mediated nephrogenic damage.

Laboratory testing is useful to differentiate which approach should be initiated. A blood urea nitrogen (BUN)/Cr ratio higher than 20 and a fractional excretion of sodium (FENa); calculated as

$$\frac{\text{Urine Na}\times\text{Serum Cr}\times 100}{\text{Serum Na}\times\text{Urine Cr}}$$

below 1%—or for those on chronic diuretic therapy, a fractional excretion of urea (FEurea); calculated as

$$\frac{\text{Serum Cr}\times\text{Urine urea}\times 100}{\text{Serum urea}\times\text{Urine Cr}}$$

below 35%—serve as indictors of a prerenal cause.

When antihypertensive therapy is indicated, fenoldopam, a potent dopamine 1A receptor agonist, is preferred because it leads to improved perfusion of the corticomedullary region and has been associated with a reduction in need for subsequent dialysis and rate of in-hospital death. Enalaprilat should be avoided because it produces differential effects on the precapillary and postcapillary glomerular vascular bed (ie, greater vasodilation in efferent than afferent arterioles), which increases the risk of further deterioration in estimated GFR. Peripheral-acting calcium channel blockers, such as clevidipine and nicardipine, have no adverse effect on glomerular autoregulation and are acceptable first-line alternatives to fenoldopam. Other agents, including labetalol and sodium nitroprusside, may also be used.

Preeclampsia and Eclampsia

Although delivery is the definitive treatment, BP control is a critical part of early management.[89] Similar to hypertensive encephalopathy, preeclampsia and, to a greater degree, eclampsia, represent an overwhelming of cerebral autoregulation, and rapid BP reduction is essential. Because they are acute (rather than chronic) complications in a relatively healthy young population, there is generally no resetting of the autoregulation curve in preeclampsia or eclampsia, and adverse consequences can develop at seemingly "low" (but relatively high) pressures. The threshold for intervention, therefore, is set lower than with other hypertensive emergencies (ie, systolic BP exceeding 160 mm Hg).[90]

Magnesium sulfate is considered first-line therapy for all cases of preeclampsia and eclampsia.[91] It relaxes smooth muscle (partly through calcium antagonism), which leads to some decrease in peripheral and cerebral vascular resistance, limits cerebral edema formation by protecting the blood-brain barrier, and has central anticonvulsant activity. However, its antihypertensive effects are modest, and additional treatment is typically needed to control BP. Hydralazine and labetalol by IV bolus are equally effective for this purpose and have a limited impact on placental blood flow.[92] Nicardipine is a reasonable alternative and may produce a more profound decrease in BP than labetalol.

Sympathetic Crises

Hyperadrenergic states can result from endogenous sources of catecholamine excess (ie, pheochromocytoma) but, more commonly, they are triggered by the intake of exogenous substances that interfere with norepinephrine—and to a lesser degree, epinephrine—metabolism, such as cocaine, amphetamines, and tyramine-containing foods, especially in patients on monoamine oxidase inhibitors. The net result is a cardiostimulatory and vasopressor response that manifests clinically as tachycardia and marked HTN. In patients with cocaine or amphetamine intoxication, such peripheral effects are compounded by central sympathetic activation, and the hemodynamic derangements can often be improved by the administration of benzodiazepines and other sedative medications.

When BP is persistently elevated and target organ compromise is present, antihypertensive treatment will be needed. Phentolamine, a reversible pure alpha blocker, is considered first-line therapy, producing a reliable decrease in peripheral and coronary vasoconstriction, with few adverse effects. Nitroglycerin can also be used and is specifically indicated for patients with associated

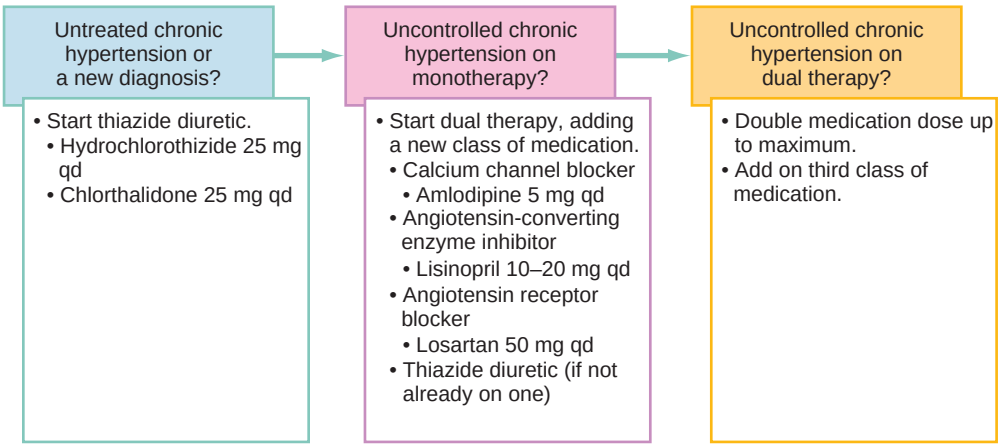

Fig. 74.4. Modified approach to initiation and escalation of antihypertensive therapy for use in ED patients Note that the proposed medications are representative of listed classes and may be substituted with equally dosed alternatives agents in the same class, as needed.

chest pain and suspected coronary artery vasospasm. Other agents, including fenoldopam, clevidipine, nicardipine, and sodium nitroprusside, are acceptable alternatives. Heart rate control may also be needed, especially in patients with pheochromocytoma, in whom adrenal release of epinephrine may be particularly high, and a short-acting beta blocker such as esmolol is ideal for this purpose. However, to avoid precipitation of unopposed alpha receptor activity and a worsening of HTN, beta blocker therapy should be paired with a vasodilator. Although labetalol has combined alpha and beta blocker properties, beta receptor effects strongly predominate when the drug is administered in IV form (alpha/beta ratio of 1:7). Consequently, IV labetalol is susceptible to a similar differential response and should be used with caution in the setting of catecholamine excess.

Chronic Antihypertensive Therapy

Poorly controlled chronic HTN on a single visit or a clear trend toward persistently elevated BP over time requires referral for timely follow-up, with reinforcement of goal BP recommendations and emphasis on the need for lifelong dietary and medication compliance. Initiation of oral antihypertensive therapy for new-onset HTN and re-initiation or uptitration for patients with chronic HTN is appropriate from the ED if follow-up cannot be ensured.[93] Although it is unclear whether this practice will have any impact on long-term outcomes, it is associated with a substantial reduction in BP at follow-up and appears to be safe.[94]

Although there are multiple medication options, a relatively simple algorithm for prescribing chronic antihypertensive therapy has been proposed by the AHA, starting with a thiazide diuretic for most patients.[95] Calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs) are included as acceptable first-line alternatives and recommended as add-ons for patients with persistent, poorly controlled BP. Because most patients with stage II HTN will ultimately require multiple agents to control their BP, initiation of two-drug therapy when the systolic BP is higher than 160 mm Hg or diastolic BP higher than 100 mm Hg is recommended.[13] There is increasing evidence that improved compliance with reduced side effects and outcome benefit can be achieved using low-dose combination tablets, especially combined ACE inhibitors and thiazide-like diuretics.[96-99]

The general approach proposed by the JNC 8 is similar but includes specific recommendations about the use of thiazide diuretics or calcium channel blockers as first-line therapy in blacks and ACE inhibitors or ARBs in patients with chronic kidney disease.[14] However, unlike the JNC 7, preferential use of ACE inhibitors or ARBs in diabetic patients is no longer recommended in JNC 8, and lower BP targets (ie, <130/80 mm Hg) for diabetics and those with chronic kidney disease are no longer endorsed. Moreover, the use of beta blockers as primary therapy has been greatly deemphasized, with inadequate BP control despite other maximum dosed agents, or the presence of underlying coronary artery disease or heart failure, serving as the main indications. Preferential beta blocker use was specifically emphasized in a recent scientific statement on the treatment of HTN in patients with coronary artery disease, as was a lower target BP (<130/80 mm Hg) when myocardial infarction, cerebrovascular disease, peripheral vascular disease, or heart failure is present.[100]

Neither the AHA algorithm nor JNC 8 recommendations specifically address treatment in the ED, but the basic principles of chronic antihypertensive therapy are relatively consistent and there is little reason to deviate from convention. Accordingly, a modified approach to the initiation and escalation of antihypertensive therapy for use in ED patients without significant comorbidity is presented in Fig. 74.4.

As emphasized throughout this chapter, acute BP reduction in the ED provides absolutely no benefit to patients with chronic HTN and exposes them to unnecessary risk of potential hypoperfusion in regions in which blood flow has been governed by long-standing autoregulation.[101] When these patients have symptoms such as headache or chest pain, and there is no suspicion of acute TOD, treatment should be directed toward the symptoms, not the BP. Anxiolytic or analgesic medication administration accompanied by resumption of chronic oral antihypertensive therapy is more rational and beneficial than initiation of short-acting antihypertensive therapy. However, care should be taken to avoid prescribing NSAIDs and other medications that can have a negative impact on BP control and results in the development of cardiovascular complications.

DISPOSITION

Individuals without evidence of acute TOD can be discharged home, but hypertensive emergency patients warrant admission, usually to an intensive care unit. Clinical features such as chest pain, dyspnea on exertion, or worsening renal function may confuse the picture, and short-term evaluation in an observation unit can be useful to determine whether the acute presentation represents a true emergency.

Outcomes associated with a given hypertensive emergency are largely a function of underlying TOD. However, data from STAT

have suggested that severe HTN (at least in the subset of patients in whom IV antihypertensives are administered) is a high-risk condition with in-hospital and 30-day mortality rates of 6.9% and 11%, respectively, and a 90-day readmission rate of nearly 40%.[102] When associated with AKI, mortality is even greater, with an odds ratio of 1.05 (P = .03)/10 mL/min estimated GFR decline.[103]

Although the risk for short-term deterioration is minimal in patients with elevated BP who lack evidence of acute TOD, the long-term risk of cardiovascular, cerebrovascular, and renovascular disease is relatively high,[8,102] underscoring the need for development of effective, patient-centric models of chronic HTN care at the system level.[99]

KEY CONCEPTS

- Elevated blood pressure with or without associated symptoms is exceedingly common in the ED.
- A true hypertensive emergency is defined by the presence of acute target organ damage and is distinct from other clinical presentations.
- An organ system–based approach to the evaluation and management of patients with elevated blood pressure can optimize decision making while ensuring timely delivery of antihypertensive therapy to those who need it.
- For patients who lack acute TOD, immediate antihypertensive therapy is not needed. However, emergency clinicians can play an important role in the care of this group, providing screening and ongoing surveillance to prevent secondary complications of this disease.
- Administration of a short-acting, potent antihypertensive agent such as clonidine, hydralazine, or nifedipine simply to improve BP values may be harmful and is not recommended in the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 74: QUESTIONS & ANSWERS

74.1. An 85-year-old man presents with acute onset of right-sided weakness that began 1 hour before arrival. His family states that he was recently diagnosed with dementia and has refused to take any of his medications for more than 1 week but had otherwise been relatively healthy. Emergency medical services (EMS) reports a prehospital blood pressure of 240/110 mm Hg. On examination, the patient has clear evidence of an acute stroke with severe deficit (National Institutes of Health [NIH] Stroke Scale = 24), but his gag reflex is intact. His initial blood pressure is 230/110 mm Hg. A head computed tomography (CT) scan shows diffuse white matter ischemic disease but no evidence of acute infarct or hemorrhage. The most appropriate next step is which of the following?

A. Contact neurosurgery for intracranial pressure monitoring.
B. Give a dose of tissue plasminogen activator (tPA) immediately.
C. Give sublingual nifedipine.
D. Intubate and paralyze the patient.
E. Repeat the blood pressure and, if 185/110 mm Hg or higher, start a nicardipine infusion at 5 mg/hr.

Answer: E. Despite his advanced age, this is a relatively high-functioning individual with acute onset of a severe stroke. He is within the time window for administration of tPA, but his blood pressure is excessively elevated. According to the American Heart Association/American Stroke Association guidelines, efforts should be made to reduce his blood pressure to less than 185/110 mm Hg before tPA administration. Other agents, such as labetalol, would also be appropriate to use.

74.2. A 27-year-old woman presents with lower back pain for 1 week. She recently moved into the community and has been busy unpacking and moving furniture. She denies any neurologic symptoms and has no medical history. Her

triage blood pressure is 170/110 mm Hg, but vital signs are otherwise normal. With the exception of appreciable muscle spasm in her lower back, the physical examination is normal. You give her 10 mg of diazepam and observe her for 1 hour. She is feeling better but her blood pressure is still elevated, at 165/90 mm Hg. At this point you should do which of the following?

A. Give her 0.2 mg of clonidine.
B. Ignore the blood pressure and discharge her without follow-up.
C. Order a renal ultrasound scan.
D. Order a 24-hour urine metanephrine and normetanephrine test.
E. Take a more extensive history to see if she is taking oral contraceptives.

Answer: E. This patient's blood pressure elevation is clearly not a reaction to her pain, and some further questioning is needed to identify a potential cause. In young women, oral contraceptive agents are a treatable cause of hypertension and should be considered when elevated blood pressure is encountered in these patients. Of note, the likelihood of contraceptive-related hypertension increases with the duration of use. It would not be unreasonable to discharge the patient without further exploring the potential cause of her elevated blood pressure, provided some provision of follow-up was sought. The clinical picture is inconsistent with renal artery stenosis or pheochromocytoma, and an evaluation for these conditions would be inappropriate at this point.

74.3. A 50-year-old man complains of dull chest pain that began 4 hours before arrival. The patient states he awoke this morning feeling well and that the pain began while shoveling his driveway. He has a 20-year history of hypertension and diabetes but has always been compliant with his medications, which include metformin, Norvasc, and Diovan. His initial blood pressure is 215/120 mm Hg, and his heart rate is 100 beats/min. On examination, his lungs are clear, heart sounds are normal, pulses are bounding and symmetric, and there are no neurologic deficits. An electrocardiogram shows nonspecific T wave inversions in the lateral leads, with no evidence of ST segment elevation or depression and normal intervals. The serum troponin level is elevated. Which of the following is the most likely explanation for his clinical presentation?

A. He has a ruptured dissecting aortic aneurysm that is leaking blood into the retroperitoneal space.
B. He is suffering from a massive pulmonary embolism.
C. He strained an intercostal muscle while shoveling.
D. He is suffering from subendocardial ischemia triggered by a cycle of increased afterload that began while he was shoveling.
E. His right coronary artery is 100% occluded.

Answer: D. Increased afterload can be triggered by exertional activation of the sympathetic nervous system. In the presence of long-standing hypertension, ventricular and aortic stiffness are likely to develop, increasing the potential for afterload-mediated effects on the heart. When suddenly faced with increased resistance, the left ventricular pressure may rise, leading to intrinsic compression of subendocardial myocytes and ischemia. Coupled with earlier transmission of the reflected arterial wave form, the diastolic coronary filling time may also be diminished, producing a clinical picture of acute coronary syndrome. He may also have a coronary artery lesion on which this is superimposed but, as described, the likelihood of his clinical presentation being caused by a complete right coronary occlusion is quite low.

74.4. Which of the following funduscopic findings would be the earliest indicator of acute hypertensive retinopathy in a comatose patient whose blood pressure is 260/140 mm Hg?

A. Copper and silver wiring appearance to the retinal arterioles
B. Cotton wool spots
C. Diffuse atrioventricular (AV) nicking
D. Focal intraretinal periarteriolar transudates
E. Retinal hemorrhages

Answer: D. Focal intraretinal periarteriolar transudates are the first abnormality to appear with acute hypertensive retinopathy, preceding all other findings, including cotton wool spots and disk edema. Other findings that are listed may also be seen, but they are indicative of chronic, not acute, retinal involvement. It is important to remember that acute retinal abnormalities may be absent in hypertensive emergency patients and, although funduscopy is an important tool, the diagnosis should be based primarily on the results of the clinical examination.

CHAPTER 75

Aortic Dissection

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PRINCIPLES

Aortic dissection (AD) is a longitudinal cleavage of the aortic media created by a dissecting column of blood. The term *dissecting aortic aneurysm* has been inaccurately applied to this entity since 1819, when Rene Laënnec first used the term *aneurysme dissequant*. Today, the term *aortic dissection* is preferred to dissecting aortic aneurysm because the affected aorta is only rarely aneurysmal. In 1955, Dr. Michael DeBakey and his team outlined the principles that remain the basis for the surgical treatment of this entity. Medical treatment of aortic dissection was first advocated in the 1960s and is indicated for certain types of dissections.[1-5] Another milestone in the management of aortic dissection was the establishment of the International Registry of Acute Aortic Dissection (IRAD) in 1996. The registry is a multinational repository of data that has been collected from 30 international centers of excellence and clinical investigators from 11 countries. Knowledge gained from the registry has been crucial because randomized controlled studies are difficult to conduct in the setting of a condition with such a high mortality.[2,5,6] The next major advance in the treatment of AD came in the late 1990s with the implementation and development of endovascular stent graft techniques for the treatment of certain types of aortic dissection. These interventional techniques have since revolutionized the treatment of some types of dissections.[7,8] Despite advances, in-hospital mortality rate for patients treated for aortic dissection remains at 27%.[4]

Epidemiology

Aortic dissection occurs three times more often in men than women, although women are more likely to present later and have a poorer prognosis. The incidence of aortic dissection also increases with age.[2,4,5] The exact incidence and prevalence of aortic dissection are difficult to determine because of underreporting of this condition. Mortality is 1 to 5/100,000 population/year. Hypertension is the most common risk factor associated with aortic dissection and is seen in most patients.[2,4,5] A history of cardiac surgery is present in 18% and bicuspid aortic valve in 14% of all patients with aortic dissections but is found more often in proximal dissections.[9] Atherosclerosis is rarely involved at the site of dissection. Patients with aortic dissection may have a positive family history.[4]

Aortic dissection is uncommon before the age of 40 years, except in association with congenital heart disease, connective tissue disease, or inflammatory vasculitides. As many as 44% of patients with Marfan syndrome, if untreated, develop aortic dissection and account for about 5% of cases. Women with Marfan syndrome are at particular risk during pregnancy.[10] In patients without connective tissue disease and with an aortic root size smaller than 40 mm, pregnancy does not appear to be an independent risk factor.[10] Loeys-Dietz syndrome is an autosomal dominant genetic syndrome associated with aortic aneurysms and skeletal features similar to Marfan syndrome. The vascular disease in these patients is rapidly progressive,and the mean age of death is 26 years.[11] Inflammatory vasculitides associated with thoracic aortic disease include Takayasu arteritis, giant cell arteritis, Behçet disease, and syphilis.[1,2] Acute aortic dissection also occurs with stimulant use, exertion, cardiac surgery[6] or intraaortic balloon pump insertion.

Blunt trauma from a high-speed deceleration injury usually causes traumatic aortic rupture, which is an entity distinctly different from aortic dissection (see Chapter 38).

Anatomy and Physiology

With each contraction, the heart simultaneously twists and swings from side to side, resulting in flexion of the ascending aorta and descending aorta. The descending aorta flexes just distal to the left subclavian artery, where the mobile aorta is tethered. At an average of 70 heartbeats/min, this sequence occurs about 37 million times annually, causing a repetitive stress on the aorta.

The aortic wall has three distinct layers—intima, media, and adventitia. The media is composed of elastic tissue and smooth muscle that give the aorta its properties for distensibility and integrity.[1,2] Dissection occurs through a degeneration of the media, characterized by loss of smooth muscle cells and elastic tissue and accompanied by scarring, fibrosis, and hyaline-like changes.

Pathophysiology

Medial degeneration is a precursor to aortic dissection and can be seen with normal aging. Hypertension hastens the progress of medial degeneration. Although initially thought to be noninflammatory, more recent evidence has suggested inflammatory cell infiltration in medial degeneration.

The repetitive hydrodynamic forces produced by the ejection of blood into the aorta with each cardiac cycle contribute to weakening of the aortic intima and to medial degeneration. These hydrodynamic forces primarily affect the ascending aorta. Sustained hypertension intensifies these forces and results in an increase in medial degeneration. A bicuspid valve, occurring in 1% to 2% of the population, is the most common congenital abnormality affecting the aortic valve and proximal aorta.[4] A bicuspid aortic valve may disrupt laminar flow and reorient the flow of blood toward the aortic wall, producing local injury. In Marfan and Ehlers-Danlos syndromes, normal hydrodynamic forces act on an aortic media that is already weakened.

As a result of medial degeneration and repeated flexion of the aorta, hydrodynamic stress tears the aortic intima, and a column of blood gains access into the aortic media. An alternative theory suggests that these forces damage the vasa vasorum of the aorta, which rupture and hemorrhage into the aortic media; this may explain the absence of an intimal tear in some cases of dissection. Regardless of which of these theories is correct, the depth of penetration into the media and distance and direction of dissection are at least partially determined by the degree of medial degeneration.

Once a dissecting hematoma is established in the media, migration of the hematoma occurs in an antegrade or retrograde fashion, or both, forming a so-called false lumen. The false lumen forms in the outer half of the media and propagates until it

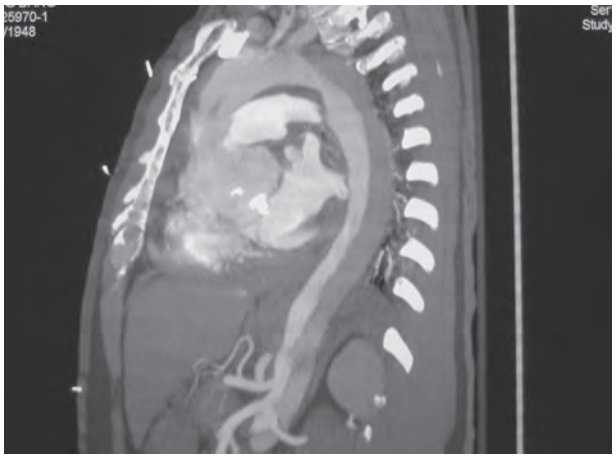

Fig. 75.1. Computed tomography reconstruction of Stanford type B or DeBakey type III dissection distal to the subclavian artery.

ruptures back into the true lumen of the aorta, resulting in a rare spontaneous cure, or through the adventitia into the pericardial sac or pleural cavity. Because the outer wall of the aorta that contains the hematoma is thin, rupture is much more likely to occur to the outside. The most important factors favoring continued dissection of the aorta are the degree of elevation of blood pressure and the steepness (slope) of the pulse wave (upstroke pattern on apex cardiogram, dP/dt). Both these hemodynamic factors need to be controlled to halt migration of the hematoma.

Classification

Anatomic classification is important for diagnosis and therapy. The Stanford Classification is the most commonly used system and is based on the anatomic location of the dissection. Type A dissections involve the ascending aorta and account for approximately 62% of all dissections. Type B dissections involve only the descending aorta and account for 38% of dissections (Fig. 75.1).[3-5] Dissections that involve the ascending aorta are more often lethal than those limited to the distal aorta and call for a different therapeutic approach. Patients with distal dissections tend to be older, smokers with chronic lung disease, and more often have generalized atherosclerosis and hypertension compared with patients who have proximal aortic dissections. A dissection is acute if it is less than 2 weeks' duration, subacute between 2 and 6 weeks duration, and chronic if present for longer than 6 weeks.[12]

Two other aortic conditions are closely related to aortic dissection, intramural hemorrhage.[13] and penetrating aortic ulcer. Both groups of patients have clinical symptoms and management recommendations similar to those for patients with aortic dissection. An intramural hemorrhage is a contained hematoma within the aortic wall and occurs in about 10% of aortic dissections.[4] Rupture of the vasa vasorum is believed to be the initial event. Penetrating atherosclerotic ulcers of the aorta occur in older hypertensive patients with evidence of coronary artery disease. Computed tomography (CT) shows a focal ulceration without dissection, usually in the distal descending aorta. The progression of penetrating ulcers results in progressive aortic enlargement, with saccular and fusiform aneurysm formation. Patients can have an intramural hematoma and penetrating atherosclerotic ulcer.

CLINICAL FEATURES

History

According to data gathered from the IRAD, pain is the most common presenting complaint, affecting more than 90% of patients.[1,2,4] Most cases of painless aortic dissection are chronic in nature. The pain is usually excruciating, occurs abruptly, is most severe at onset, and is typically described as sharp[4] more often than tearing or ripping. A family history of thoracic aortic disease may be reported.[14]

The location of the pain may help localize the dissection. Anterior chest pain is associated with the ascending aorta, neck and jaw pain with the aortic arch, pain in the interscapular area with the descending thoracic aorta, and pain in the lumbar area or abdomen with involvement below the diaphragm. Migration of the pain consistent with propagation of the dissection suggests aortic dissection but occurs in only 17% of cases.[4] The onset of aortic dissection is often accompanied by visceral pain symptoms, such as diaphoresis, nausea, vomiting, lightheadedness, and severe apprehension.

Syncope occurs early in aortic dissection in approximately 9% of cases and may be the sole presentation in some patients.[4] It usually heralds dissection into the pericardium, causing pericardial tamponade, but may occur from transient interruption of blood flow to the cerebral vasculature. Other causes of syncope from aortic dissection are hypovolemia, excessive vagal tone, and cardiac conduction abnormalities. Patients with aortic dissection and syncope have a higher mortality.[12] Neurologic symptoms such as focal weakness or change in mental status occur in up to 17% of cases.[1,2,4]

Physical Examination

The presentation varies greatly, depending on the patient and location and extent of the dissection. Generally, the patient appears apprehensive. Most patients have a history of chronic hypertension that may be exacerbated by a catecholamine release related to the acute event. Severe hypertension refractory to medical therapy may occur if the dissection involves the renal arteries with subsequent renin release. If hypotension is present, either the dissection has progressed back into the pericardium, with resulting pericardial tamponade, or hypovolemia has occurred from rupture through the adventitia.

Pseudohypotension, a condition in which the blood pressure in the arms is low or unobtainable, and the central arterial pressure is normal or high, may be present. This results from the interruption of blood flow to the subclavian arteries.

Aortic regurgitation occurs in up to 32% of patients and is more common with type A dissection.[4] The murmur of aortic insufficiency may have a musical vibrating quality of variable intensity, and congestive heart failure may develop. The patient with presumed aortic dissection should be examined carefully for findings that suggest hemorrhage into the pericardium or tamponade, such as jugular venous distention, muffled heart sounds, tachycardia, and hypotension.

When the integrity of one of the branches of the aorta is compromised, the expected ischemic findings occur. Pulse deficits and discrepancies in blood pressure between the limbs can be helpful, if present, but have a sensitivity of only around 30%.[4] Usually, these are present in the upper extremities and result from involvement of one or both of the subclavian arteries. Obstruction of one or both common iliac or superficial femoral arteries may produce pulse deficits in the lower extremities. Arterial obstruction may occur by either of two mechanisms. An intimal flap produced by the dissection may cover the true lumen of a branch vessel, or the dissecting hematoma may compress an adjacent true lumen. Frequent reexamination may detect transient pulse deficits. A so-called deadly triad of absence of chest pain, hypotension, and branch vessel involvement is an independent predictor of in-hospital death.

Neurologic findings are related to the site of blood flow interruption. Proximal dissections are a more frequent cause of strokes

or coma. Stroke treatment with a fibrinolytic agent for the patient with aortic dissection can be fatal. Distal dissection occluding the anterior spinal artery commonly causes ischemic paraparesis or ischemic peripheral neuropathy.[4]

In up to 3% of cases, a proximal dissection can dissect into the ostium of a coronary artery, usually the right coronary artery, and cause an acute myocardial infarction (MI), usually inferior to posterior.[4] Failure to identify the inciting aortic dissection, resulting in incorrect administration of a fibrinolytic agent, occurs in about 0.1% to 0.2% of MIs. Distal extension of aortic dissections into the abdomen can cause mesenteric ischemia, renal failure, femoral pulse deficits, and lower extremity ischemia.[15]

DIAGNOSTIC CONSIDERATIONS

Differential Diagnoses

The differential diagnosis for the patient with symptoms suggestive of aortic dissection is extensive. Signs and symptoms associated with aortic dissection vary and depend on the extent of aortic and branch vessel involvement. Patients with the ultimate diagnosis of aortic dissection are often initially thought to have other conditions, such as myocardial ischemia, congestive heart failure, or pulmonary embolus.[1,2,4] Several clinical syndromes are particularly suggestive of aortic dissection—chest pain that is of sudden onset, migratory pain, chest pain with concomitant neurologic deficits or syncope, and chest pain with pulse deficits.[4]

Although chest pain is the most common symptom of aortic dissection, it is also the most common presenting complaint of at least three other serious and more common clinical entities—acute MI, pulmonary embolus, and pericarditis. An electrocardiogram (ECG) can be helpful in excluding MI, although aortic dissection and MI may coexist as a result of the dissection proceeding retrograde to the ostium of a coronary artery and causing infarction. In cases in which aortic dissection is excluded, CT may reveal other abnormalities that explain a patient's presentation (eg, pulmonary embolus). Transesophageal echocardiography (TEE) is helpful in identifying causes of chest pain other than aortic dissection (eg, cardiac ischemia).

When the initial presentation of the aortic dissection is pain or dysfunction in an extremity resulting from disruption of the blood supply, peripheral neurologic diagnoses should be included in the differential diagnosis. An aortic dissection may involve the carotid artery and present as a stroke mimic. The diagnosis of aortic dissection should be considered in any patient with a new diagnosis of pericardial effusion, pericardial tamponade, or aortic insufficiency.

Diagnostic Testing

Routine laboratory tests are of little value in the diagnosis of aortic dissection. The hemoglobin level usually is normal or unchanged from the patient's baseline. The leukocyte count is commonly mildly elevated. Recently, there has been increasing interest in the biochemical diagnosis of acute aortic dissection, including using D-dimer levels.[16] Several authors have suggested that a negative D-dimer makes a diagnosis of aortic dissection unlikely,[16,17] but currently there is insufficient evidence to support using a D-dimer as a sole screening test for aortic dissection. In addition, the following conditions may result in a low or false-negative D-dimer value in patients with proven aortic dissections: presence of intramural hematoma or thrombosis, short dissection length, and young age of patient. Recent studies have also revealed a negative correlation between the absolute D-dimer values and time from onset of symptoms.[17,18] As a result, the 2010 guidelines from several major specialty societies, as well as the 2014 Clinical Policy Statement from the American College of Emergency Physicians, have recommended against the practice of using D-dimer to exclude the presence of aortic dissection.[19]

Electrocardiography

The ECG is often useful in excluding MI; however, 15% of patients with aortic dissection may have electrocardiographic abnormalities suggesting ischemia.[4] Proximal dissections that involve the right coronary artery may show an inferior wall MI, and the constellation of symptoms and signs—pain, diaphoresis, hypotension—may be difficult to distinguish from those associated with primary acute MI. The ECG typically shows left ventricular hypertrophy in 26% of cases, reflecting long-standing hypertension. Other findings include nonspecific ST-T wave changes and prior Q wave infarction. No abnormalities are noted on the ECG in 31% of cases (Table 75.1).[4]

Chest Radiography

Routine chest radiographic studies are abnormal in 80 to 90% of patients, but the abnormalities are nonspecific and rarely diagnostic.[4] Mediastinal widening is present in up to 61% of chest radiographs obtained from on patients with chest pain. The widening may occur in any portion of the aorta and may be difficult to differentiate from the aortic tortuosity associated with chronic hypertension. Up to 12% of patients with aortic dissection have a normal chest radiograph (see Table 75.1).[4] A plain chest radiograph is inadequate for ruling out aortic dissection.

Other helpful radiographic signs include a double-density appearance of the aorta, suggesting true and false channels,

TABLE 75.1

Characteristics of Aortic Dissection From the International Registry of Acute Aortic Dissection

TYPE OF AORTIC DISSECTION	CHEST PAIN (%)	SYNCOPE (%)	AORTIC INSUFFICIENCY MURMUR (%)	PULSE DEFICIT (%)	NORMAL CXR (%)	WIDENED MEDIASTINUM ON CXR (%)	NORMAL ECG (%)	ISCHEMIA (%)	LEFT VENTRICULAR HYPERTROPHY (%)
All ($n = 464$)	73	9	32	15	12	62	31	15	26
Type A ($n = 289$)	79	13	44	19	11	63	31	17	25
Type B ($n = 175$)	63	4	12	9	16	56	32	13	32

CXR, Chest x-ray; *ECG,* electrocardiogram.

Adapted from Suzuki T, et al: Clinician profiles and outcomes of acute type B aortic dissection in the current era: Lessons from the international registry of aortic dissection (IRAD). Circulation 108:312-317, 2003.

localized bulge along a normally smooth aortic contour, disparity in the caliber between the descending and ascending aorta, obliteration of the aortic knob, and displacement of the trachea or nasogastric tube to the right by the dissection. Previous chest roentgenograms, when available, are useful for comparison. Regardless of findings on the chest radiograph, further imaging is necessary in the setting of acute chest pain and concern for aortic dissection.

Echocardiography

Transthoracic echocardiography (TTE) is an insensitive tool for detecting aortic dissection because it does not visualize the aortic arch or much of the descending aorta, and imaging quality may not be optimal because of the patient's body habitus. While more sensitive imaging tests are being scheduled, however, TTE can provide valuable information about pericardial effusion or aortic regurgitation and can help determine whether cardiac tamponade is the cause of hypotension in a patient with aortic dissection.

TEE is highly sensitive (Table 75.2) for the diagnosis of aortic dissection. The proximity of the esophagus to the aorta and ability to use higher transducer frequencies help visualize the entire aorta and detect pericardial effusion and aortic regurgitation. TEE can be quickly performed at the patient's bedside with sedation or light anesthesia and does not require radiation or contrast agent injection. Visualization of the distal ascending aorta and proximal arch was formerly difficult because of the interposition of the air-filled trachea and left mainstem bronchus, but evaluation of this so-called blind spot has been aided by biplane and multiplane probes.

The diagnostic accuracy of TEE depends on the experience and availability of the echocardiographer. It is the primary diagnostic method in many institutions for detecting aortic dissection[4] and is the procedure of choice in unstable patients who cannot leave the resuscitation area or the operating room.

Computed Tomography

CT aortography is a reliable test for diagnosing aortic dissection (see Table 75.2) and is the diagnostic test of choice in most institutions.[5] Findings suggestive of aortic dissection include dilation of the aorta, identification of an intimal flap, and clear demonstration of the false and true lumens (Fig. 75.2). Sixty-four-slice (or more) multidetector computed tomography (MDCT) is being used in some centers as part of a triple rule-out CT (TRO CT) protocol for patients with low to moderate risk of acute coronary syndrome in whom pulmonary embolus and aortic dissection are also being considered. However, the larger dose of ionizing radiation, larger volumes of iodinated contrast material, and low incidence of aortic dissection in TRO CT studies limits feasibility of routinely using TRO CT to rule aortic dissection.

TABLE 75.2

Sensitivities and Specificities of Imaging Modalities for Diagnosing Aortic Dissection

TEST	TEE	HELICAL CT	MRI
Sensitivity (%)	98	100	98
Specificity (%)	95	98	98

CT, Computed tomography; *MRI,* magnetic resonance imaging; *TEE,* transesophageal echocardiography.

From Shiga T, Wajima Z, Apfel CC, et al: Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: Systematic review and meta-analysis. Arch Intern Med 166:1350–1356, 2006.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an appealing option for the detection of low-grade aortic dissection in stable patients in whom the diagnosis is uncertain. Sensitivity and specificity are excellent (see Table 75.2). MRI often demonstrates the site of intimal tear, type, and extent of dissection, presence of aortic insufficiency, and differential flow velocities in the true and false lumens and in the aortic side branches without contrast material or ionizing radiation and is noninvasive. Its availability, however, is limited and it is difficult to perform in unstable patients. It is particularly useful for the evaluation of chronic aortic dissection, in the follow-up of postoperative patients, and for monitoring nonoperative patients for progression of the dissection.

Choice of Diagnostic Test

Although aortic dissection can be suspected on the basis of the history and physical examination, diagnostic imaging is necessary to establish or rule out the diagnosis. With a mortality rate in excess of 1%/hour after the onset of aortic dissection, a diagnostic study should be performed as soon as feasible.[4] Frequently, more than one test is required to make the diagnosis and assess associated complications.

The clinical strategy should consider the following: (1) technologic capabilities available at the institution; (2) institution-specific sensitivities and specificities for the diagnostic tests; (3) benefits of diagnosing alternative causes of chest pain; and (4) ease of performing each test, especially after hours. Some tests (eg, CT, MRI, aortography) may require moving a potentially unstable patient outside the emergency department (ED). In IRAD, the initial choice of diagnostic test was CT in 61%, TTE or TEE in 33%, aortography in 4%, and MRI in 2% of patients.[4] The actual sensitivities of diagnostic tests in IRAD were CT, 93%, TEE, 88%, aortography, 87%, and MRI, 100%, and patients averaged 1.85 imaging studies.[20] A meta-analysis has suggested that TEE, helical CT, and MRI are of similar diagnostic value in ruling aortic dissection in or out.

Unless institutional circumstances do not permit, contrast CT aortography is recommended as the test of first choice. In patients with renal failure or contrast allergy, or those considered too unstable to undergo CT scanning, TEE is recommended. If the patient has a diagnostic (ie, positive) transthoracic echo, the diagnosis is established, but additional confirmatory studies may, or may not be required depending on the preference of the

Fig. 75.2. Computed tomography scan demonstrating the true lumen and false lumen.

clinician who will be assuming care of the patient. A negative transthoracic echo does not exclude dissection, and further imaging is always indicated.

MANAGEMENT

Emergency Department

Early therapy for aortic dissection is critical and should be initiated before confirmation of the diagnosis while diagnostic tests are being performed. Opioids should be administered in adequate doses to control pain and decrease sympathetic tone. Patients with aortic dissections are typically hypertensive. The two goals of medical management are to reduce blood pressure and decrease the rate of rise of the arterial pulse (dP/dt) to diminish shearing forces. A target blood pressure of 100 to 120 mm Hg systolic and a heart rate less than 60 beats/min are recommended.[1] β-Adrenergic blockers are the cornerstone of aortic dissection management and are effective when used as the sole agent, in addition to opioid analgesia for pain. Because vasodilators such as sodium nitroprusside or fenoldopam reflexively increase the heart rate and may also increase the dP/dt, they require concomitant use of a beta blocker. Initial therapy with esmolol or labetalol, as described below, and use of opioid analgesia such as morphine or fentanyl for pain is recommended.

Recommended Therapy

Esmolol and labetalol are titratable, short-acting beta blockers that can be used in treatment for hemodynamic control in aortic dissection. Esmolol is an ultra–short-acting beta blocker given as an initial bolus of 500 μg/kg, followed by an infusion of 50 to 200 μg /kg/min. Although esmolol is often used in the management of aortic dissection, an additional agent is typically required to augment the antihypertensive effects. Labetalol has both alpha and beta blocking activity and is given as an initial series of 20-mg IV boluses every 5 to 10 minutes, incrementally increased to 80 mg IV until a target heart rate of 60 beats/min is reached or a total of 300 mg is given. A maintenance infusion of labetalol is then given at a rate of 1 to 2 mg/min. If a patient is normotensive, a beta blocker should still be used to lower the dP/dt and maintain a heart rate of 60 beats/min. In patients with a history of chronic obstructive pulmonary disease or who are at risk for bronchospasm, a selective beta blocker such as metoprolol or atenolol should be considered.

Alternative Agents

Sodium nitroprusside was widely used before esmolol and labetalol became available and is a reasonable agent to use, but necessitates concomitant use of a beta blocker to mitigate reflex tachycardia and is comparatively labor intensive to prepare and administer. The initial infusion is 0.5 to 3 μg/kg/min; the infusion is adjusted to reach the same hemodynamic goals described above.

Intravenous (IV) nitroglycerin is often used initially in patients with hypertensive chest pain and possible or uncertain aortic dissection. Nitroglycerin is a less effective arterial dilator than nitroprusside and is less desirable than nitroprusside for the treatment of patients with aortic dissection. Like nitroprusside, nitroglycerin should be accompanied by a beta blocker. A reasonable alternative to nitroprusside may be fenoldopam, although it too has been shown to cause reflex tachycardia and has not been specifically studied in patients with aortic dissection.

Nicardipine can be used as a second-line agent in situations in which beta blockers are not well tolerated. It is a vasoselective calcium channel blocker that belongs to the dihydropyridine class. Nicardipine produces its antihypertensive effect by decreasing peripheral vascular resistance, and it has no negative inotropic effect. In addition, when compared to nitrates, nicardipine has very little effect on heart rate. Although recent studies comparing nicardipine to other agents have been promising, it is still not used as a first-line therapy.

Patients presenting with hypotension secondary to aortic rupture or pericardial tamponade should be resuscitated with IV fluids and expeditiously transported to the operating room if they are to have a chance to survive. Blood pressure should be measured in all four limbs, if necessary, to ensure that this is not a pseudohypotension caused by an intimal flap obstructing the extremity in which the blood pressure is measured. In patients with marked hypotension, pericardiocentesis may raise the blood pressure while awaiting definitive surgery.

Operative and Interventional Repair

Type A acute aortic dissections require prompt surgical treatment. The aortic segment containing the original intimal tear is resected when possible, with graft replacement of the ascending aorta to redirect blood into the true lumen. If aortic insufficiency is present, it can be corrected through aortic valve resuspension or replacement. Patients with type A dissections have an in-hospital mortality rate of 27% when treated surgically versus an in-hospital mortality of 56% when treated medically.[11,21,22]

Definitive treatment of type B acute aortic dissections is less clear. These patients, in general, tend to be worse surgical risks. Type B dissections are categorized into two groups based on associated symptoms—complicated and uncomplicated. Complicated dissection is any dissection that has end-organ ischemia, leaking or rupture, aortic dilation, or intractable pain and occurs in 30% of patients with acute type B dissections. Stable asymptomatic patients are categorized as uncomplicated.

Complicated distal dissections are traditionally treated surgically although, in the past decade, this practice has been challenged. Thoracic endovascular aneurysm repair (TEVAR) techniques have been replacing surgery for complicated type B dissections in many centers, especially for patients with renal and mesenteric ischemia.[7,8] Recent studies have reported that mortality rates for patients treated surgically and those treated with stent graft placement have similar initial mortality rates, whereas long-term outcomes favor the interventional approach (Fig. 75.3).

Although evidence supporting widespread use of endovascular intervention has appeared promising, the decision to implement medical therapy alone or in combination with intravascular intervention is complicated and involves complete knowledge of each patient's particular situation. The decision regarding which treatment modality is beneficial for a particular case should rest with the primary treating physician, and the patient and decision should involve a discussion of the potential risks and benefits of each approach.

DISPOSITION

Patients with type A aortic dissection require emergent cardiovascular surgery consultation as well as ED management of blood pressure and heart rate prior to intraoperative repair. Inpatient admission is frequently required to maintain adequate control of blood pressure and heart rate parameters. Patients who present with chronic aortic dissection have already survived their period of greatest mortality risk and are usually treated by blood pressure control and close monitoring, unless complications mandate surgery. Regardless of the type of definitive therapy, all patients who have sustained and survived an aortic dissection require careful long-term treatment. Major complications that may occur with time are redissection, development of a localized aneurysm, and progressive aortic insufficiency.

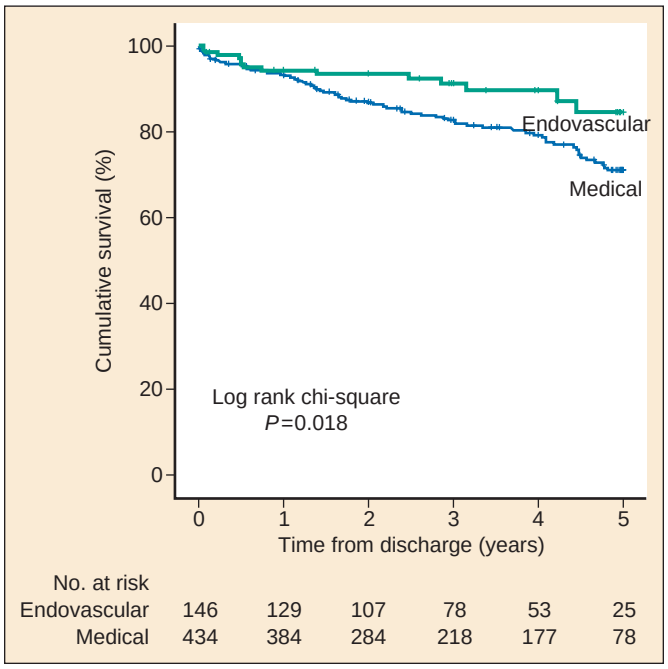

Fig. 75.3. Graphic comparison of 5-year survival of medical management alone versus thoracic endovascular aneurysm repair (TEVAR). (Courtesy International Registry of Acute Aortic Dissection (IRAD)—Dr. Rossella Fattori, Daniel Montgomery, Dr. Luigi Lovato, and colleagues.)

KEY CONCEPTS

- Most patients with aortic dissection have chest pain, typically of sudden onset, sharp, and migratory. Chest pain associated with neurologic symptoms or syncope should increase the likelihood of aortic disease.
- Physical examination findings may include pulse deficit, aortic insufficiency murmur, and neurologic findings, but often the physical examination is not diagnostic, and imaging is essential to establish or exclude the diagnosis of dissection.
- Of the confirmatory tests, CT aortography is recommended. Transesophageal echocardiography is also an excellent test and can be used when CT is not available or for patients with contrast allergy, renal insufficiency, or critical illness that precludes CT scanning.
- Patients with type A aortic dissection require emergent cardiovascular surgery consultation as well as ED management of blood pressure and heart rate prior to intraoperative repair.
- Patients with acute type B dissections also require stabilization of the blood pressure and pulse to prevent progression of symptoms and frequently require admission as inpatients for further monitoring. Long-term treatment decisions of type B dissections should be based on the patient's current symptoms, input from the cardiovascular surgical team, and discussion with the patient regarding risks and benefits of therapy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 75: QUESTIONS & ANSWERS

75.1. Which valvular abnormality is associated with aortic dissection?
- **A.** Aortic regurgitation
- **B.** Aortic stenosis
- **C.** Mitral regurgitation
- **D.** Mitral stenosis

Answer: A. Aortic regurgitation occurs in up to 32% of patients and is more common with type A dissections. A bicuspid aortic valve is found in 14% of patients with dissections and may predispose to dissection by disrupting the blood flow.

75.2. A 67-year-old man presents with ripping substernal chest pain. Physical examination is remarkable for blood pressure, 180/110 mm Hg, pulse, 110 beats/ min, respiratory rate, 18 breaths/min, and temperature, 37°C (98.6°F). The electrocardiogram (ECG) is unremarkable. Which of the following diagnostic studies is the best test to rule out aortic dissection?
- **A.** Chest radiograph
- **B.** Computed tomography (CT) aortography
- **C.** Magnetic resonance imaging (MRI)
- **D.** Transthoracic echocardiography

Answer: B. CT aortography is a reliable test with the best combination of high sensitivity and specificity for diagnosing aortic dissection. A chest radiograph may be a fast screening test, but 12% will be falsely normal. MRI is more sensitive but is not always available and is unsuitable for unstable patients.

75.3. A 59-year-old man presents with sharp chest pain. Physical examination is remarkable for blood pressure 192/116 mm Hg, pulse, 116 beats/ min, respiratory rate, 16 breaths/min, temperature, 37.2°C (98.9°F). Chest auscultation reveals a diastolic murmur. Which of the following medications is the best initial treatment choice for his condition?
- **A.** Dobutamine
- **B.** Esmolol
- **C.** Nifedipine
- **D.** Phentolamine

Answer: B. Esmolol and labetalol are titratable, short-acting beta blockers that can be used as monotherapy for hemodynamic control in aortic dissection. These can be started quickly to control blood pressure but, more importantly, to decrease the rate of pressure change.

75.4. Which of the following is the most common sign or symptom of a patient with aortic dissection?
- **A.** Aortic insufficiency murmur
- **B.** Chest pain
- **C.** Pulse deficit
- **D.** Syncope

Answer: B. Pain is the most common presenting complaint, affecting more than 90% of patients. Syncope, a pulse deficit, and aortic insufficiency murmur are all important to elicit and affect the outcome.

CHAPTER 76

Abdominal Aortic Aneurysm

Christopher B. Colwell | Charles J. Fox

PRINCIPLES

An abdominal aortic aneurysm (AAA) is a true aneurysm, meaning a localized dilation of the aorta involving all three layers (intima, media, and adventitia) of the arterial wall (Fig. 76.1). A false aneurysm, or pseudoaneurysm, is a collection of flowing blood that communicates with the arterial lumen but is not enclosed by the normal vessel wall; it is contained only by the adventitia or surrounding soft tissue. Pseudoaneurysms can arise from a defect in the arterial wall or a leaking anastomosis after AAA repair.

AAA is distinct from aortic dissection, which is sometimes incorrectly referred to as a *dissecting aortic aneurysm.* In aortic dissection, blood enters the media of the aorta and splits (dissects) the layers of the aortic wall (see Chapter 85). Aortic aneurysm and aortic dissection are distinctly different disease processes, with different clinical presentations, complications, diagnostic methods, and treatments.

An aneurysm can develop in any segment of the aorta, but most are infrarenal. The diameter of the normal adult infrarenal aorta is approximately 2 cm, and a diameter of 3 cm or more defines an AAA.

Epidemiology

AAA is a disease of aging, with prevalence increasing with advancing age and is found in 2% to 5% of men older than 50. The average age at the time of diagnosis is between 65 and 70 years old, with males affected much more often than females. The patient often has concomitant atherosclerotic occlusive disease, including coronary, carotid, or peripheral vessels, which may influence the clinical presentations, complications, and management.

Several risk factors for the development of an AAA have been established, but risk factors are epidemiologic, not individual characteristics. An AAA can be found in 5% to 10% of all elderly men who are screened with ultrasonography with increasing prevalence in those who have concomitant coronary artery disease or peripheral vascular disease.[1] The presence or absence of risk factors should not strongly influence diagnostic considerations in any individual patient (Table 76.1). A family history of an AAA is a very strong risk factor; those with an affected first-degree relative have a markedly increased risk of developing an AAA. Although awareness of high-risk groups can speed the recognition of AAA, the consideration of AAA should not be restricted to patients in these groups. Recent evidence suggest that women may experience delays in diagnosis and worse operative mortality after ruptured AAA and that up to half of AAAs in the United States occur in women, nonsmokers, or those younger than 65.[2]

Pathophysiology

AAAs have traditionally been attributed to atherosclerosis, but patients with advanced atherosclerosis have occlusive disease, not aneurysms. Patients with AAA have biochemical abnormalities leading to the loss of elastin and collagen, which are the major structural components of the aortic wall. The propensity to form aneurysms may have a genetic basis, but the exact mode of inheritance is uncertain. The Society for Vascular Surgery recommends labeling the typical degenerative AAA as "nonspecific," rather than "atherosclerotic," to reflect this uncertainty surrounding the etiology.

AAAs may also have specific etiologies, such as infection, trauma, connective tissue diseases, and arteritis. However, such aneurysms are rare compared with nonspecific, degenerative aneurysms.

Natural History

AAAs progressively enlarge, ultimately resulting in rupture of the aneurysm and fatal hemorrhage. Although other complications are possible, by far the most common and most clinically significant is rupture.

The most important factor determining the risk of rupture is the size of the aneurysm. The risk of rupture increases dramatically with increased aneurysm size, and most ruptured AAAs have diameters greater than 5 cm. The growth rate of the AAA, in addition to other anatomic factors, may also be important in determining the risk of rupture.[3] Although rupture of aneurysms smaller than 4 cm is rare, no aneurysm is completely "safe." Any aneurysm can rupture and cause significant consequences.

AAA most commonly ruptures into the retroperitoneum, where hemorrhage may be temporarily limited by clotting and tamponade at the rupture site, but 10% to 30% involve free intraperitoneal rupture, which is often rapidly fatal. Occasionally, rupture occurs into the gastrointestinal tract or the inferior vena cava.

Complications can also arise from an intact AAA. The walls of an AAA are often lined with clot and atheromatous material, which can embolize and occlude distal vessels. Sequelae of occlusion and embolization may be the only diagnostic clues to AAA. Aortic thrombosis may occur rarely and patients can also have complications caused by impingement of the aneurysm on adjacent structures.

In approximately 5% of AAAs, a dense inflammatory and fibrotic reaction develops in the aneurysm wall and adjacent retroperitoneal tissue. In these "inflammatory" AAAs, the periaortic fibrosis may incorporate and obstruct adjacent structures, such as the ureters or duodenum.

The principal concern in the patient with an AAA is the potential for rupture of the aneurysm, which can be prevented only by timely repair.

CLINICAL FEATURES

Unruptured Aneurysms

Because most AAAs do not cause symptoms until they expand or rupture, the prevalence of symptoms in patients with unruptured AAAs is difficult to determine. Patients may have symptoms that lead to the aneurysm's discovery prior to rupture. These symptoms can include pain in the abdomen, back, or flank; an awareness of

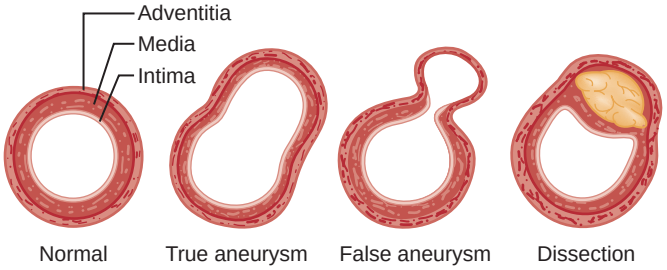

Fig. 76.1. Types of aortic aneurysms. (Adapted from LaRoy LL, et al: Imaging of abdominal aortic aneurysms. Am J Roentgenol 152:785, 1989.)

TABLE 76.1

Prevalence of Abdominal Aortic Aneurysms in Selected Risk Groups

GROUP	INCIDENCE
Men aged 65 years or older[a,b]	5% to 10%
Patients with coronary artery disease[c] or occlusive peripheral vascular disease[d]	10% to 15%
Brothers of patients with abdominal aortic aneurysms (AAAs)[e]	20% to 30%

[a]van Walraven C, et al: Incidence, follow-up, and outcomes of incidental abdominal aortic aneurysms. J Vasc Surg 52:282-289, 2010.
[b]De Martino RR, et al: Outcomes of symptomatic abdominal aortic aneurysm repair. J Vasc Surg 52:5-12, 2010.
[c]Hoffman B, et al: Successful sonographic visualization of the abdominal aorta differs significantly among a diverse group of credentialed emergency department providers. Emerg Med J 28:472-476, 2010.
[d]Gupta PK, et al: A comparison of open surgery versus endovascular repair of unstable ruptured abdominal aortic aneurysms. J Vasc Surg 60:1439-1445, 2014.
[e]United Kingdom EVAR Trial Investigators: Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 362:1763-1871, 2010.

an abdominal mass or fullness; or a sensation of abdominal pulsations.

The pain associated with stable, intact aneurysms often has a gradual onset and a vague, dull quality. It is usually constant but may be described as throbbing or colicky. Acute or severe pain is an ominous symptom that suggests imminent or actual aortic rupture.

In most cases, an AAA is asymptomatic and is discovered incidentally on physical examination, on a radiologic study done for unrelated issues, or by an ultrasonography aneurysm screening program.[4] Symptoms usually do not develop until the aneurysm ruptures.

The most prominent physical finding is a pulsatile, expansile abdominal mass above the level of the aortic bifurcation. If the iliac arteries are also aneurysmal, the mass may extend below the umbilicus. The right border of an AAA may be palpable to the right of midline, whereas a normal or tortuous aorta is usually not. Most intact AAAs are nontender; tenderness suggests aneurysm expansion or rupture.

Symptomatic aneurysms are usually fairly large and are often palpable with a careful abdominal examination. Likewise, the patient with an aneurysm large enough to warrant elective repair often has a palpable abdominal mass. However, an AAA may be difficult to palpate if the aneurysm is small or the patient is obese. Published reports indicate that 30% to 60% of unruptured aneurysms measuring 3.0 to 3.9 cm on ultrasonography can be detected by abdominal palpation; 50% to 70% of aneurysms measuring 4.0 to 4.9 cm and 75% to 85% of aneurysms 5 cm or larger can be palpated. These reports are based on the examination of patients with intact, asymptomatic aneurysms, with the examination specifically directed at sizing the aorta. The sensitivity is likely much lower when the abdomen is not palpated deeply, in hypotensive patients, or those with significant abdominal guarding. There is virtually no risk of causing aneurysm rupture by abdominal palpation.

Physical examination may reveal findings consistent with an AAA even when the aorta is of normal size. A tortuous aorta may feel enlarged, and prominent aortic pulsations, especially in a thin patient, may simulate an aneurysm. Pulsations from a normal aorta may be transmitted to an adjacent abdominal mass. Clinical suspicion of AAA, which includes both the patient's history and physical examination findings, warrants further investigation.

An abdominal bruit is an uncommon finding in patients with AAAs. The presence of a bruit is also nonspecific, because bruits can originate from a stenotic renal, iliac, or mesenteric artery. A loud continuous bruit suggests the diagnosis of arteriovenous fistula, a rare complication of AAAs.

Perfusion distal to an AAA is usually well maintained, and most patients have normal femoral pulses. Diminished femoral pulses may result from iliofemoral occlusive disease or from hypotension related to hemorrhagic shock in the patient bleeding from a ruptured aneurysm.

Thromboembolic complications can occur spontaneously or when atheromatous plaques are disrupted during invasive intravascular procedures. Large emboli can acutely occlude major vessels, such as the iliac, femoral, or popliteal artery, causing painful lower extremity ischemia with absent distal pulses. Rarely, the aneurysm itself can thrombose, rendering both lower extremities acutely ischemic. More commonly, microemboli consisting of cholesterol crystals or clot obstruct small distal vessels, such as the digital arteries of the toes and arterioles and capillaries of the skin. These patients can present with livedo reticularis; one or more cool, painful, cyanotic toes; and palpable pedal pulses. This constellation of findings, often called the *blue toe syndrome,* is highly suggestive of a proximal source of emboli. When an AAA is the source, the aneurysm is often too small to palpate and only recognized with radiologic investigation.

In rare instances an intact AAA can cause symptoms by compressing adjacent structures, with symptoms representing those structures involved. Large, long-standing aneurysms can cause vertebral body erosion and severe back pain. Compression of the duodenum between the superior mesenteric artery and an AAA can cause duodenal obstruction, vomiting, and weight loss. Obstruction of the ureters in the patient with an inflammatory aneurysm can cause symptoms suggestive of ureteral colic.

Ruptured Aneurysms

Pain-Hypotension-Mass Triad

Although the classic description of a ruptured AAA is the triad of pain, hypotension, and a pulsatile abdominal mass, many patients have only one or two components of this triad, and an occasionally none of these classic features.

Acute rupture is often the first presentation of an AAA. Not infrequently though, patients may have a previously diagnosed AAA where the decision not to operate electively may have been made because the aneurysm was small or the patient was considered too high risk. Any new or acute symptoms in these patients should be considered acute aneurysmal rupture.

Most patients with a ruptured AAA experience pain in the abdomen, back, or flank. The pain is classically acute, severe, and constant and although difficult to locate, can radiate to the chest, thigh, inguinal area, or scrotum. A history of pain may be more difficult to illicit if the patient's mental status is compromised by severe hypotension.

The source of the pain associated with aneurysm rupture is not clearly understood. It may be caused by expansion of the aortic wall or by stimulation of visceral sensory nerves in the retroperitoneum. Identical pain can occur with intact but acutely expanding aneurysms, which may be impossible to differentiate clinically from ruptured aneurysms.[5]

In patients with a ruptured aneurysm, the duration of symptoms before presentation can vary dramatically. Some patients present immediately after rupture because pain is severe, sudden in onset, and may be accompanied by hypotension. In others, rupture is initially contained in the retroperitoneum, blood loss is small, pain may be minor, waxing and waning, and the presentation delayed. Rare patients with a ruptured AAA may have symptoms for several days or even weeks before seeking medical attention; therefore a long duration of symptoms does not exclude the diagnosis of ruptured AAA.

Rupture of an AAA may be accompanied by nausea and vomiting in addition to pain or, rarely absent significant pain, and sudden hemorrhage may present as syncope or near-syncope. Compensatory hemodynamic mechanisms may restore blood pressure and cerebral perfusion to normal. Transient improvement in symptoms is common but will be followed by hemodynamic deterioration if the diagnosis and treatment are delayed. Ruptured AAAs are often large, and non-obese patients will have a palpable abdominal mass. The examination may be difficult if abdominal guarding is present or if an ileus causes significant distention; and aortic pulsations may not be prominent if the blood pressure is low.

Hypotension is the least consistent part of the triad, occurring in approximately half of patients, and is often a late finding. When the initial blood loss is small, vital signs may be normal. Patients with initially normal vital signs are more likely to be misdiagnosed and may quickly and unpredictably deteriorate and become hypotensive.

Occasionally, rupture into the retroperitoneum is sealed and contained for many weeks or months. When this occurs, patients develop abdominal or back pain, presumably at the time of aneurysm leakage, which subsequently diminishes or resolves completely. If the diagnosis is made, chronic rupture (organized hematoma) is found at surgery. These patients can have chronic pain and may progress to free rupture and massive hemorrhage at any time.

Aortoenteric Fistula

A primary aortoenteric fistula (AEF) is formed when an unrepaired AAA erodes into the gastrointestinal tract, most commonly in the third or fourth portion of the duodenum. A secondary AEF, a communication between the site of previous aortic surgery and the gastrointestinal tract, can occur as a late complication of AAA repair and should be considered in any patient with a severe gastrointestinal bleed and a history of aortic graft placement. An AAA can rupture into the gastrointestinal tract (AEF) or inferior vena cava (aortocaval fistula).

Early in the formation of a primary AEF, the adjacent AAA erodes through the bowel wall from the outside. This can lead to the leakage of intestinal contents, with local infection and abscess formation. Eventually, breakdown of the aortic wall leads to an AEF and may lead to gastrointestinal bleeding. A patient with an AEF may have abdominal or back pain, fever and other signs of intra-abdominal infection, or gastrointestinal bleeding. Because most of these fistulae are into the duodenum, hemorrhage usually manifests as hematemesis or melena. The initial bleeding results from erosion of vessels in the bowel wall and is often occult or minor. Massive bleeding from rupture into the intestinal lumen can occur days or even weeks after the initial bleeding. Primary AEF, although rare, should be considered in any patient older than 50 years with unexplained severe gastrointestinal bleeding. An AAA diagnosed by history, physical examination, or other modality, presenting with gastrointestinal bleeding should raise the concern for AEF.

Arteriovenous (Aortocaval) Fistula

An arteriovenous (usually aortocaval) fistula arises when periaortic inflammation causes adherence of the aorta to an adjacent vein, with pressure on the vessel walls causing the development of an arteriovenous communication. If concomitant extravasation of blood into the retroperitoneum occurs, the clinical presentation is similar to that of other patients with ruptured AAAs. More commonly, however, the aneurysm ruptures into the vena cava without leaking externally, and the signs and symptoms of a large arteriovenous fistula dominate the clinical picture.

As in other patients with AAAs, a patient with an arteriovenous fistula may have abdominal or back pain. An aneurysm that becomes fistulous with the vena cava is usually large, and 80% to 90% are palpable. A continuous abdominal bruit can be auscultated in approximately 75% of patients with arteriovenous fistulae, and 25% of patients have a palpable abdominal thrill.

Shunting of blood from the arterial to the venous system increases venous pressure, venous volume, and venous return to the heart. Signs and symptoms of high-output congestive heart failure (dyspnea, jugular venous distention, pulmonary edema) are often present. The increased venous volume and pressure can cause lower extremity edema or cyanosis, and dilated superficial veins can be seen on the legs or abdominal wall. Distention and rupture of veins in the bladder mucosa can cause gross or microscopic hematuria, and rectal bleeding can occur for similar reasons. Because of shunting of arterial blood into the venous system, the lower extremities may be cool with diminished pulses.

The patient with an arteriovenous fistula often has renal insufficiency caused by a decrease in renal perfusion as a result of high-output congestive heart failure and increased renal venous pressure. Such patients may exhibit hematuria, which is common when an arteriovenous fistula is present but not in other patients with AAAs. Computed tomography (CT), and preferably computed tomography angiography (CTA), can be useful in diagnosing or ruling out arteriovenous fistula formation.

DIFFERENTIAL DIAGNOSES

Symptoms consistent with ruptured AAA; abdominal, back, or flank pain, with or without hypotension, are seen in other diagnosis as well, which can lead to delayed or missed diagnoses (Box 76.1). The most common misdiagnosis is renal colic, followed by

BOX 76.1

Common Misdiagnoses in Patients With Ruptured Abdominal Aortic Aneurysms

Renal colic
Acute abdomen
Pancreatitis
Intestinal ischemia
Diverticulitis
Cholecystitis
Appendicitis
Perforated viscus
Bowel obstruction
Musculoskeletal back pain
Acute myocardial infarction

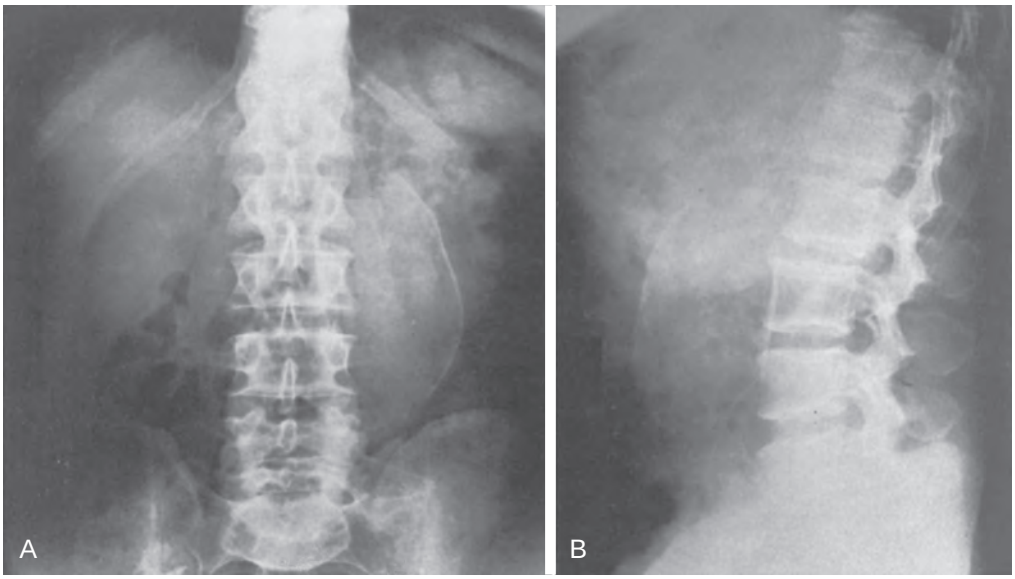

Fig. 76.2. Anteroposterior **(A)** and lateral **(B)** views of large abdominal aortic aneurysms (AAAs) with calcification of aortic wall. (From Juergens JL, et al: Peripheral vascular diseases, ed 5, Philadelphia, 1980, WB Saunders; by permission of the Mayo Foundation.)

pancreatitis, intestinal ischemia, other nonspecific intra-abdominal disorders and musculoskeletal back pain.

Presentation of epigastric pain and hypotension may lead to a presumptive diagnosis of acute myocardial infarction because patients with a ruptured AAA often have concomitant coronary artery disease, and blood loss from a ruptured aneurysm may diminish coronary perfusion and cause chest pain or electrocardiographic changes consistent with cardiac ischemia. In the setting of abdominal or back pain, these findings do not exclude the presence of a ruptured AAA.

Ruptured AAA should be considered in middle-aged or elderly patients with any part of the classic triad pain, hypotension, and a pulsatile abdominal mass. The diagnosis of ruptured AAA should also be considered in making the diagnoses listed in Box 76.1, especially when the diagnosis is not clear-cut or the patient is at risk for an AAA.

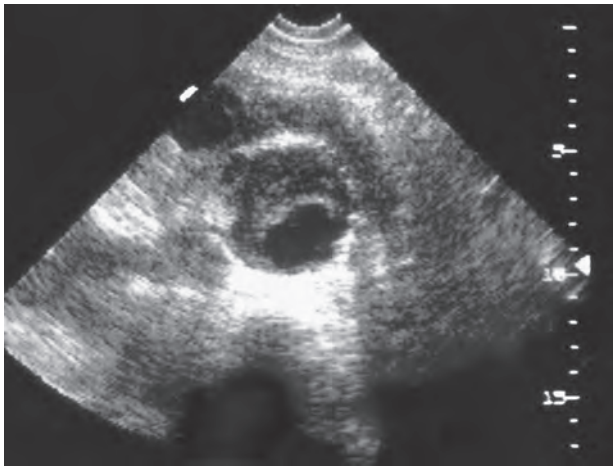

Fig. 76.3. Transverse sonogram of an abdominal aortic aneurysm (AAA). The central patent lumen is surrounded by an echogenic mural thrombus. (Courtesy Richard Rensio, MD.)

DIAGNOSTIC TESTING

Abdominal Radiography

Plain film radiography is not indicated in the evaluation of a patient for suspected AAA. A normal plain abdominal radiograph does not exclude the presence of an AAA and rarely identifies alternative pathology. Even if an aneurysm is identified on plain film because it is calcified, imaging with CT is necessary to identify whether the aneurysm is an incidental or culprit lesion in the patient's presentation (Fig. 76.2).

Ultrasonography

Ultrasonography is virtually 100% sensitive in detecting AAAs (Fig. 76.3) when a technically adequate study can be obtained. Measurements of aortic diameter are very accurate and reproducible. Because it is relatively inexpensive and requires no contrast agents or radiation exposure, ultrasonography is also used for aneurysm screening and to follow patients with known aneurysms after they have been characterized with CTA.

Point of care ultrasonography has distinct advantages in the emergency evaluation of a patient with a suspected ruptured AAA. It can be performed very rapidly at the patient's bedside, obviating the need to take a potentially unstable patient to the radiology suite. If an aorta with a normal diameter throughout its abdominal course is visualized, the patient does not have an AAA. In addition, ultrasonography sometimes provides alternative explanations for the patient's pain by revealing other conditions, such as acute cholecystitis. Emergency clinicians can accurately identify the etiology of acute nontraumatic abdominal pain, including AAAs using bedside ultrasound.[6]

Point of care ultrasonography does have certain limitations, including being more operator dependent when compared to other modalities, and is therefore more prone to technical or interpretive error. Even more than with elective studies, in the emergency department (ED) the aorta may not be well visualized because of obesity or excess bowel gas.[7] Although ultrasonography is extremely sensitive in detecting an AAA, it cannot be relied on to reveal whether an AAA has ruptured.

Free intraperitoneal or retroperitoneal blood, seen in the presence of an AAA, confirms a rupture. However, the sensitivity of point of care ultrasonography in detecting extraluminal blood is very low. The purpose of the study is to confirm or exclude the presence of an aneurysm; clinical information (or a CT scan) must be used to determine the likelihood of rupture. Ultrasonography with the use of contrast agents may aid in the detection of leaking blood, but the clinical usefulness of this modality has still not been determined. If ultrasonography reveals an AAA in an unstable patient, aneurysm rupture should be presumed, and emergent surgical evaluation for consideration of aneurysm repair should be initiated.

Computed Tomography

The abdominal CT scan is the diagnostic test of choice in the evaluation of the stable patient with suspected ruptured AAA and is virtually 100% accurate in determining the presence or absence of an AAA and the presence of bleeding. CT also provides detailed anatomic information about the aneurysm.

An intravenous contrast agent is desirable, but not essential, in emergency situations. With significant, prolonged hypotension or known renal disease, intravenous contrast can be avoided to prevent contrast-exacerbated nephropathy. Intravenous contrast will opacify the aortic lumen and distinguishes the patent lumen from mural thrombus. It can also demonstrate peri-aortic fibrosis, because the soft tissue surrounding an inflammatory AAA will often enhance. Although intravenous contrast is not necessary to identify the aneurysm or acute hemorrhage, contrast will be crucial to accurate sizing and planning if an endovascular approach is being considered.

CT is much more sensitive than ultrasonography in detecting retroperitoneal hemorrhage associated with aneurysm rupture. The reported sensitivity approaches 100% with the use of current-generation scanning technology, with falsely negative studies sometimes occurring with very small ruptures. Blood is seen as a retroperitoneal fluid collection adjacent to the aneurysm, often tracking into the perinephric space or along the psoas muscle (Fig. 76.4).

Although a CT scan sometimes reveals signs of impending aneurysm rupture, it cannot reliably determine whether an AAA is the cause of the patient's pain or whether rupture of the aneurysm is imminent. An alternative cause of pain can be diagnosed only if the CT scan shows no aneurysm or shows an intact aneurysm and clearly demonstrates an alternative explanation for the patient's symptoms.

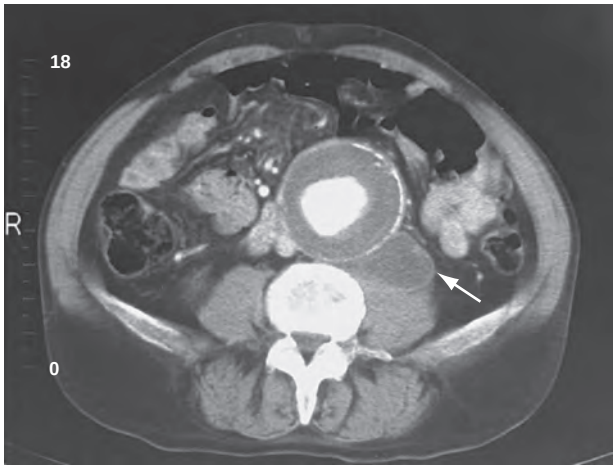

Fig. 76.4. Computed tomography (CT) scan of ruptured abdominal aortic aneurysm (AAA), with calcification of the aortic wall and intraluminal thrombus. The patent lumen enhances with the administration of contrast material, but the periaortic hematoma *(arrow)* does not. (Courtesy Richard Rensio, MD.)

Other Diagnostic Modalities

Conventional angiography has no place in the emergency evaluation of the suspected ruptured AAA. Because contrast opacifies only the patent lumen and not mural thrombus, angiography often underestimates aneurysm size and can miss an aneurysm entirely. In addition, angiography is time-consuming and performed away from the ED. If detailed information is needed about the anatomy of the aneurysm or its relationship to nearby vessels, a CT angiogram can provide the needed information.

Magnetic resonance imaging and magnetic resonance angiography are very time-consuming, logistically challenging, and provide no benefit over CT scan. Magnetic resonance scanning is not indicated in the evaluation of a patient with suspected AAA in the ED.

MANAGEMENT

Ruptured Aneurysms

The patient with a ruptured AAA is unstable until the aorta is cross-clamped in the operating room or stabilized with endovascular techniques. No patient with a known or suspected aortic rupture should be considered stable, regardless of the vital signs or initial hemoglobin level. Ruptured AAA is a time dependent disease, and patients taken to the operating room soon after ED arrival have a significantly higher survival rate than those in whom surgical care is delayed.

When the patient arrives in the ED, large-bore redundant intravenous access should be established and blood sent for type and crossmatch. At least 6 units of blood should be made available initially, with notification to the blood bank of the potential need for massive transfusion.[7] The surgical and anesthesia team should be notified emergently. Further management depends on the hemodynamic status and level of diagnostic certainty.

The hemodynamically unstable patient in whom a ruptured AAA has been diagnosed or is strongly suspected should be taken to the operating room as soon as possible (in this chapter, the term "operating room" includes other locations that may be used for endovascular aneurysm repair) and diagnostic testing should be kept to a minimum. The diagnosis can often be made on clinical grounds, and point of care ultrasonography can quickly confirm or exclude the presence of an aneurysm. A thin sliced CT scan of the abdomen and pelvis with intravenous contrast is appropriate only if it can be obtained quickly without compromising the patient's care. Time-consuming tests can lead to avoidable delay of definitive therapy and increase the risk of exsanguination. Hypotensive patients may have to be taken to the operating room based on a strong clinical presumption of the diagnosis, without definitive diagnostic imaging. Some of these patients will not have ruptured aneurysms, but they usually have other acute abdominal conditions requiring laparotomy.

Attempts to resuscitate these patients to the point of normalization of vital signs in the ED can waste valuable time and should be avoided. Hypotensive patients need to be taken to the operating room so that the aorta can be clamped, or occluded with a balloon, and hemorrhage stopped.

Fluid Resuscitation

The right amount of preoperative volume resuscitation remains controversial. Preoperative hypotension is the strongest predictor of mortality in the patient with a ruptured AAA, although

correction of hypotension before the aorta is clamped may not improve mortality and may even be harmful as hypotension slows bleeding in patients with AAA and allows local clot formation and tamponade of the rupture site. Raising the intravascular volume and blood pressure before occluding the aorta may dislodge clots and cause further bleeding.[8] Large volumes of crystalloid solution may contribute to bleeding by worsening acidosis and causing a dilutional coagulopathy. These concerns are similar to those in penetrating trauma patients with uncontrolled hemorrhage.

However, delaying resuscitation of hypotensive patients until they reach the operating room may also have deleterious effects. The patient with a ruptured AAA often survives the surgery but dies in the early postoperative period. These deaths are caused by complications of prolonged hypotension, such as myocardial infarction, respiratory failure, and renal failure. The patient with a ruptured AAA is usually elderly, often has coexisting conditions, and tolerates hypovolemia and hypotension poorly.

No prospective studies have compared different preoperative fluid regimens in hypotensive patients with ruptured AAAs, and the optimal resuscitation strategy has not been determined. The priority in these patients is expeditious transportation to the operating room for definitive control of aortic hemorrhage. In the prehospital setting and in the ED before the surgeon and the operating room are available, the blood pressure should be raised with crystalloid or preferably blood products to a level that maintains adequate cerebral and myocardial perfusion. The goal is to prevent irreversible end-organ damage. An arbitrary blood pressure goal cannot be specified because the blood pressure necessary for vital organ perfusion varies among patients, but a reasonable target is a systolic blood pressure of 80 to 100 mm Hg.

If blood products are to be administered in large amounts, fresh frozen plasma (FFP) and packed red blood cells (PRBCs) are beneficial in patients with ruptured AAAs.[8] As with trauma patients, a PRBC:FFP ratio of less than 2:1 results in improved mortality.[8]

Rarely, patients with a ruptured AAA may be hypertensive on admission because of pain or underlying chronic hypertension. Unlike with aortic dissection, no evidence exists that lowering the blood pressure is beneficial in the patient with a ruptured AAA, and these patients are at risk of developing precipitous hypotension.

Diagnostic Confirmation

If an AAA can be diagnosed with bedside testing (abdominal examination or point of care ultrasonography), the surgeon will often proceed immediately to the operating room with a clinical diagnosis of aneurysm rupture, because a delay in surgery places the patient with a ruptured AAA at risk for sudden and unpredictable hemodynamic deterioration. If the patient remains hemodynamically stable and an AAA cannot be identified with bedside testing, or if anatomic detail is needed for endovascular repair, an abdominal CT scan should be obtained. This will confirm or exclude the presence of an aneurysm, define the aortic anatomy, and determine the patient's suitability for endovascular repair. The patient who is sent for a CT scan should be monitored closely and taken to the operating room emergently if hemodynamic deterioration occurs.

CT may provide confirmation of rupture, allowing the surgeon to avoid the complications of emergency surgery in a patient with an intact aneurysm. Because emergency surgery may not allow detailed anatomic evaluation and careful preoperative planning or evaluation and optimization of the patient's cardiopulmonary and renal function, patients who are taken for emergency surgery and are found to have intact, symptomatic aneurysms have a higher mortality rate than patients undergoing elective aneurysm repair.[5]

Surgery and Mortality

Ruptured AAA is uniformly fatal unless treated surgically. Thus once this diagnosis has been made, repair should be attempted in almost all patients. Attempts have been made to identify patients with a very low likelihood of survival, and it has been suggested that surgery can be withheld in patients with prehospital or ED cardiac arrest. However, there are no variables that can be assessed in the ED, including cardiac arrest, that are universally predictive of a fatal outcome. Repair is indicated unless the patient has comorbidity making surgery unreasonable has a living will or healthcare proxy declining surgery or if the patient is mentally capable and declines surgery. Preoperative hypotension is the most significant predictor of poor outcome in patients undergoing surgery.[8]

Although patients with ruptured AAAs have a mortality of 30% to 40% with open repair, endovascular repair of ruptured aneurysms is becoming increasingly more common, even in unstable patients. There is evidence that high volume centers experienced with endovascular repair have a significantly lower operative morbidity and mortality rate.[9,10]

Not all patients with ruptured aneurysms will have an aorta that is anatomically suitable for endovascular repair. The method of repair will depend on the preference and skill set of the surgeon, as well as institutional capability and suitability for an endovascular approach. Planning for the care of such patients should include the development of a well understood protocol or pathway that advises the ED staff about which services to mobilize and which diagnostic tests to perform in patients with suspected ruptured AAA.

Intact, Asymptomatic Aneurysms

An incidental diagnosis of AAA may be made in the ED. The decision to repair an asymptomatic aneurysm depends on the risk of aneurysm rupture, comorbidities, and surgical risk. Surgical risk is determined by the patient's age and comorbidities, whereas the risk of rupture is largely a function of aneurysm size.

In two clinical trials, one of which has long-term follow-up, patients with small (<5.5 cm) aneurysms were randomized to early surgery or close follow-up. In the latter group, aneurysms were followed with serial ultrasounds or CT scans, and surgery was performed only if any symptoms developed, rapid expansion was documented, or a diameter of 5.5 cm was reached. Both studies showed equivalent survival rates in the two groups. As a result, fewer small aneurysms are now repaired electively, potentially leaving a larger group of patients who may come to the ED with complications of an AAA.

Traditional Repair

The conventional technique for repair of AAAs is an open approach with a laparotomy. The aneurysm is opened longitudinally and repaired from within (Fig. 76.5). A graft is inserted inside the aneurysm and anastomosed to uninvolved vessels above and below once lumbar vessels are ligated and the mural thrombus evacuated. When possible, a straight graft is used between the infrarenal and distal aorta, but if the aneurysm involves the aortic bifurcation or if iliac artery aneurysmal or occlusive disease is present, a bifurcation graft is used, with the distal anastomosis to the iliac or femoral arteries. Coagulopathy is addressed and the aneurysm wall is then closed around the graft to help separate it from adjacent structures in the retroperitoneum. The bowel is re-inspected, and the abdominal wall is frequently managed with temporary abdominal closure using negative pressure wound therapy when managing ruptured aneurysms.

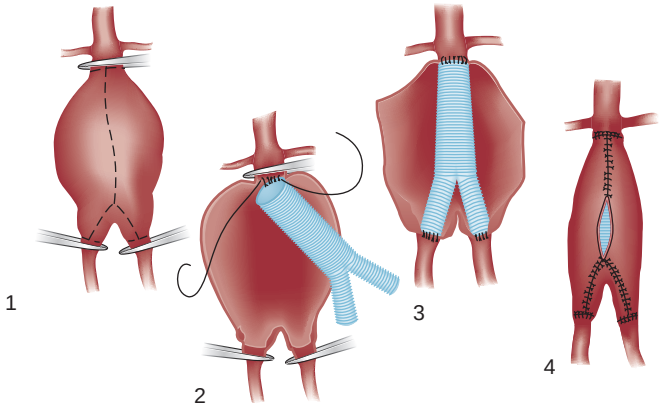

Fig. 76.5. Steps in repair of an abdominal aortic aneurysm (AAA). See text for details. (From Kent KC, et al: Surgical principles for operative treatment of aortic aneurysms. In Lindsay J Jr, editor: Diseases of the aorta, Philadelphia, 1994, Lea & Febiger, p 287.)

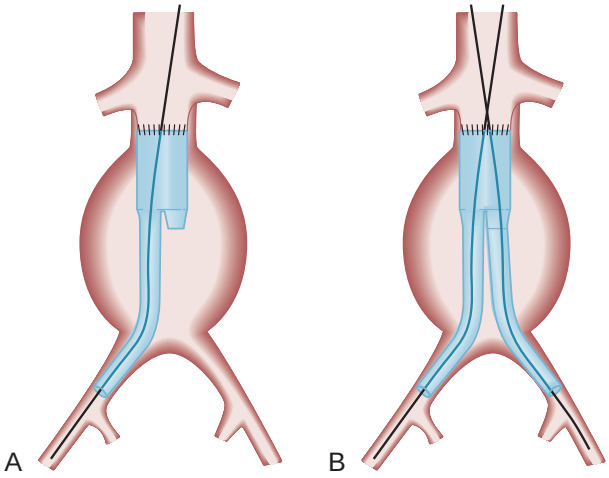

Fig. 76.6. Endovascular repair of an abdominal aortic aneurysm (AAA). **A,** Aortic section with attached iliac limb. **B,** Addition of contralateral iliac limb. (From Blum U, et al: Endoluminal stent-grafts for infrarenal abdominal aortic aneurysms. N Engl J Med 336:13-20, 1997. Copyright © 1997, Massachusetts Medical Society. All rights reserved.)

Endovascular Repair

More than half of all AAA repairs are now performed without laparotomy, with use of endovascular techniques.[11] Perioperative mortality is lower than that with open repair, but it is unclear whether this mortality benefit is sustained in the long-term.[12] More recent studies suggest the survival advantage is maintained for 3 years.[13] Numerous studies have cited a clear reduction in early mortality associated with endovascular aneurysm repair (EVAR) but continue to emphasize the importance of an organized algorithmic approach with a specialized team.[14] Hemodynamically stable patients undergo rapid 64 slice CTA with three-dimensional reformatting. Although many hospitals have hybrid operating rooms, EVAR can be done with portable fluoroscopy in the operating room.

Stable patients can undergo bilateral femoral artery cut-downs to place sheaths and wires once in the operating room. Unstable patients, however, may require transfemoral access with a 12 French sheath followed by aortic balloon occlusion in the ED. Once an arteriogram is performed with a marking flush catheter, the endovascular plan is formulated unless a contrast enhanced CT scan is available for stent graft sizing.

A stent graft (a fabric graft supported by a nitinol wire frame) is placed into the femoral artery percutaneously or through a groin incision and is advanced under fluoroscopic guidance to a position that spans the infrarenal aneurysm (Fig. 76.6A). The contralateral iliac limb is placed to form a bifurcated graft (see Fig. 76.6B). Once in position, the graft is deployed and expanded to fit tightly against the walls of the aorta. These self-expanding devices have radial forces but are also oversized 10% to 20% to ensure proper sealing. There are several devices approved by the U.S. Food and Drug Administration (FDA) and all have unique features. Standard criteria for use include an aortic transverse diameter between 18 to 32 mm, angulation less than 60 degrees, and neck (lowest renal artery to start of aneurysm) length more than 10 mm, iliac landing zone diameter of 10 to 22 mm, and femoral access diameter more than 8 mm.[12]

Endovascular repair results in more frequent reinterventions for graft-related complications.[12] Because not all aneurysms are anatomically suitable for endovascular repair, detailed preoperative imaging and planning are required to make this determination. In addition, patients who have had endovascular aneurysm repair remain at risk for several complications—most importantly rupture of the aneurysm.[12] Some authors now suggest that endovascular repair has become the first choice of AAA treatment in almost all patients with anatomical condition, remaining the most important factor for indication for open repair.[15] Lack of inventory and expert local experience with endovascular operations remain the greatest barrier to the widespread application of evolving endovascular technologies for emergency use. Percutaneous endovascular repair is becoming more common and may represent a suitable alternative to open endovascular repair in some patients.[16]

Survival

The operative mortality rate for elective AAA repair is approximately 1% to 2% for endovascular repair and 3% to 5% for open repair, in contrast to the much higher operative mortality with ruptured aneurysms.[12] Patients who survive the operation have an excellent prognosis, with a long-term survival close to that of the general population. After repair of the aneurysm, long-term survival is primarily limited by associated cardiac disease.

LATE COMPLICATIONS OF REPAIR

Graft infection, AEF formation, and anastomotic aneurysm (pseudoaneurysm) formation can occur at any time from weeks to years after the surgery. These complications can occur concurrently or sequentially and are diagnosed by similarly. In addition, endovascular aneurysm repair has several unique complications, the most important of which is endoleak.

Graft Infection

Graft infection can result from contamination of the graft at surgery, spread of a contiguous infection, or hematogenous seeding. Infection can disrupt the anastomosis between native artery and graft, leading to leakage of blood from the anastomosis and pseudoaneurysm formation. The infection can be localized to a portion of the graft, most often the inguinal portion of an aortofemoral graft, or can involve the entire graft.

Infection of the distal limb of an aortofemoral graft may cause local signs of infection or a palpable false aneurysm. Intra-abdominal graft infection is often subtle, with low-grade fever and vague abdominal or back pain. Abdominal tenderness or a palpable mass may be present if there is a leaking anastomosis. Collections of fluid or gas around the graft on CT provide evidence of infection, although CT scans can be falsely negative.

Aortoenteric Fistula

As discussed earlier in this chapter, an AEF should be considered in any patient with gastrointestinal bleeding and a history of abdominal aortic surgery. Most of these patients, however, ultimately prove to have other, more common causes of gastrointestinal bleeding. The diagnostic approach depends on the patient's hemodynamic stability.

If the patient with a suspected AEF is unstable with massive bleeding, diagnostic testing may be dangerously time-consuming. In these patients, emergency laparotomy may be necessary to control hemorrhage and diagnose or exclude the presence of an AEF. Stable patients can be evaluated with endoscopy or a CT scan. Some patients with AEF may be treated endovascularly, which may result in improved perioperative morbidity and mortality.

Upper gastrointestinal endoscopy is occasionally recommended as the initial diagnostic test. Direct visualization of the fistula into the distal duodenum is sometimes possible. Endoscopy cannot be relied on to identify an AEF, however, and its main value is in establishing another diagnosis. Emergency surgery can be avoided if an active bleeding site that is not an AEF is clearly seen.

An abdominal CT scan can also be used to evaluate a suspected AEF. Although imaging of the fistula may not be possible, graft infection is almost invariably present in patients with secondary AEFs, and the CT scan will demonstrate the associated infection. Radiographically distinguishing an AEF from intra-abdominal graft infection alone may not be possible.

Pseudoaneurysm (Anastomotic Aneurysm)

Pseudoaneurysms can arise at the site of a leaking anastomosis. They may be associated with graft infection or AEF formation but more often result from degeneration of the native vessel.

The patient with an anastomotic aneurysm may have pain or a pulsatile mass in the abdomen or groin. The aneurysm may give rise to distal emboli or may rupture and cause life-threatening hemorrhage. Suspected pseudoaneurysms can be evaluated with angiography, CT scan, or ultrasonography.

Complications of Endovascular Aneurysm Repair

A rapidly increasing percentage of elective AAA repairs are done with endovascular techniques, and these patients may come to the

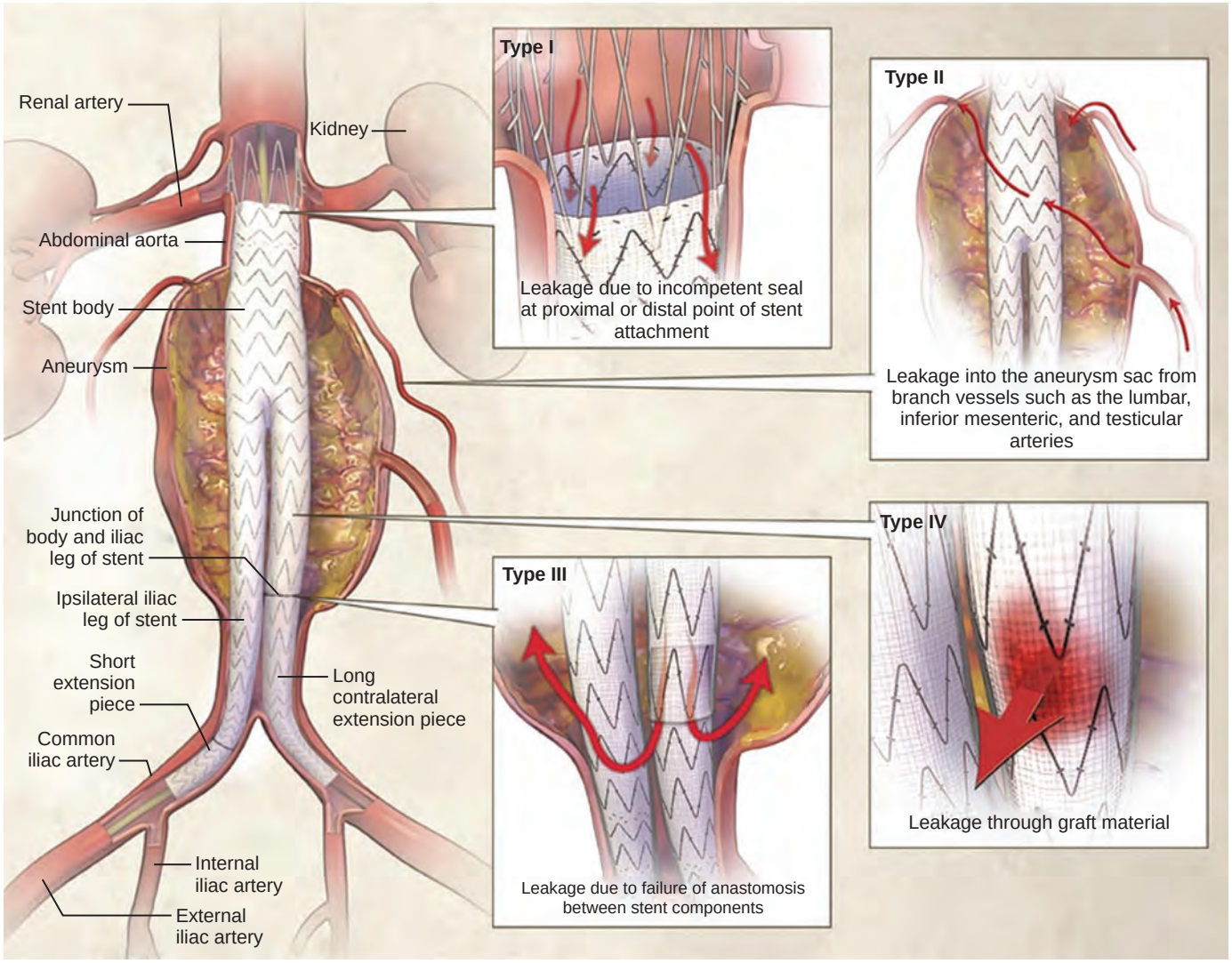

Fig. 76.7. Types and causes of endoleaks. (From Greenhalgh RM, Powell JT: Endovascular repair of abdominal aortic aneurysm. N Engl J Med 358:494-501, 2008. Copyright © 2008, Massachusetts Medical Society. All rights reserved.)

ED with postoperative complications. The most serious of these is endoleak—blood flow outside of the graft lumen but within the aneurysm sac, potentially allowing enlargement of the aneurysm. Endoleaks may be caused by separation of the proximal or distal end of the graft from the aortic wall (type I), back-bleeding into the aneurysm sac from branch vessels such as lumbar arteries (type II), leakage between the modular components of the graft (type III), leakage through the graft fabric itself (type IV), or in rarer cases when the sac enlarges without an identifiable leak, otherwise known as *endotension* (type V) (Fig. 76.7). Patients with persistent leakage of blood into the aneurysm sac are at significant risk for rupture of the aneurysm.[12]

Endoleaks may develop soon after the procedure or much later. They have been reported in as many as 20% of patients who have had endovascular aneurysm repair. Because many type II endoleaks resolve spontaneously, patients are sometimes observed for months before repair of the leak with secondary endovascular procedures or surgical intervention.

Patients sometimes sustain other complications, such as graft migration, stenosis or thrombosis, and structural failure of various elements of the graft. These complications often lead to endoleak and the risk of rupture.

In the ED, CT with intravenous contrast should be used to evaluate for possible complications of endovascular repair. A specific CT imaging protocol may be desired; this should be discussed with the radiologist or vascular surgeon. Prompt surgical consultation should be obtained for patients with any symptoms that could be related to device malfunction, and the potential for aneurysm rupture should always be considered.

DISPOSITION

A patient with an acutely symptomatic AAA requires emergency surgical evaluation and emergency repair. A patient whose aneurysm is asymptomatic and discovered incidentally should be referred for consideration of elective repair. The patient with an AAA should be referred for an outpatient evaluation only if it is clear that the symptoms prompting the ED visit are unrelated to the aneurysm. Although the incidental detection of AAA is common, such patients may suffer from poor subsequent follow-up and monitoring.[4] If the patient is discharged, appropriate referral for follow-up is crucial, and instructions should be given to seek immediate medical attention if abdominal, back, or flank pain develops.

In the patient who has had an AAA repaired, unexplained fever, abdominal pain, or gastrointestinal bleeding suggests the presence of a graft-related complication and the need for inpatient evaluation.

KEY CONCEPTS

- A ruptured AAA should be considered in any patient older than 50 years with otherwise unexplained abdominal or back pain. The complete triad of pain, hypotension, and a pulsatile mass may not be present.
- In the patient with an AAA and acute symptoms, rupture is imminent or has already occurred.
- The patient with a ruptured AAA who is initially hemodynamically stable can suddenly deteriorate at any time.
- The risk of rupture increases dramatically with increased aneurysm size, and most ruptured AAAs have diameters greater than 5 cm.
- Bedside ultrasound may be used to document an AAA or free fluid and assist in rapid diagnosis of a ruptured AAA.
- The abdominal CT scan is the diagnostic test of choice in the evaluation of the stable patient with suspected ruptured AAA; intravenous contrast is not essential in emergency situations.
- The patient who has had endovascular repair of an AAA remains at risk for aneurysm rupture.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 76: QUESTIONS & ANSWERS

76.1. What is the most common complication from abdominal aortic aneurysms (AAAs)?
- **A.** Aortoenteric fistula (AEF)
- **B.** Mesenteric ischemia
- **C.** Renal artery compromise
- **D.** Rupture
- **E.** Ureteral obstruction

Answer: D. Rupture is by far the most common complication of AAAs. Rupture typically occurs into the retroperitoneum, allowing potential tamponade of the rupture site. Only 10% to 30% have free intraperitoneal rupture, which is often rapidly fatal.

76.2. A 67-year-old man presents with the acute onset of pain and decreased temperature in his right foot. Symptoms began 2 hours ago at rest. Past medical history is significant for tobacco use, hypertension, and hyperlipidemia. The physical examination reveals moderate distress due to foot pain and is otherwise normal except for the extremity examination, which shows symmetrical and intact distal pulses but pale and patchy skin mottling of the right leg with a cool, bluish right foot. The foot is not swollen. What of the following is the best explanation for these findings?
- **A.** Abdominal aortic microemboli
- **B.** Abdominal aortic pseudoaneurysm
- **C.** Acute thrombosis of the femoral and popliteal veins
- **D.** Acute thrombosis of the iliac veins
- **E.** Popliteal artery thrombosis

Answer: A. Microemboli consist of cholesterol crystals or small clot fragments that may shower distally. The combination of normal pedal pulses and cool cyanotic and painful toes is called the *blue toe syndrome* and suggests a proximal source of microemboli. The source may be the heart or a diseased aorta, and an aneurysm may or may not be found. Venous thrombosis would cause distal swelling, and pedal pulses would not be normal with popliteal artery thrombosis.

76.3. A 79-year-old man presents with syncope. The episode occurred 1 hour before arrival, without preceding symptoms. The family reports a past history of peptic ulcer disease controlled with medications and a surgical repair of an abdominal aortic aneurysm (AAA) 15 years ago. Physical examination reveals a pale man with a heart rate of 115 beats per minute, blood pressure of 83/54 mm Hg, and respiratory rate of 22 breaths per minute. Other pertinent findings are an abdominal examination without palpable masses and gross melena on rectal examination. Concurrent with volume resuscitation, what would be the most appropriate next step?
- **A.** Addition of albumin to crystalloid infusion
- **B.** Computed tomography (CT) scan of the abdomen with contrast enhancement
- **C.** Immediate gastrointestinal service consultation for upper endoscopy
- **D.** Immediate vascular surgical consultation

Answer: D. The presence of gastrointestinal bleeding with a history of aortic surgery or current evidence of an AAA is an aortoenteric fistula (AEF) until proven otherwise. The most common site of vascular bowel erosion is the third or fourth portion of the duodenum, causing hematemesis or melena. The initial bleeding may be minor, followed days to weeks later by massive bleeding. Surgical intervention is required. Although endoscopy or CT scanning might help with diagnosis, this patient is not stable enough to undergo endoscopy or for transfer to the scanner. Hypotensive patients may have to be taken to the operating room on the basis of a strong clinical presumption.

76.4. What is the strongest predictor of mortality in patients with a ruptured abdominal aortic aneurysm (AAA)?
- **A.** Age older than 70 years old
- **B.** Anemia on ED arrival
- **C.** Hyperglycemia
- **D.** Hypotension
- **E.** Presentation more than 12 hours after symptom onset

Answer: D. Preoperative hypotension is the strongest predictor of mortality. Paradoxically, there are few data guiding volume resuscitation, fluid choices, and target blood pressures. Clearly, rapid operative or endovascular surgery is most important. Crystalloid resuscitation before repair might cause dilutional coagulopathy and clot dislodgement by raising the intravascular pressure. Judicious volume resuscitation with early use of blood products and a target systolic pressure of 80 to 100 mm Hg is probably reasonable.

76.5. A 67-year-old man presents with a several-day history of intermittent periumbilical abdominal pain. Physical examination and vital signs are unremarkable except for supraumbilical tenderness. Hemoglobin is 12 g/dL. Contrast-enhanced computed tomography (CT) scan of the abdomen details a 4.2-cm infrarenal abdominal aortic aneurysm (AAA) with an apparent old contained rupture

with no obvious new or acute blood. All of his discomfort is relieved by a single dose of morphine sulfate. Which of the following would be the most appropriate course of action?

A. Surgical consultation
B. Internal medicine admission for observation and intravenous antibiotics
C. Gastrointestinal consultation for early follow-up and upper or lower endoscopy
D. Emergency department (ED) observation for 6 to 8 hours with serial abdominal examinations
E. Vascular surgery clinic follow-up in 1 or 2 days

Answer: A. Watchful waiting is indicated only for asymptomatic aneurysms, regardless of the size (up to 5.5 cm). The majority of "stable" AAAs are neither painful nor tender, and the presence of both in this patient suggests imminent rupture. Although the CT scan did not detect acute blood, the safest course of action would be surgical consultation, with early or imminent rupture as the presumed source of this patient's symptoms.

76.6. Which of the following is most common in the patient with an intact (nonruptured) 6-cm abdominal aortic aneurysm (AAA)?

A. Abdominal pain
B. Absence of any symptoms
C. Back pain
D. Lower extremity pain
E. Sensation of abdominal distention

Answer: B. Most intact AAAs are asymptomatic. They may be discovered incidentally on physical examination or a radiologic study done for other reasons or may be found in an ultrasonographic aneurysm screening program. Pain in the abdomen or back does not usually develop until the aneurysm ruptures. Perfusion of the lower extremities is usually normal in patients with AAAs.

76.7. A 67-year-old man presents with a 1-week history of mild epigastric pain. On examination, he has a blood pressure of 150/100 mm Hg; the remainder of his vital signs are normal. He has no abdominal tenderness, guarding, or palpable masses. His hemoglobin is 14.0 g/dL. A bedside ultrasound examination reveals a 4.0-cm abdominal aortic aneurysm (AAA) without evidence of rupture. Which of the following is the most appropriate next step?

A. Arrange immediate operative intervention
B. Lower blood pressure with intravenous therapy
C. Obtain abdominal computed tomography (CT) scan
D. Refer for outpatient surgical evaluation

Answer: C. The patient has abdominal pain and an AAA, and it is unclear whether the pain is caused by aneurysm rupture; there is no indication for immediate surgery, which has a higher mortality rate than that of elective repair. However, the possibility of rupture makes outpatient referral inappropriate without further investigation. Ultrasonography cannot reliably exclude aneurysm rupture; therefore, a CT scan is indicated. If the CT scan shows no evidence of rupture, a decision about the next step should be made in consultation with a surgeon. Unlike the situation with aortic dissection (see Chapter 75), there is no evidence that lowering a mildly or moderately elevated blood pressure is beneficial in the patient with an intact or ruptured AAA.

CHAPTER 77

Peripheral Arteriovascular Disease

Tom P. Aufderheide

PRINCIPLES

Arteries are classified into three categories on the basis of their size and histologic features: (1) large or elastic arteries (the aorta and its immediate proximal, larger branches, including the innominate, subclavian, common carotid, and pulmonary arteries); (2) medium-sized or muscular arteries (located just distal to elastic arteries, including the common femoral, axillary, and carotid arteries); and (3) small arteries (usually <2 mm in diameter) that course in the substance of tissues and organs. This chapter considers diseases of medium and small arteries.

PRINCIPLES OF DISEASE

Arterial Anatomy

All arteries possess three layers: the tunica intima, tunica media, and tunica adventitia. As peripheral arteries diminish in caliber, these three layers become progressively indistinct and are no longer identifiable at the level of the arteriole (precapillary vessel containing smooth muscle).

The tunica intima has an inner lining of endothelial cells surrounded by subendothelial connective tissue. The single layer of continuous endothelium is a unique thromboresistant layer between blood and the potentially thrombogenic subendothelial tissues. The integrity of the endothelium is a fundamental requirement for normal structure and function of the vessel wall. Endothelial injury results in intraluminal thrombosis and contributes to atherosclerosis.

The tunica media is made up primarily of circular or spiral smooth muscle cells arranged in concentric layers. The outer limit of this layer is marked by a well-defined, external elastic membrane. The elastic content of the tunica media gives resilience to medium-sized arteries. With age, elastic fibers deteriorate, replaced by fibrous tissue. This loss of elasticity results in stretching and elongation and accounts for the progressive tortuosity and development of arterial aneurysms with aging. In addition, vascular smooth muscle cells may contribute to lipid accumulation in the vessel wall during atherosclerosis, which precipitates vasoconstriction and dilation.

The tunica adventitia is a layer of connective tissue in which nerve fibers and small, thin-walled nutrient vessels (vasa vasorum) are dispersed. Medium-sized arteries contain more nerve fibers than larger vessels, reflecting their role in the autonomic regulation of blood flow.

The peripheral arterial vascular system can be considered as a single end-organ subject to eight basic pathophysiologic processes: (1) atherosclerosis, (2) aneurysm, (3) embolism, (4) thrombosis, (5) inflammation, (6) trauma, (7) vasospasm, and (8) arteriovenous fistula. Two of these—atherosclerosis and thrombosis—are responsible for most disease.

Pathophysiology

Atherosclerosis

Atherosclerosis is a disease of large- and medium-sized muscular arteries. The basic lesion, the atheroma, or fibrofatty plaque, is a raised focal plaque within the intima; it has a lipid core covered by a fibrous cap. As the plaques increase in size and number, they progressively encroach on the lumen of the artery and the adjacent media. Atheromas compromise arterial blood flow and weaken the walls of the affected arteries.

The distribution of atherosclerotic plaques is rather constant. The abdominal aorta typically is susceptible to more atherosclerotic disease than the thoracic aorta, and aortic lesions are much more common and prominent around the ostia of major branches. Other vessels affected by atherosclerosis are the aortoiliac, femoral, and popliteal arteries; the descending thoracic aorta; the coronary arteries; the internal carotid arteries; and the circle of Willis. Upper extremities vessels are usually spared.

As atherosclerosis progresses, atheromas calcify, resulting in hard, brittle vessels. Rupture of the atheromatous plaques discharge debris, producing atheroemboli (cholesterol emboli). Ulcerated lesions produce in situ thrombosis, causing intraluminal occlusion.

Hemorrhage into the plaque may further compromise the arterial lumen. Although atherosclerosis primarily affects the intima, in severe cases, the tunica media undergoes pressure atrophy and loss of elastic tissue, with sufficient weakening to create aneurysmal dilation.

Aneurysms

A true aneurysm is an abnormal localized dilation of the intact vessel wall. With a pseudoaneurysm, the entire wall perforates or ruptures, and the extravasated blood is contained by the surrounding tissues, eventually forming a fibrous sac that communicates with the artery.

Mural and mechanical factors contribute to true aneurysm formation.[1] The major cause of aneurysms is a weakness or defect in the integrity of the arterial wall. The only aneurysms that develop in a normal arterial segment are poststenotic aneurysms, such as with coarctation. Acceleration of flow past a narrow point creates slower flow beyond the stenosis lateral to the jet stream, producing increased lateral pressure. Aneurysmal dilation accelerates, increasing the risk of rupture as diameter increases, as described by Laplace's law: tension (lateral pressure) in the wall of a hollow viscus varies directly with its radius (tension = pressure × radius).

The most common cause of aneurysms is severe atherosclerosis resulting from thinning and destruction of the tunica media. Atheromatous ulcers covered by mural thrombi are common.

Mural thrombi form emboli that then lodge in distal vessels. When an entire aneurysm is filled with thrombus material, arterial occlusion results.

Aneurysms cause clinical symptoms through (1) rupture with subsequent hemorrhage, (2) impingement on adjacent structures, (3) occlusion of a vessel by either direct pressure or mural thrombus formation, (4) embolism from mural thrombus, and (5) a pulsatile mass.

Arterial Embolism

An embolus, by definition, is a foreign body, most commonly a blood clot, carried by the blood to a site distant from its point of origin. Most emboli are detached thrombus formations or thromboembolism. Less common emboli include debris from ruptured atherosclerotic plaques, tumor debris, or foreign bodies. Unless otherwise specified, the term *embolus* in this chapter is defined as thromboembolus.

Thromboembolism. Most arterial emboli (85%) originate from thrombus formation in the heart. Left ventricular thrombus formation resulting from myocardial infarction accounts for 60% to 70% of arterial emboli. Atrial thrombi associated with mitral stenosis and rheumatic heart disease account for only 5% to 10% of arterial emboli.[2] Coexisting atrial fibrillation, often without mitral stenosis, is present in 60% to 75% of patients with peripheral arterial embolic events because atrial fibrillation itself predisposes patients to intracardiac clotting.[3]

Acute arterial emboli often cause distal tissue infarction. Clinical outcome depends on the amount of collateral circulation, the size of the vessel, and the degree of obstruction. Patients with long-standing atherosclerosis have well-developed collateral circulation, whereas sudden occlusion of a normal artery without collateral pathways results in severe ischemia. After acute obstruction, the embolus can propagate proximally or distally, fragment and embolize further to distal vessels, or precipitate venous thrombosis by initiating a localized inflammatory reaction.

Because vessel diameters change abruptly at branch points, embolic occlusion most often occurs at major arterial bifurcations. The common femoral artery bifurcation is the most frequent site, accounting for 35% to 50% of all cases.[2] The smaller femoral and popliteal arteries are involved twice as often as the larger aortic and iliac vessels, which reflects the small size of most emboli.

Arterial emboli, resulting in arterial occlusion and subsequent ischemia, results in cell death producing high concentrations of potassium, lactic acid, and myoglobin in the extremity distal to the occlusion. Revascularization may result in sudden release, which can produce life-threatening hyperkalemia, metabolic acidosis, and myoglobinuria. This myonephropathic-metabolic syndrome accounts for approximately one-third of the deaths from arterial embolism after revascularization.[4]

Atheroembolism. *Atheroembolism* refers to microemboli consisting of cholesterol, calcium, and platelet aggregates dislodged from proximal complicated atherosclerotic plaques that lodge in distal end arteries. In the central nervous system, atheroemboli cause transient ischemic attacks and strokes. In the peripheral vascular system, atheroemboli characteristically cause cool, painful, and cyanotic toes, or the blue toe syndrome.[5]

Atheroemboli are caused by a proximally located arterial lesion, usually atherosclerotic plaques or aneurysms. Bilateral distal extremity involvement implies an aortic source, whereas unilateral atheroemboli usually arise from sites distal to the aorta. Distal lesions are most common in the femoropopliteal arteries (60%) and the aortoiliac arteries (40%). Aortic lesions (eg, aneurysms, polytetrafluoroethylene grafts) are a less common source of microemboli.[5]

Atheroemboli are small (100 to 200 μm in size). Single atheroembolic events seldom result in tissue loss, but atheroemboli tend to cluster. If unrecognized, repeated events ultimately result in loss of collateral circulation, progressive symptoms, and extensive tissue infarction.[5]

Infectious emboli from bacterial endocarditis can produce septic infarcts that may convert to large abscesses. Rarely, cardiac and noncardiac tumors or foreign bodies may gain access to the arterial circulation and embolize. Primary or metastatic lung neoplasms, malignant melanoma, and bullet emboli have been reported. With cyanotic congenital heart disease (eg, patent foramen ovale), venous emboli may pass directly to the arterial circulation (paradoxical emboli). Although rare, this possibility should be considered in any patient with simultaneous arterial and venous emboli, particularly if a source of the arterial embolus is not evident.

Arterial Thrombosis

Thrombosis is the in situ formation of a blood clot within the uninterrupted arterial vascular system. Complicated atherosclerotic plaques are usually responsible for the two major factors that cause in situ thrombosis: endothelial injury and alterations in normal blood flow. Less common causes include acute vasculitis and trauma. Thrombosis is rare in normal arteries.[6]

Peripheral arterial thrombi are usually occlusive, firmly attached to the damaged arterial wall, and infrequently embolize. Clot propagation intensifies ischemia.

Inflammation

Inflammatory arterial injury can be caused by drugs, irradiation, mechanical trauma, or bacterial invasion. The major cause of arteritis is noninfectious systemic necrotizing vasculitis. Infectious arteritis is caused by direct invasion of the arterial wall. Septicemia, intravenous drug abuse, or infective endocarditis is most often responsible. Certain fungal infections, particularly aspergillosis and mucormycosis, are frequently associated with vasculitis and thrombosis.

Trauma

Vascular trauma results in characteristic pathologic syndromes. Partial arterial lacerations continue to bleed because the intact portion of the vessel wall prevents retraction and closure of the arterial wound. This may form an expanding hematoma. Complete arterial transection usually has only moderate or insignificant bleeding because of arterial spasm of the transected ends and formation of a temporary thrombus. Delayed hemorrhage results from relaxation of arterial spasm, liquefaction of the thrombus, or displacement of the thrombus by arterial pressure. Blunt injury produces intimal disruption. Dissection then leads to progressive obstruction and thrombosis. Vasospasm can accompany injuries adjacent to traumatized blood vessels; spontaneous resolution always occurs in the absence of arterial disruption or intimal injury.

Vasospasm

Vasospastic disorders (Raynaud's disease, Raynaud's phenomenon, livedo reticularis, acrocyanosis, erythromelalgia) produce an abnormal vasomotor response in distal small arteries. The cause is unknown but may be related to autonomic innervation of peripheral arterioles. Vasospastic disorders are characterized by the presence of ischemic symptoms and absence of tissue loss.

True organic changes within the arterial wall are absent. In contrast, patients with digital ulceration and gangrene always have fixed arterial occlusions in distal extremity arteries.

Arteriovenous Fistulae

Abnormal communication between arteries and veins may result from congenital defects, arterial aneurysm rupture into an adjacent vein, penetrating injuries, and inflammatory necrosis. The artery proximal and veins distal to the fistula become distended, tortuous, and aneurysmal. Proximal and distal veins respond to alterations in hemodynamics with intimal proliferation and fibrosis, followed by a decrease in the internal elastic lamina, resulting in distention, tortuosity, and aneurysm formation. Chronic venous hypertension causes dermatitis and ulceration of overlying skin. The size of the fistula generally increases with time.

Approximately 60% of arteriovenous fistulae are associated with a false aneurysm.[7] False aneurysm formation can occur as part of the fistulous tract or arterial or venous dilation.[7] Increase in cardiac output results in tachycardia, widened pulse pressure, or high-output failure.

CLINICAL FEATURES

History

Patients with peripheral arterial disease have pain, are at risk for tissue loss (ulceration or gangrene), or a change in sensation or appearance (swelling, discoloration, or temperature change). Related conditions providing evidence of atherosclerosis are cardiac disease, myocardial infarction, cardiac dysrhythmias (eg, atrial fibrillation), stroke, transient ischemic attacks, and renal disease. Factors that increase the likelihood of atherosclerosis are cigarette smoking, diabetes, hypercholesterolemia, and hypertension. Intravenous drug use can lead to arterial injury.

Risk factors unrelated to atherosclerosis include prior injuries or surgeries, a history of phlebitis or pulmonary embolism, autoimmune disease, arthritis, or coagulation abnormalities.

Acute Arterial Occlusion

Patients with acute arterial occlusion usually exhibit some variant of the five Ps: pain, pallor, pulselessness, paresthesias, and paralysis. Paresthesias and paralysis indicate limb-threatening ischemia requiring emergency surgical intervention regardless of the cause. In patients with non–limb-threatening ischemia, accurate differentiation between embolism and in situ thrombosis determines management. Arterial embolism is best managed by emergency Fogarty catheter embolectomy. Non–limb-threatening ischemia from in situ thrombosis is often aggravated by emergency surgical intervention and is initially best managed nonoperatively if possible (Fig. 77.1). Because acute arterial embolism usually occurs in patients without significant peripheral atherosclerosis or well-developed collateral circulation, it usually manifests as sudden limb-threatening ischemia. Patients describe a sensation of the leg's being "struck" by a severe shocking pain. Often the patient has to sit or fall to the ground during the sudden event.

In situ thrombosis usually occurs with long-standing peripheral atherosclerosis and well-developed collateral circulation, often seen sub-acutely with non–limb-threatening ischemia. A history of claudication is common with in situ thrombosis and rare with arterial embolism.

Chronic Arterial Insufficiency

Chronic arterial insufficiency causes two characteristic types of pain: intermittent claudication and ischemic pain at rest. The location of arterial occlusion determines the location of claudication. Calf claudication is associated with femoral and popliteal disease, typically a cramping pain, reliably reproduced by the same degree of exercise and completely relieved by rest (usually 1 to 5 minutes). Aortoiliac occlusive disease causes claudication in the buttocks and hips, as well as the calves. The calf pain in aortoiliac disease is generally more severe than the buttock and thigh pain, which is more often described as an aching, discomfort, or weakness. Some patients deny pain, complaining only that the thigh or hip "gives out" with exercise. Aortoiliac occlusive disease severe enough to produce bilateral claudication is almost always associated with impotence in men (Leriche's syndrome). Even in the absence of impotency, bilateral hip or thigh pain in a man should indicate the possibility of aortoiliac occlusive disease.

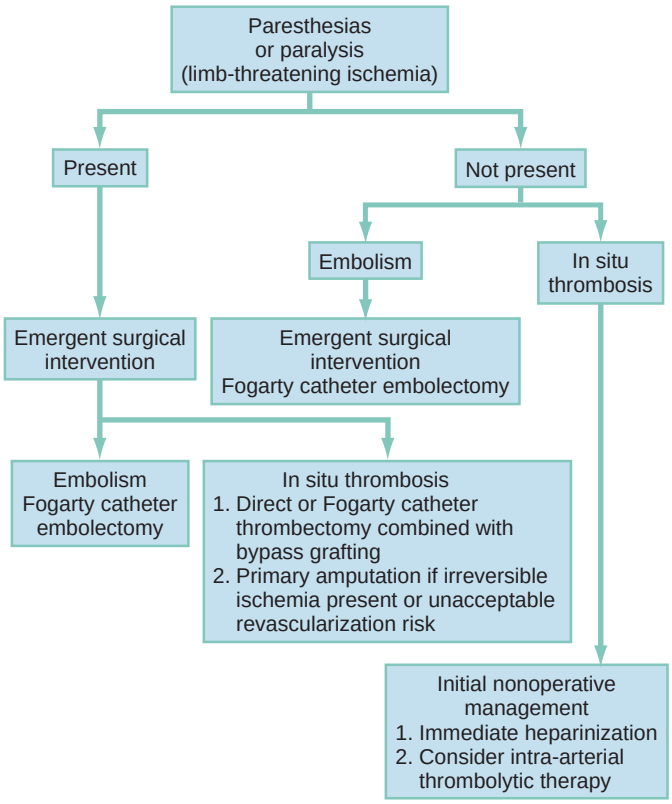

Fig. 77.1. Clinical presentation and management of acute arterial occlusion.

Chronic arterial insufficiency may progress so that ischemic pain occurs at rest. Rest pain often begins in the feet and typically involves the foot distal to the metatarsals, awakening the patient from sleep. Ischemic rest pain is a severe, unrelenting pain aggravated by elevation and unrelieved by analgesics. Patients have prompt relief with any activity involving a standing position. Patients often sleep in a chair or with the leg dangling over the bed.

Physical Examination

A systematic assessment of the peripheral vascular system includes palpation of the pulse volume in the pairs of brachial, radial, femoral, posterior tibial, and dorsalis pedis arteries documented on a scale of 0 to 4+. Important to note, approximately 10% of the population does not have one of the dorsalis pedis pulses.[8] Carotid arteries should be gently palpated one at a time.

The lower extremities should be examined for signs of chronic and advanced ischemia. Muscular atrophy, particularly in the lower extremities, and loss of hair over the toes and feet with thickening of the toenails resulting from slowness of nail growth

are common signs of arterial insufficiency. As ischemia becomes more advanced, the skin becomes shiny, scaly, and "skeletonized" from atrophy of the skin, subcutaneous tissue, and muscle.

Test areas where ischemia is suspected by blanching with finger pressure; a delay in return of normal color (compared with the unaffected extremity) implies reduced perfusion.

Buerger's sign provides reliable evidence of severe advanced ischemia. With the patient supine, the legs are elevated to 45 degrees to bring the feet more than 12 inches above the right atrium, and any pallor of the feet is noted. If the color does not change, the patient dorsiflexes the feet five or six times; pallor induced by exercise may also connote inadequate arterial flow. The patient is then moved to the sitting position with the feet hanging down. Within 10 to 15 seconds, color should return, and the veins should fill. Typically in the ischemic foot the first return of color is cyanosis, transitioning to bright red as reactive hyperemia occurs. If the veins require more than 20 seconds to become distended, advanced ischemia is present. With severely restricted arterial inflow and chronic dilation of the peripheral vascular bed, the foot turns chalk white on elevation and intensely hyperemic after 1 minute of dependency. Localized pallor or cyanosis associated with poor capillary filling is usually a prelude to ischemic gangrene or ulceration.

Doppler ultrasonography should be used in patients with questionable or absent pulses. The ankle-brachial index (ABI) is made by comparing the systolic blood pressure at the level of the ankle with the brachial systolic pressure. Ankle systolic pressure can be accurately measured with a Doppler probe placed over the dorsalis pedis or posterior tibial artery. This pressure is normally 90% or more of the brachial systolic pressure; with mild arterial insufficiency, it is between 70% and 90%; with moderate insufficiency, between 50% and 70%; and with severe insufficiency, less than 50%.

The Allen test is helpful in assessing patency of the radial or ulnar artery distal to the wrist. The patient initially opens and closes the hand and then clenches the fist to expel as much blood from the hand as possible; the examiner then compresses the radial and ulnar arteries. When the patient opens the fist, the hand is pale. The examiner then releases pressure from the radial artery but maintains it on the ulnar artery. If the radial artery is patent, the hand becomes pink rapidly; occluded, the hand remains pale. The maneuver is repeated maintaining pressure on the radial artery, releasing the ulnar artery. A comparison can be made with the opposite hand.

Arterial Embolism

The physical examination can differentiate arterial embolism from in situ thrombosis. Sudden loss of a pulse is the hallmark of arterial embolism but may be difficult to recognize if prior pulse status is unknown or is abnormal because of atherosclerosis. A bounding pulse may be felt initially at the location of an embolus from transmitted pulsations through the fresh clot. Patients with arterial embolism have few physical findings suggestive of long-standing peripheral vascular disease. Tenderness to palpation may occur at the site of an embolic occlusion.

If arterial embolism is suspected, the physical examination should be directed toward identifying its source (a left ventricular mural thrombus [prior myocardial infarction] or a left atrial thrombus [mitral valve disease]). Coexistent atrial fibrillation is common.

The limb distal to an embolic occlusion is initially chalk white. Because of absence of blood in the sub-capillary venules, demarcation between ischemic and nonischemic tissue is sharp. With time, cyanosis appears from desaturation of blood with continued ongoing ischemia. Paresthesia or paralysis indicates limb-threatening ischemia. Presence of sensitivity to light touch is the best guide to viability of the tissue. Complete anesthesia demands emergent surgical intervention. Paralysis represents severe muscle and neural ischemia, which may be irreversible. Involuntary muscle contracture with "woody" hardness represents irreversible ischemia.

Arterial Thrombosis

Physical findings of in situ thrombosis are often accompanied by evidence of atherosclerotic occlusive disease. Proximal or contralateral limb pulses are usually diminished or absent. An embolic source, such as atrial fibrillation, is usually absent. Because of collateral circulation, demarcation of limb ischemia is less well defined in these patients (Table 77.1).

Carotid, renal, and femoral arteries may have bruits, and there may be an abdominal aortic aneurysm. If an occlusion of the upper extremity vessels is suggested, the subclavian artery should palpitated for thrills and auscultated for bruits in the supraclavicular fossa.

A funduscopic examination may yield evidence of arteriosclerosis or hypertension. Hollenhorst plaques (atheromatous emboli containing cholesterol crystals in the retinal arterioles) may be detected. Roth's spots (round or oval white spots seen near the optic disk) may be present in patients with infective endocarditis.

Embolic phenomena can cause diverse end-organ damage: hemiplegia from cerebral emboli, flank pain with hematuria from renal emboli, left upper quadrant abdominal pain from splenic infarcts, and pleuritic pain with hemoptysis from pulmonary emboli. Septic pulmonary embolism from right-sided endocarditis may be confused with pneumonia.

TABLE 77.1

Differentiation of Embolus From Thrombosis

CLINICAL FINDINGS	EMBOLUS	THROMBOSIS
Identifiable source for embolus	Usual, particularly atrial fibrillation	Less common
History of claudication	Rare	Common
Physical findings suggestive of occlusive disease	Few; proximal and contralateral limb pulses normal	Often present; proximal or contralateral limb pulses diminished or absent
Demarcation of ischemia	Sharp	Diffuse
Arteriography	Minimal atherosclerosis; sharp cutoff; few collaterals	Diffuse atherosclerosis; tapered, irregular cutoff; well-developed collaterals

From Brewster DC, Chin AK, Fogarty TJ: Vascular surgery. Philadelphia, 1990, WB Saunders.

Inflammation

Inflammatory vascular disease manifests primarily as skin involvement. Skin lesions typically appear as palpable purpura; other cutaneous manifestations of vasculitis include macules, papules, vesicles, bullae, subcutaneous nodules, ulcers, and recurrent or chronic urticaria. Skin lesions may be pruritic or painful, with a burning or stinging sensation. Lesions are more common in dependent areas: lower extremities in ambulatory patients or sacral area in bedridden patients. Edema and hyperpigmentation occurs in areas of recurrent or chronic lesions.

Vasospasm

Vasospastic disorders cause a sharp border between ischemic and normal tissue. Raynaud's disease is characterized by intermittent attacks of triphasic color changes: pallor, cyanosis, and then rubor.[9] The most important element is pallor, during which the digits turn chalk white. Attacks last 15 to 60 minutes, and rewarming the hands restores normal color and sensation. Color changes do not occur above the metacarpophalangeal joints and rarely involve the thumb.

Livedo reticularis causes persistent cyanotic mottling of the skin with a typical "fishnet" appearance and may involve all parts of the extremities and trunk. Acrocyanosis, the least common vasospastic disorder, causes persistent, painless, diffuse cyanosis of the fingers, hands, toes, and feet. Cyanosis intensifies with exposure to cold and decreases with warming. The involved parts are cold, exhibit excessive perspiration, and have normal arterial pulses.

Arteriovenous Fistulae

Arteriovenous malformations and fistulae, although rare, should be distinguished from vascular bruits or aneurysms. True aneurysms and arterial stenoses are associated with a systolic murmur. Pseudoaneurysms have a loud systolic and sometimes a separate faint diastolic murmur. Arteriovenous fistulae have a constant systolic and diastolic (to-and-fro) murmur associated with a palpable thrill, similar to a dialysis arteriovenous fistula. Arteriovenous fistulae can occur at prior operative or trauma sites. Skin overlying the lesion may be warm, but distally the temperature is decreased. Peripheral veins are distended and varicose. Large arteriovenous fistulae produce high cardiac output and widened pulse pressure. Digital pressure on the artery leading to the fistula may decrease the tachycardia (Branham's sign).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis related to peripheral arteriovascular diseases can be extensive, requiring consideration of dermatologic, neurologic, neurosurgical, orthopedic, cardiac, malignant, diabetic, infectious, and other unrelated diagnoses.

DIAGNOSTIC TESTING

An accurate diagnosis of peripheral arterial occlusive disease can be achieved in most patients by careful history and physical examination supplemented by bedside testing.

Noninvasive Assessment

Doppler ultrasonography measures blood flow velocity, detecting the frequency shift of sound waves reflected from red blood cells moving toward and away from the transducer. Doppler waveform analysis detects occlusive disease but is less accurate determining exact location.

Ultrasound is useful in detecting and evaluating atherosclerotic plaques, mural thrombi, and in sizing aneurysms of the abdominal aorta, iliac, femoral, and popliteal arteries.[10] B-mode ultrasonography is noninvasive, painless, less expensive than other modalities, and universally available and is the diagnostic procedure of choice for the initial evaluation of the size of peripheral artery aneurysms. Bedside ultrasound can lead to rapid diagnosis of life-threatening conditions and reduce the number of delayed or invasive diagnostic procedures.[11] B-mode duplex ultrasonography combines B-mode ultrasonography images and sophisticated online computer analysis of Doppler waveforms to allow simultaneous acquisition of both the image of a vascular structure and the characteristics of blood flow velocity within it. Duplex scanning permits noninvasive diagnosis of peripheral vascular, cerebrovascular, and venous disease.

Color imaging of blood flow combined with duplex scanning is known as *color-coded Doppler, Doppler angiography*, or *angiodynography*. The procedure of choice for most conditions, it allows noninvasive and accurate detection of atherosclerotic plaques and stenoses, their effect on intraluminal blood flow, and the presence of venous thrombosis.

Contrast Arteriography

Angiography is the definitive test of abnormal peripheral artery anatomy but is inconclusive about the physiologic condition of the tissues. The risk/benefit ratio of this procedure should be considered. Contrast media have direct toxic effects on vascular endothelium; can produce renal failure, especially in diabetic patients; may cause peripheral vasodilation with hypotension; may result in seizures and stroke in patients with neurologic conditions; and can cause severe idiosyncratic and allergic reactions. Catheter-related complications, including embolization, catheter breakage, and vascular disruption, vary with operator skill and anatomic location but average 0.5%. Overall mortality rate from angiography is 0.03%.[12] Emergency angiography is usually necessary in the following circumstances: (1) acute arterial embolus or thrombosis if the clinical diagnosis is uncertain, (2) consideration of emergency vascular bypass grafting, and (3) characterization of vascular abnormality before emergency surgical correction.

Computed Tomography and Magnetic Resonance Imaging

Computed tomography angiography (CTA) is the most useful test for evaluation of the abdominal aorta.[13] In the peripheral arteriovascular system, CTA is useful for atherosclerotic, infected, and false aneurysms and the cerebral circulation. Magnetic resonance imaging (MRI) with angiography (magnetic resonance angiography) and has been very useful in delineating cerebrovascular problems (see Chapter 101); it is seeing expanded use in the evaluation of peripheral vascular disease. MRI detects changes in the relaxation variables of tissues before obvious structural changes, uniquely differentiating blood, thrombus, fat, and fibrosis.

MANAGEMENT

The management of acute arterial occlusion depends on the degree and cause of ischemia. Patients with limb-threatening ischemia from embolism should undergo emergency Fogarty catheter embolectomy.[14] Patients with limb-threatening ischemia from in situ thrombosis require direct or Fogarty catheter thrombectomy and vascular bypass grafting. Thrombectomy alone often fails because of recurrent thrombosis. Patients who cannot be bypassed, have irreversible ischemia, or are too ill to tolerate revascularization are treated with primary amputation.

A patient with non–limb-threatening embolism is still treated with Fogarty catheter embolectomy. Non–limb-threatening in situ thrombosis is managed nonoperatively with emergent systemic anti-coagulation and consideration of intra-arterial fibrinolytic therapy (see Fig. 77.1).

Elective surgical repair of asymptomatic atherosclerotic peripheral arterial aneurysms is accomplished by aneurysm excision with end-to-end anastomosis or graft interposition. Infected true and false peripheral aneurysms require aneurysm resection, débridement of infected tissue, and ligation of the proximal and distal uninfected arteries. Autogenous vein bypass through uninfected tissue planes is attempted; there is high risk of prosthetic graft infection. The surgical approach for uninfected false aneurysms is similar to peripheral atherosclerotic aneurysms.

Patients with thoracic outlet syndrome who have cervical ribs, arterial involvement, or neurologic symptoms require surgical decompression, removal of anomalous fibromuscular bands, or resection of the first rib if present. Subclavian axillary aneurysms are treated with resection and end-to-end anastomosis or graft interposition. Patients with distal embolic occlusions receive Fogarty catheter embolectomy. Axillary and subclavian vein thromboses are best managed with surgical thrombectomy or systemic fibrinolytic therapy. Brachial plexus involvement with minimal symptoms is followed closely with conservative treatment.

Surgical treatment of peripheral arteriovenous fistulae requires interrupting the fistula tract and restoring both arterial and venous continuity with end-to-end anastomosis or graft interposition. If the anatomic location precludes surgical intervention, percutaneous transvascular embolization with liquid tissue adhesives (eg, isobutyl 2-cyanoacrylate) is usually successful.

Noninvasive Therapy

Acute Anticoagulation With Heparin

For acute arterial embolism, acute arterial thrombosis, and subclavian vein thrombosis, heparin is indicated at standard intravenous doses (80 units/kg bolus, followed by a maintenance infusion of 18 units/kg/hr). Heparin minimizes clot propagation, which can intensify limb ischemia and jeopardize tissues. Relative contraindications include recent neurosurgery (especially within 2 weeks), major surgery within 48 hours, childbirth within 24 hours, a known bleeding diathesis, thrombocytopenia, a potentially hemorrhagic lesion, and active bleeding.

Fibrinolytic Therapy

Low-dose intra-arterial fibrinolytic therapy is increasingly used for acute arterial occlusion. Patients with limb-threatening ischemia are usually not candidates, because they cannot tolerate the time to achieve clot lysis with this approach (6 to 72 hours) without risk of tissue or limb loss. Fibrinolytic therapy is reserved for patients with in situ thrombosis and non–limb-threatening ischemia.

Intra-arterial fibrinolytic agents induce clot lysis in small, distal runoff vessels, decreasing outflow resistance and enabling the native artery to remain open longer. Fibrinolysis often uncovers a critical stenosis that, untreated, may lead to recurrent thrombosis. After successful fibrinolytic therapy, most patients require secondary bypass grafting or angioplasty. Streptokinase, urokinase, and tissue plasminogen activator have all been used successfully. Intravenous administration of a fibrinolytic agent is less effective than direct administration into the clot. Clots more than 30 days old are less likely to achieve successful lysis.

Invasive Therapy

Fogarty Catheter Thrombectomy

The Fogarty catheter is most frequently used for iliac, femoral, and popliteal embolectomy, often with only local anesthesia.[14] Aortic saddle embolus is removed by sequentially passing the Fogarty catheter through bilateral common femoral arteriotomies.

Newly formed in situ thrombosis may often be successfully removed with the Fogarty catheter. An older thrombus adheres more firmly to the damaged vessel wall, requiring direct surgical thrombectomy. The Fogarty catheter is not used in the venous system because of valves.

Peripheral Percutaneous Transluminal Angioplasty

The initial success and long-term patency achieved with angioplasty depend on the location of the lesion and the extent of atheromatous disease. Proximal larger arteries (eg, iliac, femoropopliteal) have the best initial and long-term results. Discrete stenotic lesions (<5 cm) have better long-term patency rates than vessels with diffuse involvement. Balloon angioplasty is the accepted treatment for isolated stenoses in the renal, iliac, and superficial femoral vessels.

Transluminal angioplasty with intravascular stent is used in more distal vessels, including the popliteal and tibial circulation, in cases of more diffuse lesions, and for patients who are prohibitive surgical risks, although its value continues to be assessed.[15]

Recanalization devices include the percutaneous atherectomy catheter, percutaneous angioscope, hot-tip laser, excimer laser, and high-speed rotating wire and drill.

Grafting

Vascular grafting is associated with a variety of complications that can be diagnosed in the emergency department. Autogenous vein grafts (usually a reversed greater saphenous vein) provide excellent long-term patency for small arteries. They may develop atherosclerosis, which can lead to graft stenosis and thrombosis. False aneurysms can form along the suture line.

Polytetrafluoroethylene (Teflon) prosthetic grafts are used in medium and large arteries impossible to bridge with smaller vein grafts. Prosthetic grafts have higher rates of thrombosis than venous grafts. Distal emboli result from poor fixation of luminal fibrin. Prosthetic grafts not adequately covered by viable tissue can erode into adjacent structures and hollow viscera. Prosthetic graft infection, a devastating complication, necessitates removal of the entire graft.

Vascular grafts can be used to bypass arterial occlusions, reconstruct a diseased arterial bifurcation, or can be interposed between sections of resected artery. The most common complications of both prosthetic and vein grafts are thrombosis and development of a false aneurysm at one or more suture lines. Bypass grafting is most often used as palliative treatment for symptoms of atherosclerotic occlusive disease. Patients with localized unilateral stenosis may have comparable rates of success from angioplasty with or without stent placement.[16]

Patients with calf claudication from superficial femoral or popliteal occlusive disease can slow progression if they stop smoking and maintain an active exercise regimen. Patients who have progression of disease, significant rest pain, or tissue loss require surgical revascularization.

Sympathectomy

Lumbar sympathectomy is no longer used for treatment of ischemia from arterial occlusion. The benefit of sympathectomy for

symptomatic Raynaud's phenomenon is unclear, but it remains a potential intervention for ischemic ulcers and rest pain in patients with Buerger's disease.[17]

Hyperbaric Therapy

Scant objective evidence indicates that hyperbaric therapy alters the long-term course of chronic obliterative vascular disorders, presumably by accelerating formation of fine vessels. More success has been achieved with healing chronic diabetic ischemic ulcers and salvaging ischemic skin grafts and flaps.[18] Referral to a hyperbaric unit for chronic therapy should be made by the patient's primary physician or vascular surgeon and not in the emergency department.

DISPOSITION

Disposition of most patients with a suspected or confirmed peripheral arteriovascular diagnosis should be made in consultation with a vascular surgeon.

SPECIFIC ARTERIOVASCULAR DISEASES

DISEASES OF CHRONIC ARTERIAL INSUFFICIENCY

Arteriosclerosis Obliterans

Arteriosclerosis obliterans (atherosclerotic occlusive disease, chronic occlusive arterial disease, obliterative arteriosclerosis) is the peripheral arterial presentation of atherosclerosis. Most often, arteriosclerosis obliterans affects the lower abdominal aorta, the iliac arteries, and the arteries supplying the lower extremities. Upper extremity manifestations are rare.

Arteriosclerosis obliterans is responsible for 95% of cases of chronic occlusive arterial disease. It is most common in persons older than 50 years, but as many as 19% of cases occur in patients 30 to 49 years old. Men are affected more often than women (5:1 to 10:1). Approximately one-third of patients with arteriosclerosis obliterans have coexistent coronary artery disease. The incidence of diabetes mellitus is 20% to 30%.[19]

Risk factors for arteriosclerosis obliterans include cigarette smoking, hyperlipidemia, and hypertension. Of patients with arteriosclerosis obliterans, 70% to 90% are smokers when first examined, 75% have hyperlipidemia, and 30% have hypertension.[19]

Clinical Features and Differential Diagnosis

Acute arterial occlusion from embolism, thrombosis, or trauma is ruled out primarily by history. Atheromatous emboli from proximal ulcerated plaques or aneurysms cause small scattered ischemic lesions in the toes, feet, or legs, causing blue toe syndrome (Fig. 77.2). Peripheral pulses are present. Exercise-induced claudication need be distinguished from nocturnal muscle cramps frequently seen in elderly patients. Aortoiliac occlusive disease can be differentiated from osteoarthritis of the hip, which tends to be more variable from day to day, is not relieved completely with rest, and is not reliably reproduced by the same amount of exercise. Pseudoclaudication from the cauda equina syndrome is caused by narrowing of the lumbar canal from spondylosis, intervertebral disk disease, or spinal cord tumor. The symptoms mimic intermittent claudication but are less closely related to exercise and rest than true claudication.

The cause of lower extremity ulcers should be carefully determined. Approximately 5% of lower extremity ulcerations are caused by arterial insufficiency.[20] These are usually located distal to the ankle, typically at the terminal portion of the digits, around the nail beds, or between the toes, caused by friction of one toe on another. Less common locations include the metatarsal heads, heel, and malleoli. Arterial insufficiency ulcers are painful but pain improves when the extremity is in a dependent position. They are associated with evidence of coexistent chronic arterial insufficiency (absence of hair growth on the dorsum of the feet, skin atrophy, absent pulses, and nail deformities). Ulcers are initially small, shallow, and dry. The base is gray, yellow, or black, with minimal or no granulation tissue. The rim of the ulcer is sharp and indolent, showing no signs of cellular proliferation or epithelialization.

Fig. 77.2. Clinical presentation of atheromatous emboli, or blue toe syndrome. (Courtesy Gary R. Seabrook, MD.)

About 90% of lower extremity ulcers are caused by chronic venous insufficiency.[20] These occur proximal to or in the region of the ankle, especially near the medial malleolus. Venous stasis ulcers are mildly painful and improve with elevation of the extremity. Evidence of long-standing chronic venous insufficiency, including edema, prominent superficial veins, and stasis dermatitis, is present. Ulcers are moderate in size, with a weeping base and extensive granulation tissue. Rapidly developing ulcers are more suggestive of venous insufficiency.

Most of the remaining lower extremity ulcers are caused by diabetic neuropathy, alone or with arterial insufficiency.[20] The location reflects sites of repeated trauma, including the toes, heels, and plantar surface of the feet, especially the metatarsal heads. Neurotrophic ulcers are painless. Patients may have evidence of coexistent peripheral arterial insufficiency. The ulcers are deep and penetrating, often with suppurative drainage caused by an underlying infection or chronic osteomyelitis. Neurotrophic ulcers are usually surrounded by a rim of thick callus.

Hypertensive ulcers are rare and reflect long-standing, uncontrolled hypertension. These ulcers are typically near the lateral malleolus and start as painful, reddish blue areas of infarcted skin. A hemorrhagic bleb develops then breaks down into a superficial ulcer, which can reach a size of 5 to 10 cm. The ischemic ulcer has

sharply demarcated borders, little granulation tissue, and minimal drainage. The pain is the most severe of all lower extremity ulcers.

Multiple ischemic ulcerations above and below the ankle suggest vasculitis or atheromatous embolization. Ulcers with regular edges in unusual locations may be factitial or may result from subcutaneous injection of illicit drugs. Thickened, rolled, and elevated edges with a central depression containing granulation tissue are characteristic of malignant ulcers.

Management

The first step is to identify patients whose symptoms are the sole result of arteriosclerosis obliterans without coexistent thromboembolic disease. Treatment for symptomatic patients depends on whether patients have functional ischemia or limb-threatening ischemia.[21]

Limb-threatening ischemia constitutes a surgical emergency. Angiography should be arranged to identify sufficiently localized disease to permit emergency bypass grafting.[21] Patients with functional ischemia should have outpatient arrangements for elective invasive or noninvasive vascular testing to determine treatment options. Ischemic ulcers or skin lesions should be cultured in the emergency department and systemic antibiotics initiated to cover skin organisms if infection is present. Radiographs of underlying bones should be acquired when osteomyelitis is suspected. Patients with ischemic rest pain require hospitalization even if they are not surgical candidates. Bed rest, a warm environment, and maintenance of the limb in a dependent position usually relieve pain.

Buerger's Disease (Thromboangiitis Obliterans)

Principles

First described by Buerger in 1908, thromboangiitis obliterans is an idiopathic inflammatory occlusive disease primarily involving the medium-sized and small arteries of the hands and feet.[22] Patients are usually men aged 20 to 40 years old who use tobacco, although recent reports indicate an increasing frequency of this disease in women. Buerger's disease affects people of all races but is more prevalent in the Middle and Far East.[23] In the United States, incidence is 20 per 100,000.[23] The exact pathogenesis is unknown, but virtually all patients are smokers.

Thromboangiitis obliterans is characterized by segmental acute and chronic inflammation in the smaller arteries of both upper and lower extremities. The initial arterial inflammatory process progresses to affect the adjacent veins and nerves, often leading to associated venous thrombosis and progressive fibrous encasement of these structures. These are painful, tender, or dark nodules over a peripheral artery with either a reduced or an absent pulse (phlebitis migrans).

Clinical Features

Clinical criteria for Buerger's disease include (1) a history of smoking, (2) onset before the age of 50, (3) infrapopliteal arterial occlusive lesions, (4) either upper limb involvement or phlebitis migrans, and (5) absence of atherosclerotic risk factors other than smoking. A characteristic symptom of Buerger's disease is foot or instep claudication caused by infrapopliteal arterial occlusion. Intense rubor of the affected extremity, particularly with dependency, is also characteristic. Foot pulses may be absent in the presence of normal femoral and popliteal pulses. Involvement of the hands is often bilateral and symmetrical, leading to the development of hand claudication or fingertip ulcers. Phlebitis migrans occurs early in the disease. Approximately 50% of patients experience Raynaud-type triphasic color response to cold. In the upper extremities, the digital arteries are usually more involved than the radial or ulnar arteries.[23]

Differential Diagnosis

Arteriosclerosis obliterans is most likely in patients older than 50 years old who have signs of peripheral ischemia. In young women, autoimmune diseases, such as scleroderma or systemic lupus erythematosus, should be considered.[23]

Diagnostic Testing

Adherence to diagnostic clinical criteria should suffice for emergency department diagnosis of Buerger's disease. Noninvasive vascular laboratory testing confirms the diagnosis and extent of involvement. Rarely required, angiography demonstrates multiple segmental occlusions.

Management

Permanent complete abstinence from tobacco is the only effective treatment for Buerger's disease. If a patient does not completely stop smoking, alternating periods of quiescence are followed by exacerbations of severe arterial insufficiency. Patients who quit smoking have a benign clinical course. Despite this, many individuals who have Buerger's disease continue to smoke, incurring severe pain at rest, tissue loss, and eventually amputation.

With early symptoms without threat of tissue loss, patient education and follow-up with a vascular surgeon are sufficient. Vascular surgery treatment options are varied for patients with severe symptoms or threatened tissue loss. Intractable pain can be controlled with epidural anesthesia. Intra-arterial or intravenous prostaglandin E_1 and antithrombotic agents, including aspirin and heparin, have been used successfully.[23] Patients with large-vessel arterial occlusion may benefit from arterial reconstruction. Sympathectomy is a potential treatment in advanced cases for cutaneous ulceration or relief of rest pain.[17] Because patients with Buerger's disease have good healing, intensive conservative treatment is usually successful in avoiding amputation.

DISEASES OF ACUTE ARTERIAL OCCLUSION

Arterial Embolism

Despite advances, acute arterial embolus continues to cause substantial morbidity and mortality. Approximately 50% of acute arterial occlusions are caused by arterial embolism, and the incidence is increasing. The other 50% are caused by in situ thrombosis.[2]

Differential Diagnosis

Phlegmasia cerulea dolens is a massive iliofemoral deep venous thrombosis. The initial symptom is acute onset of a swollen and painful leg. As swelling continues, secondary arterial insufficiency with associated pallor (phlegmasia cerulea albens) occurs. Early in acute arterial embolism, leg swelling is usually absent. Acute embolism produces a sharply demarcated pallor; phlegmasia cerulea dolens causes a cyanotic-appearing leg.

Aortic dissection may involve the arteries of the upper or lower extremity and may mimic acute embolus. Severe pain, the presence of aortic insufficiency, and involvement at multiple sites suggest dissection. Neurologic syndromes (eg, transverse myelitis, spinal subarachnoid hemorrhage, ruptured intervertebral disk) may produce sudden onset of unilateral or bilateral lower extremity weakness or sensory loss that mimics an acute aortic saddle occlusion.

Cold, blue extremities may result from low-output states, such as hypovolemia, decreased cardiac output, and dehydration in patients with long-standing atherosclerotic disease.

Management

Acute arterial embolism is a surgical emergency. The likelihood of limb salvage decreases after 4 to 6 hours. On the basis of clinical diagnosis alone, full doses of intravenous heparin should be administered emergently to minimize clot propagation. Patients whose clinical findings clearly indicate an acute arterial embolism should undergo urgent Fogarty catheter embolectomy without prior angiography. In these patients, preoperative ultrasonography and angiography are rarely useful diagnostically and prolong the limb's ischemic status.

If the differentiation of acute embolism and in situ thrombosis is uncertain, pretreatment angiography is usually diagnostic. Patients with acute emboli generally show minimal signs of atherosclerosis, occlusion at the site of an arterial bifurcation, sharply demarcated cutoffs, and lack of flow distal to the occlusion. In patients with in situ thrombosis, arteriography shows diffuse atherosclerosis, occlusion at sites other than arterial bifurcations, a tapered irregular cutoff, and well-developed collateral vessels (see Table 77.1).

Intra-arterial thrombolytic therapy for acute embolism remains investigational. Present limb-threatening ischemia precludes consideration of treatment with thrombolytic therapy in most patients. Potential risks of thrombolytic therapy in arterial embolism patients with non–limb-threatening ischemia include partial clot lysis with distal embolization or recurrent embolic events from the primary source of the initial embolus.[24]

Atheroembolism (Blue Toe Syndrome)

Atheroemboli are microemboli consisting of cholesterol, calcium, and hemorrhagic debris that break off from proximal atherosclerotic plaques or aneurysms and lodge in distal end arteries. In the central nervous system, atheroembolism causes transient ischemic attacks and strokes. In the peripheral vascular system, atheroemboli are found in the lower extremities with cool, painful cyanotic toes in the presence of palpable distal pulses (see Fig. 77.2).

Clinical Features

The typical presentation of atheroembolism is the sudden onset of a small, cyanotic and tender area on the foot, typically the toe.[25] If bilateral, the distribution is not symmetrical. Posterior tibial and dorsalis pedis pulses are present. Physical examination should focus on a proximal source, such as an atherosclerotic aneurysm in the aorta or iliac, femoral, or popliteal artery.

Differential Diagnosis

A variety of conditions can mimic blue toe syndrome. Acrocyanosis is painless, has a symmetrical distribution, and is located in the hands, nose, and lips. Poor peripheral perfusion from low cardiac output should be considered. Vasculitis typically causes palpable purpuric lesions and constitutional symptoms of low-grade fever and weight loss. Previous frostbite may leave the extremities sensitive to cold. Local injury to the diabetic foot is easily differentiated.

Management

Treatment is directed toward identifying and removing the proximal source of atheroembolism. Angiography is the most accurate diagnostic method for determining the source of emboli. If the source is an aortic aneurysm and the patient is a surgical candidate, operative repair should be performed. Stenotic lesions in the iliac or femoral arteries can be treated with local endarterectomy, vascular bypass, or angioplasty.[15] Medical management with aspirin, dipyridamole, warfarin sodium (Coumadin), or steroids has variable results.

Arterial Thrombosis

Approximately 50% of acute arterial occlusions are caused by in situ thrombosis.[2] Acute arterial thrombosis is almost always superimposed on a complicated atherosclerotic lesion but can be caused by vasculitis or trauma. With limb-threatening ischemia, angiography can be used to evaluate the feasibility of emergency bypass grafting. In non–limb-threatening ischemia, angiography may be required to distinguish acute embolism from thrombosis (see Table 77.1).

Management

Heparinization should be started when the diagnosis is made. Patients with limb-threatening ischemia require emergency direct or Fogarty catheter thrombectomy combined with bypass grafting. Thrombectomy alone often fails due to rethrombosis. Patients who have atherosclerotic disease not amenable to vascular bypass, are too ill to tolerate revascularization, or have irreversible ischemia require primary amputation. Patients with non–limb-threatening ischemia are best treated nonoperatively with heparin and low-dosage intra-arterial thrombolytic therapy.

PERIPHERAL ARTERIAL ANEURYSMS

A true aneurysm is an abnormal localized dilation of the intact vessel wall caused by mural weakness and hemodynamic forces. Aneurysms enlarge at a rate determined by the cause. Atherosclerosis etiologies progress slowly over years; trauma or infectious causes enlarge over days, weeks, or months. The primary risk of central aneurysms (abdominal aorta, iliac arteries, and visceral arteries) is rupture (see Chapter 84). Peripheral arterial aneurysms rarely rupture; instead, they are complicated by thrombosis or embolism jeopardizing distal tissues.[26]

The cause of an aneurysm depends on its anatomic location. Lower extremity aneurysms are most often atherosclerotic. Upper extremity aneurysms are usually caused by local trauma. Visceral aneurysms are from abnormal hemodynamics, atherosclerosis, or infectious causes.

Lower Extremity

Femoral and popliteal artery aneurysms almost always occur in older men with advanced atherosclerosis. Twenty-five percent of patients have distal atheroembolism or thromboembolism; an additional 15% have total aneurysmal occlusion from in situ thrombosis.[26]

Popliteal aneurysms are the most common peripheral aneurysms, occurring bilaterally in 60% of patients.[26] Abdominal aortic aneurysm occurs in 80% of patients with bilateral popliteal aneurysms. Most patients have claudication, thromboembolic events, atheroembolic events, or gangrene. With aneurysmal dilation, venous compression and deep venous thrombosis occur.

Femoral aneurysms are the second most common peripheral aneurysms and manifest similarly to popliteal aneurysms. Femoral aneurysm dilation can also compress the femoral nerve, producing anterior thigh pain or weakness.

Diagnosis of popliteal and femoral aneurysms is by palpation of a pulsatile mass. Plain radiographs may show unilateral or

bilateral calcified aneurysms. Ultrasonography and CT are diagnostic. Arteriography yields definitive diagnosis and involvement of distal vessels. Patients with a lower extremity aneurysm should be evaluated for the presence of other aneurysms.

Asymptomatic patients can undergo elective surgical excision of the aneurysm and end-to-end anastomosis or graft interposition. Simultaneous repair of coexisting abdominal aorta or contralateral extremity aneurysms combined with vascular bypass is typically done. Patients with limb-threatening thromboembolic events are first treated with Fogarty catheter embolectomy.[26]

Upper Extremity

Atherosclerosis generally spares the upper extremities, so peripheral arterial aneurysms in the upper extremities are rare, making localized trauma the most common cause.

The causes of subclavian artery aneurysms are thoracic outlet obstruction, trauma, and, rarely, atherosclerosis. Subclavian aneurysms from atherosclerosis represent severe disease, and 30% to 50% of patients so afflicted also have aortoiliac or other peripheral aneurysms.[27] Symptoms depend on the aneurysm's anatomic location. Patients may have chest, neck, and shoulder pain from acute expansion. Compression of the right recurrent laryngeal nerve can lead to voice change. Compression of the trachea can lead to stridor or other respiratory complaints. The chest radiograph may reveal a superior mediastinal mass, confused with a neoplasm.

The subclavian artery can be compressed by a complete cervical rib that articulates with the first rib, producing a poststenotic dilation in the proximal subclavian and distal axillary artery. This syndrome occurs more often in women and in the dominant upper extremity. Cervical ribs occur in 0.6% of the population.[28]

Axillary artery aneurysms are caused by blunt trauma from inappropriate and prolonged use of crutches. Humerus fracture or anterior shoulder dislocation are uncommon causes.[27]

Subclavian, subclavian-axillary, and axillary artery aneurysms share complications of thromboembolism, limb-threatening ischemia, neuromuscular and sensory dysfunction from brachial plexus compression, and central nervous system ischemia from retrograde vertebral and right carotid thromboembolism. A systolic bruit and palpable thrill is common.

Arteriography to confirm diagnosis and determine involvement of distal vessels is the diagnostic procedure of choice. Surgical treatment consists of aneurysm resection, vascular grafting, and reestablishment of arterial continuity.

The rare syndrome of ulnar artery aneurysm (hypothenar hammer syndrome) is associated with occupational trauma in which the heel of the palm is used to hammer, push, or twist objects.[29] Patients are often mechanics, carpenters, or machinists.

The ulnar artery fits snugly into the bony canal at the hypothenar eminence under the hook of the hamate bone. Long-term repetitive damage results in aneurysm formation.[29] The aneurysm may develop a mural thrombus that repeatedly embolizes to the superficial palmar arch or to a digital artery. Symptoms include paresthesias, pain, coolness, and cyanosis, most often in the little and ring fingers, occasionally in the middle and index fingers. The thumb is characteristically spared due to its radial artery blood supply. Diagnosis is easily made by finding a pulsatile or nonpulsatile tender mass in the hypothenar eminence of the dominant hand. The Allen test may demonstrate occlusion of the ulnar artery. Angiography of the distal vessels is diagnostic. Proximal angiography may rule out the subclavian and axillary arteries as embolic sources. Surgical aneurysm resection is required to reestablish ulnar artery continuity. Adjunctive preoperative fibrinolytic therapy may be helpful.[29]

Viscera

Splenic Artery Aneurysms

Splenic artery aneurysms account for 60% of all visceral arterial aneurysms. They are the only aneurysms that are more common in women, with a female-to-male ratio of 4:1.[30] The cause of splenic artery aneurysms has been attributed to systemic arterial fibrodysplasia, portal hypertension, and increased splenic arteriovenous shunting that occurs in pregnancy.

Splenic artery aneurysms are most often asymptomatic. Symptomatic patients exhibit vague left upper quadrant or epigastric discomfort and occasional radiation of pain to the left shoulder or subscapular area. Because most splenic artery aneurysms are less than 2 cm in diameter, a pulsatile mass is not palpable. Occasionally, a systolic bruit can be heard.

Only 2% of splenic artery aneurysms result in life-threatening rupture.[30] More than 95% of ruptures occur in young women during pregnancy and can be confused with ectopic pregnancy or placental abruption.

Splenic artery aneurysms are usually an incidental discovery on the abdominal radiograph as signet ring calcifications in the left upper quadrant. Ultrasonography, CT, and MRI can distinguish aneurysms from other cystic lesions in the left upper quadrant.[30] An angiogram is usually required to confirm the diagnosis. Symptomatic splenic artery aneurysms require urgent operative intervention, particularly in pregnant women or in women of childbearing age. The rate of maternal mortality from rupture during pregnancy is approximately 70%. In asymptomatic patients, transcatheter embolization is an alternative to surgery.[31]

Hepatic Artery Aneurysms

Hepatic artery aneurysms represent 20% of visceral artery aneurysms. The lesions are caused by atherosclerosis, infection (most often as a complication of intravenous drug abuse), major abdominal trauma, and polyarteritis nodosa. Hepatic artery aneurysms affect men twice as often as women and usually occur after 60 years of age.

Most aneurysms remain asymptomatic, but unruptured symptomatic aneurysms generally produce symptoms consistent with cholecystitis: vague, persistent, right upper quadrant, or epigastric pain radiating to the back. Large aneurysms can cause severe upper abdominal discomfort, similar to pancreatitis. Hepatic artery aneurysms may rupture into the common bile duct, peritoneum, or adjacent hollow viscera, with a mortality rate of 35%.

An abdominal bruit or palpable pulsatile mass is usually not present on physical examination. Aneurysmal calcification may be seen on a plain abdominal radiograph, but the diagnosis can be made reliably by angiography. Ultrasonography and CT can detect asymptomatic hepatic artery aneurysms.[30]

Because of the high mortality rate with aneurysmal rupture, an aggressive approach to management is warranted. Surgical resection of the aneurysm is performed in operative candidates. Transarterial catheter occlusion can be used in patients who are high surgical risks.[32]

Superior Mesenteric Artery Aneurysms

Superior mesenteric artery aneurysms are the third most common visceral aneurysms. Nearly 60% are infected aneurysms caused by nonhemolytic streptococci from left-sided bacterial endocarditis. Atherosclerosis and trauma are much less common causes. Patients are usually younger than 50 years old; men and women are affected equally.

Patients generally have intermittent upper abdominal pain consistent with abdominal angina. Fifty percent have a pulsatile

TABLE 77.2

Clinical Characteristics of Infected Aneurysms

	MYCOTIC ANEURYSM	INFECTION OF ATHEROSCLEROTIC ARTERIES	INFECTION OF EXISTING ANEURYSM	POST-TRAUMATIC INFECTED FALSE ANEURYSM
Cause	Endocarditis	Bacteremia	Bacteremia	Drug addiction Trauma
Age (years)	30–50	>50	>50	<30
Incidence	Rare	Most common	Unusual	Very common
Location	Aorta Visceral Intracranial Peripheral	Atherosclerotic Aortoiliac Intimal defects	Infrarenal Aorta	Femoral Carotid
Bacteriology	*Viridans streptococci*	*Salmonella*	*Staphylococcus*	*Staphylococcus aureus*
S. aureus	Others	Others	Polymicrobial	
Mortality	25%	75%	90%	5%

From Wilson SE, Van Wagenen P, Passaro E Jr: Arterial infection. Curr Probl Surg 15:1, 1978.

abdominal mass on physical examination. The stigmata of subacute bacterial endocarditis may be present. Plain abdominal radiographs may show a calcified aneurysm. Angiography is necessary to confirm the diagnosis.

Management of superior mesenteric artery aneurysm should address any underlying infectious process. The surgical approach is difficult, varies with the condition of the patient, the shape of the aneurysm (saccular or fusiform), and the assessment of bowel viability.

Infected Aneurysms

Mycotic Aneurysms

The term *mycotic aneurysm* is a source of confusion, because there is no association with fungal disease. Although used to describe any infected aneurysm, it should be reserved for infected aneurysms resulting from bacterial endocarditis, as originally described in 1885 by Osler.[33,34]

Septic emboli from infective endocarditis implant in one of two ways. First, hematogenous seeding of bacteria can occur in non-aneurysmal arteries damaged by preexisting atherosclerosis. Second, septic emboli can become lodged in the vasa vasorum of larger vessels, causing vessel wall ischemia and infection. In smaller vessels, septic emboli tend to lodge at arterial bifurcations, arteriovenous fistulae, or sites of arterial stenosis. Mycotic aneurysms are most common in the aorta, superior mesenteric artery, intracranial, and femoral arteries.

The infecting organism in mycotic aneurysms reflects the bacteriology of infective endocarditis. Viridans streptococci are the most common organisms, although intravenous drug abusers are most often infected by *Staphylococcus aureus.* Patients who have mycotic aneurysms tend to be 30 to 50 years old. The mortality rate is 25% (Table 77.2).[33,34]

Atherosclerotic Arteries

Currently, the most common cause of an infected aneurysm is sepsis with hematogenous spread of bacteria, such as *Salmonella, Staphylococcus,* and *Escherichia coli,* to atherosclerotic arteries. Large vessels (especially the aorta) rather than peripheral arteries are the most common site. Patients tend to be older than 50 and have well-established atherosclerosis. Perforation often occurs before diagnosis and carries a mortality rate of 75%.[33]

Preexisting Aneurysms

The incidence of infection in patients with preexisting atherosclerotic aneurysms is estimated at 3% to 4%, and patients with ruptured aneurysms have a higher incidence of positive bacterial culture results than those who have elective surgical treatment of an asymptomatic aneurysm. Gram-positive organisms, especially *Staphylococcus,* predominate (60%). The rate of mortality is extremely high (90%) because of aneurysm rupture.[34,35]

Post-Traumatic Pseudoaneurysms

Post-traumatic infected aneurysms result from invasive hemodynamic monitoring, angiography, and intravenous drug use. The most common artery affected is the femoral because of its involvement in groin injection. *S. aureus* is isolated in 30% to 70% of cases. Because of the more peripheral location and early identification, the mortality rate is low (5%).[35]

The clinical presentation of an infected aneurysm varies with anatomic location and underlying pathophysiologic process. Infected abdominal aneurysms are often misdiagnosed. Onset is usually insidious; low-grade fever may be present for several months. Common findings are fever (75%), back and abdominal pain (33%), and palpable aneurysm (53%). More peripheral aneurysms, especially infected femoral pseudoaneurysms, are characterized by a tender groin mass, some manifestation of sepsis, or bleeding.[36] Almost all are easily palpable. Although rare, fungal infections should be considered in patients who are chronically immunosuppressed, have been treated recently for disseminated fungal disease, or have diabetes mellitus.[36,37]

Positive blood cultures in a patient with a preexisting aneurysm should prompt treatment as an infected aneurysm until disproven. Bacteremia often is continuous, and blood cultures are positive in approximately 70% of cases, but negative blood cultures do not rule out this diagnosis. Angiography should be performed when an infected aneurysm is suggested.[38] Indium-111–labeled white blood cells can confirm or rule out infected aneurysms.[35]

Treatment includes both antibiotics and surgical repair. Antibiotic therapy is usually continued for at least 6 to 8 weeks, although some physicians advocate lifelong treatment after successful surgical repair.[39] The most important intervention is timely repair.[36,37] Without surgery, aneurysm rupture with exsanguinating hemorrhage is inevitable.[35]

Traumatic Aneurysms

Traumatic aneurysm refers to a pseudoaneurysm that follows perforation of the arterial wall, with formation of a perivascular hematoma. Chronic traumatic aneurysms may or may not be associated with an arteriovenous fistula. *Pseudoaneurysm* is a synonym for *false aneurysm.*

The usual presentation is a pulsatile mass found near the course of an extremity artery, with a history of trauma more than 1 month earlier.[40] The expanding aneurysm may compress associated peripheral nerves. Distal perfusion is usually well maintained, and thromboembolism is rare. A loud systolic and possibly a separate faint diastolic murmur are characteristic.

Conventional angiography, digital subtraction arteriography, or CT confirms diagnosis. Surgical excision is indicated as soon as possible to decrease the risk of complications, including rupture, thrombosis, or neurologic dysfunction caused by continued expansion.

VASOSPASTIC DISORDERS

Vasospastic disorders are characterized by an abnormal vasomotor response in the distal small arteries. Blood flow in the peripheral circulation is controlled by local, autonomic, and humoral mechanisms.[9] The cause of the increased vasospastic response is currently unknown.

Raynaud's disease is the most common vasospastic disorder and occurs five times more often in women than in men. By definition, cases of Raynaud's disease have no evidence of an underlying cause. The diagnosis is correct in 95% of cases that meet these criteria: (1) episodes are precipitated by cold or emotion; (2) symptoms are bilateral; (3) gangrene is absent or is minimal and confined to the skin; (4) no disease or condition that could cause a secondary Raynaud's phenomenon is present; and (5) symptoms have been occurring for at least 2 years.[41]

The classic Raynaud's attack is triphasic: the fingers become white, then blue, and finally red. Initially, a complete closure of the palmar and digital arteries (and possibly arterioles) occurs, producing cessation of capillary perfusion. Slight relaxation of arterial spasm then occurs, with slight blood return into the dilated capillary bed, rapidly dissipating, producing cyanosis. Arterial spasm then resolves, but reactive hyperemia produces a red extremity. Attacks are often precipitated by cold and emotional stress. Raynaud's disease usually has a benign course. True histologic changes within the vessel wall are absent. Reassurance, education, and primary care follow-up are the only treatment necessary for true Raynaud's disease.

Raynaud's phenomenon is the term given to Raynaud's disease when there is an identifiable underlying causative disorder. Connective tissue disorders, including scleroderma, rheumatoid arthritis, and systemic lupus erythematosus, have the highest association with Raynaud's phenomenon. Treatment should be directed toward identifying the underlying disorder and minimizing threatened tissue loss if present.[41]

Benign livedo reticularis is caused by spasm of the dermal arterioles. It is most common when skin is exposed to a cool environment and is never associated with histologic vascular abnormality and quickly resolves when the exposed skin is covered or the environment is warmed. Other conditions, similar to the causes of Raynaud's phenomenon, can have secondary livedo reticularis along with other peripheral vascular disease manifestations.[42]

Acrocyanosis is the least common of the vasospastic disorders and is characterized by persistent, painless, symmetrical cyanosis of the fingers, hands, lips, nose, and less often the feet. The disease is benign, unassociated with vascular abnormality or underlying disorder. Pain, trophic skin changes, and ulceration do not occur. It is more common in women, intensified by exposure to cold, and decreases with warming. The diagnosis is made by the bilateral and persistent nature of the findings, localized to the hands or feet in the presence of normal arterial pulses. The involved extremities are nearly always cold, and excessive perspiration is common. Except for reassurance and protection from cold, treatment is unnecessary.[42]

Primary erythromelalgia is a rare syndrome of paroxysmal vasodilation with burning pain, increased skin temperature, and redness of the feet and less often the hands. Secondary erythromelalgia can occur with underlying disease processes, most often systemic lupus erythematosus, myeloproliferative disorders, hypertension, venous insufficiency, or diabetes mellitus. Erythromelalgia is as common in children as adults, but in children it is less likely to be associated with underlying systemic illness. Attacks are not triggered by cold and occur in modest ambient temperatures. Skin temperature of the involved digits is high compared with the patient's core temperature. Symptoms may remain mild for years or may become disabling. Tissue loss and trophic skin changes do not occur. Although elevation of the extremities, cold compresses or immersion in ice can provide temporary relief, no consistently effective treatment has been found for the multiple, often daily episodes of pain that occur.[42]

THORACIC OUTLET SYNDROME

Thoracic outlet syndrome involves compression of the brachial plexus, subclavian vein, or subclavian artery at the superior aperture of the thorax. Thoracic outlet syndromes were previously categorized by cause as scalenus anticus, costoclavicular, hyperabduction, cervical rib, and first thoracic rib syndromes. They are now most easily divided into three types—neurologic, venous, and arterial—depending on the predominant symptoms.

Compression of the brachial plexus causes the neurologic type of thoracic outlet syndrome and accounts for approximately 95% of all cases.[43] Symptoms begin between the ages of 20 and 50 years old, with women predominating at a ratio of about 3 : 1. Compression or thrombosis of the subclavian vein constitutes the venous type of thoracic outlet syndrome and is responsible for 4% of all cases. It occurs most often in men 20 to 35 years old. The arterial type of thoracic outlet syndrome is rare, occurring in approximately 1% of all cases, but is potentially the most serious of the three types. Men and women are equally affected in a bimodal age distribution of young adults (from cervical rib compression) and patients older than age 50 (from localized atherosclerosis caused by arterial compression). Figure 77.3 demonstrates the relationship between anatomic abnormalities and neurovascular compression.

Principles

Roos has described four basic concepts of thoracic outlet syndromes[44]: (1) patients who have a thoracic outlet syndrome develop an anatomic abnormality predisposing them to symptoms under certain conditions; (2) brachial plexus compression or irritation constitutes approximately 95% of all thoracic outlet syndrome cases and is rarely caused by compression of the subclavian artery; (3) bedside testing for thoracic outlet syndrome based on positional compression of the subclavian artery is insensitive and unreliable; and (4) in advanced or refractory cases, the causative anatomic abnormalities are to be surgically corrected.

The subclavian artery courses over the first rib between the scalenus anticus muscle anteriorly and the scalenus medius muscle posteriorly, when passing under the clavicle to the axilla, where the brachial plexus lies posteriorly and laterally. Four anatomic abnormalities have been associated with thoracic outlet syndrome.

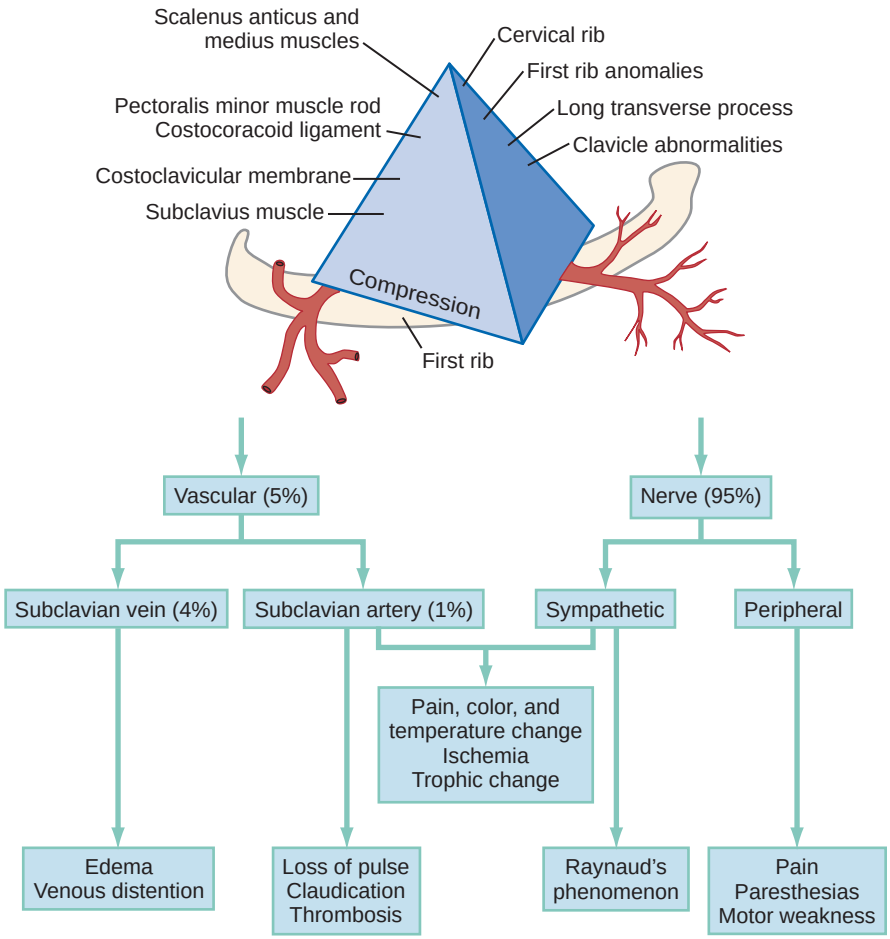

Fig. 77.3. Inter-relationships of muscle, ligament, and bone abnormalities in the thoracic outlet that may compress neurovascular structures. (From Urschel HC Jr: Management of thoracic outlet syndrome. N Engl J Med 286:1140, 1972.)

Cervical rib syndrome results from an uncommon abnormality (0.5% to 0.7% of all chest radiographs), which is bilateral in 70% of patients.[44] It occurs twice as often in women as men. Most cervical ribs are incomplete, attached to a fibrous band on the scalene tubercle of the first rib. The site of compression is the scalene hiatus, made up of the scalene anterior muscle anteriorly, the scalene medius posteriorly, and the cervical rib inferiorly.

Scalenus anticus syndrome results when the neurovascular bundle is compressed by various insertions of the anterior scalene muscle as it passes through the interscalene triangle. In some patients, the subclavian artery passes through the body of the muscle.

Costoclavicular syndrome results when the shoulders are moved backward and downward. Causes include hypertrophy of the subclavius muscle, abnormalities of the first rib, and past clavicular fractures.

Hyperabduction syndrome results from the neurovascular compression that occurs when the arms are placed in the hyperabducted position. The site of compression is in the retroclavicular space anterior to the first rib or at the point where the neurovascular bundle passes beneath the pectoralis minor muscle.

The neurologic and venous compression type of thoracic outlet syndrome can be associated with any underlying anatomic abnormality. Bony abnormalities (cervical rib, first thoracic rib, or clavicle) are the most common causes of the arterial type of thoracic outlet syndrome (Fig. 77.4A).

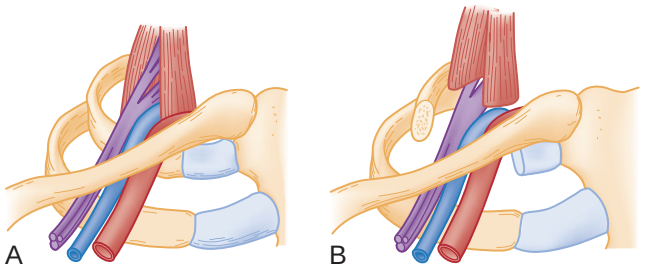

Fig. 77.4. A, Thoracic outlet compression in costoclavicular space. **B,** Decompression of thoracic outlet by resection of first rib with disarticulation of the costochondral joint. (From Etheredge S, et al: Thoracic outlet syndrome. Am J Surg 138:175, 1979.)

Clinical Features

Compression of the brachial plexus most often affects the lower two nerve roots, eighth cervical (C8) and first thoracic (T1), producing pain and paresthesias in the ulnar nerve distribution. The second most common pattern is the upper three nerve roots of the brachial plexus (C5, C6, and C7), with symptoms referable to the neck, ear, upper chest, upper back, and outer arm in the radial nerve distribution. Venous compression progresses to intimal damage and subclavian vein thrombosis, with venous engorgement and swelling of the affected extremity. Persistent

subclavian artery compression results in poststenotic aneurysm formation and its sequelae.

Physical Examination

The Adson, costoclavicular, and hyperabduction maneuvers are unreliable as diagnostic tests.[44] The most reliable test in screening for thoracic outlet syndrome is the elevated arm stress test (EAST).[44] With the patient sitting, the arms are abducted 90 degrees from the thorax and the elbows flexed 90 degrees, with the shoulders braced slightly behind the frontal plane. The patient is asked to open and close the fists slowly but steadily for a full 3 minutes and to describe any symptoms that develop. Normal patients perform this test without symptoms other than mild fatigue. The patient with thoracic outlet syndrome usually has early heaviness and fatigue of the involved limb, gradual onset of numbness of the hand, and progressive aching through the arm and top of the shoulder. Within the 3 minutes, the patient usually drops the hand to the lap for relief of the progressive, crescendo distress that becomes intolerable. Patients with carpal tunnel syndrome experience dysesthesias in the fingers but do not have shoulder or arm pain. Patients with cervical disk syndromes have pain in the neck and shoulder but no arm or hand symptoms.

The EAST evaluates all three types of thoracic outlet syndrome: neurologic, venous, and arterial. Radial pulses can be palpated by the examiner during the test. The presence of a radial pulse and a positive EAST test result are strong indications that the basis of symptoms is neurologic involvement of the brachial plexus.

The hands should be observed for changes in skin color, warmth, moisture, or muscular atrophy. Triceps muscle strength (innervated by C7) should be tested bilaterally. Muscle strength of the interosseous muscles (innervated by C8 and T1) should be tested by asking the patient to spread the fingers apart against resistance. The muscles innervated by the radial nerve are tested by having the patient hyperextend the thumb and dorsiflex the wrist against resistance. The median nerve innervates the thenar muscles, which can be tested by asking the patient to abduct the thumb away from the palm with the thumb pointing straight to the ceiling. Tinel's sign ("electric shock" to tips of fingers) is an indication of carpal tunnel compression of the median nerve and is elicited by percussing the volar aspect of the wrist. Gentle pressure with the thumb in the supraclavicular fossa over the brachial plexus may reproduce thoracic outlet symptoms.

A blood pressure difference between the two arms is a reliable indication of arterial involvement. The blood pressure in the affected arm is lower. Doppler ultrasonography may be helpful in demonstrating comparatively reduced pressure over the pairs of radial, ulnar, and brachial arteries. The supraclavicular area should be auscultated bilaterally for subclavian bruits.

Ancillary Evaluation

Cervical spine radiographs with oblique views and chest radiographs identify skeletal abnormalities (first rib, cervical rib, clavicle deformity), trauma, arthritis, scoliosis, Pancoast tumor, or other pulmonary disease. Electromyography, nerve conduction times, and somatosensory evoked potentials are generally unreliable.[44] Patients thought to have cervical disk or spinal cord disease may require cervical myelography, CT, or MRI.

Arteriography is recommended with (1) obliteration of radial pulse on the EAST, (2) blood pressure 20 mm Hg less than that of the opposite asymptomatic limb, (3) possible subclavian stenosis or aneurysm (bruit or abnormal supraclavicular pulsation), and (4) evidence of peripheral emboli in the upper extremity.[44] Venography is indicated for edema of the hand or arm, unilateral cyanosis, or a prominent venous pattern of the arm, shoulder, or chest.[45]

Differential Diagnosis

The differential diagnosis of thoracic outlet syndrome includes herniated cervical disk, cervical spondylitis, spinal cord tumor, ulnar nerve compression at the elbow, carpal tunnel syndrome, orthopedic shoulder problems, trauma, postural palsy, angina pectoris, and a variety of neuropathies, including those associated with multiple sclerosis, alcoholism, and diabetes.

Patients with a herniated cervical disk have more severe persistent pain radiating in a sharply demarcated dermatomal distribution (usually C4 to C5 or C5 to C6) and often have localized tenderness of the cervical spine at the affected level. Carpal tunnel syndrome is characterized by nocturnal symptoms of pain and paresthesias and an associated Tinel's sign. Brachial plexus compression can be confused with other vascular conditions, such as Raynaud's disease, vasospastic disorders, vasculitis, or arterial ischemia. Unilateral symptoms suggest thoracic outlet syndrome, whereas bilateral symptoms suggest a systemic process. Subclavian or axillary venous thrombosis from thoracic outlet syndrome should be differentiated from thrombophlebitis or mediastinal venous obstruction from a benign or malignant process (Pancoast tumor).

Management

Treatment depends on whether the involvement is neurologic, arterial, or venous. Brachial plexus involvement with minimal signs and symptoms often responds to conservative treatment with physiotherapy and shoulder girdle exercises. Surgery is reserved for patients with intolerable pain or loss of function and strength of the arm or hand. First rib or anomalous muscle or fibrous tissue resection provides consistent relief of symptoms and minimal morbidity (see Fig. 77-4B).

Patients with arterial complications of thoracic outlet syndrome (thrombosis, thromboembolism, or acute ischemia) require immediate heparinization and angiography; Fogarty catheter embolectomy, if appropriate; and emergency or urgent surgical exploration. Patients with axillary and subclavian vein thromboses also require emergent heparinization and venography and are treated with surgical thrombectomy or systemic fibrinolytic therapy.[45]

Disposition

The correct diagnosis of thoracic outlet syndrome can be achieved in more than 90% of patients with a careful history, physical examination, and bedside testing alone.[44] Neurologic, orthopedic, or vascular surgery consultation is indicated according to the pathologic condition.

PERIPHERAL ARTERIOVENOUS FISTULAE

Acquired peripheral arteriovenous fistulae are most often caused by trauma (gunshot wounds, stab wounds, or surgery), with malignancy, infection, and arterial aneurysms as less common causes. Patients seek care months after an invasive surgical procedure or penetrating injury.

Differential Diagnosis

An arteriovenous fistula diagnosis can be made with clinical examination alone. A constant systolic and diastolic (to-and-fro) murmur with associated palpable thrill is characteristic. Sixty percent of arteriovenous fistulae have a coexisting false aneurysm. Patients with peripheral venous disease may have similar cutaneous manifestations (varicose veins and stasis pigmentation) but lack vascular bruits. Infection may complicate large fistulae.

Management

Acquired peripheral arteriovenous fistulae usually increase in size with time if surgery is delayed. Vessel dilation, peripheral ischemia, and cardiac output increase.[46] Transcatheter embolization with detachable balloons and liquid acrylic tissue adhesives (eg, isobutyl 2-cyanoacrylate) is used for surgically inaccessible fistulae.[47]

VASCULAR ABNORMALITY CAUSED BY DRUG ABUSE

Principles

Parenteral drug use causes intravenous or intra-arterial injuries, including arterial ischemia, infected pseudoaneurysms, lymphatic obstruction, or neurologic injury.

Acute arterial ischemia results from direct drug effects or endogenous catecholamine release after injection. Endothelial wall damage stimulates platelet aggregation and thrombus formation. Precipitated crystals, talc, or foreign body emboli cause arterial occlusion. Necrotizing arteritis produces ischemia, especially in patients who abuse methamphetamines.

Infected pseudoaneurysms associated with arteriovenous fistulae result from a through-and-through puncture of the artery with simultaneous bacterial contamination. These fistulae are the most common vascular lesions resulting from intravenous drug abuse. Secondary infection of the vascular structure may be covered by a surrounding soft tissue infection (cellulitis or abscess). Infected aneurysms at sites distant from the injection can occur.

Intravenous drug abusers can develop unilateral hand edema or "puffy hand syndrome" due to gradual obliteration of the superficial venous vessels and chronic lymphatic obstruction. Direct injury to adjacent nerves, polyneuritis, and ischemic neuritis can result. Coexisting infections include cellulitis, septicemia, and bacterial endocarditis.[48]

Clinical Features

Patients withhold information about the use of intravenous drugs, but objective evidence such as track marks may be present. Distal ischemia after intra-arterial injection occurs in the upper extremity after injection of the brachial or radial artery. Immediate onset of severe, burning pain at the time of injection is a characteristic hallmark.[49] Patients have a painful, edematous upper extremity with patchy blue-purple skin discoloration. Distal pulses are generally present, but the skin temperature of the involved extremity is decreased. Because patients tend to seek attention early, the site of injection may be identifiable over the radial or brachial artery. Evidence of gangrene, pre-gangrenous changes, or neuromuscular deficits may accompany this syndrome.

Patients with infected pseudoaneurysms have a painful mass several days to weeks after injection, with resultant bleeding or "hitting pink." The mass is pulsatile, and 50% have an associated bruit.[48] Infected pseudoaneurysm is part of the differential diagnosis of cutaneous abscess in an intravenous drug user. Infected pseudoaneurysms are most often encountered in the lower extremities (80%). A peripheral vascular examination with auscultation for bruits should be performed. A radiograph can detect subcutaneous needle fragments. Angiography is the diagnostic procedure of choice for suggested pseudoaneurysm or distal ischemia. Ultrasonography is often unable to distinguish an aneurysm from an abscess or cellulitis.

Management

Therapeutic considerations for acute ischemia from intra-arterial injection are primarily conservative. Intra-arterial vasodilators, heparin, low-molecular-weight dextran, fibrinolytic therapy, analgesics, systemic warming to stimulate vasodilation, antibiotics, elevation of the affected limb to promote venous drainage, and physical therapy have not significantly altered the outcome or amputation rate in this patient population. Surgical treatment is reserved for delayed amputation. Gradual resolution without surgical intervention is the most common outcome.

Patients with infected pseudoaneurysms require aneurysm resection, débridement of infected tissue, and ligation of the proximal and distal uninfected arteries. Autogenous vein bypass through uninfected tissue planes may require an extensive surgical approach.[48] Intravenous nafcillin is recommended for mild infections, nafcillin and a second- or third-generation cephalosporin for major infections, and vancomycin and a second- or third-generation cephalosporin or an aminoglycoside for patients who are bacteremic or overtly septic.[48] Methicillin-resistant *S. aureus* and gram-negative rods are increasing in frequency as the causative agents, and vancomycin should be added if these organisms are suspected.

KEY CONCEPTS

- Acute arterial occlusion is a limb-threatening emergency requiring early heparinization and Fogarty catheter embolectomy. The clinical diagnosis is based on some variant of the five Ps: pain, pallor, pulselessness, paresthesias, and paralysis. Confirmatory tests are unnecessary and increase the limb's ischemic status.
- Atheroembolism (blue toe syndrome) is associated with cool, painful cyanotic toes in the presence of palpable distal pulses. A proximal source should be localized, most often an atherosclerotic aneurysm in the aorta or the iliac, femoral, or popliteal artery.
- Popliteal aneurysms are bilateral in 60% of patients and often coexist with an abdominal aortic aneurysm.
- The classic Raynaud attack is triphasic: the fingers become white, blue, and then red. Raynaud's disease has no detectable underlying cause and usually has a benign course. Raynaud's phenomenon has an underlying disorder, usually connective tissue disease.
- The only reliable clinical test for detection of thoracic outlet syndrome is the elevated arm stress test (EAST).
- Partial arterial lacerations continue to bleed, resulting in an expanding hematoma. Complete arterial transections initially have only moderate bleeding but can result in delayed hemorrhage. Blunt arterial injury may produce intimal disruption resulting in dissection, thrombosis, and/or obstruction. Arterial vasospasm can accompany injuries adjacent to the blood vessel but spontaneous resolution always occurs in the absence of arterial disruption or intimal injury.
- Aneurysms and arterial stenoses are characterized by a systolic murmur. Pseudoaneurysms, associated with prior surgical or trauma sites, are characterized by a loud systolic and possibly a separate, faint diastolic murmur. Arteriovenous fistulae are characterized by a harsh "to and fro" murmur associated with a palpable thrill.
- Intra-arterial injection of illicit drugs into the brachial or radial artery is associated with immediate onset of a severe, burning pain, and emergency department presentation with patchy blue-purple skin discoloration. Because patients tend to seek attention early and may withhold information about the use of intravenous drugs, identifying the site of injection is helpful in confirming this syndrome, which can be associated with persistent ischemia and tissue loss.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 77: QUESTIONS & ANSWERS

77.1. Where do most arterial emboli originate?

A. Abdominal aorta
B. Femoral artery
C. Left ventricle
D. Left atrium
E. Thoracic aorta

Answer: C. Eighty-five percent of arterial emboli originate in the heart. Of these, left ventricular thrombus formation after myocardial infarction (MI) accounts for 60% to 70%. Atrial thrombi account for only 5% to 10% of all peripheral arterial emboli.

77.2. What is the most frequent site of acute arterial embolic occlusion?

A. Carotid artery
B. Common femoral artery
C. Mesenteric artery
D. Popliteal artery
E. Renal artery

Answer: B. The bifurcation of the common femoral artery accounts for 35% to 50% of acute arterial occlusion due to arterial embolism. Embolic occlusion most often occurs at major arterial bifurcations because of the sudden change in vessel diameter at these locations.

77.3. A 63-year-old male presents with acute onset of left leg pain while walking. He describes it as a shock-like sensation that made his knee buckle. Past history is remarkable for hypertension, diabetes (diet controlled), tobacco use, and a recent lateral wall myocardial infarction. Current medications are aspirin, metoprolol, and lisinopril. Vital signs are: temperature, 37.0°C oral; heart rate, 98 beats per minute; blood pressure,

160/105 mm Hg; respiratory rate, 20 breaths per minute; and oxygen (O_2) saturation, 96%. Physical examination is remarkable for left lower extremity pallor with decreased light touch sensation, nonpalpable left foot pulses, and minimal capillary refill. What would be the most appropriate next step in the diagnosis and management of this patient?

A. Abdominal ultrasonography
B. Arteriogram
C. Serum lactate level
D. Thoracolumbar magnetic resonance imaging (MRI) scan
E. Vascular surgery consultation

Answer: E. This patient has acute limb ischemia from an acute arterial embolus, most likely originating from his left ventricle secondary to a recent myocardial infarction. Loss of light touch sensation on physical examination indicates jeopardized tissue viability, requiring immediate vascular surgery consultation for emergent Fogarty catheter embolectomy. Reliable diagnosis of an acute arterial embolism can almost always be made by history and physical examination alone. Any additional diagnostic evaluation constitutes an unnecessary delay. Serum lactate level, abdominal ultrasonography, and thoracolumbar magnetic resonance imaging (MRI) scan would not provide useful information. An arteriogram before going to the operating room is an unnecessary delay and may further exacerbate limb ischemia.

77.4. A supine patient is asked to raise his foot 12 inches above the estimated level of the right atrium and dorsiflex the foot five or six times. He is then brought to a sitting position with his feet hanging. In the absence of severe advanced ischemia, venous filling of the foot should return in less than how many seconds?

A. 1
B. 5
C. 10
D. 15
E. 20

Answer: E. This bedside test is Buerger's sign and can provide reliable evidence of advanced ischemia. In the absence of severe advanced ischemia, the lower extremity veins should fill within 20 seconds after being placed in the dependent position.

77.5. A 73-year-old man presents with acute onset of right lower extremity pain. He has a long history of tobacco use, hypertension, and a several year history of moderate calf claudication at 50 yards walking. Physical examination reveals signs of chronic atherosclerotic occlusive disease of the bilateral lower extremities, including muscular atrophy, loss of hair over the toes and feet, and thickening of the toenails. Examination of the distal right lower extremity reveals pallor, absent popliteal and foot pulses, and decreased sensation to light touch of the right foot. The cardiac examination is unremarkable, and the 12-lead electrocardiogram (ECG) reveals only normal sinus rhythm. Based on the most likely diagnosis, what is the most appropriate definitive therapy?

A. Acute hyperbaric oxygen therapy
B. Arteriogram to determine the presence of embolus versus in situ thrombosis
C. Intra-arterial thrombolysis
D. Surgical referral for Fogarty catheter embolectomy
E. Surgical referral for Fogarty catheter embolectomy with vascular bypass grafting

Answer: E. This patient has a history and physical examination consistent with long-standing peripheral atherosclerotic occlusive disease, no evidence of a proximal source for embolism, but acute onset of ischemic symptoms and loss of light touch in the affected extremity. The most likely diagnosis is a large, in-situ thrombosis precipitating acute limb-threatening ischemia. When limb-threatening ischemia is present, emergent surgical referral for Fogarty catheter embolectomy is indicated, whether caused by acute in-situ thrombosis or embolus. With limb-threatening ischemia caused by in-situ thrombosis, simple Fogarty catheter embolectomy is insufficient and usually requires additional bypass grafting. Acute hyperbaric oxygen therapy has no role in the treatment of limb-threatening ischemia due to in-situ thrombosis or embolism. An arteriogram to determine the presence of embolus versus in-situ thrombosis is unwarranted, represents an unnecessary delay, and may further exacerbate ischemia. Intra-arterial thrombolysis takes 6 to 72 hours to work and is contraindicated in cases of limb-threatening ischemia.

77.6. What percentage of patients presenting with arteriosclerosis obliterans are younger than 50 years old?

A. 1%
B. 5%
C. 10%
D. 20%
E. 40%

Answer: D. Peripheral arteriovascular disease can occur in younger patients. Nineteen percent of patients presenting with atherosclerosis obliterans are between the ages of 30 and 50 years old. Of all arteriosclerosis patients, 33% have coexistent coronary artery disease, and 70% to 90% are smokers. The non-smokers have other risk factors including significant hypertension and hyperlipidemia.

77.7. A 49-year-old woman presents with severe left ankle pain. She describes fairly sudden development of a left lateral malleolus hemorrhagic blister that transitioned to a painful superficial ulcer over 48 hours. She has no prior history of extremity ulcers, and her only significant past medical history is hypertension. She has a long-standing history of noncompliance with her hypertensive medications and smokes two packs of cigarettes per day. She has no history of myalgias, joint pain, fever, or systemic symptoms. Vital signs are: temperature, 36° C oral; heart rate, 90 beats per minute; blood pressure, 210/125 mm Hg; respiratory rate, 20 breaths per minute; and O_2 saturation, 96%. Physical examination reveals a thin black female in distress because of pain. Cardiopulmonary examination is unremarkable. Abdominal, neurologic, and extremity examinations are likewise unremarkable except for a well-demarcated, shallow 4 × 3 cm ulcer over the left lateral malleolus. There is mild erythema but no evidence of active infection. Distal pulses and capillary refill are normal. What would be the most appropriate intervention?

A. Analgesics and admission for vasculitis evaluation
B. Surgical consultation for possible embolectomy
C. Wound care and blood pressure control
D. Wound care and tapering dose of prednisone
E. Venous Doppler scans and surgical consultation for possible skin grafting

Answer: C. This patient has a hypertensive ulcer, which is the most painful of lower extremity ulcers. They typically occur over the lateral malleolus, as opposed to venous stasis ulcers, which are more common anteriorly and medially. Ischemic arterial ulcers are more common distally over the digits. Although vasculitis or a collagen vascular disease are possible, the lack of any other systemic symptoms or prodrome argue against this.

CHAPTER 78

Pulmonary Embolism and Deep Vein Thrombosis

Jeffrey A. Kline

PRINCIPLES

This chapter discusses the diagnosis and treatment of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), from the perspective of the emergency clinician and provides a resource for the diagnostic consideration and treatment of VTE in the emergency department (ED).

Anatomy and Pathophysiology of Thrombosis

As illustrated in Fig. 78.1, blood clots form when fibrin production exceeds its elimination. Factors that enhance fibrinogen synthesis and promote its catalysis to fibrin include systemic inflammation, traumatic or immune-related vascular trauma, inherited thrombophilias and hemoglobinopathies, cancer, pregnancy, and sluggish blood flow. The triad of venous injury, slow blood flow, and hypercoagulability are the cardinal inciting mechanisms for VTE, and most clinical decision rules for VTE incorporate these factors. Additionally, each year of life independently increases the likelihood of imbalanced clot formation. Clot formation can be accelerated by impaired fibrinolysis, as occurs in the metabolic syndrome, and from smoking.

DVT represents a disease spectrum ranging from a minimally symptomatic isolated calf vein thrombosis to a limb-threatening iliofemoral venous obstruction, causing the condition known as phlegmasia cerulea dolens (Fig. 78.2). In 2011, the Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample (NEDS) had demonstrated that US emergency clinicians diagnose lower extremity DVT in approximately 170,000 patients, or approximately 1 in every 500 adult ED patients.[1]

The venous anatomy of the lower extremity is divided into the deep and superficial systems (Fig. 78.3). The superficial venous system consists primarily of the greater and short saphenous veins and perforating veins. The deep venous system includes the anterior tibial, posterior tibial, and peroneal veins, collectively called the calf veins. The calf veins join together at the knee to form the popliteal vein, which extends proximally and becomes the femoral vein at the adductor canal. The femoral vein was previously named the superficial femoral vein but, because this nomenclature caused dangerous confusion, its use has been abandoned in favor of femoral vein. The femoral vein is joined by the deep femoral vein and then the greater saphenous vein to form the common femoral vein, which subsequently becomes the external iliac vein at the inguinal ligament. Proximal DVT refers to a clot in the popliteal vein or higher, whereas distal clot refers to an isolated calf vein thrombosis. Distal greater saphenous vein clots are sometimes denoted as superficial thrombosis, but greater saphenous clots near its connection with the femoral vein should be referred to and treated as proximal DVT.[2] Knowledge of venous anatomy helps practitioners understand the difference in venous ultrasound examinations. A two-point venous ultrasound includes the common femoral and popliteal vein. A three-point ultrasound includes the common femoral, femoral, and popliteal veins. A whole-leg ultrasound includes a three-point ultrasound and the peroneal and tibial calf veins.

Clinical Features

Hallmarks of DVT include unilateral limb pain and swelling. Often, DVT produces initially subtle and nonspecific symptoms, such as a mild cramping sensation or sense of fullness in the calf, without objective swelling on examination. Many patients use the term *Charley horse* to describe the sensation of an early DVT. Because the left iliac vein is vulnerable to compression by the left iliac artery (May-Thurner syndrome), leg DVT occurs with a slightly higher frequency in the left leg compared with the right; bilateral leg DVT is found in fewer than 10% of ED patients diagnosed with DVT. Similarly, the clinical signs of DVT vary and may include edema, erythema, and warmth of the affected extremity, tenderness to palpation along the distribution of the deep venous system, dilation of superficial collateral veins, and a palpable venous cord. Fever suggests an alternative diagnosis, such as cellulitis. Upper extremity DVT is, by definition, a thrombosis in the axillary vein, whereas thrombosis of the brachial vein is a superficial thrombosis.

Usually, upper extremity DVT presents with arm swelling, on the same side as an indwelling catheter or recent intravenous infusion. In the absence of a catheter, the most frequent location of arm DVT is on the dominant hand side, and patients may present with a subtle complaint, such as noting that their rings have become tight. Other sites of venous thrombosis occasionally encountered in the ED include the jugular, ovarian, mesenteric, renal, portal, hepatic, cerebral, and retinal veins. These are considered unusual sites for venous thrombosis.

DIAGNOSIS

Diagnosis of DVT and PE starts with an estimation of the pretest probability (PTP). This estimation may be accomplished by the clinical gestalt of an experienced practitioner or in conjunction with a clinical decision tool, such as that derived and validated by Wells and colleagues (Table 78.1). PTP for DVT can also be assessed by gestalt or an unstructured method with equal accuracy, although Well's score may be preferred because it has been tested in larger numbers.[3] One PTP score has been derived and initially validated for pregnant patients, the LEFt score: 1 point in case of left (***L***) leg suspicion, 1 point for edema (***E***), and 1 point if the suspicion occurred during the first trimester (***Ft***) of pregnancy, with a score of 0 or 1 tantamount to a low PTP.[4] The PTP dictates the pathway for diagnostic testing (Fig. 78.4). The Wells and unstructured (gestalt) methods have approximately equal

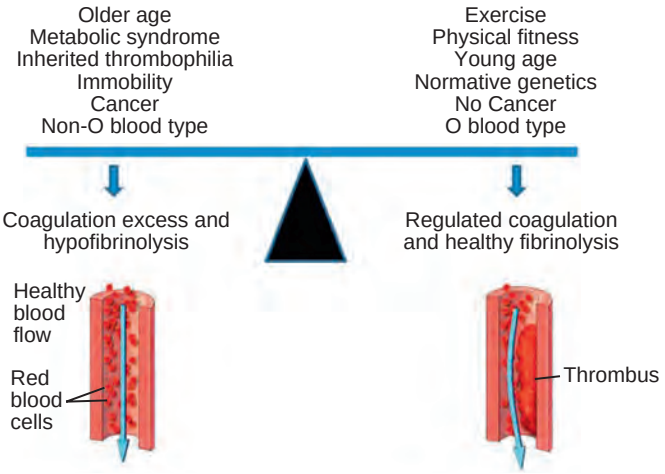

Fig. 78.1. Diagram of clotting risk.

Fig. 78.2. Patient with phlegmasia cerulea dolens.

overall diagnostic accuracy.[5,6] Either method is acceptable. Although only performed 50% of the time, all patients should have a PTP assessed and documented prior to additional testing for DVT or PE.[5] For all practical purposes, the diagnosis of DVT is confirmed by a positive compression ultrasound.

Differential Diagnosis

Venous insufficiency that causes venous hypertension and inflammation with pain is the most common alternative diagnosis to acute DVT, producing many of the same findings (Table 78.2). Cellulitis is probably the second most common alternative. However, in a patient with clinical evidence of cellulitis, the frequency of concurrent DVT is approximately 3%, suggesting that the diagnostic evaluation for DVT in cellulitis patients should be restricted to those with a high PTP.[7-9] Other conditions that mimic DVT include muscle strain, hematoma, Baker's cyst, and lymphedema.

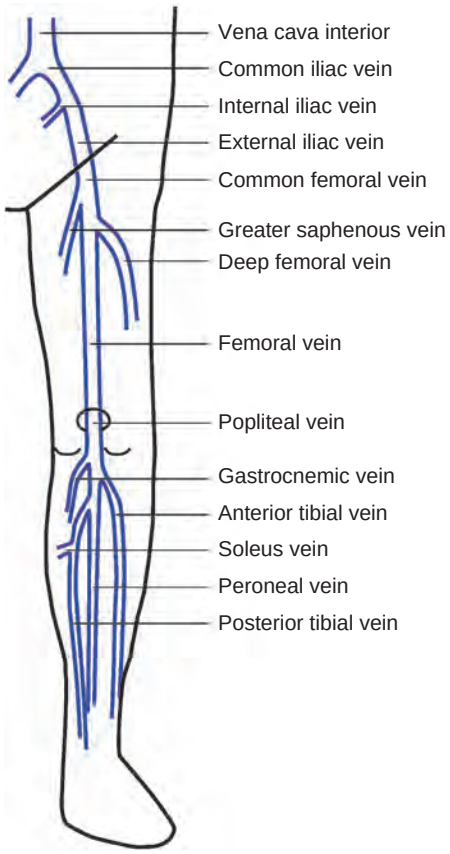

Fig. 78.3. Diagram of leg veins. A three-point ultrasound includes the common femoral, femoral and popliteal veins. A whole-leg ultrasound adds in the greater saphenous, posterior tibial and peroneal veins and, in some centers, the gastrocnemius vein.

TABLE 78.1

Well's Score for Deep Vein Thrombosis

CLINICAL FEATURE	SCORE*
Active cancer (treated within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for ≥3 days or major surgery within 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	–2

*A score <2 indicates that the probability of deep vein thrombosis is low.
Adapted from Wells PS, Anderson D, Bormanis J, et al: Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 350:1795–1798, 1994.

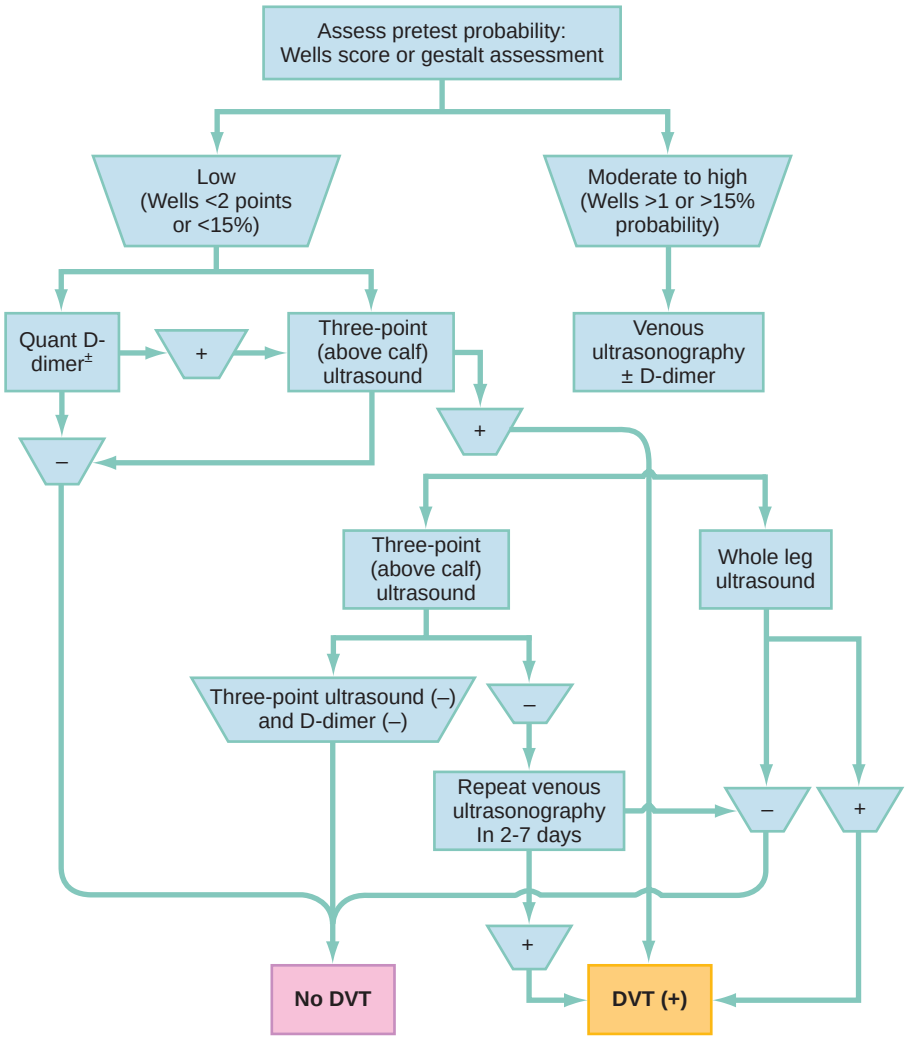

Fig. 78.4. Diagnostic algorithm to guide the diagnosis and exclusion of acute deep vein thrombosis. DVT, Deep vein thrombosis; *Quant,* quantitative; –, test negative; +, test positive.

TABLE 78.2

Conditions With Symptoms Similar to Deep Vein Thrombosis

CONDITION	APPROXIMATE FREQUENCY (%)
Chronic venous insufficiency*	60
Cellulitis	15
Muscle strain or tear	5
Baker's cyst	3
Hematoma	2
Claudication/ischemia	2
Intra-abdominal compression	2
Unrecognized trauma	2

*Venous insufficiency causes swelling and venous wall strain, leading to inflammation and pain.

Diagnostic Testing

Laboratory Evaluation

A normal quantitative D-dimer concentration in a patient with a low PTP can be used to exclude proximal DVT (diagnostic sensitivity ≅ 95%; specificity ≅ 50%). The D-dimer results from the enzymatic breakdown of cross-linked fibrin in any intravascular thrombus. Many conditions elevate the D-dimer other than DVT and PE.[10] The US Food and Drug Administration (FDA) has cleared numerous D-dimer assays, and many use varying threshold cutoffs for abnormal. Most D-dimer assays that have FDA clearance to aid in the diagnosis and exclusion of VTE have a cutoff value of 500 ng/mL. Numerous clinical laboratories, however, use D-dimer assays that do have this specific indication, and many of these assays have cutoffs other than 500 ng/mL.

Radiographic Evaluation

Venous duplex ultrasonography, performed by a certified sonographer and interpreted by a board-certified radiologist or similarly credentialed expert, has a sensitivity and specificity of approximately 95%, respectively, for proximal DVT and is the diagnostic test of choice in most centers. A patient at a low PTP may have the diagnosis of DVT effectively excluded by a negative

three-point venous duplex ultrasound, which images the common femoral, femoral, and popliteal veins (see Fig. 78.2). However, for patients at higher than low risk, a single negative three-point ultrasound is inadequate as a sole method to exclude DVT, whereas a single normal whole-leg ultrasound (including normal calf and saphenous veins) is sufficient to exclude DVT with any PTP.[11] A negative three-point ultrasound, together with a negative quantitative D-dimer, excludes DVT with any PTP.[12] If a patient with a moderate to high PTP and elevated D-dimer level (or not performed), a negative three-point ultrasound at the index visit should be followed by a repeat ultrasound in 2 to 7 days. If negative, this is sufficient to exclude DVT, and ostensibly, PE. An expertly performed and interpreted positive ultrasound is sufficient to confirm the diagnosis of DVT. Ultrasound cannot be used to rule out iliac or pelvic vein thrombosis. When duplex ultrasound is not available, patients with a moderate to high PTP should receive empirical low-molecular-weight (LMW) heparin while awaiting the availability of ultrasound imaging, whereas patients with a low or moderate to high PTP with a negative D-dimer do not need empirical anticoagulation while they wait for diagnostic imaging.[13] Aggregated data have now demonstrated that emergency clinician–performed three-point ultrasound for lower extremity DVT has adequate diagnostic accuracy (96% sensitivity, 96% specificity) to diagnose and exclude DVT in the hands of an experienced ultrasonographer.[14]

Magnetic resonance imaging (MRI) can evaluate the pelvic vasculature and vena cava, which is not possible with ultrasound. MRI does not produce ionizing radiation. Thus, MRI is a logical option to evaluate the pelvic veins of patients at high risk for pelvic vein thrombosis (eg, those with gynecologic malignancy) and for pregnant patients. Its use is limited by cost, availability, patient size, and tolerance to close quarters. MRI is not the primary diagnostic test for patients with suspected DVT.

Management

For patients with high PTP after hours, and for patients with a positive ultrasound, anticoagulation should be initiated emergently, unless contraindicated, as outlined in Table 78.3. Most patients with DVT can be treated at home, assuming that the patient can effectively adhere to the chosen anticoagulation strategy. The antiquated concept that patients with DVT should be at bed rest is categorically incorrect, and patients should be encouraged to ambulate after anticoagulation for DVT to reduce the incidence of postthrombotic syndrome. Note that the presence of a so-called free-floating DVT does not increase risk of embolization.[15] Compression stockings can no longer be advocated routinely for DVT, although patients with persistent swelling or superficial thrombosis may benefit.[16]

Superficial Leg Thrombophlebitis

Based on the results of a large randomized controlled trial, patients with a clot in the greater saphenous vein that extends above the knee are at risk for progression to DVT via the saphenous-femoral vein junction and may require an abbreviated course of anticoagulation.[17] Published evidence has suggested that distal saphenous vein thrombophlebitis can adequately be treated with nonsteroidal antiinflammatory drugs, heat, and graded compression stockings (fitted to exert 30–40 mm Hg of pressure at the ankle), followed by a scheduled repeat ultrasound in 2 to 5 days. If a greater saphenous vein clot is proximal, near the connection with the femoral vein (see Fig. 78.3), anticoagulation is indicated. The precise duration of anticoagulation treatment remains uncertain, but we recommend full-dose LMW heparin or fondaparinux for 10 days followed by a repeat ultrasound.[18] If the repeat ultrasound shows improvement, anticoagulants can be discontinued.

Isolated Calf Vein Thrombosis

The optimal management strategy for thromboses of the tibial or peroneal veins remains controversial, although it is clear that anticoagulation lowers the rate of proximal propagation and embolization.[19] For tibial or peroneal vein thrombosis in an otherwise healthy ambulatory patient, with no other indications for anticoagulation, the recommendation is short-term anticoagulation, most easily accomplished with rivaroxaban (15 mg bid for 14 days then 20 mg QD) or apixaban (10 mg bid for 7 days, then 5 mg bid for 7 days), or antiplatelet therapy with aspirin (325 mg/day of enteric-coated acetylsalicylic acid) and close follow-up with repeat duplex ultrasound scan at 2 to 5 days to evaluate for clot propagation.

Phlegmasia Cerulea Dolens (Painful Blue Leg)

Massive iliofemoral vein occlusion results in swelling of the entire leg, with extensive vascular congestion and associated venous ischemia, producing a painful cyanotic extremity. There may be an associated arterial spasm resulting in phlegmasia alba dolens (painful white leg or so-called milk leg), which may mimic an acute arterial occlusion. Prompt consultation with a vascular surgeon should be obtained because patients with phlegmasia cerulea dolens may require emergent thrombectomy. If timely consultation is not possible, early thrombolytic therapy may be a limb-salvaging procedure in the absence of contraindications. One strategy is to infuse alteplase via an infusion catheter placed into the thrombus. This procedure requires interventional radiology capabilities, and therefore emergency clinicians caring for patients with evidence of phlegmasia cerulean dolens in hospitals

TABLE 78.3

Emergency Department Anticoagulation for Deep Vein Thrombosis or Pulmonary Embolism

ANTICOAGULANT	INITIAL DOSE	RESTRICTION	TIME TO PEAK (H)
Unfractionated heparin	70–80 U/kg, then 17–18 U/kg/h, IV	Heparin-induced thrombocytopenia	1
Enoxaparin	1 mg/kg subcutaneously*	Creatinine clearance < 30 mL/min	3
Dalteparin	200 U/kg subcutaneously*	Creatinine clearance < 30 mL/min	4
Fondaparinux	5–10 mg subcutaneously*	Creatinine clearance < 30 ml/min	3
Rivaroxaban	15 mg orally with food	Creatinine clearance < 30 mL/min	2–4
Apixaban	10 mg orally, with or without food	Creatinine clearance < 30 mL/min	3–4

*Although low-molecular-weight heparin compounds are usually injected subcutaneously, no trials have been conducted to justify this route over intravenous injection. Intravenous injection achieves more rapid anticoagulation and does not produce more bleeding.

without the resources immediately available should not delay transfer to an interventional radiology–capable center.

Upper Extremity Venous Thromboses

DVTs of the upper extremity have become more common in association with the increased use of indwelling venous catheters and wires for electronic cardiac devices. Upper extremity DVT can cause PE, and all patients with DVT above the elbow require definitive treatment.: About half of all upper extremity DVTs are associated with an indwelling catheter, and peripherally inserted central catheters (PICCs) carry the highest risk.[20,21] Aggregated data have indicated that only venous ultrasound has been adequately validated as a method to diagnose and exclude upper extremity DVT, and D-dimer has only been examined in one study.[22] In the absence of pain or infection, catheter-associated DVT does not automatically warrant catheter removal if the catheter serves a current and vital purpose. However, these patients should receive anticoagulation absent contraindications. The duration of recommended anticoagulation following catheter removal for DVT remains variable, but most published guidelines recommend at least 3 months.[23] Acute PE from an axillary vein occurs in about 9% of patients with arm DVT, although the PE tends to be less severe from upper extremity DVT.[24] Isolated upper extremity DVT, especially axillary-subclavian vein thrombosis, also can be seen in relatively young, active, otherwise healthy patients after considerable exertion of the dominant arm, known as effort DVT, or Paget-Schroetter syndrome. Optimal treatment of isolated brachial vein thrombosis, often the result of a recent intravenous infusion (so-called infusion phlebitis) also remains uncertain, and no study has demonstrated clear benefit for systemic anticoagulation. I recommend the same management plan as described for superficial thrombophlebitis of the leg.

Complications

Although the most feared complication of DVT is fatal PE, DVT damages venous valves, causing venous insufficiency. Venous insufficiency, in turn, manifests as a spectrum ranging from painless varicosities to severe postthrombotic syndrome, which can cause unremitting pain and swelling, varicose veins, skin changes, and nonhealing ulcers in 5% to 10% of patients.[25] Fig. 78.5 shows the leg of a construction worker with a femoral DVT that produced moderate postthrombotic syndrome, resulting in swelling on the job, impairing his ability to work. Compression stockings reduced the swelling and provided some improvement.

Fig. 78.5. Patient with moderate postthrombophlebitic syndrome in the left leg several months after diagnosis with a common femoral DVT. Observe the swollen appearance and slight color change in the foot.

Disposition

Assuming that systemic anticoagulation can be reliably established, most patients with acute DVT can be discharged from the ED. Protocols that use monotherapy such as apixaban or rivaroxaban can facilitate this process.[26] I recommend selecting patients for home therapy using the modified Hestia criteria (Box 78.1).

PULMONARY EMBOLISM

Principles

A PE results when a clot that formed hours, days, or sometimes weeks earlier in the deep veins dislodges, travels through the venous system, and traverses the right ventricle into the pulmonary vasculature.

Pathophysiology of Pulmonary Vascular Occlusion

The right ventricle normally pumps through a pulmonary vascular tree with a low resistance to fluid flow, and young persons without cardiopulmonary disease (eg, congestive heart failure, chronic obstructive lung disease, advanced sarcoidosis, pulmonary fibrosis, scleroderma, primary pulmonary hypertension) can tolerate at least 30% obstruction from a clot, with minimal symptoms or signs. Pulmonary infarction, in contrast, can produce severe pleuritic pain. Although a segmental pulmonary artery constitutes only about $\frac{1}{16}$ of the entire pulmonary vascular circuit, a clot lodged deeply in a segmental artery can obstruct blood flow to a sufficient degree to cause tissue necrosis.

Table 78.4 presents a listing of factors that significantly increase the probability of PE in the ED population.[27] Not all variables that increase the probability of PE in epidemiologic studies also increase the probability of a PE diagnosis in individual ED patients with signs and symptoms suggesting PE. From an epidemiologic standpoint, people who smoke have a significantly higher risk for venous clots than people who do not smoke. However, in the ED, smoking does not seem to increase that person's risk for PE over that of a nonsmoker with an otherwise identical clinical presentation. It is possible that smokers are simply more likely to have other lung problems that manifest a clinical presentation similar to that of PE. As many as 50% of patients diagnosed with PE have no apparent clinical risk factors for VTE, but testing for genetic

BOX 78.1

Modified Hestia Criteria to Select Patients With Deep Vein Thrombosis and/or Pulmonary Embolism for Outpatient Treatment

Identifies low-risk PE if:

- Systolic blood pressure > 100 mm Hg
- No thrombolysis needed
- No active bleeding
- Oxygen required to maintain oxygen saturation > 94%
- Not already anticoagulated
- Absence of severe pain requiring > two doses of intravenous narcotics
- Other medical or social reasons to admit
- Creatinine clearance > 30mL/min
- Not pregnant, severe liver disease, or heparin-induced thrombocytopenia

TABLE 78.4

Evaluation of Classic Risk Factors and Physiologic Findings for Pulmonary Embolism in the Emergency Department (ED) Setting

FACTOR	MECHANISMS	STRENGTH OF ASSOCIATION WITH PE DIAGNOSIS IN ED POPULATIONS
Inherited thrombophilia	Hypercoagulability	++
Connective tissue disease	Inflammation	Unknown
Acquired thrombophilia	Hypercoagulability	Unknown
Active cancer (under treatment)	Hypercoagulability	++
Inactive cancer (considered in remission)	Presumed hypercoagulability	Not significant
Limb or generalized immobility	Stasis	++
Recent travel	Stasis	Minimal
Prior PE or DVT	Multiple	+
Trauma within past 4 wk requiring hospitalization	Inflammation, venous injury and stasis	+++
Surgery within past 4 wk requiring general anesthesia	Inflammation, venous injury and stasis	++++
Smoking	Inflammation and hypofibrinolysis	Not significant
Estrogen	Hypercoagulability	++
Pregnancy, postpartum	Hypercoagulability	Minimal
Family history of VTE	Inherited condition	Not significant
SYMPTOMS		
Pleuritic chest pain	Lung ischemia, muscle strain	+
Substernal chest pain	Presumed cardiac ischemia	Not significant
Dyspnea	$\dot{V}/\dot{Q}$ mismatch	+
Sudden onset of symptoms	Vascular obstruction	Not significant
Hemoptysis	Infarction	+++
Syncope	Vascular obstruction	Minimal
SIGNS		
Pulse rate > 100 beats/min	Cardiac stress, baroreceptors	++
Pulse oximetry reading < 95% (sea level)	$\dot{V}/\dot{Q}$ mismatch	+++
Unilateral leg or arm swelling	Venous obstruction	++++
Normalization of vital signs	Presumptive from treatment or Hawthorne effect	Not significant

DVT, Deep vein thrombosis; *PE,* pulmonary embolism; *$\dot{V}/\dot{Q}$,* ventilation–perfusion ratio.

thrombophilia has no value in the ED setting, or any other setting.[28]

Clinical Features

Symptoms vary widely during this process, ranging from no symptom to cardiovascular collapse. The patient can feel focal, sharp, pleuritic pain and exhibit a splinting response to breathing. Over several days, the infarcted segment becomes consolidated on chest radiography and exudes a pleural effusion, manifesting an intense underlying inflammatory process. Chest pain from noninfarcting PE can be highly variable and vague, with as many as 30% of patients with definite PE having no perception of chest pain.[29]

In contrast, if asked in a detailed and structured way, approximately 80% of patients with PE admit to having some sensation of dyspnea.[29] The dyspnea may be constant and oppressive or may be intermittent and perceived only with exertion, possibly due to an exercise-induced increase in pulmonary vascular resistance. Pulmonary embolism can produce hypoxemia (pulse oximetry reading <95% at sea level or <92% in Denver or Salt Lake City), but the degree of hypoxemia is unpredictable. Approximately half of all patients with PE have no evidence of hypoxemia. A swine model mimicking massive pulmonary vascular occlusion (increase in systolic pulmonary arterial pressure to ≈65 mm Hg) did not show any decrease in pulse oximetry reading (from 98% preembolization to 98% postembolization).[30] Despite its shortcomings as a single diagnostic step, the presence of hypoxemia (pulse oximetry <95%, breathing room air) that cannot be explained by a known disease process increases the probability of PE. Conversely, a normal oxygen saturation, although reassuring, cannot rule out PE. When PE is diagnosed, the severity of hypoxemia represents a significant independent predictor of patient outcome.

PE also causes highly variable effects on other vital signs. In the ED, about half of all patients with PE have a heart rate greater than 100 beats/min.[27] Tachycardia from PE probably results from impaired left ventricular filling, leading to a pathophysiologic process that parallels that of hemorrhagic shock. Only about half

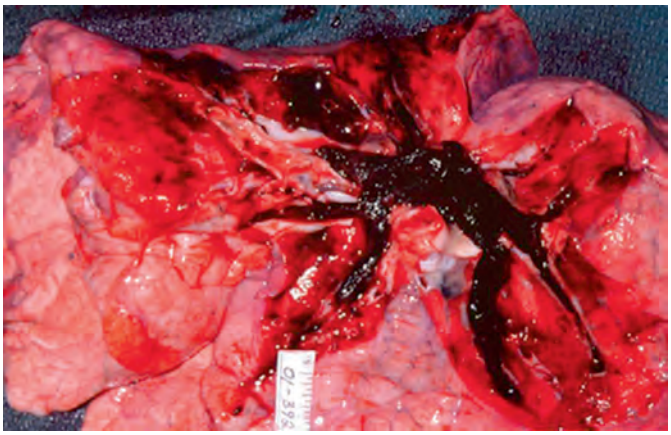

Fig. 78.6. Massive pulmonary embolism on autopsy. This man died with a large clot burden that plugged the distal lobar arterial branches, eventually producing nearly complete obstruction to blood flow and subsequent cardiac arrest. He had vague respiratory symptoms for 2 weeks, causing him to see a physician, who diagnosed bronchitis.

BOX 78.2

Pulmonary Embolism Rule-Out Criteria (PERC Rule)

Low pretest probability for PE by the treating emergency clinician's unstructured estimate, plus all the following must be true:

- Age < 50 yr
- Pulse rate < 100 beats/min
- Oxygen saturation < 94%
- No hemoptysis
- No unilateral leg swelling
- No recent major surgery or trauma
- No prior pulmonary embolism or deep venous thrombosis
- No hormone use

PE, Pulmonary embolism.

of patients have an elevated respiratory rate (>20 breaths/min). The probability of PE was not reduced in patients who normalized any vital sign while in the ED.[31] About half of patients with PE have a dilated RV on an echocardiogram obtained in the ED.[32] Arterial hypotension (systolic blood pressure < 90 mm Hg) represents an ominous hemodynamic consequence of PE; it occurs in only about 10% of patients, but signifies a fourfold increase in risk of death compared with normotensive patients.[33] In its most extreme form, PE can obstruct the right ventricular outflow entirely by casting the entire pulmonary vascular tree (Fig. 78.6) or acutely occluding the main pulmonary artery. Pulseless electrical activity (PEA) is the most common electrocardiographic result from obstructive PE. The survival rate from cardiac arrest from PE is about 20%, even if the arrest is witnessed, and treatment with bolus fibrinolysis is initiated.[34]

PE can present as cardiac arrest. Most patients with incipiently fatal PE have overt respiratory distress, syncope or seizure-like activity, or high heart rate relative to the systolic blood pressure before arrest. First responders who observe a patient dying from PE usually observe PEA as the initial cardiac arrest rhythm (>20 depolarizations/min, without palpable pulses). The mechanism for PEA manifests from right ventricular outflow obstruction and impaired right ventricular contractility. Ultrasound performed during PEA arrest from PE usually shows weak cardiac contractions, with a swollen right ventricle and small left ventricle. Some patients manifest slow agonal rhythms with fatal or near-fatal PE, possibly due to septal wall tension leading to ischemia or an ischemic-equivalent effect on the atrioventricular node and infranodal conducting pathways.

Virtually any ED visit related to weakness, shortness of breath, dizziness or syncope, pain, extremity discomfort, or nonspecific malaise or functional deterioration could represent a potential PE. However, this does not mean that every patient with these symptoms should be evaluated for PE, and these symptoms need to be rationally considered in the context of the entire clinical picture. A patient with PE typically presents with 2 to 3 days of constant or worsening shortness of breath. For many patients, the dyspnea is only present with exertion, and patients often need to be prompted to endorse this symptom. Patients usually describe chest pain with PE in vague terms, unless they have pulmonary infarction. About 20% of ED patients with PE have focal pleuritic chest pain, but many say nonspecifically that their chest hurts with breathing, usually on the lateral aspects. Those with lung infarction can present with a clinical picture similar to that of lobar pneumonia, including focal chest pain, fever, and unilateral rales on auscultation. However, a temperature greater than 101.5°F (38.6°C) suggests infection rather than infarction. On occasion, pulmonary infarction may present with an onset of pain and hemoptysis simultaneously. In contrast, lobar pneumonia, which usually presents with productive cough for a few days before rust-tinged sputum appears. Isolated substernal chest pain is a rare presentation for PE and, in general, suggests a cardiac or other origin.

Most patients with PE have no obvious abnormality on physical examination, other than an affect that gives the appearance of distress or anxiousness, with respiratory distress.[35] The only positive finding from the itemized physical examination that reliably increases the probability of PE is evidence of a DVT—unilateral leg asymmetry, unilateral edema, tenderness along a deep vein. On the other hand, wheezing, or a prolonged expiratory phase on lung auscultation, suggests the alternative diagnosis of bronchospasm, which reduces the probability of PE. Bilateral rales suggest the diagnosis of left ventricular failure, although localized rales often are heard over infarcted lung tissue.

When retrospectively comparing patients in whom the diagnosis of PE was delayed, patients who were admitted to the hospital tended to have a higher frequency of altered mental status, new or at baseline dementia, and more comorbid conditions.[36,37] Only one recent study has evaluated patients discharged and subsequently diagnosed with PE. Those patients tended to lack dyspnea and had pleuritic chest pain and hemoptysis, together with a pulmonary infiltrate on imaging, lower D-dimer concentration, and small distal clot seen on pulmonary vascular imaging. Thus, patients who were discharged with PE seemed to have isolated pulmonary infarction that was often misidentified as pneumonia. Coincidentally, in a secondary analysis of a large database of PE-positive patients, to which I applied the PERC (pulmonary embolism rule-out criteria) rule (Box 78.2) to understand the profile of the PE-positive but PERC-negative patients better, the presence of pleuritic chest pain emerged as a common feature.[38] It appears as though emergency clinicians may be prone to miss small, distal lung clots that produce a clinical picture of pneumonia. More evidence is needed to determine if these patients, in the absence of DVT, benefit from systemic anticoagulation.

Differential Diagnosis

Pneumonia is the most common alternative diagnosis found in ED patients, diagnosed in 5% to 10% of scans, and in many studies was a more common finding than PE on computed tomography pulmonary angiography (CTPA).[39] Other similar findings include exacerbations of chronic obstructive pulmonary

disease, asthma, pulmonary vascular disease, including all causes of pulmonary hypertension, pericarditis, pleurisy, costochondritis, spontaneous pneumothorax, acute coronary syndrome (ACS), and chest wall trauma. Most alternative diagnoses can be ruled out with a thorough history, physical, chest x-ray, electrocardiogram (ECG), cardiac enzyme testing, and echocardiography.[40,41] When the diagnosis is unclear, consider observation or admission.

Diagnostic Testing

Fig. 78.7 illustrates an algorithmic approach to PE exclusion and diagnosis in nonpregnant patients. Chest radiography seldom provides specific information, but is useful to suggest alternative diagnoses, such as pneumonia, congestive heart failure, or pneumothorax. If symptoms have been present for 3 days or more, a pulmonary infarction may be visible on chest x-ray as an apex-central, pleural-based, wedge-shaped area of infiltrate, producing the so-called Hampton's hump finding. Unilateral lung oligemia (Westermark's sign) is a rare radiographic manifestation of a large PE.

Likewise, a 12-lead ECG provides more information about the presence of alternative diagnoses (eg, pericarditis, cardiac ischemia) than the presence of PE. When PE causes electrocardiographic changes, this is usually a result of acute or subacute pulmonary hypertension. The most common effects of pulmonary hypertension on the ECG are rapid heart rate, symmetric T-wave inversion in the anterior leads (V_1–V_4), the McGinn-White S1Q3T3 pattern, and incomplete or complete right bundle branch block (Fig. 78.8). Any one of these findings approximately doubles the probability of PE in a symptomatic patient.

In the ED, inability to identify a cause of chest symptoms or specific signs may be an important cue to evaluate the patient for PE. Because as many as 50% of patients diagnosed with PE have no identifiable classic risk factors for thrombosis, the decision to pursue the diagnosis of PE is based on that particular patient's

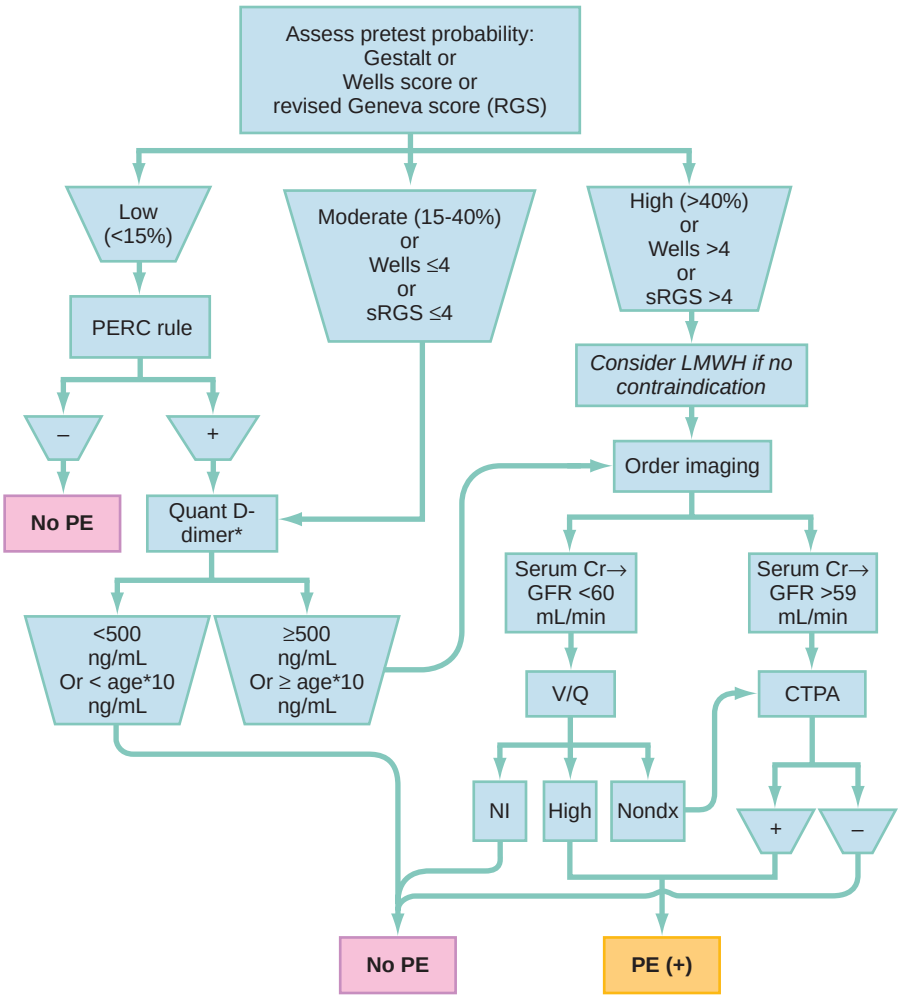

Fig. 78.7. Suggested algorithm to evaluate for pulmonary embolism (PE) in the emergency department (ED). This algorithm include the use pretest probability (PTP), enzyme-linked immunosorbent assay (ELISA) or immunoturbidometric quantitative D-dimer assay, and pulmonary vascular imaging (CT pulmonary angiography [CTPA]). The algorithm recommends V/Q scanning for patients with compromised renal function, defined by an estimated glomerular filtration rate (GFR) <60 mL/min. *Assumes a standard cutoff for normal of 500 ng/mL for D-dimer. Patients with a high pretest probability and negative CTPA or nondiagnostic V/Q scanning may require additional testing—lower extremity venous ultrasound and, if initial venous ultrasound is negative, repeat the lower extremity venous ultrasound in 1 week. *CXR,* Chest x-ray; *Cr,* creatinine; *GFR,* glomerular filtration rate; *High,* high probability scan findings; *LMWH,* low-molecular-weight heparin; *NI,* normal; *Nondx,* nondiagnostic (any reading other than normal or high probability); *PERC,* pulmonary embolism rule-out criteria; *quant,* quantitative, *sRGS,* simplified revised Geneva score; +, positive for PE; –, negative for PE.

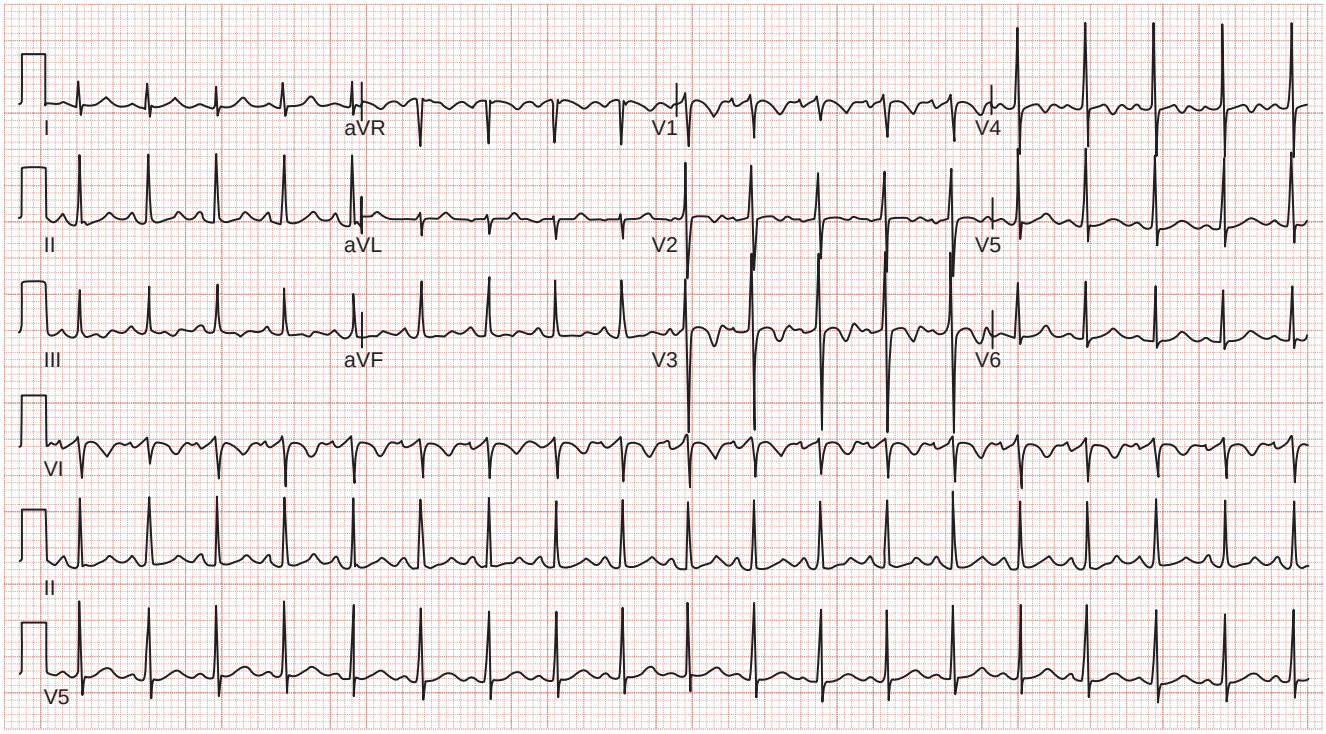

Fig. 78.8. Initial electrocardiogram tracing from an 18-year-old woman on oral contraceptives who presented to the ED with syncope. Several findings consistent with pulmonary embolism are shown, including tachycardia, early S1Q3T3 pattern, and incomplete right bundle branch block. CT angiography revealed extensive bilateral pulmonary emboli, and echocardiography showed severe right heart dysfunction.

presentation and should not rely on the presence or absence of epidemiologic risk factors.

In some cases, PE can be excluded with reasonable certainty based on data available at the bedside, gathered only by the medical history and physical examination. Multicenter studies of urban academic EDs have suggested that emergency clinicians currently evaluate approximately 2% of all patients for PE with CTPA.[42,43] Each year, more than 16 million patients, or 12% of all patients who present to the ED, have chest pain or dyspnea, and not all require an evaluation for PE. Although numerous cases of PE are likely still missed, overtesting for PE can also be harmful. Specific risks include exposure to the ionizing radiation and IV contrast necessary for CTPA and the risk of a false-positive interpretation, which may occur in as many as 10% of scans read as positive for PE.[44] The appropriate use of D-dimer testing decreases the need for imaging in all patients with non–high PTP.

A rational strategy to evaluate a patient for PE should begin with estimation of the PTP for PE. Methods for estimating PTP can be implicit, the clinician's gestalt best guess, or explicit—use of a scoring system, which is synonymous with a clinical decision rule, or clinical prediction rule to categorize the probability (eg, Well's score, Geneva criteria, Charlotte rule).[45]

One approach to the evaluation for PE is to compare the PTP with the test threshold for PE. The test threshold represents the point above which some type of evaluation should be initiated and below which the clinician can justify not starting the evaluation. For PE, the test threshold is from 1% to 5%.[46] I recommend that patients with a a PTP less than approximately 2% are more likely to be harmed than benefited by an evaluation and vice versa for patients with a PTP greater than 2%. Thus some patients with symptoms and signs of PE can have PE excluded at the bedside using the combination of PTP and additional explicit criteria. Other patients require additional objective diagnostic testing.

Evaluation for PE begins with an assessment of PTP and patients without symptoms or signs of PE (eg, no chest pain, no shortness of breath, no dyspnea on exertion, normal vital signs, and no recent syncope) should not be tested, even in the presence of risk factors. Moreover, many patients with a risk factor and a symptom or sign of PE can still have PE safely excluded without diagnostic testing. Because the evaluation for PE relies heavily on the PTP, an important question to answer is how to quantify the PTP accurately. Several clinical decision rules have been derived and validated for the risk stratification of patients with possible PE; however, difficulty with spontaneous recall and a preference for gestalt reasoning by clinicians may limit their use in clinical practice. Fortunately, gestalt reasoning appears to be comparable to other validated decision rules.[45,47]

Although gestalt reasoning and clinical decision rules may provide adequate stratification to guide the evaluation (ie, D-dimer vs. pulmonary vascular imaging), these methods alone do not reproducibly identify the very low-risk population whose PTP lies below the 2% test threshold. To identify the very low-risk group in whom PE could be safely excluded at the bedside, with no diagnostic testing, the PE rule-out criteria (or PERC rule; see Box 78.2) can be used.[48] When the physician's unstructured clinical suspicion for PE is low, and each of the eight elements of the rule is satisfied, the PERC rule identifies a very low-risk population among whom no patient has a PTP for PE greater than 2% and obviates further testing in about 20% of ED patients.[48]

For a patient with a high PTP (by any method), emergency clinicians should order pulmonary vascular imaging and consider initiating anticoagulation in the absence of contraindications.[49] Patients with a non–high PTP (simplified revised Geneva score < 5, Wells score < 5, or gestalt PTP < 40%) can have PE excluded with a normal D-dimer concentration, using the cutoff for

abnormal established by the local laboratorian. Additionally, assuming the D-dimer of use has a cutoff for abnormal of 500 ng/mL, PE can be excluded with a D-dimer concentration elevated on the basis of age using the following:

$$\text{Age} \times 10\ \text{ng/mL}$$

Thus, an 80-year-old patient with a PE unlikely or non–high PTP can have PE excluded with a D-dimer concentration less than 800 ng/mL.[50,51] This strategy maintains a diagnostic sensitivity near 95% but increases the percentage of patients who can have PE excluded without pulmonary vascular imaging. The safety of this strategy has not been tested with D-dimer assays with abnormal thresholds different than 500 ng/mL.

The most common causes of a false-negative D-dimer are very small isolated subsegmental PE and chronic PE.[39] Because the half-life of circulating D-dimer is less than 8 hours, the sensitivity of the D-dimer may decrease if the patient's symptoms have been present for longer than 3 days. False-negative D-dimer measurements may also be seen with severe lipemia and ongoing warfarin therapy.

When the PTP is high, or the screening D-dimer is positive, pulmonary vascular imaging by CTPA or V̇/Q̇ scanning is advised. Although CTPA is not perfect, it has multiple advantages over V̇/Q̇ scanning and usually can confirm or exclude the presence of PE.

Most academic centers now use CTPA as the primary method of evaluating for PE. The diagnostic sensitivity and specificity of a technically adequate CTPA scan, performed on a multidetector row scanner, are both about 90%.[52] A good-quality CTPA scan offers the highest level of diagnostic and exclusionary certainty for acute PE. Technical adequacy requires more than 200 HU of contrast opacification in the main pulmonary artery and absence of motion artifact. Emergency clinicians should consult with the radiologist interpreting the CTPA scan to ensure good-quality images for patients with a negative result but a high PTP. If the radiologist indicates that the scan was significantly compromised, the suggested next step is to perform bilateral lower leg ultrasonography and, if negative, repeat bilateral leg ultrasonography 2 to 7 days later.

Emergency clinicians have observed an increased detection of isolated subsegmental filling defects on chest CT, revealed with more thinly collimated images acquired with multidetector row scanner technology.[43] When two radiologists independently evaluate CTPA, their agreement on the presence of isolated subsegmental filling defects is poor.[53]

CTPA can provide additional information to enhance its usefulness in the ED. Although the scan can be extended to include the leg veins (CT venography), the technical reliability of this technique has been questioned, causing it to be abandoned in most centers.[54] CTPA often provides information about alternative processes that might explain the patient's symptoms.

The V̇/Q̇ scintillation scan, introduced in the early 1960s, remains a viable diagnostic option for patients with contraindications to iodinated intravenous contrast and vulnerable kidney function. The accuracy and precision of the V̇/Q̇ scan were shown in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, which compared the results of V̇/Q̇ scanning with the most accurate criterion standard test available at the time, formal pulmonary angiography. Fig. 78.9 shows the results of a high- probability V/Q scan. A high-probability V̇/Q̇ scan can confirms PE, and a normal V̇/Q̇ scan (ie, no perfusion defect) excludes PE. A moderate-probability or indeterminate scan is essentially nondiagnostic and requires additional formal pulmonary angiography or CTPA. Patients with a low PTP and a low-probability V̇/Q̇ scan require additional testing, CTPA or bilateral venous duplex ultrasonography of the legs.

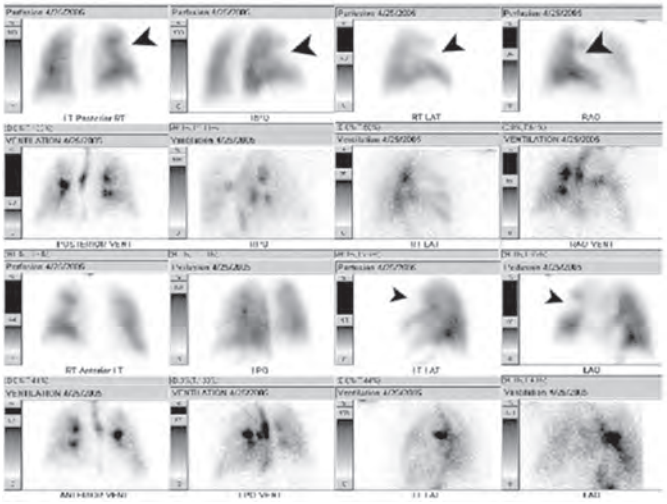

Fig. 78.9. Scintillation (^{99}Tc) ventilation–perfusion lung scan images showing high probability of acute pulmonary embolism using criteria defined in the prospective investigation of pulmonary embolism diagnosis (PIOPED). The first and third rows project the perfusion phases of the examination, and the second and fourth rows show the ventilation phases. The *black arrowheads* point to wedge-shaped defects in the perfusion images. Comparison with the corresponding ventilation view immediately below shows relatively homogeneous scintillation activity in the anatomic segments that lack perfusion. These defects are consistent with the effect of acute pulmonary embolism.

Pregnant Women

Fig. 78.10 presents an algorithm to diagnose PE in pregnant patients. It is prudent to explain the diagnostic options to the patient, including the risks and benefits of the various tests, obtain her preferences, and document these stated preferences. The algorithm starts with bilateral lower extremity venous ultrasound. If the bilateral ultrasound is positive, treatment can be started. Otherwise, the next step is determined by PTP assessment. To my knowledge, no PTP rules have been validated in pregnant patients. It is clear that over half of all VTE cases diagnosed in pregnancy occur in the third trimester.[55] Based on available patient level data from pregnant ED patients, high Wells and Geneva scores, the third trimester, or unexplained hypoxemia ($Sao_2 < 95\%$ breathing room air at sea level) predict a relatively higher PTP for PE.[56] Most patients with pregnancy selected by emergency clinicians for PE evaluation have a low clinical probability.[56] Specialty groups have acknowledged the lack of evidence regarding a recommended approach to the evaluation of pregnant patients with suspected PE, but all agree that effort should be made to avoid fetal exposure to radiation and iodinated contrast.[57,58] To minimize radiation exposure, I propose a combined approach, in which negative bilateral lower extremity venous ultrasonography is supported by a negative PERC rule and a threshold-adjusted D-dimer assay. The D-dimer threshold can be adjusted according to the trimester of pregnancy, as follows: first trimester, 750 ng/mL; second trimester, 1000 ng/mL; third trimester, 1250 ng/mL.[59-61] If the patient is has a non–high PTP, has no high-risk factors, is PERC-negative, the bilateral ultrasound is negative, and the D-dimer is below the trimester-adjusted values, PE can be excluded. Note that this recommendation does not state that the PERC criteria can be used alone in pregnancy.

If the D-dimer is abnormal or the patient fails the PERC criteria, a pulmonary vascular imaging study is warranted. The best choice of pulmonary vascular imaging is controversial and uncertain.[57] Current data indicate that CTPA or V̇/Q̇ scanning will produce adequate images to exclude and diagnose PE in a pregnant patient.[58,62,63] The data used to estimate the risk of fetal

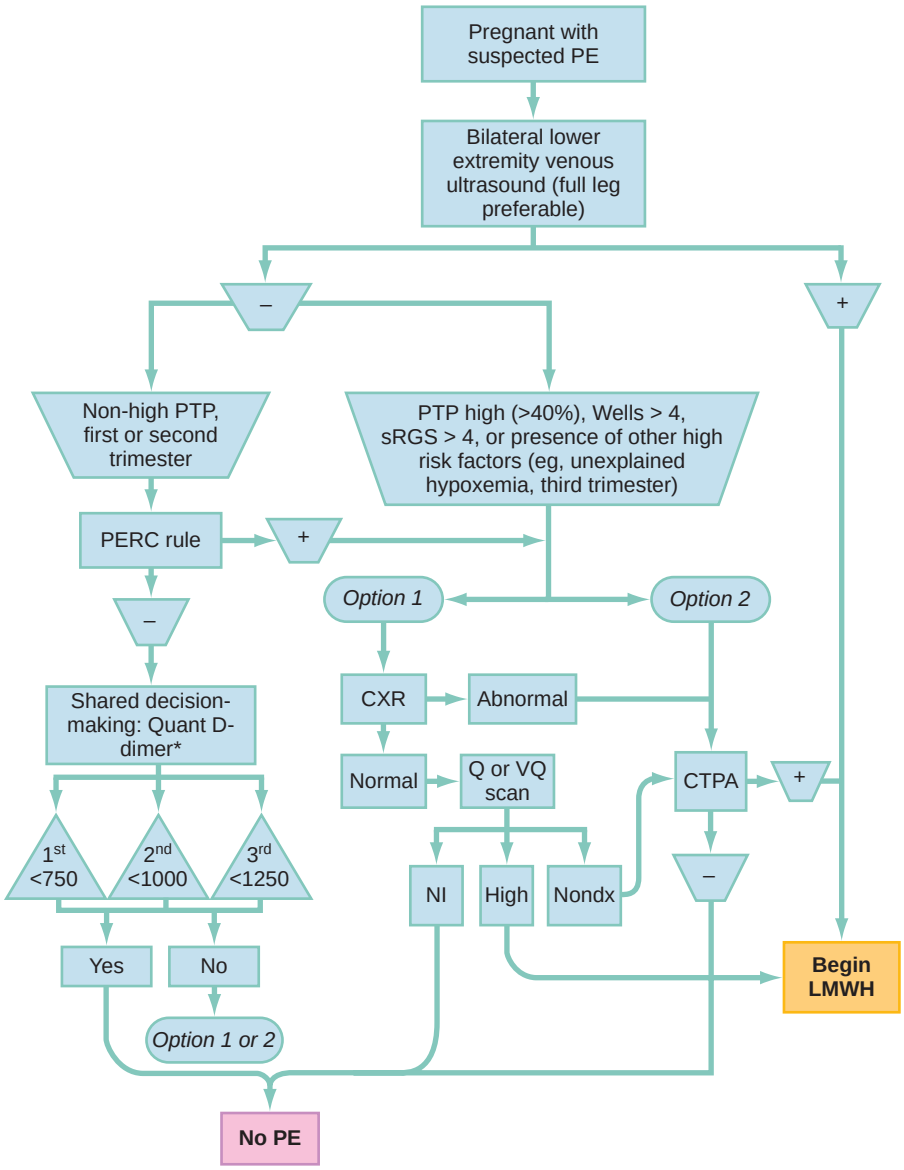

Fig. 78.10. Algorithm for exclusion and diagnosis of PE in pregnant patients. Shared decision making refers to discussion of the diagnostic options with the patient, including risks of potentially fatal PE if not diagnosed, and the potential risks of CTPA or V/Q scanning to the fetus. Non–high PTP refers to the absence of high PTP by gestalt, Wells, or sRGS. See text for references. *D-dimer concentrations per trimester given in ng/mL assuming a standard D-dimer threshold for abnormal of 500 ng/mL. *CXR,* Chest x-ray; *Cr,* creatinine; *CTPA,* CT pulmonary angiography; *High*, high probability scan findings; *LMWH,* low-molecular-weight heparin; *NI,* normal; *Nondx,* nondiagnostic (any reading other than normal or high probability); *PERC,* pulmonary embolism rule-out criteria; *Q,* perfusion lung scan; *quant,* quantitative, *sRGS,* simplified revised Geneva score; +, positive for PE; –, negative for PE.

exposure to radiation for CT scanning versus $\dot{V}/\dot{Q}$ scanning are highly speculative. Shielding the abdomen with a lead or bismuth-antimony apron during CT scanning may reduce radiation based on phantom modeling.[64] When available, tube voltage modulating technology may also serve to lower fetal radiation exposure more than shielding.[64] However, if both tests are equally available, I prefer to consult with the radiologist on duty to coordinate a stepwise evaluation of the chest radiograph first and, if normal, to proceed to perfusion-only nuclear lung scanning with a half-dose ^{99}Tc-macroaggregate. Because ^{99}Tc is excreted in the urine, prehydration with 1 L of intravenous saline and insertion of a Foley catheter appears to be a logical but unproven step to reduce fetal exposure to radiation. The risk of this approach is that if the perfusion lung scan is not normal, and CT scanning is ultimately required, the mother and fetus will be exposed to more radiation than if CTPA had been performed first.

Management

Fig. 78.11 presents a comprehensive management plan for diagnosed PE relevant to the context of a large, full- service (typically known as a tertiary care) hospital. Pathways similar to this have been adopted by multidisciplinary PE response teams.[65] At the left-most side of the algorithm, patients can be discharged to home from the ED. At the right side, patients with a massive PE and no contraindications receive bolus thrombolytic therapy.

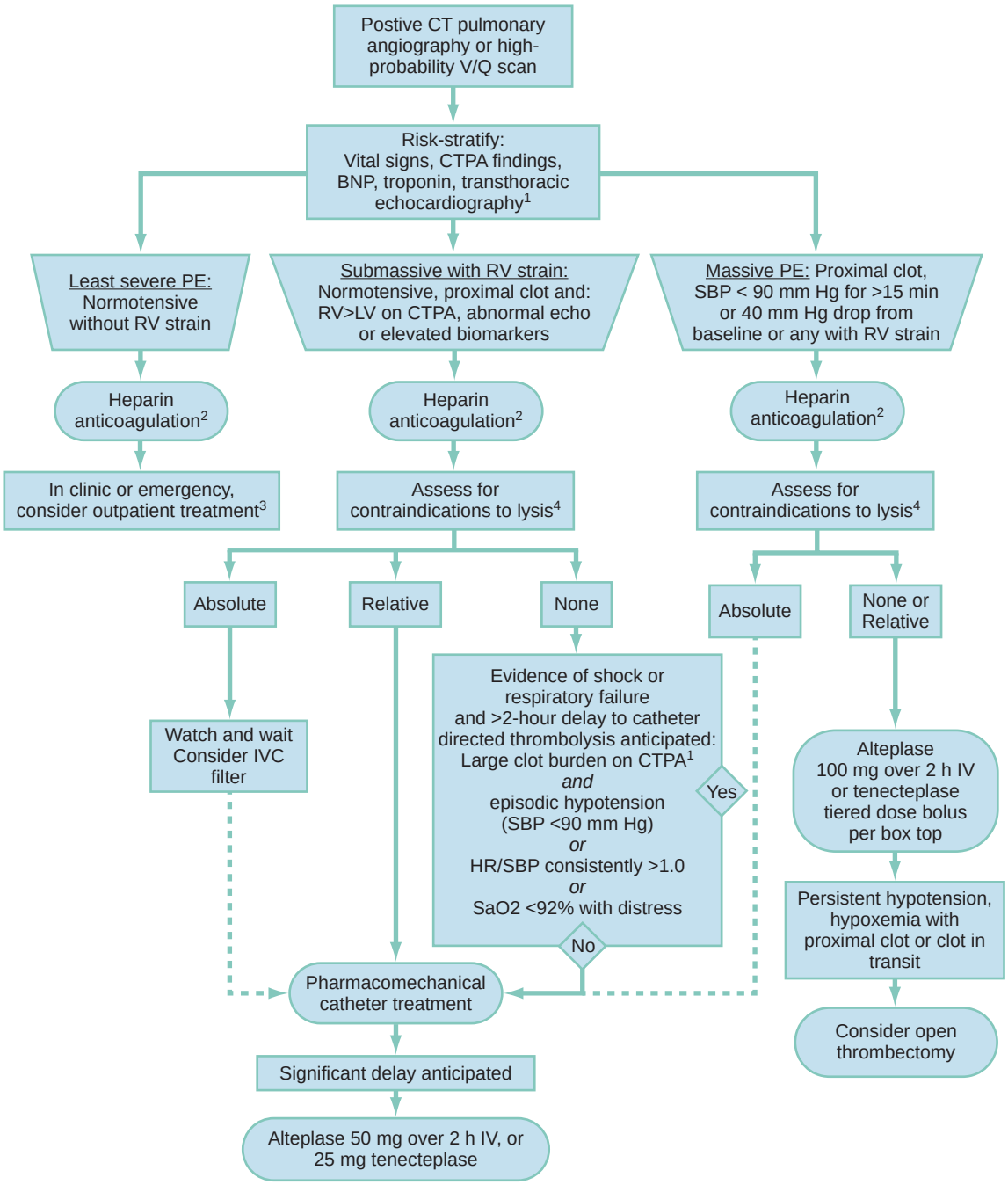

Fig. 78.11. Comprehensive treatment algorithm for diagnosed acute pulmonary embolism in a large, full-service hospital. *Denotes a controversial pathway that is not available at many smaller hospitals. Many experts believe that anticoagulation alone provides equivalent outcomes. *1, CTPA,* CT pulmonary angiography findings: filling defects in a lobar or more proximal artery; right ventricle (RV) > left ventricle (LV) on CT scan; reflux of contrast into inferior vena cava (IVC) and liver. Abnormal echographic findings include dilated or hypokinetic RV and estimated RV systolic pressure > 40 mm Hg.[84,85] Elevated biomarkers include brain natriuretic peptide (BNP) level > 90 pg/mL pro-BNP level > 900 pg/mL, or any troponin concentration > 99th percentile for normal, with <10% coefficient of variability (ie, borderline or higher).[86-88] *2,* Unfractionated heparin 80 U/kg and then 16–18 U/kg/h to maintain PTT of 2–2.5. *3,* See Beam and colleagues.[26] *4,* Contraindications to fibrinolysis. *Absolute contraindications: 1,* gastrointestinal bleeding within previous 30 days; *2,* active hemorrhage in any of the following sites at the time of enrollment—intraperitoneal, retroperitoneal, pulmonary, uterine, bladder, or nose; *3,* head trauma causing loss of consciousness within previous 7 days; *4,* any history of hemorrhagic stroke; *5,* ischemic stroke within the past year; *6,* history of intraocular hemorrhage; *7,* known or suspected intracranial metastasis; *8,* liver failure with prothrombin time abnormal (international normalized ratio [INR] > 1.7); *9,* surgery that required opening of the chest cavity, peritoneum, skull, or spinal canal within the previous 14 days; *10,* subacute bacterial endocarditis under treatment; *11,* pregnancy; *12,* large pericardial effusion. *Relative contraindications:* age > 75 years; dementia; surgery more than 30 days but less than 60 days prior; any prior stroke; symptoms suggesting transient ischemic attack in the past 30 days; any prior gastrointestinal bleeding; concurrent use of a thienopyridine (eg., clopidogrel); INR > 1.7 from warfarin use; any metastatic cancer, tongue bites, recent fracture, recent fall with head strike, history of hematuria, nosebleeds, recent dental extraction, or orthopedic surgery. *HR,* Heart rate; *SBP,* systolic blood pressure.

Standard Anticoagulation

Patients with a high PTP, no contraindication to anticoagulation, and evidence of hemodynamic instability, including recent syncope, any hypotension, hypoxemia, or clinical evidence of right heart strain (criteria defined in Table 78.4 as more severe moderate PE or high-risk PE) should receive empirical heparin prior to waiting for the results of pulmonary vascular imaging. Patients with a positive imaging for DVT or PE should receive anticoagulation using one of the agents in Table 78.3, administered in the ED as soon as the diagnosis is confirmed.[66] Low-molecular-weight (LMW) heparin is advantageous when compared to unfractionated heparin based on robust meta-analyses that have clearly demonstrated lower rates of major hemorrhage, heparin-induced thrombocytopenia, and VTE, with similar cost.[67] Patients can now be anticoagulated in the ED with apixaban (Eliquis) or rivaroxaban (Xarelto), which are orally available agents that specifically inhibit one enzyme in the clotting pathway. These drugs can be started without prior or concomitant use of heparin, and they provide therapeutic anticoagulation effect as rapidly as subcutaneous LMW heparin (see Table 78.3). By obviating the need for twice-daily subcutaneous injections and blood monitoring, these drugs can facilitate outpatient treatment of DVT and PE.

Patients with a history of heparin-induced thrombocytopenia should receive fondaparinux, argatroban, apixaban, or rivaroxaban. Most hematologists, internists, and obstetricians prefer that pregnant patients with VTE receive twice-daily LMW heparin.[68]

The anticoagulant effect of unfractionated heparin can be almost completely and rapidly reversed with protamine, whereas LMW heparin can only be 50% neutralized with protamine. Protamine has no effect on fondaparinux, rivaroxaban, or apixaban. At present, based on data in healthy volunteers, the best agent to correct coagulopathy from apixaban or rivaroxaban is four-factor activated prothrombin complex (Beriplex P/N or K-Centra, 50 U/kg, IV).[69,70] No clinical trials have been published to test the effect of these agents on bleeding in people with apixaban or rivaroxaban coagulopathy.

Regarding isolated subsegmental PE, if the patient has no evidence of DVT on bilateral lower extremity ultrasonography, no signs of cardiopulmonary stress (eg, normal biomarkers, normal ECG), and no ongoing major risk for thrombosis (eg, active malignancy, atrial fibrillation), it is reasonable and prudent to withhold anticoagulation for patients with isolated subsegmental filling defects on CTPA.[71] If a patient with a negative CTPA scan has ongoing dyspnea and signs of pulmonary hypertension—enlarged right ventricle,[72] enlarged pulmonary artery, or reflux of contrast into the liver, the mosaic pattern, acute pulmonary hypertension on the ECG[73]—or hypoxemia without an apparent alternative cause, at minimum, the patient should have transthoracic echocardiography performed. If this demonstrates pulmonary hypertension or right ventricular overload, the patient should be referred or admitted to a pulmonary specialist to guide further testing.[40,41]

Recent evidence has indicated that up to 50% of outpatients diagnosed with PE may be stable enough to be treated as outpatients (low-risk criteria; see Table 78.4).[74,75] In settings where good follow-up can be obtained, and the patient can be taught to self-administer LMW heparin and can access an anticoagulation clinic within 48 hours, a low-risk patient with PE can be discharged from the ED. My choice, however, is to implement a protocol that includes the Hestia criteria to select low-risk patients (see Box 78.1), together with monotherapy with apixaban or rivaroxaban; this has been associated with low rates of complications and economic advantages.[26,76]

For a patient diagnosed with PE in the presence of a major contraindication to anticoagulation, such as a recent cerebral hemorrhage or large cerebral infarction, or brain metastases, the appropriate consultant should be contacted for urgent placement of an inferior vena cava filter. If vena caval interruption cannot be performed within 12 hours, one option is to perform a baseline head CT scan, start an unfractionated heparin infusion at 18 U/kg/hr (without a bolus), and admit the patient to the intensive care unit for close neurologic monitoring and frequent partial thromboplastin time (PTT) determinations. The rationale for using unfractionated heparin is that it can be reversed more reliably by discontinuing the heparin drip and administering protamine, 1 mg/kg IV, than fractionated heparin. Case reports and series have suggested that inhaled nitric oxide might be helpful for patients with severe PE and an absolute contraindication to anticoagulation, but this treatment has not yet been subjected to rigorous study.[77]

Most patients with PE state that they feel better the day after starting heparin anticoagulation, and more than half go on to nearly a full recovery of pre-PE health status. The in-hospital mortality rate of patients diagnosed with PE who remain hemodynamically stable while in the ED was thought to be 10%, but a recent large, multicenter, US-based registry of 1880 patients diagnosed with PE in the ED found the in-hospital mortality rate directly attributable to PE as 1.1% and an all-cause mortality rate of 5.4%.[29] Approximately 10% to 20% of PE survivors complain of persistent dyspnea and exercise intolerance that permanently degrades their quality of life.[78]

Fibrinolytic (Thrombolytic) Therapy

Fibrinolytic therapy in PE remains a controversial treatment option. Recent meta-analyses of randomized trials that compared fibrinolysis plus heparin to heparin alone have reached different conclusions about mortality benefit, with one study finding significant improvement[79] and another no difference[80] in mortality. Most experts, even those generally opposed to fibrinolysis, believe that patients with arterial hypotension (systolic blood pressure < 90 mm Hg or >40-mm Hg drop from baseline) should receive full-dose systemic fibrinolysis (100 mg of alteplase over 2 hours or tiered-dose tenecteplase, per the TNKase label). No one doubts that the bleeding risk increases with systemic fibrinolysis, but the risk of intracranial hemorrhage appears to be mostly confined to patients older than 65 years.[79] The "to lyse or not to lyse PE" controversy has been made more complex by recent studies suggesting a possible lower risk of significant hemorrhage associated with the lower, half-dose alteplase (50 mg over 2 hours), administered by peripheral vein.[81] Moreover, many large treatment centers have adopted the use of catheter-directed thrombolysis, which administers the fibrinolytic directly into the thrombus, with or without adjunctive ultrasonic energy.[82] The potential advantage of this approach is a lower risk of hemorrhage due to the lower dose of fibrinolytic agent (eg, 20–25 mg of alteplase infused intrathrombus over 24 hours.) No evidence has yet demonstrated a survival advantage or any patient-oriented advantage of catheter-directed therapy. However, one small randomized trial has demonstrated improved quality of life end points with bolus administration of tenecteplase for severe submassive PE.[83]

The clinical course of patients with obstructive PE can be unpredictable. Many patients with massive PE remain stable in the ED. Other patients are stable on arrival, but progressively deteriorate over hours as right ventricular function declines. Of ED patients without hypotension, 3% experience cardiac arrest while in the ED and die within 24 hours.[33] A patient can be stable and then hypotensive within minutes because of the highly variable effect of the clot on right ventricular outflow obstruction, especially when it straddles the main pulmonary artery (Fig. 78.12). Additional mechanisms of rapid instability include new embolization of clot material, release of mediators of pulmonary vasospasm, sudden bradyasystolic arrhythmias, and respiratory

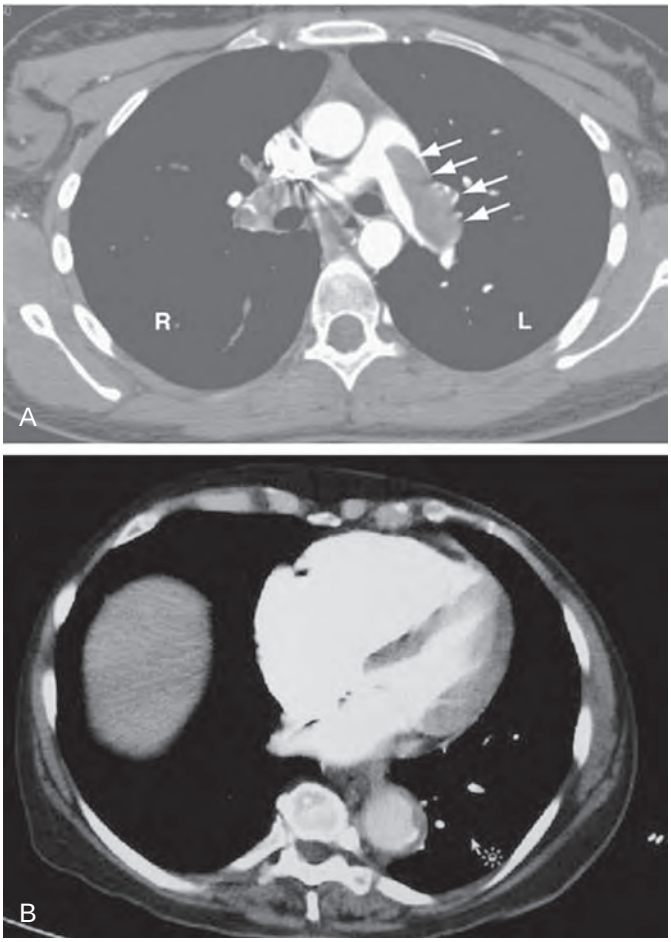

Fig. 78.12. CT evidence suggesting more severe PE. **A,** Proximal pulmonary embolism on a contrast-enhanced CT scan of the chest. This CT scan is at the level of the bifurcation of the main pulmonary artery. The left main branch of the pulmonary artery shows a massive filling defect (*arrows*). **B,** Evidence of right ventricular strain, shown by the larger size of the right ventricle compared with the left ventricle.

failure. Clues to oncoming cardiopulmonary decompensation include worsening respiratory distress and worsening hypoxemia, rising shock index (the heart rate divided by the systolic blood pressure), systolic arterial blood pressure less than 90 mm Hg, and syncope or a sharp change in mental status, including seizure-like convulsive episodes. Deterioration in the ECG from a narrow-complex tachycardia to an incomplete right bundle branch block to a complete right bundle branch block (Fig. 78.13) is evidence of life-threatening pulmonary hypertension and impending cardiac arrest.

Clinical evidence of impending or actual respiratory failure indicates the need for prompt endotracheal intubation using a standard rapid sequence intubation technique, preferably with ketamine or etomidate for induction of anesthesia with neuromuscular blockade. Other induction agents that depress cardiac function or reduce preload may precipitate severe hypotension and should be avoided or their dosage reduced. The effect of biphasic, positive pressure–assisted noninvasive ventilation (BiPAP) on hemodynamics with massive PE has not been studied. For patients with PE and persistent hypotension, the role of volume loading to resuscitate massive PE remains uncertain. Most experts use norepinephrine as the vasopressor of choice to attempt to increase blood pressure. In the case of impending respiratory or cardiac arrest, fibrinolytic therapy should be strongly considered.

Surgical Embolectomy

For patients with known floating thrombi in the right heart or patients with severe refractory hypotension, surgery is the most likely intervention to save the patient's life. Surgical embolectomy commonly includes extracorporeal cardiopulmonary bypass and an experienced cardiothoracic surgeon. Surgical embolectomy may be the best option for patients who have severe PE with a contraindication to fibrinolysis; however, extracorporeal perfusion requires intensive heparin anticoagulation, and the patient's mental status cannot be monitored during surgery—a key concern in patients with a high risk of intracranial hemorrhage.

Numerous case reports have suggested heroic results from the bolus administration of thrombolytic therapy to patients with cardiac arrest from PE. The administration of fibrinolytic therapy does not absolutely preclude surgical intervention. Patients who have been treated with a fibrinolytic agent can undergo sternotomy or thoracotomy for embolectomy and survive without fatal hemorrhage. The decision to perform embolectomy ultimately resides with the cardiac surgeon.

Disposition

Table 78.5 summarizes the criteria that can be used to risk-stratify patients with PE into four groups. This stratification may help guide the decision to place the patient in an intensive care unit versus an intermediate or regular inpatient bed and whether to administer heparin only or consider escalated therapy (see Fig. 78.11).

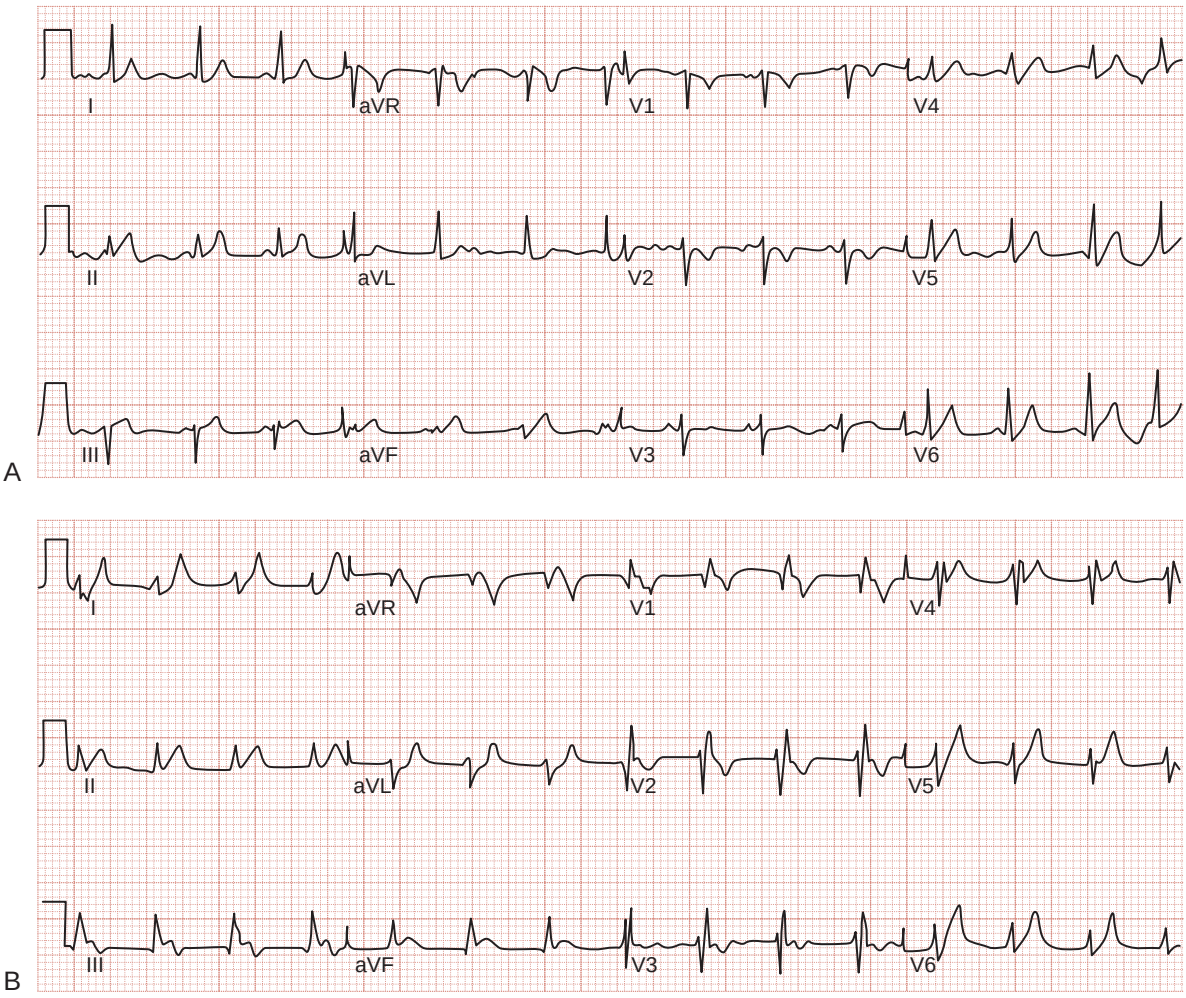

Fig. 78.13. Serial electrocardiograms obtained 2 minutes apart show the progression from a narrow complex rhythm **(A)** to a right bundle branch block pattern **(B)** in a patient with massive bilateral pulmonary emboli. Shortly after the second tracing was obtained, the patient developed cardiovascular collapse refractory to vigorous resuscitation efforts.

TABLE 78.5

Risk Stratification and Associated Treatment Recommendations for Acute PE

CATEGORY	CRITERIA	ACTION
Low-risk PE	sPESI of 0[89] Hestia criteria negative (see Box 78.1)[90] SBP > 90 mm Hg at all times and all of the following: no proximal clot or RV dilation on CTPA, shock index < 1, Sao_2 > 94%, no pulmonary hypertension on ECG (Daniel score < 3), normal troponin, BNP, or pro-BNP level	• Begin anticoagulant treatment (see Table 78.3) • Optional admission to unmonitored regular bed • Consider outpatient treatment if adequate • Compliance and follow-up can be assured
Moderate-risk PE	SBP > 90 mm Hg at all times and any one of the following: Proximal clot and RV > LV on CTPA scan (see Fig. 78.12)[72,84,85,88] Elevated troponin or BNP level (>90 pg/mL) or pro-BNP level (>900 pg/mL) Echocardiogram with any degree of right ventricular hypokinesis	• Begin anticoagulant treatment (see Table 78.3) • Fibrinolytics in minority of cases • Admission to a telemetry bed
More severe (submassive); moderate-risk PE	Any moderate risk criteria and appearance of at respiratory distress Shock index > 1 and severe right ventricular hypokinesis on echocardiography Worsening Daniel score, particularly a new incomplete right bundle branch block (RBBB) or progression of incomplete RBBB to complete RBBB Sao_2 < 90% and serum troponin level clearly elevated New altered mental status	• Begin heparin treatment • Fibrinolytic treatment in most patients without contraindications in the ED • Admission to a step-down or intensive care unit
High-risk (major) PE	Any SBP <90 mm Hg or <20 mm Hg below documented baseline and appearance of distress Any persistent SBP <90 mm Hg, regardless of appearance	• Begin heparin treatment • Fibrinolytic treatment in all patients without contraindications in the ED • Admission to intensive care unit

BNP, Brain natriuretic peptide; *CTPA,* computed tomography pulmonary angiography; *ED,* emergency department; *PE,* pulmonary embolism; *RBBB,* right bundle branch block; *RV/LV,* right ventricle–left ventricle ratio; *SBP,* systolic blood pressure.

KEY CONCEPTS

- Deep vein thrombosis often presents as a nonspecific crampy sensation in the upper or lower extremity without obvious swelling.
- An ELISA or immunoturbidimetric D-dimer concentration less than 500 ng/mL can exclude DVT in patients with a low pretest probability (PTP).
- A negative three-point ultrasound, together with a negative quantitative D-dimer test result, excludes DVT with any PTP.
- A negative three-point ultrasound in a patient with a moderate or high PTP for DVT should have additional testing, including a D-dimer test or repeat venous ultrasound within 3 to 7 days.
- An enzyme-linked immunosorbent assay (ELISA) or immunoturbidimetric D-dimer concentration less than 500 ng/mL can rule out PE non–high PTP patients, including all pregnant patients.
- A patient at a low PTP may have the diagnosis of DVT effectively excluded by a negative three-point venous duplex ultrasound performed by a qualified emergency clinician or radiologist.
- A single, whole-leg ultrasound excludes DVT in all pretest probabilities.
- When duplex ultrasound is not available, patients with a moderate to high PTP for DVT should receive empirical LMW heparin, oral apixaban, or rivaroxaban while awaiting the availability of ultrasound imaging; patients with a low PTP, or moderate to high PTP with a negative D-dimer, do not need empirical anticoagulation while they wait for diagnostic imaging.
- Patients at a low or moderate PTP for PE should have a D-dimer test done prior to performing pulmonary vascular imaging; PE can be ruled out in non–high PTP, with a D-dimer adjusted for age according to this formula: age × 10 ng/mL.
- A patient with a PTP less than 2% need not be tested for PE.
- Patients with PE and low risk according to the Hestia criteria (see Box 78.1) can be treated at home, provided they have adequate follow-up.
- Patients with PE and arterial hypotension (systolic blood pressure < 90 mm Hg) should receive systemic fibrinolysis unless they have a contraindication to fibrinolysis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 78: QUESTIONS & ANSWERS

78.1. Which of the following statements concerning the D-dimer protein level is most true?
- **A.** It is derived from the enzymatic breakdown of thrombin.
- **B.** It is elevated in patients with acute febrile illness.
- **C.** The concentration is higher in smokers but unaffected by advancing age.
- **D.** The concentration is proportional to the size of the clot.
- **E.** The serum half-life is 48 to 60 hours, making it sensitive for older clots.

Answer: D. The D-dimer concentration varies directly with clot burden. It is derived from the enzymatic breakdown of fibrin, with a serum half-life of 8 hours, making it less sensitive for older, more mature clots. Levels are not higher in smokers but may be elevated with advanced age and immobility. It is not elevated by febrile illness.

78.2. What is the sensitivity of venous duplex ultrasonography for detecting a proximal DVT?
- **A.** 80%
- **B.** 85%
- **C.** 90%
- **D.** 95%
- **E.** 100%

Answer: D. The sensitivity of a single scan is 95%. Thus, 5% are missed.

78.3. A 29-year-old woman presents with onset of left calf pain and mild swelling over a 24-hour period. She is 26 weeks pregnant, with no other medical problems and no other symptoms. The D-dimer level is 845 ng/mL. Lower extremity duplex ultrasonography is negative. What would be the most appropriate course of action?
- **A.** Contrast CT scanning of the chest
- **B.** Empirical anticoagulation
- **C.** Repeat ultrasound in 2 or 3 days
- **D.** Repeat ultrasound in 24 hours
- **E.** $\dot{V}/\dot{Q}$ scan of the chest

Answer: C. In moderate- to high-risk patients with an elevated D-dimer level, a single ultrasound may be insufficient. A repeat study in 2 to 7 days is often sufficient to confirm the diagnosis. The lack of pulmonary symptoms precludes the need for lung and embolus evaluation at this time. During pregnancy, there is a progressive rise in baseline D-dimer concentration; thus, a normal value is useful but an elevated level is of no discriminatory value.

78.4. A 43-year-old woman presents with acute pain and swelling of her right saphenous vein. Symptoms have occurred over 48 hours. She does not smoke and has no significant past medical history. Vital signs are unremarkable, and the physical examination is also unremarkable, except for isolated swelling, erythema, tenderness, and increased firmness along the track of the right saphenous vein from the malleolus to 4 cm below

the tibial plateau. There is no calf or thigh swelling or tenderness. Which of the following would be appropriate management?
A. Nonsteroidal antiinflammatory drugs (NSAIDs) and compression stockings
B. Antistaphylococcal antibiotics and antiinflammatory agents
C. Antistaphylococcal antibiotics and elevation for 24 to 48 hours
D. Systemic anticoagulation
E. Ultrasonography to rule out DVT, then antiinflammatory agents and compression stockings

Answer: E. Many patients with superficial thrombophlebitis have a synchronous DVT. Once ruled out, treatment is symptomatic, with NSAIDs and compression stockings. Ambulation is encouraged. Routine anticoagulation is not indicated for superficial thrombophlebitis.

78.5. A 46-year-old woman presents with pain and swelling of the right calf. She has a history of tobacco use, emphysema, and hypertension. Medications are albuterol inhaler, lisinopril, 20 mg/day, and oral contraceptives. She denies pulmonary or cardiac symptoms. Vital signs and the physical examination are unremarkable except for pain and tenderness to palpation, with minimal swelling of the right calf. Doppler ultrasonography reveals an isolated calf thrombosis. What is the appropriate management?
A. Aspirin therapy with repeat Doppler in 2 to 7 days
B. Intravenous fibrinolysis with tenecteplase
C. Nonsteroidal anti inflammatory agents and compression stockings
D. Reassurance
E. Systemic anticoagulation

Answer: E. Approximately 25% of isolated calf DVTs propagate proximally. Serial Dopplers as surveillance for proximal propagation may be acceptable in healthy ambulatory patients, but full anticoagulation, as for DVT, would be the safest course of action for this patient.

78.6. Which of the following statements concerning upper extremity DVTs is true?
A. After appropriate treatment, it is rare for symptoms to persist long term after upper extremity DVT.
B. Anticoagulation is not always necessary in upper extremity DVT.
C. If present, indwelling catheter removal is required for successful DVT treatment.
D. Other than catheter-related cases, most occur in patients who are young and healthy.
E. The rate of pulmonary embolus from axillary vein DVT is lower than that from the femoral vein.

Answer: D. So-called effort thrombosis is often seen in healthy patients after vigorous exercise. Many of these are later found to have anatomic abnormalities relating to the subclavian and axillary vein. Approximately 50% of upper extremity DVTs are related to indwelling catheters. Catheter removal is not always mandatory. Appropriate treatment for upper extremity DVT includes full anticoagulation and is sometimes accompanied by fibrinolysis or thrombectomy. The incidence of pulmonary embolus is the same as for femoral DVTs. Many patients remain symptomatic, with ongoing arm pain and swelling, despite appropriate treatment.

78.7. In a young healthy patient, what percentage of the cross-sectional area of the pulmonary vascular bed can be acutely occluded with only minimal symptoms?
A. 10%
B. 20%
C. 30%
D. 40%
E. 50%

Answer: C. Again, this assumes a patient with full cardiopulmonary reserve and no preexisting disease.

78.8. What percentage of patients with pulmonary embolus may present with a normal (98%–100%) pulse oximetry reading on room air?
A. 5%
B. 10%
C. 15%
D. 20%
E. 25%

Answer: B. A low oxygen saturation (<95%) increases the probability of pulmonary embolus, but a normal oxygen saturation should not dissuade one from the diagnosis.

78.9. What percentage of patients diagnosed with pulmonary embolus have no apparent clinical risk factor for venous thromboembolism?
A. 10%
B. 20%
C. 30%
D. 40%
E. 50%

Answer: E. The point here is that being healthy does not rule out the possibility of VTE. Risk factors are best applied to population analysis and are of very limited use when evaluating a single patient.

CHAPTER 79

Esophagus, Stomach, and Duodenum

Andrew W. Lee | Jamie M. Hess

DYSPHAGIA

Principles

Background

Swallowing is divided into oral, pharyngeal, and esophageal phases. Precise motor control of the act of swallowing is necessary to ensure that food is successfully transferred from the mouth through the esophagus into the stomach. Failure at any one of these levels results in dysphagia, which literally means "difficulty swallowing."

Dysphagia at any age is abnormal; it is particularly common in older adults, with up to 60% of assisted living and nursing home patients having reported difficulty feeding.[1] Dysphagia is classified as two types, oropharyngeal and esophageal. Oropharyngeal dysphagia, also termed *transfer dysphagia*, involves difficulty transferring a food bolus from the oropharynx to proximal esophagus. Esophageal dysphagia involves difficulty in transporting material down the esophagus.

Oropharyngeal Dysphagia. Neuromuscular disease causes approximately 80% of cases of oropharyngeal dysphagia, with most remaining causes being localized structural lesions. Most neuromuscular causes of dysphagia result in misdirection of the bolus, sticking, and the need for repeated swallowing attempts. Liquids, especially of extreme temperatures, cause dysphagia more commonly than solids, and symptoms are often intermittent. Cerebrovascular accidents causing pharyngeal weakness with failure of the cricopharyngeus muscle to relax is the most common cause of neuromuscular dysphagia. Weakness of the tongue may occur, resulting in poor transfer of the bolus, or weakness of the buccal muscles may produce drooling and difficulty prompting the swallowing process.

The second most common cause of neuromuscular dysphagia is inflammatory myopathy, such as polymyositis or dermatomyositis. These disorders are characterized by inflammatory and degenerative changes in striated muscle that can produce dysphagia from weakness of the palate, pharynx, and upper esophagus. Dysphagia may be a presenting symptom of patients with these disorders.

Myasthenia gravis is an important cause of oropharyngeal dysphagia. At least 40% of patients with myasthenia gravis have dysphagia, and it is the presenting symptom in up to 15% of patients. The dysphagia becomes progressively worse with repeated swallowing attempts and is temporarily reversible with edrophonium.

Congenital anomalies of the aortic arch may cause dysphagia in children and adults. In children, respiratory symptoms are usually present and commonly predominate. In adults, an anomalous right subclavian artery is the most common vascular cause for dysphagia, often termed *dysphagia lusoria*. Patients often do not become symptomatic until the fourth decade of life; the most common symptoms are dyspnea on exertion and dysphagia. Vascular compression of the esophagus causing dysphagia may also occur with aneurysms of the aortic arch and great vessels. Bronchogenic carcinoma can cause dysphagia by direct involvement of the esophagus or by compression from enlarged lymph nodes.

Esophageal Dysphagia. Esophageal dysphagia is caused by mechanical lesions or a motility disorder. Mechanical lesions may be intrinsic or extrinsic to the esophagus. Intrinsic lesions include strictures, webs, rings, tumors, esophagitis, postsurgical changes, and esophageal foreign bodies. Pressure from extrinsic lesions such as osteophytes, mediastinal masses, or aortic aneurysms can also cause dysphagia.

Patients with esophageal dysphagia who have no readily identifiable mechanical cause may have a motor disorder. Intrinsic motor disorders of the esophagus include achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter (LES). Systemic collective tissue diseases, scleroderma, CREST (***c***alcinosis, ***R***aynaud's phenomenon, ***e***sophageal dysmotility, ***s***clerodactyly, and ***t***elangiectasia) syndrome, Chagas' disease, or a paraneoplastic syndrome may cause secondary motor disorders.

Achalasia is a disorder of unknown cause in which the resting pressure of the LES is markedly increased, and peristalsis in the body of the esophagus is absent. The incidence increases with age.

Diffuse esophageal spasm is a another type of intrinsic motor disorder and, when it is severe and prolonged, with associated high-intensity peristaltic waves, it is termed *nutcracker esophagus*.[2] Nonspecific motor disorders include repetitive esophageal contractions, nontransmitted esophageal contractions, and low-amplitude esophageal contractions.

Pathophysiology

Swallowing is a complex phenomenon requiring voluntary and involuntary skeletal muscle activity coordinated by the swallowing center in the medulla. The trigeminal, glossopharyngeal, vagus, and spinal accessory cranial nerves provide afferent sensory inputs; efferent motor activity travels through the trigeminal, facial, glossopharyngeal, vagus, and hypoglossal cranial nerves.

There are intrinsic and extrinsic causes of esophageal stenosis that may lead to symptoms of obstruction. Intrinsic causes of luminal narrowing include carcinoma and webs. An esophageal web is a thin structure composed of mucosa and submucosa

usually found in the middle or proximal esophagus. Although webs can occur in isolation, they are also seen in Plummer-Vinson syndrome, which is characterized by anterior webs, dysphagia, iron deficiency anemia, cheilosis, spooning of the nails, glossitis, and thin friable mucosa in the mouth, pharynx, and upper esophagus. Most patients with this syndrome are women from 30 to 50 years of age. Patients usually report dysphagia that is initially intermittent and worse with solids. If untreated, it may progress and become constant. Rarely, motility disorders and surgical changes after a gastric bypass can also cause an esophageal obstruction.

Extrinsic compression of the esophagus can occur in a variety of conditions. In the neck, thyroid enlargement from goiter or carcinoma may cause dysphagia. Symptoms may also be seen with a pharyngoesophageal or Zenker's diverticulum, a progressive outpouching of the pharyngeal mucosa as a result of increased pressure generated by failure of proper relaxation of the cricopharyngeus muscle. Noisy deglutition, dysphagia, halitosis, and a palpable compressible mass in the neck may be present. Laryngotracheal aspiration when the patient is supine results from the emptying of contents from the diverticulum.

Clinical Features

A careful history helps differentiate oropharyngeal from esophageal dysphagia in up to 85% of patients (Box 79.1). The history focuses on determining the anatomic level involved (oropharyngeal vs. esophageal), types of food causing the symptoms (liquids, solids, or both), and whether the symptoms are intermittent or progressive. Associated pain, past gastrointestinal history, and family history are also helpful in determining the cause.

The examination should include a thorough evaluation of the head and neck and a detailed neurologic examination. The patient should be observed while swallowing. Difficulty in initiating the swallow, misdirection of the bolus with regurgitation or aspiration, and unusual posturing of the patient when swallowing should be noted. Many patients with neuromuscular disorders depend on gravity to swallow, and having the patient swallow in the prone position may be helpful in making the diagnosis.

Oropharyngeal Dysphagia

Oropharyngeal dysphagia is characterized as an inability or excessive delay in initiation of swallowing, aspiration of the ingestate, nasopharyngeal regurgitation, or residual ingestate within the pharyngeal cavity following a swallowing event. This may be caused by misdirection of the food bolus, pain, or sticking and complicated by multiple swallowing attempts. Symptoms may include discomfort or pain in the cervical region, coughing, choking, drooling, or nasal regurgitation.

Tongue weakness can result in oral regurgitation. Inability to seal the nasopharynx because of obstruction or muscular weakness can cause nasal regurgitation. Inefficient laryngeal elevation from muscular weakness or a fixed larynx can result in laryngotracheal aspiration. Delayed aspiration can occur with pharyngeal weakness and with pooling of food in the piriform recesses or in a diverticulum. Inability to contract the pharyngeal muscles is often compounded by failure of the cricopharyngeus to relax, which causes misdirection of the food bolus or necessitates repeated swallowing attempts. Inflammatory lesions of the tongue or oropharynx can result in odynophagia, which may impede swallowing.

BOX 79.1

Causes of Dysphagia

NEUROMUSCULAR

Vascular
Cerebrovascular accident

Immunologic
Dermatomyositis
Multiple sclerosis
Myasthenia gravis
Polymyositis
Scleroderma

Infectious
Botulism
Diphtheria
Poliomyelitis
Rabies
Sydenham's chorea
Tetanus

Metabolic
Lead poisoning
Magnesium deficiency

Other
Alzheimer's disease
Amyotrophic lateral sclerosis
Brain tumor
Depression
Diabetic neuropathy
Familial dysautonomia
Metabolic myopathies (eg, thyrotoxicosis)
Muscular dystrophies
Parkinson's disease

OBSTRUCTIVE
Aortic aneurysm
Esophageal motility disorder (eg, achalasia, diffuse esophageal spasm, nutcracker esophagus)
Esophageal rings
Esophageal stricture
Esophageal webs
Esophagitis
Foreign bodies
Hypertrophic cervical spurs
Inflammatory lesions
Left atrial enlargement
Mediastinal mass
Neoplasm
Thyroid enlargement
Vascular anomalies (eg, enlarged aorta, aberrant subclavian artery)
Zenker's diverticulum

OTHER
Alcoholism
Decreased saliva production (Sjögren's syndrome, postirradiation)
Diabetes
Functional
Gastroesophageal reflux disease
Postoperative

Esophageal Dysphagia

Dysphagia from upper esophageal lesions is usually perceived 2 to 4 seconds after the initiation of swallowing. Dysphagia that the patient localizes to the substernal or retrosternal area may be anatomically accurate, but localization to the neck may be referred from anywhere in the esophagus.

Dysphagia is the most common presenting symptom of achalasia and usually begins insidiously, with equal frequency for solids and liquids. Patients may report that maneuvers that increase esophageal pressure (eg, raising arms above the head, standing erect with back straight) help pass the food. Odynophagia from esophageal spasm may also be seen early in the course of achalasia. The symptoms are often worse with rapid eating and during periods of stress. The patient may also report chest pain as a symptom. As dilation occurs above the sphincter, retention of undigested food in the esophagus occurs, and the patient may be aware of gurgling while eating. Regurgitation of the undigested material can occur after a meal, prompting consideration of the diagnosis of an eating disorder, or with changes in position or vigorous exercise. The regurgitated food usually has no acid taste unless bacterial contamination causes fermentation of the undigested food. Laryngotracheal aspiration may occur, especially at night, and may cause nocturnal coughing. The physical examination is usually unremarkable, except for weight loss. Radiographically, a dilated esophagus is seen proximal to a narrowed gastroesophageal junction that has a beaklike appearance.

Esophageal spasm may be precipitated by swallowing very hot or cold liquids. Symptoms include chest pain, dysphagia, or both. Manometrically, simultaneous prolonged strong esophageal contractions are noted to be interspersed over normal peristaltic waves.

If a barium swallow is performed during a spasm, findings such as corkscrewing, or curling, of the esophagus may be noted.

Differential Diagnosis

The differential diagnosis of esophageal dysphagia includes acute coronary syndrome (ACS). Substernal chest pain is the main symptom in 80% to 90% of patients with esophageal motility disorders. The chest pain can be similar to angina, described as crushing or squeezing, with patterns of radiation similar to those of cardiac chest pain. Nitroglycerin may also relieve the pain of spasm, further confusing the picture.

Symptoms that suggest an esophageal cause of chest pain are pain that is prolonged and nonexertional, pain that interrupts sleep, pain related to meals, relief with antacids, and presence of other symptoms of esophageal disease, such as heartburn, dysphagia, or regurgitation. Because of considerable overlap in symptoms, a cardiac diagnosis must be excluded before attributing chest pain to an esophageal cause.

Diagnostic Testing

The history and physical examination direct the need for testing. Nasopharyngoscopy is used to assess for upper structural abnormalities The decision and timing of swallowing studies (eg, video esophagography), barium swallows, manometry, and impedance monitoring are best coordinated with consultants. These studies are rarely indicated in the emergency department (ED). However, patients who are unable to swallow safely or maintain adequate hydration should be admitted for further evaluation.

Management

Achalasia is the only motility disorder for which reasonably good studies support specific treatment. Pharmacologic therapy is directed at decreasing the tone of the LES. Nitrates and calcium channel blockers have been tried, but adverse effects limit their usefulness. Other therapies used with some degree of success have included botulinum toxin injection, pneumatic dilation, and surgical intervention.

Medical therapy for esophageal motility disorders is limited, and clinical results are usually minimal. Anticholinergic drugs such as hyoscyamine sulfate or dicyclomine have been used because they decrease the amplitude of esophageal peristalsis and LES pressure. However, because these drugs delay gastric emptying and decrease esophageal peristalsis, they may exacerbate reflux symptoms. Other therapies include the use of calcium channel blockers, which decrease LES pressure and amplitude of esophageal contractions.

Disposition

Patients at risk of aspiration or who are unable to hydrate are candidates for hospital admission. Otherwise, prompt outpatient evaluation by a gastroenterologist is indicated.

FOREIGN BODIES

Principles

Background

Patients with esophageal foreign bodies are classified into four major groups: (1) pediatric patients; (2) psychiatric patients and prisoners; (3) patients with underlying esophageal disease; and (4) edentulous adults. Pediatric patients account for more than 75% of cases, with the peak incidence occurring in those between the ages of 18 and 48 months. Swallowing coins accounts for most cases of pediatric ingestion, whereas most adult impactions involve food, particularly meat and bones. Patients with structural abnormalities of the esophagus are at greater risk for foreign body impaction. Edentulous adults are also at increased risk because of impaired oral sensation, which may contribute to their risk of accidental ingestion of the dental prosthesis.

Anatomy and Physiology

The esophagus begins in the hypopharynx, approximately at the level of the cricoid cartilage. On either side of this cephalad slit are the piriform recesses, which are blind pouches that may occasionally harbor a foreign body. There are four natural areas of narrowing where most foreign bodies become entrapped—at the cricopharyngeus muscle (upper esophageal sphincter [UES]), aortic arch, left mainstem bronchus, and LES at the diaphragmatic hiatus. Pediatric entrapment occurs primarily at the level of the cricopharyngeus, whereas adult entrapment occurs mainly at the UES (Fig. 79.1).

The esophagus comprises two main bands of muscle, an inner circular layer and outer longitudinal layer. The resting tone of these muscles causes the inner epithelium to fold in on itself, effectively obliterating the lumen. Elastic fibers enable the esophageal lumen to expand and allow passage of a food bolus. The upper third of the esophagus, including the cricopharyngeus muscle, contains striated muscle to allow for the voluntary initiation of swallowing. The middle portion of the esophagus is a mixture of skeletal and smooth muscle, and the distal third is composed only of smooth muscle. Although it is relatively fixed at its origin, the esophagus becomes mobile as it traverses the mediastinum and can be easily displaced by adjacent structures. An enlarged left atrium or ventricle, goiter, or mediastinal tumor may cause enough displacement of the esophagus to impede the passage of a food bolus or foreign body.

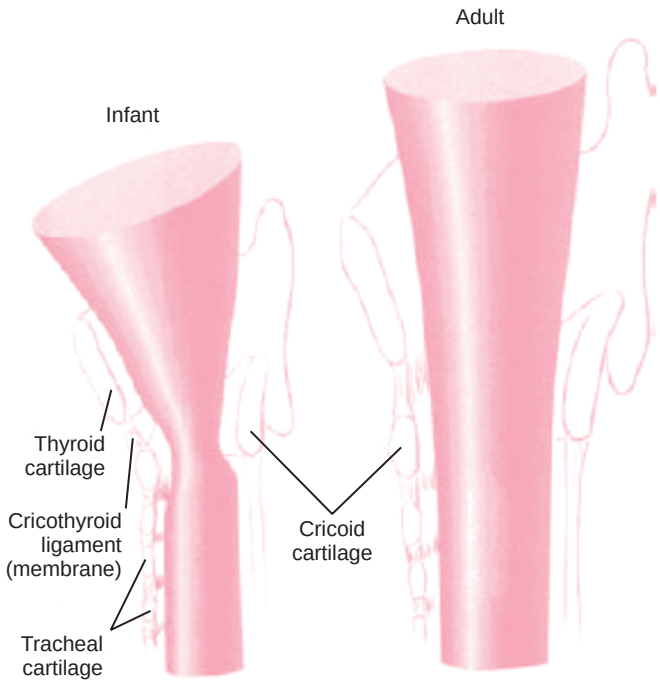

Fig. 79.1. Anatomic differences between infant and adult airways.

Pathophysiology

Although obstruction may occur in a patient with a normal esophagus, preexisting structural abnormalities such as strictures (peptic or malignant), distal esophageal mucosal rings, or eosinophilic esophagitis are identified in almost 90% of patients with an esophageal obstruction. Schatzki's ring is a specific type of mucosal ring present in 15% of the population and characterized by a fibrous, diaphragm-like stricture near the gastroesophageal junction.

Clinical Features

Patients with an esophageal obstruction have a wide range of symptoms that typically begin minutes to hours after the ingestion. Most adults are able to describe the precipitating event and commonly complain of dysphagia, odynophagia (painful swallowing), and neck or chest pain. Patients are typically able to localize retained foreign bodies due to somatic innervation of the upper esophagus. In contrast, entrapment in the lower esophagus causes more visceral-type chest and epigastric discomfort. The obstruction may be partial or complete. The patient with complete obstruction is unable to swallow oral secretions and may be violently retching in an attempt to regurgitate the obstructing bolus. Large proximal impactions can impinge on the trachea, leading to airway compromise that manifests as choking, stridor, or cough.

Pediatric patients are often brought to the ED after a witnessed ingestion. However, up to 35% of children with proven esophageal foreign body impactions are asymptomatic at the time of presentation. Symptoms that should prompt consideration of unwitnessed foreign body ingestion include fever, wheezing, stridor, rhonchi, and poor feeding.

A so-called café coronary, which is a proximal esophageal obstruction caused by food (usually an unchewed piece of meat) is characterized by sudden cyanosis and collapse as a result of airway obstruction. Similarly, steakhouse syndrome results when a large piece of food, usually improperly chewed, is swallowed and causes esophageal obstruction in the distal esophagus.

After eating fish, patients often present to the ED with sharp throat pain and concern about swallowing a fish bone. Despite the discomfort and concern of a retained fish bone foreign body, this rarely results in esophageal obstruction.

Differential Diagnosis

Esophageal foreign bodies should be distinguished from those in the airway. This distinction can be especially difficult in small children because respiratory symptoms may be the only clue about the esophageal foreign body, which may result in tracheal compression. Patients with esophageal obstruction may have retrosternal pain that can appear similar to that of an ischemic ACS. The presence of odynophagia suggests an underlying mucosal lesion such as an abrasion, laceration, or perforation.

Diagnostic Testing

In most cases, the patient's history will be all that is necessary to confirm the diagnosis and begin therapeutic intervention. Imaging studies may be needed in unknown or equivocal cases or in patients who are unable to give a history. Anteroposterior (AP) and lateral radiographs of the neck, chest, and abdomen are indicated when a radiopaque foreign body is suspected. Flat objects in the esophagus such as coins or button batteries typically orient in the coronal plane and appear as a circular object on an AP projection (Fig. 79.2). Button batteries can be differentiated from coins by a characteristic radiographic double-density appearance. Small bones or radiopaque objects may occasionally be visualized. Radiographs are unreliable for detecting a fish bone.

Nasopharyngoscopy is useful in differentiating a retained foreign body from a mucosal abrasion. In the vast majority of these patients, no fish bone is identified. Air in the tissues may be present if perforation has occurred. However, failure to demonstrate a foreign body on radiographs does not rule out its presence. Persistent or concerning symptoms in a patient without evidence of a radiographic foreign body can be further evaluated by laryngoscopy and endoscopy.

Contrast studies with barium or Gastrografin are rarely performed to evaluate for a foreign body because they present a risk for aspiration and can obscure visualization if subsequent endoscopy is necessary. Computed tomography (CT) may be used in equivocal cases to identify and localize foreign bodies before endoscopy. CT is more sensitive than radiography for identifying foreign bodies, including chicken or fish bones and other nonorganic objects. CT scans have the additional value of visualizing changes associated with perforation in the surrounding tissues.

Management

Treatment for esophageal foreign bodies depends on the type and location of the object and clinical status of the patient. Flexible endoscopy using procedural sedation is recommended in most cases of complete esophageal obstruction, because rigid endoscopy requires general anesthesia and has a higher complication rate.

Urgent intervention is indicated for button batteries, large or sharp objects, coins lodged in the proximal esophagus, impactions that impair the handling of secretions, and food boluses causing signs of high-grade esophageal obstruction. Factors associated with a risk of complications included a longer duration of impaction, bone foreign bodies, and larger foreign bodies.

Although it is acceptable to delay endoscopy briefly in stable patients without high-grade obstruction to allow possible spontaneous passage, the American Society for Gastrointestinal Endoscopy has recommended that food boluses causing incomplete obstruction be removed within 24 hours. Any object remaining in

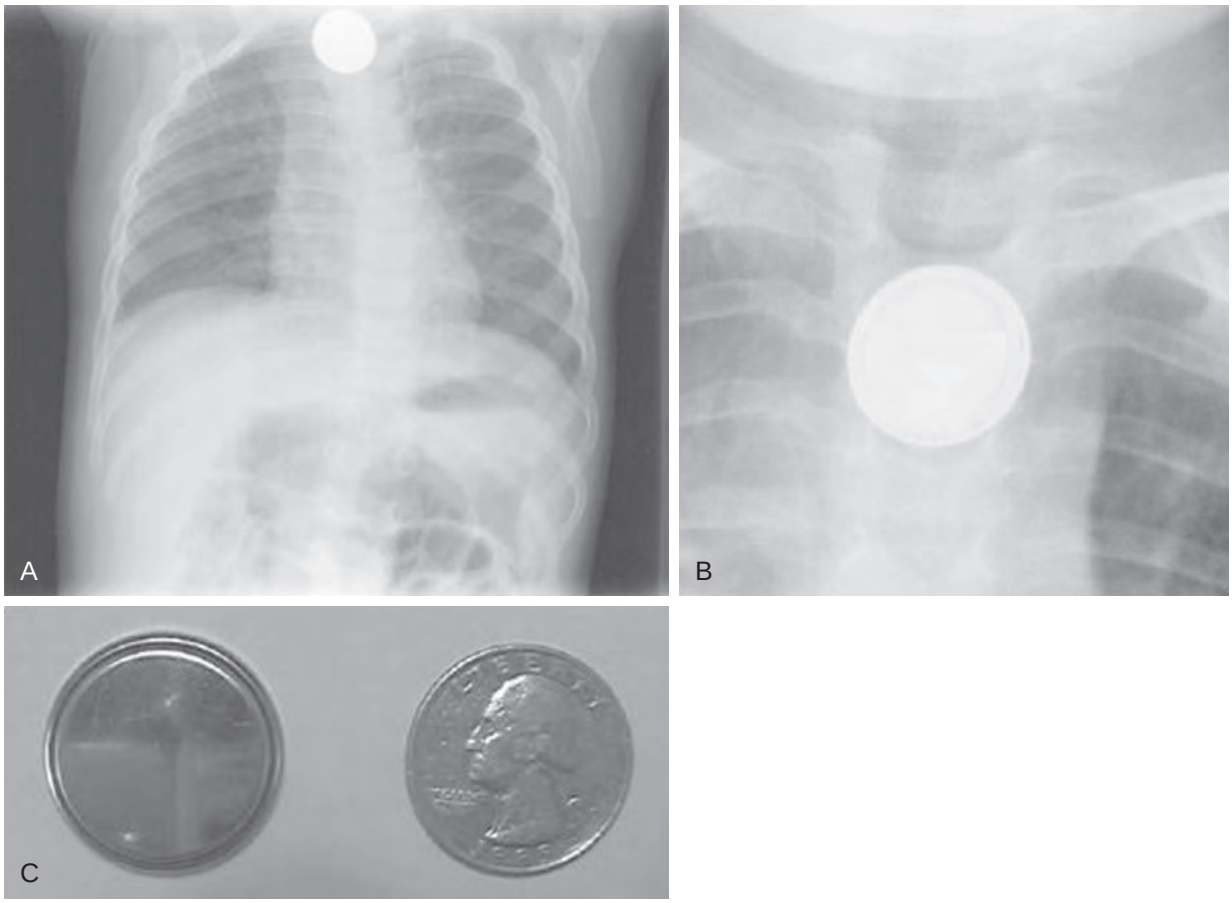

Fig. 79.2. Appearance of coin and button battery foreign body on x-ray. **A,** Coin in the upper esophagus. **B,** Appearance of button battery on x-ray. **C,** Frontal comparison of coin and button battery.

the esophagus for more than 24 hours carries a higher risk of complications, including perforation, aortoenteric fistula, tracheoesophageal fistula, and abscess. These complications may occur up to years after the ingestion. Follow-up endoscopic evaluation after an esophageal obstruction is necessary to rule out underlying pathologic conditions.

Upper Esophagus

Oropharyngeal foreign bodies can often be removed with a Kelly clamp or Magill forceps under direct visualization. Smooth upper esophageal foreign bodies such as coins can often be removed with a Foley catheter. This procedure requires an experienced clinician, cooperative patient, and fluoroscopic guidance. The patient is placed in a prone position, and the catheter is passed into the esophagus past the point of the foreign body impaction. The balloon is then inflated and the catheter withdrawn, pulling the foreign body with it. The literature reports that up to 80% of foreign bodies are successfully removed with this technique, and an additional 8% advance into the stomach. Failure rates are highest with infants younger than 1 year. Controversy exists regarding the safety of this technique because there is no direct control of the foreign body. However, large studies have shown complication rates to be less than 1% when patients are carefully chosen.

Foley catheter removal should not be used for a foreign body that has been impacted for more than 1 week, for objects that are not smooth, for patients with radiographic evidence of esophageal perforation, or for patients with any underlying structural esophageal abnormalities. This technique has a significant economic advantage when compared with the costs of general anesthesia in an operating room for the performance of rigid endoscopy.

Another technique is bougienage, which has been shown to be safe and effective in coin removal. In this technique, an esophageal dilator is passed through the mouth into the esophagus to advance the coin into the stomach; the dilator is then quickly removed. In a large study, this procedure took less than 5 seconds to perform and was successful in 95% of cases, with no serious complications.

Lower Esophagus

Lower esophageal obstruction is usually the result of an impacted food bolus. Anecdotally, intravenous (IV) administration of 1 mg of glucagon, up to a total of 2 mg, can cause enough relaxation of the esophageal smooth muscle to allow passage of a food bolus into the lower esophagus. However, the results of studies assessing the effectiveness of this treatment are mixed, and the only double-blind, placebo-controlled study found it to be ineffective. Moreover, glucagon can cause vomiting, which can increase the risk of aspiration or esophageal perforation. Based on lack of evidence and the potential risks, we do not recommend using glucagon in the management of esophageal foreign bodies. IV benzodiazepines have anecdotally been used as a first-line approach for stable patients with a meat impaction, but the evidence supporting their benefit is sparse and suggests that their effectiveness is not better than a placebo.

Small studies have examined the role of effervescent agents in treating food boluses. They have shown no clear evidence of benefit, and there is a theoretic potential of inducing perforation

of a possibly ischemic distal esophagus in cases of a complete obstruction. Similarly, the use of meat tenderizer (papain) to soften a food bolus is potentially dangerous and should not be used.

Endoscopy should be performed immediately for patients experiencing distress and for children with impaction of an alkaline button battery. Button batteries lodged in the esophagus can cause severe tissue damage in just 2 hours. Damage is primarily related to localized corrosive effects and occurs by three main mechanisms—leakage of an alkaline electrolyte, pressure necrosis, and generation of an external current that causes electrolysis of tissue fluids, thus generating hydroxide at the battery's negative pole. Larger batteries carry a greater risk of impaction and leakage. Delayed complications include esophageal perforation, tracheoesophageal fistula, esophageal strictures, and exsanguination after the development of a fistula with a major blood vessel. In a review of over 8000 battery ingestions that were reported to the National Battery Ingestion Hotline, outcomes have significantly worsened over the past decade. This is primarily attributable to the newer 20-mm-diameter lithium cell batteries that now account for 92% of fatal ingestions.

Batteries that pass into the stomach should be followed radiographically and clinically to ensure passage. Assistance with the management of a patient with button battery ingestion can be obtained through the National Button Battery Ingestion Hotline (1-202-625-3333) or at www.poison.org/prevent/battery.asp.

Stomach

Conservative outpatient management is appropriate for the vast majority of foreign bodies that have entered the stomach. However, certain foreign bodies that pass into the stomach still require endoscopic retrieval. Objects longer than 5 cm or wider than 2.5 cm in diameter (eg, toothbrushes, spoons) rarely pass the duodenum. All sharp and pointed foreign bodies (eg, toothpicks, bones) should be removed before they pass out of the stomach because there is a risk of intestinal perforation. Smaller objects that pass into the stomach can be followed with stool inspections and serial radiographs, if necessary, to confirm passage. Surgical removal should be considered for objects that remain in the stomach for more than 3 to 4 weeks or that remain in the same intestinal location for more than 1 week.

Disposition

The patient with an esophageal or stomach foreign body requires a gastroenterology consult and consideration for upper endoscopy for foreign body removal. The patient should not be discharged to home until the foreign body has been removed or deemed safe to allow transit through the intestines. Patients who undergo endoscopy should be observed until awake from sedation and able to tolerate oral intake. These patients should be discharged with a proton pump inhibitor and plan for repeat upper endoscopy to identify potential structural abnormalities. If no foreign body is found, and the patient is able to swallow liquids, she or he may be safely discharged, with outpatient follow-up.

ESOPHAGEAL PERFORATION

Principles

Background

Esophageal perforation can result from a rapid increase in intraesophageal pressure related to forceful vomiting or any Valsalva-like maneuver, including childbirth, coughing, and heavy lifting. Iatrogenic esophageal perforation can result during manipulation of the esophagus, such as during endoscopy, nasogastric tube placement, or endotracheal intubation. Other causes of perforation include foreign body ingestion, caustic substance ingestion, severe esophagitis, carcinoma, and direct injury related to blunt or penetrating trauma. Spontaneous rupture occurs because of a rapid increase in intraluminal esophageal pressure through a patent LES.

Anatomy and Physiology

More than 90% of spontaneous esophageal ruptures occur in the distal esophagus. In contrast, rupture resulting from blunt trauma to the neck or thorax usually occurs in the proximal and middle thirds of the esophagus. Most iatrogenic injuries occur at the pharyngoesophageal junction because the wall in this area is thin, there is no serosal layer to reinforce it, and force is frequently used to pass the tube beyond the level of the cricopharyngeus. Another site of frequent iatrogenic injury is the esophagogastric junction. In this area, the esophagus curves anteriorly and to the left as it enters the abdomen, and an endoscope has a greater likelihood of perforating the posterior wall. This usually occurs during therapeutic dilation for strictures or achalasia.

Clinical Features

Clinical presentations of esophageal perforation vary and depend on the cause, location, size, and degree of contamination. Symptoms related to iatrogenic perforation may not appear until several hours after the procedure. Patients with an upper esophageal perforation usually have neck or chest pain, dysphagia, respiratory distress, and fever. Odynophagia, nausea, vomiting, hoarseness, and/or aphonia may also result. Mackler's triad of subcutaneous emphysema, chest pain, and vomiting is considered pathognomonic for spontaneous esophageal rupture. However, the complete triad is seen in less than 50% of cases.

Patients with perforation of the lower esophagus may have abdominal pain, pneumothorax, hydropneumothorax, and pneumomediastinum. The pain may radiate to the back, left side of the chest, and left or both shoulders. Physical findings include epigastric or generalized abdominal tenderness, often with involuntary guarding and rigidity. Up to 30% of patients develop mediastinal or cervical emphysema, which may be noted by crepitus on palpation or by the pathognomonic Hamman's sign, with a crunching sound heard during auscultation. Patients with severe mediastinitis may be in fulminant shock.

Differential Diagnosis

Misdiagnosis occurs in more than 50% of patients with esophageal perforation or rupture because of the broad differential diagnosis of chest and abdominal pain. This includes pulmonary embolism, acute myocardial infarction, aortic dissection, perforated ulcer, pneumothorax, lung abscess, pericarditis, and pancreatitis. Esophageal perforations should be diagnosed as soon as possible because the morbidity and mortality associated with unrecognized perforations dramatically increase with time.

Diagnostic Testing

Chest and upright abdominal radiography is generally the first diagnostic study performed in patients suspected of an esophageal perforation. Radiographic abnormalities may be detected in up to 90% of patients with esophageal perforation (Fig. 79.3). Patients with upper esophageal injuries commonly have chest radiographs that show pneumomediastinum alone or a right-sided pleural effusion, whereas patients with distal esophageal perforations

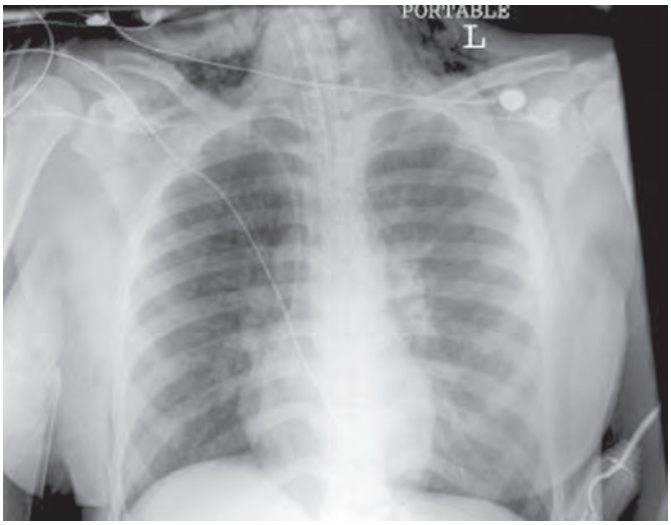

Fig. 79.3. Pneumomediastinum due to esophageal perforation following forceful vomiting.

typically have a left-sided effusion. Other radiographic abnormalities include subcutaneous emphysema, mediastinal widening, and pulmonary infiltrates. These radiographic changes are often not present in the first few hours after perforation, so a normal early radiograph should not be used to exclude the possibility of esophageal perforation.

Patients with possible perforation should undergo contrast radiographic studies. Barium sulfate is superior for identifying small perforations, but may incite an inflammatory response in tissues. Water-soluble agents (eg, Gastrografin) may be safer but they are less dense and may not demonstrate the abnormality. In addition, pneumonitis may result if these agents are aspirated because of their hypertonicity. We recommend an initial attempt with a water-soluble agent for patients who are not at risk for aspiration. If a perforation is not identified and suspicion is high, a second study with barium is recommended.

CT of the chest may be considered if a contrast study does not demonstrate a clinically suspected perforation. It can also be used in patients who are intubated or cannot complete esophagography. Findings such as mediastinal air, extraluminal contrast material, or fluid collections or abscesses adjacent to the esophagus confirm a perforation. CT also allows for the evaluation of other adjacent areas that may suggest an alternative diagnosis.

Flexible esophageal endoscopy is useful in directly visualizing the perforation, especially in cases of penetrating external trauma, with a sensitivity of 100% and specificity of 83%. This technique is not recommended for other situations because insufflation could potentially enlarge a minimal transmural opening.

Laboratory studies are not usually helpful soon after a perforation, although leukocytosis may be noted.

Management

Clinically unstable patients with esophageal perforation require rapid resuscitation and treatment. Broad-spectrum IV antibiotics should be initiated early; we recommend vancomycin 15 mg/kg and piperacillin-tazobactam, 3.375 g. Patients should receive nothing by mouth (NPO), and early surgical consultation is warranted. Treatment within the first 24 hours has been found to improve survival when compared to delayed treatment.

There is evidence that some iatrogenic perforations in select patients at low risk can be managed conservatively. These patients must be clinically stable, have minimal symptoms, and have no signs of sepsis. Additionally, they must have a perforation contained within the neck, and a surgeon must be available in the event of decompensation. Operative management in these patients has been reported to result in worse outcomes versus nonoperative management (ie, close monitoring, NPO, broad-spectrum antibiotics, and parenteral nutrition). Other so-called palliative interventions, including endoscopic stent placement, drainage gastrostomy, feeding jejunostomy, and tube thoracostomy, have become more common.

Disposition

Patients with esophageal perforation are at risk for rapid deterioration and require close monitoring in a hospital setting. Early surgical consultation is recommended.

ESOPHAGITIS

Principles

Esophagitis is an inflammation of the esophagus. The most common cause is gastroesophageal reflux disease (GERD). Other important causes include eosinophilic infiltration, infection, foreign body or toxic ingestion, and radiation. Chapter 148 discusses esophagitis caused by caustic substance ingestion.

Gastroesophageal Reflux Disease

Asymptomatic reflux of gastric contents from the stomach into the esophagus occurs in most people several times a day as a normal physiologic phenomenon. GERD occurs when reflux becomes symptomatic or causes histopathologic alterations in the upper gastrointestinal (GI) or respiratory tract. In the United States, symptomatic reflux in the form of heartburn occurs daily in 7% of adults, weekly in 14%, and monthly in 40%.

The primary mechanism that enables reflux of gastric contents into the esophagus is inappropriate relaxation of the LES. This can occur because of general hypotension of the LES, increased intra-abdominal pressure, or transient LES relaxations. Multiple risk factors can decrease LES pressure and lead to reflux, including medications (eg, nitrates, calcium channel blockers, anticholinergics, albuterol), fatty meals, and chocolate. Other mechanisms that may contribute to GERD include esophageal motility abnormalities, increased intragastric pressure (eg, obesity, pregnancy), acid hypersecretion, gastric outlet obstruction, and conditions that cause delayed gastric emptying (eg, gastroparesis, neuromuscular disease).

Repetitive exposure to acid can lead to changes in the esophageal mucosa. Continued reflux can lead to thinning of the normal stratified squamous epithelial layer. With the development of esophagitis, an inflammatory response occurs in the mucosa and submucosa, with infiltration of polymorphonuclear leukocytes. The inflammatory response is the result of chemical irritation of the esophageal mucosa from reflux of gastric acid, pepsin, and bile acids. Both acid and alkaline refluxes produce the same pathologic changes. Continued exposure can lead to further endoscopically visible changes of erosion, ulceration, and scarring. Ultimately, stricture formation may result. The most severe histologic consequence of GERD is replacement of the normal stratified squamous epithelium with metaplastic columnar epithelium in a condition termed *Barrett's metaplasia.* In patients with reflux undergoing endoscopy, approximately 10% to 15% are found to have Barrett's esophagus. There is a strong correlation between the development of Barrett's metaplasia and adenocarcinoma of the esophagus.

Eosinophilic Esophagitis

Eosinophilic esophagitis results from an eosinophilic infiltration within the esophageal mucosa or deeper tissues. Initially thought to be a disease of children, it is being diagnosed in adults with increasing frequency. The cause is unknown, although there is an association with food allergens, especially in the younger age group. More than 50% of patients have associated atopic disorders, such as asthma or eczema. The criteria necessary for diagnosis of eosinophilic esophagitis are clinical symptoms of esophageal dysfunction, more than 15 eosinophils in one high-power field on esophageal biopsy, and lack of responsiveness to high-dose proton pump inhibitors (PPIs).

Infectious Esophagitis

Esophageal infections primarily occur in immunocompromised hosts. When they occur in healthy patients, there is usually an underlying esophageal abnormality or local area of immune compromise, as might occur with the use of inhaled steroids. Iatrogenic alterations in host defenses through the use of immunosuppressive agents, potent chemotherapeutic agents, and broad-spectrum antibiotics can predispose an individual to the development of an esophageal infection. Other systemic diseases that weaken immunologic defenses in otherwise normal hosts can predispose the esophagus to infection, including diabetes mellitus, alcoholism, underlying malignancy, use of corticosteroids, and advanced age. The *Candida* species (primarily *Candida albicans*) are the most common esophageal pathogens.

Human immunodeficiency virus (HIV) is a risk factor for infectious esophagitis, but rates have decreased since the advent of highly active antiretroviral therapy (HAART). Patients with acute HIV seroconversion syndrome that occurs 2 to 3 weeks after primary exposure to HIV can develop esophageal ulcerations and severe odynophagia.

As empirical antifungal prophylaxis in immunosuppressive states has become more common, viral esophagitis has become more prominent. Herpes simplex virus 1 (HSV-1) and cytomegalovirus (CMV) are the most common viral pathogens. Human papillomavirus has been implicated as well. Bacteria, mycobacteria, other fungi, and parasitic organisms such as *Trypanosoma cruzi*, *Cryptosporidium,* and *Pneumocystis* are uncommon causes of infectious esophagitis and are usually diagnosed by culture or biopsy.

Pill Esophagitis

The exact incidence of pill esophagitis is unknown because most cases are unrecognized and therefore unreported. The condition results when a pill or capsule fails to pass into the stomach and remains in contact with the esophageal mucosa for a prolonged period. This results in inflammation and injury of the esophageal mucosa.

Pill esophagitis has been reported in all age groups. Predisposing factors include advanced age, decreased esophageal motility, and extrinsic compression. Large pills are more likely to be retained because these are e coated with gelatin. Pills can stick to a normal esophagus, especially when taken without water or by a patient in the supine position. Any area of the esophagus can be affected, although sites of natural compression may be more susceptible. Sustained-release compounds may be more damaging than standard preparations. Injury can range from minor irritation to frank ulceration, hemorrhage and, ultimately, stricture formation. Some of the more common offending medications include antibiotics (especially the tetracycline family) and antivirals, aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs), potassium chloride, quinidine, ferrous sulfate, alendronate, and pamidronate.

Radiation-Induced Esophagitis

Patients undergoing radiation treatment for underlying malignancy may develop esophagitis. The degree of injury is related to the total dose of radiation received. The mucosa becomes inflamed and friable. Agents used during sclerotherapy can also cause esophagitis.

Clinical Features

Esophagitis, regardless of cause, usually manifests with dysphagia or odynophagia. Chest pain is frequently present, and esophageal bleeding can occur, ranging from localized oozing as a result of inflammation to frank hemorrhage. Ulceration and perforation can result in mediastinitis.

Gastroesophageal Reflux Disease

The most common clinical manifestation of GERD is heartburn, defined as a burning sensation that begins in the subxiphoid area and radiates toward the neck. Reflux may also cause a dull discomfort, localized pressure, or severe squeezing pain across the middle of the chest. The patient may appear comfortable or may have associated diaphoresis, pallor, nausea, and vomiting, leading to the consideration of an ischemic cardiac syndrome. A detailed history is often helpful in differentiating cardiac chest pain from reflux, although the distinction may not be possible in the ED.

Other symptoms of GERD include regurgitation (spontaneous appearance of an acid or bitter material in the mouth or pharynx) and water brash (a vagally mediated hypersalivation response that may produce as much as 10 mL of saliva in 1 minute). Dysphagia and odynophagia may also be presenting complaints and may be associated with more serious complications.

Any condition or agent that decreases LES pressure, decreases esophageal motility, or prolongs gastric emptying predisposes patients to reflux (Box 79.2). Body positions that place the

BOX 79.2

Agents and Conditions Related to Gastroesophageal Reflux

DECREASED LOWER ESOPHAGEAL SPHINCTER PRESSURE
Anticholinergic drugs
Benzodiazepines
Caffeine
Calcium channel blockers
Chocolate
Estrogen
Ethanol
Fatty foods
Nicotine
Nitrates
Peppermint
Pregnancy
Progesterone

DECREASED ESOPHAGEAL MOTILITY
Achalasia
Diabetes mellitus
Scleroderma

INCREASED GASTRIC EMPTYING TIME
Anticholinergic drugs
Diabetic gastroparesis
Gastric outlet obstruction

esophagus dependent to the stomach or increase intra-abdominal pressure tend to precipitate reflux. Stooping, bending, leaning forward, performing Valsalva-type maneuvers, and assuming a supine position are common precipitants.

GERD can manifest itself in extraesophageal locations. Reflux-induced asthma may result from microaspiration of gastric contents into the lung or activation of a vagal reflex arc from the gut to the lung. GERD has been identified in up to 80% of asthmatic patients based on pH probe monitoring, but up to 50% of these patients have no reflux symptoms. However, studies have shown no benefit in treating poorly controlled asthmatic patients with PPIs in the absence of GERD symptoms.

If the refluxate reaches the proximal esophagus, otolaryngologic manifestations may result, even in the absence of esophageal symptoms. Reflux can cause hoarseness, chronic laryngitis, refractory sore throat, and globus sensation. Refluxate that enters the oropharynx may lead to gingivitis, halitosis, or dental problems, such as erosion of the lingual sides of the teeth as a result of acid exposure. Otalgia and hiccups can also result from reflux.

Eosinophilic Esophagitis

The most common symptom of eosinophilic esophagitis in adults is solid food dysphagia. In addition to dysphagia, patient may presents with nausea and vomiting, food impaction, and/or heartburn. Children may presents with more vague symptoms, such as vomiting, regurgitation, nausea, epigastric or abdominal pain, chest pain, water brash, and decreased appetite. Children with eosinophilic esophagitis have a higher rate of atopy, immunoglobulin E (IgE)–mediated food allergies, and family history of allergies. This diagnosis should be considered in patients who have severe GERD symptoms despite the use of acid suppression medications and in patients with chronic unexplained dysphagia or recurrent esophageal food impaction. The diagnosis is confirmed by biopsy during endoscopy.

Infectious Esophagitis

Infectious esophagitis usually causes severe odynophagia. Dysphagia of solids and liquids may be present. Pain may be so severe that the patient refuses to eat or drink. Heartburn and nausea may be presenting symptoms, but the pain is not improved by antacid therapy. Immunocompromised patients may have fever or bleeding, without dysphagia or odynophagia. Many patients with esophageal candidiasis also have oral candidiasis but it is possible only to have esophageal manifestations, which makes it more difficult to diagnose.

Pill Esophagitis

Patients with pill esophagitis commonly present with chest pain (72%), odynophagia (39%), and dysphagia (30%). Most patients have no prior history of esophageal disease and experience sudden onset of pain worsened by swallowing. Dysphagia may be present. Although some patients complain that a pill has become stuck, the history of pill ingestion can be difficult to obtain because symptoms may begin hours after the offending pill was taken. Atypical presentations include a burning type of pain, suggesting GERD as the cause.

Differential Diagnosis

Acute cardiac ischemia should be considered as a possible cause of chest pain in adults. It is difficult to differentiate between ischemic coronary disease and GERD based only on features of the pain, location, or radiation. Radiation of pain can be a feature in esophageal and cardiac chest pain. The occurrence of reflux after meals is another important feature in the history. A feeling of fullness after meals occurs commonly in reflux and is helpful in differentiating it from coronary artery disease.

Relief of chest pain from reflux by antacids is a key point in the history; however, one should not place too much weight on this point as evidence against a cardiac cause. The relief is often short-lived, and pain may recur in a short time. Esophageal pain may be provoked by swallowing. Other GI disorders such as gastritis, esophagitis, peptic ulcer disease (PUD), and biliary tract disease should be considered in the differential diagnosis.

Diagnostic Testing

GERD is a common problem, and additional diagnostic testing in the ED is rarely necessary, assuming that other, more serious causes of the patient's symptoms have been excluded. Patients with dysphagia, odynophagia, or bleeding should be referred for further study.

Endoscopy can be used to evaluate pathologic changes, but there is no direct correlation between symptoms and endoscopic features. With infectious esophagitis, direct visualization may reveal characteristic signs of infection, such as white plaques of *Candida* or herpetic vesicles. Definitive diagnosis can be made through brushings and biopsies. Radiographic studies are usually not helpful because the findings are nonspecific.

Management

Gastric Reflux

Lifestyle modification solely as an initial approach to GERD has little therapeutic benefit without concomitant medical management. Lifestyle modifications to reduce GERD symptoms include avoidance of foods that can precipitate reflux (eg, caffeine, alcohol, chocolate, fatty foods) and avoidance of acidic foods that can cause heartburn (eg, citrus products, spicy foods). In addition to these dietary changes, other behavioral modifications include weight loss, smoking cessation, elevation of the head of the bed, and avoidance of a recumbent position for several hours after eating. The only lifestyle recommendations that have evidence-based support are weight loss and head of bed elevation; however, others can be useful adjuncts in select patients.

The pharmacologic therapy of GERD includes agents that neutralize acids, decrease acid production, act on the LES or affect motility, and protect the mucosa. The most effective treatment for GERD is reduction of acid production. Many patients self-medicate with antacids, over-the-counter (OTC) type 2 histamine receptor (H_2)–receptor antagonists, or PPIs. A Cochrane systematic review has concluded that PPIs are more effective than H_2 blockers in eliminating symptoms and healing mucosal damage. However, H_2 blockers are an acceptable alternative for patients with mild to moderate GERD. These agents do not stop the reflux but reduce the potency of the refluxate. Choices of H_2 blockers and PPIs are listed in Tables 79.1 and 79.2. All these agents are generally regarded as safe and effective.

Another agent that may be of benefit in refractory cases of symptomatic esophageal reflux is sucralfate, which can be used with other agents such as PPIs and H_2 blockers. The dose is 1 g every 6 hours. Sucralfate is a mucosal protectant that binds to inflamed tissue to create a protective barrier. It blocks the diffusion of gastric acid and pepsin across esophageal mucosa and can limit the erosive action of pepsin and bile. It has limited side effects and can be safely used in pregnant women.

Prokinetic agents treat GERD by increasing LES pressure. They may also be used for patients whose symptoms suggest a superimposed motility disturbance (eg, regurgitation, choking, abdominal distention). In addition to improving the propulsive activity

TABLE 79.1

Summary of Histamine Receptor Antagonists

AGENT	GERD	PUD[a]
Cimetidine	800 mg bid or 400 mg qid	800 mg qhs or 400 mg bid
Famotidine	20 or 40 mg bid	40 mg qhs or 20 mg bid
Nizatidine	150 mg bid	300 mg qhs or 150 mg bid
Ranitidine	150 mg bid	300 mg qhs or 150 mg bid

GERD, gastroesophageal reflux disease; *PUD,* peptic ulcer disease.

[a]Maintenance dose for PUD is half the qhs dose.
GERD, Gastroesophageal reflux disease; *PUD,* peptic ulcer disease; *qhs,* at bedtime.

TABLE 79.2

Summary of Proton Pump Inhibitors[a]

AGENT	GERD	PUD OR NSAID-INDUCED ULCERS[b]
Esomeprazole	20 or 40 mg qd	40 mg PO qd
Lansoprazole	30 mg qd or 30 bid	30 mg PO qd
Omeprazole	20 mg qd or 20 bid	20 mg PO qd
Pantoprazole	40 mg qd or 40 bid	40 mg PO qd
Rabeprazole	20 mg qd or 20 bid	20 mg PO qd

[a]All doses should be administered before breakfast; second doses (when necessary) should be administered before the evening meal.
[b]Patients with duodenal ulcer should be treated for 4 weeks; patients with gastric ulcer should be treated for 8 weeks.
GERD, Gastroesophageal reflux disease; *NSAID,* nonsteroidal antiinflammatory drug; *PO,* orally; *PUD,* peptic ulcer disease.
Adapted from Wolfe MM, Sachs G: Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 118:S9–S31, 2000.

of the stomach and small and large intestines, the increase in esophageal peristalsis and LES tone is an effective therapy for reflux by improving the clearance of refluxate. Metoclopramide (10-mg dose) may be used for these patients, but its efficacy has not been conclusively demonstrated, and it can cause significant irreversible extrapyramidal side effects such as tardive dyskinesia.

Patients with clinically suggested GERD who do not improve with empirical therapy and those who are at high risk for complications should be referred to a gastroenterologist for confirmation of the diagnosis and follow-up care. In these cases, further diagnostic evaluation may be necessary. Patients who are intolerant of acid-suppressive medications may be candidates for surgical therapy with laparoscopic fundoplication. Less invasive endoscopic therapies include thermal ablation to narrow the esophagus at the LES, suturing to create a plication at the LES, and injection or implantation techniques to bulk up the LES.

Eosinophilic Esophagitis

These patients usually are seen after standard antireflux measures have failed or they have developed a food impaction. Once food impaction is eliminated as the presenting problem, empirical treatment by initiation of a daily PPI and referral to a gastroenterologist for urgent endoscopy is recommended. Untreated eosinophilic esophagitis can lead to esophageal remodeling and stricture formation in up to 40% of adult patients. Although consensus has not yet been reached regarding an optimal treatment regimen, success has been reported with the use of topical (ie, swallowed) corticosteroids. Pediatric studies have also shown efficacy of the use of oral viscous budesonide.

Infectious Esophagitis

For infectious esophagitis, therapy is directed at the causative organism. Patients with normal immune systems and mild cases of oropharyngeal candidiasis can be treated with clotrimazole troches (10 mg dissolved in the mouth, five times daily for 1 week) or nystatin (400,000–600,000 million units orally [PO] four to five times/day for 2 weeks). Patients with true esophageal candidiasis should be treated with fluconazole (400 mg as a loading dose and then 100–400 mg daily for 14 to 21 days). In patients unable to tolerate oral medication, fluconazole can be given by the IV route.

Herpes esophagitis is generally a self-limited process that resolves within 1 to 2 weeks. Immunocompromised patients should be treated with antivirals, such as acyclovir (400 mg PO, five times/day for 7–14 days, or 5–10 mg/kg IV tid for 7–14 days), famciclovir (500 mg PO, tid for 7–14 days), or valacyclovir (1 g tid for 7–14 days). For CMV, initial treatment can begin with ganciclovir (5 mg/kg IV bid for 2–3 weeks) or foscarnet (60 mg/kg IV tid or 90 mg/kg IV bid for 2–3 weeks).

Pill Esophagitis

If a patient with suspected pill esophagitis has persistent symptoms, endoscopy may be necessary. It also helps determine alternative causes. No data supports a specific treatment although, intuitively, antacid medication may prevent further erosion of damaged mucosa. Symptoms may take up to 6 weeks to resolve.

The best treatment for pill esophagitis is prevention. Patients should be instructed to drink at least 4 ounces of liquid with any pill. All medications should be taken when the patient is in an upright position, and he or she should remain upright for several minutes after medication ingestion. Patients with underlying esophageal abnormalities or who are bedridden should avoid the use of pills whenever practical.

Disposition

Treatment of esophagitis is largely symptom-based and supportive. Patients who cannot eat or drink because of injury to the esophagus should be admitted for IV fluid therapy. Treatment of GERD is directed at symptom management. GERD can be safely managed on an outpatient basis but ED disposition decisions are largely based on the ability to rule out other more serious causes of the patient's complaints, such as ischemic coronary disease. For infectious esophagitis, if the causative organism cannot be identified or the patient is severely debilitated, hospitalization may be required. In addition to therapy directed at the infecting organism, treatment with antacids, topical anesthetics, or sucralfate may provide symptomatic relief.

Patients discharged from the ED should receive appropriate follow-up with the relevant specialist (eg, gastroenterology, infectious disease).

GASTRITIS AND PEPTIC ULCER DISEASE

Principles

Background

Gastritis and PUD are often difficult to differentiate based on history alone. Strictly speaking, gastritis is a histologic diagnosis denoting inflammation of the gastric mucosa. Hence, the

diagnosis of gastritis can be made only by endoscopy and biopsy. However, it is common practice for clinicians to use the term *gastritis* to refer to symptoms of dyspepsia. To confuse the picture further, gastroenterologists frequently use the term to refer to the endoscopic finding of an edematous friable mucosa. However, without accompanying inflammation, this is more appropriately termed *gastropathy* rather than gastritis. This section considers gastritis and gastropathy together as one entity because the distinction has little importance to emergency care. Gastric and duodenal ulcers are usually grouped together as PUD because of the similarity in their pathogenesis and treatment.

Pathophysiology

The most common cause of gastritis is infection with *Helicobacter pylori.* Although most patients are asymptomatic at the time of initial exposure, acute infection with *H. pylori* can cause severe gastritis and PUD. The identification of *H. pylori* has dramatically shifted our notion of PUD from an acid-related to an infectious disease–mediated process.

H. pylori is a spiral, flagellated, gram-negative rod whose natural habitat is the human stomach, between the epithelial cell surface and overlying mucus. It is estimated that 70% to 80% of patients with duodenal ulcer and 60% to 70% of patients with gastric ulcer are infected with *H. pylori.* It is more prevalent in lower socioeconomic groups and in developing countries. It is probably spread by person to person by an oral-oral route, although the fecal-oral route and iatrogenic transmissions have also been hypothesized.

It is estimated that up to 40% of the US population is infected with *H. pylori.* It is found in people of all age groups, although infection is typically acquired during childhood. Its presence is believed to cause mucosal inflammation that disrupts the normal defense mechanisms and leads to ulceration. It also increases the risk of gastric carcinoma and, less often, lymphoma. Although there is a strong association between *H. pylori* and PUD, only 5% to 10% of infected patients develop ulcers. It is unclear what role environmental and host factors (eg, diet) play. It is now accepted that almost all non–NSAID-related ulcers are caused by *H. pylori*. Eradication of infection with *H. pylori* results in more rapid healing of ulcers, prevents relapse, and diminishes the rate of ulcer complications. It is also more cost-effective than chronic antisecretory therapy.

Suppurative gastritis, also known as acute phlegmonous gastritis, is a rare and often fatal disease that results from an acute bacterial infection of the stomach wall. *Streptococcus* bacteria species are involved in nearly 75% of all cases of suppurative gastritis. Patients usually have an underlying mucosal abnormality such as cancer, ulcer, or preexisting gastritis. Less common infectious causes of gastritis include mycobacterial, viral, parasitic, and fungal organisms.

Use of aspirin and other NSAIDs is the second most common cause of PUD. Up to 25% of chronic NSAID users develop ulcer disease, and 2% to 4% of these patients have serious complications, including perforation or bleeding. The cause of NSAID-related ulcers is suppression of gastric prostaglandin synthesis. Prostaglandins promote mucosal integrity by maintaining mucosal blood flow, promoting mucosal mucus and bicarbonate formation, and reducing mucosal acid secretion. It is believed that the inhibition of cyclooxygenase (COX) by NSAIDs leads to a diminished level of protective prostaglandins in the stomach. In addition, the antiplatelet aggregation effect of NSAIDs may increase the amount of bleeding associated with NSAID-induced ulcers.

NSAIDs differ in their ulcerogenic potential. Studies have shown a higher risk of upper GI bleeding with ketorolac and piroxicam, particularly if their use extends beyond 5 days. The COX-2–specific inhibitors (eg, celecoxib, rofecoxib, valdecoxib) were initially thought to have a better GI safety profile than traditional NSAIDs. However, further studies have refuted this belief and noted an increased risk of cardiovascular side effects, including myocardial infarction and stroke. As a result, rofecoxib (Vioxx) and valdecoxib (Bextra) were withdrawn from the market. Celecoxib (Celebrex) is still available in the United States as a treatment for arthritis and familial polyposis but has a black box warning regarding an increased incidence of GI side effects and increased cardiovascular risk (Box 79.3).

BOX 79.3

Risk of Gastrointestinal Complications From Nonsteroidal Antiinflammatory Drugs

HIGHEST RISK
Indomethacin (relative risk [RR], 2.25)
Naproxen (RR, 1.83)
Diclofenac (RR, 1.73)
Piroxicam (RR, 1.66)
Tenoxicam (RR, 1.43)
Ibuprofen (RR, 1.43)

LOWEST RISK
Meloxicam (RR, 1.24)

Patients older than 60 years, those with a prior history of an ulcer or hemorrhage, those receiving higher doses of NSAIDS, and patients concurrently taking glucocorticoids or anticoagulants are at higher risk for NSAID-induced gastroduodenal toxicity. These patients should be considered for ulcer prophylaxis with a PPI or misoprostol.

Other drugs with ulcerogenic potential include 5-fluorouracil, mycophenolate mofetil, and the bisphosphonates. Other drugs implicated in causing gastritis are potassium preparations and iron supplements. Gastritis can result from short- and long-term exposure to ethanol.

Any condition that causes hypovolemia or hypotension can lead to gastritis. Ulcer formation may ultimately result. This may be a major causative factor in the development of gastritis and upper GI bleeding in intensive care unit patients. Other causes of gastritis include radiation, autoimmune reactions, Crohn's disease, and sarcoidosis.

Many mechanisms can protect the gastric mucosa from the digestive effects of the hydrochloric acid, proteolytic enzymes, bile, and other deleterious substances to which it is exposed. Normally, a gastric mucosal barrier to intraluminal gastric acid is present and prevents the back-diffusion of hydrogen ions from the gastric lumen. Sodium ions are prevented from moving in the opposite direction. This ionic impermeability protects the gastric mucosa from gastric secretion–induced damage. Damage to the gastric mucosal barrier from any cause (Box 79.4) allows hydrogen ions and digestive enzymes to make contact with the gastric mucosa, leading to inflammation, bleeding, and potential ulceration.

H. pylori infection and use of NSAIDs account for the vast majority of PUD cases. Only 1% of PUD is caused by acid hypersecretion. Zollinger-Ellison syndrome is an acid hypersecretion syndrome caused by increased levels of circulating gastrin from gastrin-secreting tumors. The gastrin produced stimulates the parietal cells of the stomach to secrete more acid and causes parietal cell hyperplasia. Thus these patients have increased parietal cell mass and hypersecretion of acid, leading to ulcer formation.

PUD also occurs in infants and children. Infants with PUD usually demonstrate poor feeding, vomiting, or failure to thrive.

BOX 79.4

Substances and Conditions That Damage the Gastric Mucosal Barrier

Bile
Cigarette smoking
Ethanol
Glucocorticoids
Helicobacter pylori
Nonsteroidal antiinflammatory drugs
Pancreatic secretions
Shock conditions
Stress

Up to 25% of children have isolated hematemesis or melena as presenting signs. Toddlers and preschool children may have abdominal pain, vomiting, and bleeding. Of ulcers in this age group, 80% are stress ulcers associated with systemic illness such as sepsis, head trauma, burns, or sickle cell disease. Older children and adolescents usually have primary PUD, with presentations similar to those of adults.

Clinical Features

Acute gastritis and PUD may cause epigastric abdominal pain, nausea, and vomiting. By definition, gastritis or gastropathy cannot be diagnosed based on clinical features alone. However, a good clinical history such as recent NSAID use or alcohol ingestion in the setting of the epigastric burning pain supports a presumptive clinical diagnosis.

Patients with phlegmonous gastritis usually appear toxic. Patients with gastritis as a result of decreased mucosal blood flow may have symptoms of abdominal pain and upper GI bleeding in addition to those of their underlying disease. Complications of gastritis include perforation and gastric outlet obstruction.

The classic presenting symptom of PUD is epigastric pain described as burning or gnawing. However, up to 2% of patients with endoscopically proven PUD are asymptomatic. Patients may also have atypical symptoms, including pain in other areas of the abdomen, chest, or back, and may describe the pain as vague or crampy. Associated symptoms include fullness, nausea, early satiety, and bloating. Pain usually occurs 2 to 5 hours after a meal or at night. Symptoms that awaken a patient from sleep between midnight and 3 AM is a classic indicator of ulcer disease, because in most people gastric acid output is highest at about 2 AM. Ulcer pain is usually not present on awakening in the morning because gastric acid output is at its lowest at this time. Colicky pain is rarely gastric or duodenal in origin. Well-defined periods of exacerbation and remission are usually present with a duodenal ulcer and aid in the diagnosis. A constant pain lasting from weeks to months is uncommonly caused by ulcer disease. Relief of pain after eating is another feature of gastric or duodenal ulcer. The pain from a duodenal ulcer is usually worse immediately before a meal, and so-called pain-eating relief is typical.

Although some patients with ulcers may vomit, alternative diagnoses such as gastric volvulus, gastric outlet obstruction, small bowel obstruction, pancreatitis, or biliary tract disease should be considered in patients with epigastric pain and vomiting. Relief of abdominal pain with antacids is an important aspect of the history. Antacids usually afford relief of pain in PUD and gastritis. Of patients with PUD, 90% have pain relief with antacids, and 75% with gastritis have relief. Patients with duodenal ulcer usually experience pain relief within 5 minutes after taking an antacid.

Physical findings in patients with PUD are usually minimal. Mild epigastric tenderness may be elicited. A positive stool guaiac test may be evidence of a slowly bleeding ulcer, but other causes of occult bleeding should also be considered.

Complications

The most serious complications of PUD include hemorrhage, perforation, penetration, and gastric outlet obstruction. Hemorrhage is the most common complication, occurring in 15% to 20% of patients. Ulceration into an artery can lead to life-threatening hemorrhage. Patients older than 60 years are at greater risk. Approximately 2% to 10% of patients experience perforation, which occurs when an ulcer erodes through the wall and leaks air and digestive contents into the peritoneal cavity. Duodenal ulcers account for 60% of all perforations, followed by antral gastric ulcers (20%) and gastric body ulcers (20%). Penetration is pathologically similar to perforation, except that the ulcer erodes into another organ such as the liver (usually from a gastric ulcer) or pancreas (usually from a duodenal ulcer) instead of into the peritoneal cavity. Gastric outlet obstruction occurs in 2% of ulcer patients as a result of edema and scarring near the gastroduodenal junction. Symptoms may manifest as gastroesophageal reflux, early satiety, weight loss, abdominal pain, and vomiting.

Pain patterns may be helpful in diagnosing some of the complications of PUD. Pain from a perforated duodenal ulcer is usually appreciated first in the epigastrium but becomes generalized within a short time. Vomiting is present in 50% of patients, and peritoneal findings usually result. Pneumoperitoneum commonly occurs after duodenal ulcer perforation, and the accumulated air under the diaphragm may cause referred pain to the shoulder. One or both shoulders may be involved, depending on the location of the free air.

A history of ulcer-like anterior abdominal pain that begins to radiate into the back suggests penetration of a duodenal ulcer. The pain is usually described as steady and is perceived at the level of the lower thoracic and upper lumbar vertebrae. The pain becomes refractory to treatment with antacids and food. Also, the pain may radiate to the chest, right upper quadrant, and left upper quadrant in up to 20% of patients. The sudden onset of pain, especially if unrelated to eating, suggests ulcer perforation or gastric volvulus.

Differential Diagnosis

Many other disorders can produce epigastric pain that mimics the pain of gastritis or PUD. Before either of these diagnoses can be made, other diseases that cause nausea, vomiting, and upper abdominal pain should be excluded, such as pancreatitis, biliary tract disease, and small bowel obstruction. Esophageal disorders such as GERD, esophagitis, or esophageal spasm can arise with abdominal symptoms. Mesenteric ischemia should be considered, especially in older adults and those with underlying vascular disease or atrial fibrillation. The possibility of an ACS should also be considered.

It can be difficult to distinguish between gastritis and PUD. The discomfort associated with gastritis is often mild to moderate in severity and described as a hot burning pain or bloating. In particular, burning pain is twice as common in gastritis as in PUD.

Diagnostic Testing

Because the diagnosis of gastritis is made clinically, no specific diagnostic tests are necessary. Ancillary tests should be ordered as clinically indicated to rule out other possible diagnoses or assess for complications of gastritis, such as bleeding, obstruction, and perforation.

Upper endoscopy is the procedure of choice for confirming the diagnosis. This is not typically performed in the ED unless it is necessary to treat complications of PUD, such as acute bleeding.

Abdominal and chest radiographs should be ordered if obstruction, perforation, or penetration is suggested, or if a pulmonary cause is being considered, although negative radiographs do not definitively rule out these diagnoses. Electrocardiography should be performed in any patient thought to have a cardiac cause for the pain. A pregnancy test should be performed on any woman of childbearing age.

Patients can be tested for *H. pylori* by invasive and noninvasive methods. These include a urea breath test, serum antibody testing, stool antigen testing, and direct mucosal biopsy during endoscopy. None of these methods are currently practical to use in the ED.

Management

Therapy of presumptive gastritis should be directed toward treating the suggested underlying cause. Acid suppression may improve symptoms of dyspepsia in patients taking NSAIDs. Patients with persistent symptoms should be referred to a gastroenterologist for further diagnostic evaluation.

For NSAID-related ulcers, treatment should begin with discontinuation of the offending agent and initiation of a PPI. For ulcers not related to NSAIDs, it is recommended to treat for *H. pylori* infection.

Some recommended regimens combine antibiotics with acid-suppressing agents for treatment of *H. pylori* infection (Box 79.5). Commercially available combination products may also be prescribed that may assist in compliance (eg, Prevpac, which contains lansoprazole, amoxicillin, and clarithromycin, and Helidac, which contains bismuth subsalicylate, metronidazole, and tetracycline). Continued therapy with antisecretory agents after an antibiotic-containing regimen is recommended.

BOX 79.5

Suggested Treatment Regimens for *Helicobacter pylori*

TRIPLE THERAPY (10- to 14-day treatment regimen)
Clarithromycin, 500 mg bid
Plus
Amoxicillin, 1 g bid
Or
Metronidazole, 500 mg bid (if penicillin-allergic)
Plus
A PPI

QUADRUPLE THERAPY (10- to 14-day treatment regimen)
Bismuth subsalicylate (Pepto-Bismol), 525 mg PO qid
Plus
Metronidazole, 250 mg PO qid
Plus
Tetracycline, 500 mg PO qid
Plus
PPI or ranitidine, 150 mg PO bid

PO, Orally; *PPI,* proton pump inhibitor.
From Chey WD, Wong BCI: American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. Am J Gastroenterol 102:1808–1825, 2007.

Antacids

By the time most patients seek treatment for upper GI complaints, they have already tried some form of antacid therapy because these agents are readily available as OTC preparations. Antacids afford pain relief for most patients with PUD. Doses with a low neutralizing capacity (as low as 30 mEq) promote ulcer healing. Antacids may also work by binding bile acids or inhibiting pepsin.

The choice of antacid should be individualized. The magnesium-containing antacids can produce diarrhea in up to 25% of patients. Magnesium-containing antacids can also lead to an increase in serum magnesium levels and should be avoided or used with caution in patients with impaired renal function. Aluminum-containing antacids may cause constipation, and prolonged use may lead to phosphate depletion. Calcium-containing antacids have been marketed as acid neutralizers and as a means of calcium supplementation, especially for postmenopausal women. Calcium-containing antacids have been traditionally believed to cause the highest incidence of acid rebound, a paradoxical increase in gastrin secretion and acid production. Calcium antacids can also lead to constipation, and their excess consumption can lead to hypercalcemia, alkalosis, and renal insufficiency—the milk-alkali syndrome.

Antacids can also decrease the absorption of warfarin, digoxin, some anticonvulsants, and some antibiotics. It is recommended that antacids be administered 1 to 3 hours after meals and at bedtime. Antacids are the least expensive drugs available to treat PUD, but their use is limited by efficacy, side effects, and inconvenient administration schedules.

Histamine Blockers

Histamine is the primary stimulus to gastric acid secretion. It binds to the histamine-2 (H_2) receptor located on the basolateral portion of the parietal cell to stimulate the release of hydrochloric acid. The discovery of the ability of H_2 blockers to inhibit gastric acid production was a major advance in antiulcer therapy because ulcers cannot develop in the absence of acid. These drugs are highly selective competitive inhibitors of histamine for the H_2 receptor on parietal cells and reduce the volume of gastric juice and its hydrogen ion concentration. All the currently available H_2 blockers are rapidly absorbed after an oral dose, with peak levels reached within 1 to 2 hours. All have half-lives of approximately 2 to 3 hours, so their effects last for about 6 hours. Most are now available OTC in lower dosage strength.

H_2 blockers are effective in treating duodenal ulcer and, to a lesser extent, gastric ulcer, although they are not as effective as the PPIs. They are widely prescribed for symptoms of dyspepsia and work well in patients with episodic heartburn. All H_2 blockers are mainly metabolized hepatically and renally, with the exception of nizatidine, which is almost exclusively metabolized renally. Dosages of all these agents should be reduced in patients with renal failure.

H_2 blockers are safe and generally well tolerated. Side effects are rare but include central nervous system effects, such as somnolence, dizziness, and confusion. Transient increases in liver enzyme levels may be noted. Some patients may exhibit abnormalities in cardiac conduction because there are H_2 receptors in the heart. Cimetidine has been shown to cause gynecomastia. Dosages of the various agents are summarized in Table 79.1.

Proton Pump Inhibitors

The H^+,K^+-ATPase (proton pump) is located on the apical portion of the parietal cell and is responsible for the production of hydrogen ions in gastric acid. PPIs are the most potent inhibitors of gastric acid secretion. They work by irreversibly binding to

stimulated proton pumps to block the secretion of hydrogen ions. Although they have no effect on the volume of gastric juice produced, production of acid can be reduced by up to 95%. Both basal and stimulated gastric acid secretions are reduced. The antisecretory effects last up to 72 hours.

PPIs should be administered before the first meal of the day because the number of proton pumps is maximized after a fasting state. At the cellular level, additional proton pumps are continually recruited to produce more acid in response to stimulation; therefore, several doses of a PPI are necessary for the maximal antacid effect to be achieved. The use of these medications on an as-needed basis would not be expected to provide a good clinical response; H_2 blockers are more suitable for this purpose.

PPIs are hepatically metabolized, and dosage should be modified in patients with hepatic failure. Side effects are usually minimal, and the long-term safety of these drugs has been shown in multiple studies.[3] PPIs may be used at significantly higher dosages in patients with Zollinger-Ellison syndrome. Dosages of the various agents are summarized in Table 79.2. Lansoprazole, pantoprazole, and esomeprazole are available as IV formulations.

PPIs have been linked to inhibition of the effects of thienopyridines used to treat cardiovascular disease. Laboratory studies have shown a decrease in the inhibition of platelet aggregation when clopidogrel (Plavix) was combined with PPIs in healthy subjects.[4] Retrospective observational studies have also suggested a potential increase of re-infarction and hospitalization when clopidogrel was used in combination with PPIs. The mechanism hypothesized is a competitive inhibition of the cytochrome p450 isozyme (CYP2C19), which converts clopidogrel to an active state.[5] Two prospective randomized control trials have been performed, but both failed to show an increased cardiovascular risk for patients using both clopidogrel and PPIs.[6] Overall, the data are mixed, and further research is needed to determine if there is an important clinical effect on patients taking both clopidogrel and PPIs.[7] At this time, we recommend using PPIs and clopidogrel with caution and only when the benefits of PPIs outweigh the potential risks.

Prostaglandins

Prostaglandins exert protective effects on the gastric mucosa by inhibiting acid secretion and decreasing the amount of cyclic adenosine monophosphate generated in response to histamine. Inhibition of gastric acid secretion, increased secretion of mucus and bicarbonate, and stimulation of mucosal blood flow have all been demonstrated. Misoprostol is an analogue of prostaglandin E_1, with a longer duration of action and greater potency than endogenous prostaglandins. It should be used only for the prevention of NSAID-induced gastric ulcers in patients at high risk. The dose is 200 µg qid with food, but crampy abdominal pain and diarrhea may necessitate the use of a somewhat less effective dose of 100 µg qid. Misoprostol is an abortifacient and therefore is contraindicated in any female patient of childbearing age who is not using contraception.

Other Agents

Sucralfate binds to epithelial cells and especially to ulcerated surfaces, providing a protective layer that inhibits further acid damage. Its mechanism of action is not completely understood, although it has been shown to enhance epithelial growth, suppress acid secretion, and inhibit the growth of *H. pylori*. The usual dose is 1 g qid given 30 to 60 minutes before meals, and it can be used to complement other medications

Bismuth compounds such as bismuth subsalicylate decrease pepsin activity, increase mucus secretion, and form a barrier to further acid damage in ulcer craters. They also increase prostaglandin synthesis and retard hydrogen ion diffusion through the mucosal barrier. Bismuth may also help heal ulcers through its bactericidal action on *H. pylori*. Bismuth compounds are not approved for the treatment of peptic ulcers.

Disposition

Referral to a gastroenterologist is suggested if any of the following signs or symptoms are present: age 55 years or older with new-onset dyspepsia, dysphagia, progressive unintentional weight loss, persistent vomiting, iron deficiency anemia, or an epigastric mass.[8] Most patients with PUD can be safely managed as outpatients, with referral to gastroenterology for confirmation of diagnosis with an extraglottic device (EGD). Further evaluation is required for patients with high-risk clinical features (eg, anemia, report of GI bleeding, intractable pain, signs of gastric obstruction) prior to discharge.

GASTRIC VOLVULUS

Principles

Gastric volvulus is a rare cause of severe abdominal pain that occurs when the stomach rotates on itself more than 180 degrees, creating a closed loop obstruction. It is a rare condition whose true incidence is unknown because some types of volvulus are intermittent and resolve spontaneously. Gastric volvulus may be classified according to cause (primary vs. secondary), anatomy (axis of rotation), or onset (acute vs. chronic).[9]

The stomach is fixed at only two points, the esophagocardiac junction and pylorus. The remainder of the organ is relatively distensible and mobile and can occupy various positions within the abdomen. When a person is supine, the stomach lies entirely above the umbilicus, whereas it descends below the umbilicus when a person is in the erect position. Regardless of its position, the stomach maintains its familiar morphology because of ligamentous attachments to the surrounding organs. A primary (or subdiaphragmatic) volvulus occurs when the stabilizing ligaments are too lax or are congenitally abnormal in such a way that the stomach is able to twist on itself. Approximately one-third of cases are of this type.

Secondary (or supradiaphragmatic) volvulus occurs in patients with diaphragmatic defects such as a paraesophageal hiatal hernia, elevated diaphragm, gastric ulcer or carcinoma, diaphragmatic paralysis, extrinsic pressure on the stomach from other organs, or abdominal adhesions. The combination of one of these factors and ligamentous laxity makes a volvulus more likely.

Gastric volvulus can also be classified on the basis of its axis of rotation. The most common form is organoaxial volvulus, which occurs when the stomach twists on its long axis. Less commonly, the stomach folds on its short axis from its lesser to greater curvature and is classified as a mesenteroaxial volvulus. Approximately one-third of cases of gastric volvulus are of this type.

Clinical Features

Gastric volvulus usually occurs in persons 40 to 50 years of age and is typically associated with the presence of a paraesophageal hernia.[10] Approximately 20% of cases occur in infants younger than 1 year, often associated with a congenital diaphragmatic defect.

The presenting features of a gastric volvulus vary, depending on the type. Primary volvulus may arise with the sudden onset of severe abdominal pain. The upper abdomen may demonstrate

marked distention. Patients with secondary volvulus may experience predominant symptoms in the chest, with pain radiating to the back and shoulders, along with accompanying dyspnea. The abdominal examination may be unremarkable. Nonbilious vomiting is usually present and may be persistent and severe. The combination of severe epigastric pain and distention, vomiting followed by violent nonproductive retching, and inability to pass a nasogastric tube (Borchardt's triad) increases the likelihood of a gastric volvulus. Up to 25% of children with acute gastric volvulus present with life-threatening events that necessitate resuscitation, including apnea, cyanosis, and acute respiratory distress.

A volvulus may be chronic if the rotation is minimal, and there is no vascular compromise. Symptoms usually consist of mild intermittent upper abdominal pain. Early satiety, dyspnea, bloating, eructation, and upper abdominal fullness may be present. It is unknown how often a chronic volvulus can lead to an acute volvulus.

Complications

If an acute volvulus is not identified and corrected early, it may lead to gastric ischemia, perforation, and death. The mortality rate from acute gastric volvulus has been reported to be as high as 50%. Fortunately, the frequency of gastric infarction is low (reportedly 5% to 28% for organoaxial volvulus) because of the redundant blood supply of the stomach. Other complications include ulceration, perforation, hemorrhage, pancreatic necrosis, and omental avulsion.

Differential Diagnosis

The differential diagnosis of gastric volvulus includes any disease that can arise with sudden upper abdominal pain and vomiting. Perforated peptic ulcer, gastric outlet obstruction, biliary tract disease, and acute pancreatitis should be considered. Symptoms of a volvulus may suggest those of an ACS.

Diagnostic Testing

A plain abdominal radiograph often demonstrates a large, gas-filled loop of bowel in the abdomen or chest[16] (Fig. 79.4). A barium swallow may help visualize the abnormality, and CT can be used for confirmation in equivocal cases. There are no laboratory findings specific for volvulus, although elevations in amylase and alkaline phosphatase levels have been reported.

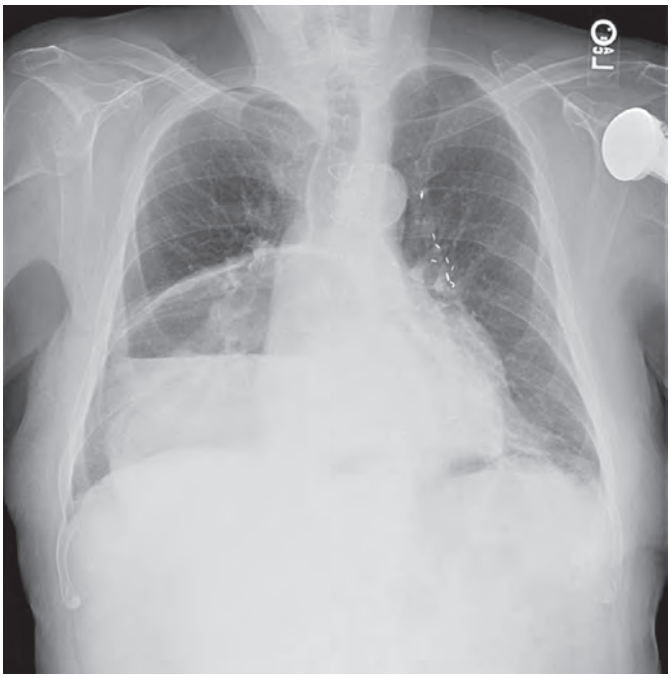

Fig. 79.4. Organoaxial gastric volvulus. (Courtesy Radiopaedia.org: Gastric volvulus. http://radiopaedia.org/cases/gastric-volvulus.)

Management

The goal of treatment of an acute gastric volvulus is reduction. Mortality rates increase with delayed diagnosis because of ischemic complications. Acutely, one should attempt passage of a nasogastric tube, which may occasionally reduce the volvulus. Although somewhat controversial, patients without signs of gastric infarction may undergo an attempt at endoscopic reduction. Ultimately, treatment is a surgical emergency, with the goal of reducing the volvulus and preventing recurrence by fixing the stomach within the abdomen. Surgical repair of predisposing diaphragmatic defects is also recommended to prevent recurrence.

Disposition

Patients with an acute gastric volvulus require admission and surgical consultation due to the high morbidity and mortality associated with the condition.

KEY CONCEPTS

Dysphagia

- Dysphagia can be caused by obstructive lesions (aortic aneurysm), motility disorders (achalasia) and neuromuscular disorders that can be vascular (eg, cerebral vascula accident), immunologic (eg, multiple sclerosis [MS]), infectious (eg, botulism), or metabolic in nature.
- The incidence of achalasia increases with age, presenting insidiously with equal frequency for solids and liquids.
- Dysphasia can be the initial presentation of myasthenia gravis.
- Treatment is directed toward the underlying cause (eg, myasthenia gravis, MS).
- An outpatient barium swallow or endoscopy is indicated for most patients with dysphagia.

Foreign Bodies

- Structural abnormalities of the esophagus are a major risk factor for foreign body obstruction, so patients who obtain relief of symptoms should be referred to a gastroenterologist for follow-up evaluation.
- Emergent (immediate) intervention is indicated for button batteries, food boluses causing high-grade obstruction, and patients in significant distress.
- Urgent (<24 hours and ideally <12 hours) intervention is indicated for no or low-grade obstructions caused by sharp objects, coins lodged in the proximal esophagus, and food boluses.
- Urgent intervention is recommended for gastric foreign bodies wider than 2.5 cm or longer than 5 cm.

Continued

KEY CONCEPTS—cont'd

- Flexible endoscopy with procedural sedation is the preferred therapeutic intervention to remove most foreign bodies.

Esophageal Perforation

- Iatrogenic causes, such as endoscopy, are the most common cause of esophageal perforations.
- Water-soluble contrast should be used for initial diagnostic imaging studies.
- Admission with broad-spectrum antibiotics (eg, vancomycin, 15 mg/kg and piperacillin, 3.375 g) and early surgical consultation should occur in most cases of esophageal perforation.
- Select stable patients with a small, contained esophageal perforation may be managed conservatively by keeping the patient NPO, scheduling broad-spectrum antibiotics, using parenteral nutrition, and having a surgeon readily available.

Esophagitis

- GERD is a diagnosis of exclusion in patients who present with chest pain. It is critical to first rule out other diagnoses, such as ACS.
- Empirical treatment of GERD with lifestyle modifications, H_2 blockers, or PPIs is appropriate, but if no improvement with these measures, the patient should be referred for further evaluation.
- Sucralfate (1 g qid) is a useful adjunct in the treatment of GERD and can be safely used in pregnant patients.
- Eosinophilic esophagitis commonly presents as solid food dysphagia. Once food impaction is ruled out, a PPI should be started and the patient referred to a gastroenterologist.
- Infectious esophagitis primarily occurs in immunocompromised patients, and its specific cause can be identified by endoscopy.
- Patients with pill esophagitis typically present with sudden onset retrosternal pain and odynophagia in the setting of taking medications without water. In such cases, the diagnosis can be made clinically on the history alone.
- Medications associated with pill esophagitis include doxycycline, aspirin, NSAIDs, and potassium chloride.

Gastritis and Peptic Ulcer Disease

- Although gastritis cannot be definitively diagnosed based on clinical features alone, a clinical history such as recent NSAID use or alcohol ingestion in the setting of the classic symptoms supports a presumptive clinical diagnosis of gastritis.
- The most common cause of gastritis is *H. pylori* infection.
- First-line treatment of *H. pylori* infection is a PPI (eg, omeprazole, 20 mg bid), amoxicillin (1 g bid) and clarithromycin (500 mg bid) for 14 days.
- The most serious complications of PUD include hemorrhage, perforation, penetration, and gastric outlet obstruction.

Gastric Volvulus

- Acute gastric volvulus often presents with the combination of severe epigastric pain and distention and vomiting followed by violent nonproductive retching.
- Volvulus has a very high morbidity and mortality. Nasogastric tube reduction can be attempted in the ED, but ultimately these patients need emergent surgical consultation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 79: QUESTIONS & ANSWERS

79.1. What is an appropriate first-line treatment regimen for *H. pylori* infection?

A. Bismuth subsalicylate, ranitidine, and clarithromycin
B. Metronidazole and sucralfate
C. Omeprazole, amoxicillin, and clarithromycin
D. Omeprazole and bismuth subsalicylate
E. Ranitidine, omeprazole, and amoxicillin

Answer: C. The recommended triple-treatment regimen for *H. pylori* infection is a PPI (eg, omeprazole, 20 mg bid), amoxicillin (1 g bid), and clarithromycin (500 mg bid) for 14 days. Quadruple therapy with Pepto Bismol, metronidazole, tetracycline, and a PPI-ranitidine is an alternative option. See Box 79.5.

79.2. What percentage of esophageal foreign bodies require an intervention (usually nonoperative) for removal?

A. <10%
B. 10%–20%
C. 20%–30%
D. 30%–40%
E. >40%

Answer: B. Most foreign bodies pass spontaneously. Approximately 10%–20% require intervention, but less than 1% require surgery for removal.

79.3. A 5-year-old child is brought to the ED by his mother after a possible ingestion of a plastic Lego piece. He has had no pulmonary symptoms but reports difficulty swallowing and declines to drink liquids that are offered. What would be the intervention of choice?

A. Contrast-enhanced CT scan of the chest
B. Endoscopy
C. Non–water-soluble barium swallow
D. Posteroanterior and lateral chest radiography
E. Water-soluble barium swallow

Answer: B. Because the patient is symptomatic, endoscopy is indicated. A CT scan of the chest is useful for organic and inorganic materials. A basic chest radiograph cannot reliably exclude a foreign body. Barium swallow is difficult in pediatric patients, particularly this child, who is refusing oral fluids. Water-soluble media risk pneumonitis if aspirated. Non–water-soluble materials risk increased inflammation if leakage occurs into the mediastinum. Barium may also obscure subsequent endoscopic visualization.

79.4. Which of the following statements regarding the pharmacologic treatment of an esophageal obstruction from a food bolus is true?

A. Carbonated beverages are a safe and useful adjunct at any point.
B. Glucagon has the additional benefit of moderate antiemetic properties.
C. Glucagon has been proven to help facilitate passage of a food bolus anywhere in the esophagus.
D. Glucagon is contraindicated with sharp-edged foreign bodies.
E. Papain (meat tenderizer) can be used to soften a food bolus and help with passage.

Answer: D. Glucagon is a smooth muscle relaxant, so it is theoretically useful only for distal esophageal foreign bodies. There are only anecdotal reports of success with glucagon, but no randomized controlled trials have shown a statistical benefit over placebo. There are many adverse effects, including flushing, nausea, and vomiting, that can potentially increase the risk of aspiration. It is contraindicated for use with sharp or damaging foreign bodies. There is only low-level evidence to support the use of effervescent agents, and they are relatively contraindicated after 24 hours because of perforation concerns. The use of meat tenderizer (papain) should be avoided because it can significantly worsen inflamed mucosa and increase the risk of perforation.

79.5. Which of the following is an indication for urgent endoscopy?

A. Button battery in the stomach
B. Chest pain due to foreign body
C. Coin in the proximal esophagus
D. Nausea and vomiting
E. Object failing to pass out of the esophagus after 12 hours

Answer: C. A coin that remains lodged in the proximal esophagus should be removed. Other indications are inability to handle secretions, sharp objects, esophageal button battery (alkaline) in the esophagus, and impactions that fail to pass after 24 hours.

79.6. By the age of 50 years, what percentage of the population has endoscopic evidence of gastritis?

A. 10%
B. 20%
C. 30%
D. 40%
E. 50%

Answer: E.

79.7. A 32-year-old otherwise healthy man presents with acute onset of epigastric pain radiating to his chest that woke him from sleep at 2 AM. It was a burning pain associated with water brash. There were no associated pulmonary symptoms. His past medical history is negative except for tobacco use and heartburn. His electrocardiogram is normal and his upright chest radiograph is also normal. Vital signs and physical examination findings are unremarkable. He is currently pain-free. His troponin

level is normal. What would be the most appropriate intervention?
A. Cardiology consultation for catheterization
B. Contrast-enhanced CT scan of the chest
C. Discharge on aspirin, 325 mg once daily
D. Serial troponins
E. Trial of twice-daily proton pump inhibitors

Answer: E. Peak gastric acid secretion occurs during the early morning hours between 1 a.m. and 3 a.m., with a typical scenario of being awakened from sleep. The shared afferent neural pathway makes the pain of gastroesophageal reflux disease (GERD) often similar to that of pain of cardiac origin. Gastric acid secretion is lowest at approximately 6 AM, so awakening in the morning with pain from GERD is unusual.

79.8. A 45-year-old woman presents several hours after an upper endoscopy with severe chest pain and neck discomfort. She is awake and alert, but rates pain as 10 of 10. What is the most appropriate test to confirm the diagnosis?
A. Abdominal x-ray
B. Barium contrast esophagography
C. Gastrografin (water-soluble) contrast esophagography
D. Ultrasound
E. Upper endoscopy

Answer: C. We recommend an initial attempt with a water-soluble agent in patients who are awake and alert and are not at risk for aspiration. Barium sulfate is superior for identifying small perforations; however, it may incite an inflammatory response in tissue and should only be used if no initial perforation is identified with water-soluble contrast. Endoscopy is generally not recommended except in cases of penetrating trauma because insufflation could potentially enlarge a minimal transmural opening.

CHAPTER 80

Disorders of the Liver and Biliary Tract

Elizabeth J. Haines | Leslie C. Oyama

HEPATIC DISORDERS

HEPATITIS

Hepatitis is a generic term referring to inflammation of the liver. It is usually a consequence of a viral infection or alcohol abuse (see below). However, it is important to remember that hepatitis can be caused by other infections (eg, bacterial, fungal, or parasitic) and other toxic exposures (eg, industrial chemicals, prescribed medications, nutritional supplements), as well as by immunologic disorders.

Viral Hepatitis

Principles

Many viruses are associated with some degree of measurable liver inflammation. However the most significant and potentially severe cases of viral hepatitis are caused by type A (infectious), type B (serum), type C (posttransfusion), and delta viruses. The Epstein-Barr virus, the causative agent of mononucleosis, is also a common cause of hepatitis, although it is more important clinically for its nonhepatic effects.

Hepatitis A. Hepatitis A virus (HAV), is an RNA enteroviral picornavirus. It is spread by the fecal-oral route directly or through contaminated water or foodstuffs. Transmission by blood is a theoretic possibility but is exceedingly rare. HAV can occur sporadically but is notorious for its association with epidemics generally linked to common source outbreaks. HAV infection is common worldwide; serologic evidence of previous infection exists in nearly 100% of the adult population in some regions. In the United States, close to 50% of all urban-dwelling adults are seropositive for antibody for HAV.[1] High rates of seropositivity in association with the relatively small number of reported episodes support the notion that many cases may be asymptomatic. Occult disease appears to be more common in children, and 70% of those infected may be asymptomatic.[1] Routine vaccination of children is recommended, which has contributed to a profound shift in reported new cases to adults—specifically, men who have sex with men (MSM), illicit intravenous drug users (IVDUs), and non–injection drug users (Fig. 80.1). The most common risk factor for hepatitis A in persons older than 15 years is travel outside of the United States.

The incubation period for hepatitis A ranges from 15 to 45 days (typically, 30 days), with a relatively short duration of viremia that is most prominent before the onset of symptoms. Fecal shedding and maximum infectivity occur before the onset of symptomatic disease and generally have waned by the time jaundice appears (Fig. 80.2). HAV is not associated with a chronic carrier state.

Hepatitis B. Hepatitis B virus (HBV) is contained in a 42-nm structure called the Dane particle. Within this enveloped virion are the viral DNA, DNA polymerase, hepatitis B surface antigen (HBsAg), and hepatitis B core antigen (HBcAg). Hepatitis Be antigen (HBeAg) is an immunologically distinct antigen not incorporated into virions; instead, it is secreted from cells into the serum of infected patients. In contrast to HAV, for which there is only a single antigenic variety, several genotypes of HBV, as defined by surface antigen, are recognized. HBV is transmitted principally by parenteral exposure but also can be transmitted through intimate contact. The highest rates of infection are among IVDUs and homosexual men. Transmission by blood transfusion, previously a common source of infection, has been eliminated because of modern blood bank screening techniques. Similar to HAV, the incidence of hepatitis B has continued to decline (Fig. 80.3).

HBsAg has been detected in a variety of bodily secretions, including saliva, semen, stool, tears, urine, and vaginal secretions. Although the presence of HBsAg is not synonymous with infectivity, HBV DNA has been identified in several of these fluids and is likely to be infectious. The typical interval between exposure and onset of clinical illness is 60 to 90 days; however, serologic markers of infection generally appear within 1 to 3 weeks (Fig. 80.4). Approximately 10% of adults and 90% of infected neonates with immature immune systems will become asymptomatic chronic carriers of HBsAg. Health care workers who routinely come into contact with blood have a prevalence of HBsAg of 1% to 2%, and 15% to 30% show serologic evidence of previous infection. Among emergency clinicians, seropositivity rates of 12% and 15% have been reported. The likelihood of becoming chronically infected with HBV varies inversely with the age at which infection occurs. This age-dependent relationship is believed to be related to the protective abilities of gut microbiota, which are known to increase with age.[2] HBV transmitted from HBsAg-positive mothers to their newborns results in HBV carriage in up to 90% of infants, whereas only 6% to 10% of acutely infected adults become carriers. In general, less than 5% of hepatitis B infections in healthy immunocompetent adults will progress to chronic hepatitis.

Chronic hepatitis is usually defined as the presence of HBsAg in serum for longer than 6 months, serum HBV DNA level greater than 20,000 IU/mL (105 copies/mL; lower values are often seen in HBeAg-negative chronic hepatitis B), persistent or intermittent elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and a liver biopsy showing chronic hepatitis with moderate or severe necroinflammation.

Hepatitis C and E. What was historically termed *non-A, non-B hepatitis* is caused by at least two distinct RNA viruses, hepatitis C virus (HCV) and hepatitis E virus. In the United States, hepatitis C infection is currently the leading cause of cirrhosis. Before widespread blood supply screening, hepatitis C was commonly transmitted through blood transfusions and organ transplantation in the United States. With the 1992 implementation of screening donor blood for surrogate markers (aminotransferases) and antibody to hepatitis C, and nucleic acid amplification testing, the hepatitis C transmission risk from blood transfusion has been reduced to approximately 1 in 1 million (0.0001%)/units transfused.[3] The strongest risk factors for HCV infection are a history

of IVDU, having had 20 or more lifetime sex partners, and having undergone blood transfusions before 1992. Among patients infected with human immunodeficiency virus (HIV), the incidence of coinfection with hepatitis C is 15% to 30%. This rate approaches 50% to 90% in those who acquired HIV through IVDU.[4] Patients coinfected with HIV and HCV generally have a more aggressive course of both infections. In 40% to 57% of cases of hepatitis C, no source of infection is identified. The incubation period for hepatitis C is 30 to 90 days (mean, 50 days). Following the incubation period, a self-limited acute phase begins. The acute phase is asymptomatic in up to 70% of individuals with hepatitis C. This phase persists for up to 12 weeks and is rarely associated with hepatic failure. Approximately 90% of HCV infections progress to chronic hepatitis. Long-term follow-up studies during a period of approximately 20 years postseroconversion have indicated that clinical liver disease develops in only 10% to 20% of those infected.[4a] In the United States, it has been estimated that 4.1 million persons are infected with HCV, and 3.2 million persons have chronic hepatitis C infection. Unlike HAV and HBV, HCV incidence has continued to increase (Fig. 80.5). Hepatitis C seroprevalence among persons born between 1945 and 1965 (baby boomers) presenting to the emergency department (ED) has been documented to be 11%, or one in every nine emergency visits in this age group. This alarming disease prevalence, coupled with decreased disease awareness among health-despaired populations, has been prompting a push for ED screening.[5,6]

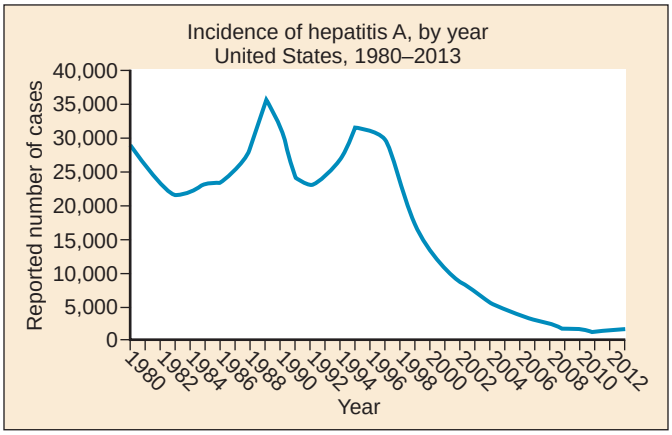

Fig. 80.1. Incidence of hepatitis A.

Hepatitis D. Hepatitis delta virus (HDV) was discovered in 1977 in liver specimens from patients with chronic HBV infection. It is a defective RNA virus that can infect only patients who are actively producing HBsAg, which is required for its viral coating.

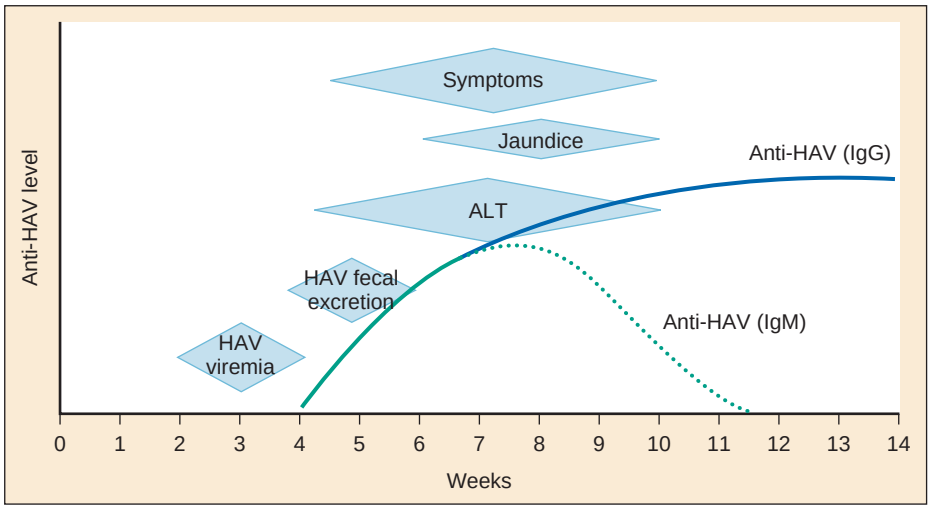

Fig. 80.2. Acute hepatitis A virus (HAV) infection. *ALT,* Alanine aminotransferase; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.

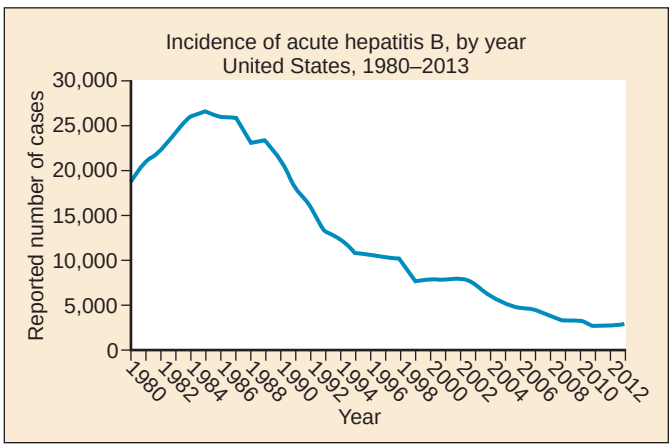

Fig. 80.3. Incidence of hepatitis B.

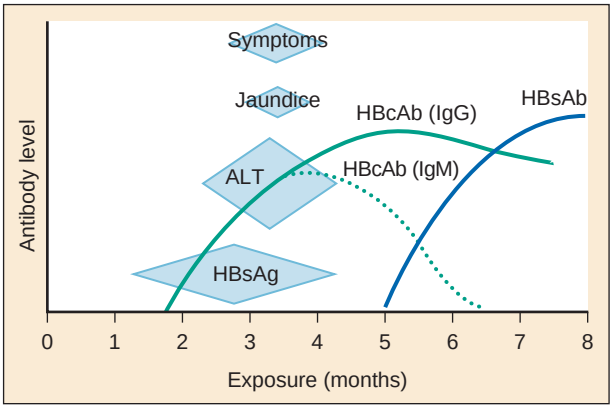

Fig. 80.4. Acute hepatitis B virus infection. *Ab,* Antibody; *Ag,* antigen; *ALT,* alanine aminotransferase; *HBc,* hepatitis B core; *HBs,* hepatitis B surface; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.

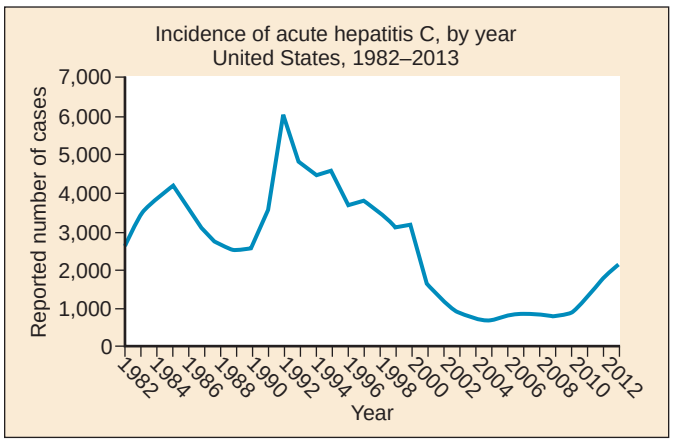

Fig. 80.5. Incidence of hepatitis C.

In the United States, the incidence of HDV antibody is 4% to 30% of patients with chronic HBV infection.[7] As a consequence of the routine association with chronic HBV infection, it is likely that many cases of HDV infection are misdiagnosed as acute or reactivated hepatitis B.

HDV is spread in a manner similar to that of hepatitis B, being most common among IVDUs, promiscuous homosexual men, and patients with hemophilia. Infection with HDV can occur concomitantly with HBV (coinfection) or subsequent to earlier HBV infection (superinfection), because HDV cannot replicate in the absence of HBV. Cases of superinfection may present as acute self-limited disease to fulminant hepatitis or chronic infection. Fulminant hepatitis is more often observed with HBV-HDV coinfection than with HBV monoinfection.

Hepatitis E and G. Hepatitis E, which is associated with fecal-oral transmission, is encountered most often in Asia, Africa, and Russia. Hepatitis E has an incubation period of 15 to 60 days.

Hepatitis G virus (HGV), also referred to as hepatitis GB virus type C, is the most recently identified cause of viral hepatitis. It is an RNA virus that is transmitted through blood transfusion, parenteral exposure to blood products, and possibly during intimate sexual contact. The virus has been identified in patients with acute and chronic hepatitis. It is believed to be an innocent bystander, with disease manifestations attributable to coinfection with another hepatitis virus.

Clinical Features

The clinical presentation of viral hepatitis is highly variable, with a significant number of those infected being asymptomatic. The most common symptoms and signs are malaise, fever, and anorexia, followed by nausea, vomiting, abdominal discomfort, and diarrhea. The first prompt to seek medical care is typically jaundice. A small number of patients with hepatitis B may experience a prodromal illness characterized by arthralgia, arthritis, and dermatitis. The joint involvement typically is polyarticular; the small joints of the hands and wrists are usually affected. Joint fluid usually is noninflammatory, with cell counts as high as 90,000/mm.[3] The characteristic dermatitis is urticarial but may be macular, papular, or petechial.

Fulminant hepatitis is characterized by an acute onset that progresses to hepatic failure and encephalopathy over a period of days characterized by altered mentation and spontaneous mucosal bleeding. Although most often encountered with HBV and HDV coinfection, fulminant hepatitis can occur in association with all the causative viruses (1% to 2% of all cases).

Physical findings include elevated temperature, scleral or cutaneous icterus, and abdominal tenderness. There may be vomiting resulting in tachycardia and supine or orthostatic hypotension. Hepatomegaly may occur and is characterized by a smooth, homogeneous, tender liver surface. Even if liver enlargement is not appreciated, tenderness to percussion over the lower right ribs may be present. Scleral icterus is generally noticeable earlier than cutaneous discoloration. Muddy sclera, commonly found among African American patients, may obscure or confuse this finding; sublingual or subungual surfaces are alternative sites to examine. Scleral icterus usually occurs once the serum bilirubin level is above 2.5 mg/dL. Spider angiomata and splenomegaly, although usually associated with cirrhosis, may be features in acute presentations. Gray or acholic stools are distinctly uncommon.

Differential Diagnosis

The protean nature of the symptoms and signs associated with viral hepatitis makes the differential diagnosis of this disorder quite broad in scope. Beyond a variety of nonhepatic viral illnesses, all the infectious, chemical, and immunologic causes of hepatic inflammation must be considered, in addition to biliary tract disease. A viral cause often is suggested by the medical history, but serologic tests are required for confirmation. Alcoholic hepatitis is associated with a history of chronic or excessive alcohol consumption, less marked elevation of hepatic transaminase levels, and AST levels elevated above those of ALT. Extrahepatic obstruction, cholecystitis, and cholelithiasis are excluded by their lack of association with significant elevation of aminotransferase levels; abdominal ultrasound imaging or abdominal computed tomography (CT) may be required to exclude these other diseases.

Diagnostic Testing

Laboratory tests are critically important in diagnosing hepatitis and determining the specific cause. The most useful tests are measurements of the hepatic aminotransferase and bilirubin levels. Typically, hepatitis is associated with elevations (10- to 100-fold) of serum AST and ALT levels, with the ALT level generally elevated in excess of AST. The bilirubin level may be moderately increased (5–10 mg/dL), and occasionally is markedly elevated (15–25 mg/dL). Hyperbilirubinemia typically emerges several days to 1 week or more after the onset of clinical symptoms. Direct and indirect bilirubin levels are elevated almost equal proportions. Alkaline phosphatase and lactate dehydrogenase levels may be elevated but are rarely more than 2 to 3 times normal.

The prothrombin time (PT) or international normalized ratio (INR) is useful in assessing the degree of hepatic synthetic dysfunction. Elevation of the PT or INR may be the first clue to a complicated course. The white blood cell (WBC) count generally is not useful in the diagnosis because values range from low overall counts with a lymphocytic predominance to marked polymorphonuclear leukocytosis. Although determining the precise cause of hepatitis can rarely be achieved in the ED, serologic testing should be initiated as soon as possible (Table 80.1) because they affect prognosis and public health issues.

Acute hepatitis A is diagnosed by the presence of immunoglobulin M (IgM) HAV antibody, whereas previous infection is determined by detection of an IgG antibody. Acute hepatitis B is characterized by the presence of HBsAg and IgM antibody to HBcAg. HBsAg alone does not establish the diagnosis of acute hepatitis B because it can be absent late in the course of acute disease or present chronically. Anti-HBcAg antibody generally is the best indicator of previous HBV infection, whereas anti-HBsAg antibody is the best marker for immunity to HBV. Figs. 80.2 and 80.4 show the temporal relationships among infection, clinical

TABLE 80.1

Serologic Markers in Hepatitis

SEROLOGIC MARKER	ABBREVIATION	INTERPRETATION
Antibody to HAV	Anti-HAV	Combination of IgG and IgM antibody defining infection with HAV, acute or past
IgM antibody to HAV	Anti-HAV IgM	Antibody to HAV, indicating acute infection
Hepatitis B surface antigen	HBsAg	Surface antigen associated with acute or chronic HBV infection
Hepatitis Be antigen	HBeAg	Antigen associated with active infection, acute or chronic, and indicative of high infectivity
Antibody to B surface antigen	HBsAb	Antibody indicative of acute or past infection or immunization
Antibody to B core antigen	HBcAb	Combination of IgG and IgM antibody defining infection with HBV, acute or past
IgM antibody to B core antigen	HBcAb-IgM	Antibody to B core antigen, indicating acute infection with HBV
Antibody to Be antigen	HBeAb	Antibody to e antigen, possibly representing resolving HBV infection and decreased infectivity
Antibody to HDV	Anti-HDV	Antibody defining infection with HDV; HBsAg should be present
Antibody to HCV	Anti-HCV	A new antibody that defines infection with HCV, acute or past

HAV, Hepatitis A virus; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HDV,* hepatitis delta virus; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.

symptoms, and serologic responses for the two most common causes of viral hepatitis, HAV and HBV.

Due to its prolonged incubation period, early diagnosis of hepatitis C is based on the exposure history and elimination of other causes. Screening is done by serologic detection of hepatitis C antibodies. Confirmation by a polymerase chain reaction (PCR) assay that detects HCV RNA facilitates a definitive diagnosis. There can be a delay between the onset of symptoms and development of assayable antibody. Furthermore, the HCV antibody test does not distinguish acute from chronic infection. Repeat PCR testing at 6 weeks may establish acute versus chronic hepatitis. Variable low levels of HCV RNA suggest acute infection, whereas nonvariable, higher HCV RNA levels are more consistent with chronic hepatitis C infection. Also, the presence of hepatic fibrosis assessed by histologic analysis (from biopsy) or noninvasive serum and ultrasonographic testing can establish that a chronic state is present.

Due to coinfectivity, diagnosing HDV infection with a serologic test for the antibody to HDV (anti-HDV) requires a thorough testing approach because it may easily be mistaken for acute or chronic HBV infection. The presence of anti-HDV in conjunction with IgM antibody to HBcAg suggests coinfection with HDV and HBV. Anti-HDV in association with IgG antibody to HBcAg supports the diagnosis of superinfection.

Management

Most patients with viral hepatitis have self-limited disease, with symptomatic and histologic resolution in 2 to 4 weeks. ED management is primarily symptomatic. It often is necessary to correct fluid and electrolyte imbalances secondary to poor oral intake or excessive diarrhea or vomiting. Antiemetics may allow resumption of adequate oral intake, thereby avoiding the need for hospitalization. In the anorexic or nauseated patient, fluid intake should be encouraged, with avoidance of solids until they are palatable. Medications requiring a primarily hepatic metabolism do not need to be discontinued nor the dosage adjusted unless there is significant hepatic dysfunction, as indicated by elevated serum aminotransferase and bilirubin levels, encephalopathy, or rising PT or INR. Nonessential drugs with hepatotoxic potential should be avoided. Alcohol consumption should be completely discontinued until signs of liver injury have disappeared. Due to the lack of evidence, we do not recommend a role for corticosteroids in the treatment of hepatitis.

Complications of acute hepatitis are usually related to fluid or electrolyte imbalance as a result of inadequate oral intake or refractory emesis. Severe vomiting can result in upper gastrointestinal (GI) bleeding from an esophageal tear. The most severe complication of acute disease is the development of liver failure, heralded by hepatic encephalopathy.

Although hepatitis A is self-limited and does not progress to a chronic state, isolation, handwashing, and attention to hygienic practices should be undertaken to prevent spread of infection. Patients are contagious during the incubation period and remain contagious until 1 week after the appearance of jaundice.

Prevention and Postexposure Management. Effective preexposure and postexposure prophylaxis for HAV and HBV has been available for more than 2 decades. Passive immunization with immune globin plays a role in overall disease prevention and should be used to treat nonimmunized individuals exposed to HBV. To be effective in prophylactic prevention, serum immune globulin must be administered within 2 weeks of exposure. However, due to cost, self-limited nature of the disease, and transmission risks inherent to the pooled, blood-derived source of hepatitis A immune globulin, its use is reserved for immune-naïve individuals who are at increased risk from hepatitis A exposure or those who are allergic to the vaccination for hepatitis A.

Emergency health care workers are at increased risk for exposure to all types of hepatitis because of frequent contact with bodily fluids, blood, and interaction with high-risk patients. Historically, the seropositivity rate among ED nurses is 30% and 12% to 15% among ED physicians. Markers for hepatitis C were identified in 18% of patients in an inner city ED; the potential associated health risk to staff is unknown.

All ED personnel involved in patient care or custodial work should be vaccinated for HAV and HBV before or soon after starting employment. The vaccines are highly effective and are associated with minimal acute or delayed toxicity. A complete three-injection series of vaccine—to the deltoid for optimal immunologic response—produces protective antibody in approximately 95% of persons. Hepatitis B immune globulin (HBIG) is recommended for immediate passive immunization of those not previously immunized who have been exposed to potentially infective material. Immune globulin diminishes the risk of HBV infection by 75%. Unvaccinated exposed people should receive HBIG, 0.06 mL/kg intramuscularly (IM), in addition to the HBV vaccine. Fig. 80.6 outlines an approach for managing health care

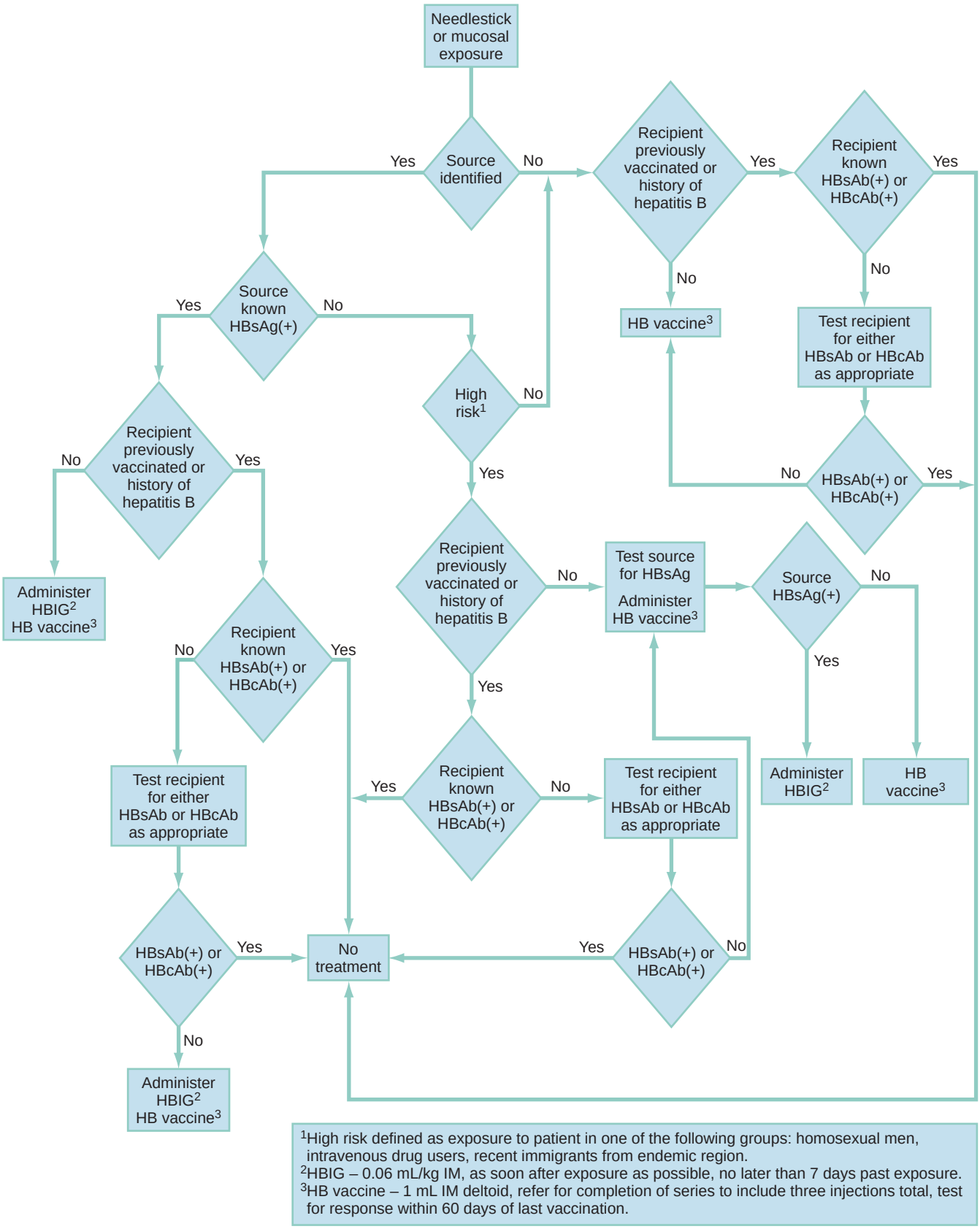

Fig. 80.6. Management of health care workers exposed to blood or other infectious secretions. *HB,* Hepatitis B; *HBIG,* HB immune globulin; *HBcAb,* hepatitis B core antibody; *HBsAb,* hepatitis B surface antibody; *HBsAg,* hepatitis B surface antigen; *IM,* intramuscularly.

workers exposed to blood or other potentially infectious secretions. A safe and effective vaccine for HAV is available; however, health care workers are currently not on the list for recommended routine immunization.

The risk of seroconversion after percutaneous exposure from an HCV-positive source is approximately 1.8%. Despite the theoretic risk of blood-borne HCV exposure among health care workers (HCWs), the prevalence of HCV infection in this group is approximately the same as in the general population. No effective vaccine for HCV is currently available. Previously, it was thought that the use of peginterferon alfa-2b may decrease seroconversion in HCWs exposed to blood from HCV-infected individuals. However, already low transmission rates, coupled with no additional benefit of prophylactically treated over untreated HCWs, has resulted in no accepted preexposure or postexposure prophylaxis regimen for HCV. Recent success in the use of direct-acting antiviral agents (eg, simeprevir, sofosbuvir, ledipasvir) has led many to consider a future role for these agents in postexposure prophylaxis.[8] Universal precautions—the use of gloves, masks, protective eyewear, and gowns—constitute the first and best means of defense for persons who work in proximity to potentially infective bodily fluids.

Disposition

Hospitalization is rarely required for the management of viral hepatitis and generally is reserved for the patient with a fluid and electrolyte imbalance or refractory vomiting. Patients with less severe illness may require hospitalization for concomitant medical problems or if suitable living arrangements are not available. Altered sensorium, a PT more than 5 seconds, or an INR more than 1.5 may suggest fulminant disease or an increased likelihood of a complicated course, necessitating hospitalization for observation. The emergence of fulminant disease should lead to consideration of transfer to a facility that can offer liver transplantation.

Treatment of chronic hepatitis C is a rapidly evolving area of medicine. Current therapy involves genotype-specific, direct-acting antiviral (DAA) regimens using nucleoside polymerase inhibitors (eg, simeprevir, sofosbuvir, ledipasvir). The goal end point is a sustained virologic response (SVR) defined as absence of HCV RNA by PCR testing 3 to 6 months after stopping treatment. Ongoing research has been investigating which patients require a combination of DAAs, with or without the addition of ribavirin and/or interferon.[9,10] Treatment regimens take into account various patient factors, including naïvety to treatment, prior relapse, prior partial or null response (quantified decline in viral load at 4 weeks), and history of protease inhibitor failure.[11] All oral curative regimens using two nucleoside inhibitors to treat genotype 1 carry a sustained virologic response rate that approaches 99% after 12 weeks of treatment.[12] Referral to a hepatic disease specialist for virus genotyping, treatment initiation, and ongoing surveillance is recommended.

Anxiety about disease communicability may affect the ease of disposition. Patients with possible HAV infection should be advised to practice meticulous personal hygiene, not to share toiletries, and ensure thorough cleaning of utensils and kitchenware between uses. In patients with suspected HBV or HDV infection, the relatively low risk of transmission by intimate personal contact or parenteral exposure should be emphasized.

Viral hepatitis is a reportable disease requiring notification of the local health department. Immunoprophylaxis should be provided to the patient's family members and close personal contacts (if not previously immunized) pending serologic determination (see Fig. 80.4; Table 80.2). Patients with HAV infection who process or handle food must not return to work while potentially infectious. Although infectivity is greatly diminished by the time jaundice emerges, it is best to delay return to work until after the jaundice has fully cleared.

Alcoholic Hepatitis

Principles

Alcohol-related liver disease accounts for just under 1% of worldwide mortality.[13] Alcohol and its metabolites are toxic to most organ systems and are largely eliminated by metabolic degradation in the liver; up to 15% of alcohol is excreted unchanged in the urine or expired air. The precise pathogenesis of alcoholic liver disease is unknown and probably is multifactorial. Probable causal factors include coexistent malnutrition, accumulation of toxic metabolites (eg, acetaldehyde), depletion of glutathione, abnormal metabolism of methionine, excessive production of nicotinamide adenine dinucleotide (NADH), induction of microsomal enzymes as a result of the metabolism of alcohol, and alteration of immune function.[14]

Although susceptibility to liver damage varies based on genetic heterogeneity, a rough correlation is recognized between the amount of ethanol ingested and risk of developing liver disease. The risk of liver injury increases as daily consumption exceeds 80 g of ethanol daily in men and 20 g in women. For men, this is equivalent to a six-pack of beer, four to six glasses of wine, or three to four mixed drinks daily. Fatty infiltration appears to depend on the duration and amount of alcohol consumed and, in general, is reversible when the patient stops drinking.

The most common variety of alcohol-induced liver disease is steatosis. Fatty infiltration of the liver is most likely a consequence of altered fatty acid metabolism resulting from a diminished NAD^+/NADH ratio, which favors triglyceride production. Beyond enlargement of the liver, which usually is painless, this tends to be a benign process.

As alcohol-related liver disease progresses beyond steatosis, fibrosis, cirrhosis and finally hepatocellular carcinoma may ensue (Fig. 80.7). In more than 90% of those who regularly consume alcohol, steatosis can be seen as early as 2 weeks. Within 5 years, 8% to 20% of those with steatosis of the liver progress to having cirrhosis. Comorbidities that contribute to the progression of disease include viral hepatitis, HIV, and hemochromatosis. Approximately 3% to 10% of chronic alcoholics will develop hepatocellular carcinoma.

Clinical Features

Alcoholic hepatitis is a potentially severe form of alcohol-induced liver disease. Most cases probably are subclinical, but the spectrum of presentation can range from nausea, vomiting, and abdominal pain to acute liver failure. Physical findings include tachycardia, fever, and supine or orthostatic hypotension. Abdominal tenderness usually can be elicited, especially in the right upper quadrant. Coexistent fatty infiltration may produce palpable hepatomegaly; cirrhosis from chronic disease may result in a small nonpalpable liver. The characteristic physical signs of cirrhosis may be present—gynecomastia, spider angiomata, muscle wasting, ascites, and palmar erythema. Jaundice can be noted in patients with a bilirubin level of at least 2.5 mg/dL. As disease advances, peripheral edema, abdominal distention, hematemesis, and melena may be present. Patients with clinical signs of alcoholic hepatitis should be assessed for symptoms of gastritis and GI bleeding.

Differential Diagnosis

The differential diagnosis of alcoholic hepatitis is broad in scope and includes many other alcohol-related GI maladies (eg, gastritis,

TABLE 80.2

Postexposure Hepatitis Prophylaxis

NATURE OF EXPOSURE		RECOMMENDED TREATMENT	
HEPATITIS A			
Close personal contact		ISG, 0.02 mL/kg IM	
Day care center • Employee • Attendee		 ISG, 0.02 mL/kg IM ISG, 0.02 mL/kg IM	
School contacts		None	
Hospital contacts		None	
Workplace contacts		None	
Food-borne source • Within 2 wk of exposure • After 2 wk of exposure		 ISG, 0.02 mL/kg IM None	
After common source outbreaks have begun to occur		None	
		EXPOSED INDIVIDUAL	
Nature of Exposure	**Source**	**Unvaccinated**	**Vaccinated**[a]
HEPATITIS B			
Percutaneous or mucosal	HBsAg (+)	1. HBIG ×1 2. Hepatitis B vaccination booster	Test exposed person for anti-HBs; if titer is adequate, no treatment. If anti-HBs titer inadequate: 1. HBIG ×1 2. Initiate hepatitis B vaccination series.
	HBsAg (–)	1. Initiate Hep B vaccination series	No treatment
	Unknown source	1. HBIG ×1	Test exposed person for anti-HBs; if titer is adequate, no treatment. If anti-HBs titer is inadequate: 1. HBIG ×1
	(Treat as if HBsAg [+].)	2. Initiate Hep B vaccination series	2. Hepatitis B vaccination booster
Intimate sexual	HBsAg (+)	1. HBIG ×1 2. Initiate hepatitis B vaccination series	Test exposed person for anti-HBs; if titer is adequate, no treatment. If anti-HBs titer inadequate: 1. HBIG ×1 2. Hepatitis B vaccination booster
HEPATITIS C			
Unknown benefit from prophylaxis; ISG, 0.06 mL/kg IM can be considered for parenteral exposures in patients with evidence of viral hepatitis and negative results on serologic studies.			
HEPATITIS DELTA			
Same as for hepatitis B			

HBIG, Hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen; *IM,* intramuscularly; *ISG,* immune serum globulin.
[a]The HB vaccine recombinant dose comes in three formulations—pediatric, adult, and those on hemodialysis. The adult formulation (without preservative) comes in a concentration of 10 μg/mL. The dose is 1 mL for adults. Each 1-mL dose contains 10 μg of hepatitis B surface antigen.
Adapted from Protection against viral hepatitis. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep 39(RR-2):1–26, 1990; and U.S. Public Health Service: Guidelines for the management of occupational exposures to HBV, HCV and HIV: recommendations for postexposure prophylaxis. MMWR Recomm Rep 50(RR-11):1–42, 2001.

pancreatitis). Initially, all the potential causative disorders must be considered; however, the clinical history and aminotransferase profile should facilitate accurate diagnosis. Mild aminotransferase level elevation and marked bilirubin level elevation are consistent with alcoholic hepatitis; ultrasonography will differentiate this from common duct obstruction. Serum should be sent for testing for anti-HAV IgM and hepatitis B core antibody (HBcAb) IgM, but results usually are not available to establish these diagnoses in the ED.

Diagnostic Testing

Laboratory tests reveal moderate elevations of AST and ALT levels. Values in excess of 10 times normal are unusual, even in severe cases associated with eventual liver failure. Compared with viral hepatitis, a relative predominance of AST to ALT is expected. The bilirubin level is commonly elevated, and the WBC count often is high, in the range of 10,000 to 20,000/mm.[3] The PT and INR provide a rough assessment of hepatic dysfunction. An acutely

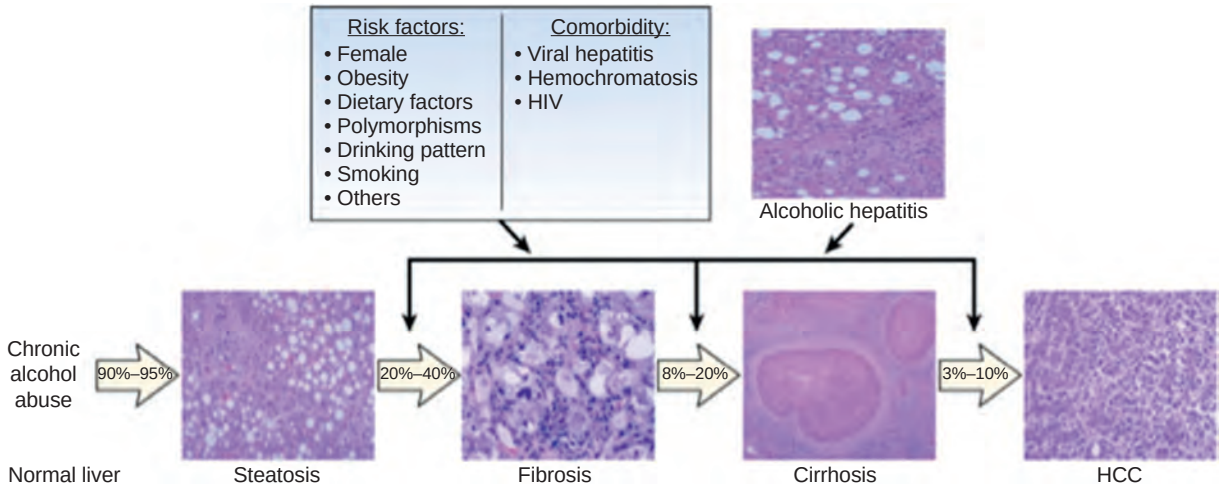

Fig. 80.7. Progression of alcoholic-related liver disease. *HCC,* Hepatocellular carcinoma.

prolonged PT or elevated INR value in a patient not suspected to have chronic cirrhotic disease suggests a complicated course. Electrolyte or acid-base disturbances may develop with excessive vomiting or alcoholic ketoacidosis.

Management

The management of alcoholic hepatitis is principally supportive. Fluid and electrolyte imbalances must be corrected, usually requiring parenteral fluid replacement; antiemetics may mitigate the need for IV treatment. Alcohol may suppress gluconeogenesis, thereby causing hypoglycemia. The blood glucose level should be measured and supplemented, as indicated. Many alcoholics are malnourished and, if thiamine deficiency is suspected, thiamine should be given at a dose of 100 mg IV. Ethanol-induced magnesium wasting may not be apparent on serum magnesium measurement, and replacement should be given empirically unless the patient has a contraindication, such as renal failure or known hypermagnesemia. Magnesium can be given as the sulfate salt in a dose of 1 g IV or IM or as an oxide, chloride salt, or amino acid conjugate for oral replacement therapy at a daily dose of 200 to 1000 mg.

The overall nutritional status of the patient should be addressed with the administration of a high-calorie, vitamin-supplemented diet. Protein content may require restriction if evidence of cirrhosis and incipient encephalopathy exists. Coexisting gastritis should be treated with histamine H_2 antagonists, proton pump inhibitors, and antacids. Variceal bleeding is associated with a 5-year mortality rate of 65%; acute bleeds require pharmacologic intervention that decreases portal blood flow, such as octreotide (50-μg bolus followed by 25–50 μg/h), somatostatin (250-μg bolus and 250 μg/h infusion), or vasopressin (0.4-unit bolus followed by 0.4–1 unit/min continuous infusion).[15] Treatment should not be delayed while identification of the source of bleeding is undertaken. Varices that continue to bleed will require balloon tamponade. If rebleeding occurs, treatment options include endoscopic variceal ligation, endoscopic variceal sclerotherapy, transjugular intrahepatic portosystemic shunt (TIPS), or surgical shunt placement.

The American Association for the Study of Liver Disease (AASLD) has recommended that treatment be based on the assessment of disease severity. There are several severity scales. The most widely used is the Maddrey discriminant function (MDF) score based on coagulation and bilirubin levels. Severe alcoholic hepatitis is indicated by an mDF score more than 32. In the absence of GI bleeding, hepatorenal syndrome, or sepsis, the American Association for the Study of Liver Disease (AASLD) recommends the initiation of corticosteroids (oral prednisolone, 40 mg daily, or parenteral methylprednisolone, 32 mg daily) for those with alcoholic hepatitis and an mDF score more than 32.[15] Pentoxifylline, an inhibitor of cytokines such as anti–tumor necrosis factor alpha, has been shown to provide mild benefit over placebo and may be used to treat those with contraindications to corticosteroids.[16] Compared to corticosteroids for the treatment of alcoholic hepatitis, pentoxifylline does not demonstrate improved 28-day survival.

Disposition

The disposition is determined by the patient's clinical state—degree of fluid and electrolyte abnormality, ability to retain oral intake, any coexistent illnesses or complications—and socioeconomic circumstances. Hospitalization generally is not required. All patients should be advised to abstain from further alcohol ingestion and should be provided referral for detoxification or alcohol dependency treatment.

CIRRHOSIS

Principles

Cirrhosis is a generic term for end-stage chronic liver disease characterized by the destruction of hepatocytes and replacement of normal hepatic architecture with fibrotic tissue and regenerative nodules. Laennec's cirrhosis is a diffuse process that involves the entire lobule, and 10% to 20% of chronic alcoholics develop this disorder. Postnecrotic cirrhosis usually is nonhomogeneous, characterized by regions of fibrosis and hepatocyte loss alternating with normal areas. It most often is a consequence of chronic hepatitis of various causes—infectious (viral, bacterial, fungal), drug-induced, or metabolic. Biliary cirrhosis is much less common and is a consequence of chronic extrahepatic biliary obstruction or is a primary disorder of autoimmune-mediated intrahepatic duct inflammation and scarring. Nonalcoholic fatty liver disease has become an increasingly recognized cause of cryptogenic cirrhosis. This still poorly understood disease, with features similar to those of Laennec's cirrhosis, is more common in obese patients and those with type 2 diabetes mellitus.

Clinical Features

The clinical manifestations of cirrhosis are related to loss of hepatocytes, leading to metabolic and synthetic dysfunction, or to fibrosis and altered hepatic architecture, resulting in impaired

portal vein blood flow and portal hypertension. Typically, the patient with cirrhosis complains of chronic fatigue and poor appetite. With the exception of those with biliary cirrhosis, many patients with cirrhosis can be asymptomatic until complications develop, such as GI bleeding, ascites, or hepatic encephalopathy. Patients with biliary cirrhosis generally complain of pruritus or exhibit obvious jaundice before end-stage cirrhosis or complications develop. Primary biliary cirrhosis may be associated with other immune-mediated disorders; these patients may have signs and symptoms characteristic of scleroderma or the CREST syndrome (***c***alcinosis cutis, ***R***aynaud's phenomenon, ***e***sophageal motility disorder, ***s***clerodactyly, and ***t***elangiectasia).

Physical examination may reveal muscle wasting, thinning of the skin with patchy ecchymosis, spider angiomata, palmar erythema, Dupuytren's contracture and, in men, gynecomastia or testicular atrophy. Jaundice generally is absent in mild cases or in those with early disease. The liver may not be palpable if it is extensively scarred, but a large regenerative nodule, tumor, or fatty infiltration can result in hepatomegaly. Complications of cirrhosis include ascites, hepatic encephalopathy, and variceal hemorrhage. Ascites is the most common of these, particularly in those with advanced disease, and may be present with abdominal wall vein distention known as caput medusa.

Diagnostic Testing

Laboratory tests are not specific. Aminotransferase levels are rarely more than minimally elevated. The bilirubin level may be increased but usually not until cirrhosis is far advanced. Elevation of the alkaline phosphatase level out of proportion to other liver enzyme levels is suggestive of biliary cirrhosis. Coagulation studies commonly show abnormalities, and the serum albumin level is low as a result of impaired hepatic synthetic function. Mild to moderate anemia and thrombocytopenia often are present in Laennec's cirrhosis. An elevated blood urea nitrogen (BUN) or creatinine level suggests dehydration or hepatorenal syndrome. Ascites can be detected on a carefully performed physical examination or ultrasound. Bedside ultrasound demonstrating a diffuse nodular surface, with or without the presence of ascites, is consistent with cirrhosis (Fig. 80.8).

In patients with ascites and fever or abdominal pain, paracentesis should be considered to rule out spontaneous bacterial peritonitis (SBP). Nuclear scintigraphy or computed tomography (CT) imaging may reveal a hepatic or splenic appearance characteristic of cirrhosis and portal hypertension but, in general, these tests should be deferred to an elective setting.

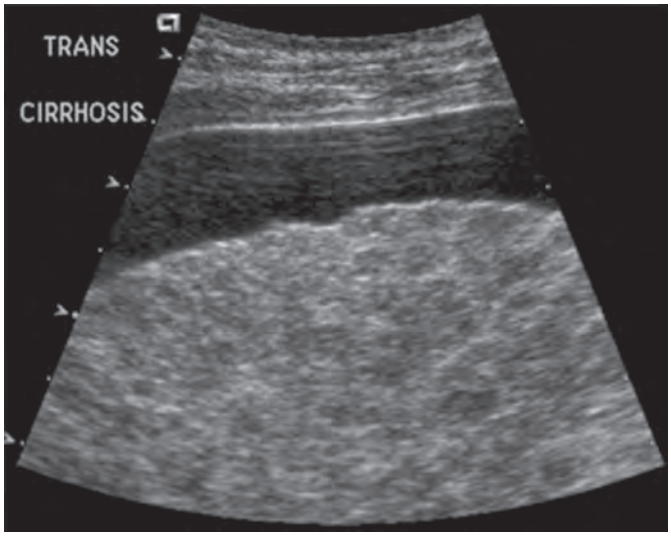

Fig. 80.8. Ultrasound of the demonstrating liver cirrhosis.

Management

Treatment of cirrhosis in the ED is limited in the absence of acute complications. Fluid and electrolyte imbalances should be corrected and vitamin and nutritional supplements provided. Most patients can be discharged with referral to a general internist for further evaluation and treatment.

The complications of cirrhosis include ascites with or without infection, GI bleeding, hepatorenal syndrome, and encephalopathy, discussed in the following section.

Ascites

Ascites occurs as a consequence of portal hypertension, impaired hepatic lymph flow, hypoalbuminemia, and renal salt retention. When severe, it can cause respiratory compromise or significant discomfort. The treatment is paracentesis with removal of 2 L of fluid or more. Removal of very large quantities of ascitic fluid can result in body fluid and electrolyte abnormalities, intravascular volume depletion, and hemodynamic instability, commonly known as paracentesis-induced circulatory dysfunction. When removing over 5 L of ascitic fluid via paracentesis, colloid infusion is necessary to avoid adverse cardiovascular, renal, and neurohumeral responses. Standard dosing of albumin after large-volume paracentesis is 8 g/L removed. Studies evaluating the use of half-dose albumin (4 g/L) for large-volume paracentesis have been promising.[17] The AASLD has established guidelines for the management of ascites secondary to cirrhosis (Table 80.3).[18]

A low-sodium diet of less than 2000 mg of sodium, in conjunction with an aldosterone antagonist such as spironolactone 100 mg daily, may be of use in the chronic management of ascites. A low-dose regimen of a thiazide or loop diuretic (furosemide, 40 mg daily) may accelerate resolution of ascites and is probably safe if the patient has coexistent peripheral edema and normal renal function. Furosemide should be given orally because IV dosing can result in a decline in renal function. The presence of peripheral edema allows the rate of fluid removal to be faster than removal in those with only ascites. To avoid brisk intravascular volume depletion and azotemia when using diuretics to mobilize fluids, individuals with ascites without peripheral edema should not exceed 500 mL of fluid removal/day.

Gastrointestinal Bleeding

Chapter 27 discusses the management of GI bleeding. In patients with cirrhosis, GI bleeding is often related to esophageal or gastric varices, but over 50% of cases result from some other source (eg, gastritis, duodenal ulcer). Coagulopathy and thrombocytopenia in conjunction with active bleeding should be corrected with platelet transfusion. The goal should be to correct the platelet count to greater than 50,000/mm^3. There is little support for the use of fresh-frozen plasma to correct asymptomatic abnormalities in PT and INR. Cryoprecipitate (1 unit/10 kg body weight) with a targeted fibrinogen level of more than 100 mg/dL may be used in active bleeding. Cyroprecipitate improves coagulopathies using a lower volume than fresh-frozen plasma. With uncomplicated prolongation of PT or INR in individuals with nutritional or gastrointestinal losses, treatment with oral vitamin K supplementation (10–20 mEq given bid to qid) may be used. If a patient has active bleeding, IV potassium (10 mEq per hour) may be substituted.

Mean arterial pressure (MAP) is an independent predictor of mortality in patients with cirrhosis. Lowering pressure may adversely affect survival. Angiotensin-converting enzyme (ACE)

TABLE 80.3

Management Guidelines for Ascites Secondary to Cirrhotic Liver Disease

CONDITION	RECOMMENDED TREATMENT
Ascites	Alcohol cessation in patients with alcohol-induced liver disease Baclofen, 5–10 mg tid, for management of alcohol cravings Diagnostic paracentesis in patients with new-onset ascites Hepatology follow up within 1 wk of hospital or ED discharge Sodium-restricted diet Diuretic use—spironolactone Spot urine sodium/potassium ratio to monitor sodium restriction Fluid restriction for sodium level < 125 mmol/L Caution in pressure lowering agents: ACE inhibitors and ARBs Avoid nonsteroidal antiinflammatory drugs (NSAIDS) Consider liver transplantation referral.
Refractory ascites	Oral midodrine, 7.5 mg tid for refractory or recurrent ascites Caution with beta blockers, such as propranolol Serial paracentesis Postparacentesis albumin infusion (6–8 g/L removed) for large-volume paracentesis (removal of >5 L) Consider referral for transjugular intrahepatic portasystemic shunt stent or surgical shunt placement. Immediate referral for liver transplantation
Spontaneous bacterial peritonitis	Paracentesis with fluid PMN count < 250 cells/mm^3 and infectious signs and symptoms requires parenteral cefotaxime, 2 g tid Paracentesis with fluid PMN count > 250 cells/mm^3 requires parenteral ceftriaxone, 2 g tid Signs of secondary peritonitis—obtain ascitic fluid for total protein, glucose, Gram stain, LDH, carcinoembryonic antigen (CEA) and alkaline phosphatase testing. Obtain CT scan. Repeat paracentesis for for patients at increased risk due to nosocomial or recent antibiotic exposure. Albumin, 1 g/kg body weight in the setting of PMN >250 cells/mm^3, renal insufficiency (blood urea nitrogen > 30 mg/dL or creatinine > 1 mg/dL)
Hepatorenal syndrome (HRS)	Obtain urinary neutrophil gelatinase-associated lipocalin to aid in the diagnosis Albumin infusion plus vasoactive midodrine or octreotide for type I HRS[a] Albumin infusion plus norepinephrine for type I HRS[a] in the intensive care setting Urgent referral for liver transplantation for type I or II HRS[a]

[a]Type I hepatorenal syndrome (HRS).
Adapted from Runyon BA: Introduction to the Revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 57:1651–1653, 2012.

inhibitors, angiotensin receptor blockers (ARBs), and beta blockers, such as propranolol, should be used with caution.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is defined as renal failure occurring in the setting of cirrhosis without obvious renal pathology. An elevated creatinine or blood urea nitrogen (BUN) level may herald the onset of hepatorenal syndrome and necessitates hospitalization of the patient for optimal fluid and electrolyte management. There are two classifications, type I HRS and type II HRS. Type I is the more severe and is associated with serum creatinine levels exceeding 2.5 mg/dL. Clinical recommendations summarized by the AASLD are outlined in Table 80.3. Despite the use of albumin and vasoactive medications such as norepinephrine to increase the MAP, hepatorenal syndrome carries a high mortality.

HEPATIC ENCEPHALOPATHY

Principles

Hepatic encephalopathy is a clinical state of altered cerebral function resulting from the diseased liver's failure to perform its normal metabolic functions adequately. Ammonia, formed primarily in the GI tract by bacteria, is normally absorbed and converted to urea in the liver. In severe hepatic disease, ammonia accumulates, crosses the blood-brain barrier, and combines sequentially with α-ketoglutarate and glutamate to form glutamine. Serum ammonia levels correlate inconsistently with the severity of encephalopathy, but there is an association of ammonia levels with cerebrospinal fluid (CSF) glutamine levels. Whether glutamine is itself toxic or simply represents a marker for disordered central nervous system (CNS) metabolism is unknown.

Clinical Features

The clinical manifestations of hepatic encephalopathy range from mild cognitive dysfunction, irritability, and confusion to profound coma. Asterixis, a low-amplitude, alternating flexion and extension of the wrist that occurs when the wrist is held in extension, is characteristic of the neuromuscular dysfunction seen in mild to moderate degrees of encephalopathy. A similar finding may be elicited in the dorsiflexed foot or with extension of the neck. Fetor hepaticus, a musty breath odor presumably from mercaptans, may be detected in severe cases. Physical examination commonly reveals signs of cirrhosis—spider angiomata, testicular atrophy, muscle wasting, superficial bruising, gynecomastia, and ascites.

Differential Diagnosis

The differential considerations in patients with suspected hepatic encephalopathy include all causes of altered sensorium. The scope of the differential diagnosis can be narrowed if the patient's

history includes previous episodes of hepatic encephalopathy or if the patient has severe underlying liver disease and its supportive physical signs. In patients without a previous history of encephalopathy, a more in-depth evaluation for altered mental status, including testing of electrolyte levels, evaluation for toxins and neuroimaging, is necessary.

Diagnostic Testing

Liver function tests, including albumin and coagulation studies are recommended, although the results may be normal. Serum ammonia levels generally are elevated but do not necessarily correlate with the severity of encephalopathy. Results of tests reflective of hepatic synthetic function (ie, serum albumin, PT) are generally abnormal. Evaluation for underlying treatable causes (Box 80.1) is imperative. Serum chemistry tests to evaluate electrolyte and metabolic derangements as well as α-fetoprotein may reveal precipitating factors.

The presence of hypoalbuminemia must be considered in patients who require medications with high protein-binding profiles. The resultant decrease in protein binding and increased volume of distribution exposes the patient to potential drug toxicity.[19] Drugs circulating in the extracellular compartment carry the largest risk. Some commonly prescribed drugs with high protein-binding profiles include phenytoin, morphine, and antimicrobial medications, including β-lactams, glycopeptides, and lipopeptides. Additional dosing consideration should be given to agents that normally undergo hepatic metabolism with large first-pass extraction. With decreased hepatic flow and shunting, these agents are more apt to increase their bioavailability and serum concentrations. Finally, glutathione reduction and decreased renal elimination, which are commonly present in cirrhosis, may predispose individuals to further toxicity and liver injury, necessitating dosing adjustments by the treating emergency clinician.

Management

Aggressive management of the patient with hepatic encephalopathy may reverse the condition. As with any comatose patient, the airway is assessed first, not only to determine the need for respiratory support but also to prevent aspiration. Affected patients generally are hemodynamically stable but have an increased incidence of GI bleeding. Hypokalemia, alkalosis, and GI bleeding contribute to increased ammonia production or absorption, and the cause must be addressed when any of these abnormalities are detected. Relatively mild degrees of hyponatremia, hypoglycemia, azotemia, or dehydration often will have a disproportionate effect on cerebral function and require immediate correction. All CNS depressants and mild sedatives should be discontinued.

The current standard of care for patients with hepatic encephalopathy is treatment with nonabsorbable disaccharides (eg, lactitol, lactulose). Lactulose decreases the absorption of ammonia through its osmotic cathartic effects and by altering the colonic pH to trap ammonia as ammonium in the stool. The usual dose of lactulose is 30 to 60 g daily or in a quantity sufficient to result in several loose bowel movements daily. The principal adverse effect is excessive diarrhea, with resultant fluid and electrolyte imbalances.

Oral aminoglycoside antibiotics (eg, neomycin, vancomycin) as well as metronidazole have been effectively used with and without lactulose to reduce ammonia-producing enteric bacteria in patients with hepatic encephalopathy. Neomycin is a poorly absorbed aminoglycoside administered orally (PO) at an initial dose of 250 mg bid to qid (maximum, 4000 mg/day). In obtunded patients, lactulose and neomycin can be administered by nasogastric tube or rectal enema. Long-term use of aminoglycosides in patients with renal impairment or injury may result in nephrotoxicity and ototoxicity. Alternatively, rifaximin is a minimally absorbed, oral antimicrobial agent that concentrates in the GI tract. It offers minimal systemic bioavailability and fewer detrimental side effects than neomycin. It has equal or greater efficacy compared with other antibiotics used for hepatic encephalopathy and appears to have a lower bacterial resistance than systemic antibiotics.[20] Glycerol phenylbutyrate may be added to a regimen of lactulose and rifaximin. Glycerol phenylbutyrate provides an alternative removal of nitrogen waste in the form of urinary phenylacetyl glutamine. The addition of glycerol phenylbutyrate to rifaximin lowers the number of hepatic encephalopathy events and decreases mean plasma ammonia levels.[21]

Less commonly used in the United States, L-ornithine–L-aspartate (LOLA) has demonstrated benefit in lowering postprandial serum ammonia levels alone and following TIPS procedures (known to increase or exacerbate hepatic encephalopathy). It may be beneficial, even in patients with minimal hepatic encephalopathy.[22] Complementary therapies include probiotics such as *Lactobacillus acidophilus* (to increase non–urease-producing bacteria), eradication of *Helicobacter pylori* (urease-producing), and zinc replacement (metabolism of ammonia is dependent on zinc and is deficient in liver disease).

Benzoate metabolizes ammonia by reacting with glycine. The benzodiazepine antagonist flumazenil, acarbose (inhibits upper GI tract carbohydrate conversion), and polyethylene glycol (increases GI excretion) all have limited studies to support their use and require more investigation.

The molecular adsorbent recirculating system uses albumin in a dialysis solution to bind and remove circulating toxins. This novel experimental approach to treat liver failure and hepatic encephalopathy appears to be safe and cost-effective but, at present, is approved in the United States only for the treatment of liver failure resulting from a drug overdose or poisoning. Although it improves hepatic encephalopathy, studies have failed to demonstrate improved survival outcomes.[23]

Constant daily management requires nutritional intake of 25 to 40 kcal/kg/day with dietary modification of protein. Protein intake should be approximately 1 to 1.5 g/kg/day. Because cirrhosis is commonly a comorbid condition associated with poor nutrition, protein should not be further restricted in patients with active hepatic encephalopathy.

Disposition

Although most patients with hepatic encephalopathy will require hospitalization, those with grade I or II encephalopathy without complicating factors and a supportive home environment can be managed on an outpatient basis. In addition to a prescription for lactulose and rifaximin, nutritional guidance to ensure adequate caloric intake and a maximum of 1.5 g/kg/day of protein is essential.

BOX 80.1

Underlying Causes of Hepatic Encephalopathy in Patients With Known Liver Disease

Gastrointestinal bleeding
Electrolyte abnormalities including hypokalemia and alkalosis
Venous thrombosis
Ileus and constipation
Sedative medications
Dehydration and hypovolemia
Acute or chronic kidney injury
Infection

SPONTANEOUS BACTERIAL PERITONITIS

Principles

Spontaneous bacterial peritonitis is an acute bacterial infection of ascitic fluid in patients with liver disease, without an apparent external or intra-abdominal focus of infection. It can occur in any patient with ascites. Retrospective studies have identified SBP in up to 27% of patients hospitalized with cirrhosis and ascites.

The pathophysiology of SBP is related to a combination of impaired phagocytic function in the liver and to portal systemic hypertension, which can cause bowel mucosal edema, alterations in gut flora, and transmural migration of enteric organisms. Bacterial seeding may also occur from other sites in the abdomen, such as the bladder, as well as the lungs and blood. Gram-negative enteric organisms, primarily *Escherichia coli* and *Klebsiella,* are the most frequently identified organisms in SBP. Newer invasive treatments of cirrhosis, including variceal ligation, transjugular intrahepatic portosystemic shunt placement, and long-term antibiotic prophylaxis, have changed the type and cause of acute bacterial infections in cirrhosis. With improved cirrhosis care, the cause of outpatients with cirrhotic neutrocytic ascites has been found to be predominantly gram-positive. Polymicrobial and anaerobic infections have been reported but are not common.

Clinical Features

The clinical presentation of SBP ranges from acute onset of severe abdominal pain to slow insidious onset of abdominal discomfort to encephalopathy. Patients may have fever, although an elevated temperature is not always detected. Chills and hemodynamic instability may be slow to develop. On physical examination, palpation of the abdomen may elicit only mild tenderness or may reveal abdominal rigidity and guarding, with rebound tenderness. Although by definition ascites must be present for SBP to develop, free peritoneal fluid may not always be clinically apparent. One study has identified a positive peritoneal fluid culture rate of 3.5% among patients who were judged to have asymptomatic ascites. This observation underscores the exceptionally broad spectrum of manifestations and often very minimal physical findings with this disorder and indicates the need to consider the diagnosis of SBP in any patient with ascites who has abdominal pain or exhibits unexplained clinical deterioration.

Differential Diagnosis

The differential diagnosis for SBP includes all entities that may lead to peritonitis and abdominal pain in patients with or without liver disease.

Diagnostic Testing

Diagnosis is made by culture of the ascitic fluid, but treatment decisions should be made in advance of these results. An ascitic fluid granulocyte count greater than 500 cells/mm^3 correlates with positive cultures in more than 90% of cases; however, ED treatment for SBP should be initiated if the neutrophil count is greater than 250 cells/mm^3. Cultures of ascitic fluid guide the antibiotic choice. Also, fluid chemistry testing may aid in the diagnosis when the fluid neutrophil count is nondiagnostic or peritonitis secondary to another abdominal source (eg, urinary tract infection, appendicitis) is suspected. Determining protein, lactate dehydrogenase (LDH), glucose, carcinoembryonic antigen, and alkaline phosphatase levels and performing Gram staining to assist with the distinction of SBP from secondary peritonitis is recommended.

A positive result of ascitic fluid testing using leukocyte esterase reagent strips (LES) has a high degree of correlation with a clinically significant elevation of the neutrophil cell count in the fluid. Although not as sensitive as cultures, LES have been found to have a high specificity and moderate sensitivity, leading many to recommend their use for rapid testing and diagnosis of SBP.

Testing of ascitic fluid prior to administering antibiotics is imperative. A single dose of antibiotic will produce negative cultures at 6 hours in 86% of patients with SBP.[23] Additional findings beyond an elevated neutrophil count include a pH of less than 7.34, pH gradient between the serum arterial blood and ascitic fluid of more than 0.1, or serum-ascites albumin fluid gradient (albumin in ascites subtracted from serum albumin level) more than 1.1 g/dL are early indicators of SBP.

Other laboratory parameters (eg, aminotransferase and bilirubin levels, peripheral blood count) are commonly abnormal, but such findings are nonspecific and more often are a consequence of underlying liver disease than infection. The PT and INR should be measured in advance of paracentesis, and fresh-frozen plasma should be administered if significant coagulopathy is identified.

Management

The treatment of SBP requires IV antibiotics. The choice of agents is driven by the anticipated bacteriology of the process. A third-generation cephalosporin, IV cefotaxime, 2 g every 8 hours, is considered to be the agent of choice.[18] In patients capable of oral therapy without prior quinolone exposure, an alternative treatment is oral ofloxacin 400 mg bid. Ampicillin with an aminoglycoside is also effective but is associated with an increased risk of renal toxicity. Unless an atypical response, risk profile, or resistant organism is identified, patients with SBP should be treated for a total of 5 days.

Peritonitis is a frequent complication in patients undergoing peritoneal dialysis. Similar to peritonitis in cirrhosis, peritonitis in patients undergoing peritoneal dialysis may be spontaneous or secondary to underlying urinary tract, GI, or lung disorders. The most common symptoms include abdominal pain and cloudy peritoneal effluent. The diagnosis is presumed with a dialysate WBC more than 100 cells/mm^3 and confirmed by culture. In patients with symptoms suggesting peritonitis, dialysate should be collected for analysis and culture, and treatment should be initiated. Consideration of catheter removal is also warranted. Intraperitoneal antimicrobial administration is preferred over an IV regimen. The International Society for Peritoneal Dialysis guidelines recommend treatment that includes vancomycin or cefazolin, plus cefepime, ceftazidime, or aztreonam.[24]

Disposition

Any patient with ascites is at risk for the development of SBP. This risk is markedly increased in patients with ascitic fluid protein levels less than 1 g/dL. Other important risk factors include serum bilirubin level greater than 3.2 mg/dL, platelet count less than 98,000/mm^3, and a previous history of SBP. Antibiotic prophylaxis for high-risk patients can reduce SBP incidence by 60% to 80% and can be cost-effective. The preferred prophylaxis regimen consists of norfloxacin, 400 mg daily; additional regimens for prophylaxis include ciprofloxacin, 500 mg bid, or trimethoprim-sulfamethoxazole (TMP-SMX), 800/160 mg daily.

In patients with cirrhosis who are admitted for GI bleeding, prophylactic ceftriaxone (1 g daily) is used until the patient is taking food orally, at which time a switch to TMP-SMX should be undertaken.

Long-term outpatient prophylaxis with norfloxacin, ciprofloxacin, or TMP-SMX is recommended for patients who have survived an episode of SBP and those with higher risk ascitic

laboratory values (protein < 1.5 g/dL, BUN level > 25 mg/dL, or serum sodium level < 130 mmol/L). If a high-risk patient with ascites is identified in the ED and contraindications are absent, prophylactic therapy should be initiated.

Finally, in patients with ascites secondary to cirrhosis, the prevention of SBP should also include consideration of discontinuation of proton pump inhibitors, which adversely alter acid secretion and gut flora, and beta blockers, which may increase risk secondary to their resultant systemic hypotension.

Patients with diagnosed SBP require hospitalization and will ultimately need a referral to a primary care physician or gastroenterologist for close outpatient follow-up. Most patients with SBP will not require repeat abdominal paracentesis. In those with inconsistent symptoms, abnormal treatment response, atypical organisms, or recent β-lactam exposure, repeat paracentesis may help differentiate secondary bacterial peritonitis requiring surgical interventions.

HEPATIC ABSCESSES

Hepatic abscesses fall into two broad categories, pyogenic and amebic. Although there may be similarities in clinical presentation, the pathophysiology and treatment differ significantly.

Pyogenic Abscess

Principles

Liver abscesses are usually associated with biliary tract obstruction or cholangitis but may be related to diverticulitis, pancreatic abscess, omphalitis, appendicitis, inflammatory bowel disease, pneumonia, or bacteremia. Often, no underlying cause for hepatic abscess is identified. Solitary and multiple abscesses occur with approximately equal frequency, usually in the right lobe of the liver. Patients with multiple lesions tend to be more severely ill, with less favorable outcomes. Causative organisms may be anaerobic and aerobic; *E. coli, Klebsiella, Pseudomonas,* and *Enterococcus* spp., anaerobic streptococci, and various *Bacteroides* spp. are usually isolated.

Clinical Features

The clinical presentation is characterized by the onset of high fever, chills, right upper quadrant (RUQ) pain, nausea, and vomiting. Patients generally have an acute presentation and appear quite ill, particularly if there is underlying cholangitis. Physical findings include elevated temperature, RUQ tenderness, hepatomegaly, and occasionally dullness to percussion and decreased breath sounds over the right lower chest. Jaundice may be apparent, especially if coexistent biliary tract obstruction is present.

Differential Diagnosis

The differential diagnosis of pyogenic hepatic abscess includes amebic liver abscess, hepatitis, cholangitis, and pancreatic and subphrenic abscesses.

Diagnostic Testing

Laboratory findings include leukocytosis in 70% to 80% of cases, elevated alkaline phosphatase levels in up to 90%, and bilirubin level in excess of 2 mg/dL in 50% of patients. Although blood culture sensitivities are approximately 30% in patients with pyogenic abscesses, they should be determined in advance of treatment and while awaiting definitive drainage and testing from the abscess site. Serum aminotransferase levels commonly are elevated 2 to 4 times normal. Chest radiographs may reveal a right pleural effusion, basilar atelectasis, and/or an elevated right hemidiaphragm. The most useful, sensitive, and expeditious imaging modalities include ultrasonography and CT (Figs. 80.9 and 80.10).

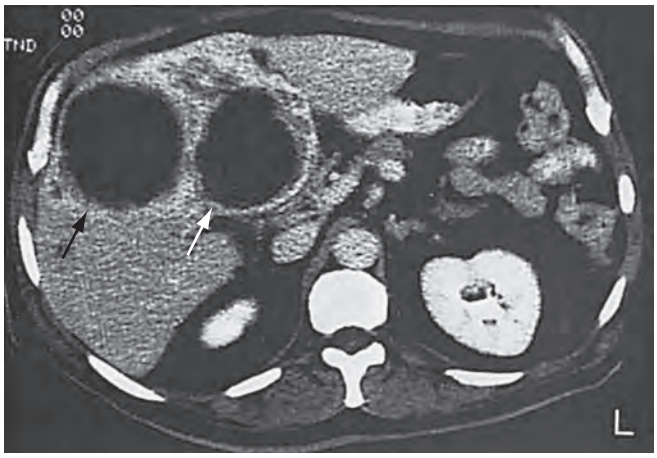

Fig. 80.9. Contrast CT scan of liver showing large cystic masses *(black arrow, white arrow)* with irregular, contrast-enhancing borders in a patient with pyogenic liver abscess caused by *Streptococcus milleri.*

Fig. 80.10. Contrast CT scan of liver showing pyogenic liver abscess. This complex cystic mass with air-fluid level *(arrow)* was caused by gas-producing *Klebsiella pneumoniae.*

Management

The initial treatment of a pyogenic hepatic abscess is hemodynamic stabilization, IV antibiotics, and pain control. Pending definitive microbial identification, broad-spectrum antibiotic coverage should be initiated and continued for 2 to 6 weeks, depending on the size of the abscess and patient response. Although there has been no consensus on treatment regimens, IV antibiotic coverage targeting gram-negative bacteria and anaerobes is recommended. This may include cefotaxime (2 g tid) plus metronidazole (500 mg tid) or ampicillin (2 g qid) in conjunction with gentamycin (1.7 mg/kg tid) and metronidazole or monotherapy with piperacillin-tazobactam (3.375 IV qid), imipenem, or meropenem. The addition of vancomycin is indicated for an acutely ill or unstable patient, as well as any patient with gram-positive cocci on staining or when suspicion for enterococcal or staphylococcal organisms is high. Fluoroquinolones, although often combined with metronidazole for continuation of treatment as an outpatient, should be avoided in areas with *E. coli* resistance greater than 10%.[25]

Definitive treatment for abscesses larger than 3 cm requires drainage. This usually is done percutaneously under image guidance, reserving open surgical drainage only for complex cases associated with intraperitoneal soiling, intestinal perforation, or biliary obstruction. Complications include rupture of the abscess into the peritoneal cavity or an adjacent anatomic structure (eg, thoracic cavity, lung, pericardium).

Disposition

Patients with pyogenic hepatic abscess require hospitalization. Consultation with a general surgeon, gastroenterologist, or interventional radiologist will be necessary.

Amebic Abscess

Principles

Amebiasis is one of the most common protozoal infections worldwide. Transmission generally occurs by the fecal-oral route, often as a consequence of ingesting contaminated water or foodstuffs. Although intestinal disease is by far the most common manifestation of infection, extraintestinal disease can occur, with the liver most commonly affected. *Entamoeba histolytica* is the only ameba responsible for invasive disease, and only certain varieties of *E. histolytica* are pathogenic after invasion of the intestinal mucosa and transit through the portal vein. As with a pyogenic abscess, involvement of the right liver lobe is more common.

Clinical Features

The clinical presentation generally is acute with fever, chills, nausea, vomiting, and abdominal pain. Diarrhea is common in children but is present in less than one-third of adults. Careful questioning of patients without diarrhea often yields a history of intestinal illness several weeks prior to presentation. Many patients complain of cough, which may direct attention away from the liver. A chronic illness of several months' duration, although less common than the acute presentation, can occur. Physical findings include an elevated temperature, RUQ tenderness, hepatomegaly, and dullness, with decreased breath sounds over the right lower chest.

Differential Diagnosis

In order of their frequency of occurrence, the differential diagnosis includes pyogenic abscess, biliary tract disease, hepatitis, pneumonia, appendicitis, and pancreatitis. Respiratory symptoms and abnormalities on the chest radiograph may cause confusion with pulmonary illnesses. Hepatic imaging is helpful in establishing the diagnosis; however, differentiation from pyogenic illness is difficult and requires additional laboratory testing.

Diagnostic Testing

Laboratory findings in patients with an amebic abscess are not specific. Neutrophilic leukocytosis is common. The alkaline phosphatase level is elevated in 75% of cases and aminotransferase levels in 50%. Hyperbilirubinemia is uncommon and, when present, is indicative of biliary obstruction. The chest radiograph may reveal a right pleural effusion, basilar atelectasis, or elevated right hemidiaphragm. Ultrasound of the liver may reveal specific findings unique to amebic abscess, specifically a peripherally based, round or oval mass, with a well-circumscribed border and homogeneous hypoechoic center (Fig. 80.11). CT and magnetic resonance imaging (MRI) are alternative abdominal imaging modalities if ultrasonography is inconclusive. The diagnosis is supported by identification of a pathogenic protozoan in the stool. Even in cases of invasive intestinal disease, the yield may be low.

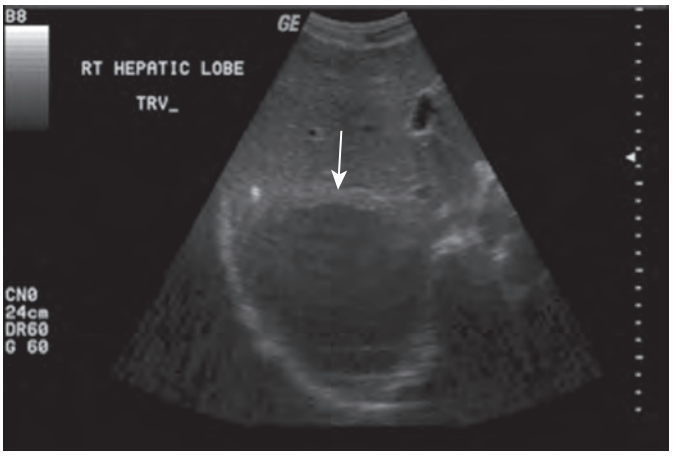

Fig. 80.11. Ultrasound of the liver demonstrating amebic abscess showing a peripherally located abscess with a homogeneous, hypoechoic center (*arrow*).

An enzyme-linked immunosorbent assay (ELISA) and counterimmune electrophoresis are the recommended diagnostic tests. The indirect hemagglutination test remains positive for an extended period and is therefore not helpful in establishing the presence of acute infection.

Management

Management of an amebic abscess consists of supportive therapy and initiation of amebicidal therapy. Metronidazole, 750 mg PO or IV tid for 7 to 10 days, is the therapeutic agent of choice. Most patients will respond to this regimen with percutaneous catheter drainage required only in refractory or complicated cases. The most serious complication of amebic liver disease is rupture into adjacent anatomic structures. Involvement of the lung occurs in 20% to 35% of cases of extrahepatic disease, often manifesting as a massive pleural effusion or consolidative pneumonia. With rupture into a bronchus, the patient can have cough productive of an anchovy paste–like substance or necrotic debris or frank hemoptysis. Abdominal pain with peritonitis can result from rupture into the abdominal cavity. Involvement of the pericardium occasionally is seen with lesions in the left lobe of the liver and can be catastrophic, either acutely as a consequence of pericardial tamponade or chronically from constrictive pericarditis.

Disposition

Select patients with amebic liver abscess can be managed as outpatients. This approach is best suited for those with mild clinical disease, stable living circumstances, and adequate access to medications and follow-up care. In patients with more severe disease, evidence of complications, or questionable social circumstances, hospitalization is advised.

MISCELLANEOUS DISORDERS AND CONDITIONS OF THE LIVER

Liver Disease in Pregnancy

The two primary hepatic disorders associated with pregnancy are benign cholestasis and acute fatty liver.

Benign Cholestasis

Benign cholestasis during pregnancy is common and has a familial linkage. Onset is in the third trimester and is heralded by the development of progressive pruritus. The bilirubin level may be elevated but not dramatically, so jaundice is uncommon. Laboratory tests reveal elevated alkaline phosphatase, 5′-nucleotidase, and bilirubin levels. Although the chief concern to the mother is discomfort from pruritus, the illness can bode poorly for the fetus, with an increased incidence of prematurity, stillbirth, and fetal distress. Malabsorption of vitamin K can result in serious coagulopathy in the fetus, predisposing to spontaneous intracranial hemorrhage. Treatment is supportive and should include subcutaneous vitamin K for the mother antepartum and for the newborn after delivery. Cholestasis resolves without incident after delivery.

Acute Fatty Liver

Acute fatty liver of pregnancy is a malignant disorder that if unrecognized, can progress rapidly to maternal and fetal demise. The illness occurs in the latter part of the third trimester and is more common in primigravidas and twin pregnancies. The initial clinical features include fatigue, anorexia, nausea, and vomiting. Physical findings include mild jaundice and abdominal tenderness, most prominently in the midepigastrium and right upper quadrant. The liver may not be palpable because of the enlarged uterus.

Abnormal laboratory findings include moderate elevation of aminotransferase levels (5 to 10 times normal) hyperbilirubinemia, hypoglycemia, and evidence of disseminated intravascular coagulation—prolonged PT and partial thromboplastin time, hypofibrinogenemia, elevated fibrin split products, and thrombocytopenia. Treatment involves aggressive fluid and electrolyte support, glucose administration, and immediate delivery. Liver disease in pregnancy generally resolves without permanent sequelae after delivery.

Budd-Chiari Syndrome

Budd-Chiari syndrome is caused by hepatic venous outflow obstruction located anywhere above the level of hepatic venules. The disorder is associated with hypercoagulable states, such as factor V Leiden, protein S and C deficiency, thrombophilia, antithrombin III deficiency, myeloproliferative disorder, Behçet's disease, paroxysmal nocturnal hemoglobinuria, and oral contraceptive use.

The clinical presentation varies from fulminant hepatic failure in acute high-grade obstruction to the insidious onset of jaundice to ascites in more subacute forms. Clinical symptoms correlate with the degree of venous obstruction and rate of venous occlusion. Fulminant disease is clinically indistinguishable from acute hepatic necrosis and hepatocellular disease secondary to viral infection. It is important to make the distinction between these two causes of hepatic failure early because treatment options differ. Prompt intervention in patients with Budd-Chiari syndrome offers the possibility of effective relief of signs and symptoms, with a potentially favorable outcome. Doppler ultrasound imaging of the hepatic vein has been reported to have a sensitivity of 85% to 95% for the diagnosis of Budd-Chiari syndrome and emerges as the diagnostic modality of choice in the ED setting.

The management of Budd-Chiari syndrome relates to the severity and acuity of disease. Newly diagnosed Budd-Chiari syndrome with acute decompensation will require immediate consultation and consideration for transjugular intrahepatic portosystemic shunt placement, percutaneous angioplasty, or thrombolytic therapy. Previously diagnosed disease with worsening ascites can be managed with modification of diuretics and therapeutic paracentesis, followed by referral to a primary care physician or gastroenterologist. Portacaval shunting and liver transplantation are options for disease refractory to medical or other less invasive percutaneous interventions.

Liver Transplantation

Human orthotopic liver transplantation offers a 5-year survival rate of approximately 80%, but complications are common. Early complications include bleeding, acute rejection, vascular and biliary tract problems, and infection. Delayed complications include malignancy, recurrence of underlying disease, infection, chronic rejection, medication toxicity, and renal failure. Many early complications will manifest during the immediate postoperative period. Delayed complications may occur 1 year or more after transplantation.

Liver transplant recipients are at increased risk for opportunistic infections as a consequence of their immunosuppressive therapy. Presenting signs and symptoms may be subtle. Chronic rejection manifests with low-grade temperature elevation, fatigue, and jaundice. Expected laboratory abnormalities include elevated bilirubin and transaminase levels, prolonged PT or INR, and low serum albumin level. Renal failure may not be clinically apparent until the glomerular filtration rate has declined significantly. Routine serum creatinine level measurement is the best means of identifying this disorder early, when successful intervention is still possible.

The most common combination of immunosuppressive agents used after liver transplantation includes a corticosteroid (eg, prednisone) along with a calcineurin inhibitor (eg, cyclosporine or tacrolimus) and sirolimus, mycophenolate, or azathioprine. Corticosteroid toxicity may produce glucose intolerance, osteoporosis, gastric ulceration, and muscle wasting. Cyclosporine and tacrolimus can cause renal impairment, which is the most common dose-limiting effect of these agents. Azathioprine can be hepatotoxic but is more often associated with bone marrow suppression, placing the patient at increased risk for infectious complications and bleeding diathesis.

Management of patients with complications related to their liver transplant is directed by the nature of the problem. Accordingly, assessment may include a complete blood count (CBC) and determination of glucose, BUN, creatinine, serum electrolyte, transaminase, bilirubin, and albumin levels, as well as coagulation studies. Hepatobiliary imaging is indicated if tumor, vascular occlusion, or biliary tract obstruction is suspected. Ultrasound studies with Doppler interrogation can be particularly useful in the ED setting. Consultation with a transplantation specialist is recommended for any patient with a problem potentially related to the organ transplant or immune-modulating medications.

BILIARY TRACT DISORDERS

CHOLELITHIASIS

Principles

The principal cause of biliary tract disease is related to the development of gallstones. There are two categories of gallstones, cholesterol stones and pigmented stones.

Cholesterol stones usually occur as a consequence of an elevated concentration of cholesterol in bile relative to the other principal constituents, bile acids and phospholipids. Bile acids and lecithin, the primary bile phospholipid, act in concert to solubilize cholesterol. As cholesterol levels rise or bile acid and lecithin levels decline, cholesterol has an increasing tendency to form crystals. These crystals, particularly in an incompletely

emptying gallbladder, serve as a nidus for stone formation. Factors associated with an increased risk of cholesterol stone formation include increased age, female gender, massive obesity, rapid weight loss, cystic fibrosis, parity, drugs (eg, clofibrate, oral contraceptive agents), and familial tendency.

Pigmented stones are of two varieties, black and brown. Black stones occur exclusively in the gallbladder, contain a high concentration of calcium bilirubinate, and are usually encountered in older adults and those with intravascular hemolytic diseases (eg, sickle cell anemia, hereditary spherocytosis). Brown stones are associated with infection and can form in the gallbladder and intrahepatic and extrahepatic bile duct systems. Although bacterial infections are usually incriminated, parasites (eg, *Ascaris lumbricoides, Clonorchis sinensis*) have also been linked to brown stone formation. Both types of pigmented stones contain calcium bilirubinate and therefore may be visible on plain abdominal radiographs. For a stone to be radiopaque, it must contain at least 4% calcium by weight.

Clinical Features

The most common clinical manifestation of cholelithiasis is biliary colic. The pathophysiology is related to the passage of small stones from the gallbladder through the cystic duct into the common bile duct. The term *colic* is often misleading; affected patients commonly report steady pain, rather than intermittent or cramping discomfort. The pain most often is perceived in the RUQ but may be localized over a wide region of the upper abdomen. Radiation of pain, if it occurs, generally is to the base of the right scapula or shoulder. Associated signs and symptoms include nausea and vomiting, which may be severe enough to lead to fluid and electrolyte imbalances. Patients with biliary colic commonly report similar self-limited occurrences in the past and may offer an association between symptom onset and eating. Physical findings include mild tenderness to palpation, without guarding or rebound in the RUQ or epigastric region.

Differential Diagnosis

Considerations in the differential diagnosis of biliary colic include cholecystitis, peptic ulcer disease of the stomach or duodenum, pancreatitis, and hepatitis. Patients with cholelithiasis may occasionally have chest pain, so cardiopulmonary syndromes must be considered as well. A compatible clinical history in conjunction with normal laboratory test values (ALT, AST, lipase, and alkaline phosphatase levels), gallstones on ultrasound, and minimal or no tenderness in the RUQ favor the diagnosis of cholelithiasis. If abnormalities are not visualized, a chest radiograph or electrocardiogram may help differentiate between cardiopulmonary and biliary pathology.

Diagnostic Testing

No pathognomonic clinical laboratory findings are recognized; results of commonly performed tests typically are within normal limits. Important tests to perform include ALT and AST level measurements to evaluate for the presence of hepatitis, bilirubin and alkaline phosphatase level determinations to look for evidence of common duct obstruction, and lipase level measurement to assess for the presence of pancreatitis.

The diagnosis of biliary colic is made clinically in conjunction with the demonstration of stones in the gallbladder. Ultrasonography is the procedure of choice for investigating the gallbladder because it can be performed rapidly, is highly sensitive, and provides the added value of permitting the evaluation of surrounding structures (Fig. 80.12). Oral cholecystography with the use of iopanoic acid is an alternative (when ultrasonography is not available or cannot be performed successfully) and can identify gallstones in 95% of patients with cholelithiasis in whom the gallbladder can be visualized.

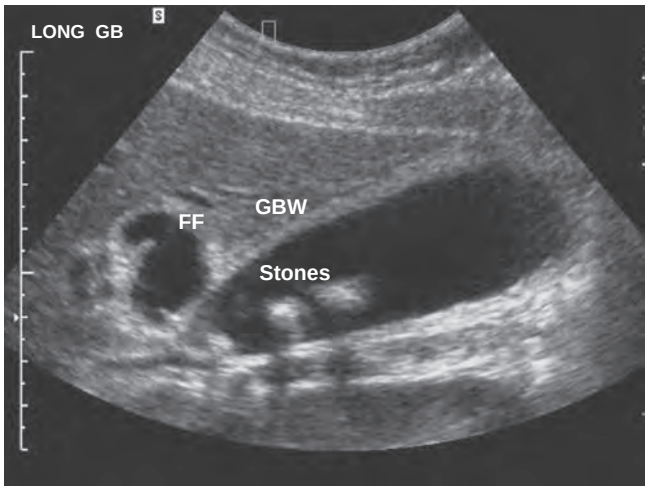

Fig. 80.12. Gallbladder with gallstones (Stones), thickened gallbladder wall (GBW), and pericholecystic fluid (FF). Together these findings constitute the sonographic signs of cholecystitis.

Management

The initial management of biliary colic is correction of fluid and electrolyte disturbances and relief of symptoms. Vomiting is managed with antiemetics and, if necessary, nasogastric suction. Pain often can be controlled with antispasmodics (eg, glycopyrrolate), nonsteroidal antiinflammatory drugs (NSAIDs), and opiate analgesic agents, as needed. The definitive management of cholelithiasis usually involves surgical removal of the gallbladder; however, other options are available. Oral administration of bile acid (eg, chenodeoxycholate, ursodeoxycholate) over a period of months to years can result in dissolution of small to medium-sized stones. Extracorporeal shock wave lithotripsy may be successful in a select, technically suitable set of patients who have functioning gallbladders and, ideally, have a small number of stones.

The most common complication of biliary colic is fluid and electrolyte imbalances secondary to vomiting. Other adverse consequences include Mallory-Weiss tears from uncontrolled emesis and cholangitis from unrecognized and persistent common bile duct obstruction.

Special Considerations

Biliary colic is an uncommon symptom in children and is usually associated with an underlying hemolytic disorder (eg, sickle cell anemia, spherocytosis). Acute management of biliary colic is the same for children and adults.

Cholelithiasis may be encountered in pregnant women. Diagnosis in this population is made more difficult by the common occurrence of nausea and vomiting, particularly in the first trimester, and the presence of an enlarged uterus in later pregnancy, which alters anatomic relationships and interferes with an abdominal examination. Ultrasound imaging is of considerable diagnostic use in this setting. ED management is the same for pregnant and nonpregnant patients; however, definitive therapy generally is delayed until after parturition.

Disposition

Hospitalization should be considered for unremitting pain, intolerance of oral intake, significant electrolyte abnormalities, or

laboratory tests indicating obstruction or possible cholecystitis. In other patients, symptom control can often be achieved and electrolyte and volume depletion corrected such that the patient can be discharged home with antiemetics and agents for pain control after demonstrating tolerance for oral intake. Referral to a general surgeon as an outpatient for further evaluation and consideration of cholecystectomy should be included in discharge planning.

CHOLECYSTITIS

Principles

Acute cholecystitis is defined as sudden inflammation of the gallbladder. The risk factors for cholecystitis are similar to those for cholelithiasis—female gender, increasing age and parity, and obesity. Although gallstones play a prominent role in the pathogenesis of cholecystitis, a minority of cases are categorized as acalculous.

Obstruction of the cystic duct appears to be the critical factor in the development of gallbladder inflammation. Gallstones are identified in 95% of patients with cholecystitis and may be located in the common bile duct in many patients with acalculous cholecystitis. Causes of cystic duct obstruction unrelated to stone disease include tumor, lymphadenopathy, fibrosis, parasites, and kinking of the duct, which leads to filling and distention of the gallbladder. The ensuing inflammatory reaction may be related to mucosal ischemia from increased hydrostatic pressure or to the action of cytotoxic products of bile metabolism (eg, lysophosphatidylcholine). Although bacteria are isolated from the bile of inflamed gallbladders in most cases, the role of infection is not completely understood. Coliforms (eg, *E. coli*) represent the most common isolates, but anaerobes have been identified in as many as 40% of cases.

Clinical Features

The most common presenting symptom of cholecystitis is pain, usually in the right upper quadrant. Although the pain initially may be colicky, it will become constant in virtually all cases. A previous history of similar but less severe and self-limited symptoms is a valuable diagnostic clue, as is documentation of previous gallstones. Nausea and vomiting are typical features, and the patient may exhibit fever or describe radiation of pain, generally to the tip of the right scapula.

Physical findings include tenderness in the RUQ or epigastric region, often with guarding or rebound. Murphy's sign (tenderness and an inspiratory pause elicited by palpation of the RUQ during a deep breath) is compatible with, but not specific for, gallbladder inflammation. Fever and tachycardia are commonly absent, so cholecystitis remains a diagnostic consideration in the absence of these findings in patients with abdominal pain and RUQ pain and tenderness to palpation.

Differential Diagnosis

Diagnostic considerations in addition to cholecystitis include hepatitis, hepatic abscess, pyelonephritis, right lower lobe pneumonia or pleurisy, pancreatitis, peptic ulcer disease of the duodenum with perforation or penetration, and appendicitis. Accurate diagnosis often requires the use of sonographic or, less commonly, scintigraphy or CT.

Diagnostic Testing

A polymorphonuclear leukocytosis with left shift is common, but a WBC count in the normal range has been seen in up to 40% of patients. Serum aminotransferase, bilirubin, and alkaline phosphatase levels may be mildly elevated but more often are within normal limits. An elevated lipase level should suggest the diagnosis of pancreatitis, instead of or in addition to cholecystitis. Plain abdominal radiographs may reveal calcified stones, gas in the gallbladder, or an upper quadrant sentinel loop, but are uncommon and nonspecific.

Ultrasound imaging is the most useful test in the ED. Visualization of the gallbladder without identification of stones has an extremely high negative predictive value for cholecystitis, whereas the presence of stones, thickened gallbladder wall, and pericholecystic fluid has a positive predictive value, in excess of 90% (Fig. 80.13).

Nuclear scintigraphy with technetium-99m–labeled iminodiacetic acid (IDA) generally is considered the most sensitive and specific imaging test for cholecystitis. IDA administered IV is taken up by hepatocytes and secreted into the bile canaliculi. Failure to obtain an outline of the gallbladder within 1 hour of administration of IDA in the presence of hepatic and common duct visualization proves cystic duct obstruction. In the appropriate clinical setting, this finding is diagnostic of cholecystitis. Conversely, visualization of the gallbladder and common duct within

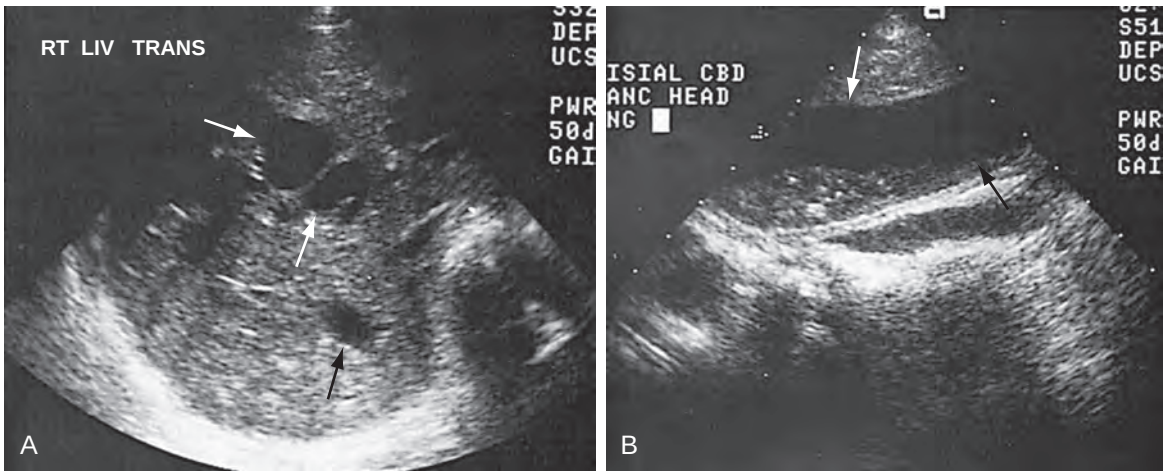

Fig. 80.13. Abdominal ultrasound images from a patient with common bile duct obstruction. **A,** Multiple dilated intrahepatic ducts *(arrows).* **B,** Significant dilated common bile duct *(arrows).* The duct measures 2 cm in diameter.

1 hour of administration has a high negative predictive value. Scintigraphy with IDA loses its sensitivity as the serum bilirubin level rises above 5 to 8 mg/dL; however, scintigraphy with diisopropyl IDA (diisopropyl iminodiacetic acid, or mebrofenin) allows visualization of the biliary tree in patients with total serum bilirubin in the range of 20 to 30 mg.

Although not the preferred imaging modality, CT can identify cholecystitis with a sensitivity of 92% and specificity of 99%. It is of particular value in cases of emphysematous and hemorrhagic cholecystitis.

Management

Supportive measures provide the foundation for initial management of acute cholecystitis—IV crystalloid administration to optimize volume status and antiemetics to manage emesis. Pain control can be addressed with NSAIDs or narcotic analgesics and possibly nasogastric suctioning, which may have the added benefit of diminishing the stimulus for biliary secretion and excretion, thereby adding to pain relief. Despite the questionable role of microbial infection in the pathogenesis of cholecystitis, antibiotics are recommended and should be continued until 1 day after the gallbladder is removed. Unless clinical evidence of sepsis exists, coverage with a single broad-spectrum antibiotic, such as IV piperacillin-tazobactam (3.375 g qid) is recommended.

The most serious complication of cholecystitis is gangrene of the gallbladder, with necrosis and perforation. Localized perforation may lead to pericholecystic abscess or fistula formation, with the latter predisposing to gallstone ileus at a later date. Patients with diabetes mellitus are at increased risk for bacterial invasion of the gallbladder wall and emphysematous cholecystitis (Fig. 80.14).

Special Considerations

Cholecystitis is uncommon in children; however, when it occurs, it should be managed as for adults. Cholecystitis in the pregnant woman poses challenges in diagnosis and therapy. Initial therapy is identical to that for the nonpregnant patient, but the issue of surgical intervention requires an individualized consultation between a surgeon and obstetrician.

Acalculous Cholecystitis. This is more common in older adults and most often is found in patients who are recovering from non–biliary tract surgery. Over the past decade, acalculous disease has been increasingly encountered as a complication of advanced acquired immunodeficiency syndrome (AIDS), usually secondary to infection with cytomegalovirus (CMV) or *Cryptosporidium*. In comparison with calculous disease, acalculous cholecystitis tends to have a more acute and malignant course, with a high mortality rate. The same techniques are used to diagnose acalculous disease as for other forms of cholecystitis but are less sensitive and specific for this entity. Sonographic findings include thickening of the gallbladder wall, pericholecystic fluid, and lack of response to cholecystokinin. Scintigraphic findings are the same as for calculous disease.

Emphysematous Cholecystitis. This is an uncommon variant of cholecystitis, occurring in approximately 1% of cases. It is characterized by the presence of gas in the gallbladder wall, presumably consequent to the invasion of the mucosa by gas-producing organisms (eg, *E. coli*, *Klebsiella* spp., *Clostridium perfringens*). It is more common in diabetic patients, has a male predominance, and is acalculous in up to 50% of cases. Clinical presentation and physical findings are similar to those for cholecystitis. Plain radiographs or CT scans of the abdomen will reveal gas in the gallbladder wall. Because of a high incidence of gangrene and perforation, emergency cholecystectomy is recommended. Antibiotic coverage should include ceftriaxone, 1–2 g every 24 hours, plus metronidazole (500 mg IV tid) or monotherapy with a β-lactamase inhibitor or carbapenem. The mortality rate for emphysematous cholecystitis is approximately 15%.

Disposition

Hospitalization for antibiotic therapy and pain management is required. Surgery is recommended for patients with cholecystitis; however, the optimal timing for surgery is not certain. Surgery usually is performed after symptoms have subsided but while the patient is still hospitalized.[26] Immediate cholecystectomy or cholecystotomy is reserved for the complicated case in which the patient has gangrene or perforation.

CHOLANGITIS

Principles

Acute obstructive cholangitis is usually the consequence of common duct blockage by a gallstone but may be associated with malignancy or a benign stricture. The key factors contributing to

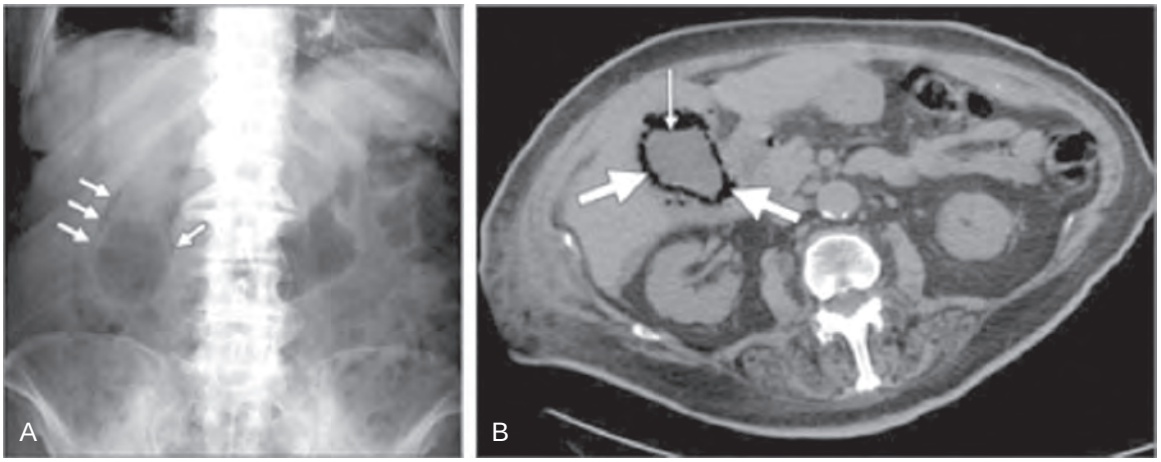

Fig. 80.14. A, X-ray demonstrating air around the wall of the gallbladder and CT scan (**B**) demonstrating a luminal air-liquid level and air within the wall of the gallbladder.

cholangitis are obstruction, elevated intraluminal pressure, and bacterial infection. Incomplete obstruction occurs more commonly than complete blockage. Bacteria may gain access to the obstructed common duct in a retrograde manner from the duodenum, by way of the lymphatics, or from portal vein blood. The most commonly encountered organisms are similar to those encountered in other varieties of biliary tract disease—*E. coli*, *Klebsiella, Enterococcus,* and *Bacteroides.*

Clinical Features

Patients most often experience fever, chills, nausea, vomiting, and abdominal pain. The classic triad of physical findings first described by Charcot consists of RUQ pain, fever, and jaundice. These findings are compatible not only with cholangitis, but also with cholecystitis and hepatitis. Sepsis is a common complication and is evidenced by tachycardia, tachypnea, and frank hypotension. The presence of Charcot's triad along with the clinical signs of sepsis—hypotension and altered sensorium—is referred to as Reynolds' pentad.

Differential Diagnosis

Although patients with cholangitis generally have a higher fever and appear more ill than those with cholecystitis, considerable variability and overlap are possible. The presence of jaundice is the clinical sign most helpful in differentiating between these two disorders. An elevated bilirubin level is characteristic of cholangitis and uncommon in cholecystitis. Ultrasonographic evidence of dilated common and intrahepatic ducts usually is required to distinguish cholangitis from cholecystitis.

Diagnostic Testing

Common laboratory abnormalities include polymorphonuclear leukocytosis, hyperbilirubinemia, elevated alkaline phosphatase level, and moderately increased aminotransferase levels. Arterial blood gas measurements are useful to identify base deficit as an early sign of sepsis.

Sonography can be helpful if it demonstrates common and intrahepatic ductal dilation, whereas identification of stones in the gallbladder or common duct suggests the underlying cause of obstruction (see Fig. 80.12). Although nuclear scintigraphy cannot determine the cause, it is a more sensitive means to diagnose early obstruction. There is a high incidence of nonvisualization of the biliary tree with cholescintigraphy in patients with common duct obstruction when sonography fails to identify dilation.

Alternative imaging techniques include CT, percutaneous transhepatic cholangiography (THC), and endoscopic retrograde cholangiopancreatography (ERCP). Although these techniques may be more expensive and time-consuming, the latter two have the added benefit of offering potential therapeutic benefit. Endoscopic cholangioscopy can permit culture of bile, direct removal of obstructing stones, or decompression of the biliary tree by sphincterotomy or stent placement.

Management

Treatment of cholangitis includes hemodynamic stabilization with crystalloid fluid and, if necessary, vasopressors. Broad-spectrum antibiotic coverage should be initiated immediately after blood culture specimens have been obtained. The choice of antibiotics should be guided by local sensitivities and must provide coverage for enteric microbes. Table 80.4 lists antimicrobial therapies for cholangitis. The key to successful treatment is early biliary tract decompression, which may be achieved with THC, ERCP, or surgery.

TABLE 80.4

Antimicrobial Treatment for Cholangitis Targeting Gram-Negative and Anaerobic Pathogens

DRUG REGIMEN	DOSAGE
FIRST-LINE SINGLE-DRUG REGIMEN	
Ampicillin-sulbactam	3 g IV qid
Piperacillin-tazobactam	3.375 g IV qid
FIRST-LINE MULTIDRUG REGIMEN	
Ceftriaxone + Metronidazole	1 g IV every 24 h + 500 mg IV tid
ALTERNATIVE TREATMENT REGIMENS	
Ciprofloxacin + metronidazole	400 mg IV every 12 h + 500 mg IV tid
Levofloxacin + metronidazole	750 mg IV every 24 h + 500 mg IV tid
Imipenem	500 mg IV qid
Meropenem	1 g IV tid
Doripenem	500 mg IV tid
Ertapenem	1 g IV every 24 h

Disposition

Patients with cholangitis require hospitalization, preferably in a monitored setting. Prompt consultation with a service that can provide for biliary tract decompression—surgery, interventional radiology, or gastroenterology—is necessary.

SCLEROSING CHOLANGITIS

Sclerosing cholangitis is an idiopathic inflammatory disorder affecting the biliary tree characterized by diffuse fibrosis and narrowing of the intrahepatic and extrahepatic bile ducts. It is commonly associated with inflammatory bowel disease, particularly ulcerative colitis; however, in 25% of cases, it appears as an isolated disorder. Patients usually report weight loss, lethargy, jaundice, and pruritus. Rarely, infective cholangitis may develop. Prompt diagnosis may be challenging because of the sclerotic nature of the bile ducts and absence of duct dilation on ultrasound imaging. Surgical exploration or ERCP often is required for diagnosis. The management of uninfected cases is primarily symptomatic. Cholestyramine, a bile acid sequestrant, may diminish pruritus.

AIDS CHOLANGIOPATHY

Manifestations of advanced HIV disease, generally associated with CD4+ counts less than 200/mm^3 , may include any one of a group of disorders collectively referred to as AIDS cholangiopathy. These disorders include bile duct stricture, papillary stenosis, and sclerosing cholangitis. The precise pathophysiology is not completely understood but is related to infection with CMV, *Cryptosporidium,* microsporidia, or *Mycobacterium avium* complex.

The clinical presentation is similar to that for other causes of cholangitis, with fever and RUQ pain. Laboratory test results include increased levels of alkaline phosphatase and minor elevation of transaminase levels. The bilirubin level is less commonly elevated than in other disorders that cause cholangitis. Ultrasonography generally is helpful in identifying bile duct stricture, thickening, or dilations, as are IDA scans. Management involves endoscopic sphincterotomy or stent placement in conjunction with treatment of the underlying infection.

KEY CONCEPTS

Hepatitis

Viral Hepatitis

The clinical presentation of viral hepatitis is highly variable, and many cases, particularly in children, are asymptomatic.

- Incubation times vary—hepatitis A, 15–45 days; hepatitis B, 60–90 days; hepatitis C, 30–90 days.
- Highly effective immunizations exist against hepatitis A and B viruses.
- Postexposure, passive immunization exists for hepatitis A and B viruses but its use is mainly limited to nonimmunized, hepatitis B–exposed individuals.
- Direct-acting antiviral regimens using nucleoside inhibitors have revolutionized hepatitis treatment. A sustained virologic response with negative HCV RNA testing is achieved in over 90% of individuals.
- Viral hepatitis is a reportable disease. Additional care in the ED and patient education should be provided to prevent disease spread.
- The process of identifying the causative agent or source should be initiated because it affects disease prognosis and public health.

Alcoholic Hepatitis

- Liver disease caused by alcohol use progresses from steatosis to fibrosis to cirrhosis, and finally to hepatocellular carcinoma. Hepatitis may accompany the cirrhosis.
- With cessation of alcohol intake, steatosis may reverse within 2 weeks.
- Alcoholic hepatitis, although generally a mild disease with minor clinical manifestations, can be a cause of fulminant hepatitis.
- Laboratory tests may help distinguish alcoholic hepatitis from viral hepatitis in that the former is associated with milder enzyme level elevations and a relative predominance of AST to ALT levels.
- Management of patients with alcoholic hepatitis should include fluid and electrolyte repletion, a high-calorie and vitamin-supplemented diet, and referral for alcohol dependence treatment.
- Variceal bleeding is treated with octreotide (50-μg bolus followed by 50 μg/h), somatostatin (250-μg bolus and 250-μg/hour infusion), or vasopressin (0.4-unit bolus followed by 0.4–1 unit/min continuous infusion) is important.
- Oral prednisone, 40 mg daily, or IV methylprednisolone, 32 mg daily, should be used for patients with alcoholic hepatitis and mDF more than 32.

Cirrhosis

Patients with cirrhosis most often present to the ED with complications of their disease—ascites, variceal bleeding, hepatorenal syndrome, or hepatic encephalopathy.

- Impaired hepatic synthetic and metabolic function in patients with cirrhosis may necessitate correction of coagulopathy before invasive procedures and modification of medication dosage.
- Prior to performing procedures, the targeted platelet count should be more than 50,000/mm^3.
- When volumes more than 5 L are removed during paracentesis to treat ascites, albumin, (8 g/L of ascitic fluid removed) should be given.
- Cryoprecipitate, 1 unit/10 kg body weight, is preferred over fresh-frozen plasma when treating liver-associated coagulopathies in a patient with active bleeding.
- Angiotensin-converting enzyme inhibiting drugs and angiotensin receptor blocking drugs should be avoided in patients with cirrhosis. Both lower mean arterial blood pressure and may increase mortality.
- Hepatorenal syndrome is heralded by an increasing creatinine level in the setting of liver failure. It is associated with a high rate of mortality and should be managed with norepinephrine, 0.5–3 mg/h in combination with albumin 1 g/kg (maximum, 100 g).

Hepatic Encephalopathy

- Hepatic encephalopathy is a state of cerebral and neuromuscular dysfunction secondary to increased ammonia levels and their effects on cerebral metabolism.
- The severity of hepatic encephalopathy does not directly correlate with the serum ammonia level.
- Consideration and evaluation for underlying exacerbating conditions, such as GI bleeding, hypokalemia, infection and dehydration, should be undertaken during the evaluation and treatment of hepatic encephalopathy.
- The differential diagnosis for hepatic encephalopathy should consider all causes of altered sensorium. The broad scope of the differential diagnosis may necessitate additional testing, including serum chemistry, CSF studies, toxicology studies, and head CT scanning.
- Management of hepatic encephalopathy includes correction of underlying electrolyte abnormalities, dietary guidance, administration of lactulose (30–60 g/day) and rifaximin (400 mg tid).
- L-Ornithine–L-arginine may be added to the regimen and has demonstrated ability to lower serum ammonia levels.
- Probiotics, acarbose, flumazenil, and polyethylene glycol require further investigation in the treatment of hepatic encephalopathy.

Spontaneous Bacterial Peritonitis

- SBP should be considered in any patient with ascites with abdominal pain, fever, or unexplained clinical deterioration.
- *E coli* and *Klebsiella* remain the two most commonly identified organisms in SBP.
- The diagnosis of SBP is dependent on obtaining ascitic fluid for cell count and culture.
- Use of leukocyte esterase reagent strips may provide a convenient means of bedside screening of ascitic fluid for SBP.
- An ascitic fluid granulocyte count greater than 250 cells/mm^3 (100 cells/mm^3 in peritoneal dialysis patients) is an indication for antibiotic treatment.
- Treatment of SBP includes cefotaxime, 2 g tid, for 5 days.
- Additional testing and imaging may assist in differentiating SBP from peritonitis secondary to other abdominal or lung pathologies.

Hepatic Abscesses

- Pyogenic abscesses often occur in the right lobe of the liver from anaerobic or aerobic microbes.
- Abdominal ultrasound and CT are the imaging modalities of choice.
- Imaging does not distinguish pyogenic from amebic abscesses.
- Treatment should be initiated prior to abscess drainage.
- Treatment regimens for pyogenic abscess include:
  - Cefotaxime + metronidazole
  - Ampicillin + gentamycin + metronidazole
  - Ciprofloxacin or levofloxacin or moxifloxacin + metronidazole
  - Piperacillin-tazobactam
  - Impinem or meropenem, or doripenem or ertapenem
- Definitive treatment for abscesses larger than 3 cm includes image-guided percutaneous drainage.
- Surgical drainage is reserved for complex cases.

Amebic Abscess

- Although similar in many ways to pyogenic abscess, diagnosis is made via stool analysis or ELISA testing.
- Most patients will have elevation in alkaline phosphatase and aminotransferase levels.
- Ultrasound may reveal specific findings unique to an amebic abscess, including a peripherally located abscess with a well-circumscribed boarder and a homogeneous, hypoechoic center.
- Coupled with imaging, laboratory data including ELISA or counterimmune electrophoresis may aide in differentiating amebic from pyogenic abscesses.
- Definitive treatment of amebic abscess is amebicidal therapy with IV or oral metronidazole (750 mg tid for 7–10 days).

Cholelithiasis

- Biliary colic should be considered in patients with nausea, vomiting, and RUQ pain.

KEY CONCEPTS—cont'd

- Diagnosis with ultrasound of the biliary system and possibly laboratory abnormalities suggests obstruction of the biliary tree.
- Initial management is supportive, with the goal of treating pain and correcting fluid and electrolyte abnormalities.
- Patients without findings of infection who are tolerating oral intake may be managed in the outpatient setting.
- Definitive care requires outpatient surgical referral for cholecystectomy.

Cholecystitis

- The vast majority of patients with cholecystitis have gallstones; however, approximately 8% have acalculous disease. The latter group of patients tend to have more severe disease and are at increased risk for complications.
- Despite an unclear relationship between bacterial infection and pathophysiology, antibiotic therapy is recommended.
- Combination therapy with a third-generation cephalosporin and metronidazole or monotherapy with a carbapenem or β-lactamase inhibitor is recommended.
- Patients with acalculous and emphysematous cholecystitis are at increased risk for gangrene and perforation and require emergency cholecystectomy.

Cholangitis

- Cholangitis is an emergency condition resulting from extrahepatic bile duct obstruction and bacterial infection.
- The classically seen triad consists of RUQ pain, fever, and jaundice
- Effective management requires prompt fluid resuscitation and administration of broad-spectrum antibiotics.
- Definitive management includes hospitalization and early biliary tract decompression, which can be achieved surgically, transhepatically, or by ERCP.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 80: QUESTIONS & ANSWERS

80.1. Which of the following statements regarding hepatitis A is true?

A. Fecal shedding and highest infectivity coincide with symptomatic disease.
B. In the United States, approximately 20% of urban-dwelling adults are seropositive.
C. Occult disease is more common in children than in adults.
D. The incidence of it is fairly consistent across ethnic groups.
E. The most common risk factor for children is travel.

Answer: C. Children are more likely to have occult disease (up to 70%). Adult seropositive rates approach 50% among urban-dwelling adults. The incidence varies widely across ethnic groups. In areas of pediatric vaccinations, increasing adult cases are seen among intravenous drug users (IVDUs) and homosexual males. The stage of highest infectivity precedes symptoms.

80.2. Which of the following statements concerning hepatitis D infection is true?

A. Hepatitis D is spread primarily via the fecal-oral route.
B. Infection with hepatitis D is an independent event with a course nearly identical to that of hepatitis A.
C. It is common to see aspartate aminotransferase (AST) level elevations far in excess of alanine aminotransferase (ALT) level elevations.
D. Many cases are misdiagnosed as acute or reactivated hepatitis B.
E. Unconjugated bilirubin levels are 2 or 3 times higher than conjugated levels.

Answer: D. Hepatitis D virus infection can only occur with (coinfection) or after (superinfection) hepatitis B infection. It is spread via the parenteral route, such as by IV drug use. Many cases are misdiagnosed as acute or reactivation hepatitis B because B markers will be positive. There are no unique biochemical or laboratory patterns for any of the viral hepatitis infections. Hepatitis D does seem to have a direct cytotoxic potential as opposed to other viral causes, where the host immunologic response causes much of the hepatitis.

80.3. A 26-year-old man presents with complaints of pruritus and a raised rash for 7 days. The rash has been associated with nausea and painful symmetrical swelling of both wrists and metacarpophalangeal joints. He has no past medical history and takes no medications. He works in a retail store. Vital signs are normal, and the physical examination is remarkable for right upper quadrant tenderness, bilateral mild wrist effusion with minimal warmth and no erythema, and diffuse skin urticaria. The remainder of the examination is negative. Blood count, chemistries, and liver studies are remarkable for WBC, 11,800 cells/mm^3, AST, 212 IU/L, ALT, 395 IU/L, normal alkaline phosphatase level, and total bilirubin of 2.3 mg/dL. Which of the following tests would be most likely to yield the diagnosis?

A. CMV titers
B. Hepatitis A antigen
C. Hepatitis B surface antigen
D. Herpes simplex I titers
E. Monospot test

Answer: C. A small number of patients with hepatitis B develop a prodrome of arthralgias and arthritis (symmetric small joints) and dermatitis. The dermatitis is typically urticarial but may be macular, popular, or petechial.

80.4. Scleral icterus becomes clinically apparent at approximately which serum bilirubin level?

A. 2 mg/dL
B. 2.5 mg/dL

C. 3 mg/dL
D. 3.5 mg/dL
E. 4 mg/dL

Answer: B. Icterus is often first noted in the sublingual or subungual areas.

80.5. Which of the following statements regarding the typical laboratory profile for a patient with acute viral hepatitis is true?
A. AST is generally elevated in excess of ALT.
B. Direct and indirect bilirubin are elevated in almost equal proportions.
C. Lactate dehydrogenase (LDH) levels are almost always normal.
D. The alkaline phosphatase level is generally elevated 5 to 10 times normal.
E. The WBC generally shows a marked polymorphonuclear leukocytosis.

Answer: B. The alkaline phosphatase level is rarely elevated more than 2 or 3 times normal, and LDH levels are modestly elevated. The WBC count may range from low, with lymphocytic predominance, to a polymorphonuclear (PMN)-predominant leukocytosis. ALT is almost always elevated in excess of AST.

80.6. A 26-year-old woman returns for follow-up after initial evaluation for possible acute hepatitis. Her hepatitis panel has returned with the following results:

Hepatitis A IgM	Negative
Hepatitis A IgG	Negative
Hepatitis B surface antigen	Positive
Hepatitis B surface antigen IgG	Negative
Hepatitis B core antigen IgM	Positive
Hepatitis B core antigen IgG	Negative
Hepatitis C antigen	Negative

Which of the following is the most appropriate diagnosis?
A. Acute hepatitis A
B. Acute hepatitis B
C. Immunity to hepatitis B
D. Previous hepatitis A
E. Previous hepatitis B

Answer: B. Acute hepatitis A is characterized by IgM to hepatitis A. Prior infection is determined by IgG antibody. Acute hepatitis B is characterized by the presence of surface antigen and IgM antibody to core antigen. Surface antigen alone may be absent late in the course of the disease or may present chronically unrelated to the current episode. IgG to the core antigen indicates previous infection. IgG to the surface antigen is the best marker for immunity.

80.7. A 39-year-old man presents with a 4-day history of abdominal pain and nausea. He has no significant past history and takes no medications. Vital signs are temperature, 37.7° C (99.9° F) oral, heart rate (HR), 98 beats/min, respiratory rate (RR), 20 breaths/min, and blood pressure, 119/68 mm Hg. The physical examination reveals scleral icterus, a normal cardiopulmonary examination, moderate right upper quadrant tenderness without rebound, and guaiac-negative stool. Laboratory assessment reveals the following:

Total bilirubin	9.8 mg/dL
Conjugated bilirubin	4.6 mg/dL
Unconjugated bilirubin	5.2 mg/dL
AST	5300 IU/L
ALT	8400 IU/L
Alkaline phosphatase	750 IU/L
Albumin	3.9 mg/dL
INR	1.2
Hematocrit	42%
Platelet count	396,000/mm^3
WBC	9900/mm^3
Blood urea nitrogen (BUN)	53 mg/dL
Creatinine	0.9 mg/dL

Which of the following courses of action is most appropriate?
A. Admission for observation and GI consultation
B. CT scan of the abdomen with contrast
C. Gastrointestinal (GI) referral for interferon therapy
D. Reassurance
E. Tapering course of corticosteroids

Answer: A. Altered sensorium and prolongation of the PT beyond 5 seconds or INR beyond 1.5 suggest fulminant hepatic failure. Similarly, an unexplained elevation of the BUN or creatinine level may portend hepatorenal syndrome, which can be fatal. The BUN level elevation in this hepatitis patient warrants admission for hydration, close observation, and GI consultation. Interferon has had some success in symptomatic hepatitis B patients but does not affect the early course. There is no role for corticosteroids.

80.8. The risk of liver injury in men increases as daily consumption of alcohol exceeds which of the following?
A. 10 g
B. 20 g
C. 40 g
D. 60 g
E. 80 g

Answer: E. This is equivalent to a six-pack of beer, four to six glasses of wine, or three or four mixed drinks daily. For women, the risk increases with a daily consumption of more than 20 g of alcohol.

80.9. A 63-year-old alcoholic man presents with altered mental status. His family reports 3 days of decreasing ambulation and increasingly nonsensical conversation. He has no other known past medical history and takes no medications. Vital signs are unremarkable. The physical examination reveals a thin, unkempt man who is oriented to person only but is cooperative and follows commands. He falls asleep easily. There is no scleral icterus, and cardiopulmonary, abdominal, stool guaiac, and neurologic examinations are negative. A noncontrast CT scan of the head is negative. Pertinent laboratory findings are as follows:

Hematocrit (HCT)	34%
Hemoglobin	11.4 g/dL
Platelet count	108,000/mm^3
WBC	9300/mm^3
AST	148 IU/L
ALT	86 IU/L
Total bilirubin	2 mg/dL
Albumin	2.2 mg/dL
Alkaline phosphatase	158 IU/L
INR	1.8
BUN	38 mg/dL
Creatinine	2.1 mg/dL
Ethanol	0 mg/dL
Bicarbonate	30 mmol/L
Sodium	133 mEq/L
Potassium	3.6 mEq/L
Chloride	95 mEq/L

What is the most appropriate intervention?

A. Admission for lactulose, 30 to 60 g daily, titrated to modest diarrhea
B. Determination of further therapy, admission, and treatment based on serum ammonia levels
C. Discharge with the family; neomycin, 500 mg every 4 to 6 hours
D. Oral metronidazole, 250 mg qid
E. Oral vitamin K for 2 weeks

Answer: A. Ammonia accumulates in severe liver disease and crosses the blood-brain barrier to eventually form glutamine. Ammonia levels correlate poorly with encephalopathy. Lactulose is an osmotic cathartic that acidifies colonic contents, causing ammonia trapping. Neomycin is a poorly absorbed aminoglycoside that reduces colonic bacteria but is relatively contraindicated in cases of renal insufficiency. Therapies for hepatic encephalopathy that have been under clinical investigation include metronidazole, zinc, flumazenil, and eradication of *Helicobacter pylori*. Vitamin K would have modest benefit due to loss of hepatic synthetic abilities. Plasma would not be indicated unless active bleeding occurred.

80.10. A 23-year-old G2P1 woman at 35 weeks of gestation presents with 3 days of fatigue, anorexia, nausea, and vomiting. She reports moderate epigastric and right upper quadrant pain. The physical examination is remarkable for icteric sclerae, slightly dry mucous membranes, and moderate tenderness in the right upper quadrant. She is afebrile and her uterus is not tender. Urgent ultrasound shows a viable moving fetus at 34 weeks' estimated gestational size, with good cardiac activity, and liver and gallbladder ultrasound reveals no obvious gallstones or ductal dilations but moderate hepatomegaly. Laboratory analysis is remarkable for the following:

AST	1050 IU/L
ALT	1265 IU/L
Total bilirubin	9.9 mg/dL
Conjugated bilirubin	4.6 mg/dL
Unconjugated bilirubin	5.2 mg/dL
Alkaline phosphatase	328 mg/dL
Glucose	62 mg/dL
Hemoglobin	9.3 g/dL
Platelet count	105,000/mm^3
Normal electrolytes	
Creatinine	0.6 mg/dL
Prothrombin time	14.8 sec
Albumin	3.1 g/dL

What is the most appropriate treatment?

A. Clear liquids, antiemetics, and follow-up outpatient ultrasound in 48 hours
B. Contrast CT scan of the abdomen
C. Hydration, antiemetics, and discharge after symptom resolution
D. Intensive care unit admission for monitoring for DIC
E. Stabilization and urgent delivery

Answer: E. Acute failing liver of pregnancy typically presents in the latter third trimester. Treatment involves aggressive fluid and electrolyte support, glucose administration, and immediate delivery. Liver disease generally resolves without sequelae. The illness is more common in primigravidas and twin pregnancies.

80.11. What is the most sensitive and specific imaging test for acute cholecystitis?

A. Contrast CT scan
B. Nuclear scintigraphy with iminodiacetic acid (IDA)
C. Serum alkaline phosphatase level
D. Serum bilirubin level
E. Ultrasonography

Answer: B. IDA administered IV is taken up by hepatocytes and secreted into bile canaliculi. Visualization of the gallbladder and common duct within 1 hour has a negative predictive value of 98%. Scintigraphy with IDA loses its sensitivity at bilirubin levels of 5 to 8 mg/dL.

CHAPTER 81

Pancreas

Rachel Berkowitz | Gabriel Rose

ACUTE PANCREATITIS

Background

Acute pancreatitis is an inflammatory condition that occurs when enzymatic autodigestion and an inflammatory cascade result in destruction of pancreatic tissue. Its presentation may range widely from mild, self-limited disease to sepsis and multiorgan failure. Recurrent intermittent bouts of acute pancreatitis may result in morphologic and functional changes of the gland, known as chronic pancreatitis.

The overall mortality due to acute pancreatitis is 4% to 10%, although in severe cases mortality may be as high as 30%.[1] Although mortality from acute pancreatitis has decreased with improvements in recognition, understanding, and therapy, the annual incidence of the disease and number of hospital admissions attributed to it have been trending upward.[2]

Causes

There are numerous causes of acute pancreatitis (Box 81.1); however, the most common causes in the United States are gallstones (40%–70%) and chronic alcohol consumption (25%–35%).[3] In women, the diagnosis is usually related to gallstones, whereas in men it is usually alcohol-related.[4] Endoscopic retrograde cholangiopancreatography (ERCP) is the third leading cause of acute pancreatitis, followed by drugs and trauma. Less common causes include infection, hypertriglyceridemia (serum triglyceride levels > 1000 mg/dL), hypercalcemia, tumors, genetic enzymatic defects, and gland architectural anomalies.[5] In 10% to 30% of cases, the cause remains unknown, although it is thought that many of these idiopathic cases are due to occult microlithiasis. The risk of biliary pancreatitis is actually correlated with the decreasing size of gallstones. Smoking and diabetes are independent risk factors for the development of pancreatitis.

Anatomy and Physiology

The pancreas is a retroperitoneal organ with endocrine and exocrine functions (Fig. 81.1). It contains three segments—head, body, and tail—that span across the upper abdomen. The pancreatic head sits within the concave C loop of the duodenum, located in the epigastrium. The body of the pancreas traverses posteriorly to the stomach, and the pancreatic tail abuts the hilum of the spleen in the left upper quadrant. A large main pancreatic duct (duct of Wirsung) courses within the pancreas from the tail to the head, where it meets the common bile duct to form the ampulla of Vater, which drains its contents into the duodenum via the sphincter of Oddi.

The exocrine function of the pancreas is carried out by the excretion of various digestive enzymes, such as trypsinogen. The endocrine function of the pancreas includes secretion of the regulatory hormones insulin, glucagon, and somatostatin.

Pathophysiology

Acute pancreatitis begins with an initial inciting event, such as exposure to a toxin or pharmacologic agent, or duct obstruction by gallstones. Cellular injury disrupts normal membrane trafficking and triggers the inappropriate activation of trypsinogen and other digestive enzymes. This in turn leads to autodigestion of pancreatic tissue and stimulation of an inflammatory cascade, which further damages the pancreas. Locally, cytokines cause increased vascular permeability, which can result in complications such as edema, hemorrhage, and/or necrosis. Systemically, inflammatory mediators may lead to a systemic inflammatory response syndrome (SIRS) response and potentially sepsis and shock. Bacteremia may occur due to translocation of intestinal flora. Distant organ dysfunction manifested, for example, by pleural effusions, acute respiratory distress syndrome, and renal failure, may also ensue.

Disease Classification

Acute pancreatitis can be classified by type—interstitial edematous versus necrotizing pancreatitis—and by local complications. Most patients have the interstitial edematous type, which usually resolves within the first week of illness. About 5% to 10% of patients develop necrotizing pancreatitis, which can involve the pancreatic parenchyma and surrounding tissue. Local complications involving the pancreas, as defined by the revised 2012 Atlanta Classification, are categorized based on whether they occur in the setting of interstitial or necrotizing pancreatitis and whether they are encapsulated (Box 81.2).[6] Necrotic tissue may remain sterile, liquefy, or become infected. Infected lesions are associated with increased morbidity. Local complications usually occur after the first week and should be suspected in patients with prolonged or recurrent symptoms, secondary elevation of pancreatic serum markers, or signs of sepsis, such as fever and leukocytosis.

Clinical Features

Patients with acute pancreatitis typically complain of the rapid onset of constant epigastric or left upper quadrant pain. Pain is usually of moderate to severe intensity, with intensity having no correlation with disease severity. The pain may radiate to the mid back or flanks, sometimes in a bandlike distribution, and may be accompanied by nausea and vomiting. Patients often relate previous episodes of similar pain, relating to biliary colic or mild bouts of pancreatitis.

The general appearance is often notable for a patient who is restless and in moderate distress, searching for a position of comfort, such as bending forward. Vital signs commonly reflect patient discomfort or an existing inflammatory process, with rises in temperature, heart rate, or respiratory rate. Blood pressure may be slightly elevated secondary to pain, although in severe or complicated cases hypotension and signs of shock may be present.

BOX 81.1

Causes of Acute Pancreatitis

TOXIC—METABOLIC
Alcohol
Drugs
Hyperlipidemia
Hypercalcemia
Uremia
Scorpion venom

MECHANICAL—OBSTRUCTIVE
Biliary stones
Congenital—pancreas divisum, annular pancreas
Tumors—ampullary, neuroendocrine, pancreatic carcinoma
Post-ERCP
Ampullary dysfunction or stenosis
Duodenal diverticulum
Trauma

INFECTIOUS
Viral—mumps, coxsackie, HIV, CMV, EBV, varicella
Bacterial—TB, *Salmonella, Campylobacter, Legionella, Mycoplasma*
Parasitic—*Ascaris*

VASCULAR
Vasculitis
Embolism
Hypoperfusion, ischemia
Hypercoagulability

OTHER
Idiopathic
Hereditary
Diabetes mellitus, DKA
Autoimmune

CMV, Cytomegalovirus; *DKA,* diabetic ketoacidosis; *EBV,* Epstein-Barr virus; *ERCP,* endoscopic retrograde pancreatography; *HIV,* human immunodeficiency virus; *TB,* tuberculosis.

Jaundice can be caused by an obstructing gallstone. Respirations may be shallow due to splinting from pain. Pulmonary examination may reveal decreased breath sounds or basilar crackles in the setting of pulmonary complications.

The abdomen can appear normal or distended. Classic descriptions of Cullen's sign (bluish periumbilical discoloration due to hemoperitoneum) and Grey Turner's sign (reddish-brown discoloration around the flanks due to retroperitoneal bleeding) are rarely seen but, in cases of hemorrhagic necrotizing pancreatitis, can carry a poor prognosis. Auscultation of the abdomen may reveal normal, diminished, or absent bowel sounds if the patient has concomitant ileus. Palpation of the abdomen often reveals epigastric tenderness with guarding, with rebound tenderness being a less common finding. Right upper quadrant tenderness and the presence of Murphy's sign may be seen in cases of gallstone pancreatitis.

BOX 81.2

Local Complications of Acute Pancreatitis

INTERSTITIAL EDEMATOUS PANCREATITIS
- Acute peripancreatic fluid collection—homogeneous fluid collection adjacent to pancreas; seen within 4 wk of symptom onset
- Pancreatic pseudocyst—homogeneous fluid collection with well-defined wall; seen >4 wk from symptom onset

NECROTIZING PANCREATITIS
- Acute necrotic collection—heterogeneous collection of fluid and necrosis; intrapancreatic and/or extrapancreatic
- Walled-off necrosis—heterogeneous collection of fluid and necrosis with well-defined wall; intrapancreatic and/or extrapancreatic; seen >4 wk from symptom onset

Adapted from Banks PA, Bollen TL, Dervenis C, et al: Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 62:102–111, 2013.

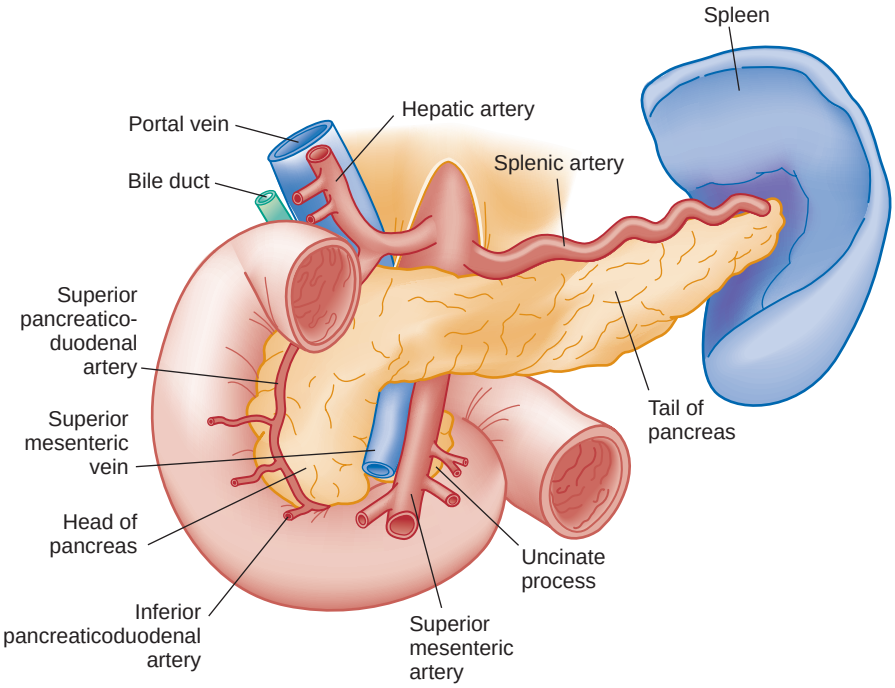

Fig. 81.1. Diagrammatic representation of the pancreas, anterior view. (Redrawn from Feldman M, Friedman LS, Sleisenger MH, editors: Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management, ed 7, Philadelphia, 2002, Saunders.)

In addition to the direct injury to the pancreas, patients may have local complications involving surrounding structures—for example, bowel necrosis, splenic or portal vein thrombosis, gastrointestinal bleeding, or gastric outlet obstruction. Most of these tend to be late findings.

Systemic complications are related to the progression of local inflammation and may result in SIRS. Although in most cases these conditions resolve within days, if persistent there may be progression to fulminant sepsis, shock, and organ failure, especially if there is underlying chronic disease. The pulmonary, cardiovascular, and renal systems are the most important determinants when assessing for organ failure. Increased microvascular permeability is the primary cause of pulmonary sequelae, although enzymatic degradation of surfactant may also play a role. Patients may develop acute respiratory distress syndrome, atelectasis, or pleural effusion, manifested as hypoxemia or respiratory distress. Pleural effusions are present in up to 50% of patients and tend to develop more frequently on the left side. Cardiovascular collapse, as evidenced by decreased mean arterial pressure or the need for inotropic support, may develop as shock results from fluid shifts and volume loss. Renal failure, demonstrated by an elevated creatinine level, may arise from a combination of hypoperfusion and the effects of inflammatory mediators.

In addition, coagulopathy occurs from cytokine-mediated activation of the coagulation cascade, potentially leading to thrombocytopenia or disseminated intravascular coagulation. Metabolic abnormalities are also common. Hyperglycemia results from decreased insulin production and hypocalcemia from low albumin and magnesium levels.

Differential Diagnoses

A number of disease processes have the ability to mimic the presentation of acute pancreatitis and should be considered in the differential diagnosis (Box 81.3). Inflammation of nearby intra-abdominal organs, such as the gallbladder, stomach, and duodenum, are often characterized by a similar pattern of epigastric or upper quadrant abdominal pain. Myocardial infarction, pneumonia, and aortic pathology may also present as lower thoracic or upper abdominal pain, with radiation to the back.

BOX 81.3

Differential Diagnosis for Acute Pancreatitis

ABDOMINAL DISORDERS
Peptic ulcer disease
Gastritis, gastroenteritis
Biliary colic, cholecystitis
Cholangitis
Ureteral stone
Bowel obstruction
Mesenteric ischemia
Abdominal aortic aneurysm (AAA)
Ectopic pregnancy
Perforated viscus

CARDIOPULMONARY DISORDERS
Myocardial infarction
Pneumonia
Pericarditis
Pleural effusion

SYSTEMIC DISORDERS
Sickle cell crisis
Diabetic ketoacidosis

Diagnostic Testing

The diagnosis of acute pancreatitis is based on the presence of at least two of three criteria—clinical features, laboratory results, and imaging. Clinical features refer to classic historical and exam findings as discussed above, for example, constant upper abdominal pain, possibly with radiation to the back, and tenderness to palpation. The other two criteria rely on diagnostic testing.

Laboratory Results

Laboratory diagnosis of pancreatitis is based on serum amylase and lipase levels. Amylase is an enzyme that functions in carbohydrate digestion that is produced by the pancreas and salivary glands, as well as several other organs to a smaller extent. Amylase levels rise in pancreatitis, but elevations can also be seen in many other conditions, such as malignancy, trauma, burns, salivary and liver disease, cholecystitis, renal failure, HIV, and pregnancy. In acute pancreatitis, the amylase level typically rises within 3 to 6 hours and remains elevated for about 3 to 5 days.

Lipase plays a major role in fat metabolism and is produced predominantly by the pancreas. Elevated lipase levels can also be seen in certain extrapancreatic disease processes, but it is more specific for pancreatitis than amylase. Although the lipase level begins to rise in the same time frame as the amylase level, it peaks more rapidly; due to renal reabsorption, rather than excretion, it remains elevated for 1 to 2 weeks.

We recommend use of the lipase level in the diagnosis of acute pancreatitis. The amylase level was once preferred because it was cheaper and more widely available, but this is no longer the case, and it is now recognized that the lipase level has greater specificity and sensitivity.[8] The difference in sensitivity is particularly notable in patients with delayed presentations and with pancreatitis due to alcohol and hypertriglyceridemia.[2] Testing for both enzymes does not improve diagnostic sensitivity or specificity. For both enzymes, three times the upper limit of normal is the most commonly used cutoff value because studies have demonstrated high sensitivity at this level. The degree of amylase or lipase level elevation does not correlate with disease severity or prognosis.

Serum transaminase, bilirubin, calcium, and triglyceride levels may be useful in determining the cause of pancreatitis. The alanine aminotransferase level has been shown to be particularly specific for biliary pancreatitis, with a positive predictive value of 95%.

Imaging

Confirmation of pancreatitis with abdominal imaging is done by computed tomography (CT) or, less commonly, magnetic resonance imaging (MRI) or ultrasound. Although CT is very sensitive and specific for acute pancreatitis, it is not routinely needed for the diagnosis or indicated in the emergency department (ED). CT is only recommended in the following circumstances: (1) in cases of diagnostic uncertainty—for example atypical abdominal pain—or normal pancreatic enzyme levels in the setting of high clinical suspicion; (2) to rule out other suspected intra-abdominal pathology—for example, bowel obstruction or aortic aneurysm; and (3) to assess for complications in patients who fail to respond to appropriate therapy after at least 48 hours.[9] The evaluation of complications by CT is best done at least 3 to 7 days after presentation. During the first few days, CT does not accurately identify the degree of pancreatic necrosis, typically underestimating its extent. Complications such as abscess and pseudocyst do not generally develop until several weeks after the onset of symptoms. Studies of patients undergoing early CT have found no benefit compared to delayed imaging.[10]

If CT is performed, it should be done with intravenous (IV) contrast. The CT scan is normal in 15% to 30% of patients with mild cases of pancreatitis. Abnormal findings include enlargement of the gland and loss of its typical texture and borders. As disease worsens, CT shows decreased or heterogeneous enhancement and increased inflammatory signs, such as surrounding fluid and fat stranding (Fig. 81.2). Pancreatic necrosis is suggested by areas demonstrating no enhancement (Fig. 81.3). In cases for which contrast is contraindicated, CT without contrast may still be useful: alternatively, MRI can be performed.

MRI findings of pancreatitis are similar to those of CT. MRI provides superior imaging of the gallbladder and biliary tract, but is more costly and has limited availability. Ultrasound may show an edematous swollen pancreas, but the study image is often obscured by bowel gas. Although it has limited value in the diagnosis of pancreatitis, ultrasound is sensitive for imaging biliary disease and should be performed early following the diagnosis of pancreatitis to help determine the cause. Abdominal radiographs show primarily nonspecific findings and do not contribute to the diagnosis of pancreatitis. Chest radiography should be performed when pulmonary complications are suspected.

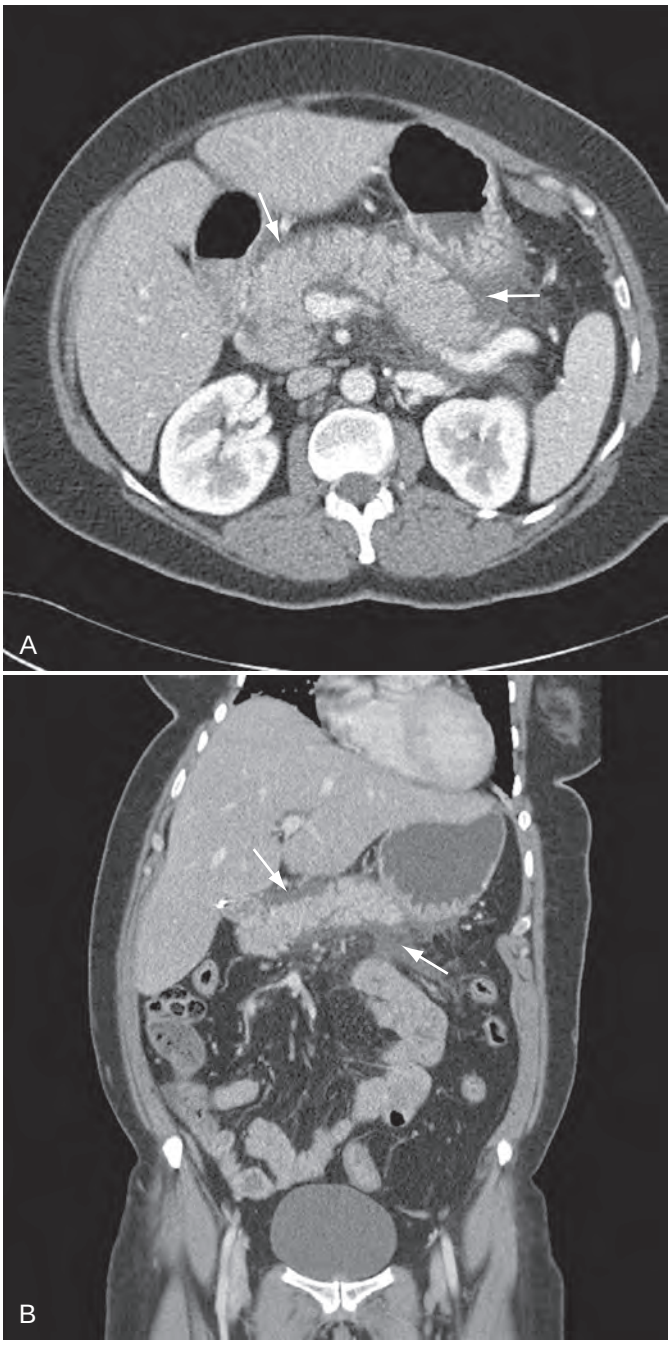

Fig. 81.2. CT scan showing acute interstitial pancreatitis with mild peripancreatic fluid and fat stranding *(arrows)*. **A,** Axial view. **B,** Coronal view. (Courtesy Dr. David T. Schwartz.)

Predicting Disease Severity

Although the diagnosis of pancreatitis is relatively straightforward, predicting the disease course is difficult. A number of classification schemes and severity scoring systems have been developed, but none are particularly helpful in the ED at the time of initial patient presentation.

The 2012 Atlanta Classification, developed by international consensus to provide a universally applicable system for categorizing pancreatitis severity, is widely recognized (Box 81.4). Based on

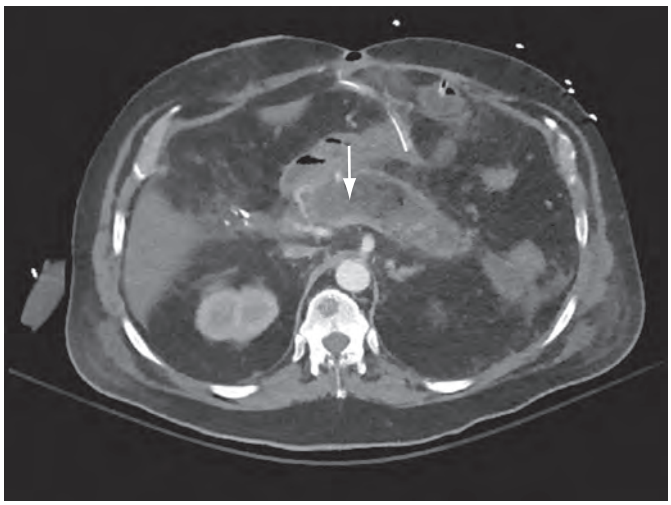

Fig. 81.3. CT scan showing necrotizing pancreatitis. There is decreased enhancement of the pancreas where the parenchyma has been replaced by necrotic fluid *(arrow)*. (Courtesy Dr. Cash Horn.)

BOX 81.4

Revised Atlanta Classification of Acute Pancreatitis

MILD
No organ failure
No local or systemic complications

MODERATE
Transient organ failure (<48 h)[a]
Local or systemic complications

SEVERE
Persistent organ failure (>48 h)[a]

[a]Organ failure defined as a modified Marshall score of 2 or more for the respiratory, cardiovascular, or renal system.

Adapted from Banks PA, Bollen TL, Dervenis C, et al: Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 62:102–111, 2013.

this classification, a patient cannot be diagnosed with severe pancreatitis until 48 hours following presentation, further underlining the dynamic nature of pancreatitis and difficulty in predicting severity at the time of ED evaluation.[6]

Scoring systems for assessing the severity of pancreatitis are based on using combinations of a variety of clinical features, vital signs, and serum markers. One of the oldest and most well-known is Ranson's criteria (Box 81.5). This system uses five criteria evaluated at presentation and six criteria evaluated 48 hours later. The total number of criteria present determine a score that can be used to predict the associated mortality rate. Another commonly used scoring system is the Acute Physiology and Chronic Health Evaluation II (APACHE II), which was designed as an intensive care unit (ICU) instrument and consists of 15 variables. A Ranson's score more than 3 or APACHE II score more than 8 is considered high risk for severe disease. There is also a classification system based on imaging for patients who undergo CT. The modified CT severity index (CTSI) allots points for various CT findings, such as pancreatic inflammation, pancreatic necrosis, fluid collections, and extrapancreatic complications. The score has been shown to correlate with hospital length of stay and development of organ failure, but is no more accurate then clinical scoring systems in predicting outcomes (Table 81.1).[11]

These systems have been criticized for their complexity, inadequate sensitivity or specificity, reliance on data that may not be immediately available, and inability to calculate a score at presentation. As a result, newer and less cumbersome schemas have been proposed. The bedside index for severity in acute pancreatitis, BISAP, is a newer scoring system based on five factors: ***b***lood urea nitrogen level, ***i***mpaired mental status, ***S***IRS, **a**ge, and ***p***leural effusions.[12] Compared to other scoring systems, it has lower sensitivity and similar specificity.[13] According to the Harmless Acute Pancreatitis Score (HAPS), in patients with no peritonitis (no rebound or guarding) and normal hematocrit and creatinine levels, there is a very low risk of mortality, necrosis, or need for hemodialysis or ventilatory support. HAPS has been shown to be 97% specific for mild disease, although not sensitive.[14] Several isolated serum markers have also been proposed as indicators of severity. C-reactive protein is the most helpful due to its high sensitivity and wide availability; however, its level does not peak until 72 hours following the onset of symptoms. Interleukin-6 and procalcitonin have also shown promise as single markers.

Management

The treatment of acute pancreatitis is mainly supportive. Volume replacement is important because patients with pancreatitis are often volume-depleted from decreased oral intake, emesis, diaphoresis, or third-spacing of fluids. Early fluid resuscitation reduces the incidence of SIRS and organ failure at 72 hours.[15] IV fluid resuscitation within the first 24 hours appears to be more important than the total volume received at 48 hours.[16] Fluid resuscitation should be targeted toward reversing hypotension and hemoconcentration and preserving urine output. Hematocrit, blood urea nitrogen, and creatinine can be used as surrogate markers for these goals. Both normal saline (NS) and lactated Ringer's (LR) solutions are good fluid choices. If available, we prefer LR because it appears to result in better outcomes.[17] In large volumes, NS use can lead to the development of a hyperchloremic metabolic acidosis. Acidosis is known to be detrimental in shock states, contributing to the systemic inflammatory cascade. Furthermore, a low pH activates trypsinogen, which makes the pancreatic acinar cells more prone to injury, thereby worsening the severity of pancreatitis.

As fluid status is being corrected, electrolyte levels may also need to be addressed. Hypocalcemia is frequently due to hypoalbuminemia, so calcium replacement is not necessary unless the ionized calcium level is low or the neuromuscular effects of hypocalcemia, such as Chvostek's or Trousseau's signs, are present. If there is concurrent hypomagnesemia, repletion with magnesium may correct the hypocalcemia. Hyperglycemia results from impaired insulin release, increased gluconeogenesis, and alterations in glucose uptake. Some patients will require exogenous

BOX 81.5

Ranson's Criteria[a]

AT ADMISSION
Age > 55 yr
WBC > 16,000/mm^3
Glucose > 200 mg/dL
AST > 250 IU/L
LDH > 350 IU/L

AT ADMISSION (if biliary cause)
Age > 70 yr
WBC > 18,000/mm^3
Glucose > 220 mg/dL
AST > 250 IU/L
LDH > 400 IU/L

AT 48 HOURS
Hematocrit drop > 10%
BUN rise > 5 mg/dL
Calcium < 8 mg/dL
Po_2 < 60 mm Hg
Base deficit > 4 mEq/L
Fluid sequestration > 6 L

AT 48 HOURS (if biliary cause)
Hematocrit drop > 10%
BUN rise > 2 mg/dL
Calcium < 8 mg/dL
Base deficit > 5 mEq/L
Fluid sequestration > 4 L

[a]One point given per criterion: 0–2 points, mortality rate, 1%; 3–4 points, mortality rate, 15%; 5–6 points, mortality rate, 40%; ≥7 points, mortality rate, 100%.
AST, Aspartate transaminase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; WBC, white blood cells.

TABLE 81.1

Test Characteristics for Scoring Systems in Prediction of Outcomes[30]

SCORING SYSTEM	PREDICTION OF SEVERE PANCREATITIS		PREDICTION OF MORTALITY	
	Sensitivity	Specificity	Sensitivity	Specificity
Ranson's	84%	90%	100%	77%
APACHE II	70%	72%	100%	66%
CTSI	86%	71%	100%	59%
BISAP	38%	92%	57%	88%

APACHE, acute physiology and chronic evaluation; CTSI, computed tomography severity index; BISAP, bedside index of severity in acute pancreatitis
Data from Papachristou GI, Muddana V, Yadav D, et al: Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. Am J Gastroenterol 105:435–441, 2010.

insulin because untreated hyperglycemia may contribute to worsening pancreatitis and immune function.

Pain control is another important aspect of management. Opioids are often required because the pain associated with pancreatitis is typically severe. When available, we prefer to use patient-controlled analgesia. Although there is a theoretical risk of morphine causing sphincter of Oddi spasm, there are no clinical studies showing that the administration of morphine causes or worsens pancreatitis or cholecystitis. There are also very little data comparing the efficacy of different opioids for the relief of pain in pancreatitis.[18] Antiemetics may also be needed for symptomatic relief.

It was once thought that oral or enteral nutrition would worsen pancreatitis by stimulating the secretions of the exocrine pancreas and thereby autodigestion; however, we now know that this does not occur and withholding enteral feeding actually has detriments. It leads to increased gastrointestinal mucosal atrophy and permeability and amplifies bacterial overgrowth and translocation of gut bacteria. It has also been established that total parenteral nutrition is associated with many complications.[19] Therefore, oral or enteral nutrition is the preferred method of feeding and may actually be therapeutic. In moderate to severe cases of pancreatitis, early enteral feeding by nasogastric or nasojejunal tube is safe and effective. In mild cases, early oral feeding is safe and may lead to less days of hospitalization.[20] A low-fat, solid diet is as safe as clear liquids and can be given as tolerated.[21]

Antibiotics are not indicated for the prevention of infectious sequelae. Even in severe cases of pancreatitis, antibiotic prophylaxis has not been shown to improve mortality or the need for surgical intervention.[22] Their use should be limited to infected necrotizing pancreatitis or extrapancreatic infections such as cholangitis and bacteremia. SIRS features such as tachycardia and tachypnea are common in acute pancreatitis but are nonspecific and do not necessarily portend sepsis or organ failure. However, during the initial ED presentation, it may be difficult to rule out sepsis as the cause. Therefore antibiotics should be initiated if there is suspicion of an infectious source, but not based on SIRS criteria alone. In cases of known infected pancreatic necrosis, the chosen antibiotic regimen should cover gram-negative and gram-positive bacteria as well as anaerobes. A quinolone plus metronidazole (ciprofloxacin, 400 mg, and metronidazole, 500 mg bid) or a carbapenem (meropenem, 1 g, or imipenem-cilastatin, 500 mg to 1 g tid) are suitable regimens due to bacterial coverage and pancreatic tissue penetration.

Protease inhibitors and histamine 2 (H2) blockers have been proposed as treatment options for acute pancreatitis in the past, but are no longer recommended because studies have shown no effect on clinical outcomes.[23]

Early ERCP is indicated for patients with cholangitis or biliary obstruction and is recommended within 24 hours of admission. Studies have shown no benefit for other patients with pancreatitis, regardless of predicted severity.[24] Because of the potential complications associated with ERCP, it should not be performed unless there is evidence of cholangitis or biliary obstruction, such as jaundice, elevated bilirubin level, and signs of sepsis. Suspicion of choledocholithiasis based on a dilated biliary tree on CT does not itself warrant ERCP. Magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) is recommended for further evaluation in this case.

Surgical intervention is rarely indicated at the time of presentation. It is recommended that patients with mild biliary pancreatitis undergo cholecystectomy during the index admission, but not emergently. Asymptomatic pancreatic necrosis and pseudocysts do not need treatment. Infected or symptomatic necrotizing pancreatitis often requires surgical, endoscopic, or radiologic intervention, but not until approximately 4 weeks later, when the collection becomes walled off.

Disposition

It is possible to discharge patients with mild presentations whose symptoms are adequately controlled, are tolerating oral intake, and have no signs of complications. However, due to the unpredictable course of pancreatitis, hospital admission for further observation and management is typically warranted. Most patients with acute pancreatitis have mild cases. They are easily managed on a general medical floor and usually discharged within 1 week. About 20% will suffer complications and require a longer hospital stay or higher level of care.

The following features should prompt consideration of ICU admission—moderately severe pancreatitis (according to the revised Atlanta classification), continued need for volume resuscitation, persistent SIRS, significant electrolyte abnormalities, older age, or other factors that render a patient high risk for deterioration. Patients who may need endoscopic, surgical, or interventional radiology procedures should be managed in or referred to a specialist center, defined as a high-volume center with daily access to these services. A nationwide analysis has shown that admission to a hospital with an annual volume of acute pancreatitis cases in the highest third is associated with shorter lengths of stay and lower mortality.[25]

CHRONIC PANCREATITIS

Chronic pancreatitis is a progressive inflammatory disorder of the pancreas in which the parenchyma of the gland is gradually replaced by fibrous tissue. It is most commonly diagnosed in middle age, with a mean age at diagnosis of 62 years. The risk is at least twice as high for men compared to women and for African Americans compared to whites.[26]

Pancreatitis exists as a spectrum, with acute pancreatitis leading to recurrent acute pancreatitis, which in turn leads to chronic pancreatitis. Only a minority of patients progress across this spectrum, with evolution dependent on a number of environmental and hereditary factors. Chronic pancreatitis can be classified as toxic-metabolic, obstructive, genetic, autoimmune, related to recurrent and postnecrotic acute pancreatitis, or idiopathic. Alcohol abuse is the most common cause. Increased risk is associated with alcohol consumption more than five drinks/day. Smoking is also a well-established independent risk factor. The exact mechanisms whereby the various risk factors ultimately result in disease are not entirely understood; however, there is a common pathophysiologic pathway involving progressive inflammation and fibrosis, leading to acinar cell dysfunction and morphologic changes that impair endocrine and exocrine functions. Patients may subsequently develop malnutrition and diabetes and, in some cases, pancreatic cancer.

Clinical Features

Patients with chronic pancreatitis may present with prolonged or recurrent abdominal pain, findings relating to local complications and structural changes (eg, bowel obstruction, vascular thrombosis), or signs of pancreatic endocrine and exocrine dysfunction (eg, glucose intolerance, malabsorption, steatorrhea). The nature of the abdominal pain will often be similar to that of acute pancreatitis, described as severe, constant epigastric pain radiating to the mid back, often associated with nausea and vomiting. Food and alcohol intake tend to exacerbate the pain, and weight loss is common. It has been proposed that as the disease process continues, pain may diminish due to progressive loss of functional acinar cells, but evidence has been conflicting.[27]

On physical examination, patients may appear jaundiced due to alcoholic cirrhosis or biliary obstruction or ill from prolonged malnutrition and malabsorption. The abdomen is usually tender,

and a palpable mass representing a pancreatic pseudocyst or tumor may be appreciated.

Differential Diagnoses

The diagnosis of chronic pancreatitis may be relatively clear-cut in a patient with a history of recurrent pancreatitis or frequent pain that is typical in the presence of risk factors for pancreatitis. However, other diagnoses should always be considered because these patients may also have pathology unrelated to the pancreas or complications of pancreatitis. The list of alternative diagnoses is similar to that for acute pancreatitis (see Box 81.3); however, chronic abdominal processes, such as peptic ulcer disease, gastritis, biliary colic, and irritable bowel syndrome are more consistent with recurrent episodes of upper abdominal pain. In addition, patients with chronic pancreatitis who are opioid-dependent may have withdrawal symptoms that mimic an exacerbation of pancreatitis.

Diagnostic Testing

The initial diagnosis of chronic pancreatitis is made by one of several imaging modalities, including CT, MRCP, or EUS. CT findings include dilated pancreatic ducts, atrophy, microcalcifications, and complications such as pseudocyst. MRCP and EUS are accurate methods for visualizing pancreatic parenchymal and ductal changes. EUS is the most sensitive imaging test for chronic pancreatitis and is best able to detect subtle and early changes.[28] ERCP has mostly been replaced by MRCP because ERCP is invasive and carries a 4% risk of precipitating pancreatitis. These imaging techniques can also rule out pancreatic cancer, which is important because 5% of patients with pancreatic cancer are initially misdiagnosed with chronic pancreatitis.[29]

For acute exacerbations of chronic pancreatitis, the same diagnostic principles apply as for acute pancreatitis—clinical features, laboratory analysis, and imaging. However, laboratory tests are less helpful in chronic pancreatitis because serum lipase and amylase levels do not rise to the same degree and may be normal. Liver function test results (eg, transaminase, alkaline phosphatase, bilirubin levels) may be elevated in patients with concurrent alcoholic liver disease or biliary duct obstruction. Hypocalcemia and hypoalbuminemia are common, and impaired pancreatic endocrine function may be reflected by hyperglycemia. Although an abdominal radiograph is not necessary, up to 30% of patients have a characteristic finding of pancreatic calcification, which is pathognomonic for the disease.[27]

Management

The treatment of chronic pancreatitis is supportive and largely focused on pain relief and correction of fluid and electrolyte imbalances. Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) are the preferred initial agents, although escalation to tramadol or a more potent opioid analgesic is often necessary.[30] In patients who fail traditional medical management, other pain control options with varying supportive evidence include oral enzyme replacement, octreotide, antioxidants, and celiac plexus block. Referral to a pain management specialist may be beneficial because pain can be difficult to control and the risk of addiction is significant.

Beyond ED care, endoscopy may be indicated for the drainage of symptomatic pseudocysts and ductal leaks that result in ascites or for stenting obstructed bile ducts. Surgery is aimed at the restoration of gastrointestinal function and pain relief by decompression of ductal obstruction, which is usually reserved for patients for whom conservative medical treatments have failed. Nutrition replacement, along with lifestyle modifications such as avoidance of alcohol and cigarettes, are also important in the long-term treatment of chronic pancreatitis.

Disposition

Patients with chronic pancreatitis typically present to the ED with acute exacerbations of pain or complications of their disease. The prognostic indices used for acute pancreatitis can be applied to these patients. Most patients will require admission, with over 90% of hospitalizations related to presentations for abdominal pain.[31]

PANCREATIC CANCER

Pancreatic cancer is a particularly lethal form of cancer because it often goes undetected until the later stages. The survival rate is less than 10%, with only about 5% of patients surviving 5 years from the time of diagnosis. Most deaths are related to metastatic disease. Metastasis usually occurs within the abdomen, especially to the liver, but also to the lungs. Ampullary masses, which make up a small percentage of cases, are associated with a better prognosis (up to 50% may be successfully resected) because they tend to cause biliary obstruction, leading to earlier presentation and diagnosis.

Pancreatic cancer typically affects people older than 40 years, with a mean age of 71 years at diagnosis. Approximately 85% of cases are adenocarcinoma. About 10% are neuroendocrine tumors such as gastrinomas (Zollinger-Ellison syndrome), insulinomas, and glucagonomas. About two-thirds of pancreatic cancers occur in the head of the pancreas. Smoking is the most clearly linked risk factor for pancreatic cancer; other associations include alcohol abuse, obesity, diabetes, and chronic pancreatitis.[32]

Clinical Features

Typical presenting symptoms include abdominal pain, back pain, anorexia, nausea, weight loss, and weakness. Tumors may cause obstruction, leading to cholestasis, jaundice, pancreatitis, or gastric outlet obstruction. Diabetes is also common. Late-onset diabetes in the setting of these symptoms is suggestive of pancreatic cancer.[33]

The presentation of neuroendocrine tumors is related to the hormone secreted by the tumor. For example, insulinomas are associated with hypoglycemia, gastrinomas with peptic ulcers, gastroesophageal reflux disease, and diarrhea, and glucagonomas with glucose intolerance, weight loss, and dermatitis.

Diagnostic Testing

Abdominal CT with IV contrast is the recommended imaging modality for confirming the diagnosis and for guiding initial management. On CT, pancreatic carcinoma appears as an area of hypoattenuation. CT may also show secondary signs such as pancreatic duct cutoff, dilation of the pancreatic or common bile duct, atrophy, or border irregularities.

Although abdominal ultrasound is sensitive for detecting ductal dilatation, it is not sensitive enough for the diagnosis of pancreatic masses. EUS, on the other hand, may be of value in the diagnosis of pancreatic cancer. It is the most sensitive test in early disease and for masses smaller than 2 cm.[33]

Management

Surgical resection can be curative, but is only possible in a very small subset of patients with no direct tumor extension. In patients with locally and systemically advanced disease, treatment is palliative. Chemotherapy and radiation may prolong survival to a small extent.[33]

Treatment in the ED generally involves pain control and management of complications such as gastrointestinal bleeding, bowel obstruction, acute cholangitis, and venous thrombosis. In situations where the diagnosis of pancreatic cancer is made in the ED, the disease process may be advanced, and patients may benefit from the emergency clinician expediting their evaluation and facilitating multidisciplinary involvement in the patient's case.

KEY CONCEPTS

- Acute pancreatitis represents a wide spectrum of disease, ranging from mild, short-lived disease to severe life-threatening disease with a mortality rate as high as 30%.
- Most cases of acute pancreatitis are caused by gallstones, followed closely by alcohol abuse.
- Diagnosis of acute pancreatitis relies on the presence of at least two of these three criteria—typical clinical features, serum amylase or lipase level 3 times the upper limit of normal, confirmatory imaging.
- Determining the serum lipase level is preferred over the amylase level because of its greater sensitivity and specificity.
- CT does not need to be performed routinely, but only for cases of diagnostic uncertainty or in the later phases to rule out complications.
- Following the diagnosis of pancreatitis, abdominal ultrasound should be performed early to determine if the cause is biliary.
- Treatment of acute pancreatitis is mainly supportive, with fluid resuscitation and pain control paramount. Lactated Ringer's solution is more physiologic than normal saline and may confer better outcomes in patients receiving large volumes of fluids. There is no evidence to support one analgesic agent over another.
- Antibiotics are not indicated for prophylaxis and are not purely based on SIRS criteria, but should be given in cases of infected pancreatic necrosis or other clear evidence suggesting infection.
- ERCP is only indicated in cases of cholangitis or biliary obstruction.
- Most patients require hospitalization for symptomatic control, monitoring of hydration and nutrition status, and management of complications.
- There is no perfect scoring system to help predict severity and outcomes in pancreatitis. The most widely accepted systems include Ranson's, APACHE-II, CTSI, and BISAP. Each has different strengths and weaknesses.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 81: QUESTIONS & ANSWERS

81.1. A 28-year-old woman presents with recurrent pancreatitis. She is otherwise healthy and takes no medications. This episode of pain was preceded by several similar episodes of intermittent epigastric pain that lasted several hours at a time. A previous ultrasound examination of the liver, gallbladder, and pancreas was normal. She does not smoke, drink, or use over-the-counter medications. The physical examination is remarkable for moderate epigastric tenderness without rebound. Vital signs are normal. Laboratory evaluation reveals an elevated lipase level and moderate leukocytosis. Urinalysis and urine pregnancy test results are normal. What would be the most appropriate intervention?

A. After stabilization, referral to a gastroenterologist for endoscopic retrograde cholangiopancreatography (ERCP)
B. After stabilization, referral to a gastroenterologist for upper endoscopy
C. Computed tomography (CT) scan of the abdomen to rule out pancreatic pseudocyst
D. Repeated ultrasound examination of the liver, gallbladder, and pancreas
E. Symptomatic treatment only unless her clinical picture worsens

Answer: A. Many cases of presumed idiopathic pancreatitis may be due to small stones or sludge that cannot be seen by ultrasound examination but may be seen by ERCP. Pancreatic pseudocyst is more likely in alcoholic pancreatitis and typically occurs gradually, several months after a severe episode.

81.2. Which of the following statements regarding acute pancreatitis is true?

A. Acute pancreatitis may develop in 20% to 30% of ERCP cases.
B. The most common adult cause is alcohol abuse.
C. The most common geriatric cause is infection.
D. The most common pediatric causes are trauma and infection.
E. The most common viral cause is HIV infection.

Answer: D. The most common viral causes are mumps and coxsackievirus B. The most common adult and geriatric cause is gallstones. Acute pancreatitis is seen in 1% to 10% of ERCP cases.

81.3. Which of the following statements about the serum amylase level is true?

A. Elevations may be seen after muscle trauma.
B. In acute pancreatitis, levels rise in 1 or 2 hours and normalize in 2 days.
C. Increasing the cutoff value decreases the sensitivity for detection of pancreatitis.
D. It is a less sensitive test than the serum lipase level for the diagnosis of pancreatitis.
E. It is not renally cleared.

Answer: A. Although amylase is produced primarily in the pancreas and salivary glands, other sources are muscle, testes, ovaries, small intestine, and fallopian tubes. Levels rise within 6 to 24 hours and normalize in 3 to 7 days. Amylase is renally excreted. Levels may be normal in up to 25% of pancreatitis cases and

elevated in normal individuals. It is likely to be as sensitive as the serum lipase level but is less specific. Increasing the cutoff value decreases the sensitivity but increases the specificity.

81.4. Which of the following statements regarding the use of radiographic studies for the evaluation of pancreatitis is true?

A. CT is indicated in pancreatitis if there is acute deterioration.

B. Oral administration of a contrast agent for abdominal CT may aggravate pancreatitis.

C. The study of choice in suspected gallstone pancreatitis is ultrasonography.

D. Ultrasonography and CT of the abdomen are equally accurate for visualizing the biliary tract.

E. Ultrasonography may help differentiate pancreatitis from pancreatic pseudocyst.

Answer: A. There is no perfect test. Ultrasonography has a sensitivity of 94% for gallstones but far less for common bile duct stones or biliary dilation, for which ERCP is the test of choice because of its sensitivity for detecting small duct stones or strictures. CT is excellent for ruling out other causes of abdominal pain (eg, pseudocyst, abscess, necrosis, vascular abnormalities, hemorrhage) and is indicated if the diagnosis is uncertain, if fever and leukocytosis are present, and with acute deterioration. Oral contrast material does not aggravate pancreatitis. A non–contrast-enhanced helical scan may also be helpful if an oral contrast agent cannot be tolerated.

CHAPTER 82

Disorders of the Small Intestine*

Chad E. Roline | Robert F. Reardon

SMALL BOWEL OBSTRUCTION

Background

Small bowel obstruction (SBO) is a common problem encountered in the emergency department (ED). Advances in imaging as well as operative techniques have greatly improved the prognosis for patients with this condition and have decreased the mortality rate from nearly 60% in 1900 to less than 8% today.

Anatomy and Physiology

There are several different types of SBO. The term *mechanical obstruction* implies the presence of a physical barrier to the movement of the intestinal contents. Obstructions of this type can be further subclassified according to the cause of the obstruction relative to the intestinal wall (Box 82.1). Lesions external to the intestinal tract cause obstruction by compressing from outside the gut. This is usually a result of postoperative adhesions, but hernias and intraperitoneal neoplasms are other causes. Lesions intrinsic to the intestinal tuberculosis itself can cause mechanical obstruction, such as primary intestinal neoplasms, localized infection (eg, intestinal wall tuberculosis), and trauma-related conditions (eg, a hematoma of the intestinal wall). Lesions within the intestinal lumen itself can lead to obstruction, such as bezoars, ingested foreign bodies, and gallstone ileus.

Another important distinction of SBO is whether the obstruction is a *simple* or *closed loop* obstruction. A simple obstruction occurs at a single point. A closed loop–type obstruction involves obstruction at two locations, thus creating a segment of bowel with compromised blood flow proximally and distally. Closed loop obstructions are seen when a twist develops in the mesentery or, in the case of an internal hernia, when a loop of bowel becomes entrapped in a defect in the mesentery (Fig. 82.1). If not promptly recognized and relieved, a closed loop obstruction can quickly lead to intestinal infarction and necrosis, which has twice the mortality rate of simple obstructions.

In contrast to a mechanical obstruction, a neurogenic or functional obstruction occurs as a result of disruption of the normal coordinated peristaltic activity of the gastrointestinal (GI) tract in the absence of a physical blockage within the intestinal lumen. This is also commonly referred to as an adynamic ileus. The causes of adynamic ileus are listed in Box 82.2. It often occurs in patients who have undergone abdominal surgery and is transient in nature. Some degree of functional obstruction is considered normal after surgery and results from multiple factors, including an inflammatory response to intestinal manipulation, effects of analgesics, and release of hormones and neurotransmitters. In addition to surgery, a number of medical conditions can lead to a functional SBO, including infection, medications, and metabolic abnormalities.

The term *pseudo-obstruction* refers to a poorly understood and complex syndrome in which the signs and symptoms of mechanical obstruction, including the appearance of dilated bowel on radiography, are present in the absence of a mechanical lesion. This is thought to involve disruption of intestinal pacemaker activity controlled by a specialized group of cells found in the GI tract called the interstitial cells of Cajal (ICCs). These cells regulate the contractility of the intestinal smooth muscle and are under the influence of the enteric nervous and autonomic systems. Pathology at any one of these sites can lead to pseudo-obstruction. Causes include degenerative neuropathies, autoimmune and paraneoplastic disease, and hereditary conditions. The symptoms of pseudo-obstruction are often chronic and respond poorly to treatment.

Pathophysiology

Interruption of normal flow through the intestinal lumen triggers a cascade of physiologic changes that correlate with the progressive development of symptoms. In the presence of a mechanical obstruction, the bowel proximal to the blockage first becomes mildly dilated by the accumulation of partially digested food and normal intestinal secretions. These secretions are referred to as succus entericus and are secreted by cells lining the intestinal wall in response to mechanical stimulation. Increased intestinal dilation causes an increase in peristalsis throughout the intestines, which can trigger frequent and loose bowel movements early in the progression of the obstruction as well as episodes of nausea and vomiting. As the process continues, the bowel wall becomes edematous and the normal absorptive function of the intestinal wall decreases, leading to further accumulation of contents in the intestinal lumen proximal to the obstruction. Owing to the loss of normal intestinal motility, bacterial overgrowth begins to occur in the proximal small bowel. It is this overgrowth in a location of the intestines that is normally relatively sterile that explains the feculent nature of the emesis frequently observed in patients with SBO. As the obstruction continues, there is a transudative fluid loss into the peritoneal cavity, leading to worsening hypovolemia and dehydration. In addition, if the obstruction is proximal in location, continued bouts of emesis can lead to electrolyte abnormalities, metabolic alkalosis, severe hypovolemia, and shock.

In a closed loop obstruction, the increase in intraluminal pressure occurs much more rapidly because the intestinal contents cannot flow retrograde. Intestinal venous congestion and then arterial obstruction can also progress quickly to intestinal ischemia and infarction, referred to as a strangulation obstruction. If not promptly relieved, necrosis and intestinal perforation can occur. The resulting leakage of the intestinal contents into the peritoneum can lead to peritonitis and sepsis.

In the developed world, the most common cause of SBO is postoperative adhesions, which account for approximately 60% of cases.[1] These adhesions develop as a result of a process involving the interaction among numerous types of cells, cytokines, and coagulation factors caused by damage to peritoneal surfaces, with a subsequent increase in fibrin formation.[2] It has been estimated that 93% to 100% of patients who undergo transperitoneal surgery will develop postoperative adhesions, and up to 25% of them will develop a SBO. In cases of emergent laparotomy for trauma, GI tract perforation is a major independent risk factor

*The contributors would like to thank Dr. Susan P. Torrey and Dr. Philip Henneman for their work in earlier editions.

BOX 82.1

Lesions Causing Small Bowel Obstruction Relative to the Intestinal Wall

EXTERNAL TO INTESTINAL WALL
Postoperative adhesions
Hernias
Volvulus
Compressing masses (tumors, abscesses, hematomas)

INTRINSIC TO INTESTINAL WALL
Primary neoplasms
Inflammatory (eg, Crohn's disease, radiation enteritis)
Infectious causes (eg, intestinal tuberculosis)
Intussusception
Traumatic (intestinal wall hematoma)
Intraluminal
Bezoars
Foreign bodies
Gallstones
Ascaris infestation

BOX 82.2

Causes of Adynamic Ileus

Metabolic disease (especially hypokalemia)
Medications (eg, narcotics)
Infection (retroperitoneal, pelvic, intrathoracic)
Abdominal trauma
Laparotomy

Fig. 82.1. Diagram of internal hernia. Note the formation of a closed loop, which creates a high risk for strangulation (*arrows*). (From Martin LC, Merkle EM, Thompson WM: Review of internal hernias: radiographic and clinical findings. AJR Am J Roentgenol 186:703–717, 2006. Reprinted with permission from the American Journal of Roentgenology.)

for the development of SBO while the patient is still in the hospital. Over the last several years, numerous physical bioabsorbable barriers and pharmacologic agents have been evaluated as potentially useful in decreasing the formation of postoperative adhesions.[3]

The second most common cause of SBO is tumors, which are responsible for roughly 20% of cases. This includes malignancies, such as adenocarcinomas, carcinoid tumors, lymphomas, and sarcomas, and benign conditions, including adenomas, leiomyomas, and lipomas. In addition to these primary GI tumors, gynecologic cancers, especially ovarian cancer, are a very common cause of SBO. Metastatic disease is yet another tumor-related cause of SBO (eg, metastatic breast, skin, and testicular cancers).

Hernias are the third most common cause of SBO, found in approximately 10% of cases. Similar to their relative frequency in general, ventral and inguinal hernias are usually encountered, but femoral, parastomal, lateral ventral (also called *spigelian hernia*), and internal hernias may also lead to SBO. Although rare in the general population, internal hernias are a recognized complication of bariatric surgery, especially when a Roux-en-Y type procedure has been performed. In this group, internal hernias have been described in up to 5% of patients and usually develop at the mesocolic window. Another rare type of hernia is the obturator hernia. This hernia develops into the obturator foramen and is especially common in older women who have recently lost a significant amount of weight. The female pelvis is wider and the obturator canal is more oblique in women than in men. This, in combination with a loss of preperitoneal fat in older, often emaciated patients, predisposes to the development of an obturator hernia. Because an external mass is absent, the diagnosis can be especially challenging, which explains why it carries the highest mortality of any abdominal hernia, nearly 70% when it is incarcerated.

Gallstone ileus is a rare but important cause of mechanical SBO (Fig. 82.2). It is responsible for 1% to 4% of all cases of mechanical obstruction and is most frequently seen in older adults with underlying medical problems. The pathogenesis involves the entry of a gallstone into the intestinal tract through a biliary-enteric fistula. This results from the localized inflammation of cholecystitis and, in most cases, entry occurs via a cholecystoduodenal fistula, although cholecystocolonic and cholecystogastric fistulae can also be involved. After entering the intestinal lumen, the gallstone migrates distally. As a stone moves through the intestinal lumen, it often increases in size as bowel content sedimentation becomes attached. Eventually, the gallstone becomes lodged, usually in the ileum, which is the narrowest segment of the small bowel, and the patient then develops symptoms of obstruction.

Fig. 82.2. Gallstone ileus of the small intestine at laparotomy. (Courtesy J.C. Campbell, Plymouth, England; www.surgical-tutor.org.uk.)

Small bowel volvulus occurs infrequently but is a potentially catastrophic cause of SBO. This condition results from the abnormal twisting of a loop of small bowel around the axis of its own mesentery. Although it accounts for only 3% to 6% of SBO cases in the West, it is much more common in Africa, India, and the Middle East, where it is responsible for up to 20% of cases. Primary small bowel volvulus occurs in an otherwise normal abdominal cavity; secondary small bowel volvulus occurs when a congenital or acquired abnormality leads to the development of the volvulus, as in the case of intestinal malrotation or as a result of postoperative adhesions.

A reported increase in small bowel volvulus during Ramadan has been attributed to eating a large amount of food bulk after prolonged fasting, causing the proximal jejunum to descend into the pelvis, displacing empty small bowel loops upward and initiating malrotation. Alterations in gut motility and increased small bowel length have also been suggested as possible predisposing factors.

Secondary causes of small bowel volvulus include intestinal malrotation caused by the arrest of normal rotation of the embryonic gut or because of postoperative adhesions. In the case of malrotation, more than 50% of affected children present for evaluation before 1 month of age with small bowel volvulus. Because a small bowel volvulus is a classic closed loop obstruction, prompt recognition and surgical treatment are imperative because the risk of strangulation is high.

The term *intussusception* describes the invagination or "telescoping" of a part of the small intestine into itself. This results in the development of venous and lymphatic congestion, with consequent intestinal edema, which can lead to intestinal ischemia and perforation. Intussusception occurs in patients of all ages but is most frequently seen in children younger than 2 years. It is the most common cause of intestinal obstruction in infants 6 to 36 months of age. Unlike ileocolic intussusception, which can often be treated nonoperatively by enema reduction, surgery is more often required in cases of intussusception limited only to the small bowel. In children, the cause is usually idiopathic, but several studies have shown an association with adenovirus infection. It has been postulated that enteric adenovirus infection may trigger stimulation of the lymphatic tissue in the intestinal tract, which may create a lead point for the intestine to be dragged into itself by the normal peristaltic activity of the intestines. In contrast to the idiopathic nature of intussusception in children, a mechanical cause is found in more than 90% of adult cases. Tumors, benign or malignant, are discovered as the initiating cause in more than 65% of adult cases. Adult intussusception has been reported in association with acquired immunodeficiency syndrome (AIDS) as a result of lymphoma or unusual infections, such as atypical mycobacterial infections.

Clinical Features

History

Patients with SBO commonly report crampy abdominal pain, abdominal distention, nausea, vomiting, constipation, and/or the inability to pass flatus. The pain is often described as periumbilical in location and typically has a crescendo-decrescendo pattern. The recurrent waves of discomfort can last from seconds to minutes. In more proximal obstruction, symptoms of nausea and vomiting can be much more severe, and the onset of symptoms is often more abrupt. Distal obstructions typically cause symptoms over a slower period of 1 to 2 days and are frequently accompanied by greater abdominal distention. The colon requires up to 24 hours to empty after the formation of an SBO, and the associated small bowel distention stimulates peristalsis; consequently, flatus and the passage of stool may continue, even in the presence of a complete obstruction. A history of previous obstructions as well as a thorough past surgical history should be obtained, and any history of malignancy or inflammatory bowel disease should be elicited. The use of medications (especially narcotics) that may affect bowel function should be reviewed.

Physical Examination

The physical examination starts with a careful evaluation of the patient's hemodynamic status, degree of distress, and general condition. Thus, patients requiring resuscitation can be quickly identified, and the appropriate interventions, including intravenous (IV) fluids, can be initiated early. Inspection of the patient includes a careful search for abdominal distention and hernias and should include a genital examination. Although bowel sounds in SBO are frequently described as high-pitched and tinkling in nature, studies have shown that they are also frequently decreased or absent. One study has shown that physicians listening to recordings of bowel sounds were able to identify SBO correctly in only 42% of affected patients.[4]

The presence of peritoneal signs usually indicates late obstruction with complications, including strangulation. However, abdominal palpation in the setting of bowel dilation can give the false impression of peritonitis, because quick compression-decompression of dilated bowel may elicit a pain response. For this reason, it may be helpful to determine the presence of pain with cough or gentle shaking of the patient's pelvis to investigate for true peritonitis better.

Differential Diagnosis

The diagnosis of SBO should be considered in any patient with abdominal pain and vomiting, especially if there is a history of prior abdominal surgery. It may be difficult to differentiate SBO from nonobstructive intestinal motility disorders, such as adynamic ileus or intestinal pseudo-obstruction, by history and physical examination alone.

Other conditions to consider in the differential diagnosis include gastroenteritis, mesenteric adenitis, constipation, cholelithiasis or nephrolithiasis, ectopic pregnancy, pancreatitis, peptic ulcer disease, atypical myocardial infarction, leaking abdominal aortic aneurysm (AAA), and mesenteric ischemia. These pathologies have typical signs, symptoms, and diagnostic findings that can help differentiate them from one another and from SBO, but this may be challenging, especially early in the course of the particular disorder.

Diagnostic Testing

Laboratory

Although laboratory tests are not helpful in diagnosing the presence of SBO, they can be useful in assessing the degree of dehydration and metabolic disruption resulting from the obstruction. Studies have evaluated the use of lactate and creatinine phosphokinase to identify strangulation complicating SBO. Intestinal fatty acid binding protein, which is released by necrotic enterocytes, has also been studied in an attempt to identify strangulation. Unfortunately, all the biomarkers studied to date may be normal until very late in the process of intestinal strangulation. While recognizing this, an elevated lactate level should increase the clinical suspicion for strangulation.

Imaging

Traditionally, plain film radiographs have been the initial imaging test of choice in the diagnosis of SBO. Abdominal plain film

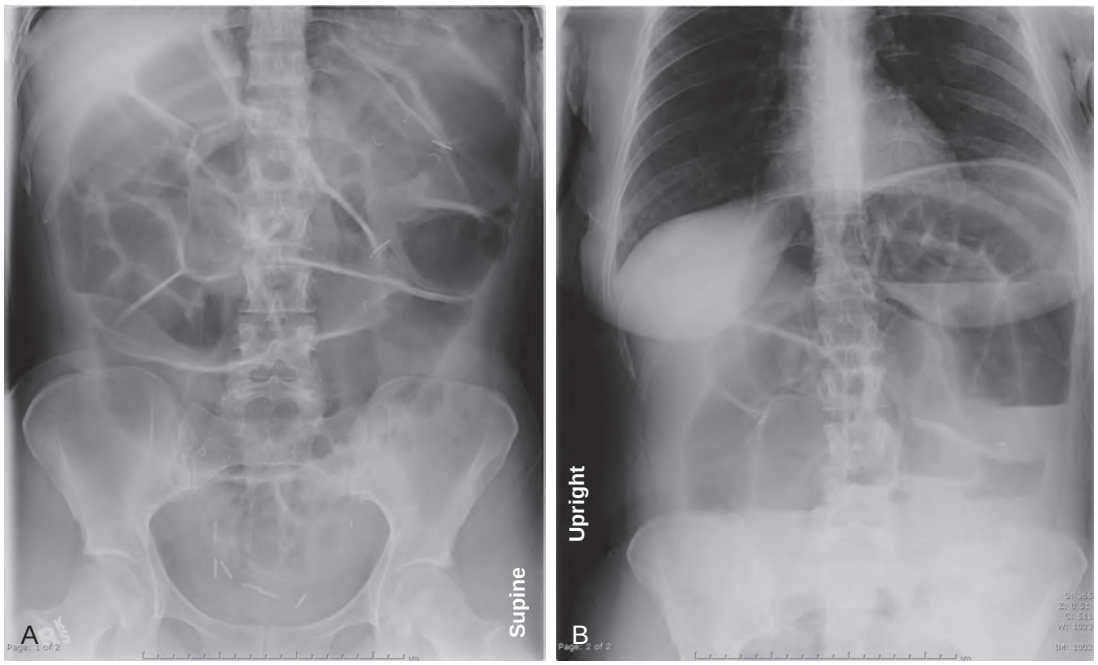

Fig. 82.3. **A,** Supine plain film radiograph showing dilated loops of small bowel in a patient with small bowel obstruction. **B,** Upright abdominal plain radiograph revealing multiple air-fluid levels and small bowel dilation, consistent with a diagnosis of small bowel obstruction.

radiographs should include supine and upright or decubitus views. An upright chest radiograph may also be obtained to evaluate for subdiaphragmatic free air resulting from a bowel perforation. Characteristic plain radiographic findings of SBO include distended loops of bowel, normally greater than 3 cm in diameter, seen centrally in the radiograph (Fig. 82.3). In addition, unlike the haustra of the large intestine, which do not cross the full diameter of the bowel, the valvulae conniventes (or plicae circulares) of the small bowel cross the entire lumen of the small intestine, thus helping differentiate SBO from large bowel obstruction. In general, the greater the number of distended loops, the more distal the obstruction. No gas should be seen in the large bowel unless the films are obtained early in the course of the obstruction or in the presence of a partial SBO. An adynamic ileus, on the other hand, tends to show extensive air-filled loops throughout the entire GI system and no small bowel dilation. Unfortunately, plain radiographic findings are diagnostic in only 50% to 60% of cases of SBO, equivocal in 20% to 30%, and normal, nonspecific, or misleading in 10% to 20%.

Computed tomography (CT) has become an increasingly popular imaging modality for the evaluation of SBO and has become the gold standard for imaging in suspected SBO. CT detects SBO with a high degree of sensitivity and specificity. In addition, unlike plain films, CT scans provides more information about the cause of obstruction, such as a tumor. More important acutely, unlike plain radiographs, CT scans are very sensitive for detecting strangulation, with a specificity of 96% and likelihood ratio of 9.3.[5] According to the American College of Radiology Appropriateness Criteria, the CT scan of choice for the evaluation of a suspected high-grade bowel obstruction is a scan of the abdomen and pelvis with IV contrast and without oral contrast. This guideline states that "oral contrast will not reach the site of obstruction, wastes time, adds expense, can induce further patient discomfort, will not add to diagnostic accuracy, and can lead to complications, particularly vomiting and aspiration."[6]

Historically ultrasound had limited value for evaluating SBO due to the significant artifact caused by gas within the GI tract.

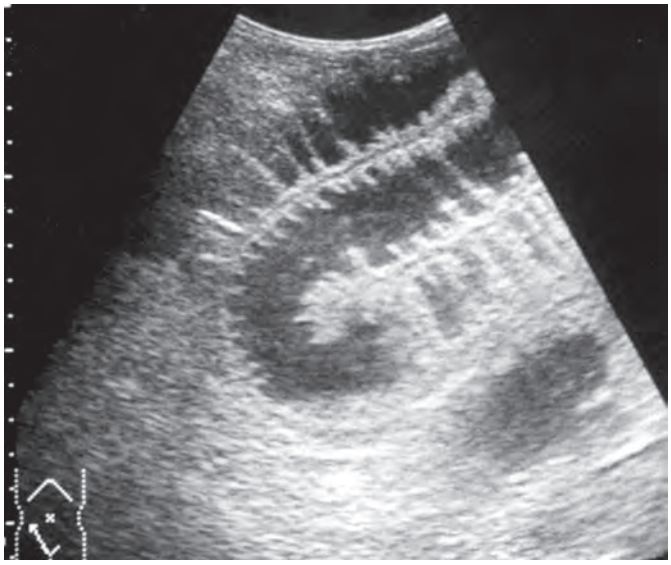

Fig. 82.4. Ultrasound image of fluid-filled dilated small bowel in small bowel obstruction. (Courtesy Masaaki Ogata, Kobe, Japan.)

However, the improved resolution of newer scanning devices has made this modality more attractive and an exciting area of exploration in the diagnosis of SBO. Typical ultrasound findings in SBO include fluid-filled bowel with dilated loops greater than 2.5 cm in diameter with decreased or absent peristalsis with proximally collapsed bowel (Fig. 82.4). Abdominal free fluid between loops of dilated bowel (the tanga sign) is suggestive of a high-grade obstruction.[7]

In summary, although the benefits of plain radiographs include rapid acquisition and lower radiation, they are diagnostic in only 50% of SBOs. Ultrasound is quickly emerging as a potentially very useful tool in the diagnosis of SBO, but further research is needed

to clarify its role. Abdominal and pelvis CT scanning with IV contrast currently remains the preferred imaging test of choice because it is the most sensitive and specific test for detecting SBO and is the most likely to identify both the cause and complications of the obstruction (specifically strangulation) with a high degree of sensitivity.

Management

Hemodynamically unstable patients should be resuscitated with crystalloid solution via a large-bore catheter. Findings suggestive of bowel strangulation should prompt rapid surgical consultation. Although many emergency clinicians and surgeons consider the use of nasogastric decompression to be dogma, its effect in decreasing the duration of SBO has scant support in the medical literature. In the era of modern antiemetics, in the setting of a simple SBO due to adhesions, if the patient's symptoms of nausea and vomiting can be controlled with medication (eg, ondansetron 4 mg IV every 6 to 8 hours or metoclopramide, 10 mg IV every 6 to 8 hours), it may be reasonable to delay nasogastric tube insertion. However, if symptoms persist or if the patient has an altered level of consciousness placing him or her at risk for aspiration, a nasogastric tube should be promptly inserted and attached to wall suction. There is no benefit to the use of long intestinal tubes instead of a traditional nasogastric tube. Placement of a nasogastric tube is a noxious procedure, and attempts should be made to anesthetize the patient's nasopharynx with topical anesthetic before insertion.

There are numerous serious complications associated with SBO. Persistent vomiting can lead to hypovolemia, metabolic alkalosis, and shock. If strangulation occurs, necrosis of the bowel can lead to perforation, and leakage of contaminated bowel contents into the peritoneal space can cause peritonitis, intra-abdominal abscess formation, and sepsis. As one would expect, complications are more common in older adults and those with comorbidities. There are also several potential complications related to surgical intervention for SBO, including wound infection and short bowel syndrome. Unfortunately, in addition to these adverse effects, the rate of recurrence of SBO is high—40% for patients treated nonoperatively and 27% for those treated operatively. For patients with SBO secondary to adhesions, the relative risk of recurrence increases with the number of prior episodes of obstruction. For those with four or more episodes of adhesional SBO, the recurrence rate is more than 80%.

There is no convincing evidence to recommend the empirical use of antibiotics for the nonoperative management of a simple SBO. In patients in whom surgical exploration is planned or perforation is suspected, antibiotics are recommended and should provide coverage against the gram-negative and anaerobic organisms that colonize the intestinal tract (eg, a second-generation cephalosporin such as cefuroxime, 1000 mg IV tid, or a broad-spectrum carbapenem such as meropenem, 1000 mg IV tid).

SBO in the presence of known malignancy is very common, occurring in up to 30% of patients with colon cancer and in 50% of patients with ovarian cancer at some time in the course of their disease. Patients who do not qualify for surgical intervention because of intra-abdominal carcinomatosis, massive ascites, or poor overall health status can be treated with self-expanding metal stents and the use of octreotide, 0.3 mg/day, given over three doses or as a continuous infusion to reduce GI secretions rapidly, may provide palliative relief. A collaborative approach with the patent's oncologist and consulting surgeon can provide the ideal individualized treatment for the patient in this situation. In the setting of terminal metastatic disease, although surgery may provide temporary symptomatic improvement, it often comes at the cost of a significant proportion of the patient's remaining days being spent in the hospital.[8]

Disposition

Patients with SBO merit admission to the hospital. Many simple SBOs related to adhesions will resolve with conservative treatment in the next 48 to 72 hours. In case of a partial SBO, in which initial imaging suggests that some colonic contents can pass the obstruction, some surgical guidelines suggest administration of a water-soluble contrast medium at admission or after 48 hours of failed conservative treatment. Appearance of contrast in the colon within 24 hours of administration predicts nonoperative resolution of the obstruction.[9,10] One study has found that patients with SBO admitted to a surgical service for inpatient management had a shorter length of stay, lower hospital charges, and lower mortality than those admitted to a medical service.[11] This was attributed largely to the fact that patients for whom conservative management was failing and needed surgical intervention were identified earlier when being managed primarily by the surgical team. Regardless of admitting service, patients with SBO need frequent reassessment to determine disease progression or resolution. Finally, although laparoscopic surgery was once considered inappropriate for the management of SBO, there has been a growing experience with its successful use in patients with SBO, particularly those with obstructions caused by adhesions.[12]

ACUTE MESENTERIC ISCHEMIA

Background

Acute mesenteric ischemia involves the sudden reduction or loss of blood flow to the small bowel and may also involve the right colon. The left colon has a much higher degree of collateral blood flow and is less prone to mesenteric ischemia. When acute mesenteric ischemia occurs, rapid intestinal injury results. This condition should be clearly differentiated from chronic mesenteric ischemia (CMI), also referred to as intestinal angina, which often manifests as recurrent episodes of abdominal pain resulting from insufficient intestinal blood flow during periods of increased postprandial metabolic demand. CMI does not usually require emergent therapy; however, it is also possible for acute mesenteric ischemia to develop in these patients.

Overall, acute mesenteric ischemia is a rare clinical problem. There are four specific clinical categories that make up the overwhelming majority of causes, each with distinct epidemiologic risk factors—mesenteric arterial embolus, mesenteric arterial thrombosis, nonocclusive mesenteric ischemia, and mesenteric venous thrombosis. Despite significant advances in the understanding of the pathophysiology, the mortality rate has remained as high as 60 to 80%, and the diagnosis and treatment of this vascular catastrophe have remained difficult.

Anatomy and Physiology

The mesenteric vessels arise from the primitive ventral segmental arteries. Although there is considerable individual variability, these vessels typically regress as embryologic development proceeds, with the exception of the 10th, 13th, and 21st segmental arteries. These become the celiac trunk, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA), respectively. The celiac trunk arises from the anterior aspect of the abdominal aorta and branches into the common hepatic, splenic, and left gastric arteries. These vessels supply the distal esophagus to the duodenum at the entrance of the bile duct. The SMA normally arises 1 cm below the celiac trunk and runs toward the cecum, terminating as the ileocolic artery. The SMA supplies the distal half of the duodenum to the proximal two-thirds of the transverse colon. The IMA originates approximately 6 to 7 cm below the SMA and gives rise to the left colic artery, sigmoid arteries, and

hemorrhoidal arteries. Anatomically, this vessel provides blood flow to the distal third of the transverse colon to the rectum.

The gut receives 20% of cardiac output at rest and up to 35% after eating. Of this, up to 70% supplies the mucosa due to the high metabolic demands required for the absorptive function of this intestinal layer.

Intestinal blood flow is regulated by a complex combination of intrinsic and extrinsic mechanisms to match intestinal demands with blood supply. Intrinsic factors provide the moment to moment control of the intestinal circulation; they function independently from neural control. This intrinsic modulation has been proposed to involve the release of local metabolites produced as a result of mucosal ischemia. These metabolites then diffuse to the local arterioles, triggering relaxation in the smooth muscle and increased blood flow, thereby allowing for efficient adjustments to the intestinal blood supply. Smooth muscle relaxation can also be brought about directly by a decrease in the perfusion pressure in the arterioles themselves. These two mechanisms are referred to as the metabolic and myogenic pathways. Intestinal blood flow is also controlled extrinsically through neural and hormonal mechanisms. Increased sympathetic tone to the paired celiac ganglia located adjacent to the celiac trunk results in mesenteric and arteriolar vasoconstriction. Hormonal influences include the direct action of angiotensin II released as a result of decreased extracellular volume, as well as vasopressin, which causes mesenteric vasoconstriction.

Pathophysiology

Although these mechanisms allow for the mesenteric circulation to adapt to wide variations in the metabolic needs of the gut and systemic perfusion, the bowel is very quickly injured in the setting of acute compromise. Because of the high metabolic demands of the intestinal mucosa, structural damage to the intestinal villi can be observed histologically within 15 minutes of absolute ischemia. If not corrected, mucosal sloughing occurs within 3 hours. By 6 hours, transmural necrosis is complete (Fig. 82.5). Complicating the situation even further, reestablishment of blood flow at this point results in the systemic release of several proinflammatory cytokines and toxic oxygen radicals caused by reperfusion, which can lead to multiorgan failure and rapid death.

Mesenteric Arterial Embolism

Arterial emboli, the most common cause of acute mesenteric ischemia, are responsible for approximately 50% of cases. The median age of patients with mesenteric arterial emboli is 70 years, and two-thirds are women. Emboli are usually cardiac in origin and arise from left atrial or ventricular mural thrombi or valvular lesions. Risk factors for the development of such thrombi include myocardial ischemia or infarction, cardiomyopathies, ventricular aneurysms, endocarditis, and atrial dysrhythmias, specifically atrial fibrillation. Compared with the estimated annual risk of stroke of 2.3%, the annual risk of AMI caused by thromboembolism secondary to atrial fibrillation is 0.14%.[13] The SMA is most frequently affected because of the large caliber of the vessel and its narrow takeoff angle from the aorta. The embolus typically lodges 3 to 10 cm distal to the origin of the SMA (Fig. 82.6). The jejunum is most often involved, as it is distant from the collateral flow provided from the celiac and inferior mesenteric arteries.

Mesenteric Arterial Thrombosis

Mesenteric arterial thrombosis results from the progression of atherosclerotic disease of the mesenteric vasculature. Risk factors for development include advanced age, hypertension, diabetes, and tobacco use. Affected patients frequently have a history suggestive of CMI of several months' or years' duration. Unlike embolic occlusions, thrombosis usually occurs in the proximal SMA at the origin of the vessel.

Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia occurs as a result of mesenteric vasospasm in the absence of a physical obstruction. This vasospasm is triggered by mesenteric hypoperfusion or excessive sympathetic nervous system activity. Mesenteric hypoperfusion can result from a wide variety of conditions, including sepsis, severe dehydration, pancreatitis, or hemorrhagic shock. Excessive sympathetic activity can result from congestive heart failure, or the use of medications and drugs such as vasopressors, cocaine, or digoxin. Once initiated, this vasospasm often persists even after correction of the underlying condition, and repeated episodes of ischemia and reperfusion occur. Studies suggest that this recurrent pattern of ischemia and reperfusion may result in more severe histologic injury than a single episode of prolonged ischemia.

Fig. 82.5. Gross pathologic image of intestinal ischemia and infarction. Note mucosal hyperemia and hemorrhage. (From Gore RM, et al: Imaging in intestinal ischemic disorders. Radiol Clin North Am 46:845–875, 2008.)

Fig. 82.6. Coronal abdominal CT angiogram with large superior mesenteric artery embolism *(arrow)*. (From Gore RM, et al: Imaging in intestinal ischemic disorders. Radiol Clin North Am 46:845–875, 2008.)

Fig. 82.7. Superior mesenteric venous thrombus (*red arrow*) in a patient with nondescript abdominal pain. Hematologic evaluation revealed factor V Leiden thrombophilia. (From Gore RM, et al: Imaging in intestinal ischemic disorders. Radiol Clin North Am 46:845–875, 2008.)

Mesenteric Venous Thrombosis

Mesenteric venous thrombosis is the least common cause of acute mesenteric ischemia (AMI), accounting for only 5% to 15% of all mesenteric ischemic events. It usually involves the superior mesenteric vein and its branches (Fig. 82.7). In the vast majority of cases (>75%), an underlying inherited thrombotic disorder or inherited or acquired hypercoagulable state can be identified. The most common cause is factor V Leiden mutation, which is thought to account for 20% to 40% of cases. Other inherited prothrombotic states implicated in the development of mesenteric venous thrombosis include deficiency in antithrombin III, protein C, or protein S. Hematologic conditions predisposing to this condition include polycythemia vera and essential thrombocythemia. Oral contraceptive use accounts for 9% to 18% of the episodes of mesenteric venous thrombosis in young women. Local intra-abdominal inflammation secondary to pancreatitis, malignancy, or inflammatory bowel disorders also increases the risk of mesenteric venous thrombosis. Finally, the venous stasis caused by portal hypertension is a recognized risk factor.

Box 82.3 summarizes causes of mesenteric venous thrombosis.

BOX 82.3

Factors Associated With Mesenteric Venous Thrombosis

HYPERCOAGULABLE STATES
Polycythemia vera
Sickle cell disease
Antithrombin III deficiency
Protein C or S deficiency
Malignancy
Myeloproliferative disorders
Estrogen therapy, oral contraceptive pills
Pregnancy

INFLAMMATORY CONDITIONS
Pancreatitis
Diverticulitis
Appendicitis
Cholangitis

TRAUMA
Operative venous injury
Postsplenectomy
Blunt or abdominal trauma

MISCELLANEOUS
Congestive heart failure
Renal failure
Decompression sickness
Portal hypertension

Unusual Causes of Mesenteric Ischemia

In addition to the conditions already described, there are numerous case reports of unusual causes of mesenteric ischemia. These include SMA dissection leading to occlusion, tumor emboli, retroperitoneal fibrosis, and various types of vasculitis, including Buerger's disease, polyarteritis nodosa, and Takayasu's arteritis. Because these conditions involve a rare cause of an already rare condition, they frequently go unrecognized until patients develop major adverse effects.

Clinical Features

History

The history at presentation of mesenteric ischemia is largely dependent on the nature of the underlying cause. The traditional historical triad of acute mesenteric ischemia is the sudden onset of poorly localized abdominal pain and gastric emptying (vomiting or diarrhea) in a patient with cardiac disease. This is especially true in cases of SMA embolism or thrombosis, in which symptoms and clinical deterioration can rapidly occur. In cases of mesenteric venous thrombosis, the symptoms are slower in onset and often have been present for several days by the time the patient seeks medical attention. Approximately one-third of patients with acute embolic mesenteric ischemia and 50% of patients with acute mesenteric venous thrombosis have a personal history of an embolic event, such as a pulmonary embolism, deep vein thrombosis, or ischemic stroke. Patients with nonocclusive mesenteric ischemia are often already critically ill and in the hospital, making it difficult or impossible for them to provide historical details to the treating physician.

Physical Examination

The pain in acute mesenteric ischemia is typically described as being out of proportion to the physical examination findings. The patient may be writhing in pain but have a soft abdomen without guarding, especially early in the course of the event, when only the visceral structures are ischemic. As the parietal peritoneum becomes ischemic, the abdominal physical findings progress. If the ischemia progresses to infarction, peritonitis may be present. Heme-positive stools may also be noted. Hypotension, tachycardia, and tachypnea are all signs of severe ischemia and suggest a poor prognosis.

Differential Diagnosis

Other potentially devastating conditions to consider in the differential diagnosis of acute-onset severe abdominal pain include leaking AAA, perforated viscus, bowel obstruction, biliary disease, and atypical myocardial infarction.

Diagnostic Testing

Laboratory Tests

Initial laboratory results in patients with acute mesenteric ischemia are often nonspecific and may include leukocytosis, an elevated hematocrit secondary to hemoconcentration, and metabolic acidosis. Several serum biomarkers have been investigated as early indicators including lactate, D-dimer, interleukin (IL)-6, and serum ischemia-modified albumin levels. A meta-analysis has shown a pooled sensitivity of 86% and pooled specificity of 42% for L-lactate, and a pooled sensitivity of 96% and a pooled specificity of 40% for D-dimer.[14] To date, no biomarkers have been found that are sufficiently sensitive and specific to diagnose or eliminate mesenteric ischemia based on laboratory results alone. Recognizing these limitations, when considering this diagnosis, the serum lactic acid level is currently the most useful laboratory test available. In addition to its wide availability and rapid turnaround time, the short half-life of serum lactic acid (≈20 minutes) may be useful for the emergency clinician to allow for serial measurements, especially early in the course of suspected acute mesenteric ischemia.

Imaging

Plain abdominal radiographs in mesenteric ischemia are usually nonspecific. Later in the disease course, plain radiographic findings may show so-called thumbprinting, in which multiple, round, smooth soft tissue densities project into the intestinal lumen because of mucosal and submucosal edema and hemorrhage. More specific but very late plain radiographic findings indicating infarction include pneumatosis intestinalis and portal venous gas.

Mesenteric angiography remains the gold standard in the radiographic evaluation for mesenteric ischemia and offers the benefit that diagnosis and initial treatment can occur concurrently. However, angiographic services are often not readily available on a routine basis. As a result, CT angiography has largely replaced conventional angiography as the initial imaging study of choice for the evaluation of mesenteric ischemia. Several studies have shown that with the emergence of multidetector scanners, the sensitivity and specificity for mesenteric ischemia are high, approximately 94% and 96%, respectively.[15]

Duplex sonography has been found to be very specific (92%–100%) for the detection of AMI, but its sensitivity is decreased (70%–89%) by limited evaluation beyond the proximal main vessel. It is also unable to provide much information about complications of acute mesenteric ischemia, including bowel infarction.

Management

Once AMI has been diagnosed, the goals of treatment are to restore mesenteric blood flow as rapidly as possible, manage underlying conditions, treat persistent mesenteric vasospasm if present, and mitigate the risk of further clot propagation. Initial interventions should focus on fluid resuscitation and hemodynamic stabilization. Because these patients are often older adults with cardiac comorbidities, invasive monitoring may be indicated. If vasopressors are required, dobutamine, low-dose dopamine, or milrinone are recommended, because these have been shown to have less of a vasoconstrictive effect on the mesenteric vasculature than other agents. With evidence of infarction, perforation, or peritonitis, antibiotics suitable for enteric coverage, such as ceftriaxone, 1g IV qd, or ciprofloxacin 500 mg qd, with either in combination with metronidazole, 500 mg IV tid, are recommended, and a surgeon should be promptly consulted. Further management depends on the cause of ischemia, and controversies exist about the optimal management of these critically ill patients.

Regardless of cause, if signs of intestinal infarction or perforation with peritonitis are present, prompt emergent laparotomy is warranted. Preoperative conventional angiography may be beneficial to attempt rapid revascularization, and studies have suggested that initial endovascular revascularization may significantly improve patient outcomes and dramatically alter the future treatment of AMI.[16,17] Numerous reports have detailed the use of thrombolytic agents, angioplasty, embolectomy, or vascular stenting to restore mesenteric blood flow. In addition, the phosphodiesterase inhibitor papaverine may be continuously infused directly into the compromised vessel. This agent results in elevated levels of cyclic adenosine monophosphate (cAMP), which results in profound smooth muscle relaxation. Because cAMP undergoes over 90% first-pass hepatic metabolism, few systemic effects are noted when it is infused directly into the mesenteric circulation.

Primary treatment of nonocclusive mesenteric ischemia involves interventions to reverse the underlying cause and consideration for papaverine infusion via angiographic catheter, as well as IV heparin to prevent thrombosis in the vasospastic vessel. Papaverine infusion is often maintained for 24 hours, at which time angiography may be repeated to evaluate for the resolution of vasospasm. If peritoneal signs develop, laparotomy is indicated. If the underlying medical condition persists, the mortality of nonocclusive mesenteric ischemia remains high.

The treatment of mesenteric venous thrombosis is unique in that in the absence of peritoneal findings, initial treatment with heparin infusion alone may be adequate. However, if peritoneal findings are present or develop later in the patient's hospital course, bowel necrosis is likely, and prompt laparotomy is indicated. If the patient recovers, long-term anticoagulation with warfarin usually is provided to prevent recurrence. An appropriate evaluation for hypercoagulable conditions should be undertaken.

Even with prompt recognition and treatment of acute mesenteric ischemia, a complicated course is expected. Secondary reperfusion injury is common, and bowel initially identified as viable may progress to necrosis. Other complications include wound infections, sepsis, and pneumonia. Given the population in which AMI tends to occur, the physiologic stress of this disease process also places patients at high risk for myocardial infarction, renal failure, and pulmonary embolism while in the hospital.

Disposition

All patients with acute mesenteric ischemia require admission to the intensive care unit.

KEY CONCEPTS

Small Bowel Obstruction

- The most common cause of SBO is postoperative adhesions. Other common causes include neoplasm and hernias.
- Abdominal CT with IV contrast is the gold standard for imaging in cases of suspected SBO. It is sensitive and specific and provides information about the cause of the obstruction and potential complication of strangulation.
- Bedside ultrasound for SBO may be a potentially useful imaging modality, but more research is needed.
- Many patients with SBO will improve with nonoperative conservative treatment; however, prompt surgical exploration is recommended when there is suspected bowel strangulation.
- Antibiotics are not indicated in cases of simple SBO.
- The recurrence rate for SBO is high, regardless whether treatment is operative or nonoperative.

Acute Mesenteric Ischemia

- Acute mesenteric ischemia (AMI) is a rare vascular catastrophe, with a very high mortality.
- AMI should be considered in patients older than 50 years with a history of cardiac disease who have acute abdominal pain, which may initially appear severe and out of proportion to physical examination findings.
- Within the diagnosis of AMI are four distinct clinical entities with specific associated risk factors, clinical presentations, and treatments—mesenteric arterial embolism, mesenteric arterial thrombosis, nonocclusive mesenteric ischemia, and mesenteric venous thrombosis.
- Although no current laboratory test has sufficient sensitivity or specificity to diagnose acute mesenteric ischemia alone, determination of the serum L-lactate level is currently the most useful.
- CT angiography is the initial imaging test of choice for the evaluation of suspected AMI.
- Successful management of acute mesenteric arterial embolism and thrombosis frequently requires multispecialty, care including general or vascular surgery, interventional radiology, and critical care, with the goal of restoring mesenteric blood flow as quickly as possible.
- Unlike cases of arterial embolism or thrombosis, in the absence of peritonitis, mesenteric venous thrombosis is often successfully managed with heparin alone.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 82: QUESTIONS & ANSWERS

82.1. What is the most common cause of small bowel obstruction in the developed world?
- **A.** Gallstone ileus
- **B.** Hernias
- **C.** Intussusception
- **D.** Postoperative adhesions
- **E.** Tumors

Answer: D. In the developed world, postoperative adhesions account for approximately 60% of cases of small bowel obstruction. Patients with a history of intestinal or pelvic surgery are at the highest risk.

82.2. Which of the following patients are at the highest risk of developing an obturator hernia?
- **A.** 2-year-old boy with no known medical problems
- **B.** 45-year-old woman with a 1-year history of hysterectomy
- **C.** 67-year-old man with a history of metastatic prostate cancer
- **D.** 80-year-old woman with a 3-month history of rapid weight loss

Answer: D. This type of hernia is especially common in older women who have recently lost a significant amount of weight. The female pelvis is wider, and the obturator canal is more oblique in women. This, in combination with a loss of preperitoneal fat, predisposes to its development. Because an external mass is absent, diagnosis is especially challenging and explains why it carries the highest mortality of any abdominal hernia, at nearly 70% when incarcerated.

82.3. A 55-year-old woman with a history of Roux-en-Y gastric bypass surgery presents with a 1-day history of worsening colicky abdominal pain and vomiting. A CT scan reveals an internal hernia. What is the most appropriate disposition?
- **A.** Administer broad-spectrum antibiotics and admit to the medicine floor.
- **B.** Arrange for barium swallow with small bowel follow-through
- **C.** Insert nasogastric tube and admit to the medicine floor.
- **D.** Prompt surgical consultation and preparation for surgery should occur.

Answer: D. Although rare in the general population, internal hernias are a recognized complication of bariatric surgery, especially when a Roux-en-Y type procedure has been performed. Because of the closed loop nature of an internal hernia, they are not suitable for conservative management and require surgical intervention.

82.4. What is the length of time from acute absolute ischemia of the intestines to completion of transmural necrosis?
- **A.** 15 minutes
- **B.** 60 minutes
- **C.** 2 hours
- **D.** 6 hours
- **E.** 24 hours

Answer: D. Although the mesenteric circulation is able to adapt to variations in circulation, the small bowel is quickly injured after acute ischemia. Within 15 minutes, structural damage to the intestinal villi can be seen histologically. If blood flow is not restored, mucosal sloughing can start to occur within 3 hours and, by 6 hours, transmural necrosis is complete.

82.5. A 35-year-old woman who currently smokes while taking oral contraceptive pills presents with 2 days of progressively worsening diffuse abdominal pain without peritoneal findings on examination. A CT scan reveals mesenteric venous thrombosis. What is the next most appropriate step?
- **A.** Arrange for formal mesenteric venous angiography to confirm and treat.
- **B.** Arrange for immediate exploratory laparotomy regardless of current clinical status, given the high risk of severe complications.
- **C.** Discharge home because this will resolve without intervention.
- **D.** Institute pain control and admit to the floor.
- **E.** Start anticoagulation with therapeutic dosing of heparin.

Answer: E. The treatment of mesenteric venous thrombosis is unique in that in the absence of peritoneal findings, initial treatment with heparin alone may be adequate. In the vast majority of cases (>75%) an underlying inherited or acquired hypercoagulable state can be identified. Oral contraceptive use accounts for 9% to 18% of cases in young women.

CHAPTER 83

Acute Appendicitis

Michael Alan Cole | Robert David Huang

PRINCIPLES

Background

The appendix was once considered a vestigial organ; however, it is currently theorized that it serves as a repository for commensal bacteria that assist in normal digestive processes and may allow for recolonization of intestinal flora in times of enteric bacterial destruction. Phylogenetic studies have supported the appendix as likely having a so-called positive fitness value during mammalian evolution, whereas recent clinical research studies have demonstrated a possible increased risk of clostridial infections in patients who have had prior appendectomies.[1-3]

Appendicitis is the most common cause of acute abdominal pain requiring operative intervention in patients younger than 50 years. It is the most common nonobstetric abdominal emergency in pregnant females, usually occurring in the second trimester. Risk factors for appendicitis include white ethnicity, male gender, and young age (69% of cases occur in patients <30 years). Although males have an increased risk of having appendicitis (1.4:1), females have an almost twofold increased risk of undergoing an appendectomy, which is partially related to the fact that women have gynecologic conditions that frequently mimic appendicitis.

Anatomy and Physiology

The vermiform appendix is a blind-ended tube that originates from the cecum, approximately 3 cm from the ileocecal valve. It is considered part of the cecum and has the same histologic arrangement as the large intestine. A unique aspect of the appendix is the large masses of lymphoid tissue in the mucosa and submucosa. Although it has an average length of 8 to 10 cm, the appendix may be more than 20 cm in length, thereby allowing it to traverse into the left lower or right upper quadrants of the abdomen. The average diameter of the appendix ranges from 6 to 11 mm; thus, appendiceal diameter alone, in the absence of other radiologic findings, often does not imply appendicitis. Finally, a normal appendix has an average wall thickness of 1.5 mm.

The appendix maintains afferent sensory fibers that follow the sympathetic innervation and enter the spinal cord at the 10th thoracic level (T10). It is these nerves that carry the sensation of pain and result in the periumbilical discomfort associated with early appendicitis.

There are three important anatomic features of the appendix that determine the site of the patient's pain and tenderness when the organ is inflamed: (1) the location of the origin of the appendix off the cecum; (2) the course the appendix takes from this origin; and (3) the length of the appendix (as described above; Fig. 83.1). All these features are variable, resulting in a wide range of symptoms and signs, which often creates difficulty with the clinical diagnosis of appendicitis. Although the location of the origin of the appendix is generally thought to be positioned at McBurney's point (exactly between an 1.5 to 2 inches from the right anterior superior iliac spine on a straight line drawn to the umbilicus), the base may be as much as 10 cm away from this site. In fact, only 40% of patients have the base of their appendix within 3m of McBurney's point, with 36% of patients having the base more than 5m away. Next, there is significant variation involving the course of the appendix from its cecal origin. The frequency with which the appendix is found in various locations is illustrated in Fig. 83.2. Finally, in rare cases, patients may present with left lower quadrant pain or right flank pain due to a very long appendix traveling into the left lower abdomen or a retrocecal location extending into the retroperitoneum, respectively.

Pathophysiology

The cause of appendicitis is rooted in obstruction of the appendiceal lumen. The underlying pathophysiology is progressive in nature and best understood in a stepwise fashion—appendiceal obstruction prevents egress of mucus and bacteria from the appendix; continued mucous production and bacterial proliferation result in luminal distention, which stimulates the T10 visceral afferent nerves, creating periumbilical pain typically lasting 4 to 6 hours. Intraluminal pressure eventually exceeds local capillary pressure in the appendiceal wall, preventing arterial perfusion and resulting in tissue ischemia and inflammation; ischemia and inflammation compromise the integrity of the appendiceal wall bacteria and then invade the appendiceal wall. This causes transmural inflammation that extends into the surrounding tissues (peritoneal, ileocecal, and pelvic areas), resulting in somatic localized pain, typically focused in the right lower quadrant. If this process continues, the appendix becomes necrotic and perforates, releasing enteric contents into the peritoneum and resulting in peritonitis and, typically, diffuse abdominal pain. The length of time from the onset of symptoms to perforation is highly variable.

Although obstruction of the appendiceal lumen is thought to be a common inciting factor in appendicitis, the cause of this obstruction is variable and, in many cases, a source of obstruction is not discovered on imaging or pathology. Fecaliths (hard stools) are the most common cause of obstruction in nonperforated appendicitis (65%), followed by appendicoliths (calcified deposits) and lymphoid hyperplasia (primary or secondary to an enteric infection). Other causes of obstruction are rare; these include fecal stasis, foreign bodies (eg, vegetable matter, inspissated barium), tumors, and intestinal parasites.

There are two additional pathologic processes associated with appendicitis. First, so-called tip appendicitis is appendiceal inflammation localized to the distal end of the appendix. The clinical significance of this disorder is that it may be missed on imaging due to the limited extent of disease and the lack of classic findings associated with appendicitis; it has been demonstrated to contribute to the false-negative rate associated with computed tomography (CT) imaging. Second, stump appendicitis is a very rare entity that results from inflammation of the appendiceal remnant that may persist after the appendix has been removed surgically. Timing of its occurrence varies; it has been diagnosed

between 4 days and up to 50 years after the initial appendectomy.[4]

CLINICAL FEATURES

Typical presentations of appendicitis often allow an experienced provider to hone in on a diagnosis in a rather rapid fashion; unfortunately, typical findings are the exception and not the rule. For historical purposes, the constellation findings classically associated with acute appendicitis include younger age, epigastric pain that migrates to the right lower quadrant (RLQ), and tenderness of the RLQ. However, the combination of these findings occurs in less than 50% of patients with acute appendicitis thus limiting their use in clinical decision making.[4a] Missed acute appendicitis is one of the most common causes of litigation surrounding emergency medicine, which speaks to the challenges in diagnosing this illness in the presence of often ambiguous symptoms.[5]

No one element of the history or physical examination can reliably be used to diagnose or exclude appendicitis. Therefore, focusing on a single finding may lead to misdiagnosis. Rather, a comprehensive approach using multiple elements of the history, physical examination, and laboratory data should be used to risk-stratify patients to make informed decisions regarding imaging, treatment, and disposition. This approach should focus on the history and physical examination findings that have the greatest predictive values.

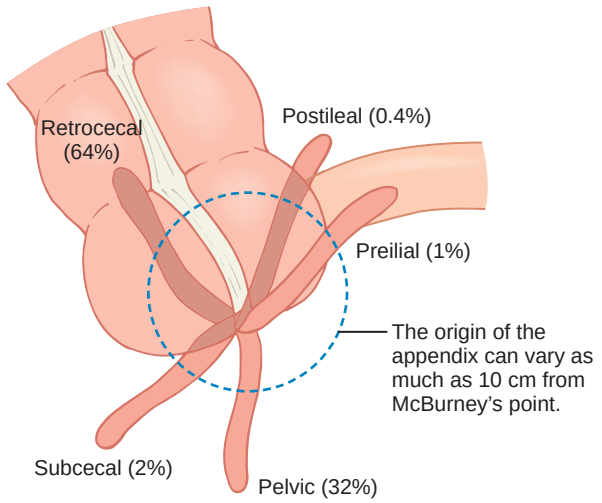


Fig. 83.1. This figure demonstrates the variation in location of the base of the appendix and its course within the peritoneum. McBurney's point classically represents the point of maximal tenderness in appendicitis; however, depending on the path, length, and degree of inflammation of the appendix, the true point of maximal tenderness is highly variable.

History

The history and review of systems provide insight into the patient's symptoms and help determine alternative diagnoses. A prior history of similar symptoms suggests an alternative diagnosis, because appendicitis is an acute illness. Furthermore, because the pathophysiology of appendicitis is a progressive process, a patient's symptoms typically worsen over the course of the illness until perforation of the appendix occurs. At this point, the patient may receive some temporary relief due to a decrease of intraluminal pressure, but will subsequently become very ill from the resultant peritonitis. See Table 83.1 for a list common symptoms and their value in predicting the likelihood of appendicitis. Duration of symptoms is variable and often is not useful in the assessment of appendicitis.

When considering features that exclude appendicitis, findings that decrease the likelihood of appendicitis include absence of RLQ pain and a history of similar pain in the past. Nevertheless, these findings in isolation do not exclude appendicitis as a possible diagnosis and are best used as part of a comprehensive clinical decision making process.

Physical Examination

All patients with abdominal pain should be fully disrobed, and female patients should ideally be placed in a room in which a pelvic examination can be performed (see Table 83.1). Classic, eponymous examination maneuvers for appendicitis have overall poor sensitivity but, if present, have a modest predictive value (Table 83.2). Although McBurney's point tenderness has a low correlation with appendiceal location and is not highly sensitive for appendicitis, tenderness at this location does have a modest predictive value for appendicitis.

A genitourinary examination should be performed to assess for testicular pathology or hernias in males and pelvic pathology in females. Cervical motion tenderness (CMT) is not specific for pelvic pathology and is noted in 28% of female patient with appendicitis. A rectal examination contributes little toward the assessment of appendicitis and is not routinely recommended.[6]

DIFFERENTIAL DIAGNOSIS

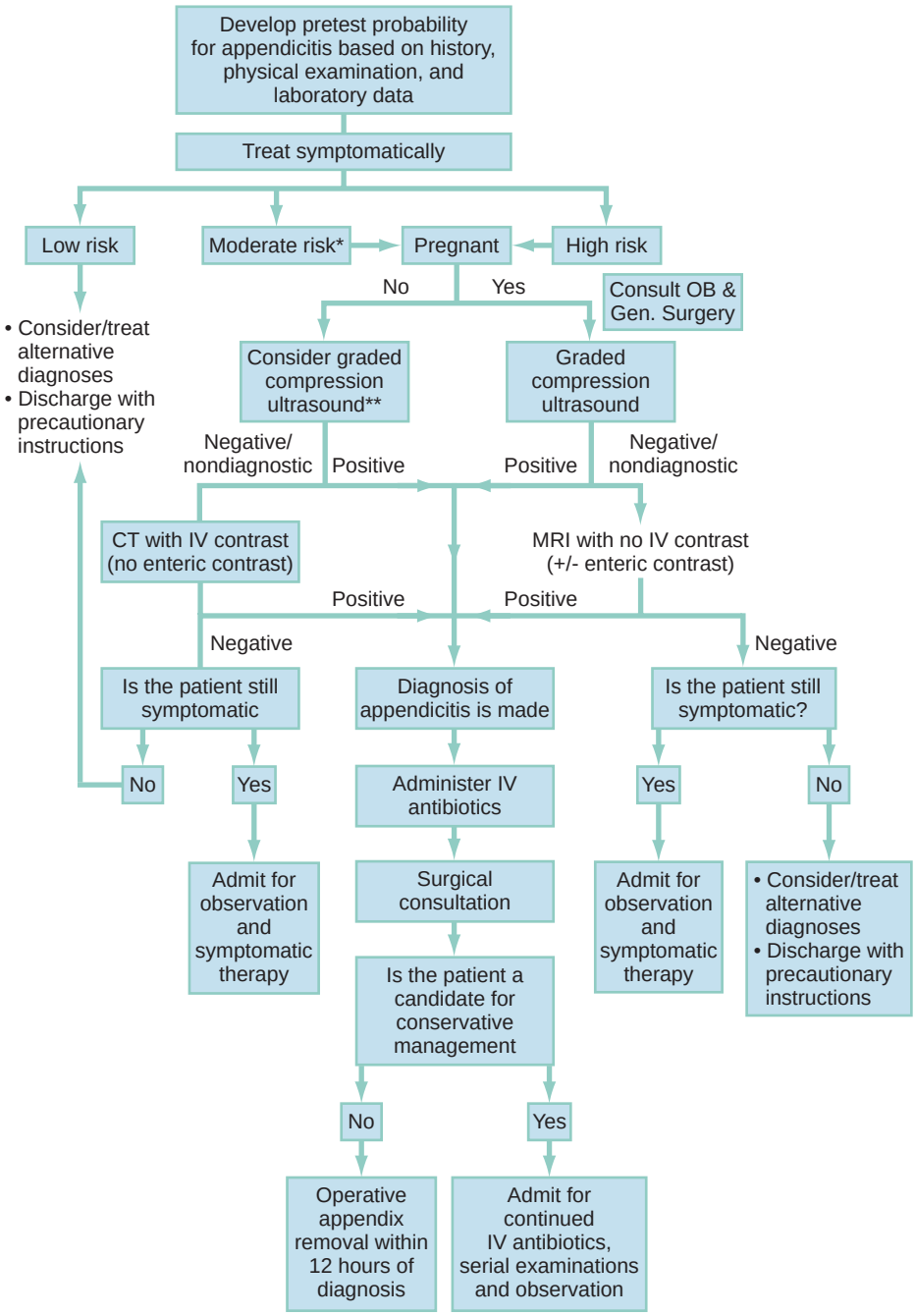
There are many diagnoses that mimic appendicitis; alternatively, appendicitis may present atypically and must be considered in all

TABLE 83.1

Predictive Value of Common Symptoms and Signs in Diagnosing Appendicitis

FEATURE	MODERATELY USEFUL	MILDLY USEFUL	NOT USEFUL
Historical features	RLQ pain Migration of pain to the RLQ Presence of pain prior to vomiting No history of prior similar pain	Vomiting Male gender Pain worsened when driving over speed bumps[34]	Anorexia Nausea Pain worse with cough or movement
Physical examination features[35]	RLQ tenderness Abdominal wall rigidity Pain focused at McBurney's point	Rebound tenderness Guarding Temperature > 38.3°C (101°F) Percussion tenderness Psoas sign	Rectal examination Increased skin temperature

RLQ, Right lower quadrant.
Adapted from Laurell H, Hansson L-E, Gunnarsson U. Manifestations of acute appendicitis: a prospective study on acute abdominal pain. Dig Surg 30:198–206, 2013.



*In moderate pre-test probability patients, the provider may consider admission for serial examinations or discharge in select cases.

**In pediatric patients, graded compression ultrasound should always be the first imaging test performed.

Fig. 83.2. Suggested clinical management pathway for emergency department patients with possible appendicitis. *Gen.,* General; *OB,* obstetrician.

patients presenting with abdominal pain, not just those with right lower quadrant pain. Table 83.3 lists the most common differential diagnoses for appendicitis.

DIAGNOSTIC TESTING

Laboratory Data

Laboratory data should not be viewed as diagnostic for appendicitis. Rather, it should be used in association with the patient's clinical history and physical examination to formulate a more comprehensive assessment of the patient's condition and further risk-stratify the patient for treatment and disposition purposes.

White Blood Cell Count

A patient's white blood cell (WBC) count does not by itself have the sensitivity, specificity, or predictive value necessary to be clinically useful in diagnosing or excluding appendicitis. An elevated WBC count (>10,000–12,000/mm^3) has a sensitivity of 62% to 85%, specificity of 32% to 82%, positive LR of 1.59 to 2.7, and negative LR of 0.25 to 0.46. Even in a subgroup analysis of

TABLE 83.2

Common Maneuvers and Physical Findings Associated With Appendicitis and Their Predictive Values[a]

MANEUVER	DESCRIPTION	SENSITIVITY AND SPECIFICITY (%)
Iliopsoas (psoas) sign	Increased abdominal pain with patient lying on left side while provider passively extends the patient's right leg at the hip with both knees extended	Sensitivity: 13–42 Specificity: 79–95
Rovsing's sign	Abdominal pain in the RLQ while palpating the left lower quadrant	Sensitivity: 7–68 Specificity: 58–96
Obturator sign	Increased abdominal pain in the supine patient as the provider internally and externally rotates the right leg as it is flexed at the hip	Sensitivity: 8 Specificity: 94

[a]Overall poor sensitivity decreases the value of these findings. However, if found, these signs moderately increase the likelihood of having appendicitis.
RLQ, Right lower quadrant.

TABLE 83.3

Differential Diagnosis in Appendicitis

ALL PATIENTS	FEMALE PATIENTS	PEDIATRIC PATIENTS
Nonspecific abdominal pain	Ectopic pregnancy	Henoch-Schönlein purpura
Gastroenteritis	Ovarian torsion	Mesenteric lymphadenitis
Epiploic appendigitis	Pelvic inflammatory disease	Meckel's diverticulum
Ureterolithiasis, nephrolithiasis	Ovarian cyst	
Inflammatory bowel disease		
Ileus or bowel obstruction		
Intestinal perforation		
Testicular torsion (males)		

increasingly high cutoff values for the WBC count (eg, >15,000 or 20,000/mm^3), it is still not significant enough to be used in clinical practice to diagnose or exclude acute appendicitis.[7,8]

C-Reactive Protein

The C-reactive protein (CRP) level is a nonspecific, systemic inflammatory marker synthesized by the liver. It has a poor predictive value in diagnosing or excluding acute appendicitis.[8] An elevated CRP (>8–10 mg/L) has a sensitivity of 65% to 85%, specificity of 32% to 87%, positive LR of 1.59 to 4.2, and negative LR of 0.11 to 3.2.[8,9] Some studies have suggested that CRP may be useful for predicting the severity of appendicitis and likelihood of complications; however, its value in diagnosing appendicitis lies in combining CRP with the WBC (see below).[10]

Combined Inflammatory Markers

The American College of Emergency Physicians clinical policy on patients with suspected appendicitis states that the combination of a WBC more than 10,000/mm^3 and CRP more than 8 mg/L has a positive likelihood ratio of 23 and a negative likelihood ratio of 0.03. These combined laboratory findings offer the greatest impact when excluding appendicitis in patients with a low pretest probability of the disease. Although more research is needed, based on the best available evidence, we recommend using the combination of low WBC (<10,000/mm^3) and CRP (<8 mg/L) in patients deemed to be low risk for appendicitis, based on the provider's clinical assessment, to exclude appendicitis. Alternatively, we do not believe that there are sufficient data to establish the diagnosis of appendicitis conclusively based on the combination of elevated WBC and CRP levels; rather, these should only assist in the decision making process regarding the need for imaging.

Urinalysis

Urinalysis demonstrates pyuria, hematuria, and/or bacteria in up to 48% of patients with appendicitis. These abnormalities are due to the inflamed appendix abutting the ureter, with resultant ureteral inflammation. Nevertheless, findings on urinalysis of more than 30 red blood cells (RBCs)/high-power field or more than 20 WBCs/high-power field are more consistent with urinary tract infections than appendicitis.

Other Laboratory Tests

A serum or urine pregnancy test is recommended for any female of childbearing age with abdominal pain. A basic metabolic panel, liver function tests, and lipase level should be obtained for patients with suspected appendicitis to assess for electrolyte derangements and alternative causes of abdominal pain. Procalcitonin does not currently play a role in the diagnosis of appendicitis due to its poor predictive value.[8] The polymorphonuclear count, in isolation, has no clinical value in the assessment of appendicitis.

Imaging Tests

General Principles

The decision to pursue imaging is based on the provider's clinical assessment, which combines the patient's history, examination, and laboratory data to decide on the likelihood of appendicitis. If the likelihood is low (and other significant disease processes have been excluded), the patient may be discharged from the emergency department (ED) or observed with serial examinations in an observation unit (see Chapter e6) or inpatient setting. However, if there is a concern for appendicitis, imaging should be carried out.

Currently, patients rarely undergo surgical removal of the appendix based on clinical features alone. The negative appendectomy rate—the number of normal appendices that are surgically removed—is far lower when imaging is used.[11] Nevertheless, in rare cases of young men with a classic presentation, the decision to perform an appendectomy in the absence of imaging may be pursued at the surgeon's discretion.

Radiography

Due to their poor sensitivity and specificity, routine radiographs are of no clinical value in the evaluation of appendicitis. The only value of radiographs is to assess for other causes of the patient's symptoms, such as bowel obstruction or bowel perforation. However, an ileus mimicking bowel obstruction may occur in appendicitis due to peritoneal inflammation, and advanced appendicitis may perforate, resulting in intraperitoneal air on

TABLE 83.4

Diagnostic Criteria for Appendicitis on Imaging

ULTRASOUND	COMPUTED TOPOGRAPHY	MAGNETIC RESONANCE IMAGING
The first two criteria below must be fulfilled: • Appendiceal diameter > 6–7 mm[a] • Noncompressible appendix	Not all criteria listed below need to be fulfilled but the combination and severity of these findings contribute to a diagnosis: Appendiceal diameter (>6 mm with surrounding inflammation or >8 mm without such changes) Appendiceal circumferential wall thickening >2 mm with mural enhancement (sign of inflammation)	Not all criteria listed need to be fulfilled but the combination and severity of these findings contribute to a diagnosis: Appendiceal diameter > 7 mm Appendiceal circumferential wall thickening > 2 mm
Fat stranding (hyperechoic signals associated with periappendiceal inflammation) (secondary finding) and peritoneal fluid	Calcified appendicolith	Signs of inflammation adjacent to the appendix, such as fat stranding or phlegmon formation
Peritoneal fluid surrounding the appendix (secondary finding)	Signs of periappendiceal inflammation (eg, fat stranding, clouding of the adjacent mesentery)	Presence of an abscess or a fluid filled appendix

[a]It is important to note that the diameter of a normal nondiseased appendix may be up to 11 mm, so the other findings of appendicitis must be factored in when making the diagnosis of appendicitis on CT or MRI. Due to the graded compression technique used in ultrasound, there is more certainty regarding diagnostic criteria for appendiceal diameter.

abdominal radiographs. Therefore, care must be taken to make the final diagnosis based on radiographic findings, although intraperitoneal air often expedites the patient's disposition to the operating room.

Graded-Compression Ultrasound

Within the medical community, there is a growing awareness of the risks associated with ionizing radiation, and efforts are being made to use methods of diagnosis that reduce or eliminate these risks.[12] Graded compression ultrasound (US) is an imaging tool commonly used in evaluating patients for appendicitis. It is a diagnostic technique in which steady pressure is applied with the US probe to the abdomen to reduce bowel gas and collapse normal bowel to promote visualization of the appendix. Studies involving graded compression US for the diagnosis of appendicitis have reported sensitivities of 75% to 90%, specificities of 83% to 95%, positive LRs of 4.5 to 5.8, and negative LRs of 0.19 to 0.27, with an average positive predictive value of 90%.[13] Table 83.4 lists US criteria for the diagnosis of appendicitis.

The benefits in using US for the diagnosis of appendicitis include decreased cost relative to other imaging modalities, lack of ionizing radiation exposure, and decreased time to diagnosis. Limitations of US use include decreased specificity and increased pain due to the transducer pressure needed for the graded compression process. Most importantly, a number of US examinations cannot visualize the appendix (ie, nondiagnostic) for a number of reasons, including lack of operator experience, patient factors (eg, obesity), superimposed bowel gas, or atypically located appendix.[14] In cases with nondiagnostic US findings, the patient typically requires further imaging with CT (or magnetic resonance imaging [MRI] in pregnancy) or admission for observation and serial examinations. Ultrasound is most useful in children, for whom the risks of ionizing radiation are greatest, and rates of overweight and obese individuals are lower than adults and pregnant females (Figs. 83.3 and 83.4).

A distinction must be made between radiology-based US and bedside (point of care) US examination performed by an emergency clinician. Recent studies have demonstrated that bedside US is not as effective at diagnosing appendicitis, with a sensitivity for diagnosis of 60% to 70%, with specificities of 94% to 98%.[15,16]

Finally, in women with CMT, masses found on pelvic examination, or concern for a gynecologic cause of the patient's symptoms, pelvic US is an important study to help determine ovarian pathology or tuboovarian abscesses. This should be performed before CT imaging in an attempt to elucidate an alternative diagnosis and may be completed simultaneously with a graded compression US to assess for appendicitis.

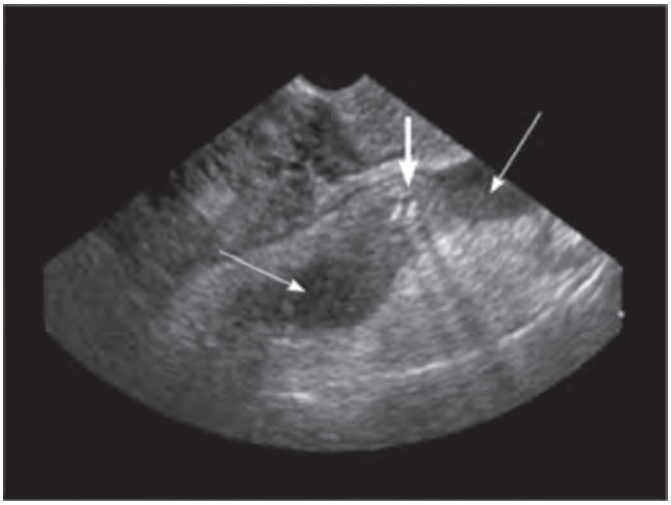


Fig. 83.3. Ultrasound image of appendicitis in an 8-year-girl. Note the dilated noncompressible appendix *(thin arrows)* and the presence of a fecalith, with posterior acoustic shadowing *(thick arrow)*. (Courtesy Dr. Michael Cole, with permission.)

Computed Tomography

CT of the abdomen and pelvis is considered the test of choice for definitive assessment of possible appendicitis in nonpregnant patients. It demonstrates an overall sensitivity of 94% to 100% and specificity of 91% to 99%, with a positive LR of 9.29 to 13.3, negative LR of 0.1 to 0.09, and positive predictive value of 95% to 97%.[13] CT is accurate and consistent in diagnosing appendicitis and decreases the negative appendectomy rate. CT is readily available in most hospitals, can be performed in a rapid fashion, is not operator-dependent, can be interpreted by most radiologists and surgeons, and has a greater likelihood of finding an alternative diagnosis (vs. US; Figs. 83.5 and 83.6).

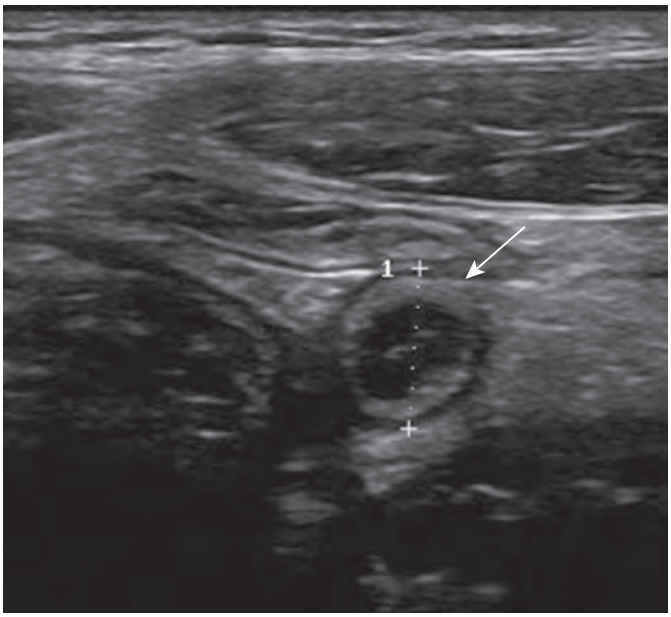


Fig. 83.4. Graded compression ultrasound scan demonstrating a dilated noncompressible appendix *(thin arrow)* representing appendicitis.

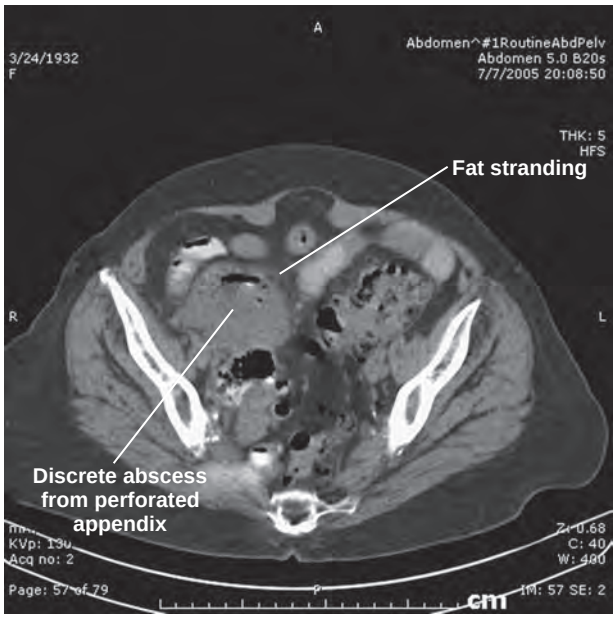


Fig. 83.6. Oral contrast CT scan showing discrete abscess from appendiceal perforation, with periappendiceal fat streaking. (Courtesy Jefferson Radiology, Avon, CT.)

Fig. 83.5. CT scan with typical findings of acute appendicitis. *thick arrow, thin arrows, dashed line arrow.*

The greatest disadvantage of CT is the ionizing radiation. A CT scan of the abdomen exposes the patient to an average dose of ionizing radiation equivalent to 8 examination 10 mSv. To put this in perspective, the average ionizing radiation dose associated with an abdominal x-ray is 0.7 mSv, and the average dose associated with coronary angioplasty is 15 mSv. An abdominal CT carries an excess risk of fatal cancer of 1 in 2000, a value that is even greater in children. However, this value must be tempered by the fact that the general population has a lifetime risk of being diagnosed with cancer of 1 in 3. The risk of radiation increases conversely with age, with children and fetuses having the greatest risk of adverse outcomes of radiation due to their smaller body habitus, more rapidly developing cells, and increased incubation time for genetic mutations to manifest.

To this end, there have been recent studies of low-dose CT protocols for the diagnosis of appendicitis. These low-dose protocols decrease the average dose to approximately 2 mSv, with no detriment in the negative appendectomy rate. However, there is less diagnostic certainty by radiologists about the diagnosis of appendicitis with these studies. These are relatively new protocols that show promise but require more studies before they can be universally adopted.[17,18]

Table 83.4 lists CT findings diagnostic of appendicitis. In some cases, the appendix cannot be visualized. In these cases, if CT demonstrates no findings of inflammation in the RLQ, it has been found that appendicitis is unlikely. However, patients with low amounts of intra-abdominal body fat may not display secondary signs of inflammation; consequently, these patients may lack this important marker of appendicitis on CT imaging, leading to false-negative study results. The term *tip appendicitis* refers to obstruction and inflammation limited to the distal tip of the appendix and is a subtle finding on CT that is a common cause of false-negative interpretation.[19]

To assess for appendicitis, CT should be performed with IV contrast only. Enteric contrast of any type, oral or rectal, contributes little to the assessment of appendicitis. In addition, studies have demonstrated that non–contrast-enhanced CT has acceptable accuracy in diagnosing appendicitis. Furthermore, according to the American College of Radiology's appropriateness criteria for imaging suspected appendicitis, CT imaging with or without IV contrast are acceptable imaging modalities, with the use of enteric contrast being deferred to institutional preference. Therefore, if there are contraindications to IV contrast, there should be little hesitation to move forward with non–contrast-enhanced CT for the evaluation of appendicitis.[17]

Magnetic Resonance Imaging

When considering the evaluation for appendicitis, current evidence supports the use of MRI for assessment in pregnant females if US is nondiagnostic. MRI has the advantage of not using ionizing radiation and is not operator-dependent. However, its use is limited by its increased cost, increased time required to acquire images, limited availability, and need for the radiologist or surgeon

to be skilled in MRI scan interpretation. MRI demonstrates a sensitivity of 85% to 100%, specificity of 95% to 99.2, average positive predictive value of 92.4, and average negative predictive value of 99.7.[20] Table 83.4 lists MRI criteria for the diagnosis of appendicitis.

In pregnant patients, IV gadolinium contrast should not be used when evaluating for appendicitis due to potentially harmful effects on the fetus.[21] Enteric contrast may be used at the discretion of the interpreting radiologist or per institutional protocol.

Combined Imaging Pathways

An imaging pathways that combine US and CT, in which abdominopelvic CT is performed if the graded compression US is nondiagnostic or negative, have demonstrated combined sensitivities of 94% to 99%, specificities of 91% to 97.5%, and significant reductions in CT utilization.[22,23] It has been projected that this pathway would save $547/patient in imaging costs and $25 million/year in aggregate by reducing imaging costs, unnecessary surgeries, and unnecessary hospitalizations, not to mention decreased radiation exposure.[24] As institutions increase their experience with the use of US to diagnose appendicitis, we think that a combined US-CT pathway will gain acceptance and improve health care delivery.

Interestingly, a so-called radiation-free imaging pathway that combines US and MRI, in which abdominopelvic MRI is performed if the US is nondiagnostic or negative, has been recently studied in the emergency pediatric population, with outcomes similar to those of the combined US-CT pathway. However, at this time, there is a paucity of sufficient data and lack of institutional resources to suggest the routine use of this approach.[25]

Summary of Imaging Methods

Fig. 83.2 illustrates a suggested pathway regarding imaging. For nonpregnant patients, graded compression US may be first considered. In nonpregnant females, a pelvic US may also be considered to assess for pelvic pathology. The ability to visualize the appendix on US is institution-dependent, and the provider's decision to use US initially may depend on the institution's level of experience with this modality. If the US studies are negative or nondiagnostic (ie, no appendix is visualized and no alternative pathology is noted), the patient may undergo CT imaging of the abdomen and pelvis with IV contrast (no PO contrast). An alternative to CT imaging in low-risk cases with nondiagnostic US is admission for observation and serial examinations.

If the patient is pregnant, graded compression and pelvic US should always be the initial studies of choice, followed by MRI of the abdomen without IV contrast in cases of nondiagnostic or negative US findings. If MRI is not available, and transfer to a facility with MRI capabilities is not feasible, then, after consultation with a radiologist, general surgeon, and obstetrician, abdominal CT scanning with IV contrast may be considered. However, in low-risk cases, admission for observation and serial examinations is an acceptable alternative.

MANAGEMENT

Supportive Care

Decisions surrounding supportive care will depend on the patient's condition and needs. Supportive care should be initiated prior to a definitive diagnosis and should continue until the patient leaves the ED. Patients should remain NPO. IV fluids (normal saline or lactated Ringer's) may be administered to maintain hydration and support hypotensive patients. Systemic signs of infection are more common in perforated appendicitis and should be supported by IV fluids, antipyretics, and antibiotics (see below). The patient's pain and nausea should be treated with parenteral opiate analgesia and antiemetics, respectively. There have been a number of good-quality studies that support the concept that opiate analgesia does not negatively affect a patient's abdominal examination when the patient has an abdominal condition that requires surgery.[26,27] Therefore, parenteral opiate analgesia should not be withheld from the patient unless there are contraindications to its use (eg, severe hypotension, allergies). In rare cases, acute appendicitis can cause severe sepsis or septic shock.

Antibiotic Therapy

Antibiotic therapy should be promptly administered on making the diagnosis of appendicitis or in patients with suspected appendicitis and severe sepsis or septic shock. The choice of antibiotics should include broad-spectrum gram-negative and anaerobic coverage. For nonperforated appendicitis, we recommend ciprofloxacin, 400 mg IV, and metronidazole (Flagyl), 500 mg IV; or ceftriaxone, 1g IV, and metronidazole, 500 mg IV; or ampicillin-sulbactam, 3g IV monotherapy. For perforated appendicitis, we recommend broader spectrum antibiotics, such as piperacillin-tazobactam, 3.375 to 4.5g IV, cefepime, 2 g IV, or imipenem-cilastatin, 500 mg IV. Methicillin-resistant *Staphylococcus aureus* (MRSA) coverage is not typically needed to treat appendicitis but may be considered if the patient has previously known MRSA colonization.[28]

Definitive Treatment

Definitive treatment of acute appendicitis will depend on whether there are associated complications, and all decisions should be made in consultation with the surgical service. Nonperforated appendicitis with a well-circumscribed abscess should be treated with IV antibiotics and percutaneous drainage. Perforated appendicitis with or without abscess is treated with IV antibiotics and urgent operative intervention.[28]

Nonperforated appendicitis without abscess (ie, uncomplicated appendicitis) is traditionally treated with IV antibiotics and surgical removal of the inflamed appendix. However, recent and historical data have demonstrated that conservative treatment of appendicitis with antibiotic therapy and a period of inpatient observation may be a viable treatment option for certain patients. There is historical precedence for nonoperative management of appendicitis, and recent studies have found that there may be value in risk-stratifying patients with appendicitis based on their CT findings. In appendicitis with low-risk features, antibiotic therapy with a period of inpatient observation is a feasible option.[29,30] Features associated with failed conservative management include the presence of a fecalith, abscess, tumor, or fluid collection or appendiceal diameter of more than 1.1 cm.[31] In patients with any of these features, operative intervention is preferred.

A minority of patients treated conservatively may fail the inpatient observation period and still require surgery; a minority of those discharged after conservative treatment carry the risk of recurrence of appendicitis. However, with a negative appendectomy rate of 3.6% to 10% and a complication rate as high as 18%—including small bowel obstruction, adhesions, surgical site infection, and abscess formation—nonoperative care is an option worth considering.[32] The decision regarding definitive treatment of acute appendicitis should be made in consultation with the surgical service and the risks and benefits of conservative treatment versus surgical intervention should be frankly discussed with the patient, surgeon, and emergency clinician.

When the decision is made to proceed with surgical removal of the appendix, in uncomplicated appendicitis, delaying surgery up to 12 hours after diagnosis is made (eg, "waiting until the

morning") is acceptable and does not lead to worse clinical outcomes; one recent study has demonstrated that inpatient delay of appendectomy by up to 24 hours does not result in worse outcomes.[33] Although limited in-hospital delay of operative care has not been shown to increase perforation risk or morbidity, delay by patients initially seeking care does increase the risk of perforation and associated morbidity. Lack of insurance, male gender, and a greater number of comorbid conditions are factors associated with increased perforation risk. The choice of laparoscopic versus open appendectomy is made by the surgeon; however, laparoscopic appendectomy has become the current method of choice.

DISPOSITION

There are three possible disposition pathways when a diagnosis of appendicitis is considered. A diagnosis of appendicitis is made based on imaging or, rarely, clinical assessment alone. In this case, antibiotics should be initiated, surgical consultation should be obtained, and the patient should be admitted for operative intervention or, in select cases, IV antibiotics and observation. Based on clinical and laboratory assessment, the risk of appendicitis is low, and no imaging study was performed. In this case, the patient may be discharged home if he or she is reliable, has improved clinical status (ie, feels better), and understands the provider's thought process and precautionary instructions. Alternatively, if these criteria are not met, the patient may be transferred to an observation unit or hospitalized for serial examinations. If the patient's imaging results are inconclusive, or if they are negative but the patient is still symptomatic, the patient may be admitted for observation, symptomatic treatment, serial examinations, and kept NPO, although select patients in this category may still be discharged at the provider's discretion.

KEY CONCEPTS

- Appendicitis is a progressive illness caused by appendiceal luminal distention followed by appendiceal wall ischemia, transmural inflammation, and eventual perforation, with resultant peritonitis.
- Clinical history, physical examination, and laboratory findings need to be combined to formulate a comprehensive assessment. No one finding can definitively diagnose or exclude appendicitis.
- The most useful historical features in evaluating appendicitis are RLQ pain, pain preceding vomiting, and migration of pain to the RLQ.
- The most useful physical findings in evaluating appendicitis are RLQ tenderness and rigidity.
- Cervical motion tenderness is not specific for pelvic pathology and is found in up to 28% of females with appendicitis.
- A rectal examination contributes little and should not be routinely performed in the evaluation of appendicitis.
- The white blood cell count alone is neither sensitive nor specific for appendicitis and offers little in the evaluation of appendicitis.
- When clinicians have a low pretest possibility for appendicitis, the combination of a WBC count below 10,000/mm^3 and CRP level below 8 mg/L support the exclusion of appendicitis as a likely diagnosis.
- Nonoperative management of acute appendicitis (IV antibiotics, admission) is gaining support. The patient should not have high-risk features (eg, presence of a fecalith, abscess, tumor, or fluid collection or appendiceal diameter >1.1 cm) and should be made aware of the risk of failed observation as an inpatient or recurrent appendicitis once discharged, both of which would then require surgical removal of the appendix.
- Once the diagnosis of appendicitis is made, in-hospital delay of appendectomy of up to 12 hours has not demonstrated negative outcomes when compared to emergent operative care.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 83: QUESTIONS & ANSWERS

83.1. What percentage of women with acute appendicitis have accompanying cervical motion tenderness (CMT)?

A. 10%
B. 15%
C. 20%
D. 25%
E. 30%

Answer: D. Prior to the advent of routine imaging of the appendix, as many as 25% of women with acute appendicitis were initially misdiagnosed because of the presence of CMT.

83.2. Which of the following statements regarding ultrasonographic visualization of the appendix is true?

A. A compressible appendix is a positive finding.
B. An appendiceal diameter greater than 6 or 7 mm is a positive finding.
C. The sensitivity of ultrasound for appendicitis is 94% to 98%.
D. Ultrasonography has good reliability for detecting a retrocecal appendix.
E. Ultrasonography compares favorably with computed tomography (CT) scanning for the detection of appendicitis.

Answer: B. A noncompressible appendix with a diameter greater than 6 or 7 mm in a setting of clinical appendicitis is considered a positive finding. Ultrasound sensitivities are 75% to 90%. It is a less useful modality in the obese, those with peritoneal adhesions, and those with a retrocecal appendix**.** The sensitivity of helical CT scanning with rectal contrast approaches 98%, much higher than ultrasonography.

83.3. A 27-year-old G3P2 woman at 22 weeks of gestation presents with 2 days of right lower quadrant (RLQ) abdominal pain. It began midline and later became more pronounced in the RLQ. The physical examination was remarkable for RLQ tenderness without rebound. The gynecologic examination was negative except for a nontender gravid uterus, with good fetal movement by transabdominal ultrasound. Urinalysis showed 8 to 10 white blood cells (WBCs)/high-power field (HPF) and occasional bacteria. Complete blood count (CBC) showed a WBC count of 12,700/mm^3 with 77% neutrophils. Hemoglobin level was 11 g/dL. RLQ ultrasound was limited, with no visualization of a normal or abnormal appendix, and transvaginal ultrasound did not show an obvious gynecologic or obstetric problem. Repeat examination showed continued RLQ tenderness. What is the most appropriate intervention?

A. Administer cephalexin for urinary tract infection and schedule a 48-hour clinic recheck
B. Admit for observation and serial examination

C. Obtain surgical consultation for laparotomy
D. Order a CT scan of the abdomen.
E. Order a magnetic resonance imaging (MRI) scan

Answer: E. MRI scanning for appendicitis may be helpful in pregnant women, in whom the avoidance of radiation exposure is a significant consideration, and exploratory surgery carries additional risks.

83.4. In men and children with classic symptoms and signs of appendicitis, what is the most appropriate initial intervention?
A. Antibiotics and serial abdominal examinations
B. CT scan of the abdomen
C. MRI scan of the abdomen
D. Surgery
E. Ultrasonography

Answer: E. In men and children with classic appendicitis, imaging adds little to the evaluation and only exposes patients to unnecessary radiation. However, it has become less and less common for a patient with a history and examination concerning for appendicitis to undergo surgery without further imaging. Ultrasound is the most appropriate initial intervention because it uses no radiation and can often visualize and diagnose appendicitis without significant delay. Graded compression ultrasound for appendicitis is specific but lacks the sensitivity of CT scan so, if the appendix is not visualized, a discussion can be had with the general surgeon to determine if it is necessary to obtain further information (via CT or MRI).

CHAPTER 84

Gastroenteritis

Thomas Nguyen | Saadia Akhtar

OVERVIEW

Background

Gastroenteritis is an inflammation of the stomach and small and large bowel intestines. Most cases present as a self-limited illness, and most patients have nausea, vomiting, and diarrhea, often with diarrhea being the predominant symptom. Diarrhea is defined as the passage of three or more unformed liquid stools a day, stools of more than 250 g/day, or stool that takes the form of the container into which it is placed.[1] Dysentery refers to an inflammation of the intestine, particularly the colon, causing diarrheas associated with blood and mucus; it is generally associated with fever, abdominal pain, and rectal tenesmus (sense of incomplete defecation).

Gastroenteritis is one of the leading causes of morbidity and mortality worldwide, especially in children. Approximately 180 million cases of acute diarrhea occur each year in the United States, most of which are self-limited and without consequence. The incidence has been increasing due to increased international travel and the increased consumption of raw produce, such as spinach and fresh fruits. Viruses account for most of the infectious causes.[2]

Diarrhea-related deaths in developed countries occur most often in older adults or debilitated patients; *Clostridium difficile* and noroviruses are most frequently implicated. Patients with *C. difficile*, HIV infection, or immunocompromised-related enteritis or those with fever and bloody stools require early diagnosis and treatment to maximize good outcomes. Diagnostic testing should be reserved for cases due to specific pathogens that cause a more severe clinical illness or cases due to an outbreak. Clinicians can play an important role in surveillance and mitigating the spread of infection.

Gastroenteritis is classified as being acute or chronic. Acute gastroenteritis is associated with symptoms that last for less than 2 weeks, usually from viral or bacterial causes. Chronic gastroenteritis consists of symptoms lasting for more than 2 weeks that is often caused by parasites or noninfectious conditions.

Pathophysiology

The pathophysiology of an infection related to gastroenteritis involves one of four mechanisms—ingestion of preformed toxins, adherence of the infectious pathogens to the intestinal cell walls, invasion of mucosal cell walls, and production of enterotoxins and cytotoxins. All these mechanisms lead to an increase in fluid secretion and/or a decrease in fluid absorption in the gastrointestinal (GI) tract.[1]

Clinical Features

History

The history should take into account epidemiologic factors that may help identify the likely organism (Table 84.1). For example, travel outside of the United States raises suspicion for traveler's diarrhea, contact with persons on a cruise ship with a GI outbreak **is** suspicious for norovirus, a recent camping trip and exposure to river water suggests giardiasis, and recent hospitalization or antibiotic use and patients in long-term care facilities are risk factors for *C. difficile* infection.

Associated factors are helpful in narrowing the list of possible causative organisms and in initiating treatments. For example, GI symptoms after a short exposure period (1–6 hours) may imply preformed toxins from staphylococcal or *Bacillus* organisms. Diarrhea lasting more than 2 weeks may indicate the presence of *Giardia* or other protozoa, although noninfectious causes should be considered, such as inflammatory bowel disease. Norovirus classically causes a sudden onset of severe vomiting and only moderate diarrhea. Large-volume diarrhea usually indicates small bowel involvement, such as viral gastroenteritis or illness due to *Vibrio cholerae*. Colonic involvement causes smaller volume loss and more likely will be bloody or have fecal leukocytes from invasive organisms. Vomiting without diarrhea generally should not be referred to as gastroenteritis. Other causes should be sought out, such as a small bowel obstruction. A history of fever, abdominal pain, tenesmus, and bloody stools are signs of dysentery and may imply invasive organisms such as *Campylobacter* or *Shigella*. *Yersinia enterocolitica* GI infection often mimics acute appendicitis or regional enterocolitis due to its invasion of the local mesenteric lymph nodes. Patients with lightheadedness and hypotension are likely to be dehydrated from diarrhea and vomiting. Muscle cramping may imply hypokalemia or hyponatremia from lack of oral intake or loss of electrolytes in the diarrhea.

Physical Examination

The physical examination focuses on the patient's general hydration status and assesses for life-threatening conditions. The emergency clinician should first assess the vital signs. In the clinical setting of gastroenteritis, hypotension and tachycardia likely indicate that the patient is dehydrated. Fever, altered mental status, and a toxic appearance may signify that the patient has severe illness and possibly sepsis. Other disease states may mimic gastroenteritis, and a thorough examination is warranted. For example, a low-grade fever in a patient with tachycardia, tremors, and diarrhea in the presence of a goiter may represent hyperthyroidism.

Evaluation of the skin for the presence of petechiae or purpura, especially in the extremities, can suggest possible sepsis or disseminated intravascular coagulation (DIC). Dry mucous membranes, decreased skin turgor, and decreased urine output may also help gauge dehydration. In infants, an accurate measure of weight loss, lack of tears, decrease in urine output, or depressed fontanelle are all good predictors of dehydration. The abdominal examination focuses on conditions that may mimic gastroenteritis, such as small bowel obstruction, bowel ischemia, appendicitis, and colitis. The examiner should listen carefully for bowel sounds. Generally, bowel sounds are hyperactive in acute gastroenteritis. Abdominal findings such as focal tenderness, rebound, guarding, distention, and rigidity may indicate a surgical abdomen. If the

TABLE 84.1

Epidemiologic Factors

FACTOR	IMPLICATIONS
Foreign travel	Traveler's diarrhea—enterotoxigenic *Escherichia coli* Southeast Asia—*Vibrio* species Rotavirus—South America, Asia, Africa
Recent camping	*Giardia, Aeromonas, Cryptosporidium*
Recent antibiotics	Increase in *C. difficile* infection
Daycare exposure	Rotavirus
Exposure to raw seafood	Noncholera *Vibrio*
Anal-receptive sex—men who have sex with men	*Shigella, Campylobacter, Salmonella*
HIV-positive status	*Mycobacterium avium-intracellulare* complex, microsporidia. cytomegalovirus, *Giardia*
Outbreaks	Cruise ships—norovirus Contaminated local water, food, products, restaurants; organism usually identified by local health department (eg, *Campylobacter, Salmonella, E. coli*)

patient reports blood or mucus in the stool or complains of rectal pain, a rectal examination should be performed to assess for gross blood, mucus, or rectal lesions.

Differential Diagnosis

Other diagnoses to consider include small bowel obstruction (SBO), diverticulitis, inflammatory bowel disease (IBD), ischemic bowel disease, appendicitis, malabsorption, celiac disease, and irritable bowel syndrome.

A patient with a history of abdominal surgery who presents with crampy abdominal pain and vomiting, distended tender abdomen, and is not passing any gas or stools is likely to have an SBO. In diverticulitis, pain is generally localized to the left lower abdomen. IBD usually first presents in the young adult as recurrent diarrhea, with cramping. The stool may contain mucus and blood. Risk factors are obesity, smoking, and a family history of IBD, with the highest risk in females and Jewish persons of European ancestry. There may be extraintestinal manifestations, such as uveitis and erythema nodosum. Patients with ischemic bowel may present with abdominal pain. ranging from mild to severe tenderness with peritoneal signs. Risk factors include older age, low-flow states such as dehydration, recent congestive heart failure exacerbation, sepsis, smoking, and atherosclerotic disease and those at risk for thromboembolic events such as atrial fibrillation. Patients with gastroenteritis are generally not critically ill and deterioration is not as rapid as seen in those with ischemic bowel disease.

Viruses account for up to 70% of cases of infectious gastroenteritis, bacteria, 15% to 20%, and parasites, about 10% to 15%. It is difficult to identify the exact organism causing the GI illness on initial presentation. The predominance of vomiting along with upper respiratory symptoms is more likely associated with a viral cause. A rapid onset of vomiting as the predominant symptom may suggest the presence of preformed bacterial toxins. The presence of high fever, fecal blood, abdominal pain, or colitis likely indicates an invasive bacterial organism.[3]

Diagnostic Testing

Diagnostic testing for patients with apparent gastroenteritis is guided by the clinical assessment. Routine laboratory tests, including a complete blood count and serum metabolic profile, are not needed in every case. Further evaluation may be required for patients presenting with severe illness or severe dehydration.

Laboratory tests should be done for patients with high fevers, severe abdominal pain, bloody stools or persistent diarrhea. Special attention should be given to older adults with abdominal pain and immunocompromised patients. For most cases of gastroenteritis, if the patient appears well and is likely to have a self-limited illness, stool cultures are not required. Stool cultures should be sent for patients with severe illness, fever of 38.5°C (101°F) or higher, dysentery, persistent diarrhea for 14 days or longer and for patients who are immunocompromised or who have been recently hospitalized or placed on antibiotics. If diarrhea is persistent, stools for ova and parasite should be sent. Stools sent for fecal leukocytes, lactoferrin, or hemoccult testing may help identify colonic inflammation with an invasive organism. Stool studies and culture should be performed when certain bacterial and parasitic infections are suspected, such as *C. difficile*, *Campylobacter*, Shiga toxin–producing *Escherichia coli* (STEC), or giardiasis because targeted antibacterial treatment may be initiated to prevent the spread (eg, in an outbreak of daycare workers) and decrease the duration of symptoms. Tables 84.2, 84.3, and 84.4 summarize specific diagnostic testing for bacterial, viral, and parasitic infections, respectively.

Management

Patients who are severely dehydrated should receive an intravenous (IV) fluid bolus of isotonic solution, such as normal saline (NS) or lactated Ringer's (LR). Electrolytes should be repleted, with special attention to the sodium and potassium levels. Antiemetics prevent ongoing loss of fluids and help with the initiation of oral rehydration therapy (ORT).

The exact cause of vomiting in gastroenteritis is not known, although it is thought to be due to peripheral stimuli arising from the GI tract primarily via the vagus nerve or by serotonin stimulation of the 5-hydroxytryptamine 3 (5-HT_3) receptors in the intestinal tract. These signals are transmitted to the emetic center in the brainstem that stimulates the muscles in the diaphragm, abdominal wall, and intestinal tract to produce vomiting. All the areas involved in the pathogenesis of vomiting are rich in serotoninergic, dopaminergic, histaminic, and muscarinic receptors, thus providing the basis for using serotonin inhibitors, dopamine inhibitors, and antihistamines. Odansetron, 4 mg IV, or metoclopramide, 10 mg IV, are safe and cost-effective and can be easily converted to an oral dose. Side effects of odansetron include headache and diarrhea.

The American Academy of Pediatrics (AAP), Centers for Disease Control and Prevention (CDC), European Society for Pediatric Gastroenterology and Nutrition (ESPGHAN), and World Health Organization (WHO) all strongly support the use of oral rehydration therapy (ORT) as first-line treatment for acute gastroenteritis, except in cases of severe dehydration. Although ORT has been extensively studied in children, the results can generally be applied to adults. It is known to be safe and effective as the treatment of choice for mild and moderate dehydration. Morbidity and mortality can be greatly reduced with the use of ORT. It is also associated with fewer major adverse events and results in shorter hospital stays.

Fluids containing glucose and electrolytes provide optimal rehydration due to the cotransport of the water across the intestinal lumen. Some choices of oral rehydration solution (ORS) are the standard WHO ORS (331 mOsm/kg), reduced osmolarity

TABLE 84.2

Bacteria: Diagnosis and Treatment

ORGANISM	DIAGNOSIS	TREATMENT
Shigella	Stool culture (conventional)	Ciprofloxacin, 750 mg daily for 3 days; *or* azithromycin, 500 mg daily for 3 days
Salmonella		
Nontyphoid	Stool culture (conventional)	No treatment in nonsevere cases. For severe cases (fever, bloody diarrhea, bacteremia)—levofloxacin (Levaquin), 500 mg daily for 7–10 days
Typhoid	Stool culture (conventional)	Fluoroquinolone daily for 7 days; IV ceftriaxone, 1–2 g for 7 days
Campylobacter jejuni	Stool culture (conventional)	Azithromycin, 500 mg daily for 3 days
Vibrio cholerae	Stool culture with salt- containing media (TCBS)	Doxycycline, 7 mg/kg up to 300 mg once
Vibrio—noncholera (*Vibrio parahaemolyticus*)	Stool culture with TCBS	Ciprofloxacin, 750 mg daily for 3 days; *or* azithromycin, 500 mg daily for 3 days
Enterotoxigenic *Escherichia coli*	Stool culture; assay for toxin	Ciprofloxacin, 750 mg daily for 3 days, rifaximin 200 mg tid for 3 days; azithromycin, 1 g once
Shiga toxin–producing *E. coli*; *E. coli* O157:H7	Sorbitol MacConkey and serotyping for O157	No treatment, supportive care only; antibiotics increase risk for HUS
Yersinia enterocolitica	Cefsulodin-irgasan-novobiocin (CIN) agar	Supportive care; in severe cases, TMP-SMX (Bactrim), fluoroquinolones
Clostridium difficile	Stool for *C. difficile* toxin	Metronidazole, 500 mg tid for 10 days; vancomycin, 125 mg PO qid for 10 days
Staphylococcus aureus	Food may be cultured for *Staphylococcus*	Supportive care
Clostridium perfringens	Detection of spores in stool	Supportive care
Bacillus cereus	Food may be cultured	Supportive care; for severe cases—vancomycin, 125 mg qid; *or* clindamycin, 500 mg tid for 7–10 days

HUS, Hemolytic uremic syndrome; *TMP-SMX*, trimethoprim-sulfamethoxazole.

TABLE 84.3

Virus: Diagnosis and Treatment

ORGANISM	DIAGNOSIS	TREATMENT
Norovirus	Stool sample—real-time reverse transcription–polymerase chain reaction (RT-PCR) assay	Supportive care
Sapovirus	PCR assay, immunoassay	Supportive care
Rotavirus	Rotavirus antigen in stool sample	Supportive care; vaccine and natural infection do not provide immunity; RotaTeq (RV5), given in three doses at ages 2, 4, and 6 mo; *or* Rotarix (RV1), given in two doses at ages 2 and 4 mo
Adenovirus	Antigen detection, PCR assay, virus isolation, serology	Supportive care
Astrovirus	PCR assay, electron microscopy, immunoassay	Supportive care

WHO ORS (245 mOsm/kg), and Pedialyte (oral electrolyte solution for children; 250 mOsm/kg). One systematic review of 15 randomized controlled trials, including 2397 children, has shown that reduced osmolarity rehydration solution is associated with a reduced need for unscheduled IV infusions, lower stool volume, and less vomiting compared with a standard WHO rehydration solution.[4] Simple home remedies such as diluted fruit drinks and chicken broth or commercial solutions such as Gatorade will also suffice.

The official recommendation by ESPGHAN is to hydrate orally with reduced osmolarity or hypotonic fluids. Oral intake of food, if tolerated, should be continued during the illness, because fasting may actually worsen the capacity of the bowel to absorb fluid. The presence of the food in the bowel lumen promotes mucosal recovery and improves fluid absorption.[5]

Antimotility drugs such as loperamide and diphenoxylate hydrochloride can help limit the number of watery stools and prevent dehydration. The initial dose of loperamide is 4 mg orally, followed by 2 mg after each unformed stool, up to a maximum of 16 mg/day for 48 hours. However, in patients with suspected bacterial dysentery, it is recommended that antimotility agents be administered in conjunction with antibiotics because antimotility agents may increase the contact time with the toxins or invasive organisms.

In general, antibiotics are not indicated for the treatment of the vast majority of cases of acute gastroenteritis. However,

TABLE 84.4

Parasitic Infections: Diagnosis and Treatment

ORGANISM	DIAGNOSIS	TREATMENT
Giardia lamblia	Stool microscopy for ova and parasite; immunoassay	Tinidazole—2 g PO single dose Metronidazole—500 mg PO bid or 250 mg tid for 5–7 days Nitazoxanide—500 mg bid for 3 days *Alternative agents* Albendazole—400 mg once daily for 5 days Mebendazole—200 mg PO tid for 5 days Quinacrine—100 mg PO tid for 5 days Paromomycin—10 mg/kg PO tid day for 5–10 days
Entamoeba histolytica	Stool microscopy, culture, immunoassay	Metronidazole—500–750 mg PO tid for 7–10 days; Tinidazole—2 g PO once a day for 3 days; Nitazoxanide—500 mg PO bid for 3 days *Intraluminal infection* Paromomycin—25–30 mg/kg PO tid for 7 days Diiodohydroxyquin—650 mg PO tid for 20 days for adults Diloxanide furoate—500 mg PO tid for 10 days for adults
Cryptosporidium	Stool microscopy, culture, immunoassay	Nitazoxanide—500 mg PO bid for 3 days
Cyclospora *cayetanensis*	Stool microscopy, stool culture, acid-fast stain, fluorescence microscopy	Trimethoprim—trimethoprim-sulfamethoxazole (TMP-SMX), one double-strength 160/800 mg tablet PO bid for 7–10 days

empirical antibiotic therapy can be considered in the following circumstances—patients who appear toxic or have fever or dysentery (see discussion below), patients with severe traveler's diarrhea, patients with suspected *C. difficile* colitis, patients who are immunocompromised, or when a known organism is isolated from a community outbreak. Tables 84.2 and 84.4 summarize recommended antibiotics for treating various bacterial and parasitic infections, respectively.

Disposition

Most patients with gastroenteritis can be managed as outpatients. Written instructions should be given with recommendations for oral fluid intake, diet, and follow-up care. Hospitalization should be considered for patients with a toxic appearance, severe or persistent symptoms, inability to tolerate oral liquids, significant electrolyte abnormalities, and severe dehydration. Special consideration should be given to patients at the extremes of age or who are immunocompromised. These patients likely will require a more extensive evaluation and further care.

BACTERIAL GASTROENTERITIS

In the United States, foodborne diarrheal illness caused by bacteria has increased over the past decades. The four most commonly reported bacterial pathogens are *Campylobacter*, nontyphoid *Salmonella*, STEC, and *Shigella*. The causes of most diarrheal illnesses are never discovered. Most laboratories are equipped to culture only the common pathogens, and routine stool cultures for diagnostic testing often miss organisms such as enterotoxigenic *E. coli,* enteroaggregative *E. coli,* enteroinvasive *E. coli,* and noncholera *Vibrio* spp.[6]

There are several risk factors that influence the development of bacterial gastroenteritis. Very young patients have low immunity, and maternal passive immunity is lost after weaning from breast-feeding. Older adults are at risk due to the age-related intestinal mucosal alteration of mucosa production, gut flora, and cell surface receptor affinity for toxins. The use of antacids such as proton pump inhibitors decreases the bactericidal effect of gastric acid. Antibiotic use reduces normal intestinal flora and therefore increases the colonization of pathogens such as *C. difficile*. Immunosuppressed patients such as those with HIV infection or patients on chemotherapy are predisposed to nontyphoid *Salmonella*. Poor sanitation and overcrowded conditions also enhance the spread of infected organisms.

Bacteria organisms are broadly categorized as invasive or noninvasive. Invasive gastroenteritis is a clinical diagnosis made in the presence of signs or symptoms of intestinal mucosal invasion, such as fever, gross or occult blood in the stool, tenesmus (feeling of constantly needing to pass stool), or severe abdominal pain (Table 84.5). Patients with noninvasive gastroenteritis generally do not exhibit fever, produce bloody stools, or experience significant abdominal pain. Noninvasive gastroenteritis likely suggests the presence of a viral pathogen or toxin-producing bacteria. This illness typically is brief and self-limited, and diagnostic testing is not likely to be of benefit (Table 84.6).

INVASIVE BACTERIA

Campylobacter Enteritis

Epidemiology

Campylobacter is the most commonly diagnosed cause of bacterial enteritis in developed countries. It is more common during the summer months. *Campylobacter* spp. are a common cause of so-called backpacker's diarrhea, along with *Giardia*, both of which are frequently acquired by drinking water from wilderness sources.

Pathophysiology

Campylobacter organisms are small, spiral-shaped, gram-negative bacteria. The most common species isolated are *Campylobacter jejuni* (94%), *Campylobacter coli* (1%), and *Campylobacter fetus. Campylobacter* spp. produce disease primarily by direct invasion of the colonic epithelium. Most infections are acquired by handling or eating raw or undercooked poultry meat. The primary

TABLE 84.5

Invasive Bacteria and Clinical Features

ORGANISM	CLINICAL FEATURES	INCUBATION PERIOD, DURATION, SOURCE
Campylobacter jejuni	Most common bacteria; organism identified in stool cultures; acute watery diarrhea, fevers, dysenteric characteristics	I, 2–5 days D, 5–14 days S, food, water, chickens
SALMONELLA		
Nontyphoid	Usually foodborne (eg, poultry); acute watery diarrhea, often with fever; common in sickle cell and immunocompromised patients	I, 12– 24 h D, 2–7 days S, eggs, poultry, unpasteurized milk, pets
Typhoid	Fever, abdominal pain, ileus, systemic effects; most infections acquired during international travel	I, 12–24 h D, 2–7 days
Shigella	Most common bacterial organism identified in stool cultures; acute watery diarrhea, fever, dysenteric characteristics; Toxigenic	I, 1–2 days D,2–7 days S, water, person to person
Yersinia enterocolitica	Acute diarrhea, dehydrating; rare in United States but common with travel to Asia; can mimic appendicitis	I, 12–48 h D, 5–14 days S, food, water, milk, cats, dogs, pigs
Vibrio, noncholera (*V. parahaemolyticus*)	Associated with seafood, shellfish watery diarrhea, dysentery	I, 8–24 h D, 5–14 days S, raw, undercooked seafood
Escherichia coli Shiga toxin-producing; *E. coli* O157:H7	Watery, bloody diarrhea; foodborne—contaminated beef and produce; toxigenic; associated with HUS and TTP	I, 3–8 days D, 5–10 days S, uncooked beef, water, person to person, raw milk

D, Duration; *HUS,* hemolytic uremic syndrome; *I,* incubation; *S,* source; *TTP,* thrombotic thrombocytopenic purpura.

TABLE 84.6

Noninvasive Toxigenic Bacteria and Clinical Features

ORGANISM	CLINICAL FEATURES	INCUBATION PERIOD AND DURATION AND SOURCE
Staphylococcus aureus	Short incubation period, 2–7 h; preformed toxin; vomiting; lasts <24 h	I, 1–6 h D, 6–12 h S, mayonnaise, potato salad, food handlers
Clostridium perfringens	Watery diarrhea, seen in large foodborne outbreaks	I, 6–24 h D, 1 day S, Steam table meat, poultry, gravies
Bacillus cereus	Vomiting and/or diarrhea Typically from contaminated rice	I, 1–12 h D, 1–2 days S, contaminated foods, rice
Vibrio cholerae	Enterotoxin; acute rice water diarrhea, dysentery, dehydrating. Rare is US but common with travel to Asia	I, 1–2 days D, 6–8 days S, raw shellfish, oysters
Noncholera *Vibrio* (eg, *V. vulnificus*)	Enterotoxin. Acute diarrhea, occasional dysentery. Seen in Gulf coast in the US. Can cause septic shock, wound infection	I, 1–2 days D, 6–8 days S, raw shellfish, oysters
Marine bacteria flora (scombroid fish poisoning)	Histamine toxin, tachycardia, itching, flushing, cramping, dizziness, metallic taste	I, 5–60 min D, 6 h S, mahi mahi, tuna
Marine dinoflagellate Gambierdiscus toxicus (ciguatera fish poisoning)	Ciguatoxin.- heat stable. Pain, paresthesias, dysesthesias, vomiting, diarrhea	I, 2–6 h D, 7–14 days S, coral reef fish
Enterotoxigenic *Escherichia coli* (ETEC)	Acute watery diarrhea. Common cause of traveler's diarrhea, but in US increasing cause of foodborne disease	I, 1–3 days D, 1–7 days S, unsanitary water and food
Clostridium difficile	Colitis, diarrhea, fever, toxic megacolon. Recent antibiotic use or proton pump inhibitor use. High mortality in elderly and immunocompromised.	I, 5–14 days D, variable S, person to person, contaminated surfaces

D, Duration; *I,* incubation; *S,* source.

reservoirs for *Campylobacter* organisms are chickens. Other causes include consumption of tainted beef, pork, raw milk, or untreated water and contact with infected pets (particularly cats and puppies) and farm animals.

Clinical Features

The incubation period for *C. enteritis* is approximately 2 to 5 days. Disease onset usually is rapid, with signs and symptoms of fever, cramping abdominal pain, and diarrhea. Constitutional symptoms of anorexia, malaise, myalgias, and headache are the rule, and some patients experience backache, arthralgias, and vomiting. Onset of diarrhea often lags 24 to 48 hours after the onset of fever and abdominal pain. Typically, the stools are loose and bile-colored but then become watery and grossly bloody or melanotic approximately 40% of the time. Gross or occult blood is found in the stool of 60% to 90% of patients with *Campylobacter* gastroenteritis. At the height of the illness, patients usually pass 8 to 10 stools or more/day.

Most patients recover within a week or less; however, diarrhea can persist for an extended period. Relapses are common, although generally milder than the original episode, and fatalities are rare.

Diagnostic Testing

Because the clinical presentation is similar to that of other invasive bacterial pathogens, the diagnosis of campylobacteriosis cannot be made on the basis of clinical presentation alone. Identification of the pathogen will require stool culture or real-time polymerase chain reaction (PCR) assay; specimens should be obtained from patients with acute enteritis associated with fever, abdominal pain, occult blood, or hematochezia. In borderline cases, stool methylene blue stain testing for fecal leukocytes is readily available and may help identify patients who are likely to harbor an invasive pathogen. Blood culture results are rarely positive, so these studies are not routinely indicated.

Management

Empirical antibiotic therapy is not recommended for otherwise healthy patients with acute invasive diarrhea, but travel-related diarrhea is an exception (see below). Initial treatment of invasive diarrhea should focus on rehydration; the decision to initiate antibiotic therapy should be deferred pending identification of a specific organism via stool studies. Treatment with antibiotics is not needed for patients who demonstrate clinical improvement by the time results become available.

For patients who are not improving, antibiotic therapy shortens the duration of campylobacteriosis by approximately 1.3 days. Erythromycin, 500 mg bid for 5 days, or azithromycin, 500 mg daily for 3 days, is the recommended first-line therapeutic regimen. Ciprofloxacin, 500 mg bid, can be used and was previously the treatment of choice, but alarming resistance to the fluoroquinolones has emerged, thought to be mainly a result of antibiotic use in the poultry industry. Roughly 20% of *Campylobacter* strains in the United States are now resistant to fluoroquinolones, and resistance of more than 80% has been documented in Thailand. *Campylobacter* organisms generally also are resistant to trimethoprim-sulfamethoxazole (TMP-SMX). Relapses can occur, but the likelihood is decreased with antibiotic treatment. Because *Campylobacter* infection causes an invasive enteritis, antimotility agents are not recommended unless treatment with antibiotics is also given.

Complications of *Campylobacter* infection are rare. Cholecystitis, pancreatitis, and massive GI bleeding all have been reported, as have meningitis, endocarditis, and osteomyelitis. There is an association between *Campylobacter* infection and Guillain-Barré syndrome, with an incidence of approximately 1/1000 cases.

Salmonellosis

Epidemiology

Salmonella is the most common cause of bacterial enteritis in the United States. Enteritis caused by this organism affects people of all age groups but particularly children, with those younger than 5 years accounting for 20% of cases. Almost all *Salmonella* infections are acquired from ingestion of contaminated food or drink. Poultry products and beef are the most common sources; other sources include unpasteurized milk, eggs, fish, and domestic pets. Outbreaks also have been associated with consumption of fruits, vegetables, baked goods, rattlesnake meat, and medicinal preparations. Approximately 10% of household dogs and cats excrete salmonellae, and pet reptiles, such as turtles, snakes, and iguanas, have been responsible for outbreaks.

Cooking contaminated foods decreases the possibility of infection but does not eliminate it. Salmonellae can survive cooking when they are deep inside certain foods and where temperatures may not reach the lethal range. Large outbreaks of *Salmonella* infection have been traced to contaminated, unbroken, grade A eggs. Although the organism is present in the uncracked egg, thorough cooking usually eradicates or reduces the inoculum to clinically insignificant levels.

Common raw egg–based sources of *Salmonella* infection include homemade hollandaise sauce, eggnog, Caesar salad dressing, ice cream, mayonnaise, tiramisu, cookie dough (often consumed unbaked), frosting, and French toast mix. *Salmonella enterica* subsp. *enterica* serovar enteritidis (ie, *S. enteritidis*) is the species universally associated with egg-related infections. Patients convalescing from *Salmonella*-related enterocolitis and those with asymptomatic infection may continue to excrete *Salmonella* organisms for weeks or months, thus serving as ongoing sources of infection.

Pathophysiology

Approximately 2000 *Salmonella* serotypes are known to cause human illness. Based on 2010 US surveillance figures, the most common isolates are the *S. enterica* serovars *typhimurium*, *enteritidis*, and *Newport*, which together account for approximately half of culture-confirmed serotypes. Different *Salmonella* serotypes show marked variations in invasive potential and are associated with particular presentations: *S. enterica* serovar *typhi* with enteric fever (typhoid fever), *S. enterica* serovar *choleraesuis* with septicemia, *S. enterica* serovar *typhimurium* with acute gastroenteritis, and *S. enterica* serovar *enteritidis* infections from eggs.

Relatively large numbers of salmonellae must be ingested for illness to be produced. However, a carrier state can be induced, with ingestion of 10 to 100 times fewer bacteria needed to induce the carrier state relative to the number needed to induce illness. In infants and adults with certain underlying diseases, a much smaller inoculum may produce illness. Decreased gastric acidity or an alteration of intestinal flora resulting from the administration of antibiotics can impressively reduce the size of the required inoculum. Rates of invasive infection and disease severity are increased in infants, older adults, and people with hemoglobinopathies such as sickle cell anemia, malignant neoplasms, or acquired immunodeficiency syndrome (AIDS).

Clinical Features

Family outbreaks and sporadic cases are more common than large epidemics. Ingested salmonellae penetrate the intestinal mucosal

cells and lodge in the lamina propria. After an incubation period of 8 to 48 hours, the typical patient with *Salmonella* gastroenteritis develops fever, colicky abdominal pain, and loose watery stools, occasionally containing mucus and blood. Nausea and vomiting are common but rarely are severe or protracted. Mild to moderate diffuse abdominal tenderness can be elicited in most patients, but severe tenderness and even rebound tenderness may occasionally be noted. Symptoms usually abate within 2 to 5 days, and recovery typically is uneventful. Sustained or intermittent bacteremia may occur, especially in those with sickle cell anemia, malignancy, or AIDS.

Diagnostic Testing

The diagnosis of salmonellosis is confirmed with stool cultures or a real-time PCR assay. Stool methylene blue staining for fecal leukocytes may help identify patients who are likely to harbor an invasive pathogen. Blood culture results occasionally are positive, and blood samples should be obtained from severely ill or immunocompromised patients. The possibility of an underlying disease or immunodeficiency state should be considered in every patient with a severe *Salmonella* infection.

Management

Empirical antibiotic therapy is not recommended for otherwise healthy patients with suspected *Salmonella* enteritis. Antibiotic therapy does not shorten the duration of the disease and may prolong the duration of the carrier state. Although its effectiveness is unproven, antibiotic therapy is recommended for patients with severe colitis and for infants younger than 3 months, adults older than 50 years, and those at risk for severe disease, including those who are immunocompromised, with sickle cell disease, and with prosthetic grafts. Persons who represent a public health risk also should be treated in an attempt to eradicate the carrier state and prevent spread of the organism. Any of these antibiotic regimens is generally effective for the outpatient management of *Salmonella* gastroenteritis: ciprofloxacin, 500 mg bid for 5 to 7 days; norfloxacin, 400 mg bid for 5 to 7 days; or azithromycin 1 g PO followed by 500 mg/day for the next 6 days. TMP-SMX also can be used if the organism is susceptible. Ciprofloxacin is effective in the treatment of chronic *S. typhi* carriers; however, treatment with fluoroquinolones can actually prolong shedding of non–*S. typhi* organisms. Patients requiring hospitalization are best treated with IV ceftriaxone until the results of sensitivity studies become available.

Follow-up with the patient's primary care physician should be arranged. Food handlers and health care personnel are not allowed to work until their carrier state has been eradicated. Repeated stool studies and further decisions regarding job or school situations will be required. Personal hygiene should be emphasized because untreated patients may continue to shed infective organisms in the stool for weeks or even months. As with other invasive pathogens, the use of antimotility drugs alone is contraindicated. These drugs prolong fever and diarrhea, increase the incidence of bacteremia, and promote development of a carrier state in patients with *Salmonella* enteritis. However, administration of loperamide is safe when given concomitantly with an antibiotic.

Prevention of salmonellosis depends on cooking meat to an internal temperature of 160°F (71°C) and minimizing how long foods are allowed to remain at room temperature to reduce the chance of bacterial growth to an infectious inoculum. Careful personal hygiene, including handwashing, also is important. Although most patients recover fully without long-term sequelae, up to 30% (primarily adults) will experience transient reactive arthritis. Reiter's syndrome, consisting of reactive arthritis, conjunctivitis, and urethritis, is a well-known complication and occurs in approximately 2% of patients.

Shigellosis

Epidemiology

Shigellosis, or bacillary dysentery, is worldwide in distribution and is particularly common in countries lacking effective sanitation. *Shigella sonnei* is responsible for approximately 75% of the infections occurring in the United States. *Shigella flexneri* causes most of the remaining cases, with *Shigella boydii* and *Shigella dysenteriae* responsible for less than 4% of cases.

Shigella infections are common in confined populations, such as those in mental or penal institutions, in nursing homes or daycare centers. Children younger than 5 years account for 30% of cases. An increased incidence has been documented among men who have sex with men and in the AIDS population. It is spread by the fecal-oral route, and humans are the only natural hosts. Shigellae can be recovered in cultures of samples taken within 3 hours after contamination. Outbreaks have been associated with recreational water venues such as swimming pools, water parks, fountains, hot tubs, and spas.

Pathophysiology

Unlike *Salmonella*, which requires a very large inoculum to produce disease, as few as 50 to 100 *Shigella* bacilli can cause infection. No other enteric pathogen is so efficient at producing overt disease in humans. Infection generally is superficial, localized to the epithelial lining of the colonic mucosa; therefore, bowel perforation or invasion into the bloodstream is extremely rare. Bleeding occurs from superficial ulcerations of the mucosa.

Clinical Features

Clinical presentation varies among *Shigella* species. *S. sonnei* typically causes high-volume, watery diarrhea, with relatively few systemic signs. Infection with *S. flexneri, S. dysenteriae,* or *S. boydii* typically causes low-volume bloody diarrhea and more severe systemic symptoms.

The usual incubation period is 24 to 48 hours, and clinical manifestations vary considerably, often appearing in a bimodal fashion. Mild watery diarrhea with few if any constitutional symptoms or asymptomatic infection occurs in a small proportion of infected persons. When true dysentery develops, it ordinarily is preceded by a recognizable period of watery diarrhea lasting a few hours to a few days. Patients with dysentery have grossly bloody diarrhea, tenesmus, and constitutional symptoms and signs, such as fever, nausea, vomiting, headache, and myalgias. If symptoms are severe enough, profound dehydration and even circulatory collapse can occur. Children younger than 2 years may have associated neurologic manifestations, usually seizures; lethargy or frank coma develops in a small percentage of patients. *S. dysenteriae* type 1 infection, rarely diagnosed in developed countries, is associated with the hemolytic uremic syndrome (HUS).

Generally, shigellosis is a self-limited disease. Patients become afebrile in 3 to 4 days, and the abdominal cramping and diarrhea resolve within 1 week. Some untreated patients continue to shed organisms in the stool for 2 weeks or longer, and approximately 10% of patients will have a relapse unless the infection is treated with antibiotics.

Diagnostic Testing

Shigellosis should be considered in every patient with an acute febrile illness associated with diarrhea, especially patients who appear ill or who have dysenteric stools. Fecal white blood cells are present, usually in large numbers, in 85% to 95% of cases,

regardless of the gross appearance of the stool. Occult blood usually is present in the stools of infected patients. Blood leukocytosis is common, and a leftward shift in the differential count is almost always seen. Results of blood cultures for *Shigella* are rarely positive.

A definitive diagnosis of shigellosis is made with stool culture or real-time PCR assay. Stool culture results are positive in more than 90% of cases when samples are obtained during the first 3 days of illness; however, results are positive in only approximately 75% if samples are obtained more than 1 week after the onset of diarrhea.

Management

Treatment primarily involves the correction of fluid and electrolyte abnormalities. If *S. sonnei* or *S. flexneri* is cultured from the stool, the decision to administer antibiotics is based on the patient's clinical condition and feasibility of sanitary control. Asymptomatic or recovering patients do not need to be treated with antibiotics unless treatment is necessary for public health measures. Patients whose condition is not improving and those who are immunocompromised should be treated with antibiotics.

Antibiotics shorten the clinical course and eradicate the pathogen from the stool, often within 48 hours. Whenever *S. dysenteriae* is isolated, the patient should be treated to prevent outbreaks of dysentery, even if the patient is asymptomatic when the culture result returns from the laboratory.

In the United States, more than 80% of *Shigella* organisms are resistant to ampicillin and 47% are resistant to TMP-SMX. Significant resistance has not yet been found to the quinolone agents. Ciprofloxacin, 500 mg PO, and norfloxacin, 400 mg PO bid, are the drugs of choice.

Treatment is required for only 3 days in immunocompetent patients but should be extended to 7 to 10 days in those who are immunocompromised. Antimotility agents may prolong the fever, diarrhea, and excretion of *Shigella* in the stools and are contraindicated in patients with invasive shigellosis. However, they may be safe when used simultaneously with antibiotics. Follow-up stool cultures should be done for patients treated for *S. dysenteriae* infection to ensure eradication of the organism. Follow-up cultures, however, are not necessary after treatment for *S. sonnei* or *S. flexneri* infection, provided that the patient's condition improves clinically.

Shigellosis is a nationally notifiable disease. Complications are rare and include bacteremia, Reiter's syndrome, HUS, toxic megacolon, colonic perforation, seizures, and toxic encephalopathy.

Yersinia enterocolitica Gastroenteritis

Epidemiology

Yersinia enterocolitica, a gram-negative facultatively anaerobic bacterium, is a member of the family Enterobacteriaceae. *Y. enterocolitica* is a relatively infrequent cause of enteritis in the United States. Yersiniosis is more prevalent in children, and infections are evenly distributed throughout the calendar year.

Pathophysiology

After oral ingestion, the bacterium invades the intestinal epithelium and localizes to lymphoid tissue of the intestinal mucosa, particularly Peyer's patches. It then invades the regional mesenteric lymph nodes. Invasive enteritis is the clinical presentation in approximately two- thirds of patients. Pseudoappendicitis and mesenteric adenitis account for the remainder of presentations. Infection originates from contaminated food or drink. The consumption of contaminated milk or contaminated raw pork has accounted for sporadic cases and several large outbreaks. Fecal-oral transmission to humans from a variety of animals (particularly dogs, cats, and pigs), and direct person to person spread probably occur, but communicability appears to be low.

Clinical Features

The clinical picture with *Y. enterocolitis* often resembles that with infection by other invasive intestinal organisms—fever (68%); colicky abdominal pain (65%); watery, greenish, and sometimes bloody (26%) diarrhea; and constitutional symptoms of anorexia, vomiting (39%), and malaise. However, in cases of *Y. enterocolitica* gastroenteritis, the abdominal pain and diarrhea usually persist for 10 to 14 days or longer.

In a substantial number of patients with yersiniosis, particularly adolescents and young adults, an ileocecitis may develop. In these cases, lower abdominal pain with little or no diarrhea is the predominant symptom, and the clinical presentation may perfectly mimic that of acute appendicitis. Postinfection manifestations, such as erythema nodosum or a persistent polyarthritis, occur in 2% to 5% of patients, mainly adults. Other presentations include sacroiliitis, ankylosing spondylitis, Reiter's syndrome, exudative pharyngitis, pneumonia, empyema, and lung abscess. *Y. enterocolitica* septicemia is rare but is known to occur, most often in patients with diabetes mellitus, severe anemia, cirrhosis hemochromatosis, or malignancy.

Diagnostic Testing

The diagnosis of yersiniosis can be confirmed with stool cultures or real-time PCR assay; however, most laboratories do not routinely include *Y. enterocolitica* in standard stool testing. *Yersinia* identification can be done by special request if clinically indicated, such as a history of *Yersinia* exposure, prolonged invasive enteritis despite a negative result on standard stool culture, or right lower quadrant pain with signs of invasive diarrhea. Stool cultures require special techniques and a long time for growth. Patients with *Y. enterocolitis* often continue to shed organisms in the stools well into convalescence, long after the diarrhea subsides. The mean duration of fecal shedding is approximately 6 weeks.

Management

Generally, *Y. enterocolitica* infection is self-limited at the diarrheal stage and resolves without treatment. As with other invasive GI pathogens, antiperistaltic drugs are not recommended unless the patient is simultaneously treated with antibiotics.

Treatment with antibiotics is not essential or efficacious in the management of uncomplicated *Y. enterocolitis*. *Yersinia* organisms usually are susceptible to TMP-SMX DS, one tablet PO bid, which is the agent of choice when antibiotic therapy is indicated. Doxycycline, 100 mg PO bid, in combination with an aminoglycoside, is an alternative regimen, as is single-agent therapy with a quinolone. In immunocompetent adults, a 3-day course is sufficient; the course is extended to 7 to 10 days if the patient is immunocompromised. Treatment should be considered for patients who are still significantly ill at the time stool results return, particularly if they are immunocompromised or have an underlying medical illness, or in cases in which the fecal shedding could represent a public health hazard. In patients who interact with potentially susceptible persons, appropriate steps should be taken to ensure that they do not spread their infection.

Vibrio parahaemolyticus Gastroenteritis

Epidemiology

Vibrio parahaemolyticus is a halophilic (salt-requiring) gram-negative bacillus found naturally in warm marine environments

such as the coastal seawaters of Japan, the United States, and other temperate zone regions. In Japan, *V. parahaemolyticus* is the most common cause of bacterial enteritis, being responsible for approximately 70% of cases. The typical source is raw fish. In the United States, *V. parahaemolyticus* disease is much less common, although its incidence has been increasing. Cases in the United States are typically related to consumption of raw or undercooked shellfish, especially oysters, although clams, shrimp, lobsters, mussels, cockles, crabs, and scallops all have been implicated. Many cases occur as outbreaks on cruise ships or in persons who have patronized a common restaurant or seafood market. *V. parahaemolyticus* enteritis is much more common in the summer months, with 70% of cases occurring in May to October, when warm seawater temperatures favor replication of the organism. Attack rates from a common source exposure are fairly high, but little evidence is available for human to human spread among family members of infected patients.

Pathophysiology

The mechanism whereby *V. parahaemolyticus* causes human enteritis is thought to be related to the production of two thermostable direct hemolysin (TDH) virulence factors. Serotypes that produce one or both virulence factors attach to the colonic epithelium and induce a secretory diarrhea, as well as local cell lysis. An infectious dose of *V. parahaemolyticus* is considered to be 100,000 colony-forming units (CFUs) or more. Although enteritis is the most common clinical presentation, accounting for 60% to 80% of cases, *V. parahaemolyticus* infections also manifest as wound infections (34%) and septicemia (5%). Serious wound infections and septicemia occur primarily in persons with underlying liver disease, alcoholism, or diabetes mellitus.

Clinical Features

Signs and symptoms usually appear 8 to 12 hours after the ingestion of contaminated food, but the incubation period can range from 4 to 48 hours. The predominant manifestation is acute diarrhea, but the volume of fluid lost generally is not large. Moderately severe abdominal cramps occur in 88%, nausea in 52%, vomiting in 39%, and fever in 33% of cases. Vomiting generally is not prominent. The illness is almost invariably self-limited and seldom lasts longer than 24 to 48 hours. *V. parahaemolyticus* infection should be suspected when a common source outbreak of acute diarrheal disease occurs in persons exposed to fresh or frozen seafood.

Diagnostic Testing

The diagnosis of *Vibrio* gastroenteritis is made by stool culture or real-time PCR assay. Although blood agar and other nonselective media support the growth of this species, isolation from the stool usually requires the use of a selective medium containing thiosulfate, citrate, bile salts, and sucrose (TCBS agar). This selective culture procedure is not part of the standard stool culture in most US hospitals but can be obtained by special request in cases of outbreaks related to consumption of raw or undercooked shellfish, especially in coastal areas.

Management

Because the disease is self-limited, most patients require no therapy. Although data on the efficacy of antibiotic therapy are lacking, patients who still have diarrhea when culture results become available may benefit from treatment with tetracycline, fluoroquinolones, ceftriaxone, or another antibiotic, as guided by susceptibility testing. Antimotility agents are not indicated. Because *V. parahaemolyticus* is widely present in coastal waters, the only effective preventive measures are adequate cooking, refrigeration, and hygienic practice in the preparation of seafood for human consumption.

Enterohemorrhagic (Shiga Toxin–Producing) *Escherichia coli*

Epidemiology

Enterohemorrhagic *E. coli* was first recognized as a human pathogen in 1982 after two outbreaks of hemorrhagic colitis were traced to undercooked ground beef contaminated with *E. coli* serotype O157:H7 and distributed at a fast food restaurant chain. It is now recognized that *E. coli* O157:H7 is one of more than 30 serotypes of *E. coli* known to produce *Shigella*-like toxins (STEC) and that these STEC serotypes as a group constitute a major cause of hemorrhagic colitis, HUS, and thrombotic thrombocytopenic purpura (TTP) in humans. Children younger than 10 years are at greatest risk for serious STEC infection. Approximately 15% of children with STEC diarrhea develop HUS.

Inadequately cooked hamburger has caused many large outbreaks. STEC, present in the intestines of healthy cattle, contaminates the meat during slaughter, and the grinding process then transfers the organisms from the surface of the meat to the interior. The infectious dose is low, approximately 100 bacteria. US Department of Agriculture food safety regulations now require that hamburger be cooked to an internal temperature of 70°C (160° F) to kill *E. coli* organisms effectively. Outbreaks also have occurred from consumption of venison, salami, pepperoni, cured mutton sausage, cheese curds, apple cider, raw milk, uncooked cookie dough, fruits and vegetables, from contamination of municipal water supplies, from animal contact in petting zoos, and from person to person spread in daycare centers. Food handlers with STEC-related diarrhea have contaminated meals, causing institutional outbreaks. STEC enteritis is more common in the summer months.

Pathophysiology

Ingested STEC multiply in competition with normal bacterial enteric flora, adhere to the intestinal epithelial cells, and elaborate Shiga toxin. Toxins bind to absorptive enterocytes on the luminal surface of the small and large intestines, enter the cell, and irreversibly inhibit protein synthesis, resulting in death of enterocytes. Shiga toxins can then enter the bloodstream via damaged intestinal epithelium and cause the death of vascular endothelial cells by the same mechanism. Endothelial cell lysis is accompanied by platelet activation and aggregation, cytokine secretion, vascular constriction contributing to fibrin deposition, and clot formation within the capillary lumen. Microangiopathy propagates distally as the toxins are carried to the kidneys, causing the clinical syndrome of hematuria and renal failure (HUS). The development of HUS is associated primarily with serotypes that produce Shiga toxin 2. The CDC has estimated that 90% of US cases of HUS are caused by *E. coli* O157:H7.

Clinical Features

After an incubation period of 3 to 4 days, patients initially produce watery diarrhea that becomes bloody hours to days later. Approximately 90% of patients report bloody stools. The amount of blood varies, but stools passed may appear to consist wholly of blood, and the infection may masquerade as GI bleeding from noninfectious causes. The bloody diarrhea typically is accompanied by severe abdominal cramps, pain, and often vomiting. Fever is a feature in fewer than one-third of cases and, if present, usually is low grade. Fecal leukocytes are found in approximately 50% of cases, but in small numbers, in contrast with the sheets of white

blood cells seen in *Shigella* dysentery. Uncomplicated infection resolves spontaneously over 7 to 10 days. A carrier state may last another 1 to 2 weeks, but also resolves spontaneously.

STEC colitis has been associated with two serious complications, HUS and TTP. These clinically similar disorders share the features of microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic deficits, and renal dysfunction. In TTP, neurologic findings predominate, and renal dysfunction is unusual. The opposite is seen with HUS, which is more common in children, especially those younger than 4 years, occurring in up to 15% of cases. Of these, 5% are fatal. Approximately 22% to 40% of older adults in nursing home outbreaks acquire HUS, and 50% to 80% of these patients die. TTP is seen in 2% to 3% of cases, most often in immunosuppressed patients. HUS and TTP typically appear 5 to 20 days after the onset of infection, and the diarrhea can be totally resolved and forgotten by the time a diagnosis is established. Death from STEC colitis alone or from one of the complications occurs primarily among older adults.

Diagnostic Testing

The CDC has recommended that all stools submitted for routine testing from patients with acute community-acquired diarrhea—regardless of age, season, or presence or absence of blood in the stool—be simultaneously cultured for *E. coli* O157:H7 and tested with an assay that detects Shiga toxins to detect non–O157 STEC. Culture-based diagnosis requires specific stool culture techniques. In addition to the routine battery of media, specimens should be plated onto sorbitol MacConkey (SMAC) medium. The O157:H7 strains of *E. coli* are sorbitol-negative at 18 to 24 hours of growth on this medium and can be rapidly identified with various serologic tests, such as latex agglutination or fluorescent antibody testing. A commercial Shiga toxin enzyme immunoassay (EIA) is available to identify non–O157 Shiga toxin–producing strains of *E. coli*.

Management

Treatment is symptomatic. Antibiotic treatment is of no clinical benefit and may increase the risk of HUS by eliminating competing bowel flora, so it is not recommended for patients with known infection with *E. coli* O157:H7.

Empirical antibiotic treatment for bloody diarrhea should be approached with caution. It is not recommended in children because of the risk of HUS. In adults, empirical treatment is recommended only for patients with a temperature over 38.5°C (101°F) because the presence of significant fever suggests a pathogen other than *E. coli* O157:H7.

NONINVASIVE TOXIN-FORMING BACTERIA

Pathogens associated with toxin-induced bacterial enteritis are summarized in Table 84.3. In general, gastroenteritis caused by toxin-forming bacteria (classically known as food poisoning) will manifest as an acute noninvasive enteritis, with watery diarrhea, minimal fever, little or no abdominal cramping, and absence of fecal leukocytes and erythrocytes. Treatment is primarily supportive, and diagnostic testing generally is not indicated for otherwise healthy patients. A specific diagnosis may be of help in attempting to identify a common source during large outbreaks.

Staphylococcus spp.

Epidemiology

Staphylococcus-related food poisoning occurs after multiplication of an enterotoxin-forming strain of *Staphylococcus* that is present in the food before ingestion. Food contamination with *Staphylococcus* is extremely common because the organism is ubiquitous in the environment. Most protein-rich foods support the growth of staphylococci, especially ham, eggs (even hard boiled), custard-filled pastries, mayonnaise, milk, and salads such as egg, tuna, chicken, potato, and macaroni. Foods that require considerable handling during preparation and are then kept slightly warm after preparation are frequent offenders. Temperatures of 45° to 140° F (7° to 60°C) for only a few hours will allow proliferation of the organism in contaminated food and production of sufficient enterotoxin to cause disease. Foods containing sufficient enterotoxin to produce violent illness usually are normal in appearance, odor, and taste. Large outbreaks are common worldwide, particularly in institutions such as school or hospital cafeterias, military bases, airlines, and restaurants.

Pathophysiology

Although the bacterium itself is killed by cooking at temperatures above 140°F (60°C), *Staphylococcus* enterotoxin is heat-stable. Thus, once it is present in food, reheating or even boiling will not prevent illness. The toxin has no local effect on the digestive tract. It is a potent stimulator of T lymphocytes in the host, resulting in their proliferation and the release of cytokines. The GI effects are believed to be mediated by the release of interleukin-2, tumor necrosis factor beta, and interferon from mast cells. Stool, vomitus, and blood can be tested for the presence of the enterotoxin, but this is typically done by local health departments or the CDC during large outbreaks and is rarely done in clinical laboratories.

Clinical Features

The illness has an explosive onset, beginning 1 to 6 hours after ingestion of the contaminated food. Cramping and abdominal pain, with violent and often-repeated retching and vomiting, are the predominant symptoms. Diarrhea is a variable feature; it usually is mild, occasionally absent entirely, and infrequently profuse. Fever occasionally is present. Staphylococcal food poisoning is short-lived, usually subsiding in 6 to 8 hours and rarely lasting as long as 24 hours. Patients often are recovering by the time they seek medical attention. The short incubation period and multiple cases among persons eating the same meal are highly suggestive of this disease. Examination of the stool is noncontributory, and no practical laboratory test is clinically available to confirm the diagnosis.

Management

Rapid, uncomplicated, spontaneous recovery is the rule. Parenteral antiemetic agents help control vomiting. IV fluids should be given to patients who are dehydrated or who have ongoing vomiting, particularly the very young, older adults, and debilitated patients. Antibiotics are of no value because staphylococcal food poisoning is caused by preformed enterotoxins and not by viable microorganisms. Adherence to strict personal hygiene practices by food handlers and immediate refrigeration of foods not intended for immediate consumption are the most important preventive measures. Ordinary refrigerator temperatures prevent production of the enterotoxin. Food should not be allowed to stand at room temperature for long periods before being served.

Clostridium perfringens

Epidemiology

Clostridium perfringens food poisoning is one of the most commonly reported foodborne illnesses in the United States, with at

least 10 to 20 outbreaks reported annually. Most cases occur in large groups, with dozens or even hundreds of persons affected. Illness is caused by the ingestion of meat or poultry heavily contaminated with *C. perfringens* type A heat-resistant spores. The organism also is ubiquitous in the environment and in human and animal feces. Typically, poisoning results from ingesting food that is cooked more than 24 hours before consumption, allowed to cool slowly at room temperature, and then served cool or rewarmed. During this period of incubation, spores that survived cooking germinate, and clostridia multiply to reach sufficient numbers to constitute an infectious inoculum.

Pathophysiology

Ingestion of live organisms is required to produce disease, but illness is not caused by infection; rather, it is caused by an enterotoxin produced by sporulation of the organism in the GI tract. The enterotoxin is responsible for all the symptoms of *C. perfringens* food poisoning.

Clinical Features

Symptoms usually appear within 6 to 12 hours but can occur up to 24 hours after ingestion of the contaminated food. Frequent passage of watery diarrheal stools and moderately severe abdominal cramping are the major symptoms. Fever, nausea, and vomiting are rare. The illness is self-limited and rarely lasts for more than 24 hours. *C. perfringens* food poisoning should be considered in a patient who experiences an acute onset of abdominal cramps and watery diarrhea shortly after eating a suspect meat or poultry dish and when others who have eaten the same meal are similarly ill. Leukocytes and erythrocytes are not present on stool examination.

Management

Occasionally, a patient will need IV fluid replacement. Antibiotics are of no value because of the toxigenic nature and brief duration of the disease. Food poisoning from *C. perfringens* can be prevented by avoiding long periods of warming or cooling of foods that have already been cooked.

Bacillus cereus

Epidemiology

Bacillus cereus is an aerobic, spore-forming, gram-positive rod that is a common cause of foodborne illness. The organism is one of the most frequently isolated soil bacteria. Because of its abundance and the hardiness of its spores, *B. cereus* contaminates nearly all agricultural products and plays a major role in the spoilage of food items, including pasteurized milk and milk products. It commonly is isolated from pasta, rice, dairy and dried milk products, spices, dried foods, meat, chicken, vegetables, seafood, fruits, and grains. Because it is ubiquitous and tolerates extremes of temperature, control of this bacterium in the food-processing environment is very difficult to achieve.

B. cereus causes two distinct clinical syndromes, an emetic form produced by a heat-stable, *Staphylococcus*-like enterotoxin known as cereulide, and a diarrheal form resulting from a heat-labile enterotoxin known as HBL (a hemolysin consisting of three proteins, B, L_1 and L_2), which is similar to that of *E. coli*. The emetic form usually is caused by the ingestion of contaminated fried rice, although beef, poultry, vanilla sauce, pasteurized cream, milk pudding, pasta, potato, cheese, and infant formula also have been implicated. The diarrheal syndrome usually is associated with ingestion of HBL in meats or vegetables, but reported outbreaks have also involved fish, vegetables, soups, sauces, and dairy products.

Pathophysiology

The heat-resistant spores of *B. cereus* survive boiling and then germinate when boiled foods such as fried rice are left unrefrigerated. The vegetative forms multiply and produce toxin. Flash frying or brief rewarming of the food before serving often is not sufficient to destroy the preformed, heat-stable, emetic toxin. Improper holding temperatures for cooked food are the most common feature of *B. cereus* foodborne illness.

Clinical Features

The emetic syndrome is clinically indistinguishable from that caused by staphylococcal enterotoxin. After an incubation period of 1 to 5 hours, profound vomiting and abdominal cramping occur in all patients. Diarrhea is present in approximately 25% to 30% of persons affected. The duration is short, usually less than 10 hours, and patients recover uneventfully.

The diarrheal syndrome begins after an incubation period of 6 to 14 hours and is characterized by diarrhea in all patients and by abdominal cramps in approximately 75%. Vomiting occurs in only 20% of cases. The duration of illness ranges from 12 to 36 hours. Symptoms are essentially the same as for food poisoning produced by *C. perfringens*. *B. cereus* food poisoning should be suspected when an illness localized predominantly to the upper GI tract develops less than 6 hours after eating or when a predominantly lower intestinal tract illness occurs 6 to 24 hours after a suspect meal, usually of meats or vegetables.

Diagnostic Testing

Because of the brief and noninvasive nature of the illness, diagnostic testing typically is not performed. In response to large outbreaks, public health authorities may elect to test common food sources. Isolation of 105 CFU/g from incriminated foods confirms the diagnosis. *B. cereus* enteric infection can also be confirmed via detection of the emetic or diarrheal toxin in stool, emesis, or foods, but this is done only in reference laboratories and only during investigation of large outbreaks.

Management

Both syndromes generally are mild and self-limited. Antibiotics are not indicated because symptoms are mediated by enterotoxins. Parenteral antiemetic agents provide effective relief in patients with violent vomiting. *B. cereus* food poisoning is preventable if boiled rice or cooked foods are promptly eaten or refrigerated and not left to sit at room temperature.

Cholera and Noncholera *Vibrio* Species

Epidemiology

In addition to *V. parahaemolyticus*, other halophilic marine *Vibrio* species have increasingly been implicated in acute gastroenteritis associated with seafood. Their epidemiology is similar to that of *V. parahaemolyticus*—presence in coastal seawater, outbreaks associated with eating raw or inadequately cooked shellfish, and an incidence markedly limited to the warmer months of the year. Outbreaks of true cholera continue to occur sporadically along the US Gulf Coast from inadequately cooked crabs or oysters. Other identified foods include imported seafood, cooked rice, frozen or fresh coconut milk, and commercially prepared cut cantaloupe. Cholera outbreaks in the developing world have led to an

increase number of cases of cholera imported into the United States.

Pathophysiology

The difference between cholera and noncholera *Vibrio* spp. versus *V. parahaemolyticus* lies in the mechanism of pathogenesis. *V. parahaemolyticus* produces disease via toxins that cause intestinal mucosal destruction, whereas cholera and noncholera Vibrio strains produce an enterotoxin in vivo that stimulates enterocyte adenylate cyclase, disrupting mucosal fluid absorption and leading to a secretory diarrhea. Therefore, symptoms resemble those of other forms of enterotoxin-induced gastroenteritis and not those caused by invasive pathogens. The enterotoxin of the noncholera *Vibrio* species is antigenically similar to *V. cholerae* enterotoxin and produces a similar secretory diarrhea, although it is much less severe.

Clinical Features

Patients with classic epidemic cholera experience copious so-called rice water diarrhea, abdominal cramps, and often nausea and vomiting within 24 to 48 hours after ingesting contaminated seafood. A low-grade fever may be present. In these severe cases (cholera gravis), rates of diarrheal fluid loss can reach 1 L/hour; fatality rates can reach 25% to 50% in untreated populations. The median duration of illness is approximately 7 days, unlike the 1- to 2-day course of *V. parahaemolyticus* infection. Despite the notoriety of the classic form of cholera, the CDC estimates that only 1 in 20 cases is associated with cholera gravis. Most affected patients experience a relatively mild diarrheal illness that may go undocumented.

Another species, *Vibrio vulnificus,* is also associated with eating raw seafood, especially oysters. *V. vulnificus* can cause self-limited gastroenteritis, with onset approximately 16 hours after ingestion of contaminated food by healthy persons. In the compromised host, this organism may cause serious wound infections when contaminated seawater comes into contact with open wounds. It may also result in a syndrome of primary septicemia characterized by hemorrhagic bullae of the skin and rapidly progressive septic shock.

V. vulnificus infection is the leading cause of death in the United States associated with the consumption of seafood. Septicemia carries a mortality rate of approximately 50% in patients with significant underlying disease, particularly chronic liver disease. All patients with chronic liver disease, alcoholism, AIDS, or other immunodeficiency states should be advised to avoid all raw shellfish.

Diagnostic Testing

Because these are noninvasive *Vibrio* species, unlike *V. parahaemolyticus*, stained fecal smears will not show leukocytes or erythrocytes. Stool cultures will quickly identify *V. cholerae* if plated on TCBS medium. *V. vulnificus* infection can be diagnosed with stool, blood, or wound cultures. The clinical laboratory should be notified when this infection is suspected so that specific culture media can be used.

Management

Patients with cholera often will lose enough fluids to require rehydration therapy. The WHO oral rehydration formula has been used successfully to treat cholera worldwide. The use of oral or IV fluid hydration is dictated by the clinical picture. The role of antibiotics in the treatment of intestinal infections caused by noncholera *Vibrio* spp. has not been clearly established. However, antibiotics will decrease the severity and duration of cholera and may have the same effect on the other diarrheal diseases caused by these marine *Vibrio* spp.

Antibiotics should be guided by strain-specific sensitivities, if available. Typical choices include a single oral dose of ciprofloxacin, 1 g, azithromycin, 1 g, or doxycycline, 300 mg, or a 3-day regimen of double-strength TMP-SMX bid, tetracycline, 500 mg qid, or erythromycin, 500 mg qid. Preventive measures include use of bottled water, meticulous attention to handwashing before eating and after using the bathroom, avoidance of fecal soiled water sources, thorough cooking of food, peeling of fruits and vegetables, and bathing and toileting at least 30 yards away from drinking water sources. Cholera is a nationally reportable infection.

An oral cholera vaccine is available outside the United States. The oral vaccine appears to provide better immunity, with fewer adverse effects than the previously available parenteral vaccine. The CDC does not recommend this vaccine for travelers, and it is not available in the United States.

If *V. vulnificus* infection is known or suspected, antibiotics should be initiated immediately because this improves survival. Wounds should be débrided because these will progress rapidly and sometimes mandate fasciotomy or amputation. Single-dose antibiotic regimens include levofloxacin or ciprofloxacin. The combination of doxycycline, 100 mg PO bid or IV, plus a third-generation cephalosporin, such as ceftazidime, 1 to 2 g IV or intramuscularly (IM) tid, is also recommended. Children can be treated with TMP-SMX plus an aminoglycoside.

Enterotoxigenic *Escherichia coli*

Epidemiology

Enterotoxin-producing *E. coli*, or enterotoxigenic *E. coli* (ETEC), is recognized as a major cause of acute diarrheal disease throughout most of the world. It is a major cause of diarrhea in persons traveling to underdeveloped areas, especially South Asia, sub-Saharan Africa, and Latin America. ETEC is increasingly being recognized as a cause of foodborne illness in developed countries, including the United States. Infection is acquired from fecally contaminated food or drink. Unpeeled fruits, leafy vegetables, unsanitary drinking water, and ice are the most common sources. Most tourists are careful about their food and drink, but there seems to be a poor correlation between individual eating habits and the incidence of traveler's diarrhea. It is likely that the quality of hygiene at a particular food source is the major determinant of risk; travelers should choose locations that have a reputation for excellence in hygiene.

Pathophysiology

For an *E. coli* strain to cause diarrhea, it must possess a surface factor that allows colonization (although not invasion) of the small intestine and the ability to secrete an enterotoxin that causes the outpouring of fluids and electrolytes into the small bowel lumen. The enterotoxin-induced secretion occurs in the absence of any demonstrable histologic damage to intestinal epithelial cells or to the capillary endothelial cells. *E. coli* produces heat-labile and heat-stable toxins. The intestinal fluid losses are qualitatively identical to those in cholera and other toxigenic diarrheas.

Clinical Features

After an incubation period of 24 to 72 hours, an abrupt onset of watery diarrhea occurs. Severity varies, with the illness ranging from a fulminant, cholera-like disease to the much more common and milder turista, in which the symptoms of mild, watery

diarrhea and abdominal cramps are more troublesome than life-threatening. Fever is unusual. Vomiting occurs in less than one half of affected adults and is seldom responsible for significant fluid losses. Even in severe cases, the diarrhea seldom lasts longer than 48 to 72 hours, and the response to oral or IV fluids is uniformly good. Milder disease generally subsides more gradually, occasionally persisting for 1 week or longer. Virtually all persons recover completely, without long-term sequelae.

ETEC disease should be suspected when a child or adult has frequent watery diarrhea and few other symptoms. It often is passed off as mild nonspecific gastroenteritis and resolves spontaneously. ETEC is the most common cause of traveler's diarrhea, so most people who acquire toxigenic diarrhea while visiting a developing nation probably have this disease.

Diagnostic Testing

There is no easy rapid means for the laboratory diagnosis of ETEC infection. Methods that rely on identification of specific *E. coli* serotypes are unreliable because *E. coli* is part of the normal colonic flora, and its ability to produce enterotoxin is not restricted to any specific serotype. Methods based on detection of the heat-stable and heat-labile toxins through the use of the real-time PCR assay have been developed but are generally available only in reference laboratories. Stool preparations show no erythrocytes or leukocytes.

Management

Because ETEC infection is almost always a self-limited disease, no treatment other than maintaining hydration is required. However, if the organism is identified while symptoms are still active, or if the patient is traveling in an endemic area, antibiotics can afford clinical relief. For milder symptoms, a single oral dose of ciprofloxacin, 750 mg PO bid, in addition to loperamide is effective. For more severe symptoms, TMP-SMX, 160 mg/800 mg, or standard doses of a fluoroquinolone for 3 days should eradicate the organism.

Clostridium difficile Colitis

Epidemiology

Clostridium difficile (*C. difficile*) is an anaerobic, spore-forming, gram-positive bacillus that is one of the leading causes of health care–associated infectious diarrhea. It has been associated with a range of illnesses, from asymptomatic colonization to severe diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation, and death. It is the leading cause of morbidity and mortality among hospitalized older adults.[7] In 2001 to 2010, there were an estimated 2,773,521 discharges with a diagnosis of *C. difficile* colitis identified in the United States based on inpatient registries. Compared with the 2001 to 2005 period, the 2006 to 2010 period witnessed a 47% increase in the rate of *C. difficile* colitis. The increased rates may be due to the increased incidence of *C. difficile* colitis and possibly the emergence of a highly virulent strain of *C. difficile*. The alarming increase in *C. difficile* cases underscores the need for contact isolation procedures when there is a suspected case in the emergency department (ED).[8]

Pathophysiology

C. difficile infections are usually related to antibiotic use that alters the gut flora and allows the *C. difficile* bacteria to colonize and proliferate. *C. difficile* colitis can manifest concomitantly with current antibiotic use and up to 3 to 4 weeks afterward, although most *C. difficile* infections will occur within 2 weeks of using an antibiotic. Other risk factors include recent hospitalization, living in a long-term care facility, and use of antacids. *C. difficile* spores are highly resistant to heat, acid, and antibiotics, making them highly contagious for person to person or surface to person infections. *C. difficile* bacteria secrete toxins A and B that cause inflammation, mucosal injury, and secretory diarrhea. Infections may lead to a pseudomembranous colitis, toxic megacolon, or even colonic perforation.

Clinical Features

Manifestations of *C. difficile* colitis include watery diarrhea up to 10 to 15 times daily, with lower abdominal pain, cramping, low-grade fever, and leukocytosis. Fever is associated with *C. difficile* colitis in about 15% of cases. The physical examination initially focuses on the patient's fluid status. The emergency clinician should assess for dry mucosa, tachycardia, hypotension, and lightheadedness. The abdomen is assessed for evidence of an acute surgical process. A rigid or distended abdomen may represent bowel perforation. A stool sample should be taken for culture and hemoccult testing. The examiner should wear gloves and a protective gown. Vigorous handwashing with soap and hot water after each patient encounter should be performed to decrease person to person infections because hand sanitizers do not kill *C. difficile* sufficiently.[9]

Diagnostic Testing

The stool of infected persons should be assayed for *C. difficile* toxins A and B. Nucleic acid amplification stests (NAATs) for *C. difficle* toxin genes, eg, PCR assays, are superior to EIA for toxins A and B and are therefore the recommended diagnostic test. Glutamate dehydrogenase (GDH) screening with subsequent toxin A and B EIA testing has a lower sensitivity but is an alternative diagnostic approach when NAAT testing is not available. In addition, a complete blood count (CBC), metabolic panel, and lactate level determination should be considered based on the patient's fluid status and severity of symptoms. Leukocytosis in the setting of *C. difficile* colitis is common and the WBC count is often greater than 15,000 cells/mm^3.

Persons at extremes of age tend to have more severe infections. The past decade has seen the emergence of a fulminant form in patients older than 65 years. Older adults with a leukocyte count greater than 20×10^9/L, nosocomial infection, renal failure, and immunosuppression are at increased risk for complications such as toxic megacolon, shock, need for colectomy, and death. If a person has any of these risk factors, appears septic, and has a tender distended abdomen, an emergent colonoscopy is recommended to evaluate for toxic megacolon or the presence of pseudomembranous colitis.[10]

Management

The management of *C. difficile* colitis includes discontinuation of any inciting antibiotic and rapid initiation of treatment. Metronidazole, 500 mg PO tid for 10 to 14 days, is the first drug of choice for mild to moderate *C. difficile* colitis. Vancomycin, 125 mg PO qid for 10 to 14 days, should be used for severe *C. difficile* colitis. Patients generally become afebrile and show clinical improvement within 36 to 72 hours.

The diarrhea usually resolves over 5 to 7 days, even though results of toxin assays and stool cultures may remain positive for weeks. Up to 50% of patients experience a relapse regardless of the antibiotic chosen, its dosage, or duration of treatment. Risk factors for recurrent disease include new exposure to antibiotics, age older than 65 years, severe underlying disease, low serum albumin level, need for admission to an intensive care unit, and

extended hospital stay of 16 to 30 days. Most of these patients will respond to another course of antibiotic therapy.[11]

Hospitalization is indicated for older adults, nursing home patients, those with comorbid conditions such as renal failure, an immunocompromised state, or severe dehydration. Patients should be placed in contact isolation and hospital protocols should be followed for *C. difficile* infections.

Outpatient therapy is appropriate for individuals without comorbid conditions who are nontoxic-appearing, with mild disease, and who can tolerate oral hydration.

VIRAL GASTROENTERITIS

Most cases of gastroenteritis have viral causes, which include norovirus, *Sapovirus*, rotavirus, adenovirus, and astrovirus. Clinical features suggestive of a viral cause consist of an intermediate incubation period (24–to 60 hours) and short infectious duration (12 to 60 hours). Since rotavirus vaccine has been increasingly used in children, the rate of rotavirus-associated gastroenteritis has significantly decreased.

Patients with a viral gastroenteritis can present with nausea, vomiting, abdominal cramping, and diarrhea. Physical findings may include fever and abdominal tenderness. Patients with a more severe illness can present with symptoms and signs of dehydration. Norovirus and rotavirus are among the two most prevalent viral causes of gastroenteritis. Table 84.7 and Table 84.3 contain summaries of common causes, clinical features, diagnostic studies, and treatment of viral gastroenteritis.

Norovirus

Epidemiology

The norovirus, previously referred to as the Norwalk-like virus, is the most common cause of acute gastroenteritis in children and adults and usually occurs in the winter months. It is also the most common cause of foodborne disease and person to person outbreaks in the United States. Norovirus causes approximately 20 million illnesses/year, with approximately 400,000 ED visits. Patients who are immunocompromised and at extremes of age (adults > 65 years and children < 5 years) are at greatest risk of complications and death.[12]

Pathophysiology

Transmission of norovirus occurs via the fecal-oral route (eg, ingestion of contaminated food and water and exposure to airborne droplets of vomitus-containing viral particles and fomites. It has an incubation period of 1 to 2 days, with symptoms typically lasting for 48 to 72 hours. Norovirus is highly infectious for all age groups, and a small amount of inoculum (≈100 virions) is needed for virus transmission. Shedding of the virus in the stool can occur up to 2 to 3 weeks after onset of symptoms.

Clinical Features

The onset of symptoms is commonly abrupt and associated with a rapid recovery. Vomiting is a prominent feature. Patients develop diarrhea that is usually moderate in amount, defined as four to eight stools over a 24-hour period. The diarrhea is characterized as nonbloody stool with a loose to watery consistency that lacks mucus. Associated symptoms include generalized malaise, myalgias, headache. and fever, which occur in approximately 50% of cases. Infection may be protracted and symptoms may be present for a longer period due to prolonged viral shedding, especially in the immunocompromised patient.[13] Postinfectious complications of the condition include dyspepsia, reflux, and constipation. In rare circumstances, patients may present with central nervous system (CNS) complications, such as seizures and encephalopathy.

Diagnostic Testing

The diagnosis of viral gastroenteritis is commonly based on clinical features of the condition. A norovirus outbreak in the community is suspected when these criteria are met: mean incubation period of 24 to 48 hours; mean duration of illness of 12 to 60 hours; presence of vomiting in more than 50% of cases, and absence of bacterial pathogens on stool cultures. These criteria have a 99% specificity and 68% sensitivity for the diagnosis.[14]

Identification of the exact causative viral agent is not necessary in most cases. However, in the setting of an outbreak, it is very important to isolate the causative organism so that successful mechanisms that disrupt viral transmission can be recognized. The main laboratory tools to diagnose norovirus infection are genomic amplification via the reverse transcriptase polymerase chain reaction (RT-PCR), immunoassays, and electron microscopy. RT-PCR can detect a stool viral load as low as less than 100 particles/g. PCR testing can also be performed on food and environmental samples. In comparison to RT-PCR, immunoassays have a lower sensitivity and specificity and hence have limited use in the diagnosis of sporadic cases of gastroenteritis. Electron microscopy is best used for the diagnosis of viral gastroenteritis due to rotavirus and astrovirus because large viral loads are shed in these conditions.

TABLE 84.7

Viral Causes and Clinical Features

ORGANISM	MODE OF TRANSMISSION	CLINICAL FEATURES
Norovirus	Ingestion of contaminated food and water; touching contaminated surfaces; extremely contagious	Most common cause of gastroenteritis in United States and most common cause of US foodborne-disease outbreaks; fever, headache, myalgias, nausea, vomiting, abdominal pain, diarrhea; incubation period, 12–48 h
Sapovirus	Ingestion of contaminated food and water; fecal-oral route	Fever, nausea, vomiting, diarrhea; usually causes mild illness
Rotavirus	Ingestion of contaminated food and water; touching contaminated surfaces	Fever, nausea, vomiting, abdominal pain and watery diarrhea; incubation period ≅ 2 days
Adenovirus	Close personal contact; touching contaminated surfaces	Rare cause of serious illness; fever, diarrhea; can cause non-GI illness (eg, bronchitis, pneumonia, conjunctivitis)
Astrovirus	Fecal-oral route	Malaise, headache, abdominal pain, diarrhea; vomiting less common

Management

Viral gastroenteritis due to norovirus has no specific treatment. Management is based on the clinical condition of the patient. Supportive care, including oral hydration or IV fluid replacement, may be required. Implementation of proper hand hygiene is key to prevent the disease from occurring. During norovirus gastroenteritis outbreaks, patients should be placed on contact precautions in a cohort setting. Routine disinfection and cleaning of environmental surfaces and equipment should also take place.[15]

Rotavirus

Epidemiology

The name rotavirus originated from the Latin word *rota,* meaning wheel, based on the classic appearance of the virus under electron microscopy. The virus predominantly infects infants and young children, with a milder disease occurring in adults. Prior to the development of the rotavirus vaccine, rotavirus was the leading cause of diarrhea in the United States among infants and children. Rotavirus is a stable virus and primarily transmitted via the fecal-oral route and direct contact with contaminated surfaces. In the United States, epidemics occur typically in the winter and spring, from December to June.

Pathophysiology

Pathogenesis of the illness is associated with diarrhea, which occurs as a result of three main mechanisms—the direct effect of the rotavirus enterotoxin NSP4, loss of brush border enzymes, and activation of the enteric nervous system.

Clinical Features

Clinical features of rotavirus infection in children include fever, nausea, vomiting and nonbloody watery diarrhea. The virus has an incubation period of approximately 2 days. Symptoms can last from 3 to 8 days. Patients may also present with loss of appetite and signs of dehydration, including dry mucous membranes and decreased urinary output. Children with rotavirus can also have concurrent respiratory symptoms; 2% to 3% have CNS complications, including seizures, encephalopathy, and encephalitis. A milder form of rotavirus infection occurs in adults, especially in household members of infected children. Older adults and immunocompromised patients are at increased risk for more severe disease with protracted illness. This is important to help determine the duration of isolation and repeat testing to ensure eradication of the virus. Rotavirus has been anecdotally implicated in cases of necrotizing enterocolitis, intussusception, and biliary atresia.[16]

Diagnostic Testing

Rotavirus infection is diagnosed using antigen detection in stool samples. Large viral loads are shed, making electron microscopy a useful diagnostic test. Additional methods include immunoassays such as the enzyme-linked immunosorbent assay (ELISA) and latex agglutination. ELISA will detect virus from the onset of clinical symptoms. Nucleic acid testing, such as via the PCR assay, is the most sensitive test.[17]

Management

Rotavirus is a self-limited illness that lasts for a few days in healthy individuals. Treatment involves supportive care and managing fluid status. Hospitalization is required in approximately 1 of 70 children infected with the virus.

Prevention of rotavirus infection occurs with the use of two, live, attenuated oral vaccines—the pentavalent human bovine rotavirus reassortant vaccine (RV5, PRV, RotaTeq) and attenuated human rotavirus vaccine (RV1, HRV, Rotarix). The two vaccines have similar efficacy and safety profiles. Studies have shown that the vaccines are very effective in preventing the viral illness and hospitalization due to rotavirus gastroenteritis.

The CDC recommends the following vaccination schedule: RotaTeq (RV5), to be given in three doses at ages 2, 4, and 6 months and Rotarix (RV1), to be given in two doses at ages 2 and 4 months. Rotavirus vaccines are contraindicated in certain infants. Children who have a latex allergy should not receive the RV1 vaccine because the applicator contains latex. Additional rotavirus vaccine contraindications include an allergy to any of the ingredients in the vaccines, anaphylaxis to a previous vaccine dose, history of intussusception, and severe combined immunodeficiency (SCID).[18] Neither natural infection nor vaccine ensures protection from future infections, so vaccinated and unvaccinated children may develop multiple episodes of rotavirus gastroenteritis. The rotavirus vaccinations have been estimated to reduce rotavirus gastroenteritis by more than 90% among infants in all care settings and more than 70% for children aged 1 to 4 years.[19]

PARASITES

Table 84.8 lists the clinical features of common parasites causing gastroenteritis; Table 84.4 summarizes appropriate diagnostic tests and treatment.

TABLE 84.8

Parasites and Clinical Features

ORGANISM	MODE OF TRANSMISSION	CLINICAL FEATURES
Giardia lamblia	Ingestion of contaminated food and water; fecal-oral route	Nausea, vomiting, abdominal cramps, flatulence, greasy stool that can float
Entamoeba histolytica	Ingestion of contaminated food and water; touching contaminated surfaces; fecal-oral route	Fever, anorexia, abdominal cramping, watery or bloody diarrhea; illness ranges from asymptomatic infection, fulminant colitis, peritonitis to extraintestinal amebiasis
Cryptosporidium	One of the most frequent causes of waterborne disease in US population	Abdominal cramping, diarrhea
Cyclospora cayetanensis	Ingestion of contaminated food and water; fecal-oral route	Nausea, vomiting, loss of appetite, weight, bloating, abdominal cramping, diarrhea

Giardia

Epidemiology

Giardia lamblia is a well-known protozoan parasite that causes sporadic or epidemic gastroenteritis worldwide. The illness occurs more commonly in developing countries that have poor sanitary conditions. Approximately 20,000 cases occur in the United States on an annual basis, with the peak being in the summer to fall months. Infants, young children, travelers, immunocompromised individuals, and patients with cystic fibrosis or hypochlorhydria are at greatest risk for developing the disease.

Pathophysiology

G. lamblia exists in two forms, trophozoite (active form) and cyst (inactive form). Trophozoites attach to the mucosal lining of the small intestine and cause symptoms. This active form of the parasite is unable to survive outside the body for an extended period of time and hence cannot spread infection to others. The cystic form, however, is viable outside of the body for prolonged periods and, once ingested, changes into the trophozoite form. Trophozoites generate the cysts that exit the body via the feces.

Giardia infection is transmitted via cysts through several routes, including ingestion of contaminated food and water and fecal-oral route transmission. Infection can result from the ingestion of as few as 10 cysts. Giardiasis is a common cause of diarrhea that occurs in hikers exposed to contaminated water. Person to person transmission can also occur in settings with poor hygiene—for example, child care settings with children who are not toilet-trained. Infection can also be transmitted via anal intercourse.

Clinical Features

Clinical features of acute giardiasis consist of sudden onset of diarrhea associated with malaise, weight loss, nausea, abdominal cramping, and bloating. Stools are characterized as being foul-smelling and fatty.

Diagnostic Testing

Immunoassays have higher diagnostic sensitivities than stool microscopy and are the preferred diagnostic modality, when available. Several immunoassay tests are available, including direct immunofluorescent assays, immunochromatographic assays, and ELISAs.

Stool microscopy can identify ova and parasites, especially in the acute phase, when cysts and trophozoites appear in the stool. In subacute, chronic, and asymptomatic cases, trophozoites may be present in the stool in small numbers or on an intermittent basis. Collection of multiple stool samples (eg, three stool samples collected on separate days) can increase sensitivity of the test.

Biopsy of duodenal-jejunal tissue or aspiration of the duodenal-jejunal area by endoscopy may be required to make the diagnosis when repeated stool samples tested for ova and parasites do not yield any organisms.

Management

Treatment of symptomatic cases consists of metronidazole, 500 mg PO bid, or 250 mg PO tid daily for 5 to 7 days. A single PO dose of tinidazole, 2 g, or nitazoxanide, 500 mg PO bid for 3 days, can also be given. Alternative agents include albendazole, mebendazole, and quinacrine.

Treatment of asymptomatic giardiasis is controversial. An asymptomatic carrier can be someone who was initially diagnosed and treated for giardiasis and who now has no clinical symptoms but still has a positive stool culture. Asymptomatic carriers, especially children and food handlers, may need to be treated to reduce the risk of spread and decrease the risk of developing chronic intermittent diarrhea. In endemic areas, the reinfection rate is high; therefore, treatment may not be cost-effective.

Prevention of the disease is promoted by the use of strict handwashing and the avoidance of ingesting contaminated water. To avoid spread of illness in hospitals, patients diagnosed with giardiasis and who are incontinent or wearing diapers should be placed on contact precautions.

Amebiasis

Epidemiology

Amebiasis is caused by the protozoan *Entamoeba histolytica*, which is found worldwide. The genus *Entamoeba* is comprised of many species, but *E. histolytica* is the only one linked to disease pathology.

Amebiasis is more common in developing countries with poor sanitary conditions. Most *E. histolytica* infections are asymptomatic, with only 10% of carriers presenting with symptoms. Approximately 50 million cases of invasive *E. histolytica* disease occur worldwide each year. Specific groups of individuals are more predisposed to amebic colitis, such as those at the extremes of age, pregnant females, and malnourished individuals. Travelers to endemic areas are also at risk for infection.

Pathophysiology

E. histolytica exists in two forms, the trophozoite and cystic forms. The parasite is transmitted by the ingestion of the cystic form, which is the infective stage of the disease. Cysts can survive in the environment for weeks to months and can be found on the contaminated hands of food handlers or in fecally contaminated food and water. The infection can also spread through ingestion of cysts via anal-oral sexual practices. Trophozoites are formed when excystation occurs in the terminal ileum or colon, resulting in the invasive stage of the disease. Trophozoites can cause tissue destruction by penetrating into the colonic mucosal barrier, leading to secretory bloody diarrhea and colitis. Extraintestinal disease can also occur by the hematogenous spread of trophozoites via the portal circulation to the liver and other organs.

Clinical Features

Acute amebic dysentery has an incubation period that ranges from 1 week to 1 year. Patients present with acute onset of severe abdominal cramps associated with fever, profuse, bloody diarrhea, and tenesmus. Gradual onset of symptoms can result in chronic amebic colitis. Individuals present with intermittent diarrhea, with two to four foul-smelling stools daily, usually containing blood-streaked mucus. Associated symptoms of fever, weight loss, abdominal cramping, and flatulence can be present. The clinical condition may have alternating symptomatic and asymptomatic periods, which last over months to years. The most common serious complication of amebic colitis is amebic liver abscess.

Diagnostic Testing

Diagnosis of amebic colitis in the past was based on microscopic identification of cysts and trophozoites in stool samples. Trophozoites can also be identified in biopsy samples that can be obtained during colonoscopy. The development of stool antigen assays has enhanced the diagnostic process for amebic colitis. EIA kits for *E. histolytica* antibody and antigen detection are available. Molecular

analysis by PCR-based assays can also be used to distinguish *E. histolytica* from the nonpathogenic *Entamoeba dispar* species.

Management

Treatment of benign cyst passers consists of paromomycin, 500 mg PO tid for 7 days. Oral iodoquinol, 650 mg tid for 20 days, or diloxanide furoate, 500 mg PO tid for 10 days, can also be given. For mild to moderate disease, metronidazole, 750 mg tid for 10 days, can be prescribed, followed by paromomycin treatment as above. Paromomycin can cause diarrhea as a side effect, thus making it difficult to assess the patient's response to the metronidazole if both drugs are given together. Preventive measures using standard precautions to prevent fecal-oral spread should be followed.

FOOD POISONING

Principles

Foodborne gastroenteritis is an illness caused by the ingestion of food contaminated by viruses, bacteria, or bacteria toxins. *Food poisoning* is the term typically used for gastroenteritis caused by the ingestion of preformed toxins, such as staphylococcal toxins, *B. cereus* toxins, histamine-like substances from scombroid fish poisoning, ciguatoxins from ciguatera fish poisoning, or *Clostridium botulinum* toxins.

The enterotoxins can also be produced in vivo after the ingestion of the bacterium and subsequent production of the enterotoxin in the intestinal lumen. Examples are *C. perfringens, B. cereus, C. botulinum,* enterotoxigenic *E. coli*, *Vibrio cholerae*, non-cholera *Vibrio* spp. such as *V. enterocolitica*, and Shiga toxin-producing *E. coli*. See the earlier section ("Noninvasive Toxin-Forming Bacteria") for detailed background, clinical presentations, diagnosis, and treatment for each of these organisms. Scombroid and ciguatera fish poisoning are discussed in this section.

Clinical Features

Food poisoning usually manifests 1 to 6 hours after the ingestion of preformed toxins from *Staphylococus, B. cereus* (short incubation form), and scombroid fish or ciguatera fish poisoning. Moderate incubation periods of 8 to 16 hours are seen after the ingestion of toxin-forming bacteria such as *C. perfringens* or *B. cereus* (long incubation form). Longer incubation periods of more than 16 hours are associated with ETEC, STEC, and *Shigella* and *Vibrio* spp.

The clinical presentation usually involves an abrupt onset of nausea, vomiting, and abdominal cramping followed by watery diarrhea. Fever is usually absent, and symptoms should resolve within 24 hours. In some cases, *B. cereus* predominantly causes diarrhea and cramping. Often, there is a clear food exposure, such as at a picnic with many people in attendance who have the same illness at the same time.

Diagnostic Testing

Diagnostic testing is usually not indicated in cases of food poisoning, and most individuals will recover within 24 hours. A detailed history of the timing, types, and places of recent sources of food ingestion should be obtained. Similar patterns of GI illness involving others who may have ingested the same foods will probably identify the causes. If identification for outbreak surveillance is needed, stool samples can be sent to test for for specific organisms.

Most state health departments encourage consumers to report food poisoning incidents to their local health department. Physicians and laboratories must report each singular diagnosed infection that is included in a notifiable disease list maintained by local, state, and/or federal agencies (www.cdc.gov/foodsafety). Foodborne illnesses are included in the notifiable disease lists. Examples include: salmonellosis, shigellosis, cholera, Shiga toxin–producing *E. coli* (STEC), norovirus, and hepatitis A.[20] Physicians should suspect an outbreak when they are seen by a larger than normal number of people exhibiting the same symptoms.

Management

In general, oral hydration is the mainstay of treatment. Antiemetics such as odansetron, 4 mg PO, or metoclopramide, 10 mg PO, may be prescribed to enhance oral hydration. Antibiotic therapy is rarely required because most patients will have a self-limited illness.

Scombroid Fish Poisoning

Epidemiology

Scombroid fish poisoning remains one of the most common forms of fish poisoning in the United States. The disease takes its name from the family Scombridae (eg, tuna, mackerel, skipjack, bonito, and related species) but results from the ingestion of a wide variety of dark meat fish, including nonscombroid species such as herring, bluefish, anchovy, sardine, amberjack, black marlin, and mahi mahi. The fish species most commonly implicated are mahi mahi, tuna, and bluefish.

Most US cases occur in Hawaii and Florida, followed in frequency by California, New York, Washington, and Connecticut. However, scombroid poisoning can occur in any location where so-called fresh fish are flown in.

Pathophysiology

The meat of implicated species naturally contains unusually high levels of histidine. Scombroid fish poisoning results from the ingestion of heat-stable toxins produced by bacterial action on the histidine present in the dark meat of the fish. The bacteria responsible are normal constituents of the surface marine flora, rather than contaminants. The histidine decarboxylase activity of these organisms produces histamine and histamine-like substances, which cause the symptoms of scombroid fish poisoning. High levels of histamine in the fish correlate directly with the occurrence of the illness.

Formation of the scombrotoxins is directly related to improper preservation and refrigeration of the fish from the time they are caught until when they are cooked. In general, the problem is caused by improper refrigeration by the supplier rather than being the fault of the restaurant serving the fish. Other foods, notably Swiss cheese, contain sufficient amounts of histidine and have also been implicated.

Clinical Features

The symptoms of scombroid fish poisoning resemble those of histamine intoxication. While eating the fish, the patient may note a metallic, bitter, or peppery taste, although many affected fish do not have an abnormal odor or taste. Symptoms usually develop abruptly within 20 to 30 minutes and consist of facial flushing, diarrhea, severe and throbbing headache, palpitations, and abdominal cramps. Other manifestations may include dizziness, dry mouth, nausea and vomiting, and urticaria. The facial flushing resembles a sunburn and can extend over the entire skin surface. The conjunctivae usually are infected. The duration of the major symptom complex generally is less than 6 hours and,

although weakness and fatigue persist longer, the clinical course usually is benign. The attack rate is very high; most persons sharing the same toxic fish will become ill.

Management

Parenteral antihistamine therapy, such as diphenhydramine, 50 mg IM or IV, or cimetidine, 300 mg IM or IV, usually relieve all symptoms promptly. This is not an allergic reaction, so patients should not be told that they are allergic to these fish, nor should they be prohibited from eating them again in the future. Suspected cases of scombroid should be immediately reported to the health department.

Ciguatera Fish Poisoning

Epidemiology

Ciguatera fish poisoning is a common public health problem, with appreciable economic significance. It is endemic in tropical regions but is found worldwide. Fish caught around Hawaii and Florida cause most US cases but, because the responsible ocean fish are now commonly transported inland, cases can be seen virtually anywhere. More than 400 fish species that frequent coral reefs have been implicated as ciguatoxin carriers, but fewer than 50 are commercially important; these include amberjack, barracuda, grouper, king mackerel, parrotfish, sea bass, snapper, sturgeon, surgeonfish, and ulua.

Pathophysiology

Ciguatera fish poisoning results from the ingestion of the ciguatoxin neurotoxin. Ciguatoxin is produced by the marine dinoflagellate *Gambierdiscus toxicus*, which attaches itself to marine algae and is passed up the food chain. The lipid-soluble toxin accumulates in the tissues of the larger predacious coral reef fish, with the highest concentrations in the liver, intestines, head, and roe. It does not affect the fish in any way. Only humans suffer its ill effects when the toxin is ingested.

Ciguatoxin is heat- and acid-stable, odorless, and tasteless. It is not deactivated by cooking or freezing, nor is the toxin eliminated by drying, salting, smoking, marinating, or pickling. It is not possible to predict whether a fish contains sufficient amounts of the toxin to produce illness.

Ciguatoxin has anticholinesterase and cholinergic properties, but its neurotoxicity is mediated by its effect on sodium channels. Ciguatoxins cause a hyperpolarizing shift of the voltage dependence of channel activation so that sodium channels are open at the resting membrane potential. Spontaneous firing of neurons occurs as tetrodotoxin-sensitive sodium channels are activated, giving rise to the typical neurologic signs and symptoms.

Clinical Features

Ciguatera fish poisoning is usually seen in the spring and summer months. The incubation period is approximately 2 to 6 hours, but a delay of 12 to 24 hours is not unusual. Attack rates are very high—80% to 90% of persons exposed become ill. Symptoms tend to be related to the amount of toxin ingested and vary considerably in their severity. If not fully recovered from an initial ingestion of ciguatoxin, affected persons are likely to have much more serious symptoms from a second ingestion.

Classically, patients exhibit GI and neurologic symptoms. The GI symptoms (eg, nausea, vomiting, profuse watery diarrhea, crampy abdominal pain, diaphoresis) tend to appear first and resolve over the first 24 hours. The constellation of neurologic symptoms consists largely of dysesthesias and paresthesias around the throat and the perioral area—burning feet, which may resemble alcoholic peripheral neuropathy, loose painful teeth, and sometimes CNS changes, such as ataxia, weakness, vertigo, visual hallucinations, and even confusion and coma.

Distortion of temperature perception is vividly described by patients with ciguatera poisoning. Cold allodynia, defined as dysesthesia experienced on contact with cold water or cold objects, is almost pathognomonic of ciguatera poisoning and often is incorrectly referred to as cold-hot temperature reversal. Another classic feature is a return or a worsening of all the symptoms after ingestion of alcohol.

Ciguatera poisoning lasts an average of 1 to 2 weeks, but at least 50% of victims are still symptomatic at 8 weeks. The neurologic symptoms, particularly the paresthesias and dysesthesias, tend to persist longer than the GI symptoms and have been reported up to years later.

Management

Treatment is primarily supportive. IV fluids are given to replace volume losses from vomiting and diarrhea, and analgesics are given as needed. In severe cases, the toxin may exhibit some anticholinesterase activity, manifested as bradycardia and hypotension, which can be treated with atropine, 0.5 mg IV, and dopamine, 5 to 20 µg/kg/min via IV drip. Patients should be told to abstain from alcohol in any amount until symptoms have completely resolved.

Pruritus may be managed with a histamine H1 receptor antagonist, such as diphenhydramine 25 mg PO qid, or cetirizine, 10 mg once daily. Amitriptyline, 25 mg bid, can bring about a dramatic reduction in the pruritus and dysesthesias, two of the most disturbing and protracted symptoms.

The naturally occurring compound brevenal was shown to inhibit ciguatoxin-induced neurosecretion in laboratory studies. This compound may prove beneficial in treating the neurologic sequelae of ciguatera fish poisoning.

SPECIFIC GROUPS WITH GASTROENTERITIS

Traveler's Diarrhea

Epidemiology

Traveler's diarrhea is the most common illness afflicting people traveling from resource-rich regions to the developing world. Approximately 10 million international travelers develop diarrhea annually, usually within the first week of travel. The traveler's destination is the most important factor in assessing the risk of developing disease. Ingestion of contaminated food and water is the primary mode of transmission of traveler's diarrhea.

Pathophysiology

A variety of viruses, bacteria, and parasites cause traveler's diarrhea. Bacterial and viral pathogens have an incubation period ranging from 6 to 48 hours. Parasitic causes have a longer incubation period, up to 2 weeks in duration. Bacterial pathogens cause approximately 80% of cases. ETEC is the most common bacterial cause for traveler's diarrhea (see earlier, "Enterotoxigenic *Escherichia coli*"). Other causative agents are listed in Table 84.9.

Clinical Features

Classically, traveler's diarrhea presents with passage of three or more unformed stools in a 24-hour period, with at least one of these symptoms: fever, nausea, vomiting, abdominal pain or cramps, or blood in the stools. Patients with a moderately severe

TABLE 84.9

Causative Organisms and Treatment of Traveler's Diarrhea

ORGANISM	TREATMENT
Enterotoxigenic *Escherichia coli* (ETEC)	Ciprofloxacin, 500 mg bid or 750 mg PO once daily for 1–3 days
Enteroaggregate *E. coli*	Ciprofloxacin, 500 mg bid or 750 mg PO once daily for 1–3 days
Campylobacter	Azithromycin, 500 mg PO daily for 3 days
Salmonella	Levaquin, 500 mg PO daily for 7 days
Shigella	Ciprofloxacin, 750 mg PO daily for 3 days
Norovirus	Supportive care
Rotavirus	Supportive care
Giardia	Metronidazole, 500 mg PO bid or 250 mg tid for 5–7 days

TABLE 84.10

Preventive Medications and Treatment for Traveler's Diarrhea in Adults

PHARMACOLOGIC AGENT	RECOMMENDED DOSE	ADVERSE EFFECTS
PREVENTION		
Bismuth subsalicylate	524 mg PO qid	Contains hydrogen sulfide, which turns stool and tongue black in color
Ciprofloxacin	500 mg once or twice daily	Achilles tendon damage; *Clostridium difficile* infection
Rifaximin	200 mg once or twice daily	Considered safe because it is not absorbed
TREATMENT		
Bismuth subsalicylate	524 mg PO qid (1 oz liquid or two tablets)	Contains hydrogen sulfide, which turns stool and tongue black in color
Loperamide	4 mg initially, then 2 mg after each unformed stool; not to exceed 8 mg/day.	Lowest effective dose should be taken to prevent post–traveler's diarrhea constipation
Ciprofloxacin	500 or 750 mg once daily for 1–3 days	Achilles tendon damage; *C. difficile* infection
Rifaximin	200 mg tid for 3 days	Considered safe because it is not absorbed
Azithromycin	500 mg daily for 3 days or 1000 mg in single dose	Nausea is common adverse effect

case have one or two unformed stools in 24 hours, with at least one of these symptoms or the passage of more than two unformed stools in 24 hours without any other symptoms. Mild disease relates to the passage of one or two unformed stools in 24 hours without the presence of other symptoms. Patients commonly present with low-grade fever, abdominal cramping, and watery diarrhea. Traveler's diarrhea is typically a self-limited illness.

Diagnostic Testing

Diagnostic testing should be reserved for patients with severe or persistent symptoms. Stool cultures are rarely necessary. Cultures are mainly sent to confirm outbreaks. If stool cultures are sent, testing should specifically look for enterotoxigenic *E. coli, Shigella*, *Campylobacter,* and norovirus. If the enteritis is chronic (>2 weeks in duration), associated with foul-smelling and excessive flatulence, the stool should be examined for *Giardia*.[21]

Management

The best strategy regarding traveler's diarrhea is prevention. Travelers should avoid eating dairy products, raw fruits and vegetables, or undercooked meat and seafood. Peeled fruits are generally safe. Individuals should use water that has been boiled, which is the most reliable method to make the water safe for consumption. Travelers should also avoid ice and food served at room temperature. Table 84.10 lists preventive medications and treatment of traveler's diarrhea.

The risk of traveler's diarrhea can be reduced by more than 90% with the use of prophylactic antibiotics. However, due to the development of adverse side effects and resistance, prophylaxis is recommended only for individuals with comorbidities that place them at high risk for complications of diarrhea (eg, renal failure patients, patients with inflammatory bowel disease, or patients with ileostomies or colostomies). Prophylactic antibiotics should not be given for more than 2 to 3 weeks.[22]

The risk of developing traveler's diarrhea is also reduced by the use of alcohol-based hand sanitizers (containing >60% alcohol) and meticulous hand hygiene. The antacid bismuth subsalicylate decreases the incidence of traveler's diarrhea by 65% due to its antibacterial and antisecretory effects. The recommended dose is two tablets qid or 1 fluid ounce qid. Bismuth subsalicylate should be avoided in those who are allergic to aspirin because it contains salicylate. Potential side effects include blackening of the tongue and stool. It should not be taken for more than 3 weeks.[23]

Loperamide, an opioid antimotility drug, can decrease the frequency of loose stools. In patients with fever or bloody stools, an antimotility agent should be given in combination with an antibiotic because it may increase the contact time of the toxin or invasive infectious agents with the intestinal mucosa. Children younger than 2 years should not receive loperamide because it is linked with rare reports of paralytic ileus associated with abdominal distention.

The mainstay of treatment for traveler's diarrhea is hydration. Antibiotics such as quinolones, azithromycin, and rifaximin and antimotility agents can be prescribed, when indicated (see Table 84.8). The decision to initiate treatment for traveler's diarrhea is based on the initial amount of diarrhea, severity of associated signs and symptoms, and need for resolution of the diarrhea in regard to the patients' travel plans. Commercially available oral rehydration packets can be used by travelers to maintain their fluid status. In patients with mild symptoms, described as having one to three loose stools/24 hours, with or without mild enteric symptoms, loperamide can be used to decrease the number of loose stools. Bismuth subsalicylate can also be taken to control nausea. Promethazine, an antihistamine, can be given in oral or suppository form for severe nausea and vomiting.

In patients with moderate to severe traveler's diarrhea, antibiotics can shorten the duration of disease by 1.5 days. The choice of antibiotic is based on the location of the traveler. A fluoroquinolone such as ciprofloxacin is the antibiotic of choice

for most geographic locations. It can be given as 750-mg oral single-dose therapy or as a 3-day course. Azithromycin, 500 mg PO daily for 3 days, is the drug of choice to treat *Campylobacter*, which is a common cause in Southeast Asia. Rifaximin, 200 mg PO tid for 3 days is an alternate antibiotic that can be prescribed for patients with noninvasive illness. It is not effective against invasive pathogens such as *Campylobacter*, *Salmonella,* and *Shigella* spp.[24]

Gastroenteritis in the Immunocompromised Host With HIV/AIDS

The evaluation of gastroenteritis in HIV-positive patients deserves special attention because these patients are at risk for opportunistic enteric infections and are more likely to develop chronic gastroenteritis. In addition to the regular enteropathic bacterial pathogens, HIV-positive patients, particularly those with a CD4+ count less than 200/mm^3, are more susceptible to certain viruses and parasites, such cytomegalovirus (CMV), *Cyclospora, Cryptosporidium, Isospora, Mycobacterium avium-intracellulare* complex (MAI), and *Giardia*. HIV itself may also cause diarrheal illness. Although not precisely clear, it is thought that HIV may cause a direct infection of the enterocytes and invasion of the lymphoid tissues of the GI tract. Patients with an extremely low CD4+ count, less than 100/mm^3, typically tend to have opportunistic infections that are chronic in nature.[25]

Clinical Features

The history should ascertain treatment with highly active antiretroviral therapy (HAART), the CD4+ count and viral load. A history of previous enteric pathogen-related diarrheal illness is important because recurrence rates are common. Anal receptive intercourse may predispose the patient to colonic pathogens, such as *Giardia, Entamoeba,* CMV, *Shigella,* and *Campylobacter*.

Antiviral therapy–induced diarrhea has been also known to be the cause of watery diarrhea in HIV-positive patients. In HAART-naïve populations, *Cryptosporidium* and CMV infections are the two most common causes. Chronic high-volume watery diarrhea often is indicative of small bowel disease from one of the coccidia, *Cryptosporidium* and *Cystoisospora belli*. Although self-limited in the healthy host, coccidial disease often is persistent in patients with CD4+ counts less than 200/mm^3. CMV and MAI also produce a chronic illness in those with CD4+ counts less than 100/mm^3.

Fever, weight loss, and abdominal pain are prominent; diarrhea is mild to moderate and sometimes bloody, typical of colonic disease. Microsporidia have emerged as a common cause of diarrhea in patients with AIDS in whom the CD4+ count is less than 100/mm^3. *Salmonella* infections, especially with *S. typhimurium,* are common in immunocompromised hosts. Patients with AIDS who acquire *Salmonella* enteritis are at increased risk for bacteremia and metastatic focal infection compared with normal hosts. *C. difficile* enteritis occurs more commonly in patients with AIDS owing to the common use of prophylactic antibiotic therapy and frequent hospitalizations. It is the most common bacterial enteritis in the AIDS population.

Diagnostic Testing

In patients with AIDS, the presenting signs and symptoms generally do not allow consistent classification of diarrheal illness, as is done for the immunocompetent host, because many patients with AIDS have multiple, concomitant enteric pathogens. However, some clinical pictures are typical. Patients with a fulminating clinical course usually have a disseminated infection, such as infection with CMV or MAI complex. Massive weight loss is also associated with diarrhea caused by infection with those two organisms and the coccidia *Cryptosporidium* and *Cystoisospora.* Voluminous watery diarrhea usually is a result of one of the coccidial organisms, including *Cyclospora* and *Isospora*. Patients with a proctocolitis-like picture most often have herpes simplex virus or CMV infection.

Laboratory testing should initially focus on testing stool samples for *C. difficile* toxins and other bacteria, specifically *Salmonella*. If the stool is bloody and the CD4+ count is less than 200/mm^3, stool should be sent for CMV and MAI testing. If the diarrhea is present for more than 14 days, three stool samples for stool ova and parasites should also be sent. An acid-fast smear should be requested to look for *Cryptosporidium, Cystoisospora, Isospora,* and *Cyclospora i*f suspected as described.

If the patient has suspected infectious colitis but recent stool analyses have been negative for any organism, an inpatient flexible sigmoidoscopy may be performed to enhance the yield of a pathogen. Small bowel biopsy and duodenal aspiration may be indicated when stool examination, cultures, and sigmoidoscopy fail to yield a definitive diagnosis. Small bowel studies are most helpful for detecting infection with *Cryptosporidium,* CMV, MAI, *Giardia*, or *C. belli.* Small bowel enterocolitis generally presents with watery diarrhea without fever or fecal leukocytes.[26]

Management

Treatment should be directed toward the presumptive causative organism. As for immunocompetent patients, a cautious approach to initiating any antibiotic is suggested. Empirical antibiotic treatment should be started if the patient has fever, bloody stool, appears ill, or has a low CD4+ count. Ciprofloxacin, 500 mg PO, may be empirically initiated while the evaluation is in progress. If *Giardia* or *C. difficile* is suspected, metronidazole, 500 mg PO, should be added. If CMV colitis is suspected, foscarnet, 90 mg/kg IV, should be given. See Tables 84.3, 84.4, and 84.5 for treatment of specific organisms.

Treatment failure is common and is often due to incorrect initial therapy. For example, CMV colitis can also mimic invasive bacterial pathogens because it can also cause severe colitis with bloody stool, fever, and abdominal cramps. Treatment failures are also due to the propensity for infections to recur or become chronic. Parasitic infections in immunocompromised patients may be difficult to eradicate, even with correct treatment.

Gastroenteritis in the HIV-positive patient is often complex, prolonged in duration, and difficult to treat. It is recommended that an infectious disease specialist be involved in the care of these patients. Patients who have AIDS or are immunocompromised should generally be admitted for further management.

KEY CONCEPTS

- Gastroenteritis is usually self-limited and requires supportive care only.
- Routine laboratory testing or stool cultures are not indicated for most patients.
- Caution should be used in the care of the very old and young. They have the highest morbidity and mortality in gastroenteritis.
- Hand hygiene with soap and water or hand sanitizers will contain the spread of most infectious agents in gastroenteritis.
- Patients with fever, dysentery, bloody stools, severe dehydration, a suspicion for *C. difficile,* or immunocompromised state should have a complete blood count, electrolytes, and stool cultures sent.

KEY CONCEPTS—cont'd

- Use of oral rehydration therapy (ORT) for dehydration is a preferred management strategy.
- Hypotonic oral rehydration solution is preferred (eg, WHO-modified ORT solution).
- The use of antiemetic medications may help with ORT. Odansetron, 4 mg IV or IM, is safe and cost-effective.
- Early realimentation with normal feeding is advised and continuation of breast-feeding is suggested, if possible.
- *Campylobacter* is the most common cause of bacterial enteritis in developed countries.
- The norovirus, previously referred to as the Norwalk-like virus, is the most common cause of acute gastroenteritis in children and adults and usually occurs in the winter months.
- Bacterial pathogens cause approximately 80% of cases for traveler's diarrhea; enterotoxigenic *Escherichia coli* (ETEC) is the most common cause.
- In patients with fever or bloody stools, an antimotility agent should be given in combination with an antibiotic because it may increase the contact time of the toxin or invasive infectious agents with the intestinal mucosa.
- Classic food poisoning manifests usually 1 to 6 hours after the ingestion of preformed toxins from bacterial organisms such *Staphylococcus*, *B. cereus*, or *C. perfringens*.
- Food poisoning is generally short-lived (24 hours), and its treatment is generally supportive care only.
- Risk factors for *C. difficile* colitis include recent antibiotic use (1–4 weeks), recent hospitalization, living in a long-term care facility, and use of antacids.
- Evaluation (colonoscopy) for toxic megacolon and pseudomembranous colitis is recommended for patients with *C. difficile* colitis who are older, have a high leukocytosis finding, appear septic, and have a tender distended abdomen. Consider empirical antibiotic treatment for suspected *C. difficile* (metronidazole, 500 mg tid for 10 days) or traveler's diarrhea (ciprofloxacin, 500 mg twice daily for 1–3 days).
- Scombroid poisoning results from eating spoiled dark meat fish; it is not an allergic reaction but results from an ingestion of histamine.
- In addition to the regular enteropathic bacterial pathogens, HIV-positive patients, particularly those with a CD4+ count $<200/mm^3$, are more susceptible to certain viruses and parasites, such as cytomegalovirus, *Cyclospora, Cryptosporidium, Isospora, Mycobacterium avium-intracellulare* complex, and *Giardia.*
- In HIV-positive patients with persistent diarrhea, a small bowel biopsy and duodenal aspiration may be indicated when stool examination, cultures, and sigmoidoscopy fail to yield a definitive diagnosis.
- Consider *Giardia* for diarrhea lasting more than 2 weeks, with foul-smelling stools and symptoms of flatulence, abdominal bloating, cramping, and recent exposure to contaminated river water.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 84: QUESTIONS & ANSWERS

84.1. What is the recommended rehydration therapy for uncomplicated gastroenteritis with moderate dehydration?

A. IV hydration with D_5 half-normal saline
B. IV hydration with normal saline
C. Oral rehydration therapy with high-osmolarity fluids
D. Oral rehydration therapy with reduced-osmolarity fluids
E. Oral hydration with plain water

Answer: D. WHO recommends oral rehydration therapy with reduced-osmolarity fluids.

84.2. What is the most common documented cause of bacterial enteritis in developed countries?

A. *Campylobacter*
B. *Escherichia coli*
C. *Giardia*
D. *Salmonella*
E. *Shigella*

Answer: A. Most infections are acquired by eating raw or undercooked poultry meat. Symptoms of anorexia, malaise, myalgias, and headache are common, as are backaches and vomiting. Diarrhea lags 1 or 2 days after the constitutional symptoms. The syndrome can mimic appendicitis. Antibiotics are rarely needed in healthy patients. Azithromycin is first-line treatment if antibiotics are indicated.

84.3. Of the following choices, which is the correct association?

A. *Yersinia*—mesenteric adenitis, pseudoappendicitis
B. *Shigella*—poultry
C. *Salmonella*—warm marine environment
D. *Campylobacter*—sickle cell anemia
E. *Vibrio*—public swimming pools

Answer: A. *Yersinia,* like *Campylobacter,* may mimic acute appendicitis. The other correct associations would be *Shigella*—public swimming pools, *Salmonella*—sickle cell anemia, *Campylobacter*—poultry, and *Vibrio*—warm marine water.

84.4. A 14-year-old boy presents with watery diarrhea that progresses to bloody diarrhea over 4 to 6 hours. He has also had moderate vomiting and significant abdominal cramping, but no other systemic symptoms. He is afebrile with a normal examination, except for diffuse, moderate abdominal tenderness to deep palpation and blood-streaked loose stool on digital rectal examination. Laboratory evaluation shows a mild leukocytosis, and the stool smear shows 12 fecal leukocytes/hpf (high-power field). Which of the following is true?

A. Articular and ophthalmologic findings would be typical.
B. Ciprofloxacin is the drug of choice.
C. Endoscopy and biopsy would be the diagnostic tests of choice.
D. He is at risk of late neurologic sequelae.
E. There is likely a recent history of eating undercooked eggs.

Answer: D. This patient is most likely infected with enterohemorrhagic (Shiga toxin) *Escherichia coli,* which often results from eating undercooked hamburger. Watery diarrhea that becomes bloody with significant abdominal pain is typical. The diarrhea may be grossly bloody and mimic inflammatory bowel disease or intestinal ischemia. Stool cultures with specific techniques for *E. coli* are the test of choice. Toxin assays are also recommended. Endoscopic findings would be identical to those of any other severe colitis. Antibiotics are not effective and may increase the risk of hemolytic uremic syndrome in children. Thrombotic thrombocytopenic purpura (TTP) is a risk in older children and adults.

84.5. A 21-year-old man presents with acute onset of vomiting and retching 2 hours after eating at a restaurant. He also reports two loose stools. He is afebrile, with an unremarkable examination, except for his nausea and retching. What would be the treatment of choice?
A. Antitoxin
B. Erythromycin
C. Fluids and antiemetics
D. Norfloxacin
E. Trimethoprim-sulfamethoxazole

Answer: C. Staphylococcal food poisoning presents in an acute and classic manner. Symptoms typically last 6 to 8 hours, and patients are often better before they decide to seek care. This is a toxin-mediated syndrome. Offending foods are usually eggs, potato salad, pastries, and mayonnaise. Only symptomatic treatment is necessary.

84.6. A 27-year-old man presents with severe abdominal cramping and diarrhea, with many frequent watery stools. He ate at a restaurant 12 hours before with two friends who have reported the same syndrome. There are no leukocytes or erythrocytes on stool examination. Which of the following statements is correct?
A. Antibiotics may shorten symptom duration.
B. Fever and vomiting are typical.
C. Freshly cooked food is the most likely cause
D. Ingestion of live organisms is not required for illness.
E. This syndrome is usually self-limited but can progress to shock and death in rare cases.

Answer: E. *Clostridium perfringens* is a common source of food-borne illness. Food cooked in advance, cooled, and rewarmed is a typical culprit. This is a toxin-mediated, diarrhea-predominant syndrome that is almost always self-limited. Ingestion of live organisms and/or spores is required, although antibiotics are of no benefit. Symptoms usually appear within 6 to 12 hours, slightly longer than for staphylococcal food poisoning. When huge numbers of organisms are ingested, a hemorrhagic necrotizing enteritis with prostration and shock can occur.

84.7. A 26-year-old woman presents with a complaint of burning pain of her hands and feet. She also reports diffuse aching of her teeth. All symptoms began gradually. They were preceded the day prior by two loose stools, but her review of systems is otherwise negative. She is healthy except for a past history of anxiety, for which she takes prn lorazepam. The physical examination and vital signs are remarkable for mild ataxia. Cutaneous temperature discrimination testing is intact but unpleasant. Which of the following is the intervention of choice?
A. IV thiamine, 100 mg
B. Magnetic resonance imaging (MRI) scan of the brain and lumbar puncture
C. Noncontrast CT scan of the brain
D. Psychiatric consultation
E. Reassurance and amitriptyline 25 mg at bedtime

Answer: E. Ciguatera fish poisoning is a toxin-mediated process in which gastrointestinal and neurologic symptoms (often bizarre) predominate. Cold allodynia and worsening of the dysesthesia with alcohol are diagnostic. Hyperventilation syndrome, gastroenteritis, and anxiety can be misdiagnosed.

84.8. A 31-year-old man with known AIDS presents with 2 weeks of profuse watery diarrhea. His only medication is trimethoprim-sulfamethoxazole bid. His last known CD4+ count was 120/mm^3. The physical examination was remarkable for oral thrush and mild cachexia. He has continued to tolerate a regular diet, and his level of dehydration is minimal. What is the most appropriate intervention?
A. Acute IV hydration, then discharge on antimotility agents
B. Admission for serial cultures and possible endoscopy
C. Combined course of ciprofloxacin and ganciclovir
D. Initiation of highly active antiviral therapy (HAART)
E. Lactose-free and low-fat dietary modifications

Answer: B. In cases of AIDS diarrhea, one or more enteric pathogens are found in 80% of cases. Serial stool cultures, blood cultures, and sometimes endoscopy are needed to identify the organisms and develop a treatment plan. HAART is also indicated, but not as a sole intervention. AIDS diarrhea is rarely self-limited with CD4+ counts less than 300/mm^3. The most common responsible organisms are *Cytomegalovirus* and C*ryptosporidium.*

84.9. An 18-month-old child presents with 2 days of copious diarrhea that was preceded by 1 day of vomiting. The past history is otherwise negative except for treatment with amoxicillin for an inner ear infection 4 weeks prior. The child is moderately dehydrated by clinical examination, and there is no abdominal tenderness. The WBC count is normal. What is the most likely diagnosis?
A. Antibiotic-associated diarrhea
B. *Clostridium difficile* poisoning
C. Norovirus
D. Staphylococcal food poisoning

Answer: C. Winter month gastroenteritis in young children is commonly norovirus, especially with the widespread use of the rotavirus vaccine. Vomiting is prominent early but rarely presents after 36 hours. There is rarely abdominal pain, fever, or leukocytosis. The diarrhea lasts 4 to 7 days and is often followed by steatorrhea. *C. difficile* may commonly present 3 or 4 weeks after antibiotic use, but vomiting is rare. Antibiotic-associated diarrhea is mild and usually occurs during the course of antibiotics.

84.10. A 28-year-old man presents with 2 weeks of watery, foul-smelling diarrhea and flatulence. He recently returned from a camping trip in which he participated in water rafting on a river. On examination, he appears nontoxic and afebrile, and the abdominal examination shows only diffuse cramping and bloating. What is the mostly likely causative organism?
A. Enterotoxin-producing *Escherichia coli* (ETEC)
B. *Giardia*
C. Rotavirus
D. *Salmonella*
E. *Vibrio parahaemolyticus*

Answer: B. *Giardia.* Giardiasis is commonly acquired from the ingestion of contaminated water, typically a camper who has ingested river water. The symptoms include diarrhea, abdominal cramping, and bloating, with foul-smelling stools. The treatment is metronidazole, 500 mg PO bid.

CHAPTER 85

Disorders of the Large Intestine

Michael A. Peterson | Andrea W. Wu

IRRITABLE BOWEL SYNDROME

Principles

Irritable bowel syndrome (IBS) is a chronic, non–life-threatening disorder characterized by abdominal pain and alteration in bowel habits. IBS is an extremely common disorder; estimates put the prevalence in the North American population at 10% to 15%, with women affected twice as often as men. IBS accounts for more than 10% of all visits to primary care physicians and more than 25% of all visits to gastroenterologists. IBS is said to contribute more impairment to quality of life than diabetes or renal failure, although it has no demonstrated long-term mortality consequence.

No specific physical or laboratory abnormalities defining IBS have been identified. It is a functional somatic syndrome that is diagnosed by clinical criteria in the absence of alarm symptoms and findings that suggest other, more urgent diagnoses. Diagnosing IBS is problematic in the emergency department (ED; typically, patients are discharged with a diagnosis of "abdominal pain of unclear cause" or the equivalent.

Although the cause of IBS is unknown, it is associated with several pathophysiologic findings suggesting a disorder of altered gut motility, gut sensation, and perception of intestinal activity.[1] Physiologic testing has since shown that patients with IBS have disturbances in the rhythmic pattern of electrical activity in the intestine and in how the intestine responds to stimulation. Recently, markers of chronic inflammation and altered bowel flora have been found in intestinal tissue of IBS patients, although their significance is not yet known.

Psychiatric conditions often coexist with IBS, ranging from generalized anxiety disorder to major depression. Other associations are fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, and history of previous sexual abuse.[2] In women, symptoms often are related to the menstrual cycle, suggesting a hormonal influence.

Clinical Features

The diagnosis of IBS is defined by clinical criteria in a patient whose symptoms have no other organic explanation. The Rome III criteria (Box 85.1) are often considered as the diagnostic standard, although some practicing gastroenterologists believe these to be inadequate because they do not include one of the most common symptoms, bloating.[3]

Patients with IBS experience symptoms intermittently, with the typical patient averaging symptoms on 1 of every 3 days. Complaints include abdominal pain, bloating, and constipation or diarrhea. Pain typically is relieved with defecation; pain that persists suggests another diagnosis. A mucoid discharge from the rectum often accompanies diarrhea. Upper gastrointestinal symptoms such as nausea and dyspepsia can also occur. The physical examination may reveal mild focal abdominal tenderness, which can vary in location, or diffuse tenderness. Constipation (IBS-C), diarrhea (IBS-D), or a mixture of the two (IBS-M) may occur.[2]

Pain that is progressive or associated with anorexia or significant abdominal tenderness suggests an alternate diagnosis. Signs and symptoms that point away from the diagnosis of IBS (alarm symptoms) include onset of symptoms after the age of 50 years, unintentional weight loss, anorexia, bloody stools, nocturnal diarrhea, or family history of significant colon disease.[2] In the absence of symptoms suggesting another diagnosis, the clinical criteria have a specificity ranging from 87% to 100%, although the sensitivity may be only 60%. In patients determined to have IBS through correct use of the clinical criteria, follow-up evaluation over many years rarely leads to a change in the diagnosis.[2]

A final diagnosis of IBS usually is made in the primary care setting and not in the ED. The ED evaluation seeks to exclude other, more urgent causes for the patient's symptoms.

Differential Diagnosis

The differential diagnosis of symptomatic IBS depends on the predominant symptoms and includes a host of disorders (Box 85.2). An assessment for pancreatitis, hepatitis, biliary colic, or urologic disorders, including urolithiasis, may be appropriate, as indicated by the pattern of the presenting complaints.

Diagnostic Testing

No specific testing should be done in the ED on individuals who fit the pattern of IBS.

Management

Not all patients with IBS require treatment; therapy should be initiated only if symptoms diminish the quality of life. Diet, behavioral, and pharmacologic therapies are all used in IBS. The specific therapy will be determined by the type of IBS—IBS-C, IBS-D, or IBS-M. Dietary suggestions include a low-fat diet, reduced nondigestible sugars, and avoidance of gas-forming foods, although none of these has any proven benefit. Although the data are mixed, the most recent evidence has suggested that fiber supplementation may aid IBS-C.[1]

Medications with antispasmodic activity (eg, dicyclomine, 20–40 mg four times daily) are used for abdominal cramping, and peripherally acting narcotics, such as loperamide (4 mg orally as an initial dose, followed by 2 mg for subsequent doses), are used to reduce diarrhea. Antibiotics such as rifaximin (550 mg, tid for 14 days) have been shown to reduce symptoms. Osmotic laxatives such as lactulose may be helpful in constipation. Tricyclic antidepressants and selective serotonin reuptake inhibitors have been effective for certain classes of patients with IBS. Evidence has suggested that peppermint oil and probiotics may be of limited use.[4] Nonsteroidal antiinflammatory drugs (NSAIDs) may worsen symptoms.

Disposition

IBS is not a life-threatening disease and can be managed on an outpatient basis as long as other disorders have been excluded.

BOX 85.1

Rome III Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain or discomfort at least 3 days/mo in the previous 3 mo associated with two or more of the following:
1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

From Kahn S, Chang L: Diagnosis and management of IBS. Nat Rev Gastroenterol Hepatol 7:565–581, 2010.

BOX 85.2

Differential Diagnosis in Irritable Bowel Syndrome

CONSTIPATION—PREDOMINANT
Bowel obstruction
Cancer
Adult-onset Hirschsprung's disease
Rectocele
Paradoxical closure of the anus during defecation

DIARRHEA—PREDOMINANT
Bacterial or parasitic intestinal infection
Inflammatory bowel disease
Lactose intolerance
Malabsorption
Radiation proctocolitis
Celiac disease

PAINFUL
Inflammatory bowel disease
Ureteral colic
Bowel obstruction
Diverticular disease
Gastroesophageal reflux or ulcer
Liver or pancreatic disease
Lead toxicity
Porphyria

The search for optimal therapy usually involves empirical trials until the correct fit is found. The disorder is chronic but, with appropriate therapy, many patients experience significant improvement in their quality of life.

DIVERTICULAR DISEASE

Principles

Diverticular disease is an affliction of middle age and Western civilization that appears to be increasing in incidence for reasons that are unclear. Diverticular disease was virtually unknown in the West before the 20th century and is still rare in other cultures. It is estimated that 5% to 10% of people older than 45 years and 80% of people older than 85 years have diverticula. Diverticula are less common in people younger than 40 years, representing only approximately 2% to 5% of all patients with the disease. The proliferation of this disease was coincident with the invention and widespread use of the flour rolling mill, which removes the fiber-containing outer part of the wheat kernel. This coincidence has prompted the labeling of diverticulosis as a modern deficiency disease, although the relationship between decreased fiber intake and diverticulosis has recently been questioned.[5] In rural Africa and Asia, where the diet is high in fiber, diverticular disease is virtually unknown.

Diverticulosis denotes the presence of diverticula in the colon. Most patients with this condition are asymptomatic. Diverticulitis denotes inflammation of diverticular tissue, which is usually painful. It is estimated that 10% to 25% of patients with diverticulosis will develop diverticulitis.[6] Complicated diverticulitis is defined by the presence of more extensive disease, including abscess formation, peritonitis, intestinal obstruction, and fistula formation.

The wall of the colon is penetrated at regular intervals by blood vessels, collectively known as the vasa recta, that supply the internal intestinal layers. The site of vessel penetration is apparently the weakest part of the colon wall because it is at these sites that diverticula form. Although the exact pathogenic mechanism is unknown, one theory is that diverticula form in response to increased intracolonic pressures generated when the colon is processing smaller, non–fiber-containing stools. Recent experimental evidence has suggested that chronic inflammation and an alteration in bowel flora may also play a role.

Patients with diverticular disease exhibit normal resting colonic pressure but higher peak pressure than those without diverticular disease[6]; higher peak pressures lead to a herniation of colonic mucosa through the intestinal wall at the vasa recta, creating small, saclike appendages. These appendages (diverticula) typically measure 5 to 10 mm in diameter but, on rare occasions, can grow into huge sacs measuring many centimeters across (giant colonic diverticula). Diverticula are generally asymptomatic. Symptoms develop when inflammation sets in and microperforations of the sac develop, resulting in inflammation of pericolonic structures and abdominal pain.

Classically, it was thought that the diverticular sac was obstructed, leading to stasis and infection, despite the lack of evidence of obstruction in pathologic specimens. Recently, it has been shown that the course of diverticulitis is not influenced by antibiotic therapy but is affected by antiinflammatory agents. Tissue specimens also show markers of chronic inflammation, similar to those found in inflammatory bowel disease.

In uncomplicated diverticulitis, only the pericolonic fat is inflamed. With time, a phlegmon, abscess, or gross perforation may develop. Any extension of disease beyond the pericolonic fat is defined as complicated diverticulitis. The involved colonic segment may fistulize to any adjacent organ, usually the bladder. Adjacent bowel may become obstructed by mass effect from an abscess or may incur an inflammatory ileus. Recurrent episodes can lead to strictures and subsequent colonic obstruction.

Diverticula can also bleed. Severe hemorrhage occurs in 3% to 5% of all patients with diverticulosis and accounts for approximately 40% of all cases of lower gastrointestinal hemorrhage. Bleeding notably occurs in the absence of inflammation and typically is painless. NSAID use is associated with this complication.

Clinical Features

Diverticulosis

Although approximately 75% remain asymptomatic throughout their lifetime, patients with diverticulosis sometimes have chronic nonspecific abdominal complaints, including bloating, crampy pain, excessive gas, and a change in bowel habits. Diverticulitis will develop in approximately 10% to 30% of patients with diverticulosis.

Diverticulitis

Because most diverticula found in persons in the West form in the left colon (in Japan, the right colon predominates), the typical

presentation of diverticulitis is persistent left lower quadrant pain and tenderness. Pain may begin in the hypogastrium before localizing to the left lower quadrant. Referred pain may occur in the penis, scrotum, or suprapubic region. Right-sided diverticulitis may manifest as right lower quadrant pain and is impossible to distinguish clinically from appendicitis. Additional findings suggest various complications—diffuse tenderness is associated with gross perforation or abscess rupture; dysuria is associated with a colovesical fistula; mass is associated with an abscess; and vomiting or abdominal distention is associated with intestinal obstruction. Fecal matter or gas emanating from the vagina suggests a colovaginal fistula. Almost any adjacent organ can be involved in the inflammatory process. Patients recently diagnosed with diverticulitis who are being treated on an outpatient basis with oral antibiotics and who visit the ED with continuing or worsening symptoms should be evaluated for the possibility of an abscess.

Special care must be taken with older patients or immunocompromised patients because clinical signs and symptoms are much less dramatic, even with more severe disease. Perforation is more common in these patients (up to 40%), manifests with less significant findings, and carries a high mortality rate.[6]

Differential Diagnosis

A tentative diagnosis of diverticulitis may be based on clinical grounds alone; however, the differential diagnosis should include colonic carcinoma, although it is usually safe to wait until after the acute episode has resolved to investigate this possibility. Additional diagnoses to consider include colitis (inflammatory or ischemic), ureteral stones, inguinal hernia, and pelvic pathology, including ectopic pregnancy or pelvic inflammatory disease, and ovarian pathology, with or without ovarian torsion. Appendicitis should be suspected when symptoms are predominantly right-sided. Diffuse abdominal pain should prompt an evaluation for other life-threatening problems, including leaking abdominal aortic aneurysm, peritonitis, hemoperitoneum from ectopic pregnancy, and bowel obstruction.

Diagnostic Testing

Uncomplicated Diverticulitis

A clinical diagnosis of uncomplicated diverticulitis can be made in a patient in the appropriate age range who is exhibiting focal left lower quadrant pain and tenderness in the absence of symptoms or signs that suggest an alternative diagnosis. No mass or peritoneal irritation should be encountered on examination, and the patient should otherwise appear well. If the patient fits this clinical picture, treatment can be initiated on an empirical basis. No laboratory tests or diagnostic imaging is required. Ancillary tests are performed primarily to exclude alternative diagnoses. When the diagnosis is unclear, studies to exclude gynecologic, renal, hepatic, biliary, or pancreatic disease may be indicated, depending on the patient's presentation and degree of distress. Computed tomography (CT) of the abdomen should be considered for older patients and immunocompromised patients to exclude the possibility of a subtle presentation of complicated diverticulitis.

Complicated Diverticulitis

Abdominal Computed Tomography. Abdominal CT, with oral and/or colonic contrast (American College of Radiologists [ACR] appropriateness score = 9) or without contrast (ACR appropriateness score = 6), is the preferred method of evaluation of complicated diverticulitis. CT has the advantage of evaluating the colon and the structures around it, so it can facilitate the diagnosis of diverticulitis and simultaneously evaluate the extent of disease. Findings on CT consistent with diverticulitis include the presence of diverticula, inflammation of pericolonic fat, thickening of the bowel wall to more than 4 mm, free abdominal air, and abscesses (Fig 85.1). CT also can help make an alternative diagnosis when diverticulitis is absent. Sensitivity and specificity for diverticulitis range from 69% to 95% and from 75% to 100%, respectively. Marked bowel wall thickening associated with diverticulitis looks like cancer; contrast enema or endoscopy may be required to differentiate the two.

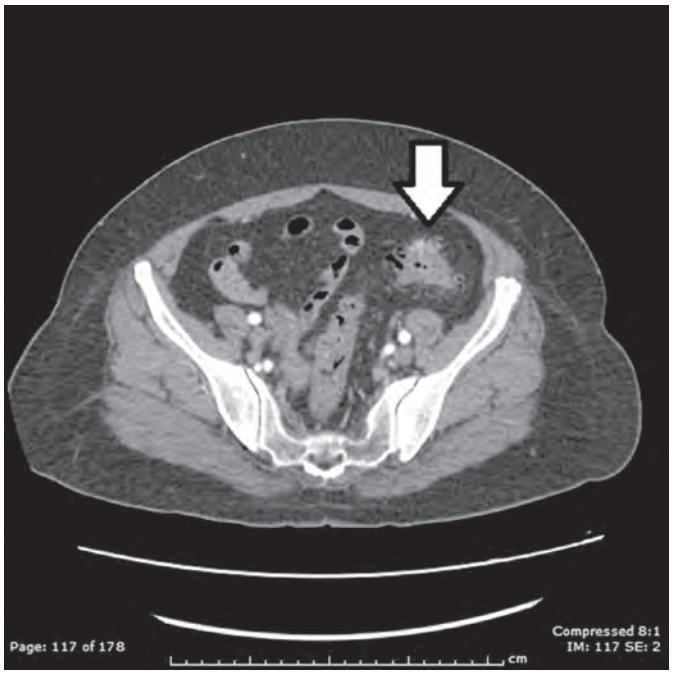

Fig. 85.1. Uncomplicated diverticulitis *(arrow)* showing multiple air-filled structures lining the edge of the left colon (diverticuli), and hazy outer border of bowel segment (fat-stranding) indicative of inflammation.

Barium Enema. Although asymptomatic diverticuli do not typically require investigation, a double-contrast barium examination with plain radiography can be used if imaging is desired. Barium should, however, be avoided in the setting of diverticulitis. The potential for preexisting occult perforation and subsequent risk of barium peritonitis limits its usefulness.

Water-Soluble Contrast Enema. Although now rarely used, a plain radiography, water-soluble contrast enema is the preferred method of imaging if a plain radiography study is needed in the acute setting. Because contrast material usually collects only in the intestinal lumen, plain radiography contrast enemas provide less information than CT about the extent of disease outside of the colon.

Ultrasonography. An ultrasound examination can detect various pathologic features characteristic of diverticulitis, including fluid collections around the colon, thickened hypoechoic bowel wall, and hyperechoicity adjacent to the bowel wall that suggests pericolonic inflammation. Diverticula can occasionally be visualized by ultrasound examination. As is often the case, the sensitivity of ultrasound imaging for these findings varies significantly with the experience of the operator. Currently, the role for ultrasonography in the evaluation of diverticulitis is not well defined.

Colonoscopy. Colonoscopy is limited in the acute setting by its more invasive nature, risk of perforation, and logistics of arranging this procedure emergently.

Plain Radiography Without Contrast. Plain radiographs of the abdomen are not likely to be helpful in the diagnosis of diverticulitis unless intestinal obstruction or perforation is suspected.

Management

Diverticulosis

It is recommended that patients with diverticulosis be placed on a high-fiber diet to reduce abdominal symptoms. The formerly common advice—to avoid foods that may obstruct diverticula, such as nuts, small seeds, and popcorn—has been discredited.[6]

Uncomplicated Diverticulitis

Despite accumulating evidence that antibiotics may not provide benefit in the treatment of uncomplicated diverticulitis, enough controversy persists to recommend that they still be used. Uncomplicated diverticulitis in an immunocompetent, non–older patient can be managed on an outpatient basis with oral antibiotics covering gram-negative aerobic and anaerobic bacteria (Box 85.3). Patients may be placed on a liquid diet for comfort, although this is not mandatory. NSAIDs or narcotics are appropriate for pain control. Evidence supporting a high-fiber diet for prevention of recurrence after resolution of an acute episode is mixed.[7]

Patients with significant comorbid illness or other problems, including inability to tolerate oral liquids, poor social support, or inability to comply with follow-up in a reasonable time frame (2 to 3 days), should be considered for hospitalization. Hospitalized patients are generally treated with intravenous (IV) antibiotics (Box 85.4) and placed on bowel rest, although patients hospitalized for psychosocial reasons can be treated with oral medications.

BOX 85.3

Oral Antibiotic Therapy for Uncomplicated Diverticulitis[a]

- Trimethoprim-sulfamethoxazole, one double-strength tablet bid, *and* metronidazole, 500 mg q6h *or*
- Ciprofloxacin, 500 mg bid, *and* metronidazole, 500 mg q6h, *or*
- Amoxicillin-clavulanate, extended-release, 1000/62.5 mg, two tablets bid

[a]All oral regimens should be taken for 5 to 10 days.

BOX 85.4

Intravenous Antibiotic Coverage for Bowel Flora

MILD TO MODERATE INFECTION
- Ticarcillin-clavulanate, 3.1 g IV q6h, *or*
- Ciprofloxacin, 400 mg IV q12h, *and* metronidazole, 1 g IV q12h

SEVERE INFECTION
- Ampicillin, 2 g IV q6h, *and* metronidazole, 500 mg IV q6h (*and* gentamicin, 7 mg/kg q24h, *or* ciprofloxacin, 400 mg IV q12h)
- Imipenem, 500 mg IV q6h

Complicated Diverticulitis

Patients with complicated diverticulitis should be hospitalized and treated with IV antibiotics and bowel rest. Emergent surgical consultation is indicated for patients with peritonitis or perforation. Newer techniques that use a laparoscopic approach have supplanted open surgical techniques in some patients. Continuing clinical decline, sepsis resistant to medical management, or a high level of suspicion for carcinoma warrants urgent surgical consultation. Small abscesses may be treated with IV antibiotics alone (see Box 85.4), whereas larger abscesses are drained percutaneously or surgically. Bowel obstruction during an attack of diverticulitis is usually self-limited and resolves with conservative management. Chronic recurrent diverticulitis can result in strictures. Fistulae are usually repaired surgically but are typically not emergent.[6]

Definitive Management

It is not known whether medical or dietary treatment is of benefit in diverticulosis. The only proven way to eradicate diverticula is to remove the affected segment of colon surgically. Most patients who recover from their first attack of diverticulitis are likely to remain asymptomatic for many years. According to some experts, younger patients (ie, <40 years) should undergo elective resection after their first bout of diverticulitis because of concerns about a higher risk for a second attack, but this recommendation has been questioned by recent studies.[8] Most resections can be done laparoscopically with a single-stage procedure (no colostomy). Estimates on the recurrence of diverticular disease after resection vary, ranging from 3% to 27%, with up to 25% of patients continuing to have chronic intermittent pain, despite surgery.[9]

Disposition

Younger and immunocompetent patients with uncomplicated diverticulitis may be sent home on oral antibiotics with referral for follow-up evaluation in 2 to 3 days to determine the success of treatment. Approximately 90% of patients will have a successful resolution with this approach.[7] Patients not improved at follow-up should undergo diagnostic imaging to look for an abscess and should be hospitalized for IV antibiotic therapy. Of patients treated medically for their first attack of uncomplicated diverticulitis, 95% remain symptom-free for the next 2 years, and 80% to 90% remain symptom-free permanently. Although it was recommended in the past that all patients should undergo an evaluation for colon cancer when the acute episode has resolved because of the high incidence of coexistent cancer, recent evidence has suggested that this is not necessary.[10]

All patients with complicated diverticulitis require hospitalization for IV antibiotic therapy and bowel rest. Most patients (65%–85%) recover with medical management alone; the rest require surgical intervention. Outcomes generally are good, with mortality rates ranging from 1% to 6% for all patients, increasing to 12% to 18% for patients requiring surgery.

LARGE BOWEL OBSTRUCTION

Principles

Large bowel obstruction (LBO) is much less common than small bowel obstruction, but LBO is a more ominous condition because it is frequently associated with malignant disease. Of all operative cases involving LBO in the United States, 50% are the result of colorectal cancer, and up to 20% of patients with colon cancer will develop acute obstruction. Adhesions, a common cause of small bowel obstruction, cause only a small number of LBOs. Other

causes of LBO include volvulus, diverticular disease, fecal impaction, strictures (often related to inflammatory bowel disease or chronic colon ischemia), adhesions, hernias, and pseudo-obstruction. Most causes are managed surgically, but pseudo-obstruction responds well to medical management alone.

When mechanical obstruction is caused by an obstructing lesion, inside the bowel (carcinoma) or outside the bowel (diverticular abscess, volvulus), the bowel becomes increasingly dilated with air and fluid that cannot be passed distally. As the distention increases, intraluminal pressure increases. When intraluminal pressure approaches systolic blood pressure, blood flow to the bowel wall is compromised, and edema sets in, with subsequent transudation of fluid into the lumen. Transudation along with decreased reabsorption of intraluminal fluid leads to dehydration. Eventually, as arterial flow to the bowel wall is compromised, ischemia and gangrene develop. The translocation of bacteria from a compromised bowel can lead to sepsis. Perforation of the bowel wall follows if the process is not interrupted.

Pseudo-obstruction, also termed *Ogilvie's syndrome,* occurs through a completely different mechanism. Pseudo-obstruction is defined as LBO in which no obstructing lesion can be identified. This condition is usually found in patients with significant acute comorbid conditions. Patients typically have a history of spine or retroperitoneal trauma, severe electrolyte disturbances, or narcotic exposure. The mechanism is believed to involve malfunction of autonomic control of the bowel. The pathophysiologic changes observed with pseudo-obstruction are the same as those described for mechanical obstruction.

Clinical Features

The typical presenting complaints in LBO are abdominal pain, abdominal distention, obstipation, and vomiting. The time frame within which these symptoms develop varies in accordance with the rapidity of onset of the obstruction. LBO associated with a volvulus can develop rapidly, whereas obstruction from cancer tends to be gradual. Patients seen later in the course of obstruction may be significantly dehydrated. Fever or tachycardia should prompt an investigation for gangrene and perforation. A palpable abdominal mass may represent a tumor, abscess, or simply a distended bowel. A rectal examination is helpful to look for an obstructing rectal mass or large volume of hard stool in the rectal vault consistent with fecal impaction.

Differential Diagnosis

The most common causes of LBO are colorectal cancer (53%), volvulus (17%), diverticulitis (12%), and compression from metastatic disease (6%). Other, less common causes are strictures, incarcerated hernia, fecal impaction, adhesions, and pseudo-obstruction.

Diagnostic Testing

Laboratory Tests

Electrolyte measurements may be helpful in guiding fluid and electrolyte replacement therapy. An elevated white blood cell (WBC) count should raise suspicion for gangrenous bowel, whereas anemia suggests the possibility of colorectal cancer.

Imaging Studies

Plain Radiography. A distended colon is the hallmark of LBO (Fig. 85.2), although the small bowel may be distended as well if the ileocecal valve is incompetent. In some cases, a gas-filled

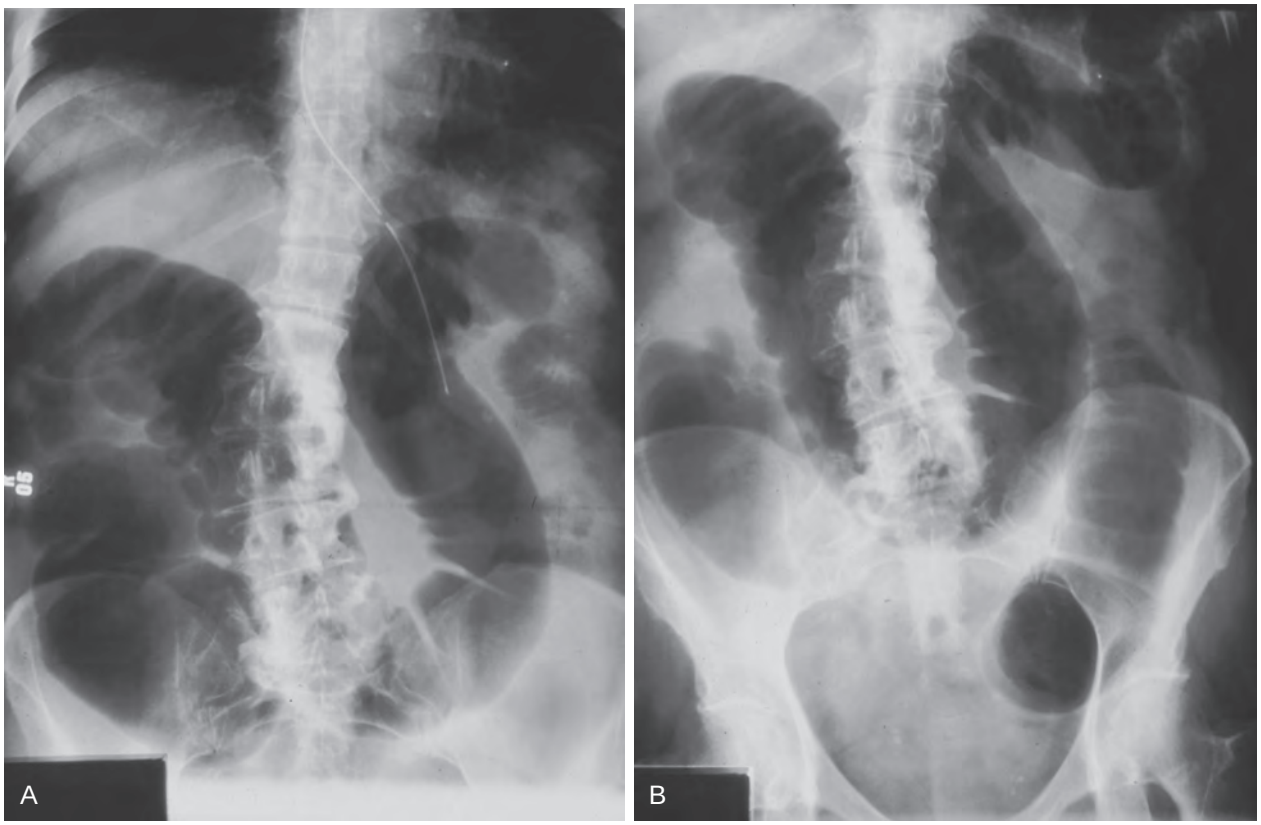

Fig. 85.2. Plain radiographs showing large bowel obstruction at the sigmoid colon caused by carcinoma. **A,** Upright view. **B,** Supine view.

small bowel may obscure visualization of the colon, leading to the misdiagnosis of small bowel obstruction. A cecal diameter exceeding 12 cm is associated with a higher risk of perforation, but perforation has been known to occur at smaller diameters.[11] The actual location and cause of the LBO are usually not evident on plain films.

Computed Tomography. CT is a valuable tool for determining the cause of the obstruction, especially if the cause is a diverticular abscess or intussusception. CT has the ability to locate the obstructing lesion in 96% of cases.[12] It typically is less helpful in pseudo-obstruction, in which colonoscopy or a water-soluble contrast enema study is needed to make the diagnosis.

Colonoscopy and Water-Soluble Contrast Enema. Patients in whom the cause of obstruction is not known and who are not candidates for urgent surgical intervention should undergo a water-soluble contrast enema study or colonoscopy to determine the cause of the obstruction. This diagnostic strategy is much more accurate in ruling out pseudo-obstruction than imaging.

Management

Management in the ED is directed at relief of symptoms. Rehydration, electrolyte replacement, and pain management are the first concerns. Gastric decompression with a nasogastric tube may be helpful in cases in which vomiting is prominent or when there is evidence of fluid or gas buildup in the small intestine; regardless, the patient should be kept NPO. Antibiotics are indicated if gangrene or perforation is suspected (see Box 85.4). Definitive management depends on the cause of the obstruction. Select diverticular abscesses may be drained percutaneously, whereas a sigmoid volvulus or pseudo-obstruction can be decompressed endoscopically. Diverticular disease and sigmoid volvulus eventually necessitate an elective surgical procedure to prevent recurrence, although this can often be delayed. Carcinoma, cecal volvulus, strictures, intussusception, adhesions, and hernias are primarily dealt with surgically. In malignant obstruction of the left colon, placement of a stent can be done palliatively or as a bridge to surgery.[11,13]

As long as the possibility of perforation is not an immediate concern, pseudo-obstruction is managed for the first 24 hours with bowel rest, hydration, and management of any acute comorbid conditions. If the colon fails to decompress, colonoscopic or pharmacologic intervention (eg, neostigmine) may be attempted, with surgery reserved for refractory cases.

Disposition

Most cases of LBO require procedural intervention (surgical, endoscopic, or percutaneous) to achieve resolution. All patients require hospitalization and consultation with a specialist capable of performing the appropriate procedure. Emergent surgical consultation is warranted for patients with evidence of gangrenous bowel or perforation.

VOLVULUS

Principles

Volvulus of the colon occurs when a loop of bowel twists and obstructs the intestinal lumen. Volvulus accounts for 1% to 7% of all LBOs.[14] Volvulus occurs in all age groups, but older adults (mean age, 60–70 years) are affected most often. One-third of cases in the developed world involve institutionalized patients.[14] Most cases are divided roughly equally between the sigmoid colon and cecum, although volvulus can occur in all other areas of the colon. Sigmoid volvulus typically is a disease of older adults. Mortality rates with sigmoid volvulus exceed 50% in patients with gangrenous bowel. In the absence of gangrenous bowel, the risk of death is less than 5%.[14]

Sigmoid Volvulus

The anatomic requirement for a sigmoid volvulus is a long redundant section of sigmoid that is attached to the abdominal wall by a narrow strip of mesentery. The narrow attachment allows the mesentery to twist on itself, thereby obstructing the intestinal lumen. After the colon twists on itself, the proximal colon continues to force gas and liquid into the obstructed segment, causing a sometimes massive dilation of the distal colon. Electrolyte disturbances can occur secondary to third spacing, and respiratory compromise occasionally occurs from massive abdominal distention. If the condition is left untreated, the vascular supply can become compromised, resulting in gangrene and perforation. In one series, approximately 10% of patients developed gangrene of the affected segment.

The exact precipitator of an acute episode of volvulus is not clear. A high-fiber diet has been implicated. Chronic constipation has been associated with volvulus, but it is unclear how the two conditions are related. Residents of long-term care facilities and patients with neurologic or psychiatric disease are predisposed to sigmoid volvulus, possibly as a result of alterations in colonic motility. No association with previous surgery has been observed.

Cecal Volvulus

As in sigmoid volvulus, a mobile segment of cecum is a prerequisite to the disease. This mobility seems to be a result of a congenitally incomplete fusion of the cecal mesentery to the posterior abdominal wall. Cadaver studies have shown that 11% to 25% of the adult population have ceca that are mobile enough to cause torsion. Despite these findings, sigmoid volvulus is relatively rare, implying that another coexisting factor such as trauma, adhesions, or malignancy must be present.[15] The tendency for cecal volvulus may be related to maneuvering room available for the colon within the abdomen. Women seem to be at a higher risk for cecal volvulus during pregnancy, presumably because of crowding of the abdominal cavity by the enlarged uterus. Even in pregnancy the condition is still rare, occurring in approximately one per million pregnancies. Gangrene of the bowel is common with cecal volvulus, occurring in 20% of patients.

Clinical Features

Sigmoid Volvulus

The hallmark of sigmoid volvulus is the triad of abdominal pain, distention, and constipation. The extent to which the sigmoid colon can twist on itself varies, so the presentation can vary from subtle to dramatic. The clinical picture may range from one of minor abdominal discomfort that has been present for many days to an acute onset of severe abdominal pain associated with gross abdominal distention and unstable vital signs. Sometimes, the diagnosis of sigmoid volvulus is not made until the patient has been hospitalized for some time, up to an average of 3 or 4 days between symptom onset and diagnosis in some studies.

The physical examination may reveal a distended tympanitic abdomen, often with most of the distention in the upper abdomen but primarily on one side. Patients may look remarkably well for the amount of distention that is encountered. Significant abdominal pain, fever, lack of bowel sounds, peritonitis, or cardiovascular instability suggests gangrenous bowel and should

prompt immediate surgical consultation. The absence of these findings does not exclude gangrene, however, and the duration of symptoms alone is not predictive of gangrene.

Cecal Volvulus

Although the vast majority of patients (90%) have abdominal pain, the clinical triad of abdominal pain, distention, and constipation is inconsistent. Patterns of presentation vary on a spectrum similar to that for sigmoid volvulus. Vomiting is seen in only 50% of patients.

Differential Diagnosis

Any process that causes LBO may mimic volvulus, including neoplastic disease, paralytic ileus, toxic megacolon, and pseudo-obstruction.

Diagnostic Testing

Sigmoid Volvulus

The diagnosis of sigmoid volvulus can be made with plain radiographs in most cases.[16,17] A grossly distended loop of colon lacking haustral markings is typical and is seen just as often on the right side of the abdomen as on the left (Fig. 85.3). The bowel may have the appearance of a bent inner tube. Free air may be seen on an upright chest radiograph or lateral decubitus radiograph of the abdomen in patients who have a perforation. Gas backing up into the rest of the colon may obscure the typical appearance of sigmoid volvulus on plain radiographs, leading to a significant number of nondiagnostic study results. Cecal volvulus and bowel obstruction from other causes may have a similar radiographic appearance. When the diagnosis is in doubt, contrast enema may be helpful. Contrast material fills up the colon to the tapering point of torsion, giving a bird's beak appearance to the column of contrast material (Fig. 85.4). Sigmoidoscopy is diagnostic in many cases, visualizing a spiral sphincter-like twist in the colonic mucosa. CT scanning, when used, is also highly accurate, but most diagnoses can be made without it.[17,18]

Cecal Volvulus

Plain radiographs often are helpful in establishing a diagnosis of cecal volvulus, but the findings are not definitive in up to 50% of cases. The cecum should be markedly dilated and may contain an air-fluid level. The small bowel often is distended as well. In contrast, with sigmoid volvulus, the distal colon should have a paucity of gas (Fig. 85.5).[19] The classic coffee bean sign, a large oval gas shadow with a line down the middle representing bowel bent over on itself, may be seen in the midabdomen. Free air suggests perforation and necessitates emergent surgical consultation. A common mistake is misinterpreting the plain radiograph as showing a sigmoid volvulus. If the diagnosis is unclear, a contrast enema is helpful in showing the site of torsion. Ultrasound imaging generally is unhelpful. On CT, a mesocolon whirl sign (Fig. 85.6) may be seen, indicating a twisted segment of mesentery; particularly helpful are multiplanar reconstructions.[20] In many cases, cecal volvulus is definitively diagnosed only at surgery.

Management

Sigmoid Volvulus

Although spontaneous reduction of a sigmoid volvulus can occur, it is infrequent enough to mandate a proactive approach to treatment. If clinical evidence of gangrenous bowel is lacking, endoscopic detorsion should be attempted by an experienced operator, during which a lubricated flexible tube is inserted through the

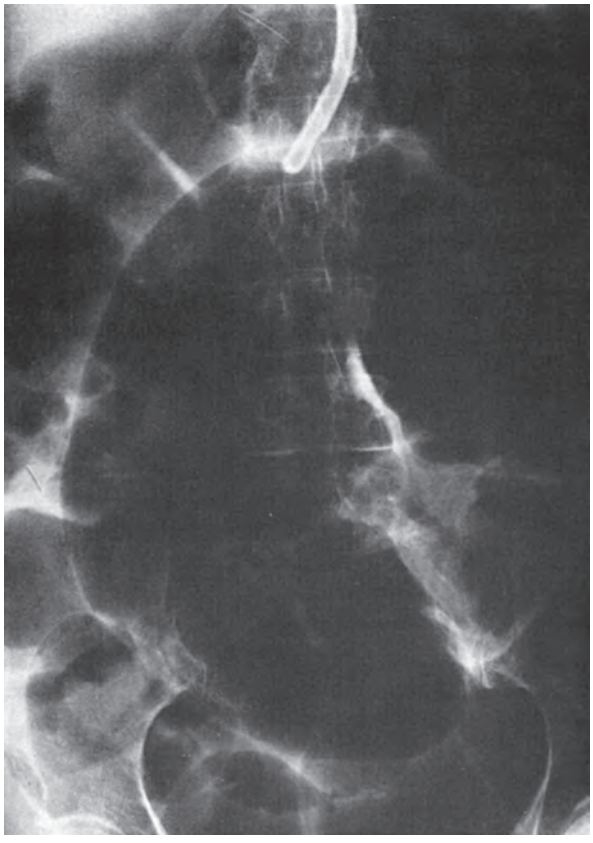

Fig. 85.3. Plain film of abdomen shows a large dilated loop characteristic of sigmoid volvulus.

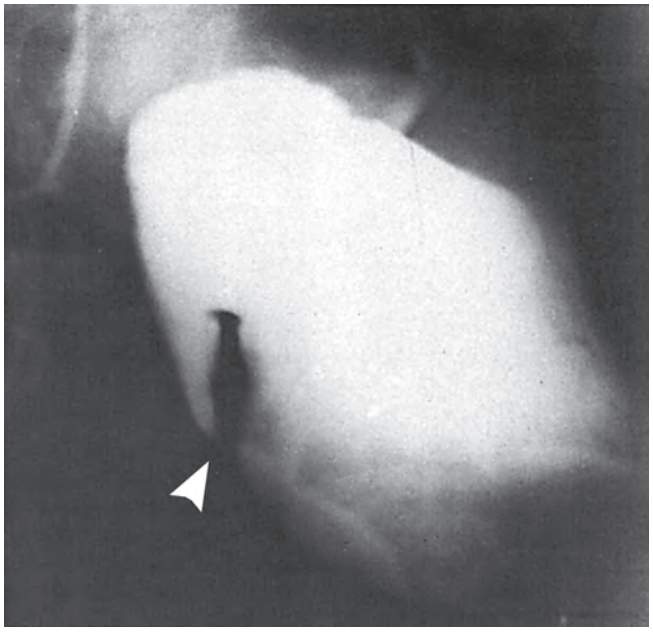

Fig. 85.4. Characteristic bird's beak sign of volvulus *(arrowhead)* shown on this image from a barium enema study.

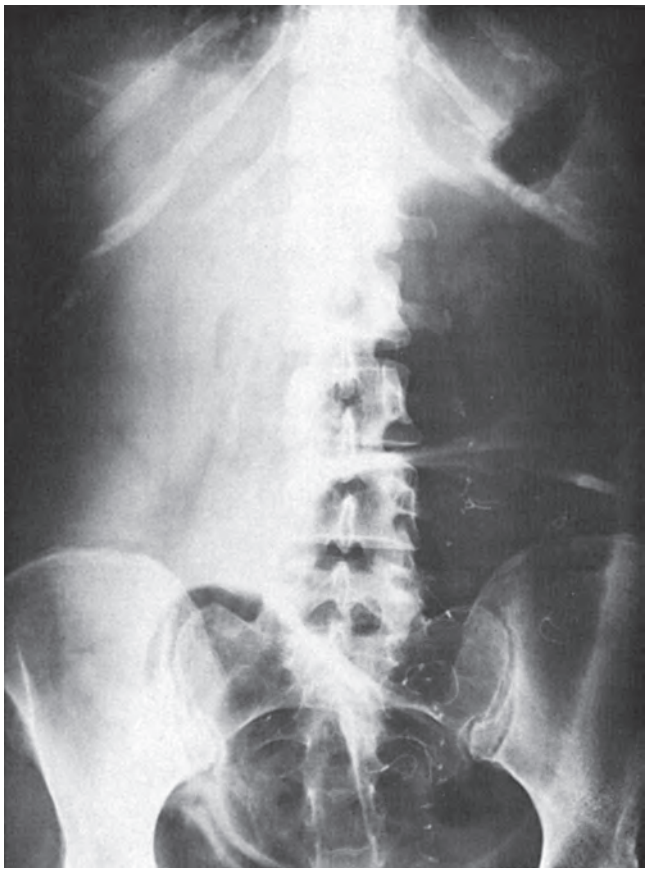

Fig. 85.5. Plain radiograph shows distended colon characteristic of cecal volvulus. Note presentation in the left lower quadrant and absence of right-sided gas shadows.

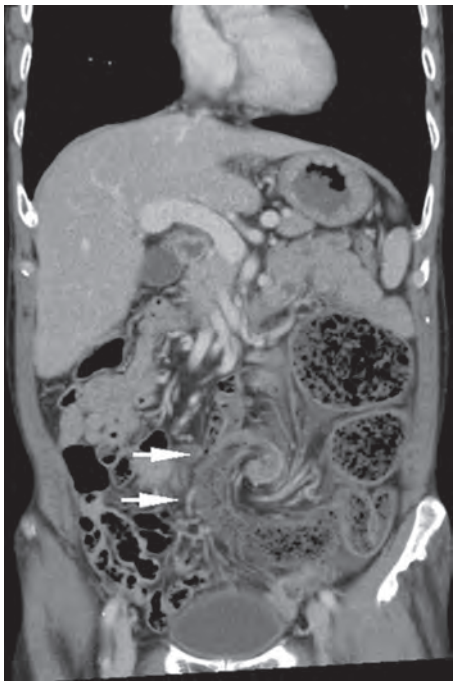

Fig. 85.6 CT scan of mesentery and intestine twisted into whirl pattern *(arrows),* in this case from a sigmoid volvulus. (From Shaw W, Huang C, Hung T, Yeh Y: Typical whirl sign in sigmoid volvulus. J Emerg Med 46:383–384, 2014.)

obstruction. With decompression of gas and liquid stool, the bowel is able to undergo self-detorsion. Endoscopic decompression is successful in 50% to 90% of cases.[18] If the patient has a gangrenous bowel or the volvulus does not respond to endoscopic decompression, surgery is indicated. Recurrence rates are estimated at 60%; elective resection of the redundant sigmoid is recommended after resolution of the acute episode. The mortality rate for sigmoid volvulus is 20% overall and exceeds 50% in the subpopulation of patients with gangrene.

Cecal Volvulus

The proximal nature of the cecum makes it unavailable for endoscopic manipulation; cecal volvulus requires resection of the cecum by an open or laparoscopic technique.[21] Recurrence is rare after resection.

Disposition

All patients with volvulus require hospitalization for invasive intervention.

INTUSSUSCEPTION

Principles

Intussusception is considered the primary cause of bowel obstruction in children and the second most common cause of acute abdomen in children after appendicitis.[22] The peak incidence in pediatric patients is between 4 and 10 months of age.[22-26] In contrast, adult intussusception is rare, accounting for only 5% of all intussusception,[23] and is more often associated with coexisting neoplasms and malignancies.[27] In adults, the condition occurs over a wide variety of ages, with a mean age at presentation of 65 years. The male-female ratio is approximately 3 : 1 in children, but the gender prevalence is equal in adults.

Intussusception has gained public attention because of its association with the rotavirus vaccine. The well-documented benefits of rotavirus vaccine have been found to outweigh the possible small risks of intussusception.[28,29]

The exact mechanism of intussusception is unknown, but it is believed that a lead point lesion changes the motility properties of the intestine, allowing a proximal segment to invaginate into a more distal segment. As peristaltic activity pushes the invaginated segment along with its mesentery and mesenteric blood vessels distally down the bowel, the blood supply to the segment can be compromised, and ischemia may occur. Edema associated with the intussusception can lead to a mechanical obstruction of the bowel. If not treated promptly, a reduced blood supply can lead to bowel necrosis and perforation. The most common locations are at the junctions between freely moving segments, retroperioneally, or adhesionally fixed segments.

In most infants, the intussusception involves the ileum invaginating through the ileocecal valve into the cecum. Of intussusceptions in children, 95% are idiopathic.[30] In the pediatric population, there is a common association with hyperplasia of Peyer's patches secondary to viral infections; 80% to 90% of adult intussusceptions have an identifiable cause. Adult intussusceptions that occur in the small bowel are caused by benign lesions 60% of the time; the remainder are caused by malignancy (30%) or are idiopathic (10%). In contrast, most colonic intussusceptions (60%–65%) are caused by malignancy.

Clinical Features

Intussusception manifests in one of two patterns, acute or subacute. In pediatric intussusception, the pattern is acute, with

abrupt onset of intermittent, colicky, abdominal pain, which can cause episodes of crying and pulling the knees up. In adults, the most common is that of acute partial intestinal obstruction, because less than 20% of intussusceptions cause complete obstruction. The typical presenting complaint is abdominal pain, with vomiting and rectal bleeding as the next most common complaints. Constipation may also be present. The abdomen may be distended, and bowel sounds often are decreased. A mass is seldom palpated; the classic triad of abdominal pain, mass, and hemepositive stools noted in children is found in less than 50% of pediatric intussusceptions and is rarely found in adults.[31] Similarly, currant jelly stools and altered mental status are rare presentations and often occur late in the disease progression. The presence of crying, abdominal mass, pallor, and vomiting are clinical indicators of pediatric intussusception. Individually, each variable is not helpful but, when all four are present, there is a high probability of the disease.[26]

The subacute presentation is much more subtle, with intermittent abdominal pain for months. The diagnosis usually is made only when the pain becomes unrelenting or has been recurrent enough to prompt imaging.

Differential Diagnosis

The differential diagnosis includes other causes of bowel obstruction.

Diagnostic Testing

Ultrasound Examination

Ultrasonography is helpful in detecting intussusception but is not as useful as CT in excluding other diagnoses. For facilities that have skilled ultrasound technicians available, ultrasound is the primary diagnostic test used in the pediatric population.[25] A transverse view of the intussusception has a doughnut or target shape, with multiple concentric rings. A longitudinal view has an ultrasound appearance similar to that of a kidney (so-called pseudo–kidney sign), with a bright central area often surrounded by a darker outer layer (Fig. 85.7).

Plain Radiography

Plain radiography is a reasonable screening test in a patient suspected of having bowel obstruction, but usually shows only nonspecific large bowel dilation.

Computed Tomography

CT is usually the most useful test for adult patients with suspected intussusception but may not detect the actual intussusception in up to 50% of cases. The characteristic findings on CT include a target- or sausage-shaped soft tissue mass with a layering effect, with mesenteric vessels within the intestinal lumen (Fig. 85.8).

Barium Enema

Although a barium enema study can demonstrate intussusception and even reduce it, it is a less desirable study than CT or ultrasound examination for initial diagnosis. It should not be performed in patients suspected of having a bowel perforation.

Colonoscopy

Colonoscopy is helpful in defining the lesion causing intussusception but does not usually detect the intussusception itself.

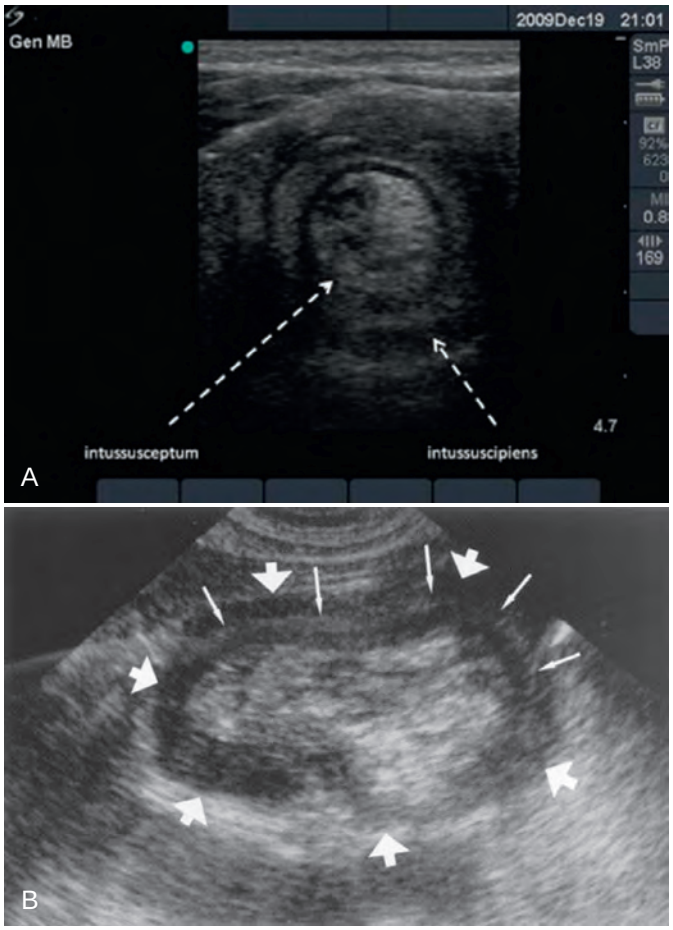

Fig. 85.7. Ultrasound of intussusception. **A,** Transverse view showing donut or target shape, with multiple concentric rings. **B,** Oblique-transverse view on ultrasound showing a kidney-shaped mass (pseudo–kidney sign). *Large arrows* indicate outer margin of the bowel; *small arrows* indicate the contiguous surfaces of telescoping bowel. (**A** from Riera A, Hsiao AL, Langhan ML, et al: Diagnosis of intussusception by physician novice sonographers in the emergency department. Ann Emerg Med 60:264–268, 2012; **B** from Dean AJ, Lafferty K, Villanueva TC: Emergency medicine bedside ultrasound diagnosis of intussusception in a patient with chronic abdominal pain and unrecognized Peutz-Jeghers syndrome. J Emerg Med 24:203–210, 2003.)

Management

In pediatric intussusception, the treatment of choice for the stable child is a trial of pneumatic or hydrostatic reduction when appropriate radiologic facilities are available. This may prevent the need for surgery, and the cause is usually benign. Reduction of pediatric intussusception is sufficient treatment in 80% of patients.

Surgery is required in most cases of adult intussusception. Because of the high incidence of malignancy and the concerns of spreading malignant cells from potentially malignant lead points, reduction often is not attempted in adults before surgical exploration. Surgical treatment is recommended for patients who are acutely ill, who have evidence of perforation, for whom nonoperative reduction is unsuccessful, who need evaluation or resection of a pathologic lead point, or who are treated in a setting where radiologic facilities are unavailable. ED care is supportive and aimed at optimizing fluid status, decompressing the stomach with a nasogastric tube, recognizing perforation, administering antibiotics if compromised bowel is suspected, and securing surgical consultation in the appropriate time frame. Occasionally,

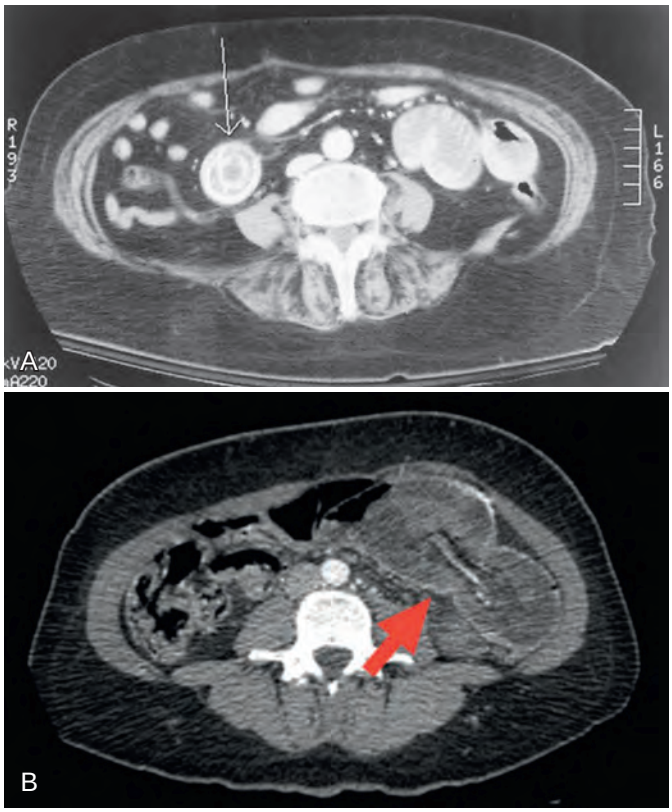

Fig. 85.8. CT with intussusception. **A,** Target- or sausage-shaped soft tissue mass with layering effect, with mesenteric vessels within the intestinal lumen. **B,** Pseudo–kidney sign *(arrow).* (**A** from Davis JM, Vilke GM: An elderly patient with intussusception. J Emerg Med 24:221–222, 2003; **B** from Shyy W, Knight RS, Teismann NA: Ultrasound diagnosis of adult intussusception. J Emerg Med 49:498–499, 2015.)

intussusception may resolve spontaneously, but an evaluation to exclude a pathologic lead point must still be undertaken.

Disposition

All patients diagnosed with intussusception require hospitalization. Operative mortality tends to be minimal.

INFLAMMATORY BOWEL DISEASE

Principles

Inflammatory bowel disease (IBD) includes two clinically similar but distinct diseases, Crohn's disease (CD) and ulcerative colitis (UC). Both diseases are characterized by chronic and unpredictable relapsing inflammation of the gastrointestinal tract. It is estimated that more than 1 million people in the United States are affected by IBD. Cases are divided approximately equally between CD and UC, with a combined annual incidence of 10 cases/100,000. The prevalence is more common in North America and Europe and is much less common in Asian and African populations.[32] IBD can occur at all ages, with a peak onset at 15 to 30 years of age.[33] Up to 25% of IBD cases develop during childhood or adolescence, whereas 10% to 15% of patients with IBD will receive their diagnosis when older than 60 years. The long-term management of IBD is a complex stepwise process that involves multiple medications and surgery. The goals of ED evaluation are to (1) recognize potential new cases of IBD, (2) consider and exclude serious complications in patients with IBD, and (3) identify patients with IBD who need in-hospital care. Treatment plans are best developed in consultation with a physician experienced in the long-term management of IBD.

IBD is thought to develop as a result of dysregulation of the immune system, driven by an immune response to normal intestinal flora in a genetically susceptible host.[34] In essence, it is the loss of the normal tolerance to these bacteria. Increased familial prevalence is found in patients diagnosed early in life, whereas environmental modifiers are thought to influence later onset. Chronic inflammation of the gut results, which can lead to complications and extraintestinal manifestations.

Ulcerative Colitis

UC causes inflammation and ulceration throughout the colon and rectum but spares the small intestine. Inflammation is more superficial than in CD. Typically, the inflammation exists as one continuous lesion originating in the rectum and extending a variable distance into the colon, although cases of discontinuous disease (so-called skip lesions) similar to that in CD have been reported in UC. The concordance rate between identical twins is low (6%–14%), suggesting that factors other than genetics are involved. A change to a Western lifestyle is associated with increased risk, and stress can trigger exacerbations.[32]

Inflammatory arthropathies and primary sclerosing cholangitis are the most common extraintestinal manifestations of UC. Other extraintestinal manifestations include involvement of the skin, eyes, and bones.

Crohn's Disease

CD may affect any part of the gastrointestinal tract, usually the distal small intestine and proximal colon and, less commonly the esophagus, duodenum, or stomach. Because of the transmural inflammation, the development of intestinal strictures, abscesses, or fistulae to adjacent organs are potential complications. Concordance between identical twins is 45% to 50%, and genetic mutations have been identified, suggesting a strong genetic predisposition that is modified by other factors. Although the onset of the disease can occur at any time of life, CD affects primarily younger patients, with onset of disease typically in the teens and 20s. Pediatric-onset disease is more often severe and extensive, with a higher chance of upper gastrointestinal tract disease compared to adult-onset disease.[34]

Extraintestinal manifestations, such as arthritis, aphthous stomatitis, uveitis, erythema nodosum, and ankylosing spondylarthropathy, occur more often in CD than UC.[35]

Clinical Features

Typical presenting complaints in patients with IBD include abdominal pain and tenesmus, with bloody diarrhea. Patients with CD may have a history of nocturnal diarrhea, which helps differentiate CD from patients who have IBS. The physical examination may reveal significant abdominal tenderness or an abdominal mass representing an abscess. Patients with CD may have fissures, ulcerated hemorrhoids, strictures, or cutaneous abscesses around the anus. Onset of symptoms usually occurs before the age of 30 years, although the diagnosis can be difficult to make in the early stages. The most useful clues of possible IBD in children with abdominal pain are diarrhea, growth and pubertal delay, weight loss, rectal bleeding, pallor, fatigue, perianal skin tags, fistulae or abscesses, and family history of IBD.

Patients often come to the ED with a known diagnosis of IBD and worsening abdominal symptoms. A common reason for relapse is interruption of the medications that have kept the disease in remission. Many patients become complacent during

quiescent periods and stop taking such medications. Adherence to continuous, lifelong, maintenance therapy has been shown to reduce the risk of acute attacks and cancer. Common complications of IBD include the formation of fistulae, strictures, and abscesses; less common but life-threatening complications include fulminant colitis, toxic megacolon, and intestinal perforation.

Toxic Megacolon

Toxic megacolon is a pathologic dilation of the colon resulting from inflammation of the smooth muscle layers of the intestine, which leads to muscle paralysis, dilation, and eventually perforation if left untreated. The hallmark of toxic megacolon is colonic dilation in a systemically toxic patient with a known inflammatory condition of the colon. Systemic toxicity differentiates toxic megacolon from other disorders that cause colon dilation, including mechanical obstruction, pseudo-obstruction, and congenital or acquired megacolon (Fig. 85.9).

The triggering event may be recent ingestion of anticholinergics, antimotility agents, narcotics, or antidepressants. Patients usually have experienced severe symptoms of colitis for several days before the onset of toxic megacolon. Patients have more than 10 stools daily, continuous bleeding, abdominal pain, distention, and acute, severe toxic symptoms, including fever and anorexia.

Extraintestinal Manifestations

Extraintestinal manifestations include inflammatory conditions of the skin (eg, erythema nodosum, pyoderma gangrenosum), eyes (eg, episcleritis, scleritis, uveitis), joints (eg, arthritis, sacroiliitis), bone (eg, osteoporosis), spine (eg, ankylosing spondylitis), and liver (eg, primary sclerosing cholangitis).[36] Thromboembolic events in IBD patients are often overlooked and underdiagnosed, affecting the venous and arterial systems. The inflammatory process initiates clotting and decreases the activity of anticoagulation mechanisms.[37] There is a 60% increase in thromboembolic disease (eg, deep venous thrombosis [DVT], pulmonary embolism [PE]) compared to that in the general population.[38] Cerebrovascular complications including cerebral sinus thrombosis are more frequent during bouts of inflammation. There is also an increased risk of ischemic heart disease and mesenteric ischemia. Peripheral neuropathy is the most common neurologic complication of IBD, thought to be due to immune-mediated changes, metronidazole toxicity, and vitamin deficiency.[35] Chronic inflammation may be the most important driver of these complications in IBD.

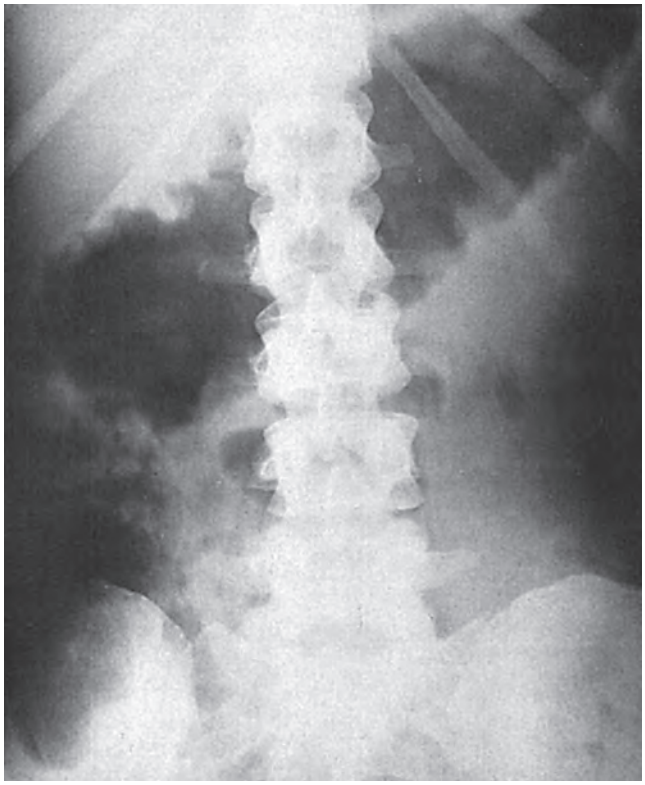

Fig. 85.9. Toxic megacolon secondary to ulcerative colitis. The smooth indentations seen along the margin of the colon represent pseudopolyps.

Differential Diagnosis

Symptoms and signs are protean and overlap with those of many common abdominal conditions, including appendicitis, infectious colitis, ischemic colitis, radiation colitis, diverticular disease, cancer, and bowel obstruction. In children, the differential diagnosis can also include Henoch-Schönlein purpura, celiac disease, and functional abdominal pain. Intestinal infections commonly mimic the symptoms of IBD, including those caused by *Escherichia coli* O157:H7, *Clostridium difficile,* and amoeba.[36]

Diagnostic Testing

Endoscopic evaluation with biopsy is required to confirm the diagnosis. Diffuse, continuous mucosal inflammation involving the rectum and extending to a point more proximal in the colon are suggestive of UC, whereas a complex or fistulizing lesion, involvement of the upper gastrointestinal tract, skip lesions, or granulomata are suggestive of CD. No specific laboratory tests to diagnose IBD are available, although recent tests targeting antibodies to *Saccharomyces cerevisiae* (ASCA) or antineutrophil cytoplasm (P-ANCA) help differentiate between CD and UC. An elevated ASCA value is more suggestive of CD, whereas an elevated P-ANCA level is more likely UC. Electrolyte abnormalities may be caused by severe diarrhea, or anemia may occur from gastrointestinal blood loss.

An elevated C-reactive protein level or erythrocyte sedimentation rate can be useful for categorizing the severity of the disease and differentiate it from IBS, because IBS is not associated with elevations in these inflammatory biomarkers.[39-41] Intestinal infections should be excluded to diagnose IBD definitively. Because intestinal infections commonly mimic the symptoms of IBD, it is suggested that new patients should have microbiologic studies for bacterial infection, including *E. coli* O157:H7, *C. difficile,* and amoeba. These tests are negative in patients with IBD. Established patients who have recently been hospitalized or been on antibiotics should be tested for *C. difficile.* Stool studies contain fecal leukocytes, but cultures and microbiologic studies should be normal.

Plain radiographs should be limited to patients suspected of having complications such as bowel obstruction, toxic megacolon, or perforation. For diagnosing toxic megacolon, plain radiographs are diagnostic and show a colon with a diameter of 6 cm or larger, although this feature may not be present in early stages (see Fig. 85.9). CT of the abdomen and pelvis with at least IV contrast, and preferably with oral contrast if tolerated, is the best study to evaluate extraluminal complications (ACR appropriateness score = 8). Magnetic resonance imaging (MRI) enterography (with oral contrast; ACR appropriateness score = 6) can locate affected bowel segments and identify fistulae, stenoses, and abscesses. It also has the advantage of not using radiation, which is preferred in children and is also a consideration in individuals likely to undergo multiple imaging studies over time.

Management

Medical management is the mainstay of therapy for most patients with IBD. Treatment is typically driven by the severity of symptoms. However, newer treatment models have recommended symptom remission and endoscopic remission to prevent complications from disease progression due to chronic inflammation.[42] Treatment regimens should be discussed with a gastroenterologist. The dosages given in this section are suggested induction doses.

In general, patients are maintained on oral aminosalicylates, also known as 5-aminosalicylic acid (5-ASA) agents while asymptomatic and then placed on steroids if symptoms recur. Once remission is achieved, steroids are discontinued and the patient is once again maintained on 5-ASA agents. If remission is not achieved with steroids, other agents such as antimetabolites and immunosuppressants are used. The choice of agents depends on classification of the disease as mild, moderate, or severe (Box 85.5). Bowel rest is not beneficial, except as preparation for surgical intervention. Surgery is reserved for patients with severe disease who do not respond to medical therapy or for those with serious complications.

BOX 85.5

Disease Severity Criteria in Inflammatory Bowel Disease

ULCERATIVE COLITIS

Mild Disease
- Fewer than four stools/day
- Stools may contain some blood
- No systemic signs of toxicity (eg, fever, tachycardia, anemia, elevated erythrocyte sedimentation rate)

Moderate Disease
- More than four stools/day
- Minimal signs of toxicity

Severe Disease
- More than six bloody stools/day
- Signs of systemic toxicity

CROHN'S DISEASE

Mild to Moderate Disease
- Patient ambulatory and able to eat
- No dehydration
- No toxicity
- No significant abdominal pain or mass
- Weight loss of 10%

Moderate to Severe Disease—Any of the Following
- Mild disease that has failed to respond to treatment
- Patient may have some systemic toxicity, significant weight loss, anemia
- Fever, some abdominal pain or tenderness, intermittent nausea or vomiting

Severe Disease
- Persistence of symptoms during corticosteroid or biologic (eg, infliximab) therapy
- High fever, persistent vomiting
- Intestinal obstruction
- Rebound tenderness
- Cachexia
- Abscess

Adapted from Hanauer SB, Present DH: The state of the art in the management of inflammatory bowel disease. Rev Gastroenterol Disord 3:81–92, 2003; and Lichtenstein GR, Hanauer SB, Sandborn WJ: Management of Crohn's disease in adults. Am J Gastroenterol 104:465–483, 2009.

5-ASA agents are the first line of therapy for mild to moderate disease and for maintenance therapy. These agents can be administered orally or rectally if the disease is in or near the rectum. Sulfasalazine, starting at 1 g every 6 hours for adults and 40 to 60 mg/kg/day q6h for pediatric patients, is one of the original drugs in this category. Its use is limited by sulfa toxicity at higher doses and has side effects that may include vomiting, anorexia, and headache; rarely it may result in bone marrow suppression, pancreatitis, hepatotoxicity, anemia, and interstitial nephritis. A newer 5-ASA derivative, mesalamine, 1 g every 6 hours PO or 2 to 4 g rectally as a daily dose at bedtime, has less toxicity, allowing higher dosages.

Antibiotics may be used for the treatment of IBD, but their use is controversial. Evidence supporting antibiotic use is stronger for CD than UC. In patients with active luminal CD or fistulizing CD, or CD patients who do not tolerate 5-ASAs or have not shown improvement within 4 weeks of 5-ASA therapy, metronidazole, 500 mg PO or IV every 8 hours and ciprofloxacin, 400 mg PO or IV every 12 hours, are used most commonly, with some evidence suggesting that tobramycin or rifaximin may be beneficial as well.[43]

Oral corticosteroids are used for patients with moderate to severe disease or patients whose IBD is unresponsive to a 5-ASA agent. Steroids should be tapered when remission is achieved to avoid typical side effects. IV steroids are reserved for hospitalized patients with severe disease. Prednisone is often initiated and then tapered, with induction dosing of 40 to 60 mg daily. Budesonide, 9 mg daily, a newer oral steroid, is degraded on its first pass through the bloodstream and has fewer systemic side effects. Prolonged use of steroids can lead to gastrointestinal mucosal injury, problems with wound healing, osteopenia with fractures, and frank osteonecrosis that may be evident only on MRI.[36]

The immunomodulating drugs azathioprine, starting at 2 mg/kg/day, and 6-mercaptopurine, starting at 1 mg/kg/day, are used in patients resistant to other therapies or to wean steroid-dependent patients. Patients on these medications should be assessed for bone marrow suppression and pancreatitis.

The immunosuppressant agent cyclosporine, 2 to 4 mg/kg IV daily, is used for severe cases, such as fulminant colitis, often when patients are not surgical candidates. Although most patients tolerate it well, cyclosporine has significant potential toxicity, including myelosuppression, electrolyte disturbances, and hepatic toxicity and nephrotoxicity. Opportunistic infections, including *Pneumocystis* pneumonia, have been known to occur.

Infliximab, an antibody to tumor necrosis factor alpha (TNF-α), is used in advanced cases, with induction doses of 5 mg/kg IV. It generally has a benign side effect profile but carries an increased risk of opportunistic infections, including tuberculosis and fungal infections. Serum sickness will be experienced by 1% to 2% of patients, with symptoms including arthralgias, myalgias, fevers, and rash.[36]

Surgery is reserved for patients with severe disease refractory to medical management and for patients with complications such as intestinal obstruction, significant bleeding, abscess, or fistula. Up to 25% of patients with UC will eventually require colectomy for uncontrolled disease. A colectomy is curative for UC and improves quality of life, but there is no curative surgery for CD. Extraintestinal manifestations usually respond to therapy for intestinal disease.

Treatment for toxic megacolon includes fluid hydration, IV corticosteroids, antibiotics covering bowel flora (see Box 85.4), and evaluation for potential intestinal infections, especially in immunocompromised patients. Hypokalemia or hypomagnesemia should be corrected if present because it can exacerbate

colonic dilation.[36] The mortality rate has decreased to less than 2% as a result of early recognition and treatment.

The prevention of DVT and PE should be on the forefront of physicians' concerns for admitted IBD patients.[38] Although there are no clear guidelines, some studies have recommended heparin or mechanical thromboprophylaxis for hospitalized patients.[37]

For patients in remission, ongoing endoscopic monitoring for cancer is required. The estimated prevalence of cancer among patients with CD is significant—at 2%—and patients with UC have a 15-fold greater risk for the development of colorectal cancer than the general population.

Disposition

Consultation with a gastroenterologist is recommended before patient disposition. Most patients with an uncomplicated mild-to-moderate exacerbation of IBD need only restart their maintenance therapy if it was interrupted, or add oral steroids to their regimen. Patients with severe disease or those in whom oral steroids have failed to effect improvement need hospitalization for administration of parenteral steroids. Emergent surgical consultation should be sought for life-threatening hemorrhage, perforation, or toxic megacolon. Urgent (not emergent) surgical intervention is indicated if the bowel is obstructed. Abscesses may be treated percutaneously with imaging guidance or surgically. Chronic fistulae initially are treated medically. After hospital discharge, close follow-up by the physician monitoring the patient's disease is indicated to ensure that remission is achieved in a timely fashion and that the patient complies with the suppressive therapy after the acute event.

COLONIC ISCHEMIA

Principles

Colonic ischemia (CI) is the most common intestinal ischemic disorder and yet remains poorly understood.[44-46] The incidence of CI is 1/2000 hospitalizations, occurring more often in women than men. Its presentation overlaps with that of many other abdominal diseases and is difficult to diagnose without endoscopic visualization of the colonic mucosa. Although 90% of CI cases occur in patients older than 60 years, the condition can occur in all age groups.

Nonocclusive CI is the predominant mechanism, usually affecting watershed areas with limited collateralization, such as the splenic flexure and rectosigmoid junction. The greater frequency in older adults suggests a relationship to degenerative vascular changes. The primary insult is a low blood flow state associated with a variety of factors, including congestive heart failure, vasoactive drugs, atherosclerosis, and renal failure. Factors that have been implicated are thrombophilia and infections, especially *E. coli* O157:H7.[44] The Shiga-like toxins act on the vascular endothelium of small blood vessels, thought to lead to colitis and resultant CI. Younger patients may develop CI in the setting of collagen vascular disease, hematologic disorders, long-distance running, or cocaine abuse. Medications associated with CI include digoxin, pseudoephedrine, and sumatriptan.[45] CI is diagnosed about 3.5-fold more frequently in patients with IBS. Although less common, it is important to consider that distally obstructing lesions of the colon can also theoretically raise intracolonic pressure and cause CI by reducing colonic blood flow. CI is also seen as a complication after major cardiovascular surgery.[47] CI complicates up to 7% of elective operations on the aorta and up to 60% of operations for ruptured abdominal aortic aneurysms and is responsible for 10% of deaths after aortic replacement.

CI can occur in any part of the colon, including the rectum, but for unknown reasons it occurs most often (80%) in the left colonic segment. Isolated right colon ischemia (IRCI) with no other segments involved occurs in only 10% to 25% of cases and has a worse outcome than CI affecting any other region on the colon.[44] Patients with IRCI more frequently suffer from atrial fibrillation, coronary artery disease, and chronic kidney disease. Because the superior mesenteric artery (SMA) supplies the right side of the colon as well as the small intestine, it is thought that IRCI could be the heralding presentation of an acute SMA occlusion.

CI represents a spectrum of disease whose manifestations vary with the extent of the ischemic insult. In most cases, the ischemic episode is self-limited, and the condition resolves completely with conservative therapy but, in one-third of patients, a prolonged or severe insult results in scarring or stricture formation of the colon and chronic symptoms. If the ischemia is transmural, gangrene and intestinal perforation are possibilities.

Clinical Features

The presentation of CI typically involves the acute onset of mild crampy abdominal pain in the left lower quadrant, with abdominal distention and blood in the stool. IRCI presents less frequently with bloody stools.[48] The typical patient has had recent surgery or significant medical illness. Nausea and vomiting can occur with obstruction secondary to a stricture or ileus. Tenderness over the affected colon may be present but often is not dramatic. Peritoneal findings, fever, and an elevated WBC count suggest gangrenous bowel and perforation. Toxic megacolon is a recognized complication. Without surgical intervention, fulminant gangrenous CI can lead to perforation, multiorgan failure, and death.[46]

Differential Diagnosis

The symptoms of CI are nonspecific and overlap with those of numerous other disorders, including IBD, diverticulitis, infectious colitis, and other causes of nonprofuse, lower gastrointestinal bleeding. If strictures are present, the possibility of diverticulitis or colon cancer should be considered.

Diagnostic Testing

Laboratory Tests

No sensitive or specific biochemical markers for CI are recognized, although abnormalities such as elevated serum lactate and alkaline phosphate levels may be present once irreversible damage has occurred. A complete blood count to exclude and look for a leukocytosis suggestive of perforation is recommended. Serum electrolyte levels should be checked if diarrhea or vomiting has been severe or prolonged. Blood and WBCs in the stool are common findings in several of the entities that present similarly to CI, including IBD and infectious colitis. Unfortunately, the definitive diagnosis of CI is rarely made in the ED.

Imaging Studies

Plain Radiography. Plain radiographs often show only nonspecific dilated bowel. Findings specific for CI occur in approximately 20% of patients. Classic findings are (1) intraluminal prominences, known as thumbprinting, which represent submucosal hemorrhage and swelling, and (2) wall thickening and ahaustral segments. Air in the portal venous system or bowel wall suggests imminent intestinal infarction.

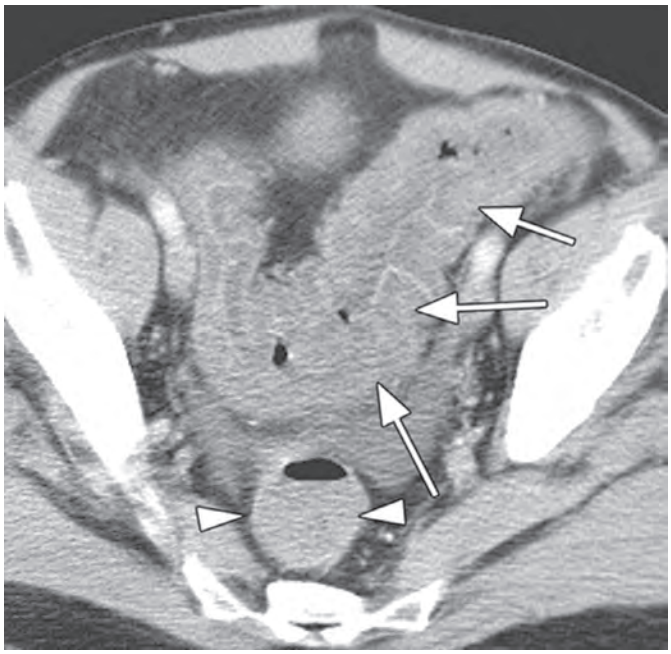

Fig. 85.10. CT scan of patient with colonic ischemia showing thumbprinting *(arrows)* with thickening of sigmoid colon associated with multiple nodular defects. Note that the rectal wall (arrowheads) is normal. (From Thoeni RF, Cello JP: CT Imaging of colitis. Radiology 240:623–638, 2006.)

Computed Tomography. Although CT does not allow the definitive diagnosis of CI, it is useful to support the clinical suspicion, assess the extent of colon involvement, diagnose potential complications, and exclude other disorders. CT features suggestive of CI include thumbprinting, wall thickening, and luminal narrowing and inner wall hypoperfusion, the so-called double halo sign (Fig. 85.10).

Barium Enema. Thumbprinting is detected more often by barium enema than by plain radiography. However, barium enemas have largely been replaced by colonoscopy.

Colonoscopy. Emergent colonoscopy should be performed after the colon is prepped with an enema. Colonoscopy with biopsy is the preferred method to diagnose CI because it visualizes the abnormal colonic mucosa, and biopsy specimens help differentiate between cancer and other nonischemic causes of colitis. Colonoscopy can also detect a necrotic bowel by its distinct cyanotic or black appearance. If colonoscopy is delayed, pathologic changes consistent with CI may have already resolved. The diagnosis may be missed on colonoscopy in up to one-third of cases.

Angiography. Angiography is usually not helpful in the diagnosis or management of CI. In most cases, the blood flow defect is at the microvascular level and has resolved by the time the patient seeks evaluation. The exception is IRCI, in which case only the ascending colon is affected, suggesting a SMA thrombosis.

Management

In the absence of surgical complications, the treatment of CI is supportive and includes bowel rest, hydration, and pain management. Broad-spectrum antibiotics covering bowel flora are indicated for patients with more significant symptoms (see Box 85.4).[49] If CI is precipitated by an episode of hypotension, the underlying cause must be sought and treated, and cardiac output should be maximized. A cardiac evaluation should be considered, and if congestive heart failure or cardiac arrhythmia is identified, medical treatment should be initiated.[45] Vasopressors, steroids, NSAIDs, and oral cathartics should be avoided. Stool studies, including cultures for bacteria, microscopy to look for ova and parasites, and a *C. difficile* titer, are helpful if the diagnosis is uncertain. Serial imaging or endoscopic evaluations of the colon and continued monitoring of the hemoglobin and electrolyte levels are indicated until the patient's condition stabilizes. Colonic distention should prompt surgical consultation and decompression with a rectal tube to lower the transmural pressure and improve colonic perfusion. Patients not recovering with medical management should receive surgical treatment. Prompt emergent surgical consultation should be obtained for the following: sepsis, peritoneal changes, free abdominal air, significant fever, massive bleeding, and a significant leukocytosis suggesting colon infarction or perforation.

Disposition

Patients with mild symptoms and minimal abdominal tenderness or bleeding can be managed on an outpatient basis and referred for urgent colonoscopy. Patients with more significant findings, especially if the diagnosis of gangrenous bowel cannot be excluded, require hospitalization and surgical consultation. A high mortality rate (60%) is expected for patients undergoing emergent surgery, although deaths before the age of 50 years are rare. Most patients improve without surgical intervention, and only 5% have a recurrence of CI. In those with continuing significant symptoms, colectomy is usually curative.

RADIATION PROCTOCOLITIS

Principles

Radiation proctocolitis (RP) is a common side effect of radiation therapy, occurring in 50% to 75% of patients receiving radiation to the pelvis. The radiation dose is a major determinant of the severity of acute and late toxicity.[50] The disease has two distinct presentations, acute and chronic. Acute RP begins during or shortly after a course of radiation therapy, typically within 6 weeks, is usually easily diagnosed, and is self-limited. Chronic RP occurs in 5% to 10% of patients who have undergone pelvic radiation therapy and begins any time after the end of radiation therapy, which can make the diagnosis challenging.

Radiation is an effective treatment for neoplastic disease, but also damages rapidly growing intestinal epithelium. The mucosal injury leads to loss of normal barrier function, and luminal microbes trigger an acute inflammatory response, leading to further mucosal damage. Impaired recognition of bacterial translocation worsens the inflammatory response and can lead to chronic inflammatory changes, such as strictures, fibrosis, and ischemia. The fixed portions of the colon, the cecum and rectum, are at a greater risk of receiving higher doses of radiation.

Acute Radiation Proctocolitis

The intestinal epithelium normally is sloughed and replaced at a rapid rate. After the start of radiation therapy, growth of replacement epithelium is slowed, but sloughing continues at the preexposure rate. This mismatch leads to gaps in the epithelium, which over time coalesce into ulcerations. In addition, edema and inflammatory changes of the submucosa cause excessive mucus secretion and bleeding. When radiation therapy has ended, the cycle of damage stops, and healing occurs over the next few weeks.

Chronic Radiation Proctocolitis

The pathologic mechanism in chronic RP is entirely different and results from a progressive endarteritis, with abnormal tissue collagen deposition. The affected intestine has a decreased microvascular density, with subsequent decreased perfusion. Over time, the affected bowel gradually becomes more ischemic, leading to ulceration, scarring, and narrowing of the bowel lumen.

Clinical Features

Acute RP manifests with abdominal and rectal pain, diarrhea, bleeding, and tenesmus. Onset during the course of radiation therapy, typically after several treatments, suggests the diagnosis. Symptoms can be severe and can lead to therapy interruption or treatment plan alteration in 5% to 15% of cases.[50]

Chronic RP has a more insidious onset, with a variety of presentations, including ulcerative disease, stricture, obstruction, fistulae, and bowel perforation or may present similarly to acute RP. Bleeding is common but usually is not hemodynamically significant. A decreased caliber of stool, with increased straining or constipation, suggests a stricture. Fistulae can develop between the affected bowel and any adjacent organ, but the most common site is rectovaginal.

Some patients with acute or chronic RP may exhibit anal sphincter dysfunction. Fecal incontinence has been reported in up to 20% of patients, which can be devastating to quality of life.

Differential Diagnosis

In chronic RP, the possibility that symptoms are a result of recurrence of the initial malignancy or a new malignancy induced by radiation exposure should be entertained. Symptoms of chronic RP are generally clinically indistinguishable from those of other causes of bowel inflammation, including IBD, infectious colitis, and ischemic colitis.

Diagnostic Testing

Acute RP is a clinical diagnosis based on the development of typical symptoms in the setting of radiation therapy. Further evaluation is usually not warranted.

Chronic RP is a diagnosis of exclusion. Endoscopy can be suggestive, revealing pale, thickened, and friable mucosa, with prominent telangiectasias. Biopsy specimens often show only nonspecific chronic inflammation.

Management

Acute Radiation Proctocolitis

Treatment of acute RP is symptomatic, and a therapeutic plan should be developed in conjunction with the patient's radiation therapist. Measures to improve the patient's nutritional status should be considered. Steroid enemas (eg, hydrocortisone enema, 100 mg bid) to reduce inflammation, sucralfate enemas (20 mL of a 10% suspension in water bid), and water-absorbing stool softeners to reduce mucus-containing diarrhea are helpful. Reduction of the daily radiation dose also can reduce symptoms significantly. Butyrate enemas may accelerate healing in acute RP because butyrate is a short-chain fatty acid, which is the preferred luminal nutrient for colonocytes.

Chronic Radiation Proctocolitis

Chronic RP treatment also is symptomatic. If rectal involvement is significant, stool softeners, analgesics, antiinflammatory agents (eg, sulfasalazine, mesalazine), and sucralfate enemas are helpful. Metronidazole, 500 mg orally tid given for 4 weeks has been shown to be beneficial in reducing rectal bleeding, mucosal ulcers, and diarrhea when added to the antiinflammatory therapy of mesalazine and betamethasone enemas. Continued rectal bleeding can be controlled with topical formalin or laser photocoagulation.[51] Minimally symptomatic strictures can be managed initially with stool softeners and enemas, which may be enough to reverse the edema and lessen the extent of narrowing. Fistulae and significant strictures generally require surgical repair. Approximately 20% of all patients with chronic radiation injury to the intestinal tract require some type of surgical intervention. Biopsy specimens from ulcerations associated with chronic injury should be obtained to exclude malignancy.

Disposition

Suspected perforation requires emergent surgical consultation, and signs of bowel obstruction should prompt urgent surgical consultation. Unless symptoms are severe, patients with acute or chronic RP can usually be managed on an outpatient basis under the care of their radiation therapist or gastroenterologist. With acute disease, symptoms typically resolve weeks after radiation treatments have been completed. Mild chronic disease typically resolves with medical therapy, but more severe symptoms often require intervention.

KEY CONCEPTS

Irritable Bowel Syndrome

- IBS is a chronic disorder effecting 10% to15% of people that presents with abdominal discomfort (bloating) associated with changes in the form or frequency of stool and is relieved by defecation.
- IBS is treated with diet, behavioral, and pharmacologic therapies.
- New or atypical symptoms in a patient with known IBS should prompt an evaluation for other abdominal pathology.

Diverticular Disease

- Colonic diverticula are present in 10% of people older than 45 years and 80% of people older than 85 years. They can cause bleeding (diverticulosis) or become obstructed and inflamed (diverticulitis).
- Mild uncomplicated cases of diverticulitis can be diagnosed without imaging and treated in the outpatient setting with antibiotics and analgesics in many patients.
- Moderate to severe cases of diverticulitis, and most cases in older patients and immunocompromised patients, require imaging to rule out complications (eg, perforation, abscess formation) and hospitalization for treatment.

Large Bowel Obstruction

- Over 50% of cases of LBO are caused by malignancies; other common causes include volvulus, diverticular disease, and fecal impaction.

KEY CONCEPTS—cont'd

- Gangrene or perforation should be suspected in any patient with persistent unexplained tachycardia, fever, or remarkable abdominal tenderness associated with intestinal disease.
- Over 50% of cases of LBO are caused by malignancies; other common causes include volvulus, diverticular disease, and fecal impaction.
- Gangrene or perforation should be suspected in any patient with persistent unexplained tachycardia, fever, or remarkable abdominal tenderness associated with intestinal disease.

Volvulus

- Volvulus occurs in all age groups but is most common in older adults. It is often associated with a history of constipation, and one-third of cases involve institutionalized patients.
- It often appears as a nonspecific large bowel obstruction on plain radiographs. Abdominal CT is the diagnostic test of choice.
- Sigmoid volvulus can often be decompressed endoscopically unless gangrenous bowel is suspected clinically, whereas cecal volvulus requires surgical management.

Intussusception

- Intussusception in adults is usually associated with a significant cause, often a malignancy.
- In adults, it usually manifests as a partial small bowel obstruction and rarely is associated with the classic triad of abdominal pain, mass, and heme-positive stool seen in children.

Irritable Bowel Disease

- IBD includes two disorders, Crohn's disease (CD) and ulcerative colitis (UC). CD may affect any part of the gastrointestinal tract, usually the distal small intestine and proximal colon. UC affects the colon and rectum but spares the small intestine.
- IBD is a lifelong relapsing disorder that can be treated with a variety of therapies. Treatment decisions are best made in consultation with the physician who will be providing ongoing care for the patient.
- Common complications of IBD include formation of fistulae, strictures, and abscesses; less common but life-threatening complications include fulminant colitis, toxic megacolon, and intestinal perforation.
- Treatment of uncomplicated IBD depends on the clinical classification of disease severity (see Box 85.5).
- Thromboembolic events in IBD patients are often overlooked and underdiagnosed, affecting the venous and arterial systems.
- A new diagnosis of IBD in an older adult should be made only after the exclusion of colonic ischemia.

Colonic Ischemia

- CI typically presents in older patients as the acute onset of mild crampy abdominal pain in the left lower quadrant, with abdominal distention and blood in the stool.
- The differential diagnosis includes diverticulitis, infectious colitis, and IBD.
- Although abdominal CT is not diagnostic for CI, it useful in supporting the clinical suspicion, assessing the extent of colon involvement, diagnosing complications, and excluding other disorders.
- In the absence of surgical complications, the treatment of CI is supportive and includes bowel rest, hydration, and pain management. Broad-spectrum antibiotics covering bowel flora are indicated for patients with more significant symptoms. Surgical management is reserved for patients who have peritoneal signs and/or sepsis or fail medical therapy.

Radiation Proctocolitis

Acute Radiation Proctocolitis

- Acute RP presents as abdominal and rectal pain, with diarrhea and bleeding beginning during or shortly after a course of radiation therapy. It is usually diagnosed clinically and is self-limited.
- Acute RP is treated symptomatically with steroid enemas, water-absorbing stool softeners, and often a reduction of the daily radiation dose.

Chronic Radiation Proctocolitis

- Chronic RP may present similarly to acute RP, but usually has a more insidious onset, with a variety of presentations based on the type of complication—stricture, obstruction, fistulae, ulceration, or bowel perforation. It usually requires endoscopy and biopsy for diagnosis.
- Chronic RP treatment depends on the presenting complication. Rectal involvement is common and can be treated with stool softeners, analgesics, antiinflammatory agents, and sucralfate enemas.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 85: QUESTIONS & ANSWERS

85.1. Which of the following symptoms is most typical for irritable bowel syndrome (IBS)?

A. Anorexia
B. Fever
C. Nocturnal pain
D. Occasional hemoccult-positive stools
E. Pain relieved by defecation

Answer: E. Pain relieved by defecation is typical for IBS. The other listed findings, along with significant abdominal tenderness, would be unusual. IBS can be constipation- or diarrhea-predominant.

85.2. Which of the following statements regarding diverticular disease of the colon is true?

A. Diverticular bleeding is usually painful.
B. Double-contrast barium enema is the emergency department (ED) test of choice for confirmation.
C. It accounts for 40% of lower gastrointestinal (GI) hemorrhage
D. Most patients with diverticulosis develop diverticulitis.
E. The most common site of fistula formation is adjacent bowel.

Answer: C. Diverticular bleeding is typically painless. The most common site of fistula formation is the bladder. Most patients with diverticulosis remain asymptomatic. Double-contrast barium enema is the outpatient test of choice for the diagnosis of diverticulosis, but is not indicated in the acute setting.

85.3. A 59-year-old man with a past history of diverticulosis and diverticulitis presents with his second episode of left lower quadrant (LLQ) abdominal pain. He is afebrile, and laboratory examination is remarkable for a leukocytosis of 13,800/mm^3. Physical examination reveals moderate LLQ tenderness without masses or rebound. A computed tomography (CT) scan of the abdomen reveals a small (4 cm) abscess adjacent to the sigmoid colon,

with moderate diverticulosis-diverticulitis. Which of the following would be the most appropriate treatment?
A. Admission for intravenous antibiotics
B. Confirmation with double-contrast barium enema
C. Discharge on oral antibiotics with 2-day follow-up
D. Radiology consultation for percutaneous drainage
E. Surgical consultation for laparotomy

Answer: A. Abscesses smaller than 5 cm are typically treated with intravenous antibiotics followed by an outpatient oral regimen. Larger abscesses may be drained surgically or percutaneously.

85.4. What is the most common cause of large bowel obstruction?
A. Adhesions
B. Colon cancer
C. Diverticulitis
D. Intussusception
E. Volvulus

Answer: B. Colon cancer accounts for 53% of cases. Volvulus and diverticulitis account for 17% and 12% of cases, respectively. Extrinsic compression from cancer accounts for 6% of cases. Adhesions, unlike for small bowel obstructions, are a rare cause of large bowel obstructions.

85.5. Which of the following is a key difference between sigmoid and cecal volvulus?
A. Clinical presentation
B. Incidence of constipation versus diarrhea
C. Incidence of spontaneous detorsion
D. Preferred method of detorsion
E. Radiographic appearance

Answer: D. Both types of volvulus present with acute or subacute onset of the triad of abdominal pain, distention, and constipation. Spontaneous detorsion is not typical. Sigmoid volvulus is very amenable to endoscopic detorsion, whereas cecal volvulus typically requires surgical detorsion.

85.6. Which of the following statements regarding intussusception is true?
A. Bowel obstruction typically occurs.
B. CT scans have a high sensitivity for detection of intussusception.
C. Most adult cases involve the large bowel.
D. Most adult cases require surgery.
E. Most children have a causative lesion.

Answer: D. In contrast to children, most adult cases have a causative pathologic lesion, usually located within the small bowel. Complete obstruction occurs in less than 20% of cases. CT scans may miss as many as 50% of cases of intussusception. Surgery is usually required FOR adults with intussusception.

85.7. A 29-year-old woman presents with a 4-month history of intermittent abdominal pain with bloating and diarrhea. The diarrhea has been watery, nonbloody, and often nocturnal. Physical examination is remarkable for mild diffuse abdominal tenderness and brown, guaiac-positive stool. Rectal examination also demonstrates a small anal fissure at the 3-o'clock position. Laboratory evaluation is remarkable only for a normocytic anemia with a hemoglobin level of 11.5 g/dL. The diagnosis would most likely be confirmed by which of the following?
A. Colonoscopy
B. CT scan of the abdomen
C. Erythrocyte sedimentation rate
D. Mesenteric angiography
E. Response to a high-fiber diet

Answer: A. This presentation is typical for inflammatory bowel disease. Nocturnal diarrhea, blood in the stool, and presence of an eccentric (nonposterior midline) anal fissure argue against IBS or a benign diarrhea. Ischemic colitis would be unlikely in this age group. Endoscopy with biopsy would be the diagnostic intervention of choice.

85.8. Which of the following statements regarding colonic ischemia is true?
A. CT scanning of the abdomen is diagnostic
B. It is rarely associated with bloody stool.
C. It is typically due to nonocclusive disease.
D. It typically occurs without predictable antecedent events.
E. Specific serum biomarkers may be helpful.

Answer: C. Colonic ischemia is typically due to nonocclusive microvascular disease. It occurs due to low-flow conditions related to congestive heart failure (CHF), renal failure, hypovolemia, or recent illness or surgery. Bloody stools are predictable. It may also occur in younger patients with collagen vascular disease, hematologic abnormalities, or cocaine abuse. There are no sensitive or specific laboratory tests and, although sometimes suggestive, CT scanning primarily rules out other processes.

85.9. Which of the following is not a diagnostic criteria for IBS?
A. Abdominal pain of at least 3 days/month for the previous 3 months
B. Association of discomfort with altered stool form
C. Association of discomfort with altered stool frequency
D. Nocturnal pain
E. Pain relief with defecation

Answer: D. Night time symptoms are generally absent in irritable bowel syndrome and should prompt the provider to look for other possible causes.

85.10. A 38-year-old man presents with his second episode of diverticulitis with LLQ abdominal pain and constipation. Symptoms largely resolve after hydration and conservative management in the E**D.** Which of the following statements is true?
A. A high-fiber diet will exacerbate symptoms acutely.
B. Abdominal CT scanning should be considered.
C. Colonoscopy is required.
D. Surgical referral is indicated.
E. Trace occult blood would be consistent with diverticulitis.

Answer: D. Surgery is reserved for patients with recurrent episodes and ongoing pain.

85.11. A 60-year-old woman without significant medical history presents with 3 days of LLQ pain without fever. The physical examination reveals moderate tenderness to the LLQ. No mass is felt. Pelvic and rectal examinations, including stool guaiac testing, show no abnormality. What is the most appropriate next step in this patient's management?
A. Admit for colonoscopy.
B. Discharge the patient with oral antibiotics.
C. Obtain a CT scan of the abdomen and pelvis.
D. Perform an ultrasound of the pelvis.
E. Request urgent general surgery consultation.

Answer: B. Patients who are otherwise healthy, and of the appropriate age, have a good clinical examination for diverticulitis, and lack any signs of an abscess or more serious disease can be treated empirically with antibiotics as outpatients.

85.12. What would be the most appropriate management strategy for the patient in question 85.11 if she were taking immunosuppressant medications for advanced rheumatoid arthritis?
A. Admit for colonoscopy.
B. Discharge the patient with oral antibiotics.
C. Obtain a CT scan of the abdomen and pelvis.
D. Perform an ultrasound of the pelvis.
E. Request urgent general surgery consultation.

Answer: C. Patients taking immunosuppressant medication who present with diverticulitis may have much more serious disease than their physical examination would suggest. Such patients are at higher risk for bowel perforation by the time of presentation and should undergo more extensive evaluation to exclude complications.

85.13. A patient with known ulcerative colitis presents with abdominal distention and significant dehydration. The patient appears acutely ill. A plain film of the abdomen shows a dilated segment of transverse colon measuring 8 cm in width. All of the following are indicated except:
A. Antibiotics covering bowel flora
B. Intravenous corticosteroids
C. Intravenous rehydration
D. Serum chemistry measurements
E. Urgent colonoscopy to decompress the bowel

Answer: E. This patient has toxic megacolon, which does not generally have an obstructing lesion.

85.14. A patient who presents with the acute onset of tenesmus and blood-streaked stool reports that he is currently undergoing pelvic radiation for prostate cancer. What is the most appropriate next step in the patient's management?
A. Admit for colonoscopy.
B. Develop a care plan with the patient's radiation therapist.
C. Refer to a gastroenterologist for proctoscopy.
D. Perform anoscopy.
E. Send a stool sample to test for *Clostridium difficile*.

Answer: B. Acute radiation proctocolitis generally responds well to lowering the dose of radiation and symptomatic treatment. It generally resolves shortly after radiation treatments are completed. Those coordinating the patient's radiation treatment should be made aware of this complication.

CHAPTER 86

Disorders of the Anorectum

Wendy C. Coates

PRINCIPLES

Patients visit the emergency department (ED) with a variety of anorectal complaints. Sensitivity and a professional demeanor should be maintained in interactions with these patients, who may find it difficult to discuss historical details openly and to describe physical complaints related to this area of the body and its function.

The anorectum begins at the rectosigmoid junction at the level of the third sacral vertebra (S3), the rectum follows the sacral curvature for 12 to 15 cm and then sharply turns posteriorly and inferiorly at the puborectalis muscle (Fig. 86.1). Here the anal canal begins its 4-cm course to the anus, which is supported by three muscle groups—levator ani and internal and external anal sphincters. Anal valves and crypts with mucous glands for lubrication are located 2 cm proximal to the anal verge at the dentate line. Proximal to the crypts are the columns of Morgagni, where the epithelium of the anal canal changes from pink columnar (as in the rectum) to squamous.

The superior, middle, and inferior hemorrhoidal arteries provide the blood supply to the anorectum. They arise from the inferior mesenteric, internal iliac, and internal pudendal arteries, respectively. The superior hemorrhoidal veins drain into the portal system, and the inferior hemorrhoidal veins drain into the caval system. Lymphatic drainage is to the inferior mesenteric nodes above the dentate line and to the inguinal nodes from all areas of the anorectum.

Sympathetic and parasympathetic nervous systems function together to retain the contents of the rectum until evacuation is desired. Sympathetic fibers from L1 to L3 (upper rectum) and presacral nerves (lower rectum) inhibit the contraction of rectal smooth muscle, and L5 fibers cause the internal sphincter to contract. Elimination occurs when parasympathetic fibers from the anterior roots of S2 to S4 cause the rectal wall to contract and the internal sphincter to relax. Voluntary external sphincter control is mediated by motor branches of the pudendal nerve (S2, S3) and the perineal branch of S4. The levator ani is supplied by the pudendal nerve and pelvic branches of S3 to S4 fibers. Sensory perception of rectal distention relies on parasympathetic fibers from S2 to S4. The abundant sensory nerve endings of the distal anal epithelium transmit via the pudendal nerve.

Defecation begins as the rectum becomes distended, the internal sphincter relaxes, and stool enters the anal canal. At an appropriate time and place, the external sphincter is relaxed to complete the process of elimination. When voluntary straining is required, abdominal muscles contract, the rectal angle straightens, and the pelvic floor descends. To postpone defecation, the external sphincter contracts voluntarily, relaxing the rectal wall and quelling the urge to defecate unless there is an underlying sphincter disorder or an overwhelming volume of stool.

CLINICAL FEATURES

A history of anorectal and gastrointestinal (GI) symptoms and the presence of systemic disease elucidate the diagnosis of most anorectal disorders (Box 86.1; Fig. 86.2). Common complaints include bleeding, swelling, pain, itching, and discharge. History should include questions about onset, duration, quality, bowel habits (changes in color, frequency, or consistency of the stool and the presence of straining, flatus, and incontinence of solid or liquid stool); a history of radiation exposure or sexual practices is helpful in select cases. Underlying GI disorders (eg, Crohn's disease, cancer, polyps) often produce atypical presentations. Patients with an underlying systemic disease such as AIDS, cancer, diabetes mellitus, and coagulopathy may develop more serious complications of standard anorectal conditions.

In patients presenting with rectal bleeding, the color, amount, and relationship to defecation are important factors in establishing the cause. Pain and bright red blood signify anal fissures or hemorrhoids. Fissure pain is sharp, sudden in onset, and not associated with swelling, whereas pain from a prolapsed or thrombosed hemorrhoid is gnawing, continuous, and of a more gradual onset. Painless rectal bleeding occurs with internal hemorrhoids, cancer, or precancerous lesions. Red blood on the toilet paper usually is caused by anal fissures or external hemorrhoids; however, minute quantities can result from any irritating condition. Bright red blood that drips into the toilet bowl or streaks around the stool is caused by internal hemorrhoids. Blood mixed with stool originates above the rectum, whereas melena indicates a more proximal source. Bloody mucus is associated with cancer, inflammatory bowel disease, and proctitis.[1]

Patients who report a perianal swelling or have the sensation of rectal fullness often list hemorrhoids as their chief complaint. Painful swellings that bleed usually are thrombosed hemorrhoids, but abscesses, pilonidal disease, and hidradenitis suppurativa should be considered. Painless, itchy swellings may be caused by condylomata acuminata or secondary syphilis. A mass protruding through the anal orifice may signal rectal prolapse or cancer (Fig. 86.3).

Severe, episodic anorectal pain that is not associated with bleeding or swelling may represent proctalgia fugax or levator ani syndrome. Perianal itching (pruritus ani) is caused by any lesion that makes hygiene difficult or may be attributed to certain foods or medications.

The physical examination should ensure the patient's comfort and privacy. With the patient in the left lateral decubitus position and covered with a sheet, inspect the buttocks and anal orifice. Note elements of personal hygiene and anatomic disruptions, such as fissures, skin tags, lesions, protruding hemorrhoids, and abscesses. Ask the patient to strain and note the integrity of the pelvic floor, prolapse of hemorrhoids, or rectal mucosa. A digital rectal examination begins by placing a well-lubricated gloved finger flat against the anal opening, exerting gentle pressure until the external sphincter relaxes, allowing the finger to enter the anus. Assess anal sphincter tone by asking the patient to squeeze the anal muscles against the examining finger. Accessible areas of the anorectum can be examined for masses and areas of tenderness with a circumferential sweep. The cervix or prostate can be palpated through the rectal wall. On withdrawal, the contents on the glove can be assessed for frank or occult blood, mucus, or pus.

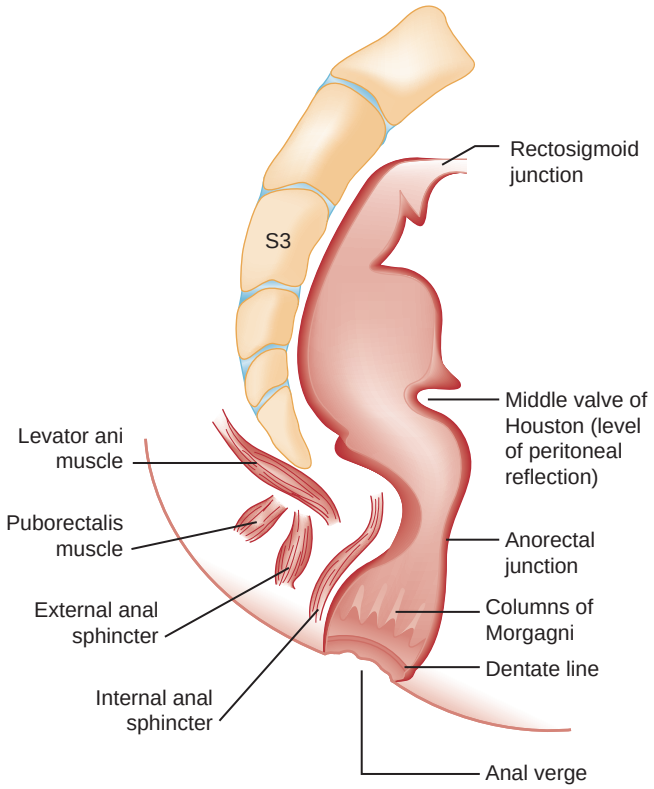

Fig. 86.1. Anorectal anatomy.

BOX 86.1

Medical History in Diagnosis of Anorectal Disorders

ANORECTAL HISTORY
Pain
Bleeding
Swelling
Itching
Discharge
Urgency

GASTROINTESTINAL HISTORY
Change in bowel habits (straining, flatus, color, consistency, frequency)
Nausea or vomiting
Incontinence of stool
Underlying GI disease (Crohn's disease, cancer, polyps)

SYSTEMIC DISEASE HISTORY
Diabetes mellitus
Coagulopathy
Cancer
HIV infection

SEXUAL HISTORY OF THE ANUS
Penetration
Known STDs
Assault

GI, Gastrointestinal; *HIV,* human immunodeficiency virus; *STD,* sexually transmitted disease.

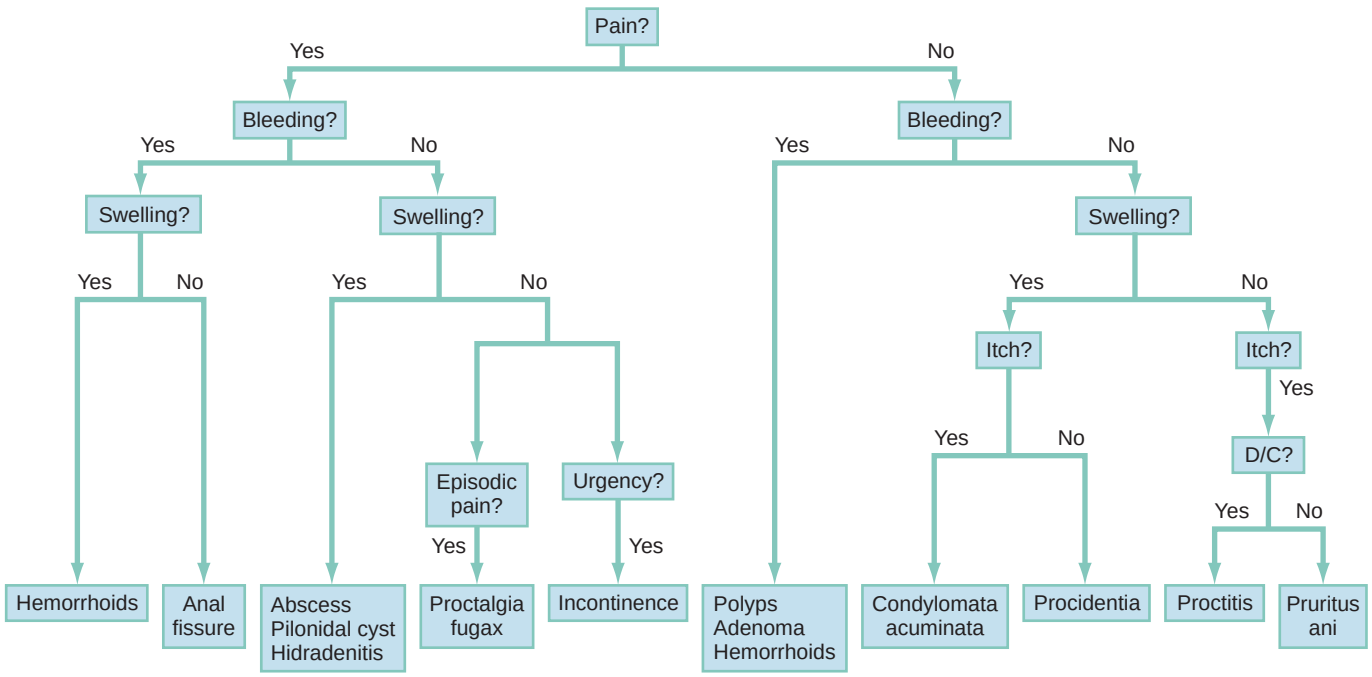

Fig. 86.2. Algorithm for anorectal complaints. *D/C,* Discharge.

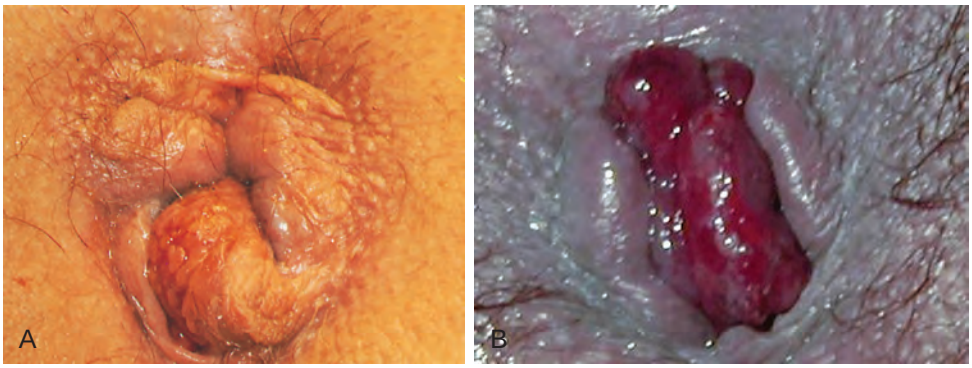

Fig. 86.3. Thrombosed hemorrhoids. **A,** External. **B,** Internal. Note the engorged external hemorrhoids surrounding the thrombosed internal hemorrhoids. (**A,** Courtesy Dr. Michelle Lin, Harbor-UCLA Medical Center; **B,** courtesy Dr. Gershon Effron, Sinai Hospital of Baltimore; from Seidel HM, et al, editors: Mosby's guide to physical examination, ed 4, St. Louis, 1999, Mosby.)

Direct visualization of the anus may be accomplished by anoscopy. A lubricated anoscope is inserted into the anus, with the obturator in place. When the obturator is removed, the rectal mucosa can be viewed for sites of bleeding, hemorrhoids, masses, or abnormal tissue and finally the dentate line and anal epithelium.

SPECIFIC ANORECTAL PROBLEMS

Hemorrhoids

Principles

Hemorrhoids occur when the three anal vascular submucosal cushions become engorged. Blood supply arises from the arterial system, causing hemorrhoidal bleeding to be bright red. The muscularis submucosa cushions the anal canal during defecation and aids fecal continence. As the supportive tissue deteriorates, venous distention, prolapse, bleeding, and thrombosis may occur. Some controversy exists about whether straining and constipation cause these changes by producing venous backflow when intra-abdominal pressure increases.[2] A familial predisposition is recognized, but whether this is a result of genetics or acquired factors such as diet is unknown. Direct pressure on a hemorrhoidal vein can produce symptomatic hemorrhoids in pregnant women, and thrombosed hemorrhoids are associated with traumatic deliveries.

Hemorrhoids are not varicose veins; they are normal structures that manifest symptoms when the muscularis submucosa weakens and the anal cushions are displaced distally. Conditions that increase sphincter tone correlate with a higher prevalence of hemorrhoids. Portal hypertension does not cause hemorrhoids in adults, although it appears to be a cause in children.[3] Bleeding in patients with portal hypertension may be caused by rectal varices, which are vascular communications between the superior and middle hemorrhoidal veins.

Clinical Features

Patients often refer to any perianal condition as hemorrhoids. Bleeding with defecation is the most common complaint and, unless the hemorrhoids are thrombosed, it usually is painless. Patients report variable amounts of bright red blood on the toilet paper or toilet bowl. Many complain of swelling, itching, mucoid discharge, or a moist perianal area. History should address recent stool patterns, such as diarrhea or constipation, chronic medical problems, such as portal hypertension or bleeding disorders, and a dietary and family history. Frequent bowel movements, prolonged sitting, heavy lifting, and straining while defecating exacerbate symptoms.

TABLE 86.1

Types of Hemorrhoids

TYPE	ORIGIN	EPITHELIUM
External	Inferior hemorrhoidal plexus Proximal to dentate line	Modified squamous epithelium (anoderm)
Internal	Superior hemorrhoidal plexus Distal to dentate line	Transitional or columnar epithelium (mucosa)
Mixed	Superior and inferior hemorrhoidal plexus	Transitional, columnar, or modified squamous epithelium (mucosa and anoderm)

TABLE 86.2

Classification of Internal Hemorrhoids by Severity

TYPE	PROLAPSE	MODE OF REDUCTION	TREATMENT
First degree	None	N/A	Medical
Second degree	During defecation	Spontaneous	Medical
Third degree	May be spontaneous or during defecation	Manual	Medical Optional surgical repair
Fourth degree	Permanent	Irreducible	Surgical repair

N/A, Not applicable.

Physical examination should ascertain the type and degree of hemorrhoids by visual inspection at rest and during straining. Nonprolapsing hemorrhoids can be visualized on anoscopy as a focus of bleeding or as they bulge when the patient is asked to strain. Anoscopy is painful and is not useful in cases of prolapsed or thrombosed hemorrhoids (Table 86.1). Table 86.2 shows the classification of hemorrhoids based on history, physical findings and reducibility.

Management

The symptoms of nonthrombosed external and nonprolapsing internal hemorrhoids can be ameliorated by a standard regimen,

WASH (***w***arm water, ***a***nalgesics, ***s***tool softeners, and ***h***igh-fiber diet) aimed at combating the problems that led to their formation (Box 86.2). Anal canal pressures decrease in warm water (40°C [104°F]).[4] Patients can direct a shower stream at the area for several minutes or take sitz baths. Drinking water helps produce softer stool. Mild oral analgesic agents such as acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) reduce pain. Passage of stool is easier with stool softeners and a high-fiber diet (20–30 g of dietary fiber/day). Several over-the-counter preparations are available for the treatment of hemorrhoidal symptoms; however, their use is directed at improved hygiene and temporary symptom relief rather than correction of the condition. Topical anesthetics, corticosteroids, astringents (eg, witch hazel), mineral oils, and cocoa butter are recommended in the literature although there is no evidence to support the use of one over the other.[4] Prolonged use of topical corticosteroids beyond a few days produces atrophic skin changes and is discouraged.

Patients with second- or third-degree internal hemorrhoids benefit from the WASH regimen and may be discharged from the ED; however, permanent resolution of symptoms may require surgical banding, sclerotherapy, or elective hemorrhoidectomy (Table 86.3). Patients with acute, gangrenous, thrombosed fourth-degree internal hemorrhoids may require emergent hemorrhoidectomy.[5]

Acutely thrombosed external hemorrhoids can be excised (not incised and drained) in the ED to provide relief within the first 72 hours after the onset of symptoms (Fig. 86.4). Incision results in incomplete evacuation of the clot, subsequent rebleeding, swelling, and formation of a skin tag. If not excised, a thrombosed external hemorrhoid resolves spontaneously after several days when it ulcerates and leaks the dark accumulated blood. Residual skin tags may persist, making anal hygiene more challenging. In the ED setting, this procedure is not commonly performed in pediatric patients, pregnant women, or immunocompromised patients.

Nonsurgical therapy with topical nifedipine (0.3%) and lidocaine (1.5%) gel may alleviate symptoms. Although not widely used, the purported effectiveness of this regimen is related to the ability of nifedipine to modulate resting sphincter tone and thereby reduce the associated pain and inflammation.[6]

BOX 86.2

WASH Regimen for Management of Hemorrhoids

Warm water
Analgesic agents
Stool softeners
High-fiber diet

TABLE 86.3

Surgical Management of Hemorrhoids

CLASSIFICATION	MANAGEMENT
Thrombosed external hemorrhoids	Excision in emergency department
Second- and third-degree internal hemorrhoids	Elective surgical repair Banding Sclerotherapy Hemorrhoidectomy
Fourth-degree hemorrhoids (nonthrombosed)	Nonemergent hemorrhoidectomy
Thrombosed or gangrenous fourth-degree internal hemorrhoids	Emergent hemorrhoidectomy

Anal Fissures

Principles

The development of an anal fissure is the most common cause of intensely painful rectal bleeding of sudden onset. A superficial tear in the anoderm results when a hard piece of feces is forced through the anus, usually in patients who are constipated. It is the most commonly encountered anorectal problem in pediatric patients, especially infants.[7] Most fissures occur along the posterior midline, where the skeletal muscle fibers that encircle the anus are weakest. Anterior midline fissures are more common in women than in men. Fissures that occur elsewhere may be associated with systemic disease such as leukemia, Crohn's disease, human immunodeficiency virus (HIV) infection, tuberculosis (TB), or syphilis. If not treated promptly, the classical so-called fissure triad of deep ulcer, sentinel pile, and enlarged anal papillae may develop (Fig. 86.5). A sentinel pile forms when the skin at the base of the fissure becomes edematous and hypertrophic; it can form a permanent skin tag and underlying fistulous tract.

Clinical Features

The patient with an anal fissure reports sudden, searing pain during defecation that may be accompanied by a small amount of bright red blood in the stool or on the toilet paper. This is followed by a nagging, burning sensation caused by internal sphincter spasm. Subsequent bowel movements are excruciating, and the external sphincter may exhibit a reflex spasm. A physical examination must be performed cautiously to avoid further spasm and pain. The depth of the fissure, its orientation to the midline, and the presence of a coexisting sentinel pile should be noted. A digital rectal examination during an acute exacerbation often is impossible because of pain and sphincter spasm.

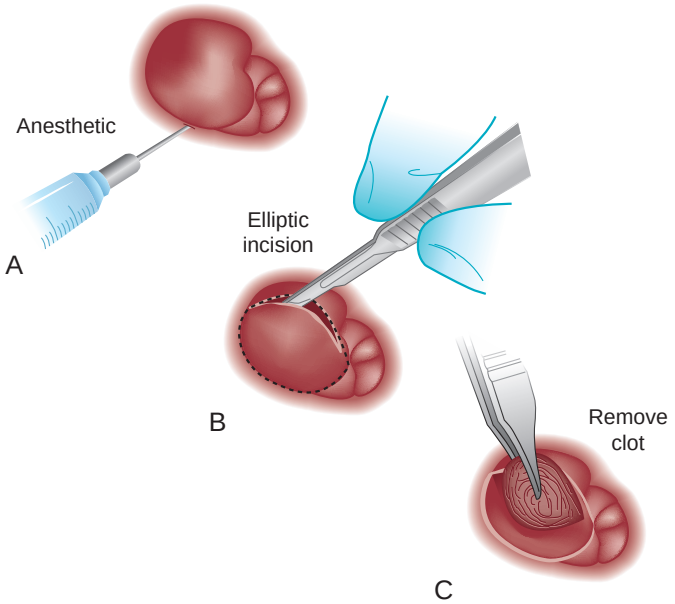

Fig. 86.4. Excision of thrombosed external hemorrhoid. **A,** Field block with local anesthetic. **B,** An elliptic incision is made around the hemorrhoid. **C,** The thrombosed hemorrhoid is removed. (From Larson S, et al, editors: Atlas of emergency procedures, St. Louis, 2001, Mosby.)

Management

Specific measures for the treatment of anal fissures are summarized in Box 86.3. Treatment with the WASH regimen (see Box 86.2) focuses on eliminating constipation with a bulking agent, stool softener, and high-fiber diet. Limited use of topical anesthetics may be helpful. Parental encouragement of pediatric patients helps prevent encopresis, which can result from a fear of painful bowel movements. Most acute uncomplicated fissures resolve in 2 to 4 weeks.

Fig. 86.5. Lateral anal fissure. (Courtesy Dr. Gershon Effron, Sinai Hospital of Baltimore; from Seidel HM, et al, editors: Mosby's guide to physical examination, ed 4, St Louis, 1999, Mosby.)

BOX 86.3

Treatment of Anal Fissures

- WASH regimen[a]
- Nitroglycerin ointment (0.4%) bid or tid
- Nifedipine gel (0.2%) bid with lidocaine (1.5%)
- Botulinum toxin (surgical consultation)
- Anal dilation performed with the patient under general anesthesia
- Surgical excision

[a]See Box 86.2.

For adult patients with chronic anal fissures, application of various topical agents aimed at reducing sphincter pressures and local pain may be effective. Nitroglycerin ointment applied topically to the anoderm 2 or 3 times daily may relieve the pain but may cause a vasodilatory headache. Nifedipine gel (0.2%) in combination with lidocaine (1.5%) applied to the anal area twice daily is effective in promoting healing and reducing discomfort in the management of anal fissures by reducing anal canal pressures through local calcium channel blockade. Referral to a colorectal surgeon for definitive management may include injection of botulinum toxin, anal dilation, or sphincterotomy.

Abscesses and Fistulae

Principles

Anorectal abscesses and fistulae occur in otherwise healthy adults when the mucus-producing glands at the base of the anal crypts occlude and may herald the presence of inflammatory bowel disease, trauma, cancer, radiation injury, or infection (TB, lymphogranuloma venereum, actinomycosis). Common causative bacteria are *Staphylococcus aureus, Escherichia coli, Streptococcus, Proteus,* and *Bacteroides.*[8]

Anorectal abscess is an acute disease that naturally progresses to fistula formation in the body's attempt to drain the infection spontaneously. Symptoms vary depending on the site of infection, but incision and drainage constitute the curative treatment in all cases (Table 86.4). Delays may allow extension of the infection and eventual compromise of the sphincter mechanism.[9] Adjunctive antimicrobial therapy is indicated in patients who are immunocompromised or diabetic or have valvular heart disease.[10]

Sites of anorectal abscess formation are depicted in Fig. 86.6. The difficulty in diagnosis is that pain often precedes physical findings of a mass or fluctuance. One-third of patients with AIDS develop anorectal abscesses and fistulae, which may also direct antibiotic therapy. HIV-infected patients may have an incomplete fistulous tract, which impedes spontaneous drainage, highlighting the urgency of treating these patients promptly.

Management

Perirectal and Perianal Abscesses. Perirectal and perianal abscesses account for 40% to 45% of anorectal abscesses. They produce painful swelling at the anal verge that is worsened by defecating or sitting. Most patients are afebrile and have localized tenderness, erythema, swelling, and fluctuance. ED management by incision and drainage is usually possible in patients who do not have comorbidities (eg, diabetes mellitus, extremes of age, compromised immune status). Some patients may be unable to

TABLE 86.4

Types of Abscesses of the Anorectum

FEATURE	PERIANAL	ISCHIORECTAL	INTERSPHINCTERIC	SUPRALEVATOR	POSTANAL
Incidence	40%–45%	20%–25%	20%–25%	<5%	5%–10%
Location	Outside and verge	Buttocks	Lower rectum	Above levator ani	Deep to external sphincter
Symptoms	Painful perianal mass	Buttock pain	Rectal fullness	Perianal and buttock pain	Rectal fullness, pain near coccyx
Fever, ↑ WBCs	–	±	±	+	+
Associated fistula	++	+	+++	+++	–
ED incision and drainage	+	±	–	–	–

ED, Emergency department; *WBCs,* white blood cells; –, does not occur; ±, occurs sometimes; ++, occurs often; +++, usually occurs.

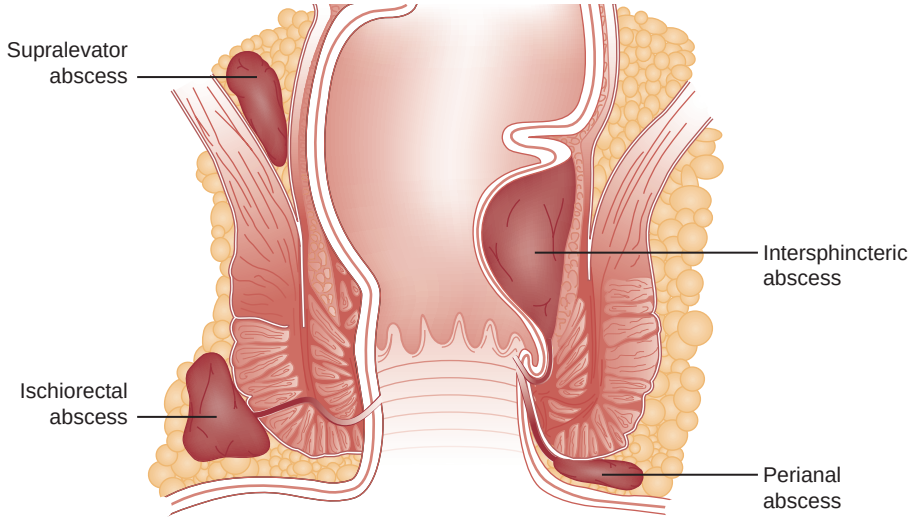

Fig. 86.6. Location of common anorectal abscesses. (Adapted from Gordon PH, Nivatvongs S: Principles and practice of surgery for the colon, rectum, and anus, St. Louis, 1992, Quality Medical Publishing.)

tolerate the procedure without general or regional anesthesia. The WASH regimen (see Box 86.2) may alleviate postprocedure discomfort. Antibiotics are unnecessary in healthy adult patients, except in cases involving associated cellulitis.[10-12]

Ischiorectal Abscess. One-fifth to one-quarter of abscesses form outside the sphincter muscles in the buttocks, and patients generally present complaining of severe pain. The diagnosis is obvious if an indurated mass is seen on the buttocks but is more difficult if the abscess is deep. Patients may have fever and leukocytosis. If there is no induration, ultrasound is useful to localize fluid collections and guide aspiration. Although many of these abscesses will require drainage performed with the patient under general anesthesia, superficial abscesses can be treated in the ED. If the patient is febrile, a short course of antibiotics, such as cephalexin, may be considered, beginning with a parenteral dose before drainage, followed by 500 mg orally qid for 3 to 7 days.[13]

Intersphincteric Abscess. One-fourth of abscesses form in the space deep to the external sphincter and inferior to the levator ani. The infection tracks cephalad and may appear to be a mass in the rectum; it can be confused with a thrombosed internal hemorrhoid. Patients report continuous rectal pressure and a throbbing pain exacerbated by defecation or sitting. They may have fever and leukocytosis. External evidence of inflammation may be lacking, but a rectal examination reveals an erythematous, indurated, and sometimes draining mass. Associated fistulae and inguinal lymphadenopathy are common. Surgical management is required to evaluate and treat the entire abscess and fistula network.

Supralevator Abscess. Accounting for less than 5% of abscesses, supralevator abscesses cause perianal and buttock pain associated with fever and leukocytosis. External evidence usually is absent, which often delays the diagnosis. Many patients are obese or have diabetes, Crohn's disease, pelvic inflammatory disease, or diverticulitis. A tender mass may be palpated on rectal or pelvic examination. Emergent surgical treatment is indicated to drain the abscess and excise the fistulous network.

Postanal Abscess. These abscesses are uncommon and occur posteriorly to the rectum, deep to the external sphincter and inferior to the levator ani. Patients experience severe rectal discomfort and coccygeal pain. They usually are febrile and have continuous pain that does not change with position. A rectal examination is painful, and anal drainage is rare. Many of these abscesses are missed on initial presentation, and patients often return with draining abscesses that are managed surgically.

Horseshoe Abscess. A large, communicating, horseshoe-shaped abscess forms in the ischiorectal, intersphincteric, or supralevator space. Surgical management is necessary.

Necrotizing Infection. A delay in management of an anorectal abscess may lead to the destruction of tissue, especially in diabetic or immunocompromised patients. Widespread cellulitis, necrotic tissue, and gas on radiography suggest the possibility of necrotizing fasciitis, Fournier's gangrene, or tetanus. Wide surgical débridement, broad-spectrum antibiotics with anaerobic coverage, and tetanus prophylaxis are indicated.

Fistulae. A fistula is a connection between two epithelium-lined surfaces and commonly develops in patients with abscesses; other causes include Crohn's disease, trauma, foreign body reactions, TB, and cancer. The anorectal complaint may be the presenting symptom of the underlying disease. Patients notice a recurrent or persistent perianal discharge that becomes painful when one of the openings becomes occluded. A digital rectal examination may reveal a tract in the perineum or canal. Probing of fistulous tracts is not recommended because the danger of creating a new tract outweighs the benefit of identifying the path of the existing fistula. Spontaneous resolution of fistula-in-ano is rare. Although symptoms may resolve when antibiotics are administered, they commonly return as soon as therapy is discontinued; definitive treatment of the fistulous network at the time of incision and drainage of the abscess prevents ongoing progression of the disease continuum. Fistulectomy or application of fibrin glue are commonly accepted practices of colorectal surgeons.[13] Nonsurgical treatments that have been proposed for patients with Crohn's disease include administration of infliximab or cyclosporine and hyperbaric oxygen therapy.

Pilonidal Disease

Principles

Abscesses containing hair and pus in the midline of the sacrococcygeal area afflict young adults with a 4:1 male predominance and are more common in obese and hirsute persons. The disease is rare in people older than 40 years, even for those who were affected in their youth, and should not be confused with anal fistulae, perirectal abscesses, hidradenitis suppurativa, or granulomatous

diseases (eg, syphilis, TB). It is believed to arise when bacteria enter the usually sterile hair follicle and produce inflammation and edema, thereby occluding the opening to the skin surface. The contents expand until the hair follicle ruptures, and the material spreads into the subcutaneous fatty tissue, where a foreign body reaction leads to abscess formation. The purulent material subsequently tracks to the presacral skin through an epithelialized tract. In those with chronic or recurrent disease, visible or palpable tracts containing hair and cellular debris may be identified.

Management

Treatment options vary, ranging from aspiration to extensive surgical excision. Supplementary antibiotics, such as cephalexin 500 mg qid, are indicated in cases accompanied by cellulitis, but are not effective as the sole treatment. ED management of pilonidal disease involves drainage of the acute abscess for relief of symptoms. Aspiration of pus plus antibiotics and referral to a surgeon in 1 week may promote faster recovery than incision and drainage.[14] If incision and drainage is done, a longitudinal incision lateral to the midline prevents reaccumulation of debris and minimizes the inflammatory response in the midline. Recalcitrant disease may require surgical unroofing, marsupialization, or wide excision.

Hidradenitis Suppurativa

Principles

Perianal hidradenitis suppurativa is an infection of the apocrine glands. It is most common in young adults and is associated with poor skin hygiene, hyperhidrosis, obesity, acne, diabetes mellitus, and smoking. Occluded apocrine ducts may be infected with strains of *Staphylococcus, Streptococcus, E. coli,* or *Proteus.* Extension through the dermis spreads the infection to neighboring ducts and a network of sinus tracts, leading to extensive scarring.[15]

Clinical Findings

Patients report one or more tender, draining pustules in the perianal area, which may be associated with fever, leukocytosis, and malaise. Local lymphadenopathy and surrounding cellulitis are common.

Differential Diagnosis

This condition commonly is misdiagnosed as pilonidal disease or fistula-in-ano. Other considerations in the differential diagnosis include sebaceous cysts, furuncles, granulomas (from TB or syphilis), and Crohn's disease.

Management

Treatment begins with careful attention to perianal hygiene, warm compresses, antibiotics (eg, cephalexin, 500 mg PO qid), and dietary modifications (avoidance of dairy products and foods with a high glycemic index). Drainage of isolated lesions may provide symptomatic relief, but the recurrence rate approaches 40%. Referral to a surgeon for wide excision of tissue involved in advanced chronic disease may be necessary.

Proctalgia

Anorectal pain (proctalgia) that does not arise from one of the organic disorders described earlier can be severe and difficult to treat. Two common causes are levator ani syndrome and proctalgia fugax. These disorders can be distinguished by their patterns of affliction. Other causes of pelvic pain, such as tumors, cauda equina syndrome and endometriosis, should be considered.

Levator Ani Syndrome

A constant dull pressure in the sacrococcygeal region precipitated by defecation or prolonged periods of sitting suggests levator ani syndrome. The patient usually has tenderness of the levator muscles, which may be firmly contracted on examination. No standard treatment regimen has been studied, but anecdotal reports indicate that sitz baths, levator ani muscle massage, and muscle relaxants can provide relief.[16]

Proctalgia Fugax

Proctalgia fugax is an intensely painful spasm in the rectal area that begins abruptly and lasts up to 30 minutes, resulting from a sudden spasm of the levator muscle complex or sigmoid colon. Professionals, managers, perfectionists, and people who frequent the toilet are more likely to be affected. Symptoms begin abruptly during sleep, defecation, urination, or intercourse. The nature of the pain has been compared to that of charley horse (painful spasms in the leg muscles) and may radiate to the coccyx or perineum. Each patient has a unique but recurrent constellation of symptoms. Treatment includes a bowel-cleansing regimen, upward manual pressure on the anus, diazepam, and topical nitrates.

Fecal Incontinence

Principles

Fecal incontinence is an embarrassing condition that affects parous women, older adults, and patients with a variety of neurologic or traumatic disorders. The delicate balance among the pelvic floor muscles, sphincters, and anorectal sensation is disrupted in this condition. Complete incontinence is the inability to control passage of solid feces. Partial incontinence is characterized by loss of control of the passage of flatus or liquid feces.

Multiple causes of fecal incontinence have been described (Box 86.4). Liquid feces may seep around tumors or foreign bodies of the rectum or anal canal. Explosive diarrhea from laxative abuse, inflammation, or infection can temporarily overwhelm a normal sphincter mechanism. Encopresis may develop in young children experiencing emotional stress. In otherwise healthy children, sexual abuse involving the anus should be considered.

Clinical Features

The anorectum should be assessed for masses, hemorrhoids, evidence of previous surgery, and neuromuscular function. Neuromuscular causes of fecal incontinence are diagnosed by anorectal physiologic testing.

Management

The approach to management of fecal incontinence depends on the cause. In cases of transient incontinence caused by diarrhea, a high-fiber diet and brief therapy with loperamide, 2 mg, after each bowel movement, up to a maximum of 8 mg a day, can solidify stool and enhance rectal compliance. Kegel exercises, which contract the perineal muscles, biofeedback training, or surgical repair may be indicated.

BOX 86.4

Causes of Fecal Incontinence

TRAUMATIC CAUSES
Iatrogenic (surgical) nerve injury
Spinal cord injury
Obstetric trauma
Sphincter injury

NEUROLOGIC CAUSES
Spinal cord lesions
Dementia
Autonomic neuropathy (eg, diabetes mellitus)
Obstetric—pudendal nerve damage from stretching during surgery, Hirschsprung's disease

MASS EFFECT
Carcinoma of anal canal
Carcinoma of rectum
Foreign body
Fecal impaction
Hemorrhoids

MEDICAL CAUSES
Procidentia
Inflammatory disease
Diarrhea
Laxative abuse

PEDIATRIC PATIENTS
Congenital
Meningocele
Myelomeningocele
Spina bifida

OTHER CAUSES
After corrective surgery for imperforate anus
Sexual abuse
Encopresis

BOX 86.5

Causes of Pruritus Ani

DERMATITIS
Fecal Irritation
Poor hygiene
Anorectal conditions—fissure, fistula, hemorrhoids, skin tags, perianal clefts
Systemic—caffeine, tea, beer, spicy foods, citrus fruits, quinidine, intravenous hydrocortisone, colchicine, tetracycline

Contact Dermatitis
Anesthetic agents, topical corticosteroids, perfumed soap

SYSTEMIC DISEASES
Dermatologic
Psoriasis, seborrhea
Lichen simplex or lichen sclerosus

Nondermatologic
Chronic renal failure, myxedema, diabetes mellitus, thyrotoxicosis, polycythemia vera
Vitamin A or D deficiency, iron deficiency
Cancer—Bowen's, Paget's, Hodgkin's disease

INFECTIONS
STDs
Syphilis
HSV infection
HPV infection

Other Infectious Processes
Scabies
Pinworm
Bacterial infection
Fungal infection

HPV, Human papillomavirus; *HSV,* herpes simplex virus; *STD,* sexually transmitted disease.

Pruritis Ani

Principles

Patients with pruritus ani complain of an uncontrollable urge to scratch the perianal area. The condition is more common in the summer and is more noticeable at night. The sensation of itching arises when the richly innervated perianal skin becomes irritated. Vigorous scratching may result in excoriation. The most common cause is the presence of feces on the perianal skin. Conditions ranging from poor personal hygiene to anatomic disorders allow feces to accumulate. Obesity, deep perianal clefts, hair, hemorrhoids, skin tags, rectal prolapse, anal fissures, and fistulae make the area difficult to clean effectively. Decreased air circulation from wearing tight pants or undergarments of synthetic nonbreathable fabric may exacerbate symptoms. The causes of pruritus ani are summarized in Box 86.5. The acronym "ITCH" categorizes typical causes—***i***nfection, ***t***opical irritants; ***c***utaneous conditions and cancer; ***h***ypersensitivity to foods and drugs.[2]

Diagnostic Testing

Pinworms are most commonly found in young children and close contacts as well as in institutionalized patients. The organisms can be identified by applying transparent tape to the perianal area and attaching it to a glass slide. Visualization of eggs under the low-power objective of a microscope confirms the diagnosis.

Management

A careful history and physical examination will generally identify the cause of pruritus ani. Important considerations include hygienic care of the anus, coexisting anorectal or systemic conditions, diet, and sexual practices.

The first-line agent for pinworms is mebendazole (Vermox), 100 mg orally. An alternative agent is pyrantel pamoate (Antiminth), 1 g orally (11 mg/kg, to a maximum of 1 g for pediatric patients).[17] A repeat dose may be needed in 2 weeks. Scabies and pediculosis pubis should be treated with 5% permethrin cream.

Dermatitis caused by a fungal infection is characterized by sharply demarcated borders and is treated with clotrimazole 1% or nystatin cream. Definitive treatment of concomitant anorectal conditions (eg, fissures, fistulae, hemorrhoids, skin tags, rectal prolapse) can prevent recurrence of pruritus ani.

Underlying systemic diseases that have perianal manifestations should be treated. Patients should clean the area thoroughly with lukewarm water after each bowel movement and pat (rather than rub) dry with tissue that is free of chemical irritants. Loose-fitting underwear and exposure to fresh air may alleviate symptoms. The treatment of acute dermatitis includes a short course of topical

corticosteroids, such as hydrocortisone 2.5%, calamine lotion, and systemic antihistamines. Some success with topical application of capsaicin cream has been reported, although there is insufficient evidence to support a recommendation.

Sexually Transmitted Disease and Proctitis

Principles

Anorectal transmission of sexually transmitted disease (STD) is a concern in all sexually active patients with anorectal complaints, but especially in those with HIV. The history should ascertain whether sexual practices involve oral-anal contact or anal penetration and whether condoms are used. Education regarding transmission of STDs and the efficacy of barrier methods is an important means of public health prevention of disease.[18] Semen has a concentrated viral load, and the damaged epithelium of ulcerated anoderm makes an easy portal for entry. Syphilis, gonorrhea, and chlamydial infection have been documented in men who have sex with men. For this reason, routine STD screening is indicated.

Gonorrhea. Gonorrhea is caused by the gram-negative diplococcus *Neisseria gonorrhoeae.* Proctitis (inflammation of the rectum) results from anal intercourse or autoinoculation from vaginal secretions and becomes symptomatic after a 5- to 7-day incubation period. Symptomatic patients report pruritus ani, tenesmus, and bloody or thick, purulent yellow drainage. Anoscopy reveals proctitis and mucus in the anal crypts. Recovery of the organism from the crypts increases the likelihood of identification on Gram staining. Water should be used to lubricate the anoscope because lubricants contain an antibacterial agent. Disseminated gonococcal infection may include arthritis, skin lesions, perihepatitis, endocarditis, and meningitis.

Chlamydial Infection and Lymphogranuloma Venereum. Infection with *Chlamydia trachomatis,* an intracellular organism that is endemic to the tropics, is a common STD in the United States. Signs and symptoms include mucoid or bloody rectal discharge and tenesmus. Some people are asymptomatic carriers of the organism. Lymphogranuloma venereum is a more serious manifestation caused by specific strains of *C. trachomatis.* It starts as a painful anal or perianal ulceration with an erythematous friable rectal mucosa, fever, and malaise. Prominent unilateral lymph nodes coalesce to form a bubo, which must be distinguished from the granuloma of secondary syphilis. Rectal cultures are unreliable because the organism is intracellular. Diagnosis is best achieved by immunofluorescent antibody testing. In the final stage, rectal strictures and rectovaginal fistulae may form.

Herpes Simplex Virus Infection. Herpes proctitis is caused by herpes simplex virus type 1 (HSV-1) and HSV-2. Symptoms appear 1 to 3 weeks after exposure. Those with proctitis may have rectal pain, bloody mucoid discharge, tenesmus, constipation, sacral paresthesias, and/or urinary difficulties. Examination may be impossible without anesthesia. Single or coalesced vesicles and ulcerations occur in the perianal area and rectum, and the rectal mucosa is erythematous, friable, and ulcerated. Chronic mucocutaneous HSV infection is considered diagnostic for AIDS. Definitive diagnosis with viral or immunofluorescent staining relies on collection of fluid and scrapings from the base of the vesicle.

Syphilis. Syphilis is caused by *Treponema pallidum,* a motile spirochete. During anal intercourse, the organism enters the rectal mucosa or anoderm and forms an ulcer (chancre) within 2 to 6 weeks. The chancre heralds the primary phase of syphilis and may resemble an anal fissure. Patients may experience discomfort during defecation, tenesmus, mucoid discharge, and inguinal adenopathy. Primary syphilis can be confused with lymphoma, but the diagnosis can be made by visualizing spirochetes on dark-field microscopy from scrapings taken from the base of the ulcer.

Serologic testing is useful several weeks after the appearance of the chancre. Treponemal tests such as the fluorescent treponemal antibody (FTA) test yield a positive result earlier than the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) test. If the chancre goes unnoticed, the patient may present with secondary syphilis, marked by a maculopapular rash that characteristically involves the palms and soles, and condyloma latum, a spirochete-laden, weeping, verrucous lesion in the perianal area that emits a foul odor. It is easily distinguishable from condyloma acuminatum, which has a drier, more keratinized appearance. Serologic testing results usually are positive. Tertiary syphilis is rare but may manifest as a rectal gumma with perianal pain and paralysis of the sphincters and may be mistaken for anal cancer.

Chancroid. Chancroid is caused by the gram-negative bacillus *Haemophilus ducreyi*; it begins as an inflammatory pustule or macule that ruptures to form an irregularly shaped ulcer. In several days, painful inguinal adenitis develops. Chancroid often is a diagnosis of exclusion.

Condyloma Acuminatum. Condyloma acuminatum (genital warts) is the most commonly encountered anorectal STD and is caused by human papillomavirus. The mode of transmission is primarily through sexual intercourse, but transmission can occur through close personal contact, as often happens in pediatric cases in which an infected person is changing a diaper and transmits the virus due to poor handwashing techniques. It is incumbent on the evaluating physician to consider sexual abuse in pediatric cases. Because half of HIV-positive patients have anal warts, HIV testing is recommended in patients with this diagnosis.

The pink to- gray papilliform growths are a result of hyperplastic epithelial growth (Fig. 86.7). They may coalesce to form a massive patch that obscures the anal verge. Patients may be asymptomatic or report pruritus ani, a hemorrhoid, or bleeding. Evaluation can include anoscopy because the warts often grow within the anal canal. Failure to treat the internal lesions results in recurrence. The differential diagnosis includes condyloma latum (secondary syphilis) and squamous cell carcinoma. Preferred treatment is cryotherapy, but outpatient treatment with 0.5% podofilox solution or gel can be successful in limited cases.

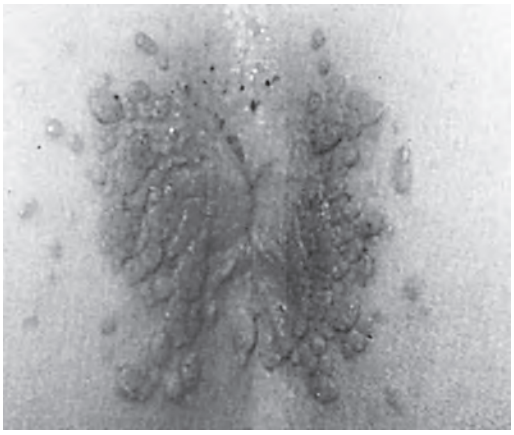

Fig. 86.7. Condylomata acuminata in a child.

Ulcerative Lesions in HIV-Infected Patients. Most patients who are HIV seropositive have current or past infection with an STD, which may be the initial reason for seeking medical attention. Anorectal complaints in this population fall into three categories: (1) routine proctologic conditions, as seen in the general population; (2) STDs; and (3) opportunistic infections (Box 86.6). The treatment of routine conditions and common STDs is similar to that in other patients except that wound healing may be delayed.

Management

A summary of common infections and treatment guidelines is presented in Table 86.5. Empirical therapy is indicated for patients who have recently practiced anal-receptive intercourse and have a rectal discharge. The recommended regimen is a single dose of ceftriaxone, 250 mg intramuscularly, plus doxycycline, 100 mg bid orally for 7 days.[18] Patients with anorectal infections should be referred for HIV testing. The possibility of sexual assault should

BOX 86.6

Anorectal Lesions in the Patient With HIV Infection

COMMON CONDITIONS
Anal fissure
Abscess and fistula
Hemorrhoids
Pruritus ani
Pilonidal disease

COMMON STDS
Gonorrhea
Chlamydial infection
Herpes
Chancroid
Syphilis
Condyloma acuminatum

ATYPICAL CONDITIONS
Infectious
TB, CMV infection, actinomycosis, cryptococcosis

Neoplastic
Lymphoma, Kaposi's sarcoma, squamous cell carcinoma

Other
Idiopathic anal ulcer

CMV, Cytomegalovirus; *HIV,* human immunodeficiency virus; *STD,* sexually transmitted disease; *TB,* tuberculosis.

TABLE 86.5

Sexually Transmitted Diseases of the Anorectum

DISEASE OR CONDITION (WITH SPECIFIC PATHOGEN WHEN KNOWN)	FINDINGS	TREATMENT
ULCERATIVE CONDITIONS		
LGV	Unilateral inguinal adenopathy Fever, malaise Mucoid or bloody discharge	Doxycycline, 100 mg PO bid, for 21 days *For pregnant patients or those allergic to tetracyclines*—erythromycin, 500 mg PO qid, × 21 days
HSV infection	Rectal pain, tenesmus, constipation Bloody mucoid discharge Vesicles and ulcerations Fever, malaise, myalgias, paresthesias	*First episode*—acyclovir, 400 mg PO tid, 7–10 days *or* Acyclovir, 200 mg PO, 5×/day, for 7–10 days *or* Famciclovir, 250 mg PO bid, for 7–10 days *or* Valacyclovir, 1 g PO daily, for 7–10 days
Early (primary) syphilis *(Treponema pallidum)*	Chancre Tenesmus, pain, mucoid drainage Inguinal lymphadenopathy	Benzathine penicillin G, 2.4 million units IM, once
Chancroid *(Haemophilus ducreyi)*	Inflammatory lesion progresses to ulcer Inguinal adenitis—bubo	Azithromycin, 1 g PO once, *or* Ceftriaxone, 250 mg IM once, *or* Ciprofloxacin, 500 mg PO bid, for 3 days *or* Erythromycin, 500 mg PO tid, for 7 days
Idiopathic (usually HIV-positive)	Eccentric, deep, poor-healing, multiple lesions	Symptomatic relief or surgical referral
NONULCERATIVE CONDITIONS		
Condylomata acuminata (HPV)	Keratinized vegetative growths in anus or skin Asymptomatic, pruritus ani, or bleeding	Podofilox, 0.5% topically, or cryotherapy
Gonorrhea *(Neisseria gonorrhoeae)*	Pruritus ani Tenesmus Purulent yellow discharge	Ceftriaxone, 250 mg IM once, *or* Cefixime, 400 mg PO, once
Chlamydial infection *(Chlamydia trachomatis)*	Mucoid or bloody discharge Tenesmus	Azithromycin, 1 g PO once, *or* Doxycycline 100 mg PO bid, for 7 days
Syphilis (secondary)	Maculopapular rash Condyloma latum	Benzathine penicillin G, 2.4 million units IM, once

HIV, Human immunodeficiency virus; *HPV,* human papillomavirus; *HSV,* herpes simplex virus; *IM,* intramuscularly; *LGV,* lymphogranuloma venereum; *PO,* orally.

be considered. The health care provider should report STDs and new diagnoses of HIV infection in accordance with state and local health department regulations.

In immunocompromised patients, the differential diagnosis of ulcerative anorectal lesions should include opportunistic infections, lymphoma, and Kaposi's sarcoma. Patients with AIDS often exhibit idiopathic anal ulcerations with pain and bleeding. Before this diagnosis is made, other possible causes of the lesions must be considered (see Box 86.6). Symptomatic relief can often be achieved with the WASH regimen (see Box 86.2), but recalcitrant lesions may require surgical excision.

Radiation Proctitis

Radiation-induced injury of the rectum is often caused by treatment of gynecologic, urologic, and GI malignancies. Immediate radiation proctitis usually is self-limited and responds to symptomatic treatment. Delayed radiation proctitis can manifest for up to 2 years after the exposure.

Signs and symptoms of radiation proctitis include bleeding ranging in severity from spotting to hemorrhage, tenesmus, diarrhea, pain, fistula-in-ano, and rectal strictures. Diagnosis is achieved by rectal mucosal biopsy, a procedure best performed with the patient under sedation or anesthesia.

Treatment regimens include supportive therapy and the use of antiinflammatory agents, botulinum toxin injection, enemas with short-chain fatty acids, oral sucralfate therapy, hyperbaric oxygen therapy, and sclerosing therapy.[19] When a patient with suspected radiation proctitis presents to the ED, initial measures should focus on pain management while coordinating a care plan with the primary physician.

Rectal Prolapse

Rectal prolapse, or procidentia, is a disease of persons at the extremes of age. Prolapse is complete if all bowel layers protrude and incomplete if only the mucosal layer is involved. In adults, complete procidentia is most common among older women and is caused by a laxity of attachment structures; it often is accompanied by uterine prolapse or cystocele. Patients report an anal mass that protrudes during defecation, coughing, or sneezing.

Findings may include fecal incontinence, bloody or mucoid discharge, and a foul odor. In some cases, the patient is able to reduce the prolapse manually, whereas in others the tissue becomes edematous, and a red ulcerated mass protrudes from the anus (Fig. 86.8). Reduction may be attempted by placing the patient prone and applying an osmotically active solution, such as sucrose-soaked gauze, to the mass. After several minutes, gentle pressure may be applied to guide the tissue back into the rectal vault. Care should be taken not to poke at the tissue, because this could cause penetration from trauma. When this is successful, the patient may be discharged with agents to relieve constipation. Surgical repair often is necessary.[20]

Fig. 86.8. Prolapse of the rectum. (Courtesy Dr. Gershon Effron, Sinai Hospital of Baltimore; from Seidel HM, et al, editors: Mosby's guide to physical examination, ed 4, St Louis, 1999, Mosby.)

In children up to 4 years of age, procidentia often is associated with chronic constipation or diarrheal disease. However, it may herald the presence of malnutrition, parasitic infection, or cystic fibrosis. Children usually have mucosal prolapse. The parent reports protrusion during defecation, with small amounts of mucus or blood. This condition must be distinguished from a protruding juvenile polyp and intussusception. Gentle reduction may be attempted. Increasing the dietary fiber and fluid intake frequently is successful as first-line therapy.

Rectal Foreign Bodies

Principles

Anorectal foreign bodies may result from the use of the anus for sexual gratification, although they also are found in children, psychiatric patients, and victims of assault or iatrogenic injury. Most objects are introduced directly into the anus, but some become lodged there after oral ingestion. Foreign bodies must be removed to prevent mucosal lacerations, intestinal perforation and obstruction, sepsis, and peritonitis.[21]

Some foreign bodies that are ingested orally pass through the GI tract and subsequently become lodged in the rectum or anal crypts. Patients at highest risk for ingested foreign bodies are children, psychiatric patients, and body packers.

Clinical Features

Rarely, a foreign body such as an enema tip or broken rectal thermometer is introduced iatrogenically. In most cases, the foreign body is placed deliberately by the patient or a partner for medicinal or sexual purposes. Objects that are commonly retrieved include fruits and vegetables, household items, especially those whose dimensions resemble the penis, and items purchased specifically with an anal erotic intent. By the time patients arrive at the ED, sometimes days after the introduction of the foreign body, they have likely tried to remove it at home. The history of the injury often is reluctantly given or is vague and inconsistent. The initial ED evaluation, conducted in a nonjudgmental manner, should ascertain the type of foreign body involved, how long it has been there, what attempts have been made to remove it, and whether the patient has fever, abdominal pain, or rectal bleeding. The possibility of assault should be considered.

Physical examination begins with an external examination for signs of trauma. If no sharp objects are suspected, a digital rectal examination and anoscopy may reveal the foreign body, lax sphincter, or mucosal injury. An abdominal examination may demonstrate signs of perforation or obstruction.

Diagnostic Testing

The foreign body may be visible on abdominal radiographs, or its presence may be inferred by a nonspecific gas pattern, free air, or signs of intestinal obstruction. If perforation is suspected, water-soluble contrast material can be introduced to delineate radiolucent foreign bodies.

Management

Treatment depends on the location and type of object found. In general, objects that are soft and low-lying (<10 cm from the anal

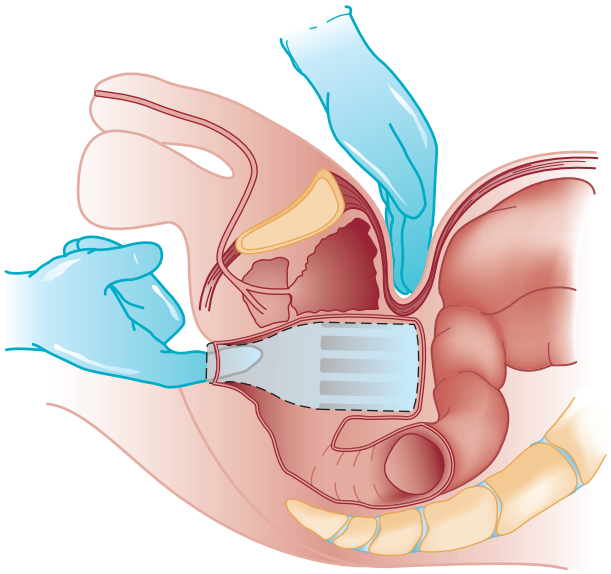

Fig. 86.9. Removal of a foreign body from the rectum.

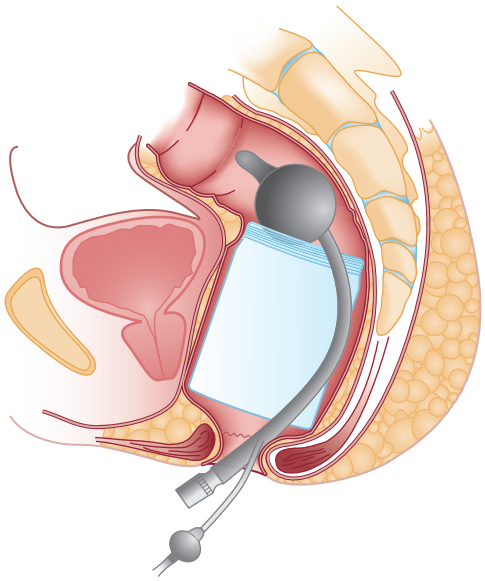

Fig. 86.10. Foley catheter–assisted removal of a rectal foreign body.

verge) can be removed safely in the ED. The awake patient can assist in expulsion by performing the Valsalva maneuver. Premedication with a benzodiazepine is helpful to relax the sphincter and patient. With the patient in the lithotomy position, suprapubic pressure can assist in removal (Fig. 86.9).

Several methods are effective for removal. The easiest is to grasp an edge of the foreign body with forceps and apply traction while the patient bears down. Most foreign bodies in the rectum do not have a convenient place to grasp, so other methods are needed. A Foley catheter can be placed beside the foreign body and the balloon inflated proximally to it (Fig. 86.10). This breaks the suction of the rectal wall mucosa and provides a way to guide the object out of the rectal vault. Hollow objects may be filled with plaster of Paris, with an inset inflated Foley catheter to be used as a handle.

Other creative ways to remove foreign bodies in the ED have been successful, and an individualized strategy for each patient is essential. Large, hard, fragile objects and those that have migrated proximally are difficult to remove without anal dilation and instrumentation to assist in the passage through the sacral curve and sphincters. These are best performed with the patient under general anesthesia. After the removal of the foreign body, one should consider the possibility of mucosal tears or perforations. Discharge instructions should warn the patient about signs and symptoms of perforation, peritonitis, and sepsis.

KEY CONCEPTS

- Anorectal conditions can be differentiated according to an algorithm (see Fig. 86.2), which addresses the presence or absence of pain, bleeding, swelling, and pruritus, in combination with an assessment of the patient's overall health.
- Patients who seek treatment for nonspecific anorectal complaints should be evaluated for the presence of underlying systemic disease (eg, cancer, diabetes mellitus, immunodeficiency) because disorders of the anus may herald the initial presentation of associated conditions.
- Patients with any STD should be evaluated for HIV infection and questioned about the use of the anus for sexual purposes and the possibility of domestic violence or abuse.
- Most anorectal conditions can be symptomatically improved by adherence to the WASH regimen (***w***arm water, ***a***nalgesics, ***s***tool softeners, ***h***igh-fiber diet).
- Thrombosed external hemorrhoids are covered by modified anoderm and may be excised and drained within 48 hours.
- Internal hemorrhoids are covered with mucosa and should be referred to colorectal surgeon for definitive management.
- Acutely thrombosed, gangrenous fourth-degree internal hemorrhoids should be referred urgently to a surgeon.
- Superficial abscesses may be drained in the ED.
- Fistulous tracts should not be probed.
- Pilonidal abscesses should be drained with needle aspiration or a longitudinal incision off the midline.
- Pruritis ani is caused by a variety of conditions, including infection, topical irritants, cutaneous conditions, cancer, and hypersensitivity to foods and drugs (see Box 86.5).
- Sensitivity is required when managing patients with anorectal foreign bodies. Health care provider safety is imperative when evaluating foreign bodies with sharp edges.
- Distal foreign bodies often can be removed in the ED using creative means, whereas proximal or sharp ones should be removed under general anesthesia in the operating room.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 86: QUESTIONS & ANSWERS

86.1. Which of the following statements regarding hemorrhoids is true?

A. Most hemorrhoidal bleeding is venous.
B. Painful bleeding is the most common symptom.
C. Portal hypertension does not cause hemorrhoids in adults.
D. Seventy-five percent of pregnant women experience late-pregnancy hemorrhoids.
E. Traumatic deliveries do not predispose to postpartum hemorrhoids.

Answer: C. Portal hypertension does not predispose to hemorrhoids, except in children. Bleeding in these cases is likely from rectal varices. Most hemorrhoidal bleeding is from the superior rectal artery and thus IS bright red. Approximately one-third of pregnant patients experience hemorrhoids in the third trimester or postpartum period. Traumatic deliveries can result in hemorrhoid development. Painless bleeding with defecation is the most common symptom (pain usually occurs if hemorrhoids are thrombosed).

86.2. What is the most common cause of sudden-onset rectal pain?

A. Anal fissure
B. Proctalgia fugax
C. Sacral radiculopathy
D. Thrombosed external hemorrhoid
E. Thrombosed internal hemorrhoid

Answer: A. Anal fissures typically result from superficial tears in the anoderm, usually occurring in the posterior midline. The pain is heightened by secondary spasm of the anal sphincter.

86.3. When performing an incision and drainage of a pilonidal cyst, which of the following is the most appropriate method?

A. Elliptic incision
B. Horizontal incision at the center of the affected area
C. Horizontal incision at the lower portion of the affected area
D. Longitudinal incision along the midline
E. Longitudinal incision lateral to the midline

Answer: E. Making a longitudinal incision lateral to the midline spares the area that is most vulnerable to reaccumulation of debris and the inflammatory response. Removal of pus, inflammatory tissue, and ingrown hairs relieves the pain of the abscess and promotes healing.

86.4. A 68-year-old woman presents with hemorrhoids. On examination, you note three protruding masses that are maroon in color and may be reduced manually into the anorectal opening. What is the most appropriate curative therapy?

A. Application of a concentrated sucrose solution to the affected area
B. Emergent surgical intervention (eg, banding, sclerosing, hemorrhoidectomy)
C. Prescription of a 7-day course of topical corticosteroid cream
D. Referral to a surgeon for an outpatient procedure
E. Removal of the hemorrhoid with an elliptic incision, including overlying tissue

Answer: D. Third-degree internal hemorrhoids may be manually reduced in the emergency department (ED) but are unlikely to heal spontaneously. Referral for operative therapy is curative. Excision of internal hemorrhoids is contraindicated. Acutely thrombosed external hemorrhoids may be excised in the ED. Temporizing measures include using the WASH regimen—using ***w***arm water to encourage reduction of the protruded hemorrhoids, maintaining hygiene, ***a***nalgesics, stool softeners to ease passage of stool, and a ***h***igh-fiber diet. Topical corticosteroids may be used for 1 or 2 days during an acute exacerbation, but their continued use promotes skin breakdown and itching. A sucrose solution may prove helpful in reducing procidentia (rectal prolapse). A thorough history should be obtained and a physical examination performed to learn if an underlying medical condition may be associated with the hemorrhoids.

CHAPTER 87

Renal Failure

Allan B. Wolfson

The evaluation of renal disease in the emergency department (ED) requires an integrative approach incorporating the urinalysis, serum and urine chemical determinations, and renal imaging studies. Combined, this approach assesses the degree of renal dysfunction and establishes the foundation for distinguishing acute kidney injury (AKI) from chronic kidney disease (CKD).

ACUTE KIDNEY INJURY

The hallmark of AKI (formerly termed *acute renal failure* [ARF]) is progressive azotemia, which commonly is accompanied by a wide range of other disturbances, depending on the severity and duration of renal dysfunction. These include metabolic derangements (eg, metabolic acidosis, hyperkalemia), disturbances of body fluid balance (particularly volume overload), and a variety of effects on almost every organ system (Box 87.1).

The causes of AKI are divided into those that decrease renal blood flow (prerenal), produce a renal parenchymal insult (intrarenal), or obstruct urine flow (obstructive, or postrenal). Identification of a prerenal or postrenal cause of AKI generally makes it possible to initiate specific corrective therapy; if these two broad categories of AKI can be excluded, an intrarenal cause is implicated. The renal parenchymal causes of AKI can be usefully subdivided into those primarily affecting the glomeruli, intrarenal vasculature, or renal interstitium. The term *acute tubular necrosis* denotes another broad category of intrinsic renal failure that cannot be attributed to a specific glomerular, vascular, or interstitial cause (Fig. 87.1).

Numerous other important systemic and organ-specific effects of renal failure occur. Uremia impairs host defenses, particularly leukocyte function, and infection is a significant cause of morbidity and mortality in AKI. Pericarditis, which has a prevalence of 10% to 20% in dialyzed patients with CKD, also may occur in patients with AKI; urgent dialysis is indicated when associated with a pericardial effusion and tamponade. Neurologic abnormalities in AKI may be precipitated by electrolyte abnormalities, medications, or uremia. Anorexia, nausea, vomiting, gastritis, and pancreatitis also are associated with AKI. Significant gastrointestinal (GI) hemorrhage is seen in about 10% of patients.

Impaired erythropoiesis, shortened red blood cell (RBC) survival, hemolysis, hemodilution, and GI blood loss all play a role in the normocytic normochromic anemia that usually accompanies AKI. Although mild thrombocytopenia may be present, it is the qualitative defect in platelet function, thought to be caused by the effect of circulating uremic toxins, that is more significant and that contributes to these patients' bleeding tendencies.

Clinical Features

When the presence of azotemia or renal failure has been discovered, the first consideration in the ED evaluation should be the possibility of potentially life-threatening complications (eg, hyperkalemia, pulmonary edema). Assuming that these have been satisfactorily ruled out, the next step is to determine whether the condition represents AKI or is the result of preexisting renal disease. The clinical distinction between AKI and CKD often is difficult, especially if old records and laboratory results are not available. The finding of small kidneys on abdominal radiographs or bone changes of secondary hyperparathyroidism on hand films suggests that the renal failure is chronic. Anemia, hypocalcemia, and hyperphosphatemia, on the other hand, should not be relied on to identify patients who have CKD because these abnormalities can develop rapidly in AKI.

In evaluating the patient with azotemia, the emergency clinician uses history, physical examination, and laboratory studies to seek clues to the cause and identify signs and symptoms of uremia, volume overload, or other complications of renal failure. In attempting to identify the cause, the general strategy is to rule out prerenal and postrenal causes before considering the many intrinsic renal causes. First, potential sources of volume loss and causes of decreased cardiac output are sought in the history, and the patient is questioned about lightheadedness, bleeding, GI fluid loss, abnormal polyuria, or symptoms of congestive heart failure (CHF). In men, a history of nocturia, frequency, hesitancy, or decreased urinary stream suggests prostatic obstruction. A history of lower tract symptoms or of abdominal or pelvic tumor in either gender is determined, as is a history of kidney stones or chronic urinary tract infection (UTI). A history of acute anuria, defined as the production of less than 100 mL of urine/day, is most often the result of high-grade urinary tract obstruction, although it also may accompany severe volume depletion, severe acute glomerulonephritis, cortical necrosis, or bilateral renal vascular occlusion. Intermittent anuria, on the other hand, is characteristic of obstructive disease.

Medication use and possible exposure to radiographic contrast agents or other exogenous toxins are other key components of the history. A history of hypertension, dark-colored urine, rash, fever, or arthritis suggests intrinsic renal disease or a multisystem disorder.

The physical examination focuses on signs of volume depletion, such as tachycardia and decreased skin turgor. Documented short-term changes in body weight offer a valuable clue in assessing volume status, particularly in chronically ill patients. In

BOX 87.1

Clinical Features of Acute Kidney Injury

CARDIOVASCULAR
Pulmonary edema
Arrhythmia
Hypertension
Pericarditis
Pericardial effusion
Myocardial infarction
Pulmonary embolism

METABOLIC
Hyponatremia
Hyperkalemia
Acidosis
Hypocalcemia
Hyperphosphatemia
Hypermagnesemia
Hyperuricemia

NEUROLOGIC
Asterixis
Neuromuscular irritability
Mental status changes
Somnolence
Coma
Seizures

GASTROINTESTINAL
Nausea
Vomiting
Gastritis
Gastroduodenal ulcer
Gastrointestinal bleeding
Pancreatitis
Malnutrition

HEMATOLOGIC
Anemia
Hemorrhagic diathesis

INFECTIOUS
Pneumonia
Septicemia
Urinary tract infection
Wound infection

addition, suspected bleeding should be specifically excluded. Similarly, volume overload is determined by the assessment of jugular vein distention and attention to the presence of rales or edema.

A distended bladder is percussible when it contains 150 mL of urine, and the dome is palpable abdominally when it contains 500 mL. Ultrasonography can be used to detect bladder distention or postvoid residual volume if there is a question of urinary retention.

A prostate examination in men and pelvic examination in women are necessary components of the examination. The presence of rash, purpura, pallor, or petechiae is noted, as is arthritis, musculoskeletal tenderness, and findings suggestive of infection or malignancy.

Differential Diagnosis

The management of AKI requires a systematic approach to the differential diagnoses that may underlie the presentation. Once prerenal and postrenal causes are considered, the diagnostic and management strategies focus on the intrarenal pathologies.

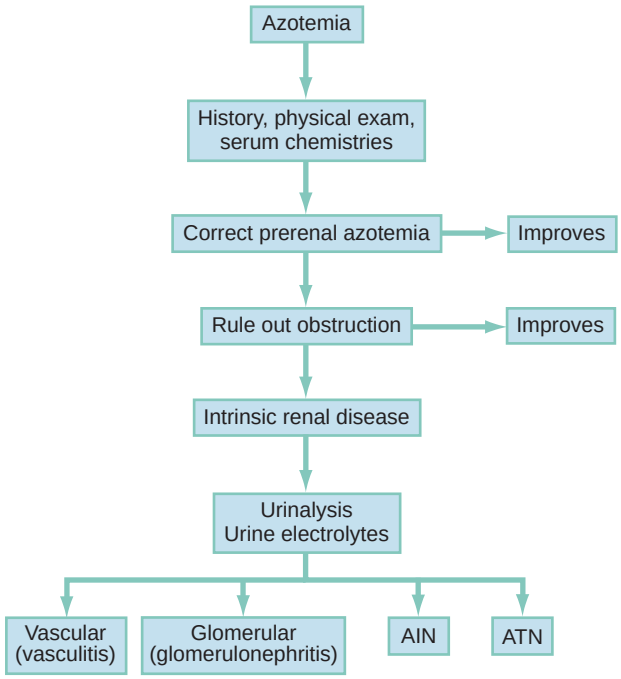

Fig. 87.1. Evaluation of azotemia. *AIN*, Acute interstitial nephritis; *ATN*, acute tubular necrosis.

Prerenal Azotemia

Decreased renal perfusion that is sufficient to cause a decrease in the glomerular filtration rate (GFR) results in azotemia. The possible causes are grouped into entities causing intravascular volume depletion, volume redistribution, or decreased cardiac output (Box 87.2). Patients who have preexisting renal disease are particularly sensitive to the effects of diminished renal perfusion.

Prerenal azotemia is characterized by increased urine specific gravity, a blood urea nitrogen (BUN) to creatinine ratio generally between 10:1 and 20:1, urine sodium concentration less than 20 mEq/dL, and fractional excretion of sodium (FENa) less than 1%. The condition generally can be corrected readily by expanding extracellular fluid volume, augmenting cardiac output, or discontinuing vasodilating antihypertensive drugs. However, severe prolonged prerenal azotemia can result in acute tubular necrosis (ATN).

Patients who have CHF or cirrhosis form an important subset of those with prerenal azotemia. These patients often are salt-overloaded and water-overloaded, yet their effective intra-arterial volume is decreased. Administration of diuretics has the potential to decrease intravascular volume further, resulting in decreased glomerular filtration and prerenal azotemia. For some patients with advanced CHF or hepatic disease, a state of chronic, stable, prerenal azotemia may be the best achievable compromise between symptomatic volume overload and severe renal hypoperfusion.

Glomerular perfusion also may be decreased in patients with normal intravascular volume and normal renal blood flow who take angiotensin-converting enzyme (ACE) inhibitors or, more commonly, prostaglandin inhibitors. All nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, inhibit prostaglandin synthesis. Renal vasodilator prostaglandins are critical in maintaining glomerular perfusion in patients with conditions such as CHF, chronic renal insufficiency, and cirrhosis, in which elevated circulating levels of renin and angiotensin II decrease renal blood flow and the GFR. In this setting, a decrease in the

BOX 87.2

Causes of Prerenal Azotemia

VOLUME LOSS
Gastrointestinal—vomiting, diarrhea, nasogastric drainage
Renal—diuresis
Blood loss
Insensible losses
Third-space sequestration
Pancreatitis
Peritonitis
Trauma
Burns

CARDIAC CAUSES
Myocardial infarction
Valvular disease
Cardiomyopathy
Decreased effective arterial volume
Antihypertensive medication
Nitrates

NEUROGENIC CAUSES
Sepsis
Anaphylaxis
Hypoalbuminemia
Nephrotic syndrome
Liver disease

BOX 87.3

Causes of Postrenal Renal Failure

INTRARENAL AND URETERAL CAUSES
Kidney stone
Sloughed papilla
Malignancy
Retroperitoneal fibrosis
Uric acid, oxalic acid, or phosphate crystal precipitation
Sulfonamide, methotrexate, acyclovir, or indinavir precipitation

BLADDER
Kidney stone
Blood clot
Prostatic hypertrophy
Bladder carcinoma
Neurogenic bladder

URETHRA
Phimosis
Stricture

production of vasodilator prostaglandins may result in acute intrarenal hemodynamic changes and a reversible decrease in renal function. This phenomenon also is seen with the selective cyclooxygenase-2 inhibitor class of NSAIDs. Other risk factors include advanced age, diuretic use, renovascular disease, and diabetes. This entity is distinct from other renal complications of NSAIDs, including interstitial nephritis and papillary necrosis.

Postrenal (Obstructive) Acute Kidney Injury

Obstruction is an eminently reversible cause of AKI and should be considered in every patient with newly discovered azotemia or worsening renal function. Obstruction may occur at any level of the urinary tract but usually is produced by prostatic hypertrophy or functional bladder neck obstruction (eg, secondary to medication side effects or neurogenic bladder; Box 87.3). Intrarenal obstruction may result from the intratubular precipitation of uric acid crystals (eg, with tumor lysis), oxalic acid (as in ethylene glycol ingestion), phosphates, myeloma proteins, methotrexate, sulfadiazine, acyclovir, or indinavir. Bilateral ureteral obstruction (or obstruction of the ureter of a solitary kidney) may be caused by retroperitoneal fibrosis, tumor, surgical misadventure, stones, or blood clots. A sudden deterioration in renal function in the setting of diabetes mellitus, analgesic nephropathy, or sickle cell disease suggests papillary necrosis.

Intrinsic Acute Kidney Injury

Of the specific intrarenal disorders that cause AKI, glomerulonephritis, interstitial nephritis, and abnormalities of the intrarenal vasculature are amenable to specific therapy and are important to consider as possible causes. These entities are responsible for only 5% to 10% of cases of AKI in adult inpatients; most are caused by ATN. In adults in whom AKI develops outside the hospital, the incidence of glomerular, interstitial, and small vessel disease is much greater. In children, these entities account for approximately 50% of the cases of AKI (Box 87.4).

Acute Glomerulonephritis. This may represent a primary renal process or may be the manifestation of any of a wide range of other disease entities (see Box 87.4). Patients may have dark urine, hypertension, edema, or CHF (secondary to volume overload) or may be completely asymptomatic, in which case the diagnosis rests on an incidental finding on urinalysis. The hematuria associated with glomerular disease may be microscopic or gross and may be persistent or intermittent. Proteinuria, although often in the range of 500 mg/day to 3 g/day, not uncommonly is in the nephrotic range, arbitrarily defined as 3.5 g/day or more. The presence of hematuria, proteinuria, or red cell casts is highly suggestive of glomerulonephritis. Conversely, the absence of red cell casts, proteinuria, and hematuria essentially excludes glomerulonephritis as the cause of AKI.

The specific diagnosis of acute glomerulonephritis caused by primary renal disease often is ultimately made by renal biopsy. However, when glomerulonephritis is secondary to a systemic disease such as systemic lupus erythematosus, the clinical signs and symptoms and results of laboratory assessment aid considerably in narrowing the scope of the differential diagnosis. As a rule, extensive laboratory testing to identify the cause of acute glomerulonephritis is not indicated in the ED setting and is more appropriately performed as part of an inpatient evaluation.

Acute Interstitial Nephritis. Acute interstitial nephritis (AIN) is usually precipitated by drug exposure or by infection. Drug-induced AIN is poorly understood, but the absence of a clear relationship to the dose and recurrence of the syndrome on rechallenge with the offending agent suggests that an immunologic mechanism is responsible. The most commonly incriminated drugs are the penicillins, diuretics, and NSAIDs. AIN has been reported in association with bacterial, fungal, protozoan, and rickettsial infections.

Patients with AIN typically have rash, fever, eosinophilia, and eosinophiluria, but it is common for one or more of these cardinal signs to be absent. Pyuria, gross or microscopic hematuria, and mild proteinuria are observed in some cases. A definite diagnosis sometimes can be made only on renal biopsy. Treatment of AIN is directed at removing the presumed cause; infections should be

BOX 87.4

Intrinsic Renal Diseases That Cause Acute Kidney Injury

VASCULAR DISEASES

Large-Vessel Diseases
Renal artery thrombosis or stenosis
Renal vein thrombosis
Atheroembolic disease

Small- and Medium-Sized Vessel Diseases
Scleroderma
Malignant hypertension
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
HIV-associated microangiopathy

GLOMERULAR DISEASES

Systemic Diseases
Systemic lupus erythematosus
Infective endocarditis
Systemic vasculitis (eg, periarteritis nodosa, Wegener's granulomatosis)
Henoch-Schönlein purpura
HIV-associated nephropathy
Essential mixed cryoglobulinemia
Goodpasture's syndrome

PRIMARY RENAL DISEASES

Poststreptococcal glomerulonephritis
Other postinfectious glomerulonephritis
Rapidly progressive glomerulonephritis

TUBULOINTERSTITIAL DISEASES AND CONDITIONS

Drugs (many)
Toxins (eg, heavy metals, ethylene glycol)
Infections
Multiple myeloma

ACUTE TUBULAR NECROSIS

Ischemia
Shock
Sepsis
Severe prerenal azotemia

Nephrotoxins
Antibiotics
Radiographic contrast agents
Myoglobinuria
Hemoglobinuria

OTHER DISEASES AND CONDITIONS

Severe liver disease
Allergic reactions
NSAIDs

HIV, Human immunodeficiency virus; *NSAIDs,* nonsteroidal antiinflammatory drugs.

treated and offending drugs discontinued. Renal function generally returns to baseline over several weeks, although chronic renal failure has been reported to occur.

Intrarenal Vascular Disease of the Kidney. This can be classified according to the size of the vessel that is affected. Disorders such as renal arterial thrombosis or embolism, which affect large blood vessels, must be bilateral—or affect a single functioning kidney—to produce AKI. Whether to attribute such cases of AKI to a prerenal or intrarenal vascular cause is a matter of semantics. The most common cause of thrombosis probably is trauma; thrombosis also may occur after angiography or may be secondary to aortic or renal arterial dissection. Renal atheroembolism is thought to occur commonly, at least on a microscopic level, after arteriography but is an uncommon cause of AKI. Similarly, patients with chronic atrial fibrillation or infective endocarditis may experience embolization of the kidney but rarely develop AKI as a result. Renal arterial embolism can cause acute renal infarction, generally manifested by sudden flank, back, chest, or upper abdominal pain. Urinary findings, including hematuria, are variable. The diagnosis usually is made by renal flow scanning or arteriography.

Several diseases that affect the smaller intrarenal vessels can cause AKI (see Box 87.4). Patients whose disease is severe enough to cause AKI also are generally found to have hypertension, microangiopathic hemolytic anemia, and other systemic and organ-specific manifestations. Infection with *Escherichia coli* O157:H7 has emerged as a major cause of hemolytic uremic syndrome, an important cause of AKI in children.

Patients with scleroderma (systemic sclerosis) may have so-called scleroderma renal crisis, characterized by malignant hypertension and rapidly progressive renal failure. Whereas vasculitis associated with glomerular capillary inflammation typically causes gross or microscopic hematuria and the formation of red cell casts, vascular involvement of the medium-sized vessels, such as that produced by scleroderma, often spares the preglomerular vessels and tends not to produce an active urine sediment. Extrarenal manifestations (eg, rash, fever, arthritis, pulmonary symptoms) are usually evident.

For malignant hypertension, both as a separate entity and as a part of scleroderma renal crisis, appropriate treatment can produce a gratifying remission of AKI. Patients with malignant hypertension have been reported to recover renal function after aggressive antihypertensive therapy, with temporary maintenance with dialysis if necessary. In patients with scleroderma renal crisis, specific therapy with ACE inhibitors has been shown to result in improvement in renal function in a significant proportion of cases.

Acute Tubular Necrosis. ATN refers to a generally reversible deterioration of kidney function associated with a variety of renal insults. Oliguria may or may not be a feature. The diagnosis is made after prerenal and postrenal causes of ARF and disorders of glomeruli, interstitium, and intrarenal vasculature have been excluded. In a few disorders, these discrete categories overlap. For example, AKI associated with multiple myeloma or ethylene glycol toxicity is associated with intrarenal obstruction and interstitial disease, as well as a probable direct toxic effect on the renal tubule itself.

The most common precipitant of ATN is renal ischemia occurring during surgery or after trauma and sepsis. The remainder of cases occur in the setting of medical illness, usually as a result of the administration of a nephrotoxic aminoglycoside antibiotic or radiocontrast agent or in association with rhabdomyolysis. Multiple causes can be identified in some cases; in others, a definitive cause is never established.

Decreased renal perfusion results in a continuum of renal dysfunction that ranges from transient prerenal azotemia at one extreme to ATN at the other. Early during the period of renal ischemia, renal function can be restored completely by restoring renal blood flow but, at some point, continued hypoperfusion results in renal dysfunction unresponsive to volume repletion, and ATN will supervene. ATN may occur in the absence of frank hypotension; even modest renal ischemia may result in ATN in susceptible persons. Individual susceptibility to ATN may be related to the balance of prostaglandin-mediated vasopressor and vasodilatory influences on the renal vasculature.

Postischemic ATN can occur in the setting of volume loss from the GI tract (upper or lower), skin, or kidneys or can result from severe hemorrhage or major burns. Heat stroke commonly is associated with the development of ATN, which is thought to result from a combination of volume loss, hyperpyrexia, and rhabdomyolysis. Another cause of ATN is hyperglycemic hyperosmolar syndrome, which can be associated with loss of as much as 25% of total body water. ATN also is seen in the setting of cardiogenic shock, sepsis, and third spacing of fluids in pancreatitis and peritonitis.

ATN is common in postoperative patients, although not all cases can be attributed to intraoperative hypotension or hemorrhage. Concomitant sepsis, increased age, preexisting renal disease, and other comorbid conditions are associated with a worse outcome.

Nephrotoxins constitute the other major cause of ATN. Among the most prominent of these are the endogenous pigments myoglobin and hemoglobin, associated with rhabdomyolysis (Box 87.5). Hypotension secondary to fluid loss into damaged muscle is thought to worsen the effects of myoglobinuria on the renal tubule, as does acidemia. Hemolysis, resulting in the release of hemoglobin into the circulation and hemoglobinuria, can cause ATN but usually only in the presence of coexisting dehydration, acidosis, or other causes of decreased renal perfusion. ATN may be associated with the hemolysis of as little as 100 mL of blood.

ATN associated with rhabdomyolysis is often oliguric; it is characterized by rapid increases in the serum creatinine, potassium, phosphorus, and uric acid levels. Creatine released from muscle is metabolized to creatinine, which may result in serum creatinine level increases of more than 2 mg/dL/day, in contrast to the increase of 0.5 to 1.0 mg/dL/day typically seen in other forms of AKI. The BUN/creatinine ratio often is less than 10:1. Intracellular potassium released from damaged muscle may raise the serum potassium level by 1 to 2 mEq/L in several hours. Likewise, phosphate released from muscle may cause dramatic increases in the serum phosphate level. Uric acid, produced by the metabolism of purines released from damaged muscle, may accumulate to levels high enough to cause acute uric acid nephropathy.

Urine dipstick testing yields a positive result for heme in, at most, 50% of patients with rhabdomyolysis, because myoglobin is rapidly cleared from the serum and may therefore be undetectable in the urine at the time of presentation.[1] Thus a negative result on urine dipstick testing does not rule out the diagnosis. Serum creatine kinase (CK) is cleared much more slowly, so measurement of serum CK levels is a more sensitive test.

Antibiotics and radiographic contrast agents are other nephrotoxins that commonly are implicated in the development of ATN. Aminoglycosides are the most commonly implicated antibiotics. Higher doses and longer duration of therapy are associated with higher serum drug levels, leading to greater accumulation of drug in the renal parenchyma and a greater likelihood of nephrotoxicity. Increased age, impaired renal function, dehydration, and exposure to other nephrotoxins are additional risk factors. Once-daily administration of a somewhat higher dose is associated with less nephrotoxicity but has equal effectiveness.

Aminoglycoside-induced ATN typically has a gradual onset. Clinically significant renal dysfunction usually occurs only after several days and often after more than 1 week of therapy. However, renal failure can develop as late as 10 days after a drug has been discontinued, an observation that appears to be explained by the prolonged tissue half-life characteristic of these agents. Renal function returns to normal after an average of 6 weeks, but the condition occasionally progresses to permanent renal injury.

Radiographic contrast agents constitute a common cause of hospital-acquired renal insufficiency. AKI produced by these agents has been defined as an increase in serum creatinine level of 25% over baseline, with a temporal relation to contrast medium administration and in the absence of other identifiable causes. Radiocontrast agent–induced ATN encompasses a spectrum ranging from asymptomatic nonoliguric renal insufficiency to severe renal failure requiring dialysis, but most cases are mild. It can occur after any procedure involving intravascular administration of contrast material. Typically, an increase in the serum creatinine level is noted within 3 days of exposure, with a return to normal within 10 to 14 days.

The most important risk factors for radiocontrast agent–induced ATN are preexisting renal insufficiency, diabetes mellitus, multiple myeloma, age older than 60 years, volume depletion, and higher doses of contrast material. Among these, preexisting renal insufficiency is the most important. Diabetic patients with a serum creatinine level less than 1.5 mg/dL are at low risk for the development of radiocontrast agent–induced ATN, whereas those whose serum creatinine level is greater than 1.5 mg/dL are at significant risk. Volume depletion appears to be an independent risk factor, and aggressive volume expansion before contrast exposure has been shown to have a protective effect.[1] Finally, large doses and repeated doses of contrast material are associated with increased risk of ATN, particularly if a second study is performed within 72 hours of the first.

In combination with periprocedural hydration, *N*-acetylcysteine decreases the incidence of contrast-associated ATN, although this has not been a consistent finding in published studies. Modest volumes of intravenous normal saline (3 mL/kg over 1 hour, followed by 1.5 mL/kg/hr for 4 hours after contrast exposure) appear to be effective in decreasing the likelihood of nephrotoxicity; sodium bicarbonate does not appear to offer an advantage over normal saline.

BOX 87.5

Causes of Pigment-Induced Acute Kidney Injury

- Rhabdomyolysis and myoglobinuria
  - Crush injury
  - Compartment syndrome
  - Electrical injury
  - Myonecrosis from coma or immobilization
  - Acute arterial occlusion
  - Vigorous exertion
  - Status epilepticus
  - Hyperthermia/heat stress
  - Metabolic myopathy
  - Drugs/toxins
  - Hypokalemia
  - Hypophosphatemia
- Hemoglobinuria
  - Acute hemolysis
  - Transfusion reaction
  - Drugs/toxins
  - Infections

G6PD, Glucose-6-phosphate dehydrogenase; *RBCs,* red blood cells.

Diagnostic Testing

The laboratory evaluation begins with a dipstick and microscopic urinalysis and measurement of urine output. BUN, serum creatinine, urine sodium, and FENa levels are determined to help evaluate renal function and provide clues about the cause of AKI. A complete blood count, serum electrolyte panel (expanded to include calcium, phosphorus, and magnesium determinations), electrocardiogram (ECG), and chest radiograph help establish the patient's baseline status and provide information about possible complications.

Urine Volume

Urine flow does not diminish until the GFR is sharply decreased; thus, urine volume is a poor indicator of renal dysfunction. Oliguria, defined as a urine volume of 100 to 400 mL/24 hr, may be seen with prerenal (blood flow–dependent), intrinsic (intrarenal), or postrenal (obstructive) causes of AKI. Although uncommon, alternating oliguria and anuria (the latter defined as less than 100 mL/24 hr), is a classic indicator of intermittent obstruction, which occurs as urine collects behind an obstructing stone or tumor and then is allowed to flow past as the obstructing material shifts position.

Urinalysis

The standard urinalysis consists of dipstick screening for heme pigment, protein, glucose, ketones, pH, leukocyte esterase, and nitrite and microscopic examination of a spun specimen of freshly voided urine. Dipstick testing for heme and protein can provide important information related to renal function.

Heme. The dipstick detects free hemoglobin from lysed RBCs (or myoglobin) and the hemoglobin inside RBCs, but is more sensitive to free hemoglobin. Although as few as three RBCs/high-power field (hpf) can be detected, on any given sample the dipstick may fail to identify 10% to 15% of patients who are otherwise found to have microscopic hematuria, as defined by more than five RBCs/hpf. A positive result on dipstick testing should prompt microscopic examination of the urine. If red cells are seen, the diagnosis of hematuria is confirmed. If the dipstick result is positive but findings on microscopic examination are negative, pigmenturia (myoglobin or free hemoglobin) is suspected.

Protein. The dipstick test for protein, which uses the color change of tetrabromophenol blue, can detect protein at concentrations of 10 to 15 mg/dL but does not yield reliably positive results until the concentration is greater than 30 mg/dL. Moreover, the relation between color intensity and protein concentration is only approximate. The dipstick reagent is three to five times more sensitive to albumin than to globulins and immunoglobulin light chains (eg, Bence Jones protein), an important limitation. False-positive results are caused by alkaline urine, hematuria, or prolonged immersion of the dipstick in the urine. False-negative results are seen with dilute urine.

After dipstick testing has been completed, the sediment from a spun urine specimen is examined under the microscope. A level of two to three RBCs/hpf is commonly accepted as normal.

Casts are formed from urinary Tamm-Horsfall protein—a product of the tubular epithelial cells that gels at low pH and high concentration and when mixed with albumin—or from red cells, tubular cells, or cellular debris in the urine. The composition of a cast reflects the contents of the tubule. Casts are classified according to their appearance or constituents (eg, hyaline, red cell, white cell, granular, or fatty casts). Hyaline casts, those that are devoid of contents, are seen with dehydration, after exercise, or in association with glomerular proteinuria. Red cell casts indicate glomerular hematuria, as seen in glomerulonephritis; the presence of even a few red cell casts is significant. White cell casts imply the presence of renal parenchymal inflammation. Granular casts are composed of cellular remnants and debris. Fatty casts, like oval fat bodies, generally are associated with heavy proteinuria and nephrotic syndrome.

Microscopic examination of the urinary sediment can be helpful in establishing the cause of AKI. A sediment without formed elements or with only hyaline casts is characteristic of prerenal azotemia or obstruction. Red cell casts suggest glomerulonephritis or vasculitis. Fatty casts also suggest glomerular disease. In ATN, the urinary sediment commonly shows granular casts and renal tubular epithelial cells. Large numbers of polymorphonuclear leukocytes are observed in interstitial nephritis, papillary necrosis, and pyelonephritis. Eosinophil-containing casts, appreciated only after staining of the sediment, are typical of allergic interstitial nephritis. Uric acid crystals suggest uric acid nephropathy but are extremely nonspecific; oxalic acid or hippuric acid crystals may be seen in cases of ethylene glycol ingestion.

Serum and Urine Chemical Analysis

Creatinine and Blood Urea Nitrogen. The normal range for the serum creatinine level extends from 0.5 mg/dL in thin people to 1.5 mg/dL in muscular persons. Spurious elevations (up to 2 mg/dL) can be caused by acetoacetate, which cross-reacts with creatinine in some commonly used assays, and by certain medications that cross-react in the assay or reversibly inhibit tubular creatinine secretion, despite a normal GFR, generally causing a creatinine elevation of less than 0.5 mg/dL. Serum creatinine concentration is a function of the amount of creatinine entering the blood from muscle, its volume of distribution, and its rate of excretion. Because the first two are usually constant, changes in the serum creatinine concentration generally reflect changes in GFR. The creatinine clearance is commonly estimated by the Cockcroft-Gault equation:

$$\text{Creatinine clearance (mL/min)} = ([140 - \text{age}] \times \text{weight}) / (72 \times \text{serum creatinine}) (\times 0.85 \text{ if female})$$

Under steady-state conditions, if the GFR is halved, the serum creatinine doubles. Abrupt cessation of glomerular filtration causes the serum creatinine level to rise by 1 to 2 mg/dL per day. Thus, a daily increment of less than 1 mg/dL suggests that at least some renal function has been preserved. Rhabdomyolysis releases creatine into the plasma and may cause the serum creatinine level to increase by more than 2 mg/dL per day. The BUN level also rises with renal dysfunction but is also influenced by many extrarenal factors. Increased protein intake, GI bleeding, and the catabolic effects of fever, trauma, infection, and drugs such as tetracycline and corticosteroids all increase protein turnover and result in increased hepatic urea production and increased BUN levels. Conversely, the BUN level tends to be decreased in patients with liver failure or protein malnutrition.

When glomerular filtrate has been formed, renal urea clearance is largely a function of flow rate. Urea clearance is thus decreased in patients with prerenal azotemia or acute obstruction, despite preservation of tubular function. In such cases, the BUN/creatinine ratio usually is greater than the normal value of 10 : 1, whereas this ratio usually is not markedly increased in cases of uncomplicated intrinsic AKI.

Urine Sodium and Fractional Excretion of Sodium. Normally, urine sodium concentration parallels sodium intake. A low urine sodium concentration thus indicates not only intact tubular

reabsorptive function but also the presence of a stimulus to conserve sodium. The urine sodium concentration, as well as the FENa, an additional measure of tubular sodium handling, helps distinguish between the two most common causes of AKI, prerenal azotemia and ATN.

Urinary indices are most helpful in oliguric patients. An oliguric patient with a urine sodium concentration less than 20 mEq/L and FENa less than 1% is likely to have prerenal azotemia, whereas a urine sodium concentration more than 40 mEq/L and FENa more than 1% suggest ATN. Values in patients with prerenal azotemia overlap somewhat with those in patients with nonoliguric ATN, particularly if the renal injury is mild and some capability to retain sodium has been preserved. Thus, intermediate values for urine sodium concentration and FENa are of little help in differentiating between the two conditions. The administration of mannitol or a loop diuretic within the several hours preceding urine collection also may make interpretation of urine values difficult because the urinary sodium level will tend to be higher and the urine less concentrated, causing the results in prerenal azotemia to resemble those in intrinsic renal failure.

In glomerulonephritis, the urinary indices generally reflect intact tubular sodium handling, but the diagnosis is more accurately made by urine microscopy. In obstructive uropathy, the values of the urinary indices depend on the duration of obstruction and cannot be relied on to indicate the presence or absence of obstruction.

Renal Imaging

Renal imaging is often helpful in the evaluation of the patient with kidney dysfunction, particularly when obstruction is suspected. Contrast-enhanced computed tomography (CT) scanning provides an anatomic image of the urinary tract but does not provide an evaluation of renal function. The classic CT findings of obstruction are kidneys that are normal to large in size, nephrograms that become increasingly dense, and delayed opacification of dilated collecting systems. However, contrast-enhanced CT subjects the kidneys of an already azotemic patient to the risk of an additional potential insult from the contrast agent. Thus, techniques such as ultrasonography and CT that do not involve contrast administration are much preferred for patients with preexisting renal insufficiency (Fig. 87.2).

Computed Tomography. Noncontrast CT may be useful in evaluating some azotemic patients. Hydronephrosis can be recognized without the use of contrast material. Often, dilated ureters can also be seen without contrast enhancement, and the level of obstruction can be determined. The cause of obstruction (eg, bilateral stones, lymphoma, retroperitoneal hemorrhage, metastatic cancer, retroperitoneal fibrosis) often can also be delineated. Occasionally, bilateral ureteral obstruction produced by malignancy or retroperitoneal fibrosis may not cause detectable proximal dilation of the urinary tract. When noninvasive studies yield negative results, the diagnosis of obstruction can be made by retrograde pyelography or antegrade pyelography performed via a percutaneous nephrostomy.

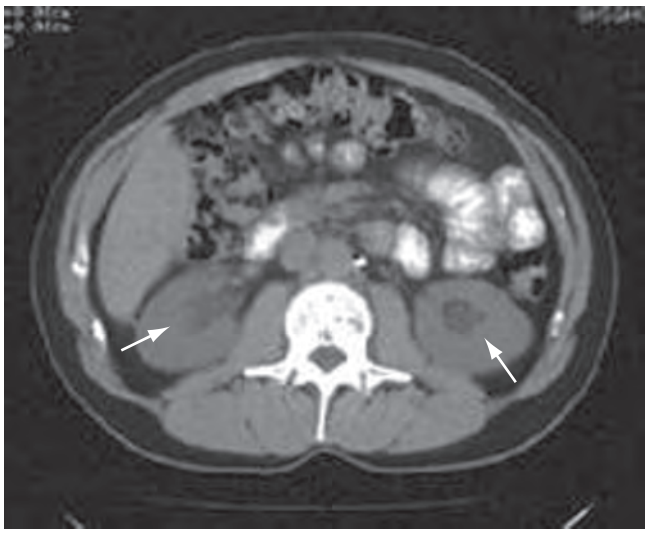

Fig. 87.2. CT scan of bilateral hydronephrotic kidneys without IV contrast medium.

Ultrasonography. Ultrasonography is a safe and reasonably reliable method for excluding obstruction as a cause of AKI. The normal kidney shows an echo-free renal parenchyma surrounding the echogenic central urothelium of the renal pelvis and calices. The sonographic appearance of the kidney in obstruction is that of an enlarged, central, sonolucent area that spreads the normal central echo densities. A similar pattern may be produced by renal cysts, but without associated ureteral dilation. Dilation of the collecting system generally is apparent within 24 to 36 hours of the onset of obstruction, but obstruction may not be evident in patients who are evaluated early in the development of obstructive AKI.

Analysis of Information

Prerenal azotemia is suspected in the setting of volume loss, volume redistribution, or decreased effective renal perfusion. It typically is associated with a normal urinalysis, high BUN/creatinine ratio, increased urine osmolality, urine sodium concentration less than 20 mEq/L, and FEN less than 1%. A rapid response to volume repletion also is characteristic.

Urethral or bladder neck obstruction is documented by the finding of significant amounts of residual urine in the bladder by catheterization or ultrasound examination after the patient has voided or attempted to void spontaneously. An important point is that the ability to void does not rule out obstruction. In fact, the urine volume in the presence of obstruction may range from zero to several liters per day. Flank pain is likewise an insensitive marker for obstruction. Urine indices and the BUN/creatinine ratio tend not to be helpful, although an increase in the latter is common in obstruction. A renal parenchymal disorder often can be diagnosed by its manifestations on microscopic urinalysis or by associated extrarenal manifestations (eg, with multisystem disease) or clinical setting (eg, recent exposure to a new medication). The absence of evidence of prerenal or postrenal causes in a patient with AKI may be taken as presumptive evidence of an intrarenal parenchymal process. Among these, the possibility of an acute or ongoing vascular insult should be kept in mind because timely intervention may be important in preserving ultimate renal function.

Management

ED management of AKI is directed at reversing decreases in GFR and urine output (if possible) while minimizing further hemodynamic and toxic insults, maintaining normal fluid and electrolyte balance, and managing other complications of AKI, as required. Because renal failure alters the metabolism and action of many drugs, often in ways that are not predictable, great care should be exercised in prescribing all medications. A compendium of guidelines for drug dosage in renal failure, such as the one by Aronoff and colleagues,[2] is of great help for this purpose.

After ensuring that the vital signs are adequate and the patient is in no immediate danger from volume or metabolic derangements, the next step is to correct prerenal and postrenal factors,

if any are identified. Intravascular volume is repleted in hypovolemic patients and maintained in euvolemic patients by matching input to measured and insensible output. Inadequate cardiac output is augmented when possible. Postrenal or obstructive AKI is treated by restoration of normal urine outflow. Bladder outlet obstruction may be relieved by passage of a Foley catheter, whereas upper tract obstruction may require percutaneous nephrostomy.

Renal insufficiency secondary to NSAIDs generally is reversible after withdrawal of the causative agent. For patients who are at increased risk but require treatment with NSAIDs, a short-acting preparation (eg, ibuprofen) should be prescribed, and follow-up monitoring of renal function and the serum potassium level should begin within days rather than weeks. If renal function is unchanged after a short course of treatment, adverse effects from continuing therapy are unlikely, although other potential mechanisms for the development of renal dysfunction (eg, interstitial nephritis) should be kept in mind.

Treatment of postrenal AKI consists of relief of the obstruction. In the absence of infection, full renal recovery is possible, even after 1 to 2 weeks of total obstruction, although the serum creatinine level may not return to baseline for several weeks. Because the onset of irreversible loss of renal function with obstruction appears to be gradual, a few days' delay in diagnosis generally is considered acceptable. Still, common sense dictates that obstructions should be detected and relieved promptly.

When prerenal and postrenal factors have been ruled out, the challenge is to identify the cause of intrinsic renal AKI, keeping in mind the multitude of known possible causes (see Box 87.4). The differential diagnosis can often be significantly narrowed by considering the clinical setting and physical and laboratory findings. The clinical picture is often most consistent with the broad category of ATN.

Patients who have oliguric AKI have a significantly higher mortality rate and much greater risk of complications than those who are not oliguric.[3] The difference in prognosis may simply reflect a more severe renal insult in patients who are oliguric, however, and it is not clear that interventions aimed at converting oliguric to nonoliguric AKI have a beneficial effect on renal function or mortality.[4] Nevertheless, because nonoliguric patients are easier to manage, an attempt to increase urine flow is warranted.

The use of loop diuretics or mannitol often is effective in increasing urine flow when intravascular volume deficits have been corrected. Furosemide has not been shown to shorten the clinical course or affect mortality. Mannitol appears to be most useful when given at the time of or shortly after the renal insult; the recommended dose is 12.5 to 25 g, intravenous (IV). If urine output does not increase, further doses may cause hyperosmolality and clinically significant intravascular volume overload in patients with impaired renal function. Dopamine also has been used, with and without furosemide, in an effort to increase urine output, but has not been proven effective.

Certain specific considerations apply to toxin-induced ATN. Pigment-induced ATN may be prevented by avoidance of hemolysis and muscle injury and correction of the factors (eg, dehydration, acidemia) known to predispose patients with pigmenturia to the development of renal failure. When hemolysis or rhabdomyolysis has occurred, treatment is directed at eliminating the cause and preventing the development of renal failure.

Mannitol has been shown to prevent AKI in experimental models of myoglobinuria, presumably by inducing osmotic diuresis and decreasing intratubular deposition of pigment. Furosemide, on the other hand, has not consistently shown a beneficial effect. Other studies have suggested that myoglobin precipitates in an acidic urine but not in an alkaline urine. Thus, aggressive volume repletion, alkalinization, and mannitol infusion have traditionally been recommended after crush injuries to reduce the likelihood or severity of AKI, although there is some evidence that aggressive volume resuscitation alone may be equally effective. When AKI has occurred, management is similar to that for other forms of AKI, but early dialysis may be required to control rapidly developing hyperkalemia, hyperphosphatemia, and hyperuricemia.

Patients who have radiocontrast agent–induced ATN usually require only supportive therapy. A more significant aspect of ED management is preventing the occurrence of contrast nephropathy, particularly by identifying risk factors in patients for whom contrast studies are being considered. BUN and serum creatinine levels should be checked before contrast exposure in a patient with risk factors, the patient should be volume-repleted before the study, and the administered dose of contrast agent should be kept as low as possible. Multiple studies should be avoided, as should concomitant use of other nephrotoxins. *N*-acetylcysteine given before and after contrast administration appears to decrease the incidence of contrast nephropathy.

In addition to general measures aimed at minimizing decreases in GFR and increasing urine output, an important component of the management of AKI is the prevention or control of systemic complications. Of particular significance in this regard are metabolic derangements (eg, hyperkalemia, hypocalcemia, hyperphosphatemia, metabolic acidosis) and complications of volume overload (eg, hypertension, CHF).

Hyperkalemia and Other Metabolic Derangements

Hyperkalemia. The most common metabolic cause of death in patients with AKI results from an inability to excrete endogenous and exogenous potassium loads. In oliguric patients, the serum potassium level typically increases by 0.3 to 0.5 mEq/L per day, but greater increases occur in catabolic, septic, or traumatized patients and in the presence of acidosis or exogenous potassium loads from diet or medication. This is of particular concern in patients with rhabdomyolysis and associated AKI.

Hyperkalemia results in serious disturbances in cardiac electrophysiology that may culminate in cardiac arrest. Although some hyperkalemic patients note muscular weakness, most are asymptomatic until major manifestations of cardiotoxicity appear. Accordingly, detection of hyperkalemia is a primary consideration in these patients. Electrocardiographic changes correlate only roughly with the serum potassium level. Mild hyperkalemia (serum potassium < 6.0 mEq/L) may be cautiously observed without specific treatment while all exogenous sources of potassium are eliminated. If the serum potassium level is greater than 6.5 mEq/L, and particularly if electrocardiographic changes are present, urgent intervention is necessary.

When cardiotoxicity must be reversed immediately (eg, when there is hemodynamic compromise), IV calcium (10 mL of 10% calcium gluconate infused over 2 minutes, repeated after 5 minutes if necessary) is the treatment of choice. Calcium directly antagonizes the membrane effects of hyperkalemia. IV insulin, given with glucose to prevent hypoglycemia, temporarily shifts potassium to the intracellular space. Bicarbonate appears to be less effective in shifting potassium into cells than once thought. It should be used with caution in patients with renal failure because of its potential to cause volume overload and provoke hypocalcemic tetany or seizures. The safety and efficacy of β-agonists in hyperkalemic patients have been well documented; like insulin, inhaled albuterol (in a dose of 10–20 mg) causes potassium to move into cells, thereby controlling hyperkalemia for 2 hours or more. Sodium polystyrene sulfonate (Kayexalate), a potassium-binding ion exchange resin, has long been administered with sorbitol to promote elimination of potassium from the body, but is no longer considered to be effective or free of adverse effects.[5]

Hypocalcemia. This is a common feature of AKI and can develop rapidly after its onset. Vitamin D–dependent intestinal absorption of calcium is decreased in AKI because of decreased renal synthesis of 1,25-dihydroxyvitamin D. Another factor promoting hypocalcemia is the complexing of calcium with retained phosphate. Rhabdomyolysis-associated AKI, in particular, is often associated with the deposition of complexed calcium in muscle and other tissues. Asymptomatic hypocalcemia requires no immediate treatment, but subtle or frank tetany should be treated with IV calcium (10–20 mL of 10% calcium gluconate infused over several minutes).

Hyperphosphatemia. Hyperphosphatemia resulting from decreased renal elimination of phosphate is another common feature. The serum phosphorus level usually ranges from 6 to 8 mg/dL but may be much higher with rhabdomyolysis or in catabolic states. A calcium-phosphate product greater than 70 mg^2/dL^2 may result in metastatic soft tissue calcification. Hyperphosphatemia often is treated with oral calcium-based antacids that bind ingested phosphate in the gut.

Acids produced in normal metabolic processes accumulate in AKI and are buffered in part by serum bicarbonate, resulting in a decrease in the serum bicarbonate level and a high anion gap metabolic acidosis. Compensatory hyperventilation may be mistakenly attributed to primary cardiac failure or volume overload. The metabolic acidosis associated with AKI usually is mild, and treatment generally is not necessary if the serum bicarbonate level is greater than 10 mEq/L. Overzealous correction may result in hypokalemia, hypocalcemia, or volume overload.

Hypermagnesemia. This may complicate AKI when patients are given magnesium-containing antacids or laxatives. Thus, these products, as well as magnesium itself (eg, when given for preeclampsia or for treatment of arrhythmia or wheezing), should be avoided in the setting of AKI.

Disturbances of Volume Regulation. These can be expected to occur in most patients with AKI. Some nonoliguric patients excrete enough salt and water to produce intravascular volume depletion if adequate fluid replacement is not provided. Volume depletion prolongs recovery from AKI. Much more commonly, AKI is complicated by volume overload because sodium and water excretion may be inadequate to match even modest intakes. Volume overload is largely responsible for the hypertension often seen in those with AKI and commonly leads to CHF and pulmonary edema. Iatrogenic volume overload is particularly common and can be prevented only by careful attention to fluid intake and output, with prudent estimates of insensible loss. Volume overload can be treated with diuretics or intravenous nitroglycerin while preparations are being made to initiate dialysis.

Disposition

Patients with new-onset AKI should be hospitalized. If nephrology consultation and dialysis facilities are not available, transfer to another institution is advisable once volume and metabolic abnormalities have been controlled and the patient is hemodynamically stable.

Decisions regarding dialysis generally are made by the nephrology consultant and take into account many factors, including laboratory test abnormalities and the presence or absence of signs and symptoms of uremia (eg, nausea, vomiting, change in mental status). Many nephrologists choose to initiate dialysis when the BUN level exceeds 100 mg/dL or the serum creatinine level exceeds 10 mg/dL. Intractable volume overload and life-threatening hyperkalemia are the two most common indications for emergency dialysis.

CHRONIC KIDNEY DISEASE

CKD denotes kidney damage or decreased renal function for 3 months or longer and is characterized by irreversible nephron loss and scarring. Chronic renal insufficiency, which denotes a condition in which the GFR has been moderately reduced but not to a degree sufficient to cause clear-cut clinical symptoms, has been replaced by an indication of the degree to which the GFR is reduced.[6] End-stage renal disease, now termed *kidney failure,* describes a condition in which renal function has diminished to a low level and in which serious, life-threatening manifestations can be expected to occur without dialysis or transplantation. At this stage, the kidneys often are shrunken and diffusely scarred to such a degree that it may be impossible to make an etiologic diagnosis, even on pathologic examination.

Causes

The causes of CKD are numerous; their relative frequency depends primarily on the population studied. As with AKI, they can be conveniently classified as prerenal (vascular), intrinsic renal (glomerular and tubulointerstitial), or postrenal (obstructive; Box 87.6). Glomerular disease accounts for approximately one-third to half of the cases of CKD; in the United States, diabetic nephropathy forms the largest group of these. Hypertensive nephrosclerosis is another important cause, particularly among blacks, in whom it may be the cause of 25% or more of cases of CKD. Among children and adolescents, reflux nephropathy is the most common cause of CKD. Renal failure related to IV drug use or human immunodeficiency virus disease is a major consideration in some populations. Clues to other specific causes may be gained from elements of the history, physical examination, and laboratory and imaging studies. Although determining the underlying cause of CKD can permit the underlying disease to be treated and can lead to some improvement in renal function in some cases, this is the exception rather than the rule.

Barring renal transplantation, CKD is an essentially irreversible condition generally characterized by a relentless decrease in renal function. The most common problems requiring emergent intervention are severe hyperkalemia and symptomatic volume overload. In the patient with CKD who has an acute problem, the focus should be on the identification and treatment of an intercurrent illness that has caused clinical decompensation, with the goal of returning the patient to a stable, chronically compensated status.

Pathophysiology

Progressive loss of renal function eventually results in a recognizable syndrome termed *uremia.* Clinical manifestations do not generally appear, however, until the GFR has been reduced to approximately 15% to 20% of normal. As the patient becomes unable to excrete an ingested salt or water load promptly, the external balance of sodium and water is affected; volume overload or hypernatremia or hyponatremia may result. Inability to concentrate the urine is an early manifestation of renal insufficiency and may be manifested as nocturia. Potassium homeostasis is likewise disrupted, and a relatively small potassium load may lead to dangerous hyperkalemia. The acid-base balance is affected because the kidney fails to clear the daily metabolic acid load owing to a decreased ability to excrete ammonium and phosphate; the result is a non–anion gap acidosis in the earlier stages of CKD and a superimposed anion gap acidosis as the GFR decreases further. Calcium and phosphate metabolism is affected as well; retention of phosphate and progressive loss of the kidney's capacity to synthesize 1,25-dihydroxycholecalciferol, the active form of vitamin D, lead to hypocalcemia, secondary hyperparathyroidism, and eventually the development of renal osteodystrophy.

BOX 87.6

Major Causes of Chronic Kidney Disease

VASCULAR CAUSES
Renal arterial disease
Hypertensive nephrosclerosis

GLOMERULAR CAUSES
Primary Glomerulopathies
Focal sclerosing glomerulonephritis (GN)
Membranoproliferative GN
Membranous GN
Crescentic GN
IgA nephropathy

Secondary Glomerulopathies
Diabetic nephropathy
Collagen vascular disease
Amyloidosis
Postinfectious
HIV nephropathy

TUBULOINTERSTITIAL CAUSES
Nephrotoxins
Analgesic nephropathy
Hypercalcemia or nephrocalcinosis
Multiple myeloma
Reflux nephropathy
Sickle nephropathy
Chronic pyelonephritis
Tuberculosis

OBSTRUCTIVE CAUSES
Nephrolithiasis
Ureteral tuberculosis
Retroperitoneal fibrosis
Retroperitoneal tumor
Prostatic obstruction
Congenital abnormalities

HEREDITARY CAUSES
Polycystic kidney disease
Alport's syndrome
Medullary cystic disease

HIV, Human immunodeficiency virus; *IgA,* immunoglobulin A.

Nitrogenous byproducts of protein catabolism retained in the blood are the presumed cause of many of the diverse abnormalities of organ function in renal failure. Most patients with CKD show decreased glucose tolerance, although it is rarely severe enough to require treatment unless the medical history includes established diabetes. In the latter case, insulin or other hypoglycemic therapy may need to be continued, but generally at a lower dosage than required before the onset of renal failure because the normal kidney has a major role in insulin degradation. Alterations in lipid metabolism result in elevated low-density lipoprotein levels and hypertriglyceridemia in many patients with CKD.

Clinical Features

Uremia has specific effects on a variety of organ systems. Many of these manifestations are relieved by dialysis, but others are not. A number have been attributed in some degree to the retention of nitrogenous wastes and to derangements in vitamin D and parathyroid hormone metabolism (see earlier).

Cardiovascular System

The cardiovascular system is perhaps most dramatically affected in CKD. Many of the manifestations can be attributed to the effects of chronic volume overload, anemia, hyperlipidemia, alterations in calcium and phosphorus metabolism, and volume- and hormone-mediated hypertension. Pericarditis, with or without pericardial fluid accumulation, also is common in CKD, particularly among patients who have not undergone dialysis.

Pulmonary Effects

Uremic pleuritis, with or without associated pleural fluid collections, may develop in some patients. So-called uremic lung, manifested radiographically by bat wing perihilar infiltrates, represents pulmonary edema and is almost always caused by volume overload or myocardial dysfunction. Noninflammatory pleural effusion caused by volume overload also is fairly common. Of special importance in the ED evaluation is that the radiographic appearance in pulmonary edema may at times be misleading, simulating an infectious lobar infiltrate or even assuming a nodular appearance in some cases.

Neurologic Features

Neurologic dysfunction is common in those with advanced uremia and usually manifests with lethargy, somnolence, difficulty concentrating, or frank alteration in mental status. Seizures may occur, although causes other than uremia alone must be ruled out. Uremic encephalopathy commonly manifests with hiccups, asterixis, or myoclonic twitching. The latter should not be confused with tetany caused by hypocalcemia, which also is common in untreated CKD patients with. In the peripheral nervous system, uremia often causes cramps and a distal sensorimotor neuropathy.

Gastrointestinal System

Anorexia, nausea, and vomiting are nearly constant features of uremia. These GI manifestations are caused by the accumulation of nitrogenous wastes which may be relieved, even in the undialyzed patient, by introduction of a low-protein diet, and seem to correlate roughly with the BUN level.

Dermatologic Features

The skin of patients with CKD has a characteristic yellowish tinge. Uremic frost, the result of the deposition of urea from evaporated sweat on the skin, is a classic finding that like so-called uremic fetor, is seen only rarely now with the widespread use of dialysis (Fig. 87.3). Diffuse pruritus is often a major source of discomfort for the patient with CKD; in some cases, it may be caused by calcium deposition in the skin secondary to derangements in calcium metabolism.

The use of gadolinium-based contrast agents for magnetic resonance imaging has been associated with the development of nephrogenic systemic fibrosis, a potentially fatal disorder that occurs in patients with chronic kidney failure.

Musculoskeletal System

The complex disturbances of calcium and phosphate metabolism in CKD result in renal osteodystrophy, a clinical entity encompassing several overlapping varieties of bone disease that can cause bone pain or frank fractures. Patients with CKD generally are treated with long-term oral calcium and vitamin D in an effort to prevent secondary hyperparathyroidism and uremic

Fig. 87.3. Uremic frost. Note the fine white powder on the skin of this patient with kidney failure.

osteodystrophy. Occasional patients will have a poor response to therapy and require parathyroidectomy. A specific type of arthritis caused by the deposition of calcium hydroxyapatite or calcium oxalate crystals in joints is seen in some patients, as are periarticular calcium deposition, spontaneous tendon rupture, myopathy, and carpal tunnel syndrome.

Immunologic Considerations

Uremic patients have long been noted to have an increased susceptibility to infection, even when not challenged by the invasive procedures associated with dialysis. Humoral and cellular immunity are affected. The relative importance of each in the pathogenesis of infection in renal failure has not been clarified, but defects in cellular immunity appear to be more significant clinically. Although patients with renal failure should be considered to be immunocompromised, most infections in patients with CKD are caused by common pathogens rather than by opportunistic organisms.

Hematologic Effects

A pronounced normochromic normocytic anemia, with a hematocrit value commonly in the range of 18% to 25%, is nearly universal in those with untreated CKD, except among patients with polycystic disease. It is caused primarily by the kidneys' decreased production of erythropoietin, a hormone that stimulates red cell production by the bone marrow. Other contributing factors are increased red cell hemolysis, nutritional deficiencies, and increased bleeding secondary to platelet dysfunction.

Although the platelet number generally is normal in uremia, the bleeding time is prolonged because of defective platelet adhesiveness and activation. Numerous ecchymoses, seen in many patients with CKD, is a common manifestation.

Differential Diagnosis

Patients with CKD commonly present with nonspecific complaints that are often of insidious onset, such as generalized weakness, poor appetite, or deterioration of mental functioning. However, because CKD can affect all systems, a number of life-threatening conditions, including hyperkalemia and myocardial infarction, are in the differential, and a comprehensive evaluation is generally indicated.

In patients without an established diagnosis of CKD, the first consideration in the differential is establishing that the renal failure is chronic rather than acute. An explicit history to that effect, obtained from previous medical records or from the patient or family, provides the most straightforward and reliable confirmation, as does the presence of a dialysis access device on physical examination. If such a history is unavailable, the finding of bilaterally small kidneys, readily detected by plain abdominal radiography or ultrasonography, constitutes equally good evidence. However, the converse is not necessarily true—a finding of normal-sized or large kidneys does not rule out CKD. In such cases, additional diagnostic steps are required to establish the diagnosis. A convincing history of the long-standing presence of the presenting symptoms or of symptoms, such as nocturia, may be helpful in suggesting chronicity, as may a history of familial kidney disease, such as polycystic kidney disease or Alport's syndrome.

Laboratory abnormalities such as anemia, acidosis, hyperuricemia, hypocalcemia, and hyperphosphatemia can occur in patients with acute kidney failure as early as 10 days after onset. Although urinary findings likewise tend not to be helpful, the presence of broad waxy casts on microscopic examination is suggestive of chronic disease, whereas the finding of an active sediment (eg, red cell casts) is good evidence for an acute process.

Although as a rule chronic kidney failure is irreversible and slowly progressive, an essential component of the ED evaluation is to exclude the possibility of potentially reversible factors (in effect, ruling out "acute on chronic" renal failure) and to ensure that treatable causes of CKD—disorders that if treated might allow for some return of renal function—have not been overlooked. These potentially reversible factors and treatable causes of CKD are important to keep in mind because they represent the only potential opportunity to reverse the patient's disease rather than simply to manage its results (Box 87.7).

Primary among superimposed reversible factors are those that lead to decreased renal perfusion. Of these, the most common is volume depletion. Regardless of the initiating cause, the process

BOX 87.7

Reversible Factors and Treatable Causes of Chronic Kidney Disease

REVERSIBLE FACTORS

Hypovolemia
Congestive heart failure
Pericardial tamponade
Severe hypertension
Catabolic state, protein loads
Nephrotoxic agents
Obstructive disease
Reflux disease

TREATABLE CAUSES

Renal artery stenosis
Malignant hypertension
Acute interstitial nephritis
Hypercalcemic nephropathy
Multiple myeloma
Vasculitis (eg, systemic lupus erythematosus, Wegener's granulomatosis, polyarteritis nodosa)
Obstructive nephropathy
Reflux nephropathy

is exacerbated by the diseased kidney's impaired ability to conserve sodium and concentrate the urine appropriately. Decreased renal perfusion caused by cardiac dysfunction of any cause is another extremely common and potentially reversible factor. An uncommonly encountered but important vascular cause of reversible deterioration of renal function is scleroderma renal crisis, a syndrome of accelerated hypertension and severe vasoconstriction in patients with underlying scleroderma that can be reversed by timely treatment with ACE inhibitors. Increased catabolism caused by infection, trauma, surgery, corticosteroids, or GI bleeding is another reversible factor that often is responsible for worsening azotemia and the development of uremic symptoms.

Drugs and toxins constitute another important group of reversible factors. Not only may these agents exacerbate renal insufficiency by causing intravascular volume depletion (diuretics), decreased renal perfusion (antihypertensive agents), or increased catabolism (tetracycline), they also can cause ATN (radiographic contrast material), AIN (many drugs), or inhibition of renal prostaglandin synthesis (NSAIDs). Particularly noteworthy is the dramatic decrease in renal function produced when an ACE inhibitor is administered to a patient with renal insufficiency caused by bilateral renal artery stenosis or renal artery stenosis in a solitary kidney.

Postrenal reversible factors also are important because of their frequency, particularly obstructive disease in the older male patient and reflux nephropathy in the child. Papillary necrosis should remain a consideration in the diabetic patient, the patient with sickle cell disease, and the patient with a history of long-term analgesic use. Stone disease, retroperitoneal fibrosis, and even rarer entities such as ureteral tuberculosis also should not be overlooked.

Finally, treatment of the underlying disorder that has caused the CKD can occasionally result in the return of some renal function, most notably in cases of myeloma kidney, some forms of secondary glomerulonephritis, and severe hypertensive disease. Although this consideration should relate to long-term care and follow-up, it is appropriate that ED management address this issue to ensure that appropriate evaluation and disposition are arranged.

Diagnostic Testing

See earlier ("Acute Kidney Injury: Diagnostic Testing").

Management

CKD patients are susceptible to infection, bleeding, and the numerous other complications associated with renal failure, as well as those that may be associated with the underlying causative disorder. Moreover, these patients are more vulnerable to the effects of any intercurrent illness or trauma. Those who are maintained with chronic hemodialysis or peritoneal dialysis are subject to potential complications from the dialysis therapy itself.

Patients with CKD also are uniquely susceptible to iatrogenic illness. First, they are less able to handle fluid and solute loads than normal persons. Just as important, the presence of renal failure significantly alters the metabolism and action of many drugs, often in ways that are not predictable (Box 87.8). Thus the dose and schedule of every agent administered, even those that are apparently innocuous, such as antacids, laxatives, antiemetics, or multivitamin preparations, should be carefully considered, and the hospital pharmacist or other dependable resource consulted. In general, consultation with the patient's nephrologist is recommended on completion of the initial ED evaluation because management and follow-up monitoring after the patient has left the ED are often complex.

In the United States, most patients with advancing CKD eventually will require dialysis, but several true emergencies may develop in the patient with CKD before chronic dialysis has been instituted. Specific diagnostic and therapeutic considerations apply to the management of these conditions, regardless of whether they occur in dialyzed or undialyzed patients.

BOX 87.8

Mechanisms of Drug Toxicity in Renal Failure

Excessive drug level
Impaired renal excretion of drug
Impaired renal excretion of active metabolite
Impaired hepatic metabolism
Increased sensitivity to drug
Changes in protein binding
Changes in volume of distribution
Changes in target organ sensitivity
Metabolic loads administered with drug
Misinterpretation of measured serum drug level (ie, change in therapeutic range)

Hyperkalemia

Potentially the most rapidly lethal complication of CKD is severe hyperkalemia. As a rule, this condition is clinically silent until it causes potentially life-threatening manifestations. Accordingly, hyperkalemia must be looked for in every patient with CKD. These patients can become severely hyperkalemic when required to handle even modest exogenous and endogenous potassium loads; moreover, even drugs that have only minimal effects on the serum potassium level in normal persons, such as β-blockers and ACE inhibitors, can cause hyperkalemia in these patients. There is concern that the use of succinylcholine in patients with CKD has the potential to cause rapid deterioration in patients who are already hyperkalemic, although this appears to be rare.

An ECG should be obtained whenever hyperkalemia is a possibility and, if signs of hyperkalemia are noted, appropriate therapy should be started immediately, even before laboratory confirmation of a high serum potassium level. Electrocardiographic changes may be completely absent, even when hyperkalemia is severe; thus, a normal ECG does not preclude the need for laboratory confirmation of a normal serum potassium level. A potassium level of 6 mEq/L should be considered potentially dangerous, even though many patients with CKD chronically tolerate levels somewhat above this threshold, without electrocardiographic changes. A patient with CKD who is in cardiac arrest should be assumed to be hyperkalemic and treated accordingly while the usual resuscitative measures are taken. See earlier ("Acute Kidney Injury: Management") and Table 87.1.

In patients who still retain some renal function, the most effective way to treat hyperkalemia in patients with CKI may be to administer an IV diuretic such as furosemide (if the patient is not hypovolemic) and to provide volume, if necessary. Large doses of diuretic may be necessary for a satisfactory diuresis to be induced. In light of the potential for ototoxicity with the use of loop-active diuretics, these drugs should be administered by slow infusion rather than by bolus and may be contraindicated in patients who also are receiving other potentially ototoxic agents. During the course of any of these therapeutic interventions, the electrocardiographic and serum potassium levels must be monitored frequently.

Pulmonary Edema

Perhaps the most common ED problem in patients with CKD is pulmonary edema secondary to volume overload. Surprisingly,

TABLE 87.1

Treatment of Hyperkalemia

AGENT OR MODALITY	DOSE AND REGIMEN	ONSET/DURATION OF ACTION	MECHANISM OF ACTION	COMMENTS
Calcium gluconate (10%)	10 mL IV (may repeat × 2 prn every 5–10 min)	1–5 min/≈1 hr	Antagonizes membrane effects of K	Monitoring of ECG required; do not mix with HCO_3^- *Beware*—hypercalcemia
Albuterol	10–20 mg (nebulized) by inhalation	30 min/2 hr or more	Intracellular movement of K	Relatively free of significant side effects; tachycardia
Glucose and insulin	10–20 units regular insulin/100 g glucose	30 min/while infusion continued	Intracellular movement of K	*Beware*—hyperglycemia, hypoglycemia Infused volume may be decreased by giving $D_{10}W$, $D_{20}W$, or $D_{50}W$
Sodium bicarbonate	150 mEq/L IV infusion (rate variable)	Approximately 10–15 min/1–2 hr	Possible intracellular movement of K	Most effective with organic acidosis
Dialysis	HD, PD	Minutes/while continued	Removal of K from blood	HD may remove 50 mEq/hr *Beware*—K rebound PD may remove 15 mEq/hr
IV diuretics (IV fluid if patient is hypovolemic)	Furosemide 40–80 mg IV	15 minutes/while diuresis continued (depending on renal function)	Urinary K excretion	Only in patients with some residual renal function

$D_{10}W$, 10% dextrose in water; *$D_{20}W$,* 20% dextrose in water; *$D_{50}W$,* 50% dextrose in water; *ECG,* electrocardiogram; *HD,* hemodialysis; *IV,* intravenous; *PD,* peritoneal dialysis; *PO,* orally.

the diagnosis is not always straightforward. A history of increasing dyspnea on exertion or paroxysmal nocturnal dyspnea may be suggestive, but the physical examination may not reveal the expected signs of CHF, and even chest radiography may be deceptive. Recent weight gain or a body weight considerably over dry weight (typically >5 pounds) is the most reliable clue and, in the absence of convincing evidence of another cause for dyspnea, volume overload should be assumed to be the cause.

Treatment of pulmonary edema in the patient with CKD is of necessity somewhat different from that in other patients. Arrangements for initiation of dialysis should be made as soon as possible because it is the most rapidly effective means to decrease intravascular volume in the absence of renal function. Other immediate measures should be instituted in the meantime. Although such measures may occasionally prove to be effective enough to avoid dialysis temporarily in patients who possess some residual renal function, it should nevertheless be anticipated that the response to even extremely aggressive medical therapy, short of dialysis, will be inadequate.

The CKD patient with pulmonary edema is placed in the sitting position, and high-flow oxygen is administered by mask. The use of continuous or bilevel positive airway pressure (CPAP or BiPAP) is a useful adjunct for patients with CKD, as for patients without renal failure. Sublingual nitroglycerin can be administered immediately and functions rapidly to reduce preload and afterload; an IV infusion beginning at 10 to 20 µg/min can be initiated promptly and titrated to effect. Diuretics are not expected to be helpful unless the patient has retained a significant level of renal function.

Infection

Because infection is a major contributor to morbidity and mortality among patients with CKD, the possibility of serious infection should be entertained, even when the expected classic findings are not all present. For example, bacteremia may manifest with fever alone, just as in other patients with impaired immunity. Patients with pneumonia may have only vague dyspnea or malaise, symptoms that may be attributed to volume overload or uremia. Thus, all diagnostic possibilities should be pursued, and empirical broad-spectrum antibiotic coverage often is advisable until infection has been ruled out in the hospital. Bacteremia resulting from vascular access infection is common in patients undergoing hemodialysis, as is peritonitis in patients undergoing peritoneal dialysis.

A UTI can occur even in patients with minimal urine output or those with long-standing renal failure. Urinary stasis is undoubtedly a predisposing factor. However, asymptomatic pyuria is common in these patients and is not necessarily indicative of infection. For patients with symptoms, urine culture is helpful in guiding treatment decisions. An upper UTI associated with a clinical picture typical of pyelonephritis or renal colic is usually seen in patients with polycystic kidney disease and requires parenteral treatment. A clinical diagnosis can be made presumptively in the ED, but invasive measures sometimes are necessary to document infection and guide therapy. For infected cysts, lipid-soluble antibiotics (eg, ciprofloxacin, trimethoprim-sulfamethoxazole) offer the best antibiotic penetration; surgical intervention for refractory infection sometimes becomes necessary, however.

Dialysis

Dialysis can normalize fluid balance, correct electrolyte and other solute abnormalities, and remove uremic toxins or drugs from the circulation when the patient's kidneys are unable to do so. Dialysis also can reverse some uremic symptoms, but generally to a lesser degree, and permit better long-term control of hypertension, anemia, and renal osteodystrophy.

Major Dialysis Modalities. The two major dialysis modalities are hemodialysis and peritoneal dialysis. Each is based on a technique whereby the patient's blood comes into contact with a semipermeable membrane, on the other side of which is a specially constituted balanced physiologic solution. Water and solutes diffuse across the membrane by moving along concentration and osmotic gradients, effectively normalizing the blood's composition.

Hemodialysis. This requires special access to the patient's circulation, generally through a surgically created arteriovenous fistula or implanted artificial graft or through a surgically placed tunneled catheter. The vascular access site must be treated with care because hemodialysis cannot be performed without it. Careless manipulation or puncture can cause bleeding, infection, or thrombosis, which may result in loss of the access. The involved arm should not be used for blood pressure determinations, and a tourniquet should not be applied.

In general, blood is drawn and IV lines are established in other locations. In exceptional circumstances, if no other site is available and it is essential to obtain blood samples quickly, the fistula or graft may be used, but with precautions. A tourniquet is not applied, the area is cleansed scrupulously before the puncture, and extreme care is taken not to puncture the back wall of the access. After the puncture, firm but nonocclusive pressure is applied for at least 10 minutes. The presence of a thrill before and after the procedure is documented. Similar precautions are taken in the exceptional cases in which the fistula or graft must be used for IV access. If this is done, an automated infusion pump is essential to control the infusion rate into these relatively high-pressure blood vessels.

Peritoneal Dialysis. Here, the patient's peritoneum functions as the dialysis membrane. Dialysate is infused through a surgically implanted Silastic catheter (Tenckhoff catheter) that penetrates the lower abdominal wall. Fluid exchanges are performed several times daily, typically by the patient at home. As compared with hemodialysis, peritoneal dialysis offers the theoretical advantages of greater patient independence, avoidance of anticoagulation, and smoother control of volume and hypertension, without the intermittent rapid shifts of solute typical of hemodialysis. Medications such as insulin and antibiotics can be administered via the intraperitoneal (IP) route, allowing smoother absorption and more stable blood levels. The main disadvantage of peritoneal dialysis is a significant incidence of bacterial peritonitis, which is, however, usually readily treatable.

Indications for Dialysis. The decision to initiate chronic dialysis in the patient with CKD generally is made by the patient's nephrologist in the setting of a gradually decreasing GFR and progressive manifestations of renal failure. The absolute value of the BUN or serum creatinine level generally is used only as a rough guide to determine when chronic dialysis should be instituted. The provision of vascular or peritoneal access usually has been arranged weeks to months before the anticipated initiation of dialysis to allow the access site to mature and minimize any mechanical complications of the procedure.

For patients who come to the ED with AKI, however, as well as for patients with CKD in whom acute problems have developed, the emergency clinician must be prepared to make the decision to arrange for emergent dialysis (Box 87.9). How urgently dialysis must be initiated depends not only on the severity and acuteness of the presenting problem, but also on the availability of technical facilities and trained dialysis personnel and effectiveness of available temporizing measures for the problem at hand.

BOX 87.9

Indications for Emergency Dialysis

- Pulmonary edema
- Severe uncontrollable hypertension
- Hyperkalemia
- Other severe electrolyte or acid-base disturbances
- Some overdoses
- Pericarditis (possibly)

The most common problem requiring emergent dialysis, particularly in the patient with CKD, is pulmonary edema secondary to volume overload. In general, the inciting cause is overingestion of fluid and salt in excess of the patient's greatly diminished renal excretory capacity. Despite the effectiveness of temporizing measures, many of these patients require immediate dialysis—emergency hemodialysis or, in the case of the patient maintained on peritoneal dialysis, intensification of the usual dialysis regimen.

A related problem that may require emergent, or at least urgent, dialysis is malignant hypertension, particularly when associated with hypertensive encephalopathy or cardiovascular decompensation. Because hypertension in patients with renal failure is commonly volume-dependent, correction of volume overload, even if not apparent clinically, is a central component of therapy. Temporizing measures such as the administration of IV nitroglycerin often permit hypertension to be controlled sufficiently for dialysis to be delayed for several hours. In many cases, hypertension and associated symptoms are difficult to control until dialysis permits the volume overload to be corrected. Because blood pressure often is dramatically responsive to reduction of circulating volume, other antihypertensive agents with more prolonged effects should be withheld until after dialysis to avoid hypotension after circulating volume has been acutely reduced.

Severe hyperkalemia is another common indication for emergent or urgent dialysis, particularly in the patient with AKI who is hypercatabolic. In the patient with CKD, hyperkalemia usually is caused by excessive potassium intake, but endogenous causes such as hemolysis or rhabdomyolysis should also be kept in mind. The available temporizing measures can be used to control the serum potassium level, but dialysis remains the most effective means of removing potassium from the body. For rapid control of the serum potassium level, hemodialysis, with its high clearance rates, is preferred to peritoneal dialysis.

Other severe electrolyte and acid-base disturbances, including diabetic ketoacidosis, may sometimes necessitate emergent dialysis. Occasional patients with renal failure and severe hypercalcemia uncontrollable by other modalities (eg, patients with multiple myeloma causing both renal failure and hypercalcemia) may require dialysis. The occasional patient with renal failure in whom severe hypermagnesemia develops after inappropriate therapy or magnesium ingestion may require immediate dialysis to reverse life-threatening paralysis or cardiac dysrhythmia. Severe metabolic acidosis in the setting of renal failure is another indication for emergent dialysis, particularly if volume overload or hypocalcemia (with the risk of tetany and convulsions) precludes the administration of bicarbonate.

A related situation is one in which a patient with renal failure has taken an overdose or inadvertently been administered medication that is ordinarily cleared by the kidneys. If the agent is adequately dialyzable and its continued presence in the circulation poses a significant risk to the patient, immediate dialysis can be lifesaving. An example is the ingestion of methanol or ethylene glycol by a dialysis patient. Similarly, ill-advised use of magnesium-containing cathartics or phosphate-containing enemas by patients with CKD can lead to dangerous hypermagnesemia and hyperphosphatemia, respectively, and may necessitate urgent dialysis.

The serum creatinine and BUN levels themselves are not considered definitive indications for dialysis. A creatinine level of 10 mg/dL or BUN level of 100 mg/dL often is used as a guideline for beginning chronic dialysis in the patient with progressive renal failure. In dialyzed patients, however, the serum creatinine level often is considerably greater than 10 mg/dL but is a reflection of total body muscle mass more than of the adequacy of dialysis. The BUN level is a somewhat better indicator; in well-dialyzed persons, it generally is in the range of 50 to 80 mg/dL and is more than

100 mg/dL in less well-dialyzed patients. Neither blood level, however, correlates more than roughly with uremic symptoms, even in undialyzed patients, or has any direct bearing on how urgently dialysis should be initiated.

The occurrence of uremic symptoms or signs such as nausea, vomiting, lethargy, or twitching indicates a need for dialysis but does not necessitate immediate initiation of dialysis unless symptoms are severe. Pericarditis, even in the absence of cardiac tamponade, often is considered an indication for urgent dialysis, but pericarditis can also occur in well-dialyzed CKD patients. In a previously undialyzed patient with progressive renal insufficiency, the appearance of pericarditis indicates that it is time to initiate dialysis, although not necessarily on an emergency basis.

COMPLICATIONS OF DIALYSIS

A number of complications can be manifest after dialysis is initiated.

Hemodialysis

Vascular Access–Related Complications

The performance of hemodialysis depends on reliable vascular access, and it is the vascular access device that is responsible for the complications of dialysis that most often require evaluation in the ED setting. These problems must be attended to promptly to minimize the risk of losing the patient's dialysis lifeline.

Bleeding from the dialysis puncture site can occur hours after a hemodialysis treatment, either spontaneously or after inadvertent minor trauma to the site. Such bleeding can usually be stopped by applying firm pressure to the access site. Care should be taken not to occlude and possibly cause thrombosis of the vessel by compressing it too vigorously, and the presence of a thrill immediately after the procedure should be documented in the chart. It may be necessary to keep the patient in the ED for a time to ensure that bleeding does not recur. Recurrent bleeding, especially from an aneurysm or a pseudoaneurysm, is best evaluated by a vascular surgeon.

Similarly, if the patient reports that the thrill in the access has been lost, a vascular surgeon is consulted immediately. Although thrombolytic agents are generally used, definitive treatment is usually surgical revision. The access device should not be forcefully manipulated or irrigated because rupture of the vessel or venous embolization may result.

Infection of the vascular access can result in persistent or recurrent bacteremia, as well as loss of the access. Infection appears to be a consequence of contamination at the time of puncture for dialysis; most infections are caused by staphylococci typical of skin flora. Infections are more likely to occur in grafts than in native fistulae. The signs and symptoms of an access infection—redness, warmth, and tenderness over the site—often are obvious, but in many cases localizing findings are absent, and the patient has only fever or a history of recurrent episodes of fever and documented bacteremia. For this reason, it is common practice to obtain blood cultures for all patients on hemodialysis who have a fever without an obvious source of infection and to treat them presumptively for an access infection.[7] A careful search for other sources of infection is performed before an inapparent access infection is concluded to be the cause. Infections such as odontogenic abscess, extremity cellulitis (particularly in diabetics), and perirectal abscess can easily be missed.

Although some nephrologists prefer to admit all dialysis patients with fever to the hospital, management of these patients on an outpatient basis often is possible, provided that they otherwise feel well and do not appear to be septic and provided that they can care for themselves at home and return promptly if their condition worsens. This course is made more practicable by the fact that they can be loaded with IV antibiotics that dependably maintain adequate blood levels until the next scheduled dialysis treatment, at which time the culture and sensitivity test results can be checked and therapy adjusted accordingly. IV vancomycin, 1 to 1.5 g, given as a single loading dose, is the drug of choice in this case because most access infections are staphylococcal and because this drug is only minimally hemodialyzable and needs to be given only every 5 to 7 days in the chronic dialysis patient. If a gram-negative infection also is thought to be likely, as in a patient who has had recent episodes of gram-negative bacteremia, a loading dose of a second drug (eg, a third-generation cephalosporin or aminoglycoside) also can be administered. Patients can be reloaded with these drugs at the end of their next hemodialysis session if culture results prove to be positive.

Non–Vascular Access–Related Complications

The hemodialysis procedure itself, which entails invasion of the vasculature, anticoagulation, and significant shifts of fluid and solutes, often is associated with acute complications such as hypotension, shortness of breath, chest pain, and neurologic abnormalities.

Hypotension. Hypotension that occurs after dialysis is usually the result of an acute reduction in circulating intravascular volume and failure of the patient's homeostatic mechanisms to compensate for it. Because hemodialysis is episodic, each treatment must remove the excess fluid that has accumulated over the period since the last dialysis (generally, 2–3 days), and patients often are relatively volume-overloaded at the beginning of each treatment. With rapid removal of extracellular fluid, there is inadequate time for transcellular fluid shifts to replace intravascular volume. Antihypertensive medications that are required when the patient is in a volume-expanded state, particularly β-blockers, can contribute to the hypotension when intravascular volume is normalized.

Most episodes of hypotension that occur during hemodialysis resolve spontaneously or can be readily managed by a decrease in blood flow rate or infusion of small volumes of saline (to cause transient volume expansion) or hypertonic solutions (to reverse transient acute hypo-osmolality). Patients with significant hypotension who do not respond to these maneuvers often are brought to the ED for further evaluation. Patients on dialysis should be considered to be at risk for acute myocardial infarction, acute dysrhythmias, and sepsis. These are common causes of hypotension among all patients in the ED, and consideration should first be given to these entities (Box 87.10).

Acute blood loss is another consideration when a hemodialysis patient presents with hypotension, symptomatic angina, or CHF. Dialysis patients are commonly treated with epoetin or darbepoetin to prevent severe anemia; untreated patients typically have low baseline hemoglobin levels.[8] Serum levels of clotting factors are normal in CKD, but patients are routinely anticoagulated for each hemodialysis treatment and, although transient thrombocytopenia may occur during the dialysis procedure, the qualitative platelet defect characteristic of renal failure is an important factor in bleeding that continues beyond the peridialytic period. This abnormality is only partially reversed by dialysis but can be corrected by the administration of desmopressin (DDAVP), which increases the release of factor VIII–von Willebrand factor polymers from vascular endothelium. DDAVP has been used successfully to normalize the bleeding time in preparation for surgery in patients with CKD. Cryoprecipitate and conjugated estrogen both have been shown to produce similar effects for a longer period.[9]

Overt bleeding from the GI tract, often caused by angiodysplasia or peptic ulcer disease, is common and can be dramatic. Occult

BOX 87.10

Differential Diagnosis of Hypotension in Hemodialysis Patients

Hypovolemia
Excessive fluid removal
Hemorrhage
Septicemia
Cardiogenic shock
Dysrhythmia
Pericardial tamponade
Myocardial infarction
Myocardial or valvular dysfunction
Electrolyte disorders
Hyperkalemia or hypokalemia
Hypercalcemia or hypocalcemia
Hypermagnesemia
Vascular instability
Drug-related
Dialysate-related
Autonomic neuropathy
Excessive access arteriovenous flow
Anaphylactoid reaction
Air embolism

hemorrhage in other locations, however, can present a diagnostic challenge because symptoms and signs of volume loss tend to be overshadowed by local manifestations of bleeding into a closed space. Thus, spontaneous retroperitoneal or pleural hemorrhage tends to manifest with flank pain or with chest pain and shortness of breath, respectively.

Acute pulmonary embolism and acute air embolism are two less likely possibilities. The former, although it does occur occasionally in dialysis patients, is unusual. The latter, although reported occasionally in the past, has been all but eliminated by improved dialysis monitoring equipment and safety mechanisms.

Two additional entities in the differential diagnosis for hypotension are of particular importance in the patient with CKD—acute pericardial tamponade and severe, life-threatening hyperkalemia. Acute pericardial tamponade may be the result of sudden pericardial hemorrhage or sudden worsening of a formerly compensated pericardial effusion after acute correction of elevated preload. The clinical features of tamponade in the dialysis patient are similar to those in other populations, but the common preexistence of cardiomegaly may make the chest film difficult to interpret unless it shows the typical water bottle shape and a definite increase in heart size from previous examinations.

Similarly, an elevated central venous pressure is of little use in differentiating tamponade from underlying right-sided heart failure. Even the finding of pericardial fluid on bedside ultrasonographic examination, although suggestive, is not proof that tamponade is present, because many dialysis patients chronically have pericardial effusions that do not cause hemodynamic compromise. The ultrasonographic demonstration of right ventricular diastolic collapse is more specific. A definitive diagnosis of tamponade depends on the direct demonstration of equal pressures in the right and left atria on cardiac catheterization.

Emergency pericardiocentesis must occasionally be performed in the ED to relieve acute tamponade, but there often is enough time for the patient to be transported to the catheterization suite or operating room for safer and more definitive therapy in a controlled setting. If immediate pericardiocentesis is believed to be necessary, the emergency clinician should not hesitate to perform this potentially lifesaving procedure, despite the many potential complications and increased risk of bleeding in patients with CKD. Similarly, in the case of a dialysis patient who is in cardiac arrest, pericardiocentesis generally should be attempted if initial resuscitative efforts have not been successful.

Severe life-threatening hyperkalemia, although unusual in a dialyzed patient, can occur in the presence of underlying catabolic illness or with a prolonged period of hypotension and low flow. Patients who are hyperkalemic can have profoundly slow heart rates, particularly if they have been treated with β-blockers or calcium channel blockers. If a dialysis patient is in cardiac arrest, it should be assumed that hyperkalemia is present, and IV calcium should be given immediately.

Shortness of Breath. Shortness of breath in dialysis patients generally is caused by volume overload. In the patient who becomes short of breath while being dialyzed, however, other causes must be sought—primarily sudden cardiac failure, pericardial tamponade, pleural effusion, or pleural hemorrhage. Air embolism and anaphylactoid reactions are unusual causes. Often, pneumonia or underlying reactive airway disease is responsible.

Chest Pain. Cardiovascular disease is a leading cause of death in patients with CKD, and most episodes of chest pain occurring during dialysis are likely to be ischemic in origin. Most dialysis patients have risk factors for coronary artery disease, related to CKD itself or the underlying condition that led to renal failure, and many have well-documented coronary artery disease. CKD is commonly associated with hypertension, hyperlipidemia, carbohydrate intolerance, and disturbances of calcium and phosphorus metabolism. In addition, dialysis patients may be anemic, and many are chronically volume-overloaded. During hemodialysis, these underlying factors may be added to acute physiologic stresses such as transient hypotension and hypoxemia, which often are associated with the dialysis procedure, thereby increasing myocardial oxygen demand while decreasing oxygen delivery.

In evaluating presumed ischemic chest pain in a patient with CKD, reversible precipitants should be considered. It should be determined whether increasing anemia, poorly controlled hypertension, or uncorrected volume overload are factors, particularly when a patient whose angina has been stable begins to experience more frequent or more severe anginal episodes,. Patients who repeatedly experience chest pain during dialysis are candidates for a complete cardiac evaluation. Dialysis patients who have repeated ED visits for chest pain should have a coordinated strategy developed by their nephrologist and cardiologist to set guidelines regarding further admissions.

The presence of renal failure and its associated electrolyte and acid-base disturbances does not in general obscure the usual electrocardiographic changes of angina or acute myocardial infarction. The pattern of change of serum cardiac enzyme levels with acute infarction also is not altered by CKD, although the baseline level of these enzymes may be higher than in the general population.[10] Troponin appears to perform best as a marker of infarction in patients with CKD.[11] Treatment of ischemic chest pain is the same as for other populations.

Among nonischemic causes of chest pain, pericarditis should always be a consideration, even in the well-dialyzed patient. The presentation is essentially the same as in nonrenal patients; fever, a friction rub, or atrial dysrhythmias may be associated findings, and signs of pericardial effusion or early tamponade should be sought. Indomethacin often is effective in relieving pain, but some patients eventually require further measures, such as pericardiocentesis with corticosteroid instillation or pericardial stripping. Patients with pericarditis often receive more frequent or intensified dialysis because pericarditis is thought to be a marker for inadequate dialysis.

BOX 87.11

Differential Diagnosis of Altered Mental Status in Dialysis Patients

STRUCTURAL CONDITIONS
Cerebrovascular accident (particularly hemorrhage)
Subdural hematoma
Intracerebral abscess
Brain tumor

METABOLIC CONDITIONS
Disequilibrium syndrome
Uremia
Drug effects
Meningitis
Hypertensive encephalopathy
Hypotension
Postictal state
Hypernatremia or hyponatremia
Hypercalcemia
Hypermagnesemia
Hypoglycemia
Severe hyperglycemia
Hypoxemia
Dialysis dementia

Neurologic Dysfunction. Neurologic dysfunction manifesting during or immediately after hemodialysis may be caused by disequilibrium syndrome, a constellation of symptoms and signs thought to result from rapid changes in body fluid composition and osmolality during hemodialysis. It usually occurs only in patients with high BUN levels who are just starting hemodialysis; the syndrome does not occur with peritoneal dialysis. Typically, patients have headache, malaise, nausea, vomiting, and muscle cramps but, in more severe cases, features may include altered mental status, seizures, or coma. Symptoms resolve over several hours as fluid and solutes are redistributed across cell membranes.

Altered mental status in the CKD patient should not be attributed to disequilibrium syndrome unless other causes have been ruled out (Box 87.11), particularly when symptoms persist, fluctuate, or worsen during a reasonable period of observation. Likewise, when seizures occur during dialysis, it is tempting but unwise to attribute them to disequilibrium syndrome without considering other, potentially serious causes, even in patients who have had seizures in the past. In particular, the finding of any new focal neurologic abnormality calls for, at a minimum, an immediate head CT scan to detect intracranial hemorrhage. Similarly, if fever or other evidence of infection is present, meningitis must be a serious consideration. Other considerations include hyperglycemia and hypoglycemia, especially in the diabetic patient, electrolyte abnormalities, hypoxic states, hypotension of any cause, and other toxic or metabolic causes. The treatment of seizures in patients with CKD is essentially the same as for other populations.

Peritoneal Dialysis

As with hemodialysis, most of the complications of peritoneal dialysis are related to the dialysis access device, in this case the peritoneal catheter. In contrast to hemodialysis, however, the dialytic process in peritoneal dialysis occasions few immediate difficulties.

Peritonitis is the most common complication of peritoneal dialysis. Fortunately, it is generally much less severe than other types of peritonitis and can be treated readily on an outpatient basis, despite the continued presence of a foreign body—the Tenckhoff catheter—in the peritoneal cavity. Occasionally, when an episode of peritonitis responds poorly to antimicrobial therapy or when a patient has repeated episodes of peritonitis caused by the same organism, the catheter must be removed and the patient sustained with hemodialysis until the infection is completely cleared and a new catheter can be placed. Repeated infections carry the risk of permanently altering peritoneal permeability or effective surface area and necessitating a permanent switch to hemodialysis.

Peritonitis in patients on peritoneal dialysis presumably is caused by inadvertent bacterial contamination of the dialysate or tubing during an exchange or by extension of an infection of the exit site or subcutaneous tunnel into the peritoneal cavity. Most cases of peritonitis are caused by *Staphylococcus aureus* or *Staphylococcus epidermidis,* and most of the remainder (≈30%) by gram-negative enteric organisms.[12] Fungal infections are uncommon but generally are refractory to medical therapy and are often considered as an indication for catheter removal. Polymicrobial infection suggests direct contamination from the GI tract and mandates a search for the site of perforation or fistula, although such a source is identified in only a minority of cases. No organism is identified in approximately 10% to 20% of cases of peritoneal dialysis–associated peritonitis.

The diagnosis of peritonitis usually is made by the patient when a cloudy dialysis effluent is noted, corresponding with the appearance of white blood cells (WBCs) in the dialysate. Peritonitis is often, but not invariably, accompanied by nonspecific abdominal pain, malaise, or fever. When a patient has fever or abdominal symptoms, even in the absence of cloudy fluid, it is advisable to consider peritonitis and check the fluid, because early peritonitis may manifest in an atypical manner. In more severe cases, peritonitis is accompanied by nausea, vomiting, severe pain, and hypotension, necessitating hospitalization and consideration of the possibility of acute surgical disease.

In the ED setting, the diagnosis of peritonitis is confirmed by the finding of more than 100 WBCs/mm^3 in the peritoneal fluid, with more than 50% neutrophils, or by a positive result on Gram staining. A sample of fluid is obtained for analysis. If a specialized dialysis nurse is available to obtain the fluid, this may be preferable. If not, the fluid is obtained through the use of sterile technique. Fluid is sent for cell count and differential, Gram staining, and culture, with the use of blood culture bottles.

Peritoneal dialysis–associated peritonitis is treated with an initial IP loading dose of antibiotic, followed by a 10- to 14-day course of IP antibiotics self-administered by the patient on an outpatient basis. After the diagnosis has been confirmed, consultation with the patient's nephrologist or dialysis nurse specialist is indicated to determine antibiotic therapy and a plan for outpatient management and follow-up evaluation or, occasionally, if peritonitis is severe or outpatient management is precluded by psychosocial considerations, for hospitalization. A common treatment regimen is a loading dose of vancomycin, 30 mg/kg IP, followed by further IP doses every 5 to 7 days, plus ceftazidime or cefepime, 1 g IP, or gentamicin, 0.6 mg/kg IP. The last two regimens are given as a loading dose followed by maintenance doses administered IP once daily at the time of an exchange.[12] Heparin, 500 to 1000 units, also may be added to each bag of dialysate for the first few days of treatment to help reduce the formation of fibrin strands that may obstruct the catheter. Patients should be seen by the dialysis nurse in 24 to 48 hours for assessment of the response to therapy and adjustment of antibiotic therapy as necessary after review of the results of culture and sensitivity testing.

Catheter contamination or leaks from the catheter, tubing, or dialysate bag should be managed in the same fashion as for frank peritonitis. The site and cause of leakage are identified, and damaged elements are promptly replaced. Occasionally, with leakage of peritoneal fluid from around the catheter, surgical correction of the underlying problem will be necessary.

Patients who have severe abdominal pain, vomiting, ileus, chills or high fever, or hypotension require hospital admission and management. Likewise, patients with severe underlying illness and those who cannot reliably perform exchanges or administer antibiotics at home also require inpatient management. Dialysis exchanges are continued on the same schedule. The inpatient antibiotic regimen is essentially the same as for outpatients.

Perhaps the most serious potential pitfall in caring for the patient maintained on peritoneal dialysis with abdominal pain or other signs of peritonitis is to overlook other serious intra-abdominal conditions whose presentation may mimic that of peritonitis. Patients on peritoneal dialysis are at increased risk for abdominal wall or inguinal hernia because of chronically increased intra-abdominal pressures; previous abdominal surgery also places them at risk for hernia, as well as for obstruction secondary to adhesions. The manifestations of serious disorders unrelated to dialysis (eg, acute appendicitis, diverticulitis, cholecystitis, acute pancreatitis, ischemic bowel, perforated viscus) also may be attributed to ordinary peritoneal dialysis–associated peritonitis, with the potential for disastrous consequences. The accessibility of the peritoneal fluid for examination may prove to be helpful in documenting the presence of an inflammatory process, but it also has the potential to mislead ED investigation of its cause. A finding of brownish or fecal material in the peritoneal drainage should suggest a ruptured viscus until proven otherwise, and immediate surgical consultation should be sought. Detection of a localized tenderness, palpable mass, or incarcerated hernia on physical examination can be extremely helpful in making the diagnosis. Abdominal radiography may be useful for demonstrating the presence of ileus, but pneumoperitoneum may reflect only the introduction of air during a recent fluid exchange rather than a perforated viscus.

Infection of the catheter exit site or tunnel is another relatively common problem for which the patient on chronic peritoneal dialysis may seek care in the ED. These infections tend to be caused by typical skin flora and manifest with local signs of infection. Although not serious in themselves, exit site infections may lead to infection of the subcutaneous tunnel, which can cause repeated episodes of peritonitis and may ultimately necessitate removal of the catheter. Any visible exudate is cultured and Gram-stained, and therapy with an oral antibiotic such as cephalexin or dicloxacillin is started, pending the results of culture and sensitivity testing. The patient is instructed to cleanse the site meticulously several times a day using povidone-iodine or peroxide solution.

Tunnel infections can be difficult to detect on physical examination and may be suspected only after the patient has several bouts of peritonitis caused by the same organism. As with other closed space infections, tunnel infections tend to be difficult to eradicate unless the tunnel is partially unroofed and drained.

Patients maintained on peritoneal dialysis also may come to the ED with any of several basically mechanical problems, of which the most common is failure of the dialysate to drain completely at the time of an exchange. Occasionally this problem is caused simply by kinking or inadvertent clamping of the external catheter or tubing. More often, though, it is the result of catheter obstruction by fibrinous debris or kinking or migration of the catheter within the peritoneal cavity, often associated with constipation. Catheter position is best assessed initially by plain radiography of the abdomen. Specific intervention may be guided by a so-called contrast catheterogram. Fibrinolytic agents have been used successfully to open occluded catheters, but surgical intervention for catheter replacement often is required.

Severe metabolic disturbances are much less common among patients on peritoneal dialysis than patients on hemodialysis, because in the former group dialysis is being performed essentially continuously and the blood remains in near-equilibrium with the dialysate. However, significant disturbances do occasionally occur, usually in association with hypercatabolic states, major dietary indiscretions, or significant GI fluid loss. One derangement that occurs occasionally in diabetic patients undergoing peritoneal dialysis is a syndrome of severe hyperglycemia—sometimes even despite continuation of the usual insulin dose—that results from absorption of glucose from the hyperosmolar dialysate, with associated nonspecific symptoms of malaise, weakness, and headache. Although glucose levels may be as high as 1500 mg/dL in these patients, they cannot undergo an osmotic diuresis and remain clinically euvolemic. Correction of hyperglycemia must be undertaken carefully to avoid causing rapid osmolar and volume shifts.

KEY CONCEPTS

- The causes of AKI can be classified as prerenal, postrenal, and instrinsic renal disorders. Abrupt cessation of glomerular filtration typically results in a rise of the serum creatinine level of 1 to 2 mg/dL per day.
- Management of AKI is directed first at potentially lethal complications such as hyperkalemia or volume overload and then at reversal of the underlying cause of renal dysfunction. It is important to avoid any further hemodynamic or toxic insults to the kidneys.
- Patients with acute or chronic kidney disease have a limited ability to handle fluid and solute loads and have altered metabolism of many drugs. Therefore, the patient's impaired renal function must be considered when fluid is administered or drugs are prescribed.
- The most rapidly lethal complication of acute and chronic kidney disease is hyperkalemia.
- The most common problems with vascular access devices used for hemodialysis are thrombosis, hemorrhage, and infection. Access infection often presents as fever without an obvious source and, in this case, appropriate IV antibiotics should be administered presumptively while awaiting blood culture results.
- Peritoneal dialysis–associated peritonitis typically presents with cloudiness of the peritoneal dialysis effluent. The diagnosis is made by a positive Gram stain or finding of more than 100 WBC/mm^3 in the effluent, with at least 50% polys. It is generally treated on an outpatient basis with intraperitoneal antibiotics self-administered by the patient.
- Chest pain in the dialysis patient should be presumed initially to be due to acute coronary syndrome, although other potentially serious causes may also be responsible. Serum troponin levels tend to be elevated in patients with poor renal function, but patients with myocardial infarction show the typical temporal pattern of rise and fall of troponin levels.
- Hypotension in CKD patients is often caused by infection, but may also be the result of rapid fluid removal during dialysis. This often responds readily to fluid administration. Pericardial tamponade is another cause of hypotension that should be considered for these patients.
- Altered mental status is most commonly due to causes similar to those seen in patients without renal disease, but is sometimes the result of overrapid shifts in intravascular fluid and solutes during dialysis, termed *disequilibrium syndrome*.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 87: QUESTIONS & ANSWERS

87.1. Of the following choices, which is the correct match between type of urine cast and pathologic condition?
- **A.** Fatty casts—glomerulonephritis
- **B.** Granular casts—renal parenchymal infection
- **C.** Hyaline casts—dehydration, exercise
- **D.** Red cell casts—nephrotic syndrome
- **E.** White cell casts—acute tubular necrosis (ATN)

Answer: C. Hyaline casts are associated with dehydration, exercise, and glomerular proteinuria. The following are the other correct associations:
- Fatty casts—nephrotic syndrome
- Red cell casts—glomerulonephritis
- White cell casts—renal parenchymal infection
- Granular casts—ATN

87.2. A 34-year-old man with chronic kidney disease has missed his last two hemodialysis treatments and presents with generalized fatigue and dyspnea on exertion. Vital signs include a blood pressure of 165/94 mm Hg, but are otherwise normal. Room air Sao_2 is 94% at rest. A portable chest x-ray shows vascular congestion. Which of the following is an indication for immediate dialysis?
- **A.** Blood urea nitrogen (BUN) level of 87 mg/dL and serum creatinine level of 10.6 mg/dL
- **B.** Serum calcium level of 6.8 mg/dL and serum albumin level of 3.0 g/dL
- **C.** Serum potassium level of 7.6 mEq/L (not hemolyzed)
- **D.** Serum sodium level of 124 mEq/L
- **E.** Serum troponin level of 0.08 ng/mL

Answer: C. Severe hyperkalemia is an indication for immediate dialysis in this patient. An ECG should be obtained stat to determine the degree of cardiotoxicity, and immediate medical treatment for hyperkalemia should be given while awaiting initiation of dialysis. Abnormalities of the serum sodium or calcium level can generally be treated without hemodialysis. A minimal troponin level elevation may be seen in patients with chronic kidney disease, but does not generally require specific treatment without other signs of cardiac ischemia; dialysis is not required.

87.3. What is the most common cause of nontraumatic hematuria?
- **A.** Carcinoma of the kidney or bladder
- **B.** Cystitis
- **C.** Kidney stones
- **D.** Prostatic hyperplasia
- **E.** Transfusion reaction

Answer: C. In descending frequency, the most common causes are kidney stones, lower urinary tract infection (UTI), benign prostatic hypertrophy (BPH), carcinoma of the kidney or bladder, urethritis, and glomerulonephritis.

87.4. A 53-year-old man presents with painless gross hematuria. His only past medical history is an aortic valve replacement for which he takes warfarin. The physical examination is nonfocal. Laboratory evaluation is remarkable for a normal chemistry panel and blood count, too numerous to count (TNTC) red blood cells (RBCs) on urinalysis, and international normalized ratio (INR) of 1.8. What is the next indicated step?
- **E.** Admission and observation
- **B.** Parenteral vitamin K
- **A.** Reassurance
- **D.** Renal imaging
- **C.** Withholding warfarin (Coumadin) for 3 days

Answer: D. When hematuria is associated with anticoagulant use, underlying disease can be identified in a significant proportion of patients.

87.5. A 33-year-old woman presents with mild nonfocal abdominal pain and subjective fever. Her past medical history is significant for hypertension-induced renal failure, for which she is on peritoneal dialysis (PD). The physical examination is remarkable for a temperature of 38°C (100.4°F), blood pressure 190/110 mm Hg, and mild nonfocal abdominal pain. Slightly cloudy peritoneal fluid is aspirated from the PD catheter and sent for analysis. Which of the following statements regarding this patient's condition is correct?
- **A.** A peritoneal fluid white blood cell (WBC) count >50/mm^3 is diagnostic.
- **B.** Intravenous antibiotics should be started empirically.
- **C.** Most cases are due to *Staphylococcus.*
- **D.** No organism is identified in 50% of cases.
- **E.** Polymicrobial infections suggest sample contamination.

Answer: C. Most PD-associated cases of peritonitis are due to *Staphylococcus aureus* or *Staphylococcus epidermidis*. No organism is identified in 20% of cases. A polymicrobial infection warrants GI evaluation for possible perforation or intra-abdominal abscess. A PD fluid count >100 cells/mm^3, with a neutrophil count >50% or positive Gram stain, is considered confirmatory. Treatment is typically with intraperitoneal antibiotics given for a 10- to 14-day course.

CHAPTER 88

Sexually Transmitted Diseases

Jeffry McKinzie

PRINCIPLES

Sexually transmitted diseases (STDs) are a diverse group of conditions caused by more than 30 viral, bacterial, and parasitic organisms that are transmitted through sexual contact.[1] Approximately 20 million newly acquired STDs occur in the United States each year, with an estimated $16 billion in associated health care costs.[2,3] STDs are seen across all demographic, cultural, and socioeconomic strata; and all sexually active persons are at risk for acquiring them. Factors associated with higher risk for STDs reflect the importance of individual sexual practices and risk-taking behaviors (ie, multiple sex partners, substance abuse, commercial sex workers, men who have sex with men, and unsafe sex practices), as well as various demographic and social determinants that influence health status (ie, adolescents and young adults, minorities, and low socioeconomic status).

STDs are among the most common urogenital conditions encountered in the emergency department (ED). The management of patients with STDs is particularly challenging for multiple reasons: (1) the clinical presentation is highly variable; (2) available diagnostic tests have limited sensitivity and results are usually delayed; (3) compliance with treatment, follow-up, and partner notification is often poor; and (4) misdiagnosis and suboptimal treatment can result in serious sequelae. In addition to the morbidity associated with individual STDs, many of these infections also increase the risk of human immunodeficiency virus (HIV) transmission and acquisition in both the infected person and their sexual partners. Thus, STDs have a significant impact on individual and public health.

Patients with STDs frequently present with complaints related to the genitalia but may also present with a variety of nonspecific dermatologic, gastrointestinal, musculoskeletal, and systemic complaints. Because the signs and symptoms of many common STDs are often nonspecific, one must maintain a high level of awareness for these conditions and their associated complications. A thorough history, including sexual history, and focused physical examination facilitate appropriate diagnosis and treatment. The sexual history should include number and gender of sexual partners, types of sexual practices, use of barrier contraception (condoms), and past history of STDs. Obtaining an accurate sexual history may be difficult due to the sensitive nature of the subject, lack of established physician-patient rapport, and other constraints of the ED setting. Evaluation is facilitated by the use of a nonjudgmental approach, maintenance of patient privacy, and assurance of confidentiality.

The differential diagnosis for STDs is extensive, including many other infectious and noninfectious conditions (Table 88.1). Most STDs can be broadly categorized as conditions characterized by one of the following manifestations: genital ulcers, genital discharge, epithelial cell infections, and infestation by ectoparasites. Some STDs, such as syphilis, frequently have associated systemic symptoms in addition to their genitourinary manifestations. Other STDs, such as HIV, may have systemic manifestations in the absence of genitourinary signs and symptoms.

STDs frequently coexist. Diagnosis of one STD should prompt consideration of other coexisting infections, which may not be clinically apparent. Screening for other STDs, including HIV, should be considered, because early diagnosis and treatment benefits both the individual patient and the public health. Despite current recommendations from the Centers for Disease Control and Prevention (CDC) for routine HIV screening among patients age 13 to 64 years in all health care settings, systematic HIV testing is not routinely performed in most EDs.[4] When available, rapid HIV testing should be considered. Patients should be counseled regarding the need for HIV testing if it is not performed in the ED.

Empirical antibiotic treatment designed to cover the most likely infecting organisms is recommended for patients with suspected STDs to maximize eradication of disease in the individual patient and reduce the spread of infection to other susceptible persons. Empirical therapy is particularly important when there are concerns about the patient's ability to obtain appropriate follow-up care. Confirmatory diagnostic studies should still be considered, even when empirical therapy is provided. Microbiologic diagnosis confirms the appropriate choice of empirical therapy, provides guidance for potential changes in treatment, and facilitates reporting of specific STDs to public health authorities.

The diagnosis of an STD provides the physician with a "teachable moment" to educate the patient regarding important factors, including (1) nature of the infection and how it is transmitted; (2) compliance with prescribed therapy and recommended follow-up; (3) importance of preventive measures, including condom use and other safe sex practices; and (4) partner notification and treatment. Patients diagnosed with STDs should be counseled to abstain from sexual intercourse for at least 7 days after the patient and partner(s) complete treatment. Proper counseling helps to ensure the success of initial treatment and reduce the incidence of reinfection. When the diagnosis of an STD is suspected but not confirmed, the patient should be informed of the uncertainty of the diagnosis and the rationale for empirical treatment. The physician should be sensitive to the stress and anxiety that may ensue when discussing the diagnosis of an STD, particularly with a patient who assumes he or she is in a monogamous relationship. A respectful, nonjudgmental, and compassionate manner should be maintained.

The CDC supports the use of expedited partner therapy (EPT) to ensure treatment in sexual partners of selected patients diagnosed with gonorrhea or chlamydia.[5] With EPT, the clinician provides patient-delivered treatment for sexual partners without personally evaluating them. Although EPT may be suitable in some practice settings, its use in the ED is potentially problematic due to lack of knowledge regarding the partner's medical history, allergies, pregnancy status, and other factors. In addition, some states prohibit the prescribing or dispensing of medications to patients who have not been seen and are unknown to the provider. Updated information regarding the use of EPT and applicable state regulations is available online from the CDC website.[6] All patients diagnosed with an STD in the ED should be advised to notify their sexual partners to seek prompt evaluation and treatment.

An organized mechanism for follow-up of positive diagnostic test results is recommended when these results are not available

TABLE 88.1

Differential Diagnosis of Common Sexually Transmitted Disease Syndromes

GENITAL ULCERS	GENITAL DISCHARGE	EPITHELIAL CELL LESIONS	ECTOPARASITES
Genital herpes	Gonorrhea	Genital warts	Pubic lice
Primary syphilis	Chlamydia	Secondary syphilis	Scabies
Chancroid	Nongonococcal urethritis (NGU)	Molluscum contagiosum	Other lice (body, head)
Lymphogranuloma venereum	Pelvic inflammatory disease	Neoplasm	Other mites (chiggers)
Granuloma inguinale	Trichomoniasis	Nevi	Ticks
Trauma	Bacterial vaginosis	Skin tags	
Neoplasm	*Candida* vaginitis		
Behçet's disease	Foreign body		
Abscess (draining)	Irritants/allergens		

until after the patient and physician have left the ED. Obtaining accurate contact information at the time of the initial ED visit is important in ensuring timely patient notification. Reporting requirements vary by state, but the following STDs must be reported in all 50 states: gonorrhea, chlamydia, syphilis, chancroid, and HIV. Reporting may be laboratory-based or provider-based, or both. The clinician should be familiar with applicable state reporting requirements and the reporting mechanism used at their hospital.

This chapter reviews the clinical features, diagnosis, and treatment of selected common STDs encountered in the ED setting. Readers are referred to the "Sexually Transmitted Diseases Treatment Guidelines" published by the Centers for Disease Control for additional information regarding the diagnosis and treatment of these conditions, as well as other less common STDs.[7] Updates regarding changes in treatment guidelines are provided by the CDC in the *Morbidity and Mortality Weekly Report,* available at www.cdc.gov/mmwr.

DISORDERS CHARACTERIZED BY GENITAL ULCERS

Genital ulcers may be caused by several different STDs, as well as various other infectious and noninfectious conditions. Genital herpes is the most common ulcerating STD seen in the United States, followed by syphilis. Chancroid is an uncommon cause of genital ulcers in the United States, and other STDs that may be manifested by genital ulcers (lymphogranuloma venereum, granuloma inguinale) are rare. Although the history, clinical appearance of the ulcers, and other associated findings provide helpful clues in differentiating the various causes of genital ulcers, these features are not specific enough to provide a definitive diagnosis. Diagnostic studies such as dark field microscopy, serology for syphilis, polymerase chain reaction (PCR), and viral culture should be considered to discriminate between the various etiologies and facilitate a definitive diagnosis, even when empirical therapy is initiated. Diagnostic testing is particularly important in patients that are unresponsive to previous empirical antibiotic therapy. Ulcerating STDs play an important role in facilitating the transmission and acquisition of HIV.

Herpes

Principles

Genital herpes is a lifelong viral infection caused by one of two types of herpes simplex virus (HSV): HSV-1 or HSV-2. Sexual transmission occurs more commonly with HSV-2, with an estimated 50 million people infected in the United States alone.[8] Many cases are undiagnosed. HSV is often transmitted by persons who are unaware that they are infected, or who are asymptomatic at the time of transmission. HSV transmission occurs through viral contact with a break in the skin or intact mucous membranes. The average incubation period is 4 days but may range from 2 to 12 days. The virus ascends via sensory nerves to the dorsal root ganglia, where it becomes latent but may reactivate periodically. Herpes, like other ulcerating STDs, facilitates the transmission and acquisition of HIV. Herpes infection in pregnant women may result in transmission to the infant at the time of delivery, with devastating associated neonatal morbidity and mortality.

Clinical Features

Typical herpetic lesions begin as a cluster of small erythematous painful vesicles, which quickly ulcerate (Fig. 88.1). Lesions may occur anywhere the organism is inoculated, but they are typically seen on the skin of the external genitalia, perineum, and buttocks and on the mucous membranes of the vagina, rectum, and oropharynx. Primary infection occurs when a patient is infected with HSV-1 or HSV-2 with no preexisting antibodies to either type. The primary infection is usually more painful and symptomatic, with associated tender regional lymphadenopathy, fever, malaise, headache, and other systemic symptoms. Dysuria is common due to the proximity of the lesions to the urethra. The symptoms of untreated primary infection typically last from 2 to 4 weeks before resolving spontaneously.

Nonprimary infection occurs when a patient is infected with HSV-1 or HSV-2 and has preexisting antibodies to the other viral type (ie, a patient with preexisting antibodies to HSV-1 due to orolabial herpes becomes infected with HSV-2 causing genital herpes). Patients with a nonprimary infection typically have fewer skin lesions and less systemic symptoms than those with primary infections. Recurrent episodes tend to be less symptomatic and shorter in duration, with lesions occurring in the same distribution due to reactivation of latent infection in the affected nerve roots. Recurrences are more frequent with infection caused by HSV-2 than with HSV-1. Recurrent outbreaks are often heralded by prodromal symptoms of itching, burning, and paresthesias prior to the development of skin or mucous membrane lesions. Reactivation of latent HSV may occur in response to a variety of stressors, including acute illness or injury, immunosuppression, psychological stress, and menses. Recurrences typically become less frequent and less severe over time. Extragenital complications of HSV infection include meningoencephalitis, transverse myelitis, hepatitis, pneumonitis, transverse myelitis, and disseminated

Fig. 88.1. Genital herpes lesions on the penile shaft.

infection. Asymptomatic viral shedding and transmission occurs even in the absence of visible lesions on the skin or mucous membranes.

Diagnostic Testing

The diagnosis of genital herpes is frequently made based upon clinical findings. Although the presence of typical skin or mucous membrane lesions is suggestive of herpes, the clinical diagnosis is both insensitive and nonspecific. A history of similar lesions in the same anatomic distribution supports the clinical diagnosis. PCR is the diagnostic test of choice, with the highest sensitivity and specificity in the presence of active lesions. Viral culture is also specific but less sensitive than PCR. Dark-field microscopy and serologic testing for syphilis should be considered to help differentiate cases of syphilis. The utility of these diagnostic studies is limited in the ED because test results are delayed, but results may be helpful at the time of follow-up. Direct fluorescent antibody (DFA) and serology for HSV are available, but less commonly used in the ED setting. Cytologic testing (Tzanck preparation) is nonspecific and insensitive and should not be relied upon to make the diagnosis of HSV.

Management

Genital herpes is treated with the antiviral medications acyclovir, famciclovir, or valacyclovir. Antiviral therapy is not curative but has been shown to decrease the duration and severity of symptoms and the development of complicated HSV infection, particularly when started early during the primary infection. Prompt initiation of antiviral treatment is key to obtaining optimal clinical benefit. Although most studies have evaluated drug initiation within 72 hours of symptom onset, antiviral therapy may still be offered after this time frame in the presence of ongoing symptoms and the development of new lesions. Multiple regimens are available for treatment of primary and recurrent episodes of genital herpes with oral antiviral medications (Table 88.2). Oral antiviral therapy is generally well tolerated with few side effects. Suppressive therapy with daily antiviral use has been shown to decrease the frequency of recurrences while the medication is being taken, but it does not affect the frequency or severity of recurrences after the drug is discontinued. Topical antiviral therapy provides minimal clinical benefit and is not recommended.

TABLE 88.2

Treatment of Common Ulcerating Sexually Transmitted Diseases[a]

DISEASE	RECOMMENDED TREATMENTS
Herpes simplex	
Primary episode	Acyclovir 400 mg PO tid for 7 to 10 days *or* Acyclovir 200 mg PO five times a day for 7 to 10 days *or* Valacyclovir 1000 mg PO bid for 7 to 10 days *or* Famciclovir 250 mg PO tid for 7 to 10 days
Recurrent episodes	Acyclovir 400 mg PO tid for 5 days *or* Acyclovir 800 mg PO bid for 5 days *or* Acyclovir 800 mg PO tid for 2 days *or* Valacyclovir 500 mg PO bid for 3 days *or* Valacyclovir 1000 mg PO daily for 5 days *or* Famciclovir 125 mg PO bid for 5 days *or* Famciclovir 1000 mg PO bid for 1 day *or* Famciclovir 500 mg PO once, then 250 mg bid for 2 days
Syphilis[b]	
Primary, secondary, and early latent syphilis	Benzathine penicillin G 2.4 million units IM single dose
Neurosyphilis	Aqueous penicillin G 3 to 4 million units IV every 4 hours for 10 to 14 days
Chancroid	Ceftriaxone 250 mg IM single dose *or* Azithromycin 1000 mg PO single dose *or* Ciprofloxacin 500 mg PO bid for 3 days

[a]Alternative treatment regimens for selected patients (including pregnancy, drug allergies) can be found at www.cdc.gov/std/treatment.
[b]Pregnant women with syphilis who are allergic to penicillin should be admitted for desensitization and treatment with penicillin.
IM, Intramuscular; *PO, per os* (by mouth).

Disposition

Most patients with genital herpes are managed as outpatients. Hospitalization for parenteral therapy with acyclovir is indicated for systemic complications of HSV infection, including meningoencephalitis, hepatitis, pneumonitis, and disseminated infection. Patients with genital herpes should be counseled that transmission may occur even in the absence of clinical symptoms. Condom use has been shown to reduce but not eliminate the incidence of HSV transmission. Discordant couples (ie, those in which one partner is HIV+) should be advised to avoid sexual contact during active outbreaks, which is when viral transmission is highest. Condoms should be used during asymptomatic periods. Patients with genital herpes should also be counseled regarding the increased risk of acquisition and transmission of HIV in the presence of genital ulcers.

Syphilis

Principles

Humans are the only known host for *Treponema pallidum,* the spirochete that causes syphilis. The incidence of syphilis has

declined significantly since penicillin became widely available in 1945, but outbreaks still occur intermittently. After a progressive decline in the incidence of syphilis from 1990 to 2000, there has been an increase in recent years. More than 17,000 cases of primary and secondary syphilis were reported to the CDC in 2013.[9] The rates of primary and secondary syphilis are higher among those between 20 to 29 years old, minority groups, and men who have sex with men. It is more common in the southeastern United States compared to other regions of the country.

Clinical Features

Syphilis has been called "the great imitator," because its clinical manifestations are protean. Syphilis is divided into primary, secondary, latent, and tertiary stages based upon clinical and serologic findings. The primary and secondary stages of syphilis are most commonly seen in the ED setting. Transmission occurs when the spirochetes gain access through disrupted epithelium of the skin or mucous membranes. The average incubation period is approximately 21 days but may range from 3 to 90 days.

Primary syphilis is initially manifested by the development of a painless papule at the site of inoculation. The lesion ulcerates, forming the chancre of primary syphilis (Fig. 88.2). The chancre is classically described as a relatively painless clean-based ulcer with well demarcated indurated edges, measuring approximately 1 to 2 cm in size. Nontender regional lymphadenopathy may be seen. Although the chancre often occurs in the genital or perianal area, it may occur at any site of inoculation, including the oropharynx, breasts, hands, and other sites. The chancre will heal spontaneously over the course of 3 to 6 weeks. Because the chancre is relatively painless, it may go unnoticed by the patient.

Secondary syphilis will develop in approximately 25% of patients with primary syphilis over a period of several weeks to months. Manifestations of secondary syphilis include rash, generalized lymphadenopathy, mucous membrane lesions, and systemic symptoms. The rash is diffuse, involving the face, trunk, and extremities, including the palms and soles. The appearance of the rash is highly variable. Lesions may be macular, papular, scaly, or pustular in appearance (Fig. 88.3). Mucous patches are multiple shallow erosions of the oropharyngeal mucosa that are usually accompanied by other dermatologic and systemic manifestations of secondary syphilis. Condyloma lata, which resemble genital warts, are broad-based papular lesions that occur on the genitalia and perineum and typically have a moist surface appearance (Fig. 88.4). Lymphadenopathy is typically diffuse, rubbery, and nontender. Epitrochlear adenopathy is particularly suggestive of secondary syphilis. A nonspecific "moth-eaten" alopecia may be seen. Systemic manifestations include low-grade fever, anorexia, headache, malaise, myalgias, and weight loss. Symptoms of secondary syphilis will resolve without treatment, with subsequent progression to latent syphilis.

Latent syphilis is present when there is serologic evidence of syphilis infection in the absence of any clinical signs or symptoms. Latent infection acquired within the past 12 months is defined as early latent syphilis, whereas late latent syphilis includes cases of latent infection of greater than 12 months or unknown duration. Patients with early latent syphilis are considered to be infectious. Those with late latent syphilis are generally not infectious, with an important exception—pregnant women with late latent syphilis can transmit the infection to the fetus. Latent syphilis can persist indefinitely before progressing to tertiary syphilis.

Tertiary syphilis, which includes cardiovascular manifestations and gummatous disease, is uncommon in the United States. Aortitis, aortic aneurysm, and gummatous lesions of the skin, bones, and other organs may be seen. In patients with untreated syphilis, the estimated risk of eventual progression to tertiary

Fig. 88.3. Rash of secondary syphilis on palms and soles. (From Morse S, Ballard RC, Holmes KK, et al, editors: Atlas of sexually transmitted diseases and AIDS, ed 4, London, 2010, Saunders/Elsevier, Fig. 7.24, p 188.)

Fig. 88.2. Chancre of primary syphilis. (From Morse S, Ballard RC, Holmes KK, et al, editors: Atlas of sexually transmitted diseases and AIDS, ed 4, London, 2010, Saunders/Elsevier, Fig. 7.9, p 185.)

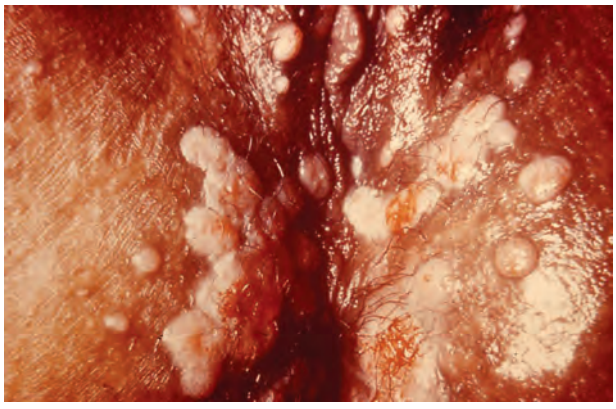

Fig. 88.4. Condyloma lata of secondary syphilis.

syphilis ranges from 25% to 40%. *Neurosyphilis* refers to infection involving the central nervous system (CNS) and may be seen in any stage of syphilis. Manifestations of neurosyphilis include altered mental status, meningitis, cranial nerve abnormalities, stroke, peripheral neuropathy, and auditory and ophthalmic abnormalities. *Congenital syphilis,* which is transmitted perinatally to the fetus, is relatively uncommon in recent years in the United States but has significant associated morbidity in infected children.

Diagnostic Testing

T. pallidum is fastidious and cannot be cultured in the laboratory. The diagnosis of syphilis can be confirmed with darkfield microscopy or by serologic testing. Visualization of the spirochete on darkfield examination of specimens obtained from a chancre or from the moist lesions of secondary syphilis provides an immediate diagnosis. Dark-field microscopy is particularly useful in primary syphilis when false negative serology is common. The sensitivity and specificity of dark field microscopy vary depending upon the experience of the microscopist and the use of proper specimen collection techniques. The utility of darkfield microscopy is limited by the need for specialized laboratory equipment and appropriately trained personnel, which are lacking at many hospitals. Serologic tests for syphilis include nonspecific nontreponemal tests and specific treponemal tests. Both types of serologic testing are necessary for the proper diagnosis of syphilis. Nontreponemal tests include the Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin (RPR). The VDRL and RPR provide quantitative measurements of nonspecific antibodies that are produced in response to *T. pallidum* infection. The titers correlate with disease activity, typically rising with active syphilis infection and declining after successful treatment. The sensitivity of nontreponemal tests is approximately 70% to 80% in primary syphilis but rises to nearly 100% in secondary syphilis. False positive nontreponemal tests may be seen in a variety of conditions, including pregnancy, endocarditis, autoimmune disease, and other acute or chronic illnesses. A positive nontreponemal test should always be confirmed with a specific treponemal test. Specific treponemal tests include the fluorescent treponemal antibody absorption (FTA-ABS) and the microhemagglutination test for antibodies to *T. pallidum* (MHA-TP). These treponemal tests provide qualitative measurements of specific antitreponemal antibodies. Although these treponemal tests are highly specific for syphilis, they may remain positive for life even after successful treatment and cure. A nontreponemal test is used for screening purposes and serves as a better marker for acute infection, with the specific treponemal test used to confirm the diagnosis.

Management

Penicillin is the cornerstone of treatment for syphilis, with *T. pallidum* remaining highly sensitive to penicillin. The dosage and preparation of penicillin and the length of treatment vary depending upon the stage of the disease and the associated clinical manifestations (see Table 88.2). A single dose of long-acting benzathine penicillin G (2.4 million units intramuscularly) is curative in the majority of cases of primary, secondary, and early latent syphilis. Patients with significant penicillin allergy can be treated with doxycycline or tetracycline for 2 weeks if no contraindication to these drugs exists. Ceftriaxone has antitreponemal activity, but the optimal dosage and duration of therapy have not been established. Azithromycin has some efficacy but is not recommended as a first line therapy due to documented resistance and treatment failures. Penicillin remains the drug of choice for patients with neurosyphilis, congenital syphilis, and syphilis during pregnancy even in the presence of penicillin allergy, due to the known efficacy of penicillin and the absence of proven alternative therapies. Patients with these conditions should be admitted for desensitization and treatment with penicillin.

The Jarisch-Herxheimer reaction is an acute worsening of symptoms that may develop after antibiotic therapy is initiated for syphilis. The patient typically reports worsening malaise, myalgias, and fever within 24 hours of antibiotic treatment. The condition has traditionally been thought to be caused by the sudden lysis of spirochetes, but the mechanism is poorly understood. Treatment is supportive, including rest, hydration, and antipyretics. The symptoms resolve spontaneously. Anticipatory guidance regarding the appropriate management of this common self-limited reaction may prevent a return visit to the ED.

Disposition

Most cases of syphilis are treated on an outpatient basis. Hospitalization is recommended for patients with penicillin allergy who require desensitization prior to penicillin therapy, including pregnant women with syphilis and patients with neurosyphilis or congenital syphilis.

Chancroid

Principles

Chancroid is an ulcerating STD caused by the gram-negative organism *Haemophilus ducreyi.* Chancroid is common in parts of the developing world but is rare in the United States, with only 10 cases reported in 2013. Like other ulcerating STDs, chancroid is a cofactor for the transmission and acquisition of HIV.

Clinical Features

After an incubation period of less than 1 week, a tender erythematous papule develops at the site of inoculation. The initial lesion rapidly ulcerates, and multiple painful ulcers subsequently develop (Fig. 88.5). The ulcers typically have an irregular, inflamed, and "dirty" appearance compared to the well circumscribed clean-based chancre of syphilis, and the smaller punched-out appearance of herpetic ulcers. Painful inguinal lymphadenopathy is common and may progress to bubo formation. A *bubo* is a large, painful, fluctuant unilateral inguinal lymph node, which may spontaneously rupture and drain purulent material.

Fig. 88.5. Multiple vulvar ulcers due to chancroid. (From Morse S, Ballard RC, Holmes KK, et al, editors: Atlas of sexually transmitted diseases and AIDS, ed 4, London, 2010, Saunders/Elsevier, Fig. 8.14, p 219.)

Diagnostic Testing

Differential diagnosis of genital ulcers includes herpes and syphilis, both of which are more common than chancroid in the United States. Although the appearance of the ulcers may suggest the diagnosis of chancroid, the clinical diagnosis may be inaccurate. Dark-field microscopy and serologic testing are useful in identifying syphilis, whereas PCR and viral culture can confirm HSV infection. Chancroid is usually a clinical diagnosis based upon the presence of typical painful genital ulcers and associated tender adenopathy. Culture provides definitive diagnosis but is difficult due to the fastidious nature of *H. ducreyi,* which requires special culture media.

Management

Patients with chancroid are treated as outpatients. Single-dose therapy with azithromycin or ceftriaxone is recommended for suspected chancroid (see Table 88.2). Alternative treatment regimens include oral ciprofloxacin or erythromycin.

DISORDERS CHARACTERIZED BY GENITAL DISCHARGE

Some STDs, including gonorrhea, chlamydia, trichomoniasis, and pelvic inflammatory disease (PID), are frequently characterized by the presence of genital discharge in absence of genital ulcers and lymphadenopathy. The differential diagnosis of genital discharge is broad, including infections that are not sexually transmitted and noninfectious conditions (see Table 88.1). For example, bacterial vaginosis and candidiasis are common conditions that are not considered to be sexually transmitted but are frequently found during the evaluation of a woman with vaginal discharge. Urethritis, cervicitis, and vaginitis caused by various organisms can present with associated genital discharge.

Infectious causes of urethritis are generally divided into two categories: gonococcal urethritis and nongonococcal urethritis (NGU). Urethritis occurs in men and women and may be asymptomatic, particularly in persons with NGU. When present, symptoms include dysuria, urethral pruritus, and urethral discharge. The absence of visible discharge does not exclude the diagnosis. A clinical diagnosis of urethritis can be made on the basis of any of the following findings in the setting of compatible symptoms: (1) mucoid, mucopurulent or purulent urethral discharge, (2) Gram stain of urethral discharge containing two or more white blood cells (WBCs) per oil immersion field, (3) first-void urine sediment containing 10 or more WBCs per high-power field, and (4) positive leukocyte esterase test on first-void urine. Diagnosis and management of specific causes of urethritis are discussed later.

Cervicitis is characterized by the presence of purulent or mucopurulent discharge from the endocervix and the presence of cervical friability. Many women with cervicitis are asymptomatic. The discharge may be visible in the endocervical canal or noted on an endocervical swab specimen. Cervical friability is demonstrated when endocervical bleeding is easily induced with gentle passage of a swab through the cervical os. Gonorrhea and chlamydia are common causes, but trichomonas and HSV may also cause cervicitis. Frequently, no organism is isolated despite the presence of clinical findings consistent with cervicitis. Women with cervicitis may complain of abnormal vaginal discharge, dyspareunia, and postcoital vaginal bleeding. Pelvic examination may demonstrate endocervical discharge and friability as described earlier. These findings are insensitive, and the absence of these findings on history and examination do not exclude the diagnosis of cervicitis. Specific causes of cervicitis and their management are discussed later.

Gonorrhea

Principles

Gonorrhea is the second most commonly reported STD in the United States, with more than 300,000 cases reported to the CDC annually. Humans are the only reservoir for the causative organism *Neisseria gonorrhoeae,* a gram-negative intracellular diplococcus. The prevalence of gonorrhea varies widely, with higher rates of gonorrhea seen among adolescents and young adults, minorities, people with low socioeconomic status, those with a history of substance abuse, and those who engage in high risk sexual behaviors.

Clinical Features

The signs and symptoms of gonorrhea vary depending upon the sex of the patient, the site of inoculation, and the local or systemic spread of the infection. The incubation period for gonorrhea typically ranges from 3 to 7 days. Most men with gonococcal urethritis become symptomatic within 1 to 2 weeks, prompting them to seek curative treatment. Patients complain of urethral discharge and dysuria. The discharge is usually copious and purulent, although the clinical appearance alone cannot differentiate gonococcal urethritis from NGU (Fig. 88.6). Women with gonococcal cervicitis are often asymptomatic until ascending infection develops. Because many women remain asymptomatic for prolonged periods, a larger reservoir of untreated women exists. When present, symptoms of gonococcal cervicitis may include abnormal vaginal discharge, dyspareunia, and intermenstrual bleeding. Women with gonococcal cervicitis may also complain of dysuria due to associated urethritis.

Gonococcal proctitis may occur in men and women who engage in receptive anal intercourse and in women who are inoculated by infected vaginal secretions. Patients with gonococcal proctitis are often asymptomatic but may complain of rectal pain, tenesmus, rectal discharge, or bleeding. Anoscopy may reveal abnormal discharge and inflamed friable rectal mucosa.

Fig. 88.6. Purulent urethral discharge due to gonococcal urethritis.

Gonococcal pharyngitis is usually acquired from oral sexual exposure. Patients with pharyngitis are usually asymptomatic but may complain of sore throat. Tonsillar erythema and cervical lymphadenopathy may be present.

Gonococcal conjunctivitis was historically seen most often in infants born to infected mothers. Because infants are now routinely prophylaxed at birth, gonococcal conjunctivitis is now more common in adults who self-inoculate by rubbing the eye with contaminated fingers. Severe conjunctival injection with copious purulent discharge is typically seen. The infection can progress rapidly to corneal ulceration, perforation, and blindness if untreated.

Disseminated gonococcal infection (DGI) results from hematogenous spread of *N. gonorrhoeae.* DGI may occur in the absence of any signs or symptoms of the initial local infection. Characteristic clinical findings include rash, polyarthralgias, tenosynovitis, and septic arthritis. The rash usually consists of petechial or pustular lesions in an acral distribution on the distal extremities. The rash is sparse, with 2 to 10 skin lesions being typical and more than 40 lesions uncommon. Septic arthritis presents as a swollen, red, warm, and painful joint. One or more joints may be involved. The knees, wrists, and ankles are the most common sites. Rarer complications of DGI include hepatitis, meningitis, and myocarditis.

Diagnostic Testing

In symptomatic men, a Gram stain of urethral discharge that reveals gram-negative intracellular diplococci has a sensitivity and specificity approaching 100% for the diagnosis of gonorrhea. Gram stain results are available rapidly. A positive Gram stain does not exclude coinfection with chlamydia or other organisms. Culture and nucleic acid amplification tests (NAATs) are both useful to confirm the diagnosis. NAATs are widely available and have replaced culture as the diagnostic gold standard. The sensitivity of NAATs for the detection of *N. gonorrhoeae* is higher than that of culture. A wider variety of specimens can be used for NAATs, including first-void urine and swabs from the urethra, cervix, and vagina. Suitable specimens can be obtained by the examining clinician or provided by the patient. Although NAATs is not yet FDA-approved for use with specimens obtained from the oropharynx, rectum, or conjunctivae, some laboratories have established performance specifications and met Clinical Laboratory Improvement Amendment (CLIA) guidelines for use of NAATs with oropharyngeal and rectal specimens. Culture with selective Thayer Martin media is still useful in selected patients and has the advantage of allowing antimicrobial susceptibility testing. Isolation of *N. gonorrhoeae* from the blood, synovial fluid, or skin lesions establishes a definitive diagnosis of DGI, but sensitivity of these cultures is poor. The organism may be more readily identified from other sites (urethra, cervix, rectum, or pharynx) even in the absence of localized symptoms at these sites. When accompanied by the appropriate clinical presentation, identification of gonorrhea by NAATs or culture from any site is sufficient for a presumptive diagnosis of DGI.

Treatment

Recommended treatment options for gonorrhea have changed in recent years due to the increasing antimicrobial resistance of *N. gonorrhoeae.* Ceftriaxone remains the drug of choice for the treatment of gonorrhea. Single-dose therapy with an intramuscular injection of ceftriaxone 250 mg is recommended for most cases of gonococcal urethritis, cervicitis, proctitis, and pharyngitis (see Table 88.2). Concomitant therapy with a single dose of azithromycin 1 g *per os* (by mouth) (PO) is recommended to provide synergistic coverage with ceftriaxone against *N. gonorrhoeae* and coverage of possible coexisting chlamydia infection. Directly observed therapy with both ceftriaxone and azithromycin can be administered in the ED to ensure compliance. The use of oral cephalosporins or fluoroquinolones is no longer recommended for the treatment of gonorrhea due to increasing antimicrobial resistance.[10,11] DGI and gonococcal arthritis are treated with parenteral ceftriaxone 1 g daily. Several parenteral antibiotic regimens are available for treatment of severe or complicated PID (discussed later in this chapter).

Disposition

Uncomplicated gonococcal infections are treated on an outpatient basis. Hospitalization may be warranted for more severe cases of upper tract infection, such as PID or epididymo-orchitis. Admission and treatment with parenteral ceftriaxone is recommended for DGI, septic arthritis, and conjunctivitis.

Chlamydia

Principles

Chlamydia is the most commonly reported STD in the United States, with more than 1.4 million cases reported to the CDC in 2013. *Chlamydia trachomatis,* an obligate intracellular organism, is the causative pathogen. Approximately 50% of men and 70% of women who are infected with chlamydia are asymptomatic. Adolescents and young adults 15 to 24 years old have the highest rate of chlamydia infection. The reported rate of chlamydia is twice as high among women compared to men, reflecting the higher number of women screened for this infection.

Clinical Features

Chlamydia infection is a common cause of NGU. When present, the urethral discharge associated with chlamydia is typically scant, mucoid, and less purulent than the discharge seen with gonorrhea. Dysuria is less pronounced and presentation is often delayed. Chlamydia cervicitis may present with mucopurulent cervical discharge or postcoital bleeding but is often asymptomatic. When untreated, chlamydia can progress to upper tract infection, including epididymitis and orchitis in men and PID in women. Patients with epididymitis and orchitis complain of unilateral scrotal pain and swelling, and they may also report symptoms of urethritis. Swelling and tenderness of the epididymis and testicle are usually present. Epididymitis is more common with chlamydia infection alone or combined gonorrhea and chlamydia infections, rather than with gonorrhea alone. Chlamydia frequently contributes to the development of PID, which may be indolent or clinically silent, but results in significant chronic sequelae.

Diagnostic Testing

Differentiation between chlamydial and gonococcal infection based solely upon history and physical examination is unreliable, and these infections frequently coexist. NAATs are the diagnostic test of choice, with sensitivity greater than 90% and specificity of 99% for the diagnosis of chlamydia. NAATs assays are approved for use with specimens obtained from the urethra, cervix, vagina, or first-void urine specimens. Some laboratories meet CLIA guidelines to perform NAATs on specimens from the oropharynx and rectum.

Management

Recommended treatment regimens for chlamydia urethritis or cervicitis include single-dose azithromycin 1 g PO or a 7-day

TABLE 88.3

Treatment of Sexually Transmitted Diseases Associated With Genital Discharge[a]

DISEASE	RECOMMENDED TREATMENTS
Gonorrhea Urethritis, cervicitis, proctitis, pharyngitis	Ceftriaxone 250 mg IM single dose *plus* Azithromycin 1 g PO single dose
Chlamydia Urethritis, cervicitis, proctitis, pharyngitis	Azithromycin 1 g PO single dose *or* Doxycycline 100 mg PO bid for 7 days
Nongonococcal urethritis (NGU)	Azithromycin 1 g PO single dose *or* Doxycycline 100 mg PO bid for 7 days
Trichomoniasis	Metronidazole 2 g PO single dose *or* Tinidazole 2 g PO single dose

[a]Alternative treatment regimens for selected patients (including pregnancy, drug allergies) can be found at www.cdc.gov/std/treatment.
IM, Intramuscular; *PO, per os* (by mouth).

course of doxycycline 100 mg PO bid (Table 88.3). Both regimens are equally efficacious when taken as directed, but single-dose azithromycin is preferable if there is concern for possible noncompliance with doxycycline. Azithromycin is the drug of choice in pregnancy. Alternative regimens for the treatment of lower tract chlamydia infection include a 7-day course of erythromycin, levofloxacin, or ofloxacin. Suspected upper genitourinary tract infection with chlamydia (ie, epididymitis, PID) requires a longer course of antibiotic therapy ranging from 10 to 14 days (Table 88.4).

Empirical treatment for both gonorrhea and chlamydia is recommended when confirmatory test results are unavailable, because history and physical examination cannot reliably differentiate these conditions and coinfections often occur. Single-dose ceftriaxone 250 mg IM plus single-dose azithromycin 1 g PO treats uncomplicated gonorrhea in addition to lower tract chlamydia infection.

Disposition

Most chlamydia infections are treated on an outpatient basis. Patients with severe upper tract infection and associated complications (tubo-ovarian abscess, severe PID) may require hospitalization for parenteral antibiotics, pain control, antiemetics, hydration, and other measures.

Nongonococcal Urethritis

NGU is most often caused by *Chlamydia trachomatis,* but may also be caused by *Trichomonas vaginalis, Mycoplasma genitalium,* other *Mycoplasma* species, *Ureaplasma* species, and other organisms. Patients with NGU are often asymptomatic. Symptoms, when present, are usually less prominent than those seen with gonococcal urethritis. Clinical features are not sufficiently specific to distinguish between gonococcal urethritis and NGU, and coinfection is common. NAATs have high sensitivity and specificity for chlamydia and gonorrhea. Wet mount microscopy can identify cases of trichomoniasis. Diagnostic testing is not routinely performed for other causes of NGU. Fortunately, most causative organisms respond to single-dose therapy with azithromycin 1 g PO. Azithromycin is more effective than doxycycline for *M. genitalium*. Additional empirical treatment with single-dose ceftriaxone 250 mg IM is recommended when gonorrhea has not been ruled out with negative NAATs. Single-dose metronidazole 2 g PO is recommended for cases of trichomoniasis.

TABLE 88.4

Treatment of Complicated or Upper Genitourinary Tract Sexually Transmitted Diseases[a]

DISEASE	RECOMMENDED TREATMENTS
Disseminated gonorrhea	Ceftriaxone 1 g IV or IM every 24 hours *plus* Azithromycin 1 g PO single dose *Hospitalization and identification consult recommended*
Gonococcal conjunctivitis	Ceftriaxone 1 g IV or IM single dose *plus* Azithromycin 1 g PO single dose *Consider hospitalization & ID consult*
Epididymitis/orchitis	Ceftriaxone 250 mg IM single dose *plus* Doxycycline 100 mg PO bid for 10 days[b] *or* Ceftriaxone 250 mg IM single dose *plus* Levofloxacin 500 mg PO every day for 10 days[c] *or* Levofloxacin 500 mg PO every day for 10 days[d]
Pelvic inflammatory disease (PID)	
Inpatient	Cefotetan 2 g IV every 12 hours *plus* Doxycycline 100 mg PO or IV every 12 hours *or* Cefoxitin 2 g IV every 6 hours *plus* Doxycycline 100 mg PO or IV every 12 hours *or* Clindamycin 900 mg IV every 8 hours *plus* Gentamicin 2 mg/kg IV loading dose, then 1.5 mg/kg every 8 hours
Outpatient	Ceftriaxone 250 mg IM single dose *plus* Doxycycline 100 mg PO bid for 14 days ± Metronidazole 500 mg PO bid for 14 days

[a]Alternative treatment regimens for selected patients (including pregnancy, drug allergies) can be found at www.cdc.gov/std/treatment.
[b]For suspected gonorrhea and/or chlamydia.
[c]For suspected gonorrhea and/or chlamydia *and* enteric organisms (ie, men who practice insertive anal intercourse).
[d]For suspected enteric organisms.
IM, Intramuscular; *IV,* intravenous; *PO, per os* (by mouth).

Trichomoniasis

Principles

Trichomonas vaginalis is the flagellated protozoan organism responsible for trichomoniasis, the most common curable STD worldwide. Women are typically more symptomatic than men, but asymptomatic infection occurs in both sexes. Trichomoniasis usually causes mild disease, but significant morbidity can occur. Trichomoniasis has been associated with PID, preterm birth among pregnant women, prostatitis, epididymitis, and increased susceptibility to HIV acquisition.

Clinical Features

Trichomoniasis causes vaginitis in women. Common symptoms include vaginal discharge, pruritus, dysuria, urinary frequency, dyspareunia, and postcoital bleeding. The discharge is classically described as malodorous, frothy, and greenish yellow in color (Fig. 88.7). Pelvic examination may reveal erythema of the vaginal mucosa and vulva, in addition to the discharge. Punctate hemorrhages of the cervix ("strawberry cervix") are seen in up to 10% of cases. Trichomoniasis is often asymptomatic in men but may cause urethritis with associated dysuria and urethral discharge.

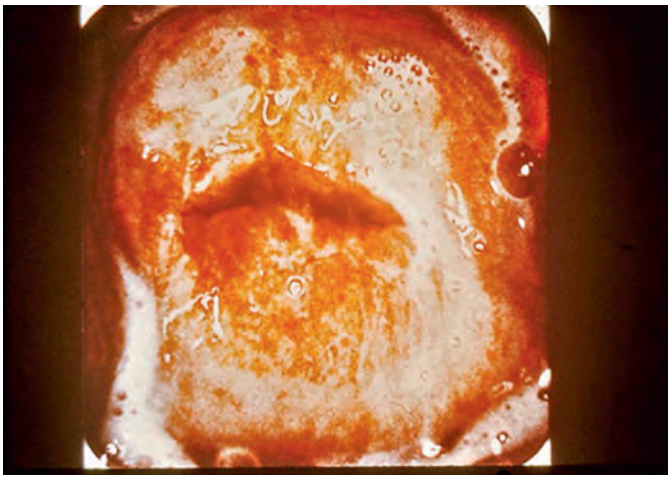

Fig. 88.7. Frothy vaginal discharge due to trichomoniasis. (From Morse S, Ballard RC, Holmes KK, et al, editors: Atlas of sexually transmitted diseases and AIDS, ed 4, London, 2010, Saunders/Elsevier, Fig. 5.23, p 140.)

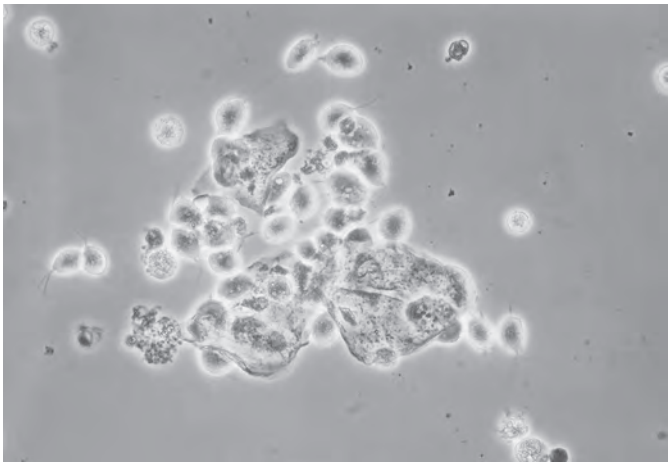

Fig. 88.8. *T. vaginalis* on a wet mount slide prep. (From Centers for Disease Control and Prevention [CDC]: Public Health Image Library [PHIL]. Image #14500. Available at phil.cdc.gov/phil/.)

Diagnostic Testing

The diagnosis of trichomoniasis is usually confirmed with microscopic examination of a saline wet mount slide, which reveals motile flagellated trichomonads and leukocytes (Fig. 88.8). The sensitivity of the wet mount slide is approximately 50% to 65%. Trichomonas may be seen incidentally on microscopic analysis of the urine sediment. NAATs are superior to microscopic examination, with reported sensitivity and specificity greater than 95% for some assays. A point-of-care antigen detection test for trichomonas is now available. Culture is also confirmatory, but seldom used in the ED.

Management

Treatment of trichomoniasis is indicated in both symptomatic and asymptomatic men and nonpregnant women. Single-dose metronidazole 2 g PO or single-dose tinidazole 2 g PO are both highly effective, with reported cure rates ranging from 90% to 95% (see Table 88.3). Alternatively, metronidazole 500 mg twice daily for 7 days can be used. Metronidazole is the recommended treatment for symptomatic trichomoniasis during pregnancy. A meta-analysis failed to reveal any relationship between metronidazole exposure during the first trimester of pregnancy and the occurrence of birth defects.[12] Current CDC guidelines advise that single-dose therapy with metronidazole may be used during any stage of pregnancy. The treatment of asymptomatic pregnant women with trichomoniasis is controversial, because there is conflicting data regarding the possible increased incidence of preterm labor in pregnant women treated with metronidazole.

Disposition

Trichomoniasis is treated on an outpatient basis. Patients should be counseled to avoid alcohol use for at least 24 hours after completion of metronidazole therapy and 72 hours after completion of tinidazole therapy, due to the occurrence of a disulfiram-like reaction following alcohol use.

Pelvic Inflammatory Disease

Principles

PID is an ascending infection that begins at the level of the endocervix but progresses to the upper reproductive tract, causing endometritis, salpingitis, and peritonitis. *N. gonorrhoeae* and *Chlamydia trachomatis* have traditionally been implicated in the development of PID, but many women diagnosed with PID do not test positive for either of these organisms.[13] Negative testing for gonorrhea and chlamydia from endocervical specimens does not reliably exclude them as a cause for upper tract infection. Polymicrobial involvement is common, with anaerobes, enteric organisms, vaginal flora, and other STDs often implicated in PID. An estimated 10% to 20% of women with gonorrhea or chlamydia may develop PID if they do not receive proper treatment. Among women with PID, 18% experience chronic pelvic pain, 9% develop ectopic pregnancy, and 8% develop infertility.[14]

Clinical Features

PID causes a spectrum of illness ranging from asymptomatic infection to severe illness with associated peritonitis and systemic toxicity. Lower abdominal pain is the most common presenting complaint. Other symptoms include dyspareunia, abnormal vaginal discharge or bleeding, dysuria, and fever. Nausea, vomiting, diarrhea, and anorexia may be present, mimicking gastrointestinal conditions. Physical findings may include lower abdominal tenderness, cervical friability, mucopurulent discharge, cervical motion tenderness, and adnexal tenderness. Vital sign abnormalities, such as fever and tachycardia, may be seen.

Diagnostic Testing

PID is a clinical diagnosis. No single historical, physical, or laboratory finding or combination of findings is sufficiently sensitive or specific to make a definitive diagnosis of PID. Because PID causes significant morbidity, the CDC recommends a low threshold for the diagnosis and empirical treatment of PID. The diagnosis of PID should be considered and presumptive treatment initiated in any sexually active woman at risk for STDs who presents with lower abdominal or pelvic pain if no alternative diagnosis is identified and if one or more of the following findings are present on pelvic examination: (1) cervical motion tenderness, or (2) uterine tenderness, or (3) adnexal tenderness. These criteria have high sensitivity but low specificity for the diagnosis of PID. Because the use of these criteria will result in the over-diagnosis of PID, one should consider other possible diagnoses. The use of the additional criteria improves the specificity of the diagnosis of PID but decreases the diagnostic sensitivity (Table 88.5).

NAATs for gonorrhea and chlamydia are recommended. A pregnancy test should always be obtained, because ectopic

TABLE 88.5

Diagnosis of Pelvic Inflammatory Disease[a]

MINIMUM CRITERIA	ADDITIONAL CRITERIA[b]
Cervical motion tenderness *or*	Mucopurulent cervical discharge
Adnexal tenderness *or*	Cervical friability
Uterine tenderness	Oral temperature >101° F Elevated erythrocyte sedimentation rate Elevated C-reactive protein White blood cells (WBCs) on microscopy of vaginal secretions Laboratory confirmation of endocervical gonorrhea or chlamydia

[a]In a sexually active woman at risk for sexually transmitted diseases (STDs) who presents with abdominal pain and no alternative diagnosis is identified, a presumptive diagnosis of pelvic inflammatory disease (PID) may be based upon the criteria listed in this table.
[b]Additional criteria increase specificity but decrease sensitivity for the diagnosis of PID.

pregnancy and other pregnancy-related conditions may mimic PID. Computed tomography (CT) and pelvic ultrasonography may reveal findings supporting the diagnosis of PID, including evidence of swelling and inflammation within the endometrial cavity and fallopian tubes. Imaging studies are also helpful in ruling out other diagnoses, such as appendicitis, and for identifying complications of PID, such as tubo-ovarian abscess. Laparoscopy can confirm the diagnosis but is of limited utility due to its invasive nature, limited availability, and expense. In addition, laparoscopy may not identify mild cases of PID.

Management

Treatment should be initiated as soon as possible after the diagnosis is made and should not await the results of microbiologic testing or other delayed diagnostic studies. Delays in the initiation of antibiotic therapy contribute to the development of complications of PID. Multiple inpatient and outpatient antibiotic regimens are available for the treatment of PID (see Table 88.4). The total duration of antibiotic therapy is 14 days. The addition of anaerobic coverage with metronidazole should be considered. The clinician must weigh the potential benefit of providing broader spectrum antibiotic coverage against the potential risks of antibiotic side effects, greater expense, and patient noncompliance with a more complicated treatment regimen. Supportive care measures include analgesics, antipyretics, and hydration. Sexual intercourse should be deferred until symptoms have resolved and antibiotic therapy has been completed by the patient and her partner.

Disposition

Most women with PID are treated as outpatients. Current recommendations no longer mandate hospitalization for adolescents or for HIV-positive patients with PID.[7] Follow-up within 72 hours is recommended to ensure appropriate response to initial treatment. Women who meet any of the following criteria should be considered for inpatient treatment of PID:

- Surgical emergencies cannot be excluded (ie, appendicitis)
- Pregnancy
- Tubo-ovarian abscess
- Severe illness, nausea and vomiting, or high fever
- Inability to follow or tolerate outpatient oral regimens
- Failure to respond to oral antibiotic therapy

In addition to chronic pelvic pain, ectopic pregnancy, and infertility, other complications of PID are common. Tubo-ovarian abscess or pyosalpinx may be identified on pelvic ultrasound or CT. Perihepatitis, known as *Fitz-Hugh-Curtis syndrome,* is occasionally seen and may result in associated right upper quadrant abdominal pain.

Bacterial Vaginosis

Principles

Bacterial vaginosis is the most common cause of abnormal vaginal discharge in the United States. Although bacterial vaginosis is not considered to be an STD, it is often encountered during the evaluation of patients with an abnormal vaginal discharge. Bacterial vaginosis is due to an alteration in the vaginal flora with replacement of normal *Lactobacillus* species by a polymicrobial group of organisms, including *Gardnerella vaginalis,* anaerobes, and others.

Clinical Features and Diagnostic Testing

Many women with bacterial vaginosis are asymptomatic. Symptomatic women complain of a malodorous thin whitish vaginal discharge. A fishy odor is often reported and can be accentuated with the addition of 10% potassium hydroxide (KOH) solution to a wet mount slide at the time of pelvic examination (the "whiff test"). The pH of vaginal fluid is greater than 4.5. Microscopic examination of the wet mount slide reveals clue cells, which are vaginal epithelial cells with indistinct borders due to a coating of bacteria. Bacterial vaginosis is associated with an increased risk of PID and complications of pregnancy (premature rupture of membranes and preterm delivery). Bacterial vaginosis may also be a cofactor in the acquisition and transmission of other STDs, including HIV.

Management

Treatment is recommended for all symptomatic women with bacterial vaginosis, regardless of pregnancy status. The established benefit of therapy is the relief of vaginal symptoms. There is conflicting data regarding the efficacy of treatment in reducing the incidence of associated illnesses in pregnant and nonpregnant women. Treatment of bacterial vaginosis in asymptomatic women is not recommended. Treatment of male sexual partners is of no benefit. Recommended treatment regimens for bacterial vaginosis include: (1) metronidazole 500 mg PO twice a day for 7 days, (2) metronidazole gel 0.75% 5 g intravaginally once a day for 5 days, and (3) clindamycin cream 2% 5 g intravaginally at bedtime for 7 days. Symptomatic pregnant women can be treated with the same oral or topical regimens recommended for nonpregnant women. The use of intravaginal *Lactobacillus* preparations and other probiotics are of no proven benefit in the restoration of normal vaginal flora or in the treatment of bacterial vaginosis.

Vulvovaginal Candidiasis

Principles

Vulvovaginal candidiasis is usually caused by the yeast species *Candida albicans.* An estimated 75% of women will have at least one episode of candidiasis during their lifetime, and recurrent episodes are common. Like bacterial vaginosis, candidiasis is not considered to be an STD but is frequently encountered in the evaluation of patients with abnormal vaginal discharge.

Clinical Features and Diagnostic Testing

Common nonspecific symptoms include pruritus, abnormal discharge, dyspareunia, and external dysuria. Pelvic examination

may reveal the vulvar erythema and edema with satellite lesions, erythema of the vaginal mucosa, and a thick curdy whitish vaginal discharge. Microscopic examination of a wet mount slide may reveal the presence of budding yeast or pseudohyphae. Diagnosis is facilitated with the use of 10% KOH, which disrupts other cellular structures and facilitates visualization of fungal elements. Fungal culture is the diagnostic gold standard but is rarely performed.

Management

Multiple topical antifungal azole drugs are recommended for the treatment of vulvovaginal candidiasis, including clotrimazole, miconazole, butoconazole, terconazole, and tioconazole. Several topical agents are available over-the-counter. Fluconazole is the only oral antifungal agent approved by the FDA for treatment of candidiasis. A single dose of fluconazole 150 mg PO is highly effective in nonpregnant women but is contraindicated during pregnancy. A 7-day course of topical azoles is recommended during pregnancy. Single-dose and short-course therapy with azoles is associated with a cure rate of 80% to 90% in uncomplicated *Candida* vulvovaginitis. Male sexual partners may develop *Candida balanitis*, which typically responds to topical antifungal therapy. Treatment of asymptomatic sexual partners is of no proven benefit.

Fig. 88.9. Perianal condyloma acuminata. (From Morse S, Ballard RC, Holmes KK, et al, editors: Atlas of sexually transmitted diseases and AIDS, ed 4, London, 2010, Saunders/Elsevier, Fig. 11.10, p 294.)

EPITHELIAL CELL INFECTIONS

Condyloma Acuminata (Genital Warts)

Principles

Genital warts are caused by human papillomavirus (HPV). More than 40 types of HPV can infect humans, with the majority of HPV infections remaining asymptomatic or unrecognized. Clinically apparent warts occur in approximately 1% of cases. HPV types 6 and 11 cause most cases of visible genital warts and are considered non-oncogenic. HPV types 16 and 18 are responsible for most cases of cervical cancer and are also associated with vaginal, vulvar, anal, penile, and oropharyngeal cancers. Bivalent and quadrivalent HPV vaccines are approved for use in the United States in children, adolescents, and young adults.

Clinical Findings

Genital warts are typically manifested by small painless fleshy papular lesions on the skin or mucous membranes (Fig. 88.9). The slow-growing lesions gradually become more lobulated, pedunculated, or verrucous in appearance. Lesions may become friable and painful due to local irritation or secondary infection. Warts are typically found on the external genitalia, buttocks, and perineum, but they may occur anywhere the organism is inoculated.

Diagnostic Testing

A clinical diagnosis of genital warts is usually made by visual inspection. Differential diagnosis includes molluscum contagiosum, skin tags, nevi, neoplasm, and condyloma lata. Genital warts may have a moist appearance in intertriginous areas, but they do not usually have the denuded surface typically seen with condyloma lata in secondary syphilis. The duration of lesions and presence of associated symptoms are helpful features, because genital warts are often present for months or years but have no associated systemic symptoms. Dark-field microscopy and serology are useful in excluding a diagnosis of syphilis. Although not generally performed in the ED, biopsy can confirm the diagnosis and exclude neoplasm. The application of topical acetic acid to mucosal lesions to screen for HPV is nonspecific and is not recommended.

Management

All available treatments for HPV have significant failure rates. Treatment options include patient-applied regimens and provider-administered regimens. Patient-applied regimens include topical application of imiquimod cream, podofilox solution or gel, or sinecatechins ointment. The patient must be able to adequately visualize and reach the lesions to use of these patient-applied agents. These modalities are preferable to some patients, because they can administer the treatment in the privacy of their own home. Provider-administered treatments include surgical excision, cryotherapy, or topical therapy with trichloroacetic acid (TCA) or bichloracetic acid (BCA). Podophyllin-based therapy is contraindicated during pregnancy due to possible teratogenic effects. The emergency clinician may elect to defer initiation of treatment for genital warts and refer the patient to a primary care provider or STD clinic, because the condition is not emergent and a prolonged course of treatment is usually required.

Molluscum Contagiosum

Molluscum contagiosum is a localized skin infection caused by a member of the pox virus family. The condition is common in childhood when it is usually acquired via nonsexual contact. It may be sexually acquired in adolescents and adults. Clinical appearance consists of one or more small 2 to 5 mm papules. The lesions have a waxy appearance, and central umbilication is common. Spontaneous resolution typically occurs within 6 to 12 months. Differential diagnosis may include genital warts, skin cancers, nevi, skin tags, and other benign skin lesions. Clinical diagnosis is made based upon the typical appearance of the lesions. No specific diagnostic testing or treatment is necessary in the ED. The patient can be referred to a primary care provider or dermatologist for curettage, cryotherapy, or treatment with topical agents for lesions that persist.

ECTOPARASITES

Pediculosis Pubis

Pediculosis pubis is a parasitic infestation caused by *Phthirus pubis,* the pubic louse. Although pubic lice are usually sexually transmitted, they can be transmitted via nonsexual contact with infected individuals or contact with infested fomites, such as linen or clothing. Symptoms include pruritus and mild discomfort at the site of the bites. Small erythematous maculopapular lesions with associated punctate bleeding may be seen. The lice are visible in the pubic hair or attached to the skin while feeding. The eggs (nits) are attached to the shaft of the pubic hairs. Diagnosis is confirmed by visual inspection.

Treatment includes topical permethrin 1% creams and rinses which are available over-the-counter. Permethrin should be applied to the affected area and washed off after 10 minutes. Alternative topical agents include pyrethrin shampoo, malathion, and lindane. The patient should attempt to remove any visible nits, because topical treatment is not always ovicidal. Potentially infested linen and clothing should be washed in hot water with detergent. Repeat topical treatment can be applied in 1 to 2 weeks to kill any newly hatched lice. Resistance to pediculicides has been widely reported. An alternative topical agent or oral ivermectin may be used for treatment failures.

Scabies

Sarcoptes scabiei is the mite responsible for scabies. The organism is transmitted via direct person-to-person contact or exposure to infested linens and clothing. Although sexual transmission is common, many cases occur from nonsexual contact. The mite creates superficial burrows in the skin where eggs and excrement are deposited. Intense pruritus is caused by a hypersensitivity reaction to the foreign material in the skin. Careful inspection often reveals characteristic burrows in the skin. Excoriations, papules, and nodules are frequently seen. Commonly affected areas include the groin, genitalia, axilla, and interdigital web spaces of the hands. Diagnosis can be confirmed by microscopic examination of scrapings from characteristic skin lesions, which reveals the mites. The preferred treatment is permethrin 5% cream applied topically and washed off after 8 to 14 hours. Permethrin is nontoxic and can be used safely in pregnancy and in patients of all ages. Alternative agents include topical benzyl benzoate, topical lindane, or oral ivermectin. Linen and clothing should be washed in hot water with detergent.

KEY CONCEPTS

- The ED diagnosis of STDs is often based on clinical findings. Empirical antibiotic treatment is warranted to cover the most likely infecting organisms based upon history and physical examination findings. Rapidly available diagnostic tests (Gram stain, darkfield microscopy, wet mount microscopy, and others) increase diagnostic sensitivity and specificity.
- Confirmatory diagnostic studies (PCR, culture, serology, and others) should be considered even when results are not immediately available. A mechanism for follow-up of test results should be established and appropriate patient contact information obtained.
- STDs frequently coexist. Diagnosis of one STD should prompt consideration and screening for others, including HIV.
- Infection with any STD increases the risk of acquisition and transmission of HIV.
- Genital herpes, the most common ulcerating STD, is often transmitted by persons who are unaware that they are infected or are asymptomatic at the time of transmission.
- Nontreponemal serologic screening tests (VDRL, RPR) may yield false-positive or false-negative results in a patient with a genital ulcer and suspected syphilis.
- In a patient with a genital ulcer, visualization of spirochetes on darkfield microscopy is highly specific for the diagnosis of syphilis and provides rapid confirmatory results.
- Single-dose antibiotic therapy should be used for treatment of STDs when possible. Directly observed therapy administered in the ED enhances treatment compliance.
  - A single dose of azithromycin 1g PO will treat chlamydia causing lower genitourinary tract infection (urethritis, cervicitis) but is inadequate for treatment of upper tract infection (PID, epididymo-orchitis).
  - A single dose of ceftriaxone 250 mg IM will treat gonorrhea causing both upper and lower genitourinary tract infection in men and women.
  - A single dose of long-acting benzathine penicillin G (2.4 million units IM) will treat primary and secondary syphilis.
  - A single dose of metronidazole 2 g PO is the treatment of choice for symptomatic trichomoniasis during all stages of pregnancy.
- Single-dose antibiotic therapy is inadequate for the treatment of PID.
- HIV, syphilis, gonorrhea, chlamydia, and chancroid are reportable diseases in all 50 of the United States.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 88: QUESTIONS & ANSWERS

88.1. A 30-year-old pregnant female presents for evaluation of a genital ulcer. Darkfield microscopy reveals spirochetes. She is allergic to penicillin. Which of the following statements is *false?*

A. Azithromycin is an acceptable treatment alternative for primary syphilis during pregnancy in a patient with known penicillin allergy.
B. Nontreponemal serologic tests for syphilis (rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]) may yield false negative results in primary syphilis.
C. Primary syphilis facilitates the transmission and acquisition of human immunodeficiency virus (HIV) infection.
D. Syphilis is a reportable disease in all 50 states.
E. The chancre of primary syphilis will heal spontaneously without antibiotic therapy.

Answer: A. Penicillin remains the drug of choice for treatment of syphilis during pregnancy. A pregnant patient with syphilis and known penicillin allergy should be admitted for desensitization and treatment with penicillin. Nontreponemal serologic tests may yield false negative results in primary syphilis when antibody titers have not yet risen. False positive serology may be seen with a variety of other medical conditions. Visualization of spirochetes on darkfield microscopy confirms the diagnosis of syphilis. All sexually transmitted diseases (STDs) facilitate the transmission and acquisition of HIV. Reportable STDs in all 50 states include gonorrhea, chlamydia, syphilis, HIV, and chancroid.

88.2. A 17-year-old female presents with complaints of pelvic pain. She reports multiple sexual partners and inconsistent condom use. Pelvic examination reveals yellow cervical discharge, cervical motion tenderness, and bilateral adnexal tenderness. Pregnancy test is negative. Which of the following statements regarding this scenario is correct?

A. All adolescents with pelvic inflammatory disease require hospital admission for intravenous antibiotics.
B. A negative nucleic acid amplification test for gonorrhea and chlamydia reliably excludes the diagnosis of pelvic inflammatory disease.
C. In the absence of an identifiable alternative diagnosis, the clinical diagnosis and empirical treatment of pelvic inflammatory disease is warranted.
D. The clinical diagnosis of pelvic inflammatory disease requires the presence lower abdominal tenderness *and* cervical motion tenderness *and* adnexal tenderness on physical examination.
E. Women treated as outpatients for pelvic inflammatory disease should have a follow up evaluation in 2 weeks.

Answer: C. The clinical diagnosis of pelvic inflammatory disease is warranted in a sexually active woman at risk for sexually transmitted diseases (STDs) if no alternative diagnosis is identified and any one of the following findings is present on examination: (1) cervical motion tenderness, (2) uterine tenderness, and/or (3) adnexal tenderness. Additional diagnostic criteria (mucopurulent cervical discharge, fever, elevated white blood count, positive testing for gonorrhea or chlamydia, and others) improve specificity but decrease sensitivity in the diagnosis of pelvic inflammatory disease (PID). Adolescents with PID may be treated as outpatients using the same criteria as adult women. Women receiving outpatient treatment for PID should be advised to seek a follow up evaluation within 48 to 72 hours.

88.3. A previously healthy 22-year-old female is diagnosed with pelvic inflammatory disease (PID). Pregnancy test is negative. She is well-perfused and nontoxic in appearance. She is tolerating oral intake without difficulty. She has no known drug allergies. Which of the following antibiotic regimens is acceptable for outpatient treatment of pelvic inflammatory disease?

A. Azithromycin 1 g *per os* (by mouth) (PO) (single dose) *and* metronidazole 500 mg bid for 14 days.
B. Ceftriaxone 125 mg IM (single dose) *and* doxycycline 100 mg bid for 7 days.
C. Ceftriaxone 250 mg IM (single dose) *and* azithromycin 1 g PO (single dose).
D. Ceftriaxone 250 mg IM (single dose) *and* doxycycline 100 mg PO bid for 14 days.
E. Metronidazole 2 g PO (single dose) *and* doxycycline 100 mg PO bid for 14 days.

Answer: D. Pelvic inflammatory disease is typically a polymicrobial infection. *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* are frequently implicated organisms, but anaerobes, enteric organisms, and normal vaginal flora may also be present. Empirical treatment of PID should include adequate coverage for gonorrhea and chlamydia. A single dose of ceftriaxone 250 mg IM is adequate treatment for upper tract gonococcal infection. A 14-day course of antibiotics is recommended for adequate chlamydia coverage in PID. The addition of anaerobic coverage, such as metronidazole, should be considered.

88.4. A 24-year-old sexually active male presents with painful genital ulcers. Physical examination reveals a cluster of 2

to 3 mm tender superficial ulcers on the penile shaft. He reports a history of similar lesions in the same location sporadically in the past. Which statement regarding this clinical scenario is *false?*

A. Both herpes simplex virus (HSV)-1 and HSV-2 can be transmitted through sexual contact.
B. Genital herpes is a lifelong viral infection.
C. Prompt initiation of antiviral medication reduces the duration and severity of symptoms.
D. Topical antiviral therapy is not recommended.
E. Use of condoms is not necessary to prevent transmission in the absence of clinically apparent lesions.

Answer: E. Genital herpes is a lifelong infection caused by herpes simplex virus. Sexual transmission is more common with HSV-2 but may also occur with HSV-1. Condom use is recommended during asymptomatic periods, because viral shedding and transmission may occur even in the absence of clinically apparent lesions. Antiviral therapy is not curative. Prompt initiation of systemic antiviral medication within 72 hours (acyclovir, famciclovir, or valacyclovir) reduces the duration and severity of symptoms, particularly at the time of primary infection. Topical antiviral therapy is not recommended.

88.5. A 24-year-old female presents to the emergency department (ED) complaining of vaginal discharge. A copious frothy whitish discharge is noted on speculum examination. Microscopic examination of a saline wet mount reveals motile flagellated organisms. Which of the following statements is correct?

A. Metronidazole is the drug of choice for treatment of symptomatic trichomoniasis during all stages of pregnancy.
B. Punctate hemorrhagic lesions are seen on the cervix in most cases of trichomonas vaginitis.
C. Tinidazole is a safe alternative for treatment of trichomoniasis during pregnancy.
D. Trichomoniasis is always symptomatic in men and women.
E. Wet mount microscopy approaches 100% sensitivity in the diagnosis of trichomonas vaginitis.

Answer: A. Metronidazole is the drug of choice for treatment of symptomatic trichomoniasis during all stages of pregnancy. Tinidazole should be avoided in pregnant women due to limited data regarding safety for use in pregnancy. Visualization of flagellated protozoans on wet mount microscopy of vaginal discharge is highly specific, but only 50% to 65% sensitive for the diagnosis of trichomoniasis. Punctate hemorrhagic lesions on the cervix (so called "strawberry cervix") is seen in up to 10% of cases. Nucleic acid amplification tests for trichomonas are highly sensitive and specific. Trichomoniasis may be asymptomatic in men and women.

88.6. Which of the following sexually transmitted diseases (STDs) can be treated with single-dose antibiotic therapy administered in the emergency department (ED)?

A. Chancroid
B. Primary and secondary syphilis
C. Trichomoniasis
D. Urethritis caused by gonorrhea or chlamydia
E. All of the above

Answer: E. Single-dose antibiotic therapy is efficacious for many STDs, including gonococcal urethritis and cervicitis, primary and secondary syphilis, trichomoniasis, and chancroid. Single-dose azithromycin is recommended for coverage of lower genitourinary tract infection with chlamydia. Treatment of upper genitourinary tract STDs, including pelvic inflammatory disease and epididymo-orchitis, requires a longer course of antibiotic therapy. Directly observed therapy administered in the ED promotes compliance.

CHAPTER 89

Selected Urologic Disorders

Carl A. Germann | Jeffrey A. Holmes

URINARY TRACT INFECTION IN ADULTS

Urinary tract infection (UTI) is the most frequent bacterial infection occurring more commonly in women than in men. In the United States, the urinary tract is the most common source of infection of patients presenting in septic shock, with an associated mortality of 10% to 20%.

UTI describes an inflammatory response of the urothelium to microorganisms in the urinary tract, resulting in clinical symptoms that include dysuria, frequency, urgency, hematuria, and suprapubic or costovertebral angle discomfort. The diagnosis of a UTI requires the presence of urinary-specific symptoms or signs in a patient who has bacteruria and no other identified source of infection.[1] Bacteriuria is the presence of bacteria in the urine but is not considered to represent a UTI in the absence of clinical manifestations. Bacteriuria accompanied by symptoms should be treated, whereas bacteriuria in the absence of symptoms should be treated only in select patients (eg, pregnant women, immunosuppressed patients).

UTIs are classified as lower (confined to the bladder) or upper (involving the ureters or kidneys) and as uncomplicated or complicated. An uncomplicated infection occurs in a nonpregnant individual with a structurally and functionally normal urinary tract. A complicated UTI is a heterogeneous term that may be associated with an underlying functional or structural abnormality, history of urinary instrumentation or organ transplantation, or systemic disease, such as renal insufficiency, diabetes, and immunodeficiency. UTIs in men are generally categorized as complicated given the higher incidence of associated urologic abnormalities. However, men can experience a UTI without an underlying structural or functional abnormality. Complicated UTIs often require a prolonged course of antibiotic therapy and a more in-depth approach to testing and anatomic evaluation.

The term *urethritis* refers to the inflammation of the urethra secondary to an infection or trauma. Frequently, urethritis may be a manifestation of a sexually transmitted disease (STD), such as gonococcal urethritis in *Neisseria gonorrhoeae* infection, but may occur in other clinical scenarios as well. Cystitis generally refers to inflammation of the bladder resulting in increased urinary frequency, urgency, dysuria, and suprapubic pain. The causes of cystitis can be separated into bacterial and nonbacterial (eg, radiation) categories. Acute pyelonephritis is a UTI involving the renal parenchyma and collecting system, manifesting with the clinical syndrome of fever, chills, and flank pain. Management and disposition of patients with acute pyelonephritis depend on whether the infection is simple or complicated.

Anatomy and Physiology

In women, the urethra is short and opens close to the vulvar and perirectal areas. This contributes to the much higher incidence of UTI in women. The route of infection in men is also usually ascending, from the urethra to the prostate to the bladder and then to the kidney. Risk factors for cystitis and pyelonephritis include sexual intercourse, use of spermicides, previous UTI, new sex partner, and history of UTI in a first-degree female relative.

Pathophysiology

UTIs arise when urinary pathogens from the bowel or vagina colonize the periurethral mucosa and ascend through the urethra and into the collecting system. Infrequently, bacterial infection of the urinary tract arises from hematogenous or lymphatic sources. This is frequently the pathologic mechanism in debilitated and chronically ill patients who are immunosuppressed. Numerous abnormalities of the urinary tract interfere with its innate ability to resist infection. Obstruction from any cause, with resultant stasis of urine, is the major causative factor. Urinary calculi may cause obstruction and increased susceptibility to the development of a UTI.

Subgroups of patients who are more susceptible than the normal population to UTIs include diabetic patients, pregnant women, older adults, patients who are unable to empty their bladder completely, patients with indwelling urinary catheters, and those with immunodeficiency disorders. Lower UTIs are more common in aging men in the setting of prostatic enlargement or obstruction.

Escherichia coli is responsible for an estimated 75% to 95% of cases of UTI and pyelonephritis in men and women.[2] Other less common bacteria that may be responsible for infection include *Staphylococcus saprophyticus* and other members of the Enterobacteriaceae family (*Klebsiella pneumonia* and *Proteus mirabilis)*. Unusual microorganisms may be found in institutionalized or hospitalized populations. Such settings and conditions predispose the patient to alterations in the normal gastrointestinal (GI) flora, leading to complex UTIs. The uropathogens in these patients include more resistant strains of *Escherichia, Klebsiella, Proteus,* and *Enterobacter,* as well as *Pseudomonas, Enterococcus, Staphylococcus, Providencia, Serratia, Morganella, Citrobacter, Salmonella, Shigella,* and *Haemophilus* spp., *Mycobacterium tuberculosis,* and fungi.

Clinical Features

UTI is usually manifested as dysuria, with or without frequency, urgency, hematuria, or suprapubic discomfort. Symptoms of dysuria, frequency, hematuria, nocturia, and urgency all increase the probability of UTI, with likelihood ratios between 1.10 and 1.7, whereas vaginal discharge decreases the likelihood of UTI.[3] The probability of cystitis is greater than 90% in women who have dysuria and frequency without vaginal discharge or irritation.

Symptoms of UTI in men may also represent storage or voiding disturbances that are common in aging men (eg, prostatic enlargement). Commonly, men with lower UTIs have symptoms of urinary urgency, frequency, dysuria, hematuria, and suprapubic pain. If fever and chills are present in association with irritative symptoms and difficulty voiding, acute bacterial prostatitis should be strongly considered. A digital rectal examination of the prostate

gland with attention to size, shape, and consistency can identify prostatic enlargement, inflammation, or cancer.

Clinical signs and symptoms suggestive of pyelonephritis include fever, chills, flank pain, costovertebral angle tenderness, and nausea or vomiting, with or without symptoms of cystitis. The presentation of pyelonephritis can be particularly challenging in those who are debilitated and older adults because they may not be able to verbalize their symptoms and can present without fever; these patients may present with nonspecific complaints such as altered mental status, lethargy, abdominal pain, or generalized weakness.

Differential Diagnosis

Bacterial UTI is the most common cause of dysuria. Differential considerations include acute urethritis or acute vaginitis from sexually transmitted infections, as well as mechanical trauma or irritation (Table 89.1). In general, if historical information includes contact with multiple sexual partners, recent change in sexual partners, or sexual partner with dysuria or discharge, *Chlamydia trachomatis* and *N. gonorrhoeae* infection should be strongly considered. Because the diagnosis of UTI is rarer in men, a high suspicion for an STD such as gonococcal or nongonococcal urethritis should be maintained. Trauma, calculi, chemical irritation, candidal infections, psychogenic disorders, neoplasm, and malformations or space-occupying lesions compressing the distal genitourinary tract can also cause dysuria. Older men may have dysuria due to prostatic hypertrophy or prostatitis.

Diagnostic Testing

Urinalysis and Urine Culture

A clean-catch, midstream specimen is the preferred type of urine sample for analysis. This is particularly important in woman in whom contamination from the perineum may result in a false-positive test result. However, even when the procedure is performed correctly, a specimen may be contaminated because the surrounding areas can be difficult to clean. A predominance of epithelial cells suggests that the specimen is contaminated. Sterile catheterization is the most accurate method of obtaining a urine specimen in women and may be the best solution for achieving a reliable urinalysis if the patient is unable to provide a clean-catch specimen or is actively menstruating. In men, the specimen is not affected significantly by lack of cleansing or by the timing of specimen collection. Therefore, it is not appropriate to catheterize an adolescent or adult man simply for the purpose of collecting a urine specimen unless he is experiencing urinary retention.

Urine screening tests provide a quick and inexpensive diagnostic tool, with a goal of reliably predicting specimens that will provide positive or negative cultures. The most commonly used screening tests measure urinary leukocyte esterase and nitrite. Both can be detected by a color change on dipstick testing. Leukocyte esterase is an enzyme found in neutrophils, and nitrite is produced from nitrate reductase, present in gram-negative bacteria. However, not all uropathogens, such as *S. saprophyticus* and *Enterococcus*, convert nitrate into nitrite.[4] Dipstick-positive hematuria has also been shown to increase the likelihood for UTI.[3] These findings often are combined to improve overall diagnostic accuracy. A urine dipstick test indicating the presence of nitrite or leukocytes and microscopic blood is moderately sensitive (75%) but less specific (66%) for predicting a UTI.[5] These tests should be used with caution because they can be less sensitive than the microscopic examination of urine (urinalysis). Given the limited negative predictive value of urine dipstick testing, a UTI may be difficult to rule out, even when all features are negative.[6] However, when there is a low pretest probability of UTI, a negative dipstick result for leukocyte esterase and nitrites excludes infection.[6] When the history is strongly suggestive of a UTI and the dipstick is negative, we recommend that a urine culture be sent.

Urine microscopy is an adjunct to the dipstick and helps reduce the number of urine cultures performed. Although no accepted level of pyuria is diagnostic of UTI, careful quantitation with a hemocytometer chamber will find pyuria in nearly all cases of acute UTI caused by coliforms. Pyuria is defined as 10 or more WBCs/mm^3. Microscopic examination of urine to identify bacteria remains the most reliable test for a diagnosis of UTI, but is often not available.

The diagnosis of a UTI can be made only with clinical symptoms and the determination of bacteriuria; however, the diagnosis is confirmed with urine culture. The Infectious Disease Society of America (IDSA) defines a positive culture as 10^5 or more colony-forming units (CFU)/mL.[7] The presence of 10^5 CFUs/mL of bacteria in a urine culture is associated with a 95% likelihood of infection, whereas 10^4 CFUs/mL is associated with a 50% likelihood of infection. There is no absolute number of CFUs that is definitive for a UTI; the culture results alone are not diagnostic of infection and must be combined with symptoms suggestive of a UTI. The presence of bacteria on culture in the absence of clinical manifestations does not always indicate infection but may be due to contamination of the specimen.

The decision to perform a urine culture should be assessed for its relevance to patient care. Patients with frequency, dysuria, urgency, and suprapubic pain should be treated on the basis of symptoms, and a urine culture is not required to guide therapy. Patients with relapse or recurrent infections, complicated infection, or those in whom multidrug-resistant organisms are suspected based on previous microbiology or exposure to antibiotics should have a culture performed (Box 89.1).

An STD may mimic a UTI and, in sexually active patients, cultures for *C. trachomatis* and *N. gonorrhoeae* should be considered. Other causes of acute dysuria include infections with *Trichomonas vaginalis* and herpes simplex virus.

TABLE 89.1

Clinical Differentiation of Major Causes of Dysuria

CAUSE	CLINICAL FEATURES
Urinary tract infection	Internal dysuria Frequency, urgency, voiding small volumes Abrupt onset Suprapubic pain Often associated with diaphragm use Presence of pyuria Presence of hematuria (50% of patients)
Sexually transmitted disease	Internal dysuria Occasional history of frequency, urgency, voiding small volumes Gradual onset History of new or multiple sexual partners Vaginal discharge
Vaginitis	External dysuria Gradual onset Vaginal discharge Vaginal odor Pruritus

From Stamm W: Protocol for diagnosis of urinary tract: reconsidering the criterion for significant bacteriuria. Urology 32(Suppl 2):6–12, 1988.

BOX 89.1

Patient Groups for Whom Urine Culture Is Indicated

- Children
- Adult men
- Immunocompromised patients
- Patients with treatment failure (ie, with persistent urinary symptoms despite recently completed course of antibiotics)
- Patients with duration of symptoms more than 4 to 6 days
- Older patients at risk for bacteremia
- Ill-appearing patients with signs and symptoms suggestive of pyelonephritis or bacteremia
- Pregnant women
- Patients with known chronic or recurrent renal infection
- Patients with known anatomic urologic abnormalities
- Patients in whom urinary tract obstruction is suspected (eg, stones, benign prostatic hypertrophy)
- Patients with serious medical diseases, including diabetes mellitus, sickle cell anemia, cancer, and other debilitating diseases
- Patients with alcoholism or drug dependence
- Recently hospitalized patients
- Patients taking antibiotics
- Patients who recently have undergone urinary tract instrumentation (eg, cystoscopy, catheterization)

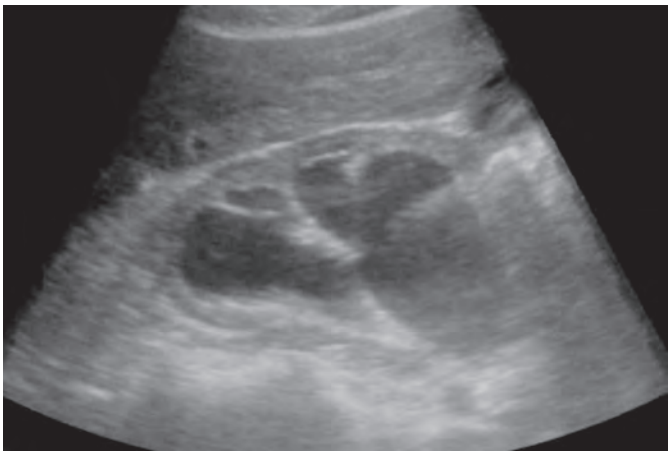


Fig. 89.1. Ultrasound image demonstrating hydronephrosis with a dilated collecting system. (Courtesy Dr. Peter Croft.)

Imaging

Most patients with acute cystitis or pyelonephritis do not need emergency imaging of the urinary tract. Imaging is reserved for patients with a clinical suspicion for underlying structural abnormalities or complicating factors such as abscess, urolithiasis, or emphysematous pyelonephritis. Patients with pyelonephritis who have severe or worsening illness or persistent fever 48 to 72 hours after the initiation of appropriate antimicrobial treatment should undergo imaging to exclude renal stones, abscesses, or obstruction.

Ultrasonography is indicated to assess for potential urinary obstruction. Although it is not as sensitive as a contrast computed tomography (CT) scan, it is a sensitive tool for detecting postvoid residual bladder volume, intrarenal and perinephric abscess, and presence of hydroureter and hydronephrosis (Figs. 89.1 and 89.2). Ultrasound can also detect the presence of pyelonephritis and congenital anomalies. Regardless of patient age, this procedure is relatively inexpensive and avoids the hazards of contrast and radiation exposure. A suggestion of obstruction based on clinical suspicion or lack of response to medical therapy necessitates performance of an abdominal ultrasound or noncontrast CT scan.

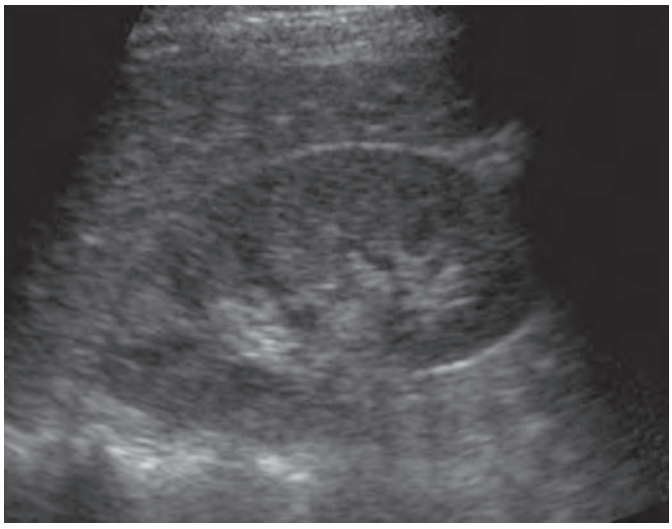


Fig. 89.2. Ultrasound image demonstrating a normal kidney. (Courtesy Dr. Peter Croft.)

A contrast CT scan of the abdomen is the most comprehensive initial test for assessing the kidneys, ureters, and bladder.[8] It has a high sensitivity for detecting abscess, obstruction, and acute inflammation. Imaging with an abdominal CT scan is recommended for those with pyelonephritis and known functional or anatomic abnormalities, recent instrumentation, immunosuppression, or concern for obstruction. Its disadvantages include radiation exposure, cost, and potential to induce contrast reactions and acute kidney injury. Contrast-induced complications occur infrequently in patients with a serum creatinine level less than 1.5 mg/dL and can be further avoided by intravenous (IV) hydration with normal saline. CT without contrast can be performed in patients with renal insufficiency and is the preferred study in patients with a clinical concern for urolithiasis.

Management

Simple Urinary Tract Infection

In 2011, the IDSA released updated clinical practice guidelines for the treatment of uncomplicated cystitis.[7] The options for treating uncomplicated lower UTI include single-dose therapy with fosfomycin, 5 days of nitrofurantoin, or 3 days of trimethoprim-sulfamethoxazole (Table 89.2). Fluoroquinolones such as ciprofloxacin or levofloxacin should not be used as first-line agents for empirical treatment of uncomplicated UTIs. Instead, they should be reserved for patients who have failed first-line therapy or have contraindications. The most recent IDSA guidelines have focused on the unnecessary use of fluoroquinolones for uncomplicated UTIs because the resistance of *E. coli* to ciprofloxacin in the United States has increased from 3% in 2000 to 17% in 2010.[7] In contrast, resistance to nitrofurantoin and fosfomycin has not meaningfully increased since their introduction.[7] The IDSA guidelines acknowledge that cystitis is often a self-resolving infection, with spontaneous symptom improvement occurring in up to 50% of patients.[9] However, there is limited evidence regarding antimicrobial-sparing treatment for UTIs.

Antibiotics should be chosen with local resistance patterns in mind. The IDSA recommends avoiding antimicrobial agents when local resistance exceeds 20%, emphasizing the need to be familiar with local outpatient resistance patterns. Although most

TABLE 89.2

Antibiotic Options for Acute Uncomplicated Cystitis

ANTIMICROBIAL	DOSE (ORAL)	DURATION	COMMON SIDE EFFECTS
Trimethoprim-sulfamethoxazole	160/800 mg bid	3 days	Nausea, vomiting, anorexia, hypersensitivity reactions
Nitrofurantoin	100 mg bid	5 days	GI disturbance, headache, allergic reactions
Fosfomycin	3 g as a single dose		Diarrhea, nausea, headache, vaginitis, dizziness

TABLE 89.3

Antibiotic Options for Acute Uncomplicated Pyelonephritis

ANTIMICROBIAL	DOSE (ORAL)	DURATION	COMMON SIDE EFFECTS
Ciprofloxacin	500 mg bid	7 days	GI disturbance, headache, dizziness, tremors, restlessness, confusion, rash, *Candida* infections
Levofloxacin	750 mg once daily	5 days	Same as for ciprofloxacin
Trimethoprim-sulfamethoxazole	160/800 mg bid	10–14 days	Nausea, vomiting, anorexia, hypersensitivity reactions

TABLE 89.4

Antibiotic Options for Complicated Pyelonephritis

ANTIMICROBIAL	DOSE (IV)	COMMON SIDE EFFECTS
Cefepime	1–2 g every 12 hours	Abdominal pain, muscle cramps, nausea, vomiting
Ceftriaxone	1 g every 24 hours	Fever, cough, sore throat, fatigue
Piperacillin-tazobactam	3.375 g every 6 hours	Diarrhea, nausea, vomiting, rash
Aztreonam	1 g every 8–12 hours	Cough, abdominal pain, nausea, vomiting
Ciprofloxacin	400 mg every 12 hours	GI disturbance, headache, dizziness, tremors, restlessness, confusion, rash, *Candida* infections
Levofloxacin	500 mg every 24 hours	Same as for ciprofloxacin

hospitals monitor the resistance of organisms cultured in their microbiology laboratory, these data may reflect drug-exposed, hospital-acquired organisms more than community-acquired, outpatient-based illnesses. Thus, hospital antibiograms likely overestimate community resistance patterns.

Nitrofurantoin is an excellent drug for the treatment of acute bacterial cystitis. It is inexpensive and maintains low serum and high urine levels. Nitrofurantoin is effective against *E. coli* but is inactive against other pathogens, such as *Proteus* and *Pseudomonas aeruginosa.* The rate of clearance is proportional to the creatinine clearance, and dose adjustments are necessary with renal impairment. The most common adverse effects of using nitrofurantoin are GI effects, including nausea, vomiting, and diarrhea.

Fosfomycin is appealing for emergency department (ED) use because it can be given as a single dose for simple cystitis and therefore does not require that a patient go to the pharmacy. Fosfomycin is an inhibitor of cell wall synthesis, structurally unrelated to any other antibiotic, and is active against most urinary tract pathogens. Both nitrofurantoin and fosfomycin remain effective against extended-spectrum, β-lactamase–producing bacteria.[10]

A useful adjunctive therapy for UTIs is phenazopyridine (Pyridium). It produces topical analgesia in the urinary tract and helps relieve dysuria. Patients should be cautioned that body secretions and excretions (eg, tears, urine) will turn orange. This side effect can stain contact lenses and alarm unknowing patients.

The clinical presentations of UTIs and STDs can overlap and, at times, empirical treatment must be directed at both possibilities. In these cases, levofloxacin (500 mg/day for 7 days) has activity against common uropathogens as well as chlamydia and can be used with a single intramuscular dose of ceftriaxone (250 mg) for gonorrhea coverage.

Complex Urinary Tract Infection

Patients with mild to moderate pyelonephritis without complicating factors can be safely treated on an outpatient basis as long as the patient is able to eat and drink, has achieved adequate pain control, and has appropriate social support in the home. Given the risk for systemic illness, bacteremia, and progression to severe sepsis, medications must achieve therapeutic levels not only in the urine but also in the renal tissues and bloodstream. Therefore, fluoroquinolones are the first-line choice (Table 89.3). In areas in which the prevalence of resistance of fluoroquinolones is less than 10%, we recommend a 7-day course of ciprofloxacin for empirical outpatient treatment for uncomplicated pyelonephritis. In areas in which there is more than 10% fluoroquinolone resistance, IDSA guidelines recommend giving a long-acting parenteral antibiotic, such as 1 g ceftriaxone, followed by 10 to 14 days of an oral cephalosporin.[7] Trimethoprim-sulfamethoxazole (TMP-SMX) for 10 to 14 days is an alternative treatment. Nitrofurantoin and fosfomycin do not achieve adequate blood and tissue levels and therefore are not effective for pyelonephritis.

A severe upper tract UTI necessitating hospitalization initially should be treated with parenteral antibiotics, such as cefepime, ceftriaxone, piperacillin-tazobactam, aztreonam, or a fluoroquinolone, with transition to oral therapy after the patient has been afebrile for 24 to 48 hours (Table 89.4).

Oral therapy should be continued for 2 weeks. Because 20% of cultures are resistant to ampicillin, cephalothin, and sulfonamides, antibiotic therapy should be initiated with a fluoroquinolone. Follow-up urine cultures are recommended given the diverse flora and high rate of antimicrobial resistance.

In men, if there are no signs of toxicity, the patient can be treated on an outpatient basis with any of the urinary antibacterial agents (eg, TMP-SMX, nitrofurantoin, fluoroquinolones) for 7 to 14 days. If concomitant prostatitis is suspected, TMP-SMX or a fluoroquinolone is recommended for 14 days. If evaluation demonstrates suspicion for prostate involvement, recurrent infection, or hematuria, the patient should be referred to a urologist for further evaluation. Patients with symptoms of prostatic enlargement can be treated with α-adrenergic receptor antagonists and/or 5-alpha-reductase inhibitor therapy (Table 89.5). Surgical treatment produces the most significant, long-term symptom improvement; it includes transurethral prostate resection, open prostatectomy, laser vaporization, transurethral microwave therapy, or needle ablation. Decisions regarding treatment options are based on the degree of obstruction and symptoms.

Disposition. Hospitalization is required in the presence of clinical toxicity (eg, fever, tachycardia, hypotension, vomiting), inability to take oral medications, an immunocompromised state, third-trimester pregnancy, failure of oral outpatient therapy, urologic abnormalities, or patients with significant comorbid conditions, including heart failure and renal insufficiency. A subgroup of patients with an upper tract UTI do not require immediate hospital admission but may benefit from IV hydration and pain and fever control, along with a first dose of an IV fluoroquinolone before discharge from the ED. Chapter e6 discusses the use of ED observation units for this type of care. If these patients do not have any contraindications, as previously discussed, improve clinically, and can tolerate food and drink, they can be safely discharged home on a 10- to 14-day course of an oral fluoroquinolone, with close primary physician follow-up. Urine culture with sensitivity testing and further diagnostic evaluation are not necessary in this patient population.

TABLE 89.5

Medication Options for Prostatic Enlargement

ANTIMICROBIAL	DOSE
ALPHA-ADRENERGIC RECEPTOR ANTAGONIST	
Alfuzosin	10 mg once daily
Doxazosin	1 mg once daily
Tamsulosin	0.4 mg once daily
Terazosin	1 mg once daily or at bedtime
5-ALPHA-REDUCTASE INHIBITORS	
Dutasteride	0.5 mg once daily
Finasteride	5 mg once daily

Complicated Urinary Tract Infection in High-Risk Populations

Pregnancy. UTI during pregnancy represents a special situation. Although the incidence of UTI in pregnancy is approximately the same as in nonpregnant women, pyelonephritis is more common during pregnancy.[1] This is likely a result of the physiologic changes that occur within the urinary tract of pregnant women, which include ureteral and renal pelvis dilation. Factors associated with a higher risk of bacteriuria include a history of prior urinary tract infection, preexisting diabetes mellitus, increased parity, and low socioeconomic status.

Unlike bacteriuria in nonpregnant females, bacteriuria in pregnant women, even if they are asymptomatic, should be treated. Untreated bacteriuria in pregnancy is associated with premature labor, low birth weight, perinatal mortality, maternal anemia, and maternal pyelonephritis. Like nonpregnant women, *E. coli* is the most common uropathogen. The symptoms of UTI and pyelonephritis are also the same as in nonpregnant patients; however, urinary frequency and urgency may be symptoms of a normal pregnancy. Specimen collection and diagnostic strategies are also similar. A urine culture specimen should be obtained, along with a follow-up culture as a test of cure.

Options for empirical treatment for UTI include amoxicillin-clavulanate, cefpodoxime, nitrofurantoin, fosfomycin, and TMP-SMX (Table 89.6). TMP-SMX and nitrofurantoin should be avoided during the first trimester. TMP-SMX is associated with teratogenic risk and nitrofurantoin may cause fetal malformations when used in the first trimester. Both medications should also be avoided during late pregnancy because TMP-SMX can cause kernicterus, and nitrofurantoin may precipitate hemolytic anemia when used after 37 weeks.[11] Fluoroquinolones should be avoided in pregnancy.

Hospital admission should be considered for patients in their last trimester, who appear ill, or who have evidence of pyelonephritis and would benefit from treatment with parenteral antibiotics and IV fluids. Parental regimens for the empirical treatment of pyelonephritis are similar to those for nonpregnant patients, except the use of fluoroquinolones, and include ceftriaxone, cefepime, aztreonam, and piperacillin-tazobactam (Table 89.7). Nitrofurantoin and fosfomycin do not achieve tissue levels adequate to treat pyelonephritis appropriately. Hospitalized pregnant patients who are afebrile for 48 hours can be discharged on oral antibiotics, directed by culture susceptibility results, to be completed in 10 to 14 days.

Indwelling and Temporary Urinary Catheters. Guidelines published by the IDSA have defined catheter-associated UTI (CAUTI) as the presence of symptoms (eg, new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with

TABLE 89.6

Antibiotic Options for Bacteriuria in Pregnancy

ANTIMICROBIAL	DOSE (ORAL)	DURATION	CONTRAINDICATIONS
Amoxicillin-clavulanate	500 mg tid	3–7 days	
Cefpodoxime	100 mg bid	3–7 days	
Nitrofurantoin	100 mg bid	5–7 days	First trimester and 38 weeks to delivery
Fosfomycin	3 g as a single dose		
Trimethoprim-sulfamethoxazole	160/800 mg bid	3 days	First trimester and term

TABLE 89.7

Parental Antibiotic Options for Pyelonephritis in Pregnancy

ANTIMICROBIAL	DOSE (IV)
Ceftriaxone	1 g every 24 hours
Cefepime	1 g every 12 hours
Piperacillin-tazobactam	3.375 g every 6 hours
Aztreonam	1 gram every 8–12 hours

no other identified cause; flank pain, costovertebral angle tenderness, acute hematuria; or pelvic discomfort) and more than 1000 CFU/mL of one or more bacterial species.[1] Screening for or treating asymptomatic bacteriuria in patients with indwelling catheters is not indicated.

Antibiotic treatment results in the development of resistant microorganisms, whereas removal of the catheter leads to the spontaneous elimination of bacteria in many patients. Treatment of patients with a UTI in whom removal of the catheter is contraindicated includes urine culture and sensitivity, antibiotic therapy, replacement of the catheter, and strong consideration for hospitalization in those who exhibit altered vital signs, systemic symptoms, or a toxic appearance.

Many patients with indwelling urinary catheters who present to the ED are older and not able to verbalize their symptoms or lack clinical signs of infection. Given that a catheter-associated UTI is a common cause of subsequent bacteremia and mortality, empirical antimicrobial therapy, in addition to replacement or removal of the catheter, is often appropriate in such patients. Urine culture with antibiotic sensitivity testing will help guide antibiotic therapy in this patient population. The most important risk factor for bacteruria is the duration of catheterization. The most effective strategy for addressing CAUTIs is to prevent the infection from occurring by placing urinary catheters only when indicated and considering the use of intermittent catheterization and condom catheters, when appropriate.

PROSTATITIS

More than 90% of men with febrile UTIs show involvement of the prostate.[12] Prostatitis encompasses four distinct clinical processes—acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis–chronic pelvic pain syndrome, and asymptomatic inflammatory prostatitis.

Acute bacterial prostatitis generally affects man between the ages of 20 and 40 years, with a second peak in men older than 60 years. Acute prostatitis is caused by a bacterial infiltration that is usually precipitated by reflux of urine infected by *E. coli, Klebsiella, Enterobacter, Proteus,* or *Pseudomonas* spp.

Chronic bacterial prostatitis is a persistent bacterial infection of the prostate lasting more than 3 months. Approximately 10% of acute bacterial prostatitis cases develop into chronic bacterial prostatitis.[13] This can be caused by undertreated acute bacterial prostatitis or highly virulent strains. Like acute bacterial prostatitis, gram-negative bacteria are responsible for most cases of chronic prostatitis.

Of patients with chronic bacterial prostatitis, 10% will develop chronic pelvic pain syndrome (CPPS).[14] CPPS is defined as urologic pain in the pelvic region associated with urinary symptoms or sexual dysfunction lasting for at least 3 of the previous 6 months. CPPS is not associated with current infection, malignancy, or structural abnormality. Symptoms of chronic bacterial prostatitis may not differ from those of CPPS. It is a heterogeneous condition with broad diagnostic criteria and uncertain cause, making it difficult to determine an effective treatment regimen reliably.

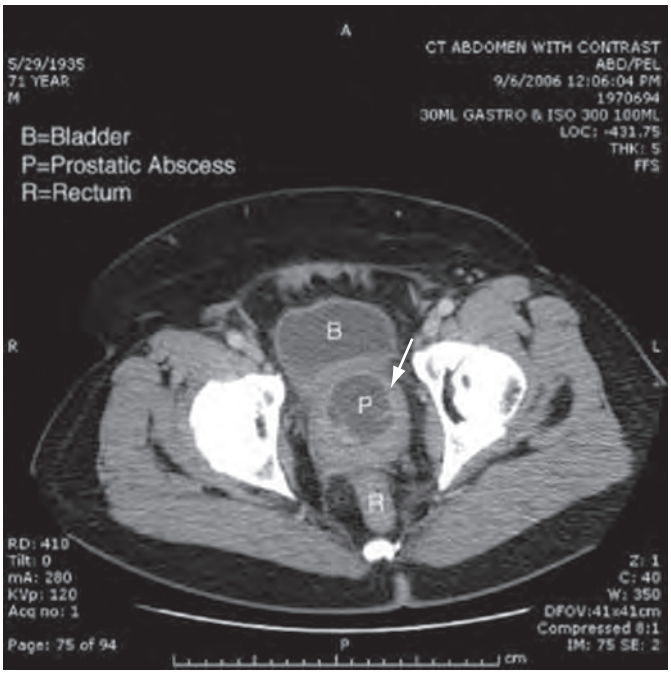


Fig. 89.3. Prostate abscess. *B,* Bladder; *P,* prostate; *R,* rectum. (From Vandover JC, Patel N, Dalawari P: Prostatic abscess. J Emerg Med 2011;40: e83–e85, 2011.)

Clinical Features

Patients with acute prostatitis often report UTI symptoms such as fever, chills, dysuria, urinary frequency or urgency, and/or perineal and low back pain. A rectal examination will reveal an exquisitely tender and swollen prostate gland in more than 90% of patients. There is no evidence that performing a rectal examination induces clinically significant bacteremia.

Clinical manifestations of chronic prostatitis vary widely, making recognition difficult. Most patients report some degree of voiding symptoms (eg, frequency, urgency, dysuria), low back and perineal pain and, occasionally, myalgias. Fever and chills are uncommon except during an acute exacerbation of the chronic infection. Findings on the physical examination, including examination of the prostate, often are unremarkable. The diagnosis is based on history, physical examination, and positive urine culture.

Diagnostic Testing

Acute bacterial prostatitis is a clinical diagnosis. A urine Gram stain and culture are recommended to identify causative organisms and guide treatment. Blood cultures are recommended for patients with acute prostatitis and fever who have not yet received antibiotics.[15] Although acute bacterial prostatitis is usually caused by typical urinary pathogens, an STD such as chlamydia and gonorrhea should be considered, especially in sexually active patients. Urethral swabs or first-voided urine, with subsequent culture or DNA amplification, should be obtained if a STD is suspected.

The most common complications of acute prostatitis are acute urinary retention and prostatic abscess. Approximately 10% of men with acute prostatitis will have some urinary retention, which can be diagnosed using bedside ultrasound. Transrectal ultrasound or CT can detect prostatic abscess and should be considered in patients who fail to improve with antibiotics (Fig. 89.3).

Management

Outpatient therapy can be used if the patient is not systemically ill, can tolerate oral medications, and does not have urinary retention. General support measures for outpatients should include bed rest, analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), hydration, and stool softeners. Alpha blocker therapy is also recommended for obstructive voiding symptoms related to prostatitis (see Table 89.5).

There is no consensus regarding an optimal treatment regimen, so regional patterns of antibiotic resistance should be considered. Few antimicrobial agents are able to penetrate the prostrate and achieve sufficient concentrations to eradicate infection. Fluoroquinolones, such as ciprofloxacin or levofloxacin, achieve the highest concentrations in the prostate and are the first-line agents in the treatment of bacterial prostatitis. Empirical parenteral antibiotics such as ciprofloxacin, levofloxacin, or ceftriaxone are recommended until fever and other symptoms have subsided. After improvement, oral antibiotics are recommended for at least 4 weeks (Table 89.8). If an STD is suspected, azithromycin can treat both chlamydia and gonorrhea.

If the patient appears systemically ill, cannot tolerate oral medications, or has urinary retention, hospitalization and parenteral antibiotics are warranted. Treatment options include ciprofloxacin 400 mg IV every 12 hours, levofloxacin 500 mg IV every 24 hours, or ceftriaxone 2 g IV every 24 hours, with or without gentamicin, 3 to 5 mg/kg per day. Following clinical improvement, the patient may be transitioned to an oral regimen, such as a fluoroquinolone. The duration of treatment should be a minimum of 2 weeks, although 4 to 6 weeks may be necessary.

The treatment of chronic bacterial prostatitis consists of antibiotics for 4 to 12 weeks (see Table 89.8). Of the researched treatments, α-adrenergic receptor blockers and antibiotics used alone or in combination result in the greatest improvement in symptoms. Antiinflammatories may also be beneficial. Patients thought to have chronic prostatitis or CPPS should be referred to a urologist.

Treatment of prostatic abscess consists of broad-spectrum intravenous antibiotics (eg, ciprofloxacin, 400 mg IV every 12 hours) and urologic consultation for perineal drainage or surgical débridement.

RENAL CALCULI

Multiple pathogenic factors interact to cause the formation of renal calculi. Risk factors include older age, male gender, obesity, and family history (Box 89.2). Its incidence depends on geographic, ethnic, dietary and genetic factors. It affects up to 20% of the population worldwide, and recurrence rates are close to 50%.[16] In the United States, prevalence rates for renal calculi are 11% in men and 7% in women; the incidence of kidney stones has continued to rise in all age groups and genders.[17] Nearly 70% of all ureteral calculi occur in individuals aged 20 to 50 years, with an increased prevalence reported in areas with hot or dry climates.

TABLE 89.8

Oral and Parental Antibiotic Options for Prostatitis (4–6 Weeks' Duration)

ANTIMICROBIAL	DOSE
Ciprofloxacin	400 mg every 12 hours (IV)
Levofloxacin	500 mg every 24 hours (IV)
Ceftriaxone	2 g every 24 hours (IV)
Ciprofloxacin	500 mg every 12 hours (PO)
Levofloxacin	500 mg once daily (PO)
Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)

Pathophysiology

Most ureteral calculi originate in the kidney and then pass into the collecting system. The chemical composition of urinary tract stones is the key factor for determining optimal management. Stone are generally composed of calcium, struvite, or uric acid. Most stones (75%) are composed of calcium oxalate, alone or in combination with calcium phosphate. The hyperexcretion of calcium is a major contributor to stone formation; its most common identified cause is hyperparathyroidism. Other medical conditions that lead to increased calcium levels include hypercalcemia of malignancy, sarcoidosis, and excessive calcium ingestion or increased absorption from the gut. The other major component of calcium stones, oxalate, is influenced by diet. Hyperoxaluria occurs in the presence of small bowel disease, bariatric surgery, Crohn's disease, ulcerative colitis, and radiation enteritis.

Magnesium ammonium phosphate (struvite) stones account for approximately 15% of all renal calculi. Struvite stones occur almost exclusively in patients with UTIs and often are referred to as infection stones. They form as a result of the presence of urea-splitting organisms, such as *Proteus, Providencia, Klebsiella, Pseudomonas,* and *Staphylococcus.* Patients with anatomic abnormalities that predispose them to recurrent UTIs are at increased risk of developing struvite stones. Most staghorn calculi—stones that fill the greater part of the collecting system—are composed of struvite.

Uric acid stones account for 10% of all stones in the United States. Approximately 15% of patients with symptomatic gout have uric acid calculi, and the incidence of uric acid stones increases with the use of uricosuric agents. In addition to hyperuricosuria, aciduria is considered necessary, because the precipitation of uric acid is unlikely at a higher urine pH. A distinctive feature of uric acid stones is their radiolucency.

Impaction along the genitourinary tract is a serious complication of renal calculi and can cause several physiologic changes. Once obstruction occurs, a rapid redistribution of renal blood

BOX 89.2

Risk Factors for Urolithiasis

Metabolic disease or disturbance
- Crohn's disease
- Milk-alkali syndrome
- Primary hyperparathyroidism
- Hypernatriuria
- Hyperuricosuria
- Sarcoidosis
- Recurrent UTI
- Renal tubular acidosis (type I)
- Gout
- Laxative abuse

Positive family history
Hot arid climates (southeast United States)
Male gender (white men affected more commonly than black men)
Previous kidney stone
Dehydration

UTI, urinary tract infection.

flow results in a decrease in the glomerular filtration rate (GFR). As glomerular and tubular function decrease, renal excretion shifts to the unaffected kidney. Obstruction also causes a rapid decrease in ureteral peristaltic activity. In the presence of infection, renal and ureteral function may be impaired. Complete obstruction of the ureters may lead to loss of renal function, with an increased incidence of irreversible damage after 1 to 2 weeks, including rupture of the renal calyx. Partial obstruction is associated with a lower likelihood of renal injury, but may still result in irreversible damage.

Although calculus size and location are important determinants of the degree of disease, the major cause of progressive renal damage is associated infection. The stone behaves as a foreign body and leads to stasis and obstruction, decreasing host resistance and increasing the incidence of infection. Subsequent infectious complications include pyelonephritis, perinephric abscess, and gram-negative bacterial sepsis.

The three primary predictors of stone passage without the need for surgical intervention are calculus size, location, and degree of patient pain. The most important factor that relates to passage of a calculus though the genitourinary tract is its size. Approximately 90% of stones smaller than 5 mm pass spontaneously within 4 weeks. This percentage decreases to 15% for stones 5 to 8 mm in size. Up to 95% of stones larger than 8 mm become impacted along the genitourinary tract, and lithotripsy or surgical removal may be required. Surgical intervention can be performed on an outpatient basis, provided the patient is able to tolerate oral intake and has adequate pain control unless the stone is infected, renal damage is considerable, there are bilateral obstructing stones, or there is obstruction of a solitary or transplanted kidney. Spontaneous passage is more frequent with stones located below the midureter than those located above the midureter.

Renal calculi seldom cause complete obstruction. There are five sites along the ureter at which calculi are likely to become impacted (Fig. 89.4). First, a stone may lodge in the calyx of the kidney or pass into the renal pelvis and become lodged at the ureteropelvic junction. The relatively large renal pelvis (1 cm) narrows abruptly at its distal portion, where it is equal in diameter to its adjoining ureter (2–3 mm). The third region is near the pelvic brim, where the ureter arches over the iliac vessels posteriorly into the true pelvis. The most constricted area along the ureter, and a common location for impaction, is the ureterovesicular junction. This is the site at which the ureter enters the muscular coat of the bladder (intramural ureter). At the time of diagnosis, up to 75% of stones are located in the distal third of the ureter. Finally, calculi may become lodged in the vesical orifice.

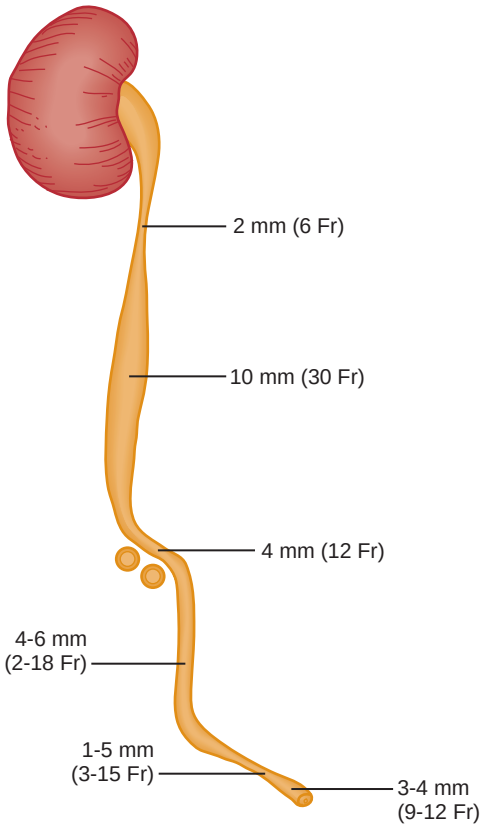


Fig. 89.4. Variations in caliber of the ureter. *Fr,* French catheter size. (Adapted from Eisendrath, Rolnick. Lich R Jr, et al: Childhood disorders and diseases. In Harrison JH, et al, editors: Campbell's urology, vol 1, ed 4, Philadelphia, 1978, WB Saunders.)

Clinical Features

The onset of pain usually is abrupt, with a crescendo of extreme pain that begins in the flank, extends laterally around the abdomen, and radiates into the groin. Pain may radiate to the testicles in men and the labia majora in women. A constant, underlying dull ache in the flank is common between episodes of colic. The cause of colicky, severe flank pain is hyperperistalsis of the smooth muscle of the calyces, pelvis, and ureter, whereas the cause of a dull ache can be acute obstruction and renal capsular tension. GI symptoms of nausea and vomiting are common.

One-third of patients experience gross hematuria, with or without blood clots in the urine. Symptoms of urinary urgency and frequency often develop as the stone nears the bladder. A history of fever and chills strongly suggests superimposed infection; these cases should be regarded as true urologic emergencies.

A patient with renal colic often is in severe pain and paces or writhes in pain on the stretcher, unable to find a comfortable position. Fever, if present, strongly suggests infection. The abdomen should be auscultated and palpated in search of bruits and thrills over the abdominal aorta and iliac vessels because the clinical manifestations of aortic abdominal aneurysms may mimic those of renal colic. Patients commonly have intermittent pain that may nearly resolve between episodes of severe discomfort.

Differential Diagnosis

A number of clinical diseases can produce pain similar to that of renal colic (Box 89.3). Potentially serious or life-threatening alternate diagnoses include pulmonary embolism, ectopic pregnancy, bowel obstruction, incarcerated inguinal hernia, pancreatitis, cholecystitis, renal vein thrombosis, and renal malignancies and infarction.[17a] One review of consecutive CT reports for patients presenting to an ED with acute flank pain has shown the most common alternate diagnoses to be biliary disease, appendicitis, pyelonephritis, ovarian cyst, renal mass, and abdominal aortic aneurysm (AAA), with and without rupture.

Diagnostic Testing

Urinalysis and Culture

Red blood cells (RBCs) generally are found in the urine of patients with urolithiasis. However, the absence of RBCs in the urine does not exclude the diagnosis. Up to 20% of patients with documented urolithiasis have no microscopic hematuria.[3] Furthermore, there is no correlation between the degree of obstruction and absence of hematuria.

Sterile pyuria can occur in the absence of infection as a result of ureteral inflammation, but the presence of a UTI should be investigated if other clinical signs of infection are present, such as

BOX 89.3

Differential Diagnosis for Pain Associated With Urolithiasis

UROLOGIC DISEASE

Upper Urinary Tract
Renal infarct
Renal parenchymal tumors
Urothelial tumors
Papillary necrosis
Pyelonephritis
Hemorrhage (blood clot)

Ureter
Urothelial tumors
Hemorrhage (blood clot)
Previous surgery (eg, stricture)
Metastatic tumors

Lower Urinary Tract
Urothelial tumors
Urinary retention

NONUROLOGIC DISEASE

Intra-abdominal
Peritonitis (especially appendicitis)
Biliary colic
Intestinal obstruction

Vascular
Abdominal aortic aneurysm
Superior mesenteric artery occlusion

Retroperitoneal
Retroperitoneal lymphadenopathy
Retroperitoneal fibrosis
Tumor

Gynecologic
Cervical cancer
Endometriosis
Ovarian vein syndrome

Musculoskeletal
Muscle strain or bony injury

From Lingeman J: Calculous disease of the kidney and bladder. In Harwood-Nuss A, Linden CH, Sternbach G, et al, editors: The clinical practice of emergency medicine, ed 2, Philadelphia, 1996, JB Lippincott.

fever and chills. A urinalysis with culture should be performed to look for pyuria and bacteriuria and to measure nitrite and leukocyte esterase levels when infection is suspected.

The kidney does not produce urine with a pH greater than 7.5 under normal conditions, so a urinary pH higher than 7.5 should raise suspicion for the presence of urea-splitting organisms such as *Proteus*. Renal tubular acidosis and ingestion of absorbable alkali also may increase the urinary pH and should be considered in the differential diagnosis. A pH less than 5 often is associated with the formation of uric acid calculi.

Other Laboratory Tests

Measurement of blood urea nitrogen (BUN) and serum creatinine levels is not routine but should be performed in patients who have a renal calculus with a solitary kidney, transplanted kidney, or history of renal insufficiency. On rare occasions, urolithiasis can present as acute renal failure resulting from obstruction of both ureters or the ureter of a solitary kidney. A slightly elevated white blood cell (WBC) count in patients with renal calculi may be the result of demargination from acute pain, but this is not a sensitive test and should be performed only in patients who are thought to be infected. A significantly elevated WBC count or left shift on the differential suggests active infection.

Fig. 89.5. In a near-term pregnant woman with an obstructed left kidney, this intravenous pyelogram demonstrates a delayed nephrogram. The right kidney has physiologic hydronephrosis from ureteral compression by the fetal head.

Imaging

Imaging is not needed in all patients with renal colic but should be performed when signs and symptoms are atypical and the diagnosis is in question, the patient has a solitary or transplanted kidney, or appears toxic, or high-grade obstruction is suspected.

Radiography of the Kidney, Ureter, and Bladder. As an initial imaging study, kidney, ureter, and bladder (KUB) radiography provides only presumptive evidence of calculi (<70% specificity), so it should be followed by a more definitive study or avoided altogether. A KUB film is the standard initial radiographic study done before injection of contrast medium during IVP (Figs. 89.5 and 89.6). It is of limited usefulness on its own except as a progress film after CT has already identified a radiopaque stone.

Intravenous Pyelography. Intravenous pyelography is an accurate imaging modality to detect renal stones, but is seldom used now because CT scanning and ultrasonography have become first-line imaging modalities. It is very sensitive, capable of establishing the diagnosis of calculous disease in 96% of cases, and it can quantify the presence and severity of obstruction.

Computed Tomography. Non–contrast-enhanced helical (spiral) CT scanning is the standard imaging modality in the United States. It is 98% sensitive and 97% specific, with a negative predictive value of 97%, in detecting ureteral calculi and ureteral

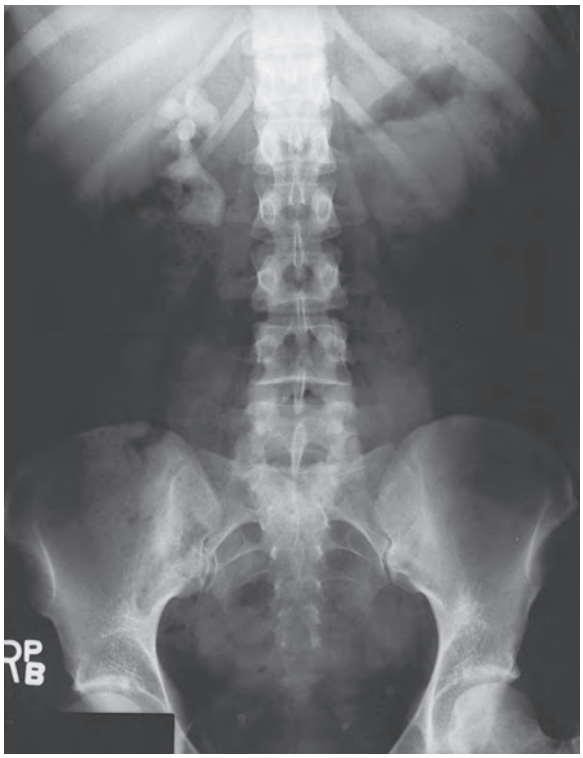


Fig. 89.6. In a near-term pregnant woman with an obstructed left kidney, this intravenous pyelogram demonstrates a delayed nephrogram. The right kidney has physiologic hydronephrosis from ureteral compression by the fetal head.

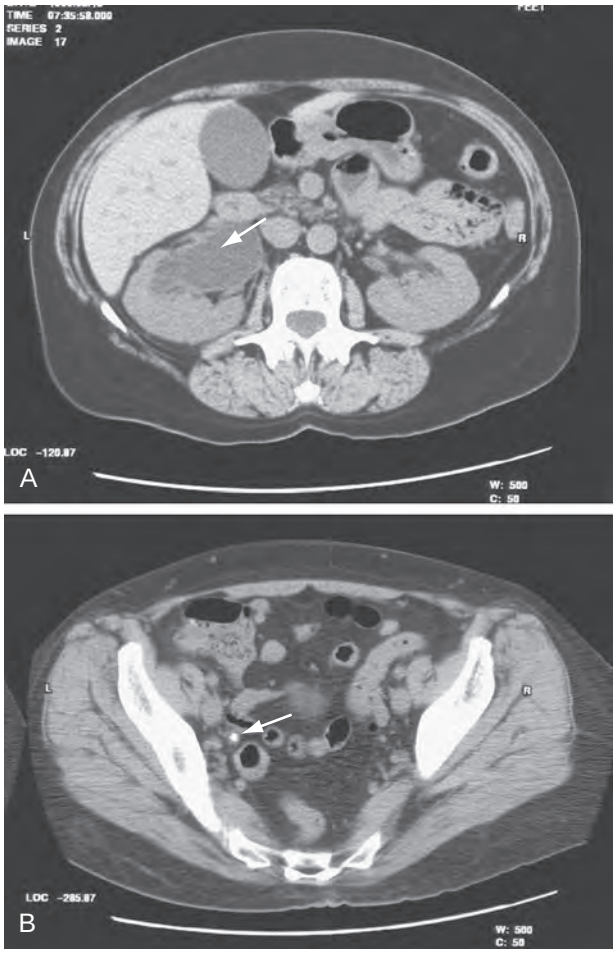


Fig. 89.7. CT scans obtained in a patient with renal colic. **A,** Right-sided hydronephrosis. **B,** Right ureteral calculi.

obstruction.[18] Rarely, some kidney stones may be radiolucent (such as those found in HIV patients on protease inhibitors). Other advantages include its ability to detect calculi as small as 1 mm in diameter and provide direct visualization of complicating conditions such as hydroureter, hydronephrosis (Fig. 89.7), and ureteral edema.

The CT scan is superior to alternate imaging modalities in its ability to recognize other pathologies, such as malignancy, renal abscess, and AAA. Other advantages include lack of contrast exposure, short duration of testing, and ease of interpretation. For patients with a body mass index less than 30 kg/m^2, low radiation dose protocols can be used, with sensitivities and specificities still reported as more than 90%.[15]

Most patients with a history of nephrolithiasis and clinical picture consistent with renal colic should not undergo any form of imaging. Imaging is appropriate in patients with a history of nephrolithiasis who do not improve with treatment, have a urinalysis showing infection, have a solitary or transplanted kidney, or in whom a diagnosis other than renal colic is suspected.[19]

Ultrasonography. Compared to CT, renal ultrasonography is associated with lower cumulative radiation exposure and shows similar results in factors such as identifying other high-risk diagnoses with complications, serious adverse events, pain scores, return ED visits, and hospitalization.[20] It is safe and easily performed, but is much less reliable than CT scanning for detecting small (<5 mm in diameter) ureteral and midureteral stones.[21] Although only 45% sensitive for detecting calculi, ultrasound examination shows hydronephrosis with a sensitivity of 85% to 94% and specificity of 100% (Fig. 89.8). It is the study of choice for ruling out hydronephrosis in a pregnant patient with pyelonephritis, if obstructive urolithiasis is a concern, or in obese patients who cannot undergo CT scanning.

Management

The first priority for a patient with a presumed diagnosis of kidney stone is adequate pain control. NSAIDs are first-line agents, but parenteral administration often is necessary because of nausea and vomiting. Ketorolac, 30 mg IV, or diclofenac, 75 mg intramuscularly (IM), provide rapid effective analgesia and decrease ureterospasm and renal capsular pressure by diminishing the GFR in the obstructed kidney. Accordingly, caution is advised with use of these agents in patients with underlying renal insufficiency or peptic ulcer disease. An IV narcotic such fentanyl (1–2 µg/kg) is also very effective in providing rapid analgesia. The combination of NSAIDS and opiates may reduce length of stay in the ED. In the patient who is unable to tolerate oral fluids, IV fluids and an antiemetic such as ondansetron, 4 mg IV, should be given. There have been no definitive studies proving that high-volume fluid therapy in those with acute renal colic facilitates stone passage or improves outcomes.[22]

Concomitant infection with an obstructive stone and hydronephrosis constitutes a true urologic emergency and may warrant immediate urologic intervention for placement of ureteral stents or decompression of the renal pelvis by percutaneous nephrostomy.

Disposition

Indications for Admission

Hospitalization is recommended for patients who are severely dehydrated, are experiencing unrelenting pain or vomiting, or

have an underlying urinary infection (Box 89.4). Sepsis and renal damage are risks in the presence of obstruction and infection, so these patients require an emergent urologic consultation to evaluate the need for immediate operative intervention to provide drainage and relieve the obstruction. If signs of sepsis (eg, tachycardia, fever, hypotension, shock) are present, ceftriaxone, 1 g IV, should be given and fluid resuscitation carried out pending urologic evaluation.

Several interventional strategies are available to the urologist for the management of stones that do not pass spontaneously. Optimal therapy depends on the size, location, and composition of the stone. Ureteroscopy and extracorporeal shock wave lithotripsy (ESWL) are the two most commonly used techniques. A Cochrane review has found that ureteroscopic removal of ureteral stones, compared to ESWL, achieves a greater stone-free state and lowers the need for retreatment, but is associated with a higher complication rate and longer hospital stay.[23] Percutaneous nephrolithotomy, which establishes a tract from the skin to the collecting system, is used for stones too large or hard for ECSWL or ureteroscopy by removing them directly from the renal pelvis.

BOX 89.4

Indications for Hospitalization of Patients With Urolithiasis

ABSOLUTE

Obstructing stone with signs of urinary infection
Intractable nausea or vomiting
Severe pain requiring parenteral analgesics
Urinary extravasation
Hypercalcemic crisis

RELATIVE

Significant comorbid illness complicating outpatient management
High-grade obstruction
Leukocytosis
Solitary kidney or intrinsic renal disease
Psychosocial factors adversely affecting home management

Outpatient Management

Most patients with nephrolithiasis may be safely managed as outpatients. They should be instructed to return to the ED immediately for intractable or severe pain, persistent nausea and vomiting, fever or chills, or difficulty voiding. Spontaneous passage usually occurs within 4 weeks after the onset of symptoms. Patients with first-time stones or those who have not had chemical analysis of their stones should strain all urine or simply void into a glass jar; the calculus should be visible at the bottom. The stone can be submitted to the follow-up urologist for analysis. If a stone has not been passed within 4 weeks, intervention is indicated, because the risk of complications such as ureteral stricture and renal function deterioration increase. The patient should be instructed to drink a moderate amount of fluids, take analgesics as needed for pain, and engage in activity as tolerated.

Medical expulsive therapy is another potentially useful treatment modality for the management of distal ureteral stones smaller than 10 mm. α_1-Antagonists (eg, tamsulosin, 0.4 mg PO

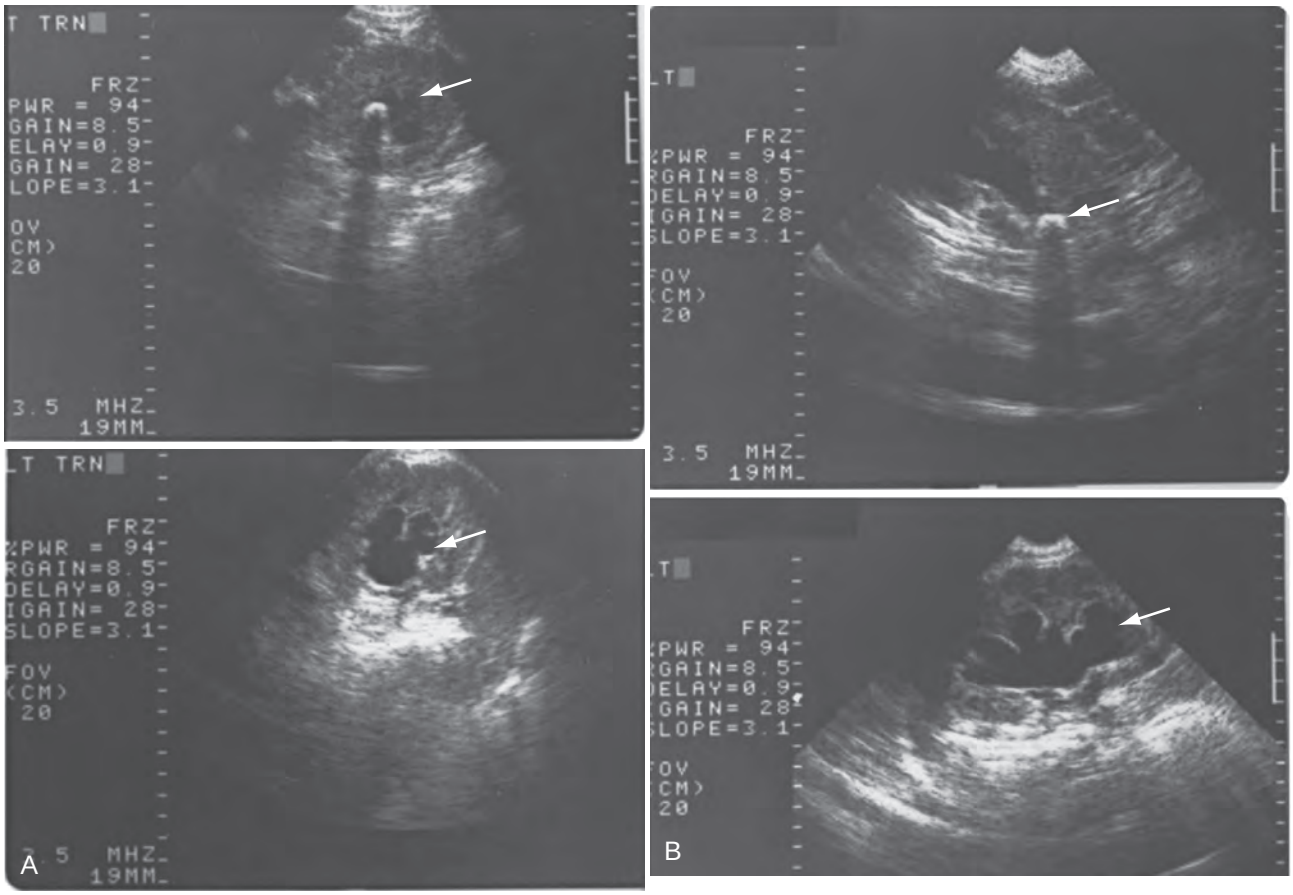


Fig. 89.8. **A,** Ultrasound images of the kidney in a patient with renal colic. Hydroneprhosis and a calcification with an acoustic shadow are visualized. **B,** Ultrasound images of the kidney in a patient with renal colic. Short axis reveals a kidney stone and hydronephrosis.

TABLE 89.9

Differentiation Among Common Causes of the Acute Scrotum

PARAMETER	TESTICULAR TORSION	APPENDIX TORSION	EPIDIDYMITIS
Age	<1 yr, puberty	7–14 yr	Adult
Onset	Hours	1–2 days	Days to weeks
Location of pain	Entire testicle	Upper pole	Epididymis
Testicle position	High-riding testicle Transverse alignment	Normal position Vertical alignment	Normal position Vertical alignment
Systemic symptoms	Nausea, vomiting	None	Possibly fever
Cremasteric reflex	No	Intact	Intact
Pyuria	Rare	No	Yes
Ultrasound findings	Diffusely hypoechoic Asymmetric testicles Normal or decreased flow Spermatic cord twist	Focally hypoechoic Symmetrical testicles Normal flow	Hypoechoic epididymis Symmetric testicles Increased flow
Treatment	Surgery	Supportive	Antibiotics; prepubescent—supportive only

Note: No single finding in patients with an acute scrotum can reliably differentiate torsion from other causative disorders. When torsion is a diagnostic possibility, prompt urology consultation and further testing are mandatory.

daily) and calcium channel blockers (eg, Nifedipine XR 30 mg PO daily) facilitate distal stone expulsion and decrease the time to spontaneous stone passage by blocking ureteral smooth muscle contraction and improving antegrade stone movement.[24] Although both have been shown to increase the stone expulsion rate, greater evidence exists for alpha blockers. A recent Cochrane review has concluded that alpha blockers reduce the episodes of colic, need for analgesic medication, and hospitalization.[25] Mild side effects, such as dizziness, palpitations, headache, rhinitis, retrograde ejaculation, fatigue and asthenia, cutaneous reactions, and postural hypotension, rarely require cessation of therapy. Both the European Urological Association (EAU) and American Urological Association (AUA) recommend alpha blockers for the expulsion of distal ureteral stones when there is no indication for immediate surgical stone removal.[26]

BLADDER (VESICAL) CALCULUS

Approximately 5% of calculi originate in the bladder. Bladder stones occur almost exclusively in older men, often as a complication of an infection of residual bladder urine with urea-splitting organisms or an indwelling catheter. Other disorders predisposing to the formation of bladder stones include bladder neck obstruction (usually secondary to prostatic hyperplasia), neurogenic bladder, vesical diverticula, damage from irradiation, and schistosomiasis.

Clinical Features

Bladder stones cause pain on voiding and hematuria. The patient may report a sudden interruption of the urinary stream, which strongly suggests a vesical stone that intermittently obstructs the bladder outlet. Frequency, urgency, and dysuria are described by up to 50% of patients, and UTIs are common.

The physical examination is rarely helpful; the rectal examination may reveal an enlarged prostate or prostatic malignancy. Poor sphincter tone may suggest a neurogenic bladder.

Diagnostic Testing

Urinalysis generally reveals pyuria, bacteriuria, and hematuria. Plain radiographs of the pelvis reveal a bladder stone in 50% of cases. Contrast scans may demonstrate obstructive changes in the upper tracts or bladder diverticula. Ultrasonography also is useful in the diagnosis of bladder stones.

Management

Surgery is currently the gold standard of care. Depending on the size of the stone, an endoscopic or open approach is used.

ACUTE SCROTAL PAIN

The most common causes of acute scrotal pain are epididymitis and torsions of the testicle and testicular appendage (Table 89.9). A delay in treatment of testicular torsion beyond 6 hours is associated with an increased risk of testicular loss and infertility (Fig. 89.9). Box 89.5 lists a number of other disorders that can present as scrotal pain. Some are emergent surgical conditions such as Fournier's gangrene and incarcerated hernias, whereas others require less invasive and time-dependent therapies, such as antibiotics for epididymitis and observation for benign masses or torsion of the appendix of the testes.

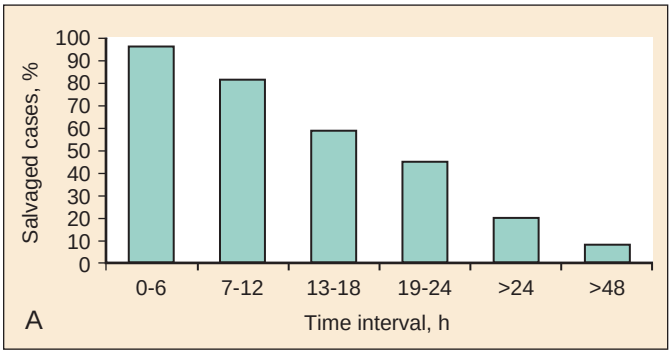
Fig. 89.10 demonstrates the anatomy of the scrotum and testis. A normal scrotum is relatively symmetric, and both testicles are of equal mass and volume. The left testicle often is higher than the right because its blood flow empties into the large, low-pressure vena cava, whereas the right drains into the relatively smaller, high-pressure renal vein. A normal testis is found in the vertical axis with a slight forward tilt, and the epididymis is above the superior pole in the posterolateral position. The epididymis is located posterolateral to the testis and is normally nontender and soft. The cremasteric reflex is elicited by stroking or pinching the inner aspect of the thigh; more than 0.5 cm of elevation of the ipsilateral testicle is considered evidence of a normal reflex. This reflex normally is absent in 50% of male infants younger than 30 months.

Specific Disorders

Testicular Torsion

Testicular torsion is present in 3% to 17% of children brought to the ED with scrotal pain. It has a bimodal incidence in the first

year of life and at puberty, when the rapid increase in testicular volume predisposes the testis to torsion (Fig. 89.11). Up to 40% of cases occur in adults. It is more common in the winter months, presumably because low ambient temperature induces contraction of the cremasteric muscles.



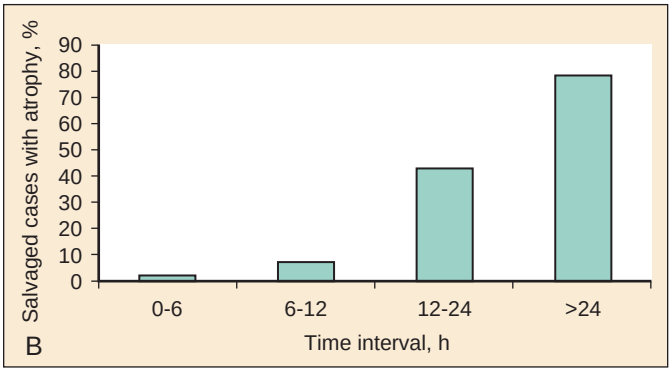


Fig. 89.9 Testicular salvage and atrophy rates over time in testicular torsion. **A,** Immediate (early) surgical salvage after torsion. **B,** Subsequent atrophy of surgically salvaged testes after torsion at various time intervals. (From Visser AJ, Heyns CF: Testicular function after torsion of the spermatic cord. BJU Int 92:200–203, 2003.)

With torsion, a congenital defect of the testis results in abnormal testicular rotation during cremasteric contraction. This leads to twisting of the spermatic cord, resulting in obstruction of venous outflow, subsequent compromised arterial flow, and testicular ischemia. Torsion from the most common congenital defect resembles the ringing of the clapper in a bell—hence, the description of a so-called bell clapper deformity.

Testicular salvage hinges on the degree of torsion and duration of the ischemia. Torsion that presents to the ED within 6 hours is associated with testicular salvage rates of 80% to 100%, whereas symptoms persisting for longer than 6 hours are as low as 44%.[27]

BOX 89.5

Causes of Acute Scrotal Swelling

INFANT
Hernia
Hydrocele

CHILD
Hernia
Torsion
Epididymitis

ADOLESCENT
Epididymitis
Torsion
Trauma

ADULT
Epididymitis
Hernia
Trauma
Tumor
Torsion
Fournier's gangrene

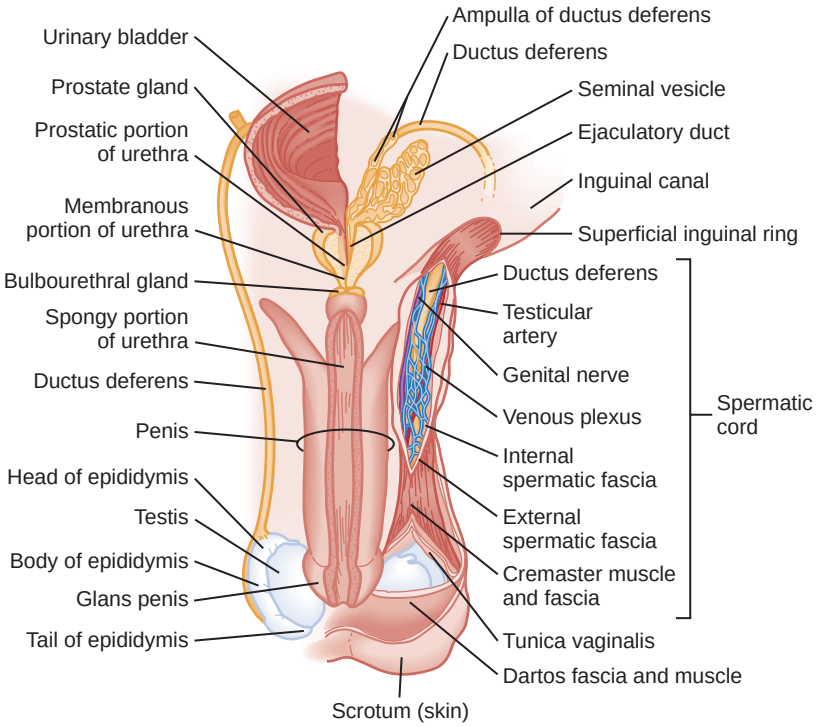


Fig. 89.10. Testes, epididymis, ductus deferens, and glands of the male reproductive system. (From Seeley RR, et al, editors: Anatomy and physiology, New York, 1989. McGraw-Hill.)

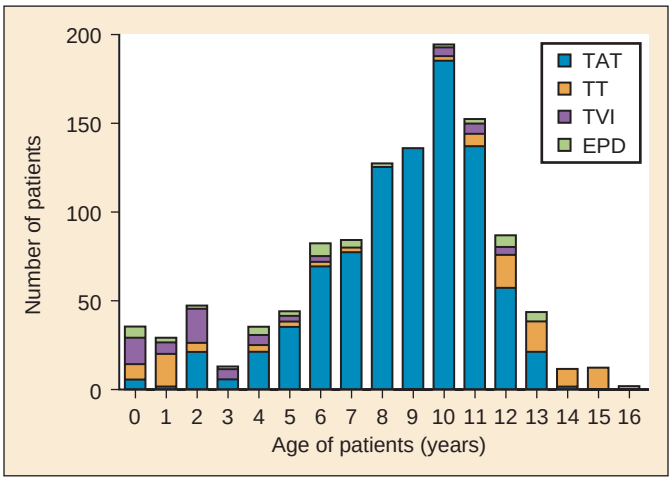


Fig. 89.11 Age distribution of boys with torsion of the appendix testis (TAT), testicular torsion (TT), tunica vaginalis inflammation (TVI), and epididymitis (EPD). (From Yang C, Song B, Liu X, et al: Acute scrotum in children: an 18-year retrospective study. Pediatr Emerg Care 27:270–274, 2011.)

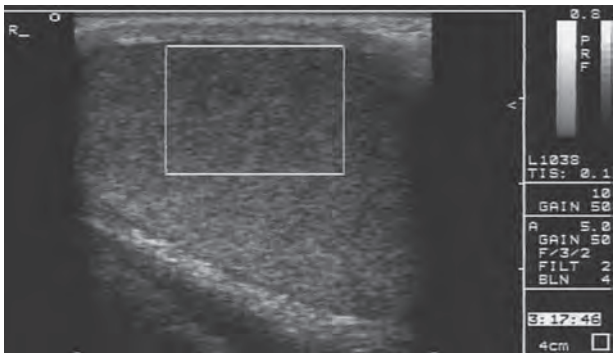


Fig. 89.12. Doppler ultrasound image showing a testicle with no flow as a result of torsion (*white box*). OK? (From Blaivas M, Brannam L: Testicular ultrasound. Emerg Med Clin North Am 22:723–748, 2004.)

Clinical Features. Patients typically report a sudden onset of rapidly escalating pain in the scrotum, lower abdomen, or inguinal area that awakens them from sleep or develops several hours after physical activity. Although a short time from the onset of symptoms to presentation favors torsion, it cannot be reliably used to differentiate it from other causes of scrotal pain. In one large study, 72% of torsion patients presented more than 12 hours after the onset of their symptoms.[28] Up to 29% of patients with testicular torsion describe similar pain in the past, caused by previous intermittent torsion in a predisposed testicle. Patients often report nausea and vomiting or abdominal pain caused by reflex stimulation of the celiac ganglion.[28] Because up to 10% of torsion cases may present with abdominal pain and no scrotal pain, the scrotum should be examined in all patients presenting with abdominal pain.

A history of scrotal trauma reduces a patient's likelihood of having testicular torsion; however, approximately 10% of patients with testicular torsion report prior acute blunt trauma to the scrotum.[29] In these cases, the symptoms of torsion often are misattributed to the trauma itself, delaying the diagnosis and worsening the rate of testicular salvage.

The physical examination is much more reliable than the history in determining the presence of testicular torsion. The cremasteric reflex is usually absent in patients with torsion; however, its presence cannot be used to rule out torsion. Patients with torsion frequently have a tender firm testicle that can be higher than the contralateral testicle owing to shortening of the spermatic cord as it twists. Twisting also can leave the testicle in the transverse position and displace the epididymis from its usual location along the posterior aspect of the scrotum. Often, the patient's scrotum is so swollen and tender that a complete physical examination is impossible. After 24 hours, the physical examination is not particularly helpful because many of the aforementioned findings are no longer present.

Differential Diagnosis. There is no single history or physical examination finding that accurately or reliably differentiates torsion from other causative disorders (see Table 89.9). Any patient with acute onset of scrotal pain in whom the diagnosis of torsion cannot be ruled out should undergo further diagnostic testing.

Diagnostic Testing

Urinalysis. In patients in whom the history and physical findings strongly suggest torsion, emergent surgical consultation is warranted. If the diagnosis is equivocal, adjunctive tests should be performed to determine the cause of the pain. Although urinalysis results suggestive of infection are consistent with epididymitis, such findings also may be noted in patients with torsion and a concomitant UTI.

Imaging. Ultrasound imaging for testicular torsion has a sensitivity of 64% to 100% and specificity of 97% to 100%.[30,31] The torsed testicle typically will be hypoechoic and enlarged (Fig. 89.12). False-negative findings occur when the testicle is examined early in the course of the disease, when blood flow is still present, and with intermittent torsion. Examination of the spermatic cord for twisting, instead of the testicle itself, has been shown to reduce the frequency of these false-negative results.

Color Doppler techniques can improve the specificity of ultrasound imaging to 100% by demonstrating reduced blood flow to the affected testicle. Doppler studies can be more difficult to interpret in younger boys because blood flow is physiologically low in the testicles of prepubertal boys. As many as 50% of boys younger than 8 years do not show intratesticular flow.[32] This hypovascularity can result in false-positive diagnoses, which could potentially lead to unnecessary surgical exploration. Comparison with the contralateral testicle can help avoid this misdiagnosis; as in normal patients, blood flow to the two testicles will be similar.

The color Doppler appearance of the testicle depends on the degree of twisting of the spermatic cord. With 180 degrees or less of twisting of the cord, venous flow from the testicle ceases but arterial flow persists. This leads to edema of the testicle on ultrasound that can be misinterpreted as inconsistent with torsion. In contrast, with more than 180 degrees of twisting of the cord, arterial flow also ceases, leading to a lack of Doppler signal on ultrasound.

Parenchymal echo texture on ultrasound may help predict the viability of the testicle. A homogenous echo texture of the parenchyma has been associated with a higher likelihood of testicular salvage. A retrospective review of 25 cases of testicular torsion has found a zero recovery rate in testes with heterogeneous echogenicity.[33] In the future, the parenchymal appearance may help determine patients who are appropriate candidates for emergent surgery.

Color Doppler ultrasound imaging has the advantage of being an inexpensive and rapid test, readily performed in the ED setting. It is helpful when it demonstrates torsion in patients with equivocal findings on the history and physical examination, but it does not have sufficient sensitivity to rule out a diagnosis of torsion.

An analysis of 669 scrotal ultrasounds has revealed a 98% negative predictive value for torsion.[26] A urologist should evaluate any patient in whom ultrasound findings are negative but history and physical findings are suggestive of torsion. Moreover, an ultrasound examination should never delay evaluation by a urologist in any patient with probable torsion.

Magnetic resonance imaging (MRI) and radionuclide scanning of the scrotum have also been used to diagnose testicular torsion but are time-consuming. They have largely been replaced by ultrasound.

Management. The first step in the management of suspected testicular torsion is immediate consultation with a urologist. The longer the spermatic cord remains twisted, the lower the likelihood of testicular salvage. In addition, early consultation allows the urologist to accompany the patient to ultrasound—if imaging is obtained—where images can be reviewed in real time with the radiologist. After consultation, IV access is established, and analgesia is provided systemically or with a block of the spermatic cord.

If the urologist is not readily available, manual detorsion should be attempted. Relief should be felt when the operator rotates the affected testicle away from the midline, as if turning the pages of a book. If this maneuver is successful, patients should report immediate improvement of symptoms. If only partial relief of pain is noticed, an attempt should be made to untwist past 360 degrees because a higher degree of rotation may be present. If pain increases or there is no relief, consider reversing the direction of reduction because up to one-third of cases can be torsed laterally. The use of ultrasound can help guide this procedure. If manual detorsion is attempted, a spermatic cord block or systemic analgesics should be administered (Fig. 89.13). In addition, evaluation by a urologist should never be delayed to perform this or any other test or maneuver.

Regardless of the outcome with manual detorsion or duration of symptoms prior to presentation, patients still require surgical evaluation. A surgeon can confirm the reduction and stabilize the testes with orchiopexy. Even for symptoms lasting beyond 24 hours, testicular salvage is possible for incomplete torsion, and orchiopexy can help prevent recurrence. Removal of a necrotic testicle speeds recovery.

Disposition. Rapid diagnosis of testicular torsion is essential and should be followed by emergent surgical scrotal exploration and bilateral orchiopexy, if necessary. Loss of the testicle is usually a result of delay in seeking medical attention. However, almost 30% of cases of failed testicular salvage have been attributed to misdiagnosis, and another 13% to a delay in treatment after the proper diagnosis was established. Misdiagnosis almost universally leads to orchiectomy and represents a common source of litigation.

Torsion of Appendages of the Testis

A normal scrotum has several vestigial appendages that can also twist and become ischemic, with resultant scrotal pain. This process is most common between 7 and 14 years of age, with a mean age of 10 years. In retrospective analyses, torsion of an appendage rivals epididymo-orchitis as the most common cause of the acute scrotum.

The appendix testis, a remnant of the paramesonephric duct, is present in 92% of patients. It is located on the superior aspect of the testicle, between the testis and epididymis (Fig. 89.14). This appendage is prone to torsion owing to its pedunculated shape. After several days of ischemia from torsion, it will undergo necrosis, with eventual reabsorption. Its loss does not permanently affect fertility or have any impact on surrounding structures.

Clinical Features. As with testicular torsion, patients with torsion of an appendage complain of scrotal pain but report milder symptoms, with a more gradual onset. They report nausea, vomiting, urinary symptoms, or previous episodes of similar pain less commonly than patients with testicular torsion. They usually seek medical attention later than patients with testicular torsion, generally after 48 hours of symptoms.

On physical examination, twisting of the appendix testis leads to formation of a hard, tender, 2- to 3-mm nodule at the upper pole of the testicle. Unlike in testicular torsion, the entire testicle is not tender. The testicle also does not change in overall size, and the scrotum typically does not swell until late in the disease process. The cremasteric reflex typically is intact. On transillumination, the ischemic appendage may rarely be seen as a blue dot.

Diagnostic Testing. Urinalysis does not show evidence of infection. On ultrasound imaging, the appendix under torsion will appear hypoechoic. Color Doppler ultrasound can show decreased flow in normal and torsed appendages. With torsion of the appendix, a hypoechoic spherical nodule with a diameter more than 5 mm is present over the superior aspect of the testicle (Fig. 89.15).

Management and Disposition. If testicular torsion is ruled out, surgical excision of the appendix is rarely necessary. Treatment consists of scrotal support, ice, and NSAIDs. Resolution of symptoms can be expected within 7 to 10 days. Surgical excision is reserved for uncontrollable pain.

Epididymitis

Epididymitis is the most common intrascrotal inflammatory disease. Most cases occur in men between 18 and 35 years of age, but the disease can affect males at any age. It is uncommon in prepubertal males. If untreated, it can lead to orchitis, testicular abscess and, rarely, sepsis.

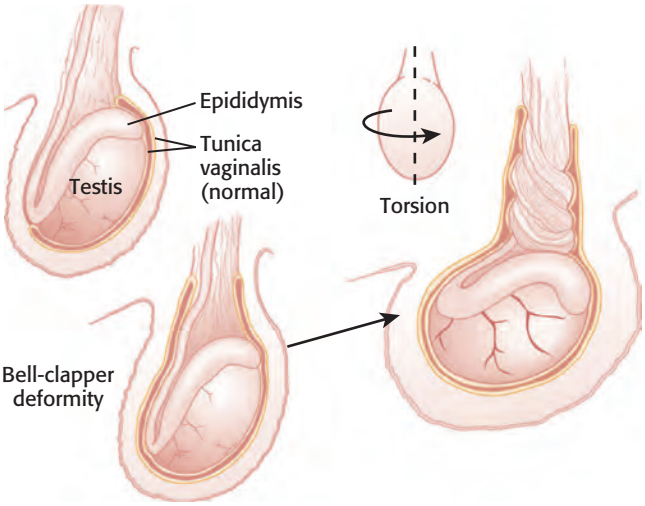
The epididymis is a tightly coiled tubular area along the posterior aspect of the testes, where sperm mature before their transit to the vas deferens. The epididymis becomes infected when organisms travel retrograde from the vas deferens. With infection, the ipsilateral testicle is also commonly involved, a condition referred to as epididymo-orchitis.

The common route of infection is local extension, mainly due to infections spreading from the urethra (sexually transmitted pathogens) or bladder (urinary pathogens). The particular organisms involved in the infection depend on the sexual activity of the patient. Although the literature classically describes men younger than 35 years who are prone to *C. trachomatis* and *N. gonorrhoeae* infections, all sexually active men, regardless of age, are at risk for epididymitis from these organisms. Acute epididymitis caused by sexually transmitted enteric organisms occurs in men who are the insertive partner during anal intercourse. Other rare causes of epididymitis include *M. tuberculosis, Treponema pallidum*, fungal infections, amiodarone use, and systemic inflammatory conditions such as Behçet's syndrome.

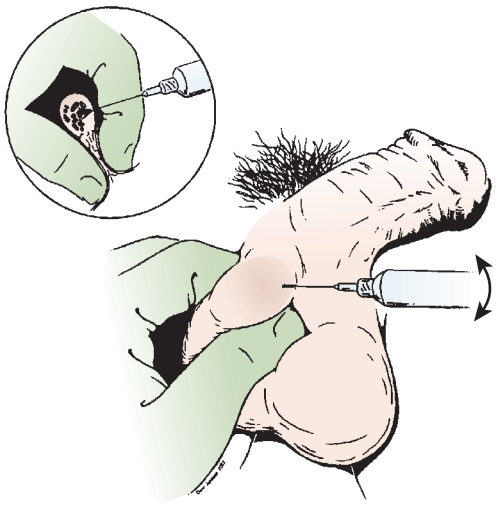
In men older than 35 years, urinary tract pathogens become the predominant cause of epididymitis. Unlike younger patients, older men with epididymitis tend to have urinary tract abnormalities that predispose them to these infections. Over 50% of men older than 60 years with epididymitis have lower urinary tract obstruction. Older men also are more likely to have concomitant prostatitis, benign prostatic hypertrophy (BPH), immunosuppression, or systemic disease or have undergone recent genitourinary instrumentation or catheterization.

Epididymitis in children is usually idiopathic, although children can also have congenital genitourinary anomalies that predispose them to recurrent infection. The most commonly

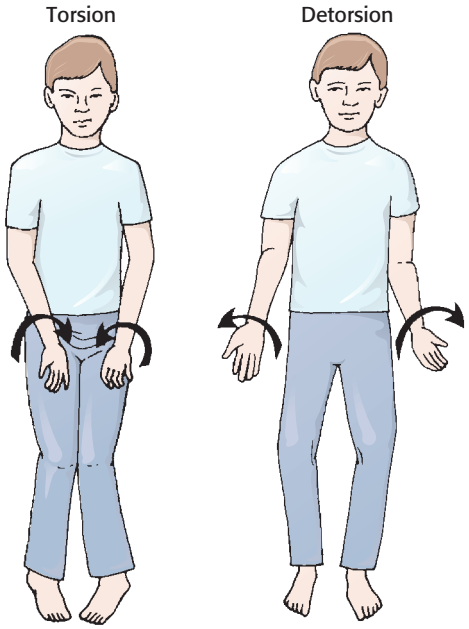
MANUAL TESTICULAR DETORSION



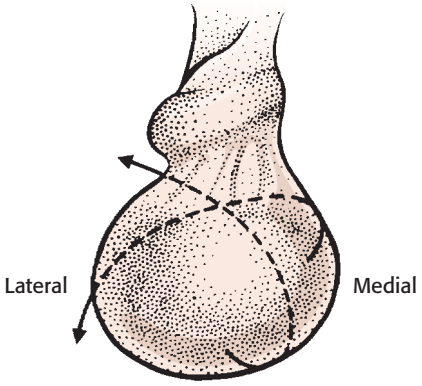
A. **Anatomy of testicular torsion**. Testicular torsion occurs when the testis twists within the tunica vaginalis. Patients with the bell clapper deformity (ie, incomplete fusion of the tunica along the epididymis, which results in incomplete attachment of the testicle to the scrotum) are at higher risk.



B. **Spermatic cord block**. Grasp the spermatic cord between your thumb and index finger. Use a 30-gauge needle to infiltrate the entire cross section of the spermatic cord and its surrounding rim with anesthetic. This will cause visual ballooning of the grasped segment of the cord. Gently massage this bulge to disperse the anesthetic. Usually about 10 mL is required.



C. Testicular torsion more commonly occurs in a medial direction. Initially attempt detorsion by rotating the testis outward toward the thigh. This is most successful if attempted within the first few hours of torsion, before the onset of significant scrotal swelling. Intravenous narcotics (eg, fentanyl) can be administered or a cord block performed before attempting detorsion.



D. **Detorsion maneuver**. Detorsion of the testicle may require testicular rotation through two planes. To release the cremasteric muscle, rotate the testis in a caudal-to-cranial direction simultaneously with medial-to-lateral rotation. The right testis is shown.

Fig. 89.13. Manual testicular detorsion. (Adapted from Roberts J, Custalow CB, Thomsen TW, editors: Roberts and Hedges' clinical procedures in emergency medicine, ed 6, St. Louis, 2014, Elsevier Health Sciences.)

associated abnormality is neurogenic bladder, which produces increased pressure during urination and reflux into the ejaculatory ducts. In infants, bacterial causes are more common.

Clinical Features. Patients with epididymitis experience scrotal pain of gradual onset, prompting them to present later in the clinical course than patients with torsion. Initially, this pain may reside in the lower abdomen or flank, caused by inflammation of the vas deferens. Fever is uncommon. In the early stages of the disease, tenderness is localized to the epididymis but quickly spreads to the ipsilateral testicle. Later in the course, the scrotum can become edematous, erythematous, and extremely tender. The

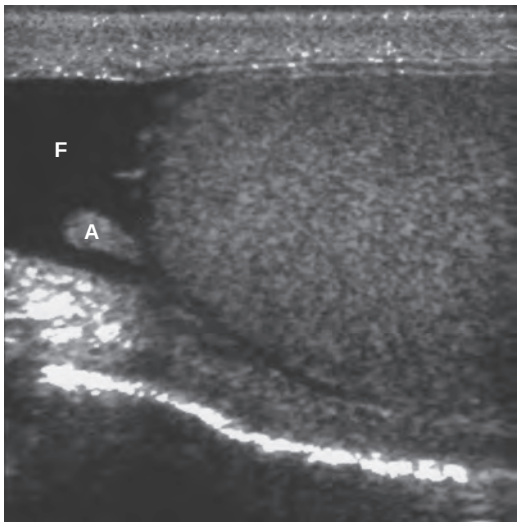


Fig. 89.14. Ultrasound image showing the testicular appendage (A) surrounded by a hydrocele (F). (From Blaivas M, Brannam L: Testicular ultrasound. Emerg Med Clin North Am 22:723–748, 2004.)

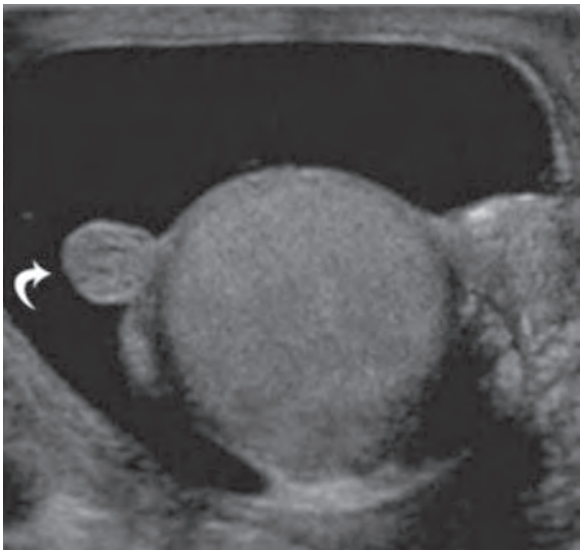


Fig. 89.15. Transverse ultrasound image shows a hyperechoic mass (*curved arrow*) with tiny central hypoechoic areas adjacent to the left testes and epididymis with a reactive hydrocele and mild scrotal wall thickening. (From Mirochnik B, Bhargava P, Dighe MK, Kanth N: Ultrasound evaluation of scrotal pathology. Radiol Clin North Am 50:317–332, 2012.)

testis is located in the normal anatomic position, with an intact cremasteric reflex. Although Prehn's sign—decrease in pain with elevation of the scrotum—has been touted as indicative of epididymitis, it has low sensitivity and specificity. Only 10% of patients with epididymitis from sexually transmitted organisms have symptoms of urethritis or a urethral discharge on examination. No single historical factor or physical finding has been shown to differentiate torsion from epididymitis reliably.

Diagnostic Testing. The diagnosis of epididymitis is typically made based on compatible physical examination findings and confirmed by laboratory testing. A urinalysis usually demonstrates evidence of pyuria. If patients are at risk for STD, a urethral swab or first-void urine sample should be tested for *C. trachomatis* and *N. gonorrhoeae;* a polymerase chain reaction (PCR) assay and other nucleic acid amplification tests have the greatest sensitivity

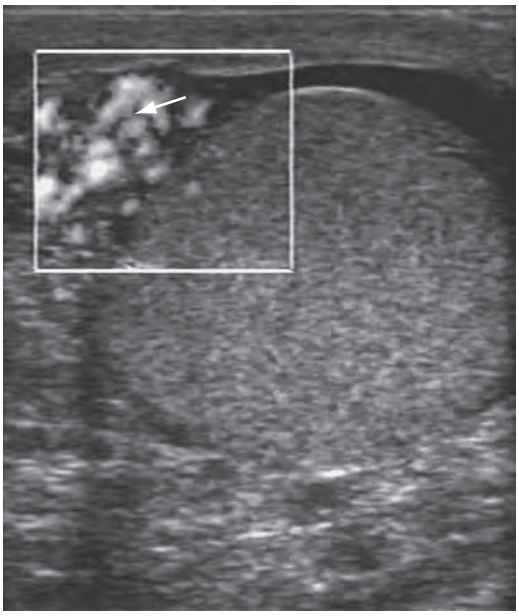


Fig. 89.16. Ultrasound of the testicle showing an enlarged epididymis and increased blood flow on Doppler ultrasound imaging *(white box).* (From Blaivas M, Brannam L: Testicular ultrasound. Emerg Med Clin North Am 22:723–748, 2004.)

and should be used, when available. Studies have suggested that this diagnostic regimen is underused, with less than 10% of adults with epididymitis undergoing testing for STDs.[34]

Systemic leukocytosis may be present but is a nonspecific finding and does not differentiate epididymitis from torsion. In prepubertal children, urinalysis and urine culture rarely are positive; a retrospective review of 73 children with epididymitis has demonstrated bacteriuria in only one child.[35] Nevertheless, in these patients, urine cultures should still be obtained to rule out bacterial infection because untreated bacterial infections may lead to long-term complications.

Because the history and physical examination features and laboratory results cannot reliably distinguish torsion from epididymitis or other diseases, equivocal presentation for epididymitis versus testicular torsion should be assessed using testicular ultrasound with Doppler. On ultrasound, an inflamed epididymis appears enlarged and hypoechoic (Fig. 89.16). However, a minority of patients with torsion have preserved flow that can appear similar to that of epididymitis; in these cases, the presence of a spermatic cord twist, indicative of torsion, should be sought.

Prepubertal children with recurrent epididymitis should undergo renal ultrasound and cystography to identify potential underlying urinary tract abnormalities. These are important to identify to reduce the risk of future inflammation.

Management. Empirical antibiotics are selected in accordance with the patient's age, sexual history, and any previous genitourinary tract abnormalities or instrumentation (Table 89.10). Treatment focuses on curing infection, improving symptoms, preventing transmission, and reducing future complications.

In patients with a suspected sexually acquired infection, ceftriaxone, 250 mg IM, should be given to treat possible *N. gonorrhoeae* infection. In conjunction, doxycycline, 100 mg PO bid for 10 to 14 days, should be started to treat *C. trachomatis* or *Ureaplasma urealyticum* infection.[36] Treatment of sexual partners should be arranged, even if the partner's culture demonstrates no growth.

In patients with infection by enteric organisms, levofloxacin, 500 mg PO once daily, or ofloxacin, 300 mg PO every 12 hours,

TABLE 89.10

Treatment of Epididymitis

DRUG OF CHOICE	DOSE AND ROUTE	ALTERNATIVE REGIMEN(S)
PRESUMED SEXUALLY ACQUIRED EPIDIDYMITIS		
Ceftriaxone *followed by*	250 mg IM once	
Doxycycline	100 mg PO bid for 10 days	
PRESUMED NONSEXUALLY ACQUIRED EPIDIDYMITIS[a]		
Levofloxacin	500 mg PO daily for 10 days	Ofloxacin, 300 mg PO bid for 10 days
Prepuberty		
Supportive care only		Obtain urine culture; administer antibiotics only if culture is positive

[a]Adjust antibacterial therapy according to results of urine culture.
IM, Intramuscularly; *PO,* orally.

is recommended. If the patient is high risk for sexually transmitted infections and enteric organisms, treatment should include ceftriaxone and fluoroquinolones. Despite the absence of evidence to support benefit, we also recommend bed rest, scrotal elevation, analgesics, and ice packs.

Most cases of pediatric epididymitis are idiopathic, and antibiotics are not routinely recommended. Urine culture specimens should be obtained for these boys, and antibiotic therapy should be initiated only if cultures reveal bacteria. Despite the absence of evidence to support benefit, we recommend that boys limit activity, elevate the scrotum with ice packs, and reduce inflammation with NSAIDs. In contrast, infants often have bacterial epididymitis and should be treated empirically with antibiotics pending urine culture results.

Disposition. Patients with systemic signs of toxicity (fever, chills, nausea, vomiting) or complications of acute epididymitis should be hospitalized and treated with parenteral antibiotics. Most well-appearing patients with uncomplicated epididymitis can be managed as outpatients. Urology follow-up should be arranged for those likely infected with enteric organisms. Signs and symptoms of epididymitis that do not subside within 3 days require reevaluation of the diagnosis and therapy.

Orchitis

Orchitis is a rare acute infection of the testis. With the exception of viral diseases, genitourinary tract infections seldom primarily involve the testis. It is most common in prepubertal boys, with viral infections such as mumps causing most cases. Orchitis rarely develops in prepubertal boys with mumps but is more common in adolescent males with mumps. It tends to arise several days after the onset of parotitis. Although vaccination has significantly reduced the incidence of mumps infection, sporadic outbreaks have occurred. Infections in vaccinated individuals are increasingly common, presumably resulting from vaccine failure or antigenic differences between the infecting and vaccine strains.

Owing to the testes' relatively high threshold of resistance to infection, bacterial orchitis usually results from local bacterial spread from the epididymis, frequently referred to as epididymo-orchitis. The most frequent bacterial pathogens are *N. gonorrhoeae, C. trachomatis, E. coli, Klebsiella,* and *P. aeruginosa.* These organisms tend to infect postpubertal males and men older than 50 years with BPH.

Clinical Features. A patient with mumps orchitis has testicular pain and swelling that commonly begins 4 to 6 days after the onset of parotitis, although it can develop in the absence of parotitis. The clinical course varies, with adults having more severe symptoms. Clinical resolution generally occurs in 4 to 5 days.

Patients with bacterial orchitis typically have fever and scrotal pain. They often have constitutional signs and symptoms, including nausea, vomiting, myalgias, and malaise. The affected testicle—the disease is unilateral in 70% of patients—and the scrotum are swollen, tender, and erythematous.

Diagnostic Testing. As with all causes of scrotal pain, the first priority is to exclude testicular torsion. If the patient clearly has mumps orchitis based on the clinical presentation and a history of preceding parotitis, no other tests are necessary. For all other patients, urinalysis, urine culture, and ultrasound should be performed. On ultrasound, orchitis shows hypervascularity, commonly described as a testicular inferno. Blood tests are typically not helpful, because false-negative results are common with serologic testing, particularly in vaccinated individuals.

Management. In sexually active patients, ceftriaxone and doxycycline should be used to cover *N. gonorrhoeae* and *C. trachomatis.* In older patients, fluoroquinolones provide the best coverage of gram-negative organisms. Treatment of viral orchitis is supportive only. Although steroids may improve symptoms, they can reduce testosterone levels. All patients should receive local scrotal care as described for epididymitis. Patients with marked pain, high fever, or constitutional symptoms merit hospitalization and parenteral antibiotics.

Testicular Tumors

Principles. Tumor of the testis is the most common malignancy in young men but accounts for only 1% of all cancers in men. These tumors are more common in infertile patients and whites. They also occur with increased frequency in the nondescended and descended testicles of patients with cryptorchidism. Approximately 95% of testicular tumors are germ cell tumors, with 50% of these being seminomas and the other 50% being mixed types, including teratomas, choriocarcinomas, and yolk sac tumors. The other 5% of testicular tumors are sex cord stromal tumors. The disease course will depend on the type of tumor present, as well as the age of the patient.

Clinical Features. Testicular cancer usually presents as a painless, unilateral scrotal mass or as an incidental ultrasound finding. However, scrotal pain may be the first symptom in up to 20% of cases of patients with testicular cancer. Unlike other painless scrotal masses, such as hydroceles and varicoceles, tumors cannot be separated from the underlying testicle. Palpable tumors are more likely to be malignant compared with tumors identified only with imaging.

Diagnostic Testing. All patients with a scrotal enlargement or palpable scrotal lesions on physical examination should undergo a scrotal ultrasound examination. This study can reveal a concomitant hydrocele or homogeneous hypoechoic lesion. Intratesticular tumors are typically hypervascular, with irregular branching vessels. Leydig cell tumors are unique, because they show hypervascularity around the lesion but no internal color

Doppler flow. Although helpful for staging purposes, CT scans of the chest and abdomen are necessary in the ED only if the patient has complaints related to these parts of the body. Most paratesticular masses are benign lesions such as epididymal cysts, epididymitis, spermatoceles, hydroceles, or hernias.

Management and Disposition. Urgent referral to a urologist is indicated for patients with intratesticular masses. The radiosensitive nature of seminomas renders the combined treatment of orchiectomy and radiation therapy highly successful for early-stage disease. Testicular cancer has become one of the most curable solid neoplasms, with an expected 5-year survival rate over 95%.[37]

Testicular Trauma

The most concerning injury associated with trauma involves rupture of the testicle. Testicular rupture is characterized by tear of the tunica albuginea and extrusion of the seminiferous tubules. The presentation can range from a tender, large, blood-filled scrotum to minimal swelling, with mild pain of the testicle. If there is any concern for rupture, scrotal ultrasound is indicated. Disruption in the echogenic tunica albuginea is 100% sensitive and 65% specific for rupture. Early surgical intervention is associated with higher rates of testicular salvage. Hematomas can be intratesticular or extratesticular, with or without testicular rupture. Similar to rupture, rapid evacuation of an intratesticular hematoma will reduce the risk of necrosis. Extratesticular hemorrhage into the tunica vaginalis is termed a *hematocele* and is the most common finding after blunt scrotal injury. Surgical exploration with hematoma extraction is recommended for patients with large hematoceles to prevent testicular atrophy. Approximately 10% of patients with testicular torsion have associated trauma and require prompt identification and detorsion.

Inguinal Hernia, Acute Hydrocele, Varicocele, and Spermatocele

Inguinal hernias, hydroceles, varicoceles, and spermatoceles are considerations in the differential diagnosis of an acute scrotal mass. These clinical entities are typically painless and readily identifiable on physical examination.

Most children with inguinal hernias will not have a palpable mass on examination but will report a history of intermittent bulge in the groin that appears with straining or crying. Less commonly, an inguinal mass is palpable and may extend into the scrotum. If this mass becomes incarcerated, it will be tender, and often the overlying skin will be edematous and erythematous. Children typically will develop irritability, vomiting, or abdominal distention. Incarcerated hernias should be reduced promptly to prevent bowel infarction from strangulation. Reduction can be accomplished by placing the patient in a Trendelenberg position and applying gentle pressure to expel the gas and stool in the bowel from the hernia. Pressure is then applied over the distal aspect of the hernia to reduce the bowel. If this technique fails, surgery is consulted. After reduction of an incarcerated hernia, children typically require hospitalization and delayed surgical repair.

Acute hydroceles typically are benign. They are caused by the accumulation of fluid between the two layers of the tunica vaginalis. They are painless, localized to the scrotum, and will transilluminate.

Varicoceles are enlarged spermatic cord veins that typically are painless or cause only minimal discomfort. On examination, they are often described as feeling similar to a bag of worms, just superior to the testicle, and decrease in size when the patient is supine. In contrast, a spermatocele is a sperm-containing cyst that is palpated as a nontender mass posterior to the testicle. Ultrasound is diagnostic of these conditions. No emergent treatment is necessary, but patients require outpatient urologic evaluation.

Regardless of the cause of the scrotal swelling, concomitant pathology is always a consideration. A careful evaluation for torsion, epididymitis, and tumors should be performed.

ACUTE URINARY RETENTION

Epidemiology

Acute urinary retention (AUR) is the sudden inability to pass urine voluntarily from the bladder. The lifetime risk of AUR increases with age, occurring in 10% of men in their 70s and in 33% of men in their 80s. AUR is usually caused by an obstructive lesion but also can be the presenting manifestation of other pathologic processes. AUR in women is much less common than in men; common causes in women include an atonic bladder, inflammation occurring postpartum or secondary to herpes, Bartholin's abscess, acute urethritis, or vulvovaginitis. In younger patients, it usually is caused by obstruction, cystitis, and neurologic disturbances.

Pathophysiology

Holding urine requires relaxation of the bladder detrusor muscle through parasympathetic inhibition and β-adrenergic stimulation and contraction of the bladder neck and internal sphincter through α-adrenergic stimulation. Conversely, micturition requires a coordinated contraction of detrusor muscle, with the simultaneous relaxation of the urethral sphincter muscle. AUR results from a disruption of this coordinated physiology caused by an increased resistance to flow via mechanical (eg, urethral stricture, clot retention) or dynamic means (eg, increased α-adrenergic activity, prostatic inflammation) or decreased neurogenic control of the detrusor muscle (eg, drugs inhibiting bladder contractility, diabetes cystopathy).

The most common cause of AUR seen in the ED is obstruction of the urinary tract distal to the bladder. In men, BPH is the most common precipitant. Enlargement of the prostate coupled with constriction of the prostatic urethra from heightened α-adrenergic tone obstructs urinary output. Strictures of the urethra after prior procedural trauma, infection, or radiation therapy can also lead to AUR. Other less common obstructive causes of AUR include prostate cancer, phimosis (inability to retract the foreskin over the glans penis) and paraphimosis (inability to reduce the foreskin over an edematous glans). In women, the most frequent obstructive causes are pelvic masses and prolapse of pelvic organs such as the bladder, rectum, or uterus. These structures cause AUR by compressing the urethra and obstructing urine flow. Finally, congenital posterior urethral valves are the most common source of AUR in children.

Infectious and inflammatory conditions can also cause AUR from urethral edema and obstruction, particularly in the setting of underlying prostatic disease. The most common infectious causative disorder is acute prostatitis, followed by urethritis and vulvovaginitis. In pediatric patients. UTIs can induce sufficient dysuria that the child refuses to void, with consequent urinary retention.

Pharmacologic agents associated with AUR include the anticholinergic and sympathomimetic agents. Anticholinergic agents inhibit detrusor muscle contraction, whereas sympathomimetic agents increase α-adrenergic tone in the prostate. NSAIDs and calcium channel blockers have also been known to increase the rate of AUR by inhibiting prostaglandin and calcium-mediated detrusor muscle contraction.

Neurogenic causes of AUR result from a cortical, spinal cord, or peripheral nerve deficit in the sensory or motor nerve supply of the detrusor muscle. Most neurologic causes of AUR are chronic conditions such as multiple sclerosis, Parkinson's disease, neoplasms, and diabetic peripheral neuropathy. Other more acute neurologic conditions that should be diagnosed emergently as causative factors in the ED include spinal trauma, stroke, epidural abscess, and intervertebral disk herniation.

Clinical Features

Although the potential causes of AUR are many, the history and physical examination can considerably narrow the scope of the differential diagnosis (Table 89.11). Most patients with AUR report sudden pain and have a distended tender bladder. Patients with dementia or limited verbal ability may only present with restlessness and agitation. With lesions proximal to the bladder, patients typically note pain in the flank, whereas lesions distal to the bladder can produce pain radiating to the scrotum or labia. With acute obstruction, pain is often quite severe. Patients with slowly developing or chronic obstructions are typically older and report overflow incontinence and little to no pain.

When obstruction is the cause of AUR, the patient often will recall multiple previous episodes of urinary retention. In addition to this history, patients with BPH report frequency, urgency, hesitancy, nocturia, difficulty initiating the urinary stream, decreased force of the stream, sensation of incomplete voiding, and terminal dribbling. The prostate is enlarged, firm, and nonnodular. Normal findings on the prostate examination do not exclude BPH. Patients with prostate cancer can have similar symptoms, but these are more often accompanied by weight loss, bone pain, and other constitutional signs and symptoms. These patients generally will have an enlarged nodular prostate. Examination of the penis is important to identify phimosis or paraphimosis. In women with obstruction, pelvic pain and pressure are symptoms commonly associated with AUR. A prolapsed bladder, rectum, or uterus and enlarged ovaries or uterus can be identified on pelvic examination.

Patients with an infectious cause for their symptoms may complain of dysuria, frequency, urgency, hematuria, fever, chills, and low back pain. In acute prostatitis, these symptoms can be associated with penile discharge and a tender boggy prostate. Despite the obstruction, the patient may nevertheless be able to void small amounts of urine. In vulvovaginitis and urethritis, presenting complaints also may include discharge, pruritus, and vulvar skin findings.

Patients with a neurogenic cause for AUR may already have a history of neurologic disease that contributes to AUR. The examination should focus on any findings suggestive of acute neurologic deficit. Strength, sensation, and reflexes in the lower extremities should be examined because they have similar innervation to that of the bladder. The status of the bulbocavernosus reflex, anal reflex, sphincter tone, and perineal sensation should also be assessed.

Differential Diagnosis

The differential diagnosis for AUR is very broad and dependent on the patient's symptoms (Box 89.6). AUR presenting as lower abdominal pain may present similarly to small bowel obstruction, urinary tract infection, or prostatitis. Flank and back pain secondary to hydronephrosis can be confused with nephrolithiasis, pyelonephritis, and spinal pathology. Urinary symptoms of overflow incontinence and urinary hesitancy can be confused with urinary tract infection or spinal cord compression. Genital pain may present similarly to trauma, testicular torsion, or inguinal hernia.

Diagnostic Testing

The only suggested diagnostic test in the ED for AUR is urinalysis. It can reveal infection or the presence of hematuria from infection, tumor, or calculi. A basic chemistry panel for the assessment of renal function should be performed only when renal damage or hydronephrosis is a concern. There is no history, physical examination, or ultrasound finding that can reliably correlate

TABLE 89.11

Presentation and Diagnosis of Acute Urinary Retention

CAUSE	HISTORY	PHYSICAL EXAMINATION FINDINGS	DIAGNOSIS[a]
Benign prostatic hypertrophy	Frequency, urgency, hesitancy Prior retention	Enlarged, firm prostate	UA
Prostate cancer	Frequency, urgency, hesitancy Previous retention Constitutional symptoms	Enlarged, firm prostate Nodular prostate	UA
Phimosis, paraphimosis	Penile pain	Nonretractable foreskin Edematous penis	Clinical only
Prostatitis	Dysuria, frequency, urgency Fever, chills	Warm, tender, boggy prostate Penile discharge	UA Urine culture
Urethritis, vulvovaginitis	Dysuria, frequency, urgency Itching	Discharge	UA Urine culture Urethral or cervical culture
Pelvic mass	Pelvic pain pressure	Prolapse of rectum, bladder, uterus	UA Ultrasound imaging, CT
Neurogenic bladder	Other neurologic complaints	Neurologic deficits	UA CT, MRI

[a]In the emergency department setting, each of these diagnoses is made primarily by the history and findings on the physical examination. Additional tests are needed as described.

CT, Computed tomography; *MRI,* magnetic resonance imaging; *UA,* urinalysis.

BOX 89.6

Causes of Acute Urinary Retention in Adults

OBSTRUCTIVE
Benign prostatic hypertrophy
Prostatitis
Phimosis
Paraphimosis
Meatal stenosis
Tumor
Foreign body
Calculus
Stricture
Hematoma
Carcinoma

INFECTIOUS, INFLAMMATORY
Urethritis (severe)
Urinary tract infection
Prostatitis
Severe vulvovaginitis
Genital herpes

NEUROLOGIC CAUSES
Motor Paralytic
Spinal shock
Spinal cord syndromes

Sensory Paralytic
Tabes dorsalis
Diabetes
Multiple sclerosis
Syringomyelia
Spinal cord syndromes
Herpes zoster

DRUGS
Antihistamines
Anticholinergic agents
Antispasmodic agents
Tricyclic antidepressants
α-Adrenergic stimulators
Cold tablets
Ephedrine derivatives
Amphetamines

PSYCHOGENIC PROBLEMS
Psychodynamic stressors (eg, lazy bladder syndrome)

with an acutely elevated creatinine level. It should be considered for patients with prolonged obstruction or preexisting renal insufficiency.

Additional studies are selectively indicated based on the history and physical examination to identify potentially serious or reversible causes, or when the diagnosis of AUR is unclear. With an equivocal history or physical examination, bedside ultrasound can confirm AUR. Renal and bladder ultrasound studies provide visualization of any elevated postvoid residual, obstruction, hydronephrosis, or other cause of upper urinary tract disease. Pelvic ultrasound examination and CT scan evaluate for masses or malignancy causing obstruction. MRI of the spine detects disk herniation, cord compression, and cauda equina syndrome. Cystoscopy and retrograde cystourethrography can identify problems in the lower urinary tract and usually are performed as outpatient procedures. A prostate-specific antigen assay is not helpful in diagnosing or differentiating prostate cancer from other causes of AUR and should not be routinely performed.

Management

Treatment focuses on bladder decompression and identification of the underlying cause. Immediate placement of a 14 Fr to 18 Fr Foley catheter should provide decompression of the bladder. If this fails, placement of an elbowed catheter (coudé catheter) with a cephalad orientation should be attempted to assist bypassing by any obstruction. If both these techniques prove to be unsuccessful, urologic surgery should be consulted. If obstruction is believed to be caused by retained blood clots, a three-way catheter should be placed to allow for bladder irrigation. When immediate bladder decompression is required and a urologist is not available, major urethral trauma is present, or the patient has recently undergone urethral surgery, suprapubic bladder drainage should be performed.

Placement of a catheter has been reported to cause postobstructive diuresis, hypotension, and hematuria. Such problems are believed to be related to rapid bladder decompression so, historically, gradual decompression has been recommended to prevent these complications. Neither has been proven to have any clinical significance. We recommend that all patients with AUR undergo rapid and complete decompression of the bladder.

Although the catheter is an inconvenience for the patient, and chronic use has been associated with UTIs, trauma, stones, and urethral strictures, early removal of the catheter is also associated with heightened risk for recurrence of AUR, which has been reported in up to 70% of cases. Leaving the catheter in place for 3 to 7 days decreases the incidence of recurrent retention.

Studies have suggested that administration of an α-adrenergic blocker, such as tamsulosin, at the time of catheter insertion improves the likelihood of spontaneous voiding after catheter removal and may also improve the likelihood that a patient will not require ongoing catheter placement. These medications are associated with an increased risk of orthostatic hypotension, particularly in older adults, so initiation of treatment should be coordinated with the patient's primary care physician. 5-Alpha-reductase inhibitors, another agent typically used for BPH, have not been shown to reduce the recurrence of AUR.

Prophylactic antibiotic therapy is not recommended for patients with AUR. Although bacteriuria often develops in patients with indwelling catheters, it typically is not clinically significant, and the use of prophylactic antibiotics only promotes resistance.

Definitive therapy often requires surgical correction of any underlying obstruction. This should not be performed emergently because early surgery is associated with increased morbidity.

Disposition

After bladder drainage, healthy and reliable patients can be safely discharged from the ED with an indwelling catheter and urology follow-up. Patients with concomitant infection, significant comorbid illnesses, impaired renal function, neurologic deficits, or complications from catheterization require further diagnosis and treatment and probably admission.

HEMATURIA

Blood in the urine can be microscopic or gross. Although generally associated with a benign process, it can reflect serious underlying pathology, such as a urothelial malignancy. Therefore, following ED assessment, patients with hematuria require outpatient follow-up. Less commonly, patients come to the ED complaining of gross blood in their urine. Compared to microscopic hematuria, gross blood in the urine is more likely to be a presenting symptom of an underlying malignancy. Regardless of age or visibility of blood in the urine, patients with hematuria require evaluation in the ED to rule out life-threatening diagnoses, such as malignancy and AAA.

Gross and microscopic hematuria can arise from anywhere along or near the urinary tract. In the upper and lower portions of the urinary tract, infection, trauma, and renal calculi are the most common causative disorders. Patients also can have more serious causes of hematuria, such as malignancy or vascular lesions (eg, AAA), and these diagnoses should be excluded. Up to 5% of patients with asymptomatic microscopic hematuria and up to 30% to 40% of patients with gross hematuria are found to have a urinary tract malignancy. The risk of urologic malignancy is increased in patients older than 35 years, male gender, and those with a history of smoking.

Occasionally, hematuria also has been attributed to warfarin use, BPH, and exercise. Supratherapeutic anticoagulant therapy can lead to blood in the urine, but therapeutic anticoagulation does not typically produce spontaneous hematuria. Similarly, BPH can lead to increased vascularity of the prostate but does not increase the risk of hematuria. High-intensity exercise also can produce hematuria. This bleeding typically is transient and clinically inconsequential. Because warfarin use, BPH, and exercise do not directly cause persistent hematuria, patients with ongoing bleeding require further urologic evaluation.

Clinical Features

A careful history will often identify a benign cause for hematuria, such as menstruation, recent heavy exercise, recent urologic procedure, sexual activity, and the use of agents that can produce red urine without blood (Box 89.7). Repeated episodes of bleeding during and after menstruation in women suggest endometriosis of the urinary tract. Patients may report frequency, urgency, and dysuria in the setting of infection. They may note flank pain with urolithiasis or pyelonephritis. Microscopic hematuria in the setting of a UTI should resolve after appropriate antibiotic treatment.

BOX 89.7

Causes of Red-Colored Urine Without Hematuria

Phenazopyridine
Nitrofurantoin
Rifampin
Chloroquine
Hydroxychloroquine
Iodine
Bromide
Food coloring
Beets
Berries
Rhubarb

The physical examination may point toward the underlying cause. For example, hypertension occurs with glomerulosclerosis and, in the setting of peripheral edema, suggests nephrotic syndrome. An abdominal bruit may be caused by an arteriovenous fistula, whereas a palpable abdominal mass may represent an AAA. Flank pain and tenderness can arise with pyelonephritis or nephrolithiasis. The external genital examination can show evidence of trauma or a tumor and may reveal a rectal or vaginal source for the bleeding. A pelvic examination should be performed in women to identify a vaginal or uterine source of bleeding.

Diagnostic Testing

Microscopic hematuria is defined as the presence of three or more RBCs/high-power field (hpf) of urinary sediment. A clean-catch or catheterized urine specimen should be obtained in all patients with hematuria. Catheterization itself induces hematuria in approximately 15% of patients, but the amount of bleeding is inconsequential, rarely exceeding three RBCs/hpf. Bedside urine dipstick testing of this urine should be performed. A negative urine dipstick rules out the presence of hematuria and obviates the need for urine microscopy. If positive for blood, urine microscopy should be performed.

As little as 1 mL of whole blood in 1 L of urine can produce gross hematuria, turning the urine red. A number of other substances and reactions can turn the urine red, and centrifugation of the urine and microscopic analysis differentiate these false-positive results from true hematuria. After centrifugation, the red color persists only in the urine sediment with hematuria. By contrast, a red supernatant that contains no RBCs on microscopic analysis typically represents a benign condition (see Box 89.7).

Microscopy will reveal WBCs in addition to RBCs in the presence of infection. Proteinuria, cellular casts, and dysmorphic red blood cells are seen with glomerular disease. Patients with these findings may also have cola-colored urine and should be referred to a nephrologist.

Management and Disposition

The combination of a careful history, physical examination, and laboratory studies should identify benign causes of microhematuria such as infection, menstruation, vigorous exercise, and trauma. According to the AUA Guideline on Asymptomatic Microhematuria, once benign causes have been ruled out, a prompt outpatient urologic evaluation should occur.[38] This evaluation generally consists of an assessment of renal function (BUN and creatinine levels, calculated GFR) and multiphasic CT urography, including sufficient phases to evaluate the renal parenchyma and urothelium of the upper tracts.

CT urography identifies hydronephrosis, urinary calculi, and renal and ureteral lesions. For patients with contraindications to contrasted CT, MR urography is an acceptable alternative imaging approach. Finally, the guidelines recommend that cystoscopy be performed on all patients aged 35 years or older or those with risk factors for urinary tract malignancy, such as tobacco use, exposure to carcinogenic chemicals (eg, aniline dye, benzidine, petroleum products), or history of chronic UTIs. Risk factors for urinary tract malignancy in patients with microscopic hematuria are listed in Box 89.8. For persistent microhematuria following a negative evaluation, yearly urinalyses are recommended, with consideration for a repeat urologic examination every 3 to 5 years.

By contrast, patients with gross hematuria require a thorough evaluation before discharge from the ED. Renal function should be assessed to rule out the development of renal insufficiency. The patient should also undergo appropriate imaging tests, although clear consensus is lacking on the appropriate radiographic study.

BOX 89.8

Risk Factors for Urinary Tract Malignancy

Age > 35 yr
Past or current cigarette smoking
Occupational exposure (chemicals or dyes)
Analgesic abuse
Chronic indwelling foreign body
Chronic urinary tract infection
Exposure to known carcinogenic or chemotherapeutic agent
Gross hematuria
Irritative voiding symptoms
Pelvic irradiation
Urologic disorder or disease

If the initial assessment fails to identify a benign cause for the hematuria, a CT scan with contrast or renal ultrasound study should be performed. CT scanning is highly sensitive for stones, masses, and other diseases of the upper urinary tract. If contrast CT must be avoided owing to pregnancy, renal insufficiency, or history of anaphylaxis to contrast medium, ultrasound imaging is the modality of choice. Ultrasound is less sensitive than a CT scan for detecting stones, small masses, and traumatic causes of hematuria.

CT is the appropriate imaging modality for traumatic hematuria because its sensitivity and specificity exceed those of ultrasound. The exact level of hematuria that should trigger imaging is unclear, but it appears that patients without gross hematuria or evidence of coexisting abdominal or pelvic injuries are unlikely to have clinically significant injuries on CT (see Chapter 40).

KEY CONCEPTS

- Urinary obstruction should be ruled out in patients with a urinary tract infection (UTI) and those in septic shock.
- Acute, uncomplicated urinary tract infections should be treated with fosfomycin, nitrofurantoin, or trimethoprim-sulfamethoxazole.
- Fluoroquinolones are not recommended as first-line therapy for uncomplicated UTI.
- The three primary predictors of stone passage without the need for surgical intervention are calculus size, location, and degree of patient pain. The most important factor that relates to passage of a calculus though the genitourinary tract is its size (stone <5 mm has a 90% chance of passing spontaneously in 4 weeks).
- Imaging is not needed in all patients with renal colic. If the signs and symptoms are atypical, the diagnosis is in question, the patient has a solitary or transplanted kidney, or appears toxic, or high-grade obstruction is suspected, imaging should be performed.
- Acute scrotal pain should be considered a result of testicular torsion until proven otherwise.
- There is no single history or physical examination finding that accurately or reliably differentiates torsion from other causative disorders. Any patient with acute onset of scrotal pain in whom the diagnosis of torsion cannot be ruled out should undergo further diagnostic testing.
- Rapid diagnosis of testicular torsion is essential and should be followed by emergent surgical scrotal exploration and bilateral orchiopexy, if necessary. Loss of the testicle usually is a result of delay in seeking medical attention.
- Scrotal pain or swelling after trauma warrants a scrotal ultrasound to evaluate for testicular rupture or torsion.
- Sexually active males should receive ceftriaxone and doxycycline to treat epididymitis. Patients in whom enteric organisms are likely the cause of epididymitis should receive fluoroquinolones. Most cases of pediatric epididymitis are idiopathic, and antibiotics are not routinely recommended.
- Acute urinary retention (AUR) is usually caused by an obstructive lesion but also can be the presenting manifestation of other pathologic processes.
- Patients with AUR and concomitant infection, pelvic mass, or neurologic deficits warrant imaging in the ED.
- Patients with AUR should have complete drainage of the bladder performed via catheterization or, if this is not possible, by suprapubic aspiration. To improve the likelihood of future spontaneous voiding in men, an α-adrenergic blocker such as tamsulosin should be given at the time of insertion.
- Most cases of microscopic hematuria are transient and idiopathic, but also can arise with infection, trauma, and exercise.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 89: QUESTIONS & ANSWERS

89.1. Which of the following drugs is not an appropriate first-line choice for treatment of an uncomplicated urinary tract infection (UTI) in women?

A. All of these
B. Ciprofloxacin
C. Fosfomycin
D. Nitrofurantoin
E. Trimethoprim-sulfamethoxazole

Answer: B. According to the Infectious Disease Society of America (IDSA) practice guidelines, fluoroquinolones should not be used as first-line agents for uncomplicated UTI because of increased resistance.

89.2. Which of the following clinical scenarios is not an indication for emergent imaging of the genitourinary tract?

A. 3-year-old girl with first episode of urinary tract infection (UTI)
B. 31-year-old woman with clinical pyelonephritis and normal urinalysis (UA)
C. 34-year-old man with classic renal colic
D. Pyelonephritis and fever more than 72 hours after antibiotic initiation
E. UTI in the patient with diminishing renal function

Answer: C. Other indications for imaging include a patient with renal colic and suspicion of obstruction and a female patient with multiple complex infections.

89.3. Which of the following antibiotics should be avoided during the first trimester of pregnancy?

A. All of these
B. Ciprofloxacin
C. Levofloxacin
D. Nitrofurantoin
E. Trimethoprim-sulfamethoxazole

Answer: A. Nitrofurantoin is associated with fetal malformations when used in the first trimester. Trimethoprim-sulfamethoxazole is associated with teratogenicity. In general, fluoroquinolones should not be used during pregnancy due to developmental toxicity risks.

89.4. All of the following are acceptable antibiotic choices for the treatment of pyelonephritis accept?
A. Ceftriaxone
B. Ciprofloxacin
C. Levofloxacin
D. Nitrofurantoin
E. Trimethoprim-sulfamethoxazole

Answer: D. Nitrofurantoin does not achieve therapeutic levels in the renal parenchyma and is therefore not effective for pyelonephritis.

89.5. Which of the following differentiates testicular torsion from other causes of a painful scrotum?
A. Blunt trauma to the testicle
B. Pyuria on urinalysis
C. Nighttime presentation
D. None of the above

Answer: D. There is no single history or physical examination finding that accurately or reliably differentiates torsion from other causative disorders. Any patient with acute onset of scrotal pain in whom the diagnosis of torsion cannot be ruled out should undergo further diagnostic testing.

89.6. A testis will tend to rotate laterally to medially in most cases of torsion. To detorse in these situations, you should rotate the testis medially to laterally. If this does not produce immediate relief, you should do which of the following?
A. Assume that the testicle is already necrotic and not amenable to further reduction attempts.
B. Attempt untwisting past 360 degrees because a higher degree of rotation may be present.
C. Both A and B.
D. Reverse the direction of reduction.

Answer: D. Most testes torse laterally to medially, but some may torse medially to laterally. If no immediate relief is obtained by rotating medially to laterally, reverse the direction of the reduction attempt.

89.7. Computed tomography should be undertaken in the patient suspected of having renal colic if which of the following is present?
A. The patient has a solitary or transplanted kidney.
B. The patient has gross hematuria.
C. The patient has had a prior history of nephrolithiasis.
D. The patient presents in severe pain.

Answer: A. Imaging is appropriate for patients who have a history of nephrolithiasis who do not improve with treatment, have a urinalysis showing infection, have a solitary or transplanted kidney, or for whom a diagnosis other than renal colic is suspected.

89.8. What is the most common cause of acute urinary retention seen in the ED?
A. Infection, inflammation
B. Obstruction
C. Medications
D. Neurogenic disorder

Answer: B. Obstruction. The most common cause of AUR seen in the ED is obstruction of the urinary tract distal to the bladder (primarily benign prostatic hypertrophy).

89.9. Acute bacterial prostatitis is diagnosed by which of the following?
A. History and examination
B. Serum studies
C. Transrectal ultrasound or CT
D. Urine gram staining and culture
E. Urethral swab

Answer: A. Acute bacterial prostatitis can be diagnosed clinically; urine gram staining and culture are recommended to guide treatment.

CHAPTER 90

Selected Gynecologic Disorders

Trevor R. Pour | Carrie D. Tibbles

Many women come to the emergency department (ED) with pelvic pain or vaginal bleeding. After the possibility of pregnancy-related problems has been eliminated, the primary goal is to recognize the presence of conditions that warrant urgent intervention, such as adnexal torsion, versus those that can be managed as an outpatient, such as new postmenopausal uterine bleeding. Most patients also benefit from relief of symptoms and reassurance. This chapter specifically addresses the ED management of adnexal torsion, ovarian cysts, abnormal uterine bleeding, and the provision of emergency contraception. The general approach to vaginal bleeding is discussed in Chapter 31, complications of pregnancy are discussed in Chapter 178, and sexually transmitted disease is discussed in Chapter 88.

OVARIAN TORSION

Principles

Adnexal torsion accounts for approximately 3% of gynecologic emergencies and refers to the twisting of the ovary and fallopian tube on the axis between the utero-ovarian and infundibulopelvic ligaments.[1] Commonly, both structures are implicated in this process. However, isolated ovarian torsion and, more rarely, isolated fallopian tube torsion may occur.[2] In ovarian torsion, venous and lymphatic obstruction occurs initially, with subsequent congestion and edema of the ovary, progressing to ischemia and necrosis.[3]

In addition to loss of tubal or ovarian function, torsion left untreated can progress further to hemorrhage, peritonitis, and infection. Because of the dual blood supply of the ovary from the uterine and ovarian arteries, complete arterial obstruction is rare. (Fig. 90.1). Ovarian torsion can occur at any age, but is most common in the reproductive years because of the regular development of a corpus luteal cyst during the menstrual cycle. Most cases of torsion in this population are associated with an enlarged ovary (>5.0 cm), either secondary to benign neoplasm or cysts, as seen in ovulation induction, hyperstimulation syndrome, or polycystic ovarian syndrome. In premenarchal patients, however, torsion frequently occurs despite normal ovarian size, thought to be secondary to the excessive mobility of the adnexa relative to older patients.[4] Masses prone to creating adhesions, such as malignant tumors, endometriomas, or tubo-ovarian abscesses, are less likely to develop torsion than benign lesions. Torsion may be a complication of pregnancy, more likely to occur in the first and early second trimesters.[5] A history of tubal ligation is a risk factor for ovarian torsion.[6] A slight predominance of torsion on the right side has been noted, likely related to the stabilizing effect of the fixed sigmoid colon on the left.

Clinical Features

The classic symptoms of ovarian torsion are severe, sharp, unilateral lower abdominal pain and nausea; however, some or all of these symptoms are often absent. Despite advances in imaging modalities, the preoperative diagnosis rate only approaches 40%, making clinical assessment more valuable. The presence of known risk factors, such as an ovarian mass or recent infertility treatments, may suggest the diagnosis in postmenarchal patients.

Patients typically report pain lasting from several hours to days. Rarely, patients report pain for weeks to months in duration, most likely due to intermittent torsion.[7] Nausea and vomiting are present in about 70% of cases.

Most patients will have unilateral tenderness on abdominal palpation, but up to 75% of patients will not have a palpable adnexal mass.[8] Clinical decision tools for ovarian torsion have been developed but suffer from poor sensitivity and therefore cannot be recommended.[9] Clinical signs of isolated tubal torsion are indistinguishable from those of ovarian torsion.

Differential Diagnosis

Considerations in the differential diagnosis include other causes of acute lower abdominal pain, such as appendicitis, ruptured ovarian cyst, urinary tract infection, nephrolithiasis, pelvic inflammatory disease, uterine leiomyoma, diverticulitis, bowel obstruction, and ectopic pregnancy. A pregnancy test, physical examination, and imaging with ultrasound or computed tomography (CT), if necessary, can usually distinguish among these possibilities.

Diagnostic Testing

Laboratory Tests

No specific laboratory tests are routinely used in the diagnosis of suspected torsion. Two small studies on serum interleukin-6, a proinflammatory cytokine, have revealed a pooled sensitivity of 85% and specificity of 84% for torsion and may evolve into a useful serum marker if reproduced by larger trials.[10] A negative pregnancy test may exclude ectopic pregnancy from the differential, but a positive test does not rule out adnexal torsion. Leukocytosis is not a reliable indicator of torsion.

Imaging

Ultrasonography. An ultrasound examination is the initial imaging test in the evaluation of patients with pelvic pain suggestive of ovarian torsion, but findings can vary depending on timing and duration of symptoms. Asymmetric enlargement of the ovary is the most common finding. Enlargement of an ovary with a heterogeneous stroma secondary to edema along with small, peripherally displaced follicles is the classic ultrasound appearance of torsion but is often absent, particularly with long-standing ischemia.[11] Ultrasound may reveal a mass in the ovary, evidence of hemorrhage, or free pelvic fluid (Fig. 90.2). Hemorrhagic cysts and other nonneoplastic masses frequently are associated with torsion; these may appear fluid-filled, exhibit a complex pattern with debris and septations, or be visualized as a solid mass. The characteristic appearance of torsion may be difficult to appreciate if the ovary is obscured by an associated mass. In isolated tubal

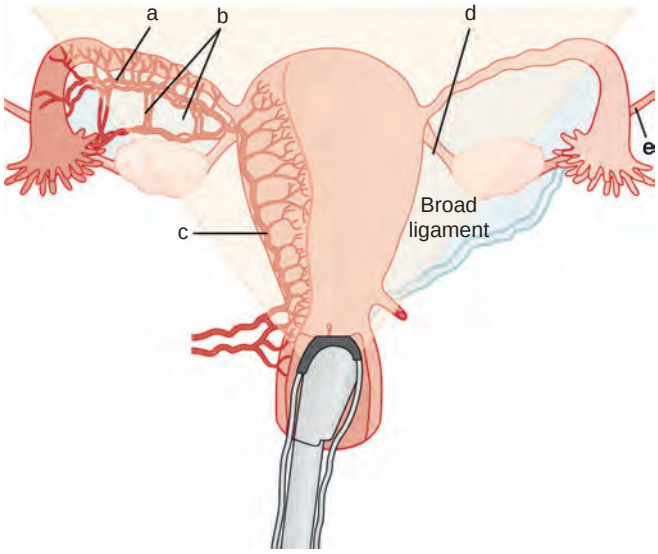


Fig. 90.1. Ovarian blood supply. **a,** Ovarian artery and vein. **b,** Branching arterioles supplying ovary. **c,** Utero-ovarian ligament. **d,** Utero-ovarian ligament. **e,** Infundibulopelvic ligament. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

Fig. 90.2. Ovarian torsion with a large pelvic mass. This transabdominal image reveals a largely homogeneous 22.8-cm pelvic mass. (From Cicchiello LA, Hamper UM, Scoutt LM: Ultrasound evaluation of gynecologic causes of pelvic pain. Obstet Gynecol Clin North Am 38:85–114, 2011.)

torsion, tubal lesions such as hydrosalpinx or a tubo-ovarian abscess may be seen.

Doppler ultrasound findings are inconsistent for diagnosing ovarian torsion. Up to 60% of surgically proven torsion will have documented blood flow on Doppler examination (Fig. 90.3).[3] Findings may vary depending on the time of the examination because torsion may occur intermittently, and clinical symptoms may precede arterial compromise. If a large mass is present, the examination may also be technically difficult to perform. Despite these limitations, the Doppler examination is still useful, and detection of abnormal venous flow is particularly important in early cases of torsion (Fig. 90.4). Absence of arterial flow is highly specific for torsion, with a positive predictive value of 94% to 100%.[3] Visualization of the twisting of the pedicle and coiled vessels is referred to as a whirlpool sign and has a 90% positive predictive value for torsion.[12]

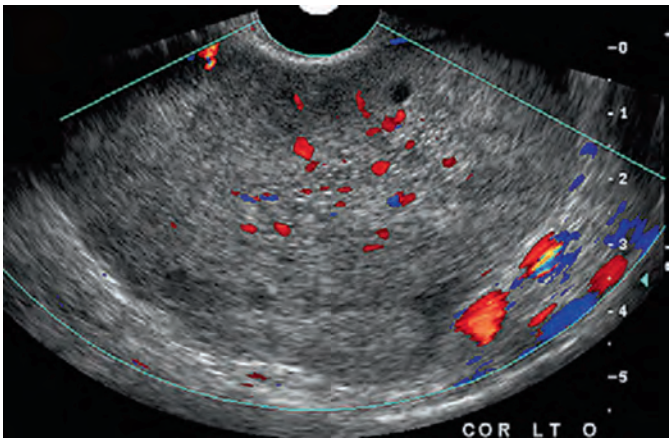


Fig. 90.3. Ovarian torsion with color Doppler image demonstrating venous and arterial flow. (From Cicchiello LA, Hamper UM, Scoutt LM. Ultrasound evaluation of gynecologic causes of pelvic pain. Obstet Gynecol Clin North Am 38:85–114, 2011.)

Computed Tomography. When alternative abdominal pathologies are strong considerations in the differential diagnosis for acute pelvic pain, abdominopelvic CT may be the best initial study, particularly in patients who have a presentation atypical for torsion. In ovarian torsion, CT findings include asymmetric ovarian enlargement or asymmetric adnexal enhancement following IV contrast, fallopian tube thickening, or twisted vascular pedicle, fat stranding surrounding the affected adnexa, and uterine deviation to the twisted side.[3] Pelvic free fluid in patients with a hemorrhagic infarction can be seen. A retrospective review of CT scans of patients with confirmed torsion has found that every CT scan had evidence of an ovarian abnormality, including enlargement or the presence of a mass, suggesting that torsion is unlikely if the CT visualized a normal ovary; another, more recent case-controlled study comparing pelvic ultrasound to CT has confirmed these findings.[13] Therefore, negative imaging findings should be interpreted with caution when clinical suspicion is high but, with lower suspicion, a normal-appearing ovary on the CT scan can be reassuring.

Magnetic Resonance Imaging. Magnetic resonance imaging (MRI) may demonstrate findings consistent with torsion. It is particularly helpful if the diagnosis is not clear, such as with intermittent pain over days, or for pregnant patients when the history is highly suggestive but ultrasound findings are inconclusive or equivocal. Findings on MRI suggestive of torsion are similar to those on CT (Box 90.1).

Laparoscopy. A diagnostic laparoscopy is the gold standard investigative modality in patients in whom clinical suspicion is high, despite negative imaging results. In one study of 100 nonpregnant patients with an acute abdomen, only 29 of the 66 laparoscopically proven cases of ovarian torsion were diagnosed preoperatively.[14] Laparoscopy also allowed diagnosis of other unsuspected conditions, including ovarian cysts, appendicitis, and pelvic inflammatory disease.

Management and Disposition

Once the diagnosis of ovarian torsion has been made, the patient should be taken to the operating room as soon as possible. The ovary often will recover, even if black or dusky in appearance at the time of surgery, because of its dual blood supply, so attempts at ovarian salvage are warranted, even if the diagnosis is made late. This is particularly true in adolescent patients. Ovarian function returns in most patients.

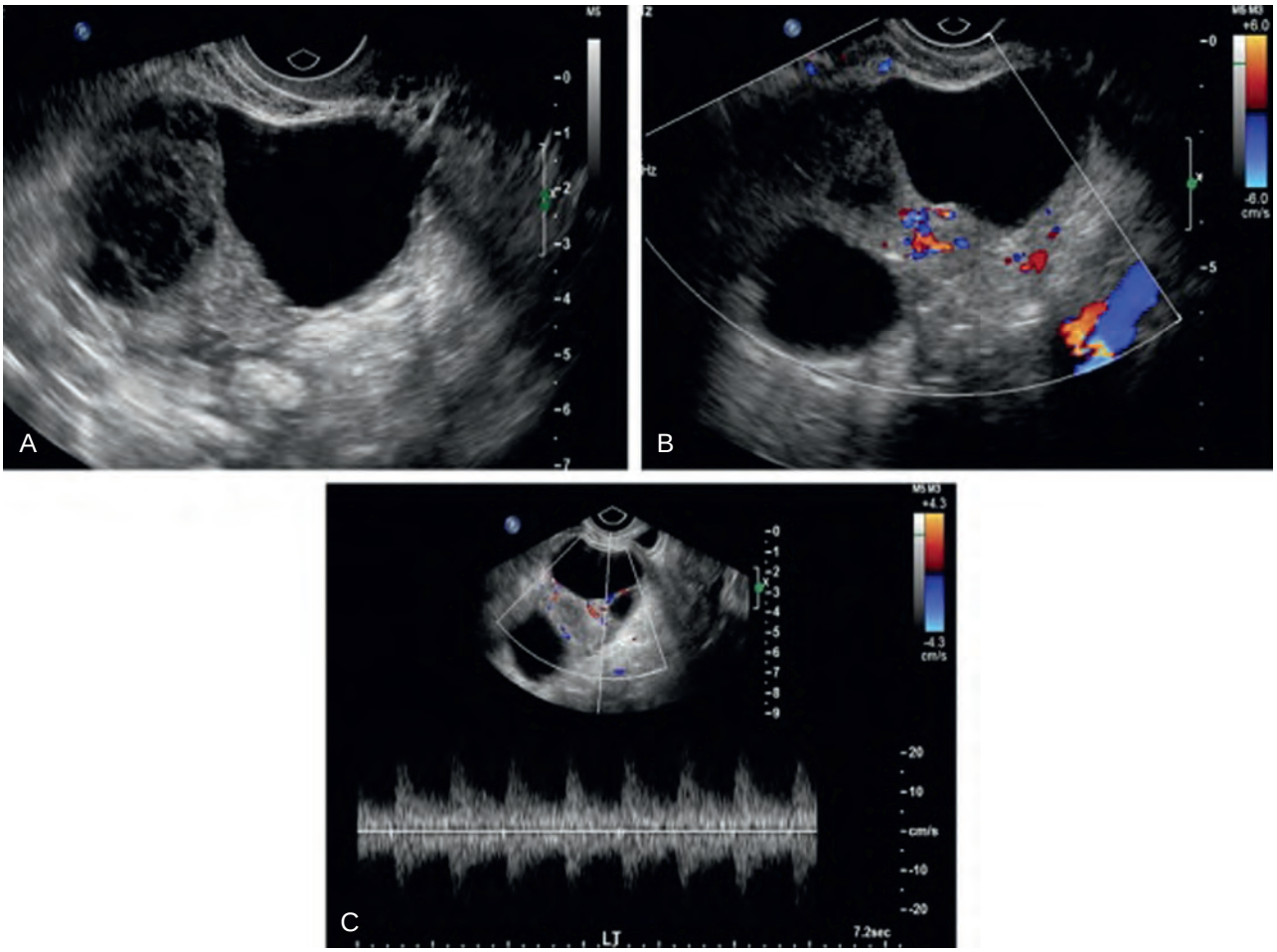


Fig. 90.4. Arterial Doppler signal without venous signal in a patient with surgically proven torsion. The ultrasound examination also demonstrated an associated hemorrhagic cyst. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

BOX 90.1

Imaging Characteristics of Adnexal Torsion

ULTRASONOGRAPHY

Enlargement of the ovary
Associated ovarian mass
Loss of enhancement
Edema
Free pelvic fluid
Loss of venous waveforms
Loss of arterial waveforms

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Enlargement of the ovary
Associated ovarian mass
Thickening of the fallopian tube
Free pelvic fluid
Edema of the ovary
Deviation of the uterus to the affected side
Associated hemorrhage

OVARIAN CYSTS AND MASSES

Principles

Cysts are the most common cause of gynecologic masses. They occur at any stage of life but are most frequent in the reproductive years because of the cyclic changes of the ovary associated with menstruation (Fig. 90.5). Most ovarian cysts in premenopausal and postmenopausal women are benign and resolve with no intervention, but on occasion they may be malignant or associated with complications such as hemorrhage or torsion.[15,16] Benign cysts are less common in premenarchal girls, however, with an incidence of malignancy as high as 25% when an adnexal mass is found.[17]

The most common type of cyst is a simple follicular, or functional cyst, developing from a follicle that fails to rupture or regress, and is defined as pathologic when the diameter exceeds 3.0 cm. Follicular cysts are typically thin-walled and filled with clear fluid, whereas a corpus luteal cyst is often filled with hemorrhagic fluid. Several other types of cystic masses can occur in the ovary, including endometriomas (chocolate cysts), nonneoplastic lesions such as benign cystic teratoma (dermoid cyst), fibroma, cystadenoma, and various types of malignant neoplasms.[18]

Clinical Features

The most common presentation for patients with an ovarian cyst is pelvic pain. Rupture of a follicular cyst may produce transient

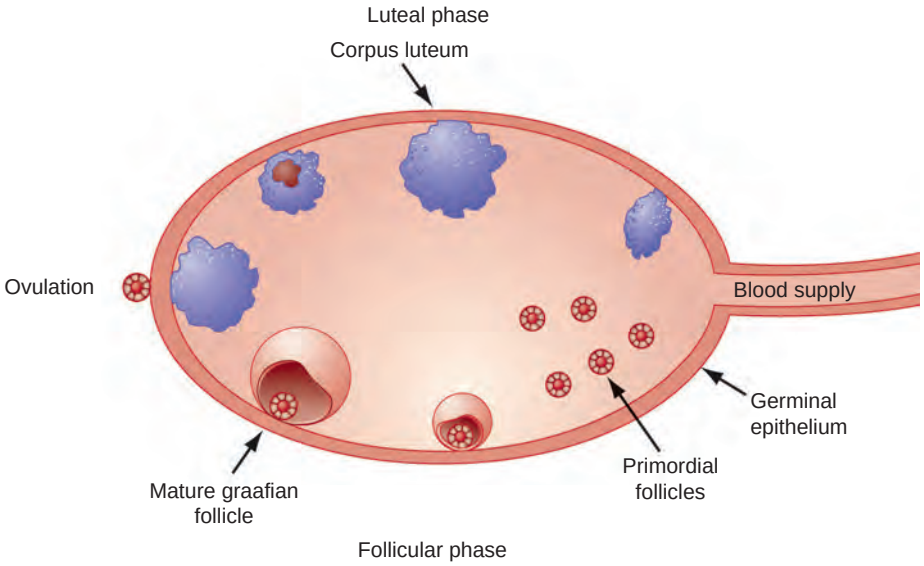


Fig. 90.5. Ovarian function during the normal menstrual cycle. (From Lambert MJ, Villa M: Gynecologic ultrasound in emergency medicine. Emerg Med Clin North Am 22:683–696, 2004.)

pelvic pain, be associated with dyspareunia, or be asymptomatic. Because of its thin fragile wall, a follicular cyst may rupture during sexual intercourse or during the pelvic examination. Follicular cysts are rarely associated with hemorrhage.

Presentation of a corpus luteal cyst may range from an asymptomatic mass to dull, chronic pelvic pain to severe pain associated with rupture. Rupture of a corpus luteal cyst is frequently associated with a significant degree of hemorrhage. As with a follicular cyst, rupture may follow a pelvic examination, sexual intercourse, exercise, or trauma. Rupture of a large or complex cyst may result in severe pain and peritoneal signs. Occasionally, a large cyst may be discovered on a routine pelvic examination as an asymptomatic mass, but this is uncommon.

Differential Diagnosis

Diagnostic considerations in the patient with ovarian cysts and masses include other causes of pelvic pain that require urgent intervention, such as ectopic pregnancy, pelvic inflammatory disease, urinary tract infections, nephrolithiasis, appendicitis, and diverticulitis. Tumors or abscesses of the gastrointestinal tract may also mimic adnexal masses.

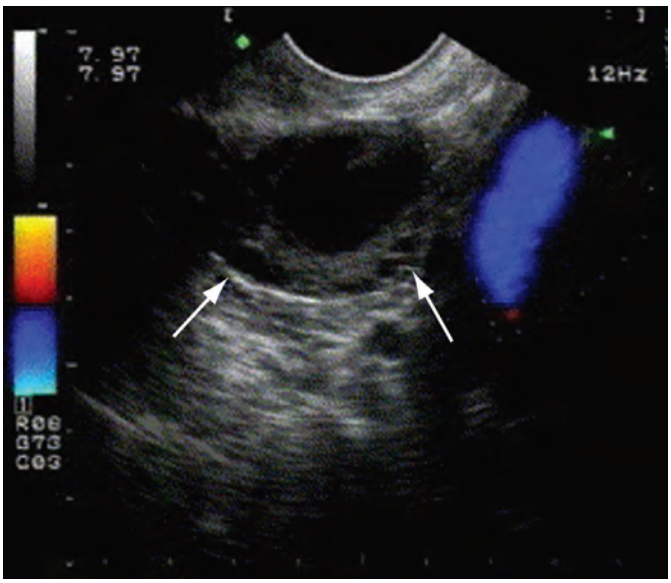


Fig. 90.6. Endovaginal ultrasound image of a normal ovary with a dominant follicle *(arrows).* (From Lambert MJ, Villa M: Gynecologic ultrasound in emergency medicine. Emerg Med Clin North Am 22: 683–696, 2004.)

Diagnostic Testing

Laboratory Tests

The initial step in the evaluation of pelvic pain or a pelvic mass is to exclude pregnancy with a urine or serum β-human chorionic gonadotropin (β-hCG) test. A hematocrit may be valuable in the unstable patient as a marker of blood loss. The serum antigen CA-125 is elevated in 80% of women with epithelial ovarian cancer but can also be elevated by nonmalignant conditions such as endometriosis, pregnancy, and pelvic inflammatory disorder, limiting its usefulness in the emergency setting.[19]

Imaging

Ultrasonography. Ultrasonography is the standard initial imaging modality used to diagnose and characterize all ovarian pathologic processes and lesions, including cysts and masses. Approximately 90% of adnexal masses are adequately characterized by ultrasound imaging alone.[20] Transabdominal and endovaginal examinations provide useful information. The transabdominal approach should be performed with a full bladder as a sonographic window. It permits an overall view of the pelvis and will visualize large masses and pelvic free fluid. Use of the endovaginal probe, which should be performed with an empty bladder to reduce artifact, provides a detailed picture of the ovary. Follicles are part of the normal architecture of the ovary and are typically smaller than 1.0 cm in diameter, whereas the dominant follicle may measure up to 2.5 cm at the time of ovulation. Depending on the timing of the scan and degree of clot formation and lysis, hemorrhage may be seen. Fig. 90.6 demonstrates a normal ovary with a dominant follicle, Fig. 90.7 demonstrates a large cyst, and Fig. 90.8 demonstrates hemorrhage and free pelvic fluid. Ultrasound findings suggestive of malignancy include internal

septations, solid elements within cystic structures, a thickened wall, and large amounts of ascites or free fluid.

Computed Tomography. When the differential diagnosis of unilateral pelvic pain is broad, particularly in the patient with symptoms or physical findings not solely confined to the pelvis, a CT scan may be a more appropriate initial imaging study. It is not recommended as the first-line imaging study if an adnexal mass is of primary concern due to poor soft tissue discrimination.[21] Once the diagnosis of malignancy has been made, however, ultrasound is insensitive for staging or follow-up imaging, and contrast-enhanced CT is indicated at that time. A CT scan can detect a cyst and associated complications, including torsion, as noted earlier. CT findings suggestive of malignancy are a cystic solid mass, necrosis in a solid lesion, complex or cystic lesion with thick, irregular walls, and the presence of ascites, peritoneal metastases, and lymphadenopathy.

Magnetic Resonance Imaging. MRI provides better soft tissue contrast as compared with CT and has been shown in multiple studies to differentiate benign from malignant adnexal masses better as compared with ultrasound. It is limited by availability, cost, and duration of examination. MRI should be considered for pregnant patients or those with equivocal findings on ultrasound or CT.

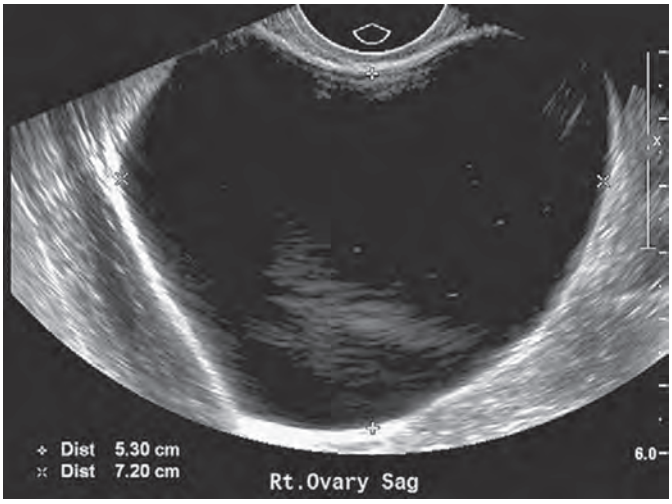


Fig. 90.7. Endovaginal ultrasound image of a follicular cyst, with smooth wall and posterior wall enhancement. (From Cicchiello LA, Hamper UM, Scoutt LM: Ultrasound evaluation of gynecologic causes of pelvic pain. Obstet Gynecol Clin North Am. 38:85–114, 2011.)

Management and Disposition

Patients with a simple cyst and improvement in symptoms may be safely discharged with referral for outpatient gynecologic follow-up to ensure resolution of the cyst. Most uncomplicated simple cysts will resolve without further intervention. Pain should be controlled with nonsteroidal antiinflammatory drugs (NSAIDs) as a first-line approach and with oral opioids reserved only for severe cases. Oral contraceptives are not recommended for the routine management of ovarian cysts; despite being theorized to accelerate the regression of ovarian cysts, multiple randomized controlled trials have shown no difference in cyst resolution when compared to expectant management.[22]

A complex cyst concerning for malignancy requires more urgent gynecologic intervention. Such patients may benefit from gynecologic consultation in the ED, particularly if reliable follow-up is unlikely or if the patient is particularly symptomatic.

ABNORMAL UTERINE BLEEDING IN THE NONPREGNANT PATIENT

Principles

An understanding of the normal menstrual cycle is needed to understand the potential causes of abnormal uterine bleeding (Fig 90.9). The menstrual cycle starts on the first day of menses. During the first part of the menstrual cycle, the endometrium thickens under the influence of estrogen, and a dominant follicle develops in the ovary, releasing an ovum at the midpoint of the cycle. After ovulation, the luteal phase begins and is characterized by the production of progesterone from the corpus luteum. Progesterone matures the lining of the uterus and, if implantation does not occur, the corpus luteum dies, accompanied by sharp drops in progesterone and estrogen levels. These changes typically are followed by menstruation. Menstrual bleeding is usually predictable, cyclic, and results from withdrawal of the effects of hormones on the endometrium, which occurs approximately 14 days after ovulation.

A revised system of terminology, PALM-COEIN, regarding abnormal uterine bleeding (AUB) was created in 2011 by the International Federation of Gynecology and Obstetrics (FIGO) to

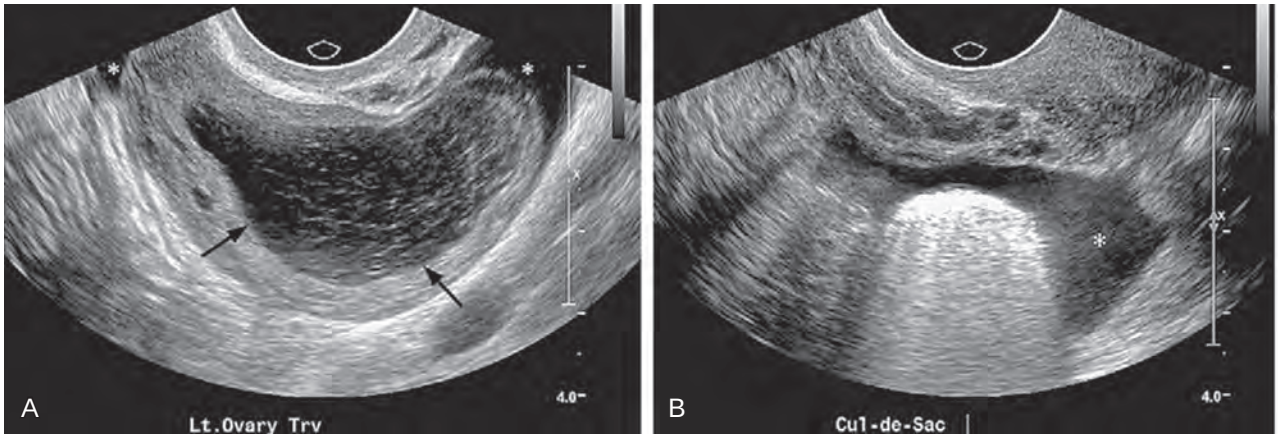
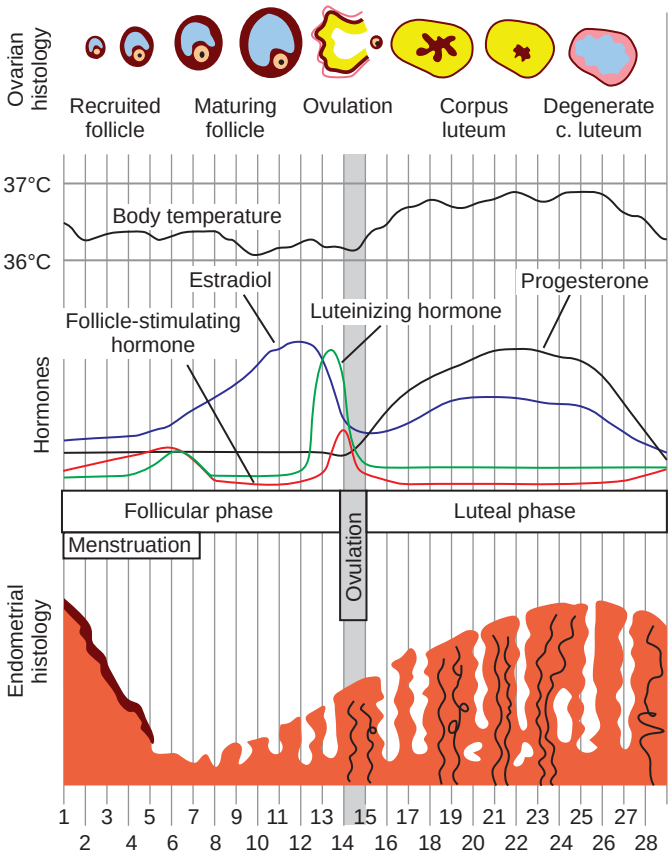


Fig. 90.8. Endovaginal ultrasound image of a hemorrhagic ovarian cyst with free fluid (*). (From Cicchiello LA, Hamper UM, Scoutt LM: Ultrasound evaluation of gynecologic causes of pelvic pain. Obstet Gynecol Clin North Am. 38:85–114, 2011.)



(Average values. Durations and values may differ between different females or different cycles.)

Fig. 90.9. Normal menstrual cycle.

standardize language and facilitate multiinstitutional investigation (Box 90.2).[23] The first four letters. PALM, represent structural causes for AUB—***p***olyp, ***a***denomyosis, ***l***eiomyoma, and ***m***alignancy or hyperplasia, whereas the last five letters, COEIN, represent nonstructural causes—***c***oagulopathy, ***o***vulatory dysfunction, ***e***ndometrial, ***i***atrogenic, and ***n***ot yet classified. The term *dysfunctional uterine bleeding* is no longer used.[24]

Disruption of the hypothalamic-pituitary-ovarian axis from a variety of causes can result in bleeding related to ovulatory dysfunction (AUB-O). Returning the balance of estrogen and progesterone with oral contraceptives will help many patients regulate the cycle, with reduction in or cessation of abnormal uterine bleeding.[25]

Clinical Features

History

A large number of conditions cause abnormal uterine bleeding, and a systematic history and physical examination can help narrow the possibilities. Vaginal bleeding before the age of menarche is abnormal and may be the result of infection, trauma, such as sexual abuse or a foreign body, or a structural lesion.[26] In a woman of reproductive age, abnormal uterine bleeding includes a change in the frequency, duration or amount of bleeding, or bleeding between menstrual cycles. In the postmenopausal woman, any bleeding 12 months after the cessation of menses or unpredictable bleeding during hormone therapy is abnormal. The amount and frequency of bleeding and the duration of symptoms, as well as the relationship to the menstrual cycle, should be established. A menstrual cycle shorter than 21 days in duration or more than 35 days apart, or flow for less than 2 or more than 7 days, is classified as abnormal. A pattern of irregular bleeding between cycles or an abrupt change in the previous pattern of bleeding should also be determined.

Systemic conditions, such as liver or thyroid disease, may be associated with abnormal uterine bleeding. Endometrial cancer is associated with underlying diabetes mellitus, metabolic syndrome and obesity, anovulatory cycles, nulliparity, and age older than 55 years. Cervical dysplasia or other genital tract pathology may cause postcoital or irregular bleeding, and patients should be questioned on risk factors for sexually transmitted infections.

Prior history of cesarean section may contribute to iatrogenic AUB; studies have found that irregular scarring postoperatively leads to a higher prevalence of vaginal spotting.[27] Disruption along the hypothalamus-pituitary-ovarian pathway leading to anovulation is frequently the cause of AUB. Disruption of this pathway may be physiologic, such as during adolescence, perimenopause, or lactation. Pathologic causes include polycystic ovary syndrome (PCOS), hypothalamic dysfunction seen in anorexia nervosa, hyperprolactinemia, and primary pituitary disease.

Patients should be questioned about excessive bleeding or bruising or any family history of bleeding disorders because up to 20% of women presenting with heavy menstrual bleeding will have an underlying coagulopathy.[28] Von Willebrand disease is the most common of these, seen in up to 13% of cases of AUB, and often first presents with heavy uterine bleeding since menarche.[29]

Physical Examination

With prolonged heavy bleeding, signs of chronic anemia may be noted on the physical examination. PCOS is a common cause of abnormal uterine bleeding, and physical findings suggestive of such include obesity, acne, hirsutism, and acanthosis nigricans. Other causes of bleeding include vaginal or cervical lesions, which may be visible on the speculum examination. A leiomyoma or fibroid uterus may be palpable on the bimanual examination.

Differential Diagnosis

The cause of abnormal uterine bleeding in the nonpregnant patient is extensive but may be narrowed by age. In adolescents, consider undiagnosed coagulopathy, pelvic infection, or

BOX 90.2

PALM-COEIN Classification for Abnormal Uterine Bleeding (AUB)

PALM—STRUCTURAL CAUSES
Polyp (AUB-P)
Adenomyosis (AUB-A)
Leiomyoma (AUB-L)
  Submucosal leiomyoma (AUB-LSM)
  Other leiomyoma (AUB-LO)
Malignancy and hyperplasia (AUB-M)

COEIN—NONSTRUCTURAL CAUSES
Coagulopathy (AUB-C)
Ovulatory Dysfunction (AUB-O)
Endometrial (AUB-E)
Iatrogenic (AUB-I)
Not yet classified (AUB-N)

hypothalamic-pituitary-ovarian axis dysregulation due to physiologic immaturity or PCOS. Patients older than adolescent age should be considered for structural lesions such as polyps or leiomyomas, endometrial hyperplasia, or anovulation secondary to PCOS or other conditions listed above. In patients older than 40 years but not yet postmenopausal, anovulatory bleeding due to perimenopause becomes more likely, as does endometrial carcinoma or hyperplasia and leiomyoma. Postmenopausal patients require an evaluation for malignancy.

Diagnostic Strategies

Laboratory Studies

In evaluating a woman of reproductive age with vaginal bleeding, a urine or serum pregnancy test is the most essential laboratory test. In a patient with excessive bleeding, hemodynamic instability, or clinical evidence of anemia (eg, excessive fatigue, pale conjunctiva), a hemoglobin or hematocrit test may be helpful. If coagulopathy is suspected, platelet count, prothrombin and partial thromboplastin time should be measured. *Chlamydia trachomatis* testing is indicated in patients at risk of infection. Thyroid dysfunction, particularly hypothyroidism, is associated with AUB, and therefore screening to determine the thyroid-stimulating hormone serum level is recommended.

Imaging

The decision to perform ultrasound imaging in the ED depends on the urgency to determine the cause of bleeding and on the reliability of outpatient follow-up. Transvaginal ultrasonography (TVUS) may reveal a fibroid uterus, endometrial thickening, or a focal mass (Fig. 90.10). In postmenopausal patients with AUB, an endometrium measuring less than 4 to 5 mm thick on TVUS reliably excludes endometrial cancer. A thickened endometrium may indicate an underlying lesion or excess estrogen.

For most nonpregnant patients with AUB, ultrasound findings do not immediately affect ED decision making. In patients who have access to gynecologic services, imaging may be deferred until follow-up evaluation with the gynecologist.

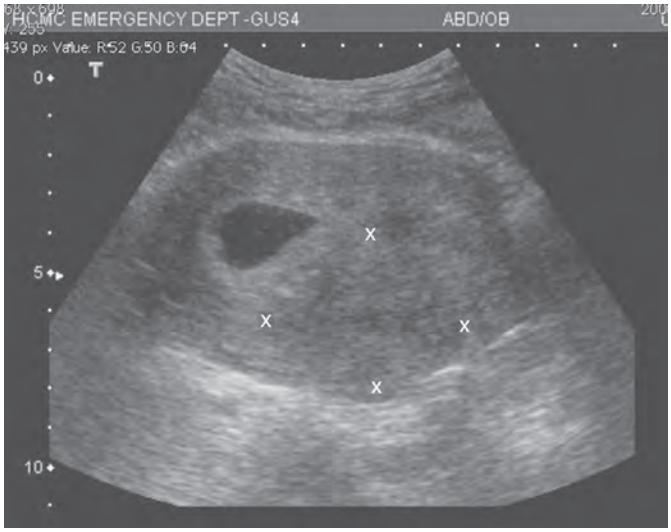


Fig. 90.10. Longitudinal view of the uterus with thickened endometrium. (Courtesy Dr. Robert Reardon, Hennepin County Medical Center, Minneapolis; with permission.)

Management

The likely causative disorder, as well as the amount of bleeding and stability of the patient, will guide ED management. NSAIDs are generally effective for relief of associated cramping pelvic pain.[30] For anovulatory bleeding, combination oral contraceptive pills can help regulate the cycle and also counteract the long-term effects of unopposed estrogen on the endometrium. We recommend a combination oral contraceptive with 35 μg of ethinyl estradiol or 20 mg or medroxyprogesterone tid for 1 week. Contraindications must be reviewed with the patient prior to prescribing these medications, specifically to determine a history of deep vein thrombosis or pulmonary embolus, cigarette smoking, breast cancer, or liver disease.

Oral tranexamic acid, a prothrombotic agent, may also be used for outpatient management of bleeding. The dose is 1.3 g orally every 8 hours for 5 days. Rarely, a patient will have uncontrolled bleeding and signs of blood loss on presentation, in which case they should receive resuscitation with blood products, as is done for other types of hemorrhagic shock. In these patients, surgical options should be considered, including urgent dilation and curettage, uterine artery embolization, or hysterectomy. Alternatively, intravenous conjugated equine estrogen may be used and was shown in one randomized controlled trial to stop bleeding in 72% of study participants in 8 hours compared to 38% treated with placebo.[25] The dose is 25 mg intravenously every 4 to 6 hours for 24 hours or until the bleeding stops.

Disposition

Most patients with pelvic pain from ovarian cysts or abnormal uterine bleeding without hemodynamic compromise may be managed with specific therapies to minimize symptoms and should be referred to a gynecologist for definitive management on an outpatient basis. Patients with severe, acute abnormal uterine bleeding and hemodynamic instability require urgent gynecologic consultation and hospitalization.

EMERGENCY CONTRACEPTION

Emergency contraception, also commonly known as the morning after pill, consists of therapy to prevent pregnancy after unprotected or inadequately protected sexual intercourse. At present, there are three oral formulations available globally—ulipristal acetate, a progesterone receptor modulator, levonorgestrel, and combined oral contraceptives consisting of progestin and estrogen.

The most commonly used regimen, and the only formulation available without a prescription in the United States, consists of a single dose of 1.5 mg or two doses of 0.75 mg levonorgestrel spaced 12 hours apart. The one-time dose is simpler to use and is at least as effective as the two-dose regimen.[31] It is labeled for use for up to 72 hours from intercourse. Another regimen, a single tablet of 30 mg of ulipristal acetate, is only available with a prescription and has demonstrated effectiveness for up to 120 hours from intercourse, making it a preferred choice over levonorgestrel beyond the 72-hour window.[32] Both forms of contraception are maximally effective when used within 24 hours.[33] Combined oral contraceptives, also known as the Yuzpe method, has largely fallen out of favor due to the simplicity and success of levonorgestrel.

Adverse effects of oral emergency contraception include nausea and headache, with combined oral contraceptives producing significantly higher rates of nausea than levonorgestrel or ulipristal alone. Irregular menstrual bleeding, which can occur within 1 week to 1 month after treatment, resolves without intervention.

In addition to oral emergency contraception, the copper intrauterine device (IUD) is highly effective when placed within 5 days

of intercourse and appears to be effective for as long as 10 days.[34] The copper IUD carries a 1/1000 risk of uterine perforation and is associated with uterine cramping, but also provides ongoing contraceptive benefit.

Both levonorgestrel and ulipristal act to delay or inhibit ovulation, whereas whereas the copper IUD prevents fertilization. As such, a common misconception is that emergency contraception is equivalent to medical abortion. None of the methods discussed involve the termination of a preexisting pregnancy, and emergency contraception has not been shown to have any adverse effects on a developing fetus when taken during an established pregnancy. It is still possible for a patient who uses emergency contraception to get pregnant in the same menstrual cycle, so she should be advised to use an alternative form of contraception and to undergo a pregnancy test if menstruation is delayed for more than 3 weeks. Patients who receive emergency contraception should be counseled regarding birth control and have a follow-up pregnancy test should they miss their next period.

KEY CONCEPTS

- Ovarian torsion is easily missed on initial presentation, and diagnosis cannot rely on radiologic findings alone. Doppler ultrasound is the optimal imaging study; absence of arterial flow, although not always present, is highly specific for torsion. Torsion should be a consideration in any patient with known risk factors, even if symptoms are subtle or atypical.
- An ultrasound examination may distinguish among the various types of ovarian cysts and identify associated complications, such as torsion, hemorrhage, and malignancy. Most ovarian cysts are simple follicular cysts that resolve without pharmacologic or surgical intervention.
- Abnormal uterine bleeding has many structural, hormonal, and coagulopathic causes. Selected imaging and laboratory testing, based on a careful history and physical examination, can often lead to determination of the cause. Combined oral contraceptive pills can help regulate the cycle and alleviate AUB.
- Emergency contraception is a safe effective option to prevent an undesired pregnancy. Levonorgestrel and ulipristal are both effective oral medications and are associated with fewer side effects than the traditional combined contraceptive method.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 90: QUESTIONS & ANSWERS

90.1. Which of the following statements regarding ovarian torsion is true?

A. Abdominal tenderness is predictable.
B. Complete arterial obstruction is common.
C. Computed tomography (CT) has a higher sensitivity than ultrasound.
D. Most cases are associated with an ovarian mass.
E. There is a left-sided predominance.

Answer: D. Most cases are associated with a benign ovarian tumor or cyst. There is a modest right-sided predominance. Due to the collateral uterine and ovarian arterial supply, complete arterial obstruction is rare. In cases of intermittent or chronic torsion particularly, abdominal tenderness may be absent. CT has a lower sensitivity than ultrasound, which is still only approximately 71%. Interpret negative studies carefully.

90.2. Which of the following patterns of menses should be considered abnormal?

A. A 23-day menstrual cycle
B. A 40-day menstrual cycle
C. Bleeding 6 months after menopause
D. Seven days of menstrual flow
E. Three days of menstrual flow

Answer: B. A menstrual cycle shorter than 21 days or more than 35 days apart, or flow that is less than 2 days or more than 7 days, is considered abnormal. In the postmenopausal woman, any bleeding 12 months after cessation of menses is considered abnormal.

90.3. A 33-year-old G3P3 woman presents with 7 days of heavy but painless vaginal bleeding. Her only other complaint is dizziness. Urine pregnancy test is negative. Vital signs are blood pressure, 85/40 mm Hg, and heart rate, 130 beats/min. The pelvic examination reveals copious vaginal bleeding through a partially open cervical os. The hemoglobin level is 6.8 g/dL. Which of the following is the most appropriate intervention?

A. 20 µg of ethinyl estradiol daily until the bleeding subsides
B. 35 µg ethinyl estradiol bid until the bleeding subsides
C. Blood transfusion and urgent gynecologic consultation for dilation and curettage
D. Premarin, 25 mg IV every 6 hours
E. Saline hydration followed by a 2-day recheck

Answer: C. This patient is symptomatic, hypovolemic, anemic, and exhibiting ongoing bleeding. Oral estrogens are indicated in cases of modest bleeding. Parenteral estrogen may be used as an adjunct to other therapies for patients requiring admission. The degree of anemia in the face of ongoing bleeding in this case warrants gynecologic intervention.

90.4. To be most effective, the emergency contraceptive ulipristal should be given as soon as possible but is approved to be given within how many hours of intercourse?

A. 12
B. 24

C. 48
D. 72
E. 120

Answer: E. The efficacy of all emergency contraceptive pills in preventing pregnancy is greatest when a contraceptive is taken soon after intercourse. Ulipristal is labeled for 120 hours post-coitus. Because it is not as effective as preplanned contraception, women should still be aware of the possibility of pregnancy after its use.

SECTION SEVEN
Neurology

CHAPTER 91

Stroke

Todd J. Crocco | William J. Meurer

PRINCIPLES

Background

Stroke is the fifth leading cause of death in the United States and a leading cause of long-term disability.[1] It affects about 795,000 people per year. On average, someone has a stroke every 40 seconds, and someone dies of a stroke every 4 minutes.[2] Stroke patients have an in-hospital mortality rate of 5% to 10% for ischemic stroke and 40% to 60% for intracerebral hemorrhage (ICH).[3] Only 10% of stroke survivors will recover completely, making stroke a leading cause of adult disability.

Stroke can be defined as any vascular injury that reduces cerebral blood flow (CBF) to a specific region of the brain, retina, or spinal cord, causing neurologic impairment. The onset of symptoms may be sudden or stuttering, often with transient or permanent loss of neurologic function. Approximately 87% of all strokes are ischemic in origin, caused by the occlusion of a cerebral vessel. Approximately 13% are hemorrhagic strokes caused by the rupture of a blood vessel into the parenchyma of the brain (ICH) or into the subarachnoid space (subarachnoid hemorrhage [SAH]). Only ischemic stroke involving the brain and ICH are discussed in this chapter. SAH is discussed in Chapter 93.

Prior to the reperfusion era, treatment for stroke was not focused on reversal of damage and consisted of stabilization, observation, and rehabilitation. Current acute interventional treatment regimens are designed to reverse or minimize brain damage.[4] Strategies include blood pressure (BP) management, anticoagulation, thrombolytic therapy, catheter-based interventions, and surgery.

Epidemiology

Ischemic Stroke

An estimated 610,000 "first-ever" ischemic strokes occur each year in the United States. These may result from either in situ thrombosis or embolic obstruction from a more proximal source, usually the heart. In more than one-third of these first-ever strokes, no clear cause is identified. Strokes of all subtypes are more common in African American and Hispanics versus non-Hispanic whites.

Approximately one-third of all ischemic strokes are thrombotic in nature. These can be caused by either large- or small-vessel occlusions. Common areas for large-vessel occlusions are cerebral vessel branch points, especially in the distribution of the internal carotid artery. Thrombosis usually results from clot formation in the area of an ulcerated atherosclerotic plaque that forms in the area of turbulent blood flow, such as a vessel bifurcation. A marked reduction in flow results when the stenosis occludes more than 90% of the blood vessel diameter. With further ulceration and thrombosis, platelets adhere to the region. A clot then either embolizes or occludes the artery.

Lacunae, or small-vessel strokes, involve small terminal sections of the vasculature and more commonly occur in patients with diabetes and hypertension. A history of hypertension is present in 80% to 90% of patients who experience lacunar strokes. The subcortical areas of the cerebrum and brainstem often are involved. The infarcts range in size from a few millimeters to 2 cm and are seen most commonly in the basal ganglia, thalamus, pons, and internal capsule. They may be caused by small emboli or by a process termed *lipohyalinosis,* which occurs in patients with hypertensive cerebral vasculopathy.

One-fourth of all ischemic strokes are cardioembolic in nature. Embolization of a mural thrombus in patients with atrial fibrillation is the most common mechanism, and patients with atrial fibrillation have an approximate fivefold increased risk for development of a stroke. Noncardiac sources of emboli may include diseased portions of extracranial arteries, resulting in an artery-to-artery embolus. One common example is amaurosis fugax, in which emboli from a proximal carotid artery plaque embolizes to the ophthalmic artery, causing transient monocular blindness.

Although stroke risk increases with age, approximately 3% to 4% of all strokes occur in patients 15 to 45 years old, and there have been trends observed showing the average age of first stroke is becoming younger.[5] Although atherosclerosis is the most common cause in elders, causative disorders and conditions in younger patients often are uncommon and may be reversible. Pregnancy, the use of oral contraceptives, antiphospholipid antibodies (such as, lupus anticoagulant and anticardiolipin antibodies), protein S and C deficiencies, sickle cell anemia, and polycythemia all predispose patients to sludging or thrombosis, thereby increasing the risk of stroke. Fibromuscular dysplasia of the cerebral vasculature also may lead to stroke, and in rare instances prolonged vasoconstriction from a migraine syndrome causes stroke. Recreational drugs such as cocaine, phenylpropanolamine, and amphetamines are potent vasoconstrictors that have been associated with both ischemic and hemorrhagic stroke. Infectious processes, particularly varicella and recently fungal meningitis, can induce vasculopathies that lead to stroke as well or can induce longer-term inflammatory processes that ultimately cause a clinical stroke.

Carotid and vertebral dissections often are associated with trauma but may follow mild events such as sneezing. Dissections are the leading determined cause of stroke in the young and are slightly less common than idiopathic strokes. Carotid and vertebral dissections also are seen more frequently in people with underlying pathology of the vessel wall, such as in fibromuscular

dysplasia and connective tissue disorders. Alteration in the vessel intima can lead to vessel stenosis, occlusion, or embolism. The patient may report a minor preceding event, such as spinal manipulation, yoga, working overhead, coughing, or vomiting. Presenting manifestations may include headache, facial pain, visual changes, cranial nerve (CN) palsies, pain over the affected vessel, Horner's syndrome, amaurosis fugax, SAH, or an ischemic stroke. The headache frequently is unilateral and may occur days before onset of the other neurologic symptoms. Dissections are typically diagnosed by noninvasive modalities, such as ultrasonography, magnetic resonance angiography (MRA), and computed tomography angiography (CTA). Medical therapy options include early anticoagulation if SAH/intracranial dissection is not suspected. The existing data comparing antiplatelet treatment to anticoagulation is generally limited and antiplatelet treatment is generally simpler and safer.[6] The use of tissue plasminogen activator (tPA) is considered as a safe and effective in extracranial carotid or vertebral dissection patients as in any other eligible patient.[7]

Transient Ischemic Attack

A transient ischemic attack (TIA) was historically defined as a neurologic deficit with complete resolution within 24 hours; however, a portion of TIA cases have evidence of permanent brain ischemia on neuroimaging. Therefore, the American Heart Association (AHA) has adopted a tissue-based definition: A transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

About 240,000 TIAs per year occur in the United States, with an incidence rate of 8 per 1000 person years. TIAs constitute an important warning sign for the future development of cerebral infarction. Approximately 10% of the patients who experience a TIA will experience a stroke within 3 months of the sentinel event, and one-half of these occur within the first 2 days.

Hemorrhagic Stroke

Spontaneous ICH causes 10% to 15% of all acute strokes, affecting approximately 65,000 patients per year. It carries a 30-day mortality rate of up to 50% with one-half of patients dying in the first 2 days. Among survivors, only one in five are living independently at 6 months.

The two major underlying causes of ICH are hypertensive vasculopathy (caused by long-standing hypertension) and cerebral amyloid angiopathy (usually found in elders, which is the result of amyloid deposition in cerebral vessel walls). Hypertensive hemorrhage results from degenerative changes in the small penetrating arteries and arterioles, leading to lipohyalinosis of small, deep penetrating arteries. Such hemorrhages generally occur in the deep regions, including basal ganglia and thalamus. The most common sites for hypertensive hemorrhage are listed in Box 91.1. ICH caused by amyloid angiopathy tends to be lobar in nature and to occur more commonly in older adults.

Other factors leading to ICH include underlying vascular malformations (ie, arteriovenous malformations [AVMs] and aneurysms, drug intoxication [particularly sympathomimetics, such as cocaine], malignant hypertension, saccular aneurysms, blood dyscrasias, venous sinus thrombosis, hemorrhagic transformation of an ischemic stroke, moyamoya disease, and tumors). High-risk features for such secondary forms of ICH include lobar location, presence of intraventricular blood, and younger age.

Pathophysiology

The cerebral vasculature supplies the brain with a rich flow of blood that contains the critical supply of oxygen and glucose necessary for normal brain function. When a stroke occurs, there are immediate alterations in CBF and extensive changes in cellular homeostasis. The normal CBF is approximately 40 to 60 mL/100 g of brain per minute. When CBF drops below 15 to 18 mL/100 g of brain per minute, several physiologic changes occur. The brain loses electrical activity, becoming electrically "silent," although neuronal membrane integrity and function remain intact. Clinically, the areas of the brain maintaining electrical silence manifest a neurologic deficit, even though the brain cells are viable. When CBF is below 10 mL/100 g of brain per minute, membrane failure occurs, with a subsequent increase in the extracellular potassium and intracellular calcium and eventual cell death.

The ischemic penumbra is the area of the brain surrounding the primary injury, which is preserved by a tenuous supply of blood from collateral vessels. This border zone of neuronal tissue is the area of greatest interest to investigators for possible salvage in both ischemic and hemorrhagic stroke. In ischemic stroke, the duration of occlusion plays a critical role in neuronal survival.

In ICH, acute vessel rupture is most often caused by underlying small vessel disease and causes injury by several mechanisms. First, there is mass effect from the hematoma itself, followed by activation of the coagulation cascade, release of inflammatory cytokines, and blood-brain barrier (BBB) disruption. This leads to perihematomal edema formation and secondary brain injury. Finally, continued bleeding, or hematoma expansion, occurs in many patients—either continued bleeding from the primary source, or secondary bleeding at the periphery of the hemorrhage.

BOX 91.1

Most Common Sites for Hypertensive Intracranial Hemorrhage

AFFECTED AREA (FREQUENCY)	COMMON CLINICAL PRESENTATION
Putamen (44%)	Contralateral motor/sensory loss
Thalamus (13%)	Limb pain, speech difficulty
Cerebellum (9%)	Uncoordinated movements of trunk and limbs
Pons (9%)	Numbness, weakness, ataxia, dizziness
Other cortical areas (25%)	Numbness, weakness, language disturbances

Anatomy and Physiology

Blood is supplied to the brain by the anterior and posterior circulations. The anterior circulation originates from the carotid system and perfuses 80% of the brain, including the optic nerve, retina, and frontoparietal and anterior-temporal lobes. The first branch off the internal carotid artery is the ophthalmic artery, which supplies the optic nerve and retina. As a result, the sudden onset of painless monocular blindness (amaurosis fugax) identifies the stroke as involving the anterior circulation (specifically the ipsilateral carotid artery) at or below the level of the ophthalmic artery. The internal carotid arteries terminate by branching into the anterior and middle cerebral arteries at the circle of Willis.

The anterior cerebral artery supplies the basal and medial aspects of the cerebral hemispheres and extends to the anterior two-thirds of the parietal lobe. The middle cerebral artery feeds

the lenticulostriate branches that supply the putamen, part of the anterior limb of the internal capsule, the lentiform nucleus, and the external capsule. Main cortical branches of the middle cerebral artery supply the lateral surfaces of the cerebral cortex from the anterior portion of the frontal lobe to the posterolateral occipital lobe.

Although the posterior circulation is smaller and usually supplies only 20% of the brain, it supplies the brainstem (which is critical for normal consciousness, movement, and sensation), cerebellum, thalamus, auditory and vestibular centers of the ear, medial temporal lobe, and visual occipital cortex. The posterior circulation is derived from the two vertebral arteries that ascend through the transverse processes of the cervical vertebrae. The vertebral arteries enter the cranium through the foramen magnum and supply the cerebellum by the posterior inferior cerebellar arteries. They join to form the basilar artery, which branches to form the posterior cerebral arteries. Some variants exist, importantly, the fetal origin posterior cerebral artery, which is where the posterior cerebral artery is actually fed by the anterior circulation.

The extent of injury in either an anterior or a posterior stroke depends on both the vessel involved and the presence of collateral blood flow distal to the vessel occlusion. A patient with excellent collateral blood flow from the contralateral hemisphere may have minimal clinical deficits despite a complete carotid occlusion. By contrast, a patient with poor collateral flow may have hemiplegia with the same lesion.

CLINICAL FEATURES

Ischemic Stroke

The signs and symptoms of an ischemic stroke may appear suddenly and without warning or may have a stuttering, insidious onset. Disruption of the flow to one of the major vascular limbs of the cerebral circulation will result in physiologic disruption to the anatomic area of the brain supplied by that blood vessel. Ischemic strokes can be classified as anterior or posterior circulation strokes, depending on the vasculature involved. The presence of neurologic deficits is highly dependent on collateral flow. In addition to the vascular supply involved, ischemic strokes can be further described by the temporal presentation of their neurologic deficits.

A "stroke in evolution" is one in which focal neurologic deficits worsen over the course of minutes or hours. Approximately 20% of anterior circulation strokes and 40% of posterior circulation strokes will show evidence of progression. Anterior circulation strokes may progress within the first 24 hours, whereas posterior strokes may progress for up to 3 days. Propagation of thrombus is postulated as a likely mechanism for progression. With anterior circulation strokes (involving variously and primarily the carotid, anterior, and middle cerebral arteries), the clinical presentation rarely includes complete loss of consciousness unless the lesion occurs in the previously unaffected hemisphere of a patient who has experienced a previous contralateral stroke.

Occlusions in the anterior cerebral artery mainly affect frontal lobe function. The patient has altered mentation coupled with impaired judgment and insight, as well as the presence of primitive grasp and suck reflexes on physical examination. Bowel and bladder incontinence may be features of anterior cerebral artery stroke. Paralysis and hypesthesia of the lower limb opposite the side of the lesion are characteristic. Leg weakness is more pronounced than arm weakness in anterior cerebral distribution stroke. Apraxia or clumsiness in the patient's gait also may be noted.

Marked motor and sensory disturbances are the hallmarks of occlusion of the middle cerebral artery. They occur on the side of the body contralateral to the side of the lesion and usually are worse in the arm and face than the leg. Such disturbances may involve only part of an extremity or the face but almost always are accompanied by numbness in the same region as that of the motor loss. Hemianopsia, or blindness in one-half of the visual field, occurs ipsilateral to the lesion. Agnosia, or the inability to recognize previously known subjects, is common, and aphasia may be present if the lesion occurs in the dominant hemisphere. Patients often have a gaze preference toward the affected hemisphere because of disruption of the cortical lateral gaze centers.

Aphasia, a disorder of language in which the patient articulates clearly but uses language inappropriately or understands it poorly, also is common in dominant-hemisphere stroke. Aphasia may be expressive, receptive, or a combination of both. *Wernicke's aphasia* occurs when the patient is unable to process sensory input, such as speech, and thus fails to understand verbal communication (receptive aphasia). *Broca's aphasia* refers to the inability to communicate verbally in an effective way, even though understanding may be intact (expressive aphasia). Aphasia should be distinguished from dysarthria, which is a motor deficit of the mouth and speech muscles; the dysarthric patient articulates poorly but understands words and word choices. Aphasia is important to recognize because it usually localizes a lesion to the dominant (usually left) cerebral cortex in the middle cerebral artery distribution. *Aphasia* and *dysphasia* are terms that are used interchangeably but must be distinguished from *dysphagia,* which is difficulty in swallowing.

Pathology in the vertebrobasilar system (ie, posterior circulation strokes) can cause the widest variety of symptoms and as a result may be the most difficult to diagnose. The symptoms reflect CN deficits, cerebellar involvement, and involvement of neurosensory tracts. The brainstem also contains the reticular activating system, which is responsible for mediating consciousness, and the emesis centers. Unlike those with anterior circulation strokes, patients with posterior circulation stroke can have loss of consciousness and frequently have nausea and vomiting. The posterior cerebral artery supplies portions of the parietal and occipital lobes, so vision and thought processing are impaired. Visual agnosia, the inability to recognize seen objects, may be a feature, as may alexia, the inability to understand the written word. A third nerve palsy may occur, and the patient may experience homonymous hemianopsia. One of the more curious facets of this syndrome is that the patient may be unaware of any visual problem (visual neglect). Vertigo, syncope, diplopia, visual field defects, weakness, paralysis, dysarthria, dysphagia, spasticity, ataxia, or nystagmus may be associated with vertebrobasilar artery insufficiency. Posterior circulation strokes also demonstrate crossed deficits, such as motor deficits on one side of the body and sensory loss on the other. In anterior circulation strokes, by contrast, abnormalities are always limited to one side of the body.

A focused neurologic examination should assess level of consciousness, speech, CN function, motor and sensory function, and cerebellar function. Level of consciousness and fluency of speech can be rapidly assessed in a dialogue with the patient to determine the presence of dysarthria or aphasia. The head should be evaluated for signs of trauma. Pupillary size and reactivity and extraocular movements provide important information about brainstem function, particularly CN III through CN VI; an abnormal third nerve function may be the first sign of tentorial herniation. Gaze preference suggests brainstem or cortical involvement. Central facial nerve weakness from a stroke should be distinguished from the peripheral causes of CN VII weakness. With a peripheral lesion, the patient is unable to wrinkle the forehead. Assessment of facial sensation, eyebrow elevation and squinting, smiling symmetry, gross auditory acuity, gag reflex, shoulder elevation, sternocleidomastoid strength, and tongue protrusion complete the CN evaluation.

Motor and sensory testing is performed next. Muscle tone can be assessed by moving a relaxed limb. Proximal and distal muscle group strength is assessed against resistance. Pronator drift of the arm is a sensitive sign of motor weakness and can be tested simultaneously by having the patient sit with eyes closed and arms outstretched, with palms toward the ceiling, for 10 seconds. Asymmetrical sensation to pain and light touch may be subtle and difficult to detect. Double simultaneous extinction evaluation tests for sensory neglect and can be easily performed by simultaneously touching the right and left limbs. The patient may feel both the right and left sides being touched individually but may not discern touch on one side when both are touched simultaneously. Similarly, the ability to discern a number gently scratched on a forearm, graphesthesia, is another easily tested cortical parietal lobe function. These tests can help differentiate a pure motor deficit of a lacunar stroke from a sensorimotor middle cerebral artery deficit.

Cerebellar testing and the assessment of reflexes and gait complete the examination. Finger-to-nose and heel-to-shin evaluations are important tests of cerebellar functions. Asymmetry of the deep tendon reflexes or unilateral Babinski's sign may be an early finding of corticospinal tract dysfunction. Gait testing is commonly omitted yet is an informative part of the neurologic examination when it can be safely performed. Observing routine ambulation and heel-to-toe walking can assess for subtle ataxia, weakness, or focal cerebellar lesions.

Several prehospital stroke scales have been created to assist emergency medical service (EMS) personnel with the rapid assessment of potential stroke patients. Many of these prehospital stroke scales have been prospectively validated for their accuracy in stroke detection. Two of the more commonly used scales include the Cincinnati Prehospital Stroke Scale (Fig. 91.1) and Los Angeles Prehospital Stroke Screen (Fig. 91.2).

The National Institutes of Health Stroke Scale (NIHSS) is a useful and rapid tool for quantifying neurologic deficit in patients with stroke and can be used in determining treatment options (Table 91.1). NIHSS scores have been shown to be reproducible and valid and to correlate well with the amount of infarcted tissue on computed tomography (CT) scan. The baseline NIHSS score can identify patients who are appropriate candidates for fibrinolytic therapy, as well as those at increased risk for hemorrhage, although it is possible for patients to have disabling strokes with an NIHSS of zero (severe truncal ataxia). In addition, it has been used as a prognostic tool to predict outcome and is currently being used by some stroke centers to stratify patients for entry into treatment trials.

Cincinnati Prehospital Stroke Scale	
Facial Droop	
Normal:	Both sides of face move equally
Abnormal:	One side of face does not move at all
Arm Drift	
Normal:	Both arms move equally or not at all
Abnormal:	One arm drifts compared to the other
Speech	
Normal:	Patient uses correct words with no slurring
Abnormal:	Slurred or inappropriate words or mute

Fig. 91.1. Cincinnati Prehospital Stroke Scale. (Adapted from Kothari RU, Pancioli A, Liu T, et al: Cincinnati Prehospital Stroke Scale: reproducibility and validity. Ann Emerg Med 33[4]:373-378, 1999.)

Hemorrhagic Stroke

The classic presentation of ICH is the sudden onset of headache, vomiting, severely elevated BP, and focal neurologic deficits that progress over minutes. Similar to ischemic stroke, ICH is often associated with a motor and sensory deficit contralateral to the brain lesion. Almost 40% of patients will demonstrate significant growth in hemorrhage volume within the first few hours.

Although headache, vomiting, and coma are common, many patients do not have these findings, and the clinical presentation can be identical to that of patients with ischemic stroke; the two cannot be reliably differentiated in the absence of neuroimaging.

Ongoing assessment of airway and mental status is of paramount importance in patients with ICH because precipitous deterioration is always a possibility. Emergency airway management requires careful judgment: On the one hand, airway control can prevent aspiration, hypoxia, and hypercarbia; on the other, sedation and paralysis can make it difficult to follow the neurologic examination, which can help monitor for hemorrhage expansion, elevated intracranial pressure (ICP), seizure activity, and brainstem herniation.

As with ischemic stroke, a careful neurologic examination is important in localizing the region and extent of injury. Baseline NIHSS and Glasgow Coma Scale scores can be used to assess stroke severity, although the Glasgow Coma Score (GCS) may be more practical to follow for neurologic deterioration (Table 91.2). In addition, serial examinations can detect early changes that may suggest ongoing bleeding during the acute phase. The ICH score can predict mortality (Table 91.3).

Poor prognostic indicators for patients with ICH include a decreased level of consciousness on arrival, intraventricular hemorrhage, and large ICH volume, all of which can be assessed in the emergency department (ED) (Fig. 91.3).

DIFFERENTIAL DIAGNOSIS

Ischemic Stroke

Extra-axial collections of blood secondary to trauma can mimic stroke. An epidural or subdural hematoma can cause an altered mental status, focal neurologic signs, and rapid progression to coma. Elders, who represent the age group at highest risk for stroke, can be victims of recurrent falls that lead to chronic subdural hematomas. Carotid dissection may occur after neck trauma or sudden hyperextension and may be associated with focal neurologic signs and symptoms, as with an aortic dissection that extends into the carotid arteries.

Other structural lesions that may cause focal neurologic signs include brain tumors and abscesses. Air embolism should be suspected in the setting of marked atmospheric pressure changes, such as in scuba diving or during medical procedures or injuries that may allow air into the vascular system. Seizures, altered mental status, and focal neurologic findings also may be manifestations of air embolism.

Metabolic abnormalities also can mimic stroke syndromes. Hypoglycemia often is responsible for an altered mental status and is a well-known cause of sustained focal neurologic symptoms that can persist for several days. Wernicke's encephalopathy causes ophthalmoplegia, ataxia, and confusion that can be mistaken for signs of cerebellar infarction.

Migraine may present with focal neurologic findings, with or without headache. A seizure followed by Todd's postictal paralysis may mimic stroke. Bell's palsy, labyrinthitis, vestibular neuronitis, peripheral nerve palsy, and demyelinating diseases may all mimic stroke. Ménière's disease may be difficult to distinguish from a posterior circulation stroke or TIA. Dizziness, vertigo, hearing loss, and tinnitus in Ménière's disease are common, whereas

Los Angeles Prehospital Stroke Scale (LAPSS)

Patient name: _____

Rater name: _____

Date: _____

Screening criteria	Yes	No
4. Age over 45 years	____	____
5. No prior history of seizure disorder	____	____
6. New onset of neurologic symptoms in last 24 hours	____	____
7. Patient was ambulatory at baseline (prior to event)	____	____
8. Blood glucose between 60 and 400	____	____

9. Exam: ***Look for obvious asymmetry***

	Normal	Right	Left
Facial smile / grimace:	☐	☐ Droop	☐ Droop
Grip:	☐	☐ Weak grip ☐ No grip	☐ Weak grip ☐ No grip
Arm weakness:	☐	☐ Drifts down ☐ Falls rapidly	☐ Drifts down ☐ Falls rapidly

Based on exam, patient has only unilateral (and not bilateral) weakness: Yes ☐ No ☐

10. If yes (or unknown) to all items above LAPSS screening criteria met: Yes ☐ No ☐

11. If LAPSS criteria for stroke met, call receiving hospital with "CODE STROKE," if not then return to the appropriate treatment protocol. (Note: The patient may still be experiencing a stroke if even if LAPSS criteria are not met.)

Provided by the internet stroke center — www.strokecenter.org

Fig. 91.2. Los Angeles Prehospital Stroke Screen. (Adapted from Kidwell CS, Starkman S, Eckstein M, et al: Identifying stroke in the field: prospective validation of the Los Angeles Prehospital Stroke Screen [LAPSS]. Stroke 31:71-76, 2000.)

difficulties with vision or speech or other focal symptoms are uncommon.

Like stroke, giant cell arteritis is a disease of older adults. It may cause severe headache, visual disturbances, and, rarely, aphasia and hemiparesis. Other symptoms include intermittent fever, malaise, jaw claudication, morning stiffness, and myalgias. The diagnosis should be suspected in patients with a very high erythrocyte sedimentation rate (ESR) and is confirmed by temporal artery biopsy. Collagen vascular diseases such as polyarteritis nodosa, lupus, and other types of vasculitis may cause stroke syndromes.

Cerebral venous sinus thrombosis (CVST) is another cause of focal neurologic symptoms that most commonly affects the superior sagittal sinus and lateral sinuses (see Chapter 93).[8] The diagnosis of CVST can be difficult because of the nonspecific nature of symptoms, as well as the variable time frame of symptom onset (from hours to a few weeks). Patients may have generalized headaches, nausea, vomiting, paresis, visual disturbances, depressed

TABLE 91.1

National Institutes of Health Stroke Scale Scoring Form

ITEM	SCORING DEFINITIONS	SCORE
1a. Level of consciousness (LOC)	0 = Alert and responsive 1 = Arousable to minor stimulation 2 = Arousable only to painful stimulation 3 = Reflex responses or unarousable	
1b. LOC-related questions: Ask patient's age and month. Must be exact.	0 = Both correct 1 = One correct (or dysarthria, intubated, foreign language) 2 = Neither correct	
1c. Commands: Open and close eyes, grip and release nonparetic hand. (Other one-step commands or mimic also acceptable.)	0 = Both correct (acceptable if impaired by weakness) 1 = One correct 2 = Neither correct	
2. Best gaze: Horizontal EOM by voluntary or doll's eye maneuver.	0 = Normal 1 = Partial gaze palsy; abnormal gaze in one or both eyes 2 = Forced eye deviation or total paresis that cannot be overcome by doll's eye maneuver	
3. Visual field: Use visual threat if necessary. If monocular, score field of good eye.	0 = No visual loss 1 = Partial hemianopsia, quadrantanopia, extinction 2 = Complete hemianopsia 3 = Bilateral hemianopsia or blindness	
4. Facial palsy: If patient is stuporous, check symmetry of grimace to pain.	0 = Normal 1 = Minor paralysis, flat NLF, asymmetrical smile 2 = Partial paralysis (lower face = UMN lesion) 3 = Complete paralysis (upper and lower face)	
5. Motor arm: Arms outstretched 90 degrees (sitting) or 45 degrees (supine) for 10 seconds. Encourage best effort. Indicate paretic limb in score box.	0 = No drift for 10 seconds 1 = Drift but does not hit bed 2 = Some antigravity effort, but cannot sustain 3 = No antigravity effort, but even minimal movement counts 4 = No movement at all X = Unable to assess owing to amputation, fusion, fracture, and so on	L or R
6. Motor leg: Raise leg to 30 degrees (from supine) for 5 seconds. Indicate paretic limb in score box.	0 = No drift for 5 seconds 1 = Drift but does not hit bed 2 = Some antigravity effort, but cannot sustain 3 = No antigravity effort, but even minimal movement counts 4 = No movement at all X = Unable to assess owing to amputation, fusion, fracture, and so on	L or R
7. Limb ataxia: Check finger-nose-finger, heel-shin position sense; and score only if out of proportion to paralysis.	0 = No ataxia (or aphasic, hemiplegic) 1 = Ataxia in upper or lower extremity 2 = Ataxia in upper *and* lower extremity X = Unable to assess owing to amputation, fusion, fracture, and so on	L or R
8. Sensory: Use safety pin. Check grimace or withdrawal if patient is stuporous. Score only stroke-related losses.	0 = Normal 1 = Mild-moderate unilateral loss but patient aware of touch (or aphasic, confused) 2 = Total loss, patient unaware of touch; coma, bilateral loss	
9. Best language: Describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis.	0 = Normal 1 = Mild-moderate aphasia (speech difficult to understand but partly comprehensible) 2 = Severe aphasia (almost no information exchanged) 3 = Mute, global aphasia, coma; no one-step commands	
10. Dysarthria: Read list of words.	0 = Normal 1 = Mild-moderate; slurred but intelligible 2 = Severe; unintelligible or mute X = Intubation or mechanical barrier	
11. Extinction or neglect: Simultaneously touch patient on both hands, show fingers in both visual fields, ask about deficit, left hand.	0 = Normal, none detected (visual loss alone) 1 = Neglects or extinguishes to double simultaneous stimulation in any modality (visual, auditory, sensation, spatial, body parts) 2 = Profound neglect in more than one modality	

Android Free App: https://play.google.com/store/apps/details?id=com.myprograms.nihss
Apple Free App: https://itunes.apple.com/us/app/nih-stroke-scale-from-statcoder/id408788598?mt=8
Online NIHSS Calculator: www.mdcalc.com/nih-stroke-scale-score-nihss/
EOM, Extraocular movement; *L,* left; *LOC,* level of consciousness; *NLF,* nasolabial fold; *R,* right; *UMN,* upper motor neuron.
Modified from Massachusetts General Hospital Stroke Service. NIH stroke scale materials. Scoring form. Available at www2.massgeneral.org/stopstroke/pdfs/scoring_form.pdf.

TABLE 91.2

Glasgow Coma Scale Score*

EYE OPENING (E)	VERBAL RESPONSE (V)	MOTOR RESPONSE (M)
4 = Spontaneous	5 = Normal conversation	6 = Normal
3 = To voice	4 = Disoriented conversation	5 = Localizes to pain
2 = To pain	3 = Words, but not coherent	4 = Withdraws to pain
1 = None	2 = No words; only sounds	3 = Decorticate posture
	1 = None	2 = Decerebrate posture
		1 = None

*Total score = E + V + M
Shoestring Graphics: Glasgow coma score.
Available at www.ssgfx.com/CP2020/medtech/glossary/glasgow.htm.

Fig. 91.3. The computed tomography (CT) slice with the largest area of hemorrhage is identified. The largest diameter of the hemorrhage on this slice is measured in centimeters *(line A)*. The largest diameter 90 degrees to A on the same slice is measured *(line B)*. C is the approximate number of 10-mm slices on which the intracerebral hemorrhage (ICH) was seen. (Many centers use 5-mm slices, in which case an adjustment can be made by dividing by 2.) The volume of the hemorrhage = A × B × C ÷ 2 (ABC/2).

TABLE 91.3

Intracerebral Hemorrhage Score Predicting Mortality After Acute Intracerebral Hemorrhage

FEATURE	POINTS
GLASGOW COMA SCALE SCORE	
3 to 4	2
5 to 12	1
13 to 15	0
INTRACEREBRAL HEMORRHAGE VOLUME	
>30 mL	1
≤30 mL	0
INTRAVENTRICULAR HEMORRHAGE (INTRAVENTRICULAR BLOOD)	
Present	1
Absent	0
INTRACEREBRAL HEMORRHAGE LOCATION	
Infratentorial	1
Supratentorial	0
AGE	
≥80 years	1
<80 years	0
30-DAY MORTALITIES FOR TOTAL INTRACEREBRAL HEMORRHAGE SCORES	
0 = 0%	
1 = 13%	
2 = 26%	
3 = 72%	
4 = 97%	
5 = 100%	
6 = Estimated to be 100%; no patients in the study fell into this category	

Adapted from Hemphill JC, et al: The ICH Score. Stroke 32:891-897, 2001.

level of consciousness, seizures, or even symptoms generally ascribed to psychiatric disorders (such as, depression). Depending on the location of the thrombus, physical examination of the patient may reveal papilledema, proptosis, or palsies of CNs III, IV, and VI, as well as other focal neurologic signs and symptoms. Risk factors for CVST include trauma, infectious processes, hypercoagulable states, low-flow states, compression of the venous sinus, dehydration, various drugs (such as, androgens, "ecstasy," and oral contraceptives), and pregnancy or the postpartum state.

Hemorrhagic Stroke

The differential diagnosis for ICH is similar to that for ischemic stroke; considerations include migraine, seizure, tumor, abscess, hypertensive encephalopathy, and trauma. Hypertensive encephalopathy and migraine also can manifest with headache, nausea, and vomiting, although focal neurologic signs are less common in these entities. With hypertensive encephalopathy, patients usually exhibit marked elevation in BP and other evidence of end-organ injury, such as proteinuria, cardiomegaly, papilledema, and malignant hypertensive retinopathy. These patients usually improve significantly with treatment of their hypertension. The posterior reversible encephalopathy syndrome is an important subset of hypertensive encephalopathy presentations and has characteristic CT or magnetic resonance imaging (MRI) changes.

Once ICH is appreciated on neuroimaging, it can be difficult to determine the underlying cause. Primary ICH typically manifests as a parenchymal hematoma with new onset neurologic symptoms. Patients with hemorrhagic transformation of an ischemic stroke may have recurrence or worsening of previously established deficits. Patients with known underlying cancer, or perihematomal edema out of proportion to the hemorrhage, should be considered for hemorrhage into a metastasis or primary tumor. Finally, patients with known underlying venous thromboembolic risk factors may have underlying CVST.

DIAGNOSTIC TESTING

Ischemic Stroke

Although clinical data can help establish the diagnosis, cause, and location of the stroke, confirmatory diagnostic tests are often required to establish the final cause or to eliminate other causes for the deficits. The immediate evaluation includes cranial imaging, an electrocardiogram (ECG) and hematologic testing, particularly blood glucose determination.

An emergent noncontrast cranial CT is the standard initial imaging technique for evaluating a patient with a potential stroke. It can quickly differentiate an ischemic stroke from ICH and other mass lesions. This information is crucial to the subsequent therapeutic decisions that will be rapidly made. A CT scan can identify almost all parenchymal hemorrhages larger than 1 cm in diameter and it has a high sensitivity for the detection of SAH.[9] In a majority of ischemic strokes, gross signs of infarction will not appear on routine CT scans for at least 6 to 12 hours, depending on the size of the infarct. However, subtle, early ischemic changes have been noted in up to 67% of noncontrast CT scans within the first 3 hours. These early ischemic changes include the hyperdense artery sign (acute thrombus in a vessel), sulcal effacement, loss of the insular ribbon, loss of gray-white interface, mass effect, and acute hypodensity (Fig. 91.4). In addition, CTA can be used to identify the presence of intravascular thrombosis, vasculature dissection, or stenosis. In cases in which arterial dissection is suspected, imaging with MRA or CTA is indicated.[10]

The clinical importance of early ischemic CT findings with regard to fibrinolytic therapy within 3 hours of symptom onset is questionable, because the ability of treating physicians to reproducibly identify these findings is poor and their clinical significance is questionable. Only acute hypodensity and mass effect have been shown to be associated with an increased risk of ICH after fibrinolysis (over that in treated patients without these findings). However, these findings do not exclude patients from fibrinolytic therapy, which is associated with an improved neurologic outcome. Patients with a hyperdense artery sign and acute hypodensity of one-third of the middle cerebral artery distribution tend to have a poorer prognosis; however, their outcomes are still better with tPA treatment than without such treatment.

MRI can visualize ischemic infarcts earlier and identify acute posterior circulation strokes more accurately than CT, and it may be as effective as CT in identifying ICH.[10] However, availability, difficulty in accessing critically ill patients, and scan time limit the use of MRI in acute stroke. Advances in MRA technology have allowed a noninvasive method of demonstrating large-vessel occlusions of the anterior and posterior circulation, although small intracranial vascular occlusions may not be readily apparent. With the improvements in MRI and MRA speed and resolution, some stroke centers are replacing CT protocols with limited "stroke protocol" MRI or MRA as the initial imaging modality of choice. The choice of initial cranial imaging modality is highly dependent on the speed with which these scans can be performed and interpreted at each individual center.

Diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) are MRI techniques that take minutes to perform and may allow differentiation between reversible and irreversible neuronal injury. Other potential imaging modalities include CTA and perfusion scans. In CTA, a CT scan is enhanced by an intravenous (IV) contrast agent to better define the vasculature of the brain. Areas of vascular stenosis and occlusion can be visualized with this technique. This information can then be used by interventionalists to determine whether a lesion is amenable to endovascular thrombectomy. Also requiring IV contrast, perfusion CT scans can reveal perfusion deficits within different regions of the brain. In addition, CTA and perfusion CT can differentiate reversible from irreversible ischemic insults.

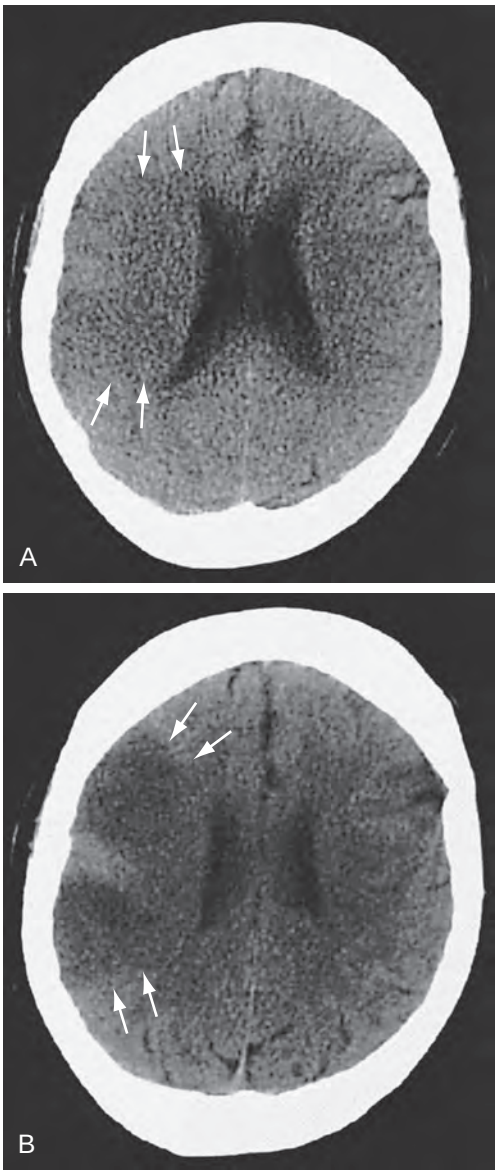

Fig. 91.4. A, Computed tomography (CT) scan taken 2 hours and 50 minutes after a large right middle cerebral artery occlusion. There are subtle, ultra-early ischemic changes, including loss of the gray-white interface *(arrows)* and subtle evidence of sulcal effacement. **B,** CT scan of same patient approximately 8 hours after symptom onset shows acute hypodensity *(arrows)* and more prominent sulcal effacement.

An ECG is indicated in all patients with acute ischemic stroke, because atrial fibrillation and acute myocardial infarction are associated with up to 60% of all cardioembolic strokes. The hematologic evaluation includes a complete blood count with platelet count, prothrombin time (including international normalized ratio [INR]), partial thromboplastin time, cardiac enzymes, and serum glucose measurement. Elevated blood viscosity, even when hematocrit levels are not frankly polycythemic, can affect blood flow and prognosis. A platelet count can identify thrombocytosis or thrombocytopenia, which may precipitate a thrombosis or hemorrhage. Coagulation studies are especially helpful to guide management for patients in whom anticoagulation is being considered or for patients with a hemorrhagic stroke.

Other ancillary diagnostic tests to consider include an echocardiogram, carotid duplex scan, and angiogram. Some centers are performing these studies as part of a TIA observation unit protocol to exclude a patent foramen ovale or valvular vegetation in those patients in whom a cardioembolic stroke is suspected. An echocardiogram should also be performed in patients with no obvious cause for their stroke.[11] Finally, conventional angiography can demonstrate stenosis or occlusion of both large and small blood vessels of the head and neck. It can detect subtle abnormalities, such as with dissection, that may not be demonstrated with noninvasive imaging techniques.

Transient Ischemic Attack

Patients with new-onset TIAs should receive an expedited evaluation and treatment owing to the substantial short-term risk of stroke and other adverse events.[12] Emergency neuroimaging, vascular imaging (such as, with a carotid Doppler study, MRA, or CTA), electrocardiography, and basic blood tests should be performed. A medically or surgically treatable cause for TIAs (eg, high-grade carotid stenosis, mural thrombus) should be sought, which would require in-hospital treatment such as anticoagulation, stenting, or carotid endarterectomy.

Hemorrhagic Stroke

The hematologic evaluation for the patient with hemorrhagic stroke should be performed in the same manner as for the patient with ischemic stroke. Particular attention should be directed to uncovering the presence of a coagulopathy. A drug screen should be obtained to evaluate for use of sympathomimetics if substance abuse is suspected. Increased sympathetic outflow secondary to the hemorrhage may lead to an increase in dysrhythmias. Dysrhythmias also may signal impending brainstem compression from an expanding hemorrhage.

As in ischemic stroke, the cranial CT scan is the diagnostic test of choice to evaluate for an ICH. The noncontrast CT scan will reliably diagnose patients with clinically relevant acute ICH. Hemorrhages that are several days old may not be as apparent as acute hemorrhages and appear as isodense regions.

Also, as with ischemic stroke, advanced neuroimaging modalities are gaining favor in ICH. CTA produces high-quality images of the larger arterial vessels and can help exclude secondary causes, such as aneurysm, AVM, or fistula. Some patients with primary ICH show contrast extravasation on CTA, and such patients are at particularly high risk of ongoing bleeding and hematoma expansion. A venous phase can be added to this study (computed tomography venography [CTV]) to evaluate for CVST. A MRI can help detect underlying lesions (such as, tumor) and may offer better resolution for evaluating perihematomal edema. When available, MRA and magnetic resonance venography (MRV) can be used in place of CTA and CTV.

MANAGEMENT

Ischemic Stroke

With a focus on rapid recognition, evaluation, and treatment of stroke, many hospitals have streamlined care to meet recommended time goals (Table 91.4). This has led to the development of stroke protocols, critical pathways, and acute interventional stroke teams that may even be deployed in the field before the patient arrives at the ED.

In the prehospital setting, the focus should be on ensuring central nervous system (CNS) oxygenation and perfusion, rapid identification, early hospital notification, and rapid transport. Although it is unusual for patients with ischemic stroke to be unresponsive on presentation, their ability to communicate may be altered by dysphasia. After an ischemic stroke, patients usually can maintain their airway unless the brainstem is affected or significant cerebral edema is compressing the opposite hemisphere. Patients with intact protective airway reflexes should receive oxygen if they are hypoxic (oxygen saturation less than 95%), and a monitor and IV line should be established. Routine oxygen supplementation of normoxic stroke patients should be avoided.[13]

Overhydration should be avoided to prevent cerebral edema. By contrast, dehydration may lead to decreased cerebral perfusion, and saline infusion should be given if dehydration is suspected. Dextrose-containing solutions should be avoided in normoglycemic patients suspected of having had a stroke because elevated blood glucose levels may worsen an ischemic deficit. Out-of-hospital personnel should attempt to rapidly ascertain the patient's blood sugar; if this is not possible, glucose should be given when hypoglycemia is strongly suspected with an understanding that hyperglycemia may be neurotoxic. Electrocardiographic monitoring is recommended to identify life-threatening arrhythmias and atrial fibrillation.

The circumstances surrounding the stroke as well as concomitant medical conditions should be ascertained. A key part of the initial information on stroke patients is the prehospital providers' documentation of the exact time the patient was last seen to be neurologically normal and the level of neurologic functioning. This is especially important because reversible defects may completely resolve by the time the patient has arrived at the hospital.

The level of consciousness, gross focal motor deficits, difficulty with speech, clumsiness, facial asymmetry, and any other focal deficits should be noted. Prehospital stroke scales assist in identifying patients who have had a stroke and who are potential candidates for fibrinolytic therapy. Early recognition, notification, and transport by EMS are associated with delivery of fibrinolytic treatment and improved patient outcomes.[14]

In the ED setting, the vital signs should be reassessed on an ongoing basis because patients may rapidly deteriorate even with subacute stroke. Some stroke patients are found at home 1 or 2 days after the event has occurred and may have concomitant illnesses, such as aspiration pneumonia, dehydration, hypothermia, rhabdomyolysis, or myocardial ischemia. Fever necessitates an evaluation to identify sources of infection, followed by prompt institution of treatment. Even minor degrees of hyperthermia have been associated with increased neurologic injury. Oral medications (and food) should be withheld until some form of swallowing assessment has been performed, given the risk of aspiration in patients with an acute stroke.

TABLE 91.4

National Institute of Neurological Disorders and Stroke Recommended Stroke Evaluation Targets for Potential Thrombolytic Candidates

MANAGEMENT COMPONENT	TARGET TIME FRAME
Door to doctor	10 minutes
Door to CT completion	25 minutes
Door to CT scan reading	45 minutes
Door to treatment	60 minutes
Access to neurologic expertise*	15 minutes
Access to neurosurgical expertise*	2 hours

*By phone or in person.
CT, computed tomography.

Blood Pressure Management

The management of BP in patients with acute ischemic stroke and TIA is controversial because of limited data. Current guidelines for the management of hypertension in patients with acute ischemic stroke recommend that antihypertensive treatment be reserved for those with markedly elevated BPs, unless fibrinolytic therapy is planned or specific medical indications are present. These medical indications include acute myocardial infarction, aortic dissection, hypertensive encephalopathy, and severe left ventricular heart failure.

Oral or parenteral agents are withheld unless the patient's systolic pressure is greater than 220 mm Hg, diastolic pressure is greater than 120 mm Hg, or mean arterial pressure (MAP) is greater than 130 mm Hg (Box 91.2). If parenteral agents are used, labetalol 10 to 20 mg IV push, or a calcium channel blocker (eg, nicardipine starting at 5 mg/hour IV), is favored because of ease of titration and limited effect on cerebral blood vessels. Sublingual nifedipine or sublingual nitroglycerin are not recommended, because either agent can produce a precipitous drop in BP.

If fibrinolytic therapy is planned, stringent control of BP is indicated to reduce the potential for intracranial hemorrhage after the thrombolytic is administered (see Box 91.2).

Thrombolytic therapy is not recommended for patients whose systolic pressure is consistently higher than 185 mm Hg or whose diastolic pressure is 110 mm Hg at the time of treatment. Simple measures can be used to try lowering BP below this level. Recommended approaches include the use of IV labetalol 10 to 20 mg or continuous nicardipine. Once thrombolytic therapy has been initiated, BP must be monitored closely and hypertension treated aggressively.

Just as problematic as high BP can be, low BP can be quite detrimental to patients with ischemic stroke. Normally normotensive stroke patients with low BP or normally hypertensive stroke patients with low or even low-normal BP are given a fluid bolus to try to increase cerebral perfusion. This is especially important in patients in a dehydrated state. If initial fluid challenge is ineffective, the patient may require vasopressor therapy (eg, with dopamine) to gradually increase MAP and improve cerebral perfusion.

BOX 91.2

Emergency Antihypertensive Therapy for Acute Ischemic Stroke

INDICATION THAT PATIENT IS ELIGIBLE FOR TREATMENT WITH INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR OR OTHER ACUTE REPERFUSION INTERVENTION

Blood Pressure Level

Systolic >185 mm Hg or diastolic >110 mm Hg
- Labetalol 10 to 20 mg IV over 1 to 2 minutes; may repeat 1 time
- *or*
- Nicardipine infusion, 5 mg/hr; titrate up by 2.5 mg/hr at 5- to 15-minute intervals, maximum dose 15 mg/hr; when desired BP attained, reduce to 3 mg/hr

Other agents (hydralazine, enalaprilat, and so on) may be considered when appropriate.

If BP does not decline and remains >185/110 mm Hg, do not administer rtPA.

MANAGEMENT OF BLOOD PRESSURE DURING AND AFTER TREATMENT WITH RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR OR OTHER ACUTE REPERFUSION INTERVENTION

Monitor BP every 15 minutes during treatment and then for another 2 hours, then every 30 minutes for 6 hours, and then every hour for 16 hours.

Blood Pressure Level

Systolic 180 to 230 mm Hg or diastolic 105 to 120 mm Hg
- Labetalol 10 mg IV over 1 to 2 minutes; may repeat every 10 to 20 minutes; maximum dose of 300 mg
- *or*
- Labetalol 10 mg IV followed by an infusion at 2 to 8 mg/min

Systolic >230 mm Hg or diastolic 121 to 140 mm Hg
- Labetalol 10 mg IV over 1 to 2 minutes; may repeat every 10 to 20 minutes; maximum dose of 300 mg
- *or*
- Labetalol 10 mg IV followed by an infusion at 2 to 8 mg/min
- *or*
- Nicardipine infusion, 5 mg/hr; titrate up to desired effect by increasing 2.5 mg/hr every 5 minutes to maximum of 15 mg/hr

If BP not controlled, consider sodium nitroprusside.

BP, Blood pressure; *IV,* intravenous; *rtPA,* recombinant tissue plasminogen activator.
Adapted from Jauch EC, Saver JL, Adams HP Jr, et al: Guidelines for the early management of adults with ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 44(3):870-947, 2013.

Thrombolytic Therapy

To date, the only IV thrombolytic agent approved by the U.S. Food and Drug Administration (FDA) for treatment of patients with acute ischemic stroke is the recombinant tissue plasminogen activator (rtPA), alteplase (Activase). Approval was initially based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) trial, although subsequent analysis of other studies has supported its use.[15,16] There was initial concern regarding the safety of alteplase when used in community practice; however, a meta-analysis of non–trial-related use in community practice has demonstrated efficacy and safety similar to that reported in the NINDS trial; this was also replicated within a cluster randomized controlled trial performed in Michigan.[17] The recommended dose for rtPA is 0.9 mg/kg IV to a maximum of 90 mg (10% of the dose given as a bolus followed by an infusion lasting 60 minutes). Although the initial recommended time window for IV rtPA administration was 3 hours because the patient was last known to be at their neurologic baseline, a subsequent study has demonstrated the usefulness of IV rtPA at 3 to 4.5 hours in a carefully selected subgroup of acute ischemic stroke patients (Table 91.5 and Box 91.3). A larger open-label randomized trial focusing on patients presenting with "reasonable uncertainty" regarding the expected benefit of rtPA found reduced death and dependency at 6 months; a large proportion of patients in this study were quite old, or had old stroke (>4.5 hours), or both.[18] These results should not influence clinical practice, because the bulk of the population included in this large trial was markedly different from the population of stroke patients who receive thrombolysis within the context of current guidelines.

The American Stroke Association recommends that rtPA be given within 60 minutes of arrival to appropriately selected ischemic stroke patients. Recent guidelines from the American College of Emergency Physicians concur but also emphasize that proper systems of care must also be in place to ensure safety and to maximize good outcomes.[19]

Studies suggests that patients with mild or rapidly resolving symptoms may still benefit from the use of IV rtPA, and a clinical trial is ongoing in this area. A promising early phase trial of tenecteplase was recently completed for patients with mild stroke and high-grade large-vessel stenosis. However, this strategy cannot be recommended yet if feasible clinicians should consider urgent transfer of patients with mild symptoms and high grade stenosis for potential reperfusion strategies, including mechanical

TABLE 91.5

Comparison of AHA/ASA Acute Stroke Management Guidelines and Previous and New FDA Prescribing Information for Alteplase (Activase) Treatment in Acute Ischemic Stroke

Inclusion criteria for fibrinolytic therapy

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms less than 3 hours before beginning treatment

CRITERION	AHA/ASA ACUTE STROKE MANAGEMENT GUIDELINE 2013[a]	OLD ALTEPLASE (ACTIVASE) PI (UPDATED 2009)	NEW ALTEPLASE (ACTIVASE) PI (FEBRUARY 2015)
Prior stroke	Exclusion: prior stroke within 3 mo	Contraindication: recent (within 3 mo) previous stroke	Removed entirely
Seizure at onset	Relative exclusion: seizure at onset with postictal neurological impairments	Contraindication: seizure at the onset of stroke	Removed entirely
Bleeding diathesis/ OACs	Exclusion: Platelet count <100 000/mm^3 Heparin received within 48 h, resulting in abnormally elevated aPTT Current use of anticoagulant with INR >1.7 or PT >15 s Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests	Contraindication: known bleeding diathesis including but not limited to: Current use of OACs (eg, warfarin sodium), an INR >I.7, or a PT >15 s Administration of heparin within 48 h preceding the onset of stroke with an elevated aPTT at presentation Platelet count <100 000/mm^3 Warning for all indications: patients currently taking OACs	Bleeding diathesis remains a contraindication, but all laboratory values and specific examples removed
ICH	Exclusion: history of previous ICH	Contraindication: history of ICH	Contraindication removed Warning added for recent ICH
BP	Exclusion: Elevated BP (systolic >85 mm Hg or diastolic >10 mm Hg)	Contraindication: uncontrolled hypertension at the time of treatment (eg, >185 mm Hg systolic or >110 mm Hg diastolic)	Contraindication: current severe uncontrolled hypertension remains, specific BP values removed Warning for BP >175/110 mm Hg remains for all alteplase (Activase) indications
Blood glucose	Exclusion: blood glucose <50 mg/dL	Warning: because of the increased risk for misdiagnosis of acute ischemic stroke, special diligence is required in making this diagnosis in patients whose blood glucose values are ≈50 or >400 mg/dL	Removed entirely
Severe stroke	Not listed	Warning: patients with severe neurological deficit (NIHSS score >22) at presentation; there is an increased risk of ICH in these patients	Removed entirely
Mild stroke	Relative exclusion: only minor or rapidly improving stroke symptoms (clearing spontaneously)	Warning: safety and efficacy in patients with minor neurological deficit or with rapidly improving symptoms have not been evaluated; therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended	Removed entirely
Neuroimaging findings	Exclusion: CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)	Warning: Major early infarct sign (substantial edema, mass effect, or midline shift on CT)	Removed entirely
SAH	Exclusion: symptoms suggest SAH	Contraindication: Suspicion of SAH on pretreatment evaluation	Contraindication: subarachnoid hemorrhage

Continued

TABLE 91.5

Comparison of AHA/ASA Acute Stroke Management Guidelines and Previous and New FDA Prescribing Information for Alteplase (Activase) Treatment in Acute Ischemic Stroke—cont'd

CRITERION	AHA/ASA ACUTE STROKE MANAGEMENT GUIDELINE 2013[a]	OLD ALTEPLASE (ACTIVASE) PI (UPDATED 2009)	NEW ALTEPLASE (ACTIVASE) PI (FEBRUARY 2015)
Use in specific populations			
Pregnancy	Relative exclusion	Warning: pregnancy Category C	No change
Nursing mothers	Not listed	Not mentioned	Unknown risk
Children	Inclusion: ≥18 y of age	Indicated for adults	Pediatric use not established
Elderly	Not listed	Warning for all indications: advanced age (eg, >75 y) may increase risks	Warning added: age >77 y was 1 of several interrelated baseline characteristics associated with an increased risk of ICH; efficacy results suggest a reduced but still favorable clinical outcome
Gastrointestinal or genitourinary bleeding	Warning: gastrointestinal or genitourinary bleeding within the past 21 d	Warning: gastrointestinal or genitourinary bleeding within the past 21 d	Warning: gastrointestinal or genitourinary bleeding

[a]From Jauch EC, Saver JL, Adams HP Jr, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 44:870–947, 2013.

AHA/ASA, American Heart Association/American Stroke Association; *aPTT*, activated partial thromboplastin time; *BP*, blood pressure; *CT*, computed tomography; *FDA*, US Food and Drug Administration; *ICH*, intracerebral hemorrhage; *INR*, international normalized ratio; *NIHSS*, National Institute of Health Stroke Scale; *OAC*, oral anticoagulant; *PI*, prescribing information; *PT*, prothrombin time; *SAH*, subarachnoid hemorrhage.

From Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al; American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 47(2):581–641, 2016.

BOX 91.3

Fibrinolytic Therapy for Acute Ischemic Stroke in the 3- to 4.5-Hour Time Window Inclusion and Exclusion Criteria

INCLUSION CRITERIA

Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms within 3 to 4.5 hours before beginning treatment

RELATIVE EXCLUSION CRITERIA

Older than 80 years old
Severe stroke (NIHSS > 25)
Taking an oral anticoagulant regardless of INR
History of both diabetes and prior ischemic stroke

INR, International normalized ratio; *IV*, intravenous; *NIHSS*, National Institutes of Health Stroke Scale; *rtPA*, recombinant tissue plasminogen activator.

thrombectomy.[20] Less favorable outcomes without thrombolysis have been demonstrated in this population of minor stroke patients in particular. Because the risk of symptomatic intracranial hemorrhage (SICH) is proportional to severity, we recommend carefully discussing the benefits and risks with patients when considering rtPA in patients with minor or improving (but not cleared) deficits. These patients are at lower risk of complications relative to patients with moderate to severe stroke, yet many who are not treated still have significant long-term disability.[21]

IV tPA is not recommended when the time of stroke onset cannot be ascertained reliably, including strokes recognized on awakening. Although the aggregate risk of symptomatic ICH is about 6% in trials and observational studies, each individual patient will have differing probabilities of benefits and risks. Optimal methods of communicating benefits and risks promptly have not been developed or widely disseminated, because all reviewed decision aids have methodological deficiencies.[22] However, younger patients and milder strokes (NIHSS < 10) clearly have a lower risk of SICH. It is reasonable to adjust outcome expectations when discussing benefits and risks with older patients with more severe strokes (including significant early CT changes). The risk of severe disability and death is quite high in this population with or without fibrinolysis. Prompt fibrinolysis of severe strokes will shift the outcomes of a population of treated patients toward less disability.[23] Several recent trials suggest these outcomes can be further improved with careful selection of patients for endovascular rescue therapy.

Endovascular Rescue Therapy

The results of several concurrent trials investigating prompt endovascular rescue therapy (usually following IV thrombolysis) versus medical management were published in late 2014 and early 2015. These studies have conclusively demonstrated that patients with severe strokes and evidence of proximal large vessel occlusions have significantly better functional outcomes when treated with the new generation devices.[24-26] Each of these trials used different imaging and clinical selection criteria, although the presence of a proximal occlusion and prompt treatment, preferably within 3 hours, were common to all of the protocols. These trials emphasize the need for better regionalization of stroke care to reduce the time to definitive reperfusion.[27] Unlike acute ischemic stroke, non-acute cases of intracranial occlusions are best treated with medical therapy and not permanent intracranial stents.[28] Intra-arterial thrombolysis currently does not have a defined role in the treatment of acute ischemic stroke.

The recent trials demonstrating clear benefit of endovascular thrombectomy come after a decade of negative studies. The difference in results is due to a combination of improved devices, emphasis on early intervention, and careful patient selection.[29-31] Data from two large trials involving almost 40,000 patients indicate that early use of aspirin in patients with acute ischemic stroke who were not treated with a fibrinolytic agent was associated with a small but significant reduction in rates of stroke recurrence and mortality. These studies in combination suggest a number needed to treat of 77 (ie, 77 stroke patients would need to be treated with daily aspirin therapy to prevent a poor outcome, such as death, dependency at discharge, or at 6 months after stroke, in one patient). The more recent CHANCE trial found that dual-antiplatelet therapy with aspirin and clopidogrel for 90 days significantly reduced recurrent stroke (from 11.7% to 8.2%) in patients initially presenting with high-risk TIA or mild stroke (NIHSS below 4).[32] Aspirin should not be given for the first 24 hours to patients who have received a fibrinolytic agent and not until a swallowing study has been performed.

Anticoagulation

The use of therapeutic dosing of low–molecular-weight heparin (LMWH) or unfractionated heparin is now generally abandoned in the routine care of stroke patients; prophylactic dosing to prevent venous thromboembolism however is a hospital level quality measure and publically reported.[33] It may be that any reduction in risk of subsequent ischemic stroke is balanced by an increased risk of hemorrhagic stroke. To date, no studies have definitively established the efficacy of anticoagulants in the management of patients with acute ischemic stroke, and current AHA guidelines recommend against the routine use of heparinoids in this population.[4] However, heparin is sometimes considered by vascular neurologists in select patients at high risk for stroke progression, including patients with crescendo TIAs or TIA from a cardioembolic source (eg, atrial fibrillation, patients with a high-grade carotid artery stenosis, patients with posterior circulation TIA, and patients with evolving strokes). Heparin or LMWH is often instituted to treat carotid and vertebral artery dissection, unless a contraindication such as intracranial extension is present. If a dissection is diagnosed and the patient has no symptoms of ischemia, treatment with antiplatelet therapy alone may be an option. Heparin therapy should not be initiated in patients with suspected endocarditis or in any patient until a CT scan has ruled out intracranial bleeding.

Intracerebral Hemorrhage

No specific therapy has been demonstrated to substantially improve the outcome of patients with ICH. One of the strongest predictors of mortality when considering ICH patients with comparable severity is the implementation of early care limitations. When health care providers initiate early do not resuscitate (DNR) orders, patients with otherwise equivalent prognoses are more likely to die. As a result, we believe that early prognostication in the ED should be avoided. Current evidence supports the benefit of aggressive medical care. Patients admitted to a specialized unit, patients who are expedited to the intensive care unit (ICU), those admitted on a weekday, and those treated more aggressively appear to have better neurologic outcomes.[61-63] Therefore, even in the absence of therapies specifically proven in phase III trials, multidisciplinary care by specially trained care teams appears to provide benefit.

The patient with suspected ICH requires rapid assessment and transport to a care center with rapid neuroimaging and intensive care management facilities. Out-of-hospital management is similar to that for ischemic stroke, including determination of time of onset, concomitant medications, and application of a prehospital stroke scale.

Supportive care involving attention to airway management and perfusion is of the highest priority. Patients with hemorrhagic stroke are more likely to have an altered level of consciousness that may rapidly progress to unresponsiveness requiring emergent endotracheal intubation. After intubation, a short-acting medication for sedation should be considered so that a neurologic examination can be repeatedly performed and the findings evaluated. Standard care includes establishing IV access and cardiac monitoring. Evaluation of blood glucose and appropriate dextrose and naloxone administration are essential in any patient with altered mental status.

Patients seen early after symptom onset are at high risk of ongoing bleeding. Approximately 30% of such patients will have significant hematoma expansion on presentation, leading to neurologic deterioration and worse outcome. Major therapies aimed at reducing this risk include BP reduction, anticoagulation reversal, and hemostatic therapy.

BP control is commonly performed after ICH. This intervention is controversial, because hypertension may potentiate further bleeding, but lowering BP in a patient with chronic hypertension may decrease CBF, worsening brain injury. One randomized trial found that lowering systolic BP to below 140 reduced ongoing bleeding, but there was no change in neurologic outcome, suggesting that this therapy may not provide clinical benefit in unselected patients. A larger trial focused on functional outcomes demonstrated that prompt reduction to a systolic blood pressure (SBP) of 140 mm Hg may slightly reduce disability and was generally safe.[34] The current consensus regarding management of ICH is to provide antihypertensive treatment with parenteral agents for systolic pressures higher than 160 to 180 mm Hg or MAP higher than 130 mm Hg. Recommended agents include labetalol, esmolol, nicardipine, clevidipine, and hydralazine.[3]

Many patients are coagulopathic at the time of their ICH; and for patients on anticoagulants, emergency reversal will theoretically minimize the risk of further bleeding, although this is not backed up by clinical trial evidence. For patients on warfarin, reversal is achieved using IV vitamin K (10 mg IV or subcutaneously), supplemented with either fresh frozen plasma (FFP) (2 to 4 units) or prothrombin complex concentrate (PCC) (Kcentra 25 to 50 units/kg depending on INR—dosing varies for other PCCs by formulation).[3] Of the new generation oral anticoagulants, at this time only dabigatran has a specific antidote (idarucizumab) proven to reverse coagulant effects in human clinical trials.[35] Four-factor PCC is likely to be the most quickly available reversal agent for apixaban and rivaroxaban; hemodialysis will rapidly eliminate dabigatran from the circulation but is not generally practical for patients with serious bleeding.[36] Hemostatic therapy (treatment with procoagulant agents; eg, recombinant activated factor VII in patients without baseline coagulopathy) was initially promising; however, a phase III trial showed no clinical benefit.

To consider other iatrogenic coagulopathies, post-thrombolytic symptomatic intracranial hemorrhage is a serious complication. Although various protocols have been employed for post-thrombolysis intracranial hemorrhage, a comparative observational study comparing reversal with FFP or cryoprecipitate versus conservative management (no reversal) demonstrated poor outcomes in both groups. Mortality was slightly higher in the reversal group, although this study only included 48 patients.[37] Based on the limited evidence, at this point in time we would recommend administering cryoprecipitate (6 to 8 units) for thrombolytic associated ICH that occurs shortly (0 to 3 hours) after alteplase administration. Later ICH (3 hours to days) is unlikely to be associated with a persistent coagulopathy, because the fibrinogen depletion following alteplase administration is transient; therefore, reversal

agents appear to confer risk without a potential biological benefit in this time window.

Finally, the data on treatment of patients with spontaneous ICH who are on preexisting antiplatelet treatments, such as aspirin or clopidogrel, is conflicting. A small subgroup of an observational trial (27 patients) suggested patients receiving a platelet infusion within 12 hours of onset had an increased odds of a good functional outcome.[38] At this time, the data do not support platelet transfusions in patients with spontaneous ICH being treated with antiplatelet agents, unless a new thrombocytopenia (platelet count <30,000) has also developed.

For patients with clinical or radiographic evidence of elevated ICP, therapies aimed at lowering ICP should be considered. First, neurosurgical consultation is obtained to evaluate the benefits of an external ventricular drain (EVD) placement or hematoma evacuation. Pending consultation, a number of medical therapies aimed at decreasing ICP are available; however, these interventions should not be used prophylactically.[3] Hyperventilation can be a temporizing measure pending more definitive treatment. Mannitol moves fluid from the intracranial compartment, thereby reducing cerebral edema. Hypertonic saline (3% or 23.4%) can be used as an alternative to mannitol or in combination. Other experimental modalities include barbiturate coma and hypothermia.

Seizure activity can cause neuronal injury, elevations in ICP, and destabilization of an already critically ill patient. However, there is observational evidence that prophylactic administration of antiepileptic drugs (AEDs) may be harmful; therefore, AEDs should be reserved for patients with known or suspected seizure, including nonconvulsive seizures.[3]

Surgical evacuation of the hematoma is not beneficial in most cases of non-cerebellar ICH. Selected patients with a sizable lobar hemorrhage that is proximal to the cortical surface and associated with progressive neurologic deterioration may benefit from surgical drainage. Recent studies have also suggested that minimally invasive surgery (eg, stereotactic insertion of a catheter) may provide some benefit to selected patients. For patients with cerebellar hemorrhage, surgery can be lifesaving, because the infratentorial space is much more limited and high ICP can disrupt vital brainstem functions. For this reason, many neurosurgeons will consider emergent surgery for patients with cerebellar hemorrhage within 48 hours of onset.

In cases of severe intraventricular hemorrhage or hemorrhages in the posterior fossae, the normal circulation of cerebrospinal fluid (CSF) can become interrupted, leading to the development of hydrocephalus. This condition is characterized by an abnormal rise in CSF volume. In such cases, neurosurgeons will often place a ventricular catheter. Some groups infuse thrombolytic agents through the catheter to help break up the clot and minimize the risk of hydrocephalus.

Finally, as with ischemic stroke, general supportive care should be provided to minimize neuronal injury. This includes treating hyperthermia (such as, with acetaminophen) and treating hyperglycemia with insulin.

DISPOSITION

Ischemic Stroke and Transient Ischemic Attacks

"Stroke center" definitions have been established, and there is a national certification process for primary stroke centers (PSCs) and comprehensive stroke centers (CSCs) in the United States. In broad terms, institutional certification as a PSC requires the establishment of a stroke infrastructure (ie, a stroke team, stroke unit, patient care protocols, and support services, including CT scanning and laboratory testing availability), as well as institutional administrative support and strong leadership.[4,39] CSCs offer advanced imaging modalities, perform surgical and endovascular interventions, and maintain a core infrastructure, such as a stroke unit and stroke registry. The establishment of PSCs and CSCs is intended to improve outcomes for stroke patients by ensuring a high level of coordinated care.

The most recent level of stroke classification for hospitals is the acute stroke-ready hospital (ASRH). These hospitals are typically smaller facilities with lower stroke patient volumes. An ASRH is capable of establishing the initial stroke diagnosis, as well as providing acute stabilization and treatment. The use of telemedicine technologies between the ASRH and PSC/CSC will likely serve a pivotal role in support of clinical care. After initial stabilization and treatment, stroke patients will frequently be transferred to PSC or CSC institutions.[40]

It is recommended that patients with symptoms consistent with an acute stroke be transported to emergency facilities capable of initiating fibrinolytic therapy within 1 hour of hospital arrival. At a minimum, this requires emergent CT capabilities, an institutional "acute stroke protocol," and availability of a physician knowledgeable in the use of thrombolytic therapy. Intensive care monitoring and neurosurgery capabilities should be available within 2 hours of drug initiation, either at the treating hospital or by helicopter or ground transport to an appropriate health care facility.[39]

In most cases, once the diagnosis of an acute stroke or stroke syndrome is established and the patient is stabilized, hospitalization will be necessary for further evaluation and treatment. Patients may deteriorate over the first 24 hours and require close in-hospital monitoring. Most patients can be managed on a general medical or telemetry unit, although there is evidence suggesting a benefit from admission to a stroke-specific unit. Patients with large acute hemispheric strokes (associated with increased risk of herniation) or with significant posterior circulation-related changes and those treated with a fibrinolytic agent should be monitored in a step-down or ICU for at least 24 hours.

In many centers, patients require admission to receive a prompt evaluation for TIA. However, some centers have developed ED observation unit protocols or rapid outpatient TIA clinics to ensure an expedited evaluation (see Chapter e6). One commonly used tool available to help select which TIA patients are at highest risk (and thus likely should be admitted) versus those at lowest

TABLE 91.6

ABCD2 Score for Assessing Stroke Risk in Patients With a Transient Ischemic Attack

RISK FACTOR	POINTS
Age >60 years old	1
Initial BP >140/90 mm Hg	1
Unilateral weakness	2
SPEECH IMPAIRMENT	
Without weakness	1
Symptoms 10 to 59 minutes	1
Symptoms ≥60 minutes	2
History of diabetes	1
RESULT	
0 to 3 = Low risk (1% risk of stroke in 48 hours)	
4 to 5 = Moderate risk (4.1% risk of stroke in 48 hours)	
≥6 = High risk (8% risk of stroke in 48 hours)	

BP, Blood pressure.

risk (who might therefore be safe for expedited outpatient evaluation) is the ABCD2 score (Table 91.6). In addition, most patients without a contraindication will be started on antithrombotic therapy in the ED after consultation with a neurologist.

The majority of patients with an acute hemorrhagic stroke should be admitted to an ICU in which specialty consultation is available. If this is unavailable at the evaluating institution, the patient should be transported to an appropriate institution.

KEY CONCEPTS

- Anterior circulation strokes result in contralateral hemiparesis of the face and body.
- Vertebrobasilar strokes result in ipsilateral CN deficits and contralateral hemiparesis.
- Posterior cerebral artery stroke causes ipsilateral CN III palsy and contralateral homonymous hemianopsia.
- Wallenberg's syndrome (lateral medullary syndrome) causes vertigo, Horner's syndrome, ipsilateral facial numbness, loss of corneal reflex, and contralateral loss of pain/temperature.
- Cervical artery dissection is a common cause of stroke in young patients; TIAs preceding stroke in these patients are often missed.
- The goal for eligible patients is to receive thrombolytics within 90 minutes of symptoms onset; the dose of alteplase is 0.9 mg per kg with 10% given as a bolus and the remaining 90% given over 1 hour.
- Acute ischemic stroke patients receiving alteplase are at risk of developing a spontaneous intracranial hemorrhage; the risk is lowest in patients with a low stroke score, no hypertension, no diabetes, and age younger than 70.
- In acute ischemic stroke, the patient and or their families should be informed of the risk and benefit of treatment with alteplase.
- Patients with a hemorrhagic stroke on coumadin should *be promptly reversed* using vitamin K and either FFP or PCC.
- Prognosis is worse in acute stroke in the setting of fever, hypotension, hypoxia, and hyperglycemia.
- Carotid Doppler, MRA, or CTA studies are recommended before discharge of a patient with TIA from the ED.
- Overly aggressive BP management should be avoided in patients with acute ischemic stroke.
- Accurate identification of the last time a patient was known to be at his or her neurologic baseline should be documented in all patients with stroke.
- IV alteplase followed by endovascular thrombectomy is recommended in patients with large anterior circulation artery occlusion.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 91: QUESTIONS & ANSWERS

91.1. Which of the following statements concerning ischemic stroke is true?

A. Anterior circulation strokes are more likely than posterior strokes to show evidence of progression at the time of presentation.

B. Anterior circulation strokes rarely present with complete loss of consciousness.

C. Posterior cerebral artery strokes are associated with incontinence, leg weakness greater than arm weakness, and gait clumsiness.

D. The presence of aphasia suggests an anterior cerebral artery (ACA) distribution stroke, typically left sided.

E. The presence of diplopia suggests an anterior circulation stroke.

Answer: B. Forty percent of posterior and 20% of anterior circulation strokes present with progressive symptoms. It is rare for anterior circulation (carotid, ACA, and middle cerebral artery [MCA]) strokes to significantly alter consciousness, unless there has been a previous contralateral stroke. ACA strokes primarily affect frontal lobe functions and may also present with primitive grasp and such reflexes. In addition to contralateral motor and sensory defects, MCA strokes may present with expressive aphasia, agnosia, and ipsilateral hemianopsia.

91.2. Which of the following is not associated with posterior circulation strokes?

A. Diplopia

B. Homonymous cranial nerve (CN) and extremity motor deficits

C. Loss of consciousness

D. Loss of visual object recognition

E. Nausea, vomiting, and ataxia

Answer: B. Posterior circulation (vertebrobasilar) strokes involve the vertebral, basilar, and posterior cerebral arteries. Because this system supplies the reticular activating system, cerebellum, brainstem, occipital lobe, and brainstem vomiting centers, loss of

consciousness with vomiting, visual changes, and cerebral ataxia may be seen. Ipsilateral CN deficits (because these nuclei largely reside in the brainstem) occur with contralateral "body" deficits resulting from motor/sensory fiber decussation.

91.3. Headache, vomiting, and a decreased level of consciousness are most commonly seen with which of the following disorders?
A. Ischemic stroke
B. Intracranial hemorrhage
C. Migraine headache
D. Subarachnoid hemorrhage (SAH)
E. Tic douloureux

Answer: D. The incidence of headache is highest by far in patients with SAH. Vomiting and depressed loss of consciousness are also generally more common in this group. Pure migraine headache rarely, if ever, causes a depressed loss of consciousness. Tic headaches do not cause loss of consciousness.

91.4. What percentage of patients with hemorrhagic stroke experience clinical deterioration because of growth in hemorrhage volume within the first hours?
A. 10%
B. 20%
C. 30%
D. 50%
E. 75%

Answer: C. Thirty percent of patients with intracerebral hemorrhage (ICH) experience early hemorrhage expansion. Progression of neurologic deficits and decreasing mental status suggest the diagnosis.

91.5. A 69-year-old male presents with headache, vomiting, aphasia, a right lower facial palsy, and right upper greater than right lower extremity weakness. The symptoms began approximately 4 hours before arrival. Vital signs are temperature 99° C, blood pressure (BP) 180/90 mm Hg, respiratory rate 18 breaths per minute, heart rate 92 beats per minute, and oxygen saturation 96% on room air. Emergent computed tomography (CT) scan shows a left temporal intracerebral hemorrhage (ICH). Soon after presentation, the patient experiences increased vomiting and a diminishing level of consciousness. What is the most likely explanation for this deterioration?
A. Accompanying subarachnoid hemorrhage (SAH)
B. Acute brainstem herniation
C. Hypoxia from neurogenic pulmonary edema
D. Increase in volume of the ICH
E. Myocardial infarction with cardiogenic shock

Answer: D. Approximately one-third of patients with ICH experience early hemorrhage volume expansion. Although brainstem herniation is a possibility, this is typically a later sequelae with a more gradual presentation. Acute myocardial infarction may be associated with intracranial emergencies but would not likely cause an abrupt mental status change. Neurogenic pulmonary edema may accompany any condition with elevated intracranial pressure (ICP) but, again, would not likely cause an abrupt mental status change.

91.6. After complete occlusion of cerebral vessels, irreversible neurologic deficits are expected to reliably occur within how many hours?
A. 2
B. 3
C. 4
D. 5
E. 6

Answer: E. Thus ischemic stroke trials, using fibrinolytic or antiplatelet agents, have attempted to recanalize occluded arteries and reperfuse ischemic areas of the brain within a 2- to 6-hour therapeutic window.

91.7. Which of the following areas of the brain is perfused by the posterior circulation?
A. Internal capsule
B. Posterior aspect of the temporal lobe
C. Putamen
D. Speech areas of the temporal lobe
E. Thalamus

Answer: E. The thalamus is perfused by the posterior circulation. The other areas are perfused by the anterior circulation.

91.8. Which of the following statements regarding stroke etiology is true?
A. Lacunar strokes reliably cause a pure motor deficit.
B. Less than 1% of strokes occur in the 15- to 45-year-old age group.
C. One-third of ischemic strokes are thrombotic.
D. Strokes resulting from atrial fibrillation likely involve small vessels.
E. Two-thirds of ischemic strokes are cardioembolic.

Answer: C. One-third of ischemic strokes are thrombotic. Lacunar strokes may cause a pure motor, pure sensory, or ataxic/hemiparesis stroke. Vessel occlusion resulting from atrial fibrillation–induced emboli more likely involves the large vessels. Three percent to 4% of ischemic strokes occur in the 15- to 45-year-old age group.

91.9. A 29-year-old female presents with a left-sided headache after a moderate-speed motor vehicle collision (MVC). She suffered no loss of consciousness and has no other complaints or obvious injuries. Physical examination is remarkable only for drooping of the left eyelid and slight miosis of the left pupil compared with the right. Which of the following would be the diagnostic test of choice?
A. Brain magnetic resonance imaging (MRI) with gadolinium
B. Contrasted computed tomography (CT) scan of the brain
C. CT angiogram of the carotid arteries
D. Uncontrasted CT scan of the brain
E. Urine drug screen

Answer: C. Carotid or vertebral artery dissection can occur after trauma or mild events, such as yoga, twisting, or prolonged static positions looking upward. The hallmark is unilateral neck pain, face pain, or headache, often with accompanying Horner's syndrome. Acutely, cerebral ischemic changes would not be seen on brain imaging. Carotid and vertebral dissection is not a contraindication for thrombolytic therapy in the eligible patient.

91.10. What percentage of patients who experience a transient ischemic attack (TIA) will develop a stroke within 3 months?
A. 5%
B. 10%
C. 15%
D. 20%
E. 25%

Answer: B. One-tenth of them will occur within 2 days of the sentinel event.

91.11. A 28-year-old G3P3 woman who is 2-weeks postpartum after an uncomplicated vaginal delivery presents with acute onset of mild headache, lethargy, and double vision. Physical examination is remarkable for normal vital signs and a left eye lateral gaze palsy. The most appropriate intervention is likely to be which of the following?

A. Computed tomography (CT) scan of the brain with possible lumbar puncture
B. CT scan of the brain and intravenous (IV) heparin
C. Erythrocyte sedimentation rate (ESR) and IV corticosteroids
D. IV magnesium
E. Lumbar puncture and IV antibiotics

Answer: B. Cerebral venous thrombosis may present with headache, lethargy, cranial nerve (CN) deficits, seizures, or even psychiatric complaints. CT scan and/or magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) are likely to reveal the diagnosis. Treatment includes heparin. Neurosurgical consultation is not useful. Subarachnoid hemorrhage (SAH) would not be expected to cause a focal neurologic deficit. Eclampsia and meningitis would be expected to give characteristic findings on history and examination.

91.12. Which of the following statements is true regarding management of acute ischemic stroke?

A. Heparin is indicated for patients in whom thrombolysis is not an option.
B. If the initial computed tomography (CT) scan shows a large left middle cerebral artery (MCA) distribution stroke but no hemorrhage, thrombolysis would be indicated.
C. Initial blood pressure (BP) greater than 185/110 mm Hg would contraindicate thrombolytic treatment.
D. Mechanical thrombectomy may be indicated up to 6 hours after stroke onset.
E. No clot retrieval devices have been U.S. Food and Drug Administration (FDA) approved for acute ischemic stroke management.

Answer: D. Intra-arterial thrombolysis may offer benefit up to 6 hours past stroke onset. BPs higher than 185/110 mm Hg are not an absolute contraindication to thrombolysis if they can be lowered to this level with one or two doses of a parenteral agent, such as labetalol or enalapril. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retrieval device was FDA approved in 2004, and several newer stent-retriever devices have been approved since then. In recent trials of thrombectomy, improved outcomes were demonstrated at least to 6 hours; and outcomes were even better when patients received reperfusion within 4.5 hours of onset. Aspirin has a proven benefit in patients who do not receive tissue plasminogen activator (tPA). There is no proven benefit to heparin, although some practitioners use it in cases at high risk of stroke progression.

91.13. An 82-year-old male presents with an apparent stroke. He is rapidly evaluated and determined to be within the 3- to 4.5-hour window for fibrinolytic therapy. Which of the following exclusion criteria applies only to the 3- to 4.5-hour criteria and not the 0- to 3-hour criteria?

A. Administration of heparin within the 48 hours preceding the stroke onset
B. Age older than 80 years
C. High clinical suspicion for subarachnoid hemorrhage (SAH)
D. Seizure at the onset of the stroke
E. Symptoms rapidly improving

Answer: B. In the 3- to 4.5-hour window, patients cannot exceed 80 years of age. Heparin administration within the 48 hours preceding stroke onset is a contraindication in both the 0- to 3-hour window as well as the 3- to 4.5-hour window. Similarly, high clinical suspicion for SAH, seizure at the onset of the stroke symptoms, and rapidly improving symptoms are contraindications to fibrinolysis in both time windows.

91.14. A 66-year-old female presents with a possible transient ischemic attack (TIA). Approximately 1 hour before her arrival, she had a 15-minute episode of strictly right arm and right leg weakness, and her symptoms have now resolved. Her blood pressure (BP) is 165/92 mm Hg. Her prior medical history is significant for hypertension, high cholesterol, and diabetes mellitus. What is her ABCD2 score?

A. 4
B. 5
C. 6
D. 7
E. 8

Answer: C. The patient's ABCD2 score is 6 (age >60 years, BP >140/90 mm Hg, unilateral weakness, symptoms lasting 10 to 59 minutes, and history of diabetes). No speech impairment is reported.

91.15. A 72-year-old male presents with an apparent stroke. Computed tomography (CT) imaging of the brain demonstrates only a hyperdense middle cerebral artery (MCA) sign and no other ischemic changes. He was last seen neurologically normal 4 hours earlier. Which of the following is a contraindication to fibrinolytic therapy in this patient?

A. His blood glucose is 372 mg/dL.
B. His National Institutes of Health (NIH) Stroke Scale score is 24.
C. His platelet count is 110,000/mm^3.
D. His systolic blood pressure (BP) is 180 mm Hg.
E. He takes warfarin daily.

Answer: E. Any oral anticoagulant treatment (regardless of the patient's international normalized ratio [INR]) is a contraindication to fibrinolysis in the 3- to 4.5-hour treatment window. Other contraindications include an NIH stroke scale score greater than 25, platelet count less than 100,000/mm^3, blood glucose greater than 400 mg/dL, and systolic BP greater than 185 mm Hg.

91.16. A 75-year-old man is brought to the emergency department (ED) for altered mental status. After computed tomography (CT) imaging of the brain is performed, he is found to have a large intracerebral hemorrhage (ICH). Which of the following options is *not* an appropriate strategy for lowering intracranial pressure (ICP)?

A. Barbiturate-induced coma
B. Hyperthermia induction
C. Hypertonic saline administration
D. Hyperventilation
E. Mannitol administration

Answer: B. Hypothermia is an experimental modality for lower ICP. Hyperventilation can serve as a temporizing measure for reducing ICP. Mannitol and/or hypertonic saline can also be administered. Inducing a barbiturate coma is also an experimental modality.

CHAPTER 92

Seizures

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PRINCIPLES

Background and Classification

Seizures are excessive abnormal neuron activity associated with alterations in sensory, motor, autonomic, and/or cognitive function. *Convulsion* refers specifically to the motor manifestations of a seizure. The *ictal period* is the time during which a seizure or seizure-like activity occurs. A *postictal period* is an interval of altered mental status immediately following a seizure, generally lasting less than 1 hour.

Seizures may be provoked by, or secondary to, an acute clinical process (eg, acute central nervous system [CNS] insults, toxins, and acute metabolic derangements) (Box 92.1). Conversely, primary seizures are unprovoked and have no acute inciting pathology.

Epilepsy refers to a condition of recurrent unprovoked seizures. For example, a patient who suffers head trauma might have a seizure but would not be considered to have epilepsy unless there are recurrent unprovoked ictal events as a result of the brain injury. Many cases of epilepsy are idiopathic, and the onset of these typically occurs during childhood or adolescence. Unprovoked seizures may begin *de novo* in adulthood, but this is rare and thus a diagnosis of exclusion.

Unprovoked seizures may recur randomly or predictably. Cyclic recurrence has been reported with awakening, sleep deprivation, emotional or physical stress, and menses. A specific sensory stimulus, such as flashing lights or a specific smell, may trigger seizures in certain patients. Note that seizures are still considered "unprovoked" when they are triggered by a process that would not cause a seizure in the nonepileptic patient.

Seizures are classified as partial (focal) or generalized (Fig. 92.1). *Partial seizures* involve abnormal neuronal firing within a confined population of neurons in one brain hemisphere, and the clinical manifestations tend to reflect the area of electrical activity. *Simple focal seizure* traditionally refers to focal seizure with preserved mental status, whereas *complex focal seizures* involve some degree of impaired consciousness. *Generalized seizure* denotes abnormal neuronal firing throughout both brain hemispheres and always involves alterations of consciousness. *Secondarily generalized* seizures start as a focal seizure and then progresses to a generalized event.

Subclassification of focal seizures, although no longer used, is clinically useful to describe the ictal origin and manifestation.[1] Symptoms can be motor (such as, facial twitching or rhythmic ipsilateral extremity movements), autonomic (such as, tachycardia or diaphoresis), somatosensory (such as, tingling or perceiving a certain smell), or psychic (such as, sense of déjà-vu). Psychic and somatosensory seizures, which involve only subjective, nonobservable symptoms, are referred to as *auras* when they precede a generalized seizure.

The symptoms of generalized seizures are more global. One subtype, *absence seizures,* manifest as brief dissociative states, often without muscle or postural changes. Other generalized seizures are classified by their specific type of motor activity: *tonic* (stiffening), *clonic* (rhythmic jerking), *tonic-clonic, myoclonic* (discrete violent muscle contractions), or *atonic* (loss of muscle tone). The common term *grand mal seizure* refers to generalized tonic-clonic seizures.

Status epilepticus is unremitting seizure activity of greater than 5 minutes' duration, or recurrent seizure activity without intervening return to baseline mental status.[2] Previous definitions of status epilepticus required 30 minutes of continuous activity based on the time thought to be required for seizures to inflict secondary damage. However, secondary effects can occur in under 30 minutes, and seizure activity is unlikely to cease spontaneously once it has continued for 5 minutes.[2,3]

Status epilepticus is divided into two basic categories: generalized convulsive status epilepticus (GCSE) and nonconvulsive status epilepticus (NCSE). GCSE typically involves tonic-clonic seizures and is a medical emergency, with mortality directly correlated with the duration of the event. NCSE presents clinically as an alteration in behavior that is associated with continuous epileptiform discharges on electroencephalogram (EEG). The altered mental status may range from a subtle change to coma, and it may be associated with subtle motor signs, such as twitching, blinking, eye deviation, persistent aphasia, or somatosensory findings. NCSE should be considered in patients in coma of undetermined etiology and patients who appear to have a prolonged post-ictal event. NCSE may be present in 10% or more of hospitalized patients with prolonged decreased cognition of undetermined etiology.[4]

A patient is considered to be in refractory status epilepticus when the seizure does not terminate after treatment with a benzodiazepine and a second antiepileptic drug. See Chapter 15 for a detailed discussion of the management of status epilepticus.

A relevant question for the emergency clinician treating the seizing patient is whether the number or duration of seizures carries any significance with regard to the potential for recurrence and how this might influence cognitive outcomes. Patients with provoked seizures show equal incidence of later development of epilepsy regardless of whether or not treatment with antiepileptic drugs was initiated immediately after the inciting event.[5] For patients with unprovoked seizures, the evidence is less straightforward.

Whether recurrent or prolonged seizure activity can lead to cognitive deterioration remains a subject of debate. In general, current data challenge the idea of a common seizure-dependent mechanism for epilepsy progression and intellectual impairment. Although some studies have proposed that status epilepticus alone may result in cognitive impairment, independent of the inciting cause, most recent studies demonstrate that the majority of patients with epilepsy do not show a progressive disorder. The rare cases of intellectual decline and progressive worsening of seizures are limited to specific epileptic events (eg, mesial temporal lobe epilepsy, which can follow a progressive course induced by recurrent seizure activity).[6]

Epidemiology

Patients presenting to the emergency department (ED) with seizures have a bimodal distribution, with the highest incidence

BOX 92.1

Etiology of Status Epilepticus: Common Causative Disorders

METABOLIC DISTURBANCES
Hepatic encephalopathy
Hypocalcemia
Hypoglycemia or hyperglycemia
Hyponatremia
Uremia

INFECTIOUS PROCESSES
CNS abscess
Encephalitis
Meningitis

WITHDRAWAL SYNDROMES
Alcohol
Antiepileptic drugs
Baclofen
Barbiturates
Benzodiazepams

CENTRAL NERVOUS SYSTEM LESIONS
Acute hydrocephalus
Anoxic or hypoxic insult
Arteriovenous malformations
Brain metastases
Cerebrovascular accident
Chronic epilepsy
Eclampsia
Head trauma
Intracerebral hemorrhage
Neoplasm
Neurosurgery
Posterior reversible leukoencephalopathy
Remote structural injury

INTOXICATION
Bupropion
Camphor
Clozapine
Cyclosporine
Flumazenil
Fluoroquinolones
Imipenem
Isoniazid
Lead
Lidocaine
Lithium
MDMA
Metronidazole
Synthetic cannabinoids
Theophylline
Tricyclic antidepressants

CNS, Central nervous system; *MDMA, N*-methyl-3,4-methylenedioxyamphetamine.

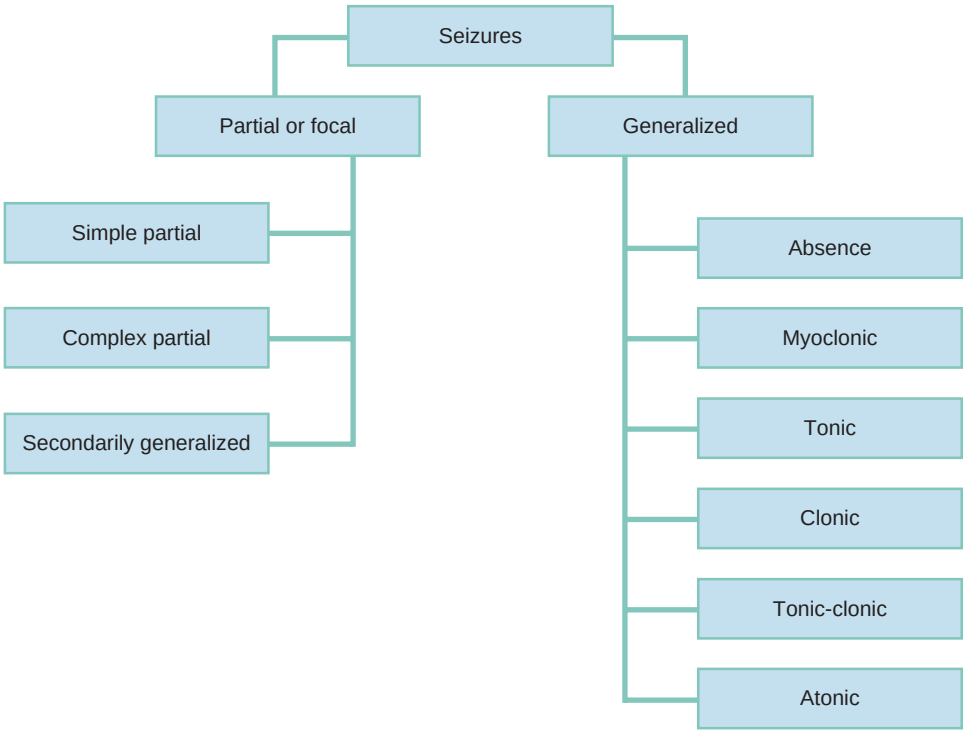

Fig. 92.1. Simplified classification of seizures. (From ILAE proposal for revised terminology for organization of seizures and epilepsies 2010. Available at: www.ilae.org/commission/class/documents/ILAE%20HandoutV10.pdf.)

among infants and individuals older than 75 years old. This is explained by the high prevalence of febrile seizures in infants and structural brain damage in elders. Up to 45% of adults presenting with a first unprovoked seizure will experience another within 2 years, most occurring in the first year. The risk is higher with known brain lesions, imaging abnormalities, or nocturnal seizures. Up to 50% of patients with epilepsy have recurrent seizures despite initiation of therapy.

Pathophysiology

When normal neurophysiology exists, neuronal cell membranes are stabilized by electrochemical gradients across the membranes and by equilibrium among inhibitory neurotransmitters, such as gamma-aminobutyric acid (GABA), and excitatory neurotransmitters, including glutamate and acetylcholine. Seizures start when the equilibrium across the cell membrane is disturbed, leading to abnormal electrical discharge of cortical and subcortical neurons.

Infection, toxins, electrolyte imbalances, and other pathologic processes can disrupt the neuronal equilibrium locally and trigger electrical activity, resulting in a seizure. Electrical activity, in turn, can lead to recruitment of nearby neurons, and a partial seizure can spread. This is the underlying mechanism for Jacksonian March, when focal motor seizure symptoms spread in a step-wise fashion.

When the electrical activity extends below the cortex to deeper structures, the reticular activating system in the brainstem may be affected, altering consciousness. In generalized seizures, the focus often is subcortical and midline, which likely explains the prompt loss of consciousness and bilateral involvement.

Typically seizures are self-limited; at some point, the hyperpolarization subsides and the electrical discharges from the focus terminate. This termination may be related to reflex inhibition, loss of synchrony, neuronal exhaustion, or alteration of the local balance of acetylcholine and GABA in favor of inhibition. Most drugs used to interrupt seizures act on $GABA_A$ subtype receptors, therefore enhancing inhibitory activity.

During ongoing seizure activity, neuronal $GABA_A$ receptors may be degraded and internalized whereas excitatory *N*-methyl-D-aspartate (NMDA) receptors may be upregulated. This perpetuates an excitatory state and leads to sustained seizure activity, making it the physiologic basis for the old adage, "seizures beget seizures." Loss of $GABA_A$ receptors in status epilepticus can decrease response to GABAergic drugs, such as benzodiazepines, barbiturates, and propofol.[3]

Seizures produce a number of secondary physiologic derangements. Sympathetic stimulation leads to increases in body temperature, heart rate, respiratory rate, serum glucose, and lactic acid. Elevated lactate occurs within 60 seconds of a convulsive event and normalizes within an hour after ictus. A rise in the peripheral white blood cell count without an increase in bands is also often seen. With more prolonged convulsions, hypoglycemia, neurogenic pulmonary edema, skeletal muscle damage, and, rarely, frank rhabdomyolysis may ensue. Autonomic discharge and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting, tongue biting, and potential airway impairment. Also rarely, the force generated by the muscle contractions in these seizures can be strong enough to cause posterior shoulder dislocations or fractures.

CLINICAL FEATURES

In caring for patients who may have seized, one must first attempt to determine whether the event in question was a seizure. A common clinical scenario for the emergency clinician is the patient who presents with a history of having had a seizure-like episode, usually involving sudden loss of consciousness and some type of motor activity. However, neurogenic seizures are not the only process that can cause these symptoms. (See the Differential Diagnosis section later for discussion of common seizure mimics.)

Identifying the circumstances surrounding the event, such as possible inciting factors and progression and duration of symptoms, will provide important clues regarding whether the episode was a seizure. However, as a general rule, no single clinical feature or diagnostic modality is 100% confirmatory for occurrence of a neurogenic seizure. A prospective study that assessed which clinical aspects help distinguish seizures from syncope found a seizure to be five times more likely than syncope if the patient was disoriented after the event and three times more likely if the patient was older than 45 years old. Remarkably, incontinence and trauma were not discriminative findings between seizure, syncope, and nonepileptic attack disorder. Additional studies have shown that postictal confusion, tongue biting, cyanosis, confirmed unresponsiveness, preceding déjà vu or jamais vu, head or eye turning to one side, and rhythmic limb shaking or dystonic posturing are also strong markers of seizure.

For the patient who is presumed to have seized or be seizing, the clinician should treat any persisting seizure activity and then consider the likelihood of underlying pathology requiring emergent treatment. A thorough history and physical examination largely directs the evaluation and can usually prevent the need for broad-based diagnostic testing. Unfortunately, the actively-seizing or postictal patient is often unable to provide reliable history or to cooperate during the initial examination. Witnesses, relatives, paramedics, medical alert bracelets, old medical records, and medication lists or containers often provide critical clues to assessing these patients.

Clinical History

The clinician should obtain any history of trauma (either before or during the seizure), alcohol intoxication or abuse, and pregnancy. See the Special Cases section for separate discussions of seizures in these contexts.

Although febrile seizures are common in children (see separate discussion of seizures in pediatric patients in Chapter 174) this is not true of adults, and fever preceding a seizure can indicate CNS infection. Patients who are immunocompromised, had recent neurosurgery, or have CNS hardware (such as, a shunt) are at particularly high risk. Fifteen percent of patients with bacterial meningitis will have at least one seizure, and surviving patients have an increased residual risk of epilepsy.

Severe headache prior to seizure raises concern for intracranial bleeding, especially in elders and anticoagulated patients. Patients with indwelling shunts and a headache prior to seizure may have shunt failure. Headache *after* a seizure may be indicative of bleeding but may also be part of a post-ictal syndrome.

Seizure patients with preceding neurologic deficits may have a seizure as a symptom of an acute stroke. Ischemic or hemorrhagic stroke is a leading cause of new-onset seizures in elders.[7,8] The overall incidence of seizures with stroke ranges from 5% to 15%; more than one-half occur within the first week after stroke. The incidence of epilepsy after stroke is 4% to 9%. Seizures that occur acutely with stroke are thought to result from local metabolic alterations in the CNS. These events are transient, and the seizures often are focal and self-limited. Stroke-related seizures that develop later are more likely to be generalized.

Symptomatic dysrhythmias can cause cerebral hypoperfusion and hypoxia, which can lead to seizure activity. Prolonged QT syndrome has been misdiagnosed as a primary seizure disorder. A careful history may identify preceding cardiac symptoms, such

as palpitations, lightheadedness, or diaphoresis. An electrocardiogram (ECG) may be diagnostic; but when it is not clear, a concurrent cardiac evaluation may be indicated.

As these examples demonstrate, obtaining a history of nonneurologic comorbid disease plays an important role in identifying underlying pathology requiring treatment. In addition to testing prompted by known or suspected cardiac disease, the existence of renal failure, immunosuppression, or recent electrolyte abnormality may drive laboratory investigations of electrolytes and uremia. Diabetes raises concern for hypoglycemia. Patients with a psychiatric history may have psychogenic seizures, but they may also suffer from hyponatremia due to pathologic water intoxication or as an adverse effect of a psychiatric medication. Those with depression or psychosis may be at higher risk for drug- or toxin-related seizures. Patients with malignancy may have a new or enlarging CNS lesion. Alzheimer's disease has been noted to increase the risk of epilepsy by tenfold.

The patient's social history is also important. Noncompliance with anticonvulsants is the most common cause for the ED presentation of recurrent seizures. Certain recreational drugs (such as, cocaine, phencyclidine, and ecstasy) are known to decrease the seizure threshold. Common causes of adult-onset partial seizures in the developing world include neurocysticercosis (especially Central and South America) and malaria, both of which should be considered in travelers and immigrants. Finally, investigation of potential precipitants (such as, sleep deprivation, infection, or new medications, especially those that can lower the seizure threshold or affect later antiepileptic drug metabolism) is key to managing the patient with a known seizure disorder who has a typical event while on medications.

Physical Examination

An accurate set of vital signs is the foundation of any physical examination. Although a low-grade fever is common immediately after a prolonged convulsion, a persistently high temperature suggests infection or drug reaction. Hypertension with bradycardia may be the result of rising intracranial pressure and impending herniation. Irregular heart rate may accompany a stroke. Anticholinergic and sympathomimetic syndromes may suggest a drug-related seizure, which may make a significant difference in management.

If the patient presents actively seizing, observe the specifics of the motor activity. Focal abnormalities and eye deviation are signs of an epileptic focus. Anecdotally, pupils are often reported to be dilated during or after a seizure; persistent mydriasis may reflect anticholinergic or sympathomimetic toxicity. Some patients in NCSE are mistakenly assumed to be postictal instead of actively seizing.

Mental status should be carefully documented and observed for change. When possible, recruit family members or contacts who know the patient's baseline mental status. Postictal confusion usually resolves within 1 hour; failure to improve should prompt a search for alternate explanations (Box 92.2).

A thorough neurologic examination is the key component of the evaluation. Hyperreflexia and extensor plantar responses are suggestive of a recent seizure and should resolve during the immediate postictal period. Neurologic deficits may represent an old lesion, new intracranial pathology, or postictal (Todd's) paralysis. Todd's paralysis is a focal motor deficit that may persist up to 24 hours after generalized or complex partial seizures and may be caused by transient focal cerebral hypoperfusion.[9] Clinical presentation ranges from weakness of one extremity to a complete hemiparesis. Todd's paralysis is associated with a high likelihood of an underlying structural cause for the seizure. In the case of suspected Todd paralysis that does not quickly resolve, the physician must rule out a new structural lesion.

BOX 92.2

Differential Diagnosis of Altered Mental Status in the Patient Who Has Seized

POSTICTAL PERIOD

NCSE or subtle convulsive status epilepticus (can mimic the following):

- Hypoglycemia
- CNS infection
- CNS vascular event
- Drug toxicity
- Psychiatric disorder
- Metabolic encephalopathy
- Migraine
- Transient global amnesia

CNS, Central nervous system; *NCSE,* nonconvulsive status epilepticus.

Seizures are often associated with injury, and the patient must be evaluated for both soft-tissue and skeletal trauma. Head trauma and tongue lacerations are common. Seizure activity can also produce dislocations and fractures. Posterior shoulder dislocations are extremely rare but, when present, should prompt suspicion that a seizure has occurred. Seizure-induced fractures are also rare but commonly missed; the humerus, thoracic spine, and femur are most commonly involved.

DIFFERENTIAL DIAGNOSIS

Convulsive Syncope

Syncope associated with seizure-like movements, *convulsive syncope,* is most commonly associated with bradycardia. In these cases, as heart rate returns to normal, abnormal muscle activity ceases, and there is no post-ictal period.[10] Based on observational studies in blood donors, up to 40% of patients with syncope will have some component of motor activity, most commonly involving tonic extension of the trunk or myoclonic jerks of the extremities. This phenomenon has been observed in patients who are in a seated position. These events are usually not associated with tonic-clonic movements, tongue biting, cyanosis, incontinence, or postictal confusion. Nausea or sweating before the event makes seizure much less likely than syncope.

Nonepileptic Attacks

Also referred to as *nonepileptic spells,* these are nonepileptic paroxysmal neurologic events that may resemble seizures in appearance but do not result from abnormal cortical discharge. Etiologies for these include breath-holding spells, involuntary movements, decerebrate or decorticate posturing, and psychogenic seizures.

Psychogenic seizures (also known as *pseudoseizures* or *nonepileptic seizures*) have been reported in 12% to 18% of patients with transient loss of consciousness and can exist concomitantly with neurogenic seizures.[11] Psychogenic seizures are rarely caused by malingering but instead are more commonly a functional neurological symptom disorder, formerly called a *conversion disorder.* Characteristic features of a psychogenic seizure include out-of-phase tonic-clonic activity, forward pelvic thrusting, and voluntary eye movements away from the examiner.

DIAGNOSTIC TESTING

Laboratory Studies

If a patient with a new-onset seizure has no significant comorbid disease and a normal examination (including mental status), the

likelihood of an electrolyte disorder is extremely low. The American College of Emergency Physicians (ACEP) published an evidence-based clinical policy on the initial approach to patients presenting with seizures in 2014. The guidelines emphasize that extensive metabolic testing in patients who had returned to a normal baseline after a first-time seizure is not indicated.[12] Also, only a serum glucose and sodium level, as well as a pregnancy test (in women of childbearing age), are likely necessary in patients who are otherwise healthy with a new-onset seizure and normal neurologic status. This is the same conclusion reached in a practice parameter published in 2007 by the American Academy of Neurology on the evaluation of first-time seizures.

Patients with persistent alteration of mental status, those in status epilepticus, and those who have fever or new neurologic deficit are unique in that they require extensive diagnostic testing. This includes serum glucose, electrolytes, urea nitrogen, creatinine, magnesium, calcium, complete blood count, pregnancy tests in women of childbearing age, antiepileptic drug levels, liver function tests, and drugs-of-abuse screening.

Hypoglycemia is a common metabolic cause of provoked seizures. Ictal activity can occur at a plasma glucose level less than 45 mg/dL, although some patients may have a seizure at higher levels. Convulsive and nonconvulsive generalized seizures and focal seizures all may occur during hypoglycemia. Note that prolonged seizures can *cause* hypoglycemia. Seizures that do not cease after correction of low blood glucose deserve further evaluation and treatment for alternative causes.

If an arterial blood gas analysis is obtained in a convulsing patient (although it is not routinely indicated), it may show an anion gap metabolic acidosis secondary to lactic acidosis. The anion gap acidosis should resolve within an hour after the seizure ends. Persistence beyond this time suggests an underlying process, such as sepsis, ketosis (alcoholic or diabetic), or poisoning (methanol, iron, isoniazid, ethylene glycol, salicylates, carbon monoxide, or cyanide).

A drug-of-abuse screen and alcohol level should be considered in patients with first-time seizures, although there is no evidence that such testing changes outcome. A positive drug-of-abuse screen does not prove causation, and the patient would still require an EEG and neuroimaging study to direct management. The screen may, however, suggest an etiology and help with future medical and psychiatric disposition. Seizure due to alcohol intoxication or withdrawal is a diagnosis of exclusion, because alcoholics are at increased risk for electrolyte abnormalities and traumatic injuries.

Both creatine phosphokinase and prolactin have been investigated as markers of seizures. Neither has been found sufficiently sensitive or specific to be used in the ED.

Electrocardiogram

Patients with a history of cardiac disease, preceding or ongoing cardiac symptoms, and those who continue to seize may benefit from cardiac monitoring. The same is true of patients suspected of overdose. An ECG is also an early screen for drug toxicity. Tricyclic cardiotoxicity may manifest as a QRS complex lasting more than 0.1 second or a rightward shift of the terminal 40 ms of the frontal plane QRS complex (a prominent R wave in lead aV_R). The ECG can also identify a prolonged QT, a delta wave, Brugada pattern, or heart block, which might contribute further insight into the seizure etiology.

Neuroimaging

There is general agreement that neuroimaging is indicated in patients with a first-time nonfebrile seizure, though in select patients who have returned to a normal baseline and who have access to follow up care, imaging can be obtained as an outpatient. The Academy of Neurology guidelines reinforce this, as do studies suggesting that computed tomography (CT) will change acute management of patients with a new seizure in up to 17% of cases.[13,15] The usefulness of emergent imaging otherwise depends on the clinical situation. Box 92.3 summarizes useful criteria in determining who will benefit from a CT scan while in the ED.

BOX 92.3

Factors Associated With Abnormal Computed Tomography Findings in Patients Presenting to the Emergency Department With Seizure

- Focal abnormality on neurological examination
- Malignancy
- Closed head injury
- Neurocutaneous disorder
- Focal onset of seizure
- Absence of a history of alcohol abuse
- History of cysticercosis
- Altered mental status
- Patient older than 65 years old
- Seizure duration more than 15 minutes

Magnetic resonance imaging (MRI) is generally the diagnostic test preferred by neurologists in evaluating first-time seizure, because it is better than CT in identifying small lesions. MRI is not better than CT for detecting acute hemorrhage, however, and there are no ED-based studies that have evaluated MRI utility in seizure management.

Lumbar Puncture

Lumbar puncture should be considered in patients with fever, severe headache, or persistent altered mental status. Asymptomatic patients with a history or strong suspicion of immunocompromise are also candidates for a lumbar puncture. There are no cases in the literature of a bacterial CNS infection presenting as isolated seizure without fever or abnormal neurologic findings in immunocompetent individuals. Theoretically, an exception may occur in cases of partially treated meningitis.

A transient cerebrospinal fluid (CSF) pleocytosis of up to 20 white blood cells/mm^3 has been reported in up to 23% of patients with seizures. However, one is obligated to assume that the presence of white blood cells in the CSF of a seizing patient represents meningitis until proven otherwise.

Electroencephalogram

The EEG is the definitive test for diagnosing a seizure disorder, although its sensitivity varies depending on timing and location of the seizure focus. It is particularly helpful when the diagnosis is in doubt, such as in acute confusion states and coma, as well as for the diagnosis of NCSE.[14] NCSE has been identified in up to 25% of patients treated for GCSE who were thought to no longer be seizing. Delay in diagnosis of NCSE is associated with increased mortality.[15]

MANAGEMENT

For the patient who has had a seizure prior to hospital arrival or in the ED but is not actively convulsing, only supportive care may be needed. Restraints may be needed during post-ictal confusion to prevent falls, especially in Todd's paralysis patients who have motor weakness in addition to confusion. However, the use of

TABLE 92.1

Management of "Special Situation" Seizures in the Emergency Department

CLINICAL SITUATION	AGENT OF CHOICE	DOSAGE/COMMENT
Hyponatremia	Hypertonic (3%) saline	2 to 3 mL/kg of 3% NaCl in rapid sequential boluses until seizures stop
Hypocalcemia	Calcium chloride or gluconate	Sequential ampules until seizures stop
Tricyclic antidepressant overdose	Alkalization	Administer 0.5 to 1.0 mEq/kg IV bolus; repeat as needed to maintain a blood pH of 7.4 to 7.5
Salicylate overdose	Alkalization; hemodialysis for severe cases	Administer 0.5 to 1.0 mEq/kg IV bolus; repeat as needed to maintain a blood pH of 7.4 to 7.5
Isoniazid overdose	Pyridoxine	5 g IV (adult) or 70 mg/kg (pediatric)
Cocaine intoxication	Benzodiazepines	As per idiopathic seizures
Lithium toxicity	Hemodialysis	
Alcohol-associated seizure	Lorazepam	0.05 to 0.10 mg/kg
MDMA	Benzodiazepines	Be aware of possible hyperthermia or hyponatremia
Eclampsia	Magnesium	IV loading dose of 4 to 6 g over 15 to 20 minutes, then 1 to 2 g/h infusion; monitor patients for hyporeflexia; alternatively, lorazepam (Ativan) 4 mg IV over 2 to 5 minutes or diazepam (Valium) 5 to 10 mg IV slowly can be used to terminate the seizure, after which magnesium sulfate is administered

IV, Intravenous; *MDMA, N*-methyl-3,4-methylenedioxyamphetamine; *NaCl,* sodium chloride.

restraints requires careful monitoring, and they should be removed as quickly as possible. Seizure pads may be protective in the case of seizure recurrence. Vascular access should be obtained in case the patient requires future abortive treatment, and the patient should be monitored for improvement to baseline.

The management of a patient experiencing a seizure begins with active, anticipatory airway management. A jaw thrust, use of a nasopharyngeal airway, and supplemental oxygen may be required. In generalized ictus, the gag reflex is suppressed and vomiting or aspiration may occur. Suction should be available and, if possible, the patient should be placed in a left lateral decubitus position to lessen chances of aspiration. Care should be taken to avoid iatrogenic trauma from forceful placement of intraoral devices. The patient should be protected from accidental trauma during the seizure, with bed rails raised and seizure pads used as available. If not already present, an intravenous (IV) line should be placed in case abortive treatment is required. Most seizures are self-limited and resolve in a few minutes; however, clinicians should anticipate the need for aggressive care if status epilepticus develops. Table 92.1 lists specific treatments for active seizures due to certain underlying pathology. Management of status epilepticus is discussed in Chapter 15.

Initiation of Antiepileptic Drugs

First-Time Seizures

Based on the best available evidence, the current ACEP Clinical Policy states that emergency clinicians do not need to initiate an antiepileptic drug in patients who have had a first provoked or a first unprovoked seizure without evidence of brain disease or injury.[12] Rather, the patient should be discharged with referral for neurologic consultation. The rationale for this approach is threefold. First, the diagnosis may be incorrect, especially if the seizure-like activity was not witnessed by experienced medical personnel. It is estimated that 20% to 25% of patients diagnosed as having seizures are eventually determined not to have seizures, with the most frequent alternative diagnoses being cardiovascular and psychopathologic etiologies.

Second, the patient may not have a recurrent seizure. It is estimated that less than 50% of patients who have had a single unprovoked seizure will experience a recurrent seizure within 2 years. The presence of EEG abnormalities suggests greater risk, but this information usually is unavailable in the ED setting. Other factors associated with an increased risk of recurrence are focal (versus generalized) ictus, status epilepticus, a history of intracranial surgery or trauma, and the presence of a persistent neurologic abnormality, such as Todd's paralysis. Furthermore, whereas treatment decreases the risk of early recurrent seizure, it does not affect long-term prognosis of epilepsy, nor does it have an impact on patient quality of life, with the exception of driving limitations.

Third, antiepileptic medications have side effects that may outweigh the benefit of treatment, especially in women of childbearing age (owing to their teratogenicity); in patients with liver, kidney, or hematologic disorders; and in patients already taking multiple medications. (The American Academy of Neurology's evidence-based guideline notes that these are usually mild and reversible.)

For patients with a history of stroke, brain trauma, tumor, or other CNS disease or injury, the ACEP guideline states that antiepileptic drug therapy may be initiated but advises that it is best done by a neurologist in coordination with the patient's primary care provider. The reason for beginning antiepileptic drugs in this group of patients is their higher probability of recurrence. See Table 92.2 for antiepileptic drug dosing.

Patients With a History of Seizures

Antiepileptic drug noncompliance and subtherapeutic antiepileptic drug levels in a patient who has had a seizure are commonly encountered in the ED. Serum antiepileptic drug levels should be checked in these patients when possible, and repleted if found to be low. Literature to support the recommendation of one route of antiepileptic drug administration over another (oral versus parenteral) is inconclusive, mainly because most available studies used antiepileptic drug serum concentration levels instead of early seizure recurrence as a primary outcome measure. Within this

TABLE 92.2

Loading Dose Route of Administration for Antiepileptic Drugs When Resuming Treatment in the Emergency Department

DRUG	LOADING DOSE, ROUTE	POTENTIAL ADVERSE EFFECTS
Carbamazepine	8 mg/kg oral suspension, single oral load IV not available	Drowsiness, nausea, dizziness
Gabapentin	900 mg/day oral at 300 mg tid for 3 days IV not available	Somnolence, dizziness, ataxia, fatigue
Lacosamide	Oral and IV preps available but loading dose not studied	Dizziness, headache
Lamotrigine	6.5 mg/kg single oral load IV not available	Nausea
Levetiracetam	1500 mg oral load Rapid IV load up to 60 mg/kg	Fatigue, dizziness
Phenytoin	20 mg/kg divided in maximum doses of 400 mg every 2 hours orally; or 18 mg/kg IV at ≤50 mg/min	IV: Hypotension, bradyarrhythmias, extravasation injuries
Fosphenytoin	20 PE/kg at maximum rate of 150 PE/min; can also give IM	Less prominent than with phenytoin
Valproate	Up to 30 mg/kg IV at maximum rate of 10 mg/kg/min	Local irritation

IM, Intramuscular; *IV,* intravenous; *PE,* phenytoin sodium equivalents.
Data from Bacon D, Fisher RS, Morris JC, et al: American Academy of Neurology position statement on physician reporting of medical conditions that may affect driving competence. Neurology 68(15):1174–1177, 2007.

limited evidence, most studies have compared phenytoin and fosphenytoin in oral and IV routes. Oral loading has been reported to have fewer adverse drug events (eg, hypotension) than either of the IV loading methods. As expected, therapeutic plasma concentrations are achieved significantly faster with the IV route. Some emergency clinicians still prefer parenteral loading of phenytoin or fosphenytoin to ensure adequate serum level on discharge. However, there is no good evidence that this practice decreases risk of seizure recurrence.

SPECIAL CASES

Alcohol-Related Seizures

Of seizure patients presenting to an ED, 20% to 40% have seizures related to alcohol abuse. Alcohol-withdrawal seizures account for a substantial portion of these alcohol-related seizures, but alcohol abuse and dependence puts patients at risk of seizure in a plethora of other ways, such as increased incidence of traumatic brain injury, hypomagnesemia due to malnutrition, and possible co-ingestion of other toxins. In more than 50% of cases, alcohol-related seizures occur as an adjunct to other risk factors, including preexisting epilepsy, structural brain lesions, and the use of recreational drugs.

A first-time "withdrawal" seizure must be evaluated as any first-time seizure, even in alcoholics who claim to have had seizures in the past but for whom no documentation of previous seizures or evaluation is available. Other conditions need to be ruled out by history, physical examination, and diagnostic testing, including electrolytes, glucose, and brain CT scan.

The diagnostic yield for CT following a first alcohol-related seizure is high. A 1988 Denver study reported head CT scan results in 259 patients with a first alcohol-related convulsion. A clinically significant lesion was found in 16 (6.2%) patients, seven of whom were alert and had nonfocal neurologic examinations and no history of trauma. Nearly 4% had CT findings that changed clinical management (eg, subdural hematoma, aneurysm, subarachnoid hemorrhage, and neurocysticercosis). In these patients, the history and physical examination did not predict the CT abnormality. This study highlights the need to strongly consider neuroimaging in this special group of patients.

The diagnosis of alcohol-withdrawal seizure, after exclusion of other etiologies, is based on a history of recurrent events temporally related to stopping or significantly decreasing alcohol intake. Alcohol-withdrawal seizures are usually generalized events and occur between 6 and 48 hours after cessation of drinking. Seizures occur in one-third of these patients.[16]

Once a diagnosis of alcohol-withdrawal seizure is made, management focuses on patient safety, minimizing the risk for a second withdrawal seizure, and patient education. Recurrent seizures have been reported in 13% to 60% of these patients, with most occurring within 12 hours of onset. Clinical findings cannot predict who is likely to have a recurrent seizure in the ED. The patient may or may not have other signs of alcohol withdrawal (such as, tachycardia, confusion, or tremors) that may indicate a likelihood of developing a seizure.

Benzodiazepines are the treatment of choice in alcohol-withdrawal seizure. They offer cross-tolerance with alcohol by acting at the GABA receptor site and reduce the signs and symptoms of alcohol withdrawal. All benzodiazepines appear to be equally efficacious in terminating an alcohol-withdrawal seizure; however, lorazepam is the only benzodiazepine that has been shown to decrease the incidence of seizure recurrence and decrease the need for hospitalization. The number needed to treat to prevent one further withdrawal seizure at 6 hours is five.

Phenytoin does not have a role in managing pure alcohol-related seizures in the ED.[17]

Toxins

Toxins can alter the brain equilibrium of excitatory and inhibitory neurotransmitters to cause seizures. Many illicit drugs disrupt the equilibrium, including cocaine and other stimulants and narcotics. Tonic-clonic seizures have been reported with use of synthetic cannabinoids (eg, "spice" and "K2").[18] Marijuana, however, is not commonly associated with seizures, and some forms of severe epilepsy may be treated with medical marijuana.[19] Seizures occurring after abuse of *N*-methyl-3,4-methylenedioxyamphetamine (MDMA) compounds (eg, "ecstasy" and "Molly") may be due to

associated hyponatremia and hyperthermia. Seizures can also result from withdrawal from benzodiazepines or barbiturates.

Cases of toxin-induced refractory status epilepticus pose a particular challenge, because the mechanism of status epilepticus may be different from status epilepticus with other causes. Some toxins (eg, isoniazid) cause depletion of GABA neurotransmitter; and because some of the typical pharmacologic agents act by sensitizing the GABA receptor, they are less effective. In these cases, early administration of pyridoxine may be advantageous, because it replenishes GABA in the brain. It is initially dosed at 5 g IV in adults and 70 mg/kg IV in children.

Most drug-induced seizures, particularly those resulting from cocaine and other stimulants, respond best to benzodiazepine therapy. Barbiturates or propofol are also good options. As with alcohol-induced seizures, phenytoin is ineffective for most drug-induced seizures; and in some cases, it may be harmful such as in theophylline or tricyclic overdose. Phenytoin administration is generally contraindicated in cases of ingestion, because its sodium channel blocking actions can worsen the hemodynamic impact of the ingestion.[20]

Post-Traumatic Seizures

The incidence of seizure after head trauma is related to injury severity. After minor head injury (Glasgow Coma Score [GCS] >12) the incidence is 1.5%, whereas the incidence increases to 17% after a severe traumatic brain injury (GCS <9). The incidence approaches 30% in patients with depressed skull fracture.[21] Immediate and early (within 1 week) post-traumatic seizures are more common in children than in adults, and children also are more likely than adults to present in status epilepticus in the immediate or early post-traumatic phase.

The incidence of post-traumatic seizures in the first week after a severe traumatic brain injury decreases to less than 4% with early treatment with phenytoin. However, after the first week there is no statistical difference in seizure incidence whether or not patients are treated with phenytoin. Thus, treatment with 1 week of antiepileptic drugs is recommended in adults and may be considered in children for prophylaxis against post-traumatic seizures. Long-term prophylactic antiepileptic drugs are not indicated to prevent late post-traumatic seizures.

Pregnancy

Seizures in pregnancy can be classified as one of three types: (1) those that occur in epileptic patients who happen to be pregnant, (2) new-onset seizures in pregnant patients, and (3) seizures that occur in the setting of eclampsia.

The most complete prospective observational study of pregnant women with epilepsy is the International Registry of Antiepileptic Drugs and Pregnancy (EURAP). Of 1956 pregnancies, over half were seizure-free, 17.3% had an increase in seizure frequency, and 15.9% had a decrease in frequency.[22] Factors that may lower the seizure threshold in women who are pregnant include noncompliance, sleep deprivation, nausea, and vomiting.

Overall, there is not an increased risk of status epilepticus during pregnancy.[23] Although there are few data guiding the use of antiepileptic drugs for status epilepticus during pregnancy, the risks to the fetus from status epilepticus–related hypoxia and acidosis are greater than the potential teratogenicity of anticonvulsant medications; therefore, patients who are actively seizing should be managed as the nonpregnant patient. In patients who are more than 24 weeks pregnant, fetal monitoring during and after a seizure should be arranged.

Pregnant patients with new-onset seizures (not with eclampsia) should be worked up as any new-onset seizure patient, with a metabolic profile, EEG, and head CT scan with appropriate abdominal shielding. Precipitating etiologies, such as infections and drug toxicities, should also be investigated. If no source is identified, anticonvulsants should be withheld and the patient referred for close follow-up.

Eclampsia is the major consideration in pregnant patients of at least 20 weeks' gestation who present with new-onset seizures. Postpartum eclampsia represents 25% of eclamptic seizures, can occur up to 8 weeks after delivery, and can be seen in women without preceding preeclampsia.

Magnesium has been demonstrated to be the therapy of choice in the treatment of acute eclamptic seizures and for prevention of recurrent eclamptic seizures. It has been shown to be substantially more effective than phenytoin with regard to recurrence of convulsions and maternal death. Complications including respiratory depression and pneumonia are less likely with magnesium than phenytoin. Magnesium sulfate is also associated with benefits for the baby, including fewer admissions to the neonatal intensive care unit.

In the eclamptic patient, magnesium sulfate 4 g IV should be given over 20 minutes, followed by a 2 g/h infusion (some centers use intramuscular regimens). According to the American College of Obstetrics and Gynecology and the National High Blood Pressure Education Program: Working Group Report on High Blood Pressure in Pregnancy, agents of choice for control of blood pressure in the emergency setting include hydralazine (first-line) and labetalol.[24] Eclamptic seizures refractory to magnesium may respond to benzodiazepines or barbiturates with or without phenytoin. An in-depth discussion of eclampsia can be found in Chapter 178.

DISPOSITION

The need for hospitalization is obvious in patients who are clinically ill, but a dilemma arises when determining disposition for the patient who returns to a normal baseline after a first-time seizure. The best predictor of seizure recurrence is the causative etiology combined with EEG findings. This information often requires modalities that are not routinely available in the ED, and there are few ED-based studies to direct disposition. Retrospective studies suggest that there is a 19% seizure recurrence rate within 24 hours of presentation to the ED, which decreases to 9% if patients with alcohol-related events or focal lesions on CT are excluded. However, selection bias in these studies makes it impossible to assess whether recurrence could have been predicted based on physical findings or comorbid factors. Thus, at present, there is insufficient evidence to guide the decision to admit. We recommend this decision be tailored to the patient and shared decision-making be employed, taking into consideration the patient's access to follow-up care and social risk factors (eg, alcoholism or lack of health insurance). Patients with comorbidities, including older than 60 years old, known cardiovascular disease, history of cancer, or history of immunocompromise, should be considered for admission to the hospital.

Patients and their families should be counseled and instructed on basic safety measures to prevent complications (such as, trauma) during seizures. For example, patients should be advised to avoid swimming or cycling following a seizure, at least until they have been reassessed by their neurologist and their antiepileptic therapy optimized, if needed. The need for a "medical alert" bracelet or other medical condition identifier should be considered.

A particularly important point for seizure patients is education against driving. Although evidence remains controversial on this issue, there is general agreement that uncontrolled epileptic patients who drive are at risk for a motor vehicle collision, with potential injury or death to themselves and others. For this reason, most states do not allow these patients to drive unless they have

been seizure-free on medications for 1 year. According to population survey data, 0.01% to 0.1% of all motor vehicle crashes are attributable to seizures.[25] Although physicians are required to report patients with seizures to driving authorities in six states (California, Delaware, Nevada, New Jersey, Oregon, and Pennsylvania), mandatory reporting has not been proven to reduce the risk of motor vehicle crash in patients with epilepsy.

The psychological and social implications of the new diagnosis of a seizure disorder for the patient can be profound. Fear of seizures and stigmatization are common; employability and insurability may be adversely affected. Although the emergency clinician is not usually in a suitable position to arrange for counseling, referral to local epilepsy support groups may be helpful.

KEY CONCEPTS

- Seizures can be provoked by many acute processes, including infections, toxins, cardiac dysrhythmias, and CNS insults.
- Epilepsy is a condition of recurrent, *unprovoked* seizures.
- Partial seizures are confined to one hemisphere of the brain and have clinical manifestations reflecting the area of electrical activity. Generalized seizures involve both hemispheres and always involve alterations in consciousness.
- There is no single test to confirm that a patient seized, and a number of seizure mimics including convulsive syncope exist. A post-ictal alteration in mental status makes a seizure five times more likely than syncope.
- Although most seizures are self-limited, management of the seizure patient involves a targeted search for underlying pathology, treatment of sequelae of seizures when necessary, and prevention of future episodes.
- Stroke is a leading cause of new seizure in elders.
- Noncompliance with antiepileptic medication is the most common cause of ED presentation for recurrent seizures.
- During a seizure, the patient should be placed in the left lateral decubitus position when possible. Suctioning may help prevent aspiration, but intraoral devices will cause trauma without yielding significant benefit.
- A patient with new-onset seizures who returns to baseline mental status and does not have comorbid disease does not require diagnostic testing beyond serum glucose and sodium levels, a pregnancy test (in women), and a non-contrast head CT.
- Non-convulsive status epilepticus should be considered in any patient with prolonged, unexplained altered mental status.
- For patients with a first-time seizure and without a clear CNS disease or lesion, evidence does not support initiation of antiepileptic drugs in the ED.
- Alcohol dependence places patients at risk of seizures in a number of ways, and alcohol-withdrawal seizures should only be diagnosed after excluding other causes. These seizures, as well as seizures due to other drugs of abuse, respond to benzodiazepines but not to traditional antiepileptic medications.
- Antiepileptic medications have been shown to reduce post-traumatic seizures in the first week after injury but not beyond that.
- In pregnant patients, evaluations for new-onset seizures prior to 20 weeks should be the same as in nonpregnant patients. After 20 weeks, eclampsia is a major cause of seizures and is treated with magnesium.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 92: QUESTIONS & ANSWERS

92.1. Which of the following statement regarding the pathophysiology of seizures is *true?*

A. During a seizure, prompt loss of consciousness implies a cortical focus.
B. Generalized seizures involve abnormal electrical activity in one hemisphere.
C. Regarding seizure activity, acetylcholine is inhibitory.
D. Regarding seizure activity, gamma-aminobutyric acid (GABA) is excitatory.
E. The clinical seizure activity typically reflects the brain focus of initiation.

Answer: E. Clinical seizure activity typically reflects the site of seizure origin. Generalized seizures involve both brain hemispheres. Acetylcholine is an excitatory neurotransmitter, and GABA is inhibitory. Prompt loss of consciousness with a seizure implies a subcortical focus involving the reticular activating system.

92.2. Which of the following statements regarding epilepsy is *true?*

A. Electrolyte disturbances are the most common cause of recurrent seizures in epileptic patients.
B. Epilepsy is a condition of recurrent provoked seizures.
C. Epileptic seizures are always generalized tonic-clonic.
D. Epileptic seizures can be triggered by smells or lack of sleep.
E. Most adult-onset epilepsy does not have an identifiable cause.

Answer: D. Epilepsy is a condition of recurrent, *unprovoked* seizures. Idiopathic epilepsy almost always starts in childhood. Medication noncompliance is the most common cause of recurrent seizures in epileptic patients. Epileptic seizures can be partial seizures. Some patients with epilepsy have seizures triggered by certain specific sensory stimuli, with flashing lights being the most well-known of these.

92.3. Which of the following factors does not put patients at risk for seizures?

A. Acute stroke
B. Chronic stroke-related lesions
C. Hyperkalemia
D. Hypomagnesemia
E. Indwelling intracranial shunts

Answer: C. Indwelling intracranial shunts and other lesions, and hypomagnesemia (as seen in malnourished alcohol-dependent patients) are all risk factors for seizures. Stroke is one of the most common causes of seizures in the elderly. Seizures occurring acutely with a stroke are often partial and reflect the affected brain area, whereas those that occur chronically are often generalized. Hyperkalemia does not cause seizures unless it precipitates hypotension and consequent hypoperfusion of the brain.

92.4. Which of the following statements regarding patients presenting with first-time seizures is *true?*

A. All patients should have basic serum electrolyte testing.
B. All patients should receive a loading dose of an antiepileptic drug and a prescription for an oral regimen prior to discharge.
C. Non-contrast head computed tomography (CT) is not indicated for most afebrile patients.
D. Non-diabetic patients do not need to have serum glucose checked if their mental status returns to normal.
E. Persistent altered mental status is an indication for a lumbar puncture.

Answer: E. Persistent altered mental status should trigger consideration of a lumbar puncture, serum glucose and an electroencephalogram (EEG) among other testing. Non-contrast CT of the head is relatively high-yield in first time seizure patients, and most guidelines recommend performing one. Patients with no comorbidities who return to baseline mental status do not need

broad-based electrolyte testing, but hypoglycemia is a common cause of seizures even in non-diabetic patients and should be routinely tested for in first-time seizure patients. Initiation of antiepileptic drugs in the emergency department (ED) for first-time seizure patients without a known structural brain lesion may do more harm than good.

92.5. Which of the following statements regarding post-traumatic seizures is *true?*
- **A.** Adults are more likely to present with status epilepticus.
- **B.** Antiepileptic drugs are effective in preventing late post-traumatic seizures.
- **C.** Immediate and early post-traumatic seizures are more common in adults.
- **D.** Most occur immediately following the traumatic injury.
- **E.** The severity of head injury correlates with the likelihood of post-traumatic seizures.

Answer: E. The severity of head injury correlates directly with the likelihood of post-traumatic seizures. The incidence of seizures is higher when the dura is violated. Children are more likely to have immediate or early (<1 week) seizures and to present in status. Antiepileptic drugs do not affect the incidence of late post-traumatic seizures (>1 week).

92.6. For which of the following causes of seizure are alcohol-dependent patients not at increased risk?
- **A.** Electrolyte disturbances
- **B.** Head trauma
- **C.** Toxin-induced (other than alcohol)
- **D.** Uremia
- **E.** Withdrawal

Answer: D. Alcoholic-dependent patients frequently fall or otherwise sustain head trauma during periods of intoxication. Alcohol withdrawal is associated with a high incidence of seizure. Alcohol intoxication can be associated with co-ingestion of illicit drugs, which also cause seizures. Chronic alcohol dependence can be associated with malnutrition causing hypomagnesemia.

92.7. Which of the following regarding seizures from illicit drug use is *true?*
- **A.** Benzodiazepines are contraindicated in cessation of these seizures.
- **B.** K2 ("spice") has not yet been reported to cause seizures.
- **C.** Marijuana use is strongly associated with seizures.
- **D.** *N*-methyl-3,4-methylenedioxyamphetamine (MDMA) compounds, such as ecstasy, may induce seizures via hyperthermia.
- **E.** Phenytoin is the first-line treatment.

Answer: D. Seizures from cocaine, MDMA compounds and other drugs are notoriously unresponsive to traditional antiepileptic agents, and benzodiazepines are considered the first line of treatment. Marijuana is generally not associated with seizures, although synthetic cannabinoids, such as K2, have been. Ecstasy and other MDMA compounds inhibit sweating and can cause seizures by inducing hyperthermia.

92.8. A 23-year-old woman is brought to the emergency department (ED) for a prolonged seizure. By emergency medical service (EMS) report, the patient has no past medical history and no history of seizures. Paramedics report tonic-clonic activity for approximately 15 minutes, refractory to diazepam 5 mg intravenously in the ambulance. Upon arrival to the ED, the patient's seizure activity abruptly ceases, and she lucidly responds to the history and physical examination. She is symptom free. What would be the most appropriate intervention?
- **A.** A trial of oral phenytoin after an intravenous (IV) loading dose in the ED
- **B.** Computed tomography (CT) scan of the head followed by lumbar puncture
- **C.** Confrontation
- **D.** Neurology referral for electroencephalogram (EEG) and consultation
- **E.** Psychiatric consultation

Answer: D. No clinical criteria are 100% specific for the diagnosis of pseudoseizures. Seizures and pseudoseizures may coexist. For many patients, these episodes may not be deliberate. The most prudent course of action would be to treat them as possible ictus and refer to a neurologist. Initiation of antiepileptic drugs in the ED is not indicated in first-time seizures of healthy patients who return to normal.

CHAPTER 93

Headache Disorders

Thomas Kwiatkowski | Benjamin W. Friedman

Headache is a common complaint, accounting for approximately 5 million visits to the emergency department (ED) per year in the United States. In addition, many more patients present with headache as part of a constitutional illness, making the symptom of headache one of the most frequent complaints in the ED.

Headache is divided into primary and secondary disorders. *Primary headache disorders* include migraine, cluster, and tension-type headaches, which represent the majority of headaches seen in clinical emergency practice.[1] *Secondary headache disorders* include a variety of organic illnesses in which head pain is a symptom of an identifiable, distinct pathologic process. To facilitate a standardized approach to headache management, the International Headache Society published a classification system and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain.[2] This comprehensive and widely accepted system includes 14 major categories of headache disorders and uses specific operational diagnostic criteria to define each headache type (Box 93.1). Most patients presenting to an ED with headache have a benign primary headache disorder requiring only symptomatic treatment and referral. The challenge for the emergency clinician is to identify the very small subset of patients who have headache as a symptom of a serious or potentially life-threatening disease.

PRIMARY HEADACHE DISORDERS

Migraine Headache

Principles

Migraine is a common, chronic, sometimes incapacitating neurovascular disease characterized by recurrent attacks of severe headache, autonomic nervous system dysfunction, and, in some patients, an aura causing visual, sensory, motor, or other neurologic symptoms. It is a primary headache disorder with a genetic basis.

Migraine headaches account for more than 1.2 million visits to the ED per year.[3] Migraine attacks typically begin in the second decade of life and peak in prevalence in the fourth decade, with a 1-year period prevalence of 7% of men and 24% of women.[4] Overall, migraine is more prevalent among women (18%) than among men (6%). During childhood, however, there is no gender difference in the prevalence of migraine. After menopause, the prevalence of migraine among women decreases.

Historically, migraine headaches have been considered to be vascular in origin. However, this hypothesis is no longer tenable as alterations in cerebral blood flow do not correlate with the various phases of the headache attack or vascular territories and do not explain features of an acute migraine, such as premonitory mood disturbances, nausea, and osmophobia. Rather, vascular changes are now thought to be an epiphenomenon to what is a primary neurologic event.[5] Abnormal trigeminal nerve activation, possibly triggered by cortical spreading depression or, less likely, a sterile neuropeptide-induced inflammatory process, leads to pain and sensitization of higher order neurons in the brainstem and thalamus. Descending modulation is likely to be compromised as well. It is not yet known what initiates the pathophysiologic process that leads to a migraine attack. Migraine is commonly thought of in two major categories: (1) migraine without aura, which is the most frequent form of migraine and accounts for approximately 80% of all cases (Box 93.2); and (2) migraine with aura, which has specific reversible neurologic symptoms that precede the actual headache (Box 93.3) and is seen less frequently.

Clinical Features

Migraine is by definition a chronic and recurrent disease. The headache, characteristically, is unilateral, pulsating in quality, moderate to severe in intensity, and exacerbated by routine activities. The side of the headache can vary with individual attacks, and the headache may be bilateral in 40% of patients. The onset usually is gradual, and the attacks typically last 4 to 72 hours. Headache frequency is variable; those patients with more than 15 headache days per month are considered to have chronic migraine. Associated symptoms and signs include nausea, vomiting, anorexia, photophobia, phonophobia, osmophobia (aversion to odors), blurred vision, lightheadedness, vertigo, muscle tenderness, and nasal congestion. Many patients have dramatic light and sound sensitivity and seek a cool, dark, and quiet room. Some patients experience premonitory cognitive impairment during the days leading up to the acute attack producing forgetfulness, irritability, and depression.

The migraine aura consists of focal neurologic symptoms that precede and herald the headache. By definition, the aura is fully reversible and typically lasts 10 to 20 minutes, although it may continue for as long as 1 hour. The most common aura is visual; features may include scintillating scotomas (bright rim around an area of visual loss), teichopsia (subjective visual image perceived with eyes open or closed), fortification spectra (zigzagged lines that slowly drift across the visual field), photopsias (poorly formed brief flashes or sparks of light), and blurred vision. Less common auras include somatosensory phenomena, such as tingling or numbness, motor disturbances, and cognitive or language disorders.

Retinal migraine is a rare syndrome consisting of recurrent attacks of monocular visual dysfunction, including positive features (such as, scintillations) or negative features (such as, blindness). As with aura, these symptoms are completely reversible.

Hemiplegic migraine is characterized by a motor aura consisting of hemiparesis or hemiplegia. The progression of the motor deficit is gradual and in most cases is accompanied by a visual, sensory, or speech disturbance. The neurologic symptoms last up to 60 minutes, followed by headache. Rarely, the motor deficit is persistent, resulting from a true migrainous stroke. A familial version of hemiplegic migraine is associated with genetic channelopathies.

Migraine with brainstem aura presents with an aura referable to the brainstem. Common neurologic findings include dysarthria, tinnitus, vertigo, diplopia, and altered level of consciousness.

BOX 93.1

International Headache Society Classification of Headache

PRIMARY HEADACHES

1. Migraine
2. Tension-type headache
3. Cluster headache and trigeminal autonomic cephalalgias
4. Other primary headaches

SECONDARY HEADACHES

5. Headache attributed to trauma or injury to the head or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to nonvascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
12. Headache attributed to psychiatric disorder

PAINFUL CRANIAL NEUROPATHIES, OTHER FACIAL PAINS, AND OTHER HEADACHES

13. Cranial neuralgias and other facial pain
14. Other headache disorders

BOX 93.2

Migraine Without Aura (Common Migraine): International Headache Society Criteria

A. At least five attacks fulfilling criteria in B, C, D, and E
B. Attack lasts 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate to severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache, at least one of the following:
   1. Nausea or vomiting (or both)
   2. Photophobia and phonophobia
E. Not attributable to another disorder

Available at http://ihs-classification.org/en/.

Status migrainosus is a severe unremitting migraine headache that persists unabated for more than 72 hours.

Many factors can trigger migraine headaches in predisposed persons. Common precipitants include sleep deprivation, stress, hunger, hormonal changes including menstruation, and use of certain drugs including oral contraceptives and nitroglycerin. In addition, some patients report specific food sensitivities to chocolate, caffeine, and foods rich in tyramine, monosodium glutamate, and nitrates. Alcohol, specifically red or port wine, has also been implicated. In others, certain sensory stimuli, such as a strong glare or strong odors, loud noises, and weather changes, can trigger an attack.

Differential Diagnoses

Among patients without stereotypical recurrent headaches, migraine may be difficult to distinguish from secondary causes of headache. Other disorders that mimic migraine include aneurysmal subarachnoid hemorrhage (SAH), cerebrovascular disease, space occupying lesions, and idiopathic intracranial hypertension (IIH).

BOX 93.3

Migraine With Aura (Classic Migraine): International Headache Society Criteria

A. At least two attacks that fulfill criterion B
B. Presence of at least three of the following four characteristics for a diagnosis of classic migraine:
   1. One or more fully reversible aura symptoms indicating focal cerebral cortical or brainstem dysfunction (or both)
   2. At least one aura symptom developing gradually over more than 4 minutes, or two or more symptoms occurring in succession
   3. No single aura symptom lasting longer than 60 minutes
   4. Headache beginning *during* aura or *afterward,* with a symptom-free interval of less than 60 minutes (also may begin *before* aura)
C. Exclusion of related organic diseases by means of an appropriate history, physical examination, and neurologic examination with appropriate diagnostic tests

Available at http://ihs-classification.org/en/.

Diagnostic Testing

Neuroimaging is not necessary for patients with typical recurrent migraine headaches.[6] Neuroimaging should be considered for older or immunocompromised patients with new-onset headaches, headaches associated with unexplained neurologic abnormalities, and headaches with an abrupt onset.[7] Such patients have a higher likelihood of having a secondary cause of headache, such as an intracranial bleed or space occupying lesion. Among patients with an acute migraine headache, laboratory testing should be limited to a pregnancy test for those who are to be treated with medications that may be teratogenic and electrolytes for those patients with marked nausea, anorexia, or vomiting who will require intravenous (IV) fluid hydration.

Management

The pharmacologic treatment of migraine is divided into abortive therapies, which attempt to limit the intensity and duration of a given episode, and prophylactic therapies, which are intended to decrease the frequency and intensity of attacks. Prophylactic therapy is usually not initiated in an ED. The goals of abortive therapy include rapid pain relief, minimization of headache recurrence and medication side effects, and restoration of the patient's ability to function.

There are several approaches to treatment of the acute headache episode, depending on the severity of the attack (Table 93.1). The choice of agents depends on the patient's previous response to specific therapies, the existence of comorbid conditions, and the presence or absence of nausea or vomiting. Gastric stasis is common during acute migraine attacks and may limit the effectiveness of oral agents.

For mild to moderate attacks, simple analgesics such as acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) are often effective.[8] In the presence of nausea or vomiting, the addition of an agent (such as, metoclopramide) enhances the absorption and effectiveness of these medications. Appropriate doses and possible side effects are listed in Table 93.1.

TABLE 93.1

Selected Medications for Acute Migraine Attacks

MEDICATION	DOSAGE AND ROUTE ADMINISTERED	COMMENTS
MILD TO MODERATE		
Acetaminophen	500–1000 mg PO	
Ibuprofen	600–800 mg PO	Gastrointestinal upset
Naproxen sodium	275–550 mg PO	Gastrointestinal upset
MODERATE TO SEVERE		
First-Line Agents:		
Dihydroergotamine (DHE)	1 mg IV or IM; may be repeated in 1 hour	Nausea (pretreat with antiemetic) Caution in inhibitors of enzyme CYP450 3A4
Triptans		
Sumatriptan	6 mg SC	Chest pain, throat tightness, flushing Contraindicated with hypertension, coronary artery disease, peripheral vascular disease, and pregnancy Cannot be used within 24 hours of ergot use
Prochlorperazine	10 mg IV	Sedation and dystonic reaction
Metoclopramide	10 mg IV	Dystonic reaction
Droperidol	2.5 mg IV	QT prolongation; dystonic reaction
Ketorolac	30 mg IV or 30 to 60 mg IM	Gastrointestinal upset; avoid this medication in elderly and in patients with renal insufficiency
Second Line Agents:		
Morphine	4 to 8 mg IM or IV	Opioids less efficacious than other treatment modalities
Magnesium	2 g IV	More efficacious in migraine with aura
Valproic acid	1 g IV	Contraindicated in pregnancy
To Prevent Headache Recurrence After Emergency Department Discharge:		
Steroids	Various regimens	Gastrointestinal bleeding, infection, cataracts, aseptic necrosis, memory disturbances

IM, Intramuscular; *IV,* intravenous; *PO,* per os (by mouth); *SC,* subcutaneous.

For moderate to severe attacks, three classes of medications can be recommended as initial parenteral therapy: the antiemetic dopamine antagonists, such as metoclopramide, prochlorperazine, and droperidol; migraine-specific agents, such as the triptans and dihydroergotamine (DHE); and parenteral nonsteroidal medications, such as ketorolac.

Dopamine antagonists, such as the neuroleptic prochlorperazine, and the antiemetics, metoclopramide and droperidol, are highly effective as monotherapy for acute migraine attacks. Because of their efficacy, safety, tolerability, and few contraindications, they are often used as first-line therapy for acute migraine. For this class of medication, clinical research has outpaced preclinical work, and thus a compelling mechanism of action is lacking. However, migraine pathogenesis likely involves dopamine pathways.[9] The most common side effects after parenteral administration include sedation, and extrapyramidal symptoms, most notably akathisia, which can be treated with diphenhydramine, 25 mg IV, or midazolam, 2 mg IV.[10,11]

DHE is administered intravenously in a dosage of 1.0 mg over 2 minutes; this can be repeated in 1 hour if pain control has not been achieved. Because DHE can cause nausea and vomiting, patients should be pretreated with an antiemetic, such as metoclopramide 10 mg IV or prochlorperazine 10 mg IV. Contraindications to use of DHE include pregnancy, breast-feeding, poorly controlled hypertension, coronary artery disease, and peripheral vascular disease. DHE should not be used if the patient has already taken any drug in the triptan class or if the patient is using macrolides or protease inhibitors.

Sumatriptan, the first-approved medication of the triptan class, a class of selective 5-HT (1B/1D) receptor agonists, is available for oral (100 mg) and subcutaneous (6 mg) administration, and it is the most common triptan preparation used in the ED setting.[3] Other oral triptans include eletriptan (40 mg), almotriptan (12.5 mg), zolmitriptan (2.5 mg), naratriptan (2.5 mg), frovatriptan (2.5 mg), and rizatriptan (10 mg). Common side effects of triptans include tingling, flushing, warm or hot sensations, heaviness in the chest, and initial worsening of the underlying headache. Sumatriptan has contraindications similar to those for DHE and should not be used within hours of administration of an ergotamine-containing medication or DHE. A smaller dose of subcutaneous sumatriptan may limit side effects. Intranasal and rectal triptan preparations do not have a place in ED migraine treatment.

Opioid analgesics (such as, morphine, dosed at 0.1 mg/kg) should be reserved for patients who do not respond to any of the medications listed or have contraindications to all standard migraine therapies. Although hydromorphone and meperidine are frequently used, they are less efficacious than other agents and are associated with frequent ED visits.

Recurrence of migraine within 24 hours of ED discharge is common, regardless of medication administered or pain intensity at discharge.[12] We recommend using dexamethasone 10 mg IV to

decrease migraine recurrence after ED discharge.[13] Also, we recommend either oral naproxen (500 mg) or sumatriptan (100 mg) because both are comparably effective.[14]

Prophylactic therapy is indicated for patients who have more than two or three functionally disabling episodes per month.[15] Several classes of medications are used for the prophylaxis of migraine, including beta-blockers, tricyclic antidepressants, and antiepileptic drugs (AEDs). Prophylactic therapy is best initiated in consultation with the patient's primary care provider or neurologist.

Disposition

Most patients who present to an ED for treatment of migraine can be treated and discharged after one or several doses of medication and IV fluids if required. Only rarely do patients with migraine require hospitalization. Patients requiring admission often have chronic migraine, with more than 15 days of migraine monthly, and concomitant *medication overuse headache,* which is a disorder characterized by worsening headache frequency in the setting of increased use of analgesic or migraine abortive medication. Migraine patients admitted to the hospital receive IV fluids, frequent doses of parenteral migraine medication, and detoxification from medications contributing to the overuse headache.

Cluster Headache

Principles

Cluster headache is the only headache syndrome that is more common in men than in women. It typically occurs in young to middle-aged adults who smoke. The headaches tend to occur repeatedly during a defined time interval, hence the term *cluster.* Several attacks can occur in a single day, and a typical cluster period may last weeks to months. Several precipitating factors have been implicated, most notably the ingestion of alcohol. Stress and climate changes may also play a role in susceptible persons. As with migraine, abnormal activation of the trigeminal nerve contributes to headache nociception. Secondary parasympathetic activation causes typical associated symptoms, such as lacrimation and rhinorrhea.

Clinical Features

Cluster headaches occur suddenly with little warning, and multiple episodes can occur within a 24-hour period. Each headache lasts from 15 minutes up to 3 hours. The headache typically begins with a unilateral sharp, stabbing pain in the eye, which may awaken the patient from sleep. The attacks occur exclusively in the territory of the trigeminal nerve. Unlike the migraineur, the patient with cluster headache predictably presents agitated and anxious, rocking, rubbing the head, and pacing. The attack subsides rapidly, often leaving the patient exhausted.

Accompanying the headache are ipsilateral autonomic symptoms, such as ptosis, miosis, and forehead or facial sweating. The eye often is injected and tearing, and many patients have unilateral nasal congestion.

Differential Diagnoses

Other headache disorders that mimic cluster headache include carotid artery dissection, trigeminal neuralgia, and rare trigeminal autonomic cephalalgias, including paroxysmal hemicranias and short-lasting uniform neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). Carotid artery dissection should be excluded as the diagnosis in patients who present with unilateral face or neck pain and Horner's syndrome. With trigeminal neuralgia, the pain peaks within seconds, lasts only a couple of minutes, and can be provoked by specific trigger points on the face or oral mucosa. The trigeminal autonomic cephalalgias are manifested by a brief unilateral headache that recurs dozens of times per day, often accompanied by the same unilateral eye and nasal symptoms as cluster.

Diagnostic Testing

For patients without an established pattern of cluster headaches, the emergency clinician should consider space-occupying central nervous system (CNS) lesions, which may be hidden in the posterior fossa, and carotid artery pathology. Magnetic resonance imaging (MRI) is required to exclude subtle posterior fossa pathology. If MRI is not available in the ED, we believe a CT scan to exclude obvious lesions followed by outpatient MRI is a reasonable alternative. Neurovascular imaging is required to exclude carotid artery dissection when this diagnosis is suspected.

Management

Cluster headache is brief in duration and may resolve before a patient presents to medical attention. High-flow oxygen is first-line therapy. Delivered through a non-rebreather mask at a rate of 12 L/min, it aborts the headache within 15 minutes in approximately 80% of patients.[16] Subcutaneous sumatriptan is also an effective therapy for acute cluster headache and should be dosed at 6 mg. Larger doses do not confer additional benefit and may contribute to medication side effects. Alternatively, subcutaneous octreotide (100 μg) may be effective.

Once the acute attack has been relieved, focus shifts to the ongoing "cluster" of headaches that likely will recur the following day. Corticosteroids have long been theorized to help break the cluster, although high-quality evidence is not available. We recommend a regimen of 100 mg of prednisone daily for 5 days, followed by a 12-day taper. Verapamil, dosed at 120 mg three times a day, may decrease the frequency of attacks by the end of the first week of therapy and should be considered in all patients with cluster headache discharged from the ED.[17]

Disposition

Patients with cluster headache usually do not require admission to the hospital. Because these headaches are likely to continue over the following days and weeks, the patient should be referred to a physician with expertise in headache management.

Tension-Type Headache

Principles

Tension-type headache is the most common recurrent headache disorder, affecting 40% of the population in the United States, but it is an infrequent cause of ED visits. Women are affected slightly more frequently than men, and as with migraine, peak prevalence is in the fourth decade of life. These headaches typically do not cause substantial functional disability, and patients are able to continue with their normal daily activities. By definition, episodic tension-type headache lasts as little as 30 minutes and as long as 7 days.

The pathophysiology underlying tension-type headache is not yet clear. There is no consistent evidence that increased muscle activity is present. Physical examination will reveal tender areas of the scalp and neck with both tension and migraine headaches. Despite different epidemiologic profiles, similar response to many therapeutics suggests that tension and migraine headaches may be part of a continuum with similar pathophysiologic mechanisms.

Clinical Features

Patients typically complain of a tight, bandlike discomfort around the head that is nonpulsating and dull. They also may experience tightening of the neck muscles. A majority of patients do not seek medical assistance, because the headache usually is mild in intensity and not functionally disabling. On occasion, the discomfort can build up slowly and fluctuate in severity for several days. Unlike in migraine, the headache does not worsen with physical activity, and accompanying symptoms (such as, nausea, vomiting, phonophobia, and photophobia) are unusual. Anxiety and depression may coexist with chronic tension headache, which by definition occurs more than 15 days a month and can be daily and unremitting.

Differential Diagnoses

Tension headache is the least distinct of all of the primary headache disorders, and its diagnosis is based mainly on the absence of features that would suggest another headache diagnosis. The most common disorders mimicking tension headache are migraine, IIH, oromandibular dysfunction, cervical spondylosis, sinus or eye disease, and intracranial masses. Subtle indolent infections (such as, cryptococcal meningitis) should be considered in the immunocompromised.

Diagnostic Testing

Patients who present with a headache similar in quality to previous headaches do not require diagnostic evaluation in the ED. New onset headache with features of tension-type headache requires evaluation in patients 50 years and older, as well as immunocompromised patients. This evaluation can take place in the outpatient setting, where a scheduled MRI offers more sensitivity for a range of pathologies than a non-contrast CT.

Management

For a majority of patients with tension headaches, simple analgesics, such as acetaminophen or a NSAID, are adequate for pain control. Antiemetics such as metoclopramide are more efficacious than NSAIDs among patients with tension-type headache who require parenteral treatment.[18] Opioids are generally not warranted. Acupuncture is an efficacious non-pharmacological therapy.[19] Despite muscle pain and tenderness in many of these patients, spinal manipulation therapy is unlikely to provide a benefit for most patients.

Disposition

Absent comorbidities, patients with tension type headache do not require admission to the hospital. Chronic tension-type headache is difficult to manage; these patients should be referred to clinicians with expertise in headache or pain management.

SECONDARY HEADACHE DISORDERS

Subarachnoid Hemorrhage

Principles

SAH refers to extravasated blood in the subarachnoid space. Presence of the blood activates meningeal nociceptors, leading to diffuse occipital pain along with signs of meningismus. SAH accounts for up to 10% of all strokes and is the most common cause of sudden death from a stroke.

Approximately 80% of patients with nontraumatic SAH have ruptured saccular aneurysms. Other causes include arteriovenous malformations, cavernous angiomas, mycotic aneurysms, neoplasms, and blood dyscrasias. SAH may be caused secondarily by an intraparenchymal hematoma that dissects its way into the subarachnoid space.

The risk for aneurysmal SAH increases with age; most cases occur between 40 and 60 years old. In children and adolescents, aneurysms are uncommon, and when SAH occurs, it usually is secondary to an arteriovenous malformation. It is estimated that 2% of the general population harbor a berry aneurysm, and the risk of rupture may increase with aneurysmal size. Other risk factors associated with SAH include hypertension, smoking, excessive alcohol consumption, and use of sympathomimetic drugs. A familial association of cerebral aneurysms with several diseases has been described, including autosomal dominant polycystic kidney disease, coarctation of the aorta, Marfan syndrome, and Ehlers-Danlos syndrome type IV.

Of all patients presenting to the ED with a primary complaint of headache, less than 1% have SAH. Many patients with SAH die before reaching the hospital; preadmission mortality rates range from 3% to 26%. Median mortality in the United States is 32% with approximately 20% of survivors having significant functional and cognitive deficits.

Clinical Features

The clinical presentation of SAH is one of the most distinctive in medicine. Approximately 80% of patients present with a sudden, cataclysmic thunderclap headache, which often is described as "the worst headache of my life." In up to 20% of patients, the onset of headache may be associated with exertion, the Valsalva maneuver, or sexual intercourse, but the majority occurs in the absence of strenuous physical activity. The headache of SAH classically peaks in intensity within seconds to minutes.[20] Headaches that take longer to peak in intensity are less likely to be SAH. Associated signs and symptoms include syncope, nausea and vomiting, neck stiffness, photophobia, and seizures.

Physical findings depend on the extent of the SAH. Meningismus is present in more than 50% of patients, and up to 20% have focal neurologic abnormalities. Funduscopic examination may reveal retinal or subhyaloid hemorrhages, and patients also may have isolated third or sixth nerve palsy. Oculomotor (third) nerve compression secondary to an expanding posterior communicating artery aneurysm leads to pupillary dilation. Approximately 50% of patients with a ruptured aneurysm are restless or have an altered level of consciousness. Up to one-third of patients recall a sentinel headache days to weeks before diagnosis of subarachnoid hemorrhage.[21]

The patient's prognosis is related to neurologic status at hospital admission. The Hunt and Hess scale stratifies patients according to their clinical signs and symptoms at the time of presentation and is predictive of outcome (Table 93.2). Patients who present with a grade 1 or grade 2 hemorrhage tend to have a good prognosis. Patients with grade 4 or 5 hemorrhages tend to do poorly, presenting with an altered mental status, ranging from stupor to deep coma, together with focal neurologic signs and symptoms. Patients with grade 3 hemorrhage present with drowsiness or confusion and are at risk for rapid clinical deterioration.

Differential Diagnoses

Several clinical entities can mimic the abrupt onset headache associated with SAH. These include cervical artery dissection (CAD), cerebral venous thrombosis (CVT), reversible cerebral vasoconstriction syndrome, hemorrhagic or ischemic stroke, and primary headache disorders, including migraine and cluster headaches.

TABLE 93.2

Hunt and Hess Clinical Grading Scale for Cerebral Aneurysms and Subarachnoid Hemorrhage

GRADE	CONDITION
0	Unruptured aneurysm
1	Asymptomatic or minimal headache and slight nuchal rigidity
2	Moderate or severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild focal deficit
4	Stupor, moderate to severe hemiparesis
5	Deep coma, decerebrate posturing, moribund appearance

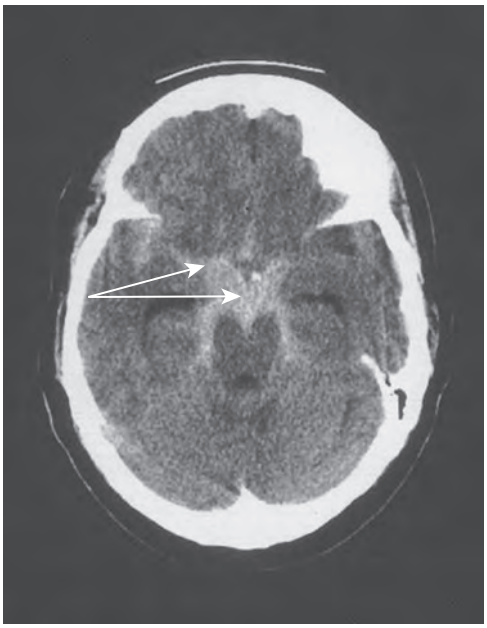

Fig. 93.1. Cerebral aneurysm. Shown is a computed tomography (CT) scan of an aneurysmal subarachnoid hemorrhage (SAH) in a 55-year-old woman. Subarachnoid blood can be seen within the interpeduncular and ambient cisterns and the right sylvian fissure from a ruptured aneurysm at the junction of the right carotid artery and the posterior communicating artery. (From Brisman JL: Neurosurgery for cerebral aneurysm. Emedicine, updated Sep 23, 2010. Available at http://emedicine.medscape.com/article/252142-overview#a1.)

CNS infections cause altered mental status and meningismus but can usually be distinguished by the presence of fever.

Diagnostic Testing

A non–contrast-enhanced head CT scan should be obtained emergently when SAH is suspected (Fig. 93.1). For acute hemorrhages less than 24 hours old, the sensitivity of third generation multidetector row CT scanners in identifying hemorrhage is greater than 90%; however, sensitivity decreases to approximately 50% by the end of the first week.[22] There is one well-designed, prospective study that demonstrated in patients scanned within the first 6 hours following the onset of headache, CT was both 100% sensitive and 100% specific for SAH.[23] However, current guidelines still recommend follow up lumbar puncture (LP) when CT is nondiagnostic.[7] Until additional studies are performed, we recommend a LP be performed in CT negative patients suspected of having a SAH.

Interpretation of LP results can be challenging because up to one-third of spinal fluid analyses contain blood or blood degradation products.[24] To differentiate a traumatic LP from SAH, the patient's CSF should be spun and the supernatant observed for xanthochromia. This yellowish pigmentation is secondary to the metabolism of hemoglobin to pigmented molecules of oxyhemoglobin and bilirubin, a process that can take up to 12 hours to occur. Prospectively gathered data indicate that visual inspection for xanthochromia alone may not diagnose all cases of SAH.[25]

The method of comparing the red blood cell (RBC) count in the first and the last tubes of cerebrospinal fluid (CSF) has not been shown to be accurate, and SAH cannot be ruled out if a substantial numbers of RBCs persist in tube 4. However, a RBC count of less than 100 in tube 4 makes aneurysmal SAH unlikely.[26] CSF xanthochromia in association with normal findings on the CT scan is suggestive of SAH. After the diagnosis is established, angiography should be performed to study the vascular anatomy and to identify the source of hemorrhage.

In lieu of a non-contrast CT followed by LP, the emergency clinician can order a non–contrast-enhanced head CT scan followed by computed tomography angiography (CTA); this is reasonably sensitive and may be appropriate for patients considered to be at lower risk of disease, patients refusing a LP, and patients in whom a LP cannot be performed.[27] Concerns of additional radiation exposure and contrast agent toxicity need to be weighed against the risks of a LP.

A normal non–contrast-enhanced head CT scan followed by a normal spinal fluid analysis definitively rules out SAH and does not need to be followed with angiography, even in patients at high risk of disease.[7] However, this strategy does not rule out other causes of thunderclap headache that may be in the differential diagnosis, such as carotid artery dissection, cerebral venous sinus thrombosis, and reversible cerebral vasoconstrictor syndrome.

Up to 90% of patients with SAH have cardiac arrhythmias or electrocardiographic abnormalities suggestive of acute cardiac ischemia, which may lead to an erroneous primary cardiac diagnosis. Typical electrocardiographic findings include ST-T wave changes, U waves, and QT prolongation.

Decision rules exist to help risk stratify patients with possible SAH; however, high sensitivity is achieved at the expense of specificity. Decision rules can help standardize evaluations but have not significantly reduced current investigation rates (CT scanning and LP).[28]

Management

The management of SAH is aimed at treating acute medical and neurologic complications, preventing recurrent hemorrhage, and forestalling the ischemic complications of vasospasm.[29] Because of an altered level of consciousness, patients with SAH of grade 3 or higher are at risk for respiratory depression and hypercapnia, which can lead to further increases in intracranial pressure (ICP); therefore, these patients require early endotracheal intubation. Blood pressure should be closely monitored because of the risk of continued bleeding or recurrent hemorrhage. Nimodipine, a calcium channel blocker, should be started soon after a diagnosis of aneurysmal SAH is made to lessen the likelihood of poor outcome due to vasospasm, even if the patient's blood pressure is normal.[30] Because nimodipine may cause transient hypotension in some patients, hemodynamic monitoring is required during its administration. The recommended dosage is 60 mg by mouth or nasogastric tube every 4 hours. Antifibrinolytics (eg, aminocaproic acid) are used to reduce the risk of early rebleeding in patients with an unavoidable delay in obliteration of the aneurysm in the absence of contraindications. Corticosteroids have not been demonstrated to be of benefit.[31]

Blood pressure management in SAH should be determined by the patient's clinical status with involvement of the treating neurosurgeon. The typical treatment goal is a systolic blood pressure below 160 mm Hg or a mean arterial pressure below 130 mm Hg unless vasospasm is present.[29]

Analgesics, including opioids, should be used for persistent headache. In patients who are nauseated or at risk for vomiting, antiemetics should be administered. Agitated patients require sedation, and all patients should be placed at bed rest in a quiet and dark environment. Clinically evident seizures should be treated with anticonvulsants, but the prophylactic use of these drugs is controversial. For definitive management, endovascular coil embolization is preferable to neurosurgical clipping, but this decision is based on size, location, and morphologic features of the aneurysm, as well as local expertise.[32]

Disposition

A majority of patients with ruptured aneurysms require hemodynamic and ICP monitoring in an intensive care setting.

Intracranial Neoplasm

Principles

Headache is the most common presenting complaint among patients with brain tumors.[33] It is less common in older patients with brain tumors, presumably because of age-related atrophy. Headache can be caused by primary neoplasms of the CNS, as well as by metastatic lesions. The most common causes of metastasis are lung and breast carcinoma, followed by malignant melanoma and carcinomas of the gastrointestinal tract.[34]

The headache of intracranial neoplasms can be caused by several mechanisms, including traction on pain-sensitive structures (such as, meninges or larger cerebral vessels), or it may be a symptom of increased ICP or hydrocephalus. The pain patterns produced are highly variable, depending on the location and size of the mass and the structures involved. Rapidly growing tumors are more likely to be associated with headache.

Clinical Features

The location of the headache may be ipsilateral, contralateral or bilateral and does not predict tumor location. The typical patient presents with complaints of a worsening headache that has been present for weeks to months. The headache may have been present initially only on awakening (most likely in patients with increased ICP), gradually becoming continuous. The classic triad of brain tumor headache—sleep disturbances, severe pain, and nausea and vomiting—is seen in a minority of patients. Vomiting, when it is present, may be projectile and not preceded by nausea and often can be attributed to increased ICP. If increased ICP is present, the headache often is bilateral and worsened by coughing, sneezing, bending, defecation, and sexual intercourse. Other presentations of intracranial neoplasms include seizures, personality changes, and cognitive difficulties.

Differential Diagnoses

A number of disease processes can mimic brain tumor headache. These include other space occupying lesions, such as an abscess or an intra-axial or extra-axial brain hemorrhage; diseases associated with increased ICP, such as idiopathic intracranial hypertension; and a vasculitis, such as giant cell arteritis (GCA). Once malignant causes of headache have been excluded, many of these patients will be diagnosed with a chronic headache disorder, such as chronic migraine, chronic tension-type headache, or *new daily persistent headache*, which is a primary headache disorder, characterized by abrupt onset and unremitting course.

Diagnostic Testing

The diagnosis of brain tumor headache may be suspected from the history and neurologic examination. Early in the course, patients may present with headache and an intact neurologic examination, although the majority of intracranial neoplasms will eventually cause focal neurologic deficits. Neuroimaging with CT or MRI is the most efficient way to confirm the diagnosis. Contrast enhancement on CT often improves the identification of the underlying mass lesion and helps differentiate it from other causes, including abscess, hematoma, and vascular malformation.

Management

The treatment of headache associated with brain tumor depends on the type of tumor, patient functional status, and stage of the disease. Management consists of urgent referral to specialty care and treatment of any acute complications, including increased ICP and seizures. For patients who present with symptoms suggestive of increased ICP (eg, headache, nausea, vomiting, confusion, weakness), treatment with corticosteroids often provides dramatic temporary relief of headache and other symptoms of increased ICP. Analgesics may also be necessary. Dexamethasone is used most often to treat edema associated with brain tumors. It has several advantages over other glucocorticoids, including a longer half-life, reduced mineralocorticoid effect, and lower associated incidence of cognitive and behavioral complications. The exact dose of steroids necessary for each patient varies in accordance with histologic features, size, and location of the tumor and the amount of edema present. In general, most patients require between 8 mg and 16 mg of dexamethasone per day. An appropriate starting dosage in the ED is 10 mg IV, followed by 4 mg every 6 hours.

Patients who have a seizure should receive a first generation AED, such as phenytoin, carbamazepine, or valproate; a second generation AED (such as, levetiracetam) is an alternative especially if the patient has liver disease. The choice of AED should be made in consultation with the specialist assuming care for the patient. Empirical or prophylactic treatment with AEDs does not appear to delay or to prevent the onset of seizure activity and may expose the patient to unnecessary complications and toxicity.[35]

Disposition

Patients with brain tumor headache should be managed in consultation with the patient's primary health care team. Hospitalization verses discharge will depend upon the severity of the patient's presentation.

Giant Cell Arteritis

Principles

GCA is an inflammatory vasculopathy that occurs in medium and large arteries with well-developed wall layers and adventitial vasa vasorum.[36] It typically involves the major branches of the aorta and has a predilection for the extracranial branches of the carotid artery (eg, temporal and occipital arteries). It can involve the ophthalmic, vertebral and distal subclavian arteries, as well as the thoracic aorta. GCA is often named *temporal arteritis* because it commonly affects the superficial temporal arteries.

The mean age at onset of GCA is 71 years old, and it is rare before 50 years old. Women are affected more commonly than men.[37] Pathologically, the arteritis causes an inflammatory

BOX 93.4

Common Clinical Features in Patients With Giant Cell Arteritis

Age older than 50 years old
Female more than male
Headache
Visual symptoms:
- Amaurosis fugax
- Visual loss
- Diplopia

Jaw claudication
Temporal artery tenderness
Systemic symptoms:
- Fever
- Weight loss
- Fatigue

infiltrate in the arterial wall resulting in intimal hyperplasia and subsequent stenosis and occlusion, leading to a variety of ischemic complications. In the vast majority of cases, loss of vision is due to arteritic anterior ischemic optic neuropathy (AAION), which is almost always caused by narrowing or occlusion of the posterior ciliary arteries.

Clinical Features

Temporal arteritis is the most typical presentation of GCA and presents with a broad spectrum of clinical features attributable to ischemia on the one hand and systemic inflammation on the other hand (Box 93.4). Headache is the most common initial manifestation and occurs in more than 70% of patients.[38] The headache often is of 2 to 3 months' duration and can be continuous or intermittent; it can worsen at night or on exposure to cold. The pain may be described as sharp, throbbing, boring, or aching and usually is localized to the temporal region but may occur anywhere in the head. The physical examination may reveal tenderness over the scalp in the area of the temporal artery, with exacerbation of the pain by wearing a hat or resting the head on a pillow. Patients also can experience jaw claudication secondary to vascular insufficiency of the masseter and temporalis muscles. Systemic signs and symptoms are often present, including fever, anorexia, and weight loss. Approximately 40% of patients develop symptoms of polymyalgia rheumatica, pain in their large proximal joints, with symptoms referable to the neck, torso, and lower back. The pain and stiffness are typically worse in the morning and lessen as the day goes on.

The most serious complication of GCA is permanent visual loss, which occurs in approximately 15% of patients.[39] Amaurosis fugax can occur before permanent visual loss. Other complications include peripheral neuropathies, transient ischemic attacks, and stroke. The physical examination may reveal abnormalities of the temporal arteries best detected by light palpation just anterior and slightly superior to the tragus of the ear. Findings include tenderness, reduced or absent pulsations, erythema, and nodularity or swelling. Visual acuity, visual field testing, and thorough funduscopic examination should be performed. The presence of a relative afferent pupillary defect (Marcus-Gunn pupil) should increase the suspicion for GCA, although these patients usually will also have a visual loss or a visual field defect.

Differential Diagnoses

The systemic symptoms of GCA are nonspecific. Therefore, the differential diagnosis is quite broad and includes infections, malignancies, and other vasculitides. Takayasu's arteritis can affect the aorta and its primary branches as well, but it affects younger patients and visual loss is uncommon. Polyarteritis nodosa, microscopic polyangiitis, and granulomatosis with polyangiitis (formerly known as *Wegener's granulomatosis*) can rarely affect the temporal artery but have different histopathology and vascular involvement. Ischemic stroke can cause headache with visual loss or amaurosis fugax. Pituitary apoplexy classically presents with thunderclap headache and bitemporal visual field loss.

Diagnostic Testing

The diagnosis of GCA is based on the history and physical examination, laboratory and imaging studies, and biopsy of the temporal artery. The majority of patients will have significant elevations of both the erythrocyte sedimentation rate (ESR), usually to more than 50 mm/hr and often more than 100 mm/hr, and C-reactive protein (CRP), as well as the presence of thrombocytosis and anemia. The sensitivity of an elevated ESR or an elevated CRP has been reported in the range of 85%, but their specificity is only 30%.[40] However, only 4% of patients with GCA have a normal ESR and CRP at the time of diagnosis. In patients in whom there is high suspicion of disease, a temporal artery biopsy should be performed even if both of these biomarkers are normal.[41] Some imaging modalities may eventually aid in the diagnosis of GCA. Color duplex ultrasonography of the temporal arteries may reveal a peri-luminal hypo-echoic halo representing vessel wall edema; however, it is highly operator dependent and its diagnostic value needs to be further determined. High resolution MRI of the temporal arteries has also been studied, but more data is needed before it can be recommended.

The only test that confirms the diagnosis of GCA is a temporal artery biopsy. A biopsy, however, has a sensitivity of only 70% to 90%, because GCA is a patchy disease with skip lesions. Therefore, some patients with GCA are diagnosed on clinical grounds alone.

Management

Patients who present with visual symptoms (such as, amaurosis fugax or diplopia) must be treated emergently with glucocorticoids, because they are at risk for visual loss, which is typically permanent. Given available evidence, we believe these patients should be treated with IV pulse therapy (eg, 1000 mg of methylprednisolone per day for 3 consecutive days) to optimize immunosuppression and suppress tissue edema. For patients without visual symptoms, lower doses of steroids, in the range of 40 to 60 mg/day of prednisone should be used.[36]

Disposition

Patients with GCA should be managed in consultation with appropriate specialists, including neurology, ophthalmology, and rheumatology.

Carotid and Vertebral Artery Dissection

Principles

Approximately 2% of all ischemic strokes are caused by CAD. In patients younger than 50 years old, CAD is the most frequent cause of ischemic stroke and accounts for 10% to 25% of cases.[42] These values likely underestimate the true incidence because patients with minimal symptoms are often not diagnosed. Although dissections may occur spontaneously, a careful history frequently identifies an association with sudden neck movement or trauma preceding the event. Reported mechanisms include neck torsion, chiropractic manipulation, coughing, minor falls,

heavy lifting, various sports including basketball and volleyball, sexual intercourse, childbirth, and motor vehicle collisions. Early symptoms and signs may be subtle, and delays in diagnosis are common in the absence of neurologic findings. The median delay from symptom onset to diagnosis can be several days.

The pathologic lesion in CADs is intramural hemorrhage within the media of the arterial wall. The hematoma can be localized or extend circumferentially along the length of the vessel, resulting in partial or complete occlusion. Damage to the intima results in platelet aggregation and thrombus formation further compromising vessel patency or causing distal embolization. The timing of these events is variable, and a patient may experience symptoms of cerebral ischemia days to years after dissection.

Clinical Features

The typical presentation of CAD is the abrupt onset of pain in the head or neck, often in association with symptoms resulting from ischemic consequences of the dissection and emboli. Neurologic findings secondary to cerebral ischemia usually occur within the first few hours following the onset of the headache or neck pain. Although carotid dissection and vertebral artery dissection have many commonalities, their clinical presentations have some unique features.

Carotid Artery Dissection. The classic triad of symptoms for carotid artery dissection includes (1) unilateral headache or neck pain, sometimes radiating to the ipsilateral eye; (2) ipsilateral partial Horner's syndrome; and (3) either blindness, due to retinal ischemia, or contralateral motor deficits, caused by cerebral ischemia. However, this complete triad is only present in a minority of patients. The headache is often severe and throbbing but may be subacute and similar to previous headaches and may be associated with pulsatile tinnitus.

Acute severe retro-orbital pain in a previously healthy person with no history of cluster headaches is suggestive of carotid dissection. Patients with a carotid dissection are at risk of sustaining embolic cerebral ischemia. Warning symptoms include transient ischemic attacks, amaurosis fugax, episodic lightheadedness, and syncope. Spontaneous dissection of the carotid artery has a favorable prognosis and recurrence is uncommon. Factors associated with a worse prognosis include older age, occlusive disease on angiography, and stroke as the initial presenting symptom.[43]

Vertebral Artery Dissection. Vertebral artery dissections are less common than carotid dissections. The classic presentation is that of a relatively young person with severe, unilateral posterior headache and a rapidly progressive neurologic deficit with symptoms of brainstem and cerebellar ischemia. Common findings include vertigo, severe vomiting, ataxia, diplopia, hemiparesis, unilateral facial weakness, and tinnitus. Stroke severity tends to be lower than that seen with carotid dissection. Spontaneous vertebral artery dissection appears to be relatively rare. Approximately 10% of patients who develop a vertebral dissection die during the acute phase, secondary to massive stroke. For patients who survive, the prognosis is usually good.[44]

Differential Diagnoses

The differential diagnoses of unilateral headache and neck pain with or without Horner's syndrome include migraine and cluster headache. Cluster headache in particular can present with ptosis. Cervical arterial dissection may present with an abrupt onset of severe headache, which may be confused with SAH or other vascular causes of headache. For patients who present with symptoms of cerebral ischemia, both ischemic and hemorrhagic stroke should be considered as possible etiologies. Conversely, CAD should be considered in patients who present with acute stroke, particularly younger patients.

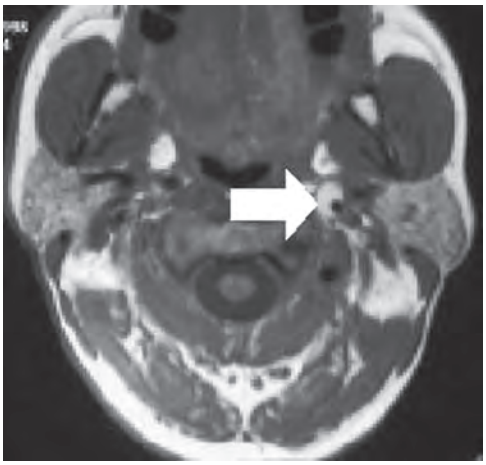

Fig. 93.2. Axial T1-weighted magnetic resonance image (MRI) demonstrating a crescent sign *(arrow)* in a patient with a left internal carotid artery dissection. (From Kidwell C: Dissection syndromes. Emedicine, updated Sep 19, 2011. Available at http://emedicine.medscape.com/article/1160482-overview.)

Diagnostic Testing

Identification of patients with dissection can be challenging especially in the absence of cerebral ischemia. A non–contrast-enhanced head CT scan is often normal in uncomplicated dissection. Digital subtraction angiography remains the diagnostic gold standard, although several studies have found CTA and magnetic resonance angiography (MRA) to be reasonably sensitive and are an appropriate choice for initial screening. Figure 93.2 shows an example of carotid artery dissection on MRI. Duplex imaging is not sufficiently sensitive to rule out disease.[45]

Management

CAD patients with acute ischemic stroke are candidates for thrombolytic therapy. Studies have shown this treatment to be safe with efficacy similar to stroke from other causes.[43]

For patients with CAD without acute ischemic stroke, the primary goal of treatment is the prevention of cerebral ischemic complications. The role of antiplatelet agents versus anticoagulation with heparin remains unclear. A Cochrane Review published in 2010 found no significant difference in efficacy between these two modalities, although it was based solely on observational studies.[46] Recently, the first randomized study was published and found that recurrent stroke at 3 months is rare with no significant difference in outcome between those patients treated with antiplatelet agents or anticoagulation.[42]

Disposition

Patients with CAD should be admitted to the hospital for monitoring and further management.

Cerebral Venous Thrombosis

Principles

Thrombosis of the intracranial veins and sinuses is a rare disorder causing approximately 1% of all strokes. It typically presents with headache and disproportionately affects younger individuals without traditional cerebrovascular risk factors.[47]

There are multiple causes for CVT, and risk factors are classically linked to the Virchow triad of blood stasis, blood vessel wall abnormalities, and a hypercoagulable state. Both genetic and acquired prothrombotic conditions have been associated with CVT. Inherited thrombophilias such as antithrombin III, protein C and protein S deficiencies, and factor V Leiden mutation are the most common genetic causes. Acquired causes for CVT include pregnancy and the puerperium, malignancy, head trauma, surgery, parameningeal infections, and exogenous hormones, such as oral contraceptives. Other causes include inflammatory systemic disorders, including vasculitis, inflammatory bowel disease and connective tissue disorders, and neurosurgical procedures.[48]

Clinical Features

Clinical findings in CVT usually fall into two major categories, depending on the mechanism of neurologic dysfunction: (1) Those that are related to increased ICP due to impaired venous drainage, and (2) those related to focal brain injury from venous resulting in ischemia, infarction, or hemorrhage. Diffuse headache increasing in severity over days to weeks is the most common symptom experienced by patients with CVT and is often associated with increased ICP. Focal neurological findings, when present, are related to the region of the brain that has been injured and bilateral brain involvement may occur. Seizures, both focal and generalized, frequently occur. Ocular findings associated with CVT include orbital pain, proptosis, chemosis, extraocular muscle paralysis, and papilledema.

Differential Diagnoses

The differential diagnoses of early CVT, when symptoms are limited to headache and papilledema, include brain tumor and idiopathic intracranial hypertension. Late presentations of CVT include altered sensorium, seizures, and focal neurological deficits. At this point, the differential diagnoses includes ischemic and hemorrhagic stroke; intracranial infections, such as brain abscess, meningitis, and encephalitis; and systemic conditions, including sarcoidosis and systemic lupus erythematosus. With CVT, neurological findings do not follow a typical arterial territory, and the presence of papilledema is suggestive of CVT. CSF findings and neuroimaging studies help differentiate CVT from these other conditions.

Diagnostic Testing

Routine blood work including a complete blood count (CBC), chemistry panel, ESR, and clotting studies, including a prothrombin time (PT) and partial thromboplastin time (PTT) should be obtained in all patients with suspected CVT. These studies are helpful in determining the presence of an underlying hypercoagulable state, an infectious process, or an inflammatory disorder contributing to the development of CVT. A normal D-dimer is helpful for patients with a low probability of CVT and, along with the clinical findings, can be used to exclude the diagnosis in individual patients at low risk of disease.[49,50] The definitive diagnosis of CVT is based on neuroimaging of the area of thrombosis. Noncontrast CT by itself is an insensitive test, but it may reveal nonspecific late lesions, such as an infarct, hemorrhage, or edema. Occasionally, hyperdensity of a cortical vein or sinus may be seen. The key to diagnosis is to image the venous system itself. This is best accomplished by a combination of MRI to visualize the thrombosed vessel and magnetic resonance venography (MRV) to detect nonvisualization of the same vessel.[51] CTA and CTV may also be used to visualize the cerebral venous system, especially in patients who have a contraindication to MRI.

Management

Patients with CVT should be anticoagulated to prevent propagation of the thrombosis and development of embolic complications (eg, pulmonary embolism). Treatment is adjusted dose unfractionated heparin or weight-based low–molecular-weight heparin in full anticoagulant doses, regardless of the presence of intracerebral hemorrhage.[52] In patients whose clinical condition worsens despite anticoagulation, thrombolysis or thrombectomy may be considered in centers with expertise in interventional procedures. Seizures are treated with antiepileptic drugs.

The prognosis with CVT is based on the underlying etiology, the patient's condition at time of diagnosis, and the development of complications. The overall mortality is low compared with other types of strokes, but morbidity may be increased with delays in recognition and treatment.[48]

Disposition

Patients with CVT require hospitalization, preferentially to a stroke unit, for systemic anticoagulation.

Idiopathic Intracranial Hypertension

Principles

Although this disease is sometimes called *pseudotumor cerebri* or *benign intracranial hypertension,* the term *idiopathic intracranial hypertension (IIH)* best reflects current understanding of the pathophysiology and the fact that this disorder is not benign, because permanent visual loss can occur. The term *pseudotumor cerebri syndrome* includes both IIH and other conditions (eg, systemic lupus erythematosus) that can cause a similar clinical presentation.[53] Compared with other headache disorders, IIH is a relatively uncommon neurologic disease seen primarily in young obese women of childbearing age. Several predisposing factors have been suggested, including antibiotics (most commonly tetracyclines), vitamin A and retinoids, and human growth hormone. The pathophysiologic mechanism of this disease is not understood, but it is often attributed to an imbalance between CSF production and reabsorption.

Clinical Features

Clinical and diagnostic criteria for IIH are listed in Box 93.5. The most prominent symptom is generalized headache, which is often gradual in onset and of moderate intensity. No specific localizing pattern has been documented, although in some patients the headache is worsened by eye movement. It may awaken the patient

BOX 93.5

Criteria for Diagnosis of Idiopathic Intracranial Hypertension

Headache that remits with normalization of CSF pressure
Papilledema
Nonfocal neurologic examination
May have CN VI palsy
Increased CSF opening pressure
    >250 mm in adults
    >280 mm in children
Normal CSF diagnostic studies
Normal neuroimaging studies
No other cause of increased ICP identified

CN, Cranial nerve; *CSF,* cerebrospinal fluid; *ICP,* intracranial pressure.

from sleep and is exacerbated by bending forward and the Valsalva maneuver, both of which impede cerebral venous return. Visual complaints are common, and patients may experience transient visual obscurations (TVOs), which are momentary blackouts of vision most likely due to temporary disruption of the microcirculation to the optic nerve head. They usually occur with postural changes and are not predictive of permanent visual loss. Patients may also complain of nausea, vomiting, dizziness, and pulsatile tinnitus. The physical examination will reveal papilledema and visual field defects or visual loss occurs in up to 50% of patients. Fortunately, in the majority of patients, visual defects are reversible with treatment.[54] On occasion, a sixth nerve palsy (ie, a false lateralizing sign) is noted.

Differential Diagnoses

The differential diagnoses of IIH include other causes of increased ICP in a patient presenting with headache. Important considerations include CVT, mass lesions, obstructive hydrocephalus, and leptomeningeal infiltration by neoplastic or infectious processes.

Diagnostic Testing

MRI with MRV is the preferred modality for diagnosing IIH because of its ability to not only detect mass lesions and hydrocephalus but also CVT and other meningeal processes. If neuroimaging is normal, a LP should be performed in the lateral decubitus position to measure CSF opening pressure and to obtain CSF diagnostic studies, including cell counts, protein, glucose, cultures, and cytology. An opening pressure of 250 mm H_2O or more (normal 70 to 180 mm H_2O) is necessary to make the diagnosis. An ophthalmology consult should also be ordered for detailed visual field testing.

Management

Many patients present without visual field loss, and symptomatic therapy is all that is necessary. Removal of a large amount of CSF (>20 mL) to decrease CSF pressure to relieve the patient's headache is recommended in all treatment guidelines for IHH. We believe this should be considered for all patients with headache caused by IIH, although the benefit of this practice has not been established in clinical studies. CSF is produced relatively quickly, which limits the duration of benefit. In patients with evidence of visual field loss, treatment with medications to lower ICP is indicated. Acetazolamide is the most potent medication for lowering ICP, and the usual starting dosage is 500 mg twice a day. Other medications that have been used include furosemide, topiramate, and steroids. If a patient is not responsive to medications or has progressive symptoms, referral to an ophthalmologist for optic nerve sheath decompression or a neurosurgeon for a CSF diversion procedure (eg, lumboperitoneal or ventriculoperitoneal shunt) may be indicated.[54]

Disposition

Because visual loss can occur early or late in the course of IIH, appropriate specialists including ophthalmology and neurology should be involved in the patient's evaluation, treatment, and disposition.

Post–Dural Puncture Headache

Principles

Post-dural puncture headache (PDPH) is a frequent complication of dural puncture, whether performed for diagnostic or therapeutic purposes or accidentally, as a complication of epidural anesthesia. The incidence is highest in the 18- to 30-year age group, and it is uncommon in young children and in adults older than 60 years old. Other than age, risk factors include female gender, low body mass index (BMI), and history of chronic headache.[55]

The pathophysiology of PDPH is not entirely clear. The most likely explanation is a persistent CSF leak that exceeds CSF production, resulting in CSF hypotension. If sufficient CSF is lost, the brain descends in the cranial vault when the patient assumes the upright position, leading to increased traction on the pain fibers. Thus the headache is characteristically positional and increases with the upright position and decreases with recumbency. The amount of time a patient remains recumbent after LP does not appear to affect the incidence of headache.

Certain equipment related factors have been implicated as causes of PDPH, including the size or diameter of the spinal needle, the orientation of the bevel during the procedure, and the amount of fluid withdrawn. Smaller-diameter needles (eg, 20- or 22-gauge cutting needle) cause less leakage, and it is postulated that insertion of the needle with the bevel up (ie, bevel pointing up when the patient is in the lateral position) minimizes damage to the dural fibers. Use of atraumatic needles (eg, Whitaker or Sprotte) also has been shown to reduce the incidence of PDPH.[56] If atraumatic needles are not available, we recommend using a 20- or 22-gauge cutting needle when possible.

Clinical Features

The cardinal feature of PDPH is orthostatic or positional headache that is precipitated by the upright position and relieved when the patient lies down. About 90% occur within the first 72 hours after the LP and typically resolve within 1 week.[57] The headache is often described as bilateral and throbbing, frequently in the frontal or occipital regions. Associated signs and symptoms include neck stiffness, nausea, vomiting, auditory disturbances including tinnitus and hypoacusis, and photophobia.

Differential Diagnoses

For most patients, PDPH is a benign disorder. However, in patients who do not respond to standard treatment modalities, other secondary headache disorders must be considered. This is especially true in postpartum period where CVT is an important consideration.

Diagnostic Testing

The diagnosis of PDPH is based on clinical features, and most patients have a benign course that requires no diagnostic testing. Spontaneous CSF leaks present with orthostatic headaches, which are sometimes severe and should be considered in the absence of a recent LP. The diagnosis is made when low CSF pressures are found on LP. In the postpartum period, CVT can be excluded with MRV.

Management

Most PDPHs resolve spontaneously within 5 to 7 days with bed rest, adequate hydration, and mild analgesics. For persistent headaches, methylxanthine agents (such as, caffeine and aminophylline) have been used, but their efficacy has not been proven. We do not recommend their routine use in the ED. For severe headaches that do not respond to conservative measures, an epidural blood patch (EBP) should be used. This procedure involves the injection of 15–30 mL of autologous blood into the epidural space near the site of the original dural puncture resulting in a

blood clot that seals off the dural hole. EBP has a very high success rate and should be used for PDPH that does not respond to conservative measures.[58]

Disposition

The vast majority of patients with PDPH will have a benign course requiring only conservative treatment. For patients with persistent complaints, consultation with anesthesia or radiology for an EBP should be considered. If a patient does not respond to an EBP, other secondary causes of PDPH should be considered, especially in postpartum patients.

Post-Traumatic Headache

Principles

Headache is the most common symptom following a concussion or other traumatic brain injury (TBI). It is often part of a complex post-concussive syndrome that can include dizziness, fatigue, insomnia, irritability, memory loss, and difficulty with concentration. Persistent headache occurs in over 50% of patients who have suffered a TBI.[59] Paradoxically, patients with milder injuries are more likely to report persistence of symptoms, as are patients with preexisting headache disorders. For the emergency clinician, management of post-traumatic headache (PTHA) is different in the immediate aftermath of trauma, when excluding life-threatening causes are of paramount importance, versus dealing with the ramifications of PTHA during the days, weeks, and months that follow the trauma when it has become clear that no neurosurgical emergencies exist. The pathophysiologic mechanism for the symptoms is unclear and may have both anatomic and functional components.

Clinical Features

By international criteria, PTHA develops within 7 days of the injury or regaining consciousness. Acute PTHA resolves within 3 months, whereas persistent PTHA persists beyond 3 months. Patients in whom PTHA develops after minor head injuries have normal findings on neurologic examination and neuroimaging studies. Most patients are concerned about the cause of the headache more than about the headache itself.

PTHA may assume a variety of characteristics, including the pulsating unilateral pain and associated features of migraine, the bland, squeezing pain of tension-type headache, or nonspecific headache often relating to the musculature of the neck.

Differential Diagnoses

In the acute setting, pathological causes of headache including intracranial hemorrhage, or skull or cervical fractures should be excluded. Cervical strain and subtle oculomotor nerve palsies are additional etiologies of PTHA that should be considered. Beyond the acute setting, it may be difficult to distinguish PTHA from migraine or tension-type headache, a distinction that, as time passes, becomes less important.

Diagnostic Testing

In the acute setting following TBI, traumatic injuries to the brain, skull, and neck should be evaluated using available clinical decision rules (see Chapter 34). Patients who return to the ED with persistent symptoms after normal initial imaging should be reassured that follow-up imaging is not required, assuming the patient has a normal neurologic examination and is not using anticoagulants or antiplatelet medication.

Management

There is insufficient evidence to determine the optimal treatment of PTHA. We recommend the same armamentarium of medications used to treat acute primary headaches, specifically, antiemetic dopamine antagonists such as metoclopramide or prochlorperazine, and NSAIDs. Opioids should be avoided.

Disposition

Patients with PTHA should be discharged home with outpatient follow-up.

Hypertensive Headache

Principles

The relationship between elevated blood pressure and headache is unclear. Ambulatory blood pressure monitoring studies have not demonstrated an association, although these studies are limited by relatively modest blood pressure elevations during the study period.[2] In the ED, nearly one-quarter of patients who present to an ED with headache have a systolic blood pressure above 150 mm Hg or diastolic blood pressure over 95 mm Hg. Patients who present with headache are more likely to have a markedly elevated blood pressure than patients with other chief complaints. However, the causal pathway, if one exists, is not apparent based on current evidence. In fact, both chronic hypertension and acute elevation in blood pressure have been linked to decreased pain sensitivity in animal and human models. International criteria attribute headache to elevated blood pressure when the pressure is greater than 180 mm Hg systolic or 120 mm Hg diastolic and when the headache resolves with resolution of the elevated blood pressure.[42]

Clinical Features

The headache of severe hypertension is generally characterized as bilateral and throbbing. Early reports of a typical hypertensive headache come from patients with marked, untreated hypertension, who had early morning headaches that were of greatest intensity before the patient arose and typically resolved as the patient engaged in morning activities.

Differential Diagnoses

Based on population prevalence, the most likely diagnoses in patients with elevated blood pressure and headache are migraine or tension-type headache with concomitant hypertension.[60]

Pre-eclampsia, a disorder characterized by elevated blood pressure and headache, should be considered in patients in the latter stages of pregnancy and the recent postpartum period. Posterior reversible encephalopathy syndrome is characterized by white matter changes on diagnostic imaging. Malignant hypertension, including drug-induced hypertension, requires evidence of end organ damage.

Diagnostic Testing

Absent focal neurological deficits, abnormal findings on retinal examination, or visual deficits, a diagnostic evalutation is not indicated.

Management

It is uncertain if strategies aimed at lowering the blood pressure acutely will alleviate the headache. We recommend use of

antidopaminergic or nonsteroidal agents, with use of antihypertensive agents reserved for patients with evidence of end organ damage. Oral antihypertensive therapy may be prescribed in the ED if timely outpatient follow-up cannot be assured.

Disposition

In the absence of objective neurological symptoms, patients with hypertensive headache do not require admission to the hospital. Elevated blood pressure should be treated on an outpatient basis.

Reversible Cranial Vasoconstriction Syndrome

Principles

Reversible cranial vasoconstriction syndrome (RCVS), also referred to as *Call-Fleming syndrome,* is a cerebral arteriopathy characterized by segmental areas of vasoconstriction within large- and medium-sized vessels. It is the same disease as postpartum angiopathy or migrainous vasospasm. RCVS causes recurrent thunderclap headache in susceptible patients and may cause ischemic or hemorrhagic stroke. The prevalence of this presumably rare disorder is not known. RCVS is being reported with more frequency given the wide availability of noninvasive neurovascular imaging. Some data suggest that this disorder may cause the majority of thunderclap headaches.[61]

Clinical Features

The headache of RCVS is characteristically a thunderclap headache, abrupt in onset, and severe. It is often throbbing and associated with nausea, vomiting, and photophobia. The headache may be provoked by use of vasoactive medications or substances.

Differential Diagnoses

The differential diagnoses for thunderclap headache include SAH and other hemorrhagic strokes, CVT, CAD, and pituitary apoplexy. Unlike these other pathological diagnoses, RCVS is characterized by recurrent thunderclap headache within a discrete period of time. Thunderclap headache during sexual activity may occur pre- or post-orgasm and is classified as *primary headache associated with sexual activity* after other causes of thunderclap headaches have been excluded. Once that happens, a diagnosis of *primary thunderclap headache* is assigned.

Diagnostic Testing

Patients with the initial presentation of thunderclap headache should have a head CT and LP performed to exclude SAH and other intracranial pathology. Repeat neurovascular imaging, or diagnostic angiography, should be pursued in patients with recurrent thunderclap headache.

Management

There are no evidence-based treatment options available for RCVS. Goals of treatment include prevention of ischemic and hemorrhagic stroke and elimination of headache. To date, the natural history of this disorder is incompletely understood. Treatment with calcium channel blockers has been described, although when to initiate treatment is unclear.

Disposition

Patients with thunderclap headache who have received an appropriate diagnostic evalutation in the ED may be discharged home with appropriate follow-up.

KEY CONCEPTS

- The goals of headache evaluation in the ED are (1) to distinguish between benign primary headache disorders and potentially life-threatening secondary causes of headache and (2) to treat the headache pain effectively and rapidly without causing undue side-effects.
- Patients with the following headache presentations are at risk for serious underlying disease: sudden explosive headache; first or "worst-ever" headache; new-onset headache after the age of 50 years; headache associated with papilledema, alteration in or loss of consciousness, or focal neurologic symptoms; subacute headache with increasing frequency or severity; headache associated with fever, cancer, or immunosuppression; and headache triggered by exertion, sexual activity, or Valsalva maneuver.
- The need for diagnostic studies is dictated by the suspected secondary cause of headache.
- Sumatriptan medications are the first line therapy for migraine headaches.
- Patients with migraine treated in the ED need to be discharged with a "rescue plan" if the headache reoccurs.
- High-flow oxygen will terminate the majority of cluster headaches.
- Opioids are not first line treatment for primary headaches and are reserved for cases refractory to other interventions.
- The differential diagnosis of sudden severe headache includes SAH, CVT, CAD, and IIH.
- CVT should be suspected in women who have a new type of headache and are pregnant or on birth control pills.
- Carotid artery dissection may result in headache, ptosis, and miosis.
- Patients suspected of having a PTHA should be evaluated for a CN IV or VI neurapraxia and for cervical strain as a cause of their headache.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 93: QUESTIONS & ANSWERS

93.1. Which of the following mechanisms is least likely to play a role in the pathophysiology of migraine headaches?
- **A.** Cortical spreading depression
- **B.** Pathologic cerebrovascular dilation activates surrounding afferent nerve endings, causing typical pulsating pain
- **C.** Sensitization of higher-order nociceptive centers in the brainstem and thalamus
- **D.** Sterile neuropeptide induced inflammatory process
- **E.** Trigeminal nerve activation

Answer: B. Trigeminovascular activation, possibly triggered by cortical spreading depression or a sterile neurogenic inflammation, causes activation and sensitization of higher-order nociceptive centers in the brainstem and thalamus. A primary vascular etiology of migraine pain is not supported by available evidence.

93.2. A 42-year-old male presents with the acute onset of a left-sided headache. He had one similar headache approximately 1 year ago that lasted 3 hours, subsided rapidly, and like this one, was associated with alcohol intake. Physical examination is remarkable for an obviously uncomfortable healthy male pacing and rubbing his left temple. You note left conjunctival injection with tearing. What should be the next step?
- **A.** Computed tomography (CT) scan
- **B.** Dexamethasone 10 mg intravenously
- **C.** High-flow oxygen by face mask
- **D.** Measurement of intraocular pressure
- **E.** Morphine 10 mg intravenously

Answer: C. Cluster headaches occur predominantly in men, occur suddenly, and often abate quickly. These headaches are typically unilateral and characterized by a sharp stabbing ocular pain that may be accompanied by a "conjunctivitis" picture, a partial Horner's syndrome, or unilateral nasal congestion. Alcohol may precipitate. Standard antimigraine agents may be helpful (eg, sumatriptan, antiemetics), but high-flow oxygen is highly effective and very well tolerated. Calcium channel blockers and corticosteroids are useful for preventing subsequent attacks of cluster headache. As with migraines, opioids should be reserved for refractory pain.

93.3. A 29-year-old female presents within 1 hour of the sudden onset of a severe, diffuse headache accompanied by meningismus and vomiting. Emergent computed tomography (CT) scan is negative. Lumbar puncture (LP) reveal 50,000 red blood cells (RBCs) in tube 1 and 30,000 RBCs in tube 4. Opening pressures are normal, and the sample is negative for xanthochromia. What would be the most appropriate next step?
- **A.** Admission and observation
- **B.** Cerebrovascular imaging study
- **C.** Hydration, analgesics
- **D.** Magnetic resonance imaging (MRI) scan with gadolinium
- **E.** Subcutaneous sumatriptan 6 mg

Answer: B. CT scan provides a sensitivity of approximately 90% for the detection of subarachnoid hemorrhage (SAH). A traumatic LP, even with diminishing RBC counts with sequential tubes, cannot differentiate between a SAH and traumatic tap. The lack of xanthochromia is predictable, given the acute onset of headache and the 12 hours required for cerebrospinal fluid (CSF) xanthochromia to develop. A cerebrovascular imaging study, such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), or standard angiography would be required next to exclude a source of bleeding, such as an aneurysm or arteriovenous malformation (AVM).

93.4. A 69-year-old male presents with several months of intermittent left-sided headaches that have been worse at night and occasionally on exposure to cold air. On several occasions, he has noted increased pain while eating. He has had no other symptoms other than modest fatigue. Physical examination is unremarkable with normal vital signs and ophthalmologic and neurologic survey. Laboratory evaluation shows only a mild anemia, with a hemoglobin of 11 mg/dL and normocytic indices. What would be the most appropriate next step?
- **A.** Computed tomography (CT) scan of the brain
- **B.** Electrocardiogram
- **C.** Erythrocyte sedimentation rate (ESR)
- **D.** Neurology consultation
- **E.** Ophthalmology consultation

Answer: C. Temporal arteritis may present with intermittent or continuous symptoms, sometimes associated with fatigue, myalgias, jaw claudication, and mild anemia. The ESR is usually, but not always, diagnostic and would confirm the diagnosis if elevated. Steroids and ophthalmology consultation would then follow. The presence of temporal artery tenderness may be variable because the vasculitis may affect any artery. The diagnosis must be suspected in any elderly patient with recurrent or continuous headaches.

93.5. With cavernous sinus thrombosis, the clinical picture is usually dominated by which of the following?
- **A.** Facial pain
- **B.** Lethargy
- **C.** Nausea and vomiting
- **D.** Ocular findings such as pain and proptosis
- **E.** Seizures

Answer: D. The symptoms may also include paralysis of extraocular movements. Ocular symptoms are most common with thrombosis of the cavernous sinus, rather than one of the other sinuses.

CHAPTER 94

Delirium and Dementia

Gallane Abraham | Leslie S. Zun

OVERVIEW

Cognition is a composite of attention, orientation, memory, language, visual-spacial ability, and executive function. Both delirium and dementia affect cognition but in very different ways and over very different time courses; that said, delirium can occur concomitantly in a patient with dementia making the diagnosis challenging. In the past, terms such as *acute confusional state, sundowning,* and *organic brain syndrome* have been used to describe a number of abnormal cognitive states. Organic brain syndrome is a nebulous term that the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) eschews because the "organic" connotation implies that so-called functional mental disorders are without a biologic basis.[1] The preferred terms are *medical* or *psychiatric etiology.* Although the DSM-5 still uses the terms *delirium, dementia, amnestic,* and *other cognitive disorders,* the preferred terminology is *neurocognitive disorders.*

Delirium is characterized by a fluctuating neurobehavioral disturbance typically progressing over a short period. It is a direct consequence of an acute systemic or central nervous system (CNS) stressor. Dementia, on the other hand, tends to follow a more gradual course, with evolution occurring over months to years. Although patients with dementia exhibit confusion, unlike delirium, manifestations of autonomic nervous system abnormalities are minimal or absent and a disturbance in level of consciousness usually is not a feature.

The evaluation of patients who present to the emergency department (ED) with a neurobehavioral disturbance is best conducted in accordance with the following basic guidelines:

1. The first step is to determine whether this state represents delirium or dementia by obtaining a careful history from the patient, family members, and caregivers, employing screening tools for delirium and cognitive assessments for dementia. The clinical findings may be subtle and establishment of the diagnosis can be challenging, especially because delirium may be superimposed on dementia, and dementia remains an independent risk factor for delirium.
2. The second step is to rapidly treat the underlying disorder in patients with delirium.
3. The third step is to establish a supportive environment and employ pharmacological adjuncts as needed.

DELIRIUM

Principles

Background

Delirium is an acute or subacute state of cognitive dysfunction caused by an underlying physiologic condition. Several key features are necessary for a diagnosis of delirium (Box 94.1). Patients with delirium may have disturbances in consciousness, memory, cognition, and perception. These disturbances tend to develop during a short time (hours to days) and are characterized as acute delirium if the symptoms last hours to days or persistent delirium if the symptoms last weeks to months.[1] The disturbance in consciousness may be manifested initially as an inability to focus attention. The fluctuating course of symptoms and inattention are the hallmarks of delirium. Deficiencies in cognition may be manifested by disorientation and memory deficits. Perceptual disturbances include hallucinations and delusions. The delirious patient may be somnolent or agitated, and the thought process may range from mildly disturbed to grossly disorganized. The clinical presentation may be subdued or explosive. The patient's sleep-wake cycle may be altered or reversed; agitation often is present during the night. There are three types of delirium: hyperactive, hypoactive, and mixed level of activity. Hyperactive type demonstrates hyperactivity with emotional lability, agitation, and may include refusal of care; the hypoactive type demonstrates sluggishness and lethargy; the mixed type is found in a person with a normal level of activity but with disturbance of attention and awareness or fluctuations in activity levels.

Delirium has been reported to be present in up to 24% of the older adults treated in the ED.[2,3] It is a frequently missed diagnosis when standardized screening tools are not used. This is problematic because the mortality rate rises from 10% of those diagnosed in the ED to 36% when it is missed. This increased mortality is associated with a high rate of incontinence, decubiti, and malnutrition.

Predisposing factors for delirium include comorbid illness, dementia, older age, male gender, medications, neurologic deficits, and psychiatric illness (Table 94.1). Precipitating factors include infections, endocrine and metabolic disorders, medications, CNS events, cardiovascular disorders, and iatrogenic related events.

Drug intoxication or withdrawal (including ethanol) are the most common cause of delirium in the younger adult population. Within the older population, drugs are also a common cause of delirium; drugs with anticholinergic properties are often implicated but almost every drug class can be a precipitant. Industrial exposures (eg, carbon disulfide, heavy metals, insecticides, cyanide, carbon monoxide), herbal medications, and ingestion of certain plants (eg, nutmeg, foxglove, jimsonweed, psilocybin-containing mushrooms) are yet other causes of delirium to consider.

Delirium can be a prominent feature of any CNS or systemic infection, particularly in the very young, elders, and immunocompromised patients. All metabolic disorders put patients at risk for delirium with hypoglycemia and hypoxia being the most common. Delirium is also associated with strokes, particularly strokes in the distribution of the nondominant middle cerebral artery and the posterior cerebral artery. CNS vasculitis and paraneoplastic syndromes are additional considerations.

Pathophysiology

At a cellular level, delirium is the result of a widespread alteration in cerebral metabolic activity, with secondary deregulation of neurotransmitter synthesis and metabolism. Both the cerebral cortex and the subcortical structures are affected, producing changes in arousal, alertness, attention, information processing, and the normal sleep-wake cycle.

BOX 94.1

Diagnostic Criteria for Delirium

FOUR KEY CHARACTERISTICS

- Disturbance in attention and awareness.
- The disturbance develops over a short time period, represents a change from baseline attention and awareness, and tends to fluctuate in severity during the day.
- There are additional disturbances in cognition, such as memory, disorientation language, visual spatial ability, or perception.
- The disturbances are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in context of a coma.

Adapted from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5, Arlington, VA, 2013, American Psychiatric Association.

TABLE 94.1

Predisposing and Precipitating Factors for Delirium

FACTORS	LEVEL OF EVIDENCE
PREDISPOSING VARIABLES	
Age	Strong
Gender	No evidence
Alcohol use	Inconclusive
Nicotine use	Inconclusive
Dementia	Strong
Hypertension	Strong
American Society of Anesthesiologists (ASA) physical status*	Inconclusive
Cardiac disease	Inconclusive
PRECIPITATING VARIABLES	
Coma	Strong
Previous delirium	Strong
Emergency surgery	Strong
Mechanical ventilation	Strong
Acute respiratory disease	Inconclusive
Kidney function	Inconclusive
Medical admission	Inconclusive
Organ failure	Moderate
Trauma	Strong
MEDICATIONS	
Analgesics/sedatives	Inconclusive
Benzodiazepines	Inconclusive
Opioids	Inconclusive
REDUCED DELIRIUM OCCURRENCE	
Dexmedetomidine	Strong

*American Society of Anesthesiologists (ASA) Physical Status Classification System.
Adapted from Zaal IJ, Devlin JW, Peelen LM, et al: A systematic review of risk factors for delirium in the ICU. Crit Care Med 43(1):40-47, 2015.

Although the exact pathophysiologic process is not well understood, multiple neurotransmitters have been implicated in causing delirium. Delirium is often associated with a derangement of central cholinergic transmission. Serum anticholinergic activity is increased, and low levels of acetylcholine are seen in elders with delirium. This is most pronounced in patients experiencing delirium secondary to anticholinergic drugs. Increased serotonin levels have been found in hepatic encephalopathy, serotonin syndrome, sepsis, and psychedelic drug ingestion. Some of the disturbances that occur in delirium are deficiencies of substrates for oxidative metabolism (eg, glucose, oxygen); disturbances of ionic passage through excitable membranes; increase in cytokines; imbalance of normal noradrenergic, serotoninergic, dopaminergic, and cholinergic homeostasis; and, in some cases, synthesis of false neurotransmitters.

Drugs and exogenous toxins can produce delirium through direct effects on the CNS. Although the limbic system appears to be particularly vulnerable to the effects of drugs, the cerebral hemispheres and the brainstem also can be profoundly affected. Tricyclic antidepressants can cause delirium by cholinergic inhibition; sedative-hypnotics depress activity in the CNS, especially in the limbic system, thalamus, and hypothalamus. Narcotics affect CNS activity primarily by interacting with various opioid receptor sites. Psychedelic drugs probably act as agonists at serotonin receptor sites. Phencyclidine (PCP) inhibits reuptake of dopamine, norepinephrine, serotonin, and α-aminobutyric acid and also may act as a false neurotransmitter.

Hyperthermia and hypothermia can cause delirium due to changes in the cerebral metabolic rate. In hypothermia, cerebral metabolism decreases 6% to 7% for each 1°C decrease in temperature from 35° to 25°C. In hyperthermia, cellular damage with uncoupling of oxidative phosphorylation begins to occur at temperatures higher than 42°C. Patients suffering from heatstroke may have cerebral edema, degenerative neuronal changes (especially involving Purkinje cells of the cerebellum), and petechiae in the walls of the third and fourth ventricles. Delirium occurring at temperatures below 40°C is multifactorial in origin and not caused solely by increased core temperature.

Delirium caused by metabolic abnormalities, such as hyponatremia, hypernatremia, hyperosmolarity, hypercapnia, and hyperglycemic disorders, is associated with a variety of metabolic disturbances at the neuronal and astrocyte levels. Such disturbances may include impairments in energy supplies, changes in resting membrane potentials, changes in cellular morphology, and changes in the brain water volume.

Most patients with delirium have reduced cerebral metabolic activity. This reduction in cerebral metabolism is reflected by a decrease in the frequency of background electrical activity on the electroencephalogram (EEG). Exceptions are hyperthermia, sedative-hypnotic withdrawal, delirium tremens, and certain drug-induced states, in which the cerebral metabolism is either normal or increased.

Clinical Features

Delirium is often the first manifestation of underlying disease. The natural history of a patient's delirium can progress from apathy to marked agitation in the course of hours (see Box 94.1). Nonspecific prodromal symptoms such as anxiety, restlessness, and insomnia typically emerge during hours to days.

Key aspects of cognitive impairment should become evident during a careful history and physical examination. Disturbance in attention is central to the diagnosis of delirium. The patient is easily distractible and has difficulty remaining focused on a particular topic or interacting with a single person. Disorientation often accompanies the inattention but is not an invariable feature. The patient usually is disoriented with respect to time and

TABLE 94.2

Common Emergency Department Assessments for Dementia

TEST	ITEM(S)	APPLICATION	ADMINISTERED BY	TIME (MINUTES)
Mini-Mental State Examination (MMSE)	30	Clinical, screening	Interviewer	5 to 10
Clock drawing test	1	Clinical, screening	Patient	3
Short Portable Mental Status Questionnaire (SPMSQ)	10	Screening	Interviewer	5
Cognitive Capacity Screening Examination (CCSE)	10	Clinical	Expert	5 to 15

Adapted from Woodford HJ, George J: Cognitive assessment in the elderly: a review of clinical methods. QJ Med 100:469-484, 2007; Wong CL, Holroyd-Leduc J, Simel DL, et al: Does this patient have delirium? Value of bedside instruments. JAMA 304(7):779-786, 2010.

occasionally to place; in extreme cases, disorientation to person also may be noted. Delirium, however, may be present in a patient who is completely oriented to person, place, and time. A mental status examination that consists solely of questions that assess orientation will not detect delirium in these instances.

The patient with delirium always has some degree of memory impairment, with the greatest impact on short-term memory. Thought processes and speech may be disorganized. Disturbance in the sleep-wake cycle often occurs early in the course of delirium. Perceptual disturbances, including misperception of the environment, poorly formed delusions, and hallucinations, are common. The delirious patient may experience visual, auditory, tactile, gustatory, or olfactory hallucinations. In addition, the delirious patient has a reduced capacity to modulate fine emotional expression and may demonstrate extreme emotional lability.

The cognitively impaired patient may provide an unreliable history. Valuable information often can be obtained from family, friends, and out-of-hospital personnel. Specific inquiry should be made about the patient's current medical problems and previous medical history, including diabetes, hypertension, kidney or liver disease, immune status, and any neurologic or psychiatric problems. A detailed medication history, including the use of prescribed and over-the-counter medications, dietary supplements, and alcohol or other substances, is essential. Out-of-hospital personnel should be able to provide information about the home environment, medication bottles belonging to the patient or found near the patient, and the possibility of trauma.

The physical examination should begin with a careful assessment of vital signs including pulse oximetry and a pain assessment. The delirious patient often exhibits autonomic nervous system abnormalities on evaluation, including elevated or decreased pulse, blood pressure, respiratory rate, and temperature. The examination also includes assessment of the head for signs of trauma and the pupils for symmetry and light reflex; funduscopic examination for hemorrhage or papilledema; examination of the ears for hemotympanum; evaluation of the neck for nuchal rigidity, bruits, and thyroid enlargement; assessment of the heart and lungs; evaluation of the abdomen for organomegaly and ascites; and examination of the extremities for cyanosis. The skin should be carefully examined for rashes, petechiae, ecchymosis, splinter hemorrhages, and needle tracks.

The neurologic examination includes assessment of the cranial nerves, motor strength, sensation, reflexes, and presence of abnormal movements (eg, ophthalmoplegia, tremor, asterixis, myoclonus). A specific constellation of neurologic findings may suggest a specific diagnosis. One such example is the classic triad of Wernicke's encephalopathy: ophthalmoplegia, ataxia, and confusion. The reflexes are assessed for symmetry and presence of hyperreflexia or hyporeflexia. Findings that typically suggest either a metabolic or a structural neurologic problem are not necessarily specific for that category of disorder. For example, asterixis is a hallmark of metabolic encephalopathy but can be seen in focal brain disease. Likewise, focal neurologic signs that typically are associated with structural CNS lesions also can be present in various metabolic abnormalities, such as hypoglycemia, hyperglycemia, hepatic encephalopathy, uremia, and hypercalcemia.

The physical examination is not often helpful in determining the specific drug or class of drugs causing acute cognitive impairment. The one exception to this rule is the presence of a "toxidrome," which is a constellations of signs and symptoms characteristic of intoxication with certain drugs or classes of drugs (see Chapter 139).

Although there are a number of delirium scales found in the literature, the Confusion Assessment Method (CAM) is a validated tool that has a sensitivity of 93% to 100% and specificity of 90% to 95%. Performing the CAM takes 5 minutes, and it is often used in conjunction with other tests (eg, the Mini-Mental State Examination [MMSE] or Richmond Agitation-Sedation Scale [RASS]) to provide a composite baseline of cognition in patients exhibiting symptoms of delirium and dementia (Table 94.2).[4-7] The CAM has four key features used in screening for delirium: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. For a definitive diagnosis of delirium, the first two features and one of the last two must be present. It has proved to be a valuable tool because of its ease of administration and high interobserver reliability. In addition, it has been shown to be more sensitive than clinical impression alone.

Differential Diagnosis

Considerations in the differential diagnosis for delirium include dementia and psychiatric disorders. Dementia, depression, mania, paranoia, and schizophrenia all may resemble delirium but can be distinguished using historical and clinical features such as onset, time course, fluctuating mental status, and inattention (Table 94.3). Unlike delirium, dementia and psychiatric disorders tend to be insidious processes that develop during months to years. Typically, the patient's vital signs are normal. In addition, cognitive impairment of dementia exhibits little fluctuation during hours or days and occurs primarily in elders. A point worthy of emphasis is that patients with dementia are more likely to develop delirium.

Diagnostic Studies

Because delirium is generally the manifestation of an underlying disorder, a comprehensive evaluation looking for structural, metabolic, and infectious etiologies is indicated (Table 94.4). Despite these diagnostic evaluations, no cause is found for delirium in up to 16% of patients. An elevated anion gap (>15 mEq/L) may indicate the presence of unmeasured anions, such as ketoacids in diabetic or alcoholic ketoacidosis; lactate in postictal states or

associated with hypotension; sulfate in renal failure; and exogenous toxins, such as ethylene glycol, methanol, and salicylates.

In addition to a pulse oximetry measurement to screen for hypoxemia, an arterial blood gas analysis is warranted in patients at risk for respiratory failure with hypercarbia. Urinalysis and chest radiography should be obtained to exclude an occult infection, which is frequently the cause of delirium in elders.

An electrocardiogram and troponin should be obtained to exclude a silent acute coronary syndrome. Furthermore, additional laboratory studies outside the scope of the ED evaluation may be appropriate when the cause of delirium remains unknown. These additional studies may include thyroid function studies, vitamin B_{12} and folic acid assays, rapid plasma reagin test, measurement of serum antinuclear antibodies, urinary porphobilinogen assay, and screens for heavy metals.

TABLE 94.3

Comparison of Delirium and Dementia

	DELIRIUM	DEMENTIA
Onset	Acute	Slow
Awareness	Reduced	Clear
Alertness	Fluctuates	Normal
Orientation	Impaired	Impaired
Memory	Impaired	Impaired
Perception	Hallucinations	Intact
Thinking	Disorganized	Vague
Language	Slow	Word finding difficulty

Adverse drug events, including drug-drug interactions, account for 30% of cases of delirium; they may occur at therapeutic doses and levels. A comprehensive review of all medications and testing for levels when available is recommended. Standard toxicology screens are overused as diagnostic tests and have limited usefulness in the evaluation of most patients with delirium.

Neuroimaging with a head computed tomography (CT) scan should be performed on patients with a history of trauma (especially those taking anticoagulant medications), previous neurosurgical procedures, immunodeficiency, or focal neurologic signs to detect structural lesions causing delirium. Additional imaging or lumbar puncture (LP) is required for early infarctions, small brainstem lesions, meningitis or encephalitis, closed head injuries, sagittal vein thrombosis, and small isodense subdural hematomas that may be missed on a CT scan. In addition, a small percent of acute subarachnoid hemorrhages are not detected by head CT scan and require LP for diagnosis.

The role of magnetic resonance imaging (MRI) in the evaluation of the delirious patient has not been clearly established. MRI is superior to CT for detection of small intracerebral and brainstem lesions, small brain contusions, certain encephalitides, and abnormalities of white matter (eg, leukoencephalopathy). MRI perfusion scans are more sensitive in detecting an acute vascular event.

Cerebrospinal fluid (CSF) analysis is an essential part of the evaluation in selected patients with delirium. In patients with fever and cognitive dysfunction, even without meningismus, a LP should be performed to rule out infectious, inflammatory or neoplastic etiologies. This test is particularly important in the very young, elders, and immunocompromised patients, who are less likely to show classic signs of meningitis. Patients with focal neurologic deficits, immunocompromised states, or evidence of increased intracranial pressure should undergo head CT before LP, and they should receive antibiotics before the CT scan.

TABLE 94.4

Delirium Diagnostic Studies and Clinical Findings

DIAGNOSTIC STUDIES	EXAMPLES OF CLINICAL FINDINGS
Vital signs	Hypoxemia, hypotension/hypertension, hypothermia/hyperthermia, pain
Fingerstick glucose	Hypoglycemia/hyperglycemia
Blood gas	Hypoxemia, hypercarbia, respiratory alkalosis, metabolic acidosis
CBC: Hemoglobin, leukocyte count with differential, platelet count, mean corpuscle volume	Anemia, occult infection, thrombocytopenic purpura, megaloblastic anemia, hyperviscosity from myelogenous leukemia, polycythemia
Serum electrolytes: Glucose, sodium, calcium, chloride, bicarbonate, BUN, creatinine, magnesium, phosphate, osmolality	Hypoglycemia/hyperglycemia, hyponatremia/hypernatremia, uremia, hypo-osmolar/hyperosmolar, anion gap acidosis
Urinalysis: Nitrites, leukocytes, ketones	Occult infection, acidosis
Chest x-ray	Occult infection, pneumothorax
Drug levels	Digoxin, lithium, quinidine, salicylate, antiepileptics
Additional tests: Troponin, liver and thyroid function studies, ammonia, PT, PTT, INR, vitamin B_{12} and folic acid assays, rapid plasma reagin test, measurement of serum antinuclear antibodies, urinary porphobilinogen assay, screens for heavy metals, toxic screens of blood and urine, methanol, ethylene glycol, carbon monoxide, cyanide	Myocardial infarction, liver failure, hypothyroid/hyperthyroid, bleeding disorder, excess anticoagulation, vitamin B_{12} or folate deficiency, occult infections, vasculitis, acute porphyria, toxins
CT head/MRI	Cerebrovascular accident, structural lesions, traumatic head injury
LP/CSF analysis	Meningitis, encephalitis, subarachnoid hemorrhage
EEG	Nonconvulsive status epilepticus, delirium

BUN, Blood urea nitrogen; *CBC,* complete blood count; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *EEG,* electroencephalogram; *INR,* international normalized ratio; *LP,* lumbar puncture; *MRI,* magnetic resonance imaging; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

Although it is rarely practical in the ED setting, the EEG can be a valuable diagnostic tool in assessing for nonconvulsive status epilepticus and determining the presence of delirium. Bilateral diffuse symmetrical electroencephalographic abnormalities are a relatively consistent feature of delirium. In most cases, the changes consist of a nonspecific generalized slowing from the baseline activity and can be useful in distinguishing delirium from other neurobehavioral abnormalities.

Management

Delirium is a medical emergency. The outcome depends on the cause, the patient's overall health status, and the timeliness of treatment. The presence of hyperactive or hypoactive delirium has some prognostic significance. The hypoactive form of delirium tends to be more common in elders and carries a worse overall prognosis, perhaps because it often goes unrecognized. Acute recognition and management of delirium in elders is essential because delirium in this population is associated with increased risk of long-term institutionalization, development of dementia, and increased overall mortality.[8]

Patients who present with acute delirium should be screened quickly for readily reversible causes, such as hypoglycemia, hypoxia, and narcotic overdose. Acute intoxication requires prompt attention and antidotes provided when available.

Other conditions requiring immediate medical intervention include infections. Patients with signs of acute meningitis or sepsis should rapidly receive antibiotics along with fluid resuscitation. Antibiotics for meningitis should be dosed according to age and predisposing factors (see Chapter 99). Other emergent conditions that may be manifested with delirium and necessitate immediate intervention include severe hypothermia, hyperthermia, and CNS vascular conditions, including hypertensive encephalopathy, acute epidural or subdural hematoma, subarachnoid hemorrhage, and stroke. Patients with Wernicke's encephalopathy require immediate treatment with 100 mg of intravenous (IV) thiamine, with titration of additional doses until the ophthalmoplegia resolves. Resistance to thiamine may result from hypomagnesemia because magnesium is a cofactor for thiamine transketolase. Glucose administration in patients with severe thiamine deficiency may precipitate Wernicke's encephalopathy. The specific treatment of delirium tremens (and other alcohol withdrawal syndromes) involves the substitution of a long-acting drug that is cross-tolerant with the alcohol. Benzodiazepines are the agents of choice to reduce agitation and other hyperactive symptoms in delirium tremens (see Chapter 142).

Delirium secondary to dehydration, hyponatremia, hypernatremia, hypercalcemia, and hepatic or renal disease gradually resolves during hours to days with fluid and electrolyte replacement.

Supportive care for all patients with delirium ideally includes an environment with adequate lighting and minimization of sensory overload; the patient should be placed in an area that can be easily observed by staff, and use of stretcher side rails to prevent falls. Use of "sitters" may be necessary to provide continuous supervision. The patient must be protected from self-harm or from injuring other patients or staff. In cases of hyperactive delirium, the patient may need to be initially restrained physically until pharmacologic control takes effect. Physical restraints should be viewed only as a temporizing action, because they can increase agitation and the risk of injury to the patient. They have been associated with injuries and even death by asphyxiation and are not a substitute for pharmacologic control.

Pharmacologic interventions are a cornerstone of behavioral management while the underlying medical condition that caused the delirium is being addressed. The ideal sedating drug should have the following characteristics: low toxicity with minimal anticholinergic effects, ease of administration, short half-life, minimal effects on the cardiovascular and respiratory systems, and no effect on the seizure threshold. Antipsychotics and benzodiazepines have been used in the management of acute agitation in the undifferentiated patient with delirium. The opioids have no role in the management of delirium.

Antipsychotic medications used to treat delirium include the typical antipsychotics, especially the butyrophenones, and the newer atypical antipsychotic agents. Although no one drug is ideal, the typical antipsychotic, haloperidol, continues to be recommended as monotherapy for controlling agitation in acute delirium on the basis of extensive clinical experience.[9] The use of the atypical antipsychotic agents for delirium and acute agitation is not well characterized. The newer atypical antipsychotic agents (risperidone, olanzapine, ziprasidone, aripiprazole) may have equal or better efficacy and fewer side effects (especially akathisia and dystonia) for management of acute agitation in the psychiatric population.

As the primary drug for control of hyperactive delirium, haloperidol is a potent dopamine-blocking medication with less anticholinergic and minimal hypotensive effects. The main effect of the drug acutely is tranquilization. The incidence of extrapyramidal side effects in patients receiving IV haloperidol for management of delirium with agitation is relatively low. Studies of the acute administration of haloperidol report an 8% to 30% incidence of extrapyramidal side effects with akathisias being most common and acute dystonia occurring in less than 10% of patients.

Haloperidol can prolong the QTc interval, more so when given intravenously, but this effect is clinically insignificant in most patients and does not require a pretreatment electrocardiogram. Caution is warranted with use of this agent in patients taking medications that prolong the QTc (eg, class IA and class III antiarrhythmics, certain antibiotics, inhibitors of the cytochrome P_{450} system) and in patients with acute coronary ischemia, uncompensated congestive heart failure, or hepatic dysfunction. The QTc effect is not usually concerning when the haloperidol is given intramuscularly.

Haloperidol dosing should vary with the patient's level of agitation, age, weight, and response to treatment. In most patients, 2.5 to 10 mg intramuscularly (adjusted according to weight and comorbidities) is well tolerated as an initial dose, and levels can be titrated as needed. For elders, a lower initial dose of 0.5 to 1.0 mg is recommended. Higher doses may be required for younger patients.

The atypical antipsychotics can be used acutely for management of agitation. These drugs have been studied for use in the psychotic patients and patients with Parkinson's disease presenting with acute agitation. The mechanism of action includes antagonism of alpha$_2$-adrenergic, serotonin, muscarinic, dopamine, and histamine receptors. These drugs block the reuptake of dopamine and serotonin, and the newer drugs also have dopamine agonist effects (aripiprazole). Compared with haloperidol, several of these atypical agents (ziprasidone, risperidone, clozapine, and olanzapine) have been shown in nonrandomized case series to control agitation as effectively with less sedation and fewer extrapyramidal side effects. Because of the limited dopamine antagonism effect, atypical antipsychotics are the preferred agent for patients with Parkinsonism and agitation.

Benzodiazepines are also considered effective as monotherapy or used in combination with the typical antipsychotics for the management of acute undifferentiated agitation, intoxication, or withdrawal syndromes.[10,11] Lorazepam, a shorter-acting benzodiazepine that undergoes glucuronide conjugation with rapid renal clearance, is the preferred agent for treatment of withdrawal symptoms. Diazepam should be avoided as an agent for treatment of agitated behavior in most delirious patients because of its long

half-life and risk of drug accumulation with repeated dosing. Long-term use of benzodiazepines can worsen confusion and falls.

The management of delirium has been identified by The National Institutes of Health Task Force on Research in Emergency Medicine as a specific area requiring further research. Based upon the best available evidence, we recommend screening and treatment of readily reversible causes of delirium and initial nonpharmacological management followed by a selection of pharmacological agents based upon the etiology of delirium and patient comorbidities.[12] We recommend either a benzodiazepine or antipsychotic (typical or atypical) used as monotherapy. As an alternative, a combination of a low-dose antipsychotic plus benzodiazepine (eg, haloperidol 5 mg IM plus lorazepam 2 mg) can be used. The combination approach has been found to be superior to either class alone in the treatment of undifferentiated acute agitation and has the added benefit of minimizing adverse effects.[12]

Disposition

Patients with delirium secondary to acute drug intoxication may be discharged from the ED provided the process readily reverses itself during a short period of observation and the drug has no potentially serious delayed toxicity. For most patients delirious from metabolic, infectious, or CNS processes, hospitalization is necessary for further diagnostic evaluation and treatment. The only readily reversible metabolic problem associated with delirium that can be completely managed in the ED is hypoglycemia.

For most patients without underlying medical illness who have delirium, the outcome is full recovery. After an episode of acute delirium, younger patients may experience mild cognitive dysfunction that lasts weeks to months. Elders, on the other hand, often experience persistent decline in their baseline level of functioning, with loss of at least one activity of daily living after acute delirium. Delirium in older adults hospitalized without baseline dementia is associated with higher 1-year mortality rates, higher rates of institutionalization, and a greater risk for development of dementia. For older adults, an episode of delirium, especially for those with baseline cognitive impairment, can have long-term consequences despite good supportive multidisciplinary care.

DEMENTIA

Principles

Background

Dementia is not a single disease entity but rather a highly variable clinical syndrome characterized by a gradually progressive deterioration of cognitive function. Prognosis depends on the underlying cause (Box 94.2). Dementia is classified as either irreversible (primary degenerative) or potentially reversible (secondary); it is further classified according to the degree of cognitive impairment. Mild dementia implies some impairment of work and social activities; however, the capacity for independent living remains intact. With moderate dementia, independent living is hazardous, and some degree of supervision is necessary. With severe dementia, continual supervision and often custodial care are needed.

Primary degenerative dementias include Alzheimer's disease, dementia with Lewy bodies, subcortical dementias involving the basal ganglia and thalamus (eg, progressive supranuclear palsy, Huntington's chorea, Parkinson's disease), and dementia of the frontal lobe type, which includes Pick's disease. Dementia with Lewy bodies, clinically manifested by persistent, well-formed visual hallucinations and prominent extrapyramidal movements, has been found to be the third most common type of dementia. With advanced aging, dementia may have mixed causes, with Alzheimer's disease and vascular dementia frequently coexisting.

BOX 94.2

Causes of Dementia

PRIMARY DEGENERATIVE DEMENTIAS
Alzheimer's disease
Lewy bodies disease
Frontal lobe disease (Pick's disease)

SUBCORTICAL DEMENTIAS
Parkinson's disease
Huntington's disease

VASCULAR DEMENTIA
Multi-infarct dementia

INTRACRANIAL PROCESSES
Space occupying lesions (tumor, subdural hematoma)
Hydrocephalus
CNS infections (HIV-1, neurosyphilis, chronic meningitis)
Repetitive head trauma

ENDOCRINOPATHIES
Addinson's and Cushing's diseases
Thyroid and parathyroid disease

NUTRITIONAL DEFICIENCIES
Thiamine
Niacin
Folate
Vitamin B_{12}

TOXIC EXPOSURES
Heavy metals
Carbon monoxide
Carbon disulfide

DRUGS
Psychotropics
Antihypertensives
Anticonvulsants
Anticholinergics

DEPRESSION
Pseudo-dementia

CNS, Central nervous system; *HIV-1,* human immunodeficiency virus type 1.
Adapted from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5, Arlington, VA, 2013, American Psychiatric Association.

A smaller percentage of dementias are attributable to causes, such as anoxic encephalopathy, hepatolenticular degeneration, tumors, and slow virus infections.

Potentially reversible dementias are caused by adverse drug reactions, endocrinopathies, metabolic abnormalities, intracranial processes, and depression. The clinical manifestation is either an acute delirium or an acute or gradual progressive cognitive impairment that reverses once the underlying etiology is addressed and resolved. Drug-induced dementia occurs primarily in elders and can be caused by various psychotropic drugs, antihypertensive medications, anticonvulsants, anticholinergics, and miscellaneous medications, such as L-dopa. Dementia also may be caused by heavy metals and other exogenous agents, such as carbon monoxide, carbon disulfide, and trichloroethylene.

Endocrinopathies and metabolic abnormalities that can cause secondary and potentially reversible dementia include hypothyroidism, hyperthyroidism, parathyroid disease, Addison's disease,

Cushing's disease, and panhypopituitarism. Metabolic abnormalities such as nutritional deficiencies that cause dementia include thiamine deficiency (Wernicke's syndrome), niacin deficiency (pellagra), vitamin B_{12} deficiency, and folate deficiency.

Intracranial processes, space-occupying lesions, and hydrocephalus may also cause dementia. Repetitive intracranial trauma resulting from contact sports can produce a chronic organic brain syndrome without evidence of hematoma or significant contusion (dementia pugilistica). Intracranial processes that may eventually lead to a chronic organic brain syndrome include infections with slow viruses, human immunodeficiency virus type 1 (HIV-1) infection, chronic meningitis (tubercular or fungal), brain abscess, and neurosyphilis. In addition to primary HIV-1 CNS infection, toxoplasmosis, cryptococcal meningitis, malignant disease, and infections due to herpesvirus, cytomegalovirus, varicella-zoster virus, and papovavirus (progressive multifocal leukoencephalopathy) can cause progressive cognitive impairment in this compromised group of patients and must be excluded.

There are two categories of primary degenerative dementias that are collectively referred to as *dementia* and that have the same neuropathologic changes: (1) a presenile dementia seen in younger patients, and (2) senile dementia. Alzheimer's disease accounts for 60% to 80% of all dementias; vascular dementia (with or without Alzheimer's disease) accounts for 20%, and the remaining 20% of cases are attributable to more than 50 known causes.

Worldwide, approximately 24.3 million persons suffer from dementia, and 4.6 million new cases are diagnosed yearly. The prevalence is approximately 1% at 60 years old but doubles every 5 years until it reaches 30% to 50% by 85 years old. In 2014, the estimated prevalence of Alzheimer's dementia was 5 million for adults in the United States aged 65 years or older and is projected to increase to 16 million by the year 2050.[13] ED based studies of cognitive impairment report that up to 70% of older adults seen with cognitive impairment have undiagnosed dementia. Dementia is a strong predictor of mortality, which varies with age and subtype.

DSM-5 criteria for the diagnosis of dementia are presented in Box 94.3. There must be cognitive impairment that interferes with independence in one of six domains: complex attention, executive function, learning and memory, language, perceptual-motor function, or social cognition.[1] Several clinical features deserve emphasis. Impairment in memory must involve both short-term and long-term memory. The cognitive impairment commonly involves abstract thinking, judgment, and other higher cortical functions. The cognitive impairment must interfere with interpersonal relationships, work, and social activities. Although mild decline in intellectual functioning characterized as inability to learn and retain new information without impairment of daily functions can be part of the normal aging process, gross intellectual impairment of short- and long-term memory or confusion is not normal. Mild cognitive impairment is distinct from early dementia.

The goals of ED evaluation for suspected dementia are (1) to recognize the signs and symptoms of undiagnosed and potentially reversible forms of dementia, (2) to identify the manifestations of acute illness in the demented patient promptly, and (3) to assess the clinical findings in lieu of the patient's cognitive impairment and facilitate a safe disposition and expedited follow-up.

BOX 94.3

Diagnostic Criteria for Dementia

A. Cognitive decline from a previous level of performance in one or more cognitive domains: Complex attention, executive function, learning and memory, language, perceptual motor function, or social cognition.
B. The disorder has an insidious onset and gradual progression.
C. The deficits do not occur exclusively during the course of a delirium.
D. The cognitive deficits are not better explained by another mental disorder, such as major depression or schizophrenia.

Adapted from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5, Arlington, VA, 2013, American Psychiatric Association.

Pathophysiology

Alzheimer's disease is the best-understood dementia and involves several characteristic anatomic, pathologic, and neurochemical changes. The predominant change is cortical atrophy most prominent in the temporal and hippocampal regions caused by progressive synaptic and neuronal loss in the cerebral gray matter. This atrophy generally is followed by loss of white matter (subcortical atrophy). There is no ischemic component to Alzheimer's disease. Cell loss does occur with the normal aging process but not to the extent seen in dementia. Not all patients with dementia have gross cerebral atrophy.

Histologic features characteristic of Alzheimer's disease include extracellular deposition of β-amyloid protein and intracellular neurofibrillary tangles contributing to neuron loss. The abnormal processing of β-amyloid protein is likely central to the pathogenesis of Alzheimer's disease. The neurofibrillary tangles are intraneuronal paired helical filaments composed of the abnormally phosphorylated protein tau, the structural protein involved in the regeneration of neurites. Senile plaques are extracellular lesions composed of the degenerating neuronal processes and abnormal β-amyloid protein. These plaques are extensively spread throughout the cerebral cortex and do not correlate with the severity of dementia. Other consistent neurohistopathologic changes in Alzheimer's disease include granulovascular degeneration, Hirano bodies, β-amyloid deposition in the small cortical blood vessels, and neuronal loss in the limbic area.

Many biochemical abnormalities have been described in patients with Alzheimer's disease. A decrease in the neurotransmitter acetylcholine is characteristic. Levels of the enzyme choline acetyltransferase, which synthesizes acetylcholine in the brain, can be reduced to 20% of that in age-matched control subjects.

Several risk factors for Alzheimer's disease are recognized, including advancing age, family history, low education level, hypercholesterolemia, and head trauma. The apolipoprotein E epsilon 4 allele on chromosome 19 has been associated with both familial and sporadic late-onset Alzheimer's disease. Apolipoprotein E is responsible for transporting of the cholesterol and phospholipids necessary for dendritic and synaptic repair. There are several allelic variants, but those homozygous or heterozygous for the E4 variant have an increased risk for the development and expression of the disease. Abnormalities on chromosomes 1 and 14 also have been associated with Alzheimer's disease.

The frontotemporal dementias are less prevalent than Alzheimer's disease and are categorized by a frontal and temporal atrophy caused by cell death. The most common histologic finding in the frontotemporal dementias is the combination of prominent cell loss and gliosis in frontal and temporal regions of the cortex, termed *dementia* lacking distinctive histology.

Approximately 15% to 20% of dementias are caused by multiple vascular insults to the CNS; the resulting deficit is termed *multi-infarct dementia.* The multiple infarcts typically involve the cerebral hemispheres and basal ganglia. Multi-infarct dementia often has an earlier age at onset than Alzheimer's disease and occurs more often in adult men and patients who have risk factors for atherosclerosis. Approximately 29% of dementias are a mixed

variety, with components of both ischemic cerebrovascular disease and Alzheimer's dementia.[13]

Inflammatory conditions of the CNS caused by conventional viruses include subacute sclerosing panencephalitis from measles virus infection, progressive multifocal leukoencephalopathy from infection by the John Cunningham (JC) virus (a papovavirus), progressive rubella encephalitis, and infection associated with HIV disease. The unconventional viral infections include kuru, Creutzfeldt-Jakob disease (CJD), and variant CJD (which appears to be linked to bovine spongiform encephalopathy, the pathologic process in "mad cow disease") and are associated with minimal inflammatory histopathologic changes in the CNS; these diseases cause a fine vacuolation of the nervous tissue and hence are referred to as *subacute spongiform viral encephalopathies.*

Slow virus infections of the CNS can cause a progressive dementia that is irreversible. With these infections, months to years pass between infection with the virus and the appearance of clinical illness. Slow virus infections of the CNS are caused by both conventional viruses and unconventional virus like agents known as *prions.* A prion is a proteinaceous infectious particle with the apparent ability to start a chain reaction that changes the shape of benign protein molecules into abnormal, slowly destructive forms. Prions are present in CJD and variant CJD.

One of the most prevalent slow virus infections causing progressive dementia is HIV-1 infection. HIV may produce a primary neurotrophic disorder in addition to causing the immunologic compromise that permits other viruses to replicate and damage nervous tissue. HIV dementia or acquired immunodeficiency syndrome (AIDS) dementia complex occurs in approximately one-fourth of patients with AIDS. It is believed to be caused by the HIV-1 virus targeting the microglial cells and the macrophages, which may produce cytotoxic substances, such as tumor necrosis factor and interleukins. Pathologic changes occur mostly in the hippocampus and basal ganglia and include atrophy, ventricular dilation, and fibrosis.

Several of the potentially reversible causes of dementia also are associated with neuropathologic or neurochemical abnormalities. Normal-pressure hydrocephalus generally affects younger people; 50% of patients are younger than 60 years. Most of the conditions that cause hydrocephalus involve a defect in uptake of CSF by arachnoid villi, which results in gradual ventricular dilation.

Chronic, heavy ethanol consumption is associated with dementia. The neurotoxicity of ethanol appears to be independent of thiamine deficiency. Heavy chronic alcohol consumption causes cerebral cortical atrophy, but no single alcohol-related dementia syndrome exists.

Clinical Features

Family or friends usually bring the patient to the ED because of a sudden worsening in mental status, a change in the patient's activities (eg, refusal to eat), or a change in the ability of the caregiver to manage the patient. Presentations vary by the cause of the dementia and the stage of progression. Many elders with dementia have a superimposed delirium on presentation.

The symptoms, signs, and progression of chronic cognitive impairment rarely are so diagnostic as to permit identification of the specific cause of the dementia. Alzheimer's disease begins insidiously. Signs and symptoms of cognitive dysfunction may be present for months to years before the diagnosis is made. The earliest symptoms and signs of Alzheimer's disease often are vague and nonspecific; patients manifest anxiety, depression, insomnia, frustration, and somatic complaints that often are more prominent than the memory loss. Patients often deny any cognitive deficits and change the subject of the conversation frequently rather than admit their increasing forgetfulness. Physicians often overlook the subtle signs of dementia in this phase of the disease. Various tests in the cognitive function can be used to improve the detection rate of subtle cases, document a change in their level of cognition or used to assist in determination of competency (see Table 94.2).

Depression often is the initial manifestation of Alzheimer's disease and is present in up to 40% of cases. Early in the illness, short-term memory is affected with forgetfulness of recent events, such as appointments and names of new acquaintances. Patients often repeat questions. The memory impairment may cause them to withdraw from social situations and recreational pursuits. Attempts to perform complex tasks may produce anxiety and confusion. The patient often has difficulty with interpersonal relationships. Affect may be shallow and labile, and minor events may trigger inappropriate laughter or tears. Compensation for early deficits includes excessive orderliness and avoidance of situations in which the defects may be observed. Patients in this early phase who are treated with antidepressants with anticholinergic properties may experience worsening of their symptoms. Sedative-hypnotics prescribed for anxiety also may accelerate cognitive dysfunction.

As the dementia progresses, cognitive deficits are more obvious and should be readily apparent on a mental status examination. Problems with recent memory, impairment of remote memory, language deficits, and difficulty with spontaneous speech may be noted. With moderate severity of the disease, patients have difficulty naming objects (dysnomia). As many as 50% of patients have delusions, usually of the paranoid type. Atypical presentations of Alzheimer's disease include aphasia, visual agnosia, right parietal lobe syndrome, focal neurologic findings, extrapyramidal signs, gait disturbances, and pure memory loss. In the final stage of dementia, patients exhibit marked cognitive impairment, apraxia, and significant personality changes. They often are bedridden and unable to perform the routine activities of daily living.

Because Pick's disease dementia affects the frontal and temporal lobes, patients often have frontal lobe release signs, including dramatic behavioral changes of disinhibition and social inappropriateness. Basal ganglia degenerative disorders that have dementia as a prominent feature are Huntington's chorea, Parkinson's disease, and Wilson's disease. One of several features that distinguish cortical from subcortical dementias is a prominent movement disorder, including posturing, ataxia, tremor, and chorea, that tends to occur early in the illness. Other features of these dementias include slowness of speech, hypotonia, and dysarthria, which can progress to mutism.

Patients with vascular dementia have a stepwise deterioration in memory and cognitive function with each cerebrovascular insult. The clinical presentation may follow one of two scenarios. In the more common scenario, the patient suffers several strokes that involve large volumes of cortical and subcortical structures in both hemispheres. The patient then exhibits dementia along with other neurologic disabilities (eg, focal weakness, hyperreflexia, extensor plantar response). In a second group of patients, the presentation is more subtle. These patients characteristically are hypertensive and suffer multiple tiny infarcts (lacunae) that involve deep subcortical structures. There may be no focal neurologic residua except progressive dementia with psychomotor retardation. Antihypertensive management in elders does not reduce the incidence of dementia.

The clinical manifestations of slow virus CNS infections are protean. After an insidious onset of mental deterioration in subacute sclerosing panencephalitis, a rapid progression ensues that is associated with myoclonic jerks, incoordination, and ataxia. In progressive multifocal leukoencephalopathy, neurologic signs and symptoms reflect diffuse asymmetrical involvement of both cerebral hemispheres. Sporadic CJD, of unknown etiology, tends to affect older people, with a rate of disease among those 50 to 70 years old of one case per million. Among these patients, rapidly

evolving dementia with myoclonus is characteristic. The hallmarks of the disorder are mental deterioration, multisystem neurologic signs, myoclonus, and typical electroencephalographic changes that evolve during months. Variant CJD affects younger patients (median age of 24 years) with key features that include early affective symptoms progressing to cognitive impairment and gait disturbances and ultimately leading to progressive neurologic deterioration. The incubation period appears to be in the range of 10 to 15 years, and most patients die within 14 months after the clinical onset of symptoms.

The classic triad of progressive dementia, ataxia, and urinary incontinence occurs in patients with normal-pressure hydrocephalus, which typically affects patients who are younger than those with primary degenerative dementia. More than half of the reported cases are in persons younger than 60 years old. Hydrocephalus secondary to previous head trauma or infection carries a more favorable prognosis than that for primary hydrocephalus.

In approximately 20% of the reversible cases, dementia is secondary to an intracranial mass. Patients may exhibit focal or nonfocal neurologic signs. Of the reversible dementias, 10% to 15% are caused by medications or chemical intoxications, frequently compounding a history of heavy alcohol use. Elders have increased susceptibility to the toxicities owing to polypharmacy and age-related changes in metabolism. The clinical presentation of a patient with a drug-related or toxin-related dementia may be indistinguishable from that of a patient with a primary degenerative process.

In addition, chronic traumatic encephalopathy (CTE) caused by repetitive mild traumatic brain injury and characterized by progressive neurodegeneration and deposition of hyperphosphorylated tau (p-tau) as neurofibrillary tangles may present as dementia and cognitive impairment.[14] This form of encephalopathy develops 8 to 10 years after trauma and progresses to dementia, gait, and speech abnormalities and Parkinsonism. CTE may be clinically mistaken for Alzheimer's disease or frontotemporal dementia.[14]

Differential Diagnosis

Senescent Forgetfulness

Subacute or chronic cognitive decline may be caused by a dementing illness or can be a manifestation of senescent forgetfulness, delirium, or depression. Senescent forgetfulness is an almost inevitable reality of aging. Mild impairment of both short-term and long-term memory is usual. Unlike dementia, the cognitive disturbance in senescent forgetfulness does not interfere with work or customary social activity.

Delirium

In most cases, the clinical distinction between delirium and dementia is obvious (see Table 94.3). The onset of symptoms, progression of signs and symptoms, perceptual disturbances, abnormalities on assessment of vital signs, and fluctuations in the level of consciousness are key distinguishing features.[13] However, dementia is a risk factor for delirium, and it is more difficult to differentiate delirium when superimposed on a patient with dementia.

Depression

Depression in older adults may closely mimic dementia. Diagnosis of pseudodementia or depression masquerading as dementia can be difficult and may require therapeutic interventions to confirm the clinical diagnosis. Confounding the issue, depression often coexists with dementia; one study found that 40% of patients with dementia were depressed. Depression, anxiety, and apathy are common in the prodrome and course of Alzheimer's disease. A number of distinguishing features suggest that the problem is depression rather than dementia: the onset of cognitive changes in pseudodementia often can be pinpointed, and symptoms usually are of short duration before medical help is sought. The progression of symptoms is rapid, and the family usually is aware of the severity of the dysfunction. A history of psychiatric illness is common. Patients with pseudodementia usually complain of cognitive dysfunction and emphasize their failures and disabilities. The affective change often is pervasive, and the patient makes little effort to perform simple tasks. Loss of social skills usually occurs early in the illness, and patients communicate a strong sense of distress and inability to function. Intellectual functioning in pseudodementia often is difficult to assess because of lack of patient cooperation or inconsistent findings on neuropsychometric testing. Attention and concentration often are intact, but patients commonly give answers such as "I don't know" on tests of orientation, concentration, and memory. Memory losses for recent and remote events usually are equally severe, and variability in the performance of tasks with similar degrees of difficulty may be marked. Tasks of high capacity (eg, testing of delayed memory with distraction) may be helpful in identifying the depressed patient.

Diagnostic Strategies

The evaluation of the patient with suspected dementia includes a focused medical, psychiatric, and medication history plus a collateral history from family and friends. Physical examination should include a detailed neurologic examination with a mental status evaluation. Dementia often goes unrecognized in the patient who is alert, pleasant, and cooperative. A validated cognitive evaluation test can play a key role in the early identification of dementia in patients who have maintained social and conversational ability.

Cognitive Evaluation

A mental status examination should be performed in all patients suspected to have cognitive dysfunction. In the demented patient, mental status testing can uncover subtle forms of delirium. Assessment of orientation to person, place, and time are not sensitive enough to establish cognitive dysfunction. A cognitive assessment should include both psychiatric and neurologic components (Box 94.4).

Several standardized tools for the cognitive assessment have been successfully applied in the ED. Mental status testing includes assessment of orientation, memory, attention, and concentration; several tests also incorporate assessments of constructional tasks,

BOX 94.4

Elements of the Mental Status Examination in the Evaluation of Dementia

ROUTINELY OBSERVED
Appearance, behavior, and attitude
Mood and affect

REQUIRE INQUIRY
Disorders of thought: Suicidal and homicidal ideation
Insight and judgment: Knowledge about illness
Disorder of perception: Hallucinations and delusions
Sensorium and intelligence: Cognitive impairment

spatial discrimination, arithmetic ability, and writing. Cognitive functioning can be rapidly assessed in approximately 7 to 10 minutes. Memory assessment requires testing of the patient's ability to repeat short series of words or numbers (immediate recall), to learn new information (short-term memory), and to retrieve previously stored information (long-term memory). Constructional apraxia is assessed by having the patient perform tasks, such as drawing interlocking geometric figures or clock faces and connecting dots. Dysnomia (inability to name objects correctly) and dysgraphia (impaired writing ability) are two of the most sensitive indicators of delirium superimposed on dementia. Almost all acutely confused patients exhibit writing impairments, including spatial disorganization, misspelling, and tremor. Therefore, if patients screen positive for delirium the standardized tools cannot be used to assess for dementia.

No single bedside cognitive test that can be administered quickly is ideal. There are various tests of cognitive function, some of which have been tested in the ED (see Table 94.2). The MMSE developed by Folstein and colleagues has been validated more than any other test and most frequently is recommended as a rapid screening tool. For hospitalized patients, this test has a sensitivity of 87% and a specificity of 82% for detection of organic brain syndrome. The MMSE does not measure executive function and is insensitive for detection of early signs of mild cognitive impairment (without dementia) or early dementia.

The MMSE consists of a short series of questions that test orientation, registration (memory), attention, calculation, recall, and language scored on a 30-point scale. The time for the test to be administered can be reduced to 5 minutes by elimination of the writing and drawing components with only a modest reduction in sensitivity. The registration section tests both immediate and short-term memory; the recall section also assesses short-term memory. The ability to recall two of three objects has 81% sensitivity and 74% specificity for exclusion of organic brain syndrome. Asking the patient to subtract "serial sevens" backward from 100 assesses attention, concentration, and arithmetic ability. This test is specific but not sensitive for absence of an organic brain syndrome; up to 40% of nondelirious, nondemented people fail to perform the tasks of this test correctly, reflecting limitations due to language ability and education. A total score of 23 or less is considered markedly abnormal and indicates an organic brain syndrome. As a general rule, patients with mild cognitive impairment have a score of 18 to 26 out of 30, those with moderate impairment have a score of 10 to 18, and those with severe impairment have a score of less than 10.

Another frequently used test is the clock drawing test. It is scored on a 6-point scale from no errors to no reasonable representation of a clock. Patients with a score of 1 to 2 points are without impairment, and those with 3 to 6 points have cognitive impairment. All bedside tests of cognition have limitations and can miss mild degrees of impairment. The patient's level of education and general intelligence can substantially affect the outcome. Furthermore, a single bedside test reflects a patient's cognitive functioning at only one point in time.

Alzheimer's disease is a clinical diagnosis typically made on probability; no routine available laboratory tests have been found to confirm the presence of the disorder (although MRI scan, functional scans looking at regional blood flow or glucose metabolism, assay for specific biomarkers, and CSF analysis can increase the probability of the presence of the disease). The physical examination is rarely helpful in detecting treatable dementias because of the considerable clinical overlap with irreversible dementias.

Laboratory Tests and Imaging Studies

Data clearly supporting or refuting the ordering of "routine" laboratory studies for evaluation of dementia are lacking; however, a number of studies are recommended to exclude treatable causes (see Box 94.2). For patients with suspected undiagnosed dementia presenting to the ED, a baseline laboratory evaluation, including CBC, comprehensive metabolic panel, and urinalysis, is indicated. If neurosyphilis is clinically suspected, a serum fluorescent treponemal antibody absorption test should be performed in addition to a Venereal Disease Research Laboratory (VDRL) test because the serum VDRL assay may yield negative results in patients with tertiary syphilis. The radiologic evaluation should include a non–contrast-enhanced head CT scan. The CT scan is used to diagnose or to exclude the presence of hydrocephalus or space-occupying lesions, and CT findings may support a vascular etiology for the dementia.

Patients require additional laboratory tests on follow-up evaluation; such tests may include determination of serum vitamin B_{12} and folate levels, thyroid function studies, erythrocyte sedimentation rate, fluorescent antinuclear antibody assay, measurement of urine corticosteroid levels, and, if indicated by history, urine screens for drugs and heavy metals. Selected patients should undergo a LP with CSF analysis, MRI, positron emission tomography scan, electroencephalography (in CJD, characteristic slowing and periodic complexes may be electroencephalographic features), neuropsychological testing, and testing of visual evoked potentials, brainstem auditory evoked potentials, and somatosensory evoked potentials.

The EEG rarely is helpful in establishing the diagnosis of senile dementia. An MRI finding of medial temporal atrophy suggests Alzheimer's disease but is not specific or sensitive for diagnosis of this disorder. Neuroimaging with head CT or MRI is controversial but indicated in patients with acute onset or rapid deterioration of cognitive impairment to identify rapidly progressive dementia and cerebrovascular accidents.

Summary

The diagnostic evaluation of the patient with suspected dementia includes a focused medical, psychiatric, and medication history, detailed neurologic and psychiatric examination with assessment of mental status and cognition followed by a baseline laboratory evaluation, including CBC, comprehensive metabolic panel, and urinalysis and non-contrast head CT. Additional evaluation should be guided by history and physical examination.

Mental status and cognitive assessment can be performed with several standardized tools that have been successfully applied in the ED. Initial mental status testing with the CAM may identify subtle forms of delirium. The CAM has four key features used in screening for delirium: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. For a definitive diagnosis of delirium, the first two features and one of the last two must be present. If the patient is CAM negative then further testing of cognition is warranted to identify dementia. The MMSE is a validated test of cognitive function that consists of a short series of questions that test orientation, registration (memory), attention, calculation, recall, and language. The clock drawing test is an alternate test of cognitive impairment that may be useful in the ED setting. All tests of mental status and cognition may be affected by the level of education and general intelligence and reflect a patient's cognitive functioning at only one point in time. Patient's identified with cognitive impairment in the ED should undergo further neuropsychiatric testing and treatment.

Management

Reversible dementias and conditions that cause worsening of baseline dementia require early diagnosis and treatment. Determination of reversible causes of dementia during the ED

evaluation occasionally is possible on the basis of the history (including medication history), physical examination, and head CT scan. Patients with acute changes in mental status or a relatively rapid onset of symptoms will require hospitalization for comprehensive evaluation. Patients presenting with recent gradual decline in cognitive function without an underlying acute medical condition can undergo further evaluation on an outpatient basis.

Pharmacotherapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate Alzheimer's disease includes the cholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). There are multiple randomized, placebo-controlled, large-scale clinical trials with these drugs establishing efficacy in improving cognitive functions and activities of daily living in patients with mild to moderate dementia. These drugs are not considered disease modifying, and there are limited data at present on the benefit of these drugs beyond 2 or 3 years (a significant number of patients discontinue medications because of side effects). The most common side effect of these agents is due to the cholinergic effects, including nausea, vomiting, and diarrhea.

In 2003, the FDA approved memantine (Namenda), a disease-modifying agent that helps regulate the excitatory effects of glutamate by antagonizing the *N*-methyl-D-aspartate receptor. Whether this drug alters the underlying disease process is unclear, but short-term studies show improved cognition in patients with moderate and moderate to severe Alzheimer's disease. There are conflicting studies on the effectiveness of other agents, such as gingko biloba, vitamin E, nonsteroidal agents, and statins. Estrogen replacement is not indicated for cognitive improvement or maintenance in women with Alzheimer's disease and can be detrimental. Ultimately, the key to altering the course of the disease is halting neuron loss. In severe dementia, the goal of management is supportive care.

Many therapies currently are under investigation for the modulation and early treatment of Alzheimer's disease. These therapies include antibiotics (directed against *Chlamydophila pneumoniae*), secretase modulators to reduce serum β-amyloid levels, immunization to reduce amyloid plaque burden, chelators to promote dissolution of β-amyloid, nonsteroidal anti-inflammatory medications, supplementation with omega-3 fatty acids, and testosterone.

Increasing evidence suggests that certain nonpharmacologic measures, including behavioral methods and avoidance of environmental triggers, may be effective in reducing agitation and anxiety in patients with dementia.[16] On occasion, medications are needed for behavioral symptoms of dementia. Affected patients typically do not improve with anxiolytics. Adverse effects offset the modest advantages in the efficacy of antipsychotic drugs for the treatment of psychosis, aggression, or agitation in many patients with Alzheimer's disease, and these drugs should be avoided when possible. However, despite the lack of consensus in the indication for use and dosages in older demented patients, butyrophenone (such as, haloperidol, 0.5 to 5 mg IM) or atypical antipsychotic olanzapine (2.5 to 5 mg IM) have been found to be effective in the management of acute agitation.

Clozapine may be effective in treating psychosis associated with both Alzheimer- and Parkinson-type dementias. However, in April 2005, the FDA issued a black box warning that the use of atypical antipsychotics to treat older patients with dementia related psychosis was associated with an increased risk for death compared with placebo, thus the risks and benefits of using these drugs must be considered.

A clear treatment choice for agitation and psychosis in those with dementia has not been identified. The antipsychotics raise a concern for QT prolongation, extrapyramidal symptoms, sedation, and anticholinergic and drug-drug interaction; the benzodiazepines have a fall risk, confusion, memory impairment, and oversedation. Regardless of intervention used, the lowest dose possible should be used and then titrated carefully to effect.

Agitation in patient with dementia may occasionally be due to unrecognized depression or pain. A trial of selective serotonin reuptake inhibitors (SSRIs) (such as, citalopram 20 mg PO) and adequate pain management may be warranted. Selection of a SSRI should be based upon side effect profile and drug interactions. Sleep disturbances may be treated with temazepam (7.5 mg oral), which is the drug of choice. The half-life of temazepam is 8 to 10 hours for patients of all ages, and the drug bypasses the oxidative hepatic enzyme system.

Disposition

Patients with dementia present to the ED because of an acute deterioration, behavioral change, or crisis due to family stress. A brief observation, acute inpatient medical or psychiatric hospitalization, nursing home stay, or other institutional stay (respite program) may stabilize patient and give the family time to mobilize resources to resume the home care regimen. Social workers can play a vital role in attempting to facilitate continued management. A key to successful disposition planning is to use screening tools to assess the cognitive, functional, and psychosocial status of patients with delirium and dementia. Anticipating and addressing cognitive or functional barriers to compliance with discharge plan and transitional care plan is essential.

KEY CONCEPTS

- Delirium is an acute condition characterized by an altered level of consciousness, disorganized thinking, and inattention. It develops during a short time, and symptoms tend to fluctuate during hours to days.
- Delirium is commonly caused by medications, drug intoxication or withdrawal, infections, metabolic disorders, CNS and cardiovascular events, and autonomic nervous system disturbances.
- Dementia is a chronic condition characterized by cognitive impairment. It is slow in onset and progressive in nature. This disorder has many causes, some of which are reversible with treatment. It is essential to search for reversible underlying etiologies that may be worsening a cognitive impairment.
- Patients with either dementia or psychiatric disorders may present with superimposed delirium, often making identification of the underlying cause of their abnormal behavior difficult.
- The clinician should be wary of attributing behavioral disturbances to psychiatric illness in the presence of abnormal vital signs or abnormal sensorium.
- Nonpharmacologic methods including behavioral methods and avoidance of environmental triggers should be considered in the treatment of agitation in patients with dementia.
- Antipsychotics and benzodiazepines are used cautiously, in the management of acute agitation in delirium and dementia. The choice of agent is determined by side effect profile and etiology of delirium or acute agitation.
- Antipsychotics and benzodiazepines are not approved for the long-term treatment of the behavioral symptoms of dementia.
- Antipsychotics may cause QTc prolongation and increased mortality especially when given intravenously.
- Lower doses of medications may be appropriate in older adults to decrease risk of adverse effects while effectively treating acute agitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 94: QUESTIONS & ANSWERS

94.1. Which of the following characteristics helps distinguish dementia from delirium?
- **A.** Autonomic nervous system derangements
- **B.** Cranial nerve dysfunction
- **C.** Disorientation
- **D.** Focal weakness
- **E.** Pain

Answer: A. Delirium is characterized by a disturbance in level of consciousness with confusion. Demented patients present with a much more gradual onset of symptoms with typically no change in level of consciousness. Delirium is further characterized by autonomic nervous system abnormalities and the presence of an underlying disease process. The disturbance also tends to fluctuate in severity during the course of the day.

94.2. A 78-year-old woman presents with 3 days of decreasing ability to concentrate, memory and cognition breakdown, sleep cycle disruption, and fluctuating levels of agitation. Her current medications include levofloxacin (Levaquin) 500 mg/day for a bladder infection, tramadol prn for knee arthritis, and hydrochlorothiazide 25 mg/day for essential hypertension. Her examination is normal except for a baseline tachycardia, moderate agitation and restlessness, and orientation to person only. Laboratory analysis shows glucose 198 mg/dL, sodium 131 mEq/L, potassium 3.8 mEq/L, creatinine 1.4 mg/dL, white blood cell (WBC) count 11,300 cells/mm^3, hemoglobin 12 g/dL, bicarbonate 25 mEq/L, and a normal urinalysis. What is the most likely etiology for her delirium?
- **A.** Early sepsis
- **B.** Hyperglycemia
- **C.** Hyponatremia
- **D.** Intracranial hemorrhage
- **E.** Medication effect

Answer: E. Medications are the most common cause of delirium in the older adult population. Common inciting medications include antibiotics (quinolones and macrolides), analgesics, sympathomimetics, antiinflammatories, sedatives, and cardiovascular agents. This level of hyponatremia would not be expected to cause a delirium. Likewise, a modest hyperglycemia without associated acidosis would be an unlikely culprit.

94.3. An 82-year-old man presents with acute delirium. On examination, he is alert and mildly agitated. He is oriented to person and place but not time. He is easily distracted and exhibits a mild bilateral upper extremity resting tremor without asterixis. His neurologic examination is nonfocal. His short-term memory is impaired. What is the central component most key to the diagnosis of delirium in this case?
- **A.** Agitation
- **B.** Disorientation
- **C.** Inattention
- **D.** Memory dysfunction
- **E.** Tremor

Answer: C. Disturbance in attention is central to the diagnosis of delirium. Disorientation often accompanies this but is not invariably present. The patient is usually disoriented to time and, less often, place. The delirious patient may also experience visual, auditory, tactile, and olfactory hallucinations; may lose the ability to modulate emotional expression; and often exhibits fluctuating symptoms. Short-term memory is usually impaired, but this is also seen in dementia.

94.4. Which of the following associations is correct?
- **A.** Droperidol: QT prolongation
- **B.** Haloperidol: Dysphoria
- **C.** Lorazepam Excessive half-life
- **D.** Meperidine: Cholinergic effects
- **E.** Phenothiazines: Hypocalcemia

Answer: A. This may also be seen, although less so, with haloperidol and the phenothiazines. Meperidine causes dysphoria and possibly some anticholinergic effects. Diazepam results in the longest terminal $T_{1/2}$ of the benzodiazepines.

94.5. A 63-year-old man presents with acute-onset delirium. He is a known alcoholic, and the family reports a cessation of alcohol intake 36 hours before presentation. He has no other known medical problems. Examination is remarkable for an acutely delirious patient who has active visual and auditory hallucinations and a mild tremor. Neurologic examination is otherwise negative, except for a left sixth cranial palsy. Finger-stick glucose is normal. Thiamine 100 mg intravenously fails to improve his symptoms. Which of the following is the intervention most likely to immediately improve his function?
- **A.** Dextrose
- **B.** Haloperidol
- **C.** Lorazepam
- **D.** Magnesium
- **E.** More thiamine

Answer: D. Magnesium is a cofactor in the utilization of thiamine. In chronically magnesium-depleted patients, Wernicke's encephalopathy may be refractory to thiamine until magnesium is also administered.

CHAPTER 95

Brain and Cranial Nerve Disorders

Brian A. Stettler

This chapter discusses cranial nerve (CN) problems, cerebral venous thrombosis (CVT), and multiple sclerosis (MS)—neurologic disorders that often provide diagnostic and therapeutic challenges in the emergency department (ED) setting (Table 95.1).

TRIGEMINAL NEURALGIA (CRANIAL NERVE V)

Principles

Trigeminal neuralgia, or tic douloureux, is a syndrome featuring painful paroxysms in one or more distributions of the trigeminal nerve (CN V). Trigeminal neuralgia is more common in women than in men, with a female-to-male ratio of 2:1. Affected persons typically are between 50 and 69 years old, and symptoms occur more frequently on the right side of the face.

Trigeminal neuralgia is an idiopathic disorder, although evidence points to vascular compression of the trigeminal nerve root in many cases. This compression commonly is caused by a tortuous arterial or venous loop in the posterior fossa, an arteriovenous malformation, or rarely a tumor. Although structural lesions are not found in all patients, surgical case series report up to 90% of cases having vascular compression of the trigeminal nerve root.

Clinical Features

Trigeminal neuralgia is manifested with unilateral facial pain, which is typically characterized as lancinating paroxysms of pain in the lips, teeth, gums, or chin. The pain is commonly associated with physical triggers, such as chewing, brushing the teeth, shaving, washing or touching the affected area of the face, swallowing, or exposure to hot or cold temperature in the affected area. The maxillary and mandibular divisions of the trigeminal nerve are most commonly involved; rarely, the ophthalmic division alone is involved. Patients tend to experience the pain in clustered episodes that last a few seconds to several minutes. The attacks can occur during the day or night but rarely arise during sleep.

The physical examination in patients with facial pain includes an evaluation of the sinuses, teeth, and the CNs. Given the location of the pain, the ears must be examined for signs of otitis, the teeth and face examined for evidence of odontogenic infection (such as, facial swelling or gingival fullness), and the skin and scalp examined for the painful vesicular eruption of zoster. Purulent drainage from the sinus indicates sinusitis as a possible underlying cause requiring treatment before continued pursuit of a diagnosis of trigeminal neuralgia.

Differential Diagnosis

Other painful facial conditions that are considered in patients with facial pain include odontogenic infections, sinus disease, otitis media, acute glaucoma, temporomandibular joint disease, and herpes zoster. Although the temporal components of the pain in these conditions are not similar to the sudden onset, lancinating pain of trigeminal neuralgia, the distribution is similar and these diagnoses should be considered before anchoring on a diagnosis of trigeminal neuralgia. Two percent to 4% of patients with trigeminal neuralgia also have MS, which should be considered in patients who present with neurologic findings that do not fit a specific pattern.

Diagnostic Strategies

Patients with normal findings on the head and neck examination and no neurologic deficits who have episodic, unilateral facial pain associated with nonpainful triggers are likely to have trigeminal neuralgia. The presence of a neurologic deficit should prompt suspicion of a structural lesion, such as aneurysm, tumor, or other intracranial lesion (eg, from MS). Patients with a neurologic deficit require urgent imaging studies, typically magnetic resonance imaging (MRI), to rule out a mass or vascular abnormality.

Management

The medical treatment of choice for trigeminal neuralgia is carbamazepine. The mechanism of action of anticonvulsant therapy for trigeminal neuralgia is unclear, but carbamazepine appears to be an effective and well-tolerated treatment. The initial dosage is 100 mg twice daily, increased to three times daily after 1 week. The dose may then be increased by 100 mg/day, up to a maximum of 1200 mg/day. A complete blood count and liver function studies are performed periodically in patients who are taking carbamazepine to monitor for hematologic and hepatic side effects. Additional agents that have been used for treatment of trigeminal neuralgia include phenytoin, baclofen, valproate sodium, lamotrigine, gabapentin, and levetiracetam. None has been shown to be more effective than carbamazepine. Several recent studies have investigated the use of onabotulinum toxin A for refractory pain management in trigeminal neuralgia. Although the studies are small, there are two randomized controlled trials that have shown decreased pain scores and increased quality of life with this therapy when combined with conventional medications.[1,2]

Both peripheral and central surgical interventions for trigeminal neuralgia are management options for difficult cases. Peripheral strategies include medication injection and cryotherapy techniques designed to temporarily block or permanently ablate branches of the peripheral trigeminal nerve. Although these procedures are relatively effective initially, recurrence is common. Central procedures include percutaneous destruction of the trigeminal ganglion, although these procedures carry the risk of corneal anesthesia, oculomotor paresis, or masticatory weakness.[3] Open surgical management includes microvascular decompression of the nerve with or without partial ablation. Although pain relief is achieved in 80% to 95% of patients, the surgery is associated with the risk of complications. Gamma knife radiosurgery, a minimally invasive, precision-directed stereotactic radiosurgery, has shown good outcomes.[4]

TABLE 95.1

The Cranial Nerves: Normal Function and Pathologic Considerations

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
CN I: Olfactory nerve	Sense of smell	Unilateral anosmia	Trauma: Skull fracture or shear injury interrupting olfactory fibers traversing the cribriform plate Tumor: Frontal lobe masses compressing the nerve
CN II: Optic nerve	Vision	Unilateral vision loss	Trauma: Traumatic optic neuropathy Tumor: Orbital compressive lesion Inflammatory: Optic neuritis (MS) Ischemic: Ischemic optic neuropathy
CN III: Oculomotor nerve	Extra oculomotor function via motor fibers to levator palpebrae, superior rectus, medial rectus, inferior rectus, inferior oblique muscles Pupillary constriction via parasympathetic fibers to constrictor pupillae and ciliary muscles	Ptosis caused by loss of levator palpebrae function Eye deviated laterally and down Diplopia Dilated, nonreactive pupil Loss of accommodation	Trauma: Herniation of the temporal lobe through the tentorial opening, causing compression and stretch injury to the nerve Ischemic: Especially in diabetes; microvascular ischemic injury to nerve causes extraocular muscle paralysis but usually is papillary sparing (often painful) Vascular: Intracranial aneurysms may press on the nerve, leading to dysfunction Myasthenia gravis can lead to atraumatic ocular muscle palsy
CN IV: Trochlear nerve	Motor supply to the superior oblique muscle	Inability to move eye downward and laterally Diplopia Patients tilt head toward unaffected eye to overcome inward rotation of affected eye	Trauma is the most common cause of nerve dysfunction
CN V: Trigeminal nerve	Motor supply to muscles of mastication and to tensor tympani Sensory to face, scalp, oral cavity (including tongue and teeth)	Partial facial anesthesia Episodic, lancinating facial pain associated with benign triggers, such as chewing, brushing teeth, light touch	Trauma: Facial bone fracture may injure one section, leading to area of facial anesthesia Tic douloureux
CN VI: Abducens nerve	Motor supply to the lateral rectus muscle	Inability to move affected eye laterally Diplopia on attempting lateral gaze	Tumor: Lesions in the cerebellopontine angle Any lesion, vascular or otherwise, in the cavernous sinus may compress nerve Elevated ICP: Because of its position and long intracranial length, increased ICP from any cause may lead to injury and dysfunction of the nerve
CN VII: Facial nerve	Motor supply to muscles of facial expression Parasympathetic stimulation of the lacrimal, submandibular, and sublingual glands Sensation to the ear canal and tympanic membrane	Hemifacial paresis: Lower motor neuron lesion leaves entire side of face paralyzed Upper motor neuron lesion leaves forehead musculature functioning Abnormal taste Sensory deficit around ear Intolerance to sudden loud noises	Lower motor neuron: Infection (viral): The likely cause of Bell's palsy Lyme disease: The most common cause of bilateral CN VII palsy in areas where Lyme disease is endemic Bacterial infection extending from otitis media Upper motor neuron: Stroke, tumor
CN VIII: Vestibulocochlear nerve	Hearing and balance	Unilateral hearing loss Tinnitus Vertigo, unsteadiness	Tumor: Acoustic neuroma Mimics Ménière's disease, perilymphatic fistula
CN IX: Glossopharyngeal nerve	General sensation to posterior third of tongue Taste for posterior third of tongue Motor supply to the stylopharyngeus	Clinical pathology referable to the nerve in isolation is very rare Occasionally painful paroxysms beginning in the throat and radiating down the side of the neck in front of the ear but behind the mandible	Brainstem lesion Glossopharyngeal neuralgia

TABLE 95.1

The Cranial Nerves: Normal Function and Pathologic Considerations—cont'd

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
CN X: Vagus nerve	Motor to striated muscles and muscles of the pharynx, larynx, and tensor (veli) palatini Motor to smooth muscles and glands of the pharynx, larynx, thoracic and abdominal viscera Sensory from larynx, trachea, esophagus, thoracic and abdominal viscera	Unilateral loss of palatal elevation: Patients complain that on drinking liquids, the fluid refluxes through the nose Unilateral vocal cord paralysis: Hoarse voice	Brainstem lesion Injury to the recurrent laryngeal nerve during surgery
CN XI: Spinal accessory nerve	Motor supply to the sternocleidomastoid and trapezius muscles	Downward and lateral rotation of the scapula and shoulder drop	Trauma to the nerve
CN XII: Hypoglossal nerve	Motor supply to the intrinsic and extrinsic muscles of the tongue	Tongue deviations: Upper motor neuron lesion causes the tongue to deviate toward the opposite side Lower motor neuron lesion causes the tongue to deviate toward the side of the lesion, and the affected side atrophies over time	Stroke or tumor can cause upper motor neuron lesion Amyotrophic lateral sclerosis can cause bilateral lower motor neuron lesion with atrophy Metastatic disease to the skull base may involve the nerve

CN, Cranial nerve; *ICP,* intracranial pressure; *MS,* multiple sclerosis.

Disposition

Patients with newly suspected trigeminal neuralgia should be referred for specialty evaluation. Coordination with a neurologist will help in therapeutic decision making. Patients with an established diagnosis who present with uncontrolled pain refractory to maximum pharmacologic management may require a neurosurgical consultation for an operative intervention.

FACIAL NERVE PARALYSIS (CRANIAL NERVE VII)

Principles

Peripheral paralysis has no geographic, gender, or race predilection; pregnancy is a risk factor.[5] The facial nerve (CN VII) innervates the muscles of facial expression and the muscles of the scalp and external ear in addition to the buccinator, platysma, stapedius, stylohyoid, and posterior belly of the digastric muscles. The sensory portion of the nerve supplies the anterior two-thirds of the tongue with taste and sensation to portions of the external auditory meatus, soft palate, and adjacent pharynx. The parasympathetic portion supplies secretomotor fibers for the submandibular, sublingual, lacrimal, nasal, and palatine glands.

The nerve originates from the pontomedullary junction of the brainstem and enters the internal auditory meatus with CN VIII. Within the temporal bone, the facial nerve has four major branches: the greater and lesser superficial petrosal nerves, the nerve to the stapedius muscle, and the chorda tympani. The facial nerve exits the temporal bone at the stylomastoid foramen and then enters the parotid gland, where it divides to supply the muscles of facial expression.

Clinical Features

The medical history in patients with facial paralysis focuses on onset of the paralysis, concentrating on timing and rapidity of onset and associated signs and symptoms. The most common causes of a CN VII palsy are Bell's palsy, Ramsey Hunt syndrome, Lyme disease, and bacterial infections of the middle ear, mastoid, or external auditory canal.

Bell's Palsy

Bell's palsy, also commonly called *idiopathic facial paralysis,* is postulated but not confirmed to have a viral cause. It is characterized by an abrupt onset of a lower motor neuron paresis that typically develops over 72 hours and can progress during 1 to 7 days to complete paralysis. A prodromal viral-like illness is described by 60% of patients. Symptoms and signs frequently associated with the facial paresis include ear pain, perception of sensory change on the involved side of the face, decreased tearing, overflow of tears on the cheek (epiphora), abnormally acute hearing (hyperacusis), and impairment or perversion of taste (dysgeusia).

To make the diagnosis of Bell's palsy, both the upper and lower facial muscles must be involved. If only lower face involvement can be elicited, there should be a suspicion for a central lesion, such as a cerebral infarct or neoplasm. Lid closure is assessed by asking the patient blink rapidly; if the patient is unable to fully close the eye, a diagnosis of Bell's palsy suspected.

Ramsey Hunt Syndrome

Ramsay Hunt syndrome (herpes zoster oticus) is characterized by unilateral facial paralysis, a herpetiform vesicular eruption, and vestibulocochlear dysfunction. The vesicular eruption, which may follow the facial paralysis by a few days, may occur on the pinna, external auditory canal, tympanic membrane, soft palate, oral cavity, face, and neck as far down as the shoulder. The pain is considerably more severe than that associated with Bell's palsy, and it frequently is out of proportion to physical findings. In addition, outcomes are worse than with Bell's palsy, with a lower incidence of complete facial recovery and the possibility of sensorineural hearing loss.

Lyme Disease

Systemic symptoms or bilateral facial paresis, especially in endemic areas, should raise the possibility of Lyme disease. Lyme disease is the most frequent vector-borne infection in the United States. It is caused by the spirochete *Borrelia burgdorferi* and is spread by the bite of *Ixodes* genus ticks. Neurologic manifestations can arise in any phase of the disease, and facial palsy accounts for up to 50% of the neurologic presentations. In regions in which Lyme disease is endemic, it has been shown to be the leading cause of facial paralysis in children.

Bilateral facial nerve paralysis is rare but can occur with systemic infections. The two diseases most commonly associated with bilateral simultaneous onset of facial paralysis are Lyme disease and infectious mononucleosis. Bilateral facial paralysis should be considered to be a manifestation of Lyme disease until further testing excludes this diagnosis. The evaluation and treatment of Lyme disease are discussed in Chapter 126.

Bacterial Ear Infections

Facial paralysis can be caused by acute bacterial infections of the middle ear, mastoid, or external auditory canal. In the pre-antibiotic era, facial paralysis was associated with acute otitis media in approximately 2% of cases; today, however, it occurs in only 0.2% of cases. Malignant otitis externa can be associated with facial paralysis. This disease entity is most commonly seen in immunocompromised patients and usually is caused by *Pseudomonas* infection.

Differential Diagnosis

In addition to the disorders previously discussed, paralysis of CN VII can be caused by facial trauma where temporal bone fracture can cause nerve transection and neoplasia. A history of recurrent ipsilateral paralysis or slow progression of symptoms is more characteristic of a tumor. Associated CN abnormalities, such as a gaze paresis, point to the possibility of a tumor or cerebral ischemic insult. Patients will occasionally describe "numbness" in the same distribution as the weakness to the face, although they rarely experience the dense sensory loss or weakness of mastication seen in CN V lesions. Potential involvement of multiple CNs suggests a stroke or a mass lesion.

Tumors of the facial nerve itself or tumors anywhere along its course that invade or compress the nerve may lead to facial paralysis. The course is typically progressive for at least 3 weeks and typically of slower onset than that which is found in Bell's palsy, although up to 25% of tumors will present with a history of sudden onset of paralysis. Although very rare overall, a neoplastic cause should be suspected in patients who suffer from recurrent ipsilateral facial paralysis, significant pain, prolonged symptoms, or any other concomitant CN abnormality.

Diagnostic Strategies

The diagnostic evaluation of acute facial nerve paresis is based on whether the clinical picture is suggestive of a disease process other than Bell's palsy. If the clinical history is classic for Bell's palsy, the American Academy of Otolaryngology recommends no imaging or laboratory studies.[6] A history that poses potential exposure to Lyme warrants serologic evaluation for the disease. Although outpatient testing including electroneurography may ultimately be performed, this usually is not part of the initial evaluation.

The presence of a "central" seventh nerve paralysis (upper face sparing) should prompt imaging with computed tomography (CT) or MRI, and consideration given to the possibility of an acute stroke or other hemispheric lesion. History or physical findings suggestive of a possible tumor require imaging to rule out a neoplasm. The study of choice will depend on the institution and preferences of the consultant but typically involves MRI.

Management

Bell's Palsy

Both medical and surgical treatments of Bell's palsy are available. The primary medical therapies for Bell's palsy center on reducing inflammatory changes to the nerve with corticosteroids and treating the presumed viral cause. If these therapies are unsuccessful, surgical decompression may be considered.

Available evidence strongly favors the use of corticosteroids for the treatment of Bell's palsy, and earlier treatment is associated with better outcomes.[7,8] Steroid therapy is believed to inhibit edema of the nerve, confined within the facial canal, which is thought to cause or contribute to the nerve injury. Based on the results of high quality, randomized trials, we recommend treatment with prednisolone, 50 to 60 mg/day per day for 10 days, with or without a short taper. Therapy should be started as soon as possible, ideally within the first 24 hours, but it is still recommended for patients without contraindications who seek treatment within 1 week of symptom onset.

A number of studies have supported the contention that Bell's palsy may be caused by herpes virus infection. Herpes simplex virus type 1 DNA has been demonstrated in the endoneurial tissue of Bell's palsy patients, although there is conflicting evidence on the efficacy of antiviral treatment. Some studies have found treatment with corticosteroids plus antiviral medications to be superior to steroids alone, particularly in the setting of severe palsy or in those treated within 24 hours of symptom onset.[9] Other studies have found conflicting results.[10] Summary statements from the American Academy of Otolaryngology recommend that antivirals "be considered" in the treatment of Bell's palsy, although they should only be offered in combination with oral steroids and should be considered more strongly for severe loss of function.[10] We recommend valacyclovir, 1000 mg orally three times daily for 7 days, or famciclovir, 750 mg orally for 7 days (Table 95.2). Valacyclovir and famciclovir have better oral absorption, are better tolerated, and are dosed less frequently, resulting in higher compliance than with acyclovir treatment. Although earlier treatment is preferred, treatment should be considered for patients presenting within 1 week of symptom onset.

Ramsay Hunt Syndrome

The treatment of Ramset Hunt syndrome is similar to that of Bell's palsy, although antiviral treatment is more strongly recommended in this disease process in addition to steroid therapy. Both prednisone and antiviral therapy should be continued for 7 to 10 days.

TABLE 95.2

Treatment of Bell's Palsy

	MILD/MODERATE DISEASE	SEVERE DISEASE
Steroids	Prednisolone 50 to 60 mg daily for 10 days, with or without taper	Prednisolone 50 to 60 mg daily for 10 days, with or without taper
Antivirals	Not recommended	Consider in *addition to steroids,* valacyclovir 1000 mg tid or famciclovir 750 qD for 7 days

Lyme Disease

The treatment of Lyme disease is discussed in Chapter 126.

Bacterial Infections

Treatment bacterial infections causing a CN VII palsy involves prolonged intravenous (IV) antipseudomonal antibiotic therapy and may require surgical débridement.

Disposition

Most patients who have a seventh CN paralysis will have a clinical diagnosis of Bell's palsy and may be discharged with referral for short-term follow-up. Patients with a possible hemispheric process, such as stroke or tumor, require further evaluation and often hospitalization. Patients thought to have Lyme disease require immediate initiation of antibiotic therapy.

In patients with a complete facial nerve paralysis and inability to close the eye, the ipsilateral eye should be patched. Patients should be advised of the risk for corneal abrasion and corneal dryness, which is associated with the inability to blink properly or to close the eye completely. Patients should be counselled regarding their expected timeline for recovery. Although mild paresis typically recovers within 2 to 3 weeks, complete paralysis may take up to 6 to 12 months for recovery. Patients with a complete facial nerve paralysis should be provided with an urgent referral to a head and neck surgeon.

VESTIBULAR SCHWANNOMA (CRANIAL NERVE VIII)

Principles

Vestibular schwannoma, formally referred to as *acoustic neuroma,* is a rare but important cause of sensorineural hearing loss. It occurs in middle-aged individuals and is usually unilateral in nature. Vestibular schwannoma is rarely bilateral, occurring in approximately 5% of cases and generally associated with type 2 neurofibromatosis. Although histologically benign, vestibular schwannoma can cause neurologic damage by direct compression on CN VIII and the other structures in the cerebellopontine angle.

Vestibular schwannomas arise from the Schwann cells covering the vestibular branch of the CN VIII as it passes through the internal auditory canal. The tumor may compress the cochlear (acoustic) branch of the CN VIII, causing hearing loss, tinnitus, and dysequilibrium. Continued growth of the tumor may result in compression of structures in the cerebellopontine angle, where CN V and CN VII may be compressed and damaged. Larger tumors may further encroach on the brainstem and, if large enough, may compress the fourth ventricle, ultimately resulting in signs of increased intracranial pressure (ICP).

Clinical Features

Asymmetrical sensorineural hearing loss is the hallmark of vestibular schwannoma. Up to 15% of patients with this tumor, however, will have normal results on audiometry. These patients typically have symptoms, such as unilateral tinnitus, imbalance, headache, fullness in the ear, otalgia, and facial nerve weakness. Thus, patients with asymmetrical symptoms should be further evaluated for vestibular schwannoma even with normal findings on audiometry.

Vestibular schwannomas are extremely slow-growing tumors, averaging an approximately 1-mm increase per year, although many do not grow at all. The median time from symptom onset to diagnosis is 12 months.

Differential Diagnosis

A majority of disease entities included in the differential diagnosis for vestibular schwannoma cause symmetrical sensorineural hearing loss. Asymmetrical sensorineural hearing loss has few causes other than vestibular schwannoma. Ménière's disease may present with asymmetrical findings, but it can be differentiated from vestibular schwannoma in that the tinnitus of Ménière's disease usually is intermittent, whereas the tinnitus of vestibular schwannoma typically is continuous. In addition, patients with Ménière's disease typically describe true vertigo, whereas patients with a vestibular schwannoma are more likely to describe imbalance or dysequilibrium.

Vestibular schwannomas account for 80% of all cerebellopontine angle tumors, meningiomas are the second most common. Meningiomas more frequently cause symptoms of facial palsy or trigeminal nerve abnormality. Of note, however, considerable similarity between the clinical picture of a meningioma and that of vestibular schwannoma in the cerebellopontine angle has been described.

Diagnostic Strategies

When vestibular schwannoma is suspected, the patient is evaluated by audiometry or gadolinium-enhanced MRI. This imaging technique is extremely sensitive and has led to earlier diagnosis and a decrease in mean size at detection of vestibular schwannoma. CT lacks the necessary sensitivity in the posterior cranial fossa to reliably rule out the presence of vestibular schwannoma. The smaller the tumor at the time of diagnosis, the more options there are for therapy and the better the prognosis.

Management

Vestibular schwannoma may be removed surgically or ablated with stereotactic radiation therapy. In appropriately selected patients, there is little difference in long-term quality-of-life segregated by type of treatment.[11] In general, tumors larger than 3 cm are recommended for microsurgery because radiation treatments, such as with the gamma knife, are less effective for local control and growth arrest in larger masses.[12] Smaller tumors are amenable to use of stereotactic radiation therapy. Stereotactic radiation therapy generally has good long-term outcomes of local growth arrest, with nerve salvage approaching 90% or greater. In patients who are minimally symptomatic with small tumors, serial monitoring with MRI is a viable option.

Disposition

Patients with suspected acoustic neuroma should be referred for audiometry or MRI and evaluation by a specialist in either otolaryngology or neurosurgery.

DIABETIC CRANIAL MONONEUROPATHY

Principles

Cranial mononeuropathies occur uncommonly, and usually are a complication of diabetes. They most often affect the extraocular muscles. The oculomotor nerve (CN III) is most commonly affected, followed by the trochlear (CN IV) and abducens (CN VI) nerves. CN palsies occur in 1% of diabetics versus 0.1% among nondiabetics. Whereas ophthalmoplegia appears to be closely related to diabetes, facial palsy is less strongly correlated with this disease.[13]

The pathologic basis of diabetic mononeuropathy appears to be ischemia caused by occlusion of an intraneural nutrient artery

serving the nerve. This occlusion leads to injury located primarily in the core fibers, whereas the peripheral nerve fibers are less affected because they also are supplied by collateral vessels. In the oculomotor nerve, the preservation of the circumferentially located parasympathetic fibers explains the pupillary sparing that usually is found in this syndrome.

Clinical Features

Patients typically describe acute onset of unilateral retro-ocular and supraorbital pain, diplopia, and ptosis. The physical manifestations of a CN III palsy include the inability to move the eye superiorly and medially, accompanied by ptosis. The pupillary light reflex usually is present. Although it is a less common finding, CN IV and CN VI may be affected. Patients with a CN IV palsy are unable to move the eye inferolaterally, and those with a CN VI palsy are unable to move the eye laterally. Because of the long intracranial course of CN VI, a patient with an isolated sixth nerve palsy should be evaluated for an intracranial lesion or increased ICP.

Differential Diagnosis

Diabetic mononeuropathy generally is a diagnosis of exclusion. Considerations in the differential diagnosis include trauma, tumor, vertebrobasilar ischemia, aneurysm, and brainstem hemorrhage.

Diagnostic Studies

Diagnostic imaging is not required in the setting of a "classic" oculomotor mononeuropathy. If a diabetic patient presents with an isolated CN III palsy with sparing of the pupillary light reflex in the absence of other CN or neurologic abnormalities, the diagnosis can be made presumptively. If the pupillary reflex is lost in the affected eye, one must be concerned about aneurysm and a computerized tomographic angiogram (CTA) is indicated. If other CNs are involved or there are other acute neurologic deficits present, stroke remains a consideration and CT or MRI should be obtained. In a patient who presents with a cranial mononeuropathy but without a history of diabetes, a hemoglobin A1c might be helpful for the providers who assume care of the patient.

Management

Treatment consists of patching the affected eye and administration of analgesics and antiplatelet therapy. Although there is no specific cure, patient education regarding glucose control is important. The prognosis is good and the neuropathy generally resolves within 3 to 6 months. Antioxidant preparations, including α-lipoic acid, have been used therapeutically and have not shown harm, but such agents have yet to be shown to have convincing clinical effect.[14]

CEREBRAL VENOUS THROMBOSIS

Principles

Cerebral blood is drained by several major veins that lead into the dural sinuses. The major dural sinuses are the superior sagittal sinus, the inferior sagittal sinus, the straight sinus, the lateral sinuses, and the sigmoid sinuses. The variability in symptoms and signs in patients who present with CVT stems from differences in thrombus location and acuity of thrombus formation. Women represent 60% to 75% of those diagnosed. The short-term mortality of CVT can be quite high, depending upon time to diagnosis and severity of neurological symptoms at the time of presentation.[15] With early diagnosis and treatment, mortality rates are low.

Infectious causes of CVT include systemic infections and local infections, such as sinusitis, otitis media, and facial cellulitis. Noninfectious causes include direct injury to the cerebral venous system from trauma, surgery, dehydration, or any other conditions causing hypercoagulable states, including the presence of a malignant neoplasm or the use of oral contraceptive agents.

Clinical Features

Patients with CVT often present with symptoms of intracranial hypertension, especially headache; patients with CVT are more prone to hemorrhagic infarction and localizing neurologic deficits. Lethargy, seizures, decreased level of consciousness, or mental status changes may be noted. A patient's symptom onset will vary in accordance with the extent of collateral vessel growth in the venous territory. Symptoms will appear only when the compensation for venous thrombosis is no longer sufficient or when hemorrhagic infarction occurs. Variability in collateralization between patients also adds to the variability and time course of symptoms. The average time from symptom onset to diagnosis of 7 days, reflecting the difficulty in diagnosis of this rare disease entity. Because of the broad spectrum of possible clinical features, the diagnosis of CVT may be difficult but should be a consideration in any patient with unexplained headache, especially in combination with focal neurologic deficit, papilledema, or seizures.

Patients with CVT will sometimes complain of diplopia or will be observed to have a dysconjugate gaze secondary to involvement of CN IV and CN VI. This can occur due to thrombosis of the cavernous sinus or simply from elevated ICP. In the presence of headache or a visual complaint, a funduscopic examination should be performed to look for papilledema, which is noted in up to 45% of patients with CVT.

Differential Diagnosis

The differential diagnosis of CVT is broad and includes the conditions that cause patients to present with the new onset of neurologic deficits, alteration in consciousness, or severe headache.

Diagnostic Strategies

Non-contrast CT scanning is commonly employed in the evaluation of patients with severe or unusual headaches, it is neither sensitive nor specific enough to reliably confirm or exclude the diagnosis of CVT. Findings on CT that are consistent with CVT include hyperdensity of a thrombosed sinus or deep vein (referred to as the *cord sign* or *attenuated vein sign,* respectively), brain edema, and hemorrhage secondary to venous congestion.

MRI can demonstrate local changes secondary to venous congestion, such as brain edema and hemorrhage. In addition, MRI can demonstrate the possibility of CVT by the lack of a "flow void." On conventional MRI, a flow void indicates the presence of moving blood within the sinus, whereas the absence of a flow void indicates a possible thrombus. Diagnostic accuracy, however, is greatly improved through use of magnetic resonance venography (MRV). This technique takes advantage of the MRI signal characteristics of flowing blood to create images of venous structures. Combination of these imaging techniques further enhances diagnostic accuracy. For imaging of a particular dural sinus, presence of the sinus on conventional MRI and lack of flow on MRV are diagnostic of a sinus thrombosis. This combined approach has diagnostic sensitivity similar to that of conventional angiography.

MRV and CT venography have similar sensitivities for the diagnosis of CVT when the CT study is performed on a multidetector row CT scanner; the sensitivity of CT venography for CVT approaches 100% and is comparable to that of MRV both in sensitivity and in inter-rater reliability. The sensitivity of CT

venography performed by scanners that do not use multidetector row technology is unknown. Based on the best available evidence, we recommend MRI/MRV as the diagnostic study of choice when CVT is suspected, because this continues to be the gold standard against which all other diagnostic studies are compared.

D-dimer assays may have a role as a screening tool to exclude CVT, particularly when MRI or CT venography is not available. Although the reported sensitivity rates are fair at 83% to 100%, larger prospective studies are needed. In general, although a normal D-dimer level does not exclude the diagnosis of CVT, the diagnosis is much less likely, particularly in a patient with symptoms of less than 2 weeks in duration.

Management

CVT is a relatively rare disease, and controlled studies evaluating its treatment are lacking. Current therapeutic consensus strongly recommends systemic anticoagulation with low–molecular-weight heparin (LMWH) or unfractionated heparin to prevent further clot formation and to promote recanalization, even in patients with intracranial hemorrhage on initial imaging. A registry comparing outcomes of patients treated with unfractionated heparin compared with LMWH found more benefit in the LMWH group, although the effect was modest.[16] Despite a paucity of randomized controlled trials, expert opinion favors anticoagulation in all groups unless another contraindication is present.

Catheter-based intervention with thrombolysis has shown promise in the management of CVT. Two case series have shown good outcomes in patients with altered mental status or coma at the time of presentation. All were treated in a non-randomized fashion with catheter-based thrombolysis with urokinase or tissue plasminogen activator (tPA), with 75% of patients recovering to a modified Rankin Scale of 0 or 1.[17,18] This promising therapy is typically considered only for patients with symptoms of decreased level of consciousness, elevated ICP, or rapid neurologic deterioration.

Disposition

All patients with suspected CVT should be admitted to a unit capable of providing a high level of care with neurologic consultation. Patients should be anticoagulated if no contraindication exists, and catheter-based thrombolysis should be considered in patients with depressed mental status or focal findings on neurologic examination.

MULTIPLE SCLEROSIS

Principles

MS is an inflammatory disease that affects the central nervous system (CNS). The pathologic manifestation of this inflammatory disease is a demyelination of discrete regions (plaques) within the CNS with a relative sparing of axons. The clinical picture is highly variable, but it is classically characterized by episodes of neurologic dysfunction that evolve over days and resolve over weeks.

The peak age at onset is 25 to 30 years old; women are slightly younger than men at onset. The incidence in women exceeds that of men by a ratio of 1.8:1. MS is more common in temperate climates. The worldwide prevalence is greatest in the United Kingdom, Scandinavia, and North America. Epidemiologic studies indicate that both genetic and environmental factors are associated with an increased incidence of MS. It is rare in Africans and Asians, but African Americans have a higher incidence than their relatives who remain in Africa. Thus, an environmental cause superimposed on genetic susceptibility appears to be a likely etiologic scenario.

MS is considered to be an organ-specific autoimmune disease. One theory proposes that genetic factors interact with an environmental trigger or infection to establish pathologically autoreactive T cells in the CNS. After a long and variable latency period (typically 10 to 20 years), a systemic trigger, such as a viral infection or superantigen, activates these T cells. The activated T cells, on reexposure to the autoantigen, initiate the inflammatory response. This sets off a complex immunologic cascade that leads to the demyelination characteristic of MS. This demyelination process releases CNS antigens that are hypothesized to initiate further episodes of autoimmune-induced inflammation.

Clinical Features

The clinical picture in MS is one of marked heterogeneity. The classic clinical syndrome consists of recurring episodes of neurologic symptoms that rapidly evolve over days and slowly resolve over weeks. Variability occurs in age at onset, location of CNS lesions, frequency and severity of relapses, and degree and time course of progression.

The clinical features of MS can be divided into areas of specific CNS impairment: cognition; CNs; motor pathways; sensory pathways; cerebellar pathways; and bowel, bladder, and sexual dysfunction. Patients with MS have frequent complaints of poor memory, distractibility, and decreased capacity for sustained mental effort. Formal neuropsychological testing suggests that cognitive involvement is common and underreported, affecting up to 65% of patients. A correlation has been found between the MRI-based total lesion load and presence of cognitive impairment.

CN dysfunction is common in MS. The most common associated CN abnormality is *optic neuritis,* which is a unilateral syndrome characterized by pain in the eye and a variable degree of visual loss affecting primarily central vision. It is often the first symptom of MS. Within 2 years of an attack of optic neuritis, the risk of MS is approximately 20%, and within 15 years, it is approximately 45% to 80%.

As a result of lesions in the vestibulo-ocular connections, the oculomotor pathways also may be affected. The deficit may be manifested as diplopia or nystagmus. The nystagmus may be severe enough that the patient may complain of oscillopsia (a subjective oscillation of objects in the visual field). CN impairment also may include impairment of facial sensation, which is relatively common. Unilateral facial paresis also may occur. In addition, the occurrence of trigeminal neuralgia in a young person may be an early sign of MS.

Motor pathways also are commonly involved; specifically, corticospinal tract dysfunction. Paraparesis or paraplegia occurs with greater frequency than upper extremity lesions owing to the common occurrence of lesions in the motor tracts of the spinal cord. In patients with significant motor weakness, spasms of the legs and trunk may occur on attempts to stand from a seated position. This dysfunction is manifested on physical examination as spasticity that typically is worse in the legs than in the arms. The deep tendon reflexes are markedly exaggerated, and sustained clonus may be demonstrated. Although these symptoms frequently are bilateral, they generally are asymmetrical.

Sensory manifestations are a frequent initial feature of MS and will be present in nearly all patients at some point during the course of the disease. Sensory symptoms are commonly described as numbness, tingling, "pins and needles" paresthesias, coldness, or a sensation of swelling of the limbs or trunk.

Impairment of the cerebellar pathway may result in gait imbalance, difficulty with coordinated actions, and dysarthria. Physical examination reveals the typical features of cerebellar dysfunction, including dysmetria, dysdiadochokinesis (an impairment of rapid alternating movements), breakdown in the ability to perform

complex movements, intention tremor in the limbs and head, truncal ataxia, and dysarthria.

Impairment of bowel, bladder, and sexual function also is common. The extent of sphincter and sexual dysfunction usually parallels the motor impairment in the lower extremities. Urinary frequency may progress to urinary incontinence as the disease advances. An atonic bladder may develop, which empties by simple overflow and often is associated with the loss of perception of bladder fullness and with anal and genital hypoesthesia. Constipation becomes common in time, and almost all patients with paraplegia require special measures to maintain effective bowel habits. Sexual dysfunction, although frequently overlooked, is common in MS. Approximately 50% of patients become completely sexually inactive as a result of this disease.

Differential Diagnosis

Other diseases that affect the CNS white matter may be clinically and radiographically similar to MS. These include CNS tumors (especially lymphomas and gliomas), spinal cord compression, vasculitides, Behçet's disease, neuro-sarcoidosis, postinfectious and postvaccinal encephalomyelitis, human immunodeficiency virus (HIV) encephalopathy, Lyme disease, and vitamin B_{12} deficiency.

Diagnostic Strategies

MS is a relapsing-remitting disorder with symptoms that fluctuate over time. Therefore, the clinical diagnosis rests on occurrence of at least two clinical episodes with different neurologic symptoms at different times.

Although no laboratory tests are diagnostic for MS, one clinical feature remains unique to this disease: *Uhthoff's phenomenon,* temporary worsening of current or preexisting signs or symptoms of MS secondary to small increases in the patient's body temperature. Accordingly, exercise, a hot bath, exposure to a warm environment, or fever can bring about Uhthoff's phenomenon. This phenomenon reflects subclinical demyelination or preexisting injury to nerves without obvious significant clinical involvement before heat exposure or temperature elevation.

Lumbar puncture is recommended for evaluation of patients with suspected MS, but mass lesions and elevated ICP should be ruled out before lumbar puncture is attempted. CSF analysis is abnormal in 90% of the cases. Fifty percent of patients will have pleocytosis, with more than five lymphocytes per high-power field. Approximately 70% of patients will have an elevated gamma globulin level, with immunoglobulin G (IgG) ranging from 10% to 30% of the CSF total protein. Electrophoresis of the CSF demonstrates oligoclonal bands of IgG in 85% to 95% of patients who carry a diagnosis of MS; however, oligoclonal bands of IgG also are seen with neurosyphilis, fungal meningitis, and other CNS infections.

The initial imaging test to aid in the diagnosis of MS is gadolinium-enhanced MRI of the brain and spinal cord. MRI is a sensitive test for the detection of lesions consistent with MS and also is useful to assess disease severity. Lesions usually are multiple and commonly are found in the periventricular white matter. In patients with an initial neurologic event consistent with CNS demyelination and an MRI cranial study showing multiple white matter lesions, the 5-year risk for development of MS is 60%. Patients with similar clinical syndromes and a normal MRI appearance have less than a 5% risk.

Management

Management of patients with MS has essentially three aspects: (1) therapies aimed at halting the progression of the disease, (2) treatment of acute exacerbations, and (3) therapies designed to modify complications.

Treatment of Disease Progression

Although there are many therapies under development for treatment of early or established disease, standard therapies aimed at halting disease progression are based primarily on the use of either interferon-β or glatiramer acetate. The interferons are a group of natural compounds with antiviral and immunomodulatory actions used in therapy for MS. Side effects of the agents interferon-β1a and interferon-β1b include influenza-like symptoms, depression, anxiety, and confusion. Interferon-β1a lowers relapse rate, prolongs time to first relapse, and lowers the accumulation of brain lesions on MRI. Interferon-β also has been shown to retard progression to clinically definite MS and to decrease the total number of brain lesions seen on subsequent MRI studies in patients who have their first demyelinating episode with MRI abnormalities at initial presentation. This finding highlights the importance of early evaluation and treatment.

Glatiramer acetate is a mixture of synthetic polypeptides designed to mimic myelin basic protein, which has successfully been used in the treatment of MS. The mechanism of action by which glatiramer acetate exerts its effect is unknown, but it is thought to modify the immune processes responsible for the pathogenesis of MS. Patients receiving glatiramer acetate experience significantly fewer relapses and are more likely to demonstrate neurologic improvement. It has also been shown to slow the progression to clinically definite MS after a first clinical demyelinating episode.

Current recommendations for management of relapsing-remitting MS are to initiate treatment with interferon-β or glatiramer acetate.[19] Such regimens have been demonstrated to decrease the volume of plaques seen on MRI and to diminish relapses. Newer disease-modifying agents include fingolimod, laquinimod, daclizumab, natalizumab, and teriflunomide; their role is yet to be fully defined.

Treatment of Acute Exacerbations

Acute exacerbations of MS will generally resolve without therapy; however, steroids diminish the duration. More than 85% of patients with relapsing-remitting MS show improvement with IV methylprednisolone. IV steroids have been shown in controlled trials to speed the recovery from the visual loss of optic neuritis compared with placebo. In addition, when patients with acute optic neuritis are treated with high-dose IV steroids, the 2-year rate of development of MS is reduced, although this effect diminishes over time. Oral prednisone is not helpful and is associated with a potential increase in disease flares.

The current standard therapy for an acute exacerbation in MS is IV methylprednisolone, 250 to 500 mg every 12 hours for 3 to 7 days. Whether this should be followed by an oral prednisolone taper remains controversial. Potential adverse effects of methylprednisolone therapy include fluid retention, gastrointestinal hemorrhage, anxiety, psychosis, infection, and osteoporosis. Diagnostic diligence should be exercised in the evaluation of an acute exacerbation of MS, because many exacerbations are brought on by other medical issues, including infection. This is especially true of patients with severe preexisting disease.[14]

Treatment of Complications

Several therapies directed toward the complications of MS may be helpful. The associated spasticity generally is treated with

baclofen starting at 5 mg tid and eventually increasing up to 20 mg tid. This is a highly effective therapy aimed at reducing the painful flexor and extensor spasms. A major side effect is drowsiness, which generally diminishes with continued use. Higher-dose therapy can cause confusion, especially in the setting of baseline cognitive impairment. For patients with intractable spasticity, baclofen is available for intrathecal administration by either bolus therapy or continuous implanted pump therapy. Additional therapeutic agents for control of spasticity include tizanidine, diazepam, and dantrolene.

The tremor and ataxia associated with MS occasionally are treated with propranolol, diazepam, or clonazepam. The results of these therapies, however, generally are unsatisfactory. Pain often is associated with MS and affects the shoulders, pelvic girdle, and face. The facial pain may be indistinguishable from that of trigeminal neuralgia. Treatment options include carbamazepine, baclofen, and tricyclic antidepressants.

Disposition

Patients with a history of MS who seek treatment for significant symptoms must first be evaluated to rule out other, non–MS-related pathologic processes. Other systemic illnesses, especially infections, which can worsen the symptoms of MS, should be excluded. If the problem is thought to be a significant exacerbation of MS, most patients will require hospital admission for IV steroid therapy. Depending on the patient's neurologic status, an alternative to hospitalization may be the initiation of IV steroids in the ED followed by a next-day appointment with the patient's primary care physician or neurologist for ongoing IV steroid administration.

Patients with the new onset of symptoms suggestive of MS should be admitted or referred to a neurologist, because early treatment has been shown to significantly decrease progression of the disease.

KEY CONCEPTS

Trigeminal Neuralgia

- Patients with unilateral, intermittent, lancinating facial pain without abnormalities on physical examination are likely to have trigeminal neuralgia.
- Carbamazepine starting at 100 mg bid is the first-line agent for medical treatment, with a typical therapeutic dose of 600 to 800 mg/day in divided doses.
- Patients who do not tolerate treatment or whose pain is refractory to medical management may be candidates for microvascular decompression or ablation.

Facial Nerve Paralysis

- Patients who have facial muscle paresis with intact forehead movement should be considered to have a central (upper motor neuron) lesion until the diagnostic investigation proves otherwise.
- Slowly progressive or recurrent facial paralysis is suggestive of a neoplasm. Recurrent unilateral paralysis may occur with Bell's palsy but frequently (30%) is seen in patients with tumor.
- Simultaneous bilateral facial paralysis is suggestive of Lyme disease, especially in endemic regions.
- Patients with Bell's palsy should be treated early in the course with corticosteroids, prednisolone at 50 mg/day for 10 days. Antiviral medication, valacyclovir, 1000 mg orally three times daily for 7 days, or famciclovir, 750 mg orally for 7 days should be considered in patients with severe loss of function.

Vestibular Schwannoma

- The onset of unilateral auditory symptoms, especially sensorineural hearing loss, requires evaluation and referral to an ear, nose, and throat specialist.
- Neurologic symptoms of lower CN dysfunction, ataxia, or raised ICP may be caused by a benign tumor at the cerebellopontine angle.

Diabetic Cranial Mononeuropathy

- Diabetic neuropathy is a diagnosis of exclusion because no definitive diagnostic testing is available, although a CN III palsy with sparing of the pupillary response in a patient with a history of diabetes is classic for the presentation.
- Both ischemic and hemorrhagic brainstem lesions must be ruled out in the case of an acute ophthalmoplegia.
- Extraocular mononeuropathy is sufficiently common in patients with diabetes mellitus that its occurrence in isolation warrants evaluation of the patient for previously undiagnosed diabetes.

Cerebral Venous Thrombosis

- The differential diagnosis for CVT includes other conditions that present with new-onset neurologic deficits, alteration in consciousness, or severe headache. CVT is more likely to be present in these patients when the etiology is unclear, the patient is thought to have a hypercoagulable state, and the head CT is normal in appearance or shows subtle signs of CVT.
- Non–contrast-enhanced CT scanning is not adequate to rule out CVT. MRI with MRV is recommended, although multidetector row CT venography is an acceptable alternative.
- Treatment of most patients with CVT includes systemic anticoagulation, even in the setting of hemorrhagic cerebral infarcts, unless another contraindication exists.

Multiple Sclerosis

- MS should be suspected in patients who present with episodes of neurologic dysfunction that evolve over days and resolve over weeks.
- Apparent exacerbations of known MS can be brought on by other medical problems, most commonly infections.
- Therapy for patients with MS will require consultation with the patient's primary care provider or neurologist to provide consistent disease management.
- IV methylprednisolone, 250 to 500 mg every 12 hours for 3 to 7 days effectively promotes earlier resolution of recurrences.
- IV methylprednisolone has been shown to speed the recovery from vision loss from optic neuritis associated with MS.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 95: QUESTIONS & ANSWERS

95.1. A 53-year-old woman presents with complaints of increasing left facial pain. She describes a pattern of brief, excruciatingly painful lancinating sensations along the left jaw associated with chewing and brushing her teeth. She notes intermittent clusters of pain that last seconds to a minute and have not occurred at night. Physical examination is normal except for triggered left jaw and buccal pain with palpation of the left mandibular area. What is the most likely finding in this patient?

A. Analgesia from a left inferior alveolar nerve block
B. Analgesia from subcutaneous sumatriptan
C. Immediate pain relief with high-flow oxygen
D. Magnetic resonance imaging (MRI) evidence of multiple sclerosis (MS)
E. Vascular compression of the trigeminal nucleus

Answer: E. In 80% to 90% of cases of trigeminal neuralgia, a vascular compression of the trigeminal nucleus is found in series of surgical cases. Microvascular decompression of the trigeminal nerve is curative in a high percentage of patients who fail to respond to medical management. Approximately 5% of patients with trigeminal neuralgia have MS. Cluster headache and migraine treatments are not effective. Peripheral nerve block is also ineffective because the pathologic process is more central at the nucleus.

95.2. A 26-year-old man presents with complaints of left facial drooping. The symptoms began painlessly 3 days ago without a prodrome. Examination reveals a left facial droop with an inability to wrinkle the forehead without other associated physical examination abnormalities. Which of the following will provide the largest potential benefit to the patient's recovery?

A. High-volume lumbar puncture
B. Initiation of oral antiviral treatments
C. Initiation of oral corticosteroids
D. Intravenous (IV) thrombolysis
E. Urgent non–contrast-enhanced computed tomography (CT) scan of the head

Answer: C. The patient has Bell's palsy, which is a painless left facial nerve palsy. The primary symptom is a left peripheral nerve paralysis often with unilateral dysgeusia, hyperacusis (stapedius muscle paralysis), and external canal and pharyngeal numbness. Facial sensation is intact. Corticosteroids are helpful, and they should be initiated as far out as a week after onset, although they should be started within 24 hours if possible. Initiation of oral antiviral treatment has shown benefit in some trials, although conflicting evidence exists. In the absence of a contraindication and in a patient who can afford the medicine, antivirals should be considered. Given the classic picture and lack of other associated neurologic findings, CT scan of the head is not required and is not likely to provide benefit. Testing for Lyme disease is indicated in Lyme endemic areas or in patients with a history of a tick bite.

95.3. A 43-year-old woman presents with her fourth episode of left facial paralysis in 1 year. She denies prodrome or associated symptoms. Examination is consistent with an isolated left peripheral facial nerve paralysis. What should be the next step in her management?

A. Antinuclear antibody level and erythrocyte sedimentation rate
B. Carotid angiography
C. Initiation of antivirals and corticosteroids
D. Magnetic resonance imaging (MRI) scan
E. Neurology referral

Answer: D. A neoplastic cause should be suspected in patients who suffer from recurrent facial paralysis, significant pain, prolonged symptoms, or any associated cranial nerve (CN) dysfunction.

95.4. Which of the following statements regarding acoustic neuroma is *true?*

A. An audiogram has a sensitivity of greater than 95%.
B. Gadolinium-enhanced magnetic resonance imaging (MRI) is the diagnostic test of choice.
C. Symptom onset is generally during 1 to 3 months.
D. Symptoms of increased intracranial pressure (ICP) are common.
E. The symptoms of Ménière's disease are essentially identical.

Answer: B. Computed tomography (CT) lacks the posterior fossa sensitivity to detect small tumors. Although asymmetrical hearing loss is the hallmark of this disease, audiograms may be normal in up to 15% of cases. Symptom onset is generally during years rather than months. Although increased ICP can happen, it is uncommon. The tinnitus of Ménière's disease is typically intermittent rather than continuous.

95.5. Which of the following symptoms is not associated with diabetic cranial mononeuropathy?
A. Diplopia
B. Inability to move the eye inferolaterally
C. Nonreactive pupil
D. Orbital pain
E. Ptosis

Answer: C. Diabetic cranial mononeuropathy may affect the third, fourth, or sixth cranial nerve (CN). Pain, diplopia, and ptosis are common. Pupillary reactivity is usually preserved because these fibers are on the third nerve periphery and less affected by the occlusion of the "penetrating" neural nutrient artery affecting the core motor fibers. Inferolateral movement paralysis may be seen with a fourth nerve palsy and lateral paralysis with a sixth nerve palsy.

95.6. A 64-year-old diabetic woman presents with the acute onset of painless diplopia. She has a 25-year history of type 2 diabetes. Her only other past history is hypertension. Physical examination reveals normal vital signs and a normal neurologic examination with the exception of an inability to look laterally with the left eye. What is the most appropriate next step?
A. Cerebral angiography
B. Contrast-enhanced computed tomography (CT) scan
C. Magnetic resonance imaging (MRI) scan
D. Ophthalmology consultation
E. Patching the affected eye and initiation of antiplatelet therapy

Answer: C. Diabetic cranial mononeuropathy may affect the third, fourth, or sixth cranial nerve (CN). It is a diagnosis of exclusion, and brainstem ischemic or hemorrhagic lesions should also be considered. The long intracranial course of the sixth nerve makes MRI scanning particularly indicated to rule out a mass lesion. Once it is diagnosed, patching, analgesics, and antiplatelet therapy should be considered for management of this diabetic complication.

95.7. A 38-year-old woman presents 8 weeks postpartum with a 1-week history of severe headache and progressively altered mental status, which culminated in a seizure several minutes before presentation. On examination, she is normotensive, appears postictal, but has no focal neurologic findings. Ophthalmoscopic examination reveals papilledema, and non–contrast-enhanced head computed tomography (CT) reveals a dense sagittal sinus and a small venous hemorrhage in the occipital region. The next most appropriate management step is:
A. 325 mg aspirin per rectum
B. Dexamethasone 10 mg IV push
C. Hypertonic saline 500-mL bolus
D. Mannitol 1 g/kg
E. Systemic anticoagulation with unfractioned heparin or low–molecular-weight heparin (LMWH)

Answer: E. The patient presents with a dural sinus thrombosis. Although large, randomized trial data do not exist, case series and expert consensus strongly suggest improved outcomes with systemic anticoagulation, even in the setting of venous hemorrhage on head CT. Osmotic agents and steroids have no proven benefit in the management of sinus thrombosis and may cause harm. Antiplatelet agents may be considered if absolute contraindications to anticoagulation exist but probably have lower therapeutic efficacy.

95.8. A 20-year-old female college student presents with her third episode of bilateral foot numbness after a game of volleyball. Each episode has occurred approximately 1 or 2 hours after a full game of indoor volleyball, which she had no trouble completing. Each of the episodes of foot numbness resolved during 2 or 3 days with no residual symptoms. Her only other complaint is of falling grades in school due to subjective poor memory and distractibility. What would be the most likely finding in this patient?
A. Elevated cerebrospinal fluid (CSF) protein levels
B. Elevated erythrocyte sedimentation rate
C. Hypocalcemia
D. Increased intracranial pressure (ICP) on lumbar puncture
E. Thrombocytopenia

Answer: A. Presenting symptoms for multiple sclerosis (MS) may be myriad. Uhthoff's phenomenon is the finding in MS in which small increases in body temperature exacerbate neurologic symptoms temporarily. Almost any neurologic complaint or finding may be a feature of MS, with up to 60% having cognitive impairment. CSF analysis is abnormal in 90% of cases with a pleocytosis and elevated protein with oligoclonal bands. ICP is normal. Lumbar puncture is undertaken after magnetic resonance imaging (MRI), which is the initial imaging test of choice.

CHAPTER 96

Spinal Cord Disorders

Andrew D. Perron | J. Stephen Huff

PRINCIPLES

This chapter focuses on nontraumatic processes affecting the spinal cord and its vascular supply, as well as processes compressing the spinal cord. The ultimate neurologic outcome of patients with many of these disorders depends on expeditious recognition and management in the emergency department (ED).

Anatomy

In adults, the spinal cord is approximately 40 cm long and extends from the foramen magnum, where it is continuous with the medulla oblongata, to the body of the first or second lumbar vertebra. Like the brain, the spinal cord is covered by three meningeal layers: (1) the inner pial layer, (2) the arachnoid, and (3) the outer dural layer. At its lower end, the spinal cord tapers into the conus medullaris, where several segmental levels are represented in a small area. The lumbar and sacral nerve roots form the cauda equina as they descend caudally in the thecal sac before exiting the spinal canal at the respective foramina. The non-neural filum terminale runs from the tip of the conus and inserts into the dura at the level of the second sacral vertebra.

Two symmetrical enlargements of the spinal cord contain the segments that innervate the limbs. The *cervical enlargement* (cord level C5 to T1) gives rise to the brachial plexus and subsequently to the peripheral nerves of the upper extremity. The *lumbar enlargement* (L2 to S3) gives rise to the lumbosacral plexus and peripheral nerves of the lower extremity. The space surrounding the spinal cord within the spinal canal is reduced in the area of the enlargements, potentially leaving the cord more vulnerable to compression in these regions. At each segmental level, anterior (ventral) and posterior (dorsal) roots arise from rootlets along the anterolateral and posterolateral surfaces of the cord. At each level, the anterior root conveys the outflow of the motor neurons in the anterior horn of the spinal cord, and the posterior root contains sensory neurons and fibers that convey sensory inflow.

The arterial supply of the spinal cord is derived primarily from two sources. The single anterior spinal artery arises from the paired vertebral arteries. This anterior spinal artery runs the entire length of the cord in the midline anterior median sulcus and supplies roughly the anterior two thirds of the spinal cord. Blood supply to the posterior third of the spinal cord is derived from the smaller paired posterior spinal arteries. The anterior and the posterior spinal arteries receive segmental contributions from radicular arteries, the largest being the radicular artery of Adamkiewicz, which typically originates from the aorta between T8 and L4. The venous drainage of the cord largely parallels the arterial supply.

The internal anatomy of the spinal cord is divided into central gray matter, which contains cell bodies and their processes, and surrounding white matter, where the ascending and descending myelinated fiber tracts are located. These fiber tracts are organized into discrete bundles; the ascending tracts convey sensory information, and the descending tracts convey the efferent motor impulses and visceral innervation.

For clinical purposes, neuroanatomy of the spinal cord may be greatly simplified, as depicted in Figure 96.1. Tracts are named with the point of origin first; the spinothalamic tract, for example, arises in the spinal cord and travels to the thalamus. Major ascending sensory tracts are represented on the right side of the figure, with motor tracts on the left side. The posterior columns carry afferent ascending proprioceptive and vibratory information on the ipsilateral side of the cord to the area stimulated; decussation of these fibers occurs in the medulla so that contralateral cortical representation is consistent. The lateral spinothalamic tract conveys afferent information about pain and temperature in a portion of the lateral column of white matter. The tract is laminated so that sacral fibers are represented most laterally. Crossing of fibers from this tract occurs near the level of entry of the spinal nerve; a cord lesion affecting only one lateral spinothalamic tract results in decreased or absent pain and temperature perception below the level of injury on the contralateral side of the body.

For clinical purposes, the major descending motor tract is represented in the lateral corticospinal tract (which, as the name implies, originates in the cortex and descends to the spinal cord). This tract also is anatomically organized, with efferent motor axons to the cervical area located medially and the sacral efferent axons located laterally. Decussation of this descending tract occurs in the medulla. The cell bodies of the lower motor neurons (anterior horn cells) are in the ventral (anterior) portion of the gray matter of the spinal cord.

Classification of Spinal Cord Syndromes

The anatomic organization of the spinal cord lends itself to a corresponding anatomic-pathophysiologic classification of cord dysfunction. Any of the different anatomic syndromes may be the final clinical picture of a variety of clinical processes. The syndromes frequently exist in partial or incomplete forms, adding to the diagnostic challenge.

Complete (Transverse) Spinal Cord Syndrome

Complete spinal cord lesions may be manifested as either acute or subacute pathologic processes. A *complete* spinal cord lesion is defined as a total loss of sensory, autonomic, and voluntary motor innervation distal to the spinal cord level of injury. Reflex responses mediated at the spinal level, such as muscle stretch (deep tendon) reflexes, may persist, although they also may be absent or abnormal. Autonomic dysfunction may be manifested acutely with hypotension (neurogenic shock) or priapism. The most common cause of the complete transverse cord syndrome is trauma, although this anatomic syndrome may apply to any pathologic etiology. Other causes of acute complete cord syndrome include infarction, hemorrhage, and entities causing extrinsic compression. In patients with acute complete transverse syndromes that persist for more than 24 hours, functional recovery almost never occurs. Any evidence of preserved cord function below the level of injury denotes a partial rather than a complete lesion. Signs

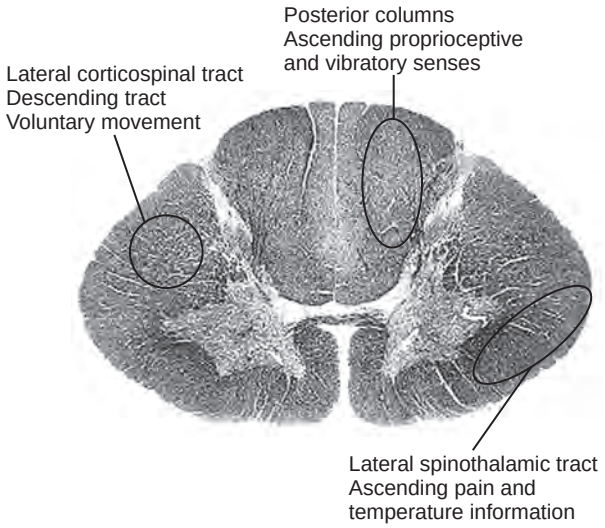


Fig. 96.1. Simplified spinal cord anatomy showing clinically essential motor and sensory tracts. (Photomicrograph courtesy John Sundsten, Digital Anatomist Project, University of Washington.)

such as persistent perineal sensation (sacral sparing), reflex rectal sphincter tone or voluntary rectal sphincter contraction, and even slight voluntary toe movement suggest a partial cord lesion, which carries a better prognosis than a complete lesion.[1]

Spinal shock refers to the loss of muscle tone and reflexes with complete cord syndrome during the acute phase of injury. Spinal shock typically lasts less than 24 hours but has been reported occasionally to last days to weeks. A marker of spinal shock is loss of the bulbocavernosus reflex, which is a normal cord-mediated reflex that may be preserved in complete cord lesions. The bulbocavernosus reflex involves involuntary reflex contraction of the anal sphincter in response to a squeeze of the glans penis or a tug on the Foley catheter. The termination of the spinal shock phase of injury is heralded by the return of the bulbocavernosus reflex; increased muscle tone and hyperreflexia follow later.

Incomplete Spinal Cord Lesions

Incomplete spinal lesions are characterized by preservation of function of various portions of the spinal cord. Of all incomplete spinal lesions, most can be classified generally as one of three clinical syndromes: (1) central cord syndrome, (2) Brown-Séquard syndrome, or (3) anterior cord syndrome (Table 96.1).

Central Cord Syndrome. Central cord syndrome is the most common of the partial cord syndromes. Because of the anatomic organization of the spinal cord, a central cord injury is characterized by bilateral motor paresis; upper extremities are affected to a greater degree than lower extremities, and distal muscle groups are affected to a greater degree than proximal muscle groups. Sensory impairment and bladder dysfunction are variable features. At times, burning dysesthesias in the upper extremities may be the dominant clinical feature.

Central cord injury affects the central gray matter and the central portions of the corticospinal and spinothalamic tracts. It is caused most often by a hyperextension injury; the postulated mechanism is squeezing or pinching of the spinal cord anteriorly and posteriorly by inward bulging of the ligamentum flavum. The most common causes are falls and motor vehicle accidents. The result is contusion to the spinal cord, with the central portion being most affected. This injury often occurs in elders with degenerative arthritis and spinal stenosis in the cervical area but may affect any patient with cervical canal narrowing of any etiology (eg, congenital narrow canal as seen in achondroplasia or acquired canal narrowing from disk protrusion or tumor). The prognosis with central cord syndrome depends on the degree of injury at presentation and the patient's age, with older age predicting a decreased functional outcome. In patients younger than 50 years old, more than 80% regain bladder continence and approximately 90% return to full ambulatory status. In patients older than 50 years old, only 30% regain bladder function and approximately 50% regain the ability to ambulate.

Brown-Séquard Syndrome. Brown-Séquard syndrome is the result of an anatomic or functional hemisection of the spinal cord. Usually associated with penetrating injuries, Brown-Séquard syndrome also may be seen with compressive or intrinsic lesions. The syndrome has been reported in association with spinal cord tumors, spinal epidural hematoma, vascular malformations, cervical spondylosis, degenerative disk disease, herpes zoster myelitis, and radiation injury and as a complication of spinal instrumentation.[1] The syndrome in its pure form is characterized by ipsilateral loss of motor function and proprioception or vibration, with contralateral loss of pain and temperature sensation below the spinal cord level of injury. Because fibers associated with the lateral spinothalamic tract ascend or descend one or two spinal cord segments before crossing to the contralateral side, ipsilateral anesthesia (pain and temperature modalities) may be noted one or two segments above the lesion, although this observation is variable. Most patients with Brown-Séquard syndrome incur only partial sensory and motor impairment, and the classic pattern is not seen. Brown-Séquard syndrome carries the best prognosis of any of the incomplete spinal cord syndromes. Fully 80% to 90% of patients with Brown-Séquard syndrome regain bowel and bladder function, 75% regain ambulatory status, and 70% become independent in their activities of daily living.

Anterior Cord Syndrome. Anterior cord syndrome is characterized by loss of motor function, pinprick, and light touch below the level of the lesion with preservation of posterior column modalities, including some touch, position, and vibratory sensation. Although most reported cases of anterior spinal cord syndrome follow aortic surgery, the syndrome also may occur after severe hypotension, infection, myocardial infarction, vasospasm from drug reaction, and aortic angiography.[2] The anatomic lesion may be caused by a cervical hyperflexion injury resulting in a cord contusion or by protrusion of bone fragments or herniated cervical disk material into the spinal canal. Rarely, it is produced by laceration or thrombosis of the anterior spinal artery or a major radicular feeding vessel.

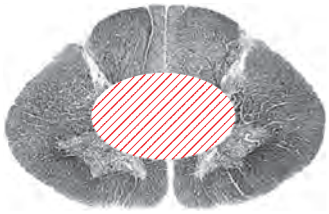
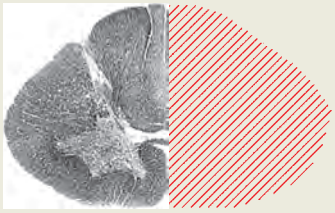
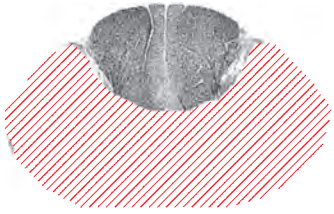
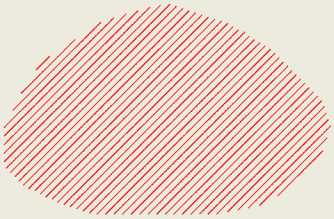
Patients present with characteristic mixed motor and sensory neurologic findings. Functional recovery varies; most improvement occurs during the first 24 hours, but little improvement is expected thereafter.[3] Although anterior cord lesions from ischemia usually are incomplete, patients without motor function at 30 days have little or no likelihood of regaining any motor function by 1 year. Overall, only 10% to 20% of patients with this entity regain some muscle function, and even in this group there is little power or coordination.

Conus Medullaris and Cauda Equina Syndromes

The separation of conus medullaris and cauda equina lesions in clinical practice is difficult because the clinical features of the disorders overlap. In addition, a combined lesion may occur that masks clear clinical symptoms or signs of either an upper or a lower motor neuron type of injury. The conus medullaris is the terminal end of the spinal cord, located at approximately the L1 level in adults.

TABLE 96.1

Spinal Cord Syndromes

SYNDROME	SENSORY	MOTOR	SPHINCTER INVOLVEMENT
 Central cord syndrome	Variable	Upper extremity weakness, distal > proximal	Variable
 Brown-Séquard syndrome	Ipsilateral position and vibration sense loss Contralateral pain and temperature sensation loss	Motor loss ipsilateral to cord lesion	Variable
 Anterior cord syndrome	Loss of pin and touch sensation Vibration, position sense preserved	Motor loss or weakness below cord level	Variable
 Transverse cord syndrome—complete	Loss of sensation below level of cord injury	Loss of voluntary motor function below cord level	Sphincter control lost
Conus medullaris syndrome	Saddle anesthesia may be present, or sensory loss may range from patchy to complete transverse pattern	Weakness may be of upper motor neuron type	Sphincter control impaired
Cauda equina syndrome	Saddle anesthesia may be present, or sensory loss may range from patchy to complete transverse pattern	Weakness may be of lower motor neuron type	Sphincter control impaired

The conus medullaris syndrome may involve disturbances of urination (usually from a denervated, spastic, autonomic bladder that is manifested clinically with overflow incontinence) and sphincter impairment or sexual dysfunction. Sensory involvement may affect the sacral and coccygeal segments, resulting in saddle anesthesia. Pure lesions of the conus medullaris are rare. Upper motor neuron signs, such as increased motor tone and abnormal reflexes, may be present, but their absence does not exclude the syndrome.

The conus medullaris syndrome can be caused by central disk herniation, neoplasm, trauma, or vascular insufficiency. Because the conus is such a small structure, with lumbar and sacral segments represented in a small area, a lesion usually causes bilateral symptoms. This finding may help distinguish conus medullaris lesions from those of the cauda equina, which often are unilateral.

The *cauda equina* (Latin for "horse's tail") is the name given to the lumbar and sacral nerve roots that continue on within the dural sac caudal to the conus medullaris. Not a true "cord syndrome," cauda equina syndrome represents dysfunction at the level of nerve roots, but the anatomic clustering of nerve roots within the lumbar dural sac allows injury to several nerve roots to occur simultaneously.

The etiologic lesion in the cauda equina syndrome usually is a midline rupture of an intervertebral disk, most commonly at the L4 to L5 level. Tumors and other compressive masses also may cause the syndrome. As in the conus medullaris syndrome, patients generally present with progressive symptoms of fecal or urinary incontinence, impotence, distal motor weakness, and sensory loss in a saddle distribution. Muscle stretch reflexes also may be reduced. Urinary retention is the most consistent finding, with a

sensitivity of 90%. A complaint of low back pain may or may not be present with cauda equina syndrome.

CLINICAL FEATURES

History

Weakness, sensory abnormalities, and autonomic dysfunction are the cardinal manifestations of spinal cord dysfunction. The tempo and degree of impairment often reflect the disease process. Past medical history is vital because a history of coagulopathy or other systemic processes may be elicited. A history of cancer should suggest the possibility of metastatic disease. Recent trauma raises the possibility of vertebral fracture or disk protrusion. The acuity of pain may help narrow the differential diagnosis. Sudden immediate pain or dysfunction is more likely to be a vascular catastrophe, whereas slower onset, midline location, and historical presence of fever points toward an infectious source.

Physical Examination

The physical examination pertinent to spinal cord dysfunction involves testing in three areas: (1) motor function, (2) sensory function, and (3) reflexes. Each component is best tested with the anatomic organization of the spinal cord in mind to help determine the level of the spinal cord dysfunction.

Motor Function

Testing of motor function encompasses examination of muscle bulk, tone, and strength. Muscle bulk is easily examined in large motor groups, such as the thigh or calf muscles, the biceps, and the triceps. Inspection of the intrinsic hand muscles also may be helpful for determination of muscle bulk; wasting may be evident as hollowed or recessed regions of the hand. Decreased mass, asymmetry, or fasciculations should be noted. Tone is tested with repeated passive knee, elbow, or wrist flexion, with the examiner assessing for abnormally increased or decreased resistance. Rapid pronation-supination of the forearm is another useful method to check tone. Increased tone may indicate spasticity or an upper motor neuron lesion, whereas decreased tone corresponds with lower motor neuron, motor end-plate, or muscle problems. Finally, motor strength is graded in the upper and the lower extremities. Motor grading for the neurologic examination is relatively straightforward. Note that a tremendous gradient of strength is within the fourth grade of the scale. Scored on a scale of 0 to 5, neuromuscular functioning is graded as shown in Table 96.2.

A rectal examination and the bulbocavernosus reflex are performed to assess voluntary sphincter contraction, and resting tone. Although it is not commonly thought of as a physical examination maneuver, a post-void residual urine volume is useful to evaluate bladder function. A post-void residual volume of more than 100 to 200 mL in a patient without prior voiding difficulty might suggest bladder dysfunction of neurologic cause.

TABLE 96.2

Grading of Neuromuscular Weakness

GRADE	PHYSICAL FINDINGS
0	No firing of the muscle is present.
1	The muscle fires but is unable to move the intended part.
2	The muscle is able to move the intended part with gravity eliminated.
3	The muscle is able to move the intended part against gravity.
4	The muscle is able to move the intended part but not at full strength.
5	Full muscle strength is present.

Sensory Function

Sensory testing requires a cooperative patient and an attentive examiner. The spinal cord–related modalities that may be clinically useful include testing for pinprick and light touch (contralateral lateral spinothalamic tract) and proprioception (ipsilateral posterior column). Assessment of the patient's response to pinprick, light touch, and proprioception in all four extremities is necessary if a neurologic injury is suspected. Testing of sacral dermatomes is indicated in patients with suspected cord injury in that sacral sparing suggests that spinal cord dysfunction may be incomplete. The sensory fibers from sacral dermatomes are more peripherally located in the ascending fiber bundles; central or partial cord lesions may ablate sensation in the extremities yet allow some perception of sensation in the sacral area.

Reflexes

Muscle stretch (deep tendon) reflexes are graded on a scale of 0 to 4+, with 2 being normal. Hyperactive reflexes suggest upper motor neuron disease (affecting the neurons or their outflow from the brain or spinal cord), as do sustained clonus and Babinski's sign. If present, hyperactive or abnormally brisk reflexes may be a key finding suggesting a myelopathy. However, absence of hyperreflexia does not exclude a myelopathy. Reflexes may be diminished or absent when sensation is lost or when spinal shock is present. Diseases of muscles or neuromuscular junctions also may decrease reflexes. In acute cord injury, reflexes may be diminished in the acute phase. The bulbocavernosus reflex may be helpful in this assessment.

DIFFERENTIAL DIAGNOSIS

The prime principle in management of spinal cord dysfunction is to consider and exclude potentially treatable clinical conditions. The clinician should rule out any nonstructural cause of neurologic dysfunction (eg, hypoglycemia, hypokalemia) early in the evaluation process. The next step, once a neurologic entity is suspected, is to try to differentiate the location of the lesion (brain versus spinal cord versus motor end-plate). When the pathologic process is suspected to be spinal in origin, liberal use of consultation and imaging is recommended. Spinal cord diseases may mimic many other disease processes, and neither the history nor physical examination may allow diagnosis until appreciable neurologic dysfunction has developed.

The picture of a *complete* transverse spinal cord syndrome with paraplegia, sensory loss at a clear anatomic level, and sphincter dysfunction cannot be fully simulated by other anatomic lesions. *Incomplete* or evolving spinal cord syndromes may be imitated by other disease processes. Ataxia may be a finding in cerebellar disease but also has rarely been reported as an isolated finding with spinal cord compression. Another example is rapidly progressive paralysis in a patient with areflexia and quadriplegia; ascending paralysis (Landry-Guillain-Barré syndrome) at times may mimic an acute cord lesion.

In general, pathologic processes involving the spinal cord may be divided into processes affecting the cord or its blood supply primarily, such as demyelination, infection, or infarction, and processes that compress the cord, most often originating outside the dura (see Table 96.2). *Myelitis* is a comprehensive term for spinal cord inflammation with dysfunction, and the potential causes are

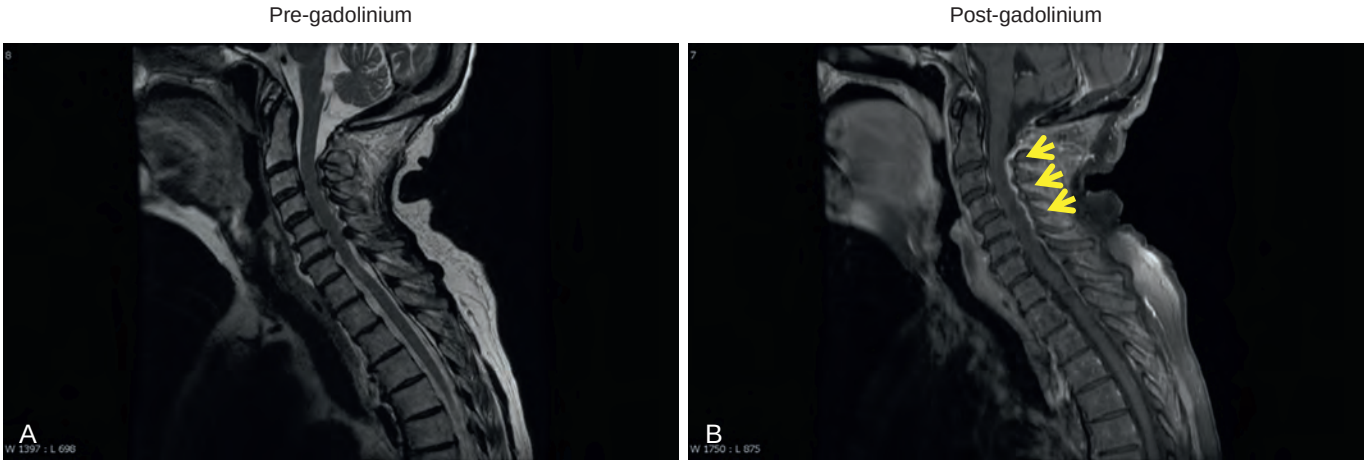


Fig. 96.2. 90-year-old female with recent pyelonephritis presenting with severe neck pain. Pre-gadolinium sequence **(A)** compared with post-gadolinium sequence **(B)** demonstrates posterior spinal epidural abscess (SEA) *(yellow arrowheads).*

legion. The clinical presentation is often similar across the variety of entities that may cause cord compression. The tempo of the process may yield a different clinical picture. In chronic compression, muscle wasting and abnormal reflexes may be present, whereas both of these may be lacking in acute compression. A neurologic deficit in concert with back pain strongly suggests a spinal cord lesion causing compression of neural elements, necessitating prompt investigation to identify a specific cause.

DIAGNOSTIC TESTING

The basic strategy for diagnostic testing in patients suspected of having spinal cord dysfunction is to detect or exclude extrinsic compressive lesions or other potentially treatable entities. Though plain radiographs and computed tomography (CT) scans may show bone and some soft tissue abnormalities, magnetic resonance imaging (MRI) has changed the diagnostic approach. Conventional radiographs and CT scans are required in patients with trauma or suspected bone involvement by tumor or degenerative processes, but MRI shows many of these abnormalities and defines the spinal cord, as well as the soft tissue structures associated with it. MRI may also detect tissue damage patterns within the cord, such as hemorrhage and edema. When MRI is used to assess the spinal cord, assessment of the entire spine should be considered because frequently there are lesions at multiple levels.

Gadolinium contrast enhancement with MRI is indicated when looking for pathology that will affect the blood–central nervous system (CNS) barrier. Specific indications include a search for primary or metastatic tumor, multiple sclerosis (MS), and spinal infections, including spinal epidural hematoma, discitis and osteomyelitis. An example of the utility of gadolinium-enhancement when searching for an infectious etiology is seen in Figure 96.2. CT myelography is an option when an MRI is unavailable or contraindicated, although it does not yield the same level of detail.

After imaging studies exclude compressive lesions or other masses affecting the spinal cord, the possibility of inflammatory or demyelinating disorders remains. In these cases, lumbar puncture with cerebrospinal fluid (CSF) analysis may be diagnostic.

MANAGEMENT

The treatment of many of the disease processes causing spinal cord dysfunction is nonspecific and based on limited evidence.

BOX 96.1

Nontraumatic Causes of Spinal Cord Dysfunction

PROCESSES AFFECTING THE SPINAL CORD OR BLOOD SUPPLY DIRECTLY

MS
Transverse myelitis
Spinal arteriovenous malformation, subarachnoid hemorrhage
Syringomyelia
HIV myelopathy
Other myelopathies
Spinal cord infarction

COMPRESSIVE LESIONS AFFECTING THE SPINAL CORD

Spinal epidural hematoma
SEA
Diskitis
Neoplasm
Metastatic
Primary CNS

CNS, Central nervous system; *HIV,* human immunodeficiency virus; *MS,* multiple sclerosis; *SEA,* spinal epidural abscess.

Steroid administration had been traditionally recommended as therapy in spinal cord trauma, although the benefit has been seriously questioned (Chapter 36).[3] Steroids have also been used with many nontraumatic causes of cord compression despite the lack of rigorous clinical studies supporting this use (Box 96.1). Based on available evidence, we cannot recommend the use of steroids for the acute management of spinal cord compression syndromes. Radiation treatment is recommended for cord compression by tumor. Surgical consultation for decompression may be considered, although the indications and timing for surgery are controversial.

SPECIFIC DISEASE PROCESSES

Spinal cord disorders are grouped into lesions resulting from processes intrinsic to the cord or vasculature and lesions causing extrinsic compression (see Table 96.2).

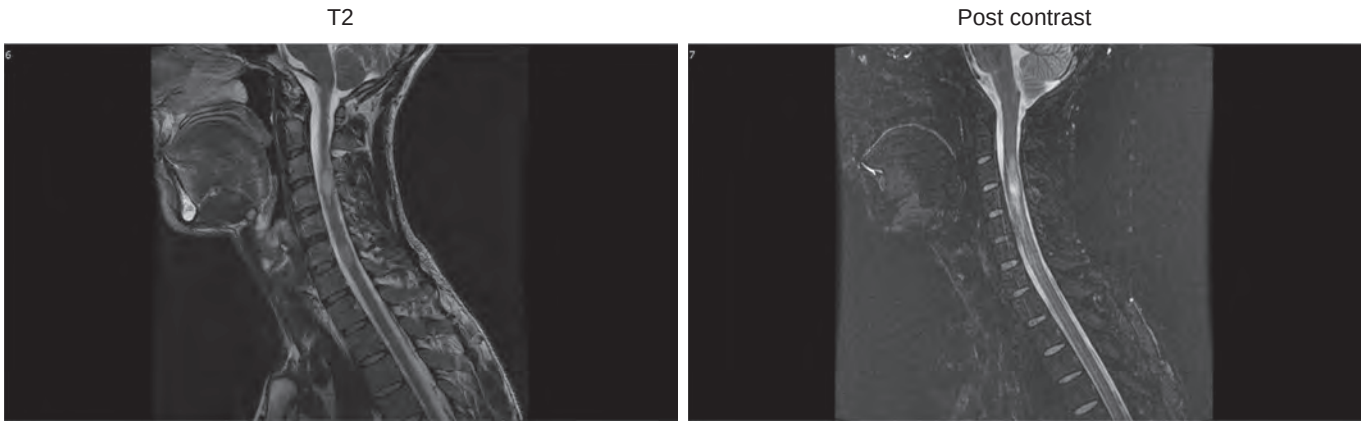


Fig. 96.3. Cervical spine magnetic resonance imaging (MRI) (T2 **[A]** and post-gadolinium **[B]** enhancement) demonstrating characteristic findings of demyelination associated with multiple sclerosis (MS).

Intrinsic Cord Lesions

Multiple Sclerosis

Demyelination denotes a disease process with the prominent feature of partial or complete loss of the myelin surrounding the axons of the CNS. MS is the most common example of such a process; spinal cord involvement may dominate the clinical picture. The spinal cord will be involved with MS in as many as 90% of patients. In approximately 20% of patients with MS, the spinal cord lesions will be the only area where plaques are identified (Fig. 96.3).[4] The pathophysiology, diagnosis, and management of MS is discussed in Chapter 95.

Transverse Myelitis

Principles. *Acute transverse myelitis* refers to acute or subacute spinal cord dysfunction characterized by paraplegia, a transverse level of sensory impairment, and sphincter disturbance. It describes a heterogeneous group of inflammatory disease processes that can affect the spinal cord by interruption of the ascending or descending pathways in the spinal cord.[5] The presentation may be mimicked by compressive lesions, trauma, infection, or malignant infiltration.

The pathogenesis of transverse myelitis is unknown, although it is noted to follow viral infection in approximately 30% of patients and commonly is termed *postinfectious myelitis.* Other postulated etiologic categories include infectious, autoimmune, and idiopathic. It can also be seen with a wide variety of connective tissue diseases, such as lupus, Sjögren's syndrome, antiphospholipid syndrome, and other mixed-connective tissue diseases. No apparent cause of acute transverse myelitis is identified in 30% of the patients. Progression of symptoms usually is rapid, with 66% of the cases reaching maximal deficit by 24 hours. Symptoms may progress, however, over days to weeks. The thoracic cord region is affected in 60% to 70% of cases.[38] The cervical spinal cord is rarely affected.

Clinical Features. In addition to motor, sensory, and urinary disturbances, patients with acute transverse myelitis may complain of back pain and may have low-grade fever, raising concern for spinal epidural abscess (SEA). As with MS, the examination may reveal weakness progressing to paresis, hypertonia, hyperreflexia, clonus, and Babinski's response. Spinal cord involvement also can result in dysautonomias (ie, dysfunction of the autonomic nervous system).

Differential Diagnosis. Considerations in the differential diagnosis for transverse myelitis include MS, SEA or hematoma, primary or metastatic spinal neoplasm, and spinal cord infarct.

Diagnostic Strategies. MRI with gadolinium enhancement is the diagnostic modality of choice for patients with suspected transverse myelitis. In cases of diagnostic uncertainty, a lumbar puncture may be performed; however, the results of CSF studies are normal in 40% of cases, with only mildly elevated protein level or pleocytosis in the remaining 60%. The most essential aspect of the evaluation is to eliminate a potentially treatable cause, such as SEA, neoplasm, or hematoma.

Management. Treatment of transverse myelitis is tailored to the suspected underlying etiology. There are no good studies supporting a role for steroids. Neurologic consultation is suggested, and hospitalization usually is required.

The clinical course of acute transverse myelitis varies widely, ranging from complete recovery to death from progressive neurologic compromise. Most patients with idiopathic disease have at least partial recovery, which usually begins within 1 to 3 months. Maximal improvement usually is obtained within 3 to 6 months with 30% of patients having a good recovery, 25% a fair recovery, and 30% a poor outcome; there is 15% mortality at 5 years.

Spinal Subarachnoid Hemorrhage

Principles. Intraspinal hemorrhage is rare and may occur in the same anatomic locations as intracranial hemorrhages; epidural, subdural, subarachnoid, and intramedullary hemorrhages are all possible.[4] Spinal subarachnoid hemorrhage usually is caused by an arteriovenous malformation.[5] Hemorrhage from tumors or cavernous angiomas and spontaneous hemorrhage secondary to anticoagulation therapy also have been reported. Bleeding may occur exclusively in the subarachnoid space or within the substance of the spinal cord itself.

Clinical Features. Patients with spinal subarachnoid hemorrhage present with excruciating back pain of sudden and severe onset at the level of the hemorrhage. This pain also may be in a radicular distribution or extend into the flank. Patients may complain of headache and exhibit cervical rigidity if the blood migrates into the intracranial subarachnoid space, simulating an intracranial subarachnoid hemorrhage. Variable neurologic deficits depend on the magnitude and anatomic location of the

hemorrhage. These deficits typically include extremity numbness, weakness, and sphincter dysfunction. Nuchal rigidity or signs of meningeal irritation may also be present. Although this is a rare etiology, when the back pain or neurologic dysfunction is sudden in onset, spinal hemorrhage should be considered.

Differential Diagnosis. Considerations in the differential diagnosis include epidural abscess, tumor, transverse myelitis, ischemia from aortic dissection, and anterior spinal artery thrombosis.

Diagnostic Testing. Because bone artifact may obscure presence of blood in the spine, the diagnostic study of choice in patients with suspected spinal subarachnoid hemorrhage is a MRI without contrast. Lumbar puncture also can confirm the presence of blood in the CSF. Angiography may be recommended if arteriovenous malformation is suspected.

Management. The treatment of spinal subarachnoid hemorrhage depends on the etiology of the hemorrhage. Neurosurgical referral is obtained for further evaluation and for clot evacuation if compression is present.

Syringomyelia

Principles. Syringomyelia is the presence of a cavitary lesion within the substance of the spinal cord. A syrinx usually is a chronic progressive lesion, and its location within the cord determines the constellation of neurologic findings on examination. Ninety percent of patients with syringomyelia have Arnold-Chiari I malformation (projection of cerebellar tonsils and medulla into the spinal canal). Syringomyelia also may result from spinal cord trauma (often months to years later) or compressive tumors, or it may follow meningitis.

Clinical Features. Headache and neck pain are the most common presenting complaints of patients with a syrinx, followed by sensory disturbance, gait disorder, and lower cranial nerve dysfunction. Symptoms may be exacerbated by a sneeze, cough, or Valsalva maneuver. The symptoms of syringomyelia develop and progress in accordance with the intracavitary pressure and location of the syrinx.

The most common features on physical examination are lower limb hyperreflexia, weakness and wasting in the hands and arms, dissociated sensory loss, and gait disorder. The classic pattern of sensory deficit involves a loss of pain and temperature sensation in the upper extremities with preservation of proprioception and light touch. This phenomenon is described as a "dissociative anesthesia" because of the discrepant loss of sensory modalities. The sensory deficit often is described as being in a "capelike" distribution over the shoulders and arms. The anatomic basis for the neurologic features of a syrinx is the location near the central canal. Crossing fibers of the lateral spinothalamic tract carrying pain and temperature fibers may be impaired. Crude touch, position, and vibratory sensation typically are unaffected. Sensory fibers from the lower limbs are similarly spared.

Differential Diagnosis. Considerations in the differential diagnosis for syrinx include intrinsic spinal tumor and demyelination.

Diagnostic Testing. Syringomyelia is best seen on MRI. No other study currently in widespread use is equal to MRI in diagnostic ability.

Management. When the diagnosis of syringomyelia is considered, emergent imaging in the ED is not necessary if follow-up evaluation can be arranged; in approximately two thirds of patients this condition is a slowly progressive process. In patients for whom MRI studies are obtained and the diagnosis is made, referral to a neurosurgeon is indicated.

Human Immunodeficiency Virus Myelopathy

Human immunodeficiency virus (HIV) myelopathy typically occurs in patients with advanced disease. Weakness, gait disturbance, sphincter dysfunction, sensory abnormalities, and signs of spasticity are features of this progressive process. This is a diagnosis of exclusion because disorders such as toxoplasmosis, lymphoma, varicella-zoster, and cytomegalovirus infection may produce a similar clinical picture in immunocompromised patients. On pathologic examination, vacuolization of myelin sheaths in the cord may be found. Treatment is directed at the retroviral infection.

Spinal Cord Infarction

Spinal cord infarction is another diagnosis of exclusion. Aortic dissection, surgery, and global ischemia are the more common causes, although this disorder may occur as a complication of systemic lupus erythematosus, vasculitis, or may be cryptogenic. An anterior spinal cord syndrome is the most common clinical picture. Recovery is variable and depends on the etiology.

Extrinsic Cord Lesions

Spinal Epidural Hematoma

Principles. Spinal epidural hematoma is a relatively rare condition. The etiology may be traumatic after lumbar puncture, epidural anesthesia, or spinal surgery. Spinal epidural hematoma is more likely to occur in anticoagulated or thrombocytopenic patients or in patients with liver disease or alcoholism. Spontaneous bleeding is rare but may arise from spinal or dural arteriovenous malformation or vertebral hemangioma. Approximately one fourth to one third of all cases are associated with anticoagulation therapy, including low-molecular-weight heparin.

Clinical Features. The patient with a spinal epidural hematoma usually presents with sudden, severe, constant back pain with a radicular component. Onset may follow a straining episode. The pain is often worsened by percussion over the spine and maneuvers that increase intraspinal pressure, such as coughing, sneezing, or straining.[6] The pain often causes the patient to seek care before the development of neurologic signs, possibly leading to delays in diagnosis. Neurologic deficits follow and may progress during hours to days.

The patient usually is in significant distress from the pain. Motor and sensory findings depend on the level and size of the hematoma and can include weakness, paresis, loss of bowel or bladder function, and virtually any sensory deficit.

Differential Diagnosis. Considerations in the differential diagnosis include abscess, epidural neoplasm, acute disk herniation, and spinal subarachnoid hemorrhage.

Diagnostic Testing. MRI (with and without intravenous [IV] contrast) is the diagnostic study of choice.

Management. In patients with a spinal epidural hematoma, recovery without surgery is rare. Neurosurgical consultation for emergent decompressive laminectomy is indicated as soon as the diagnosis is considered. Functional recovery is related primarily to the length of time the symptoms are present. Recovery after 72

hours of symptoms is rare but has been reported even without surgery.

Spinal Epidural Abscess

Principles. SEA is an infectious process usually confined to the adipose tissue of the dorsal epidural space, where there is a rich venous plexus. Major risk factors include diabetes, injection drug abuse, chronic renal failure, alcoholism, and immunosuppression, although the disease can be seen in patients who have none of these conditions.[7,8] Recent infection is also a described risk factor. Whereas the disease may be manifested in subacute and chronic forms, the acute presentation is seen most frequently in the ED.

Thoracic and lumbar sites of infection predominate, with cervical epidural abscess being much less common. Infection typically extends over four or five spinal vertebral segments. The dura mater limits the spread of an epidural infection, making subdural or intraspinal spread uncommon. Hematogenous spread of infection to the epidural space is the most common source (seen in 26% to 50% of cases), either to the epidural space or to the vertebra with extension to the epidural space.

Skin and soft tissue infections are the most frequently identified source, reported in 15% of cases; *Staphylococcus aureus* is the most prevalent organism, being cultured in more than 50% of cases. Other frequently identified pathogens include aerobic and anaerobic streptococci, *Escherichia coli,* and *Pseudomonas aeruginosa*. Multiple organisms are identified in approximately 10% of cases; no organism is identified in 40%.With SEA, damage to the spinal cord can be caused by direct compression on neural or vascular structures, by thrombosis and thrombophlebitis of nearby veins, or by a focal vasculitis mediated by bacterial and inflammatory substances.

Clinical Features. The classic clinical presentation of SEA begins with a backache that progresses to localized back pain often associated with tenderness to percussion. The duration of symptoms is typically a few days but may extend for weeks. Fever, sweats, and rigors are reported in 30% to 75% of patients. The classic triad of back pain, fever, and progressive neurologic deficits is present in only a few patients, however, and delayed clinical diagnosis is common. Radicular symptoms may not be present initially but usually develop as the disease progresses.

Without treatment, myelopathic signs will develop, usually beginning with bowel and bladder disturbance. Weakness ensues, followed by paraplegia or quadriplegia. Approximately 10% of patients with SEA present with delirium.

Differential Diagnosis. Any compressive spinal lesion can mimic SEA.

Diagnostic Testing. MRI with IV contrast is the imaging modality of choice and should be performed emergently if the diagnosis of SEA is entertained. Spinal CT is not recommended due to bone artifact.

A complete blood count may support the diagnosis, although it is neither a sensitive nor specific test; a leukocytosis is commonly present with a typical white blood cell count of 13,000 to 16,000/μL. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests, although not specific for epidural abscess, are virtually always elevated with this condition and have been used as screening tests for SEA in an "at-risk" population.[8] In one study, an elevated ESR or CRP had a sensitivity of 100% and a specificity of 67% for identifying an SEA. External validation is needed, but this may be a future promising risk-stratification method.[11]

Lumbar puncture is relatively contraindicated with known epidural abscess. If performed, CSF findings are consistent with a parameningeal infection, showing elevation of protein and some increase in inflammatory cells.

Management. Urgent surgical consultation for decompression usually is required. Antibiotics effective against the most common pathogens (particularly *S. aureus*) should be started empirically. One possible regimen that covers gram-positive and gram-negative organisms consists of a third-generation cephalosporin (ceftriaxone 2000 mg every 24 hours) plus vancomycin (15 to 20 mg/kg IV every 8 to 12 hours), both given intravenously, plus rifampin (10 mg/kg by mouth or IV once a day).

Outcome is related to the speed of diagnosis before the development of myelopathic signs. The disease is fatal in up to 25% of cases, and patients with neurologic deficit rarely improve if surgical intervention is delayed more than 12 to 36 hours after onset of paralysis. Patients operated on before development of neurologic symptoms generally have good outcomes.

Diskitis

Principles. Diskitis is an uncommon primary infection of the nucleus pulposus, with secondary involvement of the cartilaginous endplate and vertebral body. It may occur after surgical procedures or spontaneously, the latter being more common in pediatric patients.[9] An increased incidence of diskitis has been noted in immunocompromised patients and in patients with systemic infections. The lumbar spine is the most common site of disease. Both a chronic disease and a more common acute course have been described.[9]

Clinical Features. Patients present with moderate to severe pain, localized to the level of involvement and exacerbated by almost any movement of the spine. Elevated temperature is noted in more than 90% of patients. Radicular symptoms are present in 50% to 90% of cases. However, neurologic deficits are the exception with diskitis. Often there is a latent period (2 to 8 weeks) between the onset of back pain and the development of other clinical symptoms or abnormalities on the physical examination. *S. aureus* is the most common pathogen, but gram-negative, fungal, and tuberculous infections all have been recognized.

Differential Diagnosis. Considerations in the differential diagnosis include vertebral osteomyelitis, SEA, neoplasm, and hematoma.

Diagnostic Testing. Plain radiographs usually are not helpful for early diagnosis of diskitis, but destruction of the disk space is highly suggestive if present. The radiographic findings become abnormal after 2 to 4 weeks of disease. In addition to disk space narrowing, plain films may show irregular destruction of the vertebral body endplates.

MRI with IV contrast is the radiographic study of choice, because it not only diagnoses diskitis but also rules out paravertebral or epidural abscess. Laboratory studies often show an elevated ESR, but the white blood cell count usually is normal.[13]

Management. With timely diagnosis and treatment, outcome generally is good, and medical treatment with IV antibiotics that cover staphylococcus and streptococcus in accordance with local resistance patterns is usually curative. We recommend a combination of IV vancomycin (10 to 15 mg/kg) plus IV ceftriaxone (2 gm). If the infectious agent is known or suspected to be pseudomonas, then cefepime (2 gm) could be substituted for ceftriaxone. In patients with a severe penicillin allergy or contraindication to a cephalosporin, meropenem (2 gm) or aztreonam (2 gm) may be substituted for ceftriaxone. Finally, in patients

with a vancomycin allergy or high resistance, linezolid (600 mg) is recommended. Surgery is generally not necessary.

Neoplasm

Principles. Spinal cord tumors are classified according to their relationship to the dura and spinal cord (extradural, intradural extramedullary, and intradural intramedullary). Spinal cord tumors produce neurologic symptoms by compression, invasion, or destruction of myelinated tracts. The resulting neurologic symptoms are directly related to the growth rate and the location of the tumor. Spinal cord tumors account for 4% to 10% of CNS tumors but for only 1% of all cancers. Most tumors affecting the spinal cord are metastatic. Approximately 10% of patients with known cancer are diagnosed with a spinal metastasis at some point in the course of their disease, and 5% to 10% of patients ultimately diagnosed with cancer first present with a spinal metastasis.[2] Lung cancer, breast cancer, and lymphoma represent more than 50% of the primary malignant neoplasms that subsequently develop spinal metastasis, spreading by both the hematogenous route and direct extension. Most metastases occur in the thoracic spine, and nearly 20% of patients with tumor spread to the spine will have disease at multiple levels.

Clinical Features. In 95% of patients with spinal neoplasm, the initial complaint is pain, either in the back at the level of the tumor or in a radicular distribution. Pain often is characterized as dull, constant, and aching and commonly is said to worsen with recumbency (in contrast with the pain of herniated disk). Nighttime pain that is severe is characteristic of spinal neoplasm. Any action that increases intraspinal pressure (Valsalva maneuver, sneeze, cough) may be associated with increased pain. Neurologic deficits vary by the location of the lesion. Besides a thorough neurologic examination, a search for possible primary sites should be done on the physical examination.

Differential Diagnosis. Considerations in the differential diagnosis include any of the compressive lesions (eg, hematoma, infection). Tumor can also mimic intrinsic spinal cord lesions, such as transverse myelopathy and cord infarction.

Diagnostic Testing. Plain radiographs are usually the initial imaging modality in patients with new back pain and no known diagnosis of cancer. The sensitivity and specificity of plain radiographs in detecting abnormalities consistent with malignancy are 60% and 95%, respectively. In the presence of normal radiographs, a normal ESR is diagnostically helpful, in that cancer is very unlikely in a patients with an ESR <20 mm and no risk factors for cancer. Patients with neurologic abnormalities, a history of cancer, and suspicious findings on plain films or elevated ESR are candidates for emergent MRI with IV contrast; CT myelography is an option if MRI is unavailable or the patient has an implantable device precluding MRI.

Management. Acute compressive myelopathy from neoplasm constitutes an oncologic emergency. Immediate treatment is required to preserve function and to prevent deterioration. With onset of paraplegia and incontinence, less than 5% of patients regain ambulatory status. Of patients who are ambulatory at the time of diagnosis, 60% remain ambulatory. High-dose steroids (30 to 100 mg prednisone or equivalent per day), radiotherapy, and surgery all may be necessary acute interventions.

KEY CONCEPTS

- When faced with neurologic dysfunction, the clinician needs to narrow probable location down to brain, cord, or motor end-plate by history and physical examination.
- Complete cord syndromes are characterized by total loss of voluntary motor, sensory, and autonomic innervation distal to the level of cord injury. Partial cord injuries are characterized by sparing of some of these modalities.
- The bulbocavernosus reflex is cord-mediated. Return of this reflex following a spinal injury marks the termination of spinal shock.
- Central cord syndrome is frequently the result of hyperextension injuries in the setting of a narrowed cervical canal producing a syndrome of upper extremity > lower extremity effect marked by weakness > sensory deficits.
- Anterior cord syndrome is marked by symmetrical motor loss but intact proprioception and vibration sense.
- In patients with sudden severe back pain, consider spinal subarachnoid hemorrhage or spinal epidural abscess (SEA).
- Myelitis is an inflammation of the spinal cord often caused by a viral infection; steroids have no proven benefit. MRI with contrast enhancement is the diagnostic modality of choice.
- Cauda equina syndrome can be difficult to differentiate from conus lesions because both can result in overflow bladder/fecal incontinence, leg weakness, and sensory loss in the perineum. Conus lesions are more typically bilateral, whereas cauda equina syndrome is unilateral. Upper motor neuron findings are expected with conus lesions but not cauda equina syndrome.
- The diagnostic imaging of choice in the majority of suspected spinal disorders is a MRI with contrast.
- A syrinx is a cavitary lesion in the spinal cord that presents with a sensory disassociation predominately in the upper extremities. With progression, it can lead to upper extremity weakness/wasting. Exacerbation with cough or Valsalva is typical.
- With compressive lesions of the spinal cord, duration of neurologic dysfunction is directly related to ultimate neurologic outcome. The diagnosis should be made expeditiously and definitive therapy begun as soon as possible.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 96: QUESTIONS & ANSWERS

96.1. Which of the following physical findings indicates a partial rather than a complete cervical spinal cord lesion?
- **A.** Horner's syndrome
- **B.** Hypotension
- **C.** Intact perineal sensation
- **D.** Priapism
- **E.** Reflex tachycardia

Answer: C. Persistent perineal sensation, rectal sphincter tone, or even trace toe movement suggests a partial spinal cord lesion. This offers a far better prognosis than a complete transection.

96.2. Which of the following physical findings is a marker for spinal shock?
- **A.** Babinski's response present
- **B.** Bulbocavernosus reflex absent
- **C.** Lower extremity hyperreflexia present
- **D.** Perineal sensation present
- **E.** Priapism present

Answer: B. The bulbocavernosus reflex is a cord-mediated reflex signified by reflex contraction of the anal sphincter in response to squeezing of the glans penis or tugging on the Foley catheter. The termination of spinal shock is heralded by return of this reflex followed by increased muscle tone and hyperreflexia.

96.3. A 49-year-old man presents after a moderate-speed motor vehicle collision. He was an unrestrained driver who was rear-ended at a stop light. He suffered no head impact but reported a whiplash mechanism and complains of neck pain and a mild burning sensation in both palms. Vital signs and physical examination are unremarkable except for posterior cervical paraspinous muscle tenderness and modest allodynia of both palms and fingertips in a nondermatomal distribution. What is the expected finding on magnetic resonance imaging (MRI)?
- **A.** Anterior spinal cord ischemia
- **B.** C5–6 traumatic spondylolisthesis
- **C.** Cervical canal stenosis
- **D.** Normal MRI
- **E.** Unilateral C5–6 disk protrusion

Answer: C. Central cord syndrome is a typically post-traumatic event in either elderly individuals with degenerative cervical canal narrowing (osteophytes, ligamentum flavum hypertrophy, facet overgrowth) or younger individuals with congenitally narrowed canals. A hyperextension mechanism in the setting of a narrow canal produces a central cord impingement with an upper > lower extremity motor > sensory deficit pattern. Bladder dysfunction is variable. Early MRI may show no actual cord changes and only the canal narrowing. Upper extremity dysesthesia may be the only symptom.

96.4. A 73-year-old man is brought to the ED by family members for weakness. His only past history is peripheral vascular disease. He is found to be in septic shock and resuscitated with fluid, antibiotics, blood, and vasopressors. He ultimately requires both dopamine and norepinephrine for maintenance of a mean arterial pressure greater than 60 mm Hg. Approximately 5 hours after arrival, he develops bilateral lower extremity weakness. He has no prior history of back pain or neurologic problems. Which of the following is likely?
- **A.** A similar neurologic syndrome after a cervical hyperflexion injury
- **B.** Finding of a mass lesion on MRI
- **C.** Finding of an epidural hematoma
- **D.** Preservation of lower extremity temperature sensation
- **E.** Progressive return of function after 24 hours

Answer: A. Anterior cord syndrome is typically characterized by symmetrical loss of motor function and pain and temperature sensation (both tracts being located in the anterior portion of the cord). Proprioception and vibration sense are usually maintained. Although it may occur after a cervical flexion injury, it is most likely seen after periods of hypotension or instability, such as shock, infection, and myocardial infarction. Most improvement occurs in the first 24 hours.

96.5. What feature most likely distinguishes a conus medullaris from a cauda equina lesion?
- **A.** Back pain
- **B.** Bilateral symptoms
- **C.** Distal motor weakness
- **D.** Sacral anesthesia
- **E.** Urinary incontinence

Answer: B. Isolated conus lesions are rare, but because of the small size, they frequently result in bilateral symptoms. Cauda equina syndrome more frequently results in unilateral findings. An additional distinguishing feature may be the presence of upper motor neuron findings in conus medullaris syndrome. Both syndromes may cause overflow bladder incontinence, fecal incontinence, leg weakness, and sensory loss in the perineum.

96.6. A 27-year-old woman presents with complaints of back pain and difficulty walking. Her symptoms have been progressive for 2 days. She has no significant past medical history. Her only other symptom was a bout of influenza approximately 3 weeks prior. Physical examination is remarkable for lower extremity hyperreflexia, moderate symmetrical lower extremity weakness, moderate increased tone, a T10 level of sensory loss, and a postvoid residual urine volume of 350 mL. What should be the next intervention?
- **A.** Antibiotics
- **B.** Complete blood count, erythrocyte sedimentation rate (ESR), and antinuclear antibody levels
- **C.** MRI scan

D. Neurology consultation
E. Steroids

Answer: C. Transverse myelitis is postinfectious in 30% of cases and also idiopathic in 30%. Other causes are autoimmune disorders and infections. Symptoms are typically rapid in onset and progress during 1 or 2 days. Back pain may accompany it. Emergent MRI is indicated to rule out other causes. There is no proven efficacious treatment, although steroids have been used. There is an association with multiple sclerosis (MS). Prognosis for recovery is only fair.

96.7. Which of the following characteristics is a feature of syringomyelia?
A. Absence of neck pain
B. Exacerbation with cough or Valsalva maneuver
C. Loss of vibrating sensation in the arms
D. Normal cervical MRI
E. Normal lower extremity examination

Answer: B. Syringomyelia typically presents with headache, neck pain, and variable upper extremity dissociative anesthesia: symmetrical loss of pain and temperature sensation with preserved posterior column function. With progression, upper extremity weakness or wasting and lower extremity upper motor neuron changes are expected. Exacerbation with cough and the Valsalva maneuver is typical. There is a 90% association with type I Arnold-Chiari malformation (cerebellar tonsils and medulla projecting into the spinal canal—often the cause of the typical occipital headaches). MRI is diagnostic.

CHAPTER 97

Peripheral Nerve Disorders

David C. Snow | E. Bradshaw Bunney

OVERVIEW

Principles

The nervous system is divided into central nervous system (CNS) and peripheral nervous system (PNS) components. The PNS is subdivided into 12 cranial and 31 spinal nerves. Disorders of the cranial nerves are discussed in Chapter 95. Because diseases of the neuromuscular junction and the myopathies are located distal to the neuron itself, they are also considered separately in Chapter 98. Radiculopathies, which are disorders of the roots of the PNS, are so commonly associated with musculoskeletal neck and back pain that they are mentioned only briefly here and are discussed in detail in Chapter 47.

Current estimates suggest that about 2.4% of the population suffers from peripheral neuropathy, rising to 8% for those over 50 years of age.[1] Diabetes mellitus is a leading contributor.

The simplest approach to diseases of the PNS parallels the CNS model of separating focal from nonfocal disease. In the PNS, the first broad category is the focal group, which can be divided into those with evidence of single versus multiple lesions of peripheral nerves, known respectively as *simple mononeuropathies* and *multiple mononeuropathies* (or *mononeuropathy multiplex*). The second broad category, which constitutes the nonfocal group of peripheral neuropathies, contains the polyneuropathies. These tend to produce bilaterally symmetrical symptoms and signs, reflecting the widespread nature of the underlying pathologic processes.

The evaluation of PNS disease involves a goal-directed history and physical examination targeted at answering the following three questions, each of which corresponds to a stratum of the algorithm presented in Figure 97.1:

1. Are the sensorimotor signs and symptoms symmetrical or asymmetrical?
2. Are the sensorimotor signs and symptoms distal or both proximal and distal?
3. Is the modality involved exclusively motor, sensory, or mixed sensorimotor?

By systematically combining responses to these questions, seven discrete categories of peripheral neuropathy are identified, each of which contains a finite set of possible diagnoses. Because pure motor or sensory findings tend to occur mainly in an asymmetrical, distal distribution, this is the only category in Figure 97.1 subdivided into pure motor and pure sensory abnormalities.

The spinal component of the PNS is shown schematically in Figure 97.2. The anterior and posterior nerve roots exit the spinal cord at each segmental level. Just distal to the dorsal root ganglion they converge to form a mixed (motor and sensory) spinal nerve, of which there are 31 pairs: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. The spinal nerves immediately bifurcate into anterior (ventral) and posterior (dorsal) rami. The posterior ramus travels to the back. The anterior ramus innervates the anterolateral portion of the body and supplies all peripheral nerves for the upper and lower extremities through the brachial and lumbosacral plexus, respectively. Interweaving of fibers occurs within a plexus, producing a mixed sensorimotor innervation of peripheral nerves exiting the plexus.

In addition to the motor and sensory modalities of the PNS, the autonomic nervous system has a peripheral component. Anatomically and functionally, the autonomic nervous system is divided into two parts: (1) a sympathetic (thoracolumbar) component and (2) a parasympathetic (craniosacral) component. Autonomic dysfunction may cause systemic abnormalities, such as orthostasis, or local problems, such as atrophic, dry skin.

The PNS has three basic responses to pathologic stimuli (see Fig. 97.2): (1) the myelinopathies, in which the primary site of involvement is limited to the myelin sheath surrounding the axon; (2) the axonopathies, in which the primary site of involvement is the axon, with or without secondary demyelination; and (3) the neuronopathies, in which the cell body of the neuron itself is the primary site of involvement, ultimately affecting the entire peripheral nerve. Although overlap occurs, each of these prototypes has a distinctive clinical presentation, electrophysiologic profile, and microscopic appearance.

Differential Diagnosis

The differential diagnosis for any patient presenting with sensory, motor, or sensorimotor complaints, particularly if they are localized to the extremities, should include a peripheral neuropathy. Within this group, patients with focal weakness are most concerning, because they are at greatest risk for respiratory compromise. Box 97.1 lists the causes of acute, emergent weakness that may affect respiration.

As soon as the emergent causes of weakness have been excluded, the individuals with focal weakness should be assessed next to exclude CNS disease (eg, stroke; Chapter 91), after which the systematic evaluation of peripheral neuropathy is performed with the distinguishing features of each of the seven peripheral neuropathic patterns described by distribution and modality and represented by a disease prototype (see Fig. 97.1; Table 97.1).

Diagnostic Testing

Testing in the evaluation of the patient with a suspected peripheral neuropathy is presented in Box 97.2. Electrophysiologic testing (nerve conduction studies [NCSs] and needle electromyography [EMG]) detects underlying pathologic abnormalities. Because neither test is readily available in the acute care setting, they are discussed only briefly here. Information gathered from these tests can be used to obtain objective information regarding the anatomic distribution of involvement (symmetrical versus asymmetrical and distal versus proximal and distal) and the modalities involved (sensory, motor, or mixed).

NCSs and EMG can also identify the level of the neuraxis affected by the disease process (ie, root, plexus, or nerve); if the nerve is affected, electrophysiologic testing can help determine whether the lesion is mononeuropathic (either an isolated mononeuropathy or mononeuropathy multiplex) or polyneuropathic.

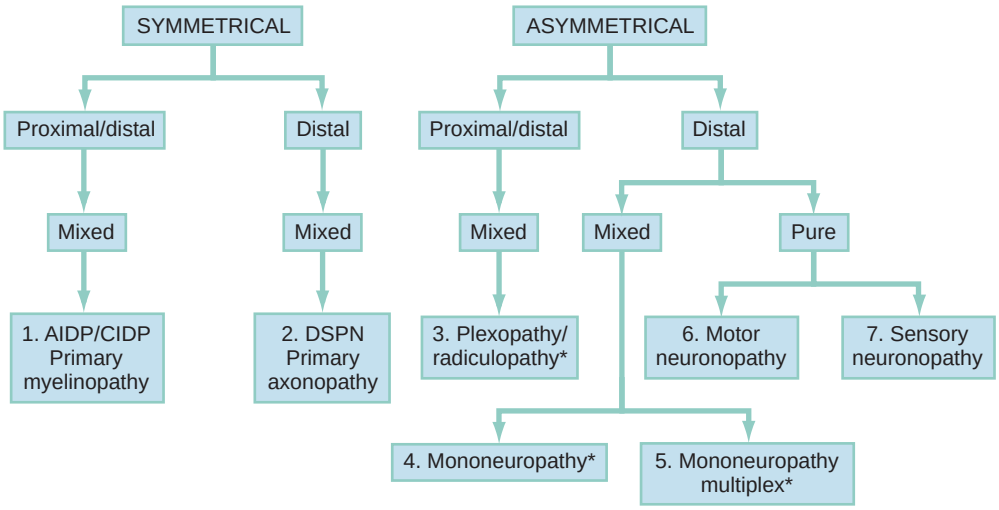

Fig. 97.1. An approach to peripheral neuropathy in the emergency department. *AIDP,* Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome); *CIDP,* chronic inflammatory demyelinating polyneuropathy; *DSPN,* distal symmetrical polyneuropathy. *A proximal distribution of sensorimotor findings may dominate the clinical picture in patterns 3, 4, and 5, depending on the location of the lesions.

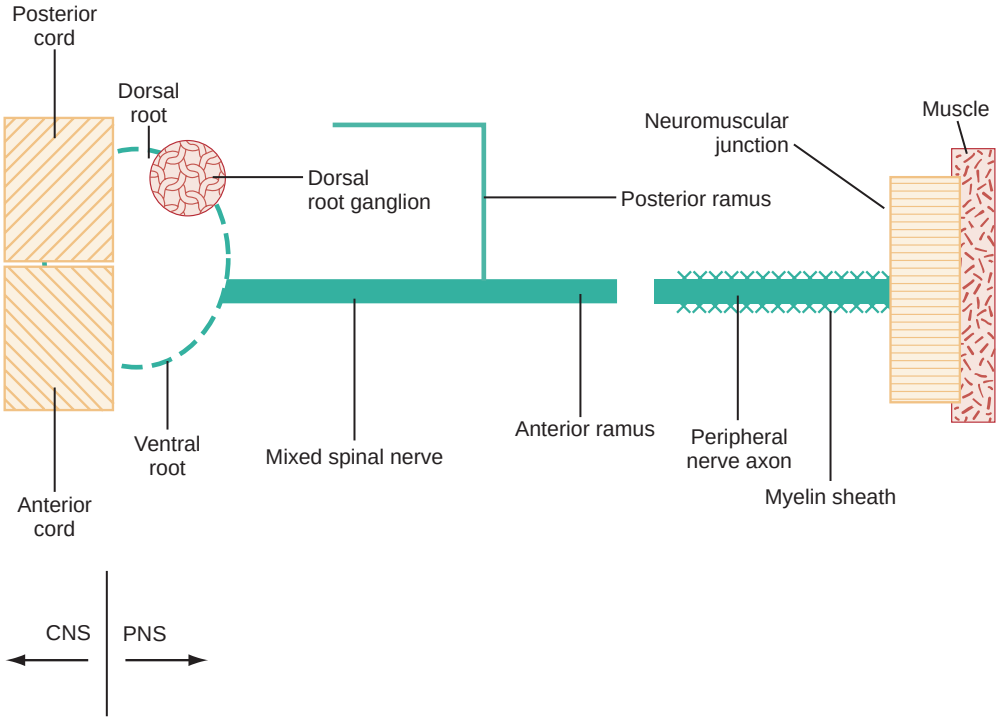

Fig. 97.2. Schematic representation of macroscopic and microscopic anatomy of the peripheral nervous system *(PNS)* and its interface with the central nervous system *(CNS).* See the text for an explanation.

Finally, EMG and NCSs can distinguish axonal from myelin disease, further narrowing the differential diagnosis. Prognosis is determined by the nature of pathologic involvement of the PNS. Primary demyelination spares the axon and thus carries the best prognosis. The prognosis is worse in axonopathies because reestablishment of nerve function is dependent on the much slower process of axonal regeneration. Neuronopathies, which begin with primary destruction of the nerve cell body, produce pure motor or pure sensory syndromes. Eventually the entire nerve is affected, resulting in the worst prognosis of the three.

Expensive batteries of tests purporting to measure a wide variety of antibodies to components of peripheral neuropathies are commercially available but have not been shown to be useful as screening tests.

SPECIFIC TYPES OF NEUROPATHIES

Type 1: Demyelinating Polyneuropathy (Guillian-Barré Syndrome)

Principles

The pattern of symmetrical weakness, usually worse distally, accompanied by variable sensory findings is characteristic of acute Guillain-Barré syndrome (GBS). It is a heterogeneous and unpredictable disorder, characterized by areflexic paralysis with albuminocytologic dissociation, with marked variation in latency between antecedent infection and symptom onset. Up to 20% of patients remain disabled from this disease process, and about 5% will die despite therapy.[1]

BOX 97.1

Causes of Acute, Emergent Weakness and Possible Respiratory Compromise

Note: Although several of the disorders listed are myopathies (see Chapter 1098), rather than peripheral neuropathies, they are lumped together here because it is important to identify patients at risk for respiratory failure early in the course of evaluation.

- Autoimmune
  - Demyelinating
    - Guillain-Barré syndrome (GBS)
    - Chronic inflammatory demyelinating polyneuropathy
  - Myasthenia gravis
- Toxic
  - Botulism
  - Buckthorn
  - Seafood
    - Paralytic shellfish toxin
    - Tetrodotoxin (puffer fish, newts)
  - Tick paralysis
  - Metals
- Arsenic
- Thallium
- Metabolic
  - Dyskalemic syndromes
    - Acquired (especially with thyrotoxicosis)
    - Familial
  - Hypophosphatemia
  - Hypermagnesemia
  - Porphyria
- Infectious
  - Poliomyelitis
  - Diphtheria

TABLE 97.1

Patterns and Prototypes of Peripheral Neuropathies

TYPE	PATTERN DISTRIBUTION	PROTOTYPICAL DISEASE MODALITIES
1	Proximal and distal, symmetrical, sensorimotor polyneuropathy Proximal and distal Motor > sensory	GBS Symmetrical
2	Distal, symmetrical, sensorimotor polyneuropathy Distal Sensory > motor	Diabetic DSPN Symmetrical
3	Proximal and distal, asymmetrical, sensorimotor neuropathy Proximal and distal Sensory and motor	Brachial plexopathy Asymmetrical
4	Distal, asymmetrical, sensorimotor mononeuropathy Distal Sensory and motor	CTS (median mononeuropathy) Asymmetrical
5	Distal, asymmetrical, sensorimotor mononeuropathy multiplex Distal Sensory and motor	Vasculitic mononeuropathy multiplex Asymmetrical
6	Distal, asymmetrical, pure motor neuronopathy Distal Motor	ALS Asymmetrical
7	Distal, asymmetrical, pure sensory neuronopathy Distal Sensory	Pyridoxine toxicity Asymmetrical

ALS, Amyotrophic lateral sclerosis; *CTS,* carpal tunnel syndrome; *DSPN,* distal symmetrical polyneuropathy; *GBS,* Guillain-Barré syndrome.

BOX 97.2

Ancillary Diagnostic Testing in Suspected Peripheral Neuropathy

OBTAINED IN MOST PATIENTS

- Complete blood count
- Erythrocyte sedimentation rate
- Glucose
- Creatine kinase
- Creatinine

OBTAINED IN SOME PATIENTS BASED ON HISTORY

- Human chorionic gonadotropin
- Magnesium
- Phosphate
- Vitamin B_{12}
- Hemoglobin A_{1c}
- Serum protein electrophoresis with immune fixation electrophoresis
- Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin screen with fluorescent treponemal antibody absorption test, as appropriate
- Thyroid function
- Human immunodeficiency virus (HIV) titer
- Lyme enzyme-linked immunosorbent assay and Western blot
- Rheumatoid factor and antinuclear antibody
- Blood, urine, hair, or nails for metal, depending on suspected chronicity of exposure
- Specific serum antibodies to components of peripheral nervous system (PNS)
- Cerebrospinal fluid (CSF) for cells, protein, Lyme titer
- Electrodiagnostic testing
  - Nerve conduction studies (NCS)
  - Electromyography (EMG)
- Neurodiagnostic imaging
  - Magnetic resonance imaging (MRI)
  - Computed tomography (CT)
  - Sonography
- Quantitative sensory testing
- Nerve biopsy
  - Sural
  - Intraepidermal nerve fiber density

BOX 97.3

Demyelinating Polyneuropathies

Guillain-Barré syndrome (GBS)
- Acute inflammatory demyelinating polyradiculoneuropathy
- Acute motor axonal neuropathy
- Acute motor and sensory axonal neuropathy
- Miller Fisher syndrome

Chronic inflammatory demyelinating polyradiculoplexoneuropathy
Malignant disease
Human immunodeficiency virus (HIV) infection
Hepatitis B
Buckthorn
Diphtheria

The most common form of GBS is an acute inflammatory demyelinating polyneuropathy, representing 90% of the cases seen in the United States. Less common variants are acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, and the Miller Fisher syndrome. Acute motor axonal neuropathy, which accounts for most of the remaining cases seen in the United States, afflicts those of Asian descent more often. Miller Fisher syndrome is a rare form of GBS characterized by the triad of ophthalmoplegia, ataxia, and areflexia (Box 97.3).

The most common infectious organisms associated with GBS is *Campylobacter jejuni,* with 30% noted in one study.[2] Cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumonia* are also associated with subsequent development of GBS.

Clinical Features

The majority of patients seek treatment days to weeks after resolution of an upper respiratory or gastrointestinal illness, presenting with progressive, symmetrical distal (and usually to a lesser extent proximal) weakness. Symptoms can progress over a period of up to 28 days, casting doubt on the diagnosis in a patient with rapidly developing symptoms. Signs and symptoms are usually worse in the lower extremities and are associated with diminution or loss of deep tendon reflexes (DTRs), variable sensory findings, and sparing of the anal sphincter. The presence of distal paresthesias increases the likelihood of GBS as the diagnosis.

The GBS disability score, which combines age, presence or absence of diarrhea, and a score of the patient's ability to ambulate independently at 2 weeks, has been shown to be predictive of prognosis at 6 months, particularly related to independent activity. Tongue weakness has been found to be associated with the development of respiratory compromise and the need for mechanical ventilation in patients with GBS.[3] Compared with adults, children who have GBS have neuropathic pain more often (80%) and require mechanical ventilation less often (13%).[4]

Diagnostic Testing

GBS is typically diagnosed on clinical findings, but additional testing is available when the diagnosis is uncertain. EMG can be used in such instances. Signs of demyelination including nerve conduction slowing with prolonged distal motor latency the most frequent demyelinating parameter.

In addition to electrophysiologic testing, cerebrospinal fluid (CSF) analysis, and respiratory function testing may aid in the diagnosis of GBS. CSF analysis is useful when it demonstrates the characteristic picture of markedly elevated protein with only a mild pleocytosis (albuminocytologic dissociation). In the clinical setting of suspected GBS, this finding is highly specific. Early in the disease, however, patients may have normal CSF values. One study noted only 50% of patients with this finding in the first week of symptoms, rising to 75% in the third week. Consequently, a normal CSF value cannot be used to exclude GBS.

Individuals with suspected GBS should have their respiratory function tested. A decrease in forced vital capacity (FVC) correlates with the need for intubation in patients with GBS. A FVC of less than 20 mL/kg is associated with pending respiratory failure and the need for intubation, whereas patients with an FVC of more than 40 mL/kg do not usually require intubation.[3] Likewise, patients with a negative inspiratory force of less than 30 cm H_2O are more likely to require mechanical ventilation. Other tests, such as the forced expiratory volume in 1 second (FEV_1) and peak flow rate (PFR), can also be used to assess respiratory function. Patients unable to perform these tests and those with less than 100% of predicted values should have an arterial blood gas sample obtained.

Management

In practice, patients with symmetrical weakness of relatively acute onset, decreased or absent DTRs, and variable degrees of sensory loss are managed as if they have GBS or one of its variants. These patients have a greater risk for respiratory compromise, which develops in 20% to 30% of patients.[3] Conversely, patients with predominantly sensory signs and symptoms are less likely to develop acute respiratory distress and have a more favorable prognosis.

About half of patients with GBS have autonomic dysfunction, experience a peak of disease severity within a week of onset, have some form of cranial nerve involvement (usually VII), and suffer long-term sequelae of their illness.

The definitive treatments for GBS are plasma exchange or intravenous immune globulin (IVIG). Both of these treatments are supported by well-designed studies, although there are no studies comparing IVIG to placebo. Combination or sequential therapy confers no therapeutic advantage over either intervention alone. Plasma exchange is cumbersome and not available at many hospitals. IVIG is more readily available and is usually administered in a dose of 400 mg/kg per day for 5 days.[5] However, IVIG is expensive, costing roughly double a standard course of plasma exchange.

Corticosteroids are not recommended; oral steroids have been shown to delay recovery, and intravenous steroids alone have been shown to impart no benefit. The combination of intravenous steroids and IVIG appears to hasten recovery but does not effect on long-term outcome and is not currently recommended.[6,7]

Disposition

Patients with probable GBS should receive neurologic consultation and admission for airway monitoring and treatment with either plasma exchange or IVIG. Evidence of alveolar hypoventilation (elevated carbon dioxide [P_{CO_2}]) in a patient with an unsecured airway requires an intensive care level of monitoring and considered for early, prophylactic intubation.

Type 2: Distal Symmetrical Polyneuropathy

Principles

Distal symmetrical polyneuropathy (DSPN) is the most common type of peripheral neuropathy. Diabetes, alcoholism, human immunodeficiency virus (HIV) disease, and toxic metabolic causes are the most frequent etiologies (Box 97.4). DSPN in diabetics, termed *diabetic polyneuropathy,* is the most common chronic complication of diabetes mellitus.[7]

Although the association between alcoholism and peripheral neuropathy has been well established for centuries, demonstration

BOX 97.4

Distal Sensorimotor Polyneuropathies

- Diabetes mellitus
- Alcoholism
- Neoplastic or paraneoplastic
- Hereditary motor and sensory neuropathies (Charcot-Marie-Tooth)
- Cryptogenic sensorimotor polyneuropathies
- HIV infection
- Toxins
  - Organic or industrial agents
    - Acrylamide
    - Allyl chloride
    - Carbon disulfide
    - Ethylene oxide
    - Hexacarbons
    - Methyl bromide
    - Organophosphate-induced delayed polyneuropathy
    - Polychlorinated biphenyls
    - Trichloroethylene
    - Vacor
  - Metals
    - Arsenic
    - Gold
    - Mercury (inorganic)
    - Thallium
  - Therapeutic agents
    - Amiodarone
    - Antiretrovirals
    - Dapsone
    - Disulfiram
    - Isoniazid
    - Metronidazole
    - Nitrofurantoin
    - Paclitaxel (Taxol)
    - Phenytoin
    - Statins (HMG-CoA reductase inhibitors)
    - Thalidomide
    - Vinca alkaloids (vincristine, vinblastine)
- Nutritional
  - Beriberi (thiamine or vitamin B_1)
  - Pellagra (niacin, B vitamins)
  - Pernicious anemia (vitamin B_{12})
  - Pyridoxine deficiency (vitamin B_6)
- End-organ dysfunction
  - Acromegaly
  - Chronic pulmonary disease
  - Hypothyroidism
  - Renal failure (uremic neuropathy)
- Paraproteinemias
  - Amyloidosis
  - Monoclonal gammopathy of unknown significance
  - Multiple myeloma
  - Waldenström's macroglobulinemia
- Porphyria

HIV, Human immunodeficiency virus; *HMG-CoA,* hydroxymethylglutaryl coenzyme A.

of a direct neurotoxic effect of alcohol remains elusive. The preponderance of evidence from both observational studies in humans and experimental data from animal models suggests that the association between alcohol and peripheral neuropathy may be confounded by nutritional status (ie, deficiency states might be the true underlying cause of alcoholic peripheral neuropathy).

With the widespread use of highly active and effective antiretroviral treatment, peripheral neuropathies have become the most common neurologic complication of HIV infection. The typical HIV neuropathy is a DSPN, estimated to affect up to 35% of the HIV population, with a currently unknown pathogenesis.

Clinical Findings

Most polyneuropathies are characterized by a pattern of distal, symmetrical sensorimotor findings, worse in the lower than in the upper extremities, with a stocking-glove distribution of sensory abnormalities that gradually diminishes as one moves proximally. Motor weakness and loss of DTRs, which lag behind the sensory features, follow a similar pattern of progression from distal to proximal. The diffuse, distal, symmetrical nature of this pattern is most consistent with a toxic-metabolic disease process that causes a length-dependent axonopathy.

Initial symptoms usually consist of "positive" sensory complaints (eg, dysesthesias, such as tingling and burning) beginning on the plantar surfaces of both feet. At the early stages of a typical DSPN, there may be some asymmetry. At this juncture, it may be impossible to distinguish a focal neuropathic process such as a mononeuropathy from a polyneuropathy, although in this location, prior probability strongly favors a polyneuropathy. As the process advances, the plantar surfaces of both feet become dysesthetic before the dorsum of either foot is involved.

Weakness of dorsiflexion of the big toe is usually the first motor sign, followed by weakness of foot dorsiflexion, footdrop, loss of the Achilles reflex, and later a "steppage gait," in which footdrop causes the toes to point downward and scrape the ground while walking, requiring the patient to lift the leg higher than normal when walking.

Sensory loss continues to move proximally, and before it reaches the knees, the fingertips are usually involved. DTRs are progressively lost, as is proprioception. If loss of proprioception becomes severe, patients may develop sensory ataxia. As the neuropathy continues to progress, sensory abnormalities ultimately involve all modalities and extend to a diamond-shaped periumbilical area. Far-advanced disease may affect sensation over the skull vertex and facial midline structures. Atrophy and areflexia occur as weakness worsens. Severely impaired patients may be unable to ambulate or to grasp objects. These symptoms have a significant impact on the patient's quality of life, affecting not only physical functioning but also sleep and emotional and social functioning. Many of these patients display signs of depression or anxiety. Polyneuropathies can be difficult to diagnose and are best approached by the performance of electrodiagnostic studies for patients with a constellation of symptoms and signs suggesting a particular neuropathy.

Diabetic foot ulcers are a common complication of diabetes, ranging from 2% to 10% of the population. Unperceived trauma is the leading cause, likely from the associated polyneuropathy.[8]

The clinical picture of alcoholic neuropathy is similar to that of diabetic DSPN. However, in alcoholism, severe myopathy and cerebellar degeneration often complicate the clinical picture. Autonomic skin changes with atrophy and hair loss accompany the sensorimotor abnormalities. Often, other systemic effects of alcoholism are so severe that the patient may not notice the neuropathic symptoms.

Differential Diagnosis

Box 97.4 lists the differential diagnoses of DSPN. On the basis of results from a case-control study, the statins have been added to the list of drugs that are implicated.

Diagnostic Testing

Electrodiagnostic studies are commonly employed in the evaluation for this entity. This includes both NCSs and needle electromyelography. Screening laboratory tests should be considered for all patients who present with this condition. The tests that provide the highest yield include blood glucose, serum B12, and serum protein immunofixation electrophoresis.

Management

Diabetic DSPN, the first step in the treatment, is intensive diabetes therapy aimed at near normoglycemia. If discomfort is severe, the etiology of the neuropathy seems likely to be diabetic, and if referral is delayed, it may be necessary to provide the patient with some symptomatic relief. Because treatment of neuropathic pain has traditionally been linked to etiology rather than to an underlying mechanism, the choice of pharmacologic agents is empirical, with substantial practice variation in the United States and worldwide. Nonsteroidal antiinflammatory drugs (NSAIDs) should not be considered first-line treatment, because they have little proven efficacy and a high potential for renal impairment. High level evidence supports the use of tricyclic antidepressants, anticonvulsants, and the serotonin and norepinephrine reuptake inhibitor nuloxetine. Imipramine or amitriptyline may be started at a daily dose of 25 mg at bedtime (10 mg in elders) and titrated slowly up to a dose of 150 mg. Carbamazepine at a dose of 200 to 400 mg every 8 hours and gabapentin at a dose of 900 to 3600 mg per day are also effective treatments. Tramadol, a mixed opioid with low potential for dependency, has been shown in two studies to have a NNT (number needed to treat) below 5.[9] Tramadol combined with acetaminophen has been found to be as effective as gabapentin in the treatment of painful diabetic neuropathy. Pregabalin 150 to 600 mg per day, a more recent treatment option, has a mechanism of action similar to that of gabapentin. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, has been found effective at a dose of 60 mg/day. Tapentadol ER 100 to 250 mg twice daily was also found to provide pain relief in patients with diabetic neuropathy.[10] Topical capsaicin provides relief in some patients, but the burning associated with its application has limited its use. Topical lidocaine patches, 5%, are another treatment option, showing similar efficacy to pregabalin.

In addition to pain management as discussed earlier, all patients with suspected alcoholic DSPN should receive dietary supplements and referral for outpatient management.

Lamotrigine has been shown to be effective in the treatment of HIV-associated painful neuropathies, especially for those patients on highly active antiretroviral therapy (HAART). However, there are no comparative studies to support its use over the other pain medications.

Type 3: Asymmetric Proximal and Distal Peripheral Neuropathies (Radiculopathies and Plexopathies)

Radiculopathies (see Chapter 47) and plexopathies often result from trauma (Box 97.5). In general, a plexopathy, whether brachial or lumbosacral, is identified by a process of elimination (ie, a pattern of sensorimotor and reflex abnormalities that fit neither a radicular nor an individual peripheral nerve distribution). Although this approach does not exclude a mononeuropathy multiplex on physical examination alone, a careful history should determine whether the patient is at risk for development of a mononeuropathy or plexopathy on the basis of underlying disease

BOX 97.5

Asymmetrical Proximal and Distal Peripheral Neuropathies

BRACHIAL PLEXOPATHY

- Open
  - Direct plexus injury (knife or gunshot wound)
  - Neurovascular (plexus ischemia)
  - Iatrogenic (central line insertion)
- Closed
  - Traction injuries
    - "Stingers"
    - Traction neurapraxia
    - Partial or complete nerve root avulsion
  - Radiation
  - Neoplastic
  - Idiopathic brachial plexitis
  - Thoracic outlet

LUMBOSACRAL PLEXOPATHIES

- Open
- Closed
  - Traction injuries
    - Pelvic double vertical shearing fracture
    - Posterior hip dislocation
    - Retroperitoneal hemorrhage
  - Vasospastic (deep buttock injection)
  - Neoplastic
  - Radiation
  - Idiopathic lumbosacral plexitis
  - Infectious
    - Herpesvirus (sacrococcygeal)
    - Herpes simplex 2
    - Herpes zoster
    - Cytomegalovirus polyradiculopathy (HIV infection)

HIV, Human immunodeficiency virus.

Most plexopathies are seen in young men after motor vehicle accidents. Most present for evaluation of radicular pain several months after the initial injury. Therapeutic intervention is often delayed to maximize the potential for spontaneous recovery. Several surgical repairs exist, including neurotization and nerve transfer.

Radiation (actinic) plexopathy occurs after a variable period of latency following treatment, which may extend to 20 years or more. Almost all series include women who received radiation treatment for breast cancer. Among neoplastic causes, most originate from the lung or breast. Patients with probable neoplastic brachial plexopathy need imaging studies and may require immediate radiation therapy. Pain control is the focus of management.

Thoracic outlet syndrome (TOS) describes a constellation of symptoms caused by compression of the neurovascular bundle at the thoracic outlet. As our understanding of this condition has improved, treatment has evolved but remains controversial.[11] Manifestations include both neurogenic and vascular (arterial or venous) TOS. It is estimated that over 90% of cases are neurogenic in origin, 3% to 5% are venous, and less than 1% are arterial.

Neurogenic TOS is caused by compression of the brachial plexus, presenting with upper extremity weakness, numbness, paresthesias, and pain in a nonradicular distribution. Symptoms are usually present during normal daily activities and sleep.

Treatment is typically nonsurgical, involving education, activity modification, and physical therapy.

Vascular TOS can be either arterial or venous and is characterized by swelling of the upper extremity, pain, and a feeling of heaviness after exertion. Discoloration can also be seen. If arterial TOS is occurring, caused by compression of the subclavian artery, the typical findings of arterial insufficiency can be seen—pain, numbness, coolness, pallor. Treatment is typically surgical, involving decompression of the thoracic outlet.

Because of the complexity of plexopathies, there is no reason to expect that one can or should do more in the ED than localize the probable pathologic process to the brachial or lumbosacral plexus. Depending on severity and suspected etiology, the patient should either be admitted or referred to a neurologist with experience in PNS disease.

Type 4: Isolated Mononeuropathies

The pattern of asymmetrical, sensorimotor, usually distal, peripheral neuropathy is characteristic of a mononeuropathy. Mononeuropathies are of two main types: isolated and multiple. The isolated mononeuropathies are discussed in this section; the multiple mononeuropathies, also termed mononeuropathy multiplex, are discussed in the next section as a type 5 peripheral neuropathy.

Isolated mononeuropathies are usually caused by trauma, either blunt or penetrating (Box 97.6). If the trauma is blunt, the injury may be secondary to compression from an internal or external source. Entrapment neuropathies are a subset of compression neuropathies occurring at anatomic locations where nerves traverse potentially constricting compartments or tunnels. Isolated mononeuropathies may be acute, intermittent, or chronic and continuous. Antecedent peripheral neuropathy may be a risk factor for development of compression neuropathy (so-called double-crush syndrome), particularly in diabetics.

Radial Mononeuropathy

Principles. The radial nerve arises from the C5 to T1 roots. After exiting the brachial plexus, it passes behind the proximal humerus in the spiral groove and takes a lateral (radial) course down the upper arm (Fig. 97.3). At about the level of the antecubital fossa, it bifurcates into the posterior interosseous (pure motor) and superficial radial (pure sensory) nerves.

The radial nerve controls extension of the fingers, thumb, wrist, and elbow (triceps). In contrast to the median and ulnar nerves, the radial nerve provides only *extrinsic* motor innervation to the hand (ie, it does not supply motor fibers to any muscles that both originate and insert within the hand). In further contrast to the median and ulnar nerves, which supply most of the

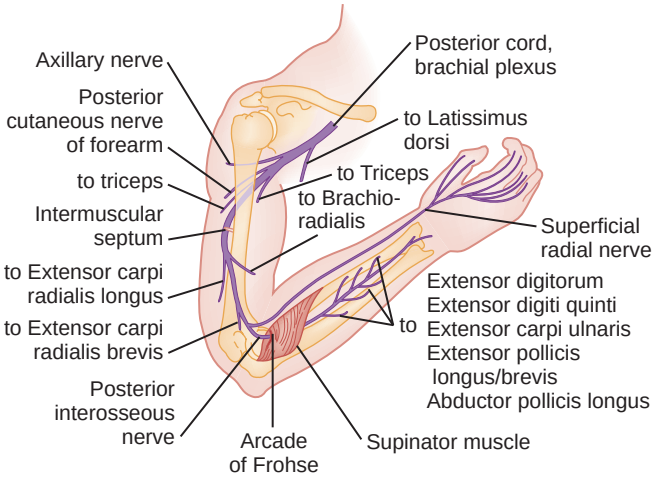

Fig. 97.3. Radial nerve, major branches, right arm, lateral view. (From Stewart JD: Focal peripheral neuropathies, ed 3, Philadelphia, 2000, Lippincott Williams & Wilkins.)

BOX 97.6

Isolated Mononeuropathies

UPPER EXTREMITY

Radial nerve
- Axilla
- Humerus
- Elbow (posterior interosseous neuropathy)
- Wrist (superficial cutaneous radial neuropathy)

Ulnar nerve
- Axilla
- Humerus
- Elbow
- Condylar groove
- Cubital tunnel
- Wrist (Guyon's canal)
- Hand
  - Superficial terminal ulnar neuropathy
  - Deep terminal ulnar neuropathy: proximal hypothenar; distal hypothenar

Median nerve
- Axilla
- Humerus (musculocutaneous mononeuropathy)
- Forearm
  - Anterior interosseus
  - Pronator syndrome
- Wrist (carpal tunnel)
- Hand (recurrent motor branch)

Suprascapular mononeuropathy
Axillary mononeuropathy

LOWER EXTREMITY

Sciatic nerve
Femoral nerve
- Iliacus compartment (proximal)
- Saphenous mononeuropathy (distal)

Lateral femoral cutaneous (meralgia paresthetica)
Peroneal nerve
- Common peroneal mononeuropathy (fibular head, popliteal fossa)
- Deep peroneal mononeuropathy (anterior compartment)

Tibial nerve
- Popliteal fossa (proximal)
- Tarsal tunnel (distal)

Sural nerve
- Popliteal fossa, calf (proximal)
- Fifth metatarsal base (distal)

Plantar nerve
- Distal to tarsal tunnel
- Interdigital neuropathies (Morton's neuroma)

Obturator mononeuropathy

sensation to the hand, the radial nerve makes a contribution only to a cutaneous dorsal area overlying the first dorsal interosseus muscle, sometimes extending part of the way up the dorsa of the thumb, index, and long fingers.

Radial mononeuropathy caused by involvement at the level of the axilla is uncommon. When it occurs, it is usually associated with other upper extremity mononeuropathies or a brachial plexopathy. Although improper use of crutches may cause this syndrome, it usually occurs after an extended period of unconsciousness during which the arm is positioned in such a way that prolonged, deep compression is applied to the axilla. Axillary radial mononeuropathy is distinguished from the more common humeral form by the finding of triceps involvement in addition to typical wrist and finger drop. Triceps involvement occurs because the innervation to the triceps is proximal to the point where the nerve is most vulnerable as it winds around the humeral shaft (see Fig. 97.3).

Most radial mononeuropathies are due to so-called Saturday night palsies. The euphemism is derived from the association of radial mononeuropathy with improper positioning of the arm during deep, commonly inebriated sleep. Consequently, the radial nerve is trapped for a prolonged period between the humeral shaft and some firm surface, causing an external compression mononeuropathy. "Bridegroom's palsy" is another eponym for radial mononeuropathy, so named because the radial nerve may be compressed by the bride's head resting on the bridegroom's arm during sleep.

Clinical Findings. Because innervation of the wrist and finger extensors occurs distal to this area of the humeral shaft, findings are characterized by wrist and finger drop and mild numbness over the skin of the first dorsal interosseus muscle. Depending on the level, degree, and duration of compression, some fascicles of the nerve may remain functional, resulting in a partial radial mononeuropathy. Thus the superficial radial nerve may remain intact, resulting in no loss of sensation, or loss of wrist and finger extension may be incomplete.

Because the finger drop of radial mononeuropathy places the hand at a mechanical disadvantage, examination of ulnar function by testing of the interossei may produce false-positive findings of weakness. To adjust for this, the examiner should ask the patient to place the palm on a horizontal supporting surface, such as a stretcher. With the fingers extended and no longer "dropped" at the metacarpophalangeal joints, interosseous strength can now be fairly tested. Failure to perform this maneuver may cause misdiagnosis of a simple radial mononeuropathy as a brachial plexopathy in an effort to explain what appears to be radial and partial ulnar nerve involvement.

About 90% of radial nerve palsies occurring during sleep, coma, or anesthesia recover fully, usually within 6 to 8 weeks. Evidence of denervation on EMG studies predicts a slower rate of recovery. Tourniquet injuries to the radial nerve usually recover spontaneously within 2 to 4 months. If axonal degeneration is seen on electrophysiologic testing, recovery may take longer, although virtually all radial mononeuropathies caused by tourniquets eventually resolve.

The radial nerve courses closely to the humerus, so it follows that about 22% of humeral shaft fractures are associated with radial nerve injury, with "wrist drop" the hallmark injury.[12] Spontaneous resolution has been reported between 60% and 92%, so many authors suggest observation of these injuries is appropriate. In contrast, surgical intervention is needed to free the nerve from entrapment associated with complex fractures.

Diagnostic Testing. There exists no diagnostic test per se for this disease entity outside of the physical examination. EMG testing is employed to aid in predicting recovery times.

Management. While patients are waiting for spontaneous recovery to occur, the hand should be maintained in about 60 degrees of dorsiflexion. Although a simple dorsal plaster or fiberglass splint treats the wristdrop, atrophy and contractures can be minimized and function of the hand can be improved if wide rubber bands anchored to the splint at a point proximal to the wrist are attached to individual fingers to provide passive dorsiflexion.

Ulnar Mononeuropathy

Principles and Clinical Findings. The ulnar nerve includes C7 to T1 roots and passes through the brachial plexus to descend medially, without branching, to the ulnar (medial) condylar groove at the elbow. It then enters the cubital canal, where it gives off branches to the ulnar wrist flexor and the deep flexors of the fourth and fifth digits.

Just proximal to the wrist, two important sensory branches leave the main trunk to supply cutaneous sensation to part of the hand (Fig. 97.4). These are the palmar and dorsal cutaneous branches, which do *not* pass through Guyon's canal. The palmar branch supplies sensation to the hypothenar eminence and the dorsal branch innervates the ulnar side of the dorsum of the hand, extending out nearly to the tip of the fifth and ulnar half of the fourth digit.

At the wrist, the nerve enters Guyon's canal (Fig. 97.5) between the pisiform and hook of the hamate, then bifurcates into the superficial terminal sensory branch and the deep motor branch.

The superficial sensory nerve supplies ulnar sensation to the palmar side of the fifth and half of the fourth digit (see Fig. 97.5). The deep motor nerve supplies the hypothenar muscles, then crosses to the radial side of the palm to innervate the ulnar intrinsics (all interossei and the ulnar lumbricals of the fourth and fifth

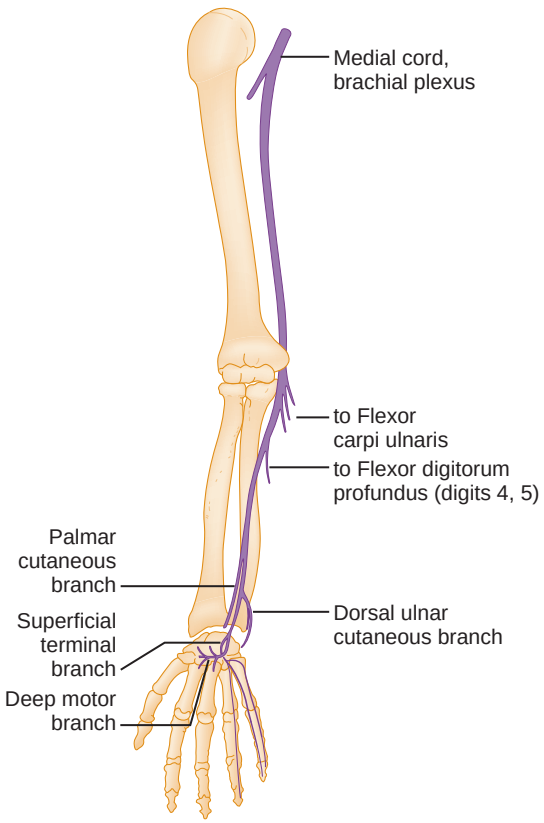

Fig. 97.4. Ulnar nerve, major branches, right arm, anterior view. (From Stewart JD: Focal peripheral neuropathies, ed 3, Philadelphia, 2000, Lippincott Williams & Wilkins.)

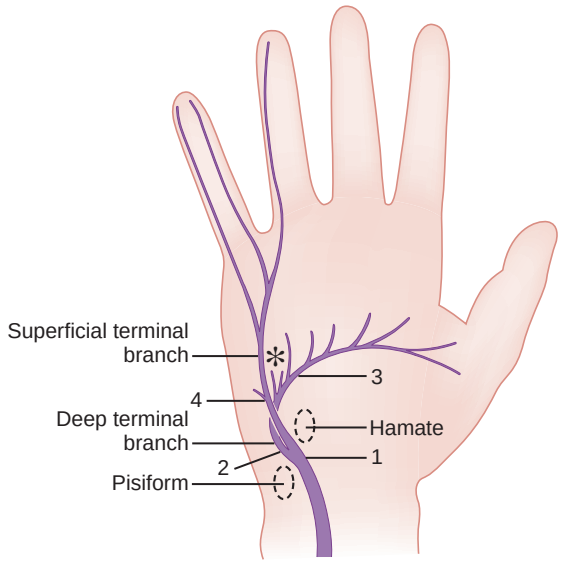

Fig. 97.5. Distal ulnar nerve and branches, right hand, palmar view. *Numbers* indicate four main sites of distal ulnar mononeuropathy in the wrist and hand. Asterisk *(*)* denotes hypothenar branches. (From Stewart JD: Focal peripheral neuropathies, ed 3, Philadelphia, 2000, Lippincott Williams & Wilkins.)

digits), terminating in the first dorsal interosseus. The interossei abduct and adduct the fingers and are all innervated by the ulnar nerve. The lumbrical muscles flex the metacarpophalangeal joints and are evenly divided between the ulnar (fourth and fifth) and median (second and third) digits. The ulnar nerve can be thought of as the complement to the median nerve in the hand, because it supplies all of the muscles and all palmar sensation not innervated by the median nerve.

The ulnar nerve may be injured at two locations near the elbow: in the ulnar condylar groove and distally in the cubital canal. Because the condylar groove is shallow, the ulnar nerve runs superficially in this location and is vulnerable to injury, usually from external pressure or from a fracture or dislocation. The ulnar nerve has a propensity to develop a "tardy ulnar palsy," occurring years after a traumatic event. Many of these delayed ulnar mononeuropathies can be localized to the elbow on electrophysiologic testing.

Some ulnar mononeuropathies occur secondary to compression just proximal to entry into the cubital canal or are entrapped within the canal itself. Transient symptoms may occur during prolonged flexion or with repeated flexion and extension at the elbow.

Although it is difficult to distinguish a condylar from a cubital ulnar mononeuropathy, it is usually possible to localize the problem to the region of the elbow or the wrist. In addition to prior probability heavily favoring the elbow, the presence of sensory abnormalities in an ulnar distribution in the hand and fingers (ie, usually including the fifth digit and "splitting" the fourth digit) strongly suggests that the lesion is at the level of the elbow rather than the wrist. The ulnar cutaneous innervation to the hand branches off from the main trunk proximal to the nerve entering Guyon's canal (see Figs. 97.4 and 97.5). Thus a lesion at the wrist should not produce sensory abnormalities, whereas one at the elbow would be expected to do so.

Compression of the ulnar nerve within Guyon's canal is rare. When it does occur, it affects all of the ulnar intrinsics (ie, the two ulnar [fourth and fifth] lumbricals) and all the interossei. However, the ulnar extrinsics (ie, the deep flexors of the fourth and fifth digits) are not affected, nor is the ulnar flexor of the wrist. The only sensory abnormalities are those in the distribution of the superficial terminal sensory branch, sparing other areas of ulnar innervation (see Fig. 97.5).

There are three ulnar mononeuropathies that occur distal to Guyon's canal in the hand. The two most common ones involve the deep terminal branch, either proximal or distal to the separation of the hypothenar branches (see Fig. 97.5). If the lesion is proximal, it produces weakness of all the ulnar-innervated muscles of the hand without sensory loss. If it is distal, the hypothenar ulnar intrinsics are spared, but the picture is otherwise similar. Usually, this occurs secondary to a laceration or repeated compression in the hand from use of certain tools, a cane, or the handle of a crutch.

Involvement of the superficial terminal branch (see Fig. 97.5) produces a pure sensory loss of the palmar surface of the fifth digit and ulnar half of the fourth digit caused by direct compression of this branch just distal to Guyon's canal. The dorsal surface of these two digits should have normal sensation except for the distal tips. This configuration of findings is due to the intact innervation provided by the dorsal and palmar cutaneous branches that enter the hand without passing through Guyon's canal (see Fig. 97.4).

Diagnostic Testing. There exists no true diagnostic entity for this disease process outside of the physical examination.

Management. Most ulnar mononeuropathies will spontaneously resolve. However, if muscle atrophy, particularly in the hypothenar area, is detected, surgery may be considered. There is no noted difference in outcomes between the two surgical options of simple decompression and decompression with transposition.[13]

Median Mononeuropathy

Principles. The median nerve arises from the C5 to T1 spinal nerve roots and exits the brachial plexus through the lower trunk (Fig. 97.6). Median mononeuropathy is usually diagnosed as carpal tunnel syndrome (CTS), which is the most common of all entrapment neuropathies. CTS is estimated to occur in 3.8% of the United States population, with a prevalence of 9.2% in women and 6% in men.[14] It is defined by the Academy of Orthopedic Surgeons as "a symptomatic compression neuropathy of the median nerve at the level of the wrist."

Clinical Findings. Although the patient may complain of bilateral symptoms, a careful history usually reveals that symptoms in one hand preceded those in the other. A common symptom of CTS is awakening at night and shaking the hand. Symptoms are often worsened by activity. For unclear reasons, the pain may spread as high as the arm or shoulder, although the paresthesias are generally confined to the fingers. Many patients on initial questioning state that their entire hand is involved, although this is not supported by careful sensory examination. Patients frequently note that their hands are clumsy or weak, especially when holding a glass or opening a screw-top container.[15] The skin of the fingers innervated by the median nerve may be drier and rougher to the touch than the corresponding ulnar skin, depending on the duration of entrapment.

When motor involvement occurs in CTS, it is confined to the median intrinsics, which innervate the *l*umbricals (flexion of the metacarpophalangeal joints) and subserve thumb *o*pposition, *a*bduction, and *f*lexion, known as the *LOAF* muscles. However, the hallmark of CTS is sensory involvement, with motor abnormalities occurring later. The typical pattern of sensory innervation of the hand by the median, ulnar, and radial nerves shows marked individual variation. The most specific finding for CTS is splitting of the fourth digit (ie, normal sensation of the ring finger on the ulnar palmar side with abnormal sensation on the median [radial]

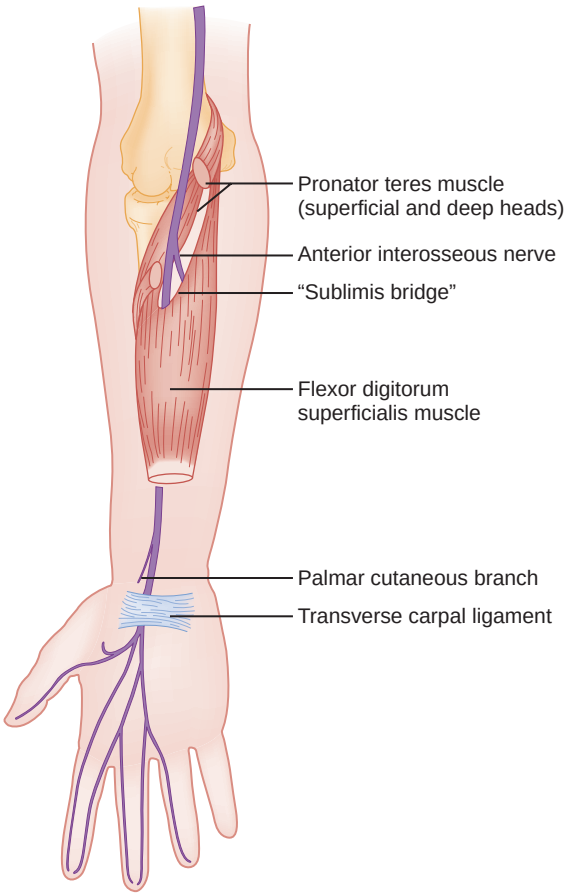

Fig. 97.6. Median nerve, major branches, right arm, anterior view. (From Stewart JD: Focal peripheral neuropathies, ed 3, Philadelphia, 2000, Lippincott Williams & Wilkins.)

BOX 97.7

Conditions Associated With Carpal Tunnel Syndrome

Acromegaly
Amyloid
Diabetes mellitus
Hypothyroidism
Obesity
Pregnancy
Renal failure
Rheumatoid arthritis

palmar side of the same finger). The most sensitive finding is abnormal sensation of the distal palmar tip of the index finger. If sensory findings are absent in the presence of motor findings consistent with median nerve involvement, it is highly unlikely that the patient has CTS, and an alternative diagnosis should be sought.

CTS appears to be associated with the conditions listed in Box 97.7. Of these, the two most common are diabetes mellitus and pregnancy.[16] CTS associated with systemic illness is commonly bilateral. CTS in pregnancy appears to be common, but the prevalence varies widely literature from 31% to 62%.[17] Most cases of pregnancy related CTS resolve spontaneously, up to 85% in some studies.

Diagnostic Testing. Tinel's sign (percussion of the median nerve at the wrist) and Phalen's sign (maximal palmar flexion at the wrist) have been classically taught as provocative tests to reproduce the sensory symptoms of CTS if neither sensory nor motor symptoms are evident on initial examination. However, more recent evaluation has shown that Tinel's and Phalen's signs do not have adequate sensitivity or specificity to determine which patients should be referred for electrodiagnostic studies. Dropping of objects is indicative of severe CTS. The best way to examine patients for sensory findings is to touch the distal palmar tips very lightly, asking the patient whether the sensation feels "abnormal."

NCS is considered to be the gold standard in the diagnosis of CTS, because it is an objective test that provides information on the physiological health of the median nerve across the carpal tunnel. Magnetic resonance imaging (MRI) allows for good imaging of the soft tissue structures of the carpal tunnel and revealing the cause of the nerve compression. It has a sensitivity of 96% but a specificity of 33% to 38%.[16] Ultrasonography has been shown to be useful, particularly in patients with symptoms and a normal NCS. The most reliable ultrasonographic measurement is to obtain the cross-sectional area of the median nerve at the level of the pisiform. Thus, if all diagnostic studies in a symptomatic patient have normal findings, or if only the MRI result is abnormal, they should be repeated within a few months if symptoms do not resolve. This recommendation is based on the theory that the CTS will progress over time to the point that an objective indicator, such as the NCS, will become positive.

Management. There are a variety of nonsurgical treatments, with splinting and steroid injections being the most common. Neutral wrist splinting has commonly been used as the initial treatment, but a recent Cochrane review found poor evidence to support this being more effective than no treatment in the short term.[18] Steroid injection has been shown to be a temporizing measure in the treatment of CTS. One recent study using methylprednisolone showed significant symptom relief at 10 weeks and also reduced the rate of surgery at 1 year.[19] Because of the possibility of a disabling "median hand" after inadvertent direct injection of the median nerve, it is recommended that emergency clinicians defer the injection of the carpal tunnel with steroids to the consulting hand surgeon. This physician can obtain NCS and determine splinting, injection, or surgical division of the transverse carpal ligament is indicated. Surgical treatment involves the division of the transverse carpal ligament, which reduces pressure on the median nerve by increasing the space in the carpal tunnel. This carpal tunnel "release" surgery can be performed open or endoscopic with no significant difference in outcomes noted.[16]

Sciatic Mononeuropathy

Principles. The sciatic nerve includes L4 to S3 spinal nerve roots that pass through the lumbosacral plexus and divides into two terminal branches: the common peroneal and tibial nerves. The nerve exits the pelvis through the sciatic notch, passes behind the hip, and remains deep in the thigh until its terminal bifurcation in the proximal popliteal fossa (Fig. 97.7).

Lesions of the sciatic nerve occur with posterior hip dislocation or with virtually any form of penetrating or blunt trauma that causes formation of a buttock hematoma. Other causes include deep gluteal injection and prolonged supine immobilization on a firm surface. Because the sciatic nerve innervates the hamstrings and provides all sensorimotor function distal to the knee, a complete sciatic mononeuropathy is a devastating injury.

Clinical Findings. Ambulation is extremely difficult because of inability to flex the knee and a flail foot (ie, neither flexion nor

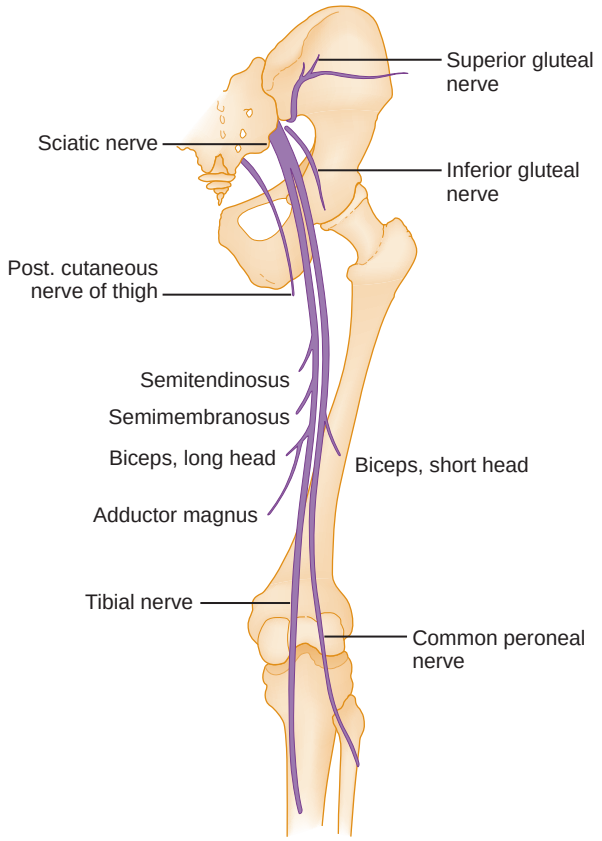

Fig. 97.7. Sciatic nerve, major branches, right leg, posterior view. (From Stewart JD: Focal peripheral neuropathies, ed 3, Philadelphia, 2000, Lippincott Williams & Wilkins.)

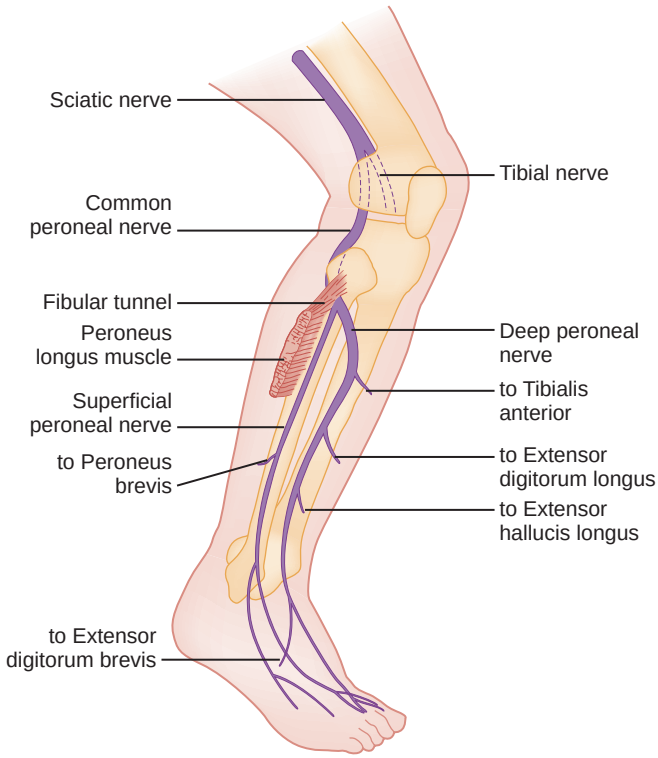

Fig. 97.8. Common peroneal nerve, major branches, right leg, anterolateral view. (From Stewart JD: Focal peripheral neuropathies, ed 3, Philadelphia, 2000, Lippincott Williams & Wilkins.)

extension is possible at the ankle). Fortunately, many sciatic mononeuropathies are incomplete. For unknown reasons, a partial lesion typically involves only the trunk of the sciatic nerve, which subsequently becomes the common peroneal nerve, sometimes making the two difficult to distinguish from one another clinically.

Diagnostic Testing. This condition is mainly diagnosed by physical findings. If used, electrophysiologic studies show evidence of involvement of gluteal muscles or of any muscles innervated by the tibial nerve. This readily distinguishes a partial sciatic mononeuropathy from a lesion of the common peroneal nerve.

Management. Treatment of footdrop requires a posterior splint to maintain the ankle at 90 degrees until a brace can be obtained (see the Common Peroneal Mononeuropathy section).

Lateral Femoral Cutaneous Mononeuropathy

Principles. Lateral femoral cutaneous mononeuropathy (meralgia paresthetica) is a common syndrome believed to be caused by injury to this pure sensory nerve as it passes through or over the inguinal ligament, where it may become entrapped or kinked. Along with facial nerve neuropathy, meralgia paresthetica is one of the most commonly reported mononeuropathies associated with HIV infection.

Clinical Findings. Numbness and dysesthesia over the skin of the upper lateral thigh is typically found on physical examination.

Diagnostic Testing. There is no diagnostic test for this disease process outside of the physical examination.

Management. Regression usually occurs spontaneously, but recurrence is common and may require a release procedure for the inguinal ligament.

Common Peroneal Mononeuropathy

Principles. The common peroneal nerve is a continuation of one trunk of the sciatic nerve. It is most vulnerable to injury where it winds around the fibular neck (Fig. 97.8). It then passes through the fibular canal and bifurcates into its terminal branches, the superficial and deep peroneal nerves. The superficial peroneal nerve innervates the peroneal muscles (foot everters) and supplies sensation to the lateral, distal lower leg and dorsum of the foot. The deep peroneal nerve traverses the anterior compartment and supplies innervation to the dorsiflexors of the foot and toes plus cutaneous sensation between the first and second toes.

Most common peroneal mononeuropathies are idiopathic and thought to be related to compression where the nerve is superficially located lateral to the fibular neck. Because this common neuropathy is often noted on awakening, it may be secondary to position during sleep. Leg crossing may also be a risk factor for development of this mononeuropathy.

Clinical Findings. The most striking feature of a complete common peroneal mononeuropathy is footdrop caused by weakness of foot dorsiflexion. At testing, the everters of the foot are also weak, but the inverters, which are innervated by the tibial nerve, remain strong. This is the single most reliable clinical feature distinguishing sciatic from common peroneal mononeuropathy. Analogous to radial mononeuropathy in the upper

extremity, sensory abnormalities in the leg and foot are inconstant and easily overlooked in peroneal mononeuropathy.

Diagnostic Testing. Most patients with peroneal palsy recover. Those who do not should be studied electrophysiologically to ensure that the point of compression is not proximal to the fibular neck (ie, in the popliteal fossa). If the point of peroneal injury appears to be in the region of or distal to the fibular neck on EMG, patients whose footdrop does not resolve should be considered candidates for exploration to determine whether the nerve is compressed within the fibular canal.

Management. Treatment of common peroneal palsy requires a posterior splint to maintain the ankle at 90 degrees until the nerve regenerates. This splinting prevents the foot from falling into sustained equinus (plantar flexion), which in turn allows the intermalleolar distance to narrow, effectively locking the talus out of the ankle mortise.

The treatment of isolated mononeuropathies depends on their etiology, location, and natural history of spontaneous recovery. All penetrating neuropathies should have surgical exploration and repair performed. Blunt trauma may cause a mononeuropathy indirectly by entrapment of a nerve within a fracture, hematoma, or compartment, requiring surgical intervention. Alternatively, nerves may be injured at a point where they are superficial, either by a single direct blow or by sustained pressure caused by immobility (pressure palsies). Most of these resolve spontaneously over time, depending on the severity of injury and length of the nerve. If entrapment can be confirmed by imaging or electrophysiologic studies, a release procedure is indicated. The mononeuropathies that do not require timely surgical exploration should be referred for further evaluation to confirm the location of the neuropathic lesion.

Type 5: Mononeuropathy Multiplex

Principles

Mononeuropathy multiplex is characterized by an asymmetrical, sensorimotor, usually distal pattern of peripheral neuropathy (Box 97.8). Common causes include vasculitis, diabetes, and Lyme disease.

BOX 97.8

Mononeuropathy Multiplex

- Vasculitis
  - Systemic vasculitis
    - Polyarteritis nodosa
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
    - Sjögren's syndrome (keratoconjunctivitis sicca)
  - Nonsystemic vasculitis
- Diabetes mellitus
- Neoplastic
  - Paraneoplastic
  - Direct infiltration
- Infectious
  - Lyme disease
  - HIV infection
- Sarcoid
- Toxic (lead)
- Transient (polycythemia vera)
- Cryoglobulinemia (hepatitis C)

HIV, Human immunodeficiency virus.

Clinical Findings

As with isolated mononeuropathies, sensory abnormalities tend to be located in the same general anatomic region as the accompanying motor findings. Whether DTRs are affected depends on which nerves are involved. For example, if the process includes the femoral nerve, the patellar reflex is likely to be diminished or absent.

Lyme Disease. The PNS manifestations of Lyme disease are divided into early and late. The early PNS syndromes commonly include facial nerve involvement (rarely other cranial nerve palsies) and radiculoneuritis. Late PNS involvement occurs as a DSPN, mononeuropathy multiplex, or radiculoneuropathy. The most common neurologic abnormality in Lyme disease is unilateral or bilateral facial nerve palsy, usually occurring within a month of exposure. Patients may also complain of headache and constitutional symptoms. Early in the course of Lyme disease, severe neuritic pain may develop in a radicular distribution, often in or near the dermatome where the tick bite occurred. There may also be associated sensory changes, motor weakness, and decreased reflexes consistent with nerve root involvement.

Patients with chronic Lyme disease present with sensory symptoms, particularly distal paresthesias in the lower extremities. Less commonly, they develop a picture consistent with mononeuropathy multiplex or a radiculopathy, which is much less severe than the early radiculoneuritis of Lyme disease. The diagnosis and management of Lyme disease is discussed in Chapter 126.

Diagnostic Testing

Vasculitis related multiple mononeuropathy is diagnosed with a sural nerve biopsy.

The most useful diagnostic tests for patients with suspected Lyme disease are a serum enzyme-linked immunosorbent assay, Western blot, and CSF examination. CSF abnormalities suggestive of Lyme disease are a lymphocytic pleocytosis, elevated protein level, and normal glucose concentration. The CSF is almost always abnormal in early radiculitis, sometimes abnormal with isolated facial palsy, and typically normal in chronic Lyme disease.

Management

Facial nerve palsy in Lyme disease without CSF abnormalities may be treated with oral doxycycline 100 mg twice a day for 2 weeks. Intravenous (IV) ceftriaxone is the drug of choice for all other neurologic syndromes associated with Lyme disease. The adult dosage is 2 g/day, and the pediatric dosage is 75 to 100 mg/kg per day. The standard course of treatment with IV ceftriaxone is at least 2 weeks.

Type 6: Amyotrophic Lateral Sclerosis

Principles

Although *amyotrophic lateral sclerosis (ALS)* and *motor neuron disease (MND)* are often used synonymously, the latter represents a spectrum of diseases ranging from primary lateral sclerosis, in which degeneration is confined to upper motor neurons, to progressive muscle atrophy, in which only lower motor neurons are involved. ALS, which requires the presence of both upper and lower motor neuron findings, resides in the middle of this spectrum, representing the most common form of MND. The incidence of ALS is 1.5 to 2.5 per 100,000. Most develop symptoms in middle-adult life, with motor weakness in the extremities,

BOX 97.9

Objective Clinical Findings Consistent With Amyotrophic Lateral Sclerosis

UPPER MOTOR NEURON SIGNS
- Hyperreflexia
  - Sustained clonus, especially at ankle
  - Finger flexors and jaw jerk
- Spasticity, especially of gait
- Presence of Babinski's sign

LOWER MOTOR NEURON SIGNS
- Positive motor phenomena
  - Fasciculations
  - Cramps
- Negative motor phenomena
  - Asymmetrical distal weakness
  - Atrophy

COMBINED UPPER AND LOWER MOTOR NEURON SIGNS
- Dysarthria
- Dysphagia
- Respiratory compromise

spasticity, paralysis, and eventually death, typically within 3 to 5 years of symptom onset.[20]

In ALS, the primary pathologic process in the PNS component of the disease is a neuronopathy of the anterior horn cell. Because this structure is located proximal to the point where motor and sensory fibers merge to form mixed spinal nerve roots, the signs and symptoms of MND are purely motor (see Fig. 97.2). In the CNS, there is a loss of Betz cells from the motor cortex with secondary degeneration of the corticospinal tracts.

Clinical Findings

Box 97.9 lists some representative upper, lower, and mixed motor signs. Patients typically demonstrate asymmetrical distal weakness without sensory findings. Positive motor phenomena in the form of fasciculations are found in almost all patients at diagnosis but are rarely an initial complaint. Although there is electrophysiologic evidence of autonomic involvement in ALS, this is generally subclinical.

Diagnostic Testing

All patients in whom this diagnosis is suspected should be referred for electrophysiologic confirmation against standardized criteria, with denervation combined with the physical findings typically confirming the diagnosis. Confirmation is particularly important because multifocal motor neuropathy, a rare disease that masquerades as ALS, responds dramatically to cyclophosphamide and immune globulin administration.

BOX 97.10

Sensory Neuronopathies (Ganglionopathies)

- Herpes
  - Herpes simplex 1 and 2
  - Varicella-zoster (shingles)
- Inflammatory sensory polyganglionopathy
- Paraneoplastic
- Primary biliary cirrhosis
- Sjögren's syndrome (keratoconjunctivitis sicca)
- Toxin induced
  - Pyridoxine (vitamin B_6) overdose
  - Metals
    - Platinum (cisplatin)
    - Methyl mercury
- Vitamin E deficiency

Management

The only drug to demonstrate survival benefit in humans with ALS is riluzole, prolonging mean survival from 12 to 15 months.[21] The development of a multidisciplinary team approach has had a much higher impact on overall quality of life for patients with ALS. This team includes ALS-focused neurologists, nurses, occupational therapy, and speech therapy amongst others.[22]

Type 7: Sensory Neuronopathy (Ganglionopathy)

Principles

This category of peripheral neuropathy is characterized by a selective or predominant involvement of the dorsal root ganglion, producing a relatively pure sensory syndrome analogous to the pure motor syndrome of ALS.

Clinical Findings

Although all sensory modalities are affected, proprioception is profoundly altered, leading to sensory ataxia and loss of DTRs without weakness. The distribution is typically asymmetrical and distal at the outset, but depending on severity and extent of progression, it may become functionally symmetrical.

Diagnostic Testing

Sensory ganglionopathies can be confirmed by MRI of the spinal cord and surrounding areas, showing degeneration of central sensory projections that localize the disease process to the dorsal root ganglion. Some of the more common causes of this type of peripheral neuropathy are listed in Box 97.10.

Management

The management of sensory neuropathies is symptomatic in nature and best left to the patient's primary physician.

KEY CONCEPTS

- It is not usually possible to arrive at the diagnosis of a specific peripheral neuropathy in the ED because of the need for confirmatory ancillary testing. One should focus on identifying one of seven categorical patterns of peripheral neuropathy, shown in Figure 97.1 and listed in Table 97.1.
- One of these seven patterns can usually be identified by combining three clinical features that are readily obtainable from a goal-directed history and physical: (1) right-left symmetry or asymmetry, (2) proximal-distal location, and (3) sensorimotor modalities affected.
- Identification of the type of peripheral neuropathy determines the need for ancillary diagnostic testing, therapeutic intervention, disposition, and timing of neurologic referral.
- Any patient with symmetrical weakness, distributed both proximally and distally, with loss or diminution of DTRs and variable sensory abnormalities should be treated as having GBS.
- Respiratory compromise is the primary life-threatening event seen in some peripheral neuropathies; GBS is by far the most common peripheral neuropathic cause of respiratory arrest.
- The definitive treatments for GBS are plasma exchange or intravenous immune globulin (IVIG).
- Most polyneuropathies are characterized by a pattern of distal, symmetrical sensorimotor findings, worse in the lower than in the upper extremities, with a stocking-glove distribution of sensory abnormalities that gradually diminishes as one moves proximally.
- High level evidence supports the use of tricyclic antidepressants, anticonvulsants, and the serotonin and norepinephrine reuptake inhibitor nuloxetine treating diabetic DSPN.
- Radial nerve mononeuropathies are characterized by wrist and finger drop and mild numbness over the skin of the first dorsal interosseus muscle.
- Humeral shaft fractures are associated with radial nerve injury, with "wrist drop" the hallmark clinical finding.
- The ulnar cutaneous innervation to the hand branches from the main trunk proximal to the nerve entering Guyon's canal thus a lesion at the wrist should not produce sensory abnormalities, whereas one at the elbow would be expected to do so.
- The most specific finding for carpal tunnel syndrome (CTS) is splitting of the fourth digit (ie, normal sensation of the ring finger on the ulnar palmar side with abnormal sensation on the median [radial] palmar side of the same finger).
- Lateral femoral cutaneous mononeuropathy (meralgia paresthetica) is caused by injury to this pure sensory nerve as it passes through or over the inguinal ligament, where it may become entrapped or kinked.
- The most striking feature of a complete common peroneal mononeuropathy is footdrop caused by weakness of foot dorsiflexion.
- The most common neurologic abnormality in Lyme disease is unilateral or bilateral facial nerve palsy, usually occurring within a month of exposure.
- ALS requires the presence of both upper and lower motor neuron findings, and is the most common form of motor neuron disease (MND).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 97: QUESTIONS & ANSWERS

97.1. Which category of peripheral neuropathy tends to occur in an asymmetrical, distal distribution?
- **A.** Autonomic neuropathy
- **B.** Large-fiber neuropathy
- **C.** Mixed motor and sensory neuropathy
- **D.** Neuropathy from vasculitis
- **E.** Pure motor neuropathy

Answer: E. Pure motor and pure sensory peripheral neuropathies tend to occur in an asymmetrical distal pattern.

97.2. A 26-year-old woman presents with a chief complaint of weakness. She notes a 1- or 2-day onset of easy fatigability and diminished ability to navigate stairs. She has no past history and takes no medications. Vital signs are normal. Physical examination reveals absent lower extremity deep tendon reflexes (DTRs); symmetrical weakness of the quadriceps, calf muscles, and foot/toe dorsiflexion; and minimal sensory loss. Cranial nerve and upper extremity examination is normal. Which of the following is likely?
- **A.** An antecedent viral illness
- **B.** Lack of anal sphincter tone
- **C.** Onset of ocular muscle dysfunction
- **D.** Sparing of the autonomic nervous system
- **E.** Urinary retention

Answer: A. Guillain-Barré syndrome (GBS) is characterized by fairly acute onset of ascending weakness, loss of deep tendon reflexes (DTRs), and variable sensory loss. Antecedent infections often trigger, with common organisms being campylobacter, cytomegalovirus, Epstein-Barr virus, and mycoplasma. Rarely, symptoms begin in the upper extremities. Urinary retention is common, but anal tone is preserved. Ocular muscles are usually spared. Autonomic neuropathy is common, with marked variations in heart rate and blood pressure. Patients with predominantly sensory symptoms tend to have less risk of respiratory embarrassment and a more favorable prognosis. Lumbar puncture shows cerebrospinal fluid (CSF) pleocytosis or may be normal early on.

97.3. A 26-year-old woman presents with lower extremity weakness and difficulty walking. Examination is remarkable for lower extremity symmetrical weakness with mild symmetrical sensory loss and absent lower extremity deep tendon reflexes (DTRs). Symptom onset has been during 2 days. What should be the next step?
- **A.** Emergent magnetic resonance imaging (MRI)
- **B.** Intravenous immune globulin (IVIG)
- **C.** Lumbar puncture and antibiotics
- **D.** Pulmonary function studies
- **E.** Urgent neurologic consultation

Answer: D. All patients with Guillain-Barré syndrome (GBS) are at risk of respiratory failure. A forced vital capacity (FVC) of less than 20 mL/kg and a negative inspiratory force of less than 30 cm H_2O are associated with impending ventilatory failure and the need for intubation.

97.4. Among patients with Guillain-Barré syndrome (GBS) who have normal pulmonary function, which of the following can be monitored to predict impending ventilatory failure?
- **A.** Deltoid strength
- **B.** Extensor neck strength
- **C.** Hand grip strength
- **D.** Masseter strength
- **E.** Rectus abdominis strength

Answer: B. Extensor muscle strength has been shown to correlate with ventilatory muscle strength.

97.5. A 53-year-old diabetic presents with a complaint of increasing difficulty walking in the last several months. He has no other past history but has been an insulin-dependent diabetic for 23 years. Current glucose level is 138 mg/dL, and chemistries and complete blood count are otherwise unremarkable. Examination is remarkable for bilateral lower extremity numbness extending symmetrically to above the knees, loss of the Achilles reflex bilaterally with footdrop, and steppage gait. Which of the following is true?
- **A.** Autonomic neuropathy is unlikely.
- **B.** Facial numbness would necessitate MRI.
- **C.** Hand numbness is expected.
- **D.** Erythrocyte sedimentation rate is likely to be elevated.
- **E.** Lumbar spine MRI will likely show a pathologic process.

Answer: C. Diabetic neuropathy is a progressive, ascending mixed polyneuropathy. Hand numbness and upper extremity symptoms usually begin before the lower extremity symptoms ascend to the knees. Extensive motor loss can occur with gait and grip abnormalities. Skull and face numbness can occur. Autonomic dysfunction is expected.

97.6. A 53-year-old diabetic presents with increasing symmetrical dysesthetic pain from his well-documented severe diabetic neuropathy. His only medications are insulin and over-the-counter analgesics. Laboratory evaluation is remarkable for a glucose concentration of 183 mg/dL and a creatinine level of 2.1 mg/dL with normal chemistries. Which of the following is indicated as a first-line analgesic in this patient?
A. Amitriptyline
B. Hydrocodone with acetaminophen
C. Naprosyn sodium
D. Paroxetine
E. Tramadol

Answer: A. First-line agents for neuropathic pain are the anticonvulsants and cyclic antidepressants. Specifically, gabapentin, pregabalin, amitriptyline, imipramine, and nortriptyline are useful. Tramadol and opiates may be effective but less so. Tramadol is renally excreted (as is gabapentin), and doses must be adjusted for falling creatinine clearances. Nonsteroidal antiinflammatory drugs (NSAIDs) do not have great usefulness for neuropathic pain (there is no "inflammatory" component) and would be contraindicated with elevated creatinine. Opiates may be beneficial, but issues of tolerance are significant. Selective serotonin reuptake inhibitors may be effective but are second-line agents (the norepinephrine-modulating ability of tricyclic antidepressants makes them more effective analgesics than the serotonin-specific agents).

97.7. Which of the following characteristics separates the clinical picture of alcoholic versus diabetic neuropathy?
A. Autonomic changes
B. Incontinence
C. Myopathy
D. Sensory loss
E. Weakness

Answer: C. The presence of myopathy and cerebellar degeneration helps distinguish alcoholic neuropathy. Otherwise, the clinical pictures are similar. Incontinence is not a typical feature of either.

97.8. What is the most common neurologic complication of HIV infection?
A. Autonomic neuropathy
B. Cerebellar dysfunction
C. Cranial nerve dysfunction
D. Peripheral neuropathy
E. Spinal anterior horn degeneration

Answer: D. It is typically a distal mixed motor and sensory polyneuropathy. It is triggered by a combination of poorly defined immune mechanisms and dideoxynucleoside therapy.

97.9. A 53-year-old woman presents with progressive pain involving her left shoulder and upper arm. She describes a deep aching pain that is poorly localized and is occasionally accompanied by tingling sensations in the left hand in a nondermatomal pattern. Her medical history is negative except for a history of left-sided breast cancer 6 years prior for which she underwent a total mastectomy followed by field irradiation and oral antiestrogen therapy. She currently takes no medications. Review of systems and laboratory results are negative. Physical examination shows only left shoulder dysesthesias. The chest radiograph is normal. What should be the next step?
A. Computed tomography scan of the chest
B. Gabapentin in titrated doses
C. Hydrocodone with acetaminophen and reassurance
D. MRI scan of the brachial plexus
E. Referral for upper extremity electromyography (EMG) and nerve conduction studies (NCSs)

Answer: D. Although plexopathies are most commonly posttraumatic, radiation, postviral, and infiltrative processes also occur. In a patient who is status post an oncologic diagnosis and radiation therapy, oncologic recurrence must be ruled out with an imaging study. Radiation plexopathy, which can occur up to 20 years out, is most often a diagnosis of exclusion and ultimately requires symptomatic treatment of neuropathic pain.

CHAPTER 98

Neuromuscular Disorders

Peter Shearer

PRINCIPLES

Disorders of the neuromuscular unit can result in clinical presentations that range from subtle symptoms to acute respiratory failure with significant morbidity and mortality. In most cases, the pathophysiologic mechanism of these disorders is well understood and permits an organization and understanding based on the level of the nervous system affected. This facilitates an approach that interprets signs and symptoms, the findings of which direct the urgency of diagnostic testing and treatment.

The neuromuscular unit has four components: the anterior horn cells of the spinal cord, the peripheral nerve, the neuromuscular junction, and the muscle innervated. The level of the pathologic process determines associated signs and symptoms (Fig. 98.1 and Table 98.1). *Myelopathies* involve the spinal cord; *radiculopathies* involve the nerve roots as they leave the spinal cord; *neuropathies* involve the peripheral nerves; and *myopathies* involve the muscle. The use of physical signs to differentiate these disorders is discussed in Chapter 10.

Neuropathies involve the axon or the myelin sheath of the nerve. Nerve conduction studies can differentiate the locations of involvement. As the conduction along the axon is disrupted, the subsequent delay in transmission first causes symptoms in the muscles controlled by longer nerve axons, resulting in a history of ascending weakness. As the myelin destruction or axonal degeneration progresses, patients usually note a slowly progressive course of symptoms.

The neuromuscular junction is composed of the presynaptic membrane, the postsynaptic membrane, and the synaptic cleft. The neurotransmitter is acetylcholine (ACh). The motor synapse is a nicotinic receptor, whereas muscarinic synapses link the central nervous system (CNS) with the autonomic nervous system. Disorders of the postsynaptic nicotinic receptors produce weakness. Postsynaptic ACh receptors are continually turned over at a rate that is related to the amount of stimulation. A disorder of transmission often leads to increased production of ACh receptors. Myasthenia gravis is the prototype of neuromuscular junction diseases.

CLINICAL FEATURES

History

The history of patients with complaints of weakness focuses on the acuity and the potential for airway compromise. Any complaint of difficulty in breathing or swallowing raises suspicion of bulbar involvement and concern for life-threatening deterioration. Weakness is the inability to exert normal force, whereas fatigue implies a decrease in force with repetitive use and the clinical history should distinguish which is present. When muscle weakness exists, the clinician should determine whether it is focal or generalized, proximal or distal. The history of present illness should include the duration of symptoms, exacerbating and mitigating factors, and presence of associated symptoms, such as fever, weight loss, and bowel or bladder changes.

Historical elements might explain the presenting complaint: a preexisting neuromuscular disorder that could lead to deterioration; prior episodes or a family history of weakness suggesting periodic paralysis; a recent respiratory or diarrhea illness suggesting a postinfectious, autoimmune process, such as Guillain-Barré syndrome or enterovirus D68, which has been reported to cause muscle weakness and paralysis in children; a cancer history suggesting a metastatic tumor as the cause of a compressive myelopathy; and a food or travel history suggesting botulism or tick exposure.[1]

Physical Examination

The examination should first assess the patient's ability to breathe and ventilate and then evaluate the degree of weakness and the location of the lesion. The presence of swallowing and a strong cough suggest that the patient has sufficient protective and ventilatory reserve. The muscles used to lift the head off the bed may weaken before those of respiration and should be assessed. A patient who is not yet intubated but is complaining of shortness of breath or difficulty in breathing should have frequent measurements of forced vital capacity (FVC). Normal FVC ranges from 60 to 70 mL/kg; when the FVC reaches 15 mL/kg, ventilatory support is necessary. If vital capacity cannot be measured, a maximal negative inspiratory force (NIF) is easily determined. NIF of less than 15 cm H_2O suggests the need for intubation. Blood gas analysis is not helpful because functional reserve can be severely diminished by the time a patient has either hypercarbia or hypoxia.

Some causes of weakness may result in dysregulation of the autonomic system and abnormal vital signs. A systematic neurologic examination assesses the patient's mental status, cranial nerves, motor and sensory function, deep tendon reflexes, and coordination, including cerebellar function. The motor examination begins by determining whether the weakness is unilateral or bilateral and which muscle groups are involved. Key components of the examination include motor strength, muscle bulk, and presence of fasciculations. Box 98.1 provides the grading system used in motor strength assessment. Table 98.2 provides the findings used to distinguish upper motor neuron from lower motor neuron processes.

DIFFERENTIAL DIAGNOSIS

Myelopathies

Myelopathies are spinal cord disorders that are manifested with signs of upper motor neuron dysfunction, such as muscle weakness with increased spinal reflexes, including an extensor plantar reflex (Babinski's response). There may be bladder and bowel involvement. When sensory findings are present, they often define the level of the lesion. The presence of back pain suggests a compressive lesion, such as a herniated intravertebral disk, epidural hematoma, abscess, or tumor. Acute, painless spinal cord lesions include transverse myelitis and spinal cord infarction. Myelopathies are discussed in Chapter 96.

Motor Neuron Disease

The characteristic findings of motor neuron disease combine signs of both upper and lower motor neuron dysfunction, including hyperreflexia, muscle wasting, and fasciculations. Pain is not a component of the clinical picture. Amyotrophic lateral sclerosis is the prototypical motor neuron disease

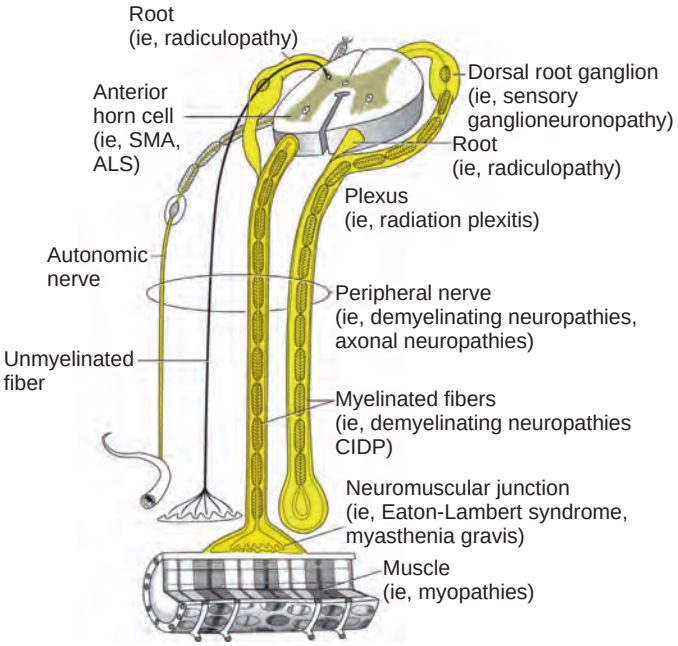

Fig. 98.1. The anatomic elements of the peripheral nervous system and related neurologic disorders. *ALS,* Amyotrophic lateral sclerosis; *CIDP,* chronic inflammatory demyelinating polyneuropathy; *SMA,* spinal muscular atrophy. (From Bertorini TE: Neuromuscular anatomy and function in neuromuscular case studies. In: Neuromuscular case studies, Philadelphia, 2008, Butterworth-Heinemann/Elsevier.)

Poliomyelitis affects the anterior horn cells and results in lower motor neuron disease without sensory involvement. The weakness can be symmetrical, although more often it is asymmetrical. Patients initially have a clinical picture similar to that of viral meningitis with fever and neck stiffness. Currently, most cases follow exposure of an immunocompromised host to the oral polio vaccine, and this should be sought in the history. The cerebrospinal fluid (CSF) analysis resembles that of viral meningitis.

Neuropathies

Weakness from a neuropathy is often noted first in distal muscles and then ascends. Decreased grip strength and foot drop are common presentations. The differential diagnosis includes Guillain-Barré syndrome, toxic neuropathies, diabetic neuropathy, and tick paralysis (which is caused by inhibition of both nerve conduction and function of the neuromuscular junction). Neuropathies are discussed in Chapter 97.

Diseases of the Neuromuscular Junction

Disorders of the neuromuscular junction cause motor fatigability. The initial depolarization at the nerve endplate stimulates a

BOX 98.1

Grading Score for Motor Strength

5 = Normal strength
4 = Weak but able to resist examiner
3 = Moves against gravity but unable to resist examiner
2 = Moves but unable to resist gravity
1 = Flicker but no movement
0 = No movement

TABLE 98.1

Clinical Characteristics of Neuromuscular Diseases

DISEASE	HISTORY	STRENGTH	DEEP TENDON REFLEX	SENSATION	WASTING
Myelopathy	Trauma, infection, cancer	Normal to decreased	Increased	Normal to decreased	No
Motor neuron disease (ALS)	Progressive difficulty swallowing, speaking, walking	Decreased	Increased	Normal	Yes
Neuropathy	Recent infection Ascending weakness	Normal or decreased Distal > proximal	Decreased	Decreased	Yes
Neuromuscular junction disease	Food (canned goods) Tick exposure Easy fatigability	Normal to fatigue	Normal	Normal	No
Myopathy	Thyroid disease Previous similar episodes	Decreased Proximal > distal	Normal	Normal	Yes

ALS, Amyotrophic lateral sclerosis.

TABLE 98.2

Distinguishing Upper Motor Neuron From Lower Motor Neuron Involvement

MOTOR NEURON	DEEP TENDON REFLEX	MUSCLE TONE	ATROPHY	FASCICULATIONS	BABINSKI'S RESPONSE
Upper motor neuron	Increased	Increased	No*	No	Present
Lower motor neuron	Decreased	Decreased	Yes	Yes	Absent

*Not significant but can occur.

maximum number of ACh receptors on the muscle cell, producing a normal or nearly normal strength response. Repeated stimulation leads to diminishing motor strength, which is caused by one of three mechanisms: blockage of the receptors, as in myasthenia gravis; decrease in the amount of ACh released, as in botulism; or inactivation of ACh by irreversible binding, as in organophosphate poisoning.

A decrease in the release of ACh can cause a combination of nicotinic and muscarinic effects. The clinical manifestations of this are anticholinergic findings, such as decreased visual acuity, confusion, urinary retention, tachycardia, low-grade fever, and dry, flushed skin. In the case of Lambert-Eaton myasthenic syndrome, weakness is more pronounced at the beginning of muscle use and improves with repeated use as more ACh builds up in the synaptic cleft with each stimulation. Diseases of the neuromuscular junction are considered in patients who present with generalized weakness in association with an acute cranial nerve deficit. Muscle tone is generally diminished and sensation is preserved in diseases of the neuromuscular junction.

Myopathies

Myopathies produce generalized, symmetrical weakness. Reflexes are diminished, muscle tone is usually diminished, but sensation is preserved. Myopathies due to inflammatory disorders (polymyositis, dermatomyositis, polymyalgia rheumatica, and viral myositis) cause muscle pain and tenderness. Metabolic disorders affecting muscle strength (eg, electrolyte and endocrine disorders) are painless in nature.

DIAGNOSTIC TESTING

Laboratory Studies

Serum potassium, calcium, and phosphorus concentrations should be assessed in patients with acute weakness. Thyroid function tests are recommended in cases of suspected myopathies. A creatine kinase (CK) level assesses for muscle inflammation; urinalysis should be performed to test for the presence of myoglobinuria and possible rhabdomyolysis, and renal function studies should be obtained when rhabdomyolysis is present.

Special Studies

Magnetic resonance imaging (MRI) is the preferred test for suspected cases of acute myelopathy. Computed tomography (CT) of the spinal cord with myelography can help differentiate compressive (herniation, abscess, tumor) from noncompressive causes when MRI is not available. CSF analysis is indicated when Guillain-Barré syndrome or transverse myelitis is suspected.

DISORDERS OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

Principles

The age at onset of myasthenia gravis is bimodal; women are most commonly affected between 20 and 40 years old and men between 50 and 70 years old. Whereas new cases of myasthenia gravis are occasionally diagnosed in the emergency department (ED), it is much more common for patients with established disease to present with exacerbations of their disorder, often caused by precipitating factors.

In most patients with myasthenia gravis, weakness and fatigue result from circulating autoantibodies against the ACh receptor on the junctional folds on the post synaptic membrane. The effects are multifactorial: direct blocking of the receptor, complement mediated destruction of the folds, and internalization and degradation of the receptors (Fig. 98.2). With repeated stimulation, fewer and fewer receptor sites are available for ACh binding, and fatigue develops. Fatigability and muscle weakness are the hallmarks of myasthenia gravis. The clinical progression of myasthenia gravis is slow, and the likelihood of short-term complications is low, so the most important aspect of emergency care is early recognition and proper referral for further evaluation when the disease is suspected. Many commonly used drugs can adversely affect patients with myasthenia gravis (Box 98.2).

Myasthenic Crisis. *Myasthenic crisis* is defined as respiratory failure leading to mechanical ventilation. It occurs in 15% to 20% of patients with myasthenia gravis, usually within the first 2 years

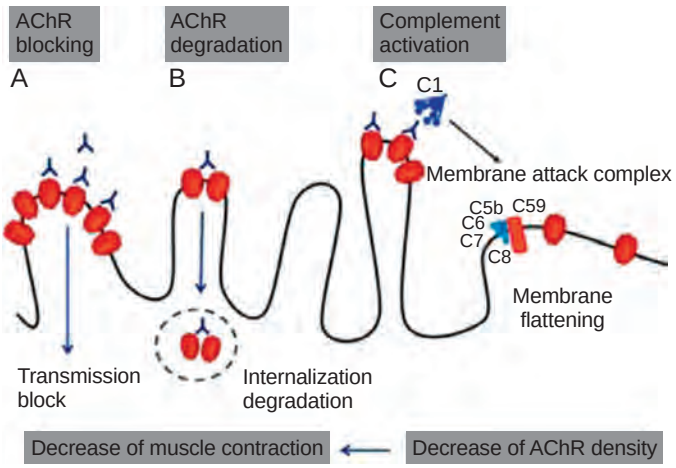

Fig. 98.2. Mechanisms of action of acetylcholine receptor *(AChR)* autoantibodies. Neuromuscular synapse in myasthenia gravis. AChR antibodies interfere with signal transduction by direct blocking of AChR **(A),** by cross-linking and increased degradation **(B),** or by immune mediated destruction including complement activation **(C).** (From Sommer N, Tackenberg B, Hohlfeld R: The immunopathogenesis of myasthenia gravis. In Engel AG, editor: Handbook of clinical neurology, volume 91, neuromuscular junction disorders, St Louis, 2008, Elsevier, pp 169–212.)

BOX 98.2

Drugs That May Exacerbate Myasthenia Gravis

- Cardiovascular
  - Beta-blockers
  - Calcium channel blockers
  - Quinidine
  - Lidocaine
  - Procainamide
- Antibiotics
  - Aminoglycosides
  - Tetracyclines
  - Clindamycin
  - Lincomycin
  - Polymyxin B
  - Colistin
- Other
  - Phenytoin
  - Neuromuscular blockers
  - Corticosteroids
  - Thyroid replacement

of disease onset. Although it is potentially life-threatening, the mortality from this complication of myasthenia gravis has declined dramatically with aggressive care in the intensive care unit (ICU) and the use of plasma exchange or immunomodulatory therapy with intravenous immune globulin (IVIG).

Crises are most often precipitated by underlying infection, aspiration, and medication changes, such as stopping anticholinergic medications or taking a new medication that precipitates weakness. Other precipitants can be surgery and pregnancy (see Box 98.2).

Lambert-Eaton Syndrome. Lambert-Eaton myasthenic syndrome is a rare disorder. Almost 50% of cases are associated with small cell carcinoma of the lung. Autoantibodies cause inadequate release of ACh from nerve terminals, affecting both nicotinic and muscarinic receptors. With repeated stimulation, the amount of ACh in the synaptic cleft increases, leading to an increase in strength, which is the opposite of that seen with myasthenia gravis. The classic syndrome includes weakness that improves with use of muscles, particularly proximal hip and shoulder muscles; hyporeflexia; and autonomic dysfunction, most commonly seen as dry mouth. Management primarily focuses on treatment of the underlying neoplastic disorder, although IVIG has been reported to be useful.

Clinical Features

Patients with myasthenia gravis present with easy fatigability—progressive weakness with repeated activity of affected muscle groups. Ocular symptoms are often the first manifestation of myasthenia gravis; typical symptoms are ptosis, diplopia, and blurred vision. Ocular muscle weakness is the first sign in up to 40% of patients, although 85% of patients with myasthenia gravis eventually have ocular involvement. When ptosis is present, it is often worse toward the end of the day. Respiratory failure is rarely the initial symptom of myasthenia gravis. Even so, up to 17% of patients may have weakness of the muscles of respiration. Bulbar muscles may be involved, producing dysarthria or dysphagia.

Diagnostic Testing

The diagnosis of new-onset myasthenia gravis is based on clinical findings and a combination of serologic testing, electromyographic testing, and bedside testing with either edrophonium or the ice bag test. Serum testing for ACh receptor antibodies is positive in 80% to 90% of patients with myasthenia gravis, but it is not available in the ED.

The edrophonium test and ice bag test are performed at the bedside for patients with suspected myasthenia gravis and ptosis. The results based on the effect of the intervention on the ptosis. Edrophonium is a short-acting acetylcholinesterase-blocking agent that produces an increase of ACh in the synaptic cleft and a reduction in ptosis after intravenous (IV) administration. With the ice bag test, cooling decreases symptoms in myasthenia gravis, whereas heat exacerbates symptoms. In both tests, the amount of ptosis is measured before and after administration of edrophonium or application of an ice bag. The distance from the upper to the lower eyelid in the most severely affected eye is measured first. If edrophonium is given, an IV test dose of 1 to 2 mg is given first because some patients have a severe reaction. If no adverse reaction is found and the patient does not dramatically improve in 30 to 90 seconds, a second dose of 3 mg is given. If there is still no response, a final dose of 5 mg is given for a total maximum dose of 10 mg. Atropine should be available at the bedside during the test. Because of the potential for cholinergic-induced increased airway secretions, this test should be used with caution in asthmatics and patients with chronic obstructive pulmonary disease. If the ice bag test is used, an ice pack is applied to the affected eye for approximately 2 minutes. An improvement in the amount of ptosis of at least 2 mm is considered positive. The pooled sensitivity and specificity of the ice bag test for detecting ocular myasthenia is 0.94 and 0.97, respectively.

Management

The initial step in managing the patient in crisis is stabilization of the airway. Biphasic positive airway pressure (BiPAP) is effective in managing patients who need ventilatory support.

All patients with myasthenia gravis who present to the ED should be assessed for signs of myasthenic crisis even when they do not complain of weakness.

Cholinesterase Inhibitors. Pyridostigmine (60 to 120 mg by mouth every 4 to 6 hours) and neostigmine (0.5 mg SC/IM) prolong the presence and activity of ACh in the synaptic cleft. They are the backbone of chronic outpatient therapy and provide symptomatic improvement. The most common side effects are those of excessive cholinergic stimulation, such as increased airway secretions and increased bowel motility. At extremes, there may be bradycardia or even worsening of weakness, simulating a myasthenic crisis. These drugs are often used as adjunctive therapy to control symptoms while other therapy is being instituted, after which they are usually discontinued. IV cholinergic drug therapy, such as pyridostigmine, is not recommended for the treatment of myasthenic crises in the ED, because plasmapheresis and IVIG are both safe and highly effective therapies.

Immunosuppressant Drugs. Immunosuppressant drugs are used for the chronic control of myasthenia gravis. Although they have no role in the acute management of a myasthenic crisis, they may be started before extubation of a patient recovering from a crisis. A Cochrane review in 2005 found support for the use of corticosteroids, although cyclosporine, cyclophosphamide, azathioprine, or mycophenolate mofetil are used to decrease the need for steroids or for refractory cases. Of note, the initiation of corticosteroids in patients with moderate to severe weakness may actually precipitate a worsening of weakness or even myasthenic crisis.

Thymectomy. Whereas the association between thymoma and myasthenia gravis is not fully elaborated, it is well known that thymectomy for patients with thymoma can lead to remission of myasthenia gravis or enable a reduction in other medications. Thymectomy for patients with myasthenia gravis without thymoma is recommended as a treatment option, although its use is not supported by randomized controlled trials.

Immunomodulatory Therapy. Plasma exchange and IVIG are used for patients with an acute exacerbation of myasthenia gravis or preoperatively in patients with stable myasthenia gravis. Plasma exchange removes the ACh receptor antibodies and other immune complexes from the blood. The fall in ACh receptor levels is associated with improvement in symptoms of myasthenia gravis. There is a risk of complications from hypotension or anticoagulation. One small trial of IVIG versus placebo demonstrated the benefit of IVIG, whereas other trials have failed to show a difference between IVIG and plasma exchange.[2] In a cohort of myasthenia gravis patients managed in an ICU over 12 years, 87% were managed with IVIG and only 18% received plasma exchange. In the years preceding this cohort, only 11.4% received IVIG and 60% received plasma exchange reflecting the change in practice patterns.[3] At the current time, the decision to institute one therapy over the other is based on the input of the consulting neurologist and the resources most rapidly available.

Studies suggest that rituximab, a monoclonal antibody that decreases B-cell function, has an emerging role in refractory cases of myasthenia gravis.[4] Newer monoclonal antibody therapies directed at the complement mediated destruction of the ACh receptor are under investigation.

Steroids in the form or oral prednisone (1 to 1.5 mg/kg) or prednisolone (1 to 1.5 mg/kg) are often given for acute exacerbations of myasthenia gravis. In the 12-year cohort, above 97% of patients received prednisolone. The evidence supporting the efficacy of corticosteroids is limited.

Disposition

The decision to admit or to discharge a patient with myasthenia gravis from the ED should take into account the potential for neuromuscular deterioration with consideration of admitting a patient to an observation unit. Patients being admitted to the hospital should have a NIF or FVC measured to help determine the level of monitoring and care needed. These measurements need to be trended during the admission.

Botulism

Principles

Botulism is a toxin-mediated illness that can cause weakness leading to respiratory insufficiency. In 2012, the Centers for Disease Control and Prevention (CDC) reported 160 cases of botulism in the United States: 16% food-borne, 76% infant botulism, 5% wound botulism, and 3% unknown etiology.[5] *Clostridium botulinum* is an anaerobic, spore-forming bacterium. Three of eight known toxins produced by *C. botulinum* (types A, B, and E) cause human disease.

There have been outbreaks of wound botulism in Washington, California, England, Germany, and Norway associated with injection drug use.[6] In 2011, there was an outbreak among eight prisoners in Utah who drank "pruno," a prison-made wine.[7] Three of the eight required intubation. Botulism is also thought to be a potential agent for bioterrorism.

The botulinum toxin works by binding irreversibly to the presynaptic membrane of peripheral and cranial nerves, inhibiting the release of ACh at the peripheral nerve synapse. As new receptors are generated, the patient improves.

Clinical Features

The botulinum toxin blocks both voluntary motor and autonomic functions. There is no pain or sensory deficit. The onset of symptoms is 6 to 48 hours after the ingestion of tainted food. Symptoms of gastroenteritis may or may not be present. The classic feature of botulism is a descending, symmetrical, flaccid paralysis. Cranial nerves and bulbar muscles are affected first, causing diplopia, dysarthria, and dysphagia, followed later by generalized weakness. Because the toxin decreases cholinergic output, anticholinergic signs may be present: constipation, urinary retention, dry skin and eyes, and increased temperature and dilated, non-reactive pupils. This can help differentiate botulism toxicity from myasthenia gravis. Deep tendon reflexes are normal or diminished.

Infantile botulism results from the ingestion of *C. botulinum* spores that are able to germinate and produce toxin in the high pH of the gastrointestinal tract of infants. Botulism spores can survive in honey, so it is recommended that honey not be fed to infants. The clinical presentation includes constipation, poor feeding, lethargy, and weak cry; consequently, this diagnosis must be included in the differential diagnosis of the floppy infant.

Diagnostic Testing

The diagnosis is made by both clinical findings and exclusion of other processes. The toxin can be identified in serum and stool, but the assay is not commonly available in most hospitals and requires a prolonged turnaround time. If the suspected food source is available, it should also be tested for the toxin.

Management

Treatment is initially focused on stabilization of the airway and supportive measures. In 2010, the CDC announced a new equine heptavalent botulinum antitoxin (HBAT) that is now the only antitoxin available in the United States for non-infant botulism.[8] For suspected cases and to obtain HBAT, clinicians should contact their state health departments. The CDC also maintains a botulism duty officer at the CDC Emergency Operations Center (770-488-7100). An IV human-derived botulism immune globulin (BabyBIG) has been developed for treatment of infantile botulism and is available through the California Department of Public Health Infant Botulism Treatment and Prevention Program on-call physician at 510-231-7600.

Disposition

All patients being treated for botulism need to be hospitalized, and most will be admitted to an ICU setting given the likelihood of progression of neuromuscular weakness. Infants and children will need to be transferred to the most appropriate neonatal intensive care unit (NICU) or pediatric intensive care unit (PICU) setting.

Tick Paralysis

Principles

This extraordinarily rare cause of an acute, ascending, flaccid paralysis is most often found in North America (Rocky Mountain region, US Pacific Northwest, and Southwestern Canada) and the east coast of Australia. Although the pathogenesis of tick paralysis is not fully understood, it is thought that a salivary toxin is injected while the tick feeds. The toxin functions like botulinum toxin to decrease the release of ACh from the presynaptic membrane of the neuromuscular junction.[9]

Clinical Features

Tick paralysis causes an acute, ascending, flaccid motor paralysis that can be confused with Guillain-Barré syndrome, botulism, and myasthenia gravis. Symptoms usually begin 1 to 2 days after the female tick has attached and begun to feed, although delays of up to 6 days have been reported. There may be associated ocular signs, such as fixed and dilated pupils, that can help distinguish it from Guillain-Barré syndrome.

Management

The management is supportive care and tick removal. A tick can be removed by use of forceps to grasp it as closely as possible to the point of attachment. Care should be taken not to leave mouth parts in the patient's tissue. Although symptoms may resolve rapidly after removal of the tick, supportive measures such as intubation should not be withheld pending resolution of symptoms. Although there is little new research on the topic, there are many reports of cases misdiagnosed as other causes of weakness (Guillain-Barré syndrome, acute inflammatory demyelinating

polyneuropathy, and so on) until the offending tick is found and removed.

Disposition

These patients may begin to show improvement upon removal of the tick and may be able to be discharged from the ED. There should be strong consideration of admission to an observation unit if the patient is slow to improve.

DISORDERS OF THE MUSCLES

Newly acquired weakness originating at the muscle level can be divided into two types: inflammatory and toxic-metabolic. Inflammatory disorders usually produce pain and tenderness, whereas metabolic disorders do not.

Inflammatory Disorders

Principles

The most common inflammatory myopathies are polymyositis and dermatomyositis. Polymyositis may be idiopathic in nature, occur secondary to infections (viral or bacterial), or be seen in conjunction with other disorders, such as sarcoidosis and hypereosinophilic syndromes. Inflammatory myopathies cause weakness, pain, and tenderness of the muscles involved.

Clinical Features

Dermatomyositis and polymyositis can occur at any age, although adults are more often affected than children. They can be associated with various malignant neoplasms, such as of the breast, ovary, lung, and gastrointestinal tract, and lymphoproliferative disorders. Proximal muscle weakness predominates and leads to complaints of difficulty in rising from a seated position or climbing stairs and weakness in lifting the arms over the head. There is often pain and tenderness in these proximal muscles as well. There is a decrease in reflexes that is in proportion to the decrease in strength. Fasciculations are not seen, and atrophy is a very late finding.

Dermatomyositis is similar to polymyositis, but it is also associated with classic skin findings. These are more prominent in childhood but are also found in adults. They include a periorbital heliotrope and erythema and swelling of the extensor surfaces of joints. The facial rash is usually photosensitive and may also involve the exposed areas of the chest and neck.

Diagnostic Testing

Electrolyte abnormalities must be ruled out and the serum CK level checked. The CK level should be interpreted in light of the entire clinical picture; an elevated CK level does not establish the cause of weakness as a myopathy because some neuropathies can also produce an elevated CK level. Similarly, a normal CK level does not rule out a myopathy as the cause of weakness. Electromyography and muscle biopsy are used to confirm the diagnosis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often normal or only mildly elevated; thus they have no role in diagnosis or prognosis.

Management

Polymyositis and dermatomyositis are usually managed with oral prednisone in a dose of 1 to 2 mg/kg/day. When steroids prove ineffective and during acute exacerbations, cytotoxic drugs such as azathioprine (initial dose of 50 mg/day) and methotrexate (initial dose of 15 mg/week) are added. Fortunately, the degree of rhabdomyolysis seen with the inflammatory myopathies is not sufficient to cause renal impairment.

Disposition

The majority of these patients will likely be discharged, some following an observation period. Hospitalization should be considered for patients with comorbidities, elders, and those who do not improve with treatment in the ED or observation unit.

Metabolic Disorders

Acute, generalized muscle weakness can be seen with a number of severe electrolyte abnormalities of any cause: hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypophosphatemia. Acute painless myopathies can also be seen with endocrine disorders involving the thyroid, parathyroid, or adrenal glands.

Of particular interest are several disorders referred to collectively as the *periodic paralyses,* which include periodic paralysis of the hyperkalemic and hypokalemic forms and thyrotoxic periodic paralysis, which is similar to hypokalemic periodic paralysis except that it is associated with hyperthyroidism.

Periodic Paralysis

Principles. Periodic paralysis of the hypo- and hyperkalemic forms are rare hereditary disorders of ion channels resulting in intermittent attacks of flaccid extremity weakness. The hypokalemic form is more common than the hyperkalemic form. Periodic paralysis is most often associated with an inherited genetic mutation. Patients usually report a personal and family history of similar episodes. Thyrotoxic periodic paralysis is an acquired rather than inherited form of hypokalemic periodic paralysis.

The clinical picture of thyrotoxic periodic paralysis is almost identical to that of periodic paralysis, and indeed a small number of patients with hypokalemic periodic paralysis have hyperthyroidism. In thyrotoxic periodic paralysis, symptoms related to hyperthyroidism are often present at the same time the patient has weakness. The relation of the hyperthyroidism to hypokalemia is probably due to increased sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) pump, which causes a rapid shift of potassium from the extracellular into the intracellular compartment. There is probably a genetic feature underlying this disorder, because there is a higher incidence of repeated attacks of hypokalemic periodic paralysis among Japanese and Chinese patients with hyperthyroidism.[10] It is important that all patients have thyroid function testing performed after a first episode of hypokalemic paralysis.

Clinical Features. Patients may suffer either isolated or recurrent episodes of flaccid paralysis. The lower limbs are involved more often than the upper, although both can be affected. Bulbar, ocular, and respiratory muscles are usually not involved. Onset is rapid often following a high oral carbohydrate intake (with subsequent insulin rise) and a period of rest. This reflects the intracellular shift of potassium rather than the total body depletion of potassium. A typical complaint is acute weakness noted on waking the morning after a large meal.

Diagnostic Testing. The electrocardiogram may demonstrate signs of hyperkalemia or hypokalemia. An immediate determination of potassium level should be obtained; in the hypokalemic form, the potassium level during an attack falls to values well below 3.0 mEq/L.

Management. Many cases resolve spontaneously with supportive care alone. The mainstay of management is the treatment of the underlying electrolyte imbalance. In the hypokalemic state, the total body potassium concentration is not depleted but has shifted intracellularly. Thus, in the repletion of potassium, caution is necessary to prevent overtreatment. For this reason, IV potassium should be used sparingly; one or two 10-mEq IV doses of potassium chloride, each over 1 hour, is the maximum IV dose. This can be done in parallel with 40 mEq oral potassium repletion and retesting of serum potassium levels. IV hydration helps redistribute the body's potassium stores. Magnesium supplementation is not necessary. Treatment of the hyperthyroid symptoms in thyrotoxic periodic paralysis, such as tachycardia, may help the paralysis as well. There are case reports of thyrotoxic periodic paralysis in which the patient's weakness did not respond to potassium replacement until propranolol was given to treat tachycardia. However, there is insufficient evidence to make specific management recommendations in this regard.

Disposition. In the past, most cases of periodic paralysis needed to be hospitalized, but with the increased availability of observation units they can likely be managed in less than 24 hours. Admission can be considered for patients with their first episode of periodic paralysis for patients needing management of thyrotoxicosis.

KEY CONCEPTS

- The approach to evaluation of patients with acute neuromuscular weakness is facilitated by first determining the location of the lesion (spinal cord, nerve, neuromuscular junction, or muscle) and then considering the most common disorders that affect the area in question.
- In patients presenting with acute neuromuscular weakness, complaints of difficulty in breathing or swallowing should heighten suspicion of bulbar involvement with possible airway compromise. In such patients, FVC of less than 15 mL/kg or maximal NIF of less than 15 mm H_2O is a potential indication for mechanical ventilation.
- Patients with a neuromuscular decline in respiratory function can be given a trial of noninvasive ventilation.
- The edrophonium and ice bag tests can be useful bedside tests in the evaluation of a suspected new diagnosis of myasthenia gravis.
- Plasma exchange therapy and IVIG are both useful for the treatment of myasthenic crises with the choice dependent on which is available and preferred in the ICU.
- Botulism usually arises as a painless descending paralysis, often first affecting the cranial nerves and bulbar muscles, without sensory deficits or significant alteration of consciousness. The treatment is airway management and administration of antitoxin.
- Injection drug use remains an important cause of wound botulism outbreaks.
- Botulism must be considered in the evaluation of a weak and floppy infant.
- In hypokalemic periodic paralysis, the total body potassium level is not depleted, only shifted intracellularly: treatment should keep this in mind as potassium is administered with frequent checks of serum potassium levels.
- In newly diagnosed hypokalemic periodic paralysis, the patient should be evaluated and treated for hyperthyroidism if present.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 98: QUESTIONS & ANSWERS

98.1. Which of the following is an indication for intubation in a 70-kg patient with weakness due to neuromuscular disease?

A. Arterial Pco_2 of 42 mm Hg
B. Forced vital capacity (FVC) of 950 mL
C. Negative inspiratory force (NIF) of 18 mm Hg
D. Oxygen saturation of 95% on room air
E. Respiratory rate of 24 breaths per minute

Answer: B. An FVC less than 15 mL/kg or an NIF less than 15 mm Hg are indications for intubations. Regarding arterial blood gas analysis, functional reserve can be severely diminished by the time a patient develops hypoxia or hypercarbia.

98.2. Match the following pathologic conditions with their correct associated finding(s):

A. Motor neuron disease—upper/lower motor neuron findings
B. Myelopathy—preserved sensation
C. Myopathy—distal weakness that ascends
D. Neuromuscular junction disease—Babinski's response
E. Neuropathy—acute cranial nerve deficit

Answer: A. Amyotrophic lateral sclerosis (ALS) and polio are the classic cases of motor neuron disease. The typical presentation is a mix of upper and lower motor neuron findings. The following are other correct associations:

Myopathy—preserved sensation
Neuromuscular junction disease—acute cranial nerve deficit
Myelopathy—Babinski's response
Neuropathy—distal weakness that ascends

98.3. You have intubated a patient in myasthenic crisis but do not have plasmapheresis immediately available in your hospital. Your next choice of therapy would be:

A. Begin intravenous (IV) pyridostigmine
B. Begin IV immune globulin 1 g/kg daily
C. Edrophonium 1 mg IV test dose followed by 3–5 mg IV
D. Start rituximab

Answer: B. Although evidence supporting IV immune globulin is weak, it is an accepted alternative to plasmapheresis. Pyridostigmine and neostigmine are used orally for maintenance and not for acute crisis, and the IV dose might cause complications from the cholinergic excess, such as increased secretions.

98.4. A 24-year-old Mexican male presents with hypokalemic periodic paralysis. His potassium level is 1.6 mEq/L. After receiving 2 L of normal saline IV and KCl 30 mEq IV over 3 hours, his vital signs are blood pressure 178/96, heart rate 126, temperature 38° C, and respiratory rate 16. His weakness is not improving. What is the most appropriate next therapeutic option?

A. KCl 20 mEq IV bolus
B. Plasmapheresis
C. Prophylactic intubation for airway protection
D. Propranolol 40 mg by mouth

Answer: D. For patients with thyrotoxic periodic paralysis, the weakness often does not correct if the hyperthyroid state is not treated along with the hypokalemia. Thyrotoxic periodic paralysis is more common in Japanese and Hispanic men. Such patients also do not usually manifest paralysis unless their potassium level drops while they are hyperthyroid.

CHAPTER 99

Central Nervous System Infections

David M. Somand | William J. Meurer

PRINCIPLES

Overview

Meningitis is an inflammation of the membranes of the brain or spinal cord and is also called *arachnoiditis* or *leptomeningitis. Encephalitis* denotes inflammation of the brain itself; *myelitis* refers to inflammation of the spinal cord. The terms *meningoencephalitis* and *encephalomyelitis* describe more diffuse inflammatory processes. Collections of infective and purulent materials may form within the central nervous system (CNS) as abscesses. Brain abscesses may be intraparenchymal, in epidural or subdural intracranial locations, or may be found in intramedullary or epidural spinal locations.

The etiologic spectrum of CNS infection has changed considerably as a result of the development and use of antibiotics and the epidemic emergence of diseases and conditions that impair the immune system (eg, human immunodeficiency virus [HIV]). Likewise, diagnostic tools have been developed that allow precise pathogen identification, including polymerase chain reaction (PCR) tests for viral nucleic acids in cerebrospinal fluid (CSF). The use of pneumococcal, *Haemophilus influenza* type b (Hib), and meningococcal vaccines has led to dramatic reductions in the incidence of meningitis. Unfortunately, despite advances, the morbidity and mortality of these disorders remain considerable.

Bacterial Meningitis

Meningeal inflammation may be caused by a variety of disease processes, but infectious etiologies predominate. Common pathogens of CNS infections are *Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes,* and *H. influenza.* Although the incidence of *S. pneumoniae* has declined, it remains the predominant pathogen in adult patients, followed by *N. meningitidis* and *L. monocytogenes.*[1,2] *N. meningitidis* is the predominant organism in adults younger than 45 years old.

Five major serogroups cause most meningococcal disease worldwide (A, B, C, Y, and W-135). Serogroup A accounts for the majority of cases of meningococcal meningitis in developing nations. A new vaccine for serogroup A may potentially reduce the impact of this disease in nearly half a billion individuals at risk.[3] Serogroup distribution for invasive disease has changed markedly in the United States, with B, C, and Y now most commonly responsible. Interestingly, higher case fatality has been observed in *N. meningitis* outbreaks versus sporadic cases, likely due to increased virulence of outbreak-related strains.

Meningeal infection may also occur in association with a dural leak secondary to neurosurgery or neurotrauma. *S. pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa,* and coliform bacteria are seen most commonly in this population.

The pathogenetic sequence in bacterial meningitis generally begins with nasopharyngeal colonization and mucosal invasion. Virulent microbes secrete immunoglobulin A proteases, induce ciliostasis of mucosal cells, and survive intravascularly by evasion of the complement pathway. The varying capsular properties of each organism protect the bacteria. Once bacteria cross the blood-brain barrier to enter the CSF, host defense mechanisms within the CSF are often ineffective due to low levels of complement, immunoglobulin, and opsonic activity. Bacterial proliferation then occurs, which stimulates a convergence of leukocytes into the CSF.

Meningeal and subarachnoid space inflammation is associated with the release of cytokines into the CSF, most notably tumor necrosis factor and interleukins 1 and 6. These cytokines incite an inflammatory cascade that promotes increased permeability of the blood-brain barrier, cerebral vasculitis, edema, and increased intracranial pressure (ICP). A subsequent decrease in cerebral blood flow leads to cerebral hypoxia. Glucose transport into the CSF is decreased concomitantly with increased glucose utilization resulting in cellular metabolic failure.

The case fatality rate for pneumococcal meningitis has improved and is less than 20%, with higher fatality rates occurring in patients with serious underlying disease or advanced age. The prognosis is related to the degree of neurological impairment on presentation. Overall, 20% to 30% of the survivors of pneumococcal meningitis have some residual neurological deficit. The case fatality rate for *Listeria* meningitis may be as high as 40%.

Tuberculous Meningitis

Death from tuberculous meningitis in the adult age group ranges from 10% to 50% of cases, with the incidence directly proportional to the patient's age and the duration of symptoms before presentation. Focal ischemic stroke may result from the associated cerebral vasculitis. In advanced disease, up to 25% of patients may require some neurosurgical procedure for obstruction (ventriculoperitoneal shunt or drainage). In most patients some neurological deficit develops, but severe long-term sequelae among survivors are unusual.

Viral Meningitis and Encephalitis

The actual incidence of viral meningitis is unknown because most cases go unreported. A prominent increase of cases is seen in summer months, which is concurrent with seasonal predominance of the enterovirus group of the picornaviruses. The same organisms responsible for viral meningitis may also be associated with encephalitis.[4] A common mechanism of transmission is via insect vectors; arbovirus infection is an example, although clinical disease develops in only a small percentage of the people bitten. Herpetic encephalitis is believed to occur via direct neuronal transmission from a peripheral site via a cranial nerve.

Viruses enter the human host through the skin (ie, insect vectors); through the respiratory, gastrointestinal, or urogenital tract; or by receipt of infected blood products or donor organs. Viral replication subsequently occurs outside the CNS, most often followed by hematogenous spread to the CNS. Additional routes into the CNS include retrograde transmission along neuronal axons and direct invasion of the subarachnoid space after infection of the olfactory submucosa.

The development of a viral CNS infection is linked to the virulence of the specific virus, the viral inoculum level, and the state

of immunity of the human host. The tropism of the virus for specific CNS cell types also influences the focality of disease and its manifestations. Particular viruses may preferentially attack cortical, limbic, or spinal neurons, oligodendria, or ependymal cells. An example is the tropism of herpes simplex virus (HSV) for the temporal lobes and the development of temporal lobe seizures and behavioral changes in afflicted patients.

With rare exceptions, the overall prognosis for complete recovery from viral meningitis is excellent. Various complications related to the systemic effects of the particular virus include orchitis, parotitis, pancreatitis, and various dermatoses. Usually all of these complications resolve without sequelae. Interestingly, HSV meningitis is often associated with the initial outbreak of genital herpes, and in contrast to HSV encephalitis the outcome is usually good.

The outcomes in viral encephalitis are dependent on the infecting agent. The mortality from HSV encephalitis before the use of acyclovir was 60% to 70%. Acyclovir treatment has reduced the mortality to approximately 30%.[4] Common complications observed among survivors include seizures, motor deficits, and changes in mentation. Encephalitis caused by Japanese encephalitis virus, Eastern equine virus, and St. Louis encephalitis virus is severe, with high mortality rates and virtually universal neurological sequelae among survivors. West Nile virus produces encephalitis in only 0.5% of those infected, yet it resulted in 120 deaths in 2003. Western equine virus and California encephalitis virus cause milder infections, and death is rare. The incidence of neurological sequelae is highly variable and appears to depend on both the host and the infecting agent. Tickborne encephalitis is endemic to parts of Europe and is an important consideration for residents and recent travelers to those regions. Reports of influenza A H1N1 encephalitis in adults have emerged, which bear striking resemblance to "encephalitis lethargica" reported as a complication of influenza like illnesses in the 1920s.

Although post-infectious encephalomyelitis (PIE) is not directly caused by CNS invasion of the measles virus, it is useful to consider the complications of PIE. Predominantly affecting adolescents, up to one quarter of measles patients with PIE will die, and many survivors have dramatic neurological sequelae and permanent disability; this process appears mediated by an immune system response that attacks myelin basic protein. The flaccid paralysis associated with enterovirus D68 left some affected children with permanent deficits similar to polio.

Fungal Meningitis

Fungal meningitis probably develops in much the same way as bacterial meningitis, although this has been incompletely studied. Pulmonary exposure followed by hematogenous spread is the primary pathogenic mechanism in most cases. Immune system defects or immunosuppressive medications compromise host defense mechanisms, with ensuing development of CNS infection. Iatrogenic injection with contaminated methylprednisolone was responsible for the largest fungal meningitis outbreak in the United States.[5]

Common CNS complications of fungal meningitis include abscesses, increased ICP, neurological deficits, seizures, bone invasion, and fluid collections. Direct invasion of the optic nerve results in ocular abnormalities in up to 40% of patients with cryptococcal meningitis. The mortality rate is high but variable and is related to the timeliness of diagnosis, underlying illness, and therapeutic regimens.

Central Nervous System Abscess

CNS abscesses may occur at any age and any time of year. They are associated with local contiguous and remote systemic infections, intravenous (IV) drug use, neurological surgery, and cranial trauma. Brain abscess secondary to otitis media most often occurs in pediatric or older adult populations. When associated with sinusitis, it most often arises among young adults. Increasingly, CNS abscesses are seen in the immunocompromised population, particularly those with HIV infection, and among bone marrow and solid organ transplant recipients. However, antimicrobial prophylaxis in immunosuppressed patients and more aggressive treatment of otitis and sinusitis have decreased the incidence of CNS abscesses.

Fig. 99.1. Central nervous system (CNS) abscess: Computed tomography (CT) of an intraparenchymal abscess *(arrows)*.

Intraparenchymal brain abscesses, subdural empyema, or intracranial or spinal epidural abscesses result from inoculation of the CNS from either contiguous spread of organisms from a sinus, middle ear, or dental infection, or from metastatic seeding from a distant site (eg, a pulmonary infection or endocarditis). The primary infection can be identified in 75% to 85% of cases. These conditions may also follow surgery or penetrating cranial trauma, particularly when bone fragments are retained in brain tissue. Otogenic abscesses occur most commonly in the temporal lobe in adults and cerebellum in children, whereas sinogenic abscesses typically occur in frontal areas. Multiple brain abscesses suggest hematogenous spread of organisms, most commonly from the pulmonary system, although solitary lesions may also occur (Fig. 99.1).

The mortality rate from brain abscess has declined dramatically from approximately 50% to less than 20% due to a number of factors including early diagnosis afforded by the use of the cranial computed tomography (CT) scan; improved antimicrobial therapy; and combined management approaches with surgery, aspiration, and medical therapy.

CLINICAL FEATURES

Meningitis

Numerous host factors have been implicated in the acquisition of meningitis, although disease also occurs when none are present

BOX 99.1

Host Factors Predisposing to Meningitis

Age younger than 5 years old
Age older than 60 years old
Male gender
Low socioeconomic status
Crowding (eg, military recruits)
Splenectomy
Sickle cell disease
African-American race
Alcoholism and cirrhosis
Diabetes
Immunologic defects
Recent colonization
Dural defect (eg, traumatic, surgical, congenital)
Continuous infection (eg, sinusitis)
Household contact with meningitis patient
Thalassemia major
Intravenous (IV) drug abuse
Bacterial endocarditis
Ventriculoperitoneal shunt
Malignancy

BOX 99.2

Complications of Bacterial Meningitis

IMMEDIATE
Coma
Loss of airway reflexes
Seizures
Cerebral edema
Vasomotor collapse
Disseminated intravascular coagulation (DIC)
Respiratory arrest
Dehydration
Pericardial effusion
Death
Others

DELAYED
Seizure disorder
Focal paralysis
Subdural effusion
Hydrocephalus
Intellectual deficits
Sensorineural hearing loss
Ataxia
Blindness
Bilateral adrenal hemorrhage
Death
Cerebral venous thrombosis
Others

(Box 99.1). The constellation of symptoms that may classically occur in an acute CNS infection consists of fever, headache, photophobia, nuchal rigidity, lethargy, malaise, altered sensorium, seizures, vomiting, and chills.[6] Unfortunately, subtle presentations are also common especially in immunosuppressed and geriatric patients where an alternation in mental status may be the only finding. However, good quality literature suggests that the absence of fever, stiff neck, and mental status change excludes meningitis in immunocompetent adults. A systematic review of prospective data in children found clinical factors useful in increasing the likelihood of bacterial meningitis included bulging fontanel, neck stiffness, and seizures in children outside the age typical for febrile convulsions.[6] No combination of factors have been identified that rule in or rule out the disease, which is not surprising given the diversity of presentations in children.[7]

The presentation of fungal meningitis can be obscure even in the healthy adult population. Headache, low-grade fever, lassitude, and weight loss may be present but often to such a mild degree that the correct diagnosis is not initially considered. This is also true of tuberculous meningitis, which often has a protracted course and a vague nonspecific presentation consisting of fever, weight loss, night sweats, and malaise, with or without headache and meningismus.

The physical findings in meningitis vary, depending on the host, causative organism, and severity of the illness. Kernig's sign (inability to straighten leg to a position of full knee extension when patient is lying supine with hip flexed to a right angle) and Brudzinski's sign (attempts to flex the neck passively are accompanied by flexion of the hips) are present in approximately 50% of adults. When patients with suspected meningitis were evaluated, the sensitivity of Kernig's sign, Brudzinski's sign, and the presence of nuchal rigidity are 5%, 5%, and 30%, respectively, suggesting that these physical findings have limited diagnostic value. On the other hand, at least in children, the 2010 National Institute for Health and Clinical Excellence guidelines found that 85% to 95% of children with meningitis had fever, 66% had Brudzinski's sign, 53% had Kernig's sign or neck stiffness, and 83% had at least one of the three objective findings.[8] Deep tendon reflexes may be increased, and ophthalmoplegia may be present, especially of the lateral rectus muscles. Papilledema, if observed, or lack of venous pulsations, are consistent with increased ICP and should raise the concern for a structural lesion. In addition, patients with coma (Glasgow Coma Score [GCS] of <9) should not undergo lumbar puncture (LP) due to risk for herniation.

The systemic findings in meningitis may include an obvious source of infection, such as sinusitis, otitis media, mastoiditis, pneumonia, or urinary tract infection. Various manifestations of endocarditis may be present. Arthritis may be seen with *N. meningitidis* and occasionally with other bacteria. Petechiae and cutaneous hemorrhages are widely reported with meningococcemia but also occur with Hib, pneumococcal organisms, *L. monocytogenes,* and echovirus infections, in addition to staphylococcal endocarditis. Endotoxic shock with vascular collapse often develops in severe meningococcal disease, but shock may be present in the advanced stages of any bacterial meningitis. Any determination of a serious systemic infection should encourage rather than dissuade the clinician from considering the possibility of a concomitant CNS infection.

The immediate and delayed complications of bacterial meningitis are presented in Box 99.2. The incidence of bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome) is dramatically higher when meningococcemia is present. Hydrocephalus may develop in as many as 5% of patients with community acquired meningitis; and when this is present on admission, the proportion dead or with an unfavorable outcome approaches 50% to 70%.[9] Delayed cerebral venous thrombosis can occur in patients who appear to initially have a full recovery from pneumococcal meningitis, suggesting an immunologic vasculopathy.

Viral Encephalitis

Patients with encephalitis may also have symptoms of meningeal irritation. An alteration of consciousness or delirium occurs in virtually all patients. Fever, headache, personality changes, confusion, and disorientation are also usually present. Hallucinations and bizarre behavior may precede motor, reflex, and other neurological manifestations by several days, occasionally prompting an

initial diagnosis of a psychiatric disorder. Because focal neurological deficits and seizures occur much more commonly with encephalitis than meningitis, early neuroimaging is indicated to assess for a brain abscess. Distinguishing the etiologic agent in encephalitis is clinically difficult, although HSV encephalitis results in a higher incidence of dysphasia and seizures relative to the other viral encephalitides. In some patients, West Nile virus produces a myelitis that affects the anterior horn cells of the spinal column, resulting in a flaccid paralysis with a clear sensorium, similar to findings in polio or Guillain-Barré syndrome. A thorough skin and mucosal examination is important to assess for the presence of herpetic lesions.

Central Nervous System Abscess

Seizures are the most common complication of an intracranial abscess, occurring in 80% of patients. Other neurological findings of intracranial abscesses, including focal motor or sensory deficits or changes in mentation, are common. Complications of a spinal abscess primarily result from cord compression, including paralysis, motor and sensory deficits, and bowel and bladder dysfunction. Patients with an intracranial abscess may be indistinguishable from those with meningitis or encephalitis at the bedside. Most patients with intraparenchymal abscess have a subacute clinical course with symptoms progressing over 2 or more weeks. Nuchal rigidity and fever are present in fewer than 50% of cases. Focal neurological deficits are often present; however, easier access to advanced imaging is facilitating earlier diagnosis before focal deficits become manifest.

Generally, the neurological symptoms associated with brain abscess will localize to the affected areas of the brain. An abrupt neurological deterioration can result from uncal herniation or abscess rupture into the ventricular system. Similar to the subacute presentation of brain tumors, subtle motor deficits, memory changes, or localized seizures are more common than the abrupt deficits observed with acute stroke.

Patients with a subdural or epidural abscess often have headache, fever, and focal deficits. Most of the patients with spinal abscess typically present with spinal pain and other symptoms and signs of cord compression.

DIFFERENTIAL DIAGNOSIS

Patients with meningitis may have symptoms and signs ranging from mild headache with fever to frank coma and shock. To facilitate the discussion of diagnosis and treatment, meningitis may be divided into three clinical syndromes based on timing: acute meningitis, subacute meningitis, and chronic meningitis.

Acute meningitis encompasses patients with obvious signs and symptoms of meningitis who are evaluated in less than 24 hours after the onset of their symptoms and who rapidly deteriorate. In many of these patients, the diagnosis of meningitis is not in doubt, and the crucial step is to initiate antimicrobial therapy immediately. The most likely pathogens in this syndrome are *S. pneumoniae* and *N. meningitidis*. Although *H. influenzae* has been reported in this context, it is not commonly implicated in the adult population. In this scenario, with abrupt onset, the most important differential diagnostic considerations are viral meningitis, acute subarachnoid hemorrhage (SAH), and acute craniocervical arterial dissection.

Distinguishing between viral and bacterial meningitis is challenging and described in more depth in the Diagnostic Testing section. Because subarachnoid blood is quite irritating to the meninges, it will cause neck pain when it migrates through the foramen magnum; it is distinguished from meningitis using CT imaging or LP. Generally, SAH and dissection will not have associated infectious symptoms and signs, such as a prodrome or fever.

In the syndrome of *subacute meningitis,* the symptoms and signs causing the patient to seek care have developed during a period of 1 to 7 days. This syndrome includes virtually all cases of viral meningitis, along with most of the bacterial and some of the fungal etiologies. The differential diagnosis depends on the symptoms and signs at presentation. Brain tumor and drug effects or toxicities are important considerations. Conversely, care must be taken to avoid early diagnostic closure, particularly in the elders and immunosuppressed individuals; for example, even when a fever is present, a patient's change in mental status may be misattributed to another disease outside the CNS, such as pneumonia or urinary tract infection; neck stiffness may be misattributed to degenerative joint disease.

The differential diagnosis of encephalitis and brain abscess occurs in the context of the subacute meningitis syndrome. Brain abscess should be considered, especially if fever is minimal or absent or if there are focal neurological findings. In addition, diagnoses such as subdural empyema, brain tumor, SAH, subdural hematoma, and traumatic intracranial hemorrhage should be considered. Non-convulsive status epilepticus is a consideration in patients with altered mental status especially if there is a seizure history or a known structural brain lesion.

The spectrum of *chronic meningitis* includes the viral meningitides, as well as meningitis caused by tubercle bacilli, syphilis, and fungi. Many of the patients in this group have had symptoms for at least 1 week before presentation and generally have a prolonged indolent course marked by difficult and changing diagnoses and multiple therapies. Causes of aseptic meningitis—simply defined as all cases with negative bacterial CSF cultures—are listed in Box 99.3.[22]

Spinal epidural abscess should be suspected in patients with sudden, atraumatic back pain. Of particular concern are patients with spinal surgery and instrumentation, IV drug abuse, and immunosuppression. Thoracic dissection or pulmonary embolism are two critical diagnoses that must be considered in these patients. Spinal epidural hematoma is another concern, particularly in patients who are anticoagulated. Some lesions as high as the cervical spine may only manifest symptoms in the lower extremities; spinal epidural abscesses in the mid thoracic spine mimicking cauda equina syndrome have been reported.

DIAGNOSTIC TESTING

Laboratory Testing

As with other infectious diseases, the complete blood count (CBC) with differential diagnosis is a nonspecific adjunct in the diagnostic evaluation of a patient suspected to have a CNS infection. The peripheral cell counts are often normal in the presence of significant disease and may even be depressed, particularly in elders or immunosuppressed persons. A "normal" leukocyte count and differential diagnosis should not dissuade the clinician from pursuing the diagnosis of a CNS infection. Procalcitonin is emerging as a promising serum marker of serious bacterial infections, and it may help to discriminate between bacterial and viral etiologies of meningitis and to track response to therapy. However, the test needs more study before it can be recommended as a marker to exclude meningitis.[10,11]

Serum electrolytes, glucose, urea nitrogen, and creatinine levels should be measured to facilitate the interpretation of the CSF glucose level and to establish the level of renal function and the state of electrolyte balance.

Two or three blood cultures should be obtained for all patients who are being evaluated for a CNS infection, even when antimicrobial therapy has already been administered. The blood cultures can improve the identification of the causative organisms, especially with pneumococcus and, to a lesser degree, meningococcus.

BOX 99.3

Causes of Aseptic Meningitis

INFECTIOUS CAUSES

Viruses
Enteroviruses—polio, Coxsackie, echovirus
Herpes group of viruses
- Herpes simplex virus (HSV) types 1 and 2
- Varicella zoster virus
- Cytomegalovirus
- Epstein-Barr virus
- Human herpes virus 6 (HHV-6)

Respiratory viruses
- Adenovirus
- Rhino virus
- Influenza virus types A and B

Arboviruses
Mumps virus
Lymphocytic choriomeningitis
Human immunodeficiency virus (HIV)

Bacteria
Partially treated meningitis
Parameningeal infection
Endocarditis
Mycoplasma pneumonia
Mycobacterium tuberculosis
Ehrlichiosis
Borrelia burgdorferi
Treponema pallidum
Brucella
Leptospirosis

Fungi
Cryptococcus neoformans
Histoplasma capsulatum
Coccidioides immitis
Blastomyces dermatitides
Candida

Parasites
Toxoplasma gondii
Neurocysticercosis
Trichinosis
Naegleria
Hartmannella
Bartonella henselae

Rickettsiae
Rocky Mountain spotted fever
Typhus

NONINFECTIOUS CAUSES

Postinfectious/Postvaccinial
Rubella
Rubella
Varicella
Variola
Rabies vaccine
Pertussis vaccine
Influenza vaccine
Vaccinia
Yellow fever vaccine

Drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Trimethoprim-sulfamethoxazole, amoxicillin
Muromonab CD3 (OKT3)
Azathioprine
Intravenous (IV) immunoglobulin
Isoniazid
Intrathecal methotrexate
Intrathecal cytosine arabinoside
Allopurinol
Carbamazepine
Sulfasalazine

Systemic Disease
Collagen vascular disorders
- Systemic lupus erythematosus
- Wegener's granulomatosis
- Central nervous system (CNS) vasculitis
- Rheumatoid arthritis
- Kawasaki's disease

Sarcoidosis
Leptomeningeal cancer
Post-transplantation lymphoproliferative disorder
Behçet's disease
Vogt-Koyanagi syndrome

Neoplastic Disorders
Leukemia
Carcinomatous meningitis secondary to primary or secondary tumors of the brain

Inflammation of Neighboring Structures
Brain abscess
Epidural abscess

Miscellaneous
Arachnoiditis
Migraine
Urinary tract infection

From Kumar R: Aseptic meningitis: diagnosis and management. Indian J Pediatr 72:57–63, 2005.

Although blood cultures are not immediately useful in the acute diagnosis of meningitis, they may be of considerable clinical importance later in the management of the disease.

Neuroimaging

A cranial CT scan or magnetic resonance imaging (MRI) scan is indicated in the evaluation of any patient with a suspected CNS infection in whom there is the possibility of an intracranial abscess, intracranial hemorrhage, or mass lesion. However, neuroimaging should not unnecessarily delay LP or antimicrobial therapy. More than 50% of neuroimaging studies in acute meningitis show no specific abnormalities.

The CT scan may show hypodense lesions in the temporal lobes in patients with HSV encephalitis, although an MRI scan reveals this abnormality much earlier in the disease process

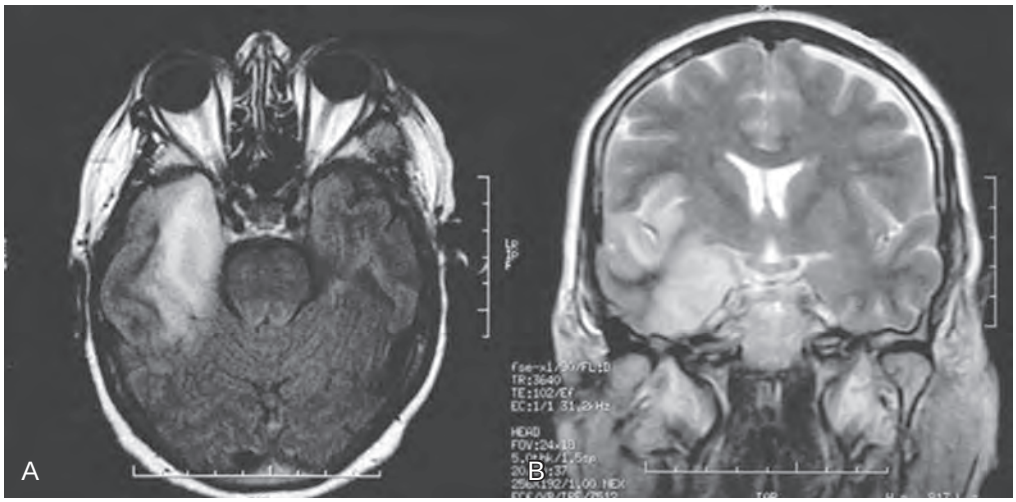

Fig. 99.2. MRI resulting in probable diagnosis of encephalitis on the right temporal lobe. Axial T1-weighted and coronal T2-weighted MR images show a hyperintense lesion on the right temporal lobe and insular cortex. The lesion displays the typical pattern of herpes virus encephalitis. MR imaging study was acquired 20 days after resection of the parasellar meningioma. (From Álvarez de Eulate-Beramendi S, Santirso-Rodríguez D, Piña-Batista KM, et al: Encefalitis por virus herpes simple 1 tras extirpación de meningioma. Neurología 30:455–457, 2015, fig 1.)

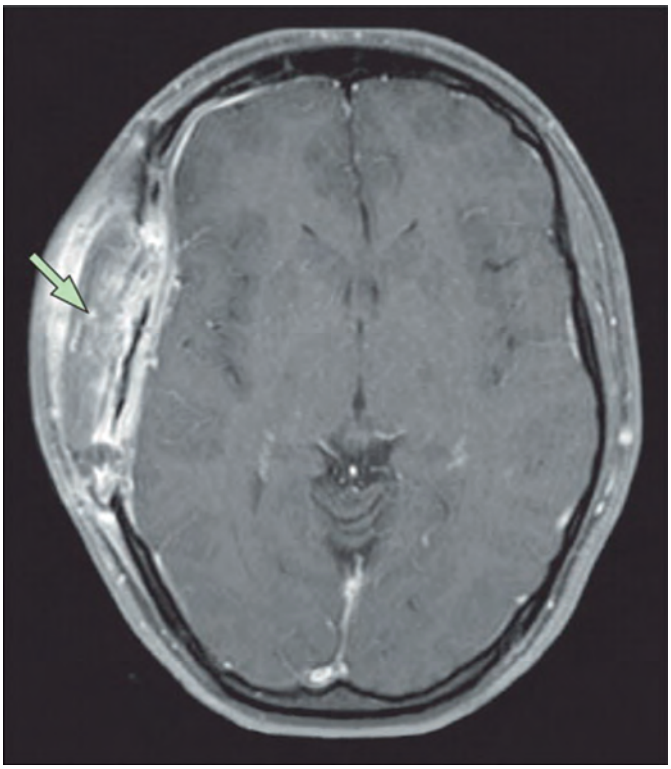

Fig. 99.3. MRI T1-weighted sequence (with contrast) showing a post-craniotomy intracranial epidural abscess. (From Pradilla, G, Ardila, GP, Hsu, W, et al: Epidural abscesses of the CNS. Available at www.thelancet.com/neurology, Vol 8, March 2009, fig 1.)

(Fig. 99.2). A contrast-enhanced cranial CT scan or MRI scan is diagnostic for a CNS abscess (Fig. 99.3). MRI scanning is also helpful in the evaluation of other infectious and noninfectious encephalitides. CT imaging of the spine is not an accurate modality for excluding spinal epidural abscess, and MRI is the test of choice (Fig. 99.4). In patients unable to have an MRI due to pacemakers or other metal implants, a CT myelogram is a potential alternative.

Cerebrospinal Spinal Fluid Analysis

CSF analysis is indicated whenever a CNS infection is suspected, unless the procedure is contraindicated by the presence of infection in the skin or soft tissues at the puncture site or the likelihood of brain herniation. In most patients with meningitis who have no focal neurologic findings (including no altered mental status), LP may be safely performed without antecedent neuroimaging studies. Because this may not be the case in other brain pathologies, in many circumstances we advise that a head CT be obtained before performing an LP. An algorithm for diagnostic and therapeutic decision making is presented in Figure 99.5. These indications should be carefully weighed against the patient's condition, the probability of meningitis, and the availability of the CT or MRI scan. In subtle cases, LP can create meningeal enhancement on a subsequent MRI. If viral encephalitis is suspected and treatment has already been initiated, we recommend performing the LP after the MRI.

It has been conventionally asserted that an LP in the presence of increased ICP may be harmful or fatal to the patient. Up to 30% of patients with bacterial meningitis will herniate even if they do not have an LP, suggesting that the herniations observed in some studies are the result of the underlying disease process and not the test. The presence of focal neurological signs, papilledema, seizures, and depressed mental status are associated with increased complications from LP and thus we recommend against the test in these patients.

Early initiation of antimicrobial therapy should not be delayed pending an LP. The algorithmic alternatives are: (1) immediate LP followed by initiation of antibiotic treatment before obtaining the results, or (2) initiation of antibiotic treatment followed by a head CT scan and then an LP. The latter choice of empirical treatment with antibiotics is now the routine in many institutions, although in some cases a third option could be considered: antibiotics and no LP despite an unremarkable CT scan.

The controversy emerging regarding not performing LP despite a lack of CT scan findings is based on some reviews and case reports describing herniation temporally related to LP in patients with normal CT scans. Raised ICP may not be reliably detected using CT. Clinical signs of increased ICP, rapid change in consciousness, and recent seizures have been identified as risk factors predicting deterioration despite a normal CT. The risks of ongoing

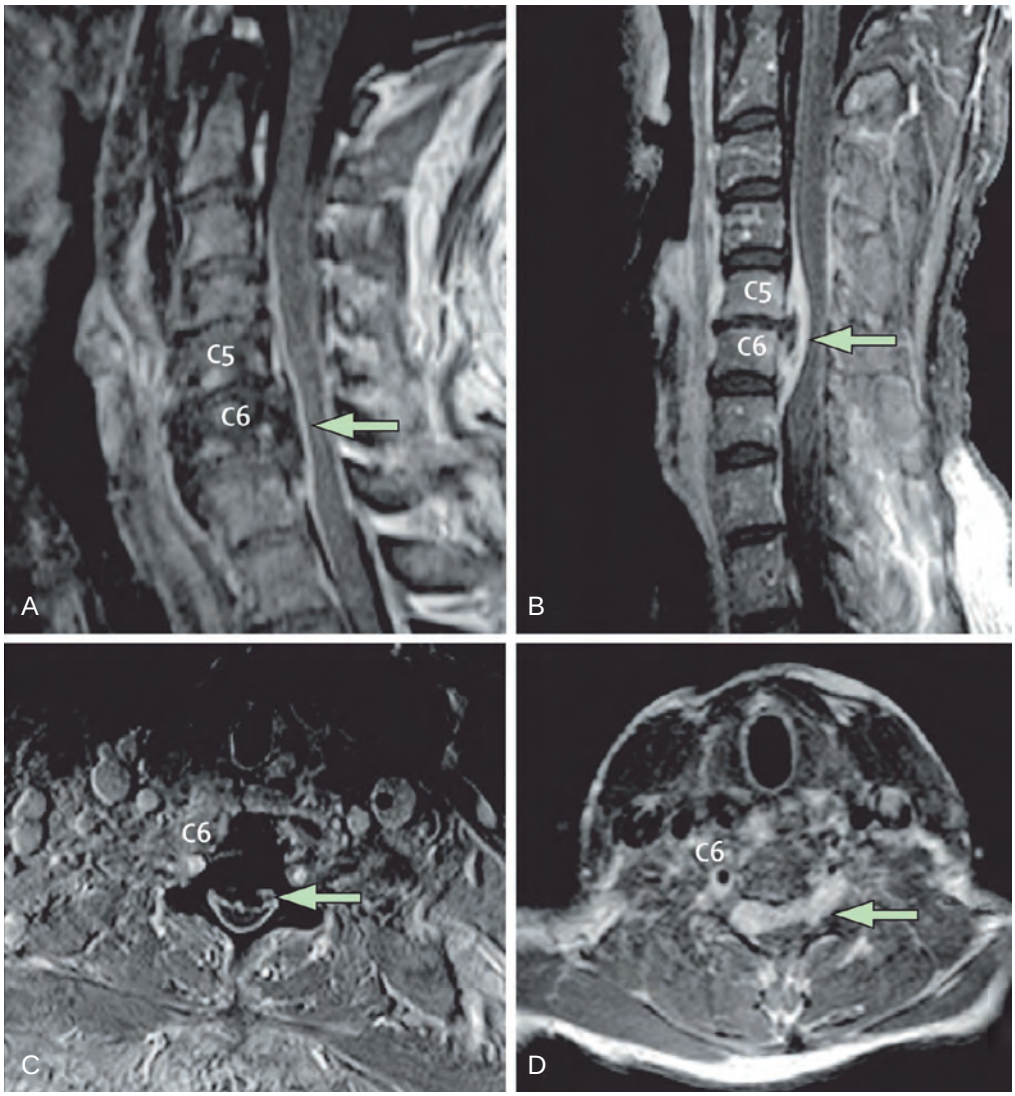

Fig. 99.4. Cervical spine MRI without (**A** and **B**) and with contrast (**C** and **D**) showing C5–C6 discitis and osteomyelitis and a large spinal epidural abscess with substantial cord compression. **A** and **C,** Sagittal views. **B** and **D,** Transverse views. (From Pradilla, G, Ardila, GP, Hsu, W, et al: Epidural abscesses of the CNS. www.thelancet.com/neurology, Vol 8, March 2009, fig 5.)

empirical treatment with antibiotics without additional information from CSF analysis appears to be low, whereas the yield from blood cultures and other diagnostic techniques such as PCR is relatively high. Therefore, we recommend against LP in patients who have rapid neurological deterioration, seizures, or signs of herniation.

Opening Pressure

The normal CSF pressure in an adult varies from 5 to 20 cm H_2O. This value applies only to patients in the lateral recumbent position and may increase substantially when the patient is in the sitting position. The pressure is often elevated in bacterial, tuberculous, and fungal meningitides and a variety of noninfectious processes. Pressure may be falsely elevated when the patient is tense or obese or has marked muscle contraction. Ultrasound may assist with identifying the midline spinous processes and the interspinous spaces (Fig. 99.6). We recommend marking patients prior to the procedure in contrast to the direct visualization during the procedure that is recommended for other procedures, such as central venous catheterization.

Cerebrospinal Spinal Fluid Collection

At least three sterile tubes each containing 1 to 1.5 mL of CSF are obtained and numbered in sequence. A fourth tube is desirable should later studies become necessary. The fluid is sent to the laboratory for immediate analysis of turbidity, xanthochromia, glucose, protein, cell count and differential diagnosis, Gram's stain, bacterial culture, and antigen testing (Table 99.1). In certain cases, a cryptococcal antigen study (which is replacing the previously used India ink stain), a bacteriologic stain for acid-fast bacilli, or a Venereal Disease Research Laboratory (VDRL) test should be obtained. When only a small amount of fluid can be obtained, the most important studies are the cell count with differential diagnosis, Gram's stain, and bacterial cultures. Ideally, the cell count should be performed on both the first and third or fourth tubes to help differentiate true CSF pleocytosis from contamination of the specimen by a traumatic LP.

The CSF is assessed immediately for turbidity or cloudiness by the person performing the LP. Normal CSF is completely clear and colorless and is indistinguishable from water, thus any degree of turbidity is pathologic. Leukocytosis is the most common cause

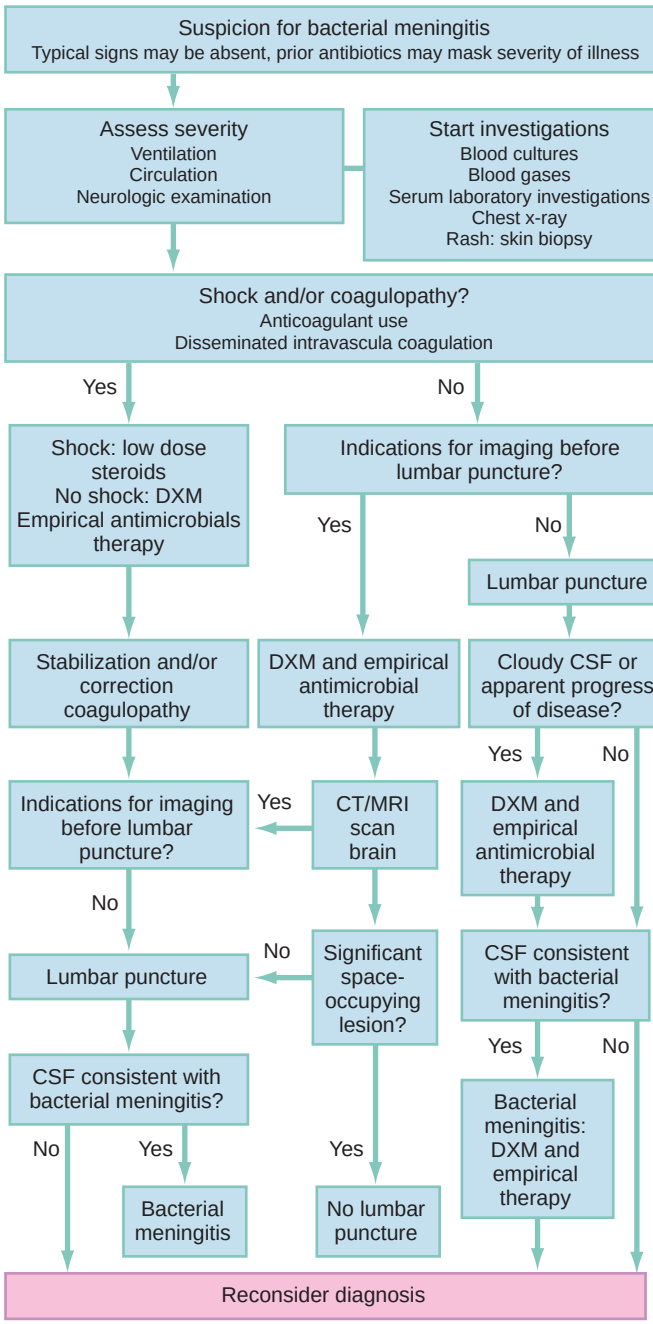

Fig. 99.5. Algorithm for diagnostic and therapeutic decision-making when bacterial meningitis is clinically suspected. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *DXM,* dextromethorphan; *MRI,* magnetic resonance imaging.

of CSF turbidity; counts greater than 200 cells/mm^3 usually cause clinically detectable changes in CSF clarity.

Cerebrospinal Spinal Fluid Cell Count

Normal adult CSF contains no more than 5 leukocytes/mm^3 with at most one granulocyte (polymorphonuclear [PMN] leukocyte); therefore, the presence of more than one PMN or a total cell count of more than 5 cells/mm^3 is evidence of CNS infection. In addition, the presence of any eosinophil in the CSF is abnormal; occasionally basophils may be seen in the absence of disease. Pretreatment with a few doses of antibiotics, although possibly diminishing the yield of Gram's staining and cultures, should not affect the CSF cell counts in meningitis.

The cell counts in bacterial meningitis are usually markedly elevated, sometimes exceeding 10,000 cells/mm^3, and demonstrate a dramatic granulocytic shift. In general, counts exceed 500 cells/mm^3 with a preponderance of PMN leukocytes. However, the initial CSF analysis exhibits lymphocytosis (lymphocyte count greater than 50%) in 6% to 13% of cases of bacterial meningitis. When only the patients with bacterial meningitis with fewer than 1000 cells/mm^3 are considered, 24% to 32% have a predominance of lymphocytes. In addition, the same population of patients often has only a mild disturbance of CSF glucose and protein levels. In well-established viral meningitis and encephalitis, counts are usually less than 500 cells/mm^3 with nearly 100% of the cells being mononuclear. Early (48 hours) presentations may reveal significant PMN pleocytosis and hence be indistinguishable from presentations in early bacterial meningitis.

Similarly, normal cell counts and differential diagnoses, although reassuring, do not absolutely exclude bacterial meningitis. Patients who have a strong clinical suspicion for meningitis require hospitalization with frequent reevaluation, repeat LP, and antimicrobial therapy.

Brain abscess and parameningeal infections, such as subdural empyema or epidural abscess, usually display CSF cell counts and differential diagnoses similar to those of viral meningitis and encephalitis, although the CSF may also be normal.

A traumatic LP is suggested by the presence of a clot in one of the tubes or the clearing of the CSF and a decreasing red blood cell (RBC) count from tubes one to three. In the presence of a traumatic LP, one may estimate the true degree of CSF white blood cell (WBC) pleocytosis with the following formula:

$$\text{True CSF WBC} = (\text{measured CSF WBC}) \times \frac{(\text{CSF RBC}) \times (\text{blood WBC})}{\text{blood RBC}}$$

Alternatively, when peripheral cell counts are normal, the CSF from a traumatic LP should contain about 1 WBC per 700 RBCs.

Gram's Stain

A properly performed Gram's stain of a centrifuged specimen of CSF identifies the causative organism approximately 80% of the time in cases of bacterial meningitis. Gram's stain characteristics of the most commonly encountered organisms are described in Table 99.2. The yield from this procedure is diminished by 20% to 30% when there has been prior treatment with antibiotics. Misidentification of gram-positive organisms as gram-negative is also known to occur more commonly among pretreated patients, because organisms with damaged walls stain unpredictably.

Xanthochromia

Xanthochromia is the yellowish discoloration of the supernatant of a centrifuged CSF specimen. It is abnormal and results from the lysis of RBCs and release of the breakdown pigments oxyhemoglobin, bilirubin, and methemoglobin into the CSF. This process normally begins within 2 hours, and pigments may persist up to 30 days; therefore early analysis of the LP specimen is essential. If a traumatic tap has introduced enough plasma to raise the CSF protein level to 150 mg/dL or more, blood pigments may cause xanthochromia. If the CSF protein level is less than 150 mg/dL, however, and systemic hypercarotenemia does not exist, xanthochromia of a centrifuged CSF specimen indicates that a SAH has occurred.

Glucose

When the serum glucose is normal, the CSF glucose is usually between 50 and 80 mg/dL. The CSF glucose is normally in a ratio

Fig. 99.6. Ultrasound guidance for lumbar puncture (LP). **A,** Prior to preparing the area, marking the locations of the L4 and L5 vertebrae using a curvilinear transducer in short axis. **B,** Markings should indicate the levels and the middle of the spinous processes. **C,** In long axis view, the locations of the spinous processes *(SP)* in the midline can be identified along with the interspinous space. **D,** In short axis, the identification of the midline of the spinous process is accomplished. (Courtesy Nik Theyyun.)

of 0.6:1 to the serum glucose, except with marked systemic hyperglycemia in which case the ratio is closer to 0.4:1. Therefore, a CSF-to-serum glucose ratio of less than 0.5 in normoglycemic subjects or 0.3 in hyperglycemic subjects is abnormal and may represent the impaired glucose transport mechanisms and increased CNS glucose use associated with pyogenic meningitis. Mild decreases in the CSF glucose level may occur with certain viral and parameningeal processes. However, bacterial or fungal meningitis should be presumed to be the cause of low CSF glucose, termed *hypoglycorrhachia,* until each is clearly excluded. If the serum glucose level has increased rapidly (eg, after IV administration of 50% dextrose in water) equilibration in the CSF may take up to 4 hours, and therefore the interpretation of CSF-to-serum glucose ratios may be unreliable.

Protein

The normal CSF protein level in adults ranges from 15 to 45 mg/dL. An elevated CSF protein, usually higher than 150 mg/dL, commonly occurs with acute bacterial meningitis. When a traumatic LP has occurred, the CSF protein can be corrected for the presence of blood by subtracting 1 mg/dL of protein for each 1000 RBCs. Elevated CSF protein concentrations can result from any cause of meningitis, SAH, CNS vasculitis, syphilis, viral

TABLE 99.1

Analysis of Cerebrospinal Fluid

TEST	NORMAL VALUE	SIGNIFICANCE OF ABNORMALITY
Cell count	≤5 WBC/mm^3 ≤1 PMN/mm^3 ≤1 eosinophil/mm^3	Increased WBC counts are seen in all types of meningitis and encephalitis; increased PMN count suggests bacterial pathogen
Gram's stain	No organism	Offending organism identified 80% of time in bacterial meningitis, 60% if patient pretreated
Turbidity	Clear	Increased turbidity with leukocytosis, blood, or high concentration of microorganisms
Xanthochromia	None	Presence of RBCs in spinal fluid for 4 hours before LP; occasionally caused by traumatic tap (if protein ≥150 mg/dL) or hypercarotenemia
CSF-to-serum glucose ratio	0.6 : 1	Depressed in pyogenic meningitis or hyperglycemia; lag time if glucose given intravenously
Protein	15–45 mg/dL	Elevated with acute bacterial or fungal meningitis; also elevated with vasculitis, syphilis, encephalitis, neoplasms, and demyelination syndromes
India ink stain	Negative	Positive in one third of cases of cryptococcal meningitis
Cryptococcal antigen	Negative	90% accuracy for cryptococcal disease
Lactic acid	≤35 mg/dL	Elevated in bacterial and tubercular meningitis
Bacterial antigen tests	Negative	≥95% specific for organism tested; up to 50% false-negative rate
Acid-fast stain	Negative	Positive in 80% of cases of tuberculous meningitis if ≥10 mL of fluid

CSF, Cerebrospinal fluid; *LP,* lumbar puncture; *PMN,* polymorphonuclear; *RBC,* red blood cell; *WBC,* white blood cell.

TABLE 99.2

Gram's Stain Characteristics of Selected Meningeal Pathogens

PATHOGEN	TYPICAL CHARACTERISTICS
Staphylococci	Gram-positive cocci: Singles, doubles, tetrads, clusters
Streptococcus pneumoniae	Gram-positive cocci: Paired diplococci
Other streptococci	Gram-positive cocci: Pairs and chains
Listeria monocytogenes	Gram-positive rods: Single or chains
Neisseria meningitidis	Gram-negative cocci: Negative paired diplococci; kidney or coffee bean appearance
Haemophilus influenzae	Gram-negative coccobacilli: "Pleomorphic" bacilli
Enterobacteriaceae (including *Escherichia coli*)	Gram-negative rods
Pseudomonas aeruginosa	Gram-negative rods

encephalitis, neoplasms, and demyelination syndromes. A greatly elevated CSF protein level (>1000 mg/dL) in the presence of a relatively benign clinical presentation suggests fungal disease.

India Ink Preparation

Historically, an India ink staining of the CSF was performed to diagnose cryptococcal meningitis. This has been replaced by cryptococcal antigen testing, which has a similar sensitivity when measured in serum, CSF, or urine.

Lactic Acid and Other Markers

Although nonspecific, elevations in CSF lactic acid concentrations (>2.8 mmol/L) are potentially indicative of bacterial meningitis, and lactate may rise prior to the decline in glucose. Normal lactate levels (<2.8 mmol/L) are usually seen in patients with viral meningitides. A recent systematic review suggests that an elevated CSF lactate outperforms glucose, protein, and leukocyte count for diagnosing bacterial meningitis, but the strength of evidence is weak.[12] At this time, we do not recommend using the CSF lactate as a definitive test, but it may have a role in the future.

C-reactive protein, CSF chloride, and the limulus lysate test do not have a defined utility in the evaluation of CNS infections.

Antigen Detection

Counterimmunoelectrophoresis (CIE), latex agglutination, and coagglutination are methods of detecting specific antigens and theoretically have value even in patients who have received antibiotics. However, no incremental yield of these methods have been found in bacterial meningitis and thus these tests are no longer recommended.[13]

Nucleic acid amplification tests such as PCR have reported sensitivities of 92% for *H. influenza,* 100% for *S. pneumoniae,* and 88% for *N. meningitides;* specificities approach 100% for all three organisms. The incremental value to diagnosis for these techniques remains unknown given the low prevalence of these pathogens and the lack of adequately sized prospective studies. The sensitivities of bacteriologic culture are much lower, especially for *N. meningitidis* at 37% to 55% and *H. influenzae* at 50%.

Antigen and antibody testing have particular utility in HSV encephalitis. Although enzyme-linked immunosorbent assays (ELISAs) can detect HSV antibody production, the appearance of antibody in CSF occurs too late to aid in any therapeutic decision analysis. PCR amplification and the identification of HSV DNA have demonstrated a sensitivity of 95% to 100% and a specificity of 100% early in the disease and have markedly decreased the need for diagnostic brain biopsy in this disorder.[14] PCR has improved the diagnosis of tuberculous meningitis, with a sensitivity of 80% to 85% and a specificity of 97% to 100%, and it is superior to standard techniques of gram stain and culture. PCR has additionally been shown to be superior in identifying enteroviruses, and other viral etiologies in both immunocompromised and immu-

nocompetent patients. PCR assays have nearly tripled the diagnostic accuracy when compared to viral cultures alone.

The growing availability of molecular techniques does not, however, suggest that they should be routinely employed as initial diagnostic tests. Most cases of acute bacterial meningitis are readily diagnosed and treated on the basis of the standard Gram stain and culture. PCR should be reserved for less clear presentations, patients pretreated with antibiotics, and cases in which concern exists for tuberculous, cryptococcal, and treatable viral CNS infections. A reasonable approach is to save the CSF and to consider ordering PCR when acute infection is strongly suspected based on the initial results from the cell count and Gram stain.

Bacteriologic Cultures

Although results are not available for emergency management, bacteriologic cultures of CSF should be performed. Bacterial culture yields are significantly decreased in patients pretreated with antibiotics. When suspicion for non-bacterial meningitis is high, viral cultures should also be considered. Although antigen testing holds promise, the low prevalence of these diseases and the lack of prospective studies have not established that antigen testing alone can replaced bacteriological cultures at this time.

Additional Investigations

As many as 50% of patients with pneumococcal meningitis also have evidence of pneumonia on an initial chest radiographic study. This association occurs in fewer than 10% of the cases of meningitis caused by Hib and *N. meningitides,* and in approximately 20% of cases of meningitis caused by other organisms. Approximately 10% of cases of brain abscess have an associated pulmonary infection on chest radiography, which may assist in identification of causative organisms and appropriate antimicrobial therapy.

Other ancillary investigations such as echocardiography, cultures of other body fluids, and bone scans may be undertaken as necessary to evaluate coexistent or complicated disease.

A number of characteristic but not pathognomonic electroencephalogram (EEG) abnormalities have been associated with HSV type 1 encephalitis. The presence of focal or lateralized EEG abnormalities in the presence of an encephalitis syndrome should be considered strong evidence supporting a diagnosis of HSV encephalitis; however, no literature exists to support emergent assessment of suspected meningitis or encephalitis with an EEG in the emergency department (ED).

MANAGEMENT

Initial management of the patient with a suspected CNS infection focuses on ensuring oxygenation and perfusion. Although there is concern regarding inducing brain edema with volume resuscitation, especially in children, establishing a mean arterial pressure that maintains cerebral perfusion takes priority. Acute cerebral edema or elevated ICP is managed with immediate endotracheal intubation and maintenance of eucapnia. Osmotic agents such as mannitol may be used while ensuring that the patient does not become volume depleted and hypotensive.

Bacterial Meningitis

Therapy for bacterial meningitis requires bactericidal antibiotics that penetrate the blood-brain barrier and achieve therapeutic CSF concentrations. Until the pathogenetic organism is identified, broad-spectrum coverage of the most common pathogens is indicated (Table 99.3). We recommend cefotaxime or ceftriaxone (2 grams IV in adults, 75 to 100 mg/kg in children, 50 mg/kg in infants younger than 1 month old), plus vancomycin (15 mg/kg) to cover potentially resistant organisms. High-dose ampicillin (100 mg/kg) is also added if concern exists about *Listeria,*

TABLE 99.3

Recommendations for Empirical Antimicrobial Therapy for Purulent Meningitis Based on Patient Age and Specific Predisposing Condition

PREDISPOSING FACTOR	COMMON BACTERIAL PATHOGENS	ANTIMICROBIAL THERAPY
Age		
<1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes,* Klebsiella species	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
1-23 months	*Streptococcus pneumoniae, Neisseria meningitides, S. agalactiae, Haemophilus influenzae, E. coli*	Vancomycin plus a third-generation cephalosporin[a,b]
2-50 years	*N. meningitides, S. pneumoniae*	Vancomycin plus a third-generation cephalosporin[a,b]
>50 years	*S. pneumoniae, N. meningitides, L. monocytogenes,* aerobic gran-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin[a,b]
Head trauma		
Basilar skull fracture	*S. pneumoniae, H. influenzae,* group A β-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin[a,b]
Penetrating trauma	*Staphylococcus aureus,* coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Post-neurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus,* coagulase-negative staphylococci (especially *S. epidermidis*)	Vancomycin plus cefepime, chalcomycin plus ceftazidime, or vancomycin plus meropenem
CSF shunt	Coagulase-negative staphylococci (especially *S. epidermidis*), *S. aureus,* aerobic gram-negative bacilli (including *P. aeruginosa*), *Propionibacterium acnes*	Vancomycin plus cefepime,[c] vancomycin plus ceftazidime,[c] or vancomycin plus meropenem[c]

[a]Ceftriaxone or cefotaxime.
[b]Some experts would add rifampin if dexamethasone is also given.
[c]In infants and children, vancomycin alone is reasonable unless Gram stains reveal the presence of gram-negative bacilli.
CSF, Cerebrospinal fluid.
From Tunkel AR, et al: Practice guidelines for bacterial meningitis. Clin Infect Dis 39:1267–1284, 2004.

particularly in elders and infants younger than 1 month old. In patients allergic to penicillin and cephalosporins, we recommend meropenem (2 grams IV) or chloramphenicol (12.5 mg/kg IV) plus vancomycin (15 mg/kg IV).

Corticosteroid treatment is additionally recommended in adult acute bacterial meningitis. However, the evidence of its efficacy is becoming less compelling over time as a result of the changing epidemiology in the developed world due to vaccines.[15] Earlier resolution of the clinical and CSF stigmata of meningitis and a decrease in long-term hearing loss are observed in infants and children given dexamethasone with cefuroxime or ceftriaxone compared with those receiving the antibiotic alone, particularly when *H. influenzae* is the offending agent.[16]

In adult bacterial meningitis, an absolute risk reduction of 10% for unfavorable outcome is seen when dexamethasone is given either 15 minutes before or concomitantly with antibiotics and continued for 4 days at 6-hour intervals.[17] This benefit is greatest in those with *S. pneumoniae.* Despite uncertainty from conflicting trials, we recommend an initial dose of dexamethasone 10 mg IV prior to or concurrent with empirical antibiotics in patients with suspected community acquired meningitis and without signs of septic shock. Given the potential adverse effects of high dose corticosteroids in patients with septic shock, the use of low dose hydrocortisone at 50 mg IV instead of high dose dexamethasone is a reasonable approach, although clear benefit has not be demonstrated.

In pediatric meningitis, the evidence supporting adjunctive dexamethasone is even less compelling. Invasive Hib and pneumococcal infections have drastically been reduced by vaccination. A randomized trial of dexamethasone in childhood meningitis in sub-Saharan Africa did not demonstrate a benefit, and a retrospective analysis from United States data did not demonstrate a mortality benefit. Current recommendations are organism specific, which presents a major limitation, because recommendations are to begin empirical therapy prior to lab results in suspicious cases. Experts do not agree on a recommendation to use corticosteroids in pneumococcal meningitis, and data are not sufficient to demonstrate a clear benefit in children. Consequently, we do not recommend adjunctive dexamethasone at this time in the treatment of pediatric meningitis.

Tuberculous Meningitis

Early chemotherapeutic intervention in acute tuberculous meningitis improves the patient's prognosis. A strong clinical suggestion of this disease is an adequate indication to begin antituberculous therapy. A standard treatment regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin. Corticosteroids have also been shown to decrease secondary complications.

Fungal Meningitis

Four agents are available to treat fungal meningitis: amphotericin B, flucytosine, miconazole, and fluconazole. Of these, amphotericin B, either alone or in combination with flucytosine, is the most commonly recommended initial therapeutic regimen. These diseases are rarely acutely life-threatening but rather are slowly progressive. Prolonged therapy, often with multiple agents, is necessary. The initiation of antifungal therapy is rarely indicated in the ED.

Viral Meningitis

No specific agents are available for treating most types of viral meningitis. Fortunately, with the exception of HSV meningitis, the viral meningitides contracted in the United States are generally characterized by a short, benign, self-limited course followed by a complete recovery. Therefore, the primary therapeutic consideration in cases of viral meningitis is the validity of the diagnosis. Early cases of viral meningitis may be indistinguishable from bacterial meningitis, and this confusion may not be resolved by CSF analysis; therefore, when any doubt exists about the veracity of the diagnosis, cultures should be obtained and the patient admitted to the hospital. Antimicrobial therapy for presumed bacterial meningitis may be initiated on the basis of the clinical presentation or may be withheld pending the outcome of close clinical observation and repeated LP in 8 to 12 hours.

Viral Encephalitis

When the diagnosis of herpes meningoencephalitis is suspected or established, IV acyclovir should be administered in a dose of 10 mg/kg every 8 hours. Ganciclovir, foscarnet, and cidofovir are also effective in human herpes virus (HHV) infections, and pleconaril has been effective in enteroviral disease. Additional antiviral treatments are in development.

As many viral encephalitides are spread by mosquitoes or other insects, prevention by control of mosquito populations is an important method to limit the impact of West Nile virus and other insect-borne diseases. Insecticides appear to have a favorable benefit risk profile based on both ecological studies and statistical modeling.[18]

Central Nervous System Abscess

The treatment of cerebral abscess requires neurosurgical consultation. The location, size, and number of abscesses influence the choice of medical management, surgical excision, aspiration, or a combination of these modalities. In general, small multiple abscesses are treated medically, whereas large, surgically accessible lesions should be excised. Empirical antimicrobial therapy before identification of specific organisms by aspiration or surgical excision should be guided by the principles of CSF penetration and the coverage of likely pathogens.

Otogenic and sinogenic abscesses are often treated with cefotaxime or ceftriaxone (75 to 100 mg kg IV, usually 2 grams IV in adults) plus metronidazole. Abscesses with traumatic or neurosurgical origins should have antimicrobial coverage for *S. aureus* or methicillin-resistant *S. aureus* with vancomycin (15 mg/kg IV). Patients at high risk for tuberculous, fungal, or parasitic abscess should also receive coverage for the suspected etiologic agent. Corticosteroids should be reserved specifically for managing any attendant cerebral edema; in other circumstances, steroid use is associated with increased mortality.

Chemoprophylaxis

Among household contacts, the incidence of transmission of meningococcus is approximately 5%; therefore, we recommend that household contacts of bacteriologically confirmed cases receive rifampin (adults, 600 mg; children older than 1 month, 10 mg/kg; children younger than 1 month, 5 mg/kg) orally every 12 hours for a total of four doses. In addition, these contacts should be advised to watch for fever, sore throat, rash, or any symptoms of meningitis. They should be hospitalized with appropriate IV antimicrobial therapy if there are signs that active meningococcal disease is developing, because rifampin is ineffective against invasive meningococcal disease.

Intimate, non-household contacts who have had mucosal exposure to the patient's oral secretions should also receive rifampin prophylaxis. Health care workers are not at increased risk for the disease and do not require prophylaxis unless they have had direct mucosal contact with the patient's secretions, as

might occur during mouth-to-mouth resuscitation, endotracheal intubation, or nasotracheal suctioning. Ciprofloxacin 500 mg by mouth (adults only) and ceftriaxone 250 mg intramuscularly (125 mg intramuscularly for children younger than 15 years old) provide single-dose alternatives.

There is no indication for chemoprophylaxis in pneumococcal meningitis. Rifampin prophylaxis for the contacts of patients with Hib meningitis is recommended for nonpregnant household contacts when there are children younger than 4 years old in the household (adults, 600 mg by mouth; children, 20 mg/kg by mouth daily for 4 days).

Immunoprophylaxis

A quadrivalent vaccine based on the polysaccharide capsule and conferring protection against group A, C, Y, and W-135 meningococci has been in routine use by the United States military since the 1980s. However, the capsular polysaccharide vaccines used to immunize adults are neither immunogenic nor protective in children younger than 2 years old because of poor antibody response. In addition, no licensed vaccine is currently available against the serogroup B meningococcus. The serogroup B capsular polysaccharide has proved to be poorly immunogenic in both adults and children.

The vaccine is recommended in established meningococcal epidemics and for travelers to countries where meningococcal disease is currently epidemic. Elective vaccination of college freshmen has been recommended by the Advisory Committee on Immunization Practices (ACIP) in the United States and public health authorities in the United Kingdom. The United Kingdom has also implemented universal childhood immunization with a group C conjugate vaccine.

The development of effective pneumococcal vaccines has been hampered by the large number of serotypes of the organism. A single dose of the vaccine should be considered for elderly or debilitated patients, especially those with pulmonary disease, and for patients with impaired splenic function, splenectomy, or sickle cell anemia. A heptavalent conjugated pneumococcal vaccine has also been developed and is recommended for universal childhood immunization by the ACIP.

A conjugate vaccine effective against Hib has been developed for use in the pediatric, but not adult, population. It appears to be approximately 90% protective and has a very low incidence of adverse reactions. Modern childhood immunization against Hib has raised the average age of patients afflicted with *Haemophilus* meningitis to 25 years and decreased the incidence of meningitis of any etiology by 55%.

Vaccination is also available to confer immune protection against Japanese encephalitis virus, and it is recommended for people performing extensive outdoor activities or spending more than 30 days in endemic areas during transmission seasons. The reported protective efficacy of the vaccine is approximately 90%. Although there is no current human vaccine for the West Nile virus, vaccines for nonhuman mammals have been developed.

DISPOSITION

With the exception of viral meningitis, all but the most chronic CNS infections require initial inpatient evaluation and treatment. Bed rest, analgesics, and the institution of appropriate IV antimicrobials are indicated.

Some patients with suspected viral meningitides merit hospitalization. These include patients with more severe disease with refractory headache, immunocompromise, and suspicion of HSV meningitis. Although local practices vary, we recommend managing patients with classical presentations of viral meningitis as outpatients with close follow-up within 24 hours.

KEY CONCEPTS

- CNS infection should be considered in all patients with headache, neck stiffness, fever, altered sensorium, or diffuse or focal neurological findings.
- *S. pneumoniae* is one of the two leading causes of bacterial meningitis in adults. Mortality from *S. pneumoniae* is 30%.
- Perform (and document) a funduscopic examination and focused neurologic examination to include mental status (pay close attention to cranial nerves 2, 3, 4, and 6).
- Altered mental status in a patient with suspected meningitis can be a sign of increased ICP or encephalitis.
- Sampling of CSF is the only reliable method of assessing the presence or absence of meningitis. In the absence of contraindications, any suspicion of meningitis is an indication to perform a CSF analysis.
- Provide critical monitoring and be aware of the risk for rapid deterioration.
- Early initiation of empirical antimicrobial therapy is recommended in cases of suspected acute CNS infection. Antibiotic administration should not be delayed for CSF analysis or performance of neuroimaging studies.
- Antibiotic chemoprophylaxis should be assured for close contacts of patients with meningitis resulting from *N. meningitidis* or *H. influenza.* Single-dose and multiple-dose regimens are available.
- Concomitant CNS infection should be strongly considered in any symptomatic patient with another severe systemic infection, such as urinary tract infection or pneumonia.
- First line treatment for bacterial meningitis is ceftriaxone plus vancomycin.
- Acyclovir is recommended for patients with suspected meningoencephalitis.
- Dexamethasone is recommended prior to treatment with antibiotics in adults.
- Discuss with patients and families the critical nature of the disease and the potential for morbidity and mortality.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 99: QUESTIONS & ANSWERS

99.1. Which of the following is typically the first step in the pathogenesis of bacterial meningitis?
A. Cutaneous colonization
B. Direct invasion via a meningeal disruption
C. Hematogenous seeding
D. Middle ear colonization
E. Nasopharyngeal colonization

Answer: E. Virulent microbes secrete proteases and induce cellular ciliostasis. They are then able to evade the complement pathway and cross the blood-brain barrier.

99.2. Which of the following is typically the first step in the pathogenesis of viral meningitis?
A. Cutaneous colonization
B. Direct invasion via a meningeal disruption
C. Hematogenous seeding
D. Middle ear colonization
E. Nasopharyngeal colonization

Answer: C. Viruses may enter the host through almost any portal, replicate outside of the central nervous system (CNS), and gain access via hematogenous spread.

99.3. In the pediatric population, where is the most common location of intraparenchymal brain abscesses that are otogenic in origin?
A. Cerebellar
B. Frontal
C. Occipital
D. Parietal l
E. Temporal

Answer: A.

99.4. A 44-year-old woman presents with fever and headache of 2 days' duration. Vital signs are remarkable for fever, tachycardia, and hypotension with a blood pressure of 80/40 mm Hg. Chest radiograph and noncontrasted computed tomography (CT) scan of the brain are unremarkable. Antibiotics are given. Laboratory evaluation is remarkable for leukocytosis with hemoglobin 12 g/dL, sodium 128 mEq/L, potassium 5.5 mEq/L, blood urea nitrogen (BUN) 25 mg/dL, creatinine 0.9 mg/dL, and bicarbonate 26 mEq/L. Lumbar puncture (LP) confirms meningitis with gram-negative cocci, pleocytosis, elevated protein, and low glucose. Opening pressure is 20 cm H_2O. Hypotension persists despite several liters of normal saline and titration of dopamine at 15 μg/kg/min. What should be the most appropriate next step?
A. Hydrocortisone intravenously
B. Mannitol 0.5 g/kg
C. Norepinephrine
D. Phenylephrine infusion
E. Transfusion of packed red cells

Answer: A. Overall, the complications from meningococcal meningitis are less than with pneumococcal disease. The incidence of Waterhouse-Friderichsen syndrome is dramatically higher. The presence of refractory hypotension, hyponatremia, and hyperkalemia strongly suggests adrenal insufficiency.

99.5. A 46-year-old man is brought to the emergency department (ED) for acute mental status changes and fever that have evolved rapidly over 24 hours. The emergency medical service (EMS) transport team reports a noticeable decline during transport. Immediately upon arrival, the patient experiences a brief grand mal seizure. Vital signs are temperature, 39.3°C; heart rate, 133 bpm; blood pressure, 110/60 mm Hg; respiratory rate, 20 breaths per minute; and oxygen saturation, 95%. Fluid resuscitation is begun. Noncontrast computed tomography (CT) scan of the head is negative. Physical examination is remarkable for modest meningismus. Which of the following statements is true?
A. The next step should be blood cultures and antibiotics.
B. The next step should be contrasted CT scan.
C. The next step should be dexamethasone 10 mg intravenously.
D. There are no predictable risk factors for herniation.
E. Raised intracranial pressure (ICP) is reliably detected by CT scan.

Answer: A. The controversy regarding not performing a lumbar puncture (LP) despite a normal CT is based on emergency reports of a fulminant herniation syndrome temporarily related to LP preceded by a normal CT. These reports reinforce the fact that CT cannot exclude raised ICP. Risk factors for the herniation syndrome are clinical signs of raised ICP, acute mental

status deterioration, and recent seizures. In these cases, blood cultures and empirical antibiotics are indicated in lieu of a confirmatory LP.

99.6. Cerebrospinal fluid (CSF) turbidity is usually seen with CSF leukocytosis above which of the following?
A. 100 cells/mm^3
B. 200 cells/mm^3
C. 300 cells/mm^3
D. 400 cells/mm^3
E. 500 cells/mm^3

Answer: B. Leukocytosis is the most common cause of CSF turbidity.

99.7. Which of the following findings should be considered the cutoff for indicating a normal cerebrospinal fluid (CSF) result?
A. Total cell count >4; polymorphonuclear (PMN) count = 0
B. Total cell count >5; PMN count = 1
C. Total cell count >6; PMN count = 2
D. Total cell count >8; PMN count = 3
E. Total cell count >10; PMN count = 4

Answer: B. Normal CSF contains at most five leukocytes with at most one PMN leukocyte.

99.8. A 27-year-old woman presents with fever, headache, and mild neck pain. Physical examination is unremarkable except for neck pain with mild meningismus and a fever of 39.5°C. Blood tests, chest radiograph, and urinalysis are negative. Lumbar puncture (LP) results are lymphocytes 3 cells/mm^3 and polymorphonuclear (PMN) leukocyte is 0. Glucose and protein levels are normal. No organisms are seen on gram stain. What should be the next step?
A. Computed tomography (CT) scan with intravenous (IV) contrast
B. IV antibiotics and admission
C. IV ceftriaxone and a 24-hour recheck
D. Magnetic resonance imaging (MRI) scan
E. Reassurance and analgesics

Answer: B. Normal cell counts and differential diagnoses, in the face of a compatible clinical picture, do not rule out meningitis. Such patients require antibiotics, admission, reevaluation, and sometimes repeat lumbar puncture (LP). Brain abscesses and parameningeal infections may likewise present with normal cerebrospinal fluid (CSF).

99.9. Cerebrospinal fluid (CSF) xanthochromia may persist for up to how long?
A. 24 hours
B. 2 days
C. 7 days
D. 14 days
E. 1 month

Answer: E. CSF xanthochromia may persist for up to 1 month. Also, if a traumatic tap introduces enough protein to raise the CSF level to 150 mg/dL, blood pigments may cause xanthochromia.

CHAPTER 100

Thought Disorders

Matthew P. Kelly | Dag Shapshak

PRINCIPLES

Patients with a history of mental illness have a higher rate of emergency department (ED) visits then the general population. Patients with at least one primary psychiatric visit to an ED were over four times more likely to become frequent ED users compared to patients with none.[1] Psychiatric patients accounted for almost 10% of all ED visits in 2010.[2]

Patients are often brought to the ED by family, police, or emergency medical service (EMS) with concerning symptoms of disorganized thought or behavior. They may express language and ideas found to be inappropriate and disruptive to accepted patterns of social interaction. Whether the issue involves thought content (delusions) or thought form (structure of thinking), the clinical impression is that of psychosis (detachment from reality and societal norms). Acutely psychotic patients raise concerns of safety for themselves and those around them.

The emergency clinician's role is to first prevent and control violent and disruptive behavior and then determine if the underlying etiology of the thought disorder is functional (psychiatric) versus organic (medical) in nature. Functional causes include schizophrenia and schizophrenia-like illness, mania or mood disorder–associated psychosis. Organic causes can mimic the psychotic behavior of functional psychosis. Medication effects, substance abuse, and certain medical disorders need to be excluded before psychosis can be attributed to an underlying psychiatric illness.

Schizophrenia often manifests as a thought disorder or psychosis. The prevalence of schizophrenia approaches 1% internationally. The incidence is approximately 1.5 new cases annually per 10,000 people. Slightly more men than women are diagnosed (1.4:1), and women tend to be diagnosed later in life.[3] The mortality rate for schizophrenia is 2.5 times that of the general population and continues to grow. Migrants, urban dwellers, those with low social economic status, and those who live at higher latitude have an increased risk for the disease.

Although the etiology of schizophrenia is multifactorial, it has a substantial genetic component with 80% of the variation in the trait of the disease attributed to genetic factors.

Alterations in the dopaminergic, serotonergic, cholinergic, and glutamatergic dependent pathways have all been implicated in the pathophysiology of schizophrenia.[4] Neuro-inflammation and white matter pathology may be associated with the disease. Neuropathological and neuroimaging studies provide consistent evidence of an association between schizophrenia and microglial activation and proliferation.[5] Schizophrenia is also postulated to be related to environmental factors interacting with neurodevelopmental factors thereby increasing risk of the disease. Stress, perinatal hypoxia, poor nutrition, infections, vitamin D deficiency, and zinc deficiency have all been associated with the development of schizophrenia.[6] Evidence supports the existence of a progressive continuum of psychotic illness, beginning with unipolar depression and progressing to bipolar disease, schizoaffective psychosis, and finally schizophrenia. Research has shown that primary cerebellar insults may occur early during brain development long before the illness is clinically expressed. Interactions between early neurodevelopmental disturbances and pathological events in postnatal brain maturation seem necessary to trigger the onset of overt schizophrenia.[7]

CLINICAL FEATURES

Thought disorders broadly affect mental activity and can be associated with varying degrees of functional impairment. The core psychopathology of schizophrenia and other thought disorders according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) includes hallucinations, delusions, disorganization, cognitive impairment, and negative symptoms.[8,9] The positive symptoms of schizophrenia manifest in many forms, including distortion of reality. Hallucinations are the perception of a sensory process in the absence of an external source. They can be auditory, olfactory, visual, gustatory, or somatic in nature. The vast majority of people with schizophrenia experience auditory hallucinations.

Another impairment present in most schizophrenics is delusional thinking. Delusions are fixed, false beliefs that persist in the face of overwhelming contradictory evidence. Due to impaired insight, patients with thought disorders often have delusional explanations for their hallucinations. Delusions can be bizarre and clearly implausible, or they can be reasonable and understandable yet untrue.

Patients with schizophrenia typically display disorganization of behavior and thinking. Their use of disjointed speech patterns reflects their internal poor organization of thought. This results in a lack of a coherent focus of ideas. The most commonly observed abnormal speech patterns are tangentiality and circumstantiality where the narrative wanders away from the initial topic of conversation. More severe thought disorders include derailment, neologisms, word salad, and perseverations. In severe cases, there may be no understandable content and speech is utterly incomprehensible. A separate group of patients with a more extreme deficit in communication are those suffering from catatonia. This behavior includes immobility, stupor, mutism, resistance to instructions, oppositionalism, echo phenomena, and withdrawal. Although classically associated with schizophrenia because of the profound communication and thought deficiencies, more recent studies highlight a strong association of catatonia with mood and medical disorders. Despite their similar

presentations, only a minority of catatonic patients suffer with schizophrenia.[10]

Along with disorganization, thought disorders can be associated with significant cognitive impairment. These difficulties with attention, memory, reasoning, verbal comprehension, and decision-making usually precede the onset of positive symptoms.[11] These features are increasingly considered a core feature of thought disorders and not the byproduct of other symptoms or medications.

Negative symptoms represent an absence or diminution of normal cerebral processes. Negative symptoms include blunted affect, emotional withdrawal, social withdrawal, poor rapport with other people, difficulty with abstract thinking, loss of spontaneous conversation, and stereotyped thinking. The negative symptoms of schizophrenia are associated with an insidious onset of disease, fewer remissions, and poorer long-term prognosis. They are also associated with worse premorbid interpersonal skills, lower intelligence quotient (IQ), and tend to progress over time.

The development of schizophrenia involves three phases. The *premorbid phase* is characterized by the development of negative symptoms with deterioration in personal, social, and intellectual functioning. The patients are often young and may progressively withdraw from social actions. They may neglect personal appearance and hygiene. They experience deterioration of work, school, and home life. The *progressive phase* is often precipitated by a stressful event with the development of positive symptoms. The progressive phase can be said to begin when the patient develops the classical characteristics of schizophrenia mentioned earlier. Patients can become agitated or exhibit a hypervigilant withdrawal state characterized by rocking or staring and the patient may be violent and acting bizarrely. It is during the progressive phase that the patient is most likely to be brought to the ED by family, friends, police, or concerned bystanders. The *residual phase* is characterized by persistence of residual symptoms and disability. Impaired social and cognitive ability, poor hygiene, delusions, bizarre behavior, and social isolation can occur. On average, functional outcome is poor and patients may have varying levels of treatment resistance. Mortality is substantially increased due to elevated suicide risk and increased rates of poorly controlled medical comorbidities.

DIFFERENTIAL DIAGNOSIS

Medical Disorders

Numerous acute and chronic medical conditions can precipitate thought disorders (Box 100.1). Additionally, patients with underlying psychiatric disease may develop medical disorders that can exacerbate behavioral symptoms and cloud the distinction between psychiatric and organic brain disease.

Factors associated with primary medical conditions include new onset of symptoms, acute change in mental status, recent fluctuation in behavioral symptoms, onset in fifth decade of life or older, onset of symptoms after the patient has already been admitted to a medical care setting, and the presence of nonauditory hallucinations, lethargy, abnormal vital signs, and poor performance on cognitive function testing, particularly orientation to time, place, and person. Primary psychiatric conditions are more commonly associated with auditory hallucinations, a family history of psychosis, and an insidious onset in the late teens to mid-twenties. Medical delirium is common in elders; therefore, special attention should be paid to symptoms of psychosis in this population. Health care providers frequently ascribe medical delirium to other causes, such as dementia, psychosis, or depression.[12] Medical delirium can be frequently missed in elders brought to the ED for alterations in behavior.[13]

BOX 100.1

Medical Disorders That May Cause Acute Psychosis

METABOLIC DISORDERS
- Hypercalcemia
- Hypercarbia
- Hypoglycemia
- Hyponatremia
- Hypoxia

INFLAMMATORY DISORDERS
- Sarcoidosis
- Systemic lupus erythematosus
- Temporal (giant cell) arteritis

ORGAN FAILURE
- Hepatic encephalopathy
- Uremia

NEUROLOGIC DISORDERS
- Alzheimer's disease
- Cerebrovascular disease
- Encephalitis (including HIV infection)
- Encephalopathies
- Epilepsy
- Huntington's disease
- Multiple sclerosis
- Neoplasms
- Normal-pressure hydrocephalus
- Parkinson's disease
- Pick's disease
- Wilson's disease

ENDOCRINE DISORDERS
- Addison's disease
- Cushing's disease
- Panhypopituitarism
- Parathyroid disease
- Postpartum psychosis
- Recurrent menstrual psychosis
- Sydenham's chorea
- Thyroid disease

DEFICIENCY STATES
- Niacin
- Thiamine
- Vitamin B_{12} and folate

HIV, Human immunodeficiency virus.

Patients intoxicated with drugs of abuse are often brought to the ED because of bizarre or dangerous behavior. Street drugs such as cocaine, amphetamines, bath salts, hallucinogens, and synthetic cannabis affect the serotonergic and dopaminergic pathways and can provoke psychotic reactions resembling a primary psychotic disease or can disclose latent schizophrenia.[14] Certain pharmacologic agents may also cause acute psychosis and mimic a thought disorder (Box 100.2).

Psychiatric Disorders

Once medical causes have been ruled out and the etiology is believed to be psychiatric, it can be helpful to classify which type of psychosis the patient is experiencing. The DSM-5 uses four classes of information to distinguish among the various types of

BOX 100.2

Pharmacologic Agents That May Cause Acute Psychosis

ANTIANXIETY AGENTS
- Alprazolam
- Chlordiazepoxide
- Clonazepam
- Clorazepate
- Diazepam
- Ethchlorvynol

ANTIBIOTICS
- Isoniazid
- Rifampin

ANTICONVULSANTS
- Ethosuximide
- Phenobarbital
- Phenytoin
- Primidone

ANTIDEPRESSANTS
- Amitriptyline
- Doxepin
- Imipramine
- Protriptyline
- Trimipramine

CARDIOVASCULAR DRUGS
- Captopril
- Digitalis
- Disopyramide
- Methyldopa
- Procainamide
- Propranolol
- Reserpine

DRUGS OF ABUSE
- Alcohol
- Amphetamines
- Cannabis
- Cocaine
- Hallucinogens
- Opioids
- Phencyclidine
- Sedative-hypnotics

MISCELLANEOUS DRUGS
- Antihistamines
- Antineoplastics
- Bromides
- Cimetidine
- Corticosteroids
- Disulfiram
- Heavy metals

BOX 100.3

Diagnostic Criteria for Schizophrenia From *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition

1. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
   A. Delusions
   B. Hallucinations
   C. Disorganized speech (eg, frequent derailment or incoherence)
   D. Grossly disorganized or catatonic behavior
   E. Negative symptoms (ie, diminished emotional expression or avolition)
2. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
3. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).
4. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
5. The disturbance is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication) or another medical condition.
6. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

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psychosis: type of psychotic symptom, course of illness, consequences of illness, and exclusions.[15] Each category can help distinguish schizophrenia from other disorders that include psychosis among their symptoms. The DSM-5 definition of schizophrenia is included in Box 100.3.

A *brief psychotic disorder* involves the sudden onset of psychotic symptoms in response to major stress and lasts from several days up to 1 month. *Peripartum psychosis* is included under the diagnosis of brief psychotic disorder. Patients with *schizophreniform disorder* have similar symptoms to a brief psychotic disorder and last from longer than 1 month to less than 6 months. Up to one-third of patients with schizophreniform disorder can recover within 6 months; the other two-thirds develop clinical schizophrenia.[16] Patients with *mood disorders* may develop psychotic symptoms as part of their disease. If psychotic symptoms develop during periods of mood disturbances, the diagnosis of mood disorder with psychotic features applies. If symptoms consistent with schizophrenia persist for more than 2 weeks in the absence of prominent mood episode, the diagnosis of *schizoaffective disorder* is made. Patients with *personality disorders* may occasionally develop brief psychotic episodes especially under stress. None of the aforementioned disturbances can be attributable to the effects of a substance or another medical condition.[9]

Delusional disorder is characterized by one or more delusions that are present for longer than 1 month and the criteria for schizophrenia have not been met. Patients may believe famous

people are in love with them (erotomanic) or that they have extraordinary powers or possess a special relationship with a deity or famous person (grandiose type). Other common delusions are of sexual partners being unfaithful (jealous type), that they are being malevolently treated (persecutory type), or that they have some physical defect or medical condition (somatic type). Function is not typically severely impaired, and behavior may not be bizarre apart from the impact of the delusions. Individuals may appear and behave normally if not actively discussing delusions, but social, marital, work, and legal problems can result from delusional beliefs.

DIAGNOSTIC TESTING

Diagnostic tests are indicated when a patient's clinical scenario cannot be explained by the history and physical examination alone. Often there is not enough information readily available to the clinician to accurately ensure that the patient is suffering from a thought disorder alone. The potential medical causes of thought disorders are very broad; therefore, if a medical evaluation is indicated, testing should be patient specific and based on the particular medical processes that the clinician feels may be causing or exacerbating the thought disorder. The clinical judgment of the treating physician, rather than panels of routine tests, should be used to efficiently and appropriately guide diagnostic test ordering.

The evaluation of a "first-time" psychosis or thought disorder presentation in an emergency patient differs substantially from the evaluation of a patient with chronic disease and recurrent symptoms. The evaluation for the first time thought disorder patient may include a larger, more detailed laboratory and radiological evaluation. Complete blood counts, electrolyte panels, glucose levels, thyroid function, urine testing, cortisol levels, vitamin B_{12}, methylmalonic acid levels, and rapid plasma regain (RPR) testing could be useful in certain clinical situations and ordered as needed for individual patients.

Whether to obtain neuroimaging on the initial evaluation of patients with thought disorders remains controversial. Incidental findings on computed tomography (CT) or magnetic resonance imaging (MRI) occur at similar rates to control patients and rarely lead to the discovery of clinically relevant disorders in the absence of neurological signs.[17] Neuroimaging for intra-cranial injury, vasculitis, demyelinating diseases, tumor, cerebrovascular disease, or abscess may be indicated based upon findings noted on the history and physical examination. Given the long-term costs of schizophrenia, neuroimaging in a young person with a first time psychosis will exclude rare and treatable causes of psychosis and can support the diagnosis of schizophrenia, and it should be considered by the treating clinician on a case by case basis.

Ancillary testing beyond that required for medical clearance of psychiatric emergency patients rarely alters care, especially for patients with an established diagnosis of schizophrenia or other chronic thought disorders. Policies that require panels of testing prior to psychiatric admission are costly and unnecessary. One of the largest unnecessary costs is incurred with the routine use of urine drug screens, which have been found to rarely alter disposition for psychiatric patients from the ED especially when combined with a good substance abuse history.[18] Greater emphasis should be placed on identifying a clinical toxidrome and history of use when attempting to determine if drugs and medications are contributing to the symptoms of psychosis.

MANAGEMENT

Patient safety and ED staff safety are a principle concern when a patient presents with aggressive and unpredictable psychotic behavior. Risk factors for violence in patients with schizophrenia include gross excitement, prior violence, auditory hallucinations, systematization of delusions, incoherence of speech, and long duration of illness. In contrast, traits such as substance abuse and antisocial episodes are not recognized as significant violence-associated factors.[19] Strategies to control disruptive and violent behavior in psychosis and thought disorders include de-escalation techniques, chemical sedation, and physical restraints.

Although chemical and physical intervention can be appropriate when patients are demonstrating dangerous behavior, non-physical intervention, such as verbal de-escaltion should be considered first. The clinician should demonstrate a calm, non-judgmental demeanor while showing appropriate concern and avoiding excessive stimulation, posturing, and prolonged eye contact. The patient should be given an opportunity to express their concerns, as well as identify unmet needs that can be easily corrected (eg, inadequate pain control, communication failures, or social concerns). If available, consider recruiting trusted others (eg, family, friends, case managers) to help prevent further agitation.[20]

When verbal de-escalation is ineffective or inappropriate, physical restraint or use of seclusion may be necessary. Risk factors for the use of restraint or seclusion include referrals initiated by a third party, patients arriving to the ED in restraints, and clinician perception of the patient as severely disruptive, already exhibiting psychosis, or experiencing a manic episode.[21]

Chemical restraint for psychomotor agitation is a common and necessary intervention. Speed of onset and reliability of delivery are two important factors to consider when selecting a route of administration of sedation in the behaviorally disturbed patient. Oral sedation is indicated when the patient can be safely verbally de-escalated, is not at imminent risk of harm to self, and agrees to take oral medications. When more expedient sedation is required, parenteral route has the advantages of immediate effect and titration of dosing. The goal of titration in this setting is the induction of rousable sleep, not unconsciousness.[22]

Benzodiazepines and antipsychotics are the two medications most commonly used for chemical restraint. Using a single agent or, for more disturbed patients, a combination of the two classes, can be considered. Common agents and dosages are listed in Table 100.1.

Combined with concurrent physical restraint and the risk of previously ingested intoxicants, there is significant risk for oversedation and respiratory compromise. The combination of haloperidol and lorazepam causes respiratory depression in up to 50% of patients with a significant number also experiencing a hypoxic event. Fortunately, most episodes are quickly corrected with verbal stimulation or airway repositioning. As a result, we recommend the use of pulse oximetry or CO_2 monitoring in chemically restrained patients to detect early signs of respiratory

TABLE 100.1

Common Drugs for Sedation

DRUG	USUAL ADULT DOSE	ADVERSE EVENTS
Midazolam	2.5 to 5 mg IM (rapid onset)	Respiratory depression Oversedation
Lorazepam	1 to 2 mg PO or IM	Hypotension
Diazepam	5 to 10 mg PO or IM (longer acting)	Paradoxical excitation reaction in patients with organic brain disease
Haloperidol	5 to 10 mg PO or IM	Increased mortality risk in elderly dementia-related psychosis
Ziprasidone	10 to 20 mg PO or IM	Caution in prolonged QT or history of neutropenia
Olanzapine	10 mg PO or IM	

IM, Intramuscular; *PO, per os* (by mouth).

depression.[15] In addition to monitoring of airway and level of consciousness, sedated and restrained patients should have frequent behavioral monitoring. The use of physical restraints may cause excess pressure on the patient's neck, chest or abdomen, and requires ongoing direct visualization. Potentially hazardous articles and possessions should be removed from the patient's area. Restrained patients are known to forcibly remove Foley catheters without deflation of the balloon if their limbs are released prior to removal of the catheter, resulting in urethral injury.

A detailed discussion of the use of physical and chemical restraints is provided in Chapter 189.

DISPOSITION

Making an appropriate disposition for patients with decompensated thought disorders is often difficult in today's emergency medicine practice environment. Although institutional and community psychiatric resources vary widely by region, there appears to be a nationwide trend of diminishing psychiatric referral resources in the presence of rising numbers of psychiatric-related ED visits.[23] The number of inpatient psychiatric beds nationwide has decreased dramatically, and many EDs "board" psychiatric patients for extended periods of time.

Appropriate disposition is based on the etiology of the underlying psychosis, response to treatment, consideration of patient and community safety, and an appropriate outpatient follow-up plan.

Patients who are actively suicidal, dangerous to others, possess severe mental debilitation precluding self-care, or are having their first psychotic episode should be admitted. The decision for inpatient psychiatric admission is not always precise. There may be disagreement between emergency clinicians and consulting psychiatrists regarding need for involuntary hold and final disposition, but psychiatric consultation can help confirm safety for discharge, help facilitate inpatient admission, and aid in outpatient follow-up.[24]

Telemedicine is emerging as a technology that may ease the growing lack of adequate psychiatric resources for ED patients by facilitating urgent psychiatric consultation. A recent study demonstrated that telemedicine can be used safely and is not associated with significant differences in care when compared with face-to-face psychiatric evaluations.[25]

Medication noncompliance is a common reason for a known schizophrenic to present to the ED with a decompensated psychotic episode. A patient whose psychosis stabilizes in the ED with medication can sometimes be safely discharged back into the community. Safe discharge planning can be accomplished provided that the patient has adequate ability to care for self and does not pose a risk of harm to self or others. Insight by the patient and judgment to adhere to an agreed course of action, including taking medication, is typically required. Patients with severe underlying psychiatric illnesses may have some degree of persistent mental disability even when optimally treated. For these patients, recruiting family or friends familiar with the patient can help establish that the patient is back to his or her baseline to ensure safety. A safe transition to the community setting requires adequate social support, including follow-up with a mental health service.[21]

KEY CONCEPTS

- Thought disorder symptoms can be precipitated by psychiatric, underlying medical, and toxicologic etiologies.
- Diagnostic testing should be patient specific and based on the particular medical processes that the clinician feels may be causing or exacerbating the thought disorder, rather than panels of routine tests.
- Consider nonphysical intervention first when appropriate, but chemical sedation and physical restraint are immediately necessary for patients who demonstrate aggressive and dangerous behavior.
- Appropriate disposition depends on the etiology of the underlying psychosis, response to treatment, and patient and community safety considerations and, more often than not, includes psychiatric consultation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 100: QUESTIONS & ANSWERS

100.1. Which of the following pharmacologic agents have been implicated in causing acute psychosis?
- **A.** Aripiprazole, hydralazine, nitroglycerin
- **B.** Diazepam, rifampin, captopril
- **C.** Hydrochlorothiazide, acetaminophen, albuterol
- **D.** Lorazepam, salsalate, rocuronium
- **E.** Penicillin, ceftriaxone, risperidone

Answer: B. Box 100.2 provides an extensive list of other agents that may cause psychosis.

100.2. Rapid tranquilization using a neuroleptic agent would be indicated in which of the following cases?
- **A.** An intoxicated schizophrenic
- **B.** Anticholinergic psychosis
- **C.** A lactating schizophrenic
- **D.** A phencyclidine overdose
- **E.** A pregnant schizophrenic

Answer: A. Neuroleptics are contraindicated in choices B to E. They should not be the sole agent for alcohol withdrawal but would be useful for acute psychotic agitation.

100.3. A 45-year-old woman presents to the emergency department (ED) for a complaint of severe anxiety and unrest. Her past history is significant only for moderate schizophrenia, for which she was placed on olanzapine 2 months prior. She has been compliant. Physical examination is remarkable for the presence of anxiety, clear sensorium and orientation, and normal speech. She is restlessly pacing the room and reports being compelled to keep moving. Urine drug screen is negative. What would be the most appropriate therapy?
- **A.** Benztropine orally
- **B.** Lorazepam orally
- **C.** Olanzapine intravenously
- **D.** Psychiatry consultation
- **E.** Ziprasidone intravenously

Answer: A. Akathisia is a state of motor restlessness characterized by a physical need to be constantly moving. The patient does not want to do so but feels compelled. It is most commonly seen in middle-aged patients within the first few months of starting treatment. It may be mistaken for an acute deterioration, but psychotic features are not increased. Treatment is with oral beta-blockers and anticholinergics (benztropine).

100.4. What is the most common adverse effect seen with neuroleptic agents?
- **A.** Akinesia
- **B.** Dystonia
- **C.** Orthostatic hypotension
- **D.** Pseudoparkinsonism
- **E.** Tardive dyskinesia

Answer: B. Dystonia occurs in 1% to 5% of this patient population. The reaction occurs because of a dopaminergic pathway disruption with a resulting cholinergic predominance. Anticholinergics should be administered parenterally (Benadryl 25 to 50 mg intravenous [IV] or Cogentin 1 or 2 mg IV), followed by 48 to 72 hours of oral follow-up treatment to prevent recurrence. Patients may experience tongue protrusion (buccolingual crisis), upward eye deviation (oculogyric crisis), back arching (opisthotonus), and, rarely, laryngospasm. Symptoms may lessen with voluntary muscle action and increase with stress.

100.5. A 27-year-old known schizophrenic is brought to the emergency department (ED) for altered mental status. His only known medication is clozapine, which he started 4 weeks ago with subsequent dose increases. He has no other past history. Physical examination is remarkable for a muscular black man who is somnolent and diaphoretic. He withdraws all extremities stiffly and grimaces to pain. Vital signs are temperature, 40.5° C; heart rate, 146 beats per minute; blood pressure, 205/125 mm Hg; and respiratory rate 28 breaths per

minute. Rectal examination is guaiac positive. Foley placement shows brown urine. What should be the next diagnostic maneuver?

A. Creatine kinase level
B. Head computed tomography (CT) scan
C. Lumbar puncture
D. Thyroid hormone levels
E. Urine drug screen

Answer: A. Neuroleptic malignant syndrome is an idiopathic condition clinically similar to serotonin syndrome and malignant hyperthermia. Milder cases may be confused with serotonin syndrome. Severe cases, related to possible hypothalamic dysfunction, present with fever, rigidity, altered mental status, autonomic instability, and elevated creatine phosphokinase (CPK) and possibly rhabdomyolysis. It is seen with both typical and atypical antipsychotics and generally occurs in the first few weeks of treatment. Complications may include hepatic/renal failure, gastrointestinal (GI) hemorrhage, and respiratory failure. Severe cases may require intravenous dantrolene or dopamine agonists (eg, bromocriptine).

CHAPTER 101

Mood Disorders

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PRINCIPLES

Mood is a subjective emotional state. It is normal human experience to have fluctuations in mood in response to occurrences in everyday life. A change in mood becomes a "mood disorder" when it significantly impairs functioning. In the emergency department (ED), patients with mood disorders often present grossly debilitated, with thoughts of suicide, homicide, or profound self-neglect. These patients frequently present in emotional crisis, but this may not be their presenting complaint. Approximately, one-fourth to one-third of ED patients screen positive for mood disorders.

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), divides mood disorders into two broad categories: depressive disorders and bipolar disorders.[1] Mood disorders may also be due to a general medical condition or substance-induced mood disorders. Because the specific pathophysiologic mechanisms of these disorders are not fully understood, they are categorized by groupings of symptoms that persist for defined lengths of time.

EPIDEMIOLOGY

Mental health patients are the fastest growing group of patients presenting to the ED. In 2007, 13% of the 94 million ED visits in the United States were for psychiatric reasons, which was an increase from 5% in 2000.[2] This increase is nearly double what would have been expected by population growth alone.[3] Up to 50% of Americans will meet the criteria for a DSM-5 disorder sometime in their life, with an estimated 21% having a mood disorder.

The World Health Organization (WHO) ranks major depressive disorder as one of the most prevalent and disabling diseases in the world. The 12-month prevalence for major depressive disorder is 5% and the lifetime prevalence is 13%. Patients with major depressive disorder frequently have other comorbid mental health issues, including anxiety disorders, personality disorders, and substance use disorders.

The lifetime prevalence of bipolar spectrum disorders is approximately 4%. Both severe depression and mania are serious and potentially life-threatening. Up to 80% of patients with bipolar disorder will exhibit suicidal behavior, and half will attempt suicide. Suicidal behavior can occur during all phases of bipolar disorder, but patients experiencing a depressed or a mixed episode are at higher risk, especially those with severe depressive symptoms and a sense of hopelessness.

PATHOPHYSIOLOGY

The pathophysiology of the mood disorders is not well established, but much is known about the neurophysiology, genetics, and psychosocial aspects of the disorders.[4]

Neurophysiology

Antidepressants work by increasing the availability and activity of serotonin and norepinephrine at the synapse to stimulate the postsynaptic neuron. This is done by direct binding to the presynaptic and postsynaptic receptors, blocking reuptake of the neurotransmitter or inhibiting the enzymatic breakdown of the neurotransmitter. Because norepinephrine and serotonin systems traverse large portions of the brain, monoamine deficiency is hypothesized as a cause of depression. Depletion of oral tryptophan and tyrosine, amino acids essential for the production of serotonin and norepinephrine, respectively, can induce a depressive episode in subjects with a history of depression but not in healthy controls. Monoamine metabolite levels in cerebrospinal fluid, plasma, urine, and postmortem brains of patients with depression have not been reliably found to be deficient, indicating that there could be downstream effects involving second-messenger systems, such as cyclic adenosine monophosphate and phosphatidylinositol.

Other neurotransmitter systems may play a role in the development of depression. Decreased levels of both glutamate and γ-aminobutyric acid have been found in the prefrontal cortex of depressed subjects. Intravenous ketamine, an *N*-methyl-d-aspartate (NMDA) antagonist, induces a rapid antidepressant effect and suggests a role for glutamate in the pathophysiologic process of depression. The brain relies on the actions of protective and regenerative cytokines, such as brain-derived neurotrophic factor (BDNF). All known antidepressants raise levels of BDNF and subsequently result in neurogenesis of certain brain regions, such as the hippocampus. Other theories include the melatonergic system and related abnormalities in circadian rhythm, decreased neurosteroid synthesis, impaired endogenous opioid functioning, monoamine-acetylcholine imbalance, inflammatory effects of cytokines, and dysfunction of specific brain structures and circuits.

The neurophysiology of bipolar disorder is less well understood than unipolar depression, in part because of the fluctuating mood states and the heterogeneity of the disorder. Bipolar disorder may in part arise from abnormalities in the connections within and between structures in the brain.[5] Specifically implicated are circuits interconnecting the amygdala, hypothalamus, striatum, and subdivisions of the frontal cortex, all of which are involved in both the generation and regulation of emotion.[5]

Neuroanatomy

Neuroimaging studies of the brain suggest that abnormalities in certain areas and the interconnections between those areas may be involved mood disorders. A common magnetic resonance imaging (MRI) finding in patients with mood disorders, especially bipolar disorder, is an increased occurrence of subcortical hyperintensities in the periventricular areas, basal ganglia, and thalamus. High-resolution MRI demonstrates reduced volumes in the hippocampus, orbital cortex, and anterior cingulate. These findings are associated with more severe illness, bipolar disorder, and increased cortisol levels. Volume reduction in the hippocampus is associated with high illness chronicity.

The amygdala is a clustering of nuclei that process emotional stimuli, especially fear, anger, and sadness. Functional neuroimaging suggests that amygdala activity is increased when the subject

is exposed to emotionally relevant stimuli. The amygdala has connections throughout the brain. A decreased amygdala volume has been associated with unipolar depression.

Endocrine System

Physiologic changes such as increased alertness, decreased appetite, increased heart rate, and activation of the hypothalamic-pituitary-adrenal (HPA) axis occur when a person is stressed. The HPA axis may play a role in depression, especially in cases of early childhood and chronic stress.[4] Activation of the HPA axis releases corticotropin-releasing hormone (CRH) from the hypothalamus. Although not specific, patients with depression may have increased levels of free cortisol in the plasma, cerebrospinal fluid, and urine. Increased CRH has been demonstrated in cerebrospinal fluid, and increased levels of CRH messenger RNA and protein have been demonstrated in limbic brain regions. Although none of these measures is reliable as a diagnostic tool, successful treatment to remission has been shown to reverse some of these abnormalities.

Genetics

Genetic vulnerability to mood disorders has not been traced to a single gene. It is likely to be due to the additive effects of many genes and environmental influences on how these genes are expressed. Family, twin, and adoption studies provide evidence that major depressive disorder is a familial disorder but is less heritable than bipolar disorder. Bipolar disorder is one of the most heritable medical illnesses with a heritability of 80% to 85% and a monozygotic twin concordance of about 40%.

Psychosocial Factors

The etiology of most psychiatric problems, including mood disorders, involves complex interactions between both biologic and psychosocial factors.[4] The complex neural mechanism that regulates mood responds to and is modified by each person's experience, including events in early childhood, such as childhood sexual abuse, reward and punishment during growth and development, other lifetime trauma, marital problems, low social support, and various kinds of loss. Psychosocial theories of mood disorder form the basis for psychotherapy.[4]

CLINICAL FEATURES

Major Depressive Disorder

Major depressive disorder is characterized by one or more major depressive episodes, as defined by DSM-5 criteria (Boxes 101.1 and 101.2).[1] A major depressive episode is characterized by disturbances in four major areas: mood, psychomotor activity, cognition, and vegetative function. The patient must have at least five symptoms for a minimum of 2 weeks and one of the five must be depressed mood or anhedonia (decreased interest or pleasure).[1]

Mood Disturbances

Patients in a depressed state often feel profoundly hopeless and helpless. There are many words and phrases that can be used to describe feeling depressed; some patients will not recognize that they are "depressed" but rather they may describe the feeling in some other manner. Someone feeling no emotion (profoundly depressed) may answer "no" when asked about depressed mood.

On the other hand, a person may meet criteria for a major depressive episode and not be experiencing a depressed mood. Depression can also be manifested as a decreased capacity to experience pleasure or interest in otherwise pleasurable activities. This loss of interest is known as *anhedonia.*

As noted previously, the patient must exhibit a depressed mood or anhedonia to meet DSM-5 criteria for a diagnosis of a major depressive episode.[1]

BOX 101.1

Summary of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* Criteria for a Major Depressive Episode

A. Five or more of the following symptoms have been present almost every day during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. *Note:* Do not include symptoms caused by a general medical condition.
   1. Depressed mood (can be irritable mood in children and adolescents)
   2. Loss of interest or pleasure in activities
   3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite
   4. Insomnia or hypersomnia
   5. Psychomotor agitation or retardation
   6. Fatigue or loss of energy
   7. Feelings of worthlessness, or excessive or inappropriate guilt
   8. Diminished ability to think or concentrate, or indecisiveness
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation, or a suicide plan or attempt
B. Symptoms cause clinically significant distress or impairment in social, occupational, or other functioning.
C. Symptoms are not caused by direct physiologic effects of a substance (eg, drug of abuse, medication) or a general medical condition (eg, hypothyroidism).
D. Symptoms are not better explained by another mental health disorder.
E. There has never been a manic or hypomanic episode.

Modified from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5, Arlington, VA, 2013, American Psychiatric Association.

BOX 101.2

Mnemonics for the Symptoms of Depression and Mania

MNEMONIC FOR THE SYMPTOMS OF DEPRESSION

Sig E Caps
Sleep amount increased or decreased
Interest (anhedonia)
Guilt
Energy level decreased
Concentration decreased
Appetite increased or decreased
Psychomotor activity increased or decreased
Suicidal ideation

MNEMONIC FOR THE SYMPTOMS OF MANIA

Dig Fast
Distractibility
Irritability
Grandiosity
Flight of ideas
Activity increased
Sleeplessness
Thoughtlessness (impulsivity, increased risk taking)

Disturbances in Psychomotor Activity

Physical activity in depression can be either increased or decreased. Psychomotor retardation is a significant slowing of physical activity. When suffering from psychomotor retardation, thinking and speaking can be slow, causing delayed responses to answers. Depressed patients often describe feeling fatigued with a general lack of energy and motivation. Conversely, patients may display psychomotor agitation, which can be manifested as fidgeting, pacing, hand wringing, or restlessness.

Vegetative Disturbances

Vegetative symptoms include disturbances in three major areas: sleep, appetite, and sexual function. Depressed patients may complain of insomnia or hypersomnia. Insomnia may be manifested as difficulty in falling asleep, frequent awakenings throughout the night, or early-morning wakening. Depressed patients with hypersomnia may report sleeping 12 to 14 hours or more a day. Alterations in appetite and eating patterns can also occur, resulting in significant weight gain or loss during a short time. Loss of interest in sexual activity and impaired sexual functioning may also accompany depression, although this is not listed as a DSM-5 criterion.

Thought Process and Content

Depressed patients often describe impaired concentration and forgetfulness. Executive functioning can also be impaired. In severe cases, this results in a decreased ability to perform basic activities of daily living.

Thought content tends to be negatively biased, such as recurrent thoughts of guilt, failure, worthlessness, and self-criticism. Patients in a depressed episode are at increased risk for suicide. Suicidal thoughts may range from vague notions that life is not worth living (passive) to fully envisioned suicide plans with definitive intent to kill themselves (active). All depressed patients must be questioned about suicidal thoughts. Because patients are not often forthcoming with their thoughts on suicide, a thorough review of risk factors and protective factors needs to form the basis of clinical decisions for providing the necessary level of care.

Patients with severe depression may have psychotic symptoms. The hallucinations and delusions that accompany depression are usually mood congruent, meaning that the themes of the psychotic content are consistent with the depressed mood.

Masked Depression

Mood disorders may not be clear at presentation. The depressed patient may have only vague somatic symptoms. Common complaints include weakness, fatigue, headache, and abdominal pain with medical evaluations occurring in response. Patients may not be aware of their depression and are often heavy users of medical care. Over half of patients with major depressive disorder initially present with somatic symptoms only which can mask a hidden depression. Clues that suggest a mood disturbance include the recent onset of a set of unusual behaviors, significant social disturbance, such as job loss, financial stress and marital difficulties, and self-destructive behavior (eg, substance abuse, sexual promiscuity).

Special Considerations

Children and Adolescents. Criteria for depression in children and adolescents are the same as for depression in adults. Depression in these age groups can, however, present differently. Prepubertal children are more likely to have somatic complaints, psychomotor agitation, and mood-congruent hallucinations and less likely to have disturbances in sleep and appetite. Some children are misdiagnosed as having attention deficit disorder, especially if symptoms involve poor concentration, listlessness, agitation, and withdrawal from daily activities.

Adolescents with depression may show increased irritability, oppositional behavior, and substance abuse. Other characteristics are social withdrawal, increased rejection sensitivity, and decline in school performance. Some adolescents may be first diagnosed with depression on receiving treatment for drug and alcohol problems.

Disruptive Mood Dysregulation Disorder. A newly described phenomenon for children who may have been previously diagnosed with depression or bipolar disorder is disruptive mood dysregulation disorder. Children and adolescents given this diagnosis display severe, recurrent outbursts that are out of proportion for the situation and are inconsistent with developmental level. The outbursts must occur three or more times a week, and the mood in between outbursts is irritable or angry most days. There are duration criteria of 12 months with no periods of three or more consecutive months not meeting criteria. Symptoms must occur prior to age 10.[1]

Geriatric Patients. Depression is more common in elders because of more frequent occurrences of loss, comorbid health issues, and loss of autonomy. The elderly have a tendency to report more somatic complaints when depressed. They are also more vulnerable to development of melancholic depression, which is characterized by early morning awakening, diurnal variation in mood, low self-esteem, and low mood reactivity. Older depressed patients can also present with symptoms involving memory loss, inattention, withdrawal from daily activities, and lapses in personal and social hygiene that suggest dementia rather than depression. When such symptoms are from depression, the condition is called *pseudodementia.* Serious depression in elders is a highly treatable, reversible condition.

Other Depressive Disorders

Postpartum Depression

Postpartum depression is a depressive disorder that occurs during or within 4 weeks of delivery and would allow for the specifier "with peripartum onset." Symptoms of depression are common in the perinatal period. As noted in the DSM-5, between 3% and 6% of women will experience the onset of major depression during pregnancy or within the following weeks to months.[1] Similarly, but less severe, up to 65% of mothers report some depressed mood after childbirth, often called *postpartum blues.* Symptoms are generally mild and transient; although in 10% of mothers, it may lead to a full-fledged episode of major depression.

Postpartum mood episodes with psychotic features can be particularly dangerous. Infanticide is most often associated with command hallucinations to kill the infant or associated delusions. The risk for this is most closely related to a past history of postpartum episodes with psychosis, a history of depression or bipolar disorder, or a family history of bipolar disorder.

Persistent Depressive Disorder

Persistent depressive disorder is a new diagnosis that combines two former diagnoses: chronic major depressive disorder and dysthymic disorder. Specific criteria include the following: depressed mood most of the day, most days for at least 2 years;

two or more of the following: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness; never more than 2 months of the 2 years without symptoms; and must cause significant distress or impairment in functioning. Exclusion criteria include a history of hypomania or mania and a history of psychotic illness. Also, it cannot be due to a substance or medical condition.[1] There are multiple specifiers that can be applied to this diagnosis.

Premenstrual Dysphoric Disorder

Premenstrual dysphoric syndrome is a new diagnosis included in the DSM-5. At least five of the listed symptoms must be present in the final week before the onset of menses and start to improve within a few days after the onset of menses and be absent or minimal in the week post menses. These symptoms must be present for most cycles over the preceding year. The onset can occur at any point after menarche. Risks for development include stress, history of interpersonal trauma, seasonal changes, and sociocultural aspects of female sexual behavior.

Seasonal Affective Disorder

Seasonal affective disorder is not a separate mood disorder, but rather, a specifier of major depressive disorder. An example of the use of a specifier is "major depressive disorder, recurrent, moderate, with seasonal pattern." This specifier can only be used with a recurrent major depressive disorder. The criteria for this include the following: a regular temporal relationship between onset of depressive episode and a particular time of year, full remissions at a specific time of year, two depressive episodes within 2 years that demonstrate a temporal relationship, no nonseasonal episodes within the same period, and substantially more seasonal depressive episodes than nonseasonal episodes over the person's lifetime.[1] Melatonin, a hormone secreted in the brain and produced at high levels in the dark, has been implicated in the etiology of this disorder. Phototherapy is an effective and safe treatment of seasonal depression. Light exposure to the eyes seems to be essential, but the exact mechanism of action is still unknown.

Bipolar Disorders

Bipolar disorder is lifelong, with episodic exacerbation of symptoms and deterioration of function characterized by extreme mood episodes. Patients with bipolar disorder may require different forms and intensities of treatment at different stages of the illness. *Bipolar I disorder* includes at least one manic episode, and patients have typically had one or more major depressive episodes, although a depressive episode is not necessary for diagnosis. *Bipolar II disorder* involves a hypomanic episode and at least one major depressive episode. A hypomanic episode includes the features of a manic episode without psychosis, marked impairment of function, or the need for hospitalization.

Manic Episode

During a manic episode (Boxes 101.2 and 101.3), the disturbance in mood must be severe enough to include psychosis, the need for hospitalization, or marked impairment in functioning. Bipolar disorders are much less common than major depressive disorder. The overall prevalence of a manic episode is about 2% in both women and men.

In many cases, manic patients are brought to the ED by someone else (eg, family, police, or emergency medical services). Patients who are experiencing a manic episode may present as gregarious, humorous, and engaging, which may suddenly alternate with belligerence and irritability. Patients may display pressured speech, in which they keep talking, often rapidly and loudly without pauses between thoughts or sentences, and are difficult to interrupt. The thought process in mania is characterized by illogical associations and flight of ideas. An inflated self-esteem and grandiose delusions may lead them to also be argumentative, impatient, and condescending. Grandiosity often centers on very broad dramatic or universal themes, such as religion or politics. The patient may describe a massive undertaking, such as "uniting the world's churches" or "solving world poverty." These severe symptoms are usually accompanied by a profound lack of insight. Despite obvious altered behavior, impaired judgment, and poor impulse control, the patient may insist that there is nothing wrong or blame problems on others.

Manic patients have decreased or no need for sleep and typically report being awake for days. They may be involved in a massive project (eg, writing a novel), may completely disregard consequences of actions, may have difficulty with spending (eg, credit cards revoked), and may engage in risky behavior (eg, sexual liaisons with strangers, risky driving). Whenever possible, a corroborating history should also be obtained from family or others who know of the patient's behavior.

Manic patients may present as trauma patients, injured by an action reflecting the patient's grandiosity (eg, attempting to fly), impulsivity, or belligerence (eg, fighting, resisting arrest). A manic episode may be punctuated by abrupt periods of tearfulness and profound depression, including suicidal ideation. When

BOX 101.3

Summary of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* Criteria for a Manic Episode

A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood, and abnormally and persistently increased goal-directed activity or energy lasting at least 1 week (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, three or more of the following symptoms have persisted (four, if the mood is only irritable) and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity
   2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
   3. More talkative than usual or pressure to keep talking
   4. Flight of ideas or subjective experience that thoughts are racing
   5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, buying sprees, sexual indiscretions, foolish investments)
C. Mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or social activities or to necessitate hospitalization to prevent harm to self or others, or psychotic features are present.
D. Symptoms are not caused by direct physiologic effects of a substance (eg, drug of abuse, medication) or a general medical condition (eg, hyperthyroidism).

Modified from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5, Arlington, VA, 2013, American Psychiatric Association.

depressive and manic features occur concurrently in such a manner, the disorder is termed *mixed* or *bipolar, mixed phase.*

Cyclothymic Disorder

Cyclothymic disorder is characterized by chronic mood swings that do not meet criteria for a hypomanic or depressive episode. The mood episodes must occur over at least 2 years, present for at least half the time, and the individual cannot be symptom free for more than 2 months at a time.[1]

Mood Disorders Caused by a General Medical Condition

This diagnosis requires a prominent and persistent period of depressed mood or anhedonia that predominates the clinical picture, with evidence that the disturbance is the direct pathophysiological consequence of a medical condition, and not better explained by another mental disorder or occurring during the course of delirium.[1] Bipolar disorder requires a prominent and persistent period of abnormally elevated, expansive, or irritable mood; and abnormally increased activity or energy that predominates the clinical picture, with evidence of direct pathophysiological consequence of another medical condition, and it is not better explained by another mental disorder or occurs during the course of delirium.[1]

Certain medical illnesses have a well-known association with mood disorder. In Parkinson's disease, electrical stimulation to a certain area of the substantia nigra alleviates symptoms of depression. Stimulation of an area only 2 mm away can cause acute reversible symptoms of depression, such as crying, not wanting to live, and hopelessness. Parkinson's disease has a well-known association with depression, with up to 40% of patients demonstrating major depression.

Certain malignant neoplasms have a well-known association with depression, including pancreatic carcinoma, brain neoplasm, and disseminated malignant disease (eg, lymphoma). Coronary artery disease, myocardial infarction, stroke, end-stage renal disease, acquired immunodeficiency syndrome, several endocrine diseases, and connective tissue disease are also associated with major depressive disorder. After a myocardial infarction, patients with depression have a 3.5-fold increase in cardiovascular mortality compared with nondepressed patients. The development of stroke, diabetes, and osteoporosis is more likely in patients with depression than in those who are not depressed.

Depression related to medical conditions may be different in some respects from primary depression and responds less favorably than primary depression to antidepressant medication.

Mood Disorders Caused by Medications or Other Substances

These are very similar to mood disorders caused by medical conditions, with the exception of that the symptoms must develop during or soon after substance intoxication or withdrawal, or after exposure to a medication capable of producing the symptoms.[1]

Many medications are associated with symptoms of mood disorders. Multiple antihypertensives, anticonvulsants, and hormones have been associated with depressive symptoms, and certain antibiotics and steroids are associated with manic symptoms. Intoxication with or chronic heavy use of alcohol, sedatives, hypnotics, anxiolytics, narcotics, and other depressants can cause symptoms of a major depressive episode. Stimulants such as cocaine, phencyclidine, hallucinogens, and amphetamines can cause symptoms of a manic episode. Mood disorder symptoms can also develop during withdrawal. To qualify for this diagnosis, the symptoms must not occur exclusively during a course of delirium, must cause significant distress or impairment of functioning, and must develop within a month of either substance intoxication or withdrawal. When the mood disorder predates the period of substance abuse or lasts longer than 1 month after the period of abuse, the diagnosis may be an underlying mood disorder, such as a major depressive disorder or bipolar disorder, with a comorbid substance abuse or dependence diagnosis.

DIFFERENTIAL DIAGNOSIS

Medical Disorders, Medications, and Substance Abuse or Withdrawal

Medical disorders, medications, and substance abuse or withdrawal can either cause or mimic mood disorders. The patient with symptoms and signs of depression may have an unrecognized malignant neoplasm or sedative intoxication. Differential diagnostic considerations for manic symptoms include stimulant abuse (eg, cocaine, amphetamines), hallucinogen abuse, alcohol or sedative withdrawal, delirium, hyperthyroidism, and other medical conditions causing agitation. See the previous section for further information. Patients may be treated with antidepressant medication for a variety of disorders other than depression, such as anxiety, obsessive-compulsive disorder, post-traumatic stress disorder, pain syndromes, smoking cessation, and vasodepressor syncope.

Grief and Bereavement

Grief and bereavement are normal human reactions to the acute loss of another person, health, social position, or job. The period of mourning is characterized by sadness, diminished sense of well-being (somatic complaints), sleeplessness, and sadness triggered by thoughts of the loss. Normal grief, however, does not include guilt, loss of self-esteem, feelings of worthlessness, suicidal intent, psychomotor retardation, or occupational dysfunction. The duration of normal grief and bereavement differs among cultures and among individuals within cultures, but severe symptoms normally resolve within 6 to 12 months.

Adjustment Disorders

Adjustment disorders are behavioral or emotional disorders that occur in response to an identifiable stress or stressors, with marked distress that is out of proportion to the severity of the stressor. The emotional component can involve sadness, low self-esteem, suicidal behavior, hopelessness, helplessness, or other self-threatening behavior. Acute adjustment disorder occurs within 3 months of the stressor and does not last longer than 6 months.[1] The stressors are typically not as severe as those precipitating bereavement reaction, and the responses are often more maladaptive.

Borderline Personality Disorder

Borderline personality disorder is characterized by unstable personal relationships, unstable self-image, and self-destructive behaviors. The disorder may include chronic feelings of emptiness, which may be misdiagnosed as depression, or reactivity of mood, which may be mistaken for mania or hypomania. These patients typically live lives of crisis and constant conflict.

Dementia

Dementia can be confused with depression but is characterized by abnormal mental status, including abnormalities in tests of memory, calculation, and judgment.

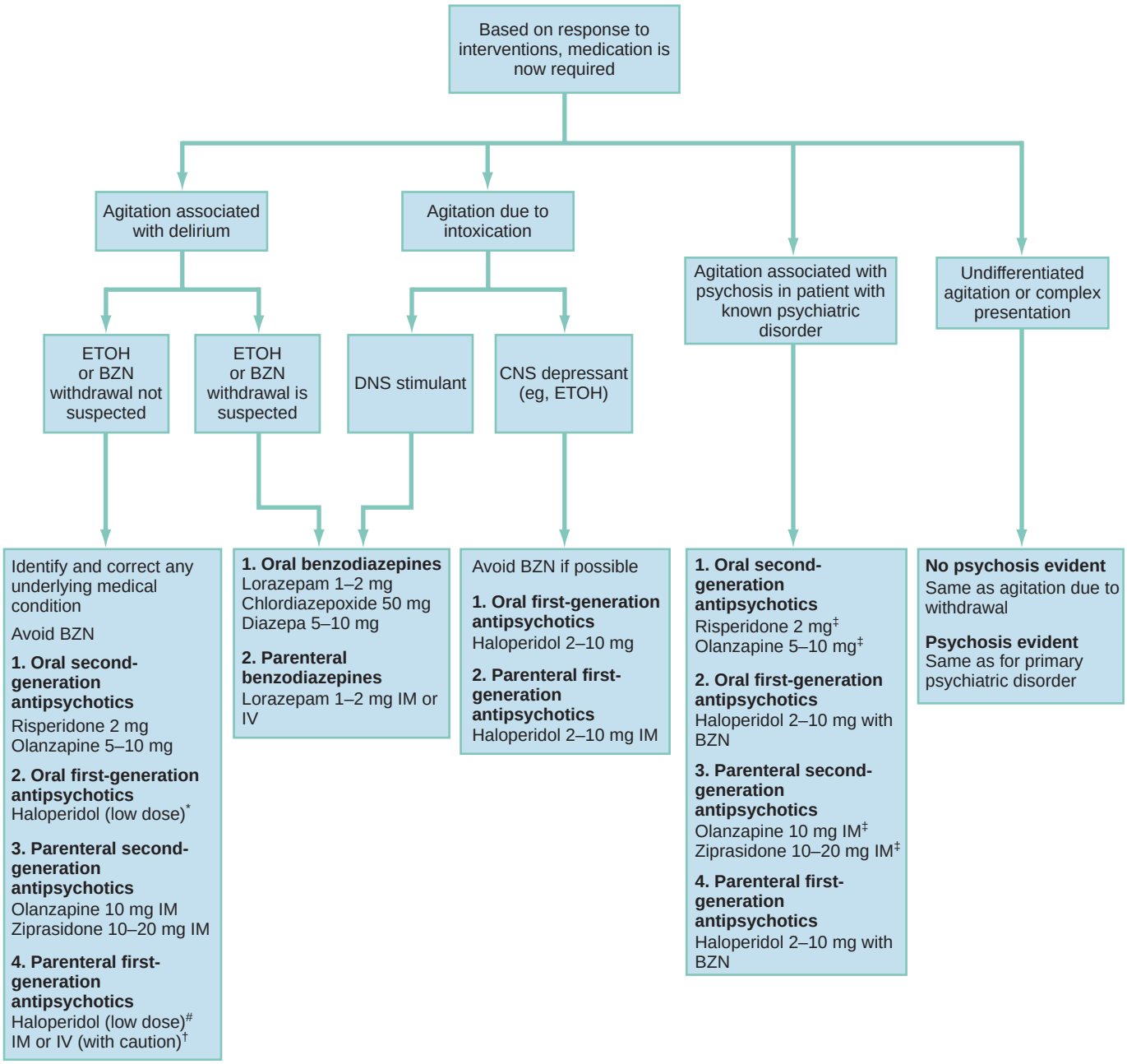

Fig. 101.1. Protocol for treatment of agitation. *BZN,* Benzodiazepine; *CNS,* central nervous system; *ETOH,* ethyl alcohol; *IM,* intramuscular; *IV,* intravenous. *There is strong evidence that doses above 3 mg (per day) in patients with dellrium are associated with significant risk of extrapyramidal side effects (EPS), so patients receiving more than 3 mg/day should be assessed carefully for EPS. †See U.S. Food and Drug Administration (FDA) guidelines. ‡If an antipsychotic alone does not work sufficiently, add lorazepam 1 to 2 mg (oral or parenteral). (Redrawn from Wilson MP, Pepper D, Currier GW, et al: The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. WJEM 13[1]:26-34, 2012.)

DIAGNOSTIC TESTING

History and physical examination should focus on determining if the patient has a mood disorder or the possibility that drug abuse, medications, or a general medical condition may be responsible for the patient's condition instead. It is essential to identify medical conditions that may exacerbate a psychiatric presentation. The psychiatric history should ask about current symptoms, precipitating events (eg, job loss or relationship), past psychiatric and substance history, history of self-harm or suicide attempts, and identification of support systems. Even if not suggested by the patient, careful questioning of suicidal thoughts is necessary. If possible, history should be confirmed by speaking with the patient's regular health care providers and interviewing family, friends, or eyewitnesses to the events that precipitated the ED visit. A tentative diagnosis can be established by use of DSM-5 criteria. Laboratory tests to investigate medical conditions may be necessary based on the specifics of the clinical presentation, but no tests can confirm or exclude mood disorders. Patients with new symptoms compatible with mood disorders need a more extensive medical and psychiatric investigation than those with a known disorder.

MANAGEMENT

Patients presenting with mood disorder symptomology are frequently in crisis, often overwhelmed, and frankly scared. The ED is a chaotic, stimulating environment that may cause or exacerbate the patients' level of agitation. Creation of a safe and stable environment for the patient is a high priority. The patient with an acute manic episode may be disruptive, refuse medical evaluation, and make repeated attempts to leave the ED. The initial step in treating such a disruptive patient is to offer assistance in reducing the agitation. A recent consensus guideline produced by the American Association for Emergency Psychiatry, noted keys to de-escalation.[6] One key is offering anxiolytic medication early in the patient's presentation. If de-escalation techniques and medication do not resolve the agitation, the patient may need to be placed in seclusion or restraints for his or her safety and that of others. This is a last resort after other de-escalation measures have failed. Chapter 189 discusses the use of seclusion and restraints in the ED. If a medical cause for agitation is found, treatment is aimed at the underlying cause (eg, oxygen for hypoxic delirium). Often in the ED, treatment may need to begin prior to the cause of the agitation being fully recognized.[7] Figure 101.1 shows a simple algorithm for approaching the agitated patient.

Treatment of depression in the ED is more controversial. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the main treatments for depression. For the patient who is awaiting inpatient psychiatric placement, these medications could be started in consultation with the admitting service. If the patient has a mild to moderate depression, not requiring hospitalization, they may be started on an SSRI as long as they have close follow-up arranged. SSRIs are known to have a myriad of side effects that can lead to premature discontinuation.[8] For the patients who are already on psychotropic medications but have discontinued them for some reason, it is reasonable to restart these medications in the ED.

A non-agitated manic patient may be able to inform the treatment team about what has worked well in the past. There are two medication choices for acute mania: antipsychotics and mood stabilizers. All of the atypical, or second generation, antipsychotics have been approved to treat acute mania as monotherapy or as an adjunctive therapy, except paliperidone and iloperidone. Lithium, valproic acid/divalproate, and carbamazepine are the most well studied mood stabilizers. Lithium and carbamazepine need to be titrated, but valproic acid can be loaded in the ED at 20 to 30 mg/kg a day (divided dose) in a healthy person with normal liver function.

The atypical antipsychotic medicines including ziprasidone, risperidone, olanzapine, aripiprazole, and quetiapine, cause fewer side effects (such as, acute dystonia) than conventional antipsychotic agents. Oral doses should be offered first, and several agents, including risperidone, olanzapine, and aripiprazole, are available in rapidly dissolving tablet form. Three are available as an intramuscular injection: ziprasidone (Geodon), olanzapine (Zyprexa), and aripiprazole (Abilify). Ziprasidone 10 mg to 20 mg is effective; however, its use is limited to 40 mg per 24 hours. Olanzapine 2.5 mg to 10 mg is effective but is associated with postural hypotension, and it is not recommended in combination with parenteral benzodiazepines because of the risk of cardiopulmonary depression. Aripiprazole is the newest agent and at doses of 9.75 mg to 15 mg seems to be the least sedating of the atypicals, but it is more likely to cause nausea and vomiting. It is valuable to obtain psychiatric consultation during the initiation of agitation treatment, because these patients will generally require significant ED treatment or psychiatric hospitalization.

DISPOSITION

To determine the appropriate disposition for patients presenting with a mood disorder, a suicide risk assessment is required. The Substance Abuse and Mental Health Services Administration developed a practical tool referred to as the Suicide Assessment Five-Step Evaluation and Triage (SAFE-T).[9] Current suicidal thoughts, risk factors and protective factors should be identified, as well as past suicidal thoughts, plans, or acts. Chapter 105 provides an in-depth discussion of suicide assessment. It is only after considering this information that an appropriate intervention can be determined. With the help of social workers or a mental health worker, many patients can be safely discharged home with close follow-up. Patients receiving initial treatment in the ED, without a proper handoff to outpatient care, are at an increased risk for return. If available, it is preferred that a social worker or mental health worker connect discharged patients with outside agencies and services, rather than providing patients with a referral list.

KEY CONCEPTS

- Patients with apparent mood disorders should be evaluated for medical disorders, medication effects, or substance abuse or withdrawal because these conditions can mimic both depression and mania.
- Mood disorders should be suspected in patients with multiple, vague, nonspecific complaints and in patients who are frequent, heavy users of medical care.
- The differentiation of depression and dementia in elders can be difficult but is important because depression often responds dramatically to treatment.
- Patients with mood disorders should be assessed for their suicide potential.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 101: QUESTIONS & ANSWERS

101.1. What is the lifetime suicide risk for people with major untreated depression?

A. 5%
B. 10%
C. 15%
D. 20%
E. 25%

Answer: C. Patients with major depression have a high lifetime suicide risk, and although episodes of acute decompensation with even higher risk can be identified and treated, a certain number of patients succeed in committing suicide.

101.2. Which of the following imbalances of central nervous system neurotransmitters is seen in patients with clinical depression?

A. Decreased hypothalamic-pituitary-adrenal (HPA) activity
B. Depressed serotonin levels
C. Elevated gamma-aminobutyric acid (GABA) levels
D. Elevated norepinephrine levels
E. Unchanged dopamine levels

Answer: B. The central biochemical features toward which pharmacologic management is directed are depressed levels of norepinephrine and serotonin. Data are also emerging that suggest decreased dopamine levels. The HPA axis may also be altered with elevated cortisol levels.

101.3. Which of the following statements regarding depression in children and elders is *true?*

A. Children with depression rarely present with somatic complaints.
B. Depression in children may be manifested as attention deficit disorder (ADD).
C. Depression presents differently from dementia in elders.
D. Diagnostic criteria for depression in children are different.
E. Serious depression in elders is generally refractory to treatment.

Answer: B. Depression in children and adolescents can be manifested as ADD. Somatic complaints are a common feature of children and adolescents presenting with depression, but the diagnostic criteria are not different. Geriatric depression may be manifested in a manner similar to dementia (pseudodementia), but unlike dementia, the depression is highly treatable and reversible once it is recognized.

101.4. A 31-year-old attorney is brought to the emergency department (ED) by his family for a chief complaint of agitation and a behavioral change. He has no past medical history and takes no medications. The family reports decreased sleep, increased talkativeness, marked increased time and involvement at work, and an uncharacteristic buying spree. Your examination is remarkable for distractibility, gregarious and pressured speech, flight of ideas, and mild psychomotor agitation. Laboratory examination and urine drug screen results are negative. The patient is adamant that he has important things to do and needs to leave. Which of the following statements is most true?

A. Antipsychotic agents are not effective.
B. Hallucinations would be atypical.
C. If treated, intravenous valproic acid is indicated.
D. Initiating treatment in the ED is not indicated.
E. Multiple antibiotics can cause this clinical picture.

Answer: E. This patient has a fairly classic presentation for acute mania with pressured speech, distractibility, grandiosity, increased involvement (in this case with work), and decreased need for sleep. Multiple drugs may precipitate this, including acyclovir, isoniazid, sulfonamides, the floxins, and chloroquine. An acute manic episode may be manifested with hallucinations and mimic an acute psychosis. ED treatment is usually indicated for this disorder. Acute stabilization is generally effective with major tranquilizers, such as haloperidol.

CHAPTER 102

Anxiety Disorders*

Leslie S. Zun | Kimberly Nordstrom

PRINCIPLES

Background

Anxiety is a specific unpleasurable state of tension that forewarns the presence of danger, real or imagined, known or unrecognized, and is often verbalized as an intense feeling of worry. Up to a point, anxiety can improve performance; however, extreme responses can lead to deterioration of performance. As the level of dysfunction increases, the patient is much more likely to have a true anxiety disorder.

Acute anxiety is common in emergency department (ED) patients who have primary anxiety disorders, concomitant anxiety disorders, and crisis situations. It is helpful to differentiate the origin of anxiety to offer appropriate treatment. As an example, many medical conditions mimic anxiety disorders, and up to 42% of patients initially thought to have anxiety disorders are later found to have organic disease.

Emergency clinicians should be able to distinguish between anxiety disorders and medical illness (Box 102.1) and, if necessary, treat both entities. Because anxiety states cause an increase in metabolic demands, they can cause a marginally compensated organ system to fail. In a recent study, 48% of patients presenting for pain complaints were found to have moderate to severe anxiety and only 1% received anxiety treatment.[1]

Epidemiology

Approximately 40 million Americans older than 18 years old, nearly 20% of adults, are affected by anxiety disorders each year. Many primary care patients have significant mood and anxiety symptoms, such as panic disorders, generalized anxiety disorders (GADs), and depression, but nearly half of these symptomatic patients never receive appropriate treatment. Patients with chronic illness and those who make frequent medical visits have higher rates of anxiety and depression. The prevalence of anxiety disorders surpasses that of any other mental health disorder, including substance abuse. There is a close relationship between alcohol abuse and anxiety disorders.

The incidence of specific anxiety disorders varies: specific phobia is 7% to 9%, social anxiety is 7%, panic disorder is 3%, and GAD is 3%.[2] The lifetime risk for post-traumatic stress disorder (PTSD) is about 9%, but the 12-month prevalence is approximately 4%. Substance or medication-induced anxiety and anxiety due to a medical condition have an unknown prevalence but may be relatively high in those seeking emergency medical care.

A different form of anxiety, related to fear of suffering from an illness, now known as *illness anxiety disorder* (formerly hypochondriasis), may be as high as 8% in ambulatory medical populations.[2] Patients may present with a physical complaint and try to disguise their anxiety rather than bear the perceived stigma associated with psychiatric complaints, and they are distinct from patients who have a somatoform disorder.

Pathophysiology

There are many forms of anxiety disorders, and the precise mechanisms underlying the development of anxiety have not been fully established. The serotonin system and the noradrenergic systems are common pathways implicated in anxiety. It is believed that low serotonin system activity and elevated noradrenergic system activity are involved, and thus selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are frequently used as treatment. There is also considerable comorbidity with depressive disorders, with evidence showing genetic and neurobiologic similarities, especially related to serotonin.

The well-established effectiveness of benzodiazepines in the treatment of anxiety has led to the study of the gamma-aminobutyric acid (GABA) system and its relationship to anxiety. GABA is the principal inhibitory neurotransmitter in the central nervous system, and benzodiazepines act on the $GABA_A$ receptors. Studies have focused on the role that corticosteroids may play in fear and anxiety. Steroids are thought to induce chemical changes in select neurons that strengthen or weaken certain neural pathways to affect behavior under stress.[3]

Family research suggests that genetic factors play a role in anxiety, but the precise nature of the inherited vulnerability is unknown. Five major anxiety disorders, panic disorder, GAD, phobias, obsessive-compulsive disorder (OCD), and PTSD, share genetic and environmental risk factors. Psychological and environmental factors also contribute in the generation of anxiety in biologically predisposed individuals.

CLINICAL FEATURES

Many patients seeking care in the ED experience anxiety related to encountering internal and external dangers, such as assaults on body integrity in the form of uncomfortable procedures and forced intimacy with strangers. In addition, the patient may experience uncertainty about his or her illness and the potential implications of the illness.

Anxiety may be a manifestation of a physical disorder or an expression of an underlying psychiatric disorder. It may be difficult to make the distinction between anxiety as a symptom and anxiety as a syndrome in the ED. The physical symptoms of autonomic arousal (eg, tachypnea, tachycardia, diaphoresis, lightheadedness) may be the only manifestations of anxiety. Classic panic disorder symptoms of chest pain, shortness of breath, and the sense of impending doom will often lead the patient to the ED, especially if it is the very first episode.[3] Anxiety associated with medical disorders is more likely to be manifested by physical symptoms and less likely to be associated with avoidance behavior (see Box 102.1).

*The authors thank Rick McPheeters and Joshua L. Tobias for their contributions to this chapter in previous editions of this text.

BOX 102.1

Predictors of Anxiety Caused by an Underlying Medical Issue

Onset of anxiety symptoms after 35 years old
Lack of personal or family history of an anxiety disorder
Lack of childhood history of significant anxiety, phobias, or separation anxiety
Lack of avoidance behavior
Absence of significant life events generating or exacerbating the anxiety symptoms
Poor response to anti-anxiety agents

BOX 102.2

Characteristics of a Panic Attack

Abrupt surge of intense fear or discomfort that reaches a peak within minutes, in which four or more of the following occur:
Palpitations
Sweating
Trembling
Shortness of breath or feeling of being smothered
Feeling of choking
Chest pain or discomfort
Nausea or abdominal distress
Feeling dizzy or light-headed
Chills or heat sensations
Paresthesias
Derealization or depersonalization
Fear of losing control or going "crazy"
Fear of dying

Adapted from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5, Arlington, VA, 2013, American Psychiatric Association.

Clinical manifestations of specific anxiety disorders are considerably different, warranting a review of each of the major types.

Panic Disorder

Panic disorder is a diagnosis of exclusion, even in patients with known psychiatric illness, because several mental illnesses cause panic attacks as a secondary manifestation. For a diagnosis of panic disorder, one must experience recurrent, unexpected panic attacks (Box 102.2), as well as either persistent concern of future attacks or a maladaptive behavioral change related to the attacks. As with other disorders, the disturbance should not be better explained by substance use, another medical condition, or another psychiatric illness.[2] A panic attack, differentiated for the disorder, is an abrupt fear or discomfort that reaches a peak within minutes and has associated physical and cognitive symptoms.[2] It may occur with any anxiety disorder or as part of another mental or physical disorder. A panic attack is not a diagnosis but rather an indication of an underlying disorder. The presence of panic attacks often influences the treatment and outcome of the primary illness. An attack can be replicated by intentional hyperventilation. Intentional hyperventilation can be distinguished from medical hyperventilation by its irregularity and interruptions. When there is doubt, formal psychiatric evaluation is indicated, particularly before a potentially dangerous or addictive drug therapy is prescribed.

BOX 102.3

Characteristics of Post-Traumatic Stress Disorder*

Exposure to actual or threatened death, serious injury, or sexual violence.
Presence of intrusion symptoms associated with the traumatic event.
Persistent avoidance of stimuli associated with the traumatic event.
Negative alterations in cognition and mood associated with the traumatic event.
Marked alterations in arousal and reactivity associated with the event.
Duration is greater than 1 month.
Disturbance causes clinically significant distress or impairment.
Disturbance is not attributable to the physiological effects of a substance or another medical condition.

*Specifiers include "with dissociative symptoms" and "with delayed expression."
From American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5, Arlington, VA, 2013, American Psychiatric Association.

Generalized Anxiety Disorder

GAD is defined as excessive worry that occurs most days over a 6-month period involving several events or activities.[2] The anxiety must cause significant distress or impairment in functioning. GAD has been linked to overuse of medical services and often is not recognized, which leads to ineffective treatment.

Post-Traumatic Stress Disorder

PTSD is caused by experiencing or witnessing a highly traumatic event. Those with PTSD manifest symptoms of re-experiencing the event, avoidance of triggers, changes in cognition and mood, and changes in arousal and reactivity (Box 102.3). Rates of PTSD are higher among military veterans and those whose occupation involves risk of traumatic exposure.[2] ED staff are also at risk for experiencing PTSD related to unusual traumatic events and unexpected deaths and, unfortunately, the support for this tends to be minimal.[4]

Specific Phobias

A phobia is an irrational fear that results in avoidance. Phobia becomes a disorder when it interferes with day-to-day function in an individual's life. A social phobia, now termed *social anxiety disorder,* is characterized by clinically significant anxiety about one or more social situations in which the individual may be scrutinized.[2] This fear often leads to avoidance behavior for such activities, such as public speaking, performing, visiting, using public showers or restrooms, or eating in public places.

Obsessive-Compulsive Disorder

OCD is characterized by recurrent, obtrusive, unwanted thoughts (obsessions), such as fears of contamination, or compulsive behaviors or mental acts (compulsions) that a person feels compelled to perform, such as handwashing or counting. OCD is considered an anxiety disorder because (1) anxiety or tension is often associated with obsessions and resistance to compulsions, (2) anxiety or tension is often immediately relieved by yielding to compulsions, and (3) OCD often occurs in association with other anxiety disorders.[2] In summary, the obsessions and intrusive thoughts increase anxiety, and the compulsions and repetitive behaviors decrease anxiety but with significant disruption of one's life.

Somatic Symptoms and Related Disorders

Although not necessarily considered anxiety disorders, this group of disorders has an undefined, but established link to anxiety and depressive disorders. This group includes somatic symptom disorder, illness anxiety disorder (formerly hypochondriasis), conversion disorder (formerly functional neurological symptom disorder), and psychological factors affecting other medical conditions. With somatic disorders, the patient will complain about one or more physical symptoms, which cause impairment notwithstanding a negative evaluation. These symptoms are not intentionally feigned, as in the case of malingering or factitious disorder. A high utilization of medical services is correlated with these disorders, independent of comorbidity. Patients with panic disorder, however, seek at least as much psychiatric attention as do those with somatoform disorders.

DIFFERENTIAL DIAGNOSIS

In patients who present with predominant symptoms of anxiety, even when the patients have known anxiety disorders, before considering which of the previously discussed *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) anxiety-related diagnoses the patient might have, the emergency clinician should first consider the possibility of medical and pharmologic-related conditions associated with anxiety.

Patients with anxiety disorders may present with apparent physical disease, and many physical diseases are strongly associated with symptoms of anxiety. Several factors help distinguish an anxiety syndrome caused by an underlying medical issue from a primary anxiety disorder (see Box 102.1). Anxiety disorder classifications in the DSM-5 include anxiety caused by another medical condition.[2]

Because anxiety may be the most obvious symptom of an underlying disease or condition, the patient should be evaluated for exacerbation of known preexisting disease, as well as for the onset of new illness, because anxiety increases the risk of acute medical exacerbation of chronic illness.

The classic scenarios of pulmonary embolism and hyperthyroidism causing anxiety are well documented. Post–myocardial infarction patients with anxiety have poorer outcomes than those without documented anxiety. Patients with respiratory diseases, such as asthma and chronic obstructive pulmonary disease, often have anxiety associated with long-standing illnesses. In addition, many of the medications used to treat these illnesses may induce anxiety. One of the most common medical causes of anxiety is alcohol and drug use from either intoxication or, more typically, withdrawal states.

Cardiac Diseases

Approximately 25% of patients with chest pain who present to the ED have panic disorder. Their disorder often goes undiagnosed, resulting in multiple visits and expensive cardiac evaluations. Symptoms of myocardial infarction and angina pectoris may include crushing chest pain, shortness of breath, nausea, palpitations, heavy perspiration, and a feeling of impending death. These are also the primary symptoms of acute anxiety, but the pain is usually described as atypical, and patients are generally female and younger. Because of the morbidity and mortality of cardiovascular disease, a patient warrants a full cardiac evaluation when the differentiation between myocardial infarction and acute anxiety is unclear.

Cardiac dysrhythmias can cause palpitations, discomfort, dizziness, respiratory distress, and syncope. A panic attack has similar symptoms. Fortunately, most dysrhythmias can be documented and characterized on cardiac monitors or by electrocardiography. Mitral valve prolapse syndrome can be associated with palpitations and panic attacks indistinguishable from a panic disorder. Benzodiazepines can be used to provide symptomatic relief to patients who experience chest pain due to anxiety.

Endocrine Diseases

The most common endocrinologic conditions associated with anxiety states are hypoparathyroidism, hyperthyroidism and hypothyroidism, hypoglycemia, pheochromocytoma, and hyperadrenocorticism. Anxiety is the predominant symptom in 20% of patients with hypoparathyroidism. Studies indicate a higher incidence of anxiety in the subset of patients with surgically removed parathyroid glands. Even though other symptoms may improve with supplementation, patients have been found to have significant depression, anxiety, somatization and phobic anxiety, even after being given calcium and vitamin D.

Anxiety symptoms are seen in up to 40% of diabetics, and 14% of diabetic patients suffer from anxiety disorders. There is evidence that diabetics who are treated with antianxiety medication not only reduce their anxiety but also decrease their glycosylated hemoglobin levels and high-density lipoprotein concentration. One study found that diabetics with mental health problems were less likely to improve glycemic control and suggested that psychological evaluation and therapy be used adjunctively.[5]

Pheochromocytomas are rare tumors that produce elevated levels of catecholamine in the body. Pheochromocytoma attacks may manifest similar to panic attacks and can be precipitated by emotional stress. Elevated urinary catecholamine or plasma metanephrine levels confirm a pheochromocytoma.

Hyperthyroidism is one of the most frequently encountered endocrine diseases associated with anxiety. As with panic disorders, hyperthyroidism is associated with acute episodic anxiety. Thyrotoxicosis causes anxiety, palpitations, perspiration, hot skin, rapid pulse, active reflexes, diarrhea, weight loss, heat intolerance, proptosis, and lid lag. A substantial portion of patients continue to have psychiatric manifestations even after treatment.

Psychiatric presentations can be the first sign of hypothyroidism, occurring as the initial symptom in 2% to 12% of reported cases along with deficits of impaired recent memory and learning. The severity of anxiety disorders in hypothyroid states is related to the rapidity of thyroid hormone level changes and not to the absolute hormone levels. In general, checking serum thyroid-stimulating hormone and free thyroxine levels will suffice in the ED to establish the diagnosis of thyroid disease.

Respiratory Diseases

Most conditions causing airway compromise or impairment of gas exchange do not mimic psychiatric disorders. However, some conditions that cause hypoxemia or hypercarbia may lead to the development of significant anxiety. Up to a third of the patients with chronic obstructive pulmonary disease meet the criteria for anxiety disorder.

Patients who have severe asthma are twice as likely to have an anxiety disorder and almost five times as likely to have a phobia compared with nonasthmatics. Acute dyspnea from a pure panic attack with good air movement and normal lung sounds is easily differentiated from an asthma attack, but studies consistently show that anxiety disorders increase asthma morbidity and mortality.

Acute shortness of breath in any patient should not be immediately attributed to anxiety, especially because pulmonary embolism can present with only shortness of breath as the major symptom. Fortunately, pulmonary embolism can almost always

be distinguished by history and physical examination, assessment of risk factors for thromboembolic disease, and laboratory testing (eg, pulse oximetry, electrocardiography, chest radiography, and D-dimer assay) as indicated.

Neurologic Disorders

Many neurologic conditions are associated with anxiety symptoms. For example, stress is one of the most common reported causes of seizures. Those who report stress as a trigger tend to have higher scores on anxiety tests, and the stress may be either acute or chronic.[6] Temporal lobe seizures, complex partial seizures, tumors, arteriovenous malformation, and ischemia or infarction have all been reported with panic attacks. Anxiety disorders also occur in the aftermath of traumatic brain injury (TBI). Approximately 23% of those who sustain a mild TBI are at risk for developing an anxiety disorder; this is frequently found in military personnel. In Huntington's disease, anxiety is the most common prodromal symptom. Anxiety occurs in up to 40% of patients with Parkinson's disease and up to 37% of patients with multiple sclerosis. Similarly, anxiety symptoms are common in moderate Alzheimer's disease.

Drug Intoxication and Withdrawal States

Amphetamines, cocaine, and other sympathomimetic drugs are abused for their stimulant and mind-altering properties. Patients often present agitated, anxious, or when these drugs are taken in large doses and with prolonged use. Caffeine is a very commonly used stimulant, and studies suggest that 240 mg to 300 mg of caffeine per day should be the upper limit of healthy consumption. When consuming higher doses, considered caffeine intoxication, restlessness, nervousness, excitement, insomnia, diuresis, gastrointestinal disturbance, tachycardia, psychomotor agitation, as well as other unpleasant symptoms may occur.[2] The acute symptoms of caffeine intoxication and GAD are almost identical.

Marijuana users believe that the drug reduces their anxiety, but some experience a depersonalization that provokes severe anxiety, fearfulness, and symptoms of agoraphobia. Cannabis intoxication is associated with behavioral or psychological changes, such as anxiety, and physical signs, such as conjunctival injection, dry mouth, and tachycardia.[5] Lysergic acid diethylamide (LSD), phencyclidine (PCP), and ecstasy (3,4-methylenedioxy-methamphetamine [MDMA]) are hallucinogens that can produce anxiety and paranoia from chronic use or "bad trips." Flashbacks affect some users of LSD; the person may experience the symptoms of anxiety and paranoia weeks or months after use.[7]

Sedative, hypnotic or anxiolytic drugs (eg, benzodiazepines, barbiturates) are taken to relieve anxiety or sleeplessness, but their discontinuation can cause sedative withdrawal and rebound anxiety.[2] The severity of the withdrawal syndrome depends on the drug, dosage, duration of use, and speed of elimination. Symptoms include hyperalertness, motor tension, muscle aches, agitation, anxiety, insomnia, tremulousness, nausea, vomiting, convulsions, delirium, and even death.[2]

Although antidepressants are rarely abused, their abrupt cessation can cause a discontinuation syndrome, which may present as sensory and gastrointestinal-related symptoms, insomnia, lethargy, and extreme anxiety.[8]

Alcohol withdrawal can appear 6 to 12 hours after the last drink or significant reduction in consumption. Patients often have a detectable serum alcohol level at this time. Anxiety is one of the first and most prominent symptoms and is seen within 24 to 48 hours of the withdrawal state.[9] Symptoms of anxiety, insomnia, and autonomic dysfunction can last up to 3 to 6 months following alcohol withdrawal.[2]

DIAGNOSTIC TESTING

The initial history and physical examination should focus on the presenting complaints to determine if the patient has an anxiety disorder or anxiety caused by drug abuse, medication use, or a general medical condition. The psychiatric history should, at minimum, include current symptoms, precipitating events (eg, job loss or relationship), past psychiatric and substance history, history of self-harm or suicide attempts, and identification of support systems. A thorough risk assessment for suicidality is key. Among ED patients, panic attacks have been found to be closely associated with suicidal ideation (43%) and intent (55%). Chapter 105 discusses suicide risk assessment.

A physical examination focused on the area of complaint is necessary, even when there is no overt evidence of physical disease. Abnormal vital signs suggest an organic medical cause of the anxiety symptoms. Laboratory tests may be necessary based on the clinical presentation, but no tests can confirm or exclude anxiety disorders. Patients with new symptoms require a more extensive medical and psychiatric investigation than those with a known disorder.

MANAGEMENT

The patient should be placed in a quiet area for evaluation. Some patients calm when they are removed from a chaotic ED environment. If that is not possible, reducing environmental stimulants, such as turning down the lights, can be helpful. If the emergency clinician encounters difficulty in calming the patient, supportive family members may help.

Pharmacologic Treatment

Use of oral, intravenous, or intramuscular medication may be necessary when an anxiety state is so out of control that there is a significant threat to safety of self or others. Medication may also be appropriate for the anxious patient experiencing a significant medical illness or undergoing a medical procedure. Lorazepam in small increments can be helpful in alleviating the anxiety associated with substance withdrawal states. Midazolam reduces anxiety and increases amnesia for ED procedures.

SSRIs and SNRIs have become first-line treatment of most anxiety disorders because of their broad spectrum of efficacy and high tolerability by most patients. They have a lower potential for dependence and are safer than older classes of antidepressants and anxiolytics. Improvement is usually seen in 4 to 6 weeks, but doses may have to be adjusted. Initiation of longer term medication is usually done by primary care physicians or psychiatrists. It is important to start the patient with low doses of SSRIs (usually half the normal starting doses used for depression) and to arrange for frequent short-term follow-up visits, because an initial increase in anxiety may be seen. We do not recommend that these medications be started in the ED unless accompanied by patient education and close follow-up with a primary care physician or psychiatrist.

Benzodiazepines can be prescribed for motivated patients with acute exogenous anxiety for time-limited stress. Benzodiazepines are an attractive alternative to the delayed response of an SSRI when an immediate reduction of symptoms is desired or a short-term treatment is needed. Benzodiazepines have a role in emergency medical treatment, but their use is questionable for long-term treatment. In most circumstances, benzodiazepines should be prescribed for a week or less. Patients who do not improve within a week are unlikely to benefit from the drug. Prescribers will commonly use a benzodiazepine for the first week while initiating SSRI or SNRI treatment. Patients with a history of alcoholism or drug abuse, who are excessively and emotionally

dependent, or who become anxious in response to normal stress are at greater risk of drug dependency and are not good candidates for this treatment.

Monoamine oxidase inhibitors and tricyclic antidepressants have been effective in treating anxiety but have been largely supplanted by SSRIs. Buspirone, a nonbenzodiazepine, has significant lag time and questionable efficacy, especially after the use of benzodiazepines.

Patients with apparent or known anxiety disorders should be referred to a primary care physician or a psychiatrist for a thorough evaluation of the type of anxiety and to create a long-term treatment plan.

Nonpharmacologic Therapy

Supportive therapy can be used to calm patients and give them room to problem-solve. Emergency clinicians and staff can also use psychoeducation to normalize what is happening and to teach simple skills, such as breathing techniques. It is also particularly useful to educate the patient on the role that stimulants (eg, caffeine) and depressants (eg, alcohol) play in promoting anxiety.

There are multiple longer-term therapies that can be helpful for anxiety but are not used in the acute care setting. Psychotherapy may be helpful for individuals whose psychological makeup, coping style, interpersonal dynamics, and situational stressors contribute to their pathologic anxiety. The use of supportive, insight-oriented family therapy is helpful when these factors appear prominently in the patient's presentation. Cognitive-behavioral therapy helps the patient correct the cognitive misperceptions and overreactions that occur. Cognitive-behavioral therapy is very effective but requires commitment from the patient. Meditation, biofeedback, and suggestive hypnosis may also have a role in long-term treatment.

DISPOSITION

Patients receiving initial treatment in the ED, without a proper handoff to outpatient care, are at an increased risk for return. If available, it is preferred that a social worker or mental health worker connect discharged patients with outside agencies and services, rather than providing patients with a referral list.

Most patients with an anxiety disorder can be safely discharged with close primary care physician or psychiatrist follow-up. Patients with an anxiety disorder associated with suicidal or homicidal ideation or with severe depression require urgent psychiatric attention and admission to the hospital.

KEY CONCEPTS

- Patients who present with predominant symptoms of anxiety may be suffering from medical disorders, medication effects, or substance abuse or withdrawal.
- Anxiety may accompany the onset of serious medical disease, cause significant metabolic demands, and stress a marginally compensated organ system.
- Anxiety caused by physical illness is usually suggested by the patient's physical findings but may require testing to further delineate the cause.
- Oral, intravenous, or intramuscular medication may be necessary for patients who are a significant threat to themselves or others and for anxious patients with significant medical illness.
- Limited benzodiazepine therapy may be helpful for select patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 102: QUESTIONS & ANSWERS

102.1. Which of the following is the most common mental health disorder?
- **A.** Anxiety
- **B.** Bipolar
- **C.** Depression
- **D.** Schizophrenia
- **E.** Substance abuse

Answer: A. Many of these patients never receive appropriate care, in part because they choose to present with a physical complaint and disguise their anxiety. Patients with chronic illnesses have higher rates of anxiety and depression than the rest of the population.

102.2. What is the most common cause of organic anxiety, anxiety that results from a physiologic origin?
- **A.** Adrenal disorders
- **B.** Alcohol and drug use
- **C.** Cardiac disease
- **D.** Hyperthyroidism
- **E.** Pulmonary embolus

Answer: B. This may be from intoxication or withdrawal states.

102.3. A 52-year-old woman presents with 2 months of recurrent episodes of anxiety, mild chest pain, subjective palpitations, hand paresthesias, and occasional muscle spasms. They have occurred weekly in the past but are now increasing in frequency. Her only past history is a thyroidectomy 4 months prior. She is taking levothyroxine (Synthroid) and had normal thyroid levels 2 weeks ago. Her vital signs, physical examination, and electrocardiogram are normal. Laboratory evaluation shows sodium 141 mEq/L, potassium 4.1 mEq/L, creatinine 1.0 mg/dL, bicarbonate 26 mEq/L, chloride 100 mEq/L, and calcium 7.1 mg/dL; a complete blood count is normal. Which of the following should be the next step in her management?
- **A.** Outpatient clonazepam
- **B.** Parathyroid hormone level
- **C.** Psychiatry consultation
- **D.** Thyroid hormone levels
- **E.** Urine drug screen

Answer: B. Anxiety is the predominant symptom in 20% of patients with hypoparathyroidism. Other symptoms include paresthesia, muscle cramps, and spasms. Most cases are idiopathic or due to inadvertent parathyroid gland harvest during thyroidectomy. The diagnosis is suggested by a low serum calcium and an elevated phosphate and is confirmed by a depressed parathyroid level.

102.4. Which of the following statements regarding anxiety and endocrine disorders is *true*?
- **A.** Anxiety can often be traced to reactive hypoglycemia.
- **B.** Anxiety is not a manifestation of hypothyroidism.
- **C.** Diabetics treated with antianxiety agents have improved hemoglobin A1c levels.
- **D.** Less than 5% of diabetics experience anxiety.
- **E.** Patterns of diaphoresis in pheochromocytoma mimic those of a panic attack.

Answer: C. Approximately 15% of diabetics have an anxiety disorder. Treatment improves hemoglobin A1c levels. Anxiety due to reactive hypoglycemia is rare despite the common perception among patients. Pheochromocytoma causes whole body diaphoresis, whereas panic disorders primarily cause sweaty palms. Hyperthyroidism or hypothyroidism can cause significant anxiety manifestations. It is more related to the rate of change than the level of thyroid hormones.

102.5. A 23-year-old woman with a history of asthma presents with increasingly frequent episodes of panic attacks. Her medications are an inhaled beta-agonist and an intermittent steroid inhaler. She reports subjective increasing asthma severity as her panic episodes have worsened. When counseling the patient, which of the following statements is most correct?
- **A.** An anxiety disorder in an asthmatic patient does not increase morbidity.
- **B.** Anxiety does not precipitate asthma attacks.
- **C.** Anxiety does not worsen airflow.
- **D.** Asthmatics are more likely to have an anxiety disorder.
- **E.** It is difficult to differentiate dyspnea related to asthma from anxiety.

Answer: D. Anxiety can precipitate and prolong an asthma attack. Morbidity and mortality are increased in asthmatic patients who have a coexisting anxiety disorder. Patients who have asthma are twice as likely to have an anxiety disorder and five times as likely to have a phobia. Acute dyspnea from "panic" dyspnea can be differentiated from asthma by clear lungs on auscultation.

102.6. Which of the following syndromes is not associated with anxiety?
- **A.** Left hemispheric strokes
- **B.** Multiple sclerosis
- **C.** Right hemispheric strokes
- **D.** Transient ischemia attack
- **E.** All of the above can be associated with anxiety.

Answer: E. Anxiety may be a component of seizures, tumors, arteriovenous malformations, and ischemic events. It may be the only manifestation of some disorders (eg, right hemispheric strokes and transient ischemic attacks [TIAs]). The coexistence of anxiety plays an important role in the prognosis and impairment of stroke patients.

102.7. A 38-year-old woman with a long history of anxiety and panic disorder presents with anhedonia, melancholy, sleep disruption, crying episodes, and some hostility feelings. She has no current anxiety symptoms. Her only medication is clonazepam. She has no known medical illness. Which of the following statements regarding this patient's symptoms is *true?*

A. Approximately 50% of patients with panic disorder develop major depression.
B. Depression with anxiety and hostility is usually refractory to treatment.
C. The first diagnostic step should be a thyroid panel.
D. The majority of patients with depression have panic attacks.
E. This is likely a drug-induced depression.

Answer: A. Approximately 50% of patients with a primary panic disorder will later develop major depression. Twenty percent of patients with depression have panic attacks. Depression with panic attacks is less responsive to treatment, but depression with anxiety and hostility responds well to antidepressants. Although benzodiazepines can exacerbate symptoms of depression, there is already a high spontaneous rate of depression with anxiety disorders.

102.8. Which of the following statements regarding benzodiazepine use and anxiety is *true?*

A. Benzodiazepines are first-line agents for anxiety disorders.
B. Several weeks of treatment are indicated after initial diagnosis.
C. Short-acting benzodiazepines produce a more severe abstinence syndrome.
D. They are particularly useful in patients with alcohol abuse.
E. Withdrawal rebound is less common than with selective serotonin reuptake inhibitors (SSRIs).

Answer: C. SSRIs are the first-line agents for anxiety and panic disorders, but the primary disadvantage is the several-week lag needed for maximal clinical benefit. Benzodiazepines work best for motivated, dependable patients when an immediate reduction of symptoms is indicated or a short-term treatment is necessary. Patients who do not benefit from benzodiazepines within a week are unlikely to do so. Patients with a history of alcoholism or drug abuse, who are excessively/emotionally dependent, or who become anxious from normal stress are at greater risk for dependency. Rebound withdrawal is more likely after short-acting agents.

102.9. A 29-year-old Caucasian female presents with excessive daytime somnolence. She states that she had been suffering from anxiety associated with her paralegal occupation, and 1 week ago her psychiatrist had started her on a 2-week course of once-daily benzodiazepine therapy, which she takes in the morning. Her anxiety symptoms are well controlled. She asks if you can change her to a new medication because the somnolence is significantly affecting her job performance. What would be the most appropriate course of action?

A. Counsel the patient that she should continue the medication as prescribed because she will soon adapt and the somnolence will likely subside.
B. Discontinue the benzodiazepine and refer her back to her psychiatrist.
C. Have her try dosing the benzodiazepine at bedtime, because this will likely continue to control her anxiety and limit daytime somnolence.
D. Switch the patient to a selective serotonin reuptake inhibitor (SSRI) and refer her back to her psychiatrist.
E. Switch the patient to a shorter-acting benzodiazepine.

Answer: C. Instituting an SSRI should be reserved for primary care physicians or psychiatrists who can monitor the patient more closely, because the response will be delayed. Some patients do adapt to the sedative effects of benzodiazepines but usually only after long-term use. Stopping the benzodiazepine may ultimately be necessary but at the risk of recurrent anxiety. Dosing benzodiazepines at bedtime may minimize daytime sedation and still provide an anxiolytic effect. Shorter-acting benzodiazepines produce a more severe abstinence syndrome when stopped abruptly, and thus most prescribers prefer longer-acting agents.

102.10. A 52-year-old male construction worker presents with chest pain. He states his symptoms began early this morning and have progressively worsened throughout the day. His symptoms include nervousness, tremors, chest pain, shortness of breath, and palpitations. He states that he has had anxiety for 30 years but has controlled it with the consumption of alcohol. He became unemployed 1 week ago, and his daily alcohol use has diminished significantly. His vital signs are blood pressure (BP) 185/95 mm Hg, heart rate 123 beats per minute, respiratory rate of 20 breaths per minute, and temperature of 98.9° F. His physical examination is remarkable for diaphoresis, tongue fasciculation, both resting and intention tremors, and mild psychomotor agitation while maintaining orientation with a congruent anxious mood and affect. What is the most likely etiology of this patient's symptoms?

A. Acute alcohol withdrawal syndrome
B. Exacerbation of endogenous anxiety secondary to diminished alcohol intake
C. Exacerbation of exogenous anxiety secondary to change in employment status
D. Hypertensive emergency with acute coronary syndrome
E. Reactive anxiety secondary to the onset of chest pain

Answer: A. Hypertensive emergency is unlikely given the level of this patient's BP. On the basis of the history alone, it may be difficult to differentiate organic versus functional anxiety or identify an exogenous trigger, but the abnormal vital signs and physical examination associated with a recent cessation of long-term alcohol consumption makes acute alcohol withdrawal the most likely cause. Given the significant morbidity associated with withdrawal states, this must be addressed acutely. Appropriate diagnosis and management of underlying psychiatric disease will be a secondary concern after the patient's withdrawal is managed.

CHAPTER 103

Somatoform Disorders

Adria Ottoboni Winter

PRINCIPLES

Somatic symptom disorders (SSDs), formerly known as *somatoform disorders,* are described as the borderland between psychiatry and medicine and are responsible for some of the most frustrating and the least understood patient encounters in the emergency department (ED). As such, it is important that emergency clinicians recognize and treat this disorder appropriately to avoid patient suffering, unnecessary testing, iatrogenic injuries, and inappropriate resource utilization. Patients with SSD are often labelled as "difficult" patients, yet appropriate mental health referrals are not made, while psychological and psychosocial causes for their presentation remain unaddressed.[1]

SSD patients present with multiple physical symptoms in the absence of detectable physical disease, and harbor excessive health concerns that are expressed emotionally, cognitively, and behaviorally.[2] These patients perceive a wide range of severe symptoms including pain, gastrointestinal, cardiovascular, sexual, and pseudo-neurological symptoms, which cause inappropriate and persistent worry, distress, and social dysfunction. Biological, psychological, and psychosocial factors interact as precipitating, aggravating, and maintaining factors of psychopathology. Somatization is best understood by focusing on the abnormalities in the patient's response to their somatic symptoms, rather than on the absence of a discernible medical cause for those symptoms. The patient's maladaptive response to somatic symptoms is the reason this behavior is classified as a psychiatric disorder. The major diagnosis in this diagnostic class, of which SSD is the most prominent, hinges on the existence of the patient's distinctive abnormal thoughts, feelings, and behaviors in response to somatic symptoms.[3]

Somatoform disorders because of their very nature and presentation have consistently been diagnoses that are difficult to make with any certainty, even after multiple visits with the same primary care physician. It is therefore a challenging diagnosis to make within the busy confines of a brief visit to the ED. For patients with functional symptoms, the strategy of pursuing a medical cause with invasive diagnostic procedures, unnecessary surgeries, and misdirected drug trials can be life-threatening, and the unwarranted costs of these measures strain limited medical resources.

SSD are typically more common in women of low socioeconomic status who present between 20 and 30 years old, with a high incidence of comorbid anxiety or depression.[4] The diagnosis of SSD is made when there are persistent and clinically significant physical complaints that are accompanied by excessive and disproportionate health-related thoughts, feelings, and behaviors regarding these symptoms.[5]

There has been much debate regarding how to name and define SSD patients, with the latest (fifth) version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) reconceptualizing the category almost entirely. The previous criteria for SSD was criticized for being overly inclusive in certain areas and difficult to employ in either real life practice or research.[5] The new diagnostic category of SSD in the DSM-5 is a radical construct change in which the number of symptoms plays only a minor role, while the distress of symptoms associated with psychological features and symptom consequences are emphasized.[3,6]

The term *somatization* was frequently used in the psychiatric literature in the past but is now disapproved of as often as its precursor *hysteria*. The DSM-5 no longer employs the term *somatization* and, in fact, has changed the criteria, as well as the nosology behind what was previously referred to as *somatoform disorders.* Recent publications refer to "medically unexplained physical or somatic symptoms," rather than somatization.

The definitions of somatoform disorders have been a subject of controversy and criticism among psychiatrists as well as primary care providers since they were first included in the DSM-III as a speculative category.[2] SSD had a central defining premise in the concept of "medical unexplained symptoms." There were several problems with this, not the least of which was that many physicians and researchers found it difficult to define a disorder based on the lack of evidence, rather than on the presence of tangible findings.[3,5]

The DSM-5 has attempted to solve many of these conflicts by restructuring and reconceptualizing the diagnosis. The major diagnosis in this diagnostic class, SSD, emphasizes that the diagnosis is made on the basis of distressing somatic symptoms plus maladaptive thoughts, feelings, and behaviors in response to these symptoms.[3]

Although experts may disagree on how to classify SSD, none disagree on the clinical importance of recognizing and appropriately managing these patients.[2] Emergency care providers are trained to focus on physical complaints and findings and to rule out life-threatening conditions. They may consciously or unconsciously avoid asking difficult questions that would make a psychiatric diagnosis apparent or suspect. They may also be wary of ascribing the entirety of a patient's complaints to a psychiatric disorder and risk missing the subtle presentation of medical illness and subsequently retreat into further testing. Proper recognition and management of somatoform disorders is, however, an essential component in minimizing the suffering of these patients and avoiding unnecessary diagnostic testing and the concurrent misallocation of resources.

CLINICAL FEATURES

Somatic and related disorders encompass the diagnoses of SSD, as well as several other psychiatric diagnoses that all share a common feature: the experience of physical symptoms associated with significant distress and impairment that cannot be adequately explained by demonstrable physical pathology despite appropriate medical investigation (Box 103.1).[5]

Hypochondriasis as a DSM classification has been eliminated, and the majority of these patients would now be classified within the DSM-5 as having *illness anxiety disorder.* Illness anxiety disorder is considered a less stigmatized and pejorative term, and describes patients with a persistent preoccupation with having a serious illness, very high levels of health anxiety, a complete absence or very mild somatic symptoms, and excessive

BOX 103.1

Somatic Symptom and Related Disorders

Conditions manifested by abnormal thoughts, feelings, and behaviors in response to distressing somatic symptoms causing impairment:
Somatic symptom disorder (SSD)
Illness anxiety disorder (formerly hypochondriasis)
Functional neurological symptom disorder (formerly conversion disorder)
Factitious disorder
Psychological factors affecting other medical conditions
Other specified somatic symptom and related disorders
Unspecified somatic symptom and related disorders

Adapted from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5, Arlington, VA, 2013, American Psychiatric Association.

BOX 103.2

Differential Diagnosis of Somatic Symptom Disorder

Major depressive disorder
Anxiety disorders
Multiple sclerosis
Porphyria
Hyperparathyroidism
Systemic lupus erythematosus
Thyroid disease
Wilson's disease
Substance abuse disorder
Personality disorder
Malingering

health-related behaviors.[5] A milder form of this disorder may be an exaggerated interest in body function and health that does not rise to the level of being classified as *illness anxiety disorder.* Typically, the patient with illness anxiety disorder commonly complains at length and in detail, using medical jargon. As part of their symptomatology, these patients often believe that they have lost control of their lives and will sometimes make an obvious effort to dominate the doctor-patient relationship to feel more powerful. Consequently, physicians perceive illness anxiety disorder patients as more angry and hostile than other patients.

The terminology of patients with neurologic symptoms that remain unexplained even after appropriate medical investigation has undergone a series of changes. Once referred to as *hysterical neurosis* and later as *conversion disorder,* this particular subset of SSDs is now termed *functional neurological symptom disorder.*

Functional neurological symptom disorder is characterized primarily by symptoms of altered voluntary motor or sensory function that are not better explained by a neurological or medical condition, and it causes clinically significant distress or functional impairment. The disorder can be further subcategorized into (1) weakness or paralysis; (2) abnormal movements; (3) swallowing symptoms; (4) dysphonia or slurred speech; (5) attacks or seizures; (6) anesthesia; and (7) visual, olfactory, or hearing disturbances. Typically, there is a sudden dramatic onset of a single symptom, simulating some nonpainful neurologic disorder for which there is no pathophysiologic or anatomic explanation.[5]

Some of these symptoms may provide gratification for unconscious dependency needs, whereas others may provide escape from painful emotional stimuli. Typical comorbid diagnoses include mood disorders, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, dissociative disorders, and obsessive-compulsive disorders. Patients with functional neurological symptom disorder (conversion disorder) often have a history of physical or sexual abuse. Although the classic description of these patients is one of inappropriate lack of concern for the sudden neurological deficit ("la belle indifference"), such presentations are, in fact, rare and should not be considered necessary for the diagnosis.[7]

DIFFERENTIAL DIAGNOSIS

It is important to remember that there are psychiatric disorders other than SSD that are initially brought to medical attention with manifested somatic symptoms, including major depressive disorder and anxiety disorders. In addition, there are several medical diagnoses that can have very subtle presentations with multiple physical symptoms, including multiple sclerosis, porphyria, hyperparathyroidism, systemic lupus erythematosus, thyroid disorders, and Wilson's disease. Other diagnoses to consider include anxiety, substance abuse disorders, personality disorders, and malingering (Box 103.2).[4]

DIAGNOSTIC TESTING

It is challenging to evaluate a patient for potentially life-threatening disease while simultaneously entertaining a psychiatric diagnosis of SSD. Repetitive or extensive diagnostic testing rarely excludes organic disease with absolute certainty and may yield false-positive results. Testing should only be performed for diagnoses that are supported by a carefully performed history and physical examination. The exception to this rule is the neurological symptom disorder patient, previously termed *conversion disorder.* Several neurological diseases have subtle presentations, multiple sclerosis being a case in point. The pace of the ED and the limited scope of diagnostic evaluation may make it difficult to discern between neurological symptom disorder and neurological pathology with any confidence. It may require imaging studies and both neurologic and psychiatric consultations to avoid the misdiagnosis of a patient who requires intervention.

MANAGEMENT

The success or failure of the emergency clinician to deal with patients who have SSD will depend on his or her ability to establish a rapport with the patient.[8] Patients with these disorders can be more challenging to care for than patients with most other psychiatric disorders, and therefore physician knowledge and attitudes are key. It is important to build and maintain rapport with the patient with SSD by listening carefully and encouraging the patient to describe their symptoms. After developing a sound rapport, legitimize the patient's complaints and then limit diagnostic investigations to address only clear cut findings of medical illness that are based on a careful history and physical examination.

One should avoid confronting or challenging the SSD patient and instead, agree that there is a problem, and work with the patient to formulate a plan of care and referral. The priority is to listen and communicate an understanding of what the patient is feeling and the extent of the functional impairment that they are experiencing. If the provider acknowledges the legitimacy of the patients claim to illness and assures the SSD patient of ongoing care, limits may be set on the patient's illness behavior. Suffering is a subjective phenomenon and, in that sense, is genuine in these patients. It is appropriate to legitimize the patient's symptoms and then use diagnostic labels after considering the needs of the individual patient encounter.[9] If one believes that the patient is

amenable to the potential diagnosis of SSD, naming the diagnosis itself can help build a therapeutic alliance with the patient.[10]

The components of the SSD diagnosis, somatic symptoms, health related anxiety, preoccupation about health concerns, and dysfunctional illness behaviors have an array of beneficial treatments that may be tried, although typically at the discretion of the primary care provider or psychiatric consultant. The potential therapeutic endeavors include cognitive therapy, behavioral techniques, psychotherapies, and in some cases psychotropic medications. If a diagnosis of SSD is seriously considered by the emergency care provider, these patients will require referral to primary care and subsequently to psychiatric consultation for evaluation and management.

Disposition

Patients with suspected SSD and those with a preexisting diagnosis of SSD should be referred to either their primary care physician or to psychiatry. They should be told that acute life-threatening diagnoses have been ruled out and that further testing and additional medications are not indicated at this time. It is appropriate to point out that continued care and periodic reassessment are indicated, although not in the ED. Patients with concurrent anxiety or depression should receive psychiatric consultation or referral, especially when they present with an acute decompensation of these symptoms.

KEY CONCEPTS

- Somatoform disorders as a diagnosis has been eliminated from the DSM-5 and reconceptualized with the category of SSDs.
- The patient with functional neurological symptom disorder, what was termed *conversion disorder* previously, requires a careful and complete neurological examination. Rather than miss the subtle presentation of a neurological disorder, it may be appropriate to perform imaging and obtain neurological and psychiatric consultation. Do not assume that the patient with neurological deficits has a psychiatric disorder.
- Success with the SSD patient depends on establishing rapport with the patient and legitimizing their complaints to avoid a dysfunctional physician-patient interaction.
- Avoid telling the SSD patient "it is all in your head" or "there is nothing wrong with you." These patients are very sensitive to the idea that their suffering is being dismissed.
- A useful approach is to discuss recent stressors with the patient and suggest to them that at times our bodies can be smarter than we are, telling us with physical symptoms that we need assistance. This approach alone may transform the ED visit from a standoff between physician and patient, to a grateful patient who develops greater insight and is amenable to referral.
- Avoid prescribing unnecessary or addictive medications to the SSD patient.
- If you suspect a diagnosis of SSD, refer the patient to primary care or psychiatry for further evaluation and treatment.
- Evaluate and refer appropriately for any concurrent anxiety or depression; psychiatric consultation is needed in the setting of acute decompensation.
- Patients with SSD are best cared for by establishing an ongoing relationship with a primary care provider, and it is appropriate to stress this with the SSD patient.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 103: QUESTIONS & ANSWERS

103.1. Which of the following is most likely to occur from ordering of excessive diagnostic tests in patients with a somatic symptom disorder?

A. A conclusive diagnosis
B. An improved physician-patient relationship
C. Morbidity from repeated diagnostic tests
D. Patients who are reassured by excessive testing
E. The exclusion of organic disease with absolute certainty

Answer: C. Repeated diagnostic testing in somatizing patients not only leads to excessive use of health care services and iatrogenic harm but, in addition, does not lead to increased patient satisfaction, decreased suffering, or improved physician-patient relationship. The most reasonable approach to the patient with a potential diagnosis of somatic symptom disorder is a rational search for biomedical causes along with an open discussion of psychosocial issues from the start of the patient encounter.

103.2. Which of the following is more likely in patients with recent-onset somatic disorder compared with patients with long-term somatic disorder?

A. Anxiety
B. Depression
C. Grief reaction
D. All of the above

Answer: D. Patients who present with the recent onset of somatization are more likely to have an acute psychological stressor that they are either unwilling or unable to directly report and may instead use somatic symptoms to legitimize their presentation to the emergency department. The diagnosis of somatization disorder requires multiple, recurrent, unexplained symptoms rather than an acute complaint in a single visit.

103.3. Which of the following approaches is the most appropriate for diagnosis and treatment of somatic symptom disorder?

A. Confront the patient and explain that there is nothing "wrong."
B. Order multiple diagnostic tests.
C. Proceed with the assumption that the patient is malingering.
D. Refer the patient to insight-oriented psychotherapy.
E. Use effective and appropriate communication skills.

Answer: E. Effective and appropriate communication skills are key to the diagnosis and treatment of patients with a somatic symptom disorder. These patients do not meet the criteria for factitious disorder or malingering. Patients with a somatic symptom disorder have reduced symptoms and improved functioning when the physician does not attempt to minimize the experience of symptoms with comments such as "It is all in your head." In addition, these patients appear to derive very little benefit from insight-oriented psychotherapy; rather, they will maintain improved functional health status and require fewer physician visits if they have an ongoing and trust-based relationship with the primary care physician.

103.4. A patient presents with the sudden onset of blindness, which cannot be explained medically. Which of the following is the most likely to be *true?*

A. The condition is under the patient's voluntary control.
B. The patient is more likely to have preexisting eye disease.
C. The patient is unlikely to have any comorbid diagnosis, such as mood disorder, panic disorder, or post-traumatic stress disorder.
D. The presentation represents the patient's own perception of neurologic illness.

Answer: D. Patients with a functional neurological disorder may present to the physician with what they believe represents a neurologic illness. They are likely to have an underlying comorbid diagnosis, such as mood disorder, panic disorder, or post-traumatic stress disorder. Interestingly, the presentation, such as blindness or paralysis of the lower extremities, is not under the patient's voluntary control.

103.5. Which of the following statements regarding somatization disorder is *true?*

A. A specific symptom may point to the diagnosis.
B. More symptoms correlate with a higher likelihood of psychiatric illness.
C. The symptoms may be feigned or voluntary.
D. There is no direct association with anxiety.
E. There is no direct association with depression.

Answer: B. Women with more than five symptoms and men with more than three symptoms have a much higher likelihood of psychiatric illness. The symptom complaints are neither feigned nor voluntary but, rather, more a manifestation of some sort of distress. There is an association with both depression and anxiety. It is the multiplicity rather than the specificity of symptoms that suggests the diagnosis.

103.6. Which of the following statements regarding chronic pain syndrome (pain disorder) is *true?*

A. Chronic pain behavior patterns are fixed after 2 weeks.
B. It may be intentionally feigned.
C. It often follows a specific traumatic event.

D. The pain is limited to the single organ system or injury.
E. There is typically a pathophysiologic explanation for the pain.

Answer: C. Most cases of chronic pain follow a specific traumatic or industrial event. It is not intentionally feigned, usually involves more than one organ system, and limits function, and the degree of pain or incapacitation cannot be explained medically. Pain behaviors are typically fixed at 3 months, and failure to improve or to return to normal function at 2 weeks should raise concerns and prompt review.

CHAPTER 104

Factitious Disorders and Malingering

Jag S. Heer

PRINCIPLES

Patients may present to the emergency department (ED) with symptoms that are simulated or intentionally produced. The reasons that cause this behavior define two distinct varieties: factitious disorders and malingering.

Factitious disorders are characterized by symptoms or signs that are intentionally produced or feigned by the patient in the absence of apparent external incentives.[1,2] Factitious disorders have been present throughout history. In the second century, Galen described Roman patients inducing and feigning vomiting and rectal bleeding.[3] Hector Gavin sought to categorize this behavior in 1834.[3] These patients constitute approximately 1% of general psychiatric referrals, but this percentage is lower than that seen in emergency medicine because these patients rarely accept psychiatric treatment.[1,4] Of patients referred to infectious disease specialists for fever of unknown origin, 9.3% of the disorders are factitious.[5] Between 5% and 20% of patients observed in epilepsy clinics have psychogenic seizures, and the number reaches 44% in some primary care settings.[6] Among patients submitting kidney stones for analysis, up to 3.5% are fraudulent.[7]

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) classifies factitious disorders into two types: factitious disorder imposed on self (FDIS) and factitious disorder imposed on another (FDIA).

Munchausen syndrome, the most dramatic and exasperating of the FDIS, was originally described in 1951.[8] This fortunately rare syndrome takes its name from Baron Karl F. von Munchausen (1720 to 1797), a revered German military officer and noted raconteur who had his embellished life stories stolen and parodied in a 1785 pamphlet.[3] The diagnosis applies to only 10% to 20% of patients with factitious disorders.[1,9] Other names applied include the "hospital hobo syndrome" (patients wander from hospital to hospital seeking admission), peregrinating (wandering) problem patients, hospital addict, polysurgical addiction, and hospital vagrant.[4,10]

FDIA, an especially pernicious variant that involves the simulation or production of factitious disease in children by a parent or caregiver, was first described in 1977.[2,11] There are approximately 1200 estimated new cases of FDIA per year in the United States.[3] The condition excludes straightforward physical abuse or neglect and simple failure to thrive; mere lying to cover up physical abuse is not FDIA.[3,11] The key discriminator is motive: the mother is making the child ill so that she can vicariously assume the sick role with all its benefits. The mortality rate from FDIA is 9% to 31%.[12] Children who die are generally younger than 3 years old, and the most frequent causes of death are suffocation and poisoning.[13] Permanent disfigurement or permanent impairment of function resulting directly from induced disease or indirectly from invasive procedures, multiple medications, or major surgery occurs in at least 8% of these children.[13,14] Other names applied include *Polle's syndrome* (Polle was a child of Baron Munchausen who died mysteriously), *factitious disorder by proxy, pediatric condition falsification, Munchausen syndrome by proxy,* and *Meadow's syndrome.*[3,8,10,12]

Malingering is the simulation of disease by the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives, such as avoidance of military conscription or duty, avoidance of work, obtainment of financial compensation, evasion of criminal prosecution, obtainment of drugs, gaining of hospital admission (for the purpose of obtaining free room and board), or securing of better living conditions.[2,8,15] The most common goal among such "patients" presenting to the ED is to obtain drugs, whereas in the office or clinic the gain is more commonly insurance payments or industrial injury settlements. The true incidence of malingering is difficult to gauge because of underreporting, but estimates include a 1% incidence among mental health patients in civilian clinical practice, 5% in the military, and as high as 10% to 20% among patients presenting in a litigious context.[8,9] The most likely conditions to be feigned are mild head injury, fibromyalgia, chronic fatigue syndrome, and chronic pain.[9,15]

CLINICAL FEATURES

Factitious Disorders

Factitious Disorders Imposed on Self

The diagnosis of FDIS depends on specific criteria (Box 104.1).[2] With a factitious disorder, the production of symptoms and signs is compulsive; the patient is unable to refrain from the behavior even when its risks are known. The behavior is voluntary only in the sense that it is deliberate and purposeful (intentional) but not in the sense that the acts can be fully controlled.[2] The underlying motivation for producing these deceptions, securing the sick role, is primarily unconscious.[6,8,9] Individuals who readily admit that they have produced their own injuries (eg, self-mutilation) are not included in the category of factitious disorders.[9] Presentations may be acute, in response to an identifiable recent psychosocial stress (termination of romantic relationship, threats to self-esteem), or a chronic life pattern, reflective of the way in which the person deals with life in general.[9] The symptoms involved may be either psychological or physical.

Psychological Symptoms. This disorder is the intentional production or feigning of psychological (often psychotic) symptoms suggestive of a mental disorder. Stimulants may be used to induce restlessness or insomnia; hallucinogens, to create altered levels of consciousness; and hypnotics, to produce lethargy. This psychological factitious condition is less common than factitious disorders with physical symptoms and is almost always superimposed on a severe personality disorder.[2,9]

Physical Symptoms. The intentional production of physical symptoms may take the form of fabricating of symptoms without signs (eg, feigning abdominal pain), simulation of signs suggesting illness (eg, fraudulent pyuria, induced anemia), self-inflicted conditions (eg, the production of abscesses by injection of contaminated material under the skin), or genuine complications

BOX 104.1

DSM-5 Criteria for the Diagnosis of Factitious Disorder Imposed on Self

1. Falsification of psychological or physical signs or symptoms, or induction of disease or injury associated with identified deception.
2. The individual presents to others as injured, ill, or impaired.
3. The deceptive behavior is apparent even in the absence of external incentives.
4. The behavior is not better explained by another mental disorder.

from the intentional misuse of medications (eg, diuretics, hypoglycemic agents).[7,10,11,15] These patients are predominantly unmarried women younger than 40 years old. They typically accept their illness with few complaints and are generally well-educated, responsible workers or students with moral attitudes and otherwise conscientious behavior.[9,15,16] Many are in health care occupations, including nurses, aides, and physicians.

These patients are willing to undergo incredible hardship, limb amputation, organ loss, and even death to perpetuate the masquerade.[10,15] Although multiple hospitalizations often lead to iatrogenic physical conditions, such as postoperative pain syndromes and drug addictions, patients continue to crave hospitalization for its own sake. They typically have a fragile and fragmented self-image and are susceptible to psychotic and even suicidal episodes.[15,16] Interactions with the health care system and relationships with caregivers provide the needed structure that stabilizes the patient's sense of self. The hospital may be perceived as a refuge, sanctuary, or womblike environment.[15,16] Some patients are apparently driven by the conviction that they have a real but as yet undiscovered illness. Consequently, artificial symptoms are contrived to convince the physician to continue a search for the elusive disease process.[15,16] Factitious illness behavior has even emerged on the Internet. "Virtual support groups" offering person-to-person communications through chat rooms and bulletin boards have been perpetrated by individuals, under the pretense of illness or personal crisis, for the purpose of extracting attention or sympathy, acting out anger, or exercising control over others.[8]

Approach to Diagnosis. The initial diagnosis of FDIS is often delayed because the possibility of factitious disease is not considered, physicians may be unfamiliar with this problem, or the patient does not exhibit the type of personality expected with this behavior.[9] Diagnosis may be confounded by genuine medical illnesses predating and coexisting with a factitious disorder. For example, patients with factitious hypoglycemia may have a history of insulin-dependent diabetes mellitus, or factitious skin disorders may be preceded by true dermatologic diseases.[1,15] Identification of a factitious disorder is usually made in one of four ways: (1) the patient is accidentally discovered in the act, (2) incriminating items are found, (3) laboratory values suggest nonorganic etiology, or (4) the diagnosis is made by exclusion.[4,7]

There has been increasing recognition of factitious illness produced by children. These children, ranging in age from 8 to 18 years old, are typically "bland, flat and indifferent during their extensive medical interventions … depressed, socially isolated, and often obese."[13] Among the most common presentations are fever without clear etiology, diabetic ketoacidosis, purpura, and recurrent infections. The prognosis is good if identification and psychotherapeutic intervention can be carried out at a young age.[12]

Munchausen Syndrome. The uncommon patient with true Munchausen syndrome has a prolonged pattern of "medical imposture," usually years in duration. The behavior usually begins before 20 years old and is diagnosed between 35 and 39 years old. Twice as many men as women are affected.[8,15,16] Patients' entire adult lives may consist of trying to gain admission to hospitals and then steadfastly resisting discharge. Their career of imposture usually lasts about 9 years but has continued unabated for as long as 50 years.[4,15] The quest for repeated hospitalizations often takes these patients to numerous and widespread cities, states, and countries.[2,8]

These individuals see themselves as important people, or at least related to such persons, and their life events are depicted as exceptional.[16] They possess extensive knowledge of medical terminology. There is frequently a history of genuine disease, and the individual may exhibit objective physical findings.[16]

The symptoms presented are "limited only by the person's medical knowledge, sophistication, and imagination."[2] The alleged illnesses involved have been termed *dilemma diagnoses* in that investigators rarely can totally rule out the disorder, clarify the cause, or prove that it did not exist at one time.[4] Common presentations are those that most reliably result in admission to the hospital, such as abdominal pain, self-injection of a foreign substance, feculent urine, bleeding disorders, hemoptysis, paroxysmal headaches, seizures, shortness of breath, asthma with respiratory failure, chronic pain, acute cardiovascular symptoms (eg, chest pain, induced hypertension and syncope), renal colic and spurious urolithiasis, fever of unknown origin (hyperpyrexia figmentatica), profound hypoglycemia, and coma with anisocoria.[4-6,10,15,16] Some self-induced conditions are highly injurious or even lethal.[10]

The patient usually presents during evenings or on weekends so as to minimize accessibility to psychiatric consultants, personal physicians, and past medical records.[16] In teaching institutions, these patients often present in July, shortly after the change in resident house officers.[10] They relate their history in a precise, dramatic, even intriguing fashion, embellished with flourishes of pathologic lying and self-aggrandizement. *Pseudologia fantastica,* or pathologic lying, is a distinctive peculiarity of these patients. In a chronic, often lifelong behavior pattern, the patient typically takes a central and heroic role in these tales, which may function as a way to act out fantasy.[17] The history quickly becomes vague and inconsistent, however, when the patient is questioned in detail about medical contacts.[3] Attempts to manage the complaint on an outpatient basis are adamantly resisted.[15] Once admitted, the patient initially appeals to the physician's qualities of nurturance and omnipotence, lavishing praise on the caregivers. Behavior rapidly evolves, however, as the patient creates havoc on the ward by insisting on excessive attention while ignoring both hospital rules and the prescribed therapeutic regimen.[15] When the hoax is uncovered and the patient confronted, fear of rejection abruptly changes into rage against the treating physician, closely followed by departure from the hospital against medical advice.[15,18]

Factitious Disorder Imposed on Another

The diagnosis of FDIA depends on specific criteria (Box 104.2).[2] The presenting complaints typically evade definitive diagnosis and are refractory to conventional therapy for no apparent reason.[19] The symptoms are usually more than five in number, presented in a confused picture; they are unusual or serious and, by design, unverifiable. They invariably occur when the mother is alone with the child or otherwise unobserved.[12] In 72% to 95% of cases, simulation, or production of illness occurs while the victim is hospitalized.[11,12,14]

Simulated illness, faked by the mother without producing direct harm to the child (eg, the addition of blood to a urine

BOX 104.2

DSM-5 Criteria for the Diagnosis of Factitious Disorder Imposed on Another

1. Falsification of psychological or physical signs or symptoms, or induction of disease or injury in another, associated with identified deception.
2. The individual presents another individual (victim) to others as injured, ill, or impaired.
3. The deceptive behavior is apparent even in the absence of external incentives.
4. The behavior is not better explained by another mental disorder.

BOX 104.3

Characteristics of Malingering

1. Medicolegal context of the presentation (eg, the patient was referred by his or her attorney)
2. Marked discrepancy between the person's claimed stress or disability and objective findings
3. Poor cooperation during the diagnostic evaluation or poor compliance with previously prescribed treatment regimens
4. The person exhibits or has a history of antisocial behavior

specimen), is present in 25% of cases. Produced illness, which the mother actually inflicts on the child (eg, the injection of feces into an intravenous line), is found in 50% of cases. Both simulated and produced illnesses are found in 25% of cases.[11-14]

FDIA most commonly arises with factitious bleeding, seizures, central nervous system (CNS) depression, apnea, diarrhea, vomiting, fever, and rash.[14] Reported techniques of simulation or production of disease include administration of drugs or toxins (eg, chronic arsenic poisoning, ipecac, warfarin, phenolphthalein, hydrocarbons, salt, imipramine, laxatives, CNS depressants), caustics applied to the skin, and nasal aspiration of cooking oil.[11,14,18] Techniques of asphyxiation include (1) covering the mouth or nose with one or both hands, a cloth, or plastic film, and (2) inserting the fingers into the back of the mouth. In such instances, even struggling infants may sustain no cutaneous markings.[19] Cases involving seizures are common and may involve third-party witnesses. On personal questioning, however, these witnesses frequently deny the occurrence of seizure activity.[6,13,14]

Perpetrator Characteristics. Ninety-eight percent of perpetrators are biologic mothers who come from all socioeconomic groups.[11-14] Many have a background in health professions or social work, or a past history of psychiatric treatment, marital problems, or suicide attempts.[11-15] Depression, anxiety, and somatization are common, but frank psychotic behavior by the mother is atypical.[14] Perpetrators of FDIA have an inherent skill in manipulating health care workers and child protection services.[13] They are pleasant, socially adept, cooperative, and appreciative of good medical care. They often display a peculiar eagerness to have invasive procedures performed on their child.[3] They often prefer to stay in the hospital with their child, cultivate unusually close relationships with hospital staff, and thrive on staff attention.[11-14] This affable relationship with the medical team rapidly changes to excessive anger and denial when the perpetrator is confronted with suspicions.[12,13]

Most of these mothers have had an abusive experience early in life, and they use the health care system as a means to satisfy personal nurturing demands.[3,12] They often cannot distinguish their needs from the child's and satisfy their own needs first. They derive a sense of purpose from the medical and nursing attention gained when their children are in the hospital.[11-13] Alternatively, the behavior may enable the mothers to escape from their own physical or psychological illnesses, marital difficulties, or social problems.[13]

Victim Characteristics. Victims of FDIA are equally male and female children. The mean age at diagnosis is 40 months, and the mean duration from the onset of signs and symptoms to diagnosis is 15 months.[11-13] A known physical illness that explains part of the symptoms is common among these children.[13] Most have a history of significant failure to thrive and have been hospitalized in more than one institution. Delays in many areas of performance and learning, difficulty with family relationships, attention deficit disorder, or clinical depression may coexist.[13] Some of these victims may have factitious disorder later in life.[3] Elders may also be victims of FDIA, although this is uncommon.[20]

Approach to Diagnosis. Suspected FDIA requires a detailed description of the event or illness and a search for caregiver witnesses, who should be interviewed personally. Although it is essential to see the child when the symptoms are present, the parents show great ingenuity at frustrating this effort.[12,13] Additional history of unusual illness in siblings and parents should be sought. Child victims who are verbal should be interviewed in private about foods, medicines, and their recollection of the symptoms or events. Prior medical records of the victim and, if possible, the siblings should be examined, although parents may impede such data gathering.

The major obstacle to early discovery of FDIA is its omission from the differential diagnosis. When it is considered, the diagnosis is generally made easily and quickly.[11-13] A suspected diagnosis may be confirmed through separation of the parent from the child or individual (with consequent cessation of symptoms), covert video surveillance during hospitalization, or toxicologic screens.[16] In the majority of cases, the caregiver attempts to induce episodes surreptitiously while in the hospital, often during the first day of admission.[11-13]

Malingering

Malingering is frequently found in association with antisocial personality disorder. On questioning, malingerers are vague about prior hospitalizations or treatments. The physicians who previously treated them are usually unavailable. At times, malingerers may be careless about their symptoms and abandon them when they believe no one is watching.[8] In some "patients," such as those seeking drugs, homeless persons seeking hospital admission on a cold night, or prisoners wanting a holiday from incarceration, the secondary gain may be clear. In other persons, the external incentive may be obscure.

In contrast to the person with factitious disorders, the malingerer prefers counterfeit mental illness, because it is objectively difficult to verify or to disprove. Amnesia is the most common psychological presentation, followed by paranoia, morbid depression, suicidal ideation, and psychosis.[15]

Malingering should be strongly suspected with any combination of certain factors (Box 104.3).[2] A definitive diagnosis of malingering is rare and can be established only with the patient's confession.[3] Because malingering constitutes criminal behavior, documentation of this diagnosis should be made with care.[15] In the absence of proof of wrongdoing, it is best to assume that the

patient is not a malingerer but rather a common somatizer.[15] Malingerers who pursue drugs may report an unusually large number of drug allergies to persuade the physician to prescribe their drug of choice or simply insist on a specific drug (eg, meperidine [Demerol] or hydromorphone [Dilaudid]).[8] Unfortunately, the Internet offers a wide availability of quality medical advice on how to convincingly feign pain and disability.

DIFFERENTIAL DIAGNOSIS

The most important diagnoses to be excluded are genuine medical and psychiatric conditions that might account for the presenting symptoms. Patients with conversion disorder, somatic disorder, delusional disorder of somatic type, and borderline personality disorder can present with symptoms similar to FDIS. The differences can be subtle and psychiatric consultation or referral is indicated.

Patients with factitious disorders are distinguished from malingerers because their desired hospitalization or surgery seems to offer no secondary gain other than to play the sick role.[2,10,15] The clinical presentation of the majority of patients with factitious disorders, unlike those with Munchausen syndrome, is relatively subtle and convincing. The complaints are generally chronic in nature rather than emergent and precipitous, and there are no obvious associated behavioral aberrations.[15] The chronicity of malingering is usually less than that associated with factitious disorder, and malingerers are more reluctant to accept expensive, possibly painful, or dangerous tests or surgery.[15]

MANAGEMENT

Factitious Disorders

Treatment options for factitious disorders depend on the patient's characteristics. Although it is challenging, management of common forms of factitious disorder can be more rewarding, especially with adolescents, than management of Munchausen syndrome.[11,15] The prognosis is more favorable for cases with an underlying depression than for those associated with borderline personalities.[11,14]

The best approach to patients with factitious disorder, other than Munchausen syndrome and FDIA, is controversial. Direct non-accusatory confrontation has been advocated as "the foundation of effective management" when it is coupled with the assurance that an ongoing relationship with a physician will be provided.[11,13,15] This may be the first step in the acceptance of outpatient therapy.[15]

Others point out that confrontation is ineffective in most patients and may even be counterproductive in that it threatens to undermine a needed psychological defense. Enforced recognition of external objective reality, while simultaneously disallowing the patient's subjective experience, may generate even more dysfunction directed at legitimizing and maintaining symptoms and may even place the patient at risk for suicide.[11,15] Some patients may relinquish this defense if they feel safe in doing so and may abandon a claim to disease if some face-saving option is offered. This approach, termed the *therapeutic double bind* or *contingency management,* involves informing the patient that a factitious disorder may exist. The patient is further told that failure to respond fully to medical care would constitute conclusive evidence that the patient's problem is not organic but rather psychiatric. The problem is therefore reframed or redefined in such a way that (1) symptoms and their resolution are both legitimized and (2) the patient has little choice but to accept and respond to a proposed course of action or seek care elsewhere.[15]

Individuals with Munchausen syndrome typically demonstrate overt sociopathic traits or a borderline personality disorder and are demanding and manipulative, especially regarding analgesics.[15] They have been described as "essentially untreatable," and successful management of this condition is, in fact, considered reportable. Early confrontation or limit setting, especially regarding drug use, is advocated.[8,10,15] Although Munchausen patients typically do not want to be examined extensively, a thorough physical examination should be performed to rule out physical disease.

FDIA constitutes a form of child (or elder) abuse, and appropriate action to protect the victim, including notification of state social service agencies, should take immediate priority.[13,14] If available, a pediatrician who has expertise in child abuse should assess the case. When the diagnosis has been established and the parents have been confronted, psychiatric care should be made immediately available to the parents because maternal suicide is a significant risk.[13,15]

Malingering

Malingerers do not want to be treated. Because they are "gaming the system" for personal advantage, the last thing they want is an accurate identification of their behavior and appropriate intervention. The emergency clinician should maintain clinical neutrality, offering the reassurance that the symptoms and examination are not consistent with any serious disease.

Some authors have characterized patients' use of medical resources under false pretenses as criminal behavior, and several states have enacted legislation against the fraudulent acquisition of medical services with successful prosecution of such behavior.[4,8] Conversely, patients with factitious disorders can and do sue. In dealing with such patients, it is advisable to involve hospital administration and risk management. Clandestine searches are inadvisable, and respect for the patient's confidentiality should be maintained.[15]

DISPOSITION

Patients suspected of having a factitious disorder should be referred for primary care follow-up, and if it is acceptable to the patient, psychiatric referral should also be arranged. Referral to other medical specialists or hospitalization should be avoided when possible.

The manner of presentation and the unavailability of past medical history often allow patients with Munchausen syndrome to achieve hospital admission. If the patient is discharged from the ED, outpatient primary care follow-up and psychiatric referral should be offered, although both are likely to be refused.[15]

Because perpetrators of FDIA typically induce symptomatic episodes soon after hospitalization, admission of the victims (children or elders) without taking appropriate precautions may actually place them at increased risk.[11,13,20] Visits by the suspected perpetrator should be closely supervised, and no food, drink, or medicines should be brought in by the family. Protective services should be notified. Out-of-home placement of children in established cases of FDIA is advisable, and the best outcomes are seen among children taken into long-term care at an early age without access to their mother. Children allowed to return home have a high rate of repeated abuse.[3,12] In 20% of reported deaths, the parents had been confronted and the child sent home to them, subsequently to die.[12,13]

After courteous but assertive reassurance, suspected malingerers should be offered primary care follow-up if the symptoms do not resolve. These individuals may become threatening when they are either denied treatment or overtly confronted.[15]

KEY CONCEPTS

- Patients who have consciously synthesized symptoms and signs may be divided into two broad diagnostic categories: (1) those with obvious secondary gain (malingering), who control their actions, and (2) those with a motivation of achieving the sick role (factitious disorders), who cannot control their actions.
- The initial management of patients suspected of fabricating disease should include a caring, nonjudgmental attitude and a search for objective clinical evidence of treatable medical or psychiatric illness. Review of old medical records and interview of family members are often helpful.
- Unnecessary tests, medications, and hospitalizations should be avoided in the absence of objective evidence of a medical or psychiatric disease, and patients should be referred for ongoing primary care.
- In cases of suspected FDIA involving children or elders, protection of the victim takes first priority.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 104: QUESTIONS & ANSWERS

104.1. Which of the following statements regarding factitious disorder is true?
- **A.** It involves voluntary and controllable symptom production.
- **B.** Patients are generally well educated and otherwise responsible.
- **C.** Presentations are not related to an identifiable event.
- **D.** The symptoms produced are always physical ones.
- **E.** The underlying motivation is a conscious one.

Answer: B. Many such patients are actually employed in the health care industry. The act of producing symptoms is voluntary but not controllable and derives from a subconscious motivation. Presentations are very often related to a "traumatic" event, such as a breakup. Produced symptoms may be physical (eg, hematuria) or psychological. The typical patient is an unmarried female younger than 40 years. Despite undergoing invasive procedures and associated hardships, these patients seek more medical care and hospitalization.

104.2. Which of the following statements concerning Munchausen syndrome by proxy is true?
- **A.** A known physical illness in the child is common.
- **B.** Most maternal perpetuators are demanding, uncooperative, and socially inept.
- **C.** Most maternal perpetrators are not a biologic parent.
- **D.** Psychosis is common in the maternal perpetrator.
- **E.** The mean age of victim diagnosis is 7 to 9 years.

Answer: A. Victim children often have a legitimate illness. Mean age at diagnosis is 40 months. Most have a history of failure to thrive and multiple hospitalizations. The perpetrator receives some personal fulfillment from the care and attention of the hospital staff, which is often admiration for her persistence, willingness to sacrifice and patience, and she is typically pleasant, medically savvy, and socially skilled. Invasive procedures on the child are often welcomed. Although psychosis is very unusual in the parent, depression, anxiety, and somatization are typical in the perpetrator.

104.3. A 2-year-old female presents with new onset seizures. Her past medical history is unremarkable. Laboratory evaluation reveals blood glucose of 20 mg/dL. The patient's mother denies a family history of diabetes or having medications the child might have ingested at home. She works as a nurse at a local hospital and has been with the child all day. The child's symptoms improve with glucose administration and a meal. Your colleague remembers evaluating the child recently for hematuria with a negative evaluation. If you suspect Munchausen syndrome by proxy, which of the following tests would be most helpful in establishing the diagnosis?
- **A.** Basic metabolic panel
- **B.** Computed tomography (CT) scan of head
- **C.** C-peptide and insulin level
- **D.** Electroencephalography (EEG)

Answer: C. The diagnostic criteria for factitious hypoglycemia include high serum insulin levels along with the absence of serum C-peptide. The C-peptide is removed during the purification of commercial insulin, and so its absence suggests the presence of endogenously administered insulin. In patients with insulinoma, both C-peptide and insulin levels are elevated and detectable.

104.4. A prison inmate presents after falling from the top bunk in his cell. He is complaining of lower lumbar pain and states he is unable to move or feel his lower extremities from his waist down. On physical examination, lower extremity reflexes are present but the patient denies feeling pain or light touch sensation below the waist. Lumbar spine CT and MRI are negative. Which of the following conditions is most likely?
- **A.** Cord contusion
- **B.** Factitious disorder
- **C.** Malingering
- **D.** Munchausen syndrome

Answer: C. Malingering is the intentional symptom production for secondary gain. There is a marked discrepancy between claimed disability and the actual objective findings. Confessions and proof are rare.

CHAPTER 105

Suicide

Marian E. Betz | Jeffrey M. Caterino

PRINCIPLES

Background

Emergency clinicians care for large numbers of patients with suicidal ideation and self-harm behaviors. Two facts are especially important to remember in the care of suicidal patients. First, many suicide attempts occur during an acute crisis, such as a personal loss or the exacerbation of an underlying psychiatric disorder. This acute crisis is usually time limited and may be resolvable or treatable. Second, suicidal patients are usually ambivalent about dying and grateful for help. An empathetic, patient-centered, and evidence-based approach offers the opportunity to save lives.

Epidemiology

In 2011, suicide was the fourth leading cause of death in the United States for adults between 18 and 65 years old.[1] There are more than one million suicide attempts and 41,000 suicide deaths in the United States, and rates are rising.[2] Between 1999 and 2010, the age-adjusted suicide rate among 35 to 64 year olds increased 28.4%.[3] In the United States, there are over 800,000 visits to emergency departments (EDs) each year for self-inflicted injuries.[4] Many patients evaluated for suicidality are discharged; in 2008, only half of ED visits for suicide attempts resulted in hospitalization.[5]

Suicide rates vary with age and are highest in elders, particularly older white men (Fig. 105.1 and Table 105.1).[6] Whites and Native Americans have higher rates of suicide than African Americans, Hispanics, or Asians. Women attempt suicide three to four times more often than men, whereas men are three to four times more likely to die after an attempt (due to use of more lethal methods) and have higher suicide death rates in all age groups (see Fig. 105.1).[7] Both pregnancy and motherhood seem to protect against suicide, except in cases of postpartum depression. Sexual orientation is also associated with suicide risk because youth identifying as lesbian, gay, or bisexual have increased risk for suicidal ideation and attempts.[8-9] Suicide also varies geographically, with higher rates in the Western United States, rural areas, at higher elevations, and in areas with higher levels of firearm ownership.[2,10,11] Among military personnel, suicide risk is increased in males and those with psychiatric history, alcohol abuse, or previous deployment.[12-14] In 2012, suicide surpassed war as the leading cause of death in the military.[15]

Risk Factors

There are many factors associated with an increased risk of suicide (see Table 105.1), although it is important to recognize that some of these have stronger associations than others. Some risk factors are dynamic, whereas others are static; thus an individual patient's risk may vary over time, but helping someone at a current low risk of suicide may prevent future escalation to high risk.[16]

Self-Harm

A prior history of non-suicidal self-harm or suicide attempt, even in the remote past, is an important risk factor (see Table 105.1).[17,18] Because 10% to 15 % of suicide attempters will ultimately die by suicide, prior suicide attempt is one of the most important predictors of a future attempt.[19] At the same time, up to 80% of suicide completers have no prior history of attempts and die on the first known attempt.[1,20]

Mental Illness

The presence of an affective disorder, especially major depression, is also a strong independent risk factor for suicide. There are increased rates of suicide in patients with schizophrenia, bipolar disorder, borderline personality traits or disorder, anxiety disorder, and post-traumatic stress disorder.[21,22] Overall, the risk of suicide in patients with mental illness increases with the presence of prior attempts, recent psychiatric hospitalization, male gender, more severe symptoms, hopelessness, comorbid psychiatric disorders, use of alcohol or drugs, and family history of suicide. The presence of comorbid depression in the setting of other mental illness is a particularly strong factor. In patients hospitalized for psychiatric disorders, the risk for suicide is greatest in the first month after discharge, especially in the first week. Some patients, particularly children and adolescents, may have increased suicidal thoughts or attempts soon after the initiation of antidepressant medications.[23] This may be due to the "mobilization of energy" theory, which suggests profoundly depressed patients have the energy to attempt suicide only as their condition improves with treatment. The clinician should recognize the time period around initiation of antidepressant therapy as one requiring heightened scrutiny for suicidal thoughts or behaviors.

Alcohol and Substance Abuse

Both chronic and acute alcohol abuse are associated with suicide. Patients with chronic alcohol use have over nine times the risk of completed suicide. Alcoholics who die from suicide usually have multiple risk factors, including major depression, unemployment, medical illness, and interpersonal loss. Acute alcohol use is associated with increased risk of suicide in both those with and without chronic alcohol abuse, and this risk persists for 24 to 48 hours after drinking, particularly heavy drinking.[24-26] This effect is largest among younger adults and is more often associated with violent means of suicide (eg, firearms or hanging).[27] Substance abuse is associated with increased frequency, repetitiveness, and lethality in suicide attempts. Illicit substances are often detected at the time of suicide; of all suicides in 16 states in 2010, 33% tested positive

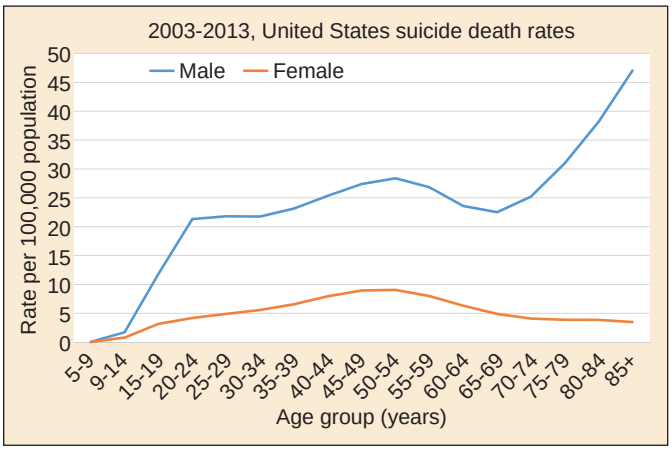

Fig. 105.1. Age-adjusted suicide death rates by gender and age group (United States, 2003 to 2013.) (Data from Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: Web-based injury statistics query and reporting system (WISQARS). Available at www.cdc.gov/injury/wisqars/index.html.)

TABLE 105.1

Risk Factors for Suicide

Demographic	Age groups: Adolescence, older age Gender: Male Ethnicity: White, American Indian, or Alaskan Native
Biopsychosocial	Mental disorders (including mood disorders, schizophrenia, borderline personality disorder, anxiety disorders, post-traumatic stress disorder) Alcohol or substance abuse Prior suicide attempt Recent psychiatric hospital discharge Family history of suicide History of trauma or abuse Chronic pain or major physical illness Terminal illness Hopelessness Impulsive and/or tendencies
Environmental	Job or financial loss (eg, unemployed, homeless) Relational or social loss (eg, widowed, bereaved, recent incarceration) Access to lethal means (eg, guns) Local suicide clusters with a contagious influence
Sociocultural	Lack of social support and sense of isolation Stigma associated with help-seeking behavior Inadequate access to care for mental health or substance abuse Certain cultural and religious beliefs (eg, suicide as a noble resolution of a personal dilemma) Exposure to, including through the media, and influence of others who have died by suicide

Adapted from Rodgers P, Suicide Prevention Resource Center (SPRC): Understanding risk and protective factors for suicide: a primer for preventing suicide, 2011. Available at www.sprc.org/sites/sprc.org/files/library/RiskProtectiveFactorsPrimer.pdf.

for alcohol, 24% for opiates, 20% for antidepressants, 15% for marijuana, 8% for cocaine, and 4% for amphetamines.[28]

Adolescence

Suicide is the third leading cause of death in people 15 to 24 years old.[29] In a national survey of high school students in the United States, in the previous year 17% had had serious thoughts of suicide, 13% had made a suicide plan, and 8% had made a suicide attempt.[30] Similar to the adult population, adolescent girls are more likely to attempt suicide, whereas boys are more likely to die by suicide. Most adolescents who die by suicide have made previous suicide threats. Suicide risk factors in adolescents and young adults have been identified (Table 105.2). History of suicide attempt and of non-suicidal self-harm are particularly strong risk factors.[31,32]

TABLE 105.2

Additional Risk Factors for Suicide in Adolescence

Demographic	Sexual orientation (lesbian; gay; bisexual; unsure)[9]
Biopsychosocial	Sedentary activities (≥3 hours day TV or video games; sleep <8 hours per night) Weight concerns (perceive self as overweight; prior fasting, diet pills, or vomiting/laxatives for weight control) Sexual health (prior sexual intercourse; sex before age 13; four or more partners; sexually active; no use of condoms)
Environmental	Exposure to violence (carried a weapon; in a physical fight, bullied electronically or in person; forced to have sex; hit by significant other; felt unsafe or threatened at school)
Sociocultural	Participation in Goth subculture

Adapted from Lowry R, Crosby AE, Brener ND, et al: Suicidal thoughts and attempts among U.S. high school students: trends and associated health-risk behaviors, 1991–2011. J Adolesc Health 54:100–108, 2014.

Older Age

Suicide rates are particularly high in elders, especially older white men, who account for over 80% of suicide deaths among older adults (see Fig. 105.1).[2,33] Older adults with suicide attempts are more likely to die because of the use of more lethal methods, more advanced planning, and a lower likelihood of asking for help, having warnings recognized by others, or having a successful crisis intervention. Suicide rates among the baby boomer generational cohort appear to be higher than in previous generations, highlighting the need for suicide prevention efforts targeted toward this group.[3] Among older adults, depression is the strongest risk factor for suicide, with a prevalence of up to 80% among older suicide decedents.[34-37] Additional important risk factors in elders include cognitive dysfunction, decreased functional ability, bereavement or other stressful life events, social isolation, and loneliness.[19,33,36]

Chronic Illness

Many chronic medical illnesses are associated with increased risk of suicide, particularly those with chronic pain or impairment in activates of daily living.[36] Infection with human immunodeficiency virus (HIV) or presence of the acquired immunodeficiency syndrome (AIDS) remains associated with increased risk of suicide, both due to an increased incidence of major depression and to increased rates of cognitive dysfunction in older patients with HIV/AIDS.[38-41]

Other Risk Factors

Financial stress can increase the risk of suicide, with both male and female suicide rates increased in times of recession and increasing unemployment.[42,43] Homeless people with mental

illness are at high risk for suicide, which is in part because of the high prevalence of other suicide risk factors. Recent incarceration is also a suicide risk factor. The risk of suicide in recently released prisoners approaches that of recently discharged psychiatric patients.

Methods of Suicide

Firearms account for more than half (52%) of completed suicides, followed by hanging or suffocation (25%), and poisoning (16%).[28] Firearms are the most common method of completed suicide among males (58%), but poisonings are more common among women (37% poisoning versus 31% firearms).[28] In one large study, poisoning with drugs accounted for 74% of acts but only 14% of fatalities; firearms and hanging accounted for only 10% of acts but 67% of fatalities. There is a well-established relationship between the presence of a firearm in the home and higher rates of suicide.[11] Compared to households without, households with a firearm have increased rates of suicide but similar rates of mental disorders, substance abuse, suicidal ideation, and suicidal planning. This suggests the presence of a firearm has an independent effect on the risk of death by suicide because of the associated high case fatality rate of firearm suicide.

Poisoning accounts for over two-thirds of ED visits for suicide attempt or self-harm.[44] Prescription drugs are much more commonly associated with these visits than are illicit drugs; among prescription drugs, anxiolytics, sedatives, and hypnotics are most commonly present (41%), followed by antidepressants (20%).[45]

Pathophysiology

The etiology of suicide is a complex mix of social, genetic, and psychological factors. Current research suggests a biologic basis for depression and suicide involving the serotonergic systems. People who attempt suicide have altered serotonin receptor function and low serotonin levels. The genetic basis of suicide is not clearly understood, but several genes affecting the serotonin system have been implicated.[46] Additional potential mechanisms include excessive noradrenergic neurotransmission and hyperactivity of the hypothalamic pituitary axis, but studies are conflicting. Low serum and cerebrospinal fluid (CSF) levels of brain-derived neurotrophic factor, a neurotrophic factor that regulates neuronal development, function, and survival, have also been associated with suicide.[47]

CLINICAL FEATURES

The potential for suicide should be considered in patients with suicide risk factors (see Table 105.1) and in patients who "unintentionally" overdose or have had "accidental" gunshot wounds, lacerated wrists, automobile crashes, or falls from heights. Providers should also consider suicidal thoughts or behavior in patients who present to the ED repeatedly because of noncompliance with treatment of their medical disorders. Patients who are not overtly depressed or suicidal but who exhibit one or more of these high-risk presentations previously described should be assessed in a sympathetic but direct manner using a "graduated" approach. Rapport can first be established during a general medical and psychiatric history, with an evaluation of the patient's home, work, and social situation, followed by specific questions about the signs and symptoms of depression and about suicidal thoughts. Such questioning does not place the concept of suicide into the mind of someone who has not been considering it.

The approach described earlier can be described as *indicated screening* (questioning of those with "red flag" acute risk factors for suicide, such as psychosocial stressors).[48] A more systematic screening approach would be *selective screening* (questioning of all patients in high-risk groups, such as those with chronic risk factors for suicide like prior attempts or mental illness).[47] *Universal screening* for suicidal risk involves questioning all patients about suicidal thoughts or behaviors.[47] Advocates of universal screening argue that other approaches miss patients with "occult" suicidality; research suggests that approximately 10% of all ED patients have recent suicidal ideation or behaviors, and 40% of suicide victims have visited an ED within the prior year.[49] A National Patient Safety Goal (15.01.01) from the Joint Commission requires "general hospitals treating individuals for emotional or behavioral disorders, to identify patients at risk for suicide."[50] This goal can be met by targeted or universal screening. For ideal functioning, any screening program should be integrated into electronic medical records and current work flow to optimize efficiency and provider uptake.[51]

DIFFERENTIAL DIAGNOSIS

Self-directed violence (SDV) encompasses both suicidal and non-suicidal self-injurious behaviors. *Non-suicidal SDV* "deliberately results in injury or the potential for injury to oneself" in the absence of suicidal intent (eg, cutting or burning).[52] *Suicidal ideation* refers to thoughts of causing one's own death, with or without a specific plan. *Suicidal behavior* is any behavior with the intent to end one's life. A *suicide attempt* is a "non-fatal self-directed potentially injurious behavior with any intent to die as a result of the behavior."[52] An *interrupted suicide attempt* is a suicide attempt aborted by the individual or another person.[52] *Occult suicide* is suicidal thoughts or behaviors not admitted to by the patient, such as self-destructive acts disguised as accidents (eg, an intoxicated, depressed driver who crashes his car). *Suicide by cop* is when a suicidal individual intentionally provokes a police officer by orchestrating a situation in which the officer is forced to shoot in self-defense or to protect other civilians.[53] Terms to avoid (because of the suggested value judgment) include *committed* or *successful* suicide, *suicidal gesture, manipulative act,* and *suicide threat.*[52]

DIAGNOSTIC TESTING

Emergency clinicians are often asked to provide *medical clearance* of patients with psychiatric emergencies. However, the preferred term is *focused medical assessment;* a negative focused medical assessment does not indicate an absence of medical problems but rather that such problems can be addressed on a non-urgent basis. A focused medical assessment should be accomplished primarily through obtaining an adequate patient history and physical examination.

The history should include details about the patient's suicidal thoughts (including onset and frequency), plans (including method, intent to act, and access to lethal means), and behaviors (including prior or recent attempts, as well as aborted or interrupted attempts). Other important points include prior medical and psychiatric conditions, prior outpatient or inpatient psychiatric care, current medications, and current drug or alcohol use (including recent use). The history should also assess symptoms suggestive of concomitant medical illness. Intoxication should not preclude taking a history, but the provider should repeat the interview when the patient is sober.

The examination should assess for evidence of drug ingestion, trauma, or associated medical illness, as well as evidence of self-harm behavior such as wrist-cutting. The patient's cognitive status, vital signs, pupils, skin, and nervous system are helpful in detecting organic conditions, particularly toxidromes associated with common ingestions (see Chapter 139). In the case of altered mental status, the provider should determine whether the condition is caused by an organic (medical) or functional (psychiatric)

TABLE 105.3

Potential Targeted Diagnostic Testing in Emergency Department Patients Presenting With Suicidality

LAB TYPE	TESTING TYPE*
General labs	Pregnancy test (in females of childbearing age) Complete blood count (for suspected anemia) Serum chemistries (for suspected electrolyte abnormalities) Urinalysis (for suspected infection) Liver function tests (LFTs), ammonia (for suspected liver disease or valproic acid use) Coagulation studies Thyroid-stimulating hormone (TSH) (for suspected thyrotoxicosis or thyroid abnormality)
Toxicologic labs	Urine screen for drugs of abuse (to explain acutely altered mental status; to assist ongoing psychiatric care) Ethanol level (to explain acutely altered mental status; to assist ongoing psychiatric care) Testing for potential toxic ingestion (eg, aspirin, acetaminophen, serum osmolar gap) Serum levels of measurable drugs (eg, lithium, valproic acid, phenytoin)
Imaging	Electrocardiogram (EKG) (in patients with cardiac history or on medications known to affect cardiac conduction) Chest x-ray Computed tomography (CT) scan of head (to explain acutely altered mental status)

*Testing should generally be targeted to the individual patient and performed where clinically indicated, not as part of a routine screening panel.
From Parmar P, et al: Value of mandatory screening studies in emergency department patients cleared for psychiatric admission. West J Emerg Med 13:388–393, 2012.

cause (see Chapter 100). The clinician should identify medical conditions requiring acute treatment in the ED or near-future and note incidental findings requiring further outpatient management or conditions that may affect psychiatric care.

Routine, non-targeted diagnostic testing of all suicidal patients (eg, mandatory laboratory or radiographic studies) is not necessary and has not demonstrated any clinical benefit.[54-56] Across several studies in both children and adults, less than 1% of patients had their disposition changed through use of testing thought to be unnecessary by the emergency clinician.[54] Targeted diagnostic testing should be based on clinical grounds (Table 105.3). However, local practices vary and some mental health facilities may require routine baseline testing.

MANAGEMENT

Care of potentially suicidal patients requires an empathetic and patient-centered approach. Patients feel more comfortable discussing personal issues when health care personnel are friendly, nonjudgmental, and supportive.[57] Providers can improve the ED experience by explaining to patients what to expect from the evaluation (eg, estimated length of wait) and attending to basic comforts (eg, food, blankets, or television).[57] Trained peer specialists, when available, can also act as advocates for patients and families and may improve the experience.[57,58] The use of a patient-centered approach can also enhance patient satisfaction and the likelihood of follow-up.[59] Unfortunately, ED staff may be unsympathetic toward patients who attempt suicide, often because of personal beliefs or because of inadequate training, time or personnel to provide appropriate psychiatric evaluation.[60] They may perceive the patient's behavior as abusive or manipulative and may become frustrated with ineffective disposition and follow-up options. Failure to anticipate and overcome these factors can result in inadequate patient assessment and reinforce these patients' already low self-esteem.

The first priority in managing patients is to complete a focused medical assessment to identify and treat associated medical conditions that may underlie a patient's altered mental status or suicidal behavior. The presence of a do-not-resuscitate order in a patient with a suicide attempt raises ethical and legal dilemmas, given the debate over whether the suicide attempt resulted from a "rational" decision. Policies vary among states, and there are unfortunately no definitive guidelines for emergency care providers.[61] When possible, consultation with an ethics consultant or committee or legal representation from the hospital can be helpful, but in time-sensitive conditions (eg, respiratory depression) the physician should err on the side of resuscitation. Patients with significant injury, poisoning, or other acute medical problems should be hospitalized so that their medical problems can be treated as they remain under constant observation for suicide risk and later receive the appropriate psychiatric evaluation.

Suicide Precautions

The ED should ensure the patient's safety and prevent suicide attempts or self-harm within the department.[62] No suicidal patient should be allowed to leave before an evaluation is completed.[63] Suicidal patients who are calm and cooperative should be placed in an area where they can be safely observed by staff. Having a dedicated "sitter" or security guard to watch the patient reduces the need for restraints.[63] Visiting family or friends can offer support to the patient, but they should not be used as sitters because they might not intervene if the patient attempts to leave. The use of "wander alert" bracelets, which set off an alarm if the patient crosses an established threshold, may help in monitoring.

Early in the ED stay, security or ED personnel should search suicidal patients for possible weapons, medications, and other possessions that might be used to inflict injury (eg, belts, neckties, and long shoelaces); having the patient change into a gown can facilitate this process.[62] In a recent root cause analysis of 10 years of suicides and suicide attempts within Veterans Affairs hospitals or EDs, the most frequent methods were cutting (most commonly with a razor blade), hanging (most commonly from a door), and strangulation.[63] The patient's room should also be cleared of all potentially harmful objects, including medications, instruments, and glass objects. Having an official ED protocol concerning these processes is useful both to ensure patient safety and to demonstrate to patients that these are standard procedures.[63]

Use of Restraints

Mechanical and chemical restraint use is based primarily on the clinician's judgment of the immediate risk of patient self-harm, harm to staff, or patient elopement. The clinician should first attempt other methods of de-escalation to calm agitated patients, because restraints have potential downsides. Mechanical restraints can impair rapport, be traumatic, and contribute to a depressed patient's diminished self-esteem; chemical restraints may make subsequent psychiatric evaluation more difficult in the short term. Nevertheless, restraints may be essential and even lifesaving for uncooperative, violent, or psychotic patients. The Joint Commission and state and federal governments have stringent requirements for the use of restraints, and every ED should have a policy that conforms to these guidelines and includes a consistently-used restraint flow sheet. A timed and dated physician order and

frequent rechecks are required for all patients placed in restraints, including those in seclusion with a security watch.

Pharmacologic Treatments

There are no generally accepted or evidence-based protocols for drug treatment of suicidal thoughts in the ED. Antidepressants, lithium, and antipsychotics have been given to suicidal patients, but these are usually prescribed by psychiatrists and their effects occur over many weeks. ED pharmacology is usually directed to the treatment of agitation as needed, with use of a benzodiazepine or short-acting antipsychotic, such as haloperidol or olanzapine (see Chapter 189).

Risk Assessment

The central goals of suicide risk assessment are to identify appropriate treatment and intervention and to inform decision making about disposition (including possible psychiatric hospitalization). The likelihood of an impending suicide attempt will drive disposition: psychiatric hospitalization, emergency psychiatric consultation, or discharge with outpatient follow-up. Many suicidal patients will require a mental health consultation to assist with the process, but patients at low risk of suicide can be managed by the emergency clinician and discharged home without a formal mental health consultation. Thus, analogous to the evaluation of chest pain and other physical complaints, the emergency clinician's role is to estimate risk, provide brief interventions, and consult specialists as indicated.

All suicide risk assessments should be performed when the patient is sober. Intoxicated patients who endorse suicidal thoughts may still be at risk even if they disavow these feelings when sober. Risk assessments should also include information from "collaterals," such as a family member or friend, because patients may give false or incomplete information.[64] Such contacts should be made with the consent of the patient if possible. However, the clinician may make such contact without consent in cases when disclosure of protected health information is required to prevent or mitigate an imminent, serious safety threat to an individual or the public.[1]

A suicide risk assessment should consider the potential lethality of the method chosen. In particular, a plan to use a highly lethal method (like a firearm) should raise concern. However, patients may be at high risk for suicide if they believe the chosen method is likely to be lethal, even if this is unlikely from a medical standpoint (eg, ingestion of ibuprofen). Patients who plan and hide their suicide attempt may also be at higher risk of death than those who make an attempt in front of a family member or who seek medical attention. In depressed patients, an intense sense of desperation is an important predictor of suicide. Another important consideration involves the patient's wish to live versus their wish to die; those patients with a wish to die are six times more likely to die by suicide.

A practical, step-wise approach to suicide risk assessment (Fig. 105.2) consists of brief and comprehensive steps. *Brief risk assessment* typically involves a short set of questions and is performed by the ED provider. No single psychological test can accurately predict suicide attempts, and most predictive scales are not designed for or suitable for use in the ED.[65-68] One option is the short version of the Columbia-Suicide Severity Rating Scale, which is available for free in English and Spanish with suggested cut-points for referral and consultation.[69] Another option is a new Decision Support Tool (Table 105.4; see Fig. 105.2), which was developed through expert consensus and identifies low risk patients who might be discharged home without psychiatric consultation.[59] A "yes" answer to any of the Decision Support Tool's six questions suggests the patient needs a comprehensive suicide risk assessment and consultation with a mental health specialist, if available.

A *comprehensive risk assessment* involves more detailed questions about a patient's various suicide risk and protective factors and is most often performed by a mental health consultant; however, the emergency clinician still should make an independent judgment about the patient's suicide risk. In cases where psychiatric consultation is not possible, the physician can complete a comprehensive suicide risk assessment assisted by the Suicide Assessment Five-step Evaluation and Triage (SAFE-T; Fig. 105.3) tool. The SAFE-T, which is available as a pocket card or smartphone application, guides the physician first in assessing a patient's risk and protective factors and the specifics of suicidal

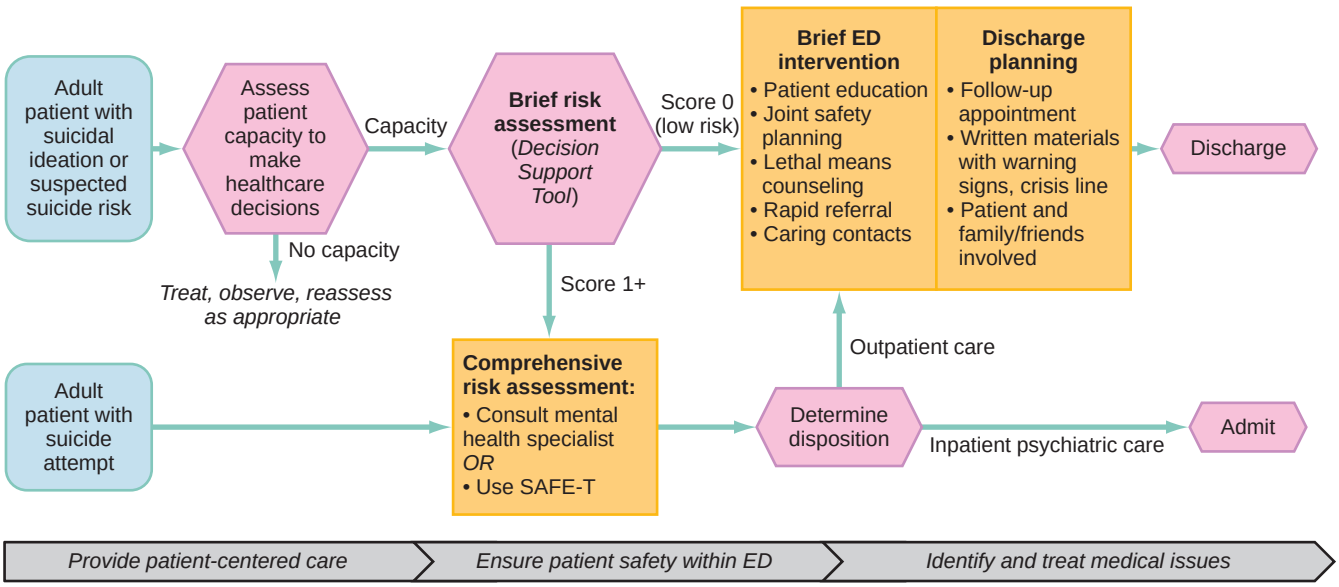

Fig. 105.2. Framework for using the decision support tool and emergency department (ED)-based suicide prevention interventions. (Adapted from Capoccia L, Labre M: Caring for adult patients with suicide risk: a consensus-based guide for emergency departments. Waltham, MA, 2015, Education Development Center, Inc., Suicide Resource Prevention Center.)

TABLE 105.4

Decision Support Tool

Transition question:

Affirm suicidal ideation	Have you had recent thoughts of killing yourself? Is there other evidence of suicidal thoughts, such as reports from family or friends?
1. Thoughts of carrying out a plan	Recently, have you been thinking about how you might kill yourself? *If yes, assess the immediate supervision needs of the patient.*
2. Suicide intent	Do you have any intention of killing yourself?
3. Past suicide attempt	Have you ever tried to kill yourself?
4. Significant mental health conditions	Have you had treatment for emotional problems? Do you have a mental health issue that affects your ability to do things in life?
5. Substance use problems	Has drinking or drug use ever been a problem for you? Or, administer CAGE or another standardized substance use disorder screener.
6. Irritability/ agitation/ aggression	Recently, have you felt so anxious or agitated that you could just jump out of your skin? Have you been having conflicts or getting into fights with other people?

Scoring: ≥1 positive response suggests need for full suicide risk assessment and emergent consultation with a mental health professional (if available); see Fig. 105.2.

From Capoccia L, Labre M: Caring for adult patients with suicide risk: a consensus-based guide for emergency departments. Waltham, MA: 2015, Education Development Center, Inc., Suicide Resource Prevention Center.

thoughts or plans and then combines these factors to estimate a level of risk.[70,71] Some patients may prefer computer-mediated (eg, web-based) assessments to discussing sensitive topics with a stranger.[72]

Ultimately, suicide risk assessment remains a highly individualized process integrating information about the crisis that precipitated the suicide event, the patient's current emotional state and prior mental health history, and the presence or absence of a safe and supportive home environment. The crises that precipitate suicide attempts are often time limited, usually lasting a few hours to a few days. If a crisis has passed or can be adequately addressed, the risk of subsequent suicide is substantially diminished. Hospitalization or emergency psychiatric evaluation should be strongly considered when a patient cannot or will not participate in an evaluation of the current crisis or when the problem is unlikely to be resolved. Tools like the Decision Support Tool or SAFE-T can inform, reinforce, and justify the provider's decision.

Documentation

Documentation is important due to the variable nature of suicide risk, the low rates of follow-up with outpatient care, and the difficulty of predicting imminent risk. It is especially important when restraints are necessary and when patients are either hospitalized involuntarily or discharged. Any use of restraints should be compliant with regulatory guidelines and be documented with a timed physician order, reevaluations, and a nursing flow sheet. If a patient requires involuntary hospitalization, providers should document why the patient is a danger to self or others. If the patient is discharged, the record should reflect the decision-making as to why the patient is estimated to be at low risk of imminent self-harm, including description of the home situation (eg, lack of potentially lethal methods of suicide), information from collateral sources, and the follow-up plan.[64]

DISPOSITION

Psychiatric Hospitalization

Following principles of empathetic, patient-centered, collaborative care, voluntary hospitalization is preferable to involuntary hospitalization. The efficacy of hospitalization as a long-term preventive measure is controversial, and a rapid referral to outpatient care is often preferable when feasible and appropriate. Hospitalization is not proven to prevent future suicide and may even precipitate adverse psychiatric consequences (eg, increased feelings of hopelessness and dependency). Still, despite the lack of hard data, hospitalization remains a primary intervention when patients are deemed acutely suicidal. Effective inpatient (and outpatient) therapeutic approaches include dialectical behavioral therapy, cognitive behavioral therapy, and Collaborative Assessment and Management of Suicidality (CAMS).[73,74]

Civil commitment statutes differ among the 50 states and the District of Columbia. Most states have "emergency commitment" provisions that typically require the patient (1) has mental illness and (2) poses a threat to self or others.[75] The length of emergency commitments vary by state, from 72 hours to 15 days.[75] In some states, patients who agree to hospitalization may still need involuntary commitment papers completed for transport to a receiving psychiatric facility; this is to provide the legal basis for holding them if they change their mind during the trip.

Discharge

Many patients who report suicidal thoughts or have symptoms of depression can be safely managed as outpatients if the risk of subsequent suicide is judged to be acceptably low. Although the clinician can make this determination in many cases (see Figs. 105.1 and 105.2), evaluation by a mental health professional can be useful if the safety of outpatient management is in doubt, and nurses also play an important role in discharge planning.[76] A family member or friend should agree to stay with—or be immediately available to—the discharged patient until follow-up is provided. The patient should be discharged to a stable and supportive home environment without access to guns or lethal medications. The discharge planning process should ideally include at least one of the following: brief patient education, joint safety planning, lethal means restriction counseling, referral for outpatient care, and "caring contacts."[59,77]

Brief patient education for suicide prevention should include the use of verbal and written information and "teach back" techniques whereby the patient explains the information back to the provider.[76] Information can include a personalized list of risk and protective factors, home care, follow-up, and warning signs that should trigger a call for help. The education process should engage the patient in an empathetic and respectful manner and should, with patient consent, include family members or close friends.[57] Educational materials are available from a number of national organizations.[78,79]

In *joint safety planning,* a provider works with a patient to develop a plan regarding what to do should symptoms worsen (Table 105.5). The plan should be in the patient's own words and easy to understand, and it should include warning signs, a list of coping strategies, and resources such as hotlines or contact information for trusted family or friends.[80] The National Suicide Prevention Hotline (1-800-273-TALK [8255]) should be given to all discharged patients; this national toll-free telephone and online

1. Identify risk factors

- **Suicidal behavior**: prior suicide attempts or self-injurious behavior
- **Current/past psychiatric disorders**: especially mood disorders, psychotic disorders, alcohol/substance abuse, ADHD, TBI, PTSD, Cluster B personality disorders, conduct disorders (antisocial behavior, aggression, impulsivity)
- **Key symptoms**: anhedonia, impulsivity, hopelessness, anxiety/panic, insomnia, command hallucinations
- **Family history**: of suicide, attempts or Axis 1 psychiatric disorders requiring hospitalization
- **Precipitants/Stressors/Interpersonal**: triggering events leading to humiliation, shame or despair (eg, loss of relationship, financial or health status—real or anticipated); ongoing medical illness (esp. CNS disorders, pain); intoxication; family turmoil/chaos; history of physical or sexual abuse; social isolation
- **Change in treatment**: discharge from psychiatric hospital, provider or treatment change
- **Access to firearms**

2. Identify protective factors

- **Internal**: ability to cope with stress, religious beliefs, frustration tolerance
- **External**: responsibility to children/pets, positive therapeutic relationships, social supports

3. Conduct suicide inquiry

- **Ideation**: frequency, intensity, duration–in last 48 hours, past month, and worst ever
- **Plan**: timing, location, lethality, availability, preparatory acts
- **Behaviors**: past attempts, aborted attempts, rehearsals (tying noose, loading gun), vs. non-suicidal self injurious actions
- **Intent**: extent to which the patient (1) expects to carry out the plan and (2) believes the plan/act to be lethal vs. self-injurious
- **Explore** ambivalence: reasons to die vs. reasons to live

4. Determine risk level & intervention

- **Assessment** of risk level is based on clinical judgment, after completing steps 1-3

Low risk	Moderate risk	High risk
• Denial of suicidal thoughts, plan, intent • No or mild sadness or anger; no psychosis • No or 1 recent attempt with low lethality • No or limited substance use • Good support, accepting of help, hopeful for future	• Suicidal ideation, plan, intent, or attempt • Moderate depression, anger, hopelessness • Frequent ideation or threats; low lethality • Substance abuse • Moderate support, unwilling to accept help • Access to lethal means	• Frequent, intense, enduring ideation • Specific plans • High intent (eg, attempt with high lethality) • Impaired self-control, severe dysphoria, hopelessness, worthlessness • Poor corroborative history • Many risk factors, refusing help

5. Document

- Risk level and rationale; treatment plan to address/reduce current risk (eg, setting, medication, psychotherapy, ECT, contact with significant others, consultation); firearm instructions, if relevant; follow up plan
- For youths, treatment plan should include roles for parent/guardian

Fig. 105.3. Suicide assessment five-step evaluation and triage. (Modified from Davidson CL, Olson-Madden JH, Betz ME, et al: Emergency department identification, assessment, and management of the suicidal patient. In Koslow SH, Ruiz P, Nemeroff CB, editors: A concise guide to understanding suicide. United Kingdom, 2014, Cambridge University Press, pp 244–255; Suicide Assessment Five-Step Evaluation and Triage [SAFE-T]. Substance Abuse and Mental Health Services Administration. Available at http://store.samhsa.gov/product/Suicide-Assessment-Five-Step-Evaluation-and-Triage-SAFE-T-/SMA09-4432; and Substance Abuse and Mental Health Services Administration [SAMHSA]; Suicide safe: the suicide prevention app for health care providers free from SAMHSA. Available at http://store.samhsa.gov/apps/suicidesafe/.)

chat resource offers crisis guidance, connection to local resources, and services for veterans. There are also mobile safety planning applications for smartphones that allow patients to store contacts and coping strategies (eg, "MY3") and that guide providers in suicide assessment and safety planning (eg, "Suicide Safe").[81] Importantly, safety planning is not the same as a "contract for safety" or "no suicide contract." Such contracts lack evidence of effectiveness and, because they lead to a false sense of security, providers should not use them. Counseling about lethal means safety—one of only two suicide prevention approaches with a strong empirical foundation—can also be helpful. The rationale behind this approach is that (1) many suicidal crises are acute and short-lived, (2) many suicide acts are impulsive (sometimes with only minutes between the decision to act and the attempt), (3) the method chosen may be the one most readily-available, and (4) the lethality of the chosen method affects the likelihood of mortality. Numerous studies have shown a consistent association between firearm access and death by suicide, even after controlling for other risk factors.[82] Safe gun storage practices (eg, locked, unloaded, and separate from ammunition) can mitigate the risk of suicide. At a population level, firearms regulations (eg, waiting periods, training requirements, and age or other restrictions) are associated with reduced rates of firearm-related suicide.[83] ED counseling about lethal means safety can affect patient behavior,

TABLE 105.5

Safety Plan Components

Warning signs	Thoughts, images, mood, situation, behavior indicating that a crisis may be developing (Write list)
Internal coping strategies	Things I can do to take my mind off my problems without contacting another person (relaxation technique, physical activity) (Write list)
People and social settings that provide distraction	(Write names and phone numbers) People: Places:
People whom I can ask for help	(Write names and phone numbers)
Professionals or agencies I can contact during a crisis	Clinician names and phone numbers/pagers Local urgent care address and phone: Suicide Prevention Lifeline Phone: 1-800-273-TALK (8255)
Making the environment safe	Things I can do to make my home safer, like removing guns and toxic medications
The one thing that is most important to me and worth living for	(Write out)

Adapted from Stanley B, Brown GK: Safety planning intervention: a brief intervention to mitigate suicide risk. Cogn Behav Pract 19:256–264, 2012.

and lethal means counseling for suicidal patients is supported by multiple physician organizations and listed as a "best practice" for suicide prevention.[78,84] Clinicians should counsel suicidal patients and their families to remove guns temporarily from the home for storage off-site in an appropriate location (eg, a gun shop, police department, or with a family member if legal under state law); gun locks or cabinets to which the patient has no access are an alternative.

Discharged patients should also be *referred for outpatient care,* ideally within 72 hours because suicide risk remains high shortly after discharge from the ED.[85] Evidence-based outpatient treatment can reduce future suicide risk, and emergency clinicians play a key role in linking patients to care.[73] A significant number of discharged ED patients do not keep their follow-up appointments, but compliance with follow-up may be increased by making a specific appointment for patients. Having the family or friends help ensure that the patient keeps the follow-up appointment is another strategy. In addition, it may be helpful to provide physician contact information or to provide a list of community mental health resources. With the patient's consent, the physician can send visit information to the patient's primary care provider or outpatient referral provider to enhance continuity of care.

Another possible intervention for discharged patients is *caring contacts,* or brief communications after discharge.[59,86,87] These empirically-supported interventions take a variety of forms, including text messages, emails, phone calls, and postcards, and they may be one- or two-directional. An automated system, supported by the electronic health record, can facilitate the process, or the contacts can be made by a clinical or non-clinical ED staff member.

KEY CONCEPTS

- Suicide is a common—but preventable—cause of death.
- Suicidal thoughts or behaviors are often triggered by a treatable or reversible short-term crisis, and most attempt survivors are grateful to be alive.
- Suicide risk changes over time, and estimation of imminent risk is not evidence based at this time.
- Routine "screening" laboratories provide little value for most ED patients with self-harm behaviors. Evaluation should be directed at specific concerning signs or symptoms.
- Many suicidal individuals see a physician shortly before their death. An ED visit for suicidal thoughts or behaviors represents a crisis and a teachable moment.
- An empathetic, patient-centered, collaborative approach that incorporates information from collateral sources (eg, family) can optimize care.
- Suicide precautions in the ED include appropriate use of "sitters" and, when necessary, physical and chemical restraints and involuntary commitment.
- Brief risk assessment by the emergency clinician can identify patients in need of a comprehensive evaluation and consultation with a mental health specialist (if available).
- Patients at low risk of suicide may be discharged home to a safe and supportive environment without access to guns or toxic medications.
- Discharged patients should receive education and safety planning in the ED and should have early mental health follow-up appointment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 105: QUESTIONS & ANSWERS

105.1. Which of the following statements about suicide is true?
- **A.** Many suicide attempts occur during an acute crisis.
- **B.** Suicide rates are highest in older men.
- **C.** Suicidal behavior may be chronic.
- **D.** Suicidal patients are usually ambivalent about dying.
- **E.** All of the above are true.

Answer: E. Many suicide attempts occur in response to a crisis that may be time limited or resolvable. Suicide rates are particularly high in older white men. With the exception of psychotic patients, suicidal patients are usually ambivalent about dying. An example of chronic suicidal behavior is drinking in the face of liver disease.

105.2. Which of the following statements about suicide is true?
- **A.** Blacks attempt suicide more than whites.
- **B.** Men attempt suicide more than women.
- **C.** Marriage decreases the likelihood of suicide.
- **D.** Pregnancy increases the risk of suicide.
- **E.** Suicide rates are highest among female teens.

Answer: C. Marriage and pregnancy/motherhood decrease suicide risk. Whites attempt suicide more than blacks, with the highest rate among older white men. Women attempt suicide far more often than men but do not choose lethal means and therefore have a lower success rate.

105.3. Which of the following is a risk factor for suicide?
- **A.** Prior suicide attempt
- **B.** Access to firearms
- **C.** Alcohol abuse
- **D.** Veteran status
- **E.** All of the above

Answer: E. Additional suicide risk factors include, but are not limited to: adolescence and older age; male gender; certain races/ethnicities (White, American Indian, Alaskan Native); mental disorders; substance abuse; prior suicide attempt; psychosocial stressors (eg, recent psychiatric hospital discharge, history of trauma or abuse, terminal illness, chronic pain, hopelessness, impulsiveness); environmental stressors (eg, job loss, bereavement); and sociocultural factors (eg, isolation, poor access to mental health care, stigma against seeking help, or media exposure to suicide).

105.4. Most completed suicides involve which of the following?
- **A.** Falls
- **B.** Firearms
- **C.** Piercing
- **D.** Poisonings
- **E.** Suffocation

Answer: B. Fifty percent of completed suicides involve firearms. Seventy percent of attempted suicides involve poisoning.

105.5. Discharge planning for suicidal patients should include which of these elements?
- **A.** Counseling about reducing access to guns and toxic medications.
- **B.** Involvement of family or friends.
- **C.** Rapid referral to outpatient mental health.
- **D.** Written materials with warning signs and hotline numbers.
- **E.** All of the above.

Answer: E. All of the listed elements are recommended components of ED care and discharge planning for patients evaluated for suicidal thoughts or behaviors but deemed safe for discharge home.

105.6. A 33-year-old Caucasian man presents with agitation and suicidal ideation. He has a long history of schizophrenia and is currently taking olanzapine and occasional clonazepam. He was hospitalized 3 weeks prior for an accelerated psychotic episode and released on an increased dose of olanzapine. His family brought him here today after visiting him in his apartment and finding him in a room with all the lights off. They note he has been unable to work for more than 2 years. He was formerly employed as an engineer. Your examination is remarkable for a blunted affect, moderate pressured speech, and a depressed mood. What is the most appropriate intervention?
- **A.** Addition of sertraline to olanzapine, 2-day follow-up
- **B.** Admission to psychiatry unit
- **C.** Increase olanzapine, release with family

D. Overnight emergency department (ED) observation, 2-day psychiatry follow-up
E. Parenteral ziprasidone, release with family

Answer: B. Approximately 10% of schizophrenic patients will kill themselves. Psychotic patients who kill themselves are often unmarried whites of high intelligence. A recent psychiatric hospitalization is a suicide risk factor, particularly during the first month post discharge. This patient is high risk and needs admission.

105.7. Which of the following statements concerning risk assessment of suicidal patients is true?
A. An empathetic approach will reinforce malingering behavior and subsequent ED visits.
B. For patients at low risk of imminent suicide, providers can consider discharge without formal consultation with a mental health professional.
C. Intoxicated patients who, once sober, disavow prior suicidal statements do not need a suicide risk assessment.
D. Routine screening labs should include serum chemistries and urine toxicologic panels.
E. Suicidal patients can be permitted to leave the ED prior to a risk assessment as long as they sign "Against Medical Advice" paperwork.

Answer: C. In a step-wise manner, the ED provider can complete a brief risk assessment to identify which patients do (or do not) require a comprehensive evaluation with a mental health professional. Diagnostic testing should be targeted to individual patients as clinical indicated. An empathetic approach can enhance patient evaluation and care and should be used with all suicidal patients. Acute and chronic alcohol use are both suicide risk factors; even if a patient denies suicidality once sober, a risk assessment may be prudent. No suicidal patient should be allowed to leave the ED before the risk assessment is complete.

105.8. Which of the following statements about involuntary commitment is true?
A. It is not associated with adverse psychiatric consequences.
B. It lowers the rate of future suicides.
C. Most states mandate attempts at involuntary commitment if there is imminent self-harm.
D. Patients who volunteer for admission may still need commitment papers.
E. Statutes are consistent among the states.

Answer: D. Statutes vary widely among the states. Some states require commitment papers even in cases of voluntary admission. Only two states mandate commitment in the face of suspected imminent self-harm. Involuntary commitment does not lower the rate of future suicides and is associated with adverse psychiatric consequences.

SECTION NINE
Immunologic and Inflammatory

CHAPTER 106
Arthritis

Nicholas Genes

PRINCIPLES

Background

Arthritis and its related disease states represent the most common cause of disability in the United States.[1] Because of the pain and limitations associated with joint inflammation, patients with complaints stemming from arthritis present frequently for emergent evaluation. Many of the arthritides are associated with premature mortality, and their treatments are associated with adverse effects. The inflamed joint may be a diagnostic clue to a serious systemic illness, and unmasking of true arthritis emergencies can prevent or attenuate devastating disability.

Arthritis and related conditions are among the oldest disease states described. Roman, Greek, and Egyptian cultures made reference to gout and rheumatoid arthritis and even associated these maladies with diet and socioeconomic status. Many celebrated figures in medicine, such as Hippocrates, Galen, and Sydenham, contributed to the description, classification, and treatment of rheumatic disorders.[2] Reiter's syndrome, however, takes its name from a discredited Nazi war criminal. Many, including the physician who first bestowed the eponym in the English literature in 1942, Ephraim Engleman, advocate for the generic term *reactive arthritis*.

Pathophysiology

As opposed to synarthrotic suture joints of the skull and amphiarthrotic fibrocartilage unions like the pubic symphysis, the joints of concern in acute arthritis are the synovial or diarthrotic (moving) joints. These synovial joints are composed of two ends of subchondral bone covered by articular cartilage, surrounded by a capsule that is lined with a thin synovial membrane and supported by ligaments, tendons, and muscle (Fig. 106.1A).

Articular cartilage is an avascular, aneural tissue composed of a matrix of collagen fibers and proteoglycans synthesized by chondrocytes. The properties of articular cartilage allow tremendous load bearing. Together with the viscous lubricating synovial fluid, an ultrafiltrate of blood supplemented with hyaluronic acid and low-molecular-weight proteins, the cartilage that articulates joint movement is nearly frictionless.

Whereas disease-specific changes receive further detail in subsequent sections, the final common pathway of arthritis is triggered by trauma, infection, or the endogenous cell and humoral inflammation stimulated by infection or autoimmune disease.

The pathologic process of arthritis can unfold during hours or years. Tissue destruction can be mediated by fast-acting catabolic pathways, or long-term changes to the composition of cartilage's extracellular matrix may be brought on by abnormal loading patterns or trauma. The synovium plays a critical role in crystal deposition and inflammatory response (see Fig. 106.1B).

CLINICAL FEATURES

History

Patients with joint problems who come to the emergency department (ED) typically complain of pain, although the distribution and chronicity can vary markedly. In addition to eliciting a history and associated symptoms, the clinician should determine whether the source of the inflammation or pain is articular or periarticular (outside the joint capsule).

True arthritis produces generalized joint pain, warmth, swelling, and tenderness. Discomfort increases with both passive and active motion of the joint because the inflamed synovium is exquisitely sensitive to stretching, and because all parts of the joint are involved in the inflammatory process. By contrast, periarticular inflammation (bursitis, tendinitis, or localized cellulitis) tends to be more focal.

If the site of the patient's pain is articular, classifying whether the arthritis is monarticular (eg, septic arthritis or gout) or polyarticular may aid in diagnosis. Polyarticular arthritis may be symmetrical (eg, rheumatoid or drug-induced) or asymmetrical (eg, rubella, acute rheumatic fever [ARF], Lyme disease, or gonococcal arthritis). In addition, it may also be migratory (eg, gonococcal or rubella), subsiding in one area before presenting in another, or additive, remaining in the first joint and progressing to additional joints (Table 106.1).

The distribution of joint involvement may give clues to the disease: the first metatarsophalangeal (MTP) joint is classically affected in gout; the metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints in rheumatoid arthritis; and the distal interphalangeal (DIP) joints and the first carpometacarpal joint in osteoarthritis. Patients with inflammatory arthritis may have low-grade fever; high fever with chills is more suggestive of a septic arthritis. Morning stiffness (synovial gel phenomenon) and improvement of symptoms with activity suggest inflammatory arthritis, whereas improvement with rest suggests mechanical disorders. Concomitant renal stones suggest gout, genital ulcerations occur in Behçet's disease and reactive arthritis, and a purulent urethral discharge suggests gonococcal arthritis or reactive arthritis. The use of isoniazid, procainamide, and hydralazine can precipitate lupus, and thiazides can increase the serum uric acid level, leading to gouty arthritis.

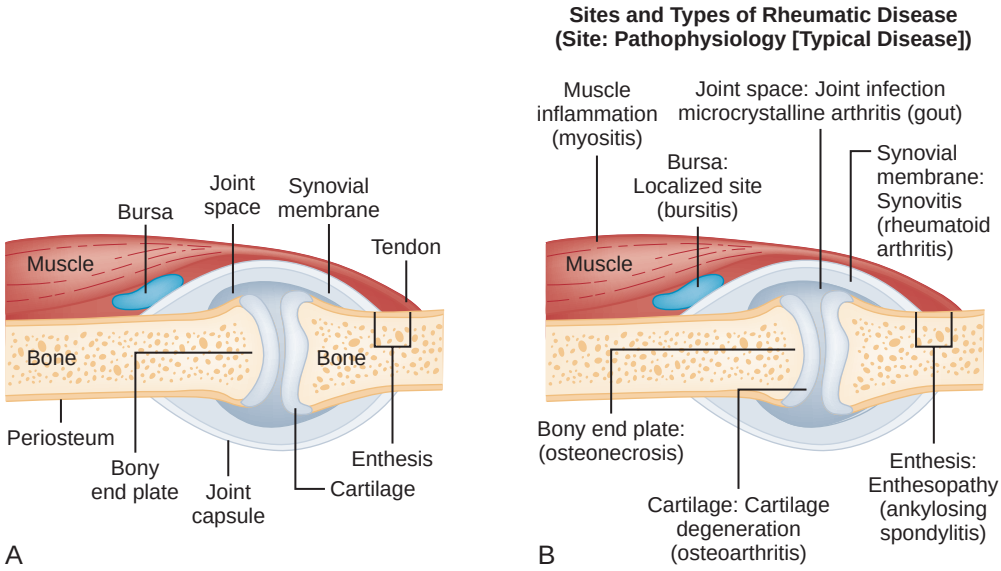

Fig. 106.1. A and **B,** Anatomic structures of the joint with location of selected arthritis diseases. (Redrawn from Goldman L, Ausiello DA, editors: Cecil medicine, ed 23, Philadelphia, 2008, Saunders/Elsevier.)

TABLE 106.1

Differential Diagnosis of Arthritis in the Emergency Department, Based on Typical Distributions

MONOARTICULAR	POLYARTICULAR: SYMMETRICAL	POLYARTICULAR: ASSYMMETRICAL
Septic arthritis	Rheumatoid arthritis flare	Gonococcal arthritis
Gout	Psoriatic arthritis	Lyme arthritis
CPPD/pseudogout	Polymyalgia rheumatica	ARF
Osteoarthritis	Enteric arthritis	Reactive arthritis
Trauma, hemarthrosis	Ankylosing spondylitis	Viral arthritides

ARF, Acute rheumatic fever; *CPPD,* calcium pyrophosphate dihydrate deposition disease.

TABLE 106.2

Systemic Signs of Arthritis Diseases*

ORGAN SYSTEM	FINDINGS	DISEASES
Airway	Airway obstruction	Rheumatoid arthritis, relapsing polychondritis
Cardiac	Pericarditis Murmurs	Rheumatoid arthritis, ARF ARF, relapsing polychondritis, ankylosing spondylitis
Eyes	Iritis, uveitis Conjunctivitis	Spondyloarthropathies Reactive arthritis
Gastrointestinal	IBD Dysentery	Spondyloarthropathies Reactive arthritis
Genitalia	Lesions, urethral discharge	Reactive arthritis, gonococcemia
Hematologic	Aplastic anemia Anemia of chronic disease	Parvovirus Any chronic arthritis disease
Neurologic	Cauda equina syndrome Cervical spine instability	Ankylosing spondylitis Ankylosing spondylitis, rheumatoid arthritis, osteoarthritis
Oral mucosa	Ulcerations	Reactive arthritis
Pulmonary	Pleuritis, nodules	Rheumatoid arthritis
Renal	Renal crisis, ARF	Scleroderma
Skin	Plaques on elbows, knees Sclerodactyly, calcinosis Erythema chronicum migrans Tophi Erythema marginatum Subcutaneous nodules	Psoriasis Scleroderma Lyme disease Gout Rheumatic fever Rheumatoid arthritis

*Excludes rheumatic vasculitis diseases.
ARF, Acute rheumatic fever; *IBD,* inflammatory bowel disease.

Physical Examination

General Examination

The physical examination searches for evidence of both local and systemic manifestations of rheumatic diseases (Table 106.2).

Joints

Joints are examined for warmth effusion, synovial thickening, deformity, range of motion, pain on actively loaded motion, and tenderness (generalized or localized, articular or periarticular). Localized tenderness and pain associated with active movement are more likely to be periarticular in origin. Generalized tenderness and pain, both at rest and with active and passive motion, suggest joint involvement.

Spine

The spine evaluation is best performed with the patient standing; the vertebral column is assessed for abnormal curvature or asymmetry. Although supporting evidence is scant, Schober's maneuver

is used to assess for the limitation of the lumbar spine motion that occurs in ankylosing spondylitis (in a healthy standing patient, the 15 cm line that begins 5 cm below L5 and runs to 10 cm above L5 should lengthen to 20 cm or more when the patient bends to touch the ground).[3]

Upper Extremities

A shoulder affected by chronic arthritis or bursitis will have atrophy of the deltoid muscle. Early signs of joint inflammation in the elbow are limitation of extension and an increase in the normal angle at which the patient holds the elbow at the side. Assessment of the wrist is difficult because it may not be obviously swollen. Discomfort and decreased range of motion, particularly on extension, may indicate synovial involvement.

The hand and wrist provide many clues to the presence of long-standing rheumatic diseases: MCP and PIP joints are affected in rheumatoid arthritis; and the first carpometacarpal, PIP, and DIP joints are affected in osteoarthritis. The fingers may be swollen or sausage-like in appearance, an indication of psoriasis or reactive arthritis. Subluxation at the MCP joints, ulnar deviation, and swan-neck deformities occur in rheumatoid arthritis. The nails may have pitting characteristic of psoriatic arthritis.

Lower Extremities

Inflammation affecting the hip joint can be manifested as pain in the anterior thigh, knee, or groin. A hip joint effusion will cause the patient to hold the hip partially flexed. An externally rotated and abducted leg in pediatric patients strongly suggests infection, as opposed to transient synovitis or Legg-Calvé-Perthes disease.[4]

An effusion of the knee joint is relatively easy to detect when it appears as a ballotable fullness medially and laterally. Fullness of the popliteal fossa may indicate Baker's cyst. Passive range of motion may elicit crepitus (suggestive of degenerative joint disease) or clicking (suggesting a meniscal tear). Tibiotalar joint effusions produce swelling under the medial malleolus and make it difficult to palpate the extensor hallucis longus tendon. Tenderness, warmth, and swelling of the great toe MTP joint occur in cases of gout but can also occur with osteoarthritis and rheumatoid arthritis. Sausage-like swellings of the toes are seen in reactive arthritis.

DIAGNOSTIC TESTING

Laboratory Tests

Laboratory testing conveys only modest diagnostic value in the ED evaluation of arthritis. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, white blood cell (WBC) count, and serum uric acid level are best used in the context of evaluating the likelihood of specific forms of arthritis; no guidelines or studies exist supporting the use of blood testing as a general screen of acute undifferentiated arthritis in the ED.

Radiologic Tests

Plain Radiography

Plain radiographs are more helpful in patients with chronic disease than in those with acute arthritis. Common findings that help distinguish the different forms of arthritis are shown in Table 106.3. For lower extremities, weight-bearing radiographs can better evaluate joint space narrowing.

TABLE 106.3

Common Radiologic Findings in Arthritis

ARTHRITIS	FINDINGS
Acute arthritis (gout, pseudogout, septic arthritis)	Soft tissue swelling
Late septic arthritis (need at least 8 to 10 days for changes to be seen)	Subchondral bone destruction Periosteal new bone Loss of joint space Osteoporosis Late joint space narrowing
Late pseudogout (knee, hip; radiocarpal, midcarpal, all MCP joints)	Linear calcification in cartilage Asymmetrical joint space narrowing MCP "hook spurs" in HHC Osteophyte formation Subchondral cyst formation Lack of osteoporosis
Degenerative arthritis (acromioclavicular, first carpometacarpal, first MTP, DIP joints; knee, hip, cervical spine, lumbosacral spine)	Asymmetrical joint space narrowing Sclerosis of juxta-articular bone Bone spurs and cysts—adjacent to severe cartilage degeneration No osteoporosis
Tuberculous arthritis (knee, hip, shoulder)	Soft tissue swelling Marked demineralization Bone rarefaction Little reactive sclerosis Late bone destruction Joint space preserved
Late rheumatoid arthritis (wrist, MCP, PIP, MTP, first IP joints; foot, atlantoaxial joint, glenohumeral joint)	Symmetrical joint space narrowing Osteoporosis of periarticular bone Marginal erosions (no overhanging margins as in gout) Little reactive bone formation

DIP, Distal interphalangeal; *HHC,* hereditary hemochromatosis; *IP,* interphalangeal; *MCP,* metacarpophalangeal; *MTP,* metatarsophalangeal; *PIP,* proximal interphalangeal.

Computed Tomography, Magnetic Resonance Imaging, and Sonography

Other radiologic modalities are occasionally performed as part of the evaluation of arthritis in an emergency setting. Ultrasonography compares favorably with plain radiography in the evaluation of joint effusions and synovitis associated with rheumatoid arthritis, and it is useful to evaluate pediatric hip effusion and to guide arthrocentesis.[5] Magnetic resonance imaging (MRI) is well suited for imaging of cruciate ligaments of the knee, detection of early edema in periarticular structures and fluid collection in tendon sheaths, and determination of the extent of cartilage destruction. MRI is also the study of choice for diagnosis of osteonecrosis and is more sensitive than plain radiography for early osteomyelitis.[6]

Arthrocentesis

Arthrocentesis is a crucial diagnostic modality for the diagnosis of septic arthritis or crystal-induced joint disease.

Indications and Contraindications. The emergency indications for arthrocentesis in the evaluation of joint pain are to obtain joint fluid for analysis, to drain tense hemarthroses in patients with trauma or hemophilia (of the elbows, knees, or ankles and after the appropriate clotting factor replacement), to evaluate whether a laceration communicates with the joint space,

and to instill analgesics and antiinflammatory agents for the treatment of acute and chronic arthritis.

The American College of Rheumatology guidelines recommend arthrocentesis to evaluate patients with an established history of arthritis who present with fever and new joint pain or effusion. Although scant literature on inoculated joint spaces exists, emergency arthrocentesis through overlying cellulitis is relatively contraindicated, and one should avoid the infected area if possible during puncture. Coagulopathy is the other relative contraindication, but arthrocentesis was safely performed in 99.8% of patients with therapeutic international normalized ratios (INRs) in one retrospective review.[7] Arthrocentesis of prosthetic joints should be performed only to rule out infection and is best done in consultation with an orthopedic surgeon.

Complications. The primary complications of arthrocentesis are bleeding or infection in the joint space, reaction to anesthetic agents, and long-term corticosteroid-related complications. Dry taps (when no fluid is aspirated after joint puncture) are more common in patients with chronic arthritis because of obstructing tophi or anatomic abnormalities in the synovium and periarticular tissues. Use of a smaller syringe or a larger needle may help in such cases.

Technique. Successful joint aspirations begin with positioning of patients so that they are comfortable, with adequate exposure and cushioned support for the joint. Muscle tension during the procedure can reduce the joint volume, making the procedure more difficult. Carefully palpate the bone landmarks and prepare the skin with an aseptic technique. Adequate local anesthesia is achieved either by use of topical vapo-coolant or local infiltration with anesthetic solution, such as 1% or 2% lidocaine. With an 18- or 19-gauge (large joints) or 20- to 22-gauge needle (smaller joints) attached to a syringe, the joint space is punctured and aspirated with care taken to avoid abrasion of the articular cartilage. Excessive suction may bring synovial tissue into the needle, limiting aspiration. After aspiration, a long-acting anesthetic can be instilled to alleviate pain. As a general rule, do not instill steroids unless a septic arthritis has been excluded. For approaches to specific joints, see Box 106.1.

Synovial Fluid Examination. Analysis of synovial fluid is essential for identification of crystalline and suppurative causes of acute arthritis (Table 106.4).

General Appearance. Bedside inspection of synovial fluid for color, clarity, and viscosity can provide diagnostic clues. Normal synovial fluid is clear and colorless, with a viscosity that permits stretching of a "string" of fluid between the thumb and forefinger. Inflamed fluid is more opaque from an elevated WBC count, with a viscosity more like water because of enzymatic breakdown of glycosaminoglycans. Hemarthrosis is manifested after acute trauma or in the presence of coagulopathy, particularly with hemophilia. Lipohemarthrosis indicates ligamentous injury or an intra-articular fracture, and brownish synovial fluid may suggest the rare diagnosis of pigmented villonodular synovitis.

Synovial Fluid Studies. Routine laboratory analysis includes a cell count with differential, Gram stain, and crystal analysis; synovial glucose and protein concentrations are of little diagnostic

BOX 106.1

Arthrocentesis Techniques for Common Joints

WRIST: RADIOCARPAL JOINT (DORSAL APPROACH)

1. Identify landmarks by palpating the Lister tubercle at the distal end of the dorsal radius.
2. Palpate the extensor pollicis longus tendon, which passes over the radial side of the Lister tubercle (best palpated while the wrist is in extension). You will insert the needle on the ulnar side of the extensor pollicis longus tendon, just distal to the Lister tubercle.
3. Lay the wrist on a cushion so that it is flexed 20 to 30 degrees.
4. Apply traction from the fingers and mild ulnar deviation, and insert a 22-gauge needle dorsally.

ELBOW: RADIOHUMERAL JOINT (LATERAL APPROACH)

1. Identify landmarks by extending the elbow and then palpating the depression between the lateral epicondyle of the humerus and the head of the radius.
2. Keeping your finger on the radial head, flex the patient's elbow, pronate the forearm, and lay the palm on a flat surface.
3. Insert a 20-gauge needle just distal to the lateral epicondyle, directed medially.

SHOULDER: GLENOHUMERAL JOINT (POSTERIOR APPROACH)

1. Lay the patient's arm, internally rotated, across the waist.
2. Identify the posterolateral comer of the acromion.
3. Insert a 20-gauge needle 2 to 3 cm inferior to this point, directed anteriorly and medially (and slightly superiorly) toward the coracoid process.

HIP: ACETABULOFEMORAL JOINT (LATERAL APPROACH)

1. Lay the patient supine and internally rotate the affected leg.
2. Palpate the greater trochanter.
3. Insert a 3.5-inch 18-gauge needle superiorly to the trochanter, horizontal and parallel to the stretcher. If the femoral neck is encountered, withdraw 2 mm to 4 mm and redirect slightly cephalad until synovium is aspirated.

KNEE: PATELLOFEMORAL JOINT (MEDIAL APPROACH)

1. Flex the knee 15 to 20 degrees (often achieved with a rolled towel under the knee). The foot should be perpendicular to the floor.
2. Palpate the anteromedial patellar edge at the patellar midpoint or superior portion.
3. Insert an 18-gauge needle 1 cm medial to this point, directed toward the posterior surface of the patella.

ANKLE: TIBIOTALAR JOINT (ANTEROMEDIAL APPROACH)

1. With the patient supine, have the patient plantarflex the foot.
2. Identify the anterior tibial tendon.
3. Insert a 3.5-inch 20- or 22-gauge needle medial to this tendon in the depression at the anterior edge of the medial malleolus.

METATARSOPHALANGEAL JOINT (DORSOMEDIAL APPROACH)

1. Identify the distal metatarsal head and the proximal base of the first phalanx.
2. Identify the extensor tendon by asking the patient to extend the great toe.
3. While the patient is supine, flex the toe 15 to 20 degrees, and then apply traction.
4. Insert a 22-gauge needle dorsally just medial to the extensor tendon.

From Genes N, Chisolm-Straker M: Monoarticular arthritis update: current evidence for diagnosis and treatment in the emergency department. Emerg Med Pract 14(5):1–19, 2012.

TABLE 106.4

Typical Synovial Fluid Findings by Arthritis Type

	NON-INFLAMMATORY	INFLAMMATORY	SEPTIC	HEMORRHAGIC
Color	Clear/yellow	Yellow/white	Cloudy/opaque	Opaque, may contain fat droplets
Viscosity	Thick, stringy	Variable	Thin, watery	Variable
Synovial white blood cells	200 to 2000/mm^3 <25,000/mm^3 +LR for SA = 0.32	2000 to 50,000/mm^3 <50,000/mm^3 +LR for SA = 0.42	>25,000/mm^3 +LR for SA = 2.9 >50,000/mm^3 +LR for SA = 7.7 >100,000/mm^3 +LR for SA = 28	<2000/mm^3
Synovial polymorphonuclear cells	Variable	Variable	>90% +LR for SA = 2.7	<25%
Gram stain	Negative	Negative	29% to 65% positive	Negative
Leading diagnosis	Osteoarthritis	Gout, reactive arthritis	Bacterial arthritis	Trauma, hemophilia

LR, Likelihood ratio; *SA,* septic arthritis.
From Genes N, Chisolm-Straker M: Monoarticular arthritis update: current evidence for diagnosis and treatment in the emergency department. Emerg Med Pract 14(5):1–19, 2012.

assistance. A positive Gram stain is diagnostic, but a negative result for bacteria does not rule out septic arthritis; culture specimens should also be obtained. Blood culture bottles are more sensitive than other media at identification of pathogens.[8]

White Blood Cell Count. Synovial WBC counts are often used to differentiate classes of synovial fluid; unfortunately, significant overlap exists between inflammatory and septic causes of acute arthritis, with very high fluid cell count or polymorphonuclear (PMN) cell pleocytosis suggesting infection, but more modest cell counts failing to exclude it. The likelihood ratio (LR) for septic arthritis increases as the joint WBC count rises. According to a systemic review, a cell count of less than 25,000/mm^3 = +LR for septic arthritis of 0.32; a cell count of more than 25,000/mm^3 = LR of 2.9; a cell count of more than 50,000/mm^3 = LR of 7.7; and a cell count of more than 100,000/mm^3 = LR of 28.0.[9] However, low cell counts do occur early in infectious arthritis and in partially treated infections; high cell counts (>50,000/mm^3) can occur in rheumatoid arthritis, gout, and pseudogout. Most of the cells in both septic and severe inflammatory arthritis are PMN cells.

Crystal Analysis. Analyzing crystals of monosodium urate or calcium pyrophosphate is best performed by polarizing microscopy of a fresh drop of synovial fluid placed on a slide with cover slip; inter-rater reliability is acceptable in differentiating the two. Monosodium urate crystals are needle shaped and strongly negatively birefringent (yellow when parallel to the compensator and blue when perpendicular), ranging in size from 2 to 10 µm. Calcium pyrophosphate crystals, in contrast, are polymorphic, rhomboid, and positively (although weakly) birefringent. Lipid appears as a spherule with a Maltese cross, and hydroxyapatite is difficult to recognize.

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

Acute Monoarticular Arthritis

Inflammatory conditions of the periarticular soft tissues, such as olecranon bursitis, rotator cuff shoulder tendinitis, and prepatellar bursitis, can mimic monoarticular arthritis, and classically polyarticular conditions, such as rheumatoid arthritis and the seronegative spondyloarthropathies, may present initially in only one joint. However, acute ED presentations of monoarticular arthritis should always prompt consideration for septic arthritis (Fig. 106.2).

Nongonococcal Bacterial Septic Arthritis

Principles

Epidemiology. In prospective series of patients presenting to the ED with monoarticular arthritis prompting arthrocentesis, significant percentages of patients had bacterial joint infections. The incidence of septic arthritis in the general population is approximately two to 10 cases per 100,000 per year, with bimodal age distribution peaks for young children and adults older than 55 years old. Additional risk factors that raise the likelihood of septic arthritis include age over 80, low socioeconomic status, injection drug abuse (in which joint infections typically involve the axial skeleton but can involve extremities), alcoholism, diabetes, skin infections, advanced human immunodeficiency virus (HIV) infection or other immunocompromised states, chronic arthritis (particularly rheumatoid, crystalline, and degenerative osteoarthritis), and recent intra-articular corticosteroid injections or prosthetic implants.[9]

Pathophysiology. Bacterial pathogens infect diarthrotic joint spaces most commonly by hematogenous spread, but direct inoculation and contiguous spread from bone or soft tissue infections also occur. Once in the joint space, bacteria proliferate essentially unchecked in the highly vascular synovium, which has no limiting basement membrane. Bacterial components and toxins, as well as the inflammatory cascade they induce, trigger synovial proliferation with neovascularization and subsequent enzymatic, cellular, and cytokine degradation of articular cartilage. Septic arthritis, unless it is rapidly recognized and treated, results in serious disabling morbidity in up to half of patients, with significant mortality rates as well.

Septic arthritis can occur simultaneously with other forms of arthritis, particularly rheumatoid arthritis and gout.[10] The diagnosis of infectious arthritis in a patient with known crystal arthritis can be challenging because acute flare-ups of gout or pseudogout can cause fever, and crystals can precipitate in an infected joint. For this reason, arthrocentesis for Gram stain and culture should be considered in select cases.

Microbiology. The microbiology of nongonococcal arthritis has remained fairly constant over time, except for the decline of *Haemophilus* and pneumococcal species in the postimmunization era, and the rise of methicillin-resistant *Staphylococcus aureus* (MRSA). Acute nongonococcal septic arthritis in adults is caused most often by gram-positive organisms (75% to 90%), followed

Clinical Pathway: Management of the Patient With Acute Monoarticular Joint Pain

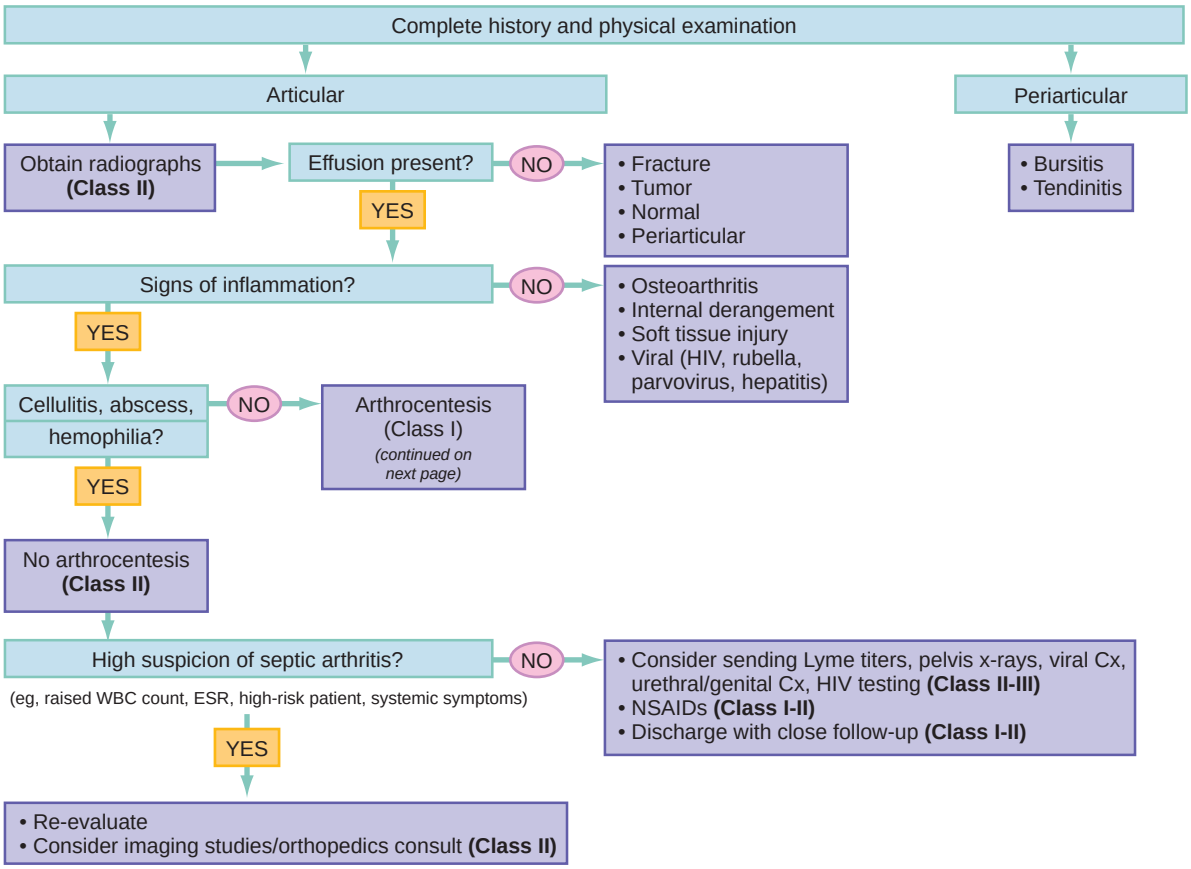

Fig. 106.2. An initial approach to the patient with monoarticular arthritis. *CBC,* Complete blood count; *Cx,* culture; *ESR,* erythrocyte sedimentation rate; *HIV,* human immunodeficiency virus; *NSAID,* nonsteroidal antiinflammatory drug; *PMN,* polymorphonuclear; *PT/PTT,* prothrombin time/partial thromboplastin time; *WBC,* white blood cell. (Modified from EB Practice LLC, 2004.)

TABLE 106.5

Microbiology of Bacterial Septic Arthritis Related to Patient

PATIENTS	ORGANISMS
Neonates and infants	*Staphylococcus aureus,* group B streptococcus, GNR bacteria
Children	*Haemophilus influenzae, S. aureus*
Adolescents and young adults	*Neisseria gonorrhoeae, Chlamydia trachomatis*
Older adults	*S. aureus, Streptococcus,* GNR bacteria
Sickle cell anemia	*Salmonella*
Injection drug abusers	*Pseudomonas, S. aureus,* GNR bacteria

GNR, Gram-negative rod.
From Noble J, Greene HL: Textbook of primary care medicine, ed 3, St Louis, 2001, Mosby.

by gram-negative bacilli (10% to 20%) and then anaerobes, mycobacteria, fungal, and other unusual organisms. *Neisseria gonorrhoeae* accounts for only 20% of cases of monoarticular septic arthritis and more commonly is manifested with polyarthritis; it is discussed separately. Select populations have higher propensities for specific infecting organisms (Table 106.5).

Prosthetic joint infections are classified as early (within a month of surgery) or late. Late infections can be caused by hematogenous spread from another infection or by indolent organisms introduced at surgery that may not surface for up to a year. Because the joint is literally replaced, antibiotic bioavailability and host immune response are both impaired in the prosthetic environment. A wide range of culprit organisms have been identified; MRSA incidence is rising. Arthrocentesis diagnosis of a suspected prosthetic joint infection is best done in consultation with the operating surgeon. A synovial WBC count of more than 1100/mm^3 or a pleocytosis of greater than 64% PMN cells is sensitive and specific for infection in the setting of prosthetic joints.

Clinical Features. Patients with septic arthritis present with fever, joint pain, and effusion, typically in a single large joint (the knee is most common). Moderate fever occurs in 50% of cases but may be less common in the presence of advancing age or immunosuppressive states. Rigors and chills are reported in only 20% of patients. Polyarticular presentation occurs in 20% of cases, particularly in patients with rheumatoid arthritis or chronic joint disease, meningococcal infections, or overwhelming sepsis. Other physical signs, such as edema, tenderness, and decreased range of motion, have not been adequately evaluated for their prognostic value.

Diagnostic Testing. Although laboratory evaluation typically includes complete blood cell count, ESR, and CRP level, a WBC count above 10,000/μL and an ESR above 30 mm/hr only

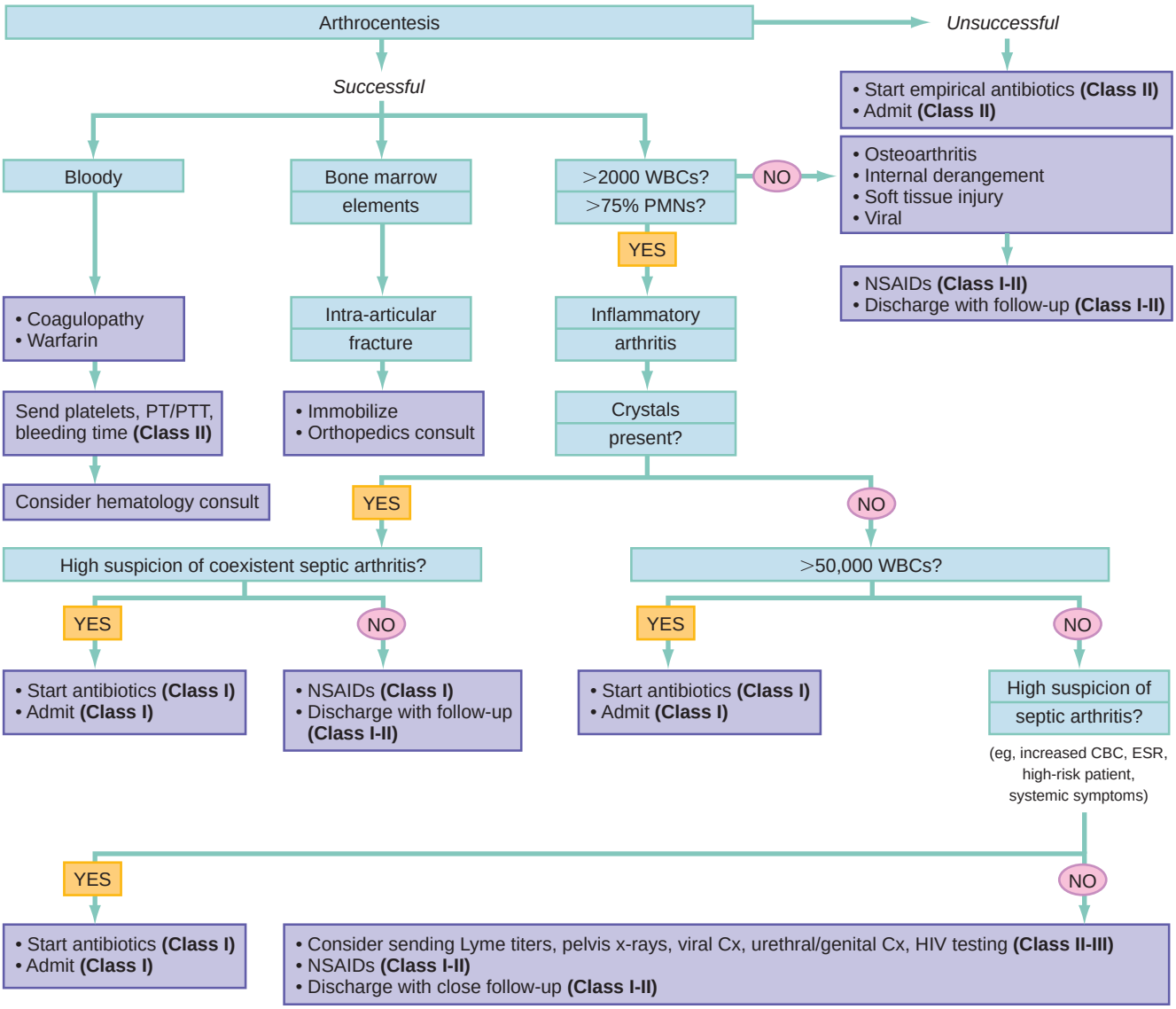

Fig. 106.2, cont'd.

minimally increase the likelihood of septic arthritis. In a prospective trial of pediatric knee arthritis in Lyme-endemic areas, no child with an ESR below 40 mm/hr with an absolute neutrophil count less than 10,000 per mm^3 had septic arthritis.[11] However, systematic reviews show insufficient evidence for a normal CRP level, ESR, WBC count, or procalcitonin level to take septic arthritis below the threshold for further evaluation in adults.[9,12,13] Serum blood cultures reveal the causative organism less than half of the time.

Radiographs demonstrate only soft tissue swelling if it is present; the bone changes of septic arthritis are not usually present on the initial examination. Radiographs may help assess for osteomyelitis or serve as a baseline for future comparisons. Computed tomography (CT) or MRI may be helpful in evaluating early bony changes or soft tissue edema in areas difficult to palpate or aspirate, such as the sacroiliac joint.

Synovial fluid analysis is the best test for septic arthritis. The likelihood of septic arthritis rises with synovial WBC count. Polymorphonucleocyte concentrations above 90% are also associated with an increased likelihood for septic arthritis. In a meta-analysis of four trials, synovial lactate levels greater than 5.6 mmol/L had LR+ from 2.4 and above, although these values were not obtained from modern point-of-care devices.[9] Synovial lactate dehydrogenase (LDH) levels above 250 U/L are sensitive for septic arthritis, and LDH levels below this threshold seem to exclude septic arthritis, according to one study. Low synovial glucose and high protein concentrations are neither sensitive nor specific for septic arthritis. Gram stain will show bacteria in a majority of infected joints. Synovial fluid cultures for both aerobic and anaerobic organisms should be performed.

Management. Early diagnosis of septic arthritis is crucial; substantial delays directly worsen prognosis. Empirical antibiotic therapy is based on Gram stain or the presumptive consideration of likely organisms. Once the diagnosis is made, hospitalization is indicated for administration of intravenous (IV) antibiotics and needle, arthroscopic, or open drainage of the affected joint.[14] Whereas the utility of performing or omitting joint drainage has not been prospectively studied, retrospective reviews suggest good cure rates with drainage, with outcomes dependent on initial severity. More severe cases require frequent, potentially daily joint aspirations.

There are no randomized controlled trials of antibiotic regimens in septic arthritis. Antibiotic selection is initially based on Gram stain results and then adjusted on the basis of final culture results and sensitivities. For gram-positive organisms, the initial

drug of choice is vancomycin 30 mg/kg daily in two divided doses, as MRSA is frequently causative. For gram-negative bacilli, use a third-generation cephalosporin, such as ceftriaxone 2 g IV once daily, cefotaxime 2 g IV three times a day, or ceftazidime with gentamicin (especially if *Pseudomonas* infection is suspected). Although no trials of antibiotic duration have been reported, antibiotic therapy is generally continued parenterally for 2 to 4 weeks, depending on the response, and followed with 2 to 6 weeks of oral antibiotic therapy.

Open arthrotomy for drainage is indicated for failure to respond to therapy within a few days of hospitalization, the presence of osteomyelitis, involvement of the hips or shoulders, or the presence of any prostheses. Parenteral opioid analgesics and immobilization are recommended for pain and discomfort.

Gonococcal Arthritis

Principles. Gonococcal arthritis was considered the most common infective arthritis in the United States in the 1970s and 1980s and remains the most common form of joint infection in the sexually active population. In recent years, the incidence has decreased, most likely because of a general decline of *N. gonorrhoeae* prevalence, particularly of the more virulent strains. Host risk factors for dissemination of gonococcal infection include pregnancy, menstruation, and complement deficiency. There has been a 4 : 1 female predominance, attributed to mucosal infections in women more likely to be asymptomatic.

Gonococcal arthritis represents a clinical and pathologic course distinctly different from that of other bacterial infections and is less likely to create long-term joint disease.

Clinical Features. Systemic gonococcal infection complicates 0.5% to 3% of mucosal infections and is manifested with two somewhat overlapping musculoskeletal syndromes. The first is a localized septic arthritis, more commonly oligoarthritis than monoarthritis, predominantly in the wrist, knee, or ankle. The effusions may be modest. True disseminated gonococcal infection (sometimes termed *arthritis-dermatitis syndrome*) is manifested with bacteremia, diffuse migratory arthralgias, characteristic skin lesions, and tenosynovitis (Fig. 106.3). A similar syndrome has been recognized as a result of *Neisseria meningitidis* infection.

Management. Microbiologic diagnosis is difficult, because both synovial and blood cultures are positive for gonococcus in no more than half of cases. The diagnostic yield is higher when specimens are plated on Thayer-Martin medium and even greater with the use of polymerase chain reaction (PCR). Synovial fluid often yields a positive Gram stain result, and the synovial WBC count tends to be lower than in nongonococcal arthritis (generally 40,000 to 60,000 cells/mm^3). Cervical, urethral, rectal, and pharyngeal cultures are positive in up to 75% of cases, so all mucosal orifices of the patient (and partner, if possible) should be cultured appropriately. In disseminated gonococcal infection, the skin lesions often contain the gram-negative diplococcus.

Fig. 106.3. Pustular lesion with disseminated gonococcal infection. (From Mandell GL, Bennett JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ed 6, Philadelphia, 2005, Elsevier/Churchill Livingstone.)

The most recent Centers for Disease Control and Prevention (CDC) guidelines recommend hospitalization, especially if etiology or compliance is uncertain, and treatment with intramuscular (IM) or IV ceftriaxone 1 g every 24 hours plus a single dose of oral azithromycin 1g. Alternatively, IV ceftizoxime or cefotaxime 1 g three times daily plus azithromycin 1g orally in a single dose, with "step down" transition within 24 to 48 hours to oral antimicrobials, dictated by sensitivities, for at least a week.[15] Partners should be evaluated. Presumptive treatment of *Chlamydia* is also advised.

Repeated therapeutic arthrocentesis may not be necessary in this form of septic arthritis. With prompt antibiotic therapy, residual joint problems are uncommon.

Gouty Arthritis

Principles

Epidemiology. Acute intermittent gout typically is manifested in middle-aged men or postmenopausal women, often in the setting of excess alcohol consumption or dietary indiscretion, acute physiologic stressors (such as, illness, trauma, or surgery), or new medications. Its prevalence in the United States is estimated at 4% of the population and up to 13% of the population older than 80 years old.[16] Risk factors include chronic obesity, hypertension, diabetes, thiazide diuretics or cyclosporine use, and lead or radiocontrast exposure. Purine-rich diets (meat; seafood, especially anchovies and shellfish; beer; and legumes) predispose at-risk individuals to attacks; high-fructose corn syrup and soft drinks are also implicated.[17] High dairy and coffee consumption have been shown to decrease risk.

Pathophysiology. Gout results from inflammation caused by the acute precipitation of uric acid crystals from supersaturated extracellular fluid. Uric acid is a normal metabolic end product of purine metabolism. Hyperuricemia results from its underexcretion in the kidney or, less commonly, from systemic overproduction caused by inborn errors of metabolism and myeloproliferative diseases. During an attack of gouty arthritis, the crystals are ingested by PMN cells, resulting in cytokine release and an inflammatory synovial reaction.

Asymptomatic hyperuricemia typically exists for decades, and less than a quarter of these patients have acute manifestations. Furthermore, not all patients with elevated uric acid levels or even joint crystals have acute attacks, and many patients with an acute gouty arthritis have a normal uric acid level.

Clinical Features. Gouty attacks most commonly occur in the great toe MTP joint (*podagra,* up to 75%, with 90% of patients eventually experiencing this joint flare), the knee *(gonagra),* the ankle, and the tarsal joints. Usually only one joint is involved initially, but approximately 20% of patients can experience polyarticular involvement, bursitis, tenosynovitis, or even skin inflammation. The pain is often exquisite at onset. Systemic symptoms can include fever. Without treatment, the attack is self-limited, peaking during 24 to 48 hours and lasting about a week.

Subsequent attacks tend to be closer together, involve more joints, and last longer, eventually morphing into the final stage of chronic gouty arthritis after a decade, if untreated. Long-term sequelae include renal stones and tophi in the musculotendinous

units, such as the olecranon bursa, Achilles tendon, ulnar surface of the forearm, hands and fingers, knees, feet and toes, and even the helix of the ear.

Diagnostic Testing. The observation, with a polarizing microscope, of intracellular negatively birefringent crystals in joint fluid aspirate remains the "gold standard" for diagnosis of gouty arthritis.

Laboratory Tests. Whereas higher levels of serum uric acid are commonly seen in gouty patients, this laboratory finding is not helpful in establishing the diagnosis of gout in the acute setting. Urate levels can be transiently normal, a process thought to be mediated by the uricosuric effects of endogenous adrenocorticotropic hormone (ACTH) and epinephrine, released as part of the pain response. Given the association of gout and renal insufficiency and the nephrotoxicity of several therapies, checking renal function is prudent.

Radiologic Tests. During an acute attack, radiographs of the affected joint will show only soft tissue swelling, but long-standing disease produces typical asymmetrical bone erosions slightly removed from the joint (as opposed to rheumatoid arthritis erosions, which are more proximal to the articular surface—see Fig 106.7). The crystal deposits of gout also cause an overhanging margin of soft tissue by the erosion. Dual-source, dual-energy CT using a mineral composition algorithm has shown promise in a small trials and observational series for diagnosis of uric acid collections in joints.[18,19] Ultrasound has also been studied to evaluate gout, because crystalline material in gouty joints reflects sound waves more strongly than soft tissue and cartilage. An protocol for experienced ultrasonographers to evaluate hyperechoic aggregates and the "double contour" sign of crystal deposition showed adequate sensitivity and specificity in a prospective case-control study of patients recruited from rheumatology clinics.[20] However, it's not yet clear if this approach can help diagnose patients presenting to the ED with acute gout flares.

Management. Gout therapies are divided into acute treatment and long-term prophylaxis. Prophylaxis is generally not an emergency consideration, but many patients present with breakthrough attacks. New guidelines for gout recommended that prophylactic agents (such as, allopurinol), or newer agents (such as, febuxostat and probenecid) should neither be stopped nor initiated during an acute attack.[21]

ED pharmacologic mainstays for acute gout are nonsteroidal antiinflammatory drugs (NSAIDs; including cyclooxygenase 2–selective agents), corticosteroids (including ACTH), and colchicine. Caution is exercised with use of these agents because hypertension, diabetes, and renal and vascular disease are prevalent in this cohort of patients.

Nonsteroidal Antiinflammatory Drugs. Whereas NSAIDs, particularly indomethacin, are considered first-line therapy for acute gout attacks, there is little evidence to support their superiority over other agents, and trials between NSAIDs have shown no apparent difference in efficacy.

For acute attacks, indomethacin is typically given at 50 mg three times a day, naproxen at 500 mg twice a day, and ibuprofen at 800 mg three or four times a day. If NSAID therapy is initiated promptly, relief occurs rapidly in the first 24 hours. Treatment should continue for another 24 hours after the symptoms abate and be tapered quickly; durations up to a week may be necessary if initiation of treatment is delayed.

Colchicine. Colchicine inhibits microtubule formation and impedes the inflammatory response to the presence of crystals in synovial fluid. Its use for gout predates the foundation of the U.S. Food and Drug Administration (FDA) in 1938 and new trials for safety and efficacy were undertaken to earn government-sanctioned exclusivity.[22] Oral colchicine has been shown to be effective for gout in small randomized placebo-controlled trials at a loading dose of 1 mg followed by 0.5 mg orally every 2 hours, or a regimen of 4.8 mg administered across 6 hours.[23] However, patients studied with colchicine at these doses eventually had gas, nausea, vomiting, or diarrhea. In 2010, a prospective double-blind study of an oral loading dose of 1.2 mg colchicine followed by 0.6 mg an hour later demonstrated superior pain relief of colchicine over placebo, with a lower incidence of gastrointestinal (GI) complaints compared to other regimens.[24] Lower dosing is recommended in elders; in several case reports, dosing of colchicine at 0.6 mg spread over three times a day has been effective for pain relief as well.[10]

Colchicine is also effective in relieving symptoms from other crystal arthritides and therefore is not helpful when it is used for diagnostic purposes.[24]

Colchicine is contraindicated in patients with hematologic, renal, and hepatic insufficiency; its low therapeutic index makes it readily lethal in overdose.[25] Similarly, IV colchicine is generally not recommended, despite its rapid onset and reduced GI toxicity. IV colchicine has a long half-life and narrow therapeutic window; more than 20 iatrogenic deaths have been reported across a broad spectrum of ages.

Steroids. Once septic arthritis has been excluded, the intra-articular injection of steroids may be effective for individuals with accessible joint involvement. Triamcinolone acetonide in a dose of 20 to 40 mg for the knee and 5 to 10 mg for smaller joints is recommended.

Systemic steroids, such as oral prednisone (40 mg/day for 3 to 5 days, with or without a taper), are commonly used. However, a Cochrane review of three trials of various steroids against other agents failed to demonstrate evidence of efficacy for systemic steroids.[26]

Adrenocorticotropic Hormone (Corticotropin). Although it is not commonly used (or studied) because of its expense and lack of general availability, synthetic ACTH is a desirable alternative to the preceding agents because of its rapid onset of action and decreased toxicity in older patients. American College of Rheumatology (ACR) Guidelines for gout management now endorse 25–40 IU ACTH subcutaneously as an appropriate alternative for *nil per os* (NPO) patients.[21]

Other Agents. Guidelines for management of acute gout recommend that if the flare occurs while a patient is receiving a diuretic, the diuretic should be stopped if at all possible.[12] Narcotic analgesics and either local or regional anesthetic blocks are potential adjunctive therapy. Ice has been shown to be a useful adjunctive therapy.[27] Rest and elevation may be helpful as well.

Summary. Both NSAIDs and colchicine are considered first-line therapies for gout; the two are often used in tandem in patients without contraindications, such as renal insufficiency. Best available evidence supports a treatment strategy of prompt initiation of NSAID therapy (eg, 50 mg of indomethacin three times daily or 500 mg of naproxen twice daily) or colchicine 1.2 mg followed by a 0.6-mg dose an hour later.

Patients for whom NSAIDs or colchicine is contraindicated can be treated with intra-articular injections of triamcinolone or ACTH (corticotropin). Systemic steroids, although commonly used, have a weaker evidence base, but one trial suggests that prednisolone 35 mg/day is comparable to naproxen 500 mg twice a day during the course of 4 days.

Follow-up, preferably with a rheumatologist, is recommended for proper prophylaxis against future flares.

Calcium Pyrophosphate Dihydrate Deposition Disease (Pseudogout)

Principles. Calcium pyrophosphate dihydrate deposition disease (CPPD) results when calcium complex crystals form

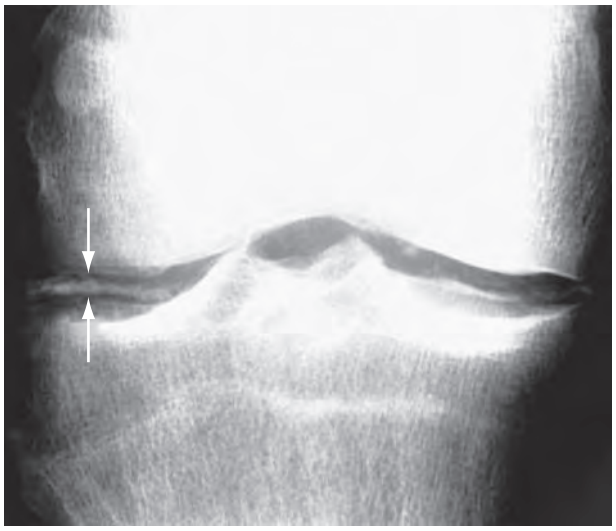

Fig. 106.4. Chondrocalcinosis *(arrows)* in calcium pyrophosphate dihydrate deposition disease (CPPD). (From Mettler FA: Essentials of radiology, ed 2, Philadelphia, 2005, Saunders/Elsevier.)

across articular surfaces. CPPD is manifested on radiographs as chondrocalcinosis (Fig. 106.4). When precipitating crystals trigger an inflammatory synovitis, it is termed *pseudogout*. The pathologic mechanisms are incompletely understood but involve overproduction of chondrocyte pyrophosphate, increased calcium, and histologic changes in the cartilage's extracellular matrix. CPPD is strongly associated with aging and joint surgery, but hemochromatosis, hypothyroidism, hyperparathyroidism, amyloidosis, hypomagnesemia, Wilson's disease, and inflammatory osteoarthritis have also been implicated. The condition is most often asymptomatic, and its true incidence is unknown.

Clinical Features. The clinical presentation of CPPD is similar to that of gout, making a synovial fluid diagnosis important. Pseudogout patients tend to be older than 65 years old, and the knee is most commonly involved.

Diagnostic Testing. Diagnosis of CPPD and pseudogout involves demonstration of the characteristic synovial crystals and radiographic changes. Radiographs demonstrate crystal deposition as punctuate, linear densities within the articular cartilage (such as the knee meniscus) or joint capsules. Joint fluid examination shows the rhomboidal, weakly positive birefringent crystals of CPPD. As with gout, the patient's symptoms may mimic septic arthritis, and the two conditions can also occur simultaneously.

Management. There are no randomized trials to support any one therapy for a pseudogout attack. Therapy is complicated by the fact that calcium pyrophosphate crystals, once present, cannot be removed. Guidelines recommend NSAIDs but with cautions related to GI bleeding, renal impairment, and cardiovascular events. Colchicine is also recommended, but at a lower dose than for gout: 0.5 mg three or four times a day, with or without a 1-mg loading dose.[28] Intra-articular glucocorticoid injections have expert approval, and a small trial supports a single IM dose of betamethasone (7 mg) or IV dose of methylprednisolone (125 mg) over a multiday oral diclofenac regimen. Treatment of secondary metabolic causes of CPPD, although important, does not appear to influence the course of disease or frequency of acute flares of pseudogout.

Basic Calcium Phosphate Hydroxyapatite Crystal Disease

A variant form of crystalline disease results from basic calcium phosphate (BCP) hydroxyapatite deposits. BCP deposition in synovial fluid is more difficult to detect with light microscopy and is more rapidly progressive and destructive than CPPD.[29] BCP arthropathy also is manifested with calcific tendinitis, calcific bursitis, and a "pseudopodagra" of the first MTP joint in young women. The *Milwaukee shoulder syndrome* is characterized by severe bilateral osteoarthritis of the glenohumeral joint, rapid destruction of the rotator cuff, and BCP crystals, leading to joint instability and upward subluxation.[29] NSAIDs, systemic and intra-articular steroids are typically cited as conventional therapy, without much supporting evidence. For refractory joint pain, a case series supports the use of aspiration and lavage.

Acute Calcific Periarthritis

Acute calcific periarthritis results when amorphous calcium hydroxyapatite deposits extravasate into periarticular soft tissue, causing a self-limited, crystal-induced inflammatory reaction.[30] It usually occurs in women and most commonly involves the hand or rotator cuff; the symptoms last less than a week, and the radiographic findings resolve after about 3 weeks. NSAIDs and steroids are recommended without clinical trial data; a randomized controlled trial suggests that extracorporeal shock wave therapy works for refractory cases.[31]

Trauma and Hemarthrosis

Trauma is a common cause of acute monoarticular effusion. One prospective series of tense knee hemarthrosis presenting within 12 hours of injury identified complete or partial anterior cruciate ligament tears in 70% of patients and meniscal tears in 16%; synovial disruption was presumed responsible in 5% with another series of acute trauma patients with normal radiographs and hemarthrosis seen on aspiration also showing serious pathologic injuries, such as anterior cruciate ligament, posterior cruciate ligament, or collateral ligament tears after prompt arthroscopy. The authors recommended aspiration of a tense traumatic effusion and urgent arthroscopy.

Chronic Monoarticular Arthritis

Osteoarthritis (Degenerative Joint Disease)

Principles. Osteoarthritis, or degenerative joint disease, is the most common form of arthritis among adults, especially in elderly and overweight patients. Mechanical signaling in cartilage mediates chondrocyte production of extracellular matrix molecules. Perturbations in loading (from trauma or excess weight), combined with biochemical and genetic factors, influence cytokine signaling and matrix composition, ultimately causing subchondral bone overgrowth, cartilage degradation, and synovial membrane inflammation.

Clinical Features. Patients with osteoarthritis classically describe pain that worsens with activity and improves with rest. The lack of systemic symptoms also helps distinguish osteoarthritis from rheumatoid arthritis. Osteophytic spurs (Bouchard's and Heberden's nodes in the PIP and DIP joints, respectively) may be palpated. Affected joints may display crepitus on active and passive ranging.

Radiographs classically show asymmetrical joint space narrowing, although the degree of narrowing often does not correlate with the patient's perception of pain. Radiographs may also show osteophyte formation at joint margins and subchondral cysts.

Synovial fluid is difficult to aspirate in osteoarthritis but classically is noninflammatory, with fewer than 2000 cells/mm^3 and few PMN cells.

Management

Nonpharmacologic Therapy. Many nonpharmacologic therapies for knee and hip osteoarthritis have been endorsed through clinical guidelines and meta-analyses, such as weight loss, exercise, patient education, and wedge-soled shoes.[32] For the hand, orthotics and splints are also endorsed, with support from prospective trial data.[32,33]

Pharmacologic Therapy. Acetaminophen at 4 g/day is supported by a systematic review of 15 trials, showing superiority to placebo, although inferiority to NSAIDs for the hip and knee. However, because the adverse effects of acetaminophen are milder and less likely than with NSAIDs, acetaminophen is considered a first-line therapy in guidelines from the European League Against Rheumatism (EULAR) and the American College of Rheumatology.[34]

Cyclooxygenase 2 inhibitors (eg, celecoxib) are associated with less GI bleeding risk than traditional NSAIDs in randomized trials, with the same apparent effectiveness. However, subsequent concerns for increased cardiovascular toxicity have limited their use.

A systematic review of 34 trials (most comparing four times daily topical diclofenac solution and gel to placebo) found the number needed to treat (NNT) of 6.4 to 11 for 50% osteoarthritis pain relief over 8 to 12 weeks. Other studies suggest similar efficacy between topical and oral NSAIDs, with topical NSAIDs showing fewer GI adverse events but more (mostly mild) skin reactions.[35]

Capsaicin is another low-toxicity topical agent that may help—particularly for hand osteoarthritis pain.[35] Opioid analgesics for osteoarthritis pain are supported by a meta-analysis for pain reduction and functional improvement; however, substantial attrition due to adverse effects of opioids limits the validity of the meta-analysis. Therapies involving glucosamine and chondroitin have shown variable benefit. A network meta-analysis revealed no clinically significant improvement with these drugs, alone or in combination, compared with placebo.[36]

Intra-articular glucocorticoid injections, such as triamcinolone, have shown pain relief lasting months but uneven efficacy in various joints and no measurable effect on physical function. The dose of triamcinolone is generally 10 mg for hand joints; 20 mg for elbows, ankles, and acromioclavicular joints; and 40 mg for knees, hips, and shoulders. Intra-articular hyaluronic acid injections have demonstrated some improvement in physical function and superior pain relief compared with intra-articular steroid injections (although apparent only after a period of many weeks to months).

Many clinicians instill amide analgesics (such as, lidocaine or bupivacaine) with intra-articular steroid or hyaluronic acid injections to produce a more rapid onset of pain relief. Recently, chondrolysis and cartilage destruction have been reported after amide analgesic pain pumps were employed postoperatively.[37] Prospective animal trials have shown chondrotoxic effects of lidocaine and bupivacaine after even a single amide injection, although damage from single intra-articular injection of amide analgesics in humans has not been reported.[38]

Summary. ED management of osteoarthritis is symptomatic relief. Acetaminophen 4 g/day is supported by many reviews for safety and efficacy. NSAIDs and opioids have shown superiority to acetaminophen for particular kinds of osteoarthritis, but concern for adverse events has limited their application. Topical NSAIDs show the same pain relief as systemic NSAIDs with fewer serious adverse events, although comparisons to acetaminophen are lacking. In patients resistant to these therapies, intra-articular injections of triamcinolone have demonstrated pain relief in the long term, depending on the joint, but with no improvement of physical activities.

Emergency clinicians should not fail to recommend proven nonpharmacologic therapies for knee and hip osteoarthritis, such as weight loss, exercise, and wedge-soled shoes, with referral to an orthopedic surgeon for further management.

Acute Polyarticular Arthritis

The differential diagnosis of polyarticular arthritis is broader than that of monoarticular arthritis (Fig. 106.5). A useful classification of polyarticular arthritis presentations are distinguishing acute (defined as <6 weeks) from chronic (>6 weeks). The acute polyarticular presentations include gonococcal arthritis, viral arthritis (eg, rubella, hepatitis), Lyme disease, reactive arthritis, and rheumatic fever. Chronic polyarticular presentations are caused by rheumatoid arthritis, systemic lupus erythematosus, scleroderma, psoriatic arthritis, dermatomyositis, and other autoimmune diseases. Alternatively, polyarticular presentations may be classified as symmetrical or asymmetrical. Rheumatoid arthritis and systemic lupus erythematosus tend to be symmetrical, the others asymmetrical. The spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and the arthropathy of inflammatory bowel disease) involve predominantly larger joints, but psoriatic arthritis affects the small joints of the hands.

Viral arthritides have varied mechanisms of inflammation (Table 106.6) but typically are manifested as an acute, self-limited, nondestructive polyarticular arthritis.[39]

Lyme Disease

Principles. *Borrelia burgdorferi* infection causes the multisystem disorder known as Lyme disease, the most common vector-borne illness in the Western world. In the United States, endemic areas for *B. burgdorferi* and its vector tick *Ixodes* include the Northeast, the upper Midwest, and northern California. More than a quarter-million cases have been reported to the CDC since 1992, with approximately 30,000 cases per year in recent years.[40]

Clinical Features. Lyme disease follows a prescribed pattern of early disseminated disease (weeks to months after a tick bite) and late disease (several months to years later). Musculoskeletal manifestations of the early stage, when present, primarily consist of migratory myalgias and arthralgias without objective evidence of actual arthritis or effusions. Arthritis is the most common manifestation of late Lyme disease.[11] When it is untreated, 50% to 60% of patients will have frank asymmetrical arthritis within 6 months—most commonly in large joints, particularly the knees. The natural history of Lyme arthritis is intermittent episodes that gradually abate in intensity and frequency during several years, even if it is untreated. Lyme arthritis appears to be autoimmune-mediated rather than a direct result of the spirochetal infection, but early antibiotic therapy clearly reduces its incidence. Lyme arthritis seems to be more prevalent in infections in the United States because the endemic *B. burgdorferi* displays stronger arthritogenic properties than other strains.

Diagnostic Testing. The history of a previous tick bite from an endemic area or the classic erythema migrans rash (although often not remembered by the patient) may aid the clinician in suspecting the diagnosis. Patients have minimal joint pain and usually are afebrile despite large joint effusions. Aspirate is inflammatory with PMN cell predominance, but *Borrelia* cannot be cultured from it. The differential diagnosis includes gonococcal arthritis, septic arthritis, ARF, rheumatoid arthritis,

Clinical Pathway: Management of the Patient With Acute Polyarticular Joint Pain

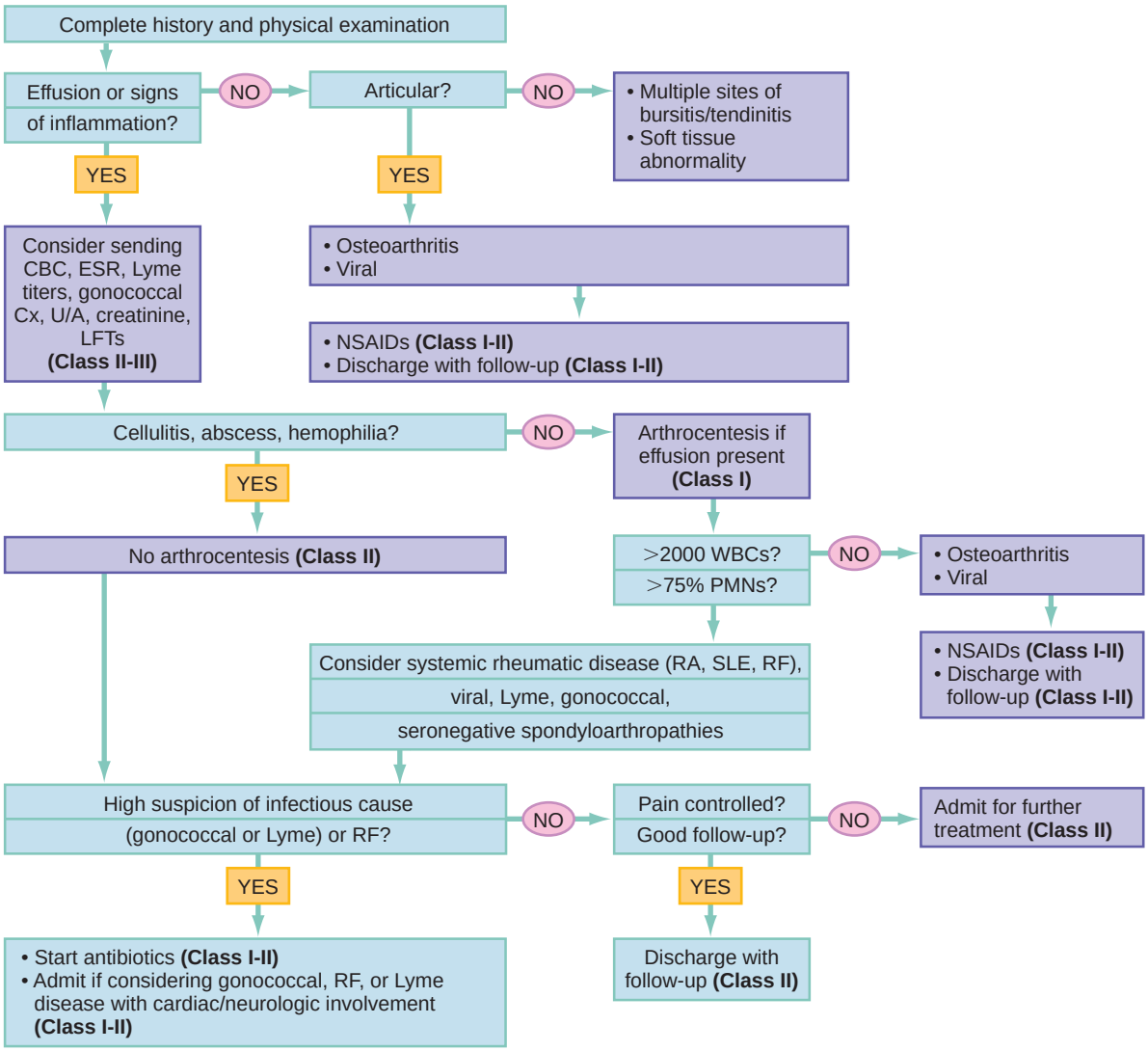

Fig. 106.5. An initial approach to the patient with polyarticular joint symptoms. *CBC,* Complete blood count; *Cx,* culture; *ESR,* erythrocyte sedimentation rate; *LFT,* liver function test; *NSAID,* nonsteroidal antiinflammatory drug; *PMN,* polymorphonuclear; *RA,* rheumatoid arthritis; *RF,* rheumatic fever; *SLE,* systemic lupus erythematosus; *U/A*, urinalysis; *WBC,* white blood cell. (Modified from EB Practice LLC, 2004.)

and reactive arthritis. Routine blood testing is nonspecific and unhelpful. Confirmatory diagnosis is by immunoglobulin M and G serologies.

Management. Prophylactic therapy after a tick bite is not generally recommended except for an *Ixodes* attachment of longer than 36 hours in an endemic region; in these cases, a single doxycycline dose of 200 mg is recommended by the Infectious Disease Society of America (IDSA) clinical guidelines. Lyme arthritis can generally be treated with a 4-week oral course of doxycycline, 100 mg twice daily. Doxycycline is preferred for its excellent oral absorption, low cost, and antiinflammatory activity as a matrix metalloproteinase inhibitor. Amoxicillin 500 mg three times daily and cefuroxime axetil 500 mg twice daily are acceptable alternatives. Amoxicillin is used instead of doxycycline for pregnant and lactating women and for children younger than 8 years old. If Lyme disease is diagnosed at the early stage of erythema migrans, only 2 weeks of treatment is recommended. For patients with neurologic or cardiac symptoms, or refractory Lyme arthritis, an infectious disease specialist should be consulted and IV antibiotics considered.

Acute Rheumatic Fever

Principles. ARF is a systemic disease triggered by a complex hyperimmune response in the weeks after group A streptococcal pharyngitis. Host cellular and humoral response to group A streptococcal infection attacks joint, cardiac, and other tissue, in part through molecular mimicry mechanisms. The incidence of ARF has dramatically declined in recent decades, in part due to transformation of group A streptococcal strains, improvements in hygiene, and widespread antibiotic use; in the United States, incidence is estimated at 2 to 14 per 100,000.

Clinical Features. The clinical diagnosis of ARF is based on the Jones criteria. The presence of two major criteria (polyarthritis, carditis, chorea, erythema marginatum, and/or subcutaneous nodules; Fig. 106.6), or one major criterion and two minor criteria

TABLE 106.6

Characteristics of Viral Arthritides

VIRUS	ARTHRITIS PRESENTATION	SYMPTOM ETIOLOGY	DURATION OF SYMPTOMS	THERAPY
Hepatitis B	Mimics rheumatoid arthritis onset with symmetrical, migratory, or additive joint symptoms	Immune complex depositions in prodromal phase affect 10% to 25% of those with hepatitis B	Subsides with onset of jaundice	Supportive
Hepatitis C	Symmetrical rheumatoid arthritis–like mimic, or intermittent monarticular arthritis, often associated with salivary inflammation	Hepatitis C–induced mixed cryoglobulinemia	Variable, intermittent	Supportive; rheumatoid arthritis drugs are often helpful
Human immunodeficiency virus (HIV)	Often monarticular arthritis, involving feet and ankles, potentially involving tendon, bursae, skin, and muscle inflammation as well	By virus itself or by reactive arthritis, drug-induced myopathy, immune reconstitution syndrome, or opportunistic septic arthritis	Variable	Driven by etiology
Parvovirus B19	The cause of fifth disease in childhood causes a connective tissue syndrome in adults	Symmetrical stiffness in PIP joint, MCP joint, without joint erosion	Self-limited, but may recur	Supportive
Rubella virus, rubella vaccine virus	Beyond classic maculopapular rash and lymphadenopathy, 30% of females and 6% of males with rubella show symptoms of arthritis	Virus grows well in synovial tissue, causing arthritis by direct infection	Symptoms appear within 2 weeks of vaccination or a week of rubella infection; self-limited	Supportive
Alphaviruses (Ross River, chikungunya, Mayaro)	Mosquito borne, often seen in epidemics after seasonal rains	Virus persists in synovial macrophages; symptoms arise from triggering of host response	Sometimes abrupt or insidious onset; symptoms can last 3 to 6 months; some patients have years of discomfort	Largely supportive; corticosteroids were once contraindicated but recently shown to be effective

MCP, Metacarpophalangeal; *PIP,* proximal interphalangeal.

Fig. 106.6. Erythema marginatum in acute rheumatic fever (ARF). The pen mark shows the location of the rash approximately 60 minutes previously. (From Cohen J, Powderly WG: Infectious diseases, ed 2, New York, 2004, Mosby/Elsevier.)

(arthralgia, fever, elevated ESR/CRP, and/or long PR interval on ECG), with laboratory evidence of prior group A streptococcal infection is required.

Group A streptococcal infection–related arthritis, typically migratory, occurs in 75% of patients and mostly affects the large joints. The arthritis lasts 2 to 3 days in each joint and 2 to 3 weeks overall; the axial skeleton is spared. Joints appear modestly inflamed, but the pain is disproportionately excruciating to the patient. ARF arthritis responds so dramatically to salicylate or steroid therapy that the diagnosis can become clouded; lack of response should promote an alternative diagnosis. Naproxen was shown to be as effective as aspirin and better tolerated in a randomized trial in children.

For patients not fulfilling Jones criteria, poststreptococcal reactive arthritis (PSRA) is another sterile group A streptococcal infection–related arthritis, with a more additive than migratory course.

Diagnostic Testing. The diagnosis of ARF is largely clinical; laboratory evaluation for suspected ARF is not conducive to ED care. Throat cultures are negative in 75% of patients with systemic manifestations of ARF. Antibody titers to streptolysin O and anti-DNase B may demonstrate antecedent group A streptococcal infection. Synovial aspirate is inflammatory in nature and sterile, with a widely variable synovial WBC count, no crystals, and a negative culture.

Management. Recommended treatment of suspected acute group A streptococcal infection is benzathine penicillin 0.6 to 1.2 million units intramuscularly or 10 days of oral penicillin (or erythromycin if the patient is penicillin-allergic). Long-term prophylactic treatment to prevent recurrences of ARF is provided with either oral or parenteral penicillin or erythromycin. The duration of prophylaxis depends on the age of the patient, the presence of cardiac involvement, the number of previous attacks, and other factors.

Besides antibiotics, ARF treatments were developed well before the era of randomized trials, so their evidentiary basis is suboptimal. High-dose aspirin (50 to 100 mg/kg/day in four daily doses) for 2 to 4 weeks improves the arthritis and fever but not the symptoms of carditis. Smaller studies have suggested a benefit to oral or IM hydrocortisone over aspirin if carditis is present (1 to 2 mg/kg/day, slowly tapered during 2 to 4 weeks).

Chronic Polyarthritis

Rheumatoid Arthritis

Principles. Although rheumatoid arthritis is usually considered a chronic and insidious disease, at least 20% of patients have an acute presentation. Rheumatoid arthritis develops in women two to three times more often than in men, with a peak incidence between the fourth and fifth decades of life. Prevalence is between 0.5% and 1% of Western populations and 5% of women by 70 years of age. There appears to be a genetic predisposition forming immune complexes that stimulate PMN cells to release the enzymes that ultimately cause joint destruction. The synovial cells increase dramatically in number and produce even more inflammatory substances. A pannus of granulation tissue is formed that ultimately destroys the joint.

Clinical Features. Patients commonly seek care after a prodromal period of fatigue, weakness, and musculoskeletal pain, with or without fevers and weight loss, that may last weeks to months. The patient's joints begin to swell in a symmetrical and additive pattern, particularly the hands (MCP and PIP joints), wrists, and elbows. Classically, patients describe morning stiffness lasting more than an hour. DIP joints of the fingers are not involved, which helps distinguish rheumatoid arthritis from osteoarthritis, reactive arthritis, and psoriatic arthritis.

Acute presentations may have only warm, tender, swollen joints that may be difficult to distinguish from a viral arthropathy. Tenosynovitis can occur with acute rheumatoid arthritis.

Long-standing changes of rheumatoid arthritis include MCP and PIP joint swelling, ulnar deviation, swan-neck and boutonnière deformities of the hands, and limitation of dorsiflexion of the wrist. Extra-articular complications are seen in half of patients with rheumatoid arthritis and include subcutaneous nodules vasculitis of the skin, pulmonary fibrosis, mononeuritis multiplex, pericarditis, and Sjögren's and Felty's syndromes. Long-standing rheumatoid arthritis is associated with atlantoaxial subluxation, as well as with laryngeal deviation, which should be recognized before endotracheal intubation.

Diagnostic Testing. The ED evaluation of the patient with suspected rheumatoid arthritis is directed at excluding other causes of arthritis, particularly septic arthritis. However, the definitive diagnosis of rheumatoid arthritis is complicated and involves confirmatory serology and a chronicity of 6 weeks or more.[41] ESR and CRP levels may be elevated but are nonspecific. Rheumatoid factor, an antibody against gamma globulin, is eventually present in approximately 75% to 85% of patients with rheumatoid arthritis, although it is present in only 50% in the first 6 months.

Early radiographic features of rheumatoid arthritis are soft tissue swelling and juxta-articular osteoporosis leading to uniform joint space narrowing (Fig. 106.7). Subluxation with loss of joint alignment is a later finding.

Synovial fluid analysis is helpful to rule out infectious or crystalline processes. Arthrocentesis reveals inflammatory fluid with WBC counts between 4000 and 50,000/mm^3 and more PMN cells (75%) than are usually seen with crystal disease.

Management. Excessive movement increases inflammation, so the initial treatment for early or mild disease is rest, in combination with antiinflammatory medication. Oral prednisone, 5 to 15 mg daily, can effectively control mild inflammation as a bridge to more advanced therapy in early disease. A systematic review concluded that short-term, low-dose steroids (prednisone 15 mg/day) are significantly more effective than NSAIDs (and placebo) for alleviation of rheumatoid arthritis symptoms. Even as recommendations for early use of disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis have grown stronger, the safety and efficacy of low-dose corticosteroids make it an appropriate first-line therapy in the ED.[42]

Fig. 106.7. Rheumatoid arthritis of the wrist, with osseous erosions shown here including triquetrum, pisiform, scaphoid, and radius. There also are erosions at the ulnar aspect of the distal radius and the ulnar styloid process secondary to involvement of the inferior radioulnar compartment. Diffuse cartilage loss also is evident in the radiocarpal compartment. (From Firestein GS: Kelley's textbook of rheumatology, ed 8, Philadelphia, 2008, WB Saunders.)

Clinical studies support the efficacy of a combination of methotrexate and a tumor necrosis factor blocker in reducing early disease activity. Combinations of sulfasalazine 1000 mg two or three times daily and hydroxychloroquine 200 to 400 mg/day are commonly prescribed. Although the choice of DMARD is typically left to rheumatologists, emergency clinicians should be familiar with their potentially life-threatening complications (Table 106.7).

Intra-articular glucocorticoid injections have been studied, but often with agents or in regimens that are not applicable to emergency medicine practice. Systematic reviews showed no evidence to support the use of muscle relaxants and limited evidence to support the use of weak opioids for rheumatoid arthritis.[43,44] Resting wrist and hand splints were not shown to improve function, symptoms, or quality of life, although patients did prefer the use of splints to nonuse. Extra-depth in-soled shoes were shown to improve walking and pain over several months.

Adult-Onset Still's Disease

Adult-onset Still's disease (AOSD) is a rare (1 to 34 cases per million, worldwide) multisystem inflammatory disorder characterized by acute arthritis, characteristic rash, and quotidian or double-quotidian fevers (with the highest temperatures seen in the late afternoon or early evening). The rash is a salmon-colored macular evanescent rash that occurs only with the fever. Manifestations of AOSD include sore throat, myalgias, splenomegaly, hepatitis, and pericarditis. The differential diagnosis includes other acute arthritides (especially rheumatic fever) and other causes of "fever of unknown origin." Based on retrospective

TABLE 106.7

Commonly Encountered Toxicities of Disease-Modifying Antirheumatic Drugs

DRUG	COMMON ADVERSE EVENTS	RARE BUT MAJOR TOXICITIES
Methotrexate	Nausea, alopecia, abdominal pain, UTI	Hepatotoxicity, interstitial pneumonitis, aplastic anemia
Sulfasalazine	Nausea, dizziness, headache, abdominal pain, diarrhea	Hepatotoxicity, folate deficiency, hemolytic anemia in G6PD deficiency
Anti-malarial drugs	Blurred vision, nausea	Agranulocytosis, aplastic anemia, eye keratopathies
Gold compounds	Rash, pruritus, mucosal ulcers	Bone marrow suppression, membranous glomerulonephritis
Azathioprine	Nausea, abdominal pain	Hepatitis, pancreatitis, lymphoma
D-Penicillamine	Rash, abdominal pain, nausea	Leukopenia, thrombocytopenia, aplastic anemia—rarely, SLE, polymyositis, MG
Cyclosporine A	Nausea, stomatitis, mucosal ulcers, rash, UTI	Nephrotoxicity
TNF inhibitors (etanercept, infliximab)	Rash, injection site reactions	Lupus rashes, sepsis, pneumonia, tuberculosis, demyelination

G6PD, Glucose-6-phosphate dehydrogenase; *MG,* myasthenia gravis; *SLE,* systemic lupus erythematosus; *TNF,* tumor necrosis factor; *UTI,* urinary tract infection.
Adapted from Aletaha D, Kapral T, Smolen JS: Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. Ann Rheum Dis 62(5):482–486, 2003; Donahue KE, Jonas DE, Hansen RA, et al: Drug therapy for rheumatoid arthritis in adults: an update [internet]. Comparative Effectiveness Reviews, No. 55. April 2012.

studies showing poor symptomatic control, NSAIDs (such as, indomethacin 150 to 250 mg/day) should only be considered as supportive therapy during the diagnostic process. Corticosteroids (prednisone 0.5 to 1 mg/kg/day) were more effective in symptom relief. Specialists may consider DMARDs, IV immunoglobulin, and biologic agents.[45]

Relapsing Polychondritis

Relapsing polychondritis, a rare multisystem disorder of unknown etiology, is manifested with recurrent severe inflammation of joints, sclera, ears, nose, and vessels of the heart and kidneys. Most patients eventually have unilateral or bilateral external ear swelling and redness. Because of the rarity of this disorder, there are no controlled trials of therapies, although prednisone 0.5 to 1 mg/kg/day and dapsone 50 to 200 mg/day are recommended.[46] In some series, flare-ups responded well to colchicine (0.6 mg twice daily). However, tracheobronchial cartilage inflammation is possible and can be precipitous, causing respiratory distress and airway compromise. For this, pulse-dose steroids (1 g/day), racemic epinephrine, and sometimes stenting are recommended.

Seronegative Spondyloarthropathies

The seronegative spondyloarthropathies share the characteristics of sacroiliac involvement, peripheral inflammatory arthropathy, absence of rheumatoid factor, pathologic changes around the enthesis (ligamentous and tendinous insertion into bone), and a genetic component related to the HLA-B27 marker. The most important of these chronic polyarthritic inflammatory diseases are ankylosing spondylitis, reactive arthritis, the arthropathy of inflammatory bowel disease (enteropathic arthritis), and psoriatic arthritis. Whereas some clinical overlap exists, each has its distinctive features.

Ankylosing Spondylitis

Clinical Features. Patients with ankylosing spondylitis are generally male, younger than 40 years old, with chronic, insidious back discomfort of more than 3 months, with radiologic evidence of sacroiliitis. Uveitis is the most common extra-articular manifestation, but life-threatening aortic root disease can rarely occur. The peripheral joints are involved in up to 30% of patients with enthesopathic involvement, such as plantar fasciitis and Achilles tendinitis. On radiologic examination, there is a symmetrical squaring of the margins of the vertebral bodies and later the development of a "bamboo spine." MRI changes occur even earlier at the sacroiliac joint.

Management. The goals of therapy are to control pain, to decrease inflammation, and to begin physiotherapy and strengthening exercises. Recent literature review and consensus with use of Delphi methodology recommend a trial of at least two NSAIDs for symptomatic patients.[47] Anti–tumor necrosis factor, sulfasalazine, methotrexate, and monoclonal antibodies are options for more severe disability and pain.

Reactive Arthritis (Formerly Reiter's Syndrome)

Clinical Features. Reactive arthritis occurs in genetically susceptible hosts after infection with *Chlamydia trachomatis* in the genitourinary tract or *Salmonella, Shigella, Yersinia,* or *Campylobacter* organisms in the GI tract. A number of other microorganisms have also been postulated as causative agents.

Reactive arthritis is generally a disease of patients from 20 to 40 years old, in whom arthritis develops 2 to 6 weeks after an episode of urethritis, cervicitis, or dysentery. The syndrome is predominantly polyarticular, asymmetrical, and often additive (Fig. 106.8). The weight-bearing joints of the lower extremities are commonly involved: knees, ankles, and feet, particularly the heels ("lover's heel;" see Fig. 106.8B). Other physical signs appear early and may disappear as musculoskeletal complaints persist. Patients may have conjunctivitis early in the disease, which may progress to uveitis. Up to 10% of patients have initially painless lesions of the oral mucosa and tongue that later develop into shallow painful ulcers. Similar lesions are seen on the glans penis (balanitis circinata), particularly in uncircumcised men (20% of patients). Fingers and toes may swell and appear sausage-like, a phenomenon that also occurs in psoriatic arthritis.

Synovial fluid aspirate is inflammatory in nature with a predominance of PMN cells. *Chlamydia, Salmonella,* and *Yersinia* antigens have been found in the synovial membrane and even in the joint fluid, but cultures are sterile. Early x-ray films show an enthesitis where ligaments attach to bone that occurs at the sacroiliac joints, ischial tuberosities, greater trochanter, and Achilles insertion. Patients may have a single episode (the mean length of an episode is 4 to 7 months) or recurrent episodes of arthritis or a continuous spectrum of disease generally involving the ankles and calcaneus.

Management. Patients with reactive arthritis respond well to NSAIDs, particularly indomethacin, up to 200 mg/day. Antibiotics improve recovery time for patients with *Chlamydia*-triggered reactive arthritis; no benefit has been found for arthritis with a GI cause.

Enteropathic Arthritis. Up to 46% of patients with inflammatory bowel disease experience musculoskeletal manifestations

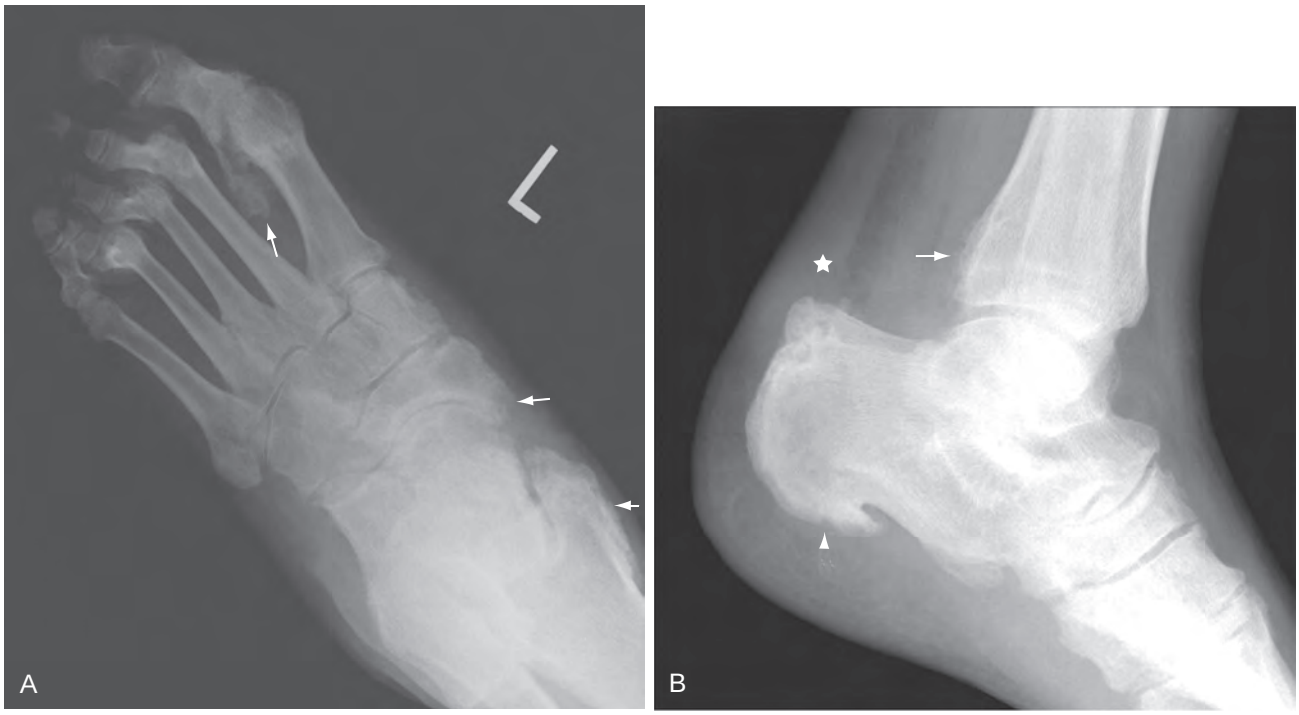

Fig. 106.8. Radiographic findings of the foot in reactive arthritis. **A,** Anteroposterior view of the foot reveals erosions and bone proliferation of the first through fourth metatarsophalangeal (MTP) joints with subluxation. Fluffy bone proliferation is noted along the medial malleolus, midfoot, and sesamoid bones of the first metatarsal head *(arrows).* **B,** Lateral view of the hindfoot shows ill-defined plantar calcaneal enthesophytes *(arrowhead),* periosteal new bone formation along the posterior aspect of the distal tibia *(arrow),* retrocalcaneal bursitis and thickening of the Achilles tendon *(star),* and erosions at the subjacent calcaneus. (From Firestein GS: Kelley's textbook of rheumatology, ed 8, Philadelphia, 2008, WB Saunders.)

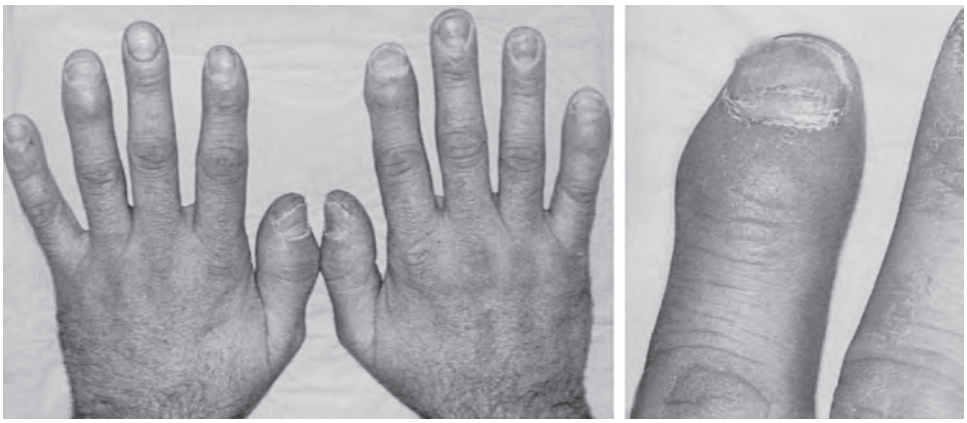

Fig. 106.9. Psoriatic arthritis. Note the asymmetry of the distal interphalangeal (DIP) joint involvement and the associated psoriatic nail disease. (From Firestein GS: Kelley's textbook of rheumatology, ed 8, Philadelphia, 2008, WB Saunders.)

of disease, typically an acute migratory, asymmetrical, inflammatory polyarthritis of the peripheral joints, especially the knees.[48] The peripheral arthritis generally correlates with flare-ups of the bowel disease, but the spinal manifestations do not. NSAIDs are first-line therapy for axial and peripheral joint inflammation, although they may exacerbate inflammatory bowel disease. Sulfasalazine and intra-articular glucocorticoid injections are also options for peripheral arthritis.

Psoriatic Arthritis. Psoriatic arthropathy occurs in up to 20% of patients with psoriasis. Several forms exist: asymmetrical oligoarthropathy (with sausage digits), symmetrical polyarthropathy, spondylitis (asymmetrical as in reactive arthritis), DIP joint involvement, and arthritis mutilans (Fig. 106.9) Although few trials have been performed on psoriatic arthritis, a recent EULAR consensus statement, derived from trials involving rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, recommended NSAIDs as first-line therapy.[49] Local glucocorticoid injections may be considered as an adjunct, but systemic steroids lack supporting evidence. Early involvement from rheumatology and escalation to DMARDs has been shown to improve outcomes, although it may take months for a flare-up to subside.

Fibromyalgia

Clinical Features. Patients with fibromyalgia commonly present to the ED with diffuse musculoskeletal pain. The encounter may be unsatisfying for both patient and provider because the disease is ill-defined, there may be suspicion of analgesic abuse, and psychiatric comorbidity is common. Current thinking about the pathophysiologic mechanism of this disorder hypothesizes that the patients process normal pain stimuli aberrantly. Patients with fibromyalgia have a history of 3 or more months of idiopathic, widespread pain (bilateral, upper and lower body, and spine), and an examination showing excessive tenderness of 11 of 18 specific muscle-tendon sites. The differential diagnosis includes the other rheumatic diseases, hypothyroidism, and depression, and more extensive evaluation should be considered with symptoms of short duration. Fibromyalgia is not consistent with the presence of synovitis, fever, or neurologic deficits.

Management. ED management includes ruling out associated diseases, provision of empathy and education, a recommendation for exercise (found to raise the pain threshold and improve symptoms) and referral of the patient to a provider experienced in chronic pain management. For patients in significant distress, initiating drug monotherapy may be considered. Low-dose tricyclic antidepressants (such as, amitriptyline 10 mg once daily at bedtime), selective serotonin reuptake inhibitors, and pregabalin have been shown to improve pain measures and sleep in patients with fibromyalgia.[50] Opioid medications are of no value for fibromyalgia.[51]

Polymyalgia Rheumatica

Polymyalgia rheumatica is manifested with symmetric musculoskeletal aching and morning stiffness of several weeks' duration, especially of the shoulder and pelvic girdle, almost always in persons older than 50 years old.

Physical signs are modest. An elevated ESR can be used to screen for an inflammatory arthritis; a prospective trial showed the vast majority of polymyalgia rheumatica cases feature an ESR >40 mm, with many above 100 mm/hr. CRP values above 10 mg/L are also suggestive of clinically significant inflammation, although scleroderma, polymyositis, and dermatomyositis are not accompanied by CRP elevation.

Polymyalgia rheumatica is usually self-limited, and a systematic review suggested most patients will respond to low-dose prednisone (15 mg/day or less). All patients should be referred for further evaluation, steroid taper, and evaluation for progression to giant cell arteritis, a closely related disorder.

Scleroderma (Systemic Sclerosis)

Scleroderma has many manifestations discussed in other chapters; musculoskeletal manifestations of scleroderma include morning joint stiffness, tendon friction rubs, symmetrical arthralgias and arthritis, sclerodactyly, and Raynaud's phenomenon. Although there are no prospective trials of therapy, the arthritis of systemic sclerosis seems generally responsive to treatment borrowed from rheumatoid arthritis, including NSAIDs and steroids.[52]

DISPOSITION

Whereas the majority of emergency presentations for arthritis can be followed up satisfactorily in the outpatient setting, the challenge for emergency clinicians evaluating acute arthritis is to decide which presentations could lead to rapidly progressive disease and potential disability, and merit further evaluation and early treatment.

Patients diagnosed with nongonococcal septic arthritis, on the basis of a positive result of Gram's stain or culture or a strong clinical suspicion in the face of a negative Gram's stain result, are admitted for parenteral antibiotics and evaluation for possible arthroscopy or arthrotomy. Patients in whom a disseminated gonococcal infection is suspected are hospitalized for parenteral antibiotics and orthopedic consultation, except in cases in which the patient is well appearing, the symptoms are mild, and the patient is able to comply with the daily follow-up plans. Patients with noninfectious causes of arthritis can be discharged, assuming their pain is controlled and appropriate follow-up can be arranged.

KEY CONCEPTS

- The most likely cause of emergency arthritis presentations can usually be identified by considering the number of joints involved (monarticular versus polyarticular), the distribution of joint involvement (large versus small joints and symmetrical versus asymmetrical joint involvement), and the time course.
- The possibility of septic arthritis should be considered in all patients who present with acute monarticular arthritis.
- There is no combination of examination findings or blood tests that places septic arthritis below the threshold for performance of arthrocentesis in adult patients presenting with a new, hot, swollen, painful joint. Synovial fluid analysis is necessary to for risk stratification of septic arthritis, and delays in treatment worsen outcomes.
- The presence of crystals in synovial fluid or a negative Gram's stain result does not completely eliminate the possibility of septic arthritis. Bacterial arthritis can coexist with gout or pseudogout, and the result of Gram's stain is positive in only 50% to 80% of cases of septic arthritis.
- Many other common arthritides, such as gout, rheumatoid arthritis, and osteoarthritis, can be managed with NSAIDs as a first-line therapy. In those who cannot tolerate or have not improved with NSAIDs, systemic or intra-articular steroid therapy has been shown to have varying levels of support. Appropriate follow-up is crucial for prophylaxis against future flare-ups.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 106: QUESTIONS & ANSWERS

106.1. Which of the following typically presents with a monoarticular arthritis pattern?

A. Drug-induced arthritis
B. Gonococcal arthritis
C. Pseudogout
D. Reiter's syndrome
E. Rheumatic fever

Answer: C. Other monoarticular processes are gout, septic arthritis, Charcot's joint, and hemarthrosis.

106.2. Which of the following typically presents with an asymmetrical polyarticular arthritis pattern?

A. Gonococcal arthritis
B. Lyme
C. Systemic lupus erythematosus
D. Viral arthritis
E. All of the above

Answer: E. Acute rheumatic fever (ARF) does also.

106.3. You perform arthrocentesis of a knee joint because of concern for septic arthritis. Which of the following

findings from joint fluid aspiration increase the likelihood of septic arthritis?
A. Synovial lactate dehydrogenase (LDH) of 300 U/L
B. Synovial lactate of 3.0 mmol/L
C. Synovial whole blood cell (WBC) count of 12,000 cells/mm^3
D. Viscous aspirate

Answer: B. Synovial LDH levels above 250 U/L are sensitive for septic arthritis, whereas lower levels seem to exclude the diagnosis. Similarly, synovial lactate above 5.6 mmol/L is associated with higher likelihood for septic arthritis. Higher synovial WBC counts are directly proportional to the likelihood of a septic joint, but 12,000 cells/mm^3 is still on the low end of the spectrum.

106.4. A 53-year-old man presents with acute onset of right knee pain and swelling. He has a history of diabetes, hypertension, and gout. Physical examination is remarkable for a temperature of 39.6° C and a significant right knee effusion with warmth and significant tenderness to palpitation and motion. Arthrocentesis yields a modestly turbid fluid with a white blood cell (WBC) count of 47,000 cells/mm^3 (mostly polymorphonuclear [PMN] cells), few urate crystals, and negative Gram's stain. Serum erythrocyte sedimentation rate (ESR) is 63 mm/hr. What should be the next step in this patient's management?
A. Admission for observation and analgesics
B. Intravenous (IV) antibiotics and orthopedics consult for admission
C. Outpatient clindamycin, hydrocodone, indomethacin
D. Outpatient colchicine, ice, elevation, hydrocodone
E. Outpatient ice, elevation, hydrocodone, indomethacin

Answer: B. Differentiation of septic arthritis from a flare of a known inflammatory arthritis is difficult because the two can occur in synchrony. Joint fluid WBC counts may be low or high in either, with even WBC counts of 25,000 having an odds ratio for infection of 0.3. There is a predominance of PMN neutrophils in both. With septic arthritis, Gram's stain is positive in only 50% to 70% of cases, so ultimately neither WBC or Gram's stain can rule out a case. Fever is likewise present in both circumstances. In this patient with diabetes and a chronically abnormal joint, empirical treatment as for a septic joint is safest.

106.5. A 54-year-old postmenopausal woman presents with acute onset of right ankle pain. She denies injury or preceding illness. Her past history is remarkable for obesity, nephrolithiasis (one episode), and hypertension that is controlled by a thiazide diuretic. Her examination is remarkable for a low-grade temperature and a tender, warm right ankle effusion requiring use of a wheelchair. Which of the following statements regarding this patient's condition is *true?*
A. A radiograph will be diagnostic.
B. A response to colchicine is diagnostic.
C. Corticosteroids may be useful.
D. Her uric acid level will likely be elevated.
E. Indomethacin has unique efficacy for this process.

Answer: C. Gout develops in men and postmenopausal women. Most patients probably had chronically elevated uric acid levels for years before clinical gout and may have had renal stones or musculotendinous problems due to urate disposition. Uric acid levels may actually normalize during acute attacks and are of no benefit (like radiographs). Both gout and pseudogout (also a crystalline deposition disease) respond to colchicines via similar mechanisms. Indomethacin is no better than any other nonsteroidal antiinflammatory drug (NSAID). Corticosteroids may be particularly useful in cases in which renal or gastrointestinal (GI) considerations contraindicate colchicines and/or NSAIDs. A common regimen is corticotropin (adrenocorticotropic hormone [ACTH]) 40 to 80 international units intramuscularly as a single dose.

106.6. Which of the following findings is consistent with osteoarthritis?
A. Lack of hand involvement
B. Morning stiffness lasting 2 or 3 hours
C. Subchondral bone cysts on radiographs
D. Systemic symptoms
E. Synovial white blood cell (WBC) count greater than 2000 cells/mm^3

Answer: C. This is seen along with osteophytes and joint space narrowing. Systemic symptoms and prolonged morning stiffness suggest rheumatoid arthritis. Synovial WBC count is generally less than 2000 cells/mm^3. Symmetrical and sometimes isolated/severe hand involvement at the proximal interphalangeal (PIP) joint (Bouchard's nodes) and distal interphalangeal (DIP) joint (Heberden's nodes) may be seen.

106.7. A 34-year-old man presents with complaints of bilateral knee swelling. He describes several weeks of diffuse transient migratory myalgias and arthralgias with mild generalized fatigue. During the past 10 days, he developed swelling in his right knee to a greater extent than the left. He has no past medical history and normally takes no medications. He does not recall a rash. He does not use alcohol or tobacco and works as a park ranger. Physical examination reveals bilateral large knee effusions. Which of the following statements regarding this patient's condition is *true?*
A. Careful inspection should reveal a rash.
B. Fever is expected.
C. Immunoglobulin M and G studies are indicated.
D. Joint pain parallels the size of the effusions.
E. Synovial fluid cultures should be diagnostic.

Answer: C. Lyme disease presents in an insidious manner. The classic rash (erythema migrans) often goes unnoticed. This is followed by a pattern of migratory myalgias and arthralgias. Joint effusions are large, not very painful, and culture negative because of the difficulty culturing *Borrelia* species.

106.8. A 47-year-old woman presents with fatigue and joint pain. She describes a 3-month history of fatigue, morning stiffness, and bilateral hand, foot, and elbow stiffness that improves somewhat over the course of the day. Laboratory evaluation reveals a normocytic anemia with a white blood cell (WBC) count of 11,300 cells/mm^3. She localizes most of her daily pain to the knuckles of both hands. Which of the following statements regarding this patient's condition is *true?*
A. Acute pericarditis only occurs after long-standing disease.
B. C1 to C2 instability is unlikely.
C. Finger distal interphalangeal (DIP) joints should reveal painful swelling.
D. The joint pain is typically migratory.
E. The presence of foot pain is not expected.

Answer: B. This presentation for rheumatoid arthritis is fairly typical. C1 to C2 instability due to transverse ligament degeneration is only after long-standing disease. Pericarditis, however, may occur as an acute presentation or chronically. More than 90% of rheumatoid arthritis patients develop foot pain, classically in the first and fifth metatarsophalangeal (MTP) joints. The joint pain is progressive and additive—not migratory.

CHAPTER 107

Tendinopathy and Bursitis

Christopher Hogrefe | Emily Martin Jones

TENDINOPATHY

Principles

Background

Emergency clinicians may see a wide variety of patients with tendinopathies due to overuse and injury due to growing involvement in athletics and fitness-related activities and overall increased participation by individuals at younger ages.[1] Approximately half of all sports participants will be injured at some time, and of these injuries, up to half will involve tendinopathy. Tendinopathies have been implicated in approximately 40% of tennis injuries, and up to 79% of runners will sustain an injury during a given year, with most of these injuries related to overuse.[2] Overall, women younger than 30 years old are at the greatest risk for overuse injuries. In the workplace, the incidence of work-related musculoskeletal disorders is higher in occupations that involve repetitive motion, localized contact stress, awkward positions, vibrations, and forceful exertion. Additionally, those working for 25 to 35 years are 7.1 times more likely to develop tendinopathy. Ergonomic and medical intervention programs may reduce the incidence of work-related injuries.

Complicating the acute pain and functional limitations, tendinopathies often become chronic (greater than 3 months in duration) and can be disabling. Patients may have symptoms for extended periods despite appropriate therapy. The management of tendinopathy focuses on identifying the cause of discomfort; eliminating the sources of primary tendinopathy; instituting treatment modalities, such as analgesic medication, protection, relative rest, optimal loading, application of ice, compression, and elevation as necessary; modifying behavior to minimize or eliminate sources of continuing irritation; and, importantly, referring patients for appropriate follow-up care and early rehabilitation.[3] However, despite these interventions, recurrence of the tendinopathy is common.[1]

Tendons are collagenous structures that connect muscle to bone. They transmit forces originating in the muscle to the bone, enabling joint motion. The diagnosis of *tendinitis,* a commonly used term implying "inflammation of the tendon," has long been attached to many overuse injuries. Many practitioners now advocate use of the term *tendinosis* as a more accurate reflection of the pathologic process, representing a degenerative process without evidence of inflammation.[1] Although it has been noted that reliable, well-conducted epidemiologic studies have not been performed for most tendinopathies, the histopathologic substratum, in many cases, is degenerative. The term *tendinopathy* is used throughout this chapter to refer to a painful, impaired tendon, encompassing the variety of pathologic processes.[4]

Mechanical overload and repetitive microtrauma to the musculotendinous unit are thought to be the major precipitating causes of most tendinopathies. This is a result of extrinsic and intrinsic factors that modify the pathophysiologic state. Intrinsic factors (eg, age, gender, blood type O, malalignment, joint laxity, muscle weakness, and imbalance) can result in excessively high or frequent mechanical loads during normal activity. Extrinsic factors (eg, ergonomics, equipment changes, abnormal movements, excessive duration of activity, and increased frequency or intensity of activity) can also contribute to the development of a tendinopathy. Other potential contributing etiologies include excessive protein intake, obesity, systemic disease, and medication use. An increased incidence of tendinopathy and tendon rupture, particularly of the Achilles tendon, is reported in patients taking fluoroquinolone antibiotics. This risk is further increased within the first month of treatment, in those over 60, patients receiving steroid treatment, or those with renal disease.[5] Most tendinopathies have a multifactorial origin. Several of the common areas affected by tendinopathy are found in Figure 107.1.

Under optimal conditions, such as appropriately graduated athletic training, the musculotendinous units are able to adapt to tension overload. This is secondary to the ability of bone to increase its load-bearing capacity along with an increase in size and strength generated by the hypertrophy of existing muscle fibers. An enhancement of tendon and ligament strength occurs by an increase in collagen content, collagen cross-linking, and mucopolysaccharide content. Unfortunately, many athletes may not allot sufficient time for this adaptive process to occur. For instance, a runner may increase mileage, intensity, or both with haste, not allowing for the cellular changes that are required to adapt to the increased stresses. Poor technique, suboptimal running surfaces or environmental conditions, and improper equipment may also contribute to the development of an overuse syndrome.

Pathophysiology

The pathophysiologic mechanism of tendon healing has mainly been described in the literature in the context of acute injury (eg, rupture), and correlation to the healing process in tendinopathies remains unclear. Acutely injured tendons go through several stages in the healing process, which are thought to involve cell proliferation, collagen disorganization, increased proteoglycans, and neovascularization.[6] It may take 6 to 12 weeks for the tendon to regain its former strength. As the healing process ensues, unrestricted activity is generally avoided. However, atrophy associated with immobilization should also be avoided because the strength in healing tendons and ligaments increases faster when controlled forces are applied. Consequently, optimal loading is now advocated as a means of advancing from rest to a balanced, incremental rehabilitation program.[3] Such rehabilitation focuses on flexibility forces, eccentric strength training, and a measured return to resistive exercises as long as pain is not produced. Most patients with overuse tendinopathies fully recover within 3 to 6 months. In summary, a prescription for good follow-up with proper rehabilitation is important in the treatment of tendinopathies.

Clinical Features

General Tendinopathy

The history of the patient presenting with a tendinopathy can be variable, although certain clinical aspects are characteristic. A

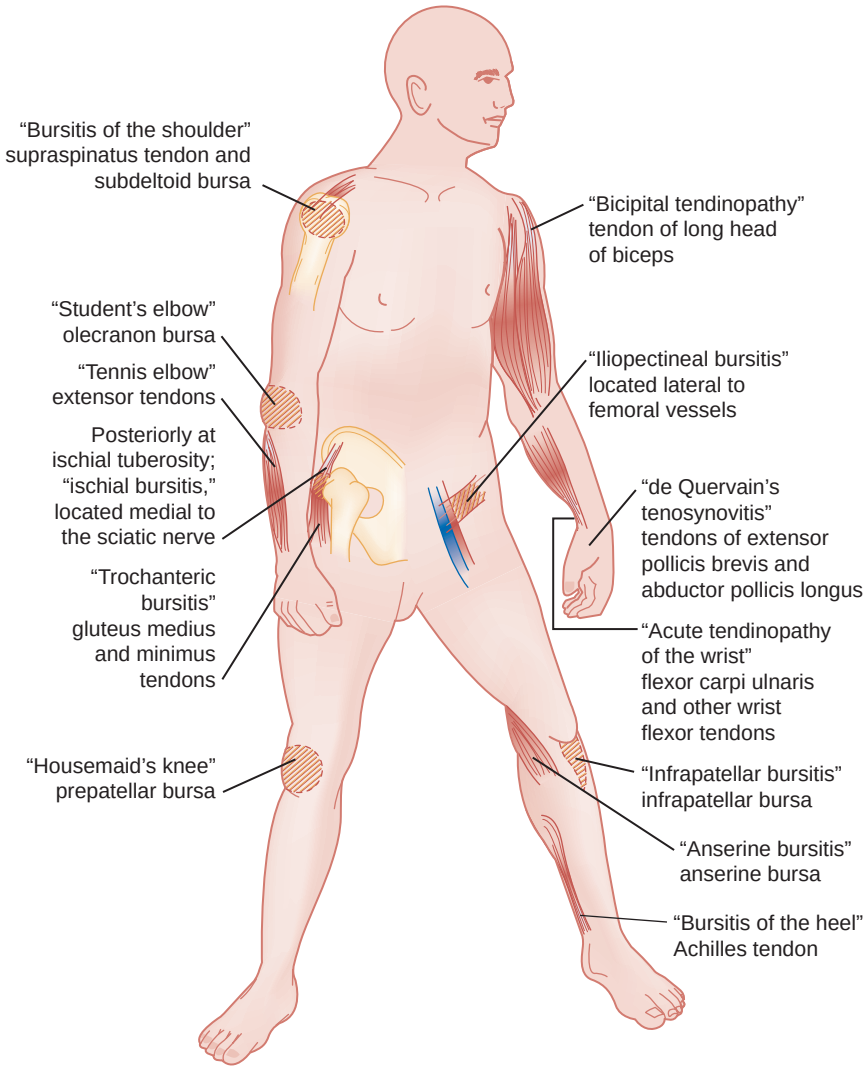

Fig. 107.1. Location of common sites for tendinopathy or bursitis. (Modified from Branch WT: Office practice of medicine, ed 2, Philadelphia, 1987, WB Saunders.)

recent history of repetitive stress may be reported due to work activities, changes in the workplace, or alterations in sport or recreational activities. It is important to ask patients to consider the weeks to months preceding the onset of symptoms; a potential inciting event or change (eg, workplace ergonomics, protective footwear, new sports equipment, and so on) may be elicited. Occasionally, no cause is identified for a mechanical overload. A history of fluoroquinolone therapy, infectious disease, or other systemic illness should also be obtained as initial presentations of rheumatologic disorders or infections, such as those from *Mycobacterium,* have been described.

Pain is the most common symptom of the patient who presents with tendinopathy. Increasing, non-radiating discomfort at the site of the affected tendon is a general symptom. The discomfort is frequently described as more severe subsequent to periods of rest. Unlike the discomfort of morning stiffness associated with arthritis, the pain of tendinopathy may resolve after initial movement, only to be manifested as a throbbing pain after the completion of exercise. Individuals may report similar prior episodes, whereas continued episodes may be accompanied by an increased severity in pain. Consequently, it may be helpful to inquire about a related previous diagnosis, how it was made, and which treatment (if any) was effective in resolving the prior episode.

In the evaluation of the patient with a tendinopathy, a thorough, directed musculoskeletal examination yields important information. Searching for signs of edema, effusion, erythema, atrophy, deformity, asymmetry, or trauma can be helpful. Palpation of the tendon, noting warmth or evidence of crepitance on movement, is important. Evidence of tenderness over the tendon, especially localized and reproducing the patient's pain, should be elicited. However, although tendon palpation can be sensitive for reproducing tendinopathy-related symptoms, it is not particularly specific in determining the pathologic structure. Underlying bone tenderness (and consideration of other differential diagnoses, including avulsion fracture and osteomyelitis; Box 107.1) should be assessed as well. Motor function (particularly passive and active range of motion), strength (and evidence of weakness or pain), and joint involvement and stability should be noted.

In narrowing the diagnosis, it is important to determine whether the source of pain is articular (within the joint capsule) or periarticular (around the joint capsule). In general, arthritis produces generalized joint pain, warmth, swelling, and diffuse tenderness. The discomfort of arthritis increases with both passive and active motion of the joint. In contrast, the pain of a tendinopathy tends to be more localized. Tenderness and swelling do not occur uniformly across the joint, and pain may be produced only with certain movements, particularly with resisted active contraction or passive stretching of the affected muscles or tendons. However, the diagnostic significance of mechanical hyperalgesia (ie, increased pain with passive and active range of

BOX 107.1

Differential Diagnosis for Tendinopathy

Tendon rupture
Ligamentous injury
Inflammatory arthritis (eg, rheumatoid)
Fractures (eg, avulsion)
Tumors
Tenosynovitis
Osteochondrosis (eg, Osgood-Schlatter disease)
Bursitis
Septic arthritis
Osteoarthritis
Foreign bodies
Osteomyelitis
Nerve entrapment syndromes
Tendon sheath infections (eg, pyogenic)

motion) is controversial because its presence may reduce the specificity of the commonly used clinical tests discussed later in this chapter.[7]

Specific Tendinopathies

Shoulder. Tendinopathies of the shoulder joint include impingement syndrome (which includes subacromial bursitis or rotator cuff tendinopathy), bicipital tendinopathy, calcific tendinopathy, and adhesive capsulitis.

Impingement Syndrome and Rotator Cuff Tendinopathies. The shoulder joint is predisposed to soft tissue injury because of its extensive range of motion and unique anatomic structure. Although it is inherently unstable, the muscles of the rotator cuff (supraspinatus, infraspinatus, teres minor, and subscapularis) and the glenohumeral ligaments serve to stabilize the joint. The muscles of the rotator cuff originate from the scapula (hence their nomenclature), and their tendinous insertion is found on the fibrous capsule of the glenohumeral joint after traversing through the subacromial space. The presence of the subacromial bursa, as for all bursae, serves to ensure fluidity of movement, but it may become inflamed as a part of an impingement syndrome.[8] Impingement of the tendons occurs because of their position interposed between the humeral head and the acromion, which may predispose to a chronic tendinopathy. The functional arc of the elevated shoulder is forward and in the anterior plane. As a result of this position, the greater tuberosity of the humerus may compress (impinge) the tendons of the rotator cuff (usually the supraspinatus) against the undersurface of the anterior third of the acromion. Additionally, the long head of the biceps may be involved in impingement syndrome due to the location between the supraspinatus and subscapularis tendons in the rotator interval.[9] Development of this tendinopathy may be a result of overuse of the extremity that leads to microtrauma of the tendinous fibers, individual anatomic differences (congenital or from the process of aging, such as osteophytic changes), or both. Other entities that may coexist and complicate an impingement syndrome include subacromial bursitis, bicipital tendinopathy, and calcific tendinopathy.

More than 30 years ago, Neer noted that 95% of rotator cuff tears are associated with impingement (excluding tears due to a one-time traumatic event). He described three progressive stages of the impingement syndrome as a result of overuse. The first stage is frequently seen in athletes younger than 25 years old who participate in sports that require repetitive overhead motions of the shoulder (eg, swimming and baseball). The pain is usually described as a dull ache over the anterolateral shoulder, extending from the shoulder to the middle upper arm, often occurring after an activity involving flexion and abduction of the arm. Point tenderness may be elicited over the greater tuberosity. No weakness or loss of motion is generally present. This condition is generally believed to be reversible with appropriate treatment. In the second stage, as mechanical trauma continues, fibrosis and thickening of the tendon and subacromial bursa can occur. This generally affects patients between 25 and 40 years old. The pain becomes constant and may worsen at night. Active motion may be limited by pain, and any activity involving overhead movement exacerbates the symptoms. Passive range of motion should be preserved, and on physical examination pain is more diffuse and intense. The third stage has symptoms similar to those of the second stage but may involve a prolonged history of shoulder problems. The range of motion of the shoulder is usually decreased because of either disuse or a partial rotator cuff tear. On pathologic examination, tendon degeneration and attrition may be present. Partial-thickness tears may occur or extend with minor trauma or stress. Complete tears of the rotator cuff, biceps tendon rupture, and osteophytic bone changes are sometimes seen.

Physical examination in the evaluation of a rotator cuff tendinopathy includes maneuvers that can exacerbate the symptoms of impingement. Because the supraspinatus tendon is most often involved, a physical examination sign (sometimes referred to as *Jobe's sign,* after Frank Jobe, former team physician of the Los Angeles Dodgers, or the *empty can test,* describing the position of emptying aluminum cans) is helpful in assessing the supraspinatus tendon with resistance testing. With the arms abducted at 90 degrees in the scapular plane (30 degrees anterior to the coronal plane), the arms are internally rotated with the thumbs pointed downward. The examiner places a downward force on the arms, and the patient is instructed to resist the examiner and to keep the arms parallel to the floor. Weakness or pain is considered a positive finding. When assessing for subacromial impingement, the empty can test has a sensitivity of between 50% and 52% with a specificity ranging from 33% to 87%.[10] If the patient is unable to resist the force of the examiner, a supraspinatus tear should be suspected.

Another sign of rotator cuff tendinopathy is elicited by the *Neer test,* which suggests mechanical impingement with a decrease of the subacromial space. The examiner forward flexes the arm to 180 degrees, which causes impingement of the greater tuberosity of the humerus with the anterior and inferior edge of the acromion. A positive result occurs if there is pain produced at the end range of the arc. Studies assessing the utility of this test report significant variability, with sensitivities ranging from 54% to 81% and specificities from 30% to 95%.[10]

The *Hawkins-Kennedy test,* also indicative of mechanical impingement, is performed by forcibly internally rotating the proximal humerus while the shoulder is forward flexed to 90 degrees and the elbow flexed to 90 degrees. Pain with this maneuver indicates a positive finding. Again, the sensitivity (58% to 74%) and specificity (40% to 89%) of this test fluctuates in the literature.[10]

A complete rotator cuff tear is evaluated by the *drop arm test,* in which the arm is passively abducted at 90 degrees and the patient is asked to maintain the abduction. If the arm drops to the side, a large rotator cuff tear should be considered. Studies have shown this test to be 74% sensitive and 66% specific for a full-thickness rotator cuff tear.[10] The *shrug sign* is exhibited when a patient with acute macrotrauma to the rotator cuff is asked to abduct the arm at 90 degrees and appears to be giving a shrug with that side. This movement results from the scapula's attempt to abduct the arm without the assistance of the rotator cuff. Although this has historically been associated with rotator cuff disease, it is somewhat nonspecific and can be associated with

other shoulder disease, including glenohumeral osteoarthritis and adhesive capsulitis.[10] Patients with adhesive capsulitis (frozen shoulder) have limitation of active and passive range of motion.

Bicipital Tendinopathy. The tendon of the long head of the biceps, given its passage between the supraspinatus and subscapularis tendons in the anterior shoulder, can be associated with impingement syndrome. The patient with bicipital tendinopathy may report pain in the anterior shoulder that radiates down to the radius. Discomfort occurs when the individual rolls onto the shoulder at night or attempts to reach into a pants pocket. Focal tenderness can be obtained by palpation of the groove between the greater and lesser tuberosities of the humerus. However, research has shown that clinician accuracy in palpating the long head of the biceps tendon is poor.[11] Yergason's sign can assist in the diagnosis of bicipital tendinopathy. This test is performed by having the patient flex the elbow to 90 degrees with the arm against the body and resisting supination of the forearm. Pain in the area of the proximal tendon is considered to be a positive finding and indicative of bicipital tendinopathy. There is significant variability in its sensitivity (14% to 75%), although its specificity is good (78% to 89%).[10]

Another physical examination tool in the diagnosis of bicipital tendinopathy is the *Speed sign*. With the elbow extended and the forearm supinated, the patient is instructed to resist forward flexion of the adducted shoulder at 60 degrees. Pain in the area of the proximal biceps tendon (bicipital groove) is indicative of a positive finding. Although this test may be suggestive of labral pathology as well, meta-analyses suggest that it is more sensitive and specific for bicipital tendinopathy.[10,12]

Calcific Tendinopathy. Calcific tendinopathy is an acutely or chronically painful condition associated with the deposition of calcium crystals that occurs in or around the tendons of the rotator cuff. The cause is unknown but has been postulated to be related to tissue hypoxia and degeneration due to overuse. Also, studies have shown an association of calcific tendinopathy with diabetes mellitus and thyroid disorders.[13] Although it can affect any of the rotator cuff tendons, it seems to have a predilection for the supraspinatus. The symptoms are similar to those of an impingement syndrome, and the condition generally affects people older than 40 years old. Calcium deposition occurs over time and then undergoes spontaneous resorption. This resorptive phase is thought to be the painful aspect, but the severity of the symptoms is not related to the size of the deposit. Pain is believed to be in response to the local chemical pathologic disorder and direct mechanical irritation. On physical examination, there may be specific tenderness over the greater tuberosity, as well as symptoms consistent with impingement. Radiographic evaluation may show evidence of calcification in or around the rotator cuff tendons (Fig. 107.2). The presence of calcium in the tendon does not necessarily affirm the origin of the pain because asymptomatic patients may have evidence of calcification on a routine radiograph.

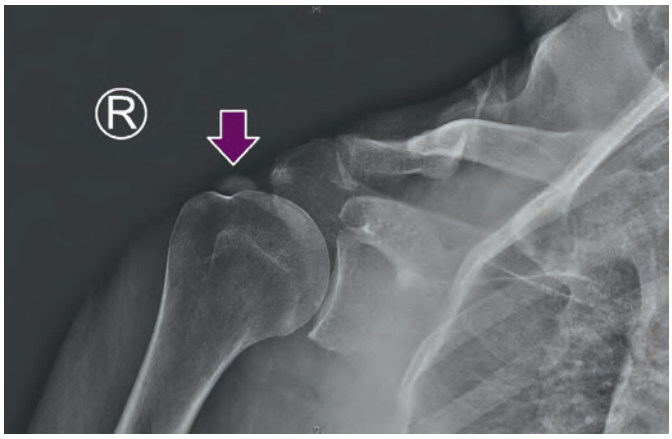

Fig. 107.2. Plain films of the right shoulder revealing a prominent calcium deposit in the supraspinatus tendon resulting in acute pain and decreased range of motion secondary to calcific tendinopathy.

Elbow

Increasingly, athletes of all ages and skill levels are participating in sports involving overhead arm motions. Consequently, the incidence of elbow injuries is increasing.[14] From an anatomic and functional perspective, the extensors and supinators of the wrist attach to the lateral elbow, and the flexors and pronators attach medially.

Lateral Epicondylitis. Lateral epicondylitis ("tennis elbow") is a painful elbow condition that occurs at the insertion of the common extensor tendon (extensor carpi radialis brevis) onto the lateral epicondyle of the humerus. Although it occurs in many tennis players, epidemiologic studies suggest that less than 5% of patients with such a syndrome actually play tennis. Activities such as driving in screws, use of a wrench, and repetitive work on an assembly line have also been implicated. In fact, it has been shown that in such strenuous jobs there is up to an 11% incidence of lateral epicondylitis. Symptoms often begin as a dull ache on the outer (lateral) aspect of the elbow. The discomfort can be exacerbated by activities that involve extension or supination of the wrist, such as grasping and twisting. *Cozen's test* is performed by having the patient keep the fist clenched while extending the wrist. The examiner grasps the forearm with the left hand while the right hand pulls the patient's hand toward flexion against the patient's resistance. A positive finding is pain at the lateral epicondyle, reproducing the patient's symptoms.

Active extension of the middle finger (ie, third digit) against resistance with the elbow in extension, which is known as *Maudsley's test,* can also reproduce the pain over the lateral epicondyle at the insertion of the extensor carpi radialis brevis. In addition, patients will typically have tenderness to palpation just distal to the lateral epicondyle, over the origin of the extensor carpi radialis brevis.

Radiographs can be helpful in cases with atypical or prolonged symptoms to rule out other pathologic conditions. Approximately 20% of patients demonstrate tendon calcification or a reactive exostosis at the tip of the epicondyle. The differential diagnosis of lateral epicondylitis includes posterior interosseus nerve entrapment (motor aspect of the radial nerve in the forearm), plica lesions, synovitis, chondromalacia, and adolescent osteochondral defects.

Medial Epicondylitis. Less common than its lateral counterpart, medial epicondylitis ("pitcher's elbow" or "golfer's elbow") can result from microtrauma at the site of the insertion of the flexor carpi radialis on the medial epicondyle. It is important to differentiate medial epicondylitis from other causes of medial elbow pain, including medial ulnar collateral ligament injury. As a result of repetitive valgus stress placed on the joint, microtraumatic injury and valgus instability at the ligament can occur. With disruption of the medial ulnar collateral ligament, abnormal stress is placed on the articular surfaces, which may lead to degenerative changes and the formation of osteophytes. In the case of medial epicondylitis, patients will generally have tenderness over the flexor pronator origin slightly distal and anterior to the medial epicondyle. The pain of medial epicondylitis can be reproduced by having the patient attempt wrist flexion and forearm pronation against resistance.

Wrist

de Quervain's Tenosynovitis. The wrist and hand comprise several tendons that pass through thick, fibrous retinacular tunnels. These help prevent subluxation of the tendons and act as

a pulley system. Overuse syndromes are thought to result from changes of the synovial lining between these tendons and the retinaculum. de Quervain's tenosynovitis involves the synovial lining of the abductor pollicis longus and extensor pollicis brevis. Although the term *tenosynovitis* indicates an inflammation of the tendon sheath, it has been noted that there are many potential forms of tenosynovitis. Classic acute inflammatory changes that are characteristic of tenosynovitis may be related to systemic manifestations of disease (eg, rheumatoid arthritis and gout). Tenosynovitis related to de Quervain's syndrome is referred to by some practitioners as *stenosing tenosynovitis.* The pathologic process of de Quervain's tenosynovitis does not generally involve inflammation because the primary change is thickening of the extensor retinaculum covering the first dorsal compartment of the wrist. It has been suggested that de Quervain's disease is a result of intrinsic degenerative mechanisms rather than extrinsic inflammatory ones.

The history may consist of chronic, repetitive trauma or unaccustomed repetitive efforts, such as firm grasping and movement of the hand in a radial direction. However, studies have not found a causal relationship between this condition and specific occupational risk factors.[15] Direct trauma, such as a direct blow or fall, has occasionally been implicated. Yet, in most cases of de Quervain's tenosynovitis the onset is gradual. The discomfort of de Quervain's tenosynovitis can be localized over the radial styloid process. Radiation of pain proximally to the forearm or distally down the thumb has been noted. The pain is generally constant but may be exacerbated by maneuvers that include grasping, abduction of the thumb, and ulnar deviation of the wrist.

On physical examination, slight swelling may be seen over the radial styloid. Crepitance may be appreciated over the tendons with flexion and extension of the thumb. An increase in the tensile load (passive stretching or active contraction) in the abductor pollicis longus or extensor pollicis brevis increases pain. The *Finkelstein test,* which exacerbates the discomfort of de Quervain's tenosynovitis, is the most pathognomonic physical sign. The patient is instructed to hold the affected thumb in the palm by the fingers and then to ulnar deviate the wrist. Pain will occur near the radial styloid, which is also the point of tenderness. Pain with this maneuver is considered to be a positive finding. Radiographs are characteristically normal. The differential diagnosis includes scaphoid fracture and osteoarthritis of the carpometacarpal joint, which features pain caused by longitudinal traction and compression. It should be noted that the Finkelstein test can produce some pain at the carpometacarpal joint, reducing its specificity. Rarely, infections such as tuberculosis or disseminated gonococcal infections can manifest as tenosynovitis.

Knee

Patellar Tendinopathy. Patellar tendinopathy ("jumper's knee") commonly occurs in sports that have a prominent jumping component, although it can also occur as a result of other sporting activities. Patients report pain at the inferior pole of the patella. The discomfort may abate with activity early in the tendinopathy but later progresses to the point of discomfort during both exercise and rest. With the knee flexed at 30 degrees, which relaxes the quadriceps, tenderness may be localized to the deep surface of the proximal attachment of the patellar tendon at the inferior pole of the patella. However, healthy active athletes sometimes have tenderness on examination as well.

The differential diagnosis includes patellofemoral syndrome, which arises from imbalances in the forces that control tracking during knee flexion and extension. The patient usually complains of anterior knee pain, described as "behind" or "around" the patella, which is classically worse with ascending or descending stairs or on rising from a seated position. On occasion, there is tenderness of the medial or lateral retinacula or facets.

Imaging with ultrasonography and magnetic resonance imaging (MRI) may reflect collagen degeneration or collagen disorganization but is generally adjunctive to the distinctive history and physical examination findings.[16] It is noted that some asymptomatic jumping athletes have imaging appearances similar to those of affected individuals and that prognosis and outcome are not predicted by such imaging.

Ankle

Achilles Tendinopathy. Achilles tendinopathy is a common overuse syndrome that typically affects male athletes. The Achilles tendon is named for the mythological Achilles, whose heel was not immersed in the river Styx as his mother dipped him in the river for its protective powers. It arises from the medial and lateral heads of the gastrocnemius muscle and the deep layers of the soleus muscle, inserting on the calcaneal tuberosity. A major function is plantar flexion of the foot. It is the strongest and largest tendon in the body and can withstand tensile loads more than 12 times the body's weight during running.

The Achilles tendon is vulnerable to injury from either trauma or overuse. A tendinopathy can also develop as a result of systemic disease (eg, ankylosing spondylitis, Reiter's syndrome, gout, and pseudogout). The use of fluoroquinolones has also been related to Achilles tendinopathy.

The occurrence of Achilles tendinopathy is highest among individuals who participate in middle- and long-distance running, track and field, tennis, badminton, volleyball, and soccer. Some studies have noted an almost 10% annual incidence of Achilles disorders in elite runners, with lifetime incidence reports up to 52%.[17] The most common Achilles disorders are tendinopathy (55% to 66%) and insertional problems, such as retrocalcaneal bursitis and insertional tendinopathy (20% to 25%). Many cases of Achilles tendinopathy are thought to be multifactorial in origin. Body mechanics and environmental factors (eg, uneven terrain) may apply valgus or varus stress to the tendon. Technique, equipment, and body mechanics can also contribute to the development of this tendinopathy. Anatomically, the vascular supply to the tendon creates a watershed area approximately 2 to 6 cm above the calcaneal insertion. This is thought to be responsible for clinical symptoms and the pathologic disruption commonly seen at this site.

The patient's history provides most of the information necessary to make the diagnosis of Achilles tendinopathy. Pain, a cardinal symptom of Achilles tendinopathy, may lead the patient to seek medical help. Some practitioners have noted that the patient's symptoms reflect the degree of the tendon abnormality, which has been validated in MRI studies assessing abnormal signal within the Achilles tendon. However, studies focusing on other changes associated with Achilles tendinopathy, such as neovascularization, have not shown a correlation with pain severity.[18] Regardless, as with many tendinopathies, pain after strenuous activities is reported in the early phase, whereas pain in the later phase occurs during activity and even at rest. At this point, the patient is often unable to perform sporting activities.

On physical examination, inspect the contour of the muscle-tendon unit and note areas of swelling and erythema. In acute Achilles tendinopathy, the tendon may be diffusely swollen and exhibit tenderness on palpation, usually greatest in the middle third. Typically, in the patient who has acute symptoms of tendinopathy, the area of swelling and tenderness does not move with dorsiflexion of the ankle joint. On palpation, local heat, crepitance, and palpable tendon nodules or defects may be noted. Examination for ankle instability and biomechanical faults should be considered.

Achilles Tendon Rupture. Although rupture of the Achilles tendon most often occurs when it is preceded by tendon damage, it is possible for untrained athletes to apply excessive force and to

rupture the tendon in the absence of prior changes of tendinopathy Partial and complete rupture may occur, most commonly in 30- to 40-year-old men. Complete rupture is more common in the middle-aged recreational athlete. Historically, the patient may note a "pop" followed by acute weakness and an inability to continue with exercise or sport. The patient may report feeling as though he or she was struck in the back of the ankle.

On physical examination, a defect in the tendon can sometimes be palpated. If enough time has elapsed to allow hematoma formation, bogginess may be noted over the injured area of the tendon. The ability to plantar flex the foot does not rule out a complete rupture of the Achilles tendon. There are multiple plantar flexors of the foot and toes. Muscles such as the tibialis posterior, flexor digitorum longus, flexor hallucis longus, peroneus brevis, and peroneus longus can remain functional and therefore disguise a complete rupture with the ability to plantar flex the foot.

A couple of observations that aid in the diagnosis of an Achilles tendon rupture can be made with the patient in the prone position. Assess for decreased resting plantar flexion compared to the opposite side, which is normally 20 degrees to 30 degrees.[19] The *Thompson (Simmonds) test* can also be performed to evaluate for a complete rupture. With the patient prone and feet hanging over the edge of the bed, the examiner squeezes the calf muscles at their widest point and looks for passive plantar flexion. The absence of plantar flexion is considered a positive finding, indicative of a complete tear of the Achilles tendon. The presence of plantar flexion does not, however, eliminate the possibility of a partial tear of the Achilles tendon. Overall, the triad of a palpable tendon defect, decreased resting tension, and a positive Thompson test has a diagnostic sensitivity greater than MRI.[19]

Differential Diagnosis

The differential diagnosis of tendinopathy is listed in Box 107.1.

Diagnostic Testing

The diagnosis of tendinopathy is generally made on clinical grounds. Although plain radiographs may be helpful in excluding bone abnormalities, ultrasonography has been recommended by some practitioners as the modality of choice for evaluation of pathologic tendon conditions. Ultrasonography can be especially useful when other conditions (eg, gouty arthritis) obscure the findings of concomitant tendinopathy. Although its efficacy in the hands of emergency clinicians relative to tendon injury is still being studied, it has been shown to be effective in identifying conditions, such as shoulder impingement and tendon disruption or rupture.[20,21] In cases of acute or chronic tendinopathy, one or more of the following features can be seen: loss of the fibrillar echotexture, focal tendon thickening, diffuse thickening, focal hypoechoic areas, extended hypoechogenicity, irregular and ill-defined borders, micro ruptures, and peritendinous inflammatory edema. Hypoechoic areas surrounding tendons provide evidence for surrounding soft tissue inflammation. In addition to tendinopathy, tendon tears, both partial and complete, can be delineated by ultrasonography.

MRI has been used to visualize pathologic conditions of the tendon. It is able to provide high intrinsic tissue contrast, which permits the distinction between normal tendons and abnormal tendons, and the high spatial resolution that permits detailed anatomic structures to be identified. MRI has superb resolution of the soft tissue structures and can aid in a variety of tendon disorders. Cost, availability, the need to have the patient remain still during the examination, and the loss of the dynamic component compared with ultrasound examination are disadvantages of this modality.[22]

Management

General Tendinopathy

The management of tendinopathy focuses on identification of the cause of discomfort; elimination of sources of primary tendinopathy; institution of treatment modalities, such as analgesic medication, protection, relative rest, application of ice, compression, and elevation as necessary; modification of behavior to minimize or to eliminate sources of continuing irritation; and, importantly, referral for appropriate follow-up care.

Cryotherapy (cold treatments, 20 minutes at a time every several hours, for the first 24 to 48 hours) may be beneficial. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also sometimes indicated to provide pain relief, although there is little evidence to support a beneficial effect with their use because tendinopathies tend to represent a degenerative rather than an inflammatory process. Graduated range-of-motion exercises may be useful after the period of immobilization. Although a corticosteroid injection is often used, its role for most tendinopathies is unclear. Most patients will experience short-term improvement in pain and/or function after a corticosteroid injection, but this comes at the expense of a higher risk of relapse in the medium- and long-term.[7] Steroids should not be injected into a major tendon such as the Achilles or patellar tendons, which may be at risk for spontaneous rupture if they are already weakened.

The use of nitroglycerin patches has been shown to be effective in the treatment of tendinopathy. Questions remain as to whether its efficacy is due to an analgesic effect or rather a healing effect on the affected tendon. Studies assessing lateral epicondylitis and Achilles tendinopathy have shown their use to be superior to placebo. Headaches are the most commonly experienced side effect of this medication. The use of this nitroglycerin patches for tendinopathy is off-label and may be considered in follow-up with a sports medicine provider or an orthopedist.

Platelet-rich plasma (PRP) injections, a process by which a patient's platelets are concentrated in a centrifuge and then injected into the affected tendon, have been introduced as a treatment modality. The literature contains numerous case reports and small studies suggesting this treatment is effective. However, a general lack of high-quality, randomized, prospective controlled trials precludes our recommending its use in the emergency department (ED) at this time.

Specific Tendinopathies

Impingement Syndrome and Rotator Cuff Tendinopathies. The treatment of rotator cuff tendinopathies and the impingement syndrome follows the treatment of tendinopathy in general. Emphasis is placed on physical rehabilitation and strengthening exercises. A significant proportion of patients will improve with conservative management. In those who do not, surgical intervention (such as, acromioplasty, débridement, or repair) may be indicated.[23]

Calcific Tendinopathy. The initial treatment of calcific tendinopathy is mainly conservative and consists of analgesia and brief sling immobilization because prolonged immobilization may result in adhesive capsulitis. The use of corticosteroids is controversial. Ultrasonography and extracorporeal shock wave therapy have been used with some success. As well as arthroscopic treatment, localized disruption by needle lavage and aspiration under ultrasound-guidance has been shown to be effective with improved pain and function outcomes compared to corticosteroid injections and extracorporeal shock wave therapy.[24,25] A small percentage of patients who do not respond to these interventions may need surgery. Follow-up care from the ED is important

because calcific tendinopathy has been described as the most well-known cause of reactive cuff failure (Fig. 107.3).

Lateral and Medial Epicondylitis. In up to 95% of patients, epicondylitis will improve with conservative therapy. Initial efforts include making the patient more comfortable with the standard principles of protection, relative rest, cryotherapy, compression, elevation, medications (NSAIDs), and modalities of physical therapy. The term *relative rest* implies the avoidance of overuse as opposed to the absence of activity. Activities that aggravate the pain should be eliminated, and an attempt to protect the tendon through such strategies as a reduction in playing time or intensity should be considered. The use of bracing (eg, counterforce brace) to control force loads, improving performance technique, and the use of appropriate equipment should also be considered. Studies regarding the efficacy of corticosteroid injections suggest a short benefit (at 4 weeks), but worse clinical outcomes at 1-year follow-up.[26,27] Follow-up evaluation for lateral or medial epicondylitis should be ensured.

de Quervain's Tenosynovitis. The initial treatment of de Quervain's tenosynovitis consists of immobilization with a thumb spica splint, antiinflammatory medications, and prompt referral. Corticosteroid injections have been shown to be an effective treatment of de Quervain's disease, and failure to respond may be due to anatomic variation or poor technique. A meta-analysis assessing the efficacy of corticosteroid injections revealed a number needed to treat (NNT) of two to obtain a beneficial outcome.[28] Surgical decompression of the first dorsal compartment may be indicated if these treatments fail.

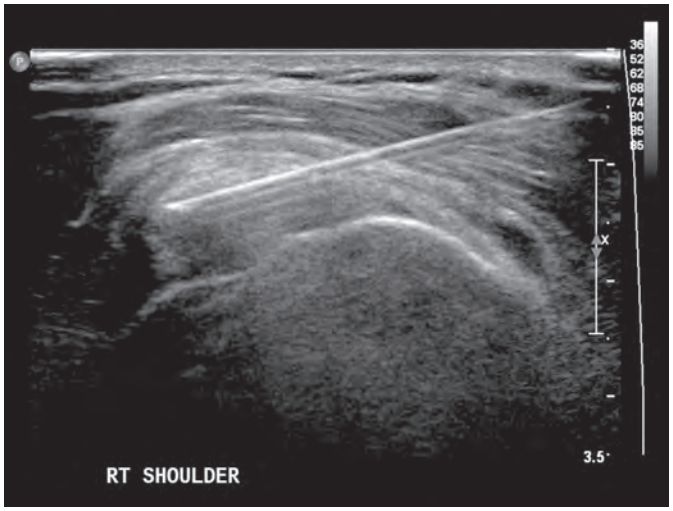

Fig. 107.3. Ultrasound-guided aspiration of a calcific deposit from the supraspinatus tendon causing calcific tendinopathy.

Achilles Tendinopathy and Rupture. In addition to routine conservative treatment, patients with Achilles tendinopathy should be referred for orthopedic evaluation and correction of limb malalignment with the use of orthotics or heel lifts. Eccentric loading exercises (Fig. 107.4) and low-energy shock wave therapy are effective therapies for Achilles tendinopathy.

The management of Achilles tendon rupture may be either operative or nonoperative, depending on the patient involved. Appropriate consultation with an orthopedist is essential. A conservative approach, including immobilization in a walking boot with heel lifts and a specific, graduated rehabilitation program may be indicated.[29] Some authors note that complete ruptures in active athletes should be treated surgically in most cases. Although other risks and benefits should be taken into consideration, some studies indicate that early surgery may be indicated because the risk for Achilles tendon rerupture is less.

Disposition

Most patients with tendinopathy are safely discharged home with proper discharge instructions, relative rest of the tendon, analgesia, and appropriate follow-up. The exceptions are elders and disabled patients who are often rendered unable to perform activities of daily living due to the tendinopathy. Although appropriate rest and analgesia provide symptomatic relief, underlying causes should be sought and modified.

BURSITIS

Principles

A *bursa* is a closed sac lined by synovial membrane, which occurs in areas of friction between two layers of tissue. It permits fluid movement of soft tissue over areas of potential impingement (eg, subacromial bursa) or friction (eg, olecranon and prepatellar

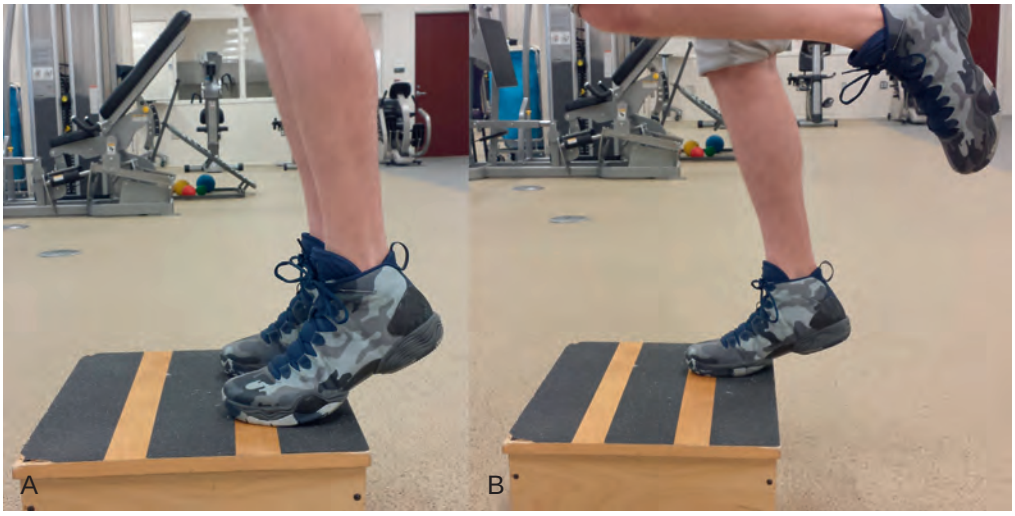

Fig. 107.4. Demonstration of eccentric Achilles tendon rehabilitation exercises, emphasizing bilateral toe raises **(A),** followed by isolating the affected Achilles tendon **(B).** One should then lower the heel below neutral.

bursae). There are more than 140 bursae throughout the body. They develop after birth, most likely as a result of frequent irritation from movement.[30] The olecranon and prepatellar are the two most common identifiably inflamed bursae and, when inflamed, they are recognizable over the extensor surface of the elbow and knee, respectively.

Many cases of bursitis are idiopathic in etiology, but common causes of inflammation include infection (most often due to *Staphylococcus aureus*), trauma (which may predispose to infection), rheumatologic disorders (eg, gout, pseudogout, ankylosing spondylitis, and rheumatoid and psoriatic arthritis) and other systemic diseases.

Clinical Features

Olecranon and Prepatellar Bursitis

Less than half of patients who present with olecranon or prepatellar bursitis show signs of an infectious etiology.[31] Distinguishing septic from nonseptic bursitis can be difficult when basing diagnosis on clinical information and diagnostic testing. Patients with septic bursitis generally present earlier in their clinical course and tend to have more pain, tenderness, erythema, and warmth compared to those with nonseptic bursitis. Trauma is a common risk factor in septic bursitis, preceding the condition in up to 70% of cases. Other predisposing factors include chronic illness (such as, diabetes mellitus or alcohol abuse), chronic skin conditions (such as, atopic dermatitis), and previous non-infectious inflammation of the bursae (such as, rheumatoid arthritis or gout). It is also more common in people whose occupation results in repetitive knee or elbow trauma.

The olecranon bursa, found on the extensor surface of the elbow, is the only bursa of the elbow joint and is easily traumatized, which results in inflammation, pain, and swelling. Infection can also occur from local trauma (eg, puncture wound or laceration) but may also be present in the absence of visible trauma. Hematogenous bacterial seeding is rare, most likely because of limited vascular supply to the bursal tissue.

On physical examination, localized swelling and fluctuance are usually present over the bursa. There may or may not be evidence of trauma. Tenderness and warmth are typical in most patients with septic bursitis. Erythema with overlying cellulitis is also common in septic bursitis, and approximately 40% of patients will also have a fever.[30,32] Tenderness, erythema, and warmth can also be seen in patients with purely inflammatory causes of bursitis, but the frequency and severity of these findings are less, and patients with septic bursitis usually present earlier in their clinical course.

Passive range of motion should not produce much pain, with the exception of full flexion, at which point there may be discomfort as the inflamed bursa is compressed. Evidence of significantly diminished range of motion, generalized joint swelling, or other signs and symptoms of joint involvement (eg, joint pain, warmth, effusion) should raise concern for septic arthritis. Although the olecranon and prepatellar bursae generally do not communicate with the joint space, septic arthritis should be considered in the differential diagnosis, especially if trauma is involved and the integrity of the underlying joint is disrupted. Arthrocentesis to rule out septic arthritis should be considered in these cases.

Subacromial Bursitis

The subacromial bursa lies between the supraspinatus tendon and the acromion. Subacromial bursitis is thought to be nearly synonymous with supraspinatus tendinopathy and may be involved in the stages of rotator cuff impingement. Pain and tenderness, localized to the lateral aspect of the shoulder, in addition to signs of impingement may be noted on physical examination.[33] Although it is uncommon, septic subacromial bursitis can occur.

Trochanteric Bursitis

The trochanteric bursa has both deep and superficial components. The deep bursa is located between the greater trochanter and the tensor fasciae latae; the superficial bursa is located between the greater trochanter and the skin. Trochanteric bursitis is more common in middle-aged women, who usually report acute or chronic pain over the bursal area, as well as the lateral thigh. Lying on the hip and walking may exacerbate the pain. It can also occur as a complication of rheumatoid arthritis. On examination, the pain of superficial bursitis may be reproduced by palpation and hip adduction, and the pain of deep trochanteric bursitis may be reproduced with hip abduction. The hip joint usually has normal examination findings. Septic trochanteric bursitis is rare but has been described.[34]

Ischiogluteal Bursitis

The ischiogluteal bursa is located adjacent to the ischial tuberosity and overlies the sciatic and posterior femoral cutaneous nerves. Inflammation, known as *weaver's bottom,* is described as pain over the center of the buttocks with radiation down the back of the leg. Sitting on a hard surface exacerbates the pain, and palpation over the ischial tuberosity causes discomfort.

Iliopsoas Bursitis

The iliopsoas bursa is the largest bursa around the hip. It lies between the iliopsoas tendon and the lesser trochanter. The pain of iliopsoas bursitis usually is manifested as anterior hip pain that can radiate down the medial thigh to the knee and is increased on hip extension.

Pes Anserine Bursitis

The anserine bursa lies deep to the three tendons (sartorius, gracilis, and semitendinosus) that form the pes anserinus ("foot of the goose") and superficial to the medial collateral ligament. The patient with anserine bursitis usually complains of medial knee pain approximately 2 or 3 cm distal to the joint line. There is usually tenderness to palpation in this area and occasionally swelling. Diabetes mellitus and possibly obesity and osteoarthritis of the knee are risk factors for development of this condition.

Diagnostic Testing

When there are signs of acute inflammation, aspiration of the bursa is indicated to exclude the presence of infection or crystal-induced disease.[31] If bursal aspiration is performed, it should be done with sterile technique. An 18- to 20-gauge needle can be used to perform this procedure. A lateral approach has been recommended to lower the risk of iatrogenic sinus track formation, although the relation between the two is unclear. A distal approach can also be used when the olecranon bursa is aspirated. In cases of septic bursitis, the aspirate usually appears purulent but can occasionally appear serosanguinous or straw-colored. In the case of nonseptic bursitis, the aspirate varies from bloody to straw-colored. The bursal aspirate should be sent for evaluation of white blood cell (WBC) count with differential, microscopy for crystals (if crystalline disease is suspected), Gram stain, appropriate cultures and sensitivities, and glucose level. A bursal fluid glucose-to-serum glucose ratio of less than 50% is almost exclusively seen in septic bursitis.[30]

Organisms found on either Gram stain or culture is diagnostic for septic bursitis. There are no definitive guidelines about using the WBC count to distinguish between septic and nonseptic bursitis. A bursal fluid WBC count higher than 1000/μL^3 is almost always seen, and one higher than 5000/μL^3 suggests bursal fluid infection, even in the presence of a negative Gram stain. However, counts can be much lower in septic bursitis and above this level in nonseptic cases. Culture is the definitive test but will not be available during the initial evaluation. *S. aureus* is by far the most common organism in bursal infection, followed by other staphylococcal and streptococcal species, and this bacteriology has not changed in the last several decades.[35,36] Because most cases of septic bursitis occur in the olecranon and prepatellar bursae, the diagnosis is made clinically in conjunction with aspiration. MRI can be used to aid in the diagnosis of inflammation or infection of deep bursae. Ultrasonography has also been used as a modality for aspiration of deep bursae.

Differential Diagnosis

Conditions that mimic bursitis include underlying fracture and osteomyelitis. Radiography and bone scan or MRI may be necessary to exclude these conditions. See Box 107.2 for details on the differential diagnosis for atraumatic, nonseptic bursitis.

Management

Septic Bursitis

The optimal treatment of septic bursitis is uncertain because large-scale clinical prospective trials in this area are lacking. Debate remains about the use of outpatient (oral) versus inpatient (intravenous [IV]) administration of antibiotics, duration of therapy, use of needle aspiration and incision and drainage, and use of operative intervention.

Patients who have bursal inflammation with suspicion (clinical or laboratory) of infection should be treated with appropriate antibiotics. Empirical therapy (including coverage for *S. aureus* and *Streptococcus* species) is indicated until definitive culture results are available. The frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) in septic bursitis is unclear, although recent literature suggests that rates are low.[33,34] MRSA was found to be the most common cause of community-onset adult septic arthritis in one case series from an ED population, so empirical coverage for this organism in septic bursitis should be considered. A trial of oral antibiotic therapy (up to 14 days) and treatment on an outpatient basis in the patient with uncomplicated septic bursitis and no underlying disease is reasonable. We recommend dicloxacillin (500 mg orally four times daily) or clindamycin (300 mg four times a day) for penicillin-allergic patients as first-line therapy. However, failure rates up to 67% have been reported for outpatient treatment of septic bursitis. One of the largest observational studies on the successful outpatient treatment of septic bursitis showed an admission rate of only 1 of 118 patients, but all patients in this study received sequential IV antibiotics for approximately 4 days at an outpatient clinic followed by a course of oral antibiotic therapy. Treatment in an observation unit or inpatient setting with IV antibiotics, therefore, is a consideration for patients with significant symptoms, overlying cellulitis, or those unlikely to receive close follow-up. For such patients, we recommend vancomycin (15 to 20 mg/kg/dose every 8 to 12 hours, not to exceed 2 g per dose) as initial empirical treatment.

Needle aspiration is a technique commonly used for the management of septic bursae. Successful treatment of septic bursitis can be achieved in patients receiving outpatient oral antibiotics after initial needle aspiration.[37] One study showed no difference between patients who received aspiration and those who did not, but patients who had more severe disease were also more likely to be selected for drainage. These patients were also initially treated with parenteral antibiotics. Furthermore, the diagnosis of septic bursitis was confirmed by culture in only 26% of these patients, potentially underestimating the importance of bursal drainage in patients with true septic bursitis. Because needle aspiration is used for the diagnosis of septic bursitis, initial drainage at the same time seems warranted. Those with a purulent aspirate may require repeated aspiration at 1- to 3-day intervals if the effusion persists. In all cases, appropriate follow-up to assess response to therapy should be arranged. Warm soaks and wound care are also indicated. Surgical incision and drainage or bursectomy may also be necessary in severe, recurrent, or refractory cases.

Nonseptic Bursitis

Most cases of nonseptic bursitis improve with conservative therapy, although complete recovery can take many months. Initial treatment typically consists of aspiration of the bursa, which can relieve pain and increase range of motion, NSAIDs, and compression to prevent recurrent fluid accumulation. Systemic causes of bursitis (eg, crystalline disease) should be treated as indicated. Avoidance of local trauma is important for treatment and successful prevention of bursitis. Recurrent olecranon bursitis may be caused by underlying anatomic disorders, such as bone spurs.

Bursal injection with a combination of local anesthetics and steroids at the time of diagnostic aspiration is often therapeutically beneficial for inflammatory bursitis of deeper areas, such as the sub-acromial, pes anserine medial collateral ligament, and trochanteric bursae. Injections into superficial bursae has been used as a treatment modality, but multiple complications have been described, including skin atrophy over the bursa, persistent pain, development of septic bursitis, bleeding, post-injection flare as a result of release of microcrystals, and tendon rupture. However, a recent systematic review of treatment for olecranon bursitis found that patients who received a corticosteroid injection were no more likely to develop an infection or persistent pain than those who did not.[33] At this point in time, we recommend non-injection treatment initially for suspected inflammatory bursitis of superficial bursae.

Disposition

Patients without underlying medical problems who present with uncomplicated septic bursitis can usually be discharged with appropriate oral antibiotics. Those with underlying diseases (eg, immunocompromise, leukopenia, and diabetes) and those with

BOX 107.2

Differential Diagnosis for Atraumatic, Nonseptic Bursitis

Rheumatoid arthritis
Pseudogout
Ankylosing spondylitis
Hypertrophic pulmonary osteoarthropathy
Oxalosis
Gout
Scleroderma
Systemic lupus erythematosus
Whipple's disease
Idiopathic hypereosinophilic syndrome

systemic toxicity or severe bursal infection (eg, purulent drainage) are candidates for IV antibiotics and inpatient therapy.[37] Patients with a purulent aspirate or persistent infection may need repeated aspiration. Close follow-up is necessary to ensure response to therapy. Patients with presumed nonseptic bursitis require close follow-up as well.

KEY CONCEPTS

Tendinopathy

- Mechanical overload and repetitive microtrauma are key underlying mechanisms in the development of tendinopathy. Patients most often present with a history of progressively worsening localized pain after work- or sports-related activities that are repetitive in nature.
- Tendinopathy may also be associated with non-mechanical causes, including systemic manifestations of diseases, infectious etiologies, and the use of fluoroquinolones.
- Most patients with tendinopathy can initially be treated with conservative measures, such as protection, relative rest, application of ice, medications, and elevation. Overuse syndromes can take at least 6 to 12 weeks to heal. Inform patients of this, and provide an appropriate referral for follow-up.
- Emergent imaging is rarely indicated in the ED, although the use of bedside ultrasound to evaluate tendinopathy can help to identify tendon disruption/rupture.
- Operative treatment may be indicated for selected cases of tendon injury that require primary repair (eg, rupture of the Achilles tendon) or that have failed to respond to conservative treatment (eg, impingement syndrome) and are amenable to surgical amelioration.

Bursitis

- Consider the possibility of an infectious cause in all cases of acute bursitis.
- The definitive diagnosis of bursitis is made by aspiration of the bursa and evaluation of the fluid.
- Septic bursitis is most commonly caused by *Staphylococcus aureus*.
- Nonseptic bursitis may be traumatic, rheumatologic (eg, gout and pseudogout), or idiopathic in nature. Other conditions, such as septic arthritis, osteomyelitis, and an underlying fracture, are in the differential diagnosis of bursitis.
- The management of bursitis includes treatment with appropriate medication (antibiotics for septic bursitis, NSAIDs for nonseptic bursitis), rest, application of ice, compression, and elevation, as well as prompt referral for appropriate follow-up. Hospitalization is considered for severe local infections, for patients who are immunosuppressed, and in the presence of high fever or systemic toxicity.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 107: QUESTIONS & ANSWERS

107.1. Work-related injuries may be associated with which of the following?
- **A.** Awkward working postures
- **B.** Forceful exertions
- **C.** Repetitive motions
- **D.** All of the above

Answer: D. Repetitive motions, forceful exertions, awkward working postures, whole body or segmental vibrations, and localized contact stress can all contribute to work-related injuries.

107.2. What is the etiology of most tendinopathies?
- **A.** Direct blow to the tendon
- **B.** Following complete tendon rupture
- **C.** High-grade inflammation of the tendon
- **D.** Mechanical overload and repetitive microtrauma

Answer: D. Tendinopathies are thought to be mainly precipitated by repetitive microtrauma and mechanical overload rather than true inflammation of the tendon.

107.3. What is the causative organism in the majority of cases of septic bursitis?
- **A.** Beta-hemolytic streptococci
- **B.** *Pseudomonas aeruginosa*
- **C.** *Prototheca wickerhamii*
- **D.** *Staphylococcus aureus*

Answer: D. *S. aureus* is the most common cause of infectious bursitis.

107.4. What is the most important predisposing factor in septic bursitis?
- **A.** Chronic obstructive pulmonary disease
- **B.** Diabetes mellitus
- **C.** Human immunodeficiency virus
- **D.** Trauma

Answer: D. Trauma is the most common predisposing factor in patients who develop septic bursitis.

107.5. A 52-year-old male presents after feeling a "pop," followed by pain to the back of his leg while playing basketball. You note a defect to his Achilles tendon and a positive Thompson's test on examination. What should be the next step in the patient's management?
- **A.** Obtain an ultrasound in the emergency department (ED).
- **B.** Obtain a magnetic resonance imaging (MRI) scan in the ED.
- **C.** Perform a steroid injection to the affected tendon.
- **D.** Splint the affected leg in an equinus position and refer for prompt follow-up with orthopedics.

Answer: D. Although ultrasound and MRI can be important adjuncts to the diagnosis of a tendon injury, obtaining these tests

from the ED is not necessary when the clinical diagnosis is obvious. Treatment consists of splinting the leg and close follow-up for either operative or nonoperative treatment.

107.6. A 42-year-old female with no significant past medical history presents with 4 days of edema, mild warmth, and mild erythema in the area of the right olecranon bursa. She is afebrile and has minimal tenderness to palpation of the bursa. You aspirate the bursa and obtain a whole blood count of 1500/μL.[3] What should be the next step in the patient's management?

A. Admit for intravenous (IV) antibiotics.
B. Apply a compression dressing and give ibuprofen.
C. Discharge the patient to home with oral antibiotics.
D. Obtain a magnetic resonance imaging (MRI) scan for further evaluation.

Answer: B. The clinical presentation and results of the fluid analysis highly suggest a nonseptic bursitis. Cases of nonseptic bursitis can be managed with a compression dressing, nonsteroidal antiinflammatory drugs (NSAIDs), avoidance of local trauma, and follow-up.

CHAPTER 108

Systemic Lupus Erythematosus and the Vasculitides

Robert T. Arntfield | Christopher M. Hicks

SYSTEMIC LUPUS ERYTHEMATOSUS

Principles

Background

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder that poses a challenge to the emergency clinician with its protean and occasionally dangerous manifestations. Morbidity for SLE patients is typically mediated through organ inflammation and destruction or the consequences of therapeutic immunosuppression. Further complicating lupus is the frequent association with the antiphospholipid syndrome (APS) and its corresponding venous and arterial thromboses. The diagnostic criteria reflective of its complexity and immunologic basis were first described in 1971. Today, the emergency department (ED) is a common venue for the evaluation and treatment of patients suffering from SLE.[1]

Epidemiology

SLE is present in 20 to 70 per 100,000 of the general population.[2] Although great variation in incidence exists worldwide, it is clear that two groups have consistently higher incidences: women, representing 90% of cases; and African Americans.[2] Dramatic rises in incidence of SLE have been described during the past several decades, but it is suspected that this may be due to the implementation of more sensitive diagnostic criteria.

Etiology

The exact etiology of SLE is not understood. It is likely to be related to multiple factors; genetics, environmental factors, race, hormones, medications, and immunology have all been implicated to varying degrees.

With women representing 90% of SLE cases, a strong role for estrogen in disease development has been well supported in large cohort studies. The disease also has a strong genetic link, with high rates of monozygotic twin concordance and tremendous genetic overlap at the human leukocyte antigen (HLA) alleles.

Pathophysiology

SLE may cause disease in nearly any organ system in the body through inappropriate immune response to self and is often described as the prototype of all systemic, autoimmune disorders. Its exact pathophysiologic mechanism is not completely elucidated. When a cell cycle ends (apoptosis), intracellular contents, including DNA-rich nucleosomes, are released into the bloodstream. For patients with SLE, this cellular debris may be regarded as nonself (ie, an antigen) by the immune system. After exposure to these self antigens, the familiar immunologic cascade of antigen-presenting cells, T cells, and ultimately B cells and their plasma cell progeny is exacted, and patients form autoantibodies against their own cellular contents. These autoantibodies (which include anti–double-stranded DNA antibody, a commonly ordered rheumatologic assay in evaluation for SLE) may then mediate organ-specific disease and inflammation. This may occur through either direct attack and injury to parenchymal tissue or other mechanisms, such as formation of immune complexes that are deposited in tissue. On the basis of this immunologic understanding of the pathogenesis of SLE, the rationale for immunosuppression as both chronic and acute therapy for SLE can be appreciated.

The pathophysiologic mechanism of SLE may be different for each organ system. Indeed, the organ systems involved in any given patient's disease may be different and may relate to the underlying presence or absence of antigens that resemble tissue from that organ system.

Clinical Features

In general, there are four broad presentations for a patient with SLE: (1) symptoms related to SLE that is not yet diagnosed (eg, idiopathic pericarditis, new rash), (2) progression or acute deterioration due to known SLE (eg, progressive nephritis, lupus enteritis), (3) complications of immunosuppression from treatment of SLE (eg, opportunistic infection), and (4) complaints or disease unrelated to SLE (eg, trauma, pregnancy).

The Patient With Undiagnosed or Suspected Systemic Lupus Erythematosus

Although some elements, such as the malar rash, that form the diagnosis of SLE are nearly pathognomonic for lupus, confidence in the initial diagnosis in the ED is difficult and probably rare. The literature is replete with ED-based case reports of extreme initial presentations with conditions such as Guillain-Barré, cardiac tamponade, and fulminant renal failure that subsequently were confirmed as complications of unrecognized SLE.[3] However, in all cases the diagnosis of SLE was applied retrospectively. Because the evaluation for SLE is commonly conducted in a series of outpatient visits and relies on laboratory investigations that are uncommonly carried out in the ED, establishment of a new diagnosis of SLE in the ED is difficult. If a new diagnosis of SLE is suspected in an otherwise well patient, referral for an expedited evaluation is reasonable in most circumstances. The American College of Rheumatology classification criteria for SLE are presented in Table 108.1.[4]

Acute Presentations in the Patient With Known Systemic Lupus Erythematosus

Emergency clinicians are commonly faced with evaluating the acute complaints of patients with an established diagnosis of SLE.[1] The evaluation of SLE-related complications is based on use of a disease-specific differential diagnosis.

TABLE 108.1

Systemic Lupus International Collaborating Clinics (SLICC) Criteria for Systemic Lupus Erythematosus*

CRITERIA	DESCRIPTION
CLINICAL CRITERIA	
Acute cutaneous lupus	May include acute cutaneous lupus (lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash) or subacute cutaneous lupus
Chronic cutaneous lupus	Classic discoid rash, generalized hypertrophic (verrucous) lupus, lupus panniculitis, mucosal lupus, others
Oral ulcers	Palate (buccal, tongue) or nasal ulcers
Non-scarring alopecia	Diffuse thinning or hair fragility
Synovitis	Involving two or more joints (swelling, effusion or tenderness and ≥30 minutes of morning stiffness)
Serositis	Pleural (pleuritis, effusion, rub) or pericardial (pericarditis, effusion, rub)
Renal disorder	500 mg protein/24 hours or red blood cell casts
Neurologic disorder	Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral and cranial neuropathies, acute confusional state
Hemolytic anemia	
Leukopenia	$<4000/mm^3$ at least once
Thrombocytopenia	$<100{,}000/mm^3$ at least once
IMMUNOLOGICAL CRITERIA	
Anti-nuclear antibody	Any level above laboratory reference range
Anti-dsDNA	Level above the laboratory reference range (or twofold the reference range if tested by ELISA)
Anti-Sm	Presence of antibody to Sm nuclear antigen
aPL antibody	As determined by positive test for lupus anticoagulant or anti-2-glycoproein, false positive result for rapid plasma regain, medium or high-titre anticardiolipin antibody level
Low compliment	May include C3, C4, or CH50
Direct Coombs test	In the absence of hemolytic anemia

*Fulfillment of at least four criteria, with at least one clinical and one laboratory criterion, is required to establish the diagnosis of systemic lupus erythematosus.
aPL, Antiphospholipid; *ds,* double-stranded; *ELISA,* enzyme-linked immunosorbent assay; *SLE,* systemic lupus erythematosus; *Sm,* Smith.

Systemic Lupus Erythematosus Exacerbation

Even with good medication compliance, SLE patients are prone to exacerbations of their disease, typified by worsening physical symptoms from increased organ inflammation and destruction. These exacerbations may involve organs already affected by SLE or new conditions manifested in previously unaffected organ systems. As a systemic disease, worsening symptoms in one organ system should reasonably prompt evaluation for progressive disease activity in other organs. True to the broad scope of SLE, the most accepted scoring system to grade SLE exacerbations accounts for 20 different markers of disease activity across nine organ systems. Although such scoring systems have little role in the ED, it is important to identify when overall disease activity is increased because it typically signals the need to initiate or to escalate systemic therapy. In many cases, patients themselves are able to provide direction about the predictable course of their exacerbations and can be helpful in decision-making for therapy and disposition.

Specific Symptoms and Presentations of Systemic Lupus Erythematosus

Fever. Improving survival for patients with SLE during the past several decades has been achieved with the use of improved immunosuppressive regimens. As a result, patients with SLE are commonly affected by infections mediated by both typical and opportunistic organisms, suffering higher than average death rates from these infections. In one case series, infection was the leading reason for SLE patients to be admitted to the intensive care unit, superseding both renal failure and cardiovascular disease. Whereas absence of fever is insufficient in many cases to rule out infection, the presence of a fever is grounds for concern. Fever may also be due to increased overall disease activity. Given the heightened risk for SLE patients with infection, determination that a fever is due strictly to disease exacerbation should be made cautiously. Most infections in SLE are due to skin, lung, or urinary sources and are caused by typical organisms. However, largely because of the immunomodulating therapies that form the cornerstone of SLE management, opportunistic diseases are possible; *Pneumocystis (carinii) jiroveci* pneumonia, cryptococcal meningitis, *Listeria* infection, and herpes zoster have all been described.

Neuropsychiatric Presentations. According to the American College of Rheumatology, there are 19 different clinical manifestations of neuropsychiatric SLE, some of which are included in the diagnostic criteria (see Table 108.1). These 19 different presentations vary widely and include seizures, confusion, cranial and peripheral neuropathies, demyelinating syndromes, myasthenia gravis, depression, psychosis, and anxiety. It may not be possible in the ED to determine whether such manifestations are due to neuropsychiatric SLE or to other, independent pathologic processes.

Headache. In general, headaches in a patient with SLE may be evaluated in a fashion similar to that for headaches in the general population. In one prospective cohort study, for instance, it was found that primary headache disorders, such as migraine and tension headaches, occur with the same frequency in SLE patients as in the general population. This was further supported by an extensive meta-analysis examining the implications of headache in SLE patients. In this study, the authors found no relationship between headache and SLE disease activity. Thus, despite recommendations to consider headache as suggestive of neuropsychiatric SLE or so-called lupus cerebritis, isolated headaches in the context of lupus may be treated in a fashion typical of other primary headache disorders. When a more malignant cause of headache is suspected, as suggested by meningismus, fever, or focal neurologic findings, an aggressive evaluation is warranted. When concern exists for an infectious cause of headache, consideration for opportunistic infections, such as cryptococcal meningitis, should be made in an immunosuppressed SLE patient.[5] Further, because of common comorbid APS, consider sinus thrombosis in the SLE patient with new-onset focal central nervous system findings and headache.

Seizure. Because of incompletely understood mechanisms, seizures may occur as result of SLE disease activity. In one large series, seizures were observed in 11% of SLE patients, and in the majority of cases, either stroke or comorbid APS was present. Because of the high incidence of seizures, nonconvulsive status

TABLE 108.2

Chest Pain and Systemic Lupus Erythematosus in the Emergency Department: Common Causes, Evaluation, and Treatment

CONDITION	DIAGNOSTIC TEST(S) IN THE EMERGENCY DEPARTMENT	TREATMENT	COMMENT
Pleuritis	Clinical, chest radiography (for commonly associated pleural effusion)	NSAIDs ± steroids	Diagnosis of exclusion
Pulmonary embolism	D-dimer, CT pulmonary angiography	Anticoagulation	Higher incidence in all SLE patients, especially those with APS
Pneumonia	Chest radiography	Antibiotics	Consider opportunistic disease
Pericarditis	Electrocardiography	NSAIDs ± steroids	Echocardiography to rule out effusion; electrocardiographic findings in less than 50%
Coronary artery disease (CAD)	Electrocardiography, troponin, CK-MB	Aspirin, heparin, percutaneous coronary intervention	Increased prevalence in SLE

APS, Antiphospholipid syndrome; *CK-MB,* creatine kinase MB fraction; *CT,* computed tomography; *ED,* emergency department; *NSAIDs,* nonsteroidal antiinflammatory drugs; *SLE,* systemic lupus erythematosus.

epilepticus is a consideration in SLE patients with an acute onset of altered mental status. The evaluation and management of seizures do not differ between patients with SLE and the general population.

Focal Neurologic Findings. On occasion, the patient with SLE may present with focal motor weakness. In those with SLE who also have APS, there is a significantly increased risk of stroke related to spontaneous arterial thrombosis. Demyelinating disease, such Guillain-Barré and cranial neuropathies, have also been occasionally attributed to SLE from unclear mechanisms.

Psychiatric Symptoms. Mood disorders, psychosis, and anxiety are considered potential manifestations of neuropsychiatric SLE. Distinguishing SLE-related from functional causes of psychiatric presentations poses a challenge. Although psychiatric presentations of SLE in the ED have not been directly studied, in the absence of concern for an organic cause of altered mental status, patients with SLE are approached in the same manner as patients without SLE. Corroboration with the patient's rheumatologist may provide insight to history of similar events or guidance for treatment.

Cardiorespiratory Presentations and Diseases. Chest pain, in the form of either pleuritis or pericarditis, is among the diagnostic criteria for SLE (see Table 108.1). In addition to pericarditis and pleuritis, coronary artery disease (CAD), pulmonary embolism, and musculoskeletal causes are also common. Other forms of cardiac disease that occur without chest pain, such as verrucous (Libman-Sacks) endocarditis and various arrhythmias, may also be present.

Coronary Artery Disease. There is a dramatically increased risk of CAD in the context of SLE. This was demonstrated in a compelling retrospective cohort study of 500 women with lupus compared with age-matched controls from the original Framingham data. In this study, a 52-fold increased risk of myocardial infarction was determined in women between 35 and 44 years old. These findings of increased risk of CAD have been supported by a number of other prospective trials. In one series, patients with SLE were found to be five times as likely to have CAD (based on coronary artery calcium scoring) as patients without SLE. In another series that profiled an even younger subset, it was found that among otherwise low- to moderate-risk women aged 22 to 45 years with complaints of chest pain, dyspnea, or decreased exercise capacity, there was an alarming 82% prevalence of CAD as determined by nuclear imaging. There was a similarly concerning prevalence of 43% of CAD in the asymptomatic "control" group who also had SLE. Further, traditional cardiac risk factors are found less often in patients with SLE who suffer consequences of CAD, suggesting that CAD in patients with SLE cannot be explained by the higher incidence of hypertension or hypercholesterolemia that these patients often exhibit. Thus, whereas there are many considerations for the cause of chest pain in patients with SLE (Table 108.2), CAD must be considered highly, and in fact more highly in patients who would otherwise be deemed to be low risk (young, reproductive age women). It is therefore appropriate to initiate an evaluation with electrocardiography, cardiac biomarkers, and stress testing to rule out acute coronary syndromes in patients with chest pain and SLE.

In addition to being at risk for development of CAD, patients with SLE who are treated with percutaneous coronary intervention appear to fare poorly. In one retrospective analysis of 28 patients with SLE receiving percutaneous coronary intervention, reintervention, death, and recurrent myocardial infarction were significantly more likely compared with a similar cohort without SLE.

Pericardial Disease. Pericardial effusion and pericarditis occur commonly in patients with SLE. It is estimated that symptomatic pericarditis occurs in 25% of patients with SLE during the course of their lives and that pericardial effusion occurs even more often, frequently in a silent fashion, in up to 50%. In clinically evident SLE-related pericarditis, dyspnea or pleuritic chest pain is common. Typical electrocardiographic findings (Fig. 108.1) have been shown to be present in less than half of cases, however. Given the increased risk of CAD in patients with SLE, ST elevation of any kind found on an electrocardiogram warrants very careful consideration. When diagnostic uncertainty exists, echocardiography, cardiac enzymes, or cardiac catheterization may be complementary. Treatment of pericarditis includes nonsteroidal antiinflammatory drugs (NSAIDs) and glucocorticoids, as discussed later.

Pericardial tamponade, because of its dramatic nature, continues to receive attention as an initial presentation of SLE.[6] However, large case series have shown that this life-threatening presentation occurs in less than 1% of patients with lupus. In large effusions without tamponade, medical management with high-dose glucocorticoids (1 to 2 mg/kg of methylprednisone) has shown favorable outcomes in averting the need for pericardiocentesis.

Pulmonary Embolism. Pulmonary embolism and deep venous thrombosis occur with increased incidence in patients

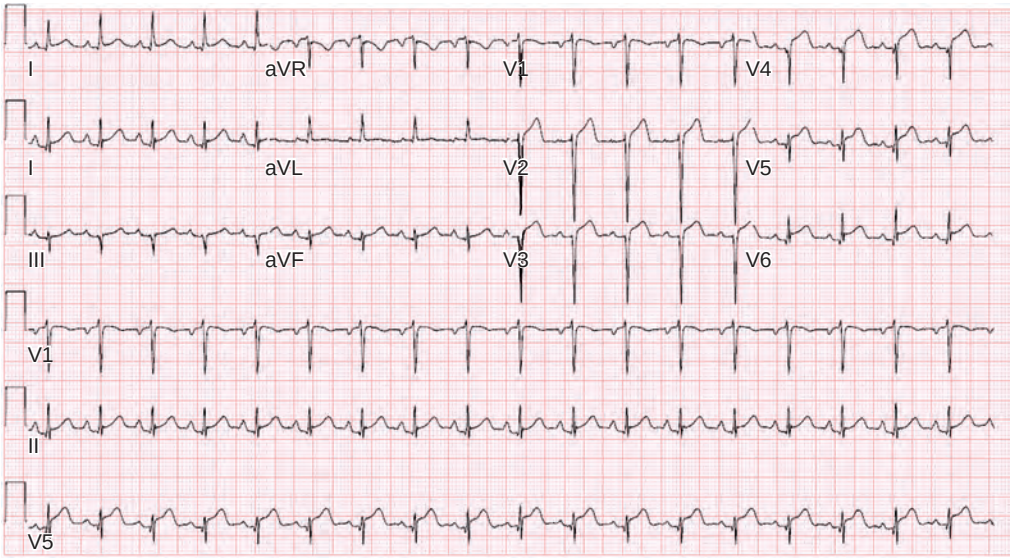

Fig. 108.1. Electrocardiogram of a 38-year-old woman with systemic lupus erythematosus (SLE) who presented to the emergency department (ED) with seizures and had chest pain while in the ED. Note diffuse ST elevation (with absence of any reciprocal changes) and PR depression (particularly evident in lead II). Q waves anteriorly are related to prior myocardial infarct.

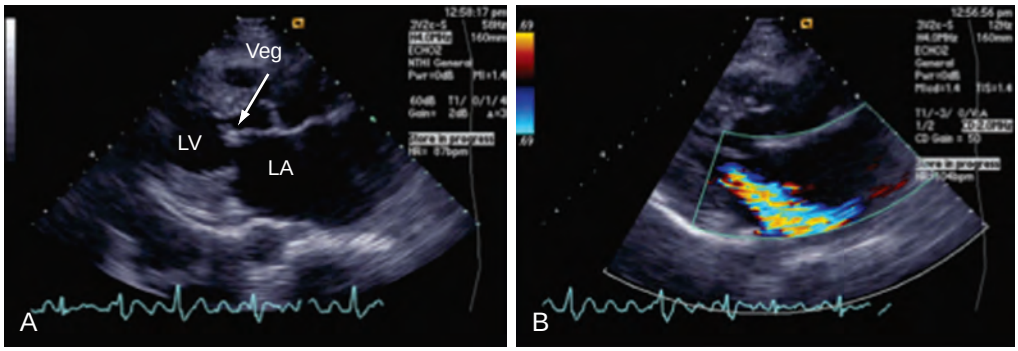

Fig. 108.2. Noninfectious endocarditis, known as a *Libman-Sacks lesion,* in a 56-year-old woman with systemic lupus erythematosus (SLE), a heart murmur, and dyspnea on exertion. **A,** A parasternal long-axis view of the heart; a vegetation *(Veg)* is identified *(arrow)* on the mitral valve. **B,** When color flow is superimposed on the valve, moderate to severe mitral regurgitation can be seen as a color jet entering the left atrium during systole. *LA,* Left atrium; *LV,* left ventricle. (Courtesy Martin Goldman, MD, Mount Sinai School of Medicine.)

with SLE. This is especially true for patients with SLE who also carry antiphospholipid (aPL) antibodies. These patients have an estimated 20- to 30-fold increased risk for thrombosis compared with the general population. Patients with SLE who do not have aPL antibodies still have a sixfold greater likelihood for development of pulmonary embolism and deep venous thrombosis compared with patients without SLE. Thus, all patients with SLE, regardless of their aPL antibody status, which is often unknown on presentation, should be considered at increased risk for venous thromboembolism.

Pleuritis. Pleuritis, due to autoantibodies acting against the pleura itself, is the most common respiratory condition occurring in SLE. Characterized by pleuritic chest pain with or without a pleural effusion or pleural rub, it has symptoms that overlap with those of other more serious conditions (see Table 108.2). If a pleural effusion is present, analysis of pleural fluid for antinuclear antibodies may be the most accurate method to confirm diagnosis but may be impractical in the ED. A diagnosis of pleuritis should be arrived at only after other causes of pleuritic chest pain in these thrombophilic, immunosuppressed patients have been ruled out.

Pneumonia. Pneumonia is the third most common infection in patients with lupus, after skin and urinary tract infections. Choice of antimicrobial coverage is determined by the severity of the infection and the degree of immunosuppression. For patients receiving long-term glucocorticoids or cyclophosphamide, coverage for organisms such as *Pseudomonas* and *Legionella* generally requires the use of a carbapenem or a fourth-generation cephalosporin in addition to either a respiratory fluoroquinolone or macrolide. There is no evidence to support the routine coverage for *P. jiroveci* in these patients.

Undifferentiated Dyspnea. Mitral valve insufficiency due to noninfectious vegetations, known as *Libman-Sacks lesions,* may cause a patient to experience dyspnea on exertion or, in rare severe cases, pulmonary edema (Fig. 108.2). Anemia, present in up to 50% of patients with SLE, may lead to a chief complaint of dyspnea. Both anemia of chronic disease and hemolytic anemia are common; hemolytic anemia is more typical in those also carrying aPL antibodies. In cases of severe anemia recognized in the ED, a Coombs test can be diagnostic for immunologic hemolytic anemia. Other less common but noteworthy causes of shortness

of breath in a patient with SLE include interstitial lung disease, lupus pneumonitis, diaphragmatic disease (so-called shrinking lung syndrome), and pulmonary hypertension.

Musculoskeletal Presentations. Musculoskeletal chest pain, related to underlying pectoral, intercostal muscle, or costochondral joint inflammation, may also occur in SLE. Similar to pleuritis, the threat of a more malicious underlying cause of pain should prompt the clinician first to seek other causes before arriving at this more benign cause. Treatment with NSAIDs or acetaminophen is generally appropriate.

Arthritis commonly afflicts those with SLE, and increasing severity of joint pain may be a marker of increasing disease activity or an SLE flare. Arthritis or arthralgias are typically symmetrical and nonerosive (unlike rheumatoid arthritis) and may involve multiple joints. Arthritis is most commonly present in the hands, wrists, and knees but may be manifested in any joint. Aside from mild tenderness, the joints are often normal on physical examination and rarely experience deformity. Uncommonly, septic arthritis may complicate SLE. In one large retrospective analysis of SLE-related hospitalizations, only 0.3% of admissions were for septic arthritis. Possibly because of immunosuppressant use, including corticosteroids, *Salmonella* is an unusually frequent culprit organism that was isolated in 59% of cases in one study and most commonly found in the hip. An isolated swollen joint is not typical of SLE and prompts consideration for infectious arthritis. If septic arthritis is suspected, diagnostic arthrocentesis is recommended. Empirical treatment with 1 gm of vancomycin and 1 gm of ceftriaxone will cover likely organisms, including *Salmonella*. Myalgias are common in SLE and may be an early marker of increasing disease activity for some patients. Generalized muscle pain is typical, but muscle weakness is uncharacteristic. If muscle weakness is present, an underlying myositis or myopathy secondary to steroid use is considered.

Gastrointestinal Presentations. The most common gastrointestinal manifestation of SLE is oral ulceration, which occurs in nearly a third of patients with SLE. Treatment includes local symptom management (chlorhexidine mouthwashes, viscous lidocaine) combined with systemic therapy (hydroxychloroquine) in more severe or refractory cases. Abdominal pain commonly complicates SLE. The causes of abdominal pain, with the exception of lupus enteritis, are largely similar to those in patients without SLE, such as pancreatitis, gastroenteritis, and peptic ulcer disease. Lupus enteritis (also known as mesenteric vasculitis) typically results in diffuse abdominal pain and is the most common cause of acute abdominal pain in SLE. The abdominal pain itself may also be associated with nausea, vomiting, and nonbloody diarrhea.[7] Laboratory investigations, such as white blood cell count, hemoglobin level, platelet count, and erythrocyte sedimentation rate (ESR), are not helpful because they do not differ significantly between those with enteritis and those with abdominal pain due to other causes. Although no "gold standard" for the diagnosis of lupus enteritis has been established, computed tomography (CT) is the most useful test to assess for this condition. Several CT scan findings are supportive, including bowel wall thickening (Fig. 108.3), engorgement of mesenteric vessels, and increased attenuation of mesenteric fat.

When lupus enteritis is suspected, early pulse steroids, at a dose of 1 to 2 mg/kg of methylprednisolone per day, should be administered. Surgical consultation should be obtained in severe cases or when bowel necrosis has occurred. With aggressive medical therapy, which may also include cyclophosphamide, the need for surgical management is uncommon. Other, less common gastrointestinal illnesses to which SLE patients are predisposed include protein-losing enteropathy and intestinal pseudo-obstruction.[8] Last, in assessing abdomen pain in patients with SLE, clinicians should be mindful of the effects of chronic steroid use and increased risk for both hollow viscus perforation and peptic ulcers, which may occur in the absence of traditional symptoms.

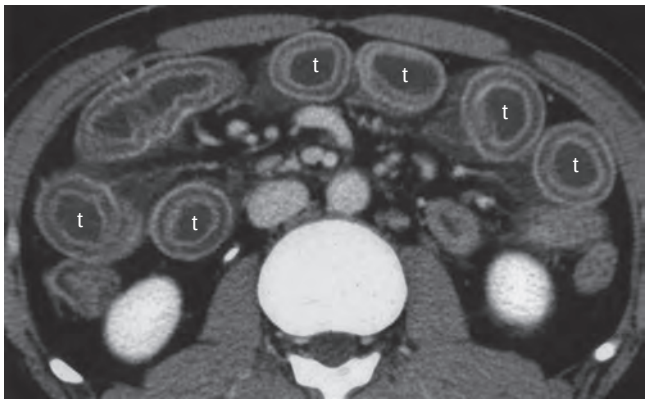

Fig. 108.3. Computed tomography (CT) scan appearance of lupus enteritis. Diffuse bowel wall thickening *(t)* in a 20-year-old patient with lupus enteritis. (From Byun JY, et al: CT features of systemic lupus erythematosus in patients with acute abdominal pain: emphasis on ischemic bowel disease. Radiology 211:203–209, 1999, with permission).

Fig. 108.4. The malar or butterfly rash is the hallmark of systemic lupus erythematosus (SLE). (From Habif TP: Clinical dermatology, ed 4, New York, 2004, Mosby, pp 592–606.)

Dermatologic Presentations. The most characteristic cutaneous manifestation of SLE is the malar rash. The rash has a "butterfly" distribution of raised erythema over the bridge of the nose and malar eminences while sparing nose and nasal-labial folds (Fig. 108.4). The other most common skin lesion found in SLE is the discoid rash. Discoid lesions are circular and raised, scaly lesions that may be commonly found on the face, scalp, and ears, often in association with pigment change, alopecia, and severe scarring (Fig. 108.5). Cutaneous lupus may exist in isolation without systemic involvement. Mild cases of worsening cutaneous lupus are treated topically with 1% hydrocortisone cream. Moderate to severe cases are treated with topical calcineurin inhibitors or even systemic therapy (eg, hydroxychloroquine) in consultation with the patient's internist or rheumatologist.[9] In nearly all cases of SLE, avoidance of sun exposure is advisable and will help minimize cutaneous disease.

Renal Disease. Renal disease develops in approximately a third of SLE patients. Given a high prevalence and morbidity of renal disease as well as its tendency to carry few if any symptoms,

Fig. 108.5. Right ear of a patient suffering from chronic discoid lupus. Note pigment change and tissue destruction. (Courtesy Professor Gregory Raugi, University of Washington.)

screening urinalysis and assessment of renal function are prudent in nearly all but the most straightforward presentations of SLE to the ED. Lupus nephritis may cause a nephrotic-type disease, primarily characterized by proteinuria (>2 g/day) or a more nephritic picture with hematuria and increased creatinine concentration. If worsening renal dysfunction is discovered, admission should be considered for hydration and escalation of therapy that may include both pulse steroids and cyclophosphamide.

Complications Due to Medications

The remarkable improvements in life expectancy and disease control in SLE are costly. Chronic steroid use is associated with well-known consequences, such as increased risk of CAD, osteoporosis, avascular necrosis, psychosis, hyperglycemia, and weight gain, among many others. More potent chemotherapeutic medications, such as cyclophosphamide, methotrexate, and azathioprine, may profoundly influence the patient's immune response and cause increased vulnerability to conventional and opportunistic infections. Chronic NSAID use for the musculoskeletal consequences of SLE may contribute to peptic ulcer disease, especially if they are coadministered with glucocorticoids. Therapy with antimalarials, such as hydroxychloroquine, is common and generally well tolerated; however, retinopathy and both QT interval prolongation and refractory ventricular arrhythmias have been associated with prolonged use.

Diagnostic Testing

Diagnostic tests will depend on the patient's presentation and whether a diagnosis of SLE is already established or being suspected for the first time.

Laboratory Tests

In all but the most trivial presentations, order a serum creatinine concentration, urinalysis, and complete blood count because renal dysfunction, proteinuria, anemia, or thrombocytopenia may silently complicate SLE and be an important marker of increased disease activity. Leukocytosis, already a nonspecific finding, may be even less contributory in SLE patients taking glucocorticoids. When a new diagnosis of SLE is being entertained, other more specific immunologic assays, such as antinuclear antibody, anti-DNA, anti-Smith (Sm) antibody, and aPL antibody, can be ordered in the ED with the intent of outpatient follow-up for evaluation of results. Of note, antinuclear antibody is present in nearly all SLE patients but is also present in 50% of people who do not have SLE. Thus, the absence of antinuclear antibody virtually excludes the diagnosis. Unlike in other inflammatory disorders, C-reactive protein does not typically rise in response to increased disease activity in SLE. It does, however, rise in the setting of infection and thus may be a useful laboratory marker to distinguish between a flare and infection. The ESR has less of a role because it has been shown to be elevated in SLE patients experiencing either a flare or an infection.[10] Coagulation profile may show an elevated partial thromboplastin time (PTT) with a normal international normalized ratio (INR) in patients with SLE. This should raise concern for the presence of comorbid APS (see Special Considerations section).

Imaging Studies

Radiography. In SLE, a chest radiograph may point to diagnoses such as pleuritis (pleural effusion); pericardial disease (enlarged cardiac silhouette); pneumonia, including atypical and opportunistic infections (airspace disease); and pulmonary embolism (normal).

Computed Tomography. CT scanning may be of particular value in identifying lupus enteritis in the patient with abdominal pain, and CT pulmonary angiography has become the preferred imaging modality for pulmonary embolism. In both cases, attention to the presence or absence of lupus nephritis must be made to guide the appropriate and safe use of intravenous (IV) contrast material.

Echocardiography and Ultrasound. Bedside echocardiography may be carried out to evaluate the presence of pericardial fluid when pericarditis is suspected on the basis of clinical or electrocardiographic findings. A number of studies have documented the safety and accuracy of emergency clinicians identifying pericardial effusions with point-of-care ultrasound examination.

Nuclear Imaging. Nuclear imaging may be helpful to assess for pulmonary embolism in patients with chronic kidney disease due to lupus nephritis.

Differential Diagnosis

In keeping with its highly varied presentations and permutations of disease activity, a number of other diseases may be confused with early SLE before its proper diagnosis. These include undifferentiated connective tissue disease, primary Sjögren's syndrome, primary APS, fibromyalgia with positive antinuclear antibody, idiopathic thrombocytopenic purpura, drug-induced lupus, and early rheumatoid arthritis. For those with an established diagnosis of SLE, chief complaint–driven considerations for acute presentations are listed in Table 108.3.

Management

Nearly all *non-infectious consequences* of SLE are managed with introduction or escalation of immunomodulatory therapy. In the majority of disease states, a pulse dose of methylprednisolone at 1 to 2 mg/kg is appropriate. See Table 108.4 for additional therapeutic options for escalating disease severity.

For SLE patients presenting with *infection* who are receiving chronic steroid therapy, consider stress dose glucocorticoids, hydrocortisone 50 to 100 mg IV every 8 hours, in addition to appropriate antimicrobial coverage.

TABLE 108.3

Common or Specific Differential Considerations for Patients With Systemic Lupus Erythematosus Based on Common Presentations, Comorbidities, or Complications

CHIEF COMPLAINT	CONDITION
Pleuritic chest pain	Pericarditis, pleuritis, pulmonary embolism, pneumonia, musculoskeletal chest wall pain
Delirium	Neuropsychiatric lupus, steroid psychosis
Leg swelling	Deep venous thrombosis, renal failure, right-sided heart failure (pulmonary embolism, pulmonary hypertension), protein-losing enteropathy
Shortness of breath	Pneumonia, anemia, pericarditis or pericardial effusion, pleuritis or pleural effusion, interstitial lung disease, shrinking lung syndrome
Pruritic or painful rash	Discoid SLE, drug reaction, sun exposure
Abdominal pain	Lupus enteritis, peptic ulcer disease, pancreatitis, pseudo-obstruction
Fever	Infection, increased disease activity
Arthritis	Arthralgias (lupus flare), osteoarthritis, septic arthritis, unrelated (gout, fibromyalgia)

SLE, Systemic lupus erythematosus.

TABLE 108.4

Medications and Typical Dosing Range for Acute Exacerbations of Systemic Lupus Erythematosus

MEDICATION	MEDICATION CLASS	TYPICAL STARTING DOSAGE AND ROUTE
Methylprednisolone	Glucocorticoid	1 to 2 mg/kg IV, once daily
Prednisone	Glucocorticoid	1 to 2 mg/kg, PO, once daily
Hydroxychloroquine	Antimalarial	200 to 400 mg PO, once daily
Cyclophosphamide	Alkylating agent	500 to 750 mg/m^2 IV, once
Azathioprine	Antimetabolite (purine analogue)	25 to 50 mg/day (IV or PO)

IV, Intravenous; *PO, per os* (by mouth).

Much of the *pain* and morbidity associated with SLE is related to inflammation that is amenable to treatment with NSAIDs. Ibuprofen 400 to 600 mg orally four times a day or naproxen 500 mg orally twice daily is useful for conditions such as pericarditis, pleuritis, arthralgias, myalgias, and fever. Use of NSAIDs in patients with chronic kidney disease due to lupus nephritis or a history of peptic ulcer disease is discouraged. In such patients, acetaminophen is used for mild to moderate pain, and narcotics are recommended for severe pain.

In cases of isolated cutaneous findings, topical treatment with corticosteroids is preferable to systemic therapy. Topical therapy may be initiated with 1% hydrocortisone cream to the affected area. In cases in which higher potency topical steroids are necessary, a preparation of 0.05% betamethasone applied once daily to the affected area for 2 weeks is appropriate.

BOX 108.1

Common Clinical Features of the Antiphospholipid Syndrome

Venous thrombosis
Arterial thrombosis (including stroke and transient ischemic attack)
Recurrent miscarriage
Livedo reticularis
Thrombocytopenia

Special Considerations

Antiphospholipid Syndrome

Principles. Present in nearly 40% of SLE patients, the APS is considered when patients both have a clinical history of thrombosis and are carriers of any one of a particular set of aPL antibodies directed against three specific serum proteins. These antibodies include the anticardiolipin antibody, the misleadingly named lupus anticoagulant, and the anti–β_2-glycoprotein I antibody. The most thrombogenic of the antibodies is the lupus anticoagulant, with an odds ratio as high as 16 for the development of venous thromboembolism and 10 for arterial thrombosis (stroke). In addition to being a strong risk factor for both venous and arterial thrombosis, the presence of APS in SLE has been shown to be an independent predictor of more severe disease and to be associated with increased intensive care unit mortality. Whether it is present in the context of SLE or independently, APS is an important cause of morbidity and mortality due to thrombosis.

Clinical Features. APS may present with any number of clinical features (Box 108.1), typically related to thrombosis or thromboembolism. A small subset of those with APS may present with multiple thrombotic sites and organ failures simultaneously. This condition is known as *catastrophic APS.*

Diagnostic Testing. Assays to detect and to measure the presence of aPL antibodies are not generally available in a timely fashion and are impractical for use in the ED setting. However, there are two laboratory findings supportive of APS that may be useful or accidentally discovered during an ED evaluation:

1. A spuriously elevated PTT in the setting of a normal PT/INR may reflect APS. This in vitro finding, which contradicts the actual in vivo hypercoagulable state of the APS patient, is due to interference of the coagulation study by aPL antibodies. Confirmation of the presence of the interfering antibody is done by carrying out a mixing study. A mixing study requires repeating the PTT with a mixture of the patient's blood and a 50% contribution from normal, control serum. In the presence of an inhibiting antibody, the PTT will remain elevated. If, however, the PTT was elevated for other reasons (most commonly heparin), the addition of normal clotting factors from the control serum will restore the PTT to normal.
2. The Venereal Disease Research Laboratory (VDRL) assay to test for syphilis contains cardiolipin and thus will commonly be falsely positive in patients with anticardiolipin antibodies or APS.

Management. For acute thrombotic events, anticoagulation with either unfractionated or low–molecular-weight heparin is generally indicated. After an initial thrombotic event, anticoagulation with vitamin K antagonists to maintain an INR between 2.0 and 3.0 is recommended. For patients with arterial thrombotic events (eg, stroke) or recurrent venous thromboembolic events, anticoagulation is recommended indefinitely. For patients

BOX 108.2

Drugs Definitively Implicated in Causing Drug-Induced Lupus

Procainamide
Hydralazine
Methyldopa
Chlorpromazine
Isoniazid
Quinidine
Minocycline

BOX 108.3

Reasons for Rheumatologic Referral for Patients With Systemic Lupus Erythematosus

To confirm a diagnosis
To assess disease activity and severity
To provide general disease management
To manage uncontrolled disease
To manage organ involvement or life-threatening disease
To manage or prevent treatment toxicities
Special circumstances: Antiphospholipid syndrome (APS), pregnancy, surgery

Modified from Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Arthritis Rheum 42:1785–1796, 1999.

suffering catastrophic APS, in addition to anticoagulation and glucocorticoids, intravenous immune globulin (IVIG), cyclophosphamide, and plasma exchange may all be indicated. Despite treatment, mortality for catastrophic APS approaches 50%.

Drug-Induced Lupus

Drug-induced lupus is an SLE-like self-resolving illness characterized by arthralgias, myalgias, rash, and serositis; it may be brought on by as many as 80 different medications. Notably, the malar rash and major organ involvement are rare in this condition. In drug-induced lupus, antibodies against the body's own histone proteins are common and purported to be a major mechanism of disease. Although the list of potentially implicated medications is long, those agents with most evidence for causing drug-induced lupus are summarized in Box 108.2. The diagnosis is typically clinical and confirmed by resolution of symptoms with the withdrawal of the offending medication. In addition to cessation of the culprit drug, NSAIDs or steroids for symptom control are indicated.

Disposition

Disposition for the patient with SLE will vary significantly by clinical presentation. For patients with non–life-threatening presentations, such as increased musculoskeletal symptom burden, simple headache, or cutaneous reactions, discharge with appropriate follow-up is usually appropriate. However, patients with poor insight into their disease, significant comorbidities, or weak social or home supports may require hospitalization.

With disorders characteristic of SLE flares (eg, progressive lupus nephritis, lupus enteritis), new thrombotic events, and infectious complications due to immunosuppression, the patient may need admission for initiation of systemic therapy (eg, glucocorticoids, anticoagulation, antibiotics) and evaluation of response or deterioration. Admission to the intensive care unit is considered for those who, despite initial resuscitation, suffer progressive circulatory or respiratory derangement. Because of the high incidence of CAD in patients with SLE, patients with undifferentiated chest pain who have acute coronary syndrome ruled out in the ED should receive an expedited evaluation with provocative testing (eg, exercise stress test) in a chest pain unit, observation unit, or on an outpatient basis. If an outpatient evaluation is pursued, prescribe daily aspirin therapy. The complexity of SLE often challenges physicians not specialized in its many nuances and intricate pathophysiologic changes. Reasons for rheumatologic referral of patients with SLE are presented in Box 108.3.

VASCULITIDES

Principles

The vasculitides are a heterogeneous group of disorders characterized by inflammatory damage of blood vessels. Arteries and veins of all sizes and their tributaries can be affected to varying degrees. Presentations can range from benign and self-limited to serious and life-threatening. Diagnosis can be challenging because early vasculitis syndromes are nonspecific and can mimic other infectious, inflammatory, or neoplastic conditions. Approximately 1 in 2000 adults are affected by some form of vasculitis, with a higher incidence in adults 65 to 74 years old. In the United States, the most common vasculitis syndromes are giant cell arteritis (GCA), Wegener's granulomatosis, and microscopic polyangiitis.

The cause of most vasculitis syndromes is unknown. Most cases are believed to result from immune complex deposition in blood vessel walls, prompting a complement-mediated inflammatory reaction. This results in vessel wall damage and necrosis, leading to stenosis, occlusion, and subsequent end-organ ischemia. The clinical manifestations are determined predominantly by the size and distribution of blood vessels involved along with the histologic subtype of inflammation.

The most recognized system for classification of the primary vasculitis is by the size of blood vessel involved (Table 108.5). Large-vessel vasculitis involves the aorta and its immediate branches and in some cases the corresponding vessels in the venous system. Medium-vessel disease involves the macrovasculature downstream from the main aortic branches. Small-vessel vasculitis involves capillaries, venules, arterioles, and glomeruli.

Clinical Features

Virtually all vasculitides involve some degree of constitutional symptoms, including fever, malaise, weight loss, and arthralgias. There is substantial overlap in the signs and symptoms associated with the large-, medium-, or small-vessel disorders. Practically, it is more useful to classify the vasculitides according to one of four patterns: (1) organ system involvement or exposure most evident on presentation vasculitis presenting with large-vessel occlusive symptoms, (2) vasculitis typified by pulmonary-renal manifestations, (3) vasculitis with characteristic cutaneous manifestations, and (4) syndromes associated with environmental or foreign antigen exposure. This approach assists in refining the differential diagnosis for a given constellation of symptoms and directing initial therapy while awaiting the results of confirmatory tests or tissue biopsy, which are in most cases not readily available in the ED.

Vasculitis Presenting With Large-Vessel Occlusive Symptoms

Giant Cell Arteritis

Principles. GCA, also known as *temporal arteritis,* is a systemic vasculitis that affects medium-sized and large vessels. The most recognized symptoms are caused by occlusion of the superficial

TABLE 108.5

Primary and Secondary* Vasculitis: Classification and Associated Features

PREDOMINANTLY LARGE VESSEL		PREDOMINANTLY MEDIUM VESSEL		PREDOMINANTLY SMALL VESSEL	
EXAMPLES	COMMON FEATURES	EXAMPLES	COMMON FEATURES	EXAMPLES	COMMON FEATURES
Giant cell arteritis (GCA)	Asymmetrical blood pressures	Polyarteritis nodosa	Cutaneous nodules	Goodpasture's disease	Alveolar hemorrhage
Takayasu's arteritis	Claudication Aortic disease Renovascular hypertension	Buerger's disease Kawasaki disease	Ulcers Mononeuritis multiplex Digital gangrene Microaneurysms Renovascular hypertension	Wegener's granulomatosis Microscopic polyangiitis Churg-Strauss disease Behçet's disease Henoch-Schönlein purpura	Glomerulonephritis Purpura Vesiculobullous lesions Uveitis, episcleritis, scleritis

*Secondary forms of vasculitis:
- Connective tissue disorders (rheumatoid vasculitis, lupus erythematous, Sjögren's syndrome, others)
- Infection (hepatitis B or C virus, human immunodeficiency virus)
- Inflammatory bowel disease
- Hypersensitivity (drug induced, others)

branches of the carotid artery, although systemic medium- and large-vessel disease involving the carotid, subclavian, aortic, vertebral, and iliac vessels may also be present. The most feared complication of GCA is irreversible visual loss, occurring in up to one-third of patients. Early treatment can help prevent this complication, and thus the diagnosis is an important consideration in patients older than 50 years old presenting with any combination of constitutional symptoms, headache, visual changes, and jaw claudication.

Clinical Features. The incidence of GCA has been increasing steadily during the past 20 to 40 years. The syndrome is tightly coupled to age, with a mean age at onset of 70 years and a range of 50 to 90 years. The incidence increases sharply after the age of 50 years, with an estimated incidence of 33 per 100,000 patients. The disease is twice as common in women than in men, and smoking increases the risk of GCA sixfold in women.

GCA is frequently associated with a spectrum of nonspecific symptoms, such as fever, weight loss, and fatigue. Common presenting complaints include headache, visual symptoms, jaw claudication, and myalgias and associated polymyalgia rheumatica. Headache, the most common presenting symptom, occurs in three quarters of patients with GCA. Although it is classically located in the temporal area and in association with tenderness along the superficial temporal artery, no specific pattern of headache location or severity is predictive of the temporal arteritis; and in untreated patients, the headache may improve or disappear, even though active disease is still present. The presence of tenderness, prominence, or beading of the superficial temporal artery on physical examination is associated with GCA, whereas the absence of any temporal artery abnormality is associated with a modest decrease in the likelihood of disease. Changes in visual acuity occur as a result of occlusive arteritis of the posterior ciliary artery or less commonly retinal artery occlusion. Visual loss may occur in one or both eyes and at times be painless; interruptions in acuity may be partial or complete, transient or permanent. The visual deficit is often profound, with 80% of patients unable to appreciate hand waving. Funduscopic findings in patients with acute visual loss include optic disk pallor and edema, in keeping with ischemic optic neuritis. Complete visual loss that is present for more than a few hours is usually irreversible. Diplopia may also occur as a result of ischemic ophthalmoplegia; oculomotor nerve lesions typically spare the pupil.

Thoracic aortic aneurysms are 17 times more likely to occur in patients with GCA compared with age-matched controls. The vertebral-basilar arteries are affected in 75% to 100% of patients, leading to signs of vertebrobasilar insufficiency, including gait disturbance, dizziness or vertigo, and vomiting. The diagnosis of GCA should be considered in elders with signs of vertebrobasilar insufficiency in conjunction with constitutional symptoms and an elevated ESR.

BOX 108.4

American College of Rheumatology Classification Criteria for Giant Cell Arteritis

Age ≥50 years old
New-onset localized headache
Temporal artery tenderness or decreased temporal artery pulse
Erythrocyte sedimentation rate (ESR) ≥50 mm/hr
Abnormal artery biopsy specimen characterized by mononuclear infiltration or granulomatous inflammation

Modified from Hunder GG, et al: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 33:1125, 1990.

Diagnostic Testing. In the presence of symptoms consistent with occlusion of superficial branches of the carotid artery, the diagnosis is usually straightforward. The American College of Rheumatology has developed a scoring system that lends equal weight to each of five diagnostic criteria (Box 108.4). Patients with a score of 2 or lower require temporal artery biopsy for the diagnosis to be confirmed; in patients with a score of 3 or higher, a biopsy adds little information beyond clinical and laboratory appraisal. An ESR of 80 mm/hr or higher is common, although approximately 20% of patients with an ESR of less than 50 mm/hr will go on to have biopsy-proven temporal arteritis. An elevated C-reactive protein level has improved sensitivity over ESR and may actually be the preferred diagnostic test, with a reported sensitivity for GCA of 97.5%. The gold standard for diagnosis remains temporal artery biopsy, with established sensitivity of 90% to 95%. Bilateral biopsies should be considered in patients for whom clinical suspicion is high and initial findings on biopsy are normal. The role of color duplex ultrasonography in the diagnosis of temporal arteritis remains controversial; one study showed no benefit in establishing the diagnosis when it was added to a carefully performed physical examination. High-resolution

magnetic resonance imaging may be used alone or as a diagnostic adjunct to biopsy in atypical or challenging cases.

Management. Given the high stakes and morbidity associated with missed or delayed diagnosis, initiate treatment for temporal arteritis as soon as the diagnosis is considered to prevent permanent visual loss. The mainstay of treatment remains high-dose corticosteroids, initiated in the ED and continued until the diagnosis can be confirmed or excluded on subsequent biopsy. A typical initial regimen is oral prednisone 60 to 100 mg daily (or 1 mg/kg) with a temporal biopsy scheduled within 1 week of presentation. More than half of patients treated within 24 hours of presentation will achieve some recovery, compared with only 6% when treatment is delayed beyond this interval. Oral corticosteroids do not alter the sensitivity of temporal artery biopsy when it is performed within 2 weeks of initiation of therapy. Some authors recommend switching to IV corticosteroid treatment for 3 days should vision continue to deteriorate despite timely initiation of oral prednisone.[11] Acetylsalicylic acid may be useful as an adjunct to decrease ischemic complications.

Takayasu's Arteritis

Principles. Takayasu's arteritis, also known as *pulseless disease* or *occlusive thromboaortopathy,* is a systemic large-vessel vasculitis of unknown etiology that primarily affects young women of Japanese and Southeast Asian descent. It is characterized by granulomatous inflammation of the aorta and its branches, leading to massive intramural fibrosis and symptoms of large-vessel stenosis, thrombosis, and aneurysm.

Takayasu's arteritis is a rare disorder worldwide, with a reported incidence of 0.2 to 2.6 cases per million in Western Europe and North America, although this number is much higher in Japan. The disease is eight times more common in women than in men; symptoms are first manifested between 15 and 25 years old. The diagnosis should be considered in women younger than 40 years old who present with signs and symptoms of large-vessel occlusion, including upper limb claudication, decreased or asymmetrical pulses, and unexplained hypertension accompanied by constitutional symptoms, such as fever and weight loss.

Clinical Features. The most common presenting symptoms related to vascular occlusion are claudication (most commonly of the upper extremity, 35%), reduced or absent pulse (25%), hypertension (most often associated with renal artery stenosis, 20%), carotidynia (20%), lightheadedness (20%), and asymmetrical arm blood pressures (15%). Cerebrovascular ischemia, stroke, aortic insufficiency, and visual symptoms are present in 10% of patients. Approximately 80% of patients will have an identifiable bruit on physical examination, and 50% will go on to have asymmetrical blood pressures. One-third of patients will have cardiac complications, including aortic insufficiency and regurgitation, myocarditis, congestive heart failure, and cardiac ischemia from coronary artery aneurysm. Patients presenting after 40 years old or without signs of vascular occlusion pose a diagnostic challenge; only nonspecific constitutional symptoms or fever of unknown origin may initially be manifested, leading to diagnostic and therapeutic delays.

Diagnostic Testing. Although an elevated ESR (>80 mm/hr) is suggestive of Takayasu's arteritis, the majority of laboratory investigations are nonspecific, and the diagnosis is almost always secured on the basis of clinical assessment and diagnostic imaging. Patients younger than 40 years old who present with symptoms of large-vessel occlusive disease (bruit, absent pulse, claudication) are candidates for axial imaging of the aorta and its major branches; options include CT angiography and magnetic resonance angiography, both of which have largely replaced digital subtraction angiography as the imaging method of choice.

Management. Once a diagnosis of Takayasu's arteritis is made, oral corticosteroids (eg, 0.5 to 1 mg/kg prednisone daily) are indicated and continued for 4 to 12 weeks, followed by a gradual taper. It is a self-limited disorder in 20% of patients; the remainder will go on to have a relapsing-remitting or chronic progressive course requiring long-term corticosteroids. Steroid-sparing agents such as azathioprine, cyclophosphamide, and tumor necrosis factor inhibitors may be added for patients who relapse. Patients should be observed closely by a rheumatologist and vascular surgeon; those who do not respond to corticosteroids may benefit from surgical reperfusion, including bypass grafting and percutaneous transluminal angioplasty. Indications for admission include signs and symptoms of acute end-organ ischemia, aortic insufficiency, myocarditis, and decompensated congestive heart failure. The most common causes of death are congestive heart failure, renal failure, and infectious complications.[102]

Vasculitis Typified by Pulmonary-Renal Manifestations

Vasculitis syndromes in this category are characterized by a predominance of pulmonary and renal manifestations, including dyspnea, cough, pulmonary infiltrates, and renal insufficiency secondary to glomerulonephritis, in addition to a variety of systemic symptoms. Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome share a strong association with the presence of antineutrophil cytoplasmic antibodies (ANCAs) of various subtypes, including cytoplasmic staining (c-ANCA) and perinuclear staining (p-ANCA), measured in the blood by enzyme-linked immunosorbent assay or direct immunofluorescence. Whether ANCA are involved in pathogenesis or are simply markers of disease is unclear. The absence of ANCA does not rule out an ANCA-associated vasculitis syndrome because between 20% and 50% will have negative assays.

A comparison of the common presenting features of Wegener's granulomatosis, microscopic polyangiitis, Goodpasture's syndrome, and Churg-Strauss syndrome is shown in Table 108.6.

Wegener's Granulomatosis

Principles. Wegener's granulomatosis is a c-ANCA–associated systemic necrotizing vasculitis of small and medium-sized blood vessels with a predilection for the upper and lower respiratory tracts and kidneys. The constellation of upper respiratory, pulmonary, and renal disease in patients with constitutional symptoms suggests Wegener's granulomatosis. In the absence of pulmonary or renal symptoms, the diagnosis is extremely challenging and often missed. Wegener's granulomatosis is more common in white individuals but otherwise shows no specific pattern of distribution for age, sex, or geography. The annual incidence is estimated to be 3 per 100,000 people.

Clinical Features and Diagnostic Testing. Constitutional symptoms including fever, malaise, and weight loss are often evident on initial presentation. Upper airway disease is the most common presenting symptom of Wegener's granulomatosis, with 90% of patients developing upper respiratory tract symptoms in some form. Upper airway manifestations include serous otitis media with or without suppurative infection, hearing loss, sinusitis, nasal mucosal ulcerations and septal perforation, epistaxis, and laryngotracheal disease. Subglottic stenosis is the most common laryngotracheal lesion, present in about 16% of patients, the severity of which can range in presentation from mild dyspnea to acute airway obstruction and respiratory extremis. Nearly 50% of pediatric and adolescent patients will have some degree of subglottic stenosis, with implications for airway management. Lower respiratory symptoms include cough, dyspnea, pleuritis, and hemoptysis. Radiographic studies may demonstrate pulmonary infiltrates and nodules, although the severity of radiographic findings does not always correlate well with symptom severity (Fig. 108.6). A minority of patients present with diffuse alveolar hemorrhage, which has an associated mortality of approximately

TABLE 108.6

Comparison of the Common Features of Wegener's Granulomatosis, Microscopic Polyangiitis, Goodpasture's Syndrome, and Churg-Strauss Syndrome

FEATURE	WEGENER'S GRANULOMATOSIS*	MICROSCOPIC POLYANGIITIS*	GOODPASTURE's SYNDROME	CHURG-STRAUSS SYNDROME*	COMMENTS
Pulmonary infiltrates or nodules	+++	++	+++	+++	Asthma and eosinophilia in CSS
Alveolar hemorrhage	++	++	+++	+	
Glomerulonephritis	+++	+++	++	++	Progressive renal failure uncommon in CSS
Upper airway disease	+++	+	–	++	ENT disease favors WG
Purpura	+	+++	+	++	
Peripheral nervous system involvement	++	+	–	+++	Often a prominent feature of CSS
Central nervous system involvement	+	+	–	++	

*Antineutrophil cytoplasmic antibody (ANCA)-associated syndromes.
CSS, Churg-Strauss syndrome; *ENT,* ear, nose, and throat; *WG,* Wegener's granulomatosis.
Data from Firestein GS: Kelley's textbook of rheumatology, ed 8, Philadelphia, 2008, WB Saunders.

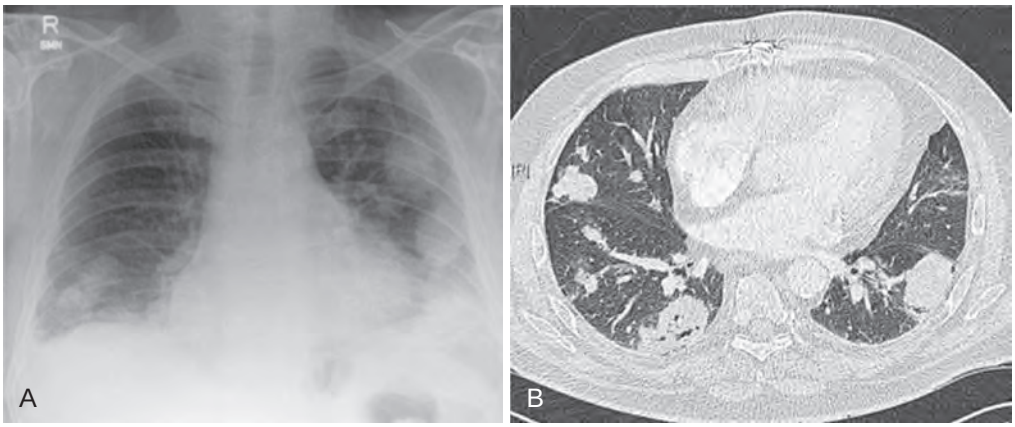

Fig. 108.6. A, Multiple intrapulmonary nodules on a chest radiograph of a patient with Wegener's granulomatosis. **B,** Pulmonary nodules seen on computed tomography (CT) imaging. (From Adam A, Dixon AK: Grainger & Allison's diagnostic radiology, ed 5, Philadelphia, 2008, Churchill Livingstone.)

50%. Renal dysfunction tends to be a later finding, developing in a subset of patients with generalized disease. Once progressive renal failure has developed, it may evolve rapidly during days to weeks, leading to end-stage renal disease that, if left untreated, is associated with a mean survival of 5 months. Chronic renal insufficiency can develop despite appropriate treatment, with a subset of patients requiring dialysis or renal transplantation.

The list of associated symptoms in Wegener's granulomatosis is myriad and speaks to the systemic nature of the disease. Ophthalmologic (scleritis, episcleritis, uveitis), cutaneous (palpable purpura, subcutaneous nodules, ulcers), neurologic (mononeuropathy and polyneuropathy, cerebral vasculitis, cerebral hemorrhage, or thrombosis), and cardiac (pericarditis, myocarditis) disease may be present to varied degrees.

Management. Initial management is directed at life-threatening pulmonary hemorrhage and sequelae from acute or decompensated chronic renal insufficiency. The combination of diffuse alveolar hemorrhage and subglottic stenosis represents a "double hit" difficult airway, requiring extreme caution during endotracheal intubation. Although a large endotracheal tube is preferred for the management of massive hemoptysis, selection of a smaller tube size may be required to bypass a narrow subglottic corridor. Fiberoptic intubation through an intubating laryngeal mask airway has been advocated.

Combination therapy with corticosteroids and cyclophosphamide is considered the current standard of care for patients with acute flares and has dramatically changed the disease prognosis. Before the use of steroids, 1-year mortality approached 90%; combination therapy with corticosteroids and cyclophosphamide has improved the 5-year survival to nearly 90%, with the majority of patients achieving remission. Methotrexate plus corticosteroids may be used instead of cyclophosphamide in less severe presentations involving systemic disease. Patients presenting with new or suspected Wegener's granulomatosis and those with severe disease require admission for high-dose IV dual-agent therapy. The diagnosis is typically confirmed by open lung biopsy. Patients who present with new respiratory symptoms or infiltrates on the chest film should be hospitalized and treated for infection, until it is proven otherwise, given the morbidity associated with pneumonia in an immunocompromised host.

Goodpasture's Syndrome

Principles. Goodpasture's syndrome describes the clinical triad of glomerulonephritis, pulmonary hemorrhage, and circulating anti–glomerular basement membrane (GBM) antibodies. The syndrome is distinct from Goodpasture's disease, which consists of glomerulonephritis and anti-GBM antibodies without pulmonary hemorrhage. Goodpasture's syndrome is not associated with ANCA; anti-GBM autoantibodies target type IV collagen found in the basement membranes of glomeruli and pulmonary alveoli, causing autoimmune damage through a type II hypersensitivity reaction. The disease can affect people of all ages, with white individuals more commonly affected. The incidence is bimodal; one peak occurs in 20- to 30-year-old men and a second in 50- to 70-year-olds of both sexes. The incidence is believed to be about 1 case per 2 million individuals.

Clinical Features and Diagnostic Testing. There is substantial variation in the presentation of patients with anti-GBM disease. Pulmonary or renal symptoms may exist alone or in combination, although the two are most often present together. Fever, malaise, and weight loss are common early symptoms. Pulmonary symptoms range from dyspnea and cough to hypoxemia and frank pulmonary hemorrhage, which can be massive and life-threatening. Chest radiographic findings may be normal or demonstrate hilar pulmonary infiltrates sparing the apices and costophrenic angles. Renal failure can be insidious or be manifested as rapidly progressive glomerulonephritis with acute kidney injury and volume overload. Urinalysis shows characteristic signs of acute glomerulonephritis, including hematuria, proteinuria, and red cell casts. Definitive diagnosis is made by lung or renal biopsy demonstrating linear deposition of anti-GBM antibodies in the alveolar or GBMs, respectively.

Management. Initial management of patients with massive pulmonary hemorrhage is focused on securing a definitive airway and addressing hemodynamic instability. Bronchoscopy or chest radiography can be used to identify the source of hemorrhage, and selective intubation of the contralateral mainstem bronchus or use of a double-lumen endotracheal tube and ventilating with the affected lung in the dependent position may improve oxygenation.

High-dose methylprednisone (10 to 15 mg/kg) and cyclophosphamide are the mainstays of immune suppressive therapy. Therapeutic plasma exchange can be used to decrease the level of circulating anti-GBM antibodies during acute presentations. Patients who have end-stage renal disease may be candidates for renal transplantation, assuming anti-GBM antibodies are undetectable with treatment because the disease may recur in the transplanted graft. The prognosis has improved in recent years owing in part to the more aggressive use of therapeutic plasma exchange.

Microscopic Polyangiitis

Principles. Microscopic polyangiitis was first recognized in a subset of polyarteritis nodosa patients who presented with segmental glomerulonephritis. This systemic small-vessel vasculitis is the most common cause of the pulmonary-renal syndrome, leading to renal failure and pulmonary hemorrhage, the two most clinically relevant features of microscopic polyangiitis. The disease affects men and women equally and typically is manifested in the fourth or fifth decade of life, although it may occur at virtually any age. The annual incidence in the United States is approximately 3.8 cases per 1 million population.

Clinical Features and Diagnostic Testing. The characteristic presentation of rapidly progressive renal failure in the context of pulmonary alveolar hemorrhage and systemic symptoms occurs in the minority of patients; in many cases, the disease presentation is protean, consisting largely of renal insufficiency and constitutional symptoms, such as fever, weight loss, and malaise.

Glomerulonephritis with subsequent renal insufficiency is a nearly universal finding in microscopic polyangiitis, and renal failure can be acute and rapidly progressive or chronic and insidious; 25% to 45% of patients require dialysis at some point during the course of the disease. The specific renal disease is that of necrotizing glomerulonephritis, including elevated serum creatinine and blood urea nitrogen concentrations and a urinalysis demonstrating red cell casts, hematuria, and proteinuria. Pulmonary disease is present in up to 50% of patients, and diffuse alveolar hemorrhage is present in about 12%. Respiratory symptoms range from cough, dyspnea, and pulmonary fibrosis to massive diffuse alveolar hemorrhage requiring active and aggressive resuscitation and airway management. Peripheral neuropathy in the form of mononeuritis multiplex is present in up to 60% of cases. Skin manifestations are common, with about 50% of patients having palpable purpura.

It can be difficult to distinguish microscopic polyangiitis from other ANCA-positive syndromes, including Wegener's granulomatosis and Churg-Strauss syndrome, on clinical grounds alone. Microscopic polyangiitis and Wegener's granulomatosis probably exist on a spectrum of illness, and it is usually not required to distinguish between the two in the emergency setting to direct management. The diagnosis is typically secured by tissue biopsy of the lung, kidney, or skin, with demonstration of pulmonary capillaritis, necrotizing glomerulonephritis, or leukoclastic vasculitis, respectively.

Management. The priority in patients presenting with acute or decompensated chronic renal insufficiency is to identify and manage immediate life threats, including volume overload, electrolyte disturbances, and refractory acidosis. Airway management is the priority in those presenting with diffuse alveolar hemorrhage, and a difficult intubation should be anticipated. Admission for renal optimization, administration of IV steroids, and possibly dialysis is often required. In the presence of serious pulmonary and renal disease, a combination of high-dose glucocorticoid and cyclophosphamide is the treatment of choice, demonstrating superiority over glucocorticoid alone. Mortality in microscopic polyangiitis is approximately 30% during 7 years; morbidity and mortality are the highest in patients with a heavy burden of renal, cardiovascular, or neurologic disease. Plasmapheresis and IVIG are options for refractory cases. Remission is much more common than in Wegener's granulomatosis and is achieved in about 90% of patients, although up to one-third will experience flares after remission.

Churg-Strauss Syndrome

Principles. Churg-Strauss syndrome, also known as *allergic granulomatosis,* is an autoimmune vasculitis of medium-sized and small vessels associated with asthma and eosinophilia. The etiology is unknown, although there is a strong association with allergy and atopy. The mean age at onset is typically in the fourth decade of life; men are affected more often than women are. The annual incidence is approximately 2.4 cases per 1 million individuals.

Clinical Features and Diagnostic Testing. Patients with Churg-Strauss syndrome may present in three distinct stages, although there may be considerable overlap and variance. Most patients with Churg-Strauss syndrome have asthma and allergic rhinitis several years before the onset of vasculitis. Over time, asthma symptoms may actually improve as the vasculitic stage of the disease sets in. The pattern of medium-sized vessels involved determines the clinical picture of the vasculitic phase, although pulmonary, renal, and neurologic symptoms are common. Pulmonary infiltrates, pleural effusion, and alveolar hemorrhage may be seen during the prodromal or vasculitic stage. Renal involvement is less common compared with other ANCA-positive vasculitis syndromes and may preferentially affect the lower urinary

tract and prostate gland, leading to obstructive uropathy. Cardiac manifestations, including restrictive pericarditis and cardiomyopathy leading to congestive heart failure, are more common in Churg-Strauss syndrome compared with Wegener's granulomatosis and microscopic polyangiitis. Mononeuritis multiplex, asymmetrical neuropathy, and cranial neuropathies are the most frequently observed neurologic symptoms, seen in up to 80% of patients. Gastrointestinal symptoms include infarction, perforation, and hemorrhage secondary to infiltration of the small bowel or stomach.

Laboratory investigation demonstrates a persistently elevated eosinophil count (>1500 cells/mm^3), although this does not correlate well with the presence of active disease. Myeloperoxidase-ANCA antibodies are seen in about 40% of cases. Pulmonary infiltrates are typically patchy and transient in nature (Löffler's syndrome). The diagnosis of Churg-Strauss syndrome is made by a combination of clinical and histologic features; evidence of necrotizing vasculitis or extravascular granulomas on skin or lung biopsy in conjunction with eosinophilia, asthma, and allergy is highly suggestive of the disease.

Management. Corticosteroids are the mainstay of treatment, although immunomodulating agents such as cyclophosphamide may be added to achieve remission in cases complicated by cardiac, renal, or gastrointestinal involvement. The overall survival for patients with Churg-Strauss syndrome approaches 80%, with an increased relative risk of death predicted by the presence of renal and gastrointestinal symptoms.

Vasculitis With Characteristic Cutaneous Manifestations

Cutaneous vasculitis involves inflammation of the blood vessels of the skin. The diseases listed here are associated with cutaneous manifestations that are often characteristic and an important element of disease recognition in the ED. Constitutional signs and symptoms of systemic multisystem disease may also be present.

Erythema Nodosum

Principles. Erythema nodosum, a vasculitis of the venules and veins of the skin, is characterized by tender, subcutaneous nodules on the tibial surfaces of the lower legs. Erythema nodosum is presumed to be a hypersensitivity response to systemic diseases or drug therapy, although no clear precipitant can be identified in 30% to 50% of cases. Peak incidence occurs in the spring or fall months among 18- to 34-year-olds, with a male-to-female ratio of approximately 1:4.

Clinical Features. The prodromal stage of erythema nodosum consists of nonspecific constitutional symptoms, fever, malaise, and myalgias. The distribution of subcutaneous nodules favors the lower extremities, although lesions may be appreciated on the forearm, trunk, and thigh (Fig. 108.7). The nodules tend to be erythematous, well circumscribed, and exquisitely tender to touch and develop a blue hue as they resolve. Arthralgias may be present in conjunction with or before the cutaneous eruption.

Viral upper respiratory tract infections, streptococcal infection, tuberculosis, and sarcoidosis are common precipitants. Drugs associated with erythema nodosum include penicillins, sulfonamides, oral contraceptive medication, and phenytoin. Less common associations include autoimmune conditions, such as inflammatory bowel disease and SLE; histoplasmosis; *Yersinia, Salmonella,* and *Chlamydia* infections; coccidioidomycosis; and psittacosis.

Management. Management of erythema nodosum is generally supportive and directed toward symptom control and treatment or elimination of the underlying cause. Cutaneous nodules secondary to infection resolve within 6 to 7 weeks; in contrast, 30% of idiopathic cases may persist beyond 6 months. NSAIDs may be useful for control of arthralgias; corticosteroids and colchicine are reserved for the management of protracted or refractory disease.

Fig. 108.7. Tender subcutaneous nodules associated with erythema nodosum. (From Kliegman R: Nelson textbook of pediatrics, ed 18, Philadelphia, 2007, WB Saunders.)

Henoch-Schönlein Purpura

Principles. Henoch-Schönlein purpura is a small-vessel vasculitis characterized by palpable purpura and gastrointestinal and renal manifestations associated with immunoglobulin A immune complex deposition in blood vessels. The 1990 American College of Rheumatology criteria for Henoch-Schönlein purpura include the presence of two or more of the following: age at onset younger than 20 years old, palpable purpura, bowel angina, and vessel wall granulocytes on biopsy (sensitivity of 87.1%, specificity of 87.7%). Although the disease can affect adults, it is most commonly seen in children younger than 5 years old.

Clinical Features and Diagnostic Testing. Henoch-Schönlein purpura usually is manifested 1 to 2 weeks after a viral upper respiratory tract infection with a triad of palpable purpura, arthralgias, and abdominal pain. Purpuric lesions cluster in dependent regions with a predilection for the legs and buttocks (Fig. 108.8). Colicky abdominal pain and bloody stools can occur secondary to gastrointestinal vasculitis. A rare complication of Henoch-Schönlein purpura in children is enteroenteral intussusception (ileoileal, jejunojejunal, jejunoileal), which may be associated with severe abdominal pain, lethargy, bloody diarrhea, and signs of obstruction or perforation. Glomerulonephritis is typically mild and may be manifested as hematuria, red cell casts on urinalysis, and azotemia.

Management. Management in mild disease is generally supportive, and symptoms can intermittently recur for several weeks. NSAIDs control arthralgias in most cases but are avoided if renal impairment is present. Glomerulonephritis is treated more aggressively, with a combination of corticosteroids and cyclophosphamide, azathioprine, or mycophenolate mofetil, and generally demonstrates full resolution with time. Enteroenteral

Fig. 108.8. Purpuric lesions associated with Henoch-Schönlein purpura, some of which have coalesced and undergone central necrosis. (From Habif TP: Clinical dermatology, ed 5, New York, 2009, Mosby.)

Fig. 108.9. Oral aphthae associated with Behçet's disease. (From Firestein GS: Kelley's textbook of rheumatology, ed 8, Philadelphia, 2008, WB Saunders.)

intussusception can be difficult to diagnose with standard approaches (ultrasonography, air-contrast enema), and if the diagnosis is strongly suspected, patients should be assessed by a pediatric general surgeon.

Polyarteritis Nodosa

Principles. Polyarteritis nodosa is a necrotizing vasculitis of unknown etiology affecting small and medium-sized blood vessels. The disease can involve multiple systems, most commonly the skin, nervous system, and gastrointestinal tract. Necrosis occurs preferentially at arterial bifurcations and branch sites, leading to microaneurysm formation, thrombosis, emboli, organ ischemia, and infarction. Polyarteritis nodosa affects men about twice as often as women, and onset occurs at any age, although the peak is typically the fourth to sixth decade of life. Annual incidence is between 2 and 9 cases per 1 million individuals.

Clinical Features. Whereas the initial presentation can be nonspecific, the combination of cutaneous lesions and adult-onset hypertension with evidence of systemic illness suggests polyarteritis nodosa. Cutaneous manifestations occur in one-third of patients. Palpable purpura with or without ulceration is noted in the fingers, ankles, malleoli, and pretibial areas. Digital cyanosis may be seen secondary to ischemia. Splinter hemorrhages and livedo reticularis may also be observed. Renovascular arteritis can cause hypertension, which may at times be severe. Peripheral neuropathies in the form of mononeuritis multiplex or polyneuropathy are present in up to 50% of patients. Mesenteric vasculitis can produce abdominal angina and in rare cases lead to frank mesenteric ischemia, infarction, and perforation, often with devastating consequences.

Management. Treatment generally begins with a corticosteroid (eg, prednisone 1 mg/kg), and a second immunosuppressive agent is added for severe or extensive disease. Abdominal catastrophes may require surgical intervention; prognosis in these cases is poor. Polyarteritis nodosa is almost always fatal if it is left untreated, although the prognosis has been much improved with the use of systemic corticosteroids. In a prospective study, the presence of two or more prognostic factors (azotemia, proteinuria, cardiomyopathy, gastrointestinal involvement, or neurologic signs) predicted a 5-year mortality of 46%; if none was present, the 5-year mortality was 12%.

Behçet's Disease

Principles. Behçet's disease is a complex, chronic small-vessel vasculitis that may affect the mucocutaneous, ocular, cardiovascular, renal, gastrointestinal, pulmonary, urologic, musculoskeletal, and central nervous systems. Early descriptions of the disease date to the time of Hippocrates and the third book of endemic diseases. The disease is defined by the presence of aphthous oral ulcers plus two or more of the following: genital aphthae; cutaneous lesions; and neurologic, oral, or rheumatologic manifestations. The exact pathogenesis remains unknown. Behçet's disease is found worldwide, with the highest prevalence in Turkey, Japan, the Middle East, and Mediterranean regions. The disease affects people of all ages, although patients often first present in the second or third decade of life. The male-to-female ratio varies somewhat according to geography; women are more commonly affected than men in northern Europe and the United States, with an estimated prevalence in these regions of about 1 in 150,000 individuals.

Clinical Features and Diagnostic Testing. The triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis in young adults is highly suggestive of Behçet's disease. Oral aphthous ulcers are the defining characteristic of the disease (Fig. 108.9). The lesions are typically found on the tongue, lips, buccal mucosa, and gingiva; the tonsils, palate, and pharynx are less commonly affected. The ulcers are painful, have a yellow, necrotic base, and may appear alone or in crops of three to ten. Genital ulcers appear on the scrotum and penis in men and the vulva or vaginal mucosa in women. Skin lesions include erythema nodosum–like subcutaneous nodules, pyoderma gangrenosum, cutaneous thrombophlebitis, and pustular acne-like folliculitis. Ocular symptoms are common and constitute a major source of morbidity in Behçet's disease. Findings may include uveitis, iritis, and optic neuritis. Hypopyon, once considered a characteristic feature of the disease, is uncommon. Visual symptoms may be bilateral or unilateral and

can occasionally lead to permanent vision loss. Neurologic manifestations include brainstem and corticospinal tract syndromes (neuro-Behçet's), aseptic meningoencephalitis, increased intracranial pressure, and cerebral sinus thrombosis complicated by optic nerve ischemia and atrophy.[140] Gastrointestinal ulcers can cause obstruction or ileocecal perforation. Inflammatory oligoarthritis of the ankles, knees, elbows, and wrists is present in 40% to 60% of patients.

The diagnosis of Behçet's disease is made primarily on clinical grounds. The appearance of genital lesions can be ambiguous, and other causes of painful genital ulcers need to be ruled out.

Management. Oral and genital ulcerations are often managed successfully with a topical steroid. Management of severe mucocutaneous disease involves systemic corticosteroids (eg, prednisone, 1 mg/kg), low-dose thalidomide, or methotrexate. Treatment of systemic disease may be accomplished with a corticosteroid alone or in combination with cyclophosphamide or azathioprine. Ocular manifestations, including uveitis, are usually managed with prednisone plus azathioprine and require a rapid referral to an ophthalmologist. The presence of cerebral venous sinus thrombosis is an indication for immediate heparinization. Behçet's disease often has a complicated and protracted course, with morbidity related primarily to ophthalmologic complications. Death can occur from neurologic, cardiovascular, and gastrointestinal sequelae or from complications related to long-term immunosuppressive therapy.

Vasculitis Associated With Environmental or Foreign Antigen Exposure

Vasculitis Caused by Cocaine Adulterated With Levamisole. Levamisole is an immune-modulating agent that has been used to treat autoimmune disorders, various forms of cancer, and the nephrotic syndrome. The drug has been withdrawn from the drug market in the United States owing to the frequency and severity of side effects, including antibody-mediated agranulocytosis and autoimmune vasculitis. Since 2005, the incidence of cocaine cut with levamisole (added at the source of supply to add bulk and weight to the raw product) has been increasing, and some 70% of cocaine seized at United States borders contains levamisole to varying degrees. Levamisole is not detected by routine blood and urine toxicology testing, and specialized testing with gas chromatography or mass spectrometry is of limited clinical utility given the short half-life of the drug (5.6 hours); it is unlikely to be detected in the plasma or urine beyond 24 to 72 hours after the last exposure.

The rash associated with levamisole involves tender palpable purpuric plaques with a predilection for the cheeks, nose, and earlobes (Fig. 108.10). Treatment is typically supportive; spontaneous resolution occurs with discontinuation of the offending agent. The agranulocytosis associated with levamisole is transient and fully reversible within a week to 10 days after discontinuation of the offending agent. Patients may present with asymptomatic agranulocytosis detected on routine blood work or with fever, sepsis, or signs of overwhelming infection. Febrile patients are treated with broad-spectrum antibiotics and a septic evaluation directed at the likely source of infection, similar to febrile neutropenia associated with chemotherapy. Afebrile patients are also often admitted for investigation and observation until their neutrophil count recovers.

Fig. 108.10. Vasculitic lesions caused by crack cocaine containing levamisole. (Courtesy Dr. Christopher Hicks, University of Toronto.)

Cryoglobulinemic Vasculitis. Cryoglobulins are immunoglobulins that precipitate from serum at cold temperatures. Damage to small and medium-sized blood vessels occurs when cryoglobulins bind to circulating antigens and deposit in vessel walls, prompting a complement-mediated inflammatory reaction and cryoglobulinemic vasculitis.

Three types of cryoglobulinemic vasculitis syndromes have been identified. Type I is associated with Waldenström's macroglobulinemia and multiple myeloma and produces a syndrome of hyperviscosity with symptoms of presyncope, altered mental status, and stroke. Types II and III are known as the mixed cryoglobulinemias and represent 80% of recognized cryoglobulinemic syndromes. There is a strong association between these subtypes and hepatitis C, Sjögren's syndrome, and SLE. The mixed cryoglobulinemias are manifested with a triad of purpura, arthralgias, and myalgias along with glomerulonephropathy and vasculitic peripheral neuropathy. Purpuric lesions are typically multiple and confluent and appear preferentially in dependent areas and the lower extremities in particular. Renal failure is the most serious consequence of cryoglobulinemia and is present in 20% to 60% of patients.

The diagnosis is based on the presence of serum cryoglobulins accompanied by typical clinical features; the most salient elements of the differential diagnosis include SLE and Henoch-Schönlein purpura. Skin biopsy can be helpful in confirming the diagnosis. Management involves identification and treatment of associated diseases, such as hepatitis C and multiple myeloma. Low-dose corticosteroids are helpful when systemic symptoms are present but should be avoided while antiviral therapy is being initiated. Plasmapheresis may be useful in life-threatening cases related to cryoprecipitation or serum hyperviscosity.

Features associated with Buerger's disease, serum sickness, and hypersensitivity vasculitis are outlined in Table 108.7.

TABLE 108.7

Summary of Buerger's Disease (Thromboangiitis Obliterans), Serum Sickness, and Hypersensitivity Vasculitis

	BUERGER'S DISEASE	SERUM SICKNESS	HYPERSENSITIVITY VASCULITIS
Pathophysiology	Small and medium-sized arteries and veins of the extremities	Immune complex deposition in blood vessel walls	Small vessel
Associated exposures	Heavy cigarette smoking Cold exposure	Foreign protein or serum Penicillin-based antimicrobials Sulfa drugs NSAIDs	β-lactam antibiotics NSAIDs Diuretics
Common symptoms	Pain, paresthesias Claudication Rest pain	Fever, arthralgias, and diffuse lymphadenopathy Pruritus, skin lesions	Typically confined to the skin (vs. serum sickness)
Physical examination findings	Poorly healing wounds, ulcerations Splinter hemorrhages Digital ischemia and necrosis Distal-to-proximal progression	Urticaria Purpuric skin lesions Scarlatiniform rash Erythema multiforme Azotemia, proteinuria Myocarditis, pericarditis	Palpable purpura in dependent regions, including legs and buttocks Urticarial vasculitis Livedo reticularis Skin nodules and ulcers
Diagnosis	Angiography: Demonstrates "corkscrew" pattern of collateral vessels; rule out other causes of ischemia	Clinical	Clinical
Management and outcome	Smoking cessation Meticulous wound care Protection from trauma and thermal injury	Supportive Systemic corticosteroids for severe disease Recovery generally within 4 to 6 weeks	Supportive Systemic corticosteroids for severe disease
Comments	Up to 50% of patients who continue to smoke will require amputation	Incidence has decreased with modern immunization programs and the use of products derived from human serum	In theory, any medication can cause a hypersensitivity vasculitis syndrome

NSAIDs, Nonsteroidal antiinflammatory drugs.

KEY CONCEPTS

Systemic Lupus Erythematosus

- Systemic lupus erythematosus (SLE) may affect any organ system. Thus, a fundamental understanding of the disease is required to tailor the differential diagnosis and evaluation.
- A 50-fold increased risk of coronary artery disease (CAD) and up to a 30-fold increased risk of venous thromboembolism in patients with SLE prompt chest pain evaluations in the emergency department (ED), even in young women.
- An elevated C-reactive protein level is more closely linked to infection in SLE patients and is not reflective of SLE disease activity.
- An isolated elevated partial thromboplastin time (PTT) in a patient with SLE prompts consideration for antiphospholipid (aPL) antibody carrier state and, if there is a history of thrombosis, antiphospholipid syndrome (APS).
- Steroids are the mainstay for management of the majority of conditions that are associated with increased SLE disease activity, including musculoskeletal, cutaneous, renal, pleural, and pericardial disease.
- APS is common in patients with SLE and carries with it a risk of venous (typically deep venous thrombosis or pulmonary embolism) and arterial (most commonly stroke) thrombosis.
- Consultation with a rheumatologist may be helpful in diagnostic, management, and disposition decisions for patients with SLE.

Vasculitides

- Vasculitis syndromes should be considered in the presence of systemic symptoms, such as fever, malaise, and weight loss plus pulmonary, renal, or cutaneous manifestations.
- Massive hemoptysis and acute renal failure can occur in Wegener's granulomatosis, Goodpasture's disease, microscopic polyangiitis, and Churg-Strauss syndrome. Tracheal stenosis may be present in Wegener's granulomatosis, further complicating airway management.
- Many patients with established vasculitis are receiving high-dose or combination immune suppressive therapy, making them vulnerable to opportunistic infections and overwhelming sepsis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 108: QUESTIONS & ANSWERS

108.1. Which of the following statements is true regarding tinea capitis?
- **A.** It is markedly contagious.
- **B.** It is not transmitted by household pets.
- **C.** Prednisone is contraindicated for the treatment.
- **D.** Topical treatment is effective.
- **E.** Treatment generally lasts 2 to 4 weeks.

Answer: A. Tinea capitis is the dermatophytosis that is markedly contagious. Systemic treatment for 4 to 6 weeks is the minimum. It may be transmitted by pets. When a kerion develops, prednisone (along with the antifungal) should be used to decrease inflammation and scarring.

108.2. A 16-year-old male presents with complaints of a chronic recurrent pruritic rash. It has primarily presented in joint flexor areas and first began at approximately 2 years old. His only other past history is asthma and hay fever. Physical examination reveals bilateral antecubital and popliteal papulovesicular lichenification and hyperpigmentation. It is intensely pruritic. Which of the following statements is true?
- **A.** Adult-onset disease is common.
- **B.** Corticosteroids are contraindicated.
- **C.** Increased immunoglobulin E (IgE) levels are expected.
- **D.** More frequent exacerbations are expected in the summer.
- **E.** Skin changes are confined to the flexor areas of involvement.

Answer: C. This patient meets almost all criteria for atopic dermatitis. Onset after 5 years old should raise the question of an alternative diagnosis. The mechanism is believed to be eosinophil, mast cell, and lymphocyte activation by T cell production of interleukin-4. Elevated IgE levels are expected. Diffuse skin dryness is another prominent finding. Exacerbations may be triggered by increased body heat or stress, but they are more common in winter. Corticosteroids are the treatment mainstay.

108.3. A 29-year-old inmate presents with recurrent skin abscesses. Previous cultures have documented methicillin-resistant *Staphylococcus aureus* (MRSA) as the causative agent. It is resistant to clindamycin and sulfonamides. Which of the following antibiotics should be used for this case?
- **A.** Cephalexin
- **B.** Ciprofloxacin
- **C.** Erythromycin
- **D.** Linezolid
- **E.** Rifamycin

Answer: D. MRSA is typically resistant to cephalosporins, macrolides, and fluoquinolones. Rifamycin is effective but should not be used as the sole agent due to rapid development of resistance.

108.4. A 23-year-old male presents with nonpurulent cellulitis of his left leg. There is no obvious abscess. He has no other medical problems. Which of the following should be the antibiotic of choice?
- **A.** Amoxicillin-clavulanate
- **B.** Ciprofloxacin
- **C.** Clindamycin
- **D.** Doxycycline
- **E.** Trimethoprim-sulfamethoxazole

Answer: C. Nonpurulent cellulitis is typically caused by staphylococcus or group A streptococcus. Group A streptococcus is typically resistant to bactrim and tetracycline/doxycycline. The potential for methicillin-resistant *Staphylococcus aureus* (MRSA) would obviate the use of amoxicillin and clavulanate potassium (Augmentin) or ciprofloxacin.

108.5. What is the parenteral treatment of choice for severe invasive *S. aureus* infection?
- **A.** Bactrim
- **B.** Clindamycin
- **C.** Rifamycin
- **D.** Vancomycin
- **E.** Vancomycin and another antistaphylococcal agent

Answer: E. The combination is likely more effective due to enhanced bactericidal potential. Clindamycin and rifamycin are not indicated as parenteral monotherapy.

108.6. Which of the following statements is true regarding gonococcal dermatitis?
- **A.** It affects primarily men.
- **B.** It occurs in 1% or 2% of patients with gonorrhea.
- **C.** Gonococci can usually be cultured from the lesions.
- **D.** The lesions have a predilection for the knees and elbows.
- **E.** The skin lesions are not tender.

Answer: B. Women are affected primarily. The lesions have a predilection for distal joint skin. They begin as red or hemorrhagic papules that evolve into pustules or vesicles with a red base. They are tender and may be confused with meningococcemia. They may later have a gray necrotic or hemorrhagic center. Skin cultures are usually negative.

108.7. Which of the following statements is *true* regarding drug eruptions?

A. A given drug produces a consistent eruption in the same patient.
B. A late-appearing drug reaction would suggest thiazide use.
C. Drug reactions tend to appear within 24 hours of drug initiation.
D. The most common cause of drug reactions are nonsteroidal antiinflammatory drugs (NSAIDs) and sulfa-based drugs.
E. The most common eruptions are urticaria and rashes.

Answer: E. The most common drug eruptions are urticaria and morbilliform rashes. Drug eruptions tend to occur within a week of drug initiation with the exception of semisynthetic penicillins, which tend to occur later. Penicillin is the most common cause of drug reactions, and patients with eczema, atopy, or asthma are at increased risk. A given drug may give widely diverse presentations in different patients or in the same patient on different occasions.

CHAPTER 109

Allergy, Hypersensitivity, and Anaphylaxis

Aaron N. Barksdale | Robert L. Muelleman

ALLERGY

Principles

Background and Terminology

The human immune system is an assemblage of cellular and humoral components working together in a highly complex, coordinated, and elegant fashion to achieve the primary goal of protecting the human host (self) from harmful offenders (nonself). Exposure to offenders activates the various immune mechanisms to bring about immune responses aimed at neutralizing the dangerous nonself while preserving self. The immune system, however, can overreact to otherwise harmless nonself agents, producing inappropriate responses that are harmful to the host, thereby giving rise to allergy or allergic diseases. These hypersensitivity reactions are manifested in clinical symptoms ranging from mildly inconvenient to fatal. For practical purposes, the term *allergy* is used in this chapter to refer to mast cell–mediated hypersensitivity reactions. For most allergic diseases to occur, predisposed individuals need to be exposed to allergens through a process called *sensitization.* Substances that elicit an allergic reaction are referred to as *allergens,* and those that elicit an antibody response (activated by B- and T-cell receptors) are called *antigens.*

On this allergic continuum, there are several important allergic syndromes frequently encountered in the emergency department (ED). *Urticaria* is a common allergic reaction to foods, drugs, or physical stimuli and is clinically characterized by an erythematous, raised, and pruritic rash. *Angioedema* is another important syndrome, mediated by either an allergic (histaminergic) mechanism in response to exposure to foods, drugs, physical stimuli, or a nonallergic (non-histaminergic) mechanism (eg, hereditary angioedema [HAE], or angiotensin-converting enzyme [ACE] inhibitor). Angioedema is characterized by edema of the subcutaneous or submucosal tissues, which can cause airway compromise if the tongue or larynx is involved.[1]

At the other extreme of this allergic continuum is *anaphylaxis,* a life-threatening systemic allergic reaction characterized by acute onset and multiorgan involvement. Mechanistically, anaphylaxis is a type I hypersensitivity reaction (allergic), mediated by immunoglobulin E (IgE). In its most common form, anaphylaxis is precipitated by exposure to allergens in previously sensitized individuals (immunologic).[2] Previously, the term *anaphylactoid reaction* referred to a syndrome clinically similar to anaphylaxis that is not mediated by IgE (non-immunologic). Its clinical presentation and treatment are identical to that of anaphylaxis. Non-IgE (non-immunologic) reactions appear to result from direct degranulation of mast cells (and basophils) and may follow a single, first-time exposure to certain inciting agents. The current World Allergy Organization (WAO) guidelines use the term *anaphylaxis* to refer to both IgE- and non–IgE-mediated reactions, obviating the need for the term *anaphylactoid reaction.*[2]

Pathophysiology

Because allergy is intimately related to immunology, a brief review is included in this chapter. Immunologic responses to *antigens* in humans are coordinated by two systems: the ancient *innate* immune system, which humans inherited from invertebrates; and the recently evolved *adaptive* immune system, which is present in humans and vertebrates (Fig. 109.1). The innate immune system is considered the first line of defense, characterized by its nonspecific but rapid responses to offending agents or microbes. Its effector components include resident cells (epithelial cells, mast cells, macrophages, dendritic cells, antimicrobial proteins), infiltrative cells (natural killer cells, neutrophils, monocytes, dendritic cells), and various proteins (antimicrobial peptides, complements, cytokines, pathogenic pattern recognition receptor [PRR] system).[3] The innate system responds to danger signals rapidly and nonspecifically, whereas the adaptive immune system takes time for antigen-specific cells (B and T cells) to amplify through a process known as *clonal expansion,* to mount a specific immune response. The T and B lymphocytes are capable of recognizing a myriad of antigens through a vast library of antibodies and receptors (up to 10^{15}). This diversity is accomplished by somatic rearrangement of fewer than 400 genes.

Development of the Immune System and Mechanism of Immune-Mediated Injury. The adaptive and innate immune systems originate from the common pluripotential hematopoietic stem cells, which are derived from the yolk sac and later reside in the bone marrow. These stem cells differentiate and develop into the lymphoid precursor cells and megakaryocyte (CFU-GEMM) stem cells. The lymphoid precursor cells differentiate into bursa-equivalent lymphocytes (B cells), thymus-derived lymphocytes (T cells), and natural killer cells. The CFU-GEMM cells develop into mast cells, basophils, and others (see Fig. 109.1). When the host encounters a foreign antigen, the cellular components of the adaptive immune system interact with the cellular and protein components of the innate immune system to mount a concerted defense aimed at neutralization of the antigen.

T-Cell Development. Lymphoid precursor cells migrate from the bone marrow into the thymus, where they continue their ontogeny. Under regulation by cytokines and cell-to-cell interactions, these precursors undergo gene rearrangement and positive and negative selection. In the process, T cells acquire the T-cell antigen receptors and various surface markers. Two types of T cells mature and come out of the thymus: CD4+, also called *T helper cells* (60% to 70%), and CD8–, also called *suppressor T cells* (30% to 40%).[3] Depending on the type of cytokine produced, T helper cells differentiate into type 1 helper (T_H1) cells and type 2 helper (T_H2) cells, with opposing activities. T_H1 cells inhibit IgE production and IgE isotype switching, whereas T_H2 cells stimulate IgE production and IgE isotype switching. The balance of these stimulatory and inhibitory activities of the T_H1 and T_H2 cells is believed to determine an individual's propensity to develop

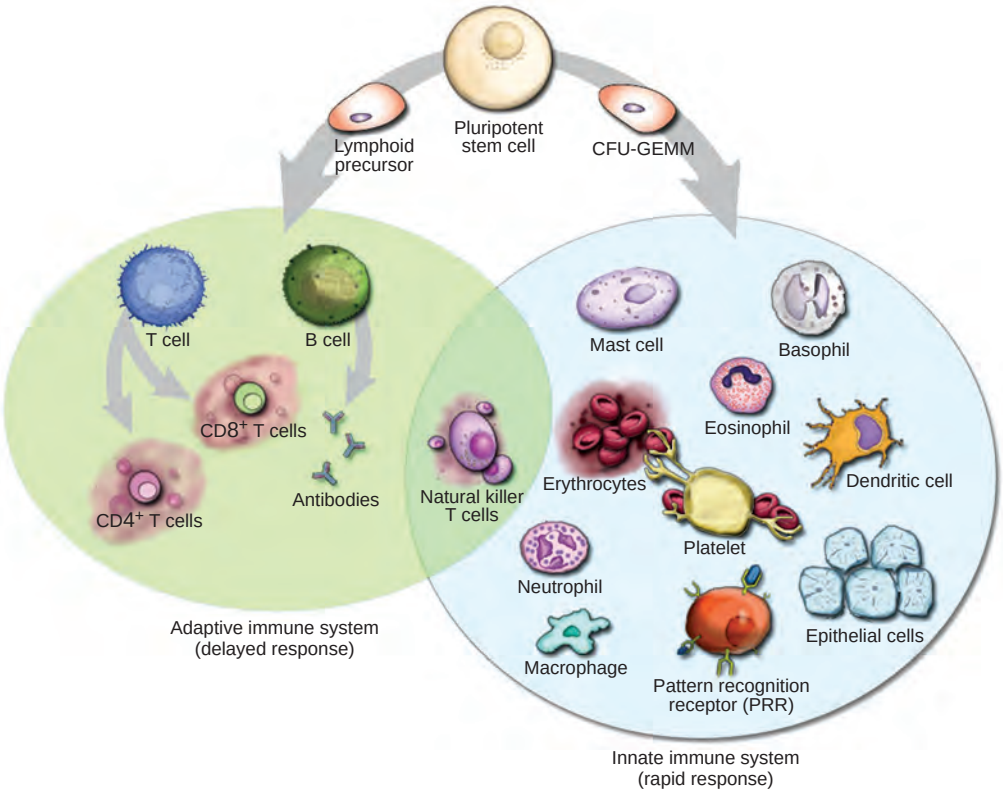

Fig. 109.1. Developmental pathways of the immune and hematopoietic systems. *CFU-GEMM,* Colony-forming unit for granulocyte, erythroid, myeloid, and megakaryocyte.

allergic disease or atopy and may help explain the increased prevalence of allergy in urbanized and Western societies in the past three decades.[3] Early in utero and soon after birth, naïve T lymphocytes in the infant's immune system are dominated by the allergy-prone T_H2 cells and their associated cytokines (interleukins 4, 5, and 13). These cytokines are important inducers for production of IgE antibodies. Later, during infancy through early childhood and adolescence, the nonatopic infant's immune system gradually shifts from this allergy-prone T_H2 environment to an allergy-protective T_H1 environment. The cytokines associated with this T_H1 environment include interleukin-2 and interferon-γ. This shift is thought to be caused by the continual exposure of the young individual's immune system to allergenic stimuli from the surrounding environment, mainly microbes. Features of Western lifestyles (such as, changes in infant diets, widespread use of antibiotics, smaller family size, and cleaner child care) are believed to reduce this stimulatory antigenic exposure in an individual's early years, leading to an environment in which the immune system is dominated by a persistent allergy-prone T_H2 system (the hygiene hypothesis). This imbalance between the two immune systems is thought to be what ultimately leads to atopy and an allergy-prone population.

B-Cell Development and Immunoglobulins. B-cell ontogeny is divided into antigen-independent and antigen-dependent stages. During the antigen-independent stage, B cells mature in primary lymphoid organs (bone marrow and fetal liver), where they undergo gene rearrangement and acquire various surface markers. Later during the antigen-dependent stage in the secondary lymphoid organs (lymph nodes and spleen), B cells differentiate into memory B cells and plasma cells and are ready to secrete immunoglobulins. Throughout B-cell ontogeny, B-cell maturation, isotype switching, and immunoglobulin production are driven by activated T cells, cytokines, and interaction with antigen and bone marrow stromal cells.[3]

Immunoglobulins are protein molecules composed of two identical polypeptide heavy chains and two identical polypeptide light chains, covalently linked by disulfide bonds (Fig. 109.2). The heavy (H) chains have one variable domain (V_H) and three or four constant domains (C_H). The light (L) chains have one variable domain (V_L) and one constant domain (C_L). The variable domains of the heavy and light chains together form a pair of identical antigen-binding sites and with the adjacent constant heavy domain pair make up the Fab (antibody-binding fragment) region of the immunoglobulin molecule. The remaining constant domains of the heavy chains together form the Fc (crystallizable fragment) region of the immunoglobulin molecule. The Fc binds to the surface receptors of effector cells, such as mast cells, B cells, or macrophages. There are five isotypes or classes of immunoglobulins (IgG, IgA, IgM, IgD, and IgE); isotype IgG has four subclasses (IgG1, IgG2, IgG3, and IgG4), and IgA has two subclasses (IgA1 and IgA2). The body usually produces IgM antibodies when it first encounters an antigen. Repeated antigenic exposure, however, may cause the constant region of the IgM to switch to another class (IgA, IgG, or IgE), a process known as *isotype switching.* Isotype IgE and IgG4 are the most important antibodies in the pathogenesis of allergic disease and anaphylaxis.[3]

Mast cells, basophils, and their mediators are the central effectors in allergy and anaphylaxis. Exposure of a genetically predisposed individual to an allergen leads to the synthesis and release of allergen-specific IgE by plasma cells into the circulation. Fixation of this allergen-specific IgE to surface receptors on mast cells completes the process known as *sensitization.* These IgE-bearing mast cells usually reside in the mucosal surfaces, submucosal tissue (around venules), and cutaneous surfaces, where they are capable of becoming activated on reexposure to a specific allergen. Cross-linking of the mast cell receptors by a specific multivalent allergen sets off a cascade of conformational and biochemical

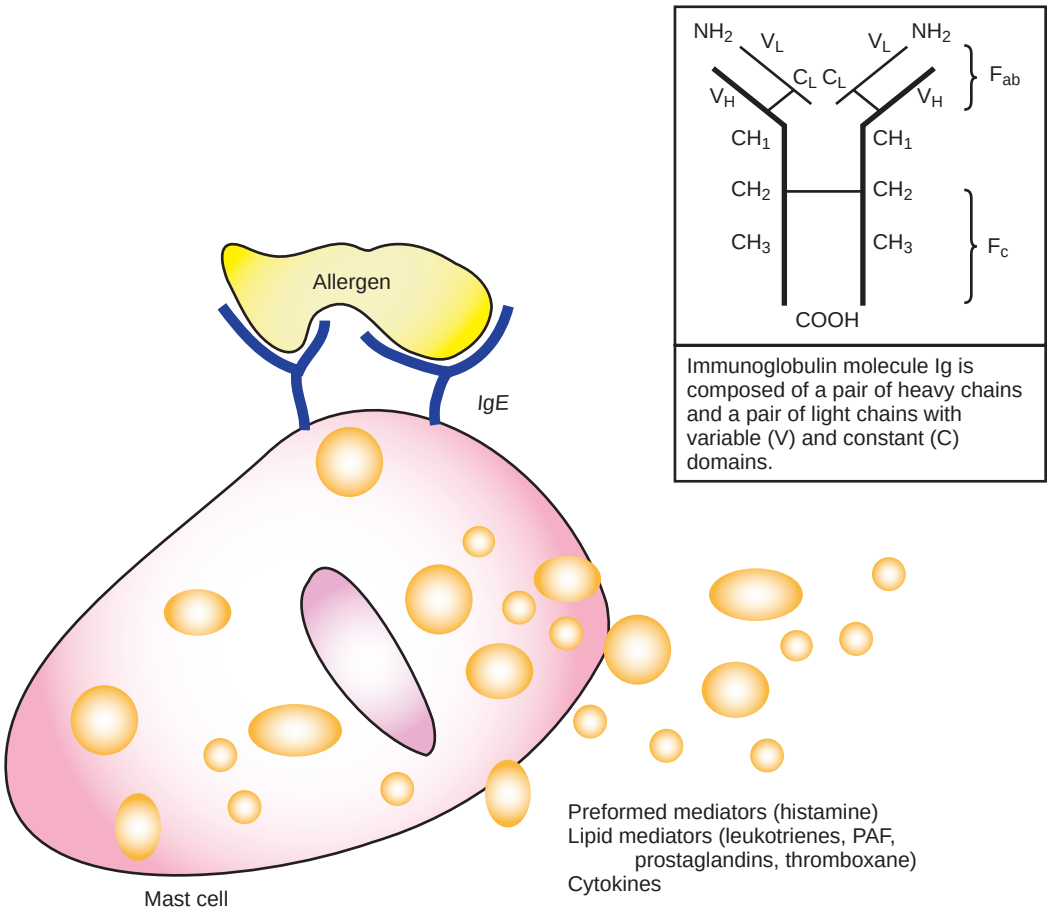

Fig. 109.2. Activation of mast cells with degranulation of mast cell mediators by antigen cross-linking of adjacent immunoglobulin E *(IgE)* on the cell surface. *PAF,* Platelet-activating factor.

events, causing the degranulation of preformed mediators, subsequent generation and release of arachidonic acid metabolites, elaboration of cytokines and chemokines, and activation of the cellular components by the innate and adaptive systems. These series of events ultimately lead to the clinical syndromes of allergy and anaphylaxis (see Fig. 109.2).

Classification of Reactions

The term *allergy* is commonly used to describe clinical illnesses produced by excessive immune responses by a normal immune system to otherwise innocuous allergens. In this chapter, we adapt the classic Coombs and Gell classification to categorize these hypersensitivity reactions (Box 109.1).

Type I reactions (immediate hypersensitivity) are IgE mediated and account for most allergic and anaphylactic reactions observed in humans. Exposure to sensitizing allergens causes mediators from mast cells and basophils to be released through both IgE-dependent and IgE-independent (direct mast cell degranulation) mechanisms. Rhinitis caused by ragweed pollen and anaphylaxis caused by foods are examples of the IgE-dependent mechanism.

Type II reactions (cytotoxic) denote antibody-mediated cytotoxic reactions. Complement-fixing IgG (or IgM) engages cell-bound antigen, activating the classic complement pathway and leading to the fixation of membrane attack complexes on the cell surface and subsequent cell lysis. In the process, anaphylatoxins C3a and C5a cause mast cell mediators to be released, producing the same clinical syndrome seen in allergic anaphylaxis.

Type III reactions (immune complex) are IgG or IgM complex mediated. Circulating soluble antigen-antibody immune complexes migrate from the circulation to be deposited in the perivascular interstitial space, thereby activating the complement system. Anaphylactic reactions to blood transfusions and blood component therapy, including serotherapy (immunoglobulin administration), are examples of the overlap of type II and type III reactivity. They have therefore been classified as complement-mediated or immune complex–mediated anaphylaxis.

Type IV reactions (delayed hypersensitivity) are T-cell mediated and have no documented relationship to the pathogenesis of anaphylaxis.

ANAPHYLAXIS

Principles

Epidemiology and Risk Factors

The exact incidence of anaphylaxis is not known, but recent evidence suggests that it is increasing and that currently there are approximately 1500 fatal cases in the United States per year.[4,5] In the last decade, experts in the field have developed specific consensus criteria to allow a more objective approach to diagnosing anaphylaxis. Recent literature suggests that over 50% of those patients presenting to EDs were misdiagnosed, and up to 80% did not receive appropriate first line treatment.[6]

Pregnant women, infants, teenagers, and elders have been shown to have an increased incidence of anaphylaxis.[7] Other risk factors include atopy (genetic predisposition to develop allergic disease), emotional stress, seasonal occurrence in summer to fall months, higher socioeconomic status, residing in northern locations (potentially correlating with vitamin D levels), and the presence of acute infection. Severe anaphylaxis has been associated

BOX 109.1

Gell and Coombs Classification of Immune Reactions

TYPE I: IMMEDIATE HYPERSENSITIVITY

Binding of multivalent antigens to IgE on the surface of mast cells and basophils leads to degranulation of mediators. In previously sensitized individuals, the reaction develops quickly (minutes). This type of hypersensitivity reaction is seen in allergic diseases (eg, hay fever, allergic asthma, urticaria, angioedema, and anaphylaxis). *Non-immunologic* (anaphylactoid) *reaction* refers to the direct release of preformed mediators of mast cells independent of IgE.

TYPE II: CYTOTOXIC ANTIBODY REACTION

Antibody (IgM, IgG) binding of membrane-bound antigens leads to cytotoxicity and cell lysis of cells through the complement or mononuclear cell system (macrophages, neutrophils, and eosinophils). This type of reaction is seen in transfusion reaction and Rh incompatibility.

TYPE III: IMMUNE COMPLEX–MEDIATED REACTION

Binding of antibody (IgM, IgG) to antigens forms soluble immune complexes, which are deposited on vessel walls, causing a local inflammatory reaction (Arthus reaction) leading to inflammation and tissue injury. This type of reaction is seen in systemic lupus erythematosus and serum sickness (after antithymocyte globulin administration).

TYPE IV: CELL-MEDIATED DELAYED HYPERSENSITIVITY

Sensitized lymphocytes (T_H1 cells) recognize the antigen, recruit additional lymphocytes and mononuclear cells to the site, and start the inflammatory reaction. No antibodies are involved. This type of reaction is seen in contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

IgE, Immunoglobulin E; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *T_H1,* type 1 helper.

BOX 109.2

Risk Factors for Anaphylaxis and Increased Anaphylaxis Severity and Mortality

RISK FACTORS FOR HAVING ANAPHYLAXIS

- Age and sex
  - Pregnant women, infants, teenagers, elderly
- Route of administration
  - Parenteral > oral
- Higher social economic status
- Time of the year
  - Summer and fall (the outdoor seasons)
- History of atopy
- Emotional stress
- Acute infection
- Physical exertion
- History of mastocytosis

RISK FACTORS FOR INCREASED ANAPHYLAXIS SEVERITY AND MORTALITY

- Extremes of age
  - Very young (under-recognition)
  - Elderly
- Comorbid conditions
  - Cardiovascular disease (heart failure, ischemic heart disease, hypertension)
  - Pulmonary disease (asthma, obstructive airway disease)
- Others
  - Concurrent use of anti-hypertensive agents, specifically beta-blockers and angiotensin-converting enzyme (ACE) inhibitors
  - Concurrent use of cognition-impairing drugs (eg, alcohol, recreational drugs, sedatives, tranquilizers)
  - Recent anaphylaxis episode

Modified from Simons ER, et al: World Allergy Organization anaphylaxis guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol 162:193-204, 2013; Muraro A, et al: Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 69:1026–1045, 2014; Ben-Shoshan M, Clarke AE: Anaphylaxis: past, present and future. Allergy 66:1–14, 2011.

with poorly controlled asthma, history of mastocytosis, heavy physical exertion, exposure to a trigger during the concomitant use of certain medications (ACE inhibitors, beta-blockers, and nonsteroidal antiinflammatory drugs [NSAIDs]), and the history of a previous anaphylactic reaction (Box 109.2).[8-10] In general, the more rapid an anaphylaxis reaction occurs after an exposure, the more likely it is to be severe and potentially fatal. The dose, frequency, duration, and route of administration of a drug can also affect the tendency to develop an anaphylactic reaction (eg, the parenteral route is more likely to lead to an anaphylactic reaction than the oral route). One interesting aspect of drug-related anaphylaxis is the constancy of administration. An anaphylactic reaction may not occur in an otherwise susceptible patient as long as a drug is administered at regular intervals. The same patient, however, may experience an anaphylactic reaction if the drug is resumed after an interruption of therapy.

ACE inhibitors can cause an accumulation of kinins and bradykinin and thus can exacerbate the angioedema component of anaphylaxis. Beta-blockers may oppose the actions of adrenergic agents used in anaphylaxis treatment. A recent study evaluating anaphylaxis in the ED demonstrated that the current use of any antihypertensive medication was associated with multi-organ involvement, more severe reaction, and increased incidence of hospitalization.[7]

Common Triggers for Anaphylaxis

Virtually any agent that is capable of activating mast cells or basophils can potentially precipitate an anaphylactic reaction. However, in up to 60% of adults and 10% of children, an inciting agent cannot be identified, and these reactions are classified as *idiopathic anaphylaxis.*[11] When a trigger can be determined, foods, insect stings, and medications are the most common causes. Box 109.3 lists many of the common agents by their proposed immunologic mechanism.[4,8]

Foods. Foods are the major identifiable causative agents, accounting for approximately one-third of the cases of anaphylaxis. The most commonly identified foods are tree nuts, peanuts, fish, shellfish, soy, cow's milk, and egg. The majority of the severe and fatal reactions appear to be associated with peanut and tree nut exposure, especially if the patient has a history of asthma.[8] The majority of these reactions occur after ingestion but may occur after inhalation of food particles or even after skin contact with vomit containing the instigating agent.[7] For a person with a known allergy, it may be difficult to avoid allergic reactions, because the allergen's identity may be obscured during processing of the product (eg, consuming wine contaminated with *Hymenoptera* venom).

Insect Stings. Insect stings are the second most common cause of anaphylactic reactions, with the majority of them associated with hymenoptera venoms (wasps, bees, ants, and saw flies) and fire ant stings. These reactions typically require a sensitizing exposure, but there have been numerous reports of anaphylactic

BOX 109.3

Etiologic Agents Causing Anaphylaxis by Immunologic Mechanisms

IMMUNOLOGIC MECHANISMS (IGE-DEPENDENT)
Foods: Egg, peanut, tree nut, milk, fruits, shellfish, soybean, sesame
Medications: Antibiotics, NSAIDs, chemotherapeutic agents, immunomodulators
Insect stings: *Hymenoptera* venoms, fire ant stings
Natural rubber latex
Hormones: Insulin, methylprednisolone, parathormone, estradiol, progesterone, corticotropin
Local anesthetics: Mostly ester family (procaine, tetracaine, benzocaine)
RCM
Occupational allergens: Enzymes, animal protein, plant protein
Aeroallergens: Pollen, dust, spores, per dander

IMMUNOLOGIC MECHANISMS (IGE INDEPENDENT)
RCM
NSAIDs
Dextrans
Biologic agents: Monoclonal antibodies, immunomodulators

NONIMMUNOLOGIC MECHANISMS (DIRECT MAST CELL ACTIVATIONS)
Physical factors: Exercise, cold, heat, sunlight
Ethanol
Medications: Some opioids

IDIOPATHIC (NO APPARENT TRIGGER)

IgE, Immunoglobulin E; *NSAID,* nonsteroidal antiinflammatory drug; *RCM,* radiocontrast media.
Modified from Simons ER, et al: World Allergy Organization Guideline for the assessment and management of anaphylaxis. J Allergy Clin Immunol 127(3):593 e1–e23, 2011.

reactions following first known stings or bites. Children tend to experience a more systemic cutaneous reaction, whereas adults are more likely to suffer hemodynamic collapse. Individuals displaying a large local reaction in the area of the sting or bite are less likely to suffer from a systemic reation.[2,8]

Drugs. Antibiotics, chemotherapeutic agents, NSAIDs, and immunomodulators are the most common reported triggers, and drugs as a class represent the third most frequent cause of anaphylactic reactions.[4]

Penicillin is the most common drug-induced cause of anaphylaxis. Although patients often report a history of penicillin allergy, this may not stand up to close scrutiny. Studies have shown that up to 90% of individuals with a reported history of penicillin allergy can safely use penicillin. These individuals are usually mislabeled as penicillin allergic or lose their allergy after years of avoidance. Parenterally administered penicillin is responsible for the majority of these anaphylactic reactions.[2,12]

Cephalosporins share the β-lactam ring structure and side chains of the penicillins, but allergic cross-reactivity appears to be low, somewhere between 1% to 8% of patients. Patients who have experienced urticaria or anaphylactic reactions after taking penicillin are more likely to have an adverse reaction to cephalosporins, but even in this setting, the risk of an anaphylactic reaction is very low. In patients with a history of penicillin allergy, a cephalosporin is considered safe if they have had a negative penicillin skin test. If penicillin skin testing is positive, they could undergo a graded challenge or rapid desensitization process.[12]

Aspirin and other NSAIDs are believed to cause anaphylaxis through interruption of arachidonic acid metabolism, a non-IgE (non-immunologic) mediated process. The incidence of anaphylaxis to aspirin and NSAIDs varies widely, and these reactions appear to be drug specific and without cross-reactivity to other NSAIDs. Aspirin exacerbated respiratory distress (AERD) and NSAID-induced respiratory distress syndromes are unique in individuals with a history asthma or allergic rhinitis and are not considered anaphylactic reactions.[12]

Although corticosteroids are often used in the management of allergic syndromes and anaphylaxis, there have been reported anaphylactic reactions to these drugs. They appear to be rare, and the majority of them have been associated with the parenteral administration of methylprednisolone and hydrocortisone. When steroids are required in the management of other conditions, skin testing may demonstrate the specific agent responsible for the hypersensitivity, and allow for the substitution of a different class.[12]

BOX 109.4

A Standard Treatment Protocol for Patients With a History of Radiocontrast-Induced Anaphylaxis

Prednisone 50 mg by mouth given 13 hours, 7 hours, and 1 hour before the procedure
Diphenhydramine 50 mg PO given 1 hour before the procedure
Consider ephedrine 25 mg by mouth given 1 hour before the procedure
Consider an H_2 antagonist, such as ranitidine 150 mg by mouth given 3 hours before the procedure

Natural Rubber Latex. Natural rubber latex (NRL) allergy is the result of sensitivity to the proteins or chemicals contained in the latex products. This sensitivity reaction can be delayed (type IV) contact dermatitis or an immediate hypersensitivity (type I) reaction (see Box 109.1). In addition to rubber gloves, NRL can be found in an array of other hospital supplies, including endotracheal tubes, blood pressure cuffs, stethoscope tubing, airway masks, tourniquets, and catheters. NRL is also found in balloons, condoms, pacifiers, sports equipment, and toys. In recent years, most health care settings have incorporated the use of non-NRL gloves and products, making anaphylactic reactions from latex an uncommon event.[2,4]

Radiocontrast Media. Radiocontrast media (RCM) represents an important class of agents that can cause an anaphylactic reaction. Approximately 10 million radiologic studies using RCM are performed in the United States annually. Anaphylactic reactions to RCM are largely idiosyncratic, occur within minutes of infusion, and are independent of the dose. The pathophysiologic mechanism of anaphylactic reactions to RCM is unknown, but it is believed to be non-immunologic (non-IgE). Risk factors for an anaphylactic reaction include a previous adverse reaction to RCM, a history of atopy or allergic disease, asthma, and certain medications. A history of an allergy to fish or shellfish is not a contraindication to the use of the currently used RCM, nor does it increase the risk of an adverse reaction to RCM. Clinically, the risk for severe adverse reaction with ionic and nonionic contrast materials is less than 1%. The death rate from RCM reactions is estimated at 1 to 3 per 100,000 administrations of contrast material. Protocols have been developed to minimize risks of a serious allergic reaction in patients who have had a previous adverse reaction to RCM but who still require additional radiographic studies with contrast agents (Box 109.4).

Exercise Induced Anaphylaxis. In certain settings, exercise has been recognized as an inciting event for an anaphylactic-like reaction. The mechanism is unclear, but the release of mediators from mast cells and basophils has been implicated. Patients with exercise-induced anaphylaxis are generally dedicated athletes who may have a personal or family history of atopy. In some individuals, anaphylaxis only occurs if specific co-triggers or cofactors are present during or prior to initiating exercise and typically do not cause symptoms without physical exertion. These may include certain foods, medications, or increased pollen levels in the area. Provocative foods, if identified, should be avoided. Patients should discontinue the exercise at the onset of rash or pruritus. When exercise is continued beyond this point, clinical deterioration is likely in susceptible individuals. Prophylactic treatment with an antihistamine may be helpful.[2,13]

Idiopathic Anaphylaxis. As previously mentioned, 30% to 60% of adults and up to 10% of children had no identifiable trigger for their anaphylactic reaction. The diagnosis of idiopathic anaphylaxis is often made after extensive evaluation by an allergist. In an attempt to prevent recurrent episodes, these patients are often treated with daily prophylactic medications, such as antihistamines and sometimes corticosteroids. Some women diagnosed with idiopathic anaphylaxis may actually represent "progesterone" anaphylaxis. Women suffering from this disorder experience recurrent episodes of anaphylaxis that are temporally related to their menstrual cycle.[11]

Mediators of Anaphylaxis

The numerous mediators released by mast cells and basophils exert overlapping physiologic effects on target organs and tissues, making it difficult to ascribe specific clinical manifestations to any one mediator. Histamine is the most important mediator and an essential contributor to immediate hypersensitivity and inflammation. Its infusion has been shown to produce the majority of the clinical features seen during an anaphylactic reaction (Table 109.1). There are three classes of histamine receptors: H_1, H_2, and H_3. H_1 receptor stimulation produces bronchial, intestinal, and uterine smooth muscle contraction. It also leads to increased vascular permeability, nasal mucus production, and eosinophil and neutrophil chemokinesis and chemotaxis. H_2 receptor stimulation increases the heart rate, force of ventricular contraction, gastric acid secretion, airway mucus production, and vascular permeability, while also causing bronchodilation and inhibition of basophil histamine release. H_3 receptors are found in neurons in the central nervous system and peripheral tissues, and they control the synthesis and release of histamine.[14]

In addition to histamine, there are several lipid metabolites produced through the prostanoid and leukotriene pathways that contribute to the adverse physiologic effects induced by histamine. Prostaglandin D_2 (PGD_2) is the main arachidonic acid metabolite released by activated mast cells. PGD_2 and thromboxanes are synthesized from arachidonic acid through the cyclooxygenase pathway (through both COX-1 and COX-2). PGD_2 induces hypotension, inhibition of platelet aggregation, and is approximately 30 times more potent than histamine in causing bronchoconstriction. The leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4 are synthesized from arachidonic acid through the lipoxygenase pathway. They are involved in cholinergic-independent bronchospasm, increased vascular permeability, and increased mucous gland production.[14]

Platelet-activating factor (PAF) is a phospholipid and a potent compound that triggers human platelet aggregation. Its other actions include neutrophil activation and chemotaxis, along with ileal and parenchymal lung smooth muscle contraction. The clinical effects of PAF include decreased myocardial contractile force, coronary vasoconstriction, pulmonary edema, and prolonged increase in total pulmonary resistance with a decrease in dynamic compliance.[14,15]

Recent data has highlighted the important roles that nitric oxide and sphingosine 1-phosphate play in anaphylaxis. Sphingosine 1-phosphate can trigger calcium influx, stimulating synthesis of cytokines and mast cell degranulation. Nitric oxide is synthesized in vascular endothelium and its action can be increased by histamine, leukotriene, tumor necrosis factor alpha (TNF-α), and PAF. It is a potent vasodilator that contributes to the hypotension sometimes seen in anaphylaxis.[14]

Clinical Features

Anaphylactic reactions vary in duration and severity, but they are typically rapid in onset and may result in death. They often present as a combination of clinical characteristics, commonly affecting an array of organ systems including the skin (80% to 90% of episodes), respiratory tract (70% of episodes), gastrointestinal tract (30% to 45% of episodes), cardiovascular (10% to 45%), and the central nervous system (10% to 15% of episodes).[5,8] Clinical presentations depend on the degree of an individual's hypersensitivity; the quantity, route, and rate of antigen exposure; the pattern of mediator release; and the target organ sensitivity and responsiveness. Symptoms of anaphylaxis usually occur minutes after an exposure, although some reactions may develop hours after encountering the triggering agent.[2] The National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) and WAO have adopted

TABLE 109.1

Mediators in Anaphylaxis and Their Physiologic Actions and Clinical Manifestations

MEDIATORS	PHYSIOLOGIC ACTIVITY	CLINICAL MANIFESTATION
Histamine, leukotrienes, thromboxane, prostaglandins, platelet-activating factor, nitric oxide	Vascular permeability, vasodilation, smooth muscle spasm, mucous gland secretion, nociceptor stimulation, myocardial depression	Generalized urticaria and angioedema, pruritus, wheezing, bronchoconstriction, rhinorrhea and bronchorrhea, coryza, conjunctivitis, syncope, tachycardia, hypotension, shock, abdominal pain, nausea, vomiting, diarrhea
Tryptase, carboxypeptidase, chymase, cathepsin G	Activation of complement system, chemoattraction, activation and degranulation of mast cells	Anaphylaxis response is amplified by recruitment and activation of the complement system and further degranulation of mast cell mediators
TNF-α, cytokines, chemokines, eosinophil chemotactic factors	Induction of anti–platelet-activating factor production, control migration of eosinophils and other inflammatory cells	May be responsible for the intensity, protracted symptoms, and multiphasic reaction of the anaphylaxis attack

TNF-α, Tumor necrosis factor alpha.

BOX 109.5

Clinical Criteria for Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Sudden onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, itching or flushing, swollen lips-tongue-uvula) *and at least one of the following:*
   a. Respiratory compromise (eg, shortness of breath, wheeze, cough stridor, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following occurring rapidly (minutes to several hours) after exposure to a likely allergen or other trigger for that patient:
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Sudden respiratory compromise (eg, shortness of breath, wheeze, cough, stridor, hypoxemia)
   c. Sudden reduced BP or symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
   d. Sudden gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: Low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*Low systolic blood pressure for children is defined as <70 mm Hg from 1 month to 1 year old, <70 mm Hg + (2 × age) from 1 to 10 years old, and <90 mm Hg from 11 to 17 years old.
BP, Blood pressure.
Modified from Simons ER, et al: 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. Curr Opin Allergy Clin Immunol 12:389–399, 2012.

BOX 109.6

Differential Diagnosis of Anaphylaxis

Acute generalized urticaria
Asthma exacerbation
Myocardial infarction
Pulmonary embolus
Syncope
Adverse cutaneous drug reaction
Anxiety/panic attacks

FLUSH SYNDROME
Flushing associated with food
- Alcohol
- MSG
- Sulfites
- Scombroidosis

Carcinoid tumor
Peri-menopause
Thyrotoxicosis
Basophilic leukemia
Mastocytosis (systemic mastocytosis and urticaria pigmentosa)
Vasointestinal peptide tumors

SHOCK SYNDROMES
Septic shock
Hypovolemic shock
Cardiogenic shock
Distributive shock

MISCELLANEOUS
Hypoglycemia
Acquired and HAE
ACE inhibitor–associated angioedema
Red man syndrome (Vancomycin)
Neurologic disorders (seizure, stroke, autonomic epilepsy)
Vocal cord dysfunction syndrome
Pheochromocytoma

ACE, Angiotensin-converting enzyme; *HAE,* hereditary angioedema; *MSG,* monosodium glutamate.
Modified from Simons ER, et al: World Allergy Organization guideline for the assessment and management of anaphylaxis. J Allergy Clin Immunol 127(3):593 e1–e23, 2011; Muraro A, et al: Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 69:1026–1045, 2014.

specific diagnostic guidelines to help clinicians increase and become more consistent in their recognition of anaphylaxis (Box 109.5). These diagnostic criteria have been validated in EDs and shown to be highly sensitive.[16,17]

The majority of anaphylactic reactions (80% to 90%) involve the skin. This may present as warmth and tingling of the face, mouth, palms, or soles, or as generalized flushing, pruritus, and diffuse urticaria. Nasal congestion, sneezing, ocular itching, and tearing are also common complaints. Patients presenting with angioedema may complain of swelling and a burning sensation in the affected area. This may be followed by mild to severe respiratory distress. The patient may present with a cough, a sense of chest tightness, dyspnea, or audible wheezes. Patients with laryngeal edema often complain of hoarseness, throat tightness, or stidor.[4,8] Hypotension or dysrhythmias may be manifested as lightheadedness or syncope. Seizure activity due to decreased cerebral perfusion may be seen in rare instances. Gastrointestinal symptoms, more common in elders, include crampy abdominal pain and associated nausea, vomiting, diarrhea, or tenesmus.[2,8] Anaphylactic reactions vary a great deal from one individual to another and even amongst different episodes in the same patient. It should be noted that hypotension and shock are rarely presenting features in infants and children and are much more common in the adult population.[4,7] A summary of the observed clinical manifestations of anaphylaxis along with their related pathophysiologic changes is presented in Table 109.2.

Differential Diagnosis

The diagnosis of anaphylaxis is readily apparent in a patient presenting with acute rash, respiratory difficulty, and hypotension after an allergenic exposure, but there are many other disease processes that may present with similar symptoms. Syncope, panic attacks, and asthma exacerbations are a few of the more common presentations to potentially instigate this diagnostic dilemma. Acute asthma exacerbation rarely presents with hypotension, abdominal pain, and a rash, but it could be very likely that a patient experiencing acute anaphylaxis has a history of asthma.[4] Flush syndrome may occur from excess endogenous histamine release following certain ingestions, such as in scrombroidosis and in foods containing monosodium glutamate (MSG), but these isolated presentations will not display other clinical criteria required to meet the definition of anaphylaxis. Vasovagal syncope often presents with bradycardia, hypotension, and pallor, rather than the tachycardia, urticaria, and respiratory distress often associated with anaphylaxis.[4,9] A list of differential diagnoses for anaphylaxis is found in Box 109.6.

TABLE 109.2

Clinical Manifestations of Anaphylaxis and Related Pathophysiologic Changes

ORGAN SYSTEM	REACTION	SYMPTOMS	SIGNS	PATHOPHYSIOLOGIC CHANGES
Respiratory tract				
Upper	Rhinitis	Nasal congestion Nasal itching Sneezing	Nasal mucosal edema Rhinorrhea	Increased vascular permeability Vasodilation Stimulation of nerve endings
	Laryngeal edema	Dyspnea Hoarseness Throat tightness Hypersalivation	Laryngeal stridor Supraglottic and glottic edema	As above, plus increased exocrine gland secretions
Lower	Bronchospasm	Cough Wheezing Retrosternal tightness Dyspnea	Cough Wheeze, rhonchi Tachypnea Respiratory distress Cyanosis	As above, plus bronchiole smooth muscle contraction
Cardiovascular system	Circulatory collapse	Lightheadedness Generalized weakness Syncope Ischemic chest pain	Tachycardia Hypotension Shock	Increased vascular permeability Vasodilation Loss of vasomotor tone Increased venous capacitance
	Dysrhythmias	As above, plus palpitations	ECG changes: Tachycardia Nonspecific and ischemic ST-T wave changes Right ventricular strain Premature atrial and ventricular contractions Nodal rhythm Atrial fibrillation	Decreased cardiac output Decreased mediator-induced myocardial suppression Decreased effective plasma volume Decreased preload Decreased afterload Hypoxia and ischemia Dysrhythmias Iatrogenic effects of drugs used in treatment Preexisting heart disease
	Cardiac arrest		Pulseless ECG changes: Ventricular fibrillation Asystole	
Skin	Urticaria	Pruritus Tingling and warmth Flushing Hives	Urticaria Diffuse erythema	Increased vascular permeability Vasodilation
	Angioedema	Nonpruritic extremity, periorbital and perioral swelling	Nonpitting edema, frequently asymmetrical	Increased vascular permeability
Eye	Conjunctivitis	Ocular itching Increased lacrimation Red eye	Conjunctival inflammation	Stimulation of nerve endings
Gastrointestinal tract		Dysphagia Cramping, abdominal pain Nausea and vomiting Diarrhea (rarely bloody) Tenesmus	Nonspecific	Increased secretion of mucus Gastrointestinal smooth muscle contraction
Miscellaneous central nervous system		Apprehension Sense of impending doom Headache Confusion	Anxiety Seizures (rarely) Coma (late)	Secondary to cerebral hypoxia and hypoperfusion Vasodilation
Hematologic	Fibrinolysis and disseminated intravascular coagulation	Abnormal bleeding and bruising	Mucous membrane bleeding, disseminated intravascular coagulation Increased uterine tone Vaginal bleeding	Mediator recruitment and activation Uterine smooth muscle contraction Bladder smooth muscle contraction
Genitourinary		Pelvic pain Urinary incontinence	Urinary incontinence	

ECG, Electrocardiographic.

Diagnostic Testing

Anaphylaxis is primarily a clinical diagnosis. A good history and physical examination are the best tools for making an accurate and efficient diagnosis of anaphylaxis. Box 109.5 lists the diagnostic criteria for anaphylaxis. Elevated serum histamine levels acquired within 1 hour and tryptase levels within 5 hours of the onset of symptoms have been shown to correlate with anaphylaxis. These laboratory tests are not helpful in the acute setting because the assays typically take over an hour to perform. Also, tryptase levels may not be elevated in food induced anaphylaxis.[7,16] Screening studies should be aimed at ruling out other emergencies that could potentially be confused with anaphylaxis (see Box 109.6).

Management

Overview

In the setting of anaphylaxis, the key to avoiding adverse outcomes is prompt recognition and initiation of the appropriate interventions. Failure to immediately provide these measures, even by a few minutes, could lead to hypoxia and even death.[7]

After recognizing that anaphylaxis is present, a quick and initial effort should be made to remove any triggering agent (ie, insect stinger, stop infusion of medication). The patient's breathing, circulation, skin, mental status, and body weight should be quickly assessed. The patient should be placed on a continuous cardiac monitor and pulse oximetry, have intravenous (IV) access established, and administered supplement oxygen.[4] The majority of the morbidity and mortality associated with anaphylaxis is caused by acute respiratory failure or cardiovascular collapse. Therefore, the next steps in management should focus on the triad of early administration of epinephrine, providing a patent airway, and expanding intravascular volume with IV fluids. Antihistamines (H_1 and H_2 blockers) and corticosteroids are commonly given in cases of anaphylaxis, but there is no objective evidence that they improve the overall outcome and should not be considered first-line medications.[4,18] Box 109.7 summarizes the treatment algorithm in anaphylaxis.

Positioning

Hypotensive patients should be immediately placed in the supine position with their lower extremities elevated. If they are experiencing airway difficulties or vomiting, allow the patients to place

BOX 109.7

Treatment Algorithm for Anaphylaxis

EMERGENCY MEASURES (TAKEN SIMULTANEOUSLY)

Remove any triggering agent.
Place patient in supine position.
Begin cardiac monitoring, pulse oximetry, and blood pressure autonomic monitoring.
Begin supplemental oxygen if indicated.
Establish large-bore IV lines (eg, 16 or 18 gauge).
Establish a patent airway.
Be prepared for endotracheal intubation with or without rapid sequence intubation.
Be prepared to use adjunct airway technique (eg, awake fiberoptic intubation, surgical airway).
Start rapid infusion of isotonic crystalloid (normal saline):
- Adults: 1000 mL IV in the first 5 minutes in the adult (several liters of normal saline may be required)
- Pediatrics: 20 to 30 mL/kg IV increments

ANAPHYLAXIS TREATMENT MEDICATIONS

First-Line Agent

Epinephrine is the first-line medication and should be given immediately at the first suspicion of an anaphylactic reaction.
- Adult: 0.3 to 0.5 mg IM (1:1000 concentration) in anterolateral thigh every 5 to 10 minutes as necessary
- Pediatric: 0.01 mg/kg IM (1:1000 concentration) in anterolateral thigh every 5 to 10 minutes as necessary
- Alternatively, epinephrine (EpiPen, 0.3 mL; or EpiPen Jr, 0.15 mL) can be administered into anterolateral thigh

Second-Line Agents (Should Not Precede the Administration of Epinephrine)

Antihistamines

Diphenhydramine:
- Adults: 50 mg IV or 50 mg oral
- Pediatric: 1 mg/kg IV or oral

Ranitidine:
- Adult: 50 mg IV (150 mg oral)
- Pediatric: 1 mg/kg IV or oral

Aerosolized Beta-Agonists (if Bronchospasm Is Present)

Adult:
- Albuterol: 2.5 mg, diluted to 3 mL of normal saline; may be given continuously
- Ipratropium: 0.5 mg in 3 mL of normal saline; repeat as necessary

Pediatric:
- Albuterol: 2.5 mg, diluted to 3 mL of normal saline; may be given continuously
- Ipratropium: 0.25 mg in 3 mL of normal saline; repeat as necessary

Glucocorticoids (No Benefit in the Acute Management)

Methylprednisolone:
- Adult: 125 to 250 mg IV
- Pediatric: 1 to 2 mg/kg IV

Prednisone/prednisolone:
- Adult: 40 to 60 mg oral
- Pediatrics: 1 to 2 mg/kg oral

REFRACTORY HYPOTENSION

Consider continuous IV epinephrine drip (dilute 1 mg (1 mL 1:1000) in 1000 mL of normal saline or D_5W to yield a concentration of 1 μg/mL)
Adults: 1 to 10 μg/minute IV (titrated to desired effect)
Pediatrics: 0.1 to 1.5 μg/kg/minute IV (titrated to desired effect)

OTHER VASOPRESSORS TO CONSIDER

Dopamine: 5 to 20 μg/kg per minute continuous IV infusion (titrated to desired effect)
Norepinephrine: 0.05 to 0.5 μg/kg per minute (titrated to desired effect)
Phenylephrine: 1 to 5 μg/kg per minute (titrated to desired effect)
Vasopressin: 0.01 to 0.4 units/min (titrated to desired effect)

PATIENTS RECEIVING BETA-BLOCKADE

Glucagon: 1 to 5 mg IV over 5 minutes, followed by 5 to 15 μg/min continuous IV infusion

D_5W, 5% dextrose in water; *IM,* intramuscular; *IV,* intravenous.

themselves in a comfortable position and attempt to elevate their legs if possible. This positioning helps prevent distributive shock and allows epinephrine to reach the heart and be distributed throughout the body.[4] Pregnant women should be placed in the left lateral decubitus position to prevent vena cava compression and to promote venous return of blood to the heart.[7]

Epinephrine

Epinephrine should be the first medication given when a clinician suspects a patient is experiencing an anaphylactic reaction. The dose of aqueous epinephrine is 0.3 to 0.5 mg of 1 : 1000 concentration (1 mg/mL) intramuscularly (IM) for adults and 0.01 mg/kg of 1 : 1000 concentration IM for pediatric patients, and it can be repeated every 5 to 10 minutes as needed. It should be administered IM in the lateral, distal thigh (vastus lateralis). This has been shown to provide more rapid peak plasma concentrations (8 minutes) when compared to the previously suggested subcutaneous route (34 minutes).[2]

If the patient remains hypotensive after multiple doses of IM epinephrine and adequate volume expansion aimed at increasing blood pressure, IV epinephrine should be considered. IV epinephrine increases the risks of cardiac dysrhythmias, thus requiring continuous cardiac and hemodynamic monitoring. Dilution and slow administration are recommended to reduce untoward effects. In adults, recent literature suggests preparing a concentration of 1.0 μg/mL and initially infusing at a rate of 1 μg/minute. The rate should be increased until hemodynamic stability is achieved or a maximum dose of 10 μg/min. This can be prepared by mixing 1 mg (1 mL) of 1 : 1000 concentration of epinephrine with 1000 mL of 5% dextrose in water or normal saline; this provides an infusion of 1 mL/minute equaling 1 μg/minute. In children and infants, an infusion rate of 0.1 μg/kg per minute is advised, increasing in increments of 0.1 μg/kg per minute to a maximum of 1.5 μg/kg per minute.[2,6]

Central venous access is recommended when administering IV epinephrine because of the risk of tissue necrosis from extravasation. In addition to the IM route, successful administration of epinephrine through the intraosseous, sublingual, and endotracheal routes has been reported anecdotally, although only the parenteral route is recommended in recent guidelines.[4,7] The dosage and concentration guidelines for these routes of administration of epinephrine are the same as those for IV administration.

Epinephrine derives its therapeutic value from its combined alpha-adrenergic and beta-adrenergic actions. Alpha$_1$-adrenergic stimulation increases vasoconstriction, increases peripheral vascular resistance, and decreases mucosal edema. Through beta$_1$-adrenergic stimulation, inotropic and chronotropic cardiac activity is enhanced. Beta$_2$-adrenergic stimulation also provides stabilization of mast cells and basophils, and it induces bronchodilation.[4] These combined effects result in decreased mediator release from mast cells and basophils, which improves hives and bronchospasm, decreases mucosal edema and swelling, and reverses systemic hypotension. Epinephrine therefore works directly to improve the clinical features most commonly observed in an anaphylactic reaction.

Epinephrine can produce a number of undesirable side effects, including palpitations, anxiety, tremor, pallor, dizziness and headache. Ventricular arrhythmias, pulmonary edema, and hypertensive crisis are more severe adverse events that are known to occur, but they are often related to IV administration or toxic levels due to inappropriate dosing.[4] Despite these concerns, the benefits of early administration of epinephrine in anaphylaxis far outweigh any of the stated risks. There are no absolute contraindications to the use of epinephrine, which is the drug of choice in anaphylaxis and anaphylactic shock.[7]

Airway

Patients in respiratory distress and receiving multiple dose of epinephrine should be placed on supplement oxygen and prepared for possible advanced airway management. Patients with bronchospasm may benefit from bronchodilators or nebulized beta-agonists, but this should not preclude the administration of epinephrine. Upper airway obstruction from laryngeal angioedema can progress rapidly, so preparations for a difficult airway should be made early. This may include an awake intubation with the assistance fiberoptic laryngoscopy or the necessary equipment to provide a surgical airway.[4,6]

Volume Expansion

Along with airway assessment, fluid resuscitation should be initiated. For adults, infuse 1 to 2 liters of normal saline rapidly through large-bore (eg, 16-gauge) IV lines. Pediatric patients should be given boluses in 20 mL/kg increments. When IV access cannot be established, intraosseous catheter placement is an alternative. The assistance of an infusion pump or pressure bag should be used when administering fluids in this manner. Large volumes of normal saline (2 to 7 liters) may be required to reverse the effects of fluid extravasation into the extravascular space and the circulatory collapse sometimes seen in anaphylaxis. Patients with heart failure or renal failure should be monitored closely for signs of volume overload.[4,6]

Antihistamines

H_1 and H_2-antihistamines may be considered as adjunctive and second line treatments, but they should not replace the administration of epinephrine in the management of anaphylaxis. H_1-antihistamines may help relieve cutaneous symptoms, such as urticaria, pruritus, angioedema, eye and nasal symptoms, and flushing. H_2-antihistamines can contribute to relief of these cutaneous symptoms and are thought to be synergistic when given with H_1-antihistamines.[4,9] See Box 109.7 for suggested dosing.

Glucocorticoids

Glucocorticoids have no immediate role in the acute management of anaphylaxis and should be considered as third line interventions. Their onset of action typically does not occur for several hours, and they should not be administered before first and second line treatments. They may, however, provide benefit by preventing protracted symptoms or a biphasic reaction, but this has never been proven.[4,9] Currently, there are no studies that have specifically evaluated the role of glucocorticoids in the treatment of anaphylaxis.[19,20] See Box 109.7 for suggested dosing.

Patients Receiving Beta-Blockade

Glucagon, with positive inotropic and chronotropic cardiac effects mediated independently of alpha and beta receptors, may be helpful in patients with anaphylactic reactions who are receiving beta-blockers and who do not respond to epinephrine and other standard treatment modalities. The initial IV dose is 1 to 5 mg for adults and 20 to 30 μg/kg (maximum dose 1 mg) for children and may be followed by an infusion of 5 to 15 μg/minute. Nausea and vomiting are common side effects, so the clinician should be prepared to administer an antiemetic when indicated.[6,9]

Disposition

Up to 20% of patients may experience a biphasic reaction defined as a reoccurrence of symptoms without reexposure to the

triggering agent. Most of these reactions occur within 8 hours but have been reported as far out as 72 hours. The majority will again respond to the appropriate treatment, and recent literature suggests that clinically important biphasic reactions and fatalities are actually much rarer than previously reported.[21,22] Biphasic reactions are more common in patients who have a history of asthma, ingest the allergen, or present with laryngeal edema, wheezing, or gastrointestinal symptoms.[4,22] Consensus guidelines suggest that patients who respond to treatment and experience complete resolution of symptoms can be discharged home after an observation period of 4 to 8 hours. Consider extended observation or hospitalization for patients who (1) present with protracted anaphylaxis, hypotension or airway involvement; (2) receive IV epinephrine or more than two doses of IM epinephrine; or (3) have poor outpatient social support.[6]

Prior to discharge, the clinician should take an active role in educating the patient about their allergy and anaphylaxis. The patient should be discharged with a prescription for two autoinjectable epinephrine devices, one to remain at their home and the other to be carried with them at all times. It is also important to thoroughly explain and demonstrate how to use the device.[6] Patients should be encouraged to develop an anaphylaxis emergency action plan and to acquire a medical identification device (eg, bracelet, wallet card). Emphasis should be place on timely follow-up, preferably with an allergist-immunologist in their community.[7]

URTICARIA AND ANGIOEDEMA

Principles and Clinical Features

Urticaria is an allergic presentation commonly encountered in the ED and is characterized by the presence of wheals (hives), angioedema, or both. Both entities are often seen alone without other clinical criteria that meet the diagnosis of anaphylaxis, and they should be distinguished from other conditions, such as autoinflammatory syndromes and other causes of non-histaminergic angioedema. Urticaria appears as papules or wheals that consist of central swelling with surrounding reflex erythema, and it is associated with itching or a burning type sensation (Fig. 109.3).[1,23] These lesions are a result of mediators (predominately histamine) released from mast cells. They tend to occur on the extremities and trunk and are usually transient, with skin often returning to its normal appearance within 24 hours. Spontaneous episodes of urticaria that last less than 6 weeks are considered acute (90%), and those persisting longer than 6 weeks are classified as chronic (10%). There are also several types of inducible urticaria including cold contact, delayed pressure, heat contact, solar, aquagenic, cholinergic, and contact urticaria.[23,24]

Fig. 109.3. Acute urticaria. (©2001–2003, Johns Hopkins University School of Medicine. http://dermatlas.med.jhmi.edu/derm.)

Angioedema is characterized by edema of the subcutaneous or submucosal tissues, commonly involving the face, mouth, lips, tongue, extremities, and genitalia. It is a result of abrupt vasodilation and increased vascular permeability, allowing fluid to move from the vascular to the interstitial space. Because the swelling is located in the deeper layers of the skin, the appearance is often normal in color and patients may complain more of a pain or pressure type sensation, rather than an itch. Of particular concern is when the tongue, posterior pharynx, or larynx is involved, which could progress to airway obstruction and compromise. Angioedema is mediated either by an allergic (histaminergic) mechanism in response to an exposure to foods, drugs or physical stimuli, or by a nonallergic (non-histaminergic) mechanism (eg, HAE or ACE inhibitor).[1]

Non-histaminergic (nonallergic) angioedema is typically a result of elevated bradykinin levels. This classification includes HAE with or without C1 esterase inhibitor deficiency, acquired C1 esterase inhibitor deficiency (ACID), ACE inhibitor–induced, and idiopathic angioedema. In the case of HAE with C1 inhibitor deficiency and ACID, the lack of C1 inhibitor causes activation of the kallikrein-kinin system, increasing the consumption of kininogen, resulting in increased production of bradykinin. In the setting of ACE inhibitor–induced angioedema, the inhibition of ACE, one of the main inactivators of bradykinin, results in increased bradykinin levels.[1,25]

Recent literature suggests that non-histaminergic angioedema is responsible for approximately 80,000 to 112,000 ED visits annually, and 30% are a result ACE inhibitor–induced angioedema. This has an overall incidence of 0.1% to 0.2%, but is three to four times more likely in African-Americans, and women are at a 50% higher risk than men. ACE inhibitor–induced angioedema has a predilection for the face, often involving the, lips, eyelids, tongue, larynx, or pharynx. The highest incidence occurs in the first month of therapy but has been reported to occur as many as 10 years after therapy was intiated.[25,26]

Diagnostic Strategies

Similar to anaphylaxis, angioedema is a clinical diagnosis. There are no laboratory tests that are helpful in the acute setting. The majority of cases of acute urticaria and angioedema are hypersensitivity reactions, commonly triggered by allergens. A detailed history should focus on identifying any recent exposures to foods, drugs, physical stimuli, infection (especially viral hepatitis), occupational elements, or insect stings. Patients should also be questioned about prior history of similar symptoms and any family history of non-histaminergic angioedema.

Management

Angioedema With Urticaria

Angioedema that occurs in conjunction with urticaria is typically histaminergic (allergic) in nature. In cases that do not meet the criteria for anaphylaxis, antihistamines are considered the first-line treatment. Second-generation H_1-antihistamines, such as cetirizine, loratadine, and fexofenadine, are the preferred agents, and up to fourfold the conventional dose may be considered. Because 15% of the histamine receptors in skin are H_2, the addition of an H_2-antihistamine (eg, ranitidine) may also be beneficial. A short course of oral corticosteroids (eg, prednisone) may be considered as a second-line therapy.[23] In patients with

severe symptoms and no cardiac risk factors, epinephrine may be considered (anaphylactic dosing). In an effort to prevent reoccurrence, the patient should be educated to avoid exposure to potential agents that triggered their event.

Angioedema Without Urticaria

Acute attacks of non-histaminergic (bradykinin-related) angioedema do not typically respond to treatment with epinephrine, antihistamines, or steroids. In situations threatening respiratory compromise, paralytics should be given with caution, and the clinician must be prepared to use alternative measures to secure the patient's airway (eg, fiberoptic laryngoscopy, surgical airway).[1]

Fresh frozen plasma (FFP), which contains C1 inhibitor, has been reported to be effective in abolishing acute attacks; however, there are rare reports of exacerbation of the angioedema by FFP. Several new agents are approved by the FDA for use in the United States in patients with known HAE. Berinert is human plasma derived C1-esterase inhibitor (C1-INH) concentrate and is approved for treatment of HAE in the United States. The dose is 20 units/kg IV. Ecallantide is kallikrein inhibitor that is administered as three separate 10 mg subcutaneous injections for a total of 30 mg. Icatibant is a bradykinin 2-receptor inhibitor that is administered as a single subcutaneous injection of 30 mg. Conestat alfa (Ruconest) is a recombinant C1-INH concentrate that is given IV at a dose of 50 units/kg.[1]

In patients presenting with airway threatening angioedema and no prior history, it is suggested to initially administer epinephrine and antihistamines at anaphylactic doses. As previously mentioned, non-histaminergic angioedema rarely responds to these treatments. For ACE inhibitor–induced angioedema, the treatment is mainly supportive. The medication should be discontinued and the patient instructed not to take any ACE inhibitor in the future. There are reports of FFP being used with success in severe cases of ACE inhibitor–induced angioedema.[26] Theoretically, the medications described for the treatment of HAE, would be effective in ACE inhibitor–induced angioedema, but none of them are FDA approved for use at this time. Initial studies looking at ecallantide have not been promising, but icanibant in phase-2 trials appears to be effective in improving ACE inhibitor–induced angioedema.[27-29] Several studies are currently underway to further evaluate the effects of these newer medications on ACE inhibitor–induced angioedema.

Disposition

There is a lack of data to provide concrete guidelines for disposition. Most will agree that patients who experience a complete resolution of their angioedema, or have facial involvement only, can be discharged home after a period of observation in the ED. Hospitalization should be strongly considered for patients with persistent angioedema of the sublingual area, tongue, soft palate, pharynx, or larynx.[1]

KEY CONCEPTS

- Anaphylaxis is a life-threatening systemic allergic or non-allergic reaction of acute onset and multiorgan involvement; timely recognition and treatment are essential to maximize good outcomes.
- A history of sudden urticarial rash accompanied by respiratory difficulty, abdominal pain, or hypotension, strongly favors the diagnosis of anaphylaxis.
- Epinephrine is the first line treatment in patients with anaphylaxis and should be given immediately.
- There are no absolute contraindications to the use of epinephrine in the setting of anaphylaxis.
- Antihistamines and corticosteroids are second- and third-line agents in the management of anaphylaxis and should not replace or precede epinephrine.
- Consider prolonged observation or admission for patients who (1) experience protracted anaphylaxis, hypotension, or airway involvement; (2) receive IV epinephrine or more than two doses of IM epinephrine; or (3) have poor outpatient social support.
- Patients discharged after an anaphylactic event should be prescribed an EpiPen and instructed on its use, encouraged to develop an emergency action plan, and be referred for appropriate medical follow-up.
- Patients with refractory hypotension may require glucagon (receiving beta-blockage) or a continuous IV epinephrine infusion.
- Non-histaminergic angioedema (nonallergic angioedema) does not typically respond to epinephrine and antihistamines. New drugs, including berinert, icatibant, ecallantide, and Ruconest have been approved for use in HAE. FFP has been used with varying success in HAE, ACID, and ACE inhibitor–induced angioedema.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 109: QUESTIONS & ANSWERS

109.1. Which of the following statements regarding anaphylaxis is true?

A. Atopy is a risk factor for parenteral allergens.
B. Food is the cause in less than 10% of cases.
C. Race and geographic locations are predisposing factors.
D. Radiocontrast media (RCM) occurs in 5% of administrations.
E. The cause is unidentified in 30% of cases.

Answer: E. Food is the cause in one-third of cases, and the cause is not identified in one-third of cases. Race and geography do not predispose. Atopy predisposes to mucosally, but not parenterally, administered allergens. RCM reactions occur in 0.22% of cases, given the hyperosmolar agents, but in only 0.04% of cases using nonionic media.

109.2. The majority of the clinical features of anaphylaxis syndrome are produced by which mediator?

A. Acetylcholine
B. Histamine
C. Leukotrienes
D. Prostaglandins
E. Tumor necrosis factor

Answer: B. All contribute, but histamine is the predominant chemomediator.

109.3. A 31-year-old man has a history of anaphylaxis to penicillin. His condition warrants administration of a cephalosporin. Which of the following is true?

A. A history of penicillin-induced urticaria carries no cross-reactivity risk.
B. An oral cephalosporin given under supervision is acceptable.
C. Most patients with a penicillin allergy history have a true penicillin allergy.
D. Oral and parenteral cephalosporins carry equal risks.
E. The risk of cephalosporin anaphylaxis is 5% to 10%.

Answer: B. Cephalosporin anaphylaxis after penicillin anaphylaxis is very rare (<1%). Parenteral agents carry a higher risk. Oral cephalosporins are likely to be safe. Penicillin-induced urticaria is a risk factor for an increased likelihood of a cephalosporin allergy. Most patients who report a penicillin allergy can safely use penicillin. Both penicillins and cephalosporins are haptens; they require cross-linkage with a host protein to become antigenic.

109.4. A 26-year-old 70-kg man is undergoing a Bier block for fracture reduction of a right distal radius fracture. Lidocaine 350 mg is used. Three minutes after drug injection, the patient develops wheezing, facial flushing, and mucosal edema. Which of the following statements regarding this scenario is true?

A. Benzodiazepines are the treatment of choice.
B. Bupivacaine was probably inadvertently substituted for lidocaine.
C. Latex allergy to the tourniquet is the most likely etiology.
D. Lidocaine toxicity is the most likely etiology.
E. This is a methylparaben reaction.

Answer: E. Local anesthetic allergies are rare. Systemic effects are not. Many authors doubt that allergies to the amide anesthetics even occur. Methylparaben is a preservative in multidose vials that is structurally related to ester local anesthetics and can produce

allergic reactions. Latex allergies are usually of slower onset and mild. Lidocaine toxicity would generally present with central nervous system (CNS) activation and seizures. Bupivacaine toxicity would present as hypotension and then cardiac collapse. Benzodiazepines may be indicated for lidocaine toxicity, not for signs of anaphylaxis.

109.5. Which of the following statements regarding radiocontrast media (RCM) reactions is true?
- **A.** A 12-hour delay in scanning may be warranted to allow adequate steroid dosing.
- **B.** Only H_1 receptor blockers are likely to have a prophylactic effect.
- **C.** Shellfish allergy is a contraindication to RCM use.
- **D.** The pathophysiology of RCM anaphylaxis is immunologically mediated.
- **E.** The specific RCM used has little bearing on the risk of anaphylaxis.

Answer: A. A delay may be necessary to allow adequate steroid dosing. Nonionic, lower weight agents have a far lower incidence of allergic reactions. Shellfish allergy has no bearing or effect. The mechanism of RCM allergy is nonimmunologic and likely involves direct histamine release and complement activation.

109.6. A 27-year-old woman presents with the acute onset of pruritus, followed by flushing, dyspnea, and vomiting. Physical examination is remarkable for urticaria, tachypnea, tachycardia, hypotension, and bronchospasm. Which of the following statements regarding diagnosis of the patient's condition is true?
- **A.** Collection of vomitus may be indicated.
- **B.** Histamine levels are useful if obtained within 6 hours.
- **C.** Serotonin levels will not be useful.
- **D.** Scombroidosis is possible.
- **E.** Tryptase levels will not be useful.

Answer: A. Collection of vomitus may allow an allergist to customize an allergen provocation test. If drawn within 1 hour and 6 hours, histamine and tryptase levels, respectively, may help support the diagnosis of anaphylaxis. Elevated serotonin levels would indicate carcinoid. Scambroid poisoning, although histamine mediated, does not cause urticaria.

109.7. What is the appropriate dose of epinephrine for treatment of acute anaphylaxis?
- **A.** 0.3–0.5 mg IM of 1:1000 concentration in anterolateral thigh
- **B.** 1 mL of 1:1000 epinephrine intravenously
- **C.** 5 mL of 1:10,000 epinephrine locally at the reaction site
- **D.** 2 mL of 1:10,000 epinephrine intravenously every 5 minutes
- **E.** 10 mL of 1:10,000 epinephrine over 10 minutes intravenously

Answer: A. Please refer to Box 109.7.

CHAPTER 110

Dermatologic Presentations

Catherine A. Marco

OVERVIEW

Principles

Background

Skin conditions are common reasons for seeking emergency care.[1,2] Diseases of the skin and subcutaneous tissue account for over 5 million emergency department (ED) visits annually, which is roughly 4% of all ED visits.[3] The entire spectrum of severity of dermatologic disorders may be encountered from life-threatening to minor conditions. Common diagnoses among ED patients include infections, inflammatory conditions, allergic reactions, and drug reactions.

Anatomy and Physiology

The skin is composed of three layers: the epidermis, dermis, and subcutaneous layer. The epidermis is a thin layer of stratified squamous epithelium, consisting mainly of keratinocytes, which progress through stages of differentiation as they migrate from the basal to the superficial layer. These layers are the stratum germinativum (base of the epithelium), stratum spinosum, stratum granulosum, and stratum corneum (superficial layer). The epidermis also includes other cells, such as melanocytes and Langerhans cells. Melanocytes produce melanin, which functions to add pigment to the skin and also to absorb ultraviolet radiation. Langerhans cells are a component of the immune system and function to ingest and process foreign antigens. The epidermis lacks direct blood supply and is dependent on the dermis for nutrients by diffusion through the dermal-epidermal junction. This junction is the site of immunologic injury resulting in bullae in conditions, such as bullous pemphigoid and epidermolysis bullosa.

The dermis consists of connective tissue, blood vessels, lymphatic vessels, nerve endings, and immune cells. The main function of the dermis is to support the epidermis and contribute to the protective functions of the skin. Fibroblasts produce procollagen and elastic fibers used to form the connective tissues that give support and elasticity to the skin. Sweat glands and the network of blood vessels in the dermis assist with thermoregulation.

The subcutaneous layer is composed of connective tissue and adipose tissue, functions to cushion the overlying skin, and contains lymph and neurovascular structures.

The skin serves several important physiologic functions. It serves as a barrier between the internal and external environment. The skin protects from external toxic and infectious materials, and assures that internal fluids and electrolytes are maintained in homeostasis; it serves an integral role in temperature homeostasis through its barrier function, sweating mechanism, and blood vessel dilation or constriction; it functions in the absorption of ultraviolet radiation and production of vitamin D; sensory nerve endings in skin serve important functions of sensation; and finally, certain cells within the skin serve important immunologic functions, including Langerhans cells, lymphocytes, mast cells, and keratinocytes.

Clinical Features

A general approach to the unknown rash is listed in Box 110.1.

Important historical information includes the time of onset, duration of symptoms, and relation to any new potential allergens, such as foods, medications, soaps, pets, jewelry, and so on. Information about changes over time should be sought, including whether the rash has progressed, improved, or waxed and waned. Associated pain, pruritus, fever, sexual history, occupation or hobbies should be identified. Relevant past medical history includes medical conditions, skin conditions, medications, illicit drug use, allergies, recent travel, sunlight exposure, and family history.

The physical examination is essential to identifying the cutaneous diagnosis. The examination should be performed with adequate lighting. Primary and secondary lesions, as well as characteristics and patterns of lesions should be identified. Lesions may be palpated wearing gloves to identify texture, blanching, or sloughing characteristics. Nikolsky's sign may be tested, and when positive, gentle rubbing of the skin results in sloughing of the top layer of the epidermis. For patients with systemic complaints, a thorough visual examination from head to soles of feet should be performed, including skin, mucosa, and genitalia.

Identification and description of lesions is essential. Lesions may be classified as primary or secondary lesions. Primary lesions arise directly as a result of the disease process. Secondary lesions result from subsequent factors, such as scratching, treatment, healing, or complicating infections. Primary and secondary lesions and descriptions are listed in Tables 110.1 and 110.2. The significance of distribution of lesions is outlined in Table 110.3.

Diagnostic Testing

Laboratory testing is unnecessary for most patients with a rash. Specific tests for clinically suspected diseases may be indicated, such as blood tests for secondary syphilis, heterophile antibodies (monospot) for mononucleosis, or throat swabs for rapid testing and culture of group A streptococcus. Adjunctive skin tests may be considered, including potassium hydroxide (KOH) prep, Tzanck smear, gram stain, erythrocyte sedimentation rate (ESR), or biopsy. For the patient with severe systemic illness, a complete blood count, blood cultures, lumbar puncture studies, electrolytes, blood urea nitrogen (BUN), creatinine, glucose, and liver function tests should be considered.

Management

Treatments for dermatologic conditions should address both definitive treatment for underlying disease states and symptomatic treatment. If causative agents are identified, they should be discontinued or eliminated from the environment. Topical or systemic therapies may be indicated for a variety of conditions.

Vehicles for topical dermatologic preparations may be important in the therapeutic effect.[4] Vehicles include creams (water-based emulsion of oil), lotions (water-based suspension of

BOX 110.1

Approach to Management of the Unknown Rash

1. Time of onset
2. Historical features
3. Medical history
4. Primary lesion
5. Secondary lesions
6. Distribution of the lesions
7. Systemic illness
8. Diagnostic tests
9. Category of rash
   a. Infectious
   b. Immune
   c. Vascular
   d. Allergic
   e. Malignancy
10. Treatment

TABLE 110.1

Primary Lesions

LESION	DESCRIPTION	SIZE
Macule	Flat circumscribed pigmented area	<0.5 cm in diameter
Patch	Flat circumscribed pigmentation area	>0.5 cm in diameter
Papule	Elevated, solid, palpable lesion, variable color	<0.5 cm in diameter
Plaque	Elevated, solid, palpable lesion, variable color	>0.5 cm in diameter
Nodule	Solid, palpable, subcutaneous lesion	<0.5 cm in diameter
Abscess	Erythematous, fluctuant, tender, fluid-filled nodule	Any
Tumor	Solid, palpable, subcutaneous lesion	>0.5 cm in diameter
Vesicle	Elevated, thin walled, circumscribed, clear fluid-filled lesion	<0.5 cm in diameter
Pustule	Elevated, circumscribed, purulent fluid-filled lesion	Any
Bulla	Elevated, thin walled, circumscribed, fluid-filled lesion	>0.5 cm in diameter
Petechiae	Flat, erythematous or violaceous non-blanching lesions	<0.5 cm in diameter
Purpura	Erythematous or violaceous non-blanching lesions, may be palpable	>0.5 cm in diameter

powder), ointments (oil-based suspension, which improves penetration of the active ingredient), gels (transparent, semi-solid, non-greasy emulsion), foams (helpful for scalp or difficult to reach areas), and pastes (ointment base with powder, stiff consistency). For dry, scaly conditions, emollients such as ointments may be more effective. For moist conditions, a dryer vehicle such as a gel or powder may be preferable. Vehicle components may vary with generic preparations, and it is important to monitor clinical success if generic preparations are prescribed. Communication with the patient about preferences may be important. Patient preference and compliance are closely linked to successful outcomes.

TABLE 110.2

Secondary Lesions

SECONDARY LESION	DESCRIPTION
Scale	Thickened area of keratinized epithelium
Crust	Dried area of plasma proteins, resulting from inflammation
Fissures	Deep cracks in skin surfaces, extending into dermis
Erosions	Disruption of surface epithelium, usually linear, traumatic
Ulcer	Deep erosion extending into dermis
Scar	Dense collection of collagen, a result of healing after trauma or procedures
Excoriation	Linear erosions typically secondary to scratching or rubbing
Infections	Bacterial, viral, fungal, or protozoal infection, caused by breaks in dermal-epidermal junction, often erythematous
Hyperpigmentation	Increase in melanin containing epidermal cells
Lichenification	Abnormally dense layer of keratinized epidermal cells

TABLE 110.3

Distribution and Patterns of Selected Disease States

DERMATOLOGIC DIAGNOSIS	DISTRIBUTION AND PATTERNS OF LESIONS
Atopic dermatitis, infantile	Face, scalp, flexor surfaces of extremities
Atopic eczema, adult	Face, neck, flexor surfaces of extremities
Dermatomyositis	Dorsal MCP joints, periorbital area
Disseminated gonorrhea	Distal extremities, near joints
Erythema nodosum	Anterior shins, ulnar surfaces
Herpes zoster infection	Dermatomal distribution, common on trunk
Lichen planus	Wrists, ankles, flexor surfaces
Nummular eczema	Distal extremities
Neurotic excoriations	Extremities, face, upper back, neck
Pityriasis rosea	Trunk, extremities, "Christmas tree" pattern
Porphyria cutanea tarda	Sun-exposed areas, hands, forearms, feet
Psoriasis	Extensor surfaces of extremities, sacral area
Rosacea	Face, neck
Sarcoidosis	Face, extremities, back
Seborrheic dermatitis	Chest, nasolabial folds
Secondary syphilis	Torso, palms, soles
Systemic lupus erythematosus	Nose and cheeks, head and neck, photosensitivity, alopecia
Tinea versicolor	Upper back and chest

MCP, Metacarpophalangeal.

Topical steroids are commonly used to treat inflammatory dermatologic conditions. Topical steroids have several mechanisms of action, including antiinflammatory effects, antiproliferative effects on fibroblasts and collagen, reduction of leukocyte adhesion to capillaries, reduction of capillary wall permeability, reduction of complement components, and histamine antagonism. Adverse effects may include skin atrophy, striae, acneform lesions, pigment changes, telangiectasia, hypothalamic-pituitary axis suppression from systemic absorption, and exacerbation of certain conditions such as fungal infections and viral infections. Topical steroids should be prescribed in the lowest potency and for the shortest duration that is effective for the individual patient. Systemic therapies are appropriate for systemic conditions. Commonly used systemic therapies include oral, intramuscular (IM), or intravenous (IV) steroids, antipruritic agents, antibiotics, antifungal agents, and antiviral agents.

Disposition

Most ED patients with dermatologic complaints can be successfully managed as outpatients. Indications for inpatient hospitalization include systemic disorders with dehydration, disorders of thermoregulation, systemic infection or other systemic disorder requiring inpatient management, and inability to care for self or maintain appropriate oral intake. Dermatologic outpatient follow-up or inpatient consultation may be appropriate.

INFECTIOUS DISORDERS

Bacterial Infections

Impetigo

Impetigo is typically caused by *Staphylococcus aureus* and/or β-hemolytic *Streptococcus.* Pediatric patients are commonly affected. Streptococcal impetigo (ecthyma) is found most often on the face and other exposed areas. The eruption often begins as a single pustule but later develops multiple lesions. It begins as 1- to 2-mm vesicles with erythematous margins. When these break, they leave red erosions covered with a golden yellow crust (Fig. 110.1). Lesions may be pruritic but usually are not painful. Regional lymphadenopathy is commonly present. Lesions are contagious among infants and young children and less so in older children and adults. Postpyodermal acute glomerulonephritis is a recognized complication of streptococcal impetigo.

Staphylococcal impetigo is differentiated from streptococcal impetigo in that it is more superficial, and there is little surrounding erythema. Other diagnostic considerations are herpes simplex virus (HSV) and inflammatory fungal infections. A Gram stain of the weepy erosion obtained after removal of the crust will reveal gram-positive cocci. Methicillin-resistant *Streptococcus aureus* (MRSA) impetigo is increasingly common. Risk factors include prior infection or colonization with MRSA.[5]

Bullous impetigo is caused by the toxin released by staphylococcus. It is seen primarily in infants and young children. The initial skin lesions are thin-walled, 1- to 2-cm bullae (Fig. 110.2). When these rupture, they leave a thin serous crust and collarette-like remnant of the blister roof at the rim of the crust. The face, neck, and extremities are most often affected. The differential diagnosis includes contact dermatitis, HSV infection, superficial fungal infections, and pemphigus vulgaris. A Gram stain of the fluid from a bulla reveals gram-positive cocci. Cultures are positive in 95% of cases.

Empirical therapy should be instituted with oral or topical antibiotics. Oral antibiotics are indicated for severe or multiple lesions. Topical therapies include either mupirocin or retapamulin. Oral therapies include be a regimen with an agent active against *S. aureus,* such as dicloxacillin or cephalexin. If MRSA is suspected, doxycycline, clindamycin, or trimethoprim-sulfamethoxazole (TMP-SMX) is recommended.

Therapy for bullous impetigo consists of a systemic antibiotic, such as dicloxacillin, erythromycin ethylsuccinate, or azithromycin. Without treatment, impetigo generally heals within 3 to 6 weeks.

Folliculitis

Folliculitis is an inflammation in the hair follicle, usually caused by *S. aureus.* It appears as pustules with a central hair. The lesions are usually on the buttocks and thighs, occasionally in the beard or scalp, and may cause mild discomfort. The differential diagnosis includes acne, keratosis pilaris, and fungal infection. Gram-negative folliculitis with *Pseudomonas aeruginosa* can occur after exposure to infected hot tubs and swimming pools or in individuals taking antibiotics for acne; it can be differentiated from staphylococcal folliculitis by a Gram stain of the lesion.

Treatment with an antiseptic cleanser such as povidone-iodine or chlorhexidine every day or every other day for several weeks is usually adequate. For patients with extensive involvement, a course of systemic antibiotics may be added, such as doxycycline or dicloxacillin.

Cellulitis

Cellulitis presents with localized erythema, swelling, and pain of the soft tissues (Fig. 110.3). Erysipelas is a streptococcal infection

Fig. 110.1. Impetigo. (Courtesy Jonathan Singer, MD.)

Fig. 110.2. Bullous impegito. (Courtesy David Effron, MD.)

Fig. 110.3. Cellulitis. (Courtesy Jonathan Singer, MD.)

Fig. 110.4. Methicillin-resistant *Staphylococcus aureus* (MRSA) abscess with cellulitis.

of the skin and subcutaneous tissue. Systemic symptoms may include fever, myalgias, and malaise. Cellulitis may be a cause of sepsis. Ultrasound may be helpful in differentiating abscess, which appears as a fluid filled cavity, from cellulitis, which appears as cobblestoning, with fine reticular areas of hypoechoic stranding.

Mild cases of cellulitis may be treated with an oral antibiotic, such as penicillin VK, a cephalosporin, dicloxacillin, or clindamycin. Moderate cases requiring IV therapy should be treated with a penicillin, ceftriaxone, cefazolin, or clindamycin. Severe cases should be treated with IV vancomycin plus piperacillin/tazobactam. Necrotizing fasciitis and emergent surgical consultation should be considered.[6]

Soft tissue skin infections are discussed in more depth in Chapter 129.

Abscess

Abscesses may present with localized soft tissue swelling, erythema, and fluctuance (Fig. 110.4). Ultrasound may be helpful in differentiating abscess, which appears as a fluid filled cavity from cellulitis, which appears as cobblestoning, with fine reticular areas of hypoechoic stranding. Mild abscesses require incision and drainage alone. Recent literature suggests higher cure rate for antibiotic treatment with TMP-SMX in addition to incision and drainage.[7] Moderate or severe abscesses should have culture and sensitivity performed. Empirical antibiotic therapy may be added, with agents such as TMP-SMX or doxycycline. If IV antibiotics are indicated, agents may include vancomycin, daptomycin, linezolid, televancin, or ceftaroline.[6]

Hidradenitis suppurativa affects the apocrine sweat glands. Recurrent abscess formation in the axillae and groin resembles localized furunculosis. The condition tends to be recurrent and may be extremely resistant to therapy. Ultrasound will help differentiate abscesses from vascular or lymphoid structures. Hidradenitis suppurativa may be treated with drainage of abscesses if they are fluctuant, painful, and large. Antistaphylococcal antibiotics are useful if they are administered early and for a prolonged period. Begin treatment for mild disease with topical clindamycin for 3 months. In patients with more severe or nonresponsive disease, begin oral clindamycin combined with rifampin for 3 to 6 months.[8] Antiandrogen therapy may be considered if antibiotics do not produce improvement. Many cases do not respond, however, and eventually require local excision and skin grafting of the involved area.

Carbuncle

A carbuncle is a large abscess that develops in the thick, inelastic skin of the back of the neck, back, or thighs and usually involves hair follicles. Carbuncles may produce severe pain and fever. Septicemia may accompany the lesions. The diagnosis of skin abscess, furuncle, or carbuncle is usually made clinically. Ultrasonography is often helpful in diagnosis of carbuncles or abscesses that may not appear fluctuant on examination.

Local heat should be applied to furuncles and carbuncles, which should be incised and drained when fluctuant. Antibiotics are unnecessary with incision and drainage unless cellulitis or septicemia is present.

Methicillin-Resistant *Staphylococcus Aureus*

The incidence of community-associated MRSA has soared since the first report in 1993. In many major cities in the United States, MRSA is now the most common pathogen cultured from ED patients presenting with skin and soft tissue infections. Concern exists that MRSA may be more virulent than methicillin-sensitive strains, and colonization with MRSA may produce more overt infections. Hospital-acquired MRSA isolates can survive on a variety of inanimate surfaces, sometimes for weeks. It is unclear whether this is also true for community acquired MRSA isolates; if it is true, their presence on such items as clothing, towels, and athletic equipment might contribute to outbreaks. Pets (including dogs and cats), livestock, and birds have been identified as MRSA carriers; their role in MRSA transmission to humans is unclear.

MRSA infections are most often manifested as skin and soft tissue suppuration, such as an abscess, furuncle, or cellulitis. Lesions frequently exhibit central necrosis and are often confused with spider bites by patients. Clinical features cannot distinguish with certainty skin and soft tissue infections caused by MRSA from those caused by methicillin-susceptible *S. aureus*. Although rare, MRSA infection can also be manifested as necrotizing fasciitis. Recurrences of MRSA cellulitis are common. Contagion among the close household contacts of patients as well as correctional facility, school, and sports team contacts is well recognized.

Several studies have demonstrated excellent outcomes for abscesses caused by MRSA that are treated with incision and drainage alone. Antimicrobial therapy is recommended in addition to incision and drainage for patients with severe or extensive disease, rapid progression in presence of associated cellulitis, systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain, associated septic phlebitis, and lack of response to incision and drainage alone.[9]

If local resistance patterns are known, they should guide antimicrobial choice. Clindamycin combines MRSA activity with effectiveness against the majority of other gram-positive organisms. A recent study found no significant difference between the efficacy of clindamycin and TMP-SMX for the treatment of uncomplicated skin infections, including both cellulitis and abscesses.[10] Rifamycin has anti-MRSA activity, but resistance readily develops, so it should not be used as monotherapy. Linezolid is active against almost all MRSA isolates and group A streptococci. Disadvantages of its use include high cost, lack of routine availability, hematologic side effects, and potential for resistance among *S. aureus* strains. Prolonged linezolid administration increases the likelihood of resistance. Other agents effective against MRSA include TMP-SMX, minocycline, or doxycycline. Cephalosporins and macrolides are typically ineffective against MRSA. Fluoroquinolones should be avoided because *S. aureus* resistance develops readily.

Patients with large abscesses, abscesses in high-risk locations, fever, signs of systemic infection, young age, or immunodeficiency prompt consideration of hospitalization. Vancomycin is considered the parenteral drug of choice for patients with invasive *S. aureus* infection, although clinical failures have been reported. It is reasonable to combine vancomycin with another effective antistaphylococcal agent because many antibiotics have better bactericidal activity. In severely ill patients, carbapenems such as meropenem, panipenem, and ertapenem are recommended, because they are active against MRSA and synergistic with vancomycin. Other effective parenteral agents may include clindamycin, linezolid, daptomycin, tigecycline, or telavancin.[6]

Recurrent infections are generally treated like initial episodes. Although "decolonization" strategies have been recommended, neither the indications for their use nor their effectiveness in reducing the risk of recurrences is established. Decolonization strategies include the use of intranasal mupirocin to reduce nasal carriage of MRSA; however, eradication of nasal colonization appears to be transient.

Common antiseptics appear to retain reasonable activity against MRSA, although the results of studies are somewhat conflicting. Good personal hygiene, including appropriate handwashing techniques, separation of infected patients from other types of patients, and routine cleaning of shared equipment, are essential to limiting MRSA spread.

Fig. 110.5. Tick.

Fig. 110.6. Erythema migrans.

Erythema Migrans

Lyme disease is caused by the organism *Borrelia burgdorferi* and is transmitted by the deer tick bite (Fig. 110.5). Most cases occur in the spring and early summer. Endemic areas in the United States include the Northeast, Midwest, West, and scattered other areas. Although 36 to 48 hours of tick attachment is necessary to transmit disease, less than 33% of patients recall a tick bite. The incubation period is 3 to 30 days.

Clinical presentations include three disease stages. Stage I occurs early and is manifested by malaise, headache, fever, lymphadenopathy, and arthralgias. Stage I typically resolves in 4 weeks. Erythema migrans occurs in 60% to 80% of cases and manifests as erythematous annular, non-scaling lesion with central clearing (Fig. 110.6). Stage II presents with secondary annular lesions, fever, lymphadenopathy, neurologic manifestations, or cardiac conduction abnormalities that may last weeks to months. Stage III manifests as chronic arthritis, dermatitis, and central nervous system (CNS) disease.

Diagnostic tests may include a nonspecific elevated ESR and serologic tests, which are helpful in establishing the definitive diagnosis but are not available acutely.

Management should include appropriate antibiotic administration. The antibiotic regimen may include doxycycline for 10 to 21 days, or as alternates, cefuroxime, ceftriaxone, or penicillin G. Amoxicillin may be used in pediatric and pregnant patients.

An in depth discussion of Lyme disease can be found in Chapter 126.

Necrotizing Fasciitis

Necrotizing fasciitis should be considered with skin and soft tissue infection with signs of systemic toxicity, or severe infection (Figs. 110.7, 110.8, and 110.9). Prompt surgical consultation is recommended. Empirical antibiotic treatment should be instituted with broad coverage (eg, vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), because the etiology can be polymicrobial (mixed aerobic/anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA).[9]

An in depth discussion of necrotizing fasciitis can be found in Chapter 129.

Meningococcal Infection

Meningococcal infection is caused by the organism *Neisseria meningitides*, typically transmitted by respiratory secretions.

Fig. 110.7. Necrotizing fasciitis.

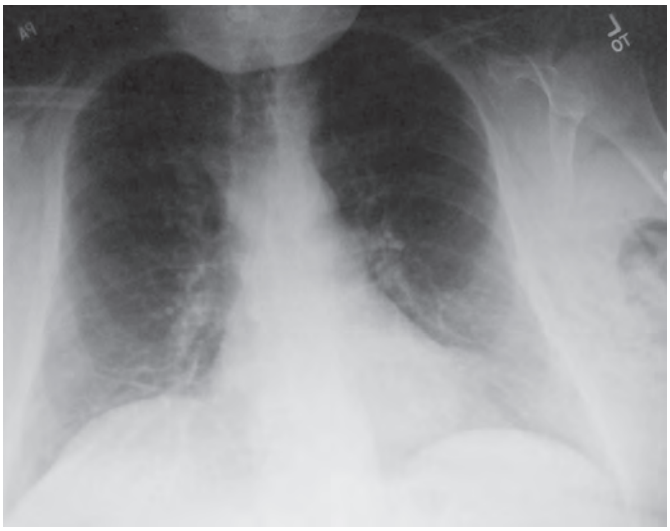

Fig. 110.8. Necrotizing fasciitis. Note air in subcutaneous tissues.

Fig. 110.9. Necrotizing fasciitis.

Meningococcal disease may manifest as one of three syndromes: meningitis, bacteremia, or bacteremic pneumonia. Meningococcal disease typically affects healthy children and adolescents, and it may result in significant morbidity and mortality. Infection is fatal in approximately 10% of cases.

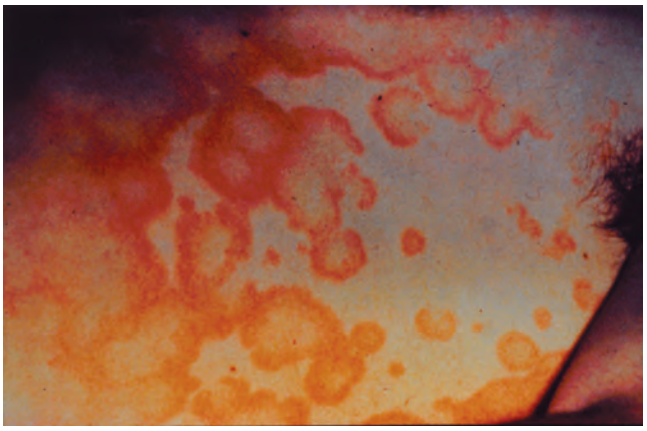

Fig. 110.10. Erythema marginatum associated with rheumatic fever. (Courtesy David Effron, MD.)

Clinical presentation may include fever, malaise, arthralgias, nausea, and vomiting. Cutaneous findings of macules, papules, vesicles, or petechiae and purpura may be present.

Ten percent of cases may present with Waterhouse-Friderichsen syndrome characterized by shock with intracutaneous hemorrhage.

An in depth discussion of meningococcal disease can be found in Chapter 121.

The diagnosis should be suspected clinically in the ED setting and treated promptly. Confirmatory tests may include blood cultures, cerebrospinal fluid (CSF) cultures, or skin scrapings.

Rapid administration of antibiotics is essential. Empirical therapy should be instituted with agents, such as a third generation cephalosporin (eg, ceftriaxone or cefotaxime) plus vancomycin. Alternative antibiotics may include penicillin G, chloramphenicol, a fluoroquinolone, or aztreonam. Dexamethasone should also be considered for suspected or proven meningitis. Immunization against meningococcal infection is recommended for groups at increased risk for infection, including adolescents and persons at risk for exposure.

Scarlet Fever

Scarlet fever results from group A strep infection. The illness has an abrupt onset with fever, chills, malaise, and sore throat, followed within 12 to 48 hours by a distinctive rash that begins on the chest and spreads rapidly, usually within 24 hours. Circumoral pallor may be noted. The skin has a rough sandpaper-like texture because of the multitude of pinhead-sized lesions. The pharynx is injected, and there may be erythematous lesions or petechiae on the palate. After the resolution of symptoms, desquamation of the involved areas occurs and is characteristic of the disease. Erythema marginatum may be seen in 10% of cases and presents with annular erythematous lesions that may be transient and reappear over days, weeks, or months (Fig. 110.10).

Complications include the development of a streptococcal infection of lymph nodes, tonsils, middle ear, and respiratory tract. Late complications include rheumatic fever and acute glomerulonephritis.

Treatment is with oral penicillin VK or IM benzathine penicillin (given as Bicillin C-R). In patients allergic to penicillin, treatment may be initiated with erythromycin, other macrolides, or a cephalosporin.

Syphilis

Syphilis is the third most common sexually transmitted infection in the United States (following chlamydia and gonorrhea) and is

Fig. 110.11. Primary syphilis. (Courtesy David Effron, MD.)

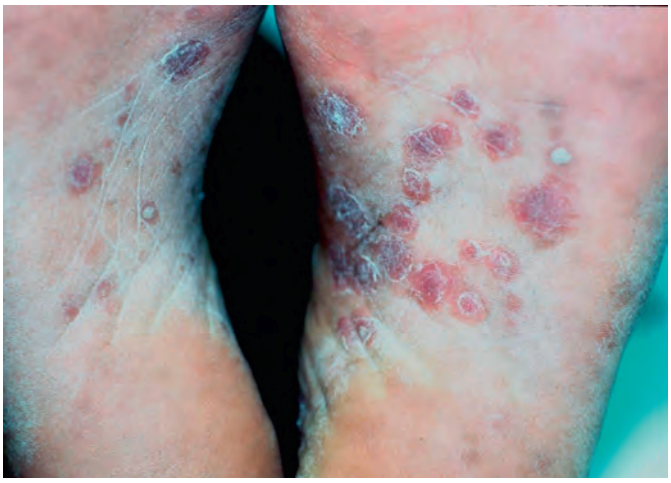

Fig. 110.12. Secondary syphilis. (Courtesy David Effron, MD.)

transmitted by direct contact with an infectious lesion. The causative organism is the spirochete *Treponema pallidum.* After an incubation period of 10 to 90 days, the primary lesion appears, which lasts 3 to 12 weeks and heals spontaneously. In 6 weeks to 6 months after exposure, the secondary stage appears, which involves a variety of mucocutaneous lesions. These lesions also heal spontaneously in 2 to 6 weeks as the disease enters the latent phase. Either a prolonged latent phase or tertiary syphilis follows. Among untreated patients, 25% display at least one relapse of mucocutaneous lesions of the oral cavity or anogenital region.

The chancre is the dermatologic manifestation of primary syphilis. Chancres usually appear as single lesions but may be multiple. They appear at the site of spirochete inoculation, usually the mucous membranes of the mouth or genitalia. The chancre begins as a papule and characteristically develops into an ulcer approximately 1 cm in diameter with a clean base and raised borders (Fig. 110.11). The chancre is painless unless it is secondarily infected, and it may be accompanied by painless lymphadenopathy. Many patients do not recall the primary chancre.

The secondary stage usually follows the primary stage by 6 weeks or more but rarely overlaps primary syphilis. There are a number of cutaneous manifestations of secondary syphilis. Lesions may be erythematous or pink macules or papules, usually with a generalized symmetric distribution. Secondary syphilis should be considered in the differential diagnosis of any maculopapular rash. Pigmented macules and papules may appear on the palms and soles (Fig. 110.12). Generalized lymphadenopathy and malaise accompany the skin lesions. Moist, flat, verrucous condyloma latum may appear in the genital area. These lesions are highly contagious.

The diagnosis of primary or secondary syphilis should be made in the ED based on clinical presentation. Definitive diagnosis is made by the identification of spirochetes with darkfield microscopy and by serologic testing. The result of the Venereal Disease Research Laboratory (VDRL) test, the most commonly used diagnostic serologic test, is positive in approximately three-fourths of patients with primary syphilis, but may be negative early in the course of the disease. The VDRL test result is invariably positive in cases of secondary syphilis, usually in titers of 1:16 or greater. The most specific and sensitive serologic test is the fluorescent treponemal antibody absorption (FTA-ABS) test. A biologic false-positive serologic test response for syphilis is defined as a positive VDRL test result with a negative FTA-ABS test result. This situation is seen acutely after vaccination or infections, especially mycoplasmal pneumonia, mononucleosis, hepatitis, measles, varicella, and malaria, and in pregnancy. Chronic biologic false-positive reactions (ie, those lasting longer than 6 months) may occur with systemic lupus erythematosus, thyroiditis, lymphoma, and narcotic addiction or in elderly patients. Most false-positive reactions are in low titer ranges of 1:1 to 1:4.

Guidelines for syphilis treatment, including in penicillin allergic individuals, are available at www.cdc.gov. Primary and secondary syphilis is treated with benzathine penicillin G in a dose of 2.4 million units IM. Human immunodeficiency virus (HIV)-infected patients require more intensive therapy. Patients with latent syphilis are treated the same as patients with primary disease; latent syphilis and tertiary syphilis are treated with benzathine penicillin G, three doses of 2.4 million units IM at weekly intervals for a total of 7.2 million units. Treatment of neurosyphilis requires infusion of aqueous crystalline penicillin, 3 to 4 million units IV every 4 hours for 10 to 14 days.[13] Within 12 hours of receiving therapy, patients may experience a febrile reaction and diffuse rash called the *Jarisch-Herxheimer reaction;* thus it is best to warn patients of this possibility. The reaction resolves spontaneously, usually within 24 hours.

Treatment may be administered in the ED if the diagnosis can be made on clinical, microscopic, or serologic grounds. If this cannot be done, a serologic sample should be drawn and the patient referred for treatment. The VDRL test response may be expected to return to nonreactive 6 to 12 months after the treatment of primary disease or 1 to 1½ years after the treatment of secondary disease. Patients with tertiary syphilis who are adequately treated may nevertheless retain a positive serologic result.

An in depth discussion of syphilis can be found in Chapter 88.

Gonococcal Dermatitis

The arthritis-dermatitis syndrome is the most common presentation of disseminated gonococcal disease. It occurs in less than 2% of patients with gonorrhea, affecting women primarily. Fever and migratory polyarthralgias commonly accompany the skin lesions. The lesions are often multiple and have a predilection for periarticular regions of the distal extremities. The lesions begin as erythematous or hemorrhagic papules that evolve into pustules and vesicles with an erythematous halo (Fig. 110.13). They may be tender and may have a gray necrotic or hemorrhagic center. Healing with crust formation usually occurs within 4 or 5 days,

Fig. 110.13. Disseminated gonorrhoea. (Courtesy David Effron, MD.)

although recurrent crops of lesions may appear even after antibiotics have been started.

The organism may be cultured from the cutaneous lesions. Gram stain only occasionally reveals the organisms. A more reliable diagnostic technique is immunofluorescent antibody staining of direct smears from pustules. This method indicates that the lesions may be the result of hematogenous dissemination of nonviable gonococci.

Current treatment of disseminated gonococcal infection is with parenteral ceftriaxones, or ceftizoxime or cefotaxime. Patients allergic to β-lactam antibiotics or those with severe penicillin allergies may be treated with spectinomycin. Ciprofloxacin and ofloxacin are not recommended because of increasing resistance patterns. Hospitalization is recommended for patients with disseminated gonococcal infection.

An in depth discussion of gonococcal disease can be found in Chapter 88.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) generally occurs in children 6 years old or younger. It is caused by an infection with phage group 2 exotoxin-producing staphylococci. The illness begins with erythema and crusting around the mouth. The erythema then spreads down the body, followed by bulla formation and desquamation. Mucous membranes are usually typically involved. After desquamation occurs, the lesions dry up quickly, with clinical resolution in 3 to 7 days.

Most group 2 toxin-producing organisms are penicillin resistant. Although most patients will recover without antibiotic treatment, IV therapy with nafcillin, cephalexin, or dicloxacillin is recommended.[14] Clindamycin, vancomycin, or linezolid may be considered in cases of suspected MRSA.

An in depth discussion of SSSS can be found in Chapter 129.

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is an acute febrile illness characterized by a diffuse desquamating erythroderma. Clinical presentation may include high fever, hypotension, constitutional symptoms, multiorgan involvement, and rash. The syndrome gained notoriety in the early 1980s because of association with tampon use. However, it is also well known in men and children. Its appearance has often been linked to exotoxin-producing *S. aureus.* Approximately 50% of cases are associated with menstruation. Other cases occur in the postoperative setting, burns, postpartum infection, osteomyelitis, arthritis, empyema, fasciitis, septic abortion, peritonsillar abscess, sinusitis, and subcutaneous abscess.

TSS is caused by *S. aureus* or group A streptococcus, also called *Streptococcus pyogenes*. It has been reported in previously healthy patients, immunocompromised patients, and elders. Fatigue, localized pain, and nonspecific symptoms herald the onset of this disease, followed by septic shock and multisystem organ failure.

Diagnosis of TSS requires the presence of (1) temperature of at least 38.9° C; (2) hypotension, with a systolic blood pressure of 90 mm Hg or less; (3) rash; and (4) involvement of at least three organ systems. Systemic involvement may include the gastrointestinal tract, muscular system, or CNS and laboratory evidence of renal, hepatic, or hematologic dysfunction. Headache, myalgias, arthralgia, alteration of consciousness, nausea, vomiting, and diarrhea may be present.

The rash is typically a diffuse, blanching, macular erythroderma. Accompanying nonexudative mucous membrane inflammation is common. Pharyngitis, sometimes accompanied by a "strawberry tongue," conjunctivitis, or vaginitis, may be seen. As a rule, the rash fades within 3 days of its appearance. This is followed by a full-thickness desquamation, most commonly involving the hands and feet.

Initial treatment of TSS consists of IV fluid replacement, ventilatory support, pressor agents, antibiotics covering *S. aureus* (including MRSA) and *S. pyogenes*. Initial empirical antibiotic regimens may include clindamycin, vancomycin, linezolid, imipenem, meropenem, ticarcillin-clavulanate, or piperacillin-tazobactam.

An in depth discussion of TSS can be found in Chapter 129.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii,* an organism harbored by a variety of ticks. The organism is transmitted to humans through tick saliva at the time of a tick bite or when the tick is crushed while in contact with the host. Many patients do not report tick exposure. Although originally described in the Rocky Mountain region, this disease occurs in other areas of North, South, and Central America. Most reported cases are from the southeastern United States.

The onset of the illness is usually abrupt, with headache, nausea and vomiting, myalgias, chills, and fever. On occasion, the onset is more gradual, with progressive anorexia, malaise, and fever. The disease may last 3 weeks and may be severe with prominent involvement of the CNS, cardiac, pulmonary, gastrointestinal and renal systems, disseminated intravascular coagulation, or shock.

The rash develops on the second to sixth day. It begins with erythematous macules that blanch on pressure, appearing first on the wrists and ankles. These macules spread up the extremities and to the trunk and face. They may become petechial or hemorrhagic (Fig. 110.14). Lesions on the palms and soles are particularly characteristic. Increased capillary fragility and splenomegaly may be present.

The diagnosis of Rocky Mountain spotted fever should be made based on clinical presentation in the ED. Definitive testing is not available in the ED, and may include the Weil-Felix reaction and more specific immunofluorescent procedures. Treatment should be initiated as soon as the disease is suspected on clinical grounds.

Doxycycline is the antibiotic of choice. Failure to administer antibiotics in a timely fashion in this illness dramatically increases morbidity and mortality. Chloramphenicol may be used for patients allergic to tetracyclines and in children younger than 9 years old. Sulfa drugs should be avoided because they may exacerbate the illness. Rickettsiae are routinely resistant to penicillins, cephalosporins, aminoglycosides, and erythromycin. Ehrlichiosis may be difficult to differentiate from Rocky Mountain spotted

Fig. 110.14. Rocky Mountain spotted fever. (Courtesy Jonathan Singer, MD.)

Fig. 110.16. Herpes simplex. (Courtesy Centers for Disease Control and Prevention [CDC] Public Health Image Library, Robert E. Sumpter.)

Fig. 110.15. Herpes simplex virus 1 (HSV-1) infection. (Courtesy David Effron, MD.)

Fig. 110.17. Herpetic whitlow. (Courtesy Jonathan Singer, MD.)

fever clinically and is also reliably treated with doxycycline. Chloramphenicol efficacy in this disease is not established.

An in depth discussion of Rocky Mountain spotted fever can be found in Chapter 126.

Viral Infections

Herpes Simplex Virus

Two known variants of HSV cause human infection: HSV-1 and HSV-2. HSV-1 primarily affects nongenital sites, whereas lesions caused by HSV-2 are found predominantly in the genital area and are typically transmitted primarily by sexual contact.

The characteristic presentation of skin infection with HSV is painful, grouped vesicles on an erythematous base (Fig. 110.15). The lesions are usually localized in a nondermatomal distribution. The skin distribution may become more generalized in patients with atopic dermatitis and other dermatoses. Adults with HSV infection should avoid contact with children with atopic dermatitis, especially in the first 3 to 5 days of infection.

The mouth is the most common site of HSV-1 infections. Children are affected more commonly than adults. Small clusters of vesicles appear but are soon denuded, leaving irregularly shaped, crusted erosions. The severity of gingivostomatitis varies from the presence of small ulcers to extensive ulceration of the mouth, tongue, and gums accompanied by fever and cervical lymphadenopathy (Fig. 110.16). The infection may be so severe that oral fluid intake is difficult, and dehydration may result. Healing typically occurs in 7 to 14 days unless a secondary bacterial infection occurs.

Herpetic whitlow is a herpes infection of the hand, typically affecting the distal phalanx (Fig. 110.17). It may be caused by HSV-1 (60%) and HSV-2 (40%).

HSV-2 infections in men present with either single or multiple vesicles on the penile shaft or glans penis. Fever, malaise, and regional adenopathy may be present. A prodrome of local pain and hyperesthesia may precede the appearance of the cutaneous lesions. The vesicles erode after several days, become crusted, and heal in 10 to 14 days. Infections in women involve the introitus, cervix, or vagina. Vesicles may be grouped or confluent. Herpetic cervicitis or vaginitis may be the cause of severe pelvic pain, dysuria, or vaginal discharge. Recurrence is common, but recurrent episodes tend to be less severe. A correlation based on serologic and epidemiologic data has been discovered between HSV-2 reproductive tract infections and carcinoma of the cervix.

Recommended treatment for a first clinical episode of genital herpes is with acyclovir, famciclovir, or valacyclovir. These agents reduce the duration of viral shedding, accelerate healing, and shorten the duration of symptoms, but they do not prevent recurrent episodes. Prophylactic administration of acyclovir may be effective in ameliorating the severity of recurrent genital herpes, but the effects of long-term administration are unknown.

IV therapy should be considered for immunocompromised patients. A mucocutaneous herpes infection in such patients is potentially fatal, because it has a propensity for generalization and dissemination to the internal organs.

Any vesicular eruption on skin or mucous membranes in a neonate should prompt concern for HSV infection, because there is a high likelihood of dissemination in this group. Unless an alternative diagnosis is established, urgent testing of the vesicle fluid for HSV along with acyclovir therapy is indicated.

Supportive care and pain control are important components of treatment. Systemic analgesics and topical anesthetic agents may be useful. Education of the patient about the prevention or spread of the disease during sexual contact and the birth process is imperative.

An in depth discussion of HSV infection can be found in Chapter 122.

Varicella-Zoster Virus

Varicella. Varicella, or chickenpox, is an infection caused by the varicella-zoster virus. After an incubation period of 14 to 21 days, the illness begins with a low-grade fever, headache, and malaise. The exanthem coincides with these symptoms in children and follows them by 1 or 2 days in adults.

The skin lesions rapidly progress from macules to papules to vesicles to crusting, sometimes within 6 to 8 hours. The vesicle of varicella is 2 or 3 mm in diameter and surrounded by an erythematous border (Fig. 110.18). An unusual form of varicella has larger bullae. The drying of the vesicle begins centrally, producing umbilication. The dried scabs fall off in 5 to 20 days.

Lesions appear in crops on the trunk, where they are seen in the highest concentration, and on the scalp, face, and extremities. The hallmark of varicella is the appearance of lesions in all stages of development in one region of the body. Extensive eruptions are often associated with a high and prolonged fever.

Complications include encephalitis or meningitis, pneumonia, staphylococcal or streptococcal cellulitis, thrombocytopenia, arthritis, hepatitis, and glomerulonephritis. Varicella pneumonia occurs more commonly in adults than in children.

Fig. 110.18. Varicella zoster. (Courtesy Jonathan Singer, MD.)

The illness is self-limited, and treatment is symptomatic. Salicylates should be avoided to minimize the risk of subsequent Reye syndrome. Oral acyclovir may be effective if it can be started within 24 hours of development of rash for patients with chronic respiratory or skin disease. Some studies report a diminution in duration and magnitude of fever and number and duration of lesions with the early use of acyclovir.

Isolation of infected patients is often futile because the disease may be transmitted before the diagnosis is clinically evident. Because the disease has the potential to be contagious until all vesicles are crusted and dried, infected persons should be kept at home until this stage is reached.

Varicella zoster immune globulin (VariZIG) is indicated for administration to high-risk individuals within 10 days (ideally within 4 days) of chickenpox (varicella zoster virus) exposure.[15]

The varicella vaccine is a live attenuated virus; it is highly efficacious and very safe. A single dose is effective in children between the ages of 1 and 13 years. For older children, two doses separated by 4 to 8 weeks are recommended. In addition, the incidence of zoster occurring after vaccination appears to be lower than that of naturally acquired disease.

An in depth discussion of varicella infection can be found in Chapter 122.

Herpes Zoster. Herpes zoster, or "shingles," is an infection caused by the varicella-zoster virus. It occurs exclusively in individuals who have previously had chickenpox. Dermatomal pain may precede the eruption by 1 to 10 days and is variable in intensity; it may be described as sharp, dull, or burning in quality. The rash consists of grouped vesicles on an erythematous base involving one or several dermatomes. The thorax is involved in most cases, and the trigeminal distribution is the next most commonly involved region.

The vesicles initially appear clear and then become cloudy and progress to scab and crust formation. This process takes 10 to 12 days, and the crusts fall off in 2 or 3 weeks (Fig. 110.19). Herpes zoster has a peak incidence in patients 50 to 70 years old and is unusual in children. Although the association with leukemia, Hodgkin's lymphoma, and other malignant neoplasms is well known, rarely does the appearance antedate the diagnosis of such diseases. Most cases of herpes zoster occur in healthy individuals.

Herpes zoster may be transmitted from patients with chickenpox to susceptible individuals. Chickenpox may also be acquired by contact with shingles, although this is less common. It is generally believed, however, that herpes zoster is caused by a

Fig. 110.19. Herpes zoster. (Courtesy David Effron, MD.)

reactivation of latent varicella-zoster virus present since the initial infection. During the latent period between the two illnesses, the virus is thought to reside in dorsal root ganglion cells.

Herpes zoster has a very low mortality rate and is rarely life-threatening, except when dissemination to the visceral organs occurs. Complications include CNS involvement, ocular infection, and neuralgia. Meningoencephalitis, myelitis, and peripheral neuropathy have been reported.

Ocular complications occur in 20% to 70% of cases involving the ophthalmic division of the trigeminal nerve. The severity varies from mild conjunctivitis to panophthalmitis, which threatens the eye. Corneal dendritic lesions may be visible on fluorescein examination. Eye involvement may produce anterior uveitis, secondary glaucoma, and corneal scarring. There is a close correlation between eye involvement and vesicles located at the tip of the nose (Hutchinson's sign).

Herpes zoster generally tends to be more severe in immunosuppressed patients, especially those with acquired immunodeficiency syndrome (AIDS), Hodgkin's disease, or other lymphomas. Cutaneous dissemination occurs more commonly in these patients than in the general population. Visceral and CNS dissemination is also more likely to occur in these patients; therefore, they should be considered for hospitalization.

Antiviral medications are indicated, especially within 48 hours of onset of rash, to decrease the duration of symptoms and associated pain. Antiviral therapy may be initiated with acyclovir, famciclovir, or valacyclovir.[16] Supportive care is important for pain and pruritus control. Burow's solution compresses diluted 1:20 to 1:40 in water may be applied to hasten drying. The administration of corticosteroids is controversial. Steroids may reduce pain and improve sleep and ability to function. Steroids have not been shown to reduce the incidence of postherpetic neuralgia.

IV administration of acyclovir may be of some benefit in the treatment of severe ocular herpes zoster. Treatment includes mydriasis and the application of topical corticosteroids. Unlike the situation with herpes simplex conjunctivitis, eye involvement caused by herpes zoster does not appear to be exacerbated by corticosteroids. Immunization against herpes zoster is recommended in older adults.

Postherpetic neuralgia may occur in 15% of patients and is more commonly in the elderly. Treatments may include opioids, amitriptyline, topical capsaicin, topical lidocaine, topical or oral gabapentin.[17,18]

The varicella vaccine has been shown to boost immunity against herpes zoster virus (shingles) and is recommended for patients 60 years old and older.[19] It reduces the occurrence of shingles and also slightly reduces pain compared with no vaccination in those who ultimately develop shingles.

An in depth discussion of herpes zoster infection can be found in Chapter 122.

Viral Exanthems

An exanthem is defined as a skin eruption that occurs as a symptom of a general disease. In the pediatric population, 72% of cases of fever and rash are caused by viruses, and 20% are caused by bacteria. Approximately 30 enteroviruses, predominantly the coxsackievirus and echovirus groups, and four types of adenoviruses are known to produce exanthems (Fig. 110.20). The exanthems of the coxsackievirus and echovirus are most thoroughly documented. Most viral exanthems are maculopapular, although scarlatiniform, erythematous, vesicular, and petechial rashes are occasionally seen. The eruptions are variable in their extent, are nonpruritic, and do not desquamate. Oropharyngeal lesions may be present.

The classic viral exanthems are rubeola (measles), rubella (German measles), herpesvirus 6 (roseola), parvovirus B19 (erythema infectiosum or fifth disease), and the enteroviruses (echovirus and coxsackievirus). Widespread immunization programs have reduced the incidence of rubeola and rubella.

Fig. 110.20. Enterovirus. (Courtesy Jonathan Singer, MD.)

An in depth discussion of viral infections can be found in Chapter 122.

Roseola Infantum. Roseola infantum, otherwise known as *exanthem subitum* or *sixth disease,* is a benign illness caused by human herpesvirus 6 and human herpesvirus 7 and is typically spread by saliva. It is characterized by fever and a skin eruption. Ninety-five percent of cases are seen in children 6 months to 3 years old. A febrile seizure may occur. The fever typically has an abrupt onset, with temperature rising rapidly to 39° to 41° C, and is present consistently or intermittently for 3 or 4 days, at which time the temperature drops precipitously to normal. The rash typically appears with defervescence. The lesions are discrete pink or rose-colored macules or maculopapules 2 or 3 mm in diameter that blanch on pressure and rarely coalesce (Fig. 110.21). The trunk is involved initially, with the eruption typically spreading to the neck and extremities. The eruptions are occasionally limited to the trunk. The rash clears during 1 or 2 days without desquamation.

Despite the presence of a high fever, the infant usually appears well. Encephalitis is a very rare complication. The prognosis is excellent, and no treatment is necessary.

Measles. Measles, or rubeola, is a highly contagious viral illness spread by contact with infectious droplets, with an incubation period of 10 to 14 days. In recent years, typically less than 100 cases are seen annually in the United States, compared to the 4 to 5 million cases per year prior to immunization. An outbreak in 2014 was seen in the United States, with over 500 cases. Measles is most likely to infect unvaccinated individuals, often including preschoolers in low-income homes or in heavily populated areas. Patients are considered to be contagious from 5 days prior to onset of symptoms until 5 to 6 days after the onset of dermatologic involvement.

Symptoms begin with fever and malaise. The fever usually increases daily in a stepwise manner until the fifth or sixth day of

Fig. 110.21. Roseola.

the illness. Cough, coryza, and conjunctivitis are associated symptoms. On the second day of the illness, Koplik spots, which are pathognomonic of the disease, appear on the buccal mucosa as small, irregular, bright red spots with bluish white centers. Beginning opposite the molars, Koplik spots may spread to involve a variable extent of the oropharynx.

The cutaneous eruption of measles typically begins on the third to fifth day of the illness. Maculopapular erythematous lesions involve the forehead and upper neck and spread to involve the face, trunk, arms, and finally the legs and feet. Koplik spots begin to disappear coincident with the appearance of the rash. By the third day of its presence, the rash begins to fade, doing so in the order of its appearance, and the fever subsides.

Complications may include otitis media, encephalitis, and pneumonitis. Otitis media is the most common complication. Encephalitis occurs in approximately 1 in 1000 cases of measles and carries 15% mortality. Measles pneumonia may also be life-threatening.

Treatment is primarily supportive and should include antipyretics, hydration, and treatment of pruritus. Vitamin A supplements have been associated with reductions of approximately 50% in morbidity and mortality and appear to help prevent eye damage and blindness. If bacterial invasion occurs with otitis or pneumonia, the use of antibiotics is indicated. Isolation of infected children is of limited value because exposure usually occurs before the appearance of the rash. Measles is not contagious after the fifth day of the presence of the rash. Infection confers lifelong immunity.

Postexposure prophylaxis may be administered with the measles virus vaccine or human immunoglobulin.[20]

Rubella. Rubella, or German measles, is a viral illness characterized by fever, skin eruption, and generalized lymphadenopathy. It is spread by droplet contact, and peak incidence is in the winter and early spring. The incubation period is typically 14 to 21 days, and the rash heralds the onset of the illness in children. The maximum time of communicability is in the few days before and 5 to 7 days after the onset of the rash. Infants with congenital rubella may shed virus for more than 1 year. In adults, a 1- to 6-day prodrome of headache, malaise, sore throat, coryza, and low-grade fever precedes the rash. These symptoms generally disappear within 24 hours after the appearance of the skin eruption.

The rash of pink to red maculopapules appears first on the face and spreads rapidly to the neck, trunk, and extremities. Those on the trunk may coalesce, but lesions on the extremities do not. The rash remains for 1 to 5 days, classically disappearing at the end of 3 days. Although clearing may be accompanied by fine desquamation, this sign is usually absent.

The major complications of rubella include encephalitis, arthritis, and thrombocytopenia. The most severe complication is fetal damage. A total of 24% of infected fetuses have a congenital defect. A maternal infection may be determined by obtaining serum for hemagglutination inhibition antibody determinations, acutely and in 7 to 21 days after the first sample onset. A fourfold rise in the titer is diagnostic of rubella infection.

No treatment is required in most cases of rubella. Antipyretics are usually adequate for the treatment of headache, arthralgias, and painful lymphadenopathy.

Erythema Infectiosum. Erythema infectiosum, or "fifth disease," is caused by parvovirus B19 infection and typically affects pediatric patients. It is characterized by mild systemic symptoms, fever in 10% to 15% of patients, and a characteristic rash. Arthralgia and arthritis occur commonly in adults but rarely in children. The rash is intensely red on the face and gives a "slapped-cheek" appearance with circumoral pallor. A reticular maculopapular eruption, which may be noted on the arms, moves caudally to the trunk, buttocks, and thighs. The rash may recur with changes in temperature and exposure to sunlight. The incubation period is usually between 4 and 14 days. The infection is benign and requires supportive care only.

Fungal Infections

Fungal infections may affect the skin, scalp, or mucous membranes. The dermatophytoses are superficial fungal infections that are limited to the skin. Dermatophytes generally grow best in warm, moist environments, and grow only in the keratin or outer layer of the skin, nails, and hair. Any potential dermatophyte infection can be examined under the microscope in a KOH preparation. The specimen is examined for the characteristic branching hyphae of the dermatophytes or the short, thick hyphae and clustered spores of tinea versicolor.

Tinea Corporis

Tinea refers to superficial dermatophytic infection of the skin, hair, and/or nails, usually by the *Trichophyton* organism. Tinea corporis, commonly referred to as "ringworm" infection, presents as a sharply marginated, annular lesion with raised or vesicular margins and central clearing (Fig. 110.22). Lesions may be single or multiple. Other related forms of tinea may be seen, including tinea cruris, which involves the groin, tinea manuum, affecting the hands, and tinea pedis, infection of the feet.

The differential diagnosis of tinea corporis includes erythema migrans, granuloma annulare, psoriasis, cellulitis, and erythrasma.

Infections of the body, groin, and extremities usually respond to topical antifungal agents. A number of effective topical antifungal agents are available, including clotrimazole, haloprogin, miconazole, tolnaftate, terbinafine, naftifine, and others. Two or three daily applications of the cream form of any of these preparations result in healing of most superficial lesions in 1 to 3 weeks.[21]

Tinea Capitis

Tinea capitis is a fungal infection of the scalp. The most common organisms include *Microsporum* and *Trichophyton* species. Although it is often seen in pediatric patients 6 to 10 years old, tinea capitis may also occur in adults. It is more common among

Fig. 110.22. Tinea corporis. (Courtesy David Effron, MD.)

Fig. 110.23. Tinea capitis. (Courtesy David Effron, MD.)

African Americans, for uncertain reasons. Nosocomial transmission of dermatophyte infections, such as *Trichophyton tonsurans,* has also been reported. Alopecia may be seen, typically with thickened, scaly scalp. Broken hairs resembling black dots near the scalp may be seen. Hair loss is the result of hyphae growing within the hair shaft, rendering it fragile, so that the hair strands break off 1 to 2 mm above the scalp. The disease may be transmitted by close child-to-child contact and contact with household pets, hats, combs, barber's shears, and similar items. Complications may include kerion formation, lymphadenitis, bacterial pyoderma, pigmenting pityriasis alba, id reaction after treatment, secondary bacterial infection, and scarring alopecia.

The differential diagnosis of tinea capitis includes alopecia areata, atopic dermatitis, nummular eczema, bacterial infection, psoriasis, seborrheic dermatitis, "tinea" amiantacea, trichotillomania (hair pulling), and Langerhans cell histiocytosis.

A KOH preparation is not helpful in the presence of a kerion or in the absence of alopecia. The diagnosis is typically made based on clinical presentation. If in question, a fungal culture specimen may be obtained.

Systemic therapy is required for tinea capitis, due to fungal invasion of the hair follicles. Treatment should be with a systemic antifungal agent, such as terbinafine or griseofulvin. Therapy should be given for 4 to 6 weeks. The patient should be referred for outpatient follow-up with primary care within 4 weeks. Alternative therapy includes fluconazole or itraconazole for 4 to 6 weeks. Family members should be evaluated for possible infection.

Kerion

A kerion is a fungal infection affecting hair follicles that is characterized by intense inflammation, and a boggy, erythematous mass, typically affecting the scalp (Fig. 110.23). The lesion may contain frank pus. The inflammation is generally uniform and does not display satellite lesions. It usually affects the scalp and is more common in children and in African Americans. Local alopecia and scarring can ensue. Lymphadenopathy may be present. Accurate differentiation of a kerion with and without superinfection can be challenging. Wood's lamp examination and a scalp scraping and KOH preparation can help differentiate kerion from secondary bacterial infection.

Kerions are treated the same as tinea capitis, with systemic antifungal agents for 6 to 8 weeks. If bacterial superinfection exists, an antibiotic is added. Antibiotic options include oral cephalexin, dicloxacillin, or clindamycin. Clindamycin is recommended when community-acquired MRSA is a concern. Surgical drainage of kerions is not helpful and should be avoided.

Tinea Pedis

Tinea pedis, commonly referred to as *athlete's foot,* presents with scaling, maceration, vesiculation, and fissuring between the toes and on the plantar surface of the foot. Common etiologies include *Trichophyton rubrum, Trichophyton interdigitale,* and *Epidermophyton floccosum.* Secondary bacterial infection may occur. The vesicular pustular form of tinea pedis should be considered when vesicles and pustules on the instep are noted. Interdigital lesions may cause minimal symptoms and serve as a portal of entry for bacterial cellulitis. The differential diagnosis includes contact dermatitis and dyshidrotic eczema. A KOH preparation is helpful to differentiate between these processes. Treatment options include topical antifungal agents, such as terbinafine twice daily for 2 to 4 weeks; miconazole cream, powder, or spray twice daily for 2 to 4 weeks; and clotrimazole cream, solution, or lotion twice daily for 2 to 4 weeks. For severe disease or if topical treatment has failed, systemic therapy may be instituted with terbinafine for 2 weeks, fluconazole weekly for 2 to 4 weeks, or griseofulvin daily for 2 weeks.

Tinea Versicolor

Tinea versicolor, or pityriasis versicolor, is a superficial fungal infection caused by genus *Malassezia*. Superficial hypopigmented or hyperpigmented patches occur mainly on the chest and trunk but may extend to the head and limbs. As the name implies, lesions can be a variety of colors, including pink, tan, and white. The disease may be associated with pruritus. On physical examination, a fine subtle scale is noted that may appear hypopigmented (Fig. 110.24). Pale yellow or orange fluorescence under Wood's light may be seen. The differential diagnosis includes vitiligo and seborrheic dermatitis. A KOH preparation reveals short hyphae mixed with spores ("chopped spaghetti and meatballs").

Tinea versicolor may be treated with topical antifungal agents, such as 2.5% selenium sulfide shampoo, imidazole creams, and ketoconazole cream or foam. Systemic therapy may be indicated, such as oral ketoconazole. Recurrence is common. Pigmentation may not return to normal for months.

Tinea Unguium (Onychomycosis)

Tinea unguium may be caused by dermatophytes, candida, or other fungal species. Paronychia or untreated tinea pedis may be predisposing factors. Onychomycosis presents with toenails or fingernails that are thickened, opaque, cracked, or destroyed. Subungual debris is present, and the nail may contain yellowish longitudinal streaks (Fig. 110.25). The nail of the great toe is most

Fig. 110.24. Tinea versicolor.

Fig. 110.25. Onychomycosis.

commonly involved. Differential diagnosis includes tinea pedis, psoriasis, or warts.

Topical therapy of the nails alone rarely results in a cure because penetration into the nail keratin is poor. Fingernails typically respond more rapidly to therapy than toenails do. Involvement of one or two nails may be treated with topical antifungal agents. More extensive infection requires systemic therapy with an antifungal agent, such as terbinafine or itraconazole.[22] Third line agents may include griseofulvin or ketoconazole, which require prolonged courses, with high relapse rates and numerous side effects. Treatment failures or relapses are common, and they may be attributed to poor patient compliance, low bioavailability, lack of drug penetration into the nail, drug resistance, and drug interactions. Additional therapies may include surgical removal of the nail, photodynamic therapy, or laser therapy.

Fig. 110.26. Candida intertrigo.

Candidiasis

Infection by *Candida albicans* may occur in patients of all ages. Many conditions predispose to infection, including diabetes mellitus, HIV infection, pregnancy, obesity, smoking, malnutrition, malignancy, or treatment with corticosteroids, antibiotics, or immunosuppressive agents.

Oral Candidiasis. Oral candidiasis ("thrush") is the most common clinical expressions of *Candida* infection. It is common in newborns, elder persons, immunosuppressed individuals, or persons wearing dentures. Oral candidiasis is common in newborns, with one-third being affected by the first week of life. It appears as patches of white or gray friable material covering an erythematous base on the buccal mucosa, gingiva, tongue, palate, or tonsils. Fissures or crust at the corners of the mouth may be present. The differential diagnosis of oral candidiasis includes lichen planus (which unlike *C. albicans* is not easily scraped off), or hairy leukoplakia. Oral mucous membrane infection with *C. albicans* is an AIDS-defining illness. If the patient does not use dentures and has not taken antibiotics recently, underlying immunosuppression should be considered.

Treatment of oral candidiasis may be undertaken with topical antifungal agents, such as clotrimazole troches five times daily, or oral nystatin suspension four times daily, or nystatin pastilles four times daily. Treatment is continued for 5 to 7 days after the lesions disappear. For esophageal candidiasis, systemic antifungal therapy is always required. Oral fluconazole, IV fluconazole, or amphotericin B are options.

Cutaneous Candidiasis. Cutaneous candidiasis favors the moisture and maceration of the intertriginous areas—the interdigital web spaces, groin, axilla, and intergluteal and inframammary folds. Lesions appear as moist, bright red macules rimmed with a collarette of scale, with small satellite papules or pustules are just peripheral to the main body of the rash (Fig. 110.26). These satellite lesions are typical indicators of a *Candida* infection. Intertriginous lesions are prone to bacterial superinfection.

The differential diagnosis of cutaneous candidiasis includes contact dermatitis, tinea cruris, intertrigo, herpes simplex such as

herpetic whitlow, and folliculitis. Candidiasis, however, is less sharply demarcated than tinea cruris and brighter red than intertrigo. A KOH preparation of a specimen taken from a pustule and roof of the lesion will reveal hyphae and pseudohyphae.

Treatment of intertriginous lesions requires the removal of excessive moisture and maceration. Lesions should be exposed to circulating air from a fan several times a day. Inflammatory lesions are either soaked in or covered with compresses of cool water or Burow's solution. Topical imidazole creams, such as clotrimazole and miconazole, are applied sparingly to affected areas. Prescription creams, such as econazole, ketoconazole, and sulconazole, are also effective.

Vulvovaginal Candidiasis. Vaginal candidiasis accounts for 20% to 25% of vaginitis. It has been estimated that 75% of women will experience vaginal candidiasis at least once. Predisposing factors include diabetes, pregnancy, immunosuppression, and hormone replacement therapy. Pruritus is a common presenting complaint. Other symptoms may include dyspareunia, dysuria, or vaginal burning. Differential diagnosis includes sexually transmitted infection, bacterial vaginosis, and urinary tract infection. A KOH preparation will reveal hyphae and budding yeast forms.

A single 150-mg dose of fluconazole is recommended for the treatment of uncomplicated Candida vulvovaginal candidiasis. For mild cases, over the counter intravaginal imidazoles may be effective.

Infestations

Scabies

Scabies, the human itch mite, from the Latin word *scabere,* to scratch, is a human skin infestation caused by the penetration of the obligate human parasitic mite *Sarcoptes scabiei-var hominis* into the epidermis. It occurs more commonly in winter months. It is transmitted mostly through close personal contacts. It may also be spread by exposure to fomites, because the scabies mite can live off the human skin for 3 days. The average number of mites a host harbors is usually less than 20. Scabies presents with intense pruritus and rash, which usually develop after 1 to 8 weeks following exposure. The pruritus is typically worst at night. Clinical findings include small (<5 mm) papules or pustules and small raised or flattened burrows. Classically scabies affects several skin sites, and they are commonly distributed between the digital webs, sides of the fingers, volar aspects of the wrists and lateral palms, trunk, elbows, axillae, scrotum, penis, and the areola in women (Figs. 110.27 and 110.28). Scabies in infants and young children often may present with generalized involvement of the skin, including the face, scalp, palms, and soles. In infants, the most common presenting lesions are papules and vesicopustules.

In *crusted scabies* (previously known as *Norwegian scabies*), hyperkeratotic plaques develop diffusely, often on the palmar and plantar regions, with thickening and dystrophy of the toenails and fingernails. Typically with crusted scabies, a host may harbor over a million mites. Individuals with human immunodeficiency virus infection, elders, and patients with medication-induced immunosuppression are at risk of developing crusted scabies.

Scabies is a clinical diagnosis and is based primarily on the history and examination. The definitive diagnosis is made by the microscopic identification of the scabies mites, eggs, or fecal pellets *(Scybala).* There are various techniques for specimen collection, including lesion scraping, or skin biopsy.[23] Because these techniques may be impractical in the ED, treatment should be instituted based on a clinical suspicion of the diagnosis of scabies.[24]

The differential diagnosis of scabies should include pityriasis rosea, papular urticaria, secondary syphilis, folliculitis, contact dermatitis, atopic dermatitis, seborrhea, dermatitis herpetiformis, lichen planus, and psoriasis.

The first line treatment of scabies is topical permethrin 5% cream (Elimite).[25] Permethrin cream should be applied from the neck down, covering all areas of the body including under the nails, in the umbilicus, around the nipples, and genitals. Face and scalp should be treated in affected infants and young children. Preferably, it should be applied prior to bedtime, left on overnight, and then washed off 8 to 12 hours later. It is vital to treat not only the patient but family members and close contacts as well. A second treatment should be administered in 1 to 2 weeks. Alternative therapy may include single dose of ivermectin 200 µg/kg by mouth, or topical crotamiton cream. For heavily infested and or immunocompromised patients, it is recommended that ivermectin be given once a week for 2 to 3 weeks. One recent study demonstrated the efficacy of empirical therapy with a single dose of ivermectin among homeless persons with pruritus. Lindane, a previously used agent, has fallen out of favor due to potential neurotoxicity and resistance.

Equally important in the treatment is the decontamination of the clothing, bed linens, and towels by washing them in hot water and hot machine drying. Items that cannot be washed and or dry-cleaned can be decontaminated by sealing the items in an airtight container for at least 72 hours.

Fig. 110.27.. Scabies. (Courtesy David Effron, MD.)

Fig. 110.28. Scabies.

Pediculosis

Pediculosis may affect the scalp hair (pediculosis capitis, caused by the mite *Pediculus humanus capitis*), body (pediculosis corporis, caused by *Pediculus humanus corporis*), or genitalia (pubic lice, caused by *Pthirus pubis*). Infestation is typically associated with significant pruritus. Lesions may be erythematous macules, papules, or wheals.

Pediculosis capitis is the most common form of lice infestation in the United States and is frequently seen in children 3 to 12 years old. An estimated 10% to 40% of school children in the United States have been infected with pediculosis capitis. It can be transmitted by sharing hair brushes, combs, and hats, and through contact with infested furniture, clothing, and linens. Hygiene and hair length are unrelated to infection. Incidence is greatest during autumn. Pediculosis capitis is less common among African American patients. Scalp, occipital, and postauricular pruritus are common in patients with pediculosis capitis. Neck and auricular erythema, papules, vesicles, and lymphadenopathy may be seen.

Pediculosis corporis can present with intense pruritus and erythematous macules or wheals. Pediculosis corporis typically occurs in patients with poor hygiene or living in crowded conditions.

Pediculosis pubic ("crabs") is a sexually transmitted disease and is most commonly seen among young adults. Other concurrent sexually transmitted diseases should be considered and ruled out.

The differential diagnosis includes conditions, such as tinea capitis, seborrheic dermatitis, atopic dermatitis, eczema, scabies, folliculitis, and contact dermatitis.

The diagnosis of pediculosis is made by identification of lice or nits on the hair shaft (Fig. 110.29). Nits, which appear as white dots or grains, are more easily identified than the actual louse. Nits fluoresce with the Wood's lamp. Examination with a louse comb improves the diagnostic accuracy and is faster than direct visualization.

Therapy for pediculosis should be initiated with a pediculicide, such as permethrin 1% (Nix, Lyclear), which is effective in 90% of cases.[26] Permethrin should be applied to the dry scalp and hair and remain for 10 minutes. Treatment should be repeated in 1 week to kill any newly hatched lice. Spinosad 0.9% suspension (Natroba) is a new agent with demonstrated pediculicidal efficacy.[27,28] Spinosad 0.9% is approved for use in patients older than 4 years old and is also effective against permethrin-resistant populations of lice. Spinosad is ovicidal, killing both eggs (nits) and lice; thus extensive nit combing is not necessary. However, the cost may be prohibitive. Oral ivermectin (Stromectol, Mectizan) has demonstrated pediculicidal efficacy.[29,30] Topical ivermectin lotion has also demonstrated safety and efficacy.[31] Other treatments may be considered, including malathion, albendazole or thiabendazole, benzyl alcohol lotion (Ulefsia), or levamisole (Ergamisol).[32] Lindane, an older therapy, should be reserved for unusual cases of resistance to first line agents, because of neurotoxicity and poor pediculicidal activity. Over the counter products have variable success rates, in part due to resistance. Nits should be removed with a special fine-toothed comb. The environment should also be treated. Hats, hair brushes and combs, and linens as well as clothing should be treated. Items should be boiled or washed and dried at high temperatures. Floors and furniture should be vacuumed. Fumigation is not necessary. Family members should be examined and treated if infested. Sexual partners of patients with pediculosis pubis should be treated. The American Academy of Pediatrics recommends that children do not miss school because of head lice.[33]

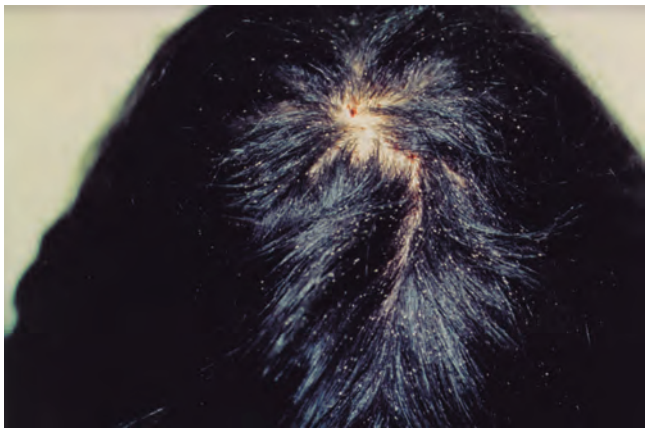

Fig. 110.29. Nits as seen in head lice. (Courtesy David Effron, MD.)

Bed Bugs

Bed bugs *(Cimex lectularius)* appear brown, approximately 5 to 6 mm in length. Bed bugs may be vectors for many fungi, viruses, and bacteria, including MRSA and vancomycin-resistant *Enterococcus faecium*, although human illness from bed bugs as carriers has not been documented.[34] Bed bugs are found not only in linens, but on furniture, luggage, and in walls, baseboards, and buildings. They often feed on humans at night with a painless bite.

Clinical presentation may appear as erythematous welts, macules, papules, urticaria, purpura, vesicles, or bullae, with intense pruritus. The distribution is often over uncovered areas, such as arms, legs, and shoulders. Lesions resolve spontaneously in 1 to 2 weeks. Symptomatic treatment should be undertaken with antihistamines and topical corticosteroids.[35,36] A patient with a scaly, persistent pruritic eruption should be treated with permethrin 5% cream, ivermectin, or crotamiton. Eradication from the environment is challenging, due in part to increasing resistance to insecticides. Eradication methods may include insecticides, heat, steam, freezing, or vacuuming. The hazards of widespread insecticide use, including potential for malignancy or CNS adverse effects, have created a dilemma of eradication.

ALLERGIC REACTIONS

An in depth discussion of systemic allergic reactions and anaphylaxis can be found in Chapter 109.

Contact Dermatitis

Contact dermatitis is an inflammatory reaction of the skin to a chemical, physical, or biologic agent, which acts as an irritant or allergic sensitizer. Allergic contact dermatitis is a form of delayed hypersensitivity mediated by lymphocytes sensitized by the contact of the allergen to the skin. It is less common than irritant contact dermatitis. Caustics, industrial solvents, and detergents are common causes of irritant dermatitis. Clothing, jewelry, soaps, cosmetics, latex, plants, and medications contain allergens that commonly cause allergic contact dermatitis. The most common allergens include rubber compounds; plants of the *Toxicodendron* species, including poison ivy, oak, and sumac; nickel, often used in jewelry alloys; paraphenylenediamine, an ingredient in hair dyes and industrial chemicals; and ethylenediamine, a stabilizer in topical medications.

The primary lesions of contact dermatitis are papules, vesicles, and bullae on an erythematous base. Streaky, linear, intensely pruritic lesions are characteristic. A pattern in the region in contact with the allergen is typical (Fig. 110.30). Eruptions associated with contact dermatitis can appear as soon as several hours after the exposure or may be delayed for days.

Fig. 110.30. Neomycin allergy. (Courtesy Joanna Marco, MD.)

Treatment of contact dermatitis includes avoidance of the irritant or allergen and treatment of inflammation. Low-potency topical steroid creams may be applied to erythematous areas around natural orifices and medium-potency creams can be used elsewhere. Topical steroids are ineffectual on blistered areas. Oozing or vesiculated lesions should be treated with cool wet compresses of Domeboro or Burow's solutions (aluminum acetate). Topical baths, available over the counter, may also be comforting. Systemic antihistamines, such as hydroxyzine and diphenhydramine, may help control pruritus; nonsedating antihistamines are preferred for use during the day. If present, secondary bacterial infection must also be treated.

Urticaria

Urticaria may occur in isolation or as part of a systemic anaphylactic reaction. The following discussion pertains to urticaria occurring in the absence of systemic symptoms. Anaphylactic reactions and angioedema are discussed in Chapter 109. Approximately 15% to 20% of the population experiences urticaria during their lifetime. Acute urticaria is seen in both sexes and is more likely to have an allergic cause. Chronic urticaria is more common in women in their 40s and 50s. Half of all patients with chronic urticaria have the disease for 5 years and one-fourth for 20 years.

Various mediators, including histamine, bradykinin, kallikrein, and acetylcholine, are thought to play a role in urticaria production. Urticaria may be initiated by immunologic or nonimmunologic mechanisms. Nonimmunologic urticaria may be produced by degranulation of mast cells, which may be caused by a number of foods and drugs, including aspirin and narcotics.

Almost any medication may produce urticaria, although penicillin and aspirin are the most common. Traces of penicillin may be present in dairy products, as well as in medications. The mechanism of production of urticaria by aspirin is unknown but is probably nonimmunologic, and the effects of aspirin may persist for a number of weeks after ingestion. The role of medications in the production of urticaria is discussed in the section on drug reactions. Substances that can cause urticaria by contact with the skin include foods, textiles, animal dander and saliva, plants, topical medications, chemicals, and cosmetics. A variety of food allergies, such as seafood, tree nuts, peanuts, and eggs, may result in urticaria. In addition, foods such as lobster and strawberries can release histamine through a nonimmunologic mechanism.

Fig. 110.31. Urticaria. (Courtesy David Effron, MD.)

Infection is a common cause of urticaria. Viral infections that produce urticaria include rhinovirus, rotavirus, hepatitis, mononucleosis, and coxsackievirus infections. Occult infections with *Candida,* the dermatophytes, bacteria, viruses, and parasites may also cause urticaria.

Inhalation of pollens, mold, animal dander, dust, plant products, and aerosols may produce urticaria. Respiratory symptoms may accompany the dermatosis, and a seasonal pattern of occurrence may be present. Stings and bites of insects, arthropods, and various marine animals may also produce an urticarial eruption.

On occasion, patients with systemic lupus erythematosus, lymphoma, carcinoma, hyperthyroidism, rheumatic fever, and juvenile rheumatoid arthritis develop an urticarial eruption.

A number of physical agents produce urticaria. Dermatographism is present when firm stroking of the skin produces an urticarial wheal within 30 minutes and is the most common form of physical urticaria. Pressure urticaria is distinct from dermatographism in that the onset of urticaria is delayed by 4 to 8 hours after the application of physical pressure.

Cold urticaria may be either familial or, more commonly, acquired. Cold urticaria may also be associated with underlying illness, such as cryoglobulinemia, cryofibrinogenemia, syphilis, and connective tissue disease. Nonsedating antihistamines, such as rupatadine, help suppress primary cold urticaria.[37] Antihistamines taken 30 to 60 minutes before cold exposure may be helpful. Cholinergic urticaria is induced by exercise, heat, or emotional stress. It may be associated with pruritus, nausea, abdominal pain, and headache. The lesions of cholinergic urticaria are wheals 1 to 3 mm in diameter surrounded by extensive erythematous flares and, occasionally, satellite wheals. Nonsedating antihistamines are generally used to treat cholinergic urticaria.

Heat is a rare cause of hives. Solar urticaria, also uncommon, is confined to sun-exposed areas of skin and clears rapidly when the light stimulus is removed. Extensive sun exposure may cause wheezing, dizziness, and syncope in a susceptible individual. Sunscreens have not been proven to be effective for the prevention of solar urticaria. Phototherapy may be used to induce tolerance.

Urticaria appears as edematous plaques with pale centers and red borders and is easily recognizable (Fig. 110.31). Individual hives are typically transient, lasting less than 24 hours, although

new lesions may continuously develop, which represents localized dermal edema produced by transvascular fluid extravasation.

The differential diagnosis of urticaria includes drug eruption, exanthems, erythema multiforme, erythema marginatum, and juvenile rheumatoid arthritis.

Treatment of urticaria involves the removal of the inciting factor, when applicable, and the administration of antihistamines or other antipruritics. Hydroxyzine (Atarax, Vistaril) is usually effective in providing symptomatic relief. For chronic urticaria, long-term therapy with antihistamines may be needed. Nonsedating antihistamines are preferred. Cetirizine, fexofenadine, or loratadine can be used. A single dose of an H_2 blocker may be added.

Steroids may be a useful adjunctive therapy.[38] Patients with moderate or severe urticaria may benefit from prednisone or dexamethasone. Patients with recurrent urticaria may benefit from longer courses of oral steroids (14 to 21 days with a taper). Chronic administration of steroids is not recommended.

Patients with chronic urticaria may be treated with a prescription for a combination of an H_1 and H_2 antihistamine. Strong evidence supporting addition of an H_2 blocker is lacking.[39] For patients with recurrent urticaria, a prescription of injectable epinephrine may be indicated.

Poison Ivy

Toxicodendron species often result in vesicular or bullous eruptions. Oozing, crusting, scaling, and fissuring may be found along with lichenification in chronic lesions. The distribution of the eruption depends on the specific contact and may be localized, asymmetric linear, or unilateral (Fig. 110.32). Mucous membranes are usually spared unless they are directly exposed to the inciting agent. Sensitization to poison ivy results in sensitization to other plants in this family, such as cashew, mango, lacquer, and ginkgo trees.

In addition to the aforementioned treatment regimens for contact dermatitis, a course of systemic corticosteroids may be indicated to treat *Toxicodendron*-associated dermatitis. A tapering dose of prednisone for 21 to 30 days may be indicated to prevent rebound of the disease. Patients should be counseled to wash all clothes or items that might have contacted the plant because the irritant plant oil can persist. Once the offending agent is reliably removed from the skin and clothes, ongoing outbreak is attributable to the initial contact, not spread from the serous fluid from the bullae. The patient is not contagious to others unless there is direct contact with the plant oil in people who are sensitized.

DRUG REACTIONS

Reactions to medications are common and are estimated to occur in 1% to 5% of patients. Cutaneous reactions are the most common type of reaction. Many medications have the potential to produce a drug reaction. Patients at higher risk of drug reactions include those with immunodeficiency, certain infections, and genetic predisposition. The most common eruptions are a morbilliform rash (Fig. 110.33), urticaria, or fixed drug eruption.[40] More severe reactions may include vasculitis, erythema nodosum, angioedema, anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, blistering dermatoses, drug-induced lupus, lichenoid drug eruptions, psoriasiform drug eruptions, drug-induced neutrophilic dermatoses (ie, Sweet's syndrome, erythema nodosum, and pyoderma gangrenosum), and cutaneous lymphoma-like drug reactions.[41,42]

Drug reactions often appear within 4 to 21 days after the drug is taken. Skin lesions may appear after a drug has been discontinued and may worsen if the drug or its metabolites persist in the system. Special note should be made of penicillin, because it is a common cause of drug reaction. Serum sickness and urticaria are common manifestations of penicillin allergy. Geriatric patients, patients with HIV infection, atopic patients, and those with a history of hay fever, asthma, or eczema are at increased risk.

A variety of skin reactions are associated with drug reactions. Exanthematous drug eruptions, including maculopapular and morbilliform drug eruption, are the most common type of cutaneous manifestation and account for over 80% of reactions.[43] Clinical presentation is typically a widespread symmetric eruption of pink or red macules and papules which may become confluent. Severe cases may progress to exfoliative dermatitis.

Other presentations may include urticarial, eczematous drug rash, vasculitis, photosensitive drug reactions, or fixed drug eruption. Fixed drug eruptions appear and recur at the same anatomic site after repeated exposure to the same drug. The lesions are usually sharply marginated and round or oval. They may be pigmented, erythematous, or violaceous. Pruritus may be prominent.

Treatment of drug eruptions begins with discontinuation of the inciting agent. Most cutaneous drug reactions fade within 1 week of discontinuation. Antihistamines, H_2-antagonists, and topical or systemic steroids may be indicated.

Fig. 110.32. Toxicodendron (poison ivy).

Fig. 110.33. Morbilliform drug eruption. (Courtesy David Effron, MD.)

Severe reactions, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, and hypersensitivity reactions warrant hospitalization.

INFLAMMATORY CONDITIONS

Atopic Dermatitis

Atopic dermatitis is a common dermatologic condition often referred to as *eczema* or *chronic dermatitis*. Atopic dermatitis is the cutaneous manifestation of an atopic state, and although it is not an allergic disorder, it is associated with allergic diseases, such as asthma and allergic rhinitis. Patients with atopic dermatitis are known to have abnormalities of both humoral and cell-mediated immunity. The exact mechanism is unclear, but eosinophil, mast cell, and lymphocyte activation triggered by increased production of interleukin-4 by specific T helper cells seems to be involved. The course of atopic dermatitis involves remissions and exacerbations. More than 90% of patients have the onset of atopic dermatitis before 5 years old.

Atopic dermatitis is an inflammatory skin condition. Diagnostic criteria include itchy skin plus three or more of the following: history of flexural involvement, generalized dry skin in the past year, history of asthma or hay fever, onset of rash before 2 years old, and flexural dermatitis.

Skin lesions generally appear as inflammatory thickened, papular, or papulovesicular lesions. The skin is typically dry and may be scaly, but in the acute phase, it may also be vesicular, weeping, or oozing. In the chronic stage, lesions are thickened and lichenified.

The distribution of lesions varies with the age of the patient. In infants, inflammatory exudative plaques are seen on the cheeks, on the extensor surfaces, and in the diaper area. Older children and adults have lesions in the antecubital and popliteal flexion areas, neck, face, and upper chest. Infantile atopic dermatitis usually begins in the fourth to sixth month of life and improves by the third to fifth year of life. The childhood form occurs between 3 and 6 years old and resolves spontaneously or continues into the adult form.

Intense pruritus is a hallmark of atopic dermatitis. During flares, patients may present with complaints of intense itching and failure of routine treatments to control their symptoms. Patients may also present with secondary infections. The itching may be focal or generalized, is worse during the winter, and is triggered by increased body temperature and emotional stress. It may be particularly annoying at night. Excoriations may be prominent, and secondary bacterial infection of excoriated lesions is common. Repeated scratching and rubbing produce lichenification, a condition of hyperpigmentation, thickening of the skin, and accentuation of skin furrows. Lichenification is a common feature of chronic atopic dermatitis.

Treatment should be aimed at control of inflammation, dryness, and itching. Management includes a careful review of daily skin care with patients or caregivers. General recommendations for all patients include avoidance of nonspecific skin irritants, wool, nonessential toiletries, and detergents and use of cotton clothing as much as possible.

Topical corticosteroids are the cornerstone of therapy and are often best prescribed in ointment form. Approximately 80% of patients have improvement of symptoms with topical steroid treatment. When the dermatitis is severe, the application of a fluorinated corticosteroid ointment such as half-strength betamethasone valerate is recommended to affected areas three times a day. Fluorinated corticosteroids should not be used on the face, because they can produce cutaneous atrophy. Milder corticosteroid preparations, such as 0.025% triamcinolone ointment, may be used on the face and intertriginous areas. Patients with extremely severe disease may require systemic steroids. Ultraviolet B treatment is moderately effective. Cyclosporine and other immunosuppressant agents are being used with some promising benefit. Further studies are needed to determine ideal dosing and safety profiles for these agents.

Skin dryness is treated with lubricating ointments such as Vaseline or 10% urea in Eucerin cream (not lotion). Treatment of exudative areas includes the application of wet dressings, which are useful for their moisturizing, antiinflammatory, and antipruritic actions. Two or three layers of gauze soaked in Burow's solution should be applied for 15 to 20 minutes four times a day for exudative lesions. Antihistamines may be helpful in reducing the pruritus and are also useful for their sedative and soporific effects, although there is no convincing evidence that H_1 antihistamines decrease itching in patients with atopic eczema.

Inpatient admission is a consideration for those patients who have generalized erythema and exfoliation (erythroderma) or intractable itching in that skin breakdown and severe secondary bacterial or viral skin infections may occur.

Patients with atopic dermatitis are susceptible to infection and colonization by a variety of organisms because of their defective skin barrier functions and local skin immunodeficiency. Widespread disseminated viral infections, such as eczema molluscum, eczema vaccinatum, and eczema herpeticum, and recurrent staphylococcal pustulosis are especially concerning.

Pityriasis Rosea

Pityriasis rosea is a mild skin eruption predominantly found in children and young adults. The etiology is unknown, although viral, bacterial, and fungal etiologies have been implicated. Ages 10 to 35 years are commonly affected. Clinical presentation includes multiple pink or pigmented oval papules or plaques 1 to 2 cm in diameter on the trunk and proximal extremities. A history may reveal an initial larger patch ("herald patch") that precedes the widespread eruption (Figs. 110.34 and 110.35). Mild scaling may be present. The lesions are parallel to the ribs, forming a Christmas tree–like distribution on the trunk and extremities. Oral lesions are rare. In children, papular or vesicular variants of the disease may occur. The eruption is usually asymptomatic, although pruritus may be present. The differential diagnosis includes tinea corporis, guttate psoriasis, lichen planus, drug eruption, Lyme disease, and secondary syphilis.

Pityriasis rosea is self-limited, resolving in 8 to 12 weeks. Recurrences are rare. Treatment should include supportive care, including alleviation of pruritus. Topical zinc oxide and calamine lotion are useful for pruritus. If the disease is severe or widespread (eg, vesicular PR), topical or oral steroids may be used. No restriction of activity or isolation is indicated.

Fig. 110.34. Herald patch of pityriasis rosea.

Fig. 110.35. Pityriasis rosea.

Fig. 110.36. Erythema multiforme.

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

Kawasaki disease (mucocutaneous lymph node syndrome) is one of the most common vasculidities of childhood. It is seen in infants and young children. The peak age is between 1 and 2 years old. The disease is very uncommon in children older than 14 years old or in adults. It is more common in boys. Although cases of Kawasaki disease have been reported in children of all ethnic origins, the highest incidence is among children of Asian descent. The disease typically occurs in winter and spring and is usually self-limiting, resolving spontaneously without treatment within 2 to 4 weeks. However, 15% to 20% of cases will have complications, such as damage to coronary arteries, leading to myocardial infarction and heart failure.

Clinical features are characterized by three phases. The acute febrile period (phase I) is manifested by the abrupt onset of fever, lasting approximately 12 days. During phase I, cutaneous findings include erythematous lesions and on the palms and soles. Within 2 days, the blotchy, erythematous, macular lesions spread to the extremities and trunk. Nonexudative injected conjunctivae, seen in approximately 90% of patients, may be present for 1 to 3 weeks. Diffuse oropharyngeal erythema with "strawberry" tongue is often present. Symptoms of diarrhea, arthritis, and photophobia may be present. In the subacute phase (phase II), desquamation, thrombocytosis, arthritis, arthralgias, and carditis may be present. This phase may last 30 days. There is a high risk for sudden death during this phase of the illness if it has gone untreated. During the convalescent phase (phase III), which occurs within 8 to 10 weeks after the onset of the illness, most signs of the illness have resolved. Coronary aneurysms present in 25% of cases and may be diagnosed by echocardiography or coronary angiography.

For epidemiologic surveillance, the Centers for Disease Control and Prevention (CDC) defines a case of Kawasaki disease as illness in a patient with fever of 5 or more days duration, and the presence of at least four of the following five clinical signs:

- Rash
- Cervical lymphadenopathy (at least 1.5 cm in diameter)
- Bilateral conjunctival injection
- Oral mucosal changes
- Peripheral extremity changes.

The diagnosis is typically made based on clinical findings. Laboratory tests that support the diagnosis include elevated liver function tests, leukocytosis, thrombocytosis and an elevated C-reactive protein (CRP). The ESR is elevated during phase II and returns to normal in phase III. Pyuria may be seen on urinalysis. Electrocardiography (ECG) may show PR and QT prolongation or acute ST/T wave changes.

Management of Kawasaki disease includes hospital admission, high dose intravenous immune globulin (IVIG) (2 g/kg single dose) therapy, and aspirin therapy (80 to 100 mg/kg per day). Treatment with IVIG within the first 10 days of illness reduces the incidence of coronary artery aneurysms fivefold compared with children not treated with IVIG. Early cardiology evaluation is important to identify and treat possible coronary artery involvement.

An in depth discussion of Kawasaki disease can be found in Chapter 170.

Erythema Multiforme

Erythema multiforme is considered to be a hypersensitivity reaction, and it may be caused by a drug reaction; HSV infection and other viral infections, especially hepatitis and influenza A; fungal diseases, such as dermatophytosis, histoplasmosis, and coccidioidomycosis; and bacterial infections, especially streptococcal infections and tuberculosis. Various collagen vascular disorders have been known to precipitate erythema multiforme, including rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and periarteritis nodosa. Pregnancy and various malignant neoplasms have also been associated with erythema multiforme. The etiology is unknown in approximately 50% of cases. Differential diagnosis includes urticaria, scalded skin syndrome, pemphigus, and pemphigoid and viral exanthems.

Erythema multiforme is an acute, usually self-limited disease. It is characterized by skin lesions that are erythematous or violaceous macules, papules, vesicles, or bullae. Their distribution is often symmetric, most commonly involving the soles and palms, the backs of the hands or feet, and the extensor surfaces of the extremities. The presence of lesions of the palms and soles is particularly characteristic. The target lesion with three zones of color is the hallmark of erythema multiforme (Fig. 110.36). It is a central, dark papule or vesicle that is surrounded by a pale zone, a halo of erythema, and is commonly found on the hands or wrists.

Treatment begins with treatment of the underlying cause. Mild forms with no systemic symptoms, lesions limited to extremities,

and no mucous membrane involvement typically resolve spontaneously in 2 or 3 weeks. Patients with lesions on the trunk and patients who are immunocompromised, especially those with multiple lesions, require a course of systemic steroids for 14 to 21 days with a taper and urgent dermatology referral. Patients with mucous membrane involvement, systemic symptoms, or vesicle formation raise concern for Stevens-Johnson syndrome.

Toxic Epidermal Necrolysis

Stevens-Johnson syndrome and toxic epidermal necrolysis are considered a continuous spectrum of the same disease, an immune-complex–mediated hypersensitivity reaction. Stevens-Johnson syndrome is considered a minor form of toxic epidermal necrolysis with less than 10% body surface area (BSA) involved. Toxic epidermal necrolysis includes patients with more than 30% BSA involved. There is overlap with patients with 10% to 30% BSA involved. The main feature of non–staphylococcal-induced toxic epidermal necrolysis, or Lyell's disease, is the separation of large sheets of epidermis from underlying dermis. Toxic epidermal necrolysis may be caused by medications, infection, malignancy, or idiopathic (30% to 50% of cases). Medications that can cause toxic epidermal necrolysis include sulfa drugs, nonsteroidal antiinflammatory drugs (NSAIDs), penicillin, aspirin, barbiturates, phenytoin, carbamazepine, or allopurinol.

Mortality may be up to 30% with toxic epidermal necrolysis. Risk factors for poor prognosis include age older than 40 years old, underlying malignancy, heart rate more than 120, initial percentage of epidermal detachment more than 10%, BUN level more than 10 mmol/L, serum glucose level more than 14 mmol/L (or 252 mg/dL), and bicarbonate level less than 20 mmol/L.

Toxic epidermal necrolysis commonly begins with prodromal symptoms, such as fever, malaise, rhinitis, sore throat, and myalgias. These are followed by the abrupt development of a macular rash that may appear as target lesions. The extremities are commonly involved, although any area may be affected. The exanthem becomes confluent, and dermal-epidermal dissociation ensues; Nikolsky's sign (denudation with shear stress) is present, and the skin is commonly painful to the touch (Fig. 110.37). Mucous membrane involvement may occur with erythema, blistering, sloughing, or necrosis (Fig. 110.38). Involvement of the conjunctivae and cornea may lead to permanent scarring and blindness. Systemic involvement may occur, with renal, gastrointestinal, or respiratory tract lesions, resulting in hematuria, diarrhea, bronchitis, or pneumonia. Morbidity and mortality are often related to infection and dehydration.

The treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis includes discontinuation of the offending agent and supportive care, including hydration, prevention of secondary infection, and expert wound management. This is usually best accomplished in a center with burn care expertise. Systemic administration of corticosteroids is controversial. They have little effect on the disease and may mask signs of impending sepsis. High-dose IVIG may be administered to patients with severe toxic epidermal necrolysis or Stevens-Johnson syndrome. Plasmapheresis is considered in consultation with a specialist.

An in depth discussion of Stevens-Johnson syndrome and toxic epidermal necrolysis can be found in Chapter 129.

Erythema Nodosum

Erythema nodosum is an inflammatory reaction of the dermis and adipose tissue that presents with painful erythematous or violaceous subcutaneous nodules. These painful nodules occur most commonly over the anterior tibia but may also be seen on the arms or body (Fig. 110.39). Fever and arthralgia of the ankles and knees may precede the rash. As the lesions evolve, they may turn yellow-purple and resemble bruises. Women are affected three times more often than men, with the highest incidence in the third to fifth decades of life. Unless lesions quickly resolve, a search for underlying conditions should be undertaken.

A number of diseases are associated with erythema nodosum; these include drug reactions, sarcoidosis, coccidioidomycosis,

Fig. 110.37. Toxic epidermal necrolysis. (Courtesy David Effron, MD.)

Fig. 110.38. Toxic epidermal necrolysis. (Courtesy David Effron, MD.)

Fig. 110.39. Erythema nodosum. (Courtesy David Effron, MD.)

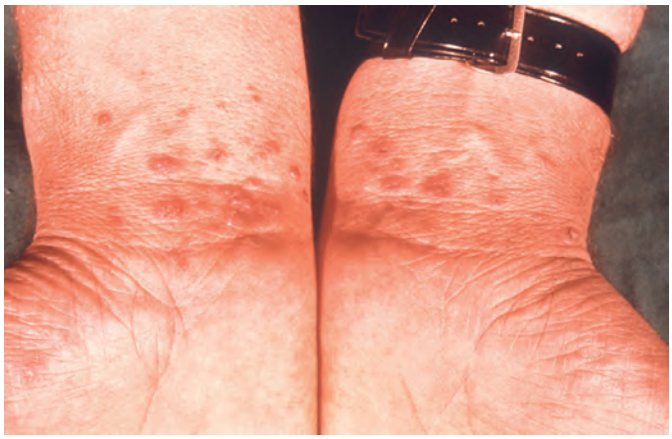

Fig. 110.40. Lichen planus. (Courtesy Centers for Disease Control and Prevention [CDC] Public Health Image Library, Susan Lindsley.)

histoplasmosis, tuberculosis, ulcerative colitis, regional enteritis, pregnancy, and infections with streptococci, *Yersinia enterocolitica,* and *Chlamydia*. As with erythema multiforme, many cases of erythema nodosum are idiopathic. The differential diagnosis includes traumatic bruises and subcutaneous fat necrosis.

Management begins with treatment of the underlying etiology. Chest radiography may be considered to rule out sarcoidosis, tuberculosis, or pulmonary fungal infection. Bed rest, elevation of the legs, and wearing of elastic stockings reduce pain and edema. Aspirin in a dosage of 650 mg every 4 hours or other NSAIDs may also afford some relief. Erythema nodosum is a self-limited process that usually resolves in 3 to 8 weeks. Patients with severe pain may be treated with potassium iodide daily for 3 or 4 weeks. Potassium iodide may act through an immunosuppressive mechanism mediated by heparin release from mast cells.

Lichen Planus

Lichen planus is an inflammatory condition of unknown etiology. Lesions are typically flat-topped violaceous papules with pruritus (also known as the five "Ps": purple, planar, polygonal, pruritic, papules). Lesions typically appear on the wrists and ankles (Fig. 110.40). The lesions may occur in an area of trauma (Koebner phenomenon). Other areas may be affected, such as oral mucosa, anogenital region, scalp, and other areas.

High potency topical steroids are treatment of choice. Pruritus may be treated with systemic agents, such as diphenhydramine or hydroxyzine. Alternate therapies include systemic steroids, oral retinoids, or phototherapy.[44]

AUTOIMMUNE DISORDERS

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune blistering disorder that most commonly affects geriatric patients. Clinical manifestations are often pruritus and generalized blistering of the skin (Fig. 110.41). Nikolsky's sign is negative. It often has a waxing and waning clinical course. Although unproven, it has been associated with numerous systemic conditions, including malignancy, diabetes, stroke, Parkinson's disease, and cardiovascular disease.

Systemic steroids are the treatment of choice. Topical steroids may be used for cases of localized or limited disease. Other treatment modalities may include azathioprine, cyclophosphamide, methotrexate, and other agents. These treatments should be undertaken in consultation with a dermatologist.[45]

Fig. 110.41. Bullous pemphigus. (Courtesy David Effron, MD.)

Pemphigus Vulgaris

Pemphigus vulgaris is an uncommon but important dermatologic disorder. The mortality rate before the use of steroids was approximately 95%. The current mortality rate is 10% to 15%, with appropriate treatment. Pemphigus is a bullous disease, affecting both sexes equally, and is most common in patients 40 to 60 years old. The disease is mostly prevalent in people of Jewish, Mediterranean, or south Asian descent.

The typical skin lesions are small, flaccid bullae that break easily, forming superficial erosions and crusted ulcerations. Any area of the body may be involved. Nikolsky's sign is present and characteristic of the disease. Nikolsky's sign is positive when gentle rubbing of the skin produces exfoliation of the outermost layer, forming a blister or bullae.

Many patients also have oral lesions (50% to 60%). The oral lesions typically antedate the cutaneous lesions by several months. The most common site is in the mouth, especially the gums and vermilion borders of the lips. Oral lesions are bullous but commonly break, leaving painful, denuded areas of superficial ulceration.

Pain control and local wound care are essential components of therapy. Once the diagnosis is made, treatment with oral glucocorticoids in initial doses of 100 to 300 mg of prednisone, or an equivalent drug, should be instituted in conjunction with a dermatologist. Other immunosuppressant drugs may also be used. Morbidity and mortality may ensue, related to an uncontrolled spread of the disease, secondary infection, dehydration, side effects of steroid therapy, and thromboembolism.

CUTANEOUS MALIGNANCIES

Approximately 5 million skin cancers are diagnosed annually in the United States.[46] The most common cutaneous malignancies are basal cell carcinoma, squamous cell carcinoma, and melanoma.[47-49]

Basal cell carcinoma is the most common skin cancer in the United States. It is more common among men. Basal cell carcinomas are commonly seen in patients with fair skin, sun exposure, outdoor occupation, and older age. Clinical presentation is

typically on sun exposed areas, commonly on the head and neck. The typical appearance is a pearly papule with well-defined borders and telangiectasias, although several variants may be seen. Suspicious lesions should be referred to a dermatologist for biopsy.

Squamous cell carcinoma is the second most common skin cancer in the United States. It is more common in men than in women. The risk of developing squamous cell carcinoma of the skin is increased with advancing age and sun exposure. Squamous cell carcinomas are typically found in sun-exposed areas, most commonly on the head and neck. The appearance is typically an irregular growth with erythema, induration, inflammation, crusting, or oozing. Suspicious lesions should be referred to a dermatologist for biopsy.

Melanoma is less common, and accounts for only 4% to 5% of skin cancers. However, it is responsible for most deaths from cutaneous malignancies. Risk factors include fair skin, dysplastic nevi, multiple (>50) nevi, prior history of melanoma, family history of melanoma, immunocompromised state, and xeroderma pigmentosum. Melanoma tends to appear more often on lower extremities in women and on the head, neck, and trunk in men, and it may occur in any area of the skin. The typical appearance is an asymmetric lesion with irregular pigmentation, border, and texture, and diameter greater than 6 mm or increasing in size. Suspicious lesions should be referred to a dermatologist for biopsy.

Kaposi sarcoma appears more often in men having sex with men than in other risk groups. Clinically, it presents with painless, raised, brown-black or purple papules and nodules that do not blanch. Common sites are the face, chest, genitals, and oral cavity, but widespread dissemination involving internal organs may occur. Because cutaneous Kaposi sarcoma is not generally associated with morbidity or mortality, therapy is indicated only for extensive, painful, or cosmetically disfiguring lesions.

Although the ED does not provide definitive management for cutaneous malignancies, recognition of possible malignant lesions may facilitate prompt and expeditious referral for definitive management. Any lesion with irregular pigmentation, irregular borders or texture, easy bleeding, or recent change in lesion should be referred to a dermatologist.

SKIN CONDITIONS ASSOCIATED WITH SYSTEMIC DISEASE

Systemic illness should be considered with significant generalized dermatologic presentations. Systemic illness should be suspected in patients with systemic symptoms, such as fever, fatigue, weight loss or gain, weakness, immunosuppression, or other generalized symptoms. Systemic illnesses with cutaneous findings may include systemic infections, autoimmune or connective tissue disorders, malignancies, diabetes mellitus, endocrine disorders, and immunodeficiency states (Table 110.4).

Cutaneous lesions most directly indicative of an internal malignant disease arise from the extension of the tumor to the skin or by hematogenous or lymphatic metastasis. The neoplasms that most commonly produce cutaneous extension are lymphomas, leukemias, and carcinomas of the breast, gastrointestinal tract, lung, ovary, prostate, uterus, and bladder. Skin metastases generally signify a poor prognosis.

Pruritus may be a sign of systemic disease, such as cholestasis, renal disease, malignancy, or myeloproliferative disease.[50] Malignancies associated with pruritus include Hodgkin's disease, leukemia, adenocarcinoma or squamous cell carcinoma of various organs, carcinoid syndrome, multiple myeloma, and polycythemia vera. It may be present years before the underlying malignant disease is identified. It may be intractable and associated with urticaria, erythroderma, excoriation, or lichenification.

TABLE 110.4

Cutaneous Signs of Systemic Disease

ANATOMIC SITE	SIGN	SYSTEMIC DISEASE
Generalized	Urticaria	Drug reaction
		SLE
		Infection
	Pruritus	Anemia
		Renal disease
		Cholestasis
		Polycythemia
		Lymphoma
		Malignancies
		Thyroid disease
Head and neck	Xanthelasma	Hyperlipidemia
	Spider nevi	Liver disease
		Hyperthyroidism
	Malar erythema	SLE
	Photosensitive rash	SLE
		Porphyria
	Alopecia	Thyroid disease
		Drugs
		Anemia
		Malnutrition
		SLE
		Fungal infection
	Heliotrope discoloration and eyelid edema	Dermatomyositis
Hands	Gottron's papules	Dermatomyositis
		Internal malignancy
	Raynaud's phenomenon	Normal
		Connective diseases
	Clubbing	Normal
		Internal malignancy
		Cyanotic cardiac disease
		IBD
		Lung disease
	Erythema multiforme	Drugs
		Infections
	Palmar erythema	Normal
		Liver disease
		Pregnancy
		Rheumatoid arthritis
		SLE
Legs	Erythema nodosum	Strep infection
		Drugs
		Pregnancy
		Tuberculosis
		Sarcoidosis
		IBD
	Pyoderma gangrenosum	IBD
		Hepatitis
		Rheumatoid arthritis
		Malignancy
	Pretibial myxedema	Hypothyroidism
		Hyperthyroidism
	Necrobiosis lipoidica	Diabetes mellitus

IBD, Inflammatory bowel disease; *SLE,* systemic lupus erythematosus.

Purpura may be a manifestation of acute granulocytic and monocytic leukemia, myeloma, lymphoma, and polycythemia vera. Purpura is caused by vascular abnormalities, thrombocytopenia, or other coagulation defects. A variety of diseases and conditions may be the underlying cause, and the treatment should be directed toward this cause whenever possible. Thrombocytopenic

and nonthrombocytopenic forms are differentiated by the results of the patient's platelet count.

Petechiae are manifestations of intradermal hemorrhage. Petechiae may be associated with thrombocytopenia, allergic reactions, infections, trauma, or malignancy (Fig. 110.42).

MANAGEMENT

Treatments for dermatologic conditions should address both definitive treatment for underlying disease states and symptomatic treatment. If causative agents are identified, they should be discontinued or eliminated from the environment. Topical or systemic therapies may be indicated for a variety of conditions.

Fig. 110.42. Palatal petechiae secondary to thrombocytopenia in a patient with acute myelogenous leukemia (AML). (Courtesy Jason R. Pickett, MD.)

Vehicles for topical dermatologic preparations may be important in the therapeutic effect.[51] Vehicles include creams (water based emulsion of oil), lotions (water based suspension of powder), ointments (oil based suspension, which improves penetration of the active ingredient), gels (transparent, semi-solid, non-greasy emulsion), foams (helpful for scalp or difficult to reach areas), and pastes (ointment base with powder, stiff consistency). For dry, scaly conditions, emollients such as ointments may be more effective. For moist conditions, a dryer vehicle such as a gel or powder may be preferable. Vehicle components may vary with generic preparations, and it is important to monitor clinical success if generic preparations are prescribed. Communication with the patient about preferences may be important. Patient preference and compliance are closely linked to successful outcomes.

Topical steroids are commonly used to treat inflammatory dermatologic conditions. Topical steroids have several mechanisms of action, including antiinflammatory effects, antiproliferative effects on fibroblasts and collagen, reduction of leukocyte adhesion to capillaries, reduction of capillary wall permeability, reduction of complement components, and histamine antagonism. Adverse effects may include skin atrophy, striae, acneform lesions, pigment changes, telangiectasia, hypothalamic-pituitary axis suppression from systemic absorption, and exacerbation of certain conditions, such as fungal infections and viral infections. Topical steroids should be prescribed in the lowest potency and for the shortest duration that is effective for the individual patient (Table 110.5).

Systemic therapies are appropriate for systemic conditions. Commonly used systemic therapies include oral, IM, or IV

TABLE 110.5

Potency of Topical Steroids

BRAND NAME	GENERIC NAME
CLASS 1: SUPERPOTENT	
Clobex lotion, spray, or shampoo, 0.05%	Clobetasol propionate
Cormax cream or solution, 0.05%	Clobetasol propionate
Diprolene ointment, 0.05%	Betamethasone dipropionate
Olux E foam, 0.05%	Clobetasol propionate
Olux foam, 0.05%	Clobetasol propionate
Temovate cream, ointment, or solution, 0.05%	Clobetasol propionate
Ultravate cream or ointment, 0.05%	Halobetasol propionate
Vanos cream, 0.1%	Fluocinonide
Psorcon ointment, 0.05%	Diflorasone diacetate
Psorcon E ointment, 0.05%	Diflorasone diacetate
CLASS 2: POTENT	
Diprolene cream AF, 0.05%	Betamethasone dipropionate
Elocon ointment, 0.1%	Mometasone furoate
Florone ointment, 0.05%	Diflorasone diacetate
Halog ointment or cream, 0.1%	Halcinonide
Lidex cream, gel, or ointment, 0.05%	Fluocinonide
Psorcon cream, 0.05%	Diflorasone diacetate
Topicort cream or ointment, 0.25%	Desoximetasone
Topicort gel, 0.05%	Desoximetasone
CLASS 3: UPPER MIDSTRENGTH	
Cutivate ointment, 0.005%	Fluticasone propionate
Lidex-E cream, 0.05%	Fluocinonide
Luxiq foam, 0.12%	Betamethasone valerate
Topicort LP cream, 0.05%	Desoximetasone
CLASS 4: MIDSTRENGTH	
Cordran ointment, 0.05%	Flurandrenolide
Elocon cream, 0.1%	Mometasone furoate
Kenalog cream or spray, 0.1%	Triamcinolone acetonide
Synalar ointment, 0.03%	Fluocinolone acetonide
Westcort ointment, 0.2%	Hydrocortisone valerate
CLASS 5: LOWER MIDSTRENGTH	
Capex shampoo, 0.01%	Fluocinolone acetonide
Cordran cream, lotion, or tape, 0.05%	Flurandrenolide
Cutivate cream or lotion, 0.05%	Fluticasone propionate
Dermatop cream, 0.1%	Prednicarbate
DesOwen lotion, 0.05%	Desonide
Locoid cream, lotion, ointment, or solution, 0.1%	Hydrocortisone

Continued

TABLE 110.5

Potency of Topical Steroids—cont'd

BRAND NAME	GENERIC NAME	BRAND NAME	GENERIC NAME
Pandel cream, 0.1%	Hydrocortisone	Verdeso foam, 0.05%	Desonide
Synalar cream, 0.03%, 0.01%	Fluocinolone acetonide	**CLASS 7: LEAST POTENT**	
Westcort cream, 0.2%	Hydrocortisone valerate	Cetacort lotion, 0.5%, 1%	Hydrocortisone
CLASS 6: MILD		Cortaid cream, spray, or ointment	Hydrocortisone
Aclovate cream or ointment, 0.05%	Alclometasone dipropionate	Hytone cream or lotion, 1%, 2.5%	Hydrocortisone
Derma-Smoothe/FS oil, 0.01%	Fluocinolone acetonide	MiCort-HC cream, 2%, 2.5%	Hydrocortisone
Desonate gel, 0.05%	Desonide	Nutracort lotion, 1%, 2.5%	Hydrocortisone
Synalar cream or solution, 0.01%	Fluocinolone acetonide	Synacort cream, 1%, 2.5%	Hydrocortisone

Modified with permission from National Psoriasis Foundation: Topical steroids potency chart. Available at www.psoriasis.org/page.aspx?pid=469.

steroids, antipruritic agents, antibiotics, antifungal agents, and antiviral agents.

DISPOSITION

Most ED patients with dermatologic complaints can be successfully managed as outpatients. Indications for inpatient hospitalization include systemic disorders with dehydration, disorders of thermoregulation, systemic infection or other systemic disorder requiring inpatient management, inability to care for self, or maintain appropriate oral intake. Dermatologic outpatient follow-up or inpatient consultation may be appropriate.

KEY CONCEPTS

- Accurate descriptions of the lesion(s) are essential for accurate diagnosis and management.
- Key steps in diagnosing the unknown rash include an accurate history, physical examination, including lesions and distribution, and appropriate diagnostic tests. Bacterial infections may present as abscess, cellulitis, impetigo, or other cutaneous infections.
- Incision and drainage is adequate therapy for simple abscesses.
- Antibiotics to cover MRSA are appropriate for most skin and soft tissue infections.
- Tinea capitis requires 4 to 8 weeks of systemic antifungal treatment.
- Onychomycosis requires long-term systemic treatment.
- Allergic reactions are common. Identification and removal of exposure to the allergen, and antihistamine treatment are the cornerstones of therapy.
- Newer nonsedating antihistamines are a useful alternative to older sedating ones to control pruritus and histamine-mediated rashes while allowing the patient to remain active.
- Infestations should be diagnosed clinically and treated expeditiously even without definitive proof of the infestation.
- Medication reactions are common and may results from any medication, typically within 4 to 21 days after taking the medication.
- Rashes that are associated with mucosal lesions, blisters, or desquamating skin are often caused by significant soft tissue infections, drug eruptions, or immune disorders.
- Patients with Stevens-Johnson syndrome and toxic epidermal necrolysis require inpatient treatment, preferably in a burn unit.
- Cutaneous signs of systemic disease may include pruritus, urticaria, erythema multiforme, erythema nodosum, pyoderma gangrenosum, and others.
- Physicians should be familiar with one or two topical steroid preparations of low, medium, and high potency and their appropriate therapeutic use.
- Most patients with dermatologic conditions can be appropriately managed with outpatient treatment and follow-up with a dermatologist. Life-threatening conditions at risk for dehydration and infection require inpatient treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 110: QUESTIONS & ANSWERS

110.1. Which of the following statements regarding tinea capitis is TRUE?

A. It is contagious.
B. It is not transmitted by household pets.
C. Tinea capitis presents with alopecia with normal underlying scalp.
D. Topical treatment is effective.
E. Treatment should be instituted for 1–2 weeks.

Answer: A. Tinea capitis is the dermatophytosis that is contagious. Systemic treatment for 4 to 6 weeks is the minimum. It may be transmitted by pets. The underlying scalp is typically inflammed.

110.2. A 16-year-old boy presents with an erythematous swelling of his left forearm. What is the appropriate initial antibiotic?

A. Azithromycin
C. Clindamycin
B. Ceftriaxone
D. Linezolid
E. Penicillin VK

Answer: C. Clindamycin or trimethoprim-sulfamethoxazole are recommended first line treatment choices. Macrolides and penicillins are often ineffective against MRSA. Linezolid, although effective, is expensive and is not recommended as a first line treatment.

110.3. What is the causative organism of erythema migrans?

A. *Borrelia burgdorferi*
B. Group A *Streptococcus*
C. Methicillin-resistant *Staphylococcus aureus*
D. *Neisseria meningitides*
E. Parvovirus B-19

Answer: A. Borrelia burgdorferi is the causative agent of erythema migrans, or Lyme disease. Treatment should be instituted with doxycycline for 10–21 days, or as alternates, cefuroxime, ceftriazone, or penicillin G. Group A *Streptococcus* is the causative organism of scarlet fever. *Neisseria meningitides* is the causative agent of Meningococcemia. *Parvovirus B-19* is the causative agent of erythema infectiosum.

110.4. A 26 year old man presents with an erythematous maculopapular eruption of his torso, palms, and soles. He had a painless lesion on his penis 1 month earlier. What is the treatment of choice?
A. Azithromycin
B. Benzathine penicillin G
C. Ceftriaxone
D. Doxycycline
E. Trimethoprim-sulfamethoxazole

Answer: B. Secondary syphilis is treated with benzathine penicillin G in a dose of 2.4 million units IM.

110.5. A 25 year old female presents with fever, migratory polyarthralgias, and hemorrhagic papules on her fingers and wrists. What is the best treatment?
A. Ceftriaxone
B. Ciprofloxacin
C. Doxycycline
D. Ofloxacin
E. Vancomycin

Answer: A. Treatment of disseminated gonococcal infection is with parenteral ceftriaxones, or ceftizoxime or cefotaxime. Patients allergic to β-lactam antibiotics or those with severe penicillin allergies may be treated with spectinomycin. Ciprofloxacin and ofloxacin are not recommended because of increasing resistance patterns. Hospitalization is recommended for patients with disseminated gonococcal infection.

110.6. Which of the following statements regarding gonococcal dermatitis is TRUE?
A. Gonococci can usually be seen on gram stain from the lesions.
B. It affects primarily men.
C. It occurs in 1% or 2% of patients with gonorrhea.
D. The lesions have a predilection for the knees and elbows.
E. The skin lesions are not tender.

Answer: C. Women are affected primarily. The lesions have a predilection for distal joint skin. The lesions are often multiple and have a predilection for periarticular regions of the distal extremities. The lesions begin as erythematous or hemorrhagic papules that evolve into pustules and vesicles with an erythematous halo. They may be tender and may have a gray necrotic or hemorrhagic center. The organism may be cultured from the cutaneous lesions. Gram stain only occasionally reveals the organisms.

110.7. A 30 year old man presents with headache, nausea and vomiting, myalgias, fever, and a rash of petechiae on the extremities and trunk. Lesions are clustered on the palms and soles. What is the best treatment?
A. Cephalexin.
B. Doxycycline.
C. Erythromycin.
D. Penicillin VK.
E. Trimethoprim-sulfamethoxazole.

Answer: B. Patients with Rocky Mountain Spotted Fever present with headache, nausea and vomiting, myalgias, chills, and fever. The disease may last 3 weeks and may be severe with prominent involvement of the central nervous system, cardiac, pulmonary, gastrointestinal and renal systems, disseminated intravascular coagulation, or shock. The rash begins with erythematous macules that blanch on pressure, appearing first on the wrists and ankles. These macules spread up the extremities and to the trunk and face. They may become petechial or hemorrhagic. Lesions on the palms and soles are particularly characteristic. Doxycycline is the antibiotic of choice. Chloramphenicol may be used for patients allergic to tetracyclines and in children younger than 9 years. Sulfa drugs should be avoided because they may exacerbate the illness. Rickettsiae are routinely resistant to penicillins, cephalosporins, aminoglycosides, and erythromycin.

CHAPTER 111

Blood and Blood Components

Matthew Emery

PRINCIPLES

Background and Importance

The modern blood transfusion era began with identification of the ABO red cell antigen system in the early 1900s. The subsequent discovery that adding citrate enabled the storage of anticoagulated blood led to the establishment of the first blood banks in the United States in the 1930s, and blood banking expanded rapidly after World War II. In subsequent decades, transfusion research focused primarily on critical issues such as developing component therapy, prolonging the storage life of blood products, and reducing the risk of transfusion reactions and transfusion-related infections.

Decisions about which patients would benefit from red cell transfusion were guided by the expert advice of early pioneers such as John Lundy of the Mayo Clinic, who proposed that patients benefited from transfusion when their hemoglobin (Hgb) level was less than 10 g/dL or after a loss of more than 15% of circulating blood volume. These recommendations were not evidence-based, however, and randomized trials reported in the past 2 decades have led to the adoption of more restrictive red cell transfusion guidelines; they also highlighted the need for emergency clinicians to weigh the risks and benefits that come with administration of all blood products carefully.

Anatomy, Physiology, and Pathophysiology

Sound transfusion decision making is informed by a thorough working knowledge of the underlying physiology and pathophysiology, as well as familiarity with the key clinical trials that support up to date, evidence-based guidelines. This knowledge facilitates the effective ordering and interpretation of laboratory tests, delivery of blood products, and management of common and serious complications.

Blood Banking

Red blood cell (RBC) storage methods aim to ensure viability of at least 75% of the cells 24 hours after infusion. Blood collection bags contain an anticoagulant that ensures a shelf life of 35 days and a hematocrit of 70% to 80% for packed RBCs (PRBCs). Additive solutions provide additional nutrients and extend maximum storage to 42 days. Leukoreduced red cell products are now used for more than 95% of patients in the United States.[1] Universal prestorage leukoreduction of blood products has been adopted by an increasing number of developed countries, but remains controversial in the United States due to concerns about whether the benefits justify the costs. I recommend the use of prestorage leukoreduced blood products, when available.

A number of biochemical and structural changes have been documented to occur during red cell storage, including loss of deformability, leakage of potassium, irreversible membrane changes, and biochemical alterations that have the potential to affect the ability of RBCs to unload oxygen in the microcirculation.[2] These changes worsen with increased storage duration and have been collectively referred to as the storage lesion. A number of observational studies and a few randomized prospective trials, have reported conflicting results as to whether these changes are clinically relevant.[3] One large randomized trial published in 2015, however, comparing the use of fresh blood (storage duration, 6.1 ± 4.9 days) versus standard issue blood (storage duration, 22.0 ± 8.4 days) to critically ill adult patients, found no change in 90-day mortality.[4] A second study, also published in 2015, compared the use of red cells stored for 10 days or less to red cells stored for 21 days or more in patients older than 12 years undergoing complex cardiac surgery and, again, found no change in the occurrence of multiple organ dysfunction.[5]

Blood Typing

Compatibility testing identifies clinically significant blood antigens and antibodies. Emergency clinicians should have a basic understanding of two common compatibility tests, the type and screen and crossmatch. The type and screen is typically ordered when an emergency clinician considers transfusion to be a possibility because it allows for the quicker selection of appropriate banked blood for complete crossmatch if a transfusion is later ordered. A type and crossmatch is ordered once a decision is made to administer blood or when administration is considered likely. Once a full type and crossmatch is ordered, the specified number of units will be held in reserve for a particular recipient until the blood products have been administered or the order has expired. Overuse of the type and cross order for patients at low risk of requiring blood products can overtax limited supplies, whereas judicious use of the type and screen order helps extend the capacity of the blood bank to meet the needs of a greater number of patients.

Type and Screen. A type and screen order requires the following tests to be carried out on a sample of the patient's blood—ABO grouping, Rh typing, and antibody screen for unexpected antibodies (non–ABO/Rh antibodies).

RBC antigens include the ABO and related carbohydrate antigens (H, P, I, and Lewis), 48 Rh system antigens, and more than 200 non–ABO/Rh antigens. ABO grouping requires that the

recipient's red cells be tested with anti-A and anti-B serum and that his or her serum be tested with A and B red cells. By about 6 months of age, most infants have formed antibodies against the A and B antigens they lack. Those with type AB blood form no ABO group antibodies. Patients with type O blood have antibodies against both. The major clinically significant Rh antigen is the D antigen. Rh typing is usually done by adding a commercial reagent (anti-D) to recipient RBCs.[6] All infants, however, require that the initial standard compatibility testing include ABO and Rh typing as well as an antibody screen.[6]

The antibody screen identifies unexpected (non–ABO/Rh) antibodies in the patient's serum. These develop in response to prior exposure to foreign RBC antigens during allogenic transfusion or pregnancy. To complete the antibody screen, the patient's serum is combined with commercially prepared mixtures of red cells expressing clinically significant antigens. The incidence of these unexpected antibodies in the general population is low (<1%–2%), but a positive screen prompts further compatibility testing.

Type and Crossmatch. When a unit of blood is ordered for transfusion, a crossmatch follows the initial type and screen. In an ideal situation, blood identical to the patient's own ABO and Rh group is used. Local blood supplies, however, might dictate that a nonidentical but compatible unit be used. Patients with blood group AB (who lack anti-A and anti-B antigens), for example, are known as universal recipients—they can receive blood from any of the ABO groups. Type O blood (lacking the A and B antigens), also known as universal donor blood, conversely, can be given to anyone. Rh compatibility is also important. Rh sensitization can occur in Rh-negative patients exposed to Rh-positive blood, and this sensitization in turn can result in hemolytic disease of the newborn with subsequent pregnancies.

The traditional crossmatch requires mixing the recipient's serum with donor RBCs and observing for agglutination as a final compatibility test before transfusion. If the antibody screen is negative, an immediate spin crossmatch at room temperature serves as a final check for ABO incompatibility. A complete crossmatch is generally done before transfusion if the antibody screen is positive. This requires incubation to 37°C (98.6°F) and the addition of antihuman globulin (Coombs' reagent) to promote agglutination. Many blood banks also substitute a computer crossmatch for patients whose blood has been tested at least twice in their system. Full compatibility testing takes time. An antibody screen and immediate spin crossmatch at a minimum requires approximately 45 to 60 minutes. This assumes a negative antibody screen followed by an immediate-spin crossmatch performed at room temperature. If the antibody screen is positive, the antibody is identified via more elaborate procedures, and a complete crossmatch (using a Coombs' test with incubated serum) is required. This process can take up to several hours, or even days, an unacceptable delay in some emergent situations.

Although ABO compatibility is mandatory in all patients, non-ABO antigens are less likely to cause immediate intravascular hemolysis.[7] Universal (group O) PRBCs are therefore often used when RBCs are needed in hemorrhaging unstable patients before any testing can be done.[8] Female patients receive O-negative blood to prevent hemolytic disease of the newborn unless there is no chance of subsequent pregnancy. All others may receive O-positive blood because, even if sensitization occurs, Rh antibodies generally do not fix complement; therefore, this would be unlikely to cause an acute life-threatening intravascular hemolytic reaction in the unlikely event that an Rh-negative recipient twice received an emergent transfusion of Rh-positive blood. Conversely, the universal type for fresh-frozen plasma (FFP) is type AB, which contains no antibodies to A or B antigens. Type-specific blood (with ABO and Rh testing) can generally be made available within 15 minutes of receiving a sample of the patient's blood.

Similarly, if complete compatibility testing following a positive antibody screen would substantially delay transfusion of blood products to a critically ill patient, the emergency clinician may choose to bypass this step. Direct communication with the blood bank will facilitate determination of the best course of action.

MANAGEMENT

Decision Making

To select the most appropriate blood products in the emergency setting, emergency clinicians consider the cause of the deficit, severity of symptoms, likelihood of ongoing hemorrhage, tissue oxygen requirements, and the patient's ability to compensate for decreased oxygen-carrying capacity, which is in turn influenced by the patient's age, underlying medical conditions, and their hemodynamic stability. Clinical evaluation, including appearance (pallor, diaphoresis), mentation (alert, confused), heart rate, blood pressure, and nature of the bleeding (active, controlled, uncontrolled), can be supplemented by laboratory evaluation.

Numerous trials have now been done that support a restrictive strategy for red blood cell transfusions in stable patients, and I recommend using a trigger of 7 to 8 g/dL for euvolemic patients without significant ongoing hemorrhage.[9] Randomized trials have also supported the use of prophylactic platelet transfusions for thrombocytopenia in stable, uncomplicated adult patients—those without fever, infection, or use of drugs known to inhibit platelet function—and I recommend that a platelet count less than 10,000/μL is an appropriate trigger for this purpose.[10] For children, a similar threshold should prompt discussion with a pediatric hematologist about the need for platelet transfusion. A Cochrane Review has found that there ae no high-quality trials regarding the use of FFP, and appropriate triggers for FFP are not as clearly defined.[11] Further review of transfusion triggers and special circumstances will be covered below in the sections describing specific blood products.

Before a blood product can be infused, two qualified personnel check it at the bedside to prevent a potentially fatal clerical error. This check includes recipient and unit identification, as well as confirmation of compatibility, and the expiration date. Automated patient identification (eg, a bar code reader) may be substituted for the second individual if only one person is available.

If typed and crossmatched blood arrives with the patient from a transferring facility, it is important that the temperature be maintained between 1° and 10°C (33.8° and 50°F) during transport. If the blood is not used right away and the blood bank is asked to hold the blood for the patient, it is processed and crossmatched as for other issued blood and quarantined for 24 hours. It can be sent back to the blood bank to have this done only if it has been constantly maintained at a temperature between 1° and 10°C (33.8° and 50°F), all container seals are intact, and tubing segments have remained attached to the blood container.

Pharmacology

PRBCs are run through a filter with a large-bore intravenous (IV) line with normal saline. No other solutions should be used unless FDA (US Food and Drug Administration)–approved (eg, Normosol-R, pH 7.4; Plasma-Lyte 148).[6] Lactated Ringer's solution, for example, can lead to clotting secondary to the added calcium, and hemolysis may result from using a hypotonic solution such as a dextrose-containing fluid. Medications should also not be added to the unit or pushed through the transfusion line with blood components, although there is limited literature indicating that morphine, hydromorphone and meperidine can be

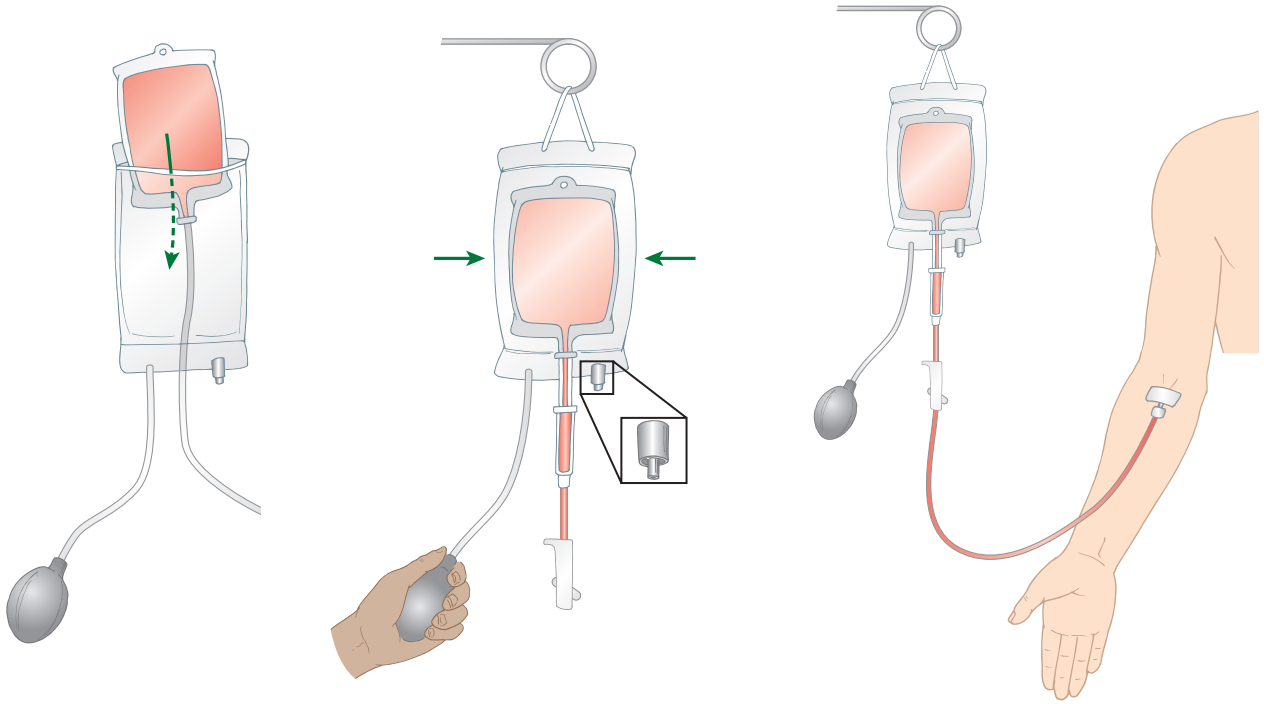

Fig. 111.1. The blood product bag is slipped into the sleeve of the pressure bag. The bulb is then used to inflate the bladder of the pressure bag until the desired pressure is indicated by the gauge.

given safely if there are no alternative sites available. The widespread use of antihistamines to prevent mild allergic reactions, and antipyretics to prevent febrile, nonhemolytic transfusion reactions, although poorly studied, is appropriate as long as the risk of side effects is considered. Most transfusions are given over 60 to 90 minutes, never longer than 4 hours. Unused blood should be returned promptly to the blood bank. Any units unrefrigerated for more than 30 minutes are discarded.

Research into Hgb-based oxygen carriers and perfluorocarbon emulsions has been ongoing[12,13] but, as yet none are FDA-approved for general clinical use in the United States. Several problems remain unsolved. Hgb-based carriers, for example, have been found to cause vasoconstriction through nitric oxide (NO) scavenging, endothelin release, and peripheral α-adrenergic receptor sensitization. Perfluorocarbon emulsions require relatively high partial pressure of oxygen (Po_2) levels and therefore require delivery of pure oxygen.

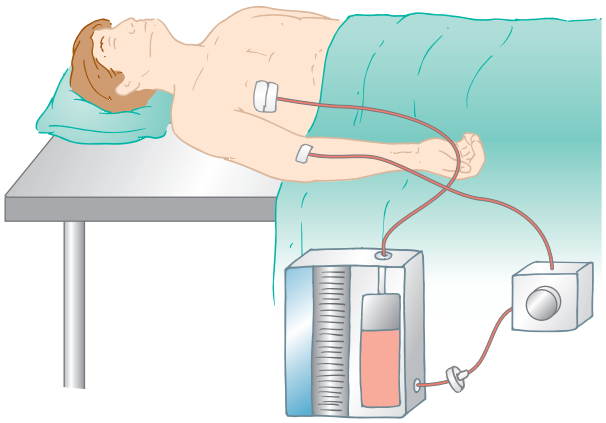

Fig. 111.2. Several commercial products are available to facilitate the use of autologous blood transfusion in patients with chest trauma.

Devices and Techniques

Urgent transfusion situations require flow rates faster than gravity can provide. An administration set with an in-line pump that is squeezed by hand is the simplest method to speed infusion. Pressure bags (Fig. 111.1) are also available that completely encase the blood bag and apply pressure evenly. With high-pressure infusion, large-bore needles are recommended so that hemolysis is prevented. If only a small-gauge needle is available, the transfusion may be diluted with normal saline, but this may cause unwanted volume expansion. In elective transfusions, no significant hemolysis occurs when small-gauge needles are used if the maximum rate of infusion is less than 100 mL/hr. Autotransfusion (Fig. 111.2) may be used in the emergency setting in the event of severe chest trauma and was found in a large retrospective trial to be safe and effective.[14] This strategy has numerous advantages—immediate availability, blood compatibility, elimination of donor to patient disease transmission, lower risk of circulatory overload, and fewer direct complications (eg, hyperkalemia, hypothermia, hypocalcemia, metabolic acidosis). It is also more acceptable to patients whose religious convictions prohibit transfusions. It is impractical in some settings, however, because of the limited number of appropriate trauma patients, training required to operate the equipment, and time required for equipment setup.

Thromboelastography, an older technology attracting renewed interest, particularly in trauma and sepsis in the emergency department (ED),[15-17] may prove useful in guiding coagulation therapy but is not now widely used in the ED setting. A full description is beyond the scope of this chapter, but this test provides information on the function of platelets and coagulation factors, including fibrinogen.

Whole Blood

Intriguing reports on the use of fresh whole blood in military field hospitals have been published. In civilian practice in the United States, however, it has generally been unavailable and rarely used,

comprising only 0.15% of all transfusions in 2011.[18] Interest in the use of whole blood has been growing, however, including the use of banked and fresh warm whole blood, despite the obvious logistic hurdles, and civilian trials have been proposed.[19,20]

Packed Red Blood Cells

PRBCs are indicated only to improve oxygen delivery to tissues at the microvascular level and thus improve intracellular oxygen consumption, yet definitive demonstration of the efficacy of red cells for this purpose (or improved clinical outcomes) has proven elusive.[21] A definitive randomized prospective study in which RBCs are withheld completely from one treatment group is unlikely to be done at this point.

I agree with the recommendations published in 2012 by the AABB (formerly, the American Association of Blood Banks), which were based on a systematic review of trials published between 1950 and February 2011. This review found strong support for using a restrictive transfusion strategy (7–to 8 g/dL) for most stable hospitalized patients.[22] It was also recommended that transfusion decisions be influenced by symptoms and hemoglobin concentration and specifically addressed the case of hospitalized patients with preexisting cardiovascular disease, suggesting that emergency clinicians consider transfusion for these patients when they had symptoms or a hemoglobin level of 8 g/dL or less. Literature support for these additional recommendations was noted to be weak, however, and no specific recommendations could be made with regard to hospitalized, hemodynamically stable patients with an acute coronary syndrome.[22]

For many patients, the decision to transfuse RBCs requires clinical judgment. The appropriate trigger for patients with active hemorrhage, for example, is not well established, although a trial in patients with acute gastrointestinal bleeding found somewhat improved survival outcomes overall in patients treated with a restrictive 7-g/dL transfusion trigger.[23] I recommend transfusing any patient with ongoing severe hemorrhage and unstable vital signs, despite adequate fluid resuscitation. Conversely I would occasionally consider withholding transfusion for Hgb levels even lower than 6 g/dL in a young, healthy, asymptomatic patient at low risk for further bleeding. Another interesting area of investigation is the use of physiologic transfusion triggers (eg, lactate, mixed venous oxygen saturation), but further research is needed.[24]

Fresh-Frozen Plasma

A unit of FFP contains all clotting factors and typically has a volume of 200 to 250 mL. It must be ABO compatible and is administered through blood tubing. FFP is given within 24 hours of thawing.

Indications for FFP are based primarily on observational trials and expert opinion.[22] These indications seem reasonable based on current evidence: coagulopathy of trauma, hemorrhaging patients with coagulopathy resulting from hepatic dysfunction or disseminated intravascular coagulation (DIC), plasma exchange for thrombotic thrombocytopenic purpura (TTP), and emergency reversal of a vitamin K antagonist in the presence of clinically significant hemorrhage.[25] It is worth noting, however, that the therapeutic effect is difficult to predict. A large volume of FFP is needed to reverse coagulopathy caused by vitamin K antagonism (at least 10 mL/kg, and perhaps as much as 30 mL/kg), enough for an older patient with congestive heart failure to develop pulmonary edema. Guidelines published by the American College of Chest Physicians have recommended that prothrombin complex concentrate (PCC) be used for the reversal of an elevated international normalized ratio (INR) in patients with life-threatening bleeding or intracranial hemorrhage, and available evidence has shown that a more rapid normalization of the INR in these patients occurs with the administration of PCC rather than FFP. Both three- and four-factor PCC products are now FDA-approved in the United States, with four-factor products containing all the vitamin K–dependent clotting factors, whereas three-factor products lack factor VII. A systematic review comparing three- and four-factor PCC in patients with serious warfarin-associated bleeding has found that the four-factor product is more reliable in reducing the INR to below 1.5 within 1 hour, and I recommend its use, when available.[26] I also recommend that all patients with life-threatening warfarin-associated hemorrhage also receive 10 mg of vitamin K by slow IV infusion (no faster than 1 mg/min).

As noted below in the section on massive transfusions, evidence from retrospective trials has supported increased use of FFP in patients anticipated to require more than 10 units of PRBCs. This should not be generalized to all patients receiving a transfusion, however. A retrospective case-control trial of 1716 transfused trauma patients receiving fewer than 10 units of blood has found that the administration of FFP is associated with no survival benefit but has a higher risk of complications, including acute respiratory distress syndrome, pneumonia, sepsis, and multiple organ dysfunction.[27]

FFP is typically not recommended for volume expansion, nonurgent reversal of a vitamin K antagonist, or treatment for abnormal INR from any cause in the absence of bleeding. Likewise, limited available evidence has failed to support the use of FFP in patients with an elevated INR before invasive procedures such as central line placement and lumbar puncture, although it is common practice to administer FFP for an INR greater than 1.5 to 2.0.[6] One problem has been that the INR often proves to be a poor predictor of clinical bleeding.

If a specific factor deficiency is identified (eg, hemophilia), targeted replacement of that factor, if available, is usually more practical. Crossmatching is generally unnecessary for platelet transfusions, but Rh-negative patients are treated with Rh-negative platelets because there may be enough red cells in the platelet concentrate to cause Rh sensitization. The use of leukoreduced platelets has been shown to reduce the risk of human leukocyte antigen (HLA) sensitization and is therefore beneficial in patients receiving frequent platelet transfusions. Once sensitization has occurred and patients have developed immune-mediated platelet refractoriness, various management strategies may be considered in consultation with a hematologist, including HLA-based donor selection or platelet crossmatching.

Platelet transfusions have traditionally been given prophylactically when the count is less than 10,000/μL; this includes a margin of safety because it appears that hemostasis is well maintained, even at counts of 5000/μL, a threshold sometimes used for stable afebrile inpatients. There have been no large randomized trials on which to base recommendations for the use of prophylactic platelet transfusion before invasive bedside procedures such as lumbar puncture or central line placement.

Retrospective data have supported the safety of performing lumbar puncture with platelet counts as low as 10,000/μL. For central line placement, a platelet count of 20,000 to 30,000/μL is generally considered adequate, and at least one retrospective study has supported a threshold of 20,000/μL.[28] For major surgery, a count of 50,000/μL is acceptable, although higher cutoffs (100,000/μL) are often used for high-risk procedures, such those done on the eye or brain.[2] Transfusing red cells can improve platelet function in anemic patients as the red cells push platelets to the periphery of vessels and closer to the endothelium.[2]

Lastly, when thrombocytopenia results from immune-mediated platelet destruction caused by idiopathic thrombocytopenic purpura or TTP, transfusion is generally ineffective, although it may still be considered in the presence of life-threatening hemorrhage. If immune-mediated destruction is a result of HLA

sensitization from prior transfusions, a variety of strategies may be helpful, including the use of completely or partially HLA-matched platelets. Consultation with a hematologist can be helpful in such cases.

OUTCOMES

Safety and Effectiveness

See Table 111.1 for safety considerations. In an average adult, 1 unit (450 mL) of PRBCs increases the Hgb level by about 1 g/dL or the hematocrit by about 3%. A similar increase in pediatric patients is obtained by administering 10 mL/kg.

One unit of activity for any coagulation factor is equal to the clotting activity found in 1 mL of FFP. Appropriate dosing of FFP has not been well grounded in evidence from clinical trials. As noted e, in massive transfusion, many centers now use FFP in a 1:1 ratio with red cells. For other indications, it seems reasonable to start with infusions of 10 to 30 mL/kg, realizing that results will be somewhat unpredictable, and follow-up laboratory and clinical assessment will be necessary to guide further management.[6]

Although not evidence-based, platelets are often given to adults in a dose of 6 units of platelet concentrate (a so-called six-pack of platelets) and in children at a dose of 1 unit/10 kg of body weight, an amount expected to raise the platelet count by about 40,000 to 60,000/μL. Because hemostasis is maintained with

TABLE 111.1

Adverse Effects of Red Blood Cell (RBC) Transfusion

REACTION	INCIDENCE	DESCRIPTION AND CAUSE	CLINICAL PRESENTATION	MANAGEMENT
ADVERSE EFFECTS OF NONMASSIVE RBC TRANSFUSION				
Immune-Mediated Adverse Effects				
Acute intravascular hemolysis	1:76,000	Intravascular hemolytic transfusion reaction is the most serious transfusion reaction. It generally results from ABO incompatibility, usually caused by clerical error. The resulting antigen-antibody reaction leads to the intravascular destruction of transfused red cells, producing hemoglobinemia and hemoglobinuria.	The onset of symptoms is immediate and may include fever, chills, headache, nausea, vomiting, sensation of chest restriction, severe joint or low back pain, burning sensation at the site of the infusion, and feeling of impending doom. Clinical effects can include hypotension, DIC, and acute tubular necrosis.	Treatment requires stopping the transfusion immediately, replacing all old tubing with new, and initiating vigorous crystalloid fluid therapy; vasopressors if the patient remains symptomatic. Diuretic therapy can also be used to maintain urine output at 1–2 mL/kg/hr. Blood and urine specimens are sent to the laboratory, as well as the remainder of the transfusion and blood tubing. The diagnosis can be confirmed by detection of free Hgb in blood and urine and a positive result of Coombs' test on posttransfusion, but not pretransfusion, specimens.
Febrile nonhemolytic transfusion reaction (FNHTR)	0.1%–1%	It is defined as a temperature elevation of 1°C (33.8°F) or higher that occurs with transfusion and for which no other medical explanation is found. Reactions are believed to result from antileukocyte antibodies, usually as a result of prior transfusion.	Fever, chills, and occasionally rigors	The increasing use of leukoreduced RBCs can decrease the risk of this reaction and lends further support to the use of prestorage leukoreduction. If a febrile reaction occurs in a first-time transfusion, it should be treated as an acute hemolytic reaction until proven otherwise. For recurrent reactions, treatment is symptomatic with antipyretics and antihistamines. Patients with severe chills and rigors may also benefit from analgesics. Pretreatment with antipyretics is appropriate for patients with recurrent reactions.
Mild allergic reactions	1%–3%	Urticaria, or hives, may occur during a transfusion without other signs or symptoms and with no serious sequelae. It is generally attributed to an allergic, antibody-mediated response to a donor's plasma proteins.	Pruritis, urticaria	The transfusion does not need to be stopped, and treatment with an antihistamine is usually sufficient. Pretreatment of patients with recurrent mild allergic reactions with an antihistamine is common practice and appropriate for most patients.

Continued

TABLE 111.1

Adverse Effects of Red Blood Cell (RBC) Transfusion—cont'd

REACTION	INCIDENCE	DESCRIPTION AND CAUSE	CLINICAL PRESENTATION	MANAGEMENT
Anaphylaxis	1:20,000–1:50,000	Full-blown anaphylaxis may be caused by an anti-immunoglobulin A (IgA) reaction to IgA in the donor's blood. The patient is likely to have a genetic IgA deficiency.	The presentation is similar to anaphylactic reactions from other causes	Treatment is with epinephrine, antihistamines and corticosteroids. Recurrence can be prevented with subsequent transfusions by the use of washed RBCs or plasma products from IgA-deficient individuals.
Transfusion-related acute lung injury (TRALI)[37,38]	1:1,200–1:190,000; now the leading cause of transfusion-related mortality reported to the FDA	TRALI has been defined as new acute lung injury (ALI) occurring during or within 6 hr after a transfusion without temporal relationship to an alternative explanation for ALI, and resulting in the following clinical findings: • Bilateral pulmonary edema • Hypoxemia (ratio of arterial oxygen concentration to fraction of inspired oxygen [Pa_{O_2}/F_{IO_2}] ≤ 300, or oxygen saturation < 90% as measured by pulse oximetry on room air). If there is an alternate explanation, the diagnosis of possible TRALI is appropriate. A proposed cause includes a reaction between transfused antibodies and leukocytes in the recipient, as well as the effects of biologically active factors that accumulate in stored blood (cytokines and lipids).	Clinical effects can include noncardiogenic pulmonary edema, with dyspnea, hypoxemia, and bilateral infiltrates on the chest radiograph. Fever, hypotension, and transient leukopenia may also be seen.	One strategy suggested for reducing TRALI has been to use only male donors for plasma to avoid allotypic leukocyte antibodies, which can occur in women as a result of prior pregnancies, or to screen for these antibodies and exclude donors when the antibodies are found. Stop the transfusion, notify the blood bank, and provide respiratory support, which may include intubation and mechanical ventilation. It is safe to continue transfusion of blood products from a different donor, Complete resolution is usually seen within 48–96 hours. Overall prognosis is better than would be expected with many other causes of ALI, with a reported mortality rate of 6% in one series.
Extravascular hemolytic transfusion reaction	1:2,500–1:11,000	This can result from a non–ABO-mediated immune response, usually caused by an anamnestic response in a patient previously sensitized to red cell antigens by transfusion, pregnancy, or transplantation. Less commonly, primary alloimmunization can occur after transfusion.	Clinical effects can include fever, anemia, and jaundice. Symptoms are not usually severe, but rare cases of oliguria or DIC do occur. Hemoglobinemia and hemoglobinuria are generally absent.	Treatment is primarily supportive, but the blood bank should be notified.
Transfusion-associated graft-versus-host disease	Rare	This rare but usually fatal complication, results when transfused lymphocytes proliferate and attack the recipient. Cell-mediated immunodeficiency puts patients at risk, as does having an HLA type that is identical between donor and recipient (most often seen between first-degree relatives).	Symptoms begin 3 to 30 days after transfusion and include fever, erythematous skin rash, diarrhea, elevated liver enzyme levels, and pancytopenia.	Mortality is greater than 95%. Efforts are directed at prevention by using gamma irradiation of all cellular components, which renders the donor lymphocytes incapable of proliferating. The use of leukocyte-poor components is also advocated. This condition should be kept in mind when transfusion is being considered for these high-risk patients: • Congenital immunodeficiency • Hematologic malignancy • Stem cell transplantation • Treatment with purine analogues (eg, fludarabine) • Directed donor products from a close relative Consult a hematologist when deciding whether to use irradiated cellular components in these high-risk groups.

TABLE 111.1

Adverse Effects of Red Blood Cell (RBC) Transfusion—cont'd

REACTION	INCIDENCE	DESCRIPTION AND CAUSE	CLINICAL PRESENTATION	MANAGEMENT
Non–Immune-Mediated Adverse Effects				
Circulatory overload	Variable	Chronically anemic, normovolemic older patients are at greatest risk for developing congestive heart failure with the rapid infusion of blood.	Patients present with typical findings of circulatory overload, varying from mild respiratory distress to overt pulmonary edema.	Standard treatment for congestive heart failure is appropriate. The transfusion rate should be adjusted accordingly; transfusing more slowly (over a period of 4 hr) and administering diuretics are useful in preventing this complication.
Bacterial contamination	1/2000–3000 units of platelets	Bacterial contamination, usually with *Yersinia enterocolitica*, which grows well in cool, iron-rich environments, occurs in less than 1/million units of stored RBCs. The risk of bacterial contamination is greater, however, with platelets, stored at a higher temperature.	During or after the transfusion, the patient may develop rigors, vomiting, abdominal cramps, fever, shock, renal failure, and DIC.	Mortality can be as high as 60%. The transfusion should be stopped, blood cultures obtained from the bag and patient, and broad-spectrum antibiotics and hemodynamic support initiated.
Human immunodeficiency virus (HIV) and hepatitis	HIV: 1:1,467,000 Hepatitis C: 1:1,149,000 Hepatitis B: 1:282,000–357,000	Improved techniques for selecting and testing blood donors have dramatically reduced the risk of viral transmission of disease by transfusion. The US blood supply is safe.	The presentation is typical of the particular virus.	Patients suspected of these complications should be managed in standard fashion, including appropriate subspecialty referral.
Cytomegalovirus (CMV)	Variable	CMV can be transmitted by blood transfusion as well, but this risk can be decreased by leukoreduction.	Vulnerable populations include recipients of allogeneic stem cell or solid organ transplantation and neonates.	CMV-negative blood products should be considered in vulnerable patients.
West Nile virus		This has been virtually eliminated by nucleic acid amplification testing.		

DIC, Disseminated intravascular coagulation; *FDA,* US Food and Drug Administration; *Hgb,* hemoglobin; *HLA,* human leukocyte antigen; *RBC,* red blood cell.

platelet counts as low as 5,000/μL, it seems likely that smaller, more frequent platelet transfusions should be equally efficacious but more cost-effective, particularly in hospitalized patients. This practice is supported by a randomized trial that enrolled nearly 1300 patients undergoing prophylactic platelet transfusion, which demonstrated no increase in bleeding complications with the use of a low, medium, or high dose of platelets (amounts corresponding to roughly 2, 4, or 6 units of platelet concentrate).[29] This may be impractical in outpatients, for whom increasing the frequency of transfusion can be more of a burden, and discussion with the patient's hematologist is often helpful.

Complications

Adverse Effects of Massive Transfusions

When the clinician anticipates large and ongoing blood losses, complications resulting from massive transfusion should be considered. Massive transfusion has no formal definition, but administration of at least 10 units of RBCs in 24 hours is a commonly used cutoff point. Although patients receiving any amount of blood are susceptible to a variety of infectious, physiologic, and immunologic insults, this section will discuss adverse effects that are particularly associated with massive transfusion, as well as management strategies that attempt to address these concerns.

Some of the complications of massive transfusion are well understood and easily managed. Hypothermia is common in these patients and can reduce clotting factor activity. Warmed IV fluids, blood warmers, and warming lights and blankets are often needed. Frequent laboratory testing will identify electrolyte disturbances (low magnesium and calcium levels; high and low potassium levels), which are in general treated in a standard fashion by replenishing deficits or administering calcium for hyperkalemia. Acidosis is a common finding with massive hemorrhage but can also be caused by hypoperfusion, and the contribution of transfused blood to acidosis is thought to be variable. Citrate from banked blood, for example, is metabolized in the liver to bicarbonate, which can sometimes result in metabolic alkalosis. With rapid infusion or reduced hepatic function, however, this pathway can be overwhelmed, and the net effect of infusing large amounts of citrate can be worsening metabolic acidosis. A rational response to metabolic acidosis is to optimize oxygen delivery and ventilation. The benefits of administering sodium bicarbonate are unproven, and I do not recommend it.

Patients receiving massive transfusion are also prone to coagulopathy and thrombocytopenia. Consumption and dilution of clotting factors and platelets occur in these patients owing to ongoing hemorrhage, fluid boluses, and transfusion of PRBCs. This undoubtedly plays a role in the coagulopathy of trauma, but coagulopathy often occurs in massive trauma, even before these mechanisms have taken effect.[30,31] A number of retrospective reports have suggested that a more proactive approach to administering plasma and platelets in massive transfusion is associated with better outcomes. In response, many institutions have adopted massive transfusion protocols that call for plasma. and often platelets, to be given in a 1:1 ratio with RBCs.[32] A systematic review has concluded that the available evidence could not support any definite recommendations regarding specific ratios of blood components in massive transfusion.[33] The only large, multicenter randomized clinical trial (published early in 2015), the PROPPR trial, compared the use in massively transfused trauma patients of a 1:1:2 ratio (plasma to platelets to PRBCs) versus a 1:1:1 ratio and found no difference in mortality at 24 hours or 30 days, although fewer patients in the 1:1:1 group had died of exsanguination at 24 hours.[34]

When set ratios are not used, clinical assessment and judgment often augment laboratory values such as the INR, partial thromboplastin time, and fibrinogen and platelet counts, because there is no direct evidence supporting any particular threshold for platelet or coagulation factor replacement in patients with severe hemorrhage.[35] Commonly recommended goals in this setting would be to consider maintaining an INR below 1.5, fibrinogen level higher than 1 to 2 g/L, and platelet count above 50,000 to 100,000/μL.[35,36]

Adverse Effects of Nonmassive RBC Transfusion

See Table 111.1.

KEY CONCEPTS

- Red blood cell transfusion is indicated only to increase oxygen delivery at the tissue level.
- One unit of PRBCs can be expected to raise an adult's hemoglobin level by 1 g/dL. A similar increase is expected in children following the transfusion of 10 mL/kg of PRBCs.
- Large randomized controlled trials have supported newer, restrictive, red cell transfusion strategies. Pending further trials, a transfusion trigger of 7 to 8 g/dL is appropriate for most stable hospitalized patients.
- Platelet transfusions are typically used prophylactically for counts less than 10,000/μL in patients without bleeding and for counts less than 50,000/μL for patients undergoing surgery. Patient's undergoing high-risk surgical procedures, such as neurosurgery, are often transfused for platelet counts less than 100,000/μL.
- Prospective and retrospective reports have suggested a benefit to massive transfusion protocols, and the results of the PROPPR trial comparing a 1:1:1 ratio of FFP to platelets to PRBCs to a 1:1:2 ratio showed no difference in mortality at 24 hours or 30 days, although a post hoc analysis did find fewer deaths by exsanguination in the first 24 hours with a 1:1:1 ratio.
- FFP is not recommended for volume expansion, nonurgent reversal of a vitamin K antagonist, or treatment for an abnormal INR from any cause in the absence of bleeding. PCC is recommended for these cases, and four-factor concentrates are preferred, if available.
- Intravascular hemolytic transfusion reaction is the most serious transfusion reaction. It is usually the result of ABO incompatibility and typically results in immediate symptoms that can include fever, chills, headache, nausea, vomiting, sensation of chest restriction, severe joint or low back pain, burning sensation at the site of the infusion, and feeling of impending doom.
- Transfusion-related acute lung injury is now the leading cause of transfusion-related mortality reported to the FDA.
- Improved techniques for selecting and testing blood donors have dramatically reduced the risk of viral transmission of disease by transfusion. It is believed that the blood supply in the United States has never been safer.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 111: QUESTIONS & ANSWERS

111.1. Which one of the following immune-mediated transfusion reactions is most common and least serious?
- **A.** Allergic reaction
- **B.** Extravascular hemolysis
- **C.** Febrile reaction
- **D.** Intravascular hemolysis
- **E.** Transfusion-related acute lung injury

Answer: C. Febrile transfusion reaction is the most common and least serious transfusion reaction. It is defined as a 1°C (33.8°F) or higher temperature elevation that occurs with transfusion and for which no other medical explanation is found. Reactions are believed to result from antileukocyte antibodies, usually as a result of prior transfusion. Treatment is symptomatic with analgesics, antipyretics, and antihistamines.

111.2. An 81-year-old woman with a history of congestive heart failure (CHF) requires transfusion. She suffers from chronic anemia and is currently normotensive but tachypneic because of her CHF. You want to minimize the risk of fluid overload by transfusing slowly. Over how many hours can the transfusion be given?
- **A.** 2
- **B.** 3
- **C.** 4
- **D.** 6
- **E.** 12

Answer: C. Chronically anemic, normovolemic older patients are at greatest risk for developing congestive heart failure with the rapid infusion of blood. Transfusing more slowly (over a period of 4 hours) and administering diuretics are useful in preventing this complication.

111.3. Which of the following transfusion reactions is usually the result of ABO incompatibility, usually caused by human error, and considered to be the most serious transfusion reaction?
- **A.** Extravascular hemolytic transfusion reaction
- **B.** Febrile transfusion reaction
- **C.** Intravascular hemolytic transfusion reaction
- **D.** Transfusion-associated graft-versus-host disease
- **E.** Transfusion-related acute lung injury

Answer: C. An intravascular hemolytic transfusion reaction is considered to be the most serious of the transfusion reactions. It is usually caused by ABO incompatibility and is most often secondary to human error.

111.4. A 15-year-old male is receiving transfusion of packed red blood cells after a traumatic injury when he complains of itching. On examination, hives are found, and soon the patient develops difficulty breathing, tachypnea, tachycardia, and hypotension. The transfusion is stopped.

Which of the following medications should be administered?

A. Acetaminophen
B. Epinephrine and corticosteroids
C. Furosemide
D. RhoGAM
E. Third-generation cephalosporin

Answer: B. Occasionally, full anaphylaxis may be caused by an anti-immunoglobulin A (IgA) reaction to IgA in the donor's blood components. The patient is likely to have a genetic IgA deficiency. The presentation is similar to anaphylactic reactions from other causes. Treatment is with epinephrine and corticosteroids. Washed red blood cells (RBCs) and plasma products from IgA-deficient individuals can be used to avoid recurrence with subsequent transfusions.

CHAPTER 112

Anemia and Polycythemia

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ANEMIA

Principles

Background and Importance

Anemia is an absolute decrease in the number of circulating red blood cells (RBCs). The diagnosis is made when laboratory measurements fall below accepted normal values (Table 112.1).

Anemia is divided into two broad categories: emergent, having immediate life-threatening complications; and nonemergent, with less imminent danger to the patient. Factors other than the absolute number of circulating RBCs may place the patient in one category or another (eg, rate of onset and underlying hemodynamic reserve of the patient). Both groups necessitate a sound diagnostic approach, but emergent anemia may require supportive therapy concomitant with or in advance of the definitive diagnosis. Although patients with nonemergent anemia are usually referred to a specialist, the urgency of consultation depends predominantly on the patient's hemodynamic tolerance of the anemia.

Anatomy and Physiology

The major function of the RBC is oxygen transport from the lung to the tissue and carbon dioxide transport in the reverse direction. Oxygen transport is influenced by the amount of hemoglobin, its oxygen affinity, and blood flow. An alteration in any of these major components usually results in compensatory changes in the other two. For example, a decrease in hemoglobin is compensated by both inotropic and chronotropic cardiac changes that result in increased blood flow and decreased hemoglobin affinity at the tissue level, thereby allowing more oxygen release. Due to disease severity or underlying pathologic conditions, these compensatory responses may fail, resulting in tissue hypoxia and cell death.

Anemia stimulates the compensatory mechanism of erythropoiesis controlled by the hormone erythropoietin, which is a glycoprotein produced in the kidney (90%) and the liver (10%). It regulates the production of RBCs by controlling differentiation of the committed erythroid stem cell and is stimulated by tissue hypoxia and products of RBC destruction during hemolysis. Elevated in many types of anemia, erythropoietin enhances the growth and differentiation of erythroid progenitors.

Bone marrow contains pluripotent stem cells that can differentiate into erythroid, myeloid, megakaryocytic, and lymphoid progenitors. When the late normoblast extrudes its nucleus, it still contains a ribosomal network, which identifies the reticulocyte. The reticulocyte retains its ribosomal network for approximately 4 days, 3 days of which are spent in bone marrow and 1 day in the peripheral circulation. The RBC matures as the reticulocyte loses its ribosomal network and circulates for 110 to 120 days. The erythrocyte is then removed by macrophages that detect senescent signals. Under steady-state conditions, RBC mass remains constant because an equal number of reticulocytes replace the destroyed, senescent erythrocytes.

Pathophysiology

Common sites of blood loss in trauma include the pleural, peritoneal, pelvic, and retroperitoneal spaces. In nontraumatic circumstances, especially in patients receiving anticoagulants, the gastrointestinal tract, retroperitoneal space, uterus, and adnexa need to be considered.

Certain unusual hemolytic conditions can also cause rapid intravascular destruction of RBCs (Box 112.1). More common are patients with chronic compensated hemolytic anemia (eg, sickle cell disease), who may decompensate as a result of decreased erythrocyte production triggered by a viral infection.

Beyond red cell destruction, carbon monoxide poisoning, methemoglobinemia from nitrates, cyanhemoglobin from cyanide, and sulfhemoglobinemia from hydrogen sulfide may severely decrease functional hemoglobin. These patients often have fatigue, altered mental status, shortness of breath, and other manifestations of hypoxia without signs of RBC loss or volume depletion.

Clinical Features

The clinical manifestation of anemia depends on how rapidly the hematocrit falls and also on the patient's ability to compensate. Clinical signs and symptoms of acute blood loss include tachycardia, decreased blood pressure, postural hypotension, lightheadedness, increased heart rate, and increased respiratory rate. Complaints of thirst, altered mental status, and decreased urine output may also be present. The patient's age, concomitant illness, and underlying hematologic, cerebral, and cardiovascular status tremendously influence the presenting clinical findings. Children and young adults may tolerate significant blood loss with unaltered vital signs until a precipitant hypotensive episode occurs. Elderly patients commonly have underlying disease states that compromise their ability to compensate for blood loss.[1] Pertinent elements of the history and physical examination of patients with acute anemia are listed in Box 112.2.

In contrast, nonemergent anemias are usually seen in ambulatory patients complaining of fatigue and weakness, irritability, headache, postural dizziness, angina, decreased exercise tolerance, shortness of breath, or decreased libido. For patients without evidence of acute bleeding or emergent condition, elements of history and physical examination may help identify the cause (Box 112.3). When the anemia is of slow onset, the patient may adapt until the hemoglobin is very low. Most of these patients do not need immediate stabilization and can be further evaluated as outpatients.

Differential Diagnosis

The differential diagnosis of anemia is facilitated by classification of the anemia into one of three groups: decreased RBC production, increased RBC destruction, and blood loss. A complementary approach uses RBC morphology and indices. Figure 112.1 presents an algorithm for the evaluation of anemia.

TABLE 112.1

Hemogram Normal Values

AGE	HEMOGLOBIN (g/dL)	HEMATOCRIT (mL/dL)	RED BLOOD CELL COUNT ($\times 10^6$)
3 months old	10.4–12.2	30–36	3.4–4.0
3 to 7 years old	11.7–13.5	34–40	4.4–5.0
Adult man	14.0–18.0	40–52	4.4–5.9
Adult woman	12.0–16.0	35–47	3.8–5.2

BOX 112.1

Causes of Rapid Intravascular Red Blood Cell Destruction

Mechanical hemolysis associated with disseminated intravascular coagulation
Massive burns
Toxins (eg, some poisonous venoms: brown recluse spider, cobra)
Infections such as malaria or *Clostridium* sepsis
Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency with exposure to oxidant stress
ABO incompatibility transfusion reaction
Cold agglutinin hemolysis (eg, *Mycoplasma* organisms, infectious mononucleosis)
Paroxysmal nocturnal hemoglobinuria exacerbated by transfusion
Immune complex hemolysis (eg, quinidine)

BOX 112.2

History and Physical Examination for Clinically Severe Anemia

HISTORY

General
Out-of-hospital status, therapy, response to therapy
Bleeding diathesis
Previous blood transfusion
Underlying diseases, including allergies
Current medications, especially those causing platelet inhibition

Trauma
Nature and time of injury
Blood loss at scene

Nontrauma
Skin: Petechiae, ecchymoses
Gastrointestinal: Hematemesis, hematochezia, melena, peptic ulcer
Genitourinary: Last menstruation, menorrhagia, metrorrhagia, hematuria

PHYSICAL EXAMINATION

Vital Signs Measured Serially
Blood pressure, pulse, respiratory rate, oxygen saturation
Orthostatic blood pressure and pulse (contraindicated with severe hypotension)
Level and content of consciousness

Skin
Pallor
Diaphoresis
Jaundice
Cyanosis
Purpura, ecchymoses, petechiae
Evidence of penetrating wounds

Cardiovascular
Murmurs, S_3, S_4
Quality of femoral and carotid pulses

Abdomen
Hepatosplenomegaly
Pain, guarding, rebound on palpation
Rectal and pelvic examination
Masses
Stool hemoglobin testing

Diagnostic Testing

In a patient suspected of acute blood loss, samples for the following initial laboratory tests are drawn:

- Complete blood count and peripheral smear
- Blood sample for type and crossmatch
- Prothrombin time and international normalized ratio
- Partial thromboplastin time
- Electrolyte levels
- Glucose level (if the patient has altered consciousness)
- Creatinine level
- Urinalysis for free hemoglobin
- Clotting and unclotted blood samples for later testing

If possible, a hematocrit or hemoglobin should be measured in the emergency department (ED). Although it may take hours before the hematocrit or hemoglobin correctly reflects the degree of blood loss, the initial value is useful in determining a baseline. On occasion, this value reveals an underlying anemia with superimposed acute blood loss. Depending on severity, a blood sample is sent for type and crossmatch. Peripheral smear interpretation is done on pretreatment blood samples.

The initial laboratory evaluation for a patient with *non*emergent anemia also includes a complete blood count with leukocyte differential, reticulocyte count, peripheral smear (Fig. 112.2), and RBC indices, including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). RBC indices are useful in classifying anemias caused by a production deficit (Table 112.2). MCV is a measure of RBC size; decreases and increases reflect microcytosis and macrocytosis, respectively. MCH incorporates both RBC size and hemoglobin concentration. It is influenced by both and is the least helpful of the indices. The MCHC index is a measure of the concentration of hemoglobin. Low values represent hypochromia, whereas high values are noted only in patients with decreased cell membrane relative to cell volume, such as in the case of spherocytosis. An additional index is the RBC distribution width (RDW), a measure of RBC homogenicity. RDW is automatically calculated as the standard deviation of MCV divided by MCV multiplied by 100. A normal RDW is 13.5 ± 1.5%. The RDW is elevated in anemias caused by nutritional deficiencies; however, it is not specific for any abnormality.

Measurements of coagulation status, electrolytes, glucose, blood urea nitrogen, and creatinine are useful in the diagnosis of underlying disease processes that may relate to the patient's anemia. Because values of folate, vitamin B_{12}, iron, total iron-binding capacity, reticulocytes, and direct antiglobulin (Coombs test) are altered by transfusion, pretreatment samples should be obtained in patients where the cause of anemia is not known.

BOX 112.3

History and Physical Examination for Nonemergent Anemia

HISTORY

Symptoms of Anemia
Chest pain, decreased exercise tolerance, dyspnea
Weakness, fatigue, dizziness, syncope

Bleeding Diathesis
Bleeding after trauma, injections, tooth extractions
Spontaneous bleeding, such as epistaxis, menorrhagia
Spontaneous purpura and petechiae

Sites of Blood Loss
Respiratory: Epistaxis, hemoptysis
Gastrointestinal: Hematemesis, hematochezia, melena
Genitourinary: Abnormal menses, pregnancies, hematuria
Skin: Petechiae, ecchymoses

Intermittent Jaundice, Dark Urine

Dietary History
Vegetarianism
Poor nutrition

Drug Use and Toxin Exposure, Including Alcohol

Racial Background, Family History

Underlying Disease
Uremia, liver disease, hypothyroidism
Chronic disease states, such as cancer, rheumatic or renal disease
Previous surgery

Miscellaneous
Previous treatment of anemia
Weight loss
Back pain

PHYSICAL EXAMINATION

Skin
Pallor
Purpura, petechiae, angiomas
Ulcerations

Eye
Conjunctival jaundice, pallor
Funduscopic hemorrhage, petechiae

Oral
Tongue atrophy, papillary soreness

Cardiopulmonary
Heart size, murmurs, extra cardiac sounds
Rales, other signs of pulmonary edema

Abdomen
Hepatomegaly, splenomegaly
Ascites
Masses

Lymph Nodes

Neurologic
Altered positions or vibratory sense
Peripheral neuritis

Rectal and Pelvic

TABLE 112.2

Calculation of Red Blood Cell Indices and Normal Values

INDEX	FORMULA FOR CALCULATION	NORMAL RANGE
Mean corpuscular volume	Hematocrit (%) divided by RBC count ($10^6/\mu L$)	81–100 fL
Mean corpuscular hemoglobin	Hemoglobin (g/dL) divided by RBC count ($10^6/\mu L$)	26–34 pg
Mean corpuscular hemoglobin concentration	Hemoglobin (g/dL) divided by hematocrit (%)	31%–36%

fL, Femtoliter; RBC, red blood cell.

Management

Stabilization of emergent anemia commonly runs parallel to assessment. If the signs and symptoms suggest potential life-threatening conditions, intravenous lines are placed.

Disposition

Criteria for the admission of patients with nonemergent anemia are shown in Box 112.4.

BOX 112.4

Admission Criteria for Nonemergent Anemia

Developing cardiac symptoms, such as shortness of breath or chest pain, or neurologic symptoms
Initial unexplained hemoglobin value less than 8–10 g/dL or hematocrit less than 25% to 30%*
Major difficulty in obtaining outpatient care for patients whose hemoglobin levels are significantly low or when comorbidity is present*

*Consider observation unit for initial evaluation and stabilization.

ANEMIAS DUE TO DECREASED RED BLOOD CELL PRODUCTION

Principles

Background and Importance

Anemias caused by decreased RBC production are insidious in onset and are associated with decreased reticulocyte count. A subclassification by indices of anemias caused by decreased RBC production is listed in Box 112.5. The RBC indices and a peripheral smear are useful in securing the diagnosis. The definitive

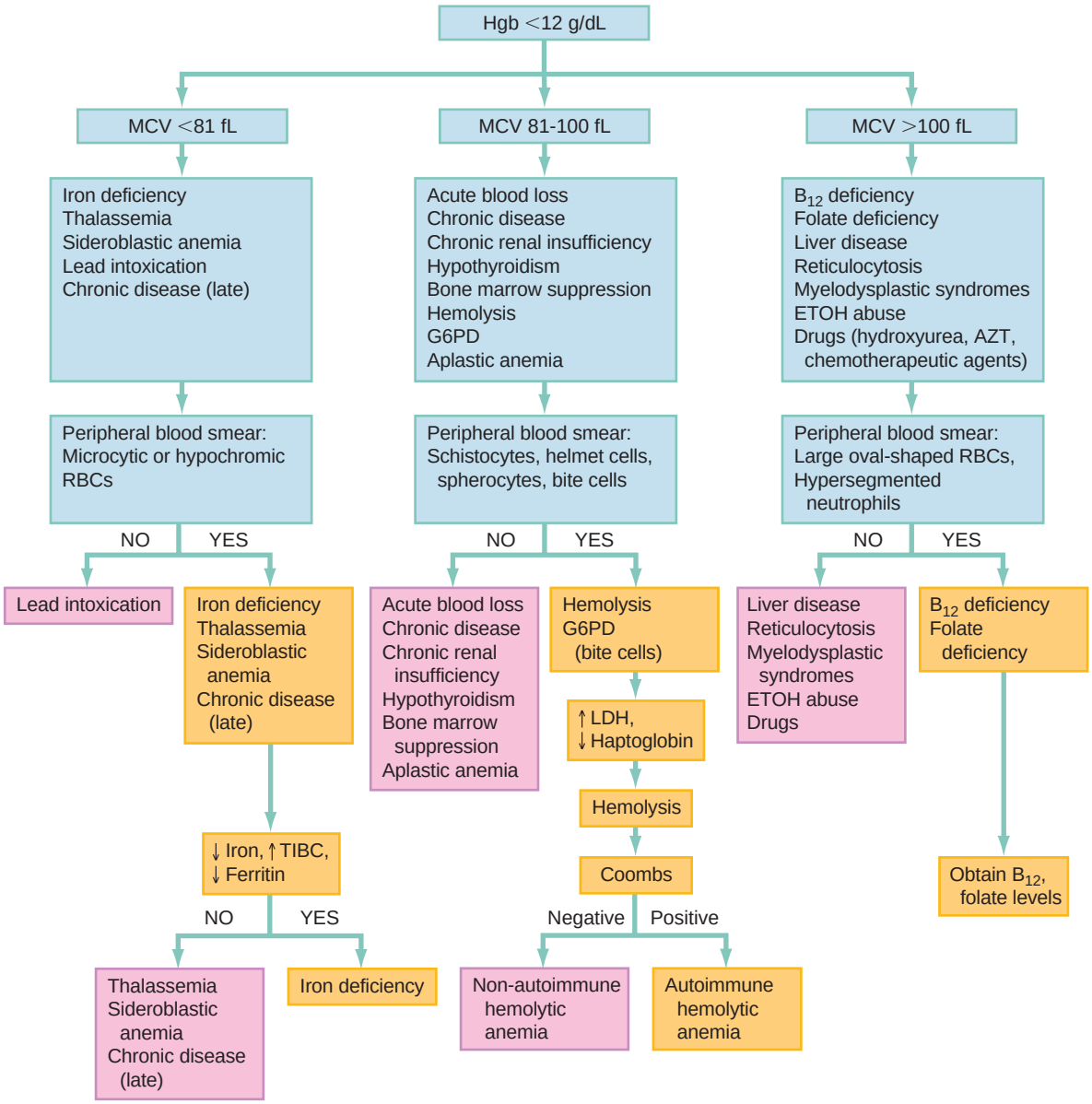

Fig. 112.1. Algorithm for the evaluation of anemia. *AZT,* Azathioprine; *ETOH,* ethanol; *fL,* femtoliter; *G6PD,* glucose-6-phosphate dehydrogenase; *Hgb,* hemoglobin; *LDH,* lactate dehydrogenase; *MCV,* mean corpuscular volume; *RBCs,* red blood cells; *TIBC,* total iron-binding capacity.

diagnosis may require bone marrow examination. The emergency clinician rarely initiates replacement therapy, except in circumstances that require transfusion. Replacement of iron, vitamin B_{12}, or folate without proof of cause is generally unnecessary and unwise.

Hypochromic microcytic anemias are subdivided into deficiencies of the three building blocks of hemoglobin: iron (iron deficiency anemia; Fig. 112.3), globin (thalassemia), and porphyrin (sideroblastic anemia and lead poisoning). Anemia of chronic disease, a secondary iron abnormality, rounds out the differential diagnosis. Not all microcytic anemias are the result of iron deficiency, and routine iron therapy for a patient with a low MCV and MCHC is inappropriate.[2]

Iron Deficiency Anemia

Principles. Iron deficiency is a frequent cause of chronic anemia seen in the ED. It is the most common anemia in women of childbearing age. In older patients, occult blood loss, especially gastrointestinal, may initially appear as iron deficiency anemia. Because changes in RBC size and hemoglobin content occur only after bone marrow and cytochrome iron stores are depleted, a patient may have early symptoms of iron deficiency (eg, fatigue) without manifesting changes in RBC structure.

Clinical Features. Most anemias secondary to iron deficiency are nonemergent. The symptoms related to anemia are secondary to the body's ability to adapt to the low hemoglobin levels over time and the eventual inability of the tissues to receive enough oxygen for their metabolic demands. The clinical features of iron deficiency anemia are the same as those described earlier.

Diagnostic Testing. The diagnosis is made by laboratory evaluation of the fasting level of serum iron, serum ferritin, and total iron-binding capacity. The laboratory interpretation and pitfalls are outlined in Table 112.3. A concentrated search for occult blood loss is vital.[3]

Management. Therapy consists of oral iron replacement. A cost-effective form is ferrous sulfate. The dosage is 300 mg for adults (60 mg of elemental iron) or 3 mg/kg/day for children. This medication is generally well tolerated, although it may cause

nausea, vomiting, or constipation. Patients should be warned that iron turns their stools black and that bleeding from the digestive tract can also be manifested as black stool. In patients with poor oral tolerance or absorption, parenteral iron therapy may be necessary.[3]

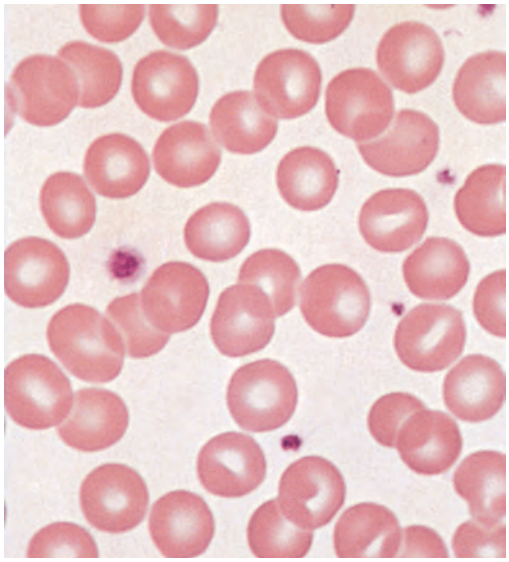

Fig. 112.2. Normal smear. (From Hoffbrand AV, Pettite JE: Color atlas of clinical hematology, ed 3, London, 2000, Mosby, p 22.)

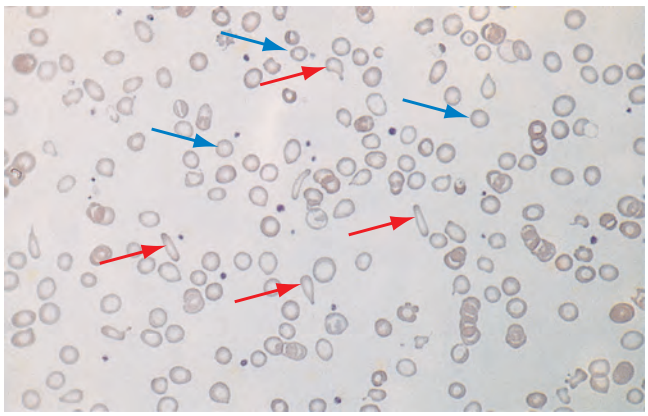

Fig. 112.3. Iron deficiency anemia with hypochromic, microcytic cells and poikilocytes (abnormally shaped cells). (From Hoffbrand AV, Pettite JE: Color atlas of clinical hematology, ed 3, London, 2000, Mosby, p 44.)

The patient may experience a sense of improvement in as few as 24 hours. Reticulocytosis appears during a 3- or 4-day period in children but may take more than 1 week in adults. The hemoglobin concentration rises on a similar schedule. Explanations for response failures to iron therapy include the following: patient noncompliance with iron supplementation, insufficient replacement, incorrect diagnosis, or there is an additional process complicating the iron deficiency.[4]

Thalassemia

Principles. The hemoglobin molecule is present as two paired globin chains. Each type of hemoglobin is made up of different globins. Normal adult hemoglobin (HbA) is made up of two alpha chains and two beta chains ($\alpha_2\beta_2$). HbA_2 is $\alpha_2\delta_2$ and is a variant of hemoglobin A and has two alpha and two delta chains. Fetal hemoglobin (HbF) is $\alpha_2\gamma_2$. A separate autosomal gene controls each globin chain.

BOX 112.5

Differential Diagnosis of Anemias Caused by Decreased Red Blood Cell Production Subclassification by Red Blood Cell Indices

HYPOCHROMIC MICROCYTIC ANEMIAS (DECREASED MCV AND HEMOGLOBIN CONCENTRATION)

Iron deficiency
Thalassemia
Sideroblastic anemia or lead poisoning
Chronic disease (eg, cancer, renal or inflammatory disease); normochromic and normocytic indices often found

MACROCYTIC (ELEVATED MCV)

Vitamin B_{12} deficiency
Folate deficiency
Liver disease
Hypothyroidism

NORMOCYTIC (NORMAL MCV AND HEMOGLOBIN CONCENTRATION)

Primary bone marrow involvement: Aplastic anemia, myeloid metaplasia with myelofibrosis, myelophthisic anemia
Resulting from underlying disease: Hypoendocrine state (thyroid, adrenal, pituitary), uremia, chronic inflammation, liver disease

MCV, Mean corpuscular volume.

TABLE 112.3

Diagnostic Tests for Iron Deficiency Anemia

TEST	NORMAL RESULT	IRON DEFICIENCY LEVEL	INTERPRETATION
Fasting serum iron	60–180 μg/dL	<60 μg/dL	Diurnal variation (draw in morning); increased by hepatitis, hemochromatosis, hemolytic anemia, and aplastic anemia; decreased in infection
Total iron-binding capacity	250–400 μg/dL	>400 μg/dL	Increased in late pregnancy or hepatitis; decreased in infection
Percentage of saturation (serum iron) of total iron-binding capacity	15%–45%	<15%	
Serum ferritin	10–10,000 mg/mL	<10 mg/mL	Reflects iron stores; may increase as an acute-phase reactant in infection
Bone marrow stainable iron	Hemosiderin granules in reticuloendothelial cells	Absent	Standard for assessment of iron stores

Pathophysiology. Thalassemia is a genetic autosomal defect reflected by the decreased synthesis of globin chains. Deletions in these globin genes result in an absence or decreased function of the messenger RNA that codes for that globin. The various globins (α, β, δ, and γ) may be affected by a number of genetic combinations. Decreased globin production in thalassemia results in decreased hemoglobin synthesis and ineffective erythropoiesis, which causes increased intramarrow hemolysis with destruction of RBCs. Beta thalassemia has an excess of alpha-globins, leading to the formation of alpha-globin tetramers and α-thalassemia results in an excess of β-globins, which leads to the formation of β-globin tetramers called *hemoglobin H.* The abnormal formation of hemoglobin at various concentrations results in complications, such as red cell membrane breakage and hemolysis. Clinical classification is by phenotype: thalassemia may be major, intermedia, minor, or silent. Normal erythropoiesis has a 10% to 20% incidence of ineffective release, but ineffective release of erythropoiesis may double or triple in patients with thalassemia.[5,6]

Clinical Features. Although many variations in thalassemia are possible, only three are commonly considered. Homozygous β-chain thalassemia (thalassemia major) occurs predominantly in Mediterranean populations. It represents one of the most common single-gene disorders. The disease is characterized by severe anemia, hepatosplenomegaly, jaundice, abnormal development, and premature death. Patients are transfusion dependent and die as a result of iron deposition in tissues, particularly the myocardium, or infection.[7,8]

Heterozygous β-chain thalassemia (thalassemia minor) is manifested as a mild anemia and most patients are asymptomatic.

Alpha-thalassemia varies in spectrum from an asymptomatic carrier state to prenatal death. Four gene loci control this range. The tolerated forms are more commonly seen in Asians and African Americans.

Diagnostic Testing. Thalassemia is a microcytic, hypochromic anemia. Hypochromia, target cells, and basophilic stippling are noted on the peripheral smear. The MCV is commonly lower than seen with iron deficiency and serum iron levels are normal. The diagnosis is made with hemoglobin electrophoresis and genetic testing. Screening for carriers is performed by measurement of RBC indices and estimation of the HbA_2 concentration. Prenatal diagnosis can be made by analysis of fetal blood or by fetal DNA obtained by chorionic villus sampling.

Management. Therapy consists of blood transfusions, where the goal of transfusion therapy include correction of anemia, suppression of erythropoiesis, and inhibition of increased gastrointestinal iron absorption. Iron chelation therapy is often required. Deferoxamine, a subcutaneously administered chelator, has been the chelation therapy of choice and is still used. However, many centers prefer the oral chelator deferasirox (Exjade) because of greater patient satisfaction and ease of administration. Deferasirox is renally cleared; thus dose adjustments may be necessary for chronic renal insufficiency, and it is contraindicated in end-stage renal disease.[6,9]

Bone marrow transplantation from human leukocyte antigen (HLA)-identical donors has resulted in disease-free survival in 60% to 90%, but its role in thalassemia has yet to be determined, and gene therapy does not yet exist.[10]

Usually, no treatment is necessary for thalassemia minor.

Sideroblastic Anemia

Principles. Sideroblastic anemia involves a defect in porphyrin synthesis. The resultant impaired hemoglobin production causes excess iron to be deposited in the mitochondria of the RBC precursor, increased serum iron and ferritin levels, and transferrin saturation. The defective heme synthesis results in ineffective erythropoiesis, mild to moderate anemia, and a dimorphic peripheral smear with hypochromic microcytes along with normal and macrocytic cells.

Clinical Features. Although sderoblastic anemia is found in a rare sex-linked hereditary form, the idiopathic form is a common type of refractory anemia in elderly patients. Pallor and splenomegaly may be noted, and iron staining of the peripheral smear may demonstrate iron-containing inclusion bodies in RBCs. Idiopathic sideroblastic anemia is considered a preleukemic state, and acute myelogenous leukemia develops in approximately 5%.

Differential Diagnosis. Secondary causes of sideroblastic anemia include toxins, such as chloramphenicol, isoniazid, and cycloserine, as well as diseases, such as hemolytic and megaloblastic anemia, infection, carcinoma, leukemia, and rheumatoid arthritis. The exact mechanisms of these causative agents and diseases are unknown. Lead poisoning, one reversible cause of sideroblastic anemia, may be suggested by basophilic stippling on the peripheral smear. Elevated blood lead levels are diagnostic. Alcohol abuse may also result in disordered heme synthesis, which can be corrected by alcohol cessation or by parenteral pyridoxal phosphate in cases of continued abuse. Oral pyridoxine may be ineffective because of impaired conversion to the active form in alcoholic patients.[11]

Management. Some patients with primary sideroblastic anemia are deficient in pyridoxine (vitamin B_6) and respond to treatment with 100 mg of pyridoxine three times a day. About two-thirds will respond but most remain anemic. These patients are susceptible to iron overload if long-term transfusion therapy is necessary, but they may respond to chelation. Treatment for secondary forms are supportive.

Anemia of Chronic Disease

Principles. Anemia of chronic disease is secondary to reduced RBC bone marrow production and reduced RBC survival time in the peripheral circulation. Malignancies, chronic inflammation, renal insufficiency, chronic heart failure, chronic obstructive lung disease, and infection are common causes.

Clinical Features. Symptoms are usually those related to the underlying disease and not from the anemia.

Diagnostic Testing. Anemia of chronic disease is common and typically normochromic, normocytic. It is characterized by low serum iron levels, low total iron-binding capacity, and normal or elevated ferritin levels. Bone marrow is normal, but staining reveals an abnormality in the mobilization of iron from reticuloendothelial cells. This anemia can be differentiated from iron deficiency by total iron-binding capacity, serum ferritin level, bone marrow examination, and nonresponsiveness to a trial of iron therapy. A complete search for occult blood loss is necessary during the evaluation of this diagnosis because iron deficiency may be superimposed.

Management. Because the hematocrit is seldom less than 25% to 30%, therapy is not usually required. Treatment should be directed at the underlying causes.[12,13]

Macrocytic and Megaloblastic Anemias

Principles. The hematologic manifestation of a total-body alteration in DNA synthesis, megaloblastic anemia is caused by vitamin B_{12} and folic acid deficiency, which appears clinically in tissues with rapid cell turnover, including hematopoietic cells and those of mucosal surfaces, particularly in the gastrointestinal tract. This deficiency is characterized by ineffective erythropoiesis and pancytopenia. Vitamin B_{12} and folate deficiencies have different developmental histories, but the clinical result is similar. Differentiation of folate and vitamin B_{12} deficiencies usually depends on laboratory measurements.

Clinical Features. Table 112.4 lists a number of the problems associated with megaloblastic anemia and their underlying pathologic states. A unique feature of vitamin B_{12} deficiency is its

TABLE 112.4

Clinicopathologic Correlation of Manifestations of Megaloblastic Anemia

CLINICAL FEATURES	PATHOLOGIC CONDITION
Lemon yellow skin	Combination of pallor with low-grade icterus from ineffective erythropoiesis
Petechiae, mucosal bleeding	Thrombocytopenia
Infection	Leukopenia
Fatigue, dyspnea on exertion, postural hypotension	Anemia
Sore mouth or tongue	Megaloblastosis of mucosal surfaces
Diarrhea and weight loss	Malabsorption from mucosal surface change
Paresthesias and ataxia	Related to myelin abnormality in vitamin B_{12} deficiency only

BOX 112.6

Causes of Folate Deficiency

- Inadequate dietary intake
  - Poor diet or overcooked or processed food diet
  - Alcoholism
- Inadequate uptake
  - Malabsorption with sprue and other chronic upper intestinal tract disorders, drugs such as phenytoin and barbiturates, or blind loop syndrome
- Inadequate use
  - Metabolic block caused by drugs, such as methotrexate or trimethoprim
  - Enzymatic deficiency, congenital or acquired
- Increased requirement
  - Pregnancy
  - Increased red blood cell (RBC) turnover: Ineffective erythropoiesis, hemolytic anemia, chronic blood loss
  - Malignant disease: Lymphoproliferative disorders
- Increased excretion or destruction or dialysis

BOX 112.7

Causes of Vitamin B_{12} Deficiency

- Inadequate dietary intake
  - Total vegetarianism: No eggs, milk, or cheese
  - Chronic alcoholism (rare)
- Inadequate absorption
  - Absent, inadequate, or abnormal intrinsic factor, as seen in patients with pernicious gastrectomy and anemia; in anemia, autoimmune antibodies act against gastric parietal cells and intrinsic factor
  - Abnormal ileum, as can occur in sprue and inflammatory bowel disease
- Inadequate use
  - Enzyme deficiency
  - Abnormal vitamin B_{12}–binding protein
- Increased requirement by increased body metabolism
- Increased excretion or destruction

neurologic involvement. Patients may have paresthesias in their hands and feet, decreased proprioception, or decreased vibratory sense; weakness and spasticity of the lower extremities with altered reflexes; and variable mental changes, such as depression, paranoid ideation, irritability, and forgetfulness. The last two complaints have also been noted with folic acid deficiency. Vitamin B_{12}–deficient patients have some of the lowest hemoglobin levels seen in any disease state.

Differential Diagnoses. Folic acid, absorbed in the duodenum and jejunum, is commonly found in green vegetables, cereals, and fruit. It may be destroyed completely by cooking. The body requires approximately 100 µg/day and usually stores 6 to 20 mg. Therefore, a 2- to 4-month supply is available before megaloblastic changes occur. Causes of folate deficiency are listed in Box 112.6. Most patients with folate deficiency have either an inadequate dietary intake, such as alcoholic patients, or increased use, as in pregnancy.

Vitamin B_{12} is found in foods of animal origin and is absorbed in the ileum after binding to intrinsic factor, which is a glycoprotein secreted by gastric parietal cells. The adult requirement is 1 or 2 µg/day, with a body store of 5 mg. Therefore, megaloblastic changes may take up to 4 years to develop after cessation of vitamin B_{12} uptake. The various causes of vitamin B_{12} deficiency are listed in Box 112.7. The most common cause is chronic malabsorption.

Megaloblastic anemia that is not responsive to folate or vitamin B_{12} is commonly related to antimetabolites used in chemotherapy or rare inherited disorders of DNA synthesis.

Macrocytic anemias unrelated to megaloblastic changes are seen frequently. Liver disease, often associated with alcoholism, is the most common cause. Macrocytic target cells may be seen on the peripheral smear in conjunction with this disorder. Hypothyroidism and hemolysis may also be manifested as macrocytic anemia.

Diagnostic Testing. Macrocytic anemia is suggested when the MCV is greater than 100 fL, but other criteria need to be met for megaloblastosis to be considered the cause of the macrocytic anemia. On the peripheral smear, large oval red cells (macro-ovalocytes) and hypersegmented polymorphonuclear neutrophils are diagnostic (Fig. 112.4). A bone marrow aspirate may reveal morphologic changes consistent with megaloblastic erythropoiesis. Other potentially useful laboratory tests include vitamin B_{12} and folate levels, red cell folate, and lactate dehydrogenase (LDH). Laboratory techniques, values, and interpretations are listed in Table 112.5. Screening tests to differentiate between megaloblastic anemia and macrocytic anemia of other causes include a peripheral smear for macro-ovalocytes, hypersegmented polymorphonuclear neutrophils, and the LDH level.

Management. Because one deficiency may cause gastrointestinal absorption changes that beget other deficiencies, the emergency clinician may be forced to initiate therapy before the final diagnosis is made. However, it is important to obtain baseline laboratory specimens. The usual dosage for patients with megaloblastic anemia secondary to folate deficiency is 1 mg of oral folic acid per day. Parenteral administration is generally unnecessary because most cases are due to dietary deficiency. In contrast, malabsorption is the most common cause of vitamin B_{12} deficiency, and parenteral therapy is initiated at 100 µg/day intramuscularly for the first 7 to 10 days. Thereafter, only monthly 100-µg doses are necessary. The response is often dramatic, with reticulocyte counts rising up 30% to 50% and normalization of RBC, white blood cell (WBC), and platelet counts in 6 to 8 weeks. We do not recommend vitamin B_{12} or folate supplements in patients with undiagnosed anemia. Unfortunately, the routine injection of vitamin B_{12} in the elderly is still a common practice.[14]

Normochromic and Normocytic Anemias

Principles. The origin of normochromic and normocytic anemias secondary to decreased production is not as obvious as that of macrocytic and microcytic anemias, because the latter give clues to their origin by alterations in RBC indices. One hematologic parameter that can aid in the diagnosis of normocytic anemia associated with hypoproduction is the reticulocyte count, which reflects RBC bone marrow production. Reticulocytes are released from bone marrow every 1 to 3 days and contain residual RNA that can be detected by supravital staining. With an average MCV of 160 fL, sufficient numbers of reticulocytes can increase the MCV of the total erythrocyte count. The reticulocyte count is expressed as a percentage of the total RBC population and needs to be related ("corrected") to the RBC count of the patient. The corrected reticulocyte count is equal to the measured percentage of reticulocytes times the patient's hematocrit (%) divided by 45% (taken as the normal hematocrit). The normal range is 1% to 3%.

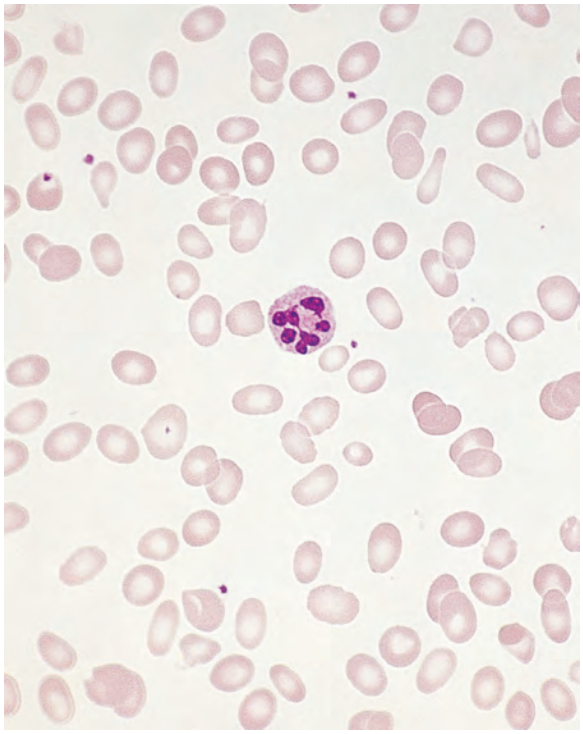

Fig. 112.4. Megaloblastic anemia with macrocytic red cells and hypersegmented polymorphonuclear neutrophils. (From Hoffbrand AV, Pettite JE: Color atlas of clinical hematology, ed 3, London, 2000, Mosby, p 61.)

Normocytic anemia may be classified as being due to primary bone marrow involvement or a secondary marrow response to underlying disease.

Differential Diagnoses. Myelophthisic anemia is bone marrow failure resulting from replacement by an invading tumor, leukemia, lymphoma, or, rarely, granuloma. A more basic defect or inhibitor may complicate the problem because the degree of anemia cannot always be correlated with the extent of bone marrow invasion. Any patient with oncologic disease may develop this type of anemia. Useful clues are signs of extramedullary hematopoiesis, such as hepatosplenomegaly and a leukoerythroblastic peripheral smear demonstrating immature WBCs, nucleated RBCs, and poikilocytosis (teardrop-shaped red cells). The final diagnosis is made by bone marrow examination, and therapy is directed at the underlying disorder.

Myelofibrosis of unknown origin is the usual cause of primary bone marrow failure associated with extramedullary hematopoiesis. The diagnosis may be made by bone marrow examination. Treatment is supportive, although a splenectomy or alkylating agents may help treat complications of extramedullary blood cell production, such as hepatosplenomegaly.

The hypoplastic anemias of secondary origin are commonly seen as mild chronic anemias with low reticulocyte counts. They have a normal MCV and RDW. These are diagnoses of exclusion. Anemia of chronic disease may have microcytic or normocytic indices. It is associated with chronic inflammation (eg, rheumatoid arthritis, chronic infections such as tuberculosis and osteomyelitis, and malignant disease). Hypoendocrinism caused by hypothyroidism, hypoadrenalism, or hypopituitarism results in a hypometabolic state in which the bone marrow responds poorly to erythropoietin, and erythropoietin levels may be low. The anemia of chronic renal failure is thought to be caused by a number of factors including decreased erythropoietin production, hemolysis, suppression by dialyzable factors, and increased blood loss caused by platelet abnormalities. If necessary, it may be corrected by erythropoietin replacement therapy.[15]

Aplastic Anemia

Principles. Aplastic anemia is rare but may have severe manifestations. It is suspected in anemic patients with normal indices, a low reticulocyte count, and a history of exposure to certain drugs or chemicals (Table 112.6), which is the cause in 50% of cases. Autoimmune disease, viral hepatitis, radiation, and pregnancy have also been associated with aplastic anemia. The aplastic state may extend to all cell lines and results from destruction by immune-stimulated lymphocytes or failure of the marrow stem cell. On occasion, only one cell line fails, as in RBC aplasia. This condition represents injury occurring at a later stage of cellular differentiation.

TABLE 112.5

Serum Tests for Diagnosis and Differentiation of Megaloblastic Anemia

TEST	TECHNIQUE	VALUE	INTERPRETATION
Vitamin B_{12}	Microbiologic or radioisotope	Normal: 300–900 μg/L Deficient: <200 μg/L	Although they may overlap clinically, vitamin B_{12} level is usually normal in folate deficiency.
Folate	Microbiologic or radioisotope	Deficient: <3 μg/L	Vitamin B_{12} deficiency may elevate folate levels by blocking transfer of serum folate to RBCs; hemolysis may elevate folate levels.
Red cell folate	Calculated	Normal: 200–700 μg/L Folate deficiency: <140 μg/L	Index of tissue folate is less influenced by diet and is increased in vitamin B_{12} deficiency because of block.
Lactate dehydrogenase	Spectrophotometric	Normal: 95–200 IU Megaloblastic anemia: 4 to 50 times normal	Normal in other macrocytic anemias; elevated two to four times normal in hemolytic anemias; isoenzymes may be helpful.

RBC, Red blood cell.

TABLE 112.6

Aplastic Anemia Caused by Drugs or Chemicals

CAUSE	RELATIVE INCIDENCE (%)
Chloramphenicol	61
Phenylbutazone	19
Anticonvulsants	4
Insecticides	4
Solvents	4
Sulfonamides	3
Gold	3
Benzene	2

From Silver BJ, Zuckerman KS: Aplastic anemia: recent advances in pathogenesis and treatment. Med Clin North Am 64:607, 1980.

Clinical Features. Clinical presentation can be related to the anemia itself, such as fatigue. However, the more common presentation is from infections secondary to neutropenia or mucosal bleeding from the accompanying thrombocytopenia.

Diagnostic Testing. The diagnosis of aplastic anemia is suggested by the presence of low hemoglobin, low WBC count, and low platelets. Low reticulocyte count is also present, but the precise diagnosis necessitates bone marrow examination.

Management. General treatment of aplastic anemia includes removal of suspected marrow toxins from the environment, avoidance of aspirin, oral hygiene, and suppression of menses. Transfusions are given in life-threatening circumstances. Bone marrow or peripheral blood stem cell transplantation from a histocompatible sibling can cure bone marrow failure, with survival rates of 78% to 94%.[16] However, only 30% of patients have suitably matched sibling donors to allow allogeneic transplantation. Immunosuppression with antithymocyte globulin, antilymphocyte globulin, and other cytotoxic chemotherapy is used in the majority of patients who are not stem cell transplantation candidates. Unrelated donors are preferred to avoid sensitization of the patient against the non-HLA antigens that are present in bone marrow from a family donor. The disease has a wide range of severity, and the overall 5-year survival rate is 30% to 40%. Even with supportive therapy, up to 80% of patients with severe aplastic anemia still die. Although difficult to find an immunologic match, bone marrow transplantation before blood product sensitization has resulted in an 80% 5-year survival rate. This is usually combined with immunosuppressive therapy consisting of antilymphocyte globulin.[17,18]

INCREASED RED BLOOD CELL DESTRUCTION

Principles

Pathophysiology

Defined by a shortened life span of the erythrocyte, acute hemolytic anemias can be devastating and require rapid diagnosis and intervention (see Box 112.1). Fortunately, they are relatively rare in comparison to the chronic hemolytic conditions. Chronic disorders may be related to primary blood disorders (eg, sickle cell anemia) or may be a result of other disease states (eg, chronic renal failure). These disorders may be manifested as acute hemolytic anemia if the tenuous balance between RBC production and destruction is upset. If the patient can be simultaneously demonstrated to have a normal hematocrit and reticulocyte count, differentiation between acquired and inherited hemolytic anemia is possible.

Clinical Features

The clinical signs and symptoms of hemolytic anemia are, in general, caused by either intravascular or extravascular processes, and this division assists in the differential diagnosis approach.

Intravascular hemolysis is usually associated with an acute process and has a dramatic appearance. Large numbers of RBCs may be lysed within the circulation. The pathologic process primarily involves the handling of released hemoglobin and a compensatory response to an acute decrease in oxygen-carrying capability. Free hemoglobin initially binds to haptoglobin and hemopexin. This complex is transported to the liver, converted to bilirubin, conjugated, and excreted. When this binding and transport system is overwhelmed, free hemoglobin may appear in the blood and tint it pink. In contrast, myoglobin is a small molecule that is rapidly cleared from serum. Examination of spun whole blood demonstrates clear serum in myoglobinemia, pink serum with free hemoglobin from intravascular hemolysis, and yellow serum from extravascular hemolysis with increased bilirubin production. In severe cases, the last mechanism may also result in free hemoglobin.

The clinical appearance of intravascular hemolysis may vary from mild chronic anemia, as seen in cases of mechanical hemolysis, to prostration, fever, abdominal and back pain, and mental changes, as seen with transfusion reactions. Jaundice, brown to red urine, and oliguria associated with acute renal failure induced by the hemoglobin complex can also occur.

The clinical picture of extravascular hemolysis is usually mild to moderate anemia, intermittent jaundice, and enlargement of the spleen. The signs and symptoms vary with the severity and chronicity of the hemolysis. Splenic blood flow slows as RBCs travel in the sinusoids close to the reticuloendothelial system, which is uniquely designed for removal of older or damaged cells. Primary splenic overactivity, antibody-mediated changes, or RBC membrane abnormalities may cause this normal splenic function to increase to a pathologic degree. Hemolysis may also occur within the bone marrow. Normal erythropoiesis is ineffective 10% to 20% of the time and can increase when abnormal RBCs are produced, as in thalassemia, megaloblastic anemia, or some hemolytic anemias.[19] After hemoglobin is disassembled in the reticuloendothelial cell, globin returns to the amino acid pool, iron is transported by transferring to the bone marrow or iron stores, and the pyrrole ring is converted to bilirubin. The unconjugated bilirubin circulates to the liver and is transformed and excreted in urine as conjugated bilirubin.

Differential Diagnoses

Hemolytic anemias may be classified as congenital or acquired, Coombs positive or Coombs negative, or caused by processes intrinsic or extrinsic to the cell membrane. The last method gives a useful differential diagnosis classification of hemolysis (Box 112.8).

Intrinsic Enzyme Defects. Eighty-five percent to 90% of the membrane-sustaining energy production of the erythrocyte is through the anaerobic glycolytic pathway. At least eight known enzyme deficiencies are associated with this pathway. The most common is pyruvate kinase deficiency, which is manifested with hemolytic jaundice and is usually diagnosed in infancy.

The remaining 10% to 15% of RBC glycolysis occurs by way of the hexose monophosphate shunt. This bypass mechanism occurs in the early stages of the glycolytic pathway and generates reduced nicotinamide adenine dinucleotide phosphate (NADPH),

BOX 112.8

Classification of Hemolytic Anemia

INTRINSIC

Enzyme defect
- Pyruvate kinase deficiency
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Membrane abnormality
- Spherocytosis
- Elliptostomatocytosis
- Paroxysmal nocturnal hemoglobinuria
- Spur cell anemia

Hemoglobin abnormality
- Hemoglobinopathies
- Thalassemias (anemias)
- Unstable hemoglobin
- Hemoglobin M

EXTRINSIC

Immunologic
- Alloantibodies
- Autoantibodies

Mechanical
- Microangiopathic hemolytic anemia
- Cardiovascular, such as prosthetic heart valve disease

Environmental
- Drugs
- Toxins
- Infections
- Thermal

Abnormal sequestrations, as in hypersplenism

BOX 112.9

Drugs Associated With Hemolysis in Glucose-6-Phosphate Dehydrogenase Deficiency

Analgesics and antipyretics: acetanilid, aspirin, phenacetin
Antimalarials: Primaquine, quinacrine, quinine
Nitrofurans
Sulfa drugs: Sulfamethoxazole, sulfacetamide, sulfones
Miscellaneous: Naphthalene, fava beans, methylene blue, phenylhydrazine, nalidixic acid

which is important in maintaining reduced glutathione. Glutathione is essential in the protection of hemoglobin from oxidant injury. A deficiency of the first enzyme in this pathway, glucose-6-phosphate dehydrogenase (G6PD), occurs in 11% of African American men. In this form, the enzyme deteriorates with age, and older RBCs are subject to hemolysis by oxidant stress. G6PD deficiency is sex linked and has a wide range of severity. The most common form in African Americans is self-limited because as the bone marrow responds, younger cells with normal levels of G6PD predominate and handle the oxidant stress. The variants in Sicilians, Greeks, and Arabs can be particularly devastating. The clinical manifestation is usually an acute hemolytic episode that may be both intravascular and extravascular. It occurs 24 to 48 hours after the ingestion of an oxidant drug (Box 112.9) or after acute infections, such as viral hepatitis. The anemia induced by oxidant drugs is dose related. The older cells lyse at certain drug levels. The oxidant creates forms of activated oxygen, such as peroxide, that either denature the hemoglobin or destroy cell membranes. The former process produces Heinz bodies, which are clumps of denatured hemoglobin found in RBCs that are removed by the spleen. The diagnosis is made by enzymatic screening for G6PD, but this test cannot be performed immediately after the hemolytic episode. A 3-week delay avoids a false-negative result caused by a predominance of young cells. Treatment includes volume and RBC support and avoidance of oxidant drugs.

Intrinsic Membrane Abnormality. These abnormalities are manifested in a number of ways. An altered shape is the main feature of autosomal dominant hereditary spherocytosis or elliptocytosis. The spleen sequesters these abnormal cells. Clinical sequelae range from compensated asymptomatic anemia to severe life-threatening acquired aplastic crises. The diagnosis is made by reviewing the family history, blood smear, and osmotic fragility testing. Splenectomy is the treatment of choice for patients requiring therapeutic intervention.

Paroxysmal nocturnal hemoglobinemia is a stem cell defect causing abnormal erythrocyte, neutrophil, and platelet sensitivity to complement. It is most often seen as chronic hemolysis, hemosiderinuria, leukopenia, and thrombocytopenia. The peripheral smear is normal and the direct Coombs test result is negative. Its major complication is thrombosis, with a predilection for the hepatic vein. Normal activation of complement with the use of sucrose or acid hemolysis (the Ham test) is diagnostic. Transfusion can be a life-threatening in patients with this disease because RBC lysis is caused by donor complement. Thus, only washed packed cells should be used.

Intrinsic Hemoglobin Abnormality. More than 350 types of abnormal hemoglobin have been documented. Problems that may be seen include unstable hemoglobins that appear as Heinz body–positive anemia, M hemoglobins that fix iron in its ferric or methemoglobin state, and hemoglobins with increased oxygen affinity that result in tissue hypoxia and erythrocytosis.

Extrinsic Alloantibodies. Alloantibodies are formed in response to foreign RBC antigens. In the case of the ABO system, these antibodies are preformed. One of the most important RBC wall antigens, ABO incompatibility resulting in donor cell destruction by the recipient's alloantibodies can be a life-threatening reaction. These immunoglobulin M (IgM) antibodies can act as a hemolysin, both agglutinating RBCs, fixing complement, and consequently causing intravascular hemolysis.

The Rh system is another set of antigens on the RBC. Individuals do not have antibodies that correspond to antigens in the Rh system unless they have been sensitized by previous exposure to antigens that they lack. The antibodies produced are IgG in nature, and they accelerate extravascular destruction of RBCs by the spleen and liver. Most autoimmune antibodies are directed toward antigens in the Rh system.

Extrinsic Autoantibodies. Evaluation of autoimmune hemolysis is as complex as its origin. The major feature of autoimmune hemolysis is the production of an IgG or IgM antibody to an antigen present on the RBC membrane. IgM antibodies can agglutinate, fix complement, and act as intravascular hemolysins. IgG antibodies may fix complement to the cell but do not usually complete the hemolysis process. These IgG- or C3-labeled cells undergo accelerated extravascular destruction. The direct antiglobulin test is useful in revealing labeled cells.[20]

Autoimmune hemolytic anemias are acquired disorders, with 40% to 50% being idiopathic. The remainder are associated with a number of diseases (Box 112.10). Classification of autoimmune hemolytic anemias is based on the optimal temperature at which the antibody reacts with the RBC membrane. Therefore, there are warm-reacting (>37° C) and cold-reacting (<37° C) antibodies.

BOX 112.10

Diseases Associated With Autoimmune Hemolytic Anemia

NEOPLASMS
Malignant: Chronic lymphocytic leukemia, lymphoma, myeloma, thymoma, chronic myeloid leukemia
Benign: Ovarian teratoma, dermoid cyst

COLLAGEN VASCULAR DISEASE
Systemic lupus erythematosus
Periarteritis nodosa
Rheumatoid arthritis

INFECTIONS
Mycoplasma
Syphilis
Malaria
Bartonella
Virus: Mononucleosis, hepatitis, influenza, coxsackievirus, cytomegalovirus

MISCELLANEOUS
Thyroid disorders, ulcerative colitis
Drug immune reactions

BOX 112.11

Drugs Associated With Immune Hemolytic Anemia

Hapten type with antibodies to the drug
- Complement-fixing antibody: Quinidine, quinine, phenacetin, ethacrynic acid, *p*-aminosalicylate, sulfa drugs, oral hypoglycemic agents
- Non–complement-fixing antibody: Penicillin dosages >20 million units/day

Autoimmune type with antibodies to the red blood cell (RBC) membrane: D-methyldopa, L-dopa, mefenamic acid, chlordiazepoxide
Cephalosporins at dosages >4 g/day may cause hemolysis by direct membrane injury

Warm-reacting antibodies are characterized by a higher incidence in younger patients (30 to 60 years old), predominance in women, variable complement fixation, and positive direct antiglobulin test result for IgG. Cold-reacting antibodies, or cold agglutinins, are seen predominantly in men and older patients (50 to 80 years old) and with IgM complement fixation. They may also be found in patients with infectious mononucleosis, *Mycoplasma* infection, and lymphoma. Hemolysis may be intravascular and extravascular, and the direct antiglobulin test result is positive for complement.

Drug-induced hemolytic anemia may be difficult to diagnose. The emergency clinician should know the drugs most often associated with this Coombs-positive phenomenon and realize that the result of this test is sometimes positive only in the drug's presence. Common drugs and mechanisms of action are listed in Box 112.11.[17]

Extrinsic Mechanical Causes. Hemolysis may be caused by trauma to RBCs. The peripheral smear may demonstrate schizocytes or fragmented cells (Fig. 112.5). Microangiopathic hemolytic anemia, cardiac trauma, and exercise-induced hemoglobinemia are the most commonly encountered forms of traumatic hemolysis.

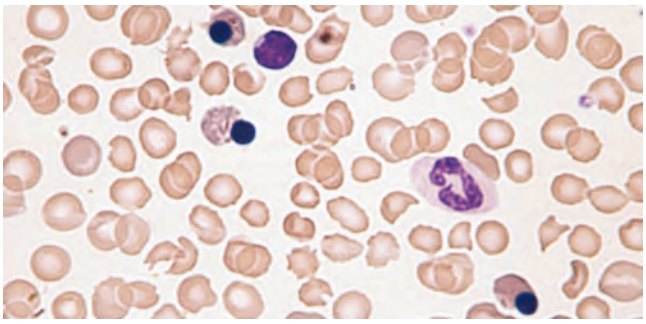

Fig. 112.5. Schizocytes (fragmented cell and nucleated red cells). (From Hoffbrand AV, Pettite JE: Color atlas of clinical hematology, ed 3, London, 2000, Mosby, p 115.)

Microangiopathic hemolytic anemia is a form of microcirculatory fragmentation by threads of fibrin deposited in the arterioles. An underlying disease may be found in renal lesions, such as malignant hypertension and preeclampsia, vasculitis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and vascular anomalies. Signs and symptoms are those of intravascular hemolysis; treatment is directed at the cause.

Cardiac trauma to RBCs results from increased turbulence. It may be found in patients with prosthetic valves, traumatic arteriovenous fistula, aortic stenosis, and other left-sided heart lesions. Surgical correction may be necessary. Supportive therapy with iron is usually required.

March hemoglobinemia is a form of trauma caused by breaking of intravascular RBCs by repetitive pounding. Soldiers, marathon runners, and anyone with repetitive striking against a hard surface may incur this problem. Reassurance and a change in the patient's pattern of activity are the recommended therapy.

Environmental Causes. Hemolysis may be seen in cases of severe burns, freshwater drowning, and hyperthermia. Toxic causes of hemolysis have been documented to be of animal origin, such as brown recluse spider and some snake bites; vegetable origin, such as castor beans and certain mushrooms; and mineral origin, such as copper. Certain infections are associated with hemolytic states, including malaria, *Bartonella* infection, and *Clostridium* sepsis.

Abnormal Sequestration. Hypersplenism may be caused by any disease that enlarges the spleen or stimulates the reticuloendothelial system. An unfortunate cycle can be set up in which the enlarged spleen traps more blood components and grows larger. It is usually seen as splenomegaly with pancytopenia and marrow hyperactivity. Chromium-labeled RBCs may demonstrate increased trapping in the spleen. Therapy for symptomatic or severe disease is splenectomy. Adults usually tolerate splenectomy well, but children should be approached conservatively because the risk of postsplenectomy life-threatening sepsis is increased significantly.

Diagnostic Testing

Once hemolysis is suspected, the history and laboratory tests have diagnostic precedence over physical examination. Important historical and physical examination points are listed in Box 112.12. Important diagnostic tests for hemolysis are provided in Box 112.13, and the interpretations of the laboratory evaluation of hemolytic anemias are included in Table 112.7. The blood smear

is often more diagnostic than bone marrow examination. The typical cell seen in intravascular hemolysis is the schizocyte (see Fig. 112.5). The classic cell of extravascular hemolysis is the spherocyte. It may be seen in congenital spherocytosis but more commonly indicates splenic activity against an antibody-coated RBC membrane. An increase in macrocytes reflects the presence of younger cells associated with reticulocytosis. The specific diagnosis may be made by a blood smear, as with sickled cells or Heinz bodies in G6PD deficiency.

Haptoglobin binds hemoglobin on a molecule-for-molecule basis. Its absence implies saturation and degradation after binding with hemoglobin and is an early finding in hemolysis. It has a normal range of 40 to 180 mg/mL, is decreased in hepatic failure, and increases as an acute-phase reactant. After haptoglobin is bound, hemoglobin binds with hemopexin, transferrin, and albumin before circulating in its free form. Plasma free hemoglobin levels are determined in suspected cases of intravascular hemolysis. The result is considered positive if the level is greater than 40 to 50 mg/dL. Hemoglobin is excreted by the kidney and may appear as a smoky red pigment that is orthotoluidine positive with no associated RBCs. Prussian blue–staining granules of hemosiderin may be found intracellularly in renal tubule cells excreted in urine during chronic hemolytic states.

BOX 112.12

Pertinent Factors in the History and Physical Examination for Hemolytic Anemia

HISTORY

Alteration of color in urine or feces
Association with drugs, cold, sleep
Early or recent-onset anemia history with symptoms
Ethnic background
Family history of anemia or jaundice
Drug or toxic exposure
Disease states associated with hemolysis, such as systemic lupus erythematosus, renal failure, lymphoma, infectious mononucleosis, prosthetic heart valve

PHYSICAL EXAMINATION

Jaundice
Hepatosplenomegaly
Ulcerations, particularly in the lower extremities
Enlarged lymph nodes

BOX 112.13

Diagnostic Tests for Hemolysis

Peripheral blood smear
Corrected reticulocyte index or reticulocyte production index
Haptoglobin levels
Plasma free and urinary hemoglobin
Lactate dehydrogenase level
Fractionated bilirubin level
Direct and indirect Coombs test
Red blood cell (RBC) membrane stability (osmotic fragility)

TABLE 112.7

Laboratory Evaluation of Hemolytic Anemias

EXTRAVASCULAR DESTRUCTION	LACTATE DEHYDROGENASE	HAPTOGLOBIN	RETICULOCYTE COUNT	COOMBS TEST	PERIPHERAL SMEAR
CONGENITAL RED BLOOD CELL DEFECTS					
Enzyme defects (eg, G6PD)	↑	↓	↑	Negative	"Bite" cells
Hemoglobinopathies (sickle cell disease)	↑	↓	↑	Negative	Sickle cells
Membrane defects (eg, hereditary spherocytosis)	↑	↓	↑	Negative	Spherocytes
ACQUIRED RED BLOOD CELL DEFECTS					
Autoimmune hemolytic anemia	↑	↓	↑	Positive	Spherocytes
liver disease	↑	↓	↑	Negative	Spur cells
Infections (eg, malaria)	↑	↓	↑	Negative	RBCs with inclusions
Toxins (eg, nitrates, dapsone, aniline dyes)	↑	↓	↑	Negative	Spherocytes
Hypersplenism	↑	↓	↑	Negative	Howell-Jolly bodies
INTRAVASCULAR DESTRUCTION					
Microangiopathic hemolytic anemia (eg, DIC, TTP, HUS)	↑	↓	↑	Negative	Schistocytes, helmet cells
Transfusion reactions	↑	↓	↑	Positive	Schistocytes, helmet cells
Sepsis	↑	↓	↑	Negative	RBC "ghost" cells, schistocytes, helmet cells
Paroxysmal nocturnal hemoglobinuria	↑	↓	↑	Negative	Schistocytes, helmet cells
Heat injury	↑	↓	↑	Negative	Schistocytes, helmet cells

DIC, Disseminated intravascular coagulation; *G6PD,* glucose-6-phosphate dehydrogenase; *HUS,* hemolytic uremia syndrome; *RBC,* red blood cell; *TTP,* thrombotic thrombocytopenic purpura.

LDH is released when the RBC is broken down peripherally or in the marrow. It is elevated in hemolytic, thalassemic, sideroblastic, and megaloblastic anemia but may also be seen in cases of uremia, polycythemia vera, and erythroleukemia. Normal levels of LDH range from 95 to 200 IU and may be fractionated.

In extravascular hemolysis, bilirubin is often delivered to the liver faster than the conjugating mechanism can handle it. Normal total levels are less than 1.5 mg/dL, with an indirect component less than 0.5 mg/dL. Unconjugated or indirect bilirubin may rise as high as 4 or 5 mg/dL even with normal liver function. Higher levels connote some degree of underlying hepatic insufficiency.

The direct antiglobulin (Coombs) test detects antibody or complement on human RBC membranes. It is an essential test in the evaluation of hemolysis. Approximately 90% of patients with autoimmune hemolytic anemia have a positive direct Coombs test result (warm agglutinin autoimmune hemolytic anemia). The indirect test measures antibody titers in serum (cold agglutinin autoimmune hemolytic anemia). The key to the direct antiglobulin test is the reagent, which contains an antihuman immunoglobulin G (IgG) produced in rabbits. This antihuman IgG in its broad-spectrum form reacts with the IgG, IgM, or C3 proteins that may coat RBCs. The reaction causes an agglutination of RBCs that is graded 0 to 4. Agglutinating properties depend on the size of the immunoglobulin. IgM is a large antibody form that can bridge the distance between cells, cause agglutination, and fix complement. The direct antiglobulin test is limited in diagnosis of IgM-mediated hemolysis. It is best in determining IgG or complement on the RBC surface. IgG is not large enough to cause agglutination, and the antihuman globulin attaches to RBC-bound IgG, which allows agglutination. C3 is detected in a similar manner. Both represent possible immunologic causes of hemolysis. This form of hemolysis is usually mediated extravascularly through the spleen, because IgG is a poor initiator of the complement system. The direct antiglobulin test evaluates the RBC surface for immunologic markers. The indirect test assumes that IgG or C3 is in the serum and tests for serum antibody activity against RBCs. Positive tests for immunologic markers do not correlate agglutination activity with the severity of hemolysis.

Management

In patients with newly diagnosed reticulocytopenia or severe hemolytic anemia, the emergency clinician may need to institute transfusion therapy. Compatible blood may be almost impossible to find because the antibody can react with almost all donors. The most compatible donor cells in terms of the ABO and Rh systems should be transfused with the knowledge that they will be no more compatible than the patient's own blood cells. If emergency blood transfusion is required, type-specific or type O blood (Rh-positive for men; Rh-negative for women of childbearing age) is indicated, as well as prednisone or its equivalent in a dose of 1 mg/kg. Prednisone may produce an improvement in 60% of patients with warm antibody reactions. Splenectomy and immunosuppressive therapy are also effective. Cold agglutinin hemolytic anemia may be self-limited, as after infectious mononucleosis. Other forms respond well to cold avoidance, variably to immunosuppressive agents, but poorly to steroids and splenectomy. Death commonly results from uncontrolled hemolysis, the underlying primary disorder, and pulmonary embolism.[16]

Sickle Cell Disease

Principles. Sickle cell disease is genetically determined. An abnormal allele at the gene loci for hemoglobin beta chains produces altered messenger RNA, which in turn results in replacement of glutamic acid by valine at the sixth position from the N-terminal end of the beta chain. The result is a sickled cell that is less deformable, an increase in the viscosity and sludging tendency of blood, and the sequestration of RBCs in the spleen and liver. The clinical complex of vaso-occlusive events, chronic hemolysis, thrombosis, and organ injury is derived from this pathologic process. Patients with sickle cell disease generally fall into two phenotypic groups: hemolysis phenotype and vaso-occlusion phenotype. These groups are not genetically determined, and it is still unknown why some people fall into one group versus the other. Patients prone to hemolysis typically do not have pain, stroke, or acute chest syndrome; instead, they typically have pulmonary hypertension and leg ulcers. Their hemoglobin tends to be very low, but their LDH is usually high. Patients with the vaso-occlusion phenotype typically have pain, acute chest syndrome, and stroke; they have a higher hemoglobin or high WBC level and lower LDH and indirect bilirubin concentrations.

The globin in hemoglobin is made up of two pairs of identical polypeptide globin chains. Each person has two non–sex-linked gene foci for β-globin chains, one from each parent. Normal individuals express six different types of hemoglobin from varying globin chain combinations: three embryonic hemoglobins, HbA ($\alpha_2\beta_2$), HbA_2 ($\alpha_2\delta_2$), and HbF ($\alpha_2\gamma_2$). Embryonic hemoglobins are expressed only in utero, and after 6 months of age, HbA accounts for more than 95% of hemoglobin in a normal individual. The sickle syndromes result from mutations in the β-globin gene. Instead of HbA ($\alpha_2\beta_2$), an abnormal hemoglobin HbS is produced. Embryonic and fetal hemoglobins do not contain β-globin; thus, there are no clinical manifestations in early infancy. As their production declines, normal HbA ($\alpha_2\beta_2$) cannot be produced, and symptoms develop.

In sickle cell trait (HbAS), the patient is heterozygous and only one parent contributes the abnormal S allele. In each cell, approximately 40% of the hemoglobin is HbS. Sickle disease (HbSS) is homozygous, and more than 85% of the hemoglobin is HbS. Because a parent may contribute alleles other than S, a wide number of variants can exist. Two clinically important S variants are sickle cell–β-thalassemia and sickle cell–hemoglobin C disease. Therefore, not all hemoglobinopathies that cause sickling are HbS. In addition, HbSS is not limited to the African American population. Up to 10% of patients with various sickling disorders are not ethnically African American.[19,21]

The sickle cell trait is found in 8% to 10% of African Americans. The diagnosis is usually made after sickle cell screening (Sickledex) and a characteristic result on hemoglobin electrophoresis. Most individuals with sickle cell trait are asymptomatic but can present with spontaneous hematuria, renal papillary necrosis, splenic infarction, venous thromboembolism, traumatic hyphema, exertional rhabdomyolysis, and exertional sudden death. Recent literature suggests that pregnancy in women with sickle cell trait is not associated with an increased risk of adverse events.[22] In patients with sickle cell trait who have eye trauma, serial tonometry and observation are indicated to monitor for ocular complications.

Clinical Features. Sickle cell disease is characterized by two major clinical features, hemolysis and acute vaso-occlusive events. The hallmark manifestation of sickle cell disease and the most common reason for ED visits is the painful vaso-occlusive crisis.[23] Preceding infection, cold exposure, and stress such as trauma are all potential precipitating factors. The painful crisis is believed to have its origin in tissue ischemia caused by increased viscosity, sludging, and microvascular obstruction as a result of irreversibly sickled cells. Sludging and vascular blockage cause stasis, deoxygenation, and local acidosis, which promotes continued sickling. The pain is commonly deep and aching and is most often found in the abdomen, chest, back, and extremities. The disease may mimic an acute abdomen (eg, cholecystitis), pulmonary embolus, renal colic, or other painful problems. A directed history that relates this pain pattern to previous sickling episodes, a careful repeated physical examination, and specific organ-related laboratory tests

can be used to differentiate "uncomplicated" crises from a more serious pathologic condition. Children may be seen more often with skeletal crises leading to bone deformities. In these cases, osteomyelitis and bone infarct needs to be differentiated.[24]

Neurologic complications can occur and include transient ischemic attacks, cerebral infarction, spinal cord infarction, vestibular hearing problems, and hearing loss. Neurologic complications occur in 25% of patients with sickle cell anemia by the time they are 45 years old; 13% demonstrate infarction or ischemia in the absence of symptoms.[25] Transcranial Doppler study may be useful in identifying individuals with sickle cell disease who are at risk for stroke.[26] The use of regular blood transfusions can reduce the risk of cerebrovascular events by 54%.[27] In the setting of an acute stroke, exchange transfusion is recommended with the goals of hemoglobin S of less than 30% and a total hemoglobin level limited to 10 g/dL.[27,28] Tissue plasminogen activator (tPA) should be considered in adult sickle cell disease patients with acute nonhemorrhagic strokes. The use of tPA in this setting is the same as for acute stroke without sickle cell disease.[28]

Acute chest syndrome is the most common pulmonary disease associated with sickle cell disease and one of the most common causes of death.[29] It is a common cause of hospitalization in sickle cell disease, second only to vaso-occlusive crisis. Patients with acute chest syndrome have fever, cough, chest pain, dyspnea, and new infiltrates on the chest radiograph. The pathophysiologic mechanism of the syndrome is not well understood, but it may be a specific form of acute lung injury. The injury is postulated to be related to pulmonary microvascular sludging, infarction of pulmonary parenchyma, and bone marrow fat embolization from infarcted bone. Macrovascular pulmonary embolism and infection may also have a pathogenetic role. Although the causes of acute chest syndrome are uncertain, approximately 54% of the cases are associated with infection, including *Mycoplasma* and *Chlamydia*. The differential diagnosis includes pneumonia, pulmonary embolism, congestive heart failure, and adult respiratory distress syndrome. Management is primarily supportive and consists of hydration, analgesia, incentive spirometry, maintenance of adequate oxygenation and ventilation, and empirical antibiotics. Approximately 13% of patients will have respiratory failure severe enough to require mechanical ventilation. Antibiotic choice is similar to that for pneumonia in other populations. Exchange blood transfusions, as used in a similar fashion with acute stroke, are often used and have been associated with better gas exchange in acute chest syndrome.[30] However, there are no randomized controlled studies demonstrating an improvement in outcome with the transfusions.

Although most of the diagnostic and therapeutic problems of sickle cell disease are related to vaso-occlusive crises, other serious complications should be anticipated. Sickle cell disease is a chronic hemolytic state with reasonably compensated hematocrit values in the 20% to 30% range and elevated reticulocyte counts. This compensated balance may be disrupted by a rare iron deficiency or, more commonly, by folate deficiency. A potentially life-threatening aplastic crisis may be seen as a result of suppression of erythropoiesis by an acute postinfectious condition or folate deficiency. This aplastic condition is suspected when the hemoglobin level falls 2 g/dL or more from previous stable levels and the reticulocyte count remains low (<2%).

Finally, children may have an acute splenic sequestration syndrome. This syndrome involves acute splenic enlargement from increased intrasplenic sickling and obstruction. The child may demonstrate lassitude and be in shock. Each of these conditions may result in a rapidly falling RBC count and progressive symptoms of anemia. Patients with HbSS are also subject to all other causes of anemia, such as hemolysis from G6PD deficiency. An increased susceptibility to infection is well documented with HbSS.[31]

In infancy, pneumococcal sepsis and meningitis may lead to death. A WBC count and blood cultures should be performed on all febrile children with sickle cell anemia. HbSS patients who are younger than 2 years old and have associated temperatures of 39.5° C or higher and WBC counts greater than 20,000/mm^3 should be given intravenous antibiotics immediately. Adults with fever require careful evaluation and laboratory assessment, including appropriate cultures. Early institution of appropriate antibiotics, such as ceftriaxone 1 to 2 g, adult dose, intravenously or intramuscularly, is necessary in patients with a discernible source of infection. In children and adults, infections with *Staphylococcus* and *Pneumococcus* species and *Haemophilus influenzae* are particularly common.[32] An increased incidence of *Salmonella* osteomyelitis also occurs. The origin of this related immunologic deficiency is believed to be multifactorial, involving functional asplenia, poorly migrating neutrophils, and decreased opsonin production.

Major, chronic organ damage in patients with sickle cell anemia is common and is listed in Table 112.7. Based on clinical and autopsy findings, the leading causes of death in HbSS patients are acute chest syndrome (22%), sepsis (22%), and multiorgan failure (17%).[33]

In a patient with suspected sickle cell disease, inquiry should be made into the family history, previous pain episodes, and symptoms relative to chronic anemia, susceptibility to infection, and ischemic organ damage. Table 112.8 suggests an outline to follow for the physical examination.

Differential Diagnoses

Sickle Cell–β-Thalassemia. Sickle cell–β-thalassemia disease is seen most commonly in people of Mediterranean descent. The severity of the disease is related to the concentration of HbS in RBCs and the decrease in MCHC. It should be

TABLE 112.8

Organ Damage Seen in Sickle Cell Disease

ORGAN OR SYSTEM	INJURY
Skin	Stasis ulcer
Central nervous system	Cerebrovascular accident
Eye	Retinal hemorrhage, retinopathy
Cardiac	Congestive heart failure
Pulmonary	Intrapulmonary shunting, embolism, infarct, infection
Vascular	Occlusive phenomenon at any site
Liver	Hepatic infarct, hepatitis resulting from transfusion, hepatic sequestration, intrahepatic cholestasis
Gallbladder	Increased incidence of bilirubin gallstones caused by hemolysis
Spleen	Acute sequestration
Urinary	Hyposthenuria, hematuria
Genital	Decreased fertility, impotence, priapism
Skeletal	Bone infarcts, osteomyelitis, aseptic necrosis
Placenta	Insufficiency with fetal wastage
Leukocytes	Relative immunodeficiency
Erythrocytes	Chronic hemolysis

considered in a patient with a low MCV and a positive response on sickle preparation. It is generally a milder form than homozygous HbSS but can be as severe as sickle cell disease. HbSC disease falls between HbSS and HbS-thalassemia in terms of severity. In addition to many of the complications of HbSS, HbSC disease has an increased incidence of eye hemorrhage and pregnancy complications and may cause splenomegaly. The peripheral smear demonstrates a combination of sickled cells and normocytic target cells.

Diagnostic Testing

Most patients, other than those with mild pain crisis, should have a complete blood count performed and compared with those of previous visits. A reticulocyte count is recommended whenever the patient's hemoglobin level has decreased by 2 g/dL from baseline. In sickle cell disease, the typical absolute reticulocyte count is three or four times the upper limit of normal. A reticulocyte count 3% or lower than the patient's usual value may suggest an aplastic crisis. A reticulocyte count greater than 12%, particularly if it is accompanied by numerous nucleated RBCs, may indicate rapid hemolysis. Unfortunately, no test is available that detects whether a patient is in a crisis and is based on clinical presentation. In undiagnosed cases, the peripheral smear may show sickled cells (Fig. 112.6), but the definitive diagnosis of sickle cell disease is confirmed by hemoglobin electrophoresis.

Management

The antisickling agent hydroxyurea reduces the frequency of painful crises in adults with a history of three or more crises annually. The beneficial effects of hydroxyurea in sickle cell disease are assumed to be due to induction of hemoglobin F, but additional mechanisms may be operative. Hydroxyurea can reduce the incidence of acute painful crisis, as well as increase survival. However, the effects of hydroxyurea can take weeks to be appreciated, and it is not routinely recommended for acute episodes.[34,35] Other agents, including clotrimazole, magnesium, 5-azacitidine, erythropoietin, L-glutamine, and butyric acid, may have a future role. Bone marrow transplantation offers the only current cure for sickle cell disease and is associated with survival rates greater than 90% and disease-free survival rates of 80% to 90%. However, the role of bone marrow transplantation remains uncertain because of the inability to predict which patients will benefit, limited patient eligibility as a result of advanced pulmonary and neurologic vasculopathies, and concerns related to transplantation mortality and treatment-induced malignant neoplasms.[36]

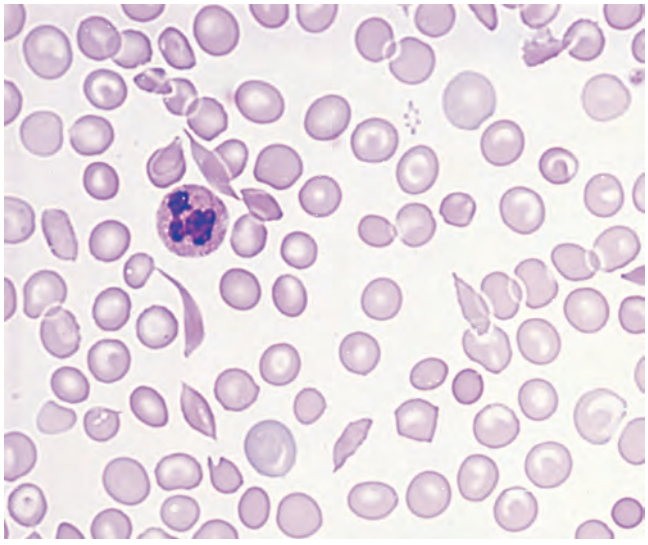

Fig. 112.6. Sickle cells. (From Hoffbrand AV, Pettite JE: Color atlas of clinical hematology, ed 3, London, 2000, Mosby, p 103.)

Current therapies, including rest, adequate nutrition, hydration, oxygenation, analgesia, transfusion, and therapy for infection, are directed toward symptomatic relief and attempts to stop the cycle of deoxygenated sickling and intravascular sludging. Most patients with sickle cell anemia are mildly dehydrated because of difficulty in concentrating urine. Fluid replacement can be oral or intravenous. Fluid replacement is not recommended unless signs of shock and a conservative approach for most patients recommends infusions of 5% dextrose in half-normal saline at a rate not to exceed 1.5 times maintenance.[37] Although the use of supplemental oxygen may have some theoretical advantages in sickle cell disease, it has not been shown to reduce opioid use or hospitalization in patients that are not hypoxic.

Analgesia is a major benefit and essential early therapy for acute sickle cell crisis. Because a small subgroup of patients repeatedly and frequently seek care in the ED, caregivers may become understandably suspicious of needs and motivations. Many emergency clinicians caring for large populations of sickle cell patients have developed protocols to establish better physician-patient rapport and to lessen the chance of narcotic addiction and manipulation. The following is a protocol for severe pain in adults and children weighing more than 50 kg: patients are evaluated, treated with oxygen and hydration, and given intravenous morphine sulfate, 5 to 10 mg every 2 to 4 hours, or intravenous hydromorphone, 1.5 mg every 3 to 4 hours. For children weighing less than 50 kg, intravenous bolus doses of morphine sulfate, 0.1 to 0.15 mg/kg, can be given every 2 to 4 hours, or intravenous hydromorphone, 0.015 to 0.020 mg/kg, can be given every 3 to 4 hours. At 4 to 6 hours, the patient is allowed to decide whether inpatient or outpatient therapy is desired. Outpatient therapy includes 4 to 6 days of an effective oral analgesic. A 40-mg dose of oral morphine sulfate or equivalent is given 1 or 2 hours before the infusion is stopped. Such a protocol may bring uniformity to the patient's expectations for care and the physician's decisions about therapy and admission. Its major disadvantage has been a tendency to treat patients automatically rather than closely considering the potential acute complications of sickle cell disease. No standard pain management exists for sickle cell disease. A variety of analgesics (nonsteroidal antiinflammatory drugs, mixed opioid agonist-antagonists, and opioids), dosages, and timing intervals may be chosen. Because many sickle cell disease patients can have varying degrees of hepatic or renal dysfunction, acetaminophen and nonsteroidal antiinflammatory drugs should be used with caution. Because many patients with acute pain episodes are undertreated, the most important aspect of pain management is a consistent, thorough, and attentive approach that offers true pain relief.

Selected blood transfusion can decrease the chronic transfusion problems of antigen sensitization, iron overload, and hepatitis. Aplastic or splenic sequestration crises may necessitate transfusion. Whereas the overall goal of simple transfusion therapy for symptomatic anemia is a hemoglobin level no higher than 10 g/dL, asymptomatic patients should not be transfused, regardless of hemoglobin value.[38]

Priapism is a painful complication of sickle cell disease and may lead to impotence. First-line therapy for priapism lasting longer than 2 hours is aspiration of blood from the corpus cavernosum and irrigation with an α-adrenergic agent (eg, phenylephrine). Urologic surgical management is reserved for patients who fail aspiration and irrigation.[38] Exchange transfusions in the treatment of priapism is controversial but is currently not recommended.[39]

Exchange transfusions are recommended for other complications, such as cerebrovascular accidents, in pregnancy and before major surgery. Acute stroke symptoms may be reversed and the frequency of recurrence decreased with a regulated 3- or 4-week transfusion program. The goal is to suppress reticulocytosis and to decrease the HbS level to less than 25%. Rarely, transfusions are given to control bone or visceral crises. This is not an ED procedure and is considered only after hematologic consultation.

Disposition

Many patients with painful crisis can be controlled in the ED and discharged with analgesics. Hospitalization may be warranted if pain cannot be controlled with two to three doses or if the patient is unable to take oral analgesics.

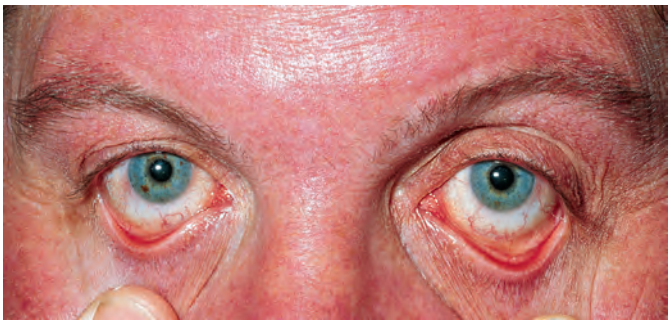

Fig. 112.7. Polycythemia vera. Facial plethora and conjunctival suffusion in a 40-year-old woman (hemoglobin, 19.5 g/dL). (From Hoffbrand AV, Pettite JE: Color atlas of clinical hematology, ed 3, London, 2000, Mosby, p 248.)

POLYCYTHEMIA

Principles

Polycythemia is a term commonly used for erythrocytosis (ie, increased number of RBCs). This disorder is seen occasionally in emergency medicine but rarely requires emergency intervention. An elevated RBC count, usually greater than the hematocrit, defines the disorder. It results in a low MCV, usually related to low serum iron and iron stores. Specific laboratory testing is discussed in the Differential Diagnosis section.

Erythropoiesis is controlled by the kidney-produced glycoprotein hormone erythropoietin. It is activated in the liver and regulates the committed erythropoietic stem cell. Its major stimulant is tissue hypoxia. Neoplastic dysfunction of bone marrow may also result in an elevated absolute RBC count.

The major complications of polycythemia are related to the increase in blood viscosity associated with increased RBC numbers. As the hematocrit rises past 60%, viscosity increases in an almost exponential manner, resulting in reduced tissue flow, thrombosis, and hemorrhage. This hazard is mitigated by an associated increase in blood volume and some viscosity-reducing vascular dilation.[40]

BOX 112.14

Causes of Apparent and Secondary Polycythemia

- Appropriately increased erythropoietin caused by tissue hypoxia
  - Congenital heart disease with a right-to-left shunt
  - Pulmonary disease (eg, bronchial-type chronic obstructive pulmonary disease)
  - Carboxyhemoglobinemia
  - High-altitude acclimatization
  - Decreased tissue oxygen release from hemoglobinopathies with high oxygen affinity
- Inappropriate autonomous erythropoietin production
  - Renal origin: Carcinoma, hydronephrosis, cyst
  - Other lesions: Uterine fibroids, hepatoma of adrenal origin, cerebellar hemangioma
  - Congenital overproduction
  - Pure or essential erythrocytosis
  - Acquired immunodeficiency syndrome (AIDS) and zidovudine treatment

Clinical Features

Symptoms may range from only mild headaches to a full-blown syndrome of hypervolemia (vertigo, dizziness, blurred vision, and headache), hyperviscosity (venous thrombosis), and platelet dysfunction (epistaxis, spontaneous bruising, and gastrointestinal bleeding).

On physical examination, the skin and mucous membrane manifest plethora, engorgement, and venous congestion (Fig. 112.7). Other systems to be examined include the fundus for venous congestion, the abdomen for evidence of splenomegaly, and the cardiopulmonary system for signs of congestive heart failure. Investigation for uterine, central nervous system, renal, and hepatic tumors should be sought, because these are associated with secondary polycythemia.

Differential Diagnosis

Polycythemia is classified as apparent, primary, or secondary (Box 112.14). Apparent polycythemia is a decrease in plasma volume, and RBC volume does not exceed the upper limit of normal. Found in overweight, hypertensive middle-aged men, "stress" polycythemia is the tendency for an elevated hematocrit possibly due to cigarette smoking with its associated increased carboxyhemoglobin level. The treatment includes weight loss and blood pressure control. The risk of vascular occlusive complications is minimal. The hematocrit is usually less than 60% and RBC mass measurements are normal.[41]

Primary polycythemia vera is a myeloproliferative disorder found predominantly in middle-aged or older patients. Nonspecific symptoms are reported in up to 30% of patients and include headache, weakness, dizziness, excessive sweating, and pruritus. The most serious problems are thrombotic episodes (cerebrovascular accident, myocardial infarction, and deep venous thrombosis), bleeding, and bruising. Primary polycythemia vera involves all cell lines—hematopoietic stem, erythroid, granulocytic, and megakaryocytic. Elevated hemoglobin and RBC mass is present in virtually all, but a platelet count above 400,000/μL occurs in only 60% and a WBC count above 12,000/μL in only 40%. Bone marrow cellularity is increased in 90% of patients, and storage iron is absent from the marrow in 94%. The diagnostic criteria used by the Polycythemia Vera Study Group are listed in Box 112.15.[42]

Polycythemia vera may be satisfactorily treated by phlebotomy. The reduced hematocrit improves some symptoms, but neither the leukocyte nor the platelet count is decreased. Maintenance of the hematocrit at less than 55% is recommended to decrease hypervolemia and hyperviscosity. Complications necessitating additional therapy include hyperuricemia, refractory increased RBC mass, severe pruritus, excessive splenomegaly, and thrombocytosis.

BOX 112.15

Diagnostic Criteria for Polycythemia Vera*

CATEGORY A

Increased RBC mass
- In men: Hemoglobin >18.5 g/dL
- In women: Hemoglobin >16.5 g/dL

Normal arterial oxygen saturation (>92%)
Splenomegaly

CATEGORY B

Thrombocytosis: Platelets >400,000/mm^3
Leukocytosis: WBC count >12,000/mm^3 (with no fever or infection)
Leukocyte alkaline phosphatase score >100
Vitamin B_{12} >900 pg/mL, unbound vitamin B_{12}–binding capacity

*For polycythemia vera to be diagnosed, either all three criteria in category A or the first two criteria in category A along with any two criteria in category B needs to be present.
RBC, Red blood cell; *WBC,* white blood cell.

Although studies do not consistently demonstrate improvement in long-term survival, additional therapy may include hydroxyurea, busulfan, chlorambucil, interferon alfa, anagrelide, or radioactive phosphorus (^{32}P).[43] The natural history of the disease is that it burns out after 15 to 20 years. However, myelofibrosis with myeloid metaplasia may develop. In 10% of cases, a rapid and poorly responsive acute leukemia develops. The 15-year survival for polycythemia vera is 65%.[44,45] The most common causes of death are thrombosis (29%), hematologic malignant neoplasms (23%), nonhematologic malignant neoplasms (16%), hemorrhage, and myelofibrosis with myeloid metaplasia.

Diagnostic Testing

Secondary polycythemia is classified according to the appropriate erythropoietin response to abnormal tissue oxygen levels. This group of disorders may be ruled out by normal measured arterial oxygen saturation. Second, inappropriate autonomous erythropoietin production is considered. This condition can be assessed with an erythropoietin assay. Because of a strong association with renal pathologic conditions, computed tomography should be used to evaluate a patient with a suspected inappropriate erythropoietin response. Most patients with secondary polycythemia have no central nervous system symptoms or splenomegaly. Because erythropoietin stimulates only the red cell pathway, these patients should have normal WBC and platelet counts.

Management

The emergency treatment of symptomatic polycythemia is phlebotomy. Usually, approximately 500 mL of blood is removed and replaced with a comparable amount of saline. No hemodynamic compromise should occur if this procedure is performed slowly. In true emergencies, up to 1 to 1.5 L of blood may be removed during a 24-hour period. The initial goal is to lower the hematocrit toward 60%. The final goal is a level less than 55%. Low-dose aspirin, 80 to 100 mg/day, has been shown to prevent thrombotic complications in patients with polycythemia vera and can be used in the acute and chronic treatment of this disorder.[46]

Disposition

Selected patients with known polycythemia may be managed by serial outpatient phlebotomies. Any newly diagnosed or symptomatic patient should be considered for admission to the hospital for full evaluation.

KEY CONCEPTS

- Anemia is caused by three basic mechanisms: bleeding, destruction of RBCs, and decrease in production of RBCs.
- The use of RBC indices and a peripheral blood smear can help determine the mechanism of anemia.
- Anemia in the elderly often occurs as an exacerbation of preexisting comorbid diseases.
- Anemia of uncertain etiology should be thoroughly evaluated. If the patient has no adverse hemodynamic consequences, the evaluation can proceed on an outpatient basis or management initiated in an observation unit until the patient is stable and can be managed as an outpatient.
- Patients with sickle cell disease should be considered to have an acute pain crisis and treated appropriately until it is proved otherwise.
- Acute chest syndrome is one of the most common causes of death in sickle cell disease.
- Transfusion therapy is most useful in sickle cell disease associated with acute stroke (in children), acute chest syndrome, and splenic sequestration.
- Polycythemia is classified as apparent (eg, dehydration), primary (eg, myeloproliferative disorder), or secondary (eg, carcinoma or other conditions), and treatment is targeted at the cause.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 112: QUESTIONS & ANSWERS

112.1. Anemia with an elevated mean corpuscular volume (MCV) is *not* typically seen with which of the following conditions?

A. Folate deficiency
B. Hypothyroidism
C. Iron deficiency
D. Liver disease
E. Vitamin B_{12} deficiency

Answer: C. Iron deficiency anemia typically presents as a microcytic anemia. Liver disease may present with either a macrocytic anemia or a normocytic anemia reflecting an anemia caused by multiple mechanisms.

112.2. An elevated mean corpuscular hemoglobin concentration (MCHC) is expected in which of the following conditions?

A. Anemia of chronic disease
B. Iron-deficiency anemia
C. Sideroblastic anemia
D. Spherocytosis
E. Vitamin B_{12} deficiency

Answer: D. The MCHC index is a measure of the concentration of hemoglobin. Low values represent hypochromia, whereas high values are noted only in patients with decreased cell membrane area relative to volume, such as spherocytosis.

112.3. A 31-year-old woman presents with complaints of easy fatigability and heavy regular menses. She is not pregnant and is otherwise healthy. Complete blood count shows the following:
White blood cell (WBC) count: 7300 cells/mm^3
Platelet count: 453,000 cells/mm^3
Hemoglobin: 8.4 g/dL
Hematocrit: 25%
Mean corpuscular volume (MCV): 82 fL^3 (81–100 fL^3)
Mean corpuscular hemoglobin concentration (MCHC): 29% (31% to 36%)
Physical examination is only remarkable for conjunctival pallor. Which of the following statements regarding this patient's condition is *true?*

A. Hemoglobin rise from iron therapy begins in a week.
B. Parenteral iron therapy is indicated.

C. Reticulocytosis from iron therapy will be seen in 24 to 48 hours.
D. The normal MCV should prompt an in-depth anemia evaluation.
E. Transfusion is indicated.

Answer: A. Microcytic anemia, in cases of iron deficiency, occur late because marrow and cytochrome iron sources must first be exhausted. The treatment for chronic iron-deficiency anemia is oral iron replacement, which in adults produces a reticulocytosis and hemoglobin rise in approximately 1 week. Parenteral iron therapy is almost never indicated. Transfusion is rarely required unless the blood loss is acute or comorbidities necessitate immediate improvement of blood oxygen-carrying capacity.

112.4. A 21-year-old man presents with easy fatigue and lack of energy. During a recent clinic visit, he was found to be anemic with a hemoglobin of 8 g/dL, mean corpuscular hemoglobin concentration (MCHC) of 25%, mean corpuscular volume (MCV) of 61 fL, and a peripheral smear remarkable for target cells and basophilic stippling. Serum iron levels were normal. What is the most likely explanation for his anemia?
A. Iron deficiency
B. Lead poisoning
C. Porphyria
D. Sideroblastic anemia
E. Thalassemia

Answer: E. Hypochromic, microcytic anemias with normal serum iron imply thalassemia (a defect in globin chain production). Both alpha- and beta-thalassemia show a hypochromic microcytic picture with target cells and basophilic stippling. The microcytosis is generally more severe than with iron-deficiency anemia. Sideroblastic anemia generally presents with elevated serum iron.

112.5. A 73-year-old woman presents with progressive fatigue. Her only past medical history is rheumatoid arthritis for which she takes methotrexate. She has no cardiopulmonary history and does not smoke. Physical examination is remarkable only for bilateral metacarpophalangeal, chronic swelling, and mild splenomegaly. Recent blood tests from the clinic are remarkable for a high normal serum iron, hemoglobin of 10 g/dL, and mean corpuscular volume (MCV) of 69 fL, with peripheral smear showing both microcytes and macrocytes. Which of the following is the most appropriate intervention?
A. A trial of pyridoxine
B. Hematology consultation for bone marrow biopsy
C. Hematology consultation for iron chelation
D. Send blood for vitamin B_{12} and folate levels
E. Toxicology consultation for lead chelation

Answer: A. Sideroblastic anemia may be acquired or inherited. It is typically a refractory anemia in the elderly characterized by hypochromia and microcytosis but a dimorphic smear also showing normal cells and macrocytes. Some of these patients are pyridoxine deficient and may respond to a course of vitamin B_6. This anemia is a defect in porphyrin synthesis and is associated with rheumatoid arthritis, cancer, and infections. Lead poisoning is a subset. Elevated iron and ferritin levels are seen because the porphyrin defect does not allow iron incorporation and cells hemolyze in the bone marrow.

112.6. Which of the following statements regarding anemia of chronic disease is *true?*
A. A search for occult blood loss is indicated.
B. Hematocrits frequently fall to the 20% to 24% range.
C. Iron levels are always normal.
D. Iron therapy is beneficial.
E. It is a microcytic anemia.

Answer: A. Anemia of chronic disease (ACD) is a normocytic anemia most commonly associated with cancer, infection, and uremia. Hematocrit drops are generally modest, with levels seldom below 25% to 30%. An iron-deficiency anemia may often be superimposed, and a search for occult blood loss is indicated. It is characterized by low serum iron, low iron binding capacity, and increased ferritin. Bone marrow examination is often normal except for increased reticuloendothelial staining for iron, which cannot be mobilized. It is refractory to iron therapy.

112.7. A 43-year-old woman presents with difficulty walking and complaints of depression that have progressively worsened over several weeks. She has no past medical history, takes no medications, and does not drink alcohol or smoke. Physical examination is remarkable for clinical depression, a spastic gait, decreased extremity proprioception, and lower extremity hyporeflexia. What test should be obtained next in this patient's evaluation?
A. Complete blood count with differential diagnosis and RBC indices
B. Lumbar puncture
C. Magnetic resonance imaging (MRI) of the spine
D. Serum potassium and calcium levels
E. Serum thyroid-stimulating hormone (TSH)

Answer: A. Vitamin B_{12} deficiency presents classically with very low hemoglobin levels, a macrocytic picture, decreased proprioception and/or vibration, lower extremity spasticity/weakness with hyporeflexia, and often mental status changes, such as depression, forgetfulness, or even paranoia. Irritability and forgetfulness are also seen with folate deficiency.

112.8. A 43-year-old man presents with fatigue and dyspnea on exertion. He has no significant past history. Physical examination is remarkable for pale conjunctivae. Vital signs are heart rate, 108 beats per minute; blood pressure, 115/70 mm Hg; respiratory rate, 18 breaths per minute; temperature, 37° C; and O_2 saturation, 96% on room air. Laboratory examination is remarkable for the following:
White blood cell (WBC) count: 3200 cells/mm^3
Hemoglobin: 7 g/dL
Hematocrit: 21%
Platelet count: 71,000 cells/mm^3
Reticulocyte count: 0.9%

Which of the following tests will most likely to lead to the diagnosis?
A. Drug/toxin exposure history
B. Fecal hemoccult test
C. Liver function tests
D. Serum creatinine
E. Urinalysis

Answer: A. Aplastic anemia typically presents as a normochromic, normocytic anemia with a low reticulocyte count. Most cases

involve all cell lines. More than 50% of cases are due to drug or chemical exposures. See Table 112.6.

112.9. Which of the following conditions is associated with macrocytic anemia?
A. Adrenal insufficiency
B. Hypothyroidism
C. Pituitary insufficiency
D. Renal failure
E. Tuberculosis

Answer: B. Hypothyroidism may be associated with macrocytic or normocytic indices. The latter is the typical case in anemia of chronic disease (ACD). All of the other choices may be associated with ACD and typically normocytic (occasionally microcytic) indices and low erythropoietin levels.

CHAPTER 113

White Blood Cell Disorders

Timothy G. Janz | Alan A. Dupré

WHITE BLOOD CELL DISORDERS

Principles

Background and Importance

The white blood cell (WBC) count and accompanying differential count are the most common laboratory tests ordered in the emergency department. Unfortunately, the WBC count has not proved to be a highly sensitive or specific test, and the absence of leukocytosis does not exclude the presence of significant disease. In evaluation of the bacterial infectious potential in febrile children, the WBC and differential counts have demonstrated limited usefulness.[1] Other biomarkers, such as procalcitonin and C-reactive protein (CRP), may have more predictive value.[2] Thus, the WBC test should be viewed as having limited screening value in the acute care setting because multiple agents and conditions can increase the WBC count. Although the WBC count may be nonspecific and nonsensitive, studies evaluating the WBC count for the diagnosis of abdominal pain have found it to be a useful in selecting patients for observation, and the differential count may provide helpful information.[3] The absolute neutrophil count and a high band count may be more helpful than the total WBC count in identifying bacterial infection.[1,4] Thus, it is essential that the basic physiology, pathophysiology, and clinical evaluation of WBCs be understood.

Anatomy and Physiology

The WBC series has three morphologically indistinguishable cell types: B cells (humoral immunity), T cells (cellular immunity), and null cells. Because lymphocytes can freely leave and return to the circulation, the storage pools are less well defined. Only 5% of the total lymphocytes in the body are in circulation. No marginal pool exists. Leukocytes primarily function extravascularly, and their function is closely integrated with the other types of white cells. WBCs reach their site of action through the circulation. The rate that new cells enter the circulation is usually in equilibrium with the rate of loss in tissues.

The granulocytic and lymphocytic series are the two WBC cell lines. The granulocytic series is primarily involved in phagocytic activity. Its origin is the pluripotential stem cells located in the bone marrow. A subset of these cells differentiates and matures into the phagocytic cell lines, which include neutrophils, monocytes, basophils, and eosinophils. Granulocytes are maintained in developmental and storage pools. The most important is the postmitotic storage pool for neutrophils, which represents 15 to 20 times the circulating population, and contains metamyelocytes, band neutrophils, and mature neutrophils (polymorphonuclear neutrophils). The pool can be drawn on as a ready reserve during rapid consumption of granulocytes. Circulating neutrophils are subdivided equally into the circulating neutrophil pool and the marginal pool, consisting of mature cells adherent to the blood vessel walls. The marginal pool can rapidly enter the circulating pool and cause a substantial increase, even doubling, of the WBC count. This involvement does not alter the maturity pattern of the differential count.[5] The lymphocytic series matures in lymphoid tissues located in the bone marrow, thymus, spleen, lymph nodes, and elsewhere. They are involved in the immune response against foreign substances.

One unique problem in WBC disorders is the wide variability in normal values and the multiple factors influencing them. WBC counts are generally performed automatically by electrical impedance or optical diffraction techniques. Although differential counts are commonly performed by direct examination of 100 to 500 cells with the oil immersion lens of the microscope, automated techniques are becoming more popular. Normal values for the WBC count are listed in Table 113.1. The "normal" count is age dependent and may be shifted upward by exercise, gender (women), smoking, and pregnancy. Decreases in the total WBC count range by 1000 to 1200 cells/mm^3 have been noted in the African American population.[5] Laboratory errors may be due to improper sample preparation, nucleated RBCs, or platelet clumping. The blood smear differential count may also be influenced by small sample size, improper cell identification, and age group (children). Differential ranges are listed in Table 113.2. One common but easily corrected error in laboratory reporting is to give results in terms of the percentage of cell types. Absolute counts for each cell type are more accurate and useful in assessing the risk for infection.

Pathophysiology

Abnormal cell counts are due to changes in production, the marginal pool, or the rate of tissue destruction. Just as in anemia or platelet count abnormalities, the differential diagnosis of increased (leukocytosis) or decreased (leukopenia) WBC counts can be organized by processes altering production, destruction, loss, and sequestration.

Because of the wide range of normal values, all abnormal WBC counts should be interpreted in the context of the patient's condition. A careful history and physical examination, absolute cell counts, and review of the peripheral smear differential count are the starting points to determine the origins of quantitative WBC disorders.

Most cases of leukocytosis are caused by increases in the neutrophil or lymphocyte cell lines. Neutrophil leukocytosis (neutrophilia) is an absolute neutrophil count greater than 7500 cells/mm^3 and is commonly associated with infection or inflammation (Box 113.1). Because increased neutrophil destruction is associated with both of these pathologic processes, the usual ratio of 1 band to 10 neutrophils increases. This increase is manifested as a "left shift" in the differential count and represents movement of immature neutrophils from the postmitotic pool into the circulation.

WBC counts can increase without a left shift or an increase in band forms by demarginating neutrophils from the vessel walls. It is often seen as a response to stress, exercise, or epinephrine. Severe stress can raise the WBC count to 18,000 to 20,000 cells/mm^3.[6]

Clinical Features

WBC disorders do not present with specific signs or symptoms but rather have clinical features associated with the underlying cause of the WBC disorder (eg, infection). The exception to this is hyperleukocytosis (WBC >100,000/mm^3). Although most patients with hyperleukocytosis are febrile, the major organ systems involved are the lungs and the central nervous system (CNS). Pulmonary signs and symptoms include dyspnea and hypoxemia. CNS findings may include headache, tinnitus, visual changes, and altered mental status. Because cerebral hemorrhage and ischemia are not uncommon in hyperleukocytosis, signs and symptoms of an acute stroke are also possible.[7]

Differential Diagnoses

Elevated WBC can be caused by primary WBC disorders (eg, myeloproliferative disorders, hereditary leukocytosis and congenital anomalies and leukemoid reaction, or secondary forms). Secondary forms are much more common (see Box 113.1).

Diagnostic Testing

Complete blood count (CBC) is the initial test, which usually identifies the WBC disorder. Presence of anemia, thrombocytopenia, or thrombocytosis on the CBC may also have diagnostic significance. As an example, the presence of an anemia, particularly hemolytic, and thrombocytopenia might suggest thrombotic thrombocytopenic purpura (TTP) or hemolytic uremia syndrome (HUS). Additional laboratory tests that may aid in the evaluation of a WBC disorder include a peripheral blood smear, sedimentation rate and CRP. In the setting of hyperleukocytosis, a chest radiograph and neurologic imaging, if CNS signs or symptoms are present, are also indicated.

Management

The management of WBC disorders is related to the underlying disease process associated with the disorder. Hyperleukocytosis, however, is a hematologic emergency and efforts should be made to lower the WBC as rapidly as possible. Reduction in the WBC can be achieved with chemotherapy, often hydroxyurea, and leukapheresis. Rapidly reducing the WBC with chemotherapy may induce the tumor lysis syndrome. The choice between chemotherapy and leukapheresis should be made in consultation with a hematologist. Because patients with pulmonary or CNS clinical features from hyperleukocytosis have a high mortality rate, leukapheresis is often the therapeutic modality of choice in this patient population.[7]

TABLE 113.1

Normal Ranges for the Blood Leukocyte Count (cells/mm^3)

AGE	AVERAGE	95% RANGE (AVERAGE VALUE ±2 STANDARD DEVIATION)
1 week	12,200	5000–21,000
6 months	11,900	6000–17,500
12 months	11,400	6000–17,500
4 years	9100	5500–15,500
8 years	8300	4500–13,500
Adults	7400	4500–11,000

Modified from Miale JB: Laboratory medicine: hematology, ed 6, St Louis, 1982, Mosby.

BOX 113.1

Causes of Leukocytosis

LEUKOCYTOSIS

Primary

Myeloproliferative disorders: Chronic myeloid leukemia (CML), polycythemia vera
Hereditary neutrophilia
Familial myeloproliferative disease
Chronic idiopathic neutrophilia

Secondary

Infection
Tissue necrosis: Cancer, burns, infarctions
Metabolic disorders: Diabetic ketoacidosis, thyrotoxicosis, uremia
Non-hematologic malignant disease
Stress: Exercise, pain, surgery, hypoxia, seizures, trauma
Drugs: Epinephrine, corticosteroids, lithium, cocaine
Laboratory error: Automated counters, platelet clumping, precipitated cryoglobulin

LYMPHOCYTOSIS

Viral infection: Mononucleosis, rubeola, rubella, varicella, toxoplasmosis
Lymphoproliferative: Acute or chronic lymphocytic leukemia (CLL)
Immunologic response: Immunization, autoimmune diseases, graft rejection

TABLE 113.2

Normal Percentage Ranges for the Leukocyte Differential Count in Blood*

AGE	SEGMENTED NEUTROPHILS	BAND NEUTROPHILS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	BASOPHILS
1 week	34 ± 15 (4100)	11.8 ± 4 (1420)	41 ± 5 (5000)	9.1 (1100)	4.1 (500)	0–4 (50)
6 months	23 ± 10 (2710)	8.8 ± 3 (1000)	61 ± 15 (7300)	4.8 (480)	2.5 (300)	0–4 (50)
12 months	23 ± 10 (2680)	8.1 ± 3 (990)	61 ± 15 (7000)	4.8 (550)	2.6 (300)	0–4 (50)
4 years	34 ± 11 (3040)	8.0 ± 3 (730)	50 ± 15 (4500)	5.0 (450)	2.8 (250)	0–6 (50)
8 years	45 ± 11 (3700)	8.0 ± 3 (660)	39 ± 15 (3300)	4.2 (350)	2.4 (200)	0–6 (50)
Adult	51 ± 15 (3800)	8.0 ± 3 (620)	34 ± 10 (2500)	4.0 (300)	2.7 (200)	0–5 (40)

*Numbers in parentheses indicate the average number of cells per cubic millimeter.
Modified from Miale JB: Laboratory medicine: hematology, ed 6, St Louis, 1982, Mosby.

Disposition

Because WBC disorders are most commonly associated with an underlying disease process, the disposition of the patient depends on the type and severity of the underlying cause.

CHRONIC MYELOID LEUKEMIA

Principles

Anatomy and Physiology

Accounting for approximately 15% to 20% of adult leukemias, chronic myeloid leukemia (CML) is one of the myeloproliferative causes of neutrophilic leukocytosis.[8] Although it is the least common of the major leukemias (60% acute, 31% chronic lymphocytic leukemia [CLL], and 15% CML), it should be considered in neutrophilia.

Pathophysiology

Patients with CML are usually older than 40 years old and have WBC counts greater than 50,000 cells/mm^3. The differential count shows elevated polymorphonuclear neutrophils and metamyelocytes. Less often, the basophil and eosinophil counts are also increased. CML is a stem cell disorder in which the WBC count is elevated and the differential count is normal. Mature and intermediate granulocytes are overproduced. Platelets may also be increased, but RBC production is down, thereby resulting in anemia.

Clinical Features

Fatigue, anorexia, sweating, weight loss, and abdominal fullness are common symptoms associated with CML; however, up to 20% may be asymptomatic and the diagnosis suspected on routine blood count. Physical findings include pallor, sternal pain and tenderness, and splenomegaly (76% of patients; Fig. 113.1).[9]

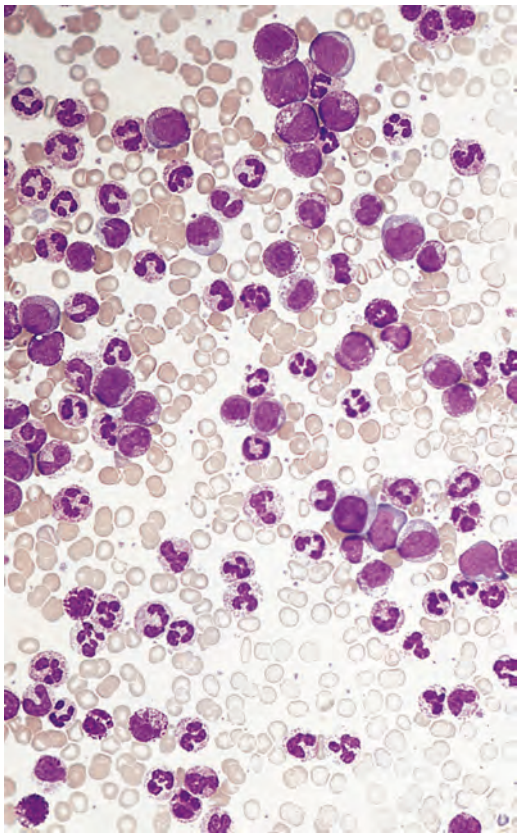

Fig. 113.1. Chronic myeloid leukemia (CML). (From Hoffbrand AV, Pettite JE: Color atlas of clinical hematology, ed 3, London, 2000, Mosby, p 169.)

Differential Diagnoses

The differential diagnoses include a leukemoid reaction, lymphocytic leukocytosis, including CLL and ALL, which are discussed further later. A leukemoid reaction is a nonleukemic reactive granulocytic leukocytosis that resembles CML but has no associated Philadelphia chromosome (Ph^1), no absolute increase in basophils and eosinophils, and an increase in leukocyte alkaline phosphatase. It is difficult to distinguish from CML in the emergency department, and both need to be considered a potential diagnosis in granulocytic leukocytosis. WBC counts are usually greater than 50,000 cells/mm^3. A leukemoid reaction may be seen in tuberculosis, Hodgkin's disease, sepsis, and metastatic tumor, particularly bronchogenic, gastric, and renal carcinoma.[1]

Diagnostic Testing

In the laboratory, decreased leukocyte alkaline phosphatase and increased vitamin B_{12} levels are found, which helps differentiate CML from other causes of neutrophilia. The Ph^1 is associated with the disease.

Management

The chronic phase of CML is treated with an alkylating agent (eg, busulfan) or an antimetabolite (eg, hydroxyurea). Selected patients may benefit from bone marrow transplantation.[10,11]

The need for urgent therapy in CML is usually related to hyperuricemia and renal injury or severe anemia and subsequent angina or heart failure. Rarely, hyperleukocytosis occurs, but the more mature, "less sticky" cells in CML do not usually cause problems unless the count exceeds 500,000 cells/mm^3. A higher cell count may cause leukostasis and result in deafness, visual impairment, pulmonary ventilation-perfusion abnormalities, and priapism. Treatment involves hydration, leukapheresis, transfusion as necessary, allopurinol to prevent severe hyperuricemia, and specific chemotherapy.

Disposition

Late problems in the natural history of CML involve progressive loss of cell differentiation and response to therapy. The term *blastic crisis* represents the sudden appearance of an acute form of leukemia, which is a rare substage of the evolving deterioration.[12,13] The condition may occur in lymphoid or myeloid forms. Blast counts greater than 50,000 cells/mm^3 may predispose the patient to the complications of leukostasis.

LYMPHOCYTIC LEUKOCYTOSIS

Principles

Anatomy and Physiology

Lymphocytic leukocytosis (lymphocytosis) is an age-dependent definition: 9000 cells/mm^3, ages 1 to 6 years; 7000 cells/mm^3, ages 7 to 16 years; and 4000 cells/mm^3, adults. It is seen in a variety of disorders, primarily infections, and lymphoproliferative disease.

Pathophysiology

In the past, before therapy was available, *acute* and *chronic* were descriptive terms applied to lymphocytic neoplasms with respect to patient survival time. The terms *acute* and *chronic* are currently used to describe the cell maturity, rapidity of onset, and aggressiveness of therapy. CLL is primarily a B-cell disorder and is the most common type of leukemia in the population 50 years or older. Acute lymphocytic leukemia (ALL) is most commonly diagnosed in children younger than 10 years old. It is the most frequent malignant neoplasm in children younger than 15 years old.[14]

Clinical Features

Patients with CLL initially complain of fatigue, weight loss, and increased susceptibility to infection, rashes, and easy bruising. The lymph nodes are nontender and smooth, and they may appear in only one or two areas. Splenic and hepatic enlargement occurs in more than 50% of patients.

The most common presenting symptoms of ALL are nonspecific and include fever, bleeding, bone pain, and lymphadenopathy. Although the most common symptoms associated with ALL are nonspecific, the persistence of any of these should prompt consideration of a malignancy. The potential for leukostasis increases in ALL when the blast count rises above 50,000 cells/mm^3.

Diagnostic Testing

Laboratory support of the diagnosis of CLL is an absolute lymphocyte count greater than 5000 cells/mm^3 in adults. Anemia, thrombocytopenia, and neutropenia are often found. Autoimmune hemolytic anemia, a positive direct antiglobulin test result, and other altered immune system problems are seen.

Management

Early therapy for CLL may be directed toward complications of anemia, thrombocytopenia, impaired or accentuated immune response, or enlarged lymph nodes or spleen. Leukostasis is seldom seen in CLL, but therapy is considered when the total count rises to higher than 200,000/mm^3.[15] The risk for a second incident cancer is higher in patient with CLL compared to the general public, particularly for melanoma.[16]

Oncologic therapy for ALL is based on clinical staging and includes chemotherapy or radiation therapy. Therapy has improved childhood survival; current 5-year overall survival rates are estimated at 78% to 85%. This response to treatment has not been found to the same degree in adults.[17,18]

LEUKOPENIA

Principles

In adults, leukopenia is defined as an absolute blood cell count less than 4000 cells/mm^3. Leukopenia is commonly associated with a reduction in one cell type, the neutrophil, and this decrease has the greatest clinical significance.[19] The absolute neutrophil count is calculated by multiplying the WBC count by the combined percentage of band and segmented neutrophils. The absolute neutrophil count can be classified as mild (1000 to 1500 cells/mm^3), moderate (500 to 1000 cells/mm^3), or severe (<500 cells/mm^3) according to the risk for infection.

Pathophysiology

Neutropenia may be caused by decreased production, increased destruction, or movement of circulating neutrophils into marginal or tissue pools. Neutropenia is a potentially life-threatening state because the patient is markedly susceptible to overwhelming infection. Neutropenia is often caused by decrease in bone marrow production but is becoming more commonly diagnosed, because it is thought to have a role in acquired immunodeficiency syndrome (Table 113.3).[20] Mild chronic neutropenia can be caused by drugs, nutritional deficiencies, collagen vascular disorders, infections, myelodysplastic disorders, or benign ethnic neutropenia. Acute severe neutropenia without anemia or thrombocytopenia is usually related to drugs or toxins.[19] Although neutropenia in the pediatric patient can be caused by congenital disorders and from similar etiologies as those in adults, postinfection may be one of the most common causes. Postinfectious neutropenia in children can be caused by bacterial as well as viral infections and is usually benign and of short duration.[21]

TABLE 113.3

Linkage of Leukopenia to Phases of Neutrophil Maturation

MECHANISM	EXAMPLE
Proliferation in bone marrow	Aplastic anemia, leukemia, cancer chemotherapy (cyclophosphamide, azathioprine, methotrexate, chlorambucil) Drugs: Phenothiazines, phenylbutazone, indomethacin, propylthiouracil, phenytoin, cimetidine, semisynthetic penicillins, sulfonamides Infection: Viral, tuberculosis, sepsis
Maturation in bone marrow	Folate or vitamin B_{12} deficiency, chronic idiopathic neutropenia Starvation
Distribution	Hypersplenism: Sarcoidosis, portal hypertension, malaria
Increased use	Infection: Viral most common (mononucleosis, rubella, rubeola), *Rickettsia* organisms, overwhelming bacterial infection Autoimmune disease: Systemic lupus erythematosus, AIDS, Felty's syndrome
Laboratory error	Leukocyte clumping, long delay in performing test

AIDS, Acquired immunodeficiency syndrome.

Clinical Features

The physical signs of infection may be minimal in severe neutropenia because there are too few cells to generate a substantial inflammatory or purulent response.

The clinician should ask patients found to be neutropenic about their medication list, a prior history of neutropenia, a family history, and a review of recent infections. The review of systems focuses on bleeding problems, fatigue, sweats, weight loss, and autoimmune symptoms. The physical examination is directed toward sites of infection, lymphadenopathy, hepatosplenomegaly, and underlying disease.

Diagnostic Testing

In patients with severe neutropenia and fever, a full radiologic and direct examination of commonly involved areas, such as the chest and urine, should be performed, and sputum, urine, and blood culture specimens should be obtained.

Management

Basic isolation techniques, early admission, and consultation with another specialist are recommended. Specific therapies may be started after cultures and consultation are completed. A number of empirical antibiotic regimens are recommended for febrile patients with neutropenia.[22] Human granulocyte colony–stimulating factor is often used in the setting of neutropenia, but it is best done in consultation with a hematologist.[23]

Disposition

Patients with a clear reversible source or without significant clinical findings and mild to moderate levels of neutropenia may have outpatient follow-up arranged, preferably after discussion with their physician.

KEY CONCEPTS

- CLL is the most common leukemia in the elderly, and ALL is the most common leukemia in children.
- Splenomegaly is a common finding in leukemias.
- Leukostasis is usually not accompanied by clinical sequelae until the WBC is more than 500,000.
- Neutropenia plus a fever should be treated as a life-threatening infection until proven otherwise.
- Postinfection is the most common cause of neutropenia in children.
- WBC determination in the emergency department has poor sensitivity and specificity for any specific disease process.
- Inflammatory markers, absolute neutrophil count and bandemia may be more useful for identifying infection than the absolute WBC.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 113: QUESTIONS & ANSWERS

113.1. A febrile patient who has abdominal pain arrives to the emergency department (ED). The surgery consultant demands to know the value of the white blood cell (WBC) count, "because it will help determine whether the patient has a bacterial infection in the abdomen." Which of the following statements best describes the use of WBC in the care of emergency patients?

A. May be useful in selecting patients for observation
B. The absolute neutrophil count and a bandemia may be more helpful than the total WBC count in identifying bacterial infection
C. The WBC is nonspecific and nonsensitive and has little screening value in the ED
D. All of the above

Answer: D. All of the above statements are true. The WBC count and accompanying differential count are the most common laboratory tests ordered in the ED. Unfortunately, the WBC count has not proved to be a highly sensitive or specific test, and the absence of leukocytosis does not exclude the presence of significant disease. In evaluation of the bacterial infectious potential in febrile children, the WBC and differential counts have demonstrated limited usefulness. Other biomarkers, such as procalcitonin and C-reactive protein (CRP), may have more predictive value. Thus, the WBC test should be viewed as having limited screening value in the acute care setting because multiple agents and conditions can increase the WBC count. Although the WBC count may be nonspecific and nonsensitive, studies evaluating the WBC count for the diagnosis of abdominal pain have found it to be a useful in selecting patients for observation, and the differential count may provide helpful information. The absolute neutrophil count and a high band count may be more helpful than the total WBC count in identifying bacterial infection.

113.2. Which of the following can affect the "normal" white blood cell (WBC) count?

A. Age and race
B. Exercise
C. Gender
D. Smoking
E. All of the above

Answer: E. All of the above statements are true. One unique problem in WBC disorders is the wide variability in normal values and the multiple factors influencing them. Normal values for the WBC count are listed in Table 113.1. The "normal" count is age dependent and may be shifted upward by exercise, gender (women), smoking, and pregnancy. Decreases in the total WBC count range by 1000 to 1200 cells/mm^3 have been noted in the African American population.

113.3. In evaluating a patient with severe neutropenia, which of the following is false?

A. If the patient also has a fever, basic isolation techniques and specific therapies should be initiated after cultures are completed.
B. If the patient also has a fever, urine and blood cultures should be obtained.
C. The clinician should ask about their medication list, a history of neutropenia, a family history, and a review of recent infections.
D. The physical signs of infection should be obvious because of the inflammatory response.
E. The review of systems focuses on bleeding problems, fatigue, sweats, weight loss, and autoimmune symptoms.

Answer: D. The physical signs of infection may be minimal in severe neutropenia because there are too few cells to generate a substantial inflammatory or purulent response.

113.4. A patient with a known history of chronic myeloid leukemia (CML) presents with shortness of breath. His white blood cell (WBC) count is 25,000 cells/mm. The etiology of his shortness of breath is least likely to be due to which of the following:

A. Angina
B. Heart failure
C. Hyperleukocytosis resulting in pulmonary ventilation-perfusion abnormalitiesD. Renal failure and fluid overload
E. Severe anemia

Answer: C. Hyperleukocytosis occurs, but the more mature, "less sticky" cells in CML do not usually cause problems unless the count exceeds 500,000 cells/mm^3. A higher cell count may cause leukostasis and result in deafness, visual impairment, pulmonary ventilation-perfusion abnormalities, and priapism. Treatment involves hydration, leukapheresis, transfusion as necessary, allopurinol to prevent severe hyperuricemia, and specific chemotherapy. The need for urgent therapy in CML is usually related to hyperuricemia and renal injury or severe anemia and subsequent angina or heart failure.

113.5. When applied to lymphocytic neoplasms, the terms *acute* and *chronic* describe all of the following except:
A. Aggressiveness of therapy
B. Cell maturity
C. Patient survival time
D. Rapidity of onset

Answer: C. In the past, before therapy was available, *acute* and *chronic* were descriptive terms applied to lymphocytic neoplasms with respect to patient survival time. The terms *acute* and *chronic* are currently used to describe the cell maturity, rapidity of onset, and aggressiveness of therapy. Chronic lymphocytic leukemia (CLL) is primarily a B-cell disorder and is the most common type of leukemia in the population 50 years or older. Acute lymphocytic leukemia (ALL) is most commonly diagnosed in children younger than 10 years. It is the most frequent malignant neoplasm in children younger than 15 years of age.

CHAPTER 114

Disorders of Hemostasis

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PRINCIPLES

Background and Importance

Hemostasis is the process of blood clot formation and represents a coordinated response to vessel injury. It requires an orchestrated response from platelets, the clotting cascade, blood vessel endothelium, and fibrinolysis. Thrombin-stimulated clot formation and plasmin-induced clot lysis are closely related and regulated. This dynamic process is often viewed in phases: formation of a platelet plug, propagation of the coagulation cascade, clot development, and fibrinolysis of the clot.

Most hemostatic abnormalities are acquired and result from drugs (eg, aspirin or warfarin [Coumadin]), from associated disease (eg, hepatic insufficiency), or from iatrogenic causes (eg, multiple transfusions).

Anatomy and Physiology

Vascular integrity is maintained by a lining of nonreactive overlapping endothelial cells supported by a basement membrane, connective tissue, and smooth muscle. These cells are important in maintaining a barrier to macromolecules and, when injured, in contributing to the metabolic response and local vasoconstriction. The endothelium contributes to both clot formation and regulation by producing substances, such as von Willebrand's factor (vWF), antithrombin III, heparin sulfate, prostacyclin, nitric oxide, and tissue factor pathway inhibitor.

Platelets have multiple roles in hemostasis. They are complex cytoplasmic fragments released from bone marrow megakaryocytes under the control of thrombopoietin. Platelets contain lysosomes, granules, a trilaminar plasma membrane, microtubules, and a canalicular system. Granules are an important component of hemostasis and contain over 300 metabolically active substances, including platelet factor 4, adhesive and aggregation glycoproteins, coagulation factors, and fibrinolytic inhibitors. Each participates in the process of coagulation and contributes to overall wound healing through the mediation of inflammation, immune response, and infection control. The platelet's role is termed *primary hemostasis,* and it is the initial defense against blood loss.[1] A fibrin clot that incorporates coagulation factors usually reinforces a platelet plug. Platelet activity is summarized in Box 114.1. Any of the steps listed may be absent, altered, or inhibited by inherited or acquired disorders.

The coagulation pathway is a complex system of checks and balances that results in controlled formation of a fibrin clot. Coagulation factors have been given standard Roman numerals matching their order of discovery (Box 114.2). A simplified version of the coagulation pathway is presented in Figure 114.1. The clotting cascade is traditionally depicted as consisting of intrinsic and extrinsic pathways. The intrinsic pathway is initiated by exposure of blood to a negatively charged surface, such as a glass surface in the activated partial thromboplastin clotting time. The extrinsic pathway is activated by tissue factor exposed at the site of vessel injury or thromboplastin. Both pathways converge to activate factor X, which then activates prothrombin to thrombin. The primary physiologic event that initiates clotting is exposure of tissue factor at the injured vessel site. Tissue factor is a critical cofactor that is required for activation of factor VII. Activated factor VII activates factor X directly, as well as indirectly by activating factor IX.

Pathophysiology

Hemostasis depends on normal function and integration of the vasculature, platelets, and coagulation pathway. Because of limited amounts of tissue factor and rapid inactivation by tissue factor pathway inhibitor, the extrinsic pathway initiates the clot process, but sustained generation of thrombin and clot formation depend on the intrinsic pathway through activation of factor IX by activated factor VII. Intrinsic, extrinsic, and common pathways function normally for hemostasis to occur, and each may be evaluated with laboratory tests. The clinically important groups of coagulation factors are shown in Box 114.3.

Thrombin-sensitive factors are activated by thrombin and may give rise to a bleeding disorder if defective synthesis occurs. Vitamin K–sensitive factors may also cause bleeding from defective synthesis, as occurs with liver disease and warfarin anticoagulants. Heparin in combination with antithrombin III affects the coagulation pathway at multiple sites.

All components of the coagulation reaction are necessary to prevent excessive bleeding. Hemostasis is a balance between the excessive bleeding state and thrombosis. Once coagulation is initiated, controls are necessary to prevent local or generalized thrombosis (Box 114.4).

CLINICAL FEATURES

History and Physical Examination

An outline of the history and physical examination is presented in Box 114.5. The history alone may be useful in differentiating between platelet and coagulation factor abnormalities. Platelet disorders are usually manifested as acquired petechiae, purpura, or mucosal bleeding and are more common in women. Platelet abnormalities can be caused by congenital disorders, but most are from acquired conditions. The bleeding source is usually a capillary with resultant cutaneous and mucosal petechiae or ecchymosis. Epistaxis, menorrhagia, and gastrointestinal bleeding are common initial symptoms. The bleeding is generally mild and occurs immediately after surgery or dental extractions. Petechiae and purpura may be noted on physical examination, and superficial ecchymoses may be found around a venipuncture site. The purpura associated with platelet disorders is typically asymptomatic and not palpable. This is in contrast to purpura associated with vasculitis, which can burn or itch and is palpable. Deep muscle hematomas and hemarthroses are not aspects of the clinical picture. The bleeding time is prolonged, and the platelet count may be low, normal, or high.

Coagulation problems are commonly congenital, characterized by delayed deep muscle or joint bleeding, and seen more often in men. Vascular disorders have signs and symptoms similar to those of thrombocytopenic states. The inherited forms are rare. Acquired forms are usually associated with connective tissue changes or endothelial damage.

BOX 114.1

Role of Platelets in Hemostasis

Adhesion to subendothelial connective tissue: Collagen, basement membrane, and noncollagenous microfibrils; serum factor VIII (von Willebrand's factor [vWF]) permits this function; adhesion creates the initial bleeding arrest plug
Release of adenosine diphosphate, the primary mediator and amplifier of aggregation; release of thromboxane A, another aggregator and potent vasoconstrictor; release of calcium, serotonin, epinephrine, and trace thrombin
Platelet aggregation over the area of endothelial injury
Stabilization of the hemostatic plug by interaction with the coagulation system:
- Platelet factor 3, a phospholipid that helps accelerate certain steps in the coagulation system
- Platelet factor 4, a protein that neutralizes heparin
- Pathway initiation and acceleration by thrombin production
- Possible secretion of active forms of coagulation proteins

Stimulation of limiting reactions of platelet activity

Thrombocytopenia

Thrombocytopenia from decreased bone marrow production is usually caused by the effects of chemotherapeutic drugs, myelophthisic disease, or direct bone marrow effects of agents, such as alcohol or thiazides. Splenic sequestration is a rare cause of thrombocytopenia but is seen primarily with hypersplenism resulting from hematologic malignant disease, portal hypertension, or disorders involving increased splenic red blood cell (RBC)

BOX 114.2

Coagulation Factors

I. Fibrinogens
II. Prothrombin
III. Tissue thromboplastin
IV. Calcium
V. Labile factor (proaccelerin)
VI. Not assigned
VII. Proconvertin
VIII. Antihemophilic A factor
IX. Antihemophilic B factor (plasma thromboplastin component, Christmas factor)
X. Stuart-Prower factor
XI. Plasma thromboplastin antecedent
XII. Hageman factor (contact factor)
XIII. Fibrin-stabilizing factor

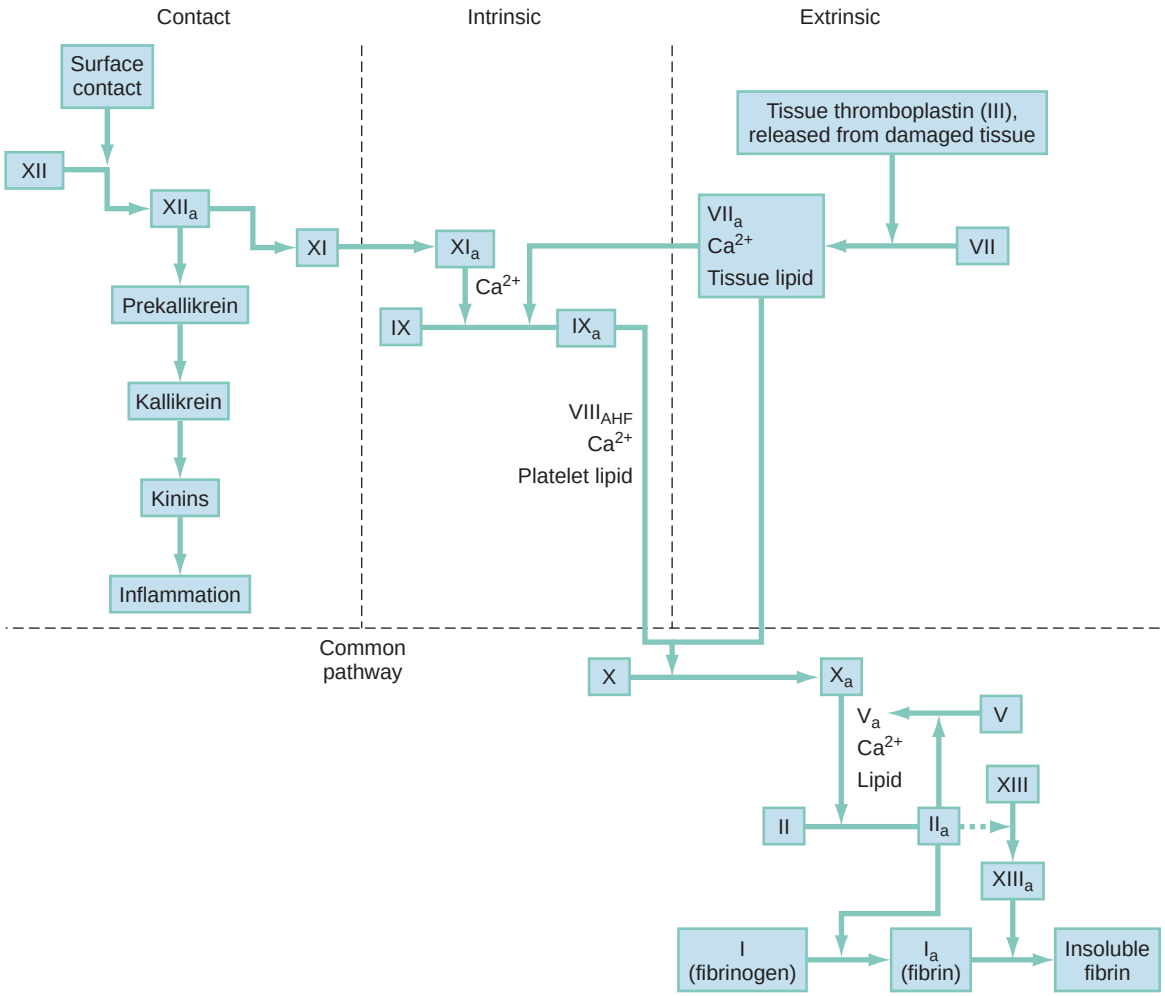

Fig. 114.1. Coagulation pathway.

BOX 114.3

Clinically Important Groups of Coagulation Factors

Thrombin-sensitive factors contributing to the metabolic response and local vasoconstriction: I, V, VIII, XIII
Vitamin K-sensitive factors: II, VII, IX, X
Sites of heparin activity: IIa, IXa, Xa (major site), XIa, platelet factor 3

BOX 114.4

Normal Controls of Coagulation

Removal and dilution of activated clotting factors through blood flow, which also mechanically opposes growth of the hemostatic plug
Alteration of platelet activity by endothelium-generated nitric oxide and prostacyclin
Removal of activated coagulation components by the reticuloendothelial system
Regulation of the clotting cascade by antithrombin III, protein C, protein S, and tissue factor pathway inhibitor
Activation of the fibrinolytic system

BOX 114.5

Clinical Evaluation of a Bleeding Patient

HISTORY

Nature of bleeding
- Petechiae
- Purpura
- Ecchymosis
- Significant bleeding episodes

Sites of bleeding
- Skin
- Mucosa: Oral or nasal
- Muscle
- Gastrointestinal
- Genitourinary
- Joints

Patterns of bleeding
- Recent onset or lifelong
- Frequency and severity
- Spontaneous or after injury

Challenges to hemostasis
- Tooth extraction
- Operative procedures
- Association with medication, particularly aspirin

Medications
Associated diseases
- Uremia
- Liver disease
- Infection
- Malignant neoplasm

Previous transfusion
Family history

PHYSICAL EXAMINATION

Vital signs
Skin: Nature of bleeding, signs of liver disease
Mucosa: Oral or nasal
Lymphadenopathy
Abdomen: Liver size and shape, splenomegaly
Joints: Signs of previous bleeding
Other sites of blood loss: Pelvic, rectal, urinary tract

destruction, such as hereditary spherocytosis or autoimmune hemolytic anemia. Thrombocytopenia resulting from increased destruction has several clinical important etiologies.

Immune Thrombocytopenia. Thrombocytopenia associated with increased peripheral destruction of platelets and shortened platelet survival caused by an antiplatelet antibody is seen in a number of diseases. Collagen vascular diseases, particularly systemic lupus erythematosus, may cause an antiplatelet antibody-related platelet decrease. Similar associations have been noted with leukemia and lymphoma, particularly lymphocytic lymphoma. All evaluations of suggested immune thrombocytopenia should include a complete blood count, peripheral smear, antinuclear antibody test, and bone marrow examination.

A number of drugs have been associated with thrombocytopenia of immunologic origin. Quinine and quinidine are common offenders that affect platelets through an "innocent bystander" mechanism. The platelet is coated with a drug-antibody complex, complement is fixed, and intravascular platelet lysis occurs. Because of its relatively high frequency, heparin is an important cause of drug-induced thrombocytopenia in hospitalized patients. Platelets are activated by the formation of an immunoglobulin G (IgG)–heparin complex.

Low–molecular-weight heparin (LMWH) may be associated with less thrombocytopenia than standard, unfractionated heparin (UFH); however, both forms of heparin demonstrate cross-reactivity.[2] Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated side effect associated with heparin.[3] The overall risk for HIT is around 1.2% for all patients receiving UFH or LMWH with certain surgical and medical illnesses conferring higher risk.[2] It usually occurs 5 to 7 days after the initiation of heparin treatment. Thrombus develops in approximately half the patients with HIT. The thrombotic complications can lead to limb loss in up to 20% and death in as many as 30%. The diagnosis is suggested with absolute thrombocytopenia or a greater than 50% reduction in platelets after the initiation of heparin. The most specific diagnostic tests for HIT are serotonin release assays, heparin-induced platelet aggregation assays, and solid-phase immunoassays. Platelet-associated IgG levels are commonly elevated, but this finding is less specific or sensitive than the other diagnostic tests. More concerning to the emergency clinician is delayed-onset HIT. This form of HIT occurs a median of 14 days after the initiation of heparin, but it can occur up to 40 days after heparin is started. Arterial or venous thrombosis typically develops in patients with HIT. The administration of heparin results in the generation of antibodies to the heparin and platelet factor 4 complex, which is removed from the circulation, and results in thrombocytopenia. However, this complex also results in the generation of microparticles that have procoagulant properties and thrombus formation.

Digoxin, sulfonamides, phenytoin, and aspirin are other drugs that may be associated with a thrombocytopenia. The patient has usually ingested the medication within 24 hours. An idiopathic thrombocytopenic purpura (ITP) type of syndrome has also been reported in intravenous cocaine users. Clinical trials with platelet glycoprotein IIb/IIIa antagonists suggest that intravenous glycoprotein IIb/IIIa inhibitors may confer an increased risk for associated thrombocytopenia, independent of heparin therapy.[4] The platelet count may fall below 10,000/mm^3 and be complicated by serious bleeding. Laboratory testing may confirm the presence of antibody, especially with the use of quinine and quinidine. After the drug is stopped, platelet counts improve slowly during a period of 3 to 7 days. A short course of corticosteroid therapy, such as prednisone in a dose of 1 mg/kg with rapid tapering, may facilitate recovery.[5]

Postinfectious immune thrombocytopenia is usually associated with viral diseases, such as rubella, rubeola, and varicella.

Although many cases associated with sepsis have a mechanical origin, some immune mechanisms have been demonstrated.[5]

Post-transfusion thrombocytopenia is a rare disorder that causes a precipitous fall in platelets approximately 1 week after the transfusion. In 90% of cases, its origin is linked to the 98% of the population carrying a PLA1 antigen on platelets. Despite the fact that 2% of blood recipients are mismatched with respect to this antigen, it is fortunately a rare occurrence. When a PLA1 antigen–negative patient receives a platelet transfusion, the platelets with attached PLA1 antibodies provoke an anamnestic response, but the actual mechanism of platelet destruction remains unknown. The platelet count often falls precipitously below 10,000/mm^3, with a significant risk for major bleeding. Intracranial hemorrhage occurs in approximately 10% of such cases. Patients are usually middle-aged women with a history of pregnancy who may have been previously sensitized to the PLA1 antigen during pregnancy. Plasma exchange therapy is an effective intervention.[5]

Idiopathic Thrombocytopenic Purpura. Autoimmune ITP is considered after other causes of thrombocytopenia have been excluded. ITP is associated with an IgG antiplatelet antibody that has proved difficult to detect. The two clinically important forms are acute and chronic.[6]

The acute form of ITP is seen most often in children 2 to 6 years old. A viral prodrome commonly occurs within 3 weeks of its onset. The platelet count decreases, usually to less than 20,000/mm^3. The course is self-limited, with a greater than 90% rate of spontaneous remission. Morbidity and mortality rates are low, although full recovery may take several weeks. Treatment of acute ITP is supportive. Steroids and intravenous immune globulin therapy are reserved for patients with active bleeding.[5]

The chronic form of ITP is primarily an adult disease found three times more often in women than in men. The onset of chronic ITP is insidious, without a prodrome, and it is manifested as easy bruising, prolonged menses, and mucosal bleeding. The patient may have petechiae or purpura, and platelet counts between 30,000/mm^3 and 100,000/mm^3 are common. Bleeding complications are of unpredictable frequency and severity, although the long-term mortality rate is approximately 1%.[7] Splenomegaly is unusual in either acute or chronic ITP.

A similar pattern of thrombocytopenia has been recognized among human immunodeficiency virus (HIV) patients. Although the clinical findings and response to therapy mimic those of ITP, the mechanism is multifactorial involving the action of immune complexes, anti-platelet and anti-HIV antibodies that cross-react with the platelet membrane, and secondary effects of drugs and opportunistic infections. Since the advent of highly active antiretroviral therapy (HAART), the prevalence of HIV associated thrombocytopenia has declined.[8]

Nonimmune Thrombocytopenia. Nonimmune platelet destruction is usually consumptive or mechanical. Consumption occurs as part of the process of intravascular coagulation, although it may be seen at sites of significant endothelial loss. Thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and vasculitis all initiate platelet destruction through endothelial damage.[7] The most striking difference between the first two is the age at onset and the prognosis.

Thrombotic Thrombocytopenic Purpura. The pathologic state of TTP is the result of subendothelial and intraluminal deposits of fibrin and platelet aggregates in capillaries and arterioles. HUS is considered to be similar to TTP; however, HUS is associated with less central nervous system and more renal involvement than TTP. A more complete discussion of HUS is found in Chapter 173. Although the initiating event is unclear, prostacyclin and abnormal platelet aggregation are believed to play a central role in pathogenesis of the disease. The disease may affect patients of any age or sex, but the majority of patients are 10 to 40 years old, and 60% of cases occur in women. Most cases of TTP are idiopathic. However, TTP can be associated with medications. Quinine has traditionally been associated with the disease. The antiplatelet drugs ticlopidine and clopidogrel, which are used to treat a variety of cardiovascular and cerebrovascular disorders, have also been associated with TTP. It is classically seen as the constellation of thrombocytopenic purpura, microangiopathic hemolytic anemia, fluctuating neurologic symptoms, renal disease, and fever. However, the classic pentad is not commonly seen, and the diagnosis should be suspected and treatment initiated for unexplained thrombocytopenia in association with microangiopathic hemolytic anemia.

The platelet count in TTP ranges from 10,000/mm^3 to 50,000/mm^3, and generalized purpura and bleeding complaints are common. Anemia is universal, and hematocrit levels are commonly less than 20%. The hemolysis may cause jaundice or pallor, and the blood smear characteristically contains numerous schistocytes and fragmented RBCs. Neurologic symptoms include stroke, seizures, paresthesias, altered levels of consciousness, and coma, all of which characteristically fluctuate in severity. The renal component varies from hematuria and proteinuria to acute renal failure. Fever is present in 90% of patients.

Dilutional Thrombocytopenia. Dilutional thrombocytopenia occurs in cases of massive transfusion, exchange transfusion, or extracorporeal circulation. Volume replacement with stored blood is platelet poor because platelets have a life span of only 9 days. The number of transfusions directly correlates with the degree of thrombocytopenia. Current transfusion practice is to monitor platelet counts for every 10 units of RBCs and to transfuse once the platelet count approaches 50,000/mm^3.

Thrombocytopathy

Knowledge of abnormal platelet function as a clinical disorder has grown rapidly in recent years. The drug-induced form may be one of the most commonly seen causes, especially in intensive care unit (ICU) patients.[7] Defects may occur at any level of platelet function, including adhesion, release, and aggregation.

Adhesion Defects. The representative adhesion disorder is von Willebrand's disease (vWD), which is a factor VIII problem more than a platelet deficiency. Platelets are normal in terms of their morphologic condition, number, release, and aggregation. The abnormal adhesion results not from the platelet but from an endothelium-based plasma deficiency of a factor VIII component (vWF) that permits platelet adhesion.

Release Defects. Release defects include "storage pool" syndromes in which release is normal but amounts of adenosine diphosphate, calcium, and serotonin are decreased. Release defects may be congenital or acquired, such as in systemic lupus erythematosus, alcoholism, or lymphoma. Drugs induce the most common release problem. Aspirin and related drugs block the enzyme cyclooxygenase, which participates in thromboxane A_2 formation. Decreased release of thromboxane A_2 results in decreased aggregation and less local vasoconstriction. Both may increase the risk of bleeding. Testing for this risk may be performed with post-aspirin bleeding time. Aspirin is unique in that it permanently poisons this reaction for the life of the platelet in doses of only 300 to 600 mg. Indomethacin affects function only while it is present in the circulation. A similar problem may occur in patients with uremia or dysproteinemia and as a rare inherited form.

Aggregation Defects. Primary aggregation defects are associated with the rare recessive trait thrombasthenia. This platelet membrane abnormality may be detected by the lack of clot retraction during a 2-hour clot retraction test.

Thrombocytosis

Thrombocytosis is a platelet count higher than 600,000/mm^3; Box 114.6 presents the list of potential causes. It is often caused by infection or iron deficiency, in which case it is not generally associated with platelet-associated complications. The primary or autonomous state may be associated with bleeding or thrombosis. It is often an associated finding in patients with polycythemia vera, myelofibrosis, or chronic myelogenous leukemia, and in children with Kawasaki disease. Suggested autonomous thrombocytosis requires a full hematologic evaluation.

Disorders of the Coagulation Pathway

The coagulation system accomplishes secondary hemostasis through a complex enzymatic cascade. The clinically significant disorders have a number of characteristic features that help differentiate them from platelet disorders (Box 114.7).

The prothrombin time (PT) and partial thromboplastin time (PTT) are the basic laboratory diagnostic tools for the evaluation of coagulation disorders and can be used to organize the approach to their diagnosis.

BOX 114.6

Differential Diagnosis of Platelet Disorders

THROMBOCYTOPENIA

Decreased production
- Decreased megakaryocytes secondary to drugs, toxins, or infection
- Normal megakaryocytes with megaloblastic hematopoiesis or hereditary origin
- Platelet pooling and splenic sequestration

Increased destruction
- Immunologic
  - Related to collagen vascular disease, lymphoma, leukemia
  - Drug related
  - Infection
  - Post-transfusion
  - Idiopathic (autoimmune) thrombocytopenic purpura
- Mechanical
  - Disseminated intravascular coagulation (DIC)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic-uremic syndrome (HUS)
- Vasculitis

Dilutional secondary to massive blood transfusion

THROMBOCYTOPATHY

Adhesion defects such as von Willebrand's disease (vWD)
Release defects: Acquired and drug related
Aggregation defects, such as in thrombasthenia

THROMBOCYTOSIS

Autonomous (primary thrombocythemia)
Reactive (secondary thrombocythemia)
Iron deficiency
Infection or inflammation
Trauma
Nonhematologic malignant disease
Postsplenectomy
Rebound from alcohol, cytotoxic drug therapy, folate or vitamin B_{12} deficiency

Abnormal Prothrombin Time and Other Test Results Normal

An elevated PT reflects an extrinsic pathway abnormality mediated through deficiency of factor VII. The hereditary form is caused by a rare autosomal recessive gene. The acquired form is commonly seen and may be a result of vitamin K deficiency, warfarin use, or liver disease. Because factor VII has the shortest half-life (3 to 5 hours) of the coagulation factors, it is the first to manifest a deficiency when its active form is underproduced. The PT is a sensitive gauge of hepatic function and the efficacy of warfarin administration. International normalized ratios (INRs) calculate the prothrombin ratio raised to the power of an international sensitivity index for specific thromboplastin reagents. It is recommended with most warfarin therapy that the INR be maintained between 2.0 and 3.0, except in the setting of cardiac valvular disease, in which the target INR is 2.5 to 3.5.

Abnormal Partial Thromboplastin Time and Other Test Results Normal

Two groups of inherited disorders manifest as an isolated elevation in the PTT. The first group involves deficiencies of the contact factors (eg, XII [Hageman factor]), prekallikrein (Fletcher factor), and high-molecular-weight kininogen. They cause a benign disorder in which the PTT is elevated but the patient has no bleeding diathesis. These deficiencies exist as isolated laboratory abnormalities, and thus they should not be invoked as a cause of the patient's bleeding problem. They may be specifically assayed when a precise diagnosis is necessary.

The second group causes significant bleeding problems resulting from deficiencies of factors within the intrinsic coagulation system. They are the most common inherited abnormalities of the entire clotting system. Deficiencies of factors VIII, IX, and XI account for 99% of inherited bleeding disorders. Patients with active life-threatening bleeding who are thought to have a congenital bleeding disorder can be supported with fresh frozen plasma, 15 mL/kg, while diagnostic studies are being performed.

In a patient with a prolonged PTT and a lifelong history of bleeding, the most important test is assay of factor VIII and factor IX. This test measures the ability of the patient's plasma to correct the prolonged PTT of plasma deficient in factor VIII. This ability is compared with that of normal plasma, and the result is given as a percentage of normal. The test measures the procoagulant activity of factor VIII but does not discriminate between abnormal activity resulting from abnormal factor VIII and low levels of normal factor VIII. The two forms of this deficiency are hemophilia A and vWD.

BOX 114.7

Features of Coagulation Disorders Which Differentiate From Platelet Disorders

The bleeding source is often an intramuscular or deep soft tissue hematoma from small arterioles.
The congenital form of the disease occurs predominantly in men, often as a sex-linked inheritance.
Bleeding may occur after surgery or trauma but is delayed in onset up to 72 hours.
Epistaxis, menorrhagia, and gastrointestinal sources of bleeding are rare, whereas hematuria and hemarthrosis are common in severe cases.
The bleeding time is normal except in patients with von Willebrand's disease (vWD).

Hemophilia A. Hemophilia A is caused by a variant form of factor VIII that is present in normal levels but lacks a clot-promoting property. Factor VIII circulates in plasma in very low concentration and is normally bound to vWF. The source of factor VIII production is uncertain, but the liver is thought to be a significant source because hemophilia A can be corrected by liver transplantation. The incidence of hemophilia A is 60 to 80 persons per million population. Of known cases, 70% have been found to have a sex-linked recessive nature; that is, the disease is carried on the X chromosome at location Xq28. The remaining 25% to 30% of cases of the disease are believed to result from a spontaneous genetic abnormality. The familial form has a remarkable consistency of severity from generation to generation, although the degree of severity has considerable variation. This severity may be directly related to the level of factor VIII coagulant (factor VIII:C) activity. Cases with less than 1% activity are severe, with a tendency toward spontaneous bleeding. Cases with 1% to 5% activity are moderate, with rare spontaneous bleeding but increased problems with surgery or trauma. Cases with 5% to 10% activity and above are considered mild, with little risk of spontaneous bleeding but still with hazards after trauma and surgery. A number of hemophiliacs may have activity above 10% but have few problems under normal conditions. The PTT may lack sensitivity for this group because it is significantly prolonged only at factor VIII:C levels less than 35% to 40%.[9]

The disease is seen as a disorder of secondary hemostasis with a characteristic pattern of bleeding. Bleeding can occur anywhere, but deep muscles, joints, the urinary tract, and intracranial sites are the most common. Recurrent hemarthrosis and progressive joint destruction are major causes of morbidity in hemophilia. Intracranial bleeding is the major cause of death in all age groups of hemophiliacs. Mucosal bleeding, such as epistaxis and oral bleeding, or menorrhagia is rare unless the disease is associated with vWD or platelet inhibition, such as with aspirin use. Gastrointestinal bleeding is rare unless peptic ulcer disease is also present. Trauma is a common initiator of bleeding in all grades of severity. This potential hazard should be viewed expectantly in all hemophiliacs because late bleeding may occur, usually by 8 hours but potentially up to 1 to 5 days and, rarely, even longer after traumatic injury.[10]

von Willebrand's Disease. To understand vWD, it is helpful to review the nomenclature used to refer to factor VIII in some centers. Factor VIII has at least three activities. First is its antihemophilic, or coagulant, activity, VIII:C. All references to factor VIII in this chapter thus far have been to this activity. A second activity supports platelet adhesion and in vitro aggregation with the antibiotic ristocetin; it is called *von Willebrand's factor activity,* or *VIII/vWF.* A third component reacts with rabbit antibodies to factor VIII; it is termed the *factor VIII antigen,* or *VIII:Ag,* and relates to the measured plasma level rather than to the activity of factor VIII. The antigen and cofactor activity for platelet function are structurally related. vWD has both decreased factor VIII:Ag levels and decreased VIII:C activity secondary to underproduction. The patient's platelets are normal in number, morphologic condition, and other functions, but in the absence of circulating factor VIII/vWF, their adhering properties are diminished. vWD is the most common hereditary bleeding disorder, with an estimated prevalence of 1%. The disease occurs in 5 to 10 persons per million population as an autosomal dominant trait with a variable penetrance pattern. A rare X-linked inheritance has been described.[11]

Manifestations of vWD are usually milder and less crippling than those of hemophilia. The factor VIII:C level is in the 6% to 50% range. Bleeding sites are predominantly mucosal (eg, epistaxis) and cutaneous. Hemarthroses are rare, but menorrhagia and gastrointestinal bleeding are common. Laboratory differentiation from hemophilia A includes abnormal bleeding time, decreased level of factor VIII:Ag, and abnormal platelet aggregation with ristocetin.

Hemophilia B (Christmas Disease). Hemophilia B is a deficiency of factor IX activity. Its genetic pattern and clinical findings are indistinguishable from those of hemophilia A, but its incidence is only a fifth that of hemophilia A. Factor IX is a vitamin K–dependent glycoprotein. Its deficiency is diagnosed by a factor IX assay, usually after the factor VIII:C assay is found to be normal.

Miscellaneous Coagulation Disorders

A number of other disorders may be caused by a deficiency in the common coagulation pathway. An altered fibrinogen level or abnormal function is a relatively common cause. Patients with this deficiency also have an abnormal thrombin time. The inherited forms are rare. The acquired forms have been related to fibrin-blocking substances and hypofibrinogenemia, which are found most often in cases of disseminated intravascular coagulation (DIC) and dysfibrinogenemia associated with macroglobulinemia, multiple myeloma, and hepatoma. In the context of emergency medicine, fibrinogen's most important role relates to its activity in DIC.

The other components of the common pathway (factors II, V, and X) have rare inherited deficiencies. The acquired forms are far more common and relate to vitamin K deficiency (decreased factor II, VII, IX, and X activity), warfarin use (same factors as with vitamin K deficiency), hepatic insufficiency (potentially all factors except VIII), and massive transfusion of stored blood (low in factors V and VIII and platelets).

Disseminated Intravascular Coagulation. DIC is a relatively common acquired coagulopathy. Its ubiquitous nature, multiple origins, and potentially devastating sequelae, balanced by an effective mode of therapy, make early diagnosis of this hematologic process critical. It is most often encountered in the critical care setting. Hemostasis is achieved by a fine balance between procoagulants and inhibitors, and thrombus formation and lysis. The balance may be disturbed by pathologic processes that result in an out-of-control coagulation and fibrinolytic cascade within the systemic circulation. The abnormal clotting sequence observed in DIC is shown in Box 114.8.

The clinical consequence of these processes is the life-threatening combination of a bleeding diathesis from loss of platelets and clotting factors, fibrinolysis, and fibrin degradation product interference; small-vessel obstruction and tissue ischemia

BOX 114.8

Disseminated Intravascular Coagulation Abnormal Clotting Sequence

Platelets and coagulation factors are consumed, especially fibrinogen and factors V, VIII, and XIII.
Thrombin is formed, and it overwhelms its inhibitor system and acts to accelerate the coagulation process and directly activate fibrinogen.
Fibrin is deposited in small vessels in multiple organs.
The fibrinolytic system by means of plasmin may lyse fibrin and impair thrombin formation.
Fibrin degradation products are released and affect platelet function and inhibit fibrin polymerization.
Coagulation inhibition levels (eg, antithrombin III, protein C, and tissue factor pathway inhibitor) are decreased.

TABLE 114.1

Laboratory Diagnosis of Disseminated Intravascular Coagulation

TEST	FINDING	PATHOPHYSIOLOGY
Peripheral smear	Low platelets, schistocytes, RBC fragments	RBC fragmentation on fibrin strands; schistocytes not always seen
Platelet count	Low (usually <100,000/mm^3)	Consumed in clotting; lower numbers are reflected in the bleeding time
Prothrombin time (PT)	Prolonged	Factors II and IV consumed
Partial thromboplastin time (PTT)	Prolonged	Factors II, V, and VIII consumed
Thrombin time	Prolonged	Decrease in factor II and fibrin degradation products
Fibrinogen level	Low	Factor II consumed; may be difficult to interpret because it is an acute-phase reactant
Fibrin degradation products (D-dimer)	Zero to large	Dependent on the amount of secondary fibrinolysis
Serum creatinine or urinalysis	May be abnormal	Functional assessment of the organ most commonly injured by fibrin deposition

RBC, Red blood cell.

from fibrin deposition; and RBC injury and anemia from fibrin deposition. The condition needs to be considered in any patient in whom purpura, a bleeding tendency, and signs of organ injury, particularly of the central nervous system and kidney, develop. This broad description is further confused clinically by the variable acuteness and intensity of intravascular clotting, the effectiveness of fibrinolysis, and other systemic manifestations of the initiating disease. The clinical diagnosis of DIC is confirmed by laboratory tests (Table 114.1).

Two conditions that may simulate DIC are severe liver disease and primary fibrinolysis. Liver disease of this severity is usually manifested by clinical jaundice and splenomegaly. Primary fibrinolysis is a rare disorder that affects fibrinogen and fibrin but generally leaves the coagulation components (platelets, factor V, and factor VIII) in the low-normal range. Additional laboratory tests can be used to confirm the diagnosis of primary fibrinolysis, but these are not typically obtained in the emergency department (ED) and are best ordered in conjunction with a hematologist.

DIFFERENTIAL DIAGNOSIS

When a bleeding disorder is diagnosed or suggested, the assessment initially includes stabilization, which may necessitate volume, RBC, and coagulation factor replacement. If the disorder is known, clinical complications associated with its underlying pathophysiologic condition needs to be considered. If the disorder is unknown, a rapid differential diagnosis must be made. The differential diagnosis of vascular disorders is listed in Box 114.9. The differential diagnosis of platelet disorders is listed in Box 114.6.

DIAGNOSTIC TESTING

A definitive diagnosis depends on laboratory evaluation. Tests pertinent to the ED are discussed in the following sections and listed in Box 114.10.

BOX 114.9

Differential Diagnosis of Vascular Disorders

INHERITED

Disorders of connective tissue
- Pseudoxanthoma elasticum
- Ehlers-Danlos syndrome
- Osteogenesis imperfecta

Disorders of blood vessels
- Hemorrhagic telangiectasia

ACQUIRED

Scurvy (vitamin C deficiency)
Simple or senile purpura
Purpura secondary to steroid use
Vascular damage
- Infection (meningococcemia)
- Hemolytic-uremic syndrome (HUS)
- Hypoxemia
- Thrombotic thrombocytopenic purpura (TTP)
- Snakebite
- Dysproteinemic purpura

BOX 114.10

Coagulation Studies

Complete blood count and smear (EDTA—purple top)
Platelet count (EDTA—purple top)
Bleeding time
Prothrombin time (PT; citrate—blue top)
Partial thromboplastin time (PTT; citrate—blue top)
Other coagulation studies: Fibrinogen level, anti-Xa assay, thrombin time, clot solubility, factor levels, inhibitor screens
As necessary: Electrolyte values; glucose, BUN, and creatinine concentrations; type and crossmatch

BUN, Blood urea nitrogen; *EDTA,* ethylenediaminetetraacetic acid.

Complete Blood Count and Blood Smear

The complete blood count assesses the degree of anemia associated with the bleeding episode. Reductions in hemoglobin and hematocrit often lag behind the actual loss of RBCs in acute hemorrhage because of a slow equilibration time. The peripheral blood smear may demonstrate schistocytes or fragmented RBCs in microangiopathic hemolytic anemias, such as TTP or DIC. Teardrop-shaped or nucleated RBCs may reflect myelophthisic disease. A characteristic white blood cell morphology is seen with thrombocytopenia associated with infectious mononucleosis, folate or vitamin B_{12} deficiency, or leukemia.

Platelet Count

The platelet count may be estimated from the smear. Normally, one platelet is present per 10 to 20 RBCs. Often, the count is automated, the normal range being 150,000 to 400,000/mm^3. Platelet counts less than 100,000/mm^3 define thrombocytopenia. With normal platelet function, the bleeding time increases in direct relation to a decrease in the platelet count below 100,000/mm^3. Levels below 20,000/mm^3 may be associated with serious spontaneous hemorrhage. However, the count gives no information about the functional capability of platelets.

Bleeding Time and Platelet Function Assay

Historically, bleeding time was considered the best test to determine both vascular integrity and platelet function. However, this test is insensitive in identifying medication related platelet dysfunction, vWD, and in predicting surgical bleeding.[12] Some institutions have replaced the traditional bleeding time with a platelet function analyzer instrument, which is more convenient, with similar clinical value. A normal time is 8 minutes, a time of 8 to 10 minutes is borderline, and a time longer than 10 minutes is typically abnormal. The platelet function assay has been found to be highly sensitive in detecting moderate to severe vWD, medication related platelet dysfunction, and severe platelet function disorders. Although less sensitive to more mild disease, the platelet function assay is useful in detecting platelet pathology relevant to the emergency clinician.[12] Because of the high incidence of drug-induced platelet dysfunction, ask the patient about medications, particularly aspirin and other antiplatelet medications (eg, clopidogrel). Platelet function testing is independent of the coagulation pathways.

Prothrombin Time

The PT tests the factors of the extrinsic and common pathways. The patient's anticoagulated plasma is combined with calcium and tissue factor prepared from rabbit or human brain tissue. Sensitivity to factor deficiencies depends on the source of the tissue factor. The PT detects deficiencies in fibrinogen, prothrombin (factor II), factor V, factor VII, and factor X. Results are reported in seconds or as the prothrombin ratio. To generate the prothrombin ratio, the time in seconds of the sample is given over the time of a normal control, for example, 12.5/11.5. Results are also usually reported as the INR, which compensates for differences in sensitivity of various thromboplastin reagents to the effects of warfarin. The test is helpful in monitoring the use of coumarin anticoagulants, and the time may be prolonged in patients with liver disease and other abnormalities of vitamin K–sensitive factors.

Partial Thromboplastin Time

The PTT tests the components of the intrinsic and common pathways, that is, essentially all factors but VII and XIII in the entire clotting cascade. In this test, a phospholipid source and a contact-activating agent (kaolin) are added to anticoagulated citrate plasma. After an incubation period that allows factor XII to become activated, calcium is added and the clotting time is recorded. A normal control sample is run simultaneously. Normal ranges may vary by laboratory. The average time is 25 to 29 seconds. The sensitivity of the test varies from factor to factor, but factor levels usually are less than 40% before the PTT is prolonged. The test may be altered by clotting factor inhibitors of external origin (eg, heparin) or internal origin (eg, anti-VIII antibody). Inappropriately high values may occur if the plasma is too turbid or icteric. The activated PTT is most sensitive to abnormalities in the sequence of the coagulation cascade that precedes activation of factor X.

Anti-Xa Assay

The anti-Xa assay is a chromogenic assay which is becoming increasingly available to emergency clinicians for monitoring of unfractionated and LMWH levels and drug quantification of rivaroxaban and apixaban. When monitoring heparin levels, the test should ideally be performed 3 to 4 hours after medication administration for peak level monitoring. Because this test is not subject to the variability of the PTT, this test has become more attractive as costs have declined in recent years. The test is considered the reference standard for measurement of in vivo heparin activity and represents the only reliable means of quantifying rivaroxaban and apixaban drug levels.

Fibrinogen

Fibrinogen is present in sufficient concentration to be measured directly. Because it is the final coagulation substrate, its level reflects the balance between production and consumption. It may be decreased by low production, as in severe liver disease, or by overconsumption, as in DIC. Low levels and altered function increase the PT, PTT, and thrombin clotting time. Because fibrinogen is an acute-phase reactant, certain conditions, including malignant disease, sepsis, inflammation, and pregnancy, may alter the test result.

Thrombin Time

Measurement of the thrombin clotting time bypasses the intrinsic and extrinsic pathways by directly converting fibrinogen to fibrin. It is a useful screening test for both qualitative and quantitative abnormalities of fibrinogen and inhibitors, such as heparin and fibrin split products. The test is also a valuable means to measure drug activity of direct-thrombin inhibitors, such as dabigatran.

Clot Solubility

The result of clot solubility testing may be the only abnormality in disorders involving factor XIII deficiency. A washed clot is incubated in acetic acid or urea. If the fibrin clot is not properly cross-linked by factor XIII, it dissolves.

Factor Level Assays

Factor levels are determined either by bioassay, in which the ability of the sample of plasma to normalize controlled substrate-deficient plasma is evaluated, or by immunologic assay. Inhibitor screening tests reveal antibodies in plasma that prolong the normal plasma clotting time when mixed.

MANAGEMENT

Out-of-Hospital Treatment

The out-of-hospital treatment of hemostatic disorders presents no special concerns beyond potential identification and bleeding control. Local pressure and volume repletion are the mainstays of therapy for blood loss. Coagulopathies may complicate any medical or traumatic problem, and coagulopathy can rapidly develop in critically ill patients. Patients who do not respond quickly to the usual measures of hemostasis in the field should be considered to have a potential bleeding disorder.

Platelet Disorders

Platelet Transfusions. Most platelet function disorders *are not* treated by platelet transfusion, because its efficacy is questionable and alloimmunization may occur. Platelet transfusions are commonly indicated for primary bone marrow disorders (eg, aplastic anemia or acute leukemia). Assessment of the risk for spontaneous bleeding by platelet counts is an imprecise science. Less mature platelets associated with peripheral consumption or sequestration are less likely to allow spontaneous hemorrhage than are those associated with primary bone marrow involvement. An estimate of functionality is combined with the platelet count for a better predictor of primary hemostasis potential. At counts below 40,000 to 50,000/mm^3, a variable degree of risk exists,

especially associated with trauma, ulcers, or invasive procedures. At counts higher than 50,000/mm^3, hemorrhage caused by platelet deficiency is unlikely. Spontaneous bleeding in the absence of surgery, trauma, or other risk factors may occur in patients with platelet counts below 5000 to 10,000/mm^3, and prophylactic platelet infusions should be reserved for this level of thrombocytopenia. Transfusion of platelets in this setting should be initiated in consultation with a hematologist.

Medication-Induced Thrombocytopenia

As mentioned earlier, digoxin, sulfonamides, phenytoin, aspirin, glycoprotein IIb/IIIa antagonists, quinine and quinidine, and aspirin are drugs that may be associated with a thrombocytopenia. After the drug is stopped, the platelet count improves slowly during a period of 3 to 7 days. A short course of corticosteroid therapy, such as prednisone in a dose of 1 mg/kg with rapid tapering, may facilitate recovery.[5]

Post-Transfusion Thrombocytopenia

For the rare disorder that causes post-transfusion thrombocytopenia, plasma exchange therapy is an effective intervention.[5]

Heparin-Induced Thrombocytopenia

Treatment of thrombotic complications in patients with HIT involves the use of direct thrombin inhibitors (lepirudin, argatroban), factor Xa inhibitors (fondaparinux), or heparinoids (danaparoid).[3]

Idiopathic Thrombocytopenic Purpura

Treatment of acute ITP is supportive. Steroids and intravenous immune globulin therapy are reserved for patients with active bleeding.[5] However, with chronic ITP, associated diseases, such as lymphoma and systemic lupus erythematosus, needs to be ruled out before the diagnosis of ITP can be made. Quantitative laboratory tests of antiplatelet antibody may differentiate between patients who will favorably respond to therapy and those who will not. Hospitalization is recommended during the initial evaluation, because the differential diagnosis is complex and the risk of bleeding is significant. Management includes stopping all nonessential drugs, particularly those that inhibit platelet function (eg, aspirin). The initial treatment of chronic ITP is typically corticosteroids (prednisone 1 mg/kg per day). Intravenous immune globulin and anti-D immunoglobulin, in conjunction with steroids, have also been used as first-line therapy. However, these therapies are best used after consultation with a hematologist. Splenectomy, monoclonal antibody therapy, and immunosuppressives are considered in steroid-failure cases.[5] A thrombopoietin-receptor agonist, eltrombopag, has recently been shown in a well-designed trial to increase platelet counts in patients with relapsed or refractory ITP and thus might have a future role.[13] Platelet transfusions are used only to control life-threatening bleeding because of increased antiplatelet antibody titers and short-lived hemostatic effect. Although it is rare, life-threatening bleeding is treated with platelet transfusions, intravenous immune globulin (0.7 g/kg), and methylprednisolone (15 mg/kg intravenously).[5] Although recombinant factor VIIa has been used in ITP to stop bleeding, concern for thrombosis limits its use when safer alternatives are available.

Thrombotic Thrombocytopenic Purpura

Before the availability of plasma exchange, TTP followed a progressive and fatal course, with 90% mortality rate 1 to 3 months after diagnosis. Therapy has included corticosteroids, splenectomy, anticoagulation, exchange transfusion, and dextran. However, plasma exchange with fresh frozen plasma (plasmapheresis) is the standard treatment, often with adjunctive rituximab.[14] This therapy has reduced the mortality to as low as 6.4%.[15] In addition to plasma exchange, initial therapy may also include steroids (such as, prednisone) and antiplatelet agents (such as, aspirin and dipyridamole). If TTP is suspected in the ED, a hematologist should be consulted before any therapy is initiated. With the exception of life-threatening bleeding, platelet transfusion is avoided because platelets may cause additional thrombi in the microcirculation.

Hemophilia A

Management of Hemophilia A

Comprehensive management of hemophilia involves a team effort of physicians, specialized nurses, physical therapists, social workers, the patient, and the patient's family. The therapeutic responsibility of the emergency clinician consists of three areas: (1) preparation for and identification of the problem, initial evaluation, and admission of newly diagnosed hemophilia patients; (2) replacement therapy for bleeding episodes; and (3) anticipation of potential life threats and admission of patients with known hemophilia A for observation in selected circumstances. At one time, treatment of hemophilia-associated bleeding was a relatively common emergency medicine activity, but since 1975, hemophilia home therapy has increasingly been instituted. Therefore, many hemophiliacs now come to the ED only with complicated problems or trauma-related difficulties, and most are knowledgeable about their disease.

Preparation. ED management of hemophilia is best accomplished with advanced planning that includes protocols developed with a hematologist for the administration of factor VIII. Emergency clinicians should have rapid access to hemophilia patients' relevant information, including primary physician and hematologist, diagnosis, factor VIII activity level, blood type, presence of antihemophilic factor antibodies, and time of last hospitalization. This may be accomplished through an electronic medical record system or a maintained file of known hemophilia patients.

Replacement Therapy. The accepted therapy for hemophilia A is factor VIII replacement with cryoprecipitate or factor VIII:C concentrates. These concentrates are exposed to heat treatment or solvent-detergent mixtures to decrease transmission of hepatitis B virus, hepatitis C virus, and HIV. Factor VIII is also produced by recombinant DNA techniques and is considered to be the replacement product of choice.[16] Recombinant-derived factor VIII is comparable to plasma-derived factor VIII in terms of characteristics and control of bleeding. Factor VIII:C concentrates are commonly used in severe hemophilia and for home therapy. Cryoprecipitate is the cold precipitable protein fraction derived from fresh frozen plasma thawed at 1° to 6° C. It was once the mainstay of hemophilia A therapy and may be used when noninfectious factor VIII concentrates are not available.[10]

Before 1985, plasma-derived replacement therapies posed risk for transmission of hepatitis C virus, hepatitis B virus, and HIV. However, with the current methods of donor screening, antiviral techniques, and safety testing and with the availability of recombinant clotting factors, the risk of viral transmission is extremely low.

Therapy for a bleeding episode includes a number of considerations: the circumstances in which factor VIII is given, the dosage, the timing of maintenance, the duration of the dosage, the presence of antibodies, and the means of gauging effectiveness. As a general rule, 1 U/kg of factor VIII will increase the circulating

TABLE 114.2

Recommended Factor VIII Therapy for Specific Problems in Hemophilia

TYPE OF BLEEDING	INITIAL DOSAGE	DURATION	COMMENT
SKIN			
Abrasion	None	None	Treat with local pressure and topical thrombin
Laceration			
Superficial	Usually none; if necessary, treat as minor	None	Local pressure and anesthetic with epinephrine may benefit; watch 4 hours after suturing; reexamine in 24 hours
Deep	Minor bleeding (25 mg/kg)	Single-dose coverage	May need hospitalization for observation; repeated dose may be necessary for suture removal
NASAL EPISTAXIS			
Spontaneous	Usually none; may need to be treated as mild bleeding	None	Uncommon; consider platelet inhibition; treat in usual manner
Traumatic	Moderate bleeding (25 mg/kg)	Up to 5 to 7 days	Trauma-related bleeding can be significant
ORAL			
Mucosa or tongue bites	Usually none; treat as minor if persists	Single dose	Commonly seen
Traumatic (laceration) or dental extraction	Moderate (25 U/kg) to severe (50 U/kg)	Single dose; may need more	Saliva rich in fibrin lytic activity; oral ε-aminocaproic acid (Amicar) may be given as 5 g (100 mg/kg) during the first hour, then 1 g per hour for 8 hours or until bleeding is controlled to block fibrinolysis; check contraindications; hospitalize patients with severe bleeding
Soft tissue or muscle hematomas	Moderate (25 U/kg) to severe (50 U/kg)	2 to 5 days	May be complicated by local pressure on nerves or vessels (eg, iliopsoas, forearm, calf)
HEMARTHROSIS			
Early	Mild (25 mg/kg)	Single dose	Treat at earliest symptom (pain); knee, elbow, ankle more common
Late or unresponsive cases of early hemarthrosis	Mild to moderate (25 U/kg)	3 to 4 days	Arthrocentesis rarely necessary and only with 50% level coverage; immobilization is critical point of therapy
Hematuria	Mild (12.5 U/kg)	2 to 3 days	Urokinase, the fibrinolytic enzyme, is in urine; with persistent hematuria, an organic cause should be ruled out
Major or life-threatening bleeding	Major bleeding (50 U/kg)	7 to 10 days or 3 to 5 days after bleeding ceases	In head trauma, therapy should be given prophylactically; early computed tomography scan of head is recommended for all

TABLE 114.3

Dosage of Factor VIII (Antihemophilic Factor)

BLEEDING RISK	DESIRED FACTOR VIII LEVEL (%)	INITIAL DOSE (U/kg)
Mild	5 to 10	12.5
Moderate	20 to 30	25
Severe	50 or greater	50

factor VIII level by 2%. The dose of factor VIII needed is the desired percentage increase in factor VIII activity × 0.5 × the weight in kilograms. The typical percentage factor VIII activity goals are 25% to 40% for minor bleeding or trauma, greater than 50% for moderate bleeding, and 80% to 100% for serious, life-threatening bleeding or trauma. Tables 114.2 and 114.3 include guidelines for the recommended treatment in a variety of circumstances. The standard calculation dosage of factor VIII (antihemophilic factor) is as follows:

1. Patient's plasma volume (50 mL/kg × weight in kg) × (desired level of factor VIII [percent]) − (present level of factor VIII [percent]) = number of units for initial dose.
2. In emergency therapy, the present level of factor VIII is assumed to be zero.
3. One unit is the activity of the coagulation factor present in 1 mL of normal human plasma.
4. Because the half-life of factor VIII is 8 to 12 hours, the desired level is maintained by giving half the initial dose every 8 to 12 hours.
5. Cryoprecipitate is assumed to have 80 to 100 U of factor VIII:C per bag; factor VIII:C concentrates list the units per bottle on the label.

Most importantly, the emergency clinician should act and institute early therapy for patients who say that they are bleeding.

The response to therapy can be monitored by clinical improvement, a decreasing PTT, and, optimally, serial factor VIII:C activity levels. The lack of a response to factor VIII administration should raise the possibility of circulating antibodies. All hemophiliacs should be screened for the development of these antihemophilic factor antibodies when they are given in-hospital therapy or if their condition becomes refractory to home therapy. The 7% to 20% of patients in whom these IgG antibodies develop usually have a severe deficiency necessitating multiple factor VIII transfusions. The treatment may be complex, and hospitalization is necessary. A variety of therapies have been considered, but current

treatments of choice include bypassing agents and immune tolerance induction.[17] Recombinant factor VIIa used in hemophilia complicated by alloantibody inhibitors has been shown to stop bleeding in 93% of cases.[18] Serious or intractable bleeding may be improved in some nonhemophiliac patients with the use of recombinant factor VIIa. However, no improvement in survival has been proved, and the incidence of thromboembolism may be increased.[19] Until more data are available, the role of recombinant factor VIIa in settings outside of congenital coagulation disorders remains to be determined. Acquired IgG antihemophilic factor antibodies may exist in nonhemophiliac patients. They can occur in the postpartum period; as immunologic reactions to penicillin or phenytoin; and in association with systemic lupus erythematosus, rheumatoid arthritis, or inflammatory bowel disease. The diagnosis is made by the occurrence of an acquired hemophilia-like syndrome with positive antibody titers in the appropriate setting.

Desmopressin acetate has been shown to increase levels of factors VIII:C and VIII:Ag in patients with hemophilia A and in some with vWD. It is given intravenously at 0.3 μg/kg per dose. Benefits are primarily noted in patients with mild to moderate disease, and the effects of a single dose last for 4 to 6 hours.[20] Use of desmopressin in the ED is probably best reserved for patients who have been successfully treated with it in the past or in consultation with the patient's hematologist.

Prophylaxis. The anticipation of delayed bleeding in patients with hemophilia may necessitate admission and observation for a variety of trauma-related injuries. Candidates for prophylactic admission are patients with deep lacerations; those with soft tissue injuries in areas where the pressure from a developing hematoma could be destructive, such as in the eye, mouth, neck, back, and spinal column; and patients with a history of major trauma forces without injury. Head trauma is potentially life-threatening to hemophiliacs, and central nervous system bleeding is the major cause of death for patients in all age groups. Studies find a 3% to 13% risk of intracranial hemorrhage. In patients with severe disease who sustain head trauma, patients are significantly less likely to suffer delayed intracranial bleeding if given replacement therapy within 6 hours. Patients who sustain head trauma but who have normal computed tomography scans should have factor VIII therapy initiated to greater than 50% activity level. All hemophiliacs with head trauma should be considered for admission with early hematology consultation.

Gene therapy represents a potential development in the treatment of hemophilia. With the goal of increasing expression of functional factor VIII, the possibility exists for either a partial or complete cure of hemophilia through various gene therapy approaches. Early studies are encouraging, but significant challenges still prevent gene therapy from being an approved treatment at this time.[20] However, genetic testing and counseling are currently available.

Hemophilia B

The replacement schedule for factor IX is similar to that for hemophilia A, but a purified factor IX concentrate or recombinant factor IX preparation is used. The plasma prothrombin complex (factors II, VII, IX, and X) and fresh frozen plasma are also useful, but they pose a higher risk of viral transmission and venous or arterial thrombosis. The maintenance dosage schedule is increased to every 24 hours because of the longer half-life of factor IX. Clinical concerns and treatment strategies associated with hemophilia A also apply to hemophilia B.

Similar to hemophilia A, gene testing and counseling are available. Gene therapy in hemophilia B has advanced beyond hemophilia A due to a relative simplicity and smaller gene size. Multiple recent clinical trials using gene therapy to treat hemophilia B have been initiated.[21]

von Willebrand's Disease

In patients with severe vWD, replacement therapy with factor VIII in the form of intermediate purity factor VIII concentrate is the method of choice. The initial dose is 50 IU/kg followed by 20 to 40 IU/kg every 12 hours to keep vWF levels at 50% or to control bleeding.[22] A unique response to the transfusion of plasma components in patients with vWD is the stimulation of a progressive increase in VIII:C activity that lasts 12 to 40 hours. After the initial dose, fewer units are necessary, and longer dosage schedules may be followed by a clinical response and a combination of factor VIII:C activity and serial bleeding times. Cryoprecipitate is no longer recommended because of the risk of viral transmission.

Desmopressin is of benefit in patients with mild to moderately severe vWD. Because most patients fall within this category, it is a preferred treatment given the low cost and risk associated with this medication. Adjunctive antifibrinolytic agents, such as tranexamic acid, have also shown benefit in vWD.[22] In extreme circumstances without alternatives, fresh frozen plasma may be used. A factor VIII concentrate (Humate-P) has also demonstrated sufficient VIII/vWF to treat the disease.

Medication-Induced Bleeding

Excessive anticoagulation from warfarin occurs from a number of causes, including interactions between warfarin and other drugs or foods and accompanying diseases that interfere with the absorption or metabolism of warfarin. Management of excessive anticoagulation from warfarin depends on the degree of elevation of the INR and if bleeding accompanies the excessive anticoagulated state. If the INR is below 5.0 and not accompanied with bleeding, treatment consists of withholding of additional warfarin. If the INR is between 5.0 and 9.0 without bleeding, in addition to withholding of additional warfarin, 1.0 to 2.5 mg of oral vitamin K therapy is recommended. Patients presenting with an INR above 9.0 but not bleeding are treated with 5 mg of oral vitamin K. Patients presenting with an elevated INR and bleeding require 10 mg of vitamin K and the administration of fresh frozen plasma or prothrombin complex concentrates. Vitamin K can be administered orally, intravenously, or subcutaneously. Oral dosing is superior to other routes of administration, and subcutaneous dosing is the least desirable method of administration. In cases of excessive anticoagulation with warfarin that are accompanied by serious or life-threatening bleeding, vitamin K is often administered intravenously. Vitamin K given intravenously should be administered as an infusion during 20 to 30 minutes and not given as a bolus injection.

Bleeding from heparin therapy is less of an issue in the ED but still can be a problem (eg, patient coming from a dialysis center). In addition to discontinuation of the heparin, the administration of protamine sulfate can urgently reverse the effects of heparin. The full neutralizing effect of UFH is achieved with 1 mg of protamine for every 100 units of heparin. Protamine can also be used to reverse the effects of LMWH; however, it does not completely abolish the anticoagulant effects as it does with UFH. When it is used for bleeding caused by LMWH, the dose of protamine is 1 mg for every 1 mg of LMWH. Because rapid injection of protamine results in hypotension, the recommended rate of administration is no more than 50 mg during 10 minutes. Recombinant factor VIIa may be considered in resistant forms of bleeding from anticoagulation; however, it is not a substitute for vitamin K, protamine, or blood product transfusions.

Over the past several years, new target-specific oral anticoagulants (TSOACs) have been gaining popularity. The first to gain

U.S. Food and Drug Administration (FDA) approval, dabigatran, is a direct thrombin inhibitor. The other two approved medications, rivaroxaban and apixaban, are selective factor Xa inhibitors. Unlike warfarin and heparin, specific clinical guidelines pertaining to the TSOACs do not address reversal in the case of bleeding. This poses a challenge to the emergency clinician who is likely to encounter patients on these medications who are bleeding. For all three medications, the PT and activated PTT are insensitive in excluding clinically relevant drug concentrations. As discussed in the Diagnostic Testing section, thrombin time may be used for drug quantification of dabigatran, and anti-Xa activity may be used for drug quantification of rivaroxaban and apixaban.[23] Because of the short half-life of these agents, in mild to moderate bleeding, clinical support and observation while holding anticoagulation may be sufficient in most patients. In severe life-threatening bleeding, prothrombin complex concentrate is recommended to support reversal as no specific reversal agents are currently approved. In addition, dialysis may be considered in cases involving dabigatran, because approximately 57% of the drug is removed with 4 hours of dialysis. In the case of apixaban, activated charcoal has been shown to reduce absorption if given within 6 hours of ingestion.[24] Several TSOAC specific reversal agents are currently in development.

Disseminated Intravascular Coagulation

When planning therapy, the emergency clinician needs to remember that DIC is secondary to a serious underlying pathologic process. Once the diagnosis is confirmed, the initial treatment is focused on reversal of the triggering mechanism. Many episodes of DIC are self-limited, such as in a transfusion reaction, or compensated, such as in association with a tumor mass, and do not require intervention other than support.

Replacement therapy is usually instituted simultaneously with attempts to control the primary process. The goal is to avoid depletion of clotting factors. Treatment is partially based on which of the two major pathologic components of DIC dominates the clinical picture. If active bleeding is present, replacement therapy with platelets, fresh frozen plasma, and cryoprecipitate (I, V, VIII) is recommended. Selective replacement therapy can be based on the laboratory and clinical response. Retardation of bleeding, a decrease in fibrin degradation products, and a rise in platelet counts and fibrinogen levels are useful monitors. Normalization of clotting times occurs too late to be of value in monitoring.

Heparin has selective use in the treatment of DIC when fibrin deposition and thrombosis dominate the pathologic picture. Certain disease states are associated more with fibrin deposition, in which case heparin therapy should be considered. Examples include purpura fulminans, retained dead fetus before delivery, giant hemangioma, and acute promyelocytic leukemia. Heparin therapy is of little benefit in cases of meningococcemia, abruptio placentae, severe liver disease, and trauma. Low doses of heparin (300 to 500 units/hr) as a continuous infusion are currently recommended. LMWH may also be used instead of UFH. Continuous monitoring of the clinical response, heparin levels, and bleeding status is necessary.

Other therapeutic agents, such as antithrombin III and activated protein C, have been evaluated. However, none has demonstrated an improved outcome in DIC, and only recombinant activated protein C (drotrecogin alfa) has been associated with improved outcomes in septic shock, regardless of whether DIC was present.[25]

The goals of emergency care of patients with DIC include initial recognition, pursuit of the diagnosis, understanding of potential life-threatening complications, and only rarely initiation of therapy.

DISPOSITION

All patients with bleeding disorders of unknown cause or of a significant degree should be admitted to the hospital for further evaluation. The circumstances in which a patient with a known bleeding disorder may be discharged for home care are discussed in earlier sections on individual disease states. Transfer of these patients may be necessary, particularly if hematologic consultation is not readily available. The standard criteria of hemodynamic stability, appropriate monitoring, and full knowledge and understanding on the part of the family and accepting physician should be met before transfer. Because of the delayed bleeding pattern in hemophiliacs, long distance transports may be especially hazardous. Therefore, the importance of advance knowledge and preparation is emphasized. Outpatients are usually treated under the auspices of the hematologic consultant. Early notification and appropriate follow-up arrangements should be made with these specialists.

KEY CONCEPTS

- Although hemostatic disorders are confirmed by specific patterns of laboratory test results, a careful history and focused physical examination are often the key to the diagnosis of hematologic diseases.
- All patients with bleeding disorders of unknown cause or of a significant degree should be admitted to the hospital for further evaluation.
- The frequency of hemostatic disorders seen in the ED is unknown; however, they are likely to be more common than thought. Although classic diseases such as hemophilia and DIC are uncommon, the use of antiplatelet and anticoagulation agents is common in other disease states, such as cardiovascular diseases.
- Hemophilia patients are often highly informed about their disease. Patient input should be solicited and respected, and early consultation with the patient's hematologist is encouraged. Consider early treatment with replacement factor while diagnostic testing proceeds.
- Patients with active life-threatening bleeding who are thought to have a congenital bleeding disorder can be supported with fresh frozen plasma, 15 mL/kg, while diagnostic studies are being performed.
- Platelet dysfunction is often equated with low platelet counts. Even though critical thrombocytopenia increases the risk of bleeding, particularly with trauma and surgery, dysfunction can occur at normal counts. For example, aspirin therapy and renal disease can alter platelet function without reducing blood counts.
- All evaluations of suggested ITP should include a complete blood count, peripheral smear, antinuclear antibody test, and bone marrow examination.
- TTP should be suspected in the setting of thrombocytopenia and microangiopathic hemolytic anemia and early treatment with plasma exchange therapy should be initiated even in the absence of the classic pentad. Platelet replacement should be avoided.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 114: QUESTIONS & ANSWERS

114.1. Platelet counts below what level may be associated with severe spontaneous hemorrhage?
- **A.** 100,000 mm^3
- **B.** 50,000 mm^3
- **C.** 20,000 mm^3
- **D.** 10,000 mm^3
- **E.** 5000 mm^3

Answer: C. Remember that the count provides no information about the adequacy of platelet function.

114.2. An elevated partial thromboplastin time (PTT) may be caused by an abnormality or deficiency in which of the following?
- **A.** Calcium
- **B.** Factor VII
- **C.** Factor XIII
- **D.** Fibrinogen
- **E.** Platelets

Answer: D. The PTT tests the components of the intrinsic and common pathways—essentially all factors except VII and XIII. Fibrinogen function is reflected in both prothrombin time (PT) and PTT values. Calcium derangements do not typically cause aberrations in PT or PTT.

114.3. Which of the following statements regarding bleeding resulting from a platelet disorder is true?
- **A.** Males are affected more than females.
- **B.** Most platelet disorders are inherited.
- **C.** Preceding trauma does not usually cause the bleeding incident.
- **D.** Prothrombin time (PT) and partial thromboplastin time (PTT) may both be elevated.
- **E.** The bleeding often presents as hemarthrosis or muscle hematoma.

Answer: C. Platelet abnormalities are seen most commonly in females and are acquired, often because of drugs, infections, or triggered immunologic mechanisms. The bleeding is typically capillary and does not involve joints or deep muscle. Most of the bleeding is spontaneous.

114.4. A 48-year-old man presents with complaints of leg pain and swelling. Physical examination is remarkable for right lower extremity pallor, mild edema, and absent distal pulses. Laboratory examination is remarkable only for a platelet count of 21,000/mm^3. Which of the following statements is true?
- **A.** A history of a recent blood transfusion is likely.
- **B.** A history of intravenous cocaine use is likely.
- **C.** A recent viral illness is likely.
- **D.** Recent digoxin use is likely.
- **E.** Recent heparin use is likely.

Answer: E. Heparin-induced thrombocytopenia (HIT) is characterized by post heparin thrombocytopenia (onset 7 to 40 days) and arterial or venous thrombosis. Intravenous cocaine, digoxin use, sulfonamide use, phenytoin use, recent blood transfusion (PLAI antigen mediated—usually a precipitous drop in platelets 1 week post-transfusion) are all associated with thrombocytopenia but not thrombosis. Treatment of HIT is with direct thrombin (lepirudin) or factor Xa (fondaparinux) inhibitors.

114.5. A 4-year-old boy is brought to the emergency department (ED) by his parents, who report several days of easy bruising on his lower extremities with even minor trauma. He has no past medical history and takes no medications. Physical examination is remarkable for a well-appearing child with lower extremity ecchymoses with some petechiae. You do not suspect child abuse. Laboratory evaluation reveals the following: white blood count (WBC) count, 9300/mm^3; hemoglobin (Hb), 12.6 g/dL; hematocrit (Hct), 37%; and platelet count (Plt), 21,000/mm^3.
Which of the following statements regarding this scenario is true?
- **A.** A history of antecedent viral illness is likely.
- **B.** Coagulation factor levels are probably low.

C. Corticosteroids are indicated.
D. Platelet transfusion is indicated.
E. The adult form of this entity is of shorter duration.

Answer: A. Idiopathic thrombocytopenia purpura is an autoimmune process. In children, it typically follows an antecedent viral illness and remits spontaneously in 90% of cases. Steroids are not helpful. Platelet transfusion is rarely, if ever, required. Coagulation factors are not affected. The adult form is more insidious, chronic, and more likely to be associated with systemic disease, such as lupus or lymphoma.

CHAPTER 115

Selected Oncologic Emergencies

Michael T. McCurdy | David A. Wacker

INTRODUCTION

As improved therapy prolongs the lives of cancer patients, the prevalence of oncologic emergencies continues to increase. However, nonspecific clinical features misattributed to the underlying cancer complicate their diagnosis. In this chapter, we review febrile neutropenia, metastatic spinal cord compression (MSCC), malignant pericardial disease, hypercalcemia of malignancy, tumor lysis syndrome (TLS), leukostasis, and superior vena cava (SVC) syndrome.

FEBRILE NEUTROPENIA

Principles

Whether due to underlying malignancy or as a cytotoxic effect of chemotherapeutics, cancer patients regularly experience depleted levels of circulating neutrophils. Risk of infection rises when a patient's absolute neutrophil count (ANC) drops below 1000 cells/mm^3. However, the increase in risk is most marked in patients with ANC less than 500 cells/mm^3. Historically, ANC of 1000 to 1500 cells/mm^3 has been considered mild, 500 to 1000 cells/mm^3 moderate, and more than 500 cells/mm^3 severe. Current guidelines do not emphasize these gradations, and neutropenia is defined as an ANC less than 500 cells/mm^3 or an ANC expected to drop below this threshold within 48 hours.[1,2] Neutropenic patients remain particularly susceptible to infection, even from their own existing microbial flora. The ANC is calculated from a complete blood count (CBC) with differential count by the following formula:

$$\frac{([\%\,\text{granulocytes}]+[\%\,\text{bands}])\times[\text{total WBC count}]}{100}$$

Infection in a neutropenic patient carries significant mortality risk. For patients experiencing neutropenic fever, overall mortality approaches 20%; and when compared with controls not experiencing neutropenic fever, hazard ratios for overall mortality and mortality during the first chemotherapy course are 1.35 and 1.15 respectively.[3] Most commonly, neutropenic fever is caused by pneumonia, anorectal lesion, skin infection, pharyngitis, or urinary tract infection. However, because local inflammatory responses are dampened by the absence of granulocytes, the only sign of infection may be fever. Defined as a single temperature at or above 38.3°C or a sustained temperature of at least 38.0°C for at least 1 hour, fever is not a requisite for infection.[1,2] Any neutropenic patient with signs or symptoms of infection should be treated as having neutropenic fever, whether actually febrile or not. In fact, in a study of neutropenic patients with suspected infection, suppressed temperature on presentation (less than 36.5°C) portended higher mortality than fever or normothermia.[4]

Clinical Features

Due to underlying immunosuppression, neutropenic patients often do not manifest infectious signs or symptoms beyond fever, making a thorough history and physical examination crucial. The interview should include a standard infectious review of systems, probing for diarrhea, nausea or vomiting, headache, neck stiffness, rashes, dysuria, cough, dyspnea, and pain at any location, including the abdomen, chest, joints, throat, sinuses, and ears. Specific note should be made of indwelling venous catheters, because these increase the risk of bacteremia and skin infection. To evaluate for perianal infection, the perineal region should be examined and inquiry made about pain with defecation. Although there is no hard evidence, expert opinion suggests against digital rectal examination to avoid compromise of the barrier between blood and rectal flora.[1] Due to the chemosensitivity of the rapidly dividing epithelial cells of the mouth, mucositis is a common adverse effect of chemotherapy and provides a portal for oral flora into the bloodstream. This can be evaluated by examination and inquiry about oral pain.

Differential Diagnoses

Causes of fever in cancer patients are varied and include infection, venous thrombus or embolus, adverse effect of chemotherapy or other medication, and direct effect of tumor burden. A clear source of infection is identified in only about one-third of neutropenic fever cases. Nonetheless, because of the potentially life-threatening effects of an infection in this population, all febrile neutropenic patients warrant empirical antibiotics and a full evaluation for an infectious source.

Diagnostic Testing

Neutropenic patients with fever should have at least two sets of blood cultures drawn before administration of antibiotics. Both may be drawn peripherally in patients without preexisting central access. In patients with a preexisting central line, one of the two blood cultures should be obtained peripherally, whereas other cultures should be simultaneously drawn off each lumen of the central catheter. Bacterial growth in the catheter-drawn samples greater than 2 hours prior to the peripheral samples is suggestive of a catheter-associated infection. Patients with neutropenic fever should also have a CBC with differential count performed to assess severity of neutropenia, as well as urinalysis, urine culture, chemistries, and renal and hepatic function tests.[1] Additional cultures may be sent according to the clinical presentation (eg, sputum culture if productive cough, stool culture and testing for *Clostridium difficile* if diarrhea or abdominal pain).[1]

Initial imaging usually consists of chest x-ray, although at least one prospective observational study suggests that this will be low-yield in the absence of specific respiratory symptoms. If fever persists for 72 hours without identified source, empirical computed tomography (CT) scan of the chest and sinuses, and bronchoalveolar lavage may be considered to evaluate for occult fungal infection.[2] Directed CT scans may be performed sooner in the setting of appropriate clinical signs (eg, chest CT for a patient with coughing and bronchial breath sounds, but a clear chest x-ray, abdominal CT for a patient with unexplained abdominal tenderness).

Management

Febrile neutropenic patients should receive antibiotics prior to confirmation of an infectious source.[1,2] Recommendations for specific regimens are based on risk of clinical decompensation. According to the Infectious Disease Society of America (IDSA), high-risk features include an expected duration of neutropenia greater than 7 days, expected nadir ANC less than 100 cells/mm^3, hypotension, pneumonia, new-onset abdominal pain, neurologic changes, or existence of other significant medical comorbidities.[1] The European Conference on Infections in Leukemia (ECIL) also suggests that additional high-risk features include a current or prior infection with a resistant organism and treatment at a center with a high prevalence of resistant organisms.[5] Alternatively, the Multinational Association for Supportive Care in Cancer (MASCC) risk index identifies low-risk patients based on clinical features (Table 115.1). Patients scoring at least 21 points are considered low-risk, because nearly 90% of cases have uncomplicated resolution of their fever within 5 days.

High-risk patients should receive a parenteral, broad-spectrum antibiotic regimen. Local antibiograms should be considered when choosing specific agents, but guidelines recommend monotherapy using a broad-spectrum beta-lactam with antipseudomonal coverage, such as ceftazidime, cefepime, piperacillin-tazobactam, or a carbapenem.[1,2] Although a meta-analysis suggests an increased rate of all-cause mortality with cefepime use and a decreased rate with piperacillin-tazobactam, most studies comparing broad-spectrum beta-lactams suggest they offer similar rates of effectiveness and survival.[6-9] A fluoroquinolone or aminoglycoside may be added.[5] However, a meta-analysis of studies comparing beta-lactam monotherapy with combination beta-lactam/aminoglycoside therapy showed that patients receiving aminoglycoside had no survival benefit and were more likely to suffer adverse events, including nephrotoxicity and fungal superinfection.[10] We recommend antipseudomonal beta-lactam monotherapy for patients with neutropenia and fever. Further empirical antibiotics administered will depend on clinical presentation and consultation with oncology or infectious disease consultants.

Despite increasing rates of bacteremia with gram-positive organisms in cancer patients, randomized-controlled studies and meta-analyses have failed to demonstrate a survival benefit to immediate empirical gram-positive coverage, but rather suggest increased rates of adverse effects.[11] Empirical gram-positive therapy is not recommended except in cases of suspected cellulitis, catheter-associated infection, or pneumonia, or in the case of clinical instability.[1,2] Similarly, a different randomized-controlled trial failed to show a benefit in immediate, empirical antifungal therapy with voriconazole on the rate of invasive fungal infections.[12] Guidelines suggest against immediate antifungal therapy, unless there is specific concern for a fungal source, in which case, one meta-analysis suggests liposomal amphotericin B to be the most effective agent.[1,2,13]

Neutropenic patients with community-acquired pneumonia should be covered for atypical pathogens and possibly pneumocystis pneumonia (PCP).[2] For patients with gastrointestinal symptoms, one randomized controlled trial suggests improved 28-day survival with cefepime/metronidazole combination therapy when compared to piperacillin-tazobactam monotherapy.[14] Patients with a vesicular rash or other evidence of herpes infections should receive empirical acyclovir.[2]

Although some observational studies suggest worsening mortality associated with delays in antibiotic administration, this finding is not universal.[15-18] No specific timing of antibiotic administration is recommended in the official guidelines at present. Nonetheless, we recommend that high-risk patients receive antibiotic therapy as soon as possible after obtaining blood cultures.

Observational studies and a meta-analysis have demonstrated that low-risk patients may be treated with an enteral regimen, usually amoxicillin/clavulanate and ciprofloxacin, but moxifloxacin monotherapy has shown similar outcomes.[19-22] Alternatively, low-risk patients may be started empirically on a parenteral broad-spectrum therapy with transition to an enteral regimen after 24 to 48 hours if no complications arise.[23]

Disposition

Regardless of risk category, the majority of febrile neutropenic patients will be hospitalized for observation and initial treatment, ideally to a unit specialized for oncology patients. Hemodynamically unstable patients and those with a deteriorating course should be admitted to an intensive care unit (ICU). A small fraction of patients may be treated with enteral antibiotics in the outpatient setting. These patients should (1) meet low-risk criteria; (2) have no evidence of pneumonia, line infection, cellulitis, or organ failure; (3) have reliable daily follow-up with their oncologist; and (4) demonstrate clinical stability during observation in the emergency department (ED) for at least 4 hours.[20,21,24] Reliable follow-up must be ensured, and discharge should only be made following discussion with the patient's oncologist.

TABLE 115.1

Clinical Features and Corresponding Point Values for the Multinational Association of Supportive Care in Cancer (MASCC) Risk Index*

CLINICAL FEATURE	POINT VALUE
Age younger than 60 years old	2
Onset of fever while outpatient	3
Overall moderate symptom burden	3
Absence of dehydration	3
No prior fungal infections or solid tumor type	4
No history of COPD	4
Absence of hypotension	5
Asymptomatic or overall mild symptom burden	5

*A score of 21 or greater suggests low-risk of complication and likely resolution of fever within 5 days.
COPD, Chronic obstructive pulmonary disease.

KEY CONCEPTS

- Patients whose absolute neutrophil count is or is expected to soon be 500 cells/mm^3 or less are considered severely neutropenic. A single temperature of 38.3°C or sustained temperature of 38.0°C for at least 1 to 2 hours is considered fever.
- Any neutropenic patient with fever or with infectious signs or symptoms (even in the absence of fever) should be worked up for an infectious source, including drawing of blood cultures, and started on empirical antibiotics. Those with high-risk features (eg, prolonged or profound neutropenia, pneumonia, hypotension, abdominal pain, neurologic changes, MASCC score <21) should be started on an antipseudomonal beta-lactam (eg, cefepime, piperacillin-tazobactam, antipseudomonal carbapenem). Those with low-risk features may be appropriate for oral antibiotics. Empirical gram-positive bacterial, antifungal, and antiviral coverage is unnecessary unless the clinical situation dictates otherwise.
- Neutropenic patients with fever should generally be hospitalized, including all high-risk patients. Select low-risk patients may be managed as outpatients.

METASTATIC SPINAL CORD COMPRESSION

Principles

Malignancy-related compromise of the spinal cord most commonly occurs from an extradural neoplasm that has hematologically metastasized to the vertebral column. The lesion then typically expands locally from the marrow space through a vertebral vein foramen to invade the spinal canal. Although the resulting cord injury is termed *metastatic spinal cord compression (MSCC),* direct nerve compression by tumor is uncommon. Cord injury is more commonly caused by occlusion of the epidural venous plexus, leading to breakdown of the blood-cord barrier and vasogenic edema. If untreated, tumor expansion eventually leads to arterial obstruction, causing cord ischemia and infarct. Less commonly, direct compression of the cord over time may lead to demyelination and axonal injury.

The most common tumors causing MSCC are prostate, breast, and lung cancer, each accounting for about 15% to 20% of total cases. Renal cell cancer, non-Hodgkin lymphoma, and multiple myeloma each account for an additional 5% to 10% of all cases. Most cases of MSCC affect the thoracic spine (60%), with the lumbosacral and cervical spine each making up 25% and 15% of cases, respectively. Twenty to forty percent of patients with MSCC have multiple loci of spinal metastasis.

Clinical Features

Back pain, weakness, sensory loss, and autonomic function loss are the most frequent presenting symptoms of MSCC. Back pain occurs in more than 95% of patients with MSCC and is the most common initial symptom. Extremity weakness occurs in up to 75% and generally (but not always) precedes sensory loss, which is found in nearly 70% of patients presenting with MSCC. Present in almost 60% of patients with MSCC, autonomic nerve dysfunction, including loss of bowel or bladder function, is a late finding and rarely presents in isolation.

Differential Diagnoses

In addition to MSCC, patients with back pain with or without neurological symptoms should be considered for nonmalignant musculoskeletal etiologies (eg, muscle strain/sprain, pathological fracture, disc displacement, radicular stenosis, vertebral osteoarthritis) and paraspinal or vertebral infections (eg, paraspinal abscess, vertebral osteomyelitis, discitis). In patients with known malignancy, new back pain or neurological deficits (motor, sensory, or autonomic) may be up to 100% specific for MSCC, and this diagnosis should be presumed until proven otherwise. In patients without known cancer, however, new back pain is the heralding symptom of cancer in 20% of cases of MSCC, which commonly takes up to 2 months from original presentation to diagnose.

Diagnostic Testing

A thorough physical examination should be performed, including palpation of the entire spine, as well as testing of strength, sensation, deep tendon reflexes, and rectal tone. The diagnosis is confirmed by imaging, for which magnetic resonance imaging (MRI) has become the gold standard with sensitivity of 93% and specificity of 97% (Figure 115.1). Even in patients in whom MSCC has been established by another modality, MRI should still be performed when possible, because its added resolution changes treatment strategy in approximately 50% of cases. Because of the 20% to 40% incidence of multiple separate lesions occurring simultaneously, both the thoracic and lumbar spine should be imaged in any patient with MSCC. Although the incidence of a second lesion in the cervical spine is only around 1%, this segment should ideally be included when possible.

Fig. 115.1. Magnetic resonance imaging (MRI) short tau inversion recovery (STIR) image of T9 vertebral malignancy with pathological fracture causing spinal cord compression in a patient with multiple myeloma. Vertebral numbering as marked. (Photo courtesy of the Department of Radiology, University of Maryland School of Medicine and Lauren George MD and Georgia Thomas MD, Department of Internal Medicine, University of Maryland School of Medicine.)

If MRI is unavailable or contraindicated (eg, patients with incompatible pacemakers), CT scan of the spine is the next most informative study. If vertebral metastasis is seen on initial scans, presence of cord compression can be assessed by CT myelography, in which contrast is introduced into the subarachnoid space. Sensitivity of this technique rivals that of MRI, but MRI offers similar information noninvasively. Thus, CT myelography is reserved for those rare patients in whom MRI is contraindicated, but radiographic confirmation of cord compression as the cause of symptoms is required prior to intervention.

Plain radiographs and radionuclide scans may demonstrate vertebral metastasis, but sensitivity is limited. Furthermore, these techniques provide no information about the state of the spinal cord itself or the precise location of suspected compression.

Management

Treatment of MSCC in the ED entails administration of corticosteroids and initiation of definitive treatment with surgery, radiation therapy, or both. Corticosteroids provide the most immediately available therapy for cord compression; unlike surgery or radiation, their administration does not require significant logistical planning or knowledge of the exact anatomic location of tumor. Early steroid administration has been shown to improve ambulation rates at 3- and 6-month intervals, and patients receiving corticosteroids have improved long-term pain scores. Current guidelines suggest a 10 mg intravenous bolus of dexamethasone

followed by 16 mg orally per day in divided doses for any patient with neurological deficits believed secondary to MSCC.[25] Patients with severe deficiencies, such as paraplegia, may receive a higher dose of 100 mg intravenous dexamethasone, followed by 96 mg orally per day in divided doses.[25] However, steroids may be unnecessary in patients with vertebral metastases on imaging without neurological deficits.[25]

Corticosteroids temporize vasogenic cord edema, but cord damage will ensue without definitive correction with radiation therapy, surgery, or both. For patients who can tolerate surgery and have goals of care in line with surgery, a combination of surgical decompression followed by radiation therapy provides superior long-term rates of continence, ambulation, and survival than radiation therapy alone, and combined management is recommended in the most recent guidelines.[25,26] Surgical intervention is especially important in patients with spinal instability, cord compression by bony fragments, sphincter dysfunction, tumor histology known to be radio-insensitive, or compression in an area that has already received a maximum allowable radiation dose.

Thirty-day mortality rates for spinal cord decompression exceed 10% and overall complication rates exceed 50%. For patients unable to tolerate surgery or with incompatible goals of care, radiation alone may be pursued. If surgery is anticipated, though, it should precede any radiation treatment to prevent wound healing complications. Although external beam radiation remains the standard of care, newer techniques such as radiosurgery and stereotactic body radiation therapy provide more focused radiation treatment with less collateral damage to surrounding tissues.[27,28]

Although no direct evidence exists to guide the exact timing of treatment, most experts recommend definitive treatment within 24 hours whenever possible. Neurological status at initiation of treatment is the strongest indicator of outcome, and every effort should be made to expedite appropriate therapy to prevent further neurological decline.

Disposition

Following corticosteroid administration, patients with neurological deficits (ie, motor, sensory, or autonomic) should be hospitalized for definitive therapy. Asymptomatic patients with incidentally noted vertebral metastasis may be managed as outpatients, provided they have reliable follow-up.

KEY CONCEPTS

- Vertebral metastasis and spinal cord compression should be considered in any patient, particularly those with known cancer who have back pain, peripheral strength or sensory loss, or loss of bowel or bladder function.
- MRI of the spine is the preferred diagnostic test when evaluating spinal cord compression. CT of the spine with myelography may be performed if MRI is contraindicated or unavailable. Plain films are not sufficiently sensitive to rule out spinal cord compression.
- Intravenous corticosteroids (dexamethasone 10 mg bolus) should be given to any patient with neurological deficits from known or suspected MSCC. Consideration should be given to emergent surgical and radiotherapeutic intervention if compatible with goals of care.

MALIGNANT PERICARDIAL DISEASE

Principles

Pericardial manifestations of malignant disease, including pericarditis, pericardial neoplasm (usually metastatic), and pericardial effusion affect greater than 10% of cancer patients and cause about 25% of all effusive pericardial disease in the developed world.[29,30] Approximately two-thirds of malignancy-associated pericardial disease is clinically insignificant.[29] However, in the remaining one-third of cases, hemodynamic compromise, organ failure, or death occur.

Neoplastic disease is believed to cause pericardial effusion when lymphatic flow, which normally drains fluid from the pericardium, becomes obstructed or reversed by congestion in proximal malignant lymph nodes. An effusion develops both by obstruction of fluid outflow, and by metastatic spread to the pericardial lining, leading to a non-physiologic increase in pericardial fluid production. The most common culprits in this process are lung, breast, and hematologic tumors, as well as melanoma.[30] Effusions not directly caused by malignancy may also develop in cancer patients secondary to hypoalbuminemia or as an adverse effect of radiation or chemotherapy.[29]

Although the pericardial sac has the elastic potential for gradual expansion to more than 1 L, it is poorly distensible in short (ie, hours to days) timeframes, and rapid accumulation of even a few hundred milliliters of fluid may precipitate cardiac tamponade. This life-threatening condition occurs when intrapericardial pressures rise to match or surpass those of the atria and then ventricles, reducing or eliminating cardiac output and leading to shock.

Clinical Features

The classic presenting symptoms of pericardial disease are dyspnea and chest pain.[31] Weakness and fatigue are often associated, and large, slowly accumulating effusions may result in mass-effect on nearby structures, causing nausea, early satiety, cough, hiccups, hoarseness, or dysphagia.[31] Cardiac tamponade presents with shock, but other classic stigmata of the disease are unreliable. Pulsus paradoxus, defined as a 10 mm Hg systolic blood pressure gradient between inspiration and expiration in the respiratory cycle, is the most sensitive sign, present in about 80% of cases.[32] Kussmaul's sign (paradoxically increased jugular venous pressure [JVP] with inspiration) and Beck's triad (hypotension, elevated JVP, and muffled heart sounds) are seen in less than half of cases.[32] Hypotension may not even be a presenting symptom, particularly in patients with underlying hypertension.[32,33]

Differential Diagnosis

Because of its nonspecific presentation, the differential diagnosis for malignant pericardial effusion is broad. Considerations should include acute coronary syndrome, acute heart failure or valve failure, pulmonary embolism, pleural effusion, pneumonia, and pneumothorax.

Diagnostic Testing

Evaluation for a patient with suspected malignant pericardial effusion should include chest radiography, electrocardiogram (ECG), and transthoracic echo (TTE).[31,34] Electrocardiographic manifestations may include nonspecific ST or T changes, or low amplitude QRS voltage. Electrical alternans (alternating high and low QRS amplitudes) is only seen in 10% of cases. An enlarged cardiac silhouette on chest x-ray may suggest a large effusion. Echocardiography, which approaches 100% sensitivity and specificity for pericardial effusion, can also identify the cardiac chamber collapse characteristic of tamponade physiology.[31] Emergency clinicians, who are trained in basic bedside cardiac ultrasound, can reliably identify pericardial effusion and should perform the initial examination to hasten diagnosis (Figure 115.2).

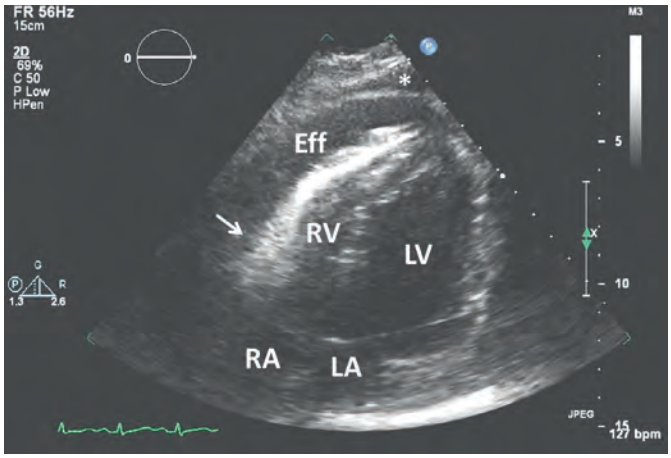

Fig. 115.2. Four-chamber apical view demonstrating pericardial effusion *(Eff)* with tamponade physiology in a patient with breast cancer. Buckling of the right ventricle wall is marked by a *white arrow.* Left ventricle *(LV),* left atrium *(LA),* right ventricle *(RV),* and right atrium *(RA)* are all as marked. Incidentally noted pleural effusion is marked with an asterisk *(*).* (Photo courtesy of the Division of Cardiology, Department of Internal Medicine, University of Maryland School of Medicine.)

Management

Malignant pericardial effusion generally serves as evidence of advanced cancer, and therapies should be tailored to match each patient's goals of care.[31,35] If aggressive therapy is desired, cardiac tamponade is a medical emergency and warrants immediate drainage, ideally under real-time ultrasonographic guidance (Figure 115.3). Ultrasound-guided drainage by the intercostal approach results in fewer complications and higher success rates than blind drainage by subxyphoid approach. If ultrasound is unavailable, a subxyphoid approach should be employed by inserting the needle at a 15° angle to horizontal between the xyphoid process and left costal margin. After clearing the rib cage, the needle should be leveled and advanced toward the left shoulder until return of fluid is achieved. Temporizing measures such as inotropes (epinephrine in hypotensive patients, dobutamine in normotensive patients) or intravenous fluids may be attempted, but, despite early successes in trials on anesthetized animal models, these measures have not demonstrated reproducible benefit in humans and should not be viewed as a substitute for timely drainage.

Effusion without tamponade can be managed non-emergently. Fluid sampling for cytology and tumor marker analysis can help confirm etiology of effusion.[31,36,37] This also allows intrapericardial

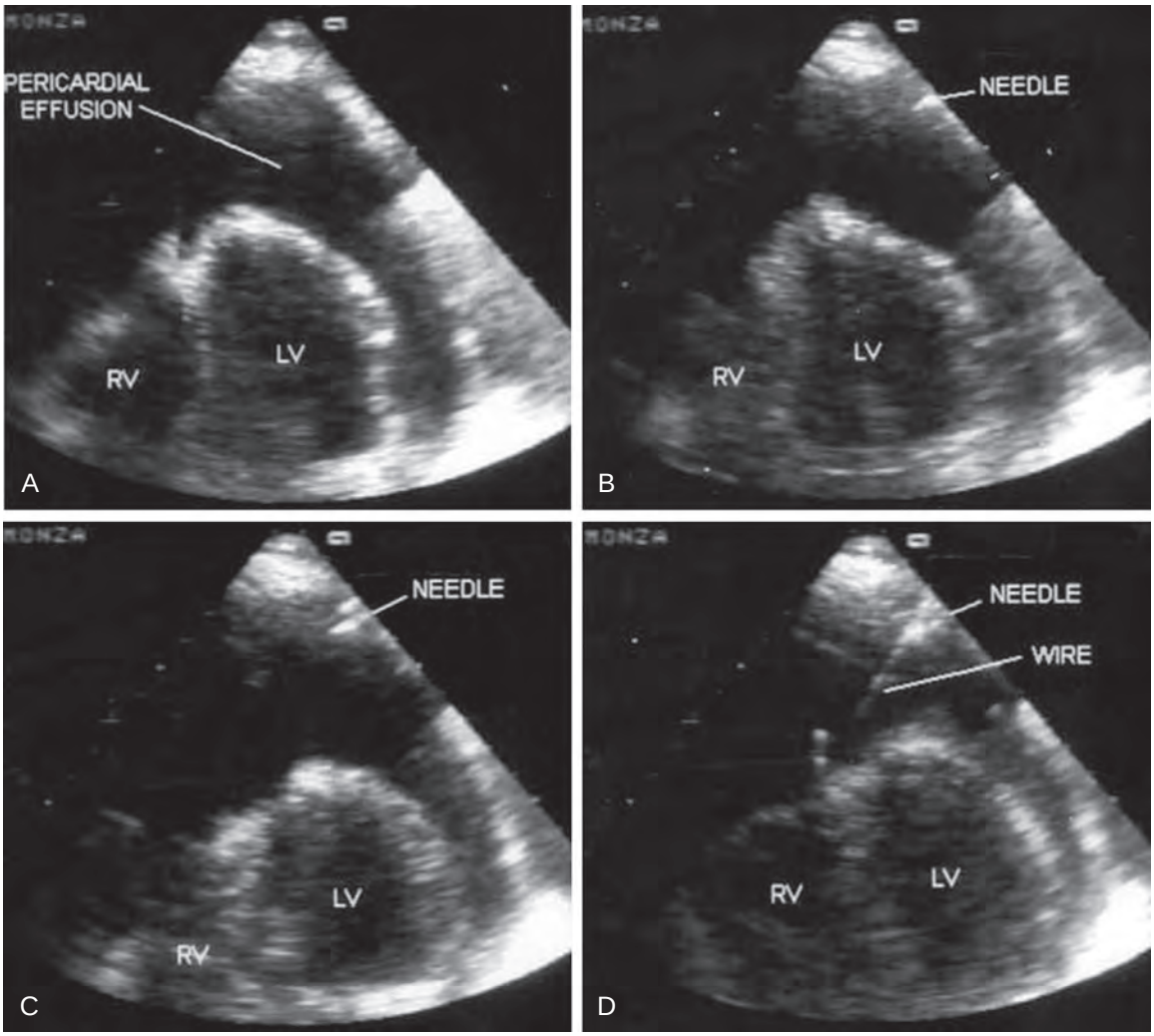

Fig. 115.3. Ultrasound-guided drainage of pericardial effusion. **A,** A four-chamber apical view reveals a large pericardial effusion. **B** and **C,** Under ultrasound guidance, a needle is advanced through an intercostal space and to the pericardial sack. **D,** Upon reaching the pericardial sack fluid can be drained directly, or a wire advanced for drain placement by Seldinger technique. *LV,* Left ventricle; *RV,* right ventricle. (Reproduced from Maggiolini S, et al: Echocardiography-guided pericardiocentesis with probe-mounted needle: report of 53 cases. J Am Soc Echocardiogr 14:821-824, 2001, with permission.)

chemotherapy or injection of sclerosing agents in a more controlled fashion.[29,31] Malignant effusions tend to recur, so a long-term evacuation strategy with drain or surgical window should be considered.

Disposition

Disposition depends on the hemodynamic effect of the pericardial effusion. Patients without tamponade or with a low likelihood of tamponade in the near future (ie, slow evolution of symptoms) can be managed non-emergently as an outpatient. Those with tamponade or rapid development of effusion should undergo pericardiocentesis and be hospitalized to monitor for re-accumulation of fluid.

KEY CONCEPTS

- Cardiac tamponade occurs when pericardial pressures inhibit cardiac filling and output. No clinical sign or symptom is entirely sensitive for cardiac tamponade, but echocardiogram findings of large pericardial effusion (anechoic stripe around the heart), and atrial or right ventricular collapse during diastole, combined with clinical findings of shock are highly suggestive.
- If compatible with goals of care, pericardial effusion causing tamponade should be emergently drained. Intravenous fluid or inotrope administration may be trialed as a temporizing measure, but these therapies are unreliable and should not delay definitive management.

HYPERCALCEMIA

Principles

Serum calcium regulation is achieved by parathyroid hormone (PTH) and calcitriol (the activated form of vitamin D), which both increase serum calcium level, and to a lesser extent by calcitonin, which decreases it (Figure 115.4).[38] Approximately 30% of cancer patients will experience dysregulation of calcium homeostasis, usually caused by one or more of the following: (1) synthesis of the PTH analog PTH-related protein (PTHrP), (2) overproduction of calcitriol, (3) bone osteolysis due to direct spread of tumor, or, (4) less commonly, ectopic production of PTH. In most cases, malignancy-associated hypercalcemia signifies advanced disease, with median survival of less than 2 months.[39]

Synthesis of PTHrP, classically called *humoral hypercalcemia*, causes about 80% of cases of malignancy-associated hypercalcemia, and is usually associated with squamous cancers, such as lung, esophagus, head and neck, cervical, ovarian, and endometrial carcinomas.[40] Calcitriol overproduction is usually seen in Hodgkin and non-Hodgkin lymphomas, in which secreted cytokines inappropriately activate the vitamin D-activating enzyme 1α-hydroxylase in macrophages. Bony metastasis can cause local cytokine-induced osteolysis and, if extensive, can lead to hypercalcemia.[35] Ectopic PTH production is a rare feature of malignancies, mainly limited to case reports.[41] Primary hyperparathyroidism occurring coincidentally with cancer is much more common.

Clinical Features

Presenting symptoms often include weakness, lethargy, confusion, abdominal pain, nausea, vomiting, constipation, polyuria, polydipsia, and kidney injury. Manifestations depend not only on the absolute value of serum calcium but also on patient's age and comorbidities and the rate of increase of serum calcium.[40] Acute hypercalcemia mainly presents with neurological abnormalities and acute kidney injury, as well as cardiac dysrhythmia if severe. Nephrolithiasis and nephrocalcinosis occur more commonly with chronic hypercalcemia, and they are infrequent manifestations of malignancy-associated hypercalcemia.[38] Physical examination findings are often nonspecific. Electrocardiogram findings may initially exhibit QT interval shortening, progressing to dysrhythmias and heart block as hypercalcemia worsens.[40]

Differential Diagnoses

Because of its nonspecific presentation, the differential diagnosis for malignancy-associated hypercalcemia is quite broad. Consideration should be given to infection with systemic manifestations, direct neurological injury (such as, cerebrovascular accident or central nervous system [CNS] infection), or other metabolic derangements (such as, hyper- or hyponatremia, acidemia, or TLS).

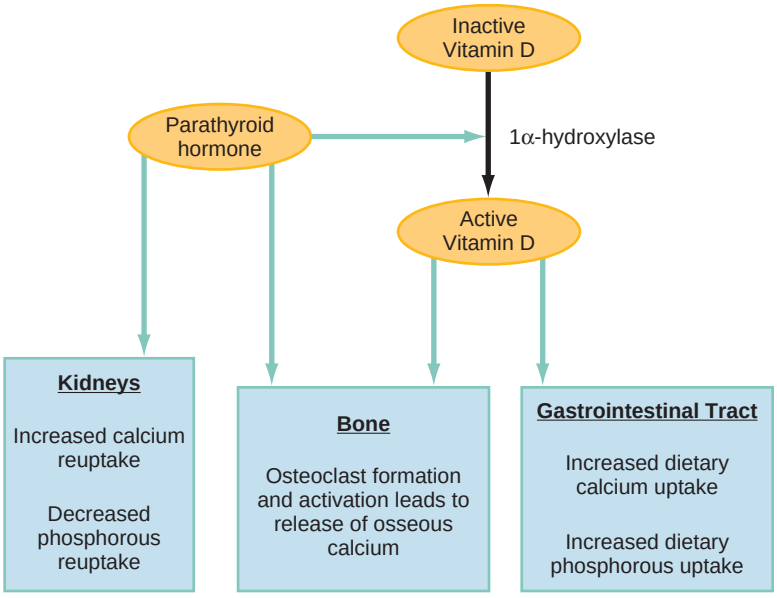

Fig. 115.4. Schematic representation of normal calcium homeostasis. Signaling molecules are represented by *circles,* targets of each signaling molecule and effects on the target are represented by *green arrows* and *boxes.* Activation of vitamin D by 1α-hydroxylase is represented by a *black arrow.*

Diagnostic Testing

Accurate measurement of the free serum calcium level is the most important step in the evaluation of malignancy-associated hypercalcemia. Measurements of total serum calcium, which are often included in basic metabolic panels, include a large fraction of physiologically inert calcium, which is bound to albumin and other serum proteins. Approximations of the bound fraction of serum calcium can be made using serum albumin measurements, but factors affecting the avidity of calcium for serum proteins, such as pH and the presence of medications that compete for binding sites, as well as abnormal concentrations of non-albumin proteins, may lead to inaccuracies in this calculation. It is therefore recommended that free or ionized levels of calcium be obtained for any patient with suspected malignancy-associated hypercalcemia.

Testing for additional metabolic abnormalities including serum levels of sodium, potassium, bicarbonate, chloride, magnesium, and phosphorous should be performed, as should assessment of kidney function with blood urea nitrogen and creatinine.[42] A brief review of reversible factors exacerbating hypercalcemia such as thiazide diuretic use or exogenous calcium supplementation may be helpful.[43] Further testing to determine the etiology of malignancy-associated hypercalcemia (PTH, PTHrP, and calcitriol levels, as well as skeletal survey for bone metastasis) may eventually be undertaken but is generally unnecessary in the ED, because initial therapy is not etiology-specific.

Management

Severe hypercalcemia, especially if rapidly developing, will lead to death if untreated.[40,42] First-line treatment for malignancy-associated hypercalcemia is intravenous fluid. Hypercalcemia impairs renal resorption of water and sodium, leading to hypovolemia. Hypovolemia further limits the kidneys' ability to eliminate calcium, creating a feedback loop that propagates hypercalcemia and hypovolemia. To break this loop, euvolemia must be restored, generally by administration of intravenous fluid at rates of at least 200 to 500 mL/hr.[40] We recommend that patients with acute oliguria or anuria be vigorously volume challenged, because poor urine output may simply be a product of hypovolemia. However if urine output does not improve, as may be the case with heart or kidney failure, resulting hypervolemia should be treated with a combination of diuresis, dialysis, and positive-pressure ventilation. Historically, loop diuretics have been used even for euvolemic patients in an attempt to force calciuresis; however, this has led to high complication rates and the calciuretic effect is minimal.[38] We therefore recommend use of loop diuretics only for volume management. Thiazide diuretics enhance distal tubule calcium resorption and should be avoided in hypercalcemic patients. Hypercalcemic patients with baseline oliguria or anuria may require dialysis.

Bisphosphonates are the primary pharmacologic treatment for hypercalcemia. Analogs of pyrophosphate, which is produced in bone catabolism, bisphosphonates inhibit bone turnover by reducing osteoclast function and directly stabilizing hydroxyapatite crystals. Typical regimens consist of single doses of either 90 mg of pamidronate given over 2 to 4 hours, or 4 mg of zoledronate given over 5 minutes.[38] Both should be given intravenously, because oral availability may be limited.[38] An average reduction of serum calcium concentration of 3 to 4 mg/dL can be expected with either regimen, but maximum effect may not be seen for 7 to 10 days. Bisphosphonates can cause an acute phase reaction in up to one-third of cases, consisting of fever, myalgia, arthralgia, and headache, usually within 36 hours. Such side effects can be managed with antipyretics and antihistamines. Bisphosphonates have also been associated with renal dysfunction and jaw osteonecrosis.

Although effective, bisphosphonates require days to lower serum calcium levels. Calcitonin has a quicker onset (12 to 24 hours) and may be useful for manifestations of hypercalcemia requiring immediate reduction of serum calcium level, such as dysrhythmias.[40] The effects of calcitonin are short-lived due to tachyphylaxis, so definitive therapy with bisphosphonates should be simultaneously given. Calcitonin should be given subcutaneously or intramuscularly 4 to 8 units/kg every 6 hours, which typically reduces the serum calcium level by 1 to 3 mg/dL.

Other pharmacological therapies include denosumab, a human monoclonal antibody inhibiting the RANK ligand that has been used in patients with bisphosphonate-resistant hypercalcemia, as well as plicamycin (mithramycin) and gallium nitrate, which have both fallen out of favor due to long administration times and unfavorable adverse effect profiles.[38,44-46] Hemodialysis can quickly reduce serum calcium levels and should be considered in patients who are dialysis-dependent, recalcitrant to other therapies, or have life-threatening manifestations of hypercalcemia. Regardless of other therapies, treatment of the underlying malignancy should be immediately pursued if this is compatible with goals of care, because this is the only way to reverse the underlying cause of hypercalcemia and generally does not increase serum calcium levels.[47]

Disposition

Patients with severe hypercalcemia (>14.0 mg/dL) or an acutely increasing calcium level should be admitted to a monitored bed. Patients with a stable serum calcium concentration less than 14 mg/dL, and close, reliable follow-up may be managed on an outpatient basis in consultation with the patient's oncologist and/or primary care doctor.

KEY CONCEPTS

- Calcium levels in hypercalcemic patients should be assessed by measuring ionized calcium concentration, rather than total calcium concentration.
- First-line management of hypercalcemia includes intravenous fluids, and loop diuretics only for volume management, as well as bisphosphate therapy (pamidronate 90 mg or zoledronate 4 mg, intravenously). Calcitonin is faster acting than bisphosphonates, but tachyphylaxis may develop; consider calcitonin in hypercalcemic patients with active cardiac or neurologic symptoms (eg, dysrhythmias, seizures).

TUMOR LYSIS SYNDROME

Principles

TLS occurs when destruction of malignant cells occurs with such volume and speed that the body's mechanisms for regulating the unwanted products of this destruction are overwhelmed. Such cell lysis releases intracellular contents, causing hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Acute kidney injury, caused by crystal deposits of uric acid or calcium-phosphate in the renal tubules or by crystal-independent mechanisms of damage by uric acid, often accompanies TLS, further compounding the patient's ability to regulate serum electrolyte levels and eliminate products of cellular destruction.[48] TLS is most likely to occur in patients with tumors that are high-burden, rapidly growing, and highly chemosensitive, such as Burkitt's lymphoma or acute lymphoblastic leukemia (ALL). TLS occurs less commonly in rapidly growing solid tumors, such as breast, testicular, and small cell lung cancers; overall the diversity of malignancies with potential for TLS is growing as we develop more effective and fast-acting chemotherapeutics.[49,50] Patient

factors predisposing to TLS include preexisting renal failure, hypovolemia, and hyperuricemia.

Clinical Features

Although spontaneous TLS is possible, patients undergoing cytotoxic therapy are particularly at risk for TLS. Symptoms result from metabolic derangements or kidney failure and include nausea, vomiting, lethargy, confusion, edema, seizure, myalgias, and tetany; dysrhythmias may result in cardiac arrest. Release of immunoactive proteins such as cytokines from lysed cells may cause sepsis-like symptoms.[51] Due to the immunocompromised state of these individuals, an infectious source should be presumed in patients with septic symptoms and empirical antibiotics should be administered. Electrocardiographic changes may include QT interval prolongation due to hypocalcemia and P-wave flattening, PR and QRS interval prolongation, and T-wave peaking due to hyperkalemia.

Differential Diagnoses

Differential diagnosis for patients with TLS varies with presenting symptoms. For those with nonspecific symptoms such as fatigue or myalgia, consideration should be given to other metabolic derangements such as malignancy-associated hypercalcemia, or systemic manifestations of an infectious source. Patients presenting with cardiac dysrhythmia should be considered for acute coronary syndrome, pulmonary embolism, other sources of metabolic derangements, and other causes of myocardial irritation. Seizure and other neurologic symptoms may suggest cerebrovascular accident, CNS infection or metastasis, or other metabolic abnormalities.

Diagnostic Testing

Evaluation begins with measurement of serum potassium, phosphate, ionized calcium, urea nitrogen, creatinine, uric acid, and lactate dehydrogenase (LDH). If the patient is presenting with sepsis-like symptoms, investigation for a source including cultures and appropriate imaging should be undertaken. Renal imaging (eg, ultrasound) to rule out obstructive pathology as well as urinalysis and measurement of fractional excretion of sodium (FE_{Na}) should be performed for patients presenting with acute kidney injury. Further evaluation may be indicated by specific presenting symptoms, such as head imaging for patients presenting with seizure, or abdominal imaging for patients with nausea and vomiting.

Management

Intravenous fluids to promote renal clearance of unwanted metabolites should be the initial therapy for TLS; volumes of 3 L/m^2/day are suggested, or as high as 5–6 L daily. Acutely oliguric or anuric patients should be similarly fluid challenged because these may be the result of hypovolemia, but plans should be made for diuresis or renal replacement therapy if urine output does not improve or hypervolemia ensues. Patients with oliguria or anuria at baseline may require initial management with renal replacement therapy. Although previously recommended, treatment guidelines no longer support alkalinization of the urine, because this may instigate worse metabolic derangements, including phosphate nephropathy and xanthine crystal nephropathy.[51]

Hydration provides the primary therapy for hyperphosphatemia, but limiting dietary phosphate intake and eliminating phosphate-containing supplements are indicated. Hypocalcemia is a direct result of free calcium precipitating with excess phosphate to form the insoluble, nephrotoxic compound calcium phosphate. The extent of calcium phosphate formation is directly related to the product of serum calcium and phosphate concentrations. Products greater than 55 suggest a worsened long-term risk of calcium phosphate deposition in the viscera, although short-term outcomes are not well studied. To minimize the risk of calcium phosphate nephropathy, asymptomatic patients should go without calcium repletion. Patients with cardiac (eg, dysrhythmia, heart blocks) or neurological (eg, seizure, coma) manifestations of hypocalcemia should receive intravenous calcium repletion.

Management of hyperkalemia is the same as that from any other etiology. Intravenous calcium given as a bolus can transiently (less than 1 hour) stabilize the myocardium of patients with existing or an imminent dysrhythmia (eg, QRS widening). Efforts can then be made to shift potassium intracellularly via administration of insulin, bicarbonate, and beta-agonists. Ultimately potassium must be removed from the body by the gastrointestinal tract with administration of potassium binders, by the kidneys with hydration and possibly loop diuretics, or by dialysis.

Uric acid is a metabolite in the degradation pathway of nucleic acids. Hyperuricemia from massive release of free nucleic acids can cause nephropathy both directly and by crystal formation in the renal tubules.[48] In addition to hydration, hyperuricemia can be managed pharmacologically by administration of allopurinol or rasburicase. Allopurinol, an analog of the uric acid precursor xanthine, competitively inhibits enzymatic conversion of xanthine to uric acid. Although this decreases uric acid production, it does not eliminate uric acid already present in the body, and it leads to buildup of xanthine, which itself has limited solubility and potential to cause nephropathy. Rasburicase, a recombinant form of the enzyme urate oxidase, eliminates uric acid directly by converting it into the more soluble metabolite allantoin. It is usually given as a single, intravenous dose. Significant reduction in uric acid levels within 1 day have been observed with weight-based doses of 0.05 mg/kg, and with fixed doses of 3 to 6 mg.[52,53] Those with glucose-6-phosphate dehydrogenase (G6PD) deficiency should not receive rasburicase, because hydrogen peroxide is a byproduct of its activity and this may trigger hemolytic crisis. Methemoglobinemia may also result from rasburicase administration.[54]

Disposition

The Cairo-Bishop definition of TLS, a systematic classification of lab abnormalities and clinical manifestations of TLS, divides patients with only laboratory manifestations of TLS (laboratory TLS, or LTLS) from those with clinical manifestations of TLS (clinical TLS, or CTLS), such as kidney injury, dysrhythmia, or seizure. Patients with clinical TLS consisting of dysrhythmia or seizure should be admitted to an ICU; those with kidney injury may be admitted to a standard telemetry bed, but ICU care should be considered as mortality in patients with kidney injury and TLS has been observed as high as 50%.[55] Patients with laboratory TLS only may be admitted to a monitored bed for observation and treatment.

KEY CONCEPTS

- TLS is manifested by the combination of hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia, often accompanied by acute renal failure.
- Patients with TLS should have their potassium, phosphate, calcium, and uric acid levels, as well as renal indices monitored closely. Intravenous fluids should be administered, as well as therapies to reverse hyperkalemia. Hyperuricemia may be prevented with allopurinol or treated with rasburicase. Calcium should only be repleted in patients with cardiac or neurologic manifestations of hypocalcemia.

LEUKOSTASIS

Principles

Leukostasis arises when the white blood cell (WBC) count is sufficiently high to cause vascular congestion, leading to organ dysfunction, typically in the lungs or CNS.[56] No single threshold exists for leukostasis to occur, and different types of leukemia cells cause leukostasis at widely variable cell counts. Patients with chronic lymphocytic leukemia (CLL) may tolerate WBC counts greater than 500,000 cells/μL, whereas patients with acute myeloid leukemia (AML) may develop leukostasis with WBC count less than 100,000 cells/μL.[56]

Two mechanisms are believed to drive leukostasis. First, blast cells are larger and less deformable relative to normal WBCs. As the number of blast cells in the blood increases, blood viscosity increases.[56] Second, because certain cell types are more prone to causing leukostasis than others with similar size and physical characteristics, intrinsic features of leukemic cells, such as cytokine-induced activation of endothelial adhesion mechanisms, may also contribute.[56]

Clinical Features

Pulmonary leukostasis presents as dyspnea, tachypnea, and hypoxemia.[56] Auscultation of pulmonary leukostasis may mimic lung infection with crackles or rhonchi, and bilateral opacities are often seen on imaging.[56] CNS leukostasis may present with confusion, audio or visual abnormalities, headache, ataxia, or coma, and intracranial hemorrhage may be seen on head imaging.[56] Other manifestations may include retinal hemorrhage, myocardial infarction, acute limb ischemia, priapism, renal vein thrombosis, and renal infarction.

Differential Diagnoses

Diagnosis of leukostasis is challenging, because symptoms of leukostasis are similar to those of other problems common to leukemia patients. Pulmonary leukostasis presents with similar history, physical examination findings, and imaging as pneumonia or pulmonary edema.

Patients with CNS leukostasis may present with nonspecific alteration of mental status, similar to that seen in metabolic derangement, medication side-effect, or systemic manifestation of infection. Intracranial hemorrhage seen on head imaging may be related to leukostasis itself, or may result from thrombocytopenia or disseminated intravascular coagulopathy (DIC), both of which often accompany hyperleukocytosis.

Diagnostic Testing

The gold standard diagnostic test for leukostasis is the presence of leukocyte-clogged blood vessels on tissue pathology.[56] Because this is rarely available, the diagnosis must often be inferred and empirically treated based on knowledge of leukocyte count, cancer type, and clinical picture. A CBC with peripheral smear should be sent from the ED. Further evaluation is indicated to determine cancer type (if not known), including cytology and immunostaining, although this is rarely feasible from the ED. Symptom-specific imaging should be performed, such as chest plain films or CT for respiratory problems, and head CT or MRI for neurological symptoms. Normal imaging findings does not exclude leukostasis, however. If sent, blood gases should be processed immediately, because metabolically-active leukocytes will continue to consume oxygen in the phlebotomized sample, resulting in falsely low oxygen levels.[56]

Management

ED management of leukostasis centers on reduction of blood viscosity. Intravenous fluids should be administered to dilute the blood as much as possible. Although patients with hyperleukocytosis are often anemic, transfusion of red blood cells should be avoided in asymptomatic patients, because erythrocytes exacerbate blood viscosity. Platelets and plasma may be given as needed because these components make little or no contribution to blood viscosity.[57]

The definitive treatment for hyperleukocytosis is reduction of leukocyte count, either by physically removing excess cells using leukapheresis, or by destroying excess cells pharmacologically. Leukapheresis involves continuous removal of fractions of the patient's blood, selective extraction of leukocytes from the fractions, and return of the remaining product to the patient. Leukapheresis can reduce leukocyte count by 20% to 50% in only a few hours, but insertion of a central large bore catheter is necessary, and leukapheresis requires specialized equipment not available at all institutions.[56] Studies of outcomes with and without leukapheresis are small and nonrandomized. Although some symptomatic or short-term survival benefits may exist, no benefits to long-term survival have been demonstrated.[56,58-60] Hydroxyurea, an inhibitor of deoxyribonucleotide synthesis, can pharmacologically reduce leukocyte burden by similar margins over 24 to 48 hours. Chemotherapy induction, which should only be initiated in consult with an oncologist, can also quickly reduce leukocyte count, but the patient should be monitored for signs of TLS. Due to the difficulty of clinically distinguishing leukostasis from other serious pathologies, treatments for other diagnoses may be simultaneously initiated. Such concomitant therapy (eg, antibiotics) is particularly important for suspected pneumonia, because patients with hyperleukocytosis may be functionally neutropenic.

Disposition

Patents with leukostasis require hospitalization for monitoring, hydration, and leukocyte-reducing therapy. Asymptomatic patients with leukocytosis also warrant hospitalization if their blast count is greater than 20,000 cells/μL, have a tumor type of AML, or have a new leukemia of unknown type. Patients with asymptomatic hyperleukocytosis who do not meet these criteria may be discharged with close, reliable follow-up, but this decision should be made in conjunction with the patient's oncologist.

KEY CONCEPTS

- Leukostasis arises due to congestion of blood vessels by excessive numbers of leukocytes. This most often occurs in the lungs and CNS, and the resulting clinical picture may be difficult to differentiate from other diseases which afflict cancer patients (eg, pneumonia, pulmonary embolism, CNS hemorrhage).
- Intravenous fluids should be administered in the ED to reduce blood viscosity, and red blood cell transfusions should generally be avoided. Therapies to lower the WBC count should be performed in consultation with an oncologist, and may include leukapheresis, administration of hydroxyurea, or initiation of chemotherapy.

SUPERIOR VENA CAVA SYNDROME

Principles

The superior vena cava (SVC) spans the final stretch of venous return from the upper body, spanning from the juncture of the

brachiocephalic veins to the heart. The SVC is thin-walled, and blood pressures in the SVC are relatively low (≈2 to 8 mm Hg), making it particularly susceptible to external compression. When SVC flow is compromised, its internal pressure can reach 20 to 40 mm Hg, potentially resulting in symptoms or cardiac decompensation. Such clinical deterioration constitutes SVC syndrome.

Causing greater than 60% of cases, malignancy remains the most common cause of SVC syndrome. Lung cancer and lymphoma cause over 90% of cases of malignancy-induced SVC syndrome. SVC syndrome due to an intraluminal mass, such as thrombosis, is increasing in prevalence. Cancer patients are at high risk for thrombosis due to their hypercoagulable state and indwelling venous catheters in the SVC.[61-63]

Clinical Features

Patients with SVC syndrome most commonly present with upper extremity, chest, or face edema or erythema, but dyspnea, dysphagia, chest pain, or cough may also be present. Physical examination findings often reflect elevated venous return pressures, including jugular venous distention (JVD) and edema, flushing, or cyanosis of the face, arms, and upper trunk. Distention of the SVC and compression of other nearby structures may cause vocal cord paralysis, blurred vision, and Horner's syndrome. Pleural effusion may be apparent on chest films or bedside sonography. Overall, the type and severity of symptoms greatly depend on the acuity of SVC compression; patients with a slowly developing obstruction develop collaterals, which enable asymptomatic high-grade compression.

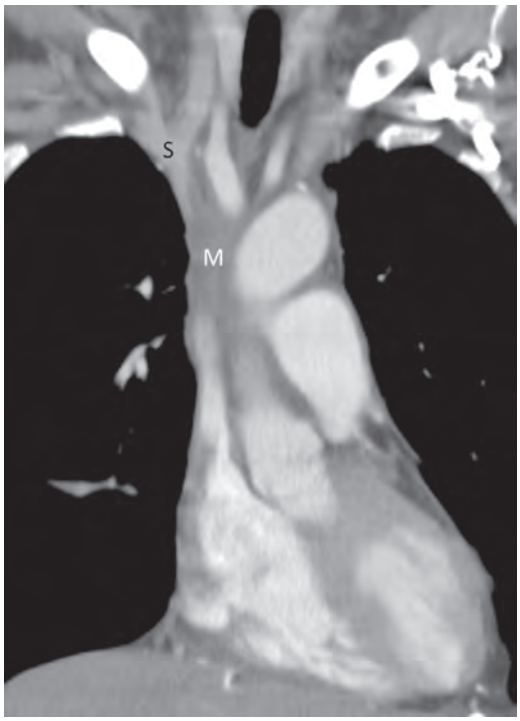

Fig. 115.5. Computed tomography (CT) scan of the chest with intravenous contrast demonstrating superior vena cava (SVC) compromise due to external mass in a patient with primary lung malignancy. *S,* SVC; *M,* intrathoracic mass. (Photo courtesy of the Department of Radiology, University of Maryland School of Medicine.)

Differential Diagnoses

Edema and flushing isolated to the upper body is highly suspicious for SVC syndrome, particularly in a patient with known lung cancer or lymphoma. Other considerations include cellulitis or deep tissue infection (eg, Ludwig's angina), thoracic inlet syndrome, or obstruction of other deep veins (eg, occlusive deep venous thrombosis in an internal jugular vein or subclavian vein). Other symptoms such as JVD, dyspnea, or cough are less specific and may suggest congestive heart failure, pneumonia, pericardial tamponade, or pulmonary embolism.

Diagnostic Testing

Thoracic imaging, and contrast-enhanced CT in particular, is the most important and commonly employed diagnostic modality for SVC syndrome (Figure 115.5), but MRI is a viable alternative. In confirmed cases of SVC syndrome, a tissue diagnosis of the offending mass should be made prior to initiation of treatment.[64] This may be obtainable by sputum cytology, or by invasive means, such as bronchoscopy, lymph node biopsy, mediastinoscopy, or thoracotomy. Moderate sedation or general anesthesia may be used safely to enable these procedures, however, in cases involving tracheal compromise, an airway should be emergently and carefully (eg, consideration of awake fiberoptic intubation) established prior to anesthesia induction.[65]

Management

In the ED, management of SVC syndrome is largely conservative. Elevating the head of bed to promote gravitational drainage of the upper body, and administration of supplemental oxygen, when appropriate, may provide significant symptomatic relief. For patients with SVC syndrome due to obstructing thrombus, anticoagulation with or without thrombolytics should be initiated.[63] Diuretics or steroids have historically been administered, but they have no proven benefit and may simply provoke complications.

Although the symptoms of SVC syndrome are unpleasant, risk to life occurs only with the rare and extreme complications of cerebral edema or hemodynamic compromise. Definitive treatment of malignant SVC syndrome can often be safely delayed until biopsy specimens are obtained because of the rare need for emergent therapy and the increasing ability to tailor anti-cancer therapy based on exact tissue diagnosis. Once a histological diagnosis is made, chemotherapy, radiation, and surgery, if indicated, may be tailored to the diagnosis.

Endovascular stenting of SVC may be employed in cases of treatment failure, expected treatment failure (eg, tumor poorly sensitive to radiation or chemotherapy), or hemodynamic compromise or cerebral edema in which immediate patency of the SVC is needed.[66] Open surgical bypass or replacement of the SVC can be performed but is reserved for the most extreme cases, because less invasive measures are often successful.[67]

Disposition

Although SVC syndrome is seldom life threatening, symptomatic relief first requires diagnosis and treatment tailored to the underlying etiology, and hospitalization often expedites this evaluation. Patients with hemodynamic compromise, cerebral edema, or tracheal compromise should be admitted to an ICU following initial stabilization (eg, intubation for tracheal compromise).

KEY CONCEPTS

- SVC syndrome occurs due to either external (eg, tumor) or internal (eg, thrombus) obstruction of the SVC.
- ED management of SVC syndrome is largely supportive. The head of the bed should be elevated and supplemental oxygen provided if needed. If the cause of SVC syndrome is determined to be thrombus, anticoagulation may be initiated if not contraindicated.
- SVC syndrome is life threatening in the rare case of cerebral edema, hemodynamic collapse, or tracheal compromise. Definitive anti-cancer treatment should be postponed to allow for tissue diagnosis of the underlying mass if not already known.

CONCLUSION

Oncologic emergencies pose unique challenges because their presentations are often nonspecific and may be mistaken for natural progression of underlying malignancy. Vigilance and clinical suspicion must be maintained whenever treating cancer patients in the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 115: QUESTIONS & ANSWERS

115.1. Which of the following statements regarding infections in cancer patients with febrile neutropenia is *true?*

A. Blood cultures should be obtained from an indwelling catheter if present.
B. Head computed tomography (CT) is always indicated.
C. Lumbar puncture (LP) should be routinely undertaken.
D. Most isolated pathogens are gram negative.
E. Sinus imagery should be routinely undertaken.

Answer: A. In patients with a preexisting central line, one of the blood cultures should be obtained peripherally while other cultures should be simultaneously drawn off each lumen of the central catheter. Bacterial growth in the catheter-drawn samples more than 2 hours prior to the peripheral samples is suggestive of a catheter-associated infection. Head CT is not routinely indicated. It may be performed if the patient demonstrates focal neurological deficits, alteration in mental status, or a lumbar puncture is planned. LP and CT scan of the sinuses are not routinely done unless signs or symptoms suggest these are involved.

115.2. A 33-year-old woman with breast cancer presents with fever and neutropenia. She is status post mastectomy and undergoing chemotherapy. Vital signs are remarkable for temperature, 38.8° C; heart rate, 110 beats/min; and blood pressure, 89/50 mm Hg. Examination is otherwise normal. She has no indwelling catheters. Which of the following is the most appropriate empirical antibiotic regimen?

A. Antibiotics should be withheld pending radiographs and cultures
B. Cefepime as monotherapy
C. Ceftazidime and gentamicin
D. Meropenem and vancomycin
E. Ticarcillin and amikacin

Answer: B. Monotherapy with imipenem, meropenem, ceftazidime, or cefepime is as effective as traditional dual therapy with an antipseudomonal penicillin and aminoglycoside. However, vancomycin should be included as well if any of the following exist:

- Hypotension or evidence of cardiovascular impairment
- Clinically suspected catheter infection
- Positive blood cultures for gram-positive organisms
- Known colonization with methicillin-resistant *Staphylococcus aureus* or cephalosporin-resistant *Pneumococcus*

115.3. A 57-year-old man presents with exertional dyspnea, facial swelling, cough, and bilateral hand swelling. His past medical history is unremarkable except for many years of heavy smoking. Physical examination is remarkable for moderate conjunctival suffusion, jugular venous distention (JVD), upper extremity venous prominence, and facial plethora. Which of the following statements regarding this patient's likely condition is *true?*

A. Corticosteroids are indicted urgently.
B. Intravenous furosemide should be initiated emergently.
C. Treatment depends upon the tissue diagnosis.
D. Urgent radiotherapy is indicated.
E. Venography is the initial test of choice.

Answer: C. Superior vena cava (SVC) syndrome is most commonly caused by lung cancer, although non-oncologic etiologies (thrombosis from indwelling catheter) are increasing. Unless the patient is in acute respiratory distress, emergent interventions are not indicated and intervention should follow tissue diagnosis. The main "rule outs" are congestive heart failure and pericardial tamponade. Diuretics may provide symptomatic relief but are not emergently indicated. Corticosteroids are not useful unless there is airway compromise.

115.4. Which of the following is *not* a risk factor for acute tumor lysis syndrome (TLS)?

A. High-burden, rapidly growing and highly chemosensitive leukemias.
B. Hypovolemia
C. Old age
D. Preexisting renal dysfunction
E. Rapidly growing solid tumors

Answer: C. TLS is most likely to occur in patients with tumors that are high-burden, rapidly growing, and highly chemosensitive, such as Burkitt's lymphoma or acute lymphoblastic leukemia (ALL). TLS occurs less commonly in rapidly growing solid tumors, such as breast, testicular, and small cell lung cancers; overall the diversity of malignancies with potential for TLS is growing as we develop more effective and fast-acting chemotherapeutics. Patient factors predisposing to TLS include preexisting renal failure, hypovolemia, and hyperuricemia. Old age is not a known risk factor for TLS.

115.5. A 65-year-old male with a history of a large head and neck tumor presents with symptoms of fatigue, weakness, confusion, depression and malaise, nausea, vomiting, constipation, polyuria, and palpitations. His electrocardiogram (ECG) demonstrates a shortened QT interval. Which of the following electrolyte abnormalities is likely to underlie his presentation?

A. Hypercalcemia
B. Hyperkalemia
C. Hyperuricemia
D. Hypocalcemia
E. Hypokalemia

Answer: A. Approximately 30% of cancer patients will experience dysregulation of calcium homeostasis. malignancy-associated hypercalcemia (MAH) signifies advanced disease, with median survival of less than 2 months. Synthesis of PTHrP, classically called *humoral hypercalcemia,* causes about 80% of cases of MAH, and is usually associated with squamous cancers, such as lung, esophagus, head and neck, cervical, ovarian, and endometrial carcinomas. Presenting symptoms often include weakness, lethargy, confusion, abdominal pain, nausea, vomiting, constipation, polyuria, polydipsia, and kidney injury. Electrocardiogram findings may initially exhibit QT interval shortening, progressing to dysrhythmias and heart block as hypercalcemia worsens.

CHAPTER 116

Acid-Base Disorders

Reuben J. Strayer

PRINCIPLES

The treatment of many acid-base derangements requires identification and treatment of the underlying cause. Emergency clinicians should recognize when an acid-base disorder is present and use a systematic approach that incorporates an understanding of the essential elements of acid-base physiology, the most important causes of acid-base derangements, and key steps in their management. Many basic cellular processes are sensitive to small changes in serum pH; the kidneys, lungs, and physiologic buffers determine serum pH, which is normally between 7.36 and 7.44. Serum pH is determined by the relative concentrations of bicarbonate (HCO_3) and carbon dioxide ($Paco_2$) = [1.5 × serum HCO_3^-] + [8 ± 2]; when two of these variables are known, the third may be calculated. Most blood gas analyzers measure pH and $Paco_2$ and report a calculated [HCO_3^-]. Most laboratories, when they report a serum bicarbonate concentration, are reporting a measured total carbon dioxide concentration, which is the sum of the serum bicarbonate and dissolved carbon dioxide. The dissolved carbon dioxide usually contributes negligibly to total carbon dioxide concentration, but can become significant in patients with hypercapnia.

An acidosis is a process that lowers HCO_3^- or raises $Paco_2$, creating an acidemia when the serum pH is below 7.36. Conversely, an alkalosis represents a process that raises HCO_3^- and/or lowers $Paco_2$, creating an alkalemia when the serum pH is above 7.44. The terms *acidemia* and *acidosis* are not interchangeable—acidosis or alkalosis describes a process that pushes serum pH down or up respectively; acidemia and alkalemia are descriptors of the serum pH. A patient who is acidemic has at least one acidosis but may have two or more acidoses and one or more alkaloses. Patients with a normal serum pH may have acidoses and alkaloses whose net effect is serum neutrality.

Bicarbonate concentration is predominantly regulated by the kidneys; $Paco_2$ is primarily regulated by lung ventilation. Diseases that affect kidney function may produce a metabolic acidosis or alkalosis, for which the lungs will try to compensate by decreasing or increasing $Paco_2$, respectively. Likewise, pulmonary diseases can cause a respiratory acidosis or alkalosis, for which the kidneys will try to compensate by raising or lowering serum HCO_3^-, respectively. Severe acidemia or alkalemia (<6.80 or >7.80) is considered unsustainable and may cause cardiac hypocontractility and irritability, seizures, cerebral edema, and metabolic disturbances such as hyperkalemia and catecholamine resistance.[1] In these cases, empirical therapy may be directed at normalization of serum pH while simultaneously searching for the underlying cause.

A reduced serum bicarbonate concentration defines a metabolic acidosis, which may be the primary disorder or a compensation for a primary respiratory alkalosis. An elevated serum bicarbonate concentration defines a metabolic alkalosis, which may be the primary disorder or a compensation for a primary respiratory acidosis. Likewise, a reduced $Paco_2$ represents a respiratory alkalosis, and an elevated $Paco_2$ represents a respiratory acidosis. When only a primary disturbance and its corresponding compensation are present, it is described as a simple acid-base disorder. A mixed acid-base disorder exists when more than one primary disturbance occurs simultaneously.

Alterations in serum pH are initially resisted by intracellular and extracellular physiologic buffers, followed by specific responses from the lungs and kidneys. Peripheral and central chemoreceptors adjust pulmonary minute ventilation in response to changes in serum pH. In a primary metabolic acidosis, an increase in minute ventilation lowers $Paco_2$ and pushes the serum pH closer to normal. Likewise, a primary metabolic alkalosis leads to a reduction in minute ventilation to elevate $Paco_2$.

The kidneys' response to alterations in serum pH occurs over hours to days. A sustained acidemia promotes renal excretion of H^+ and retention of HCO_3^-, whereas alkalemia causes renal HCO_3^- excretion and H^+ retention. The kidney transports hydrogen ions in exchange for potassium, whose serum concentration must also be maintained within tight parameters. This may become clinically important when, for example, correction of alkalemia is attempted; retention of H^+ cannot occur unless potassium stores are sufficient to allow urinary K^+ excretion. Potassium supplementation may therefore be necessary to alkalinize the urine (eg, in heterocyclic antidepressant toxicity).

Often, acid-base disturbances are first identified when the results of laboratory tests ordered to evaluate the patient's symptoms demonstrate alterations in the bicarbonate level, pH, or $Paco_2$. The possibility of an acid-base disorder is suggested by clinical events such as toxic ingestions, severe vomiting, or diarrhea, as well as in patients with diseases primarily affecting the lungs and kidneys. All critically ill patients and all patients being mechanically ventilated should have an assessment of their acid-base status. When an acid-base disturbance is identified or suspected, elucidation of its underlying cause(s) is central to appropriate management. When the cause of an acid-base disturbance is not evident, the emergency evaluation begins with a full history and physical examination and proceeds with targeted laboratory studies.

Simple acid-base disorders are categorized by the serum pH, $Paco_2$, and HCO_3^- concentrations (Table 116.1). When the primary disturbance is identified, the next step is to determine its cause and whether an appropriate compensation has occurred. An inappropriate compensation suggests that the process underlying the primary disturbance has hindered an appropriate response or that more than one primary disturbance is present. Once the primary disturbance has been identified, simple formulas can be used to calculate an appropriate response. Compensatory

TABLE 116.1

Categorization of Simple Acid-Base Disorders

DISORDER	pH	$Paco_2$	HCO_3^-	EXPECTED COMPENSATION
Metabolic acidosis	↓	↓	↓	$\Delta Paco_2 = 1.2\ \Delta HCO_3^-$
Respiratory acidosis	↓	↑	↑	$\Delta HCO_3^- = 0.10\ \Delta Paco_2$ (acute) $\Delta HCO_3^- = 0.35\ \Delta Paco_2$ (chronic)
Metabolic alkalosis	↑	↑	↑	$\Delta Paco_2 = 0.9\ \Delta HCO_3^-$
Respiratory alkalosis	↑	↓	↓	$\Delta HCO_3^- = 0.2\ \Delta Paco_2$ (acute) $\Delta HCO_3^- = 0.5\ \Delta Paco_2$ (chronic)

processes generally return pH toward normal, but not to normal and never beyond normal; such an exaggerated "compensation" represents a second primary disorder.

Blood gas and serum chemistry analyses allow the calculation and interpretation of the serum anion gap:

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

Plasma must remain electrically neutral: the sum of anions and cations (measured or unmeasured) must be equal. The higher the anion gap, the more likely that one or more unmeasured anions is generating a metabolic acidosis. Because routinely measured cations exceed routinely measured anions, the anion gap represents the concentration of anions other than chloride and bicarbonate in the blood. A variety of these anions are normally present, but serum albumin accounts for most of the physiologic (normal) anion gap, usually between 9 and 15. The impact of albumin can be factored into the anion gap equation by multiplying the reported albumin concentration (g/dL) by 2.5:

$$\text{Albumin corrected anion gap} = \text{l anion gap} + 2.5 \times (\text{normal albumin} - \text{measured albumin})$$

Correction for albumin is important because significant depression of the serum albumin level will reduce the anion gap, potentially masking the presence of an important unmeasured anion. For example, a chronically malnourished alcoholic may present with alcoholic ketoacidosis but may also have long-standing hypoalbuminemia, which causes a substantial increase in the serum bicarbonate concentration. An acute ketonemia will reduce the serum bicarbonate level to normal, resulting in no anion gap. Patients at risk for hypoalbuminemia who present with significant illness should have their serum albumin level measured. In these patients, if albumin is low, a normal serum bicarbonate concentration represents a metabolic acidosis.

In addition to albumin, classic unmeasured anions such as lactate and ketones can also be measured and incorporated into a diagnostic pathway. For example, a lactate level of 4 mEq/L can be presumed to account for an anion gap of 16 mEq/L, but not an anion gap of 25 mEq/L; in this case, other unmeasured anions should be sought. Unmeasured cations are also present and may account for an elevated anion gap in a case of hypomagnesemia or hypocalcemia, often in combination with hypokalemia; because the serum potassium concentration varies so little, it is usually left out of anion gap calculations and is therefore functionally an unmeasured cation. Elevated concentrations of unmeasured cations may cause a low anion gap (<3 mEq/L), such as in cases of lithium toxicity and hypergammaglobulinemia seen in multiple myeloma. Bromide toxicity may cause spurious hyperchloremia, and hypertriglyceridemia may cause spurious hyponatremia, which can also cause a low or negative anion gap. Overall, a normal anion gap does not exclude clinically significant acidosis or high concentrations of unmeasured anions. Direct measurement of compounds that often produce an elevated anion gap (eg, lactate, ketones, toxic alcohols) should still be pursued when there is clinical concern, despite a normal anion gap.

Independent of bicarbonate levels, sodium and chloride play an important role in acid-base status. When the strong ion difference ($[Na^+ + K^+] - [Cl^-]$) is significantly less than 40, an acidosis is present. An alternative to using the anion gap to identify the presence and cause of acid-base disorders begins with the base excess, as calculated by a blood gas analyzer, subtracting the sodium chloride effect[a] and subtracting the albumin effect.[b] What remains is, in the case of metabolic acidosis, the unmeasured anions (eg, lactate, ketones, uremic acids, toxic alcohols, other toxins).[2]

$$\text{Unmeasured anions} = \text{base excess red anion} - [Cl^-] - 38) - 2.5 \times (4.2 - [\text{measured albumin}])$$

This physicochemical (Stewart) approach may identify acid-base derangements with more sensitivity than the conventional anion gap,[3] although the clinical relevance of metabolic abnormalities occult to bicarbonate-centered calculations is uncertain. Some have suggested integrating principles of the two approaches,[4] whereas others have questioned the value of the physicochemical method in clinical practice.[5] Using the classic anion gap to identify acid-base disorders is appropriate in most emergency scenarios, especially if the lactate and albumin levels are measured and incorporated.

Painful arterial blood sampling is unnecessary for the evaluation of acid-base disturbances. $Paco_2$, HCO_3^-, and pH values taken from peripheral venous, central venous, intraosseous, and capillary blood are all suitable for acid-base assessment.[6]

SPECIFIC ACID-BASE DISORDERS

Respiratory Acidosis

Respiratory acidosis occurs when hypoventilation leads to an inappropriately elevated $Paco_2$ and resulting acidemia. Any condition that reduces minute ventilation may cause respiratory acidosis (Box 116.1). This commonly occurs acutely in the setting of airway compromise, pulmonary insults, major trauma, intracranial catastrophe, and central nervous system (CNS) depressants; it occurs chronically in progressive lung disease, neurologic muscle weakness, and obesity hypoventilation syndrome. Respiratory acidosis may be accompanied by hypoxemia, which, depending on its pace and severity, will cause end-organ effects such as headache, ischemic chest pain, altered mental status (usually agitation), bradycardia, and circulatory collapse. Hypercapnia is better tolerated than hypoxemia; when tissue oxygenation is adequate, hypercapnia will tend to produce somnolence and obtundation, with cerebral vasodilation and resulting elevation of intracranial pressure.

Beginning 6 to 12 hours after onset and progressing for 3 to 5 days, the kidneys respond to a respiratory acidosis by retaining bicarbonate. The resulting compensatory metabolic alkalosis, with an elevated serum bicarbonate level, partially corrects serum pH. Because chloride ions are excreted in the urine to increase the serum HCO_3^-, patients with chronic respiratory acidosis (eg, as seen in chronic obstructive pulmonary disease) are often noted to

[a]Sodium chloride effect = $[Na^+] - [Cl^-] - 38$.
[b]Albumin effect = $2.5(4.2 - [\text{albumin}])$.

BOX 116.1

Causes of Respiratory Acidosis

ACUTE

- Airway obstruction
- Pulmonary disease
  - Pneumonia
  - Asthma
  - Pulmonary edema
  - Aspiration pneumonitis
- Central nervous system depression
  - Recreational drugs (opiates, barbiturates, benzodiazepines, alcohol, gamma hydroxybutrate [GHB])
  - Intracranial catastrophe (intracerebral hemorrhage, subarachnoid hemorrhage, cerebrovascular accident)
  - Intravenous sedation
- Neuromuscular disorders
  - Myasthenia gravis
  - Guillain-Barré syndrome
- Thoracic trauma
  - Pneumothorax
  - Flail chest

CHRONIC

- Lung disease
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease, idiopathic pulmonary fibrosis
- Neuromuscular disorders
  - Amyotrophic lateral sclerosis
  - Muscular dystrophy
- Obesity hypoventilation (pickwickian) syndrome

BOX 116.2

Causes of Respiratory Alkalosis

- Hyperventilation caused by hypoxia
  - High altitude
  - Severe anemia
  - Ventilation-perfusion mismatch
- Central hyperventilation
  - Voluntary or psychogenic
  - Cerebrovascular accident
  - Increased intracranial pressure (tumor, hemorrhage, trauma)
- Toxic or pharmacologic
  - Salicylates
  - Caffeine, nicotine
  - Catecholamines
  - Thyroxine
- Pulmonary
  - Pulmonary embolism
  - Pneumonia
  - Pulmonary edema
  - Asthma
  - Mechanical hyperventilation (iatrogenic)
- Endocrine
  - Pregnancy
  - Hyperthyroidism
- Septicemia
- Hepatic encephalopathy
- Hyponatremia

have hypochloremia. An appropriate metabolic compensation for respiratory acidosis is an increase of approximately 3.5 mEq/L in the serum HCO_3^- concentration for every increase of 10 mm Hg in $Paco_2$. A patient with chronic respiratory disease resulting in a baseline $Paco_2$ of 60 mm Hg would therefore be expected to have a serum bicarbonate level of approximately 30 mEq/L and a slight acidemia, because without another primary acid-base abnormality, correction is never to a normal pH.

Acute respiratory acidosis is the most immediately dangerous of the acid-base disturbances. Relief of airway obstruction and provision of noninvasive or mechanical ventilation will often correct imminently dangerous hypoxemia or hypercapnia as therapy directed at the underlying disorder are initiated.

Patients with chronic respiratory acidosis are often hypoxemic at baseline and may be susceptible to further hypoventilation if normal oxygen saturation levels are promptly restored.[7] Typically, a patient with chronic obstructive pulmonary disease being treated for an acute exacerbation receives high-flow oxygen and is later found to be obtunded, with profound hypercapnia. The chronic respiratory acidosis results in a respiratory drive that is more dependent on Po_2 than Pco_2 levels. When high-flow oxygen is applied, the respiratory drive is suppressed, and Pco_2 further increases, leading to somnolence and eventually apnea. It is therefore prudent to target a lower than normal oxygen saturation in patients thought to be so habituated; Spo_2 fractions in the low 90s and high 80s are usually well tolerated in this population.

However, supplemental oxygen must not be withheld from patients with dangerously low oxygen saturation (SpO_2 in the 70s or less) or patients with end-organ hypoxic dysfunction, such as myocardial or cerebral ischemia. In these cases, aggressive oxygenation therapies should be instituted, preferably in combination with noninvasive ventilator support, with preparations made for mechanical ventilation, if needed. Standard ventilator settings applied to patients who chronically hypoventilate may precipitate posthypercapnic metabolic alkalosis. Clinicians should target a slightly acidemic serum pH (≈7.35), which, depending on the severity and chronicity of the patient's baseline respiratory acidosis, may correspond to remarkably high $Paco_2$ levels.

Respiratory Alkalosis

Respiratory alkalosis occurs when increased minute ventilation causes a decreased $Paco_2$ and subsequent increase in the serum pH. Although commonly associated with anxiety-related hyperventilation, the emergency clinician should consider medical conditions before arriving at a psychiatric diagnosis (Box 116.2).

An important cause of acute respiratory alkalosis is salicylate toxicity, a dangerous, treatable mixed acid-base disorder (described later) that may manifest with hyperventilation. Suicidal aspirin ingestions often produce the classic syndrome of tinnitus, hyperthermia, confusion, and a variety of metabolic derangements, ultimately leading to seizures, coma, and cardiovascular collapse. Chronic salicylism, however, is notoriously subtle in its presentation and occurs in older sicker patients who seemingly have more likely explanations for their symptoms. Salicylate toxicity should be strongly considered in these patients, as well as those with an unexplained respiratory alkalosis.

Blood pH alters the binding affinity of calcium for albumin. When the pH lowers, calcium loses some affinity for albumin (increasing free calcium); when the pH increases, calcium binds more strongly to albumin (decreasing free calcium). Thus, clinical features of respiratory alkalosis include those from hypocalcemia—lip and extremity paresthesias, carpal pedal spasm, muscle cramps, lightheadedness, and syncope. The homeostatic response to respiratory alkalosis first involves cellular secretion of H^+ in exchange for K^+; if respiratory alkalosis persists, the kidneys excrete bicarbonate and retain chloride, leading to a compensatory metabolic acidosis, with reduced serum HCO_3^-, hypokalemia, and hyperchloremia.

Pregnant women hyperventilate throughout gestation and normally have a $Paco_2$ between 31 and 35 mm Hg, serum pH between 7.46 and 7.50, and serum bicarbonate concentration between 18 and 22 mEq/L. Thus, eucapnia ($Paco_2 \cong 40$ mm Hg) may represent hypoventilation in pregnant patients.

As with other acid-base disorders, the management of respiratory alkalosis should be directed at the underlying cause. When organic causes of respiratory alkalosis have been excluded, hypocapnia symptoms can be relieved in patients with psychological hyperventilation by reassurance. The technique of using a paper bag to cause rebreathing probably works through the placebo effect rather than by changes in $Paco_2$ but carries the potential danger of inducing hypoxemia.

Metabolic Acidosis

Metabolic acidosis, defined by a reduced serum bicarbonate concentration, occurs when acids are added by intrinsic processes or from exogenous sources, acid excretion is impaired, or there is inappropriate loss of alkali. Metabolic acidoses are classically divided into normal anion gap and elevated anion gap to assist in determining their causes.

Elevated Anion Gap Metabolic Acidosis

Common unmeasured anions that cause an elevated anion gap include lactate, keto acids (usually from diabetic ketoacidosis), acidic products of exogenous toxins (eg, the toxic alcohols), and organic acids that accumulate in renal failure. The causes of elevated anion gap metabolic acidosis are classically remembered by the mnemonic ***MUDPILES***; however, it is more useful to focus on the identity of the unmeasured anion (Box 116.3). For example, if the cause of an elevated anion gap metabolic acidosis is found to be lactate or ketones, the next step is to determine the cause of lactatemia or ketonemia.

Lactic Acidosis. Increased production of lactate is a common cause of elevated anion gap metabolic acidosis, and the serum lactate level should be measured whenever another cause is not apparent. Because of the coincident acid-base disturbances that may be present in patients with a high serum lactate level, a normal anion gap does not exclude clinically important lactic acidosis.[8] Causes of lactic acidosis can be divided into hypoxic or hypoperfusion states (eg, shock) and exogenous cellular toxins, such as cyanide and carbon monoxide. Idiosyncratic causes of lactic acidosis include short gut syndrome (usually after bariatric surgery), reverse transcriptase inhibitor therapy for human immunodeficiency virus (HIV) infection, and metformin therapy. The likelihood of metformin causing lactic acidosis is thought to be enhanced by renal insufficiency (serum creatinine level > 1.5 mg/dL), congestive heart failure, coexisting metabolic acidosis, and exposure to intravenous (IV) radiologic contrast media. However, in patients who take metformin but have normal renal function and no liver dysfunction, alcohol abuse, cardiac failure, myocardial or peripheral muscle ischemia, or sepsis or severe infection, metformin need not be discontinued prior to IV contrast, and renal function need not be checked afterward.[9]

Exposure to carbon monoxide and cyanide cause lactic acidosis through tissue hypoxia. Although patients extricated from fires have a variety of reasons to have a high lactate concentration, most of these patients, especially if they are obtunded or in cardiac arrest, should be empirically treated for carbon monoxide and cyanide toxicity. The preferred initial treatment for cyanide toxicity is hydroxocobalamin.[10] If using the older antidote kit and simultaneous cyanide and carbon monoxide exposure is suspected, the nitrite portion should be withheld because the additional tissue hypoxia from the resultant methemoglobinemia will be poorly tolerated, given the carboxyhemoglobin burden. The severity of carbon monoxide exposure and treatment requirements may be better predicted by the degree of initial acidemia than by the carboxyhemoglobin level.[11,10] (For more detail, see Chapter 153.)

BOX 116.3

Causes of Elevated Anion Gap Metabolic Acidosis

KETOACIDOSIS
Diabetic ketoacidosis
Alcoholic ketoacidosis
Starvation ketoacidosis

LACTIC ACIDOSIS
Global tissue ischemia
- Shock
- Grand mal seizure (in status unresponsive to standard treatment, consider isoniazid toxicity)

Focal end-organ ischemia (limb ischemia, mesenteric ischemia)
Inadequate blood oxygenation
- Hypoxia (from airway or breathing disorder)
- Carbon monoxide, methemoglobinemia

Inability of tissues to use oxygen from cellular poisons
- Cyanide (or nitroprusside therapy), hydrogen sulfide, aspirin, iron

Impaired lactate clearance
- Liver failure
- Metformin or phenformin (increased risk with concomitant renal insufficiency [creatinine > 1.5 mg/dL]) congestive heart failure, coexisting metabolic acidosis, and exposure to intravenous radiologic contrast media)
- Reverse transcriptase inhibitors (for HIV infection therapy)

RENAL FAILURE

TOXINS METABOLIZED TO ACIDS
Toxic alcohols (methanol, ethylene glycol)
Toluene
- Paraldehyde
- Aspirin

SEVERE RHABDOMYOLYSIS

Diabetic Ketoacidosis. Diabetic ketoacidosis (DKA) is a common acid-base disorder defined by hyperglycemia, ketonemia, and acidemia. Patients with DKA classically complain of progressive polyuria, polydipsia, and malaise, but DKA may be manifested atypically with chief complaints of vomiting, abdominal pain, and/or altered mental status. Sodium concentration is not corrected for hyperglycemia in the anion gap calculation because this dilutional effect influences other ions in the calculation as well. DKA is often caused by medication noncompliance, but may complicate any physiologic stress; when DKA is diagnosed, identification of the precipitant is a management priority. Treatment of DKA focuses on volume expansion with IV fluids, insulin therapy, and careful attention to and replacement of electrolytes, particularly potassium. (For more detail, see Chapter 118.)

Alcoholic Ketoacidosis. Alcoholic ketoacidosis (AKA) causes an elevated anion gap metabolic acidosis that may be mistaken for DKA. AKA can occur when a long-standing ethanol user abruptly stops drinking; ketones are generated by a combination of malnutrition and dehydration. Patients with AKA may demonstrate a high anion gap, but a mixed acid-base disorder may be present due to concomitant ethanol withdrawal, which

may cause a respiratory alkalosis and metabolic alkalosis from vomiting. As a result, the serum pH can be acidemic, normal, or alkalemic. Like DKA, AKA includes the symptoms of vomiting, abdominal pain, dehydration, altered mental status, prostration, and lethargy; however, AKA patients generally do not demonstrate hyperglycemia or glycosuria. In AKA, the ratio of the keto acid β-hydroxybutyrate to its metabolites acetoacetate and acetone is double the ratio seen in DKA because metabolites of alcohol cause a reduction of acetoacetate to β-hydroxybutyrate. A urine dipstick can detect acetoacetate but not β-hydroxybutyrate; this causes an apparent worsening ketonuria as the patient metabolizes β-hydroxybutyrate to acetoacetate, although the patient is actually recovering. The treatment of AKA is dextrose-containing fluids; insulin is contraindicated. (For more detail, see Chapter 141.)

Methanol and Ethylene Glycol. The toxic alcohols, methanol and ethylene glycol, represent important potential causes of an elevated anion gap metabolic acidosis. There considerable morbidity and mortality can be prevented by timely therapy, and the presence of a wide anion gap may be the most conspicuous sign of these dangerous ingestions. Toxic alcohols are typically consumed by alcoholics seeking a less expensive drink, by children as an accidental ingestion (usually ethylene glycol, which is sweet), or in a suicide attempt. The first measurable sign of toxic alcohol poisoning is an osmol gap, which precedes an elevated anion gap. As the parent compounds are converted to their toxic metabolites, the osmol gap closes, and the anion gap widens. Treatment centers on prevention of the enzymatic conversion of methanol and ethylene glycol into their toxic metabolites by the use of ethanol or fomepizole. Many laboratories will report a spuriously elevated lactate concentration in the presence of glycolate, a byproduct of ethylene glycol poisoning. Isopropyl (rubbing) alcohol ingestion causes intoxication, ketosis, and an osmol gap but does not cause acidosis. (For more detail, see Chapter 141.)

Renal Failure. The body normally generates a net acid load that the kidneys must continuously excrete. Any condition that reduces the glomerular filtration rate will undermine this function, and unmeasured anions such as sulfate, phosphate, urate, and hippurate will generate an elevated anion gap metabolic acidosis. In chronic renal failure, patients with uremia-associated metabolic acidosis may receive sodium bicarbonate or sodium citrate as a bridge to renal replacement therapy. In acute renal failure causing metabolic acidosis, sodium bicarbonate can temporize acidosis until the patient can be dialyzed. Health care providers should be cautious in patients with oliguria or volume overload because sodium bicarbonate may deliver a hemodynamically significant volume load. (For more detail, see Chapter 87.)

Isoniazid Toxicity. Isoniazid (INH) toxicity is usually listed in the differential for metabolic acidosis, but consideration of INH toxicity should primarily be prompted by intractable seizures. It is the seizures that cause the lactic acidosis, not INH directly. INH toxicity is an important consideration in these cases because it causes seizures that do not respond to usual treatments. Continuous seizure activity, in addition to cardiorespiratory compromise, causes a profound, life-threatening acidemia from lactate generation. The initial treatment of status epilepticus related to INH toxicity is the administration of vitamin B_6 (pyridoxine). Specific therapies targeting nonepileptic causes of seizures, such as hypoglycemia, eclampsia, hyponatremia, and cyanide toxicity, should also be considered in the patient with seizures unresponsive to standard therapy.

Salicylate Toxicity. Salicylate toxicity first produces a respiratory alkalosis, as previously described. Untreated, the syndrome evolves into a complex acid-base disorder with paradoxical aciduria during the initial respiratory alkalosis, followed by an elevated anion gap metabolic acidosis and hyperthermia due to its interference with cellular metabolism. The serum pH can be normal during the initial phase of the disease, a false reassurance. Dehydration, electrolyte disturbances, fatigue, and lung injury ultimately lead to decompensation with respiratory acidosis—completing the so-called triple acid-base disturbance—followed by cardiovascular collapse. Management of aspirin toxicity includes gastrointestinal decontamination, urine alkalinization, meticulous supportive care, and hemodialysis. (For more detail, see Chapter 144.)

Iron Ingestion. Iron ingestion is a dangerous cause of metabolic acidosis that presents with gastric irritation causing prominent vomiting and other gastrointestinal symptoms. This phase is followed by one of systemic toxicity—myocardial depression, liver injury, and lactic acidosis from cellular mitochondrial poisoning. A plain radiograph of the abdomen may provide evidence of an iron ingestion while the serum iron concentration is determined. Treatment measures include fluid resuscitation, gastrointestinal decontamination, and chelation with deferoxamine. (For more detail, see Chapter 151.)

Normal Anion Gap Metabolic Acidosis

Normal anion gap metabolic acidosis is less likely to be immediately dangerous or caused by an imminently dangerous condition. Most cases encountered in the emergency department (ED) are caused by gastric loss of bicarbonate in the setting of diarrhea. A variety of other conditions and medications may cause a normal anion gap metabolic acidosis (Box 116.4), including renal tubular acidosis and bladder-diverting urologic procedures. A common iatrogenic cause of normal anion gap metabolic acidosis is the rapid infusion of large volumes of normal saline, which contains 154 mEq/L of sodium and chloride without bicarbonate or any

BOX 116.4

Causes of Normal Anion Gap Metabolic Acidosis

GASTROINTESTINAL HCO_3^- LOSS
Diarrhea
Colostomy or ileostomy
Enteric fistulas
Ion exchange resins (eg, sodium polystyrene sulfonate [Kayexalate])

RENAL HCO_3^- LOSS
Renal tubular acidosis
Tubulointerstitial renal disease
Hyperparathyroidism

RAPID NORMAL SALINE INFUSION
Urologic procedures
Ureterosigmoidostomy
Ureteroileal conduit

INGESTIONS
Acetazolamide
Calcium chloride ($CaCl_2$)
Magnesium sulfate ($MgSO_4$)

OTHER
Hypoaldosteronism
Hyperkalemia
Toluene (after initial elevated anion gap metabolic acidosis)

other buffer and is therefore acidic compared to serum. The hyperchloremic acidosis associated with normal saline therapy is generally well tolerated. Intensive care unit (ICU) studies comparing chloride-liberal and chloride-restrictive fluid strategies have been observational[12,13]; however, consensus currently favors isotonic, physiologic crystalloid. Although 1 to 2 L of normal saline is likely inconsequential compared to other fluid preparations, patients requiring large-volume resuscitation, particularly when accompanied by acidemia, hyperkalemia, or kidney injury, should receive a balanced fluid (eg, lactated Ringer's solution, Normosol, Plasma-Lyte).[14,15]

Physiologic Compensation for Metabolic Acidosis

Immediate physiologic compensation for a metabolic acidosis occurs via the extracellular bicarbonate–carbonic acid system and intracellular protein buffers. Medullary chemoreceptors augment alveolar ventilation to blow off carbon dioxide, partially correcting the serum pH. In severe metabolic acidosis (pH < 7.1), hyperventilation is profound and assumes the appearance of Kussmaul's respirations, in which hyperpnea (increased tidal volume) is seen out of proportion to tachypnea (increased respiratory rate). In cases of prolonged metabolic acidosis, the kidney generates a compensatory aciduria by secreting H^+ and retaining HCO_3^-.

Metabolic Alkalosis

Metabolic alkalosis occurs from loss of H^+ or retention of HCO_3^-. It is usually a consequence of prolonged vomiting or nasogastric suction or a compensation for chronic respiratory acidosis. The differential diagnosis includes a variety of predominantly endocrine and electrolyte disorders (Box 116.5). Patients taking diuretic medications may reduce their plasma volume around a steady concentration of HCO_3^-, causing a contraction alkalosis. Contraction alkalosis often presents with hypokalemia, which itself causes a metabolic alkalosis as intracellular K^+ is exchanged for extracellular H^+.

In the acute phase, the lungs compensate for a metabolic alkalosis by decreasing minute ventilation and retaining carbon dioxide; the P_{CO_2} should increase by approximately 0.7 mm Hg for every 1-mEq/L increase in serum HCO_3^-. (Of note, hypoventilation should be assumed to be a more dangerous primary respiratory disorder until proven otherwise.) Prolonged metabolic alkalosis leads to compensatory renal HCO_3^- excretion.

BOX 116.5

Causes of Metabolic Alkalosis

VOLUME-CONTRACTED (SALINE-RESPONSIVE)
Vomiting, gastric suction
Diuretics (contraction alkalosis)
Postrespiratory acidosis
Ion-deficient baby formula
Chloride-secreting colonic villous adenomas

EUVOLEMIC, VOLUME-EXPANDED (SALINE-RESISTANT)
Hyperaldosteronism
Hypercortisolemia
Severe potassium depletion
Adenocarcinoma
Bartter'artterrcin

UNCLASSIFIED
Hypoalbuminemia
Milk-alkali syndrome
Penicillin and related compounds
Hypercalcemia of malignancy
Massive transfusion (from citrate), especially with renal insufficiency

DIAGNOSTIC TESTING AND MIXED DISORDERS

A simple acid-base disorder is a combination of a primary disturbance and subsequent compensation. Mixed acid-base disorders occur when two or more primary acid-base lesions coincide. These simultaneous conditions may push the serum pH in the same or opposite direction, and each will generate its own compensatory responses; mixed disorders may therefore be difficult to recognize by clinical or laboratory features. In ED patients with mixed acid-base disorders, there is commonly a dominant precipitating problem that complicates an existing disease or causes failure of compensatory mechanisms.

The body usually does not fully compensate for a primary acid-base disorder so, for example, a primary metabolic acidosis should generate a compensatory respiratory alkalosis, but the serum pH is expected to still be below 7.36. Whether an appropriate respiratory compensation to a metabolic acidosis has occurred can be approximated by comparing the P_{aCO_2} to the last two digits of the serum pH. In a primary metabolic acidosis with appropriate respiratory compensation, these two values should be similar; that is, a patient with a serum pH of 7.20 should have a P_{aCO_2} of 20 mm Hg. If the serum pH is 7.17 and the P_{aCO_2} is 30 mm Hg, the respiratory compensation is less than expected and a primary respiratory acidosis is present. This is commonly seen in patients whose dominant condition causes a metabolic acidosis but also impairs respiration, such as sepsis.

The delta gap (ΔG) describes the difference between the deviation of the anion gap (AG) from normal and the deviation of the serum bicarbonate concentration from normal:

$$\Delta G = (AG - 12) - (24 - [HCO_3^-])$$

Conceptually, calculation of the delta gap tried to determine whether the anion gap is accounted for by the change in serum bicarbonate concentration. In patients with an elevated anion gap and a delta gap greater than +6, meaning that the serum bicarbonate level is significantly higher than would be predicted by the number of unmeasured anions, a metabolic alkalosis in addition to a metabolic acidosis is likely to be present. This is commonly seen when the dominant acidosis condition causes severe vomiting (eg, diabetic ketoacidosis). In patients with an elevated anion gap and delta gap more negative than −6, meaning that the serum bicarbonate level is significantly lower than expected given the anion gap, a normal anion gap metabolic acidosis is likely be present in addition to the elevated anion gap metabolic acidosis. This is usually seen when a lactic acidosis complicates severe diarrhea.

MANAGEMENT

Acidosis

Management of metabolic acidosis is directed at identification and treatment of the underlying cause while appropriate resuscitative and supportive care are provided. An example of this paradigm is the management of generalized seizures; seizures often cause profound acidemia but, if terminated promptly, the serum pH normalizes quickly and without sequelae.

The role of IV sodium bicarbonate in the treatment of acidemia is controversial. Theoretic harms include the following:

- Paradoxical CNS acidosis—because sodium bicarbonate does not readily cross the blood-brain barrier, serum alkalinizes much faster than the cerebrospinal fluid. As the serum pH

rises, minute ventilation slows and carbon dioxide, which readily crosses the blood-brain barrier, delivers an additional acid load to the CNS.
- Hypokalemia, which can cause respiratory muscle weakness, impairing respiratory compensation, hypocalcemia, hypernatremia
- Volume overload
- Hyperosmolality
- Overshoot alkalosis

Many authors question the value of bicarbonate therapy, even in cases of severe acidemia, given these potential harms and the absence of demonstrated benefit.[16] Although it is commonly recommended to treat a serum pH less than 7.1 with sodium bicarbonate (1 mEq/kg),[17] we believe that best evidence currently supports withholding bicarbonate therapy as an empirical treatment for acidemia in favor of treating its underlying cause. If bicarbonate is used, endpoints of therapy include a pH above 7.1 and serum bicarbonate concentration above 10 mEq/L. An isotonic bicarbonate drip is prepared by adding 150 mEq sodium bicarbonate (three crash cart ampules, which are usually 50 mL of 8.4% solution) to 1 L of 5% D_5W, infusing as slowly as the clinical situation permits (eg, 75–200 mL/hr). Sodium bicarbonate should generally not be added to normal saline because of concern of hypertonicity.

An important clinical pitfall is using sodium bicarbonate to treat metabolic acidosis without recognizing the presence of a concomitant respiratory acidosis. For example, a severe DKA patient with profound metabolic acidosis may tire after hours of respiratory compensation; the respiratory alkalosis in this case becomes inadequate, which is then considered a primary respiratory acidosis. Providing ventilatory support to address the respiratory acidosis is much more important than bicarbonate therapy. In an appropriate respiratory compensation for metabolic acidosis, the $Paco_2$ drops by the same amount as the serum bicarbonate concentration. It is thought that spontaneous respiration cannot sustainably reduce $Paco_2$ beyond 10 to 12 mm Hg, which is the appropriate compensatory respiratory alkalosis for a metabolic acidosis that drives the pH down to about 7.10. Noninvasive or mechanical ventilation may be required to prevent a more severe acidemia, which is likely to result in multiorgan dysfunction. Winter's equation ($Paco_2 = [1.5 \times \text{serum } HCO_3] + [8 \pm 2]$) can be used to calculate the expected arterial Pco_2 for the serum bicarbonate level. If the Pco_2 is higher than expected, the patient may be fatiguing and require ventilator support.

Although administration of sodium bicarbonate is unlikely to be beneficial in most cases of acidemia caused by endogenous acid production (eg, lactic acidosis, ketoacidosis), sodium bicarbonate therapy is theoretically more attractive for conditions in which the underlying problem is bicarbonate loss, which generally causes a hyperchloremic or normal anion gap metabolic acidosis, or impairment of acid secretion, such as renal failure. Many of the acidosis syndromes caused by exogenous toxins (eg, aspirin, heterocyclic antidepressants) call for bicarbonate as a specific therapy; these cases are distinct from the empirical use of bicarbonate to treat the acidemia itself.

Bolus dosing of hypertonic (8.4%) sodium bicarbonate is ineffective and should not be used to treat hyperkalemia.[18,19] Hyperkalemic patients (especially if acidemic) may be treated with an isotonic sodium bicarbonate infusion, as described above. Normal saline may exacerbate hyperkalemia and is likely inferior to the use of alternative crystalloid solutions in this context.[18,19]

Bicarbonate has been variously recommended and used as an empirical therapy in cardiac arrest. However, most studies have shown no benefit or poorer outcomes with its use, and the 2010 American Heart Association guidelines stated that routine use of sodium bicarbonate is not recommended for patients in cardiac arrest.[20]

In summary, sodium bicarbonate should not routinely be used to treat undifferentiated acidemia or acidemia caused by lactic acidosis or ketoacidosis. If the serum pH is so severely depressed that the acidemia itself is thought to be an immediate life threat, bicarbonate therapy is an option. A lower treatment threshold is appropriate in acidemia caused by bicarbonate loss or renal failure, and bicarbonate should not be withheld when it is specifically indicated to treat the underlying cause of an acidosis.

Acidemia causes hyperkalemia as H^+ is brought into cells in exchange for K^+. Emergency clinicians managing patients with acid-base disturbances should carefully monitor the serum potassium concentration; as the acidosis resolves, the serum potassium level will fall and may require supplementation. This is classically seen in DKA patients, who are invariably potassium-depleted, irrespective of their initial serum potassium concentration.

Alkalosis

Metabolic alkalosis rarely causes dangerous alkalemia, so the management of metabolic alkalosis is directed at the identification and treatment of dangerous underlying causes. IV fluids and electrolyte replacement for patients with volume loss, vomiting, or hypokalemia will address the resulting saline-responsive metabolic alkalosis. Edematous or euvolemic patients with conditions that cause renal Na^+ retention—and accompanying H^+ loss—may have a saline-resistant metabolic alkalosis, but this generally does not require emergency therapy. In rare cases, severe metabolic alkalosis may cause hypocalcemic tetany, seizures, altered mental status, or dysrhythmias and require emergent empirical therapy, usually in consultation with nephrology, with acetazolamide or hydrochloric acid.

KEY CONCEPTS

- Patients with an acute severe metabolic acidosis rely on a robust respiratory compensation; in these cases, the adequacy of the ventilatory response should be assessed and augmented, with noninvasive or invasive ventilation, if needed.
- The strong ion difference = $([Na^+ + K^+] - [Cl^-])$. When significantly less than 40, an acidosis is present.
- The delta gap (ΔG) = $(AG - 12) - (24 - [HCO_3^-])$. Its calculation determines if the anion gap is accounted for by the change in serum bicarbonate concentration. An elevated anion gap and ΔG more than 6 indicates that a metabolic alkalosis in addition to a metabolic acidosis is likely to be present.
- Patients who have a chronic respiratory acidosis (eg, in chronic obstructive pulmonary disease) are at risk for dangerous alkalemia if they are ventilated with routine parameters. Blood gas analysis in these cases should be performed frequently and settings titrated to the serum pH.
- Alcoholic ketoacidosis may be manifested similarly to diabetic ketoacidosis but is much less common; insulin is contraindicated in alcoholic ketoacidosis.
- When an elevated anion gap is recognized, the initial assessment focuses on identifying one of four causes: ketoacidosis, toxic ingestions, lactic acidosis, and renal failure. Typically, only chronic renal failure causes significant acidosis.
- Anion gap = $Na^+ - (Cl^- + HCO_3^-)$. Causes of an elevated anion gap include ketoacidosis, lactic acidosis, toxins metabolized to acids, and renal failure.
- When the cause of an elevated anion gap is determined to be lactate or ketones, diagnostic efforts are directed at identifying the cause of the lactic acidosis or ketoacidosis.
- Sodium bicarbonate is not recommended for the empirical treatment of acidemia; it is an option in cases of severely depressed pH thought to pose an immediate life threat.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 116: QUESTIONS & ANSWERS

116.1. A 31-year-old man has the following laboratory values:
Sodium = 142 mEq/L
Potassium = 3.8 mEq/L
Chloride = 110 mEq/L
Bicarbonate = 29 mEq/L
Creatinine = 1.0 mg/dL
Which of the following is true?
A. He may have a low albumin level.
B. Ionized calcium will be low.
C. Organic alcohol ingestion should be considered.
D. The blood glucose level is likely elevated.
E. The serum lactate level will be elevated.

Answer: A. This patient has an anion gap of 3. Because the anion gap is due to unmeasured anions such as albumin, sulfate, phosphate, and citrate, isolated depressions of these may cause a low anion gap. Hypoalbuminemia would be such a case.

116.2. What is the most common cause of normal anion gap metabolic acidosis?
A. Acetazolamide use
B. Diarrhea
C. Hypoaldosteronism
D. Magnesium sulfate
E. Renal tubular acidosis

Answer: B. Chronic diarrhea is the most common cause.

116.3. A 61-year-old man presents with nausea, vomiting, and lethargy. He was found in his apartment by neighbors, who called emergency medical services. There were no signs of trauma and no medications discovered. There were several empty liquor bottles but no smell of intoxication. Examination reveals a thin unkempt male who is lethargic but grossly neurologically intact. Vital signs are temperature 35°C (95°F), heart rate (HR) 120 beats/min, blood pressure 105/60 mm Hg, respiratory rate (RR) 28 breaths/min, and O_2 saturation 96%. Laboratory evaluation reveals the following:
P_{O_2} = 88 mm Hg
P_{CO_2} = 30 mm Hg
pH = 7.47
Sodium = 138 mEq/L
Potassium = 3 mEq/L
Chloride = 90 mEq/L
HCO_3^- = 30 mEq/L
Glucose = 140 mg/dL
Urinalysis = specific gravity (SG) 1.024 and trace ketones
Which of the following is true?
A. A chest CT is indicated.
B. Crystalloid alone will correct the abnormalities.
C. His urinary ketone levels will increase with treatment.
D. Insulin infusion is indicated.
E. The pH is appropriate for the HCO_3 and P_{CO_2} levels.

Answer: C. Alcoholic ketoacidosis (AKA) usually presents after abrupt alcohol intake cessation following a binge. Ketoacidosis, malnutrition, and dehydration all coexist. Urine ketone levels may be minimal due to the lack of detection of e hydroxybutyrate, prominent in AKA. This is later converted to acetoacetate and acetone, transiently worsening the ketosis while improving the ketoacidosis during treatment. Measurement of urine ketone levels can therefore produce paradoxical results. Dextrose-containing fluids are the mainstay of treatment; insulin is contraindicated. This patient has a complex acid-base disorder with a combination of an anion gap acidosis caused by AKA, with secondary respiratory alkalosis and primary metabolic alkalosis from vomiting.

116.4. How does isoniazid (INH) cause a metabolic acidosis?
A. INH acts as a cellular toxin by uncoupling oxidative phosphorylation.
B. INH causes bicarbonate wasting at the level of the glomerulus.
C. INH causes increased lactic acid production by liver toxicity.
D. INH is acidic and lowers serum pH directly.
E. INH overdose causes seizures, which lead to a metabolic acidosis.

Answer: E. Isoniazid overdose is an important cause of seizures, especially seizures that are unresponsive to conventional therapies. Treatment of INH-induced seizures is vitamin B_6 (pyridoxine).

116.5. A 26-year-old G3P2 woman at 32 weeks of gestation presents with mild dyspnea on exertion for several weeks. She has no pain and no other complaints. Physical examination is remarkable only for a RR of 26 breaths per minute. Arterial blood gas reveals the following:
Po_2 = 98 mm Hg
Pco_2 = 32 mm Hg
pH = 7.49
HCO_3^- = 19 mEq/L
The complete blood count, electrocardiogram, and chest radiograph with shielding are normal. Which of the following is true?
A. No intervention is indicated.
B. Salicylate levels are indicated.
C. Serum lactate level will be helpful.
D. There is an underlying metabolic acidosis.
E. Ventilation-perfusion scan is indicated.

Answer: A. Alkalemia of pregnancy occurs early and is sustained throughout gestation. A Pco_2 of 31 to 35 mm Hg with a compensatory drop in serum HCO_3^- is normal. The pH ranges from 7.46 to 7.50. All these values are normal for pregnancy.

116.6. A patient with severe, long-standing chronic obstructive pulmonary disease presents in respiratory distress and requires endotracheal intubation. Blood gas analysis 20 minutes later shows the following:
pH = 7.55
Po_2 = 140 mm Hg
Pco_2 = 37 mm Hg
HCO_3^- = 44 mEq/L
What is the likely explanation for these results?
A. The patient has a chronically elevated serum bicarbonate level.
B. The patient has coexisting hypoalbuminemia.
C. The patient is receiving too much supplemental oxygen.
D. The patient received supplemental bicarbonate therapy.

Answer: A. Patients with long-standing respiratory acidosis develop a compensatory metabolic alkalosis with an elevated serum bicarbonate level. When these patients are mechanically intubated, minute ventilation should be reduced compared with normal patients and should be titrated to pH.

116.7. An older patient presents with altered mental status without a clear cause after a history and physical examination. Blood gas analysis shows the following:
pH = 7.44
Po_2 = 94 mm Hg
Pco_2 = 19 mm Hg
HCO_3^- = 21 mEq/L
These results should prompt consideration of which cause of altered mental status?
A. Acute coronary syndrome
B. Intracranial hemorrhage
C. Salicylate toxicity
D. Urosepsis

Answer: C. Chronic salicylate toxicity is an important concern in older patients, and an unexplained respiratory alkalosis may be the most important presenting finding. A history targeting long-standing salicylate use and measurement of the serum salicylate level are appropriate next steps.

116.8. A patient presents with diabetic ketoacidosis. The initial blood gas shows a serum pH of 7.05. Resuscitation with normal saline can cause which acid-base disturbance?
A. Metabolic acidosis
B. Metabolic alkalosis
C. Respiratory acidosis
D. Respiratory alkalosis

Answer: A. Because normal saline is acidic compared with serum, use can cause a non–anion gap hyperchloremic metabolic acidosis. Although this type of acidosis is generally well tolerated, if the serum pH is severely depressed, switching to a more balanced electrolyte solution may be prudent.

116.9. In which case should sodium bicarbonate be used?
A. A patient in cardiac arrest of uncertain cause
B. A patient pulled from a fire thought to be exposed to cyanide
C. A patient with heterocyclic antidepressant overdose
D. A patient with sepsis, lactic acidosis, and serum pH of 6.9

Answer: C. Sodium bicarbonate as an empirical treatment for acidemia or undifferentiated cardiac arrest is not recommended; however, sodium bicarbonate should be administered when indicated as a specific therapy, such as in certain toxic ingestions.

CHAPTER 117

Electrolyte Disorders

Camiron L. Pfennig | Corey M. Slovis

Electrolyte abnormalities are common in emergency medicine and can vary greatly in importance, severity, and symptoms. Asymptomatic electrolyte abnormalities can be gradually corrected, whereas those causing alterations in consciousness or life-threatening dysrhythmias require immediate therapy to avoid permanent sequelae or death. In some cases, therapy for life-threatening electrolyte disorders may precede laboratory confirmation.

HYPERKALEMIA

Principles

Hyperkalemia, defined as serum potassium level greater than 5.0 mEq/L, is the most dangerous acute electrolyte abnormality, potentially leading to life-threatening arrhythmias and death. Although hyperkalemia may have vague and varied symptoms, it is usually totally asymptomatic and can present with cardiac arrest as its first "symptom." Serum potassium concentration is normally between 3.5 and 5.0 mEq/L and is tightly regulated by the kidneys. Hyperkalemia usually develops from impaired renal excretion or intracellular release; however, in advanced chronic kidney disease or end-stage renal disease, dietary intake of potassium may be a significant factor in its development. Risk factors for hyperkalemia include impaired potassium excretion, such as dehydration and renal failure, as well as medications that cause potassium retention. Evaluation of the 12-lead electrocardiogram (ECG) of patients at risk for this electrolyte disturbance helps steer management decisions. Hyperkalemia can be rapidly progressive, requiring lifesaving interventions at the earliest suspicion of toxicity.

Hyperkalemia causes cardiotoxicity by increasing the resting membrane potential of the cardiac myocyte, causing "membrane excitability," and conversely, sluggish depolarization, as well as decreased duration of repolarization. At very high levels, potassium causes the depolarization threshold to rise, leading to overall depressed cardiac function. Nearly any cardiac arrhythmia can be seen with hyperkalemia, including heart blocks, bradydysrhythmias, pseudoinfarction ST-segment elevation, Brugada pattern, and the classic "sine wave" pattern.[1] As hyperkalemia advances, the end result is cardiac arrest, usually from disintegration into ventricular fibrillation, pulseless electrical activity, or asystole. A serum potassium level of 10.0 mEq/L is usually fatal, but decompensation and death can occur at any level above 7 to 8 mEq/L.

The most common cause of hyperkalemia is spurious elevation due to hemolysis during or after the blood draw. Thus, an ECG should be used to assess for true hyperkalemia while another sample is analyzed. Box 117.1 organizes the most common causes of hyperkalemia. The presence of one of these conditions may be the lone historical clue in hyperkalemia.

Clinical Features

Hyperkalemia is a difficult diagnosis to make on clinical grounds alone. Hyperkalemia is classified as mild (K 5.5 to 6.0), moderate (K 6.1 to 6.9) or severe (K >7.0). Patients with mild to moderate hyperkalemia are often identified during routine blood sampling for an unrelated condition. Patients with moderate to severe hyperkalemia may have gastrointestinal effects, such as nausea, vomiting, and diarrhea, which are often associated with their underlying disease. Patients with severe hyperkalemia may present with neuromuscular findings, including muscle cramps, generalized weakness, paresthesias, tetany, and focal or global paralysis. The signs and symptoms of progressive muscle weakness, paresthesias, dyspnea, and depressed deep tendon reflexes are neither sensitive nor specific, nor do they appear reliably with a particular serum potassium level. Patients with severe hyperkalemia may present with hemodynamic instability and cardiac arrhythmias requiring immediate intervention.

Diagnostic Strategies

The ECG is helpful in making the diagnosis of hyperkalemia and can be used in unstable patients to initiate treatment (Figs. 117.1 to 117.3). Classic electrocardiographic changes—the peaked T wave, flattened p wave with prolonged PR interval or a totally absent P wave, wide QRS, and sine wave pattern, portending imminent cardiac arrest—have been well described as appearing sequentially with rising serum potassium levels. Peaked T waves usually appear as serum potassium levels exceed 5.5 to 6.5 mEq/L; P wave disappearance and PR prolongation are common with levels above 6.5 to 7.5 mEq/L; and levels above 7.0 to 8.0 mEq/L can result in QRS prolongation. Although these changes may occur in only half the patients, recognition of these patterns is vital to rapid diagnosis and initiation of lifesaving treatment. A serum potassium level above 5.0 mEq/L is diagnostic of hyperkalemia, but the value itself does not always predict electrocardiographic changes or the degree of cardiotoxicity. Furthermore, stable patients who are otherwise unlikely to have elevated potassium should not be presumptively treated for hyperkalemia based on subtle electrocardiographic changes alone. When correcting severe hyperkalemia, atrial flutter cycle length can shorten, progressing to atrial fibrillation as the atria become more excitable.[2] In addition, hyperkalemia may present as an atropine resistant bradycardia, with or without apparent heart block.[2a]

Management

Patients with suspected or known hyperkalemia should have intravenous (IV) access and continuous cardiac monitoring. Treatment of hyperkalemia should be directed by the clinical scenario combined with the ECG and laboratory potassium value, and consists of three main steps: (1) stabilization of the cardiac membrane, (2) shifting of potassium into the cells, and (3) removal of potassium from the body. A variety of treatment options are considered for the acute management of hyperkalemia, including calcium, insulin, beta$_2$-adrenergic agonists, sodium bicarbonate, resins, and dialysis (Table 117.1).

IV calcium stabilizes the cardiac membrane by restoring the electrical gradient. Calcium increases the depolarization threshold and the calcium gradient across the cardiac membrane, quieting

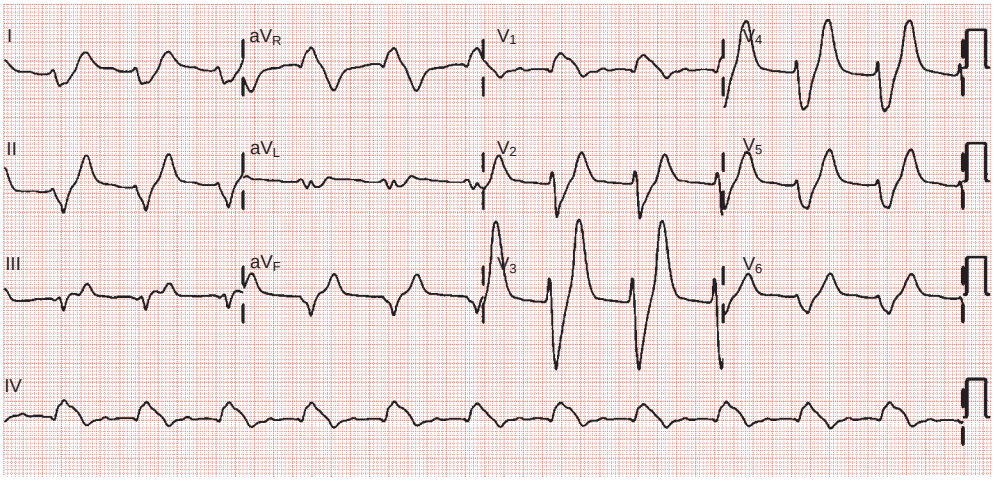

Fig. 117.1. Hyperkalemia with QRS widening merging into T wave, absent P wave.

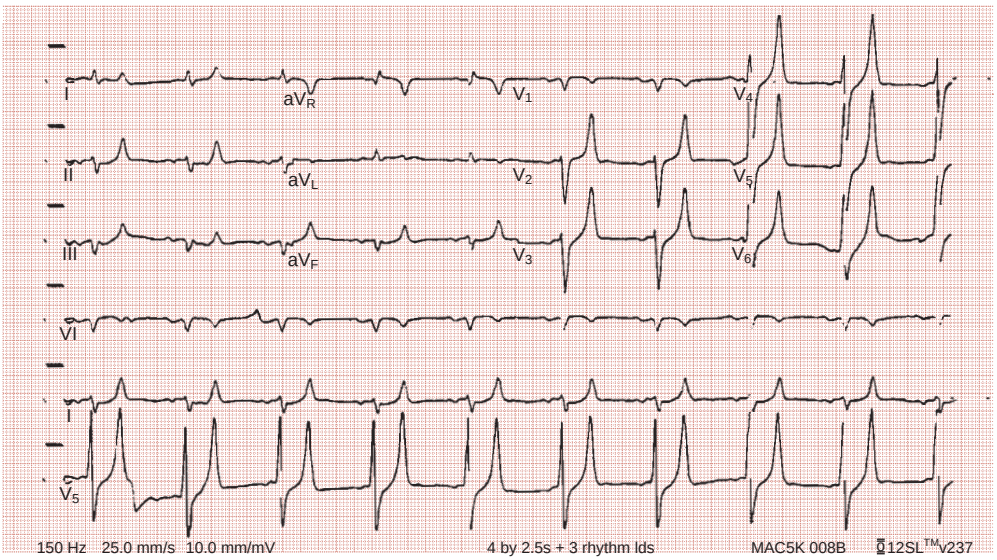

Fig. 117.2. Hyperkalemia in the same patient as in Figure 117.1 after potassium-lowering therapy has begun. Tall peaked T waves, decreased P wave.

BOX 117.1

Five Most Common Causes of Hyperkalemia

- Spurious elevation: Hemolysis due to drawing or storing of the laboratory sample or post–blood sampling leak from markedly elevated white blood cells, red blood cells, or platelets
- Renal failure: Acute or chronic
- Acidosis: Diabetic ketoacidosis (DKA), Addison's disease, adrenal insufficiency, type 4 renal tubular acidosis
- Cell death: Rhabdomyolysis, tumor lysis syndrome, massive hemolysis or transfusion, crush injury, burn
- Drugs: Beta-blockers, acute digitalis overdose, succinylcholine, angiotensin-converting enzyme inhibitors, angiotension receptor blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), spironolactone, amiloride, potassium supplementation

myocyte excitability and increasing cardiac conduction speed, thus narrowing the QRS. Calcium does not decrease serum potassium levels, and its effect is rapid (within 1 to 3 minutes), but transient (30 to 60 minutes or less). The dose is one ampule, or 10 mL of 10% calcium chloride solution. Calcium chloride is preferably administered through a central venous line due to the risk of tissue necrosis should it extravasate at the injection site. More than 10 mL of calcium gluconate will often be required, because it contains only one-third the calcium contained in calcium chloride. Calcium gluconate is preferred in pediatric cases, as well as in patients with less emergent (ie, more chronic) hyperkalemic patients, when a slow infusion is desired.

Potassium shifts intracellularly with beta$_2$-agonists, insulin, saline, and potentially sodium bicarbonate. Insulin is the most reliable agent to move potassium into cells, but beta$_2$-adrenergic receptor agonists also provide benefit in some patients. Insulin, given IV in combination with glucose to prevent hypoglycemia, also shifts potassium into cells by stimulation of the sodium-potassium adenosine triphosphatase (Na^+, K^+-ATPase) pump. The onset of action is less than 15 minutes, and the effect is maximal between 30 and 60 minutes, with a maximal drop of 0.6 mEq/L on average.

Nebulized albuterol is effective in shifting potassium into cells by stimulation of the Na^+, K^+-ATPase pump. Nebulized albuterol begins to take measurable effect after 15 minutes and lowers the serum potassium level by 0.5 to 1 mEq/L, depending on the dose. The effective dose is at least four times higher than that typically used for bronchodilation. The combination of nebulized albuterol

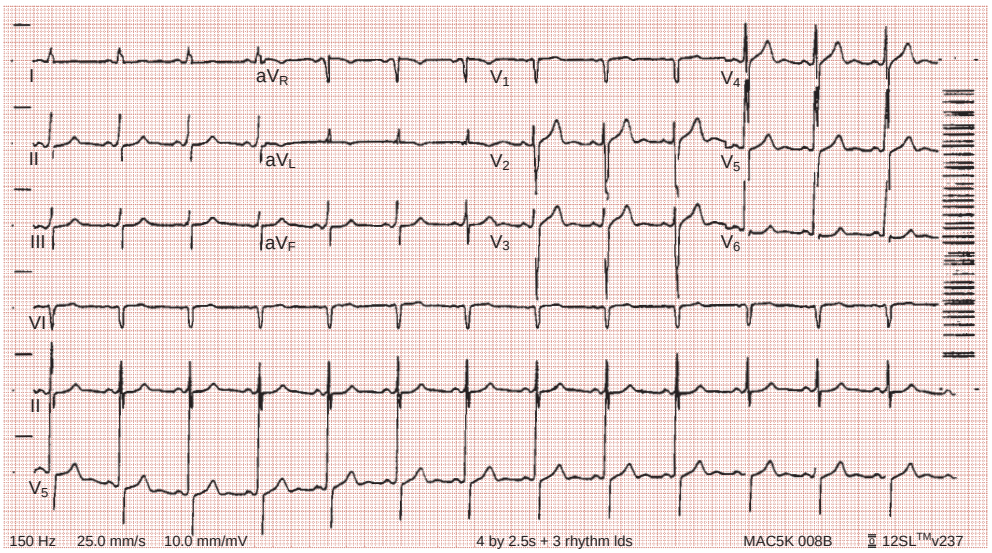

Fig. 117.3. The same patient as in Figures 117.1 and 117.2 after dialysis. The electrocardiogram (ECG) is now normal.

TABLE 117.1

Treatment of Hyperkalemia

TREATMENT	MEDICATION	FEATURES
Stabilize cardiac membrane	Calcium chloride (10 mL, maximum 20 mL) or calcium gluconate (10 to 30 mL), IV push	For wide QRS, restores the electrical gradient; does not decrease serum potassium Onset within minutes; lasts 30 to 60 minutes
Shift potassium into cells	Insulin, 10 units, IV push, combined with 100 mL of 50% dextrose, IV push High-dose nebulized albuterol by face mask (15 to 25 mg by continuous inhalation) Bicarbonate 50 to 100 mL Normal saline 100 to 250 mL	Insulin: Onset <15 minutes; maximum effect 30 to 60 minutes (~0.6 mEq/L decrease) Nebulized albuterol: Onset <15 minutes (0.5 to 1 mEq/L decrease) If severely acidotic In conjunction with nephrologist if dialysis dependent
Remove potassium from the body	Hemodialysis Normal saline and furosemide Ion exchange resin	Emergently in cardiac arrest, urgently in renal failure; may delay if renal function is normal In patients with rhabdomyolysis or tumor lysis syndrome with intact urine output, not effective acutely

IV, Intravenous.

and insulin with glucose appears to be additive, lowering serum potassium by a mean of 1.2 mEq/L.

Saline infusions also stimulate the Na^+, K^+-ATPase pump; only a few hundred milliliters is required for beneficial effects. Saline infusions should be given judiciously in anuric patients and in consultation with a nephrologist. Sodium bicarbonate is effective in hyperkalemic patients who are acidotic and has no benefit when used for hyperkalemia in non-acidotic patients. Sodium bicarbonate buffers hydrogen ions extracellularly while shifting potassium intracellularly, but it should be used in combination with other treatment options and reserved for patients with confirmed acidosis.[3]

Hemodialysis effectively and reliably decreases serum potassium levels by at least 1 mEq/L in the first hour and another 1 mEq/L during the next 2 hours. It is the only reliable method of potassium removal that has been experimentally studied and should be instituted early in the treatment of life-threatening hyperkalemia in patients with renal failure. In patients with intact renal function, medical management alone is usually sufficient, even in extreme cases, and hemodialysis may not be necessary unless multiple medical modalities fail. There are no randomized trials addressing the use of diuretics (eg, furosemide) in the emergent management of hyperkalemia; but in cases such as rhabdomyolysis or tumor lysis syndrome, it may be appropriate to use a normal saline infusion supplemented by furosemide to enhance diuresis and urinary potassium excretion. Cation exchange resins, such as sodium polystyrene sulfonate (Kayexalate), do not decrease the serum potassium level within the first 4 hours of treatment and is not effective in the acute management of hyperkalemia.[4]

Control of hyperkalemia in patients with chronic kidney disease and in those with heart failure continues to be difficult. However, two different oral medications, patiromer and sodium zirconium cyclosilicate (ZS-9), have shown clinical promise in ongoing trials to lower serum potassium levels.[5,6] ZS-9 is a highly selective cation exchanger that entraps potassium in the intestinal tract in exchange for sodium and hydrogen. Patiromer is a non-absorbed polymer that binds potassium in exchanged for calcium, predominantly in the distal colon where the concentration of free potassium is the highest.

Diabetic ketoacidosis (DKA) may result in serum hyperkalemia, although most hyperkalemic patients with DKA are actually total body deficient in potassium. In this insulin-deficient and acidotic state, serum potassium levels rise as intracellular potassium shifts out of cells. Simply treating the patient's underlying DKA will also treat the hyperkalemia. In fact, the mainstay of treatment of DKA—fluids and insulin—closely mirrors the treatment of isolated hyperkalemia.

Progressive hyperkalemia can lead to cardiopulmonary arrest due to ventricular fibrillation, pulseless electrical activity, or asystole. In a known or suspected hyperkalemic arrest, treatment should start with standard advanced cardiac life support combined with the use of multiple potassium-lowering medications.[3] Epinephrine has been shown to lower potassium by 0.25 mEq/L.[7] Calcium chloride should be given immediately by IV push, followed by insulin and glucose. Bicarbonate should be given by bolus dose if the patient is believed to be acidotic. For patients with renal failure or life-threatening hyperkalemia not responsive to the above measures, we recommend expedited transfer to an available dialysis center for emergent hemodialysis. Hemodialysis through central venous access can be used during ongoing cardiopulmonary resuscitation (CPR) to acutely lower the serum potassium level and may result in return of spontaneous circulation with intact neurologic status, despite prolonged resuscitative efforts and failure of conventional medications and defibrillation.

HYPOKALEMIA

Principles

Hypokalemia is the most common electrolyte abnormality encountered in clinical practice. More than 20% of hospitalized patients and up to 40% of outpatients on thiazide diuretics have potassium values less than 3.5 mEq/L.[8] Moderate hypokalemia is a serum level of 2.5 to 3 mEq/L; severe hypokalemia is defined as a level less than 2.5 mEq/L. Although hypokalemia is usually asymptomatic, due to potassium's effect on the heart and muscle, very low levels can result in severe cardiac dysrhythmias or rhabdomyolysis respectively.[9] Hypokalemia is often seen in association with hypomagnesemia, and patients with low serum potassium levels should be assumed to be hypomagnesemic also.

The five most common causes of hypokalemia are renal losses, increased nonrenal losses, decreased potassium intake, intracellular shift, and endocrine etiologies (Box 117.2). Increased excretion of potassium, especially coupled with poor intake, is the most common cause of hypokalemia, and patients receiving diuretics represent the single most common patient group encountered in clinical practice. Thiazide diuretics are more likely than loop or osmotic diuretics to cause hypokalemia, but both the thiazide and loop diuretics block chloride-associated sodium and increase delivery of sodium to the collecting tubules. Hypokalemia is a common adverse effect of treatment with diuretics and may cause fatal arrhythmias and increase the risk of digitalis toxicity.[10] In addition to diuretics, other drugs and disorders can cause significant renal potassium losses, including hyperaldosteronism, steroid excess, metabolic acidosis, DKA, renal tubular acidosis, and alcohol consumption. When given in large doses, penicillin and its synthetic derivatives promote renal potassium excretion by increasing sodium delivery to the distal nephron. Individuals with secondary hyperaldosteronism, whether due to congestive heart failure (CHF), hepatic insufficiency, or nephrotic syndrome, may also exhibit hypokalemia. Patients with renal tubular acidosis can become hypokalemic, because a defect in the distal tubule leads to increased potassium excretion.

Administration of insulin may cause a reduction in serum potassium because of insulin's ability to stimulate the Na^+, K^+-ATPase pump and move potassium intracellularly; hypokalemia can be a dangerous complication with intentional overdoses of insulin or during treatment of DKA. Although most patients with DKA present with high-normal or mildly elevated serum potassium levels, patients are usually 2 to 3 mEq/kg deficient in total body potassium. To avoid hypokalemic arrhythmias or cardiac arrest from hypokalemia, a potassium infusion should be started once significant hyperkalemia has been ruled out and intact renal function confirmed.

Hypokalemia can also occur from gastrointestinal and dermal losses. In diarrheal states, large quantities of potassium can be lost in the stool, with consequent secondary hyperaldosteronism. Large doses of laxatives and repeated enemas also cause excessive potassium loss in the stool. Although hypokalemia is often seen after protracted vomiting or nasogastric suctions, only 5 to 10 mEq/L of potassium is lost in gastric fluid. Hypokalemia in this setting is secondary to metabolic alkalosis, chloride losses, and hyperaldosteronism. On occasion, excessive sweating can lead to hypokalemia from potassium losses through the skin. Patients with extensive burns can also suffer from hypokalemia because of significant skin losses. Dietary potassium deficiency should be considered in the severely malnourished patient or chronic alcoholic. Poor potassium intake combined with increased nonrenal losses can result in severe hypokalemia.

Hypokalemia can also result from an acute shift of potassium from the extracellular compartment into cells, most commonly in patients with metabolic alkalosis or hyperventilation, and in patients taking medications such as beta-agonists or decongestants. Stimulation of beta-receptors can lead to hypokalemia, especially in patients using repetitive and high doses of beta-agonists for chronic obstructive pulmonary disease or asthma. A standard dose of nebulized albuterol reduces serum potassium by 0.2 to 0.4 mEq/L, and a second dose taken within 1 hour can reduce it by almost 1 mEq/L. Patients with starvation or near-starvation may develop hypokalemia when fed, as insulin secretion and increased cellular uptake can cause an acute exaggerated intracellular migration of potassium.

BOX 117.2

Five Most Common Causes of Hypokalemia

- Renal losses: Diuretic use, drugs, steroid use, metabolic acidosis, hyperaldosteronism, renal tubular acidosis, diabetic ketoacidosis (DKA), alcohol consumption
- Increased nonrenal losses: Sweating, diarrhea, vomiting, laxative use
- Decreased intake: Ethanol, malnutrition
- Intracellular shift: Hyperventilation, metabolic alkalosis, drugs
- Endocrine: Cushing's disease, Bartter's syndrome, insulin therapy

Clinical Features

Hypokalemia is usually asymptomatic but can present with nonspecific complaints, primarily weakness and muscle pain.[11] Although short periods of mild potassium depletion are typically well tolerated in healthy individuals, severe potassium depletion can result in serious cardiovascular instability, neurologic dysfunction, glucose intolerance, gastrointestinal symptoms, and renal failure, as well as affect the acid-base balance in the body.[11] The likelihood of symptoms appears to correlate with the rapidity of the decrease in serum potassium.

In patients without underlying heart disease, abnormalities in cardiac conduction are extremely unusual, even when the serum potassium concentration is below 3.0 mEq/L. Paresthesias, depressed deep tendon reflexes, fasciculations, muscle weakness,

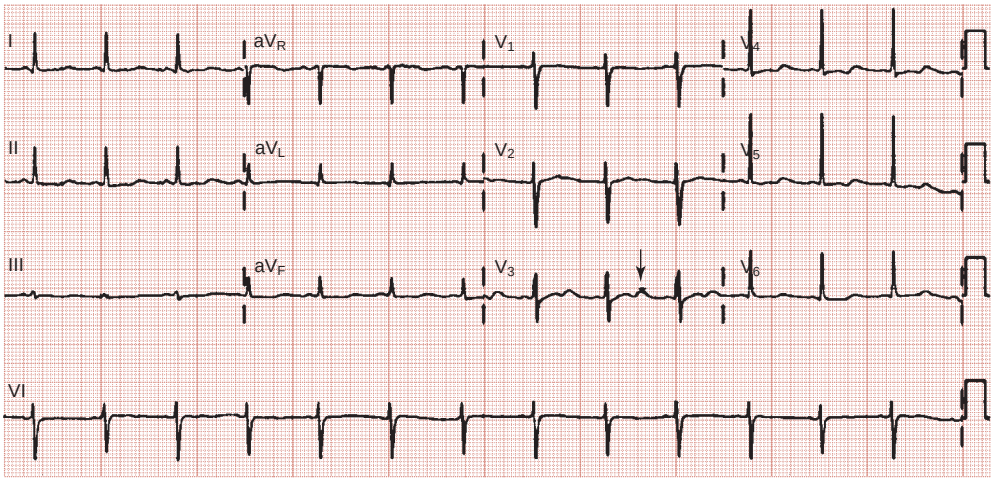

Fig. 117.4. Hypokalemic electrocardiographic changes, including flattened T wave, prolonged QT interval, nonspecific ST changes, and prominent U wave *(arrow)*.

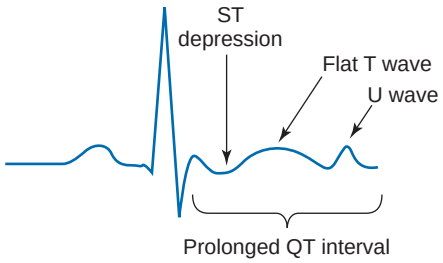

Fig. 117.5. Electrocardiographic changes in hypokalemia.

and confusion can occur when the serum potassium level is less than 2.5 mEq/L. However, in patients with cardiac ischemia or heart failure, even mild to moderate hypokalemia increases the likelihood of cardiac arrhythmias secondary to potassium's effect on the action potential. Hypokalemia is an independent risk factor contributing to reduced survival of cardiac patients and increased incidence of arrhythmic death. On the basis of available evidence, serum potassium concentrations should be maintained above 4.5 mEq/L in patients having an acute myocardial infarction. Hypokalemic patients can demonstrate first- and second-degree heart block, atrial fibrillation, ventricular fibrillation, and asystole. Life-threatening cardiac arrhythmias are managed by restoration of serum potassium levels into the normal range. Hypokalemic periodic paralysis is a rare disorder characterized by episodes of muscle weakness, potentially fatal when involvement includes respiratory muscles.

Diagnostic Testing

Hypokalemia is rarely diagnosed on clinical presentation alone and is typically made by measurement of the serum potassium concentration during routine laboratory studies. If there is any suspicion for hypokalemia or a patient presents with generalized weakness, palpitations, or arrhythmias, an ECG should be obtained. Just as tall-peaked T waves are characteristic of hyperkalemia, flattened T waves can be seen in hypokalemia. Hypokalemia may produce U waves, which are small deflections after the T wave (Figs. 117.4 and 117.5). Hypokalemia may also cause a dangerously prolonged QT interval. Although there is no threshold of QT prolongation at which torsades de pointes is certain to occur, once the QT interval becomes longer than 500 milliseconds, the risk torsades de pointes increases twofold to threefold.[12] Hypokalemia is also notorious for causing nonspecific ST and T wave changes. In addition, prolonged potassium depletion of even modest proportion can provoke or exacerbate kidney injury or hypertension. A severe degree of hypokalemia with paralysis is a potentially life-threatening medical emergency and may be seen as levels drop below 2.0 mEq/L.

Management

Because potassium is an intracellular cation; a low serum potassium level almost always reflects a significant total body potassium deficit; each 0.3 mEq potassium drop below normal correlates with an approximately 100 mEq total body deficit. In the absence of nausea or vomiting as the cause of their hypokalemia, patients with mild or moderate hypokalemia may only need oral potassium replacement therapy. Oral replacement is available in liquid, powder, and tablet form. Potassium chloride is the most commonly used supplementation, and 40 to 60 mEq orally every 2 to 4 hours is typically well tolerated. If the cause of hypokalemia is not clear, or the hypokalemia is severe and associated with profound weakness, obtain a spot urine potassium level before starting therapy to assess whether the patient's kidneys are inappropriately wasting potassium from a renal or endocrine cause.

Treatment of hypokalemia is essential in multiple populations of patients. Hypokalemia is arrhythmogenic, especially in the settings of acute myocardial infarction, high catecholamine states, and hypertrophied or dilated ventricles. Hypokalemia is an important independent risk factor for morbidity and mortality in patients with heart failure, requiring serum potassium levels to between 4.0 and 5.0 mEq/L in this population.

If IV infusion is necessary, potassium chloride can be safely given at a rate of 10 to 20 mEq/hr. In the rare instance when IV repletion is planned at more than 20 mEq/hr, the patient should have continuous cardiac monitoring and central line access established.

Hypokalemia is associated with hypomagnesemia, and the severity of the hypokalemia correlates with a similar degree of hypomagnesemia. Magnesium replacement should usually accompany potassium repletion.[12a] Unless the patient receives at least 0.5 g/hr of magnesium sulfate along with potassium replacement, potassium will not move intracellularly and the patient will lose potassium through excretion. Correction of large potassium deficits may require several days, with simultaneous oral and IV replacement.

HYPERNATREMIA

Principles

Hypernatremia is defined as a serum sodium concentration above 145 mEq/ L. It is rarely seen in previously healthy patients and usually portends a poor prognosis. Most hypernatremic patients have either an impaired sense of thirst or no access to water: elders, infants, patients with mental impairment, and those who are intubated and paralyzed are at highest risk for this disorder. Hypernatremia can be divided into three physiologic pairings: (1) hypernatremia with dehydration and low total body sodium, (2) hypernatremia with low total body water and normal total body sodium, and (3) hypernatremia with increased total body sodium (Box 117.3). Diabetes insipidus, an insufficient production of (or lack of response to) antidiuretic hormone, can lead to life-threatening hypernatremia (Box 117.4).

Clinical Features

Patients often have multiple causes of severe hypernatremia. Hypernatremia in adults is almost exclusively due to a free water deficit and should be considered in any patient presenting with altered mental status—individuals with severe mental retardation, cerebral palsy, and head injury, as well as in bed-ridden patients with no access to water. Patients with impaired antidiuretic hormone function may complain of polyuria or polydipsia. Others may have obvious causes of extrarenal fluid losses, while some may have no complaints at all.

Diagnostic Testing

In addition to routine serum chemistries, serum osmolarity and urine sodium concentration and osmolality should be obtained. The degree of hypernatremia almost always equals the total body water (TBW) deficit in adults. The patient's TBW deficit can be estimated by the formula

$$\text{TBW deficit} = \text{TBW} \times (\text{serum } Na^+/140) - 1$$

A patient's TBW is calculated by multiplying the patient's body weight in kilograms times 0.6. However, because of percentage body fat differences based on the age and sex of the patient, it is more accurate to use the correction factors listed in Table 117.2.

Management

The treatment of hypernatremia has three interdependent goals: first, to quickly correct underlying shock, hypoperfusion, or significant hypovolemia with normal saline; second, to treat the underlying cause of hypernatremia, such as fever, vomiting, or diabetes insipidus; and third, to carefully lower the serum sodium level, usually by replacement of the body's total water deficit. Until hypoperfusion and hypovolemia are corrected, homeostatic mechanisms for sodium balance will promote sodium resorption to maintain intravascular volume, even at the expense of the serum sodium concentration.

The rate of correction in hypernatremia is extremely important to minimize morbidity and mortality. Both too quick and too slow

BOX 117.3

Three Types of Hypernatremia

HYPERNATREMIA WITH DEHYDRATION AND LOW TOTAL BODY SODIUM
Heatstroke
Increased insensible losses: Burns, sweating
Gastrointestinal loss: Diarrhea, protracted vomiting, continuous gastrointestinal suction
Osmotic diuresis: Glucose, mannitol, enteral feeding

HYPERNATREMIA WITH LOW TOTAL BODY WATER AND NORMAL TOTAL BODY SODIUM
Diabetes insipidus
Neurogenic
Elderly with "reset" osmostat
Hypothalamic dysfunction
Suprasellar or infrasellar tumors
Renal disease
Drugs (amphotericin, phenytoin, lithium, aminoglycosides, methoxyflurane)
Sickle cell disease

HYPERNATREMIA WITH INCREASED TOTAL BODY SODIUM
Salt tablet ingestion
Salt water ingestion
Saline infusions
Saline enemas
IV sodium bicarbonate
Poorly diluted interval feedings
Primary hyperaldosteronism
Hemodialysis
Cushing's syndrome
Conn's syndrome

IV, Intravenous.

BOX 117.4

More Common Causes of Diabetes Insipidus

CENTRAL
Idiopathic
Familial disease
Cancer
Hypoxic encephalopathy
Infiltrative disorders
Post supraventricular tachycardia
Anorexia nervosa

NEPHROGENIC
Chronic renal insufficiency
Polycystic kidney disease
Lithium toxicity[a]
Hypercalcemia
Hypokalemia
Tubulointerstitial disease
Hereditary
Sickle cell disease

[a]Andreasen A, Ellingrod VL: Lithium-induced diabetes insipidus: Prevention and management. Current Psychiatry 12(7):42, 2013.

TABLE 117.2

Calculation of Body Water

POPULATION	TOTAL BODY WATER
Children and adult men	Body weight (kg) × 0.6
Adult women	Body weight (kg) × 0.5
Elderly men	Body weight (kg) × 0.5
Elderly women	Body weight (kg) × 0.45

correction speeds are associated with an increased risk of death, regardless of the initial sodium level.[13] In adult patients who develop hypernatremia over a short time as a result of sodium loading, "rapid correction" at a 1 to 2 mEq/hr decrease in serum sodium appears relatively safe.[14] However, most adult patients develop hypernatremia over days to weeks. In this group of patients, serum sodium concentration should be corrected slowly, at no more than 0.5 mEq/hr or 10 to 12 mEq/day.

Normal saline should be started for volume replacement until the patient is hemodynamically stable, and then changed to half-normal saline at 100 mL/hr once vital signs have normalized. The treatment of central diabetes insipidus with desmopressin (DDAVP) is an effective means of improving polyuria and hypernatremia; initial doses in the acute setting range from 1 to 2 µg.

HYPONATREMIA

Principles

Hyponatremia, defined as serum sodium concentration of less than 135 mEq/L, is the second most common electrolyte abnormality encountered in clinical practice and can be a marker of underlying disease. The most common cause of severe hyponatremia in adults are therapy with thiazides, the postoperative state the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), psychogenic polydipsia, exercise-associated hyponatremia, and unintentional water intoxication. Gastrointestinal fluid loss, ingestion of overly dilute formula, accidental ingestion of excessive water, and receipt of multiple tap water enemas are the main causes of severe hyponatremia in infants and children. Most patients presenting to the emergency department (ED) with hyponatremia are asymptomatic and do not require emergent therapy. If symptoms are present, they are typically based on the degree of hyponatremia and how acutely the hyponatremia developed. Symptoms range from headache, nausea, and vomiting to confusion, seizures, and coma. There are two groups of hyponatremic patients that will require treatment with either normal saline or hypertonic saline: (1) severe but asymptomatic hyponatremia with a sodium level of 110 mEq/L or less and (2) acute symptomatic hyponatremia with a sodium level below 120 mEq/L.

Central nervous system (CNS) damage due to hyponatremia may be caused by cerebral edema and increased intracranial pressure, by osmotic fluid shifts during overly aggressive treatment, or by both. When neurons are subjected to a hyponatremic environment, they become depleted of sodium and potassium in an attempt to limit their own osmolarity to prevent intracellular fluid shifts that would lead to cerebral edema. If fluid therapy raises extracellular sodium levels too quickly, fluids shift out of neurons and can cause diffuse demyelination. This can result in a flaccid paralysis and death due to central pontine myelinolysis, a syndrome more accurately labeled as the *osmotic demyelinating syndrome (ODS)*.[15]

Causes of hyponatremia fall into four general categories: pseudohyponatremia, hyponatremia with dehydration and decreased extracellular volume, hyponatremia with increased extracellular volume, and euvolemic hyponatremia with increased TBW (Box 117.5).

BOX 117.5

Causes of Hyponatremia

PSEUDOHYPONATREMIA
Hyperlipidemia
Hyperproteinemia (multiple myeloma, macroglobulinemia)

DILUTIONAL
Hyperglycemia*

HYPOVOLEMIC HYPONATREMIA: DECREASED TOTAL BODY WATER AND SODIUM, WITH A RELATIVELY GREATER DECREASE IN SODIUM
Body fluid losses: Sweating, vomiting, diarrhea, gastrointestinal suction
Third spacing: Bowel obstruction, burns, pancreatitis, rhabdomyolysis
Renal causes: Diuretics, mineralocorticoid deficiency, osmotic diuresis, renal tubular acidosis, salt-wasting nephropathies

HYPERVOLEMIC HYPONATREMIA: INCREASED TOTAL BODY SODIUM WITH A RELATIVELY GREATER INCREASE IN TOTAL BODY WATER
Heart failure
Chronic renal failure
Hepatic failure or cirrhosis

EUVOLEMIC HYPONATREMIA: INCREASED TOTAL BODY WATER WITH NEARLY NORMAL TOTAL BODY SODIUM
SIADH
Drugs causing SIADH (diuretics, barbiturates, carbamazepine, chlorpropamide, clofibrate, opioids, tolbutamide, vincristine)
Psychogenic polydipsia
Beer potomania
Hypothyroidism
Adrenal insufficiency
MDMA (ecstasy)
Accidental or intentional water intoxication

*Hyperglycemia is referred by some as pseudohyponatremia, but hyperglycemia is actually a dilutional hyponatremia.
MDMA, N-methyl-3,4-methylenedioxyamphetamine; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone.

Pseudohyponatremia

Pseudohyponatremia is a falsely low sodium reading caused by the presence of other osmolar particles in the serum. The phenomenon of pseudohyponatremia is explained by the increased percentage of large molecular particles that do not contribute to plasma osmolality relative to sodium. Severe hypertriglyceridemia and hyperproteinemia are two common causes of this condition. Blood draw or laboratory error should also be considered as a possible cause of hyponatremia, especially if the blood sample was drawn near an infusion site using 5% dextrose in water (D_5W) when a very abnormal sodium level is reported in an otherwise healthy patient

Hyperglycemia is sometimes considered a cause of pseudohyponatremia; however, it actually causes a dilutional hyponatremia by pulling water into the vascular space through osmosis. In true pseudohyponatremia, serum osmolality is normal and no shifts of water occur. Two different formulas based on the degree of a patient's hyperglycemia are currently used to correct serum sodium levels. The most commonly recommended formula advocates for the addition of 1.6 mEq/L to the measured sodium for every 100 mg/dL of glucose above 100. However, another acceptable formula recommends use of 2.4 mEq as the correction factor because glucose values above 400 mg/dL may lower sodium values by 4 mEq/L per each 100 mg/dL of glucose rise.[14] Either formula is acceptable to use, the key concept being that as glucose levels rise significantly, a "normal" serum sodium is distinctly abnormal.

Hypovolemic Hyponatremia

Hypovolemic hyponatremia, or hyponatremia with dehydration, occurs when there is decreased extracellular volume combined with an even greater loss of sodium. Hyponatremia secondary to

body fluid losses should be differentiated from that due to renal losses. Hyponatremia with dehydration due to body fluid losses includes sweating, vomiting, diarrhea, and gastrointestinal suction. Hypovolemic hyponatremia is also seen with "third spacing" in bowel obstruction, burns, and intra-abdominal sepsis. Hypovolemic hyponatremia due to renal causes includes diuretic use, mineralocorticoid deficiency, renal tubular acidosis, and salt-wasting nephropathy. Hypovolemic hyponatremia can be further exacerbated when fluid losses are replaced with hypotonic saline.

Hypervolemic Hyponatremia

Hypervolemic hyponatremia, or hyponatremia with increased extracellular volume, occurs when sodium and water are retained, but water retention exceeds sodium retention. Most of these patients present with edema. Hyponatremia with increased total body sodium occurs in patients with heart failure, chronic renal failure, and hepatic failure. The fluid retention in these states is secondary to renal hypoperfusion, resulting in increased aldosterone secretion and a decrease in free water excretion.

Euvolemic Hyponatremia

The final category of hyponatremia is one in which patients are euvolemic but have increased TBW. Causes of this type of hyponatremia include SIADH, psychogenic polydipsia beer potomania, hypothyroidism, diuretic use in patients with mild CHF, and accidental or intentional water intoxication. Euvolemic hyponatremia has also been described in patients after the use of the recreational drug *N*-methyl-3,4-methylenedioxyamphetamine (MDMA; or ecstasy). MDMA-induced hyponatremia is multifactorial and related to increased free water intake to avoid dehydration and rhabdomyolysis, along with the tendency to be very active while using the drug, leading to sweating and antidiuretic hormone secretion.[16] For similar reasons, there are extensive case reports of significant exercise-associated hyponatremia in endurance athletes.

SIADH is an important cause of hyponatremia that occurs when antidiuretic hormone is secreted independent of the body's need to conserve water. The process results from excess antidiuretic hormone production that increases TBW, causing the serum sodium to decrease. Patients with SIADH inappropriately concentrate their urine, despite a low serum osmolality and normal circulating blood volume. Despite excess TBW, they have no signs of edema, ascites, or heart failure, because most of the increased water is intracellular rather than intravascular. The three most common causes of SIADH are (1) pulmonary lung masses and infections, (2) CNS disorders, and (3) drugs (Box 117.6). Lung cancers (especially small cell cancer), pneumonia, and tuberculosis can lead to SIADH. CNS infections, masses, and psychosis can also cause SIADH. A large number of medications are associated with SIADH, the most common of which are thiazide diuretics, narcotics, lithium, oral hypoglycemics, barbiturates, and antineoplastics. The mainstay of treatment of most patients with SIADH and other causes of euvolemic hyponatremia is free water restriction.

Diagnostic Testing

A spot urinary sodium or urinary chloride level can help determine if hyponatremia is renal in origin (Table 117.3). Patients with hypovolemic hyponatremia due to nonrenal causes typically have a low urinary sodium or chloride level (<20 mEq/L), because they try to retain solute. Patients with hypovolemic hyponatremia due to renal causes will have elevated urine sodium and chloride levels (>20 mEq/L), because their kidneys cannot retain sodium or chloride. Patients with euvolemic hyponatremia typically have a urinary sodium concentration more than 20 mEq/L secondary to volume expansion caused by water retention. Patients with psychogenic polydipsia who are ingesting large quantities of water will try to diurese and have dilute urine with low quantities of urinary sodium. Patients with hypervolemic hyponatremia secondary to CHF or cirrhosis have urine sodium levels of less than 20 mEq/L because of renal hypoperfusion, whereas those with

BOX 117.6

Three Most Common Causes of Syndrome of Inappropriate Secretion of Antidiuretic Hormone

LUNG MASSES
Cancer (especially small cell)
Pneumonia
Tuberculosis
Abscess

CENTRAL NERVOUS SYSTEM DISORDERS
Infection (meningitis, brain abscess)
Mass (subdural, postoperative, cerebrovascular accident)
Psychosis (with psychogenic polydipsia)

DRUGS
Thiazide diuretics
Narcotics
Oral hypoglycemic agents
Barbiturates
Antineoplastics

TABLE 117.3

Spot Urine Interpretation

	HYPOVOLEMIC HYPONATREMIA	HYPOVOLEMIC HYPONATREMIA	EUVOLEMIC HYPONATREMIA	EUVOLEMIC HYPONATREMIA	HYPERVOLEMIC HYPONATREMIA	HYPERVOLEMIC HYPONATREMIA
Underlying etiologies	Non-renal causes	Renal causes	SIADH, endocrinopathies	Psychogenic polydipsia	Edematous disorders: eg, CHF, cirrhosis	Renal failure
Urinary sodium	<20 mEq/L	>20 mEq/L	>20 mEq/L	<20 mEq/L	<20 mEq/L	>20 mEq/L
Mechanism	Extrarenal solute loss	Renal solute loss	Volume expansion	Normal renal response to excess volume and sodium retention	Renal hypoperfusion	Renal solute loss

CHF, Congestive heart failure; *SIADH,* syndrome of inappropriate antidiuretic hormone secretion.

renal causes of hypervolemic hyponatremia or with SIADH have sodium levels more than 20 mEq/L, because their kidneys do not retain sodium. In interpreting serum sodium levels, consider the possibility of sampling error if the reported value does not seem consistent with the patient's presentation and confirm that a diuretic such as furosemide, which will increase urinary sodium losses, has not been recently administered. Consider adrenal insufficiency when a dehydrated patient has both hyponatremia and hyperkalemia.

Clinical Features

The signs and symptoms of hyponatremia worsen as sodium levels decline and also correlate with how rapid hyponatremia develops. Nonspecific signs of hyponatremia include anorexia, nausea, vomiting, and generalized weakness. Acutely hyponatremic patients whose sodium level drops below 120 mEq/L over 24 to 48 hours may present with severe neurologic findings, including confusion, seizures, coma, and brainstem herniation. Determination of the hydration status of the patient may help establish the etiology of the hyponatremia and direct subsequent treatment. *Hypovolemic* hyponatremia is more likely in the patient with diminished skin turgor, increased capillary refill, dry mucous membranes, and orthostasis, while the patient with jugular venous distention, peripheral edema, or pulmonary congestion is much more likely to have *hypervolemic* hyponatremia. Patients with SIADH will have no edema and normal skin turgor. Of note, in geriatric patients, the risk of hyponatremia doubles for those presenting with large-bone fractures.

Management

Treatment of hyponatremia is guided by the patient's clinical presentation, severity of symptoms, estimated duration of illness, fluid status, and underlying cause of the sodium disturbance. Typically, sodium should be corrected during a time course of 48 to 72 hours. The neurological changes, including flaccid paralysis, dysarthria, dysphagia, and hypotension, associated with overly rapid sodium correction are referred to as *osmotic demyelinating syndrome (ODS),* previously termed *central pontine myelinolysis.* Most ODS cases occur in the alcoholic, malnourished, and elder population, although this devastating side effect can occur in young healthy patients as well. If a patient develops symptoms of ODS during therapy, all sodium-containing fluids should be stopped and D_5W administered immediately to temporarily lower sodium values. Most patients presenting to the ED with hyponatremia are stable and require no emergent therapy. However, patients who have serum sodium levels of significantly less than 120 mEq/L and those who have acute alterations in mental status, seizures, or new focal findings due to hyponatremia need immediate intervention. Table 117.4 presents the sodium concentration of various infusates, and the following equation is helpful to estimate the effect of 1 liter of any infusate on serum sodium:

$$\text{Change in serum } Na^+ = \text{infusate } Na^+ - \text{serum } Na^+ / TBW + 1$$

There is no consensus regarding the optimal treatment of symptomatic hyponatremia. However, there is agreement that correction should occur at a sufficient pace and magnitude to reverse the manifestations of hypotonicity but not be so rapid as to pose a risk for development of ODS.[15,17] For relatively asymptomatic patients with sodium values of 115 to 135 mEq/L, free water restriction is typically the single most important treatment.

In more severe cases when the sodium value is 120 mEq/L or less and the patient has alterations in mental status, has focal findings, or is seizing, 3% hypertonic saline (513 mEq/L of sodium) is indicated.[18,19] Correction of hyponatremia by 4 to 6 mEq/L within 6 hours, with bolus infusions of 3% saline if necessary, is sufficient to manage the most severe manifestations of hyponatremia. Initially, 100 mL of 3% hypertonic saline should be infused over 10 minutes. If a second bolus is required, an additional 100 mL of the 3% solution may be administered during the next 50 minutes. To minimize the likelihood of ODS, it is essential that symptomatic patients with severe hyponatremia have serum sodium levels raised slowly. Previous guidelines have endorsed the safety of raising the serum sodium by up to 10 to 12 mEq within the first 24 hours. However, in patients believed to have been hyponatremic for more than 48 hours, severe hyponatremia should be corrected by no more than 8 mEq in the first 24 hours.[20,20a]

Potassium deficits should be replaced aggressively in the treatment of hyponatremic patients with a sodium disorder. If patients are retaining volume and diuresis is not adequate, furosemide can be used; D_5W is infused if the sodium level is rising too quickly.[18] Patients may be able to make full neurologic recoveries from ODS with the reinduction of hyponatremia in these extreme cases. Demeclocycline in a dosage of 600 to 1200 mg daily is effective in patients with refractory hyponatremia.

TABLE 117.4

Characteristics of Infusates

INFUSATE	INFUSATE SODIUM (mmol/L)	EXTRACELLULAR FLUID DISTRIBUTION (%)
3% Hypertonic saline	513	100
0.9% Normal saline solution	154	100
Lactated Ringer's solution	130	97
Half-normal saline solution	77	73
0.2% Sodium chloride + D_5W	34	55
D_5W	0	45

D_5W, 5% dextrose in water.

Hypovolemic Hyponatremia

Treatment of hypovolemic hyponatremia begins with rehydration. Hypotensive, dehydrated patients should be volume resuscitated with normal saline. Once the patient is hemodynamically stable, the infusion rate should be slowed. Typically, normal saline is started at 500 to 1000 mL/hr until the blood pressure is stable and then slowed to 200 mL/hr with frequent sodium checks. If the sodium value is below 120 mEq/L, the sodium concentration should be allowed to rise only by an average of 0.5 mEq/hr or 10 to 12 mEq/day.[19] The underlying cause of hyponatremia should be identified and treated.

Hypervolemic Hyponatremia

Normal saline and hypertonic saline can cause pulmonary edema in the hypervolemic hyponatremic patient. Restriction of fluid and sodium is the preferred treatment, although loop diuretics can be used in severe cases. Hemodialysis is an alternative in patients with renal impairment and should be considered for significantly hyponatremic renal failure patients with volume overload. Patients with CHF will usually benefit from diuretics that will increase water excretion and cause vasodilation to improve cardiac output.[21] In patients with liver failure, albumin is a consideration, along with diuretics and possibly paracentesis to improve the underlying pathologic process. Water restriction

may make the largest impact on the long-term care of these patients.

Euvolemic Hyponatremia

The mainstay of treatment of euvolemic hyponatremia is free water restriction, as hypo-osmolality in SIADH results from a relative abundance of water in the intracellular and extracellular spaces, maintained by a reduced ability to excrete water. However, water restriction is insufficient to treat acute severe hyponatremia and is not recommended as a sole intervention for patients requiring more rapid correction based on clinical presentation. The only definitive treatment of SIADH is elimination of its underlying cause. Most cases of SIADH caused by malignant disease resolve with effective antineoplastic therapy; most due to medication resolve promptly when the offending agent is discontinued.

In patients with SIADH, normal saline may cause the serum sodium concentration to fall even more as free water is retained and hypertonic urine is excreted. If a patient is symptomatic because of a rapid decrease in serum sodium concentration, treatment with hypertonic saline is recommended. Rapid correction of hyponatremia may occur during hemodialysis. To minimize the risks of ODS, hemodialysis is reserved for patients with documented renal failure under close monitoring. Vaptans, which are oral agents that inhibit the effects of vasopressin, have been studied for treatment of patients with hyponatremia due to SIADH but need further evaluation before becoming standard of care.[18,22]

HYPERCALCEMIA

Principles

Hypercalcemia is usually defined as a serum calcium level above 10.5 mg/dL; normal levels are usually defined as between 9 and 10.5 mg/dL. Hypercalcemia is considered mild if the total serum calcium level is between 10.5 and 12 mg/dL; levels higher than 14 mg/dL can be life-threatening. Hypercalcemic crisis typically evolves from preexisting mild hypercalcemia, which develops into an acute severe hypercalcemic emergency.

There are five major causes of hypercalcemia (Box 117.7). Hyperparathyroidism is the most common cause of hypercalcemia in outpatients, whereas malignancy is the most common cause in hospitalized patients; together, these two etiologies account for 80% of hypercalcemia cases.[22a] Mild hypercalcemia, in an otherwise normal person, may be due to thiazide diuretics in the setting of minimal dehydration. Other less common causes of elevated calcium concentration should be considered after malignant disease and parathyroid disease are ruled out. Malignancy-associated hypercalcemia occurs in up to 10% of all patients with advanced cancer and generally conveys a poor prognosis. Other causes of hypercalcemia include granulomatous disease, such as sarcoidosis and tuberculosis; medications and pharmacologic agents; and a number of diverse conditions, such as rhabdomyolysis and prolonged immobilization.

BOX 117.7

Five Most Common Causes of Hypercalcemia

MALIGNANT DISEASE
Ectopic secretions of parathyroid hormone, multiple myeloma, cancer metastatic to bone
Most common: Breast, lung, hematologic, kidney, prostate

ENDOCRINE
Hyperparathyroidism, multiple endocrine neoplasias, hyperthyroidism, pheochromocytoma, adrenal insufficiency

GRANULOMATOUS DISEASE
Sarcoidosis, tuberculosis, histoplasmosis, berylliosis, coccidioidomycosis

PHARMACOLOGIC AGENTS
Vitamins A and D, thiazide diuretics, estrogens, milk-alkali syndrome

MISCELLANEOUS
Dehydration, prolonged immobilization, iatrogenic, rhabdomyolysis, familial, laboratory error

Clinical Features

The clinical presentation of hypercalcemia is often vague and nonspecific. Symptoms include nonfocal abdominal pain, constipation, fatigue, body aches, anorexia, polydipsia, polyuria, nausea, and vomiting. Symptom severity depends on the degree of hypercalcemia, the rapidity of onset, and the patient's baseline neurologic and renal function. Neuropsychiatric disturbances include anxiety, depression, and hallucinations. The CNS manifestations that often predominate in more severe cases include lethargy, altered mental status, seizures, and coma. Death due to hypercalcemia is usually related to complications caused by coma, dehydration, or electrolyte disturbances. Cardiac conduction abnormalities may occur; bradydysrhythmias are the most common. Severe hypercalcemia (>14 mg/dL) has also been associated with sinus arrest, atrioventricular block, atrial fibrillation, and ventricular tachycardia.

Diagnostic Testing

The diagnostic evaluation of a patient with suspected hypercalcemia begins with obtaining of electrolyte and renal function tests and an ECG. Calcium is measured by determination of either a total serum calcium level or an ionized calcium level. Ionized calcium is the active form of the total calcium level. Ionized calcium is more accurate in the diagnosis and treatment of hypocalcemia but does need to be routinely evaluated in hypercalcemia. The serum total calcium level represents both bound and unbound calcium and, thus, should be corrected on the basis of the albumin concentration. The adjustment to serum albumin is accomplished by adding or subtracting 0.08 mg/dL to the measured total serum calcium for every 1.0 g/L of albumin below or above 4 g/L albumin, respectively.

A short QT interval can be seen in hypercalcemia and is considered a classic finding. However, although the incidence and duration of QT shortening appear to be correlated with the degree of hypercalcemia, it is not a reliable finding and is not routinely seen in most patients (Fig. 117.6.). ST segment elevation may be the least well documented but most consistent electrocardiographic finding, making hypercalcemia aa potential cause of ST segment elevation caused by conditions other than myocardial infarction.[23] In severe cases of hypercalcemia, sinus bradycardia, bundle branch block, and high-degree atrioventricular block may also been seen.

Management

Patients in hypercalcemic crisis are usually dehydrated, often obtunded, and also predisposed to arrhythmias as a result of concomitant electrolyte disturbances; thus, they require IV access with a normal saline infusion and close monitoring. Normal saline will inhibit proximal tubule reabsorption of calcium and correct the patient's volume depletion. Normal saline should be infused "wide open" until blood pressure and perfusion are

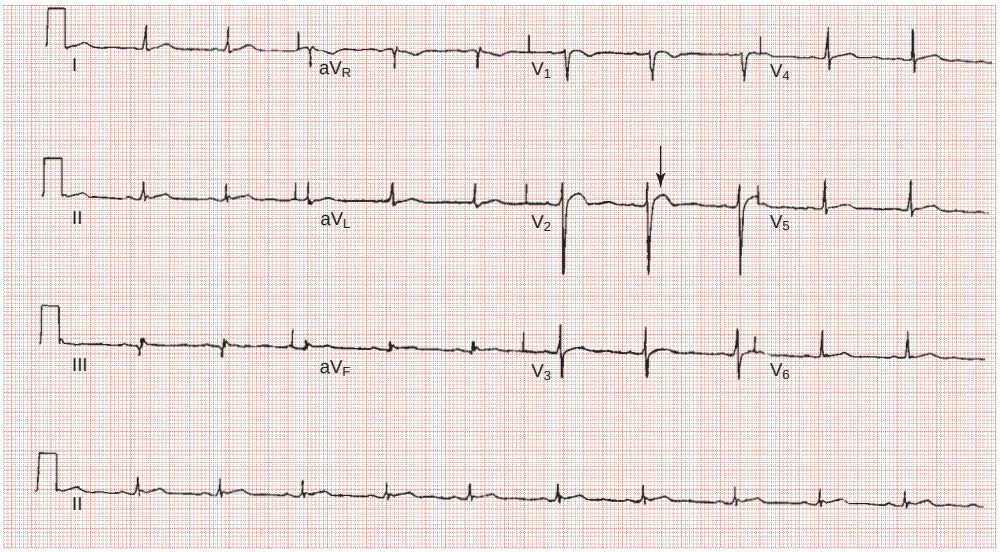

Fig. 117.6. Short QT interval *(arrow)* in a patient with multiple myeloma and a calcium level of 14.2 mg/dL. (Courtesy Dr. Barton Campbell.)

normalized. After the initial bolus, the saline infusion should be adjusted to a rate of approximately 200 to 300 mL/hr (depending on the patient's age, renal function, cardiac and other comorbid diseases) to establish adequate urine output (2 L/day).[24] Although the administration of higher volumes of saline may further augment calcium excretion, it is much more likely to result in increased morbidity and mortality from volume overload, pulmonary edema, and myocardial ischemia. The routine use of furosemide in the management of hypercalcemia is no longer recommended. Furosemide was once thought to block the distal reabsorption of calcium, thus complementing saline's proximal tubule effects. However, furosemide has not been shown to have significant calcium reabsorption blocking effects. The use of furosemide should be reserved for augmenting saline diuresis to avoid volume overload during the treatment of hypercalcemia. If a loop diuretic is given to patients who are not yet volume replete, not only can the patient's hemodynamics and renal status deteriorate, but hypercalcemia may worsen. Once calcium excretion by saline infusion has begun, other electrolyte values should be carefully monitored, with particular attention to serum potassium levels.

Osteoclast-inhibiting therapies for severe hypercalcemia are generally considered in consultation with the patient's primary physician or oncologist. Drugs that inhibit osteoclast-mediated bone resorption include the bisphosphonates, mithramycin, calcitonin, and glucocorticoids. IV bisphosphonates are the most extensively studied and most efficacious agents for the treatment of malignancy-associated hypercalcemia. Their calcium-lowering effect is achieved predominantly by inhibition of osteoclast function and survival. Zoledronic acid is the bisphosphonate of choice in hypercalcemia of malignancy.[17] The infusion takes 15 minutes; zoledronic acid may be more effective than other bisphosphonates at keeping the calcium level down over time. The use of IV bisphosphonates is restricted to the treatment of acute hypercalcemia associated with serum calcium concentrations above 15 mg/dL and rapid deterioration of CNS, cardiac, gastrointestinal, and renal function.

In the rare case in which a patient has a life-threatening hypercalcemic arrhythmia or heart block, phosphates and hemodialysis should be considered. In cases of hypercalcemic crisis resulting from primary hyperparathyroidism, urgent parathyroidectomy is potentially curative. Isolated mild hypercalcemia rarely requires urgent treatment; however, an outpatient hypercalcemia evaluation should be discussed in patients' discharge plans, because up to 20% will ultimately be diagnosed with hyperparathyroidism.[25]

BOX 117.8

Most Common Causes of Hypocalcemia

Hypoalbuminemia
Hypoparathyroidism: inherited, postsurgical, autoimmune, infiltrative
Vitamin D deficiency and vitamin D resistance: Malabsorption syndrome, liver disease, malnutrition, sepsis, anticonvulsants, lack of sunlight exposure
Chronic renal failure
Hyperphosphatemia
Hypomagnesemia
Respiratory alkalosis
Severe pancreatitis
Drugs: Bisphosphonates, phenytoin, phosphate, calcitonin
Tumor lysis syndrome
Rhabdomyolysis

HYPOCALCEMIA

Principles

Calcium regulation is critical for normal cell function, neural transmission, membrane stability, bone structure, blood coagulation, and intracellular signaling. Total body calcium is controlled by a feedback system in which parathyroid hormone induces the bone and the kidneys to increase serum calcium levels. Vitamin D facilitates intestinal calcium absorption. Conversely, elevated calcium levels normally inhibit parathyroid hormone release.

There are multiple causes of hypocalcemia, of which hypoalbuminemia is the most common (Box 117.8). Because calcium is bound to albumin and other serum proteins, hypoalbuminemia will cause a fall in the measured serum calcium by about 0.8 mg/dL for every 1 g/dL reduction in serum albumin. The active form of calcium is the ionized calcium, which is not affected by changes in albumin.

Hypoparathyroidism is a common cause of hypocalcemia and often develops after surgery for head and neck cancers; it develops in 1% to 2% of patients after total thyroidectomy. Patients with vitamin D deficiency, including those with malabsorption syndromes, liver disease, malnutrition, and very little sunlight exposure, are at high risk for development of hypocalcemia. Derangements in magnesium and phosphate can also lead to hypocalcemia. Hyperphosphatemic patients often have hypocalcemia because of phosphate's affinity to bind calcium, whereas hypomagnesemia causes end-organ resistance to parathyroid hormone and inhibits the hypocalcemic feedback loop. Patients with sepsis demonstrate hypocalcemia usually associated with hypoalbuminemia.

The most common causes of symptomatic hypocalcemia are massive blood transfusions, toxins, pancreatitis, tumor lysis syndrome, and chronic malnutrition (Box 117.9). Patients receiving massive blood transfusions are at risk for development of hypocalcemia because of citrate toxicity. Rapid blood transfusions and radiocontrast dyes containing citrate infusions should be monitored closely in patients with hepatic failure, CHF, or other low-output states to avoid hypocalcemia.

Hypocalcemia in acute pancreatitis is caused primarily by precipitation of calcium soaps in the abdominal cavity, but glucagon-stimulated calcitonin release and decreased parathyroid hormone secretion may play a role. Toxic exposures to hydrofluoric acid and ethylene glycol can cause profound hypocalcemia secondary to their abilities to complex and chelate with calcium. Patients being treated for malignant neoplasms are at risk for development of tumor lysis syndrome and multiple secondary electrolyte abnormalities. Hypocalcemia has been attributed to the precipitation of calcium phosphate salts. Finally, one should expect to encounter hypocalcemia in malnourished patients and chronic alcoholics who present to the ED, especially alcoholics with hyperventilation due to alcohol withdrawal.

Clinical Features

Although there are many clinical manifestations of hypocalcemia, neuromuscular and cardiovascular findings predominate. Severity of symptoms is related to not only the absolute calcium level, but also the rate calcium rise. The patient may complain of muscle cramping, perioral or finger paresthesias, shortness of breath secondary to bronchospasm, and tetanic contractions. Symptomatic hypocalcemia may result in cardiovascular collapse, hypotension, and dysrhythmias. More severe hypocalcemia can lead to cardiovascular collapse, hypotension, syncope, dysrhythmias, CHF, angina, hypotension, and QT prolongation.[25a] Chronic hypocalcemia may manifest with cataracts, poor dentition, dry skin, coarse hair, and pruritus. Chvostek's sign may be present: when the examiner taps the facial nerve, facial or eye muscle twitching will be elicited. Trousseau's sign may also be present; when the examiner inflates the blood pressure cuff to 20 mm Hg above the systolic blood pressure for 3 minutes, carpal spasms will be induced because of the increased excitability caused by local ulnar and median nerve ischemia. Trousseau's sign is relatively specific for hypocalcemia, whereas Chvostek's test is less diagnostic.

BOX 117.9

Five Most Common Symptomatic Causes of Hypocalcemia Seen in the Emergency Department

- Hyperventilation: Anxiety, sympathomimetics
- Ethanol abuse, chronic malnutrition: Hypoalbuminemia
- Massive blood transfusion: More than 10 units
- Toxins: Hydrofluoric acid, ethylene glycol
- Severe pancreatitis

Diagnostic Strategies

Most cases of hypocalcemia are discovered by clinical suspicion followed by appropriate laboratory testing. A serum calcium level less than 8.5 mg/dL or an ionized calcium level less than 2.0 mEq/L is considered diagnostic. Total serum calcium is approximately 50% free (ionized) and 50% bound, primarily to albumin; thus the serum level should be "corrected" when hypoalbuminemia exists. The ionized calcium level, which is not affected by the albumin level, is more accurate. It is best to perform the whole blood ionized calcium determination rapidly to avoid changes in chelation and pH. In select cases, a parathyroid hormone level may be sent to assist the admitting or consulting physician. Electrocardiography and cardiac monitoring are recommended in suspected hypocalcemia patients to evaluate the QT interval and to provide continuous monitoring for potential dysrhythmias.

Management

Most asymptomatic patients and those with mild symptoms can be treated with oral calcium supplementation, such as calcium carbonate. IV calcium is administered, either as calcium chloride or calcium gluconate, to patients with moderate to severe symptoms; 100 to 300 mg of elemental calcium given over 5 to 30 minutes will raise the ionized calcium level 0.5 to 1.5 mEq. Calcium chloride contains 272 mg of elemental calcium but can be caustic to veins, so it should be given via central venous access unless patients are critically ill without central access. Calcium gluconate contains 92 mg of elemental calcium. Although this is one-third the amount contained in calcium chloride, it is safer to administer and can be given peripherally. Most patients requiring IV calcium should be admitted to the hospital for monitoring and treatment of nausea, vomiting, hypertension, and bradycardia. Patients taking digoxin have increased cardiac sensitivity to fluctuations in serum calcium, so IV calcium administration should be accompanied by continuous electrocardiographic monitoring.[20]

HYPERMAGNESEMIA

Principles

Hypermagnesemia is a relatively rare electrolyte abnormality defined as a serum magnesium concentration above 2.2 mg/dL. Hypermagnesemia is most often seen in patients who cannot optimally regulate magnesium excretion (eg, renal insufficiency), especially as their magnesium load increases. There have been reports of fatal and near-fatal cases involving hypermagnesemia in patients receiving magnesium with unrecognized renal failure. Hypermagnesemia can also be caused by over-the-counter laxatives and antacids. Even though most patients at risk for hypermagnesemia have underlying renal impairment, hypermagnesemia has been reported in patients with normal renal function, especially in elders. Box 117.10 lists the most common causes of increased serum magnesium levels.

Iatrogenic hypermagnesemia most commonly occurs from excessive IV infusions of magnesium in patients being treated for preeclampsia or eclampsia, cardiac arrhythmias, or asthma exacerbations. Magnesium administration during eclampsia can also cause fetal hypermagnesemia as magnesium crosses the placental

BOX 117.10

Five Most Common Causes of Hypermagnesemia

- Iatrogenic: IV administration, dialysate
- Oral administration: Laxatives, antacids, vitamins, cathartics, dialysate, parental
- Impaired elimination—hypomotility: Bowel obstruction, chronic constipation
- Impaired elimination—medications: Anticholinergics, narcotics, lithium therapy
- Miscellaneous: Hypothyroidism, tumor lysis syndrome, adrenal insufficiency, milk-alkali syndrome

TABLE 117.5

Clinical Effects of Hypermagnesemia

EFFECT	LEVEL (mg/dL)
Decreased deep tendon reflexes	4 to 5
Hypotension	5 to 7
Respiratory insufficiency	10
Heart block	10 to 15
Cardiac arrest	10 to 24

barrier. Hypermagnesemia may also be seen in patients with chronic renal failure on hemodialysis if the dialysate solutions are not closely monitored for magnesium content.

In patients with normal renal function, large amounts of magnesium can be excreted daily in the stool and urine. However, in patients with impaired renal function, hypermagnesemia can be seen even with therapeutic doses of magnesium-containing products. An adult dose of 10 ounces of laxative syrup results in consumption of approximately 2.0 g of elemental magnesium per single dose. A healthy adult can excrete more than 6.0 g of magnesium daily, but renally impaired patients may not be able to tolerate small doses of laxative syrup.[26] Thus, a patient with renal insufficiency should not use magnesium citrate for treatment of constipation. Hypermagnesemia resulting from Epsom salt gargles and salt enemas has been reported.[26a]

Decreased gastrointestinal elimination and increased gastrointestinal absorption of magnesium due to intestinal hypomotility can also result in toxicity. Hypermagnesemia can be seen with bowel obstruction, colitis, gastric dilation, and use of medications that decrease motility, including narcotics and anticholinergics. Other less common causes of hypermagnesemia include rhabdomyolysis, tumor lysis syndrome, adrenal insufficiency, hyperparathyroidism, and hypothyroidism.

Clinical Features

Patients with hypermagnesemia may present with flushing, nausea, vomiting, headache, and diminished deep tendon reflexes. Typically, symptoms begin to manifest around magnesium levels of 4 mg/dL (Table 117.5). Magnesium is a CNS and neuromuscular depressant and can cause cardiac instability. Magnesium acts as a calcium channel blocker and also blocks potassium channels needed for repolarization. As magnesium levels rise, hypotension and electrocardiographic changes, including QRS widening and QT and PR prolongation, begin to occur. When serum magnesium levels rise above 7 mg/dL, patients can have signs and symptoms of hypotension, respiratory insufficiency, and heart block. Cardiac arrest and death have been reported in patients with serum magnesium levels above 10 mg/dL. Hypermagnesemia can interfere with blood clotting by interfering with clotting time and platelet adhesiveness.[26b] Finally, hypermagnesemia causes suppression of parathyroid hormone secretion and can be associated with hypocalcemia.

Diagnostic Testing

Measured plasma magnesium levels often do not reflect total magnesium content, making it difficult to consistently correlate symptoms to specific magnesium levels.[26c] Although there is some question of the role of measuring ionized magnesium in patients with hypomagnesemia, only total body magnesium needs to be followed in hypermagnesemic patients.

Management

Management of hypermagnesemia is dictated by the neuromuscular, cardiovascular, and CNS changes that occur. Most stable or asymptomatic hypermagnesemic patients can be treated with cessation of their magnesium therapy. As symptoms become more pronounced, IV isotonic fluids are administered to dilute the extracellular magnesium. Diuretics can be used to promote excretion of magnesium while more definitive treatment is arranged.

In patients with higher levels of serum magnesium or more severe symptoms, renal consultation should be initiated immediately to arrange for dialysis. IV calcium therapy to reverse magnesium toxicity should be reserved for patients with life-threatening symptoms while dialysis is being arranged. Calcium directly antagonizes the neuromuscular and cardiovascular effects of magnesium and is recommended in hypotensive patients with respiratory depression and cardiac instability. In treating life-threatening hypermagnesemia, initially administer 100 to 200 mg of IV calcium as either calcium chloride or calcium gluconate (1 to 2 mL of 10% calcium chloride or 5 mL of 1% calcium gluconate over 2 to 5 minutes) and then titrate to effect.[27] When needed, a continuous infusion at 2 to 4 mg/kg/hr can be administered while dialysis is being arranged.

HYPOMAGNESEMIA

Principles

Hypomagnesemia is a common electrolyte abnormality that often goes undetected. Normal serum magnesium levels range from 1.5 to 3.0 mEq/L. Symptoms of hypomagnesemia typically begin to be manifested at serum levels below 1.2 mEq/L, although symptoms are often not well correlated with the patient's serum level. This is because most of the body's magnesium is intracellular, and thus a single blood sample with a low serum magnesium level may not accurately reflect total body magnesium or the extent of true hypomagnesemia.

Magnesium exists in three states: (1) ionized magnesium, (2) protein bound, and (3) complexed to serum anions. Even though studies show the importance of measuring ionized calcium, most research shows that ionized magnesium can be inferred from total magnesium. Currently, the clinical role of measurement of ionized magnesium is unclear, and measurement of ionized magnesium is not standard practice in the ED; there may be a role for measurement of ionized magnesium in the intensive care setting.[28]

There are many causes of hypomagnesemia (Box 117.11). The following sections describe the five most common ED presentations of hypomagnesemia.

BOX 117.11

Most Common Causes of Hypomagnesemia

Dietary
Gastrointestinal
Renal
Endocrine or metabolic
Drug induced

Patients Maintained on Diuretics

Patients using either loop or thiazide diuretics are at increased risk for hypomagnesemia. Both types of diuretics can inhibit magnesium reabsorption. Conversely, potassium-sparing diuretics are also magnesium sparing, because they enhance magnesium reabsorption and decrease magnesium excretion. The degree of hypomagnesemia induced by the loop and thiazide diuretics is generally mild, in part because the associated volume contraction will tend to increase proximal sodium, water, and magnesium reabsorption.

Malnourished and Alcoholic Patients

Healthy patients consume enough magnesium in green vegetables, legumes, fruits, shellfish, fresh meat, and cocoa on a regular basis to maintain normal total body magnesium stores. However, hypomagnesemia is common in patients with chronic protein-calorie malnutrition because of an associated lack of essential minerals and vitamins including magnesium. This is especially true in chronic alcoholics who may not eat foods rich in magnesium. Magnesium losses are further increased in chronic alcoholics because of alcohol's diuretic effects. Hypomagnesemia may also be seen in patients with malabsorption disorders (celiac sprue and short bowel syndrome), patients with increased magnesium excretion (chronic diarrhea or inflammatory bowel conditions), and patients with severe body dysmorphic disorders. Mild hypokalemia is common following CPR, but severe hypokalemia below 2.5 mmol/L after resuscitation should prompt concern about underlying eating disorders and further evaluation due to extreme accidental self-induced hypokalemia.

Patients With Hypokalemia

Both potassium and magnesium are critical to help stabilize the membrane potential, to decrease cell excitability, and for function of the Na^+, K^+-ATPase pump. Approximately 50% of patients with hypokalemia also have concomitant magnesium deficiency. Increasing degrees of hypokalemia are correlated with an increasing likelihood of a magnesium deficit. Hypokalemic patients who are refractory to potassium replacement are likely to also be hypomagnesemic.[12a]

Patients With Acute Coronary Artery Disease and Ventricular Arrhythmias

There appears to be a relationship between low serum magnesium levels and the subsequent development of coronary heart disease. Patients who have a myocardial infarction are more likely than controls to be hypomagnesemic.[28a] At present, magnesium supplementation is recommended only for those acute coronary syndrome patients who have evidence of hypokalemia, prolonged QT, or known hypomagnesemia. Similarly, patients with acute myocardial infarction who have mild hypomagnesemia appear to have a twofold to threefold increase in the frequency of ventricular arrhythmias in the first 24 hours compared with those with normal magnesium levels. There is controversy about whether magnesium should be administered empirically after acute myocardial infarction.[29] Dysrhythmia is the most common cardiovascular manifestation of hypomagnesemia. Magnesium affects the duration of phase 2 of the action potential, and hypomagnesemia can prolong the QT interval. Magnesium also has effects on phase 4, the resting membrane potential, where it keeps the cell more negative by stimulating the sodium-potassium pump. The exact mechanism underlying a possible association between hypomagnesemia and arrhythmias is unknown. Arrhythmias are likely to be due to concurrent hypokalemia, hypomagnesemia, or both, resulting in a prolonged QT interval and increases in spontaneous depolarization.

Patients Receiving Specific Medications

In addition to diuretics, many medications are associated with hypomagnesemia. Many nephrotoxic drugs, including aminoglycosides, amphotericin B, cisplatin, and pentamidine, can produce magnesium wasting. Long-term use of proton pump inhibitors may be associated with changes in intestinal absorption of magnesium.[30] Severe hypomagnesemia can also be seen in patients preparing for colonoscopy with polyethylene glycol–based bowel preparations.

Clinical Features

Determination of the clinical consequences of isolated hypomagnesemia is often confounded by coexisting hypokalemia, hypocalcemia, or hyponatremia. However, many signs and symptoms are reported to correlate with hypomagnesemia, including muscle cramping, diffuse weakness, palpitations, vertigo, ataxia, depression, and seizures. Women with an adequate intake of magnesium are less likely to be affected by preeclampsia. The clinical manifestations most likely seen in the ED involve the neuromuscular and cardiovascular systems. Patients may present with hyperactive deep tendon reflexes, muscle cramps, Trousseau's and Chvostek's signs, and dysarthria and dysphagia from esophageal dysmotility.[30a] Cardiac conduction abnormalities secondary to magnesium depletion, and often coexisting hypokalemia, can result in PR, as well as QT interval prolongation. Dysrhythmias including atrial fibrillation, multifocal atrial tachycardia, premature ventricular complexes, ventricular tachycardia, torsades de pointes, and ventricular fibrillation are the most common cardiovascular manifestations of hypomagnesemia. Severe hypomagnesemia can also precipitate digoxin-induced dysrhythmias.[31,32]

Diagnostic Testing

Clinical manifestations of hypomagnesemia begin at serum levels below 1.2 mEq/L, but symptoms do not always correlate with the total serum magnesium level. Because most of the total body magnesium is intracellular, the magnesium level alone does not guide therapy. However, the possibility of hypomagnesemia is considered in patients with malnourishment, significant or refractory hypokalemia, and ventricular arrhythmias. Electrocardiographic findings in hypomagnesemia are nonspecific and may be caused by both the hypomagnesemia and concomitant hypokalemia. Hypomagnesemia should be suspected whenever electrocardiographic findings of hypokalemia are noted, including PR and QT interval prolongation, ST segment depression, flattening and widening of the T waves, loss of voltage, and U waves.

Management

The route of magnesium repletion varies with the severity of the clinical manifestations. Parenteral magnesium is recommended

for life-threatening conditions. In patients with normal renal function, 1 to 2 g of magnesium sulfate is an appropriate loading dose. A stable patient with hypomagnesemia can be treated with a loading dose of 1 to 2 g of magnesium sulfate during 10 to 60 minutes, followed by a maintenance dose of 0.5 to 1 g/hr until symptoms have resolved. However, patients in cardiac arrest should receive a bolus of 1 to 2 g magnesium sulfate by IV push.

Magnesium administration is strongly encouraged for patients receiving IV potassium repletion. A dose of 0.5 g/hr is safe in patients who are well hydrated and have normal renal function. There are potential adverse effects to rapid magnesium replacement at more than 1 to 2 g/hr, including decreased deep tendon reflexes, respiratory depression, and heart block. Magnesium gluconate oral supplementation can be given if the patient is only mildly hypomagnesemic and asymptomatic. Oral absorption is variable, but most commonly magnesium oxide 400 mg twice daily can be administered to patients with adequate renal function. When preparing any patient for discharge, physicians can encourage lifestyle changes, including adequate magnesium intake that may benefit blood pressure control, promote weight loss, and improve chronic disease risk.

HYPERPHOSPHATEMIA

Principles

Hyperphosphatemia is defined as a serum level above 2.5 mg/dL, but it is usually clinically significant only when levels are greater than 5 mg/dL. Although it is rare in the general population, hyperphosphatemia is extremely common in patients with renal insufficiency or renal failure. Almost all patients with renal failure experience hyperphosphatemia at some time during the course of their disease. Hyperphosphatemia can occur because of four major pathways: (1) decreased phosphate excretion, (2) excessive phosphate intake, (3) increased renal tubular reabsorption, and (4) shift of phosphate from intracellular to extracellular space. In addition, physicians should be aware of spurious elevations in phosphate (Box 117.12).

Decreased excretion of phosphate combined with excessive intake is the most common mechanism for the development of hyperphosphatemia. Excessive phosphate intake alone is an uncommon cause of hyperphosphatemia in patients with normal renal function. When patients have glomerular filtration rates below 30 mL/min, the kidneys do not excrete the full amount of ingested phosphate to maintain homeostasis. Exogenous phosphate, including IV or oral phosphate administration and phosphate enemas and laxatives can cause a large burden on the kidneys if they do not have normal baseline function.[8] In 2014, the U.S. Food and Drug Administration (FDA) made a drug safety announcement after identifying over 50 cases of adverse events warning against utilizing a single dose of sodium phosphate larger than recommended or taking more than one dose in a day, especially in patients also taking medications that act on renal function.[26,32] Hypoparathyroidism, vitamin D intoxication, and thyrotoxicosis increase renal phosphate reabsorption and may cause elevated phosphate levels. Hyperphosphatemia may also occur when there is a large shift of phosphate from the intracellular to the extracellular space and the kidney's ability to excrete phosphate is overwhelmed. This cause of hyperphosphatemia is seen in rhabdomyolysis, tumor lysis syndrome, and DKA.

Hyperphosphatemia can be a spurious finding in cases of hyperproteinemia, such as multiple myeloma, hyperlipidemia, hemolysis, or hyperbilirubinemia. Drawing of a blood sample from a line containing heparin is another cause of a falsely elevated phosphate level.[32a]

BOX 117.12

Five Most Common Causes of Hyperphosphatemia

DECREASED PHOSPHATE EXCRETION
Acute and chronic renal failure

INCREASED RENAL TUBULAR REABSORPTION
Hypoparathyroidism
Thyrotoxicosis
Excess vitamin D administration

EXCESSIVE PHOSPHATE INTAKE
Phosphate enemas or laxatives
IV or oral phosphate administration

SHIFT OF PHOSPHATE FROM INTRACELLULAR TO EXTRACELLULAR SPACE
DKA
Tumor lysis
Rhabdomyolysis

SPURIOUS HYPERPHOSPHATEMIA
Paraproteinemia
Hyperbilirubinemia
Hemolysis
Hyperlipidemia

DKA, Diabetic ketoacidosis; *IV,* intravenous.

Clinical Features

Patients with hyperphosphatemia may present with multiple complaints related to electrolyte abnormalities, particularly hypocalcemia. Hyperphosphatemia causes hypocalcemia by precipitating calcium out of the blood and decreasing vitamin D production. It is this secondary hypocalcemia that can cause muscle cramping, tetany, and seizures. Chronic hyperphosphatemia can also lead to metastatic calcifications in joints, tissues, and arteries.

Management

Dietary restriction alone may suffice for control of hyperphosphatemia in persons with mild renal insufficiency, but it is inadequate for control in those with overt renal failure. Because most patients presenting with severe hyperphosphatemia also have hypocalcemia, treatment focuses on the correction of both. In patients with normal renal function, phosphate excretion can be increased by saline infusion coupled with loop diuretics. Hyperphosphatemia usually resolves in 6 to 12 hours in patients with normal renal function. In patients with hyperphosphatemia with renal failure, hemodialysis or peritoneal dialysis should be considered early in the management. Currently, phosphate control is initiated only when hyperphosphatemia occurs, but it may be beneficial to intervene earlier in patients with chronic kidney disease.[33] The optimal method for control of serum phosphate in patients undergoing dialysis is unknown and may involve combinations of dietary modification and enhancement of phosphate clearance through longer dialysis sessions.[34]

HYPOPHOSPHATEMIA

Principles

Hypophosphatemia is defined as mild (2 to 2.5 mg/dL), moderate (1 to 2 mg/dL), or severe (<1 mg/dL). Mild to moderately severe

hypophosphatemia is usually asymptomatic and, like hypomagnesemia, often goes unrecognized. Although most patients remain asymptomatic, severe hypophosphatemia may result in potentially life-threatening complications. Major clinical sequelae usually occur only in severe hypophosphatemia.

Symptoms of hypophosphatemia typically begin to be manifested at serum levels below 1.0 mg/dL. Acute hypophosphatemia is most commonly due to a rapid intracellular shift. Hyperventilation, glucose, insulin, volume expansion, and resolving acidosis can lead to hypophosphatemia by rapid intracellular shift. The many causes of hypophosphatemia include decreased phosphate intake or increased absorptive states, hyperventilatory states, hormonal and endocrine effects, medications, and disease states (Box 117.13).[35] The ED patients most likely to have hypophosphatemia are those who are malnourished with alcohol withdrawal, acute hyperventilation, or sepsis and patients with DKA or alcohol ketoacidosis in whom reintroduction of insulin and glucose causes phosphate uptake into cells.

BOX 117.13

Five Most Common Causes of Hypophosphatemia in the Emergency Department

DECREASED INTAKE OR INCREASED ABSORPTIVE STATES
Chronic alcoholism
Home parenteral nutrition
AIDS
Chemotherapy
Vomiting
Malabsorption syndromes
Secretory diarrhea
Vitamin D deficiency

HYPERVENTILATORY STATES
Sepsis
Alcohol withdrawal
Salicylate poisoning
Neuroleptic malignant syndrome
Panic attacks
DKA
Hepatic coma

HORMONAL AND ENDOCRINE EFFECTS
Insulin loading
Glucose loading
Exogenous epinephrine
Hyperparathyroidism

MEDICATIONS[a]
Diuretics
Chronic antacid ingestion
Steroids
Phosphate binders
Xanthine derivatives
Beta$_2$-agonists

DISEASE STATES
Trauma
Severe thermal burns
Acute renal failure
Gout

[a]Kaplan LJ, Kellum JA: Fluids, pH, ions and electrolytes. Curr Opin Crit Care 16:323-331, 2010.
AIDS, Acquired immunodeficiency syndrome; *DKA*, diabetic ketoacidosis.

Clinical Features

Mild to moderate hypophosphatemia is usually asymptomatic, but major clinical manifestations can occur with severe hypophosphatemia. Because phosphate is an essential component to adenosine triphosphate, hypophosphatemia can affect a variety of organ systems and a wide variety of symptoms (Box 117.14). Patients with hypophosphatemia may present with nonspecific complaints including joint pain, myalgias, irritability, and depression. Severe hypophosphatemia can be manifested as seizures, arrhythmias, cardiomyopathy, insulin resistance, acute tubular necrosis, rhabdomyolysis, and acute respiratory failure.

Management

We recommend patients with phosphate levels below 2.0 mg/dL be given phosphate repletion; patients with levels below 1.0 mg/dL necessitate treatment. Because hypophosphatemia is often coupled with hypokalemia, patients with hypophosphatemia often require potassium repletion as well. Oral phosphorous, 250 to 500 mg twice daily, can be given to stable or asymptomatic patients. IV preparations are available as sodium phosphate (Na_2PO_4 and $NaPO_4$) or potassium phosphate (K_2PO_4 and KPO_4), and rate of infusion and choice of initial dosage should be based on severity of hypophosphatemia and presence of symptoms.

BOX 117.14

Clinical Manifestations of Hypophosphatemia

CENTRAL NERVOUS SYSTEM
Irritability
Confusion
Paresthesias
Depression
Dysarthria
Seizure
Coma

CARDIOVASCULAR
Cardiomyopathy
Depressed myocardial contractility
Arrhythmias

RESPIRATORY
Acute respiratory failure
Depressed myocardial contractility

GASTROINTESTINAL
Ileus, dysphagia

HEMATOLOGIC
Depressed levels of 2,3-diphosphoglycerate and adenosine triphosphate
Leukocyte dysfunction
Hemolysis
Platelet dysfunction

RENAL
Acute tubular necrosis
Metabolic acidosis
Hypercalcemia

ENDOCRINE
Insulin resistance
Hyperparathyroidism

If the serum phosphorus concentration is less than 1.5 mg/dL (0.48 mmol/L), 1.3 mmol/kg of elemental phosphorous (up to a maximum of 100 mmol) can be given in three or four divided doses in a 24-hour period. For routine replacement, give 0.5 mL/hr K_2PO_4; this may be increased to 1 mL/hr in severe symptomatic patients. Each milliliter of K_2PO_4 contains 3 mmol of phosphorus and 4.4 mEq of potassium.

Typical replacement therapy provides approximately 1 g of phosphorus per day. Patients should be monitored for the development of hypocalcemia, hyperkalemia, and hyperphosphatemia while IV phosphate is administered, especially in patients with renal insufficiency. Patients with DKA are initially hypophosphatemic. However, no studies have shown significant benefit to routine phosphate therapy in DKA. Risks of routine treatment with phosphate include hyperphosphatemia, renal failure, hypocalcemia, and hypomagnesemia. In patients with severe malnutrition or significant hypophosphatemia, replacement can be considered, but never administer more than 60 mmol/day without reason.

KEY CONCEPTS

- Asymptomatic electrolyte abnormalities can usually be corrected slowly, but those that cause profound mental status changes or life-threatening arrhythmias require immediate correction to avoid cardiac arrest or seizures.
- IV calcium should be used only for hyperkalemic emergencies, defined as the following: widening QRS; sine wave; cardiac arrest believed to be due to hyperkalemia; or rapidly evolving electrocardiographic changes, from normal to development of tall peaked T waves and loss of the P wave. Acute, rapid rises in serum potassium concentration are rare but may be seen in tumor lysis syndrome, rhabdomyolysis, or massive hemolysis.
- After the critical decision about administration of calcium has been made, a $beta_2$-agonist, insulin and glucose, normal saline, and bicarbonate (if the patient is acidotic) can be given to shift potassium intracellularly.
- In treatment of hypokalemia, the physician should also replace magnesium sulfate, in addition to potassium, or the patient will excrete most of the infused potassium in the urine.
- Low serum potassium levels reflect a much greater total potassium deficit; correction of large deficits can require several days.
- Hypertonic saline should be reserved for severely hyponatremic patients (typically in the 100 to 110 mEq range) who present with coma, seizures, or focal neurologic deficits. Central pontine myelinolysis can occur if serum sodium concentration is raised rapidly by more than 10 to 12 mEq/day.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 117: QUESTIONS & ANSWERS

117.1. A patient with end-stage renal disease misses dialysis and presents feeling weak. His 12-lead electrocardiogram (ECG) shows peaked T waves, absent P waves, and a QRS duration of 240 milliseconds. Which of the following is the next step in emergency department (ED) management?

A. Calcium chloride
B. Furosemide
C. Hemodialysis
D. Insulin with glucose
E. Nebulized albuterol

Answer: A. Calcium chloride is the first medication that should be administered in this patient with a widened QRS. The treatment of hyperkalemia is based on the clinical scenario combined with the 12-lead ECG and the laboratory potassium value. Evaluating the ECG of patients at risk for this electrolyte disturbance is critical because results of the serum potassium level can be delayed. Hyperkalemia can be rapidly progressive, and lifesaving interventions should be instituted at the earliest suspicion of toxicity. Intravenous (IV) calcium is used to stabilize the cardiac membrane by restoring the electrical gradient. Calcium increases the depolarization threshold and the calcium gradient across the cardiac membrane, quieting myocyte excitability and increasing cardiac conduction speed, thus narrowing the QRS.

117.2. A young pregnant woman with eclampsia is transferred to the emergency department (ED) on a magnesium sulfate drip. She is barely arousable and has slow respirations. On examination, she has diffuse crackles in her lungs and absent reflexes. After oxygen is provided and she is attached to a monitor, what is the best treatment?

A. Activated charcoal
B. Calcium gluconate
C. Glucagon
D. Naloxone
E. Sodium bicarbonate

Answer: B. Calcium gluconate is the medication of choice in patients with suspected hypermagnesemia. Patients with hypermagnesemia may present with flushing, nausea, vomiting, headache, and diminished deep tendon reflexes. Intravenous (IV) calcium therapy to reverse magnesium toxicity should be reserved for patients with life-threatening symptoms while dialysis is being arranged. Calcium directly antagonizes the neuromuscular and cardiovascular effects of magnesium and is recommended in hypotensive patients with respiratory depression and cardiac instability.

117.3. For which of the following patients would it be most appropriate to supplement potassium to keep serum levels above 4 mEq/L?
- **A.** A 23-year-old woman with palpitations and no past medical history
- **B.** A 42-year-old woman with poorly controlled diabetes mellitus
- **C.** A 51-year-old man with hypertension, recently started on lisinopril
- **D.** A 55-year-old man with history of coronary artery disease, chest pain, and premature ventricular complexes
- **E.** A 68-year-old-man with chronic bronchitis and fever

Answer: D. The 55-year-old patient is at highest risk for life-threatening complications from hypokalemia secondary to his underlying comorbidities. In patients with cardiac ischemia or heart failure, even mild to moderate hypokalemia increases the likelihood of cardiac arrhythmias secondary to potassium's effect on the action potential.

117.4. A malnourished man with a long history of chronic obstructive pulmonary disease is brought to the emergency department (ED) in respiratory distress. He receives bronchodilators, intravenous (IV) dextrose, and thiamine. He improves significantly, but then begins to complain of severe muscle aches, diffuse weakness, and the feeling that he cannot breathe deeply. Supplementation with which of the following might have prevented his new symptoms?
- **A.** Calcium gluconate
- **B.** Diazepam
- **C.** Normal saline
- **D.** Potassium phosphate
- **E.** Sodium bicarbonate

Answer: D. Patients with hypophosphatemia may present with nonspecific complaints, including joint pain, myalgias, irritability, and depression. Severe hypophosphatemia can be manifested as seizures, arrhythmias, cardiomyopathy, insulin resistance, acute tubular necrosis, rhabdomyolysis, and acute respiratory failure. Because hypophosphatemia often presents with hypokalemia, phosphate repletion should be considered in conjunction with potassium administration.

117.5. A patient in diabetic ketoacidosis (DKA) receiving insulin and intravenous (IV) fluids develops diffuse muscle weakness and pain. Her cardiac monitor shows broad T waves, U waves, and frequent premature ventricular complexes. What therapy is indicated?
- **A.** Calcium gluconate
- **B.** Dextrose
- **C.** Potassium chloride
- **D.** Sodium bicarbonate
- **E.** Sodium phosphate

Answer: C. Hypokalemia can be a dangerous complication during treatment of DKA, and potassium chloride should be administered to this patient demonstrating both clinical and diagnostic signs of hypokalemia. Administration of insulin may cause a reduction in serum potassium because of insulin's ability to stimulate the sodium-potassium adenosine triphosphatase (Na^+, K^+-ATPase) pump and move potassium intracellularly. If there is any suspicion for hypokalemia or a patient presents with generalized weakness, palpitations, or arrhythmias, an electrocardiogram (ECG) should be obtained. A flattened broad T wave can be seen in hypokalemia. U waves, which are small deflections after the T wave, may also be seen. Patients should have their potassium repleted to prevent further complications.

117.6. A 58-year-old man with history of small cell lung cancer is brought in for weakness and pleuritic chest pain. He is alert, with normal vital signs, nonfocal neurologic examination, and serum sodium concentration of 129 mEq/L. What is the most appropriate management of the hyponatremia?
- **A.** Free water restriction
- **B.** Hypertonic saline bolus
- **C.** Intravenous (IV) furosemide
- **D.** Normal saline bolus
- **E.** Sodium chloride tablets

Answer: A. The patient with small cell lung cancer is demonstrating signs and symptoms of hyponatremia. Lung cancers, especially small cell cancer, can lead to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The mainstay for treatment of euvolemic hyponatremia is free water restriction. As the hypo-osmolality in SIADH results from a relative abundance of water in the intracellular and extracellular volumes and is maintained by a reduced ability to excrete water, the restriction of free oral water intake is usually the most effective therapy. For relatively asymptomatic patients with sodium values of 115 to 135 mEq/L, a trial of free water restriction to less than 0.8 mL/day to 1.25 L/day should be attempted.

117.7. A runner is brought in after collapsing during a race. He has been careful to drink at each mile marker. He has altered mental status and is combative even after 10 mg of diazepam. What is the most appropriate treatment after his witnessed tonic-clonic seizure?
- **A.** 5% Dextrose solution
- **B.** Fosphenytoin
- **C.** Hypertonic saline
- **D.** Lorazepam
- **E.** Pentobarbital

Answer: C. This runner is demonstrating symptoms concerning for exercise-associated hyponatremia, the occurrence of hyponatremia during or up to 24 hours after prolonged physical activity. Hypertonic saline is indicated in severe cases of hyponatremia when a patient has alterations in mental status, focal neurologic findings, or seizures.

CHAPTER 118

Diabetes Mellitus and Disorders of Glucose Homeostasis

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DIABETES MELLITUS

Principles

Background

Diabetes mellitus is the most common endocrine disease. It comprises a heterogeneous group of hyperglycemic disorders characterized by a high serum glucose concentration and disturbances of carbohydrate and lipid metabolism. Acute complications include hypoglycemia and hyperglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS). Long-term complications affect multiple organ systems through involvement of the microvasculature and include retinopathy, nephropathy, neuropathy, and angiopathy. As a result, complications such as coronary and cerebral vascular disease, blindness, chronic kidney disease, complicated infections, and amputations are present in a much higher incidence in diabetics than in nondiabetics. Diabetes is frequently ranked as one of the five major chronic diseases that account for a significant proportion of our health care spending. Several trials have shown to varying degrees that tight glucose control can reduce the risk of death and severe microvascular complications. Patients with diabetes mellitus incur emergency department (ED) costs three times higher than those of nondiabetic patients and are admitted to the hospital four times more often.

Normal Physiology

Because plasma glucose is the predominant metabolic fuel used by the central nervous system (CNS), maintenance of the plasma glucose concentration is critical to survival. The CNS cannot synthesize glucose, store more than a few minutes' supply, or concentrate glucose from the circulation. Brief hypoglycemia can cause profound CNS dysfunction, and prolonged severe hypoglycemia may cause cellular death. Glucose regulatory systems have evolved to prevent and correct hypoglycemia.

The plasma glucose concentration is normally maintained within a relatively narrow range, between 60 and 150 mg/dL, despite wide variations in glucose levels after meals and exercise. Glucose is derived from three sources—intestinal absorption from the diet, the breakdown of glycogen (glycogenolysis), and the formation of glucose from precursors (gluconeogenesis), including lactate, pyruvate, amino acids, and glycerol. After glucose ingestion, the plasma glucose concentration increases as a result of glucose absorption. Endogenous glucose production is suppressed, and the plasma glucose level rapidly declines in response to insulin to a level below the baseline.

Insulin. Insulin receptors on the beta cells of the pancreas sense elevations in the blood glucose concentration and trigger insulin release into the blood. For incompletely understood reasons, glucose taken by mouth causes more insulin release than parenteral glucose. Certain amino acids induce insulin release and even cause hypoglycemia in some patients. Sulfonylurea oral hypoglycemic agents work, in part, by stimulating the release of insulin from the pancreas.

The number of receptor sites helps determine the sensitivity of the particular tissue to circulating insulin. The number and sensitivity of receptor sites are also the primary factors in the long-term efficacy of the sulfonylurea oral hypoglycemic agents. Receptor sites are increased in glucocorticoid deficiency and may be relatively decreased in obese patients.

Under normal circumstances, insulin is rapidly degraded through the liver and kidneys. The half-life of insulin is 3 to 10 minutes in the circulation. Whereas insulin is the major anabolic hormone implicated in diabetes, glucagon is the major catabolic hormone in disorders of glucose homeostasis.

Although most tissues have the enzyme systems required to synthesize and hydrolyze glycogen, only the liver and kidneys contain glucose-6-phosphatase, the enzyme necessary for the release of glucose into the circulation. The liver is essentially the sole source of endogenous glucose production. Renal gluconeogenesis and glucose release contribute substantially to the systemic glucose pool only during prolonged starvation.

Glucose Regulatory Mechanisms. Maintenance of the normal plasma glucose concentration requires precise matching of glucose use with endogenous glucose production and dietary glucose intake. The regulatory mechanisms that maintain systemic glucose balance involve hormonal, neurohumoral, and autoregulatory factors. Glucose regulatory hormones include insulin, glucagon, epinephrine, cortisol, and growth hormone. Insulin is the main glucose-lowering hormone. Insulin suppresses endogenous glucose production and stimulates glucose use. Insulin is secreted from the beta cells of the pancreatic islets into the hepatic portal circulation and has important actions on the liver and peripheral tissues. Insulin stimulates glucose uptake, storage, and use by other insulin-sensitive tissues, such as fat and muscle.

Counterregulatory hormones include glucagon, epinephrine, norepinephrine, growth hormone, and cortisol. When glucose is not transported into the cells because of a lack of food intake or lack of insulin, the body perceives a fasting state and releases glucagon, attempting to provide the glucose necessary for brain function. Glucagon is released in response to hypoglycemia as well as to stress, trauma, infection, exercise, and starvation. It increases hepatic glucose production within minutes, although transiently.

Epinephrine both stimulates hepatic glucose production and limits glucose use through both direct and indirect actions mediated by α-adrenergic and β-adrenergic mechanisms. Epinephrine also acts directly to increase hepatic glycogenolysis and gluconeogenesis. It acts within minutes and produces a transient increase in glucose production but continues to support glucose production at approximately basal levels thereafter. Norepinephrine

exerts hyperglycemic actions by mechanisms similar to those of epinephrine, except that norepinephrine is released from axon terminals of sympathetic postganglionic neurons.

Pathophysiology

Type 1 diabetes results from a chronic autoimmune process that usually exists in a preclinical state for years. The classic manifestations of type 1—hyperglycemia and ketosis—occur late in the course of the disease, an overt sign of beta cell destruction. The most striking feature of long-standing type 1 diabetes is the nearly total lack of insulin-secreting beta cells and insulin, with the preservation of glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic polypeptide–secreting cells.

Although the exact cause of diabetes remains unclear, research has provided many clues. Studies of the pathogenesis of diabetes mellitus have demonstrated that the cause of the disordered glucose homeostasis varies from individual to individual. This cause may determine the presentation in each patient. Individual patients are currently not studied for the source of their disease, except on an experimental basis. The goals of work in progress, however, are to identify who is susceptible to the development of diabetes and prevent diabetic emergencies and sequelae or prevent expression of the disease.

Types of Diabetes

The American Diabetes Association (ADA) defines four major types of diabetes mellitus—type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, and diabetes due to secondary disease processes or drugs.[1] The 1997 National Diabetes Data Group reported discontinued use of the terms *insulin-dependent diabetes mellitus* and *non–insulin-dependent diabetes mellitus* because they were confusing and clinically inaccurate. In addition, the use of Arabic numerals, 1 and 2, instead of Roman numerals is the standard. The most recent update to the standards of care for diabetes was published in January 2015.[1] The diagnostic criteria for the diagnosis of diabetes were changed in 2010 from the previous standards of elevated fasting glucose concentration and abnormal result of the 2-hour oral glucose tolerance test (OGTT) to use of the hemoglobin A_{1c} (HbA_{1c}) value as the preferred confirmatory test.[1] An HbA_{1c} value above 6.5% is now considered diagnostic of diabetes. However, the fasting plasma glucose concentration and 2-hour OGTT are still considered valid, as is the presence of a random glucose measurement of more than 200 mg/dL in a nonfasting patient with symptoms of diabetes. Use of the fasting plasma glucose concentration may help identify patients at risk for diabetes—that is, the glucose concentration is elevated but does not cross the threshold for the diagnosis of diabetes.

Type 1 Diabetes Mellitus. Type 1 diabetes is characterized by an abrupt failure of insulin production with a tendency to ketosis, even in the basal state. Parenteral insulin is required to sustain life. From 85% to 90% of patients with type 1 diabetes demonstrate evidence of one or more autoantibodies implicated in the cell-mediated autoimmune destruction of the beta cells of the pancreas. The autoimmune destruction has multiple genetic predispositions and may be related to undefined environmental insults.

Type 2 Diabetes Mellitus. Patients with type 2 diabetes may remain asymptomatic for long periods and show low, normal, or elevated levels of insulin. Ketosis is rare in type 2 disease. Patients frequently have hypertriglyceridemia and a high incidence of obesity. No association exists with viral infections, islet cell autoantibodies, or human leukocyte antigen (HLA) expression. Hyperinsulinemia may be related to peripheral tissue resistance to insulin because of defects in the insulin receptor. Defects in muscle glycogen synthesis have an important role in the insulin resistance.

Gestational Diabetes. Gestational diabetes mellitus is characterized by an abnormal OGTT result that occurs during pregnancy and reverts to normal during the postpartum period or remains abnormal. The clinical pathogenesis is thought to be similar to that of type 2. The clinical presentation is usually nonketotic hyperglycemia during pregnancy. Screening is performed around the 24th to 28th week with a 75-g oral glucose load in a woman with no prior history of diabetes.

Diabetes of Other Causes. Myriad causes of diabetes have been identified, including chronic pancreatitis, cystic fibrosis, genetic defects in the beta cell or in insulin receptors, and chemical-induced (eg, Vacor; chemotherapeutic, antipsychotic, or antiretroviral medications). The management of diabetes due to these conditions is cause-specific and depends on whether the underlying pathophysiologic process more closely resembles type 1 or 2 diabetes.

Prediabetes. Impaired glucose tolerance (IGT) has been replaced by the term *prediabetes* to identify individuals at high risk for the development of diabetes.[1] The pathogenesis of prediabetes is thought to be related to insulin resistance. This group is composed of persons whose plasma glucose levels are between normal and diabetic; they are at increased risk for diabetes and cardiovascular disease. Presentations of prediabetes include nonketotic hyperglycemia, insulin resistance, hyperinsulinism, and often obesity. Prediabetes is not associated with the same degree of complications of diabetes mellitus, and many of these patients have normal glucose tolerance spontaneously. However, each year, about 1% to 5% of patients with IGT will develop diabetes mellitus.[1]

Epidemiology

The most recent data estimate that 9% of Americans and 12% of adults older than 20 years have diabetes.[1] The incidence of diabetes in those younger than 20 years approaches as high as 45/100,000 by the teenage years. The type of diabetes depends on age; most of those younger than 10 years have type 1, whereas type 2 predominates in the 10- to 19-year-old group.[1]

Type 1 is less common than type 2. The peak age at onset of type 1 diabetes is 10 to 14 years, and approximately 1 of every 600 schoolchildren has this disease. In the United States, the prevalence of type 1 is approximately 0.26% by the age of 20 years, and the lifetime prevalence approaches 0.4%. The annual incidence among persons from birth to 16 years of age in the United States is 12 to 14/1 million population. The incidence is age-dependent, increasing from near-absence during infancy to a peak occurrence at puberty and another small peak at midlife.[1]

The morbidity in diabetes is related primarily to its vascular complications. A mortality rate of 36.8% has been attributed to cardiovascular causes, 17.5% to cerebrovascular causes, 15.5% to diabetic comas, and 12.5% to renal failure.

Clinical Features

Type 1

The patient with type 1 diabetes is usually lean, younger than 40 years, and prone to ketosis. Plasma insulin levels are absent to low; plasma glucagon levels are high but suppressible with insulin, and patients require insulin therapy to treat their symptoms. The

onset of symptoms may be abrupt, with polydipsia, polyuria, polyphagia, and weight loss developing rapidly. In some cases, the disease is heralded by ketoacidosis. Myriad problems related to type 1 diabetes may prompt an ED visit, including acute metabolic complications, such as DKA, and late complications, such as cardiovascular or circulatory abnormalities, retinopathy, nephropathy, neuropathy, foot ulcers, severe infections, and various skin lesions.

Type 2

The patient with type 2 diabetes is usually middle-aged or older and overweight, with normal to high insulin levels. Insulin levels are lower than would be predicted for glucose levels, however, leading to a relative insulin deficiency. Type 2 patients demonstrate impaired insulin function related to poor insulin production, failure of insulin to reach the site of action, or failure of an end-organ response to insulin. Although most adult patients with type 2 are obese, 20% are not.

Symptoms in type 2 diabetes tend to begin more gradually than in type 1. The diagnosis of type 2 is often made by the discovery of an elevated blood glucose level on routine laboratory examination. Hyperglycemia may be controlled by dietary therapy, oral hypoglycemic agents, or insulin administration. Decompensation of disease usually leads to HHS rather than to ketoacidosis.

Diagnostic Testing

Serum Glucose Level

The diagnosis of diabetes can be established in one or more of four ways—random plasma glucose level above 200 mg/dL, fasting plasma glucose concentration above 126 mg/dL, 2-hour, 75-g postload OGTT higher than 200 mg/dL, or HbA_{1c} value above 6.5%. In the absence of hyperglycemia with metabolic decompensation, these criteria should be confirmed by repeated testing on a different day. Confirmation can be made by the same test or two different tests (eg, fasting plasma glucose and HbA_{1c}). A fasting value above 150 mg/dL is likely to distinguish diabetic from nondiabetic patients more accurately. Formal OGTTs are unnecessary except during pregnancy or in patients who are thought to have diabetes, but who do not meet the criteria for a particular classification. The World Health Organization and ADA have provided protocols for performing the OGTT.[1]

Glycosylated Hemoglobin

Measurement of glycosylated hemoglobin (HbA_{1c}) is one of the most important ways to assess the level of glucose control. An elevated serum glucose level binds progressively and irreversibly to the amino-terminal valine of the hemoglobin β chain. The HbA_{1c} measurement provides insight into the quality of glycemic control over time. Given the long half-life of red blood cells, the percentage of HbA_{1c} is an index of glucose concentration of the preceding 6 to 8 weeks, with normal values approximately 4% to 6% of total hemoglobin, depending on the assay used. Levels in patients with poorly controlled disease may reach 10% to 12%. The ADA has recommended at least biannual measurements of HbA_{1c} for the follow-up of all types of diabetes. The ADA currently sets an HbA_{1c} value of less than 7% as a treatment goal.

Urine Glucose Level

Urine glucose measurement methods are of two types, reagent tests and dipstick tests. The reagent tests (eg, Clinitest) are copper reduction tests. The reagent tests are rarely used because they are difficult to perform, and the test material is toxic for ingestion or dermal exposure. Dipstick tests generally use glucose oxidase, which may also be affected by different substances. Dipsticks are inexpensive and convenient but may vary in their sensitivity and strength of reaction to a given concentration of glucose. Dipstick interpretation can vary significantly, depending on the observer and type of lighting. Both falsely high and falsely low urine glucose readings can also occur. With the plus system, 1+, 2+, 3+, and 4+ have different implications about urine glucose concentrations, depending on the brand of dipstick. The use of reflectance colorimeters to read dipsticks increases accuracy.

Urine Ketone Level

Urine ketone dipsticks use the nitroprusside reaction, which is a good test for acetoacetate but does not measure β-hydroxybutyrate. Although the usual ratio of acetoacetate to β-hydroxybutyrate in DKA is 1:2.8, it may be as high as 1:30, in which case the urine dipstick does not reflect the true level of ketosis. When ketones are in the form of β-hydroxybutyrate, the urine ketone dipstick may infrequently yield negative reactions in patients with significant ketosis.

Dipstick Blood Glucose Level

Dipsticks for testing the blood glucose level are clearly more accurate than urine dipsticks as a means of monitoring blood glucose concentration, but they also may be inaccurate. Hematocrits below 30% or above 55% cause inaccurately high or low readings, respectively, and a number of the strips specifically disclaim accuracy when used for neonates. Sensitivity of dipsticks to a variety of factors varies with the particular brand. The largest errors are in the hyperglycemic range. Dipstick readings rarely err more than 30 mg/dL when the actual concentration is below 90 mg/dL. Although specific glucose concentrations may not be accurately represented, blood glucose dipsticks are useful for estimating the general range of the glucose value. Reflectance meters increase the accuracy of the dipstick blood glucose level determination. The use of glucometers has supplanted the use of dipsticks in most clinical settings and tends to be fairly accurate, except, again, at the extremes of glucose levels (<30 mg/dL or >600 mg/dL). If maximum accuracy is desired, a laboratory blood glucose level should be determined.

Management

Approach to New-Onset Hyperglycemia in the Emergency Department

Patients often present to the ED with typical diabetic symptoms, such as polyuria, polydipsia, and polyphagia. Many have serum glucose concentrations above 200 mg/dL but are not ketotic. Patients with newly diagnosed hyperglycemia with normal electrolyte values may be treated with intravenous (IV) hydration alone or with insulin, often reducing the glucose concentration to 150 mg/dL. In reliable patients whose initial glucose concentration is greater than 400 mg/dL, initiation of oral hypoglycemic therapy may be appropriate, with lifestyle modification. An HbA_{1c} value should be obtained before initiation of therapy to confirm a diagnosis of diabetes and to establish a baseline.

Initial therapy with sulfonylureas is appropriate; glyburide (2.5–5 mg once daily) or glipizide (5 mg once daily) is recommended.[1,2] Metformin may be initiated as well, at a dose of 500 mg daily; however, it lowers the blood glucose level on average only by about 100 mg/dL, and newly diagnosed diabetics frequently require additional agents to control their glucose concentration. Patients with kidney disease may have complications from use of

a sulfonylurea or metformin and will likely need insulin therapy. Follow-up should be stressed and warning signs of hypoglycemia discussed.

Management of Diabetes

Although emergency clinicians will rarely provide longitudinal care for diabetic patients, these patients present frequently to the ED, and we believe it is helpful for them to understand basic management principles and modern trends in the treatment of this important disease. The basic concepts of the diabetic diet remain unchanged, although many studies emphasize foods and medications that alter glucose absorption. Various high-fiber diets have improved glycemic control. The number of supplements or low–glycemic index snacks has risen in the last decade. Exercise continues to be a cornerstone of diabetes management, although care must be taken to balance it with appropriate calorie intake and medication use.

Oral Hypoglycemic Agents. Goals of diabetic management include lowering the hemoglobin A_{1C} to less than 7% and maintenance of the fasting blood sugar level to within 90 to 130 mg/dL. When started on monotherapy, after 3 years, approximately 50% of patients need a second drug. There have been an increasing number of oral agents for hyperglycemia available in recent years. Some of these have serious side effects, requiring the emergency clinician to be familiar with these drugs. If these effects are expected to be prolonged, the patient may require observation. Categories of oral agents may be divided into those that increase the insulin supply, including sulfonylureas, secretagogues, and insulin itself. Medications that decrease insulin resistance include the biguanides and thiazolidinediones; drugs that reduce the rate of glucose absorption include α-glucosidase inhibitors. Oral hypoglycemic agents generally lower HbA_{1C} levels by 0.5 to 1.5%. Metformin is generally used as the first-line agent for oral therapy. If the goal of lower HbA_{1C} levels is not achieved, addition of a sulfonylurea or pioglitazone should be considered.

Biguanides. The ADA and European Association for the Study of Diabetes have recommended lifestyle changes, including weight control, at the time of diabetes diagnosis. Metformin (a biguanide) is the initial drug of choice because it does not induce weight gain, has low cost and good tolerability, and tends not to induce hypoglycemia. Used alone, metformin does not cause hypoglycemia, but is contraindicated in patients with renal insufficiency. Metformin is renally excreted and should be used cautiously if the serum creatinine level is over 1.4 in females or 1.5 in males.

Metabolic acidosis is always a concern with biguanides. Ideally, metformin should be withheld for 48 hours prior to the administration of iodinated contrast media. In the emergency setting, metformin should be withheld after contrast administration for 48 hours due to the risk of acidosis. It is advisable to check the serum creatinine level before resuming this medication after contrast administration or surgery. Metformin must be used with caution in patients with hypoxemia, pregnancy, heart failure, liver compromise, and alcohol abuse. These patients may be at risk for developing lactic acidosis, which has been associated with a 50% mortality rate.

Sulfonylureas. Developed in the 1940s, the sulfonylureas have historically been a mainstay of oral diabetes treatment. These drugs increase insulin secretion by binding to specific beta cell receptors. This class of drugs is especially useful for patients with early-onset, type 2 diabetes mellitus and fasting blood glucose levels less than 300 mg/dL. This class of drug is contraindicated in patients with a known allergy to sulfa agents. Patients with renal failure may be predisposed to hypoglycemia. Examples of sulfonylureas include glipizide (Glucotrol, Glucotrol XL), glimepiride (Amaryl), and glyburide (DiaBeta, Glynase PresTab, Micronase). These interact with potassium channels in the beta cell membrane. The risk of hypoglycemia is greater in older adults and in those with impaired renal and hepatic function; they may be associated with weight gain. They generally lower the glucose level by 20%, and HbA_{1c} levels by 1% to 2%. Glipizide is shorter acting and therefore less likely than the other sulfonylureas to induce prolonged hypoglycemia. However, for all sulfonylureas, there have been several case reports of delayed onset of hypoglycemia from 12 to 21 hours after ingestion, leading to general recommendations to observe the patient for a 24-hour period.

Thiazolidinediones. Thiazolidinediones reduce insulin resistance and are especially useful in patients who require large amounts of insulin and still lack adequate glucose control. They have been associated with hepatotoxicity and require liver function monitoring for at least 1 year after initiation. For this reason, troglitazone has been removed from the market; pioglitazone (Actos) and rosiglitazone (Avandia) remain approved for monotherapy. Cardiovascular risks, including myocardial infarction, may be higher with rosiglitazone. These agents may also be associated with weight gain, fluid retention, and heart failure. They increase insulin sensitivity and may be expected to reduce the HbA_{1c} value by 0.5% to 1.4% points. They are contraindicated for patients with New York Heart Association class III or IV heart failure.

α-Glucosidase Inhibitors. The *α-glucosidase inhibitors* delay intestinal monosaccharide absorption and prevent complex carbohydrate breakdown; these agents include acarbose (Precose and generic) and miglitol (Glyset). They must be titrated to minimize gastrointestinal (GI) side effects and should not be used in patients with certain GI disorders. Liver function must be monitored because of dose-dependent hepatotoxicity. They should be taken with meals because they delay absorption of glucose. Side effects include abdominal pain, diarrhea, and flatulence from unabsorbed carbohydrates. They lower the $HgbA_{1c}$ by 0.5% to 0.8% points.

Meglinitides. The nonsulfonylurea secretagogues, the meglinitides, are similar to the sulfonylureas in action and mechanism. They bind to adenosine triphosphate (ATP)–sensitive potassium channels of beta cells to increase insulin secretion. They have a rapid onset of action and should be taken before a meal, involve less risk of hypoglycemia, and are suitable for patients allergic to sulfa medications. The specific agents available are nateglinide (Starlix) and repaglinide (Prandin). These may be better for patients with impaired renal function due to their liver metabolism. Management of refractory hypoglycemia in these agents may be done in a manner similar to that for sulfonylureas, with use of octreotide by bolus or infusion.

Glucagon-Like Peptide Analogues and Agonists. Glucagon-like peptide (GLP-1) analogues and agonists stimulate the release of insulin from pancreatic cells. Exanatide (Byetta) is US Food and Drug Administration (FDA)–approved for twice-daily subcutaneous injection in patients with type 2 diabetes who have not achieved satisfactory control with metformin, a sulfonylurea, pioglitazone, or lifestyle modifications. It lowers serum glucagon concentrations and slows gastric emptying. Liraglutide (Victoza) is also in this class. GLP itself has a half-life of only a few minutes. The GLP agonists bind to the GLP receptor on the pancreas and have a much longer half-life. Exanetide has been demonstrated to improve attainment of HbA_{1c} goals, even when administered once weekly. Clinical experience with their toxicology is limited, but there have been episodes of hypoglycemia reported. Observation recommendations are not established but, given the long half-life of the medications, we recommend a period of at least 24 hours.

Dipeptidyl Peptidase-4 Inhibitors. Dipeptidyl peptidase-4 (DPP-4) inhibitors include sitagliptin (Januvia), saxagliptin

(Onglyza), and linagliptin (Tradjenta). DPP-4 degrades endogenous GLP; the DPP-4 inhibitors, by preventing this degradation, prolong the half-life of GLP and increase insulin secretion. These are generally used as second- or third-line agents. Sitagliptin is FDA-approved as monotherapy, but is also available in combination with other oral hypoglycemic medications. Patients with chronic kidney disease may be at risk for hypoglycemia and should be treated symptomatically. These inhibit glucagon release and delay gastric emptying. They may be expected to produce a decrease in the HbA_{1c} of 0.4% to 0.8%.

Amylin Analogue. Pramlintide, administered three times daily before meals, is an amylinomimetic agent, or amylin analogue, and decreases gastric emptying and glucagon secretion. It has been approved for use in patients with types 1 and 2 diabetes and may promote weight loss.

Sodium-Glucose Cotransporter 2 Inhibitors. Dapagliflozin (Farxiga), canagliflozin (Invokana), and SGLT2 are sodium-glucose cotransporter 2 inhibitors. SGLT2 is a protein that transports filtered glucose from the proximal renal tubule into tubular epithelial cells, enhancing urinary excretion levels of glucose. They may also lower blood pressure and induce some degree of weight loss.[3]

Insulin. Certain principles apply to all insulins, such as their ability to enhance gluconeogenesis and lipogenesis and suppress glycogenolysis. Human insulins are available today as regular insulin and neutral protamine hagedorn (NPH). Regular insulin, which is used in the treatment of DKA, has an onset of action within 30 to 60 minutes and is typically dosed 30 to 45 minutes before a meal. Its duration of action is approximately 4 to 12 hours. NPH insulin (eg, Humulin, Novolin), being longer acting, is typically dosed 4 to 6 hours before a meal; it has a 12- to 24-hour duration of action and is administered two or three times daily. Regular and NPH insulin may be mixed together to lessen the number of daily injections.

More recently, insulin analogues have been developed. These entail modification of the terminal end of the A or B chain of the insulin molecule. The rapid-acting insulins currently on the market are glulisine, insulin lispro (Humalog), and insulin aspart (NovoLog); their onset of action is approximately 10 to 30 minutes and duration is 3 to 5 hours. They are typically administered 5 to 20 minutes before a meal. Long-acting insulin analogues are detemir (Levemir) and glargine (Lantus); their onset of action is 3 to 4 hours and their duration of action approaches 24 hours, similar to that of NPH. Insulin glargine and detemir, being long-acting but without a peak response, more closely mimic continuous pump infusion.

Although treatment for type 2 diabetes has traditionally started with oral agents, analogue insulin therapy has been recently advocated as an initial therapy for type 2 diabetes. Type 2 diabetes is associated with a decline of beta cell function over time, and intensive insulin therapy has been advocated early to rest the beta cells and possibly preserve their function over time. Starting patients on 10 units/day of glargine, with 6 units of aspart at mealtime, has been used as primary treatment for type 2 diabetes.[4] Basal insulin titration algorithms from the ADA, American College of Endocrinology, Canadian Diabetes Association, and International Diabetes Federation have recommended initial starting dosages of 10 units/day, titrating upward by 1 to 3 units every 1 to 3 days, with a target HbA_{1c} level below 6.5% to 7%.[5]

Ultrafast-acting insulin analogues reduce postprandial glucose fluctuations and abnormalities.[6] The intent is to match insulin absorption and action to food-related rises in the plasma glucose level.[7] These basal insulin analogues may enable the time of administration of the insulin to vary widely.[4] Although many emergency clinicians are more comfortable starting patients on oral hypoglycemic agents in the management of type 2 diabetes, more patients can be started on insulin as initial treatment for type 2 diabetes. Glargine, detemir, or NPH insulin may be initiated at 0.1 to 0.2 units/kg, or roughly 10 units/day, with follow-up within 3 to 4 days for dose adjustment. Unless the emergency clinician is particularly well versed in insulin therapy, this latter approach frequently involves the development of an outpatient protocol with a specialty consultant (eg, endocrinologist).

Pancreas Transplantation. Solid organ pancreas transplantation has become more common; several centers have performed combined pancreas and kidney transplants in those with end-stage kidney disease due to diabetic nephropathy. Transplantation ameliorates many secondary complications of diabetes, such as nephropathy, neuropathy, gastroparesis, retinopathy, and microvascular changes. The percentage of grafts functioning after 1 year and 1-year survival rate of patients are greater than 75% in selected medical centers. However, rejection, posttransplantation pancreatitis, and graft thrombosis, as well as other vascular and immunosuppression problems, continue to plague transplant recipients.

New Trends in Diabetes Management. Changes in the therapy of diabetes have recently included greater use of human insulin, which has prevented some of the adverse reactions to beef and pork products.[2,7] Unfortunately, some patients demonstrate sensitivity reactions, even to human insulin. Some physicians are teaching their diabetic patients and families how to administer glucagon to treat severe hypoglycemia.

The initiation of immunosuppressive therapy at the initial diagnosis of type 1 diabetes can prolong the patient's ability to secrete insulin. This beneficial effect, whether achieved by azathioprine or cyclosporine, is not usually sustainable.[2,7] The potential side effects of immunosuppressive agents have precluded large trials in patients early in their disease. Prophylactic insulin therapy, nicotinamide, oral insulin, or glutamate decarboxylase and avoidance of cow's milk may prevent or delay the onset of type I diabetes in patients at risk.

Glycemic control now involves improved technology and more widespread individual monitoring of daily insulin dosage adjustments. Diabetic patients with tight glycemic control benefit by limiting the progression of microvascular disease—neuropathy, renal disease, and certain types of retinopathy. However, they are more likely than other diabetic patients to experience hypoglycemic episodes.

Emergency clinicians and out-of-hospital care providers are encountering patients with insulin pumps.[2,7] Many insulin pumps are available, with each having a pump mechanism, reservoir for insulin, tubing, and indwelling subcutaneous needles. They are attached, usually with tapes, to the patient's body and administer insulin at a regular adjustable rate. Most pumps also allow the patient to administer additional boluses of insulin, as necessary. These pumps support tight glycemic control and are acceptable to some patients. However, motivated patients can achieve equivalent control by adjusting daily injections. Insulin pumps are associated with a variety of problems, including hypoglycemia. More recently, a wearable, automated bionic bihormonal pancreas has been noted to improve mean glycemic levels, with less frequent hypoglycemic episodes among adults with type 1 diabetes mellitus. The bionic pancreas receives data from a continuous glucose monitor to control subcutaneous delivery of insulin and glucagon.[8]

Because glucose rotates the polarization of light waves, new fiberoptic technology has been developed to determine the blood glucose level noninvasively.[2,7] This technique may be applied to the insulin pumps of the future. Ultrafast-acting insulins and biosimilar insulins may also be available in the near future. An inhaled insulin (Afrezza) has recently been released, but has been

associated with coughing and may exacerbate symptoms of reactive airway disease.

Newer insulin analogues are being developed, such as deglutec and U-500, which improve glycemic control without contributing to hypoglycemia.[2,7] Agents in the DPP-4 inhibitor class have not been associated with weight gain. Therefore, pharmacologic agents offer the promise of improving glycemic control for longer periods, with fewer glycemic fluctuations, less weight gain, and less hypoglycemia. Other new areas of research have included agents that increase the urinary excretion of glucose or increase hepatic gluconeogenesis.

DIABETIC KETOACIDOSIS

Principles

Pathophysiology

DKA is a syndrome in which insulin deficiency and glucagon excess combine to produce a hyperglycemic, dehydrated, acidotic patient, with profound electrolyte imbalance. All derangements producing DKA are interrelated and based on insulin deficiency (Fig. 118.1). DKA may be caused by cessation of insulin intake or by physical or emotional stress, despite continued insulin therapy. The effects of insulin deficiency may be mimicked in peripheral tissues by a lack of insulin receptors or insulin sensitivity at receptor or postreceptor sites. When the hyperglycemia becomes sufficiently marked, the renal threshold is surpassed, and glucose is excreted in the urine. The hyperosmolarity produced by hyperglycemia and dehydration is the most important determinant of the patient's mental status.[9]

Glucose in the renal tubules draws water, sodium, potassium, magnesium, calcium, phosphorus, and other ions from the circulation into the urine. This osmotic diuresis, combined with poor intake and vomiting, produces the profound dehydration and electrolyte imbalance associated with DKA (Table 118.1). Exocrine pancreatic dysfunction closely parallels endocrine beta cell dysfunction, producing malabsorption that further limits the body's intake of fluid and exacerbates electrolyte loss.

In 95% of patients with DKA, the total sodium level is normal or low. Potassium, magnesium, and phosphorus deficits are usually marked. As a result of acidosis and dehydration, however,

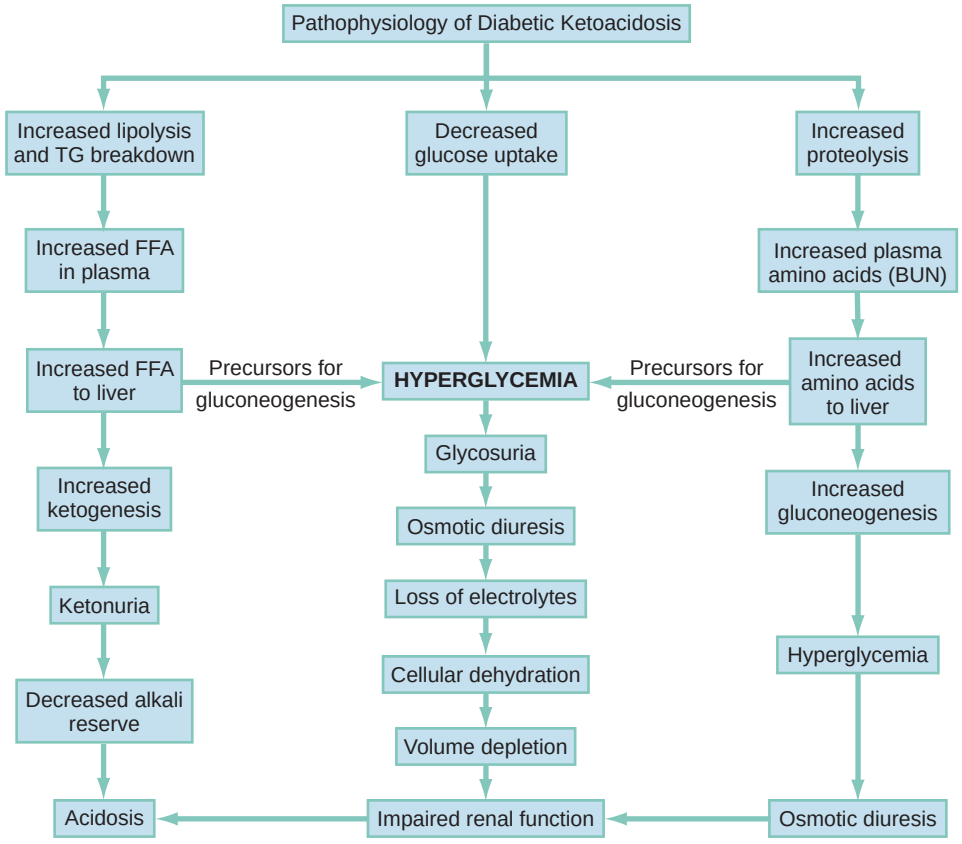

Fig. 118.1. Syndrome of diabetic ketoacidosis. *BUN,* Blood urea nitrogen; *FFA,* free fatty acids; *TG,* total glucose concentration.

TABLE 118.1

Average Fluid and Electrolyte Deficits in Severe Diabetic Ketoacidosis[a]

WEIGHT	WATER (mL/kg)	SODIUM (mEq/L)	POTASSIUM (mEq/L)	CHLORIDE (mEq/L)	PHOSPHORUS (mEq/L)
≤10 kg	100–120	8–10	5–7	6–8	3
10–20 kg	80–100	8–10	5–7	6–8	3
≥20 kg	70–80	8–10	5–7	6–8	3

[a]Per kilogram of body weight.

the initial reported values for these electrolytes may be higher than actual body stores. Hypokalemia may also inhibit insulin release.

The cells, unable to receive fuel substances from the circulation, act as they do in starvation from other causes. They decrease amino acid uptake and accelerate proteolysis so that large amounts of amino acids are released to the liver and converted to two-carbon fragments.

Adipose tissue in the patient with DKA fails to clear the circulation of lipids. Insulin deficiency results in activation of a hormone-sensitive lipase that increases circulating free fatty acid (FFA) levels. Long-chain FFAs, now circulating in abundance as a result of insulin deficiency, are partially oxidized and converted in the liver to acetoacetate and β-hydroxybutyrate. Despite the increased pathologic production of ketones, the body acts as it does in any form of starvation to decrease the peripheral tissue's use of ketones as fuel. The combination of increased ketone production with decreased ketone use leads to ketoacidosis.

Acidosis plays a prominent role in the clinical presentation of DKA. The acidotic patient attempts to increase lung ventilation to rid the body of excess acid with Kussmaul's breathing. Bicarbonate is used up in the process. Acidosis compounds the effects of ketosis and hyperosmolality to depress mental status directly.

Acidemia is not invariably present, even with significant ketoacidosis. Ketoalkalosis has been reported in diabetic patients vomiting for several days and in some with severe dehydration and hyperventilation. The finding of alkalemia, however, should prompt consideration of alcoholic ketoacidosis, in which alkalemia is much more common. Although these cases are rare, if there is concern for a mixed acid-base disorder, an arterial blood gas sample should be obtained instead of a venous gas sample to delineate the metabolic abnormalities present further.

Causes

DKA most commonly occurs in patients with type 1 diabetes and is associated with inadequate administration of insulin, infection, or myocardial infarction. DKA can also occur in type 2 diabetics and may be associated with any type of stress, such as sepsis or GI bleeding. Approximately 25% of all episodes of DKA occur in patients whose diabetes was previously undiagnosed.

Clinical Features

Clinically, most patients with DKA complain of a recent history of polydipsia, polyuria, polyphagia, visual blurring, weakness, weight loss, nausea, vomiting, and abdominal pain. Approximately 50% of these patients, especially children, report abdominal pain. In children, this pain is usually idiopathic and probably caused by gastric distention or stretching of the liver capsule; it resolves as the metabolic abnormalities are corrected. In adults, however, abdominal pain more often signifies true abdominal disease that may be triggering the DKA.

Physical examination may or may not demonstrate a depressed sensorium. Typical findings include tachypnea with Kussmaul's breathing, tachycardia, frank hypotension or orthostatic blood pressure changes, odor of acetone on the breath, and signs of dehydration. An elevated temperature is rarely caused by DKA itself and suggests an inciting infection.

Diagnostic Testing

Initial tests allow preliminary confirmation of the diagnosis and initiation of therapy (Table 118.2).[9] Subsequent tests are carried out to determine more specifically the degree of dehydration, acidosis, and electrolyte imbalance and reveal the precipitant of DKA.

TABLE 118.2

Typical Laboratory Values in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS)

	DKA	HHS
Glucose (mg/dL)	>350	>700
Sodium (mEq/L)	Low 130s	140s
Potassium (mEq/L)	≈4.5–6.0	≈5
Bicarbonate (mEq/L)	<10	>15
Blood urea nitrogen (mg/dL)	25–50	>50
Serum ketones	Present	Absent

Laboratory studies should include serum glucose, electrolyte, and blood gas levels. Although serum ketoacid levels are frequently measured, they are not necessary to diagnose DKA and make be elevated in non-DKA states (eg, starvation ketosis from inadequate utilization of glucose stores) or dehydration. If determination of the pH is the sole concern, venous blood gas samples correlate well with arterial pH. An arterial blood gas sample should be tested if there is concern for the adequacy of respiratory compensation or concern for a mixed acid-base disorder (eg, concomitant metabolic alkalosis from vomiting). Winter's formula (expected $Paco_2 = [1.5 \times \text{serum } HCO_3^-] + [8 \pm 2]$) can be applied to determine if there is appropriate respiratory compensation or the presence of multiple acid-base disorders. The glucose level is usually elevated above 350 mg/dL; however, euglycemic DKA (blood glucose level ≤ 300 mg/dL) has been reported in up to 18% of patients. Blood gas measurement usually reveals a low pH, with the aforementioned rare exception of a concomitant alkalemia, which may result in a pseudonormalization of the pH. Metabolic acidosis with an anion gap is primarily the result of elevated plasma levels of acetoacetate and β-hydroxybutyrate, although lactate, FFAs, phosphates, volume depletion, and several medications can also contribute. Rarely, a well-hydrated patient with DKA may have a pure hyperchloremic acidosis with no anion gap if they have been aggressively rehydrated with normal saline. Again, although rare, there have been case reports of a normal anion gap in a patient with DKA. This occurred if the vomiting was sufficient to cause a concomitant metabolic alkalosis to such a degree that the pH and bicarbonate level appear to be in the normal range because the combined derangements result in false normal-appearing laboratory values.[9] If an immediate potassium level is not available through blood gas analysis, an electrocardiogram can reveal signs of hyperkalemia or hypokalemia. Initial serum potassium levels are typically normal or high in DKA due to intracellular potassium shifting out of cells in exchange for elevated serum hydrogen ions. However, as potassium is lost in the urine, the total body potassium usually declines by several hundred milliequivalents. This, in combination with the insulin doses administered in DKA, can result in life-threatening hypokalemia. A basic metabolic panel should be obtained to evaluate renal function, acid-base status, and glucose and electrolyte levels. Because magnesium and potassium deficits are common in DKA, we recommend determining these levels as well. Urinalysis, in addition to the presence of ketones, may also help confirm a urinary tract infection as a precipitant of DKA. Use of blood or urine cultures should be determined by the clinical picture.

The serum sodium level is often misleading in DKA; it is often low in the presence of significant dehydration because it is strongly affected by hyperglycemia, hypertriglyceridemia, salt-poor fluid intake, increased GI and renal losses, and insensible loss. When hyperglycemia is marked, water flows from the cells

into the vessels to decrease the osmolar gradient, thereby creating dilutional hyponatremia. Elevated lipid levels cause a pseudohyponatremia by decreasing the fraction of serum that is water. Newer autoanalyzers remove triglycerides before assay, thus eliminating this artifact. The true value of the sodium level may be approximated by adding 1.6 mEq/L to the sodium value on the laboratory report for every 100-mg/dL glucose above the norm. Thus, if the laboratory reports a serum sodium level of 130 mEq/L and blood glucose level of 700 mEq/L, the total serum sodium level is more accurately assessed to be 139.6 mEq/L.

Acidosis and the hyperosmolarity induced by hyperglycemia shift potassium, magnesium, and phosphorus from the intracellular to extracellular space. Dehydration results in hemoconcentration, which contributes to normal or high initial serum potassium, magnesium, and phosphorus readings in DKA, even with profound total body deficits. The effect of acidosis on the serum potassium level determination can be corrected by subtracting 0.6 mEq/L from the laboratory potassium level for every 0.1-decrease in pH noted in the arterial blood gas analysis. Thus, if the potassium level is reported as 5 mEq/L and the pH is 6.94, the corrected potassium value would be only 2 mEq/L, representing severe hypokalemia. As insulin is administered and the hydrogen ion concentration decreases, the patient needs considerable potassium replacement. Finally, hyperglycemia and the anion gap have significant effects on the plasma potassium concentration, independent of acidosis. No conversion factor has been developed for the estimation of true magnesium levels, although initial values may be high.

All laboratory determinations must be interpreted with caution. Serum creatinine level determinations made by autoanalyzer may be falsely elevated. Leukocytosis more closely reflects the degree of ketosis than the presence of infection. Only the elevation of band neutrophils has been demonstrated to indicate the presence of infection, with a sensitivity of 100% and specificity of 80% from a single small retrospective study. Historically, the diagnosis of pancreatitis in a patient with DKA could be confounded by the elevation of amylase levels in DKA. Given the strength of the current literature demonstrating greater specificity of lipase for the diagnosis of pancreatitis, lipase should be the blood test of choice if pancreatitis is a concern.

BOX 118.1

Summary of Treatment of Diabetic Ketoacidosis

Identify diabetic ketoacidosis—serum glucose, electrolyte, and ketone levels and arterial blood gas analysis; also obtain complete blood count with differential, urinalysis, chest radiograph, and electrocardiogram, if indicated.

Supplement insulin.
- Insulin replacement—0.1 unit/kg/hr regular insulin IV
- Change IV solution to D_5W/0.45% normal saline (NS) when glucose concentration is ≤300 mg/dL.

Rehydrate.
- 1–2 L NS IV during 1–3 hours
- Children—20 mL/kg NS during first hour

Correct electrolyte abnormalities.
- Sodium—correct with administration of NS or 0.45% NS.
- Potassium—ensure adequate renal function. Add 20–40 mEq KCl to each liter (when serum potassium < 5.5 mEq/L) of fluid until ketoacidosis is corrected and potassium is normalized. (Do not give insulin until potassium 3.3 mEq/L or greater.)
- Phosphorus—usually unnecessary to replenish.
- Magnesium—correct with 1–2 g $MgSO_4$. Serum magnesium levels may not correlate with body stores.

Correct acidosis.
- Administer IV fluids and insulin.

Search for and correct underlying precipitant.

Monitor progress and keep meticulous flow sheets.
- Vital signs
- Fluid intake and urine output
- Serum glucose, K^+, Cl^-, HCO_3^-, CO_2, pH
- Amount of insulin administered

Admit to hospital or intensive care unit.
- Consider outpatient therapy in children with reliable caregiver *and*
- Initial pH ≥ 7.35
- Initial HCO_3^- ≥ 20 mEq/L
- Can tolerate oral fluids
- Resolution of symptoms after treatment in emergency department
- No underlying precipitant requiring hospitalization

Differential Diagnoses

Alcoholics, especially those who have recently abstained from drinking, with Kussmaul's breathing, fruity odor to the breath, and acidemic arterial blood gas values may have alcoholic ketoacidosis. These patients may be euglycemic or hypoglycemic, and a large part of their acidosis is often caused by the unmeasured β-hydroxybutyric acid. Alcoholic ketoacidosis accounts for approximately 20% of all cases of ketoacidosis. Ketoacidosis can also develop with fasting, commonly in the third trimester of pregnancy and in nursing mothers who do not eat.

The differential diagnosis for DKA is broad and includes any entity that may cause elevated anion gap acidosis, ketosis, or both. The presence of DKA should not exclude investigation for other causes of anion gap metabolic acidosis, such as sepsis, poisoning, or lactic acidosis, because physiologic stress from one of these other causes can precipitate DKA.

Management

The comatose patient, especially if vomiting, requires intubation. Once the patient is intubated, maintenance of hyperventilation prevents worsening acidosis. The patient in hypovolemic shock requires aggressive fluid resuscitation with isotonic crystalloids rather than vasopressors; consider other possible causes of shock (eg, sepsis or myocardial dysfunction secondary to myocardial infarction). Bedside ultrasonography may be of benefit in excluding other causes of hypotension and evaluating the volume status of an individual patient. Although it is not routinely used in the ED setting, in cases in which the volume status is difficult to ascertain because of complex underlying physiologic derangements (eg, congestive heart failure, renal failure), the rapid ultrasound for shock and hypotension examination (see Chapter e5) or invasive hemodynamic monitoring may be required to guide fluid therapy.

When hyperglycemia, ketosis, and acidosis have been established, fluid, electrolyte, and insulin therapy should be initiated (Box 118.1).

Insulin

DKA cannot be reversed without insulin, and insulin therapy should be initiated as soon as the diagnosis is certain. There have been no randomized trials comparing insulin with placebo or other therapies for DKA. However, the mortality from DKA was 90% in historical controls before the development of exogenous insulin and 50% after insulin was introduced; with appropriate supportive therapy, it has reached the current levels of 5% to 7%.[9]

Although the dosing of insulin infusions has been established, the value of an IV bolus before the infusion remains controversial

and is no longer routinely recommended. More recently, in selected patients with mild DKA, the subcutaneous or intramuscular administration of insulin has been proven safe and as effective as IV administration of insulin. In selected cases with good outpatient follow-up, treatment of DKA with intermittent bolus dosing of regular insulin by the subcutaneous or intramuscular route without admission has also been shown to be safe. Such a strategy requires a well-hydrated, mildly acidemic patient who is well versed in his or her disease management and has excellent outpatient follow-up. Poor perfusion may hamper the absorption of intramuscular or subcutaneous insulin, resulting in erratic absorption, making IV infusion the route of choice in sicker DKA patients.[1,9] The current initial therapy of choice, as recommended by the ADA, is regular insulin infused at 0.1 units/kg/hr up to 5 to 10 units/hr, mixed with IV fluids.

Children with DKA pose additional management challenges. Whereas the general principles of fluid and electrolyte repletion in concert with insulin therapy remain the same, controversy exists about the dosing and administration of fluids and insulin because of concerns related to the risk of inducing cerebral edema in children with DKA. Despite frequently voiced concerns about this complication, it remains rare, with an overall incidence of 1% in pediatric DKA patients. Virtually all current evidence supporting the contention that the use of higher doses of insulin and aggressive fluid resuscitation contribute to the development of cerebral edema has come from retrospective reviews and small case studies. The best available evidence shows associations only with lower $Paco_2$ and higher blood urea nitrogen levels, indicating that severity of disease, rather than treatment interventions, plays the most significant role. DKA-related cerebral edema is more likely in children younger than 5 years, and good prospective data are needed to help guide recommendations. Currently, there is an ongoing clinical trial to assess risk and outcomes prospectively (clinicaltrials.gov). Given currently available data, patients should be carefully monitored and receive mannitol at the earliest suspicion of cerebral edema.

Because the half-life of regular insulin is 3 to 10 minutes, insulin should be administered IV by constant infusion rather than by repeated bolus. When the blood glucose concentration has dropped to 250 to 300 mg/dL, adding dextrose to the IV fluids reduces the risk of iatrogenic hypoglycemia and cerebral edema caused by rapid shifts in osmolarity. In patients with euglycemic DKA, dextrose should be added to the IV fluids at the start of insulin therapy.

Insulin resistance occurs rarely in diabetic patients and requires an increase in dosage for a satisfactory response to be obtained. Resistance may be caused by obesity or accelerated insulin degradation.

Intravenous Fluids

The severely dehydrated adult patient is likely to have a fluid deficit of 3 to 5 L. No uniformly accepted formula exists for the administration of fluid in this disorder. If the patient is in hypovolemic shock, isotonic crystalloid solution should be given as rapidly as possible in the adult or in boluses of 20 mL/kg in the child until a systolic pressure of 80 mm Hg is obtained. There is no consensus regarding the ideal fluid to use; concerns have been raised with the use of large amounts of normal saline exacerbating metabolic acidosis. At least one small trial has studied the use of a balanced crystalloid solution (Plasmalyte) in DKA, with reports of more rapid restoration of normal physiologic parameters.

In the adult who has marked dehydration in the absence of clinical shock or heart failure, 1 L of fluid may be administered in the first hour. In general, 2 L of fluid resuscitation during the first 1 to 3 hours is followed by a slower infusion of a hypotonic solution, such as 0.45% normal saline solution. DKA patients without extreme volume depletion may be successfully treated with a lower volume of IV fluid replacement. An initial bolus of 20 mL/kg during the first hour is the usual fluid resuscitation therapy for a child. The fluid rate should be adjusted according to age, cardiac status, and degree of dehydration to achieve a urine output of 1 to 2 mL/kg/hr.

Fluid resuscitation alone may help lower hyperglycemia. Because a low level of circulating insulin may be present, increased perfusion may transport insulin to previously unreached receptor sites. In addition, a large volume of glucose may be cleared by the kidneys in response to improved renal perfusion. The mean plasma glucose concentration has been noted to drop by 18% after the administration of saline solution without insulin.[1]

Acidosis also decreases after fluid infusion because increased perfusion improves tissue oxygenation and diminishes the formation of lactate. Increased renal perfusion promotes renal hydrogen ion loss, and the improved action of insulin in the better hydrated patient inhibits ketogenesis. Although fluid administration decreases the serum glucose concentration and improves acidosis, the underlying deficiency in DKA still requires administration of insulin for correction of ketoacidosis.

Potassium

Potassium replacement is invariably needed in DKA. The initial potassium level is often normal or high, despite a large deficit because of severe acidosis. Potassium levels often plummet with correction of acidosis and administration of insulin. Once potassium levels reach 5.0 to 5.5 mEq/L and the patient is making urine, potassium should be administered while monitoring renal function.[1,2] In patients with relatively lower serum potassium concentration at presentation (3.3 to 5.0 mEq/L), hypokalemia may become life-threatening when insulin therapy is administered; therefore, IV administration of potassium in concentrations of 20 to 40 mEq/L should be given with insulin administration. In patients with hypokalemia (<3.3 mEq/L), insulin should only be initiated once potassium has been replaced to achieve levels of 3.3 mEq/L or higher. The primary rationale for such conservative recommendations regarding potassium administration is that serum levels do not correlate with total body stores in the DKA patient, and the potassium level can drop more rapidly than anticipated with administration of insulin.

It was once believed that there was always a phosphorus deficit in DKA. As a result, after initial potassium administration was completed with potassium chloride, potassium phosphate was used for follow-up potassium administration to correct the phosphorus deficit. There is no scientific evidence to support this practice, and only isolated case reports have supported concerns about clinically significant hypophosphatemia in DKA. If the measured serum phosphorus level is low, it should be replaced with potassium phosphate.

Magnesium

Magnesium deficiency is a common problem in patients with DKA without renal disease. Both the initial pathophysiologic process and therapy for DKA induce profound magnesium diuresis. Magnesium deficiency may exacerbate vomiting and mental changes, promote hypokalemia and hypocalcemia, and/or induce fatal cardiac dysrhythmia. If there is concern for hypomagnesemia, we recommend adding magnesium to the IV fluids, with the typical adult patient requiring 1 to 3 g for repletion.

Acidosis

In the past, sodium bicarbonate was recommended for severely acidemic patients (pH < 7.0). However, research has demonstrated

worse outcomes for patients receiving bicarbonate, including exacerbation of electrolyte deficits such as hypokalemia, delaying clearing of ketosis, paradoxical worsening of acidosis in the CSF due to suppression of respiratory compensations and preferential permeability of the blood-brain barrier to CO_2. Unless needed to stave off impending cardiac arrest in a severely acidemic patient, we do not recommend routine bicarbonate administration.

Complications

The precipitating causes of DKA may have associated morbidity and mortality rates equal to or worse than those of DKA itself. These include iatrogenic causes, infection, and myocardial infarction. Morbidity in DKA is largely iatrogenic—hypokalemia from inadequate potassium replacement, hypoglycemia from inadequate glucose monitoring, failure to replenish glucose in IV solutions when the serum glucose concentration drops below 250 to 300 mg/dL, alkalosis from overaggressive bicarbonate replacement, and pulmonary edema from overaggressive hydration.

The mortality rate in treated DKA is approximately 5% to 7%. The primary causes of death remain infection, especially pneumonia, arterial thromboses, and shock. The decrease in the mortality rate has demonstrated that appropriate therapy can make a difference. Cerebral edema remains an important cause of morbidity and mortality in children with DKA.

Cerebral edema should be considered when the patient in DKA becomes altered or lapses into coma after the reversal of acidosis. Cerebral edema generally occurs 6 to 10 hours after the initiation of therapy; there are no warning signs, and the associated mortality rate is 90%.[2] Cerebral edema is less common in adults or children older than 5 years and appears to be most strongly associated with severity of illness (acidemia and azotemia), although subclinical cerebral edema in children is probably common. Furthermore, subclinical cerebral edema may precede or follow the onset of therapy, raising the question of whether it is caused by therapy or is simply a manifestation of the basic pathophysiologic mechanisms of DKA. The treatment of cerebral edema is largely supportive and outcomes are poor. No large clinical trials have identified effective treatment, although some authors recommend mannitol. Steroids have not been shown to be effective.

Disposition

Most patients with DKA require hospital admission, often to the intensive care unit. The use of observation units to manage uncomplicated DKA in selected patients has been shown to be effective (see Chapter e6). All pregnant diabetic patients in DKA require admission and consultation with an endocrinologist and obstetrician specializing in the care of high-risk pregnancies. Some children (initial pH ≥ 7.35; bicarbonate ≥ 20 mEq/L) with resolution of findings who can tolerate oral fluids after 3 or 4 hours of treatment may be discharged home with a reliable caregiver. Patients who have mild DKA may be treated on an outpatient basis if the patient or parent is reliable, underlying causes do not require inpatient therapy, and close follow-up is pursued.

HYPERGLYCEMIC HYPEROSMOLAR STATE

Principles

HHS represents a syndrome of acute diabetic decompensation characterized by marked hyperglycemia, hyperosmolarity, dehydration, and decreased mental function that may progress to frank coma. The terminology has changed recently from the former term *hyperglycemic hyperosmolar nonketotic coma* because some patients have mild degrees of ketosis, and coma is not universally present.[1,9] Ketoacidosis is generally minimal or absent, although metabolic acidosis from another source, such as lactic acidosis from sepsis or uremia from acute renal failure, may be present. Focal neurologic signs may be present, or there may be a global encephalopathy. DKA and HHS may occur together.

Pathophysiology

As with DKA, the pathophysiologic mechanisms of HHS vary with the particular patient. Because most patients with HHS are older adults, decreased renal clearance of glucose produced by the decline of renal function with age often contributes to the illness. Decreased insulin action results in glycogenolysis, gluconeogenesis, and decreased peripheral uptake of glucose. The hyperglycemia pulls fluid from the intracellular into the extracellular space, transiently maintaining adequate perfusion. Soon, however, this fluid is lost in a profound osmotic diuresis, limited finally by hypotension and a subsequent drop in the glomerular filtration rate (GFR). The urine is extremely hypotonic, with a urine sodium concentration between 50 and 70 mEq/L, compared with 140 mEq/L in extracellular fluid. This hypotonic diuresis produces profound dehydration, leading to hyperglycemia, hypernatremia, and associated hypertonicity. Often, the patient is prevented from taking in adequate fluids because of stroke, Alzheimer's disease, or other diseases, greatly exacerbating the dehydration.

The reason for the absence of ketoacidosis in HHS is unknown. FFA levels are lower than in DKA, thus limiting the substrates needed to form ketones. The most likely reason for the blunted counterregulatory hormone release and lack of ketosis seems to be the continued secretion of tiny amounts of insulin that block ketogenesis.

Causes

HHS is a syndrome of severe dehydration that results from a sustained hyperglycemic diuresis in which the patient is unable to drink sufficient fluids to offset the urinary losses. The full-blown syndrome does not usually occur until volume depletion has progressed to the point of decreased urine output.

HHS is most common in geriatric patients with type 2 diabetes, but has been reported in children with type 1 diabetes. HHS may occur in patients who are not diabetic, especially after burns, parenteral hyperalimentation, peritoneal dialysis, or hemodialysis.

Clinical Features

The prodrome of HHS is significantly longer than that of DKA. Clinically, extreme dehydration, hyperosmolarity, volume depletion, and CNS findings predominate. If they are awake, patients may complain of fever, thirst, polyuria, or oliguria. Approximately 20% of patients have no known history of type 2 diabetes. The most common associated diseases are chronic renal insufficiency, gram-negative pneumonia, GI bleeding, and gram-negative sepsis. Approximately 85% of patients have underlying renal or cardiac impairment as a predisposing factor. Arterial and venous thromboses are common and often complicate the picture.

The patient often exhibits orthostatic hypotension or frank hypotension, tachycardia, and fever, with signs of marked dehydration. The depression of the sensorium correlates directly with the degree and rate of development of hyperosmolarity. Some patients have a normal mental status. Neurologic issues are common in HHS. Whereas a decreased level of consciousness is the most common neurologic finding, seizures, stroke syndromes,

and movement disorders have been reported in various case series. Whether HHS is the cause of or result of these disorders is unclear, and there is no current evidence to recommend the prophylactic use of antiepileptics or antithrombotic agents in HHS patients.

Diagnostic Testing

Laboratory findings usually reveal a blood glucose level above 600 mg/dL and serum osmolarity above 350 mOsm/L. The blood urea nitrogen concentration is invariably elevated. Although patients with HHS do not have a ketoacidosis caused by diabetes, they may have a metabolic acidosis secondary to some combination of lactic acidosis, starvation ketosis, and retention of inorganic acids attributable to renal hypoperfusion.

The patient with HHS typically has a more profound electrolyte imbalance than the patient with DKA. Levels of potassium, magnesium, and phosphorus may seem initially high, even in the presence of a marked total deficit. In the absence of acidemia, however, the discrepancy between the initial electrolyte reading and body stores is less than that of DKA. Initial serum sodium readings are inaccurate because of hyperglycemia.

Differential Diagnoses

The differential diagnosis of HHS is identical to that of DKA. In addition, diabetic patients receiving chlorpropamide are subject to water intoxication with dilutional hyponatremia, which may be manifested as coma without acidosis that is clinically indistinguishable from HHS. The patient with HHS who has a sharply depressed sensorium may not be initially distinguishable from the patient with profound hypoglycemia. When the blood glucose concentration cannot be rapidly checked, the immediate administration of one ampule of $D_{50}W$ minimally worsens HHS and may be lifesaving for patients with hypoglycemia.

Management

The fluid, electrolyte, and insulin regimens for the initial resuscitation in HHS are subject to the same controversies as the therapies for DKA (see Box 118.1). There have been varying recommendations about which IV fluids to administer, generally based on calculations of water deficits. There have been no well-done randomized trials comparing isotonic versus hypotonic fluid resuscitation; use of an isotonic crystalloid is a reasonable choice in the volume-depleted patient. Cerebral edema has been noted in isolated case reports in adults, especially with glucose levels above 700 mg/dL. An association between IV fluid resuscitation and cerebral edema has not been shown in the literature; previous reports of this association may have been due to the confounder that it is seen in sicker patients who often receive more aggressive fluid resuscitation.

Intravenous Fluids

For patients in hypovolemic shock, initial IV fluid infusion is given as rapidly as possible. Glucose should be added to resuscitation fluids when the blood glucose level drops below 300 mg/dL. Because many HHS patients are older adults with coexisting disease, such as congestive heart failure and renal failure, noninvasive or invasive forms of hemodynamic monitoring may be required to guide fluid administration when there is clinical suspicion of pulmonary edema or volume overload.

Electrolytes

Measurement of serum electrolyte levels should be used to guide replacement in the HHS patient. In particular, because the degree of acidosis is generally less, potassium levels more accurately reflect total body stores than they do in DKA.

Insulin

The pathophysiologic mechanisms of HHS are different from those of DKA, and there is usually enough basal insulin function to prevent frank ketoacidosis. Therefore, a continuous IV insulin infusion is not required in these patients, as it is with DKA. However, there are times when the use of an IV insulin infusion may help lower the glucose concentration in a more controlled fashion, particularly in patients with very high glucose levels (>700 mg/dL) or those who are severely hypoperfused, in whom intramuscular or subcutaneous insulin absorption may be erratic. If an IV insulin infusion is used, it should be done at an infusion rate similar to that for DKA (0.1 unit/kg/hr).

Other Considerations

A vigorous search for the underlying precipitant of HHS should be pursued. Response to therapy should be followed in the manner described for patients in DKA. Phenytoin (Dilantin) is contraindicated for the seizures of HHS because it is often ineffective and may impair endogenous insulin release.[1,9] Admitted patients should be given low-dose subcutaneous heparin to lessen the risk of thrombosis, which is increased by the volume depletion, hyperviscosity, hypotension, and inactivity associated with HHS.

Acute Complications

Reasons for high morbidity and mortality rates are not always clear, but many patients with HHS are older adults who have underlying cardiac and renal disease. Pediatric HHS differs from adult HHS in that children have a much higher incidence of fatal cerebral edema. Other causes of morbidity and mortality are similar to those described for DKA. The mortality rate of treated HHS patients has been 40% to 70% in the past but now ranges from 8% to 25%.[1,9]

Disposition

In general, patients with HHS require hospitalization for IV hydration, glucose control, and evaluation of precipitating and complicating conditions.

LATE COMPLICATIONS OF DIABETES

Late complications of diabetes cause significant morbidity and mortality and develop approximately 15 to 20 years after the onset of overt hyperglycemia. The Diabetes Control and Complications Trial has shown that tight glycemic control significantly reduces the risk of microvascular disease, such as microalbuminuria (the earliest sign of nephropathy), neuropathy, and retinopathy, but at the expense of greatly increasing the risk of recurrent hypoglycemia.[1]

Vascular Complications

Diabetes is associated with an increased risk for atherosclerosis and thromboembolic complications, which are a major cause of morbidity and premature death. The cause of accelerated atherosclerosis is unknown, although it is probably related to oxidated low-density lipoprotein and increased platelet activity. Atherosclerotic lesions are widespread, causing symptoms in many organ systems. Coronary artery disease and stroke are common. Diabetic patients have an increased incidence of so-called silent myocardial infarction, complicated myocardial infarctions, and congestive

heart failure. Peripheral vascular disease is noted clinically by claudication, nonhealing ulcers, gangrene, and impotence. In addition, standard treadmill stress tests have a decreased sensitivity in the detection of coronary artery disease in diabetics. For this reason, exercise or pharmacologic stress echocardiography or a nuclear medicine imaging study should be considered when a provocative test is needed to evaluate the diabetic patient for acute coronary syndrome.[1]

Diabetic Nephropathy

Renal disease is a leading cause of death and disability in diabetic patients. Approximately 50% of cases of end-stage renal disease in the United States is caused by diabetic nephropathy. The appearance of microalbuminuria correlates with the presence of coronary artery disease and retinopathy. Azotemia generally does not begin until 10 to 15 years after the diagnosis of diabetes. Progression of renal disease is accelerated by hypertension. Meticulous control of diabetes can reverse microalbuminuria and may slow the progression of nephropathy. Blood pressure should be aggressively managed; angiotensin-converting enzyme inhibitors are effective in controlling hypertension and lowering microalbuminuria. Chronic hemodialysis and renal transplantation are unfortunate endpoints for many diabetic patients with renal disease.

Retinopathy

Diabetes is a leading cause of adult blindness in the United States. Approximately 11% to 18% of all diabetic patients have treatable diabetic retinopathy, ranging from mild to severe, and manifested in many forms. The severity of diabetic retinopathy is clearly related to the quality of glycemic control. Background retinopathy is found in most patients with prolonged diabetes and characterized by microaneurysms, small vessel obstruction, cotton wool spots, soft or hard exudates, and macular ischemia. Proliferative retinopathy defines an entity of new vessel formation and scarring, as well as associated vitreal hemorrhage and retinal detachment. The diabetic patient may present with complaints ranging from acute blurring of vision to sudden unilateral or even bilateral blindness. Less often, diabetic patients have more gradual vision loss caused by the common senile cataract (or snowflake cataract), which may disappear as the hyperglycemia is corrected. Diabetic patients with retinopathy should be referred to an ophthalmologist. Even in those with normal vision, ophthalmologic procedures may limit visual loss or prevent crises such as neovascular glaucoma.

Neuropathy

Autonomic and peripheral neuropathies are well-known complications of diabetes. The prevalence of peripheral neuropathy ranges from 15% to 60%. The cause of the neuropathy is not clearly understood, but studies have suggested several factors in its development, including the effects of diabetic vascular disease on the vasa nervorum. Neurologic manifestations of diabetes may regress with improved glycemic control.

Several distinct types of neuropathy have been recognized in diabetes.[10] Peripheral symmetric neuropathy is a slowly progressive, primary sensory disorder manifested bilaterally with anesthesia, hyperesthesia, or pain. The pain is often severe and worse at night. It affects the upper and lower extremities, although the lower extremities and distalmost sections of the involved nerves are most often affected. There may be a motor deficiency as well. The pain may be very difficult to control; opioid analgesics have been used, but nonopioid medications such as gabapentin, pregabalin, and amitriptyline are preferred. Pregabalin is the newest of these agents and seems to hold the most promise when used at higher dosages (up to 600 mg/day). Duloxetine at a dosage of 60 mg/day is also effective. Both pregabalin and duloxetine achieve significant pain control in at least 50% of patients. Gabapentin, 300 mg tid, has some efficacy, achieving significant pain relief in about one-third of patients; amitriptyline 25 mg daily demonstrates similar results. A reasonable approach for the emergency clinician is the initiation of duloxetine or pregabalin, because these have shown the best efficacy in pain control, with the understanding that it may take several days for a peak effect to be reached.[11] Gabapentin in particular has a narrow toxic to therapeutic margin; for many patients, full therapeutic benefits do not occur until the dosage is 600 mg tid or more, at which point sedation frequently becomes severe enough to make the treatment intolerable.

Mononeuropathy, or mononeuropathy multiplex, affects motor and sensory nerves, generally one nerve at a time. The onset is rapid, with wasting and tenderness of the involved muscles. There may be a sudden onset of wrist drop, foot drop, or paralysis of cranial nerves III, IV, and VI. Diabetic truncal mononeuropathy occurs rapidly in a radicular distribution. In contrast to other mononeuropathies, it is primarily if not exclusively sensory. If it causes pain, it may mimic that of a myocardial infarction or acute abdominal inflammation. Like diabetic mononeuropathy, it may be most bothersome at night and generally resolves in a few months. Whereas diabetic mononeuropathy is often the first indication of diabetes, truncal mononeuropathy is more often found in known diabetic patients. Management is similar to other diabetic neuropathies, with the exception of CN III palsy, which is usually expectant management.

Autonomic neuropathy occurs in many forms. Neuropathy of the GI tract, with resultant gastroparesis, is manifested by difficulty in swallowing, delayed gastric emptying, constipation, and/or nocturnal diarrhea. Impotence and bladder dysfunction or paralysis may occur. Orthostatic hypotension, syncope, and even cardiac arrest have resulted from autonomic neuropathy. Diabetic diarrhea responds to diphenoxylate and atropine, loperamide, or clonidine. Orthostatic hypotension is treated by sleeping with the head of the bed elevated, avoidance of sudden standing or sitting, and use of full-length elastic stockings. For gastroparesis, we recommend metoclopramide for its prokinetic and antiemetic properties. Many patients with gastroparesis present with abdominal pain; opioids are not recommended for this group due to the risk of worsening dysmotility of the GI tract.

The Diabetic Foot

Approximately 20% of hospitalizations in diabetic patients are related to foot problems.[1] Sensory neuropathy, ischemia, and infection are the principal contributors to diabetic foot disease. Loss of sensation leads to pressure necrosis from poorly fitting footwear and small wounds going unnoticed. The most common cause of injury is pressure on plantar bone prominences. All neuropathic foot ulcers should be assessed for infection, devitalized tissue débrided, and radiographs obtained to evaluate for the presence of foreign bodies, soft tissue gas, or bone abnormalities.[1]

Not all ulcers are infected. Infection is suggested by local inflammation or crepitation. Conversely, some uninflamed ulcers are associated with underlying osteomyelitis. Most mild infections are caused by gram-positive cocci, such as *Staphylococcus aureus* or streptococci, and may be treated with oral antibiotics with activity against gram-positive organisms, such as trimethoprim-sulfamethoxazole, 800/160 mg bid, a first-generation cephalosporin such as cephalexin, 500 mg qid, or clindamycin, 300 mg qid. A strict non–weight-bearing regimen, meticulous wound care, and daily follow-up are also vitally important to wound healing.

TABLE 118.3

Common Serious Infections in Diabetics and Their Antimicrobial Therapy

INFECTIOUS CONDITION	ANTIMICROBIAL THERAPY
Diabetic foot infection	Mild—consider trimethoprim-sulfamethoxazole, 800/160 bid or clindamycin 300 mg q6h Moderate to severe—clindamycin, 600 mg IV q6h ± piperacillin-tazobactam (Zosyn), 3.375 g IV q6h and vancomycin,n 15 mg/kg IV q12h
Malignant otitis externa	Oral—ciprofloxacin, 500 mg PO bid for 10–14 days IV—ceftazidime, 2 g IV q8h ± gentamicin, 2 mg/kg IV q8h
Mucormycosis	Amphotericin B, 1–1.5 mg/kg/day Posaconazole, 400 mg bid
Mucocutaneous candidiasis	Ketoconazole, 200 mg PO daily; may need several weeks of therapy
Nonclostridial gas gangrene (including Fournier's)	Clindamycin, 600 mg q6h + third-generation cephalosporin + vancomycin, 15 mg/kg q12h

TABLE 118.4

Common Oral Diabetic Medications

MEDICATION	FUNCTION	DETAILS
Biguanides (metformin)	Decrease hepatic glycogenolysis	500–1000 mg bid
Sulfonylureas (glipizide, glimepiride)	Stimulate pancreatic insulin release	2.5–5 mg daily
Thiazolidinediones (pioglitazone, rosiglitazone)	Insulin sensitizers, decrease hepatic gluconeogenesis	Increased risk of adverse cardiac events
Meglitinides (repaglinide, nateglinide)	Stimulate postprandial insulin release	Take with meals only
Dipeptidyl peptidase 4 inhibitors (sitagliptin)	Decrease insulin degradation and gluconeogenesis	Once daily; can be found in multiple combination medications
α-Glucosidase inhibitors (acarbose, miglitol)	Delay breakdown of carbohydrates in the intestines	Major side effect is diarrhea

This approach may not be possible when patients are deemed unreliable, do not have good home support, or do not have ready access to follow-up care.

Deeper, limb-threatening infections—as evidenced by full-thickness ulceration, cellulitis more than 2 cm in diameter, with or without lymphangitis, bone or joint involvement, or systemic toxicity—are usually polymicrobial in origin and caused by aerobic gram-positive cocci, gram-negative bacilli, and anaerobes. These patients require hospitalization and, after culture, broad-spectrum IV empirical antimicrobial therapy (Table 118.3), strict non–weight-bearing status, tight glycemic control, early surgical intervention for débridement, and meticulous wound care. Occult osteomyelitis should be considered in all cases of neuropathic ulceration.[1] Hyperbaric oxygen has been shown to have some efficacy in the treatment of complicated infection, especially with anaerobic organisms. Up to one-third of patients eventually undergo amputation.

Infections

Diabetic patients are more susceptible to complications of infections because of their inability to limit microbial invasion with effective polymorphonuclear leukocytes and lymphocytes. They have an increased incidence of extremity infections and pyelonephritis compared with the general population. In addition, they are particularly susceptible to certain other infections, such as tuberculosis, mucocutaneous candidiasis, intertrigo, mucormycosis, soft tissue infections, nonclostridial gas gangrene, osteomyelitis, and malignant *Pseudomonas* otitis externa (Table 118.4); glycemic control and generally hospitalization are recommended.

Cutaneous Manifestations

Dermal hypersensitivity is manifested by pruritic erythematous indurations that occur at insulin injection sites. The declining prevalence of this condition has paralleled the improved purification of insulin. Similarly, insulin lipoatrophy seems to be a result of insulin impurities and is manifested as subcutaneous depressions at injection sites. Although lipoatrophy is now more common than dermal hypersensitivity, its prevalence has also declined sharply because of improved insulin preparations. Insulin lipohypertrophy is manifested by raised areas of subcutaneous fat deposits at insulin injection sites. These lesions generally reflect the failure of the patient to rotate injection sites adequately. They resolve spontaneously over months if insulin injection is avoided in the affected areas and sites are properly rotated.

Insulin pumps are often associated with localized skin problems, usually a reaction to the tape securing the tubing and needles. On occasion, sensitivity to the catheters is seen. Skin infections at the site of injection are the most common complication of insulin pumps. Changing the patient from unbuffered beef-pork insulin to buffered pure pork is the only intervention that seems to reduce the rate of infection. A few patients have been noted to have hard nodules at the injection site. The cause of these nodules is uncertain.

Diabetic patients who use oral hypoglycemic agents may have rashes associated with these medications. After consumption of ethanol, approximately 38% of type 2 patients taking chlorpropamide exhibit a flush consisting of redness of the face and neck and a sense of warmness or burning. Patients may demonstrate urticaria in response to insulin and oral hypoglycemics.

Skin Conditions. Diabetic skin conditions include fungal infections, acanthosis nigricans, necrobiosis lipoidica diabeticorum, xanthoma diabeticorum, bullosis diabeticorum, and diabetic dermopathy.

Acanthosis Nigricans. This is characterized by a velvety, brown-black thickening of the keratin layer, most often in the flexor surfaces. It is the cutaneous marker for a group of endocrine disorders with insulin resistance.

Necrobiosis Lipoidica Diabeticorum. This begins as erythematous papular or nodular lesions, usually in the pretibial area but in other areas as well. The early lesions may contain telangiectasias. These lesions spread and frequently form a single pigmented area of atrophic skin, often with a yellow and sometimes ulcerated center and an erythematous margin. A history of previous trauma is sometimes found.

Xanthoma Diabeticorum. This is evidence of the hyperlipidemia associated with diabetes. It is similar to the xanthoma

found in nondiabetic hyperlipidemic patients. Xanthomas have an erythematous base and a yellowish hue.

Bullosis Diabeticorum. This is a rare occurrence. Bullae are usually filled with a clear fluid and are most often found on the extremities, especially the feet. The fluid is occasionally slightly hemorrhagic. The bullae usually heal spontaneously, without scarring.

Diabetic Dermopathy. Also known as skin spots, this is the most common finding in diabetes. It arises as discrete, depressed, and brownish lesions generally less than 15 mm in diameter and found in the pretibial area.

Impetigo or Intertrigo. Resistant, aggressive impetigo or intertrigo suggests diabetes.

DIABETES IN PREGNANCY

Before the discovery of insulin in 1922, diabetes in pregnancy was associated with a fetal death rate of 60% to 72% and maternal morbidity of approximately 30%.[12] In 1977, a linear relationship between glycemic control and perinatal mortality was discovered. Strict metabolic control is now a goal in all diabetic pregnancies.[13]

Pregnant patients should be watched extremely closely and aggressively treated for impending or actual DKA. For a variety of reasons, pregnant women have a special predisposition to glucose intolerance and excess ketone production. Although uncommon, DKA may reduce fetal oxygen delivery and cause perinatal asphyxia. Intellectual deficits in the offspring have been associated with maternal ketonuria from any cause.

Hypoglycemia is common in pregnancy, in part because of intensive insulin treatment to maintain euglycemia. The effects of hypoglycemia on the fetus are unclear. Severe ketoacidosis is associated with a 50% to 90% fetal mortality rate due to hypoperfusion of the placenta.[13]

HYPOGLYCEMIA

Principles

Hypoglycemia is a common problem in patients with type 1 diabetes, especially if tight glycemic control is practiced; it is the most dangerous acute complication of diabetes. The estimated incidence of hypoglycemia in diabetic patients is 9 to 120 episodes/100 patient-years. As significant efforts continue to keep fasting and postprandial glucose concentrations within the normal range, the incidence of hypoglycemia may increase. The most common cause of coma associated with diabetes is an excess of administered insulin with respect to glucose intake. Severe hypoglycemia is usually associated with blood glucose levels below 40 to 50 mg/dL and impaired cognitive function.

Protection against hypoglycemia is normally provided by cessation of insulin release and mobilization of counterregulatory hormones, which increase hepatic glucose production and decrease glucose use. Diabetic patients using insulin are vulnerable to hypoglycemia because of insulin excess and failure of the counterregulatory system.

Hypoglycemia has many causes, such as missing a meal (decreased intake), increased energy output (exercise), and increased insulin dosage. It can also occur in the absence of any precipitant. Oral hypoglycemic agents have also been implicated in causing hypoglycemia, both during the course of therapy and as an agent of overdose.

Hypoglycemia without warning symptoms, or hypoglycemia unawareness, is a dangerous complication of type 1 diabetes and is probably caused by previous exposure to low blood glucose concentrations,[14] because even a single hypoglycemic episode can reduce neurohumoral counterregulatory responses to subsequent episodes. Other factors associated with recurrent hypoglycemic attacks include overaggressive or intensified insulin therapy, longer history of diabetes, autonomic neuropathy, and decreased epinephrine secretion or sensitivity.

The Somogyi phenomenon is a common problem associated with iatrogenic hypoglycemia in the type 1 diabetic patient. The phenomenon is initiated by excessive insulin dosing, resulting in an unrecognized hypoglycemic episode that usually occurs in the early morning while the patient is sleeping. The counterregulatory hormone response produces rebound hyperglycemia, evident when the patient awakens. Often, the patient and physician interpret this hyperglycemia as an indication to increase the insulin dosage, which exacerbates the problem. Instead, the insulin dosage should be lowered or the timing changed.

Clinical Features

Symptomatic hypoglycemia occurs in most adults below a blood glucose level of 40 to 50 mg/dL. The rate at which the glucose level decreases, however, and the patient's age, gender, size, overall health, and previous hypoglycemic reactions contribute to symptom development. Signs and symptoms of hypoglycemia are caused by excessive secretion of epinephrine and CNS dysfunction; these include sweating, nervousness, tremor, tachycardia, hunger, and neurologic symptoms, ranging from bizarre behavior and confusion to seizures and coma. In patients with hypoglycemia unawareness, the prodrome to marked hypoglycemia may be minimal or absent, and these individuals may rapidly become unarousable. They may have a seizure or show focal neurologic signs, which resolve with glucose administration.

Differential Diagnoses

Hypoglycemia in the nondiabetic patient may be classified as postprandial or fasting. The most common cause of postprandial hypoglycemia is alimentary hyperinsulinism, such as that seen in patients who have undergone gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy. Fasting hypoglycemia is caused when there is an imbalance between glucose production and use. The causes of inadequate glucose production include hormone deficiencies, enzyme defects, substrate deficiencies, severe liver disease, and drugs. Causes of overuse of glucose include the presence of an insulinoma, exogenous insulin, sulfonylureas, drugs, endotoxic shock, extrapancreatic tumors, and a variety of enzyme deficiencies.

Diagnostic Testing

The cardinal laboratory test for hypoglycemia is determination of the blood glucose concentration. It should be performed, if possible, before therapy is begun. As noted, fingerstick readings are helpful in permitting rapid, reasonably accurate blood glucose level estimates before therapy.

Laboratory testing should address any suggested cause of the hypoglycemia, such as ethanol or other drug ingestion. If factitious hypoglycemia is suggested, testing for insulin antibodies or low levels of C peptide may be helpful. A patient who is surreptitiously administering exogenous insulin will have normal to low levels of C peptide and markedly elevated insulin levels.

Management

In alert patients with mild symptoms, oral consumption of sugar-containing foods or beverages is often adequate. In other patients, after blood is drawn for glucose determination, one to three ampules of $D_{50}W$ is administered IV while the patient's airway, breathing, and circulation are assessed and maintained.

Augmentation of the blood glucose level by administration of an ampule of $D_{50}W$ may range from less than 40 mg/dL to more than 350 mg/dL. If alcohol abuse is suggested, thiamine is administered. In children younger than 8 years, providers should use $D_{25}W$ or $D_{10}W$. $D_{25}W$ may be prepared by diluting $D_{50}W$ 1:1 with sterile water. The dose is 0.5 to 1 g/kg body weight or 2 to 4 mL/kg when using $D_{25}W$.

If IV access cannot be rapidly obtained, 1 to 2 mg of glucagon may be given intramuscularly or subcutaneously. The onset of action is 10 to 20 minutes, and a peak response occurs in 30 to 60 minutes. It may be repeated as needed. Glucagon may also be administered IV; 1 mg has an effect similar to that of one ampule of $D_{50}W$. Glucagon is ineffective in causes of hypoglycemia in which glycogen is absent, notably alcohol-induced hypoglycemia.

Families of type 1 diabetic patients are often taught to administer glucagon intramuscularly at home. Of the families so instructed, only 9% to 42% actually inject the glucagon when indicated. Intranasal glucagon has not been widely used. All patients with severe hypoglycemic reactions require aspiration and seizure precautions. Although the response to IV administration of glucose is generally rapid, older patients may require several days for complete recovery.

Treatment of hypoglycemia secondary to oral hypoglycemic agents depends on the agent. Metformin and the thiazolidinediones rarely cause significant or prolonged hypoglycemia, whereas sulfonylureas, which are insulin secretagogues, do cause hypoglycemia. Sulfonylurea oral hypoglycemic agents pose special problems because the hypoglycemia they induce tends to be prolonged and severe. Patients with an overdose of sulfonylurea hypoglycemic agents should be observed for a period of 24 hours if hypoglycemia recurs in the ED after management of the initial episode. Patients at risk for hypoglycemia from oral sulfonylureas include patients with impaired renal function, pediatric patients, and patients who are naïve to hypoglycemic agents. Although symptoms may occur after an overdose, several case reports in patients (eg, with renal failure and pediatric patients) have described refractory hypoglycemia after ingestion of a single pill. One case series of pediatric patients presenting with sulfonylurea ingestion who were euglycemic initially demonstrated an average time to onset of 8 hours to the initial hypoglycemic episode.[15] However, in some patients, onset of symptoms was delayed for up to 18 hours. As a result, we recommend 24 hours of observation for patients with known or suspected ingestion of hypoglycemic agents.

A patient with hypoglycemia from sulfonylureas, in addition to standard glucose replacement, frequently requires treatment with an agent to inhibit further insulin release, such as octreotide, a somatostatin analogue. Several case series have described the use of octreotide in adult and pediatric patients suffering from sulfonylurea-induced hypoglycemia, frequently reporting successful results, with a significant decrease in the number of episodes of recurrent hypoglycemia. A randomized clinical trial has concluded that patients receiving octreotide had a decreased glucose supplementation requirement.[16] No single set protocol for use has been described; however, typical adult doses have ranged from 50 to 100 μg IV or subcutaneously every 12 hours, with pediatric dosages of 0.1 mcg/kg IV or subcutaneously. Although experience thus far with octreotide has been positive, it does not obviate the need for prolonged observation and serial glucose level measurements.

Disposition

Type 1 diabetic patients with brief episodes of hypoglycemia uncomplicated by other disease may be discharged from the ED if a cause of the hypoglycemia can be identified and corrected by instruction or medication. All patients should be given a meal before discharge to ensure their ability to tolerate oral feedings and to begin to replenish glycogen stores in glycogen-deficient patients. Patients who are discharged should receive short-term follow-up for ongoing evaluation. Patients with hypoglycemia caused by long-acting sulfonylurea medications should be observed in the hospital if they have recurrent hypoglycemia after a period of observation in the ED. Other agents, such as metformin, do not typically produce hypoglycemia, although they may have other issues, such as lactic acidosis, that may require admission.

The determination of inpatient versus outpatient evaluation of hypoglycemia in a nondiabetic patient should be based on the suggested cause and nature of the episode (ie, factors such as severity, persistence, and recurrence).

KEY CONCEPTS

- The diagnosis of diabetes can be determined by one or more of four methods—random plasma glucose level above 200 mg/dL, fasting plasma glucose concentration above 126 mg/dL, 2-hour, 75-g postload OGTT > 200 mg/dL, or HbA_{1c} value above 6.5%.
- DKA is diagnosed by the presence of hyperglycemia, anion gap metabolic acidosis, and elevated ketoacid levels.
- The essential treatment of DKA includes restoration of insulin, correction of dehydration, correction of potassium level, correction of acidosis, and treatment of the underlying cause.
- Use of sodium bicarbonate to correct acidosis in DKA has not demonstrated any benefit and may be associated with worse outcomes.
- A hyperglycemic hyperosmolar state is usually seen in older adults with multiple comorbid conditions and is distinguished from DKA by the absence of ketoacidosis. In addition to fluid resuscitation and correction of hyperglycemia, treatment should address the underlying cause of the state, which includes infection, myocardial infarction, and cerebrovascular accident.
- Diabetic peripheral neuropathy is common and has multiple treatment modalities, including gabapentin, pregabalin, and duloxetine.
- Diabetic foot ulcers and other diabetic soft tissue infections (eg, gas gangrene, Fournier's gangrene) are frequently polymicrobial and require broad-spectrum antibiotic therapy covering gram-positives, gram-negatives, and anaerobes.
- Hypoglycemia may be associated with significant morbidity and mortality. When the diagnosis is suggested and, if possible, confirmed by laboratory evaluation, therapy should be initiated immediately.
- Hypoglycemia caused by sulfonylurea oral hypoglycemic agents may be prolonged. Patients should be observed for an extended period or hospitalized.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 118: QUESTIONS & ANSWERS

118.1. Which of the following statements regarding patients with impaired glucose tolerance is true?
- **A.** Spontaneous reversion to normal glucose tolerance is rare.
- **B.** The condition is associated with fewer complications than diabetes mellitus.
- **C.** The rate of decompensation to diabetes mellitus is greater than 10%/year.
- **D.** There is a predisposition to ketosis.
- **E.** There is no increased risk of cardiovascular complications.

Answer: B. Patients with impaired glucose tolerance have a glucose level between normal and diabetic. They are at increased risk of cardiovascular disease and development of diabetes (1%–5%/year), but it is not associated with the same degree of complications as with true diabetes. Many patients spontaneously develop normal glucose levels.

118.2. What percentage of adults with type 2 diabetes are obese?
- **A.** 20%
- **B.** 40%
- **C.** 60%
- **D.** 80%
- **E.** 100%

Answer: D. Nonobese patients form a subgroup with a different disease, more similar to type 1 diabetes. Young people with maturity-onset diabetes often have an autosomal dominant inheritance, are nonobese, and have a relatively mild disease course.

118.3. A 56-year-old man with a 10-year history of type 2 diabetes and poor glucose control (HbA_{1c} = 10.7%) complains of constant burning pain in both feet. Which agent would be most appropriate to start in this patient for initial management of his symptoms?
- **A.** Aspirin, 325 mg PO daily
- **B.** Carbamazepine, 200 mg tid
- **C.** Naproxen, 500 mg bid
- **D.** Oxycodone/acetaminophen, 5/325 mg qid
- **E.** Pregabalin, 600 mg daily

Answer: E. Pregabalin in a dose of 600 mg daily gives pain relief in approximately 50% of patients with diabetic neuropathy. Duloxetine, 60 mg daily, achieves similar results. Gabapentin, 300 mg once a day up to tid, and amitriptyline, 25 mg daily, provide pain relief in approximately 33% of patients.

118.4. A 27-year-old juvenile-onset diabetic is brought by emergency medical services (EMS) for a hypoglycemic coma. Fingerstick glucose level is 30 mg/dL. The paramedics were not able to obtain intravenous (IV) access, and two immediate attempts at IV cannulation failed in the emergency department (ED). What should be the next step in the patient's management?
- **A.** Albuterol, 2.5 mg nebulized
- **B.** Central venous catheter placement, then $D_{50}W$ IV
- **C.** Epinephrine, 1 mg IV
- **D.** Glucagon, 2 mg intramuscularly
- **E.** Peripheral IV catheterization via cutdown and then $D_{50}W$

Answer: D. Intravenous dextrose (25–75 g for adults, 0.5–1 g/kg for children) is preferable but, if unable to obtain IV access, administer glucagon, 1 or 2 mg intramuscularly (IM) or subcutaneously (SC; 0.025–0.1 mg/kg IM or SC in children). Onset of action is 10 to 20 minutes. It is ineffective in cases of glycogen absence, such as alcohol-induced hypoglycemia.

118.5. A 33-year-old juvenile-onset, insulin-dependent diabetic suddenly faints without prodrome or warning while walking through the ED. Relatives report that diabetes is his only past history. Which of the following findings is most likely?
- **A.** Autonomic neuropathy on later orthostatic testing
- **B.** Fingerstick glucose 27 mg/dL
- **C.** Hemoccult-positive stool
- **D.** Positive enzyme-linked immunosorbent assay (ELISA) D-dimer
- **E.** Supraventricular tachycardia on electrocardiogram (ECG)

Answer: B. Hypoglycemia without warning, or hypoglycemia unawareness, is a complication of type 1 diabetes caused by previous hypoglycemic episodes. A single hypoglycemic episode may blunt neurohormonal counterregulatory responses to later hypoglycemic episodes. Risk factors are overaggressive insulin therapy, longer history of diabetes, and autonomic neuropathy, which usually causes orthostasis on first standing or after being upright in a static position. These patients may become abruptly unarousable without warning.

118.6. A 47-year-old man presents with hypoglycemia. He is a known type 2 diabetic on glyburide. Fingerstick glucose is 27 mg/dL. Twenty minutes after two ampules (50 g) of dextrose, his glucose level is 29 mg/dL. Which of the following agents is indicated?
A. Adenosine
B. Epinephrine
C. Glucagon
D. Hydrocortisone
E. Octreotide

Answer: E. A patient with hypoglycemia from sulfonylureas, in addition to standard glucose replacement, frequently requires treatment with an agent to inhibit further insulin release, such as octreotide (a somatostatin analogue). Sulfonylureas are insulin secretagogues.

118.7. What is the most important determinant of mental status in a patient with diabetic ketoacidosis (DKA)?
A. Acidemia
B. Calcium level
C. Glucose level
D. Osmolarity
E. Potassium level

Answer: D. The hyperosmolarity produced by dehydration and hyperglycemia is the most important determinant of mental status during an episode of DKA.

118.8. A 73-year-old male patient presents with a draining sore on the bottom of his foot. He is noted to have a 3- × 4-cm ulcerated, malodorous lesion on his plantar foot, with surrounding erythema. Which antimicrobial agent should be included as part of the management of this infection?
A. Cefazolin, 1 g qid
B. Ceftriaxone, 1 g every 24 hours
C. Levofloxacin, 500 mg every 24 hours
D. Metronidazole, 500 mg qid
E. Piperacillin/tazobactam, 3.375 g qid

Answer: E. Piperacillin/tazobactam and vancomycin are considered the first-line agents for management of complicated diabetic foot infections.

118.9. A 43-year-old patient is brought to the ED with altered mental status. Other past history is unavailable, there are no signs of trauma, and the physical examination is normal except for the patient's mental status. Laboratory assessment reveals the following:
Sodium = 132 mEq/L
Potassium = 3.0 mEq/L
Chloride = 82 mEq/L
Bicarbonate = 36 mEq/L
Creatinine = 1.4 mg/dL
Blood urea nitrogen (BUN) = 26 mg/dL
Urine ketones—trace positive
Arterial blood gases (ABG)
Po_2 = 90 mm Hg,
Pco_2 = 30 mm Hg
pH = 7.49
What additional finding is the most likely?
A. Elevated glucose level
B. Elevated iron level
C. Elevated salicylate level
D. Evidence of toluene ingestion
E. History of alcohol abuse

Answer: E. The finding of alkalemia with ketoacidosis should prompt the consideration of alcoholic ketoacidosis, in which the acidosis is counterbalanced by alkalosis from severe nausea and vomiting. This may also be seen with DKA but is less likely.

118.10. What percentage of cases of DKA occur in patients whose diabetes was previously undiagnosed?
A. 10%
B. 25%
C. 50%
D. 75%
E. 90%

Answer: B. 25%.

118.11. A 28-year-old juvenile-onset diabetic presents in DKA. Laboratory assessment reveals a sodium level of 130 mEq/L and serum glucose level of 700 mg/dL. What is the approximate total serum sodium value?
A. 125 mEq/L
B. 130 mEq/L
C. 135 mEq/L
D. 139 mEq/L
E. 144 mEq/L

Answer: D. The true value of sodium may be approximated by adding 1.6 mEq/L to the reported sodium value for every 100-mg/dL glucose over the norm.

118.12. A 31-year-old insulin-dependent diabetic presents in DKA. His reported serum potassium level is 5 mEq/L, with a pH of 6.90. What is his corrected potassium level value?
A. 2 mEq/L
B. 2.5 mEq/L
C. 3 mEq/L
D. 3.5 mEq/L
E. 4 mEq/L

Answer: A. The effect of acidosis on the serum potassium can be corrected by subtracting 0.6 mEq/L from the laboratory potassium value for every 0.1 decrease in pH noted on the ABG analysis. For this patient, assuming a normal pH of 7.40,
7.40 − 6.90 = 0.5 (five 0.1 pH increments)
5 × 0.6 = 3 mEq/L correction factor

118.13. Which of the following statements regarding the laboratory evaluation of DKA is true?
A. Amylase levels maintain their sensitivity for detecting pancreatitis.
B. Creatinine levels may be falsely elevated.
C. Hypertriglyceridemia is unusual.
D. Leukocytosis is often present in the absence of infection.
E. True magnesium levels may be estimated by a conversion factor.

Answer: B. Serum creatinine levels may be falsely elevated if measured by autoanalyzer. No conversion factor exists for estimating magnesium. Leukocytosis typically parallels the degree of ketosis. A bandemia, however, indicates the presence of infection, with a sensitivity of 100% and specificity of 80%. Elevated triglyceride levels are seen routinely. Elevated amylase levels (salivary) are routinely seen; however, lipase maintains its sensitivity for pancreatitis.

118.14. Alcoholic ketoacidosis accounts for what percentage of all cases of ketoacidosis?
A. 10%
B. 20%
C. 30%
D. 40%
E. 50%

Answer: B. Ketoacidosis may also develop with fasting in the third trimester of pregnancy and in nursing mothers who do not eat well.

118.15. A 26-year-old known diabetic presents with altered mental status. EMS reports a fingerstick glucose of 750 mg/dL. The patient vomited once en route. The physical examination is remarkable for a comatose patient with the following vital signs—respiratory rate, 30 breaths/min; heart rate, is 140 beats/min; blood pressure, 85/40 mm Hg. Which of the following should be the first intervention?
A. Dopamine, 10 μg/kg/min
B. Endotracheal intubation
C. Isotonic fluid bolus, 20 mL/kg
D. Regular insulin 0.1 units/kg IV
E. Sodium bicarbonate IV

Answer: B. The comatose DKA patient, especially if vomiting, requires intubation. Hyperventilation should be rapidly initiated to prevent worsening acidosis. Isotonic fluid resuscitation, insulin bolus and infusion, and meticulous attention to electrolyte management must follow.

118.16. What is the half-life of regular insulin when administered intravenously?
A. 3–10 minutes
B. 10–15 minutes
C. 15–20 minutes
D. 20–25 minutes
E. 25–30 minutes

Answer: A. With a half-life of only 3 to 10 minutes, regular insulin requires an infusion rather than intermittent bolus therapy for optimal effect.

118.17. A patient with severe DKA is treated with fluid resuscitation and an insulin infusion. Six hours later, the patient develops confusion, disorientation, and hypercarbia from altered respiratory muscle performance. A repeat serum glucose level is 193 mg/dL. Which of the following treatments is most appropriate?
A. Calcium replenishment
B. Magnesium replenishment
C. Phosphorus replenishment
D. Potassium replenishment
E. Sodium bicarbonate replenishment

Answer: C. Phosphorus levels may fall dramatically after initiation of standard DKA therapy. Hypophosphatemia may cause a left shift in the hemoglobin desaturation curve, depressed myocardial and respiratory muscle function, hemolysis, thrombocytopenia, platelet dysfunction, confusion, and disorientation. Cerebral edema would be in the differential diagnosis because it also occurs in the 6- to 10-hour range after initiating therapy.

118.18. Which of the following is not associated with cerebral edema after DKA?
A. Bicarbonate therapy
B. Blood glucose level > 350 mg/dL
C. Elevated BUN level
D. Hypocarbia
E. Onset 6 to 10 hours after initiation of therapy

Answer: B. Clinically evident cerebral edema does not usually occur unless the blood glucose level is less than 250 mg/dL and insulin is being used. The other listed factors are associated with this syndrome.

118.19. Which of the following may be associated with or cause the hyperglycemic hyperosmolar state (HHS)?
A. All of these
B. Anion gap metabolic acidosis
C. Chlorpropamide use
D. Choreoathetosis and segmental myoclonus
E. Confusion with depressed sensorium from hypoglycemia

Answer: A. HHS may be associated with many drugs and illnesses. Symptoms range from lethargy to focal neurologic changes and seizure or coma. Initial differentiation from hypoglycemic coma may be difficult until serum glucose levels are checked. Metabolic acidosis is not uncommon and may yield an elevated anion gap—lactic acidosis, starvation, and retention of inorganic acids. HHS may occur in nondiabetics after burns or peritoneal hemodialysis.

118.20. A 69-year-old patient presents with new-onset seizures, serum glucose level of 850 mg/dL, and serum osmolarity of 340 mOsm/L. His past history is remarkable for chronic renal insufficiency resulting from hypertension. His only current medications are amlodipine and furosemide. Which of the following statements regarding the patient's condition is true?
A. Emergent dialysis is indicated.
B. Furosemide may have precipitated this event.
C. Heparin has no therapeutic role.
D. Insulin is contraindicated in cases of renal insufficiency.
C. Phenytoin is indicated.

Answer: B. Regardless of the cause, the management of the hyperosmolar hyperglycemic state (HHS) centers on aggressive fluid management and low-dose insulin. Phenytoin is contraindicated in hyperosmolar hyperglycemic nonketotic coma (HHNC) because of its impairment of endogenous insulin release and ability to precipitate HHNC. Low-dose heparin may be indicated to lessen the risk of thrombosis. Furosemide is one of many drugs that may precipitate HHNC.

CHAPTER 119

Rhabdomyolysis

Ram Parekh

PRINCIPLES

Background

Rhabdomyolysis is a potentially life-threatening condition characterized by the breakdown of skeletal muscle and the release into the circulatory system of intracellular contents, including creatine kinase, aspartate transaminase, lactate dehydrogenase, aldolase, the heme pigment myoglobin, and electrolytes. The severity of illness ranges from asymptomatic elevations in serum muscle enzyme levels to life-threatening electrolyte imbalances and acute renal failure.

A healthy 70-kg man has approximately 28 kg of muscle. Skeletal muscle is 80% water and 20% protein, accounting for about half of the total body protein stores, and is the largest organ in the human body.

Physiology

Even at rest, muscle function requires a large amount of adenosine triphosphate (ATP). ATP generation by muscle accounts for 30% of the body's oxygen consumption at rest and up to 85% at extremes of physical activity. Resting muscle uses fatty acids for ATP generation. With activity, muscle draws on stored ATP for the first 8 seconds of activity, using the phosphagen (creatine phosphate) stores for the next 10 to 15 seconds. Finally, muscle depends on anaerobic glycogen metabolism to lactate for enough ATP for an additional 30 to 40 seconds of activity. Aerobic ATP production provides the bulk of the energy needed for muscle activity, but it requires oxygen. Glucose, amino acids, and fatty acids are incorporated into the Krebs cycle to produce much larger quantities of ATP by energy-rich compounds, such as the reduced forms of nicotinamide adenine dinucleotide and flavin adenine dinucleotide.

Myoglobin, like hemoglobin, binds and releases oxygen and delivers it to active skeletal muscle. Unlike hemoglobin, myoblobin's ability to deliver oxygen is unaffected by pH, resulting in a relatively increased affinity for oxygen in comparison to hemoglobin and delivery of oxygen to cellular mitochondria at low partial pressures of oxygen.

The integrity of muscle cells is dependent on healthy cell membranes, which rely on ATP for proper membrane ion pump function. The sarcolemma, a thin membrane that encloses striated muscle fibers, contains numerous pumps that regulate electrochemical gradients. Under normal physiologic conditions, the sodium-potassium–adenosine triphosphatase (Na^+,K^+-ATPase) pump, located in the sarcolemma, maintains intracellular sodium concentrations of 10 mEq/L and intracellular potassium concentrations of 150 to 160 mEq/L. It achieves this by actively transporting sodium from the interior of the cell to the exterior, thereby making the interior of the cell more negative by the efflux of net positive charge—three sodium ions pumped out per two potassium ions pumped in. This electrical gradient pulls sodium to the interior of the cell through a separate channel in exchange for calcium, effectively removing calcium from the cytoplasm. Low intracellular calcium levels are also maintained by an active calcium exchanger (Ca^{2+}-ATPase pump) that promotes calcium entry into the sarcoplasmic reticulum and mitochondria. As their names indicate, these ATPase pumps depend on ATP as a source of energy.

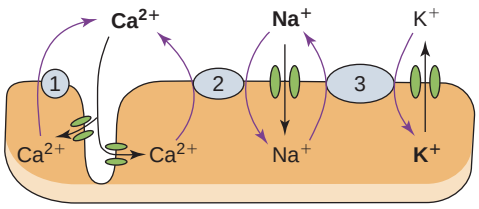
Under normal physiologic conditions, the concentration of free ionized calcium in the extracellular space is approximately 10,000 times greater than that in the intracellular space. The high concentration of free calcium in the extracellular pool compared with the intracellular compartment and the resulting large electrochemical force on Ca^{2+} are particularly convenient to its role as an intracellular regulator. Even minor changes in the permeability of the plasma membrane to calcium will produce significant fluctuations in the cytosolic concentration, with potentially unfavorable consequences for the integrity of the cell.

Several transmembrane proteins exist to regulate calcium homeostasis. The plasma membrane transmembrane proteins are the energy-consuming Ca^{2+} channels, Na^+-Ca^{2+} exchangers, and Ca^{2+}-ATPase pumps. The last removes Ca^{2+} from the intracellular space by transporting Ca^{2+} out of the cytosol into the extracellular space, as well as into the sarcoplasmic reticulum. Plasma membrane Ca^{2+} channels bring Ca^{2+} into the cytosol when activated at the neuromuscular junction. Na^+-Ca^{2+} exchangers are complicated in that the direction of ion movement depends on the chemical and electrical gradients of each ion within the cell, which vary according to the contractile state of the myocyte (Fig. 119.1).

Pathophysiology

Although the causes of rhabdomyolysis are diverse, the pathogenesis appears to follow a final common pathway—increased cytoplasmic calcium concentration, leading to myocyte destruction, with the release of muscle components into the circulation. There are two primary mechanisms whereby calcium pathologically accumulates in the cell, direct cell membrane damage and ATP depletion.

Membrane damage from trauma and genetic or biochemical factors results in a massive influx of extracellular calcium into the cytoplasm driven by electrical and chemical gradients. ATP depletion results in failure of cellular transport and increased permeability to sodium ions. Any event that increases cytosolic sodium concentrations, whether from increased membrane permeability and inward Na^+ traffic or decreased ATP-dependent pump removal of intracellular Na^+, results in increased Na^+-Ca^{2+} ion exchanger function and increased cytosolic calcium concentrations. ATP depletion results in dysfunction of energy-dependent ion pumps, such as Na^+,K^+-ATPase and Ca^{2+}-ATPase in the sarcolemma. Na^+,K^+-ATPase pump dysfunction leads to increased intracellular Na^+, causing a temporary increase in Na^+-Ca^{2+} exchanger function and resultant increase in intracellular Ca^{2+}. The Na^+-Ca^{2+} exchanger requires ATP, however, and continued activity of the Na^+-Ca^{2+} exchanger further deprives the cell of ATP, leading to increased Ca^{2+}-ATPase dysfunction and rising intracellular Ca^{2+} levels. The sarcoplasmic reticulum and mitochondria are also equipped with these same energy-dependent transmembrane calcium transport



1 = ATP-dependent Ca^{2+} pump
2 = Na^+-Ca^{2+} exchanger (3:1)
3 = Na^+, K^+-ATPase pump (3:2)

Fig. 119.1. Normal membrane ionic pump function of skeletal muscle cell. When the ATP supply is impaired, the intracellular sodium concentration increases, reversing the function of the Na^+-Ca^{2+} exchanger, with a subsequent increase in the intracellular calcium level.

mechanisms (Ca^{2+}-ATPase) as well as an ATP-dependent Ca^{2+} uniporter, further exacerbating the cell's inability to remove intracellular Ca^{2+} in the low-energy conditions resulting from by rhabdomyolysis.

An abrupt increase in cytoplasmic Ca^{2+} leads to a corresponding increase in mitochondrial Ca^{2+} because the mitochondria serve as the Ca^{2+} safety net. In addition to triggering apoptotic cell death by upregulating expression of proapoptotic factors, this mitochondrial Ca^{2+} overload leads to dysfunction of oxidative phosphorylation through structural and functional alterations, disrupting ATP production and further worsening the ATP debt and intracellular homeostasis of Ca^{2+}.

Increased mitochondrial Ca^{2+} also leads to increased production of reactive oxygen species (ROS), which are a broad group of chemical substances that include free oxygen radicals (O_2^-, $OH^\cdot$) and powerful oxidants (hydrogen peroxide, nitric oxide) that lead to free radical production. Free radicals carry extra unpaired electrons (e^-) that have a strong tendency to pair off, causing oxidation by extracting electrons from other chemical species. Under normal physiologic conditions, 2% to 5% of oxygen consumed by the mitochondria is transformed during electron transport to ROS that are neutralized by endogenous antioxidants such as glutathione. When the antioxidant capacity of the endogenous system is overwhelmed during times of intense, sustained physical activity or illness, so that rhabdomyolysis results, a condition termed *oxidative stress* ensues. The resulting ROS-induced destruction of lipids and proteins injures the structure of membranes as well as DNA with mutations, leading to disruptions in cellular architecture and mitochondrial respiratory protein integrity. The cumulative effect exacerbates the inability to regulate intracellular Ca^{2+} homeostasis. Whereas ROS may have adaptive physiologic functions in exercising muscles, significant damage to muscle cells occurs when ROS are triggered by pathologic stimuli.

Damage of the sarcoplasmic reticulum and mitochondria results in the release of stored calcium ions into the cytoplasm. The decreased removal of Ca^{2+} into the extracellular fluid, along with inadequate intracellular storage and increased entry into the cytoplasm, leads to myocytic Ca^{2+} overload and initiation of the cascade of cellular death.

Calcium-induced activation of proteases, phospholipases, and other proteolytic enzymes degrades the protein structure of myofibrils, cytoskeleton, and membrane composition, leading to further cellular damage. Increased Ca^{2+} leads to sustained contraction of the myofibrils, resulting in severe ATP depletion in the initial stages while leading to myofibrillar breakdown as rhabdomyolysis progresses. Breakdown of the myofibrillar network hastens the disintegration of the myocyte, whereas high Ca^{2+} concentrations within the mitochondria arrest cellular respiration and block ATP production.

Diminished ATP production after Ca^{2+}-mediated activation of degradative cellular enzymes, with large metabolic energy requirements of their own, exacerbates the preexisting energy crisis within already ischemic cells. This process releases free fatty acids and lysophosphates, which cause direct toxic damage to the sarcolemma, intracellular organelles, and plasma membrane carrier proteins, effecting increased Ca^{2+} entry into the cytosol.

Microelectrode studies of intercostal myocytes have shown that the intracellular calcium concentration rises to 1.27 µmol/L after induction of rhabdomyolysis by exhaustive physical exertion compared with 0.12 µmol/L in normal muscles, representing nearly an 11-fold increase in the intracellular calcium concentration. Dantrolene, a known inhibitor of Ca^{2+} release from the sarcoplasmic reticulum, has been shown to lead to an 83% reduction of cytosolic Ca^{2+} and an improvement in the clinical symptoms of muscle stiffness, rigidity, and pain, highlighting the essential role of increased cytosolic Ca^{2+} in the pathophysiologic process of rhabdomyolysis.

Rhabdomyolysis results in muscle cell breakdown, with the release of toxic contents into the extracellular space and damage to adjacent capillaries, resulting in local edema, increased compartmental pressures, and regional ischemia, which further induces energy depletion and destroys more capillaries. Circulating leukocytes adhere to these damaged capillaries, become activated, and transmigrate to the site of myocyte injury, where they release ROS and proteolytic enzymes that injure the cell further.

In cases in which ischemia is the inciting event (eg, crush syndrome, arterial thromboembolism) of rhabdomyolysis, myocyte destruction primarily takes place during reperfusion (Fig. 119.2).

Rhabdomyolysis is classified into four basic pathophysiologic processes:

1. Impairment of the muscle's production or use of ATP at the cellular level. ATP concentrations within the cell fall; energy-dependent mechanisms falter, including Na^+,K^+-ATPase pumps, leading to disruption of chemical gradients, sarcolemma and cell membrane compromise, and cell destruction.
2. Disruption in the delivery of oxygen, glucose, and other nutrients to skeletal muscle
3. Increases in metabolic demands beyond the ability of the organism to deliver oxygen and nutrients
4. Direct myocyte damage

Box 119.1 lists the various causes of rhabdomyolysis.

CLINICAL FEATURES

The clinical presentation of rhabdomyolysis is variable because of its many causes. Its course may be mild and subclinical or it may be severe and life-threatening, depending on the extent of muscle damage and associated complications. It may be evident from the patient's primary complaint or found incidentally on laboratory evaluation. The identification of rhabdomyolysis in the trauma patient is straightforward, whereas the nontraumatic causes may pose a diagnostic challenge.

Rhabdomyolysis should be suspected in patients who present with altered mentation and risk factors for the development of rhabdomyolysis (eg, intoxication, immobility, drug ingestion, electric shock, neuroleptic malignant syndrome). The presence of acute renal failure without another attributable cause also prompts consideration of rhabdomyolysis.

The classic presentation of rhabdomyolysis includes localizing myalgias, muscle stiffness, cramping, swelling, tenderness, and tea-colored urine. The most frequently involved muscle groups are the thighs, calves, and lower back. Nonspecific constitutional symptoms include malaise, fever, nausea, and vomiting. Unfortunately, most cases do not have characteristic physical signs; up to 50% of patients do not report myalgias or muscle weakness,

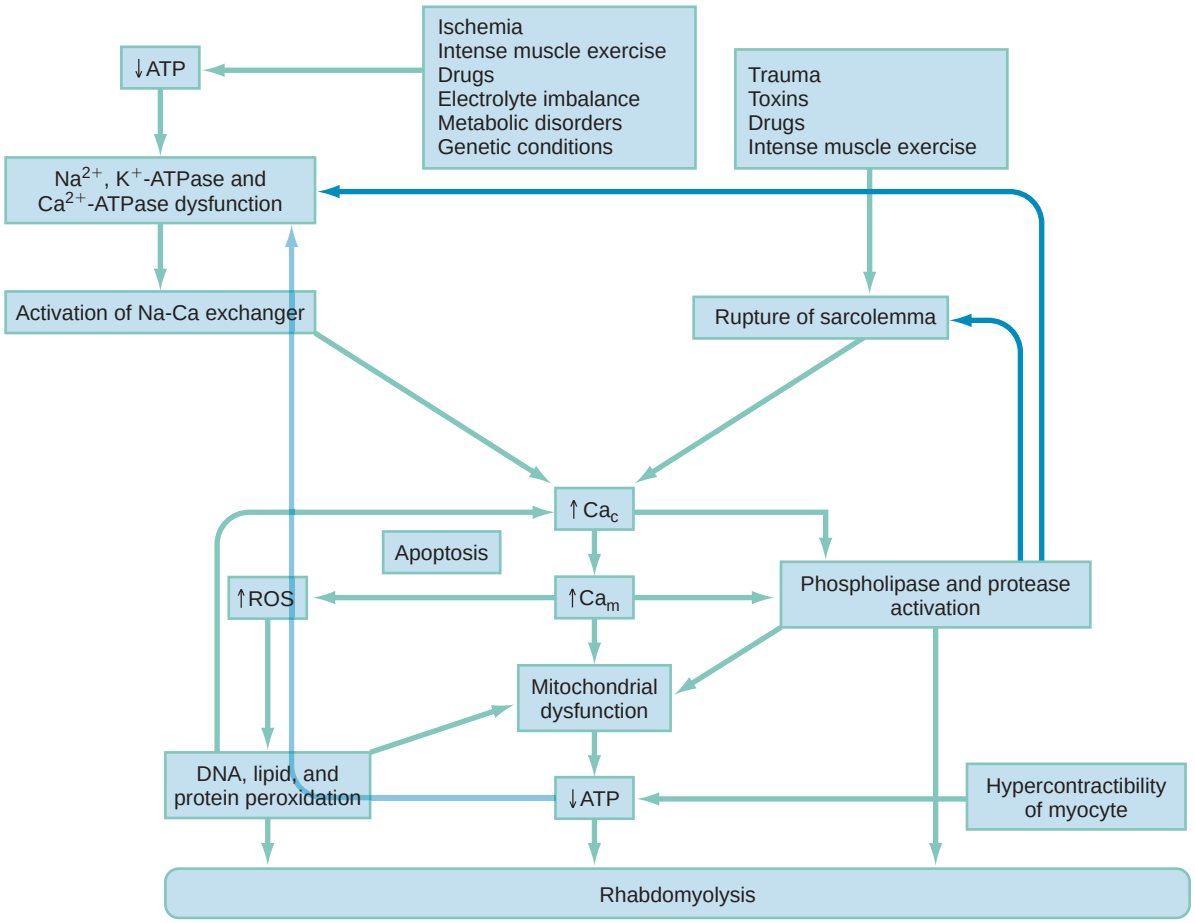


Fig. 119.2. Pathophysiology of rhabdomyolysis. Ca_c, cytosolic [Ca]; Ca_m, mitochrondrial [Ca].

despite serologically proven rhabdomyolysis. Children with rhabdomyolysis may lack many of the classic symptoms; muscle pain and weakness occur in most pediatric patients, but reports of dark urine have been found to be as low as 5%.[1]

History by first responders or witnesses can be helpful, especially when the patient has an altered mental status. In these cases, the physical examination and high clinical suspicion become increasingly important. Findings may include extremity swelling, tenderness, motor weakness, sensory deficits, pain with passive range of motion, and overlying skin changes (particularly in cases of limb ischemia). Muscle swelling may only be evident after resuscitation and rehydration with intravenous (IV) fluids.

Complications

Early Complications

Compartment Syndrome. Most skeletal muscles are encased in compartments formed by bones, fascia, and other structures. The massive influx of calcium and sodium in rhabdomyolysis leads to the accumulation of large amounts of extracellular fluid in the muscle cells, causing local edema and raised intracompartmental pressures, further leading to increased muscle ischemia. Prolonged ischemia and infarction of muscle tissue can lead to replacement of muscle tissue with inelastic fibrous tissue, resulting in severe contractures (Volkmann's contracture). Intracompartmental pressures above 50 mm Hg or sustained pressures of more than 30 mm Hg during a maximum 6-hour period are indications for fasciotomy. Patents with rhabdomyolysis from traumatic compartment syndrome are at high risk of developing acute kidney injury, with concomitant illicit drug or alcohol use and ischemic injuries increasing the odds of injury.[2]

Electrolyte Disorders and Acidosis. Potassium release by damaged muscle leads to potentially lethal hyperkalemia, the most serious complication of rhabdomyolysis. Most potassium, 98%, is found in the intracellular space; 60% to 70% of the total cellular mass of the human body consists of skeletal muscle. Therefore, necrosis of as little as 100 g of muscle mass could increase the serum potassium level by 1.0 mEq/L. For comparison, the average 45 year-old man has a total body muscle mass of approximately 30 kg. Acidemia contributes to hyperkalemia and can be exacerbated by oliguria. The resulting fluid sequestration or myoglobin-induced kidney injury reduces the kidney's ability to excrete acid. Metabolic acidosis is also induced by the release of organic acids (eg, lactic acid, uric acid, sulfur-containing proteins).

The disruption of muscle cells releases large amounts of phosphoric components into circulation, leading to hyperphosphatemia and ectopic calcification, typically depositing in necrotic tissue. Calcium phosphate crystal deposition in damaged muscle can lead to early-phase hypocalcemia, with potentially fatal dysrhythmias. Hyperkalemia coupled with hypocalcemia predisposes patients to malignant dysrhythmias. Furthermore, excessively high phosphate levels shut down the 1α-hydroxylase enzyme of the kidneys through negative feedback, decreasing production of the active form of vitamin D, further reducing calcium absorption from the gut and contributing to early hypocalcemia. Late in the course of rhabdomyolysis, the calcium initially deposited in the cytoplasm of necrotic muscle cells can mobilize and reenter the plasma, resulting in late hypercalcemia.

BOX 119.1

Causes of Rhabdomyolysis

PROLONGED IMMOBILIZATION
Prolonged immobilization can cause rhabdomyolysis by pressure on gravity-dependent body parts. This pressure-related phenomenon may be enhanced by the underlying cause of the immobilization (eg, drugs or trauma).

EXCESSIVE MUSCLE ACTIVITY
ATP depletion from excessive muscle activity leads to a mismatch of cellular energy needs and ATP supply. This leads to malfunction of ATP-dependent cellular membrane ion pumps, net influx of ionized calcium, and subsequent rhabdomyolysis. Exertion-related cases of rhabdomyolysis have been reported in sporadic and prolonged muscle activity of high and low intensity.

MUSCLE ISCHEMIA
ATP production is limited by interruption of blood perfusion of any cause to muscle tissue, including arterial occlusion, carbon monoxide poisoning, and external compression. Muscle cell hypoxia leads to muscle damage in as little as 2 hours, with irreversible anatomic and functional changes within 4 hours and muscle necrosis in as little as 6 hours.

TEMPERATURE EXTREMES
Extremes of temperature are known to cause rhabdomyolysis by sarcolemma disruption. The physiologic concept of thermal maximum describes the core temperature and duration at which human cells break down. A core body temperature of 42° C (107.6° F) for more than 45 to 60 minutes leads to cellular damage. Heat stroke, neuroleptic malignant syndrome, and malignant hyperthermia are conditions known to lead to excess heat and muscle breakdown. Similarly, hypothermia causes sarcolemma membrane dysfunction below critical temperatures necessary for membrane protein structural integrity. Rhabdomyolysis has been attributed to therapeutic hypothermia in a post–cardiac arrest trauma victim.[13]

ELECTRICAL CURRENT
Muscle sarcolemma is directly injured by electrical current–induced membrane permeability (electroporation) and thermal injury; high-voltage electrical injury, including lighting, poses the highest risk. Secondary injury by coagulation of blood in muscle capillary beds may lead to localized muscle ischemia. Rhabdomyolysis has also been seen after cardioversion for refractory ventricular tachycardia and fibrillation.

ELECTROLYTE ABNORMALITIES
Hypokalemia by whatever mechanism can cause rhabdomyolysis. Extracellular potassium leads to localized microvascular vasodilation, and low concentrations can lead to focal muscle vasoconstriction and ischemia, with subsequent muscle injury. Hypophosphatemia may result in rhabdomyolysis in that phosphate groups are needed for ATP-dependent cell functions. Hyponatremia has been reported to cause rhabdomyolysis in endurance athletes[14] and in those with psychogenic polydipsia. Hypernatremia may also have direct links to rhabdomyolysis in the absence of other known causative agents.

ILLICIT DRUGS
A number of illicit drugs, such as opioids, antipsychotics, benzodiazepines, amphetamines, ecstasy, LSD, and synthetic cannabinoids,[15,16] can result in rhabdomyolysis by direct or indirect effects, including immobilization with muscle tissue hypoperfusion and hypoxia, psychomotor agitation, direct myotoxicity, and electrolyte abnormalities, particularly hypokalemia and hypophosphatemia.

MEDICATIONS
Statin-induced rhabdomyolysis is well documented. Its precise mechanism is not fully known but is hypothesized to be due to membrane instability from inhibition of cholesterol synthesis by hydroxymethylglutaryl–coenzyme A reductase inhibition, impaired intracellular protein messaging from abnormally prenylated proteins, and abnormal mitochondrial respiration from coenzyme Q10 deficiency. Similarly, fibric acid derivatives, which decrease hepatic triglyceride production, have been associated with rhabdomyolysis. Many if not most other classes of prescription medications have been associated with rhabdomyolysis, including the typical and atypical antipsychotics.

INFECTIONS
Rhabdomyolysis has been reported after infections with bacterial, viral, fungal, and parasitic agents. Sepsis-induced tissue hypoxia, direct bacterial myocyte invasion, decreased glycolytic and oxidative enzyme activity, lysosomal enzyme activation, and endotoxin-related injury have all been implicated as pathogenetic mechanisms involved in infectious causes of rhabdomyolysis. Rhabdomyolysis has been found in patients with influenza A and should be considered in patients presenting with marked body aches and weakness during flu season.[17]

Legionella is the most common bacterial cause of rhabdomyolysis. It is unclear if rhabdomyolysis is caused by a common pathway of sepsis-related systemic inflammation or species-specific processes.

METABOLIC MYOPATHIES
Inherited disorders are manifested with enzyme deficiencies in carbohydrate and lipid metabolism or myopathies. These lead to defects in glycolysis, gluconeogenesis, fatty acid oxidation, and mitochondrial cellular respiration. These disorders are typically manifested during childhood and are recurrent.

CONNECTIVE TISSUE DISORDERS
Although rare, cases of rhabdomyolysis have been reported in conditions such as polymyositis, dermatomyositis, and Sjögren's syndrome.

RHEUMATOLOGIC DISORDERS
Systemic lupus erythematosus, usually associated with mild myositis, has also been reported in a case of fulminant myositis with rhabdomyolysis.

ENDOCRINE DISORDERS
Hypothyroidism has been reported to cause rhabdomyolysis.

BIOLOGIC TOXINS
Snakebite, Africanized bees, wasps[18,19] and honey bee envenomations are known to release myotoxic agents causing rhabdomyolysis.

OTHER AND UNKNOWN CAUSES
Case reports have documented the development of rhabdomyolysis after succinylcholine administration to patients with neuromuscular disorders,[20] as well as in some bariatric surgery patients[21] and patients undergoing cardiopulmonary resuscitation. Caffeine toxicity from an overdose can also cause rhabdomyolysis.[22]

Hypovolemia. In rhabdomyolysis, fluid moves from intravascular compartments into damaged muscle, causing profound intravascular volume depletion. This shift may exceed 15 L.

Hepatic Dysfunction. Large elevations in serum liver enzyme levels may occur after nontraumatic rhabdomyolysis. The cause of this finding is not fully understood, but proteases released by muscle cells have been implicated. However, aspartate transaminase level elevations may also be of skeletal muscle origin. These derangements are generally reversible. Preexisting hepatic dysfunction can also potentiate statin-induced rhabdomyolysis.[3]

Late Complications

Myoglobin-Induced Acute Kidney Injury. Experimental evidence has suggested that the mechanisms involved in the pathophysiologic process of myoglobinuric acute renal failure are myoglobin cast formation in the distal convoluted tubules, direct cytotoxic action of myoglobin on the epithelial cells of the proximal convoluted tubules, and intrarenal vasoconstriction and ischemia (Fig. 119.3).

Myoglobin becomes concentrated along the renal tubules and precipitates in acidic urine along with uric acid to form obstructive casts. This process is enhanced by volume depletion and renal vasoconstriction, which reduces blood flow and the glomerular filtration rate (GFR), promoting the accumulation of necrotic epithelial cells into tubular casts and further worsening the GFR. Tubule obstruction occurs at the level of the distal tubule, whereas direct tubule cytotoxicity occurs mainly in the proximal tubules. There remains some controversy about the exact mechanism of renal dysfunction in rhabdomyolysis; some experts believe that casts and tubular obstruction are not the cause but rather the consequence of poor tubular clearance.

When the concentration of myoglobin filtered at the glomerulus exceeds the normal level, tubular cells at the proximal convoluted tubule increase their reabsorption capacity to limit the excretion of myoglobin into the urine, protecting the kidney from its nephrotoxic effects. At a urine pH of 5.6 or lower, myoglobin, an iron-containing heme protein, dissociates into free iron (Fe), ferrihemate (Fe-heme complex), and globin inside the proximal tubular epithelial cell. Free hydroxyl radicals are produced when ferrous oxide in the Fe-heme complex is oxidized by molecular oxygen (O_2) and when free iron reacts with H_2O_2. Free iron may also act as a free radical, although its role in rhabdomyolysis-induced renal injury is unclear. Myoglobin itself has been shown to exhibit peroxidase-like enzyme activity. Ferrihemate causes direct nephrotoxic effects along with the resultant increased oxidative stress within the tubular epithelial cell, leading to acute tubular necrosis through lipid, protein, and DNA peroxidation. More recent evidence has argued against free iron's role in oxidative stress–induced renal injury and emphasized the role of ferrihemate-induced lipid peroxidation in cell injury.

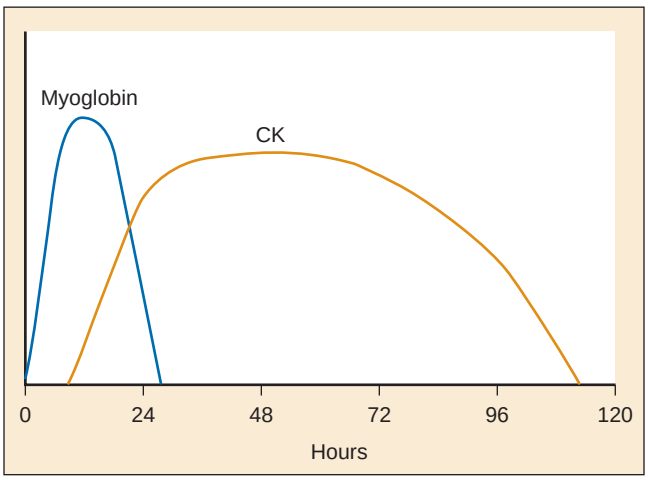


Fig. 119.3. Variations of myoglobin and creatine kinase (CK) levels during the course of rhabdomyolysis. Myoglobin is the first enzyme that increases but, because of its rapid clearance from the plasma, it returns to normal levels within the first 24 hours after the onset of symptoms. The CK level increases a few hours later than myoglobin, reaches its peak value within the first 24 hours, and remains at these levels for 3 days. CK is considered to be a more useful marker for the diagnosis and assessment of the severity of muscle injury because of its delayed clearance from the plasma.

Fluid shifts and renal dysfunction lead to activation of the renin-angiotensin-aldosterone system and sympathetic nervous system and production of vasoconstricting molecules such as endothelin 1 and vasopressin. There is also decreased production of vasodilatory prostaglandins. Nitric oxide (NO), a potent vasodilatory agent, is known to be responsible for the maintenance of renal blood flow; myoglobin released from damaged muscle may act as a scavenger of NO in the renal microcirculation, itself reduced by NO buffering against oxidant injury by ferrihemate. When NO is overcome by increased myoglobin concentrations, the kidney is deprived of the ability to autoregulate organ blood flow and maintain adequate perfusion in times of shock. Thus, myoglobin is free to cause damage in proximal tubular epithelial cells (under appropriate acidotic conditions), as previously described. Other locally stimulated vascular mediators, such as thromboxane A_2, tumor necrosis factor alpha, and F_2-isoprostanes, which themselves are byproducts of free radical lipid peroxidation, have also been implicated in the reduction of renal blood flow as a result of endothelial disruption and inflammation, as well as oxidant injury.

Disseminated Intravascular Coagulation. Prothrombotic substances, mainly thromboplastin, released from destroyed muscle cells activate the coagulation cascade. They can lead to the formation of thrombi in the capillary tufts of the glomeruli.

DIAGNOSTIC TESTING

Serum Creatine Kinase

The definitive diagnosis of rhabdomyolysis is reliably made by serologic testing for creatine kinase (CK). This test can assist the clinician in assessing at-risk patients when historical and examination findings are lacking. Elevated levels of CK are the hallmark of rhabdomyolysis. CK functions as an energy reservoir for ATP: creatine + ATP = creatine kinase + ADP (adenosine diphosphate). CK has a half-life of 1.5 days; its level elevated in the first 12 hours, peaks during the first 3 days, and normalizes at around 5 days after injury. A CK level five times the upper limit of normal (≈1000 U/L), without apparent cardiac or brain injury, confirms the diagnosis.

Serum and Urine Myoglobin

Myoglobin is a dark red protein composed of globin and a molecule of heme. Its normal function is to supply oxygen to skeletal and cardiac muscle in times of need. The excretion of myoglobin occurs renally. It is initially filtered at the glomerulus and reabsorbed by endocytosis in the convoluted tubules, where it is broken into its component parts, globin and heme, by proteolytic enzymes. As with all other low-molecular-weight proteins, a small amount is excreted in the urine. The normal concentration of myoglobin in the urine is less than 10 μg/L. A normal serum concentration of myoglobin is less than 100 μg/L.

During rhabdomyolysis, myoglobin released by damaged muscle is increasingly filtered at the glomerulus. This leads to an initial increased reabsorptive capacity by glomerular and tubular epithelial cells, developed presumably as a protective response to increased filtered myoglobin. When serum myoglobin concentrations exceed 0.3 mg/L and the renal threshold of 1.0 mg/dL is met, this reabsorptive capacity is overwhelmed, and excess myoglobin appears in the urine. This myoglobin is detected by urine dipstick as positive for blood (Table 119.1).

In the past, the diagnosis of rhabdomyolysis was made by serum myoglobin; however, myoglobin has a serum half-life of only 1 to 3 hours and is completely absent after 24 hours. This

TABLE 119.1

Causes and Microscopic Features of Red and Brown Urine

CAUSE	RESULTS FOR BLOOD IN URINE[a]	SEDIMENT[b]	SUPERNATANT
Hematuria	+++	Red	Yellow
Myoglobinuria	+++	Normal	Red to brown
Hemoglobinuria	+++	Normal	Red to brown
Porphyria	–	Normal	Red
Bile pigments	–	Normal	Brown
Food and drugs[c]	–	Normal	Red to brown

[a]Urine tested with dipstick test.
[b]Normal refers to white or yellow color.
[c]Food and drugs that can cause red urine include beets, blackberries, rhubarb, food coloring, fava beans, phenolphthalein, rifampin, doxorubicin, deferoxamine, chloroquine, ibuprofen, and methyldopa. Those that cause brown urine include levodopa, metronidazole, nitrofurantoin, iron sorbitol, chloroquine, and methyldopa.
Adapted from Bosch X, Poch E, Grau JM: Rhabdomyolysis and acute kidney injury. N Engl J Med 361:62–79, 2009.

short window makes serum myoglobin an unreliable diagnostic test. This also applies to urine myoglobin levels, which depend on the degree of muscle injury, volume status of the patient, and urinary flow rate. A well-hydrated patient with normal renal function can rapidly clear plasma from the body. Although myoglobin is pathognomonic, because it is only detectable early in the course of disease, the absence of plasma or urine myoglobin does not rule out rhabdomyolysis (Fig. 119.4).[4]

Urine Dipstick and Urinalysis

Myoglobinuria causes a positive result for blood in urine dipstick testing. The drawback of this test is its inability to distinguish among heme compounds. However, in myoglobinuria, microscopic analysis will show few if any red blood cells, thereby distinguishing between hemoglobin and hemoglobin-rich red blood cells (from hemolysis or hematuria). Myoglobinuria, in combination with an elevated plasma CK level, confirms rhabdomyolysis. At plasma concentrations above 100 to 300 mg/L, macroscopic myoglobinuria manifests as tea-colored urine.

The urine dipstick test or urinalysis result is generally acidic in rhabdomyolysis, which plays a role in cast and uric acid crystal formation, as well as pathologic myoglobin metabolism in tubular epithelial cells. Proteinuria may also be noted because of the detection of the globin component of myoglobin. Urine sediment analysis will show myoglobin casts and dead epithelial cells (see Table 119.1).

Other Laboratory Findings

Common electrolyte disturbances in patients with rhabdomyolysis include hyperkalemia, hyperphosphatemia, and early hypocalcemia followed by late hypercalcemia. Late hypercalcemia is postulated to be due to the mobilization of calcium that was initially sequestered in damaged muscle.

Hyperuricemia from the release of muscle nucleic acids is especially common in patients with large muscle mass. Metabolic acidosis typically occurs from the generation of organic acids from damaged muscle—namely, lactate and uric acid. Hypoalbuminemia and anemia result from capillary damage and release into the extracellular space.

Both the blood urea nitrogen (BUN) and creatinine (Cr) concentrations increase, but with a characteristic decrease in the BUN/Cr ratio due to large amounts of creatinine released into the serum from damaged muscle. A normal BUN/Cr ratio is 10 : 1; in rhabdomyolysis, it can be 5 : 1 or even less. In severe cases, coagulation disorders such as disseminated intravascular coagulation (DIC) can ensue, triggered by the released thromboplastin from damaged tissue.

Prognostic Tests in Rhabdomyolysis

Most studies evaluating the ability for the CK level to predict renal injury have been retrospective and conducted in admitted patients. In these reports, the degree of CK level elevation has not been found to be a reliable predictor of acute kidney injury, with most showing no correlation or a weak one.[5,6] One study of admitted pediatric trauma patients did find a correlation between CK levels above 3000 U/L and acute kidney injury.[7] This suggests that age and etiology of rhabdomyolysis may permit the use of CK as a predictor for kidney injury in certain populations.

In one of the only studies of emergency department (ED) patients with rhabdomyolysis, the CK level did not correlate with the primary outcomes of need for dialysis or death at 30 days.[8] However, the estimated glomerular filtration rate (eGFR), calculated as $175 \times (\text{Cr}/88.4)^{-1.154} \times (\text{age})^{-0.203}$ for males, multiplied by 0.742 for females, did correlate with the primary outcomes, with no patients with an eGFR of less than 60mL/min/1.73 m^2 developing acute kidney injury or dying. Based on the cumulative evidence, I recommend that the CK level should be used as a diagnostic marker for rhabdomyolysis and not as a prognostic indicator of acute renal injury. Once the diagnosis is made, the eGFR can be used to predict renal injury and determine the need for admission; I recommend using a computer application to calculate eGFR from the formula. The degree of creatinine level elevation at the time of admission has been shown to correlate with 30-day mortality rates.[6]

MANAGEMENT

Management of rhabdomyolysis focuses on treatment of the cause, prevention of renal failure, and management of life- or limb-threatening complications.

Fluid Replacement and Urine Alkalinization

Volume expansion is critical to avoiding myoglobin-induced acute renal failure. Fluid expansion increases renal blood flow and therefore glomerular filtration and urination. Patients with rhabdomyolysis typically present with severe dehydration due to fluid sequestration in the affected skeletal muscles. Several case series, mostly from victims of natural disasters (eg, earthquakes with building collapse), have shown that some degree of intravascular volume contraction is a prerequisite for developing acute renal failure. Because acute renal failure appears to develop in patients with a longer delay to supportive therapy, fluid resuscitation should be instituted early. For victims of mass casualty events with prolonged extrication times, fluid resuscitation should begin before complete extrication.

Although the need for early volume expansion is universally accepted, the composition of the fluid is more controversial, especially regarding the concept of urine alkalinization. The principles of urine alkalinization have been derived empirically from animal data: (1) myoglobin precipitation is increased in acidic urine; (2) reduction-oxidation (redox) cycling of myoglobin and lipid peroxidation, and thus tubule injury, are inhibited by alkaline urine; and (3) myoglobin induces renal vasoconstriction only in an acidic medium. Myoglobin-induced lipid peroxidation occurs

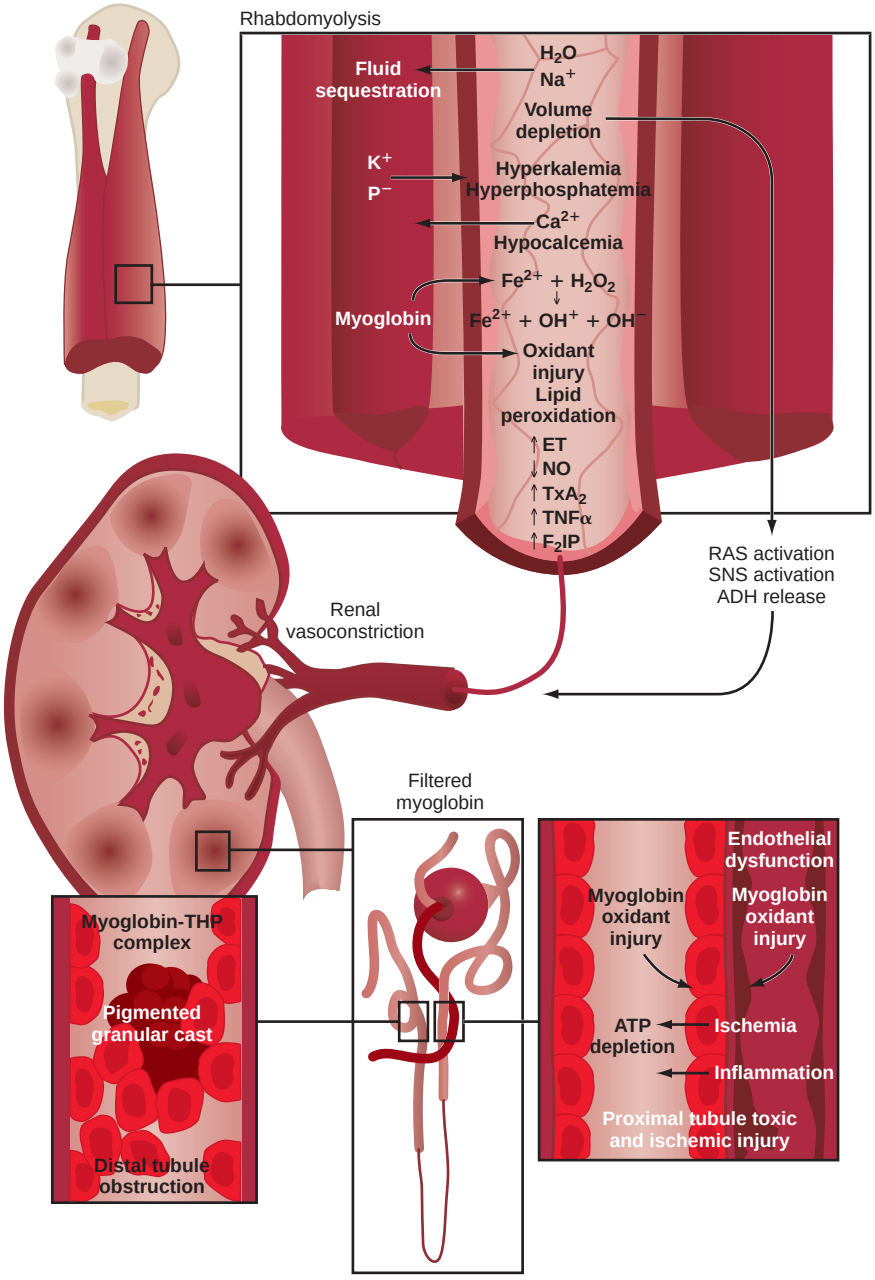


Fig. 119.4. Pathophysiologic mechanisms in rhabdomyolysis-induced acute kidney injury. *ADH,* Antidiuretic hormone; *ATP,* adenosine triphosphate; *ET,* endothelin; *F_2IP,* F_2-isoprostanes; *NO,* nitric oxide; *RAS,* renin-angiotensin system; *SNS,* sympathetic nervous system; *THP,* Tamm-Horsfall protein; *TNFα,* tumor necrosis factor alpha; *TxA_2,* thromboxane A_2. (Adapted from Bosch X, Poch E, Grau JM: Rhabdomyolysis and acute kidney injury. N Engl J Med 361:62–72, 2009.)

at concentrations several orders of magnitude lower than those that lead to the precipitation of casts in the distal tubules.

The theory of alkalinization has been supported by the discovery that alkalinization inhibits redox cycling of myoglobin and lipid peroxidation.[9] However, the clinical benefits of alkalinization compared with simple saline volume repletion are not firmly established, and sodium bicarbonate therapy has not been proven necessary or superior to normal saline diuresis at increasing urine pH. Comparative studies have been limited by their small sample sizes and variability in the severity of rhabdomyolysis, determined by CK level. They have been further complicated by the administration of multiple therapeutic measures (eg, bicarbonate plus mannitol), making the impact of any one measure difficult to interpret.

Although the precise benefit of alkaline therapy in rhabdomyolysis is unknown, what is known is the impact of large volumes of normal saline on the serum pH. Normal saline contains supraphysiologic concentrations of chloride ions. Massive infusion of normal saline leads to a disproportionate increase in serum chloride concentrations, inducing an iatrogenic metabolic (hyperchloremic) acidosis that exacerbates myoglobin precipitation, tubular obstruction, and risk of hyperkalemia-related complications.

The administration of both normal saline and sodium bicarbonate, especially in patients with metabolic acidosis, may be one approach to fluid resuscitation. If sodium bicarbonate therapy is used, the urine and serum pH and serum bicarbonate, potassium, and calcium levels should be monitored. The urine should be

alkalinized to a pH above 6.5 and serum pH of 7.40 to 7.45. Bicarbonate therapy should be discontinued and switched to normal saline if calcium levels become dangerously low (total corrected calcium concentration < 9 mg/dL or ionized calcium concentration < 4.5 mg/dL), or if no improvement in urine pH is noted after 4 to 6 hours. If a saline-only approach is used, the serum chloride and pH levels should be monitored and the saline discontinued if a hyperchloremic metabolic acidosis is iatrogenically induced. In this case, a less acidifying solution (eg, Isolyte, lactated Ringer's solution) can be used. Evidence for this approach is lacking but reasonable given current experimental and clinical knowledge.

Precise guidelines for the duration of fluid administration are lacking, but IV fluid administration should be continued until the plasma CK concentration decreases to less than 1000 U/L. A total of 10 to 20 L of IV fluid is often administered in the first 24 hours, depending on the severity of illness and underlying comorbidities that may preclude large-volume fluid administration (eg, congestive heart failure). In general, titration to a urinary output of 300 mL/hr or more is a reasonable target for adults.[10]

Diuretics

Mannitol

Although mannitol is the only diuretic with evidence to support a benefit in rhabdomyolysis, its use remains controversial.[10] As an osmotic diuretic, its theoretic benefit is its ability to increase urinary flow (ie, wash out nephrotoxic agents) and draw out fluid accumulated from damaged muscle into the intravascular space, thereby also improving hypovolemia. Mannitol is also a free radical scavenger; however, at the concentrations used therapeutically, these antioxidant properties are likely irrelevant. Most data on mannitol therapy have come from animal studies, which demonstrated that the bulk of its therapeutic effect is attributable to its osmotic diuretic action. In human studies, the addition of mannitol has not been shown to be more beneficial than fluid expansion alone, and no randomized controlled trials have shown any beneficial effect. Large accumulated doses of mannitol may be detrimental by causing renal vasoconstriction and tubular toxicity, a condition known as osmotic nephrosis. However, mannitol therapy, may be beneficial to relieve compartment pressures. If mannitol is used, the plasma osmolality and osmolal gap should be frequently monitored; treatment should be discontinued if adequate diuresis is not achieved or if the osmolal gap rises above 55 mOsm/kg.

Furosemide

Loop diuretics also increase urinary flow, but no study has shown a clear benefit in patients with rhabdomyolysis. Therefore, they are not recommended as prophylaxis against myoglobin-induced renal failure.

Acetazolamide

Carbonic anhydrase inhibitors for urine alkalinization have been used when bicarbonate therapy results in metabolic alkalosis with persistent acidic urine. Acetazolamide has theoretic advantages because it induces bicarbonate diuresis, with restorative effects on acid-base status from natriuresis. Case reports have shown potential benefit, but this has not been confirmed experimentally or clinically and cannot be recommended at this time.

Experimental Therapies

Antioxidants such as glutathione and vitamin E analogues have shown promise in experimental animal models of myoglobin-induced oxidant injury and may have a future role in management. Grape seed proanthocyanidin extract has been shown to have renoprotective effects in rat models of rhabdomyolysis.[11] The xanthine oxidase inhibitor, allopurinol, is being studied as a prophylactic agent in nonathletes at risk for exertional rhabdomyolysis.[12]

Renal Replacement Therapy

As with non–rhabdomyolysis-related causes of renal failure, the indications for emergent dialysis or filtration remain uncorrectable metabolic acidosis, life-threatening hyperkalemia and other electrolyte disturbances despite medical management, manifestations of uremia, and anuria or oliguria, despite volume expansion with complications related to fluid overload. Fluid overload is particularly problematic when it results in pulmonary edema or in patients with poor cardiac reserve. Conventional hemodialysis does not filter myoglobin effectively because of its large size. Renal replacement therapy (RRT) is indicated, with intermittent hemodialysis to correct electrolyte abnormalities rapidly. Continuous venovenous hemofiltration or hemodiafiltration has shown promise for the removal of myoglobin in case reports, although outcome data are lacking. Continuous renal replacement therapy (CRRT) may be more desirable than intermittent RRT because of the theoretic hemodynamic and homeostatic benefits of continuous versus intermittent therapy. However, three small, poorly designed randomized trials of CRRT have failed to show a decrease in mortality, despite more rapid removal of myoglobin and improvement in electrolyte, BUN, and creatinine levels.[9] The need for RRT in the acute setting of rhabdomyolysis does not predict the need for long-term hemodialysis.

DISPOSITION

The need for fluid resuscitation in rhabdomyolysis and close monitoring of renal function and electrolytes require hospitalization in most cases. Observation stays can be considered in milder cases but more complicated cases warrant admission to a monitored setting until resolution of metabolic and hemodynamic perturbations. The type of hospital bed is contingent on the cause of rhabdomyolysis, presence of comorbidities, and severity of illness at presentation. Fluid resuscitation should generally be initiated at CK levels more than five times the upper limit of normal (typically, 1000 IU/L) and should be continued until levels trend down and drop below this level.

Prognosis

Rhabdomyolysis, when recognized and treated early, carries an excellent prognosis. With the exception of hyperkalemia-related death or the rare complication of DIC, acute kidney injury is the most serious complication of rhabdomyolysis, regardless of cause. Of patients who have acute renal failure, most will recover full renal function when treatment is instituted in a timely fashion. Mortality data for patients with renal failure vary widely in the literature according to the study population, cause, presence of multiple causative agents, and comorbidities; however, long-term survival among patients with rhabdomyolysis and acute renal injury tends to be very good when timely management is provided.

KEY CONCEPTS

- Rhabdomyolysis is generally a benign syndrome, but with potentially fatal complications. Acute renal failure and hyperkalemia are accompanied by high mortality.
- Rhabdomyolysis should be suspected in at-risk patients (see Box 119.1) who present with muscle pain or altered mentation.
- The diagnosis of rhabdomyolysis is confirmed with an elevated serum CK level (>1000 U/L).
- In patients with rhabdomyolysis, the degree of CK elevation is not a reliable predictor of risk of acute renal injury.
- IV fluid administration should be aimed at maintaining a urine output of at least 300 mL/hr in the average-sized adult patient with rhabdomyolysis.
- Diuretics have no role in the management of most cases of rhabdomyolysis.
- Survivability hinges on prompt recognition and resuscitation with a liberal fluid strategy, with or without urine alkalinization.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 119: QUESTIONS & ANSWERS

119.1. Which of the following statements regarding muscle cell physiology and rhabdomyolysis is true?
- **A.** Acute renal failure from rhabdomyolysis is very rare.
- **B.** Hemoglobin has a higher oxygen affinity than myoglobin.
- **C.** The final common pathway of injury in rhabdomyolysis is cell membrane damage.
- **D.** The normal intracellular Na^+ concentration is high.
- **E.** The normal intracellular Ca^{2+} concentration is low.

Answer: E. Normal intracellular concentrations of Na^+ are low, creating a negative intracellular environment. This allows more facilitated transfer of Ca^{2+} from the intracellular to extracellular space, maintaining low intracellular Ca^{2+} concentrations. The final common pathway of injury is sarcolemma damage with intracellular Ca^{2+} accumulation, proteolytic enzyme inhibition, actin-myosin coupling dysfunction, and cell damage with release of intracellular contents (eg, myoglobin, PO_4^-, uric acid, lactate dehydrogenase). Myoglobin, which has four times the O_2 affinity of hemoglobin, overwhelms the haptoglobin-binding capacity, is filtered at the glomerulus, and precipitates in renal tubules. Approximately 5% to 15% of cases of acute renal failure in the United States are related to rhabdomyolysis. This myoglobin precipitation is markedly facilitated by acidosis.

119.2. Which of the following statements regarding exertion (exercise)-related rhabdomyolysis is true?
- **A.** Eccentric (lengthening) muscle work is more damaging than concentric.
- **B.** Hypocalcemia increases the risk for this syndrome.
- **C.** It is the result of voluntary muscle exertion.
- **D.** It is seen exclusively in untrained athletes.
- **E.** The mechanism is different than after a crush injury.

Answer: A. Exertional rhabdomyolysis is seen in trained and untrained individuals as well as after exercise or situations of involuntary muscle activity (eg, psychoses, seizures, tetany, myoclonus). The mechanism (eg, failure of energy supplies, sarcolemma breakdown, intracellular calcium accumulation, enzyme dysfunction, cellular swelling) is the same. Hypokalemia is a risk factor because a low potassium level limits microvascular dilation and muscle perfusion.

119.3. Which of the following statements regarding drug-induced rhabdomyolysis is true?
- **A.** Cocaine myotoxicity is not related to the degree of intoxication.
- **B.** Colchicine and cyclosporine are myotoxins.
- **C.** Ethanol myotoxicity is potentiated by high carbohydrate intake.
- **D.** Statin myotoxicity is unrelated to state of hydration.
- **E.** The use of the drug ecstasy is not associated with rhabdomyolysis.

Answer: B. Statins, ethanol, cocaine, colchicine, cyclosporine, and many other drugs are myotoxic. Illicit drugs include amphetamine, ecstasy, LSD, and other sympathomimetics. Ethanol is a direct muscle membrane toxin, and this effect is potentiated by starvation, binge drinking, and coexisting electrolyte abnormalities (low K^+, PO_4^-, and Mg^{2+}). Intravenous cocaine use is more myotoxic than inhaled cocaine, and the severity seems to parallel the degree of intoxication.

119.4. What is the most common viral cause for rhabdomyolysis?
- **A.** Cytomegalovirus
- **B.** Epstein-Barr virus
- **C.** Herpesvirus
- **D.** Human immunodeficiency virus
- **E.** Influenza virus

Answer: E. Influenza is the most common viral etiology followed by HIV infection and enteroviral infection.

119.5. What is the most common bacterial cause for rhabdomyolysis?
- **A.** *Legionella*
- **B.** *Pseudomonas*
- **C.** *Salmonella*
- **D.** *Staphylococcus*
- **E.** *Streptococcus*

Answer: A. Legionella is the bacterium classically associated with rhabdomyolysis in adult patients. The pathogenesis is believed to be due to direct invasion and toxic degeneration of muscle fibers.

119.6. Which of the following electrolyte abnormalities has not been associated with rhabdomyolysis?
- **A.** Hypermagnesemia
- **B.** Hypernatremia
- **C.** Hypocalcemia
- **D.** Hyponatremia
- **E.** Hypophosphatemia

Answer: A. There are no reported cases of hypermagnesemia induced rhabdomyolysis to date.

119.7. A 53-year-old intoxicated alcoholic is brought to the ED by EMS after being found unconscious for an unknown reason. He is now awake but mildly lethargic. He has no complaints of pain or disability. The physical examination is nonfocal. Which of the following statements is true?
- **A.** A CK-MB fraction of 5% would indicate myocardial damage.
- **B.** A negative urine myoglobin level would exclude rhabdomyolysis.
- **C.** His lack of pain complaints would exclude rhabdomyolysis.
- **D.** Hypocalcemia would be expected in the presence of rhabdomyolysis.
- **E.** If rhabdomyolysis were found, normal phosphate level would be reassuring.

Answer: D. Hypocalcemia is the most common electrolyte abnormality after rhabdomyolysis. Hypercalcemia may follow later. Only 50% of patients with serum evidence of rhabdomyolysis have complaints of muscle pain. Likewise, the presence of urine myoglobin reflects the glomerular filtration rate, plasma myoglobin concentrations, urine flow, and plasma myoglobin binding. This test result may be negative, especially late in the course of the process. Hyperphosphatemia is expected, and a normal level raises the suspicion that hypophosphatemia was the cause of the rhabdomyolysis. CK-MB levels of 3% to 5% are often seen and reflect skeletal rather than cardiac muscle damage.

119.8. Which of the following is a proven cornerstone of management for rhabdomyolysis, along with saline hydration?
- **A.** Alkalinization
- **B.** Chelation therapy
- **C.** Furosemide
- **D.** Mannitol
- **E.** None of the above

Answer: E. Furosemide is somewhat contraindicated because of its tendency to acidify the urine. Mannitol and alkalinization are not proven, although they are often used. Chelation therapy is under investigation.

CHAPTER 120

Thyroid and Adrenal Disorders

Molly E.W. Thiessen

Thyroid dysfunction (hyperthyroidism and hypothyroidism) arguably represents the most common form of endocrine disorder. Together with adrenal insufficiency, these disease states are often manifested with nonspecific symptoms, such as fatigue and weakness, making them a diagnostic challenge. In their advanced states, classic manifestations develop, rendering each disorder more recognizable. Each disorder is also capable of producing life-threatening symptoms when it is untreated or precipitated by other stressors.

HYPERTHYROIDISM

Principles

Background

Hyperthyroidism is a condition caused by overproduction and increased circulation of thyroid hormone. The disorder runs the spectrum from subclinical hyperthyroidism to thyrotoxicosis, a life-threatening disorder. Thyrotoxicosis is a hypermetabolic condition that results from elevated levels of thyroid hormones—triiodothyronine (T_3) and thyroxine (T_4). This can occur from hormone overproduction (Graves' disease, toxic multinodular goiter), increased thyroid hormone release from an injured gland (thyroiditis, trauma), or exogenous thyroid hormone (thyrotoxicosis factitia). Most cases of thyrotoxicosis (>80%) are due to autoimmune disease.[1] For the purpose of this discussion, the terms *hyperthyroidism* and *thyrotoxicosis* are used interchangeably.

Anatomy and Physiology

The normal adult thyroid gland is a highly vascular bilobar organ overlying the anterior trachea (Fig. 120.1). The thyroid's function is to secrete two iodinated hormones, T_3 and T_4. Only about 20% of circulating T_3 is directly secreted by the thyroid; the remainder is produced by peripheral conversion of T_4 to the more biologically active T_3. The thyroid is the only endocrine gland that stores large quantities of hormone, with enough for a 100-day supply.

Hormone production is regulated by a negative feedback loop involving the hypothalamic-pituitary-thyroid axis (Fig. 120.2). As the serum levels of T_4 and T_3 fall, the hypothalamus releases the tripeptide thyrotropin-releasing hormone (TRH), which in turn stimulates the anterior pituitary gland's release of the polypeptide thyroid-stimulating hormone (TSH) from its thyrotroph cells. TSH then binds to epithelial cells on the thyroid gland, stimulating follicular cells to synthesize and secrete the thyroid hormones T_4 and T_3. TRH release may also result from exercise, stress, malnutrition, hypoglycemia, and sleep.

The function of thyroid hormone is to influence the metabolism of cells by increasing their basal metabolic rate. It has a role in protein synthesis and functions together with other hormones necessary for normal growth and development. Of note, T_3 and T_4 increase the expression and sensitivity of β-adrenergic receptors, dramatically increasing response to endogenous catecholamines.

Pathophysiology

T_4 is a prohormone with only mild intrinsic activity; its deiodination produces T_3, the biologically active hormone. More than 99.5% of thyroid hormones are protein-bound in the serum to thyroxine-binding globulin (TBG) and other proteins, rendering them metabolically inactive. As a result, only free T_4 and free T_3 are clinically relevant.

Although iodide is a necessary substrate for thyroid hormone production, excess iodide can have two opposing effects. In the Wolff-Chaikoff effect, excess iodine inhibits the release of thyroid hormone from the gland by blocking iodide trapping and thyroglobulin iodination. This inhibition is transient, typically lasting only a matter of days. Iodide load can induce hyperthyroidism (Jod-Basedow effect) in some patients with multinodular goiter and occult Graves' disease.

Graves' Disease. Graves' disease is the most common form of hyperthyroidism in the United States; autoantibodies bind to the TSH receptor and stimulate thyroid hormone production and release. Graves' disease has a strong genetic relationship, with frequent occurrence in the setting of other autoimmune disorders and positive family history,[2] and 20% of cases have been found to be related to environmental causes, such as smoking.

Toxic Multinodular Goiter. Toxic multinodular goiter is the second leading cause of hyperthyroidism in the United States. Itis characterized by multiple autonomously functioning nodules, usually in women older than 50 years. The hyperthyroidism in toxic multinodular goiter is milder than Graves' disease and gradual in onset, but acute presentations can occur when iodine replacement is given to an iodine-deficient individual.

Toxic Adenoma. A toxic adenoma is a single hyperfunctioning nodule within the thyroid. It typically affects the same population as toxic multinodular goiter, but is less common.

Thyroiditis. Any inflammatory process that results in thyroid gland inflammation can lead to thyroiditis. The inciting process may be autoimmune, drug-induced, infectious, or traumatic. Inflammation leads to follicular cell breakdown, with resultant release of preformed thyroid hormone, causing acute thyrotoxicosis. The most common form of thyroiditis in the United States is Hashimoto's thyroiditis, an autoimmune disorder characterized by the presence of thyroid antibodies and lymphocytic infiltration of the thyroid gland. Typically, patients present with a painless goiter and hypothyroidism, but some have transient thyrotoxicosis (hashitoxicosis) that may last a few months.

Silent Thyroiditis. Painless, or silent, thyroiditis is typified by a small nontender goiter and mild symptoms. It is more common in women than men, with a peak from age 30 to 40 years. It has an autoimmune cause and is seen more commonly in areas of adequate iodine intake.[3]

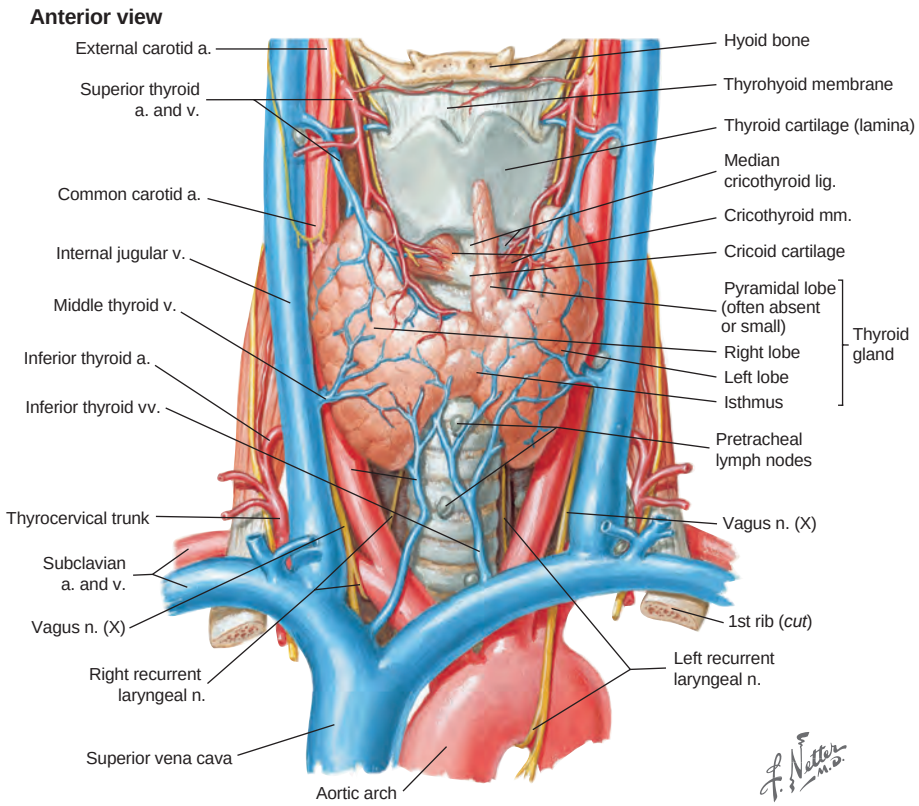

Fig. 120.1. Anatomy of the thyroid gland and related structures. (Netter illustration from www.netterimages.com. Copyright Elsevier. All rights reserved.)

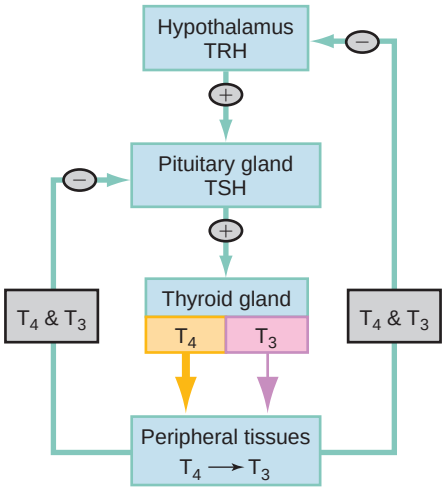

Fig. 120.2. Negative feedback loop of thyroid hormone regulation—hypothalamic-pituitary-thyroid axis. Thyroid hormone production is regulated by the hypothalamus and pituitary gland. Hypothalamic thyrotropin-releasing hormone (TRH) stimulates pituitary thyrotropin (TSH) synthesis and secretion. In turn, TSH stimulates the production and release of thyroxine (T_4) triiodothyronine (T_3) from the thyroid gland. Once released, T_4 and T_3 exert a negative feedback mechanism on the production of TRH and TSH. T_4 is converted to T_3 in the peripheral tissues.

Postpartum Thyroiditis. Of pregnant women, 5% to 10% will develop postpartum thyroiditis. The diagnostic triad consists of the lack of previous history of thyroid disorder, an abnormal TSH concentration during the first postpartum year, and the absence of TSH receptor antibodies or a toxic nodule. Typically, these patients have a triphasic course: (1) thyrotoxicosis, 2 to 6 months postpartum, although this phase may be asymptomatic; (2) a hypothyroid state lasting 2 to 3 months; and (3) finally, a euthyroid state by the end of the first postpartum year. Although this triphasic course is classically described, many have only thyrotoxicosis (20%–30%) or hypothyroidism (40%). The recurrence rate in subsequent pregnancy is estimated at 70% in genetically predisposed women; some women have permanent hypothyroidism.[4]

Subacute Thyroiditis. Subacute thyroiditis (de Quervain's thyroiditis) is thought to be caused by a viral infection of the thyroid. It is manifested with a viral prodrome—fever, fatigue, myalgias, and pharyngitis— followed by anterior neck pain. Pain may radiate to the jaw, ears, or occipital area. The thyroid is exquisitely tender, and pain can occur with head movement or swallowing. During the acute painful phase, about 50% of patients have symptoms of hyperthyroidism (diaphoresis, palpitations, and tremor) lasting 3 to 6 weeks. These symptoms are usually mild. About one-third of patients will then have hypothyroidism for up to 6 months. Subacute thyroiditis occurs most commonly in the fourth and fifth decades of life and is more common in women.

Suppurative Thyroiditis. Suppurative thyroiditis is a rare but potentially life-threatening infection of the thyroid. Patients present with fever and anterior neck pain, neck swelling, induration, and erythema, as well as dysphonia and dysphagia. Infectious causes are overwhelmingly bacterial (aerobic and anaerobic) and very rarely parasitic, mycobacterial, or fungal.[4] Most patients have preexisting thyroid disease and are immunocompromised (eg, AIDS).

Drug-Induced Thyroiditis. Amiodarone contains a high amount of iodine (37%, about 400 times the daily requirement) and, as a result, has a significant effect on thyroid function. It is

estimated that between 5% and 20% of patients treated with amiodarone will develop thyrotoxicosis, higher in areas of iodine deficiency. Two proposed mechanisms have been described, an iodine-induced hyperthyroidism and drug-induced destructive thyroiditis.[5] It is thought that the iodine load may unmask hyperthyroidism in patients with multinodular goiter and subclinical Graves' disease. More commonly, the cytotoxic effects of amiodarone destroy thyroid cells, resulting in a release of preformed hormone. An exacerbation of the tachyarrhythmia for which the patient is being treated or heart failure is the typical presentation of a patient with thyrotoxicosis related to amiodarone. Other drugs that may induce thyroiditis include interferon alpha, highly active antiretroviral therapies, tyrosine kinase inhibitors, interleukin-2, and lithium. Lithium induces sporadic thyroiditis by direct toxic effects.[3,6]

Factitious Thyroiditis. Thyrotoxicosis factitia results from the ingestion of thyroid hormone. Most cases involve medical personnel with psychiatric illness who surreptitiously self-administer the medication. Cases of factitious thyrotoxicosis have also been reported in patients taking nutritional supplements that are marketed to improve thyroid function or aid in weight loss. In some cases, these supplements include doses of thyroid hormone beyond that which is typically prescribed, even with the recommended dose.[7]

Subclinical Hyperthyroid. Subclinical hyperthyroid, identified by a low TSH and normal concentrations of free T_4 and T_3, has recently been identified as a risk factor for cardiovascular morbidity and mortality. These patients have overall increased mortality and are at risk for coronary heart disease, events, and atrial fibrillation.[8]

Clinical Features

History and Physical Examination

Hyperthyroidism induces a hypermetabolic state and increases β-adrenergic activity. The resulting clinical manifestations range from vague constitutional symptoms to more organ-specific symptoms (Box 120.1). Variables that affect the severity of disease include age and disease duration and do not necessarily correlate with the degree of biochemical abnormality. Altered mental status and coma typify thyroid storm, the most severe manifestation of disease.

Hyperthyroidism in older adults often manifests in more subtle ways, often asymptomatic or with nonspecific symptoms of weight loss, shortness of breath, and/or dementia. Older adults are more prone to cardiac manifestations and often present with atrial fibrillation; older adults who smoke or have higher circulating thyroid hormone levels appear to have more severe symptoms.[9] Thyrotoxic periodic paralysis is manifested as a sudden and profound muscle weakness progressing to flaccid paralysis. It closely resembles familial hypokalemic periodic paralysis. Superior vena cava syndrome and dyspnea can occur as a result of the compression of vascular and tracheal structures by an enlarged thyroid. Dysphagia is common and can be due to compression of the esophagus by an enlarged thyroid gland or dysmotility related to thyrotoxic myopathy.

Ophthalmopathy is a classic finding in Graves' disease; it is thought to result in a proliferation of orbital fibroblasts differentiating into adipocytes and orbital infiltration of inflammatory cells. Patients subsequently present with diplopia, photophobia, tearing, grittiness, and pain because of corneal exposure, as well as eyelid edema, hyperemia, conjunctival hyperemia, and chemosis.[10] Graves' ophthalmopathy is also associated with restrictive extraocular myopathy, and exophthalmos. As the disease progresses, patients may experience restriction of their upward gaze from infiltration of the inferior rectus muscle and visual loss from optic nerve involvement (compression by inflamed, enlarged orbital contents).[10]

Physical examination findings of hyperthyroidism depend largely on age (Box 120.2). Younger patients typically present with signs of sympathetic stimulation, whereas older adults often lack the same adrenergic response and present with weight loss and fatigue, more consistent with apathetic hyperthyroidism.[11] In Graves' disease, patients uncommonly have classic pretibial myxedema, in which mucopolysaccharide infiltration of the dermis yields marked thickening of the pretibial skin. These lesions are confluent, painless, reddish raised nodules and plaques over the pretibial area and dorsum of the feet, often described as orange skin. Hyperpigmentation and induration are present, but pitting is absent. Pretibial myxedema is almost always associated with Graves' ophthalmopathy.[10]

Tachycardia is the most common cardiac finding. Other findings include a widened pulse pressure, bounding peripheral pulses

BOX 120.1

Symptoms of Thyrotoxicosis

Constitutional: Weight loss despite hyperphagia, fatigue, generalized weakness
Hypermetabolic: Heat intolerance, cold preference, excessive perspiration
Cardiorespiratory: Palpitations, dyspnea, dyspnea on exertion, chest pains, poor exercise tolerance
Gastrointestinal: Nausea, vomiting, diarrhea, dysphagia
Neuropsychiatric: Anxiety, restlessness, hyperkinesis, emotional lability, confusion, insomnia, poor attention
Neuromuscular: Myopathy, myalgias, tremor, proximal muscle weakness (difficulty getting out of a chair or combing hair)
Ophthalmologic: Tearing, irritation, wind sensitivity, diplopia, foreign body sensation
Thyroid gland: Neck fullness, dysphagia, dysphonia
Dermatologic: Flushed feeling, hair loss, pretibial swelling
Reproductive: Oligomenorrhea, amenorrhea, menometrorhaggia, decreased libido, gynecomastia, erectile dysfunction, infertility

BOX 120.2

Physical Findings in Thyrotoxicosis

Vital signs: Tachycardia, widened pulse pressure, bounding pulses, fever
Cardiac: Hyperdynamic precordium, systolic flow murmur, prominent heart sounds, systolic rub (Means-Lerman scratch), tricuspid regurgitation, atrial fibrillation, evidence of heart failure
Ophthalmologic: Widened palpebral fissures (stare), lid lag, globe lag, conjunctival injection, periorbital edema, proptosis, limitation of superior gaze
Neurologic: Fine tremor, hyperreflexia, proximal muscle weakness
Psychiatric: Fidgety, emotionally labile, poor concentration
Dermatologic: Warm, moist, smooth skin; rosy cheeks, blushing face; fine brittle hair; alopecia, flushed facies; palmar erythema; hyperpigmented pretibial plaques, nodules, or induration that is nonpitting; onycholysis (Plummer's nails, separation of the distal portion of the fingernail from the nail bed)
Neck: Diffuse symmetric thyroid enlargement, sometimes with a bruit and palpable thrill; thyroid with multiple irregular nodules or a prominent single nodule; tracheal deviation, venous prominence with arm elevation (Pemberton's sign)

and, rarely, a friction rub heard along the left sternal border (Means-Lerman scratch). Atrial fibrillation is more common in older adults, with an incidence of 13% in patients older than 65 years with hyperthyroidism. Dilated cardiomyopathy may develop as a complication of a high cardiac output state. Patients can also develop primary pulmonary hypertension, sometimes associated with tricuspid regurgitation and right-sided heart failure.,

Increased activity at the sympathetic innervation of the eyelids leads to widening of the palpebral fissures, resulting in the characteristic stare and lid lag of thyrotoxicosis. Most hyperthyroid patients have an enlarged thyroid gland. Enlargement is common in patients with toxic multinodular goiter or Graves' disease. However, many older adults with Graves' disease have nonpalpable thyroids. Retrosternal enlargement can occur, making detection difficult while causing the obstructive symptoms discussed earlier. Facial and neck vein engorgement can be elicited when arms are elevated above the head, Pemberton's sign.

Negligible to moderate thyroid enlargement can be seen in patients with Hashimoto's or painless thyroiditis (postpartum and sporadic). The thyroid gland in subacute thyroiditis is slightly enlarged and exquisitely tender. The addition of overlying erythema or warmth is seen in suppurative thyroiditis. The absence of thyroid enlargement should suggest exogenous (factitious) thyroiditis as well as ectopic thyroid hormone production, such as a hydatidiform mole or struma ovarii, an ovarian tumor composed of some thyroid tissue.

Thyroid Storm

Thyroid storm is a rare, life-threatening form of severe thyrotoxicosis. Although it can occur as the result of unrecognized or undertreated thyrotoxicosis, more often it is an acute reaction to thyroid or nonthyroid surgery, trauma, infection, iodine load (contrast media or amiodarone), or parturition in patients with preexisting hyperthyroidism. Other precipitants include acute myocardial infarction, pulmonary embolism, hyperemesis gravitum, toxemia of pregnancy, and diabetic ketoacidosis. Untreated, mortality approaches 100%, but prompt recognition and therapy have lowered mortality from 10% to 30%. Death in thyroid storm is caused by multiorgan dysfunction, congestive heart failure, respiratory failure, arrhythmias, disseminated intravascular coagulation, hypoxic brain insult, or sepsis.

The typical clinical manifestations of thyroid storm include marked pyrexia (104°–106° F [40°–41° C]), extreme tachycardia (often out of proportion to level of fever), and altered mental status (agitation, delirium, or coma). These findings, coupled with the clinical picture of a patient with hyperthyroidism, lid lag, stare, goiter, ophthalmopathy, and tremor should alert the emergency clinician to the diagnosis. Cardiovascular collapse can result in congestive heart failure, hypotension, and cardiac arrhythmias. Hypotension can also result from volume depletion secondary to nausea, vomiting, and diarrhea. Abdominal pain is common; hepatic failure with cholestatic jaundice is less common and carries a poor prognosis.[12] Although no validated diagnostic criteria exist, a scoring system developed by Bahn Chair and colleagues can help distinguish among thyrotoxicosis, impending thyroid storm, and frank thyroid storm (Table 120.1).[3]

TABLE 120.1

Diagnostic Criteria for Thyroid Storm

CRITERIA	SCORE[a]
FEVER (° F)	
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
≥104	30
TACHYCARDIA (beats/min)	
90–109	5
110–119	10
120.129	15
130–139	20
≥140	25
MENTAL STATUS	
Normal	0
Mild agitation Delirium, psychosis	10
Extreme lethargy	20
Coma, seizures	30
CONGESTIVE HEART FAILURE	
Absent	0
Mild (edema)	5
Moderate (rales)	10
Pulmonary edema	15
Atrial fibrillation	10
GASTROINTESTINAL AND HEPATIC SYMPTOMS	
None	0
Nausea, vomiting Diarrhea, abdominal pain	10
Unexplained jaundice	20
PRECIPITATING EVENT	
None	0
Present	10

[a]Tally the maximum score from each category. A score of 45 or higher suggests thyroid storm, a score of 25-44 suggests impending storm, and a score below 25 is unlikely to represent thyroid storm.

Diagnostic Testing

The initial diagnosis is based on the clinical picture coupled with confirmatory laboratory values. Measurement of the serum TSH level is the most sensitive test for hyperthyroidism; a normal TSH level excludes hyperthyroidism, and an elevated TSH level is generally diagnostic for hypothyroidism. In thyrotoxicosis, the serum TSH concentration is depressed or undetectable (<0.01 μU/mL in third-generation assays). Accuracy of the TSH determination is improved when free T_4 is added. Assessment of thyroid function during acute nonthyroidal illness is difficult, especially in critically ill patients. Severe systemic illness depresses TSH production, leading to low levels of TSH, free T_3, and free T_4. Once referred to as the euthyroid sick syndrome or, more recently, nonthyroidal illness syndrome (NTIS), it appears to be a transient form of central hypothyroidism that occurs in critically ill patients. Although its molecular basis remains unclear, the presence of thyroid dysfunction in critically ill patients predicts adverse outcomes and mortality. At this time, there are no recommendations to treat critically ill patients with NTIS.[13]

TABLE 120.2

Thyroid Function Test Interpretation

TSH	FREE T_4	FREE T_3	DISEASE
Normal	Normal	Normal	None
Low	High	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Low	Normal	High	T_3 toxicosis
Low	High	Normal	Thyroiditis, T_4 ingestion, hyperthyroidism in older adults or those with comorbid illness
Low	Low	Low	Euthyroid sick syndrome; central hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism; recovery from euthyroid sick syndrome

T_3, Triiodothyronine; *T_4,* thyroxine; *TSH,* thyroid-stimulating hormone.

Elevation of free T_4 and free T_3 levels in conjunction with TSH suppression is diagnostic of thyrotoxicosis. Because nearly all T_3 and T_4 is bound to TBG, assays measuring total T_3 or T_4 are influenced by changes in TBG; they are therefore unreliable and should not be used. Subclinical hyperthyroidism is likely if TSH is suppressed and the free T_4 level is normal.[2] T_3 toxicosis occurs in about 5% of patients with thyrotoxicosis. These patients have an elevated free T_3 level and a normal free T_4 level. When the reverse pattern is present—normal free T_3 level and elevated free T_4 level, the differential includes thyroiditis, exogenous levothyroxine ingestion, and hyperthyroidism in older adults, often with suppressed T_4 to T_3 conversion due to comorbid illness (Table 120.2).[6]

Many thyrotoxic patients have hyperglycemia. This is likely to be the result of increased glycogenolysis and catecholamine-mediated antagonism of insulin. Mild hypercalcemia can be seen, is related to hormone-mediated bone resorption, and is associated with osteoporosis and increased fracture risk.

The results of liver function tests can be abnormal in thyrotoxic patients. Mild increases in serum aspartate transaminase, alanine transaminase, lactate dehydrogenase, bilirubin, and alkaline phosphatase levels may be seen. Elevations in the serum bilirubin level do not typically result in clinical jaundice. Other frequent laboratory abnormalities include leukocytosis, mild anemia, and low serum cholesterol levels.

In thyroiditis, the diagnostic evaluation is more difficult. An exquisitely tender gland and erythrocyte sedimentation rate (ESR) above 100 mm/hr make the diagnosis of subacute thyroiditis likely. The other forms of thyroiditis lack these findings. Doppler ultrasound examination of the thyroid may be helpful in differentiating among the various causes of thyrotoxicosis. High blood flow in the superior thyroid artery and increased overall tissue blood blow on ultrasound favor Graves' disease as a cause and make thyroiditis less likely.[14] If factitious thyrotoxicosis is suspected, low thyroglobulin levels may confirm the diagnosis because these levels are elevated in all other forms of thyrotoxicosis. Furthermore, radioactive iodine uptake is depressed in thyroiditis and factitious thyrotoxicosis but increased in hyperthyroidism.

Differential Diagnosis

The differential diagnosis for the thyrotoxic patient is broad. An anxious patient may be interpreted to be manic or experiencing a panic attack. The hyperadrenergic state may be confused with that seen in patients with sympathomimetic intoxication, suffering from anticholinergic crisis, or experiencing withdrawal from alcohol or sedative-hypnotics. The hyperpyrexia and altered mental status seen in thyroid storm may mimic other hyperthermic disorders such as heat stroke, neuroleptic malignant syndrome, serotonin syndrome, bacterial meningitis, and sepsis. Older adults with apathetic hyperthyroidism may be mistakenly diagnosed with psychiatric illness.

Management

Management of thyrotoxicosis is based on symptom severity. For those with mild symptoms, outpatient referral and management are appropriate. Patients with moderate to severe symptoms are best managed in the emergency department (ED) setting. Treatment is divided into supportive, symptomatic, and thyroid-directed (Box 120.3) therapy. In addition, it is important to identify and treat the precipitating cause of thyroid storm.

Supportive Treatment

Supportive therapy for thyroid storm patients should include management of hyperthermia with cooling and acetaminophen. Aspirin should be avoided in thyrotoxic patients because it decreases the protein binding of T_4 and T_3. Agitation is controlled with benzodiazepines. Fluid resuscitation is needed to compensate for insensible and gastrointestinal (GI) losses; dextrose-containing solutions are helpful because glycogen stores are often depleted. Electrolyte replacement is guided by laboratory values.

Symptomatic Treatment

Symptomatic treatment consists primarily of beta blockade to diminish the adrenergic response. Traditionally, propranolol has been the beta blocker of choice because it has the added benefit of blocking conversion of T_4 to T_3; its nonselective effects also improve tremor, weakness, hyperpyrexia, restlessness, irritability, and emotional lability. Dosage recommendations vary, but most authors suggest 60 to 80 mg orally every 4 hours.[3] The onset of action after oral dosing is about 1 hour.

For rapid beta blockade, propranolol is administered intravenously (IV) as a bolus dose of 0.5 to 1 mg via slow IV push. Propranolol dosing can be repeated, 1 to 2 mg every 15 minutes, as tolerated, until the desired effect is achieved. A short-acting agent such as esmolol may be used when concerns about beta blockade exist. A typical esmolol loading dose is 250 to 500 μg/kg, followed by an infusion of 50 to 100 μg/kg/min. In asthmatics, a β_1-selective drug such as esmolol or metoprolol (50 mg PO every 6–12 hours) may be considered.

If beta blockers are contraindicated, reserpine, 2.5 to 5 mg intramuscularly every 4 hours, is also an option. Patients should be closely monitored for hypotension, regardless of the agent used, because thyrotoxicosis can lower systemic vascular resistance and cause congestive heart failure. Patients who develop clinically significant heart failure should be treated with the usual medications for heart failure, including diuretics and angiotensin-converting enzyme inhibitors. Atrial fibrillation is often refractory to rate control until antithyroid therapy is instituted.

Thyroid-Directed Treatment

Thyroid-directed therapy has three goals—reduce thyroid hormone production, prevent thyroid hormone release, and block peripheral conversion of T_4 to T_3. In conjunction with this treatment, an additional goal is the avoidance of therapeutic interventions that may worsen thyrotoxicosis. As such, certain drugs should be avoided in the thyrotoxic patient. Amiodarone

BOX 120.3

Management of Thyroid Storm

β-ADRENERGIC BLOCKADE
Propranolol 60–80 mg PO every 4 hours
or
Metoprolol, 25–50 mg PO qid
If IV route is required—propranolol, 0.5–1.0 mg IV slow push test dose, then repeat 1–2 mg every 15 min as tolerated to desired effect, then 1–2 mg every 3 hr
or
Esmolol, 50–100 μg/kg/min infusion
Strict contraindication to beta blocker—reserpine 2.5–5 mg IM every 4 hr

INHIBITION OF THYROID HORMONE SYNTHESIS
Propylthiouracil, 500–1000 mg loading dose, then 250 mg every 4 hr
or
Methimazole, 60–80 mg/day in divided doses
Preferred route, PO or nasogastric (NG); alternative route: PR (in rectum), enema prepared by pharmacy; same dose for all routes

INHIBITION OF THYROID HORMONE RELEASE
Saturated solution of potassium iodide (SSKI, 50 mg iodide/drop), 1–2 drops PO or PR tid
or
Lugol's solution (8 mg iodide/drop), 5–7 drops PO or PR tid
or
Sodium iodide, 500 mg IV bid in solution prepared by pharmacy
or
If allergic to iodine, lithium carbonate, 300 mg PO or NG qid

ADMINISTRATION OF CORTICOSTEROIDS
Inhibit T_4 to T_3 conversion; treat relative adrenal insufficiency.
Hydrocortisone, 300 mg IV, followed by 100 mg tid
or
Dexamethasone, 2–4 mg IV qid

DIAGNOSIS AND TREATMENT OF UNDERLYING PRECIPITANT
Consider empirical antibiotics if critical.

SUPPORTIVE MEASURES
Volume resuscitation and replacement of glycogen stores
D_5/0.9 NS, 125– 000 mL/hr, depending on volume status and CHF
Tylenol, with caution
Cooling blanket, fans, ice packs, ice lavage

MISCELLANEOUS
Lorazepam or diazepam as anxiolytic and to decrease central sympathetic outflow
Cholestyramine (blocks enterohepatic recirculation of thyroid hormone), 1–4 g PO twice daily for severe or refractory thyrotoxicosis

CHF, Congestive heart failure; *D_5W/0.9 NS,* 5% dextrose in 0.9% normal saline; *IV,* intravenously; *NG,* by nasogastric tube; *PO,* by mouth; *PR,* by rectum; *T_3,* triiodothyronine; *T_4,* thyroxine.

and iodinated contrast material both contain iodine and can increase thyroid hormone production. Aspirin can increase free thyroid hormone concentrations through its effect on protein binding. Pseudoephedrine, ketamine, and albuterol increase sympathetic tone and can exacerbate the adrenergic effects of thyrotoxicosis; when indicated, they should be used cautiously.

Reducing Thyroid Hormone Production. Thionamides inhibit oxidation and organic binding of iodine to thyroglobulin, thereby blocking the synthesis of thyroid hormone. Propylthiouracil (PTU) or methimazole can be used. PTU has the additional effect of impairing the conversion of T_4 to T_3; methimazole has a longer duration of action. PTU is given as an initial loading dose of 500 to 1000 mg orally, followed by 250 mg every 4 hours.[3] The recommended dose for methimazole is 80 to 120 mg daily, divided every 4 to 6 hours.[12] Both PTU and methimazole may be given by nasogastric tube or rectum as needed. Methimazole is available in IV form outside the United States. Although IV administration of methimazole has been attempted, its use is only supported by case reports and should be considered only as a last resort.[15]

Side effects of thionamide therapy range from mild to life-threatening. Mild reactions—urticaria or macular rash, arthralgia, and GI upset—occur in up to 5% of patients receiving methimazole or PTU. Life-threatening side effects are associated with ongoing therapy and occur within the first 90 days of treatment. Agranulocytosis can occur with either drug and should prompt drug discontinuation. PTU-induced hepatotoxicity has earned the drug a black box warning from the US Food and Drug Administration (FDA). Finally, polyarthritis and vasculitis (drug-induced lupus) can occur; vasculitis is associated with PTU more than with methimazole. Side effects are dose-related for methimazole but not for PTU.

Inhibiting Thyroid Hormone Release. Inorganic iodine blocks the release of stored thyroid hormone. Because an iodine load can increase the synthesis of thyroid hormone, these agents should not be administered until 1 hour after the initiation of PTU or methimazole therapy. Traditionally, oral iodine in the form of potassium iodide (SSKI [saturated solution of potassium iodide], 50 mg iodide/drop), 1 or 2 drops, or Lugol's solution (8 mg iodide/drop), 5 to 7 drops every 8 hours, is administered. Like the thionamides, these agents may be given via nasogastric tube or retention enema, as needed. Lithium may be considered an alternative therapy for iodine-allergic patients. The lithium dose is 300 mg every 6 to 8 hours orally to obtain a lithium serum concentration of 0.6 to 1.0 mEq/L. Lithium is also the agent of choice for iodine-induced hyperthyroidism, which is usually the result of the administration of amiodarone or iodinated contrast material.[3]

Inhibiting Conversion of T_4 to T_3. Corticosteroids are capable of inhibiting the peripheral conversion of T_4 to T_3 and blocking the release of hormone from the thyroid gland. When steroids are used in conjunction with PTU and iodide, the concentration of T_3 can return to normal within 48 hours. In addition, corticosteroids will treat adrenal insufficiency that can occur concomitantly with thyroid storm. Adrenal insufficiency is usually due to increased clearance of cortisol in thyroid storm and the increased demand for cortisol in these critically ill patients. Hydrocortisone can be administered as an initial bolus of 300 mg IV, then 100 mg tid for several days. Dexamethasone is an alternative.

Miscellaneous Therapies

Cholestyramine, an anion exchange resin, interrupts the enterohepatic recirculation of thyroid hormone by binding it in the bowel lumen. Although it has been shown to result in a more rapid decline in hormone levels compared with thionamides alone, it requires weeks of therapy and, as such, is reserved for outpatient management. Because it may help to decrease the level of circulating hormone more rapidly, dosages of 1 to 4 g twice daily are recommended for severe or refractory thyroid storm. Although the literature is split on their efficacy, plasmapheresis and dialysis have been used in thyroid storm as an attempt to remove circulating thyroid hormone.[12] Neither radioactive iodine

BOX 120.4

Thyrotoxicosis and Thyroid Storm Special Situations

CONGESTIVE HEART FAILURE
If rate-related, high-output failure:
- Beta blockade is first-line therapy (dose as in Box 120.3)
- ACEI, digoxin, diuretics as needed

If depressed ejection fraction:
- Avoid beta blocker or one-quarter dose
- ACEI if blood pressure adequate
- Digoxin and furosemide as needed

If pulmonary hypertension:
- Oxygen
- Sildenafil

ATRIAL FIBRILLATION
Beta blocker preferred for rate control (dose as in Box 120.3)
Calcium channel blockers prone to hypotension; diltiazem, 10-mg test dose. Avoid verapamil.
Digoxin less effective but may be tried
Amiodarone should be avoided because of iodine load
Refractory to conversion to sinus rhythm unless euthyroid first

THYROIDITIS (SUBACUTE)
NSAIDs for inflammation and pain control
Prednisone, 40 mg/day, if refractory to NSAIDs
Beta blockade to control thyrotoxic symptoms
No role for PTU, methimazole, or iodides

FACTITIOUS THYROTOXICOSIS
Beta blockade for thyrotoxic symptoms
Cholestyramine to block absorption of ingested thyroid hormone
No role for PTU, methimazole, or iodides

ACEI, Angiotensin-converting enzyme inhibitor; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PTU,* propylthiouracil.

nor surgery plays a role in the management of thyroid storm or thyrotoxicosis until a sustained euthyroid state has been established because these interventions can precipitate thyroid storm.

First-line treatment of subacute thyroiditis is the use of nonsteroidal antiinflammatory drugs (NSAIDs). Corticosteroids should be used in refractory cases, with an initial dose of 40 mg prednisone daily for 1 to 2 weeks, followed by a taper over at least 2 to 4 weeks. Symptomatic patients should be treated with beta blockers. Management of drug-induced hyperthyroidism involves removal of the offending agent (eg, amiodarone, lithium) and treatment based on the determination of the type of reaction present (eg, iodine-induced thyroiditis, destructive thyroiditis, autoimmune thyroiditis; Box 120.4).[3]

Identification and Treatment of the Precipitating Event

Thyroid storm is often precipitated by a physiologic stressor, usually an infection. Empirical antibiotics are not necessary without an identified source of infection. Other common stressors include myocardial ischemia, pulmonary embolism, and stroke. Management of thyroid storm with PTU, followed by iodine, beta blockers, corticosteroids, fluid resuscitation, rapid cooling, and treatment of the precipitating illness, can resolve fever, tachycardia, and altered mental status within 24 hours. Interruption in therapy should be avoided because it can lead to a sudden recrudescence of symptoms and death.

Disposition

Disposition is guided by symptom severity, with intensive care unit (ICU) admission for patients in thyroid storm. Patients with mild thyrotoxicosis (tremor, tachycardia, nervousness) controlled with a first-line medication who are otherwise stable can be managed as outpatients. Admission to the hospital may be appropriate for patients who require more than beta blockers for symptom control or whose symptoms persist despite therapy. Patients with rapid atrial fibrillation should be admitted to a monitored setting. Patients managed as outpatients can be sent to a primary care physician or referred to an endocrinologist.

HYPOTHYROIDISM

Principles

Background

Hypothyroidism is a condition in which the thyroid gland fails to produce or secrete sufficient circulating thyroid hormone to meet the needs of the peripheral tissues. The condition results from lack of stimulation of the thyroid gland (central or secondary hypothyroidism) or intrinsic gland dysfunction limiting hormone production (primary hypothyroidism). Hypothyroidism is the most common functional disorder of the thyroid gland.

Hypothyroidism is a relatively common disorder of endocrine dysfunction, with an annual incidence affecting approximately 80/100,000 men and 350/100,000 women.[1] Thyroid disorders are the second most common endocrine condition after diabetes mellitus. Higher incidence rates are found in women than in men, which is attributed to the higher prevalence of autoimmune disease found in women in general. In the United States, 1% to 2% of women are affected by hypothyroidism. Subclinical hypothyroidism affects 4% to 10% of the population.[16] There is no specific race or ethnic predilection, but older age groups are at a higher risk for the development of hypothyroidism. The incidence of overt and subclinical hypothyroidism in pregnancy is estimated at up to 0.5% and 3%, respectively.

Pathophysiology

Intrinsic gland failure accounts for up to 99% of all cases of hypothyroidism. Factors that may result in primary hypothyroidism include autoimmune disorders, infiltrative disorders, congenital thyroid dysfunction, pregnancy, radiotherapy, medications, infection, surgery, inadequate dietary iodine intake, thyroid medication noncompliance, and previous treatment of thyrotoxicosis. Worldwide, iodine deficiency is the most common cause of hypothyroidism; however, in iodine-replete regions, the primary cause is autoimmune. Hypothyroidism may also be associated with other autoimmune diseases, such as diabetes mellitus, pernicious anemia, Addison's disease, and hyperparathyroidism.

Hashimoto's thyroiditis, or chronic autoimmune lymphocytic thyroiditis, first described in 1912 by Hakaru Hashimoto, is one of the most common organ-specific autoimmune diseases and the most common cause of primary hypothyroidism. It is characterized by infiltration of the thyroid gland by lymphocytic inflammatory cells, which is then often followed by hypothyroidism as a result of destruction and eventual fibrous replacement of the gland's follicular tissue.

Neonatal hypothyroidism results from decreased T_4 production in the newborn and is the most preventable cause of intellectual disability. Most infants with congenital hypothyroidism have thyroid dysgenesis, which includes thyroid agenesis, thyroid hypogenesis, and a defect in thyroid migration leading to ectopic thyroid tissue, usually found at the base of the tongue (lingual

thyroid). With thyroid dysgenesis, the thyroid tissue, if any, has insufficient function to sustain normal thyroid hormone production. In some cases of a lingual thyroid, patients may have local symptoms of dysphagia, dysphonia, hemorrhage, or upper airway obstruction decades later in life.[17] The longer the diagnosis and treatment of congenital hypothyroidism are delayed, the greater the cognitive deficit.

Lithium and amiodarone use are well-known causes of hypothyroidism. Lithium, commonly prescribed for the treatment of bipolar disorder, has a side effect profile that includes goiter in up to 40% and hypothyroidism in about 20% of patients. The most relevant clinical action of lithium on the thyroid is the inhibition of T_4 and T_3 release. Lithium also increases thyroid autoimmunity if it is present before the initiation of lithium treatment. Treatment with exogenous thyroid hormone is effective, and lithium therapy need not be discontinued.

Amiodarone is a class III antiarrhythmic medication that has a chemical structure similar to that of T_4 and contains large amounts of iodine. As such, it inhibits the peripheral conversion of T_4 to T_3, leading to hypothyroidism.[18] In addition, amiodarone is directly cytotoxic to the thyroid, has the intrinsic effect of blocking thyroid hormone entry into cells, and decreases T_3 receptor binding. If amiodarone therapy must be continued for arrhythmia control, patients with amiodarone-induced hypothyroidism may be successfully treated with exogenous thyroid hormone replacement. Patients should be screened with a TSH prior to starting amiodarone. Patients receiving some chemotherapeutic agents are also at risk for thyroid dysfunction.[19]

Insufficient dietary iodine intake leads to reduced T4 and T3 production. Although it is uncommon in developed nations, this is still a major concern in areas where the iodine content in the water is low. The compensatory increase in TSH concentration over time results in the proliferation of gland cells and enlargement of the gland, with a resultant goiter.

Thyroid physiology is altered during pregnancy because increased circulating estrogen increases TBG levels by up to 150%, resulting in lower free T_4 levels.[20] Human chorionic gonadotropin (hCG) and TSH have identical subunits, which then both stimulate the release of T_4 and T_3, resulting in a decreased level of TSH at 8 to 14 weeks of gestation. Increased peripheral metabolism of thyroid hormone occurs primarily in the second and third trimesters. Women with preexisting hypothyroidism will generally require increased doses of replacement hormone in pregnancy.

Although congenital hypothyroidism is one of the most common preventable causes of mental retardation, newborn screening programs in the developed world have made this a rare occurrence in the United States. There are conflicting data and opinions about whether there should be universal screening for thyroid function and subsequent treatment in pregnant women without overt symptoms or risk factors for hypothyroidism.[20–22] Other obstetric complications of hypothyroidism include miscarriage, anemia, abruptio placentae, postpartum hemorrhage, low birth weight, and neonatal respiratory distress.

Central causes of hypothyroidism are rare and result from hypothalamic dysfunction in the secretion of TRH or pituitary dysfunction in the secretion of TSH. Pituitary adenoma is the most common cause of central hypothyroidism. Other causes include pituitary hemorrhage (Sheehan's syndrome), pituitary infiltrative processes such as amyloidosis and sarcoidosis, brain injury, and space-occupying mass. Sheehan's syndrome is a result of postpartum pituitary hemorrhage that leads to pituitary ischemia and necrosis. Patients often have lactation failure, amenorrhea, adrenal insufficiency, and central hypothyroidism.[23]

With advancing age, the thyroid gland changes anatomically, with a reduction in gland size and weight, an increase in fibrosis with lymphocytic proliferation, and a change in colloid content. These changes do not, however, correlate with gland function. TSH levels increase with age, but this is not associated with an increase in T_4 concentration.[24]

Clinical Features

History and Physical Examination

Signs and symptoms of hypothyroidism range from asymptomatic to overt organ failure, which may lead to death (Box 120.5). Patients with early hypothyroidism often present with vague complaints. As such, emergency clinicians should consider thyroid dysfunction in patients with generalized arthralgias, infertility or menstrual changes, depression, and hypercholesterolemia.

Typical symptoms develop insidiously and include fatigue, weakness, constipation, heavier menstruation, weight gain, cold intolerance, hypertension, and bradycardia. Skin may be dry, coarse, and pale from fluid accumulation and decreased circulation. Paresthesias of the hands mimicking carpal tunnel have been described.

As the disease progresses, symptoms may include altered or decreased taste, hoarseness, edema of the hands and feet, and slow speech. Body and scalp hair is brittle and coarse, with a high rate of at least some degree of alopecia, thickening of the skin, and thinning of the lateral third of the eyebrows. Facial changes include periorbital edema, broadened nose, swollen lips, macroglossia, and flat facial expression.

Patients with subclinical hypothyroidism may present with varying nonspecific signs and symptoms similar to those of patients with overt hypothyroidism, but less pronounced. Patients with Hashimoto's thyroiditis present typically with an insidiously developed goiter and hypothyroidism.

The thyroid has a fundamental role in maintaining cardiovascular homeostasis in physiologic and pathologic states; it influences cardiac contractility, heart rate, diastolic function, and systemic vascular resistance. Increased peripheral vascular resistance and low cardiac output have been suggested to be additional links between hypothyroidism and impaired blood pressure regulation and resultant hypertension. Antihypertensive medications are usually ineffective in noneuthyroid individuals.[25]

The accelerated atherosclerosis in hypothyroidism is ascribed to dyslipidemia, diastolic hypertension, and impaired endothelial function.[26] In addition, T_3 increases the production and secretion of renin. In patients who are hypothyroid, renin levels are found to be low, which plays an important role in the acceleration of atherogenesis.[27]

Overt hypothyroidism leads to significant neuropsychiatric impairments of mood and cognition. Subclinical hypothyroidism may cause subtle deficits in memory and cognition. Treatment of subclinical hypothyroidism remains controversial.[28]

Pulmonary abnormalities in hypothyroidism are primarily related to hypoventilation and hypercapnia; up to 65% of patients with pulmonary hypertension have concomitant thyroid dysfunction. Although the exact relationship is unknown, pulmonary artery pressures normalize after treatment of thyroid disease.

In pregnancy, hypothyroidism may be manifested typically, but it is often subtle and difficult to distinguish from normal changes in pregnancy. The secretion of hCG is greatest in the first trimester of pregnancy and plateaus in the second; hCG has inherent TSH-like activity and results in elevated T_4 and T_3 levels and decreased TSH levels. The fetus begins to produce TSH toward the end of the first trimester; before this time, the fetus relies on maternal TSH production. Normal maternal thyroid hormone production is therefore critical to fetal development.

In children, hypothyroidism may affect growth, development, and cognitive capacity. Declining growth velocity noticed during several years might be the first clue to evaluate for thyroid

BOX 120.5

Symptoms and Signs of Hypothyroidism

VITAL SIGNS
Systolic blood pressure, normal or low
Diastolic blood pressure, normal or elevated
Slow pulse to sinus bradycardia
Respirations, normal or slow, shallow
Temperature, normal, but prone to hypothermia with stress

HYPOMETABOLIC COMPLAINTS
Cold intolerance
Fatigue
Weight gain, but decreased appetite

CUTANEOUS
Coarse, brittle hair
Alopecia
Dry skin, decreased perspiration
Pallor, cool hands and feet
Coarse, rough skin
Yellow tinge from carotenemia
Thin, brittle nails
Lateral thinning of the eyebrows

NEUROLOGIC
Slow mentation and speech
Impaired concentrating ability and attention span
Lethargy
Decreased short-term memory
Agitation, psychosis
Seizures
Ataxia, dysmetria
Mononeuropathy
  Carpal tunnel syndrome
  Sensorineural hearing loss
Peripheral neuropathy, paresthesias

MUSCULAR
Proximal myopathy
Pseudohypertrophy
Delayed relaxation of reflexes (hung up or pseudomyotonic)

CARDIAC
Decreased exercise capacity
Dyspnea on exertion
Sinus bradycardia
Long QT with increased ventricular arrhythmia
Chest pain, accelerated coronary disease
Diastolic heart failure (delayed ventricular relaxation)
Pericardial effusion (asymptomatic)
Peripheral edema

RESPIRATORY
Dyspnea on exertion
Obstructive sleep apnea
Primary pulmonary hypertension

GASTROINTESTINAL
Constipation
Ileus
Gastric atrophy

REPRODUCTIVE
Oligomenorrhea and amenorrhea
Menorrhagia
Decreased fertility
Early abortions
Decreased libido
Erectile dysfunction

RHEUMATIC
Polyarthralgias
Joint effusions
Acute gout or pseudogout

HEAD, EAR, EYES, NOSE, AND THROAT
Hoarseness
Deep husky voice
Macroglossia
Hearing loss
Periorbital swelling
Broad nose
Swollen lips
Goiter

disorders. This is secondary to retarded skeletal development and growth arrest from epiphyseal dysgenesis. T_4 replacement will induce a rapid growth spurt, although predicted bone maturation size might not be achieved. In adults, thyroid hormone functions to regulate and maintain bone mass; patients with hypothyroidism are at increased risk for fracture, although the underlying mechanism resulting in this association is unclear.

Myxedema Coma

Myxedema coma is a life-threatening event, most often precipitated by some stressful occurrence in patients with untreated hypothyroidism. Precipitating events include myocardial infarction, infection, sepsis, stroke, pulmonary embolus, prolonged exposure to cold, or exposure to drugs that suppress the central nervous system (Box 120.6). Diagnosis must often be made on the basis of clinical findings (Box 120.7), and hypothermia is often seen. Treatment of myxedema coma requires potentially toxic doses of thyroid hormone and can precipitate thyroid storm. Mortality rates are high, even with optimum therapy. Without treatment, the mortality approaches 100%. Myxedema is associated with a range of severe mental disorders, from depression to severe psychoses, sometimes called myxedema madness.

Diagnostic Testing

Determination of an elevated TSH level is considered to be the most sensitive and single best screening test to confirm the diagnosis of primary hypothyroidism. TSH levels peak in the evening and are at their lowest in the afternoon, but are also affected by physiologic conditions such as physical stress, illness, trauma, and malnutrition. An elevated TSH level with a low T_4 level is indicative of primary hypothyroidism. Central hypothyroidism is associated with a low or normal TSH level, with a low T_4 level. An increased TSH concentration with a normal T_4 level represents subclinical hypothyroidism (Table 120.3).

BOX 120.6

Myxedema Coma: Aggravating or Precipitating Factors

Infection, sepsis (especially pneumonia)
Exposure to cold
Cerebrovascular accident
Drug effect
- Altered sensorium—sedative-hypnotics, narcotics, anesthesia, neuroleptics
- Decreased T_4 and T_3 release—amiodarone, lithium, iodides
- Enhanced elimination of T_4 and T_3: phenytoin, rifampin
- Inadequate thyroid hormone replacement: noncompliance; interference with absorption (iron, calcium, cholestyramine)

Myocardial infarction
Gastrointestinal bleeding
Trauma, burns
Congestive heart failure
Hypoxia
Hypercapnia
Hyponatremia
Hypoglycemia
Hypercalcemia
Diabetic ketoacidosis

T_3, Triiodothyronine; *T_4,* thyroxine.

BOX 120.7

Recognition of Myxedema Coma

Patient profile—older woman in the winter
Known hypothyroidism; thyroidectomy scar
Hypothermia—temperature usually <95.9° F (36° C); <90° F (32° C) is poor prognostic sign; as low as 75° F (24° C) reported; nearly normal in presence of infection
Altered mental status—lethargy and confusion to stupor and coma, agitation, psychosis, and seizures (myxedema madness)
Hypotension—refractory to volume resuscitation and pressors unless thyroid hormone administered
Slow, shallow respirations with hypercapnia and hypoxia; high risk of respiratory failure
Bradycardia (sinus), long QT and ventricular arrhythmias
Myxedema facies—puffy eyelids and lips, large tongue, broad nose
Evidence of severe chronic hypothyroidism—skin, hair, reflexes, bradykinesis, voice
Acute precipitating illness (eg, pneumonia)
Drug toxicity (eg, sedative, narcotic, neuroleptic)
Hyponatremia

TABLE 120.3

Definitions of Thyroid Dysfunction

FUNCTION	TSH	FREE T_4
Clinical hypothyroidism	Elevated	Low
Subclinical hypothyroidism	Elevated	Normal
Hypothyroxinemia	Normal	Low

T_4, Thyroxine; *TSH,* thyroid-stimulating hormone.
Adapted from Gyamfi C, Wapner RJ, D'Alton ME: Thyroid dysfunction in pregnancy: The basic science and clinical evidence surrounding the controversy in management. Obstet Gynecol 113:702–707, 2009.

If the TSH level is normal but the T_4 level is low, hypothyroxinemia exists; patients are often asymptomatic but can experience pathologic effects. A useful confirmatory test is the presence of thyroid antibodies (antithyroglobulin, antimicrosomal). They may help determine the cause of hypothyroidism or may serve to predict a future occurrence. Other laboratory findings may include mild anemia, hypercholesterolemia, elevated hepatic enzyme levels, elevated prolactin level, and hyponatremia secondary to extracellular volume expansion produced by an elevated antidiuretic hormone level. Blood glucose levels may be normal to low as a result of decreased gluconeogenesis and reduced insulin clearance.

The electrocardiogram is nonspecific in hypothyroidism. It might reveal sinus bradycardia with low-voltage complexes and nonspecific ST-T wave changes.

Differential Diagnosis

Differential considerations include other causes of the common clinical presentations of hypothyroidism, such as congestive heart failure, pulmonary edema, depression, encephalopathy, hypothermia, systemic infection, and shock.

Management

Hypothyroidism

Replacement with levothyroxine (T_4) remains the treatment of choice and resolves most physical and psychological signs and symptoms in most patients. Synthetic levothyroxine is a levo isomer of thyroxine and has activity identical to that of the endogenous hormone. Approximately 70% to 80% is absorbed from the GI tract, predominantly in the small intestine. T_4 levels peak approximately 4 hours after ingestion.[54] The T_3 concentration rises more slowly because it is dependent on conversion from T_4. Dose optimization is guided by monitoring of serum TSH levels and symptoms.

Levothyroxine is the drug of choice for patients with subclinical hypothyroidism and a serum TSH concentration above 10 mIU/L and for symptomatic patients with a serum TSH concentration between 5.1 and 10.0 mIU/L. The usual daily dosage is between 50 and 75 μg. The TSH concentration should be guide thyroid hormone dosing. The serum TSH concentration should be checked every 6 to 8 weeks after initiation of treatment until TSH levels normalize. It is recommended that levothyroxine be taken at bedtime or 60 minutes before breakfast to improve absorption.[29]

Studies comparing combination therapy of levothyroxine (T_4) and T_3 (liothyronine [Cytomel]) with levothyroxine monotherapy alone have not established a significant benefit. The most recent American Thyroid Association guidelines do not recommend combination therapy for routine treatment.[29]

Myxedema Coma

The cornerstone for the treatment of myxedema coma is rapid replacement of IV thyroid hormone (Box 120.8). An initial loading dose of 200 to 400 μg IV should be given, using lower doses in patients who are smaller, older, or have a history of coronary artery disease or arrhythmia. Subsequent daily replacement dose is 1.6 μg/kg body weight, decreasing the dose to 75% if given IV. Controversy exists regarding the use of IV T_3 because it has been shown to increase mortality, and data regarding its use is limited. Stress doses of an IV glucocorticoid are recommended due to possible concomitant adrenal insufficiency. Hydrocortisone, 100 mg IV, is the drug of choice because it has mineralocorticoid and glucocorticoid effects.

BOX 120.8

Treatment of Myxedema Coma

Protect airway, ventilatory support; monitor for alkalosis
Fluid resuscitation
- 0.9 NS or D_5/0.9 NS if hypoglycemia
- Watch for unmasking of CHF

Thyroid hormone replacement
- T4 200–400 μg IV (give lower doses to patients who are smaller, have coronary artery disease or a history of arrythmia) loading dose
- Subsequent daily replacement of 1.6 μg/kg body weight PO, give 75% of this dose if given IV

Hydrocortisone—100 mg IV every 8 hrs
Hyponatremia
- Consider fluid restriction.
- Avoid hypotonic fluids; use only 0.9 NS or D_5/0.9 NS.
- If <120 mEq/L, consider 3% saline, 50- to 100-mL boluses.

Passive rewarming
- Regular blankets; prevent heat loss
- If heating blankets are considered, pretreat with IV fluids and monitor blood pressure closely.
- Avoid mechanical stimulation.

Treatment of any precipitating illness, with special attention to infectious causes

CHF, Congestive heart failure; *D_5/0.9 NS,* 5% dextrose in 0.9% normal saline; *IV,* intravenous; *PO,* by mouth; *T_3,* triiodothyronine; *T_4,* thyroxine.

Hypotension may respond to crystalloid infusion, but vasopressors are occasionally required. In patients with initially refractory hypotension, the mere replacement of thyroid hormone may have a beneficial effect on improvement of blood pressure.

Passive rewarming with blankets and removal from the cold are generally sufficient until the administered thyroid hormone takes effect.

Hyponatremia is not uncommon in patients and is associated with increased mortality. As with other causes of hyponatremia, hypertonic saline should be administered for severe cases of altered mental status or seizures and then corrected more slowly to avoid osmotic demyelination syndrome. The metabolism of sedatives, narcotics, and anesthetics may be slowed, prolonging their effects; lower dosages should be considered.

Disposition

Most patients with hypothyroidism may be treated on an outpatient basis. Patients with severe hypothyroidism who require management or patients with myxedema coma require inpatient care, often in an ICU setting.

ADRENAL INSUFFICIENCY

Principles

Background

First described in 1855 by Thomas Addison, Adrenal insufficiency remains a potentially life-threatening disease. The clinical manifestations are the result of primary adrenal failure or secondary adrenal disease from malfunction of the hypothalamic-pituitary-adrenal (HPA) axis in its production of adrenocorticotropic hormone (ACTH). The predominant symptoms are fatigue, generalized weakness, weight loss, and nonspecific GI symptoms, such as nausea, vomiting, and abdominal pain. Acute manifestations of disease may result in severe refractory hypotension.

Secondary adrenal insufficiency is more common than primary adrenal insufficiency. Its most common cause is exogenous corticosteroid administration.

Anatomy and Physiology

The adrenal glands are responsible for the release of the hormone aldosterone, corticosteroids, and catecholamines. They are paired structures that sit in the retroperitoneum, one atop each kidney. The adrenal gland has two distinct structures—the outer adrenal cortex, comprised anatomically of the zona glomerulosa, and the medulla, comprised anatomically of the zona fasciculata and reticularis. The medulla acts in concert with the central nervous system to produce and secrete epinephrine and norepinephrine in response to sympathetic stimulation. It also secretes the mineralocorticoid cortisol from the zona fasciculata and androgens from the zona reticularis. The outer cortex, which includes the zona glomerulosa, secretes the mineralocorticoid aldosterone.

ACTH, produced and secreted by the anterior pituitary, stimulates the adrenal cortex to synthesize and produce cortisol, which regulates carbohydrate, protein, and lipid metabolism, and aldosterone, which regulates fluid and electrolyte balance through sodium and potassium homeostasis. Cortisol is the primary glucocorticoid in humans, accounting for approximately 95% of all glucocorticoid activity.

Pathophysiology

Primary adrenal insufficiency, or Addison's disease, is the failure of the adrenal gland to produce cortisol, aldosterone, or both. with an intact HPA axis (Fig. 120.3). In developed countries, it is usually a result of autoimmune destruction.[30] Adrenal insufficiency may occur alone, with other autoimmune diseases (eg, polyglandular autoimmune syndrome type 2, polygenic inheritance), or with hypoparathyroidism and mucocutaneous candidiasis (polyglandular autoimmune syndrome type 1). In primary disease, the HPA axis remains intact. Primary adrenal insufficiency is characterized by absent or low cortisol with high levels of circulating ACTH because of reduced negative feedback effects on the anterior pituitary. The increased ACTH concentration results in secretion of other hormones with similar chemical structure. One classic feature exemplifying this relationship is ACTH stimulation of melanocyte-stimulating hormone, which causes melanocytes to form a black pigment and the characteristic skin hyperpigmentation seen in those with primary adrenal insufficiency.

Secondary adrenal insufficiency is a result of impaired stimulation of the adrenals from the disruption of normal secretion of ACTH by the pituitary (see Fig. 120.3). It is characterized by a low plasma cortisol level, with low circulating ACTH levels. Tertiary adrenal insufficiency is caused by hypothalamic disease. There is a decrease in release of corticotropin-releasing hormone, resulting in minimal ACTH and cortisol production. Aldosterone, sex hormone, and catecholamine synthesis are normal; the most common cause is long-term exogenous steroid administration.

Adrenal insufficiency may be further characterized as acute or chronic (Box 120.9). The most common cause of acute adrenal insufficiency is the exogenous administration of glucocorticoids, which results in suppression of the HPA axis. The degree of suppression varies on the basis of the pharmacokinetics, dose, and duration of the steroid administered. Larger doses of agents with longer half-lives and an extended course of therapy will prolong the suppression of the HPA axis. Although the time for HPA axis recovery after exogenous suppression is highly variable, adrenal insufficiency should be anticipated to occur in patients who

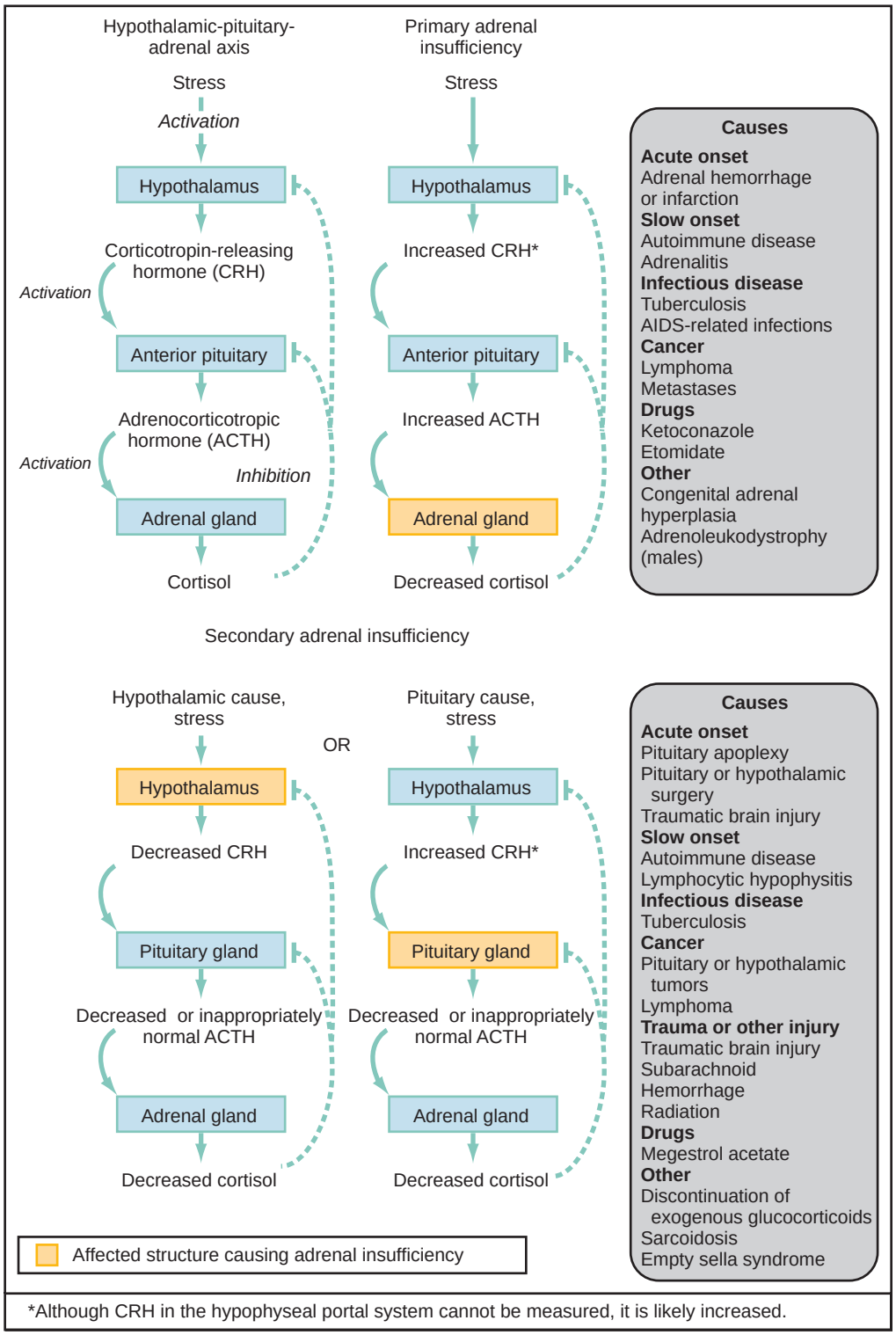

Fig. 120.3. Hypothalamic-pituitary-adrenal axis and causes of primary and secondary adrenal insufficiency. (Adapted from Wallace I, Cunningham S, Lindsay J: The diagnosis and investigation of adrenal insufficiency in adults. Ann Clin Biochem 46[Pt 5]:351–367, 2009.)

BOX 120.9

Causes of Adrenal Insufficiency

PRIMARY ADRENAL INSUFFICIENCY

Chronic

Autoimmune adrenalitis (Addison's disease)—isolated or polyglandular deficiency, human immunodeficiency virus (HIV) infection (direct involvement or disseminated cytomegalovirus, *Mycobacterium avium-intracellulare,* tuberculosis, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, *Pneumocystis* pneumonia)
Tuberculosis and disseminated infections as seen with HIV
Metastatic cancer (breast, lung)
Infiltrative (sarcoid, hemochromatosis, amyloid)
Congenital (adrenal hypoplasia, adrenoleukodystrophy, ACTH resistance)
Bilateral adrenalectomy
Drug toxicity (eg, etomidate, ketoconazole, rifampicin)

Acute

Adrenal hemorrhage
Meningococcemia and other sepsis
Anticoagulation (heparins and warfarin)
Anticardiolipin antibody syndrome
Trauma

SECONDARY ADRENAL FAILURE

Chronic

Pituitary tumor (primary or metastatic)
Pituitary surgery or irradiation
Chronic steroid use with functional deficiency
Infiltrative (sarcoid, eosinophilic granuloma, tuberculosis)
Traumatic brain injury
Postpartum pituitary necrosis (Sheehan's syndrome)
Empty sella syndrome

Acute

Pituitary apoplexy (hemorrhage into a pituitary tumor)
Postpartum pituitary necrosis (Sheehan's syndrome)
Traumatic brain injury
Relative adrenal insufficiency (sepsis, hepatic failure, severe acute pancreatitis, trauma)

ACTH, Adrenocorticotropic hormone.

BOX 120.10

Clinical Features of Adrenal Insufficiency

GENERAL	
Weakness, fatigue	100%
Anorexia	100%
Gastrointestinal symptoms	92%
Weight loss	100%
Hyponatremia	90%
Blood pressure ≤ 110/70 mm Hg	88%–94%
Fevers (mild)	Common
Depression, apathy	20%–40%
Myalgia, arthralgias	6%–13%
Auricular calcifications	5%
PRIMARY	
Hyperpigmentation	94%–97%
Salt craving	16%–22%
Orthostasis, syncope	12%–16%
Vitiligo	10%
Hyperkalemia	65%
Hyperchloremia and acidosis	65%
Hypoglycemia	Mild, occasional
SECONDARY	
Hyperkalemia	Not present
Hyperpigmentation	Not present
Hypoglycemia	More severe, common
Orthostasis, hypotension	Uncommon
Amenorrhea	Common
Axillary and pubic hair loss	Occasional
Decreased libido	Occasional
CRISIS	
Refractory hypotension	100%

receive corticosteroid therapy for prolonged periods, typically more than several weeks.

Adrenal crisis is usually seen in patients with Addison's disease because of mineralocorticoid deficiency but can also present in patients with secondary or tertiary adrenal insufficiency who undergo severe physiologic stress, such as surgery, trauma, respiratory distress, hypothermia, myocardial infarction, sepsis, hypoglycemia, pain, depression, and exogenous steroid withdrawal (after suppression of the HPA axis). These stressors deplete cortisol stores, and impair the ability to mount a normal stress response

Etomidate, an IV imidazole agent, has recently been debated as a cause of acute adrenal insufficiency. Etomidate is a selective inhibitor of adrenal 11β-hydroxylase, the enzyme that converts deoxycortisol to cortisol. For this reason, continuous infusions are not recommended. Bolus administration for rapid sequence intubation is regarded as safe.

Clinical Features

The clinical manifestations of chronic adrenal insufficiency are nonspecific and include fatigue, weakness, anorexia, nausea, vomiting, intestinal cramps, and dizziness (Box 120.10). Primary and secondary adrenal insufficiency result in hyponatremia from different mechanisms—aldosterone deficiency and sodium wasting in primary adrenal insufficiency and a low cortisol level and free water retention in secondary adrenal insufficiency.

Primary adrenal insufficiency characteristically has more pronounced clinical manifestations than secondary adrenal insufficiency. Patients have symptoms related to a deficiency of glucocorticoids, mineralocorticoids, and androgens. Primary adrenal insufficiency more commonly presents with skin hyperpigmentation, particularly in areas exposed to the sun or subject to friction or pressure, salt craving, hyperkalemia, and acidosis. These patients may show signs of sodium and volume depletion (eg, orthostatic hypotension and tachycardia). In secondary adrenal insufficiency, patients more often present with pale skin, loss of axillary and pubic hair, decreased libido, and impotence. Glucocorticoid deficiency and low ACTH concentrations may result in hypotension and hyponatremia with normal potassium levels.

Adrenal crisis presents with hypotension and shock that does not respond to fluid resuscitation and pressors. Patients may have many other nonspecific symptoms, as listed above, but shock is the hallmark.

Diagnostic Testing

Although there are many tests available to confirm the diagnosis of adrenal insufficiency, they require a significant amount of time or serial testing. For this reason, if there is suspicion of adrenal crisis, treatment should be initiated immediately, prior to confirmatory tests.

In stable patients, cortisol measurement is the mainstay for an accurate diagnosis; measurement of the cortisol level in the ACTH

stimulation test is the standard method. The test is based on the inability of the adrenal gland to secrete appropriate amounts of cortisol after administration of corticotropin. The test cannot differentiate between primary and secondary adrenal insufficiency because the HPA axis is bypassed and therefore will not alter endogenous ACTH. Baseline cortisol concentrations are determined before and 30 and 60 minutes after IV or intramuscular administration of ACTH, 250 μg. Testing may indicate ACTH concentrations of more than 1000 times the normal physiologic peak for adrenal cortex responsiveness.

Random basal serum cortisol concentrations are of limited value for assessment of HPA axis reserve but can confirm an intact adrenocortical reserve if basal morning concentrations are above 500 nmol/L. Cortisol levels peak between 6 and 8 AM, which is the appropriate time to draw blood for the determination of a cortisol level. With cortisol concentration measurements between 100 and 500 nmol/L, further dynamic testing is indicated. More than 90% of cortisol is protein-bound, so changes in protein binding can affect total measured serum cortisol concentrations without affecting free cortisol concentrations.

Mild to moderate hyponatremia, with levels typically above 120 mEq/L, is seen in primary adrenal insufficiency. Aldosterone deficiency leads to sodium wasting, and decreased cortisol levels lead to increased antidiuretic hormone, resulting in increased water absorption. Hyperkalemia may be seen in primary adrenal insufficiency secondary to low circulating aldosterone concentrations, but is not seen in secondary causes when aldosterone is not affected.

Differential Diagnosis

Because of the vague and nonspecific symptoms, the differential diagnosis of hypoadrenalism is extensive. The wasting associated with chronic adrenal insufficiency resembles that of anorexia nervosa or an occult carcinoma. The generalized weakness, fatigue, and myalgias can be confused with chronic fatigue syndrome, polymyalgia rheumatica, myopathy, hypothyroidism, or influenza syndromes.

Lack of recognition of acute adrenal crisis with refractory hypotension can result in evaluations for sepsis, GI bleeding, myocardial ischemia, and/or anaphylaxis. Abdominal pain in crisis may be clinically indistinguishable from an acute abdomen, especially if precipitated by adrenal hemorrhage. The headache and visual field cuts in pituitary apoplexy may resemble those of a hemorrhagic stroke. Finally, the constellation of symptoms seen in acute adrenal insufficiency—weakness, malaise, fatigue, nausea, dizziness, and arthralgias—is also present in steroid withdrawal syndrome. Because both can occur with the cessation of chronic glucocorticoid administration, a proper history is critical to distinguish between the two disease processes.

Management

Patients with adrenal insufficiency require hormone replacement to correct a lack of circulating glucocorticoid and mineralocorticoid. Treatment of adrenal crisis should begin as soon as possible and prior to diagnostic testing when crisis is suspected. The first-line treatment is hydrocortisone, 100 mg IV, with IV fluids, pressor support and glucose administration, as indicated (Box 120.11). In hemodynamically stable patients without a known diagnosis, dexamethasone (4-mg IV bolus) can be considered; in contrast to hydrocortisone, it does not interfere with serum cortisol assays.

In adults, the typical oral dose of hydrocortisone is 30 mg total daily in split doses. To mimic natural diurnal adrenal variation, two-thirds of the daily dose is usually given in the morning and one-third in the late afternoon. Mineralocorticoid should also be replaced in the form of fludrocortisone, 50 to 200 μg/day. In the setting of fever, infection, or intercurrent illness, the dose of hydrocortisone is doubled. In severe illness, it is commonly increased to 75 to 150 mg daily.

Whereas definitive treatment of secondary adrenal insufficiency is directed at replacement of missing hormone (ACTH or CRH) at the level of the hypothalamus or pituitary, simple steroid hormone replacement is administered in the ED setting. Steroid tapering is necessary when gradual downregulation of the HPA axis has been provoked by exogenous glucocorticoids. There is no universally recommended method for steroid tapering.

BOX 120.11

Treatment of Hypoadrenalism

MAINTENANCE

Hydrocortisone, 20 mg AM, 10 mg PM
Fludrocortisone, 50–100 μg/day

Maintenance During Minor Illness

Hydrocortisone, 40 mg AM, 20 mg PM
Fludrocortisone, 50–200 μg daily

Coverage During Procedural Stress

Hydrocortisone, 100 mg IV (one time only)

ADRENAL CRISIS OR RELATIVE ADRENAL INSUFFICIENCY OF CRITICAL ILLNESS

Dexamethasone, 4 mg IV bolus
or
Hydrocortisone, 100 mg IV bolus
0.9 NS, 2–3 L in the first few hours
Switch to D_5/NS if hypoglycemia
Treat precipitating illness

D_5/NS, 5% dextrose in normal saline; *0.9 NS,* 0.9% normal saline.

Disposition

Most patients with mild symptoms of hypoadrenalism may be discharged for outpatient evaluation and treatment. Severely ill patients should have the underlying disease process identified and treated; an ICU setting is indicated due to the high mortality rate.

KEY CONCEPTS

Hyperthyroidism

- Thyroid hormone exerts effects on nearly every organ system. A high degree of suspicion is needed to diagnose hyperthyroidism.
- The laboratory evaluation of choice is determination of the TSH concentration with free T_4 and T_3 levels. Total T_4 and T_3 levels are of limited value.
- Thyroid storm is a life-threatening thyrotoxic crisis that requires prompt recognition and therapy, as well as identification and treatment of any precipitating cause, such as infection.
- The order of medication administration in thyroid storm is critical. Iodine can precipitate thyroid storm and must be given a minimum of 1 hour after thionamide therapy (PTU or methimazole). As such, the typical order is beta blocker (propranolol), PTU, or methimazole, and then iodine (SSKI, Lugol's solution).

Hypothyroidism

- Hypothyroidism results from lack of stimulation of the thyroid gland (central or secondary hypothyroidism) or intrinsic gland dysfunction limiting hormone production (primary hypothyroidism).
- Signs and symptoms of hypothyroidism range from asymptomatic to overt organ failure, which can lead to death.
- Determination of an elevated TSH level is the most sensitive and single best screening test to confirm the diagnosis of primary hypothyroidism.
- Replacement with levothyroxine (T_4) remains the treatment of choice and resolves most physical and psychological signs and symptoms in most patients.
- Myxedema coma is a life-threatening event that is most often precipitated by some stressful event in patients with untreated or undertreated hypothyroidism. Treatment with thyroid hormone replacement must be initiated, often solely on clinical findings.

Adrenal Insufficiency

- Clinical manifestations of primary and secondary adrenal insufficiency may be vague and nonspecific and require a high index of suspicion for diagnosis.
- Predominant complaints include fatigue, weakness, dizziness, nausea, vomiting, and other nonspecific GI symptoms.
- Patients with primary adrenal insufficiency characteristically have more pronounced clinical manifestations and skin hyperpigmentation. Measurement of cortisol in the ACTH stimulation test is the standard and most convenient method to assist in confirming the diagnosis.
- Refractory hypotension in the acutely ill patient may be the only clue to adrenal insufficiency and is readily treated with the IV administration of glucocorticoids (dexamethasone, 4 mg, or hydrocortisone, 100 mg).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 120: QUESTIONS & ANSWERS

120.1. Which of the following is the single best test to assess thyroid function?
- **A.** Free T_3
- **B.** Free T_4
- **C.** Total T_3
- **D.** Total T_4
- **E.** TSH

Answer: E. Reliable assays for serum TSH and free T_4 have made the laboratory diagnosis of hyperthyroidism straightforward. Measurement of the serum TSH level is the single best test to assess thyroid function. A normal TSH level excludes hyperthyroidism, and an elevated TSH level is generally diagnostic for hypothyroidism.

120.2. What is the most common cause of hyperthyroidism in the United States?
- **A.** Graves' disease
- **B.** Hashimoto thyroiditis
- **C.** Hot nodule (toxic adenoma)
- **C.** Multinodular goiter
- **D.** Subacute thyroiditis

Answer: A. In the United States, Graves' disease (diffuse toxic goiter) is the most common form of hyperthyroidism.

120.3. In thyroid storm, which of the following is the proper sequence of drug administration?
- **A.** All three together (antithyroid drugs, sodium or potassium iodide, steroid) at the same time
- **B.** Antithyroid drugs, sodium or potassium iodide, steroid
- **C.** Sodium or potassium iodide, steroid, antithyroid drugs
- **D.** Steroid, sodium or potassium iodide, antithyroid drugs

Answer: B. Because an iodine load can increase the synthesis of thyroid hormone, it should not be administered until 1 hour after the initiation of antithyroid drugs (PTU or methimazole therapy).

120.4. Which of the following medications may cause hypothyroidism secondary to the inhibition of the peripheral conversion of T_4 to T_3?
- **A.** Amiodarone (Cordarone)
- **B.** Digoxin (Lanoxin)
- **C.** Dopamine (Intropin)
- **D.** Phenytoin (Dilantin)
- **E.** Propranolol (Inderal)

Answer: A. Amiodarone is a class III antiarrhythmic medication that has a similar chemical structure to T_4 and contains large amounts of iodine. As such, it inhibits the peripheral conversion of T_4 to T_3 leading to hypothyroidism. In addition, amiodarone is directly cytotoxic to the thyroid, has the intrinsic effect of blocking thyroid hormone entry into cells, and decreases T_3 receptor binding. If amiodarone therapy must be continued for arrhythmia control, patients with amiodarone-induced hypothyroidism may be successfully treated with exogenous thyroid hormone replacement.

120.5. Cardiovascular manifestations of subclinical hypothyroidism include which of the following?
- **A.** Advanced atherosclerotic plaque formation
- **B.** Cardiac conduction abnormalities
- **C.** Decreased peripheral vascular resistance
- **D.** Labile hypertension
- **E.** Increased ejection fraction

Answer: A. Hypothyroidism is responsible for multisystem organ pathology. Even mild thyroid failure is a significant risk factor for the development of arterial stiffness from impaired endothelial function and artery intima–media wall thickening.

Arterial stiffness is an important determinant of premature atherosclerosis and changes in arterial wall elasticity.

The accelerated atherosclerosis in hypothyroidism is ascribed to dyslipidemia, diastolic hypertension, and impaired endothelial function. Additionally, T_3 increases production and secretion of renin. In patients who are hypothyroid, renin levels are found to be low, which plays an important role in the acceleration of atherogenesis.

120.6. In a patient with suspected adrenal crisis, what is the treatment of choice for hypotension refractory to isotonic fluid replacement?
A. Adrenocorticotropic hormone (ACTH)
B. Continued normal saline (0.9%) fluid boluses
C. Dobutamine (Dobutrex)
D. Dopamine (Intropin)
E. Hydrocortisone (Solu-Cortef)

Answer: E. Acute manifestations of disease may result in severe and possibly refractory hypotension. Refractory hypotension in the acutely ill patient may be the only clue to adrenal insufficiency and is readily treated with IV glucocorticoids (dexamethasone, 4 mg, or hydrocortisone, 100 mg IV).

120.7. Laboratory confirmation of adrenal insufficiency is performed by measuring the level which of the following?
A. Adrenocorticotropic hormone (ACTH)
B. Aldosterone
C. Corticotropin-releasing hormone (CRH)
D. Cortisol
Melanocyte-stimulating hormone

Answer: D. Maintaining a high index of suspicion for adrenal insufficiency is of primary importance. Several tests are available to assist in confirmation. Whether screening for chronic disease or working up an acutely ill patient, cortisol level measurement is the mainstay of making an accurate diagnosis.

SECTION TWELVE
Infectious Diseases

CHAPTER 121

Bacteria

Madonna Fernández-Frackelton

DIPHTHERIA

Principles

Background

In the fifth century BC, Hippocrates first described what was likely diphtheria, characterized by sore throat, membrane formation, and death from suffocation. In 1821, Pierre Bretonneau named the condition *diphtherite* (Greek for leather) describing the characteristic pharyngeal membrane. In 1883, Klebs observed the *Corynebacterium diphtheriae* organism on smears from pharyngeal membranes. In 1890, von Behring and Kitasato created the first diphtheria antitoxin (DAT) and 1 year later administered the first dose of antitoxin to a human with diphtheria. Immunization dramatically decreased the incidence of diphtheria in the United States from 200,000 cases in 1921 to only 55 cases between 1980 and 2010.[1,2]

Epidemiology

Humans are the only known reservoir for *C. diphtheriae.* Spread is by person-to-person through respiratory droplets or by direct contact with secretions, skin lesion exudates, or rarely fomites or food. Transmission is associated with crowded living conditions. Individuals may spread the disease when they are actively ill, in the convalescent stage, or as asymptomatic carriers.[1,3,4]

Immunization against diphtheria is highly effective (Fig. 121.1). Before widespread immunization in the United States, the incidence of diphtheria exceeded 100 cases per 100,000 population, and the disease predominantly affected children. Most people acquired natural immunity to diphtheria by age 15, and recurrent exposure to toxigenic strains of the bacteria acted as a booster. Because childhood immunization nearly eliminates toxigenic strains in a population, adult immunity wanes, so more adults in industrialized nations are susceptible to diphtheria. By the 1980s the Centers for Disease Control and Prevention (CDC) reported 0 to 5 cases per year nationwide. Currently, sporadic cases occur primarily in inadequately immunized adolescents and adults.[2] Three urban outbreaks of cutaneous diphtheria occurred in Seattle between 1972 and 1982 among a population of urban alcohol abusers. Outbreaks are associated with poor hygiene, crowding, underlying skin disease, contaminated fomites, pyoderma, and the appearance of new *C. diphtheriae* strains.[1] Even in industrialized nations in which childhood vaccination rates are high, more than 50% of adults older than 40 years old lack protective antibodies. The ease of international travel and the epidemic in Eastern Europe underscore the importance of continuation of childhood immunizations and re-immunization of adults.

Etiology

Diphtheria is caused by *C. diphtheriae,* an unencapsulated, nonmotile, gram-positive bacillus named for its shape (*korynee,* for "club") and its characteristic clinical presentation (*diphtheria,* for "leather," describing the leathery pharyngeal membrane).[1]

Infection with *C. diphtheriae* can occur at various sites of the respiratory tract or the skin. Respiratory diphtheria includes faucial (pharyngeal or tonsillar), nasal, and laryngeal (tracheobronchial) types, named for the primary location of infection. Cutaneous diphtheria can occur as a primary skin infection or as a secondary infection of a preexisting wound.[1,3]

Pathophysiology

Toxigenic strains of *C. diphtheriae* bacterium are lysogenized with the B phage and produce an exotoxin that inhibits cellular protein synthesis. The diphtheritic membrane, composed of leukocytes, erythrocytes, fibrin, epithelial cells, and bacteria, results from necrosis caused by local effects of the exotoxin. Initially, the pharynx appears erythematous, but as necrosis occurs, grayish white patches appear and eventually coalesce. The membrane causes surrounding edema and cervical adenitis. The initial grayish white, filmy appearance changes to a thick, grayish black membrane with sharply defined borders. This membrane adheres to the underlying tissue, and bleeding occurs if removal is attempted.[1]

Circulating exotoxin causes the systemic symptoms of diphtheria, most profoundly affecting the nervous system, heart, and kidneys.[1,3] The degree of local and systemic toxicity depends on the location and extent of membrane formation. Pharyngeal diphtheria has the greatest toxicity and cutaneous diphtheria has the least. The exotoxin disrupts cellular protein synthesis and causes peripheral neuropathy manifested by muscle weakness. About 5% of patients with respiratory infection will have polyneuritis, but 75% of patients with severe disease have some form of neuropathy.[5] The muscles of the palate are usually affected first. Less commonly, other cranial nerves, peripheral nerves, and the spinal cord are affected. Degenerative lesions develop in dorsal root and ventral horn ganglia of the spinal cord and in cranial nerve nuclei. Cortical cells are spared. Proximal muscle groups are affected first. In severe cases, paralysis may develop in the first few days of illness. In general, the paralysis does not last more than 10 days, but may last up to 3 months. Complete recovery over a longer time is the rule.[1]

Signs of myocardial dysfunction usually appear 1 to 2 weeks after the onset of illness, but may arise earlier in severe cases. The exotoxin directly damages myocardial cells. Electrocardiographic changes suggestive of myocarditis occur in up to two-thirds of

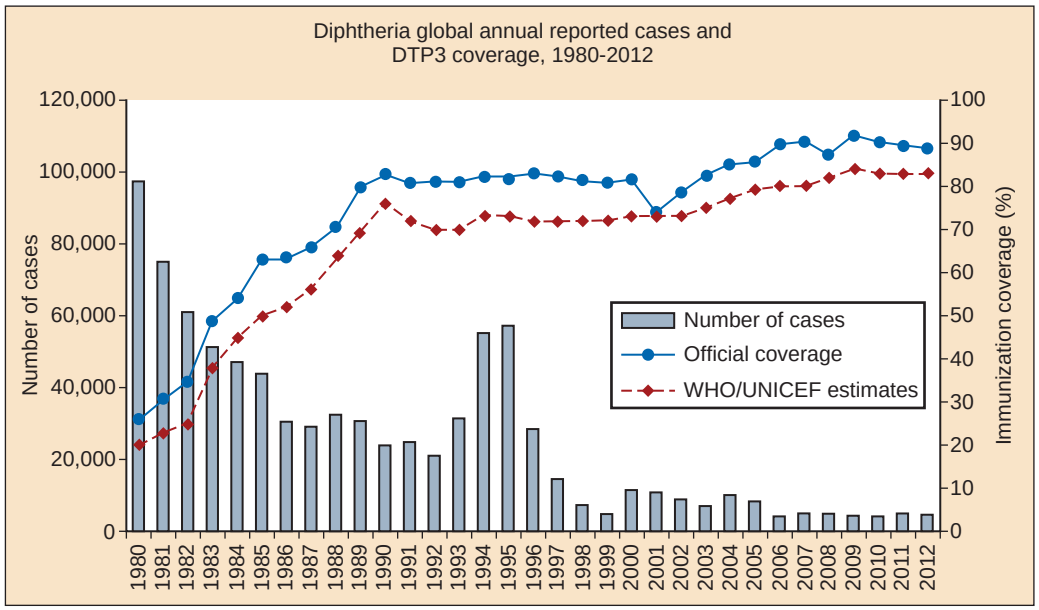


Fig. 121.1. Global annual reported cases of diphtheria compared with percentage of immunization coverage from 1980 to 2012. *DTP3,* Third dose of diphtheria-tetanus-pertussis vaccine; *UNICEF,* United Nations Children's Fund; *WHO,* World Health Organization. (From World Health Organization, 2013 Global Summary. Geneva, WHO, 2013. World Health Organization: Immunization, vaccines and biologicals: diphtheria. Available at: www.who.int/immunization/monitoring_surveillance/burden/diphtheria/en/.)

patients, but clinical manifestations of myocarditis occur in only 10% to 25% of cases.

Clinical Features

Symptoms and Signs

The average incubation period of respiratory tract diphtheria is 2 to 4 days (range 1 to 8 days). Signs and symptoms are indistinguishable from those of other upper respiratory tract infections. Low grade fever and sore throat are the most frequent presenting complaints. Weakness, dysphagia, headache, voice changes, and loss of appetite are also common. Cough, shortness of breath, nasal discharge, and neck edema occur in less than 10% of patients. Cervical adenopathy occurs in approximately one-third of patients, and a membrane is observed in more than half of all patients.

In patients with faucial diphtheria, the extent of the membrane parallels clinical toxicity. If the membrane is limited to the tonsils, the disease may be mild; if it covers the entire pharynx, the onset of illness is usually abrupt and the disease severe. Cervical lymphadenopathy and infiltration of neck tissues may be so extensive that the patient has a "bull-neck" appearance. Patients with this form of malignant diphtheria usually have high fever, severe muscle weakness, vomiting, diarrhea, restlessness, and delirium. Death occurs from respiratory tract obstruction or cardiac failure from myocarditis. Nasal diphtheria presents with serous or serosanguineous nasal discharge. A membrane may be visible. These patients do not usually have constitutional symptoms. Treatment is important to prevent a persistent carrier state. Laryngeal diphtheria may begin in the larynx or spread downward. Respiratory tract edema with subsequent upper airway obstruction may develop.

Patients with cutaneous diphtheria typically do not develop systemic toxicity. The skin characteristically has an ulcer with a grayish membrane. Wounds from which *C. diphtheriae* is cultured are clinically indistinguishable from other chronic skin conditions.[1]

Complications

The most serious complications of diphtheria are airway obstruction, congestive heart failure, cardiac conduction disturbances, and muscle paralysis. Overall mortality is less than 3% but rises to 7% in patients with myocarditis and 26% in patients with the malignant form of the disease with neck swelling.[5] Although invasive disease is rare, endocarditis, mycotic aneurysms, osteomyelitis, and septic arthritis have all been described in immunocompromised hosts.[1]

Diagnostic Strategies

When *C. diphtheriae* is suspected, the laboratory should be notified because routine cultures do not identify the organism. Throat or nasopharyngeal swabs should be obtained for respiratory diphtheria, and if present, membranous material should be examined. Samples should be obtained from skin lesions in cutaneous infections. Specimens should be collected before antibiotic therapy is initiated and transported to the laboratory immediately for rapid inoculation onto tellurite selective culture medium.[1,3] Definitive identification is made by use of a combination of colony morphology, microscopic appearance, and fermentation reactions.[1] *C. diphtheriae* isolates should be tested for toxin production. The Elek test for toxin A is technically demanding and subject to misinterpretation by inexperienced users but is available at the CDC. Polymerase chain reaction (PCR), which is more reliable but not as readily available, can be used to detect the toxin structural gene. Newer methods that rapidly detect the toxin by mass spectrometry are not readily available but may be used in the future.[6] A positive culture for group A beta-hemolytic streptococcus does not exclude diphtheria, because up to 30% of patients with diphtheria test positive for streptococcal coinfection or carrier state.

Leukocytosis, mild thrombocytopenia, and proteinuria are common but neither sensitive nor specific for diphtheria. Changes on electrocardiogram (ECG) are nonspecific and include ST-T wave changes, varying degrees of atrioventricular block, and

dysrhythmias.[1] An ECG may be normal even in the presence of myocarditis. An echocardiogram may show dilated or hypertrophic cardiomyopathy. Cardiac enzymes may be elevated, and serum troponin levels correlate with the severity of myocarditis.

Differential Diagnosis

It may be difficult to differentiate respiratory diphtheria from many other respiratory conditions, especially in the early phase of infection (Box 121.1). In general, the diphtheritic membrane is darker, grayer, more fibrous, and more firmly attached to the underlying tissues than in other conditions that have a membrane-like appearance. Vincent's angina frequently involves the gingivae, which are unaffected in diphtheria. Acute bacterial epiglottitis generally has a much more rapid onset than diphtheria, and laryngoscopy reveals an erythematous, edematous epiglottis without membrane formation.[1]

Cutaneous diphtheria is difficult to differentiate from other acute and chronic ulcerative skin lesions. *C. diphtheriae* can secondarily infect any of these lesions, especially in high-risk patients such as alcoholic, and unimmunized or underimmunized people.

Management

Patients with clinical evidence of diphtheria should be placed in respiratory isolation and treated presumptively for *C. diphtheriae*. The goals of therapy are to protect the airway, limit the effects of already produced toxin, and stop future toxin production by terminating bacterial growth. Although airway obstruction from diphtheria is rare in the United States, the management is identical to that for other forms of airway obstruction. Early intubation should be considered for patients with laryngeal involvement. Patients may be dehydrated from fever and decreased oral intake related to dysphagia or neurologic impairment. Fluid resuscitation should be undertaken cautiously because the toxin's effect on the myocardium may result in congestive heart failure.[1]

Equine serum DAT should be administered promptly after the clinical diagnosis of respiratory diphtheria is deemed probable (Box 121.2) and before laboratory confirmation.[1,7] DAT is not licensed by the U.S. Food and Drug Administration (FDA) for use in the United States, and several countries do not currently hold DAT stockpiles.[8] The CDC can distribute DAT to physicians as an investigational new drug. DAT can be obtained by contacting the CDC Emergency Operations Center at 770-488-7100. The size and location of the membrane, duration of illness, and patient's overall degree of toxicity determine the DAT dose. Patients with probable or confirmed respiratory diphtheria are eligible to receive DAT (20,000 to 40,000 units for pharyngeal or laryngeal involvement of 2 days' duration; 40,000 to 60,000 units for nasopharyngeal lesions; 80,000 to 100,000 units for systemic disease of 3 days' duration or more or for diffuse swelling of the neck).[7] After conjunctival or intradermal sensitivity skin testing, the antitoxin is administered intravenously. If the patient exhibits sensitivity to the antitoxin, desensitization should be performed. Active immunization against diphtheria should also be initiated because clinical infection does not necessarily confer immunity.

Antibiotics prevent growth and spread of the organism but are no substitute for antitoxin. Erythromycin 40 mg/kg/day (maximum of 2 g) intravenously or orally in divided doses is the preferred treatment. Procaine penicillin G 300,000 units/day in two divided doses intramuscularly for those weighing 10 kg or less, and 600,000 units/day in two divided doses for those weighing more than 10 kg is an acceptable alternative.[1,3] Treatment failures are more common with penicillin than with erythromycin. Azithromycin and clarithromycin have activity similar to erythromycin in vitro and may result in better compliance. These agents have not been adequately tested in clinical disease. Daily oral therapy may be substituted when the patient is able to swallow. Negative cultures should be documented after treatment.

Myocarditis and neuritis are treated with supportive care and careful monitoring. Patients with ECG changes consistent with myocarditis have three to four times the mortality rate of those with normal ECGs. The mortality rate for patients with left bundle branch block and atrioventricular block is 60% to 90%. Serial

BOX 121.1

Differential Diagnosis of Respiratory Diphtheria

Streptococcal pharyngitis
Viral pharyngitis (Epstein-Barr virus, adenovirus, herpes simplex)
Tonsillitis
Vincent's angina (*Borrelia vincenti*)
Acute epiglottitis
Mononucleosis
Laryngitis
Bronchitis
Tracheitis
Candida albicans (thrush)
Rhinitis

BOX 121.2

Check List for Assessing a Patient With Suspected Diphtheria

SUSPECT CASE

- Pharyngitis, nasopharyngitis, tonsillitis, laryngitis, tracheitis (or any combination of these), absent or low-grade fever
- Grayish adherent pseudo-membrane present
- Membrane bleeds, if manipulated or dislodged

PROBABLE CASE

Suspect case above, plus one or more of the following:

- Stridor
- Bull-neck (cervical edema)
- Toxic circulatory collapse
- Acute renal insufficiency
- Submucosal or subcutaneous petechiae
- Myocarditis
- Death
- Recent return (<2 weeks) from travel to area with endemic diphtheria
- Recent contact (<2 weeks) with confirmed diphtheria case or carrier
- Recent contact (<2 weeks) with visitor from area with endemic diphtheria
- Recent contact with dairy or farm animals or domestic pets
- Immunization status: Note up-to-date DTaP/DT/Tdap/Td shot within past 10 years

LABORATORY CONFIRMED CASE

- Positive culture of *Corynebacterium diphtheriae* (or *Corynebacterium ulcerans*) *and*
  - Positive Elek test *or*
  - PCR for tox gene (positive for subunit A and B)

DT, Diphtheria-tetanus; *DTaP,* diphtheria, tetanus, and acellular pertussis; *PCR,* polymerase chain reaction; *Td,* diphtheria-tetanus; *Tdap,* tetanus, diphtheria, activated pertussis.
Available at: www.cdc.gov/diphtheria/downloads/dip-cklist-diag.pdf.

ECGs are recommended, and survivors may have permanent conduction abnormalities. No data support the use of steroids.

Cutaneous lesions should be débrided of necrotic tissue and cleansed vigorously. A course of antibiotics is recommended, but the DAT for cutaneous lesions is of questionable value. Some experts recommend 20,000 to 40,000 units of antitoxin, but few data support its use in this setting.[1,7]

Carriers of *C. diphtheriae* should receive oral penicillin G or erythromycin for 7 days or intramuscular (IM) benzathine penicillin (600,000 units for those weighing less than 30 kg and 1,200,000 units for those weighing more than 30 kg). Active immunization should also be provided to unimmunized and partially immunized carriers. After 2 weeks of therapy, cultures should be obtained; if positive, erythromycin therapy should be given for 10 additional days.[1]

Individuals who have been in close contact with infected patients should have cultures taken and be kept under surveillance for 7 days. Previously immunized close contacts should receive a booster of diphtheria toxoid if the last booster was more than 5 years earlier. The vaccine should be diphtheria, tetanus, and acellular pertussis (DTaP) or diphtheria-tetanus (DT or Td) as appropriate for age. Close unimmunized contacts or those whose immunization status is unknown should receive the same antimicrobial therapy as carriers (previously described), have culture specimens taken before and after therapy, and have active immunization initiated. Close contacts who cannot be kept under surveillance should receive benzathine penicillin intramuscularly to ensure compliance and a Td booster (appropriate for age and immunization history). DAT is not recommended for this group because of the risk of horse serum allergy.[7]

A universal primary immunization program with regular boosters every 10 years is the most effective method for controlling diphtheria. Emergency clinicians should routinely administer age-appropriate tetanus and diphtheria toxoids as part of wound management.

Disposition

All patients with possible pharyngeal diphtheria should be isolated, admitted, and monitored for detection of arrhythmias. A cardiologist should be consulted for patients with evidence of myocarditis. The CDC should be contacted for all suspected or proven cases of diphtheria.

PERTUSSIS

Principles

Background

Pertussis is an acute respiratory disease first described in 1578 when an epidemic swept through Paris. *Pertussis* means "violent cough." It is also called *whooping cough* because the severe episodes of coughing are followed by forceful inspiration, which creates a characteristic whooping sound. Bordet and Gengou identified the causative organism in 1900. In the prevaccination era, pertussis was a major cause of mortality among infants and children in the United States. A vaccine was developed in the 1940s, but pertussis still remains a significant cause of morbidity and mortality worldwide.[9]

Epidemiology

Pertussis is a highly contagious respiratory illness transmitted by aerosolized droplets. It can occur at any age but is predominantly a pediatric and adolescent illness. Attack rates are greater than 50% in adults exposed more than 12 years after completion of a vaccination series and up to 90% in susceptible individuals with a household exposure. Half of the cases in the United States occur from June through September. The average incubation period is 7 to 10 days (range less than 1 week to 3 weeks). Neither vaccination nor prior infection confers lifelong immunity.

Pertussis is prevalent worldwide. The World Health Organization (WHO) estimates more than 16 million cases in 2008 with 195,000 deaths.[10] In the United States, annual pertussis rates declined sharply after the introduction of the vaccine, reaching a nadir of 1010 cases in 1976. Since then, there has been a steady increase, with 11,647 cases reported in 2003, 25,616 in 2005, and more than 28,000 cases in 2014 (Fig. 121.2A and B).[11] The incidence is highest in infants who have not received the entire vaccine series (see Fig. 121.2C). Waning immunity in the adult population and increased reporting may be contributing factors. A 1991 report found a possible relationship between the vaccine and acute encephalopathy. Although there appears to be no relationship between the vaccine and long-term neurologic complications, the report resulted in a decline in the use of the whole-cell pertussis vaccine. The acellular pertussis vaccine has been approved in the United States since 1991 for persons 15 months to 64 years and since 1997 for infants.

Etiology

Pertussis is caused by organisms of the *Bordetella* genus, which are small, aerobic, gram-negative coccobacilli. *Bordetella pertussis* and *Bordetella parapertussis* are primarily responsible for human disease. The organisms are fastidious and require a medium containing charcoal, blood, or starch, and an optimal temperature of 95° to 98.6°F (35° to 37°C) to grow. *Bordetella bronchiseptica,* a flagellated, motile organism, causes illness in animals, including kennel cough, and may rarely cause respiratory infection in immunocompromised humans.[12]

Pathophysiology

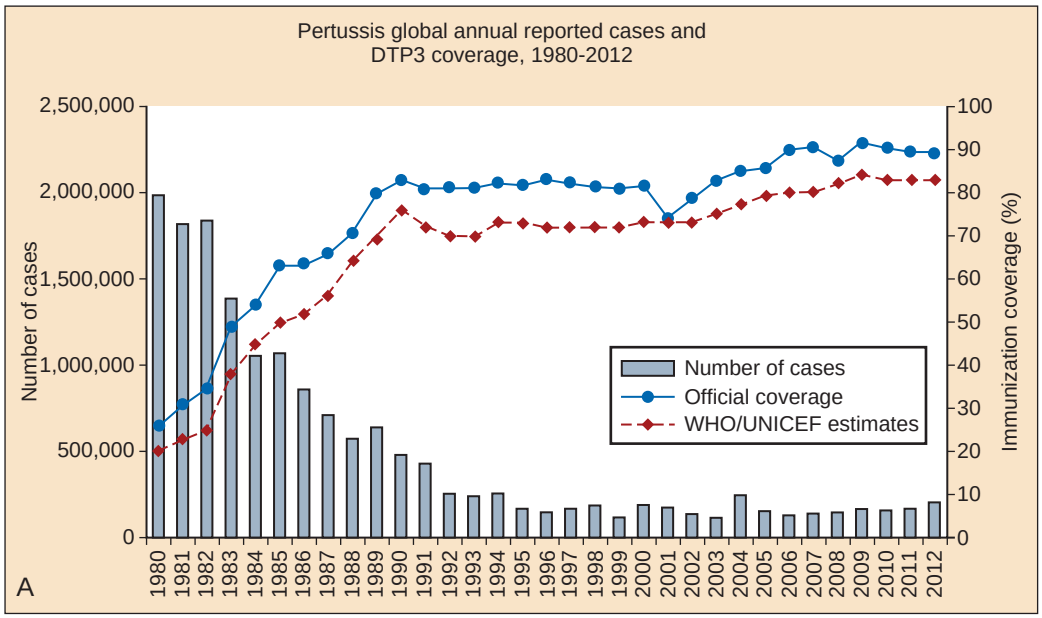
Bordetella adheres preferentially to ciliated respiratory epithelial cells, but does not invade beyond the submucosa and is almost never recovered in the bloodstream. It elaborates several toxins that act locally and systemically, including pertussis toxin, dermonecrotic toxin, adenylate cyclase toxin, and tracheal cytotoxin. Local tissue damage consists of inflammatory changes in the respiratory mucosa. Secondary pneumonia or otitis media may occur. Systemic effects of pertussis toxin include sensitization to the lethal effects of histamine and increased excretion of insulin. This hyperinsulinemia can cause hypoglycemia, particularly in young infants.[9]

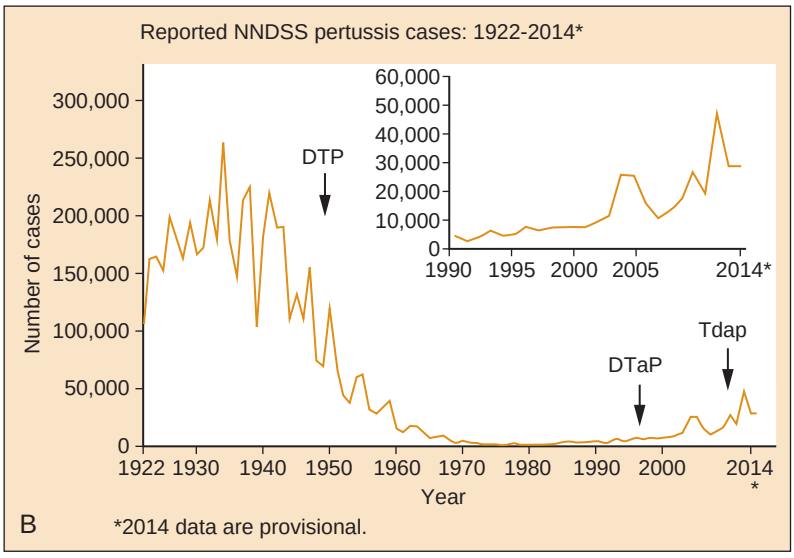
Clinical Features

Symptoms and Signs

Pertussis has three clinical stages: the catarrhal phase, the paroxysmal phase, and the convalescent phase. The *catarrhal* or *prodromal phase* begins after an incubation period of approximately 7 to 10 days and lasts approximately 1 to 2 weeks. Infectivity is greatest during the catarrhal phase, when the disease is clinically indistinguishable from other upper respiratory tract infections. Signs and symptoms include rhinorrhea, low-grade fever, malaise, and conjunctival injection. A dry cough usually begins at the end of the catarrhal phase.[9,12]

The *paroxysmal phase* begins as fever subsides. Cough increases and lasts 1 to 6 weeks, but it may persist for up to 10 weeks. Paroxysms of staccato coughing occur and average of 15 times per day and are followed by a single, sudden, forceful inhalation that produces the characteristic "whoop." Only one-third of adults





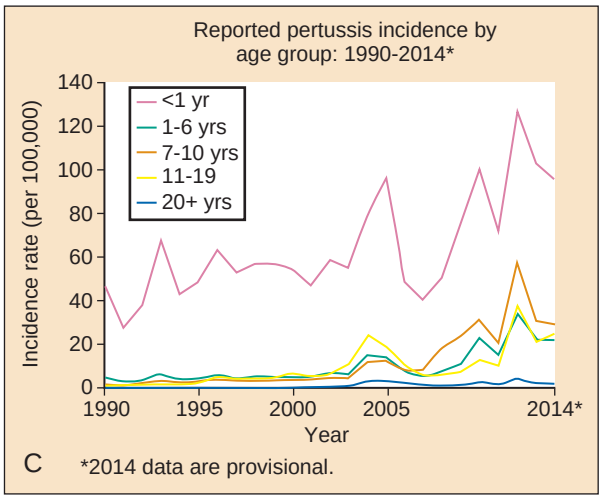


Fig. 121.2. **A,** Global annual reported cases of pertussis compared with percentage of immunization coverage. **B,** Incidence of reported pertussis cases in the United States by year. **C,** Pertussis incidence in the United States by age, Centers of Disease Control and Prevention 2014. *DTaP,* Diphtheria, tetanus, and acellular pertussis; *DTP3,* Third dose of diphtheria-tetanus-pertussis vaccine; *NNDSS,* National Notifiable Diseases Surveillance System; *Tdap,* tetanus, diphtheria, activated pertussis; *UNICEF,* United Nations Children's Fund; *WHO,* World Health Organization. (**A,** From World Health Organization: WHO/IVB database 2013; 194 WHO states. Available at: www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/. **B** and **C,** From Centers for Disease Control and Prevention: National Notifiable Diseases Surveillance System: Pertussis (whooping cough). Available at: www.cdc.gov/pertussis/surv-reporting.html.)

with pertussis develop this whoop, and it is rare in young infants, who may present with apneic episodes and no other symptoms. Paroxysms may be spontaneous, occur more frequently at night, or be precipitated by noise or cold. During the paroxysm, the patient may exhibit cyanosis, diaphoresis, tongue protrusion, salivation, and lacrimation. Post-tussive vomiting, syncope, and apnea may occur. Infants may be exhausted after a typical paroxysm. Between episodes of coughing, patients do not appear acutely ill.[9,12]

In the *convalescent phase* a residual cough may last several weeks to months. Paroxysms of coughing may be triggered by unrelated respiratory infection or by exposure to a respiratory irritant. This recurrence of coughing does not represent recurrence of pertussis infection.

Atypical presentations can occur in young and preterm infants. Fever is usually absent in uncomplicated neonatal pertussis. Tachypnea, apnea, and cyanotic and bradycardic episodes may be the predominant symptoms.[13] Older children and adults who have partial protection from vaccination or previous illness may have a long-lasting intractable dry cough that is frequently misdiagnosed as bronchitis. Post-tussive vomiting in adults is highly suggestive of pertussis.[9,14]

Physical findings are nonspecific. Tachypnea is variably present and may be related to the degree of pulmonary involvement. Low-grade fever, conjunctival injection, and rhinorrhea are common during the catarrhal phase. Fever during other stages of illness suggests secondary infection. Petechiae above the nipple line, subconjunctival hemorrhages, pneumothorax, and epistaxis may occur because of increased intrathoracic pressure during coughing paroxysms.[9,12] Chest examination may reveal rhonchi; the presence of rales suggests pneumonia.

Complications

Box 121.3 lists the complications of pertussis. Bacterial or viral pneumonia superinfection complicating pertussis is a leading cause of death, especially in infants and young children. Aspiration of gastric contents and respiratory secretions may occur during paroxysm of coughing, whooping, and vomiting. Secondary pulmonary infection may result from decreased respiratory clearance cause by the *Bordetella* organism and its toxins on bronchial and lung mucosa. A fever during the paroxysmal phase should alert the physician to a possible superinfection.[9,10,12]

Seizures and encephalopathy occur in about 1% of patients but are more common in infants. This may be due to hypoxia, hypoglycemia, cerebral petechia, toxin effect, or secondary infection by neurotropic viruses or bacteria. Central nervous system (CNS) hemorrhages may occur from the increased cerebrovascular pressures during paroxysm of coughing. Sudden increases in intrathoracic and intra-abdominal pressures can result in several other complications.[9,12]

Bradycardia, hypotension, and cardiac arrest can occur in neonates and young infants with pertussis. Severe pulmonary hypertension has been recognized in this age group and can lead to systemic hypotension, worsening hypoxia, and increased mortality.[13] Intensive care monitoring is recommended for these patients, regardless of how well they appear on admission.

BOX 121.3

Pertussis Complications

Periorbital edema
Subconjunctival hemorrhage
Petechiae
Epistaxis
Hemoptysis
Subcutaneous emphysema
Pneumothorax
Pneumomediastinum
Diaphragmatic rupture
Umbilical and inguinal hernias
Rectal prolapse

Diagnostic Strategies

Pertussis should be considered in patients with cough lasting longer than 2 weeks with either paroxysms, whoops, or post-tussive emesis, regardless of previous vaccination status.[13] Up to 27% of adults in the United States with a prolonged cough have serologic evidence of pertussis.

Ancillary studies are of limited value in the emergency department. During the late catarrhal and early paroxysmal phases, a marked leukocytosis and a characteristic lymphocytosis are often present. A white blood cell (WBC) count of great than 20,000/mL is not uncommon.[12] Adults with pertussis frequently do not have the characteristic leukocytosis and lymphocytosis, and some infants and immunocompromised hosts may not mount this response. The chest radiograph may show peribronchial thickening, atelectasis, or pulmonary consolidation.

Laboratory confirmation is important for epidemiological purposes. Nasopharyngeal aspirate or swab (synthetic, non-cotton) should be obtained for culture and PCR, if both are available; sputum and throat swabs are inadequate because ciliated respiratory epithelial cells are required.[12] The *Bordetella* organism is fastidious, and isolation requires a medium impregnated with antibiotics to reduce overgrowth of competing bacteria. Colonies of *B. pertussis* take 3 to 7 days to appear. Pertussis cultures are 30% to 50% sensitive, and this drops to less than 3% 3 weeks after the onset of cough. Direct fluorescent antibody techniques are useful as a rapid screening test for pertussis but are variably specific and should not be relied upon as laboratory confirmation of *B. pertussis.* Adults generally come to medical attention late in the disease when cultures are rarely positive. PCR is more likely to identify the organism during the first 3 weeks of illness, but it has a high false-positive rate. Serological testing is often performed as well. Most laboratories use enzyme-linked immunosorbent assay, which rises 2 to 3 weeks after infection or primary immunization. Paired serologic tests showing a twofold increase are considered positive, but they are reported as "probable" cases by the CDC unless performed at the CDC or the Massachusetts state laboratory. See Box 121.4 for the case definition.

Differential Diagnosis

The differential diagnosis includes acute viral upper respiratory tract infection, pneumonia, bronchiolitis, cystic fibrosis, tuberculosis, exacerbation of chronic obstructive pulmonary disease, and foreign body aspiration. The marked leukocytosis may suggest leukemia.

Management

Acute Treatment

Treatment of pertussis is supportive and includes oxygen, frequent suctioning, appropriate hydration, parenteral nutrition as needed, and avoidance of respiratory irritants. Patients with suggested pertussis and associated pneumonia, hypoxia, CNS complications, or those experiencing severe paroxysms should be hospitalized. Children younger than 1 year old should also be admitted, because they are not yet fully immunized and have the greatest risk for

BOX 121.4

Pertussis Case Definition

CLINICAL CASE

Cough and illness for more than 2 weeks with no apparent other cause *plus* one of the following:

- Paroxysms of coughing
- Inspiratory "whoop"
- Post-tussive emesis

PROBABLE CASE

All of the following:

- Meets clinical case definition
- Not laboratory confirmed (Only PCR and culture are considered laboratory confirmation.)
- Not epidemiologically linked to a laboratory confirmed case

CONFIRMED CASE

One of the following:

- Acute cough illness of any duration with a positive culture for *Bordetella pertussis*
- A case that meets the clinical case definition and is confirmed by PCR for *B. pertussis*
- A case that meets the clinical case definition and is epidemiologically linked directly to a case confirmed by either culture or PCR

PCR, Polymerase chain reaction.

morbidity and mortality. Neonates with pertussis should be admitted to a neonatal intensive care unit (NICU) because apnea and significant cardiac complications can occur without warning.[9,12]

Antibiotic treatment does not significantly reduce the severity or duration of illness at any phase. The goal of antibiotic therapy is to decrease infectivity and carriage.[14] The CDC recommends erythromycin estolate ester 40 to 50 mg/kg/day (maximum of 2 g/day) in four divided doses for 14 days. A 7-day course of erythromycin estolate ester at 1 g/day is just as effective at eradicating *B. pertussis* with better compliance. Azithromycin 10 mg/kg/day for 5 days is recommended in infants younger than 1 year old because of an association between oral erythromycin and hypertrophic pyloric stenosis. Alternative treatments include azithromycin (10 mg/kg on day 1, followed by 5 mg/kg on days 2 to 5) or clarithromycin (15 mg/kg/day; maximum of 1 g/day in two divided doses). Trimethoprim-sulfamethoxazole (8 mg/kg/day of trimethoprim) is an alternative for macrolide-allergic patients, but efficacy is unproven. Patients should be considered infectious for 3 weeks after the onset of the paroxysmal phase or until at least 5 days after antibiotics are started.[9] Strict droplet isolation is recommended during this period.

Corticosteroids, especially in young critically ill infants, may reduce the severity and course of illness, but effectiveness is not established. $Beta_2$-adrenergic agonists do not reduce the frequency or severity of paroxysmal coughing episodes but may be helpful in patients with reactive airway disease. Trials with pertussis immune globulin are limited and to date show no proven benefit. Standard cough suppressants and antihistamines are ineffective.[15]

Postexposure prophylaxis with an appropriate macrolide is recommended for those at high risk for developing severe pertussis, including household contacts of a pertussis case, infants and women in their third trimester of pregnancy, persons with preexisting health conditions that may be exacerbated by a pertussis infection, and contacts who themselves have close contact with any of the above listed people. This includes but is not limited to those who work in NICUs, childcare settings, and maternity wards. Women in their third trimester of pregnancy may be a source of pertussis to their newborn infant.[16]

Vaccination

Whole-cell and acellular pertussis vaccines are distributed in combination with diphtheria and tetanus toxoids as DPT and DTaP, respectively. The whole-cell vaccine is 70% to 90% effective at preventing serious pertussis infection. Most recipients have fever, irritability, behavioral changes, and local discomfort at the site of inoculation. Moderately severe reactions are uncommon but include temperature above 104° F (40° C), persistent, high-pitched crying, and seizures. Severe neurologic complications (prolonged seizures and encephalopathy) occur rarely but led to decreased use of the whole-cell form of the vaccine and the development of DTaP.[17] The acellular pertussis vaccines contain inactivated pertussis toxin and one or more other bacterial components; they are less effective than the whole-cell vaccine but have fewer reported adverse reactions.[18,19] DTaP has replaced DPT for childhood immunizations in the United States and is approved for children ages 6 weeks to 6 years old.[12,20] There are three pediatric acellular pertussis vaccines available in the United States. None contains thimerosal as a preservative. Infanrix and Daptacel contain 2-phenoxyethanol as a preservative, and Tripedia is preservative free.

Pertussis immunity wanes 5 to 10 years after immunization and 15 years after natural infection, causing an increasing incidence of the disease in people older than 15 years old. Tetanus, diphtheria, activated pertussis (Tdap) (with reduced diphtheria toxoid and acellular pertussis) is indicated as a booster vaccine in persons 11 to 18 years old. It is safe and effective in adults, including pregnant women and those over 65 years of age. Persons older than 65 years old who have never received Tdap and anticipate close contact with infants younger than 12 months old should receive a single dose of Tdap, regardless of interval since last Td vaccination.[20,21] A live attenuated nasal vaccine has recently completed phase one trials in humans.[22]

TETANUS

Principles

Background

Tetanus is a toxin-mediated disease characterized by severe uncontrolled skeletal muscle spasms. Respiratory muscle involvement leads to hypoventilation, hypoxia, and death. Dramatic descriptions of this disease date to ancient Egypt, when physicians recognized a frequent relationship between tissue injury and subsequent fatal spasm.[23] Prophylactic injection of tetanus antitoxin provided passive immunity to wounded soldiers during World War I. In 1924, an effective vaccine was developed, and large-scale testing during World War II indicated that the tetanus toxoid confers a high degree of protection against disease.[24]

Epidemiology

Despite the availability of an effective vaccine, tetanus remains endemic worldwide. It is more common in warm, damp climates and relatively rare in cold regions. The global annual incidence of reported cases of tetanus has declined with the introduction of vaccination programs (Fig. 121.3A). The WHO reported 14,860 cases of tetanus in 2011 but estimates that thousands of unreported cases occur annually resulting is approximately 58,000 neonatal deaths. Most of these cases occur in Africa and Southeast Asia due to low immunization rates and poor hygiene.[23,25]

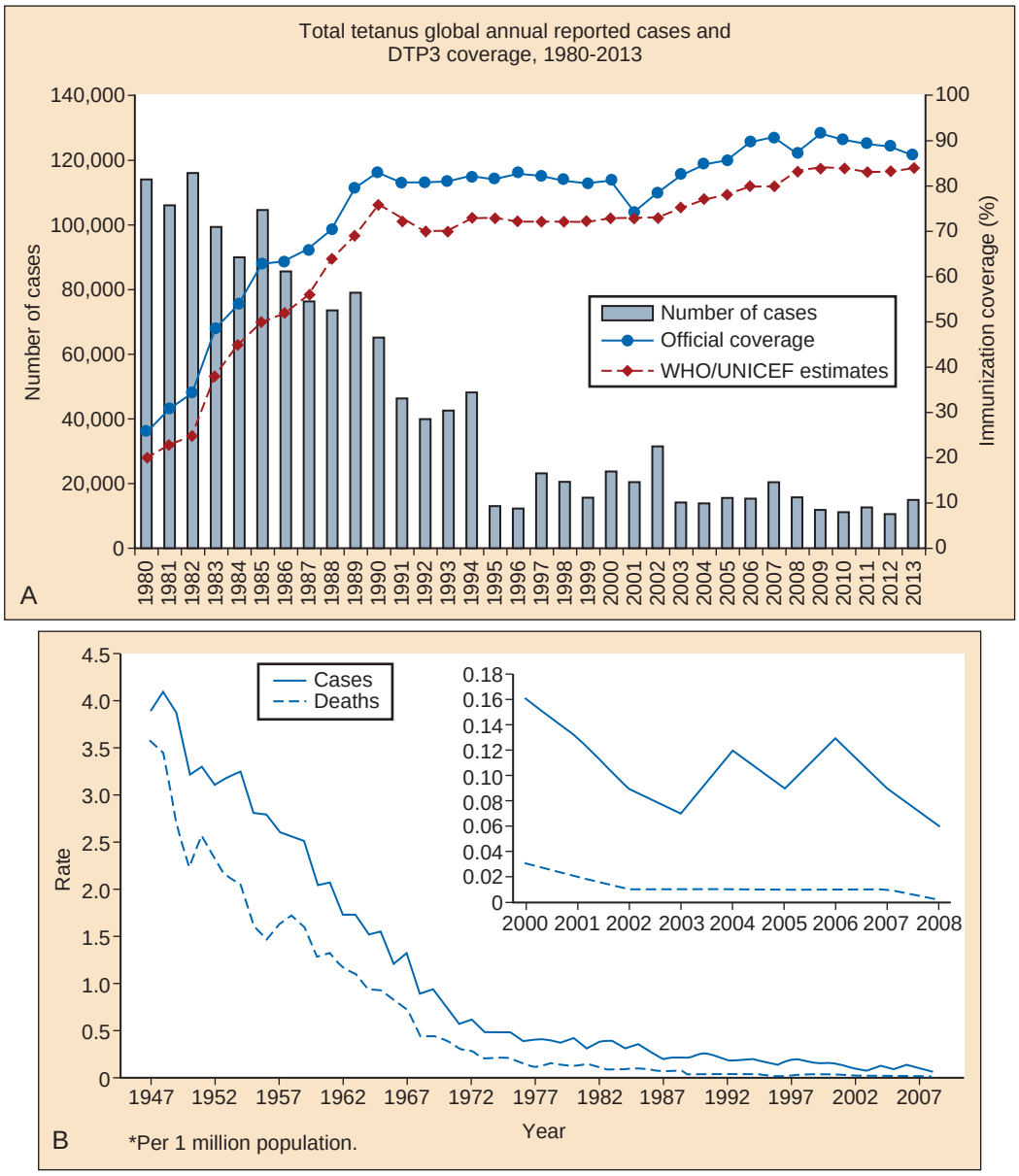


Fig. 121.3. **A,** Global annual reported cases of tetanus compared with percentage of immunization coverage. **B,** Incidence of reported tetanus cases in the United States by year. *DTP3,* third dose of diphtheria-tetanus-pertussis vaccine; *UNICEF,* United Nations Children's Fund; *WHO,* World Health Organization. (**A,** From World Health Organization: Immunization, vaccines and biologicals: tetanus. Available at: www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/tetanus/en/. **B,** From Centers for Disease Control and Prevention National Notifiable Diseases Surveillance System. Reproduced from *Morb Mortal Wkly Rep* 60:365-369, 2011.)

Since the introduction of vaccination programs in the United States, the incidence of tetanus has steadily declined from 4 cases per million population in the 1940s to fewer than 0.01 case per million population in 2010 (see Fig. 121.3B).[26] The highest incidence occurs in people older than 65 years old (0.23 case per million population), and the incidence in Hispanic Americans is almost twice that in non-Hispanics. Half of cases occur in injection drug users. The overall case fatality rate is 18% but approaches 50% in patients older than 70 years old (Fig. 121.4). Cases have been reported in fully vaccinated patients, but no deaths occurred.[26]

Tetanus classically occurs as a result of a deep penetrating wound. A history of injury is present in more than 70% of patients, but the injury may be trivial. The remainder may have another identifiable condition or no apparent source.[23] The most common portals of entry are puncture wounds, lacerations, and abrasions. Tetanus has also been reported in association with chronic skin ulcers, abscesses, otitis media, foreign bodies, corneal abrasions, childbirth, and dental procedures. Postoperative tetanus has been reported in patients who have undergone intestinal operations and abortions. In these cases, the source of bacteria is probably endogenous because up to 10% of humans harbor *Clostridium tetani* in the colon.

Inadequate primary immunization and waning immunity continue to be the primary risk factors for tetanus in the United States. As tetanus vaccination of children has improved, older people have accounted for an increasing percentage of reported cases.

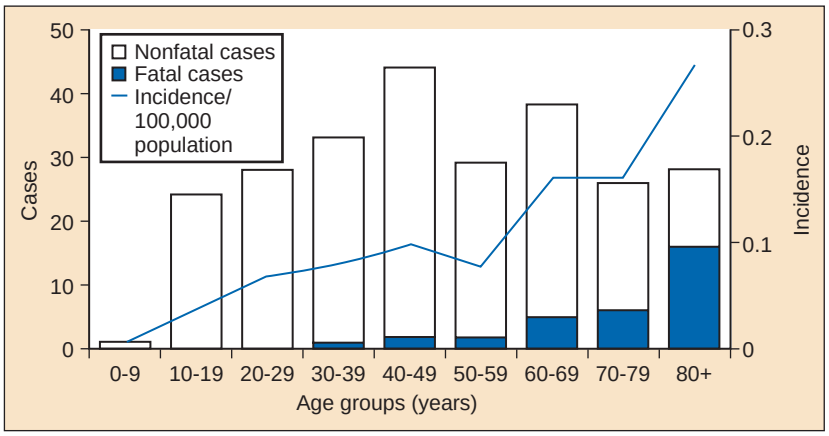


Fig. 121.4. Incidence of and mortality from tetanus by age group in the United States, 2000-2009. (Centers for Disease Control and Prevention: Manual for the surveillance of vaccine-preventable diseases. Available at: www.cdc.gov/vaccines/pubs/surv-manual/chpt16-tetanus.html.)

Etiology

C. tetani is a spore-forming, motile, rod-shaped, obligate anaerobic bacillus. It stains gram-positive in fresh culture but has a variable staining pattern in culture and tissue samples. *C. tetani* is ubiquitous in soil and dust and is also found in the feces of animals and humans. Spores are resistant to heating and chemical disinfectants and can survive in soil for months to years. When introduced into a wound, spores may not germinate for weeks because of unfavorable tissue conditions. When injury favors anaerobic growth, the spores germinate into mature bacilli, which form a single spherical terminal endospore to produce a characteristic drumstick appearance. Only these mature bacilli produce the tetanus toxin that causes clinical disease.[23]

Pathophysiology

C. tetani is a noninvasive organism. The development of clinical disease requires a portal of entry and tissue conditions that promote germination and growth in a susceptible host. Tetanus-prone wounds have damaged or devitalized tissue, foreign bodies, or other bacteria. Under these conditions, *C. tetani* produces the neurotoxin that causes clinical illness. Germination and replication of *C. tetani* can occur without clinical signs of wound infection.

C. tetani produces the neurotoxin tetanospasmin at the site of tissue injury. Tetanospasmin binds the motor nerve ending and moves by retrograde axonal transport and trans-synaptic spread to the CNS. It binds preferentially to inhibitory (GABAergic and glycinergic) neurons and blocks the presynaptic release of these neurotransmitters. Interneurons afferent to alpha motor neurons are affected first. Without inhibitory control, the motor neurons undergo sustained excitatory discharge, resulting in the muscle spasm characteristic of tetanus.[27]

Tetanospasmin may also affect preganglionic sympathetic neurons and parasympathetic centers, resulting in autonomic nervous system dysfunction. The clinical manifestations include dysrhythmias and wide fluctuations in blood pressure and heart rate. The binding of tetanospasmin at the synapse is irreversible; recovery occurs only when a new axonal terminal is produced.[23]

Clinical Features

Symptoms and Signs

The incubation period for tetanus ranges from 1 day to several months. A shorter incubation period portends a worse prognosis.[23] The duration of the incubation period is not useful in making the diagnosis of tetanus because many patients have no history of an antecedent wound. Four types of clinical tetanus have been described.

Generalized Tetanus. Generalized tetanus, the most common form of the disease, results in spasms of agonist and antagonist muscle groups throughout the body. The classic initial presenting symptom is trismus or "lockjaw," caused by masseter muscle spasm, and is present in 50% to 75% of patients. As the other facial muscles become involved, a characteristic sardonic smile (risus sardonicus) appears. Other early symptoms include irritability, weakness, myalgias, muscle cramps, dysphagia, hydrophobia, and drooling. As the disease progresses, generalized uncontrollable muscle spasms occur spontaneously or as a result of minor stimuli, such as touch or noise. Spasms can cause vertebral and long bone fractures and tendon rupture. Opisthotonos is prolonged tonic contraction that resembles decorticate posturing. Spasms of laryngeal and respiratory muscles can cause ventilatory failure and death. Autonomic dysfunction is the major cause of death in patients who survive the acute phase and is manifested by tachycardia, hypertension, hyperpyrexia, cardiac dysrhythmias, and diaphoresis. The illness progresses over 2 weeks. If the patient survives, recovery is complete after 4 weeks or more. Throughout the course of this illness, patients remain completely lucid unless they are chemically sedated.[23]

Localized Tetanus. Localized tetanus is a form of the disease characterized by persistent muscle spasms close to the site of injury. Symptoms may be mild or severe, but mortality is lower than with generalized tetanus. Local tetanus may progress to generalized disease. This form of illness may reflect partial immunity to tetanospasmin and may be present for weeks to months before resolution.[23]

Cephalic Tetanus. Cephalic tetanus, a rare variant of localized tetanus, results in cranial nerve palsies and muscle spasms. The palsies precede the spasm in many cases, resulting in misdiagnosis. The most commonly involved cranial nerve is the facial nerve (VII), mimicking Bell's palsy. Most cases occur after facial trauma or otitis media. Patients have trismus and palsies of cranial nerve III, IV, VII, IX, X, or XII ipsilateral to the site of local infection. The clinical course is variable. In one-third of cases, resolution of symptoms is complete. The remainder progress to generalized tetanus with an overall mortality rate of 15% to 30%.[18,23]

Neonatal Tetanus. Neonatal tetanus is generalized tetanus of the newborn and occurs almost exclusively in developing countries where maternal immunization is inadequate and contaminated material is used to cut and dress umbilical cords. Symptoms begin during the first week of life and include irritability and poor feeding. Mortality approaches 100% because of the high toxin load for body weight and inadequate medical support. Even with limited resources, mortality can be reduced to less than 50% with basic medication and experienced medical personnel.

Complications

Acute respiratory failure results from respiratory muscle spasms or laryngospasms and airway obstruction. If the patient survives the acute onset of illness and has adequate ventilatory support, autonomic dysfunction becomes the leading cause of death. Autonomic instability occurs several days after the onset of generalized spasms. Disinhibition of the sympathetic nervous system predominates and causes dysrhythmias, hypertension, myocarditis, and pulmonary edema. Dysrhythmias and myocardial infarction are the most common fatal events during this phase.

Forceful tetanic muscle spasms can cause vertebral subluxations and fractures, long bone fractures, and shoulder and temporomandibular joint dislocations. Rhabdomyolysis occasionally occurs and can cause acute renal failure. Renal failure may also result from dehydration and sympathetic nervous system hyperactivity.

Secondary infection may occur in the initial inoculating wound or as a complication arising from invasive treatment modalities, such as mechanical ventilation. Hyperthermia may also result from muscle spasms and sympathetic hyperactivity. Prolonged immobility can lead to deep venous thrombosis and pulmonary embolism. Gastrointestinal complications include peptic ulcers, ileus, intestinal perforation, and constipation. The syndrome of inappropriate secretion of antidiuretic hormone occurs in a small number of patients. Hemolysis has also been reported.

Mortality is a function of the previous immunization status, incubation period, severity and rapidity of onset of illness, comorbid disease, age, and sophistication of medical treatment available. With appropriate intensive care treatment, elders may fare as well as their middle-aged counterparts. Long-term physical complications in survivors are rare. The most common persistent problem is psychological trauma related to the disease and its treatment.[23]

Diagnostic Strategies

The diagnosis of tetanus should be made on clinical grounds alone. Wound cultures are of little value and are positive in only one-third of cases. A positive culture does not indicate whether the bacterium is a toxin-producing strain. There are no laboratory tests to confirm or to exclude the diagnosis of tetanus.[23]

Lumbar puncture may be indicated to exclude meningitis in the neonate when the diagnosis of tetanus is uncertain. A computed tomography (CT) scan is helpful in assessment for intracranial disease. A serum calcium level is helpful to exclude hypocalcemia. Electromyography may be useful if the diagnosis of cephalic or localized tetanus is in doubt.

The spatula test involves touching of the oropharynx with a tongue blade. With a negative test result, the patient gags and expels the tongue blade. With a positive test result, the patient has reflex masseter muscle spasm and bites the spatula. This test is 94% sensitive and 100% specific for tetanus.

Differential Diagnosis

Strychnine poisoning is the only clinical condition that truly mimics generalized tetanus. Strychnine, like tetanospasmin, antagonizes glycine release, but unlike tetanospasmin, it has no effect on gamma-aminobutyric acid (GABA) release. Patients have opisthotonos while remaining alert. The annual incidences of tetanus and strychnine poisoning are similar in the United States, and serum and urine tests for strychnine should be performed when tetanus is considered.[23]

BOX 121.5

Differential Diagnosis of Tetanus

Acute abdomen
Black widow spider bite
Dental abscess/infection
Dislocated mandible
Dystonic reaction
Encephalitis
Head trauma
Hyperventilation syndrome
Hypocalcemia
Meningitis
Peritonsillar abscess
Progressive fluctuating muscle rigidity (stiff-man syndrome)
Psychogenic
Rabies
Sepsis
Status epilepticus
Strychnine poisoning
Subarachnoid hemorrhage
Temporomandibular joint syndrome

In patients who present with diffuse generalized spasm, the diagnosis is unlikely to be missed, but ideally the disease should be considered and diagnosed in the early stages to minimize complications and to decrease mortality. Some conditions with clinical similarities to tetanus are listed in Box 121.5. Trismus is most commonly caused by intraoral infections. These can be excluded with careful history and physical examination. Mandibular dislocation can be ruled out with appropriate radiographs of the mandible and temporomandibular joints. Dystonic reactions can be differentiated from tetanus by medication history and symptoms that are alleviated by benztropine or diphenhydramine. Patients with encephalitis usually exhibit an altered mental status. Meningitis can be excluded by examination of the cerebrospinal fluid (CSF). Rabies should be considered when there are symptoms of brainstem dysfunction, including dysphagia and respiratory muscle dysfunction. A history of exposure to secretions of an infected animal is the most helpful historical point. In addition, rabies does not cause trismus.

Cephalic tetanus is especially difficult to diagnose when the cranial nerve palsy precedes trismus. The differential diagnosis of cephalic tetanus also includes Bell's palsy, botulism, cranial nerve palsies, and facial cellulitis with facial nerve compression and ophthalmoplegia.

Management

Acute Treatment

The four treatment strategies for patients with tetanus should be undertaken simultaneously: aggressive supportive care, elimination of unbound tetanospasmin, active immunization, and prevention of further toxin production.[23,24]

Supportive Care. Supportive care begins with controlling muscle spasms. Reflex spasms result from stimulation of the patient caused by any movement or loud noises. Unnecessary

stimulation should be avoided. Benzodiazepines are the mainstay of symptomatic therapy for tetanus. These drugs are GABA agonists and indirectly antagonize many of the effects of tetanospasmin. They have no effect on the inhibition of glycine release by tetanospasmin. Diazepam is the most extensively studied, but lorazepam and midazolam are equally effective. Diazepam has a rapid onset of action, wide safety margin, and can be given orally, rectally, or intravenously. It is inexpensive and available in most parts of the world. Its long cumulative half-life and active metabolites can cause prolonged sedation and respiratory depression. The IV formulations of diazepam and lorazepam contain propylene glycol, which, at high doses, can produce lactic acidosis. Gastrointestinal delivery of these agents is limited by motility problems associated with tetanus. Midazolam has a short half-life and does not contain propylene glycol, but should be given by continuous infusion and is cost-prohibitive in most areas of the world. Propofol infusion is effective but expensive, and patients may not tolerate the lipid vehicle. Neuroleptics, barbiturates, and intrathecal baclofen have no advantage over benzodiazepines. Dantrolene is a direct muscle relaxant without CNS activity. It has been reported as an adjunctive agent for muscle spasms and may decrease the need for mechanical ventilation.[19] Magnesium sulfate infusion has been advocated as both adjuvant and first-line therapy for tetanus, although there are no data to support its use in this setting.[28]

If spasm cannot be controlled with these regimens or signs of airway compromise develop, the patient should receive neuromuscular blockade and mechanical ventilation. Succinylcholine can be used in the *initial* phase of the disease, but there is a risk of severe hyperkalemia resulting from its use in any neuromuscular disease. This effect does not begin until about 4 days after the onset of disease. Long-acting nondepolarizing agents are preferred. Pancuronium has traditionally been used, but it is an inhibitor of catecholamine reuptake and may worsen autonomic instability. Vecuronium and rocuronium are shorter acting, lack significant cardiovascular side effects, but require continuous infusion. Whichever agent is used, adequate sedation should be provided, and neuromuscular blockade should be withheld at least once a day to assess the patient's status. All intubated patients should be considered for early tracheostomy to decrease reflex spasms caused by the endotracheal tube.

Autonomic instability requires monitoring and aggressive treatment. Sympathetic hyperactivity can be treated with combined alpha- and beta-adrenergic antagonists, such as labetalol and propranolol. The use of beta-antagonists alone can lead to unopposed alpha-activity, resulting in severe hypertension. If beta-antagonists are necessary, a short-acting agent such as esmolol should be used. Clonidine has variable success at modulation of sympathetic outflow in these cases. Morphine and magnesium sulfate infusions as well as spinal anesthesia and intrathecal baclofen have been shown to improve autonomic dysfunction.[23] Diuretics should be avoided for blood pressure control as volume depletion can worsen autonomic instability. Bradydysrhythmia should be treated with temporary pacing. Atropine and sympathomimetic drugs should be used with caution as the autonomic instability is essentially due to catecholamine excess.

Elimination of Unbound Toxin and Active Immunization. Passive immunization with human tetanus immune globulin (HTIG) and active immunization with Td should be initiated as soon as possible in all patients with suspected tetanus. HTIG neutralizes circulating toxin, as well as toxin at the site of production, and reduces mortality; it does not neutralize toxin already present in the nervous system, nor does it treat any existing symptoms. HTIG should be administered at a site separate from the Td. A dose of 500 units is as effective as higher doses. Adult and pediatric doses are the same. Administration of a portion of the HTIG proximal to the site of inoculation is often recommended but has not been studied. The preparation of HTIG available in the United States is not licensed for intrathecal administration, which is questionable benefit.[23]

TABLE 121.1

Pediatric Doses of Metronidazole Based on Age and Weight

WEIGHT AND AGE	DOSAGE
Neonates <1200 g and 0 to 7 days	7.5 mg/kg IV or orally every 24 hours
Neonates <1200 g and 8 to 28 days	7.5 mg/kg IV or orally every 12 hours
Neonates >1200 g and 0 to 7 days	7.5 mg/kg IV or orally every 12 hours
Neonates >1200 g and 8 to 28 days	25 to 30 mg/kg/day IV or orally every 12 hours
Infants and children	30 mg/kg/day IV divided every 6 hours, maximum 4 g/day

IV, Intravenous.

Prevention of Further Toxin Production. Toxin production is eliminated by treatment of the *C. tetani* infection. Wound débridement and antibiotic administration can cause a transient release of tetanospasmin, so these measures should be delayed until after the HTIG is administered. Metronidazole (500 mg orally or IV every 6 hours) is the antibiotic of choice for *C. tetani*. Table 121.1 lists pediatric doses of metronidazole based on age and weight.

Penicillin has good in vitro and in vivo activity against *C. tetani,* but it also has GABA antagonistic activity and may potentiate the effects of tetanospasmin. Metronidazole has better penetration than penicillin into devitalized tissue and abscesses and is superior in terms of recovery time and effect on mortality. Macrolides, doxycycline, chloramphenicol, and tetracycline are effective alternatives in metronidazole-allergic patients.[23]

Vaccination

Tetanus toxoid is an inactivated form of tetanospasmin. Vaccination confers protective antibody levels in nearly 100% of people who receive three doses. Immunity wanes between 5 and 10 years after completion of the series. In high-risk patients such as elders, injection drug users, and patients with human immunodeficiency virus (HIV) infection and other causes of immunocompromise, immunity wanes more quickly and response to the vaccine is slower.

Adults with an uncertain history of a complete primary immunization series should receive a primary series of three tetanus toxoid doses, followed by booster doses every 10 years. Age-specific guidelines for tetanus prophylaxis have been developed by the Advisory Committee on Immunization Practices (ACIP) and published by the CDC (Tables 121.2 and 121.3).

Tetanus vaccination should be updated for all patients who present for wound management. Patients with unknown or uncertain immunization status should be considered to have no previous tetanus immunization. Those younger than 7 years old should receive diphtheria-tetanus or DTaP. Patients 7 years old or older should receive Tdap.

HTIG prophylaxis (250 units IM) is recommended for unimmunized and underimmunized patients with high risk wounds

TABLE 121.2

Routine Diphtheria, Tetanus, and Pertussis Vaccination Schedule for Children and Adults—United States

DOSE	CUSTOMARY AGE	AGE/INTERVAL	PRODUCT
Primary 1	2 months old	6 weeks or older	DTaP
Primary 2	4 months old	4 to 8 weeks after first dose[b]	DTaP
Primary 3	6 months old	4 to 8 weeks after second dose[b]	DTaP
Primary 4	15 to 18 months old	6 to 12 months after third dose[b]	DTaP
Booster	4 to 6 years old, not needed if fourth vaccination administered after birthday[a]		DTaP
Additional booster	11 to 18 years old		Tdap
Adult booster	>18 years old All pregnant women	Every 10 years	Tdap or Td[c]

[a]If primary immunizations are started after the age of 6 years, the series should begin and continue with Tdap.
[b]Prolonging the interval does not require restarting of the series.
[c]Td should be given to adult patients who have previously received Tdap. Tdap can be given regardless of interval since Td.
DTaP, Diphtheria, tetanus, and acellular pertussis; *Td,* diphtheria-tetanus; *Tdap,* tetanus, diphtheria, activated pertussis.
Modified from Recommended childhood immunization schedule—United States, 2011. Available at www.cdc.gov/vaccines/recs/acip and *MMWR* 62(7):131-135, 2013.

TABLE 121.3

Summary Guide to Tetanus Prophylaxis in Routine Wound Management

HISTORY OF ABSORBED TETANUS TOXOID (DOSES)	CLEAN MINOR WOUNDS		ALL OTHER WOUNDS[a]	
	Tdap[b] or Td	TIG	Tdap[b] or Td	TIG
Unknown or less than three	Yes	No	Yes	Yes
Three or more[c]	No[d]	No	No[e]	No

[a]Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.
[b]For children younger than 7 years old, DTaP is preferred. For persons older than 7 years old, Tdap is preferred to tetanus toxoid alone. Td is preferable in adults who have previously received one dose of Tdap.
[c]If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.
[d]Yes, if older than 10 years old since last dose.
[e]Yes, if older than 5 years old since last dose. (More frequent boosters are not needed and can accentuate side effects.)
HTIG, Human tetanus immune globulin; *Td,* diphtheria-tetanus; *Tdap,* tetanus, diphtheria, activated pertussis.
Modified from Pink Book. Centers of Disease Control and Prevention: National enteric disease surveillance: botulism annual summary in 2012. Available at: www.cdc.gov/nationalsurveillance/PDFs/Botulism_CSTE_2012.pdf.

(>6 hours old, >1 cm deep, contaminated, stellate, denervated, ischemic, infected). When tetanus toxoid and HTIG are given concurrently, separate injection sites should be used. The only contraindication to tetanus and diphtheria toxoids is a history of a neurologic or severe hypersensitivity reaction to a previous dose. The most common side effects of tetanus vaccine are minor: local swelling, pain, erythema, pruritus, fever, nausea, vomiting, malaise, and nonspecific rash. Local reactions do not preclude future use of toxoid. Serious anaphylactic reactions are rare. If a patient who requires toxoid gives a history suggestive of a neurologic or severe anaphylactic reaction, HTIG should be administered alone to protect the patient from development of tetanus as a result of the present injury. HTIG does not confer active immunity, and such patients should be referred to an allergist for measurement of antibody levels, antitoxin desensitization, and immunization. No evidence exists that tetanus and diphtheria toxoids are teratogenic. HTIG is not contraindicated in pregnancy. For inadequately immunized patients of any age, referral should be made to ensure that the patient receives the remainder of the immunizations required.

BOTULISM

Principles

Background

Botulism is a rare life-threatening paralytic illness caused by neurotoxins produced by *Clostridium botulinum*. The disease occurs in one of five forms: food-borne botulism, infant botulism, wound botulism, unclassified botulism, and inadvertent botulism.[29] Since the approval of botulinum toxins A and B by the FDA for cosmetic and therapeutic uses in the United States, cases of iatrogenic botulism have been reported.[30]

In 1820, Kerner first noted an association between sausage ingestion and a paralytic illness. The term *botulism* comes from the Latin *botulus,* meaning "sausage," because of these early descriptions of the disease. Botulism first received attention in the United States during World War I when women were encouraged to preserve fruits and vegetables. The recommended heating methods for home canning did not destroy the spores, and epidemics of botulism occurred. Wound botulism was first described in 1943. In 1950 the CDC began surveillance of this form of the disease. Infant botulism, which is now the most common form of the illness, was first described in 1976.

Epidemiology

Seven toxins (A through G) are produced by *C. botulinum*. Types A, B, E, and F cause illness in humans, and types C and D cause disease in animals. Type G has been found in soil but has not been linked to human or animal outbreaks. *C. botulinum* spores are found throughout the United States. Type A is more common in the West and type B in the East. Type E is frequently associated with fish products.[29] A total of 160 cases of botulism were reported to the CDC in 2012, which was an increase from 121 cases in 2009; 16% were food-borne botulism, 76% were infant botulism, and 5% were wound botulism.[31] Despite the ubiquitous nature of botulinum spores and the variety of possible routes of toxin entry, the incidence of disease is low.

Typical food-borne botulism results from the ingestion of preformed heat-labile toxin rather than from the ingestion of spores or live bacteria. Food-borne botulism usually results from exposure to home-canned foods that are inadequately preserved and undercooked, but large outbreaks occasionally occur after the ingestion of contaminated food at restaurants or from commercial sources. A variety of preserved foods have been implicated, and

botulism has also been reported to result from ingestion of improperly prepared and stored fresh foods.

Infant botulism occurs in children younger than 1 year old with a peak incidence between the ages of 6 weeks and 6 months. In contrast to food-borne botulism in adults, infant botulism is caused by the ingestion of spores with in vivo production of toxin. Honey and to a lesser extent corn syrup have been implicated as sources of *C. botulinum* spores in infant botulism. Soil and vacuum cleaner dust have also been implicated, but the source of ingestion remains unknown in most cases. Types A and B botulinum toxins have been responsible for almost all infant cases. There appears to be no relationship between infant botulism and sudden infant death syndrome.

Wound botulism once accounted for approximately one botulism case per year, but the increased use of black tar heroin has resulted in a dramatic increase in cases. Most cases occur in California among injection drug users. Toxin type A is the most frequent causative agent.[31,32]

Unclassified or adult infectious botulism is a rare illness that is analogous to infant botulism. The *Clostridium* bacterium produces its toxin in vivo. Patients with compromised gastric acidity, disturbances of gastrointestinal motility, or abnormal gastrointestinal bacterial flora may be susceptible to in vivo production of botulinum toxin.

Inadvertent botulism is an iatrogenic form of the disease that occurs in patients who have been treated with injections of botulinum toxin for dystonia and other movement disorders and for cosmetic purposes. Inadvertent generalized weakness as well as unintentional focal weakness may be seen.[33]

The potential exists for botulinum toxin to be used as a biologic weapon. It is highly potent and easy to produce. The Aum Shinrikyo, responsible for the 1995 sarin gas attack on the Tokyo subway, produced and dispersed aerosols of botulinum toxin in Japan on at least three occasions between 1990 and 1995. In 1995, Iraq admitted to the United Nations that it had produced 19,000 L of concentrated botulinum toxin and loaded approximately 10,000 L into warheads. These 19,000 L are not fully accounted for and constitute three times the amount needed to kill the entire human population by inhalation.

Etiology

C. botulinum is an anaerobic, gram-positive, rod-shaped organism. It forms spores that germinate under certain environmental conditions. It produces a potent exotoxin that is responsible for the disease. Each strain of *C. botulinum* produces a specific toxin type—A through G. Only types A, B, E, and F produce disease in humans.[34] Botulinum toxins are the most potent known biologic compounds. Doses as small as 0.09 to 0.15 μg IV or 0.7 to 0.9 μg inhaled can cause death in a 70-kg human.[35] Heating at 185°F (85°C) for 5 minutes destroys any botulism toxin, and heating of toxin-contaminated food just before ingestion prevents food-borne botulism. Spores are highly heat resistant and can survive at a temperature of 212°F (100°C) for several hours.

Pathophysiology

Food-borne botulism results from ingestion of food that contains preformed toxin. Toxin-contaminated food may have a normal appearance and taste or exhibit signs of spoilage caused by proteolytic enzymes produced by the type A and B strains. Because of the tremendous potency, one taste can expose a person to enough toxin to cause clinical illness. Digestive enzymes do not destroy preformed toxin. Infant and adult infectious botulism results from in vivo bacterial elaboration of toxin in the gastrointestinal tract. Achlorhydria and recent antibiotic use predispose the gastrointestinal tract to colonization with *C. botulinum*. Wound botulism results from in vivo bacterial elaboration of toxin in a wound. Inadvertent or iatrogenic botulism results from injection of preformed toxin for medical purposes.[34] Primate studies indicate that aerosolized botulinum toxin can also be absorbed systemically through the respiratory tract.[35]

The botulinum neurotoxin is similar in structure and function to the tetanospasmin toxin produced by *C. tetani,* but the clinical effects differ dramatically. Tetanospasmin targets inhibitory interneurons in the CNS, causing generalized muscle spasm, whereas botulinum toxin targets peripheral neuromuscular junctions and autonomic synapses, causing flaccid paralysis. When botulinum toxin is absorbed, it circulates until it reaches the neurons. The toxin binds to the presynaptic nerve membrane, becomes internalized, and inhibits the release of acetylcholine predominantly at the cholinergic synapses of the cranial nerves, autonomic nerves, and neuromuscular junction. Clinically, this is manifested by cranial nerve palsies, parasympathetic blockade, and descending flaccid paralysis. Once affected with type A toxin, the nerve is permanently damaged, and recovery requires axonal regeneration and the formation of new synapses, which may take several months. Recovery after type F toxin is substantially faster.[29]

Clinical Features

Symptoms and Signs

Food-borne botulism is the prototype for understanding the clinical signs and symptoms of all forms of botulism. Symptoms begin 6 hours to 8 days after the ingestion of toxin-containing food. A shorter incubation period is associated with a more severe form of illness. Early symptoms include weakness, malaise, lightheadedness, nausea, vomiting, and constipation. These symptoms are generally not severe and occur in fewer than half of the patients.

Neurologic symptoms may begin immediately or be delayed in onset for several days. The cranial nerves are first affected. Patients experience diplopia, blurred vision, dysphonia, dysphagia, dysarthria, and vertigo. Next, a symmetrical descending muscle weakness occurs, involving the upper and lower extremities and the muscles of respiration. Blockade of the cholinergic fibers of the autonomic nervous system leads to a variety of symptoms. Decreased salivation causes a dry mouth, which may be so severe that the patient complains of a painful tongue and sore throat. Ileus and urinary retention may occur.

The patient with botulism is usually alert and afebrile unless secondary infection is present. Postural hypotension may be present. Ocular signs are prominent and include ptosis, extraocular palsies, and markedly dilated and fixed pupils; the absence of ocular abnormalities does not exclude the diagnosis. The oropharynx may be erythematous, with dry mucous membranes. The gag reflex is depressed or absent. Muscle weakness is usually present and varies from mild to severe. Neck muscles are often weak. Upper extremity muscles are affected more than those of the lower extremity, and proximal muscles are weaker than distal muscles. Deep tendon reflexes may be normal, symmetrically decreased, or absent. The sensory examination is normal. The abdomen may be distended with hypoactive or absent bowel sounds. Bladder distention may be apparent on examination. Respirations may be tachypneic and shallow or normal. In advanced illness, signs of respiratory failure may be present.

Atypical presentations of food-borne botulism have been reported, and certain serotypes produce distinct variations in the pattern of symptoms. Type A disease may be more severe and is more commonly associated with bulbar findings and upper extremity weakness. Type A and type B disease may rarely cause a decreased level of consciousness. Type E is associated with a greater incidence of gastrointestinal symptoms.[29]

The presentation of *infant botulism* is different from that of food-borne botulism. Constipation is a common presenting complaint, followed by several days to weeks of poor feeding, weak cry, loss of head control, and hypotonia. On physical examination, patients have decreased muscle tone and depressed deep tendon reflexes. Cranial nerve involvement causes alterations in facial expression, ptosis, and extraocular palsies. Respiratory failure occurs in 50% of patients. Fever is absent unless secondary infection is present.[36]

Wound botulism has notable differences from food-borne botulism. The incubation period is longer, from 4 to 14 days, because the toxin must be produced within the wound after the spores have germinated. If the wound is infected, the patient may be febrile. Gastrointestinal symptoms are notably absent in wound botulism. Recurrent episodes are well described.[32]

The clinical presentation of *unclassified (adult infectious) botulism* is similar to that of food-borne botulism, although the mortality rate is significantly greater. Recovery from botulism is slow, and survivors are hospitalized for several weeks to months.

Complications

Complications from botulism are related to respiratory failure and problems associated with prolonged intensive care management. Aspiration of oral secretions and gastric contents because of loss of protective airway reflexes can occur. In the past 50 years, the overall mortality rate has decreased from 50% to less than 1% with modern intensive care. Mortality rates are higher in wound botulism patients (15% to 17%) and lower in infant botulism patients (<1%). For those who recover, muscle strength and endurance may not return to normal for up to 1 year, and persistent psychological problems are common.[31]

Diagnostic Strategies

Botulism is a clinical diagnosis that should be considered in any patient who presents with the constellation of gastrointestinal, autonomic, and cranial nerve dysfunction. Bilateral cranial nerve involvement and the progression of neurologic findings should increase clinical suspicion. Routine laboratory studies are of no value in the diagnosis. If a lumbar puncture is performed, the CSF in patients with botulism is normal or may show a slight elevation of protein.[34]

The diagnosis is confirmed by detection of botulinum toxin in the patient's blood; botulinum toxin or *C. botulinum* in the gastric contents, stool, or wound of the patient; or toxin or organisms in the suspected food source. Local health departments and the CDC should be notified for instruction on the handling of specimens. Ideally the specimens should be obtained before administration of antitoxin, but treatment should not wait for laboratory confirmation. Serial measurements of the patient's vital capacity are helpful in recognizing deteriorating ventilatory function.[29]

Electromyography can detect abnormalities consistent with the diagnosis of botulism and may be useful in differentiating botulism from other paralytic illnesses. The electromyographic signature of botulism is decreased amplitude of the compound muscle action potential in response to a supramaximal stimulus and facilitation of the muscle action potential with repetitive nerve stimulation. Not all motor units are affected, and normal test results do not exclude the diagnosis.[29]

Differential Diagnosis

The differential diagnosis of *adult botulism* includes a wide variety of illnesses. Commonly, the first presenting case is misdiagnosed because early symptoms suggest pharyngitis or gastroenteritis, both of which can affect several members of a single household. Only after one or more cases progress to classic botulism is the diagnosis usually suggested.

Botulism should be differentiated from other illnesses that cause paralysis. In Guillain-Barré syndrome, weakness usually starts distally and ascends, paresthesias may be present, and the CSF protein level may be elevated. Tick paralysis is an ascending paralysis, which is notable for a lack of bulbar involvement and the presence of a tick. In myasthenia gravis, eye signs are also prominent, but pupillary response is preserved, no autonomic symptoms are present, and weakness responds to the administration of edrophonium or ice applied to the affected muscle group. Of note, minimal improvement in weakness after the administration of edrophonium has been reported in botulism.[37] Poliomyelitis causes fever, asymmetrical neurologic signs, and CSF abnormalities. Diphtheria can be distinguished by the prolonged interval between pharyngitis and neurologic symptoms. Eaton-Lambert syndrome does not usually involve bulbar muscles. Cerebrovascular accidents of the brainstem have an acute onset and asymmetrical, neuroanatomically localizing signs and symptoms.

Certain toxins should also be considered in the differential diagnosis of botulism. Anticholinergics (atropine, belladonna, jimson weed) cause pupillary dilation and dry, red mucous membranes but also cause delirium with alterations in mental status. Organophosphate insecticides cause hyperthermia and altered mental status. Dystonic reactions are self-limited and respond to diphenhydramine or benztropine. Neuromuscular blockade from the administration of aminoglycosides is distinguished by medication history. Heavy metal poisoning produces changes in mental status. Magnesium toxicity may mimic botulism, but the history and serum magnesium levels distinguish these entities. In paralytic shellfish poisoning, paresthesias are prominent, a history of shellfish ingestion is present, and recovery occurs within 24 hours.

Infant botulism has a broader differential diagnosis. Common illnesses that mimic the presentation of infant botulism include sepsis, viral illnesses, dehydration, encephalitis, meningitis, and failure to thrive. Neurologic illnesses such as Guillain-Barré syndrome, myasthenia gravis, and poliomyelitis should also be considered.[36] Hypothyroidism, hypoglycemia, diphtheria, and toxin exposures are all part of the differential diagnosis consideration, as are less common conditions such as inborn errors of metabolism, congenital muscular dystrophy, and cerebral degenerative diseases.

Management

The treatment of botulism consists of supportive care and specific treatment with antitoxin and other medications to block the effects of the toxin. All patients with suspected botulism should be admitted to the hospital and placed in an intensive care unit (ICU) because respiratory failure may develop rapidly. A decrease in vital capacity to less than 30% of predicted or less than 12 mL/kg is an appropriate criterion for intubation. Ileus should be treated with nasogastric suction and urinary retention with an indwelling urinary catheter. Fortunately, the autonomic dysfunction of botulism is much less severe than that of tetanus and rarely requires intervention.[31]

Saline enemas and cathartics have been recommended by some authors to cleanse the gastrointestinal tract of residual toxin. Cathartics should not be given in the presence of ileus. Magnesium-containing cathartics should be avoided because elevated serum magnesium levels can exacerbate muscle weakness. Special care should be taken with use of gastrointestinal clearance in infants with botulism. Because the source of toxin is outside the gastrointestinal tract in wound botulism, bowel decontamination is not indicated.[31]

Equine antitoxin contains antibodies to toxin types A, B, and E. It should be administered as soon as possible after appropriate laboratory specimens have been obtained. It neutralizes circulating toxin but has no effect on bound toxin. Early administration prevents the progression of illness, decreases hospital length of stay, prevents respiratory failure, and shortens the duration of respiratory failure in patients with severe disease. Antitoxin can be obtained from the CDC or state health department. After skin testing for hypersensitivity, one 10-mL vial should be given IV. The serum half-life is 5 to 8 days. For these reasons, and contrary to the information in the package insert, only one vial of antitoxin is required. Repeated doses are unnecessary and increase the risk of hypersensitivity reactions, which occur in approximately 9% of patients.[31]

Infant botulism is treated with human botulism immune globulin (BabyBIG), which is pooled plasma from immunized adults with high titers of antibodies to toxins A and B.[37] BabyBIG shortens hospital length of stay by a mean of 3.1 weeks and mechanical ventilation by a mean of 1.7 weeks. It can be obtained by calling the California Department of Public Health Infant Botulism Treatment and Prevention Program at 510-231-7600 or 510-540-2646.[36,37]

Antibiotics are not currently recommended for food-borne botulism and may increase cell lysis and promote toxin release. Because the source of toxin is in vivo production within an infected wound, débridement and antibiotic administration should be considered only after antitoxin has been administered. Otherwise, the use of antibiotics should be limited to treatment of secondary infections that may develop. Antibiotic treatment of both infant and wound botulism has no proven benefit. If an antibiotic is used for any reason in a botulism patient, all attempts should be made to avoid the aminoglycosides and tetracyclines because they can impair neuron calcium entry and worsen the effects of botulinum toxin.[29]

Guanidine hydrochloride may enhance the release of acetylcholine from terminal nerve fibers and has been recommended as an experimental component of botulism therapy.[37]

Disposition

All patients with possible botulism should be admitted to the hospital and placed in an ICU as respiratory failure may develop rapidly and insidiously. An infectious disease specialist should be consulted for management issues. The CDC should be called for assistance in any case of suggested botulism. The CDC can be reached by calling 404-639-3311 (days) and 404-639-2540 (nights, weekends, and holidays). State and local health departments may also be helpful in investigating and preventing major epidemics. Area emergency departments should be alerted so that subsequent cases can be looked for and diagnosed.

PNEUMOCOCCEMIA

Principles

Background

Streptococcus pneumoniae is a significant cause of morbidity and mortality worldwide. Pneumococcemia is defined as the presence of *S. pneumoniae* in the blood. The clinical presentation ranges from a mild illness to a fulminant, life-threatening, systemic syndrome. *S. pneumoniae* also causes myriad localized infections, including otitis media, pneumonia, meningitis, and, less commonly, endocarditis, septic arthritis, and peritonitis.[33,38]

S. pneumoniae was discovered in 1881 by Sternberg in the United States and simultaneously by Pasteur in France. It was called *pneumococcus* because it was the most common cause of lobar pneumonia. The first pneumococcal vaccine was licensed for use in the United States in 1977, and today there are two forms available: one for infants younger than 2 years old and individuals with impaired host defenses, and one for otherwise healthy individuals older than 2 years old.[39-42]

Epidemiology

S. pneumoniae remains a substantial cause of serious illness despite the availability of antibiotics and vaccines. Pneumococcal infection appears sporadically in normal individuals and in patients with impaired host defenses. Most cases of pneumococcal infections are community acquired, and the peak incidence is in winter.[33] Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile site (blood, pleural fluid, CSF). Pneumococcemia occurs in less than 2% of all hospitalized patients with community-acquired pneumonia, but up to 7.3% of those admitted to the ICU, 11.5% of those with multilobar infiltrates, 15% of those with a temperature 104° F (40° C) or higher or 95° F (35° C) or lower, 20% of those with a systolic blood pressure below 90 mm Hg, and 22% of those with HIV. Other sources include the meninges (8%) and the sinuses or middle ear (4%). Bacteremia is primary in 18% of adults but much higher in children. People at higher risk for pneumococcemia include those with chronic respiratory or cardiovascular disease, chronic alcohol abusers, patients with cirrhosis, diabetes mellitus, or an absent or functionally impaired spleen (post-splenectomy or sickle cell disease), those receiving immunosuppressive therapy, those with chronic renal failure, nephrotic syndrome, organ transplantation, lymphoma, Hodgkin's disease, multiple myeloma, and acquired immunodeficiency syndrome (AIDS).[41] Pneumococcus is spread from person to person by close contact, and crowded living conditions are associated with epidemics.

The mortality rate from pneumococcemia is 10% to 20% for young adults and much higher for elders, those with underlying disease, and those with localized infections, such as meningitis.[43] The case fatality rate is significantly lower for children.

Etiology

Pneumococcemia is caused by *S. pneumoniae,* an encapsulated, gram-positive, facultative anaerobic coccus. Antigenic differences in the polysaccharide capsule separate *S. pneumoniae* into 90 serotypes.[33] In the United States, the seven serotypes present in Prevnar account for most of invasive disease in children younger than 6 years old and 50% of invasive disease in people older than 6 years old. Worldwide, 10 capsular types account for two-thirds of invasive disease.

Pathophysiology

S. pneumoniae enters the blood by one of two routes: (1) It begins as a pulmonary infection and spreads to mediastinal lymph nodes, the thoracic duct, and into the circulation; (2) it colonizes or causes infection in the upper respiratory tract and spreads to the subarachnoid space through the arachnoid villi to the venous sinus and into the blood (with or without meningeal involvement).

S. pneumoniae bacteremia causes a clinical picture that ranges from a minor febrile illness to life-threatening septic shock. Different capsules of *S. pneumoniae* confer varying levels of resistance to phagocytosis, resulting in a spectrum of virulence among these serotypes. Multiple virulence factors contribute to adherence to tissues, inhibition of phagocytosis, activation of complement, and stimulation of cytokines.[33]

Host defenses rely heavily upon antibody and complement production, and people who have impaired humoral immunity

are more susceptible to IPD. In patients with pneumococcal infections, antibodies specific to the capsule serotype develop within several days of onset of infection. This response occurs approximately 30 days after a patient receives the pneumococcal vaccine. Patients who demonstrate substantial host resistance are able to develop active immunity, and some children can spontaneously clear culture-proven pneumococcemia.

Clinical Features

Symptoms and Signs

The clinical presentation of pneumococcemia ranges from mild illness to fulminant disease, progressing to death within several hours. Occult bacteremia begins as a febrile illness in which the only direct indication of pneumococcemia is a positive blood culture (often at 24 to 48 hours). Sepsis is the systemic response to infection, manifested by two or more of the following: (1) temperature higher than 100.4°F (38°C) or lower than 96.8°F (36°C); (2) heart rate higher than 90 beats/minute; (3) respiratory rate of more than 20 breaths/minute or partial pressure of carbon dioxide in arterial gas of less than 32 mm Hg; and (4) WBC count higher than12,000/mm^3, lower than 4000/mm^3, or more than10% immature (band) forms.[44] Patients may present with lethargy, signs of poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Either occult bacteremia or sepsis can occur in conjunction with a localized infection.

Symptoms may include fever, chills, cough, shortness of breath, headache, and rash. The shaking chills that occur with pneumococcemia are believed to be caused by a toxin. The clinical presentation of pneumococcemia is similar to that of other common febrile illnesses. Although signs of focal infection, such as pneumonia, may be present, often the only indication of pneumococcemia is fever or other signs of bacterial toxicity.

Most adult patients have fever or hypothermia. Cough, rigors, pleuritic pain, and gastrointestinal symptoms occur in about one-third of adult patients. Patients complain of vague, nonspecific constitutional symptoms similar to those of common viral illnesses. Fever (temperature >101.3°F [38.5°C]) occurs in 90% of younger patients but in less than 60% of those older than 65 years old. Patients with signs of sepsis have an increased risk for a fulminant course with rapid deterioration. Physical examination findings vary with the site of primary infection. A focal primary source of infection is more common in adults than in children. Clinicians should evaluate for signs of otitis media, sinusitis, and meningitis. Pneumococcemia is considered primary in 18% of adults and 30% of children, so lack of localized infection as a source does not rule out IPD.

Complications

Cardiovascular collapse can occur with fulminant pneumococcal sepsis. Patients who develop severe illness from pneumococcemia may have end-organ damage from inadequate perfusion, disseminated intravascular coagulation (DIC), septic emboli, respiratory failure, meningitis, gastrointestinal bleeding, hepatic coma, renal failure, and myocardial infarction.

Pneumococcemia occasionally results in hematogenous seeding, causing peritonitis, arthritis, endocarditis, meningitis, and cellulitis. Adults and children with functional or anatomic asplenia may have fulminant pneumococcemia, called *overwhelming postsplenectomy infection (OPSI),* characterized by septic shock, adrenal hemorrhage, and DIC. Although the incidence of OPSI is unknown, studies demonstrate that it is substantial and that the risk for it does not decrease over time after splenectomy. Most invasive pneumococcal infections occur in the first 2 years post-splenectomy, and about two-thirds occur between 5 and 20 years. OPSI may arise with symptoms indistinguishable from those of common viral illnesses.[45,46] The 100-fold increased incidence of pneumococcal bacteremia and meningitis in children with sickle cell disease is probably primarily due to splenic dysfunction, but complement abnormalities may also play a role.[47]

Diagnostic Strategies

The only test specific for pneumococcemia is a blood culture that grows *S. pneumoniae.* Ancillary testing should include a complete blood count with differential, blood and urine cultures, electrolyte values, glucose concentration, serum creatinine level, serum lactate, and blood urea nitrogen level. A chest radiograph may demonstrate pneumonia. The results of sputum Gram's stain, culture, and sensitivity testing may help direct later inpatient care. Sputum specimens should be collected before antimicrobial therapy is instituted if possible; however, therapy should not be delayed for the sole purpose of obtaining sputum. Antigen testing of urine for pneumococcal polysaccharide is up to 100% sensitive in IPD.[47]

If the patient appears toxic or has signs of respiratory compromise, an arterial blood gas, serum lactate, and coagulation profile should be obtained. If signs of meningitis or alterations in mental status are present, a lumbar puncture should be performed. Gram's stain of the buffy coat may be positive in cases of overwhelming pneumococcal sepsis. The WBC count is usually elevated. A normal or low WBC count is suggestive of more serious disease, as are hypoxemia and hypercarbia. Increased mortality occurs in patients with serum creatinine levels higher than 2.0 mg/dL, bilirubin levels higher than 1.5 mg/dL, and albumin levels below 2.5 g/dL.

Differential Diagnosis

Pneumococcemia in its more benign form should be differentiated from other febrile illnesses, such as viral infections. The combination of clinical findings and culture results enables one to distinguish between bacteremia and sepsis of other origins. The presence of fever and shock, with or without a distinct rash, suggests the possibility of sepsis caused by *Haemophilus influenzae, Neisseria meningitidis,* and other streptococcus types. The presence of confirmed pneumococcemia does not exclude other diagnoses, such as influenza and lung cancer.

Management

Acute Treatment

Management of pneumococcemia consists of stabilization of life-threatening conditions, eradication of the infection, and treatment of predisposing or coexisting conditions. All septic patients should be managed with early goal-directed therapy (see Chapter 130).[48,49] The decision to initiate antibiotic therapy is often made with limited objective data, which include the clinical findings, age of the patient, underlying conditions, and possible preliminary laboratory studies.

Prompt initiation of antibiotics is essential to reduce the morbidity and mortality of pneumococcal infection, and should begin in the ED. To simplify selection of a treatment strategy, patients can be divided into three groups:

1. Bacteremia or sepsis suggested by clinical findings; organism not identified: Patients in this group are given broad-spectrum antibiotics, based on the most likely organism, patient's age, immune status, presence of coexisting disorders, and local patterns of antibiotic resistance. The antibiotic regimen is altered after positive identification of the organism and its sensitivities.

2. *S. pneumoniae* growth is reported from blood cultures (usually 1 to 2 days prior): The treatment regimen for occult bacteremia is guided by the patient's age, history, physical examination, general appearance, and ancillary test results. The antibiotic selected on initial visit may be sufficient to treat pneumococcal bacteremia subsequently identified by the laboratory. The patient should be reevaluated promptly. Repeated blood culture should be obtained if the patient has not been taking an antibiotic. For well-appearing children, a 7- to 10-day course of an appropriate oral antibiotic is reasonable. The decision to admit a child is based on the findings at the time of reevaluation.
3. Bacteremia or sepsis is suggested, and *S. pneumoniae* is identified from a site of local infection, such as Gram's stain of sputum: The antibiotic regimen is focused narrowly.

Adult patients with laboratory-proven pneumococcemia may be treated with penicillin G if susceptibility has been documented: 2 to 4 million units IV every 4 hours if local penicillin resistance patterns are still low. Meningitis is treated with 4 million units of penicillin G every 4 hours. In children, the dosage for meningitis is 250,000 units/kg per 24 hours in divided doses every 4 hours IV up to a maximum of 20 million units.

S. pneumoniae susceptible to penicillin in the United States continues to decline.[50] Unless penicillin susceptibility has been documented, treatment should begin with either ceftriaxone (1 to 2 g IV every 12 to 24 hours; 50 to 100 mg/kg/day in children) or cefepime (1 to 2 g IV every 12 hours; 50 mg/kg every 8 hours in children). When meningitis is present, the higher doses should be given. In areas where ceftriaxone resistance has emerged, vancomycin should be given (1 g IV every 12 hours; 40 mg/kg/day divided every 6 to 8 hours in children) should be considered. An infectious disease consultant may be able to assist with antibiotic.

IM ceftriaxone is commonly administered to children with suggested occult bacteremia treated as outpatients while blood culture results are pending. Ceftriaxone (initial dose of 50 to 100 mg/kg IM or IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours, up to a maximum of 4 g) and cefotaxime (200 mg/kg/day in divided doses every 6 hours IV, up to a maximum of 12 g) are excellent antibiotics for *N. meningitidis* and *H. influenzae*. Alternative initial treatment of pneumococcemia in penicillin- or cephalosporin-allergic patients includes vancomycin, imipenem, and chloramphenicol. Chloramphenicol has the associated risk of toxicity and interaction with anticonvulsant medications.

Patients with pneumococcemia may not respond to treatment for the first 24 to 48 hours of therapy. This may be attributed to the normal course of the disease, an incorrect diagnosis, the underlying illness, or an antibiotic regimen that does not treat the infection sufficiently.

Vaccination

Pneumococcal vaccine is effective in preventing infection; the currently available 23-valent vaccine contains the purified polysaccharide antigens of the serotypes that cause 70% to 88% of pneumococcemia infections in the United States. Although it is only 60% to 70% effective at preventing invasive disease, it is safe, inexpensive, and of substantial value for well-defined groups at risk.[39,41] The 23-valent pneumococcal vaccine has limited immunogenicity in children younger than 2 years. The heptavalent conjugate vaccine PCV7, licensed in 2000, linked the polysaccharide to proteins, resulting in an improved immunogenic response in children younger than 2 years old.[51] This vaccine significantly decreased IPD caused by the included serotypes, but an increase in disease caused but non-vaccine serotypes prompted the development of a 13-valent conjugate vaccine. PCV13 was licensed in the United States in 2010 and has replaced PCV7.[39] Recommendations for the use of the PVC13 and 23-valent (PPSV23) vaccines are given in Tables 121.4, 121.5, and 121.6.[52,53]

Approximately 50% of IPD in children with comorbidities is caused by serotypes not included in either the 13-valent or 23-valent vaccine.[54] Other preventive measures for pneumococcemia include passive immunization with immunoglobulins for patients with congenital or acquired immunodeficiency diseases and daily antibiotic prophylaxis for children with functional or anatomic asplenia.[55]

Disposition

Disposition of the patient depends on the patient's age, clinical condition, and presence of coexisting illnesses. Toxic-appearing patients of any age should be promptly treated with antibiotics and admitted to the hospital. Patients with underlying or coexisting conditions and those with an unclear course of illness should also be admitted or observed.

Children who are afebrile and appear well at the time of the initial examination are unlikely to have serious sequelae. The decision to treat a febrile child with antibiotics on an outpatient basis should be based on clinical findings, vaccination history, medical history, ability of the parents to follow the discharge instructions, and availability of timely follow-up.

MENINGOCOCCEMIA

Principles

Background

Few clinical situations in emergency medicine produce greater anxiety than meningococcal infection. Virtually all experienced emergency clinicians have had a patient who appeared relatively well on initial presentation, only to be moribund and in critical condition with fulminant infection several hours later. Vieusseux initially described "Epidemic cerebrospinal fever" in 1805, and Weichselbaum identified the causative bacterial agent in 1887. The introduction of sulfonamide therapy in 1937 dramatically improved outcome. Sulfonamide prophylaxis was also effective at eradication of the carrier state and was used to prevent epidemics that occurred in military barracks. In the 1940s, sulfonamide resistance began to emerge. In 1963 an outbreak of resistant meningococcal disease occurred in the United States, which spurred efforts to develop a vaccine. Subsequent worldwide resistance has resulted in continued efforts to develop safe and effective vaccines.[55]

Epidemiology

Humans are the only reservoir for *N. meningitidis*. In 2013, 564 cases of meningococcal disease were reported in the United States. Active Bacterial Core surveillance by the CDC reports an incidence of 0.14 per 100,000 population, a marked decrease since the licensing of the first conjugated meningococcal vaccine in 2005 (Fig. 121.5). Of the more than 13 serogroups, groups A, B, C, Y, and W-135 cause most of the infections. Most cases occur sporadically, with occasional outbreaks, notably on college campuses in dormitories or in other crowded living situations. More than half of the cases in infants are caused by serogroup B, for which there is no effective vaccine. Serogroups C, Y, and W-135 cause 75% of meningococcal disease in patients older than 11 years old.[56] Although grouping is important for tracking of the disease, all groups are capable of causing the same spectrum of clinical disease.

TABLE 121.4

Centers for Disease Control and Prevention Recommendations for the Use of the PVC13 and PPSV23 in Adults

		PCV13	PPSV23[a]	
RISK GROUP	UNDERLYING MEDICAL CONDITION	RECOMMENDED	RECOMMENDED	REVACCINATION AT 5 YEARS AFTER FIRST DOSE
Immunocompetent persons	Chronic heart disease[b]		✓	
	Chronic lung disease[c]		✓	
	Diabetes mellitus		✓	
	CSF leaks	✓	✓	
	Cochlear implants	✓	✓	
	Alcoholism		✓	
	Chronic liver disease		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓
Immunocompromised persons	Congenital or acquired immunodeficiencies[d]	✓	✓	✓
	HIV infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin disease	✓	✓	✓
	Generalized malignancy	✓	✓	✓
	Iatrogenic immunosuppression[e]	✓	✓	✓
	Solid organ transplant	✓	✓	✓
	Multiple myeloma	✓	✓	✓

[a]All adults 65 years old or older should receive a dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine
[b]Including congestive heart failure and cardiomyopathies
[c]Including chronic obstructive pulmonary disease, emphysema, and asthma
[d]Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease)
[e]Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy
CSF, Cerebrospinal fluid; *HIV,* human immunodeficiency virus.

TABLE 121.5

Centers for Disease Control and Prevention Recommendations for the Use of the PCV13 Vaccine Among Infants and Children Who Have Not Received Previous Doses of PCV7 or PCV13, by Age at First Dose

AGE AT FIRST DOSE	PRIMARY PCV13 SERIES[a]	PCV13 BOOSTER DOSE[b]
2 to 6 months old	3 doses	1 dose at age 12 to 15 months old
7 to 11 months old	2 doses	1 dose at age 12 to 15 months old
12 to 23 months old	2 doses	—
24 to 59 months old (healthy children)	1 dose	—
24 to 71 months old (children with certain chronic diseases or immunocompromising conditions (Table 121-5B)	2 doses	—

[a]Minimum interval between doses is 8 weeks except for children vaccinated at age <12 months old for whom minimum interval between doses is 4 weeks. Minimum age for administration of first dose is 6 weeks old.
[b]Given at least 8 weeks after the previous dose.
Advisory Committee on Immunization Practices (ACIP), United States, 2010.

TABLE 121.6

Underlying Medical Conditions That Are Indications for Pneumococcal Vaccination Among Children, by Risk Group

RISK GROUP	CONDITION
Immunocompetent children	Chronic heart disease[a] Chronic lung disease[b] Diabetes mellitus CSF leaks Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection Chronic renal failure and nephrotic syndrome Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation Congenital immunodeficiency[c]

[a]Particularly cyanotic congenital heart disease and cardiac failure.
[b]Including asthma if treated with prolonged high-dose oral corticosteroids.
[c]Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).
CSF, Cerebrospinal fluid; *HIV,* human immunodeficiency virus.
Advisory Committee on Immunization Practices (ACIP), United States, 2010.

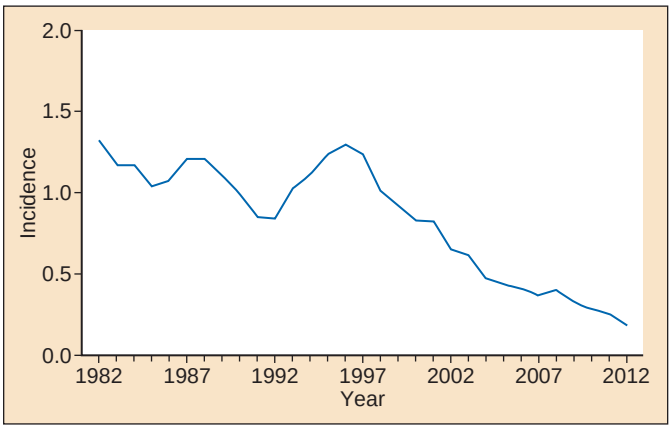


Fig. 121.5. Meningococcal disease incidence by year in the United States from 1982 to 2012. (From Adams D, et al: Summary of notifiable diseases—United States, 2012. *MMWR: Weekly* 61[53]:1-121, 2014.)

The incidence of meningococcal disease peaks in the winter. Superimposed on this annual variation are cyclic peaks of disease every 5 to 15 years. Approximately every 10 years, massive outbreaks of serogroup A occur in sub-Saharan Africa (the "meningitis belt"). The last outbreak was in 2013 with over 9000 cases and close to 900 deaths.[57] During nonepidemic periods, children younger than 5 years old have the highest incidence of infection. During epidemics, the incidence increases among children aged 5 to 9 years, an observation that may be of value in predicting the beginning of an epidemic. Crowded living conditions increase the risk for spread of meningococcal disease. The incidence of disease and the carrier state are several times higher among military recruits in the first few weeks of service than in the general public. This is also true of college freshmen, particularly those living in dormitories. Other risk factors for development of invasive meningococcal disease include close contact with an infected patient, complement deficiency, properdin deficiency, asplenia, chronic alcohol abuse, active and passive smoking, corticosteroid use, and recent respiratory illness.

The mortality rate of meningococcemia is 40% in the United States. Septicemia without meningitis carries a much higher mortality rate (up to 70%) than meningitis alone (less than 10%).[55,56,58]

Etiology

Meningococcal disease is caused by *N. meningitidis*, a fastidious, aerobic, gram-negative diplococcus. *N. meningitidis* is an encapsulated organism classified into at least 13 serogroups on the basis of the capsular polysaccharides.[55]

Pathophysiology

N. meningitidis is an obligate human pathogen. It attaches to nonciliated epithelial cells in the nasopharynx. It may either remain on the epithelial surface, causing an asymptomatic carrier state, or produce mild symptoms of an upper respiratory tract infection. The carriage state acts as an immunizing process. In certain patients, the bacteria enter the bloodstream and cause localized infection, bacteremia, sepsis, or fulminant infection. Multiple host and microorganism characteristics may determine whether clinical disease develops, but the presence of bactericidal antibodies is protective. Complement deficiency plays a role in a host's inability to fight this infection. The capsule is required for *N. meningitidis* to adhere to epithelium, but only unencapsulated meningococci enter epithelial cells; capsular biosynthesis has been shown to stop as the bacteria enter the epithelial cell.[55] The release of lipo-oligosaccharide (LOS) and endotoxin by autolysis of the *N. meningitidis* cell is the initial event in the development of meningococcal sepsis. LOS stimulates a massive host mediator response. All of the major pathophysiologic events of meningococcal sepsis are caused by the host's inflammatory response to the organism causing functional and histologic damage to the microvasculature, resulting in increased vascular permeability, pathologic vasoconstriction and vasodilation, loss of thromboresistance, DIC, and profound myocardial dysfunction.[55]

Clinical Features

Symptoms and Signs

Presentation of meningococcemia ranges from a mild febrile illness to fulminant disease progressing to death within hours. Most patients have fever on presentation. Other complaints include headache, irritability, lethargy, myalgias, emesis, diarrhea, cough, and rhinorrhea. Anywhere from 27% to 77% of patients will present with the classic hemorrhagic skin lesions.[55] These patients can rapidly progress to purpura fulminans, with hypotension, adrenal hemorrhage, and multiorgan failure. The following categories detail the five patterns of presentation.

Occult Bacteremia. This condition is a febrile illness in which the only direct indication of meningococcemia is a positive blood culture, with results available most often 24 to 48 hours after initial evaluation. In its mildest form, meningococcal bacteremia cannot clinically be distinguished from more benign febrile illnesses. Initial diagnoses in these patients include common childhood infections, such as otitis media, acute viral upper respiratory infections, and gastroenteritis. For some patients the illness resolves after treatment with an oral regimen of antibiotics; others experience spontaneous resolution without antibiotic treatment. *N. meningitidis* accounts for less than 1% of occult bacteremia cases, but these patients are much more likely to develop meningitis (up to 58%) than are those with *S. pneumoniae*. Despite the total absence of clinical clues to meningococcal infection at initial presentation, some untreated patients subsequently deteriorate rapidly.

Meningococcal Meningitis. Patients with meningococcal meningitis present similarly to those with meningitis of other causes, with headache, photophobia, vomiting, fever, and signs of meningeal inflammation. This classic triad of fever, neck stiffness, and altered mental status is present in less than 30% of patients.[59] Infants and small children may present with fever, irritability, and vomiting as the only complaints. More than half of patients with meningococcal meningitis have rash on presentation, and 20% present with seizures. Onset of symptoms is less abrupt (usually during 24 hours) and prognosis is better for patients with meningococcal meningitis than for patients with meningococcemia without clinical signs of meningitis.

Meningococcal Septicemia. Patients with meningococcal septicemia present with lethargy, poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Hemorrhagic skin lesions are present in 28% to 77% of patients, but a macular or maculopapular rash may occur and be mistaken for a variety of viral exanthems. Petechiae generally appear on the extremities and under pressure points, such as the elastic bands of socks and underwear. They may progress to involve almost any body surface, including the mucosa and sclera, but typically spare the palms, soles, and head. Macular lesions may progress to purpura and ecchymoses in fulminant meningococcemia. The purpurae are not a coalescence of petechiae but a distinct entity that more specifically characterizes meningococcemia. *Purpura fulminans,*

the most advanced form of meningococcal septicemia, occurs most often in children and is usually associated with DIC. This condition is characterized by rapidly spreading ecchymoses and gangrene of the extremities. Mucosal and gastrointestinal bleeding as well as oozing from intravenous (IV) sites may occur. Clinical signs of meningitis and CSF pleocytosis may not be present, even when diplococci are isolated from the CSF. This is probably because the systemic progression of the disease is so rapid that it precludes a host meningeal inflammatory response to the organism in the CSF. Shock results from both intravascular volume loss and congestive heart failure, probably related to myocarditis. Renal failure, coma, and bilateral adrenal hemorrhage often occur.[55]

Fever and a Nonblanching Rash. Up to 30% of patients present without signs of meningitis or septicemia. They are typically admitted for fever and a nonblanching rash and no other specific findings. If they are untreated, meningitis or fulminant septicemia and shock can develop.[52,58]

Chronic Meningococcemia. This syndrome is characterized by fever, rash, and arthritis in conjunction with a positive blood culture for *N. meningitidis*. Headache and upper respiratory symptoms are often present. This is the rarest form of meningococcal disease, accounting for less than 2% of cases. It may progress to meningitis, endocarditis, or fulminant meningococcemia regardless of treatment.

Complications

Circulatory collapse is a common complication of meningococcemia and the most common cause of death. Many of the inflammatory mediators released during sepsis cause peripheral vasodilation, capillary leak, and myocardial dysfunction. Acidosis, hypoglycemia, hypokalemia, hypocalcemia, hypophosphatemia, and hypoxia also contribute to the myocardial dysfunction, which may become unresponsive to positive inotropic medications.

Acute respiratory failure occurs from capillary leak, DIC, and large volume requirements in the setting of decreased cardiac function. Patients frequently require mechanical ventilation. Renal failure is common due to impaired renal perfusion. If meningitis accompanies meningococcemia, focal neurologic deficits and seizures may occur but are less common than with pneumococcal meningitis. Long-term neurological sequelae include hearing loss, visual deficits, neurodevelopmental impairment, cranial nerve palsies, and hemi- and quadriparesis. Purpura fulminans may result in skin lesions that necessitate plastic surgery and loss of digits or limbs from gangrene. Purulent or immune complex arthritis and pericarditis with tamponade may also occur. Herpes labialis occurs in 5% to 20% of patients with meningococcal disease.

Poor prognostic indicators include seizures, hypothermia, hyperpyrexia, total peripheral WBC count of less than 500/mm^3, platelet count of less than 100,000/mm^3, metabolic acidosis (pH <7.30), development of purpura fulminans, onset of petechiae within 12 hours of admission, absence of meningitis, presence of shock, low sedimentation rate, and extremes of age. In one study, all patients who developed organ system failure had one or more of the following at the time of initial presentation: circulatory insufficiency (hypotension or shock), peripheral WBC count of less than 10,000 cells/mm^3, or a coagulopathy.[53]

Diagnostic Strategies

The tentative diagnosis of meningococcemia is based on clinical findings and confirmed by the isolation of *N. meningitidis* from blood cultures or any other usually sterile site, such as CSF or synovial, pleural, or pericardial fluid. Ideally, blood culture specimens should be obtained before the administration of antibiotics unless this unduly delays the patient's treatment. Blood cultures are positive in approximately 50% to 80% of cases. A lumbar puncture should be performed only in stable patients without evidence of DIC. The CSF shows either gram-negative diplococci on Gram's stain or a positive culture in about 46% to 94% of cases. Even patients without clinical signs of meningitis frequently have the organism grown from the CSF. Gram's stain of petechial scrapings may show gram-negative diplococci in up to two-thirds of cases, and the organism can rarely be seen in the peripheral blood buffy coat. Highly specific antigen tests for CSF are available but have a high false-negative rate. PCR of the buffy coat or CSF is more sensitive and specific than any of the preceding tests and is not affected by prior antibiotic therapy.[55,56]

Ancillary laboratory tests are of little value in establishing a specific diagnosis of meningococcal sepsis but may be useful in ruling out other disease, determining prognosis, and monitoring complications. The WBC count may be high, low, or normal, but a bandemia is typically present. The symptoms and signs of CNS infection may be nonspecific in the infant and child younger than 2 years old. If meningitis is present, the CSF opening pressure is usually elevated, the protein level is increased, and the glucose concentration is decreased. Pleocytosis is usually present, with a predominance of polymorphonuclear leukocytes. Gram-negative diplococci may be seen on microscopy. Early in the disease or with fulminant disease, the CSF may be free of inflammatory cells. Serologic evidence of DIC is frequently present.[56,57] A chest radiograph is useful in evaluation for pneumonia and acute respiratory distress syndrome. An echocardiogram helps assess for myocardial dysfunction and pericardial effusion. Serum lactate may help direct therapy.

Differential Diagnosis

It is difficult to distinguish the clinical signs of meningococcemia from those of bacteremia caused by *S. pneumoniae,* other streptococcal groups, *H. influenzae,* and *Neisseria gonorrhoeae.* A hemorrhagic rash is more commonly associated with meningococcal disease. The differential diagnosis of meningococcemia also includes viral exanthems, Rocky Mountain spotted fever, typhus, typhoid fever, endocarditis, vasculitis syndromes (polyarteritis nodosa and Henoch-Schönlein purpura), toxic shock syndrome (TSS), acute rheumatic fever, dengue fever, drug reactions, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura.

Management

Acute Treatment

Morbidity and mortality in meningococcemia are reduced with prompt recognition and immediate antibiotic therapy. Delays of therapy for the completion of diagnostic studies or admission to an inpatient unit should be avoided. To simplify selection of a treatment strategy, patients can be divided into three general groups:

1. Bacteremia or sepsis suggested by clinical findings; no organism identified: Patients should receive broad-spectrum antibiotics based on factors that include the most likely organism, patient's age and immune status, presence of coexisting disorders, and local patterns of antibiotic resistance. A narrower spectrum agent is selected after positive identification of the organism and its sensitivities.
2. *N. meningitidis* growth is reported from prior blood cultures: Treatment for occult bacteremia is guided by the patient's age, history, physical examination, general appearance, and

ancillary test results. The antibiotic selected at the time of the initial visit may be sufficient to treat the meningococcal bacteremia subsequently identified by the laboratory. The decision to hospitalize the patient is based on the findings at the time of reevaluation and the risk of sequelae. Regardless of clinical appearance, most physicians would draw blood for repeated cultures, consider lumbar puncture, and admit the patient to the hospital until results of repeated cultures are obtained.

3. Bacteremia or sepsis is suggested and *N. meningitidis* is identified: The antibiotic regimen is focused narrowly.

The standard antibiotic regimen for laboratory-proven meningococcemia is penicillin G (4 million units every 4 hours IV for adults) and penicillin (250,000 to 300,000 units/kg/day in divided doses every 4 hours IV for children, up to a maximum of 20 million units). Penicillin resistance in *N. meningitidis* remains low in the United States but has been reported in Spain and the United Kingdom.[55]

Although appropriate first-line therapy, penicillin is rarely given as the initial agent in patients with suspected meningococcal sepsis or meningitis. Ceftriaxone (100 mg/kg IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours, up to a maximum of 4 g) and cefotaxime (100 mg/kg/day IV in divided doses every 6 hours, up to a maximum of 12 g) are appropriate initial antibiotics as well. The cephalosporins are safe and have rapid onset of action and excellent coverage for *S. pneumoniae* and *H. influenzae*. Chloramphenicol (100 mg/kg/day divided every 6 hours to a maximum of 4 g/day) should be considered in penicillin- and cephalosporin-allergic patients. IM ceftriaxone is occasionally administered to children with suspected bacteremia who are treated as outpatients while culture results are pending. Several reports have demonstrated the efficacy of ceftriaxone (80 to 100 mg/kg IV) in a single daily dose; however, twice-daily dosing remains the standard recommendation at this time. Ceftriaxone-treated patients have a more rapid sterilization of the CSF and a lower incidence of hearing loss than conventionally treated patients.

Patients with fulminant meningococcemia require prompt airway management, IV fluid resuscitation, and vasopressor support. Fluid requirements may be high because of third spacing of fluid; and in the setting of frequent myocardial dysfunction, intensive cardiovascular monitoring is required. Electrolyte and acid-base abnormalities should be corrected. If the patient is oliguric or anuric, hemodialysis may be necessary to correct these abnormalities. Fresh frozen plasma should be considered for patients with bleeding complications.

The role of steroids for the treatment of meningococcemia without meningitis remains controversial. Although corticosteroids were once widely recommended for the treatment of the adrenal insufficiency associated with fulminant meningococcemia, more recent studies demonstrate that adrenal function is not impaired in all patients. We believe that patients with persistent shock despite vigorous fluid resuscitation and vasopressor therapy should receive glucocorticoid therapy and adrenal function testing.[59]

The use of corticosteroids in patients with bacterial meningitis is currently recommended for adults and children but not for neonates. Corticosteroid administration before antibiotic administration decreases long-term neurologic sequelae in adults and children. There is also a mild decrease in mortality. Although these benefits are not seen in patients with meningococcal meningitis, the organism is typically not identified when steroids are initiated. Dexamethasone (0.4 to 0.6 mg/kg/day every 6 hours for 4 days) should be given to patients with bacterial meningitis. The first dose should be given before the first dose of antibiotics if possible.[60,61]

Plasmapheresis, blood exchange, and extracorporeal membrane oxygenation have been described, but data are limited.

Antibiotic Prophylaxis and Vaccination

Close patient contacts (household, nursery schools, daycare centers, military recruits, college dormitories, teammates) should receive antibiotic prophylaxis. Intimate contacts and health care workers with intimate exposure (eg, mouth-to-mouth resuscitation, intubation, or suctioning) should receive rifampin, 10 mg/kg (up to 600 mg) orally every 12 hours for four doses. The dose for neonates is 5 mg/kg. Patients should be warned that rifampin discolors the urine and secretions; contact lenses should be removed to avoid permanent staining. IM ceftriaxone (125 mg for children younger than 15 years old and 250 mg for those older than 12 years old) is effective and is an alternative for pregnant women and for people in whom compliance with an oral regimen cannot be ensured. Ciprofloxacin (500 mg orally) is another alternative for adults.[58]

Meningococcal vaccine should be considered an adjunct to prophylaxis in epidemics and for close contacts in sporadic cases if one of the serotypes contained in the vaccine is identified as the causative agent. The currently available vaccines are quadrivalent vaccines containing for serogroups A, C, Y, and W-135. No vaccine is licensed for group B, a serogroup that causes a significant portion of meningococcal infection in the United States, but trials are currently under way.[62] The conjugate vaccines (MCV4: Menactra and Menveo) produce a superior immune response compared to the polysaccharide vaccine (MPSV4: Menomune). Routine vaccination with MPSV4 is not recommended and should be limited to patients over 55 years old, or when MCV4 is unavailable. Routine vaccination with MCV4 is for persons 11 or 12 years old with a booster at 16 years old. Vaccination is also recommended for those at increase risk of meningococcal disease, including microbiologists who are routinely working with *N. meningitides*, military recruits, children with functional or anatomic asplenia, people traveling to endemic areas of the world, such as sub-Saharan Africa.[56]

Disposition

All patients with possible or confirmed meningococcemia should be placed in respiratory isolation and hospitalized, preferably in an ICU, because they can decompensate rapidly and without warning. A possible exception is the well-appearing child who has culture-proven *N. meningitidis* that has been taking appropriate antibiotics as an outpatient. This child should have a lumbar puncture performed to determine CSF involvement if one was not performed at the initial evaluation. Antibiotics should be continued on an inpatient basis, but an ICU may not be necessary if the child appears well.

TOXIC SHOCK SYNDROME

Principles

Background

TSS is a toxin-mediated systemic inflammatory response syndrome that was first described in 1978 in a series of seven children 8 to 17 years old who had high fever, rash, headache, confusion, conjunctival injection, edema, vomiting, diarrhea, renal failure, hepatic dysfunction, DIC, and shock. *S. aureus* was cultured from various body sites but not from the blood in five of the seven cases.

The disease gained notoriety in the early 1980s when many cases were reported in association with tampon use in young, healthy menstruating women. The term *toxic shock syndrome* was coined to describe the constellation of signs and symptoms. Investigators noted positive vaginal cultures for *S. aureus,* recurrence of illness during subsequent menses, and the value of

antistaphylococcal antibiotics in preventing recurrences. In response to the growing concern about TSS, changes were made to reduce the absorbency and composition of tampons. Non-menstrual cases were also recognized in both men and women as a result of a variety of predisposing conditions, and a case definition was published in 1982 (Box 121.6).[63,64]

In the late 1980s, several reports described group A streptococcus infection associated with shock and multisystem organ failure. This is called *streptococcal toxic shock syndrome* because it shares many features with staphylococcal TSS. Box 121.7 shows the case definition for streptococcal TSS.[67]

Epidemiology

The peak incidence of TSS occurred in 1980, when 890 cases were reported, 91% of which were associated with tampon use. Since then, the reduction in cases of the menstrual form of TSS has followed an active effort to decrease the absorbency of tampons and to change their composition. Menstruation remains the most common setting for TSS, but non-menstrual TSS accounts for just under half of the reported cases. TSS has also been reported in association with barrier contraceptives and childbirth. Non-menstrual TSS occurs in people of all ages and in both sexes. The CDC reported an average of about 200 cases a year (about 1 case per 100,000 population) from 1994 to 2010, with a steady increase in the incidence of streptococcal TSS and a decrease in the incidence of staphylococcal TSS. The age and sex distribution reflects the association with menses. Streptococcal TSS accounts for two-thirds of the cases.[65]

Non-menstrual staphylococcal TSS is associated with superinfection of various skin lesions, including burns, surgical sites, dialysis catheters, and lung (influenza associated). It may also occur in association with staphylococcal respiratory infections or even with colonization by a toxigenic strain of the organism, without an obvious infectious source. Streptococcal TSS is classically associated with more severe soft tissue infections, such as necrotizing fasciitis and myositis, as well as with pneumonia, peritonitis, myometritis, and osteomyelitis.

The mortality rate from staphylococcal TSS has declined since the disease was first described. The case fatality rate in 1980 was 10% and is now 5%. Streptococcal TSS remains a highly fatal disease, with a mortality rate of 30% to 70%.

BOX 121.6

Case Definition of Toxic Shock Syndrome (Revised)

CLINICAL CASE DEFINITION

Fever: Temperature >102° F (38.9° C)
Rash: Diffuse macular erythroderma
Desquamation 1 to 2 weeks after onset of illness, particularly of palms and soles
Hypotension: Systolic blood pressure <90 mm Hg for adults or below fifth percentile by age for children younger than 16 years old, orthostatic drop in diastolic blood pressure >15 mm Hg from lying to sitting, orthostatic syncope, or orthostatic dizziness
Multisystem involvement—*three* or more of the following:
- Gastrointestinal: Vomiting or diarrhea at onset of illness
- Muscular: Severe myalgia or creatine kinase level at least twice the upper limit of normal for laboratory
- Mucous membrane: Vaginal, oropharyngeal, or conjunctival hyperemia
- Renal: BUN or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (>5 leukocytes/high-power field) in the absence of urinary tract infection
- Hepatic: Total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory
- Hematologic: Platelets <100,000/mm^3
- CNS: Disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

LABORATORY CRITERIA FOR DIAGNOSIS

Negative results on the following tests, if obtained:
- Blood, throat, or CSF cultures (blood culture may be positive for *Staphylococcus aureus*)
- Rise in titer to Rocky Mountain spotted fever, leptospirosis, or rubeola

CASE CLASSIFICATION

Probable: A case that meets the laboratory criteria and in which four of the five clinical findings are present
Confirmed: A case that meets the laboratory criteria and in which all five of the clinical findings are present, including desquamation, unless the patient dies before desquamation occurs

ALT, Alanine transaminase; *AST,* aspartate transaminase; *BUN,* blood urea nitrogen; *CNS,* central nervous system; *CSF,* cerebrospinal fluid.

BOX 121.7

Case Definition of Streptococcal Toxic Shock Syndrome

CLINICAL CASE DEFINITION

Hypotension: Systolic blood pressure ≤90 mm Hg for adults or below fifth percentile by age for children younger than 16 years old
Multisystem involvement—*two* or more of the following:
- Renal: Creatinine >2 mg/dL (177 μmol/L) for adults or more than twice the upper limit of normal for age or more than twofold elevation above baseline for patients with preexisting renal disease
- Hematologic: Platelets <100,000/mm^3 or DIC, defined as prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
- Hepatic: Total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory, or a twofold increase in patients with preexisting liver disease
- Acute respiratory distress syndrome: Defined by acute onset of pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
- Generalized erythematous maculopapular rash that may desquamate
- Soft tissue necrosis, including necrotizing fasciitis, myositis, or gangrene

LABORATORY CRITERIA FOR DIAGNOSIS

Isolation of group A streptococcus

CASE CLASSIFICATION

Probable: A case that meets the clinical case definition in the absence of another identified cause of the illness and with isolation of group A streptococcus from a nonsterile site
Confirmed: A case that meets the clinical case definition and with isolation of group A streptococcus from a normally sterile site (eg, CSF or joint, pleural, or pericardial fluid)

ALT, Alanine transaminase; *AST,* aspartate transaminase; *CSF,* cerebrospinal fluid; *DIC,* disseminated intravascular coagulation.

Etiology

Staphylococcal TSS is caused by colonization or infection with toxigenic strains of *S. aureus*, which produce toxic shock syndrome toxin 1 (TSST-1). *S. aureus* is present in virtually all cases of both forms of the illness. *S. aureus* has been isolated from the vagina or cervix in 98% of women with menstrual TSS, compared with a colonization rate of less than 10% of unaffected women. Because the organism is often not invasive, the blood cultures are often negative. Streptococcal TSS is caused by invasive infection with toxigenic strains of group A streptococcus.[63,64,66]

Pathophysiology

The effects of various exotoxins produced by *S. aureus* and group A streptococcus cause the shock and multiorgan dysfunction associated with TSS. *S. aureus* produces TSST-1 and enterotoxin B. TSST-1 is identified in more than 90% of menstrual cases and 60% of non-menstrual cases. Other toxins may play a role in non-menstrual TSS. Antibodies to these toxins are protective against disease. Group A streptococcus produces streptococcal pyrogenic exotoxins A and B. These exotoxins are absorbed into the bloodstream through inflamed or traumatized mucous membranes or from areas of focal infection. Absorbed toxins act as superantigens, inducing mononuclear cells to synthesize and to release cytokines, tumor necrosis factor alpha (TNF-α), and interleukins at a rate and magnitude many fold greater than with the normal antigen presentation, which begin the cascade of systemic vasculitis and the multisystem manifestations of the disease. Host immune factors are important in the pathogenesis of TSS. Group A streptococcus is an invasive organism, and circulating group A streptococcus organisms induce the production of TNF-α and other cytokines by mononuclear cells.[64]

Clinical Features

Symptoms and Signs

The clinical presentations of streptococcal TSS and staphylococcal TSS are similar. The primary difference is that an identifiable infectious source is virtually always present with streptococcal TSS, and colonization alone may be the source in staphylococcal TSS.

TSS should be considered in patients who present with fever, rash, hypotension, and evidence of end-organ damage, such as respiratory failure or altered mental status. Patients may have a prodromal illness with fever, chills, nausea, vomiting, watery diarrhea, headache, myalgias, and pharyngitis, which can last 2 to 3 days before progression to frank sepsis and organ dysfunction. Other patients may become abruptly symptomatic within hours. Rapid progression is more typical of streptococcal TSS. Patients may complain of pain at a site of infection more often with streptococcal TSS. Risk factors for TSS are listed in Box 121.8.

The fever is usually high and abrupt in onset, although septic patients may have hypothermia. The classic rash is a nonpruritic, diffuse, blanching, macular erythroderma. It develops in the first few days of the illness and may be faint, evanescent, and mistaken for the flush associated with a fever. It is usually diffuse but may be localized to the trunk, extremities, or perineum. After about a week, fine flaky desquamation occurs on the face, trunk, and extremities, followed by full-thickness peeling of the palms, soles, and fingers. This classic rash progression is much more common in staphylococcal TSS and is present in less than 10% of patients with streptococcal TSS. Patients with streptococcal TSS may have a scarlet fever–like rash, petechiae, or maculopapular lesions. Mucosal involvement may also occur, including conjunctival and scleral hemorrhages, "strawberry tongue," and mucosal ulceration.

The patient's mental status is frequently abnormal—out of proportion to the degree of hypotension. Confusion, somnolence, agitation, and combativeness are present in 55% of patients with streptococcal TSS and in even more patients with staphylococcal TSS.

Other findings on physical examination include pharyngeal and conjunctival erythema and peripheral edema. Vaginal mucosal erythema and purulent vaginal discharge may be present in menstrual TSS but are not required for the diagnosis to be made. As multiple organ systems become involved, a wide constellation of signs and symptoms may be seen. Gastrointestinal involvement is manifested by vomiting, diarrhea, and severe abdominal pain. Hepatomegaly may be present. Acute respiratory distress syndrome develops in more than half of patients and is manifested by rales on pulmonary examination and hypoxia. Comparisons between staphylococcal and streptococcal TSS are presented in Table 121.7.

BOX 121.8

Risk Factors for Toxic Shock Syndrome

Use of superabsorbent tampons
Postoperative wound infections
Postpartum period
Nasal packing
Cancer
Common bacterial infections
Ethanol abuse
Infection with influenza A virus
Infection with varicella virus
Diabetes mellitus
Human immunodeficiency virus (HIV) infection
Chronic cardiac disease
Chronic pulmonary disease
Nonsteroidal anti-inflammatory drug (NSAID) use (may mask symptoms rather than be a risk factor)

TABLE 121.7

Comparison of Staphylococcal and Streptococcal Toxic Shock Syndrome

FEATURE	STAPHYLOCOCCAL	STREPTOCOCCAL
Age	Primarily 15 to 35 years old	Primarily 20 to 50 years old
Sex	Greatest in women	Either
Severe pain	Rare	Common
Hypotension	100%	100%
Erythroderma rash	Very common	Less common
Renal failure	Common	Common
Bacteremia	Low	60%
Tissue necrosis	Rare	Common
Predisposing factors	Tampons, packing, NSAID use?	Cuts, burns, bruises, varicella, NSAID use?
Thrombocytopenia	Common	Common
Mortality rate	<3%	30% to 70%

NSAID, Nonsteroidal anti-inflammatory drug.

Complications

Complications of TSS include acute respiratory distress syndrome, shock, gangrene, DIC, and a constellation of neuropsychiatric symptoms. Renal failure occurs in 80% of patients but is irreversible in only 10%. Less common findings in staphylococcal TSS include rhabdomyolysis, seizures, pancreatitis, pericarditis, and cardiomyopathy. Women with the menstrual form of TSS may experience one or more recurrent episodes; recurrences of the non-menstrual form are rare. Complication rates are higher with streptococcal TSS. Rhabdomyolysis occurs in up to 63% of patients with streptococcal TSS and is usually related to the underlying soft tissue infections.

Diagnostic Strategies

Diagnosis of TSS does not require a positive culture for *S. aureus,* but isolation of *Streptococcus* organisms is a criterion. The case definitions (see Boxes 121.6 and 121.7) are useful, but they are neither specific nor foolproof.

No specific laboratory changes are associated with TSS, but many abnormalities are common. Leukocytosis or leukopenia can occur. A marked bandemia is common, and myelocytes and metamyelocytes may be seen. Elevated creatinine levels and hemoglobinuria occur in most patients. Renal dysfunction occurs before hypotension in half of the patients. Hypoalbuminemia (85%) and life-threatening hypocalcemia (79%) are prominent initially and persist throughout the course of the disease. Other abnormalities include anemia, thrombocytopenia, prolonged prothrombin and activated partial thromboplastin times, hyper-bilirubinemia, elevated transaminase levels, severe metabolic acidosis, and sterile pyuria. Creatine phosphokinase (CPK) levels may be elevated in patients with necrotizing fasciitis and myonecrosis.[66]

Blood cultures are positive for bacteria in 60% of cases associated with group A streptococcus but are rarely positive in staphylococcal TSS. Gram's stains and cultures from wounds may identify the organism. Culture of the cervix or vagina is positive in 90% of menstrual cases of TSS, even in the absence of local infection.

Chest radiography may reveal acute respiratory distress syndrome or a pulmonary source of the organism. Plain radiographs of any infected skin or soft tissue site typically show only soft tissue swelling but may reveal evidence of a retained foreign body or air in the soft tissue. A lack of air in the soft tissue does not rule out a necrotizing soft tissue infection.

An ECG may reveal evidence of ischemia, arrhythmias, and varying degrees of atrioventricular block in association with sepsis. A blood gas analysis may indicate metabolic acidosis secondary to hypotension or hypoxia. A lumbar puncture should be performed in febrile patients with altered mental status to evaluate for meningitis. It is prudent to wait for the results of a coagulation profile before the lumbar puncture is performed, because these patients may have DIC at presentation. The CSF is normal in patients with TSS.

Differential Diagnosis

The differential diagnosis of TSS includes any septic illness with exanthems. Other diseases to consider include heat stroke, cellulitis, Kawasaki disease, staphylococcal scalded skin syndrome, scarlet fever, drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Rocky Mountain spotted fever, clostridial gas gangrene, leptospirosis, meningococcemia, gram-negative sepsis, atypical measles, and viral illnesses.

Kawasaki disease occurs almost exclusively in children, usually does not progress to shock, lacks multisystem involvement, is manifested with a protracted fever, and is associated with thrombocytosis later in its course.[67] Staphylococcal scalded skin syndrome presents with a desquamating rash acutely, whereas the desquamation of TSS occurs in the convalescent phase. Staphylococcal scalded skin syndrome does not progress to shock, is not associated with multisystem illness, and lacks mucous membrane involvement. Scarlet fever differs in its clinical course by lack of shock and multisystem involvement, positive cultures for group A streptococcus, and a rise in the convalescent titer. Stevens-Johnson syndrome usually occurs after drug administration, has characteristic mucous membrane lesions, and lacks desquamation. TEN may be difficult to distinguish from TSS; TEN patients are typically febrile, are in shock, and can progress to multisystem failure. The desquamation of TEN occurs early in the course of the disease, and it usually occurs after administration of a drug.[68] Rocky Mountain spotted fever occurs after a tick bite, has a distinctive rash, and is associated with a severe headache without an altered mental status or hypotension. Leptospirosis occurs in endemic areas and may be distinguished by positive serologic studies and cultures. Petechiae and purpura occurring anywhere on the skin characterize the rash of meningococcemia.

Management

Patients with TSS should receive fluid resuscitation with crystalloids and may require up to 10 to 15 L/day. Supplemental oxygen should be provided to all septic patients, regardless of the initial pulse oximetry reading. This allows maximum tissue oxygenation and reduces acidosis. Patients should be placed in a monitored setting. Assisted ventilation may be necessary in patients with acute respiratory distress syndrome. The source of bacteria, such as tampons, nasal packs, and other foreign bodies, should be removed. Prompt surgical consultation should be obtained to débride wounds. If specimens are sent for culture, the laboratory should be informed of the suspected diagnosis. Patients who do not respond to fluid resuscitation require vasopressors, such as norepinephrine, dopamine, phenylephrine, and epinephrine.

Antibiotics should be initiated early in the treatment of TSS because the clinical presentation of the disease is similar whether the source is staphylococcal or streptococcal. For septic patients without an identified organism, broad-spectrum antibiotics should be administered. Although the penicillinase-resistant penicillins (nafcillin, oxacillin) have been widely used in the treatment of TSS, we recommend clindamycin as a first-line agent. Clindamycin is a potent suppressor of bacterial toxin synthesis; it also facilitates phagocytosis of streptococci by inhibiting M protein synthesis, decreases monocyte synthesis of cytokines, and has a longer postantibiotic effect than the β-lactams. The dose is 600 to 900 mg IV every 8 hours. (The pediatric dose is 20-40 mg/kg/day divided every 6 to 8 hours.)[66]

Patients who do not respond to massive fluid resuscitation, antibiotics, and vasopressors should be considered for intravenous immune globulin (IVIG) treatment, especially if pulmonary edema develops and mechanical ventilation is required. Pooled immune globulin has high titers for antibodies to TSST-1 and other exotoxins, and significant improvement has been reported with its use in streptococcal TSS. Because the data in staphylococcal TSS are inconclusive, and the mortality is relatively low, immunotherapy should be reserved for life-threatening cases. If it is used, the recommended dose is 1 to 2 g/kg on day 1 administered intravenously during several hours, followed by 400 to 500 mg/kg/day for up to 5 days.[63]

Hemodialysis or hemoperfusion may be necessary as more than half of streptococcal TSS patients develop renal failure. Both modalities may reduce concentrations of circulating toxins, and a study in Sweden demonstrated the lowest mortality rate ever recorded for strep TSS.[66]

The value of corticosteroids in TSS is unresolved. They are not currently recommended for treatment of staphylococcal or streptococcal TSS but should be given to patients thought to have adrenal insufficiency related to underlying disease or chronic steroid use.

Disposition

All patients thought to have TSS should be admitted to an ICU. Prompt surgical consultation should be obtained for patients with a wound source.

KEY CONCEPTS

- All patients appearing septic should be treated with broad-spectrum antibiotics as soon as possible, even before a definitive diagnosis is made.
- A surgeon should be consulted as soon as possible for patients with sepsis and a débridable source of infection.
- Immunity to diphtheria, tetanus, and pertussis wanes significantly in adults. Pertussis should be considered a cause of persistent cough in adults. A tetanus vaccination history should always be obtained from patients with trauma or infection. When there is doubt about the history, the age-appropriate vaccine according to CDC guidelines is administered.
- Neonates with suspected pertussis should be admitted to an intensive care setting.
- Botulism should be kept in the differential diagnosis for the infant with failure to thrive, constipation, or decreased muscle tone and for the injection drug user with neurologic symptoms.
- Patients with pneumococcemia, meningococcemia, and TSS can decompensate rapidly. Antimicrobial therapy should be initiated promptly, before identification of an organism.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 121: QUESTIONS & ANSWERS

121.1. An 18-year-old male Hispanic immigrant presents with acute-onset sore throat, fever, and weakness. He has no past medical history. Examination is remarkable for a grayish white exudative coat over both tonsils and the posterior pharynx. There is modest neck swelling with cough, low-grade fever, and hoarseness. Rapid strep testing and monospot results are negative. Which of the following statements regarding this patient's disease is *true?*

A. Emergent antibiotics and corticosteroids are the main therapy.
B. Neuromuscular examination is critical.C. Rapid treatment will obviate the need for intubation.
D. The electrocardiogram (ECG) is a sensitive indicator of myocarditis.
E. The highest mortality occurs in the presence of myocarditis.

Answer: B. Diphtheria can be a more benign upper respiratory/nasal infection or a "malignant" process with airway obstruction, myocarditis, and neuropathy (palate is involved first; the only cells spared are cortical). Antibiotics stop further organism growth, but diphtheria equine antitoxin is the key to therapy. Death is usually from myocarditis or airway obstruction, with the highest mortality seen in patients with the "bull neck" appearance. The ECG is an insensitive indicator of myocarditis.

121.2. An 11-year-old child presents with coughing paroxysms for 10 days. This was preceded by a mild upper respiratory tract infection. The paroxysms occur multiple times per day and have occasionally caused vomiting. The child is relatively well between paroxysms. Vaccination history is sketchy. Which of the following statements regarding this patient's disease is *true?*

A. Antibiotics will shorten illness duration.
B. Erythromycin should be given to unimmunized contacts.
C. Fever is expected.
D. Thoracic petechiae should prompt a septic evaluation.
E. Throat culture is diagnostic.

Answer: B. Pertussis, caused by a gram-negative bacterium, is a three-phase illness: catarrhal (upper respiratory tract infection), paroxysmal, and convalescence of weeks to months. The coughing phase is characterized primarily by complications related to the paroxysms, such as subconjunctival hemorrhage, pneumomediastinum, headache, rectal prolapse, chest wall petechiae, and even seizures. Fever is rare unless there is secondary infection. Antibiotics only reduce the carrier state. Corticosteroids may help younger children. Antibiotic prophylaxis is indicated for nonimmunized contacts. Nasal culture is diagnostic. Standard cough suppressants are ineffective.

121.3. After which of the following circumstances has tetanus been reported?

A. Childbirth
B. Chronic skin ulcers
C. Corneal abrasion
D. Otitis media
E. All of the above

Answer: E. It has also been reported after dental procedures, abortions, and intestinal operations. In these cases, the source of the bacteria is endogenous because up to 10% of humans harbor *Clostridium tetani* in the colon.

121.4. Which of the following statements concerning the tetanus neurotoxin (tetanospasmin) is *true?*

A. A shorter incubation period portends a better prognosis.
B. It blocks presynaptic release of gamma-aminobutyric acid (GABA).
C. Sensory nerves are blocked, followed by motor nerves.
D. Synaptic binding is reversible and overcome by acetylcholinesterase therapy.
E. The autonomic nervous system is relatively spared.

Answer: B. The toxin migrates in the motor nerve from the injury site to the central nervous system (CNS). Presynaptic release of the inhibitory neurotransmitter GABA and glycine is diminished. The unopposed excitatory action results in muscle spasm. Presynaptic inhibition of the autonomic nervous system is also lost, and wide heart rate and blood pressure fluctuations are seen. The toxin binding is irreversible and diminishes only with axon synaptic regeneration. A shorter incubation period is a harbinger of a worse outcome.

121.5. A 62-year-old male farmer with no medical problems presents with leg pain and muscle spasms. He reports moderate to severe pain and muscle spasms in the calf that have occurred and worsened during 3 days. Two weeks prior, he suffered a puncture wound to his ankle just above his boot top with a piece of metal. Examination is remarkable for a heart rate of 115 beats/minute, blood pressure of 170/110 mm Hg, and a healing clean wound above the medial malleolus with no evidence of active infection. The calf is in active spasm with some increased tone in the peroneal musculature also. Which of the following statements regarding this patient's disease is *true?*

A. A radiograph should be obtained to assess for subcutaneous air.
B. Admission for intravenous (IV) antibiotics is indicated.

C. Lumbar spine magnetic resonance imaging (MRI) is indicated.
D. Outpatient management is indicated.
E. Tetanus immune globulin is indicated.

Answer: E. Localized tetanus reflects a local neuromuscular process with pain and spasm. It is likely due to a partial immunity. Immune globulin is indicated. Although mortality is lower, it can progress to generalized tetanus, and admission is warranted.

121.6. Generalized tetanus may be confused with which of the following conditions?
A. Malignant hyperthermia
B. Neuroleptic malignant syndrome
C. Organophosphate poisoning
D. Serotonin syndrome
E. Strychnine poisoning

Answer: E. Strychnine poisoning is the only clinical condition that mimics generalized tetanus. Strychnine, like tetanus toxin, antagonizes glycine release but has no gamma-aminobutyric acid (GABA) effect. Patients develop opisthotonos while remaining alert. The annual incidences of the two processes are similar. Serum and urine strychnine tests should be performed when tetanus is suspected.

121.7. Which of the following statements regarding botulism is *true?*
A. It does not affect the autonomic nervous system.
B. The gastrointestinal system is spared.
C. The syndrome may mimic Guillain-Barré syndrome onset.
D. The toxin has its primary effect at the spinal cord.
E. Urinary retention may occur.

Answer: E. The toxin blocks the presynaptic release of acetylcholine at peripheral and autonomic nerve junctions. This proceeds in a descending manner, ultimately resulting in both a muscarinic and a nicotinic anticholinergic syndrome with muscle weakness, cranial nerve dysfunction, and diffuse parasympathetic diminution with constipation, ileus, and urinary retention. The descending, "cranial nerve first" pattern is opposite the ascending Guillain-Barré syndrome picture. Orthostatic hypotension may be profound.

121.8. Which of the following statements regarding wound and food-borne botulism is *true?*
A. Incubation times are similar.
B. The sequence of neural involvement is different.
C. Wound botulism affects central nervous system (CNS) gamma-aminobutyric acid (GABA) tone.
D. Wound botulism does not have gastrointestinal involvement.
E. Wound botulism is more common.

Answer: D. Wound botulism also has a longer incubation period.

121.9. A 31-year-old man presents with double vision and difficulty swallowing. He has no medical history and takes no medication. Your examination is remarkable for bilateral ptosis, mildly dilated pupils, dry mucous membranes, difficulty swallowing, and weakness of the trapezius and deltoid muscles. Bowel sounds are absent. Vital signs are temperature, 97.3°F (36.3°C); heart rate, 93 beats/minute; blood pressure, 84/63 mm Hg; and respiratory rate, 20 breaths/minute. Which of the following is indicated?
A. Antitoxin
B. Blood cultures and antibiotics
C. Lumbar puncture
D. Magnetic resonance imaging (MRI) of the brain and spine

Answer: E. Organophosphate treatmentAnswer: A. Botulism presents as a descending paralysis/anticholinergic syndrome. Autonomic dysfunction with orthostatic hypotension is common. Ileus and urinary retention may occur. Antitoxin, intensive care unit (ICU) admission, and early intubation are often indicated.

121.10. Fever and a nonblanching rash should suggest which of the following?
A. Disseminated tuberculosis
B. Meningococcemia
C. Plague
D. Pneumococcal sepsis
E. Tularemia

Answer: B. Up to 30% of meningococcemia patients will present with this picture and no immediate evidence of meningitis or sepsis.

CHAPTER 122

Viruses

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PERSPECTIVE

The vast majority of viral infections, such as the common cold, are minor and self-limiting. However, some are highly pathogenic, contagious, and have the potential to cause devastating illness. In addition to century old infections such as tuberculosis, there are also newer infections such as avian influenza, Middle East respiratory syndrome (MERS), and enterovirus D68 (EV-D68). With increased international travel occurring, emergency clinicians must be familiar with emerging infections that are spreading beyond their endemic origins. Patients are presenting to emergency departments (EDs) in the United States with infections traditionally thought to be tropical or foreign. In addition to recognizing symptoms and knowing the treatment for these infections, emergency clinicians should be familiar with isolation and reporting practices for the sentinel infections that can be vital to preventing global pandemics.

Advances in molecular biology have increased our knowledge of these infections, improved our diagnostic ability, and allowed more treatment options. Viruses are classified according to the type and structure of nucleic acid, capsid, and presence or absence of an envelope (Table 122.1). In practice, it is useful to group viruses based on clinical syndromes. This chapter reviews select viral illnesses that have high morbidity and mortality, those with specific treatments, and those that have major public health consequences. We begin by reviewing several preventable diseases that are reemerging because of decreasing immunization rates caused by largely unfounded fears of complications or side effects.

VACCINE-PREVENTABLE INFECTIONS OF CHILDHOOD

Childhood immunization is among the most important public health measures and has saved millions of children from serious illness, disability, and even death. An example of this is the eradication of smallpox in 1977. However, there has been a troubling trend of increasing nonmedical exemptions from mandated school-entry vaccines in developed nations, and routine immunizations have been rejected by some because of question of their safety and the lack of perceived threat for serious vaccine preventable diseases.[1] The emergency clinicians may therefore play a significant role in educating parents as to the safety and efficacy of childhood immunizations. The U.S. Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians recommend a specific childhood immunization schedule each year. Table 122.2 summarizes the currently available viral vaccines and recommended schedule.

Mumps

Principles

Mumps is an RNA virus that is a member of the *Paramyxoviridae* family. It causes a febrile illness with swelling and tenderness of the parotid gland. Since the advent of the mumps vaccine in 1967, there has been a 99% decrease in the incidence of mumps in the United States. Despite the vaccine, recent outbreaks in developed nations, even in vaccinated individuals, raised concerns about resurgence of mumps.[2] Mumps is spread via infected respiratory secretions that enter a susceptible respiratory tract. The incubation period is 16 to 18 days, ranging from 12 to 25 days. Infected patients are most contagious 1 to 2 days before onset of disease but can be contagious as early as 7 days before symptoms and up to 9 days after symptoms start.

Clinical Features

Parotitis, either unilateral or bilateral, is the hallmark of this infection, occurring in over 95% of symptomatic patients (Fig. 122.1). The other salivary glands are not as commonly affected. The symptoms usually begin with fever, malaise, and headache. About one-third of mumps infections are asymptomatic. Up to 30% of mumps infections cause orchitis, which usually occurs 1 week after the onset of parotitis and is more commonly seen in older individuals. Orchitis is usually unilateral but can occur in both testes in up to a third of the cases. There is a high incidence of cerebrospinal fluid (CSF) pleocytosis in patients with mumps, but less than 10% have symptomatic meningitis, and less than 1% have encephalitis. The mortality from mumps is very low, but the majority of morbidity and mortality associated with mumps occurs in the encephalitis cases.

Differential Diagnosis

During an outbreak, mumps can be easy to diagnose. Other viral infections that can cause parotitis (Epstein-Barr virus [EBV], parainfluenza, influenza A virus, coxsackievirus, adenovirus, parvovirus B19, lymphocytic choriomeningitis virus, and human immunodeficiency virus [HIV]), bacterial infections, facial cellulitis, and tumor are all other diagnoses that should be considered.

Diagnostic Testing

Mumps can be confirmed by detection of viral RNA, via reverse transcription polymerase chain reaction (RT-PCR), detection of the virus itself from clinical specimen, or detection of antibodies (immunoglobulin M [IgM] or fourfold rise in immunoglobulin G [IgG] between acute and convalescent serum specimen). This entails collecting a buccal or oral swab specimen for virus isolation and blood sample for serologic testing. Collecting samples early improves yield as virus isolation greatly diminishes beyond the first week of symptoms.

Management and Disposition

The mainstay of treatment is supportive care with antipyretics and analgesics. There is no specific antiviral treatment. Most of cases have a benign, self-resolving course and will not require admission to the hospital. In the hospital setting, these patients should have

TABLE 122.1

Classification of Viruses

FAMILY	EXAMPLES	REPRESENTATIVE DISEASES, COMMENTS
DNA VIRUSES		
Poxviridae	Variola Orf	Smallpox Contagious pustular dermatitis
Herpesviridae	HSV-1, HSV-2 CMV VZV HHV-6 EBV Kaposi's sarcoma herpesvirus	Mucocutaneous ulcers, herpes encephalitis Pneumonitis in immunocompromised patients Chickenpox, shingles Roseola infantum Mononucleosis Kaposi's sarcoma
Adenoviridae	Adenovirus (50+ species)	Upper respiratory tract infections, diarrhea
Papillomaviridae	Papillomavirus (80+ species)	Warts (eg, plantar, genital)
Polyomaviridae	John Cunningham virus	PML
Hepadnaviridae	Hepatitis B	Hepatitis
Parvoviridae	Parvovirus B19	Aplastic anemia
RNA VIRUSES		
Reoviridae	Colorado tick fever Rotavirus	Fever and rash Gastroenteritis
Togaviridae	EEE Rubella	Epidemic encephalitis German measles
Flaviviridae	Yellow fever Dengue WNV Hepacivirus, hepatitis C	Hemorrhagic fever DHF West Nile encephalitis Chronic hepatitis
Coronaviridae	Coronavirus SARS-CoV	Upper respiratory tract infections SARS
Paramyxoviridae	RSV Measles Parainfluenza	Bronchiolitis Measles (rubeola), SSPE Croup
Rhabdoviridae	Rabies	Rabies
Filoviridae	Ebola	Hemorrhagic fever
Orthomyxoviridae	Influenza A, B	Influenza
Bunyaviridae	La Crosse Hanta	Encephalitis Hemorrhagic fevers, ARDS
Arenaviridae	Lassa Lymphocytic choriomeningitis virus	Hemorrhagic fever Meningoencephalitis
Retroviridae	HIV	AIDS
Picornaviridae	Poliovirus Coxsackievirus B Hepatitis A Rhinovirus (115+ species)	Polio Myocarditis Enteric hepatitis URIs
Caliciviridae	Norwalk virus	Gastroenteritis
Unclassified viruses	Hepatitis E	Enteric hepatitis

AIDS, Acquired immunodeficiency syndrome; *ARDS,* acute respiratory distress syndrome; *CMV,* cytomegalovirus; *DHF,* dengue hemorrhagic fever; *EBV,* Epstein-Barr virus; *EEE,* Eastern equine encephalitis; *HHV,* human herpesvirus; *HIV,* human immunodeficiency virus; *HSV-1,* herpes simplex virus type 1; *HSV-2,* herpes simplex virus type 2; *PML,* progressive multifocal leukoencephalopathy; *RSV,* respiratory syncytial virus; *SARS,* severe acute respiratory syndrome; *SARS-CoV,* severe acute respiratory syndrome–coronavirus; *SSPE,* subacute sclerosing panencephalitis; *URI,* upper respiratory infection; *VZV,* varicella-zoster virus; *WNV,* West Nile virus.

TABLE 122.2

Viral Vaccines

VIRUS	VACCINE	TYPE	INDICATION	RECOMMENDED SCHEDULE
Smallpox	Vaccinia	Live	For persons at risk or for emergency responders	Once, before anticipated risk of exposure
Polio	Oral polio vaccine (Sabin) Inactivated polio vaccine (Salk)	Live Inactivated	During outbreaks Unvaccinated travelers All children	Inactivated polio vaccine preferred in almost all cases At 2, 4, and 6 to 18 months old, and at 4 to 6 years old
Measles	Measles, mumps, and rubella (MMR)	Live	All normal children	At 12 to 15 months old and 4 to 6 years old
Mumps	MMR	Live	All normal children	Same as for measles
Rubella	MMR	Live	All normal children	Same as for measles
Hepatitis A	Hepatitis A virus (HAV) vaccine	Inactivated	Persons at risk (eg, travelers, persons living in areas of high prevalence)	Two doses, 6 months apart Ideally should be given 1 month prior to travel Immune globulin should be given if travel is imminent
Hepatitis B	Hepatitis B virus (HBV) vaccine	Inactivated or recombinant	All children Persons at risk of exposure (eg, health care workers)	At birth, 1 to 2 months old, and 6 to 18 months old Hepatitis B immune globulin (HBIG) should be given in addition in case of high-risk exposure
Influenza A and B	Influenza vaccine Intranasal vaccine	Inactivated Live, cold adapted	In 2010, Centers for Disease Control and Prevention (CDC) expanded recommendation for annual influenza vaccination to include all persons 6 months old and older As above, for persons 2 to 49 years old Avoid in pregnant, immunosuppressed, young children with asthma, allergic to eggs	One dose yearly in the fall or winter As above
Rabies	Human diploid cell vaccine (HDCV) Purified chick embryo cell (PCEC)	Inactivated Inactivated	Postexposure prophylaxis or for preexposure prophylaxis in high-risk individuals Postexposure prophylaxis or for preexposure prophylaxis in high-risk individuals	Postexposure—HDCV or PCEC 1.0 mL IM in the deltoid region on days 0, 3, 7, and 14 Rabies immune globulin (RIG) 20 IU/kg should be administered around the wound site, as possible, with the remainder given IM at an anatomically distant site Preexposure—HDCV or PCEC 1.0 mL IM in the deltoid region on days 0, 7, 21, and 28 As above
Yellow fever	17D virus strain	Live	Persons 9 months to 59 years old traveling to endemic areas Contraindicated in younger than 6 months old, precaution in age 6 to 8 months old and 60 years old and older	Boosters every 10 years
Rotavirus	RV1 RV5	Live Live	All healthy children All healthy children	Two dose series at 2 and 4 months old Three dose series at 2, 4, and 6 months old
Varicella	Varicella	Live	All healthy children At-risk adults (those without evidence of immunity and high risk for exposure or transmission)	At 12 to 15 months old and 4 to 6 years old Persons older than 13 years old should receive two doses 4 to 8 weeks apart
Zoster	Zoster	Live	Anyone 60 years old and older, contraindicated in severe immunodeficiency	A single one time dose in adults 60 years old and older

Fig. 122.1. Mumps infection demonstrating parotitis. (Courtesy Centers for Disease Control and Prevention: Public health image library [PHIL]. Available at: http://phil.cdc.gov/phil/details.asp?pid=130.)

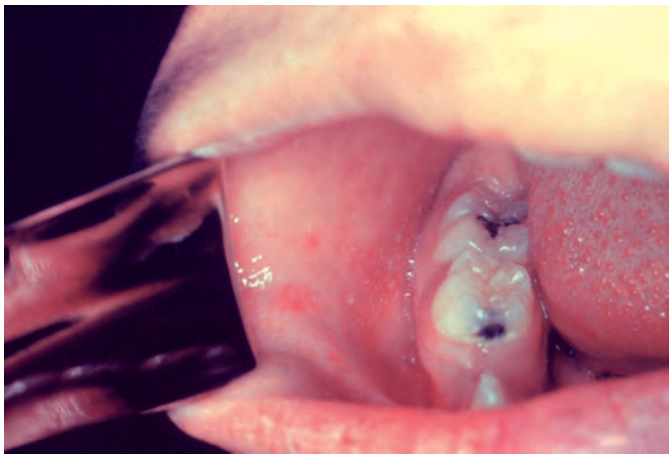

Fig. 122.2. Koplik spots. (Courtesy Centers for Disease Control and Prevention: Public health image library [PHIL]. Available at: http://phil.cdc.gov/phil/details.asp?pid=6111.)

droplet precautions observed. Patients should be isolated for 5 days after the onset of parotid swelling. Individuals with close contact with the infected patient should receive vaccination if not immunized.

Measles (Rubeola)

Principles

Measles is an RNA virus thought to be the most contagious known to humans. It was a common childhood illness, causing 3 to 4 million cases per year in the United States the 1960s, but the number of cases has dramatically decreased since the advent of the measles vaccine. Despite introduction of the measles vaccine in the 1960s, measles remains common in developing countries, mostly in parts of Africa and Asia. Global health initiatives aimed at eliminating measles focus on reaching and maintaining over 95% coverage with two doses of measles containing vaccination. Progress has been made toward measles elimination; from 2003 to 2013, the annual measles incidence decreased by 73% and measles-related deaths decreased by 63% in the World Health Organization (WHO) South-East Asia region.[3]

Measles still occurs in the United States and other developed nations, mostly among unvaccinated or incompletely vaccinated individuals who have exposures to individuals infected from an endemic region. In 2011, France had a measles outbreak with nearly 15,000 cases. The most recent outbreak in the United States has been linked to exposure to a Disney theme park in California with over 100 cases occurring—often in children too young for vaccination or in those whose parents have unfounded fears about vaccine safety.[4]

Clinical Features

The incubation period is 7 to 21 days. The first symptoms manifest during the prodromal phase, which lasts approximately 3 days. During this phase patients have fever, malaise, and the classically taught three Cs (cough, coryza, and conjunctivitis). Koplik spots, small raised bluish white spots on oral mucosa on roof of mouth (Fig. 122.2), are pathognomonic for the diagnosis and can be seen during the prodromal phase. The patient will then develop the typical rash; a nonpruritic maculopapular rash that begins on the head and face and spreads down the entire body over the next 2 to 3 days (Fig. 122.3). Patients are contagious 4 days before and 4 days after onset of the rash.

Fig. 122.3. Typical rash associated with measles infection. (From Kremer JR, Muller CP: Measles in Europe—there is room for improvement. Lancet 373[9661]:356-358, 2009.)

Complications of measles include otitis media, laryngitis, tracheobronchitis, bronchiolitis, pneumonitis, severe diarrhea, and acute encephalitis. The virus itself can also cause pneumonia. Bacterial superinfection can also occur. The populations that are at high risk for severe disease or complications include children younger than 5 years old, adults older than 20 years old, pregnant women, and the immunocompromised.

Subacute sclerosing panencephalitis (SSPE) is a rare but fatal complication of measles. SSPE is a slow progressive infection of the central nervous systems (CNS) that results from a prior measles infection. It is thought to be due to continual measles infection of the CNS. The mean time of onset of SSPE is 7 years after measles infection. Symptoms include behavior change, decreased intellect, ataxia, and myoclonic seizures followed by

progressive neurologic deterioration and death. Since the development of measles vaccine, this disease has almost disappeared in the United States.

Differential Diagnosis

Measles can be mistaken for other acute respiratory viral illnesses with rash or even noninfectious illnesses that present with fever and rash. Other diagnoses to consider include rubella, roseola, dengue, Kawasaki disease, and drug rash. Measles should be considered in patients that have travelled to endemic regions and return with fever and rash.

Diagnostic Testing

The diagnosis is usually made clinically, by visualizing both Koplik spots and the characteristic rash along with cough, coryza, and conjunctivitis. However, the disease is not common in the developed world, and it may be mistaken for other illnesses. Providers suspecting a diagnosis of measles should contact local health departments. They can be helpful in instructing practitioners to obtain the necessary samples for diagnosis and surveillance. The most common methods of confirmation are serologic testing for measles specific IgM antibody and detection of measles RNA by RT-PCR. For surveillance purposes, nasopharyngeal and urine samples can be obtained for virus isolation.

Management

The mainstay of treatment is supportive care. Bacterial superinfection should be treated appropriately. Post-exposure prophylaxis is important in individuals who do not have evidence of measles immunity and have a measles exposure, because it can provide protection or lessen the severity of disease. Post-exposure prophylaxis consists of either the measles, mumps, and rubella (MMR) vaccine within 72 hours, or immunoglobulin within 6 days. Healthy infants should receive 0.25 mL/kg of immunoglobulin intramuscularly, and immunocompromised children should be given 0.5 mL/kg intramuscularly, up to 15 mL. Children and the malnourished who are hospitalized with severe measles may benefit from vitamin A.

Disposition

Patients with measles require admission to the hospital based on the severity of illness. Uncomplicated measles patients should be treated at home to prevent spread of the disease. It is important, however, to observe appropriate isolation precautions in the hospital setting. Infected individuals should have airborne isolation for 4 days after they develop the rash.

Rubella (German Measles)

Principles

Rubella is a single stranded RNA virus that is a member of the *Togaviridae* family. Since the wide scale implementation of the vaccine, cases have dropped by greater than 99%. As a result, rubella is no longer considered endemic in the United States. The virus is spread via contact with respiratory droplets. In pregnant patients, the virus spreads to the placenta with subsequent infection of fetal organs.

Clinical Features

Acquired rubella is a mild febrile illness associated with a diffuse maculopapular rash, malaise, headache, and arthritis. Encephalitis and thrombocytopenia are rare complications. Rubella is generally a mild disease, but consequences in pregnant patients can be devastating. It can cause miscarriage, intrauterine death, premature delivery, or congenital rubella syndrome. Congenital rubella syndrome is characterized by severe birth defects, including hearing impairment, cataracts, retinopathy, mental retardation, microcephaly, and a variety of congenital heart defects.

Differential Diagnosis

The diagnosis of rubella on a clinical basis can be difficult because of the overlap with many other illnesses. Diseases that share common features include measles, roseola, erythema infectiosum (fifth disease), toxoplasmosis, and scarlet fever.

Diagnostic Testing

The diagnosis of rubella can be made by virus detection or serologic testing. The most common method is detection of IgM antibodies or fourfold increase in IgG antibody titer between acute and convalescent specimen. Virus culture and RT-PCR can also be isolated from blood or the nasopharynx.

Management and Disposition

There is no specific antiviral treatment for rubella. The management centers on symptom control with antipyretics and analgesics. The course of this disease is short and benign. These patients can be treated at home for the most part.

VIRAL INFECTIONS WITH VESICULAR RASH

Herpes Simplex

Principles

Herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are double-stranded DNA viruses of the *Herpesviridae* family. Herpes simplex infections primarily involve the skin or mucosal surfaces with occasional serious involvement of organs. Herpes simplex virus (HSV) infections range in acuity from asymptomatic to life threatening. HSV-1 typically causes orofacial infections but can affect liver, lung, eye, genitalia, and the CNS. HSV-2 typically causes genital herpes but can also affect the other systems as well. HSV infections are common, the seroprevalence of HSV-1 has been reported to be 57.7% in persons aged 14 to 49 years old in the United States, and the seroprevalence of HSV-2 has been reported to be 17.0% in the same population.

Initial HSV-1 infection usually occurs in childhood. HSV gains entry via breaks in the skin or mucosal surfaces. Viral replication is then initiated in epidermal and dermal cells. The infection then spreads to the nervous system, where it lays latent in the sensory nerve ganglia. Any stressor such as emotional stress, trauma, intense sunlight, or fever can trigger reactivation of the virus. Recurrence rates are high for herpes infections. HSV-2 infections usually are acquired in adolescence or adulthood through sexual contact. Neonatal HSV-2 infections occur during childbirth via contact with the infected mother's birth canal.

Clinical Features

Oral Infection. The first episode of HSV-1 infections usually occurs early in life and manifests as a gingivostomatitis and pharyngitis. Symptoms include fever, malaise, and vesicular lesions anywhere in the mouth or oropharynx. Infections can last between 10 to 14 days. Reactivation is usually much less severe and occurs as herpes labialis, small vesicles at the vermilion border

Fig. 122.4. Herpes labialis. (Courtesy Centers for Disease Control and Prevention: Public health image library [PHIL]. Available at: http://phil.cdc.gov/phil/details.asp?pid=1573.)

of the lip (Fig. 122.4). These vesicles usually crust over within 48 hours.

Genital Herpes. This infection is characterized by painful vesicles and ulcers on the external genitalia. The first infection is usually the most severe and can be accompanied by systemic symptoms like fever, headache, malaise, and myalgias. It is also common to have dysuria and tender inguinal lymphadenopathy. Infections can also spread to the perianal and rectal region as well.

Central Nervous System Infection. HSV-1 is a common cause of infectious encephalitis; it causes necrotizing hemorrhagic encephalitis, typically involving the temporal lobes. Herpes simplex encephalitis is characterized by acute onset of symptoms, including fever, headache, altered mental status, seizures, and focal neurologic deficits resulting from frontal and temporal lobe necrosis. If left untreated, mortality is greater than 70%. HSV-2 can cause meningitis in over 25% of patients with primary infection, more commonly in women. In contrast to HSV encephalitis, HSV meningitis has a benign course. Neonatal HSV encephalitis is caused by HSV-2 acquired during vaginal delivery of an infected mother.

Other Infections. Herpes can cause a variety of cutaneous manifestations. They typically present with the classic painful grouped vesicles on an erythematous base on the affected area. Herpetic whitlow is when this occurs on the finger. Herpes gladiatorum is a skin infection that can occur anywhere on the body and is associated with contact sports. Herpes can also cause ocular infections, including keratitis, conjunctivitis, and acute retinal necrosis. The immunocompromised patients are at risk for rare infections like HSV pneumonitis, esophagitis, or hepatitis.

Differential Diagnosis

When suspecting orofacial HSV infection, other considerations include other diseases with vesicles and ulcers, such as aphthous ulcers, coxsackievirus infections (herpangina and hand-foot-and-mouth disease), infectious mononucleosis, Stevens-Johnson syndrome, or Behçet's disease. The differential diagnosis for genital herpes infection should include other sexually transmitted infections that have ulcers and vesicles, such as syphilis or chancroid or noninfectious diseases like Behçet's disease. HSV encephalitis can be difficult to distinguish from other acute CNS emergencies like bacterial meningitis, brain abscess, other viral encephalitides, brain tumor, or stroke.

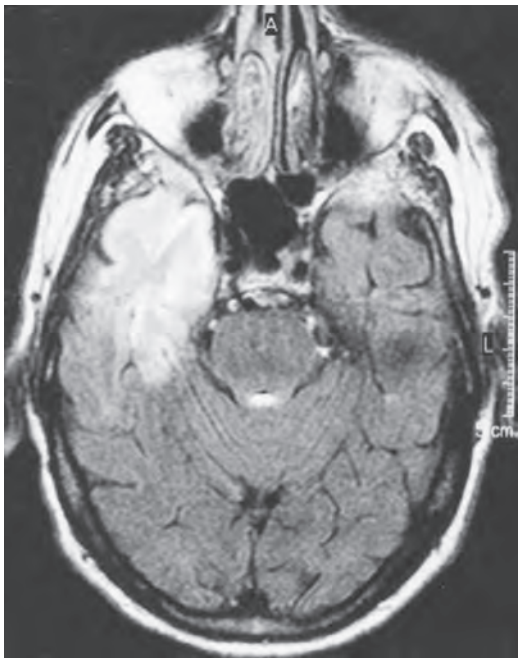

Fig. 122.5. T-2 weighted MRI with gadolinium demonstrating temporal lobe enhancement secondary to HSV-1 encephalitis. (From Martin K, Franco-Paredes C: Herpes encephalitis. Lancet 360[9342]:1286, 2002.)

Diagnostic Testing

Oftentimes, clinicians will diagnose oral or genital HSV infections clinically given the classic appearance of the vesicles and ulcers. However, because of the stigmata and risk of transmission, testing should be performed if possible. Definitive diagnosis can be made by viral culture, direct fluorescent antibody (DFA), or polymerase chain reaction (PCR) from vesicles, ulcers, or mucocutaneous sites. PCR is more sensitive than viral culture. Tzanck smear has a low sensitivity and specificity and is mainly of historical interest.

The diagnosis of HSV encephalitis is made by PCR from the CSF. The routine laboratory tests sent after a lumbar puncture (LP) to assess for bacterial meningitis will not adequately assess for HSV encephalitis. Classically, CSF analysis will show an elevated white blood cell (WBC) count, with lymphocyte predominance. Depending on the degree of brain necrosis, an elevated red blood cell (RBC) count can also be seen. Although it is rare, CSF results can be normal in HSV encephalitis, particularly in immunocompromised individuals.[5] This underscores the importance of waiting for PCR results before considering discontinuation of treatment in suspected cases of HSV encephalitis. In cases of negative CSF PCR with a high suspicion of HSV encephalitis, we recommend continuing empirical treatment and resending CSF PCR in 72 hours. Neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI) can be highly suggestive of HSV encephalitis, but imaging can be negative early in the course of illness (Fig. 122.5).

Management

Antiviral agents are the mainstay of treatment. The treatment dose and duration for herpes simplex depends on the clinical syndrome that is present. Acyclovir, valacyclovir, and famciclovir are the commonly used antiviral drugs with activity against HSV. These

drugs are nucleoside analogues that work by inhibiting viral DNA synthesis. Acyclovir is the only agent that is available in an intravenous (IV) formulation.

Herpes gingivostomatitis or labialis: First episodes are treated with oral acyclovir 200 mg five times a day (alternative regimen: 400 mg three times a day), valacyclovir 1 g twice daily, or famciclovir 250 mg three times a day for 7 days. Recurrent infections are treated with acyclovir 400 mg five times a day for 5 days, valacyclovir 2 g twice daily for 1 day, or famciclovir 1500 mg as a single dose.

Genital herpes: First episodes are treated with oral acyclovir 200 mg five times a day (alternative regimen: 400 mg three times a day), valacyclovir 1 g twice daily, or famciclovir 250 mg three times a day for 7 to 10 days. A shorter course is usually adequate for treatment of recurrence. For suppression of recurrent episodes, acyclovir 400 to 800 mg twice daily or valacyclovir 500 mg daily can be used.

Herpetic whitlow and other mucocutaneous manifestations: Administer acyclovir 200 mg five times a day or 400 mg three times a day for 5 days.

Herpes keratitis: Administer acyclovir 400 mg five times a day. Valacyclovir and famciclovir are probably also effective but have not been studied in clinical trials. If used for keratitis, we recommend using herpes zoster dosing. Topical antiviral therapy with trifluridine, acyclovir, or ganciclovir are all equally effective[6]

HSV encephalitis: Administer IV acyclovir 10 mg/kg every 8 hours for 14 to 21 days. Given the high mortality associated with this condition, antiviral therapy should be started as soon as the diagnosis is suspected. We recommend empirically treating all patients that are being ruled out for bacterial meningitis as well, because there is such overlap with the clinical presentation.

Disposition

The majority of herpes infections can be treated with oral antiviral therapy on an outpatient basis. Patients that are immunocompromised and have severe mucocutaneous disease or disseminated disease will benefit from inpatient admission with IV acyclovir treatment. All patients with suspected encephalitis should be admitted for empirical treatment and diagnostic results. Intensive care unit (ICU) admission may be necessary depending on the severity of neurologic symptoms. For HSV encephalitis patients, we recommend early involvement of infectious disease consultants to help guide treatment and neurology for management of cerebral edema and severe neurologic symptoms.

Varicella-Zoster Virus

Principles

The varicella-zoster virus (VZV) is another double-stranded DNA virus that is a member of the *Herpesviridae* family. VZV causes two common infections: varicella (chicken pox) and zoster (shingles). Transmission occurs via the respiratory tract through respiratory droplets and also by direct contact with virus present in the fluid filled vesicles that occur with this disease. VZV initially infects the nasopharynx and spreads to the lymphoid tissue. The virus present in vesicles that develop on the skin then infects the nerve endings in the skin and travels to the dorsal ganglia where it lays latent.

Primary infection of VZV occurs as varicella (chicken pox). Varicella is highly contagious and occurs year round with a predilection for winter and spring months. Prior to the development of the varicella vaccine in 1995, most people would develop this infection in childhood. After widespread uptake of the vaccine the incidence of varicella has decreased by 90%, with subsequent decline in mortality. Zoster (shingles) is a result of reactivation of the latent virus. Risk factors for developing shingles include older age and immunosuppression.

Clinical Features

Varicella. Chicken pox is a febrile illness characterized by malaise and rash. The rash begins first on the scalp and face and then spreads to the trunk and extremities. The lesions start as maculopapular, and progress to fluid filled vesicles that eventually crust over and form scabs (Fig. 122.6). The lesions occur as crops at various stages of development. Patients are contagious until all lesions are scabbed over, which can typically take 1 to 2 weeks.

For the most part this disease has a benign course. Adults have a more severe course than children. The most common complication is a secondary bacterial infection of the skin lesions. VZV has been associated with invasive group A streptococcal infections and necrotizing fasciitis.[7] Immunocompromised patients are at risk for disseminated disease and visceral organ involvement. Pregnant patients are also at risk for severe disease. Varicella pneumonia accounts for most of the morbidity related to this disease. Neurologic complications are rare but can include encephalitis, aseptic meningitis, transverse myelitis, and Reye syndrome. Although exceedingly rare, it is important to recognize the association of aspirin use with Reye syndrome, a progressive encephalopathy

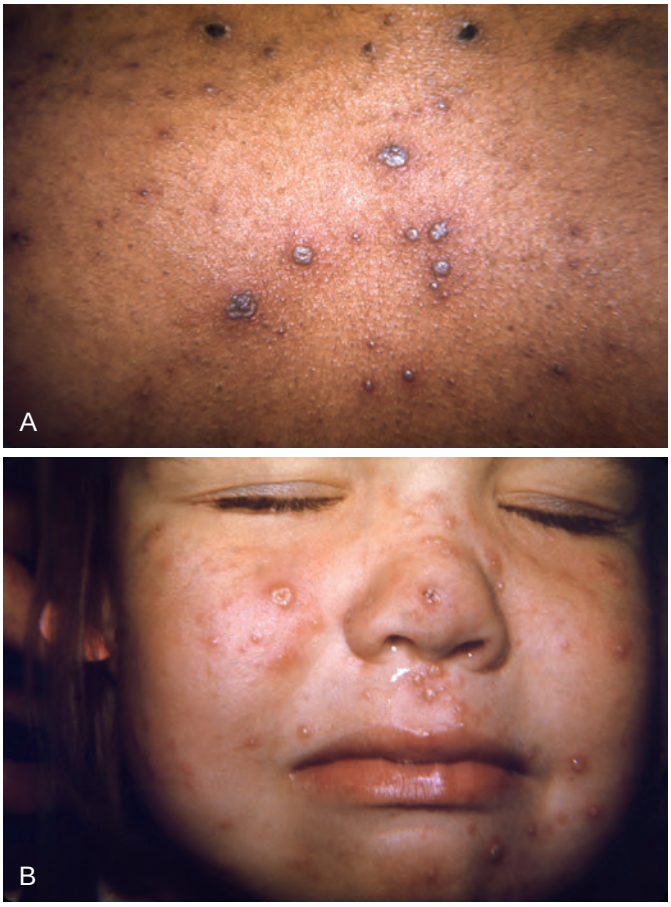

Fig. 122.6. A and **B,** Varicella infection demonstrating the typical rash with lesions in different stages of healing. (Courtesy Centers for Disease Control and Prevention: Public health image library [PHIL]. Available at: http://phil.cdc.gov/phil/details.asp?pid=10484; http://phil.cdc.gov/phil/details.asp?pid=10486.)

Fig. 122.7. Herpes zoster infection.

with acute liver injury. Thus aspirin use should be avoided in varicella treatment, especially in children.

Zoster. Herpes zoster typically causes a vesicular rash with an erythematous base that occurs unilaterally in a single dermatome (Fig. 122.7). The rash is very painful and is often preceded by paresthesias or hypesthesia. In immunocompetent individuals, the rash will crust in 7 to 10 days and at that time patients are no longer contagious. Post-herpetic neuralgia, defined as pain that persists for more than 90 days, is the feared complication. Risk factors for post-herpetic neuralgia include older age and severity of pain at onset.[8] Herpes zoster ophthalmicus is viral reactivation within the trigeminal nerve ganglion. Ocular involvement occurs in over 50% of these cases. Hutchinson's sign, vesicle on the tip of the nose, has been associated with ocular involvement. Herpes zoster oticus (Ramsay Hunt syndrome) is characterized by facial nerve palsy, pain, and vesicular rash on the ear and in the auditory canal. Disseminated zoster involving multiple dermatomes can occur in immunocompromised patients.

Differential Diagnosis

Classic varicella is distinctive, but the other major diagnoses to consider are other febrile illnesses with rashes like disseminated HSV infection, coxsackievirus infection, measles, or rickettsialpox. Prior to eradication, smallpox was a consideration, presenting with lesions in the same stage of development. The rash of zoster is also usually very characteristic. Other diagnoses to consider include herpes simplex infection or contact dermatitis.

Diagnostic Testing

The majority of chickenpox and shingles diagnosis is made clinically. Confirmatory diagnosis can be made through viral culture, DFA, or PCR testing of the vesicle fluid.

Management

Varicella. The management is mainly supportive care with antipyretics and antihistamines to decrease the pruritus caused by the skin lesions. Aspirin should be avoided in children because of the association with Reye's syndrome. Antiviral therapy with acyclovir has been shown to decrease duration of fever and total number of lesions in healthy children but not reduce the number of varicella related complications. Therefore, we do not recommend treatment of otherwise healthy children with varicella. We recommend treating groups at high risk for varicella complications with acyclovir, including those older than 12 years old, adults, pregnant patients, persons with chronic cutaneous or pulmonary disorders, persons on long-term salicylate therapy, persons on aerosolized corticosteroids, and immunocompromised patients. The treatment should be initiated within 24 hours after the rash appears for the most benefit. The dose of acyclovir for VZV treatment is higher than that of HSV, 800 mg orally four times a day for 5 days. If the patient is immunocompromised and has severe disease, IV acyclovir should be administered.

Zoster. The goals of treatment for zoster are to treat the viral infection and control the pain that occurs with the rash. Uncomplicated zoster in the immunocompetent host can be treated with the following regimens for 1 week: acyclovir 800 mg five times a day, famciclovir 500 mg three times a day, or valacyclovir 1 g three times a day. Antiviral treatment should be initiated within 72 hours of onset of rash, because the efficacy beyond 72 hours is unclear. Immunocompromised patients should be treated regardless of time of onset of rash. Zoster involving more than one dermatome or disseminated zoster should be treated with IV acyclovir. The disease is often very painful and requires opioid agents. Currently there are no treatments that have reliably shown a reduction in the occurrence of postherpetic neuralgia. Antiviral treatment has shown mixed results in preventing postherpetic neuralgia. Corticosteroids have been studied extensively, but the latest Cochrane review did not support their use in preventing postherpetic neuralgia.[9]

Disposition

Most patients with varicella and zoster can be treated at home. Patients with varicella are highly contagious and should be instructed to avoid people who have not fully been vaccinated or never had the disease, immunocompromised persons, or pregnant individuals until all of their lesions have crusted over. Immunocompromised patients, patients with disseminated zoster, or patients with complications will generally require admission to the hospital. In general, patients with varicella should be under contact and airborne precautions until all of the lesions have crusted over. An immunocompetent localized zoster patient only requires standard precautions, whereas an immunocompromised or disseminated zoster patient is treated like patient with varicella, requiring contact and airborne precautions.

VIRAL INFECTIONS CAUSING NONSPECIFIC FEBRILE ILLNESS

Epstein-Barr Virus

Principles

EBV is a member of the *Herpesviridae* family. It is classically known for causing infectious mononucleosis. It is also associated with several types of cancer, including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, and B cell lymphoma. EBV is ubiquitous with most individuals testing positive for antibodies by adulthood. One study demonstrated that 50% of 6- to 8-year-olds had antibodies to EBV, whereas 89% of 18- to 19-year-olds tested positive.[10] EBV is spread via salivary secretions. The virus infects the oropharynx and then spreads through the bloodstream and infects B lymphocytes. There is a resultant proliferation of infected B lymphocytes and T lymphocytes, which leads to enlargement of lymphoid tissue.

Clinical Features

EBV infection in young children is usually asymptomatic or presents as mild pharyngitis. Adolescents and young adults tend to have the classic infectious mononucleosis (fever, exudative

pharyngitis, lymphadenopathy, myalgias, and fatigue). Splenomegaly is common—seen in up to 50% of cases. Hepatomegaly and jaundice occur less than 10% of the time. The symptom duration is typically 1 to 3 weeks, with some cases having malaise and fatigue for several months. Splenic rupture is rare, occurring in less than 0.5% of patients. It should be suspected in patients with left upper quadrant pain and is more common during the first 3 weeks of illness. Airway obstruction occurs in less than 5% of children with mononucleosis and is one of the common causes of hospital admission. Rare neurologic complications include encephalitis, aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, retrobulbar neuritis, and peripheral neuropathies. Patients treated with amoxicillin or ampicillin for presumed streptococcal pharyngitis develop a nonallergic maculopapular rash.

Differential Diagnosis

EBV causes 90% of infectious mononucleosis; the remaining is caused by cytomegalovirus (CMV). Acute HIV infection, streptococcal pharyngitis, toxoplasmosis, and other causes of viral pharyngitis should all be considered in potential mononucleosis patients.

Diagnostic Testing

It is difficult to diagnose mononucleosis based on history and physical examination alone. Laboratory data can help confirm the diagnosis. Historically, the heterophile antibody test (monospot) has been the test of confirmation for primary EBV infection. The test has sensitivity ranging from 63% to 84% and specificity ranging from 84% to 100%.[11] The test is often not positive in younger children. The WBC count typically demonstrates lymphocyte predominance, and atypical lymphocytes can sometimes be seen on peripheral smear. A lymphocyte count less than 4×10^9/L in adults has been shown to be highly predictive of a negative monospot test.[12] Health care providers can test for antibodies to EBV viral capsid and nuclear antigen if the aforementioned testing is equivocal.

Management

Infectious mononucleosis typically has a self-limiting course. The treatment is supportive care with rest, antipyretics, and analgesia. Glucocorticoids have been used to decrease severity of symptoms, but there is insufficient evidence to support this practice. Antiviral treatment with acyclovir has not been shown to be effective in reducing the clinical symptoms of the disease. It is important to advise patients to avoid contact sports for at least 3 weeks to avoid the feared complication of splenic rupture. Abdominal ultrasound for assessment of spleen size may have a role in determining when it is safe to return to sports.[13]

Disposition

The majority of patients will be treated at home. Admission is necessary in those with airway obstruction and in patients with significant complications, like splenic rupture.

Cytomegalovirus

Principles

CMV is a double-stranded DNA virus that belongs to the *Herpesviridae* family. Depending on geographic location, the seroprevalence ranges from 45% to 100%.[14] The spectrum of illness caused by CMV ranges from asymptomatic to severe disseminated disease in the immunocompromised patient. CMV is particularly harmful in pregnant patients, because it can lead to congenital infection, causing profound neurologic defects and permanent hearing loss. CMV is present in breast milk, saliva, feces, urine, semen, cervical secretions, and blood. The virus spreads via prolonged exposure to these body fluids. After primary infection, CMV establishes a lifelong latent infection.

Clinical Features

The primary CMV infection is subclinical in most individuals. Some immunocompetent adults will develop a mononucleosis-like syndrome. The illness can last from 2 to 6 weeks and is characterized by fever, fatigue, malaise, myalgia, and headache. Unlike EBV mononucleosis, the exudative pharyngitis and lymphadenopathy are less common. Although it is rare, CMV can cause severe disease in the immunocompetent individual. CMV colitis and CNS infection (meningitis, encephalitis, transverse myelitis) are the most frequent sites of severe CMV infection in the immunocompetent host. Up to one-third of critically ill immunocompetent patients have evidence of CMV reactivation.

The majority of newborns who are infected with congenital CMV appear healthy or normal at birth. Common problems caused by congenital CMV infection include premature birth, intrauterine growth retardation, microcephaly, seizures, thrombocytopenia, hepatosplenomegaly, or pneumonitis. Sequelae of congenital CMV infection can present up to 2 years after birth. Frequent complications that occur are hearing loss, neurologic impairment, and ocular disturbances.

CMV can cause a serious, life-threatening disease in immunocompromised patients. CMV infection occurs in over 40% of solid organ transplant patients during the first 3 months when immunosuppressive therapy is the strongest. Transplant patients that are CMV seronegative and receive a CMV seropositive donor are at highest risk. HIV patients with CD4 count less than 100/μL are at high risk of CMV infection as well. In the immunocompromised host, CMV manifests initially as fever, malaise, and myalgias. The infection can then progress to cause leukopenia, pneumonia, esophagitis/gastritis, hepatitis, colitis, encephalitis, polyradiculopathy, and retinitis. CMV retinitis is the most common cause of blindness in HIV patients.

Differential Diagnosis

It is difficult to make the diagnosis of CMV infection solely on a clinical basis. Infectious mononucleosis caused by EBV presents very similarly. In the perinatal phase, infants with apparent infections should be evaluated for the other common congenital infections: toxoplasmosis, rubella, herpes simplex, syphilis, VZV, and parvovirus B19. Because the CMV infection can cause a wide array of disease in the immunocompromised host, the differential diagnosis should be broad and include other viral pathogens, bacterial infections, *Pneumocystis* infection, and fungal infections.

Diagnostic Testing

It is unlikely to make this diagnosis in the ED. Confirmation of this diagnosis centers on either virus isolation, serologic testing, or histopathology. Common methods involve PCR, viral culture, or antibody testing. The WBC count may show lymphocyte predominance with more than 10% atypical lymphocytes, much like EBV infections.

Management

For the most part, CMV infection in the immunocompetent host only requires symptomatic care for the mononucleosis-like

syndrome. The treatment recommendations for critically ill immunocompetent patients with CMV infection are less clear.[15,16] Immunocompromised patients with CMV infection are treated more aggressively. Antiviral treatment is necessary in sight and life-threatening infections.

Ganciclovir is an IV agent that is used to treat CMV infections. The treatment for CMV retinitis is induction therapy: 5 mg/kg/dose every 12 hours for 14 to 21 days followed by 5 mg/kg/dose once daily maintenance therapy for a prolonged course. Fever, diarrhea, and thrombocytopenia are common adverse reactions. Valganciclovir is an oral prodrug that is metabolized to ganciclovir. The treatment regimen is induction: 900 mg twice daily for 21 days followed by maintenance of 900 mg once daily. Foscarnet and cidofovir are IV agents used to treat CMV resistant to ganciclovir, and both can also be used to treat HSV resistant to acyclovir. The main limiting toxicity of these drugs is renal impairment.

Disposition

Most immunocompetent patients with CMV infection can be managed at home. In contrast, immunocompromised patients with CMV infection will usually require admission to the hospital and depending on the extent of end organ damage may require ICU admission. Only standard precautions are required to care for these patients.

Enteroviruses

Principles

Enteroviruses are a group of single-stranded RNA viruses that are able to multiply within the gastrointestinal tract. Most infections are asymptomatic or mild undifferentiated illnesses. Despite their name, their major manifestation is not gastroenteritis. There are a multitude of enteroviruses; common ones include poliovirus, coxsackievirus A and B, echovirus, and enterovirus. These viruses are found globally and are transmitted via the fecal-oral route. Vaccination exists for poliovirus; and in the United States and other developed nations, the disease has been declared eradicated.

Clinical Features

Most of the infections caused by enteroviruses are asymptomatic or self-limiting febrile illnesses. More of the severe infections are discussed in the following sections.

Poliovirus. The poliovirus causes a nonspecific febrile illness with malaise, myalgias, headache, and sore throat. The most feared presentation of the poliovirus infection is paralytic poliomyelitis. This manifests as aseptic meningitis followed by back, neck, and muscle pain then the development of motor weakness. The paralysis is usually asymmetric, and affects proximal muscles more. Usually some recovery of motor function occurs months later, but approximately two-thirds of patients have some form of permanent weakness.

Non-Polio Enteroviruses. Most enterovirus infections are subclinical, but they can also cause a variety of symptoms and syndromes. Enteroviruses account for most causes of viral meningitis and encephalitis. Pericarditis and myocarditis are commonly caused by enteroviruses, particularly coxsackievirus B. Symptoms usually include chest pain, fever, dyspnea, and can progress to severe heart failure. Enteroviruses are a common cause of viral exanthems as well. Herpangina is caused by coxsackievirus A and presents with fever, sore throat, odynophagia, and vesiculopapular lesions on the cheeks and soft palate (Fig. 122.8).

Fig. 122.8. Herpangina. (From Cohen J, Powderly WG: Infectious diseases, ed 2, St Louis, 2004, Mosby.)

Hand-foot-and-mouth disease is caused by coxsackievirus A or enterovirus 71 and commonly manifests as fever and malaise, followed by vesicles in the mouth, and vesicles on the hands and feet (Fig. 122.9). Pleurodynia is a painful illness characterized by fever and spasms of the chest wall and abdomen that occur in paroxysms.

In 2014, there was an outbreak across the United States of EV-D68.[17] The virus affected mostly children and was severe in children with asthma. Typically EV-D68 causes mild respiratory illness, rhinorrhea, sneezing, cough, and myalgias but occasionally causes severe disease with wheezing and respiratory distress. There has also been an association with flaccid paralysis with anterior myelitis with EV-D68 infection.[18]

Differential Diagnosis

Clinicians should consider other diagnoses depending on the specific symptoms and syndrome caused by enterovirus infection. For the diseases with skin and oropharyngeal lesions, herpes simplex, aphthous stomatitis, mononucleosis, and bacterial pharyngitis should be considered. The diseases with primary neurologic manifestation will present similarly to bacterial meningitis, and other causes of viral meningitis or encephalitis, including herpes simplex encephalitis. Myopericarditis can present similar to pulmonary embolism, myocardial infarction, or pneumonia.

Diagnostic Testing

Diagnosis is confirmed by viral culture, serology, or PCR. Samples can be sent from nasopharynx or oropharynx via swabs or washings, CSF, serum, stool, or pericardial fluid. Other diagnostic testing should be tailored toward the symptoms, such as ECG, chest x-ray, and cardiac biomarkers for evaluation of myopericarditis. If safe, LP should be performed for meningitis or encephalitis evaluation.

Management

The treatment is primarily symptomatic, because there are no specific antiviral therapies for enteroviruses that are currently recommended. Hand-foot-and-mouth disease can cause severe dehydration, because children will refuse to eat secondary to the painful lesions in the mouth. This illness is typically treated with

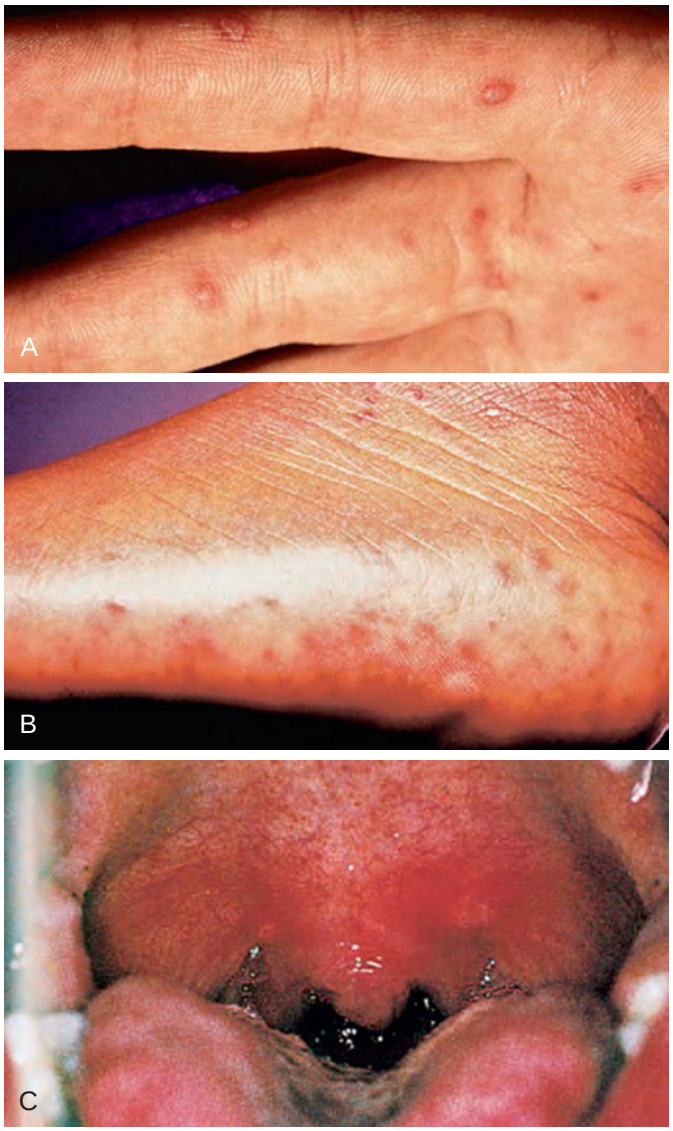

Fig. 122.9. A to **C,** Hand-foot-and-mouth disease. (From Cohen B: Pediatric dermatology, ed 4, St Louis, 2013, Elsevier, p 110.)

analgesia and encouragement of oral intake. Topical analgesia with diphenhydramine and aluminum hydroxide and magnesium hydroxide can be used. Viscous lidocaine and topical benzocaine should be avoided in young children because of the risk of systemic toxicity and also questionable efficacy.[19] If there is concern for meningitis, empirical therapy for bacterial meningitis and herpes simplex encephalitis should be instituted while awaiting culture and PCR results, because both of the aforementioned diseases have a significantly higher morbidity and mortality with delayed treatment.

Disposition

The majority of enteroviruses cause a benign disease, and patients can be treated at home and expect no sequelae. Depending on the severity of symptoms, some patients may require hospitalization for dehydration, severe respiratory illness, or neurologic infection. Viral myocarditis can cause severe heart failure and dysrhythmias requiring hospitalization and ICU care. The outcome after viral myocarditis can be variable and range from return of normal heart function to severe cardiomyopathy requiring heart transplantation.

BOX 122.1

Conditions That Increase Risk for Severe Influenza and Influenza Related Complications

- Age younger than 2 years old
- Age 65 years and older
- Chronic pulmonary disorders, including asthma
- Chronic cardiovascular disorders except hypertension alone
- Chronic renal insufficiency
- Chronic hepatic disorders
- Chronic hematological conditions, including sickle cell disease
- Metabolic and endocrine disorders, including diabetes mellitus
- Neurologic disorders, including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, seizure disorders, stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury
- Immunosuppression, including that caused by medications or by human immunodeficiency virus (HIV) infection
- Pregnancy or postpartum state (within 2 weeks after delivery)
- Ethnicity belonging to American Indians/Alaska Natives
- Morbid obesity (ie, body mass index ≥40)
- Residency in nursing homes and other chronic care facilities

Adapted from Fiore AE, Fry A, Shay D, et al: Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 60:1-24, 2011.

VIRUSES ASSOCIATED WITH RESPIRATORY INFECTIONS

Influenza

Principles

Influenza is an RNA virus from the *Orthomyxoviridae* family that causes acute respiratory symptoms. This virus is highly contagious and is transmitted through large particle respiratory droplets. Transmission usually requires close contact between individuals less than 1 meter apart. Epidemics and outbreaks occur almost annually, with the peak influenza activity usually occurring in the winter months in the United States. Influenza occasionally causes devastating pandemics. During the 1918 influenza pandemic, approximately 50 to 100 million people were killed across the globe. The most recent pandemic occurred in 2009, when a new strain of the H1N1 influenza emerged.

There are three major types of influenza: A, B, and C. The majority of human infections are caused by influenza A and B. Influenza can be further subdivided based on the two major surface glycoproteins present, hemagglutinin (H) and neuraminidase (N). Influenza A is responsible for most of the severe epidemics and pandemics because of its ability of surface antigens to undergo periodic changes. This is known as *antigenic drift* when the changes are minor and *antigenic shift* when the changes are major.

Clinical Features

Influenza typically presents as fever with constitutional (headache, malaise, and myalgias) and respiratory symptoms (cough, sore throat, rhinitis). These symptoms typically last for 3 to 7 days. Individuals are usually contagious 1 day prior to symptom onset and up to 1 week after. The majority of influenza is a benign self-limited disease. Patients with following conditions are at risk for severe influenza and influenza related complications (Box 122.1). The common influenza related complications are bacterial

pneumonia (typically due to *Staphylococcus aureus*), sinusitis, and otitis media. Influenza can also assert its pathogenic effects by exacerbating underlying cardiopulmonary and other chronic health conditions. Occasionally influenza itself can cause a rapidly progressing pneumonia that leads to acute respiratory distress syndrome (ARDS).

Differential Diagnosis

The differential diagnosis is broad, because many different infectious diseases can present with similar symptoms. Other respiratory viruses like RSV, rhinovirus, or coronavirus can have a similar presentation. Additionally bacterial infections like pneumonia and meningitis can present similarly.

Diagnostic Testing

Influenza can be diagnosed clinically based on the signs and symptoms, especially during influenza season, but the accuracy of clinical diagnosis in the absence of supportive tests is not high because influenza shares common features with many viral and bacterial infections. Clinical diagnosis alone yields a sensitivity of 62% to 65% and a specificity of 63% to 67%.[20] There are several diagnostic tests available to the emergency clinician. Rapid influenza diagnostic tests are based on immunochromatographic assays that detect specific influenza antigens, yielding results in less than 30 minutes. The sensitivity of these tests can vary from 50% to 70%, with specificities above 95%.[21] Confirmatory tests are viral culture and RT-PCR. Viral cultures can take 3 to 10 days to result and are not useful in the emergency setting. RT-PCR can take between 1 to 6 hours to result and can be useful if there is a high suspicion of influenza, and confirmation of diagnosis will change management.

Management

The management of influenza centers on symptom control with antipyretics, analgesics, and hydration. There are several antiviral agents that are available to treat influenza, but there is some controversy surrounding treatment with these agents.

Neuraminidase Inhibitors. Oseltamivir, zanamivir, and peramivir are the currently available neuraminidase inhibitors. They work by inhibiting the release of viral progeny from infected cells. These drugs are active against both influenza A and B.

Oseltamivir is available orally as a capsule or suspension. The treatment dose in adults and children weighing more than 40 kg is 75 mg twice daily for 5 days. For children younger than 1 year old, the dose is 3 mg/kg twice daily. For children 1 year or older, the dose varies by weight: for those weighing less than or equal to 15 kg the dose is 30 mg twice daily, for those weighing >15 to 23 kg it is 45 mg twice daily, and for those weighing >23 to 40 kg it is 60 mg twice daily. The dosing does require adjustment in renally impaired individuals based on creatinine clearance. The main side effects reported have been nausea and vomiting.

Zanamivir is available as an aerosol powder and is administered via inhalation through a specialized inhaler and is approved for use in patients 7 years old and older. The treatment dose is two inhalations twice daily for 5 days. It is not recommended in patients with underlying asthma and chronic obstructive pulmonary disease (COPD), because it can cause bronchospasm.

Peramivir is the first IV neuraminidase inhibitor available for treatment in influenza patients. It gained U.S. Food and Drug Administration (FDA) approval in December of 2014. The treatment dose is 600 mg IV administered once as a single dose.

Adamantane Antivirals. Amantadine and rimantadine are the currently available adamantane antivirals. They prevent or greatly reduce the uncoating of the viral RNA of influenza A after attachment and endocytosis by host cells. They have no activity against influenza B. In the past, they have been used for prophylaxis and treatment for influenza A. In recent years, the circulating influenza strains have demonstrated greater than 90% resistance to these drugs. Therefore they are not currently recommended for use for influenza treatment.

The controversy surrounding use of neuraminidase inhibitors (NIs) has centered on its modest effect with treatment. The most recent Cochrane review found that oseltamivir reduced symptom duration by 16.8 hours in those treated within 48 hours of symptom onset, but it had no effect on hospitalization or reduction of severe influenza complications.[22] However, another recent meta-analysis found that treatment with oseltamivir was associated with accelerated symptom improvement, reduction of risk in lower respiratory tract complications, and decreased admission to hospital.[23] Investigations have also found that treatment of hospitalized patients with NIs is associated with reduction in mortality.[24,25] The greatest benefit is in very early treatment (within 6 hours of symptoms onset), but some studies have demonstrated benefit up to 5 days after symptoms onset in hospitalized patients.[26] The Centers for Disease Control and Prevention (CDC) recommendations are to treat all patients as early as possible who are hospitalized, have severe illness, or are at risk for influenza related complications.[27] The patient population at risk for influenza related complications is listed in Box 122.1.

Disposition

The majority of patients with influenza are discharged home with symptomatic treatment instructions, although this depends on the specific virulence of the circulating strain of the season. Patients with severe influenza require admission. These patients usually have accompanying cardiopulmonary comorbidities. A prospective study in the ED demonstrated that only 6% of patients with culture or PCR confirmed influenza were hospitalized.[28] A small number of influenza patients will require ICU admission because of primary influenza or acute exacerbation of an underlying illness. Influenza can cause rapidly progressive ARDS with refractory hypoxemic respiratory failure. These patients with rapidly progressive ARDS may benefit from transfer to centers that perform extracorporeal membrane oxygenation (ECMO). During the 2009 H1N1 pandemic, some centers had success with managing ARDS patients on ECMO.[29]

Coronavirus

Principles

Coronaviruses are single-stranded RNA viruses that cause respiratory illness. There are several strains known to occur in humans with most of them causing the common cold. Severe acute respiratory syndrome–coronavirus (SARS-CoV) is a particularly virulent coronavirus that first appeared in China in November 2002. SARS-CoV caused the severe acute respiratory syndrome (SARS). SARS affected at least 8,098 individuals in 29 countries across Asia, Europe, and North and South America. Most of the cases were from China and Hong Kong, with a mortality rate near 10%. Since 2004, there have not been any reported cases of SARS. The incubation period for SARS-CoV is typically between 3 to 10 days. SARS is transmitted through close contact with infected individuals via respiratory droplets. The virus can also be transmitted by touching a surface contaminated with infectious secretions. Patients are considered contagious for up to 10 days after resolution of fever if respiratory symptoms are improving.

In 2012, another novel coronavirus causing international concern emerged called *Middle East respiratory syndrome–coronavirus (MERS-CoV)*. The majority of cases have been reported from Saudi Arabia and United Arab Emirates, but cases have been reported in the United States, Europe, and Asia. All reported cases have been associated with direct or indirect exposure to travel or residence in the following countries: Saudi Arabia, the United Arab Emirates, Qatar, Jordan, Oman, Kuwait, Yemen, Lebanon, and Iran.[30]

This virus has a high mortality rate and shares many features with SARS-CoV. The mode of transmission has not fully been elucidated yet, but the most likely route is via direct aerosol transmission. It is unclear how contagious MERS-CoV is. There have been case reports of transmission in the health care setting via a less than 10-minute encounter, maintaining 3 feet distance, but without any personal protective equipment (PPE).[31] On the other hand, investigations have also revealed no transmission among close contacts.[32] The reported incubation time for MERS-CoV is between 5 to 14 days.

Clinical Features

Severe Acute Respiratory Syndrome. SARS initially causes high fevers, malaise, myalgias, chills, and rigors. This is followed by cough, shortness of breath, tachypnea, and pleuritic pain. Sore throat and fever are less commonly manifested in SARS, and diarrhea can occur later in the course of the disease. Close to one-third of patients will have improvement in symptoms after the initial febrile illness. Approximately 20% to 30% go on to require mechanical ventilation secondary to hypoxemia. Severe respiratory failure, sepsis, and multiorgan failure are the common causes of death in these patients. Risk factors for mortality include age above 60 years old, presence of diabetes mellitus, and heart disease.

Middle East Respiratory Syndrome. MERS causes an acute respiratory illness with fever, cough, dyspnea, sore throat, myalgias, and up to a third have gastrointestinal symptoms as well. MERS can rapidly deteriorate to acute respiratory failure. Close to half of the patients will require ICU admission and median time to ICU admission from symptoms onset is 2 days.[33,34] Similar to SARS, age, diabetes mellitus, ischemic heart disease, and other chronic health problems are risk factors for poor prognosis.[35]

Differential Diagnosis

The less severe, more common coronaviruses have similar presentations to the other benign upper respiratory tract infections like rhinovirus, adenovirus, parainfluenza, and other viral causes of upper respiratory infection (URI). For SARS and MERS other diagnoses to consider include bacterial pneumonia, influenza, other viral pneumonias, or other causes of ARDS.

Diagnostic Testing

Routine laboratory testing is not indicated for the benign URI caused by coronavirus. Laboratory diagnosis for SARS can be made via PCR, serologic testing, or viral culture. Samples can be sent from nasal secretions, blood, and even stool. The diagnosis of MERS can be also be confirmed by RT-PCR from upper or lower respiratory tract samples. There are no lab abnormalities that are pathognomonic for SARS but common abnormalities include anemia, leukopenia, lymphocytopenia, thrombocytopenia, and transaminitis. MERS patients tend to have leukopenia, lymphocytopenia, and elevated transaminases also. A chest x-ray should be obtained; from 60% to 100% of SARS patients will have abnormalities at some point during the course of illness. Over 80% of MERS patients have abnormalities on chest x-ray ranging from subtle findings to extensive bilateral infiltrates.[36]

Management

There is no specific antiviral treatment for coronavirus infections, including SARS and MERS. The mainstay of treatment is supportive care. For the benign URI, nothing more than rest, antipyretics, and analgesics are needed. On the other hand, patients with SARS and MERS may require more invasive supportive measures. The diagnosis of SARS or MERS will not be immediately apparent, so they should be initially treated with antibiotics covering community acquired or health care–associated pneumonia. If mechanical ventilation is required, they should be ventilated according to the ARDSNet strategy with low tidal volumes to further limit lung injury.

Prevention of transmission is an important component of SARS and MERS management. This involves early identification of cases and prompt isolation of suspected cases. Obtaining an accurate travel history in all febrile patients with a respiratory illness is key to early identification of cases of SARS and MERS. Nosocomial outbreak was a critical component of the 2003 SARS outbreak. CDC guidelines on infection control measures for these infections can be found at www.cdc.gov/sars/infection/index.html and www.cdc.gov/coronavirus/mers/infection-prevention-control.html.

Disposition

Most patients with coronaviruses can be treated at home. Patients with SARS may require admission to the hospital, with up to 30% requiring ICU care. MERS patients have a case fatality rate of 35% and will likely require admission to the hospital and ICU, depending on severity of illness. Patients with suspected SARS and MERS should be properly isolated with contact precautions and airborne isolation. The hospital infection control team and department of public health should be notified immediately for patients under investigation for SARS and MERS.

Rhinovirus

Principles

Human rhinovirus is the most common cause of the common cold. Infections peak in the fall and spring but can occur all year. The infection is spread via infected respiratory secretions and direct contact with infected patients. The virus can remain contagious on surfaces for several hours. Hand-to-face inoculation is likely one of the predominant mechanisms of spread, underscoring the importance of frequent handwashing to decrease transmission.

Clinical Features

Symptoms of rhinovirus infection are usually limited to the nose, nasopharynx, and pharynx. The common symptoms that occur are sore throat, nasal congestion, low-grade fever, sneezing, and cough. Less commonly in children, rhinovirus can cause lower respiratory tract infections like pneumonia and tracheobronchitis.

Differential Diagnosis

Other viruses that cause respiratory illness, such as coronaviruses, respiratory syncytial virus (RSV), parainfluenza viruses, influenza viruses, adenoviruses, and enteroviruses, can produce clinical syndromes similar to those produced by the rhinoviruses.

Diagnostic Testing

Definitive diagnostic testing is usually not necessary for rhinovirus. Virus panels do exist that use PCR to detect rhinovirus.[37] Samples are typically taken from nose, nasopharynx, or oropharynx.

Management and Disposition

The cornerstone of treatment is symptomatic relief with analgesics and antipyretics. Cough medicines should be avoided in children younger than 6 years old. This infection has a benign course and can be treated at home.

Adenovirus

Principles

Adenoviruses are double-stranded DNA viruses that commonly cause upper respiratory tract infections, gastrointestinal symptoms, and conjunctivitis. Infection is spread via respiratory droplets and close contact. The viruses are resilient and can survive outside of the body for up to 2 weeks.

Clinical Features

The most common presentation of adenovirus is as a URI with sore throat, cough, and fever. Gastroenteritis and conjunctivitis are also common manifestations. Other syndromes less frequently caused by adenoviruses include hemorrhagic cystitis, infantile diarrhea, myocarditis, encephalitis, and meningoencephalitis. In infants and immunocompromised patients, particularly hematopoietic stem cell transplant and solid organ transplant patients, adenovirus can cause severe life-threatening illness.

Differential Diagnosis

Other pathogens causing similar atypical pneumonia syndromes include influenza and parainfluenza viruses and *Mycoplasma pneumoniae*. Diarrheal syndromes may be similar to those caused by rotaviruses.

Diagnostic Testing

Because adenovirus mostly causes a benign self-limiting disease, routine diagnostic testing is unnecessary. If testing is required, qualitative or quantitative PCR from serum, tissue, or body fluid is the most diagnostic method.

Management and Disposition

The majority of these infections require only symptomatic treatment. There is no specific antiviral therapy that is routinely recommended. There have been reports of using cidofovir in immunocompromised patients with life-threatening adenovirus infection, but this is not routinely recommended. The majority of these patients will be treated at home. The most severe cases may require admission.

Parainfluenza

Principles

Parainfluenza is a single-stranded RNA virus that belongs to the *Paramyxoviridae* family. This infection is usually acquired in childhood. In the United States, parainfluenza infections have been reported to account for up to a quarter of respiratory disease in children. In adults, the burden of illness caused by parainfluenza is much less. There are four types each with their own clinical presentation. Parainfluenza is transmitted by close contact via infected respiratory secretions.

Clinical Features

Parainfluenza type 1 is the most common cause of croup. Parainfluenza type 2 is also associated with croup but causes less morbidity. Croup symptoms usually worsen at night and are characterized by a barky cough. Typically patients will have a fever and URI symptoms 1 to 2 days before the cough. Tachypnea and hoarse voice are common as well. In severe cases, stridor at rest may be present. Parainfluenza type 1 and 2 also cause lower respiratory tract infections in children. Parainfluenza type 3 more often causes bronchitis, bronchiolitis, and pneumonia. Parainfluenza type 4 is less common and causes a mild respiratory illness. In adults and older children, parainfluenza infections are mild and present as a simple URI.

Differential Diagnosis

Adenoviruses, rhinoviruses, influenza viruses, RSV, echoviruses, coxsackieviruses, and coronaviruses all can cause similar URI symptoms. If the primary presentation is croup, it is important to consider epiglottitis as a potential diagnosis.

Diagnostic Testing

Diagnosis is made from viral culture, rapid antigen test, or PCR. Specimens are usually obtained from nasal or throat swabs, or nasopharyngeal washings.

Management

There is no specific antiviral treatment for parainfluenza infection. The treatment is mainly symptomatic. For mild and moderate croup, a single dose of oral dexamethasone (0.6 mg/kg, maximum dose 20 mg) can be given.[38] For severe croup, nebulized racemic epinephrine should be administered in addition to oral or intramuscular corticosteroids.

Disposition

Most parainfluenza infections can be treated as an outpatient. Patients with mild croup can be discharged home. Patients with moderate and severe croup should be observed in the ED to ensure improvement before discharged home. If no improvement occurs after 4 hours, admission should be considered. Patients who receive racemic epinephrine should be monitored for at least 2 hours to ensure their severe symptoms do not recur. If they are well appearing, they can be discharged home. Patients that have continued stridor at rest, moderate to severe chest retractions, or hypoxemia should be admitted to the hospital.

Respiratory Syncytial Virus

Principles

RSV is an RNA virus that belongs to the *Paramyxoviridae* family. RSV causes significant morbidity in children. It is an important cause of death in young children in the developing world. In the United States, RSV is associated with approximately 20% of hospitalizations and 18% of ED visits in children younger than 5 years old. RSV is also an important cause of respiratory illness in the elders, affecting 3% to 10% of the population older than age 65 each year. RSV is spread via contact with

infected individuals, by exposure to respiratory secretions and fomites.

Clinical Features

RSV causes a range of respiratory disease. The illness is most severe in infants, causing pneumonia and bronchiolitis. Newborns with RSV can present with apnea. Symptoms usually begin with nasal congestion, rhinorrhea, low grade fever, and cough. Then 1 to 2 days after symptom onset, patients develop wheezing and increased respiratory effort. Symptoms can last up to 2 weeks. In adults and older children, RSV usually causes a benign URI typically lasting less than 5 days. Elders, immunosuppressed patients, and adults with chronic medical problems can develop severe lower respiratory tract disease.

Differential Diagnosis

The clinical presentation caused by RSV infections is similar to other upper and lower respiratory tract pathogens, including rhinovirus, parainfluenza, influenza, enteroviruses, coronaviruses, and bacterial causes of pneumonia. It is important to consider noninfectious causes of hypoxemia in infants, such as foreign body aspiration and asthma.

Diagnostic Testing

The common methods of diagnosis include viral culture, PCR, and rapid antigen detection tests. Specimens are typically obtained from nasopharyngeal swabs or washings. Other routine diagnostic testing is generally unnecessary and should be symptom targeted.

Management

The mainstay of treatment is supportive care. Beta-agonist bronchodilators are not recommended by the most recent guidelines published by the AAP.[39] We agree that routine inhaled bronchodilators should not be used for RSV bronchiolitis given the lack of evidence of improved outcomes. However, it is reasonable to administer a trial of inhaled albuterol for severe disease, because most of these patients were excluded from studies and some of the patients may actually have viral-induced asthma exacerbation. Corticosteroids have not been shown to provide any benefit. Supplemental oxygen should be provided for pulse oximetry less than 90%. Nebulized hypertonic saline can be used as an inpatient, currently data do not support use in the ED. For severe cases nasal continuous positive airway pressure (CPAP) can be trialed to avoid intubation. It is also important to treat dehydration associated with the disease with IV or nasogastric fluids if the patient cannot maintain oral intake. For prevention of RSV infection in high risk patients, the AAP recommends the use of palivizumab, a monoclonal anti-RSV antibody preparation, during the first year of life for infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants younger than 32 weeks gestation who require more than 21% oxygen for at least the first 28 days of life.

Disposition

Healthy adults and older children have a short disease course that is mild and can be treated at home. The majority of infants with the RSV will also be treated at home but may have prolonged illness. Infants younger than 1 year old that visit the ED for bronchiolitis have a median duration of symptoms of 15 days, and over a third of them have a subsequent unscheduled medical visit.[40] Approximately 1% to 3% of infants with RSV will require hospitalization for hypoxemia, respiratory distress, or dehydration. Approximately 15% of elders hospitalized with an acute cardiopulmonary diagnosis are diagnosed with RSV infection requiring ICU care.

VIRUSES ASSOCIATED WITH DIARRHEAL ILLNESS

Norovirus and Rotavirus

Principles

Norovirus is a member of the *Caliciviridae* family and is the most common cause of nonbacterial gastroenteritis. The infection is highly infectious because only a few particles are necessary to transmit the disease. Norovirus is spread through direct transmission from person to person via the fecal-oral route. Transmission can also occur through contaminated water, food, and surfaces. Norovirus is very stable in the environment and is resistant to most disinfectants, including alcohol hand wash. Outbreaks of norovirus occur in areas where people are in close proximity, including long-term care facilities, restaurants, hospitals, schools, and cruise ships. The number of ED visits for norovirus peaks in the winter months.

Rotaviruses are double-stranded RNA viruses that belong to the *Reoviridae* family. These viruses are present all over the world, and by 5 years old most children have been exposed to them. They are the leading cause of severe gastroenteritis in children. Since the introduction of rotavirus vaccine in developed countries, medical encounters for this disease have drastically decreased.[41,42]

Clinical Features

Norovirus. The disease causes a severe gastroenteritis, with vomiting, diarrhea, and abdominal cramping. In infants and children, vomiting is the primary symptom, whereas adults more commonly have diarrhea. The gastrointestinal symptoms can be accompanied by fever, headache, and myalgias as well. The diarrhea is typically non-bloody, watery, and profuse. The acute illness usually lasts for ½ to 3 days.

Rotavirus. The illness manifests as sudden onset of nausea, vomiting, and profuse watery diarrhea, with fever, headache, and myalgias. The disease course is usually 3 to 7 days. The spectrum of disease can range from asymptomatic to severe fatal dehydration.

Differential Diagnosis

Other causes of viral gastroenteritis include adenovirus, enterovirus, and certain coronaviruses. *Clostridium difficile* infection and some bacterial gastroenteritis can present similarly as well.

Diagnostic Testing

Norovirus diagnosis can be confirmed by PCR of stool or vomit specimen. Rapid antigen detection test of stool specimen is the most common method of diagnosis for rotavirus.

Management

There is no specific treatment for these viral gastrointestinal infections. Management centers on ensuring that patients are adequately hydrated and correcting significant electrolyte derangements. Most patients can be treated with oral rehydration alone. Patients with severe dehydration warrant IV rehydration. Meticulous attention to standard precautions and hand hygiene is important to prevent spread of these diseases.

Disposition

The majority of patients can be managed at home with oral therapy. Very young patients or patients with chronic illness may be at risk for more severe disease and benefit from IV therapy and monitoring. Depending on the severity of illness, these patients could be managed in an observation unit or may require inpatient admission.

VIRAL INFECTIONS WITH NEUROLOGIC MANIFESTATIONS

Principles

Arboviruses are a group of viruses that are transmitted via arthropod vectors, generally mosquitoes and ticks. Encephalitis is a common manifestation of arboviral infection. Most of these viruses are primarily transmitted from the arthropod vector to another animal, and humans are only incidentally infected. The arboviral viruses that cause encephalitides belong to the following families: *Flaviviridae, Togaviridae, Bunyaviridae,* and *Reoviridae.*

St. Louis encephalitis virus, West Nile virus (WNV), and Japanese encephalitis virus belong to the *Flaviviridae* family. These viruses are primarily maintained in a natural cycle of bird-mosquito-bird transmission. Given the mosquito vector, in North America and other temperate climates, these infections have a higher incidence in the summer months. WNV was popularized at the turn of the 20th century because of its first time appearance in the western hemisphere. WNV was originally localized to Africa and the Middle East, but in 1999 WNV emerged in New York City and since then has spread to the Pacific coast, as far south as Argentina, and as far north as Canada. Now WNV is the leading cause of domestically acquired arboviral infection in the United States.[43] In Asia, Japanese encephalitis virus is the most prevalent cause of viral encephalitis with the greatest morbidity as well.

La Crosse virus and California encephalitis virus belong to the *Bunyaviridae* family. According to data from the state health departments, La Crosse virus was the most common cause of encephalitis among children in the United States from the years 2003 to 2012.[44] Eastern equine encephalitis (EEE) virus, Western equine encephalitis virus, and Venezuelan equine encephalitis virus belong to the *Togaviridae* family and cause infections in certain parts of North and South America.

Clinical Features

Arboviral infections cause a wide range of presentation including subclinical disease, nonspecific febrile illness, hemorrhagic fever, meningitis, acute flaccid paralysis, and severe encephalitis. Typically encephalitis patients will begin with a nonspecific febrile illness accompanied by malaise, sore throat, and respiratory symptoms. Headache, photophobia, meningismus, lethargy, somnolence and altered mental status will then follow. Severe disease can manifest as paralysis, coma, and seizures. Depending on the virus, it can be common for patients that recover to have some neurologic sequelae.

West Nile Virus

The majority of people who become infected with WNV are asymptomatic. The most common presentation of symptomatic WNV is West Nile fever, a self-limiting illness characterized by fever, headache, malaise, and myalgias. Patients can also experience gastrointestinal symptoms as well. Between a quarter to half of the patients can also have an accompanying maculopapular rash on the chest, back, and arms. It is estimated that around 1% of WNV causes neuroinvasive disease. The neuroinvasive disease manifests as meningitis, encephalitis, or a flaccid paralysis. WNV neuroinvasive disease carries with it a 10% mortality rate. Age and organ transplantation have been identified as a risk factor for more severe neuroinvasive disease and mortality for WNV infections.[45]

Eastern Equine Encephalitis Virus

EEE virus is the most dangerous of the viruses that cause equine encephalitides. It occurs along the Gulf and Atlantic coast with predominance in the late summer months. The usual manifestation is fever, chills, headache, and myalgias lasting 1 to 2 weeks, typically followed by resolution. A small portion of patients will go on to develop encephalitis with headache, nausea, vomiting, altered mental status, and focal neurologic deficits. Approximately 2% to 6% of infected patients develop rapidly deteriorating severe encephalitis that results in coma. EEE virus infection that results in encephalitis is associated with 30% mortality.

St. Louis Encephalitis Virus

The majority of infections are asymptomatic, but as patients get older the rate of symptomatic infections increases dramatically. The incubation period varies from 4 to 21 days. Symptomatic disease presents as fever, myalgias, and headaches. Patients older than 60 frequently present with encephalitis, with mental status ranging from lethargy to coma. Acute flaccid paralysis occurs in approximately 6% of patients with encephalitis.

Differential Diagnosis

The diagnosis of arboviral encephalitis is difficult based on clinical presentation alone. It shares many features with other arboviral infections, other viral causes of encephalitis, bacterial meningitis, HSV encephalitis, leptospirosis, Lyme disease, and brain abscess.

Diagnostic Testing

The primary method of diagnosis is CSF analysis for serologic markers or PCR. WNV encephalitis is diagnosed by detecting IgM antibody in CSF. Viral culture is not commonly used for these diagnoses. There is often a broad differential diagnosis when evaluating these patients, so it is very important to elicit travel and potential exposure history to narrow the differential diagnosis. When performing a LP, it can be helpful to obtain an extra tube or vial of CSF to put on hold. This extra CSF sample is useful because testing for arboviral infections is often sent after the initial evaluation, assessing for more common etiologies of neurologic infection, such as bacterial meningitis or HSV encephalitis, is completed. CSF will demonstrate an elevated WBC count, with lymphocyte predominance. Early during a WNV infection there may be a neutrophil predominance. Ancillary testing with CT or MRI may be indicated, depending on the severity of neurologic symptoms.

Management

The treatment for these entities remains largely symptomatic. There is no specific antiviral therapy or immunoglobulin treatment with proven benefit. In patients that develop cerebral edema, the therapies focus on preventing secondary brain injury and treatment of cerebral edema by maintaining adequate cerebral perfusion pressure, treating seizures, and avoiding hypoxemia, high fever, and hypoglycemia or hyperglycemia.

Disposition

Patients with neurologic symptoms should be admitted to the hospital. These patients often require neurology and infectious disease specialists to consult in their care. Arboviral infections are reportable diseases. Long-term outcomes for these patients can vary. Full recovery can usually be expected in patients with WNV meningitis. WNV encephalitis patients often have residual effects, with over half of them reporting some type of persistent symptoms (fatigue, muscle aches, decreased activity, memory difficulty, concentration difficulty) beyond 6 months.[46]

VIRAL HEMORRHAGIC FEVERS

Dengue Virus

Principles

Viruses in the *Flaviviridae* family can also cause hemorrhagic fevers. Dengue is the most common virus in this family to cause human infection. It can be found all over the world, with most infections occurring in Southeast Asia, the Western Pacific, and Central and South America. It is one of the most important causes of fever in the returned traveler. It is transmitted via the mosquito vector, *Aedes aegypti* and *Aedes albopictus,* and humans are the natural host.

Clinical Features

Dengue can cause a wide spectrum of disease. Many infected individuals with dengue are asymptomatic. Dengue fever is a self-limited illness characterized by fever, headache, retroorbital pain, severe myalgias, and arthralgias. Symptoms can last up to 1 week. Dengue hemorrhagic fever (DHF), a more severe syndrome, occurs when the following four criteria are present: (1) increased vascular permeability (pleural effusion, ascites, hemoconcentration), (2) thrombocytopenia, (3) fever lasting 2 to 7 days, and (4) hemorrhagic tendency or spontaneous bleeding. Dengue shock syndrome (DSS), the most severe presentation of dengue infection, is present when DHF occurs with circulatory shock.

Differential Diagnosis

Other diagnoses to consider in suspected dengue patients include malaria, chikungunya, rickettsial infections, leptospirosis, and other viral hemorrhagic fevers, including Ebola, Marburg, yellow fever, or bunyaviruses. It is also important to consider the diagnosis of measles in a returned febrile traveler with a rash, because many countries that have endemic dengue also have endemic measles.[47]

Diagnostic Testing

The diagnosis can be made via serologic testing with IgM assay or viral RNA detection with RT-PCR. Other laboratory findings that may be present with dengue infection include leukopenia, thrombocytopenia, elevated hematocrit (due to hemoconcentration from fluid loss), and abnormal liver function tests. In DHF, coagulopathy can be present.

Management

There are no specific antiviral agents that treat dengue. The treatment is mainly supportive. Dengue fever is usually a self-limited illness and can be treated with rest, antipyretics, analgesics, and fluid replacement therapy. Nonsteroidal anti-inflammatory drugs and aspirin should be avoided given the bleeding tendencies associated with these medications. Patients with DHF and DSS require close monitoring, IV fluid replacement therapy, and organ support as indicated. Hemorrhagic sequelae are treated with blood product transfusions as needed. Steroid therapy for severe dengue has been evaluated in several low quality studies, but the evidence to date is inconclusive and steroid treatment cannot be recommended at this time.[48] The control of epidemics revolves around reducing the mosquito vector population and preventing humans from being bitten by mosquitoes.

Disposition

Depending on the severity of illness, patients with dengue fever can be treated as an outpatient; some may require admission for rehydration therapy. Patients with DHF will require admission to the hospital for monitoring and IV fluid resuscitation and patients with DSS will require admission to the ICU.

Chikungunya Virus

Principles

Chikungunya is an arbovirus in the *Alphaviridae* family that was originally endemic to West Africa. Since early this millennium, the infection has spread broadly, responsible for multiple outbreaks in Asia, Europe, and the Indian subcontinent. In 2013, local transmission was identified in the Americas for the first time.[49] The vectors are the same as dengue, the *Aedes aegypti* and *Aedes albopictus* mosquitoes.

Clinical Features

Chikungunya causes a self-limiting disease very similar to dengue. Fever, myalgias, and polyarthralgias are the hallmark of this disease. The joint pain can be so severe that ambulation is impaired. Symptoms typically last for 7 to 10 days. More than half of infected individuals will develop a maculopapular rash several days after fever onset. Risk factors for severe disease with a higher mortality include age older than 65 years old, diabetes, and underlying cardiopulmonary disorders.

Differential Diagnosis

Other febrile illnesses with rash and myalgias, and arthralgias should be considered, including dengue, malaria, African tick bite fever, leptospirosis, measles, rubella, relapsing fever, EBV, and meningococcal disease. Noninfectious disorders such as adult onset Still's disease and other rheumatologic disorders should also be considered.

Diagnostic Testing

The diagnosis can be confirmed via enzyme-linked immunosorbent assay (ELISA) testing for antibodies, RT-PCR for detecting viral RNA, or viral culture. Lab abnormalities that may be associated with acute infection include abnormal liver function tests, thrombocytopenia, and lymphopenia.

Management and Disposition

Treatment is mainly supportive. Antipyretics, anti-inflammatory agents, and analgesics play an important role in symptom control. IV fluids may be necessary, depending on disease severity. Prevention of disease centers on reducing mosquito exposure. Most patients can be treated at home. Patients that present with severe disease may require admission IV hydration and observation until they are stable.

Yellow Fever Virus

Principles

Yellow fever virus is another arbovirus in the *Flaviviridae* family that can cause a viral hemorrhagic fever. Prior to the discovery of its mosquito vector transmission, there were multiple yellow fever epidemics in Africa, Europe, and the Americas. The vector is the *Aedes* or *Haemagogus* mosquito. Vector control and development of a vaccine have greatly reduced the burden of this disease over the past several decades. Currently yellow fever occurs in tropical regions of Africa and South America.

Clinical Features

The incubation period is between 3 to 6 days. Patients present with an acute febrile illness accompanied by chills, malaise, headache, myalgias, nausea, and dizziness. Patients can have a much lower heart rate than expected in reference to the high fever that is present. This acute febrile phase of the illness can last between 3 to 6 days. Patients then experience a short period of remission, lasting up to 24 hours; some patients recover completely, whereas others go on to have a more severe recurrence of illness with fever, vomiting, jaundice, acute liver injury, acute renal failure, and hemorrhagic manifestations. The hallmark feature of yellow fever is jaundice with hemorrhagic fever. The mortality of patients with hepatorenal involvement ranges from 20% to 50%.

Differential Diagnosis

One must consider other febrile illnesses that occur in these endemic areas, including leptospirosis, relapsing fever, viral hepatitis, malaria, other viral hemorrhagic fevers, and dengue.

Diagnostic Testing

Laboratory diagnosis is usually made by detecting IgM and neutralizing antibodies in the serum. There are a number of laboratory abnormalities that occur in this illness, including elevated aspartate transaminase (AST), alanine transaminase (ALT), and direct bilirubin. Patients with severe disease also have hematologic labs consistent with disseminated intravascular coagulation (DIC).

Management

There are no specific antiviral treatments for yellow fever. The treatment is supportive. Fluids, antipyretics, and analgesia are the main symptomatic treatments. Given the risk of hemorrhagic fever, aspirin and nonsteroidal anti-inflammatory drugs should generally be avoided. If severe disease with shock develops, then patients may require IV fluid resuscitation, blood product resuscitation, vasopressors, mechanical ventilation, and renal replacement therapy.

Since there is no specific treatment for yellow fever, much attention has been placed on prevention. Personal protection measures to avoid mosquito bites and vector control at the community level are important in preventing disease. A live-virus vaccine is available for persons travelling to endemic areas. The vaccine is recommended for individuals 9 months old and older who live in or are travelling to endemic areas. Many countries where yellow fever is endemic require a certificate of vaccination for entry.

Disposition

Depending on the severity of illness, patients can be treated at home or may require admission to the hospital. Severe illness may require ICU admission given the high mortality associated with it.

Ebola

Principles

Ebola virus is an RNA virus that belongs to the *Filoviridae* family. Ebola virus disease (EVD) causes a severe viral hemorrhagic fever. Ebola was first described in 1976 in Sudan and what is now the Democratic Republic of the Congo (Zaire at that time). Since then, there have been a number of outbreaks occurring in rural areas in Africa. The current 2014 Ebola outbreak in West Africa is the most severe outbreak in history. It began March 2014 in Guinea and then spread to Sierra Leone and Liberia. Nigeria, Senegal, and Mali have also been affected but to a much lesser degree. As of April 1, 2015, this outbreak has affected 25,228 people and claimed 10,462 lives.[50] Prior to this outbreak, the largest recorded outbreak had resulted in fewer than 300 deaths. This outbreak has also resulted in the first cases of Ebola acquired outside of Africa. A female nurse assistant in Spain acquired the disease after caring for an Ebola patient who was transported from Sierra Leone to Spain.[51] Subsequently two nurses contracted Ebola in the United States after caring for an Ebola patient who contracted the virus in Liberia.

The mortality rate for Ebola infections ranges from 25% to 90%. Transmission of the virus occurs by direct contact of infected tissue or infected bodily fluids, including blood, saliva, vomit, feces, or semen. Individuals are not contagious until they show symptoms. The usual incubation time is 5 to 7 days but can range from 2 to 21 days.

Clinical Features

The initial symptoms include high fever, headache, myalgias, malaise, sore throat, and profuse vomiting and diarrhea. After 5 to 7 days, patients can progress to develop the hemorrhagic manifestations, which include spontaneous bleeding, ecchymosis, and petechia. It is also common for patients to not develop any hemorrhagic complications.[52,53] An erythematous maculopapular rash can occur during that time that eventually desquamates. Patients can become hypovolemic and develop severe metabolic derangements secondary to fluid losses via the gastrointestinal tract. Eventually patients advance to shock and multiorgan failure.

Differential Diagnosis

The symptoms of Ebola are initially nonspecific and overlap with other diseases. Other more common infections from the endemic regions include malaria, typhoid fever, other viral hemorrhagic fevers (ie, Marburg, bunyaviruses), meningococcemia, leptospirosis, or other bacterial illnesses.

Diagnostic Testing

Testing should only be conducted for patients that meet clinical criteria of having exposure history *and* signs or symptoms of EVD. The hospital should also have a protocol for handling lab specimens of potential EVD patients. The risk of acquiring EVD through lab testing is low but not zero. RT-PCR assay using a plasma specimen is currently the main method of Ebola diagnosis. The turnaround time for this testing can vary from 12 to 24 hours. Recently a rapid antigen point-of-care test, with a turnaround time of 15 minutes has been developed with good sensitivity and specificity as compared to RT-PCR.[54] Laboratory findings that can accompany Ebola infection include thrombocytopenia, anemia, coagulopathy, transaminitis, elevated creatinine, hypocalcemia,

and hypokalemia. All patients should have testing for malaria performed with thin and thick smear of the blood. Malaria is much more likely than Ebola in the endemic population and returned travelers. Coinfection is also common; in one study of Ebola patients in Guinea, 11% of the patients had concomitant malaria infection.[53]

Management

The important guiding principles when managing a suspected EVD case are to treat the patient and prevent the spread of the infection. The CDC has developed practical algorithms for evaluating suspected EVD cases in United States EDs (www.cdc.gov/vhf/ebola/pdf/ed-algorithm-management-patients-possible-ebola.pdf). The basic tenets are to identify, isolate, and inform (Box 122.2).

The main therapy for Ebola victims is supportive care. Patients are empirically managed with malaria treatment, broad spectrum antibiotics, and antipyretics. They also require rehydration therapy, preferably with IV fluid and electrolyte repletion. Additionally, many EVD patients will require support of organ failure. This may necessitate renal replacement therapy, mechanical ventilation, vasopressors, or blood product administration.

There are a number of experimental therapies currently being tested for EVD. Two United States health care workers that contracted Ebola in Liberia and were treated in the United States received an investigational therapy called *ZMapp* under emergency investigational new drug approvals from the FDA.[55] ZMapp is a combination of three humanized mouse monoclonal antibodies against Ebola viral antigens. The WHO also approved the use of convalescent serum from Ebola patients to treat acute EVD patients.[56]

BOX 122.2

Centers for Disease Control and Prevention Algorithm for Emergency Department Identification of Ebola Virus Disease

1. Identify: Emergency department (ED) providers should identify patients at risk for Ebola virus disease (EVD) by identifying exposure history and then determining if signs and symptoms of EVD are present.
   Exposure history:
   - Has the patient lived in or travelled to a country with Ebola?
   - Has the patient had contact with an individual with confirmed EVD in the past 21 days?

   Identify signs and symptoms:
   - Fever (subjective or ≥100.4° F or 38.0° C)
   - Headache
   - Weakness
   - Myalgias
   - Vomiting
   - Diarrhea
   - Abdominal pain
   - Hemorrhage
2. Isolate: Once a patient has been screened positive as a potential EVD patient (has *both* exposure history *and* signs or symptoms compatible with EVD), he or she should be isolated immediately to a private room that can be closed, with a private bathroom or covered bedside commode. The staff caring for this patient needs to wear appropriate personal protective equipment (PPE) and a log should be kept of everyone entering and leaving the room.
3. Inform: Hospital infection control and the health department should be immediately notified. To protect health care providers and prevent the spread of Ebola, ED providers should be familiar with these procedures for potential EVD patients.

Disposition

It is paramount that providers caring for potential EVD patients be familiar with proper isolation practices. The CDC stresses is that health care providers should receive extensive training and demonstrate competency in Ebola-related infection control procedures specifically in putting on and removing the PPE. Many hospitals have developed internal guidelines, but the CDC website is a useful resource and gives comprehensive guidance regarding how to deal with potential EVD patients in the United States health care setting (www.cdc.gov/vhf/ebola/healthcare-us/index.html).

The CDC has also developed a strategy to help hospitals prepare for suspected EVD cases (www.cdc.gov/vhf/ebola/pdf/preparing-hospitals-ebola.pdf). There is a tiered system categorized by frontline health care facilities, Ebola assessments hospitals, and then Ebola treatment centers. All hospitals should have and follow infection control protocols, ensure staff is trained and competent in safe PPE practices, and have a system in place to manage waste disposal, cleaning, and disinfection. Patients with suspected EVD are admitted to hospital isolation rooms, and many of them will need ICU care. As previously stated, the mortality of EBV is high, but with access to modern medical facilities with ICUs, patients are likely to have much better outcomes than previously reported.

Marburg

Principles

Marburg virus is an RNA virus that belongs to the *Filoviridae* family. It is an important cause of viral hemorrhagic fever in central Africa. Marburg cases have occurred in the following countries: Uganda, Zimbabwe, the Democratic Republic of the Congo, Kenya, and Angola. Cases have been reported outside Africa, including Germany, the former Yugoslavia, Netherlands, and the United States, all with confirmed exposure to an African source. The virus was described first in 1967 after an outbreak occurred in Marburg, Germany, when laboratory personnel working with African Green monkeys developed fever and hemorrhagic shock. Direct transmission occurs with contact with blood, secretions, or solid organs of infected individuals. It is currently thought that the natural host of the Marburg virus is the African fruit bat. The incubation period is 3 to 9 days. The disease carries a similar fatality rate to Ebola, with case fatality rate ranging from 24% to 88%.

Clinical Features

Marburg and Ebola virus cause a very similar clinical syndrome. Marburg virus illness initially causes fever, headache, malaise, and myalgias. After the 3rd to 5th day, severe abdominal pain, cramping, vomiting, and diarrhea occurs. Around the same time, a maculopapular rash may develop. Half of the patients will also develop hemorrhagic manifestations during this time. Hematemesis, diarrhea, oropharyngeal bleeding, and bleeding from venipuncture sites can all occur. Death usually occurs because of acute blood loss and septic shock.

Differential Diagnosis

The differential diagnosis of Marburg infection is very similar to that of Ebola infection in that the symptoms are initially

nonspecific and overlap with other diseases. Other more common infections from the endemic regions include malaria, typhoid fever, other viral hemorrhagic fevers (ie, Marburg, bunyaviruses), meningococcemia, leptospirosis, or other bacterial illnesses.

Diagnostic Testing

Diagnosis requires laboratory testing, because the clinical features overlap with many other viral hemorrhagic fevers. Diagnosis can be made via RT-PCR, ELISA, antigen detection tests, serum neutralization tests, and viral culture.

Management

The priorities of managing a suspected Marburg hemorrhagic fever (MHF) case are similar to a suspected EVD case. Early recognition is key for controlling the spread of this infection. It is important to consider this disease in potential patients by assessing the patient for travel history to countries with endemic MHF or contact with someone who has had MHF within the past 3 weeks and then assessing if symptoms consistent with MHF are present. Patients identified at risk by the screening process should be isolated to a private room with private bathroom. Public health authorities and hospital infection control personnel should be immediately informed. Please refer to the Ebola section of this chapter for further details.

There is no specific treatment for MHF. The treatment is mainly supportive and directed at the patient's symptoms. Patients will initially require large fluid volume resuscitation and antipyretics. Patients that develop end-organ failure will require advanced therapies, such as vasopressors, mechanical ventilation, and renal replacement therapy. Patients with hemorrhagic manifestations will also require blood product resuscitation with packed red blood cells (PRBCs) and fresh frozen plasma.

Disposition

Patients with MHF will require admission to the hospital and many will require ICU admission. It is important to observe strict isolation practices and ensure that staff use PPE when caring for the patient. When appropriate, patients should be transferred to specialized treatment centers that are prepared and designated to care for patients with viral hemorrhagic fevers.

Lassa Fever

Principles

Lassa virus is an *Arenavirus* that is endemic to West Africa. Its reservoir is an African rodent *Mastomys natalensis.* Humans contract the disease by exposure to urine or feces of *Mastomys natalensis.* Human to human transmission can occur via contact with blood or bodily secretions from infected humans. The incubation period is usually around 10 days, but can range from 3 to 21 days. Unlike Ebola and Marburg, the majority of Lassa infections are asymptomatic. The case fatality rate is less than 2%.

Clinical Features

When patients are symptomatic with Lassa fever, symptoms usually begin with gradual onset of fever and malaise. Headache, myalgias, sore throat, cough, chest pain, abdominal pain, nausea, vomiting, diarrhea can all occur after a few days. Patients can also develop facial edema, pleural effusion, myocarditis, and encephalitis. Less than 20% of symptomatic patients progress to develop hemorrhagic manifestations. Patients that do go on to have full-blown hemorrhagic fever have a much higher mortality rate. Third trimester pregnancy is associated with a more severe disease with high mortality as well.

Differential Diagnosis

The differential diagnosis is broad and includes that of other viral hemorrhagic fevers.

Diagnostic Testing

Diagnosis on clinical grounds alone is difficult, because Lassa fever shares features with many other diseases. Diagnosis can be made via RT-PCR, ELISA, antigen detection tests, and viral culture.

Management

Ribavirin has been shown to decrease overall mortality. The greatest effect occurs when treatment is initiated early within the first 6 days after fever onset. The remainder of treatment is supportive care with volume resuscitation, antipyretics, and blood product administration if hemorrhagic disease occurs. As with other viral hemorrhagic fever support of organ failure with mechanical ventilation, vasopressors, and renal replacement therapy may also be needed. Although high quality evidence does not exist, guidelines do recommend ribavirin as postexposure prophylaxis for definitive high-risk exposures.[57] Prevention of Lassa fever at the community level centers on good hygiene and rodent control.

Disposition

Symptomatic patients with Lassa fever will require hospital admission. The same principles of the other viral hemorrhagic fevers of prompt recognition, identification, isolation, and informing authorities apply to Lassa fever as well. Please refer to the prior sections in this chapter on Ebola and Marburg for more details.

KEY CONCEPTS

- There have been recent outbreaks of vaccine-preventable childhood infections secondary to unvaccinated individuals and travel to areas where disease is still endemic. Emergency clinicians should recognize the possibility of these once rare diseases.
- Herpes simplex encephalitis is a severe disease that is fatal if left untreated. Clinicians should suspect this diagnosis when evaluating severely ill patients for suspected meningitis or encephalitis, and promptly institute empirical therapy with IV acyclovir while awaiting diagnostic results.
- Primary varicella can be dangerous in select populations, including older children, adults, and pregnant patients. These patients require treatment with acyclovir.
- Zoster patients should be treated with acyclovir if they present within 72 hours of symptoms onset or if they are immunocompromised regardless of duration of illness. Disseminated zoster should be treated with IV acyclovir.
- In generally healthy patients with influenza infection, the duration of illness can be shortened by almost 1 day if antiviral treatment is administered within 48 hours of symptom onset. Hospitalized patients with influenza infection should be treated with antiviral medication regardless of duration of symptoms, because it may decrease mortality and influenza complications.
- There are many emerging viral infections including SARS-CoV, MERS-CoV, and Ebola that should be considered in febrile patients. It is important to identify patients at risk by determining travel history and exposure history to individuals with confirmed infection. Once a patient is deemed at risk, the patient should be promptly isolated according to established guidelines while further investigation occurs. It is also important to immediately inform the hospital infection control program and public health agencies.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 122: QUESTIONS & ANSWERS

122.1. Which of the following patients does not require antiviral treatment for confirmed influenza infection?
- **A.** 1-year-old male with 24 hours of symptoms.
- **B.** 22-year-old otherwise healthy female with symptoms for 3 days.
- **C.** 25-year-old male with a history of asthma and morbid obesity with symptoms for 2 days.
- **D.** 35-year-old male with no significant past medial history with symptoms for 5 days, intubated with severe hypoxemic respiratory failure, admitted to the intensive care unit (ICU).
- **E.** 65-year-old male with history of asthma, coronary artery disease, congestive heart failure with 2 days of mild symptoms.

Answer: B. The 22-year-old female with no risk factors for influenza related complications does not require antiviral treatment since her symptoms have been present for 4 days. The Centers for Disease Control and Prevention (CDC) recommends treating all patients as early as possible who are hospitalized, have severe illness, or are at risk for influenza related complications. The greatest efficacy for antiviral treatment is within 48 hours of symptom onset, but admitted patients with severe disease should be treated regardless of symptom onset.

122.2. A 19-year-old female presents to the emergency department (ED) with fever, altered mental status, and seizures. She is a college student and lives in a dormitory. Her only past medical history is occasional cold sores. She had been in her usual state of health until 2 days ago when she developed fevers up to 38.5°C and headache. Today she became more lethargic and had two generalized seizures prior to ED arrival. What is the next best course of action?
- **A.** Administer 2 g intravenous (IV) ceftriaxone, 1g IV vancomycin, IV acyclovir 10 mg/kg every 8 hours, order computed tomography (CT) scan of head, and then perform lumbar puncture (LP).
- **B.** Administer 2 g IV ceftriaxone and admit to internal medicine service for further evaluation.
- **C.** Administer 650 mg acetaminophen, 2 liters of IV fluids, and admit to the observation unit with the diagnosis of viral syndrome.
- **D.** Order magnetic resonance imaging (MRI) of the brain, administer 1 g phenytoin, and consult neurology.
- **E.** Prescribe 1 g valacyclovir twice daily for 10 days and 650 mg acetaminophen every 4 to 6 hours as needed and discharge home.

Answer: A. This patient has herpes simplex virus (HSV) encephalitis. Given the high mortality associated with this condition, antiviral therapy should be started as soon as the diagnosis is suspected. There is significant overlap in the clinical presentation of bacterial meningitis and HSV encephalitis, so patients should empirically be treated for both diagnoses while awaiting cerebrospinal fluid (CSF) results. HSV encephalitis cannot be treated as an outpatient and requires 14 to 21 days of treatment with IV acyclovir. An MRI may be necessary eventually to look for temporal lobe involvement but is not necessary at the time of ED presentation and can be negative early in the course of disease.

122.3. Which of the following associations is correct?
- **A.** Chikungunya virus—viral hemorrhagic fever
- **B.** Ebola virus—febrile illness with severe arthralgias and myalgias
- **C.** Herpes simplex virus type 1 (HSV-1)—benign meningitis
- **D.** Herpes simplex virus type 2 (HSV-2)—necrotizing hemorrhagic encephalitis
- **E.** Middle East respiratory syndrome–coronavirus (MERS-CoV)—severe acute respiratory failure

Answer: E. MERS-CoV causes an acute respiratory illness with fever, cough, and dyspnea. HSV-1 causes necrotizing hemorrhagic encephalitis, typically involving the temporal lobes. HSV-2 can cause meningitis in over 25% of patients with primary infection. In contrast to HSV encephalitis, HSV meningitis has a benign course. Ebola virus causes a severe hemorrhagic fever. Chikungunya causes a self-limiting disease with fever, myalgias, and polyarthralgias.

122.4. An 18-year-old male who arrived from Sierra Leone 2 weeks ago presents with fever, headache, vomiting, and rash. He has a temperature of 103.1°F (39.5°C) and erythematous maculopapular rash over his trunk, back, and arms. He appears ill and severely dehydrated. Which of the following is immediately indicated?
- **A.** 2 g ceftriaxone and lumbar puncture (LP)
- **B.** Intravenous (IV) acyclovir for 10 days
- **C.** Isolation and contact the public health department
- **D.** Ribavirin
- **E.** Thin and thick smear to check for malaria

Answer: C. This is a classic presentation for Ebola virus disease (EVD). The exposure history is important. Patients should be asked if they have lived or travelled to a country with Ebola or had contact with a confirmed EVD patient in the past 21 days. If the answer is yes, then the next task is to assess for any signs or symptoms compatible with Ebola, including fever, headache, weakness, myalgias, vomiting, diarrhea, abdominal pain, or hemorrhage. Once a patient has been screened positive as a potential EVD patient, he or she should be immediately isolated and hospital infection control and the health department should be notified at once.

122.5. Which of the following viruses is not transmitted by a mosquito vector?
- **A.** Chikungunya virus
- **B.** Dengue virus
- **C.** Lassa fever virus
- **D.** West Nile virus (WNV)
- **E.** Yellow fever virus

Answer: C. The reservoir for the Lassa virus is an African rodent *Mastomys natalensis.* Humans contract the disease by exposure to urine or feces of *Mastomys natalensis.* Human to human transmission can occur via contact with blood or bodily secretions from infected humans. The other viruses are all arboviruses transmitted via a mosquito vector.

CHAPTER 123

Rabies

Jeffrey Bullard-Berent

PRINCIPLES

Rabies is one of the first infectious diseases described in recorded history, and it remains a huge public health problem, particularly affecting vulnerable populations in poor and rural areas.[1,2] Human rabies disproportionately affects children, with an estimated 40% of rabid bites occurring in those 15 years of age and younger.[3] The World Health Organization (WHO) has estimated approximately 61,000 deaths worldwide from rabies annually, with 95% of these occurring in Asia and Africa (Fig. 123.1). As a result of the successful vaccination of domestic animals started in 1947, human rabies is extremely rare in the United States today, with only two or three cases annually; these are typically caused by domestic transmission from non–dog vectors, organ transplantation, or victims infected in other countries from dog or bat bites who are now in the United States.[4]

Epidemiology

All mammals may be infected with rabies, but dogs remain the largest reservoir, the most commonly infected, and the leading vector for human rabies.[5] Dogs are the primary reservoir of rabies in Asia and Africa, but many countries in South America with active vaccination programs have shown tremendous reductions in dog and human rabies cases over the past 25 years.[6] In the United States, Canada, Mexico, South America, western Europe, and Australia, bats are an important reservoir and important source of human rabies. In Europe, Canada, and the Arctic, the fox is the principal carrier; in Puerto Rico, it is the mongoose.

The total number of rabies cases in the United States has remained relatively constant over the past 20 years. Over 90% of cases were caused by exposure to the secretions of raccoons (36%), bats (27%), and foxes (25%; Figs. 123.2 to 123.4; and Table 123.1).[7]

Rabies caused by exposure to domestic animals represented only 8% of all cases in the United States in 2013. The most common vectors were cats (56%), dogs (19%), and cattle (18%).[7]

Since 2013, 34 cases of human rabies have been diagnosed in the United States. Most occurred in males and resulted from exposure to dogs, bats, or foxes or from organ transplantation.[8-10] Transmission of the rabies virus to humans has been documented by bite and scratch from reservoir animals, with bite transmission much higher than scratch. Human to human transmission has been confirmed through transplantation only.[8]

Pathophysiology

Rabies is caused by an RNA virus from the genus lyssavirus, in the family Rhabdoviridae (Fig. 123.5), The rabies virus (RABV) is responsible for most human and animal rabies cases worldwide, but other lyssavirus have also been implicated.[9,10] RABV is found extensively throughout the world in terrestrial carnivores, but non-RABV lyssavirus is rarely encountered in nonflying carnivores.[10]

Bites through the dermis allow the virus to enter tissues and initiate infection. The virus spreads from muscle tissue to the peripheral nervous system via the neuromuscular junction and then travels to the spinal cord and brain. Host cell machinery is usurped, and rapid replication occurs, at which time clinically apparent disease is seen (Fig. 123.6). Host recognition of the virus stimulates an interferon response, but this is antagonized by the virus phosphoprotein.[11] Infection of the brain is followed quickly by peripheral viral dissemination. For the reservoir species, transmission to the salivary glands proceeds through the parasympathetic and sympathetic nervous systems.[12] The associated aggressive behavior and hypersalivation promotes transmission to new hosts.

The unique spread of RABV via direct nerve conduction routes has given rise to circuit-tracing studies that can detect direct monosynaptic inputs. Using glycoprotein (G)-deleted rabies virus (RVdG) as a marker, the retrograde transmission of rabies virus can be followed over distances of micrometers to centimeters. Wild-type rabies virus spreads across multiple synaptic steps at once because the G protein is not only responsible for binding to the host cell, but also mediates budding of the host cell–derived viral particles. RVdG significantly decreases the release of these particles, thus limiting the spread and allowing tracing of the specific viral migration. This technique is also useful in describing central and peripheral nervous system transmission to genetically identified cell types in mouse cell lines,[13,14] single neurons,[15] and neurons with particular cell surface receptors.[16]

Neither the rabies virus avoidance of peripheral immune surveillance nor its mechanism for causing death are well understood.[3] In the periphery, the virus replicates slowly and may induce immune suppression; both slow replication and immune suppression have been proposed as causes of its insidious presentation.[17,18] Infection in the central and peripheral nervous systems leads to multiorgan failure. Upregulation of chemokines, cytokines, and interferons has been demonstrated experimentally in the central nervous system (CNS).[19,20] Upregulation of interferons drives T cells in to the CNS, but this influx does not control the infection, which is invariably fatal. The incubation period of rabies normally extends from 20 to 90 days but has been reported from 10 days to 7 years postexposure. Two forms of clinical rabies are described, encephalitic (furious) and paralytic (dumb). The encephalitic form predominates and represents approximately 70% of all human virus rabies presentations.[21] The initial symptoms of rabies infection are vague and may be confused with other flulike illnesses. Presenting symptoms of furious rabies include headache, malaise, pharyngitis, and weakness. These are typically followed by pruritus and paresthesia at the site of inoculation. Early signs of human rabies include fever, tachycardia, and tachypnea, which are commonly found in other illnesses but, unlike other viral infections, the mortality from human rabies infection is almost 100%. To date, only four patients have survived rabies infection.[20]

Encephalitic Rabies

This progresses rapidly over days, and the presenting signs and symptoms are supplanted by diffuse neurologic involvement.

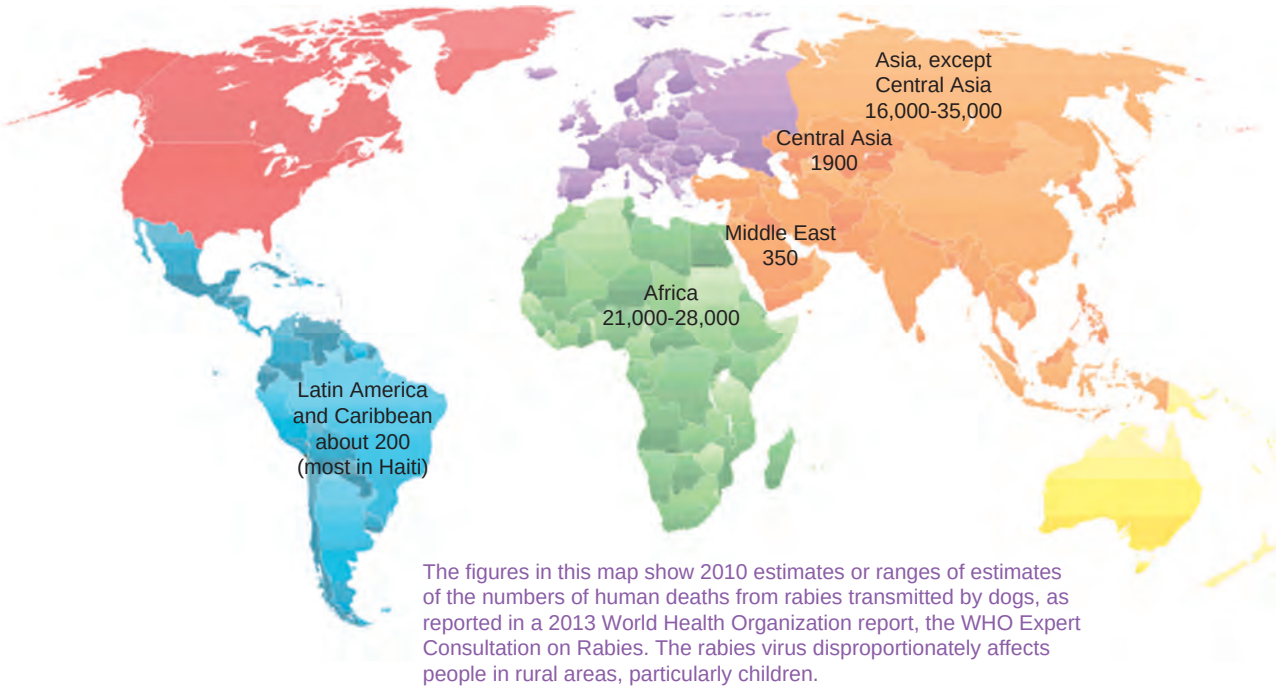

Fig. 123.1. Distribution of human rabies infections worldwide. (Adapted from World Health Organization: WHO Expert Consultation on Rabies re-evaluates the burden and methods of treatment. Available at www.who.int/neglected_diseases/support_to_rabies_elimination_2013/en.)

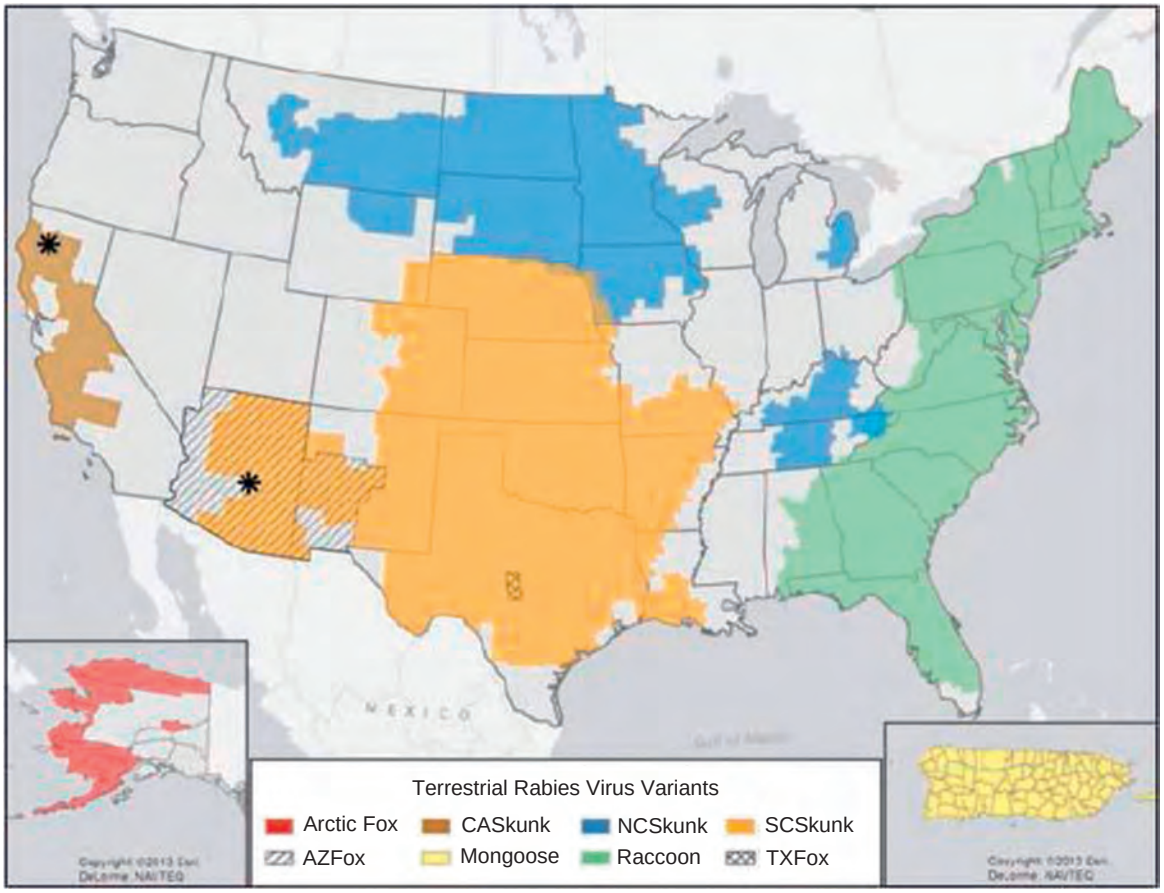

Fig. 123.2. Distribution of terrestrial rabies variants. (From Dyer J, et al: Rabies surveillance in the United States during 2013. J Am Vet Med Assoc 245:1111–1123, 2014.)

The neurologic findings of anxiety, confusion, insomnia, and cerebellar dysfunction are present and are soon replaced by frank delirium, hallucinations, and clinically defining behavioral changes. Hydrophobia, aerophobia, aggressive behavior, and seizures are the feared clinical symptoms most associated with rabies infection, and these portend death.[20] In the final stage of furious rabies, the patient has difficulty swallowing, with involuntary muscles spasms of the pharynx, and hypersalivation occurs. If water is offered, the patient may develop pharyngeal spasm, with resultant gagging. Handling salivary secretions becomes problematic, leading to characteristic drooling and foaming of the mouth. The findings of hydrophobia with resultant gagging and hypersalivation are so characteristic of rabies infection that in many developing countries, water is offered to the patient as a diagnostic test. Coma and death follow rapidly, usually within 5 days of presentation.

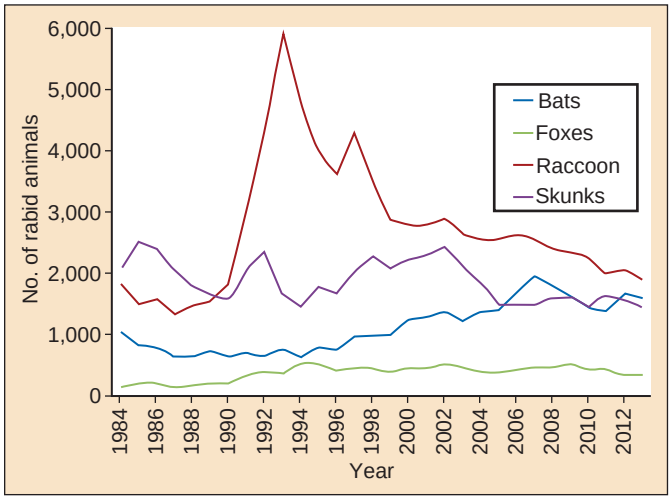

Fig. 123.3. Cases of rabies among wildlife in the Unites States, by year and species, 1984 to 2013. (From Dyer J, et al: Rabies surveillance in the United States during 2013. J Am Vet Med Assoc 245:1111–1123, 2014.)

Paralytic Rabies

This accounts for approximately 30% of human rabies infections. The presenting symptoms are similar to encephalitic rabies and include headache, weakness, and malaise. Muscle weakness and paresthesia occur at the site of the bite and, over days to weeks, an acute flaccid paralysis ensues. Unlike the encephalitic form, the patient does not develop agitation, hypersalivation, or hydrophobia. Rather, muscle weakness occurs over days to weeks, and the progression to coma and death takes longer than in the encephalitic form.[20] Postexposure prophylaxis (PEP) and rabid bat bites are associated with the paralytic form. Patients are more likely to get rabies from PEP when the recommendations of the WHO and the Advisory Committee on Immunization Practices (ACIP) are not closely followed or rabies immunoglobulin is not given. Patients receiving the nerve cell–derived vaccine that is still used in a few countries are also at greater risk of developing the paralytic form.

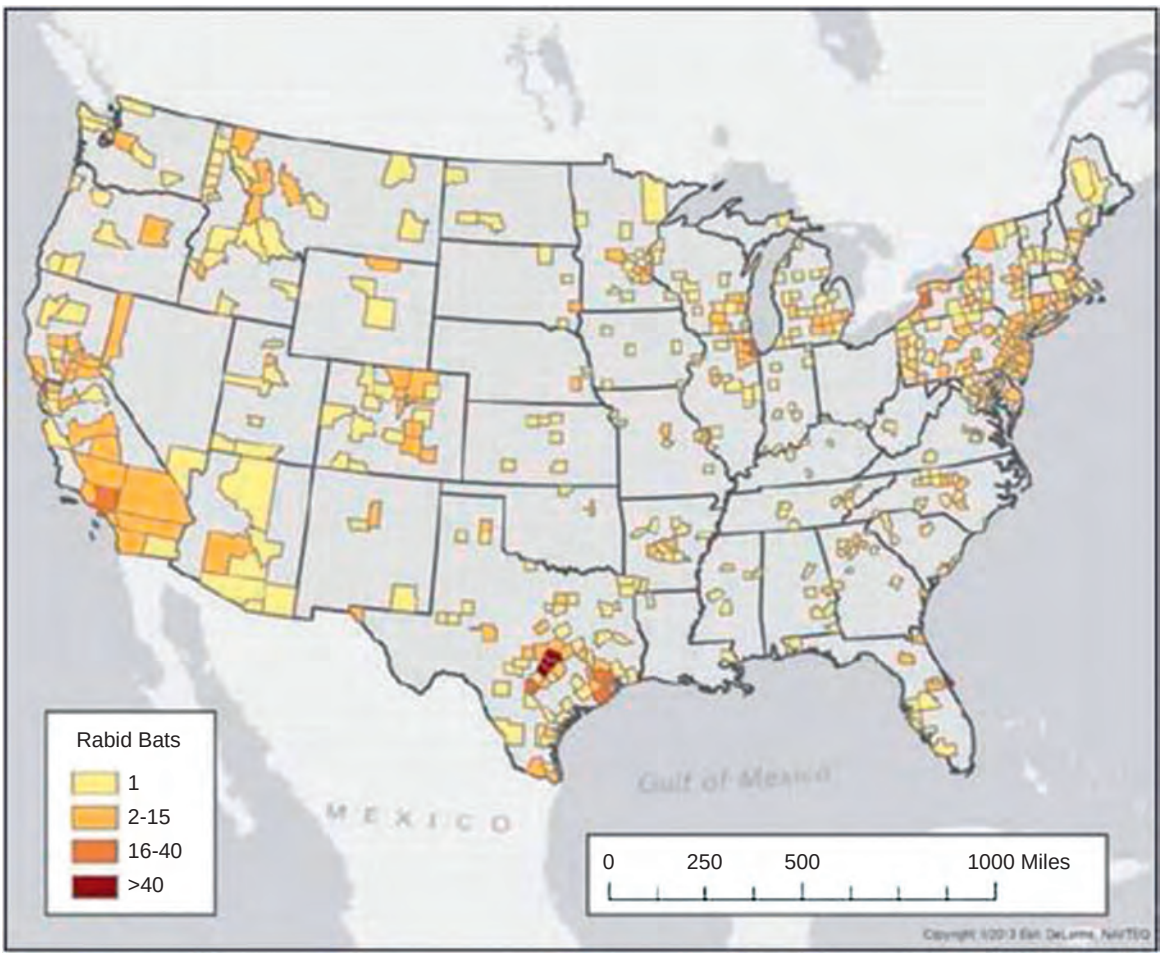

Fig. 123. 4. Reported cases of rabies involving bats, 2013. (From Dyer J, et al: Rabies surveillance in the United States during 2013. J Am Vet Med Assoc 245:1111–1123, 2014.)

TABLE 123.1

Numbers of Rabid Animals and Samples Tested for Rabies, 2008–2013

ANIMALS	2013		2008–2012			
	NO. OF RABID ANIMALS	SAMPLES WITH POSITIVE RESULTS[a]	NO. OF RABID ANIMALS		SAMPLES WITH POSITIVE RESULTS[a]	
			Mean	95% CI[a]	Mean	95% CI[a]
DOMESTIC ANIMALS						
Cats	247[b]	1.06	291.4	274.2–308.5	1.2	1.1–1.3
Cattle	86	6.62	76.8	57.4–96.2	6.4	5.3–7.5
Dogs	89[b]	0.41[b]	75.8	70.0–81.6	0.3	0.3–0.4
Horses and mules	31[b]	3.81	39.8	34.0–45.6	4.5	3.8–5.2
Sheep and goats	9	1.64	10.2	7.5–12.9	2.2	1.6–2.8
WILDLIFE						
Raccoons	1898[b]	16.25[b]	2181.0	2007.5–2354.5	14.6	13.2–16.0
Bats	1598	5.84	1584.8	1429.2–1740.4	5.7	5.5–5.9
Skunks	1447[b]	33.04[b]	1561.2	1499.0–1623.4	29.7	27.2–32.2
Foxes	344[b]	18.70[b]	430.8	378.6–483.0	22.8	19.7–26.0
All rabid animals	5865	6.03	6156.6	5833.3–6479.9	5.8	5.4–6.2
Rabid domestic animals	467[b]	0.98	493.2	478.2–508.2	1.0	0.9–1.1
Rabid wildlife	5398	11.17	5663.4	5331.9–5994.9	10.3	9.0–11.6

[a]Does not include data from California.
[b]Significantly different from mean values for 2008–2012 ($P < 0.05$).
Adapted from Dyer J, et al: Rabies surveillance in the United States during 2013. J Am Vet Med Assoc 245:1111–1123, 2014.

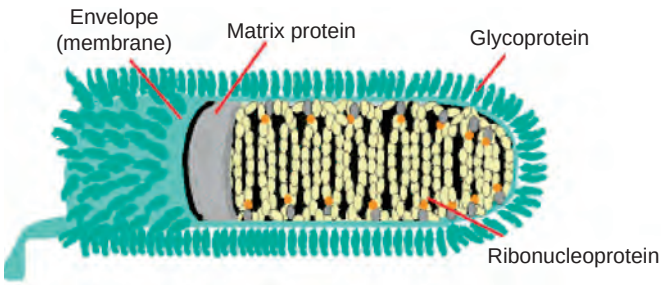

Fig. 123.5. Rabies is an RNA virus. The genome encodes five proteins designated as N, P, M, G, and L. The order and relative size of the genes in the genome are shown. The arrangement of these proteins and the RNA genome determine the structure of the rabies virus. (From Centers for Disease Control and Prevention: The rabies virus. Available at www.cdc.gov/rabies/transmission/virus.html.)

DIAGNOSTIC CONSIDERATIONS

Differential Diagnoses

Encephalitic rabies may be confused with other infectious and noninfectious causes of encephalitis. The early presentation of paralytic rabies may suggest Guillain-Barré syndrome, but is distinguished by the onset of encephalitis, asymmetry of limb involvement, persistent fever, bladder incontinence, intact sensory function, and percussion myoedema.[20] Percussion myoedema is the mounding of muscle at the site of percussion, lasting a few seconds. This is most easily elicited on the chest, deltoid, and thigh.

In atypical presentations of encephalitic rabies or paralytic rabies, the diagnosis may not be clear and delay institution of appropriate public health and infection control measures. As improved antemortem techniques arise, we can look forward to a decrease in unnecessary treatment and tests, more timely institution of preexposure and postexposure rabies prophylaxis to family members or staff, and more timely discussions with family regarding prognosis.[21]

Diagnostic Testing

Postmortem testing of fresh brain samples remains the gold standard for the diagnosis of rabies in all mammalian species. The WHO and World Organization for Animal Health (OIE) recommend fluorescent antibody testing (FAT) of brain smears or touch impressions. FAT provides reliable results within a few hours that are very sensitive and specific. The best results are obtained with fresh brain tissue, but saline-washed tissue preserved in 50% glycerol saline also works well. Decomposed brain tissue and formalin fixed tissue do not yield results that are as reliable. The limitations of FAT are that it requires brain tissue, expensive fluorescence microscope, and appropriately skilled staff.

If FAT results are equivocal, the OIE recommends virus isolation tests to grow the virus from suspected specimens, which also allows for characterization of the virus. The mouse inoculation test (MIT) and rapid tissue culture infection test (RTCT) can both be used for this purpose. In the MIT, mice are inoculated intracerebrally with supernatant homogenate of brain material. The mice are observed for 28 days and signs of rabies typically develop after 5 to 7 days. The RTCT gives much more rapid results, generally in 24 to 48 hours. Appropriate cell lines are inoculated with brain homogenate, incubated for 24 hours, and stained by the FAT technique. Although RTCT is faster and cheaper than MIT, it requires sophisticated laboratories that have fluorescent microscopes and cell culture facilities.

The direct rapid immunohistochemical test (dRIT) provides results in 1 hour and uses light microscopy rather than expensive fluorescent-labeled antibodies and fluorescent microscopes. The dRIT was developed at the Centers for Disease Control and Prevention (CDC); it has been field-tested in endemic areas and found to be 100% sensitive and specific when compared to FAT.[22] The use of dRIT will allow regions with limited resources to obtain important incidence data, as well as the possibility of carrying out more informed postexposure prophylaxis. However, one significant drawback of dRIT is that the reagents used for the test are only available through the CDC.

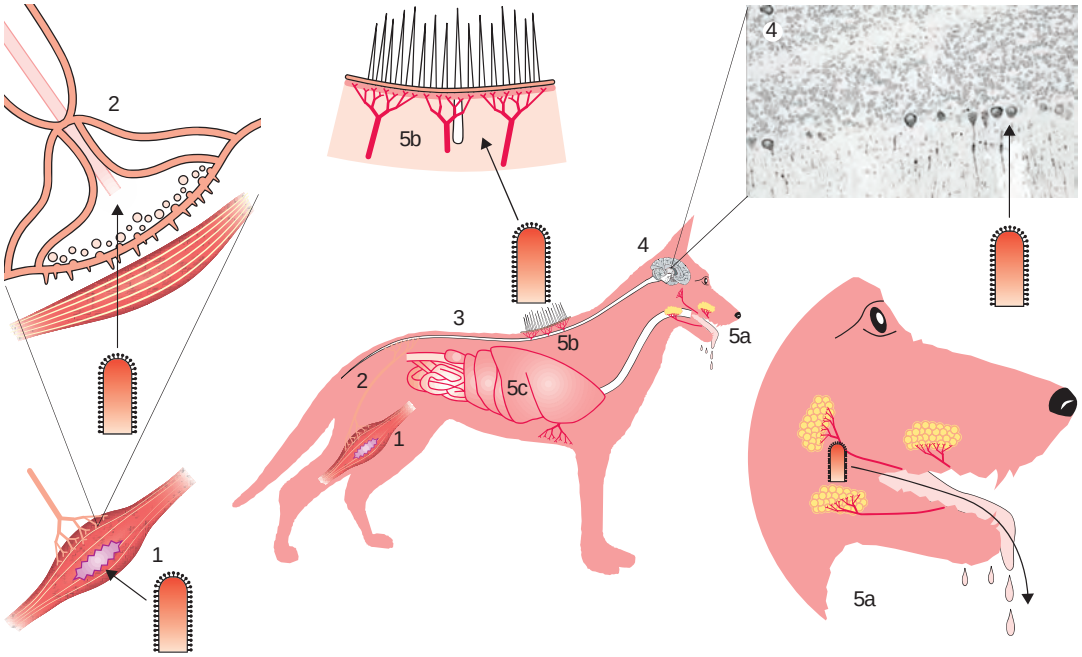

Fig. 123.6. Pathogenesis of rabies virus. **1,** The virus enters muscle tissue of the host through the bite wound. **2,** It enters the peripheral nervous system (PNS) via the neuromuscular junction. **3,** It then travels from the PNS to the spinal cord and brain. **4,** The virus enters the brain and undergoes extensive replication, leading to neuronal dysfunction. *Inset,* Virus in Purkinje cells of the cerebellum; ×40. **5a,** The virus replicates in the salivary glands and is excreted in saliva. **5b,** It enters the peripheral nerves of skin and Purkinje cells. **5c,** It spreads from the brain to infect many tissues and organs in the host. (From Singh SK, Ruzek D: Rabies virus neurovirulence. In Singh SK, Ruzek D, editors: Neuroviral infections, Boca Raton, FL, 2013, Taylor & Francis, CRC Press, p 376.)

Effective antemortem testing remains elusive. Various forms of molecular methods—reverse transcription (RT) and polymerase chain reaction (PCR) assays—have demonstrated high sensitivity for RABV in dog brain tissue and shown promise for highly sensitive antemortem diagnosis of nuchal skin biopsy, serial saliva, or multiple simultaneous site testing (eg, cerebrospinal fluid [CSF], hair follicles, saliva, urine).[23,24] Real-time PCR testing of cerebral spinal fluid, nuchal skin, and saliva using the TaqMan probes has demonstrated excellent sensitivity and specificity. Antemortem serologic testing via the use of magnetic resonance imaging may be useful in distinguishing rabies from other forms of encephalitis as typical changes have been described.[23]

PROPHYLAXIS AND VACCINATION

Preexposure Prophylaxis

Pasteur described the first rabies vaccine in 1885.[26] Nerve tissue–derived vaccines similar to Pasteur's were used worldwide until the 1940s, when they were replaced by cell culture–derived vaccines (CCVs) that were safer and more immunogenic.[27] Despite warnings from WHO, some countries still continue to manufacture and use nerve tissue–derived vaccines.

Preexposure vaccine (PrEP) is recommended for travelers to endemic areas and those in high-risk professions (eg, veterinarians, laboratory staff handling the virus). The PrEP regimen recommended by the WHO and ACIP is a three-dose schedule (Table 123.2).[28] Intramuscular or intradermal administration of vaccine is recommended. The intradermal method uses less total vaccine and is thus less expensive in many parts of the world. Approximately 50% of all rabies deaths occur in children younger than 15 years, so preexposure prophylaxis for children in endemic areas should be considered.[29] The current three-dose PrEP regimen is cost-prohibitive in endemic areas, even with the lower cost intradermal method, and a cost-benefit analysis has suggested that for economic viability, a PrEP regimen that induces immunity with a single injection is needed.[30]

Numerous serologic studies have provided evidence of robust production of neutralizing antibody in response to cell culture–derived vaccines. Following the use of WHO-approved vaccines, 100% of healthy individuals were found to have a significant antibody response. No individuals with circulating neutralizing antibody levels above 0.5 IU/mL have ever contracted rabies.

Postexposure Prophylaxis and Vaccination

It has been estimated that 40,000 people receive PEP for rabies in the United States each year.[31] The CDC has reported the cost for treatment at roughly $1000/person, but earlier data suggested an actual cost of $2500 or more.[31] Accordingly, it is imperative that emergency clinicians evaluate each exposure in terms of the regional risk of rabies, animal handling procedures, and indications for PEP. Local or state agencies are familiar with the reservoir populations in that area and serve as a resource. If local public health authorities are unavailable, emergency clinicians evaluate each exposure in terms of the regional risk of rabies, animal handling procedures may call the CDC's information line, 877-554-4625 or 800-CDC-INFO, 24 hours/day, 7 days/week.

The WHO categorizes exposures in areas enzootic for rabies into three categories.[32] Category I includes touching or feeding animals, licks on intact skin, and contact of intact skin with secretions or excretions of a rabid animal or human. These are not regarded as exposures, and no postexposure prophylaxis is required. Category II includes nibbling of uncovered skin, minor scratches, or abrasions without bleeding. Vaccine should be injected as soon as possible. Category III includes single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks, and exposure to

TABLE 123.2

Rabies Pre- and Postexposure Vaccination Recommendations

	NO. OF VACCINE DOSES/ NO. OF CLINIC VISITS	ADMINISTRATION ROUTE	INJECTION SCHEDULE
PREEXPOSURE			
Routine intramuscular	3/3	Intramuscular	Days 0, 7, 21, or 28 (one dose each)
Routine intradermal	3/3	Intradermal	Days 0, 7, 21, or 28 (one dose each)
POSTEXPOSURE			
Essen	5/5	Intramuscular	Days 0, 3, 7, 14, 28 (one dose each)
Zagreb	4/3	Intramuscular	Day 0 (two doses) Days 7, 21 (one dose)
Reduced four-dose vaccination	4/4	Intramuscular	Days 0, 3, 7, 14 (one dose each)
Modified Thai Red Cross	8/4	Intradermal	Days 0, 3,7,28 (two doses each)
POSTEXPOSURE FOR PREVIOUSLY VACCINATED PEOPLE			
Intramuscular	2/2	Intramuscular	Days 0 and 3 (one dose each)
Intradermal	4/1	Intradermal	Day 0 (four doses)

From Fooks A, et al: Current status of rabies and prospects for elimination. Lancet 2014:384:1389–1399.

TABLE 123.3

Guidelines to Determine Need for Rabies Postexposure Prophylaxis (PEP)

ANIMAL	EVALUATION AND DISPOSITION OF ANIMAL	POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS
Dogs, cats, ferrets	Healthy and available for 10 days' observation[a]	No vaccination unless animal develops symptoms
	Rabid or suspected rabid	Vaccinate immediately.
	Unknown or escaped	Consult public health officials.
Raccoons, skunks, foxes	Regard as rabid unless animal is proved to be seronegative by laboratory testing.[b]	Consider immediate prophylaxis.
Livestock, rodents, rabbits, hares, other mammals	Consider individually.	Consult public health officials; bites of rodents or lagomorphs rarely require PEP.

[a]During the 10-day observation period begin postexposure prophylaxis at the first sings of rabies in a dog, cat or ferret. If the animal exhibits clinical signs of rabies it should be euthanized and tested.
[b]The animal should be euthanized and tested as soon as possible. Do not hold for observation. If laboratory studies are negative in the animal vaccine may be discontinued.
Adapted from Manning SE, et al: Human rabies prevention-United States 2008: Recommendations of the Advisory Committee on Immunization Practices MMWR Recomm Rep 57:1–28, 2008.

bats. Vaccine and rabies immunoglobulin should be administered at distant sites as soon as possible. Immunoglobulin can be administered up to 7 days after injection of the first dose of vaccine.

In the United States, PEP is provided to individuals exposed to the body fluids—usually from bites and scratches—of raccoons, bats, skunks, foxes, and coyotes, as well as dogs along the Mexican border and wild carnivores in rabies-endemic areas (Table 123.3).

Exposure to bats is responsible for the greatest number of rabies PEP treatments in the United States.[32] The CDC recommends initiating PEP when bats are found indoors; the person may be unaware of bites or direct contact because he or she was asleep, and unattended children and developmentally challenged individuals should undergo PEP.

If a wild animal responsible for the bite or exposure is caught, it should be euthanized immediately. The head should be refrigerated and sent to a reference laboratory for fluorescent antibody testing. While waiting for the results of animal testing, the patient should be treated and, if the results are negative, PEP may be discontinued. Domestic animals that appear well may be observed for 10 days; if they remain symptom-free, the victim does not require treatment. If the animal displays symptoms, it should be sacrificed and the victim treated (see Table 123.3).

PEP is almost 100% effective when administered according to WHO guidelines. Treatment failures usually occur when local wound care is not complete, immunoglobulin is not given, or nerve cell–derived vaccine is used. Since 1987, only nine PEP treatment failures have been reported in which WHO recommendations were followed and documented.[33,34]

Once the decision to initiate PEP has been made, it should be started immediately. Currently, four regimens are approved for postexposure treatment of unimmunized individuals, three intramuscular and one intradermal PEP regimens (see Table 123.2). All these regimens include four doses of vaccine following the ACIP recommendations published in 2010.[35] The intramuscular dose is 1.0 mL/injection, and the intradermal dose is 0.1 mL. Effective intradermal injections must form a bleb at the site. Two vaccines are currently available in the United States, RabAvert (Novartis, Chiron Behring GmbH) and Imovax (Sanofi Pasteur).[36] In addition to vaccination, rabies immunoglobulin (RIG) should be given promptly in patients not previously vaccinated. RIG inhibits viral spread during the interval when antibodies are produced in response to the rabies vaccine.[3] Human rabies immunoglobulin produced by Grifols (HyperRAB) is available, but the availability of Sanofi Pasteur's Imogam has been limited.[36]

Human rabies immunoglobulin, 20 IU/kg, should be administered soon after the bite occurs and not more than 7 days after the first dose of rabies vaccine. Much of the RIG is injected into and around the site of the wound, with the remainder injected intramuscularly at a distance from the vaccine administration site. ACIP recommends the reduced four-dose vaccine schedule for postexposure prophylaxis in previously unvaccinated individuals. This regimen should start as soon as possible after the exposure, day 0, and should then be followed by repeated doses on days 3,7 and 14. The dose is 1 mL of vaccine administered intramuscularly. The deltoid is the preferred site for adults; the anterolateral thigh is the preferred site in children. There is a diminished immunologic response to gluteal injection of vaccine, so this site should be avoided. The intradermal method requires two doses (0.1 mL) be administered in distant body parts on days 0, 3, 7, and 28.

Postexposure vaccination for previously vaccinated individuals requires wound care and a two-dose intramuscular vaccination (days 0 and 3) or four-dose intradermal vaccination (all on day 0). RIG is not needed in previously vaccinated individuals (Table 123.4)—those who have received ACIP- or WHO-approved PrEP or PEP or other vaccinations with documented rabies virus–neutralizing antibody response.

All US-licensed rabies vaccines are inactivated cell culture vaccines that can be administered to immunocompromised individuals. Patients with immunosuppressive disorders and those taking corticosteroids, immunosuppressive agents, and/or antimalarials may have a reduced response to the vaccine, necessitating a five-dose regimen. In this setting, serologic testing for neutralizing rabies antibody may be considered 4 weeks after the last vaccine dose to determine if a booster is necessary.

Adverse reactions to rabies vaccines include local reactions, mild systemic reactions, and immediate hypersensitivity reactions. Typical local reactions include pain, swelling, redness, and induration at the injection site. These symptoms are reported by 60% to 85% of recipients of the human diploid cell vaccine (HDCV) and by 11% to 57% of of recipients of the purified chick embryo vaccine (PCEV). From 6.8% to 55.6% and up to 31% of recipients of HDCV and PCEV, respectively, have reported systemic reactions, including gastrointestinal symptoms, headache, dizziness, and fever. Immediate hypersensitivity occurs in 1.2% of previously unimmunized HDCV recipients and in up to 6% of those previously immunized receiving HDCV as a booster. No deaths have been reported from recipients of the human diploid cell vaccine or purified chick embryo cell vaccine.[37]

Rare severe neurologic reactions have occurred with PCEV and HDVC, but a causal relationship has not been verified. Guillain-Barré–like illness has been described with the use of both vaccines. Adverse reactions to human RIG are common, but these are primarily local reactions. Pain, induration, swelling, and erythema have been reported in 30% to 100% of injections. Headache is the most common systemic reaction to HRIG occurring in more than 50% of recipients. No deaths have been reported from human RIG.[37]

Outside the United States, RIG is in short supply, and some countries do not use WHO-approved vaccines.[5] Exposed travelers from these areas may require further vaccination on return to their native country. The CDC recommendations differ from those of WHO in that all PEP in unimmunized victims includes RIG in the United States but only category III wounds carry this recommendation from WHO.

TABLE 123.4

Rabies Postexposure Immunoprophylaxis

PARAMETER	PROPHYLACTIC MEASURES
Wound cleansing	Immediate, thorough cleansing with soap and water; use povidone-iodine or benzalkonium chloride
Exposures in the nonimmunized	
Human rabies immunoglobulin (RIG)	20 IU/kg infiltrated around wound; if any remaining, inject at IM site distant from vaccine site.
Vaccine	1.0 mL deltoid or anterolateral thigh days 0, 3, 7, and 14. Immunosuppressed persons need five doses, days 0, 3, 7, 14, and 28.
Previously immunized	
RIG	Should not be administered
Vaccine	1.0 mL IM, days 0 and 3

Adapted from Rupprecht CE, et al; Centers for Disease Control and Prevention (CDC): Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee On Immunization Practices. MMWR Recomm Rep 59(RR-2):1–9, 2010.

Wound Care

Rabies virus is very sensitive to sunlight, soap, and drying. When performed within 3 hours of inoculation, scrubbing and flushing with benzalkonium chloride, 20% soap solution, or Ivory soap is nearly 100% protective. Wounds from high-risk animals should be scrubbed with soap, water, and a virucidal agent (eg, povidone-iodine) and then flushed with saline or water. As with other mammalian bites, bacterial infection, cosmetic results, and tetanus prophylaxis need to be considered.

The bite location is a significant determinant of disease potential. Wounds to the face are at highest risk and require meticulous wound care. Highly vascular areas are high risk as well and include the head, neck, genitals, and hands.

MANAGEMENT OF HUMAN RABIES INFECTION

Reversal of the disease process in rabies remains elusive, and palliative care continues to be the mainstay of therapy. Severe agitation is treated with sedation and analgesia. The basic mechanisms of pathogenesis are still poorly understood, making the discovery of a specific therapeutic drug unlikely.[12,21,38] Intensive care therapy has prolonged the time until death, but care remains symptomatic. In resource-poor areas, aggressive intensive care therapy should include consideration of these factors: rabies vaccination prior to onset of disease, young age, rabies in previously healthy and immunocompetent individuals, initiation of treatment when neurologic signs are mild, New World bat variant rabies virus, and early detection of neutralizing anti–rabies virus antibodies in the serum and cerebrospinal fluid.[39]

KEY CONCEPTS

- Postexposure prophylaxis (PEP) for rabies should be administered to individuals exposed to the secretions of high-risk animals—raccoons, bats, skunks, foxes, coyotes, dogs along the Mexican border, and wild carnivores in rabies-endemic areas.
- PEP given strictly according to WHO or CDC guidelines is extremely effective in preventing rabies. PEP includes wound care, passive immunization with RIG, and active immunization with rabies vaccine.
- Discussion with public health officials is recommended to guide decisions regarding when PEP should be considered. The CDC clinician information line is 877-554-4625 or 800-CDC-INFO.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 123: QUESTIONS & ANSWERS

123.1. Which of the following is the only US state or territory that is rabies-free?
- **A.** Alaska
- **B.** Hawaii
- **C.** Puerto Rico
- **D.** Vermont
- **E.** Washington, DC

Answer: B. There are no rabid bats or terrestrial mammals in Hawaii.

123.2. What domestic animal in the United States is most frequently reported as rabid?
- **A.** Cat
- **B.** Dog
- **C.** Ferret
- **D.** Gerbil
- **E.** Monkey

Answer: A. Cats account for the largest number of domestic rabies cases in the United States. The median age of rabid cats and dogs is 1 year. Most human cases in the United States are from bats.

123.3. Which of the following statements concerning human rabies is true?
- **A.** Encephalitic rabies is the most common form.
- **B.** Humans with impaired immunity are more likely to have encephalitis.
- **C.** It has a predilection for the neuromuscular junction.
- **D.** Most cases present with paralysis.
- **E.** The incubation period is independent of bite site.

Answer: A. Of human rabies cases, 80% are of the encephalitic (furious) form. Symptoms start as mild, with headache, fever, and paresthesia at the site of the bite, but rapidly progress over days to agitation, hypersalivation, hydrophobia, aerophobia, seizure, coma, and death.

123.4. An 18-year-old man presents with lower extremity weakness of 2 days' duration. He has no past medical history and takes no medication. Which of the following factors would help differentiate Guillain-Barré syndrome from paralytic rabies?
- **A.** Ascending pattern
- **B.** Cranial nerve dysfunction
- **C.** Diminished vision
- **D.** Fever
- **E.** Loss of deep tendon reflexes

Answer: D. Persistent fever from the onset of weakness, bladder dysfunction, and percussion myoedema suggest rabies. Preservation of sensory function is more likely with rabies.

123.5. Worldwide, which species is the dominant reservoir for rabies?
- **A.** Bats
- **B.** Dogs
- **C.** Foxes
- **D.** Raccoons
- **E.** Skunks

Answer: B. Worldwide, dogs remain the largest reservoir, the most commonly infected, and the leading vector for human rabies.

Dogs are the most common cause of rabies in Asia and Africa where the vast majority of cases occur.

123.6. Postexposure care in a case of suspected rabies transmission should include which of the following?
- **A.** B, C, and E
- **B.** Active immunization
- **C.** Immediate suturing of all wounds
- **D.** Passive immunization
- **E.** Vigorous soap and water scrubbing and then virucidal flushing

Answer: A. Aggressive wound cleansing may be the most important action in the rabies prophylaxis. Vigorous soap and water scrubbing and flushing should be followed by copious application of a virucidal agent, such as benzalkonium chloride or povidone-iodine. Passive immunization with RIG and active immunization with an approved World Health Organization vaccine should quickly follow. Wounds should initially be left open, with a planned delayed closure when appropriate.

123.7. Which of the following statements regarding the administration of human rabies immune globulin (HRIG) and human diploid cell vaccine (HDCV) is true?
- **A.** HRIG and HDCV may be given at the same site.
- **B.** HRIG may be given at any time after the vaccine is administered.
- **C.** Postexposure prophylaxis is active only.
- **D.** Prophylaxis does not change in a pregnant patient.
- **E.** The gluteal region is the preferred vaccination site.

Answer: D. No protocol changes are indicated in pregnant patients. The deltoid is the preferred HDCV site to avoid injections into an area of more fat with less antibody production. It is critical that active and passive immunization occur. As much of the HRIG as possible should be infiltrated into the wound and the rest injected at a distant site. The immune globulin and vaccine should be injected at different sites. A typical plan is to inject HRIG into the wound, with the balance in one deltoid, and the vaccine administered into the opposite deltoid.

123.8. A 32-year-old emergency medicine intern crawls into bed after a 24-hour shift in the medical intensive care unit. Her 36-week pregnant spouse and 18-month-old daughter are asleep as she climbs into their bed. She is awakened from a dead sleep 3 hours later when her wife asks, "What is that brown thing on the ceiling?" Using a tennis racket, the bat is successfully encouraged out of the window. The intern calls you and asks if they need to be vaccinated. Your recommendations should include which of the following?
- **A.** PEP (postexposure prophylaxis) is contraindicated in the pregnant spouse.
- **B.** The 18-month-old and intern need PEP.
- **C.** The spouse needs PEP.
- **D.** They need better screens on their windows.

Answer: B. In spite of little evidence for a bite or scratch, the intern and 18-month-old fulfill requirements for PEP. Per Centers for Disease Control and Prevention recommendations, based on developmental staging, the 18-month-old girl cannot know whether an exposure may have happened. The intern does not explicitly meet the requirements for PEP because she is not a child, developmentally challenged, or intoxicated but, after a 24-hour shift, she was likely in a state of deep sleep and would not have been aware of her surroundings. Initiating PEP for her should be seriously considered. Although there is no contraindication for PEP during pregnancy, at 36 weeks, her spouse probably was not sleeping well and was certainly more aware of her surroundings than the intern. PEP should be considered for her but, if she is adamant that no bite or scratch occurred, it may be held.

123.9. A 3-year-old presents with a dog bite to the face. He was playing at his uncle's house in Oregon and grabbed the tail of the family dachshund while the dog was eating. The dog turned and bit him on the face. The dog is fully vaccinated. The parents are very concerned about the risk of rabies. You explain that all the below are true except which of the following?
- **A.** Dog bites in the United States carry a very low risk for rabies.
- **B.** Effective canine rabies vaccine in the United States has existed since 1947, so only dogs in the border towns at the border between the United States and Mexico are at risk.
- **D.** Immediate immunization with human rabies immune globulin (HRIG) and rabies vaccine should be initiated.
- **C.** Wound care appropriate for a dog bite is the recommended management.

Answer: D. Domesticated antagonized dogs carry a very low risk of rabies infection, but may bite when irritated by a small child. Simple wound management is indicated.

CHAPTER 124

HIV Infection and AIDS

Sukhjit S. Takhar | Rachel L. Chin

PRINCIPLES

Background and Epidemiology

Acquired immunodeficiency syndrome (AIDS) is a pandemic caused by the human immunodeficiency virus (HIV). This disease is a relatively new phenomenon that has caused a tremendous degree of human suffering and has had an immeasurable impact on demographics, cultures, economics, and politics in most societies around the globe. There are an estimated 35 million people living with HIV infection worldwide, and 39 million people have died of AIDS-related illnesses.[1] Significant strides have been made in areas of prevention and treatment, resulting in stabilization of the epidemic, and the annual number of new infections has steadily decreased since the 1990s. The decline in incidence of new cases of HIV infection and widespread use of highly active antiretroviral therapy (ART), have led to a decrease in AIDS-related deaths, resulting in an increase of the global prevalence of HIV/AIDS (Figs. 124.1 and 124.2).

Means of transmission of HIV and the demographic distribution of the virus vary from country to country. Sub-Saharan Africa is the epicenter of the pandemic, with 25.0 million adults and children living with HIV infection.[1] Unprotected heterosexual intercourse with subsequent transmission of HIV to newborns and breast-fed babies (mother to child transmission) is the dominant mode of transmission worldwide, accounting for about 85% of all HIV infections.[2] The main pattern of transmission in the higher income countries of North America and western and central Europe is in men who have sex with men. Other significant modes of transmission in these regions include injection drug use and paid unprotected sex.[1]

Pathophysiology

HIV, a retrovirus from the lentivirus subfamily, is the cause of AIDS. There are two subtypes of HIV, HIV-1 and HIV-2. The most common cause of HIV infection and AIDS throughout the world is HIV-1. HIV-2, a closely related virus, is much less common and is typically seen in West Africa.

The mature HIV virion is a spherical structure with an outer envelope and inner core (Fig. 124.3). The core contains two copies of the RNA genome, enzymes (reverse transcriptase and integrase) and regulatory proteins. Surrounding the core is the viral membrane, containing the glycoproteins responsible for the attachment and entry of the virus into a $CD4^+$ cell. In a multistep process, the HIV virion invades the host cell and integrates its genetic material into the host's chromosome (Fig. 124.4). The infection begins with binding of the virus to the $CD4^+$ host cell. The virus enters the cell by fusing its envelope with the target cell membrane. After internalization, reverse transcriptase forms viral DNA from the original RNA. The viral enzyme integrase then transports the newly formed viral DNA into the nucleus, where it integrates with human chromosomal DNA. Viral polyproteins and RNA are formed, and new infectious viral particles are created. This cycle continues with HIV infecting more $CD4^+$ cells. Major targets of ART include reverse transcriptase, protease, integrase, and the CCR5 coreceptor.

The hallmark of HIV infection is $CD4^+$ T cell destruction, leading to a deficient cell-mediated arm of the immune system. Humoral immunity is also impaired through B cell proliferation and production of abnormal antibodies, making HIV-infected individuals more vulnerable to infections by encapsulated bacteria.

HIV infection also leads to a chronic immune activation. Ongoing viremia, along with proinflammatory cytokines, B cell proliferation, and hypergammaglobulinemia, leads to a chronic inflammatory state that contributes to cardiovascular disease, cancer, and other chronic diseases in long-term, HIV-infected individuals.[2] Increased immune activation persists, even in patients with immune reconstitution on antiretroviral therapy.

Risk Factors for HIV Transmission

HIV has been isolated from a wide range of body fluids, including semen, vaginal secretions, lymphocytes, cell-free plasma, cerebrospinal fluid (CSF), tears, saliva, urine, and breast milk. However, only semen, blood, vaginal secretions, and breast milk are significantly infectious. For transmission to occur, these fluids must come into contact with damaged tissue or with a mucous membrane or be directly injected into the bloodstream.

The highest risk exposure is transfusion with HIV-positive blood. Other factors associated with an increased risk of HIV transmission include exposure to serum with a high viral load, lack of male circumcision, and presence of an ulcerative, sexually transmitted infection. The risk of transmission of HIV varies by the type of sexual contact: it is 1% to 30% for receptive anal intercourse, 0.1% to 10% for receptive vaginal and insertive anal intercourse, and 0.1% to 1% for insertive vaginal intercourse.

After transmission, the virus replicates in the mucosal surface or lymphoid tissue at the site of entry in lymphocytes and macrophages. If enough cells are infected, the virus spreads to draining lymph nodes and infection is established, usually within 48 to 72 hours.

CLINICAL FEATURES

The clinical manifestations of HIV infection are varied. Patients may present to the emergency department (ED) with acute HIV infection, medication side effects, or unusual opportunistic infections from advanced AIDS. The natural history of the disease has been altered significantly with the advent of ART. However, there still is no cure. In addition to causing progressive immune dysfunction, chronic HIV infection causes an ongoing inflammatory state, leading to the development of numerous manifestations that have not been classically thought of as HIV disease. These include malignant neoplasms, coronary artery disease, and neurocognitive disorders. The dramatic immune recovery that is seen with modern ART can also cause an inflammatory syndrome that resembles the original opportunistic infection. Overall, the spectrum of HIV infection is changing because of longer life expectancy and better treatment. However, many patients still

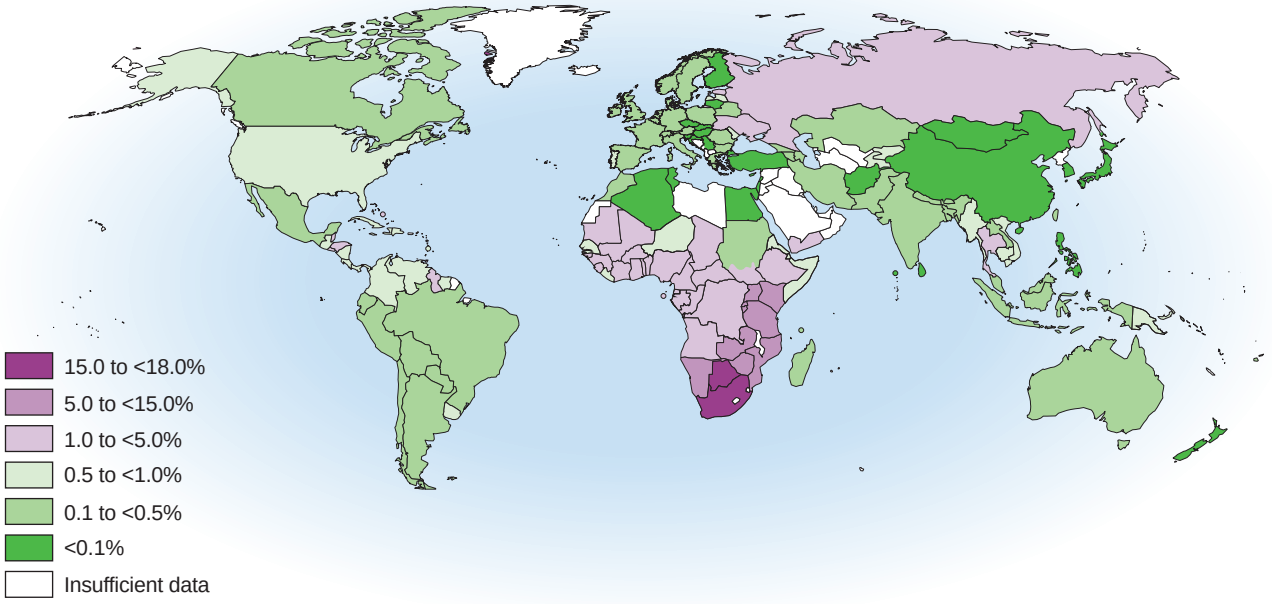

Fig. 124.1. Human immunodeficiency virus prevalence by country. (From Bennett JE, et al, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ed 8, Philadelphia, 2015, Elsevier/Churchill Livingstone.)

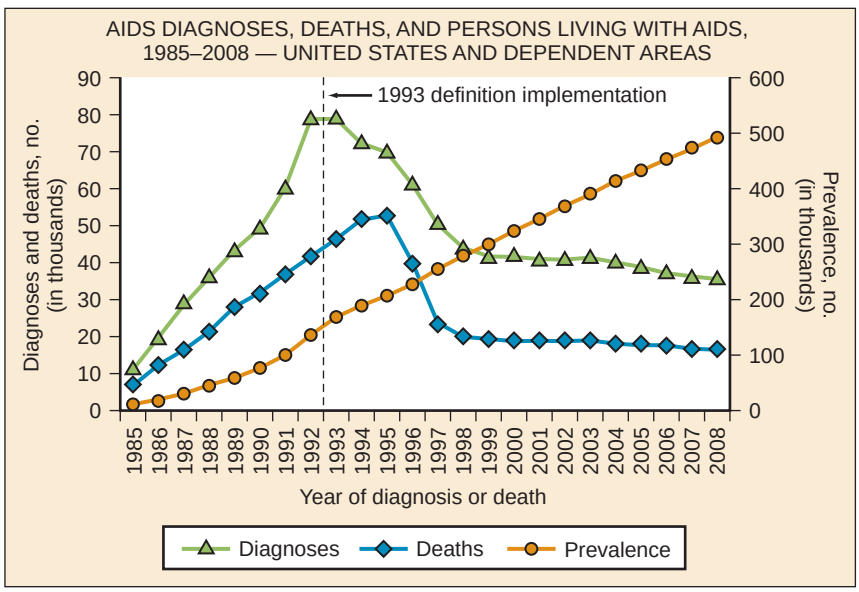

Fig. 124.2. AIDS diagnoses, deaths, and persons living with AIDS—United States. (From the Centers for Disease Control and Prevention: AIDS surveillance—trends [1985-2009]. www.cdc.gov/hiv/topics/surveillance/resources/slides/trends/index.htm.)

have undiagnosed HIV infection and present in later stages of disease.

Primary HIV Infection

Primary infection with HIV often causes an acute, self-limited viral infection. The most common findings are mononucleosis-like symptoms that consist of fever, pharyngitis, and lymphadenopathy. This usually occurs 2 to 6 weeks after transmission. During this time, the virus is actively replicating, and antibodies to HIV have not been produced. The virus has many potential targets, and viral loads are often enormous. The diagnosis of acute HIV infection has significant public health benefits. Patients with acute HIV infection transmit the infection disproportionately;

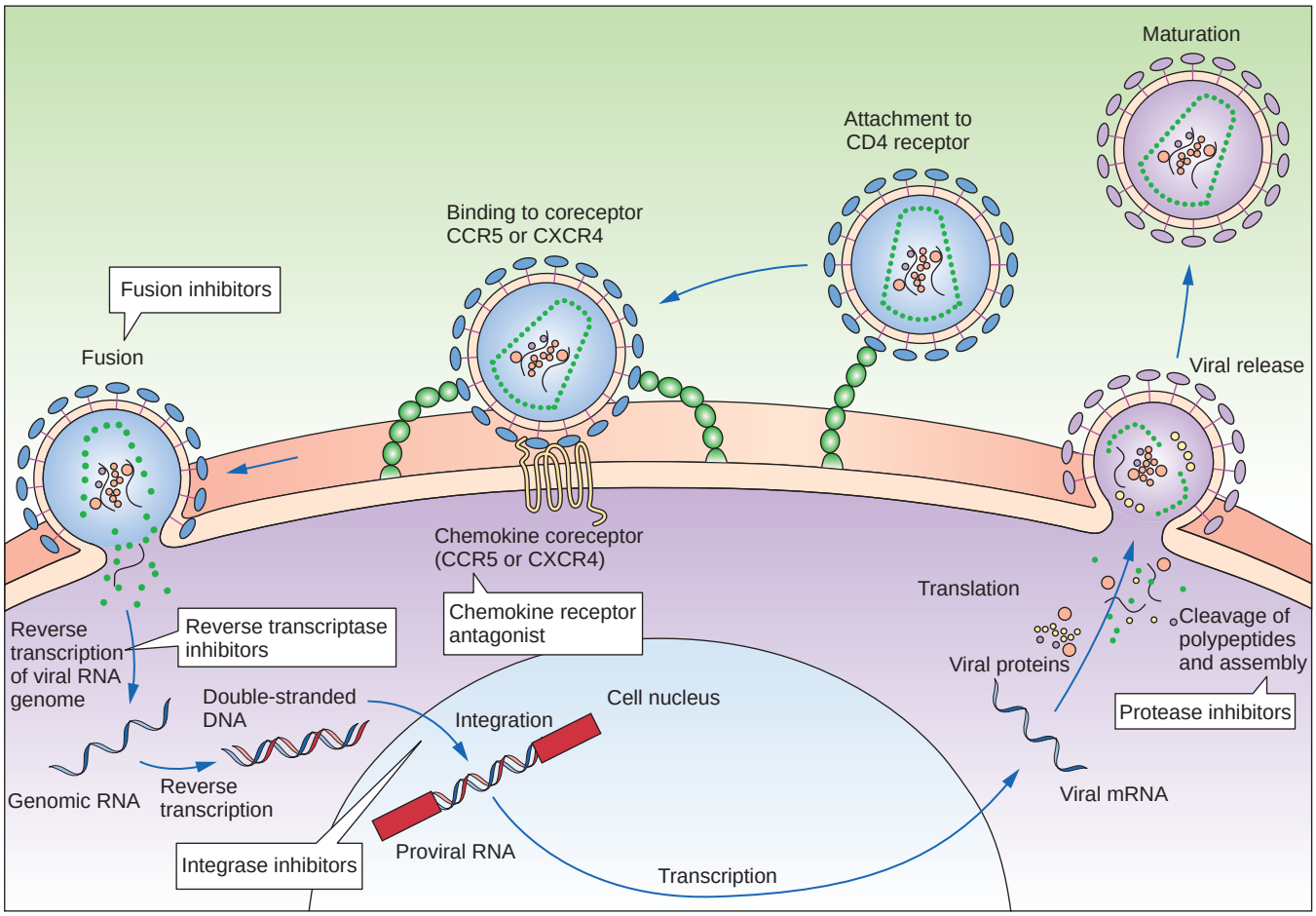

Fig. 124.3. Replicative cycle of the HIV virion. (Adapted from Maartens G, et al: HIV infection: epidemiology, pathogenesis, treatment, and prevention. Lancet 384:258–271, 2014.)

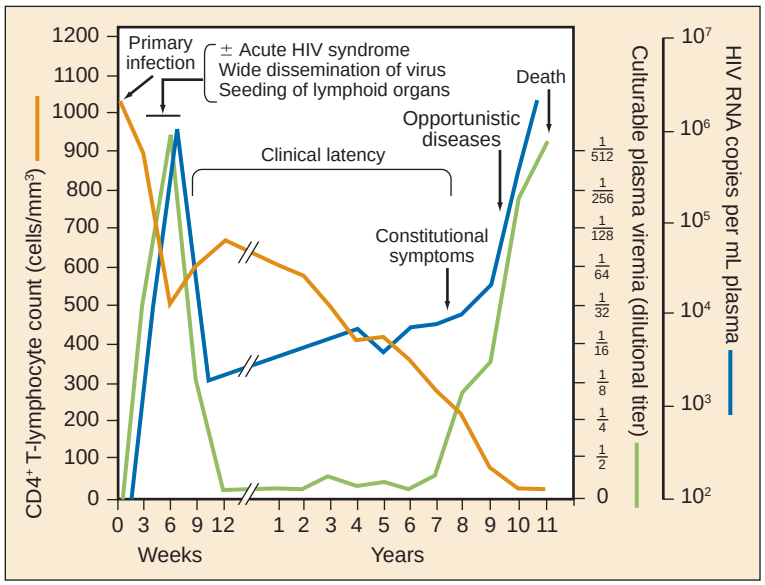

Fig. 124.4. Natural history of HIV infection in the absence of therapy in a hypothetical patient. (Adapted from Fauci AS, et al: Immunopathogenic mechanisms of HIV infection. Ann Intern Med 124:654–663, 1996.)

these patients often do not know that they are infected, and their viral load may be in the range of millions of RNA copies per milliliter.

Symptoms are nonspecific and are often not recognized as signs of HIV infection. The illness usually lasts for less than 2 weeks, although some patients may have a prolonged course. Cases of encephalitis, Guillain-Barré syndrome, and mononeuritis have occurred. $CD4^+$ counts also transiently drop, occasionally to the level at which opportunistic infections can occur. Among others, *Pneumocystis jiroveci* pneumonia (PCP), toxoplasmosis,

TABLE 124.1

HIV Testing by Laboratory Stage

	LABORATORY MARKER				
STAGE	RNA	p24 Antigen	Third-Generation Antibody (EIA)	Western Blot	HIV STAGE
1	+	–	–	–	Acute HIV infection
2	+++	+	–	–	Acute HIV infection
3	+++	+/–	+	–	Seroconversion
4	+++	+/–	+	Intermediate	Seroconversion
5	++	+/–	+	+	Seroconversion
6	+–+++	+/–	+	+	Chronic HIV infection (all Western blot bands are positive, older antibody tests react)

EIA, Enzyme immunoassay.
Adapted from Fiebig EW, et al: Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 17:1871–1879, 2003.

cytomegalovirus (CMV) infection, and thrush may occur in this stage.

Diagnosis of acute HIV infection requires keeping the constellation of symptoms in mind and understanding the pitfalls of laboratory testing for early infection. The results of routine HIV antibody testing may be negative for several weeks or even months after exposure. The diagnosis of acute HIV infection is confirmed with the presence of high titers of viral RNA and a negative antibody screen. Assay reactivity is dynamic; a plasma RNA test will detect HIV infection approximately 1 week before the ability to detect the p24 antigen and 12 days before antibodies to HIV develop (Table 124.1). A viral load test in the absence of symptoms of acute HIV infection is not recommended; false-positive results occur, and the test is costly. Confirmed cases of acute HIV infection should be referred immediately to a specialist for consideration of starting antiretrovirals.[3]

Chronic HIV Infection

After the primary infection, there generally is a prolonged clinical latent period. In this stage, aside from frequent generalized lymphadenopathy, many patients have little or no clinical manifestations of HIV infection. There are several host and viral factors that are involved and affect the rate of progression. As a result, the asymptomatic period is variable; the average onset to AIDS from seroconversion is approximately 8 to 10 years. Certain patients are long-term nonprogressors, and they have remained free of symptoms, without ART, for more than 25 years. Less fortunate individuals have progressed to AIDS within 3 years after transmission. Patients, however, typically lose approximately 80 $CD4^+$ cells/μL/year.

AIDS

The Centers for Disease Control and Prevention (CDC) definition of AIDS is a $CD4^+$ cell count below 200 cells/μL or the presence of an AIDS-defining condition (Box 124.1). At this level, immune dysfunction is severe and, without ART, survival is short. Those with a $CD4^+$ cell count below 50 cells/μL have advanced AIDS and are at much higher risk for death and development of opportunistic infections. Some infections are so common in patients with AIDS that primary prophylaxis is indicated and is cost-effective. Prophylaxis is started for PCP when $CD4^+$ counts are less than 200 cells/μL, for toxoplasmosis, when $CD4^+$ counts are less than 100 cells/μL and, for *Mycobacterium avium* complex (MAC) infection, when $CD4^+$ counts are less than 50 cells/μL (Table 124.2).

BOX 124.1

AIDS-Defining Conditions

Bacterial infections, multiple or recurrent
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 mo duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 mo duration)
Lymphoma, Burkitt's (or equivalent term)
Kaposi's sarcoma
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii,* disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 mo
Wasting syndrome attributed to HIV

Isoniazid is given to patients with a positive response to purified protein derivative. The risk of opportunistic infection in relation to the $CD4^+$ cell count is progressive rather than an all or none phenomenon.

Initial Evaluation

HIV-infected patients are at risk for some of the same infections and medical problems as noninfected patients, but they are more

TABLE 124.2

Prophylaxis to Prevent First Episode of Selected Opportunistic Infections

PATHOGEN	INDICATION	FIRST-CHOICE THERAPY	ALTERNATIVE
Pneumocystis jiroveci pneumonia (PCP)	• $CD4^+$ < 200 cells/μL or oropharyngeal candidiasis • $CD4^+$ < 14% or history of AIDS-defining illness • $CD4^+$ > 200 cells/μL but <250 cells/μL if monitoring is not possible every 1–3 mo	TMP-SMZ	TMP-SMZ Dapsone Dapsone + pyrimethamine + leucovorin Aerosolized pentamidine Atovaquone Atovaquone + pyrimethamine + leucovorin
Toxoplasma gondii encephalitis	• *Toxoplasma* IgG–positive patients with $CD4^+$ count < 100 cells/μL • Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have *Toxoplasma* serology retested if $CD4^+$ count declines to <100 cells/μL • Initiate prophylaxis if seroconversion occurs.	TMP-SMZ	TMP-SMZ Dapsone + pyrimethamine + leucovorin Dapsone + pyrimethamine + leucovorin Atovaquone ± pyrimethamine + leucovorin
Disseminated *Mycobacterium avium* complex (MAC) disease	• $CD4^+$ count < 50 cells/μL (after active MAC infection is ruled out)	Azithromycin Clarithromycin	Rifabutin (adjust dose on basis of ART interactions); rule out active TB before rifabutin is started.

ART, Antiretroviral therapy; *TB,* tuberculosis; *TMP-SMZ,* trimethoprim-sulfamethoxazole.
Adapted from Kaplan JE, et al: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm.

vulnerable to opportunistic and unusual infections. Knowledge of the $CD4^+$ count, along with the patient's clinical presentation, is critical in ED management. Before ART, patients were primarily hospitalized for opportunistic infections. Patients with HIV infection are now dying of diseases that were not traditionally considered as an AIDS disease, such as heart disease, liver failure, and non–AIDS-related cancers.[4]

The current $CD4^+$ count is a marker of the degree of immunosuppression and is critical background information for the interpretation of signs and symptoms. However, many patients have undiagnosed HIV infection, and they often present in later stages of disease. Others may not be taking ART because of issues involving access to care, difficulties with medication adherence, or viral resistance to ART. Opportunistic infections such as PCP, disseminated mycobacterial infections, cryptococcal meningitis, and CMV disease do not occur until the $CD4^+$ count is dramatically reduced. A total lymphocyte count may provide a rough approximation of the absolute $CD4^+$ count; a count between 1000 and 2000 cells/μL appears to be a reasonable surrogate of significant immunosuppression. Acute illness will decrease peripheral lymphocyte counts and thus limits the value of the peripheral lymphocyte count as a diagnostic aid in an acute setting. However, an ED study has shown that patients with a peripheral lymphocyte count below 950 cells/μL are highly likely to have AIDS.[5]

Certain clinical features suggest the possibility of a new diagnosis of HIV infection. A careful look at the skin and in the mouth may be revealing; certain skin findings, such as oral hairy leukoplakia and Kaposi's sarcoma, are found almost exclusively in HIV-infected individuals. Unexplained oral candidiasis is often the initial presenting symptom in someone with an undiagnosed HIV infection.

Clinical Manifestations by Organ System

Cardiac Manifestations

Cardiovascular manifestations of HIV infection vary greatly, depending on the patient's immune status and whether the patient is receiving ART. Patients with advanced HIV infection can have a constellation of cardiac manifestations, including pericarditis, myocarditis, cardiomyopathy, pulmonary vascular disease, pulmonary hypertension, valvular disease, and neoplastic involvement of the heart. Purulent pericarditis and cardiac tamponade are potentially lethal clinical manifestations of cardiovascular disease in patients with AIDS; *Mycobacterium tuberculosis* is often the causative organism, especially in low-resource countries.

The success of ART has led to prolonged survival in patients with HIV. Cardiovascular disease is now the major cause of morbidity and mortality. HIV-infected patients have a 50% increased risk of acute coronary syndrome compared to the general population, after adjustment for risk factors.[6] It is unclear whether this is the result of unmeasured traditional risk factors, the HIV infection itself, a complication of ART, or a combination of these factors. Patients receiving ART suffer from a number of metabolic abnormalities (eg, hyperglycemia, hyperlipidemia, lipodystrophy) and accelerated atherosclerosis, which may increase their risk for cardiovascular disease and acute coronary syndrome. Studies have shown that the virus alone is associated with dyslipidemia, endothelial damage, inflammation, and hypercoagulability.[7-10] Discontinuing ART has been shown to result in systemic inflammation, coagulation cascade activation, an increase in biomarkers associated with endothelial activation, and increased risk of major cardiovascular events. Antiretroviral agents cause varying degrees of dyslipidemia. Protease inhibitors, particularly ritonavir in higher doses, can especially be a problem. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are associated with increases in low-density lipoprotein cholesterol and total cholesterol but also a significant increase in high-density lipoprotein cholesterol. Modern regimens appear to be less toxic. Despite the reality that ART is likely to contribute to the development of coronary artery disease, the benefits of therapy outweigh the risks of accelerated atherosclerosis.

Pulmonary Manifestations

Pulmonary diseases have been the most important complications of HIV/AIDS. Infectious and noninfectious pulmonary diseases are more common in those with HIV infection compared to

uninfected indivuals.[11] The most frequent respiratory infections in people with HIV infection are upper respiratory tract infections and acute bronchitis. The incidence of lower respiratory tract infections increases as $CD4^+$ counts decline. Potential causes of lower respiratory tract infections include viruses (influenza, respiratory syncytial, parainfluenza), bacteria, and fungi (*P. jiroveci*; Table 124.3). Bacterial pneumonia is more frequent in people infected with HIV than in uninfected persons; the most common organism is *Streptococcus pneumoniae*. The incidence of PCP also increases as the $CD4^+$ count drops below 200 cells/μL.

A number of noninfectious causes of pulmonary disease are associated with HIV infection. Although the incidence is greatly reduced in the era of ART, pulmonary manifestations of Kaposi's sarcoma and non-Hodgkin's lymphoma can occur. HIV-infected patients also appear to be at increased risk for lung cancer, emphysema, cryptogenic organizing pneumonia, sarcoidosis, drug hypersensitivity, primary effusion lymphoma, foreign body granulomatosis, and lymphocytic interstitial pneumonitis.

Diagnostic evaluation of patients with HIV infection who present with respiratory complaints should be based on their HIV disease stage, as well as their clinical presentation (Table 124.4). Specific algorithms are difficult because of geographic differences in epidemiology.[12] Evaluation includes pulse oximetry, chest radiography, and complete blood count. Additional tests may include arterial blood gas analysis to determine the need for corticosteroids in patients with PCP, levels of serum lactate dehydrogenase (elevated in PCP), 1,3-β-D-glucan (elevated in PCP), serum cryptococcal antigen, and urine *Histoplasma capsulatum* antigen, and sputum studies (including Gram staining, acid-fast bacillus, and staining for *P. jiroveci*). Blood cultures should be considered before antibiotic therapy initiation; an aggressive search for the pathogen is generally recommended in patients with HIV infection.

PCP is one of the most common AIDS-defining opportunistic infections. With the widespread use of ART, as well as chemoprophylaxis against PCP in patients with $CD4^+$ counts below 200 cells/μL, the incidence of PCP in developed countries has greatly

TABLE 124.3

Differential Diagnosis of Respiratory Infections in HIV-Infected Patients by $CD4^+$ Count

$CD4^+$ COUNT AND STAGE	DIFFERENTIAL DIAGNOSIS
Present at any stage	Acute bronchitis Bacterial pneumonia Tuberculosis
>500 cells/μL	Bacterial pneumonia[a]
Early HIV infection	PCP[a] HHV-8–related Kaposi's sarcoma
200–500 cells/μL	Bacterial pneumonia[a] PCP[a]
<200 cells/μL	Bacterial pneumonia[a] (consider bacteremia)
AIDS	PCP[a] *Histoplasma capsulatum* or *Coccidioides immitis* pneumonia *Cryptococcus neoformans* pneumonia Extrapulmonary or disseminated tuberculosis[a]
≤50 cells/μL	Bacterial pneumonia[a]
Advanced HIV infection	PCP[a] *Toxoplasma gondii* pneumonia Pulmonary Kaposi's sarcoma *Histoplasma capsulatum* or *Coccidioides immitis* pneumonia *Mycobacterium avium* complex pneumonia

HHV-8, Human herpesvirus 8; *PCP, Pneumocystis jiroveci* pneumonia.
[a]Occurs more frequently as immune function declines.

TABLE 124.4

Pulmonary Manifestations of Disease in HIV-Infected Patients

DISEASE	PRESENTATION	DIAGNOSTIC EVALUATION	TREATMENT
Bacterial pneumonia	Acute onset (<1 wk) Cough Purulent sputum Fevers, chills, rigors	Elevated white blood cell count Chest radiograph—unilateral focal consolidation $CD4^+$ count variable	Antibiotic therapy targeting *Streptococcus pneumoniae* and *Haemophilus influenzae* Also cover atypical bacterial pathogens
Pneumocystis jiroveci pneumonia (PCP)	Gradual onset (>2 wk) Nonproductive cough Dyspnea Fever	Exercise-induced hypoxia Elevated serum lactate dehydrogenase level Chest radiograph—bilateral reticular or interstitial pattern Computed tomography scan—ground glass opacity (56%) $CD4^+$ < 200 cells/μL	Trimethoprim-sulfamethoxazole for 21 days If Pao_2 < 70 mm Hg at room air or alveolar-arterial oxygen gradient > 35 mm Hg, give prednisone; taper over 21 days.
Mycobacterium tuberculosis infection (TB)	Gradual onset (>2 wk) Cough Fever Night sweats Weight loss Lymphadenopathy	Chest radiograph—alveolar pattern (±cavitation), miliary pattern, nodules, adenopathy, effusions $CD4^+$ count variable	Determine antituberculosis therapy with infectious disease consultant. Consider possibility of drug resistance. Multiple drug interactions exist between TB medications and antiretroviral therapy.
Kaposi's sarcoma	Gradual onset (>2–4 wk) Cough Dyspnea Fever	Chest radiograph—bilateral perihilar nodules, opacities, effusions, adenopathy $CD4^+$ < 200 cells/μL	Cryotherapy, radiation therapy Infrared coagulation Sclerosing agents, intralesional vinblastine Systemic chemotherapy

declined.[12,13] The clinical presentation of PCP is characterized by the gradual onset of fever (79% to 100% of cases), cough (95%), and progressive dyspnea (95%). The cough is nonproductive, although sputum production does not exclude this diagnosis, and patients can be coinfected with a bacterial pneumonia. Some patients, especially those taking nonsystemic prophylaxis (eg, aerosolized pentamidine), may have extrapulmonary manifestations of PCP, such as hepatosplenomegaly, skin lesions, and ocular lesions. The most common associated laboratory abnormalities are a $CD4^+$ count below 200 cells/μL and elevated lactate dehydrogenase level. Whereas chest radiographs can be normal, they usually show diffuse, bilateral, interstitial, or alveolar infiltrates (Fig. 124.5). High-resolution computed tomography (CT), which has a high sensitivity for PCP, often reveals ground glass or cystic lesions; a normal scan makes the diagnosis of PCP very unlikely (Fig. 124.6). The definitive diagnosis is made by isolation of the organism, commonly from respiratory specimens obtained by sputum induction, bronchoalveolar lavage, or endotracheal aspiration.

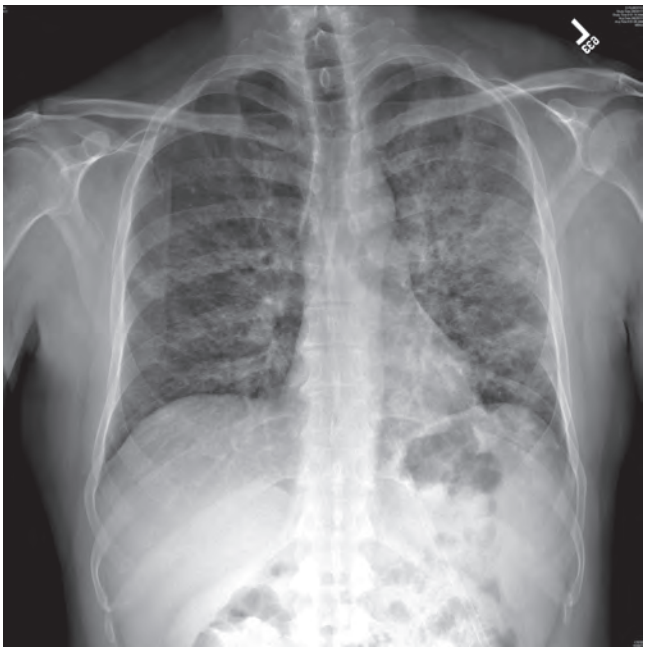

Fig. 124.5. Chest radiograph of *Pneumocystis* pneumonia. (From Mocroft A, et al: Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 362:22–29, 2003.)

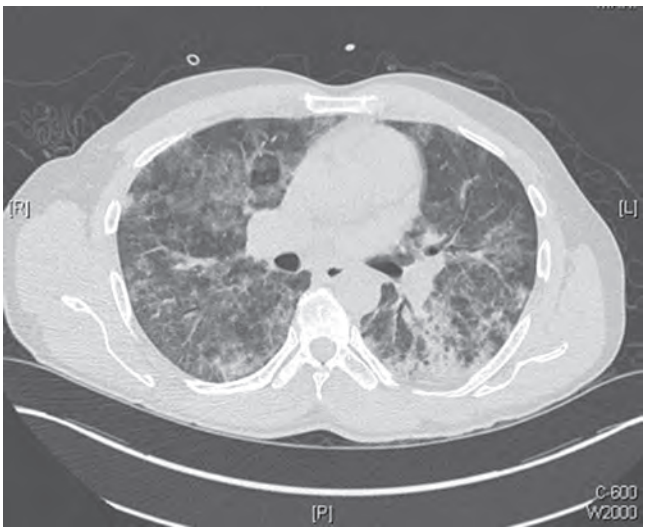

Fig. 124.6. Chest computed tomography scan of *Pneumocystis* pneumonia.

Double-strength trimethoprim-sulfamethoxazole (TMP-SMZ) administered orally daily is the preferred PCP prophylaxis. TMP-SMZ is also the preferred treatment of PCP; the route is dependent on the severity of disease. There are a number of other possible regimens for those who are intolerant (Table 124.5).

Hypoxic patients (partial pressure of oxygen ≤ 70 mm Hg or an alveolar-arterial oxygen gradient ≥ 35 mm Hg) receive significant benefit from concurrent corticosteroid treatment. Hypoxic patients should receive a 21-day prednisone taper in addition to antibiotic therapy.[13,14]

The risk of tuberculosis (TB) increases with declining immune function; it doubles within the first year after HIV seroconversion. Patients with HIV infection are more likely to develop active TB from reactivated latent infection, and TB co-infection increases the risk of progression to AIDS or death.

Clinical manifestations and radiographic findings of TB vary by the degree of underlying immunosuppression of the patient. Patients with early HIV infection and TB have presentations similar to those of individuals without HIV infection; they often have classic symptoms of pulmonary TB, such as fever, cough, weight loss, malaise, and night sweats. The typical radiographic findings of cavitation in the upper lung fields are usually present. With worsening immune function, there is less likelihood of pulmonary cavitation. In these cases, atypical radiographs are more common, such as pulmonary infiltrates without preference for the upper lung fields, and normal radiographs have been reported. With advanced HIV infection and severe immunosuppression, there is greater risk of extrapulmonary and disseminated TB.

In patients thought to have TB regardless of radiographic findings, diagnostic tests should be pursued, and the patient should be placed in respiratory isolation. Evaluation of extrapulmonary disease includes specimens of suspected areas of involvement (eg, CSF, lymph nodes, pleural fluid, pericardial fluid, blood, urine). The treatment of TB in people with HIV infection is complicated, and drug interactions between ART and anti-TB therapy are severe and common. After initiation of anti-TB therapy, the patient requires close monitoring for assessment of adequate treatment response and for observation of signs of immune reconstitution inflammatory syndrome (IRIS), a complication more common in patients with $CD4^+$ counts below 200 cells/μL.

TABLE 124.5

Treatment of *Pneumocystis jiroveci* Pneumonia in Patients with HIV Infection

SEVERITY OF ILLNESS	PREFERRED THERAPY	ALTERNATIVE THERAPY
Moderate to severe	TMP-SMZ, IV; switch to oral administration after clinical improvement 21-day therapy	Pentamidine *or* Primaquine + clindamycin
Mild to moderate	TMP-SMZ	Dapsone + trimethoprim *or* Primaquine + clindamycin *or* Atovaquone

TMP-SMZ, Trimethoprim-sulfamethoxazole.

US Department of Health and Human Services: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. www.aidsinfo.nih.gov.

Although outpatient therapy is possible, most HIV-infected patients with a low $CD4^+$ cell count and respiratory complaints require hospitalization. Bronchoscopy and high-resolution CT chest scanning are often required to make the definitive diagnosis. Patients with presumed bacterial pneumonia require treatment with antibiotics that cover the usual community-acquired organisms.

Oropharyngeal and Gastrointestinal Manifestations

Oropharyngeal and gastrointestinal (GI) diseases often complicate HIV infection. HIV-infected patients with GI symptoms may present with common abdominal disease or may have opportunistic infections, malignant neoplasms, or medication side effects. Patients receiving ART may suffer treatment-related adverse gastrointestinal events, including pancreatitis, hepatic steatosis, lactic acidosis, and drug-induced hepatotoxicity. Furthermore, a number of patients with HIV infection have concomitant hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and may also have GI manifestations from these causes as well. Although improvements have been noted, end-stage liver disease remains a common cause of mortality in HIV-infected patients.[4,15]

As in other organ system disease, patients with higher $CD4^+$ counts tend to be infected by common, more pathogenic bacteria. Patients with $CD4^+$ counts below 100 cells/μL are more likely to have opportunistic infections and suffer from hepatobiliary problems, such as acalculous cholecystitis.

Primary HIV infection has a variety of oropharyngeal manifestations, including pharyngitis and severe aphthous ulcers. With progressive immunodeficiency, the pathogens change. Thrush, caused by *Candida,* is an extremely common opportunistic infection and is often the first manifestation of HIV infection. Oral hairy leukoplakia, caused by Epstein-Barr virus (EBV), is manifested as raised white lesions on the side of the tongue. Unlike in thrush, the lesions cannot be scraped off and are not responsive to topical antifungal agents. Kaposi's sarcoma, which can occur in the mouth, is usually found on the palate.

Esophagitis may occur in HIV-infected patients, particularly those with $CD4^+$ counts below 100 cells/μL. Patients present with dysphagia or odynophagia. The most common cause of esophagitis in patients with HIV infection is *Candida*. Other potential causes include herpes simplex virus, CMV, and deep aphthous ulcers. The underlying cause can be confirmed by endoscopy with biopsy. Given that biopsy is invasive, and fungal sphagitis common, most patients with esophagitis first undergo a course of fluconazole for empirical treatment of *Candida* infection; a clinical response should occur within 5 to 7 days. Gastroesophageal reflux is another common complaint, and treatment is with antacids. However, certain antiretrovirals, such as atazanavir, require an acidic environment to aid in absorption. Consideration of potential drug interactions is important when new medications are started in HIV-infected patients.

Small or large bowel enteritis, characterized by abdominal pain, cramping, diarrhea, dehydration, and fever, is a common problem and can be caused by a number of underlying factors. Bacterial infections are the usual offenders, such as *Clostridium difficile* and *Salmonella, Shigella, Campylobacter,* and *Yersinia* spp. Patients with advanced immunosuppression can have chronic diarrhea, often from opportunistic infections with the parasites *Cryptosporidium, Isospora,* and microsporidia. CMV causes large bowel enteritis and generally occurs in severely immunosuppressed hosts with $CD4^+$ counts below 50 cells/μL. In developing countries, TB should also be considered a cause of abdominal disease in patients with HIV infection. Malignant diseases, such as lymphoma and Kaposi's sarcoma, can affect the bowels. Kaposi's sarcoma lesions in the GI tract can cause massive bleeding and obstruction. The evaluation for diarrhea often involves laboratory stool studies (ova and parasite, *C. difficile* toxin, bacterial culture, modified acid-fast staining) and, occasionally, colonoscopy. Therapy is usually supportive, maintaining hydration; symptoms often persist until immune reconstitution.

Disseminated opportunistic infections can also involve the liver, including MAC and *Bartonella* infections. AIDS-related cholangiopathy, biliary obstruction from infection-associated strictures of the biliary tract, is seen with severe immunosuppression. However, noninfectious causes, such as cholecystitis, have become more common.

Central Nervous System Manifestations

The differential diagnosis of patients who present with headaches, abnormal findings on neurologic examination, or change in mental status varies on the basis of the current status of their immune system and results of neuroimaging. Common problems include cryptococcal meningitis, toxoplasmosis, primary central nervous system (CNS) lymphoma, and progressive multifocal leukoencephalopathy. Many patients with untreated HIV infection, symptomatic or not, will have abnormal CSF findings.

HIV itself is a neurotropic virus, and patients with acute infection can present with aseptic meningitis with complaints of fever, headaches, and meningismus. There usually is lymphocyte-predominant, moderate pleocytosis. Syphilis has also reemerged, and CNS infection can occur at any stage of HIV infection.

Cryptococcus neoformans is the most common cause of meningitis in patients with AIDS. It usually affects patients who are profoundly immunosuppressed, with $CD4^+$ counts below 100 cells/μL. The disease is subacute, and patients present with fevers, malaise, and headache. Later in the course, because of increased intracranial pressure, patients experience vomiting and altered mental status. *Cryptococcus* often does not cause a significant inflammatory response, and meningeal signs are frequently absent. A lumbar puncture is diagnostic, demonstrating elevated opening pressures (70% with pressures > 200 mm Hg), presence of cryptococcal antigen (CRAG), and low white blood cell count in the CSF (typically, <50/μL in the CSF). Serum CRAG testing is readily available, sensitive, and especially useful in resource-poor settings.[16] If the serum CRAG is negative, it will unlikely be positive in the CSF and not the cause of cryptococcal meningitis. Poor prognostic factors for cryptococcal meningitis are altered mental status, absence of CSF pleocytosis, CSF antigen titers greater than 1:1024, and a positive serum fungal culture.[17,18] These signs are indicative of a high organism burden, elevated CSF pressure, and lack of an inflammatory response. If left untreated, cryptococcal meningoencephalitis is fatal. Therapy involves three phases—induction, consolidation, and maintenance. If the patient can tolerate it, aggressive initial treatment with 2 weeks of amphotericin B and flucytosine is recommended.[19] Fluconazole is used for the consolidation phase and is continued until immune reconstitution ($CD4^+$ count > 100 cell/μL for more than 1 year). Elevated intracranial pressure is treated with repeated lumbar punctures; on occasion, a lumbar drain is needed. Cryptococcal meningitis immune reconstitution syndrome can cause rapid clinical deterioration. A multicenter randomized trial has shown improved survival when ART is started 5 weeks after antifungal treatment compated to 1 to 2 weeks in those with risk factors.[20]

Patients may present with focal CNS lesions. Severely immunocompromised hosts ($CD4^+$ count < 200 cells/μL) are likely to have opportunistic infections or AIDS-associated tumors (Table 124.6). In developed countries, common causes of mass effect are toxoplasmosis and EBV-related primary CNS lymphoma; in developing countries, the cause is more likely to be tuberculomas. Toxoplasmosis is caused by reactivation of latent infection by the parasite *Toxoplasma gondii*. Most infected patients have a $CD4^+$ count below 100 cells/μL. Patients present with signs of increased

TABLE 124.6

Differential of Focal Central Nervous System Lesions in Patients With HIV Infection

	COMMON CLINICAL PRESENTATION	IMAGING AND DIAGNOSTIC TESTING
Toxoplasma encephalitis	Fever Headache Altered mental status Focal neurologic findings Seizure Evolves during days to weeks	Ring enhancing (≈90% of the time) CNS lesions Frequent edema and mass effect Toxoplasma antibodies (reflects past exposure) CD4+ often <100 cells/μL PCR detection of *Toxoplasma gondii*
Primary CNS lymphoma (PCNSL)	Confusion Lethargy Memory loss Hemiparesis Aphasia Seizure Fever Night sweats Weight loss Evolves during months	CNS lesion or lesions (may have mass effect) Solitary lesions are often large (>4 cm) Some ring enhancement may occur but less regular PCR assay for Epstein-Barr virus (associated with PCNSL)
Progressive multifocal leukoencephalopathy (PML)	Progressive focal neurologic deficits (during months) Hemiparesis Visual field defects Ataxia Aphasia Cognitive impairment	Multifocal areas of demyelination primarily involving white matter Less frequent mass effect or ring-enhancing PCR assay for DNA of JC virus (causes PML)
HIV encephalopathy	Memory and psychomotor speed impairment Depressive symptoms Movement disorders	Multiple hyperintense signals in T2-weighted images Often symmetric; not well demarcated
Cytomegalovirus encephalitis	Delirium Confusion Focal neurologic abnormalities	Magnetic resonance imaging shows multifocal scattered micronodules and ventriculoencephalitis. $CD4^+$ < 50 cells/μL
Brain abscess	Focal neurologic deficit Headache Bacteremia or craniofacial infection	Often concomitant evidence of disseminated infection
Tuberculoma	Focal neurologic deficit Headache Tuberculosis infection	Single or multiple mass lesions Can be manifested as focal lesion or meningeal infection

CNS, Central nervous system; *PCR,* polymerase chain reaction.

intracranial pressure, such as headaches, confusion, lethargy, and seizures. Lesions are typically multiple and ring enhancing on CT. Although the definitive diagnosis is made after a brain biopsy, patients who are serologically positive for toxoplasmosis are usually treated empirically with pyrimethamine and sulfadiazine, keeping in mind that toxoplasmosis is much less common in patients who have been receiving TMP-SMZ prophylaxis for PCP. Most patients will show radiographic improvement in 2 weeks; response to treatment will obviate the need for a brain biopsy (Fig. 124.7).

Primary CNS lymphoma often looks identical to toxoplasmosis on magnetic resonance imaging (MRI) or CT scans. It also occurs with profound immunosuppression ($CD4^+$ count < 50 cells/μL). EBV is the cause of primary CNS lymphoma, and a polymerase chain reaction (PCR) analysis of the CSF, looking for the virus, has become an integral step in the evaluation of mass lesions. Treatment involves ART and chemotherapy.

Progressive multifocal leukoencephalopathy, caused by the JC virus, is characterized by demyelinating lesions in the CNS. The diagnosis is suggested by nonenhancing, hypodense lesions on CT or MRI, with a CSF PCR assay positive for JC virus. Advanced imaging with positron emission tomography, MRI, and single-photon emission CT can help differentiate among toxoplasmosis, lymphoma, and progressive multifocal leukoencephalopathy.

The gold standard for the diagnosis of CNS mass lesions remains brain biopsy. Corticosteroid therapy can cause false-negative results on brain biopsies in patients with lymphoma, and therefore the use of corticosteroids should be limited to patients with life-threatening mass lesions.[21]

Renal Manifestations

The two main categories of HIV-related kidney disease are HIV-associated nephropathy (HIVAN) and HIV immune complex kidney disease. HIVAN is a form of focal glomerulosclerosis that usually occurs in untreated individuals of African descent.[22] Proteinuria, often severe, and an elevated creatinine concentration occur. Some patients recover renal function with ART, but many progress to end-stage renal disease and require dialysis. Transplantation is now widely accepted for patients with stable HIV infection.[22]

ART can also affect the kidney. Indinavir, although less commonly used in industrialized countries, is associated with renal calculi. Tenofovir can cause acute renal failure, a Fanconi-like

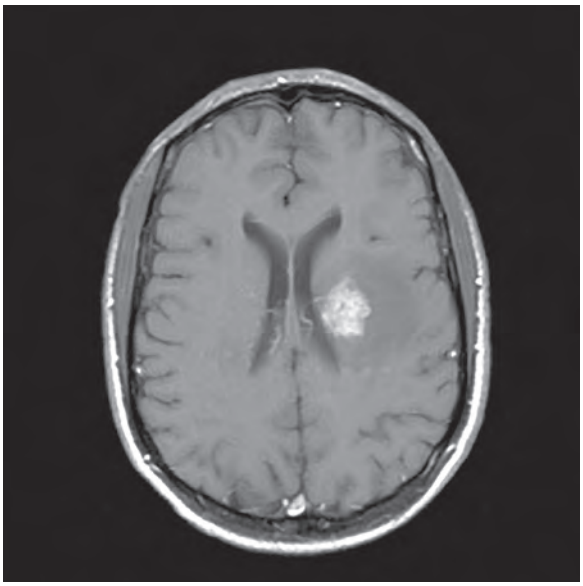

Fig. 124.7. Brain magnetic resonance image of a 38-year-old man with AIDS and *Toxoplasma* encephalitis. (From Mandell GL, et al, editor: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ed 7, Philadelphia, 2010, Elsevier/Churchill Livingstone.)

syndrome, and nephrogenic diabetes insipidus. Medications used to treat opportunistic infections can cause acute renal failure; amphotericin, pentamidine, and foscarnet are especially notorious.

Rheumatologic and Orthopedic Manifestations

HIV-infected patients are susceptible to the same types of orthopedic injuries and musculoskeletal disorders as patients without HIV infection, but there are certain conditions specific to HIV infection. Disseminated diseases such as TB are much more common in HIV-infected patients than in noninfected patients. Patients with HIV infection are prone to extrapulmonary manifestations, including septic arthritis, spondylitis, osteomyelitis, and bursitis. In general, however, septic arthritis is relatively uncommon in HIV-infected individuals. Risk factors include injection drug use and hemophilia. The most common organism involved is *Staphylococcus aureus*. Disseminated gonococcus causing septic arthritis is another possibility, especially in sexually active individuals. Unusual and atypical infections occur in late-stage AIDS. Bacillary angiomatosis, for example, is caused by *Bartonella henselae* and *Bartonella quintana* and causes disseminated disease affecting the skin, lymph nodes, liver, and CNS and can cause long bone osteomyelitis.

Fractures of the hip, spine, and wrist are more common in HIV-infected individuals because they have lower bone mineral density than that of age-matched controls. Osteonecrosis, especially of the femoral head, is common. Predisposing factors include corticosteroid use, ethanol abuse, and hypertriglyceridemia.

HIV-related polymyositis can occur at any stage of infection. These patients may have proximal muscle weakness, myalgias, and fatigue. Medications, especially nucleotide reverse transcriptase inhibitors (NRTIs), such as azidothymidine (AZT), can be toxic to the mitochondria and are common causes of polymyositis. Myopathies, spondylarthritis, pyomyositis, and HIV-associated arthritis are also common musculoskeletal problems. Reactive arthritis and other seronegative arthropathies are common, although it is unclear if this is because of sexual activity, generalized immune suppression, or the inflammatory response from the virus itself.

BOX 124.2

Dermatologic and Mucocutaneous Manifestations of WHO Stage 4 HIV Disease

Chronic herpes simplex virus ulcers
Extrapulmonary tuberculosis
Kaposi's sarcoma
Extrapulmonary cryptococcosis
Disseminated mycosis
Atypical disseminated leishmaniasis
Disseminated nontuberculous mycobacterial infection
Extrapulmonary cryptococcosis including meningitis

WHO, World Health Organization.

Hematologic Manifestations

HIV infection can cause anemia, thrombocytopenia, and leukopenia. Thrombocytopenia can occur in any stage of HIV infection. The cause is often immune-related, presenting as a disease process similar to idiopathic thrombocytopenic purpura; the treatment is ART. Thrombotic thrombocytopenic purpura is also well described in HIV-infected patients and tends to occur at later stages of disease.

Anemia and leukopenia occurs in later stages of HIV infection. Various medications can cause bone marrow toxicity; AZT, TMP-SMZ, and ganciclovir are common offenders. Systemic fungal infections and mycobacterial disease such as disseminated MAC disease can infect the bone marrow and decrease all three cell lines. Nutritional deficiencies, such as folate and vitamin B_{12}, are also common.

AIDS-related lymphoma (Hodgkin's and non-Hodgkin's) occurs more frequently in patients with advanced HIV infection. Most non-Hodgkin's lymphomas are of B cell origin and tend to be more aggressive in HIV-infected than in noninfected patients. CNS lymphomas and Burkitt's lymphoma are almost always associated with EBV, and primary effusion lymphoma is associated with human herpesvirus 8. The treatment involves standard chemotherapy and ART.

Cutaneous Manifestations

Dermatologic manifestations of HIV infection are extremely common, occurring throughout the course of HIV infection. Some skin findings are manifested early in the disease; others, found later, can be suggestive of profound immunosuppression (Box 124.2). Skin problems increase as HIV infection progresses. Recognition of HIV-related dermatologic conditions can lead to early diagnosis and can help the emergency clinician gauge the patient's immune status (Box 124.3).

Acute HIV infection often is manifested with a generalized maculopapular or morbilliform rash shortly after the onset of fevers. Oral ulcers, lesions on the palms and soles, and mucosal lesions can all be present. Aside from HIV itself, a variety of viruses can involve the skin. Herpes simplex virus infections are often more severe and recur frequently. Chronic ulcerating herpes simplex occurs later in the disease course and is an AIDS-defining opportunistic infection. Other common viral diseases include molluscum contagiosum, human papillomavirus infection, and oral hairy leukoplakia.

Kaposi's sarcoma, a vascular neoplasm, is the most common AIDS-related malignant disease in the United States, and the skin is the most commonly involved organ. Lesions are violaceous patches, nodules, or plaques (Fig. 124.8). Bacillary angiomatosis is manifested with lesions that resemble those of Kaposi's sarcoma.

BOX 124.3

Cutaneous Findings Highly Suggestive of HIV Disease

Any WHO criteria for stage 4 HIV disease
Facial molluscum in an adult
Proximal subungual onychomycosis
Herpes zoster scarring
Oral hairy leukoplakia
Bacillary angiomatosis
Widespread dermatophytosis
Severe seborrheic dermatitis

WHO, World Health Organization.

Fig. 124.8. Kaposi's sarcoma lesions.

Disseminated fungal infections are often signs of severe immunosuppression, and patients can present with skin manifestations. Disseminated cryptococcosis can be manifested with centrally umbilicated skin lesions resembling those of molluscum contagiosum. Other fungi (eg, *Histoplasma capsulatum*, *Coccidioides immitis, Blastomyces dermatitidis*, *Penicillium marneffei*) can cause cutaneous disease and are a significant cause of morbidity and mortality.

Noninfectious skin disorders are common. Seborrheic dermatitis, characterized by greasy scaly patches that are often located on the nasolabial folds, eyebrows, and scalp, affects up to 80% of patients with AIDS.[22] Cutaneous drug reactions occur with increased frequency and severity, such as toxic epidermal necrolysis. Often, the reaction is from sulfa-containing drugs. Abacavir can cause a hypersensitivity reaction that can be fatal if it is not recognized.

DIAGNOSTICCONSIDERATIONS

Differential Diagnosis

The possibility of HIV infection in patients presenting to the ED must be considered on a case by case basis. HIV infection should be considered in any patient who presents with unusual or recurrent serious infections without another explanation, especially patients with risk factors for HIV infection, such as IV drug users (IVDUs) and high-risk sexual practices. Although the opportunistic infections associated with AIDS can also occur in the absence of HIV infection, they usually develop in patients with some form of immunosuppression. HIV infection should also be considered in younger patients who develop conditions that typically don't occur until later in life, such as herpes zoster.

Diagnostic Testing

HIV Testing

The diagnosis of HIV infection involves the detection of specific antibodies or viral antigens (see Table 124.1). Laboratory detection of HIV infection is a two-step process. The first step is a screening test; if the result is positive, a confirmatory test is performed.

The balance between public health and patient confidentiality has been an issue surrounding HIV testing and reporting. Most states and hospitals have developed policies related to these concerns. Regardless, testing should be done in a confidential manner, with appropriate follow-up and counseling.

With the advent of enhanced testing capabilities as well as the push to diagnose existing cases of HIV infection in difficult to reach populations, some experts have recommended routine screening tests. Advantages of testing in the ED include increased detection of HIV infection in difficult to reach populations and earlier diagnosis of HIV infection, allowing earlier ART implementation and therefore decreased viral transmission.

In 2006, the CDC published revised recommendations for HIV testing in health care settings, including hospital EDs. This report recommended the use of diagnostic HIV testing and opt-out HIV screening in routine clinical care. Routine screening is recommended for 13- to 64-year-old patients, all patients who require TB treatment, those seeking treatment for sexually transmitted infections, and all pregnant women. Repeat annual screening is recommended for people at high risk. Providers should encourage patients to have HIV screening before the initiation of sexual relationships and after occupational exposures. Recommendations specify that consent should be obtained for HIV testing, pretest information should be shared with patients, and those responsible for the patient's care should be notified verbally of the planned testing.[23]

MANAGEMENT

ART has led to dramatic reductions in morbidity and mortality from opportunistic diseases and non-AIDS conditions. The goal of therapy is to suppress viral replication and reconstitute the immune system. Primary and secondary prophylaxis against opportunistic infections can be safely stopped with a return of $CD4^+$ cells. The best evidence for successful treatment is in those patients with $CD4^+$ counts below 350 cells/μL. However, $CD4^+$ counts below 500 cells/μL indicate that there is an impairment of immune function, and recent guidelines have recommended treatment of asymptomatic patients at any stage.

Antiretroviral therapies target the major viral enzymes—reverse transcriptase, protease, and integrase—and their attachment and fusion sites. ART involves the use of three active drugs,

usually two NRTIs and another agent, often an integrase strand transfer inhibitor, protease inhibitor, or NNRTI. Zidovudine, an NRTI, was the first drug released. Several NRTIs are currently available and have been approved by the US Food and Drug Administration for the treatment of HIV infection. Protease inhibitors, released in 1995, revolutionized the treatment of HIV infection and were the beginning of ART. NNRTIs are also commonly a part of the three-drug regimen. The initial regimen of ART needs to be individualized. Factors to consider in choosing a regimen include tolerability, viral resistance, dosing frequency, cost, and comorbidities.

Side effects from antiretroviral medications are extremely common. Protease inhibitors are notorious for GI side effects; most cause nausea and diarrhea. The NRTIs are mitochondrial toxic and can cause pancreatitis and hepatitis. Nevirapine, an NNRTI, can cause hepatic necrosis. Atazanavir causes a Gilbert-like syndrome. Efavirenz is commonly associated with self-limited neuropsychiatric problems

Postexposure Prophylaxis

All efforts should be made to minimize the potential for occupational exposure to body fluids. When exposure to body fluids occurs, however, the risk of acquiring HIV infection is low. Before ART, a large study examining HIV transmission from needle stick injuries to health care workers showed that transmission occurred in only 1 of 300 cases (0.33%), and there were no known cases of transmission through intact skin.[24] Currently, with postexposure prophylaxis (PEP) using ART, the risk of transmission is thought to be greatly reduced. Factors associated with increased risk of transmission from occupational exposure involving needle stick injuries include depth of injury, injury from a device visibly contaminated with the patient's blood, and needle stick into a vein or artery.

Recommendations regarding the use of PEP are based on the type of injury and body fluid involved. Body fluids of concern include semen, vaginal secretion, and any fluid contaminated with visible blood. Potentially infectious body fluids include CSF and synovial, pleural, peritoneal, pericardial, and amniotic fluids. Unless they contain blood, the following fluids are not considered infectious for HIV: vomitus, feces, nasal secretions, saliva, sputum, sweat, tears, and urine. Low-risk injuries are those involving solid needles (eg, suture needles), those that are superficial, and those involving a low-risk source patient or body fluid. High-risk injuries include those involving hollow bore needles with visible blood and percutaneous injury from a needle that was in an artery or vein of the source patient. Unless a mucocutaneous exposure involves large volumes of blood from a source patient with a plasma HIV viral load more than 1500 copies/μL, mucocutaneous exposures are considered to be low risk. Transmission is estimated to be as low as 0.09% (1/1000) for a splash of infectious body fluid to mucous membranes or broken skin.

The initial response to an exposure is immediate cleansing of the exposed or injured site; soap and water can be used for intact skin, and virucidal antiseptic agents, such as alcohol-based hand hygiene agents, can be used for small punctures and wounds. Mucosal surfaces and eyes should be flushed with copious amounts of water. Efforts should be made to document clinical information about the source patient, including risk factors and previous test results for HIV, HBV, and HCV, as well as to provide a description of the exposure and the time it occurred.

In 2013, the US Public Health Services updated their guidelines on managing occupational exposures to HIV. The new guidelines recommended three or more antiretroviral drugs for all occupational exposures to HIV.[25] Preferred regimens for PEP mirror the treatment of HIV—three-drug combination therapy with a dual NRTI backbone plus an integrase strand transfer inhibitor (INSTI), boosted protease inhibitor, or NNRTI. A commonly recommended regimen with a low toxicity profile and minimal drug interaction is tenofovir-emtricitabine (Truvada), along with the INSTI raltegravir .Other regimens include tenofovir-emtricitabine plus atazanavir with ritonavir or tenofovir-emtricitabine plus darunavir with ritonavir. Obtaining expert consultation should be considered for those with high-risk exposure, with comorbidities, or exposed to a drug-resistant virus, and those who present 72 hours or more after exposure. The National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) can be contacted at 888-448-4911 if local expertise is not immediately available.

If the exposed person is to receive PEP, the goal is to initiate therapy within 1 to 2 hours after exposure; the efficacy of PEP greatly decreases after 24 to 36 hours. Follow-up HIV testing should occur at 6 weeks, 3 months, and 6 months. If fourth-generation HIV antigen-antibody assays are used, HIV testing is performed at baseline, 6 weeks, and 4 months after exposure. Testing can be concluded 4 months after exposure as opposed to 6 months with other HIV antibody assays. An additional test at 12 months can be considered for those exposed to source patients co-infected with HIV and HCV. Revaluation of the patient within 72 hours of exposure is recommended. PEP should be continued for 28 days or until the source patient tests negative for HIV.

Some patients may present after possible exposure to HIV/AIDS with concern about the potential of transmission. Possible means of exposure include sexual contact, injection drug use, and exposure to body fluids through broken skin or mucous membranes. The risk of transmission varies with the means of exposure. For sexual exposure, receptive anal intercourse carries a higher risk of transmission among men who have sex with men compared with other sexual contact exposures because of the potential for mucosal breakdown and rectal bleeding. Similarly, the presence of genital ulcerative disease increases the likelihood of HIV transmission through sexual contact. Among heterosexual contact, the likelihood of HIV transmission is greatest after receptive anal intercourse, followed by receptive vaginal intercourse and insertive vaginal intercourse. Male to female transmission of HIV is more common than female to male transmission. The risk of transmission after the use of injection needles is greater after percutaneous injection of a contaminated needle into an artery or vein. Other important factors influencing the risk of HIV transmission include HIV status and viral load of the source.

The CDC recommends PEP for persons presenting within 72 hours after an exposure to a source known to be HIV-positive if contact of body fluid contaminated with blood (including semen, vaginal secretions, rectal secretions, and breast milk) was made with the vagina, rectum, eye, mouth or other mucous membrane, or nonintact skin or by percutaneous injection. Efforts should be made to determine the current HIV status of the source. HIV status of the individual seeking care should also be obtained.

A three-drug combination therapy is recommended. Because each of these medications has its side effects and toxicities, the decision of which agents to use should be made in conjunction with an infectious disease specialist. The patient should be observed closely so his or her progress can be monitored. PEP should continue for 28 days. Whereas most seroconversions will occur in the first 3 months after the exposure, these patients should be checked for HIV at 6 weeks, 12 weeks, and 6 months. The PEPline is also available to provide advice (see earlier).

DISPOSITION

It is important for emergency clinicians to be aware of the available resources for patients who have a high suspicion for HIV or have recently tested positive to ensure appropriate follow-up and further evaluation. The personal and public health consequences

of patients who have been lost to follow-up are significant, and a proactive approach for ensuring outpatient care is essential.

The widespread use of ART among HIV-positive individuals has dramatically changed the course of the disease; individuals often have sustained and lasting immune reconstitution and live relatively normal lives. Knowledge of their immune status is critical for disposition and treatment; patients with a normal or near-normal $CD4^+$ count should be treated like non–HIV-infected patients. Drug interactions are common. Patients with AIDS, unlike immunocompetent patients, often suffer from multiple, simultaneous underlying pathologic processes, making evaluation and treatment decisions even more difficult; a unifying diagnosis is not the norm. These patients are at greater risk of morbidity and mortality from common disease entities, as well as from complications of HIV/AIDS. Emergency clinicians who approach these patients with background knowledge of the potential manifestations of HIV/AIDS will be poised to deliver the best emergent care.

KEY CONCEPTS

- HIV/AIDS can affect any organ system, and the nonspecific complaints seen with viral illness are common. Consider acute HIV infection in the evaluation of patients with mononucleosis-like syndromes in the presence of risk factors.
- The presenting illness may originate from acute HIV infection, opportunistic infections, medication side effects, inflammation, and IRIS.
- Patients a with $CD4^+$ count above 500 cells/μL tend to have illnesses similar to those of individuals without HIV infection.
- Opportunistic infections are more frequent as the $CD4^+$ count declines but can occur at any stage of HIV infection.
- Formulation of the differential diagnosis should be guided by the patient's immune status—consider $CD4^+$ count, viral load, current medications, and prior opportunistic infections.
- Patients with HIV infection are at a greater risk of morbidity and mortality from common disease entities than noninfected patients.
- Patients with advanced AIDS suffer unusual diseases and often have multiple co-infecting pathogens.
- The current medications used for treatment of HIV infection (especially ART) can interact with many commonly prescribed drugs.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 124: QUESTIONS & ANSWERS

124.1. A 52-year-old man with acquired immunodeficiency syndrome (AIDS) presents with dysphagia. The pain radiates to his chest. He does not appear toxic. There is white plaque on his tongue and oropharynx, which is easily scraped off. His $CD4^+$ count was 52 cells/μL. He was just recently started on highly active antiviral therapy (HAART) and is taking atazanavir-ritonavir, tenofovir, and emtricitabine. What is the most appropriate treatment?

A. Acyclovir
B. Fluconazole
C. Ganciclovir
D. Immediate endoscopy
E. Proton pump inhibitor

Answer: C. Odynophagia with a $CD4^+$ count less than 100 cells/μL and oral thrust suggests esophageal candidiasis. If the patient can tolerate oral therapy, fluconazole is first-line treatment. Endoscopy is reserved for treatment failure or those with an atypical presentation. Cytomegalovirus and herpes simplex virus can cause esophagitis but are less common. They are diagnosed with endoscopy, often after treatment failure with fluconazole. Patients with HIV can have esophagitis due to reflux but, in this setting, empirical treatment for candidiasis is the most appropriate. Proton pump inhibitors can decrease the absorption of atazanavir and should not be prescribed without first discussing the case with the patient's human immunodeficiency (HIV) physician.

124.2. Which of the following is not an AIDS-defining condition?

A. Cellulitis
B. Extrapulmonary *Cryptococcus*
C. Invasive cervical cancer
D. Recurrent pneumonia
E. *Salmonella* septicemia

Answer: A. All the answers except A are AIDS-defining conditions.

124.3. A 52-year-old male patient presents with 3 days of confusion, fever, and headache. He was diagnosed with HIV 3 weeks ago and is not currently taking antiretroviral medications. His $CD4^+$ count at that time was 32 cells/μL. He has lived in the United States all his life. A head CT scan with contrast on this visit reveals multiple ring-enhancing lesions. Which of the following is the most likely cause of this central nervous system (CNS) lesion?

A. Cytomegalovirus encephalitis
B. HIV encephalopathy
C. *Mycobacterium* tuberculosis
D. Progressive multifocal leukoencephalopathy
E. *Toxoplasma gondii*

Answer: E. *Toxoplasma* encephalitis presents over days to weeks with fever, headache, altered mental status, focal neurologic findings, and/or seizures. In 90% of cases, there are ring-enhancing CNS lesions. the $CD4^+$ count is typically less than 100 cells/μL, and often the count is much lower. The main differential diagnosis in developed countries is CNS lymphoma. Patients with ring-enhancing CNS lesions are often empirically treated for *Toxoplasma,* and then a repeat CT scan is performed. A brain biopsy is diagnostic. Tuberculoma must be considered in patients with an exposure to tuberculosis and in those who live in areas highly endemic for tuberculosis.

124.4. A 36-year-old woman presents with a warm, red, painful lower leg. She has multiple other dermatologic concerns, including flesh-colored, dome-shaped lesions on her face, a new dark pigmented lesion on her arm, cold sores, and facial erythema. Which of her cutaneous findings suggests HIV disease?

A. Cellulitis
B. Facial molluscum
C. Melanoma
D. Oral herpes
E. Rosacea

Answer: B. HIV has many cutaneous manifestations. In this case, her facial molluscum is highly suggestive of HIV disease.

124.5. A 35-year-old man with AIDS presents with fever and a productive cough for 1 day. His last known $CD4^+$ count 1 month ago was 538 cells/μL. He has a lobar pneumonia in the left lower lobe on his chest radiograph. There is no evidence of lymphadenopathy. What is the most likely culprit pathogen in this case?

A. *Cryptococcus neoformans* pneumonia
B. Disseminated *Mycobacterium avium* complex
C. *Pneumocystis jiroveci* pneumonia (PCP)
D. Pulmonary tuberculosis
E. *Streptococcus pneumoniae*

Answer: E. It is critical to have an understanding of diseases relative to the absolute $CD4^+$ T cell count. Patients with CD4 counts higher than 500 cells/μL typically develop illnesses similar to the general population. This patient presents with a lobar pneumonia, and *S. pneumoniae* is the most common cause. PCP is the most common opportunistic pathogen in AIDS patients, usually occurring in those with a $CD4^+$ T cell count lower than 200 cells/μL. It would be extremely unusual for PCP to cause a lobar pneumonia in someone who is immune-reconstituted. Tuberculosis can occur at any stage of HIV infection. However, the symptoms tend to be more gradual in onset, and a lobar pneumonia is unlikely.

CHAPTER 125

Parasites

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OVERVIEW

An understanding of parasitology has become increasingly important for physicians practicing emergency medicine. There has been a dramatic increase in immigration from Southeast Asia, Central and South America, and Africa into the United States during the last few decades. Many of these people have emigrated from their countries of origin under dire circumstances, fleeing civil unrest, war, famine, economic hardship, political persecution, and environmental devastation; many had lived in regions where parasitic infections were, and continue to be, endemic. Business and adventure travel, including ecotourism, frequently transports immunologically naïve and vulnerable hosts to sites rich in parasitic disease. Patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) who travel to countries where parasitic illnesses are endemic are at higher risk of contracting these illnesses. Patients with AIDS who immigrate or travel to the United States may harbor a number of devastating parasitic illnesses. There continues to be a significant prevalence of endemic parasitic disease in many rural areas of the southeastern and southwestern United States and, in some parts of Europe, climate change is extending the habitat of what were known as tropical parasites and vectors to previously temperate regions. The growing population of patients with parasitic illness often initially seek treatment for their clinical symptoms in an emergency department (ED).

When parasitic illness is correctly diagnosed and treated promptly with effective chemotherapy, patients generally recover rapidly and completely (Table 125.1); however, parasitic illness often begins insidiously, and delayed treatment or mismanagement of parasitic diseases can be disastrous. Without appropriate treatment, many parasitic diseases will pursue a chronic and relentless course, resulting in damage to the host's end organs, severe morbidity, and even death. To diagnose parasitic infection, the emergency clinician must be vigilant and must obtain a thorough travel history, perform a detailed physical examination, and order appropriate laboratory studies. This information must be integrated with a strong understanding of the basic life cycles of parasites, variations in presentation of infection, intersecting geography of the organism and host, and characteristics of incubation periods between inoculation and clinical presentation.

The incubation period for the development of symptoms for parasitic diseases ranges from days (falciparum malaria) to months (vivax malaria) to years (filariasis). Uncovering parasitic illness depends heavily on Osler's principle—to *make* the diagnosis, the clinician must first *think* of the diagnosis.

Travel History

Parasitic illness should be considered in the differential diagnosis of almost every sign or symptom of illness in patients who recently have spent time in areas of the world with endemic parasitic illnesses (Table 125.2). Accordingly, a travel history should be included in the evaluation of most, if not all, patients presenting to the ED, and should include the questions summarized in Box 125.1. For patients who have recently immigrated to the United States, the emergency clinician should elicit additional information specific to the country of origin, also summarized in Box 125.1.

Therapy

New and more effective antiparasitic agents are continually being developed. The list of drugs used to treat parasitic infestations is large and varied. Table 125.3 includes some of the newest pharmaceutical agents as well as other older medications that are still recommended.

The newer antiparasitic drugs are less toxic and more effective. Parasite biochemical pathways are generally different from those in the human host, permitting selective metabolic interference by using relatively small doses of chemotherapeutic agents. In many cases, single-dose treatment can eradicate an entire parasite burden, leading to implementation of effective mass treatment programs in infected populations in endemic areas. One dose of ivermectin given annually to patients living in endemic areas prevents onchocerciasis. Treatment and disposition in the ED, however, focuses only on the individual patient and particular disease entity.

The evolutionary goal of the successful parasite is to live with and at the expense of the living host; a parasite that kills its host has a significant survival disadvantage. Most parasitic infections (with certain important exceptions, such as falciparum malaria) pursue a chronic course and are not acutely life-threatening. Nevertheless, alterations in host immune function can change the virulence and morbid course of more benign infections. Strongyloidiasis can become fulminantly disseminated in patients receiving immunosuppressive medication after organ transplantation, as treatment for cancer and more serious rheumatologic diseases, or after the initiation of long-term steroid therapy. Because of the subacute or chronic nature of most parasitic infections, the clinician should first make a diagnosis, initiate chemotherapy, and then arrange careful follow-up and repeated laboratory examinations to ensure that the patient is cured. When parasites are not eliminated promptly, repeated doses or alternative drugs may be needed because drug resistance among parasitic organisms is becoming increasingly common. In cases of suspected drug resistance, referral to a travel medicine or infectious disease clinic is indicated. A patient who appears clinically ill or has presumptive falciparum malaria—by symptoms or travel history—will usually require hospitalization for initial diagnosis, treatment, and observation.

PRESENTATIONS

The consideration of parasitic diseases is usually approached by correlating historical features such as exposure and travel history with presenting symptoms that can be associated with a number of illnesses, including parasitic infections. It is therefore useful to approach a patient with risk factors and certain presenting complaints as a possible manifestation of infection—fever, anemia,

Text continued on p. 1647

TABLE 125.1

Drug Classes and Modes of Action of Agents Used for Treatment of Parasitic Disease

TYPE OF DRUG	EXAMPLES[a]	USEFUL IN THE TREATMENT OF:	LIKELY TARGET IN THE PARASITE	PROPOSED EFFECTS ON TARGETS
Anthelmintic	Thiabendazole Mebendazole Albendazole	*Ascaris, Enterobius,* hookworm, *Strongyloides, Trichuris,* hydatid disease (long-term therapy)	Tubulin polymerization	Blocks cellular structural integrity and egg production; secondary effects on mitochondrial fumarate reductase and glucose uptake
	Ivermectin (Stromectol)	Many nematodes of humans (except hookworms) Filariasis Onchocerciasis	GABA-sensitive neuromuscular interface	Flaccidity or contraction (tight-binding drug effective at low dose)
Trematodicide	Praziquantel (Biltricide)	Schistosomes Most other flukes, such as *Clonorchis, Paragonimus,* Fasciolopsis (many tapeworms of humans)	Surface structure Carbohydrate metabolism	Vacuolization and surface disruption followed by immune attacks by the host; contraction of the muscles due to flooding of calcium through a permeable tegument; initial increase of glucose metabolism followed by shutdown
Antiprotozoal	Metronidazole (Flagyl) Tinidazole Niridazole	Amebiasis Balantidiasis Giardiasis *Schistosoma haematobium*	Molecular electron transport systems Acetylcholine recycling systems	Failure to sustain energy-producing systems Binds to acetylcholinesterase, inactivating normal neuromuscular function
Antimalarial	Chloroquine phosphate (Aralen)	Many species of susceptible malaria	Parasite digestive vacuole hemoglobinase	Local pH is changed so enzyme becomes inoperative
	Mefloquine	Many species of susceptible malaria		
	Proguanil-atovaquone	Many species of susceptible malaria	Mitochondrial electron transport prevents the normal function of the apicoplast	Works on erythrocytic and hepatic stages
	Doxycycline	Many species of susceptible malaria		Kills *Plasmodium falciparum*

[a]Some drugs may be available only from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, GA 30333; telephone: 404-639-3670 (nights, weekends, and holidays: 404-639-2888).
GABA, γ-aminobutyric acid.

BOX 125.1

Comprehensive Travel History for Evaluation of Parasitic Disease in the Emergency Department

QUESTIONS FOR ALL PATIENTS

- What were the exact dates of travel?
- What countries did the patient visit?
- How much time was spent in each country?
- What was the patient doing in the country, and where was he or she living?
- Was the patient a tourist, an adventure traveler, or a worker?
- Did the patient stay in cities or rural villages?
- Was the patient sleeping in hotels or tents?
- Did the patient engage in protected or unprotected sexual intercourse?
- What did the patient eat and drink?
- What were the patient's activities (eg, swimming in fresh water leads to schistosomiasis)?
- Did the patient receive prophylactic immunizations before travel?
- Did the patient take malaria chemoprophylaxis and comply with the regimen?
- Did the patient use mosquito repellent and netting?
- Does the patient have underlying chronic medical problems?
- What medications does the patient take?
- When did symptoms start, and what has been the chronology of symptoms, particularly fever and diarrhea?

QUESTIONS FOR PATIENTS WHO ARE RECENT IMMIGRANTS TO THE UNITED STATES

- When did the patient arrive, and from where?
- What acute and chronic illnesses did the patient have previously while living in the country of origin?
- What treatment did the patient receive there?
- If a refugee or immigrant, what countries did the patient pass through, and what were the living conditions (especially relevant for persons who have lived in numerous refugee camps)?
- What was the season during the patient's stay or travel in the countries (eg, monsoon vs. dry)?
- What animal exposures and bites has the patient experienced?
- Has the patient had exposure to fresh water in work or recreational activities?

TABLE 125.2

Parasites Causing Human Disease: Geographic Location and Portal of Entry

PARASITE	GEOGRAPHIC DISTRIBUTION	COMMON INFECTIVE STAGE AND PORTAL OF ENTRY
PROTOZOA		
Entamoeba histolytica	Cosmopolitan; especially prevalent in warm climates	Cyst via mouth
Balantidium coli	Warm climates	Cyst via mouth
Giardia lamblia	Found all throughout temperate and warm climates	Cyst via mouth
Trichomonas vaginalis	Cosmopolitan; United States	Trophozoite via vulva or urethra
Leishmania tropica	Mediterranean area to western India	Bite of sandfly introducing promastigote via skin, leading to visceral disease
Leishmania infantum	Southern Europe and Mediterranean	Bite of sandfly introducing promastigote via skin, leading to visceral disease
Leishmania donovani	China, India, Africa, Mediterranean area, continental Latin America	Bite of sandfly introducing promastigote via skin, leading to visceral disease
Leishmania chagasi	South America	Bite of sandfly introducing promastigote via skin, leading to visceral disease
Leishmania braziliensis	South America and Central America	Bite of sandfly introducing promastigote via skin, leading to cutaneous or mucocutaneous disease
Leishmania major, L. tropica	Africa and Asia	Bite of sandfly introducing promastigote via skin, leading to cutaneous disease
Leishmania mexicana, L. amazonensis, L. guyanensis, L. costaricensis	Central and South America	Bite of sandfly introducing promastigote via skin, leading to cutaneous disease
Trypanosoma gambiense	West and Central Africa	Trypanosome via skin from bite of the tsetse fly
Trypanosoma rhodesiense	Central and East Africa	Trypanosome via skin from bite of the tsetse fly
Trypanosoma cruzi	Continental Latin America	Trypanosome via skin from reduviid bug
Plasmodium vivax	Warm and cooler climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium ovale	Warm and cooler climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium malariae	Warm climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium knowlesi	Warm and cooler climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium falciparum	Warm climates	Sporozoite via skin from *Anopheles* mosquito
NEMATODES		
Trichinella spiralis	Cooler and temperate climates	Encysted larva in pork or bear via mouth
Trichuris trichiura	Warm, moist climates	Embryonated egg via mouth
Strongyloides stercoralis	Warm, moist climates	Filariform larva via skin
Necator americanus	Common in warm climates	Filariform larva via skin
Ancylostoma duodenale	Common in warm climates	Filariform larva via skin
Enterobius vermicularis	Cosmopolitan; common in the United States	Embryonated egg via mouth
Ascaris lumbricoides	Global distribution; common in the United States	Embryonated egg via mouth
Wuchereria bancrofti	Prevalent in warm climates	Filariform larva via skin from bite of *Anopheles* or *Culex* mosquito
Brugia malayi	Asia	Filariform larva via skin from bite of *Anopheles* or *Culex* mosquito
Onchocerca volvulus	Tropical Africa, Mexico, Central America, and northern South America	Filariform larva via skin from bite of the blackfly
Loa loa	Tropical West Africa	Filariform larva via skin from bite of the *Chrysops* fly
Dracunculus medinensis	Increasingly rare	Ingestion of larva by copepod via mouth

Continued

TABLE 125.2

Parasites Causing Human Disease: Geographic Location and Portal of Entry—cont'd

PARASITE	GEOGRAPHIC DISTRIBUTION	COMMON INFECTIVE STAGE AND PORTAL OF ENTRY
CESTODES		
Taenia saginata	Global distribution; uncommon in the United States	Cysticercus in beef via mouth
Taenia solium	South America, Central America, Mexico, East Africa, India, China, Indonesia	
• Adult worm		Cysticercus in pork via mouth
• Cysticercus stage		Eggs in human infections via mouth
Echinococcus granulosus	Mediterranean, Russian Federation and neighboring countries, China, Central Asia, North and East Africa, and South America	Eggs from canines via fecal-oral transmission
Echinococcus multilocularis	Central Europe, northern Asia, Alaska	Eggs from foxes, dogs, and cats via fecal-oral transmission
Hymenolepis nana	Warm climates	Eggs in human infections via mouth
Hymenolepis diminuta	Warm climates	Larva in arthropod host via mouth
Diphyllobothrium latum	US Great Lakes region and Alaska, Scandinavia, Russia, Japan, Pacific Coast of South America, and Uganda	Sparganum larva in fish flesh via mouth
TREMATODES		
Fasciola hepatica	Sheep-raising countries	Larva on vegetation via mouth
Fasciolopsis buski	Asia	Larva on water nuts
Clonorchis sinensis	Asia	Larva encysted in freshwater fish
Opisthorchis felineus	Europe, Asia	Larva encysted in freshwater fish
Opisthorchis viverrini	Thailand	Larva encysted in freshwater fish
Paragonimus westermani	Primarily Asia; also South America and Africa	Larva encysted in crabs or crayfish via mouth
Schistosoma japonicum	China, Southeast Asia, Philippines	Cercarial larva in water via skin
Schistosoma mansoni	Africa, Latin America, Middle East, Caribbean	Cercarial larva in water via skin
Schistosoma haematobium	Africa, Middle East	Cercarial larva in water via skin

Adapted from Beaver PC, Jung RC, Eddie Wayne Cupp EW: Clinical parasitology, ed 9, Philadelphia, 1984, Lea & Febiger.

TABLE 125.3

Drug Regimens for Treatment of Parasitic Infections

		DOSAGE	
INFECTION	DRUG[a]	ADULTS	CHILDREN
AMEBIASIS (*Entamoeba histolytica*)			
Asymptomatic			
	DRUG OF CHOICE • Iodoquinol	650 mg tid × 20 days	30 mg/kg/day in 3 doses × 20 days
	ALTERNATIVES • Diloxanide furoate *or*	500 mg tid × 10 days	25–35 mg/kg/day in 3 doses × 7 days
	• Paromomycin	25–30 mg/kg/day in 3 doses × 7 days	25–30 mg/kg/day in 3 doses × 7 days
Mild to Moderate Intestinal Disease			
	DRUG OF CHOICE • Metronidazole *followed by* • Paromomycin or iodoquinol	750 mg tid × 10 days	35–50 mg/kg/day in 3 doses × 10 days
	ALTERNATIVES • Tinidazole *followed by* • Paromomycin or iodoquinol	2 g/day × 3 days	50 mg/kg (max, 2 g) qd × 3 days

TABLE 125.3

Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG[a]	DOSAGE	
		ADULTS	CHILDREN
Severe Intestinal Disease, Hepatic Abscess			
Drainage of liver abscess	DRUG OF CHOICE • Metronidazole *followed by* • Paromomycin or iodoquinol	750 mg IV or PO tid × 10 days	35–50 mg/kg/day in 3 doses × 10 days
	ALTERNATIVES • Tinidazole *followed by* • Paromomycin or iodoquinol	2 g/day × 5 days	50 mg/kg or 60 mg/kg (max, 2 g) qd × 3 days
Amebic meningoencephalitis, primary (*Naegleria* spp.)	DRUG OF CHOICE • Amphotericin B	1 mg/kg/day IV, uncertain duration	1 mg/kg/day IV, uncertain duration
ANISAKIASIS (*Anisakis*)			
Treatment of choice	Surgical or endoscopic removal		
ASCARIASIS (*Ascaris lumbricoides*)			
Roundworm	DRUGS OF CHOICE		
	• Mebendazole	100 mg bid × 3 days	100 mg bid × 3 days
	• Albendazole	400 mg × 1 dose	>6 yr, same dose as for adult
	• Nitazoxanide	500 mg bid× 3 days	200 mg bid × 3 days
	• Ivermectin	150–200 μg/kg for 1 dose	Should be avoided in young children
BALANTIDIASIS (*Balantidium coli*)			
	DRUG OF CHOICE		
	• Tetracycline	500 mg qid × 10 days	40 mg/kg/day in 4 doses × 10 days (max, 2 g/day)
	ALTERNATIVES	650 mg tid × 20 days	40 mg/kg/day in 3 doses × 20 days
	• Iodoquinol		
	• Metronidazole	750 mg tid × 5 days	35–50 mg/kg/day in 3 doses × 5 days
CUTANEOUS LARVA MIGRANS			
Creeping eruption	DRUG OF CHOICE • Ivermectin	200 μg/kg once daily × 1 or 2 days	
Dracunculus medinensis			
Guinea worm; worm also needs to be extracted	DRUG OF CHOICE • Metronidazole	750 mg tid × 5–10 days	25 mg/kg/day (max, 750 mg/day) in 2 doses × 10 days
	ALTERNATIVE • Thiabendazole	50–75 mg/day bid × 3 days	50–75 mg/kg/day in 2 doses × 3 days
Enterobius vermicularis			
Pinworm	DRUGS OF CHOICE		
	• Albendazole	Single dose of 400 mg; repeat after 2 wk	11 mg/kg once (max, 1 g); repeat after 2 wk
	• Mebendazole	Single dose of 100 mg; repeat after 2 wk	Single dose of 100 mg; repeat after 2 wk
FILARIASIS (*Wuchereria bancrofti, Brugia malayi*)			
	DRUG OF CHOICE • Diethylcarbamazine	Day 1: 50 mg PO Day 2: 50 mg tid Day 3: 100 mg tid Days 4–21: 6 mg/kg/day in 3 doses	Day 1: 1 mg/kg PO Day 2: 1 mg/kg tid Day 3: 1–2 mg/kg tid Days 4–21: 6 mg/kg/day in 3 doses
Loa loa	DRUG OF CHOICE • Diethylcarbamazine	Day 1: 50 mg PO Day 2: 50 mg tid Day 3: 100 mg tid Days 4–21: 9 mg/kg/day in 3 doses	Day 1: 1 mg/kg PO Day 2: 1 mg/kg tid Day 3: 1–2 mg/kg tid Days 4–21: 6 mg/kg/day in 3 doses

Continued

TABLE 125.3

Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG[a]	DOSAGE: ADULTS	DOSAGE: CHILDREN
Onchocerca volvulus	DRUG OF CHOICE • Ivermectin	150 μg/kg PO once, repeated every 3–12 mo	150 μg/kg PO once, repeated every 3–12 mo
HERMAPHRODITIC FLUKE			
Clonorchis sinensis (Chinese liver fluke)	DRUG OF CHOICE • Praziquantel	25 mg/kg/day in 4–6 doses × 1 day	25 mg/kg/day in 4–6 doses × 1 day
Fasciola hepatica (sheep liver fluke)	DRUG OF CHOICE • Bithionol	30–50 mg/kg on alternate days × 10–15 doses	30–50 mg/kg on alternate days × 10–15 doses
Fasciolopsis buski (intestinal fluke)	DRUG OF CHOICE • Praziquantel	25 mg/kg/day in 4 to 6 doses × 1 day	25 mg/kg/day in 4 to 6 doses × 1 day
Opisthorchis felineus	DRUG OF CHOICE • Praziquantel	25 mg/kg/day in 4 to 6 doses × 1 day	25 mg/kg/day in 4 to 6 doses × 1 day
Paragonimus westermani (lung fluke)	DRUG OF CHOICE • Praziquantel ALTERNATIVE • Bithionol	25 mg/kg/day in 4 to 6 doses × 2 days 30–50 mg/kg on alternate days × 10–15 doses	25 mg/kg/day in 4 to 6 doses × 2 days 30–50 mg/kg on alternate days × 10–15 doses
Giardiasis (*Giardia lamblia*)	DRUG OF CHOICE • Metronidazole ALTERNATIVES • Nitazoxanide *or* • Tinidazole	250 mg tid × 5 to 7 days 500 mg bid × 3 days 2 g as a single dose	15 mg/kg/day in 3 doses × 5 to 7 days 200 mg PO bid × 3 days (>4 yr) 50 mg/kg as a single dose
HOOKWORM INFECTION (*Ancylostoma duodenale, Necator americanus*)			
	DRUGS OF CHOICE • Albendazole *or* • Mebendazole *or* • Pyrantel pamoate	400 mg × one dose 500 mg × one dose 11 mg/kg (max, 1 g) × 3 days	 500 mg × one dose 11 mg/kg (max, 1 g) × 3 days
LEISHMANIASIS			
Leishmania braziliensis, Leishmania mexicana, Leishmania tropica, Leishmania donovani (kala-azar, black fever)	DRUGS OF CHOICE • Miltefosine *or* • Stibogluconate sodium ALTERNATIVE • Amphotericin B	Not indicated in those ≤12 yr 20 mg/kg/day IV or IM × 20–28 days 0.25–1 mg/kg by slow infusion daily or every 2 days for 8 wk	2.5 mg/kg/day PO × 28 days 20 mg/kg/day IV or IM × 20–28 days 0.25–1 mg/kg by slow infusion daily or every 2 days for 8 wk
MALARIA, TREATMENT OF (*Plasmodium falciparum, P. ovale, P. vivax, P. malariae*)			
All *Plasmodium* Species (Except Chloroquine-Resistant *P. falciparum*)			
Oral	DRUG OF CHOICE Chloroquine phosphate	600 mg base (1 g), then 300 mg base (500 mg) 6 hr later, then 300 mg base (500 mg) at 24 and 48 hr	10 mg base/kg (max, 600 mg base), then 5 mg base/kg 6 hr later, then 5 mg base/kg at 24 and 48 hr
Parenteral	DRUGS OF CHOICE • Quinine dihydrochloride *or* • Quinidine gluconate *or* • Artesunate for treatment failure or adverse reactions from quinidine or quinine (available from the CDC)	20 mg/kg loading dose in 10 mg/kg 5% dextrose during 4 hr, followed by 10 mg/kg during 2–4 hr q8h (max, 1800 mg/day) until oral therapy can be started 10 mg/kg loading dose (max, 600 mg) in normal saline slowly during 1–2 hr, followed by continuous infusion of 0.02 mg/kg/min for 3 days max	Same as adult dose Same as adult dose

TABLE 125.3

Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG[a]	DOSAGE	
		ADULTS	CHILDREN
	ALTERNATIVE		
	• Chloroquine hydrochloride	200 mg base (250 mg) IM q6h if oral therapy cannot be started	0.83 mg base/kg/hr × 30 hr continuous infusion or 3.5 mg base/kg q6h IM or SC
Chloroquine-Resistant *P. falciparum*			
Oral	DRUGS OF CHOICE		
	• Quinine sulfate *plus*	650 mg tid × 3 days	25 mg/kg/day in 3 doses × 3–7 days
	• Doxycycline *or*	100 mg bid × 7 days	
	• Clindamycin	900 mg tid × 3–5 days	20–40 mg/kg/day in 3 doses × 3–5 days
	ALTERNATIVES		
	• Mefloquine	1250 mg once	25 mg/kg once (<45 kg)
	• Atovaquone-proguanil	1000/400 mg qd × 3 days	
	• Artemether-lumefantrine	4 tabs bid × 3 days	
Parenteral	DRUGS OF CHOICE		
	• Quinine dihydrochloride *or*	Same as above	Same as above
	• Quinidine gluconate *or*	Same as above	Same as above
	• Artesunate	Same as above	Same as above
Prevention of relapses—*P. vivax* and *P. ovale* only	DRUG OF CHOICE		
	• Primaquine phosphate	15 mg base (26.3 mg)/day × 14 days or 45 mg base (79 mg)/wk × 8 wk	0.3 mg base/kg/day × 14 days
MALARIA, PREVENTION OF			
	DRUG OF CHOICE		
	• Chloroquine phosphate	300 mg base (500 mg salt) PO, once/wk beginning 1 wk before and continuing for 4 wk after last exposure	5 mg/kg base (8.3 mg/kg salt) once/wk, up to adult dose of 300 mg base, same schedule as for adults
Chloroquine-resistant areas	DRUGS OF CHOICE		
	• Mefloquine *or*	250-mg tablet PO once/wk × 4 wk, then every other wk, continuing for 4 wk after last exposure	Same schedule as for adults with the following dosing guidelines: 15–19 kg, ¼ tablet; 20–30 kg, ½ tablet; 31–45 kg, ¾ tablet; >45 kg, 1 tablet
	• Atovaquone-proguanil *or*	250/100 mg qd 1 day before travel, each day in endemic region, and for 1 week afterward	
	• Doxycycline	100 mg daily during exposure and for 4 wk afterward	>8 yr: 2 mg/kg/day PO, up to 100 mg/day
SCHISTOSOMIASIS			
Schistosoma haematobium	DRUG OF CHOICE		
	• Praziquantel	20 mg/kg/day in 4–6 doses × 1 day	20 mg/kg/day in 4–6 doses × 1 day
Schistosoma japonicum	DRUG OF CHOICE		
	• Praziquantel	20 mg/kg/day in 4–6 doses × 1 day	20 mg kg/day in 4–6 doses × 1 day
Schistosoma mansoni			
	DRUG OF CHOICE		
	• Praziquantel	20 mg/kg/day in 4–6 doses × 1 day	20 mg/kg/day in 4–6 doses × 1 day
	ALTERNATIVE		
	• Oxamniquine	15 mg/kg once	20 mg/kg/day in 2 doses × 1 day
Schistosoma mekongi	DRUG OF CHOICE		
	• Praziquantel	20 mg/kg/day in 4–6 doses × 1 day	20 mg/kg/day in 4–6 doses × 1 day
Strongyloidiasis (*Strongyloides stercoralis*)			
	DRUGS OF CHOICE		
	• Ivermectin *or*	200 μg/kg/day × 1–2 days	200 μg/kg/day × 1 or 2 days
	• Thiabendazole	50 mg/kg/day in 2 doses (max, 3 g/day) × 2 days	50 mg/kg/day in 2 doses (max, 3 g/day) × 2 days

Continued

TABLE 125.3

Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG[a]	DOSAGE	
		ADULTS	CHILDREN
TAPEWORM INFECTION			
Adult (Intestinal Stage)			
Diphyllobothrium latum (fish), *Taenia saginata* (beef), *Taenia solium* (pork), *Dipylidium caninum* (dog)	DRUG OF CHOICE Praziquantel	5–10 mg/kg once	5–10 mg/kg once
Hymenolepis nana (dwarf tapeworm)	DRUG OF CHOICE • Praziquantel	25 mg/kg once	25 mg/kg once
Tapeworm Infection, Larval (Tissue) Stage			
Echinococcus granulosus (hydatid cysts)	DRUG OF CHOICE • Albendazole	400 mg bid × 28 days, repeated as necessary	15 mg/kg/day × 28 days, repeated as necessary
Echinococcus multilocularis—treatment of choice	Surgical excision		
Cysticercus cellulosae (cysticercosis)	DRUG OF CHOICE • Praziquantel ALTERNATIVE • Surgery	50 mg/kg/day in 3 doses × 15 days	50 mg/kg/day in 3 doses × 15 days
Trichinosis (*Trichinella spiralis*)	DRUGS OF CHOICE • Steroids for severe symptoms *plus* • Mebendazole	200–400 mg tid × 3 days, then 400–500 mg tid × 10 days	Same as adult dose
TRICHOMONIASIS (*Trichomonas vaginalis*)			
	DRUG OF CHOICE • Metronidazole	2 g once or 250 mg tid or 375 mg bid PO × 7 days	15 mg/kg/day PO in 3 doses × 7 days
TRICHURIASIS (*Trichuris trichiura*, WHIPWORM)			
	DRUGS OF CHOICE • Mebendazole *or* • Albendazole	100 mg bid × 3 days 400 mg once	100 mg bid × 3 days 400 mg once
TRYPANOSOMIASIS			
Trypanosoma cruzi (South American trypanosomiasis, Chagas' disease)	DRUG OF CHOICE • Nifurtimox	8–10 mg/kg/day PO in 4 doses × 120 days	1–10 yr: 15–20 mg/kg/day in 4 doses × 90 days 11–16 yr: 12.5–15 mg/kg/day in 4 doses × 90 days
	Alternative • Benznidazole	5–7 mg/kg/day × 30–120 days	Same as adult dose
Trypanosoma brucei gambiense, Trypanosoma brucei rhodesiense (African trypanosomiasis, sleeping sickness), hemolymphatic stage	DRUG OF CHOICE • Suramin	100–200 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	20 mg/kg on days 1, 3, 7, 14, and 21
	ALTERNATIVE • Pentamidine isethionate	4 mg/kg/day IM × 10 days	4 mg/kg/day IM × 10 days
Late disease with central nervous system involvement	DRUG OF CHOICE • Melarsoprol (*Trypanosoma brucei rhodesiense*)	2–3.6 mg/kg/day IV × 3 days; after 1 wk, 3.6 mg/kg/day IV × 3 days; repeat again after 10–21 days	18–25 mg/kg total during 1 mo; initial dose of 0.36 mg/kg IV, increasing gradually to max, 3.6 mg/kg at intervals of 1–5 days for total of 9 or 10 doses

TABLE 125.3

Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG[a]	DOSAGE	
		ADULTS	CHILDREN
	ALTERNATIVES (*T. b. gambiense* only)		
	• Tryparsamide	One injection of 30 mg/kg (max, 2 g) IV every 5 days to total of 12 injections; course may be repeated after 1 mo	Unknown
	• Eflornithine *plus*	400 mg/kg/day in 4 doses x 14 days injections; course may be repeated after 1 mo	Same as adult dose
	• Suramin	One injection of 10 mg/kg IV every 5 days to total of 12 injections; course may be repeated after 1 mo	Unknown
VISCERAL LARVA MIGRANS			
Toxocariasis	DRUG OF CHOICE		
	• Diethylcarbamazine	6 mg/kg/day in 3 doses × 7–10 days	6 mg/kg/day in 3 doses × 7–10 days
	ALTERNATIVES		
	• Mebendazole *or*	100–200 mg bid × 5 days	Same as adult dose
	• Albendazole	400 mg bid × 3–5 days	400 mg bid × 3–5 days

[a]Some drugs may be available only from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta; telephone, 404-639-3670 (nights, weekends, and holidays: 404-639-2888).
CDC, Centers for Disease Control and Prevention; *max,* Maximum.
Adapted from Drugs for parasite infections. Med Lett Drugs Ther 37:99–108, 1995.

peripheral edema, visual impairment, skin complaints, and symptoms related to the pulmonary, cardiovascular, and gastrointestinal (GI) systems.

Fever

Fever is an important presenting symptom for a number of parasitic diseases. The most prevalent and medically devastating globally is malaria, with its classic history of recurring bouts of shaking chills and drenching sweats.

Malaria

The febrile patient with shaking chills and a time-appropriate history of travel to an endemic region requires evaluation for malaria. *Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax, Plasmodium malariae,* and *Plasmodium knowlesi* are the species responsible for human malaria. More than 41% of the world's population lives in malaria-endemic areas (eg, parts of Africa, Asia, Oceania, Central America, and South America). The World Health Organization (WHO) has estimated that in 2013 malaria caused 198 million clinical episodes and 500,000 deaths. Most of these deaths would be caused by *P. falciparum.*[1] Approximately 1500 cases of malaria are diagnosed yearly in the United States. The female *Anopheles* mosquito is the arthropod vector that transmits malaria after ingesting gametocytes from infected humans. The gametocytes reproduce in the gut of the mosquito; sporozoites are then released from the salivary glands of *Anopheles* into a human host during a blood meal. Sporozoites rapidly penetrate the liver parenchymal cells of their host. The protozoans, now termed *cryptozoites* or *exoerythrocytic schizonts,* multiply rapidly. Eventual lysis of the hepatic cells results in the release of merozoites into the bloodstream, which invade erythrocytes. In *P. vivax* and *P. ovale* infection, dormant hypnozoites can reside in hepatocytes; recrudescence of infections can occur many months to years later.

After invading red blood cells (RBCs), the merozoites transform into trophozoites, which feed on the hemoglobin in RBCs. Trophozoites mature into schizonts, which divide asexually into additional merozoites. The RBCs undergo lysis, releasing merozoites into the blood. Although some merozoites are destroyed by the host's immune system, many enter new erythrocytes. After several repetitions of this erythrocytic cycle, the cyclic process changes, and male or female macrogametocytes may develop instead of merozoites. These gametes subsequently complete the reproductive cycle by fusion, which is accomplished sexually within the gut of a new female *Anopheles* mosquito after she has taken a blood meal from an infected host. Most people contract malaria after being bitten by an infected vector mosquito in an endemic region. Other mechanisms of transmission have been reported, including blood transfusions, injection drug use with contaminated syringes, maternal-fetal perinatal transmission, transmission from infected organs after transplantation (worsened by immunosuppression), and so-called airport malaria. This occurs when the infected mosquito is transported from the endemic region and released when the plane arrives, surviving long enough to transmit the parasite to a human host and then dying without establishing itself in its new location.[2]

Clinical Features. All patients presenting from a region endemic for malaria with a fever or acute illness should be evaluated for the possibility of malaria. Most patients with malaria present with cyclic or irregular fevers. Other signs and symptoms include anemia, headache, nausea, chills, lethargy, abdominal pain, and upper respiratory complaints.[3] The important difference between *P. falciparum* and the other malaria species is the capability of *P. falciparum* to cause severe organ system damage and death. RBCs infected with P. *falciparum* are rendered sticky and sludgelike in small arterioles and capillaries, causing ischemia in the host's metabolically sensitive organs.

The manifestations of acute falciparum infection include cerebral malaria with cerebral edema and encephalopathy,

hypoglycemia (especially in children), metabolic acidosis, severe anemia, which may lead to high output cardiac failure, renal failure, pulmonary edema, disseminated intravascular coagulation, and death. In chronic malaria, increased cellularity from the host's exuberant immune response may lead to hepatosplenomegaly. Within the liver, parasites and malarial pigment distend the Kupffer cells. Parasitized RBCs also adhere to the sinusoidal system of the spleen, reducing its immunologic effectiveness. Anemia results from acute and chronic hemolysis. Blackwater fever—hemoglobinuria caused by severe hemolysis—may occur in patients with chronic or acute falciparum malaria.

Diagnostic Testing. Light microscopic examination of thick and thin blood films remains the gold standard for the diagnosis of malaria. The emergency clinician may have to view several slides and multiple fields to make the diagnosis if the parasite burden is small. Peripheral blood smears are stained with Giemsa or Wright stain and examined with ordinary light microscopy. The diagnosis can be made in a simply equipped laboratory. Even if the parasite is not visualized in the smear, treatment of malaria is indicated if the disease is suspected on clinical grounds. The US Food and Drug Administration (FDA) has approved the use of an antigen-based rapid diagnostic test for screening of patients. The Alere BinaxNOW kit provides qualitative testing for all four species and is available on the Internet for approximately $5 per test. The test is not as sensitive as microscopy, which should still be performed for all patients who have positive antigen test results to determine the species and severity of parasitemia.

Management. In the past, chloroquine phosphate was the treatment of choice for acute uncomplicated attacks of malaria. Resistance to chloroquine has been steadily increasing, and the drug is now recommended only in regions of known chloroquine sensitivity—Haiti, Dominican Republic, Central America, and limited regions of the Middle East. For uncomplicated malarial infections in patients from chloroquine-resistant regions, oral quinine is given with doxycycline or clindamycin. Another suitable alternative combination is proguanil-atovaquone. For complicated *P. falciparum* infection (eg, cerebral malaria, involvement of multiple organ systems, inability to tolerate oral medication), intravenous (IV) quinine (not available in IV form in the United States) or quinidine is used. Rapid infusion of IV quinine can cause profound hypoglycemia, as well as hyponatremia and coma vigil, a neurologic impairment due to high rates of parasite destruction. Patients should not receive IV quinine without cardiac monitoring.

The artemisinin agents are excellent antimalarials and are available as enteral and parenteral preparations. They have a rapid onset of action and are well tolerated. An oral agent known as artemether-lumefantrine (Coartem) is now available for uncomplicated malaria. The other artemisinins are not approved for use in the United States; however, parenteral artesunate is available as an investigational drug for patients who have complicated malaria not responding to quinidine. To obtain this drug, contact the Centers for Disease Control and Prevention (CDC) Malaria Hotline at 770-488-7788 (or, during off hours, at 770-448-7100).[4] Primaquine is used to eliminate the hepatic phases of *P. ovale* and *P. vivax* to prevent recrudescent disease. Primaquine therapy is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency because it can precipitate severe hemolysis. Untreated falciparum malaria can lead to coma and death; early treatment reduces morbidity and mortality.

Babesiosis

Babesiosis is a malaria-like illness that is becoming increasingly prevalent in the northeastern United States (*Babesia microti*), northwestern United States (*Babesia gibsoni*), and Europe (*Babesia divergens*). Babesiosis is particularly endemic to Long Island, Cape Cod, Martha's Vineyard, Nantucket, and Block Island and, is suspected, along with ehrlichiosis and Lyme disease, in patients on Cape Cod, Block Island, and Long Island who present with the summer flu. The organism is a protozoan, similar in structure and life cycle to the plasmodia. It is transmitted by the deer tick *Ixodes dammini,* the vector of Lyme disease. Several cases have been attributed to transfusions with infected blood.[5] Patients with babesiosis experience fatigue, anorexia, malaise, and emotional lability, with myalgia, chills, high spiking fevers, sweats, headache, and dark urine. Other manifestations include hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, elevated liver enzyme levels (particularly the transaminases), and signs of hemolysis, with hyperbilirubinemia and decreased haptoglobin. In an otherwise healthy person, the disease may remit spontaneously. In asplenic, older, and immunocompromised patients, especially patients with AIDS and those taking corticosteroids, up to 85% of RBCs may contain organisms.

Clinical Features. Clinical syndromes in these patients include massive hemolysis, jaundice, renal failure, disseminated intravascular coagulation, hypotension, and adult respiratory distress syndrome (ARDS). Diagnosis is based on clinical suspicion, multiple thin and thick blood smears (*Babesia* organisms resemble plasmodia in blood smears), and serologic testing (convalescent titers may not be positive for several weeks after infection).

Management. The treatment of choice consists of atovaquone plus azithromycin or, for severe illness, quinine plus clindamycin.[6] Patients infected with *B. divergens* tend to be sicker and require more supportive care. Coinfection with *Borrelia burgdorferi,* the agent of Lyme disease, results in more severe and prolonged illness.

Other Parasites

Other parasitic illnesses that commonly cause significant fever include schistosomiasis, fascioliasis, African and American trypanosomiasis, leishmaniasis, toxoplasmosis, and amebic liver abscess.

Katayama fever may be the initial phase of schistosomiasis. Infected patients report brief exposures to fresh water in endemic areas. Clinical manifestations include spiking fevers, diaphoresis, wheezing, and cough. Eosinophilia is common.[7]

Fascioliasis, caused by the liver fluke *Fasciola hepatica,* is endemic throughout all the continents except Antarctica and is found in over 50 countries, especially where sheep or cattle are reared. Infection begins with ingestion of the metacercariae often found in watercress. Within 6 weeks, patients exhibit right upper quadrant abdominal pain, fever, and eosinophilia.[8]

American trypanosomiasis (Chagas' disease) is endemic to Central and South America. The vector, the reduviid bug, sheds trypomastigotes in its feces proximal to the bite site. The host responds to local inflammation and infection by excoriating the site, inoculating the wound with trypomastigotes and initiating systemic spread. Acute Chagas' disease begins with a chagoma, an infected and swollen bite site, often periorbital, and quickly progresses to fever, malaise, facial swelling, and pedal edema. Parasitization of cardiac muscle leads to the dysrhythmias and ventricular dysfunction that are classically found in late disease (chronic Chagas' cardiopathy).[9]

Leishmaniasis is spread to humans by the sandfly and is found in the Middle East, India, East Africa, Brazil, and along the Mediterranean coast. Although leishmaniasis can involve the skin (cutaneous) and mucosa (mucosal), fever is seen only in visceral

leishmaniasis in immunocompetent persons. Signs and symptoms also include massive hepatosplenomegaly, neutropenia, and weight loss.[10]

The patient who has amebic liver abscesses from *Entamoeba histolytica* infection presents with high fevers, right upper quadrant pain, and elevated white blood cell count.[11]

Neurologic Symptoms

Headache, altered mental status, and seizures are common presenting symptoms of parasitic infections caused by organisms that are neurotrophic. Some of the most common are malaria, cysticercosis, echinococcosis, and trypanosomiasis.

Cerebral Malaria

Cerebral malaria is a common, life-threatening complication of *P. falciparum* infection. Parasitized RBCs express malarial cell surface glycoproteins called knobs that are sticky. They adhere to capillary walls, causing sludging in the cerebral microvasculature, localized ischemia, capillary leak, and petechial hemorrhages.

Clinical Features. Clinical manifestations include fever, altered mentation, including obtundation, coma, and occasionally seizures. A careful history and early diagnosis and therapy are essential to prevent severe morbidity and death.

Management. Treatment of cerebral malaria consists of IV quinine, quinidine, or artemisinin (if available), supportive care, including mechanical ventilation for comatose patients and patients with noncardiogenic pulmonary edema, antiepileptics, and correction of acidosis and hypoglycemia, associated with quinine use and cerebral malaria. The mortality rate is high, especially in children but, if the patient recovers, neurologic sequelae are rare. Corticosteroids, including dexamethasone, provide no benefit and can worsen outcomes in those with cerebral malaria.

Cysticercosis

Cysticercosis is caused by the larval form of *Taenia solium,* a common central nervous system (CNS) pathogen in many tropical areas. Cysticercosis is acquired by humans when they eat undercooked pork containing the larval cysts. The adult worm matures in the small intestine; the larval forms may penetrate through the gut wall and end up anywhere in the body. They are trophic for the CNS, muscle, and soft tissue.

Clinical Features. In the brain, clusters of larvae of *T. solium* form an expanding cyst that induces an intense immunologic reaction from the host, including inflammation, fibrosis and, ultimately, calcification. Neurologic abnormalities develop when neural tissue cannot accommodate the enlarging cyst. Seizure activity is often the first indication of cysticercosis, which should be considered in the differential diagnosis of new-onset seizures in adults. The diagnosis of *T. solium* infection is established by the finding of characteristic proglottids (gravid segments) or scolices (worm heads) in stool preparations.

Diagnostic Strategies and Management. Cranial computed tomography (CT) with contrast enhancement or magnetic resonance imaging may reveal an enhancing ring lesion. These lesions can mimic a CNS abscess, metastatic malignant disease, or primary tumor such as glioblastoma multiforme. Albendazole is the therapeutic agent of choice, and corticosteroids and antiepileptics are important adjunct medications during therapy, because CNS cysts can release highly antigenic inflammatory material at the time of treatment.[12,13] Neurosurgical consultation is warranted because neurocysticercosis is commonly associated with acute obstructive hydrocephalus.

Echinococcosis

Principles and Clinical Features. *Echinococcus granulosus* is another tapeworm capable of causing CNS disease. Cerebral hydatid cysts are loculated structures containing *E. granulosus* scolices (heads) and the remains of the germinal epithelium, termed *hydatid sand*. Common types of exposure include ingestion of food or water contaminated by the ova from feces of sheep or cattle infected by the adult worm and close contact with an infected sheep-herding dog that is shedding ova. Infection results in the liberation of the embryo oncosphere into the small intestine. After penetrating the intestinal wall, the larvae travel through the bloodstream to multiple sites for encystment. The liver is the target organ in nearly two-thirds of cases, but 7% of patients have brain involvement; infected patients may present with seizures or focal neurologic signs.

Diagnostic Strategies and Management. The diagnosis of hydatid cyst disease is suggested by the appearance and localization of the cyst on ultrasound examination or CT scan. Serologic evaluation of serum or cerebrospinal fluid (CSF) may help confirm the diagnosis. Aspiration of the cyst should not be attempted because of the risk of seeding the host's body with metastatic cysts. Treatment options include albendazole and surgical resection. Resection of the cyst may cause an anaphylactoid reaction if there is spillage of hydatid sand, which contains parasite antigenic proteins (Figs. 125.1 and 125.2).[14]

Fig. 125.1. Hydatid cysts removed surgically.

Fig. 125.2. Additional hydatid cysts removed surgically.

African Trypanosomiasis

African sleeping sickness is caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. This infection is endemic in limited areas of West and East Africa. Several recent cases have been reported in travelers who have returned from safari in East Africa. The motile organisms are transmitted by the bite of the *Glossina* (tsetse) fly, which introduces the infective form of the trypanosome into the host's blood. A small lesion or boil may develop and persist for several days. The flagellated organism travels throughout the bloodstream, invading the lymph nodes and spleen.

Clinical Features. Winterbottom's sign, which is posterior cervical lymphadenopathy, usually is apparent at the time of initial treatment. The patient generally is febrile, and a maculopapular rash can be seen in fair-skinned people. Once the parasite invades the CNS, cerebral inflammation causes severe headache. Patients may display a change of mental status, psychiatric symptoms, and eventually extreme sleepiness and lethargy. Coma and death from starvation and trypanotoxins are inevitable in untreated patients.[15]

Diagnostic Strategies and Management. An appropriate exposure history and characteristic symptoms should prompt the clinician to obtain diagnostic studies. Trypanosomes in peripheral blood, CSF, or lymph node and bone marrow aspirates establish the diagnosis. The presence of parasites in the CSF indicates advanced progression of the disease. Suramin sodium is the treatment of choice for early infection with *T. b. rhodesiense*. Pentamidine isethionate is the preferred treatment for early *T. b. gambiense* infection. Melarsoprol is used in CNS disease from *T. b. rhodesiense*; eflornithine is used in CNS disease from *T. b. gambiense* infection.

Other Parasites

Several other parasitic infections can lead to CNS findings. CNS involvement with *Trichinella spiralis* has been reported in severe cases; larval migration of this parasite into the brain and meninges leads to meningitis, encephalitis, seizures, paresis, coma, and death. The pathophysiologic changes may reflect obstruction of small cerebral arterioles by migrating larvae, with subsequent vasculitis or cerebral edema resulting from inflammatory immunologic reaction to the larvae or larval fragments. Therapy for trichinosis with severe muscle or CNS involvement includes mebendazole or thiabendazole as well as steroids, which depress the host's inflammatory response to infection.[16]

Amebic abscess of the brain or meningoencephalitis caused by *E. histolytica* is a rare complication of infection with this intestinal parasite. Infestation occurs after ingestion of amebic cysts. Spread of amebae to the brain or meninges from the colonized large bowel wall is rare but should be considered in any patient with amebiasis and subsequent neurologic impairment. The diagnosis may be made by microscopic identification of trophozoites (motile amebae) in CSF; however, biopsy of affected tissue is more specific. CNS amebiasis is treated with IV metronidazole but may require neurosurgical intervention.

Naegleria and *Acanthamoeba* are free-living freshwater amebae that infect patients while they are swimming and diving in ponds and lakes. They invade the CNS through the olfactory neuroepithelium or compromised corneal epithelium that has been violated by abrasion or contact lens wear, leading to amebic meningoencephalitis. The pharmacologic regimen of choice is amphotericin B plus miconazole when these motile amebae are identified in CSF.[17]

Strongyloides stercoralis infection is a common disease in the tropics. The worm enters through the skin and migrates to the small bowel. Infection with *Strongyloides* is more clinically significant in immunosuppressed patients, who may suffer larval dissemination, with subsequent encephalitis and pyogenic meningitis. *Strongyloides* infection is treated with thiabendazole or albendazole. Ivermectin has recently been found to be as effective, with fewer side effects.[18]

Granulomas may occur in the brain from egg deposition by *Schistosoma*. In general, they do not cause major symptoms; however, several cases of transverse myelitis with paraplegia have been reported when the immunogenic and inflammatory eggs lodged in the spinal cord of infected patients.

Anemia

Anemia in the traveler may reflect hemolysis from malaria, intestinal bleeding from hookworm or whipworm, or nutritional deficiency from tapeworm. These organisms have a profound effect on populations where the disease is endemic, but can also cause symptoms in travelers.

Malaria

Malaria infection often is associated with anemia, especially in children younger than 5 years (Fig. 125.3). Anemia may develop quickly, from massive hemolysis in acute infection, or may have a more insidious onset, developing over months. Mature merozoites lyse parasitized RBCs. Uninfected RBCs undergo immune destruction from cell surface antibodies produced in response to parasite-associated changes in RBC surface proteins. This process of destruction is abetted by increased reticuloendothelial activity. The reticulocyte response in infected persons is blunted by the inhibition of erythropoietin secretion. The antimalarial drug primaquine can precipitate hemolysis in patients who have G6PD deficiency, which is common in many Africans and some Asians.

Fig. 125.3. Severe life-threatening anemia (hematocrit of 9) in a 5-year-old child in association with chronic malaria.

Whipworm and Hookworm

Infestation by the whipworm *Trichuris trichiura,* and especially by the two human hookworms *Necator americanus* and *Ancylostoma duodenale,* is a major cause of iron deficiency anemia worldwide. Adult worms penetrate into intestinal mucosa and feed, causing significant luminal blood loss. The host's feces contain eggs that mature in the soil through a rhabditiform larval form to the infective filariform larva. These larvae penetrate the human skin, usually through the feet. In trichuriasis, anemia is seen only with massive parasite infestation. Ova from the whipworm are ingested through food and water contaminated with feces. Diagnosis of these infections requires identification of characteristic ova in the stool. As with most helminthic infections, peripheral eosinophilia is common. Mebendazole or albendazole effectively controls trichuriasis and hookworm infections in adults and children.[19] Anemic patients should be further worked up and receive iron supplementation.

Tapeworm

Infection with the fish tapeworm *Diphyllobothrium latum* is associated with pernicious anemia. This tapeworm competes with the human host, absorbing vitamin B_{12} from the host's intestine. When the host ingests raw freshwater fish that contains the embryo plerocercoid larvae in its muscle fibers, the large adult tapeworm develops in the human small intestine. The diagnosis is made by identification of the ova in the feces. Praziquantel is the drug of choice for adults and children.[20]

Peripheral Edema

Lymphedema is classically associated with filarial infection, although it can also be associated with parasite-induced malnutrition and hypoproteinemia.

Elephantiasis

Elephantiasis, or filariasis, is manifested in the host by the development of massive peripheral edema, with distention and thickening of the overlying epidermis, which acquires the appearance and texture of elephant skin. Elephantiasis is caused by infection with the filarial worm *Wuchereria bancrofti* or *Brugia malayi*. The infection is confined to humans and is widely distributed in the equatorial regions of the world, including Africa, Asia, South America, and Oceania. More than 90% of all infections are found in Asia, where the disease has reached epidemic proportions. Even in endemic regions in which most residents are infected, the disease is rare among travelers. Infected mosquitoes introduce microfilariae into the bloodstream of the human host during a blood meal. After infecting the host, the worms migrate into the lymphatic system and mature into coiled gravid adults. The adult worm triggers a robust inflammatory reaction in the lymphatic vessels, particularly in the lower extremities and genitalia. The macrophages, lymphocytes, plasma cells, giant cells, and eosinophils migrate to the inflamed and fibrotic lymphatic vessel, which becomes erythematous, edematous, and tender, suggesting the diagnosis of filariasis.

Clinical Features. Chronic manifestations of filariasis include fibrosis of a lymphatic vessel containing a dead or calcified worm. Subsequent mechanical blockage of the lymphatic system leads inevitably to severe lower extremity and genital edema accompanied by thickening of the skin. Recurrent cellulitis is common in these patients; prevention of superinfection requires meticulous skin care.

Diagnostic Strategies and Management. The adult female worm produces microfilariae, which reach the peripheral blood through the lymphatics, whereupon the patient experiences shaking chills and fever. Thick peripheral blood smears may show infection, particularly at night, when the release of microfilariae is most common. Diethylcarbamazine rapidly clears the microfilariae from the peripheral blood and slowly sterilizes the gravid female nematode. Combined therapy with diethylcarbamazine and albendazole, or ivermectin and albendazole, may be more effective.[21] Established elephantiasis of the scrotum can be successfully treated surgically. Chronic lymphatic obstruction of the limbs rarely responds to operative intervention.

Dermatologic Symptoms

Dermatologic symptoms reflecting parasitic infection are more likely to be encountered by physicians working in countries where the organisms are endemic, but can be seen in the United States in tourists returning from the Caribbean, Central, and South America.

Cutaneous Leishmaniasis

Cutaneous leishmaniasis is one of the most important causes of painless, chronic, ulcerating skin lesions in the world. *Leishmania braziliensis* and *Leishmania mexicana* are responsible for New World leishmaniasis; *Leishmania tropica* and *Leishmania major* commonly cause Old World leishmaniasis. The female *Phlebotomus* sandfly transmits the promastigotes during a blood meal, which are ingested by host macrophages and survive in their leishmanial form in the skin.

Clinical Features. Skin papules and nodules are seen early in the course of infection at the site of the insect bite. A raised macule also can appear, which subsequently develops painless central ulceration and a raised border. Lymphocyte and macrophage invasions of the epidermis and dermis cause the induration that occurs at the ulcer border. Secondary bacterial infections of these ulcers increase the associated scarring. *L. braziliensis braziliensis* (subspecies of *L. braziliensis*) attacks the mucocutaneous skin borders (ie, in tissues of the nose and mouth). Mutilation of the face occurs after massive tissue and nasal cartilage destruction. The larynx and trachea also can be involved, compromising the airway. Disseminated cutaneous leishmaniasis (*L. mexicana amazonensis* in South America and *L. tropica aethiopica* in Ethiopia) is characterized by diffuse nodules and papules resembling those of lepromatous leprosy (Fig. 125.4). Persons with this manifesta-

Fig. 125.4. Cutaneous leishmaniasis.

tion of leishmaniasis are thought to have a defect in their cell-mediated immunity response.

Diagnostic Strategies and Management. Definitive diagnosis of leishmaniasis is made by direct visualization of the parasite with light microscopy. Diagnosis can also be made by an indirect fluorescent antibody test. Results of intradermal skin testing often are negative during the acute stages of the disease. Many forms of cutaneous leishmaniasis, especially *L. tropica* and *L. mexicana* infection, are self-limited and require no treatment unless the wounds become secondarily infected. Treatment options for advanced disease include sodium stibogluconate, meglumine antimonate, and amphotericin B. In 2014, the FDA approved the first oral medication, miltefosine, which can be used to treat leishmaniasis.[22] These treatments are rarely initiated in the ED setting.

Dracunculiasis

Principles and Clinical Features. *Dracunculus medinensis*, the fiery serpent, is also referred to commonly as guinea worm disease (GWD). GWD appears in the host as the adult worm migrates through the subcutaneous tissues of the leg. The head of the gravid adult female erodes through the skin of the leg and releases larvae into the water when the host wades in a pond or open well. The larvae promptly infect the *Cyclops* water flea. Humans who drink water containing the infected crustacean complete the cycle of infection. The patient may complain of rash, intense pruritus, nausea, vomiting, dyspnea, and diarrhea before the female worm erupts through the skin.

Management. The classic treatment in developing countries has been to wind the worm around a stick and slowly extract the parasite from the skin during the course of 1 or 2 days. If the worm breaks while it is being extracted, the patient experiences an intense inflammatory reaction, with cellulitis along the worm track. The diagnosis is confirmed when microscopic larvae are found in the fluid of the cutaneous ulcer or when the adult female worm is identified extruding from the skin. The use of metronidazole to shorten the time of extraction is controversial. WHO has set a goal to eradicate this disease through public health awareness—encouraging the covering of wells, filtering well water to remove the fleas, and keeping infected persons with active skin lesions out of potable water. These efforts have had a tremendous impact on the eradication of dracunculiasis from Africa.[23]

Other Parasites

Cutaneous larva migrans, the creeping eruption, occurs in the host's epidermis when the skin is penetrated by *Ancylostoma braziliense* (dog or cat hookworm) larvae. Exposure usually occurs after walking barefoot or lying on beaches or other warm soil contaminated by animal feces. The diagnosis is suggested by the presence of a characteristic meandering erythematous track on the skin surface caused by larval migration. Visceral larva migrans occurs in young children after the ingestion of soil containing ova from the dog ascarid *Toxocara canis*. Thiabendazole, ivermectin, or albendazole may be used for treatment of cutaneous larva migrans, and antipruritics give symptomatic relief. Diethylcarbamazine treats visceral larva migrans. An alternative is thiabendazole.[24]

Swimmer's itch is a dermatitis that occurs when skin is penetrated by the nonhuman schistosome of avians and mammals, usually from swimming in northern US freshwater lakes. The infection spontaneously resolves when the nonhuman schistosome is destroyed by the human host's immune system. A similar dermatitis also can occur after infection with schistosome species that are trophic for humans. Treatment is symptomatic.

Strongyloides can cause a transient pruritic rash that may appear and then disappear within hours. *Taenia solium* can cause cysts in the soft tissues and muscles. These cysts often are an incidental finding. Onchocerciasis (from *Onchocerca volvulus*), which is common in West Africa and parts of South America, can cause severe pruritus and the development of nodules on bony protuberances.

Visual Symptoms

Onchocerciasis

Onchocerciasis is a major cause of blindness in the world. Of all cases, 95% occur in Africa. The parasite is found only in humans and is transmitted by the bite of the *Simulium* fly. These flies live near rivers—hence, the common name of the disease, river blindness. Microfilariae of *O. volvulus* are released by adult nematodes, which coil in subcutaneous nodules in the infected host; the microfilariae then migrate through the dermis and epidermis. The presence of adult worms stimulates a brisk immune response, including the infiltration of lymphocytes, macrophages, plasma cells, and eosinophils.

Clinical Features. The skin becomes chronically edematous and pruritic; it then atrophies, resulting in loose thin folds of skin. River blindness is more likely to develop in patients with nodules in proximity to the eyes. When the microfilaria dies during its migration in the eye, the foreign tissue that is deposited in the iris musculature incites an immune sclerosing keratitis, which is the major cause of the ocular destruction and subsequent blindness (Fig. 125.5).

Diagnostic Strategies and Management. The diagnosis of onchocerciasis requires the identification of characteristic microfilariae in skin snipped from the patient. Ivermectin is the therapeutic drug of choice. In many countries in which the disease is endemic, the manufacturers of ivermectin have donated the drug in an attempt to eradicate the disease.[25] Surgical excision of the subcutaneous nodules is recommended when they are located on the head.

Loiasis

Clinical Features. Another filarial infection that causes ocular problems is loiasis. Loiasis is confined to forest areas in West and Central Africa. Transmission of *Loa loa* occurs through

Fig. 125.5. Patient with onchocerciasis (river blindness).

the bite of flies of the genus *Chrysops*. The edema initially associated with migration of the worm is called a Calabar swelling. The disease is caused by migration of the adult worm in the subcutaneous tissue. The adult worm occasionally migrates through the subconjunctival tissues of the eye and can be surgically excised from the conjunctiva. Although it is upsetting to the patient, the disease is generally fairly benign. The adult worm releases sheathed microfilariae into the peripheral bloodstream during the daytime.

Diagnostic Strategies and Management. Microfilariae can be detected in a thick blood smear, securing the diagnosis of loiasis. The treatment of choice for *L. loa* infection is diethylcarbamazine. Corticosteroids or antihistamines should be used to supplement specific chemotherapy because of the intense allergic reaction that occurs when the killed adult worms and microfilariae disintegrate.

Other Parasites

Toxocara canis (dog roundworm) has a trophism for the host's eyes. Toxocariasis is a roundworm infection found in urban dogs. Humans ingest eggs by the fecal-oral route. The larvae migrate and often enter the retina, where they become trapped. They stimulate an immune response that culminates in granuloma formation. These granulomas can impair vision and sometimes are mistaken for retinal tumors. There is no means of direct diagnosis except tissue biopsy. Although serologic tests are available, results need to be interpreted with caution. Infection is treated with albendazole and steroids; larvae visible in the retina can be destroyed with a laser.

Toxoplasma gondii infection can precipitate a vitreal inflammation with retinal hemorrhages. Immunocompromised patients may have chorioretinitis and optic neuritis, with visual field defects and ocular palsies. Erythrocytes with sticky knobs from *P. falciparum* infection can cause retinal vascular congestion and ischemia with hemorrhage, exudate, infarction, and macular destruction. Cerebral malaria can produce cortical blindness. Mucocutaneous leishmaniasis can involve the eyelids, tear glands, retina, and/or iris and may result in total ocular destruction. *Acanthamoeba* can cause a dangerous keratitis in contact lens wearers. The patient complains of severe pain, tearing, and photophobia. Early infection may be misdiagnosed as herpetic keratitis. The infection may become chronic and necessitate keratoplasty for preservation of vision. Many different worms migrate to or through the eye, causing inflammation, tissue destruction, and blindness. *Echinococcus* and *Cysticercus* can initiate destructive cystic lesions in the eye.

Pulmonary Symptoms

A number of parasitic infections may be associated with pulmonary symptoms, although the presence of pulmonary findings may not be sufficient to differentiate between various forms of parasitic diseases. Patients with *P. falciparum* malaria initially may seek treatment for fever and cough, further necessitating the consideration of malaria in travelers with apparent respiratory symptoms. Early in the course of treatment for severe malaria, noncardiogenic pulmonary edema or ARDS may develop, necessitating mechanical ventilation with positive end-expiratory pressure.

E. histolytica can cause sympathetic pleural effusions, pulmonary or pleural involvement by direct extension or rupture of an amebic liver abscess, or direct hematogenous seeding of the lungs, leading to considerable additional morbidity and mortality among patients with underlying amebic infection.

Pneumocystis pneumonia, caused by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), is one of the most common respiratory opportunistic infections seen in patients with HIV infection in the United States and Europe; surprisingly, however, it is responsible for less than 10% of pulmonary opportunistic infections in Africa and the developing world. The reason for this discrepancy is unclear. Many patients with AIDS in these countries die with CD4+ cell counts higher than those associated with *P. jiroveci* pneumonia in the United States.[26]

Löffler's syndrome, characterized by persistent and nonproductive cough, substernal chest pain, wheezing, rales, pulmonary infiltrates on the chest radiograph, and marked eosinophilia, often is seen when larvae from the roundworm *Ascaris lumbricoides,* the hookworms *N. americanus* and *A. duodenale,* and the threadworm *S. stercoralis* transit the lungs as part of their developmental cycles. *Ascaris* larvae penetrate the small intestinal wall to gain entry into the small venules of the GI tract and then migrate to the lungs.

Strongyloides and the hookworm filariform larvae penetrate through the skin of the feet, entering small cutaneous venules before migrating to the lungs. The pulmonary infiltrates and symptoms are transient, resolving within 2 weeks. Diagnosis depends on the discovery of larvae in sputum or gastric aspirates. Negative stool examinations initially are nondiagnostic because eggs do not appear in the stool for at least 1 month after initial infection.

The patient's immune response to the microfilariae of *W. bancrofti* and *B. malayi* is the cause of tropical eosinophilic pneumonia. Affected persons present with malaise, weight loss, new-onset nocturnal wheezing and asthma, shortness of breath, and chest discomfort. Chest radiographs may show nodular or interstitial infiltrates, consolidations, or cavitation. Microfilariae can be seen in lung biopsy material. Untreated infection may result in obstructive or restrictive lung disease. Patients have marked eosinophilia and elevations of serum immunoglobulin E levels.

Paragonimus westermani and echinococcal species are trophic for the lungs in their human hosts. *P. westermani* eggs are shed in stool, hatch in fresh water and, as miracidia, infect a snail intermediary. After further development, cercariae are released from the snail, penetrating and encysting in freshwater crabs or crayfish. If the human host consumes raw or undercooked shellfish, the metacercariae excyst within the host's duodenum, penetrating the duodenal wall into the abdominal cavity. The larvae migrate from the peritoneal cavity through the diaphragm into the pleural cavity, finally migrating to the lungs, where they cause hemorrhage, necrosis, and a granulomatous response. Early in the process, patients may have infiltrates and eosinophilia; later disease is marked by bronchiectasis, chronic bronchitis, fever, hemoptysis, and cachexia. Pulmonary nodules and cysts may cavitate. Many of these patients may have a positive result on purified protein derivative (PPD) testing, and their symptoms and chest radiographic findings may mimic those of tuberculosis.[27] Sputum often is blood-streaked and flecked with dark brown particles containing ova. Finding of ova in sputum is diagnostic. Radiography, stool examination, and immune testing of sputum and blood are all helpful in making the diagnosis. Praziquantel is the therapeutic agent of choice.

E. granulosus causes pulmonary hydatid cyst disease; the host remains asymptomatic until a cyst grows large enough to cause a mass effect, becomes superinfected, or leaks cyst material, which is highly immunogenic and causes a severe anaphylactoid reaction. Pulmonary hydatid cysts also can be associated with cough, expectoration of sandlike material, chest pain, and hemoptysis. Primary hydatid disease in the liver can metastasize to the lungs or brain. A thoracic CT scan may show a unilocular lung cyst; on a plain radiograph, a ruptured cyst is said to resemble a water lily, a pathognomonic finding. Cysts can be treated with careful surgical excision and pharmacotherapy.

Early schistosomal disease, or Katayama fever, manifests with fever, cough, eosinophilia, and diffuse pulmonary nodules as the

schistosomula pass through the lungs. In long-standing disease, ova shed from worm pairs can lodge in the vasculature of the lungs, causing pseudotubercles, granulomatous lung disease, pulmonary hypertension, and cor pulmonale. In patients with long-standing, latent, and asymptomatic *S. stercoralis* infections who are started on corticosteroids or immunosuppressive therapy, the helminth disseminates widely. Fatal, massive pulmonary infections with radiographic whiteouts and unsupportable respiratory failure have been reported in patients who have received organ transplants; this clinical disaster usually occurs in patients who emigrate from developing countries and receive organ transplants and immunosuppressive therapy without being evaluated for *Strongyloides* infection.[28] *Strongyloides* pulmonary infection can cause wheezing and cough, leading to an initial misdiagnosis of bronchospasm and asthma. If the patient is given steroids, the strongyloides may disseminate, with markedly increased morbidity and mortality.[28]

Cardiovascular Symptoms

Chagas' Disease

Trypanosoma cruzi infection often leads to acute and chronic myocarditis. *T. cruzi* is endemic in South and Central America and causes Chagas' disease. The vector is the reduviid bug (kissing bug) that inhabits the walls and roofs of thatched dwellings built adjacent to a forest. Urban transmigration has expanded the epidemiologic scope of Chagas' disease, previously a disease of rural populations. The disease is not seen commonly in travelers. The reduviid bug's bite is no longer the only source of *T. cruzi* infection; transfusion with blood containing live trypanosomes from infected hosts has been a growing source of infection. Oral transmission also has been reported.[28]

The reduviid bug bites the patient, often around the eye, and excretes feces containing the trypomastigote of *T. cruzi*. The trypomastigote enters the inflamed bite wound or other mucosal or conjunctival surfaces, causing a local swelling called a chagoma. Romaña's sign (painless unilateral periorbital edema) is pathognomonic but rarely seen. The trypomastigote migrates to trophic tissues, including smooth muscle, cardiac muscle, and autonomic ganglia in the heart, esophagus, and colon, causing local inflammation and tissue destruction.

Clinical Features. Acute infection is heralded by fever, facial and dependent extremity edema, hepatosplenomegaly, lymphadenopathy, malaise, lymphocytosis on peripheral blood smear, and elevated liver transaminase levels. At this stage, fatal left ventricular dysfunction and dysrhythmias are uncommon. Early illness lasts 1 to 2 months and resolves spontaneously, resulting in a latency known as the indeterminate phase, which can persist throughout the patient's lifetime. In approximately 25% of cases, the infection progresses to chronic Chagas' disease, principally with cardiomyopathy and GI pathology. Amastigotes invade cardiac muscle and the cardiac conduction system, causing chronic inflammation, mononuclear cell infiltration, and fibrosis. Patients whose disease involves the conduction system may present with atrial bradydysrhythmias, right and left bundle branch blocks, complete heart block, and ventricular dysrhythmias, including ventricular fibrillation. Cardiac muscle is replaced by fibrosis and scarring, leading to the development of right and left ventricular dysfunction and dilated cardiomyopathy. Mural thrombi are common. The first indication of long-standing asymptomatic infection can be thromboembolic disease, such as pulmonary embolism, stroke, or peripheral arterial embolism. Congestive heart failure is generally rapidly progressive and fatal within months unless treated with pharmacologic intervention and transplantation.[29]

Diagnostic Strategies. Acute Chagas' disease can be diagnosed by the presence of motile trypomastigotes in anticoagulated blood specimens. The organism also can be cultured in special liquid media. Chronic Chagas' disease can be diagnosed by one of several serologic tests, including complement fixation, enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence testing. The assays are nonspecific, cross-reacting with malaria, syphilis, leishmaniasis, and some collagen vascular diseases. Polymerase chain reaction (PCR) technology has been improving and soon will provide the gold standard modality for diagnosis.[30]

Management. Nifurtimox and benznidazole are used for treatment of *T. cruzi* infection. Cure rates rarely exceed 50%. The duration of treatment with nifurtimox is prolonged, and the drug has many serious side effects. Its production has been discontinued; however, it is the only antitrypanosomal medication available in the United States today (it can be obtained from the CDC by calling 404-639-2888). Benznidazole has fewer side effects. It is now recommended for indeterminate-phase treatment. Late complications of chronic diseases are modulated by autoimmune activity and do not respond to antiparasitic pharmacotherapy. Chronic Chagas' disease of the heart, esophagus, or colon is treated symptomatically. Automated implantable cardioverter-defibrillators decrease the incidence of sudden death in infected patients.[31] Patients receiving immunosuppressive therapy to prevent rejection after cardiac transplantation have developed recurrent disease in the transplanted myocardium.

Other Parasites

Aberrant migration of *Ascaris* to the myocardium, causing myocarditis and pericardial effusions, has been well described. *E. histolytica* abscesses of the liver also may cause pericardial effusions if they erode through the diaphragm.

Gastrointestinal Symptoms

Diarrhea

Diarrhea is one of the most common symptoms for which travelers seek medical attention. Gorbach wrote that "Travel expands the mind and loosens the bowels."[32] Diarrhea also is the leading cause of death in children younger than 5 years in developing countries and a major source of morbidity for older children and adults. Most diarrheal disease is viral or bacterial; however, some clinically significant diarrheal disease is caused by parasites.

Cryptosporidium parvum and *Cyclospora cayetanensis* are foodborne and waterborne coccidians that cause watery diarrhea. Both are particularly significant causes of morbidity in malnourished children and patients with AIDS. Cryptosporidial oocysts can be seen in stool when an acid-fast stain is used. ELISA and immunofluorescent assays of stool also are available for this organism. Paromomycin decreases diarrheal frequency in patients with AIDS who have cryptosporidial infections, who would have prolonged disabling symptoms without treatment. *Cyclospora* oocysts can be detected in stool samples with a Ziehl-Neelsen stain. Trimethoprim-sulfamethoxazole treats this infection.[33]

E. histolytica causes an invasive or inflammatory diarrhea. Patients complain of fever, tenesmus, abdominal pain, and watery stool containing blood and mucus. Untreated disease can progress to widespread colitis and perforation of the bowel wall, with peritonitis and death. Stool examination reveals mobile trophozoites containing ingested RBCs. Cysts noted on stool studies do not necessarily reflect active infection because there are nonpathogenic ameba species that can be found in the bowel of healthy adults. Immune assays of stool can now differentiate between *E.*

histolytica and these nonpathogenic ameba species. Serologic tests may be useful for an infected patient from a nonendemic region but patients will not have a positive test result for 1 month after initial infection. Metronidazole is the drug of choice for treatment of amebiasis.

Balantidium coli is another protozoan that can cause invasive diarrhea. It has trophism for the terminal ileum, sometimes causing a clinical picture suggestive of appendicitis. Tetracycline and metronidazole are active against *B. coli*.

Giardia lamblia can cause persistent diarrhea, abdominal bloating, cramps, flatulence, and significant weight loss. The organism is ingested and reproduces exponentially in the small bowel. In severe infection, the entire jejunum becomes covered with organisms, and the patient has malabsorption with steatorrhea. The organisms are rarely seen in fresh stool preparations because they quickly break down and become indiscernible. Accordingly, an antigen test often is used to confirm the diagnosis. *Giardia* has many animal reservoirs, including the beaver—thus the reference to beaver fever. Campers who drink unfiltered, "pure" mountain spring water in the United States commonly contract *Giardia* infection. Metronidazole, tinidazole, or nitazoxanide treats the disease.[33]

S. stercoralis, *Capillaria philippinensis*, *T. trichiura*, and *Schistosoma* have been associated with diarrhea. Hyperinfection or dissemination of *Strongyloides* can cause persistent diarrhea, weight loss, and abdominal pain. *Trichuris* causes diarrhea when the parasite load in the intestine is high. Schistosomiasis can cause a chronic granulomatous colitis, which may resemble inflammatory bowel disease, or an acute, bloody, febrile colitis associated with Katayama fever in the immunologically naïve patient.

In chronic schistosomiasis, worm pairs in patients' mesenteric and portal venous systems lay eggs that become ensnared in the liver, causing intense local inflammation, scarring, and the classic pipestem cirrhosis, with periportal fibrosis. Clinical manifestations in these patients include portal hypertension, ascites, and esophageal varices (Figs. 125.6 and 125.7). Upper GI bleeding is not as common as in patients with alcoholic cirrhosis; however, a large number of patients are infected with schistosomiasis in endemic regions, so variceal bleeding is an important cause of GI hemorrhage in these populations.

Abdominal Pain

Several parasites have been identified in the pathologic examination of appendices of patients diagnosed with tropical appendicitis. These infections have included enterobiasis, amebiasis, ascariasis, trichuriasis, and taeniasis.[34]

A. lumbricoides (roundworm) can cause significant persistent or recurrent abdominal pain in adults and partial intestinal obstruction in children with significant worm loads. Anthelmintics and conservative supportive therapy usually eliminate the problem, thereby avoiding surgical intervention. Clinicians diagnose ascariasis by identifying eggs in the stool. Patients with large worm loads may excrete adult worms, especially after therapy is started. Severe intestinal amebiasis can be complicated by colonic perforation and peritonitis.[35]

Angiostrongylus costaricensis, a nematode known as the rat lung worm, is common in Central America. Infected children may appear clinically to have Meckel's diverticulum or acute appendicitis. Manifestations of the infection include nausea, vomiting, fever, abdominal pain localized to the right lower quadrant, and a tender mass. Surgical exploration may uncover abscesses, obstruction, or intestinal infarction. Anisakiasis is characterized by severe abdominal pain after the ingestion of raw fish (sushi and sashimi primarily). *Anisakis marina,* a nematode that burrows into the intestine, is the pathogen.

The liver fluke *Fasciola hepatica* causes a syndrome that mimics that of viral hepatitis—right upper quadrant pain, fever, nausea and vomiting, jaundice, tender enlarged liver, and elevated transaminase levels. Patients also have eosinophilia and urticaria. Imaging studies, including CT, show the tracks of burrowing flukes. Serologic testing establishes the diagnosis; the patient's stool may not contain eggs for several months after ingestion.[36] Eggs of schistosomes become trapped in the portal venules, where they trigger an inflammatory response, leading to granulomatous liver disease, fibrosis, and cirrhosis. Hepatic granulomas also are seen in disseminated strongyloidiasis and aberrant biliary ascariasis.

E. histolytica can cause hepatic abscesses. Affected patients typically do not have amebic dysentery and do not shed *Entamoeba* in their stool, but results of serologic studies are almost always positive. Patients have fever, weight loss, anorexia, and right-sided abdominal pain, but no jaundice. These patients are

Fig. 125.6. Pipestem cirrhosis with extensive ascites in a patient with chronic schistosomiasis.

Fig. 125.7. Extensive ascites in a child, which may be from schistosomiasis or kala-azar (leishmaniasis).

treated with metronidazole or tinidazole and a luminal amebicide, such as iodoquinol.[37] *E. granulosus* produces hydatid cysts of the liver that on CT contain septations and so-called daughter cysts. Pharmacotherapy with albendazole and careful excision remain the treatments of choice. Leaking cyst material can initiate a severe anaphylactoid reaction in the host.

Jaundice may result from hemolysis secondary to direct infection of RBCs with *Plasmodium* or *Babesia* or from biliary obstruction with pigmented stones. *Ascaris* can cause biliary colic, pyogenic cholangitis, pancreatitis, or liver abscess. Dead worms can be the nidus for gallstone formation. Biliary imaging and endoscopic retrograde cholangiopancreatography will show worms in the biliary tree. Mechanical removal by endoscopy combined with anthelminthic therapy is curative. *Clonorchis sinensis* and *F. hepatica* are trophic for the biliary tree. These worms can be present without producing symptoms for years before eventually precipitating cholecystitis, cholangitis, or cholangiocarcinoma.

Pruritus Ani

Enterobius vermicularis, or pinworm, causes pruritus ani, a syndrome of intense perianal itch occurring primarily in children. Autoinfection is common because children (and adults) scratch the pruritic anal area and then bite their nails or put their fingers in their mouth. The worm has a worldwide distribution. Diagnosis is clinical and is confirmed by finding the small adult worms wiggling about on the anal verge. Eggs are rarely seen in the stool but can be visualized by the tape test—transparent tape touched to the perianal region collects eggs, which can be seen with light microscopy. Albendazole or mebendazole is the drug of choice.

PARASITIC CO-INFECTIONS IN PATIENTS WITH HIV INFECTION AND AIDS

HIV infection and AIDS are prevalent in developing countries. Heterosexual transmission and perinatal transmission are common; young children and young adults of both genders are primarily infected. Patients presenting to the ED may be coinfected with HIV and any other infectious agent, including all the parasites discussed in this chapter. HIV co-infection may worsen the symptoms and outcome, alter the presentation, increase the virulence, or assist the infective process.

AIDS causes abnormalities in almost every aspect of a host's immune response to infection; cell-mediated immunity, which is important in combating parasitic infection, is most affected.[37] The diagnosis and response to therapy of many parasitic infections are monitored serologically. HIV infection interferes with this response, rendering many of these tests unreliable. Therapies that are extremely effective in the normal host may be ineffective in a patient with HIV infection. Pharmacologic agents may have to be given for long periods or for the patient's entire life.

Specific Parasites

Malaria is not an opportunistic infection in patients with AIDS; however, many patients, especially children, with recurrent malaria and anemia from hemolysis have required transfusions from blood supplies not screened for HIV and have become infected.[37] In regions where malaria is endemic, it is a common practice to treat most febrile patients with antimalarials. Some antimalarials are sulfonamides. Patients with AIDS have more severe allergic reactions to drugs, especially sulfonamides. Fever alone is not predictive of malaria in patients with AIDS; therefore, diagnosis should precede therapy. Patients with HIV infection are at greater risk for severe clinical manifestations of babesiosis.[6]

Visceral leishmaniasis is usually disseminated and fatal in patients with AIDS. Latent leishmanial infections may be reactivated, and a prolonged febrile illness in an HIV-positive patient with a lifetime history of travel in leishmaniasis-endemic areas of the world should prompt consideration of this co-infection. Cutaneous infection also may become disseminated in these patients. Several clinical trials have been examining the role of chemoprophylaxis for leishmaniasis in HIV-positive persons who live in endemic regions. Chagas' disease in the indeterminate phase can be reactivated in patients infected with HIV. These patients frequently have CNS involvement, with meningoencephalitis and severe myocarditis.[31] Single-drug therapy may be insufficient because benznidazole penetration into the CSF is minimal.

T. gondii infection is well recognized throughout the world as a common opportunistic infection of patients with AIDS, with a particular trophism for the CNS.

The coccidial organisms *Isospora belli, C. parvum,* and *C. cayetanensis* have been associated with prolonged diarrhea in patients with AIDS. These organisms cause infections that are difficult to treat and are almost impossible to eradicate in these patients. The diarrhea is extremely debilitating and can be as profuse as that seen in cholera.

E. histolytica has a high prevalence among homosexual men who practice unprotected anal intercourse; however, invasive amebiasis is not an opportunistic infection associated with HIV infection.

Schistosomiasis enhances the pathogenesis of HIV infection and is more difficult to treat and eradicate in patients who are HIV-positive. *S. stercoralis* infection is more likely to be manifested as hyperinfection and disseminated disease in patients who are HIV-positive.[28] In patients who are at risk for HIV infection and parasitic illness, it is essential to consider coinfection in the differential diagnosis.

KEY CONCEPTS

- Parasitic diseases may manifest with almost any symptom or constellation of signs and symptoms. Accordingly, a travel history should be obtained from all patients with clinically significant signs and symptoms of unclear cause. The combination of presenting signs and symptoms and a history of recent travel to specific geographic regions can lead to early diagnosis and the initiation of pharmacotherapy, decreasing morbidity and mortality and increasing the probability of eradication of the infection.
- Parasitic coinfections are particularly common in patients with HIV infection and AIDS. A travel history is essential because the clinical presentation may be atypical, morbidity and mortality are more severe, and treatment and eradication of the parasite are often prolonged.
- Acute malaria should be suspected in patients with irregular high fevers associated with headache, abdominal pain, or respiratory symptoms. Falciparum malaria, which has a unique morphology easily identifiable on the peripheral blood smear, is the only species of malaria that causes coma and death. Furthermore, it is the most highly resistant to chemotherapy, demanding close observation and clinical follow-up of patients. Patients who are clinically ill or who are suspected of having falciparum malaria should be hospitalized for evaluation and treatment.
- Cysticercosis should be considered in the differential diagnosis for new-onset seizures, especially in immigrants from Central and South America.
- Giardiasis should be suspected in patients with diarrhea who have recently been camping or drinking unfiltered mountain spring water. Patients may have tolerated several weeks of severe bloating, flatulence, eructation, and weight loss without fever before seeking medical attention.

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CHAPTER 125: QUESTIONS & ANSWERS

125.1. A 33-year-old man presents with irregular fevers, shaking chills, intermittent abdominal pain, and fatigue. The fever comes in cycles during approximately 2 or 3 days. He has no medical history and takes no medications. He works as a baggage handler in Miami, Florida. Physical examination reveals a low-grade fever and mildly tender hepatosplenomegaly. Laboratory evaluation is remarkable for hemoglobin 9.6 g/dL, leukocytosis, lactate dehydrogenase 1850 IU/dL, elevated bilirubin, and urine dipstick "blood positive" but no red blood cells or white blood cells. He has had no international travel. Peripheral smear reveals few possible parasites with fragmented red blood cells. What is this patient's most likely infection?

A. Babesiosis
B. Early sepsis
C. Leishmaniasis
D. Lyme disease
E. Malaria

Answer: E. Airport malaria has been reported in people who have never been in endemic areas but who work in or live near an international airport. The infected mosquito is transported from the endemic region and released when the plane arrives. Babesiosis is a parasitic illness with a clinical picture like that of malaria. It is tickborne and is endemic in the northeastern United States.

125.2. A 21-year-old Hispanic male immigrant presents with new onset of seizures. Paramedics report a right upper extremity focused seizure with loss of consciousness and postictal period of approximately 20 minutes. He has had no previous seizures, symptoms, medications, trauma, or ingestions. Laboratory examination is normal except for HCO_3^- 17 mmol/L. Which of the following statements regarding the most likely cause of this patient's seizures is TRUE?

A. A ring-enhancing lesion suggests HIV infection.
B. Albendazole may be effective.
C. Contaminated beef ingestion should be suspected.
D. The stool examination will likely be negative.
E. There is no role for corticosteroids.

Answer: B. *Taenia solium* infection (cysticercosis) results from contaminated pork ingestion. The larvae penetrate the small intestine and may travel anywhere, with brain, muscle, and soft tissue being the likely areas of cyst occurrence with accompanying inflammatory reaction. The enlarging cyst (often a ring-enhancing lesion) causes the symptoms. Stool examination is diagnostic. Albendazole and corticosteroids are indicated for the central nervous system lesion. Postseizure acidosis is common and generally clears within 1 hour.

125.3. Fever, headaches, and posterior cervical adenopathy in a recent African traveler should suggest which of the following?
A. Central nervous system amebiasis
B. Cysticercosis
C. Falciparum malaria
D. Schistosomiasis
E. Trypanosomiasis

Answer: E. Trypanosomiasis causes central nervous system inflammation and headache that may progress to psychiatric symptoms, lethargy, and coma. The posterior cervical adenopathy in this scenario is called Winterbottom's sign.

125.4. A macrocytic anemia would suggest infection from which parasite?
A. *Ancylostoma duodenale*
B. *Diphyllobothrium latum*
C. Falciparum malaria
D. *Necator americanus*
E. Whipworm

Answer: B. The fish tapeworm is associated with pernicious anemia. Hookworm and whipworm are associated with gastrointestinal iron loss and microcytic anemia. Malaria causes hemolytic anemia.

125.5. A 42-year-old man from Ethiopia presents with complaints of skin nodules and skin ulcerations. He has no known past illnesses, exposures, medication use, or systemic symptoms. Examination is remarkable for four 2- or 3-cm cutaneous ulcers on the arms and legs and scattered 1-cm nodules. Vital signs are normal, and physical examination is otherwise unrevealing. Which of the following statements regarding this infection is TRUE?
A. Respiratory tract symptoms would suggest an alternative diagnosis.
B. The lesions always require treatment.
C. The lesions are likely painful to touch.
D. The skin pattern may be confused with leprosy.
E. This infection does not affect mucocutaneous areas.

Answer: D. Leishmaniasis is transmitted by the sandfly bite. Skin papules and macules develop at bite sites. These may ulcerate into painless ulcers. A microcutaneous variant may be seen, and the inflammatory process may involve the larynx and trachea. Disseminated cutaneous leishmaniasis may resemble lepromatous leprosy.

125.6. Parasite-induced loss of vision would be suggested by which of the following?
A. Cardiomegaly
B. Edematous and pruritic skin
C. Fever
D. Hepatosplenomegaly
E. Iron deficiency anemia

Answer: B. Onchocerciasis is a major cause of blindness worldwide. Ninety-five percent of cases occur in Africa. The biting flies are found near rivers, and humans are the only host for the parasite. It occupies the skin, resulting in pruritus, edema, and later atrophy with redundant skin folds. The following are other causes of parasite-induced visual loss: *Toxoplasma* can cause retinal hemorrhages, *Toxocara* can cause inflammatory retinal granulomas, and *Acanthamoeba* may cause a keratitis in contact lens wearers.

125.7. Which of the following is the correct association between the type of parasitic infection and pulmonary symptoms?
A. Hookworm—positive PPD response
B. Leishmaniasis—pulmonary nodules
C. Löffler's syndrome—ascariasis
D. Pneumocystis—90% of opportunistic infections in Africa
E. Whipworm—anaphylaxis

Answer: C. Ascariasis and hookworm may cause Löffler's syndrome of chest pain, fever, rales, wheezing, and eosinophilia. The following are the other correct associations:
Pneumocystis—less than 10% of pulmonary opportunistic infections in Africa
Paragonimus westermani—positive tuberculin skin test response and chest radiograph resembling tuberculosis
Echinococcus—anaphylaxis from leakage of cystic contents
Schistosomiasis—diffuse pulmonary nodules (Katayama fever)

125.8. Which of the following statements regarding AIDS and parasitic infections is TRUE?
A. AIDS patients have more severe reactions to antiparasitic agents.
B. Diarrheal illness is reliably eradicable.
C. Invasive amebiasis is an opportunistic infection.
D. Malaria is an opportunistic infection.
E. Parasitic illnesses do not enhance the pathogenesis of HIV infection.

Answer: A. *Isospora* and coccidial organisms may cause an almost cholera-like diarrheal illness. Eradication is very difficult. Malaria and invasive amebiasis are not considered opportunistic infections. AIDS patients have much more severe allergic manifestations to the antiparasitics. Schistosomiasis enhances HIV pathogenesis.

125.9. A 34-year-old man presents with 2 weeks of fever with temperature of up to 102° F, anorexia, and 5-pound weight loss. He had recently been traveling in Central America in Belize, Nicaragua, and Guatemala. He had done some camping but mostly stayed in hostels. He never had nausea, vomiting, or diarrhea. His physical examination is noteworthy only for right upper quadrant tenderness and a palpable liver edge. He is not icteric or jaundiced and denies chalky stools or dark urine. He has a white blood cell count with a left shift. His transaminases are elevated, but otherwise his laboratory results are relatively normal. Stool examination for ova and parasites is negative. Hepatitis panel was sent but is still pending. What is the most likely diagnosis?
A. *Entamoeba histolytica* infection
B. *Fasciola hepatica* infection
C. Hepatitis A
D. Hepatitis B
E. *Schistosoma mansoni* infection

Answer: A. *Entamoeba histolytica* infection with a hepatic abscess. *E. histolytica* can cause hepatic abscesses. Affected patients typically do not have amebic dysentery and do not shed *Entamoeba* in their stool, but results of serologic studies almost always are positive. Patients have fever, weight loss, anorexia, and right-sided abdominal pain but no jaundice. Treatment is with metronidazole or tinidazole and a luminal amebicide, such as iodoquinol.

125.10. A 26-year-old female medical student presents with a 3-month history of diarrhea and a 20-pound weight loss. She has not had fevers, chills, cough, headache, or rash. Four months ago, she had done a rotation in Nepal working at a rural health clinic associated with an American medical school. Toward the end of her rotation, she began to develop diffuse abdominal bloating and discomfort. This was accompanied by flatulence and intermittent watery diarrhea. She felt like she had swallowed a basketball and all of her pants were "too tight." "I thought I was pregnant, but my tests were all negative." She had lost her appetite and was very worried by the weight loss. The results of her laboratory tests, including complete blood count, Chem-20, and stool for ova and parasites, were negative. What is the most likely diagnosis?

A. *Cryptosporidium parvum* or *Cyclospora cayetanensis* infection
B. *Entamoeba histolytica* infection
C. *Giardia lamblia* infection
D. *Salmonella typhi* infection
E. *Shigella dysenteriae* infection

Answer: C. *Giardia lamblia* can cause persistent diarrhea, abdominal bloating, cramps, flatulence, and significant weight loss. The organism is ingested and reproduces exponentially in the small bowel. In severe infection, the entire jejunum becomes covered with organisms, and the patient has malabsorption with steatorrhea. The organisms are rarely seen in fresh stool preparations because they quickly break down and become indiscernible. Accordingly, an antigen test often is used to confirm the diagnosis. *Giardia* has many animal reservoirs, including the beaver. Campers who drink unfiltered, pure mountain spring water in the United States commonly contract *Giardia* infection. Metronidazole, tinidazole, or nitazoxanide treats the disease.

125.11. A 64-year-old man recently emigrated from Laos is referred to the emergency department for fever, hemoptysis, anorexia, positive PPD response, and chest radiograph with several cavitary lesions. He had been started on a three-drug regimen for presumptive tuberculosis but seems to be getting worse. Several sputum samples had not grown out mycobacteria. He immigrated to the United States from Laos 6 months ago. He had lived in a rural district and worked farming rice before emigration. Through a translator, he reported having several bouts of pneumonia in the last year treated with antibiotics in Laos, but he never really got any better. He has had a persistent cough, which has gotten worse with recent hemoptysis. He has lost more than 20 pounds and appears cachectic and ill. Physical examination of the lungs reveals scattered rhonchi, rales, and wheezes. His complete blood count shows 12% eosinophils. What is the most likely diagnosis?

A. Löffler's syndrome from *Ascaris lumbricoides* infection
B. Multiply drug resistant mycobacteria
C. *Paragonimus westermani* infection
D. *Pseudomonas pseudomallei* infection
E. Tropical eosinophilic pneumonitis from *Wuchereria bancrofti* infection

Answer: C. *Paragonimus westermani* is trophic for the lungs in their human hosts. If the human host consumes raw or undercooked shellfish, the metacercariae excyst within the host's duodenum, penetrating the duodenal wall into the abdominal cavity. The larvae migrate from the peritoneal cavity through the diaphragm into the pleural cavity, finally migrating to the lungs, where they cause hemorrhage, necrosis, and a granulomatous response. Early in the process, patients may have infiltrates and eosinophilia; later disease is marked by bronchiectasis, chronic bronchitis, fever, hemoptysis, and cachexia. Pulmonary nodules and cysts may cavitate. Many of these patients may have a positive result on purified protein derivative (PPD) testing, and their symptoms and chest radiographic findings may mimic tuberculosis. Sputum often is blood streaked and flecked with dark brown particles containing ova. Finding of ova in sputum is diagnostic. Radiography, stool examination, and immune testing of sputum and blood are all helpful in making the diagnosis. Praziquantel is the therapeutic agent of choice.

CHAPTER 126

Tickborne Illnesses

Edward B. Bolgiano | Joseph Sexton

OVERVIEW

Ticks are hematophagous parasites of humans and animals, distributed worldwide. They transmit rickettsial, bacterial, spirochetal, viral, and protozoal diseases and cause disease by means of their own toxins (Table 126.1). As vectors of human disease, ticks rank second in importance only to mosquitoes. Although it is generally understood that people who travel during the summer months may return from endemic areas with tickborne disease, increasing reports of infection acquired within urban areas emphasize the need to consider tickborne illness, even in the absence of a history of travel to high-risk areas. In addition, tularemia and Q fever are now considered by the Centers for Disease Control and Prevention (CDC) to be significant threats during biologic warfare. For this reason, research involving ticks and tickborne diseases has become increasingly important.

Reports on ticks, their feeding habits, and their possible relation to disease can be found from early human history. Pliny (CE 77), in *Historia Naturalis,* referred to "an animal living on blood with its head always fixed and swelling, being one of the animals which has no exit [anus] for its food, it bursts with over-repletion and dies from actual nourishment."[1] Tickborne illness was first recognized on the North American continent by Native Americans. According to legend, Shoshone men avoided the evil spirits that caused illness by sending only women into certain areas of the Rocky Mountain region known to be especially hazardous. The causative association of the tick vector with Rocky Mountain spotted fever (RMSF) was noted by missionaries and early settlers, who named the affliction tick fever, and physicians in Idaho and Montana recorded the classic clinical descriptions of the disease in 1899.

Identification of Ticks

Ticks are arthropods but not insects. They have eight legs instead of six and generally two fusing body parts—a capitulum (head) and opisthosoma (abdomen)—instead of three. Identification of an arthropod as a tick and subsequent categorization into family and some genera are not difficult (Figs. 126.1 and 126.2). Speciation requires a trained acarologist. However, tick identification has limited importance in clinical decision making. Color, which varies seasonally, and size, which varies by amount of blood ingested at the time of presentation, are unreliable criteria for identification purposes.

Physiology of Tick Feeding

An understanding of the physiology of feeding in arthropods is more essential than species identification when assessing the risks of transmission of diseases. Blood-sucking arthropods are divided into two groups according to their method of acquiring blood. The solenophagic feeders insert their mouthparts directly into capillaries to obtain blood. Telmophagic feeders insert their mouthparts indiscriminately, lyse tissue along with capillaries, and feed on the resultant pool of blood, extracellular fluid, and tissue. Ticks and deer flies, for example, are telmophagic feeders, whereas mosquitoes are mostly solenophagic.

Argasid ticks (soft-bodied ticks) are short, rapid feeders with preformed distensible endocuticles. They therefore need to feed for only minutes to hours to acquire a full meal. As a result, they tend to be found in nests and burrows where their hosts visit frequently. The genus *Ornithodoros* is the vector for relapsing fever. Ixodid ticks (hard-bodied ticks) include the genera *Ixodes, Dermacentor, Amblyomma,* and *Rhipicephalus,* which are those responsible for the remainder of human tickborne diseases in the United States discussed in this chapter. These ticks need to form a new exocuticle (phase I of feeding) and thus feed slowly during the first 12 to 24 hours. Once it is fully formed, the new endocuticle allows rapid feeding (phase II) and significant engorgement.

In the capitulum of ticks, the sucking structure, consisting of the chelicerae, is surrounded by a sheath from which it protrudes during feeding. When a suitable location is found, adjacent cheliceral digits incise the skin, and the chelicerae and barbed hypostome are inserted. Two mechanisms prevent the tick from being removed from the skin—the barbed hypostome and a cement-like salivary secretion from the base of the hypostome, composed of lipoproteins and glycoproteins. This allows ixodid ticks to remain attached for as long as 2 weeks. Because argasids are much faster feeders, they secrete no cement substance.

During a bite, trauma and salivary gland products can cause local inflammation, hyperemia, edema, hemorrhage, and skin thickening. The saliva injected during feeding contains many different substances. Hard and soft ticks produce a histolytic secretion that liquefies tissue, which is then sucked into the gut. Eventually, the secretion breaks down the walls of the dermal blood vessels and the released blood is ingested. To prevent hemostasis, the saliva contains a thrombokinase inhibitor, apyrase, which prevents platelet aggregation by depleting adenosine diphosphate, prostaglandin E_2, and prostacyclin (prostaglandin I_2) to prevent vasoconstriction, and cytolysins. *Ixodes scapularis* also secretes a carboxypeptidase that destroys other inflammatory mediators, such as anaphylatoxins and bradykinin, as well as anti–complement C3 factor. These other mediators normally would cause further inflammation, which would enhance hemostasis. All infectious agents and excretory liquids from some argasids are transmitted through this saliva. Transmission of a disease from *Ixodes* ticks is unlikely if the tick is not yet engorged with blood at the time of removal. Likewise, a tick removed within a few hours after attachment is unlikely to transmit disease. The neurotoxins responsible for tick paralysis also are found in tick saliva.

The local physiologic changes associated with tick feeding produce the characteristic 1- to 4-mm erythematous mark typically seen on the skin after a tick bite. This is a common finding from most blood-sucking arthropods. The mark should not be confused with certain rashes associated with disease progression—for example, erythema migrans. Informing patients of this difference may be reassuring.

TABLE 126.1

Tickborne Illnesses

TYPE	DISEASE	PATHOGEN	ARTHROPOD VECTOR	GEOGRAPHIC DISTRIBUTION
Bacterial (including spirochetal)	Lyme disease	*Borrelia burgdorferi*	*Ixodes scapularis*	Northeastern United States
			Ixodes pacificus	Upper Midwestern United States
			Ixodes ricinus	Pacific Coast Europe
	Tularemia	*Francisella tularensis*	*Ixodes scapularis* *Amblyomma americanum* *Dermacentor variabilis*	Southwest central United States
Rickettsial	Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor andersoni* *Dermacentor variabilis* *Rhipicephalus sanguineus*	Predominantly southeastern United States Arizona
	Q fever	*Coxiella burnetii*	*Dermacentor andersoni*	Worldwide
	Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum*	South central and southeastern United States
	Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis*	New England and north central United States
			Ixodes pacificus	Northern California
Parasitic (protozoal)	Babesiosis	*Babesia microti*	*Ixodes scapularis*	Coastal New England
Viral[a]	Colorado tick fever	Orbivirus	*Dermacentor andersoni*	Mountain areas of western United States and Canada
Miscellaneous	Tick paralysis	Ixobotoxin	*Dermacentor andersoni* *Dermacentor variabilis* *Amblyomma americanum* *Ixodes scapularis* *Ixodes pacificus* *Ixodes holocyclus*	Worldwide

[a]Many other viruses are transmitted to humans by ticks. In the United States, only Colorado tick fever occurs with any significant frequency.

LYME DISEASE

Lyme disease, the most common vector-borne disease in the United States, is a tickborne illness caused by the spirochete *Borrelia burgdorferi*. The story of Lyme disease began in 1975, when health officials at the Connecticut State Department of Health and physicians at Yale University were alerted by two skeptical mothers to an unusually large number of cases of apparent juvenile rheumatoid arthritis occurring in their small coastal community of Old Lyme, Connecticut. Investigation led to the description of a new entity called Lyme arthritis. The causative agent of Lyme disease was isolated in 1982.

Lyme disease occurs worldwide and has been reported on every continent except Antarctica. It now accounts for more than 95% of all reported cases of US vector-borne illness. The actual overall incidence of Lyme disease is unknown because many cases go unreported. Lyme disease occurs in people of all ages but is more common in children younger than 15 years and in adults 30 to 60 years of age.[2] Persons at greatest risk live or vacation in endemic areas. In the United States, three distinct endemic foci are recognized—the northeastern coastal, Mid-Atlantic, and north central states. During 2000, a total of 17,730 cases of Lyme disease were reported from 44 states and the District of Columbia. Twelve states (Connecticut, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Washington, and Wisconsin) accounted for 92% of US cases reported (Fig. 126.3).[3]

The principal tick vectors are *I. scapularis* in the Northeast and Midwest and *Ixodes pacificus* in the West. The *I. scapularis* population density depends on that of its preferred hosts, the white-footed field mouse, *Peromyscus leucopus,* for the larval and nymphal forms, and the white-tailed deer, *Odocoileus virginianus,* for the adult form. The white-footed mouse readily becomes infected after being bitten by infected ticks and remains highly infectious for periods that approach its life span in nature, thereby providing an important reservoir for *B. burgdorferi*. Adult *I. scapularis* ticks feed primarily on deer, which are key hosts in the tick life cycle and in whose fur the adult tick may survive the winter. The repopulation of several areas in the United States by white-tailed deer preceded the recent emergence of Lyme disease in those regions.

Although all stages of the tick may feed on humans, the nymph is primarily responsible for the transmission of Lyme disease. It is not surprising that more than two-thirds of patients with Lyme disease do not recall a tick bite, in view of the small size (1–2 mm) of nymphs (Fig. 126.4). The nymph feeds in the spring and summer, which correlates with a peak incidence of early Lyme disease occurring between May and August. In addition, recreational and occupational exposure is greatest during this time. Later manifestations of Lyme disease may appear throughout the year.

The spirochete *Borrelia burgdorferi* persists and multiplies in the midgut of its tick vector, *I. scapularis*. Transmission of the spirochete to humans occurs during feeding, generally about 2 days after attachment. The mechanism of transmission probably is inoculation with infectious saliva or, alternatively, with tick gut fluids periodically regurgitated during the feeding process.

After an incubation period that lasts several days to several weeks, spirochetemia develops, and *Borrelia* organisms may migrate outward in the blood or lymph to virtually any site in the body. The spirochete appears to be tropic for synovial tissue, skin, and cells of the nervous system, but the mechanism of this tropism

Fig. 126.1. Scanning electron micrographs of two tick species. **A,** Dorsal view of adult female, *Dermacentor variabilis*. **B,** Dorsal view of adult female, *Ixodes scapularis*. **C,** Dorsal close-up view of *D. variabilis* head. **D,** Dorsal close-up view of *I. scapularis* head. (Courtesy Dr. J. E. Keirans, Georgia Southern University, Statesboro, Georgia.)

is not yet understood. Infection by the spirochete itself accounts for early clinical manifestations. It remains unclear whether late disease manifestations require the continued presence of viable spirochetes or whether an ongoing host immune response to initial infection is sufficient to cause some late disease effects. Although the exact roles of infecting spirochetes, spirochetal antigens, and host immune responses are unknown, it is likely that persistent live spirochetes are responsible for most later manifestations of the disease. The variable severity of Lyme disease may in part result from genetic variations in the human immune system. For example, patients with chronic Lyme arthritis have an increased frequency of human leukocyte antigen (HLA) specificity, in particular for HLA-DR4 and, less often, for HLA-DR2.

Clinical Features

Lyme disease, a multisystem disorder, can be classified into three stages—early localized, early disseminated, and late disease. Virtually any clinical feature may occur alone or recur at intervals, and some patients who had no early symptoms may have late symptoms. The disorder usually begins with a rash and associated constitutional signs and symptoms, suggesting a viral syndrome (early Lyme disease). Neurologic, joint, or cardiac manifestations may emerge weeks to months later (early disseminated Lyme disease), and chronic arthritic and neurologic abnormalities may appear weeks to years later (late Lyme disease). The time course for the clinical features of untreated Lyme disease is illustrated in Fig. 126.5.

Early Lyme Disease

Ticks may attach to human hosts at the initial point of contact, generally around ankle level, or move about until they encounter an obstruction. The groin, popliteal fossae, gluteal folds, axillary folds, and earlobes are common sites of attachment. After transmission of *B. burgdorferi* through a tick bite, the initial site of infection is the skin at the site of the bite. After an incubation period of approximately 1 week (range, 1–36 days), the spirochetes cause a gradually spreading localized infection in the skin and a resultant skin lesion, erythema migrans. Erythema migrans

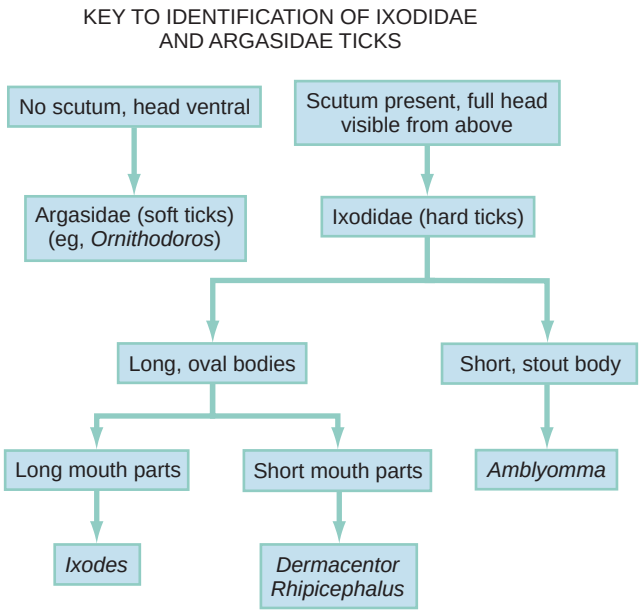


Fig. 126.2. Identification scheme for Ixodidae and Argasidae genera, the two primary disease-transmitting families of ticks.

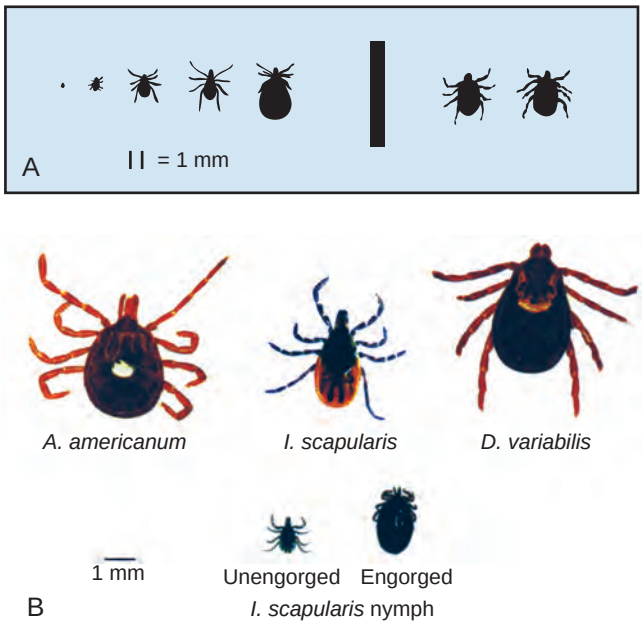
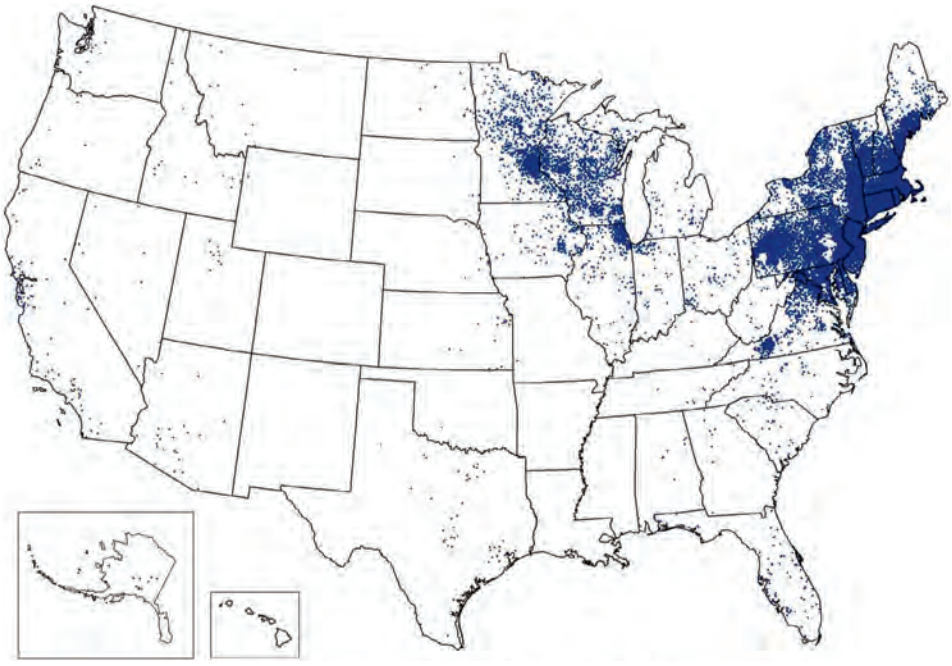


Fig. 126.4. **A,** *Left to right,* Larva, nymph, adult male, adult female, and engorged adult female *Ixodes* ticks and adult male and female *Dermacentor* ticks; actual size. **B,** Adult female *Amblyomma americanum* (Lone Star tick), adult female and nymphal *Ixodes scapularis* (deer tick), and adult female *Dermacentor variabilis* (dog tick). (From Hayes EB, Piesman J: How can we prevent Lyme disease? N Engl J Med 348:2424–2430, 2003.)

Reported Cases of Lyme Disease—United States, 2013

One dot is placed randomly within the county of residence for each confirmed case. Although Lyme disease cases have been reported in nearly every state, cases are reported based on the county of residence, not necessarily the county of infection.



One dot placed randomly within county of residence for each confirmed case

Fig. 126.3. Reported cases of Lyme disease cases by county in the United States in 2013. The number of confirmed cases totaled 27,203. (Adapted from Centers for Disease Control and Prevention: Lyme disease maps. www.cdc.gov/lyme/ stats/maps/map2013.html.)

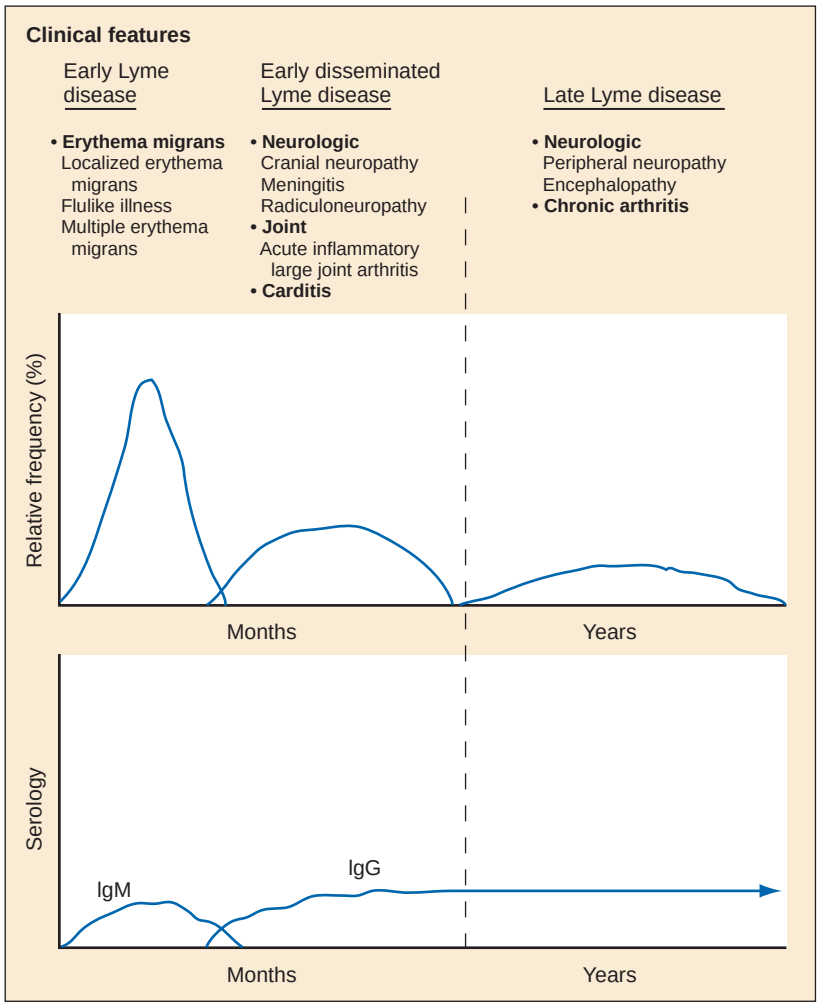


Fig. 126.5. Natural history of serologic response, with clinical features, in untreated Lyme disease. *IgG,* Immunoglobulin G; *IgM,* immunoglobulin M. (Adapted from Rahn DW: Natural history of Lyme disease. In Rahn DW, Evans J, editors: Lyme disease. Philadelphia, 1998, American College of Physicians, pp 35–48.)

(EM) is the most characteristic clinical manifestation of Lyme disease and is recognized in 90% or more of patients. EM may go unnoticed if the entire skin surface is not examined. The characteristic rash begins at the site of the tick bite with an erythematous papule or macule. The lesion expands gradually (1–2 cm/day, a rate of expansion slower than that of cellulitis). The patch of erythema may be confluent or may have bands of normal-appearing skin. Central clearing may occur but is not an invariable feature. The lesion borders usually are flat but may be raised. The lesions generally are sharply demarcated and blanch with pressure. Most lesions are oval or round, but triangular and elongated patches may occur. In patients presenting 1 to 7 days after the appearance of lesions, the average lesion size is approximately 8 by 10 cm (range, 2 by 3 cm to 25 by 25 cm). In some cases, the center of some early lesions becomes red and indurated or vesicular and necrotic. The lesion is warm to the touch and may be described by the patient as nontender to minimally tender (Figs. 126.6 and 126.7).

Hematogenous spread of viable spirochetes (not additional tick bites) may result in one or more secondary lesions. These secondary lesions are smaller, migrate less, and typically spare the palms and soles. In all, 10% to 15% of patients have more than 20 such lesions; on rare occasions, they may number more than 100. Blistering and mucosal involvement do not occur. The primary and secondary skin lesions generally fade after approximately 28 days (range, 1 week to 14 months) without treatment

Fig. 126.6. Lyme disease usually begins with a slowly expanding skin lesion, erythema migrans, which occurs at the site of the tick bite. The classic bull's-eye or target lesion has partial central clearing, a bright red outer border, and a target center. (From Bhate C, Schwartz RA: Lyme disease. Part I. Advances and perspectives. J Am Acad Dermatol 64:619–636, 2011.)

Fig. 126.7. Early erythema migrans on the lower leg. The erythematous nodular appearance could lead to misdiagnosis as a spider bite or MRSA cellulitis. (From Bhate C, Schwartz RA: Lyme disease. Part I. Advances and perspectives. J Am Acad Dermatol 64:619–636, 2011.)

and within several days of antibiotic therapy. Recurrent lesions may develop in patients who do not receive antibiotic therapy but apparently not in those who receive appropriate antibiotics.

Constitutional signs and symptoms commonly appear in early Lyme disease (Table 126.2). Malaise, fatigue, and lethargy are most common (seen in ≈80% of patients) and may be severe. Fever typically is low grade and intermittent. Lymphadenopathy usually is regional in the distribution of EM or may be generalized; splenomegaly may occur. Musculoskeletal complaints, such as arthralgias and myalgias, are common, and the discomfort typically is short-lived and migratory, sometimes lasting only hours in one location. Frank arthritis may occur at this stage but is rare.

Clinical manifestations of meningeal irritation are frequently seen. Headache, the most common symptom, usually is intermittent and localized. Nausea, vomiting, and photophobia occasionally accompany the headache. Kernig's and Brudzinski's signs typically are absent, and neck stiffness usually is noted only on extreme forward flexion. At this stage, the neurologic examination and cerebrospinal fluid (CSF) assessment usually yield normal findings.

Signs and symptoms of hepatitis, including anorexia, abdominal pain, right upper quadrant tenderness, nausea, and vomiting, may be present. Mild pharyngitis also may be present, but other upper respiratory symptoms, such as rhinorrhea, do not occur. Although the systemic symptoms of early Lyme disease often are described as flulike, a term that can be misleading because clinically significant cough usually does not occur. Conjunctivitis develops in approximately 10% of patients.

The incidence of Lyme disease without EM appears to be approximately 10%. Because of the variety of nonspecific signs and symptoms at this stage, in the absence of the characteristic rash or history of tick bite, early Lyme disease may be easily confused with a viral or collagen vascular disease. The intermittent and rapidly changing nature of the early signs and symptoms of Lyme disease may be a helpful distinguishing feature, especially in a patient from an endemic area. In untreated disease, early symptoms usually last for several weeks but may persist for months.

TABLE 126.2

Early Clinical Manifestations of Lyme Disease

MANIFESTATION	NO. OF PATIENTS (%)
SIGNS	
Erythema chronicum migrans[a]	314 (100)
Multiple annular lesions	150 (48)
Lymphadenopathy	
Regional	128 (41)
Generalized	63 (20)
Pain on neck flexion	52 (17)
Malar rash	41 (13)
Erythematous throat	38 (12)
Conjunctivitis	35 (11)
SYMPTOMS	
Malaise, fatigue, lethargy	251 (80)
Headache	200 (64)
Fever and chills	185 (59)
Stiff neck	151 (48)
Arthralgias	150 (48)
Myalgias	135 (43)
Backache	81 (26)
Anorexia	73 (23)
Sore throat	53 (17)
Nausea	53 (17)
Dysesthesia	35 (11)
Vomiting	32 (10)

[a]Required for inclusion in this study.
From Steere AC, Bartenhagen NH, Craft JE, et al: The early clinical manifestations of Lyme disease. Ann Intern Med 99:76–82, 1983.

Acute Disseminated Infection

Shortly after disease onset, hematogenous spread can cause a variety of systemic signs and symptoms and result in secondary sites of infection. Organ systems commonly affected are the nervous system, heart, and joints. Less commonly, the eyes, liver, skeletal muscle, subcutaneous tissue, and spleen are infected.

Neurologic Manifestations. A relatively symptom-free interval usually occurs between early and disseminated infection; however, neurologic signs and symptoms may be the presenting manifestations of Lyme disease or may overlap with early or late manifestations. Beginning at an average of 4 weeks (range, 0–10 weeks) after the onset of erythema migrans, neurologic involvement occurs in approximately 15% of untreated patients.

The most common neurologic manifestation of Lyme disease is a fluctuating meningoencephalitis, with superimposed symptoms of cranial neuropathy, peripheral neuropathy, or radiculopathy. A triad of meningitis, cranial neuropathies (usually Bell's palsy), and radiculopathy has been described, but each entity may occur alone. Headache of variable intensity usually is present; other signs and symptoms of a mild meningoencephalitis may be noted, including lethargy or irritability, sleep disturbances, poor concentration, and memory loss. At this point, the disease often

is misdiagnosed as viral meningitis. As in early disease, Kernig's and Brudzinski's signs are absent and computed tomography (CT) findings are normal. Unlike in early disease, however, findings on CSF examination often are abnormal, with a lymphocytic pleocytosis and moderately elevated protein level. CSF glucose concentration usually is normal. Intrathecal *B. burgdorferi* antibody (usually immunoglobulin G [IgG] or IgA) is present in 80% to 90% of patients. CSF polymerase chain reaction (PCR) assay results are positive in less than 50% of patients, probably reflecting the low number of organisms usually present in spinal fluid. Routine testing of CSF by PCR assay is not recommended.

Cranial neuropathies are common, occurring in approximately 50% of patients with Lyme meningitis; the seventh nerve is usually involved. Other cranial nerves are affected less often. Bell's palsy is bilateral in approximately one-third of patients. Its duration usually is weeks to months, and the condition generally resolves spontaneously without treatment.

Peripheral nervous system manifestations also may occur in early disseminated Lyme disease. The spinal root and plexus and peripheral nerves may be involved in the form of thoracic sensory radiculitis, brachial plexitis, mononeuritis, and motor radiculoneuritis in the extremities. Patients may complain of weakness, pain, or dysesthesia. Examination may reveal loss of reflexes. Involvement of the extremities usually is asymmetric, but cervical and thoracic dermatomes may be affected. Other rare neurologic abnormalities described in association with Lyme disease include chorea, transverse myelitis, ataxia, and pseudotumor cerebri. Cerebral vasculitis associated with Lyme disease also has been reported.

Cardiac Manifestations. Cardiac involvement in Lyme disease is uncommon. Estimates of the incidence of carditis in untreated patients with Lyme disease range from 4% to 10%. Cardiac involvement occurs during the early disseminated phase of the disease. The average time from initial illness to the development of carditis typically is 3 to 5 weeks (range, 4 days to 7 months). Direct myocardial invasion has been demonstrated with endomyocardial biopsy. Electrophysiologic testing has demonstrated widespread involvement of the conduction system.

The most common cardiac manifestation of Lyme disease is atrioventricular (AV) block, although conduction defects may involve any level of the conducting system. Myopericarditis, tachydysrhythmias, and ventricular impairment occur less often. In a review of 105 reported cases of Lyme carditis, 49% of cases were third-degree, 16% were second-degree, and 12% were first-degree AV block. The degree of AV block seen in a specific patient may fluctuate rapidly.

A commonly observed feature of AV block in patients with Lyme carditis is its gradual resolution, resembling that occurring after an acute inferior wall myocardial infarction and presumably related to the resolution of inflammation. Assessment of the level of the AV block is important to determine the prognosis of a patient with Lyme carditis. In most cases, the block appears to be at or above the level of the AV node; therefore, the prognosis is favorable. However, infranodal AV block does occur and may be characterized by slow escape rhythms of wide QRS pattern, asystole, or fluctuating left and right bundle branch block. Other electrocardiographic findings include nonspecific ST and T wave abnormalities and intraventricular conduction delay.

Patients with high-degree AV block usually are symptomatic. Symptoms include lightheadedness, palpitations, syncope, chest pain, and dyspnea on exertion. The physical examination may reveal flow murmurs and murmurs of mild mitral regurgitation, pericardial friction rub, or evidence of congestive heart failure. Associated left ventricular dysfunction may be present and has been documented by two-dimensional echocardiography and radionuclide studies; in most reported cases, it has been mild and transient. Sudden cardiac death attributable to Lyme disease has also been reported.[2,4]

Arthritis. Although it is generally considered a sign of late Lyme disease, acute arthritis may begin during the acute disseminated stage. Monarticular or oligoarticular arthritis, primarily affecting large joints, especially the knee, may develop weeks to months after the onset of initial illness. In an early study of the natural history of Lyme arthritis, approximately 50% of untreated patients experienced one episode or multiple intermittent attacks of arthritis. Acute arthritis typically is monarticular, with involvement of only one knee. The shoulder, elbow, temporomandibular joint, ankle, wrist, hip, and small joints of the hands and feet are involved less commonly. Episodes of arthritis typically are brief (lasting weeks to months) and are separated by variable periods of remission.

Arthrocentesis generally is nondiagnostic, yielding an inflammatory synovial fluid with a mean white blood cell count of approximately 25,000 cells/μL (75% polymorphonuclear leukocytes). Higher white blood cell counts have been reported, simulating septic arthritis. The synovial glucose concentration usually is normal, and protein levels are variable, ranging from 3 to 8 g/dL. Cultures of the fluid rarely identify the causative spirochete. The complement level generally is greater than one-third that of serum. Synovial biopsy reveals hypertrophy, vascular proliferation, and a mononuclear cell infiltrate. Findings therefore are similar to those in rheumatoid arthritis, except that rheumatoid factor and antinuclear antibody assays yield a negative result in Lyme arthritis. Radiography may reveal nonspecific abnormalities such as juxtaarticular osteoporosis, cartilage loss, cortical or marginal bone erosions, and joint effusions.

Ophthalmic Manifestations. Ocular involvement also may be seen in early disseminated disease; manifestations include conjunctivitis, keratitis, choroiditis, retinal detachment, optic neuritis, and blindness. These findings also may be seen in late disease.

Late Lyme Disease

The chronic phase of Lyme disease is characterized by arthritic and, less commonly, neurologic symptoms. Transition from a pattern of episodic inflammation in early disease to a more indolent persistent inflammation is observed over time. The term *chronic* (or *late*) *Lyme disease* is used to describe continuous inflammation in an organ system for more than 1 year.

A pattern of exacerbation and remission of arthritis may extend for several years, with a gradual tendency toward less frequent and less severe occurrences. The spontaneous long-term remission rate approximates 10% to 20% annually in untreated patients. However, patients commonly have episodes of periarticular involvement, arthralgias, or fatigue interspersed between attacks of frank arthritis. During the second or third year of illness, attacks of joint swelling sometimes become longer in duration, lasting months rather than weeks. Chronic arthritis eventually develops in approximately 10% of patients.

Late neurologic complications include a wide variety of abnormalities of the central and peripheral nervous systems, as well as fatigue syndromes. Diagnosis may be difficult because of the large number of other neurologic conditions that Lyme disease may imitate and because late neurologic symptoms may be the first symptoms of the disease. The manifestations of chronic neuroborreliosis usually appear months to years after the onset of infection.

The most common late neurologic manifestation of Lyme disease is a chronic encephalopathy that is manifested as a mild to moderately severe impairment of memory and learning.

Hypersomnolence and mild psychiatric disturbances (depression, irritability, paranoia) also may develop.[5]

Peripheral nervous system manifestations often are seen in late disease, with involvement of cranial nerves, spinal roots, spinal plexuses, and peripheral nerves. A predominantly sensory polyradiculoneuropathy that is manifested as radicular pain or distal paresthesia is common. Significant overlap occurs with early symptoms. Less commonly, a demyelinating condition resembling multiple sclerosis may appear in late disease. Symptoms are variable and, as in multiple sclerosis, may undergo exacerbations and remissions. CT and magnetic resonance imaging (MRI) may reveal multiple white matter lesions.

Chronic inflammation also may occur in the skin, causing a seldom-recognized late cutaneous manifestation of Lyme disease, acrodermatitis chronica atrophicans. This condition usually involves the skin of distal extremities at the site of a tick bite. It is characterized in its initial stages by an edematous infiltration, which progresses to an atrophic lesion resembling localized scleroderma in its more established form. *B. burgdorferi* has been demonstrated in the skin of patients with acrodermatitis chronica atrophicans as well as positive findings on serologic studies.

Differential Diagnosis

The diagnosis of Lyme disease should be considered on the basis of clinical and epidemiologic features. Identification of the disorder often is difficult, however, especially in the early stage. Although Lyme disease is manifested in many ways, each stage has characteristic clinical findings that are helpful in narrowing the scope of a differential diagnosis, which at first may seem overwhelmingly broad. Early Lyme disease (EM and associated constitutional symptoms) may be easily confused with a variety of other diseases, especially if the characteristic rash of EM is absent. A common clinical presentation is an influenza-like illness with headache, nausea, fever, chills, myalgias, arthralgias, stiff neck, and anorexia, occurring during the summer months. Even in endemic areas during the summer months, most patients with such symptoms do not have Lyme disease. When headache and stiff neck are the predominant symptoms, the principal diagnostic distinction to be made is between Lyme disease and the enteroviral diseases (and other causes of aseptic meningitis). The enteroviral diseases also have their peak incidence during the summer months; however, diarrhea, commonly associated with enteroviral infection, is not a feature of Lyme disease. Abdominal pain, anorexia, and nausea suggest hepatitis, sore throat, adenopathy, and fatigue suggest mononucleosis, and myalgias and arthralgias suggest connective tissue diseases. In many areas where Lyme disease is endemic, *Ixodes* ticks can be infected simultaneously with *B. burgdorferi*, *Anaplasma phagocytophilum*, and *Babesia microti*. Co-infection with more than one of these agents can occur.[6]

The rash of EM is characteristic of but not pathognomonic for Lyme disease. Some patients are not aware of having had such a rash and, in others, its appearance is atypical. An EM skin lesion is frequently misdiagnosed as a spider bite or community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) cellulitis, resulting in treatment with ineffective antibiotics. Other cutaneous entities in the differential diagnosis for EM include fungal infection, plant dermatitis, and fixed drug eruptions. Secondary lesions may be confused with the target lesions of erythema multiforme, which generally are smaller and nonexpanding. Erythema multiforme also may involve the mucous membranes, palms, and soles; EM does not. The presence of a malar rash in association with Lyme disease suggests systemic lupus erythematosus. Erythema nodosum generally causes more painful induration than EM and has a predilection for the extensor surfaces of the legs. Erythema marginatum of acute rheumatic fever also is in the differential diagnosis for EM; the Lyme disease rash differs in comprising generally fewer, larger, less evanescent lesions that migrate more slowly. Atypical EM manifesting as a urticarial rash may suggest hepatitis B infection or serum sickness. Lyme disease should be considered in a patient with any atypical rash accompanied by a viral syndrome or meningitis-like illness, especially during the months of peak incidence.

Acute rheumatic fever, coronary artery disease, or viral myocarditis may be suggested by the cardiac manifestations of Lyme disease. The carditis of Lyme disease, like the carditis of rheumatic fever, may follow pharyngitis and migratory polyarthritis. Erythema marginatum usually occurs with the onset of arthritis, in contrast with EM, which usually precedes the carditis. Although some patients with Lyme disease may satisfy the clinical aspects of the Jones criteria for acute rheumatic fever, they lack evidence of a preceding streptococcal infection; in addition, valvular involvement is not a prominent feature of Lyme carditis.

The differential diagnosis of the neurologic manifestations caused by Lyme disease is extensive. Considerations include aseptic meningitis, herpes simplex encephalitis, Bell's palsy of other causes, multiple sclerosis, Guillain-Barré syndrome, dementia, primary psychosis, cerebral vasculitis, and brain tumor. Neurologic symptoms often occur in the absence of any epidemiologic clues or preceding clinical symptoms suggestive of Lyme disease, making the diagnosis particularly challenging.

Lyme arthritis may mimic other immune-mediated disorders. The arthritis of Lyme disease generally is asymmetric, oligoarticular, and episodic. In contrast to patients with rheumatoid arthritis, those with Lyme arthritis rarely have symmetric polyarthritis, morning stiffness, a positive result on rheumatoid factor assay, or subcutaneous nodules. Lyme arthritis commonly is mistaken for seronegative rheumatoid arthritis; however, Lyme arthritis is most similar to the spondyloarthropathies, particularly reactive arthritis. Lyme disease and reactive arthritis both commonly cause huge knee effusions but, in Lyme disease, absence of the extraarticular features of reactive arthritis (conjunctivitis, urethritis or cervicitis, balanitis, keratosis blennorrhagica) at the time of the arthritis helps distinguish it from reactive arthritis. In children, Lyme arthritis may mimic juvenile rheumatoid arthritis, but joint involvement in Lyme disease usually occurs in short intermittent attacks, and iridocyclitis typically is absent. Rheumatoid factor titers will be negative in juvenile rheumatoid arthritis and Lyme disease. The diseases resemble one another closely enough to have been confused at the time of the initial description of Lyme disease. Other diseases in the differential diagnosis for Lyme arthritis include acute gouty arthritis, septic arthritis, gonococcal arthritis, rheumatic fever, polymyalgia rheumatica, and temporomandibular joint syndrome.

Diagnostic Testing

Results of routine laboratory studies are nonspecific, and such studies generally are not helpful in the diagnosis of Lyme disease. Abnormalities may include an elevated erythrocyte sedimentation rate, mild anemia, total white blood cell count in the normal range with a decreased absolute lymphocyte count, microhematuria, proteinuria, and increased alanine transferase level. Cultures of blood, tissue, and body fluids (including CSF and synovial fluid) for *B. burgdorferi* and direct visualization techniques are difficult to perform properly and have such a low yield that they are not clinically useful.

Serologic testing is the most practical and useful means of confirming a clinical diagnosis of Lyme disease, but is not without limitations. Results of serologic tests should be interpreted cautiously within the clinical context, and such tests should be regarded only as adjuncts in the diagnostic process. Current serologic tests measure host antibody response (for IgG and IgM) to *B. burgdorferi*. Problems with the performance of these tests and

interpretation of their findings often result in diagnostic confusion. False-negative and, especially, false-positive results are common. The antibody response to *B. burgdorferi* develops slowly. The peak of IgM titers appears between 3 and 6 weeks after the onset of illness. Earlier in the course of the illness, IgM titers may be negative. IgM antibody usually returns to nondiagnostic levels 4 to 6 weeks after the peak, but elevations may persist. IgG antibody may be detectable 2 months after exposure and peaks at approximately 12 months. Early antibiotic therapy may blunt or even abolish the antibody response.

A two-tier strategy is recommended for serologic testing—a sensitive enzyme-linked immunosorbent assay (ELISA) followed by a Western blot (immunoblot). Positive or equivocal ELISA results should be followed by a Western blot. If the ELISA is negative, no further testing is necessary.

IgM and IgG immunoblots should be obtained if early disease is suspected. If late disease is suspected, IgG Western blot alone should be obtained. Criteria for positive Western immunoblotting (requiring the presence of bands at particular locations) have been adopted by the CDC.

About one-third of patients with early localized Lyme disease (erythema migrans) are seropositive at the time of presentation by the two-tier method. Patients with skin lesions typical of EM do not require confirmatory serologic testing, and the rash itself is sufficient for the diagnosis to be made. If the cause of the rash is uncertain, acute and convalescent phase serologic testing may be considered, with the convalescent sample drawn 2 to 4 weeks after the acute sample. In contrast to early localized disease, most patients with early disseminated Lyme disease or late Lyme disease are seropositive.

IgG (and occasionally IgM) antibody may persist for several years after adequate treatment and symptom resolution. Persistent seropositivity is not diagnostic of ongoing infection. Even an IgM response cannot be interpreted as a demonstration of recent infection or reinfection unless the appropriate clinical characteristics are present. IgG antibody that developed after natural infection does not always confer immunity against future infection by *B. burgdorferi*. Patients who are treated for EM may become reinfected; patients with Lyme arthritis, however, usually have high antibody titers to many spirochetal proteins and seem not to become reinfected.[7] Thus, the expanded immune response of late disease appears to be protective against reinfection, at least in most patients, whereas the immature immune response of early disease does not.[7]

False-positive ELISA results are common. Serologic cross-reactivity can occur between *B. burgdorferi* and other spirochetes, most notably *Treponema pallidum*. False-positive results for Lyme disease also can occur with relapsing fever, gingivitis, leptospirosis, enteroviral and other viral illnesses, rickettsial diseases, autoimmune diseases, malaria, and subacute bacterial endocarditis. In addition, it is estimated that up to 5% of the normal population will test positive for Lyme disease by ELISA. Bayes' theorem states that if the pretest likelihood of the disease is low, the positive predictive value is low: a positive test result is more likely to be a false-positive result. For this reason, screening serologic tests are not indicated in the absence of objective clinical evidence of Lyme disease.

Patients suspected of having acute Lyme neuroborreliosis should be evaluated with serologic tests and routine CSF examination. Paired serum and CSF samples should be obtained to evaluate for intrathecal production of antibody, although most patients with neuroborreliosis have positive results on serum serologic testing, thereby making additional laboratory confirmation with CSF serology unnecessary. The PCR assay has low sensitivity when performed on CSF and is not routinely recommended. However, the PCR assay is superior to culture for the detection of *B. burgdorferi* in synovial fluid and has a sensitivity of 73% and specificity of 99% in untreated Lyme arthritis.

Management

Prompt treatment of early disease can shorten the duration of symptoms and prevent progression to later stages of disease. Most of the various manifestations of Lyme disease can be treated successfully with oral antibiotic therapy, with the exception of neurologic abnormalities, which usually require intravenous (IV) therapy. Treatment of Lyme disease is summarized in Table 126.3.

Early Disease

Prompt antibiotic therapy is essential in early Lyme disease because it generally shortens the duration of the rash and associated symptoms and, more importantly, prevents later illness in most patients. Some patients with severe early disease, however, progress to later stages, despite appropriate antibiotic regimens.

The drug of choice for men, nonpregnant and nonlactating women, and children older than 8 years is doxycycline, 100 mg bid for 3 weeks. An advantage of doxycycline is that it also is effective for the treatment of human granulocytic anaplasmosis, which is transmitted by the same tick that transmits Lyme disease. Pregnant or lactating women and children younger than 8 years should receive amoxicillin, 500 mg orally (20 to 40 mg/kg/day in three doses for children). Cefuroxime axetil has been shown to be as effective as doxycycline and may be used in children of any age, but cephalexin is ineffective in Lyme disease.

Macrolide antibiotics are not recommended as first-line agents for therapy for early Lyme disease. They should be reserved for patients who cannot tolerate doxycycline, amoxicillin, and cefuroxime axetil. Macrolide regimens for adults include azithromycin, 500 mg orally daily for 7 to 10 days, erythromycin, 500 mg orally qid for 14 to 21 days, and clarithromycin, 500 mg orally bid for 14 to 21 days.

A Jarisch-Herxheimer type of reaction may occur in the first 24 hours of antibiotic treatment, consisting of fever, chills, myalgias, headache, tachycardia, increased respiratory rate, and mild leukocytosis. Defervescence usually takes place within 12 to 24 hours. The pathogenesis of this reaction is controversial, but it probably is caused by the killing of spirochetes, with the release of pyrogens. The Jarisch-Herxheimer reaction occurs more commonly with penicillin and doxycycline than with erythromycin, probably because of their superior spirocheticidal activity.

Early Disseminated Infection

Neurologic Disease. For patients with relatively mild symptoms (eg, solitary facial nerve palsy with normal findings on CSF examination), doxycycline or amoxicillin can be used in the same dosage as for early disease, but the duration of therapy should be extended to 28 days. The use of prednisone for facial nerve palsy from Lyme disease has been suggested but is not currently recommended.

Parenteral antibiotic therapy is required for patients with other objective neurologic abnormalities (eg, meningitis or encephalitis, peripheral neuropathies, cranial neuritis other than facial nerve palsy) or evidence of the spirochete in the CSF. Ceftriaxone, 2 g/day IV for 14 days (75 to 100 mg/kg/day for pediatric patients), or penicillin G, 18 to 24 million units daily IV for 10 to 14 days, may be used. Ceftriaxone may be more effective than penicillin, and many experts recommend longer courses (eg, up to 4 weeks). In cases of penicillin or cephalosporin allergy, oral doxycycline may be used for 28 days.

Cardiac Disease. Patients with mild cardiac conduction system involvement (first-degree AV block with a PR interval < 0.30 second) and no other significant symptoms usually can be treated safely on an outpatient basis with oral doxycycline or

TABLE 126.3

Treatment of Lyme Disease

SYNDROME AND MANIFESTATION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE[a]
Early Lyme disease	Doxycycline[b]	100 mg PO bid for 21 days	
	or		
	Amoxicillin	250–500 mg PO tid for 21 days	25–40 mg/kg/day tid
	ALTERNATIVE		
	Cefuroxime axetil	500 mg PO bid for 21 days	250 mg bid
	or		
	Erythromycin (less effective than doxycycline or amoxicillin)	500 mg PO qid for 14–21 days	
Neurologic disease			
• Facial nerve paralysis	With an isolated deficit, oral regimens for early disease, used for at least 28 days, may suffice. For a deficit associated with other neurologic manifestations, intravenous therapy is warranted (see below).		
• Lyme meningitis[c]	Ceftriaxone	2 g IV by single dose for 14– 8 days	75–100 mg/kg/day IV
	Penicillin G	20 million units daily in divided doses for 10–14 days	300,000 units/kg/day IV
	ALTERNATIVE		
	Chloramphenicol	1 g IV qid for 10–21 days	
Cardiac disease			
• Mild[d]	Doxycycline[b]	100 mg PO bid	
	or		
	Amoxicillin	250–500 mg PO tid	25-50 mg/kg/day tid
• More severe	Ceftriaxone	2 g IV daily by single dose for 14–21 days	75-100 mg/kg/day IV
	or		
	Penicillin G	20 million units daily in divided doses for 14–21 days	300,000 units/kg/day IV
Arthritis	ORAL		
	Doxycycline[b]	100 mg PO bid for 30 days	
	or		
	Amoxicillin	500 mg PO tid for 30 days	50 mg/kg/day divided tid
	PARENTERAL		
	Ceftriaxone	2 g IV by single dose for 14–21 days	75–100 mg/kg/day IV
	or		
	Penicillin G	20 million units daily in divided doses for 14–21 days	300,000 units/kg/day IV

[a]Pediatric dosage should not exceed adult dosage.
[b]Tetracycline, 250 to 500 mg PO qid, may be substituted for doxycycline. Neither doxycycline nor any other tetracycline should be used for children younger than 8 years or for pregnant or lactating women.
[c]Regimens for radiculoneuropathy, peripheral neuropathy, and encephalitis are the same as those for meningitis.
[d]Oral regimens are reserved for mild cardiac involvement (see text).
Adapted from New drugs for allergic conjunctivitis. Med Lett Drugs Ther 42:39–40, 2000; and Wormser GP, Dattwyler RJ, Shapiro ED, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 43:1089–1134, 2006.

amoxicillin for 21 to 30 days.[8] Patients with higher degrees of AV block, including first-degree block with a PR interval of more than 0.30 second or evidence of global ventricular impairment, should be hospitalized for cardiac monitoring and treatment with parenteral antibiotics. Penicillin G, 18 to 24 million units IV in 4 divided doses, or ceftriaxone, 2 g daily for 21 days (50 to 80 mg/kg/day for children), may be used.

The benefit of the adjuvant use of aspirin or prednisone in the treatment of Lyme carditis is uncertain. Temporary cardiac pacing may be necessary in patients who have severe heart block with hemodynamic instability. The block generally resolves completely with antibiotic treatment, so the recognition of Lyme carditis in young patients with unexplained heart block is critical for avoidance of unnecessary permanent pacemaker implantation.

Late Infection

Arthritis. In established Lyme arthritis, the response to antibiotic therapy may be delayed for several weeks or months. An oral regimen for 30 days, such as doxycycline, 100 mg orally bid, or amoxicillin, 500 mg tid, usually are effective and, for reasons of cost and convenience, may be selected as first-line therapy given on an outpatient basis before parenteral antibiotic therapy is considered. Persistent or recurrent joint swelling after recommended courses of antibiotic therapy can be treated with another 4-week course of oral antibiotics or with a 2- to 4-week course of IV ceftriaxone. A small percentage of patients with Lyme arthritis, particularly those with HLA-DR4 specificity or antibody reactivity with OspA, may have persistent joint inflammation, despite treatment with oral or IV antibiotics. Such patients often do not respond to any antibiotic therapy and may require arthroscopic synovectomy.

Neurologic Disease. Patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (2 g once daily IV for 2 to 4 weeks). Alternative parenteral therapy may include cefotaxime (2 g IV tid) or penicillin G (18–24 million units IV daily, given in divided doses every 4 hours). Response to treatment is usually slow and may be incomplete.

Lyme Disease and Pregnancy

Similar to the spirochetal agents of syphilis and relapsing fever, *B. burgdorferi* can be passed transplacentally. In rare cases, Lyme disease acquired during pregnancy may lead to infection of the fetus and possibly to stillbirth, but adverse effects on the fetus have not been documented conclusively. Counseling about the termination of a pregnancy because of maternal Lyme disease is unwarranted.

Lyme disease contracted during pregnancy can be treated and cured. Treatment of pregnant patients can be identical to that of nonpregnant patients with the same disease manifestations, except that doxycycline should be avoided. Most women give birth to normal infants despite documented Lyme borreliosis during their pregnancies.

Vaccination

No vaccine against Lyme disease is currently available in the United States. The LYMErix vaccine (SmithKline Pharmaceuticals, Philadelphia), initially licensed in 1999, was withdrawn from the market in 2002. The vaccine, directed against the outer surface protein A of *B. burgdorferi* (OspA), was apparently safe and efficacious but required multiple and repeated doses for optimal protection. Ongoing questions about its safety and cost-effectiveness dampened demand for the vaccine.

A history of vaccination with the previously licensed vaccine should not change the approach to management. Because protective immunity produced by the vaccine is short-lived, it is unlikely that previous vaccination will provide any residual protective effect. Vaccination may cause a persistently positive ELISA result but a negative Western blot result.

Prophylaxis and Asymptomatic Tick Bites

Although previous expert consensus has recommended that persons bitten by deer ticks (*I. scapularis*) should not routinely receive antimicrobial chemoprophylaxis, this recommendation should be modified in accordance with the findings of a well-designed trial in which a single 200-mg dose of doxycycline given within 72 hours after tick bite effectively prevented Lyme disease. A single 200-mg dose of doxycycline should be considered for adult patients and children 8 years of age and older (4 mg/kg, up to a maximum dose of 200 mg) when all the following criteria are met: (1) the tick is an adult or nymphal *I. scapularis*; (2) the tick has been attached for 36 hours or more, as indicated by certainty of the time of exposure or degree of engorgement; (3) prophylaxis can be started within 72 hours after tick removal; (4) the local rate of infection of these ticks with *B. burgdorferi* is 20% or greater; and (5) doxycycline is not contraindicated. Infection rates of 20% or greater of ticks with *B. burgdorferi* generally are reported from highly endemic areas such as New England, parts of the Mid-Atlantic region, and parts of Minnesota and Wisconsin. Most other areas of the United States do not have infection rates high enough to warrant prophylaxis.

The efficacy of single-dose doxycycline in patients who present more than 72 hours after removal of a tick is unknown. In children, the dosing and efficacy of prophylactic treatment have not been evaluated. The effectiveness of doxycycline for the prevention of other infections transmitted by *I. scapularis* ticks (eg, babesiosis, human granulocytic anaplasmosis) is unknown and should not be assumed.[9] Other antimicrobial agents effective for the treatment of Lyme disease (eg, amoxicillin) and even other regimens of doxycycline (eg, 100 mg bid) have unknown efficacy for Lyme disease prophylaxis. Anyone who has been bitten by a tick should be instructed to seek medical evaluation if symptoms of tick borne illness develop.

RELAPSING FEVER

Relapsing fever is caused by bacteria of the *Borrelia* species, order Spirochaetales. Human *Borrelia* infections occur worldwide, and all are associated with arthropod vectors. The epidemic (louse-borne) form of relapsing fever is caused solely by *Borrelia recurrentis* and is found mostly in Africa, where mortality rates can reach 70% with outbreaks. The endemic form, tickborne relapsing fever (TBRF), is caused by a group of closely related *Borrelia* species, their names derived from the species names of *Ornithodoros* tick vectors that carry them. The more common species in North America are *Borrelia hermsii, Borrelia turicatae,* and *Borrelia parkeri. B. burgdorferi* has been recognized as the causative agent of the third and most recently described borrelial disease, Lyme disease.

TRIS is maintained in an animal reservoir consisting primarily of wild rodents, including squirrels, mice, rats, chipmunks, and rabbits. It is found predominantly at altitudes of 2000 to 7000 feet in coniferous forest habitats. The tick vectors are argasids (soft ticks) belonging to several species of the genus *Ornithodoros,* which routinely reside in the nests and burrows of their mammalian hosts. Ticks acquire the infection by feeding on a spirochetemic rodent. The borreliae remain viable in the ticks for several years and can be passed transovarially to the next generation; thus, the tick is a major reservoir and vector. These soft ticks feed for brief periods (15– 20 minutes), usually at night, and their painless bite generally is unnoticed by the sleeping victim. Transmission occurs by injection of infected saliva through the bite site or intact skin. Less common modes of transmission (eg, by way of venipuncture equipment in injection drug users) have been reported.

In the United States, TBRF occurs primarily in the western Mountain and Pacific states, including Montana, Wyoming, Nevada, Colorado, California, and Washington. Between 1990 and 2011, the CDC received 504 reports of TBRF. The groups most commonly affected were males and people between the ages of 10 to 14 and 40 to 44 years. Of all reported cases, 70% were collectively from California, Washington, and Colorado. Most cases involved visitors to those states. Although TBRF is not nationally reportable, it was reported in 12 states in 2011.[5] Persons who come into contact with infected ticks from wild rodents are at greatest risk. Outbreaks have been reported among groups of persons sleeping overnight in hunting cabins inhabited by wild rodents. In Texas, most cases were reported in the winter months among people who had been exploring caves.

Clinical Features

In TBRF, the initial febrile episode lasts 3 days. This is followed by an asymptomatic period of variable duration, usually approximately 7 days, during which patients generally feel better and may return to their usual daily activity levels under the assumption that they have recovered from another viral illness. Relapse then occurs, with symptoms that mimic those of the original illness. With TBRF, this cycle repeats itself three to five times. Each successive relapse usually is less severe. Relapse is caused by the spirochete's unique ability to undergo antigenic variation within the body of the infected host. Each successive antigenic variation is cleared from the bloodstream by specific host antibodies, and a characteristic relapsing febrile course results.

Clinical illness is manifested in two classic stages as each fever episode resolves. The first stage is called the chill phase (high fevers with reported temperatures of up to 106.7° F (41.5° C), mental status changes, tachycardia, and tachypnea), lasting approximately 30 minutes, followed by a flush phase (rapid temperature decrease, sweats, and hypotension), which can be confused with a Jarisch-Herxheimer reaction.[6]

After a postbite incubation period of 4 to 18 days, during which time the host concentration of spirochetes increases, fever of abrupt onset occurs, often accompanied by shaking chills, headache, arthralgias, myalgias, nausea, and vomiting. On occasion, a pruritic eschar may be noted at the site of the tick bite, but this usually is absent by the onset of clinical symptoms. Consequently, the nonspecific nature of the clinical presentation often leads to misdiagnosis of the disease as a viral illness. The patient's temperature is high, and generalized muscle weakness and lethargy are common. Hepatomegaly, splenomegaly, and jaundice are sometimes seen. Neurologic involvement is less common but can be manifested as delirium, nuchal rigidity, peripheral neuropathy, or pupillary abnormalities. Uveitis, iritis and other cranial neuropathies can present acutely or, rarely, as long-term sequelae. A macular or petechial rash, more apparent on the trunk than on the extremities, may be present. There is evidence that febrile illness caused by relapsing fever might cause *Plasmodium vivax* malaria relapse.[10]

Severe cases of TBRF resulting in acute respiratory distress syndrome (ARDS) in California and Nevada near the Lake Tahoe area and in the state of Washington prompted a comprehensive epidemiologic investigation of cases in those areas during a 10-year period. This study showed that ARDS may be more common than was previously suspected. Reported occurrence rates for Jarisch-Herxheimer reaction varied between 6% and 21%, 16% for hypoxia, 8% for elevated liver function test values, and 6% for ARDS; 46% of patients required hospitalization.[1]

Differential Diagnosis

On initial presentation, the differential diagnosis is extensive; however, it narrows with the occurrence of relapse. A history of possible soft tick exposure together with recurrent fever should suggest the diagnosis. Other conditions that initially may be considered include malaria, typhus, dengue, yellow fever, Colorado tick fever, and tularemia. Careful examination of blood smears, together with clinical data and other laboratory tests, aid in making the correct diagnosis.

Diagnostic Testing

The definitive diagnosis of relapsing fever depends on the demonstration of spirochetes in peripheral blood smears during a febrile episode. This is not a typical finding with other spirochetal diseases. In most cases, spirochetes are readily visible on a routine blood smear prepared with Wright or Giemsa stain. Thick or thin blood smears, such as those prepared for malaria evaluation, also are satisfactory. The organisms are seen within the plasma spaces between blood cells or may overlie the blood cells. Several organisms per high-power field typically are visible in smears from febrile patients with relapsing fever. Blood specimens for the smears should be obtained as the temperature curve swings up, and repeated samples may be required before a positive result is observed because sensitivity approaches only 70%.

Spirochetes also may be visible in wet mounts with the use of phase contrast microscopy. Culture, although it is the most sensitive diagnostic method available, requires a special medium, does not yield rapid results, and therefore is not commonly performed. Genus-specific PCR testing has been used successfully and may be higher in sensitivity than serology or blood smear, especially in the acute phase of disease. Serologic testing is available through public and private health facilities but is not useful for immediate diagnosis. Nonspecific laboratory findings may include mildly increased bilirubin and liver function levels, thrombocytopenia, and an elevated erythrocyte sedimentation rate.[6]

Management

Relapsing fever is effectively treated with tetracycline or erythromycin. Tetracycline should be avoided in children younger than 8 years and in pregnant women. Tetracycline or erythromycin should be given in an oral dose of 500 mg for 7 days; single-dose therapy is also effective. Other treatment regimens have been recommended, including doxycycline and chloramphenicol. Treatment with penicillin G has been associated with an increased rate of relapse. Success with ceftriaxone has been reported in a patient with relapsing fever who did not respond to penicillin. Prophylaxis with doxycycline for TBRF in exposed subjects in high-risk infested areas has been shown to be effective.

As many as one-third of patients experience a Jarisch-Herxheimer type of reaction during treatment with antibiotics. The reaction can be severe, especially with louseborne relapsing fever. This phenomenon may be related to release of high levels of cytokine intermediaries or endogenous opioids. Approximately 4 hours after antibiotic treatment, and coinciding with the clearance of spirochetes from the blood, the patient usually experiences an increase in temperature and severe rigors, accompanied by a drop in the leukocyte and platelet counts and onset of hypotension. Anticipation of this reaction is crucial because volume expansion with saline solution may be required to maintain the blood pressure; the reaction can be more threatening than the disease itself. Meptazinol, an opioid antagonist with agonist properties, has been proposed for use in treatment of this reaction.

The prognosis is good for treated patients with relapsing fever; approximately 95% achieve complete recovery. Poor prognostic signs include the presence of jaundice, high spirochete counts in the blood, and hypotension. Transplacental transmission can occur in infected pregnant women. Perinatal death of the fetus or infant and spontaneous abortions occur in nearly 50% of cases in pregnant women. Death is rare in TBRF and is limited to infants and older adults.

TULAREMIA

Tularemia was first characterized in 1837 by Soken, who described a febrile illness with generalized lymphadenopathy in people who had eaten infected rabbit meat. In 1912, McCoy first isolated *Bacterium tularense,* now known as *Francisella tularensis,* from rodents in Tulare County, California, giving rise to the name of the disease. Edward Francis, for whom the genus *Francisella* was later named, contributed much to the understanding of the bacteriology and epidemiology.

Tularemia occurs worldwide and is endemic between 30 and 71 degrees north latitude. The incidence of tularemia is low. There were 247 reported cases of tularemia in the United States between 2004 and 2005, although it is not a notifiable disease in all states. Tularemia has been seen in every state but is most common in the southwest central region (Arkansas, Louisiana, Oklahoma, Texas, and Mississippi). Of reported cases, 56% have come collectively from Missouri, Oklahoma, South Dakota, and Arkansas. It is more common in men than in women. Persons at increased risk for infection include hunters, trappers, butchers, agricultural workers, campers, sheep herders, mink farmers, and laboratory workers.

Ticks, lagomorphs (hares, rabbits), and rodents (mice, rats) are believed to be the most important sources of transmission to humans; however, the organism has been recovered from animals of more than 100 species. Significant epidemics have been linked to contact with a variety of them, including domestic cats.[11] In 2002, a large number of commercially distributed prairie dogs from Texas died of tularemia.

The ticks most commonly involved in transmission in the United States are the deer tick (*I. scapularis*), Lone Star tick (*A. americanum*), and dog tick (*D. variabilis*), all of which have been

associated with other tickborne illnesses. Whereas mosquitoes are major vectors in many European countries, horse fly and deer fly bites have been implicated in endemic situations in the United States. In 2007, an outbreak in Utah was associated with deer fly bites.[12]

Transmission to humans most commonly occurs through tick bites or handling of infected animals. It also can occur with ingestion of infected food or water, inhalation of dust or water aerosol, and insect bites. Nonimmune laboratory workers who work with *F. tularensis* can acquire the disease. Person to person transmission is rare. Tularemia has a bimodal prevalence in the United States; an increased incidence in May to August is associated with tickborne transmission, and a December to January peak is associated with hunting and skinning of infected mammals (primarily rabbits). *F. tularensis* has been found to coexist in reservoir populations harboring the agent responsible for Lyme disease. Eleven cases of pneumonic tularemia, found to be from aerosolization of contaminated vegetation clippings, were discovered in Martha's Vineyard, Massachusetts. Outside the United States, tularemia has been confirmed in hundreds of cases in Kosovo through rodent contamination of food. Sweden has reported a high number of cases, usually associated with aquatic environments and mosquitoes.[13]

Tularemia is manifested in different ways, depending on the portal of entry of the organism. The primary route of infection by *F. tularensis* is through the skin. Entry can occur through hair follicles or small cuts and abrasions that may be contaminated by exposure to an infected animal; tick exposure can also introduce the bacteria. Because the bacterium has not been isolated from the salivary glands of ticks, it is thought that they transmit the organism through their feces. Scratching after a tick bite introduces the infected feces into the skin. Inhalation or ingestion of the organism or transmission through the conjunctivae also can cause infection. The incubation period is approximately 2 to 6 days, depending on the size of the inoculum.

After penetration of the skin or epithelial membrane, the organism usually spreads to the regional lymph nodes. An erythematous tender papule develops at the primary infection site, followed by inflammation and skin ulceration. The regional nodes enlarge, necrose, and may rupture. The necrotic, purulent, painful lymph node is termed a *bubo*. In the ulceroglandular form of the infection, the organism may not spread farther than the regional lymph nodes. If the inoculum is sufficiently large or host defenses are inadequate, bacteremia ensues, with dissemination to phagocytic cells of the reticuloendothelial system.

Pulmonary tularemia may result from inhalation of small-particle aerosols containing *F. tularensis* or from hematogenous dissemination. Small areas of localized pneumonitis are most commonly seen, although chest radiographic findings are nonspecific; lobar consolidation or abscess formation is rare. Oculoglandular tularemia occurs when the conjunctiva becomes infected from contact with material from an ulcer or contaminated finger. Typhoidal tularemia follows the systemic spread of *F. tularensis* from the oropharynx and probably the gastrointestinal tract when a large inoculum is swallowed.

Clinical Features

Presentations

Tularemia has six clinical presentations, depending on whether disease is localized to an entry site and its regional lymph nodes—ulceroglandular, glandular, oculoglandular, and oropharyngeal forms—or is more invasive and generalized—typhoidal and pulmonary forms.

Ulceroglandular Tularemia. This accounts for approximately 80% of cases. Typically, a skin lesion on an extremity at the site of primary inoculation begins as an erythematous papule, which then ulcerates 2 to 3 days later. The ulcer is slow to heal and often is still present when the subsequent regional lymphadenopathy and fever develop. The distribution of the regional adenopathy reflects the primary entry site; patients with tickborne tularemia usually have inguinal or femoral adenopathy, whereas those who acquire rabbit-associated tularemia have axillary or epitrochlear nodal involvement. Generalized lymphadenopathy also may be seen. On occasion, nodes suppurate and drain.

Glandular Tularemia. This is the second most common form. It is characterized by the development of lymphadenopathy (usually cervical) without an associated skin ulcer.

Oculoglandular Tularemia. This is seen in less than 2% of cases. It is characterized by unilateral conjunctivitis, with regional adenopathy involving preauricular lymph nodes.

Oropharyngeal Tularemia. This is manifested as severe exudative pharyngitis, with associated cervical lymphadenitis. It has been known to cause acute glaucoma.

Typhoidal Tularemia. This is a systemic form of the disease in which no obvious entry site can be found; it occurs in approximately 10% of cases. Only 10 to 50 organisms are required to induce disease; incubation time is 2 to 10 days. Symptoms and signs may include fever, chills, constipation or diarrhea, abdominal pain, and weight loss. A 30% to 60% case fatality rate is associated with untreated typhoidal tularemia.[14]

Pulmonary Tularemia. This has symptoms similar to those of other bacterial pneumonias—fever and chills, cough (usually nonproductive), substernal burning, dyspnea, malaise, and prostration. It may result from direct inhalation of aerosolized organisms or bacteremic spread from another site.

Other Considerations

Uncommon complications of tularemia include pericarditis, meningitis, endocarditis, peritonitis, appendicitis, perisplenitis, and osteomyelitis. Guillain-Barré syndrome associated with tularemia also has been reported.

Tularemia is one of the most widely studied diseases with respect to potential biologic warfare. The United States developed an aerosolized form in the 1950s, and the Japanese allegedly contaminated prisoners with the disease in the 1930s. It was removed from the national list of notifiable diseases in 1995 but then was reinstated in view of the heightened biologic weapons threat. It is classified by the CDC as one of the six category A critical biologic diseases.[8] An aerosolized form of the bacterium would be the most likely delivery mechanism used in biologic warfare. With the release of aerosolized particles, disease would be manifested clinically as acute fever, progressive pneumonia, pleuritis, and hilar lymphadenopathy, beginning as early as 3 to 5 days after delivery. The mortality rate for untreated tularemia in general ranges from 5% to 30%, but the rate for the pulmonary form can reach 60%.[15] With appropriate antibiotic treatment, death is rare (mortality rate < 1%). Only approximately 55% of emergency departments (EDs) have been adequately educated on the recognition of and preparedness for tularemia.

Diagnostic Testing

The diagnosis of tularemia is based on clinical findings and serologic testing. Antibody titers begin to rise approximately 7 to 10 days after exposure and peak in 3 to 4 weeks. In a patient with a clinical presentation suggesting tularemia, an antibody titer of

1:160 or higher in a single specimen is diagnostic. Confirmatory evidence is provided by a fourfold or greater rise in titer in a second sample obtained 2 weeks later. Unfortunately, titers of IgG and IgM can continue to be high for up to 10 years, and cell-mediated immunity can be maintained for up to 25 years. Rapid testing with PCR assay is available,[9] and point of care analysis using an immunochromatographic approach has proven useful in testing water sources.

As for most infectious organisms, culture is the gold standard for diagnosis; however, aspiration of affected lymph nodes for culture is not routinely recommended because of the associated risk to laboratory personnel. If tularemia is suspected, the laboratory should be alerted so that appropriate precautions can be taken in specimen handling and enriched culture medium can be used.

Management

Isolation of patients with tularemia is not required. Streptomycin is the drug of choice for the treatment of all forms of tularemia, but is not widely available. When given intramuscularly in a dose of 30 to 40 mg/kg/day bid, streptomycin usually produces symptomatic improvement and resolution of fever in 1 to 2 days. After the third treatment day, half of the dose is given for a total course of 7 to 14 days. With this regimen, relapses are unusual.

Gentamicin is effective for treatment, especially in children (3 to 5 mg/kg/day for 10 to 14 days), and is more readily available.[16] Tetracycline and chloramphenicol are also effective; however, the risk of relapse is greater than that associated with the aminoglycosides. Imipenem-cilastatin, an antibiotic without nephrotoxicity, has been used successfully to treat pulmonary tularemia in a patient with acute renal failure. Ceftriaxone is not effective against *F. tularensis* infections. Prophylaxis for possible exposure requires doxycycline, 100 mg bid for 14 days. Doxycycline or ciprofloxacin prophylaxis is recommended for a large biologic attack. Ulcers and tender lymph nodes usually heal within 7 to 10 days; however, enlarged nodes occasionally develop into fluctuant sterile buboes, requiring incision and drainage after completion of the course of antibiotics. The unique ability of *F. tularensis* to attenuate host inflammatory responses has been emerging as a basis for research investigating the use of immunomodulatory agents or antibodies for adjunctive treatment.[17] There continues to be no approved vaccine for tularemia. Because of recent interest in biologic warfare, however, research on tularemia vaccines has resurged.[18]

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever (RMSF) is an acute, febrile, systemic tickborne illness caused by *Rickettsia rickettsii*. The genus *Rickettsia* is divided into the spotted fever group and typhus group. *R. rickettsii* is considered the typical representative of the spotted fever group. Twenty-six species now exist.[19]

RMSF is found in North, South, and Central America and is a nationally reportable disease. All cases are to be registered with the respective state department. As of 2010, reported cases of RMSF are categorized in the broader name of spotted fever rickettsiosis (Box 126.1).[20] The number of reported cases in the United States more than tripled between 2000 and 2007, especially in suburban areas.[21] The increase during this period was thought to be due to more widespread use of ELISA. Use of the assay has also resulted in a significantly lower case fatality rate, which could be related to the high cross-reactivity of serologic tests with more benign rickettsioses. Higher awareness and more aggressive empirical treatment of RMSF might also have contributed to the decreased fatality rate. The number of reported spotted fever cases in the United States rose 9% in 2010, which included all spotted fever rickettsioses, not just RMSF, in accordance with the surveillance changes mentioned.[22] Another rare rickettsiosis that emerged in North America in 2004 was caused by *Rickettsia parkeri*, transmitted through the Gulf Coast tick, *Amblyomma maculatum*. It is distinguished from RMSF by sometimes causing eschars or a vesicular rash.

RMSF ranges in clinical severity from mild or even subclinical illness to a fulminant disease, with vascular collapse and death within several days of onset. It is the only rickettsiosis still associated with significant mortality, causing approximately 40 deaths in the United States each year, with a mortality rate ranging from 3% to 5%, despite appropriate treatment. Before tetracycline and chloramphenicol were available, death occurred in as many as 30% of cases in the 1930s. The highest mortality rates occur in patients between the ages 5 and 9 years or older than 70

BOX 126.1

Diagnostic Criteria for Spotted Fever Rickettsiosis (*Rickettsia* spp.)

- Clinical criteria
  - Any reported fever and one or more of the following: rash, eschar, headache, myalgia, anemia, thrombocytopenia, or hepatic transaminase level elevation
- Laboratory-confirmed
  - Serologic evidence of a fourfold change in immunoglobulin G (IgG)–specific antibody titer reactive with *Rickettsia rickettsii* or other spotted fever group antigen by indirect immunofluorescence assay (IFA) between paired serum specimens (one taken in the first week of illness and a second 2 to 4 weeks later) *or*
  - Detection of *R. rickettsii* or other spotted fever group DNA in a clinical specimen via amplification of a specific target by PCR assay, *or*
  - Demonstration of spotted fever group antigen in a biopsy or autopsy specimen by immunohistochemistry (IHC), *or*
  - Isolation of *R. rickettsii* or other spotted fever group *Rickettsia* from a clinical specimen in cell culture
- Laboratory-supportive
- Has serologic evidence of elevated IgG or immunoglobulin M (IgM) antibody reactive with *R. rickettsii* or other spotted fever group antigen by IFA, enzyme-linked immunosorbent assay (ELISA),[a] dot ELISA, or latex agglutination
- Exposure
  - Exposure is defined as having been in a potential tick habitat within the 14 days preceding the onset of symptoms. The patient's occupation should be recorded if relevant to exposure. A history of a tick bite is not required.
- Case classification
  - Suspected: A case with laboratory evidence of past or present infection but no clinical information available (eg, laboratory report)
  - Probable: A clinically compatible case (meets clinical evidence criteria) that has supportive laboratory results
  - Confirmed: A clinically compatible case (meets clinical evidence criteria) that is laboratory-confirmed

From Centers for Disease Control and Prevention, National Notifiable Diseases Surveillance System: Spotted fever rickettsiosis (*Rickettsia* spp.) 2010 case definition. www.cdc.gov/NNDSS/script/ casedef.aspx?CondYrID=853&DatePub=2010-01-01.

[a]**NOTE:** Current commercially available ELISA tests are not quantitative, cannot be used to evaluate changes in antibody titer, and hence are not useful for serologic confirmation. IgM tests are not strongly supported for use in the serodiagnosis of acute disease because the response might not be specific for the agent (resulting in false-positives) and the IgM response might be persistent. Complement fixation (CF) tests and older test methods are neither readily available nor commonly used. CDC uses in-house IFA IgG testing (cutoff ≥ 1:64), preferring simultaneous testing of paired specimens, and does not use IgM results for routine diagnostic testing.

years, among Native Americans, and among immunosuppressed patients. In the South Atlantic United States, mortality reaches 9% in patients older than 70 years.[23] The median time between onset of illness and death is 9.5 days, whereas death occurs in hospitalized patients in a median time of 3 days.[14]

The recorded history of RMSF suggests that the disease was present at least before the European settlement of western North America among inhabitants of wooded Rocky Mountain regions. Early terms used to name the disease included *tick fever* and *black measles*. In 1899, RMSF was described as "an acute, endemic, noncontagious but probably infectious, febrile disease, characterized by a continuous moderately high fever, severe arthritic and muscle pains, and a profuse petechial or purpuric eruption in the skin, appearing first on the ankles, wrists, and forehead, but rapidly spreading to all parts of the body."[24] In 1906, the causative organism, *R. rickettsii,* was identified by Howard T. Ricketts, who also described the importance of the tick vector in transmission to humans.

Although RMSF was first described in Montana and Idaho, it is now relatively rare in the Rocky Mountain states. Endemic in all 48 contiguous states except Maine, the disease continues to be most prevalent in the southeastern United States. RMSF has been reported in Canada, Central America, Mexico, and South America but never outside the Western Hemisphere. In 1987, four cases of RMSF were reported among residents of the Bronx in New York City; none of the affected persons had recently traveled to an area known for endemic disease, raising the possibility that other urban foci of RMSF may exist.

RMSF also tends to be focally endemic, with clustering of cases within a larger endemic area that may correspond to islands of infected ticks. These areas, ecologically distinct from surrounding areas, may be ideally suited to ticks; they usually consist of wild open fields, deciduous forests with thick ground cover and poor water drainage, or uncultivated areas. Geographic clusters of severe disease have been reported.[25] In areas with frequent occurrence of RMSF (Oklahoma, North and South Carolina, Tennessee, Pennsylvania, Missouri, Arkansas), an infectivity rate of 2% to 15% of the tick population has been reported. North Carolina and Oklahoma carry the highest incidence rates (35% of all cases) for RMSF.

R. rickettsii organisms are obligate intracellular bacteria with tropism for human endothelial cells. They often occur in pairs and possess a cell wall similar in structure and chemical composition to that of gram-negative bacteria. *R. rickettsii* contain RNA and DNA and, in contrast with other rickettsial organisms, can invade the nucleus as well as the cytoplasm.

The American dog tick, *Dermacentor variabilis,* and the Rocky Mountain wood tick, *Dermacentor andersoni,* have been the vectors responsible for human RMSF cases in the United States to date. However, the common brown dog tick, *Rhipicephalus sanguineus,* has emerged as a third vector. *R. sanguineus* has been the main RMSF vector in Mexico and Central America. *Amblyomma imitator,* in the genus of the Lone Star tick, has been implicated as yet another vector because *R. rickettsii* has been found in its eggs.[26]

Ticks feed on virtually any available warm-blooded animal and human; the occurrence of *R. rickettsii* in the United States does not depend on the presence of any given order of mammal. Domestic dogs infected with *R. rickettsii* can demonstrate clinical illness similar to that seen in humans. Although dogs do not play an important role in the amplification cycle of RMSF, they can serve as a conduit for infected ticks, carrying them into close contact with pet owners. Dogs may serve as sentinels for RMSF in humans. A high prevalence of rickettsial antibodies in stray dogs in Arizona was thought to be a major factor in the 70 cases and 8 deaths from RMSF reported there between 2003 and 2008.[27] It has been speculated that the reason Native Americans have a fourfold greater incidence and case fatality rate than other ethnic groups is a result of their more frequent exposure to free-roaming dogs.[28] The deadliest spotted fever, Brazilian spotted fever, is also caused by *R. rickettsia*. The capybara, a common mammal in Brazil, appears to be the main reservoir through the vector tick *Amblyomma cajennense*.[29]

Communication between physicians and veterinarians is important when cases of zoonotic diseases are detected. Humans serve only as accidental participants in the cycle of infection. A retrospective study has revealed that none of 10 recipients of blood products found to be from donors with confirmed or probable RMSF contracted the disease.[13]

Pathophysiology

After introduction of *R. rickettsii* into the host by the tick vector, the organisms invade and multiply in the vascular endothelial cells. They then enter deeper areas of the vessel walls and infect vascular smooth muscle. Rickettsial organisms move from cell to cell by actin-based motility. Damage to endothelial cells not only exposes subendothelium but also releases tissue plasminogen activator and von Willebrand factor, thereby causing microhemorrhage, microthrombus formation, and increased vascular permeability. In addition, antibody forms, with antigen activating the complement system (type III immune response), and a cellular response is recruited.

These widespread vascular lesions form the basis for most of the clinical features associated with RMSF. Hypotension, edema, and increased extravascular fluid space result from the increased small-vessel permeability. The early rash results from the vasculitis and associated changes in permeability; later petechial and hemorrhagic lesions are secondary to the vasculitis and thrombocytopenia. Microinfarcts and focal lesions develop in various organs, including the brain, heart, lungs, kidneys, adrenal glands, liver, and spleen. Rickettsial encephalitis and diffuse microinfarcts are usual features of central nervous system involvement. An interstitial pneumonitis caused by direct lung invasion by the organism may occur, and ARDS can ensue. Acute renal failure and hypovolemic shock, the primary causes of death, can occur as early as the second week of illness.

Clinical Features

Children from 5 to 9 years of age are the most common victims of RMSF. Two-thirds of all cases are in children younger than 15 years. More than 90% present with a fever and rash. A history of tick bite or presence in possible tick-infested areas is elicited in 60% to 70% of all patients with RMSF, although only 49% of the pediatric population reports a bite. The incubation period ranges from 2 to 14 days, with a mean of 7 days. A short incubation period may indicate a more serious infection. Factors that bring higher risk of death include delayed onset of rash, glucose-6-phosphate dehydrogenase deficiency, hepatomegaly, neurologic deficits, renal insufficiency, increased period between symptoms and antibiotic treatment, and lack of tick bite history.

Onset of symptoms usually is generally abrupt but may be gradual in approximately one-third of patients. Early symptoms are nonspecific and similar to those of many acute infectious diseases, making early diagnosis difficult. Typical patients experience sudden onset of fever, severe headache, myalgias, prostration, nausea, and vomiting. Tenderness may be noted in large muscle groups (Table 126.4). As many as 80% of patients may have gastrointestinal symptoms secondary to myositis of the abdominal wall. Fever (temperature usually > 102° F [39° C]) is nearly always present during the first 2 to 3 days of illness and may precede other signs by 1 week or more. On occasion, the onset of illness is mild, with lethargy, headache, anorexia, and low-grade

TABLE 126.4

Symptoms and Signs of Rocky Mountain Spotted Fever[a]

SYMPTOM OR SIGN	FREQUENCY DURING ILLNESS (%)	
	Any Time	First 3 Days
Fever (temperature of 37.8° –38.9° C [100°–102° F])	99	73
Headache, mild to moderate	91	71
Fever (≥102° F [38.9° C])	90	63
Any rash	88	49
Myalgia, mild to moderate	83	57
Rash, maculopapular	82	46
Rash, palms and soles	74	28
Triad of fever, rash, history of tick exposure	67	3
Nausea and vomiting	60	38
Headache, severe	57	40
Abdominal pain	52	30
Rash, petechial and hemorrhagic	49	13
Myalgia, severe	47	25
Conjunctivitis	30	13
Lymphadenopathy	27	13
Stupor	26	6
Diarrhea	19	9
Edema	18	3
Ataxia	18	7
Meningismus	18	5

[a]In 262 patients.
From Helmick CG, Bernard KW, D'Angelo LJ: Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. J Infect Dis 150:480–488, 1984.

fever; these patients may remain ambulatory. Although the triad of fever, rash, and tick exposure traditionally was seen in only approximately 3% to 18% of cases, more recent data have shown that it is found in up to 45% of children with the disease. An extreme complication of RMSF is gangrene, which probably is induced by small-vessel occlusion.

Cutaneous Manifestations

Vasculitis secondary to rickettsial invasion of vascular endothelial cells causes the rash commonly associated with RMSF; however, the rash reportedly is absent in 4% to 16% of laboratory-confirmed cases, referred to as Rocky Mountain spotless fever. In addition, the rash may go unnoticed in dark-skinned patients. It usually appears on the third to fifth febrile day but can emerge as early as the second and as late as the sixth day. The initial lesions generally are restricted to the ankles and wrists, spreading to the palms and soles. The rash then spreads centripetally to the forearms, arms, legs, thighs, and trunk. The face can be involved, although it is usually spared. Despite the common belief that the palms and soles are critical for diagnosis, they are not consistently involved; rash on the palms and soles is reported in approximately 50% of cases. Involvement of the scrotum or vulva can be an evasive clue for RMSF. The rash of RMSF typically begins as 1- to 5-mm blanchable pink to bright red discrete macules that may be pruritic (see Fig. 126.7). At this initial stage, the lesions fade when pressure is applied and are not palpable. A warm compress applied to the area enhances the rash. After 6 to 12 hours, the rash spreads centripetally. After 2 to 3 days, the rash becomes maculopapular and changes to a deeper red; at this stage, skin changes can be appreciated on light palpation. By approximately the fourth day, the rash becomes petechial and no longer fades with applied pressure. Applying tourniquets for several minutes or taking the blood pressure may cause additional petechiae to form distal to the site of occlusion (Rumpel-Leede phenomenon). The lesions occasionally coalesce to form large ecchymotic areas that may slough and form indolent ulcers (Fig. 126.8).

Prompt institution of specific therapy can cause the initial nonfixed lesions to disappear rapidly, unlike the later fixed lesions. Patients who have had the typical rash may exhibit brownish discolorations at the site during the convalescent period.

Cardiopulmonary Manifestations

Echocardiographic evidence of decreased left ventricular contractility secondary to myocarditis is commonly seen and often is detectable even before clinical signs of RMSF appear. Clinical manifestations of left ventricular dysfunction are uncommon, however, and hypotension and pulmonary edema, when present, usually have noncardiogenic causes. Chest radiographs may demonstrate cardiac enlargement. Electrocardiographic changes include low-voltage, nonspecific ST-T changes, first-degree AV block, dysrhythmias (eg, sinus and nodal tachycardia, paroxysmal atrial tachycardia, atrial fibrillation), and left ventricular hypertrophy. Most cardiac abnormalities are transient, but persistent echocardiographic changes have been described. Decreased systolic function, elevated serum cardiac markers, no finding of vascular lesions, and a fourfold rise in antibody titers are consistent with myocarditis from RMSF.

Interstitial pneumonitis and increased pulmonary capillary permeability may result from infection of the pulmonary capillaries with rickettsiae. Nonproductive cough and dyspnea secondary to pneumonitis are sometimes seen on presentation. Chest radiographic abnormalities are identified in approximately 25% of patients. These abnormalities include interstitial infiltrates, patchy alveolar infiltrates, pleural effusions, and cardiomegaly with pulmonary edema. Pulmonary consolidation is rare. In severe cases, progression to noncardiogenic pulmonary edema and ARDS may occur.

Neurologic Manifestations

Neurologic manifestations of RMSF range from mild headache and lethargy to seizures and coma. Acute disseminated encephalomyelitis has been described. Headache, generally severe, is common, occurring in 50% to 90% of cases. Meningismus is present in 16% to 29% of patients. The CSF may be normal or show a slight protein elevation and pleocytosis of lymphocytes and polymorphonuclear cells (usually 8 to 35 cells/mL). The CSF glucose level and opening pressure usually are normal. Resolution of eosinophilic meningitis during RMSF after appropriate antibiotic treatment has been reported. Less than 40% of patients have a positive CSF finding.

Cerebral thrombovasculitis may cause focal neurologic deficits, which usually are transient. Seizures can occur, especially during the acute phase of the illness. Generalized cerebral dysfunction ranging from lethargy to coma can occur secondary to systemic toxicity (eg, fever, hypotension, hyponatremia) or vasculitic lesions involving the central nervous system. Coma is a late finding in patients with severe disease and is seen in less than 10%

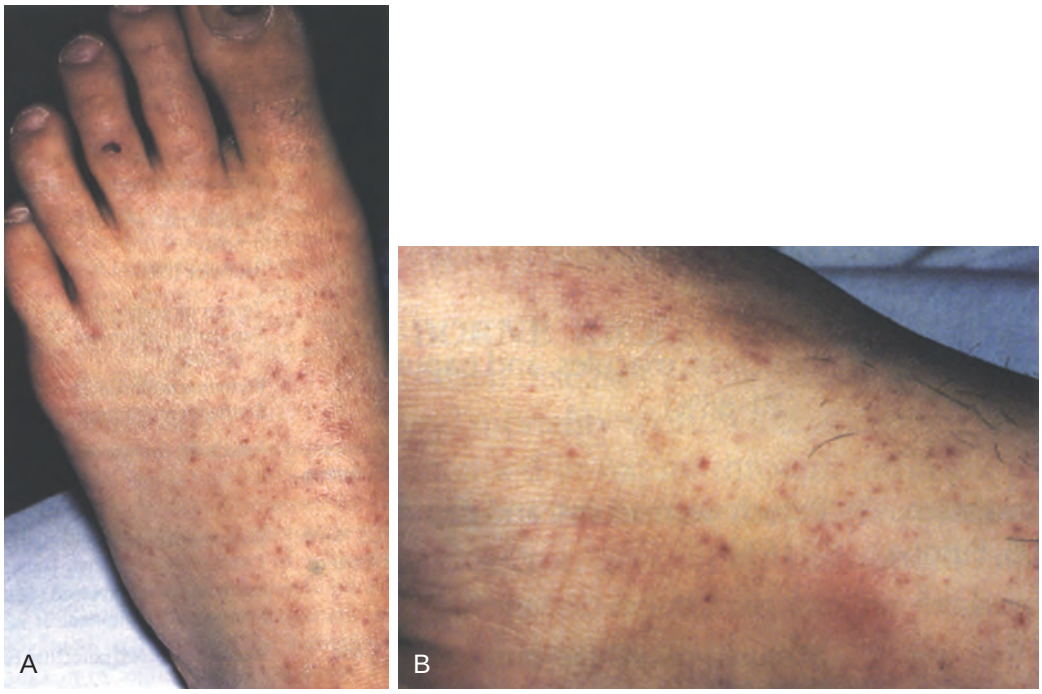


Fig. 126.8. A, Exanthem of Rocky Mountain spotted fever. **B,** Exanthem of Rocky Mountain spotted fever, close-up view. (From McGinley-Smith DE, Tsao SS: Dermatoses from ticks. J Am Acad Dermatol 49:363–392, 2003.)

of cases. Some reports have described patients who remain alert but are amnesic for their illness after recovery. Other reported neurologic manifestations include transient deafness, tremor, rigidity, athetoid movements, paralysis, ataxia, opisthotonos, aphasia, and blindness. In general, neurologic signs abate without residual deficits, and permanent neurologic deficits are rare. Behavioral disturbances and learning disabilities have been reported after recovery from RMSF-associated coma in children.

Differential Diagnosis

Delayed diagnosis or misdiagnosis is the principal reason for the historically significant mortality associated with RMSF. Clinical diagnosis is difficult, especially early in the course of the illness, because of its nonspecific presentation. For avoidable deaths to be prevented, a diagnosis of RMSF should be considered in any patient with an unexplained febrile illness, with or without a rash and headache, even in the absence of a history of tick bite or travel to an area known to be endemic for the disease. The emergency clinician should remember to ask routinely about recent tick bites, especially when assessing children with unexplained febrile illness, because parents do not always spontaneously provide this important information. An atypical presentation or manifestation of RMSF also should be considered during the differential diagnosis, including the following: (1) absence of a rash (Rocky Mountain spotless fever) or late appearance of a rash (Fig. 126.9); (2) predominant gastrointestinal features or abdominal pain suggestive of an acute condition in the abdomen; (3) cough and pulmonary congestion suggestive of pneumonitis; and (4) meningismus suggestive of viral meningitis.[30] A presumptive diagnosis is advised, with the initiation of specific therapy, well before specific confirmatory laboratory values are available.

A wide variety of other infections with similar exanthems can be confused with RMSF.[31] The most common include meningococcal infection, measles (rubeola) and atypical measles, gonococcemia, infectious mononucleosis, toxic shock syndrome, and enteroviral infections. Less common diseases include dengue fever, leptospirosis, murine typhus, and epidemic typhus. *R. parkeri* rickettsiosis should be considered.

Fig. 126.9. Late appearance of the rash of Rocky Mountain spotted fever on the lower extremity. (Courtesy Dr. Theodore Woodward.)

Diagnostic Testing

Most immediately available laboratory tests provide little help in the diagnosis of RMSF. Early in the course of the illness, the

diagnosis is based primarily on clinical evidence, so epidemiologic features should be correlated with clinical signs and symptoms. The initial presentation of RMSF is similar to that of many acute febrile infectious diseases, and almost invariably a therapeutic decision must be made on clinical grounds alone, without the luxury of confirmatory laboratory evidence. Abnormalities such as thrombocytopenia, hyponatremia, and acute renal failure may be detected by routine laboratory tests, but they are nonspecific and unhelpful diagnostically. Up to 30% of patients present with anemia. A definitive diagnosis of RMSF requires positive results on one or more of several tests—serologic study, skin biopsy, or direct isolation and identification of the organism (see Box 126.1).

Skin Biopsy

Identification by immunofluorescent assay (IFA) and immunoperoxidase staining of *R. rickettsii* in biopsy specimens of the rash from patients with suspected RMSF are the best rapid diagnostic tests currently available. In experienced laboratories, the diagnosis of RMSF can be confirmed as soon as 4 hours after the specimen is obtained. The organisms can be detected as early as day 3 of clinical illness and as late as day 10. Unfortunately, this technique can be used only when a rash is visible for accurate localization of the biopsy site. Biopsy specimens generally are obtained with a 3-mm punch in the center of the skin lesion. Immunofluorescent demonstration of rickettsiae in frozen sections of skin biopsy specimens has a sensitivity of 70%. Results of immunohistochemical staining of tissues at autopsy were positive in all fatal cases in one study, whereas IFA results were negative in most cases. Failure to obtain a biopsy specimen of a rickettsial cutaneous lesion or failure to obtain sections through its center is associated with false-negative results. Treatment with antirickettsial drugs for 24 hours does not appreciably alter the sensitivity of the test; however, after 48 hours, rickettsiae are substantially reduced in number.

Serologic Studies

Rickettsial infection can be confirmed by demonstration of an antibody rise in paired sera. Even with the most sensitive serologic tests, however, elevations in antibody titers do not occur until approximately 5 to 7 days after the onset of initial symptoms. Accordingly, serodiagnosis is retrospective. It is achieved by comparing acute serum, which typically yields negative findings, with convalescent serum, which yields positive results for antibodies. The indirect IFA generally is considered to be the reference standard for RMSF diagnosis and is the test currently used by the CDC and most state public health laboratories. It has a high specificity and sensitivity (94%). IFA can be used to detect IgG or IgM antibodies. An RMSF latex agglutination test that reportedly gives a turnaround result in less than 24 hours is available in selected laboratories.[13]

A prior study has shown a 12% seroprevalence, with antibody titers of 1:64 or higher, in the pediatric population in the southeastern and south central regions of the United States. Accordingly, clinical correlation with titers in these regions is critical.

Convalescent-stage blood samples are best obtained 2 to 3 weeks after the onset of clinical illness. Antibiotic therapy does not affect the time of appearance of antibodies or their ultimate titer if this treatment is begun several days after the onset of illness. However, if antibiotic therapy is initiated earlier in the course of the illness, the rise in titers can be delayed for 4 weeks or more. Under these circumstances, antibody titers should be tested again at 4 to 6 weeks after the onset of illness.

Nested PCR testing with a turnaround time between 1 and 2 days has been used but is not specific for individual rickettsial species. Real-time PCR assays that can be completed in 1 hour and are 100% specific for RMSF have been developed but are not readily available.[32]

Isolation of Organism

For most pathogenic infections, the standard diagnostic criterion is isolation and identification of the causative organism from the patient's blood or tissues. This is seldom attempted in rickettsioses, however, because the isolation procedures are time-consuming, expensive, and hazardous to laboratory personnel. In addition, primary isolation of rickettsiae by inoculation in the yolk sac of a chick embryo usually fails because of the small number of organisms in the patient's blood.

Management

Treatment of RMSF consists of antibiotic therapy, supportive care, and possibly administration of steroids. An understanding of the underlying pathophysiologic changes and appreciation of the systemic complications that can occur in the patient afflicted with RMSF are necessary for the formulation of a balanced therapeutic regimen. The course of the disease can be complicated by circulatory collapse, coma, renal failure, and electrolyte imbalances. Although these complications are often absent in the mildly ill patient, for whom antibiotic therapy alone usually suffices, they should be anticipated in the seriously ill patient, especially if the patient is first seen late in the disease course.

The most important factor contributing to the persistent case fatality rate of 5% is delayed administration of specific antibiotic therapy. Without appropriate treatment, the fatality rate rises to 25%. For a select group of early-stage, mildly ill patients, outpatient therapy with oral antibiotics can be successful if the patient is reliable and close follow-up observation is arranged. More severely ill patients in whom the diagnosis is uncertain should be hospitalized for the administration of IV antibiotics.

Supportive Care

Major complications of RMSF, such as shock, congestive heart failure, disseminated intravascular coagulation, and ARDS, should be anticipated and standard supportive measures instituted when appropriate. Circulatory collapse is common in patients with severe illness and is a major contributor to morbidity and mortality in RMSF. Hypotension unresponsive to fluid administration may require the use of vasopressors, such as dopamine. In the critically ill patient with widespread vasculitis, however, a delicate balance exists between maintenance of effective circulating volume and excessive leakage of fluids into the tissues, including the lungs and brain. Under these circumstances, the excessive administration of IV fluids can be catastrophic. Isolation of the patient is unnecessary unless the diagnosis is still uncertain and other highly communicable illnesses, such as meningococcemia and measles, have not been excluded.

Antibiotics

Antibiotic therapy is most effective when initiated during the early stages of disease, coincident with the initial appearance of the rash. Although data from randomized clinical trials about antibiotic selection for RMSF are lacking, doxycycline is still widely regarded as the therapeutic agent of choice for most patients, including children.[33] Chloramphenicol should be considered only for patients in whom tetracyclines have caused significant adverse events and for pregnant women, except those who are near term. The recommended doses of doxycycline and chloramphenicol are summarized in Table 126.5.

TABLE 126.5

Antibiotic Therapy for Rocky Mountain Spotted Fever[a]

PATIENT	DOXYCYCLINE[b] (ORAL OR IV)	CHLORAMPHENICOL[c] (ORAL OR IV)
Adult	100 mg bid; consider initial loading dose of 200 mg IV for seriously ill patients	50–75 mg/kg/day, divided q6h
Child (<45 kg)	2.2 mg/kg PO q12h	50–75 mg/kg/day, divided q6h

[a]Continue treatment at least 3 days after fever subsides or until unequivocal clinical improvement is seen; minimum course, 7 to 14 days.
[b]Doxycycline should not be given to pregnant women.
[c]Chloramphenicol should not be given to patients with thrombocytopenia; maximum of 1 g/day for children.
From Centers for Disease Control and Prevention, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases: Rocky Mountain spotted fever, www.cdc.gov/rmsf/ symptoms/index.html#treatment; and Cunha BA: Clinical features of Rocky Mountain spotted fever. Lancet Infect Dis 8:143–144, 2008.

The American Academy of Pediatrics and CDC recommend doxycycline as the agent of choice for treatment of RMSF in children of all ages.[15] The risk of cosmetically perceptible tooth staining appears to be small for a single course of treatment and is subordinate to the potential lethality of this illness.[34]

The effectiveness of therapy depends on the duration of therapy and interval between the onset of illness and the initiation of therapy. Treatment should begin as early as possible and continue for 7 to 10 days or until the patient is afebrile for 2 to 5 days. Patients who are clinically ill should be hospitalized for parenteral antibiotic treatment. Response to treatment, as manifested by decreasing fever and subsiding rash, generally occurs 36 to 48 hours after antibiotic therapy is begun. Resistance to chloramphenicol or tetracyclines has not been reported. Penicillin, erythromycin, cephalosporins, aminoglycosides, clindamycin, and sulfonamides are ineffective against RMSF.[35] In fact, empirical use of these agents for presumed bacterial infections could permit progression of the illness.

Symptom overlap between early meningococcal infection and RMSF frequently leads to both diagnoses being considered simultaneously. After blood and CSF culture specimens are obtained, empirical antibiotic coverage with ceftriaxone plus doxycycline should be administered.

On occasion, secondary bacterial infection from the RMSF rash may occur. Although sulfonamides have become a mainstay for the empirical treatment of MRSA skin infections, the use of these agents should be avoided in RMSF patients because their mechanism of inhibiting *p*-aminobenzoic acid may worsen the primary RMSF infection. The role of the new quinolones as potential replacements for doxycycline and chloramphenicol in the treatment of RMSF is as yet unproved. At present, no vaccine is available for RMSF.

Corticosteroids

The use of steroids in RMSF is controversial and is not routinely recommended. However, these agents should be considered for severe cases of RMSF complicated by extensive vasculitis, encephalitis, and cerebral edema. In these critically ill patients, short-term, high-dose steroid therapy is recommended, along with concomitant specific antibiotic therapy.

Q FEVER

Q fever was first described in 1937 in Australia as an occupational disease of abattoir workers and dairy farmers. Cattle, sheep, goats, and ticks are the primary reservoirs of the causative rickettsia, *Coxiella burnetii,* but many other species may be infected. The disease is now endemic worldwide, although it is rare in Scandinavian countries. The southern area of the Netherlands experienced a serious outbreak and reported more than 4000 cases since 2007 and 500 cases, with 11 deaths, in 2010 alone. France and Australia have significantly more cases than the United States. In the United States, the Midwest and California have had the highest incidences of Q fever. More than 30 cases have been seen in US military personnel deployed in Iraq and Afghanistan. Approximately 80% of cases of Q fever occur in males.[36]

Pathophysiology

C. burnetii is extremely infectious for humans and animals; a single inhaled organism is sufficient to initiate infection in guinea pigs and probably in humans as well. The Q fever rickettsiae are extremely resistant to desiccation and physical and chemical agents and can survive for long periods in an inanimate environment. Consequently, it is classified as a category B biologic warfare agent by the CDC and has been a nationally notifiable disease since 1999.[37] The organism's infectivity and estimated casualty rate have been judged to be comparable with those of anthrax. Humans most commonly are infected by inhalation of aerosolized particles from contaminated environments. Patients with Q fever rarely can recall a history of tick bite. The Rocky Mountain wood tick, *D. andersoni*, is the only currently known tick vector.

Clinical Features

The incubation period of Q fever ranges from 14 to 39 days, with an average of 20 days. Up to 60% of initial infections are asymptomatic. The acute form of the disease includes clinical manifestations such as severe retrobulbar headache, fever with temperatures to 40° C (104° F) or higher, shaking chills, general malaise, myalgia, and chest pain. Although Q fever is widely regarded as primarily a respiratory disease, the reported incidence of pulmonary involvement varies, ranging from 0% to 90%. The reasons for this reported variation are unclear, but explanations include geographic strain variation, plasmids that may regulate virulence, and source, route, and dose of the agent. Hepatic involvement may be common, but liver dysfunction is usually minimal. Osteomyelitis in children, acute renal failure, and lymphocytic meningitis secondary to *C. burnetii* have been described.

Q fever also may be a chronic infection, with or without an antecedent acute episode. Clinical syndromes with the chronic form of the disease include granulomatous hepatitis and culture-negative endocarditis. Endocarditis has been documented in up to 68% of patients with chronic Q fever; the mortality rate for this group approaches 25%. Q fever accounts for 3% to 5% of all cases of endocarditis. Most patients with Q fever in whom endocarditis develops have a history of valvular heart disease, particularly affecting the aortic valve. These patients should be especially cognizant of the potential hazards of Q fever infection and should be restricted from certain at-risk occupational settings. Patients with aneurysms and vascular grafts also are at risk.

Human fetal demise and deaths have been attributed to *C. burnetii* infection. Persons infected with human immunodeficiency virus (HIV) are at increased risk for contraction of Q fever.

Diagnostic Testing

The diagnosis of Q fever should be suspected in any patient with a severe febrile illness without obvious cause, especially someone who has had recent contact with sheep, cattle, goats, or animal byproducts. Because of the laboratory hazards associated with the cultivation of Q fever rickettsiae, isolation of *C. burnetii* is not recommended for routine diagnosis. Rather, serologic studies such as IFA and ELISA are the preferred diagnostic tests, but the results are not identifiable until 2 to 3 weeks after the onset of illness.

C. burnetii displays an antigenic phase variation. In patients with acute Q fever, phase II antibodies dominate the humoral immune response and are detectable by the second week of illness, whereas phase I antibodies are prominent only in patients with chronic Q fever. Confirmation of a Q fever case requires (1) a fourfold increase in IgG titers between acute and convalescent samples or the presence of IgM phase II antibodies, (2) a positive PCR test result, (3) the culture of *C. burnetii* from a clinical specimen, or (4) the positive immunostaining of the organism in tissue. Measurement of IgA and IgG together has been useful in the diagnosis of endocarditis. The finding of granulomatous changes on bone marrow biopsy can be characteristic of Q fever in patients with osteomyelitis.

Management

Uncomplicated acute Q fever is treated with doxycycline (200 mg once daily for 2–3 weeks). Acute disease with concomitant valvular heart disease is treated with doxycycline (200 mg once daily) plus hydroxychloroquine (600 mg once daily) for 1 year. Chronic sufferers should be given the same regimen for 1.5 to 3 years. Combination therapy with doxycycline and hydroxychloroquine has been shown to be effective for treatment of endocarditis in HIV-infected patients. Strong evidence has recommended combination therapy for endocarditis for 18 and 24 months in patients with native valves and prosthetic valves, respectively, when serologic results are suboptimal.[38] Cotrimoxazole is the recommended alternative treatment. Quinolones, some macrolides, and rifampin may also be effective.[39] Treatment of pregnant women with Q fever with long-term cotrimoxazole, although not always curative, has been shown to decrease complications to the fetus.

In mass casualty situations, prophylaxis is accomplished with 5 to 7 days of doxycycline.[40] Most acute Q fever infections resolve without treatment, but the risk of chronic infection makes treatment advisable. The mortality rate is less than 1% in untreated patients and lower still in those treated with antibiotics. The prognosis is worse in patients with protracted illness and hepatic involvement or endocarditis. Inactivated whole-cell vaccines for Q fever have proven to be effective for as long as 5 years. Vaccination can afford considerable protection to slaughterhouse and dairy workers and others at risk.[41,42] Information on the handling of suspected or confirmed exposure to *C. burnetii* or bioterrorist threats can be found on the CDC website.

EHRLICHIOSES

There are currently two major forms of human ehrlichiosis in the United States—human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), caused by the bacteria *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum,* respectively. In 2001, restructuring of the *Ehrlichia* phylogenetic branches placed the previously known bacteria of human granulocytic ehrlichiosis into the genus *Anaplasma*—hence, the revised name. Both genera, *Ehrlichia* and *Anaplasma,* are now considered to be in the tribe Ehrlichieae, family Anaplasmataceae, but are still collectively referred to as being in the group of diseases called ehrlichioses. Before 1986, *Ehrlichia sennetsu* was the only member of the genus of these organisms thought to infect humans, having been isolated in Japan in 1954 as the causative agent of sennetsu fever, a mononucleosis-like illness. A third species, *Ehrlichia ewingii,* has been shown to cause human disease in the United States. HME was discovered in 1986 and HGA (previously human granulocytic ehrlichiosis) in 1994. Both have been identified as emerging diseases by the CDC and are nationally notifiable diseases, reportable through the appropriate state departments.

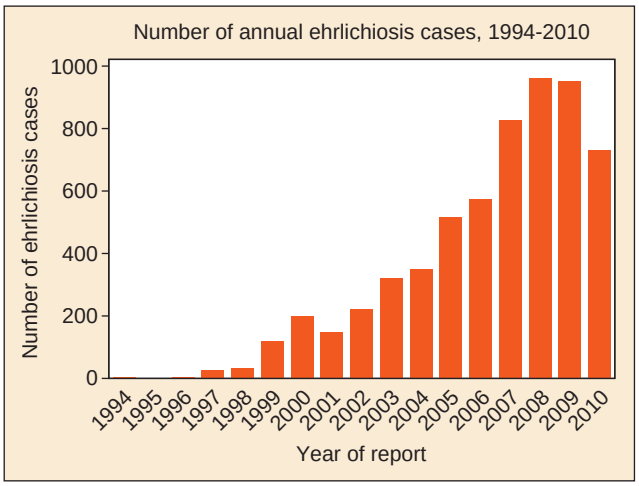


Fig. 126.10. Number of human cases of ehrlichiosis reported to the CDC annually from 1994 through 2010. The number increased steadily from 200 in 2000, when the disease became nationally notifiable, to 961 in 2008, and then decreased significantly from 944 in 2009 to 740 in 2010. update? (From Centers for Disease Control and Prevention: Ehrlichiosis: statistics and epidemiology. www.cdc.gov/ehrlichiosis/stats.)

More than 1220 cases of *E. chaffeensis* were reported in the United States between 1986 and 1997. From 1999 through 2001, the CDC collected a mean number of 81 and 190 cases, respectively, for HME and HGA. Since then, the number of cases has increased dramatically, as indicated on Fig. 126.10.[43] Seroprevalence rates up to 13% for *E. chaffeensis* in children in the southeast and south central United States and 3% to 15% for *A. phagocytophilum* in adults in New York and Wisconsin have strongly suggested that these diseases are highly underdiagnosed, underreported, or both. Misclassification from failure to confirm *Anaplasma* serologically most likely has led to underreporting of this disease.

Both diseases peak around June through August. High-risk populations are similar to those at high risk for Lyme disease, including those living in endemic areas or having frequent contact with wildlife or rural wooded areas. HME has been reported predominantly in the south central and southeastern United States; HGA mostly is found in the upper Midwest, New England, parts of the Mid-Atlantic states, northern California, and many parts of Europe.

Pathophysiology

The causative agents in the ehrlichioses are gram-negative, obligate, intracellular, rickettsia-like coccobacilli. Transmitted from the midgut and salivary glands of their tick vectors, these organisms reside in specific circulating leukocytes in human and other mammalian hosts. Reservoirs include the white-tailed deer and white-footed mouse. *Ehrlichia canis* is the common pathogenic species in dogs. The species *Ehrlichia equina* has been isolated in

California elk. HME, transmitted by the Lone Star tick, *A. americanum,* is caused by the organism *E. chaffeensis* (named for Fort Chaffee, Arkansas), which invades monocytes. *Ehrlichia ewingii* and *Ehrlichia muris* are also now known to be causative organisms.[44] *E. chaffeensis* has been isolated from *I. pacificus* ticks in California. *A. phagocytophilum* invades neutrophils (granulocytes), causing HGA and, in the United States, is transmitted by the black-legged tick, *I. scapularis*, and its West Coast counterpart, the western black-legged tick, *I. pacificus*. Deer, elk, and wild rodents are the main reservoirs for *Anaplasma*. Both ticks also are the vectors for Lyme disease. *A. phagocytophilum* has been detected in significant numbers in various *Ixodes* human tick species in mainland Portugal, Italy, and Japan. Two cases of HGA in Italy have been reported.

Clinical Features

The clinical presentations of HME and HGA are similar and, for case management, it is not necessary to differentiate between the two illnesses. The average time to onset of symptoms (for HME) from tick discovery is 9 days but ranges from 0 to 34 days. More than 90% of patients with HME report a history of tick bite or tick exposure. Ehrlichiosis characteristically is manifested with abrupt onset of fever, headache, myalgia, and shaking chills. Other, less frequent manifestations include nausea, vomiting, diarrhea, abdominal pain, cough, and confusion. Leukopenia, thrombocytopenia, and elevated liver function test values can be seen in 50% to 90% of patients.

Rashes occur in approximately one-third of patients with HME but in only 2% to 11% of those with HGA. In a small series of pediatric patients (average age, 7.4 years) with HME, a rash rate of 67% was found. Most of these patients suffered permanent cognitive or other neurologic damage.

Ehrlichiosis (HME) also has been associated with optic neuritis.[122] ARDS, meningitis, pancarditis, renal failure, and disseminated intravascular coagulation have been associated with the ehrlichioses. Case fatality rates vary between studies but range from 0.5% to 3% for both diseases, with HGA usually reported as the lower of the two. Approximately 45% of patients with HGA require hospitalization, although almost all recover without residual problems. HME has been associated with hemophagocytic lymphohistiocytosis.[45]

Diagnostic Testing

For HME and HGA, the initial diagnosis is based largely on clinical presentation. With most tests, the diagnosis will be retrospective; results are rarely available immediately. The most common mode of diagnosis is confirmation of acute and convalescent antibodies with IFA. Enzyme immunoassay and confirmatory tests with Western blot have been developed but are not readily available. They provide only positive or negative results without titers. PCR testing for DNA fragments, although also not as readily available in most institutions, probably is most reliable in the acute phase of illness (at 1 week after onset of symptoms).[46] Diagnostic serologic testing is available at the CDC through state health departments.[47]

Laboratory criteria required in the CDC's 2008 case definition to establish the presence of HME or HGA include detection of *E. chaffeensis* or *A. phagocytophilum,* respectively, through the use of the following diagnostic tests: (1) fourfold change in antibody titer to the organism antigen by IFA in paired serum samples; (2) positive result on PCR assay and confirmation of organism-specific DNA; (3) identification of morulae in leukocytes and a positive titer to the organism antigen; (4) immunostaining of the organism's antigen in a biopsy or autopsy specimen; or (5) culture of the organism from a clinical specimen. All tests require compatible clinical findings. Most patients with acute ehrlichiosis have antibody titers higher than 1:160.[48]

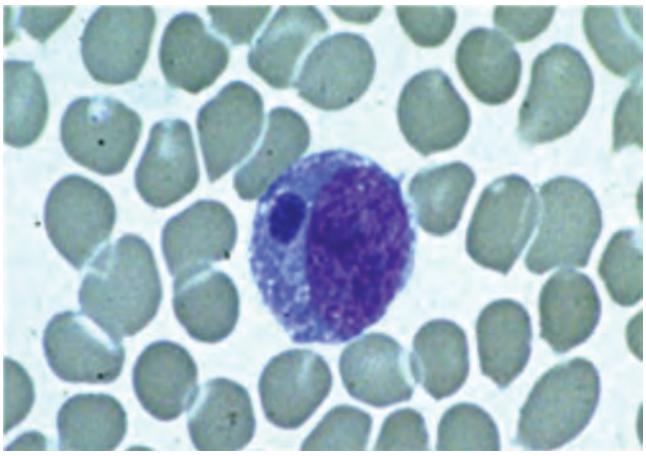


Fig. 126.11. Morulae detected in a monocyte on a peripheral blood smear associated with *Ehrlichia chaffeensis* infection (Wright's stain; ×1000). (From Centers for Disease Control and Prevention: Ehrlichiosis: symptoms, diagnosis, and treatment. www.cdc.gov/Ehrlichiosis/symptoms/index.html.)

Cytopenia and abnormal liver function usually resolve after the acute phase of illness by 14 to 28 days. Microscopic identification of mulberry-like clusters (morulae) inside leukocytes on peripheral blood smears is helpful (Fig. 126.11), but this finding usually has disappeared after the first week of illness with HGA, especially if the patient has been treated with doxycycline. Cultures take up to 2 weeks to grow the organisms.

Management

Tetracycline, which has been shown to be effective in cases of canine ehrlichiosis, is also effective in cases of human ehrlichiosis. Doxycycline (100 mg bid; 2.2 mg/kg body weight bid for children weighing < 45 kg) and tetracycline regimens for 7 to 14 days are curative. Most patients respond rapidly after treatment is begun, and fever subsides within 24 to 48 hours. Tooth staining is no longer considered a concern for children and should not be a reason to withhold therapy. Rifampin, as an alternative, has been shown to be effective in children with human ehrlichiosis. Data supporting the use of chloramphenicol are still inconclusive. The same ticks that transmit HGA (*Ixodes* spp.) also are responsible for Lyme disease and babesiosis. Each disease entity requires a full diagnostic evaluation because amoxicillin treats Lyme disease but not HGA or babesiosis, and doxycycline alone does not treat babesiosis. Failure of fever to resolve beyond 6 or 7 days of treatment of a suspected tickborne disease should heighten suspicion for another disease organism.

BABESIOSIS

Babesiosis is a tickborne, malaria-like, acute febrile illness caused by intraerythrocytic protozoal parasites of the genus *Babesia*. Babesiosis has long been recognized as an important veterinary disease and probably was known in ancient times; it has been proposed that the fifth plague described in the book of Exodus was actually babesiosis.

The first human cases of babesiosis were reported in Montana in 1904. Investigators seeking the cause of RMSF examined blood smears from local inhabitants and described parasitic forms now known to be characteristic of *Babesia*. Since the late 1950s, several widely scattered cases (mostly in Europe) of human babesiosis have been reported in splenectomized persons. *Babesia divergens,*

a species primarily infecting cattle, is the most common agent reported in Europe, but other species have been implicated as well, including *Babesia bovis, Babesia equi,* and a single case of *Babesia caucasia* infection. Two strains, WA1, related to a canine pathogen, *Babesia gibsoni,* and MO1, related to *B. divergens,* also have been found to cause disease in humans. In all these reported cases, the course was fulminant and the disease usually fatal.

Until to the late 1960s, more than 350 cases had been documented in the United States. Almost all these cases were caused by *Babesia microti,* a rodent parasite, and occurred in the coastal regions of southern New England, where *B. microti* is endemic. New Jersey and the eastern part of Long Island were found to be endemic with babesiosis as well. In 2011, babesiosis became a nationally reportable condition. Of the 27 states that elected to participate, 1762 cases were reported from 22 of them; 95% of cases came from seven states—Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin, and 85% of these patients presented with symptoms in June through August, coinciding with the nymphal feeding period and time of maximal human exposure in endemic areas.[49] Recently, case numbers have increased significantly in the lower Hudson Valley in New York and in eastern Pennsylvania.[50,51]

These cases differ from the European cases in that most (≈80%) occurred in persons with intact spleens. Significant morbidity has been low in the United States, despite lack of specific therapy. Asplenic persons, older adults, and otherwise immunosuppressed patients usually have more severe disease.

Pathophysiology

B. microti is associated with deer and mice rather than with cattle. The ecology of *B. microti* is similar to that of *B. burgdorferi,* the causative agent of Lyme disease, with the same major vector, *I. scapularis,* and the same mammalian reservoirs—white-footed mice, which host the larval and nymphal stages of the tick, and white-tailed deer, which host the adult ticks.

Human babesiosis results from accidental human intrusion on the natural cycle of infection. The nymphal form of the *Ixodes* tick most commonly transmits the disease to humans, although babesiosis also can be transmitted by the adult tick. *I. scapularis* nymphs measure only 1 to 2 mm long and thus are easily overlooked by the patient (see Fig. 126.4). In more than 50% of all cases of babesiosis, patients cannot recall tick exposure. Babesiosis acquired through blood transfusion has been well documented.

Clinical Features

Babesiosis has an incubation period of 1 to 4 weeks after tick exposure. A nonspecific influenza-like illness, with fever, chills, headache, fatigue, and anorexia, is characteristic. Less common manifestations are nausea, diaphoresis, depression, photophobia, myalgias, arthralgias, dark urine, emotional lability, and hyperesthesias. Unlike in Lyme disease, rash is not a feature of this illness; however, erythema figuratum, a widespread exanthem with well-established annular lesions, has been associated with septic babesiosis. The physical examination usually reveals normal findings, except for fever, which typically is present, and splenomegaly, which occurs in some patients. Meningeal signs are absent. More severe disease occurs in splenectomized patients; hypotension, severe hemolytic anemia, hemoglobinuria, jaundice, renal insufficiency, ARDS, and disseminated intravascular coagulation can be seen in these cases. Some patients with babesiosis are only mildly ill, and asymptomatic infection also may occur, as demonstrated by serologic surveys in endemic areas. The diagnosis of babesiosis should be considered in any febrile patient from an endemic area during the tick season and should be part of the differential diagnosis for posttransfusion infections.

Diagnostic Testing

The diagnosis may be established through microscopy, antibody detection through IFA staining, or PCR assay. Microscopic examination is done with thick and thin Giemsa-stained blood smears. Characteristic intraerythrocytic forms (piriform, ring, tetrad) may be present. Babesiosis has been known to be misdiagnosed as malaria. Malaria may be excluded by the absence of intracellular pigment granules, schizonts, and gametocytes. The presence of parasites in budding tetrad formation, resembling a Maltese cross, is more suggestive of babesiosis. Contrary to what is commonly taught, this finding is uncommon. Because parasitemia may vary, serial smears over the course of several days may be necessary in suspected cases. An immunohistochemical assay has been developed that further allows easier microscopic differentiation between babesiosis and malarial organisms.

The diagnosis can be confirmed by serologic studies. IFA antibody to *B. microti* is available through the CDC, and titers usually rise to 1:1024 or greater within the first few weeks of illness. IgM–indirect IFA is sensitive and specific in acute babesiosis. Serologic tests for Lyme disease, which shares a common tick vector with babesiosis, also should be performed; concurrent Lyme disease has been reported in up to 50% of cases of babesiosis. ELISA and IFA sensitivities rise significantly after 5 days of illness, whereas PCR is more useful in the earlier days of sampling.[52]

Parasitemia observed at 1 to 4 weeks after inoculation of blood from infected patients into gerbils or hamsters supports the diagnosis. Other nonspecific laboratory findings include mild to moderate hemolytic anemia, which is present in most patients, and resultant mild elevations in bilirubin and serum lactate dehydrogenase levels.

Management

Patients who have not undergone splenectomy generally recover without specific therapy, although prolonged malaise and fatigue are common. In patients with severe disease and those who have had splenectomies, the combination of clindamycin (1.2 g bid IV or 600 mg tid orally) plus quinine (650 mg tid orally) has been shown to be effective and is the treatment of choice. An alternative regimen that may be better tolerated, especially by children and infants, consists of atovaquone (750 mg bid orally) plus azithromycin (500–1000 mg once followed by 250 mg once daily orally); up to 25% of patients may have an adverse effect from quinine. Pediatric doses need to be adjusted accordingly. Therapy should be continued for a minimum of 7 to 10 days. Development of resistance during treatment with azithromycin-atovaquone in immunocompromised patients has been described.[53]

Other antimalarial drugs, such as chloroquine and quinacrine, are not effective. Fulminantly ill patients with marked degrees of parasitemia and hemolysis have benefited from exchange transfusion. Effective live vaccines have been developed for bovine babesiosis but have not been developed yet for human disease.[54]

COLORADO TICK FEVER

Endemic to the Rocky Mountain area, Colorado tick fever is an acute, tickborne viral infection characterized by headache, back pain, biphasic febrile course, and leukopenia. The causative agent of Colorado tick fever is a small RNA virus of the genus *Coltivirus,* family Reoviridae. It is one of more than 500 viruses in the heterogeneous group of arthropod-borne viruses (arboviruses). Colorado tick fever has a sharply defined endemic zone encompassing mountainous and highland areas, from an altitude of approximately 4000 to more than 10,000 feet, in the Canadian provinces of British Columbia and Alberta and in at

least 11 western states (California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, South Dakota, Utah, Washington, and Wyoming). The largest number of cases has been reported in Colorado. The distribution of the virus coincides with that of its principal tick vector, *D. andersoni,* the Rocky Mountain wood tick. Although RMSF is transmitted by the same vector, that disease is far less common in Colorado. The cases of RMSF are outnumbered at least 20-fold by cases of Colorado tick fever.

Pathophysiology

The Colorado tick fever virus has been isolated from at least eight species of ticks, but *D. andersoni* is the only proven vector for humans. The tick is a significant reservoir for the virus because transstadial transmission (from larva to nymph to adult) of virus occurs, and the tick remains infected and infectious for life, up to 3 years. The primary vertebrate host species for Colorado tick fever virus maintenance are the chipmunk, *Tamias minimus,* and golden-mantled ground squirrel, *Spermophilus lateralis*; many other vertebrate hosts have been identified as well, including a species of porcupine in Colorado in Rocky Mountain National Park. Larval and nymphal stages of *D. andersoni* ticks are responsible for the transmission of Colorado tick fever virus among rodents, and overwintering of the virus is accomplished by nymphal and adult *D. andersoni*. Only adult ticks transmit Colorado tick fever virus to humans.

The CDC indicates that there were 83 cases reported between 2002 and 2012 in the United States. The actual incidence undoubtedly is much higher because many cases are diagnosed as nonspecific viral illness, and other cases may be mild or entirely subclinical. Human susceptibility to Colorado tick fever is universal, but it occurs most commonly in young men, reflecting greater occupational and recreational tick exposure.

Clinical Features

After an incubation period of approximately 3 to 5 days (range, 0–14 days), a moderate to severe influenza-like illness occurs abruptly, with signs and symptoms similar to those in early-stage RMSF. Fever, chills, headache, retrobulbar pain, myalgia, lethargy, anorexia, and nausea are common; vomiting and abdominal pain are reported occasionally. Early physical findings are nonspecific. A macular or maculopapular rash has been reported in 5% to 12% of patients but, unlike the rash of RMSF, the rash of Colorado tick fever is not a prominent feature of the illness.

A distinct feature of the illness is a biphasic course that occurs in approximately 50% of patients, causing a characteristic saddleback fever curve. Initial symptoms resolve after 2 to 3 days, and the patient feels relatively well for 1 or 2 days, after which the fever, headache, and myalgias return. The second phase may be more intense than the first phase and generally lasts 2 to 4 days. There may even be a third febrile period. Alternatively, a single prolonged febrile illness may occur. Recovery from Colorado tick fever usually occurs within 2 weeks, but convalescence can be prolonged, especially in patients older than 30 years.

Colorado tick fever is a self-limited disease, and virtually all patients recover without sequelae. Reports of severe complications, such as meningoencephalitis and hemorrhagic diathesis, have been limited to children. Only a few fatal cases have been recorded.

Diagnostic Testing

The peripheral leukocyte count often is depressed during the acute phase of illness to as low as 1000/μL, with a relative lymphocytosis. Transient thrombocytopenia can accompany the leukopenia and, less often, a mild anemia can occur. These hematologic abnormalities normalize during convalescence, but persistence of the virus in red blood cells causes a prolonged viremia, even when clinical recovery is complete. Transfusion-acquired infection has been reported and is caused by this persistent viremia in asymptomatic blood donors.

The diagnosis of Colorado tick fever can be confirmed by serologic testing (IFA, neutralizing antibody, complement fixation, enzyme immunoassay) of acute and convalescent samples, but serologic study is of little help early because of the slow rise of titers. The most rapid confirmation of Colorado tick fever, with corresponding elimination of concern about possible RMSF, is provided by direct immunofluorescent staining of virus in red blood cells in peripheral blood smears. PCR testing is now available for more rapid diagnosis. ELISA has shown promising sensitivity in detection of the Colorado tick fever virus.

Management

The treatment of Colorado tick fever is supportive only. Most patients do not require hospitalization, but if RMSF remains a diagnostic possibility, initial treatment with tetracycline or chloramphenicol and a period of observation are necessary until the diagnosis of RMSF can be ruled out.

OTHER TICKBORNE VIRUSES

In addition to the virus responsible for Colorado tick fever, at least 40 viral species have been transmitted to humans by ticks and caused illness, approximately 25 of them in the United States. Tickborne viruses are found predominantly in the RNA virus families. Historically, the most severe cases involved the tickborne encephalitis virus and Crimean-Congo hemorrhagic fever virus, but these have not been reported in the United States. Recently, however, a few tickborne viral illnesses have received notable press in the United States because of their mortality rates—the Heartland virus, a phlebovirus (family Bunyaviridae), the Bourbon virus, a thogotovirus (family Orthomyxoviridae), and a reported severe fever with thrombocytopenia syndrome.[55]

Eight cases of Heartland virus (RNA) disease were found among residents of Tennessee and Missouri as of March 2014. Four patients were hospitalized, and there was one death. All cases presented with leukopenia, thrombocytopenia, and fever.[56] The Bourbon virus, named after the county of its discovery, caused the death of a man in Kansas. Presentations and laboratory results of these new viral syndromes resembled those of other tickborne illnesses and were treated with antibiotics empirically and unsuccessfully. Various neurologic symptoms and encephalitis have been well-described with tickborne viral illnesses. As with most viral illnesses, treatment remains mostly supportive. The emergence and discovery of these newer tickborne diseases suggest that they have been underreported.[57,31]

TICK PARALYSIS

Tick paralysis occurs when an adult female tick attaches to a host and releases a neurotoxin that can produce cerebellar dysfunction or an ascending paralysis. Tick paralysis was recognized as early as the beginning of the 19th century. Hovell, while traveling through Australia, wrote in 1824 of "the small insect called the tick, which buries itself in the flesh, and would in the end destroy either human or beast if not removed in time."

Tick paralysis has been reported worldwide, but most cases occur in the southeastern and northwestern regions of the United States, western Canada, and Australia. Cases have been reported to occur in clusters; 43 species of ticks have been found to cause tick paralysis in humans, other mammals, or birds. Most cases in

North America and Canada are caused by *D. andersoni* (Rocky Mountain wood tick) and *D. variabilis* (American dog tick). Species responsible for paralysis cases that also are associated with other tickborne diseases include *A. americanum* (Lone Star tick), *I. scapularis* (black-legged tick), and *I. pacificus* (western black-legged tick); in Australia, *Ixodes holocyclus* is primarily associated with this disorder. Family Argasidae ticks (soft ticks) also have been implicated. Tick paralysis usually occurs in the spring and summer months and most reported cases are in children, primarily girls, probably because ticks are more easily concealed in longer hair.[30] Among adults, however, more men than women acquire the disease.

Pathophysiology

Tick paralysis is thought to be caused by a toxin secreted from the salivary glands of the tick during a blood meal. The toxin, ixobotoxin, affects sodium flux across axonal membranes without affecting the neuromuscular junction itself. The mechanism of action of the toxin is poorly understood, but it appears to produce a conduction block in the peripheral branches of motor fibers, resulting in a failure of release of acetylcholine at the neuromuscular junction. Electrophysiologic studies have confirmed a rapid reversal of significant impairment of motor nerve terminal function after tick removal, indicating that the disturbance is not a result of a neuromuscular junction defect. Possible central sites of action of the toxin have been postulated to explain cases in which the clinical picture is dominated by cerebellar dysfunction.

Clinical Features

The onset of symptoms usually occurs 4 to 7 days after the tick attaches. Initial manifestations include restlessness and irritability, followed by ascending flaccid paralysis, acute ataxia, or both. Deep tendon reflexes are almost invariably lost. These signs and symptoms can progress rapidly during a few days to bulbar involvement, respiratory paralysis, and ultimately death if the tick is not detected and removed.

The ascending nature of tick paralysis has been noted in most descriptions; however, ataxia and associated cerebellar abnormalities in the absence of muscle weakness may be seen. Thus, tick paralysis may sometimes be manifested as so-called tick ataxia. Isolated facial paralysis has been reported in patients with ticks embedded behind the ear. Fever, other systemic symptoms, and sensory deficits are unusual. Concomitant infection with Colorado tick fever has been reported.

Differential Diagnosis

Tick paralysis should be considered in the differential diagnosis for any patient thought to have Guillain-Barré syndrome, Eaton-Lambert syndrome, myasthenia gravis, poliomyelitis, botulism, diphtheritic polyneuropathy, or any disease with an acute onset of ascending flaccid paralysis or acute ataxia. Ocular findings, such as decreased convergence, unresponsive dilated pupils, and nystagmus (horizontal and vertical), seen early in tick paralysis can help distinguish this disease from Guillain-Barré syndrome.

Diagnostic Testing

No diagnostic tests to confirm tick paralysis are available other than the combination of the clinical scenario, presence of a tick, and improvement after its removal. The Tensilon test yields a negative result in patients with this condition, and CSF is normal.

BOX 126.2

Recommended Method for Tick Removal

1. Remove an embedded tick by grasping it with blunt forceps or tweezers as close to the point of attachment as possible.
2. Do not use bare fingers to remove ticks from animals or humans; when tweezers are unavailable, fingers should be shielded with a tissue, paper towel, or rubber glove.
3. Apply gentle, steady, upward traction with the forceps; do not twist or jerk the tick. Avoid squeezing or crushing the tick.
4. Do not handle the tick with bare hands. After removal of the tick, thoroughly disinfect the bite site and wash hands with soap and water.
5. Dispose of ticks by placing them in a container of alcohol or flushing them down the toilet.

Adapted from Needham GR: Evaluation of five popular methods for tick removal. Pediatrics 75:997–1002, 1985.

Management

Treatment in the United States consists simply of removing the tick; improvement generally is seen within a few hours and complete recovery within 48 hours. Supportive care, including mechanical ventilation, may be necessary. The mortality rate is approximately 10%; nearly all patients who die are children. The recommended procedure for the removal of any tick, including ticks causing tick paralysis, is summarized in Box 126.2. Traditional methods, such as burning, forceful removal, and application of petroleum, viscous lidocaine, or gasoline, are not consistently successful and do not guarantee removal of mouthparts, where the salivary glands and toxin may remain. Retained mouthparts also may cause infection.

Tick paralysis in Australia often is more devastating than in the United States. Symptoms and signs of illness caused by the Australian tick, *I. holocyclus,* do not resolve and often worsen after tick removal. Hyperimmune serum is available in Australia and often is needed because symptoms may worsen up to 48 hours after removal.

TICK BITE PROPHYLAXIS WITH INSECT REPELLENTS

Insect repellents have long been used to prevent mosquito bites. With recent increased public awareness of and concern about tickborne illness, especially Lyme disease, skin and clothing repellents are now also being marketed for tick protection. Three active ingredients in repellents have been shown to be effective against blood-sucking arthropods, including ticks—*N,N*-diethyl-*m*-toluamide (DEET), picaridin in KBR 3023 (known as Bayrepel, Hepidanin, and Autan Repel outside the United States), and *p*-menthane-3,8-diol (PMD) in oil of lemon eucalyptus. The most effective and most studied is DEET. Formulation percentages of DEET vary widely, ranging from 4.75% to 23.8%, giving 1½ to 5 hours of protection, respectively.[58] A long-acting 35% DEET formulation (US Army Extended Duration Topical Insect/Arthropod Repellent [EDTIAR]), available in the United States as Ultrathon (3M), provides protection for 6 to 12 hours. Picaridin is as effective as the 35% DEET formulation. Despite some earlier concerns, toxic and allergic reactions to DEET have been uncommon, and serious adverse effects are rare. Used as directed, concentrations up to 50% appear to be safe, even in young children, although toxic encephalopathy rarely can occur. Use for infants younger than 2 months is not recommended.

Permethrin is actually a contact insecticide rather than a repellent. It can be used as a clothing spray for protection against ticks.

Applied to the clothing as an aerosol, it is nonstaining, nearly odorless, and resistant to degradation by light, heat, or immersion in water. Permethrin is toxic to the nervous system of insects, but in mammals it is poorly absorbed and rapidly inactivated. Reported adverse effects have been limited to the skin and are uncommon.

Topical DEET and clothing impregnated with permethrin have been shown to be effective in field trials when each is used alone. Wearing protective clothing treated with permethrin in addition to the use of DEET on exposed skin provides the greatest degree of protection against tick bites.

KEY CONCEPTS

- Tickborne illnesses frequently are misdiagnosed as viral or bacterial infections. Early diagnosis can be facilitated by considering these diagnoses in patients who live in or recently have traveled to endemic areas and by routinely asking for a history of recent tick or insect bites in patients who present with febrile illnesses.
- Lyme disease should be suspected in patients who present with signs of a viral illness, monarticular arthritis, meningitis, multiple neurologic abnormalities, or heart block. Diagnosis can be confirmed with serologic testing of acute and convalescent serum samples. Normal physiologic changes from bites should not be confused with erythema migrans.
- Relapsing fever should be suspected in patients who present with recurrent viral-like illness associated with high fever. The diagnosis can be confirmed by the identification of spirochetes on a blood smear obtained during a period of rising temperature.
- Ulceroglandular tularemia should be suspected in patients with slow-healing extremity ulcers associated with large lesions of regional adenopathy (buboes). The diagnosis can be confirmed with serologic testing.
- RMSF should be considered in patients who present with an unexplained febrile illness, even in the absence of a rash or known tick exposure. Delayed diagnosis and late initiation of specific antirickettsial therapy may lead to a fatal outcome. Treatment never should be delayed pending laboratory diagnosis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 126: QUESTIONS & ANSWERS

126.1. What is the most common vector-borne disease in the United States?

A. Babesiosis
B. Cysticercosis
C. Lyme disease
D. Malaria
E. Tick paralysis

Answer: C. Lyme disease accounts for 95% of cases.

126.2. Which of the following statements regarding erythema migrans (EM) is true?

A. The incidence with Lyme disease is 70%.
B. The lesion center may become necrotic.
C. The lesion is tender and warm to touch.
D. The rash does not begin at the tick bite site.
E. Satellite lesions do not occur.

Answer: B. EM occurs in 90% of cases. It begins at the bite site and expands. There may be central clearing, skip areas, central necrosis, vesicles, and marked erythema. It is warm but not tender. Satellite and secondary lesions may occur due to hematogenous seeding by spirochetes. They are smaller, nonmigratory, and spare the palms and soles. All lesions fade after approximately 1 month.

126.3. Which of the following clinical pictures is not seen with Lyme disease?
- **A.** Conjunctivitis
- **B.** Hepatitis
- **C.** Meningitis
- **D.** Pharyngitis
- **E.** Pleuritis

Answer: E. Clinical pictures consistent with hepatitis, conjunctivitis, pharyngitis, and meningitis may be seen with Lyme disease.

126.4. A 26-year-old woman presents complaining of muscle and joint aches. She has no past history and takes no medications except over-the-counter analgesics. She describes a pattern of migratory and intermittent muscle aches, which she reports as lasting only hours at any single location and then migrating. The physical examination reveals a mild pharyngitis and conjunctivitis and is otherwise normal. Which of the following statements is true?
- **A.** A history of tick bite should be sought.
- **B.** A rheumatoid factor (RF) level should be determined.
- **C.** An erythrocyte sedimentation rate (ESR) would be confirmatory.
- **D.** Creatine phosphokinase (CPK) levels are likely elevated.
- **E.** Fibromyalgia is likely.

Answer: A. The migratory, short-lived, and intermittent nature of the Lyme-related arthralgias is sometimes the best clue to the diagnosis. The ESR, RF, and CPK values will likely be normal. Both rheumatoid arthritis and fibromyalgia present with progressive and usually symmetrical symptoms. Conjunctivitis, pharyngitis, meningitis, and hepatitis pictures may be part of the Lyme presentation.

126.5. Which of the following statements concerning neurologic manifestations of Lyme disease is true?
- **A.** Bilateral Bell's palsy is suggestive of Lyme disease.
- **B.** Extremity involvement is symmetric.
- **C.** Reflexes are not lost.
- **D.** Spinal roots and plexi are spared.
- **E.** The most common cranial nerve affected is the third.

Answer: A. The seventh cranial nerve is most commonly affected. Bilateral Bell's palsy should suggest a possible Lyme diagnosis. Reflexes may be lost. Extremity involvement is usually asymmetric. Plexopathies, thoracic radiculopathies, mononeuritis, and motor radiculitis may all be seen.

126.6. Which of the following statements regarding Lyme carditis is true?
- **A.** Cardiac involvement is uncommon.
- **B.** Electrocardiographic changes are stable and persistent.
- **C.** Onset time from initial illness is 2 or 3 months.
- **D.** The most common manifestation is bundle branch block.
- **E.** Ventricular dysfunction is common and persistent.

Answer: A. Cardiac involvement is uncommon. The most common manifestation is atrioventricular block, which may fluctuate significantly but often resolves as the cardiac inflammation recedes. Onset time from illness is an average of 3 to 5 weeks. Ventricular dysfunction is not common, and the prognosis is good.

126.7. A 33-year-old woman presents with worsening depression, irritability, and hypersomnolence. She was diagnosed with Lyme disease 2 years prior and underwent a full course of antibiotics that was initiated 12 weeks after initial symptom onset. Her psychiatric issues began approximately 6 months ago. Her only medication is citalopram. The physical examination is remarkable for a depressed affect and poor short-term memory by bedside assessment. Which of the following statements is true?
- **A.** A demyelinating syndrome may occur after Lyme disease.
- **B.** Late cranial nerve involvement is not seen.
- **C.** Magnetic resonance imaging (MRI) scanning of the brain will be normal.
- **D.** Paranoia would imply a separate cause from Lyme disease.
- **E.** Peripheral neuropathy is the expected late finding in Lyme disease.

Answer: A. The most common late neurologic manifestation is an encephalopathy that may include memory impairment, learning issues, depression, and paranoia. A demyelinating multiple sclerosis–like picture with central nervous system plaques on MRI may be seen. Any portion of the nervous system, including cranial nerve dysfunction, may be seen.

126.8. A patient returns to the emergency department for follow-up of Lyme titers drawn 2 days earlier during an initial evaluation for ongoing arthralgias, myalgias, and history of a rash. The rash came and went approximately 10 weeks prior. Which of the following statements is true?
- **A.** Early antibiotic therapy will not abolish the antibody response.
- **B.** IgG (immunoglobulin G) antibody may persist for years after successful treatment.
- **C.** IgM (immunoglobulin M) positive and IgG negative suggest Lyme disease.
- **D.** IgM positive and IgG positive suggest Lyme disease.
- **E.** IgM becomes positive within 1 week of infection.

Answer: B. IgM may be negative early on but peaks at weeks 3 to 6. IgG may be detectable at 2 months. Early antibiotic therapy may blunt or abolish the antibody response. Thus, two windows of negative titers may be seen, very early and again in the second month, when IgM has waned and IgG has not risen. In patients with an illness longer than 1 month, an isolated IgM test is likely to be a false-positive and should not be used to support the diagnosis. IgM should have waned when IgG levels rise. Overall, acute and convalescent titers 1 month apart may be necessary for accurate diagnosis. IgG levels may persist for years; these levels are not diagnostic of ongoing infection and do not confer immunity.

126.9. A 26-year-old man presents with 2 weeks of headache, fever, and stiff neck during the summer months. Which of the following characteristics would best differentiate Lyme disease from enteroviral infection?
- **A.** Cerebrospinal fluid protein and glucose levels and cell count
- **B.** Enteroviral rash morphology

C. Lyme IgM titer
D. Presence of arthralgias
E. Presence of diarrhea

Answer: E. Lyme disease most closely resembles reactive arthritis, with an asymmetric, oligoarticular, episodic picture. Eye and genital findings help differentiate, although 10% of Lyme disease patients may have conjunctivitis. Lyme disease and reactive arthritis have huge knee effusions, with a paucity of pain compared with effusion size in Lyme disease. Juvenile rheumatoid arthritis and Lyme disease have negative rheumatoid factor test results. Erythema marginatum occurs with the arthritis of rheumatic fever. Lyme disease patients may meet clinical Jones criteria for rheumatic fever but lack serologic evidence of streptococcal infection.

126.10. A 29-year-old pregnant female camper presents with concerns about a tick bite and Lyme disease. She was camping in Connecticut 3 days ago and had several tick bites. The last tick was removed yesterday. What should you do?
A. Administer azithromycin daily for 2 weeks.
B. Counsel her about signs and symptoms of Lyme disease.
C. Prescribe amoxicillin.
D. Prescribe antiinflammatories.
E. Prescribe outpatient intramuscular ceftriaxone.

Answer: C. Antibiotic prophylaxis is indicated in certain circumstances. Lyme disease may be transmitted transplacentally, so prophylaxis is likely indicated. Amoxicillin and macrolides are only first-line agents when doxycycline is contraindicated. Macrolides are third-line agents after doxycycline and amoxicillin.

CHAPTER 127

Tuberculosis

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PRINCIPLES

The emergency department (ED) serves as the front line of contact for many persons with untreated tuberculosis (TB) in the United States. Undiagnosed patients, incompletely treated patients, or those with active disease who develop complications may first seek medical care in EDs. For this reason, emergency clinicians must fully understand the complexities of the disease, including the multiple presentations of undiagnosed disease, complications, and initial therapeutic options.

Background

TB is currently the world's second leading infectious cause of death, and one-third of the world's population has been infected by TB.[1] Each year, more than 8 million people acquire active TB infection globally, and over 1.5 million die of the disease. In the United States, close to 10,000 new cases of TB are diagnosed each year, and 65% of these cases are in patients who are foreign-born.[2] New challenges of the 21st century include human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), high rates of immigration from countries with high TB prevalence, increasing occurrence of TB in institutional living settings, increasing rates of poverty, substance abuse, and homelessness, and urban overcrowding. Immigration from endemic countries is major factor.[1] The largest numbers of people with TB originate from Eastern Europe, Africa, and Asia. Homelessness and urban crowding also have contributed to the spread of TB in the United States and globally.

The HIV/AIDS epidemic has affected the continued presence of TB in the United States. The pandemic of HIV-related TB also increased TB cases among non–HIV-infected people owing to the higher numbers of source cases in the community. The rate of TB among patients who are HIV-infected and have a positive TB skin test is approximately 200 to 800 times higher than that estimated for the US population overall.

Pathophysiology

One microorganism, *Mycobacterium tuberculosis* (MTB), causes human TB in nearly all cases. Humans constitute the sole known reservoir for MTB. Two other pathogenic mycobacteria, *Mycobacterium bovis* and *Mycobacterium africanum* have, on rare occasions, been implicated in causing TB. *M. bovis* is transmitted by drinking milk from diseased cows, which is rare in industrialized nations. *M. africanum* also is a rare cause of human TB in rural Africa.

MTB is an intracellular, aerobic, nonmotile, non–spore-forming bacillus with a waxy lipid coat. This coating makes MTB resistant to decolorization with acid alcohol after staining—hence, the term *acid-fast bacillus* (AFB). MTB grows slowly. Its generation time is 15 to 20 hours, compared with less than 1 hour for some common bacteria, and cultures take 4 to 6 weeks to grow on standard solid media. MTB produces neither endotoxins nor exotoxins. Its cell components are immunoreactive; some are immunosuppressive, and others are the agents of granuloma formation, macrophage activation, host toxicity, and modification of the immune response.

Transmission

TB is transmitted with rare exception by the respiratory route, including droplet spread and true aerosolization into microparticles. Patients with active disease expel MTB in liquid droplets during coughing, sneezing, and vocalizing. A single cough or 5 minutes of talking can produce 3000 infectious droplets, and sneezing can produce an even higher number. The droplets rapidly evaporate, and the desiccated bacilli circulate airborne for prolonged periods. These infective particles, or droplet nuclei, measure 1 to 5 μm in diameter, contain one to three tubercle bacilli and, when inhaled, can travel to the distal alveoli. Transmission by nonrespiratory routes, such as direct inoculation, occurs primarily among health care workers.

The susceptible host may become infected when only a few of the droplet nuclei are inhaled. Fomites are not important in the transmission of the disease, and patients' rooms, eating utensils, and bedding do not require special decontamination procedures. Because the infectious droplet nuclei are airborne, exchange of contaminated air is the most important environmental control. In addition, MTB is susceptible to ultraviolet radiation, so transmission rarely occurs outdoors because of the dilution of infectious particles and exposure to ultraviolet radiation.

The risk for TB transmission increases when source patients have airway and cavitary disease. Infectivity correlates with the number of organisms seen on sputum smear, extent of pulmonary disease, and frequency of coughing. After 2 weeks of chemotherapy, most patients with initially AFB-negative sputum smears can be considered noncontagious. In contrast, patients who initially were smear-positive may still have viable MTB detectable in their post-treatment sputum cultures after 2 weeks of treatment. Patients with extensive disease may still have AFB detectable on their post-treatment sputum smears; these two groups should be considered contagious. There is currently no clear epidemiologic evidence to define contagiousness of patients better after they have started effective therapy. The Centers for Disease Control and Prevention (CDC) has published guidelines requiring the presence of three negative smears on different days as the criteria for removal of a patient from respiratory isolation, but debate about this recommendation is ongoing.

Extrapulmonary TB also may be infectious, but only if it is in the oral cavity or open skin lesion. Transmission of MTB to health care workers caring for patients with skin ulcers and draining tuberculous abscesses has been reported. Irrigation of the abscess may aerosolize the bacilli, forming infectious droplet nuclei.

Pathogenesis

When infectious droplet nuclei are inhaled, the airflow through the bronchial tree tends to deposit them in the midlung zone on the respiratory surface of the alveoli. The deposition launches a

complex series of immunologic events. The pathogenesis of TB is divided into four stages.

Stage 1

The first stage begins when an alveolar macrophage phagocytoses the recently inhaled bacillus. A macrophage from a resistant host can immediately destroy a less virulent bacillus. In these cases, no tuberculous infection develops and the process ends. If a virulent bacillus can overcome a macrophage's microbicidal capability, the infection may progress to the next stage.

Stage 2

When the alveolar macrophage is unable to destroy the inhaled tubercle bacilli, the bacilli replicate until the macrophage lyses. Circulating monocytes are attracted to the site of infection by the released bacilli, cellular debris, and various chemotactic factors. The monocytes differentiate into macrophages and ingest the free bacilli. Initially, these new macrophages are not activated and cannot destroy or inhibit the mycobacteria. The bacilli multiply logarithmically within macrophages and accumulate at the primary focus of infection, called a tubercle. The infected macrophages also may be transported through lymphatics to regional lymph nodes, from which they can reach the bloodstream, with subsequent spread. During this lymphohematogenous dissemination, the pathogens tend to distribute preferentially to lymph nodes, kidney, epiphyses of long bones, vertebral bodies, meningeal areas, and apical posterior areas of the lungs.

Stage 3

The third stage of TB begins 2 to 3 weeks after the initial infection, with development of the immune response that terminates the unimpeded growth of MTB. Cell-mediated immunity occurs through CD4+ helper T cells. These T cells secrete cytokines that attract and activate monocyte-macrophages. Once activated, the macrophages, containing previously ingested mycobacteria and their progeny, kill the bacilli. Mild fever and malaise may develop in association with the immune response at 4 to 6 weeks, but the primary infection is generally insignificant clinically. Eventually, the caseous center inspissates (thickens), and the disease is arrested. This sequence of events, from stage 1 to stage 3, represents the pathogenesis of primary TB in the immunocompetent patient. In most cases, primary TB is subclinical and self-limited. Clinically active TB develops in 8% to 10% of otherwise healthy persons. By contrast, in persons also infected with HIV, progression to acute primary TB occurs at a rate of 37% within 6 months. In the immunocompetent host with strong cell-mediated immunity, the primary lesion is effectively walled off by epithelioid cells.

Stage 4

The final stage usually occurs months to decades after an apparent recovery from the initial infection. TB may progress to stage 4, even in immunocompetent persons. Usually, host factors lead to decreased resistance and reactivation of dormant foci of MTB. Reactivation of dormant foci is responsible for the major clinical manifestations of TB. Exogenous reinfection of patients with well-documented previous TB infection causes clinical disease indistinguishable from that of reactivation TB. Because it may be incorrect to label all late-onset cases as reactivation disease, the preferred term is *postprimary TB*. Postprimary TB is active or chronic disease in a patient previously infected. In the United States and other developed countries, reactivation is thought to be the primary mechanism of postprimary TB. The primary walled-off tubercle eventually may erode through the bronchial wall and drains its contents, forming a cavity. The liquefied caseous material, teeming with mycobacteria, enters other parts of the lung and outside environment. The spilling of this liquefied material within the lung may produce a caseous bronchopneumonia.

CLINICAL FEATURES

History

Present Illness

Patients with TB may present with a primary infection or, more commonly, reactivation of an old infection. A high index of suspicion should be maintained, and TB should be included in the differential diagnosis of common presenting complaints, such as isolated fever, chronic weakness, weight loss, failure to thrive, and night sweats.

Clinically significant pulmonary TB often is indolent, and signs and symptoms are absent or minimal until the disease advances. The constitutional symptoms of anorexia, weight loss, fatigue, irritability, malaise, weakness, headache, chills and, most commonly, fever can be caused by many other diseases. The fever usually develops in the afternoon; defervescence occurs during sleep, leading to the classic night sweats of TB.

Cough is the most common symptom of pulmonary TB patients presenting to the ED. It may initially be a dry nonproductive cough or, less commonly mucopurulent in nature. Hemoptysis, caused by caseous sloughing or endobronchial erosion, usually is minor but often indicates extensive lung involvement. Many asymptomatic MTB patients present for medical attention because they are alarmed by the hemoptysis. Patients also may complain of pleuritic chest pain, which is caused by parenchymal inflammation adjacent to the pleural surface. Dyspnea with chest pain may indicate a spontaneous pneumothorax. Shortness of breath from parenchymal lung involvement is unusual, however, and, if present, indicates extensive parenchymal disease or tracheobronchial obstruction.

The clinical manifestation of TB in patients presenting to the ED may be especially challenging. In one study, only one-third of ED patients with active pulmonary TB had pulmonary chief complaints. Any vague systemic disorder or fever of unknown cause may represent TB. Atypical presentations are particularly common in infants, older adults, and immunocompromised persons. In infants and young children, the development of large hilar lymph nodes is common. Pulmonary TB should be considered in older adults with chronic cough and failure to thrive. Young adults show the adult pattern of apical pulmonary disease, including cavity formation, suggesting reactivation. Because of reduced immunocompetence, older adults typically have disease manifestations similar to those in young children.

Clinical manifestations of TB in patients coinfected with HIV are even more subtle and nonspecific, especially because these patients are vulnerable to opportunistic infections and neoplasms that can cause the same constitutional symptoms as TB. A synergy between MTB and HIV leads to a greatly increased viral load. Active TB with HIV coinfection has been associated with an increased risk for opportunistic infections and death. Patients with advanced HIV infection commonly have extrapulmonary involvement (seen in 30%) as well as combined pulmonary and extrapulmonary TB (in 32%).

Risk Factors

All ED patients who have been coughing, and with risk factors, should be screened for the presence of TB risk factors (Box 127.1). Foreign-born individuals and those living with persons who

BOX 127.1

Population Groups With Increased Risk for Tuberculosis

Close contacts of known case
Persons with HIV infection
Foreign-born from Asia, Africa, Latin America
Medically underserved, low-income populations
Older adults
Residents of long-term care facilities (eg, nursing homes, correctional facilities)
Injection drug users
Groups identified locally (eg, homeless, migrant farm workers)
Persons who have occupational exposure

HIV, Human immunodeficiency virus.

recently emigrated from endemic areas of the world are at risk, as are patients with unexplained weight loss or cachexia. One of the most important risk factors is HIV/AIDS with CD4+ levels below 500 cells/μL. Overseas, coinfection with HIV and TB is common and results in increased TB mortality rate. Risks for acquiring TB may also be stratified by age. Because infants and toddlers have poorly developed cell-mediated immunity, they have a much higher incidence of TB than adults. Patients on immunosuppressant drugs such as steroids or antiarthritic immunosuppressant agents are at increased risk. Patients with a history of purified protein derivative (PPD) conversion should be asked about the presence of immunosuppressive medical conditions, which are associated with an increased risk for the development of active postprimary disease through reactivation. Household contacts also have increased risk of TB infection. Health care providers should ask patients with a history of active TB about all antituberculosis medications previously or currently taken and about compliance. Failure to improve after 2 months with an appropriate regimen may signal nonadherence to therapy or the presence of a resistant strain.

Physical Examination

A wasted patient with a cachexic appearance is a hallmark of advanced disease. The patient may show signs of dyspnea or tachypnea. The mental status examination may show subtle abnormalities. Examination of the chest can reveal abnormalities, but is unlikely to establish the extent of disease. Over areas of infiltration, rales may be heard when the patient breathes in after a short cough (posttussive rales), and bronchial breath sounds may be present over areas of lung consolidation. Distant, hollow breath sounds (amphoric breath sounds) may be heard over cavities. Most physical findings are a result of complications of TB or from the extrapulmonary forms of the disease (see later, "Extrapulmonary Tuberculosis").

Complications of Pulmonic Tuberculosis

Hemoptysis

Minor hemoptysis is a common complication of acute infection. The destruction of lung parenchyma leads to the rupture of blood vessels. TB also may cause massive hemoptysis. An uncommon complication is the erosion of a tuberculous lesion or cavity into a pulmonary artery, leading to pseudoaneurysm formation (Rasmussen's aneurysm), with potentially fatal hemoptysis. Alternatively, superinfection of cavities by invasive organisms or tumor development in the scarred lung may cause erosion of bronchial or pulmonary vessels, with resultant major hemorrhage. Affected patients often require emergency surgical resection or selective embolization.

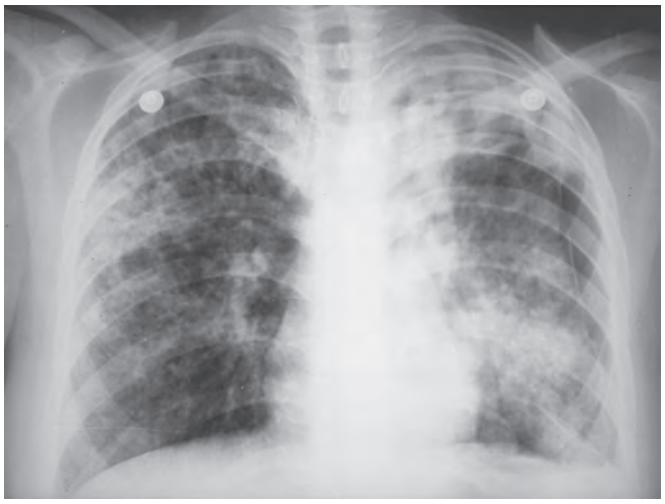

Fig. 127.1. Chest radiograph demonstrating cavitary tuberculosis with left-sided pneumothorax. The underlying cause of the pneumothorax was later determined to be a bronchopleural fistula. (Courtesy Dr. John Pearce.)

Pneumothorax

Spontaneous pneumothorax is uncommon (affecting <5% of patients with severe cavitary disease) but may occur when a tuberculous cavity ruptures and creates a bronchopleural fistula or when a bleb ruptures into the pleural space (Fig. 127.1). Delayed tube thoracostomy and suction result in progressive infection and fibrosis of the pleura that leads to air trapping in the affected lung.

Pleural Effusion

Pleural extrapulmonary TB may occur early after primary infection with MTB and is manifested as pleurisy with effusion. More rarely, it may occur late in postprimary cavitary disease and arise as an empyema. Tuberculous pleural involvement often causes no symptoms and resolves spontaneously; however, a 65% relapse rate has been reported in untreated patients, with development of active pulmonary or extrapulmonary TB within 5 years. The diagnosis usually is confirmed by microscopic and chemical examination of pleural fluid or pleural biopsy tissue. White blood cell counts usually range from 500 to 2500 cells/mL. The fluid is an exudate with protein usually exceeding 50% of the serum protein, and the glucose concentration may be normal to low. Because there are few bacilli, AFB smears rarely are positive, and cultures grow MTB for only 25% to 30% of patients known to have the disease. Pleural biopsy can confirm the diagnosis in most patients.

Empyema

An empyema, characterized by extensive, progressive parenchymal disease and cavitation, may develop in patients with TB. Although it is rare, empyema is more common late in the course of the disease in debilitated patients. Rupture of a cavity into the pleural space usually is catastrophic and often is associated with bronchopleural fistula formation. An untreated empyema can result in spontaneous pleurocutaneous fistula formation, presence of a chest wall mass on the radiograph, or rib and vertebral destruction.

Airway Tuberculosis

When a cavity drains its highly infectious material into the bronchial tree, the airways not only spread the infection but also develop endobronchial TB. Bronchiectasis commonly complicates endobronchial TB. Bronchial stenosis may result from extensive damage caused by endobronchial TB or from direct extension of infection by tuberculous adenitis or lymphatic dissemination to the airway. Tuberculous bronchostenosis may appear radiographically as persistent segmental or lobar collapse, lobar hyperinflation, and obstructive pneumonia. Tracheal and laryngeal TB are less common than endobronchial TB. Laryngeal disease is the most infectious form; it results from the proximal extension of lower airway disease, pooling of infected secretions in the posterior larynx, or hematogenous dissemination to the anterior larynx. Patients with laryngeal TB also usually have active pulmonary disease.

Superinfection With Fungi

Extensive TB infection often heals with open cavities and areas of bronchiectasis. Superinfection may occur with a wide variety of organisms, including *Aspergillus fumigatus*. The characteristic finding on chest radiographs is the aspergilloma or so-called fungus ball (Fig. 127.2). Aspergillomas are of particular clinical significance because they may cause massive and fatal hemoptysis.

Primary Tuberculous Pericarditis

Primary tuberculous pericarditis usually results from direct extension of infection from the tracheobronchial tree, mediastinal or hilar lymph nodes, sternum, or spine. Pericardial involvement also may result from hematogenous spread secondary to acute miliary TB or from another focus elsewhere in the body. TB is the leading cause of pericarditis among HIV-infected patients in the United States. The predominant symptoms are cough, chest pain, and dyspnea, and the most common signs are cardiomegaly, audible rub, fever, and tachycardia. Complications of pericardial TB include pericardial effusion, constrictive pericarditis, myocarditis, and cardiac tamponade. Cardiac tamponade may result from the accumulation of pericardial fluid or rupture of enlarging lymph nodes into the pericardium. Emergency echocardiography reliably confirms the presence of pericardial fluid.

Fig. 127.2. Chest radiograph showing superinfection of healed tuberculous cavity. An aspergilloma can be seen in the right upper lung. (Courtesy Dr. John Pearce.)

DIFFERENTIAL DIAGNOSIS

Pulmonary Tuberculosis

Bacterial Pneumonia

Segmental or lobar infiltrates on chest radiographs in bacterial pneumonia may easily be confused with those seen in TB, especially primary disease. Compared with TB, however, bacterial pneumonias usually arise with more profound symptoms of systemic toxicity, more acute onset, and elevated white blood cell count. In pulmonary TB, there is no prompt response to antibiotics, as seen in bacterial pneumonia.

Fungal and Nontuberculous Mycobacterial Infections

Histoplasmosis, coccidioidomycosis and blastomycosis, as well as nontuberculous mycobacterial infections—mainly with *Mycobacterium avium* complex and *Mycobacterium kansasii*—may be radiologically indistinguishable from TB. The incidence of these infections is influenced by geographic location. Nontuberculous mycobacterial infection usually involves chronic pulmonary infection in HIV-infected patients. Immunocompetent persons also may become infected with MTB, especially patients with chronic lung disease, such as cystic fibrosis. Other important risk factors include work in the mining industry, warm climate, advancing age, and male gender.

Pneumonias in Patients With HIV Infection

Bacterial pneumonias including upper lobe *Pneumocystis* pneumonia (due to *Pneumocystis jiroveci*) and, rarely, *Nocardia* and *Rhodococcus* infections may mimic TB in patients with HIV infection.

Cavitary Lesions

Lung abscess or cavitating pneumonia caused by *Klebsiella pneumoniae, Staphylococcus pyogenes,* or aspiration may appear similar to cavitary TB on chest radiographs. In older patients, especially smokers, bronchogenic carcinoma may mimic TB; this is particularly true of squamous cell carcinoma, which tends to cavitate. Because cancer may cause a focus of TB to spread, the two diseases may be present simultaneously. Other causes of nontuberculous cavitary lesions include *M. avium* complex infection in HIV-negative patients, pulmonary infarction secondary to pulmonary embolus, Wegener's granulomatosis, and upper lobe bullous disease secondary to emphysema or neurofibromatosis.

Mediastinal Lymphadenopathy

The main considerations in the differential diagnosis for adenopathy include lymphoma and sarcoidosis. In sarcoidosis, lymphadenopathy usually is bilateral, symmetric, and asymptomatic. Lymphadenopathy tends to be unilateral in TB; if it is bilateral, it is asymmetric and associated with parenchymal lung disease. Lymphoma tends to involve bulky mediastinal lymphadenopathy.

Extrapulmonary Tuberculosis

Tuberculous infection involving multiple sites is usually seen in populations of patients less capable of containing MTB infection,

such as infants, older adults, and immunocompromised persons. Extrapulmonary TB may occur in multiple sites, with decreasing relative frequencies in lymphatic, pleural, bone or joint, genitourinary, meningeal, peritoneal, and other sites. The lymph nodes are the most common site of extrapulmonary TB for otherwise normal and HIV-infected patients. Involvement of the meninges is more common in young children than in other age groups (present in ≈4% of children with TB), and the incidence of TB in the remainder of the extrapulmonary sites increases with age. Less commonly involved locations for extrapulmonary TB include the skin, heart, pericardium, thyroid gland, mastoid cells, sclerae, and adrenal glands.

Lymphadenitis

Tuberculous lymphadenitis (scrofula) is the most common form of extrapulmonary TB. Scrofula is common in children but most commonly is seen in young women. The patient usually has an enlarging, painless, red, firm mass in the region of one or more lymph nodes, most commonly in the anterior or posterior cervical chain or supraclavicular fossa. Early on, the nodes are discrete rubbery masses that are freely mobile, and the overlying skin is normal. Eventually, the nodes may become matted and harder and the overlying skin inflamed. Fluctuance as well as an abscess or sinus tract may be present if a node erodes through the skin. Systemic signs and symptoms are uncommon, except in HIV-positive patients, in whom lymphadenitis usually is generalized. Pulmonary infection is present in a minority of cases. Considerations in the differential diagnosis include lymphoma, metastatic cancer, fungal disease, cat-scratch disease, sarcoid, toxoplasmosis, reactive adenitis, and bacterial adenitis.

The diagnosis of scrofula usually is made by fine-needle aspiration of an affected lymph node. Although AFB smears are positive in only approximately 20% of cases, granulomatous inflammation may be obvious. Overall, fine-needle aspiration has a sensitivity of 77% and specificity of 93% for TB infection. First-line treatment of scrofula consists of antituberculosis drugs, but surgical excision may be performed when medical therapy has failed or if the diagnosis is unclear. Incision and drainage should not be done because permanent sinuses and prolonged drainage can result.

Bone and Joint Infection

Bone and joint TB remains a disease of older children and young adults in developing countries, and it is increasingly a disease of adults in developed countries. Skeletal TB presumably develops from reactivation of dormant tubercles originally seeded during stage 2 of the primary infection or, in the case of spinal TB, from contiguous spread from paravertebral lymph nodes to the vertebrae. In general, spinal TB (Pott's disease) accounts for 50% to 70% of the reported cases; the hip or knee is involved in 15% to 20% of cases, and the ankle, elbow, wrists, shoulders, and other bones and joints account for 15% to 20% of cases. Approximately 50% of patients have a previous history or concurrent case of pulmonary TB, and the chest radiograph is normal in appearance in up to 50% of cases.

Patients with Pott's disease may simply complain of back pain or stiffness. Early changes of spinal TB can be difficult to detect on plain radiographs and include loss of the so-called white stripe of the vertebral endplate subsequent to destruction of subchondral bone. Thus, computed tomography (CT) and magnetic resonance imaging (MRI) should be used when the disease is suspected. Paraspinal cold abscesses develop in 50% or more of cases, with occasional formation of sinus tracts. The abscess can spread the infection up and down the spine, sometimes sparing vertebral bodies along its course, forming the so-called skip lesions. These skip lesions can easily be missed in imaging of the spine for Pott's disease. The main complication of Pott's disease is spinal cord compression.

Renal Disease

The kidney is highly vascularized, and hematogenous dissemination to that organ is fairly common. After the typical tuberculous lesions develop within the parenchyma, infection can spread into the calyces, renal pelvis, ureters, and bladder. As a result, tuberculous granulomas, scarring, and obstruction can occur anywhere along the urinary tract. Advanced renal disease and destruction may occur before the diagnosis is made. The urinalysis often reveals pyuria, hematuria, and albuminuria. Sterile pyuria is a classic finding in renal TB but, in many cases with this finding, cultures will be positive for other urinary pathogens. The finding of pyuria in an acidic urine with no organisms isolated should increase clinical suspicion for TB. Complications of renal TB include nephrolithiasis, ureteral obstruction or reflux, recurrent bacterial infections, hypertension, papillary necrosis, renal insufficiency, autonephrectomy and, rarely, development of transitional cell cancer.

Genital Disease

Male genital TB is usually associated with coexistent renal TB. Spread of infection from the kidney may involve the prostate, seminal vesicles, epididymides, and testes. A painless or slightly painful scrotal mass is a typical finding, and the patient may have symptoms of prostatitis, epididymitis, or orchitis. Epididymal or prostatic calcifications may be clues to the diagnosis. TB involvement of the seminal vesicles may lead to infertility.

In women, genital TB disease usually begins with a hematogenous focus in the fallopian tubes. The infection then spreads to the endometrium (in 50% of cases), ovaries (30%), cervix (5%–15%), and vagina (1%). Clinical manifestations may include abdominal or pelvic pain, ascites, infertility, menstrual irregularities and, rarely, vaginal discharge. An ulcerating mass may be present on the cervix. Genital TB may be confused with ovarian or endometrial cancer, Meigs' syndrome, vulvar or vaginal ulcer, pelvic abscess, cervicitis, or cervical carcinoma. Sexual transmission of TB by persons with active genital TB has been described.

Multisystem Disease

The term *acute disseminated tuberculosis* refers to active hematogenous spread of MTB to several organs in the body. The term *miliary tuberculosis* was first used to describe the pathologic lesions, which resemble small millet seeds. This is now used as a clinical term referring to the massive dissemination that leads to systemic illness. Miliary TB occurs when the host is unable to contain a recently acquired or dormant TB infection. In the past, miliary TB occurred mainly in young children after primary infection; today, it is more common in older adults and in persons infected with HIV. Miliary TB often is a subtle disease associated with alcoholism, cirrhosis, neoplasm, pregnancy, collagen vascular disease, or use of corticosteroids or immunosuppressive medications. A presumptive diagnosis can be made rapidly if chest radiographs show a miliary infiltrate (Fig. 127.3). Unfortunately, the classic miliary pattern is absent on radiographs in approximately 50% of cases. Routine laboratory tests generally are not helpful. Hyponatremia from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is common and often is associated with meningitis. Panculturing usually has a high yield, and HIV-infected patients may have positive results on blood cultures.

Mortality rates for miliary TB are higher than for the other forms of TB, with one case series reporting a rate of 21%. The

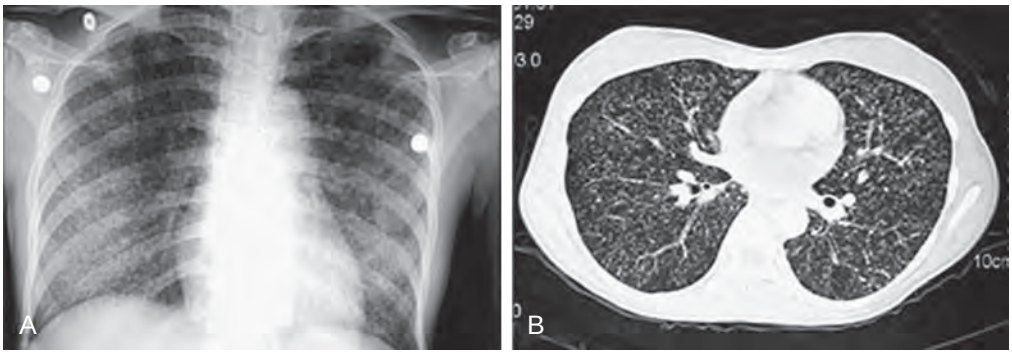

Fig. 127.3. Chest radiograph (**A**) and computed tomography scan (**B**) demonstrate a miliary pattern. (Reprinted with permission from Golden MP, Vikram HR: Extrapulmonary tuberculosis: an overview. Am Fam Physician 72:1761, 2005. Copyright 2005, American Academy of Family Physicians. All rights reserved.)

high mortality rate often is caused by delay in treatment, which should be initiated immediately on the basis of clinical suspicion and not delayed until confirmation of the diagnosis. A fulminant form of miliary TB may cause the acute respiratory distress syndrome and disseminated intravascular coagulation. In these cases, the addition of corticosteroids (prednisone, 60 mg/day) is indicated.

Central Nervous System Disease

Approximately 6% of all cases of extrapulmonary TB involve the central nervous system (CNS), and CNS involvement remains a grave consequence of tuberculous infection. The peak incidence of CNS TB occurs in newborns to 4-year-old children.

Tuberculous meningitis usually results from the rupture of a subependymal tubercle into the subarachnoid space rather than from direct hematogenous seeding of the CNS. When it is a complication of miliary TB, meningitis usually develops within several weeks of infection. In children, it is an early postprimary TB event, usually appearing within 6 months. Tuberculous cerebral involvement is most marked at the base of the brain, and vasculitis of local arteries and veins may lead to aneurysm formation, thrombosis, and focal hemorrhagic infarction. The vessels to the basal ganglia are usually involved, leading to formation of lacunar infarcts or deficits associated with movement disorders. Involvement of other vessels, such as the middle cerebral artery, may lead to hemiparesis or hemiplegia. Tuberculous meningitis begins with a prodrome of malaise, intermittent headache, and low-grade fever. In 2 to 3 weeks, a protracted headache develops. Vomiting, confusion, meningismus and focal neurologic signs, and coma may follow. Nuchal rigidity may be absent. Diplopia resulting from basilar exudate is present in up to 70% of patients. Hyponatremia may be present because SIADH is common. The cerebrospinal fluid (CSF) white blood cell count usually ranges from 0 to 1500 cells/mL, with a predominance of lymphocytes; however, polymorphonuclear cells may predominate early in the course of the disease. The CSF protein concentration usually is elevated, and the CSF glucose concentration typically is low. The classic triad of neuroradiologic findings in patients with TB meningitis consists of basal meningeal enhancement, hydrocephalus, and cerebral or brainstem infarction. CT or MRI also may reveal rounded lesions typical of evolving parenchymal tuberculomas (Fig. 127.4).

Gastrointestinal Disease

Gastrointestinal TB infection usually is secondary to hematogenous or lymphatic spread but also may result from swallowed bronchial secretions or direct spread from local sites, such as lymph nodes or fallopian tubes. TB may occur in any gastrointestinal location from the mouth to the anus, but lesions proximal to the terminal ileum are rare. The ileocecal area is the most common site of involvement, producing signs and symptoms of pain, anorexia, diarrhea, obstruction, hemorrhage and, often, a palpable mass. The most common clinical manifestations of gastrointestinal TB are abdominal pain, fever, weight loss, anorexia, nausea, vomiting, and diarrhea. The nonspecificity of these findings, as well as of those on the physical examination, may lead to the misdiagnosis of gastrointestinal TB as an acute abdomen, appendicitis, intestinal obstruction, or cancer. The clinical manifestations of anal TB include fissures, fistulae, and perirectal abscesses.

Fig. 127.4. Head CT scan demonstrating tuberculomas in a patient with AIDS.

Tuberculous peritonitis may develop from local spread of MTB infection from a tuberculous lymph node, intestinal focus, or infected fallopian tube. In addition, peritonitis can develop from seeding of the peritoneum in miliary TB or from the reactivation of a latent focus. The patient with tuberculous peritonitis commonly has pain and abdominal swelling associated with fever, anorexia, and weight loss. Diagnosis may be confounded by the similarity of this disease to alcoholic hepatitis and by the fact that

this disease often coexists with other disorders, especially cirrhosis with ascites. Paracentesis is thus essential. The peritoneal fluid is exudative, with a cell count of 500 to 2000 cells/mL. Lymphocytes usually predominate, with rare exceptions early in the process, when polymorphonuclear leukocytes may predominate. AFB smears of the fluid have a low diagnostic yield. Peritoneal biopsy often is necessary to confirm the diagnosis. Treatment is the same as for pulmonary TB, with a 6-month therapeutic regimen.

DIAGNOSTIC TESTING

Laboratory Tests

Routine laboratory studies generally are not useful in suggesting or establishing the diagnosis of TB in the ED. Normochromic normocytic anemia, elevated erythrocyte sedimentation rate, elevated C-reactive protein (CRP) and serum globulin levels, hyponatremia, and hypercalcemia can occur in active pulmonary TB, but these findings are nonspecific.

White Cell Stimulation Tests

The patient's blood can be tested for sensitivity of its T cells to tuberculin antigens.[3] These tests are called interferon-gamma (IFN-γ) release assays (IGRAs). The QuantiFERON-TB Gold (Quest Diagnostics) and T-Spot (Oxford Immunotec) tests are the most widely available IGRAs. They uses an enzyme-linked immunosorbent assay (ELISA) to measure the amount of IFN-γ released in response to PPD. IFN-γ is a cytokine associated with cell-mediated immunity. Determination of IFN-γ levels also can be used as a diagnostic test for tuberculous pleural effusions, ascites, and pericardial effusions. Clinical studies have reported sensitivity ranges from 90% to 100%. TB infection can be rapidly confirmed in an individual in 2 days, compared with several weeks for a traditional culture.[3] However, a normal study does not completely exclude TB; therefore, cultures should be sent when person thought to have TB has a negative QuantiFERON-TB Gold test result.

Serology

Although ELISAs have been developed for several MTB serum antigens, in practice no serodiagnostic approach to the diagnosis of TB currently is in widespread clinical use in the United States. Other countries have discouraged the use of serology.[4] Limitations of the ELISA include inadequate accuracy and reproducibility, inability to distinguish active from latent infection, poor discrimination between MTB and other mycobacteria, and relative cost.

Diagnostic Imaging

Plain radiography of the chest is the most useful study for a presumptive diagnosis of pulmonary TB. Increased use of chest CT scans has enhanced the sensitivity of detecting classic TB findings in the lung. Chest radiographic abnormalities are not limited to the classic upper lobe cavitary infiltrates. Primary TB infection and postprimary disease have distinctive radiographic features. A normal appearance on the chest radiograph has a high negative predictive value and is therefore useful in screening ED patients for active pulmonary TB. However, the low false-negative rate among immunocompetent adults increases significantly in HIV-positive patients. Therefore, depending on the clinical circumstances, the absence of specific abnormalities on the chest radiograph does not always exclude active TB, especially in patients with concomitant endobronchial disease and HIV infection.

Primary Tuberculosis

Chest radiographic manifestations of primary disease in adults often are not recognized as TB. Primary tuberculous infiltrates can occur in any lobe. In any age group, a pneumonic infiltrate with enlarged hilar or mediastinal nodes should strongly suggest the diagnosis. The infiltrate usually is homogeneous and most commonly involves a single lobe. Thus, primary TB may appear radiographically identical to a bacterial pneumonia, with associated lymphadenopathy, if present, being the only distinguishing feature.

Lymphadenopathy is considered the radiologic hallmark of primary TB in children but is seen less commonly in adults. When present, adenopathy usually is unilateral and associated with parenchymal infiltrate (Fig. 127.5). It may occur bilaterally or, less commonly, may be an isolated finding on chest radiography. Other primary TB chest radiographic findings include a moderate to large pleural effusion, which often is an isolated finding whose prevalence increases with age, and miliary TB characterized by the presence of innumerable, 1- to 3-mm noncalcified nodules dispersed throughout both lungs with mild basilar predominance. When the healed primary focus is visible on the chest radiograph as a calcified scar, it is known as the Ghon focus. Calcified secondary foci of infection are known as Simon's foci. A Ghon focus associated with calcified hilar nodes is called a Ranke complex. A right-sided predominance in the distribution of the Ghon foci and Ranke complexes is well recognized and probably reflects the higher statistical probability that an airborne infection will affect the right lung. Calcification seen on the chest radiograph indicates healing, but viable bacilli may still exist in a partially calcified lesion.

Postprimary Tuberculosis

Postprimary TB typically appears as an upper lung infiltrate or consolidation, with or without cavitation. The lesion may be small or extensive and usually is located in the apical or posterior segment of the upper lobe, but may appear in the superior segment of the lower lobe. Postprimary disease also occurs in the lower lung. In addition, bronchogenic spread can occur, leading to the involvement of multiple lobes (Fig. 127.6). Patients with bilateral upper lobe disease are extremely likely to have TB. The other important recognizable characteristics of postprimary disease are fibrosis and cavitation. These lesions are not purely exudative in that they are associated with a fibrotic pattern of nodules and a

Fig. 127.5. Chest radiographic findings in a child with primary tuberculosis. Note the active Ghon focus, with associated hilar adenopathy and presence of bilateral infiltrates. (Courtesy Dr. John Pearce.)

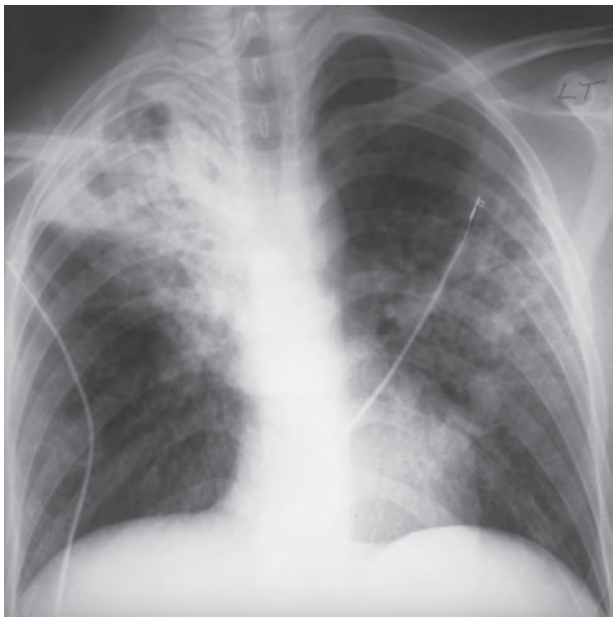

Fig. 127.6. Chest radiograph showing evidence of right upper lobe cavitary disease. Also note the left-sided infiltrate, secondary to endobronchial spread.

few fine, linear densities. Fibroproductive lesions often are irregular and angular in contour, have strands extending toward the hilum, and demonstrate calcification of one or more nodules and distortion of vascular and mediastinal structures. Severe fibrosis with upper lobe volume loss may eventually lead to retraction of the interlobar fissure and upward displacement of the hilum. The chest radiographic appearance at this stage has been variably referred to as "old scarring," "no active disease," or "fibrotic, apparently well-healed TB." Cavitation should alert one to the potential for high infectivity of the patient and associated complications, such as bronchogenic spread of TB (see Fig. 127.4). The walls of the cavities initially are thick and rough and become thinner and smoother with healing. Chest radiographs of patients with pulmonary TB and HIV infection may be atypical in approximately one-third of cases. Patients with late HIV infection more often demonstrate mediastinal adenopathy or atypical infiltrates and less often have cavitation. Severe immunosuppression has been reported to be associated with a miliary pattern of disease on chest radiographs.

Microbiologic Testing

Sputum Studies

If the clinical or chest radiographic findings suggest the diagnosis of pulmonary TB, mycobacteriologic studies of the patient's sputum should be ordered. A positive smear supports a presumptive diagnosis, and the number of bacilli seen correlates with infectivity. For patients who are not producing sputum, nebulized induction of sputum is the method of choice for the collection of samples. Induction of sputum with nebulization may increase the risk of TB transmission to health care workers and should be performed only in specially ventilated rooms, preferably not in the ED. When the sputum is not diagnostic in adults, fiberoptic bronchoscopy with bronchial washings, brushings, and bronchoalveolar lavage or transbronchial biopsy may be necessary for the laboratory diagnosis of TB.

Direct Microscopy. Direct microscopic examination of a stained sputum specimen for AFB (ie, an AFB smear) is the most rapid laboratory test widely available to support a presumptive diagnosis of TB, and results usually are available from hospital laboratories within 24 hours. Fluorochrome stains are more sensitive than the traditional Ziehl-Neelsen or Kinyoun methods for the detection of AFB from clinical specimens. Negative findings on an AFB smear, however, do not rule out active pulmonary TB because microscopy is relatively insensitive when performed on samples with small numbers of bacilli. At least 5000 bacilli/mL of sputum must be present for a positive result by microscopy. Overall, AFB smears have a sensitivity of 20% to 80% and a specificity of 90% to 100%. Despite its limitations, microscopy remains an essential diagnostic test because of its ease of performance, low cost, rapid turnaround time, and reasonable diagnostic yield.

Nucleic Acid Amplification Tests

Nucleic acid amplification (NAA) tests take only 24 to 48 hours to yield results. Their overall positive predictive value is about 95%. In some cases, patients with positive TB sputum smears have had negative NAA test results because of inhibitors that may prevent amplification. This has been a rapidly growing field in TB diagnostics, although most EDs do not yet have bedside capabilities. The best role of NAA is to aid emergency clinicians in decision making for patients thought to have active TB. It should not be ordered routinely when the clinical suspicion for TB is low.

Culture

Sputum culture is more sensitive than microscopy for the detection of MTB and is still considered the gold standard diagnostic modality. Liquid culture can detect 10 to 100 bacilli/mL, compared with 5000 to 10,000 bacilli/mL for an AFB smear. When the presence of mycobacteria is established, the specific identification of MTB may be accomplished by subjecting the initial mycobacteria to various isolation techniques. These include the detection of pigmentation on solid culture media, various biochemical tests, high-performance liquid chromatography, and nucleic acid probes. A presumptive diagnosis of TB based on a positive sputum smear usually is confirmed by isolation of MTB by culture. Traditional culture methods using solid media require 3 to 8 weeks for colony formation. The development of liquid culture systems has shortened the detection time to 7 to 14 days.

Tuberculin Skin Test

Although newer serologic diagnostic tests have become widely used in most US hospitals, the tuberculin skin test still continues to be the diagnostic workhorse for the detection of exposure to MTB. The tuberculin test is based on the principle that MTB infection induces sensitivity to certain antigens of the bacillus. These antigens are contained in the tuberculin preparation called PPD. In a person infected with TB, the PPD test result usually turns positive 3 to 8 weeks after the infection, when the immune response is developed. The standard 0.1-mL dose used in skin testing contains 5 tuberculin units (TU). A properly placed needle should leave a blanched distinct wheal 6 to 10 mm in diameter. If the tuberculin dose is incorrectly administered, the test may be repeated immediately at a site several centimeters away. Test results are read 48 to 72 hours after administration of PPD. The largest diameter of palpable induration is measured and recorded in millimeters; erythema by itself is not measured. The precise measurement that denotes a positive test result depends on the patient's other clinical factors. The current CDC guidelines use 15 mm of induration as a positive test response for people without TB risk factors. Persons with previous TB immunization (see later, "Vaccines for *Mycobacterium tuberculosis*") may have a positive PPD result even though they are not infected with TB. However,

a significant reaction to PPD and a long time interval between bacilli Calmette-Guérin (BCG) vaccination and the current skin test make it more likely that the reaction is due to MTB infection. Because the BCG vaccine is imperfect in protecting against MTB infection, and because most vaccinated persons come from areas of high TB prevalence, the CDC has recommended that tuberculin skin test results be interpreted without regard to BCG vaccination status.

MANAGEMENT

Initial Management in the Emergency Department

Hemoptysis

The most emergent presentation of pulmonary TB is massive hemoptysis, defined as loss of at least 600 mL of blood in 24 hours. Exsanguination rarely occurs, and the major morbidity is due to asphyxiation from aspirated blood. Secure the airway with a large-diameter (8-mm) endotracheal tube that can accommodate a fiberoptic bronchoscope. Position the patient with the bleeding lung in a dependent position. Consider selective main bronchus intubation to allow ventilation of the unaffected lung and minimize the spread of blood from the affected lung. Emergent consultation for bronchoscopy, surgical resection, or angiography with selective embolization is required. Immediately place patients thought to have active pulmonary TB in respiratory isolation.

Fever or Wasting

Patients with fever and wasting generally should be admitted for an in-hospital evaluation. Patients should be placed in respiratory isolation until the diagnosis of TB has been excluded.

History of Tuberculosis, Therapy Discontinued

In patients with vague symptoms and a history of TB, consider reactivation. If necessary, consult the local TB health officer or infectious diseases specialist.

Antituberculosis Medications

Three basic therapeutic principles govern the treatment of TB: (1) any treatment regimen must contain multiple drugs to which the MTB organism is susceptible; (2) the therapeutic agents must be taken regularly; and (3) therapy must continue for a sufficient period. In clinical practice, the last principle is the most problematic. The most up-to-date recommendations for the treatment of TB are available from the CDC through online publications or at the CDC website.[5] Medications used to treat MTB generally are divided into first-line and second-line agents. Of these, 10 have been approved by the US Food and Drug Administration (FDA) for the treatment of MTB. The most commonly used first-line agents are isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB).

First-Line Agents

INH demonstrates extremely potent early bactericidal activity and can rapidly decrease the patient's infectiousness. A small risk of hepatitis (<3%) occurs with long-term treatment. Supplemental pyridoxine is recommended for these patients. RIF also demonstrates strong early bactericidal activity. This agent causes orange discoloration of body fluids, including urine, tears, sweat, and sputum. PZA works against organisms contained in the acid environment of the macrophage. The chief side effect is hepatotoxicity, but this risk is very low at daily doses of 25 mg/kg or less. Polyarthralgias occur commonly (up to 40% of patients) but usually respond to nonsteroidal antiinflammatory drugs or aspirin. EMB is a first-line agent that helps prevent the emergence of RIF resistance during TB treatment. Retrobulbar neuritis can occur, resulting in decreased visual acuity to the point of blindness.

Second-Line Agents

Streptomycin must be given parenterally and has a peak of action 1 hour after the intramuscular dose is given. The chief side effects of this potentially teratogenic agent are ototoxicity and nephrotoxicity. Amikacin, kanamycin, and capreomycin also are injectable agents used for drug-resistant TB. As with streptomycin, ototoxicity and neurotoxicity are their major adverse effects. TB strains resistant to streptomycin usually are sensitive to amikacin and kanamycin, and resistance to these last two drugs usually is linked. Cycloserine, ethionamide, and *p*-aminosalicylic acid (PAS) are oral agents used for the treatment of patients with drug-resistant TB when the strain is presumed or known to be sensitive to these agents. The main adverse effect of cycloserine is psychosis or seizures, which occur in 3% to 16% of patients. Ethionamide is similar to INH in structure and toxicity. Major adverse effects of PAS include gastrointestinal distress (most common), hypothyroidism, and hepatitis. Fluoroquinolones have played a more recent role in the treatment of TB. They are less effective than the first-line agents and are used mainly in the treatment of drug-resistant disease.

Corticosteroids

Corticosteroids may prevent constriction in tuberculous pericarditis and decrease the neurologic sequelae in all stages of tuberculous meningitis, especially if they are given early in the disease. The CDC strongly recommends corticosteroids for MTB pericardial or CNS infections.[5] Corticosteroids may provide some benefit to children with bronchial obstruction caused by enlarged lymph nodes. In addition, in patients with pulmonary TB, prednisone, 20 to 60 mg/day may benefit those who continue to experience temperature spiking and lose weight, despite a good bacteriologic response to appropriate antituberculosis therapy.

Initial Therapy

Emergency clinicians generally will not initiate treatment prior to consulting public health and infectious diseases specialists. To be successful, treatment must be continuous, ongoing, and monitored closely. A one-time dose of medications is fruitless in a patient who could be lost to follow-up. In some locations, this will require hospital admission with appropriate respiratory isolation.

ED management is appropriate and necessary in certain circumstances, such as TB sepsis or miliary TB, critically ill HIV patients with TB, or life threatening conditions. The CDC website should be reviewed for the most up-to-date treatment guidelines. The goals of therapy are to rapidly kill large numbers of bacilli (bactericidal activity), prevent emergence of drug resistance, and prevent relapse by elimination of dormant or slowly dividing bacilli (sterilizing activity). There are four basic recommended regimens.[5] These are used when the organism is known or presumed to be susceptible to INH, RIF, PZA, and EMB.

Adequate treatment of active TB in patients coinfected with HIV is critical. It has been observed that immune activation from TB enhances systemic and local HIV replication and may accelerate the natural progression of HIV infection. Active TB in

HIV-infected patients has been associated with increased risk for opportunistic infections and death. TB treatment alone leads to a reduction in viral load in these patients. Current recommendations for the initial treatment of MTB in HIV-infected patients are the same as those for patients who are not HIV-infected, with exceptions for complex drug interactions. For example, significant drug interactions between rifamycins used for TB and antiretroviral drugs (protease inhibitors and nonnucleoside reverse transcriptase inhibitors [NNRTIs]) used for HIV infection complicate the treatment of patients with active TB who are coinfected with HIV. For treatment of MTB in patients who are taking protease inhibitors, rifabutin can be used instead of the other rifamycins. When TB treatment is initiated in HIV-positive patients, a paradoxical reaction to medical therapy may develop in some cases. The reaction is manifested with the development of fever, new or enlarging lymph nodes, or worsening of radiographic disease. Severe paradoxical reactions may be managed with a 2-week tapering course of prednisone or methylprednisolone.

Drug-Resistant Tuberculosis

Two types of drug-resistant MTB have emerged as a result of spontaneous mutations. Multidrug-resistant TB (MDR-TB) is defined as TB in which the mycobacteria are resistant to two or more first-line antituberculosis agents. Extensively drug-resistant TB (XDR-TB) is TB characterized by resistance to first-line and at least three second-line drugs.

Multidrug-Resistant Tuberculosis

The World Health Organization (WHO) has estimated the world wide number of MDR-TB cases at close to one-half million persons.[6] Airborne transmission of MDR-TB is a threat to those who come in contact with infected individuals, including family members, contacts in crowded living situations, and health care personnel. The spread of primary drug resistance is faster when HIV infection is highly prevalent in a population. Because initial TB infection in HIV-infected patients progresses rapidly to active disease, newly infected persons can quickly become source cases for further transmission of the resistant bacilli. In reports on hospital outbreaks of MDR-TB, more than 90% of patients had coinfection with HIV, and case fatality rates were as high as 70% to 90%. However, patients without HIV infection demonstrate excellent clinical responses when treated for MDR-TB.

For the identification of potential cases, health care workers should know the prevalence of drug resistance in their community and the risk factors for drug resistance (Box 127.2). Rapid identification and prompt isolation of these patients, along with other control measures, can reduce the nosocomial transmission of MDR-TB to patients and health care workers. Failure to control drug resistance may lead to wide dissemination of MDR-TB and to a public health crisis that physicians may confront without effective medications.

Treatment of drug-resistant TB can be challenging and requires familiarity with second-line agents. For MDR-TB, specialist consultation is essential. A general principle that applies in such cases is to use at least three drugs to which the organism is susceptible and that have not been used previously. In general, one of these medications should be an injectable agent. TB infection with strains that are resistant only to INH can be managed with shorter courses of RIF, PZA, and EMB.

Extensively Drug-Resistant Tuberculosis

XDR-TB was first recognized in patients coinfected with AIDS in South Africa in 2005 and is a major threat in Africa, Asia, and areas of the former Soviet Union.[7] XDR-TB is found in 10% of patients presenting with MDR-TB.[7] The strain has virulence similar to that of MTB, and disease does not progress faster in the absence of antibiotics. As resistance to so many antibiotics has developed, however, this strain has become a major threat, especially in patients with AIDS. Most alarming is a report that as many as 33% of patients with TB coinfected with HIV and MDR-TB had the XDR-TB strain. Mortality rates for this population of patients are high, because few alternative drugs exist. The CDC has reported cases in in the United States and has isolated patients as soon as they are identified. EDs could become a major focus for spread of this disease because of overcrowding, initial lack of recognition, and long wait times, exposing innocent patients to XDR-TB. Reports from Africa have shown that XDR-TB also can be transmitted directly to health care workers. Of great concern is the potential for transmission of the disease within the ED by a previously undiagnosed patient with XDR-TB, recently arrived from an endemic country, who presents for treatment of TB-related symptoms or an unrelated condition.

BOX 127.2

Risk Factors for Drug-Resistant *Mycobacterium tuberculosis* Infection

Previous unsuccessful antituberculosis treatment
Failure to respond or adhere to a good treatment regimen
Human immunodeficiency virus infection
Injection drug abuse
Close contact with source cases
Recent immigration from area with a high prevalence of drug resistance
Cavitary lung disease
Homelessness
Imprisonment
Drug malabsorption due to gastrectomy or ileal bypass surgery

Adapted from O'Brien RJ: Drug-resistant tuberculosis: etiology, management and prevention. Semin Respir Infect 9:104–112, 1994; and Ellner JJ: Multidrug-resistant tuberculosis. Adv Intern Med 40:155–196, 1995.

Vaccines for *Mycobacterium tuberculosis*

No universally accepted vaccine program exists for MTB. The BCG vaccine has been used since 1921, but its overall efficacy, duration of protective immunity, and optimal age for administration remain unclear. In the United States, BCG is rarely recommended because of the belief that it may undermine the epidemiologic and diagnostic value of PPD skin testing. BCG use in children is common in some countries, and some hospitals overseas require that staff have a BCG vaccination as a requirement for work.[8] Tuberculin skin tests in patients given previous BCG vaccination usually demonstrate less than 10 mm of induration. Thus, previous BCG vaccination status should be ignored in the interpretation of skin test results. Institutional outbreaks of TB and the emergence of MDR-TB have been sparking reassessment of the BCG issue in the United States. Reports of BCG vaccine efficacy range from 0% to 80%. One meta-analysis has reported the efficacy of BCG vaccine to be approximately 50%. A 60-year study in a Native American population showed a 50% reduction in the development of TB in persons receiving BCG vaccine.

BCG vaccine is currently recommended in the United States only for tuberculin-negative infants and children who cannot take INH and have ongoing exposure to a persistently untreated or inadequately treated patient with active TB, who are continuously exposed to persons with INH- and RIF-resistant TB, or who belong to groups with rates of new MTB infection exceeding 1%

per year.[5] WHO recommends that all infants in developing countries receive the vaccine.[6]

One decision analysis suggested that BCG vaccination would be more effective than the current annual testing strategy for health care workers. What is not controversial is that the vaccine is strongly contraindicated in persons with HIV infection or another immunosuppressive disease. New vaccines against MTB are being researched, including those using attenuated strains of the MTB complex, recombinant mycobacteria, subunit proteins, and DNA vaccines.

DISPOSITION

Acutely ill or older patients may require hospitalization during the first few days of treatment because adverse reactions to TB chemotherapy are common and may occasionally be life-threatening. In addition, severely ill patients may require parenteral drug administration. Patients with TB have a high rate of HIV coinfection, and the comorbid illnesses associated with HIV infection, complex synergy between MTB and HIV, and potentially harmful drug interactions between the antiretroviral agents and rifamycins may favor inpatient treatment for the initial management of these complicated cases.

Hospital admission also is indicated for patients with active or suspected MDR-TB. These patients commonly require observation during initiation of therapy because of the complexity of the treatment regimens, toxicity of the drugs, and need for close monitoring to ensure adherence to treatment and isolation measures. Finally, social issues such as homelessness, presence of infants or immunocompromised persons in the household, substance abuse, and inability for self-care may necessitate hospitalization. The recalcitrant patient constitutes a potential threat to public health, and legal measures for involuntary hospitalization may be required.

Patients who are otherwise well but have suspected TB may be eligible for outpatient treatment in consultation with local county health officials, who agree to assume responsibility for ongoing care of the parent and investigate contacts for possible exposure to TB.

PREVENTION OF TRANSMISSION IN THE EMERGENCY DEPARTMENT

EDs often care for patients at increased risk for active pulmonary TB, such as those who are homeless, foreign-born, recently incarcerated, or chronically ill. Accordingly, ED personnel can be at high risk for occupational TB infection. Increased hospital occupancy and ED crowding can lead to extended waiting periods for ED beds and hospital beds. Some EDs may lack an adequate number of TB isolation rooms.

Early Identification

For the most effective minimization of infectious exposures among health care workers and other patients, all patients with active pulmonary TB would ideally be placed in respiratory isolation when they initially present at triage, and the CDC has recommended screening for TB at triage. Triage screening protocols can detect patients with more classic presentations of TB, but reported protocols are only moderately sensitive and somewhat cumbersome. Immediate respiratory isolation should be considered for patients with high-risk chief complaints, such as the HIV-positive patient with cough, the person with hemoptysis, or the patient with a history of TB presenting with cough or fever. The best guideline is to initiate respiratory isolation as soon as TB is considered a possible diagnosis. Masks should be placed on these patients before chest radiography is performed.

Isolation and Environmental Control

In addition to triage screening, the use of proper isolation facilities and environmental control measures can help prevent TB exposures. Airflow in the ED plays a central role, and inadequate ventilation has been a contributing factor in many nosocomial outbreaks of TB. Ideally, there should be single-pass airflow from waiting rooms to outside the facility. Within the ED, air should flow from clean areas to less clean areas, rather than vice versa. For EDs that frequently see patients with TB, at least one true respiratory isolation room should be available. The CDC recommends that respiratory isolation rooms have at least 12 air changes per hour and have negative pressure (air flows into the room from other ED areas). Other engineering approaches to TB infection control include the use of high-efficiency particulate air (HEPA) filters and upper room ultraviolet light irradiation.

Personal Respiratory Protection

ED personnel should be familiar with the appropriate use of respiratory protection against TB. Surgical masks (eg, string tie masks) should be placed on potentially contagious patients to decrease the release of infectious droplets into the air. Air can leak around such masks, however, so they may not adequately prevent health care workers from inhaling infectious droplet nuclei. Thus, surgical masks are used only for source control, not for health care worker protection. More advanced personal respiratory protection devices include N95 particulate respirators. HEPA-filtered masks can also be used for health care worker respiratory protection; these masks were used more extensively before development of the N95 masks.

Preventive Therapy After Inadvertent Exposure

Health care workers who are exposed to patients with active pulmonary TB require referral to their primary care physicians or employee health services for follow-up testing and treatment. Tuberculin skin testing or IGRA blood testing usually is performed within days following exposure to establish whether the health care worker was previously infected with MTB. If the baseline test result is negative, a follow-up is performed 3 months later to determine whether conversion has occurred. The CDC has developed guidelines for the treatment of exposed personnel, which can be found on the CDC website.[9]

KEY CONCEPTS

- Early recognition of patients with risk for TB should begin at ED triage. Patients thought to have active pulmonary TB should be placed in respiratory isolation as soon as possible.
- TB should be considered in the differential diagnosis of patients who present with fever, cough, and weight loss.
- Risk factors for TB include HIV-infection, immunosuppression, age older than 60 years, foreign-born, homeless, and close contact with known cases.
- Beyond pulmonary manifestations, a variety of extrapulmonary manifestations may occur, including involvement of lymph nodes, pleura, bones, or joints and CNS, genitourinary, and gastrointestinal systems.
- Therapy should be determined based on consultation. The most commonly used agents are INH, RIF, PZA, and EMB. Resistant strains, including MDR-TB and XDR, have been increasing in frequency.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 127: QUESTIONS & ANSWERS

127.1. Which of the following is not a typical vehicle for tuberculosis transmission?
- **A.** Coughing
- **B.** Eating utensils
- **C.** Parenteral transmission
- **D.** Sneezing
- **E.** Talking

Answer: B. Bedclothes and eating utensils do not require special decontamination. Parenteral transmission is largely a risk of health care workers (eg, skin ulcers, draining wounds). Talking, coughing, and sneezing all may produce significant droplet spread.

127.2. Which of the following anatomic areas is not a site of preferential organism spread during stage 2 spread of TB?
- **A.** Kidneys
- **B.** Long bone epiphyses
- **C.** Lung bases
- **D.** Lymph nodes
- **E.** Meninges

Answer: C. Lung apices are favored rather than the bases. These sites are preferred, possibly because of high oxygen tension.

127.3. Clinically active TB develops in what percentage of immunocompetent purified protein derivative (PPD) converters?
- **A.** 1%
- **B.** 5%
- **C.** 10%
- **D.** 15%
- **E.** 20%

Answer: C. TB develops in 10%—3% to 5% in the first 2 years (acute primary) and 5% later in life (reactivation). Patients with HIV infection develop primary TB at a rate of 37% within 6 months and then develop active TB at a rate of 7% to 10%/year.

127.4. Which of the following statements regarding clinical tuberculosis is true?
- **A.** Exogenous reinfection after past TB gives a clinically distinct picture.
- **B.** Most clinical TB is from acute primary infection.
- **C.** Acute infection is usually asymptomatic.
- **D.** Most ED patients with pulmonary TB have pulmonary complaints.
- **E.** Large hilar nodes are most common in older adults.

Answer: C. Acute infection is very often asymptomatic or, at most, vague. Exogenous reinfection looks just like primary or reactivation TB. Most clinical TB is from reactivation of dormant foci. Many ED patients with active pulmonary TB have no pulmonary symptoms. Large hilar nodes are most common in infants and children.

127.5. Which of the following is a risk factor for reactivation of tuberculosis in a previously infected person?
- **A.** All of these
- **B.** Body weight more than 10% below ideal
- **C.** Diabetes
- **D.** Intestinal malabsorption syndrome
- **E.** Silicoses

Answer: A. Other risk factors are listed in Box 127.2.

127.6. A 26-year-old man with HIV infection presents with chest pain and fever. The evaluation yields a likely diagnosis of pericarditis with effusion. What is the most likely cause?
- **A.** Cryptococcal infection
- **B.** *Haemophilus influenzae*
- **C.** Lymphoma
- **D.** *Streptococcus pneumoniae*
- **E.** Tuberculosis

Answer: E. Tuberculosis is the leading cause of pericarditis in HIV-infected individuals in the United States. The incidence is 15%.

127.7. Which of the following statements regarding chest radiography findings in pulmonary tuberculosis is true?
- **A.** Adenopathy may distinguish TB from bacterial pneumonia.
- **B.** Primary TB typically appears as an upper lobe cavity lesion.
- **C.** The false-negative rate is 10% in immunocompetent patients.
- **D.** The false-negative rate is 40% in HIV-infected patients.
- **E.** The typical TB infiltrate is heterogeneous and multilobed.

Answer: A. Hilar adenopathy may be the only way to suspect TB as opposed to a typical bacterial pneumonia. Primary TB is usually a single-lobe infiltrate with a homogeneous appearance. It is postprimary TB that has a predilection for the upper lobes, with or without cavitation. The false-negative rate for chest radiography in immunocompetent patients is very low, 1%. The rate increases to 7% to 15% in HIV-infected patients and those with endobronchial disease.

127.8. Which of the following statements regarding the radiographic appearance of tuberculosis and infectivity is true?
- **A.** Chronic fibrotic changes are unlikely to be infective.
- **B.** Normal radiographs are uncommon with HIV infection.
- **C.** Only the presence of adenopathy can determine active disease.

D. Patients with late HIV infection are less likely to have adenopathy.
E. The presence of cavitation implies high infectivity.

Answer: E. Cavitation suggests high infectivity. Chronic fibrotic changes cannot differentiate old versus active disease, and many of these patients will have positive sputum. Active disease can only be determined radiographically by serial radiographs. Patients with late HIV infection are more likely to have mediastinal adenopathy and less likely to show cavitations. Normal radiographs are common with HIV infection.

127.9 What is the most common form of extrapulmonary tuberculosis?
A. Genitourinary
B. Lymphatic
C. Meningeal
D. Peripheral bone or joint
E. Vertebral

Answer: B. Lymphatic involvement (eg, scrofula) accounts for 42% of cases.

CHAPTER 128

Bone and Joint Infections

Neha P. Raukar | Brian J. Zink

PRINCIPLES

Background

Historically, bone and joint infections (BJIs) have been described in grim terms. *Aids to Surgery,* written in 1919, noted that "acute infective osteomyelitis … is a very fatal disease." With septic arthritis, "the patient becomes exhausted from toxaemia or pyemia," and "ankylosis is the usual most favourable termination."[1] Advances in diagnostic methods, antibiotic therapy, and surgical techniques have resulted in better patient outcomes; however, new challenges are arising. Antibiotic resistance is evolving, and many patient subsets have reduced host immunity. This combination results in greater complexity in the management of BJIs than has ever been encountered. The emphasis of modern management of BJIs has shifted from prevention of sepsis and death to prompt diagnosis, initiation of treatment, and avoidance of the complications and morbidity associated with chronic bone or joint infections.

The overall occurrence of BJIs appears to have remained constant during the past 4 decades.[2] In hospitalized patients in the United States, the incidence is approximately 1%. Osteomyelitis in children younger than 13 years occurs in 1 in 5000, whereas the incidence of septic arthritis ranges from 5.5 to 12/100,000 individuals.[2] In contrast to the rest of the world, there is no correlation between socioeconomic factors or race and the incidence of BJI in the United States. Both bone and joint infections show a bimodal age distribution, occurring most commonly in people younger than 20 years or older than 50 years. In children, BJIs usually occur in previously healthy individuals, with boys having a slightly increased susceptibility to bone infections. In adults, there are several known risk factors that lead to a higher risk of BJIs.

Orthopedic infections can be classified according to the site of involvement and include osseous (osteomyelitis), articular (septic, pyogenic, or suppurative arthritis), bursal (septic bursitis), subcutaneous (cellulitis or abscess), muscular (infectious myositis or abscess), and tendinous (infectious tendinitis or tenosynovitis) varieties. The terms *osteomyelitis* literally means inflammation of the marrow of the bone, but it is colloquially used to refer to infection in any part of the bone.

Infectious processes can also be categorized by their onset and are generally designated as acute, subacute, or chronic. An acute infection is one that lasts less than 2 weeks, a subacute infection is one that lasts 2 to 6 weeks, and chronic infections are those that last longer than 6 weeks. Chronic osteomyelitis is also used to define a bone infection that fails to respond to a a normal course of antibiotic therapy. A histologic diagnosis of chronic osteomyelitis depends on the presence of necrotic bone.

For the emergency clinician, the most practical way to classify osteomyelitis is as hematogenous, which is more common, or contiguous, with the contiguous type further subdivided based on the presence or absence of vascular insufficiency. This method of classification assists in the interpretation of diagnostic imaging examinations and helps guide management, including antibiotic therapy and surgical intervention.

Anatomy and Physiology

Histologically, bone tissue is classified as compact or spongy. Compact bone forms the shaft of long bones and outer shell of all bone. Spongy bone is found at the ends of long bones and makes up irregular bones. Compact bone is dense and without cavities and consists of longitudinally running Haversian systems, which contain Haversian canals that house vasculature and nerves. Spongy bone, conversely, consists of a bony lattice, the trabeculae, which contains marrow, is more metabolically active, and is less dense than compact bone. The central Haversian canals run parallel to the long axis of the bone and contain the blood supply and reticular connective tissue for the Haversian system. Spongy bone, also called cancellous or medullary bone, has numerous cavities, is located within the medullary cavity, and consists of extensively connected trabeculae.

The gross structure of long bones can be divided into several sections. The diaphysis is the shaft of the bone and contains the compact cortical bone with an overlying periosteum and a medullary canal containing marrow. The metaphysis is the junctional region between the epiphysis and diaphysis. The metaphysis contains abundant trabecular bone, but the cortical bone thins here relative to the diaphysis. Finally, the epiphysis is the area at either end of a long bone and is made up of abundant trabecular bone and a thin shell of cortical bone (Fig. 128.1). In the skeletally mature individual, the epiphysis of most bones is involved in articulation and, instead of being covered by a periosteum, is covered with a thin layer of articulating cartilage, a very thin layer of secretory cells sitting on a loose fibrous stroma that allows frictionless movement of the bones.

Joints are enclosed by a synovial capsule, which consists of a dense fibrous connective tissue that offers structural integrity and is lined with synovial cells that secrete synovial fluid. This forms a sleeve around the articulating bones to which it is attached. In some joints, such as the shoulder, hip, and knee, the synovial membrane extends beyond the epiphysis and attaches to the metaphysis. This anatomic relationship allows bacteria to spread directly from the metaphysis into the joint.

Pathophysiology

Osteomyelitis is an infection of the bone and medullary cavity. Bone is typically resistant to infection unless it is subjected to trauma, disruption of blood flow that deprives the bone of normal host immunity, a large inoculum of blood-borne or external microorganisms, or a foreign body. Hematogenous inoculation usually starts in the metaphysis, given the slow flow of blood in the sinusoidal blood vessels. Acute inflammatory cells migrate to the area, causing edema, vascular congestion, and small vessel thrombosis, which then leads to an increase in the intraosseous pressure compromising blood flow to the bone. Eventually, lack

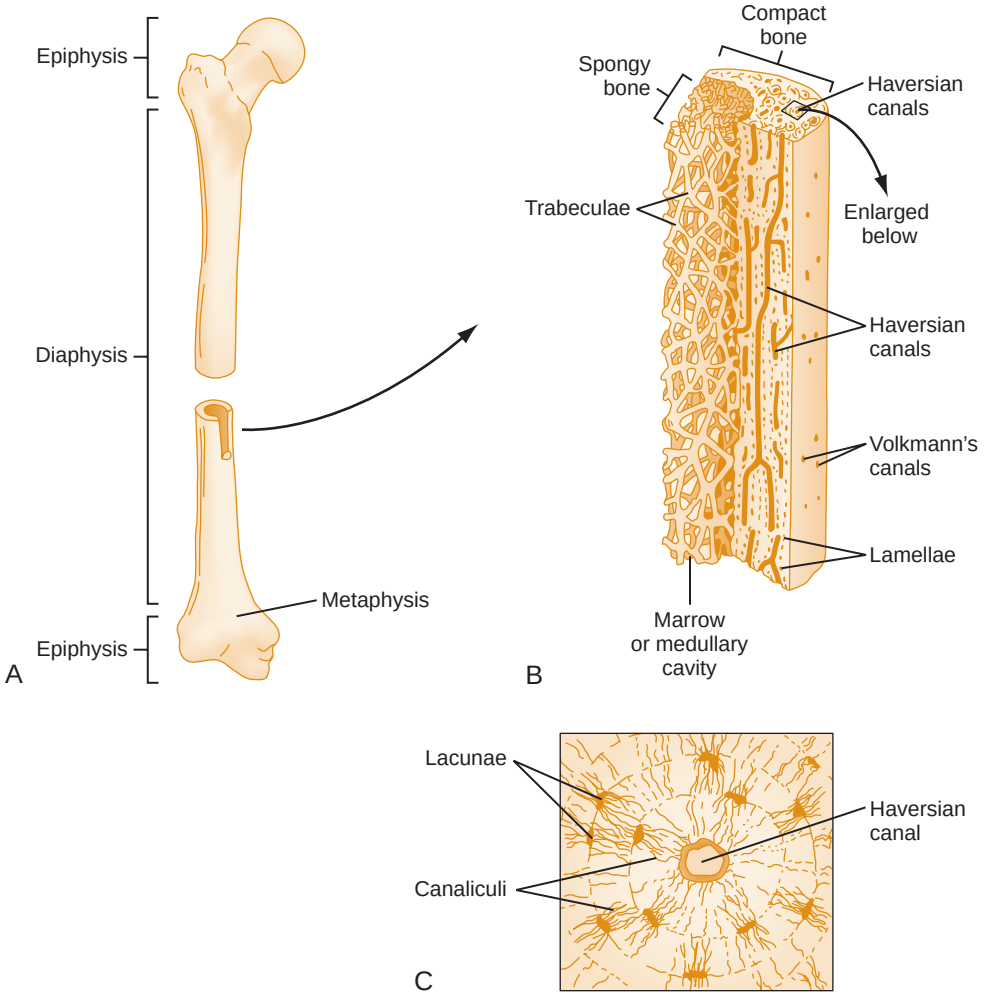

Fig. 128.1. Schematic drawing of long bone. **A,** Regions of long bone. **B,** Cross-sectional structure of long bone. **C,** Microscopic structure.

of blood supply to the medullary canal and periosteum leads to areas of necrotic bone termed *sequestra*. Bony tissue attempts to compensate for the tensile stresses caused by infection by creating new bone around the areas of necrosis. This new bone deposition is called an involucrum. Given that there is significantly reduced blood supply to this necrotic bone tissue, bacterial infection is often difficult to eradicate with medication alone and, frequently, chronic osteomyelitis requires a combination of surgical débridement and antibiotic therapy.

The evolution of blood flow patterns at the metaphyseal-epiphyseal junction and development of vascular anatomy explain the pathologic features of hematogenous osteomyelitis in the different age groups. In neonates and infants, osteomyelitis readily advances from the metaphysis to the epiphysis and adjacent joint space, leading to septic arthritis. After the first year of life, the infection usually spreads laterally through Volkmann's canals, breaks through the cortex, and lifts the periosteum to form a subperiosteal abscess. In the adult, after the epiphyseal plate ossifies, anastomoses form between the metaphyseal and epiphyseal blood vessels and infection can once again spread from the metaphysis to the epiphysis and eventually into the synovium and joint space. In addition, the periosteum becomes firmly attached to the underlying bone, limiting subperiosteal abscess formation.

Bacteria congregate in a highly structured community, the biofilm, which plays an important role in the pathogenesis of septic arthritis and osteomyelitis. Within the biofilm, the bacteria are at varying stages of metabolism—some are active, some are slow-growing, and some are dormant. Antibiotics target metabolically active bacteria, such as those in the single cell state (planktonic state), but bacteria in other stages in the biofilm community are more resistant to the effects of antibiotics. Furthermore, Gram staining only identifies planktonic bacteria, which helps explain why Gram stains of aspirated synovial fluid in a suspected septic joint are often negative; therefore, a definitive diagnosis is made only by culture of the synovial fluid aspirate or synovial tissue. Biofilm formation also explains why optimal treatment of a septic joint, especially of prosthetic joints, involves complete surgical débridement.

Hematogenous spread of bacteria causes almost all cases of osteomyelitis in children and in the subset of adults who have vertebral osteomyelitis. In the appendicular skeleton of adults, such as in the foot, hand, skull, maxilla, and mandible, osteomyelitis usually occurs by spread of the pathogens from a contiguous source of infection or direct implantation. Head and neck osteomyelitis is usually caused by sinus disease and odontogenic infection.

Infections from direct implantation of bacteria are caused by deep puncture wounds, such as by an animal bite, and tend to occur in the hands and feet. Although cats account for only 10% of animal bites, significant infection results from 20% to 50% of cat bites versus only 5% of dog bites because of the morphology of feline teeth. Most human bite injuries are related to fistfights and contamination of the metacarpophalangeal joints

and metacarpals, with infection due to oral flora. Direct implantation of pathogens is also common with open fractures and surgical instrumentation.

Septic arthritis is usually a consequence of hematogenous spread unless there is direct injection of bacteria into the joint. The lack of a basement membrane makes the highly vascular synovium vulnerable to bacterial seeding. Infection occurs first in the synovium, spreads into joint fluid, and finally affects the articular cartilage. Bacterial enzymes and toxins directly damage cartilage. The synovial membrane responds to infection by increasing synovial fluid production, resulting in a large joint effusion, and progresses to ischemic damage to cartilage. Even a small bacterial load in the joint space elicits profound and persistent inflammatory and immune responses. Bacteria can be cleared from the joint, resulting in a sterile-appearing inflammatory response.[3] In response to infection, synovial cells and polymorphonuclear leukocytes release lysosomal enzymes, which irreversibly degrade articular cartilage, creating a painful joint with limited range of motion. In addition, other structures that are enclosed within or adjacent to the synovium, such as bursae, tendons, and bone, may also become damaged in those with septic arthritis.[3]

Causes and Microbiology

Typically, hematogenous osteomyelitis or septic arthritis is caused by a single strain of bacterium, with gram-positive organisms being responsible for most infections. Even though gram-negative organisms account for 43% of cases of community-acquired bacteremia, they result in only about 10% of septic arthritis cases. Trauma predisposes patients to osteomyelitis by environmental pathogens. Patients who are wounded or sustain open fractures in fresh water are susceptible to infections with the gram-negative bacillus *Aeromonas hydrophila.* People who are bitten by animals, particularly dogs and cats, are at risk for the development of osteomyelitis from *Pasteurella multocida.* Osteomyelitis caused from human bites is most common in the hand and involves human oral flora, such as *Streptococcus anginosus, Fusobacterium nucleatum,* and *Eikenella* spp. In the population of injection drug users, *Staphylococcus aureus* is the most likely cause of infection, followed by *Pseudomonas* spp. *Pseudomonas aeruginosa* is also an important cause of osteomyelitis in puncture wounds, postsurgical wounds, and patients with sickle cell anemia.

Certain underlying disease states predispose a patient to BJI. These conditions include diabetes mellitus, sickle cell disease, AIDS, alcoholism, injection drug use, chronic corticosteroid use, preexisting joint disease (especially rheumatoid arthritis), and other immunosuppressed states. Postsurgical patients are also susceptible to BJIs, especially those who have implanted prosthetic devices.

Although most BJIs are bacterial, other pathogens include viruses, fungi, and parasites. The microbiology of osteomyelitis and septic arthritis is a function of several host and environmental factors. A patient's living environment also has some role in determining the incidence of BJIs. For example, people living in crowded conditions where tuberculosis is prevalent are at increased risk for tubercular BJIs, whereas older patients in hospitals and institutions may be more susceptible to infections with gram-negative bacteria. A summary of the organisms that cause osteomyelitis and septic arthritis is presented in Tables 128.1 and 128.2. The following points deserve special mention:

- In all age groups except neonates, *S. aureus* is the leading cause of osteomyelitis. In neonates, group B streptococci, *Escherichia coli* and other gram-negative coliforms, and *Staphylococcus epidermidis* are the most common pathogens responsible for BJIs.
- Since the introduction of the vaccine, *Haemophilus influenzae* type b, once a common cause of septic arthritis and osteomyelitis in children younger than 2 years, has essentially disappeared as a pathogen in vaccinated children.[4] Another gram-negative coccobacillus in the Neisseriaceae family, *Kingella kingae* has been encountered with increasing frequency. *K. kingae* can be part of the normal flora of the nasopharynx; like *H. influenzae,* it can be spread hematogenously to bones and joints. It is a fastidious organism and may be mistaken for *Haemophilus* or *Neisseria* spp.
- *P. aeruginosa* has been reported as a cause of cervical spine osteomyelitis in injection drug users and lumbar spine osteomyelitis in patients with urinary catheters in place for a long time. *Pseudomonas* colonizes the rubber and plastic inserts in footwear and is therefore seen in soft tissue infections and osteomyelitis of the foot after a puncture wound.
- In older adults and patients with diabetes, gram-negative bacteria account for a higher percentage of cases of bone and joint infections.
- Methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis,* and vancomycin-resistant enterococci (VRE) have emerged as a significant microbiologic problem in the past 2 decades. Multiresistant enterococci pose the greatest potential danger in that no currently available antibiotic regimen is reliably bactericidal against such organisms.

Certain disease processes are more likely to be due to a polymicrobial infection. This would include diabetic foot osteomyelitis, posttraumatic osteomyelitis, and chronic septic arthritis or osteomyelitis. Furthermore, anaerobic bacteria can complicate polymicrobial infection and may be present more often than is

TABLE 128.1

Microbiology of Bacterial Septic Arthritis as Related to Age of the Patient

ORGANISM	CHILD (%)[a]	YOUNG ADULT ENGAGING IN HIGH-RISK SEXUAL BEHAVIOR (%)	ADULT (%)	OLDER ADULT (%)
Staphylococcus aureus	10–20	15–20	60–0	45–65
Streptococcus species	5–10	1–5	15–20	10–15
Gram-negative bacterium	1–5	Rare	10–5	15–35
Haemophilus influenza	Rare[b]	Rare[b]	Rare[b]	Rare[b]
Neisseria gonorrhoeae	1–5	60–80	1–5	Rare

[a]Ages 6 months to 5 years.
[b]With widespread immunization.
Reprinted with permission from Esterhai JL Jr, Rao N: The epidemiology of musculoskeletal infections. In Cierny G 3rd, McLaren AC, Wongworawat MD, editors: Orthopaedic knowledge update: musculoskeletal infection. Rosemont, IL, 2009, American Academy of Orthopaedic Surgeons.

TABLE 128.2

Microbiology and Initial (Empirical) Antibiotic Treatment of Bone and Joint Infection

	OSTEOMYELITIS		SEPTIC ARTHRITIS	
AGE GROUP	**Common Organisms**	**Antibiotic Regimen**	**Common Organisms**	**Antibiotic Regimen**
Neonate to <3 mo	*Staphylococcus aureus* Group B streptococcus Enterobacteriaceae Gram-negative rods	Ceph 3 PRP + gentamicin Consider vancomycin instead of PRP for MRSA.	*S. aureus* Group B streptococcus Enterobacteriaceae	PRP + Ceph 3 Alt—PRP + APAG Consider vancomycin instead of PRP for MRSA.
3 mo–14 yr	*S. aureus* Group A streptococcus *Haemophilus influenzae*	PRP + Ceph 3 Alt: vancomycin + Ceph 3, chloramphenicol PRP or Ceph 3 with allergy to penicillin or clindamycin with allergy to penicillin + Ceph 3	*S. aureus* Group A streptococcus *Streptococcus pneumoniae* *H. influenzae*	PRP + Ceph 3 Alt—vancomycin + Ceph 3
14 yr–adult	*S. aureus*	PRP Alt—vancomycin	*S. aureus* Streptococcal spp. Enterobacteriaceae	PRP or Ceph 3 Alt—vancomycin + Ceph 3 *or* penicillin + aminoglycoside or Ceph 3
INFECTION SUBSETS				
Sexually active adolescents or adults with acute arthritis			*Neisseria gonorrhoeae*[a]	Ceph 3 Alt—spectinomycin *or* penicillin if sensitive
Chronic osteomyelitis and diabetic foot infections	*S. aureus* Enterobacteriaceae Anaerobic bacteria	PRP + FLQ + metronidazole Alt—PRP + Ceph 3 + clindamycin		
Infected orthopedic joint prosthesis	*Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa*	Vancomycin + FLQ Alt—imipenem	*S. aureus* *S. epidermidis* *P. aeruginosa*	Vancomycin + FLQ Alt—PRP + APAG
Sickle cell disease	*Staphylococcus aureus* *Salmonella* sp.	PRP + Ceph 3 Alt—FLQ	*S. aureus* *Salmonella* spp.	PRP + Ceph 3 Alt—FLQ
Injection drug abuse	*Staphylococcus aureus* *Pseudomonas aeruginosa* Enterobacteriaceae	Ceph 3 + aminoglycoside Alt—Ceph 3	*P. aeruginosa* *S. aureus* Enterobacteriaceae	PRP + APAG or FLQ Alt—vancomycin + FLQ
Plantar puncture wound	*Pseudomonas aeruginosa*	AP Ceph Alt—FLQ	*P. aeruginosa*	AP Ceph Alt—FLQ
Human or animal bites	*Eikenella corrodens* *Pasteurella multocida*	Penicillin ± AC Alt—Ceph 3, TS	*E. corrodens* *P. multocida*	Penicillin ± AC Alt—Ceph 3, TS

[a]Concurrent treatment of *Chlamydia trachomatis* infection should be given to patients with suspected *N. gonorrhoeae* septic arthritis.
Alt, Alternative antibiotics; *APAG,* antipseudomonal aminoglycoside; *AP Ceph,* antipseudomonal cephalosporin (ceftazidime or cefepime); *Ceph 3,* third-generation cephalosporin (eg, ceftriaxone, cefotaxime, cefamandole, ceftizoxime, ceftazidime, cefazolin, moxalactam); *FLQ,* fluoroquinolone; *MRSA,* methicillin-resistant *S. aureus*; *PRP,* penicillinase-resistant penicillin (oxacillin, nafcillin, methicillin, amoxicillin-clavulanate [*AC*]); *TS,* trimethoprim-sulfamethoxazole.

commonly recognized. This is because standard culture techniques may be inadequate to identify them. For example, anaerobic bacteria are reportedly discovered in up to 40% of cases of chronic osteomyelitis.

Mycobacterium tuberculosis may infect bones and joints, usually in the axial skeleton. The two most common forms of skeletal infection are vertebral osteomyelitis (Pott's disease), in which the spine is affected in 50% of cases, and tubercular arthritis, which manifests as a chronic, low-grade inflammatory process that resembles rheumatoid arthritis more than acute septic arthritis.

Patients with human immunodeficiency virus (HIV) infection and AIDS are predisposed to a variety of common and opportunistic pathogens. Although *S. aureus* is still the most likely cause of bone and joint infections in patients with AIDS, fungal and other atypical organisms should be considered. One unusual but particularly characteristic form of osteomyelitis in HIV-positive patients is bacillary angiomatosis. This infection is caused by a ram-negative, rickettsia-like organism that frequently causes osteolytic bone lesions.

OSTEOMYELITIS

Clinical Features

History and Physical Examination

The symptoms and signs of osteomyelitis in adults are predictable, although not always present. Patients with osteomyelitis often present with fever, more reliably seen in children, and rigors and may even appear toxic. Systemic complaints of headache, fatigue, malaise, and anorexia are inconsistently reported and are less likely with chronic osteomyelitis. In children with lower extremity osteomyelitis, a sudden limp or inability to bear weight, localized warmth, swelling, and erythema may be reported. A careful review

of the patient's past medical history should be performed to identify risk factors that may predispose to bone infection.

The physical examination findings of osteomyelitis are fairly specific. The predominant symptom of osteomyelitis is pain over the affected bone. Palpation usually elicits point tenderness over the infected segment. Palpable warmth and soft tissue swelling with erythema may be present, but these findings are variable. In chronic advanced osteomyelitis, the involucrum or sequestrum may be palpated, and sinus tracts that fistulize to the skin may be noted. A so-called sympathetic effusion in the adjacent joint may develop in patients with osteomyelitis, even when the joint is not infected.

Complications

In addition to the development of chronic osteomyelitis, complications of acute osteomyelitis include bacteremia and sepsis. Depending on the location of osteomyelitis, local extension of an invasive suppurative process can lead to septic arthritis, brain abscess, meningitis, spinal cord compression, pneumonia, and empyema. In children, osteomyelitis damages the developing skeleton. If infection involves the epiphysis, permanent growth alterations can occur, resulting in a shorter or deformed extremity on the affected side. Pathologic fractures may occur through sites of osteomyelitis.

Clinical Subsets of Osteomyelitis

Osteomyelitis in Children. Osteomyelitis in children tends to be acute, usually arising from hematogenous seeding of bone, and can often be treated with antibiotics alone. Acute hematogenous osteomyelitis (AHO) is seen in children as young as 3 months and as old as 16 years. *S. aureus* is the most common infecting organism in children of all ages, except neonates (see Tables 128.1 and 128.2). As noted, *H. influenzae* is no longer a common cause of AHO.

AHO has a well-established male preponderance (male-female ratio of 2:1 to 3:1) and involves long bones approximately 80% of the time. The site of infection is usually the distal metaphysis because of its increased vascularity, but up to 30% of AHO occurs in other parts of the bone. Children with AHO may have fever, chills, vomiting, dehydration, and malaise, but they usually do not appear toxic. Most children have characteristic pain, limited use of the limb, and are point tender. The diagnostic evaluation for AHO is shown in Fig. 128.2. Blood cultures are positive for the bacterial cause of osteomyelitis in 60% of patients with AHO. A positive blood culture and physical examination consistent with osteomyelitis may be sufficient for a diagnosis of AHO to be made. Figs. 128.3 and 128.4 show typical radiographs of AHO.

Neonatal osteomyelitis is difficult to diagnose because of minimal systemic findings. Osteomyelitis in the neonate is more commonly seen after an abnormal pregnancy or delivery and often accompanies other acute illnesses. Multiple sites of bone involvement are found in approximately 50% of reported cases. Because of the unique vascular anatomy of the neonate, septic arthritis often accompanies osteomyelitis. Osteomyelitis of the flat bones, such as the facial bones, is more common among neonates than any other age group. Group B streptococcus is the leading causative bacterium in neonatal osteomyelitis, but staphylococcal species are still common. As with adults, plain radiographs are a good initial test because abnormalities are identified within days of development of neonatal osteomyelitis; they are usually abnormal by the time the disease is suspected. In the presence of a normal radiograph, the next step for the emergency clinician who suspects neonatal osteomyelitis is magnetic resonance imaging (MRI) in consultation with the orthopedic surgical service.

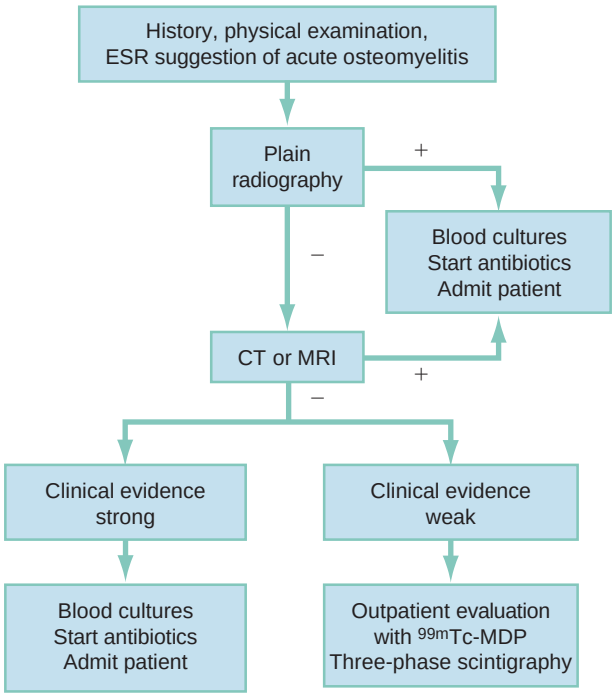

Fig. 128.2. Algorithm for the use of imaging studies in the emergency department diagnosis of osteomyelitis. *CT,* Computed tomography; *ESR,* erythrocyte sedimentation rate; *MRI,* magnetic resonance imaging; *^{99m}Tc-MDP,* technetium Tc-99m–labeled methylene diphosphonate.

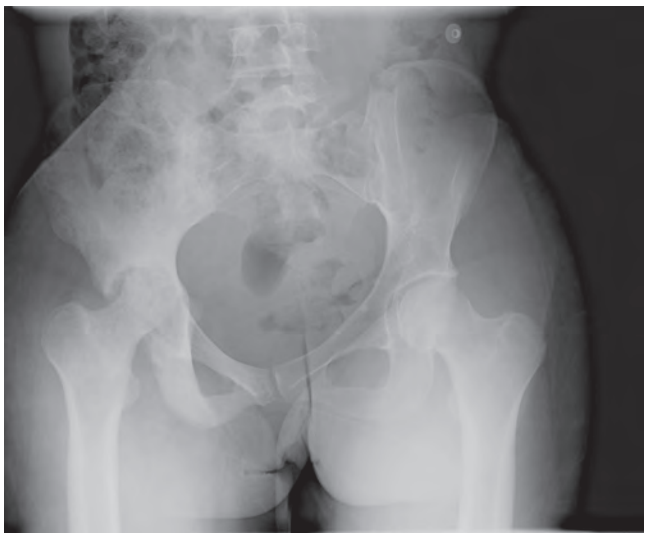

Fig. 128.3. Radiograph of chronic osteomyelitis. Diffuse sclerosis of the right hemipelvis includes the ischium and iliac bone, with extension to the right sacroiliac joint. The right acetabulum demonstrates whittling of the femoral head and neck, with marked loss of bone stock. Abutting the right symphysis pubis is increased cortical lucency suggestive of subchondral cystic changes. (Courtesy Dr. Peter Evangelista, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

Two less common forms of osteomyelitis can occur in children, subacute osteomyelitis and chronic recurrent multifocal osteomyelitis (CRMO). Subacute osteomyelitis refers to a form of the disease in which clinical symptoms and signs are slow to appear, and radiographs show small areas of osteomyelitis, usually in the metaphysis of long bones. Cultures of blood and bone are negative more than 50% of the time but usually implicate staphylococcal species when they are positive.

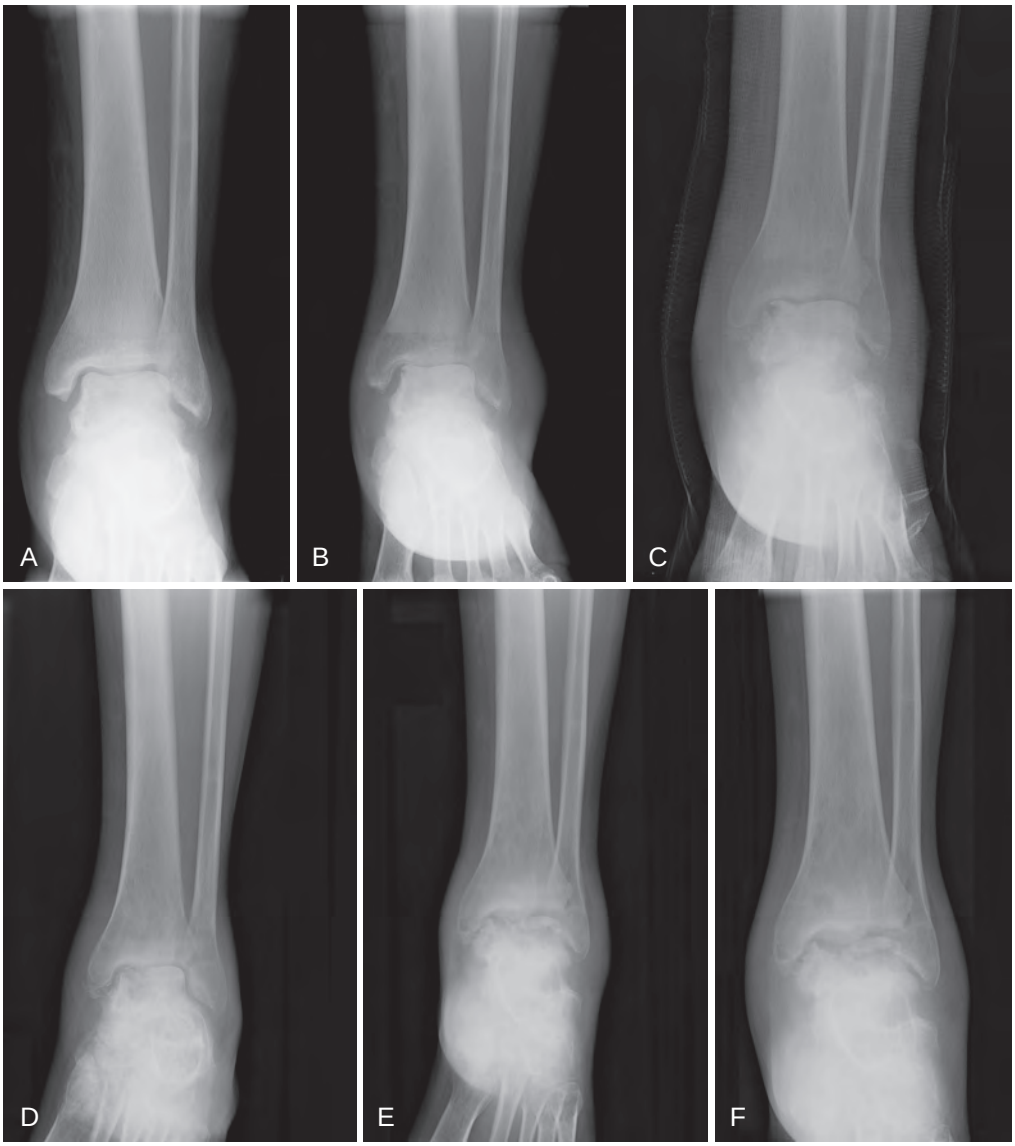

Fig. 128.4. Radiographic progression of acute osteomyelitis. **A,** Soft tissue swelling at the medial and lateral aspects of the ankle, with a moderately sized effusion (August 2, 2006). **B,** Large ankle effusion with extensive soft tissue swelling. There is complete loss of the tibiotalar joint space and widening of the medial joint space, suggesting chondrolysis. There are lucent areas in the distal tibia and fibula, suggestive of hyperemia, and the talus is diffusely sclerotic (September 11, 2006). **C,** Increased erosion of the medial aspect of the talar dome, with increased joint effusion (October 12, 2006). **D,** Talar bone destruction with demineralization involving all the osseous structures. There is also a small joint effusion (January 2, 2007). **E,** Avascular necrosis of the talus and destruction of the articular surfaces of the tibia and talus is present, consistent with chronic osteomyelitis. There is diffuse osteopenia and loose bodies within the joint (April 19, 2007). **F,** There is continued irregularity of the articular surface of the tibia and collapse of the talus. Loose bodies are still present within the joint, and there is a persistent joint effusion and soft tissue swelling (June 14, 2007). (Courtesy Dr. Thomas Egglin, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

Like subacute osteomyelitis, CRMO usually affects older children (6–10 years) and adolescents. CRMO is characterized by small foci of infection at various sites in the skeleton. The disease is defined by multiple episodes of indolent infection. Diagnosis is made by radiography because culture of the bone sites is almost always negative. This disease may be associated with certain psoriatic subtypes.

Vertebral Osteomyelitis. Vertebral osteomyelitis usually afflicts older adults in a manner analogous to that of AHO in children and appears to be increasing in frequency as the population ages and has more chronic medical diseases. Risk factors in older adults include intravenous (IV) access devices, indwelling lines, and asymptomatic urinary infections, whereas in younger individuals, risk factors include injection drug abuse. The spine is susceptible to bacterial infection because the venous system surrounding vertebral bodies is valveless, permitting two-way flow of blood, and has transverse and longitudinal anastomoses. Infection can readily spread to adjacent vertebral bodies. Vertebral osteomyelitis usually results from hematogenous seeding, direct inoculation at the time of spinal surgery, or contiguous spread from an adjacent infection. A clear source of bacterial hematogenous seeding with positive blood cultures occurs in approximately 40% of cases of vertebral osteomyelitis. *S. aureus* (including MRSA) is

the most common offending agent, followed by aerobic gram-negative rods from urinary or gastrointestinal sources.

Only 10% of patients with vertebral osteomyelitis appear septic or toxic; most patients present with insidious symptoms, leading to delays in diagnosis of up to 4 months. Back pain, seen in roughly 90% of patients, is the most common presenting symptom, and physical examination often reveals tenderness over the spinous process. Neurologic deficits are reported in less than 40% of patients with vertebral osteomyelitis and often coincide with a concomitant epidural abscess.[5] Up to 60% of patients with these abscesses present without fever or leukocytosis. On laboratory testing, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are elevated in 98% and 100% of cases, respectively.[5] Blood culture specimens should be obtained before antibiotic treatment is initiated. Rapid diagnosis and treatment of this medical emergency starts with the initiation of empirical antibiotics, immediate imaging, and early orthopedic involvement.

The imaging strategy for the diagnosis of vertebral osteomyelitis starts with plain radiography, which may show disk space narrowing or destruction of the vertebral endplates or vertebral body. Similar to osteomyelitis in other parts of the body, findings on plain radiographs are not seen until at least the second week of vertebral infection. Bone scintigraphy has been largely replaced by MRI in further imaging of suspected vertebral osteomyelitis. Although computed tomography (CT) is good for defining bone destruction and is often used to assist needle aspiration of the lesion, MRI can identify an epidural abscess and rule out other noninfectious vertebral conditions. MRI has a sensitivity of 90% for vertebral osteomyelitis, with T2-weighted images most valuable in establishing the diagnosis.

Vertebral infections can occur in the lumbar (58%), thoracic (30%), and cervical (11%) spine. Cervical spine osteomyelitis can cause a retropharyngeal abscess; lumbar spine osteomyelitis may be complicated by a psoas muscle abscess. The spinal cord may also suffer ischemic injury if the vertebral infection causes septic thrombosis or compression of local blood vessels. When osteomyelitis affects the thoracic spine, infection can spread to the chest. Paraspinal abscesses, reactive pleural effusions, and empyema have been reported and may mislead the emergency clinician to suspect that the primary problem is not in the spine. The most dreaded complication of vertebral osteomyelitis is the spread of infection into the spinal canal, development of an epidural abscess, and progression of the infection to cause spinal cord injury and permanent paralysis. Fortunately, this occurs in less than 15% of cases of vertebral osteomyelitis. Patients who are at increased risk for paralysis include older adults, those with cervical spine osteomyelitis, and those with serious underlying diseases (eg, rheumatoid arthritis, diabetes mellitus).

The diagnostic procedure of choice for vertebral osteomyelitis is needle biopsy, which can isolate the causative organism. Patients who present with a clinical picture consistent with that of vertebral osteomyelitis require rapid diagnostic confirmation through imaging or by direct needle biopsy performed by a radiologist or surgeon, with or without CT guidance. A delay in the definitive diagnosis puts the patient at risk for the progression of vertebral osteomyelitis to spinal cord compression.

Patients with vertebral osteomyelitis initially require IV antibiotic therapy based on the offending microorganism and its susceptibility. Vertebral osteomyelitis can usually be successfully treated with antibiotics alone; surgery may be required for diagnostic purposes, when there is spinal cord compression, for abscess drainage or débridement, for correction of the progressive deformity, and if the infection recurs after adequate treatment.[5]

Diskitis is a variant of vertebral osteomyelitis. The disk is an avascular structure that depends on nutrient diffusion from adjacent blood vessels in the vertebral body and endplates. The avascular disk creates a rich environment for the bacteria to flourish. Because of the vascular anatomy, adult pyogenic diskitis coexists with vertebral osteomyelitis; in children, however, isolated diskitis is more common. The patient complains of back pain and may refuse to walk. Although bone scintigraphy may show increased uptake in the disk space, MRI better demonstrates the anatomy of diskitis. CT is used to guide aspiration. Cultures of the disk from needle aspiration are reported to be positive for bacteria 30% to 60% of the time, usually y for *S. aureus*. The disease typically resolves with nonoperative treatment.

Posttraumatic Osteomyelitis. Posttraumatic osteomyelitis is a form of contiguous focus osteomyelitis that results from open fractures, burns, bites, puncture wounds, and surgery and invasive procedures. At least 10% of open fractures later develop osteomyelitis, with the tibia being the bone that is usually affected. The fracture site may be contaminated directly from the environment or iatrogenically secondary to emergency procedures or surgery. The intraoperative implantation of prosthetic devices increases the chance of infection. Severe damage to adjacent soft tissues results in a necrotic nidus of infection that can spread to bone. Polymicrobial infection is more common with this type of osteomyelitis. The imaging of posttraumatic osteomyelitis is complicated by changes induced by surgery and new bone formation in the fracture; therefore, the optimal imaging modalities are MRI and CT.

Osteomyelitis due to direct inoculation associated with joint arthroplasty typically becomes evident about 12 weeks after surgery, but these patients generally do not report relief of their pain after surgery. Patients who have symptoms of infection more than 12 weeks after surgery and who have postoperative improvement of their pain are considered to have a hematogenous source of infection. If either of these presentations is recognized within the first 2 weeks of onset of infectious symptoms, the prosthesis is considered salvageable. After 2 weeks, the chance of eradicating the infection without removal of the prosthesis decreases substantially.

The most common form of postsurgical osteomyelitis is infection of a hip prosthesis, which occurs in 1% to 5% of hip replacement surgeries. Postsurgical osteomyelitis is difficult to diagnose. Fever is often absent, and the patient often presents with a painful joint. *S. aureus* and *S. epidermidis* account for 75% of postsurgical and prosthesis-related cases of osteomyelitis. Radiographs are often normal but may show subtle signs of bone resorption and loosening of the prosthetic components. It is difficult to distinguish mechanical from infectious loosening; therefore, joint aspiration, synovial fluid analysis, and bone biopsy performed in a sterile operative setting are undertaken to establish a firm diagnosis. Other imaging techniques such as CT and MRI are used but are difficult to interpret because of scatter from the metallic components and postsurgical changes. Systemic antibiotics cannot penetrate the biofilm, and surgical removal of the prosthesis is usually the only way to cure the infection.

Puncture wounds to the feet have approximately a 2% incidence of development of osteomyelitis. The causative organism is usually *S. aureus* or beta-hemolytic streptococcus. *P. aeruginosa* is commonly associated with plantar wounds that occur while a person is wearing rubber-soled shoes. Puncture wounds to other parts of the body are typically nosocomial and are often due to subclavian venipuncture, fetal scalp monitoring, and other invasive procedures.

Diabetic Foot Osteomyelitis. The pathologic changes induced by long-standing diabetes mellitus, such as compromised vascularity, encourage the development of osteomyelitis. The typical patient with diabetic foot osteomyelitis is older than 50 years and has advanced, insulin-dependent diabetes. Over 60% of

patients report polyneuropathy, over 50% report retinopathy, and at least 30% have concurrent cardiovascular disease. The neuropathy leads to repetitive trauma and subsequent foot ulcers. Once the skin has been violated and infected, the altered host defenses of diabetic patients make it easier for infection to occur and spread. Hyperglycemia resulting from the infection allows bacteria to proliferate, impairs leukocyte function, and results in defective chemotaxis, abnormal phagocytosis, decreased bactericidal function, defective antibody synthesis, and decreased complement levels, all of which impair healing and exacerbate osteomyelitis. The infection typically starts in the periosteum of the phalanges, spreads to the cortex, and eventually disrupts medullary bone.

Local findings in diabetic foot infections include swelling, erythema, and sometimes pain. Indolent ulcers and frank cellulitis are seen in more than 50% of cases. Because the process is often chronic, radiographic changes are often notable. Mottled lytic lesions are typical, and air may be present in the soft tissues. The only reliable way for the bacteriologic diagnosis to be made is by surgical culture of the bone; however, wounds that can be probed all the way to the bone have a 90% positive predictive value for osteomyelitis.[6] Bone biopsy for diabetic foot osteomyelitis has a reported sensitivity of 94%. Diabetic foot osteomyelitis is usually polymicrobial. *S. aureus* is the most common pathogen; other organisms include streptococci, Enterobacteriaceae, and anaerobes. Surgical treatment with amputation had been the mainstay of treatment; however, a 10-week antibiotic treatment regimen, including IV administration followed by oral antibiotics, can be successful.[7]

Osteomyelitis in Sickle Cell Disease. Patients with sickle cell disease (so-called sicklers) are at increased risk for hematogenous infection, including osteomyelitis. In contrast to AHO in nonsicklers, AHO in children with sickle cell disease usually affects the diaphysis instead of the metaphysis. Also, although *S. aureus* is the most common bacterium in children with sickle cell disease who have osteomyelitis, *Salmonella* spp. are the next most common infecting organism. Reasons for this are not completely understood, although it has been postulated that microinfarcts in the bowel allow *Salmonella* bacteremia to seed the bloodstream and lead to hematogenous osteomyelitis.

The differentiation of bone infection from bone infarction in sickle cell patients is a challenge. Fever, toxic appearance, and elevated ESR are more commonly associated with osteomyelitis than with bone infarction. Plain radiographs are not helpful in distinguishing between the two entities, but MRI has been proving useful in differentiating between the two. Another approach is to note the response to conservative therapy—bone infarctions usually improve within 24 to 48 hours, whereas bone infection worsens. Antibiotic treatment of osteomyelitis in the sickle cell patient should include coverage against *Salmonella* with a third-generation cephalosporin.

Chronic Osteomyelitis. Most chronic bone infections occur as a complication of posttraumatic infection, surgical procedures, or diabetic foot infections. The inflammatory response to infection triggers bone resorption and cartilage destruction and ultimately leads to bone death (see Fig. 128.3). The necrotic bone acts like a foreign material, providing an inanimate surface to which microorganisms adhere. Clinical signs that the infection has become chronic include the formation of sequestra and presence of draining tracts or fistulas. Chronic infection is almost always polymicrobial and commonly involves anaerobes. Because sinus tract culture is not a reliable method to predict which bacteria are active in the underlying bone infection, direct biopsy of bone is the only option for the accurate diagnosis of most cases of chronic osteomyelitis. Chronically established infections can be remarkably persistent or evolve even in the face of prolonged antibiotic therapy; therefore, treatment commonly involves surgery.

Differential Diagnosis

Many processes involving bone may masquerade as osteomyelitis. Bone tumors, such as osteoid osteomas and chrondroblastomas, may produce local pain and radiographic changes consistent with osteomyelitis, such as small, round, radiolucent lesions. Ewing's sarcoma is a tumor of bone marrow in children that can be mistaken for osteomyelitis. Metastatic bone tumors and lymphomas should also be considered in the differential diagnosis of osteomyelitis. Finally, occult fractures, such as buckle fractures in children, present with point tenderness that may be mistaken for osteomyelitis.

Diagnostic Testing

Laboratory Tests

Initial evaluation in the emergency department (ED) often involves laboratory and radiographic evaluation, but the gold standard to confirm diagnosis is bone biopsy and culture, which also helps guide treatment. Laboratory data are not specific and can only suggest the diagnosis of osteomyelitis. In acute osteomyelitis, the white blood cell (WBC) count can be elevated—typical values range from normal to 15,000/mm^3—whereas in chronic osteomyelitis, the WBC count is often normal.

The ESR, a nonspecific measure of inflammation, is more helpful than the WBC count. The ESR is a relatively sensitive marker for infection, and many series have reported elevated ESR and CRP values[8] in patients who have confirmed osteomyelitis. An elevated ESR in the presence of appropriate physical findings should lead one to suspect osteomyelitis, but a normal or slightly elevated ESR does not eliminate the diagnosis. Other inflammatory conditions, such as cellulitis, can cause an elevated ESR, although the degree of elevation of the ESR is often higher with osteomyelitis. In the evaluation of a diabetic foot infection, an ESR greater than 70 mm/hr predicts the presence of an underlying bone infection.

The CRP level, another nonspecific marker of inflammation, increases within the first 24 hours of infection, peaks within approximately 48 hours, and is usually normal within 1 week of therapy. The CRP level may be a better early indicator of disease, but the ESR is most valuable in following response to treatment. Typically, the ESR falls steadily as osteomyelitis resolves and increases should it recur. However, it is common to see elevations in one and not the other parameter, especially when there is development of a concurrent illness or the infection has progressed so that the ESR rises but the CRP rises and falls. In children, an elevated ESR or CRP level is seen in all cases of osteoarticular infection; sensitivity of the use of both the ESR and CRP value is 98%, but a leukocytosis is reportedly seen in only 35% of cases.[8]

Diagnostic Imaging

Conventional Radiography. Conventional radiography is the initial modality of choice to evaluate osseous changes and, in most cases, will be the only imaging technique used to aid in the diagnosis of osteomyelitis. This is true even though radiographic evidence of osteomyelitis lags behind the clinical picture, and less than one-third of patients have abnormalities on plain radiographs in the first 7 to 10 days after the onset of symptoms,.

Conventional radiography is readily available, relatively inexpensive, and useful in the differentiation of infection from trauma and tumors. The characteristic findings of early osteomyelitis on

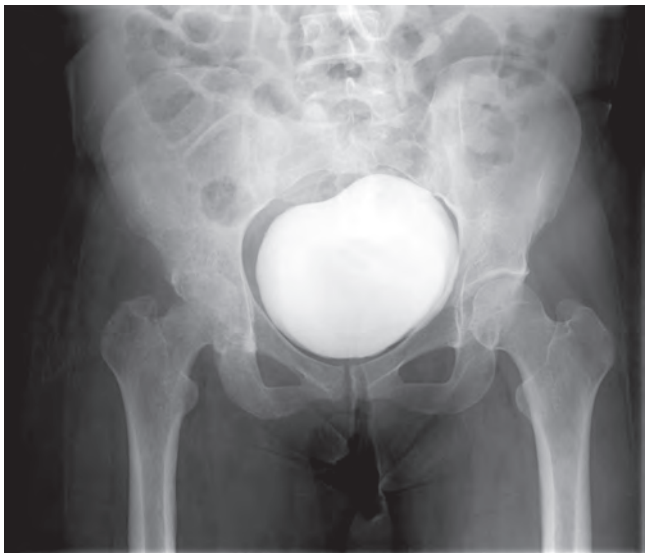

Fig. 128.5. Radiograph of right hemipelvis and proximal femur demonstrate permeative moth-eaten changes, with resultant femoroacetabular joint space narrowing consistent with osteomyelitis. (Courtesy Dr. Peter Evangelista, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

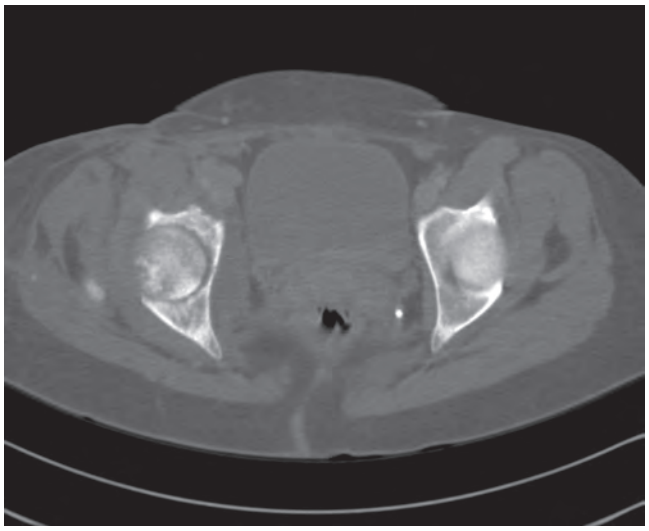

Fig. 128.6. CT scan of osteomyelitis. There is a diffuse moth-eaten appearance involving the right hemipelvis and right femoral head, with abundant periosteal reaction. (Courtesy Dr. Peter Evangelista, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

the plain radiograph are lucent lytic areas of cortical bone destruction (see Fig. 128.4). However, lucency is not detected on radiographs until approximately 50% of bone mineral is lost, which often takes up to 2 weeks from the onset of infection. Although these findings are often difficult to identify on plain radiographs, soft tissue edema, deep soft tissue swelling, distorted fascial planes, and altered fat interfaces may be present within 3 to 5 days from the onset of infection and can serve as a clue to osteomyelitis in the underlying bone. A periosteal reaction, hypertrophy or elevation of the periosteum, and presence of an involucrum can also be seen, especially in children, given their thinner periosteum (Fig. 128.5). In advanced disease, the lytic lesions are surrounded by dense sclerotic bone, and sequestra may be noted. By 28 days from the onset of osteomyelitis, 90% of the plain radiographs are abnormal.

Radionuclide Bone Scanning. Radionuclide skeletal scintigraphy (bone scanning) is more sensitive than plain radiography for the early diagnosis of osteomyelitis. Bone scanning is especially useful in the presence of prosthetics or other hardware. Radionuclide scans can detect osteomyelitis within 48 to 72 hours after the onset of infection. A radioactive tracer is injected into the bloodstream and given time to bind or accumulate in body tissues, after which a camera is used to determine released radioactivity. An image is created that is evaluated for an increase or decrease in expected uptake of the radionuclide. Given the radiation burden associated with this modality, however, in the past 2 decades, there has been a movement away from skeletal scintigraphy to MRI to diagnose osteomyelitis.

Computed Tomography. CT may be also useful in the diagnosis of osteomyelitis. The bony cortex is particularly well seen on CT, and involucrum and sequestrum formation is easily identified. CT is generally used to detect and define areas of possible infection in bones that are difficult to visualize on plain radiographs, such as the sternum, vertebrae, pelvic bones, and calcaneus. On CT scan, osteomyelitis appears as lucent areas (Fig. 128.6), and gas may be seen in bony abscess cavities. The limitation of CT for the early diagnosis of osteomyelitis is the same as that for plain radiography, in that the disease must be present for more than 1 week for changes to be apparent. The CT scan can guide the surgeon in débridement and resection of infected bone and in choosing a site for diagnostic biopsy.

Magnetic Resonance Imaging. The use of bone scans and CT for the evaluation of osseus anatomy has been decreasing as the availability and image quality of MRI improves while its cost decreases. MRI is useful to help diagnose osteomyelitis but is not helpful in diagnosing septic arthritis. The anatomic resolution of MRI is far superior to that of bone scans and plain radiographs. MRI findings are often evident before an abnormality is detected by other modalities because of the earlier detection of bone marrow involvement and medullary or cortical destruction, periosteal reaction, edema, soft tissue extension, joint effusion, articular damage, and complications of osteomyelitis, such as abscess formation. Whereas the presence of ferromagnetic material is a contraindication to the use of MRI, most materials used in orthopedic surgery, such as titanium and chrome cobalt, do not interfere with this imaging modality. Metal may cause distortion of the signal in the area adjacent to a joint prosthesis, but this does not exclude MRI in this group of patients. Optimal MRI images are obtained with a combination of spin echo T1- and T2-weighted images, short tau inversion recovery (STIR) images, and fat-suppressed, T2-weighted images. Osteomyelitis produces a diminished intensity of the normal marrow signal on T1-weighted images and a normal or increased signal on T2-weighted images (Fig. 128.7). These findings, however, are not specific to osteomyelitis; the differential diagnoses for the MRI findings in acute osteomyelitis are trauma, noninfectious inflammatory and metabolic lesions, and cancer. In cases in which a surgical procedure will be done to obtain a microbiologic diagnosis or is needed to treat osteomyelitis, MRI has obvious advantages over other modalities in detailing the anatomy for the surgeon.

The administration of gadolinium as a contrast agent enhances the interface between normal and abnormal marrow and helps distinguish devitalized bone from normally perfused bone. Gadolinium becomes localized in areas of increased vascularity and blood flow and also helps distinguish soft tissue infections, such as abscesses and cellulitis from osteomyelitis. Whereas contrast agents increase reader confidence in the diagnosis of osteomyelitis,

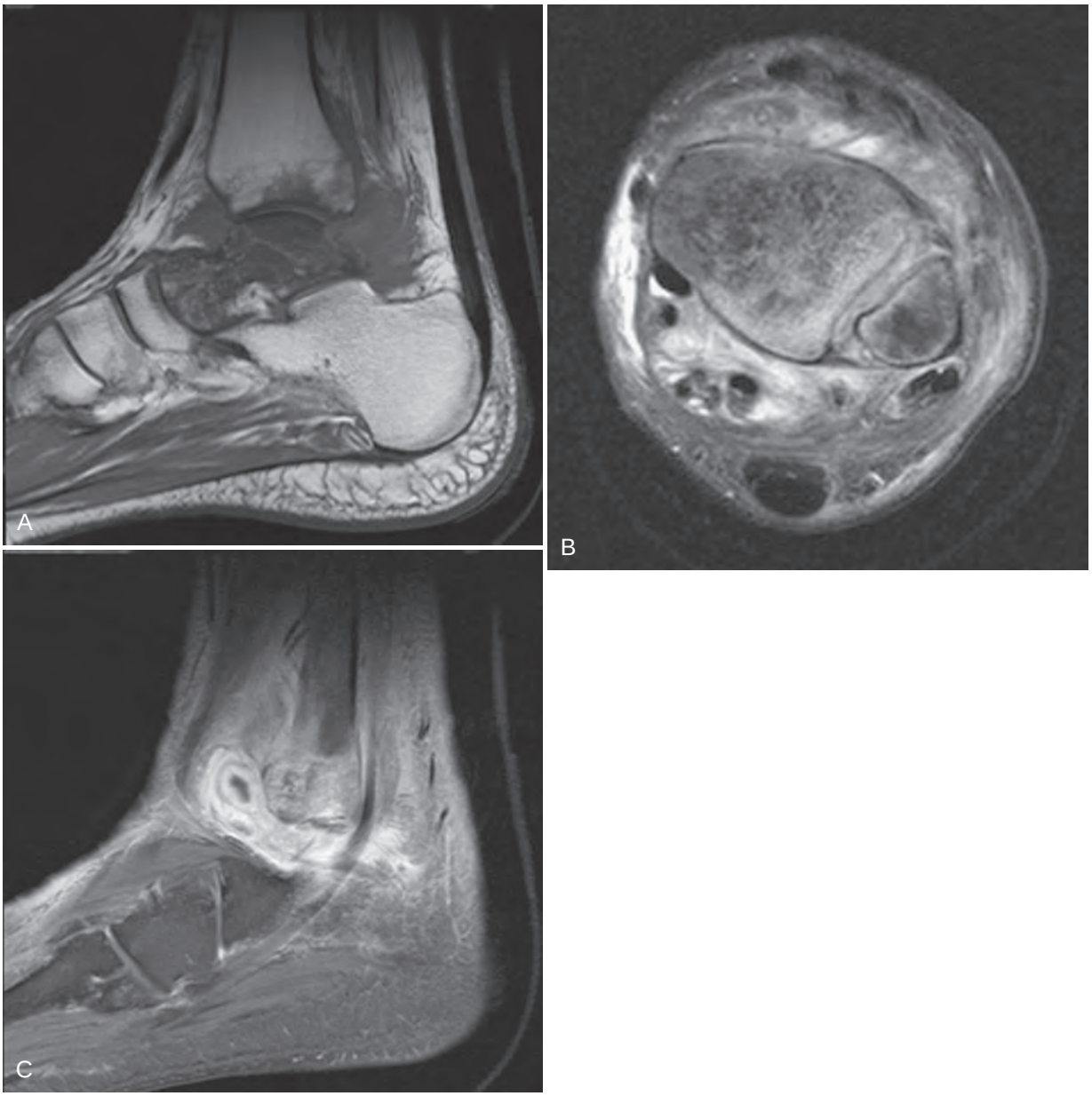

Fig. 128.7. MRI scan of osteomyelitis. **A,** Sagittal T1 image shows decreased signal within the talus, suggesting osteomyelitis. **B,** Axial T2 image demonstrating increased signal throughout the talus and distal fibula consistent with osteomyelitis (fat-suppressed image). **C,** Sagittal T1 image after the administration of gadolinium demonstrates a small focus of nonenhancing fluid just anterior to the distal fibula, suggestive of an abscess. (Courtesy Dr. Thomas Egglin, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

they do not increase the sensitivity or specificity of the diagnosis of osteomyelitis (Fig. 128.8).

Microbiologic Diagnosis

The most definitive way to diagnose osteomyelitis is to obtain infected bone by needle aspiration or surgical resection. This also helps guide antimicrobial therapy. Culture of draining fistulas or sinus tracts is not an acceptable substitute because these cultured organisms often differ from those in the underlying infected bone. Because osteomyelitis may be polymicrobial or due to unusual microorganisms, especially in immunocompromised patients, cultures for fungal and anaerobic organisms should be included.

Particularly in cases of hematogenous osteomyelitis, cultures of blood, urine, cerebrospinal fluid, when necessary, and pus from other sites of infection can help identify the infecting bacteria. Blood cultures in patients with acute untreated osteomyelitis are positive for the offending bacteria approximately 50% of the time. In chronic osteomyelitis, blood cultures are almost always negative.

The emergency clinician's diagnostic approach in suspected osteomyelitis has become simpler as radionuclide scintigraphy becomes obsolete. The algorithm in Fig. 128.2 provides a simplified approach to the diagnostic strategy in a patient with suspected osteomyelitis. A few key points should be considered with use of this algorithm:

- Radiographs lag behind the clinical picture.
- In infants and children, the amount of radiation exposure with imaging techniques must be considered.
- If the clinical presentation strongly suggests osteomyelitis, a lengthy diagnostic evaluation should not delay empirical treat-

Fig. 128.8. MRI scan of osteomyelitis. **A,** There is diffuse, abnormal, decreased T1 signal increase. **B,** There is an increased STIR signal through the T12 and L1 vertebral bodies, with loss of the normal disk space and enhancement of these vertebral bodies consistent with osteomyelitis and diskitis. (Courtesy Dr. Peter Evangelista, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

ment. Culture specimens of blood, urine, and other appropriate sites should be obtained and antibiotic treatment started.

- Imaging studies other than plain radiographs are not required to make the diagnosis of osteomyelitis. Advanced imaging is reserved for surgical planning

Management

Once the diagnosis of osteomyelitis is considered, the next step is to obtain culture specimens and commence treatment rapidly. The goal of therapy is to contain the infection before bone necrosis occurs because cure rates fall dramatically once this happens. Medical management with antibiotics is usually sufficient for asymptomatic osteomyelitis that is coincidentally discovered during the evaluation of a patient with fever, weight loss, or bacteremia, hematogenous infection caused by sensitive microbacteria or fungi, or hematogenous vertebral osteomyelitis caused by sensitive pathogens.

For all other types of osteomyelitis, including contiguous focus osteomyelitis, diabetic foot infections, posttraumatic osteomyelitis, and implant-related infection, definitive care is frequently surgical. In these cases, a discussion with an infectious disease or orthopedic surgery specialist, depending on the scenario and available services, is appropriate to plan or initiate surgical and medical therapy. The ideal antibiotic for treatment of osteomyelitis should be bactericidal against the offending bacteria, such as beta-hemolytic streptococci and staphylococci (including MRSA), have low toxicity, be chemically stable at the site of infection, and be relatively inexpensive. The low pH of infected bone limits the bactericidal action of some antibiotics, particularly the aminoglycosides. Cephalosporins and penicillins are more stable in this environment. In the ED, empirical broad-spectrum treatment of suspected osteomyelitis should be initiated with an awareness of regional resistance patterns. Although gram-negative organisms are uncommon pathogens, the serious consequences of inadequate treatment justify the inclusion of anti–gram-negative coverage in the initial drug regimen. Once culture results are obtained, the antibiotic regimen can be tailored.

In the case of posttraumatic osteomyelitis, appropriate initial emergency care may help prevent the disease. The proper management of open fractures in the field is to cut away surrounding clothing, pour sterile saline or water over the exposed bone, and cover the wound with moist sterile gauze bandages or a sterile sheet. Only in the case of severe vascular compromise to the distal limb should an open fracture site be manipulated or realigned because of the danger of introducing bacteria deeper into the wound. Because wound surface cultures in the ED setting are not reliable in predicting future pathogens in bone infections, they need not be done as part of emergency care.

The first treatment priority is adequate coverage of *Staphylococcus* spp. with a penicillinase-resistant penicillin, such as oxacillin or nafcillin, or first-generation cephalosporin. In patients with a penicillin allergy, vancomycin is an acceptable alternative; however, cure rates with vancomycin are inferior to those with nafcillin or cefazolin. Vancomycin should be reserved for those patients with an actual type I penicillin allergy. Nonenterococcal streptococci are usually sensitive to antibiotics used to combat staphylococci. Gram-negative bacteria, including Enterobacteriaceae, *E. coli, Proteus mirabilis,* and *Serratia marcescens,* are rare causes of osteomyelitis. Third-generation cephalosporins, aminoglycosides, imipenem-cilastatin, and ampicillin are the usual choices for broad gram-negative coverage. Beyond this initial broad-spectrum therapy, treatment for anaerobic bacteria, *Pseudomonas,* and fungal organisms should be based on clinical suspicion.

The increase in antimicrobial resistance highlights the need for new antibiotics to expand therapeutic options. Second-generation fluoroquinolones, such as ciprofloxacin, and third-generation agents, such as levofloxacin, offer excellent bone and joint penetration and are active against a broad spectrum of gram-positive and gram-negative organisms. Because the blood concentrations of orally and parenterally administered fluoroquinolones are similar, transition to oral treatment protocols for osteomyelitis is pursued after an initial course of parenteral antibiotics. Successful treatment of osteomyelitis correlates best with serum levels of the antibiotic, not the route of administration. Antibiotics should be

dosed to ensure a serum level eight times greater than its minimum inhibitory concentration. Table 128.2 lists common treatment regimens for the variety of bacteria that cause osteomyelitis. The standard recommendation is parenteral antibiotics for 4 to 6 weeks transitioned to an oral course of antibiotics. Treatment of chronic osteomyelitis is a difficult surgical problem. A variety of adjunctive therapies are have been investigated, such as instillation of antibiotic-containing beads into infected bone and hyperbaric oxygen therapy.[9]

Disposition

Patients with osteomyelitis are admitted for IV antibiotic treatment and some will also need operative débridement. After steady-state serum antibiotic levels have been achieved, patients can receive outpatient IV or oral antibiotic therapy.

SEPTIC ARTHRITIS

Principles

Septic arthritis is an orthopedic emergency, and the incidence appears to be increasing. Even with prompt recognition and appropriate care with antibiotics and joint decompression, septic arthritis leads to a loss of function in 25% to 50% of patients. In the United States, the incidence of septic arthritis in native joints ranges from 2 to 10/100,000 and, in the subset of patients with rheumatoid arthritis, the incidence jumps to 30 to 70/100,000.

Septic arthritis usually results from hematogenous migration of bacteria into a joint and is often a monoarticular process. Like osteomyelitis, septic arthritis may also result from the spread from a contiguous focus of infection or by direct inoculation of bacteria. Direct inoculation can result from penetrating trauma or iatrogenically as a consequence of joint aspiration or injection or from infected foreign material, such as a prosthesis. The synovial membrane extends beyond the epiphysis and attaches to the metaphysis in the knee, hip, and shoulder joints, causing the infection to spread from the metaphysis of the femur or humerus into the joint. This explains why septic arthritis may occur concomitantly with osteomyelitis, with infection spreading from bone to joint, and osteomyelitis may also be the result of septic arthritis. The most commonly isolated organism is *S. aureus.* Polyarticular involvement is present in less than 10% of pediatric cases and less than 20% of adult cases. In children, concomitant infection is seen most of the time and can be predicted by age older than 3.6 years, CRP level more than 13.8 mg/L, more than 3 days of symptoms, platelet count <314 × 10 cells/μL, and absolute neutrophil count (ANC) >8.6 × 10 cells/μL. Patients with more than three of these findings would benefit from an MRI to identify any adjacent foci.[10] A reactive arthritis, which is more common than bacterial arthritis, is a sterile secondary inflammation of a joint, with no identifiable infecting microorganisms in the synovial fluid. Commonly, reactive arthritis occurs after a systemic viral infection but can also develop after a group A streptococcal infection.

Clinical Features

History and Physical Examination

Septic arthritis is usually more acute in onset than osteomyelitis. The predominant symptom of septic arthritis is joint pain, exacerbated with range of motion. The lower extremity is more commonly affected. In infants and children, this includes the knee and hip; in adults, the knee is the site of septic arthritis 50% of the time, followed by the hip (25%) and shoulder (15%). Immunosuppressed patients, especially those receiving corticosteroids, may have septic arthritis with minimal joint pain. It is important in obtaining the patient's history to identify underlying joint disease, such as osteoarthritis, gout, rheumatoid arthritis, or joint surgery or a past medical history for chronic systemic disease, immunodeficiency, prolonged steroid use, and/or history of injection drug use. In these patients, a careful history may help differentiate chronic joint pain from the acute pain associated with septic arthritis.

On presentation, more than 80% of children and 40% of adults with septic arthritis have a fever; however, constitutional symptoms such as weakness, malaise, anorexia, nausea, and diffuse myalgias are inconsistently reported. Many children who have septic arthritis will not use the involved limb. If the hip is infected, the patient may present with referred pain to the thigh or knee.

On physical examination, tachycardia and hypotension may indicate a generalized septic process. In the neonate or infant, there may be a so-called pseudoparalysis of the affected limb. This can be mistaken for a neurologic problem; however, an isolated true paralysis is far less common than septic arthritis. The inability of a child to bear weight on a lower extremity or to move any joint spontaneously should be considered a sign of septic arthritis and should be adequately ruled out.

In the older child and adult, signs may be more localized. The extremity will usually be held motionless in the position of greatest comfort, which is slight flexion. Palpation of the septic joint will cause exquisite pain, and any maneuver that stretches the synovium, such as flexion and extension, will cause severe pain. The cardinal signs of inflammation—swelling, erythema, and warmth—are commonly found in the infected joint. Joint pain is 80% to 100% sensitive for septic arthritis, and tenderness is 100% sensitive. Periarticular processes such as bursitis, tendinitis, and cellulitis may produce erythema, warmth, and tenderness, but these processes can usually be differentiated from septic arthritis. Palpation of the joint line and maneuvers that stress the synovium and joint are usually not painful in cellulitis. Periarticular processes also do not commonly produce an effusion. In general, the triad of fever (seen in 45 to 60% of cases), pain (seen in 75% of cases), and impaired range of motion suggests septic arthritis. One caveat with the physical examination is that an increasing number of patients have been receiving chronic immunosuppressive drugs; in these patients, the classic history and examination findings may be significantly less dramatic than in their immunocompetent counterparts.

Complications

Septic arthritis leads to two types of serious complications, those involving the joint itself and those that are systemic. The introduction of bacteria into a joint triggers a profound immune response that leads to destruction of the articular cartilage. Bacteria, host synovial cells, chondrocytes, neutrophils, and macrophages all release enzymes and inflammatory chemicals such as collagenase, elastase, hyaluronidase, lipase, and lipoproteinase, which may be destructive to the joint. Damaged articular cartilage has limited repair capacity, and a common result of articular cartilage destruction is arthritis or ankylosis, which results in a stiff immobile joint.

Children are at great risk for epiphyseal damage if the infection extends through subchondral bone. This can result in impaired growth and limb length discrepancy.[11] Other tissues adjacent to the joint can be invaded, leading to suppurative destruction of bursae, tendons, ligaments, and/or muscles. Sinus tracts may lead the infection out through the skin. In the hip, the pressure and edema of a septic synovial effusion can occlude the blood supply, resulting in avascular necrosis of the femoral head, especially in neonates.

Systemic complications from septic arthritis are less common but the hematogenous spread of bacteria from an infected joint can produce sepsis, septic shock, and death. Seeding of other sites with bacteria is also a possibility, and this can produce endocarditis, pneumonia, and abscesses.[12-14]

Clinical Subsets of Septic Arthritis

Bites. The human mouth is a polymicrobial environment comprised of aerobic organisms, such as *Staphylococcus*, oral gram-negative rods, such as *Eikenella corrodens*, and anaerobes, such as *Fusobacterium*, making bone and joint infections caused by human bites difficult to treat. Similarly, animal bites also lead to a polymicrobial infection, with *Pasteurella multocida* an important additional organism. Antibiotics should be empirically started, but treatment also requires drainage and débridement.

Infants and Children. Septic arthritis is more common in children than in adults, and the incidence of septic arthritis is twice that of osteomyelitis in children. Two-thirds of pediatric cases occur in children younger than 2 years, and boys are affected twice as often as girls. The offending agent in septic arthritis varies with age. In the post–*H. influenzae* vaccine era, overall, *S. aureus* (methicillin-sensitive more than methicillin-resistant) is the most common infecting organism in all pediatric and adult age groups, followed by group A streptococci and *Streptococcus pneumoniae*. In neonates, group B streptococci, *S. aureus,* and gram-negative enteric bacilli are usual pathogens. *Candida albicans* should also be considered in neonates and premature infants. *K. kingae* has been emerging as an important cause of septic arthritis and osteomyelitis in children younger than 2 years. In children between 3 months and 5 years of age, concomitant respiratory infection or otitis media is often present. Prior trauma or skin infection may be more common with staphylococcal septic arthritis.

The Kocher criteria can be used to help identify children with septic arthritis of the hip. However, the sensitivity of the algorithm has been challenged[15] and should be used wisely. The four criteria are fever (temperature ≥ 38.5° C [101° F]), non–weight-bearing on the affected side, ESR greater than 40 mm/hr, and peripheral blood WBC count more than 12,000 cells/mm^3 (Table 128.3). Laboratory work, including complete blood count and determination of the ESR and CRP level, are part of the routine evaluation of the limping child but, individually, do not have adequate sensitivity or specificity to rule in or rule out the diagnosis. A synovial fluid analysis should also be done if there is any suspicion for septic arthritis.

Even when cultures of synovial fluid and blood are tested, a causative organism is not discovered in up to 30% of cases of septic arthritis in children. Prior antibiotic treatment in children decreases the yield on synovial fluid cultures from 80% to 38%. In the pediatric population, the hip and knee have equal rates of infection, with each accounting for about one- third of infections. In children, hematogenous osteomyelitis is often associated with septic arthritis of the hip. Concurrent osteomyelitis is present in 20% of infants and in almost 50% of all neonates with septic arthritis.

TABLE 128.3

Kocher Criteria

NO. OF KOCHER CRITERIA MET	LIKELIHOOD OF SEPTIC ARTHRITIS OF THE HIP
1	3
2	40
3	93
4	99

Gonococcal Septic Arthritis. In the United States, *N. gonorrhoeae* is the most common cause of septic arthritis in sexually active patients. A person with gonorrhea of the urethra, cervix, rectum, or pharynx has a 1% to 3% chance for the development of disseminated gonococcal infection (DGI). More than 75% of cases of DGI occur in women, possibly because of their increased risk of asymptomatic infection. DGI is common during pregnancy or after menstruation, when the alkaline vaginal environment makes the organisms more resistant to host defenses in the bloodstream and therefore more likely to disseminate.

The classic triad of gonococcal bacteremia is migratory polyarthritis, tenosynovitis, and dermatitis. Asymmetric polyarthralgia, which may be migratory, is the most common presenting complaint, occurring in two-thirds of cases; 25% of patients have monoarthralgia. Polyarthralgia is usually asymmetric and most frequently involves the knee, although the elbow, wrist, metacarpophalangeal, and ankle joints are also affected. The sacroiliac and sternoclavicular joints may be involved, although these sites are far less common. Hemorrhagic pustules on the skin, scattered, painless, nonpruritic, small (0.5- to 0.75-cm) papules distributed below the neck that can involve the palms and the soles, are seen in 41% of cases. These papules can turn into pustules on a broad erythematous base with a necrotic or hemorrhagic center. There are usually fewer than 50 lesions, distinguishing DGI from the rash of meningococcus.

Septic arthritis develops in approximately 40% of patients with DGI. It is usually a monarticular process, although polyarticular septic arthritis has been reported. The patient will present with classic signs of a septic joint, including a joint effusion, warmth, tenderness, decreased range of motion, and marked erythema. There is usually no clear progression of DGI and polyarthralgias to purulent monarticular arthritis, and many patients are afflicted with dermatitis and tenosynovitis without the development of true arthritis. Some strains of *N. gonorrhoeae* that produce DGI favor the development of tenosynovitis and dermatitis, whereas others favor the development of purulent arthritis.

The diagnosis of gonococcal arthritis is made by synovial fluid culture results, but gonococci are recovered from synovial fluid in less than 50% of cases. In septic arthritis due to gonorrhea, the synovial fluid WBC count is often less than 50,000 cells/mm^3, Gram stains of aspirated joint fluid are positive for bacteria only 25% of the time, and cultures of the joint fluid are negative in approximately 50% of cases. This may be due to poor culture techniques or because a suppurative reactive process can occur in the joint in DGI, even when bacteria are no longer present. When gonococcal arthritis is suspected, cultures of the synovial fluid should be plated on prewarmed chocolate agar for the highest yield, and cultures for *N. gonorrhoeae* should be obtained from mucosal surfaces, because these may be the only places where bacteria are readily recovered. Cultures of the genital tract, pharynx, or rectum will be positive in 80% of cases of gonococcal arthritis. The use of urine nucleic acid amplification tests to detect gonorrhea has been gaining in popularity, given their ease of use. However, in women, vaginal swabs detect more infections than urine sample,[16] whereas in men, detection of gonorrhea from urine samples is equivalent to rates of detection from urethral swabs.[17]

Gonococcal septic arthritis responds rapidly to antibiotic treatment and, unlike other types of bacterial arthritis, rarely causes permanent damage to the joint. Patients with gonococcal septic arthritis require hospital admission, with antibiotic coverage against the likely pathogens until laboratory results are available. With the rise in fluoroquinolone-resistant gonorrhea, the

recommended treatment of gonococcal arthritis is a third-generation cephalosporin, such as ceftriaxone, ceftizoxime, or cefotaxime. Patients are given the first dose via the IV route or intramuscularly in the ED and admitted until culture results are available. If the diagnosis of gonococcal arthritis can be definitely established in the ED, patients with reliable follow-up can be treated with an IV or intramuscular dose of antibiotics and then sent home with an oral regimen, which should be continued for 1 week.

Lyme Arthritis. Lyme disease, the most common tick borne disease in the United States, is caused by infection with a spirochete, *Borrelia burgdorferi.* Transmitted by the *Ixodes* tick, it is an important cause of arthritis in endemic areas, and its incidence has been increasing. Lyme disease has been reported in all 50 states, but endemic areas, including Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Wisconsin, Connecticut, Delaware, and Rhode Island, account for 93% of all cases annually. There is a bimodal age distribution in children aged 5 to 9 years and adults aged 55 to 59 years. Children infected by *B. burgdorferi* are more likely than adults to have arthritis as the initial manifestation of the disease. Whereas it is important to determine a history of a tick bite, up to 30% of people do not remember being bitten. There are three phases of the infection—early localized, early disseminated, and late.

Arthritis, which is the most distinguishing feature of late-stage Lyme disease, develops in up to 60% of untreated Lyme patients and is manifested months after disease onset. After infection, spirochetes are disseminated and invade synovial joints, resulting in a profound immune response, similar to that seen in bacterial arthritis. Patients with Lyme arthritis present with migratory polyarthralgia that also involves bursae and tendons. This usually evolves into a monarticular process and usually involves single large joints. More than 90% of patients report knee inflammation, but other affected joints include the wrist, elbow, ankle, and hip. The Centers for Disease Control and Prevention has defined Lyme arthritis as "recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints."

The rash is often overlooked by patients and is generally not present in patients when they present with arthritis. However, fever is noted in up to 50% of all children who have Lyme arthritis.[18] Clinically, the arthritis is similar to other inflammatory processes of the joint and includes warmth, erythema, swelling, and pain on motion of the joints; however, the effusion is usually large and out of proportion to the patient's complaints. The effusion also generally recurs after aspiration, even when the joint is appropriately treated.

The most widely used test for the diagnosis of Lyme disease is the serum antibody titer, including enzyme-linked immunosorbent assay (ELISA) and Western blot testing, but serum testing does not differentiate between acute and past infections. Synovial fluid analysis is not helpful in distinguishing Lyme arthritis, but it usually reveals an inflammatory process with WBC counts that have been reported to have a very wide range, from 500 to 98,000 cells/μL. Arthrocentesis cannot differentiate between bacterial and Lyme arthritis because serologic analysis is similar. Cultures of synovial fluid in Lyme arthritis are usually nondiagnostic. Testing of synovial fluid with ELISA or Western blot methods for Lyme disease is not recommended because no consensus exists on how to interpret these data. Lyme arthritis can be successfully treated with oral doxycycline, amoxicillin, or cefuroxime for 30 days. If this is unsuccessful, patients can be retreated with the same oral regimen for another 30 days, or the antibiotic can be changed to IV ceftriaxone for 14 to 30 days.

Fortunately, Lyme arthritis has an excellent prognosis. Up to 95% of children remain asymptomatic after a single course of antibiotics; adults may show an increased incidence of persistent joint swelling months to years after the initial infection, even after appropriate antibiotics. A small minority of patients have chronic Lyme disease despite appropriate treatment, with symptoms similar to those of chronic fatigue syndrome.

Periprosthetic Joint Infections. Infections occurring after joint replacement are a challenging and dangerous complication of arthroplasty, with rates reported to be 1% to 2% at 2 years postoperatively in native joints and up to 7% in patients undergoing joint revision.[19,20] The prosthesis and cement are foreign bodies and are ideal sites for bacterial colonization. The most common infectious agents are *S. epidermidis* (40% of cases), *S. aureus,* methicillin-sensitive and methicillin-resistant (20%), and streptococcal species (20%). Risk factors for periprosthetic joint infections have been identified to be rheumatologic disease, preoperative anemia, coagulopathy, diabetes, depression, and low socioeconomic status.[20] The American Academy of Orthopaedic Surgeons clinical practice guideline summary recommends that patients who present to the ED should initially be stratified to high or low probability for a periprosthetic joint infection. As with many diagnostic maneuvers performed in the ED, a pretest probability helps guide the evaluation.[19]

On history and physical examination, the patient will complain of pain that is constant and present at rest, along with impaired function of the joint secondary to loosening of the hardware. Radiographs may also reveal movement of the prosthesis, bone erosion, new subperiosteal bone growth widening, or more than a 2-mm lucency at the bone-cement interface. The investigation starts with laboratory data, including ESR and CRP level. If both test results are negative, a periprosthetic infection is unlikely (negative likelihood ratio, 0–0.06); when both test results are positive, a periprosthetic infection must be considered (likelihood ratio, 4.3–12.1). However, many inflammatory processes can result in an elevation of the ESR and CRP level, and these are not specific tests. The use of either test alone is less reliable, and no definitive conclusion can be drawn with just one result. In patients with an elevated ESR or CRP level in whom a prosthetic joint infection is suspected, the next step is to consult the orthopedic service to obtain fluid from the joint under sterile conditions.

If synovial fluid is submitted for analysis, a synovial WBC count more than 1100 cells/mm^3 with more than 64% neutrophils is a sensitive and specific marker for periprosthetic joint infection in a patient with an elevated ESR (>30 mm/hr) and CRP level (>10 mg/L). Aspiration may be more difficult in this situation because of scarring and alteration of the joint space. Consultation with the patient's orthopedic surgeon about the decision to perform joint aspiration in the ED and the selection and timing of antibiotics in suspected periprosthetic joint infection is advisable. Patients who have received antibiotics within 2 weeks will have a very low yield with intraarticular cultures, even if infection is present. Because of the difficulty in isolating infectious organisms from the prosthetic joint, even if done intraoperatively, orthopedists have generally recommended that antibiotics not be started until after culture specimens are obtained.[71]

Patients With Existing Joint Disease. Patients with underlying joint disease, especially rheumatoid arthritis and a crystal arthropathy, are more likely to have septic arthritis than their counterparts with normal joints. If septic arthritis is suspected, laboratory and radiographic evaluation is of lower yield and, to reduce mortality, antibiotics are started immediately after synovial fluid is sent for testing. In patients with a crystal arthropathy, neutrophil invasion secondary to septic arthritis also leads to increased precipitation and release of crystals. Therefore, the emergency clinician who discovers crystals on joint fluid aspiration should not abandon the search for an infectious agent.

Atypical Joints. Septic arthritis can be particularly difficult to diagnose and treat if it occurs in fibrocartilaginous joints, such as the sternoclavicular, acromioclavicular, and sacroiliac joints and the symphysis pubis. Septic arthritis of the axial skeleton, especially of the sternoclavicular joint, is commonly seen in injection drug users, with *Pseudomonas* a common infecting agent. In patients who do not have other predisposing factors, the most common bacterial causes are *S. aureus* and *S. epidermidis*. The presentation is usually pain and point tenderness over the involved joint. Fever and an elevated ESR are commonly reported, although they are not always present because of the suppressed immune status of the patient. When imaging is required, CT and MRI are preferred and are helpful in the diagnosis of septic arthritis in the fibrocartilaginous joints.

Differential Diagnosis

Many disease processes can be confused with septic arthritis. Metaphyseal osteomyelitis may mimic septic arthritis because the adjacent joint may develop an effusion, and the two infections can be concurrent. Juvenile rheumatoid arthritis is usually more gradual in onset and produces polyarticular arthritis in children younger than 16 years but may be manifested as a monoarticular process that mimics septic arthritis. Toxic or transient synovitis, an inflammatory process common in children, especially after an upper respiratory infection, can be confused with septic arthritis. It occurs in the 3-month to 6-year age range, usually affects the hip, and is a self-limited disease, with no long-term morbidity. Children with transient synovitis have less pain with passive joint motion than patients with septic arthritis; they do not usually have a fever or appear ill but tend to favor the unaffected leg, as in septic arthritis. The diagnostic evaluation typically reveals a normal WBC count and ESR and no radiographic abnormalities.

Other diseases of the hip in children that are included in the differential diagnoses are Legg-Calvé-Perthes disease (avascular necrosis of the femoral head) and slipped capital femoral epiphysis; however, these processes are not as acutely disabling as septic arthritis. Rheumatic fever commonly presents with a migrating polyarthritis and may mimic gonococcal bacteremia. Patients with Lyme arthritis are not as debilitated as those with septic arthritis but, in endemic areas, serum antibody titers should be determined during evaluation of the patient with an effusion.

In the adult, osteoarthritis, gout, and pseudogout may produce findings on joint examination similar to the findings of septic arthritis. Other arthropathies, such as psoriatic arthritis, arthritis associated with inflammatory bowel disease, ankylosing spondylitis, crystal-induced arthritis, and drug-induced arthritis should also be considered in the differential diagnosis of septic arthritis. Collectively, these are known as the seronegative spondyloarthropathies. Trauma to the joint can produce synovitis and hemarthrosis, which may be mistaken for septic arthritis. In a patient with hemophilia, hemarthrosis causes joint inflammation and destruction, and there may be superimposed infection.

Reactive arthritis has traditionally been considered to be a sterile inflammatory response to a distant infection. However, antigens from the infectious trigger are often present in the joint. Several viral and bacterial microorganisms can produce reactive arthritis. The most recognized syndrome is poststreptococcal reactive arthritis. Some other common organisms that cause reactive arthritis are *Chlamydia, Salmonella, Shigella, B. burgdorferi* (Lyme disease), *Yersinia,* human T-lymphotropic virus type 1, rubella virus, hepatitis B virus, adenoviruses, parvovirus, and Epstein-Barr virus. Reactive arthritis can usually be distinguished from septic arthritis because it tends to involve multiple joints in a migratory pattern, the inflammatory process is less severe with reactive arthritis, there is less effusion, the joint is not as hot or tender as it is with septic arthritis, and joint fluid cell counts are usually below 50,000 cells/mm^3.

Diagnostic Testing

Serum and Urine Tests

Blood tests are not consistently helpful in making a diagnosis of septic arthritis. Serum leukocytosis is nonspecific and nonsensitive for diagnosis of septic arthritis. Traditionally, a serum WBC count more than 10,000 cells/mm^3 may suggest a systemic illness but is present in only 50% of patients with septic arthritis, and many sterile inflammatory processes create a similar leukocytosis. The ESR is elevated in approximately 90% of cases and, along with the CRP level, can be used to help diagnose the infection and track resolution. When low thresholds are used in the ED, the sensitivity of ESR is reported to be 98%, with a cutoff of 10 mm/hr or more, and the sensitivity of CRP is 92%, with a threshold of 20 mg/L or more.[21] A sensitivity of 96% for an ESR higher than 30 mm/hr has been demonstrated. A procalcitonin level more than 0.5 ng/mL is another possible serum marker for septic arthritis, but is also nonspecific and is often not readily available in the ED.[22]

Two sets of blood culture specimens should be obtained; however, blood cultures reveal the infecting organism in only 25% to 50% of cases. Cultures of infectious foci, such as the throat, cervix, and urine, may demonstrate the bacteria responsible for septic arthritis. Urine leukocyte esterase has been studied as a possible new indicator for a septic arthritis; it is especially sensitive and specific in prosthetic joints, with initial studies showing a high a sensitivity and specificity.[23,24]

Joint Fluid Analysis

The diagnosis of septic arthritis requires joint fluid for culture and analysis. It is fortunate that the knee joint is the most likely to be infected and the easiest to aspirate. Aspiration of other joints, such as the hip, usually requires interventional radiology or orthopedic surgical consultation. When violating the joint capsule, septic technique should always be practiced, even though the risk of introducing infection into a joint during intraarticular aspiration or injection has been reported to be between 1 in 2000 to 15,000 injection, which seems to be related to the number of precautions taken to avoid it.

Because joint fluid analysis is not performed as often as other diagnostic tests in the ED, a joint fluid protocol is useful to ensure that all necessary tests are prepared and ordered properly. Joint fluid cultures must be inoculated as soon as possible after the fluid is obtained. To increase the bacterial yield from joint fluid, it is advised to inoculate blood culture bottles with joint fluid immediately after joint aspiration. This allows some bacteria, which would normally die before being inoculated on culture media in the laboratory, to survive and grow in the blood culture bottle (brain-heart infusion broth). The sample should include special media to test for fastidious organisms such as *N. gonorrhoeae.* Anaerobic and fungal organisms are cultured in patients with risk factors for these infections.

The definitive test to determine bacterial arthritis is synovial culture. When only a small volume of synovial fluid is recovered from a joint aspiration, the single most important test is a bacterial culture. Culture of the synovial fluid or of synovial tissue itself, obtained by arthrotomy, is the only definitive method for the diagnosis of infectious arthritis. If extra fluid is available after a culture specimen is obtained, other tests can be performed.

Gram stain, synovial WBC count and differential, percentage of polynuclear cells, crystal analysis, and joint fluid glucose level have traditionally been used to differentiate bacterial arthritis

from other joint diseases. Other tests of the synovial fluid are commonly performed, but many studies have refuted the efficacy of other additional tests.

Even with an adequate joint fluid sample, proper culture techniques, and the presence of fastidious organisms, synovial Gram staining results in clinically suspected septic arthritis are negative about one-third of the time, likely due to the planktonic state of the bacteria in the joint. A positive result of Gram staining can be used to guide antibiotic treatment; however, empirical treatment should not be delayed if the result is negative because Gram staining has a 45% to 71% false-negative rate.

Traditionally, a synovial fluid leukocyte count of more than 50,000 cells/mm^3 with a predominance of polymorphonuclear leukocytes was used to define septic arthritis, but other processes can produce similar cell counts. Up to 30% of patients with septic arthritis have been documented to have counts well below 50,000 cells/mm^3.

Many studies have supported the idea that a specific range of elevation of the synovial fluid leukocyte count can be reliably used to diagnose septic arthritis. One large study found that for a synovial fluid WBC count higher than 17,500 cells/mm^3, the sensitivity was 83% and specificity was 67%. The positive likelihood ratio at this level was 2.5, with a negative likelihood ratio of 0.25. A synovial fluid leukocyte differential count with at least 90% neutrophils suggests septic arthritis, with a likelihood ratio of 3.4; a count of less than 90% decreases the likelihood ratio. There is mounting evidence that one cannot rely solely on the synovial fluid leukocyte count to exclude or include the diagnosis of septic arthritis; that this value should be used with the clinical, radiographic, and laboratory findings to help guide therapy as Grams staining and culture results become available.

The examination of synovial fluid under polarizing microscopy for the presence of crystals may be useful in the differentiation of inflammatory from noninflammatory joint disease but is not helpful in identifying infection in this population because the two often coexist. The identification of crystals should not deter the emergency clinician from continuing to search for an infectious cause of the joint pain.

Imaging

Plain radiography is not an effective tool for the early evaluation of septic arthritis but may detect surrounding osteomyelitis. In most joints, the small areas of attachment of the synovial membrane to bone are devoid of cartilage. These so-called bare areas at the margins of the joint appear as lucencies or erosions early in the course of septic arthritis. Bone beneath the articular cartilage may start to erode 1 to 3 weeks into the disease. Air in the joint may be a sign of infection with gas-forming organisms but may be the result of a previous joint aspiration. In patients with existing joint disease, radiographs provide minimal assistance in the diagnosis of septic arthritis.

For joints that are not visualized, other than a physical examination, a variety of modalities are available to help detect a joint effusion, which under the right circumstances could suggest septic arthritis. However, the differential diagnoses for a joint effusion is long, and aspiration of the fluid must be done to make the diagnosis. Ultrasonography is a useful modality to help detect a joint effusion and assist in joint aspiration, particularly of the hip[25] (Fig. 128.9). CT and MRI can identify joint fluid but not necessarily an effusion, because a volumetric analysis cannot be done to assess the amount of fluid. In adult patients with an antalgic gait and painful internal and external rotation of the hip, MRI findings of bone marrow edema led to a diagnosis of septic arthritis only 6% of the time. Other conditions that cause bone marrow edema include reactive arthritis, transient osteoporosis, avascular necrosis, osteoarthritis, tuberculous arthritis, osteomyelitis, sickle cell anemia, lymphocytic leukemia, and femoral stress fracture and should be considered.

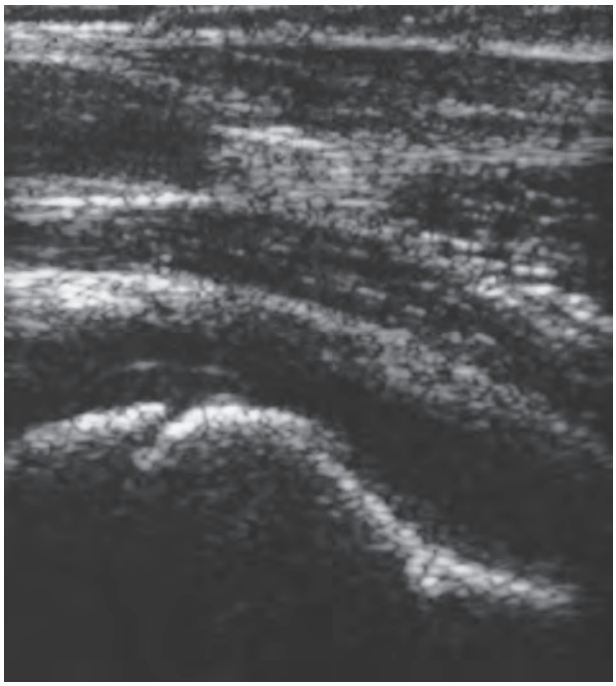

Fig. 128.9. Ultrasound image of the right hip in an 8-year-old girl with septic arthritis. A significant joint effusion can be seen just superior to the round contour of the femoral head. Joint aspiration revealed purulent fluid, with a white blood cell count of 71,000/mm^3.

CT and MRI provide detailed anatomic images of the joint, and MRI can also help determine if septic arthritis is complicated by concurrent osteomyelitis. Skeletal scintigraphy (bone scanning) has been used in the diagnosis of septic arthritis, but its use has been decreasing. The main advantage of skeletal scintigraphy is for the detection of septic arthritis earlier than with other imaging techniques. In septic arthritis, scintigraphy shows symmetric areas of increased uptake on both sides of the joint. In a three-phase ^{99m}Tc scan, all three phases will be hot with septic arthritis. In general, skeletal scintigraphy is used only when there is enough uncertainty about the diagnosis to warrant further investigation, such as in the hip joint. In joints in which aspiration is easier, skeletal scintigraphy has little role in diagnosis.

Management

Septic arthritis is an orthopedic emergency and, once synovial fluid is obtained, empirical antibiotics should be promptly administered on the basis of Gram stain results, when possible, if the diagnosis is strongly suspected (Table 128.4). Whereas most joint infections require surgical joint decompression, there are a few cases in which medical management will suffice, such as with gonococcal septic arthritis and Lyme arthritis.

Unlike most other infectious emergencies encountered in the ED, when time to antibiotic administration decreases morbidity and mortality, definitive management for most cases of septic arthritis requires surgical intervention and a prolonged course of antibiotics. Therefore, it is more important to obtain synovial fluid for Gram staining and culture than to start antibiotics, because this will guide long-term antibiotic treatment. In the hemodynamically stable patient in whom septic arthritis is a strong consideration, antibiotics should be held until blood and synovial fluid cultures are obtained.

TABLE 128.4

Guidelines for Choice of Empirical Antibiotic Based on Gram Staining Results

GRAM STAIN OR CLINICAL CONDITION	PROBABLE ORGANISM	PREFERRED ANTIBIOTICS	ALTERNATIVE ANTIBIOTICS
Gram-positive cocci	*Staphylococcus aureus* Streptococci	Nafcillin or cefazolin	Clindamycin Trimethoprim-sulfamethoxazole Vancomycin
Gram-negative cocci or negative stain Healthy, sexually active patient	*Neisseria gonorrhoeae*	Ceftriaxone	Doxycycline
Gram-negative bacilli	*Pseudomonas aeruginosa* Enterobacteriaceae	Piperacillin ± gentamicin	Third-generation cephalosporin
Gram-positive bacilli	*Propionibacterium acnes*	Penicillin G	Nafcillin Vancomycin

Reprinted with permission from Rao N, Esterhai JL Jr: Septic arthritis. In Cierny G 3rd, McLaren AC, Wongworawat MD, editors: Orthopaedic knowledge update: musculoskeletal infection. Rosemont, IL, 2009, American Academy of Orthopaedic Surgeons.

The selection of antibiotics for the treatment of septic arthritis is outlined in Table 128.2. In most cases, the emergency clinician does not know the identity of the causative organism, but treatment should be tailored to the most likely causative agents based on the patient's age, history, and immune status. *S. aureus* accounts for 44% of cases and remains the predominant pathogen for all age groups. Unless gonococcal arthritis is confirmed, the antibiotic selected should be bactericidal against *S. aureus*. Empirical antibiotics active against MRSA should be considered but should be based on the prevalence of this pathogen in the community. Risk factors for MRSA include older age, chronic illness, and health care exposure. Group B streptococci have emerged as invasive pathogens in older adults, especially those with diabetes mellitus, cirrhosis, and neurologic disease. Gonococcal septic arthritis is the most common cause of arthritis in young adults. Penicillin- and fluoroquinolone-resistant strains have become more prevalent, and a third-generation cephalosporin is the best choice for gonococcal arthritis. In older adults, gram-negative septic arthritis is more common, and agents such as the third-generation cephalosporins and aminoglycosides are added to the antistaphylococcal regimen. Establishment of good bactericidal serum levels of antibiotics will ensure that the levels in joint fluid are also bactericidal. In pediatrics, there is some evidence to support the early administration of dexamethasone (0.15 mg/kg qid for 4 days) to accelerate clinical improvement.[26]

Disposition

Any patient thought to have septic arthritis requires joint aspiration. Patients for whom septic arthritis is considered to be the diagnosis should be given an initial parenteral dose of antibiotics in the ED and admitted for culture results and continued management. If the joint fluid aspirate is not consistent with septic arthritis and clinical findings are equivocal, the patient can be discharged and reevaluated in 24 hours. In immunosuppressed patients, patients with preexisting joint disease, and patients with a joint replacement, septic arthritis can be difficult to detect. A conservative approach with in-hospital observation and treatment should be considered if there is any possibility of septic arthritis in these patients.

The prognosis for the patient with septic arthritis is favorable in most cases. From 50% to 75% of afflicted patients can expect to recover completely and achieve full painless range of motion of the afflicted joint. About one-third of patients have complications such as decreased mobility or ankylosis, pain on joint movement, chronic infection, or overwhelming sepsis and death. The patients most likely to do poorly include those who have had a delay in diagnosis and treatment, patients with underlying joint disease (especially rheumatoid arthritis), those with polyarticular septic arthritis, and those who have positive blood cultures. Despite many advances in diagnosis and treatment, the overall morbidity for patients with septic arthritis has not decreased in the last 3 decades. A general rule is that if the diagnosis of septic arthritis is made and treatment is initiated within 1 week of the onset of symptoms, the outcome is almost always favorable. Diagnosis and rapid treatment of septic arthritis have proven to be most elusive in two groups of patients, infants and people with existing joint disease. In infants and children, early symptoms can be nonspecific and difficult to assess; consequently, children with septic arthritis, especially of the hip, who experience a delay in diagnosis and treatment have a disappointingly high rate of complications. In patients with existing joint disease, septic arthritis may be mistaken for an acute exacerbation of the underlying disease process, so emergency clinicians must remain vigilant in their pursuit of the correct diagnosis.

KEY CONCEPTS

- Skeletal infection should be considered in the differential diagnosis of all patients who present with bone or joint pain.
- Hematologic evaluation is of little value in the diagnosis of bone and joint infections, with the exception of the ESR and CRP level, which are elevated in approximately 90% of cases of bone and joint infections.
- The diagnostic evaluation for septic arthritis includes complete blood count, ESR, and CRP level. Joint aspiration is the definitive diagnostic procedure, and synovial culture is the only reliable joint fluid test for establishing a diagnosis.
- The diagnosis of osteomyelitis involves an operative culture of the infected bone. MRI has become the best diagnostic modality to detect osteomyelitis.
- With suspected septic arthritis, joint fluid and blood culture specimens are obtained before IV antibiotics are administered. With suspected osteomyelitis, blood culture specimens are obtained, and IV antibiotics are administered while plans are made for further imaging studies or surgical aspiration or resection of bone.
- The most important aspect of antibiotic treatment of suspected bone and joint infections is to provide potent bactericidal activity against *S. aureus* with additional empirical antibiotic coverage aimed at suspected organisms on the basis of age, risk factors, and regional variability.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 128: QUESTIONS & ANSWERS

128.1. Which of the following statements regarding osteomyelitis is true?

A. Contiguous focus osteomyelitis is most common in the knee.
B. Hematogenous osteomyelitis begins in medullary bone.
C. Head and neck osteomyelitis is usually from hematogenous spread.
D. Septic arthritis begins in joint fluid and spreads to synovium.
E. Septic arthritis morbidity is related to joint size.

Answer: B. Hematogenous osteomyelitis begins in medullary bone and spreads outward. Contiguous focus osteomyelitis, most common in the foot and hand, begins outside of bone and spreads inward via Volkmann's canal. Head and neck osteomyelitis is usually from a contiguous sinus or otic process. Septic arthritis begins in synovium and later involves joint fluid. Morbidity is related to the degree of hyaline cartilage destruction.

128.2. Which of the following associations between osteomyelitis and pathogenic organism is true?

A. Dog bite—*Pasteurella*
B. Freshwater wounds—*Pseudomonas*
C. Human bite—*Aeromonas*
D. Intravenous drug use—*Fusobacterium*
E. Sickle cell anemia—*Haemophilus influenzae*

Answer: A. The following are correct associations:
Freshwater—*Aeromonas hydrophila*
Intravenous drug use (IVDU)—*Staphylococcus aureus*
Sickle cell—*Pseudomonas and Salmonella*
Cat or dog bite—*Pasteurella multocida*
Human bite—mixed with *Fusobacterium, Eikenella, and Streptococcus anginosus*

128.3. Which of the following statements regarding septic arthritis is true?

A. Despite vaccination, *Haemophilus influenzae* remains a frequent pathogen in children.
B. *Pseudomonas aeruginosa* is associated with IVDU-related osteomyelitis.
C. *Pseudomonas aeruginosa* is not associated with prosthetic device joint infection.
D. The most common organism in neonates is *Staphylococcus aureus.*
E. The most common organism in patients younger than 30 years is *S. aureus.*

Answer: B. *Pseudomonas* is associated with IVDU-related cervical osteomyelitis and lumbar osteomyelitis in cases of prolonged urinary catheterization. *H. influenzae* has largely disappeared as a joint pathogen in vaccinated children. The most common neonatal joint pathogens are group B streptococci, *Escherichia coli,* and *Staphylococcus epidermidis.* The most common cause of septic arthritis in people younger than 30 years is gonococcal.

128.4. Which of the following statements regarding acute hematogenous osteomyelitis in children is true?

A. Blood cultures are not usually positive.
B. Skeletal scintigraphy is indicated in neonates.
C. The child usually appears toxic.
D. The most common site is the long bone epiphysis.
E. There is a female preponderance.

Answer: C. Children may be ill but not usually toxic. There is a 2:1 or 3:1 male predominance, with the most likely site being the distal metaphysis. Blood cultures are positive in 60% of cases. Scintigraphy is not useful in neonates due to a limited inflammatory response. Radiographs are more useful and sensitive early on than in adults.

128.5. Which of the following statements regarding vertebral osteomyelitis is true?
- **A.** Children are less prone to isolated diskitis.
- **B.** Of the cases of epidural abscesses, 30% are due to osteomyelitis.
- **C.** The diagnostic procedure of choice is a magnetic resonance imaging scan.
- **D.** The most common location is the lumbar spine.
- **E.** Vertebral osteomyelitis typically involves a single vertebra.

Answer: D. The incidence of associated epidural abscess is 15%. The most common location of vertebral osteomyelitis is the thoracic, lumbar, and cervical spine. The diagnostic procedure of choice is needle biopsy. The disease usually involves two vertebrae and the disk in between. Children are more prone to isolated diskitis, although it may also occur in adults.

128.6. An 18-year-old woman with known sickle cell disease presents with leg pain of 2 days' duration. Her typical pain syndrome is lower extremity tibial and femur pain. Today's episode is primarily right tibial. She complains bitterly of pain, but there are no gross findings other than trace bilateral anterior tibial swelling, with no discernible warmth or erythema. Vital signs are remarkable for a low-grade fever and heart rate of 110 beats/min. Which of the following statements regarding this patient's condition is true?
- **A.** Bony infection would be expected in the bony diaphysis.
- **B.** Plain radiography can differentiate bony infarction from infection.
- **C.** *Salmonella* would be the most likely infectious cause.
- **D.** Technetium scintigraphy (bone scanning) will differentiate infection from infarction.
- **E.** The erythrocyte sedimentation rate (ESR) is elevated in sickle pain crises.

Answer: A. Sickle cell osteomyelitis is more typically seen in the diaphysis than in non–sickle cell situations, which more often involve the metaphysis. Fever, toxicity, and an elevated ESR suggest infection. The most likely infectious cause is still *Staphylococcus aureus,* followed by *Salmonella*. Often, observation and response to therapy (eg, analgesics, hydration) ultimately help differentiate the two. Plain technetium lights up infection and infarction. Indium or gallium is necessary to show a hot spot of infection; an infarctive site would be cold.

128.7. Which test will most likely confirm a diagnosis of gonococcal arthritis in a female?
- **A.** Pelvic culture
- **B.** Serum gonococcal culture
- **C.** Synovial gonococcal culture done on chocolate agar
- **D.** Thorough history

Answer: A. It is recommended that cervical culture be used to confirm the likely presence of GC arthritis.

128.8. When should antibiotics be administered in cases of suspected septic arthritis?
- **A.** After radiographic confirmation of the diagnosis
- **B.** After serologic confirmation of the diagnosis
- **C.** After synovial fluid is sent for culture
- **D.** After synovial Gram staining comes back positive

Answer: C. To guide effective antibiotic therapy, it is recommended to withhold antibiotics until synovial fluid has been obtained.

CHAPTER 129

Skin Infections

Daniel J. Pallin

PRINCIPLES

Background and Importance

Skin and soft tissue infections run a gamut from mild conditions such as cellulitis, abscess and fungal infections to more severe conditions with high mortality, despite modern therapy, such as necrotizing fasciitis and toxic shock syndromes.

The epidemiology of skin infections has changed significantly over the past 2 decades with the emergence of a new organism—community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Abscesses became more common and accounted for an increasing proportion of emergency department (ED) visits until the epidemic stabilized, around 2010.[1] More recently, attention has turned from the threat of CA-MRSA to the threat of antibiotic overuse because studies have found no benefit from antibiotic treatment of abscesses and no benefit from targeting CA-MRSA in cellulitis.[1-3]

Anatomy and Physiology

The skin is the largest organ in the body and accounts for about 15% of total body weight. It has three layers, the hypodermis, dermis, and epidermis (Fig. 129.1). Hair is present throughout the body except on glabrous skin, which is the heavily keratinized skin found on the palms, soles, and parts of the genitals.

The skin has a rich supply of blood vessels, lymphatics, and nerves, although the epidermis is entirely avascular and relies on the dermis for nourishment. The main cell type in the epidermis is the keratinocyte, which has a cytoskeleton composed of keratin filaments, which are proteins. Also living in the epidermis is the Langerhans cell, a motile, macrophage-like, antigen-presenting member of the immune system that originates in the bone marrow. Melanocytes in the epidermis produce melanin in response to ultraviolet light–induced DNA damage.

The epidermis contains the pilosebaceous follicles and sweat glands, known collectively as epidermal appendages. The combination of the hair apparatus and sebaceous gland is known as a pilosebaceous follicle. The epidermal appendages are important as sites of infection because they provide a break in the otherwise continuous protective layer of keratinocytes and create a potential space for bacterial replication. There are two types, sweat glands and follicles. Sweat glands take three forms—eccrine, apocrine, and apoeccrine.

The dermal-epidermal junction is a complex basement membrane whose disruption results in vesicles and bullae. The dermis consists of cells, fibers, and ground substance, which is an acellular material composed of glycoproteins and other macromolecules. The hypodermis, or subcutaneous tissue, is composed largely of adipocytes. The lymphatic system drains interstitial fluid, and its disruption leads to interstitial fluid accumulation and edema.

Pathophysiology

The source of a skin infection may not always be evident. Many skin infections arise from breaks in the protective epidermal layer, such as a cut, injection, or abrasion, known as portals of entry. Hematogenous seeding from another infected site is another possible source. Often, the source is not clear. Venous blood and lymph drain from the orbits and skin around them into the cavernous sinuses; thus, bacterial infections in this area can lead to central nervous system infection.

Clinical Features

Most skin infections present with redness (erythema), warmth, and induration. Erythema can be difficult to see in darkly pigmented people. It is caused by microvascular dilation due to the immune response. Confluent erythema is typical of most skin infections; discrete macules and morbilliform (measles-like) eruptions are not typical. Induration simply means hardening and is a common finding with many inflammatory lesions of the skin. Skin that is indurated because of cellulitis sometimes becomes engorged with interstitial fluid and takes on the texture of an orange peel due to dimpling where the skin is anchored by hair follicles. This classic finding is known by the French phrase *peau d'orange*—that is, orange peel skin.

Fluctuance describes a fluid collection palpated on examination. "Pointing" or "coming to a head" conveys a sense of imminent rupture. Crepitance describes skin that feels crackly when it is palpated and suggests that gas is present in the soft tissues. This suggests necrotizing infection, discussed later.

Fever is present in 50% of patients with bacterial skin infections presenting to the ED. Febrile skin infections are more common in children; in adults, fever may indicate a more serious infection.

Many skin infections have characteristic appearances. Well-demarcated erythema with a raised border, particularly on the face, is typical of erysipelas, a streptococcal cellulitis. Linear erythema tracking distally to proximally along a vascular pathway suggests lymphangitis or phlebitis and usually represents the action of cytokines involved in combating the infection, although proximal spread of the infection itself is a possibility.

Less common color changes associated with infection stem from small hemorrhages, vasculitis, or septic emboli. Janeway's lesions are painless red, purple, or brown spots, usually seen on the hands or feet, due to septic emboli from infective endocarditis. Painless discolorations of the palms and soles should also trigger concern for secondary syphilis or Rocky Mountain spotted fever. When the diagnosis of infection is not clear, vasculitides such as Kawasaki syndrome in children and Wegener's granulomatosis should be considered. Petechiae and purpura can indicate overwhelming bacterial infection, as with meningococcemia. Vesicles suggest contact dermatitis, herpes simplex, varicella-zoster, or impetigo. Intracutaneous pustules on the palms or soles of the feet are often due to a form of psoriasis called palmoplantar pustulosis, which is troublesome but benign.

Pruritic serpiginous (snakelike) lesions that are not particularly tender suggest an intracutaneous parasite, such as scabies (hands, intertriginous areas), hookworm larvae (feet or buttocks), or strongyloidiasis. Parasitic nematodes (eg, Guinea worm) and insects (eg, botfly) should be considered in the setting of

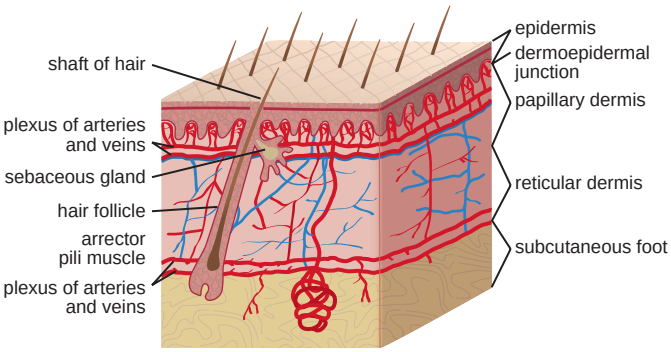

Fig. 129.1. Anatomy of the skin. (From Amirlak B: Skin anatomy. Available at http://emedicine.medscape.com/article/1294744-overview#a1.)

a nodule after exposure to fresh water or insects in developing countries.

Skin infections can suggest underlying systemic illness. For example, a young man who presents with a first episode of balanitis may have diabetes as the underlying problem. Disseminated varicella (other than a first episode of chickenpox) suggests immunocompromise.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC TESTING

Wound Cultures

For cellulitis and abscess, the only relevant laboratory test is a wound culture and Gram staining when pus is present. However, there has been debate about the necessity of obtaining culture specimens from skin infections. Advocates of culturing abscesses view the procedure as inexpensive and specific. Opponents view it as an unnecessary inconvenience that is unlikely to change management; they also are concerned that cultures may be biased toward detection of robust aerobes such as *Staphylococcus* and against detection of anaerobes and fastidious organisms. I recommend culturing complicated purulent infections, such as surgical wound infections that may involve deep structures or abscesses in immunocompromised patients. Uncomplicated skin abscesses are usually caused by CA-MRSA, and culture is not required. However, in the setting of diagnostic uncertainty, as with abscesses associated with animal bites, which may be caused by *Pasturella multocida* or CA-MRSA, I recommend Gram staining as soon as possible. Nonpurulent cellulitis is not routinely cultured.

Blood Cultures

Blood cultures are not indicated in patients with skin infection, except in cases where deep tissue infection or systemic infection is likely, such as septic shock, necrotizing infections, immunocompromise, multifocal infections suggesting hematogenous seeding, and infections complicating lymphedema.

Early studies had found pediatric facial cellulitis often to be accompanied by *Haemophilus influenzae* bacteremia. However, the relevant strain is type b, which is now covered by childhood vaccination. Moreover, this organism is typically targeted presumptively in the treatment of facial cellulitis, and there is no evidence that blood culture is of benefit. In fully vaccinated children and adults with facial cellulitis, I do not recommend blood culture as long as an agent effective against *H. influenzae* (eg, cephalexin, amoxicillin-clavulanic acid) is used.

Radiographic Studies

When a foreign body is suspected, plain radiographs are traditionally obtained, although they occasionally miss foreign bodies that are small or radiolucent. Ultrasonography has also been promising for the detection of foreign bodies.[4] The location and extraction of foreign bodies can be challenging, and emergency clinicians must use their judgment in deciding when to use plain films, ultrasound, or both.

For necrotizing infection, plain radiographs or computed tomography (CT) may reveal soft tissue gas or inflammation along fascial planes, but cannot rule out necrotizing infection. Ultrasound examination is useful for differentiating abscess from cellulitis, as discussed later.

Plain radiographs are used to evaluate for evidence of osteomyelitis for chronic skin infections, especially in patients with diabetes, peripheral vascular disease, and secondarily infected nonhealing ulcers. Plain films are not definitive, and bone scanning and magnetic resonance imaging (MRI) have higher sensitivity for detecting osteomyelitis. CT is helpful when there is concern that a skin infection is actually an extension of a deeper infection, such as after surgery or in the case of recurrent perianal abscesses.

Other Diagnostic Tests

Skin scrapings for microscopy are key to the accurate diagnosis of some infections, including scabies, varicella, herpes simplex, tinea, candidiasis, and leishmaniasis. When necrotizing infection is clinically suspected, operative exploration by a surgeon is considered the definitive rule-out procedure.

CELLULITIS

Principles and Clinical Features

Cellulitis is an inflammatory condition of skin and subcutaneous tissue thought to be the result of bacterial infection. Cellulitis may be purulent or nonpurulent and may occur in the setting of wounds, foreign bodies, or impaired perfusion. Purulent cellulitis drains freely, in contrast to abscesses, which are walled off by fibrous tissue and epidermis. CA-MRSA is the leading cause of purulent skin and soft tissue infections in ED patients, but its role in nonpurulent cellulitis is unknown.[1,5]

The cardinal feature of cellulitis is inflammation due to increased local blood flow. In darkly pigmented patients, inflammation may be subtle. Pain may be variable, but some experts believe that all cases are tender (in patients without neuropathy). The inflammation of cellulitis is typically confluent, although it may be patchy. The borders are typically poorly defined and irregular. Linear or circular lesions should prompt a search for other underlying causes, such as contact dermatitis or Lyme disease. In some cases of cellulitis, there are streaks of inflammation extending proximally from the main area of inflammation, along vascular tracts. This finding is known as lymphangitis and is commonly seen with cellulitis due to streptococci and bite wound–associated *Pasteurella multocida*.

When localized edema becomes severe, epidermal layers can separate, leading to vesicles or bullae. This can make it difficult to distinguish cellulitis from other infectious and noninfectious causes of dermatitis. When the border of an area of cellulitis becomes well demarcated, raised, and palpable, the term *erysipelas* is used. This form of cellulitis is most often caused by *Streptococcus pyogenes*. The bacterial causes of cellulitis vary according to body site, comorbidities, and environmental exposures (Table 129.1).

TABLE 129.1

Skin Infections: Bacteriology and First-Line Antibiotic Therapy

ANATOMIC VARIANT OR PREDISPOSITION	LIKELY BACTERIAL CAUSE	FIRST-LINE THERAPY (NONTOXIC AND IMMUNOCOMPETENT)[a]
Uncomplicated cutaneous abscess	CA-MRSA, others	Incision and drainage without antibiotics
Nonpurulent bacterial skin infections	Various *Streptococcus* spp., *Staphylococcus aureus*	Cephalexin or clindamycin; adjunctive measures
Purulent cellulitis and wound infections	CA-MRSA, others	Cephalexin plus trimethoprim-sulfamethoxazole, or clindamycin monotherapy; adjunctive measures
Diabetic foot infection	Mixed gram-positive, gram-negative, and anaerobes	Amoxicillin–clavulanic acid plus trimethoprim-sulfamethoxazole; avoid antibiotics for uninfected ulcers.
Any cat bite or infected dog bite	*Pasteurella multocida*, others	Amoxicillin–clavulanic acid
Human bite (treat presumptively)	Oral anaerobes, others	Amoxicillin–clavulanic acid
Erythema migrans	*Borrelia burgdorferi* (Lyme disease)	Doxycycline
Puncture wound through sole of shoe (treat presumptively)	*Pseudomonas aeruginosa*	Ciprofloxacin
Buccal cellulitis	*Haemophilus influenzae* type b (vaccine serotype)	Ceftriaxone or ampicillin-sulbactam
Balanitis	*Candida albicans* or group A streptococcus	Fluconazole plus penicillin or amoxicillin; consider diabetes
Liposuction	*Peptostreptococcus* (anaerobe), group A streptococcus	Ampicillin–clavulanic acid ± trimethoprim-sulfamethoxazole
Saltwater exposure	*Vibrio vulnificus*	Doxycycline
Freshwater exposure	*Aeromonas* species	Ciprofloxacin
Butcher, clam handler, veterinarian	*Erysipelothrix rhusiopathiae*	Amoxicillin
Black necrotic eschar with raised border and severe surrounding edema	*Bacillus anthracis* (anthrax)	Ciprofloxacin

[a]For life- or limb-threatening infections, use IV equivalents and add vancomycin.
CA-MRSA, Community-associated methicillin-resistant *Staphylococcus aureus.*

Diabetic Foot Infections

Diabetic foot infections are the most common cause of hospitalization for patients with diabetes, and an infected wound precedes two-thirds of lower extremity amputations in patients with diabetes. Neuropathy, vascular insufficiency, and hyperglycemia are important factors in the development of diabetic ulcers and foot infections. Although early antibiotic therapy is important in diabetic infections, it is important to avoid antibiotic overuse, and uninfected ulcers should not be treated with antibiotics.

The most likely organisms in an acute diabetic foot infection are *S. aureus* and streptococci. Chronic wounds are more likely to be polymicrobial with gram-positive and gram-negative organisms, as well as anaerobes. Chronic wounds that have previously been treated with antimicrobials are more likely to involve multidrug-resistant organisms. *Pseudomonas* is a traditional concern but is uncommon. Deep tissue specimens for aerobic and anaerobic culture or bone samples should be obtained at the time of débridement if deep tissue infection or osteomyelitis is suspected. Organisms cultured from superficial swabs are not reliable for identifying pathogens responsible for deeper infection. Osteomyelitis should be considered a potential complication of any deep or extensive ulcer, especially one that is chronic or overlies a bony prominence. In addition to antibiotics, diabetic foot infections require careful wound care and, in some cases débridement, revascularization, or amputation.

Bite Wounds

A high proportion of cat bites become infected, and presumptive antibiotic treatment is appropriate in the absence of signs of infection. The typical agent is *P. multocida*. Human bites also become infected frequently, and oral anaerobes such as *Bacteroides a*re typical. Dog bites become infected infrequently, and only severe wounds and sutured wounds require antibiotics. Amoxicillin–clavulanic acid is an appropriate agent for cat and human bites and for infected or sutured dog bites.

Water-Borne Infections

Exposure and travel history are important considerations in the evaluation of skin and soft tissue infections. *Vibrio* spp., in particular *Vibrio vulnificus,* are associated with exposure to seawater and can cause severe soft tissue infections and septicemia. Patients with liver disease, such as cirrhosis, are particularly at risk. Infection occurs from contamination of open wounds by seawater or shellfish and rarely by hematogenous spread from the ingestion of contaminated seafood, such as raw oysters. *Edwardsiella tarda* is a rare cause of wound infection after seawater exposure; it has been implicated in serious soft tissue infections, including myonecrosis, particularly in patients with liver disease. *Erysipelothrix rhusiopathiae* is usually associated with a localized erysipeloid eruption with minor trauma, often on the hands of seafood workers.

Aeromonas myonecrosis is associated with exposure to fresh water by penetrating trauma or exposure to aquatic animals. It causes rapidly progressive suppurative infections that often require surgical drainage. *Mycobacterium marinum* causes so-called fish tank granuloma. It typically is manifested weeks after exposure as a papule or nodule that may ulcerate and drain serosanguineous fluid. Multiple nodular lesions may develop along lymphatics.

Differential Diagnosis and Diagnostic Testing

When lymphangitis and fever are present, a bacterial infection is probable. In the absence of these signs, other possibilities include contact dermatitis, fungal infection, burns, viral infections, and allergies, including fixed drug eruptions, which can manifest with localized inflammation. Cellulitis must be distinguished from more severe necrotizing infections, as discussed later.

Consider Lyme cellulitis in endemic areas. Lyme disease causes a typical rash known as erythema chronicum migrans. It a bright red, round lesion, usually larger than 5 cm, with central clearing that gives it a targetoid appearance. It occurs in only 80% of cases of Lyme disease. When the rash is observed in an endemic area, Lyme disease can be diagnosed and treated without further testing. Lyme disease is transmitted by the deer tick, *Ixodes*, and attachment of the tick for at least 24 hours is necessary for infection. Other insect-bite–associated skin infections can occur, such as cellulitis and abscess; however, insect bite reactions are frequently mistaken for infections, and this possibility should be considered before initiation of antibiotics.

Needle aspiration and even biopsy of cellulitis lesions are unlikely to reveal the cause and are not recommended.[6] Blood cultures are not recommended except in the presence of a presumed hematogenous source of infection, in septic shock, and in cellulitis complicating lymphedema. Blood cultures are also traditional for facial cellulitis but may be omitted in well-appearing patients who are treated with agents active against *H. influenzae*.[7] The role of high-sensitivity pathogen identification, such as polymerase chain reaction analysis of surface skin swabs, has yet to be determined.

Venous stasis dermatitis is similar in appearance to cellulitis but is not infectious in origin. It is typically located above the ankle and is often (but not always) circumferential. When above-ankle dermatitis is accompanied by fever, cellulitis may be present, but other causes of fever should be sought, especially if the inflammation is bilaterally symmetric. Symmetric venous stasis dermatitis in the afebrile patient should not be confused with cellulitis. When there is inflammation near a joint, the differential diagnosis includes gout, pseudogout, septic arthritis, tenosynovitis, ruptured Baker's cyst, traumatic joint effusion, hemarthrosis, and autoimmune arthritis.

Management

Emergency clinicians have changed their prescribing practices dramatically since CA-MRSA was first described.[1] In 1993, antibiotics targeted to CA-MRSA were almost never prescribed for skin and soft tissue infections. By 2005, 38% of antibiotic regimens included an agent typically active against CA-MRSA; however, multiple studies have shown that antibiotics do not make a difference in the treatment of abscess. Only one trial has evaluated the effectiveness of agents targeting CA-MRSA in cellulitis, and this trial found no treatment benefit.[2,3] I recommend that cellulitis be treated with cephalexin or an equivalent β-lactam. Penicillin-allergic patients may take β-lactams unless they had anaphylaxis or another life-threatening allergy, in which case clindamycin is the recommended alternative.

Table 129.2 summarizes relevant antibiotics. Oral agents with activity against CA-MRSA include trimethoprim-sulfamethoxazole (TMP-SMZ), clindamycin, tetracyclines, and linezolid. The common strains of CA-MRSA (ie, USA-300) are almost universally susceptible to TMP-SMZ in vitro. TMP-SMZ is well tolerated in most patients and adverse reactions (eg, Stevens-Johnson syndrome) are no more common than with other agents, such as ampicillin. However, TMP-SMZ is not considered effective against streptococci. Thus, when CA-MRSA is suspected but streptococci remain a possibility, we recommend TMP-SMZ plus a β-lactam such as cephalexin, with clindamycin monotherapy being a good alternative.[3,7]

Dicloxacillin is commonly suggested as an agent for treatment of cellulitis because of its appropriate spectrum and high potency. However, it must be taken four times daily on an empty stomach—a very challenging task—and causes gastrointestinal upset. Doxycycline is another option for coverage of CA-MRSA. However, this agent must also be taken on an empty stomach and also causes gastrointestinal upset. Moreover, it is not thought to cover streptococci well. As with TMP-SMZ, when doxycycline is prescribed for skin and soft tissue infections, a β-lactam should be added to target streptococci unless the cause of the infection is known. Doxycycline causes photosensitivity, and patients should be warned to avoid sun exposure.

Clindamycin has been used increasingly because most CA-MRSA isolates are sensitive to it, and it is an excellent agent for streptococci. CA-MRSA can become resistant to clindamycin during a single course of treatment. This phenomenon is termed *inducible resistance* and occurs in about 2% of CA-MRSA isolates.[5] Most microbiology laboratories in the United States now test for inducible resistance among MRSA strains that are susceptible to clindamycin in vitro. The test for inducible resistance is known as the D-test. The name comes from a D-shaped pattern of the area of clindamycin's inhibition of bacterial growth, which results from resistance induced by a pellet (disk) of erythromycin that is placed next to the clindamycin pellet.

Early reports of susceptibility of CA-MRSA to rifampin gave way to later reports of widespread resistance, inducible and de novo. This agent is not recommended for skin infections.

Vancomycin is the standard parenteral agent for MRSA. Others include linezolid, daptomycin, tigecycline, and telavancin. No penicillin or cephalosporin is active against CA-MRSA, except ceftaroline, a parenteral cephalosporin approved by the US Food and Drug Administration in 2010 and indicated for complicated skin infections.

The first-line agent for treatment of nonpurulent cellulitis is cephalexin, which is safe, well tolerated, and well absorbed, and need not be taken on an empty stomach. Relatively severe infections are commonly managed with one or more initial doses of the intravenous (IV) equivalent cefazolin, which, like cephalexin, is given in maximal doses (eg, 2 g tid for adults); there is insufficient evidence to recommend for or against this practice. Nafcillin is an equivalent option. In patients allergic to cephalexin, clindamycin is an excellent choice. Table 129.1 provides further treatment recommendations. Agents effective against CA-MRSA are not recommended for nonpurulent skin infections, except in cases not initially responsive to first-line therapy or when septic shock is present.

Adjunctive measures are important in the treatment of cellulitis, according to expert opinion, but without evidentiary support. Extremity cellulitis responds dramatically to compression and elevation. The extremity should be elevated above the level of the heart. A splint is useful as an anchor for elevation and can be hung from an IV pole. Patients with cellulitis complicating venous stasis or lymphedema should be educated about the importance of compression with elastic socks, sleeves, or wraps. This is helpful for the acute infection and also to prevent future episodes. Nonsteroidal antiinflammatory drugs (NSAIDs; eg, ibuprofen) are helpful, and I recommend them in the absence of contraindications.

Fig. 129.2 is a universal treatment algorithm for skin and soft tissue infections. The algorithm assumes no prior treatment and no toxic shock syndrome. Previously treated infections require broader spectrum antibiotic coverage and customized management decisions.

TABLE 129.2

First-Line Oral Antibiotics for Skin and Soft Tissue Infection

DRUG	BACTERIOSTATIC (S), BACTERICIDAL (C), OR VARIABLE (V)	SITE OF ACTION	PEDIATRIC DOSE (mg/kg; adult dose is max)	ADULT DOSE (mg)	FREQUENCY (doses/day)	SPECIAL INSTRUCTIONS
Cephalexin	C	Cell wall synthesis	25	500–1000	4	
Dicloxacillin	C	Cell wall synthesis	10	250–500	4	Empty stomach
Amoxicillin	C	Cell wall synthesis	15	500	3	
Amoxicillin–clavulanic acid	C	Cell wall synthesis	30	875 or 2000 for extended release formulation[a]	2	
Clindamycin	S	Ribosome	6	300–450	3	
Trimethoprim-sulfamethoxazole	S	DNA synthesis (folate metabolism)	10[b]	1600	2	
Doxycycline	S	Ribosome	—	100	2	Empty stomach, sun sensitivity

[a]Dose by amoxicillin component.
[b]Dose by trimethoprim.
CA-MRSA, Community-associated methicillin-resistant *Staphylococcus aureus*; *MRSA,* methicillin-resistant *S. aureus*; *MSSA,* methicillin-sensitive *S. aureus.*

Disposition

Immunocompetent patients with cellulitis who can be trusted to adhere to recommended medications and adjunctive measures can be managed as outpatients. In severe cases, such as those with fever or more extensive infection, one or more initial IV doses are often given in the ED. Hospitalization is generally required for immunosuppressed patients and patients with diabetic foot infections, infected lymphedema, and multifocal cellulitis or suspected necrotizing infection.

ABSCESS

Principles and Clinical Features

An abscess begins when bacteria multiply in the lumen of a hair follicle or at other locations beneath the epidermis. Neutrophils are drawn to the site of infection, and various cytokines combine with bacterial toxins to promote the development of purulence. The overlying epidermis prevents drainage. A painful red mass is usually seen; it may be tender and often is warm. Skin abscesses are rarely fatal, and most will eventually rupture through the epidermis and drain spontaneously. Historically, abscesses were usually caused by methicillin-sensitive *S. aureus* or mixed flora but, by 2004, CA-MRSA accounted for 61% of abscesses in the United States.

Bartholin's cyst abscess is caused by an obstructed Bartholin duct. Bartholin's gland is located at the upper part of the lower third of the labium majus, and its duct opens onto the mucosa in this area medially but externally to the labium minus. Bacteria cultured are usually a mixture of aerobic and anaerobic flora from the vagina. *Chlamydia trachomatis* or *Neisseria gonorrhoeae* is isolated approximately 10% of the time.

A pilonidal abscess is an abscess at the superior aspect of the gluteal cleft between the buttocks. Also known as a pilonidal cyst, this abscess often recurs. Treatment is the same as for other cutaneous abscesses.

A stitch abscess is a collection of pus around a suture. Often, stitch abscesses are sterile, but a deeper wound infection can be confused with a stitch abscess.

Differential Diagnosis and Diagnostic Testing

The differentiation of abscess from cellulitis can be challenging. Bedside ultrasound examination is the best option. A high-frequency linear probe is used. Abscesses are seen as hypoechoic areas with posterior acoustic enhancement. The hypoechoic areas are pus and may be heterogeneous, with some bright signals (Fig. 129.3A). Cellulitis is seen as a uniformly hyperechoic area or as hyperechoic areas separated by curvilinear hypoechoic areas (see Fig. 129.3B). This appearance is known as cobblestoning and results from interstitial edema.

Necrotizing fasciitis, discussed below, is always a consideration, although it is extremely rare relative to cellulitis. Fistula should be considered when perianal or perivaginal infections are evaluated, and the mucosa should be examined digitally. When perirectal abscess recurs, a deep abscess may be the source, and external examination may be unreliable. In this case, CT scanning should be considered.

The epidermoid cyst represents another diagnostic challenge. These lesions, formerly known as sebaceous cysts, are benign cystic tumors resulting from the pathologic accumulation of keratinaceous material. Patients report a long history of a cutaneous mass, often intermittently painful. These lesions become inflamed periodically and sometimes rupture spontaneously. With rupture, they drain a pearly white or yellowish, glistening, waxy material. Pus, which appears dull and viscous rather than waxy, may indicate an infected epidermoid cyst. Isolated mild inflammation of an epidermoid cyst does not contraindicate primary excision , although primary excision is more difficult during an episode of inflammation. A brief course of antibiotics and NSAIDs with delayed excision is also an option.

Vascular aneurysms and enlarged lymph nodes can be misdiagnosed as abscesses. Ultrasound examination can be helpful in this regard, and a color Doppler study should be used to investigate perivascular abscesses. When there is doubt, needle aspiration should be used to confirm the presence of pus and absence of blood.

Inflamed cutaneous nodules and cystic masses in returning travelers and immigrants from developing countries present special diagnostic challenges. Typical staphylococcal abscesses are

COMMONLY SEEN MAJOR NONALLERGIC CONTRAINDICATIONS	STREPTOCOCCUS	MSSA	CA-MRSA (USA-300)	NOSOCOMIAL MRSA (USA-100)	ANAEROBES	ENTEROBACTERIACEAE
	+	+	–	–	–	±
	+	+	–	–	–	–
	+	+	–	–	±	±
	+	+	–	–	+	+
	+	+	+	±	±	–
Coumadin, glucose-6-phosphate dehydrogenase, or folate deficiency	–	+	+	±	±	±
	±	+	+	±	–	±

most common, but parasitic causes, such as dracunculiasis and myiasis, should be considered.

Management

The treatment of abscess is surgical, and antibiotics are usually not indicated.[3] Exceptions for which antibiotics may be beneficial include severe or extensive disease (eg, involving multiple sites of infection), severe associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (eg, face, hand, genitalia), septic phlebitis, and poor response to incision and drainage alone. Needle aspiration alone has not been found to be an adequate alternative to incision and blunt dissection.[8]

Abscess incision and drainage is a nonsterile procedure, but the operator and all environmental fomites should be protected from contamination and transmission of MRSA. The main challenge is to attain adequate analgesia. Injection of local anesthetics into the skin overlying an abscess is difficult because the skin is usually edematous and tense. Also, superficial anesthesia is often inadequate for blunt dissection. An alternative is to administer procedural sedation. Another excellent option is regional anesthesia (nerve block). Oral analgesia plus a ring block may also provide adequate anesthesia and analgesia. The following medications are safe together and have additive effects: ibuprofen, acetaminophen, oxycodone, and low-dose diazepam. The ring block is performed with a 25-gauge needle (3.5-inch spinal needle for large areas) to inject bupivacaine in a ring around the abscess, with as few punctures through the skin surface as possible and with care taken that the injection not spread bacteria from infected to healthy tissue. At least 20 minutes should be allowed for this to take effect.

Once anesthesia has been attained, incision and drainage of an abscess involves four steps— incision, blunt dissection to disrupt loculations, irrigation, and packing. The skin is prepared with povidone-iodine, although this is a nonsterile procedure and expensive sterile gloves are not needed. A single incision across the abscess is made, but there is little evidence to guide us in determining how large to make the incision. Incisions parallel to cutaneous tension lines will leave smaller scars. A small clamp is used to probe the cavity and disrupt loculations by opening the clamp through the loculations. Blunt dissection rarely risks injury to vessels and nerves, but the initial sharp incision should be made with such structures in mind. The drained cavity can be irrigated to break loculations further, although there is no evidence to support the practice. Traditionally, the abscess is then packed and left to heal without closure. However, recent research has suggested that packing may not be beneficial, and abscesses may safely be sutured closed immediately after incision and drainage.[9-11] Further study may be required before this practice becomes widespread.

Bartholin's abscesses are drained from the mucosal rather than from the cutaneous surface. The Word catheter is a device used to keep the surgical wound from closing (Fig. 129.4) because the abscess will recur if the wound is allowed to close. A very small incision (≈3 mm) is made, and the cavity is drained. Testing for chlamydia or gonorrhea is recommended. The catheter is inserted and inflated with about 4 mL of water or saline. The catheter should be left in place for 4 to 6 weeks so that a sinus tract will have time to form. Sitz baths may help keep the area clean and draining. Antibiotics are usually not necessary but should be considered when there is extensive surrounding erythema or induration. Marsupialization is used in recurrent cases to prevent further recurrences and is usually deferred until the acute inflammation has subsided. A large incision is made, and the interior of the abscess is then sutured to the surrounding mucosa so that the abscess is sutured open.

Disposition

Self-sufficient immunocompetent patients can be discharged to home after incision and drainage of an uncomplicated superficial abscess. It is traditional to schedule one or more visits for wound checks, but many patients can remove the packing themselves after 2 to 4 days and be instructed to return for reevaluation only case of persistent or worsening pain or other symptoms indicative of treatment failure.

IMPETIGO

Principles

Impetigo is a common superficial skin infection that is most prevalent in children aged 2 to 5 years, but it can occur at any age.

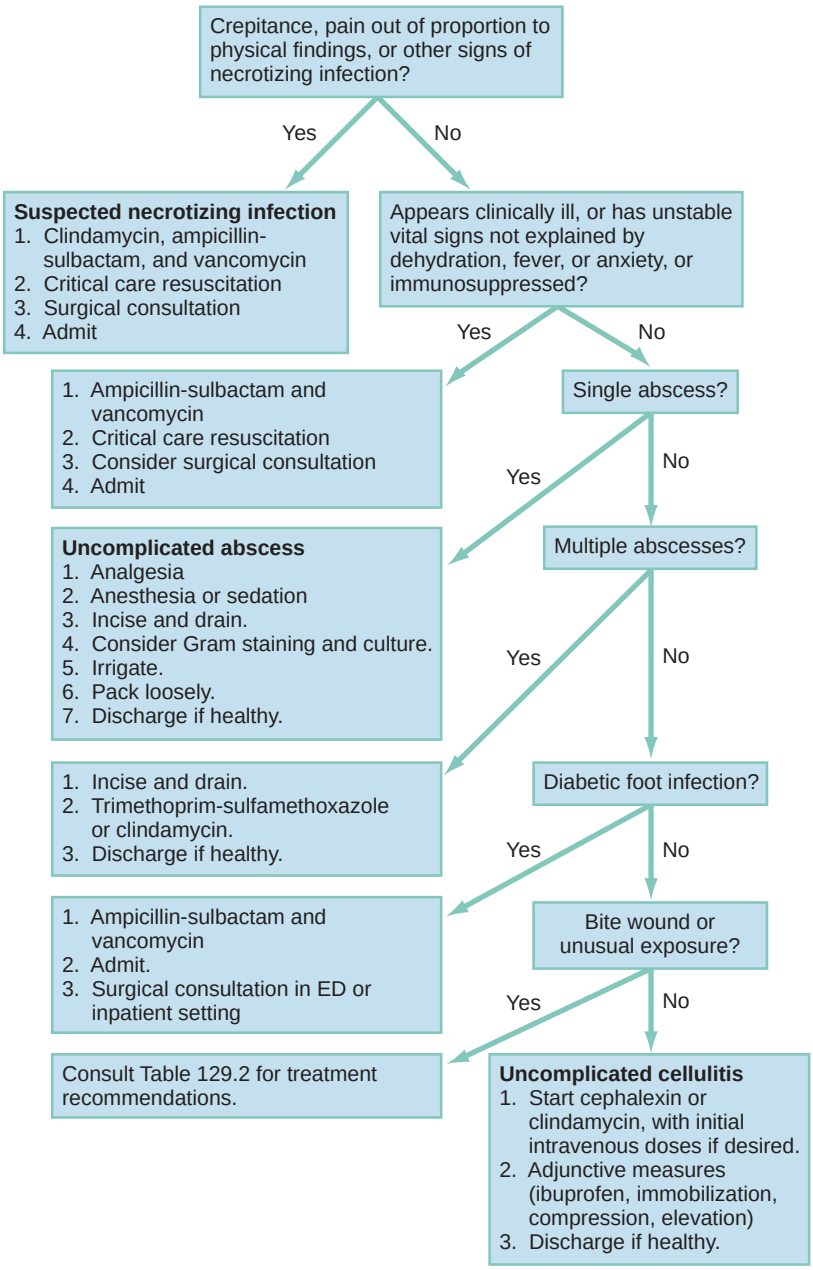

Fig. 129.2. Universal algorithm for skin and soft tissue infections, assuming no prior treatment.

It is communicable, spread by person to person transmission, autoinoculation, and fomites. It may be manifested as an infection of previously intact skin or may infect skin that has been damaged from minor trauma or atopic dermatitis.

Impetigo rarely progresses to systemic illness. However, most cases of poststreptococcal glomerulonephritis are believed to be caused by impetigo and not pharyngitis. Its onset is usually 10 days after the onset of impetigo but may occur up to 5 weeks later.

Clinical Features and Differential Diagnosis

The two main forms of impetigo are nonbullous and bullous. Nonbullous impetigo, or impetigo contagiosa, is the most common. It was believed for many years that group A streptococci were the primary cause of this disorder, but studies have subsequently shown that most cases are due to *S. aureus*. Approximately one-third of cases have *S. pyogenes* isolated, usually in combination with *S. aureus*. The lesions begin as thin-walled vesicles that progress to pustules; subsequent rupture results in the characteristic so-called honey crusted lesions, typically found on the face or extremities. Associated lymphadenopathy is common.

Bullous impetigo is caused by *S. aureus,* including CA-MRSA. The bacteria produce an epidermolytic toxin that causes separation of the dermal-epidermal junction, resulting in bullae. The lesions in bullous impetigo are fewer and larger (0.5–3 cm) but rupture less readily than the vesicles of the nonbullous form. After rupture, the bullae leave a thin brown crust.

Ecthyma, or deep impetigo, is a less common ulcerative form of impetigo that extends through the epidermis into the dermis. It is manifested as ulcers with a punched-out appearance, with raised reddened margins covered with thick crust. It has a predilection for the lower extremities. Unlike impetigo, ecthyma can result in cutaneous scarring.

Impetigo can be confused with contact dermatitis, varicella, herpes simplex, bullous pemphigoid, and Stevens-Johnson syndrome. It does not affect mucous membranes.

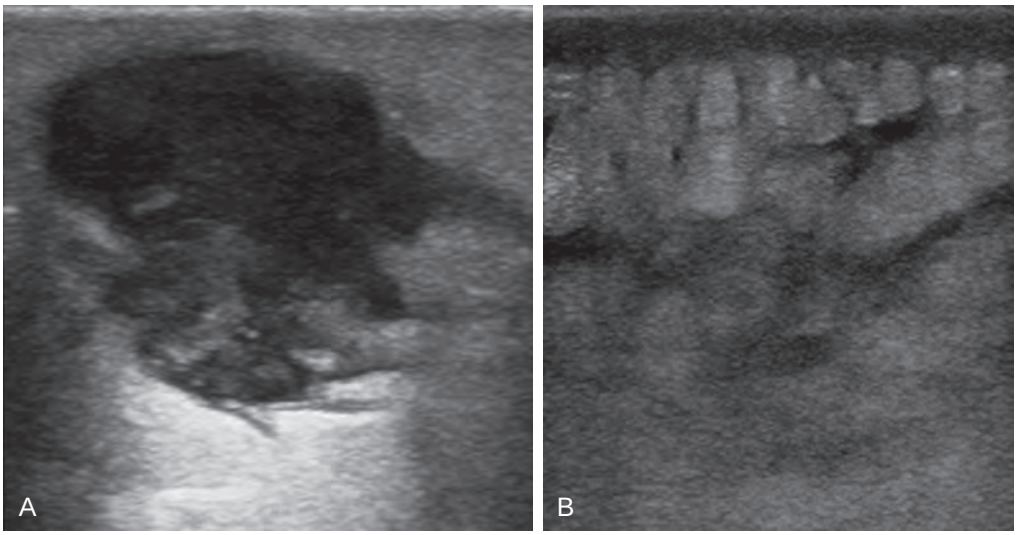

Fig. 129.3. Ultrasound examination to distinguish abscess from cellulitis. **A,** Abscess visualized with 8-MHz linear probe demonstrating dark areas (pus) with posterior acoustic enhancement. **B,** Cellulitis visualized with 8-MHz linear probe demonstrating cobblestoning. (Courtesy Dr. Mark W. Byrne, Department of Emergency Medicine, Brigham and Women's Hospital, Boston.)

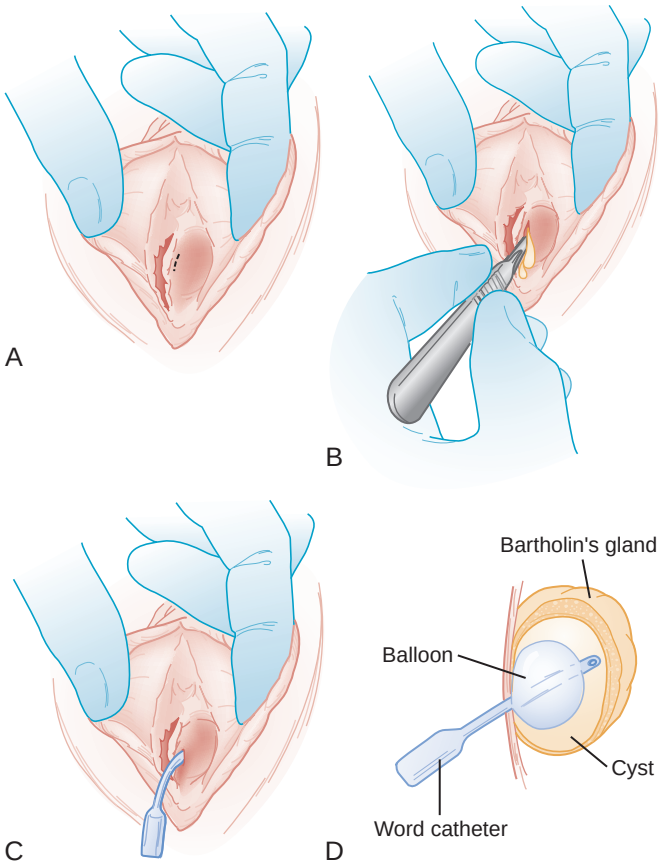

Fig. 129.4. **A–D,** Drainage of Bartholin's abscess and use of a Word catheter.

Management

Nonbullous impetigo should be treated with topical mupirocin, which is active against most MRSA strains; however, extensive disease or multiple lesions should be treated with oral agents effective against MRSA. Bullous impetigo should be treated with systemic antibiotics active against MRSA and streptococcus. I recommend clindamycin or cephalexin plus trimethoprim-sulfamethoxazole.

INFECTIONS OF THE PILOSEBACEOUS FOLLICLE

Principles

Folliculitis, furuncles, and carbuncles are purulent infections originating in the hair follicle. They are more likely to occur after damage to the hair follicle, such as from shaving. Acne and hidradenitis suppurativa (acne inversa) result from the obstruction of sebaceous glands.

Clinical Features and Management

Folliculitis is a superficial inflammation of the hair follicle that is limited to the epidermis. It has many causes, including eosinophilic and drug-related factors, but it is usually an infection due to *S. aureus*. The diagnosis is made clinically by its characteristic appearance of a small (2–5 mm), raised, erythematous, painful, tender lesion that is typically pruritic. It can affect any hair-bearing area of the skin. Folliculitis barbae involves the shaved beard area of the face or shaved scalp. Hot tub folliculitis is a pruritic condition caused by *Pseudomonas aeruginosa* that develops within 48 hours of bathing in a contaminated hot tub or swimming pool or from use of contaminated sponges. The rash consists of larger pustules and may have well-demarcated margins, typically involving the area of skin that was under the bathing suit. Candidal folliculitis occurs primarily in immunosuppressed patients and in individuals treated with broad-spectrum antibiotics. Eosinophilic folliculitis is a noninfectious recurrent disorder of unknown cause. It is more likely to occur in immunocompromised patients and is considered an AIDS-defining illness.

Folliculitis usually resolves on its own but can be treated with warm compresses or topical mupirocin. Multiple sites or a large cluster can warrant systemic antibiotics, although no randomized trials have been conducted on the efficacy of this treatment. Shaving of the involved area should be avoided. Hot tub folliculitis usually resolves on its own without specific treatment,

but antihistamines and ciprofloxacin are treatment options. Fungal folliculitis is treated with topical antifungal agents. AIDS-associated folliculitis may be eosinophilic or fungal and may be treated with isotretinoin topically or systemic antifungals, respectively.

Furuncles and Carbuncles

A furuncle, or boil, is an infection of the hair follicle in which suppuration extends through the dermis into the subcutaneous tissue (see Fig. 129.1). Furuncles are painful and erythematous and often drain spontaneously. The most common cause is *S. aureus,* both methicillin-sensitive and CA-MRSA. Whirlpool baths at nail salons have been implicated in mycobacterial furunculosis. A carbuncle comprises multiple furuncles with loculations and connecting sinuses, often with multiple sites of drainage. Systemic symptoms may occur. Carbuncles are more likely to occur on the back of the neck and are more prevalent in diabetics.

Furuncles and carbuncles are treated in the same manner as skin abscesses, primarily with incision and drainage. There is insufficient evidence to recommend for or against antibiotics, but I suggest coverage for streptococci and MRSA when disease is severe. Small furuncles may be treated initially with a trial of warm compresses to promote drainage.

Acne

Acne results from the obstruction of sebaceous glands. It is most common during adolescence because of hormonal stimulation. Recommended therapies include oral doxycycline, topical clindamycin, or topical retinoids.

Hidradenitis Suppurativa (Acne Inversa)

Hidradenitis suppurativa (acne inversa) is an exquisitely painful condition usually seen in the axilla. It may also occur in other apocrine gland–bearing skin, including the perineum, breasts, and inner thighs. It is about three times more common in females than in males. There is some familial predisposition. The typical onset is between puberty and 40 years. It is currently believed to be an acneiform disorder that begins with follicular occlusion, rather than infection of the sweat glands. This has led to suggestions that the term *hidradenitis suppurativa,* which means suppurative inflammation of the sweat glands, be replaced with the term *acne inversa,* which implies an origin of follicular obstruction. The pathophysiologic mechanism remains incompletely understood and is likely to be a complex interaction of hormonal, environmental, and genetic factors.[12]

The clinical course varies from intermittent isolated inflamed nodules to recurrent draining cysts and sinuses that can progress to a chronic and debilitating condition that is difficult to treat. Recurrences can lead to scarring, sinus tract formation, and disfigurement. This is a debilitating disease, and patients suffer not only from pain but also from social stigma due to the odor that may accompany the lesions and may suffer reactive depression.[12]

The diagnosis of abscess is made on the basis of the characteristic clinical presentation. Perianal and vulvar manifestations of Crohn's disease may be similar. Most emergency clinicians manage exacerbations with incision and drainage, although it is uncertain whether this accelerates healing. I recommend incision of painful nondraining abscesses for symptomatic relief. Systemic antibiotics are usually prescribed and should cover CA-MRSA. Perianal lesions should be treated more broadly with agents active against CA-MRSA, gram-negative organisms, and anaerobes. Amoxicillin–clavulanic acid plus trimethoprim-sulfamethoxazole is recommended.

Long-term treatment is complex and remains a subject of debate.[12] Options include immunomodulators (eg, steroids, cyclosporine), hormones, and en bloc resection. All patients should be instructed to stop smoking and keep the area clean and dry. Pain control is essential. Patients rarely show signs of systemic illness and thus can be discharged and referred to a plastic surgeon or dermatologist.

NECROTIZING SKIN AND SOFT TISSUE INFECTIONS

Principals and Clinical Features

Necrotizing infections progress rapidly, cause extensive tissue destruction, and can be fatal, despite aggressive treatment. Clinical manifestations that suggest a necrotizing infection are signs of systemic toxicity, including abnormal vital signs, severe pain or pain out of proportion to physical findings, altered mental status, rapidly advancing infection, crepitus, hemorrhage, sloughing, and blistering. Some patients appear well at presentation, and overlying skin may not be involved initially. Extensive tissue destruction occurs eventually; the mortality rate is 20%.

Risk factors include diabetes, vascular insufficiency, and immunosuppression, although healthy people are vulnerable. Inciting events include penetrating trauma, recent surgery, varicella infection, injection drug use, burns, and childbirth.

Typical bacterial isolates include group A beta-streptococci, *S. aureus*, including CA-MRSA, enterococci, Enterobacteriaceae, and the anaerobes *Bacteroides* and *Clostridium*. Most cases are polymicrobial. The classification schemes historically used for necrotizing infections are less important than the general principles discussed earlier.

Necrotizing fasciitis is an aggressive infection of subcutaneous tissues that spreads rapidly along fascial planes. In the operating room, the fasciae are inflamed, and tissue layers separate friably. It is caused by direct extension from a skin lesion in 80% of cases. Two types are described. Type I is polymicrobial, with aerobes and anaerobes; it is more common in diabetics and immunocompromised individuals. Type II is caused by a single organism, in any age group and in patients who are not chronically ill. Group A streptococci are most common; this aggressively virulent agent is known as flesh-eating bacteria. CA-MRSA is also a cause, although it appears to be less virulent. Initial symptoms may be vague (eg, malaise, fever, body aches, nausea, diarrhea). There may initially be diffuse or fusiform swelling of an extremity, or it may appear to be a simple cellulitis or wound infection. Physical findings may not be obvious initially, and pain out of proportion to physical findings is a clue. Eventually, the skin turns violaceous or ecchymotic. Anesthesia may develop over the involved tissue because of infarction of superficial nerves. Subsequent inflammation may result in the classic sign of so-called wooden-hard subcutaneous tissues.

Skin infections in the perineum warrant extra caution. *Fournier's gangrene* is the term given to necrotizing polymicrobial infections of the perineum. Fournier's gangrene progresses rapidly to extend to the entire perineum or abdominal wall. It can be recognized by severe pain, tenderness, and induration.

Myonecrosis, myositis, and pyomyositis refer to infections of muscle, which are rare. They may result from local spread of an adjacent infection, penetrating trauma, vascular insufficiency, or hematogenous spread. Clostridial myonecrosis, also known as gas gangrene, has two forms, a more common traumatic form and a rare spontaneous form. The traumatic form typically occurs from an injury that results in an interruption in the blood supply, and crush injuries are often implicated. The infection is most commonly due to *Clostridium perfringens,* a gram-positive spore-forming bacillus that is ubiquitous in nature, including the normal human body. Inoculation of the organism into tissue with low

oxygen tension allows proliferation. Exotoxins destroy tissue, contribute to shock, and may cause intravascular hemolysis, with anemia and disseminated intravascular coagulation (DIC). Patients present with severe pain. The skin may initially be pale, then bronze, and eventually purplish red. Hemorrhagic bullae may develop. Soft tissue gas may not be present initially. Systemic toxicity and shock ensue when aggressive treatment is not initiated early and sometimes occurs despite aggressive treatment. The spontaneous form of clostridial myonecrosis is very rare and occurs without any inciting wound. It is usually due to *Clostridium septicum* and occurs in patients with bowel disease, such as colon cancer. Synergistic nonclostridial myonecrosis is a related syndrome, usually seen in the immunocompromised.

Anaerobic streptococcal myositis usually results from trauma or is a postoperative complication. It resembles clostridial myonecrosis but has a more insidious course. It is caused by anaerobic streptococci, including *Peptostreptococcus,* but the infection may also include group A streptococci and *S. aureus*.

Spontaneous gangrenous myositis—also known as spontaneous streptococcal gangrenous myositis, group A streptococcal necrotizing myositis, or streptococcal myonecrosis—is rare but aggressive and fatal in most cases. It occurs spontaneously, without trauma, in immunocompetent hosts. It is preceded by a prodromal influenza-like phase. Gangrenous necrosis of skeletal muscle then results in severe pain, with tense local swelling.

Pyomyositis is a deep abscess within striated muscle resulting from the hematogenous spread of bacteria in the setting of muscle injury. It is usually due to *S. aureus,* including CA-MRSA, and is more common in those who are immunocompromised. Mortality is less than 10%.[13]

Differential Diagnosis and Diagnostic Testing

A necrotizing infection should be considered when a patient with cellulitis presents with a rapidly progressing course or pain out of proportion to clinical findings or when the patient appears acutely ill or has tachypnea, hypotension, or tachycardia not explained by fever or dehydration. Crepitance or radiographic air is diagnostic of a necrotizing infection unless there is another explanation (eg, recent surgery).

Phlegmasia cerulea dolens is iliofemoral vein thrombosis, which can be confused with necrotizing fasciitis. Arterial insufficiency causes gangrene, and it may be difficult to determine whether infection is present in severe or chronic cases. Similarly, compartment syndrome can be confused with necrotizing infection or coexist with it.

The diagnostic gold standard is the characteristic appearance of the tissue by direct visualization in the operating room. Some surgeons may elect to perform an exploration at the bedside.

A panel of blood tests has been evaluated as a way to differentiate necrotizing infections from other skin infections, the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score. Points are assigned for laboratory abnormalities, and a score of 6 or more is strongly predictive of necrotizing infection, with a positive predictive value of 92% and negative predictive value of 96%. However, this tool is too preliminary for clinical applicability for several reasons, including methodologic flaws, lack of validation of the findings at other sites, uncertainty about how the score should be implemented in ill-appearing patients, and absence of any data to indicate when the score should be calculated for well-appearing patients.[14] An even simpler decision aid relies on serum sodium concentration and white blood cell count but is similarly lacking in external validation and other criteria needed for clinical application. Necrotizing infections are very rare, and other skin infections are common. The diagnosis of necrotizing infection remains clinical, and universal laboratory screening of well-appearing patients is not recommended.

Plain radiographs may show air in the soft tissues, but absence of this finding does not rule out necrotizing infection. Ultrasound examination can visualize the abscess of pyomyositis. CT and MRI may show compelling evidence of a necrotizing infection, but their negative predictive values have not been quantified. Published studies have not supported a single approach to imaging patients at risk for necrotizing infections. The decision to begin evaluation with lower cost tests with low sensitivity versus higher cost tests with higher sensitivity will depend on a patient's clinical status and the emergency clinician's index of suspicion for the disorder.

Management and Disposition

Patients with suspected necrotizing infections should be resuscitated aggressively and have coagulation studies and a type and screen performed because emergent surgery may be needed. Renal function should be assessed and goal-directed therapy used to guide resuscitation.

I recommend prompt administration of broad-spectrum antimicrobials. A good regimen is clindamycin plus a broad-spectrum β-lactam such as ampicillin-sulbactam plus vancomycin to cover MRSA, in that order. Maximal doses should be used. In patients at risk for hospital-acquired infections, drug-resistant *P. aeruginosa* and extended-spectrum, β-lactamase–producing gram-negative bacteria should be considered.

When a necrotizing infection is suspected, a surgeon should be consulted. Repeated operative débridement is often needed. Fasciotomies are often necessary because these syndromes are associated with elevated compartment pressures, which contribute to myonecrosis. The efficacy of hyperbaric oxygen in the management of necrotizing infections is unproven, and treatment should not delay surgery.

TOXIC SHOCK SYNDROMES

Principles and Clinical Features

The main systemic, toxin-mediated, bacterial skin syndromes are staphylococcal scalded skin syndrome, streptococcal toxic shock syndrome, and staphylococcal toxic shock syndrome. These are caused by bacterial exotoxins known as superantigens because they cause a severe and pathologic host immune system response by stimulating T lymphocyte activation and functioning as mitogens in vitro.[15] Systemic disease results from the immune system's response to the toxin, but may be accompanied by or simply resemble bacteremic septic shock (Table 129.3).

Streptococcal Toxic Shock Syndrome

Streptococcal toxic shock syndrome (TSS) is a severe, toxin-mediated syndrome that rapidly progresses to shock, with multiorgan failure and death. Identified in the mid-1980s, this syndrome is caused by group A streptococci, often in the setting of a severe soft tissue infection. Most victims were previously healthy. The syndrome is a rare sequel of disseminated varicella (chickenpox).

Invasive group A streptococcal infections are often due to M-type isolates with potent exotoxins. Signs and symptoms are caused by pyrogenic exotoxins A and B. These act as superantigens and cause overactivation of T cells with a massive release of cytokines, including interleukins and tumor necrosis factor.[15]

Patients may have an influenza-like prodrome with nausea, vomiting, diarrhea, myalgias, and chills. High fever, hypotension, and tachycardia are typical. Altered mental status with confusion is common. A diffuse rash is present in 10% of cases, which may make differentiation from staphylococcal TSS more difficult.

TABLE 129.3

Comparison of Features of Streptococcal Toxic Shock Syndrome (TSS), Staphylococcal Toxic Shock Syndrome, and Staphylococcal Scalded Skin Syndrome (SSSS)

PARAMETER	STREPTOCOCCAL TSS	STAPHYLOCOCCAL TSS	SSSS
Organism	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Staphylococcus aureus*
Toxin	Pyrogenic exotoxins	TSS type 1; enterotoxins A, B, C	Epidermolytic toxin A or B
Patient	Previously healthy	Tampon use or wound infection	Infant
Source	Necrotizing infection	Nasal or wound packing, tampon; infection not obvious	Skin flora
Rash	Erythematous rash in only 10%; stigmata of necrotizing infection present; exfoliation weeks later	Initially diffuse erythroderma, with exfoliation after 1–2 wk; mucosal hyperemia	Tender erythematous rash, localized blisters, extensive exfoliation if no antibodies to toxin; mucosa spared
Systemic illness	Hypotension, shock, multiorgan failure likely	Hypotension, shock, sometimes multiorgan failure	Fever, irritability
Mortality	30%–80%	<5%	<5%
Treatment	Critical care resuscitation, operative débridement	Critical care resuscitation	Wound care, hydration

On presentation, the patient has a severe streptococcal infection; necrotizing fasciitis is present in 50% of cases. Pain is often out of proportion to physical findings. Most patients present with shock or develop it within 4 to 6 hours. Bacteremia is common, with positive blood cultures in about 60% of cases. Serious multisystem complications are common, including DIC, acute renal failure, and acute respiratory distress syndrome. In contrast to staphylococcal TSS, which is infrequently fatal, about 30% to 80% of patients diagnosed with streptococcal TSS die. Epidermolysis, typical of staphylococcal TSS, is not characteristic of the streptococcal variety.

Staphylococcal Toxic Shock Syndrome

Although staphylococcal TSS is not as severe as the streptococcal variety, it remains a life-threatening systemic illness. The classic presentation is of fever, rash, and hypotension, often in patients who were previously healthy. It was first described in 1978 and, beginning in 1980, there was an epidemic of cases associated with the use of highly absorbent tampons. Menses-associated cases have since declined dramatically when these tampons were eliminated from the market, although tampon use continues to remain a risk factor.

Nonmenstrual cases, which currently account for about 50% of cases, are associated with a variety of conditions, including surgical procedures (eg, rhinoplasty, abortion), nasal packing, burns, injection drug use, and the postpartum state. To the emergency clinician, menstrual and nonmenstrual staphylococcal TSS appear similar, and the source infection is often not readily apparent. Of note, prevention of TSS was a traditional indication for systemic antibiotic therapy after nasal packing for epistaxis, but recent evidence has suggested that this is not necessary, and topical antibiotics may be a preferred approach.

S. aureus exotoxins are superantigens that are able to activate large numbers of T lymphocytes, resulting in the massive release of inflammatory mediators, including interleukins, tumor necrosis factors, and interferon. Toxic shock syndrome toxin 1 (TSST-1) is associated with most menstrual cases. A lack of antibody against this toxin has been demonstrated in patients with menstrual staphylococcal TSS. Episodes of recurrent staphylococcal TSS have been reported in patients who do not mount a long-term antibody response, and it has been postulated that the toxin may interfere with antibody generation against itself.

Patients often have an acute onset of fever, chills, malaise, myalgia, muscle tenderness, and diffuse blanching macular rash that is not pruritic. There may be nausea, vomiting, or diarrhea. Patients may have altered mental status. Vitals signs usually indicate fever and low blood pressure.

Severe hypotension may ensue as a result of massive vasodilation and fluid shifts out of the intravascular space. Toxic cardiomyopathy may also contribute to the low blood pressure. Hypotension or rhabdomyolysis may cause acute tubular necrosis. Anemia, thrombocytopenia, and leukocytosis are common, and DIC may develop. Desquamation of the skin, including the palms and soles, eventually occurs 7 to 14 days after onset. The overall mortality is below 5% with aggressive supportive care.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is a desquamating skin disorder caused by exfoliating toxins produced by *S. aureus*. SSSS was historically known as fourth disease and in newborns as Ritter's disease. A disease of infants, it is rare in older children and adults. It can cause outbreaks in nurseries and daycare centers.

SSSS is caused by certain strains of *S. aureus,* including CA-MRSA, that produce epidermolytic toxin A or epidermolytic toxin B. These toxins probably act as proteases that target the protein desmoglein 1 on the stratum granulosum layer of the epidermis. Whether they meet the T lymphocyte mitogenic criterion for a superantigen has been a subject of debate, and this may be relevant to the prognosis, which is good relative to TSS.

The severity of the disease ranges from a few blisters at the site of infection to exfoliation of most of the body. People with preexisting toxin antibodies develop the localized form, in which toxin is found in the wound periphery; those without preexisting toxin antibodies develop the generalized form, in which toxin spreads through the bloodstream. Cultures of the bullae are negative unless they are contaminated or secondarily infected.

Typically, a young child presents with fever, irritability, and tender red rash. The erythema progresses to bullae formation and subsequent exfoliation of the affected skin. The skin exhibits

Nikolsky's sign, which is separation of the epidermal layer of skin on gentle stroking. Desquamation may be patchy or sheetlike, leaving the skin denuded, with a red moist base and predisposing it to secondary infection. Perioral, perianal, and flexural skin may be affected more severely. Mucous membranes are spared. SSSS is not associated with multisystem illness and typically does not lead to shock. Mortality is 1% to 5% and is usually a result of complications from comorbid conditions or superimposed infection.

Early SSSS may be difficult to differentiate from bullous impetigo. The lack of mucosal involvement helps differentiate SSSS from toxic epidermal necrolysis and Stevens-Johnson syndrome. Other differential considerations include Kawasaki syndrome, Rocky Mountain spotted fever, meningococcemia, leptospirosis, and heat stroke.

Differential Diagnosis and Diagnostic Testing

Streptococcal TSS should be suspected in any patient presenting with shock, especially if the patient was previously healthy. Diagnostic criteria for streptococcal TSS include the presence of group A streptococcal infection, hypotension, and two of the following: renal impairment, liver abnormalities, acute respiratory distress syndrome, coagulopathy, necrotic soft tissue infection, and rash. These criteria were developed for epidemiologic purposes; failure to meet all criteria should not exclude the clinical diagnosis in suspicious cases.

Staphylococcal TSS should be considered in any patient presenting with diffuse rash and hypotension. The diagnosis is made on the basis of the clinical presentation. The characteristic rash often raises suspicion and ultimately aids in establishment of the diagnosis. Isolation of *S. aureus* is not necessary for the diagnosis to be made; in fact, blood cultures are positive in a small minority of cases. In severe cases, laboratory abnormalities are those resulting from shock and organ damage.

Management

Streptococcal and staphylococcal TSS require critical care resuscitation. In streptococcal TSS, immediate surgical consultation for operative débridement of necrotizing infections is critical. In staphylococcal TSS, any potential source of infection should be removed, such as tampons or wound packing, and all postoperative wounds should be explored for infection.

Clindamycin and vancomycin should be administered. Gram-negative coverage should be added when the diagnosis of TSS is uncertain because the clinical picture overlaps with that of septic shock.

IV immune globulin has theoretic benefit, but its efficacy has not been shown in clinical trials. It is a reasonable option in cases of presumed staphylococcal TSS unresponsive to IV fluids and vasopressors, but this is not standard in the ED setting. There has been conflicting evidence on its efficacy for the treatment of streptococcal TSS. SSSS is treated with antibiotics active against *S. aureus,* including MRSA. Wound care and hydration are important.

Disposition

Patients with suspected TSS should be admitted, usually to the intensive care unit, for IV fluids, antibiotics, and close monitoring due to the potential for decompensation. Patients with necrotizing soft tissue infections associated with streptococcal TSS usually require surgical débridement.

Children with mild SSSS may be considered for outpatient management with oral antibiotics and close follow-up. Those with more severe skin involvement often need admission for pain control as well as for temperature regulation and fluid and electrolyte management. Severely affected patients may need intensive or burn center care. With proper supportive care and antibiotic treatment, the prognosis is excellent, with an overall mortality of less than 5%. Scarring is rarely severe.

OTHER INFECTIONS WITH SKIN MANIFESTATIONS

Borrelia burgdorferi is the spirochete that causes Lyme disease, endemic in the United States, especially in New England. It produces a characteristic targetoid rash known as erythema migrans, which emerges about 1 month after the infecting tick bite. The targetoid appearance results from central clearing of the erythema. However, 20% of Lyme disease patients do not report a rash, and the rash does not always have the characteristic round and targetoid appearance (see Chapter 126).

Another spirochete, *Treponema pallidum* (syphilis), is an increasingly rare cause of rash. The primary lesion of syphilis is a painless ulcer at the inoculation site, known as a chancre, with raised borders and regional lymphadenopathy. The chancre appears days to months after infection and resolves in approximately 1 month. Secondary syphilis develops weeks to months later in about 25% of infected patients. It involves a rash that can take any form other than vesicular and includes the palms and soles; there is usually diffuse lymphadenopathy. Syphilis is uncommon in the United States, although about 10,000 cases still occur annually (see Chapter 88).

Rocky Mountain spotted fever, caused by *Rickettsia rickettsii,* is even more uncommon, diagnosed only about 2000 times each year in the United States. A few days after a bite by a dog tick or wood tick, the characteristic rash begins on the wrists and spreads everywhere, including the palms and soles. It starts macular and becomes petechial and then dusky. Of those infected, 10% never develop a rash. The untreated mortality for Rocky Mountain spotted fever approaches 25%, but treated patients do well.

Cutaneous anthrax is transmitted from animal products of infected animals, such as wool or pelts, to exposed areas of veterinarians and farmers. A spore of the gram-positive anaerobe *Bacillus anthracis* enters a break in the skin and, after an incubation period of about 1 week, a vesicle forms. This ruptures, leaving a shallow-based ulcer with a raised border. The lesion progresses to painless necrosis and the characteristic eschar. Severe surrounding edema is due to bacterial toxins. The lesions may be confused with recluse spider bites. Unlike the case with inhalational anthrax, treated cases do well, and even untreated cases have a mortality rate of less than 20%.

Tularemia is a rare disease resulting from exposure to animals such as rodents, rabbits, and hares and is endemic in much of the United States, especially the south central states. The ulceroglandular form is most common and involves an influenza-like illness with a single raised ulcer that has a mild central eschar formation. The lesion itself is raised, rather than the border, which might suggest anthrax (see Chapter 126).

The floor of the mouth is a dangerous location for soft tissue infections. Severe infections may progress to Ludwig's angina, in which the floor of the mouth becomes severely indurated. Ludwig's can be fatal due to airway obstruction. Broad-spectrum antibiotics are indicated. Steroids may reduce swelling. Intubation should be considered and a difficult airway anticipated (see Chapter 65).

Scabies is a skin infestation of the parasitic mite *Sarcoptes scabiei*. It is endemic worldwide and can cause institutional outbreaks. Lesions are most prominent on the dorsal aspect of the hand and in intertriginous areas. It is diagnosed by visualization of characteristic burrows and, in ambiguous cases, by microscopy of skin scrapings. It is treated with topical permethrin or a single dose of oral ivermectin (200 μg/kg). Norwegian scabies, also

known as crusted scabies, is an aggressive infestation that occurs in the immunocompromised; it is treated with permethrin and ivermectin (see Chapter 110).

Cat-scratch disease results from *Bartonella henselae* infection after a cat bite or scratch. Its hallmark is regional lymphadenopathy that appears weeks after a primary lesion at the site of inoculation. Treatment is with a standard 5-day course of azithromycin, with a double dose on day 1.

Strongyloidiasis is caused by infection with the parasitic helminth *Strongyloides stercoralis*. Skin lesions can appear years after infection and are urticarial or serpiginous. A rapidly extending burrow that is pruritic and erythematous is diagnostic; this finding, due to rapid migration of larvae in the skin, is known as larva currens (running larva). Such findings or unexplained eosinophilia in people who have lived in Southeast Asia or tropical Africa should prompt consideration of strongyloidiasis. Diagnosis is by an enzyme-linked immunosorbent assay performed on serum. Detection is important because, unlike other nematodes, strongyloides can complete its life cycle in the human host, leading to lifelong infection. When the infected patient becomes immunosuppressed by medications or illness, the strongyloides hyperinfection syndrome can result and is often fatal (see Chapter 125).

Cutaneous larva migrans is another serpiginous skin lesion caused by migrating larvae. In this case, the organism is hookworm, and the site is typically the foot or buttock; it is often seen after a vacation on the beach in Mexico. Treatment is with a single dose of ivermectin 200 mg/kg (see Chapter 125).

Cutaneous leishmaniasis is common in many parts of the world and is found on every continent except Australia and Antarctica. It is caused by protozoans of the genus *Leishmania* and is transmitted by sandflies. Lesions are most common on the face and are painless, ulcerative, and disfiguring. Papules in returning travelers and immigrants should raise suspicion of myiasis (botfly) and, rarely, dracunculiasis (Guinea worm).

KEY CONCEPTS

- Skin infections are common and are rarely life-threatening. Deadly necrotizing skin and soft tissue infections are rare, and there is insufficient evidence to motivate screening by laboratory tests.
- Necrotizing infection is suggested by pain out of proportion to physical findings, crepitance, gas seen on imaging studies, or clinical instability. Suspected necrotizing infection is managed aggressively, with broad-spectrum antibiotics, critical care resuscitation, and surgical consultation.
- Emergency clinicans should be familiar with toxic shock syndromes and Rocky Mountain spotted fever, which are rare, life-threatening, skin infection–related syndromes. Lyme disease should be considered in endemic areas.
- For the management of most skin abscesses, antibiotics are not recommended. Adequate analgesia or sedation are essential to good patient care. There is debate about the necessity of wound culture and Gram staining.
- Current recommendations for the treatment of cellulitis suggest agents effective against streptococci and methicillin-sensitive *Staphylococcus aureus* (eg, cephalexin at maximal doses). Adjunctive measures are essential to a good treatment response—NSAIDs, immobilization, elevation, and compression.
- Clindamycin monotherapy is an excellent choice for the treatment of skin infections because it covers streptococci and most staphylococci, including most CA-MRSA isolates.
- Although they are active against CA-MRSA, trimethoprim-sulfamethoxazole and tetracyclines may not be effective for streptococci and are not recommended for cellulitis monotherapy.
- There is insufficient evidence to recommend measurement of the white blood cell count in patients with skin infections.
- Blood cultures are not necessary for the evaluation of skin infections, except with septic shock, necrotizing infections, immunocompromise, multifocal infections suggesting hematogenous seeding, infections complicating lymphedema, and perhaps facial cellulitis.
- Skin infection mimics include venous stasis dermatitis and other forms of dermatitis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 129: QUESTIONS & ANSWERS

129.1. Which of the following statements regarding cellulitis is true?

A. Bilateral cellulitis of the lower extremities is a common bacterial infection.
B. Computed tomography (CT) can rule out necrotizing fasciitis.
C. Fever and leukocytosis are key to the diagnosis.
D. Needle aspiration of the leading edge is unlikely to identify the causative organism.
E. Ultrasound evaluation cannot rule out a large abscess.

Answer: D. Needle aspiration and even biopsy are rarely able to identify a causative organism in nonpurulent cellulitis. Fever and leukocytosis are often absent, and measurement of the white blood cell count is not indicated. Ultrasound evaluation is sensitive and specific and can rule out a large abscess, although distinguishing small abscesses from the cobblestoning of cellulitis can be difficult. Bilateral lower extremity inflammation is usually venous stasis dermatitis, which can be confused with cellulitis. Bilateral cellulitis is rare and suggests hematogenous dissemination.

129.2. A 7-year-old girl presents with right periorbital pain and swelling. Physical examination reveals a temperature of 38° C (100.4° F), periorbital edema, erythema, and warmth. Some erythema and edema of the eyelids occur as well. Vision, extraocular movements, and pupils are normal. Which of the following statements regarding this patient's condition is true?

A. An urgent CT scan is indicated.
B. Plain radiographs of the sinuses are indicated.
C. Progression to the other eye is likely.
D. Progression to vision loss is likely.
E. She should be treated as an outpatient with antibiotics targeting staphylococci.

Answer: E. Well-appearing children with no eye pain or pain on extraocular movement may be diagnosed with preseptal cellulitis and treated as outpatients if the parents can be trusted to return for failure to improve. Historically, *Haemophilus influenzae* type B was an important organism but, in vaccinated children, this is less likely; unvaccinated children should receive an agent effective against this organism. Orbital cellulitis is suggested by change in vision, eye pain, pain with extraocular movements, or a toxic appearance. When there is doubt, CT scanning is appropriate but not mandatory in all cases. Most cases are unilateral. Progression to endophthalmitis and vision loss is not expected with preseptal cellulitis, although it can occur in orbital cellulitis.

129.3. A 53-year-old woman presents with fever and painful swelling of the left side of her face. The physical examination is remarkable for a toxic-appearing woman with a sharply demarcated, raised, bright red, and extremely tender eruption involving the left side of her face. Which of the following statements regarding this patient's condition is true?

A. Echocardiography is indicated.
B. Fluoroquinolones are first-line antibiotics.
C. Penicillin G monotherapy is the correct treatment.
D. The face is the most commonly involved site.
E. There is an association with glomerulonephritis.

Answer: E. Erysipelas is an acute cellulitis typically caused by group A streptococci. It presents with an angry red area of inflammation that is well-demarcated from the surrounding skin and has a raised border. Like other group A streptococcal skin infections, erysipelas can give rise to poststreptococcal glomerulonephritis. Penicillin G is probably the ideal therapy, but any toxic-appearing patient should be treated more aggressively, with goal-directed therapy and broad-spectrum antibiotic coverage. *H. influenzae* is a classic cause of facial cellulitis but is more common in children, is rare in the era of HiB vaccination, and typically causes transdermal cellulitis, rather than the more superficial form of cellulitis known as erysipelas. The lower extremities are usually involved.

129.4. A 5-month-old girl presents with fever and a diffuse dermatitis characterized by bulla formation, with surrounding vesicles leading to the loss of large sheets of epidermis. She has no past medical history and has been on no medications. The areas of desquamation are tender and red. Which of the following statements regarding this patient's condition is true?

A. Antibiotics are not indicated.
B. Corticosteroids will help prevent progression.
C. Culture of the bullae is not indicated.
D. Mortality is greater than 30%.
E. Mucous membranes are likely affected.

Answer: C. Staphylococcal scalded skin syndrome is a toxin-mediated process occurring in the very young (6 months–6 years) and older adults. The cornerstone of treatment is hydration and

antistaphylococcal antibiotics. Culture of bulla fluid is generally negative. Mucous membranes are spared. This condition is rarely fatal.

129.5. A 7-year-old boy presents with a left leg rash. The mother describes an initial sequence of a patch of small red papules that rapidly became vesicular, then pustular, and then crusted over. You observe a 2- × 3-cm area on the left thigh, with heavily crusted erythematous macules. There is moderate left inguinal lymphadenopathy. The lesions are not tender, and the child is not toxic-appearing. Which of the following statements regarding this patient's condition is true?
A. Acute rheumatic fever is a risk.
B. Corticosteroids are indicated.
C. Systemic antibiotics are necessary.
D. The streptozyme test is highly reliable.
E. Topical mupirocin is indicated.

Answer: E. Impetigo involves a blistering eruption with a honey-colored crust. It may be caused by streptococci or staphylococci. For limited disease, topical mupirocin is the treatment of choice. Oral or systemic antibiotics are only indicated for more severe cases. Corticosteroids are not indicated. No laboratory test is useful. Acute rheumatic fever does not occur after impetigo. Poststreptococcal glomerulonephritis may occur, but is less likely than after pharyngitis.

129.6. Which of the following statements about skin infections in the age of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is false?
D. Abscesses should be treated with antibiotics active against CA-MRS**A.**
A. CA-MRSA is usually associated with mild disease.
E. Evidence is lacking that CA-MRSA plays a role in nonpurulent skin infections.
C. The cause of most cases of cellulitis is unknown.
B. There is no clinical trial evidence to support the use of trimethoprim-sulfamethoxazole for any skin infection.

Answer: D. Multiple trials have suggested that antibiotics are not beneficial when an abscess is treated with incision and drainage. Only extraordinarily large abscesses, multiple abscesses, and other special cases merit antibiotic treatment. When antibiotics are used, they should cover CA-MRS**A.** Most cases of CA-MRSA disease are mild, purulent, skin infections. So far, no clinical trial has demonstrated benefit of trimethoprim-sulfamethoxazole for the treatment of any skin infection. The cause of nonpurulent cellulitis is usually impossible to ascertain because even biopsy rarely yields a positive culture. There is insufficient evidence that CA-MRSA is an important pathogen in nonpurulent cellulitis to justify the use of anti–CA-MRSA antibiotics in its treatment.

129.7. A young woman presents complaining of a painful itchy rash. She has just returned from a vacation in the Caribbean, where she was snorkeling. Examination reveals streaks of erythema with slight vesiculation along the lateral aspect of the right leg. The lesions are oriented diagonally, not along vascular lines, and are about 15 cm long. What is the most appropriate next step in this patient's management?
A. Obtain a CT scan to assess for necrotizing fasciitis.
B. Perform a Tzanck smear performed on an unroofed vesicle.
C. Treat with acyclovir.
D. Treat with corticosteroids.
E. Treat with trimethoprim-sulfamethoxazole.

Answer: D. This is an example of contact dermatitis, likely from seaweed or jellyfish stings. Nothing in the presentation is suggestive of an infection. Trimethoprim-sulfamethoxazole monotherapy is rarely appropriate because abscesses generally do not require antibiotics, and streptococci are thought to be covered poorly by this antibiotic. A Tzanck smear and acyclovir treatment would be appropriate if herpetic infection were suspected, but neither herpes simplex nor varicella zoster would present with 15-cm streaks.

CHAPTER 130

Sepsis Syndromes

Nathan I. Shapiro | Alan E. Jones

PRINCIPLES

Background

Sepsis syndrome represents the body's host response to an infection. The causative agent and host's activated inflammatory cascade overwhelm the body's defenses and regulatory systems, leading to disruption in homeostasis. Tachycardia, tachypnea, fever, and immune system activation are common manifestations. If the body is unable to overcome this insult, cellular injury, tissue damage, shock, multiorgan failure, or death may ensue.

In 1992, the American College of Chest Physicians and Society of Critical Care Medicine issued a consensus statement to establish uniform criteria defining the sepsis syndromes. The goal was to create a common nomenclature for disease classification and systematic comparisons across studies of septic patients. The term *systemic inflammatory response syndrome* (SIRS) is defined as two or more of the following: tachycardia, tachypnea, hyperthermia or hypothermia, high or low white blood cell count, or bandemia. Sepsis is the combination of infection plus SIRS, severe sepsis is sepsis plus organ dysfunction, and septic shock is sepsis plus hypotension, defined as a systolic blood pressure below 90 mm Hg, not responsive to a fluid challenge (Box 130.1). This nomenclature is intended to provide clinicians and researchers with a common classification. Efforts to validate this classification scheme in the emergency department (ED) population have demonstrated that the term *sepsis,* when characterized by fulfilling the SIRS criteria alone, is overly sensitive and nonspecific and does not convey an increased mortality risk. SIRS is not specific because it can be present in noninfectious inflammatory states and in localized infections that are not inclined to lead to sepsis, such as streptococcal pharyngitis or viral illnesses. However, organ dysfunction and shock have been shown to portend worse outcomes. Newer efforts have proposed the PIRO approach, which may help us better understand and prognosticate the severity of illness. PIRO stands for assessment of ***p***redisposing conditions, ***i***nfection source, ***r***esponse of the host, and ***o***rgan dysfunction and has been proposed to help improve classification.[1]

Bacteremia may be present, but positive cultures are not obligatory in the diagnosis of sepsis. Culture-negative and culture-positive septic populations have similar outcomes in patients with similar severity of illness. Pneumonia, abdominal abscess with viscus perforation, and pyelonephritis are common primary causes of sepsis. Gram-positive organisms account for 25% to 50% of infections, gram-negative organisms for 30% to 60%, and fungi for 2% to 10%. The distribution varies with the study and, more importantly, with host factors such as the status of the host immune system, age of the patient, recent hospitalizations, and presence of indwelling vascular catheters.

The health status of the host is a potentially important risk factor in the development and progression of sepsis. Older adults and those with multiple comorbidities may be more susceptible to developing a systemic infection. Chemotherapy-induced neutropenia, acquired immunodeficiency syndrome, and steroid dependency increase susceptibility to sepsis. Increased use of indwelling devices such as intravascular catheters, prosthetic devices, and endotracheal tubes also contribute to the risk of systemic infection and sepsis.

Pathophysiology

Sepsis results from the complex interaction of detection molecules, signaling molecules, and numerous inflammatory and coagulation mediators in response to infection. Although our understanding of the pathophysiologic process of sepsis has evolved, it remains incomplete. The initial host response is to mobilize inflammatory cells, particularly neutrophils and macrophages, to the site of infection. These inflammatory cells then release circulating molecules, including cytokines, which trigger a cascade of other inflammatory mediators that result in a coordinated host response. Synthesis of the components of the cascade is increased at many steps along the pathway. If these mediators are not appropriately regulated, sepsis will occur. In the setting of ongoing toxin release, a persistent inflammatory response occurs, with ongoing mediator activation, cellular hypoxia, tissue injury, shock, multiorgan failure, and potentially death.

Mediators of Sepsis

Host response and pathogen characteristics are both important in the pathogenesis of sepsis. More than 100 discrete markers have been identified and attributed to the sepsis cascade, but the true culprits have not been clearly identified.[2] A pathogen is sensed by pattern recognition receptors, most notably Toll-like receptors, located on the surface of the white blood cell. The resulting host-pathogen interaction activates the inflammatory and coagulation cascades. The subsequent inflammatory signaling occurs through cytokines, chemokines, and other soluble mediators, including increased circulating levels of the interleukins IL-1, IL-6, and IL-8 and tumor necrosis factor alpha (TNF-α). Activation of the clotting cascade may result in increased D-dimer levels and decreased circulating levels of protein C.

In benign conditions, a self-limited response helps clear the pathogen. If the innate immune response is inadequate, mediators create a procoagulant state. Coagulation and fibrinolytic components are proinflammatory, precipitating a worsening cycle of procoagulant and proinflammatory mediators. Propagation of this cascade ultimately contributes to end-organ damage and often to disseminated intravascular coagulation (DIC). If it is not effectively reversed, the process leads to cellular hypoxia, organ dysfunction, shock, and death.

The primary mediators are cytokines that are primarily proinflammatory, antiinflammatory, or growth-promoting. The molecular mechanisms whereby they are regulated are not well understood. An initial cytokine, TNF-α, is found in serum approximately 90 minutes after the administration of endotoxin to healthy volunteers. IL-6 and IL-8 reach peak levels at approximately 120 minutes. The main proinflammatory cytokines include IL-1, TNF-α, and IL-8. The primary antiinflammatory cytokines are IL-10, IL-6, transforming growth factor-β, soluble receptors to

BOX 130.1

Definitions of Sepsis

- Bacteremia (fungemia)—presence of viable bacteria (fungi) in the blood, as evidenced by positive blood cultures
- Systemic inflammatory response syndrome (SIRS)—at least two of the following conditions: oral temperature > 38° C (100.4° F) or < 35° C (95° F); respiratory rate > 20 breaths/min or partial pressure of arterial carbon dioxide ($Paco_2$) < 32 mm Hg; heart rate > 90 beats/min; leukocyte count > 12,000/dL or < 4000/dL; or >10% bands
- Sepsis—systemic inflammatory response syndrome (SIRS) that has a proven or suspected microbial source
- Septic shock—sepsis with hypotension that is unresponsive to fluid resuscitation plus organ dysfunction or perfusion abnormalities, as listed for severe sepsis
- Multiple organ dysfunction syndrome (MODS)—dysfunction of more than one organ, requiring intervention homeostasis

Adapted from Bone R, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The APP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101:1644–1655, 1992.

TNF, and IL-1 receptor antagonist (IL-1RA). If the resultant inflammatory response is adequate, the infection is controlled and cleared. If the response is deficient or excessive, however, a persistent and worsening cascade is produced, ultimately leading to (once again) shock, organ failure, and potentially death.

Instability in vascular tone has become increasingly important in understanding the pathophysiologic mechanism of sepsis. Vasopressin, also known as antidiuretic hormone, is a naturally occurring hormone that is essential for cardiovascular stability. It is produced as a prohormone in the hypothalamus. The hormone is stored in the pituitary gland and released in response to stressors such as pain, hypoxia, hypovolemia, and hyperosmolality. In severe sepsis, there is a brief rise in circulating vasopressin levels followed by a prolonged and severe suppression. This pattern of secretion is different from other forms of shock, in which vasopressin levels remain elevated. Vasopressin has numerous physiologic effects, including vasoconstriction of the systemic vasculature, osmoregulation, and maintenance of normovolemia.

Nitric oxide (NO) is a gas that has an important role in septic shock, regulating vascular tone by an indirect effect on smooth muscle cells. NO also contributes to platelet adhesion, insulin secretion, neurotransmission, tissue injury, and inflammation and cytotoxicity. Its half-life is short (6–10 seconds), and it easily diffuses into cells. Although its mechanisms of action are not well understood, it seems to be a key mediator of sepsis. Animal data have shown that nitric oxide synthase, the enzyme that produces NO, is upregulated in cases of sepsis. Enhanced NO production is thought to contribute to the profound vasodilation found in patients in septic shock.

In the setting of ongoing inflammatory activation, the mediators of sepsis continue to be produced, and the cascade is perpetuated. Unless it is appropriately and rapidly controlled, the ultimate effect is a sequence of events starting with cellular dysfunction and ultimately leading to tissue damage, organ dysfunction, and death.

Organ System Dysfunction

The organ dysfunction that results from sepsis is central to the pathogenesis of the disease. The mortality of patients with sepsis increases as the number of failing organs increases (Fig. 130.1A). In one large study, the mortality rate was 1% for sepsis patients with no organ dysfunction, whereas the rates for patients with

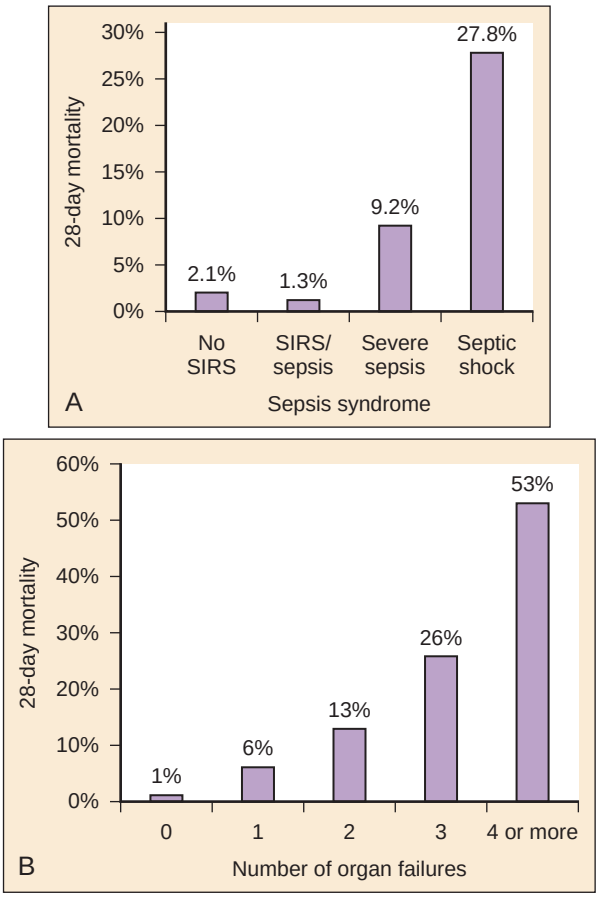

Fig. 130.1. Mortality rates by sepsis syndrome (**A**) and number of organ dysfunctions (**B**). *SIRS,* Systemic inflammatory response syndrome.

dysfunction of a single organ, two organs, three organs, and four or more organs were 6%, 13%, 26%, and 53%, respectively (see Fig. 130.1B).

Neurologic Impairment. Patients with sepsis may display neurologic impairment manifested by altered mental status and lethargy, commonly referred to as septic encephalopathy. The incidence has been reported as between 10% and 70%. The mortality rate in patients with septic encephalopathy is higher than that in septic patients without significant neurologic involvement. Although the pathophysiologic process has not been clearly defined, contributing factors may include direct bacterial invasion, endotoxemia, altered cerebral perfusion or metabolism, metabolic derangements, multiorgan system failure, and iatrogenic injury. In addition, impaired renal or hepatic function in the absence of overt organ failure has been shown to correlate with encephalopathy.

Cardiovascular Dysfunction. Cardiovascular dysfunction is common with sepsis. The cardiovascular dysfunction and failure arise from direct myocardial depression and distributive shock. Gram-negative, gram-positive, and killed organisms can cause myocardial depression. The direct insults of the toxic mediators as well as the mobilization of host mediators of sepsis produce a distributive shock. Early in sepsis, a hyperdynamic state develops, characterized by increased cardiac output and decreased systemic vascular resistance. Although the cardiac output is increased, it is at the expense of ventricular dilation and decreased ejection fraction (EF). Vigorous fluid resuscitation usually increases preload and, secondarily, EF, thereby improving

the cardiac index, even late in shock. Much of the cardiovascular compromise from septic shock is reversible, and normal cardiovascular function usually returns within 10 days.

Pulmonary Involvement. Involvement of the lung is often seen in the inflammatory response to infection. These effects are apparent, irrespective of the primary infection that caused sepsis. Early infiltration with neutrophils, surfactant dysfunction, and edema give way to monocyte infiltration and fibrosis. Significant right-to-left shunting, arterial hypoxemia, and intractable hypoxemia occur. The resulting morbidity is high and is a common endpoint to sepsis-related deaths.

Sepsis produces a highly catabolic state and places significant demands on the respiratory system. At the same time, airway resistance is increased, and muscle function is impaired. Irrespective of whether pneumonia is the cause of sepsis, the common pulmonary endpoint is acute respiratory distress syndrome (ARDS). ARDS is defined clinically and correlates with the pathologic finding of diffuse alveolar damage. The development of ARDS occurs hours to days after radiographic abnormalities develop. Because of alveolar-capillary membrane damage, fluid accumulates in the alveoli. Rather than being a diffuse disease, ARDS is a heterogeneous process that results in interspersed damaged and normal alveoli.

Gastrointestinal Effects. A shock state causes significant deleterious effects on a hollow viscus and its oxygen supply. A prolonged ileus accompanies hypoperfusion and persists beyond the perfusion deficit. Splanchnic blood flow is dependent on mean arterial pressure because there is relatively little autoregulation. Therefore, hemodynamic dysfunction may have a profound effect on viscus metabolism.

Solid organ involvement is also common. Even in the previously normal host, elevations in aminotransferases and bilirubin levels are common early in sepsis. The liver has also been implicated in the pathogenesis of sepsis; some of the mediators of sepsis are produced by the liver.

Endocrine Disorders. An absolute or relative adrenal insufficiency is common in sepsis. Depending on the balance of circulating cytokines, augmentation or suppression of the hypothalamic-pituitary axis is possible. IL-1 and IL-6 both activate the hypothalamic-pituitary-adrenal axis. TNF-α and corticostatin depress pituitary function. Other factors that may contribute to adrenal insufficiency in sepsis include decreased blood flow to the adrenal cortex, decreased pituitary function, and decreased pituitary secretion of adrenocorticotropic hormone due to severe stress. As a result of these interactions, the hypothalamic thermoregulatory mechanism may be reset, and temperature fluctuations may develop.

Hematologic Abnormalities. Sepsis causes abnormalities in many parts of the coagulation system. Endotoxin, TNF-α, and IL-1 are the key mediators. Pathologic activation of the extrinsic (tissue factor–dependent) pathway, protein C, protein S, and fibrinolysis lead to consumption of essential coagulation factors, causing DIC. The activation of the coagulation cascade produces fibrin deposition and microvascular thrombi. If these depositions are not corrected, they can compromise organ perfusion and contribute to organ failure. Tissue factor expression on monocytes is increased. This results in fibrin deposition and perhaps contributes to an increased incidence of multiorgan failure due to microvascular thrombi.

Protein C has been identified as an important modulator of inflammation and coagulation in patients with sepsis. Impairment of the protein C–dependent anticoagulation pathway is critical to the development of the thrombotic complications of sepsis. In healthy peoples, protein C is activated by a combination of thrombin and thrombomodulin. The activation of protein C results in the downregulation of many portions of the coagulation cascade, including release of tissue factor, inactivation of factors VIIIa and Va, and stimulation of fibrinolysis. It is possible that protein C activation in early sepsis is impaired because of an inflammatory cytokine–mediated downregulation of thrombomodulin. As a result, a consumptive coagulopathy ensues. This leads to increased fibrin deposition and a resulting upregulation of the fibrinolytic pathway, as identified by low plasma levels of the fibrinolytic proteins and increased fibrin split products. This sequence of events leads to consumption of coagulation factors and DIC. In late sepsis, the fibrinolytic system is suppressed.

Genetic Factors

There has been increasing evidence that genetics are a risk factor for the outcome of sepsis.[3] An individual may contain a set of individual characteristics or polymorphisms that may affect the ways in which he or she responds to sepsis in general, or perhaps there may be differences in response to specific sepsis therapeutics. Identifying and understanding these differences in an individual's genetic makeup is likely to lead to tailored approaches to diagnosis and therapy. The impact of genetics on future treatment modalities for sepsis remains unclear, but the prospect of customized genetic therapy for sepsis is a promising early development.

CLINICAL FEATURES

Symptoms and Signs

The approach to a patient with sepsis relies on identification of the presence of a systemic infection and localization of the source of the initial infection. This allows appropriate treatment directed to the source of infection. Often, the source is not readily apparent, but early identification of the septic state allows implementation of broad-spectrum antibiotics.

The septic patient may manifest signs of systemic infection through tachycardia, tachypnea, hyperthermia or hypothermia and, if severe, hypotension. A septic patient will often have flushed skin with warm, well-perfused extremities secondary to the early vasodilation and hyperdynamic state. Alternatively, the severely hypoperfused patient with an advanced shock state may appear cyanotic. Very early in the patient's presentation, vital sign changes such as tachycardia and tachypnea may be first indicators of sepsis. If the patient is in shock, a rapid assessment that excludes other causes, such as hypovolemic or cardiogenic shock, is essential to the proper initial treatment. A complete detailed clinical examination will help the emergency clinician determine the cause of the shock state (see Chapter 6). These are classic signs; however, these findings may not be manifested in a septic patient, and signs and symptoms may be subtle or absent.

Both underlying comorbidities and the cause of sepsis should be considered. Risk factors such as immunocompromised states (eg, acquired immunodeficiency syndrome, malignant disease, diabetes, splenectomy, concurrent chemotherapy), older age, debilitation, high-risk environments for iatrogenic infections (eg, acute care hospitalizations, long-term care facilities), and multiple comorbidities should be considered.

The respiratory system is the most common source of infection in the septic patient. A history of a productive cough, fevers, chills, upper respiratory symptoms, and throat and ear pain should be sought. Physical examination should also include a detailed evaluation for focal infection, such as exudative tonsillitis, sinus tenderness, tympanic membrane injection, and crackles or dullness on lung auscultation. Also, pharyngeal thrush should be noticed as a potential marker of an immunocompromised state.

The gastrointestinal system is the second or third (depending on the study) most common source of sepsis. A history of abdominal pain, including its description, location, timing, and modifying factors, should be sought. Further history, including time of the last bowel movement and presence of nausea, vomiting, and diarrhea, should be noted. A careful physical examination, looking for signs of peritoneal irritation, abdominal tenderness, and hyperactive or hypoactive bowel sounds, is critical in identifying the source of abdominal sepsis. Particular attention should be paid to physical findings suggestive of common sources of infection or disease—Murphy's sign indicating cholecystitis, pain at McBurney's point indicating appendicitis, left lower quadrant pain suggesting diverticulitis, or rectal examination revealing a rectal abscess or prostatitis.

The neurologic system is examined by looking for signs of meningitis, encephalitis, or epidural abscess, including nuchal rigidity, fevers, and change in consciousness. Lethargy or altered mentation may indicate primary neurologic disease or may be the result of decreased brain perfusion.

The genitourinary (GU) history includes queries about the presence of flank pain, dysuria, polyuria, discharge, Foley catheter placement, and genitourinary instrumentation. However, one must also remember that GU infection is a common source of infection in older patients and is a common offender in patients with nonspecific symptoms. A sexual history should assess for the risk of sexually transmitted diseases. The genital examination could reveal ulcers, discharge, penile or vulvar lesions, or the woody induration of Fournier's gangrene. A rectal examination could reveal a tender, boggy prostate, consistent with prostatitis. A red and friable cervix, cervical discharge, or cervical motion tenderness is consistent with a sexually transmitted disease. Adnexal tenderness in a toxic-appearing woman may represent a tubo-ovarian abscess. Also, a pelvic examination in women should also include an inspection to ensure that there is no retained tampon that may serve as a source for toxic shock syndrome.

The musculoskeletal history includes the presence of any localizing symptoms to a particular joint. Redness, swelling, and warmth over a joint, especially if there is a decreased range of motion in that joint, may be signs of septic arthritis and may mandate arthrocentesis. The skin should be examined for evidence of cellulitis, abscess, wound infection, or traumatic injury. Deep injuries, foreign bodies, and fasciitis may be difficult to identify clinically. The emergency clinician should look for crepitus, bullae, or skin edema extending beyond areas of erythema that may indicate the presence of an aggressive, gas-forming organism. Back pain and fever may be signs of an epidural abscess. Local lymphadenopathy, swelling, and streaking should also be noted as signs of an advancing infection. Petechiae and purpura may represent a *Neisseria meningitidis* infection or DIC. Generalized erythroderma and rash may represent an exotoxin from pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*.

A history of fevers or chills in the setting of injection drug abuse, artificial heart valve, or mitral valve prolapse should increase the suspicion for endocarditis. The emergency clinician should suspect endocarditis in the presence of a murmur or other stigmata of endocarditis (eg, splinter hemorrhages, Roth's spots, Janeway's lesions).

Emergency clinicians must identify the severity of illness in patients with infection and initiate early resuscitation for those with the potential of becoming critically ill. Although a patient may meet SIRS criteria, this alone has little predictive value in determining the severity of illness and mortality. There are many scoring systems that have been developed to risk-stratify illness severity. Most scoring systems are not clinically relevant and are not routinely used. The Mortality in Emergency Department Sepsis (MEDS) score is one proposed method to risk stratify ED patients with sepsis.[4] The MEDS prediction rule assigns point values to specific clinical characteristics (Table 130.1). The total score can be used to assess risk of death. Thus, the greater the number of risk factors, the more likely a patient is to die during hospitalization. Although typically not calculated for all patients, the elements of the score may be identified and considered as a red flag when risk-stratifying a patient.

TABLE 130.1

Mortality in Emergency Department Sepsis (MEDS) Prediction Rule

RISK FACTOR	ODDS RATIO FOR DEATH	MEDS SCORE (points)
Terminal illness (death within 30 days)	6.1	6
Tachypnea or hypoxia	2.7	3
Septic shock	2.7	3
Platelet count < 150,000/mm^3	2.5	3
Bands > 5%	2.3	3
Age > 65 yr	2.2	3
Pneumonia	1.9	2
Nursing home resident	1.9	2
Altered mental status	1.6	2
RISK OF DEATH	**TOTAL MEDS SCORE (% OF SEPSIS DEATHS)**	
Very low	0–4 (1.1%)	
Low	5–7 (4.4%)	
Moderate	8–12 (9.3%)	
High	13–15 (16.1%)	
Very high	>15 (39%)	

DIAGNOSTIC CONSIDERATIONS

Differential Diagnoses

The sepsis syndromes represent a spectrum of disease and clinical presentations. Often, noninfectious sources can cause a syndrome that mimics that of sepsis[5]; thus, one must keep in mind a broad differential diagnosis when approaching these patients (Box 130.2). A detailed history and physical examination are the first steps in narrowing the differential diagnosis to identify the true source.

Diagnostic Testing

Diagnostic studies are used to identify the type and location of the infecting organisms and define the extent and severity of the infection to assist in focusing therapy. As a result, the diagnostic approach should be tailored to the particular patient.

Laboratory Testing

Hematology. The white blood cell count can be an indicator of inflammation and activation of the inflammatory cascade. Leukocytosis is associated with infection and is incorporated in the consensus definition of sepsis; however, it is often insensitive and nonspecific, limiting its value in the ED. The febrile neutropenic patient has been shown to be at increased risk for severe infection. Thus, a neutrophil count of less than 500 cells/mm^3

BOX 130.2

Differential Considerations for Source of Sepsis

SEPSIS

Dehydration
Acute respiratory distress syndrome
Anemia
Ischemia
Hypoxia
Congestive heart failure
Vasculitis
Toxicologic
- Poisonings
- Overdose
- Drug-induced

Pancreatitis
Hypothalamic injury
Disseminated intravascular coagulation
Anaphylaxis
Metabolic
Hyperthyroidism
Diabetic ketoacidosis
Adrenal dysfunction
Environmental
- Burn
- Heat exhaustion or stroke

Trauma
- Blood loss
- Cardiac contusion

Neuroleptic malignant syndrome

SEPTIC SHOCK

Hypovolemic shock
Acute blood loss
Severe dehydration
Cardiogenic shock
Pulmonary embolus
Myocardial infarction
Pericardial tamponade
Tension pneumothorax
Vasogenic shock
Anaphylaxis
Paralysis

should prompt consideration for admission, isolation, and empirical intravenous (IV) antibiotics in most chemotherapy patients. A bandemia (≥5%–10% bands on a peripheral smear) represents the release of immature cells from the bone marrow and may be a sign of infection and inflammation. Like the white blood cell count, it is an imperfect indicator of infection. The absence of leukocytosis or bandemia does not preclude the possibility of severe sepsis nor does their presence confirm it. The hemoglobin and hematocrit levels should be determined to ensure adequate oxygen delivery in shock. Platelets are an acute-phase reactant and may be elevated in the presence of infection. Conversely, a low platelet count may be seen in patients with sepsis and septic shock. Thrombocytopenia, elevated prothrombin time, elevated activated partial thromboplastin time, decreased fibrinogen, and increased fibrin split products are associated with DIC and severe sepsis syndrome.

Blood Chemistry. Electrolyte abnormalities should be identified and corrected. A low bicarbonate level suggests acidosis and inadequate perfusion. An elevated anion gap acidosis in the setting of sepsis syndrome commonly represents lactic acidosis or diabetic ketoacidosis, but other causes need to be ruled out. An elevated serum creatinine concentration or decreased glomerular filtration rate signals renal dysfunction or failure, which, if due primarily to sepsis, indicates organ failure and a worse prognosis. Calcium, magnesium, and phosphorus levels should be checked.

An elevated lactate level is associated with inadequate perfusion, shock, and poorer prognosis. One study has shown a progression in mortality rate with increasing venous lactate level—a lactate level of 0 to 2.5 mg/dL was associated with a 5% mortality rate, a lactate level of 2.5 to 4.0 mg/dL, 9% mortality, and a lactate level greater than 4 mg/dL, 28% mortality. An arterial blood gas assessment may be helpful in identifying and classifying acid-base disturbances. Metabolic acidosis suggests inadequate tissue perfusion. Liver function tests can be used to identify liver failure or dysfunction. An elevated bilirubin level may suggest the gallbladder as a cause of sepsis. An elevated lipase level may represent pancreatitis as the cause of SIRS.

Microbiology. Proper blood, sputum, urine, cerebrospinal fluid, and other tissue culture samples are important in guiding therapy. Although the results of culture are not helpful in the initial management, culture samples should be obtained before or soon after the administration of antibiotics in the patient with sepsis syndrome. The initiation of antibiotic therapy should not be delayed significantly while waiting for culture samples to be obtained. Studies have suggested that the yield of initial blood cultures is low (5%–10%), but this is probably an artifact of the lack of reliable discriminatory guidelines for obtaining blood culture samples in the ED. Among patients with clinical sepsis, only 30% to 40% of patients will have positive cultures. The results of initial microbiologic tests, including Gram staining whenever possible, will help guide subsequent antibiotic treatment. Initial empirical therapy should be broad spectrum to allow early treatment of all likely organisms.

Special Procedures

We believe that a central venous pressure (CVP) line is helpful in guiding fluid resuscitation in sepsis patients. Although CVP measurements do not correlate well with volume responsiveness, a low CVP usually indicates the need for continued fluid repletion. The use of arterial lines and Swan-Ganz catheters can be helpful in managing sepsis, but they are rarely available in the ED setting. When available, arterial lines can be useful for close monitoring of hypotensive patients, especially when one or more vasopressors are being titrated to maintain an adequate blood pressure. Swan-Ganz catheters are rarely used in sepsis management in the ED, although the physiologic measurements may be useful in identifying the cause of shock and guiding fluid and inotropic therapy. Low systemic vascular resistance and high cardiac output are usually associated with sepsis, although this may vary with the stage of shock and individual patient. The science and technology of noninvasive or minimally invasive cardiac output monitoring has been evolving and, where available, may help guide fluid administration by evaluating cardiac output alone or in conjunction with a fluid challenge or passive leg raise approach.

Radiology

Imaging studies are generally used to identify the source of infection. A chest radiograph should be considered in patients with suspected sepsis syndrome, looking not only for a focal infiltrate representing pneumonia but also for the fluffy bilateral infiltrates indicative of ARDS. The pathophysiologic changes of ARDS are often delayed as much as 24 hours after radiographic identification. An upright chest radiograph should be considered for suspected bowel perforation to detect free air under the diaphragm.

The presence of pneumomediastinum is suggestive of esophageal perforation and current or impending mediastinitis.

Soft tissue plain radiographs of infected areas can be obtained, looking for air in the soft tissues associated with necrotizing or gas-forming infection, although plain x-rays are not sensitive for tissue infection. Periosteal thickening or bone erosion may be seen on plain radiographs of patients with osteomyelitis; a bone scan may be diagnostic. Computed tomography (CT) of superficial infections may be more helpful to quantify the extent of infection further and identify abscesses that are not readily evident on physical examination. A CT scan of the abdomen and pelvis may identify abdominal or pelvic pathologic lesions, provided there is no clear clinical indication for immediate operative intervention. Suspected disease, such as diverticulitis, appendicitis, necrotizing pancreatitis, microperforation of the stomach or bowel, or formation of an intra-abdominal abscess, may be best diagnosed by a CT scan. A head CT scan can identify septic emboli from endocarditis or increased intracranial pressure from a mass and should be considered before a lumbar puncture is performed. An abdominal ultrasound examination may be indicated for suspected cholecystitis, and a pelvic ultrasound examination may be indicated for tubo-ovarian abscess or endometritis. If endocarditis is suspected, a transesophageal cardiac ultrasound study may be performed for the detection of any valvular vegetations. Magnetic resonance imaging (MRI) can be useful to identify soft tissue infection, such as necrotizing fasciitis or epidural abscess.

MANAGEMENT

Early detection and appropriate treatment can reduce the mortality from sepsis. The primary goal is timely administration of appropriate antimicrobial therapy—or interventional source control as required—and maintenance of adequate tissue oxygenation and perfusion through titrated resuscitation. With early detection and early resuscitation there is increasing evidence that the natural history of sepsis can be altered. Initial resuscitation, including appropriate airway management, IV access, oxygen, early and appropriate antibiotics, fluid resuscitation, and vasopressor support, remains the foundation on which new efforts may be applied.

From a historical perspective, Rivers and associates have provided compelling evidence supporting the importance of this concept when they published a protocol of standardized timely and titrated care being used to guide resuscitation in the ED.[6] This randomized, double-blind, placebo-controlled study showed a 16% mortality reduction in patients with severe sepsis and septic shock. The protocol, termed *early goal-directed therapy* (EGDT), measures targeted goals and uses a resuscitation algorithm to guide the resuscitation. The theory behind the protocol was to normalize preload and pressure and prevent tissue hypoxia by matching oxygen delivery with consumption. Use of this protocol, which facilitated earlier and more aggressive fluid resuscitation through the use of increased fluids, increased blood products, increased use of dobutamine, and greater degree of normalization of tissue hypoxia, reduced mortality at their center. The interventions in combination were likely responsible for the better outcomes in the intervention group.

The principles of EGDT, as well as efforts such as the Surviving Sepsis Campaign, helped underscore the importance of early identification and timely resuscitation. However, until 2014, the evidence in support of the formal EGDT protocol was only in the form of the original single- center trial and subsequent observational efforts. More recently, the ProCESS, ProMISE, and ARISE studies have all been large multicenter trials that sought to validate the value of EGDT.[7-9] Each of the trials showed no mortality benefit to EGDT as compared to usual resuscitation measures; thus, although EGDT is one strategy to consider, it is not a superior approach from an evidence-based perspective. It is, however, important to underscore that the usual care groups in these newer trials were all identified early, received antibiotics, and received generous amounts of fluids (on average, ≈40–60 mL/kg in the first 6 hours across the trials), supporting the principle that early identification of sepsis, early antibiotics, and carefully titrated resuscitation should remain a core tenant.

Respiratory Support

Altered mental status is common in patients in septic shock, and they may require rapid airway protection. Because patients with impending respiratory failure use a disproportionately large amount of energy for the muscles of respiration, improved oxygen delivery to other organs is achieved by mechanical ventilation, sedation, and paralysis. Although there are no clear intubation guidelines, hypercapnia, persistent hypoxemia, airway compromise, and profound acidosis are valid indicators for intubation.

In addition to airway protection, intubation and mechanical ventilatory support provide positive-pressure ventilation. The pattern of injury in ARDS is such that normal lung parenchyma is adjacent to affected tissue. Therefore, increased airway pressures are required to maintain normal oxygen delivery. Current recommendations are to maintain transalveolar pressures (measured as plateau pressures) below 35 cm H_2O because increased pressures are associated with ventilator-induced lung injury. Maintenance of a relatively low transalveolar pressure with increasing end-expiratory pressure is an effective way to increase arterial oxygen delivery. The ARDSNet trial established the benefit of low tidal volumes (6 mL/kg) in mechanically ventilated patients with acute lung injury to prevent iatrogenic lung damage.

Cardiovascular Support

Fluid Resuscitation

Patients with sepsis often require IV fluid to maintain adequate perfusion. The primary reasons for this intravascular hypovolemia are venodilation and diffuse capillary leak. Initial therapy for adults with septic shock should generally be up to 2 L of isotonic crystalloid. As much as 6 to 10 L of crystalloid may be required in the first 24 hours. Fluid replacement should be titrated to clinical parameters such as heart rate, blood pressure, change in mental status, capillary refill, cool skin, and adequate urine output (0.5–1 mL/kg/hr). Normal saline (0.9%) and lactated Ringer's solution are equally effective and neither worsens lactic acidosis. Colloids are as effective as crystalloids, but they are more expensive and less readily available. Although one should be increasingly vigilant in watching for fluid overload in patients who are predisposed, such as older adults, those with congestive heart failure (CHF) and a known impaired EF, or those with renal impairment, these patients are not precluded from volume resuscitation, as described above. Efforts to identify ways to measure regional perfusion more directly, such as direct measurement of splanchnic blood flow, have been proposed. Even in the absence of global hypoxia and impaired tissue perfusion, there is evidence that regional hypoperfusion and ischemia exist.

Vasoactive Drug Therapy

If appropriate fluid resuscitation has failed, vasopressor support may be required (Table 130.2). Only in cases of profound hypotension should vasopressors be started before adequate fluid resuscitation has been initiated. Use of mean arterial pressure alone as an indicator of overall efficacy of therapeutic intervention is not always helpful. A mean arterial pressure of 65 mm Hg has been recommended in otherwise healthy, normovolemic adult

TABLE 130.2

Dosing of Vasoactive Therapy

DRUG	DOSAGE
Dobutamine	5–15 μg/kg/min
Dopamine	2–20 μg/kg/min
Epinephrine	5–20 μg/min
Norepinephrine	5–20 μg/min
Phenylephrine	2–20 μg/min

patients but must be correlated with other indicators of adequate perfusion, such as mental status and urine output. Patients with previously uncontrolled hypertension may require a mean arterial pressure of 75 mm Hg or even higher.

The 2012 Surviving Sepsis Campaign guidelines have provided consensus recommendations for treatment of septic shock.[10] Fluid resuscitation remains the fundamental treatment option and should be the initial treatment. Norepinephrine should be used as the initial vasopressor, with the addition of epinephrine or vasopressin to norepinephrine as a reasonable adjunct. Vasopressin alone has been shown to be ineffective compared with norepinephrine in the initial treatment of refractory septic shock. Dobutamine should be used as the primary inotropic agent if myocardial dysfunction is evident. After an initial stabilization period, vasopressors should be titrated down, as tolerated; however, the duration of this stabilization period is variable and may be hours to days.

Norepinephrine. Norepinephrine is a mixed α- and β-agonist with minimal β_2 activity and primarily functions to increase cardiac output and systemic vascular resistance. In a large study examining patients with shock from multiple causes, norepinephrine was shown to have fewer adverse events (particularly arrhythmias) compared with dopamine, which had a higher mortality rate in patients with cardiogenic shock.[11] In another meta-analysis, norepinephrine was shown to be superior to dopamine in both in-hospital and 28-day mortality.[12]

Compared with dopamine in septic patients, norepinephrine increases glomerular filtration and urine output equally well. It is an important component of the therapy for septic shock as a sole vasopressor or in conjunction with other vasopressors. Recommended doses are 8 to 12 μg/min.

Dopamine. Dopamine is also often used for septic shock unresponsive to adequate volume expansion. Dopamine is the immediate precursor of norepinephrine and epinephrine. It is primarily an α-, β_1-, and dopaminergic agonist. Although low doses alone are not effective, they may be effective in combination with other agents. So-called renal dose dopamine has not been shown to reduce mortality or decrease dialysis dependence and should not be used. Dosages higher than 20 μg/kg/min may produce significant vasoconstriction. Persistent tachycardia, decreased partial pressure of arterial oxygen, and increased pulmonary artery occlusion pressure are common side effects of dopamine use.

Phenylephrine. Phenylephrine is a selective α_1-agonist, increasing systemic vascular resistance without significant changes in cardiac output. It can produce a reflexive bradycardia or suppression in cardiac output. A single small study has shown that phenylephrine is effective in restoring perfusion in patients with septic shock refractory to dopamine or dobutamine. Another small study has demonstrated that phenylephrine is less effective than norepinephrine in the treatment of hypotension in septic patients; however, there was no difference in other measured hemodynamic parameters, including oxygen delivery. Phenylephrine does not impair cardiac and renal function and may be a good choice when significant tachyarrhythmia limits the use of other agents.

Epinephrine. Epinephrine is a potent mixed α- and β-agonist. Epinephrine infusion is also associated with increased oxygen consumption, increased systemic lactate concentrations, and decreased splanchnic blood flow. The rise in the lactate level is short term, and there is no evidence regarding its long-term effects. As a result of all the possible adverse effects of epinephrine, it is currently recommended only for those patients who are unresponsive to other vasopressors. Adverse effects may include peripheral vasospasm and a critical reduction in extremity perfusion, leading to gangrene.

Vasopressin. Vasopressin is a naturally occurring peptide that is synthesized as a large prohormone in the hypothalamus. In states of septic shock, there is an early surge of vasopressin followed by a profound drop in circulating vasopressin levels. This is the foundation for the use of vasopressin as an adjunct therapy for patients with severe sepsis. Vasopressin should not be used as the sole initial therapy for refractory septic shock. In a well-designed randomized trial, investigators demonstrated no change in mortality for patients with severe sepsis when vasopressin was added to catecholamine vasopressors.

Dobutamine. Dobutamine is a mixed α- and β-agonist. In dosage ranges from 2 to 28 μg/kg/min, the cardiac index is increased at the expense of heart rate. In addition, decreased splanchnic blood flow is common. Dobutamine should be used in patients with depressed cardiac index and persistent hypoperfusion in spite of adequate volume expansion and the use of other vasopressor agents. In patients undergoing formal, early, goal-directed therapy, when preload, perfusion pressure, and oxygen-carrying capacity have been normalized and a low $Scvo_2$ persists, dobutamine is used to increase cardiac output and oxygen delivery. One study has suggested that survival in sepsis is associated with the patient's increase in stroke volume in response to dobutamine.

Bicarbonate

Bicarbonate supplementation was previously the standard treatment for patients with presumed lactic acidosis. Current consensus is that it should be reserved for severe acidemia (pH < 7.0–7.2) because there may be a paradoxical decrease in intracellular pH as a result of diffusion of soluble carbon dioxide across the cell membrane. Alternatively, hyperventilation has been suggested to help increase systemic pH.

Antibiotics

Early antibiotic therapy should target the nidus of infection if known. If the patient's condition permits, appropriate culture specimens should be obtained before the administration of broad-spectrum antibiotics (Table 130.3). Surgically correctable conditions, such as intra-abdominal abscesses, perforated viscus, retained products of conception, or retained foreign body (eg, a tampon), should be treated concurrently. Antibiotics should be administered as soon as possible in patients with serious infections. Although some observational studies and national benchmarks have called for the administration of antibiotics within a predefined time period of 3 hours from ED presentation, a comprehensive meta-analysis failed to support an association between

TABLE 130.3

Suggested Initial Antibiotic Management[a]

INFECTION	MODIFYING FACTORS	ANTIBIOTIC
Sepsis, unknown source	Immunocompetent	Antipseudomonal cephalosporin *plus* aminoglycoside or fluoroquinolone, *or* antipseudomonal penicillin *plus* aminoglycoside or fluoroquinolone, *or* carbapenem *plus* aminoglycoside or fluoroquinolone
	Anaerobic infection	Add metronidazole or clindamycin to above regimen.
	Methicillin-resistant *Staphylococcus aureus* (MRSA)	Add vancomycin to above regimen.
	Neutropenia	Antipseudomonal penicillin *plus* aminoglycoside or fluoroquinolone, *or* carbapenem *plus* aminoglycoside or fluoroquinolone
	Splenectomy	Cefotaxime *or* ceftriaxone
	HIV infection	Ticarcillin-clavulanate *plus* tobramycin
Pneumonia	Immunocompetent	Second- or third-generation cephalosporin *plus* second-generation macrolide *or* fluoroquinolone
	Legionella suspected	Azithromycin, fluoroquinolone, or high-dose erythromycin
Abdominal infection	Immunocompetent	Ampicillin *plus* aminoglycoside *plus* metronidazole
	Multidrug-resistant organism suspected	Ticarcillin-clavulanate or carbapenem, *or* piperacillin-tazobactam *plus* aminoglycoside
	Urinary tract source	Fluoroquinolone, *or* third-generation cephalosporin, *or* ampicillin *plus* aminoglycoside
Cellulitis	Nonnecrotizing fasciitis	Cefazolin *or* nafcillin
	MRSA possible	Vancomycin
	Necrotizing fasciitis (surgical drainage)	Ampicillin-sulbactam, *or* ticarcillin-clavulanate, *or* piperacillin *plus* aminoglycoside *plus* clindamycin, *or* carbapenem
Intravenous catheter infection (remove catheter)	Outpatient-acquired	Third-generation cephalosporin
	MRSA suspected	Add vancomycin.
	Fungal infection	Amphotericin B
Cerebrospinal infection	Immunocompetent	Ceftriaxone *plus* vancomycin
	Older adult or immunocompromised patient	Add ampicillin.
Injection drug abuse	MRSA not suspected	Nafcillin *plus* aminoglycoside
	MRSA suspected	Vancomycin *plus* aminoglycoside

[a]Pending microbiologic identification of organism and sensitivity.

antibiotics administered after 3 hours and mortality.[13] Thus, early antibiotics are important, but their exact timing remains undefined.

In the absence of an obvious source of infection, the use of broad-spectrum antibiotics is recommended. The specific agent depends on many variables, including institutional preference and local resistance patterns. As results from cultures become available, therapy should be modified. There is no consensus about the need for double or triple antibiotic coverage for particular organisms, although it is common practice to double-cover virulent organisms, such as *Pseudomonas aeruginosa,* as well as areas commonly infected with multiple organisms, such as the peritoneum. With increasing rates of methicillin-resistant organisms, combinations that include nonpenicillin choices may be warranted.

Steroid Therapy

It has been nearly 40 years since the first treatment attempts to block inflammation in sepsis. Because sepsis involves a systemic inflammatory response, corticosteroids are a logical treatment modality as antiinflammatory agents. Physicians have been working for decades to prove or disprove their value. Steroids appear to be more effective in reducing the amount of time patients spend in a hypotensive state, but increase the rate of secondary infection, contributing to a null effect overall. At this time, we believe that the role of steroid therapy in sepsis remains controversial and recommend their use in patients on chronic steroid therapy when there is refractory cardiovascular insufficiency, despite maximal supportive therapy and replacement therapy.

DISPOSITION

Once ED management is complete, patients who are deemed at increased risk should be admitted to the hospital into a setting that is deemed appropriate for the severity of the patient's condition. For example, in patients who remain hypotensive, are on vasopressors, or who are unstable and require more frequent monitoring, the intensive care unit may be appropriate. Other patients who are more stable but still require monitoring and perhaps IV therapy may be admitted to a hospital ward. Finally, in certain cases, patients initially meeting sepsis criteria but who are not severely ill (eg, young patients with pharyngitis) may be appropriate for discharge.

KEY CONCEPTS

- Sepsis is a progression of disease due to a dysregulated inflammatory cascade, leading to organ dysfunction and circulatory compromise in severe cases.
- Sepsis is subtle and often difficult to detect, so the emergency clinician should maintain a high index of suspicion when assessing patients in the ED.
- Older adults, immunocompromised and neutropenic patients, and patients with multiple comorbidities are at increased risk for the development of sepsis syndromes.
- A thorough history and physical examination should guide the diagnostic evaluation.
- Early treatment should focus on appropriate identification, improvement of tissue perfusion (through administration of fluids and vasopressor medications), improvement of tissue oxygenation (through administration of oxygen and positive-pressure ventilation), administration of antibiotics, and early identification of infections requiring surgical management.
- Prompt administration of antibiotics is essential and should be based on the suspected source of infection.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 130: QUESTIONS & ANSWERS

130.1. Which of the following patients meets the criteria for systemic inflammatory response syndrome (SIRS)?
- **A.** 6-year-old boy with pneumonia, temperature 39.0° C (102.2° F)
- **B.** 21-year-old woman with abdominal pain, temperature 38.3° C (100.9° F)
- **C.** 53-year-old man with respirations, 30 breaths/min, white blood cell (WBC) count, 16,000 cells/mm^3
- **D.** 74-year-old woman with chest pain, heart rate 130 beats/min
- **E.** 81-year-old man with WBC count, 2700 cells/mm^3, heart rate, 73 beats/min

Answer: C. SIRS is defined as two or more of the following—tachycardia, tachypnea, temperature higher than 38° C (100.4° F) or lower than 35° C (95° F), high or low WBC count, or bandemia. Sepsis is SIRS with infection. Severe sepsis includes organ dysfunction. Septic shock involves systolic blood pressure below 90 mm Hg.

130.2. Sepsis is characterized by which of the following?
- **A.** Depression of arachidonic acid metabolites
- **B.** Depression of tumor necrosis factor levels
- **C.** Increased endogenous anticoagulant levels
- **D.** Prolonged suppression of nitric oxide levels
- **E.** Prolonged suppression of vasopressin levels

Answer: E. Clinical sepsis is induced by sustained levels of proinflammatory and procoagulant mediators. Cytokines (interleukin-1, interleukin-6, and tumor necrosis factor alpha) and prostaglandins are primary mediators. Nitric oxide synthase is upregulated, resulting in sustained elevations of the serum nitric oxide level, with subsequent vasodilations. Sustained suppression of vasopressin adds to this sometimes refractory vasodilated state.

130.3. Which of the following statements regarding septic shock is true?
- **A.** Cardiac output is always decreased.
- **B.** Much of the cardiac decompensation is reversible.
- **C.** Systemic vascular resistance is high.
- **D.** The ejection fraction is always increased.
- **E.** Ventricular dilation is unusual.

Answer: B. Sepsis affects myocardial function and peripheral vascular tone. The systemic vascular resistance is usually markedly depressed. Cardiac output is generally increased because of a compensatory tachycardia that can at least partially overcome the ventricular dilation and depressed ejection fraction. The myocardial effects are typically reversible.

130.4. What are the two most common sources of infection in cases of sepsis?
- **A.** Genitourinary > respiratory
- **B.** Musculoskeletal > genitourinary
- **C.** Respiratory > gastrointestinal
- **D.** Respiratory > genitourinary
- **E.** Skin > respiratory

Answer: C. Epidemiology studies show that pneumonia is the most common cause of sepsis, followed by an intra-abdominal source. However, a careful investigation to identify the source of infection should occur.

130.5. In most chemotherapy patients, which neutrophil count should prompt admission, isolation, and empirical antibiotics?
- **A.** <250 cells/mm^3
- **B.** <500 cells/mm^3
- **C.** <750 cells/mm^3
- **D.** <1000 cells/mm^3
- **E.** <2000 cells/mm^3

Answer: B. Patients with an ANC <500 cells/mm^3 are at increased risk of infection; thus, a conservative approach should be taken in these patients.

130.6. Among patients with clinical septic shock, which percentage will have positive blood cultures?
- **A.** 0%–30%
- **B.** 30%–60%
- **C.** 60%–90%
- **D.** 90%–100%
- **E.** Varies according to patient comorbidities

Answer: B. While blood cultures are perhaps a gold standard for identification and isolation of bacteria, they may negative, even when the etiology of illness is clearly infectious. Empiric antibiotic treatment in the ED remains a standard approach.

130.7. A 65-year-old man presents with blood pressure of 88/40 mm Hg, heart rate of 105 beats/min, respiratory rate of 24 breaths/min, O_2 saturation of 92%, and temperature of 38.5° C (101.3° F). Fluid resuscitation, oxygen, and empirical antibiotics are begun. Blood pressure after 2 L of saline is 98/50 mm Hg. A central venous catheter is placed, with a central venous pressure of 11 mm Hg. A venous blood gas sample drawn from this catheter shows hematocrit of 24%, Po_2 of 34 mm Hg, Pco_2 of 46 mm Hg, pH of 7.29, and O_2 saturation of

63%. O_2 saturation by pulse oximeter is now 96%. What is the most appropriate next step according to the early goal-directed therapy protocol?

A. Dopamine, 10 μg/kg/min
B. Endotracheal intubation
C. Packed red blood cell transfusion
D. Phenylephrine, 50 μg/min
E. Saline 0.9%, 2 L more

Answer: C. For the optimal management of sepsis, central venous pressure monitoring (ideally with oximetric capabilities) and mixed venous blood gas monitoring are indicated. This patient meets criteria for septic shock. Intermittent central venous (eg, mixed) blood gas analysis is likely to be adequate. Therapeutic targets are a central venous pressure of 8 to 12 mm Hg in the nonintubated patient and a mixed venous O_2 saturation of 70% (review of the oxyhemoglobin desaturation curve reminds us that 75% is normal). After volume resuscitation, this patient still had a low mixed venous saturation, indicating inadequate peripheral oxygen delivery and increased extraction by the tissues. With O_2 saturation nearly normal (96%), the only way to increase oxygen delivery is by red blood cell transfusion to increase the plasma hemoglobin concentration.

CHAPTER 131

Frostbite and Nonfreezing Cold Injuries

Ken Zafren | Daniel F. Danzl

FROSTBITE

Principles

Background

Unlike other mammals that live outside the tropics, humans are susceptible to local cold injuries. Local cold injuries may occur in conjunction with systemic hypothermia. Frostbite involves tissue freezing with formation of ice crystals in the tissues. Immersion injury (trench foot) is a nonfreezing injury that results from exposure to wet cold. Pernio (chilblains) is a nonfreezing injury that occurs in susceptible individuals, usually after exposure to dry cold.

Historically, frostbite has been a disease of wars. Frostbite caused over 1 million casualties in World Wars I and II and the Korean War. Trench foot was common in the world wars and during the conflict in the Falkland Islands. Frostbite and immersion injuries are risks for anyone who ventures outdoors in severely cold conditions for recreation or work. Homeless or displaced people are also at risk, especially during disasters.

Physiology

The human body attempts to maintain a core temperature of about 37°C (98.6°F). Skin cooling activates the anterior hypothalamus, causing catecholamine release, thyroid stimulation, shivering thermogenesis, and peripheral vasoconstriction. People are physiologically adapted to tropical conditions. In cold conditions, humans have a limited ability to protect themselves against decreased core temperature. Behavioral responses are far more effective if adequate clothing or shelter is available.

Cutaneous circulation is one of the keys to maintenance of a constant core temperature. Baseline cutaneous circulation greatly exceeds nutritional requirements. In warm conditions, the skin acts as a radiator to shed excess heat. Cold-induced vasoconstriction can reduce flow to 10% of baseline without damage to the skin.

During cold stress, peripheral vasoconstriction limits radiant heat loss. Acral skin structures (eg, fingers, toes, ears, nose) contain a plethora of arteriovenous anastomoses. These anastomoses shut down in the cold, causing drastic reductions in blood flow. This so-called life-versus-limb mechanism is a means of preventing systemic hypothermia.

Cooling of digits to 15°C (59°F) results in maximal peripheral vasoconstriction, with minimal blood flow. Continued cooling to 10°C (50°F) produces cold-induced vasodilation (the so-called hunting response), a counterbalance to cold-induced vasoconstriction. Vasodilation follows 5- to 10-minute cycles, interrupting vasoconstriction and protecting the extremity. Eskimos, Lapps, and other northern peoples have stronger cold-induced vasodilation than individuals from tropical regions. There is evidence of adaptation in addition to genetic control.

Pathophysiology

Frostbite occurs only when the tissue supercools well below 0°C (32°F). The required temperature is at least −4°C (24.8°F) and may be as low as −10°C (14°F) under some conditions. Tissue injury occurs due to structural damage to cells from ice crystal formation and to microvascular thrombosis and stasis. In the prefreeze phase, tissue temperatures drop below 10°C (50°F), and cutaneous sensation is lost. Before ice crystals form, microvascular vasoconstriction can occur, with endothelial leakage of plasma into the interstitium. In the freeze-thaw phase, the timing, location, and rate of ice crystal formation depend on conditions. Wind and moisture increase the freezing rate. The phases vary with the extent and rapidity of the cold response and may overlap (Box 131.1).

Except in extremely cold conditions, ice crystal formation initially occurs extracellularly. Water then exits the cell to maintain osmotic equilibrium. Cellular dehydration increases the intracellular osmolarity and electrolyte concentrations. After approximately one-third of the cellular volume is lost, the cell collapses and dies, even if there is no direct structural damage from ice crystals. Extracellular crystallization increases the tissue pressure on cell membranes and vascular structures. Sludging, stasis, and cessation of flow occur at the capillary level.

A third phase, progressive microvascular collapse, first affects venules and then arterioles. Red blood cells sludge and form microthrombi during the first few hours after the tissues are thawed. Factors that decrease flow include hypoxic vasospasm, hyperviscosity, and direct endothelial cell damage. Ischemic conditions extend the surrounding injury. Plasma leakage and arteriovenous shunting result in thrombosis, increased tissue pressure, ischemia, and necrosis.

Progressive dermal ischemia is partially mediated by thromboxane. Prostaglandins are found in clear vesicles. When subdermal vascular plexi are injured, hemorrhagic blisters develop, which also contain prostaglandins. Arachidonic acid breakdown products released from underlying damaged tissue into blister fluid include prostaglandins and thromboxane. These mediators produce platelet aggregation, vasoconstriction, and leukocyte immobilization.

Injury to the microvasculature is the ultimate determinant of progressive tissue damage. Endothelial cells are very susceptible to freezing injury. After thawing, the vasculature may be temporarily patent. Platelet and erythrocyte aggregates promptly clog and

BOX 131.1

Freezing Injury Cascade

PREFREEZE PHASE
Superficial tissue cooling
Increased viscosity of vascular contents
Microvascular constriction
Endothelial plasma leakage

FREEZE-THAW PHASE
Extracellular fluid ice crystal formation[a]
Water movement across cell membrane
Intracellular dehydration and hyperosmolality
Cell membrane denaturation or disruption
Cell shrinkage and collapse

VASCULAR STASIS AND PROGRESSIVE ISCHEMIA
Vasospasticity and stasis coagulation
Arteriovenous shunting
Vascular endothelial cell damage and prostanoid release
Interstitial leakage and tissue hypertension
Necrosis, demarcation, mummification, or slough

[a]Extremely rapid cooling produces more initial intracellular than extracellular ice crystallization.

distort the vasculature. Intense vasoconstriction and arteriovenous shunting occur at the interface between normal and damaged tissue. Injured viable vasculature remains distorted. Local arteritis, medial degeneration, and intimal proliferative thickening occur. Nerve and muscle tissues are more susceptible than connective tissue to cold injury. Nonviable hands and feet can be moved after thawing if the tendons are intact.

Edema progresses for 48 to 72 hours after tissue is thawed. Necrosis becomes apparent as edema resolves. The dry gangrene carapace of frostbite is superficial in comparison to arteriosclerosis-induced, full-thickness gangrene. Although the historical surgical aphorism was "frostbite in January, amputate in July," advances in imaging modalities can accelerate the identification of the demarcation between viable and nonviable tissue.

Predisposing Factors

The extent of peripheral cold injury is determined by the type and duration of cold contact with the skin (Box 131.2). Risk factors include physiologic, mechanical, psychological, environmental, and cardiovascular factors.

Any condition affecting judgment can jeopardize the physiologically tropical human. Cold injuries are often due to psychiatric impairment or intoxication, primarily ethanol intoxication. Ethanol also produces peripheral vasodilation, which increases heat loss. Blunting of self-protective instincts can cause people to put themselves at increased risk by their not wearing appropriate clothing or finding shelter in cold conditions.

Although air is a poor thermal conductor, the combination of cold and wind (wind chill index) markedly increases heat loss. Direct skin contact with good thermal conductors such as metal, water, and volatile liquids increases the rate and extent of tissue destruction. Commercial aerosol spray propellants, such as propane and butane, and carbon dioxide in fire extinguishers are potentially hazardous. Liquid oxygen and Freon can also cause frostbite. Overenthusiastic application of ice or frozen gel packs for soft tissue injuries can cause frostbite, with tissue loss. Contact with vapor coolant sprays such as chloroethane or dry ice can also cause frostbite.

BOX 131.2

Predisposing Factors

PHYSIOLOGIC
Genetic
Core temperature
Previous cold injury
Acclimatization
Dehydration
Overexertion
Trauma—multisystem, extremity
Dermatologic disease
Physical conditioning
Diaphoresis, hyperhidrosis
Hypoxia

MECHANICAL
Constricting or wet clothing
Tight boots
Vapor barrier, Aveolite liners
Inadequate insulation
Immobility or cramped positioning

PSYCHOLOGICAL
Mental status
Fear, panic
Attitude
Peer pressure
Fatigue
Intense concentration on tasks
Hunger, malnutrition
Intoxicants

ENVIRONMENTAL
Ambient temperature
Humidity
Duration of exposure
Wind chill factor
Altitude and associated conditions
Quantity of exposed surface area
Heat loss—conductive, evaporative
Aerosol propellants
Cardiovascular
Hypotension
Atherosclerosis
Arteritis
Raynaud's syndrome
Cold-induced vasodilation
Anemia
Sickle cell disease
Diabetes
Vasoconstrictors, vasodilators

Clinical Features

The term *frostnip* refers to a superficial freezing injury manifested by transient numbness and tingling that resolves after rewarming. No tissue destruction occurs. The most common presenting symptom of frostbite is numbness, which is nearly universal. All patients have initial sensory deficits in light touch, pain, or temperature. Anesthesia is produced by intense vasoconstrictive ischemia and neurapraxia, usually in acral areas and distal extremities. Fingers, toes, nose, ears, and penis are the specific areas at risk. Patients often complain of clumsiness and report a so-called block of wood sensation in the extremity. Complete anesthesia in a cold digit suggests a severe injury.

Fig. 131.1. Frostbite that is still frozen. The victim is thawing the foot using a car heater. This technique is not advisable due to a high likelihood of causing further damage. (Courtesy Dr. Nicholas Kanaan.)

Fig. 131.3. Early appearance of severe frostbite of the hand after thawing. A purple color and absence of blisters are very unfavorable prognostic signs. (Courtesy Dr. Ken Zafren.)

Fig. 131.2. Severe frostbite of the toes immediately after thawing. The injury appears deceptively benign. (Courtesy Dr. Ken Zafren.)

Fig. 131.4. Early appearance of severe frostbite of the foot. A purple color and absence of blisters are very unfavorable prognostic signs. (Courtesy Dr. Ken Zafren.)

Initial presentation of frostbite is often deceptively benign. Most patients do not arrive in the emergency department (ED) with frozen insensate tissue. Frozen tissues feel hard and appear mottled or violaceous white, waxy, or pale yellow (Fig. 131.1). In severe cases, it is not possible to roll the dermis over bony prominences. Rapid rewarming results in an initial hyperemia, even in severe cases (Fig. 131.2). After thawing, there is usually partial return of sensation until blebs form.

Favorable initial symptoms after rewarming include normal sensation, warmth, and color. Soft pliable subcutaneous tissue suggests a superficial injury. A residual violaceous hue after rewarming is ominous (Figs. 131.3 and 131.4). Early formation of large blebs with clear fluid that extend to the tips of the digits (Fig. 131.5) is more favorable than a delayed appearance of smaller, more proximal hemorrhagic vesicles that are produced by damage to subdermal vascular plexi (Fig. 131.6). Bullae and vesicles usually form in 1 to 24 hours.

Lack of edema formation suggests significant tissue damage. Postthaw edema usually develops within 3 hours. In severe cases, frostbitten skin forms a black dry eschar that mummifies, with apparent demarcation (Figs. 131.7 and 131.8).

Fig. 131.5. Frostbite with clear vesiculations. (Courtesy Dr. Bill Mills.)

Fig. 131.6. Severe frostbite with early hemorrhagic vesicles. (Courtesy Dr. Bill Mills.)

Fig. 131.7. Severe frostbite of the hand. Dry gangrene is clearly demarcated. There was significant tissue loss. (Courtesy Dr. Ken Zafren.)

Fig. 131.8. Severe frostbite of the foot. Dry gangrene is clearly demarcated. There was significant tissue loss. (Courtesy Dr. Ken Zafren.)

Historically, frostbite, like burns, was classified into degrees of injury. Anesthesia and erythema were considered to be first-degree frostbite. Superficial vesiculation surrounded by edema and erythema indicated second-degree frostbite. Third-degree frostbite produced deeper hemorrhagic vesicles. Fourth-degree injuries extended into subcutaneous, tissues, including bones and muscles.

Classification by degrees does not correlate well with the amount of tissue damage and is therapeutically misleading. A simpler, more useful classification divides frostbite into superficial or mild frostbite, which does not result in loss of tissue, and deep or severe frostbite, which causes loss of tissue. It is difficult to predict the amount of tissue loss at the time of initial presentation.

Significant pain usually accompanies reestablishment of perfusion. A dull continuous ache evolves into a throbbing sensation in 48 to 72 hours. This may persist until tissue demarcation occurs weeks to months later. Short-term and long-term sequelae are common (Box 131.3).

Differential Diagnosis

The differential diagnosis of frostbite is limited. Burns, cellulitis, gangrene (from other causes), vascular injuries, diabetic neuropathies, and pressure necrosis can resemble frostbite, but can usually be distinguished based on history. Severe, nonfreezing, cold injuries can also mimic frostbite. After thawing, before edema develops, frostbitten areas may appear deceptively normal for a few hours.

Diagnostic Testing

Except in patients being considered for thrombolytic therapy, diagnostic imaging has a limited role in the emergency care of patients with frostbite. Ancillary diagnostic imaging techniques can be used to help grade the severity of injury, but no technique consistently predicts tissue loss at the time of initial examination.

Patients with frostbite should undergo laboratory testing and imaging, as indicated for coexisting conditions and injuries. We recommend obtaining baseline plain radiographs of frostbitten tissue. Follow-up radiographs may begin to demonstrate specific frostbite abnormalities 4 to 10 weeks after injury.

Patients being considered for thrombolytic therapy should undergo computed tomography (CT) or magnetic resonance (MR) angiography for intraarterial therapy or radionuclide scanning for intravenous (IV) therapy. Otherwise, angiography or scintigraphy should be delayed.

Magnetic resonance imaging (MRI) of developing hyaline cartilage can demonstrate physeal injury, which has the largest impact on longitudinal growth. Bone scanning may also help predict prognosis early in the hospital course.

Management

Prehospital

Napoleon's Surgeon General, Baron Larrey, first recorded the disastrous effects of the freeze-thaw-refreeze cycle. During the 1812 to 1813 Russian campaign, soldiers would thaw frozen extremities directly over open fires, only to have them refreeze, with resultant tissue destruction. Unfortunately, gangrene was misattributed to rapid thawing. Gradual thawing, often including friction massage with snow, became the standard treatment regimen until the 1950s. In 1961, William Mills, Jr., popularized rapid thawing in warm water after extensive research with severe Alaskan frostbite cases.

Field rewarming of frozen tissue is rarely practical. If possible, constricting or wet clothing should be removed and affected areas

BOX 131.3

Sequelae of Frostbite and Nonfreezing Cold Injuries

NEUROPATHIC
Pain
- Phantom pain
- Complex regional pain syndrome
- Chronic pain

Sensation
- Hypesthesia
- Dysesthesia
- Paresthesia
- Anesthesia

Thermal sensitivity
- Heat
- Cold

Autonomic dysfunction
- Hyperhidrosis
- Raynaud's syndrome

MUSCULOSKELETAL
Atrophy
Compartment syndrome
Rhabdomyolysis
Tenosynovitis
Stricture
Epiphyseal fusion
Osteoarthritis
Osteolytic lesions
Subchondral cysts
Necrosis
Amputation

DERMATOLOGIC
Edema
Lymphedema
Chronic or recurrent ulcers
Epidermoid or squamous cell carcinoma
Hair or nail deformities

MISCELLANEOUS
Core temperature afterdrop
Acute tubular necrosis
Electrolyte fluxes
Psychological stress
Gangrene
Sepsis

BOX 131.4

Emergency Department Rewarming Protocol

PRETHAW
Assess Doppler pulses and appearance.
- Protect part—no friction massage.
- Stabilize core temperature.
- Address medical and surgical conditions.
- Administer volume replacement as indicated.

THAW
Provide parenteral opiate analgesia as needed.
- Administer ibuprofen 400–600 mg (or aspirin, 325 mg).
- Immerse part in circulating water at 37° C–39° C (98.6° F–102.2° F), monitored by thermometer.
- Encourage gentle motion, but do not massage.

POSTTHAW
Dry and elevate.
- Aspirate or débride clear vesicles.
- Débride broken vesicles and apply topical antibiotic or sterile aloe vera ointment every 6 hours.
- Leave hemorrhagic vesicles intact.
- Administer tetanus prophylaxis if indicated.
- Provide streptococcal prophylaxis if high risk.
- Consider phenoxybenzamine in severe cases.
- Perform imaging, including angiography, if thrombolysis may be indicated.
- Carry out thrombolysis, if indicated and available.
- Obtain admission photographs.

insulated and immobilized. Massage is not efficacious and increases tissue loss. Frozen parts should be kept away from dry heat sources, such as heated forced air during transport.

In general, the longer tissue has been frozen, the greater the extent of cellular damage. However, rewarming should not be initiated in the field if there is any possibility that thawing will be interrupted or incomplete or that tissue will refreeze during evacuation. Tissue refreezing is disastrous. It is better to walk to safety on frozen feet if rescue will be delayed. When evacuation is not possible, rapid field rewarming, preferably in water at 37° C to 39° C (98.6° F–102.2° F), may be the only option.

Emergency Department

Prethaw. Stabilize hypothermia and other life-threatening conditions before warming frostbitten extremities.[1,2] Treatment should not be delayed while waiting for the results of laboratory and radiographic studies. Most patients are volume-depleted, partly due to poor oral intake and hypothermia-induced cold diuresis, and should receive volume replacement with crystalloid at 40° C (104° F) to decrease blood viscosity and sludging.

Thaw. Frozen or partially thawed tissue should be rapidly rewarmed by immersion in gently circulating water that is carefully maintained at a temperature of 37° C to 39° C (98.6° F–102.2° F).[1,2] A whirlpool is ideal, but a large container can be used for the hands or feet. Do not let frostbitten areas bump or rub against the side of the container. Water warmer than 39° C (102.2° F) does not warm significantly faster, but causes more pain.[1] Tissue can suffer thermal injury when the water temperature exceeds 42° C (107.6° F). Rewarming should be continued until distal erythema is noted. The part should feel pliable, which usually requires 10 to 30 minutes of submersion. Encourage active gentle motion during rewarming, but do not massage the tissue. Premature termination of rewarming results in a partial thaw, with increased tissue damage.

Parenteral analgesia is often indicated during rewarming. Reperfusion may be intensely painful, with throbbing, burning pain and tenderness. Sensation is usually diminished after thawing until it disappears with bleb formation.

Patients with completely frozen extremities are usually hypothermic and at risk for significant fluid and electrolyte fluxes during rewarming. The acute thawing of large amounts of distal musculature extinguishes peripheral vasoconstriction, resulting in a sudden return of cold, hyperkalemic, acidotic blood to the central circulation. This can produce what is termed *core temperature afterdrop*, with ventricular fibrillation. In the most severe cases, extracorporeal rewarming should be considered (Box 131.4).

Postthaw. We keep injured extremities elevated to minimize edema formation, apply sterile dressings loosely, and handle frostbitten areas gently. Due to cold-induced anesthesia, soft tissue injuries are often not appreciated by the patient or emergency clinician. Persistent cyanosis in the extremities after a complete thaw may reflect increased compartment pressure. Tissue should be monitored carefully, but decompression fasciotomies are usually not necessary during initial treatment.

Although there is no definitive supporting evidence, we recommend the use of topical aloe vera with oral aspirin or ibuprofen. Topical aloe vera every 6 hours inhibits thromboxane when applied directly to frostbitten areas. It has not been shown to improve tissue salvage. Aspirin and ibuprofen inhibit the arachidonic acid cascade, although there is no evidence of efficacy for either agent. Some authors prefer ibuprofen because it also produces fibrinolysis.[2] However, aspirin is used widely, especially in Europe.[3]

Large clear blisters can be left intact, débrided or aspirated. We débride broken or intact nonhemorrhagic blisters. Hemorrhagic blisters should be aspirated rather than débrided. When hemorrhagic blisters are débrided, secondary desiccation of deep dermal layers appears to extend the injury.

Although there has been no demonstrated benefit of penicillin for streptococcal prophylaxis, it is used routinely in some centers. We recommend against using prophylactic antibiotics for frostbite unless there is associated gross contamination. Tetanus can occur after frostbite. Tetanus prophylaxis should follow usual wound care guidelines.

Thrombolytic therapy has been used to treat microvascular thrombosis in frostbite. In one retrospective study, IV tissue plasminogen activator (tPA) and heparin reduced predicted digit amputations in severe frostbite.[4] In another study, intraarterial tPA decreased the incidence of amputations when it was administered within 24 hours of thawing.[5]

Selection and treatment guidelines have been proposed for thrombolysis.[2] Thrombolysis should be reserved for patients with severe injuries likely to produce significant tissue loss, such as frostbite that extends to the proximal phalanges. If there are no contraindications to thrombolysis, and frostbite can be treated within 24 hours of thawing, angiography is performed with intraarterial vasodilators. If flow is not reestablished, continuously infuse intraarterial, catheter-directed tPA to a maximum dose of 1 mg/hr. Administer heparin concurrently and continue for 72 to 96 hours. Intraarterial thrombolysis should only be performed in centers that have intensive care capabilities and are familiar with the technique. An alternative approach combines systemic IV thrombolytic therapy with subsequent vascular evaluation by technetium scanning. One suggested prognostic strategy uses appearance after rapid rewarming, coupled with early bone scanning, to predict eventual tissue loss.

There are many unproven therapies for frostbite, including low-molecular-weight dextran, vasodilator therapy, and phenoxybenzamine. Hyperbaric oxygen may accelerate demarcation, but has not been shown to increase tissue salvage in severe frostbite.

Iloprost, a prostacyclin analogue, has vasodilatory properties that mimic a chemical sympathectomy. The risk of amputation was significantly lower in a controlled trial of patients with severe frostbite who received IV iloprost plus aspirin after thawing.[3] Selected patients in this series with severe frostbite were also treated with recombinant tPA.

Chemical or surgical sympathectomy does not decrease tissue loss. Surgical sympathectomy produces a smoother initial clinical course but no long-term benefits, with the possible exception of decreased long-term pain. Forearm nerve blocks produce a chemical sympathectomy that increases finger skin temperature. Although prehospital wrist blocks may achieve rapid pain control with rewarming, there have been no systematic studies of outcomes.

Disposition

Patients with superficial frostbite can be safely discharged to a warm place unless there is another indication for admission. Social services can be consulted if the patient is homeless. All other patients with frostbite should be admitted for further evaluation and treatment. Transfer or further consultation is indicated when the admitting service lacks experience in the care of frostbite. Patients who potentially meet the criteria for intraarterial thrombolysis should be transferred to a suitable facility if thrombolysis can be initiated after transfer within 24 hours of thawing.

NONFREEZING COLD INJURIES

Principles

Nonfreezing cold injury occurs when tissue fluids have not frozen. The most common nonfreezing cold injury is immersion injury, often referred to as trench foot, although the hands may also be affected. This is a significant threat during recreational activities and military expeditions in cold wet climates. Trench foot is produced by prolonged exposure to wet cold at temperatures above freezing. It usually develops slowly over several days and results in neurovascular damage. Immersion injury commonly develops while a person is wearing socks that are wet from immersion in water.

Immersion injury can also occur from sweat, especially with the use of neoprene socks, vapor barrier boots, or constrictive gaiters. People who soak their feet for hours in cool water for pain relief are also at risk. Bullae and tissue loss in immersion injury may be due to pressure necrosis rather than to cold injury. Most patients with severe immersion injury are military personnel who have worn boots continuously for days or weeks. Prevention of immersion injury may require frequent drying of feet and socks.

Pernio (chilblains) is a mild form of cold injury that often follows repetitive exposure in susceptible individuals. Chilblains can also occur with little or no exposure to cold in individuals who have underlying diseases.

Clinical Features

Immersion Injury

Immersion injury is classically described in four stages.[6] In the first stage (during cold exposure), numbness is the most common symptom. The extremities may appear bright red, but soon become pale or white due to extreme vasoconstriction (Fig. 131.9). There is no pain or swelling at this stage.

In the second stage (following cold exposure) after removal from a cold environment and during rewarming, peripheral blood flow slowly returns, and the extremities become a mottled pale blue. This change may be subtle in highly pigmented skin. The extremities remain cold and numb, although pain and edema can result from active rewarming. This stage usually lasts for a few hours, but occasionally persists for several days.

In the third stage (hyperemia), blood flow increases markedly. The extremity suddenly becomes hot and red, with bounding pulses, while the microcirculation is sluggish, as evidenced by prolonged capillary refill. Dependent redness (rubor) and pallor on elevation may occur due to vasomotor paralysis. At the same time, numbness gives way to severe pain with hyperalgesia, even to light touch. Edema often develops. In severe cases, bullae, like those seen in frostbite, can form. In rare cases with tissue loss,

Fig. 131.9. Nonfreezing cold injury (trench foot, immersion foot) in a homeless man in the emergency department, shortly after removal of wet socks and shoes. (Courtesy Dr. Ken Zafren.)

Fig. 131.10. Pernio in a woman who was working in an unheated high-altitude clinic. (Courtesy Alice Murray.)

necrosis becomes evident. The third stage may last weeks to months.

In the fourth stage (following hyperemia), the limb generally appears normal except in cases with tissue loss, but pain may persist. Tissue that was necrotic in the third stage becomes gangrenous and is lost. This stage can last from weeks to years or be permanent. Most cases of immersion injury present to the ED during the first or second stage, but pain that is often resistant to usual pain medications may be a presenting complaint during later stages.

Short- and long-term sequelae of cold immersion injury are similar to those of frostbite, although only the most severe immersion injuries result in tissue loss (see Box 131.3).

Pernio

Chilblains, or cold sores, appear within 24 hours after exposure and most often affect the face, dorsa of the hands and feet, and pretibial areas (Fig. 131.10). Young women with Raynaud's phenomenon, systemic lupus erythematosus (SLE), or antiphospholipid antibodies are at increased risk. Persistent vasospasm and vasculitis result in burning, pruritus, erythema, and mild edema. Plaques, blue nodules, and ulcerations can develop. These painful lesions often last 1 to 2 weeks.

Differential Diagnosis

Frostbite can mimic nonfreezing cold injury, but can usually be diagnosed by history. Frostbite and nonfreezing cold injuries can also occur together. Warm immersion injuries, including jungle foot (paddy foot) or tropical immersion foot, may appear similar to immersion injuries due to wet cold, but resolve with drying and elevation within a few days.

Pernio has a wide differential diagnosis. The diagnosis is usually clear when pernio is associated with recent cold exposure. Cases of suspected pernio with uncertain cause mandate a search for underlying conditions, such as SLE.

Diagnostic Testing

Infrared thermography in response to cold stress may support the diagnosis of immersion injury and help assess severity.[7] Diagnostic testing in patients with pernio is directed toward finding an underlying condition.

Management

Immersion Injury

Hypothermia, if present, should be treated before treating nonfreezing cold injuries. Volume replacement with warm IV fluids should be given if the patient is clinically volume-depleted. Immersion injuries should be allowed to rewarm slowly. Rapid rewarming or rubbing may worsen the injury. No medications are known to be helpful. Local cooling lowers metabolic requirements and improves pain and edema.[4] Cooling should be continued until hyperemia resolves.

Pernio

There is no standard treatment for pernio. We recommend drying the skin if it is damp and gentle massage if the patient can tolerate it. Avoid warming the skin above 30°C (86°F). Pernio is very painful and may require opioid analgesia. Nifedipine (20–60 mg daily) is the only medication that has been shown to be potentially effective in the treatment of severe pernio.

Disposition

Many patients with significant immersion injury require admission for pain control, as well as assistance with activities of daily living. Patients with mild immersion injuries can be discharged if there are no other indications for admission and the patient can be released to a warm environment. Patients with pernio are usually managed as outpatients.

KEY CONCEPTS

Frostbite

- Premature termination of thawing in 37° C to 39° C (98.6° F–102.2° F) water is a common error. Reperfusion of completely frozen tissue may be painful and may require parenteral analgesia.
- The early formation of clear blebs is more favorable than delayed formation of hemorrhagic blebs, which reflect damage to the subdermal vascular plexi.
- The patient should be advised that accurate prediction of eventual tissue loss is not always possible at presentation, despite imaging.
- Thrombolytic agents may restore some flow to severely frostbitten limbs if administered within 24 hours of thawing.

Nonfreezing Cold Injuries

- Immersion injuries should be rewarmed slowly and not above 30° C (86° F).
- Cooling of nonfreezing cold injuries may be helpful to relieve pain and edema.
- Pernio can be treated by drying and gentle massage. The skin should not be warmed above 30° C (86° F).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 131: QUESTIONS & ANSWERS

131.1. What is the most common presenting symptom of frostbite?
- **A.** Blisters
- **B.** Discoloration
- **C.** Numbness
- **D.** Pain
- **E.** Skin sloughing

Answer: C. Numbness is the presenting symptom in more than 75% of cases. Even when numbness is not the presenting symptom, it is still present in all cases of frostbite. Pain often does not develop until rewarming and the reestablishment of perfusion. Discoloration, blister formation, and skin sloughing can all occur but are often delayed by hours to days or weeks.

131.2. A 27-year-old man presents complaining of numb feet and hands. Several hours ago, he returned from an overnight hike in some nearby mountains. He reports that the temperature was consistently below −10° C (14° F). After immediate rewarming, you reexamine his hands and feet. Which of the following, if present, would portend the worst prognosis?
- **A.** Bounding pulses
- **B.** Edema
- **C.** Large clear vesicles
- **D.** Pale color
- **E.** Violaceous hue

Answer: E. After rewarming, extremities may still remain slightly pale or become slightly erythematous, both of which are normal. A violaceous hue indicates more severe damage. Edema is actually an expected and favorable finding. Lack of edema again indicates severe damage and lack of circulation. Large clear vesicles are also expected and are not poor prognostic indicators. However, the formation of small hemorrhagic vesicles is a poor prognostic sign. These vesicles usually form somewhat later in the course. Pulselessness would be a poor sign, but return of pulses or even bounding pulses should be expected.

131.3. At initial presentation of a frostbite injury, which imaging modality is indicated?
- **A.** Computed tomographic angiography
- **B.** Doppler ultrasonography
- **C.** Magnetic resonance angiography (MRA)
- **D.** Plain film radiography
- **E.** Scintigraphy

Answer: D. Multiple studies, including the other four listed, have been tested to predict the extent of tissue loss accurately, but none have been consistently successful. Plain film radiography is indicated to evaluate for other injury. Because frostbite results in near-total anesthesia of the extremity, accompanying skeletal injury can go undiagnosed. Subsequently, MRA may help predict the line of demarcation for tissue loss. The patient should be advised that, in severe cases, accurate prediction of eventual tissue loss is not possible at presentation.

131.4. What is the best method to rewarm a frostbitten extremity?
- **A.** Manual friction
- **B.** Room temperature air convection
- **C.** Room temperature water immersion
- **D.** Warm air convection
- **E.** Warm water immersion

Answer: E. Ideally, water should be 37° C to 39° C (98.6° F–102.2° F). Additional damage can be caused when the water temperature exceeds 42° C (107.6° F). In general, water temperature of 35° C to 39° C (95° F–102.2° F) is rapidly effective, well tolerated, and will not cause additional injury. Typically, 10 to 30 minutes is required. Analgesia is necessary during rewarming because pain should be expected. Friction is contraindicated because this will almost always cause additional injury. Room temperature air, water, and warm air will all slowly thaw a frostbitten extremity, but the length of time frozen is directly related to the extent and degree of injury, so rewarming should be accomplished using the quickest measures.

131.5. What is the most common error made when treating frostbite injury?
- **A.** Débridement of broken blisters
- **B.** Inadvertently causing systemic hyperthermia during thawing
- **C.** Premature termination of thawing
- **D.** Use of nonsteroidal antiinflammatory drugs (NSAIDs) for analgesia
- **E.** Use of thrombolytic agents to restore blood flow

Answer: C. Often, a patient's extremities are initially thawed appropriately with circulating warm water, but the thawing is terminated because of severe pain. Pain during thawing is typical and should be expected. Parenteral analgesics are necessary. Broken blisters should be débrided, clear blisters can be aspirated or débrided, and hemorrhagic blisters should be left intact. Inadvertently causing systemic hypotension can occur because many frostbite patients are already cold. Submerging an extremity in warm water will cause local vasodilation and may actually cause systemic hypothermia. An NSAID is the drug of choice for analgesia because the inhibition of thromboxane and arachidonic acid may improve long-term outcome (this is controversial, but NSAIDs are still effective). Thrombolytic agents, such as tissue plasminogen activator (tPA; in small studies), improve outcome and decrease digit amputations.

CHAPTER 132

Accidental Hypothermia

Ken Zafren | Daniel F. Danzl

PRINCIPLES

Background

Reported reanimations of profoundly cold victims in prolonged cardiac arrest and the emergence of therapeutic hypothermia after cardiac arrest have made hypothermia a compelling topic. The lowest recorded core temperature in accidental hypothermia with successful resuscitation was 13.7°C (56.7°F) in a 29-year-old Norwegian physician; cardiopulmonary resuscitation was initiated at the scene. The 9-hour resuscitation included 179 minutes of cardiopulmonary bypass.[1]

The treatment of accidental hypothermia has been controversial. Biblical references have recounted the truncal rewarming of King David by a damsel. Various remedies, including rubbing of the extremities with hot oil, were mentioned by Hippocrates, Aristotle, and Galen.

Cold weather has had a major impact on military history. Hannibal lost nearly half of his army of 46,000 while traversing the Alps in 218 BCE. The winter of 1777 took its toll on Washington's troops at Valley Forge. Napoleon's chief surgeon, Baron Larrey, reported that only 350 of the 12,000 men in the 12th division survived the cold during their retreat from Russia in 1812. Those soldiers who were rapidly rewarmed closest to the campfire died. Many lessons were relearned during both world wars. Pilots and U-boat crews perished in the cold waters of the North Atlantic. The toll continues today in the high mountains of Asia.

Cold-related tragedies also affect civilians, including hunters, skiers, climbers, boaters, swimmers, and survivors of natural disasters. Hypothermia can occur in a wide range of climates and seasons. Large numbers of cases occur in urban settings. Primary hypothermia fatalities can be classified as accidental, homicidal, or suicidal. Death certificate data have underreported mortality from secondary hypothermia, in which cold complicates systemic diseases. The effect of cold on mortality from cardiovascular and neurologic disorders is greatly underestimated.

Hypothermia is defined as a core temperature below 35°C (95°F). Many variables contribute to the development of accidental hypothermia. Exposure, old age, poor health, inadequate nutrition, and various medications and intoxicants can decrease heat production, increase heat loss, or interfere with thermostability. Compensatory responses to heat loss through conduction, convection, radiation, and evaporation are often overwhelmed by exposure, even in healthy persons. Medications can also interfere with thermoregulation. Central nervous system (CNS) problems may limit the efficiency of thermoregulation.

Physiology of Temperature Regulation

Human basal heat production increases with food ingestion, muscle activity, fever, and acute cold exposure. Cold stress increases preshivering muscle tone, potentially doubling heat production. Maximal heat production, primarily due to shivering, lasts only a few hours because of fatigue and glycogen depletion.

Shivering thermogenesis increases the basal metabolic rate up to five times, markedly increasing oxygen consumption. Shivering begins at normal core temperature when the skin is cooled. Shivering intensity is modulated by the posterior hypothalamus and the spinal cord. The preoptic anterior hypothalamus orchestrates nonshivering heat conservation and dissipation.

Heat loss occurs by radiation, conduction, convection, respiration, and evaporation. In a normally clothed resting human at room temperature, 55% to 65% of heat loss is by radiation. Heat loss by radiation is greatest when a person is spread out unclothed and lowest when a person is curled up and insulated. Radiative heat loss depends on the temperature gradient between the environment and exposed body surface area. Conduction normally accounts for 2% to 3% of the heat loss, but increases up to five times in wet clothing. Conduction and convection in cold water can increase heat loss by a factor of 25.

Individuals with greater amounts of subcutaneous fat lose heat more slowly than thin people. Convective losses increase with shivering. Respiration and evaporation account for heat lost in the heating of inspired air and by insensible evaporation from the skin and lungs.

Cutaneous and respiratory heat loss are markedly influenced by the ambient temperature, air motion, and relative humidity. Greater losses occur in a cool, dry, windy environment. When there is no sweating, most heat loss is through radiation and convection. Convective losses are significant in immersion-induced hypothermia. Children cool faster than adults because they have higher ratios of surface area to mass. Chronic cold exposure may result in thermal acclimation (Fig. 132.1).

When the core temperature ranges from 37°C to 30°C (98.6°F–86°F), vasoconstriction, shivering, and nonshivering basal and endocrinologic thermogenesis generate heat. From 30°C to 24°C (86°F–75.2°F), a progressive depression of the basal metabolic rate occurs without shivering. At temperatures below 24°C (75.2°F), autonomic and endocrinologic mechanisms for heat conservation become inactive.

Pathophysiology

The physiologic characteristics of hypothermia are described in Table 132.1.

Cardiovascular System

Initial tachycardia is followed by progressive bradycardia. The pulse decreases by 50% at 28°C (82.4°F). If the degree of tachycardia is inconsistent with the core temperature, associated conditions such as hypoglycemia, drug ingestion, and hypovolemia should be considered.

The bradycardia of hypothermia results from decreased spontaneous depolarization of cardiac pacemaker cells and is refractory to atropine. The electrocardiographic features of hypothermia include the Osborn (J) wave seen at the junction of the QRS complex and ST segment with core temperatures below 32°C (89.6°F; Fig. 132.2). J waves are neither unique to hypothermia nor of any prognostic value. J waves are normally upright in aVL, aVF, and the left precordial leads. J waves can also be seen during local cardiac ischemia, with sepsis or CNS lesions, and

hypercalcemia. J waves may resemble myocardial injury current and may not be recognized by computer interpretations. This can result in mistaken thrombolysis, which could exacerbate preexistent coagulopathies. Hypothermia can also cause electrocardiographic changes that mimic Brugada syndrome.

Atrial and ventricular dysrhythmias are common in moderate or severe hypothermia. Because the conduction system is more sensitive to the cold than the myocardium, cardiac cycle prolongation occurs. As hypothermia worsens, the PR interval, then the QRS interval, and finally the QTc interval become prolonged. Even in the absence of shivering, increased muscle tone may obscure P waves or produce artifacts. Atrial fibrillation is common when the core temperature is below 32° C (89.6° F). Sinus atrial or junctional rhythms also occur. Atrial fibrillation usually converts spontaneously during rewarming, but mesenteric embolization is a hazard.

Ventricular fibrillation (VF) may be caused by tissue hypoxia, physical jostling, electrophysiologic or acid-base disturbances, and autonomic dysfunction. Asystole and VF can occur spontaneously when the core temperature falls below 25° C (77° F), but vital signs may persist well below 24° C (75.2° F).[2]

The term *core temperature afterdrop* refers to a decrease in an individual's core temperature after removal from the cold. Temperature equilibration by conduction contributes to afterdrop, but countercurrent cooling of blood perfusing cold tissues results in a greater decrease in the core temperature.

Active external rewarming of the extremities abolishes peripheral vasoconstriction and reverses arteriovenous shunting. In one human experiment, cooling followed by immersion in a warm bath produced a 30% fall in mean arterial pressure, with a 50% decrease in peripheral vascular resistance.

Core temperature afterdrop is a clinically relevant consideration in the treatment of patients with a large temperature gradient between the core and periphery. Large afterdrops can occur in severely hypothermic patients if frostbitten extremities are thawed before the core is rewarmed.

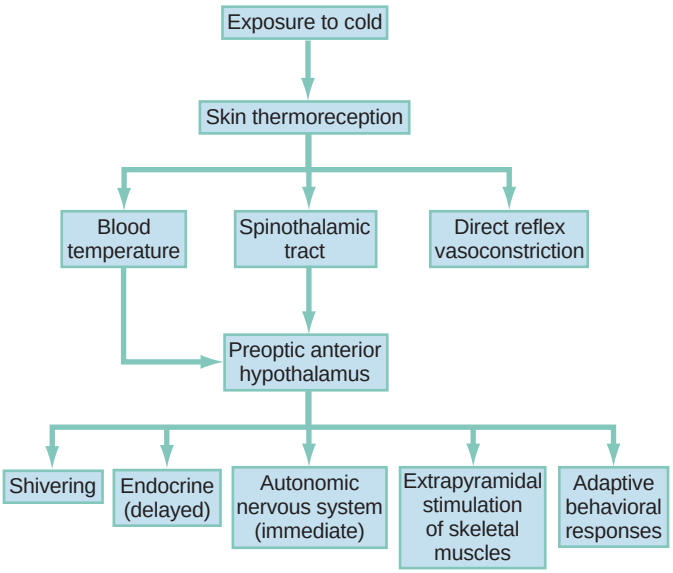

Fig. 132.1. Physiology of cold exposure.

Central Nervous System

Hypothermia progressively depresses the CNS. Significant alteration of the brain's electrical activity begins below 33.5° C (92.3° F). The electroencephalogram silences at 19° C to 20° C (66.2° F–68° F). Cerebral autoregulation is maintained with an increase in vascular resistance until 25° C (77° F). In cases of severe hypothermia, there is a redistribution of blood flow to the brain. Like the heart, the brain has a critical period of tolerance to hypothermia.

Renal System

Exposure to cold induces a diuresis, regardless of the state of hydration. The kidneys excrete a large amount of dilute urine that is essentially glomerular filtrate and does not clear nitrogenous

TABLE 132.1

Physiologic Characteristics of the Four Zones of Hypothermia

STATE	CORE TEMPERATURE °C (°F)	CHARACTERISTICS
Mild	35 (95)	Urine temperature, 34.8° C (94.6° F); increased shivering thermogenesis; increase in metabolic rate
	34 (93.2)	Amnesia and dysarthria develop; normal blood pressure; maximum respiratory stimulation
	33 (91.4)	Ataxia, apathy develop
Moderate	32 (89.6)	Stupor; 25% decrease in oxygen consumption
	31 (87.8)	Decreased shivering thermogenesis
	30 (86)	Atrial fibrillation and other dysrhythmias; poikilothermia; pulse and cardiac output two-thirds normal; insulin ineffective
	29 (85.2)	Progressive decrease in level of consciousness, pulse, and respiration; pupils dilated
Severe	28 (82.4)	Ventricular fibrillation susceptibility; 50% decrease in oxygen consumption and pulse
	27 (80.6)	Losing reflexes and voluntary motion
	26 (78.8)	Major acid-base disturbances; no reflexes or response to pain
	25 (77)	Cerebral blood flow one-third normal; cardiac output 45% normal; pulmonary edema may develop
	24 (75.2)	Significant hypotension
	23 (73.4)	No corneal or oculocephalic reflexes
	22 (71.6)	Maximum risk of ventricular fibrillation; 75% decrease in oxygen consumption
Profound	20 (68)	Lowest resumption of cardiac electromechanical activity; pulse 20% of normal
	19 (66.2)	Flat electroencephalogram
	18 (64.4)	Asystole develops
	14.2 (57.6)	Lowest accidental hypothermia survival in an infant
	13.7 (56.7)	Lowest accidental hypothermia survival in an adult
	9 (48.2)	Lowest therapeutic hypothermia survival

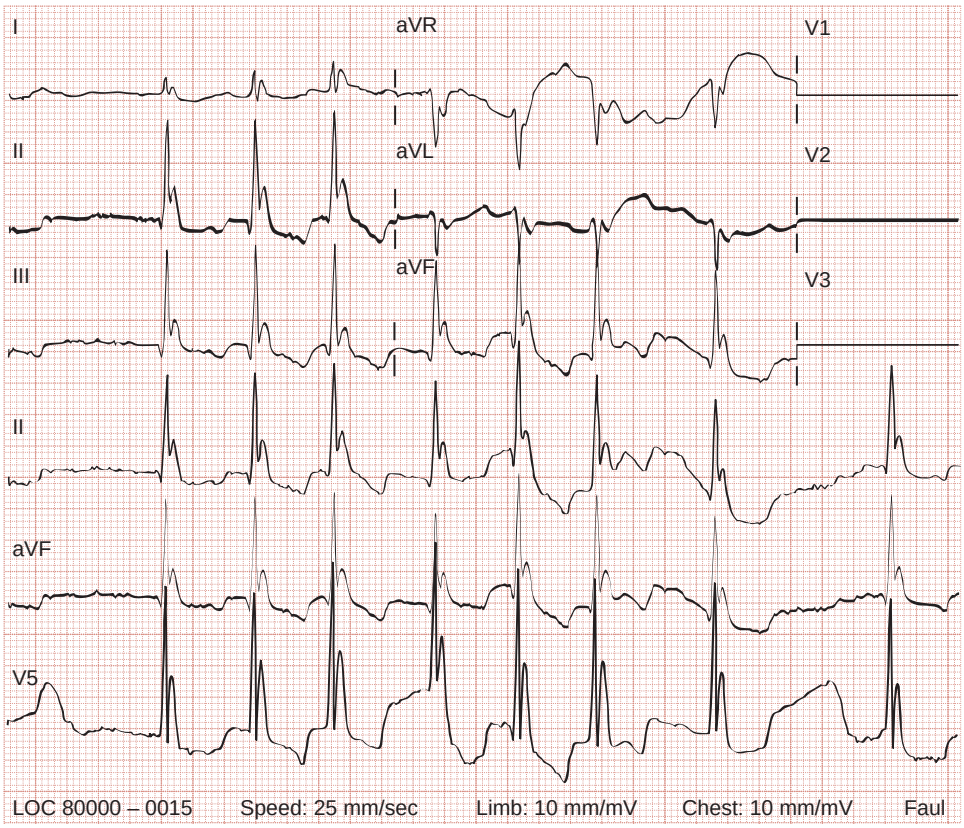

Fig. 132.2. Hypothermic J waves.

waste products. Severe hypothermia causes relative central hypervolemia due to peripheral vasoconstriction. Cold diuresis may act as a volume regulator to diminish the capacitance vessel overload. Cold water immersion can further increase urinary output by 3.5 times. Ethanol also increases urinary output.

Respiratory System

Hypothermia initially stimulates respiration, followed by a progressive decrease in the respiratory minute volume. Carbon dioxide production decreases 50% with an 8°C (46.4°F) decrease in temperature. Stimuli for respiratory control are altered in severe hypothermia. Carbon dioxide retention with respiratory acidosis can occur. Hypercapnia increases core temperature cooling during snow burial. Other pathophysiologic factors that adversely affect the respiratory system include viscous bronchorrhea, decreased ciliary motility, and noncardiogenic pulmonary edema.[3]

Predisposing Factors

Factors that predispose to hypothermia include decreased heat production, increased heat loss, and impaired thermoregulation (Box 132.1). Hypothermia can occur, even in warm conditions.[4]

Decreased Heat Production. Decreased thermogenesis may be due to endocrine dysfunction, such as hypopituitarism, hypoadrenalism, or myxedema. Myxedema coma is several times more common in women, up to 80% of whom are hypothermic. Hypothyroidism is often occult, with no history of lassitude, dry skin, arthralgias, or cold intolerance.

Hypoglycemia can predispose to hypothermia.[4] Another cause of decreased heat production is malnutrition, with a decrease in subcutaneous fat. Severe malnutrition with wasting contributes to heat loss. Kwashiorkor is less of a risk due to the insulating effect of hypoproteinemic edema.

Neonates are at particular risk of hypothermia due to large surface area–to–mass ratio, relatively deficient subcutaneous tissue, and inefficient shivering.[5] Neonates lack behavioral defense mechanisms. Acute neonatal hypothermia is common after emergency delivery or resuscitation and has also been reported after abandonment of infants.[5] Hypothermic neonates are lethargic, fail to thrive, and have a weak cry. Many have paradoxical rosy cheeks. Late-onset hypothermia, which occurs after 72 hours of life, is often due to septicemia. Hypothermia can occur in shaken baby syndrome and may be a factor in some cases of sudden infant death syndrome.

Most older adults are capable of normal thermoregulation, but conditions such as immobility and systemic disease may interfere with heat production and conservation. Geriatric autonomic dysfunction may cause an inability to sense cold, abnormal adaptive behavioral responses, and decreased peripheral blood flow.

Increased Heat Loss. Patients with erythrodermas, such as psoriasis, exfoliative dermatitis, ichthyosis, eczema, and burns, can have increased peripheral blood flow. Iatrogenic causes of heat loss include exposure during resuscitation, cold or room temperature infusions, overcooling of patients with heat stroke, and overzealous burn treatment.

Ethanol is metabolized slowly in hypothermia and interacts with thermoregulatory neurotransmitters. Ethanol may directly suppress the activity of the posterior hypothalamus and mammillary bodies. Cutaneous heat loss increases through vasodilation. Shivering thermogenesis is decreased. Ethanol is the most common cause of excessive heat loss in urban settings.[6] Aging is associated with an increased sensitivity to the hypothermic

BOX 132.1

Factors Predisposing to Hypothermia

DECREASED HEAT PRODUCTION
Endocrinologic failure
Hypopituitarism
Hypothyroidism
Diabetes
Insufficient fuel
Hypoglycemia
Malnutrition
Marasmus
Kwashiorkor
Extreme exertion
Neuromuscular inefficiency
Age extremes
Impaired shivering
Inactivity
Lack of adaptation

INCREASED HEAT LOSS
Environmental
Immersion
Nonimmersion
Induced vasodilation
Pharmacologic
Toxicologic
Erythrodermas
Burns
Psoriasis
Ichthyosis
Exfoliative dermatitis
Iatrogenic
Emergency deliveries
Cold infusions
Heatstroke treatment

IMPAIRED THERMOREGULATION
Peripheral failure
Neuropathies
Acute spinal cord transection
Diabetes
Central failure, neurologic
Central nervous system trauma
Cerebrovascular accident
Toxicologic
Metabolic
Subarachnoid hemorrhage
Pharmacologic
Hypothalamic dysfunction
Parkinson's disease
Anorexia nervosa
Cerebellar lesion
Neoplasm
Congenital intracranial anomalies
Multiple sclerosis

MISCELLANEOUS ASSOCIATED CLINICAL STATES
Recurrent hypothermia
Episodic hypothermia
Sepsis
Pancreatitis
Carcinomatosis
Cardiopulmonary disease
Vascular insufficiency
Uremia
Paget's disease
Giant cell arteritis
Sarcoidosis
Shaken baby syndrome
Multisystem trauma
Shapiro's syndrome
Wernicke-Korsakoff syndrome
Hodgkin's disease

actions of ethanol. Intoxicated persons may be incapable of adaptive behavior to avoid cold. Hypothermic alcoholic ketoacidosis also occurs.

Impaired Thermoregulation. Thermoregulation can be impaired centrally, peripherally, or metabolically. Skull fractures, particularly basilar fractures, and chronic subdural hematomas are associated with central impairment. Other causes include strokes, neoplasms, anorexia nervosa, and Hodgkin's and Parkinson's diseases. The final common pathway in these disorders may be centrally mediated vasodilation. Cerebellar lesions produce choreiform inefficient shivering.

In therapeutic or toxic doses, antidepressants, mood stabilizers, antipsychotics, anxiolytics, and general anesthetics interfere with thermoregulation by impairing centrally mediated vasoconstriction. Other overdoses, including by organophosphates, heroin, sedative hypnotics, barbiturates, and carbon monoxide, predispose to hypothermia.

Peripheral thermoregulatory failure occurs in neurogenic shock after acute spinal cord transection. In cord injury, disruption of the autonomic nervous system eliminates vasoconstriction. The patient effectively becomes poikilothermic and can rapidly become hypothermic. Neuropathies and diabetes are also peripheral causes of heat loss. Abnormal plasma osmolality may cause hypothalamic dysfunction in uremia, lactic acidosis, diabetic ketoacidosis, and hypoglycemia.

Traumatic Factors

After trauma, hypotension and hypovolemia jeopardize thermostability. In patients with major injuries, there is a fall in skin and core temperatures, without shivering. Thermoregulation is impaired, and heat production decreases.

Hypothermia may exacerbate blood loss by inducing coagulopathy due to impaired activity of coagulation factors and enhanced plasma fibrinolytic activity, with decreased function and sequestration of platelets. Hypothermia in trauma is a risk factor for multiorgan dysfunction.

Traumatic injuries may be missed if hypotension or neurologic findings such as areflexia or paralysis are misattributed to hypothermia. Major risk factors for hypothermia in trauma patients include extremes of age, severe injury, intoxication, large transfusion requirements, and prolonged field, emergency department (ED), and operating room times.

Hypothermia can protect the brain from ischemia only when induced before shock develops. This reduces adenosine triphosphate (ATP) use while ATP stores are nearly normal. In trauma patients, ATP stores are already depleted.

CLINICAL FEATURES

Appreciation of subtle presentations facilitates the early diagnosis of mild to moderate hypothermia. Vague symptoms include hunger, nausea, confusion, dizziness, chills, pruritus, and dyspnea (Box 132.2). During outdoor activities, individuals may simply become uncooperative, uncoordinated, moody, or apathetic. Indoors, older patients may exhibit confusion or become less communicative and may display lassitude or a peculiar flat affect. Progression of mental deterioration or motor skill impairment may mimic dementia. Symptoms such as slurred speech and ataxia may resemble symptoms of stroke or intoxication. Some older adults have a decreased ability to sense cold and fail to take adaptive action.

Paradoxical undressing has been widely reported in hypothermic patients. This last preterminal effort may be related to the peripheral vasoconstrictive changes of hypothermia. Patients have been mistaken for victims of sexual assault or as having a psychiatric disorder.

In urban settings, hypothermia is usually associated with alcohol consumption or underlying illness. Other common causes include stroke, overdose, psychiatric emergency, and major trauma.

Neurologic manifestations vary widely. A progressive decrease in the level of consciousness is usually proportional to the degree of hypothermia. Some patients, however, continue to be verbally responsive and display intact reflexes at 27°C to 25°C (80.6°F–77°F).

Eye movement abnormalities and extensor plantar responses do not correlate directly with the degree of hypothermia. Cranial nerve signs may be seen with bulbar damage from central pontine myelinolysis. Above 22°C (71.6°F), it should be assumed that

BOX 132.2

Presenting Signs of Hypothermia

HEAD, EYE, EAR, NOSE, THROAT
Mydriasis
Decreased corneal reflexes
Extraocular muscle abnormalities
Erythropsia
Flushing
Facial edema
Epistaxis
Rhinorrhea
Strabismus

CARDIOVASCULAR
Initial tachycardia
Subsequent bradycardia
Dysrhythmias
Decreased heart tones
Hepatojugular reflux
Jugular venous distention
Hypotension

RESPIRATORY
Initial tachypnea
Adventitious sounds
Bronchorrhea
Progressive hypoventilation
Apnea

GASTROINTESTINAL
Ileus
Constipation
Abdominal distention or rigidity
Poor rectal tone
Gastric dilation in neonates or in adults with myxedema

GENITOURINARY
Anuria
Oliguria
Polyuria
Testicular torsion

NEUROLOGIC
Depressed level of consciousness
Ataxia
Hypesthesia
Dysarthria
Antinociception
Amnesia
Initial hyperreflexia
Anesthesia
Hyporeflexia
Areflexia
Central pontine myelinolysis

PSYCHIATRIC
Impaired judgment
Perseveration
Mood changes
Peculiar flat affect
Altered mental status
Paradoxical undressing
Neuroses
Psychoses
Suicide
Organic brain syndrome

MUSCULOSKELETAL
Increased muscle tone
Shivering
Rigidity or pseudo–rigor mortis
Paravertebral spasm
Opisthotonos
Compartment syndrome

DERMATOLOGIC
Erythema
Pernio
Pallor
Frostnip
Cyanosis
Frostbite
Icterus
Popsicle panniculitis
Sclerema
Cold urticaria
Ecchymosis
Necrosis
Edema
Gangrene

nonreactive dilated pupils reflect inadequate tissue perfusion rather than hypothermia.

Neuromuscular examination may reveal stiff posture, pseudo–rigor mortis, or opisthotonos. Reflexes are usually hyperactive to 32°C (89.6°F)and then become hypoactive, disappearing around 26°C (78.8°F). Cremasteric reflexes are absent because the testicles are already retracted. The plantar response usually remains flexor until 26°C (78.8°F). The knee jerk is the last reflex to disappear and the first to reappear with rewarming. Diagnosis of CNS disorders, including spinal cord lesions, may be obscured by hypothermia.

From 30°C to 26°C (86°F–78.8°F), both contraction and relaxation phases of the reflexes are equally prolonged. If intact, the ankle jerk is helpful to diagnose hypothermic myxedema. Myxedema characteristically prolongs the relaxation phase more than the contraction phase.

Psychiatric disorders do not improve when the patient is cold. Mental status alterations include anxiety, perseveration, neurosis, and psychosis. Individuals who are functional in warm conditions may decompensate in colder weather. Hypothermia-induced psychiatric presentations and suicide attempts are commonly misdiagnosed.

DIAGNOSTIC CONSIDERATIONS

Differential Diagnosis

The differential diagnosis of hypothermia is broad and includes hypothyroidism, hypopituitarism, diabetes, hypoglycemia, malnutrition, intracranial and spinal cord injuries, and sedative-hypnotic and alcohol intoxication (see Box 132.1). Hypothermia is also common in patients with Wernicke's encephalopathy. Hypothermia can mask the usual clinical triad of ophthalmoplegia, confusion, and truncal ataxia. Intravenous thiamine can be diagnostic and therapeutic.

Hypothermia occurs in conjunction with infections, most commonly overwhelming gram-negative sepsis, pneumonia, meningitis, and encephalitis. Other infections that can lead to hypothermia include bacterial endocarditis, brucellosis, malaria, syphilis, typhoid, miliary tuberculosis, and trypanosomiasis.

Medical conditions associated with hypothermia include carcinoma, pancreatitis, peritonitis, and cerebrovascular disease. Low cardiac output resulting from myocardial infarction can induce hypothermia. Fetal and maternal bradycardia and hypothermia may result from magnesium sulfate infusion during preterm labor. Delayed recovery from neuromuscular blockade may result from hypothermia.

Although many conditions can cause or be associated with accidental hypothermia, as noted, there is no true differential diagnosis of accidental hypothermia once the diagnosis has been established by core temperature measurement.

Diagnostic Testing

Except in mild cases of hypothermia, initial laboratory evaluation should include glucose level, complete blood cell count, comprehensive metabolic panel, serum lipase level, and coagulation studies. Blood urea nitrogen and creatinine levels should be checked because renal failure may occur after rewarming in patients with chronic hypothermia. Arterial or venous blood gases, if obtained, should not be temperature-corrected.

A serum ethanol level and urine toxicology screen may be helpful based on history or when a depressed level of consciousness is inconsistent with the degree of hypothermia. Thyroid function studies, cardiac markers, and serum cortisol levels may also be indicated.

Acid-Base Balance

Blood gas analyzers warm blood to 37°C (98.6°F), increasing the partial pressure of dissolved gases. This results in arterial blood gases with higher oxygen and carbon dioxide and lower pH than in vivo values. Attempting to maintain a corrected pH at 7.4 and arterial partial pressure of carbon dioxide ($Paco_2$) at 40 mm Hg during hypothermia depresses cerebral and coronary blood flow and cardiac output and increases the incidence of VF. The ideal acid-base goal is an uncorrected pH of 7.4 and $Paco_2$ of 40 mm Hg.

Cold blood buffers poorly; in normothermia, pH decreases by 0.08 unit for every 10-mm Hg increase in $Paco_2$. At 28°C (82.4°F), the decrease in pH doubles. Because the neutral point of water at 37°C (98.6°F) is a pH of 6.8, the normal 0.6-unit pH offset between blood and intracellular water should be maintained at all temperatures (Fig. 132.3). Intracellular electrochemical neutrality ensures optimal enzymatic function at all temperatures. Relative alkalinity affords myocardial protection and improves the heart's electrical stability.

Hematologic Evaluation

The hematocrit can be deceptively high due to decreased plasma volume. The hematocrit increases 2% for every 1°C (33.8°F) fall in temperature. A low-normal hematocrit level in a moderately to severely hypothermic patient should suggest acute or chronic blood loss.

Splenic, hepatic, and splanchnic sequestration in hypothermia decreases leukocyte and platelet counts. A normal white blood cell count never excludes infection, especially if the patient is debilitated, alcoholic, myxedematous, or at either age extreme.

Frequent evaluation of serum electrolyte levels during rewarming is essential. There are no safe predictors of values or trends. Changes occur in membrane permeability and in the sodium-potassium pump. The patient's preexisting physiologic status, severity and chronicity of hypothermia, and method of rewarming alter the serum electrolyte values.

The plasma potassium level is independent of hypothermia. Hyperkalemia can be associated with metabolic acidosis, rhabdomyolysis, or renal failure. Hypothermia enhances the cardiac toxicity of hyperkalemia and obscures premonitory electrocardiographic changes. Hypokalemia is most common with chronic

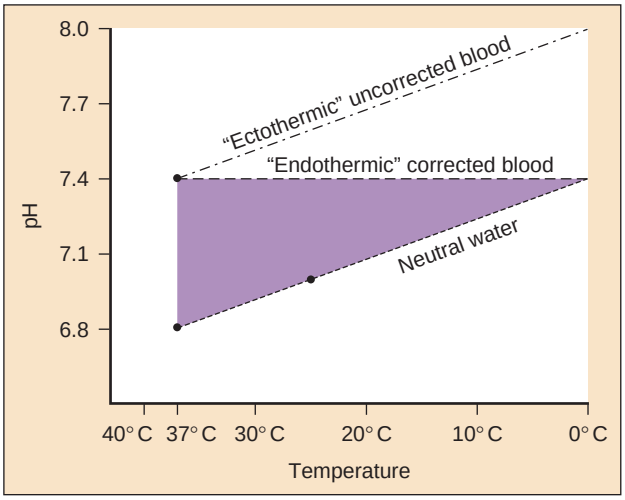

Fig. 132.3. Neutrality reflects the pH of water at any given temperature. The pH of water is 6.8 at 37°C (98.6°F) and 7.0 at 25°C (78.8°F). The physiologically ideal intracellular-to-extracellular, 0.6-unit pH offset will be maintained if the arterial pH is kept at 7.42, uncorrected for temperature.

hypothermia. It results from potassium entering muscle, rather than potassium diuresis. A decline in the serum potassium level despite a decreasing serum pH is caused by intracellular pH fluxes greater than extracellular pH fluxes.

Conditions associated with hypokalemia include preexisting diabetic ketoacidosis, hypopituitarism, inappropriate secretion of antidiuretic hormone, previous diuretic therapy, and alcoholism. If the potassium level is less than 3 mEq/L, supplementation should be given during rewarming.

Blood urea nitrogen and creatinine levels are elevated with preexisting renal disease or decreased clearance. Because of hypothermic fluid shifts, hematocrit and blood urea nitrogen levels are poor indicators of actual fluid status.

The blood glucose level may provide a subtle clue to the type of hypothermia. Acute hypothermia initially elevates the blood glucose level by catecholamine-induced glycogenolysis, diminished insulin release, and inhibition of cellular membrane glucose carrier systems. Subacute and chronic hypothermia produce glycogen depletion, leading to hypoglycemia. Hypoglycemia can also develop during rewarming in acute hypothermia.[3] Symptoms of hypoglycemia can be masked by hypothermia. A cold-induced renal glycosuria neither implies hyperglycemia nor guarantees normoglycemia.[7]

When hyperglycemia persists during rewarming, one should suspect hemorrhagic pancreatitis or diabetic ketoacidosis. Patients with diabetic ketoacidosis should be actively rewarmed past 30° C (86° F) because insulin is ineffective below that temperature. Correction of hypoglycemia corrects the level of consciousness only to that corresponding to the level of hypothermia.

Severe hypothermia also causes serum enzyme level elevation because of the ultrastructural cellular damage. Rhabdomyolysis is commonly associated with cold exposure. Ischemic pancreatitis may result from the microcirculatory shock of hypothermia. Decreased pancreatic blood flow then activates proteolytic enzymes, increasing the serum lipase level.

Hypothermic Coagulation

A physiologic hypercoagulable state occurs with hypothermia and can be associated with a disseminated intravascular coagulation (DIC)–type syndrome. The cause may be catecholamine or steroid release, circulatory collapse, or release of tissue thromboplastin from cold, ischemic tissue.

Coagulopathies also occur because the enzymatic activity of the activated clotting factors is depressed by the cold. Clotting prolongation is proportional to the number of steps in the cascade. Because kinetic tests of coagulation are performed in the laboratory at 37° C (98.6° F), there is a disparity between in vivo, clinically evident coagulopathy and deceptively normal prothrombin time, partial thromboplastin time, or international normalized ratio reported by the laboratory. The only effective treatment is rewarming, not administration of clotting factors.

Leukopenia and thrombocytopenia usually reverse with rewarming. Clinically significant coagulopathies can still occur, particularly in association with trauma. Cold-induced thrombocytopenia may be from direct bone marrow suppression or splenic and hepatic sequestration. Platelet thromboxane B2 production is also temperature-dependent. Thrombocytopenia is more common at both age extremes.

Elevated viscosity seen in hypothermia may be exacerbated in patients with cryoglobulinemia or cryofibrinogenemia, especially in older patients. Cryofibrinogen, a cold-precipitated fibrinogen, is associated with collagen vascular diseases, carcinomas, and coliform sepsis. Cold hemagglutination from cold agglutinins produces hemolysis or agglutination with thrombosis, which might explain the increase in coronary and cerebral thromboses in winter.

Imaging

If the patient is not alert and there is suspicion of trauma, standard trauma imaging is indicated, including a focused assessment with sonography in trauma (FAST) bedside ultrasound examination and computed tomography (CT) scan of the head. CT scanning of the abdomen and pelvis may show pancreatic calcifications, unsuspected pneumoperitoneum, small bowel dilation from hypothermia-induced mesenteric vascular occlusion, or colonic dilation associated with myxedema coma.

MANAGEMENT

General Measures

Patients who are cold, stiff, and cyanotic, with fixed pupils, inaudible heart tones, and no visible thoracic excursions, can still be successfully resuscitated.[1] Unexpectedly, some patients still recover completely in the morgue.

Pertinent history includes information about preexisting cardiac, pulmonary, neurologic, or endocrine disease. The duration of exposure, circumstances of discovery, associated injuries, and predisposing conditions should be documented. Initial management should emphasize prevention of further heat loss. Specific goals of prehospital care include prevention of further heat loss with insulation, avoidance of afterdrop, gentle handling, and transporting in a horizontal position.[8] Patients should be actively rewarmed in the field, if possible.[8]

A patient who is unresponsive and not shivering should be treated for severe hypothermia. At core temperatures below 32° C (89.6° F), one should expect an irritable myocardium, temperature gradient between core and periphery, and relative hypovolemia.

In the ED, hypothermia should be confirmed and monitored with continuous core temperature evaluation. Clinically, the rectal temperature is most widely used. However, it lags behind core temperature changes and is influenced by lower extremity temperatures and probe placement. The probe should be inserted to 15 cm and not placed into cold feces.

Epitympanic temperature equilibrates rapidly with core temperature and is closest to the hypothalamic temperature. Most epitympanic probes are not suitable for field use.[8] Infrared thermography (tympanic temperature) is too unreliable be used, except to exclude hypothermia. If the airway is protected, an esophageal probe placed in the lower third of the esophagus is the ideal method for continuous core temperature monitoring. If the probe is placed higher, the reading can be falsely elevated by inhalation of heated oxygen.

Hand-held Doppler may be useful to establish the presence of a spontaneous pulse. Bedside cardiac ultrasonography should precede chest compressions.[9] Pulse oximetry is usually unreliable in hypothermia with peripheral vasoconstriction. It is often not possible to obtain an accurate reading. End-tidal carbon dioxide measurements accurately assess tissue perfusion and tracheal tube placement, but only at normal temperatures. Commercially available devices do not function when humidified air is used for airway rewarming.

Endotracheal intubation or placement of a supraglottic airway may be indicated unless the patient has intact protective airway reflexes. Cold depression of ciliary activity allows for the accumulation of secretions with frothy sputum and chest congestion. It may be hard to differentiate between bronchorrhea and pulmonary edema. Nasotracheal intubation can be useful to avoid a surgical airway when cold-induced trismus is present.

Dysrhythmias during intubation are rare. These may be due to failure to preoxygenate, mechanical jostling, acid-base changes, and electrolyte level fluctuations.

A nasogastric tube is indicated after endotracheal intubation. Decreased gastric motility and gastric dilation are common. Physical examination of the abdomen is unreliable because cold can induce rectus muscle rigidity. Many moderately and severely hypothermic patients have decreased or absent bowel sounds. It is important to evaluate the patient for an associated ileus, pancreatitis, or occult trauma.

In moderate and severe hypothermia, indwelling urinary catheters are useful to monitor urine output and help determine the severity of vascular fluid shifts.

Cardiac monitoring should be continuous. Avoid insertion of a central venous pressure catheter tip into the heart, which can precipitate dysrhythmias. Arterial catheters for continuous monitoring of intraarterial blood pressure may be helpful in profoundly hypothermic patients. Placement a of pulmonary artery catheter risks perforation of a cold, stiff, pulmonary artery.

Volume Resuscitation

Patients with moderate or severe hypothermia are usually volume-depleted. They are prone to thromboembolism resulting from increased viscosity. During rewarming, the total plasma volume is usually high but the circulatory plasma volume is usually low due to increased peripheral vascular resistance.

Rapid volume expansion can be lifesaving, especially in hypothermic neonates. Adult patients with moderate or severe hypothermia should initially receive a 500-mL fluid challenge of heated normal saline. Lactated Ringer's solution should be avoided because the cold liver metabolizes lactate poorly.

Fluids administered via the intravenous (IV) should be heated to 40° C to 42° C (104° F–107.6° F). If a commercial fluid or blood warmer is not available, IV fluids can be heated in a standard microwave. The fluid bag should be shaken before administration to avoid hot spots. Rapid central venous administration, which may produce myocardial thermal gradients, should be avoided. Another option in vasoconstricted patients is administration via the intraosseous route.

Countercurrent heat exchangers effectively heat crystalloids and blood from 10° C to 35° C (50° F–95° F). There can be significant conductive heat loss through IV tubing, especially with long lengths of tubing at slow flow rates. It is preferable to administer fluids as boluses to effect rather than as drips.

Normally, hypothermia increases natriuresis. Preexisting gastrointestinal losses or previous diuretic treatment can also contribute to sodium loss. Patients with a normal sodium level and osmolality may have preexisting sodium overload as a result of cirrhosis, nephrosis, or congestive heart failure. However, most patients will be free water–depleted, elevating the sodium level and osmolality.

Hemoconcentration due to decreased plasma volume, fluid shifts, and increased vascular permeability usually is present. Hemodilution can occur from parenteral crystalloid administration, but a low hematocrit can also result from acute hemorrhage or preexisting anemia.

Advanced Life Support

During hypothermic cardiac arrest, cardiac output and cerebral and myocardial blood flows are much less than those during normothermic closed chest compressions. Metabolic demands, however, are also less during hypothermia.

Blood flow during cardiopulmonary resuscitation (CPR) in patients with hypothermia differs from flow during normothermia. In normothermia, some flow results from phasic alterations in the intrathoracic pressure rather than from direct cardiac compression. In hypothermia, the heart is a passive conduit, and phasic alterations in the intrathoracic pressure are exerted equally on all cardiac chambers. The mitral valve remains patent during systole, and blood continues to circulate through the left side of the heart. This explains an observation of a thoracotomy in a patient who ultimately survived severe hypothermia: "the heart was found to be hard as stone and it is hardly conceivable how effective external cardiac massage could have been."[10] There have been many neurologically intact survivors after prolonged closed chest compressions.[11,12]

Chest wall elasticity and pulmonary compliance are decreased with cold. More force is needed to depress the chest wall sufficiently to generate adequate intrathoracic pressure gradients. Powered thoracic compression devices are useful during prolonged resuscitations pending decisions about extracorporeal rewarming. Apparent rigor mortis and fixed dilated pupils are not reliable criteria for withholding CPR in a hypothermic patient.[8] Dependent lividity has been questioned as a criterion for death in hypothermia, although there have been no reports of survivors. Because intermittent flow may provide adequate support during evacuation, CPR should not be withheld just because continuous compressions cannot be ensured.[13]

Rescuers should initiate CPR in accidental hypothermia unless the do-not-resuscitate status is known, obviously lethal injuries are present, chest wall depression is impossible, signs of life are present, or rescuers are endangered.[8] If possible, verify that there is no spontaneous mechanical cardiac activity with bedside ultrasonography before chest compressions are initiated.

Pharmacologic Treatment

The efficacy of most medications is temperature-dependent. Protein binding increases during hypothermia. Liver metabolism is decreased. Large doses could be required to achieve a therapeutic response. Toxic levels could develop with rewarming. In severe hypothermia, withhold medications until the patient is warmer, and then leave longer intervals between doses. No medication should be given orally because of the patient's decreased gastrointestinal motility. Intramuscular medications are also contraindicated because of poor absorption from vasoconstricted sites.

Cardiovascular Medications

The effects of hypothermia on the autonomic nervous system are variable. In primates, sympathetic response increases rapidly to cooling from 37° C to 31° C (98.6° F–87.8° F) and then switches off at about 29° C (84.2° F). This suggests that modest catecholamine support might be useful below 29° C (84.2° F).

Pharmacologic manipulation of the pulse and blood pressure should be avoided. Epinephrine and other vasoconstrictors may be dysrhythmogenic and have a minimal effect on the maximally constricted peripheral vasculature. There are no clear indications for vasopressors[9] although, in animal models, the return of spontaneous circulation after induced VF below 30° C (86° F) is higher after the administration of vasopressors.

Inotropes usually are not necessary to support blood pressure. Inotropic support may be considered in disproportionately hypotensive patients who do not maintain a mean arterial pressure of 60 mm Hg in response to volume replacement and rewarming.

Atrial dysrhythmias are common below 32° C (89.6° F), associated with a slow ventricular response. Atrial fibrillation is common but self-limited. It usually converts spontaneously during rewarming. Beta blockers and calcium channel blockers are contraindicated unless there is a rapid ventricular response.

Preexisting, chronic, premature ventricular contractions can be suppressed during hypothermia and recur during rewarming. Most hypothermia-induced dysrhythmias convert spontaneously during rewarming. Asystole that develops during rewarming is not as ominous as asystole in normothermic patients. For

VF, defibrillation should be attempted at the usual energy. Successful defibrillation has been reported at 20°C (68°F) but attempted defibrillation is often unsuccessful until the core temperature is above 30°C (86°F).[14] If a defibrillation attempt is unsuccessful, active rewarming should be initiated while continuing CPR. Defibrillation attempts can be given occasionally during rewarming. Once the core temperature is above 30°C (86°F), further attempts can be made.[9]

The ideal approach to ventricular dysrhythmias in the hypothermic patient has not been well studied. Lidocaine and propranolol have minimal hemodynamic effects during hypothermia. Their efficacy in the treatment of ventricular dysrhythmias appears limited. In a canine model of severe hypothermic VF, neither amiodarone nor bretylium was effective. Human chemical defibrillations with bretylium tosylate in cases of severe hypothermia have been reported. There was a case report in which recurrent VF was controlled by isoproterenol.[15] Amiodarone can cause torsades de pointes by QT prolongation. The safety of amiodarone during accidental and induced hypothermia is not known.

In hypothermia, at least one Group 1 antidysrhythmic agent, procainamide, increases the incidence of VF. Another drug in the same group, quinidine, can prevent VF during induced profound hypothermia and during cardiac manipulation at 25°C to 30°C (77°F–86°F).

Transvenous cardiac pacing is hazardous for bradydysrhythmias in hypothermia. External pacing may be worth trying in the rare setting of profoundly disproportionate bradycardia. Transcutaneous pacing has been used to facilitate continuous arteriovenous rewarming in perfusing patients by raising the systolic blood pressure above 60 mm Hg. Other active rewarming techniques do not require specific pressure gradients.

Antibiotics

Hypothermia compromises host defenses and predisposes to infection. In hypothermia, the usual signs of infection, including fever, are absent. Shaking chills from sepsis may be mistaken for shivering. If a patient's mental status remains altered, despite rewarming, CNS injury or infection should be suspected.

In hypothermic children younger than 3 months, empirical antibiotics are indicated after cultures have been obtained. There are no reliable clinical or laboratory indicators of infection, but bradycardia, anemia, uremia, and high serum glucose levels, as well as leukocyte abnormalities, are common clues. The role of empirical antibiotics in adults is less clear. Although gram-negative septicemia may cause hypothermia, coexistent infections from gram-positive cocci, Enterobacteriaceae, and oral anaerobes are common.

Older adults with thermoregulatory failure have a high risk of mortality and should be considered septic until proven otherwise. Routine empirical antibiotics do not appear warranted in hypothermic, non–older adults. Antibiotics should be administered if the clinical picture is consistent with septic shock or if there is failure to rewarm. Cellulitis, myositis, bacteriuria, or infiltrate on chest x-rays warrants immediate antimicrobial therapy.

Failure to Rewarm

Cold abolishes adrenal responsiveness to adrenocorticotropic hormone (ACTH). A false diagnosis of decreased adrenal reserve is possible. The increase in ACTH level seen in hypothermic individuals may be a neurogenic or emotional response to the cold.

Acute cold stress initially stimulates cortisol secretion. There may already be a very high level as a result of underlying stress. In clinical series, total serum cortisol levels are commonly elevated; however, the active free fraction is decreased due to increased protein binding. Failure to rewarm may be due to adrenocortical insufficiency or steroid dependence. If either condition is suspected, hydrocortisone, 100 mg IV, should be administered.

Empirical treatment with thyroxine should be reserved for patients thought to have myxedema. Thyroid hormone should be replaced if there is a history of hypothyroidism, suggestive neck scar, or failure to rewarm. After thyroid function study samples have been drawn, levothyroxine, 250 to 500 μg IV, should be cautiously administered over several minutes. Daily injections of 50 to 100 μg are necessary for 5 to 7 days. Hydrocortisone (100–200 mg) should be added to the first several liters of crystalloid fluid.

The absorption of oral or intramuscular levothyroxine is variable. IV administration has a smooth effect after the onset of action at 6 to 12 hours. This will be manifested by improvement in vital signs and rewarming rate. Half the dose is converted by the peripheral tissues into L-triiodothyronine (T_3). An underlying infection can also compromise thermogenesis. In an urban setting, infection is the leading cause of failure to rewarm and subsequent mortality.

Rewarming

No controlled studies comparing rewarming methods in hypothermia have been published. Rigid treatment protocols are not evidence-based. The emergency clinician should choose specific methods on a case by case basis, taking into account availability and clinical experience.

Passive External Rewarming

Spontaneous passive external rewarming is noninvasive. It is the treatment of choice for patients with mild hypothermia when active rewarming is not available. The patient should be able to generate sufficient metabolic heat to maintain an acceptable rate of spontaneous rewarming. Older adults are commonly glycogen-depleted, have central hypovolemia, and are not capable of normal cardiovascular or metabolic homeostasis.

The normal processes of heat dissipation are minimized by passive external rewarming. Cessation of evaporation and convection is coupled with insulation against further radiation of heat. This technique simply involves covering the patient with an insulating material in a favorable atmospheric condition. The ambient temperature should exceed 21°C (69.8°F). When the air is stationary, less heat is lost to conduction, convection, and radiation.

Shivering is the most effective thermoregulatory neuromuscular response to cold in humans. Without shivering, endogenously generated metabolic heat is insufficient to raise the core temperature. When the core temperature exceeds 32°C (89.6°F), unless complete glycogen depletion occurs, the major source of heat production is shivering thermogenesis.

Recommended rewarming rates vary between 0.5°C and 2.0°C/hr (32.9°F–35.6°F/hr). The rewarming rate should be rapid enough to avoid prolonged exposure to dysrhythmias. Below 32°C (89.6°F), humans are functionally poikilothermic. Shivering is ineffective below 32°C (89.6°F) and absent below 30°C (86°F).

Active Rewarming

Active rewarming is the direct transfer of exogenous heat to the patient. It can be accomplished by external or internal techniques. Active rewarming is useful in mild hypothermia to decrease metabolic requirements of rewarming and improve thermal comfort.

In moderate to severe hypothermia, cardiovascular instability and decompensation require prompt elevation of the core temperature while minimizing afterdrop (Box 132.3). Defibrillation

BOX 132.3

Indications for Active Rewarming

Cardiovascular instability
Moderate or severe hypothermia (≤32° C [89.6° F])
Inadequate rate of rewarming or failure to rewarm
Endocrinologic insufficiency
Traumatic or toxicological peripheral vasodilation
Secondary hypothermia impairing thermoregulation

is rarely successful at temperatures below 28° C (82.46° F). Active rewarming is indicated with strokes and other conditions that impair CNS control of thermoregulation. Active rewarming is also indicated for patients when endogenous thermogenesis is insufficient or when glycogen depletion is present, usually from endocrine causes that include hypopituitarism, adrenal insufficiency, hypothyroidism, and Wernicke's encephalopathy. Active rewarming is recommended in diabetic ketoacidosis because the core temperature must be elevated above 30° C (86° F) before insulin becomes effective.

Pharmacologically induced peripheral vasodilation or acute spinal cord transection prevents sufficient thermogenesis and requires active rewarming. Patients with severe hypothermia do not necessarily require invasive extracorporeal rewarming techniques, especially if they have a sustained perfusing rhythm.

Aggressive treatment of hypothermia is indicated in infants. Rapid rewarming is advantageous because it minimizes energy expenditures. Hypothermic neonates have been successfully rewarmed using minimally invasive methods. A neonate with a core temperature of 14.8° C (58.6° F) receiving CPR made a full neurologic recovery after being rewarmed by active external rewarming (AER), warmed IV fluids, and heated, humidified ventilator gases.[5]

Active External Rewarming

Early concern with AER was sparked after a 1961 study,[16] in which 20 of 23 patients died. Retrospective analysis of clinical series has shown widely varying mortality rates with AER.

Various methods conduct heat directly to the skin. Rewarming options include plumbed garments that circulate warm fluids, hot water bottles, heating pads, forced air warming systems, and radiant sources. Thermal injury to vasoconstricted hypoperfused skin is a potential hazard with local heat application.

Forced air warming systems efficiently transfer heat. They can be used in field conditions or in the ED.. These devices circulate hot air through a blanket. The air flows through apertures on the patient's side, allowing convective transfer of heat. Hypotension and core temperature afterdrop are not seen in forced air warming for accidental hypothermia in the ED. Like all active methods, forced air warming decreases shivering. Forced air warming transfers large amounts of heat while minimizing afterdrop. Other options include the reverse use of endovascular devices intended to produce therapeutic hypothermia in patients after cardiac arrest or thermoregulatory systems that circulate warm water through energy transfer pads.[17]

Arteriovenous anastomosis (AVA) rewarming is a unique, noninvasive, AER technique.[18] Exogenous heat is provided by immersion of distal extremities (upper extremities to the elbows and lower extremities to the knees) in hot (44° C–45° C [111.2° F–1136° F]) water. The heat opens the AVAs, which are 1 mm below the epidermal surface in the digits. As a result, there is an increased flow of warmed venous subcutaneous blood returning directly to the heart. The forearms and calves must be included for this technique to be effective. The AVA technique was designed for use on ships and is not practical in most situations. In addition, many patients cannot tolerate the very hot water. Burns of vasoconstricted skin are a potential hazard.

Previously healthy patients with acute hypothermia are optimal candidates for AER. They have minimal dehydration and pathophysiologic circulatory changes. If AER is used, and the extremities are vasoconstricted, the heat source should be applied preferentially to the thorax rather than to the extremities. Application of heat to the extremities increases the cardiovascular load by increasing the metabolic requirements of the peripheral musculature. The depressed cardiovascular system may not be able to meet the demands, resulting in cardiovascular collapse.

Combining truncal AER with core rewarming can also be successful. The provision of heated humidified oxygen and warmed IV fluids, in addition to AER, may help prevent hypoxia, metabolic acidosis, core temperature afterdrop, and hypotension. If AER is used to treat moderate or severe hypothermia, it can be combined with one or more active core rewarming techniques.

Active Core Rewarming. Many methods achieve active rewarming of the core. These techniques minimize rewarming collapse in patients with a core temperature below 32° C (89.6° F).

Airway Rewarming. Airway rewarming with heated humidified oxygen is a simple and inexpensive method that can be used an adjunct to other forms of active rewarming in moderate or severe hypothermia. Airway rewarming improves oxygenation, helps avoid afterdrop, stimulates pulmonary cilia, decreases viscosity of pulmonary secretions, and reduces cold-induced bronchorrhea. Pulmonary absorption of moisture does not adversely affect surfactant or increase pulmonary congestion.

The respiratory tract is a limited site for heat exchange, but heated humidified oxygen increases blood oxygen content and temperature in the pulmonary circulation. The myocardium is perfused by warmer oxygenated blood, decreasing intermittent temperature gradients.

Sufficient minute volume and complete humidification are necessary for maximal heat delivery. Because dry air has low thermal conductivity, ventilation with warm dry air provides negligible heat. Reported increases in rewarming rates from 1° C to 2.5° C/hr (33.8° F–36.5° F/hr) have been reported with heated humidified oxygen. The rates with endotracheal intubation are higher than those with a mask. Positive-pressure ventilation with a mask can be used, but has not been studied.

Maintenance of sufficient oxygenation is important in moderate to severe hypothermia. In patients on cardiopulmonary bypass cooled to 28° C to 30° C (82.4° F–86° F), the capacity of hemoglobin to unload oxygen to the tissue is less than half that found in normothermic patients. Despite lower metabolic requirements, this decrease in so-called functional hemoglobin, combined with a depressed respiratory minute volume, results in minimal oxygen reserves.

Some patients maintain a level of spontaneous respiration appropriate to depressed carbon dioxide production. This is not the case in patients with coexisting toxicologic, traumatic, or metabolic depression of the respiratory center.

The technique for patients with spontaneous respirations requires a heated cascade nebulizer. An immersion heater can be connected to a hose with a warming wire. Because patients with a depressed level of consciousness do not complain of pain, it is essential to check the temperature of the inspired air frequently with an in-line temperature probe. The gas temperature should be maintained at 42° C to 45° C (107.6° F–113° F). Most heater modules require modification to allow the temperature to reach 42° C to 45° C (107.6° F–113° F). Modified heater modules should be labeled to avoid routine use.

Most humidifiers will not exceed 41° C (105.8° F) close to the patient outlet with a 2-m tubing length. Strategies to circumvent the 41° C (105.8° F) ceiling include reduction of tubing length, addition of more heat sources, disabling of the humidifier safety system, and placement of the temperature probe outside the patient circuit. Because of the modest clinical benefit in stable patients, it is probably not worth the effort to circumvent the 41° C (105.8° F) ceiling. The only report of thermal airway injury has been in a patient ventilated by endotracheal tube for 11 hours with an 80° C (176° F) inhalant.

Peritoneal Dialysis. Peritoneal dialysis delivers dialysate at 40° C to 45° C (104° F–113° F). Heat is conducted directly to the intraperitoneal structures through the posterior parietal peritoneum to the solid viscera and through the hemidiaphragms to the heart and lungs. A double-catheter system with suction at the outflow can increase the rate of rewarming to about 6 L/hr. Two liters are infused, retained for 20 minutes, and then aspirated. Rewarming rates average 1° C to 3° C/hr (33.8° F–37.4° F/hr).

An additional benefit of peritoneal dialysis is hepatic rewarming, which reactivates detoxification and conversion enzymes. Serum electrolyte levels should be monitored because peritoneal dialysis can exacerbate preexisting hypokalemia. Peritoneal lavage is useful primarily in severe cases in combination with other rewarming techniques for patients without spontaneous perfusion, but has also been used alone in patients undergoing CPR for whom extracorporeal circulation was thought to be contraindicated due to coagulopathy[19] or was not available.[20]

Heated Irrigation. Heat transfer from irrigation fluids is usually limited due to the minimal surface area available for heat exchange. Gastric or colonic irrigation can cause fluid and electrolyte level fluxes.

Closed thoracic lavage is useful in severe hypothermia. Two large-bore thoracostomy tubes are inserted into one or both hemithoraces. One is inserted anteriorly in the second or third intercostal space at the midclavicular line, the historical classic site for needle thoracostomy. The other is inserted between the fifth and sixth intercostal spaces in the posterior axillary line, the usual site for tube thoracostomy. Normal saline solution is heated to 40° C to 42° C (104° F–107.6° F), infused into the superior tube. The inferior tube is used for drainage. Left-sided tube insertion in perfusing patients risks causing VF. Efficiency of the heat transfer varies with flow rate and dwell times. Pleural adhesions prevent adequate infusion and can result in a tension hydrothorax. Adequate drainage should be ensured to prevent intrathoracic hypertension.

Thoracic lavage is usually reserved for the severely hypothermic patient who does not respond to standard techniques or the patient with another indication for a chest tube. It should be combined with other rewarming modalities in potentially salvageable cardiac arrest patients. However, thoracic lavage has been used successfully in patients requiring CPR when extracorporeal circulation was not available.[21] The rate of rewarming averages 3° C/hr (37.4° F/hr).

Mediastinal irrigation and direct myocardial lavage should be considered only in patients without spontaneous perfusion. The procedure requires a standard left lateral thoracotomy incision. The pericardium is not incised unless an effusion or tamponade is present. The heart is bathed in 1 to 2 L of an isotonic solution heated to 40° C (104° F) for several minutes. The fluid is then removed and the lavage repeated. Internal defibrillation is attempted at intervals of 2° C (35.6° F) after the myocardial temperature exceeds 26° C to 28° C (78.8° F–82.4° F). When a perfusing rhythm is achieved, lavage is continued until the myocardial temperature exceeds 32° C (89.6° F). A median sternotomy approach allows ventricular decompression in addition to direct defibrillation. Open cardiac massage of a cold, rigid, and contracted heart may not generate flow.

Endovascular Rewarming. Another active core rewarming option uses endovascular warming devices that are intended for therapeutic cooling and subsequent rewarming of comatose, resuscitated, cardiac arrest patients. These systems involve femoral vein catheterization with a closed-loop catheter that has a thermostat at the tip. If the core temperature is below 30° C (86° F), the fail-safe feature on the console must be circumvented to allow rewarming.

Diathermy. Truncal diathermy involves the conversion of energy waves into heat. Large amounts of heat can be delivered to deep tissues with ultrasonic and low-frequency microwave irradiation. Frostbite, burns, significant edema, and the presence of all types of metallic implants and pacemakers are contraindications. In spite of successes in piglets,[22] infants,[22] and a few adults,[23] diathermy is still experimental.

Extracorporeal Blood Rewarming. The four common extracorporeal techniques to rewarm blood are venovenous rewarming, hemodialysis, continuous arteriovenous rewarming, and extracorporeal circulation—cardiopulmonary bypass (CPB and extracorporeal membrane oxygenation [ECMO]; Table 132.2).

In venovenous rewarming, blood is removed, ideally by a large peripheral venous catheter, heated to 40° C (104° F) and returned through a second venous catheter. Flow rates are 150 to 400 mL/min. The circuit is simple and efficient. There is no oxygenator, and the system does not provide circulatory support. Volume infusion is the only option to augment inadequate cardiac output.

Standard hemodialysis is a widely available and practical rewarming technique.[24,25] It is portable and efficient and can also be used to treat electrolyte abnormalities, renal failure, or intoxication with a dialyzable substance.

Continuous arteriovenous rewarming is an option if the blood pressure is at least 60 mm Hg. This involves the use of percutaneously inserted femoral arterial and contralateral femoral venous catheters. Heparin-bonded tubing circuits obviate the need for systemic anticoagulation. The blood pressure of spontaneously

TABLE 132.2

Extracorporeal Blood Rewarming Options

OPTIONS	CONSIDERATIONS
Venovenous circuit	Central venous catheter to central venous or peripheral catheter rewarming No oxygenator, circulatory support Flow rates, 150–400 mL/min Rate of rewarming 2° C–3° C/hr (35.6° F–37.4° F)
Hemodialysis circuit	Single- or dual-vessel cannulation; stabilizes electrolyte or toxicologic abnormalities Exchange cycle volumes 200–500 mL/min Rate of rewarming 2° C–3° C/hr (35.6° F–37.4° F/hr)
Continuous arteriovenous rewarming circuit	Percutaneous 8.5-Fr femoral catheters Requires blood pressure of 60 mm Hg systolic No perfusionist, pump, anticoagulation Flow rates, 225–375 mL/min Rate of rewarming, 3° C–4° C/hr (37.4° F–39.2° F/hr)
Cardiopulmonary bypass circuit	Full circulatory support with pump and oxygenator Perfusate-temperature gradient, 5° C–10° C (41° F–50° F) Flow rates, 2–7 L/min (average, 3–4 L/min) Rate of rewarming up to 9.5° C/hr (49.1° F/hr)

From Danzl DF: Hypothermia and frostbite. In Kasper D, Fauci A, Hauser S, et al, editors: Harrison's principles of internal medicine, ed 19, New York, 2015, McGraw-Hill.

perfusing, traumatized, hypothermic patients creates a functional arteriovenous fistula by diverting part of the cardiac output out the femoral artery through a commercially available countercurrent heat exchanger. The heated blood is then returned with admixed heated crystalloids through the femoral vein. Continuous arteriovenous rewarming avoids the need for specialized equipment and a perfusionist necessary for cardiopulmonary bypass. The average rate of rewarming is 3° C to 4° C/hr (37.4° F–39.2° F/hr). Because the catheters are 8.5 Fr, the patient should weigh at least 40 kg.

Extracorporeal circulation usually refers to cardiopulmonary bypass or ECMO.[26,7] In one review, the mean temperature increase was 9.5° C/hr (49.1° F/hr) with CPB.[27] ECMO appears to reduce the risk of intractable cardiorespiratory failure or severe pulmonary edema after rewarming.[28]

The major advantage of extracorporeal circulation in perfusing patients is the preservation of flow if mechanical cardiac activity is lost during rewarming. Other candidates are patients who do not respond to less invasive rewarming techniques, those with completely frozen extremities, and those with rhabdomyolysis accompanied by major electrolyte disturbances. In some European centers, patients without obvious trauma are admitted directly to the operating suite for extracorporeal circulation.[29]

Very rapid rates of rewarming do not necessarily improve survival. Complications of rapid rewarming include DIC, pulmonary edema, hemolysis, and acute tubular necrosis. Extracoroporeal circulation can provide cardiovascular support in perfusing but hemodynamically unstable patients.

Extracorporeal rewarming should be considered in hypothermic cardiac arrest patients if there are no contraindications to CPR. A realistic assessment of the risk-benefit ratio for debilitated patients with secondary hypothermia should be made. The lowest temperature in a survivor of induced hypothermia was 9° C (48.2° F).[30] Extracorporeal blood rewarming is unlikely to succeed below 5° C to 10° C (41° F–50° F). Resuscitation should be discontinued if frozen or clotted intravascular contents are identified.

DISPOSITION

Otherwise healthy patients who have mild primary accidental hypothermia (35° C–32° C [95° F–89.6° F) usually rewarm easily. They can be safely discharged if a warm environment is available. Patients with mild hypothermia associated with trauma are more difficult to rewarm and require admission.

Patients with more severe hypothermia (<32° C [89.6° F]) generally require admission to an intensive care setting. These patients should be evaluated for the presence of underlying medical disorders (see Box 132.1). Cardiac monitoring should be considered for patients with persistent toxicologic or metabolic abnormalities and is essential for patients with cardiovascular instability or an inadequate rate of rewarming. Transfer of patients to tertiary care centers is generally not necessary, but severely hypothermic patients may be most easily managed in facilities capable of extracorporeal circulation.

In the past, the treatment dictum was that "no one is dead until they are warm and dead." Some patients are cold and dead. It would be useful and humane if they could be safely identified. Because human physiologic responses are variable, it is difficult to predict outcome.[31] The type and severity of the underlying or precipitating disease process are the major determinants. Age of the patient is not an independent predictor of mortality.

Trauma, infection, and toxin ingestions unpredictably affect survival. Outcome prediction based on the Glasgow Coma Scale score is unreliable. Significant predictors of poor outcome include asphyxia,[7] prehospital cardiac arrest, low or absent blood pressure, elevated blood urea nitrogen level, and need for endotracheal or nasogastric intubation in the ED. Patients with hypothermic cardiac arrest due to alcohol intoxication may have better neurologic outcomes than patients with hypothermic cardiac arrest from other causes.[6]

The search for a valid triage marker of death continues. Grave prognostic indicators include evidence of intravascular thrombosis (fibrinogen < 50 mg/dL), cell lysis (hyperkalemia > 10–12 mEq/L),[31] and ammonia levels greater than 250 mmol/L.

KEY CONCEPTS

- Indications for active rather than passive rewarming include cardiovascular instability, temperature below 32° C (89.6° F), poor rate of rewarming, and endocrinologic insufficiency.
- Consider hypoglycemia, hypovolemia, or an overdose if there is a tachycardia disproportionate to the temperature.
- The efficacy of most medications is temperature-dependent. Overmedication to achieve an effect when the patient is cold could cause toxicity during rewarming.
- Laboratory coagulation tests are performed at 37° C (98.6° F). Despite a clinically obvious coagulopathy, the values will be deceptively normal.
- There are no safe predictors of serum electrolyte levels. Hypothermia enhances the cardiac toxicity of hyperkalemia and obscures premonitory electrocardiographic changes.
- Failure to rewarm despite good technique should suggest infection, endocrine insufficiency, or a futile resuscitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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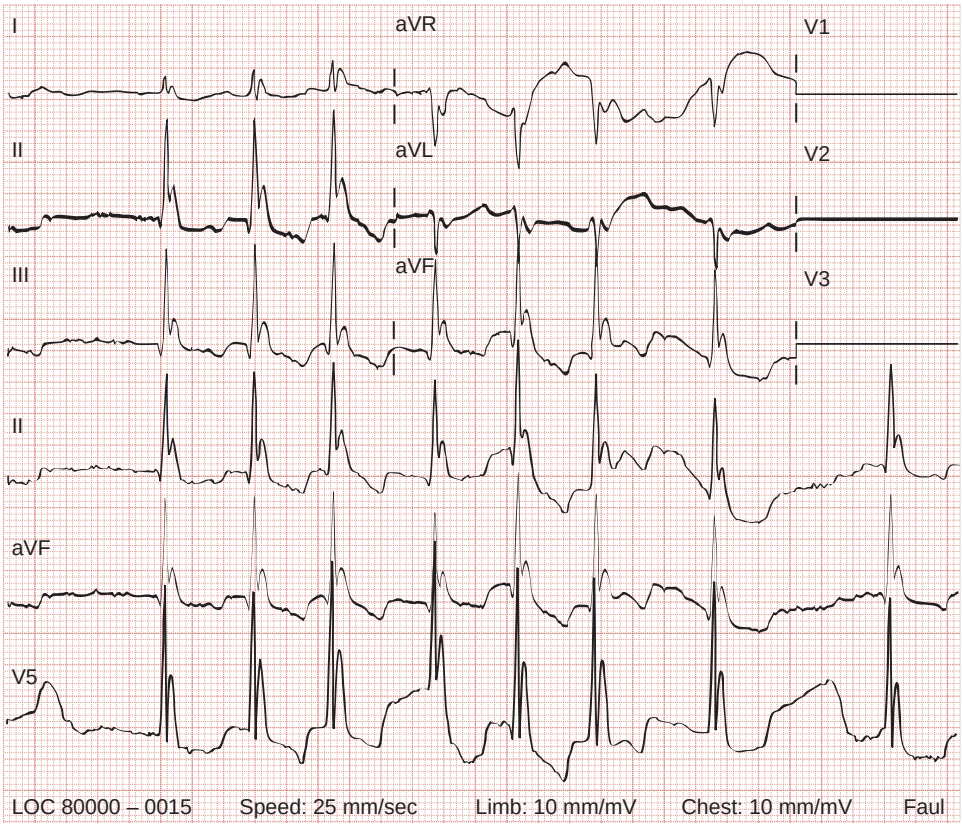
CHAPTER 132: QUESTIONS & ANSWERS

132.1. What type of energy transfer results in the greatest amount of heat loss in a cold environment?

A. Conduction
B. Convection
C. Evaporation
D. Radiation
E. Respiration

Answer: D. At an average metabolic rate, radiation accounts for 55% to 65% of heat loss. Heat loss through radiation depends on the temperature gradient of the person and environment. A greater differential results in greater heat loss. Heat loss through radiation can be minimized by reducing the body surface area (curling up), warming the room or, most effectively, insulation. Conduction is the transfer of heat between two objects in direct contact (eg, bare feet on a tile floor) and only accounts for 2% or 3% of heat loss, but can increase up to 25 times in cases involving submersion. Convection is the transfer of heat to a fluid medium (air or liquid) as it moves across the body. This usually accounts for approximately 10% of heat loss but is increased when shivering or in windy conditions. Respiration accounts for approximately 30% of heat loss and is relatively constant. Evaporation (sweating) is the dominant mode of heat loss in hot environments but is negligible in cold environments.

132.2. Emergency medical services (EMS) notifies your emergency department (ED) that an unknown male who was "found down" is being transported. No history is available. Paramedics report that the patient's pulse is 42 beats/min and blood pressure is difficult to obtain. Spontaneous respirations are present at a rate of 10 breaths/min. The electrocardiogram (ECG) shown here is faxed before the patient's arrival. What treatment should you administer upon the patient's arrival?



A. Epinephrine intravenous (IV)
B. Normal saline bolus
C. Pericardiocentesis
D. Synchronized cardioversion
E. Warming the patient

Answer: E. The patient has the classic electrocardiographic finding of hypothermia, the Osborn or J wave. The wave is seen at the junction of the QRS complex and ST segment. Depending on the lead, the wave can be mistaken for ST segment elevation myocardial infarction (STEMI), early repolarization, or simply a widened QRS of unknown cause. The Osborn wave is potentially diagnostic of hypothermia and may be seen at any temperature below 32° C (89.6° F). Epinephrine is potentially indicated in cardiac arrest. Crystalline fluid boluses are generally indicated for any hypotensive patient, especially when hypovolemia is suspected. Pericardiocentesis is only indicated for cardiac tamponade. Synchronized cardioversion is indicated for a variety of tachydysrhythmias.

132.3. Rapid rewarming is the mainstay of treatment for hypothermia. However, rewarming can cause complications. Which of the following complications should be anticipated and prevented when rewarming a hypothermic patient?
A. Cerebral edema
B. Hypokalemia
C. Hyponatremia
D. Hypotension
E. Rhabdomyolysis

Answer: D. When the surface or extremities of a patient are initially warmed, the cold-induced peripheral vasoconstriction is reversed. Rapid peripheral vasodilation can result in up to a 50% decline in peripheral vascular resistance and a 30% decline in mean arterial pressure. The effects are particularly prominent in patients who are also dehydrated—and exposure to cold induces a diuresis—or have frostbitten extremities. The same vasodilation is responsible for core temperature afterdrop, which refers to a further decline in core temperature, partially resulting from the fact that blood is now perfusing cold tissue, and the cold blood is returned to the core. This core afterdrop can also increase the incidence of dysrhythmias. Rhabdomyolysis is commonly seen in hypothermic patients but not specifically when rewarming. None of the other answer choices are commonly seen on rewarming a hypothermic patient.

132.4. A 4-day-old male patient is brought in by parents for poor feeding. His birth history is uneventful; he was full term. He was discharged from the hospital with his mother 2 days ago. Vital signs are within normal limits for his age, with the exception of a temperature of 33.5° C (92.3° F). Physical examination reveals a drowsy but arousable boy. Otherwise, the physical examination is unremarkable. What is the most likely diagnosis?
A. Congenital heart disease
B. Hypernatremia
C. Hyponatremia
D. Sepsis
E. Still's disease

Answer: D. Neonates have poor thermoregulatory mechanisms, and neonatal hypothermia is relatively common after precipitous delivery. However, with proper care, the hypothermia resolves and does not cause long-term problems. Hypothermia 72 hours after birth is frequently caused by sepsis. A full septic evaluation is indicated in this case. Neonatal hypothermia is also associated with hypoglycemia and child neglect or abuse. Poor feeding and dehydration can result in hyperthermia, whereas dilution of infant formula can result in hyponatremia. Neither should result in hypothermia. Congenital heart disease frequently presents with distress during feedings but, similarly, should not result

in hypothermia. Still's disease is a rare rheumatologic disease associated with fever, arthralgia, and rash.

132.5. Which substance directly interferes with thermoregulatory neurotransmitters, may directly damage the thermoregulatory centers of the brain, and therefore predisposes to hypothermia?
A. Cocaine
B. Ethanol
C. Nicotine
D. Phencyclidine
E. Tetrahydrocannabinol (THC)

Answer: B. Ethanol interacts with all thermoregulatory neurotransmitters and may damage the posterior hypothalamus and mammillary bodies. It also causes vasodilation and decreased shivering, as well as inhibiting normal adaptive behavior to cold. In urban settings, most cases of hypothermia are associated with ethanol. Cocaine and phencyclidine are stimulants and may cause hyperthermia. Nicotine and THC do not directly interact with the thermoregulatory centers.

132.6. A 47-year-old man is brought to the ED after being "found down." No further history is available. His vital signs are normal with the exception of temperature, which is 31°C (87.8°F). He is lethargic and only responds to painful stimuli by withdrawing. He has several scalp lacerations that are bleeding profusely. You appropriately intubate this patient to secure his airway. Despite direct pressure, injection of epinephrine, and all other techniques at your disposal, the patient continues to bleed from his scalp lacerations. You also notice multiple new areas or bruising and bleeding on various parts of the patient. What should be done to reverse the coagulopathy most rapidly?
A. Intranasal desmopressin
B. IV vitamin K
C. Transfusion of fresh-frozen plasma (FFP)
D. Transfusion of platelets
E. Warming the patient

Answer: E. Hypothermia decreases the activity of all clotting factors, which can result in disseminated intravascular coagulation. The only effective treatment is to warm the patient. There is nothing inherently wrong with the patient's clotting factors; they are merely inactivated by the cold. Any additional clotting factors transfused will also be inactivated by the cold. Hypothermic patients are not thrombocytopenic. Desmopressin enhances the release of von Willebrand factor and factor VIII. Vitamin K is needed for the synthesis of factors II, VII, IX, and X. FFP provides all clotting factors.

132.7. A 30-year-old woman in cardiac arrest is brought to the ED by emergency medical services. She was intubated in the field, and chest compressions have been continuously performed. Her temperature is 25°C (77°F). When placed on the cardiac monitor, she is noted to be in ventricular fibrillation. A defibrillation attempt is made at the appropriate setting, but she remains in ventricular fibrillation. A nurse resumes providing chest compressions and asks for further instructions. What should be done next?
A. IV amiodarone
B. IV lidocaine
C. IV procainamide
D. Repeating defibrillation
E. Warming the patient

Answer: E. Defibrillation attempts are usually unsuccessful at core temperatures less than 32°C (89.6°F). Chest compressions should continue while the patient is aggressively warmed. Many dysrhythmias spontaneously convert once hypothermia is resolved. If ventricular fibrillation persists at temperatures above 30°C (86°F), another defibrillation attempt should be made. Amiodarone, lidocaine, and procainamide are all antidysrhythmics that could potentially be used in normothermic patients.

132.8. Which of the following is an indication for active rather than passive rewarming in a hypothermic patient?
A. Altered mental status
B. Associated burns
C. Associated trauma
D. Hypoglycemia
E. Temperature below 32°C (89.6°F)

Answer: E. Other indications for active rewarming include cardiovascular instability, poor rate of rewarming, endocrinologic insufficiency, and vasodilation.

132.9. Which of the following patients meets the definition of hypothermia?
A. A patient with a core temperature of less than 35°C (95°F) but with no symptoms
B. A patient with a core temperature of less than 36°C (96.8°F) with symptoms of hypothermia
C. A patient with an oral temperature of less than 34°C (93.2°F) but with no symptoms
D. A patient with an oral temperature of less than 35°C (95°F) with symptoms of hypothermia
E. A patient with frostbite, regardless of temperature

Answer: A. Hypothermia is defined as a core temperature less than 35°C (95°F). Oral temperatures are not reliable. The presence or absence of symptoms can guide management but does not change the definition of hypothermia.

132.10. The search for a valid triage marker of death in the setting of severe hypothermia continues. Which of the following is most suggestive?
A. Ammonia level, 100 mmol
B. Fibrinogen, >50 mg/dL
C. Hyperkalemia, 9 mEq/L
D. International normalized ratio (INR) of 3.2
E. Low blood urea nitrogen (BUN) level
Answer: B. Ominous markers include an ammonia level > 250 mml/L, hyperkalemia (cell lysis) > 10 to 12 mEq/L, fibrinogen < 50 mg/dL (intravascular thrombosis). The INR is not prognostic because kinetic tests of coagulation are performed in the laboratory at 37°C (98.6°F).

CHAPTER 133

Heat Illness

Melissa Platt | Timothy G. Price

PRINCIPLES

Background

Humans have been plagued by heat illness throughout recorded history, often as the result of military exercises, athletic events, or recreational activities. When environmental heat stress is maximal, strenuous exercise is not required to produce heat illness. Modern military organizations continue to encounter heat illness because of the requirement to train unacclimatized troops with heavy physical exercise. Heat stroke is the third leading cause of death among all US athletes. Of the major sports, football has the greatest number of heat stroke fatalities and a 10 times higher rate for heat illnesses.[1] The health hazards associated with extreme environmental working conditions in many industries have been increasingly recognized worldwide.[2-4]

Older adults and the poor, who often lack adequate air conditioning and nutrition, and those with preexisting disease are prone to heat illness during environmental extremes. It is estimated that at least 10 times as many heat-aggravated illnesses occur in patients with comorbid conditions, such as coronary artery disease, cerebrovascular disease, and diabetes. In heat wave years in the United States, approximately 10 times as many deaths are reported as during non–heat wave years. Climate models have suggested an increase in frequency and intensity of heat waves in temperate areas of the world.[5] Before the advent of air conditioning, mortality increased three- to fivefold in nursing homes and threefold in the general population during heat waves.[6] Microclimates conducive to heat illness are produced in the interiors of automobiles, military tanks, and tents in the sun, as well as in engine rooms, mines, hot tubs, and saunas.[6] Children are more susceptible to heat stressors because their higher surface area–to–mass ratios allow increased absorption of heat. They also have lower sweat rates per gland.

Anatomy and Physiology

Heat Production

Humans are essentially biochemical furnaces that burn food to fuel with a complex array of metabolic functions. These chemical reactions consume substrate, generate usable energy, and produce byproducts that must be eliminated for continued operation of the system. Water and carbon dioxide are produced and eliminated in large quantities, as are urea, sulfates, phosphates, and other chemical products. These reactions are exothermic and combine to produce a basal metabolic rate that amounts to approximately 100 kcal/hr for a 70-kg person. In the absence of cooling mechanisms, this baseline metabolic activity would result in a 1.1°C (34°F) hourly rise in body temperature.

Heat production can be increased 20-fold by strenuous exertion. Rectal temperatures as high as 42°C (107.6°F) have been recorded in trained marathon runners, without ill effects. Metabolic factors, such as hyperthyroidism and sympathomimetic drug ingestion, can dramatically increase heat production. Environmental heat not only adds to the heat load but also interferes with heat dissipation. The physics of heat transfer as it relates to human physiology involves four mechanisms—conduction, convection, radiation, and evaporation.[6]

Conduction. This is the transfer of heat energy from warmer to cooler objects by direct physical contact. Air is a good insulator; therefore, only approximately 2% of the body heat loss is by conduction. In contrast, the thermal conductivity of water is at least 25 times that of air.

Convection. This is heat loss to air and water vapor molecules circulating around the body. As the ambient temperature rises, the amount of heat dissipated by convection becomes minimal. Once the air temperature exceeds the mean skin temperature, heat is gained by the body. Convective heat loss varies directly with wind velocity. Loose-fitting clothing maximizes convective, and also evaporative, heat loss.

Radiation. This is heat transfer by electromagnetic waves. Although radiation accounts for approximately 65% of heat loss in cool environments, it is a major source of heat gain in hot climates. Up to 300 kcal/hr can be gained from radiation when someone is directly exposed to the hot summer sun.

Evaporation. This is the conversion of a liquid to the gaseous phase. Evaporation of 1 mL of sweat from the skin cools the body by 0.58 kcal. As the ambient temperature rises, evaporation becomes the dominant mechanism of heat loss. Panting mammals such as dogs have an oropharyngeal countercurrent flow mechanism (carotid rete mirabile) that results in selective cooling of the brain. In humans, respiratory and countercurrent mechanisms are minimal sources of heat loss.

Heat Regulation

The regulation of body temperature involves three distinct functions—thermosensors, a central integrative area, and thermoregulatory effectors.

Thermosensors. Temperature-sensitive structures are located peripherally in the skin and centrally in the body. Skin temperature changes, however, correlate poorly with changes in the rate of heat loss. Thermosensitive neurons, located in the preoptic anterior hypothalamus, are activated when the temperature of the blood circulating through that area exceeds a set point (Fig. 133.1).

The skin temperature affects heat loss when a person resting in a warm environment initiates sweating, even though the core temperature remains constant. In contrast, changes in core temperature are more dominant than skin temperature changes in producing heat-dissipating responses.

Central Integrative Area. The central nervous system (CNS) interprets information received from the thermosensors to instruct thermoregulatory effectors properly. The concept of a central thermostat whereby an alteration shifts effector thresholds

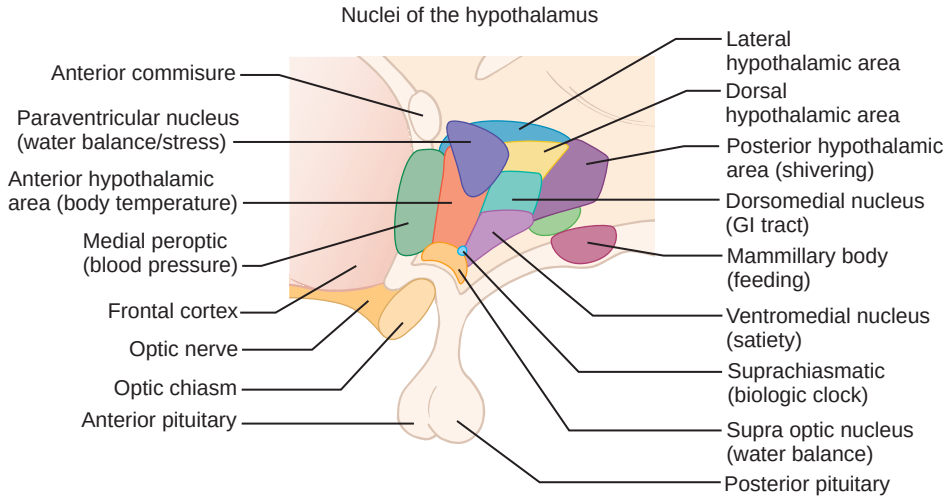


Fig. 133.1. Preoptic anterior hypothalamus. (Adapted from Nuclei of the hypothalamus. bhavanajagat .files.wordpress.com/2012/07/nuclei-of-hypothalamus.jpg.)

in the same direction fits a variety of clinical situations. For example, fever, the circadian rhythm of temperature variation, and the difference in rectal temperature after ovulation can be explained by variation of a thermal set point.

Thermoregulatory Effectors. Sweating and peripheral vasodilation are the major mechanisms whereby heat loss can be accelerated. In a warm environment, evaporation of sweat from the skin is the most important mechanism of heat dissipation. Heat loss from the skin by convection and radiation is maximized by increased skin blood flow to facilitate sweating.

Humans possess apocrine and eccrine sweat glands. Apocrine glands are concentrated in the axillae and produce milky sweat, rich in carbohydrate and protein. They are adrenergically innervated and respond to emotional stress as well as to heat. Most glands producing so-called thermal sweat are eccrine glands. These are cholinergically innervated and distributed over the entire body, with the largest number on the palms and soles. Eccrine sweat is colorless, odorless, and devoid of protein. Individuals exercising in hot environments commonly lose 1 or 2 L/hr of sweat. A loss of up to 4 L/hr is possible with strenuous exercise.

Cooling is best achieved by evaporation from the body surface; sweat that drips from the skin does not cool the body. Each liter of completely evaporated sweat dissipates 580 kcal of heat. The ability of the environment to evaporate sweat is termed *atmospheric cooling power* and varies primarily with humidity, but also with wind velocity. As humidity approaches 100%, evaporative heat loss ceases.

The vascular response to heat stress is cutaneous vasodilation and compensatory vasoconstriction of the splanchnic and renal beds. These vascular changes are under neurogenic control and allow heat to be dissipated quickly and efficiently, but they place a tremendous burden on the heart.[7] To maintain blood pressure, cardiac output increases dramatically. For this reason, saunas and hot tubs may be dangerous for patients with cardiac disease. Cardiovascular and baroreceptor reflexes also affect skin blood flow. Reduced forearm sweating and vasodilation have been observed in severely dehydrated subjects exercising in a warm environment.

Acclimatization

Acclimatization is the constellation of physiologic adaptations that occur in a normal person as the result of repeated exposures to heat stress. Daily exposure to work and heat for 100 min/day results in near-maximal acclimatization within 7 to 14 days.[8,9] This is characterized by an earlier onset of sweating (at a lower core temperature), increased sweat volume, and lowered sweat sodium concentration.[9] Acclimatization is hastened by modest salt deprivation and delayed by high dietary salt intake.

The cardiovascular system plays a major role in acclimatization and endurance training, largely resulting from an expansion of plasma volume. Heart rate is lower and associated with a higher stroke volume. Other physiologic changes include earlier release of aldosterone, although acclimatized individuals generate lower plasma levels of aldosterone during exercise heat stress. Total body potassium depletion of up to 20% (500 mEq) by the second week of acclimatization can occur as a result of sweat and urine losses, coupled with inadequate repletion.

Although many similarities exist among thermoregulatory responses to heat and exercise, the well-conditioned athlete is not necessarily heat-acclimatized. For heat- and exercise-induced adaptive responses to be maintained, heat exposure needs to continue intermittently, at least on 4-day intervals. Plasma volume decreases considerably within 1 week in the absence of heat stress.

Pathophysiology

Predisposing Factors

Advanced age, psychiatric conditions, chronic disease, obesity, and certain medications increase the risk for classic heatstroke during periods of high heat and humidity.[10] Adequate fluid intake is essential. Older adults often overdress during hot weather conditions. Heat loss is maximized by light, loose-fitting garments.

Exertional heatstroke is most likely to occur in young healthy people involved in strenuous physical activity, especially if they have not acclimatized to environmental factors that overwhelm heat-dissipating mechanisms. Fluid intake is the most critical variable. Dehydration can be minimized by education on work-rest cycles and fluid consumption and through provision of cool flavored fluids.

The goal is to maximize voluntary fluid intake and gastric emptying so that fluid can rapidly enter the small intestine, where it is absorbed. Gastric emptying is accelerated to 25 mL/min by large fluid volumes (500–600 mL) and cool temperatures (10°C–15.8°C [50°F–60.4°F]). High osmolality inhibits gastric emptying; osmolality of less than 200 mOsm/L is optimal. Most commercially available electrolyte solutions contain excessive

sugar. Hydration can be monitored by measurement of body weight before and after training or athletic competition. An athlete with a loss of 2% to 3% body weight (1.5–2 L in a 70-kg man) should drink extra fluid and be permitted to compete only when his or her body weight is within 0.5 to 1 kg (1 or 2 pounds) of the starting weight on the previous day. A weight loss of 5% or 6% represents a moderately severe deficit and usually is associated with intense thirst, scanty urine, tachycardia, and increase in rectal temperature of approximately 2° C (35.6° F). These athletes should be restricted to light workouts after hydration until they return to normal weight. A loss of 7% or more of body weight represents severe water depletion; participation in sports should not be permitted until the athlete is evaluated by a physician or sports trainer. Wrestlers frequently fast, restrict food and fluid intake, and exercise vigorously wearing vapor-impermeable clothing to lose weight quickly so that they can compete in a lower weight class.

The administration of salt tablets during strenuous exercise can cause delayed gastric emptying, osmotic fluid shifts into the gut, gastric mucosal damage, and hypernatremic dehydration. A 6-g sodium diet is sufficient for successful adaptation for work in the heat, with sweat losses averaging 7 L/day. Excessively high salt intake in relation to salt losses in sweat during initial heat exposure can impair acclimatization because of the inhibition of aldosterone secretion. Excessive salt ingestion can also exacerbate potassium depletion.

Evaporative cooling can be lost when clothing inhibits air convection and evaporation.[11] Loose-fitting clothing or ventilated fishnet jerseys allow efficient evaporation. Light-colored clothing reflects rather than absorbs light. Water evaporated from clothing is much less efficient for body cooling than water evaporated from the skin.

The body's heat dissipation mechanisms are analogous to the cooling system of an automobile (Fig. 133.2). Coolant (blood) is circulated by a pump (heart) from the hot inner core to a radiator (skin surface cooled by the evaporation of sweat). Temperature is sensed by a thermostat (CNS), which alters coolant flow by a system of pipes, valves, and reservoirs (vasculature). Failure of any of these components can result in overheating.

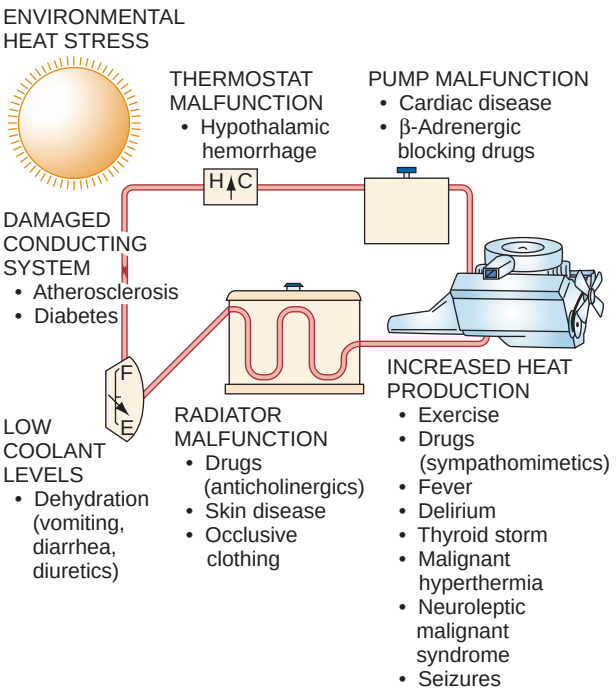


Fig. 133.2. Predisposing factors for heat illness, an automotive analogy.

Effective circulation requires an intact pump and adequate coolant levels. Individuals with cardiac disease or those taking β-adrenergic blocking agents or calcium channel blockers may be unable to increase their cardiac output sufficiently to produce the necessary peripheral vasodilation to dissipate heat. Dehydration caused by gastroenteritis, diuretics, or inadequate fluid intake predisposes to heat illness. Individuals working in the heat seldom voluntarily drink as much fluid as they lose and replace only approximately two-thirds of net water loss (so-called voluntary dehydration). Dehydration alone increases body temperature at rest by increasing the work of the sodium-potassium adenosine triphosphatase pump, which accounts for 25% to 45% of the basal metabolic rate. This is particularly true in cases of hypernatremic dehydration. The pipes and valves of the coolant system may be abnormal in diabetic or older patients with extensive atherosclerosis.

Radiator function depends on the skin and sweat glands. Occlusive, vapor-impermeable clothing hinders evaporative and convective cooling. Anticholinergic medications and stimulant drugs of abuse interfere with sweating and contribute to heat illness.[12] Various skin diseases, including miliaria (prickly heat rash), extensive burns, scleroderma, ectodermal dysplasia, and cystic fibrosis, are risk factors. Anhidrosis can also be secondary to central or peripheral nervous system disorders.

Increased heat production causing heat illness most often accompanies exercise in a hot humid environment. When heat and humidity are extreme, exertion is not necessary to produce heat-related problems. Several indices help objectify heat strain. These indices can be divided into two categories, heat scales based on meteorologic parameters and heat scales that combine environmental and physiologic parameters.

The wet bulb globe temperature heat index is an excellent meteorologic measure of environmental heat stress (Box 133.1). It includes the effects of temperature, humidity, and radiant thermal energy from the sun. When climatic conditions exceed 25° C (77° F) wet bulb, even healthy people are at high risk during exercise. Above 28° C (82.4° F), exercise and strenuous work should be avoided or limited to extremely short periods.

The heat strain index is widely accepted as an example of an index that includes environmental and physiologic factors. There are several variations and modified heat strain indices, with varying ease of use and accuracy.[13]

Fever Versus Hyperthermia

It is diagnostically and therapeutically important to identify patients suffering from a febrile response rather than heat illness. Fever does not cause primary pathologic or physiologic damage to humans and does not require primary emphasis in the therapeutic regimen, which is directed at the underlying disease state. If temperature-related physiologic changes, such as febrile seizures

BOX 133.1

Wet Bulb Globe Temperature (WBGT)

$WBGT = 0.7T_n + 0.2T_g + T_a$

T_n = "Natural" wet bulb temperature—the temperature achieved by a thermometer covered with a moistened white wick and left exposed to the ambient environment

T_g = Globe temperature—the temperature inside a blackened hollow copper sphere exposed to the ambient environment

T_a = Ambient temperature

These measurements can be done manually or calculated automatically with the help of computer algorithms.

and tachycardia, compromise a patient with marginal cardiac reserve, her or his temperature should be artificially regulated with antipyretics. These antipyretics are not effective against heat illness and are not recommended to control environmental hyperthermia.

MINOR HEAT ILLNESS

Prickly Heat

Principles

Prickly heat, also known as miliaria rubra, lichen tropicus, and heat rash, is an acute inflammatory disorder of the skin that occurs in tropical climates. It is the result of the blockage of sweat gland pores by macerated stratum corneum and secondary staphylococcal infection. The acute phase is characterized by vesicles in the malpighian layer of the skin, caused by dilation and rupture of the obstructed sweat gland ducts.

Clinical Features

Clinically, this initially produces intensely pruritic vesicles on an erythematous base. The rash is confined to clothed areas, and the affected area is often completely anhidrotic. During approximately the next week, a keratin plug develops and fills these vesicles, causing a deeper obstruction of the sweat gland duct. The obstructed duct then ruptures a second time, producing a deeper vesicle within the dermis. This is known as the profunda stage, and it can persist for weeks. Profunda vesicles are not pruritic and closely resemble the white papules of piloerection; chronic dermatitis is a common complication (Fig. 133.3).

Differential Diagnosis

Alternatives diagnoses include, contact dermatitis, cellulitis, and allergic reactions.

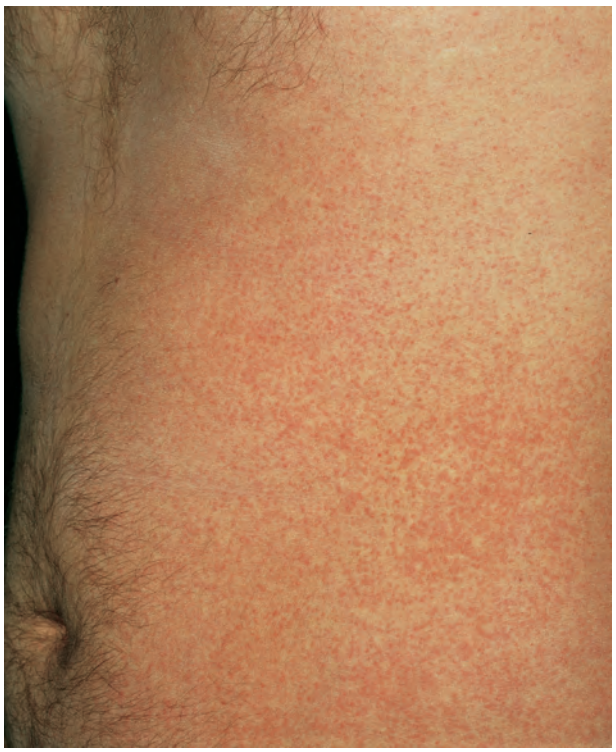


Fig. 133.3. Prickly heat. (From Habif TP: Clinical dermatology: a color guide to diagnosis and therapy, ed 3, St. Louis, 1996, Mosby.)

Diagnostic Testing

Laboratory data is generally not indicated in cases of prickly heat.

Management and Disposition

Chlorhexidine in a light cream or lotion is the antibacterial treatment of choice during the acute phase. Salicylic acid, 1% tid, can be applied to localized affected areas to assist in desquamation, but it should not be used in children or over large areas because of possible salicylate intoxication. For diffuse or pustular rashes, erythromycin can be helpful.

Patients can be discharged home, with a dermatologic follow-up. Prickly heat can be prevented by wearing light, loose-fitting, clean clothing and avoiding situations that produce continuous sweating. The routine use of talcum or baby powder should be avoided.

Heat Cramps

Principles

Heat cramps are brief, intermittent, and often severe muscle cramps occurring typically in muscles that are fatigued by heavy work. Heat cramps appear to be related to a salt deficiency. They usually occur during the first days of work in a hot environment and develop in persons who produce large amounts of thermal sweat and subsequently drink copious amounts of hypotonic fluid.

Clinical Features

Athletes, roofers, steelworkers, coal miners, field workers, and boiler operators are among the most common victims of heat cramps. Heat cramps tend to occur after exercise, when the victim stops working and is relaxing (Box 133.2). In this respect, they differ from the cramps experienced by athletes during exercise, which tend to last for several minutes, are relieved by massage, and resolve spontaneously.

Differential Diagnosis

Heat cramps are occasionally confused with hyperventilation tetany, which can occur during heat exhaustion. Hyperventilation tetany can be distinguished by the presence of carpopedal spasm and paresthesias in the distal extremities and perioral area.

Diagnostic Testing

Heat cramps accompanied by systemic symptoms may be part of salt depletion heat exhaustion. Heat cramp victims exhibit hyponatremia and hypochloremia, so serum electrolyte levels should be measured. Rhabdomyolysis or resultant renal damage is not present with isolated heat cramps.

BOX 133.2

Heat Cramps: Essentials of Diagnosis

Cramps of most worked muscles
Usually occur after exertion
Copious sweating during exertion
Copious hypotonic fluid replacement during exertion
Hyperventilation not present in cool environment

Management and Disposition

Heat cramps are usually rapidly relieved by salt solutions. Commercially available flavored electrolyte solutions are commonly ingested. Mild cases without concurrent dehydration are treated orally with a 0.1% or 0.2% salt solution (two to four 10-grain salt tablets [56–112 mEq] or ¼ to ½ teaspoon of table salt dissolved in 1 quart of water), which is the general limit of palatability. Severe cases respond rapidly to an intravenous (IV), isotonic salt solution (0.9% NaCl). Salt tablets are gastric irritants, delay gastric emptying, and are not recommended. Although most patients do not seek medical treatment, most people with heat cramps may be safely discharged after the administration of balanced salt solutions and clinical improvement.

Heat Edema

Principles

It is presumed that hydrostatic pressure and vasodilation of cutaneous vessels, combined with some degree of orthostatic pooling, lead to vascular leak and accumulation of interstitial fluid in the lower extremities. Simultaneously, the aldosterone level increases in response to the heat stress and perceived central volume deficit.

Clinical Features

Swollen feet and ankles are often reported by nonacclimatized individuals, especially older adults, who encounter climatic stresses of tropical and semitropical areas. Such individuals often have no underlying cardiac, hepatic, venous, or lymphatic disease. They commonly have schedules that involve long periods of sitting or standing. The edema is usually minimal, is not accompanied by any significant impairment in function, and often resolves after several days of acclimatization.

Differential Diagnosis

Heat edema should be differentiated from congestive heart failure, liver disease states, lower extremity infections, and deep venous thrombosis.

Diagnostic Testing

Awareness of this clinical presentation prevents overly vigorous diagnostic and therapeutic intervention. A brief diagnostic evaluation to rule out thrombophlebitis, lymphedema, or congestive heart failure is appropriate, but invasive diagnostic techniques are not indicated.

Management and Disposition

Pharmacologic therapy is not indicated, and diuretic therapy is not effective. Simple leg elevation or thigh-high support hose should be used. In most individuals, the problem resolves through adequate acclimatization or with the individual's return to a temperate climate. Given its benign nature, patients with heat edema can be safely discharged for outpatient management.

Heat Syncope

Principles

Individuals adapt to a hot humid environment by dilation of cutaneous vessels to deliver heat to the body surface. Thus, an increased portion of the intravascular pool is located in the periphery at any given time. Increasing blood flow to compliant cutaneous veins raises skin vascular volume at the expense of thoracic blood volume. Individuals who stand for protracted periods tend to pool blood in the lower extremities. Combined with volume loss and peripheral vasodilation, this pooling can result in inadequate central venous return, a concomitant drop in cardiac output, and cerebral perfusion inadequate to maintain consciousness.

Clinical Features

Heat syncope is a multifactorial disorder that results in a temporary loss of consciousness in the presence of heat exposure. Older adults have a special predilection for this disorder, with a host of concomitant underlying mechanisms.

Differential Diagnosis

The diagnosis of heat syncope requires the appropriate clinical setting and exclusion of other possible causes of syncope, given a patient's age and underlying medical disorders (see Chapter 12).

Diagnostic Testing

Heat syncope can be precipitated by an underlying metabolic or cardiac disorder, so cardiac monitoring, electrocardiography, and hemoglobin determination are warranted. Other tests are individualized based on clinical suspicion following a thorough history and physical examination (see Chapter 12).

Management and Disposition

The disorder is self-limited, and placing the patient in a horizontal position is generally curative. Older patients with comorbidities may require admission to address cardiac or neurologic causative factors. These individuals are at risk for recurrent heat syncope and should be warned to move often, flex leg muscles repeatedly when standing stationary, avoid protracted standing in hot environments, and assume a sitting or horizontal position when prodromal warning symptoms or signs occur.

MAJOR HEAT ILLNESS

Heat Exhaustion

Principles

Heat exhaustion (heat prostration) is a clinical syndrome characterized by volume depletion that occurs under conditions of heat stress. Two types of heat exhaustion are classically described, water depletion and salt depletion.

Water depletion heat exhaustion results from inadequate fluid replacement by individuals working in a hot environment and incapacitated individuals without free access to water. Those working in the heat seldom drink as much as they lose, and this voluntary dehydration results in progressive hypovolemia. Left untreated, water depletion heat exhaustion will progress to heatstroke because they are a continuum of the same disease.

Salt depletion heat exhaustion takes longer to develop than the water depletion form. It occurs when large volumes of thermal sweat are replaced by water with too little salt. It differs from heat cramps in that systemic symptoms occur. Symptoms are similar to those seen in water depletion heat exhaustion; the body temperature usually remains nearly normal.

BOX 133.3

Heat Exhaustion: Diagnosis

- Vague malaise, fatigue, headache
- Core temperature often normal; if elevated, <40° C (104° F)
- Mental function essentially intact; no coma or seizures
- Tachycardia, orthostatic hypotension, clinical dehydration (may occur)
- Other major illness ruled out
- If in doubt, treat as heatstroke.

BOX 133.4

Heat Exhaustion: Management

Rest
Cool environment
Assessment of volume status—orthostatic changes, blood urea nitrogen level, hematocrit, serum sodium concentration
Fluid replacement—normal saline to replete volume if the patient is orthostatic; replace free water deficits slowly to avoid cerebral edema.
Healthy young patients are usually treated as outpatients; consider admission if the patient is older, has significant electrolyte abnormalities, or would be at risk for recurrence if discharged.

Clinical Features

The symptoms and signs associated with both types of heat exhaustion are variable and include weakness, fatigue, frontal headache, impaired judgment, vertigo, nausea and vomiting and, occasionally, muscle cramps (Box 133.3). Orthostatic dizziness and syncope can occur. Sweating persists and may be profuse. The core temperature is only moderately elevated, usually below 40° C (104° F), and signs of severe CNS dysfunction (eg, altered mental status) are not present.

Differential Diagnosis

Mild heat exhaustion and full-blown heatstroke represent extremes of the spectrum of heat illness, and intermediate cases may prove difficult to differentiate. Nevertheless, heat exhaustion should not be diagnosed in the presence of major CNS dysfunction (eg, seizures, coma) or severe hyperthermia (40.5° C [104.9° F]).

Diagnostic Testing

This syndrome is characterized by hyponatremia, hypochloremia, and low urinary sodium and chloride concentrations. The creatine phosphokinase (CPK) level and renal function should be determined. Measurement of hepatic transaminase levels may prove helpful. Elevations to several thousand units can be seen in patients with heat exhaustion or in healthy runners after a marathon, whereas in patients with heatstroke, such levels are usually in the tens of thousands after 24 hours.

Management

Pure forms of either type of heat exhaustion are rare, and most cases of heat exhaustion involve mixed salt and water depletion. Heat exhaustion is primarily a volume depletion problem, and rapid recovery generally follows fluid administration. Decisions regarding the type of fluid and electrolyte replacements should be based on serum electrolyte level measurements and the estimation of hydration status by clinical and laboratory parameters.

Patients with significant volume depletion or electrolyte abnormalities require IV fluids. If the patient is orthostatic, normal saline should be administered until vital signs normalize. Free water deficits should be replaced slowly during 48 hours to avoid a decrease of serum osmolality of more than 2 mOsm/hr. Overly rapid correction of hypernatremia is associated with cerebral edema and seizures.

Disposition

Young, otherwise healthy patients who do not have significant laboratory abnormalities and who respond rapidly to hydration do not require hospitalization. These patients should be instructed to drink plenty of fluids and avoid heat stress for 24 to 48 hours. Older patients, particularly those with cardiovascular disease or other chronic diseases, may benefit from more cautious inpatient fluid and electrolyte replacement and frequent reassessment (Box 133.4).

Heatstroke

Principles

In the previously discussed forms of heat illness, although the body temperature rises, homeostatic thermoregulatory mechanisms remain intact. Heatstroke is the catastrophic life-threatening emergency that occurs when these mechanisms fail. This failure results in the elevation of body temperature to extreme levels, usually higher than 40.5° C (105° F), producing multisystem tissue damage and organ dysfunction.

As heatstroke develops, energy will be insufficient to sustain thermoregulatory mechanisms, resulting in dramatic increases in core temperature and the clinical manifestations of heatstroke. Tissue damage is a function of a complex interaction of body temperature, exposure time, workload, tissue perfusion, and individual factors. The exact temperature at which cellular damage begins to occur in an individual patient varies. Full recovery is possible, despite rectal temperatures up to 46.5° C (115.7° F).

Neurologic dysfunction is a hallmark of heatstroke, and cerebral edema is common. Other pathologic changes include petechiae in the walls of the third and fourth ventricles and marked cerebellar Purkinje cell damage.[14] Interestingly, the hypothalamus, the predominant site of central thermoregulatory control, is usually not damaged.

Heat stress creates tremendous demands on the cardiovascular system, and patients who succumb to heatstroke show signs of circulatory failure. Although such pathologic changes are common, cardiac damage alone is not lethal.

Prolonged heat stress produces impressive increases in skin blood flow (peripheral vasodilation) and a reduction of the thermal gradient between the core and the skin (Fig. 133.4). Functional hypovolemia is avoided by compensatory vasoconstriction of the splanchnic and renal vasculatures. The resulting splanchnic and renal ischemia may explain the nausea, vomiting, and diarrhea observed in runners after a marathon. Hepatic damage is a consistent feature of heatstroke, and its absence should cast doubt on the diagnosis.

If severe heat stress continues, compensatory splanchnic vasoconstriction will eventually fail, resulting in reduced mean arterial pressure and a continued cascade of exaggerated systemic inflammatory responses. Failure to perfuse the skin with heated blood from the core results in a dramatically increased rate of heat storage. This produces elevated intracranial pressure, which, in

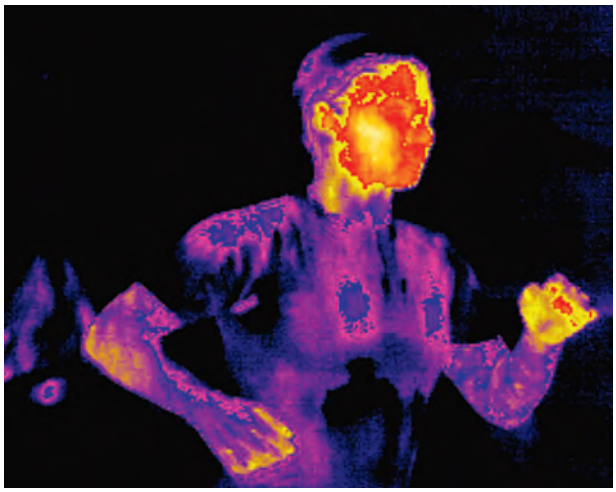


Fig. 133.4. Human infrared image. Note that the palms and face are substantially warmer than the rest of the body. (From Auerbach PS: Wilderness medicine, ed 6, Philadelphia, 2012, Mosby/Elsevier.)

BOX 133.5

Heatstroke: Diagnosis

- Exposure to heat stress, endogenous or exogenous
- Signs of severe central nervous system dysfunction (coma, seizures, delirium)
- Core temperature usually > 40.5° C (105° F), but may be lower
- Hot skin common, and sweating may persist
- Marked elevation of hepatic transaminase levels

combination with the reduction in mean arterial pressure caused by failure of compensatory splanchnic vasoconstriction, conspires to produce a decrease in cerebral blood flow. This results in the major CNS dysfunction characteristic of heatstroke.

Clinical Features

Heatstroke Versus Heat Exhaustion. The onset of heatstroke is sudden, and the patient's level of consciousness is altered. Prodromal symptoms lasting minutes to hours occur in approximately 20% of cases. These are nonspecific and may include weakness, dizziness, nausea, vomiting, anorexia, frontal headache, confusion, drowsiness, disorientation, muscle twitching, ataxia and signs of cerebellar dysfunction, and psychiatric symptoms, ranging from anxiety and irritability to psychosis. These prodromal symptoms are reminiscent of the description of heat exhaustion. Heat exhaustion, particularly the water depletion variety, can progress to heatstroke if untreated.

The usual manifestations of heatstroke include hyperpyrexia above 40.5° C (105° F), profound CNS dysfunction, and hot skin (Box 133.5). Persistent sweating can be observed in patients with rectal temperatures of 41.5° C to 42.4° C (106.7° F–108.3° F). In one large series of exertional heatstroke victims, sweating persisted in 50% of cases. Therefore, the cessation of sweating is not the cause of heatstroke, and continued sweating does not preclude the diagnosis.

Although in heatstroke the core temperature is elevated above 40.5° C (105° F), significant cooling may occur in the out-of-hospital phase, and the first temperature obtained in the emergency department (ED) may not represent the original maximum core temperature.

TABLE 133.1

Characteristics of Classic Versus Exertional Heatstroke

EXERTIONAL	CLASSIC
Healthy	Predisposing factors or medications
Younger	Older
Exercise	Sedentary
Sporadic	Heat wave occurrence
Diaphoresis	Anhidrosis
Hypoglycemia	Normoglycemia
DIC	Mild coagulopathy
Rhabdomyolysis	Mild CK level elevation
Acute renal failure	Oliguria
Marked lactic acidosis	Mild acidosis
Hypocalcemia	Normocalcemia

CK, Creatine kinase; *DIC,* disseminated intravascular coagulation.

Classic Heatstroke Versus Exertional Heatstroke. The two forms of heatstroke have significantly different presentations and manifestations—classic (epidemic) heatstroke (CHS) and exertional heatstroke (EHS; Table 133.1).

CHS occurs during periods of sustained high ambient temperatures and humidity, such as during summer heat waves. Victims are often older adults and poor and live in underventilated dwellings without air conditioning. Debilitated patients who have limited access to oral fluids may develop water depletion heat exhaustion, which progresses to heatstroke if untreated. Victims of CHS commonly suffer from chronic diseases, alcoholism, or schizophrenia, which predisposes to heat illness. Such patients are often prescribed medications (eg, diuretics, antihypertensives, neuroleptics, anticholinergics) that impair the ability to tolerate heat stress. Sweating ceases in most CHS patients. Factors such as advanced age, hypotension, altered coagulation status, and the necessity for endotracheal intubation on arrival at the ED predict a poor outcome, despite successful cooling measures.

In contrast, patients with EHS are usually young and healthy individuals whose heat-dispelling mechanisms are overwhelmed by endogenous heat production. Athletes and military recruits are typical victims. Rhabdomyolysis and acute renal failure, rarely seen in patients with CHS, are common in patients with EHS. Sweating is present in 50% of cases of EHS. Hypoglycemia may occur as the result of increased glucose metabolism and hepatic damage, resulting in impaired gluconeogenesis. Coagulopathy is common; the mechanism is depicted in Fig. 133.5.

Hyponatremia with serum sodium levels of less than 130 mmol/L has been detected in summer hikers in the Grand Canyon; many were found to have with neurologic symptoms or seizures. Signs of profound CNS dysfunction dominate the early course of heatstroke. Delirium or coma is characteristic, but virtually any neurologic abnormality, including bizarre behavior, opisthotonos, hallucinations, decerebrate rigidity, oculogyric crisis, and cerebellar dysfunction, can be seen. Convulsions occur in up to 75% of patients and can be precipitated by therapeutic cooling maneuvers. Profound muscle rigidity with tonic contractions, coarse tremor, and dystonic movements can mimic seizures. Pupils may be fixed and dilated, and the electroencephalogram may be isoelectric. All these changes are potentially reversible, although permanent damage, including cerebellar deficits, hemiplegia, dementia, and personality changes, is common in severe

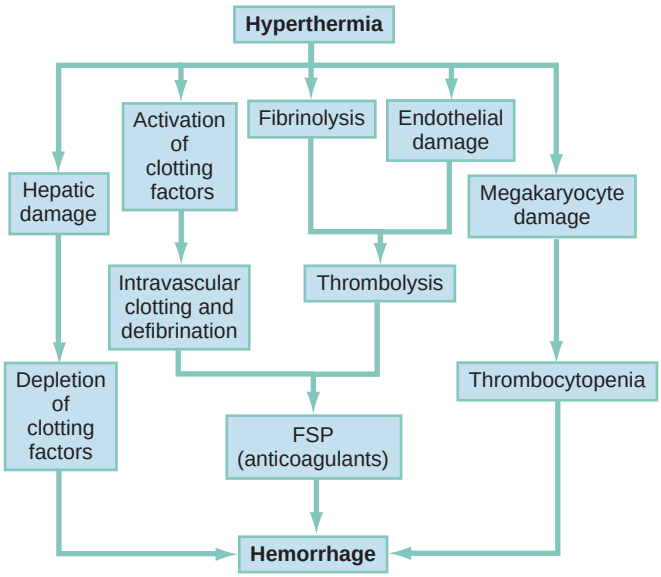


Fig. 133.5. Pathogenesis of hemorrhage. *FSP,* Fibrin split products.

cases. Patients with heatstroke usually have hyperdynamic cardiovascular systems with low peripheral vascular resistance, tachycardia (up to 180 beats/min), and an elevated cardiac index.[7] Elevation of cardiac troponin I is not uncommon with CHS; however, it is rarer in EHS. The central venous pressure (CVP) is usually elevated. The combination of elevated CVP with right-sided cardiac dilation suggests right-sided heart failure, which is also seen after shock or sepsis.[15] These changes are expected because skin blood vessels dilate to dissipate heat; however, this low peripheral vascular resistance has persisted in patients after reduction of body temperature to nearly normal.

Respiratory alkalosis is a physiologic response to active or passive heating and may be severe enough to produce tetany. Although most patients with CHS have respiratory alkalosis, those with EHS usually have a relatively pure lactic acidosis. Lactic acidosis is associated with a poor prognosis in cases of CHS but not necessarily in cases of EHS. Both CHS and EHS cause the hemoglobin-oxygen dissociation curve to shift to the right. An increase in the temperature denatures the bond between oxygen and hemoglobin, decreasing the concentration of oxyhemoglobin. Aberrations in coagulation are common in patients with severe heatstroke, and their presence is a poor prognostic sign. Abnormal hemostasis is manifested clinically by purpura, conjunctival hemorrhage, melena, bloody diarrhea, hemoptysis, hematuria, myocardial bleeding, or hemorrhage into the CNS. Diarrhea, probably caused by intense splanchnic vasoconstriction, is commonly seen. Cooling aggravates the diarrhea, creating an unpleasant treatment problem. Pancreatitis is described, with elevated serum amylase and lipase levels.

Differential Diagnosis

Heatstroke occurs when the thermoregulatory responses are overwhelmed and fail. If the patient is evaluated as this is occurring, differentiation between heat exhaustion and heatstroke is difficult. If heatstroke cannot be excluded, efforts to cool the patient should begin immediately. Only after the initial assessment and cooling have been initiated is the differential diagnosis relevant. When a history of collapse under conditions of heat stress is present, rapid improvement in mental status and blood pressure with cooling essentially eliminates alternative diagnoses. If, however, the temperature does not respond, and the patient does not recover neurologically, other causes of fever and coma should be considered (Box 133.6).

BOX 133.6

Differential Diagnosis of Heatstroke

- Central nervous system hemorrhage
- Toxins, drugs
- Seizures
- Malignant hyperthermia
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Thyroid storm
- High fever, sepsis
- Encephalitis, meningitis

Meningitis and Encephalitis. These can masquerade as heatstroke. In patients with heatstroke, the spinal fluid should be clear, with occasional lymphocytic pleocytosis and elevated protein levels. Cerebral falciparum malaria, which has a clinical picture of high fever and encephalitis, is seen in tropical areas where heat illness can also occur.

Thyroid Storm. In patients with thyroid storm, the clinical symptoms resemble those of heatstroke. It should be suspected if the thyroid gland is enlarged or nodular, but a normal thyroid gland does not exclude the diagnosis. Thyroid function test results are elevated, but these are not available on an emergency basis. Fortunately, thyroid storm is rare, and some critical aspects of treatment, such as rapid cooling, coincide with those for heatstroke.

Drug-Induced Heat Illness. This is an important consideration, particularly anticholinergic poisoning. Differentiation may be difficult because heatstroke and anticholinergic poisoning cause hyperpyrexia, hot and dry skin, tachycardia, and abnormal mental status. Constricted pupils are present in many heatstroke patients. Mydriasis should be present in patients with anticholinergic poisoning, and its absence argues strongly against this diagnosis. Typhoid fever, typhus, delirium tremens, and hypothalamic hemorrhage all produce a symptom complex similar to that of heatstroke.

Drug overdose of sympathomimetics or stimulants, such as amphetamines, cocaine, and phencyclidine, can cause fatal hyperpyrexia. A high ambient temperature is associated with a significant increase in mortality from cocaine overdose. Many younger patients who die of hyperthermia test positive for cocaine. Heatstroke can occur with delirium resulting from ethanol withdrawal. Aspirin and clopidogrel attenuates the skin vasodilatory response and shifts the onset of peripheral thermoeffector mechanisms toward a higher body temperature during exercise heat stress.[14] Heatstroke has occurred in well-trained military soldiers and athletes who ingested dietary supplements containing ephedrine or the ergogenic aid creatine. Some antipsychotics also cause suppression of thirst recognition. Individuals with a history of heatstroke, with or without an inherent aberration that predisposed them to the initial episode, are at increased risk for a recurrence.

Neuroleptic Malignant Syndrome. This is induced by antipsychotic medications and is characterized by muscle rigidity, severe dyskinesia or akinesia, hyperthermia, tachycardia, dyspnea, dysphagia, and urinary incontinence. Although the so-called lead

pipe rigidity and hyperthermia are reminiscent of malignant hyperthermia, the putative mechanism is different. Dopamine receptor blockade in the corpus striatum caused by butyrophenones (eg, haloperidol) and similar agents produces severe muscle spasticity and dystonia, leading to the overproduction of heat (see Chapter 155).

Serotonin Syndrome. This can also mimic heatstroke because of the elevated body temperature tremors, clonus, and CNS alterations that occur. Serotonin syndrome is classically a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities secondary to increased CNS serotonergic activity. A history of recent exposure to an illicit or therapeutic medication is an important clue (see Chapter 146).

Diagnostic Testing

Most standard measurements of body temperature vary significantly from the actual core temperature. Oral thermometry is affected by mouth breathing and is a poor approximation of the core. Rectal thermometry is less variable but responds to changes in core temperature slowly. Thermistors that are inserted 15 cm into the rectum offer continuous monitoring of temperature and have less variability. Although rectal measurements are slower to respond to changes in core temperature than tympanic temperature readings, rectal measurements are not biased by head skin temperature. An esophageal thermistor positioned adjacent to the heart is another option.

The hematologic evaluation should include arterial blood gas determination, complete blood cell and platelet counts, electrolyte values (including calcium), and glucose, blood urea nitrogen, and serum creatinine levels. Hypoglycemia with a serum glucose level less than 65 mg/dL is often found in cases of EHS. With the risk of acute rhabdomyolysis, the creatine kinase and myoglobin levels should be measured and urinalysis performed. Severe heatstroke can induce disseminated intravascular coagulation (DIC); therefore, prothrombin and partial thromboplastin times, international normalized ratio, and fibrin degradation products should be measured. Serum cardiac troponin I levels should be obtained.[12,16] Metabolic acidosis is common, especially in patients with EHS. Lactate levels are usually elevated and may persist or even worsen with improved extremity perfusion.

Renal damage is common. The initial urine specimen, usually obtained by catheterization, is a scanty, brownish, turbid fluid resembling machine oil. Microscopic examination reveals proteinuria, with abundant granular casts and red blood cells. Acute oliguric renal failure complicates 25% to 30% of EHS cases and 5% of CHS cases. The glomerular filtration rate, renal plasma flow, urine flow, and sodium excretion diminish markedly during exercise. Heavy physical exertion in hot climates produces acidic and maximally concentrated urine, which can result in acute oliguric renal failure in combination with hypotension and myoglobinuria.

Because heatstroke patients are prone to liver failure, aspartate transaminase, alanine transaminase, lactate dehydrogenase, and liver other enzyme levels should be monitored. Hepatic transaminase level elevations may be diagnostically helpful. In most febrile states that include altered mental status or coma, these enzyme levels will be normal or minimally elevated, although they are usually dramatically elevated early in the course of heatstroke. Hepatic damage is consistently featured in heatstroke. Hepatic injury is evidenced by markedly elevated levels of hepatic aminotransferases (serum aspartate transaminase and alanine transaminase). Early experimental models have shown that high-mobility group box 1(HMGB1) as a mediator of systemic inflammation is elevated in heatstroke, and its inhibition may be liver-protective.[15,17] Jaundice typically appears 24 to 72 hours after the onset of severe heatstroke and gradually recedes if the victim survives. Survivors generally have no permanent impairment of liver function.

Management

Cooling. Immediate cooling is the cornerstone of treatment. Patients who present to the hospital with heatstroke have high mortality rates ranging from 21% to 63%, and mortality increases significantly when cooling is delayed. A thermistor probe should be inserted as soon as possible, and the patient's temperature should be continuously monitored.

Evaporative cooling is recommended because it is effective, easy to perform, noninvasive, and less likely to interfere with other patient care activities than other cooling techniques. The patient is stripped of all clothing, and tepid tap water is sprayed while fans blow air continuously over the body, causing evaporative cooling. One reported method of evaporative cooling uses a body cooling unit on which the patient lies suspended on a net surface while being sprayed with atomized 15°C (59°F) water from above and below. Air warmed to 45°C to 48°C (113°F–118.4°F) is blown over the skin surface at a rate of 3 m/min. This approach maximizes evaporative cooling by maintaining cutaneous vasodilation and avoiding heat generation caused by shivering. When the patient's body temperature reaches 39°C (102.2°F), cooling measures should be discontinued to avoid hypothermic overshoot. Continuous monitoring is necessary to maintain the core temperature at 37°C to 38°C (98.6°F–100.4°F).

Immersion in ice water results in a rapid reduction of core temperature to below 39°C within 10 to 40 minutes but can complicate the resuscitation process. Vigorous skin massage to maintain cutaneous circulation has been advocated, but there is no evidence that this is efficacious. Military studies of EHS patients treated with ice water immersion have reported no fatalities or permanent sequelae. Immersion is technically difficult in the ED. Vasoconstriction from ice water immersion may be beneficial to hypotensive patients and may be better than evaporative cooling for victims in shock who have poor peripheral circulation.

Cooling modalities other than evaporation and immersion should be considered adjunctive treatments (Box 133.7). Application of ice packs to high heat transfer areas (eg, neck, groin, axillae) is commonly used. Cooling blankets may be a useful adjunct but will not produce rapid cooling if used exclusively. Cold irrigant gastric or rectal lavage will not provide significant heat exchange if used as the primary cooling modality. Antipyretics have no role in the treatment of heat-related illness.[18]

BOX 133.7

Cooling Modalities to Lower Body Temperature in Heatstroke

PREFERRED

Evaporative cooling with large circulating fans and skin wetting
Ice water immersion

ADJUNCTS

Ice packs to axillae and groin
Cooling blanket
Peritoneal lavage (unproven efficacy in humans)
Rectal lavage
Gastric lavage
Cardiopulmonary bypass

Resuscitation. Mortality correlates with the temperature and number of dysfunctional organ systems, with an increased risk of death if patients present with anuria, coma, or cardiovascular failure. Aspiration and seizures are common in patients with heatstroke, and airway control is indicated. Hypoxemia may occur because of aspiration, pneumonitis and pulmonary infarction, hemorrhage, or edema. Metabolic demands are high, and normal pulmonary ventilation may be inadequate in this setting.

Crystalloid fluid resuscitation is essential. Circulatory fluid requirements are modest in some cases, averaging 1200 mL of isotonic crystalloid solution in the first 4 hours. Pulmonary edema occurs in patients with heatstroke and can be exacerbated by overzealous fluid administration. The use of a CVP catheter to monitor fluid resuscitation may be deceptive. Most patients have a hyperdynamic circulation with a high cardiac index, low peripheral vascular resistance, and elevated CVP as a result of right-sided heart failure. These patients may require only modest IV fluids because cooling produces vasoconstriction and increases blood pressure. Hypotension is common in patients with heatstroke and is usually caused by peripheral vasodilation resulting in high-output cardiac failure in addition to dehydration. Blood pressure usually rises with cooling. If this does not occur, or if the patient being monitored invasively has a low CVP, a fluid challenge of 250 to 500 mL of 0.9% saline should be given rapidly while blood pressure, pulse, and urine output are monitored. Fluid replacement is continued until the blood pressure reaches 90/60 mm Hg or the CVP exceeds 12 mL H_2O. On occasion, patients exhibit hypodynamic responses with a low cardiac index, elevated CVP, and hypotension. These patients may be cyanotic, whereas patients with hyperdynamic circulation are initially pink. This clinical observation can be helpful in identifying patients who may respond to catecholamines.

A variety of tachyarrhythmias commonly occur during heatstroke. These usually resolve with cooling, and electrical cardioversion should be avoided until the myocardium is adequately cooled. The use of α-adrenergic agents such as norepinephrine is not recommended because they promote vasoconstriction without improving cardiac output or perfusion, decrease cutaneous heat exchange, and may exacerbate ischemic renal and hepatic damage. Atropine and other anticholinergic drugs that inhibit sweating should be avoided.

The pathophysiologic processes of heatstroke and fever differ, so antipyretics are not indicated and may be harmful. Salicylates, particularly in large doses, may worsen hyperthermia by uncoupling oxidative phosphorylation and aggravating coagulopathies. Large doses of acetaminophen can result in further hepatic damage. The efficacy of dantrolene has not been established.

If rhabdomyolysis is present, maintenance of urinary output of at least 2 mL/kg/hr is recommended. Urinary alkalinization higher than a pH of 6.5 should be considered early in these patients with acidemia, dehydration, or underlying renal disease. After volume repletion, administration of mannitol may be considered to increase intravascular volume and increase the glomerular filtration rate. Mannitol should not be used in an oliguric patient. Persistent anuria, uremia, or hyperkalemia is an indication for consideration of hemodialysis.

Cooling modalities that drastically lower skin temperature may induce violent shivering; this increases metabolic heat production and may impede cooling. IV benzodiazepines are the treatment of choice for shivering. The administration of neuroleptics, like chlorpromazine, should be avoided. These agents have anticholinergic properties that can interfere with sweating and cause hypotension or precipitate seizures. Many patients are extremely agitated during the initial cooling period. Short-acting benzodiazepines can be used for sedation and to control seizures. Barbiturates are less desirable because the metabolism is altered by hepatic dysfunction.

Coagulopathies can occur during the first day of illness but are more common on the second and third days. Initial treatment after cooling should include replacement therapy with fresh-frozen plasma and platelets. The emergency clinician should monitor the laboratory signs of DIC—(hypofibrinogenemia, elevated fibrin split products, prolonged prothrombin time, and thrombocytopenia. The bleeding diathesis seen in patients with heatstroke may be the result of fibrinolysis. Although α-aminocaproic acid can impede fibrinolysis, administration of this compound is associated with rhabdomyolysis, and its use is not recommended in patients with heatstroke.

Disposition

Patients presenting with classic or exertional heat stroke should be stabilized in the ED, with admission to an intensive care setting. Patients with more complex end-organ damage (eg, renal failure requiring dialysis) may require transfer to a center with more comprehensive tertiary care capabilities.

KEY CONCEPTS

- Classic heatstroke is generally diagnosed in older patients with comorbidities during heat waves, whereas exertional heatstroke is more common in young athletic patients or military personnel.
- Patients with exertional heatstroke are commonly diaphoretic.
- Rapid cooling of the potential heatstroke patient should be initiated before the diagnosis is firmly established. The most effective minimally invasive cooling measure is with evaporative techniques using cool mist sprays and standing fans.
- Antipyretics are ineffective and should not be used to control environmental hyperthermia.
- Heatstroke can cause right-sided cardiac dilation and elevated CVP and clinically resemble pulmonary edema, but still requires vigorous crystalloid resuscitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 133: QUESTIONS & ANSWERS

133.1. An 18-year-old female marathon runner presents to the ED during a hot summer race. She is extremely irritable and diaphoretic. She is complaining of generalized weakness, dizziness, nausea, and headache. The physical examination reveals an oral temperature of 40.5°C (105°F), heart rate of 120 beats/min, muscle twitching, and ataxia. What is the most appropriate management?

A. Assess her volume status and immediately start normal saline to replete volume loss before transfer to a hospital.
B. Encourage her to drink cold water to replace her free water deficit rapidly.
C. Immediately remove her from the hot environment and begin cooling before transfer to a hospital.
D. Prescribe immediate rest, after which she may be allowed to finish the race.

Answer: C. The onset of heatstroke is sudden. Prodromal symptoms lasting minutes to hours can occur that are nonspecific and similar to those of heat exhaustion. Signs and symptoms may include weakness, dizziness, nausea, frontal headaches, confusion, muscle twitching, ataxia and signs of cerebellar dysfunction, and psychiatric symptoms, ranging from anxiety and irritability to psychosis. Heat exhaustion can progress to heatstroke if it is untreated. If the patient is evaluated as this is occurring, differentiation between heat exhaustion and heatstroke is difficult. If heatstroke cannot be excluded, efforts to cool the patient should begin immediately.

Whereas rest is part of the treatment for heat exhaustion, it is not the only treatment. She must be removed from the hot environment, not be allowed to finish the race, and assessed for her volume status. Normal saline is used to replete volume if the patient is orthostatic; free water deficits are replaced slowly to avoid cerebral edema.

133.2. Which of the following statements regarding heat exhaustion is true?

A. It causes body temperatures that often exceed 40.5°C (105°F).
B. It exists in two discrete forms, salt depletion and water depletion.
C. It is associated with systemic symptoms.
D. It is characterized by hyponatremia and hyperchloremia.
E. It occurs when muscles are fatigued by heavy work.

Answer: C. Heat exhaustion is a clinical syndrome. Whereas there are typically two types of heat exhaustion, water depletion and salt depletion, pure forms of either type are rare. Most cases of heat exhaustion involve mixed salt and water depletion. In salt depletion heat exhaustion, the syndrome is characterized by hyponatremia, hypochloremia, and low urinary sodium and chloride concentrations. The symptoms and signs associated are variable and nonspecific but usually systemic, such as weakness, fatigue, frontal headache, vertigo, nausea, and vomiting. The body temperature usually remains nearly normal.

133.3. Despite cooling measures, poor outcomes are seen in heatstroke patients with which of the following?

A. Altered coagulation status
B. History of schizophrenia
C. Need for 100% oxygen
D. Presentation with acute renal failure
E. Presentation with acute rhabdomyolysis

Answer: A. Factors such as advanced age, hypotension, altered coagulation status, and the necessity for endotracheal intubation on arrival at the ED predict a poor outcome, despite successful cooling measures.

133.4. The usual characteristics of classic heatstroke include which of the following?

A. Diaphoresis
B. Disseminated intravascular coagulation
C. Hypoglycemia
D. Marked lactic acidosis
E. Usual occurrence during heat waves

Answer: E. Usual characteristics of classic heatstroke include predisposing factors or medication, older population, sedentary lifestyle, anhidrosis, normoglycemia, mild coagulopathy, mild elevation in creatine kinase level, oliguria, mild acidosis, and occurrence during heat waves. Diaphoresis, hypoglycemia, disseminated intravascular coagulation, and marked lactic acidosis are characteristics of exertional heatstroke.

CHAPTER 134

Lightning and Electrical Injuries

Kelly P. O'Keefe | Rachel Semmons

PRINCIPLES

Background

Electrical Injury

The first recorded death from electric shock occurred in 1879 in Lyons, France, after a carpenter sustained an injury from a 250-V alternating current source. The first electrocution in the United States occurred in 1901, when an intoxicated gentleman made contact with a DC generator terminal in front of a World's Fair crowd in Buffalo, New York. The patient's death appeared to be quick and painless, prompting the suggested use of electrocution for capital punishment.

Electrical injuries have a trimodal age distribution. Toddlers and younger children experience low-voltage injuries in the household as the result of contact with electric sockets and cords. Adolescents and young adults more frequently experience high-voltage injury from contact with electric lines outside of houses. Another peak occurs in the third to fourth decade of life, almost exclusively in men with occupational injuries due to high-voltage encounters with power lines and, to a lesser extent, from electric tools. Electrical injuries comprise only a small percentage of workers' compensation claims but are the second highest source of indemnity and paid medical claims, are responsible for many days of lost work, and are significant causes of permanent disability.[1] Electrical burns comprise only a small percentage of admissions to burn centers, but these patients have a more prolonged hospital course, require more interventions (eg, fasciotomies, escharotomies, amputations), and have higher mortality rates than patients with thermal burns.

Although electrical injuries from inadvertent household and occupational exposure have been on the decline, the use of electronic conduction weapons (eg, Tasers, stun guns) is increasing. These weapons, which deliver brief bursts of high-voltage, low-amperage direct current, are favored by law enforcement because they incapacitate subjects with minimal morbidity and lethality. Industry manufacturers report over 1.5 million discharges since these devices were made available for commercial use, and they are largely believed to be safe.[2]

Lightning

The incidence of lightning-related deaths in the United States has declined from a long-standing average of over 100/year to less than 40/year in recent times, perhaps as the result of American urbanization. Approximately 10% of lightning strike victims die, usually within the first hour from fatal arrhythmias or respiratory failure, and most survivors suffer permanent disabilities. Victims are most commonly young males who work or play outdoors in the spring and summer months, often during thunderstorms. Lightning usually strikes single victims but injuries to multiple victims can occur when a bolt lands in an outdoor group, often athletes or observers at sporting activities.

Physics of Electricity

Electrical Injury

The degree of injury from electrical shock depends on multiple factors, including the type of circuit, current, resistance (measured in amperes), voltage, duration of contact, and pathway of flow (Box 134.1).

Type of Circuit. Electrical sources create current that flows in one direction (direct current, DC) or alternates direction cyclically at varying frequencies (alternating current, AC). The few systems that use DC include batteries, automobile electronics, and railroad tracks. Exposure to DC most frequently causes a single, strong, muscular contraction. This may throw the subject back from the source in a way that limits duration of exposure but can result in other injuries. AC is more commonly used (eg, household currents) because it conveniently allows for an increase or decrease of power at transformers. It is more dangerous than DC of similar voltage because amperage above the so-called let-go current will cause muscular tetanic contractions. Because the flexor muscles of the upper extremities are stronger than extensor muscles, these contractions pull the victim closer to the source and result in prolonged exposure. Box 134.2 shows the physical effects of different amperage levels at a common 60-Hz AC exposure.

Capacitors store electric charge in circuits, and discharge from these devices may result in sudden bursts of very large amounts of electrical energy. Injury from a capacitor may occur even when the electrical device is not energized (plugged in), often involving the unwary repairman.

Current. Current is the flow of electrons down an electrical gradient. It is measured in units of amperage. According to Ohm's law, current is directly proportional to the voltage of the source and inversely proportional to the resistance of the material through which it flows. Key laws regarding the physics of electrical injury are summarized in Box 134.3.

Resistance. Resistance is the degree to which a substance resists the flow of current; it varies among body tissues. Neurovascular tissues are good conductors of electricity, whereas tendons, fat, and bone are relatively poor conductors (Box 134.4). Within a given tissue, resistance differs based on the fluid and electrolyte content of cells. Dry skin offers the largest resistance, up to 100,000 ohm (Ω) in thick, calloused skin, but dermal resistance decreases to as little as 1000 Ω when wet. Current that is initially unable to pass through skin will create thermal energy and cause significant burns. As the skin blisters and deteriorates, its resistance decreases.

Current may jump across skin surfaces in a behavior called arcing, resulting in prominent burns across flexor surfaces. Internally, current follows the path of least resistance, and the degree of burns seen on the surface typically underestimates the damage occurring below the surface. As current strength increases, the

BOX 134.1

Factors Affecting Electrical Injury

Circuit type
Amperage
Resistance
Voltage
Current pathway
Current duration

BOX 134.2

Physical Effects of Different Amperage Levels[a]

1 mA—barely perceptible
6–9 mA—usual range of let-go current
16 mA—maximum current that an average person can grasp and let go
20 mA—paralysis of respiratory muscles
100 mA—ventricular fibrillation threshold
2 A—cardiac standstill and internal organ damage

[a]At 60-Hz AC exposure.
From Centers for Disease Control. Worker deaths by electrocution: a summary of NIOSH surveillance and investigative findings. www.cdc.gov/niosh/docs/98-131/pdfs/98-131.pdf.

BOX 134.3

Electrical Formulas

$P = I^2RT$
$I = V/R$

I, Amperage of current; *P*, thermal power; *R*, resistance; *T*, time or duration of exposure; *V*, voltage.

BOX 134.4

Resistance of Body Tissues[a]

Lowest
Nerve
Blood vessels
Muscle
Skin
Tendon
Fat
Bone
Highest

[a]Lowest to highest.

relative resistance of tissues ceases to determine the pathway of current, and the entire body functions as a conductor.

Voltage. Voltage is the electrical potential, or difference in electrical energy, between two points. Joule's law, which describes the amount of thermal energy applied to tissues from electricity, is described by this formula:

$$P = I^2RT$$

where I is the amperage, R is the resistance, and T is the duration (time) that the electricity is applied. As the formula indicates, voltage is not the only factor responsible for damage, but it is often the only property that is known in cases of electrical injury. As a result, injuries are conventionally classified as being caused by high- or low-voltage sources, with 1000 V as the dividing line. In the United States and Canada, household sources are low voltage, typically 120 or 240 V. High-voltage injuries are impressively characterized by partial- to full-thickness skin burns, deep tissue destruction, and frequent cardiac or respiratory arrest. Low-voltage exposure causes less surface damage, but may be equally lethal, particularly in cases in which skin resistance is low.

Fig. 134.1. Taser X26.

Duration of Contact. The degree of tissue damage is directly proportional to the duration of exposure for all voltage levels. Exposure times greater than the length of one cardiac cycle tend to generate arrhythmias, likely in a manner analogous to the R-on-T phenomenon.

Pathway. The pathway followed by electrical current determines morbidity and mortality. The entrance and exit sites of the electrical current typically demonstrate greater evidence of skin damage, with full-thickness burns commonly encountered. These sites are properly referred to as the source and ground contact points. A patient may have one or multiple source and ground contact points. The most common locations are the hands, wrists, and arms, but children also present with burns from oral contact with electric cords or sockets. The most common ground contact points are the heels.

Electrical current passing through a limb causes greater local tissue damage than current passing through the trunk because the smaller cross-sectional area limits the ability to dissipate heat. However, current passing through the trunk results in greater mortality due to the involvement of more vital organs. Transthoracic pathways (arm to arm) are more likely to generate arrhythmias and have higher mortality rates than vertical currents (leg to arm) or straddle pathways (leg to leg).[3]

Conducted Electrical Weapons. The most commonly used conducted electrical weapon (CEW) is the Taser X26 (Fig. 134.1). The weapon consists of a hand-held unit with two barbs deployed through connecting cables. The sharp portions of these barbs are 9 mm thick (Fig. 134.2) and typically lodge in the skin, but can discharge current through clothing as well. The standard initial discharge is a 5-second burst of stimuli at 19 Hz. The peak voltage delivered to the subject is 1200 V, but the amperage is low, at 2.1 mA. The primary burst is followed by 100-msec pulses

Fig. 134.2. Taser barbs.

intended to inhibit myoneurons, causing the subject to fall to ground. These weapons can also be used as a direct contact device in a technique called drive stun. When used in this way, the unit's barbs are not deployed, and the subject experiences pain, but not muscular paralysis. Newer commercial devices designed for personal protection have the potential for increased amperage and time of exposure, thereby increasing the opportunity for more detrimental outcomes.[2]

Lightning Injury

Although the same basic scientific principles of electricity apply to lightning, there are several major differences. Lightning strikes involve hundreds of millions of volts, significantly more than those from electrical sources. In contrast, the duration of contact is drastically shorter, averaging 30 microseconds. As a result, current flow is altered, with a reduction in penetration causing less destructive tissue effects overall.

Lightning occurs as the result of a tremendous potential difference between positively and negatively charged particles. Water particles carried on warm updrafts rise from the earth and are cooled in the upper air, where cloud formation takes place. The phase change of the water from gas to liquid, and even solid, is associated with the generation of an electric charge. An intense electric field is created, with positive charges concentrated in the upper portions of the cloud and negative charges in the lower portions. The earth, which is normally negatively charged with respect to the atmosphere, becomes positively charged when the thunderstorm, with its negatively charged cloud base, passes overhead. A potential difference in charge as great as 100 to 300 million volts is created in this process. When the potential difference surpasses the resistance of the intervening air and other elements, a lightning bolt, like a huge spark, is generated. Initially, small sparks are emitted and travel a short distance from the ground upward, but these enlarge quickly as the distance between charged items shortens and the potential difference increases. Pilot strokes from the ground eventually meet a leader stroke from the cloud, a conducting pathway is formed, and a massive surge of electrical discharge follows. It takes approximately 20 milliseconds for a leader to reach the ground from the cloud, but only 20 microseconds for the return stroke from the ground up to be completed. Several discharges may take place in the same channel, with each discharge often exceeding 10 million volts. Thunder is a result of the superheating of the channel (estimated at 50,000° F [27,760° C]), which causes rapid expansion and compression of the local air, creating a tremendous sound pulse. Lightning takes various forms, described as streaked, forked, ribbon, sheet, or beaded. The most unusual form is ball lightning, which appears as a globe, rolls along structures, and may even pass through open doors or windows. Strikes occur from cloud to cloud, cloud to ground, or even ground to cloud.

Lightning may strike a person directly, strike a tree or other object and injure anyone in direct contact with it (contact voltage), or strike its target and then travel through the air to affect the victim (side flash, or splash injury). A person's chances of being struck are increased by wearing or carrying metal objects or other conductors. Side flashes may travel as far as 30 m after striking the first object to affect another. Lightning may also strike the ground and be conducted to the victim. A greater distance from the ground strike lessens transmission of the charge. The risk of injury from a ground strike is increased when one contact point on the victim (eg, the right foot) is closer to the strike than a second contact point (eg, the left foot), thus creating a potential difference. This is referred to as stride voltage and is likely responsible for cattle deaths in a pasture after a thunderstorm. Hence, when out in the open during a storm, caution must be taken to place an insulating material, such as a raincoat, between the ground and the body and assume the lightning position—a squatting configuration with the feet together—or to curl up in a ball on the ground to reduce the number of contact points. Box 134.5 lists tips for avoiding lightning strikes.

Injury occurs from the force of a strike, blunt trauma effects when the victim is thrown, the superheating of metallic objects in contact with the patient, blast-type effects and barotrauma, or shrapnel.

BOX 134.5

Tips to Avoid Lightning Strike

- Seek shelter inside an enclosed building or metal-topped automobile.
- Avoid large flat, open areas or hilltops.
- Avoid contact with metal objects and remove metal objects, such as jewelry or hairpins.
- Avoid trees, boats, and open water.
- If caught on open ground, curl up on your side with hands and feet close together to reduce contact points, or squat with feet together. If possible, place a rubber raincoat under your body or feet to reduce ground current effects.
- If in a forest, seek shelter under a thick growth of shorter trees.
- If indoors, avoid the use of wired phones and contact with plumbing or electrical appliances.

CLINICAL FEATURES

Electrical Injury

General Tissue Effects

At the cellular level, current causes damage to cell membranes and alters membrane solubility, leading to electrolyte abnormalities and cellular edema. This process, termed *electroporation*, eventually leads to irreversible cell damage and death.[3] At the tissue and organ levels, electrical current produces damage when electrical energy is converted to thermal energy.

Skin

Most electrical injuries result in skin burns, which fall into one or more of four patterns (Box 134.6). The relatively high resistance

Fig. 134.3. Kissing burn. (Courtesy Dr. Mary Ann Cooper.)

BOX 134.6

Types of Burns Associated With Electrical Injury

Entrance and exit site burns
Arc burns, kissing burns
Thermal burns
Flash burns

of skin in many cases leads to significant partial- or full-thickness burns at entrance and exit sites, most commonly seen over the upper extremities, particularly at the hand and wrist. The skull is another common source contact point. Visible burns may be insignificant in comparison with the damage that occurs beneath the surface and, as a result, are associated with significantly greater morbidity than simple thermal burns involving a similar surface area. Burns at entrance and exit sites will typically have a punctate appearance, with central depression and necrosis surrounded by a hyperemic border.

Arc burns, or so-called kissing burns (Fig. 134.3), occur when electricity jumps from skin surface to skin surface, typically across flexed areas of the body. Temperatures may reach 3500° C (6332° F) and cause severe damage. Arc burns are usually noted across the volar forearm and elbow and along the inner arm and axilla.

In cases in which clothing catches fire, patients also experience typical thermal burns. Flash burns are skin burns caused by brief, intense flashes of light, electrical current, or thermal radiation. Cutaneous burns across the chest and upper abdomen hint at transthoracic current and a worse prognosis.[3]

Cardiovascular System

Cardiac or respiratory arrest is the most common cause of death immediately following electrical injury. Traditionally, it is believed that AC causes ventricular fibrillation and DC causes asystole. In reality, exposure to either type of circuit is associated with both dysrhythmias.[3] Respiratory arrest may occur as a result of tetanic paralysis of the thoracic respiratory muscles or as a result of damage to the brainstem respiratory centers. Prolonged apnea in these situations leads to hypoxic cardiac arrest.

Dysrhythmias are seen immediately or in a delayed fashion following electrical injury. These include malignant arrhythmias, but more frequently involve sinus tachycardia or bradycardia, atrial fibrillation, and ectopic beats. A variety of electrocardiographic abnormalities may be present, including transient ST elevation or depression that does not correlate with myocardial ischemia or infarction. Injury to coronary arteries or directly to the myocardium may result in infarction, but this is rare. Nonspecific cardiac biomarker levels are frequently elevated in the period following electrical injury, but this is usually due to skeletal muscle injury and is only rarely related to cardiac damage.

Head and Neck

Ocular involvement is common following exposure to electrical current, with cataracts being the most frequent manifestation. Other forms of injury include vitreous and anterior chamber hemorrhages, retinal detachment, macular lacerations, and corneal or conjunctival burns. Injury to structures of the ear is less common, but sensorineural deafness can be seen as a result of nerve damage. Patients frequently develop vertigo, which may be transient or persistent.[4] Toddlers and young children sustain orofacial injuries after chewing or sucking on electrical cords or from lingual contact with sockets. Full-thickness burns may be sustained on the mucous membranes and lips, with destruction to the tongue and teeth as well. Injuries to the oral commissure produce cosmetic difficulties and, more significantly, the well-recognized complication of delayed labial artery bleeding, typically occurring 2 days after injury, when the resultant eschar separates from the wound.[5]

Extremities

Neurovascular bundles have low resistance and are particularly prone to damage from electrical current. Muscle necrosis occurs primarily or is secondary to compromise of the blood supply. Vascular injury is most prominent at the intimal and medial layers. Involvement of the intima results in immediate coagulative necrosis and thrombosis, whereas injury to the media causes aneurysmal dilation and hemorrhage in a delayed fashion. Decreases in tissue perfusion lead to edema and tissue death. Areas of infarction may be distributed sporadically throughout the injured region, with areas of surviving tissue adjacent to necrotic tissue. Muscle that initially appears viable may deteriorate with time, especially in the periosteal regions. Endothelial and smooth muscle function are depressed for many weeks following the initial injury, contributing to a hypercoagulable state that increases the risk of delayed deep venous thrombosis.[6] The combination of tissue edema and perfusion defects makes compartment syndrome likely, with fasciotomy and even amputations required. Cyanosis or pulselessness may be transient or may indicate permanent damage; in a similar fashion, limbs that appear initially well perfused may later necrose.[7]

Bony injury is common. Because bone is highly resistant to electrical current flow, great amounts of heat are generated, resulting in periosteal burns and osteonecrosis. Exposure to DC typically causes a single, strong muscle contraction, throwing the victim away from the electrical source. This can result in a variety of skeletal injuries, including fractures or dislocations. Exposure to AC causes muscular tetany, which occasionally results in similar skeletal injuries.

Nervous System

Electrical injury damages the central and peripheral nervous systems. The most common immediate central symptoms are altered mentation, seizure, and/or coma. Seizures may occur as an isolated event or as a lasting seizure disorder. Vascular injury may cause cerebral infarction, and secondary trauma may result in intracranial hemorrhage. Cerebral venous sinus thrombosis has been reported.

Patients may experience transient spastic paralysis with accompanying sensory deficits immediately following electrical injury.

Delayed and chronic manifestations include ascending paralysis, transverse myelitis, and amyotrophic lateral sclerosis. Peripheral neuropathies are a common result, most often involving the median and ulnar nerves.

Neuropsychiatric sequelae include anxiety, depression, mood lability, difficulty concentrating, and insomnia. These may become a persistent source of disability.[8]

Other Viscera

Extensive muscle damage may result in significant myoglobinuria, subsequent renal failure, and life-threatening hyperkalemia. These complications are more likely in patients who are hypotensive or volume-depleted.

Stress ulcers are a common gastrointestinal complication. Uncommon but severe intra-abdominal injuries include a ruptured hollow viscus and necrosis of the pancreas or gallbladder. Pulmonary edema is rare. Although early deaths are due to respiratory and cardiac arrest, late deaths occur from sepsis, pneumonia, and renal failure. For obstetric patients, the overall risk to the fetus is small, but a spontaneous abortion can occur. Secondary trauma may lead to placental abruption.

Clinical Features After Discharge of a Conducted Electrical Weapon

Most patients who sustain shock from a CEW do not need medical treatment. Barbs usually attach to the chest or back, although there is potential for penetration of more sensitive areas, such as the genitals, face, eyes, or skull. Patients frequently have minor transient increases in heart rate and variable effects on blood pressure. Transient, clinically insignificant electrocardiographic changes include sinus arrhythmia, PR shortening, and ST changes. More concerning findings, such as alterations in QRS or QT intervals, have not been reported. At least one study has demonstrated no significant increases in troponin after discharge. Secondary injuries rarely result from the victim falling to the ground while incapacitated. Use of these devices has been cited as a potential factor in police custody deaths of patients with multiple comorbidities including psychiatric conditions, intoxication, and excited delirium, although the mechanism is unknown and the causation unclear.[2]

Lightning Injury

Cardiovascular System

The most severe effects of lightning strike are cardiac and respiratory arrest. The massive surge causes cardiac standstill and cessation of all respiratory efforts. Therefore, the initial arrhythmia is asystole. At some point, the intrinsic pacemaker activity of the heart brings about a resumption of cardiac activity. However, if the respiratory center has not been reactivated, hypoxia follows, and the cardiac rhythm will deteriorate into ventricular fibrillation. Research into the actual effects of lightning on humans is limited but it has been interestingly hypothesized that the strike leads to a state of suspended animation and cessation of metabolism in all cells, including the brain.[3] This may explain reports of successful resuscitation and full recovery of lightning strike victims after being apneic and pulseless for 15 minutes and following resuscitations lasting up to 8 hours. This observation has led to the practice of treating the apparent dead first at the scene of a multiple-victim lightning strike because early resuscitative efforts may prevent death.

Myocardial contusion from the lightning shock wave is the most common pathologic finding. Myocardial infarction from prolonged hypoxia can occur. A variety of dysrhythmias may arise, generally resolving with time. A lightning strike in close proximity to a patient with an automatic implantable cardioverter defibrillator can cause firing of the device. A number of electrocardiographic changes, usually with gradual resolution, have been reported (Box 134.7).

BOX 134.7

Electrocardiographic Changes Seen With Lightning Strike

ST segment elevation
QT interval prolongation
Atrial fibrillation
Inverted or flattened T waves
Myocardial infarction pattern without cardiac sequelae

Nervous System

A wide variety of very serious neurologic effects follow lightning strike. Apnea, due to effects on the medullary respiratory center, may persist for several hours. Direct trauma may result in skull fractures, intracerebral and extracerebral hematomas and hemorrhages, cerebral edema, and elevated intracranial pressure. More common findings include transient loss of consciousness, amnesia for the event, and transient paresthesias and paralysis of the extremities.[9] Charcot, in 1889, described the phenomenon termed *keraunoparalysis*, with the victim of a strike awakening to find himself or herself on the ground, unable to move the limbs. This flaccid paralysis, which is usually accompanied by marked vasomotor changes that result in extremities that appear blue, mottled, and pulseless, may persist up to 24 hours. The lower extremities are more commonly involved, and the typical pattern is recovery over minutes to days.

Prolonged loss of consciousness may be related to trauma or hypoxia. So-called miraculous recoveries have been documented, despite prolonged arrest and apnea. Conversely, death may occur rapidly from massive brain swelling and herniation. Permanent peripheral nerve damage can occur. Other neurologic sequelae include seizures, cerebellar ataxia, Horner's syndrome, cognitive dysfunction, facial nerve palsy, neuritis, and neuralgia.

Some psychiatric effects are predictable, usually anxiety and a logical fear of thunderstorms. Other negative effects include prolonged depression, sleep disturbances, nightmares, nocturnal enuresis, and separation anxiety. Hysterical blindness, deafness, and muteness have been observed.

Skin

Roughly 90% of lightning strike victims suffer skin burns, but less than 5% are deep burns. Although the voltages involved in a strike are substantial, the duration of contact is so brief that significant damage does not usually occur. Skin resistance is typically lessened by rain or perspiration, contributing to the flashover effect, where current preferentially flows over the integument rather than through it (following the path of least resistance). The result is the arborescent or fernlike patterns of erythematous streaks (typically first-degree burns) that have been termed *Lichtenberg figures* (Fig. 134.4). Deeper burns may occur at the direct point of contact or wherever metal is involved (due to superheating), such as with a belt buckle or jewelry. Clothing may catch on fire, resulting in thermal burns. Unlike conventional high-voltage electrical exposures, exit wounds are not seen, and the overall effects are much less severe.

Fig. 134.4. Lightning burn. (Courtesy Dr. Mary Ann Cooper.)

Ears

The tympanic membranes of patients involved in lightning events are commonly ruptured due to the shock wave and blast effect produced by the rapid expansion of the air as lightning passes through it. Bleeding and cerebrospinal fluid leaks may accompany this injury. Other effects include hearing loss, tinnitus, vertigo, and nystagmus. Specific injuries include avulsion of the mastoid process, ossicle damage, rupture of Meissner's membrane, and strial degeneration.[10]

Eyes

The most common ocular event after lightning strike is the development of cataracts, occurring immediately or in a delayed fashion. Damage to almost every part of the eye has been described. Fixed and dilated or asymmetric pupils due to autonomic dysfunction may accompany a strike, a finding that by itself should not prevent resuscitative efforts.

Other Injuries

The lungs, gastrointestinal tract, and other internal organs may suffer injury from blunt trauma or a blast effect. Strikes to the face may produce damage to the tongue and oral structures, esophagus, and trachea. Various fractures, dislocations, and soft tissue injuries occur. Myoglobinuria is relatively unusual due to the brief duration of contact.

Vasomotor changes may occur at the time of the strike and can last for variable periods. Mottling or cyanosis appears, and pulses may be absent. Vascular changes mimic those seen in compartment syndromes, but fasciotomy is generally not indicated. When pregnant women are struck by lightning, the effects on the fetus are not predictable.

DIFFERENTIAL DIAGNOSES

Electrical Injury

Most electrical injuries are self-evident, except in bathtub accidents and other water-related situations where there is an absence of witnesses to the events and evidence of skin burns. In such cases, patients may present with cardiac arrest, dysrhythmias, or altered mentation.[3] Victims of known electrical injury who present with altered mentation may be suffering from one or more of the following: electrical injury of the central nervous system, associated traumatic brain injury, or underlying metabolic disease.

BOX 134.8

Findings Suggestive of a Lightning Strike

Clothing wet from rain
Tears or disintegration of clothing
Multiple victims
Typical arborescent pattern of erythema or superficial linear or punctate burns
Tympanic membrane injury
Cataracts, especially in a younger patient
Magnetization of metallic objects on the body or clothing
Electrocardiographic changes

Lightning Injury

In cases in which lightning strikes are not witnessed, they may be suspected in patients presenting with altered mentation during thunderstorms in the presence of typical skin burn patterns or when their clothes have burst off, appear singed, or have punctate holes or metal pieces (zippers or grommets) that show signs of melting. Other suggestive findings are listed in Box 134.8.[1] The differential diagnosis of altered mentation in lightning strike victims is the same as that of other high-voltage injuries.

DIAGNOSTIC TESTING

Electrical Injury

No evidence-based guidelines direct the ancillary testing of electrical injury victims. We believe that testing is not indicated for victims of low-voltage electrical injuries who are asymptomatic or have minimal localized symptoms and physical evidence of burn injury. Evaluation for underlying injury should be undertaken in patients who have been exposed to high-voltage sources and those who, regardless of the source voltage, have lost consciousness or present with altered mentation or neurologic deficits, other significant symptoms, entrance and exit wounds, and/or burns assessed as being more than superficial partial-thickness burns.

Because the location and extent of injury cannot be predicted clinically, we recommend electrocardiography, complete blood count, determination of basic serum electrolyte, serum myoglobin and troponin, blood urea nitrogen, and serum creatinine levels, renal function studies (blood urea nitrogen and creatinine), and urinalysis, with testing for myoglobin. Patients suspected of intra-abdominal injury from electrical current or associated trauma should have hepatic and pancreatic enzyme levels measured and coagulation studies performed. Radiographs of injured extremities are indicated; computed tomography or magnetic resonance imaging should be used when intracranial, spinal, intra-abdominal or pelvic injuries are clinically suspected.

Lightning Injury

The Wilderness Medical Society has recommended that an electrocardiogram (ECG) be obtained on lightning strike victims with high-risk indicators, such as suspected direct strike, loss of consciousness, focal neurologic complaint, chest pain or dyspnea, associated traumatic injuries, pregnancy, and burns of the cranium or legs or on more than 10% of the total body surface area.[11] Cardiac markers are often elevated in victims of lightning strikes, but they do not correlate with myocardial injury and are not prognostic. Patients with altered mentation or symptoms and signs suggestive of traumatic injury should be evaluated

thoroughly because of the massive shock wave and muscle spasm associated with lightning strikes.

Complaints of diffuse muscle pain or findings of compartment syndrome should prompt evaluation for rhabdomyolysis and vascular sufficiency, bearing in mind that lightning has unique effects on the vascular system of extremities that often clear without sequelae.

MANAGEMENT

Electrical Injury

Low-voltage electrical injuries associated with minimal signs and symptoms generally require only local wound treatment and patient reassurance. The treatment of other patients is directed at the organ systems involved.

Patients who present in cardiopulmonary arrest should be resuscitated, regardless of cardiac rhythm, because good outcomes have been documented in patients presenting in asystole. Patients with electrocardiographic signs of cardiac injury or dysrhythmias and patients with more than minimal local signs and symptoms should be monitored in the emergency department (ED), observation unit, or inpatient setting, depending on the extent and severity of associated injuries. Dysrhythmias are treated according to advanced cardiovascular life support (ACLS) guidelines. Hypotension may be caused by third spacing of intravascular volume secondary to electrical injury of deep tissues, so fluid management is similar to that of crush injuries, often requiring much more fluid than typically recommended by thermal burn wound protocols. Intravenous crystalloid fluids are given to maintain adequate urine output: over 100 mL/hr in adults and 1.5 to 2 mL/kg/hr in young children. Serum potassium levels should be closely monitored in patients with renal insufficiency or myoglobinuria. Importantly, hypotensive patients should be evaluated for possible blood loss from associated traumatic injuries.

Patients with myoglobinuria should be monitored with determination of serial serum myoglobin levels and renal function studies. The management of rhabdomyolysis is discussed in Chapter 119.

Injured extremities require burn wound management (see Chapter 56). They should be monitored for the development of compartment syndromes (see Chapter 42).

Patients injured by CEWs rarely need intervention or ancillary testing. Retained barbs can be removed with firm in-line traction.

Lightning Injury

Lightning strike victims who present without symptoms or signs of injury, including those with minor first-degree burns (see Fig. 134.4), do not require treatment in the ED unless their electrocardiograms show signs of ischemia or significant dysrhythmias.

Patients who present with altered mentation or significant symptoms are approached in a manner similar to that used for victims of high-voltage electrical injury. However, a few differences should be noted.[11,12] Lightning strikes can result in a spectrum of peripheral and central neurologic injuries, including pupils that are dilated and fixed in the absence of irreversible brain injury. This factor should be kept in mind when deciding when to discontinue resuscitative efforts in patients who present in cardiac arrest. Lightning strikes can cause extensive catecholamine release or autonomic stimulation, resulting in transient hypertension and tachycardia that can be treated with β-adrenergic blockers and hydralazine or with alpha blockers, such as clonidine, to reduce adrenergic excesses.[13]

Although AC causes thrombotic injury to blood vessels, DC can result in transient vasospasm that results in extremities that appear blue, mottled, and pulseless. This should be kept in mind when deciding when surgical intervention is indicated. Skin and vascular findings are likely to resolve with supportive care only but, if significant thrombosis (immediate or delayed) develops, amputation may be required. The presence of pulseless and mottled extremities may limit the ability to detect hypotension with basic tools, and central monitoring lines may be required to assess volume status correctly.

DISPOSITION

Electric Injury

Asymptomatic patients who present after low-voltage exposures may be safely discharged. Other patients will be monitored and treated in the ED, observation unit, or inpatient setting, depending on their clinical status and extent and severity of identified injuries. Patients with significant burns should be stabilized and transferred to a burn unit, if available.

Pediatric patients with oral electric injuries are usually hospitalized for hydration, wound and pain management, and plastic surgery consultation. Patients with minor burns confined to the oral commissure can be discharged with close follow-up but should be provided with information regarding the possibility of delayed labial artery bleeding, which can be managed by the parents with direct pressure and a return visit to the ED.

Pregnant patients should receive a period of fetal monitoring when age-appropriate. Women who are subsequently discharged should be counselled regarding the remote risk of spontaneous abortion and referred for high-risk obstetric follow up. Patients may experience delayed neuropsychiatric sequelae, so discharge instructions regarding this possibility should be provided.

Lightning Injury

The Wilderness Medical Society has recommended that victims of direct lightning strikes and those with an abnormal ECG be monitored with telemetry for a minimum of 24 hours.[11] Other patients can be discharged but should be counselled regarding the need to seek further care if they develop delayed-onset symptoms, which can be cardiopulmonary, neurologic, psychiatric, ophthalmologic, or otolaryngologic in nature.

KEY CONCEPTS

- Electrical current follows the path of least resistance, often neurovascular bundles. Deep tissue and organ damage is often much more extensive than would be indicated by examination of the overlying skin.
- Testing is not indicated for victims of low-voltage electrical injuries who are asymptomatic or have minimal local symptoms and physical evidence of burn injury. These patients may be discharged home after evaluation.
- Testing is indicated for patients exposed to high-voltage sources and those with syncope, altered mentation, or any other neurologic abnormality, significant burns, entry and exit wounds, or significant ongoing symptoms. Testing should include electrocardiography, complete blood count, basic chemistry panel, myoglobin and troponin level determination, and urinalysis. Additional testing is directed at suspected areas or injuries.
- Patients with electrocardiographic signs of cardiac injury or dysrhythmias, or with evidence of significant local injury, should be monitored for at least 6 hours in the ED, observation unit, or inpatient setting.
- The enormous current of a lightning strike may cause critical injury or death, or the current may be directed superficially over the patient to the ground, resulting in no injury or only superficial burns.
- Electrocardiography is indicated for all patients evaluated for lightning strike. Additional testing should be based on specific signs and symptoms.
- Lightning strike patients who present without symptoms or signs of injury, or with only minor first-degree burns, and with a normal ECG can be discharged home after evaluation. Patients who present with altered mentation or significant symptoms are evaluated in a manner similar to that used for victims of high-voltage electrical injury.
- Lightning strike can cause fixed, dilated pupils in the absence of irreversible brain injury.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 134: QUESTIONS & ANSWERS

134.1. A man walking through a park after a storm accidentally steps on a downed electrical wire and is rendered unconscious. Before rescuing him, how can prehospital providers ensure their own safety and that of bystanders?

A. Call the power company to disconnect the power.
B. Loop a leather belt around the wire to move it.
C. Use a dry rope to loop around the wire and pull it away from the victim.
D. Use a tree branch or piece of wood, such as a 2 by 4, to move the wire.
E. Use electrical gloves to move the wire manually.

Answer: A. The prime tenet of rescue work is create no further victims. The only safe and reliable way to ensure that the power is off is to notify the power company to have the power turned off. None of the other choices is safe, and they could result in severe injury to the rescuer using them.

134.2. A 37-year-old woman presents with blurred vision. Her vision has been progressively worsening for approximately 2 months. She denies eye pain or direct eye trauma. She reports that approximately 2 months ago, just before the beginning of her vision problems, she was struck by lightning while playing golf. She states that she went to an emergency department (ED) at that time, had no major injuries, and seems to have recovered well. What is the most likely cause of her decreased vision?

A. Cataracts
B. Glaucoma
C. Iritis
D. Macular degeneration
E. Retinal detachment

Answer: A. Cataracts are a well-known complication of electrical injury, either from artificial electrical sources or from lightning. They may occur immediately or have a delayed presentation. Approximately 6% of victims of electrical injury develop cataracts. Glaucoma is due to elevated intraocular pressure and is often painful. Iritis and retinal detachment can be caused by electrical injury but are manifested acutely. Macular degeneration is a chronic condition of older adults with central vision loss and is not associated with electrical injury. Macular holes may occur acutely with lightning injury.

134.3. A 42-year-old man suffers an electrical injury while working on power transmission lines near your hospital. Paramedics report that he is unresponsive and that he was initially in ventricular fibrillation but spontaneously converted to sinus tachycardia before treatment. His initial electrocardiogram (ECG) from the field shows ST segment elevation in the inferior leads. An ECG repeated in the ED shows continued inferior ST segment elevation but with decreased magnitude. Creatine kinase (CK) and CK-MB levels are markedly elevated. He continues to be unresponsive, has no spontaneous respirations, and has bilateral fixed and dilated pupils. What is the appropriate next action?

A. Brain death testing
B. Cardiac catheterization
C. Mannitol infusion
D. Observation and supportive care
E. Thrombolytic administration

Answer: D. Electrical injury can cause a variety of cardiac manifestations, including multiple dysrhythmias, transient ST elevation, and conduction blocks. Myocardial infarction, although reported, is rare. Extensive skeletal muscle damage can be seen in electrical injuries and results in marked elevations of CK and CK-MB levels. Respiratory muscle paralysis and ocular injuries often occur. This patient is probably not brain-dead, nor has he suffered a myocardial infarction. Mannitol is used in cases of impending cerebral herniation, which is not expected in this patient.

134.4. A 3-year-old boy is brought to the ED by his parents after burning his mouth while chewing on an electrical cord. He has partial-thickness burns to the left side of his upper and lower lips and an oral commissure. What complication of this injury needs to be considered in planning patient treatment and disposition?

A. Cardiac dysrhythmias
B. Cataracts
C. Contractures involving the orbicularis oris muscle
D. Delayed labial artery bleeding
E. Rhabdomyolysis

Answer: D. When the initial eschar separates, there is risk of exposure of the labial artery, with resultant significant arterial bleeding. Traditionally, admission for observation has been advocated for these patients but, if there is good social support, discharge with specific instructions and close follow-up are appropriate. These types of electrical injury have only local effects, so dysrhythmias, cataracts, and rhabdomyolysis are not complications. Contractures are common and may require reconstructive surgery, but this complication is not life-threatening.

134.5. You are camping with a group of five students. A sudden thunderstorm arises and lightning strikes your camp. You are uninjured, but all five students are injured and are lying on the ground. Their conditions are described here.

You are the only person available to provide medical support. After quickly calling 911, which student should receive your primary attention?

A. Student A is unconscious and has no spontaneous respirations, an irregular pulse, and no obvious injuries.
B. Student B is unconscious and has spontaneous respirations, a rapid and faint pulse, and no obvious injuries.
C. Student C is conscious, is screaming in pain, and has an easily palpable pulse an obvious open femur fracture after being thrown against a tree.
D. Student D is conscious, is screaming in pain and has an easily palpable pulse and obvious second- to third-degree burns involving his face, left arm, and left leg.
E. Student E is conscious, is talking rapidly, has an easily palpable pulse, and complains of complete blindness.

Answer: A. This student has suffered respiratory arrest. Unlike in traditional mass casualty triage guidelines, patients without spontaneous respirations take first priority. Lightning frequently causes complete cardiopulmonary arrest, but cardiac automaticity often returns spontaneously. However, respiratory muscle paralysis can persist for several minutes. If patients are adequately ventilated during this time, prognosis for recovery is excellent. Student B may have a dysrhythmia or internal injuries causing shock. Although both conditions are potentially serious, there is little that a single rescuer in the field can do. Patients without cardiopulmonary arrest rarely die in the field.

134.6. A 29-year-old man is brought to the ED after a reported lightning strike. He is unresponsive and has been intubated before arrival by emergency medical services. The monitor reveals a sinus tachycardia at a rate of 125 beats/min, and his blood pressure is 196/118 mm Hg. Pupils are fixed and dilated. The lower extremities are cool and mottled, with absent pulses in the feet. Which of the following is the most appropriate for managing the patient?

A. Begin heparin, order lower extremity angiography, and consult vascular surgery.
B. Consult neurosurgery for determination of brain death.
C. Initiate treatment for hypertension with a titratable intravenously infused beta blocker.
D. Obtain a computed tomography (CT) scan of the head.

Answer: D. Nonreactive pupils are not a reliable method of determining neurologic status immediately after lightning injury. Vasospasm may result in pulseless mottled extremities but usually resolves spontaneously within a few hours. Similarly, hypertension is common and should not be treated initially. Any patient with loss of consciousness or persistent neurologic impairment should have CT scanning of the head to rule out an intracranial anatomic cause.

CHAPTER 135

Scuba Diving and Dysbarism

Richard L. Byyny | Lee W. Shockley

PRINCIPLES

Background

Underwater free diving to salvage wrecks and to harvest seafood, sponges, coral, and mother-of-pearl has been practiced for more than 5000 years. The earliest artificial underwater breathing devices, hollow tubes, were impossible to use at depths greater than 3 feet because of restricted inspiration caused by the pressure of the water. However, subsequent inventions in the sixteenth to the nineteenth centuries allowed dives to greater depths.

With the advent of these technologies, the symptoms of diving-related illness, also known as *dysbarisms,* began to be recognized. Colonel William Pasley, the officer in charge of a unit of the British Royal Engineers that salvaged the sunken warship HMS *Royal George* in 1840, observed symptoms in his divers. At approximately the same time, similar symptoms and even fatalities were observed among caisson workers.* The ailment became known as *caisson disease,* but the construction workers on the Brooklyn Bridge (built from 1870 to 1883) called it "the bends," because the symptoms often caused the victim to bend forward in pain. The first clinical description was by Paul Bert in 1878. He correctly attributed the disease to nitrogen gas coming out of solution in the tissues during decompression leading to the recommendation of slow ascents for pressurized workers and the development of the first recompression chambers.

The breakthrough that allowed more widespread adoption of diving at depth was the invention of the aqua-lung by Jacques-Yves Cousteau and Emile Gagnan in 1943. The lighter and less expensive equipment, widely known by its acronym SCUBA (self-contained underwater breathing apparatus), does not require a surface supply of air or the support personnel that are necessary for helmet diving. Millions of divers have become certified to date.

Most amateur divers use compressed air, open-circuit scuba equipment at depths of less than 130 feet of seawater (fsw). Systems with artificial mixtures of various gases, however, are used to extend the depths to which divers can descend or the duration that a diver may safely remain submerged ("bottom time").

Other variations of supplying air for divers are closed-circuit and semiclosed-circuit diving apparati ("rebreathers") that use calcium hydroxide to absorb expired carbon dioxide. Oxygen is then added to the decarboxylated gas before rebreathing. The advantages of rebreathers over compressed air scuba are that they are more efficient (less gas is used for a given time), allow deeper dives and longer bottom times, and generate few if any bubbles.

The exact number of diving-related injuries is unknown; however, approximately three injuries of any kind happen per 100 dives based upon a 2011 survey performed by the Diver Area Network.[1] Divers experience decompression-related illnesses, one of the most serious dive-related injuries, in 1.55 dives per 1000.[1,2] Although the rate of patients experiencing decompression illness has remained relatively constant, the absolute numbers have increased with the ever growing number of certified divers and dives being performed.[2]

Pathophysiology

Scuba divers may encounter emergencies common to environmental exposures (eg, hypothermia, sunburn, and physical trauma) or aquatic activities (eg, submersion accidents, motion sickness, and marine envenomations), but they are also subject to the unique injuries related to dysbarisms and barotrauma. The pathophysiologic mechanism of dysbarisms and barotrauma primarily results from volume-pressure changes within the air-filled cavities of the body or from increased dissolution of gases, particularly nitrogen, in body tissues.

Atmospheric pressure varies with altitude and weather patterns, but 760 mm Hg (14.7 psi or 1 atm) is the standard used at sea level. Water is far denser than air. A mountain climber would need to ascend to 18,000 feet to reduce atmospheric pressure by 50% from sea level, but a diver needs to descend only 33 feet in seawater (34 feet in fresh water) to double the atmospheric pressure, an increase of 23 mm Hg per foot of depth. It is for this reason that it is extremely uncommon to see dysbarisms related to altitude changes except in military aircraft pilots or in the rare instance of sudden depressurization of an airliner.

To understand the pathophysiologic processes of dysbarisms and barotrauma, one should be familiar with several of the laws of physics that define the behavior of liquids and gases (Table 135.1; Figs. 135.1 to 135.5). The human body is composed mostly of water and behaves like a liquid subject to Pascal's law, which states that a pressure applied to any part of a liquid is transmitted equally throughout. Pressure changes, however, do alter the volume within the air-filled spaces of the body, including the lungs, bowel, sinuses, and middle ear, according to Boyle's law. This law states that at constant temperature, the absolute pressure and the volume of gas are inversely proportional ($PV = k$). In other words, as pressure increases (with descent), the gas volume is reduced; as the pressure is reduced (with ascent), the gas volume increases.

Temperature also affects the pressure and volume of a gas as described by Charles' law. At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature ($V_1/T_1 = V_2/T_2$). Thus, with heat the volume increases, and with cold the volume decreases. The general gas law ($P_1 \cdot V_1/T_1 = P_2 \cdot V_2/T_2$) combines Boyle's and Charles' laws to predict the behavior of a given quantity of gas when any of these factors change.

Barotrauma results when a diver is unable to equalize the pressure within air-filled structures to the ambient pressure of the environment during ascent or descent. Fractional changes in volume are greater near the surface. Thus the greatest risk for barotrauma is in shallow water, where the proportional pressure changes are also the greatest.

Dalton's law states that the total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of

*Caissons are construction chambers filled with pressurized air that permit working in a dry environment. They have been used in the construction of bridge footings and tunnels in places that would otherwise have been underwater.

TABLE 135.1

Laws of Physics

GAS LAW	FORMULA	SIGNIFICANCE
Pascal's law: A pressure applied to any part of a liquid is transmitted equally throughout.	$\Delta P = \rho g (\Delta h)$ ΔP is the hydrostatic pressure. ρ is the fluid density. g is acceleration due to gravity. Δh is the height of fluid.	Pressure increases in a contained space are transmitted throughout; significant for IEBT and MEBT (see Fig. 135.1)
Boyle's law: At a constant temperature, the absolute pressure and the volume of gas are inversely proportional. As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases.	P1 • V1 = P2 • V2	Relates to change in the volume of a gas caused by the change in pressure due to depth, which defines the relationship of pressure and volume in breathing gas supplies (see Fig. 135.2)
Charles' law: At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature.	V1/T1 = V2/T2	Increasing pressure (filling a scuba tank) causes heat; cooling a tank decreases the pressure (see Fig. 135.3)
The general gas law combines these concepts to predict the behavior of a gas when the factors change.	P1 • V1/T1 = P2 • V2/T2 P1 is the initial pressure. V1 is the initial volume. T1 is the initial temperature. P2 is the final pressure. V2 is the final volume. T2 is the final temperature.	A means of relating pressure, volume, and temperature together in one equation when variables are not constant
Dalton's law: The total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of each of the different gases making up the mixture, with each gas acting as if it alone is present and occupies the total volume.	PTotal 3 P1 + P2 + P3 + … + Pn	Nitrogen under pressure acts as if other gases are not present (see Fig. 135.4)
Henry's law: The amount of a gas that will dissolve in a liquid at a given temperature is directly proportional to the partial pressure of that gas.	$e^{p} = e^{kc}$ *e* is approximately 2.7182818 (the base of the natural logarithm). *p* is the partial pressure of the solute above the solution. *c* is the concentration of the solute in the solution. *k* is the Henry's law constant.	More nitrogen is taken into solution (eg, serum) at high pressures than comes out of solution at lower pressures (see Fig. 135.5)

IEBT, Inner ear barotrauma; *MEBT,* middle ear barotrauma.

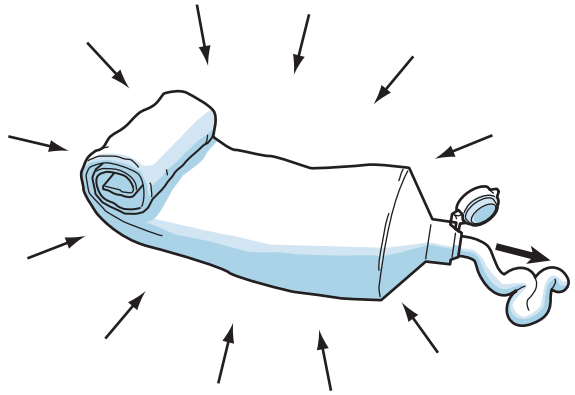

Fig. 135.1. Pascal's law. A pressure applied to any part of a liquid is transmitted equally throughout.

the individual gases making up the mixture, with each gas acting as if it alone is present and occupies the total volume ($P_{total} = P_1 + P_2 + P_3 + \ldots + P_n$). Henry's law states that the amount of any gas that dissolves in a liquid at a given temperature is directly proportional to the partial pressure of that gas. Therefore, at higher ambient pressures, an increasing concentration of each component gas of the inhaled air will dissolve in solution until a new steady-state concentration is achieved.

The length of time the diver is breathing the gas at the increased pressure and the inherent solubility of the gas also govern the quantity of a particular gas that dissolves. The dissolved gas remains in solution as long as the pressure is maintained. As the diver ascends, however, increasingly more of the dissolved gas comes out of solution. A rapid ascent may reduce the pressure at a rate higher than the body can accommodate, and the bubbles (particularly nitrogen) may accumulate and disrupt body tissues and systems, a phenomenon termed *decompression sickness (DCS).* This is similar to the way that rapid opening of a bottle of soda allows bubbles of carbon dioxide to come out of solution rapidly.

If the ascent rate is controlled (ie, through the use of the safe decompression tables or submersible dive computers), the gas is carried to the lung vascular bed and is exhaled before it accumulates to form significantly large or numerous bubbles in the tissues, similar to how opening of a soda bottle slowly reduces the bubbling of the contained carbonated liquid.

CLINICAL FEATURES

The clinical features of the injuries and illnesses related to diving will be presented in this section based on when the symptoms are

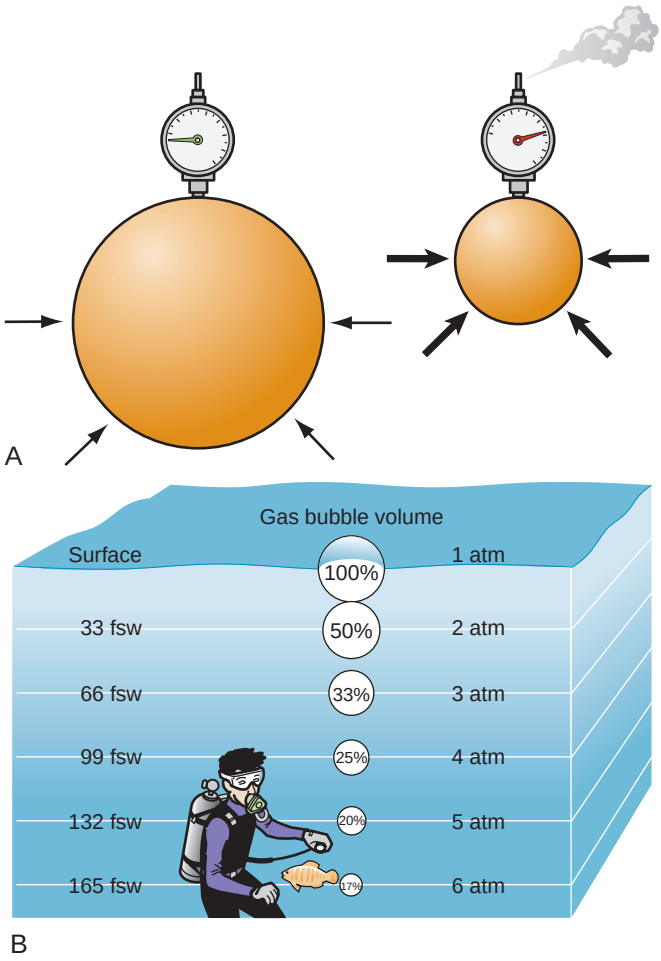

Fig. 135.2. Boyle's law. **A,** At a constant temperature, the absolute pressure and the volume of gas are inversely proportional. **B,** As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases. *fsw,* Feet of seawater.

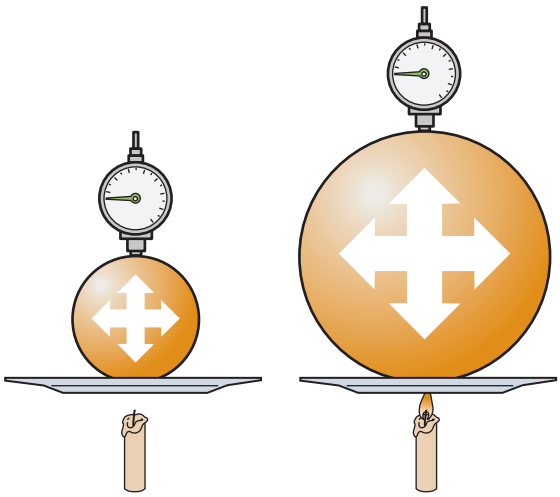

Fig. 135.3. Charles' law. At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature.

likely to start during a dive, first those that occur on descent, then those that occur at depth, and finally those that occur upon surfacing. This organization is used to help the clinician stratify the likelihood of a specific disorder based on when the symptoms started during the dive. Box 135.1 lists the components of a focused dive history.

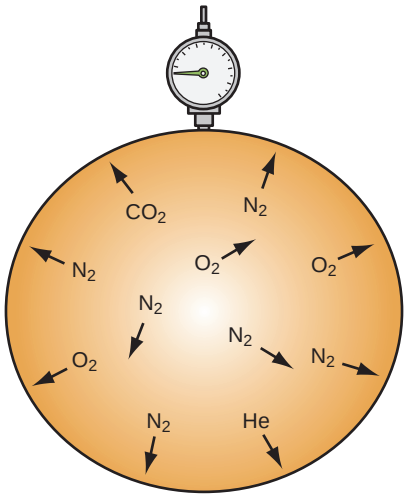

Fig. 135.4. Dalton's law. The total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of each of the different gases making up the mixture, with each gas acting as if it alone is present and occupies the total volume. *CO_2,* Carbon dioxide; *He,* helium; *N_2,* nitrogen; *O_2,* oxygen.

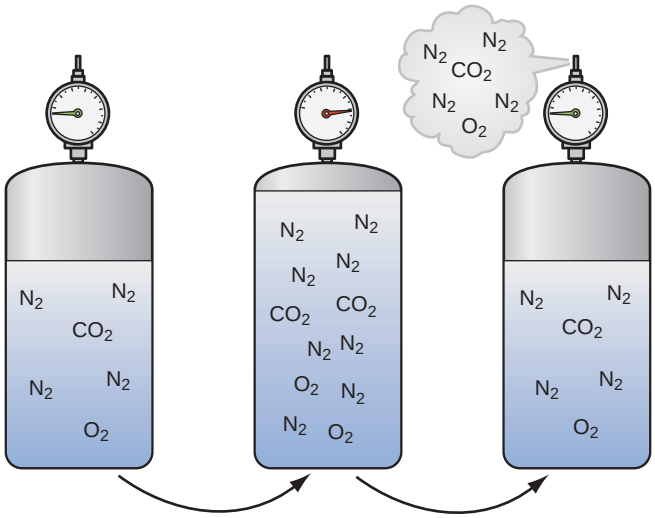

Fig. 135.5. Henry's law. The amount of a gas that will dissolve in a liquid at a given temperature is directly proportional to the partial pressure of that gas. *CO_2,* Carbon dioxide; *N_2,* nitrogen; *O_2,* oxygen.

Disorders Related to Descent

Middle Ear Barotrauma

Middle ear barotrauma (MEBT), also known as *barotitis* or *ear squeeze,* is the most common complaint of scuba divers. It is experienced by approximately 30% of novice scuba divers and 10% of experienced divers. The middle ear is an air-filled space with solid bone walls except for the tympanic membrane (Fig. 135.6). The eustachian tube is the only anatomic passage to the external environment.

As the diver descends, the water exerts increasing pressure against the intact tympanic membrane. Typically, the diver performs various maneuvers to force air into the middle ear through the eustachian tubes in an attempt to maintain equal pressure across the tympanic membrane. If the diver fails, the floppy medial third of the eustachian tube collapses shut, making any further attempts at equalization futile. This is typically painful and can be associated with tinnitus; some patients develop transient vertigo.

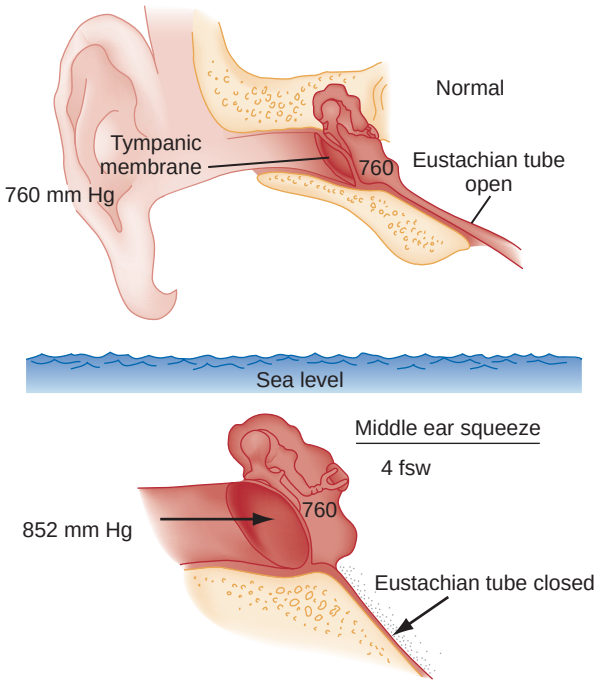

Fig. 135.6. Middle ear barotrauma symptoms include fullness and pain caused by stretching of the tympanic membrane. (From Van Hoesen KB, Bird NH: Diving medicine. In Auerbach PS, ed: Wilderness medicine, ed 6, Philadelphia, 2012, Elsevier, p 1529.)

BOX 135.1

Focused Dive History

When was the first onset of symptoms?
What type of equipment was used? Compressed air, mixed gas, enriched air, rebreather? What was the source of the gas?
Did the dive approach or exceed decompression limits? Was a dive computer used?
What were the number, depth, bottom time, total time, and surface intervals for all dives in the 72 hours preceding symptoms (the dive "profiles")?
Were decompression stops used? Was in-water decompression attempted?
What was the time delay from the last dive to air travel?
Did the diver experience difficulty with ear or sinus equilibration? Did the pain occur on descent or ascent?
Was the diver intoxicated? Dehydrated? Working strenuously?
How long after the dive did symptoms present? Were they present at surfacing? Delayed? Progressive?
Is a medical history of ear or sinus infections or abnormalities present? Emphysema or asthma? Coronary artery disease? Patent foramen ovale (PFO)? Neurologic illness?

Further descent without successful equalization can cause the tympanic membrane to rupture. The pain may or may not resolve as the tympanic membrane ruptures. The ruptured tympanic membrane can cause caloric stimulation by exposure of the middle ear to cold water, inducing a transient nystagmus and vertigo. The pressure of the water in the middle ear may lead to a facial palsy in certain individuals where the seventh cranial nerve passes unexposed through this space. On occasion, this disorder can be life-threatening during a dive as the subject becomes disoriented and can drown.

External Ear Barotrauma

External ear barotrauma is less common than MEBT and results from the outward bulging of the tympanic membrane during descent. Normally, the external auditory canal is filled with water during descent; however, obstruction of the external auditory canal for any reason (eg, cerumen, stenosis, earplugs, or a tight-fitting wet suit hood) can trap air, causing a relative negative pressure. This may lead to localized pain and/or hemorrhages in the wall of the external auditory canal on examination. These symptoms are typically self-limited.

Inner Ear Barotrauma

Inner ear barotrauma (IEBT) results in damage to the cochleovestibular apparatus. It is much less common than MEBT but is associated with greater morbidity. A large negative pressure gradient develops in the middle ear if the diver is unable to equalize pressure during descent, similar to MEBT. Inward deflection of the tympanic membrane is transmitted to the oval window of the cochlea through the ossicles. Movement of the oval window creates a pressure wave within the perilymph of the cochlea, which causes an outward distention of the round window into the middle ear. Sudden equilibration of pressure in the middle ear or a vigorous Valsalva maneuver may rupture the round window, lead to hemorrhage into the inner ear, or tear the labyrinthine (Reissner's) membrane.

Symptoms associated with IEBT include variable hearing loss, severe vertigo, nausea, tinnitus, and fullness in the affected ear. Signs include severe nystagmus, positional vertigo, ataxia, and vomiting. The degree of sensorineural hearing loss is variable. Distinguishing IEBT from inner ear DCS can be challenging but should not delay recompression in a patient in whom the diagnosis is in doubt.

Barosinusitis

Obstruction of the sinus ostia for any reason (eg, mucosal thickening, polyps, pus, or deviated septum) predisposes to sinus barotrauma, the second most common complaint among divers.[3,4] The air-filled maxillary, frontal, and ethmoidal sinuses are susceptible to volume-pressure changes on ascent or descent; the most commonly affected is the maxillary sinus, followed by the frontal. The most common symptoms are facial pain and epistaxis.

Facial Barotrauma

As water pressure increases during descent, a negative pressure develops within the dive mask over the eyes and nose, which must be equalized by forced exhalation through the nose. When this is not adequately performed, the large negative pressure gradient may lead to facial and conjunctival edema, diffuse petechial hemorrhages on the face, and subconjunctival hemorrhages. Very rarely, optic nerve damage can result from severe facial barotrauma.

Disorders Arising at Depth

Nitrogen Narcosis

Nitrogen narcosis, known as *rapture of the deep,* results from the intoxicating effects of increased tissue nitrogen concentration at depth. Symptoms include euphoria, false feeling of well-being, confusion, loss of judgment or skill, disorientation, inappropriate laughter, diminished motor control, and tingling and vague numbness of the lips, gums, and legs. With breathing of compressed air, symptoms typically begin to occur at approximately

100 feet and often become profound at depths of more than 150 feet. Because of these dangers, the use of compressed air is not recommended and instead mixed gases with a lower concentration of nitrogen are suggested for sport diving to depths of more than 120 feet. Although the effects of nitrogen narcosis resolve with ascent to shallower depths and are variable between individuals, the diver may drown because of poor judgment or seriously impaired motor skills in the presence of a dive emergency.

Oxygen Toxicity

At elevated partial pressures for extended periods, oxygen can be toxic to the central nervous system (CNS) or lungs. Oxygen becomes toxic to the CNS when its partial pressure exceeds 1.6 atmosphere absolute (ata). Oxygen partial pressures below 1.4 ata are unlikely to produce CNS toxicity. A diver breathing compressed air would attain a partial pressure of 1.6 ata of oxygen at a depth of 218 fsw. This far exceeds the depth to which sport divers would go. Deep divers prevent oxygen toxicity by breathing mixed gases with decreased oxygen content (eg, hypoxic trimix).

Pulmonary oxygen toxicity (low-pressure oxygen poisoning) can occur after 24 hours of exposure to partial pressures of oxygen in excess of 0.6 ata. The symptoms of pulmonary oxygen toxicity include a burning sensation or pain on inspiration and coughing. Pulmonary function gradually becomes normal after the exposure is terminated, but pneumonitis and permanent fibrosis are possible. It is extremely unlikely that a sport diver would ever be exposed for the duration that is required to produce toxicity; however, long exposures to higher levels of oxygen, such as those administered for certain recompression protocols, may lead to pulmonary oxygen toxicity.

Contaminated Air

Rarely, other gases, such as carbon monoxide and carbon dioxide, can contaminate the air that is compressed into a tank. This can happen, for example, if the compressor intake is placed too close to the compressor's engine exhaust. As in the case of oxygen and nitrogen, the partial pressure of these contaminants in the tissues increases dramatically with depth, potentiating their clinical effects. The symptoms of hypercarbia or carbon monoxide poisoning are more severe at elevated partial pressures. Hypercarbia increases a diver's susceptibility to CNS oxygen toxicity.

Rebreathers release microscopic calcium hydroxide or "soda lime" dust particles into the apparatus. These particles are small enough and have geometric characteristics that allow them to be deposited in the alveoli. When soda lime comes into contact with water, it forms a caustic liquid. In the event of a hose rupture allowing seawater contamination of the circuit, caustic burns to the mouth, throat, and airways may result. Chronic exposure to soda lime dust may contribute to long-term effects on respiratory function.

Disorders Arising on Ascent

Alternobaric Vertigo

Alternobaric vertigo (ABV) results from an inability to equalize pressure within the middle ear during ascent. Although equalization during descent requires active maneuvers to maintain eustachian tube patency, air normally exits the middle ear without difficulty during ascent because the pressure within the middle ear exceeds ambient pressure. In the setting of mucosal edema or thickening within the eustachian tube, however, the passage of air may be impeded. The problem is typically unilateral. When the pressure gradient within the middle ear reaches 60 cm H_2O, increased labyrinthine discharge produces nystagmus. Clinically, the patient experiences a profound but transient sense of vertigo during ascent that may be associated with nausea and vomiting. Unlike those of IEBT, the symptoms are self-limited.

Barodontalgia

On occasion, air that is trapped beneath a poorly filled dental cavity or within a dental abscess expands on ascent, leading to dental pain. This condition is relatively benign and self-limited.

Gastrointestinal Barotrauma

Serious gastrointestinal barotrauma is a rare condition in scuba divers. It results from the expansion of bowel gas in the small intestine and colon on ascent after diving. Predisposing factors include consumption of carbonated beverages, large meals, or gas-producing foods before diving, as well as performance of the Valsalva maneuver in the head-down position. Symptoms include eructation, flatulence, bloating, and crampy abdominal pain. In divers with inguinal or other hernias, the potential for expansion of trapped gas within the hernia exists, and expansion may result in incarceration or strangulation. Gastric rupture is a rare complication. Although gastrointestinal barotrauma is a rare entity, it should be suspected in the diver-patient with a provocative history and abdominal pain.

Pulmonary Barotrauma

Without continuously expiring on ascent, the lungs of a scuba diver who takes a full breath at 33 fsw would have to expand to double their volume by the time they reached the surface (Boyle's law). However, the expansion of the alveoli is limited. The increase in pressure either forces gas bubbles across the alveolar-capillary membrane or causes the wall of the alveoli to rupture. A change in depth of 3 to 4 feet (or pressure difference of 80 mm Hg) is all that is required to force air bubbles across the alveolar-capillary membrane.

In fact, the greatest risk for pulmonary barotrauma occurs in less than 10 feet of water. Therefore, it is important for the clinician to consider this disease entity in patients with consistent symptoms even after exposure to shallow depths. Pulmonary barotrauma can result in the following four conditions: pneumothorax, pneumomediastinum, subcutaneous emphysema, and alveolar hemorrhage. Risk factors elicited from the dive and medical history may suggest the diagnosis of pulmonary barotrauma. In most cases, fast ascent, panic, problems in regulating buoyancy, or running out of air is noted.

Patients with restrictive and obstructive lung diseases are at particular risk. Asthmatics have a twofold-increased risk for pulmonary barotrauma compared with the general diver population. Box 135.2 lists six mechanisms that contribute to the increased risk in asthmatics.[5]

Asthma severity can wax and wane. Because symptoms may worsen for 4 to 6 weeks after an upper respiratory infection or during certain seasons, asthmatics should refrain from diving until they are completely free of symptoms. Box 135.3 summarizes the recommendations from the multiple national scuba governing agencies, as well as expert consensus.[5]

Pneumomediastinum and subcutaneous emphysema result when air crosses the alveolar endothelium and dissects into the pulmonary interstitium. Most commonly, the air then travels into the neck, mediastinum, or pericardium. The manifestations of pneumomediastinum may include fullness in the neck, palpable subcutaneous crepitance, and a change in voice quality or timbre. Unless evidence of either hemodynamic instability or airway compromise exists, interstitial air or subcutaneous emphysema is not a life-threatening condition.

BOX 135.2

Factors That Increase Pulmonary Barotrauma Risk in Asthmatics

1. Bronchospasm and mucus plugging predispose local regions of lung to injury.
2. When air is compressed, it becomes denser. This may contribute to greater turbulent flow through narrow airways.
3. During scuba diving, there is a reduction in breathing capacity related to the effects of immersion. At 33 feet underwater, the maximum breathing capacity of a normal scuba diver is only 70% of the surface value. At 100 feet underwater, the reduction is approximately 50%.
4. When compressed air (from the scuba tank) expands in the regulator before delivery to the lungs, it cools (Charles' law). Breathing of chilled air may trigger bronchospasm in asthmatics who have a cold-induced component of their disease.
5. Scuba diving takes some effort; asthmatics who have an exercise-induced component of their disease may experience bronchospasm.
6. Compressed air may be contaminated by pollen and other allergens.

BOX 135.3

Recommendations for Asthmatic Patients

A thorough history and physical by a trained physician
The patient's asthma should be well controlled
Normal spirometry: FEV1 ≥80%, FEV1/FVC ≥75%
Successful completion of a bronchial provocation challenge
Cold, exercise, or emotion induced asthmatics should not dive
Asthmatics requiring rescue medication with 48 hours should not dive

FEV_1, Forced expiratory volume in 1 second; *FVC,* forced vital capacity.
Adapted from Coop CA, Adams KE, Webb CN: *SCUBA diving and asthma: clinical recommendations and safety.* Clin Rev Allergy Immunol 50(1):18-22, 2016.

Pneumothorax may occur when the air that escapes from alveoli as a result of pulmonary barotrauma crosses the visceral pleura. A tension pneumothorax is a rare complication. The symptoms and signs of a pneumothorax secondary to pulmonary barotrauma are typical for a pneumothorax of any cause.

Pulmonary barotrauma can also cause alveolar hemorrhage. Patients may present with hemoptysis coincident with chest pain and dyspnea. Chest radiography may reveal an interstitial infiltrate.

Decompression Sickness

The term *decompression sickness (DCS)* refers to a spectrum of clinical illnesses resulting from the formation of small bubbles of nitrogen gas in the blood and tissues on ascent. The clinical expression of DCS depends on the location, destination, and degree of nitrogen bubble formation in blood and tissues. Small, asymptomatic venous gas emboli are common in the ascending diver and are filtered by the lungs without apparent permanent damage. Persistent intravascular bubbles, however, elicit inflammatory cascades, cytokines, the complement system, platelet aggregation, and thrombosis. Furthermore, the bubbles can cause mechanical obstruction, ischemia, and tissue hypoxia. Nitrogen is highly fat soluble, and the heavily myelinized white matter of the CNS is at particular risk for DCS.

The incidence of DCS is estimated to be 1.55 per 1000 dives based upon self-reporting; however, some divers may fail to present to a health care professional. The potential for development of DCS increases with the length and depth of a dive. Other risk factors include age, obesity, fatigue, heavy exertion, dehydration, fever, cold ambient temperatures after diving, diving at high altitude, and flying after diving. Tobacco and ethanol use may also increase susceptibility to DCS. The risk of DCS is 2.6 times greater for men than for women, possibly due to risk-taking behaviors. There appears to be no increase in DCS in women who are taking oral contraceptive agents or menstruating during diving.

A patent foramen ovale (PFO) is a risk factor for increased susceptibility to DCS. Sixty-five percent of divers who present with serious DCS have a PFO.[5-8] Brain lesions occur in 27% of all sport divers. This percentage is roughly the same as the prevalence of PFO or other right-to-left shunts in the general population. These multiple brain lesions may be caused by bubbles in the venous circulation that are not filtered by the vasculature of the lungs but enter the arterial circulation, even in the absence of other DCS symptoms. Most sport divers do not undergo screening for PFO with echocardiographic bubble studies; some PFOs may open only at increased ambient pressures so that bubble studies conducted at 1 ata might be normal.

The United States Navy dive tables estimate the amount of nitrogen that accumulates in the body during a dive to a particular depth and duration. The tables calculate a maximal dive time, called the *no-decompression limit.* If the no-decompression limits are exceeded, underwater decompression stops are recommended. Many sport scuba divers use submersible dive computers to calculate maximum dive times in lieu of the tables. These tables and computers are meant to reduce the likelihood of exceeding the solubility of nitrogen at sea level to produce DCS. The diver still must ascend in a slow, controlled manner to allow the gradual release of nitrogen. Off-gassing continues after the diver has surfaced. Repetitive dives within several hours result in accumulation of tissue nitrogen and shorter no-decompression limits. Because dive tables are based on several assumptions about nitrogen elimination, even strict adherence to these tables does not guarantee that DCS will not occur. The risk of DCS increases as a diver approaches the no-decompression time limits rarely occurs after dives to less than 6 meters and is uncommon at less than 10 meters. It is important for emergency clinicians to realize that divers can develop DCS even when they are within any calculated no-decompression limits.

DCS typically is manifested within hours after surfacing. Approximately 40% of symptoms occur within 1 hour after diving, 60% within 3 hours, 80% within 8 hours, and 98% within 24 hours. In a recent review of 5278 cases of DCS at a single hyperbaric unit more than 98% had symptoms within 6 hours and the mean time to symptom onset was 62 minutes.[9] Flying shortly after diving or ascending to altitude, however, may cause symptoms in patients later than expected, and some patients present days after diving with DCS.[3]

Traditionally, DCS has been divided into two categories, type I and type II. Type I DCS affects the musculoskeletal system, skin, and lymphatic vessels. Type II DCS involves any other organ system. The more inclusive "decompression-related illness" is now also used to encompass DCS I, DCS II, and arterial gas embolism (AGE). This terminology is adapted to aid clinicians in remembering that the distinction is irrelevant in the selection of treatment. All types of decompression illness require recompression.[4,10] DCS I, DCS II, and AGE can coexist. The symptoms of DCS may be subtle and resolve by the time of evaluation. A distribution of the most common symptoms and the first symptoms is presented in Figure 135.7.

Type I DCS can be experienced as variable and periarticular pain in the arms and legs. The elbow and shoulder joints are most commonly affected. Local tenderness and erythema are uncommon. The placement of a blood pressure cuff inflated to 150 to

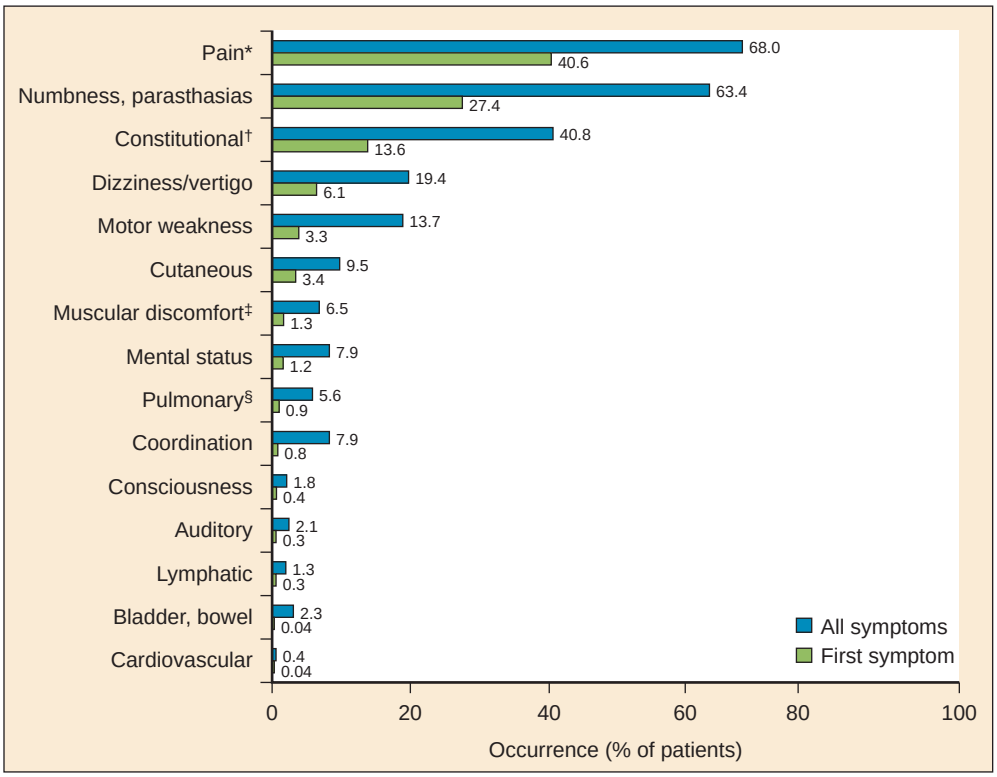

Fig. 135.7. Classification of initial and of all eventual manifestations of decompression illness in 2346 recreational diving accidents reported to the Divers Alert Network (DAN) from 1998 to 2004. *For all instances of pain, 58% consisted of joint pain, 35% muscle pain, and 7% girdle pain. Girdle pain often portends spinal cord involvement. †Constitutional symptoms included headache, lightheadedness, inappropriate fatigue, malaise, nausea or vomiting, and anorexia. ‡Muscular discomfort included stiffness, pressure, cramps, and spasm but excluded pain. §Pulmonary manifestations included dyspnea and cough. (From Vann RD, Butler FK, Mitchell SJ, et al: Decompression illness. Lancet 377:153-164, 2011.)

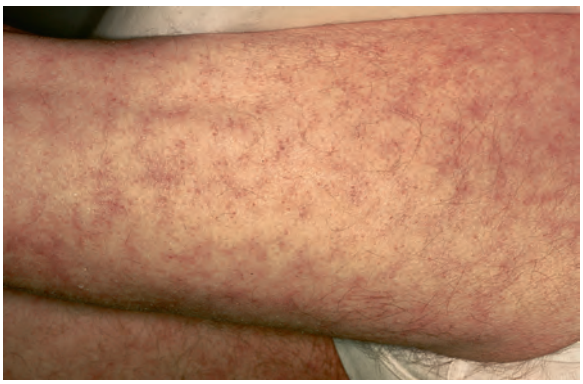

Fig. 135.8. Marbling of the thigh in cutaneous decompression sickness (DCS). (From Maeyens E: Aquatic skin disorders. In Auerbach PS, ed: Wilderness medicine, ed 6, Philadelphia, 2012, Elsevier, p 1665.)

200 mm Hg on an affected joint produces relief of pain and confirms the diagnosis; however, the sensitivity of this maneuver has been reported to be as low as 60%. Skin marbling, known as *cutis marmorata* (patchy cyanotic marbling of the skin), results from venous stasis.[11] It may begin as severe pruritus and progress into an erythematous rash and then skin mottling. Cutis marmorata does not follow a dermatomal distribution and commonly involves the trunk and torso. Lymphatic obstruction by air bubbles can also occur, causing extremity edema (Fig. 135.8).

Type II DCS includes symptoms that can involve the CNS, the inner ear, and the lungs. The CNS is particularly susceptible to decompression illness because of its high lipid content. The spinal cord, especially the upper lumbar area, is more often involved than cerebral tissue. Symptoms of spinal DCS include limb weakness or paralysis, paresthesias, numbness, and low back and abdominal pain. Limb symptoms often begin as a distal prickly sensation that advances proximally, followed by progressive sensory or motor loss. A dermatome sensory level occurs in some spinal DCS patients, often at the T12 to L1 dermatomes. Bladder symptoms, fecal incontinence, and priapism may occur. Unlike patients with spinal cord trauma, patients experiencing DCS may have patchy or unequally distributed sensory and motor findings.

Spinal DCS can occur alone or in combination with cerebral, inner ear, or pulmonary symptoms. Cerebral symptoms include mild to moderate headache, blurred vision, diplopia, dysarthria, unusual fatigue, inappropriate behavior, and a sense of detachment. Loss of consciousness in CNS DCS is rare (in marked contrast to AGE).

Inner ear DCS is commonly called the *staggers.* Approximately 24% to 36% of patients that present with DCS report cochlear vestibular symptoms.[12] The symptoms of inner ear DCS are the same as those of IEBT and include nausea, dizziness, vertigo, nystagmus, and hearing loss. The most common symptoms are vestibular in nature with only 25% of patients exhibiting hear loss or tinnitus.[12] This can usually be distinguished from IEBT because the onset happens during ascent or after surfacing.

Pulmonary DCS is called the *chokes.* All divers are exposed to some degree of microbubble emboli to the lungs on ascent. The progression to symptoms depends on the number and volume of bubbles. The deposition of venous gas emboli in the pulmonary arterial circulation produces progressive dyspnea,

cough, and chest pain. The cough may progress to paroxysmal fits with worsening pain.

The physical examination of patients suffering from pulmonary DCS may reveal cyanosis and hypotension in association with increased central venous pressure and pulmonary arterial pressure. The condition may progress to respiratory arrest.

DCS may be particularly dangerous to a developing fetus of a scuba diving mother because the majority of the fetal circulation bypasses the pulmonary bed through the foramen ovale and the ductus arteriosus. This bypass prevents the fetal lungs from acting as a filter for microbubbles. In addition, venous gas emboli may appear in the fetal circulation before they are apparent in the maternal circulation. Data on the effects of diving on pregnant women suggest a higher incidence of low-birth-weight infants, prematurity, congenital malformations, stillbirths, and spontaneous abortions. There are no safe-diving tables that would protect a fetus from DCS; therefore, pregnant women should be advised to refrain from scuba diving.

Arterial Gas Embolism

AGE results when air bubbles are forced across the alveolar-capillary membrane, escape into the pulmonary venous circulation, and proceed through the left atrium and ventricle into the arterial circulation. It is one of the most common causes of death in divers. Clinical symptoms and signs are in part the result of mechanical obstruction by gas bubbles. AGE can also result from a right-to-left shunt of venous bubbles, such as in a diver with a PFO. AGE may occur alone or in conjunction with DCS.

Although air bubbles may embolize to any organ, the coronary and cerebral arteries are associated with the most serious consequences. Emboli to the coronary arteries may cause cardiac ischemia, myocardial infarction, dysrhythmias, or cardiac arrest. Dysrhythmias are also indirectly caused by centrally mediated autonomic dysfunction from cerebral emboli. Mechanical occlusion of the cerebral vasculature from emboli, most commonly to the anterior and middle cerebral arteries, causes a variety of symptoms and signs similar in appearance to an acute stroke. Large volumes of gas can lead to cardiac "vapor lock" where the intracardiac bubbles mechanically displace blood in the ventricles leading to a precipitous fall in cardiac output with resultant hypotension or even death.

The clinical manifestations of AGE may be sudden, dramatic, and life-threatening. Divers who have supposedly "drowned" may actually have lost consciousness during ascent as a result of cerebral gas emboli. Any diver breathing compressed air at any depth underwater and who surfaces unconscious or who loses consciousness within 10 minutes of reaching the surface should be assumed to be suffering from AGE. The most common presentation of AGE includes a global alteration of consciousness, headache, dizziness, convulsions, and visual changes. Other common presenting symptoms and signs include cranial nerve symptoms, unilateral weakness, unilateral or bilateral sensory loss, ataxia, and speech changes. Pulmonary symptoms, including dyspnea, pleuritic chest pain, and hemoptysis, occur in 25% to 50% of cases.

Pulmonary Edema

Pulmonary edema while scuba diving was first reported in the 1980s. An increase in afterload (from vascular hyper-reactivity, possibly triggered by cold) combined with an increase in preload (from the hyperbaric underwater environment) may be the cause.

DIFFERENTIAL DIAGNOSES

Most diving injuries have limited differential diagnoses that include medical disorders and trauma unrelated to dysbarism. The differential diagnosis of IEBT includes inner ear DCS, ABV, and isolated MEBT with a rupture of the tympanic membrane. It is relatively easy to distinguish IEBT from MEBT and ABV because the vestibular symptoms associated with the last two entities are transient and self-limited (Table 135.2). When IEBT occurs simultaneously with MEBT, the presence of both may be documented by an audiogram, which demonstrates both a conductive and a sensorineural hearing loss.

The differentiation of IEBT from inner ear neurologic DCS is crucial because the treatments differ. An IEBT is more likely when symptoms begin during descent or the diver relates a history of difficulty equilibrating or performing a vigorous Valsalva maneuver. If the dive profile is examined and the no-decompression limits are approached and symptoms began soon after surfacing, inner ear DCS is more likely. A history of difficulty in equalizing the ears on descent, or the onset of symptoms early in the dive, suggests barotrauma. A history of a dive that approaches decompression limits, or the onset of symptoms during or soon after ascent, and the presence of other neurologic findings suggest DCS. A trial of recompression therapy is prudent if concerns for DCS exist.

The differential diagnosis of pulmonary DCS includes AGE. Table 135.3 provides factors that differentiate the two conditions. Although the treatment of both requires recompression therapy, they may be differentiated by the timing of the onset of symptoms. Almost all cases of AGE present within the first 10 minutes of surfacing, whereas DCS presents more typically after 10 minutes: 40% of pulmonary DCS symptoms begin within 1 hour of surfacing, 60% within 3 hours, 80% within 8 hours, and 98% within 24 hours.

TABLE 135.2

Middle Ear Barotrauma, Inner Ear Barotrauma, and Alternobaric Vertigo

	MIDDLE EAR BAROTRAUMA	INNER EAR BAROTRAUMA	ALTERNOBARIC VERTIGO
Symptoms	Ear pain during descent Hearing loss Possible transient vertigo	Ear pain during descent Hearing loss Severe vertigo and nausea	Ear pain during ascent Transient hearing loss Nausea
Signs	Conductive hearing loss TM injury Unilateral face paralysis	Nystagmus Emesis Ataxia Romberg's sign Neural hearing loss	Nystagmus Emesis TM injury

TM, Tympanic membrane.

TABLE 135.3

Decompression Sickness Versus Arterial Gas Embolism

DECOMPRESSION SICKNESS	ARTERIAL GAS EMBOLISM
DIVE HISTORY	
Depth and length dependent	Independent of dive profile
Decompression limits approached	Rapid ascent
Flying after diving	Inexperience
Diving at altitude	Out of air
RISK FACTORS	
Fatigue	Obstructive lung disease
Dehydration	Emphysema
Fever, hypothermia	Mucus plugging
Obesity	Patent foramen ovale (PFO)
Strenuous activity	
SYMPTOMS AND SIGNS	
Progressive onset	Rapid onset
Spinal symptoms predominate	Cerebral symptoms predominate
Headache	Headache
Unusual fatigue	Loss of consciousness
Limb weakness or paralysis	Confusion
Paresthesias	Convulsions
Abdominal pain	Motor or sensory loss
Urinary retention	Cardiac dysrhythmias or arrest
Fecal incontinence	
Periarticular joint pain	
Skin marbling	
Vertigo or nystagmus	
TREATMENT	
Recompression	Recompression

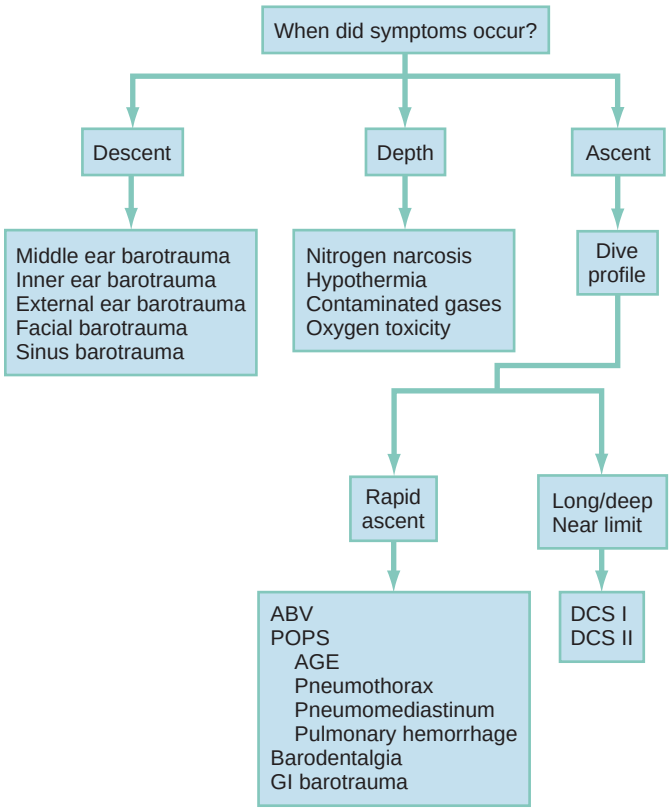

Fig. 135.9. The approach to the injured diver. *ABV,* Alternobaric vertigo; *AGE,* arterial gas embolism; *DCS,* decompression sickness; *GI,* gastrointestinal; *POPS,* pulmonary overpressure syndrome.

Diagnostic Testing

Imaging and laboratory studies for ruling in decompression are generally not useful and should not delay definitive recompression therapy. Focused questions concerning the dive profile, including the depth and length of the dive and a careful assessment of when the symptoms first occurred, may provide important diagnostic clues (see Box 135.3). A physician unfamiliar with the specifics of scuba diving may rely on the assessment of members of the dive group to determine whether maximum dive limits were approached. In making the diagnosis of a dive injury, it is helpful to think of the injuries in terms of occurring during descent, while at depth, or during ascent (Fig. 135.9). Because recompression therapy is time sensitive, it is important to concentrate on treatment decisions rather than on securing an absolute diagnosis.

Pulmonary barotrauma can also cause alveolar hemorrhage. Patients may present with hemoptysis coincident with chest pain and dyspnea. Chest radiography may reveal an interstitial infiltrate. Magnetic resonance imaging (MRI), computed tomography (CT), and single-photon emission CT with technetium (Tc-99m)–labeled hexamethyl propyleneamine can identify the bubbles of CNS DCS. However, *no* imaging studies are sensitive enough to exclude DCS, and normal imaging results should not delay transfer for definitive therapy. DCS can cause right-sided strain on an electrocardiogram and decreased end-tidal carbon dioxide level. Ancillary tests for pulmonary DCS are not only insensitive but also lead to unnecessary treatment delays. Even after ascent from very shallow saturation dives, microbubbles in the venous circulation can be routinely detected by M-mode ultrasonography; however, their presence does not necessarily correlate with symptoms.

MANAGEMENT

Patients with stable vital signs and suspected dive injuries should receive 100% oxygen until the clinician can exclude pulmonary barotrauma or decompression illness. First aid with normobaric 100% oxygen can improve outcomes and should be provided until the patient can be definitively treated. Patients with unstable vital signs or in cardiac arrest should be treated according to advanced cardiac life support (ACLS) guidelines. The clinician should take a thorough history, including elements in Box 135.3, and then perform a detailed physical examination.

Diving-related illnesses are diagnosed and treated on the basis of the history and physical examination, and several invaluable resources are available for advice. The Divers Alert Network (DAN), located at Duke University in Durham, North Carolina, is a membership association that provides courses on diving-related emergencies and publishes data on diving accidents and fatalities. DAN provides a 24-hour medical emergency hotline at 1-919-684-9111 (collect calls are accepted) and a nonemergency advisory line Monday through Friday, 8:30 AM to 5 PM Eastern time, at 1-919-684-2948 or 1-800-446-2671 (Box 135.4). In addition, DAN international contacts are in Europe, Brazil, Japan, Asia Pacific, and southern Africa. DAN maintains a website with links

BOX 135.4

Important Contact Information

DIVERS ALERT NETWORK HEAD QUARTERS	PHONE NUMBER	WEBSITE
DAN America Emergency Hotline	1-919-684-9111	www.diversalertnetwork.org
DAN America nonemergency line (Monday to Friday 8:30 AM to 5:00 PM Eastern time)	1-919-684-2848 or 1-800-446-2671	
DAN Europe	+3906-4211-5685	www.daneurope.org
DAN South Africa	+27-10-209-8112	www.dansa.org
DAN Asia-Pacific	+61-39886-9166	www.danap.org
DAN Japan	+81-3-3812-4999	www.danjapan.gr.jp

DAN, Divers Alert Network.

BOX 135.5

Diving Disorders That Require Recompression Therapy

Decompression sickness type I
Decompression sickness type II
Arterial gas embolism (AGE)
Contaminated air (carbon monoxide poisoning)

to key information at www.diversalertnetwork.org. DAN uses a telephone intake form, the DAN On-Site Neurological Assessment for Diver's History (Fig. 135.10); familiarity with this form may facilitate the emergency clinician's communications with DAN.

The United States Navy has its current diving manual (revision 6) available at its website, www.usu.edu/scuba/navy_manual6.pdf. This manual, updated in 2008, contains a wealth of information about diving principles, equipment, operations, and recompression.

Diving Disorders Requiring Recompression Therapy

Diving disorders that require recompression therapy are listed in Box 135.5. Early consultation with a hyperbaric specialist is recommended.

Treatment with 100% oxygen replaces inert gases in the lungs with oxygen. By establishment of a large gradient from the tissues to the alveoli, removal of the inert gases is enhanced and bubble size is reduced. In addition, oxygen administration treats the tissue hypoxia caused by gas bubbles. Normobaric oxygen treatment during preparation for recompression therapy is associated with a need for fewer recompressions.

Dehydration can increase the seriousness of DCS. Hydration decreases bubble formation after decompression. It also decreases the endothelial inflammation and damage associated with hemoconcentration and hemodynamic instability seen in dehydrated DCS patients. Therefore, intravenous fluids should be administered to divers suspected of having nonpulmonary ("chokes") DCS. Overly aggressive hydration in divers with pulmonary DCS may worsen pulmonary edema.[13] Similarly, fluid overload should be avoided in patients with cerebral or spinal cord edema. There is no clear consensus that the best fluid is crystalloid (normal saline or lactated Ringer's solution) or colloid; however, we advise against dextrose in water without electrolytes (eg, dextrose 5% in water [D_5W]). Fluids should be given to ensure a urinary output of 0.5 mL/kg per hour.

The intravenous fluid treatment recommendations differ in AGE. Divers with AGE are less likely to be dehydrated than are divers with DCS. This may be because of a shorter period of immersion or because they experience less bubble-induced endothelial damage. Further, CNS injuries in AGE may be worsened by cerebral edema. Therefore, large-volume fluid resuscitation is not recommended in divers with AGE after a short, shallow dive.

The goals of recompression therapy are to reduce the mechanical obstruction of air bubbles, to facilitate the washout of nitrogen by increasing the tissue-blood nitrogen gradient, and to increase oxygen delivery to ischemic tissue. Recompression is the only definitive treatment of DCS and AGE. Treatment of DCS or AGE should not be withheld even if a significant time delay in transfer to a hyperbaric chamber is unavoidable. Although delayed recompression is less effective than immediate recompression in serious cases, the time beyond which recompression offers no benefit is not well documented.

Hyperbaric therapy for AGE should be initiated as soon as possible, because there are cases of significant improvement even in the face of long delays until recompression. Patients with AGE who are recompressed within 5 minutes of surfacing have a mortality rate of 5%, and there is an extremely low risk of morbidity among the survivors. If recompression is delayed by 5 hours or more, the mortality rate increases to 10%, with 50% morbidity. Although spontaneous resolution of symptoms may occur in patients with AGE, all patients should be recompressed. The rationale is that although microbubbles may clear from the cerebral circulation, secondary capillary edema and swelling may result in a delayed recurrence of symptoms. Furthermore, more subtle symptoms may be appreciated only after the resolution of more prominent ones. Finally, minor symptoms may progress, and the relapse rate is high in untreated cases.

Similarly, the prognosis for DCS when it is treated with recompression is generally good but depends on the severity of symptoms at onset and the delay to recompression. A delay to definitive recompression treatment is associated with a worse outcome in cases of severe DCS. Patients can obtain some benefit from recompression, however, even if treatment is initiated more than 24 hours after the dive. Recompression therapy for DCS may be initiated as late as 10 to 14 days after exposure if necessary.

Recompression for DCS and AGE is most often performed in a multiplace chamber with one or more in-chamber attendants. DCS and AGE have also been successfully treated in monoplace chambers. Monoplace chambers are compact, lightweight, and more widely available than multiplace chambers. Unfortunately, because of their design, most cannot be pressurized beyond 3 ata (100 fsw) or deliver air-oxygen mixtures. The most common recompression schedule is United States Navy treatment (or an equivalent procedure); the diver is compressed to 2.8 bar (60 fsw pressure) while breathing 100% oxygen. The time to complete treatment is 4 hours 45 minutes, not including descent time.

Ground transport to a hyperbaric facility is preferred to air transportation, if feasible, because an increase in altitude lowers

DAN On-Site Neurological Assessment for Diver's History

Last Name: _____ **First Name:** _____ **MI:** _____

Date: (mm/dd/yy): _____ **Time: (hh:mm)** _____

COMPLETED BY: _____

How do you feel? _____

Symptoms? _____

Did symptoms start during descent, on bottom, during ascent, or after surfacing? _____

_____

Dive profile, breathing gas, ascent and time of surfacing, recent dive history _____

_____

_____

_____

Unusual features of dive (eg, out of air, rapid ascent) _____

Decompression computer, table _____

Difficulty with middle ear equalization? _____

Numbness, tingling? Where? _____

Pain? Where? What makes it better or worse? _____

Rate the pain on a scale of 0 (no pain) to 10 (the worst pain imaginable) _____

Shortness of breath? _____

Ringing or buzzing in ear? _____ Decreased hearing? _____

Dizziness? Vertigo? _____

"Vertigo" implies a sensation of the world spinning around. Vague "dizziness" is not vertigo.

Weakness? _____

Difficulty walking? If so, is this due to difficulty with balance or leg weakness? _____

Nausea, vomiting? _____ Able to urinate? _____

From "observer" (eg, dive buddy, companion) _____

Confirm dive profile _____

His/her version of events _____

_____

_____

Did the diver breach safe procedures (eg, ascent rate, out of air, was he/she breathing during ascent)?

_____

Has the diver been acting inappropriately? _____

Was there loss of consciousness, seizure? _____

Fig. 135.10. The Divers Alert Network (DAN) On-Site Neurological Assessment for Diver's History.

the ambient pressure and allows microbubbles to expand. If air transportation must be used, it is important to maintain cabin pressure at less than 1000 feet. Commercial aircraft are typically pressurized to a cabin altitude of 5000 to 8000 feet in cruise flight (30,000 feet). Many of these aircraft are capable of near–sea level cabin pressures if flying no higher than 15,000 to 20,000 feet. Because helicopters are not pressurized, it is recommended that they maintain an altitude of no more than 500 feet above the departure facility.

In addition to recompression therapy, several adjunctive treatments are proposed in the treatment of DCS and AGE. The treatment or prevention of hypothermia may increase tissue perfusion and off-gassing. The nonsteroidal anti-inflammatory drug (NSAID) tenoxicam (Mobiflex) decreases the number of recompressions required for symptom resolution in DCS but does not change the ultimate outcome. Aspirin therapy (as a platelet aggregation inhibitor) has previously been recommended for DCS and AGE. Because of the lack of studies demonstrating safety and efficacy for DCS or AGE treatment, however, it cannot be recommended. Steroids have previously been advocated clinically for neurologic DCS and AGE. No significant improvements in neurologic sequelae have been demonstrated; however, the elevated blood glucose levels associated with steroid treatment may worsen the outcome of CNS injury.

Anticoagulants should not be used routinely in the treatment of DCS. The one exception is in divers with lower extremity paralysis caused by neurologic DCS or AGE. Low-molecular-weight heparin (eg, enoxaparin, 30 mg, subcutaneously every 12 hours; dose adjustment should be made for patients with renal impairment) after recompression therapy may be used in patients with inability to walk to prevent venous embolic disease. Intermittent pneumatic compression devices are alternatives.

Lidocaine is not effective in DCS but may have neuroprotective effects in patients with AGE and serious neurologic symptoms. It is administered as an intravenous bolus of 1 mg/kg, followed by a drip infusion of 2 to 4 mg/min.

Cardiac dysrhythmias may be refractory to standard treatments until the diver is recompressed. Defibrillation in a hyperbaric environment may be a fire hazard and is not recommended. Seizures may be managed with benzodiazepines; however, mannitol should be avoided. Spinal DCS patients often develop urinary retention requiring bladder catheterization. Of note, endotracheal tube and urinary catheter balloons should be inflated with saline (not air) before recompression therapy is initiated. Nitrous oxide should be avoided because it can increase the size of tissue bubbles by inward diffusion.

Although the head-down position (Trendelenburg) has previously been advocated to prevent migration of intra-arterial bubbles to the brain, it is not effective and may result in worsening cerebral edema and intracranial pressure. Transport of the patient with AGE in a flat supine position is recommended to maximize arterial-venous flow.

There is limited experience with carbon monoxide poisoning from contaminated air supplies in a diving environment. This condition should be treated immediately with normobaric 100% oxygen and may require hyperbaric oxygen therapy. Consultation with a hyperbaric specialist or toxicologist is recommended.

Diving Disorders Not Requiring Recompression Therapy

Diving disorders that do not require recompression therapy are listed in Box 135.6.

External Ear Barotrauma

Treatment of external ear barotrauma includes cleaning of the external canal and removal of foreign bodies. Earplugs should not be worn when diving.

BOX 135.6

Diving Disorders That Do Not Require Recompression Therapy

Middle ear barotrauma (MEBT)
External ear barotrauma
Inner ear barotrauma (IEBT)
Barosinusitis
Facial barotrauma
Nitrogen narcosis
Oxygen toxicity
Pneumothorax
Pneumomediastinum
Subcutaneous emphysema
Alveolar hemorrhage
Alternobaric vertigo (ABV)
Barodontalgia
Gastrointestinal barotrauma
Avascular osteonecrosis

Middle Ear Barotrauma

Prevention of MEBT requires that the diver equalize the pressure in both middle ears. Any diver who cannot clear both ears on the surface should not dive. The diver should not perform a forceful Valsalva maneuver during descent or ascent to clear the ears because of the risk of ABV, round or oval window rupture (descent), or pulmonary barotrauma (ascent). The prophylactic use of pseudoephedrine (60 mg taken 30 minutes before diving) or oxymetazoline nasal spray may reduce the incidence and severity of MEBT. The use of these medications to facilitate diving with symptoms of an upper respiratory infection, however, is not recommended. Antihistamines should be avoided before diving. Sinusitis and upper respiratory infections increase the likelihood of suffering barotitis. Diving should be avoided for 2 weeks after the resolution of an upper respiratory infection.

Treatment of uncomplicated serous otitis from MEBT includes topical nasal vasoconstrictors, such as phenylephrine and oxymetazoline hydrochloride, and repeated Frenzel maneuvers to displace the fluid through the eustachian tube. The Frenzel maneuver is performed by pinching the nose, placing the tongue on the roof of the mouth, as far forward as possible, and gently moving the back of the tongue upward, as when starting to swallow; this is repeated as many times as necessary until equalization occurs. If the physical examination reveals a ruptured tympanic membrane, prophylactic treatment should also include an oral antibiotic. Oral steroids (prednisone) may speed recovery when a seventh nerve palsy is diagnosed in conjunction with a perforated tympanic membrane, although this disorder is typically self-limited. Diving must also be suspended until the tympanic membrane heals to prevent calorically induced vertigo.

Internal Ear Barotrauma

A conservative treatment approach to IEBT includes bed rest for 5 to 7 days with the head elevated, avoidance of straining and the Valsalva maneuver, and decongestants to facilitate drainage of the middle ear. Early surgical intervention may benefit patients with total or near-total hearing loss but not isolated high-frequency hearing loss. All patients with IEBT should be referred to an otolaryngologist, because IEBT suggests significant injury to the cochleovestibular system.

Barosinusitis

Treatment of barosinusitis is typically conservative, including the use of decongestants and, occasionally, antibiotics. If symptoms persist, referral for antrostomy should be considered, particularly to prevent future recurrences. The patient should be advised not to dive until any underlying respiratory infection or acute inflammatory process has resolved.

Facial Barotrauma

The victim of facial barotrauma may have a dramatic appearance, but the condition is usually benign and requires no specific treatment. The patient should be advised not to resume diving until facial edema resolves.

Nitrogen Narcosis

Nitrogen narcosis symptoms should resolve on ascending when the partial pressure of nitrogen decreases. Seemingly persistent symptoms should prompt a search for other causes, such as DCS, cerebral AGE, contaminated air, and near-drowning.

Pulmonary Barotrauma

With the exception of AGE, none of the pulmonary barotrauma disorders (pneumothorax, pneumomediastinum, subcutaneous emphysema, and alveolar hemorrhage) requires recompression therapy. Treatment with 100% oxygen may aid in the resolution of the disorders. Although tube thoracostomy may not be required for the treatment of a small pneumothorax, a tube should be placed if the diver is to undergo recompression therapy for concomitant AGE or DCS to prevent a tension pneumothorax. Catheter aspiration of the pneumothorax is an acceptable alternative to tube thoracostomy if the patient will not receive positive-pressure ventilation or recompression therapy.

The evaluation and management of pneumomediastinum include serial chest radiographs to ensure that no coexisting pneumothorax develops. One hundred percent oxygen therapy may hasten the resolution of symptoms. In the rare case of respiratory compromise, tracheal intubation may be required. Most important, the presence of interstitial pulmonary emphysema should alert the physician to the possible coexistence of more severe forms of pulmonary barotrauma. The need for a surgical decompressive treatment of subcutaneous emphysema alone is extremely unlikely. Supportive therapy to correct hypoxia is indicated in the treatment of alveolar hemorrhage.

Alternobaric Vertigo

Careful equalization during a slow ascent can prevent the occurrence of ABV. Oral and intranasal decongestants may be indicated if symptoms persist. Myringotomy is occasionally required.

DISPOSITION

Decompression tables are based on the premise that the diver returns to an ambient pressure of 1 atm on surfacing. However, with ascent in altitude after diving or on diving at altitude, a further reduction in ambient pressure occurs. Commercial airliners may be pressurized to a cabin altitude of 5000 to 8000 feet in cruise flight. Many cases of DCS have a delay in the onset of symptoms in divers who fly after diving even if they are symptom free before departure. Divers who experience DCS symptoms before departure but nevertheless fly are more likely to have type II DCS, less likely to achieve complete relief after recompression, and more likely to have residual symptoms for at least 3 months.

The recommended post-dive preflight surface interval (PFSI) before ascending to higher altitudes (or flying) depends on the diver's repetitive group designator (residual nitrogen time). The relative risk for development of DCS increases with greater residual nitrogen times and shorter PFSI (Fig. 135.11). For example, the risk for development of DCS is seven times greater for PFSIs of 12 hours after a dive to 130 fsw than for PFSIs of 24 hours after a dive to 60 fsw. Long PFSIs (up to 48 hours) may be necessary to reduce the risk of DCS after deep, multiday repetitive diving, particularly if the dives required decompression stops (exceeding the no-decompression limits). Some dive computers calculate time-to-flight intervals, which tend to be somewhat shorter than most guidelines based on residual nitrogen timetables. Flying should be delayed for at least 12 hours after diving if less than 2 hours of total dive time was accumulated in the preceding 48 hours. For multiple-day, unlimited diving, flying should be delayed for at least 24 hours. It is prudent to admit all recompressed patients or to advise them to remain within 60 minutes of the hyperbaric facility for 24 hours. Patients recompressed after DCS or AGE should not fly for 72 hours.

United States Navy guidelines recommend that the patient not return to diving for 7 days after recompression for type I DCS and for 4 weeks after type II DCS. The sport diver who experiences DCS type II symptoms or AGE should be discouraged from future diving again.

After treatment for pulmonary barotrauma, divers are evaluated with a spiral volumetric chest CT scan to determine whether there are any preexisting pathologic conditions (eg, bullae) that could put the diver at risk for recurrence before further diving. Chest CT is not used in routine medical screening before participation in scuba diving without a history of pulmonary barotrauma.

Echocardiography to assess for a PFO is often recommended for divers with severe or recurrent neurologic DCS.[43] A substantial amount of venous gas must embolize through the PFO for significant symptoms to occur; that is unlikely to happen in conservative depth-time profiles. A diver with a diagnosed PFO should weigh the risks of continuing to dive and the risks of surgical repair.

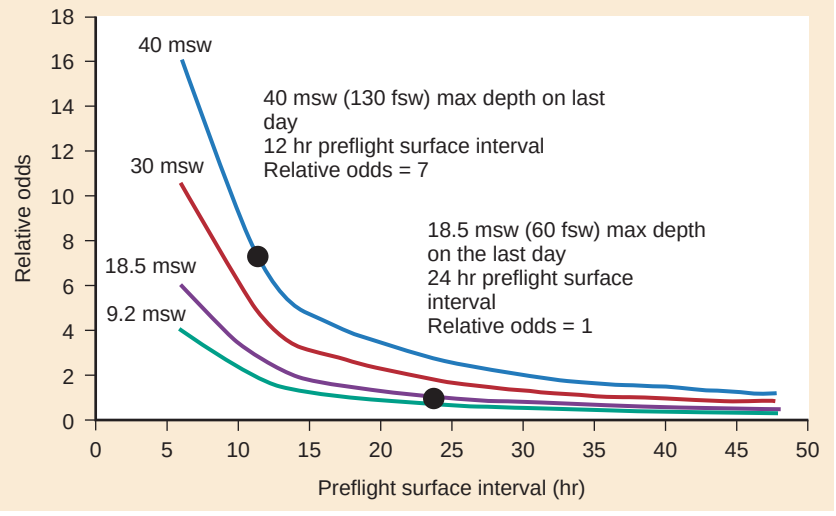

Fig. 135.11. The risk of decompression sickness (DCS) relative to flying. *fsw,* Feet of seawater; *msw,* meters of seawater. (From Freiberger JJ, et al: The relative risk of decompression sickness during and after air travel following diving. Aviat Space Environ Med 73:983, 2002.)

KEY CONCEPTS

- The majority of dive injuries are diagnosed on the basis of the focused dive history and physical examination alone and are best differentiated into disorders of descent, disorders of depth, and disorders of ascent.
- The *U.S. Navy Diving Manual* and the Divers Alert Network (DAN) are valuable resources for the clinician presented with a diving emergency. DAN provides a 24-hour medical emergency hotline at 1-919-684-9111 (collect calls are accepted) and a nonemergency advisory line Monday through Friday, 8:30 AM to 5 PM Eastern time, at 1-919-684-2948 or 1-800-446-2671 (see Box 135.3).
- Treatment with 100% oxygen is the initial therapy for all diving emergencies until the diagnoses can be determined. It has been demonstrated to reduce the morbidity and mortality related to decompression illness and can be helpful in patients with pneumothorax.
- Imaging and laboratory studies are not useful for ruling in decompression and should not delay definitive recompression therapy.
- With the exception of DCS, AGE, and possibly carbon monoxide poisoning from contaminated air, most dive-related disorders can be treated without recompression therapy. Recompression treatment is recommended for patients with DCS and AGE.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 135: QUESTIONS & ANSWERS

135.1. When is a diver most likely to suffer barotrauma?

A. When the diver also suffers from decompression sickness (DCS)
B. When the diver is at extreme depth
C. When the diver is near the surface
D. When the diver stays at depth for an extended period of time
E. When the diver uses specialized gas mixtures with decreased partial pressure of nitrogen

Answer: C. Barotrauma refers to injuries due to pressure changes. Boyle's law states that pressure and volume are inversely proportional ($P \times V = k$ or $P_1V_1 = P_2V_2$). As the pressure decreases, the volume of gas increases and can damage gas-filled structures (sinuses, inner/middle ears, lungs, and intestines). The incremental changes in pressure (and therefore volume) are greatest at the surface, so barotrauma most commonly occurs near the surface (either at the beginning or at the end of a dive). Long or deep dives are not required for barotrauma.

135.2. A 55-year-old man presents with the acute onset of left-sided weakness and confusion. Family members report that they are on vacation and had just finished scuba diving when the patient complained of chest pain, became confused, and stopped moving his left arm and leg. This happened 30 minutes ago. The patient has no known medical history and takes no medications. Physical examination reveals a drowsy and confused male who follows commands but does not move his left arm or leg. His blood pressure is 162/98 mm Hg, and his other vital signs are within normal limits. What is the appropriate treatment?

A. Computed tomography (CT) of the brain
B. Endotracheal intubation
C. Intravenous labetalol
D. Intravenous tissue plasminogen activator
E. Recompression in a dive chamber

Answer: E. This patient has suffered an arterial gas embolism (AGE). In AGE, air bubbles gain access to the arterial circulation and can cause mechanical obstruction of the artery. Symptoms can mirror an acute thrombotic or embolic event including myocardial infarction or stroke. Treatment with 100% oxygen should be instituted immediately, but the only definitive treatment is emergent recompression.

135.3. Which of the following individuals should be advised not to dive?

A. A 10-year-old boy with no known medical problems
B. A 19-year-old woman with no medical problems but who just landed from an intercontinental commercial flight
C. A 20-year-old man with well-controlled asthma
D. A 27-year-old woman who is 20 weeks' pregnant
E. A 70-year-old man with asymptomatic coronary artery disease

Answer: D. Upon surfacing, small nitrogen bubbles form in the circulation of all divers. If proper technique is followed, these bubbles are small and asymptomatic. They form in the venous circulation and are eliminated in the lungs. However, if these bubbles are transmitted into the arterial system, embolization with serious consequences can occur. The fetus has a patent foramen ovale (PFO) and ductus arteriosus, both of which would allow air to bypass this filtering effect of the lungs and proceed into the systemic circulation. Therefore adults with a known PFO should not dive. Asthmatics can dive as long as symptoms are well controlled. There are no definite age recommendations for diving. Flying immediately after diving should be avoided; flying prior to diving is of less concern.

135.4. A 24-year-old woman presents with complaints of severe chest pain and shortness of breath. The symptoms started approximately 1 hour ago while surfacing from a dive. She denies loss of consciousness or other symptoms. Physical examination reveals decreased breath sounds in the right chest and crepitus in her neck; otherwise, it is normal. Vital signs are normal except for a slight tachypnea. A chest radiograph shows a moderate right-sided pneumothorax and a pneumomediastinum. You place a chest tube on her right side. What is the next course of action?

A. Computed tomography (CT) of the brain
B. CT of the chest
C. Observation and supportive care
D. Pericardiocentesis
E. Recompression in a dive chamber

Answer: C. This patient has suffered from pulmonary barotrauma. Although this injury does predispose one to arterial gas embolism (AGE), the diagnosis of AGE is clinical. The treatment for a pneumothorax from pulmonary barotrauma is the same as for a pneumothorax from another cause—that is, aspiration, catheter insertion, or chest tube placement. Management of pneumomediastinum is supportive. Recompression is only necessary for decompression sickness (DCS) or AGE, not for barotrauma.

135.5. A 32-year-old man presents with bilateral lower extremity numbness and weakness. The patient reports several days of scuba diving without incident until his most recent dive, when the symptoms started. Physical examination reveals bilateral lower extremity weakness and decreased sensation to pinprick and light touch. Priapism is also noted. The remainder of the physical

examination and all vital signs are within normal limits. You decide that recompression therapy is indicated, but your emergency department does not have a dive chamber and the nearest chamber is 50 miles away. The patient has been accepted in transfer. What is the most appropriate way to transfer this patient?

A. Air ambulance, lying flat
B. Air ambulance, Trendelenburg position
C. Ground ambulance, lying flat
D. Ground ambulance, Trendelenburg position
E. This patient has not yet been stabilized for transport; he should remain at the current hospital.

Answer: C. This patient is suffering from spinal decompression sickness (DCS II). Recompression therapy is the treatment of choice. Unless an inordinate delay to the recompression chamber would result, anything that further decreases ambient pressure should be avoided (eg, flying). If a patient must be flown, the aircraft should fly at the lowest possible altitude or pressurize the cabin at the highest possible pressure. Traditionally, the Trendelenburg position was advocated because it was believed that it would decrease the incidence of AGE to the brain. This is not the case. In addition, the Trendelenburg position increases cerebral edema and the incidence of coronary artery air embolism. Therefore, the Trendelenburg position should never be used for patients with diving injuries.

135.6. A scuba tank is inadvertently filled with air that contains 100 ppm CO. The diver breathes the compressed air at the surface and has no symptoms. Twenty minutes later at a depth of 100 feet, the diver becomes symptomatic of carbon monoxide poisoning. Why?

A. At depth, blood is preferentially shunted to the brain, so although the concentration of CO does not change, its effects become more prominent.
B. At depth, the body becomes more sensitive to toxins of any sort.
C. At depth, the partial pressure of CO increases and so the concentration in the blood also increases.
D. At depth, the partial pressure of O_2 decreases and so the relative concentration of CO in the blood increases.
E. The depth does not matter; the diver has now been breathing CO for 20 minutes and it has had time to dissolve in the blood.

Answer: C. The partial pressure of all gases increases with depth (pressure). This is Henry's law. At 100 feet, the total pressure on the body is approximately four times that on the surface. Likewise, the amount of gas dissolved in blood is approximately four times that on the surface. Thus at this depth, it is roughly equivalent to breathing air with a CO concentration of 400 ppm. The diver also has more O_2 dissolved in blood, but this cannot counter the effects of CO because it has a much higher affinity for hemoglobin. Blood flow is not changed at depth. In general, the body is not more susceptible to toxins at depth. Although the amount of time in contact with a poison (eg, CO) does correlate with effects, this is of negligible effect in this case.

135.7. You decide that a 27-year-old patient with an arterial gas embolism (AGE) following scuba diving requires recompression therapy. Which of the following treatments should be initiated before hyperbaric therapy?

A. Administer 40% oxygen.
B. Administer steroids.
C. Ensure that the endotracheal tube and urinary catheter balloons are filled with water, rather than air.
D. Place prophylactic thoracostomy tubes bilaterally.
E. Place the patient in the Trendelenburg position.

Answer: C. Inflate endotracheal tube and urinary catheter balloons with sterile saline. There is no evidence that steroids are effective. The Trendelenburg position increases intracranial pressure and facilitates coronary gas embolization.

CHAPTER 136

High-Altitude Medicine

N. Stuart Harris

PRINCIPLES

Background

Acute high altitude illnesses result from exposure to low oxygen states caused by low atmospheric pressure (hypobaria). Syndromes of the brain and lung are the primary clinical manifestations of high altitude illness. They most typically result from ascent too rapid to allow for adequate acclimatization. Cerebral forms of altitude illness occur as a continuum, from common and benign acute mountain sickness (AMS), to rare, but potentially lethal high-altitude cerebral edema (HACE). High-altitude pulmonary edema (HAPE) is the primary lung syndrome. HAPE is the leading cause of death from altitude illness.

All forms of altitude illness have their origins in acute oxygen insufficiency due to hypobaria. All can be treated with oxygen and descent. Although the percentage of atmospheric oxygen is a constant 20.9%, as elevation increases, atmospheric pressure decreases and with it, oxygen availability. Human physiology is remarkably adaptable when given sufficient time to acclimatize by gradual ascent. Rapid ascent to elevations greater than 8000 feet prevents adequate acclimatization and can lead to debilitating and deadly—and completely avoidable—high altitude illnesses. On the summit of Mt. Everest (8848 m), the partial pressure of inspired oxygen (PiO_2) is only 29% of the sea level value. Although gradual ascents (over weeks) of Mt. Everest without oxygen are not uncommon, a rapid, unacclimatized ascent to the same summit would result in rapid loss of conscious and death. Gradual ascent reduces symptoms and can save lives. Serious altitude illness inevitably follows from unheeded warning symptoms of mild altitude illness. The importance of patient and public education to reduce the morbidity and mortality of serious altitude illness cannot be overstated.

Epidemiology

It is estimated that approximately 40 million individuals worldwide live above 8000 feet. These individuals do not suffer acute altitude illness. Instead, it is the individual (whether for skiing, climbing, travel) who rapidly travels to high altitude who is at greatest risk. In the United States alone, approximately 35 million visitors travel to high-altitude recreation areas every year. Internationally, millions more travel to high mountain ranges of Europe, Asia, Africa, and South America. Each of these transient sojourners is at risk.

The incidence and severity of altitude illness are directly related to elevation and rapidity of ascent. Other variables influencing AMS development including prior acclimatization, individual genetic susceptibility, sleeping elevation, and duration of stay.[1,2] Rapid ascent to 8000 feet is associated with an approximately 25% incidence of AMS, whereas a rapid ascent (1 or 2 days) to 14,410 feet on Mt. Rainier has rates as high as 67%. Rapidity and mode of ascent also matter; trekkers who fly into the Khumbu region to explore the Mt. Everest area are more likely to develop AMS (47%) than those who walk in from lower elevations (23%).

HACE is much less common than AMS, occurring at well less than 1% of rapid ascents to more than 14,000 feet. Although rare, it carries a grave prognosis if not quickly recognized and treated. The incidence of HAPE varies from 0.01% to 2% in most studies but has reached 15.5% among soldiers flown directly to 14,500 feet without a chance to acclimatize at a lower altitude.[3] Both HAPE and HACE are more common with a longer duration of visit (more than 2 days) and higher sleeping altitude.

Age may be a relative risk factor. Most studies of children suggest that they have the same incidence of AMS as adults. One small study of tourists in Chile evaluated children 4 to 48 months old and found higher AMS scores and lower oxygen saturations compared with those of their parents.[4] Younger individuals (younger than 20 years old) are more likely to have HAPE, although HAPE is extremely rare in children younger than 2 years old. Gender does not affect the incidence of AMS; however, women may have less risk for development of HAPE. No relationship appears to exist between AMS development and the menstrual cycle.

The number of older travelers visiting mountain resorts is increasing. Many of these individuals have underlying health problems, including lung disease, heart disease, and hypertension. Despite these conditions, the risk for AMS development in adults older than 50 years old may be less than in younger age groups. One study found no difference in the incidence or severity of AMS in climbers older than 50 years old compared with a matched cohort of younger climbers.[4] Nevertheless, there are indications that elders may not react well to acute high-altitude exposure. Pulmonary vital capacity decreases almost one-third in elders ascending from sea level to 14,000 feet for 1 week, producing a large decrease in both oxygen saturation and maximal oxygen uptake during exercise.

Definitions

Moderate altitude is between 5000 and 8000 feet of elevation. Rapid ascent to this altitude may result in mild, transient symptoms, but severe altitude illness is uncommon. *High altitude* is between 8000 and 14,000 feet. Although most people do not experience significant arterial oxygen desaturation until they reach higher altitudes, high-altitude illness is common with rapid ascent above 8000 feet, and individuals with underlying medical problems may be predisposed to development of altitude illness at lower levels. The pathophysiologic effects of high altitude begin when the oxygen saturation of the arterial blood begins to fall below the 90% level. The sigmoidal shape of the oxyhemoglobin dissociation curve prevents a significant fall of arterial oxygen saturation (Sao_2) in most individuals until an altitude of approximately 12,000 feet. At this altitude, the steep portion of the curve is encountered, and marked oxygen desaturation may occur with relatively small increases in altitude (Fig. 136.1). Some predisposed individuals may desaturate to less than 90% at altitudes as low as 8000 feet. *Very high altitude* is between 14,000 to 18,000 feet. At this elevation, the likelihood of altitude illness is high, and the risk of serious altitude illness (HAPE and HACE) notably increases.

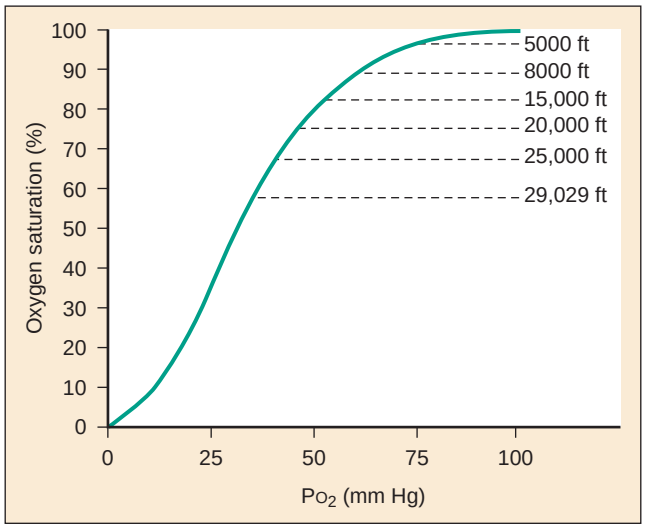

Fig. 136.1. Oxygen-hemoglobin dissociation curve. Approximate oxygen saturations are marked for several altitudes. *P_{O_2},* Partial pressure of oxygen. (Data for 15,000 to 29,029 feet from Sutton JR, et al: Operation Everest II: oxygen transport during exercise at extreme simulated altitude. J Appl Physiol 64:1309, 1988.)

Extreme altitude is above 18,000 feet. Although climbers using careful acclimatization schedules can transiently tolerate this height, complete acclimatization generally is not possible and long visits above this level result in progressive deterioration. Given limitations in physiologic reserves, climbers who become incapacitated at this elevation typically are dependent on others to survive.

Environmental Considerations

Barometric pressure decreases logarithmically as the altitude rises. The pernicious effects of altitude are due to hypobaric hypoxia; as atmospheric pressure decreases the partial pressure of oxygen (P_{O_2}) decreases. The earth is slightly flat at the poles and bulging at the equator. The atmospheric envelope that surrounds the earth has a similar shape; therefore, the barometric pressure at any one elevation tends to be lower at higher latitudes than at the equator. Although subtle, the physiologic reserves are so limited at extreme elevations that it has been calculated that if Mt. Everest happened to be at a more northern latitude, it would be impossible to climb without supplemental oxygen.

The atmospheric envelope also undergoes seasonal variations in local thickness. In the winter, barometric pressures tend to be lower making "relative altitudes" physiologically higher. Local weather can also significantly effect the barometric pressure. A low-pressure front can reduce the barometric pressure 12 to 40 mm Hg and so increase the "relative altitude" by 500 to 2500 feet. At extreme elevations this can be physiologically relevant.

Acclimatization

Exposure to acute hypobaric hypoxia results in myriad physiologic responses that act to improve oxygenation. *Acclimatization* is both immediate (within minutes the carotid bodies sense hypoxemia) and continuous over months (hemoglobin increases may continue over more than 6 weeks). It involves multiple systems from protein synthesis to respiratory, cardiovascular, renal, and hematologic responses.

Acclimatization begins as the oxygen saturation of arterial blood falls below sea-level values. The altitude at which this occurs depends on the rate of ascent, the duration of exposure, and the individual's physiology. People with preexisting conditions that limit cellular oxygen delivery and pulmonary reserves may have a decreased altitude tolerance. Most healthy, unacclimatized visitors to high altitude will not desaturate significantly (to less than 90%) until they reach elevations higher than 8000 feet.

The risk of high-altitude illness depends on an individual's inherent ability to acclimatize. Some people acclimatize easily without having any clinical symptoms. Others may transiently have AMS during acclimatization, and a few have marked reactions to altitude exposure, developing severe altitude illness. This variability involves many genetic and epigenetic factors that influence acclimatization.[5-8] Previous successful acclimatization may be predictive of future responses for adults in similar conditions, but this may not be the case for children.

One of the most fundamental physiologic changes that occurs during acclimatization is an increase in minute ventilation. Within minutes of exposure to high altitude, the peripheral chemoreceptors in the carotid bodies sense the decrease in the partial pressure of oxygen in alveolus (P_{AO_2}) and signal the respiratory control center in the medulla to increase ventilation. Increased minute ventilation causes a decrease in the partial pressure of carbon dioxide in alveolus (P_{ACO_2}). As described by the alveolar gas equation, for any given inspired oxygen tension, the level of ventilation determines alveolar oxygen: as the P_{ACO_2} decreases, P_{AO_2} correspondingly increases (Box 136.1). This increased ventilation in response to hypoxic challenge is known as the *hypoxic ventilatory response (HVR).* The magnitude of the HVR varies among individuals and may be genetically predetermined. HVR may also be inhibited or stimulated by numerous factors, including ethanol, sleep medications, caffeine, cocoa, prochlorperazine, and progesterone.

As minute ventilation increases, carbon dioxide exhalation increases; and within minutes, a resulting respiratory alkalosis acts on the central respiratory center to limit further increases in ventilation. To compensate for this respiratory alkalosis, the kidneys begin to excrete bicarbonate. Acetazolamide enhances this excretion. Gradual, progressive renal excretion of bicarbonate allows ventilation to rise slowly, reaching a maximum after 6 to 8 days at a given altitude. An individual's HVR is related to their ability to acclimatize. A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE. For the majority of people with intermediate HVR's, however, ventilatory drive appears to have no predictive value for AMS development.

The stress of acute hypoxia leads to rapid release of catecholamines. This results in increased cardiac output and elevations in heart rate, stroke volume, blood pressure, and venous tone. Except at extreme altitudes, acclimatization over weeks results in the gradual return of the resting heart rate to near sea-level values. Continued resting tachycardia is evidence of poor acclimatization. As the altitude increases, the maximal heart rate capacity decreases. At the limits of acclimatization, maximal and resting heart rates converge. Ultimately, pulmonary, not cardiac reserves typically limit high altitude performance.

BOX 136.1

Alveolar Gas Equation

$$P_{AO_2} = P_{IO_2} (P_{ACO_2}/R)$$

P_{AO_2}	Partial pressure of oxygen in alveolus
P_{IO_2}	Partial pressure of oxygen in inspired air
P_{ACO_2}	Partial pressure of carbon dioxide in alveolus
R	Respiratory quotient

The hematopoietic response to high-altitude acclimatization includes an increase in both hemoglobin and the number of red blood cells. As a result of fluid shifts into the extravascular space, mean corpuscular hemoglobin concentration increases up to 15% after rapid ascent to high altitude. Long-term acclimatization leads to an increase in plasma volume and total blood volume. Erythropoietin is secreted in response to hypoxemia within hours of ascent, which in turn stimulates the production of red blood cells, leading to new circulatory red blood cells in 4 or 5 days. During the next 2 months, red blood cell mass increases in proportion to the degree of hypoxemia.

Hypoxemia also results in an increase in 2,3-diphosphoglycerate, causing a rightward shift of the oxyhemoglobin dissociation curve, which favors a release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhemoglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The result is a net null change in the oxyhemoglobin curve and an increase in oxygen-hemoglobin binding in the lung, which raises Sao_2. Some individuals with mutant hemoglobin and high oxygen-hemoglobin affinity are found to acclimatize more efficiently than their normal counterparts at moderate altitudes.

Pathophysiology

Although acute hypoxia elicits a broad array of physiologic responses, the clinical syndromes of high-altitude illness predominantly affect the brain and lungs. Hypobaric hypoxia's effects on central nervous system homeostasis give rise to AMS and HACE. AMS is the common, benign form that unheeded, can develop into rare, but potentially lethal HACE. HAPE results from overly exuberant increases in pulmonary arterial pressures that lead to stress failures of the delicate pulmonary capillary beds.

Although discrete physiologic responses occur within minutes of exposure to acute hypoxia, the clinical syndromes of high altitude typically require hours to days to manifest themselves. AMS can develop within 4 to 8 hours of acute exposure to hypobaric hypoxia. HACE and HAPE typically occur 2 to 4 days after exposure to high altitude. Because hypobaric hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness. Instead, it appears to be the initiating factor for a complex pathologic process that leads to the development of the various clinical syndromes. The proposed mechanisms for the development of AMS, HAPE, and HACE are represented schematically in Figure 136.2.

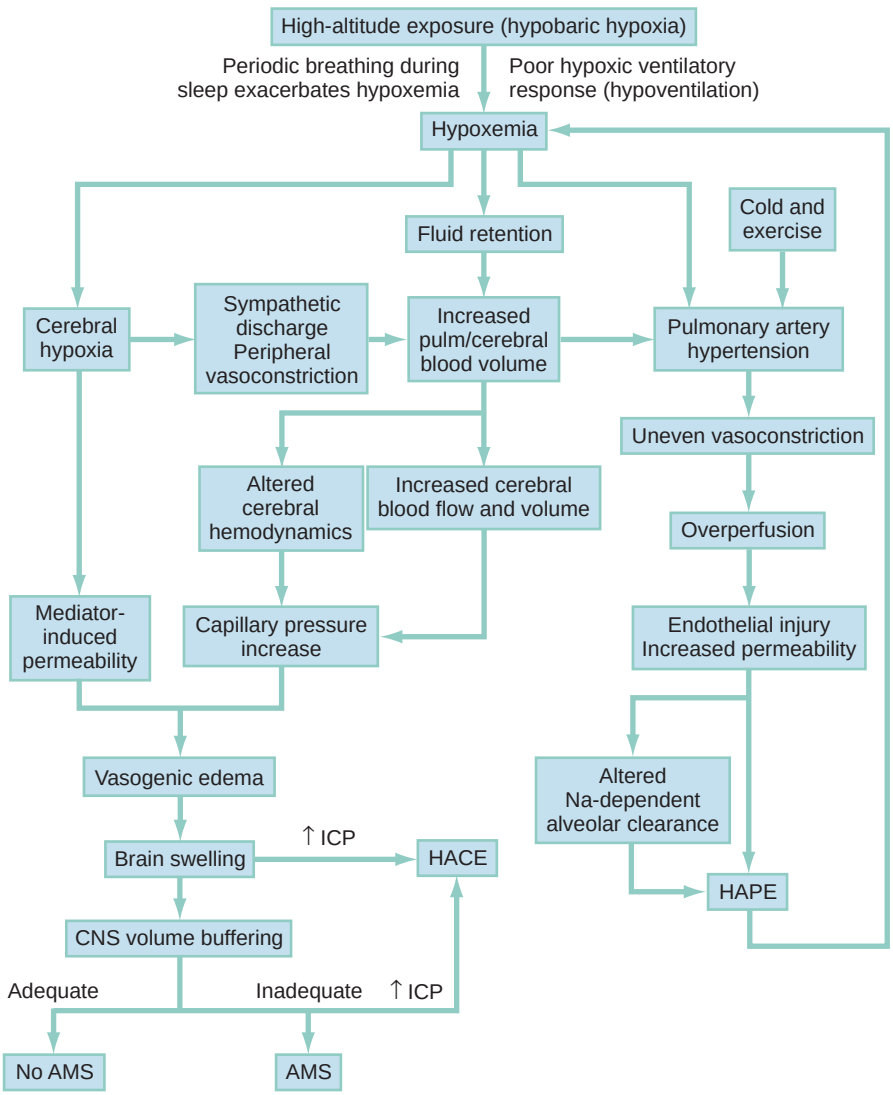

Fig. 136.2. Proposed mechanisms for the development of acute mountain sickness *(AMS)*, high-altitude pulmonary edema *(HAPE)*, and high-altitude cerebral edema *(HACE)*. *CNS*, Central nervous system; *ICP*, intracranial pressure.

HVR is the first response to insufficient oxygen, leading to increased minute ventilation. A robust HVR tends to be protective by encouraging compensatory ventilation. A limited HVR leads to relative hypoventilation and inadequate response to the hypoxemia of high altitude.

Centrally mediated periodic breathing associated with high-altitude exposure may result in periods of apnea during sleep, causing severe arterial oxygen desaturation, which further exacerbates hypoxemia. Significant hypoxemia initiates multiple systemic responses that involve the circulatory, pulmonary, endocrine, and central nervous systems.

Hypoxemia alters fluid homeostasis, resulting in a generalized fluid retention followed by the shift of fluid into the intracellular spaces. This is manifested by peripheral edema, decreased urinary output, decreased central vascular volume, and increased body weight in patients with AMS.[186] Several different mechanisms may account for these fluid shifts, including arginine vasopressin levels and sympathetic stimulation that may be centrally mediated. Arginine vasopressin levels are elevated in some cases of AMS and HAPE and decreased in others. Aldosterone, plasma renin, and atrial natriuretic levels are higher in people with AMS.

HAPE results from hypoxia-induced acute pulmonary hypertension leading to stress failure of pulmonary capillaries with consequent alveolar and interstitial edema. Although exercise and cold stress at altitude may increase hypoxemia and exacerbate pulmonary hypertension, the hypoxic pulmonary vasoconstrictive response (HPVR) acts as the primary mediator. HPVR results in pulmonary arterial smooth muscle contraction within the typically low-pressure pulmonary arterial system, with consequent increases in pulmonary arterial pressures within minutes.[9] The HPVR can vary widely between individuals and can even vary widely in different regions of the lungs of the same individual. This unevenness of pulmonary vasoconstriction within an individual's lung is thought to contribute to the pathophysiology of HAPE. In patients with HAPE, exaggerated pulmonary arterial pressures (mean pressure 36 to 51 mm Hg) occur.[10] Uneven vasoconstriction forces the pulmonary hypertension to be transmitted to delicate capillary vessels in an uneven fashion, leading to the failure of capillary endothelium with resultant alveolar and interstitial edema.[11] This uneven edema explains the patchy nature of the infiltrate seen on a chest radiograph with HAPE. It should be noted that although elevated pulmonary arterial pressure is the sine qua non of HAPE, even marked acute pulmonary hypertension is not alone sufficient to cause HAPE.[12]

The mechanism for the uneven vasoconstriction in HAPE may be due to decreased nitric oxide bioavailability at the pulmonary tissue level. That HAPE has its origins in acute pulmonary hypertension and resultant over-perfusion is supported by studies revealing that pharmacologic agents that limit excessive rises in pulmonary artery pressure prevent HAPE and findings that patients with congenital unilateral absence of a pulmonary artery (and so the entire cardiac output is delivered to one lung) have increased HAPE susceptibility.

Once mechanical injury and pulmonary edema occur, other factors come into play. Acute inflammatory mediators appear and likely contribute to worsening lung function. As alveolar fluid accumulates, impairment in a patient's transepithelial sodium transport may decrease their ability to clear alveolar fluid and so worsen HAPE. Sodium channel-mediated alveolar fluid clearance is upregulated by inhaled beta-adrenergic agonists, which have been proven to decrease risk of HAPE.

Preexisting inflammation may also be a risk factor for HAPE. Particularly in children, preexisting respiratory infection during ascent to high altitude increases susceptibility to HAPE.[31] Inflammation may "sensitize" the pulmonary endothelium to mechanical injury and increase susceptibility to alveolar fluid accumulation and HAPE during ascent.

The definitive etiology of the cerebral forms of altitude illness remains unclear. Evidence suggests that clinical manifestations of AMS and HACE result from the combined effects of altered cerebral hemodynamics and inflammatory mediators. Within minutes of exposure to hypoxia, cerebral vasodilation occurs with increased arterial blood velocity and volume. Hypocapnia (secondary to increased ventilation) creates a countervailing cerebral vasoconstriction. The overall effect is one of increased cerebral blood flow. Given the rigid confines of the skull, increases in intracranial blood volume require compensatory changes in the brain and cerebral spinal fluid or intracranial pressures will inevitably increase. CNS hypoxemia leads to impaired vascular autoregulation, causing increased pressures within the brain's capillary beds. In addition, systemic hypertension from strenuous exercise at high altitude may overwhelm the brain vasculature, resulting in transcapillary leakage and vasogenic edema. In susceptible individuals, these hemodynamic changes are likely to contribute to clinical manifestations of AMS and HACE.

Additional circumstances, however, may be necessary for the development of vasogenic edema and clinical symptoms. Inflammatory mediators may contribute to edema formation. Vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation may mediate brain endothelial permeability. The roles that these play in the pathophysiologic process of altitude illness remain unclear.

The role of vasogenic edema in AMS is of unclear significance. Magnetic resonance imaging (MRI) of subjects acutely exposed to hypoxia reveal similar signal changes in both subjects with and without clinical AMS. In patients with HACE, MRI studies reveal characteristic white matter changes consistent with vasogenic edema that correlate with symptoms. Although still an area of active research, AMS and HACE pathophysiology is likely due to disturbances in the blood-brain barrier through a combination of mechanical factors and biochemical mediation of permeability.

In severe AMS, MRI studies have revealed cytotoxic edema to present. Rather than being the primary mechanism of severe AMS/HACE, this cytotoxic edema is likely secondary to increased cell ischemia resulting from initial hemodynamic changes, vasogenic edema, biochemical mediators, and increased ratios of brain volume to intracranial space.[13]

Increasing data highlight the independent role of hypobaria in the development of AMS and on physiologic responses, including heart rate.[14] In experiments where subjects are exposed to identical levels of alveolar oxygen deprivation, subjects exposed to normobaric hypoxia (by decreasing fraction of inspired oxygen [FiO_2]) alone have much lower AMS incidence than subjects exposed to a hypobaric hypoxia. The exact pathophysiologic role of hypobaria in altitude illness remains unclear.

Although the "tight fit" hypothesis was proposed more than three decades ago to explain AMS development and its inherent individual susceptibility, the role of increased intracranial hypertension in AMS remains of area of active research. This theory suggests that susceptibility to AMS and HACE increases as a subject's ability to accommodate hypoxia-related increased intracranial blood volume and cerebral edema decreases. As brain volume increases from increased cerebral blood volume, the volume-buffering capacity of the central nervous system may prevent an immediate rise of intracranial pressure. As brain volume increases, the intracranial cerebrospinal fluid (CSF) is displaced through the foramen magnum into the spinal canal. Increased absorption of CSF by the arachnoid villi and decreased CSF production also occur. Individuals with less intracranial and intraspinal CSF buffering capacity have less compliance, and so larger increases in intracranial pressure, and become more symptomatic (ie, develop AMS) from mild brain swelling. The tight fit hypothesis is supported by lumbar puncture, MRI, and computed tomography (CT) studies. More recently, optic nerve sheath

ultrasonography has emerged as an early, noninvasive diagnostic tool to assess intracranial pressure. Increasing intracranial pressure correlates directly with optic nerve sheath diameter (ONSD). Studies have demonstrated that elevated intracranial pressure is associated with AMS and HACE.

ACUTE MOUNTAIN SICKNESS

Clinical Features

AMS is a clinical diagnosis. As defined by the Lake Louise Criteria, the diagnosis of AMS requires a patient to have recently ascending to an elevation to 8000 feet, with report a headache *plus* at least one of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness or lightheadedness, or difficulty in sleeping (Box 136.2). The headache may vary from mild to severe, is generally bitemporal and throbbing in nature, and is worse during the night and on awakening or on suddenly becoming upright. Anorexia and nausea, with or without vomiting, are common, and the other symptoms described can range in severity from mild to incapacitating. The disturbance of sleep caused by periodic breathing is common in all visitors to high altitudes but may be exacerbated in the setting of AMS. The symptoms of AMS develop within a few hours after arrival at high altitude and generally reach maximum severity between 24 and 48 hours, followed by a gradual resolution. Most individuals become symptom free by the third or fourth day. Patients with continued symptoms should not ascend until symptoms abate, and descent and alternative diagnoses should also be considered.

Given its subjective nature, AMS is difficult to definitively diagnose in infants and pre-verbal children. AMS may be manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance. Although AMS, or a change in environment, sleeping accommodation, or eating habits may result in a fussy, unhappy child, the differential diagnosis for these nonspecific findings must remain broad. If occult bacteremia or another serious illness is suspected in a young child, prudence requires descent to lower altitude and an appropriate diagnostic and treatment regimen.

Differential Diagnosis

AMS is a clinical diagnosis without objective diagnostic physical findings. A prudent physician maintains a broad differential diagnosis when treating these nonspecific symptoms (Box 136.3). Less common, but lethal etiologies of headache, nausea, and fatigue must be considered before the benign diagnosis of AMS is made. Any evidence of ataxia or altered mentation gives evidence of HACE and mandates immediate descent. Benign focal neurologic findings and transient global amnesia have been described at altitude but should be assumed to be malignant in etiology until proven otherwise. Acute carbon monoxide (CO) poisoning is more likely than in other environments. Although dyspnea on exertion is universal and expected at high altitudes, dyspnea at rest gives evidence of HAPE. A careful examination for pulmonary edema is indicated.

Diagnostic Testing

Serial measurement of ONSD using ultrasound has demonstrated that subjects with symptoms and signs of worsening AMS or HACE have enlarged ONSDs on serial measurements, which may prove a useful adjunct in the diagnosis and monitoring of AMS and HACE (Fig. 136.3).

Management

Patients with AMS should not ascend to a higher sleeping altitude until symptoms resolve to allow acclimatization to occur. Continued ascent exacerbates the underlying pathologic processes and may lead to severe AMS or lethal HACE. If patients develop neurologic abnormalities (eg, ataxia or altered mentation) or evidence of severe pulmonary edema, immediate descent is indicated.

Mild AMS may be treated by symptom management and cessation of ascent until acclimatization occurs. This may take 1 to 4 days. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention necessitates descent. A descent of as little as 500 feet may be sufficient. Descent of 1500 to 3000 feet effectively reverses high-altitude illness in most cases. Descent should be continued until improvement is seen, and efforts to minimize exertion should be instituted during the descent.

Oxygen Therapy

All forms of altitude illness, including AMS, are effectively treated with supplemental oxygen. In mild AMS, supplemental oxygen is a luxury. For severe forms of altitude illness, oxygen can be lifesaving. In resort settings, oxygen can often be rented directly from the hotel or condominium. For AMS, low flow oxygen (1 to 2 L/min), including small amounts during sleep, is often sufficient. In

BOX 136.2

Acute Mountain Sickness

Incidence: 12% to 67%, varies widely with elevation, rate of ascent and individual susceptibility; rare below 8000 feet, most common with rapid ascent to altitudes above 10,000 feet.
Symptoms and signs: Headache, anorexia, nausea, fatigue, dizziness, difficulty sleeping.
Treatment: Mild cases are usually self-limited and do not require treatment; discontinue ascent, rest. For moderate cases, administer acetazolamide; ibuprofen, aspirin, or acetaminophen for headache; prochlorperazine for nausea; supplemental oxygen if available; descend if persistent or severe; add dexamethasone in severe cases.
Prevention: Gradual ascent to allow acclimatization; high-carbohydrate diet, avoidance of ethanol or smoking; acetazolamide if ascent is rapid or known history of recurrent acute mountain sickness (AMS).

BOX 136.3

Acute Mountain Sickness Differential Diagnosis

- Tension headache
- Viral syndrome
- Alcohol intoxication/toxidrome
- Carbon monoxide (CO) poisoning
- Dehydration
- Caffeine withdrawal
- Migraine headache
- Infectious (meningitis, encephalitis/viral syndrome)
- Intracranial hemorrhage or mass
- Central nervous system aneurysm
- Venous sinus thrombosis
- Abdominal process (eg, gastroenteritis)
- Acute angle closure glaucoma/ocular process

Fig. 136.3. Optic nerve sheath ultrasonography. **A,** Probe positioning: This study is typically performed with the subject supine and with eyes closed. The probe is placed on the closed lid, lateral of the center of the pupil, and adjusted until a longitudinal, cross-sectional image of the optic nerve (deep to the retina) is obtained. For clarity, this figure does not show the use of ultrasound gel, occlusive dressing, or a high frequency (7- to 10-MHz) linear probe. **B,** Optic nerve sheath ultrasonogram with measurements. (Courtesy N. Stuart Harris, MD.)

the wilderness, oxygen tanks are heavy and are usually unavailable in adequate amounts. To overcome this, remote clinics often use solar-powered oxygen generators. In these settings, oxygen therapy is reserved for the more serious manifestations of high-altitude illness. Hyperbaric therapy with a portable fabric chamber that simulates descent is also effective.

Analgesics and Antiemetics

Symptomatic treatment of headache and nausea can be beneficial during the course of mild AMS. Aspirin, ibuprofen, and acetaminophen are useful for the treatment of high-altitude headache. Narcotic analgesics should be avoided because of depression of the hypoventilation response (HVR) and respiratory drive during sleep. For nausea and vomiting, prochlorperazine unlike other antiemetics, stimulates the HVR.

Acetazolamide

Periodic breathing causes insomnia, which is best treated with the respiratory stimulant acetazolamide. Doses of acetazolamide as low as 62.5 mg to 125 mg bid may prevent periodic breathing and eradicate insomnia. Most benzodiazepines and other sedative-hypnotics should be avoided because of their tendency to decrease ventilation during sleep. Even individuals who have previously used diazepam at lower altitudes without difficulty describe unusual reactions, including agitation, hallucinations, and disorientation when this agent is used at high altitude. Studies suggest that low doses of benzodiazepines in combination with acetazolamide are safe at high altitude. A study comparing a single 7.5 mg dose of temazepam to 125 mg of acetazolamide found temazepam significantly improved sleep quality and reduced episodes of nocturia, without increasing oxygen desaturation.[15] Nonbenzodiazepine sleep agents (such as, zolpidem and zaleplon) do not depress ventilation and may prove useful in AMS-related insomnia.

Acetazolamide accelerates acclimatization and, if given early in the development of AMS, may rapidly resolve symptoms. Although the optimal dose has not yet been definitively established, a dose of 250 mg of acetazolamide at the onset of symptoms and repeated twice daily is effective therapy for AMS. The treatment of AMS in children is not formally studied, but anecdotal experience supports the use of acetazolamide in children. The dose for children is 2.5 mg/kg/dose or 125 mg given twice daily to a maximum of 250 mg.

Acetazolamide has myriad beneficial effects. By acting as a carbonic anhydrase inhibitor, it enhances renal bicarbonate diuresis and so improves renal correction of the ventilation-related respiratory alkalosis encouraging increased ventilation and arterial oxygenation. It decreases nocturnal period breathing and so improves sleep. It acts as a diuretic and so attenuates fluid retention common in patients with AMS. It lowers CSF volume and pressure, which may play an additional role in its therapeutic effect. In addition, it has positive effects beyond its role as a carbonic anhydrase inhibitor, with beneficial chemoreceptor effects on ventilatory drive, alterations of cerebral blood flow, relaxation of smooth muscles, and upregulation of fluid resorption in the lungs.

The most common adverse reactions to acetazolamide are paresthesias and polyuria. Less common reactions include nausea, diarrhea, drowsiness, tinnitus, and transient myopia. Carbonic anhydrase inhibition at the tongue causes dysgeusia, altering the flavor of carbonated beverages, including beer. Acetazolamide is a non-antibiotic sulfa compound that carries a low risk of cross-reactivity for individuals with an allergy to sulfa antibiotics.[55] Patients with known sulfonamide allergy may consider administration of a trial dose of acetazolamide in a controlled environment before ascent. Acetazolamide is contraindicated in patients with a history of anaphylaxis or severe skin reactions to any sulfa-containing medication, and it should be avoided in breast-feeding mothers and pregnant women.

Dexamethasone

Dexamethasone is an effective alternative treatment of moderate to severe AMS. An initial dose of 8 mg, followed by 4 mg every 6 hours is recommended. Anecdotal reports indicate doses as low as 2 mg may be sufficient. As a treatment option, concurrent use with acetazolamide is advocated by some to promote acclimatization.[15] Dexamethasone known to have anti-inflammatory properties, possibly to reduce cerebral blood flow, and to block the action of vascular endothelial growth factor. Reduction of AMS symptoms with the use of dexamethasone may be the result of these or its euphoric effects. Prophylactic use of dexamethasone should generally be reserved for use in individuals forced to rapid ascent (eg, professional mountain search and rescue operations). Although dexamethasone effectively relieves the symptoms of AMS, unlike acetazolamide it does not enhance acclimatization. If used as a prophylactic agent to allow ascent beyond physiologic acclimatization, acute cessation can result in rapid onset of severe

altitude illness. For treatment, use should be limited to patients with acetazolamide intolerance or more advanced cases of AMS, especially to help facilitate descent. Common side effects of dexamethasone include gastrointestinal irritation, gastritis, esophagitis, altered mood, and gastroesophageal reflux disease (GERD). Dexamethasone should not be used for more than 3 days in this indication.

Disposition

Individuals with AMS may resume their ascent after symptoms resolve. Re-ascent with acetazolamide use in these individuals is recommended. Further ascent should be halted if symptoms recur.

Prevention

Most of the symptoms of mild AMS are benign and well tolerated. These symptoms, however, can be unpleasant and debilitating to the point that travel, business, or vacation plans should be interrupted. Up to 50% of individuals with AMS report a decrease in activity.

The best method of prevention is a gradual or staged ascent that allows adequate time for acclimatization; however, the time constraints of many vacationers and inexperienced guides often make such an ascent unrealistic. The altitude of sleep during any individual ascent is critical. Ideally, the first night should not be spent at an altitude higher than 9200 feet, with a subsequent increase (to a new sleeping altitude) of not more than 1600 feet each night. One extra night of acclimatization (at the same sleeping altitude) should be added for every 3000 to 5000 feet of altitude gain above 10,000 feet. Excursions to higher altitudes during the day with a return to a lower sleeping altitude ("climb high, sleep low") aid in acclimatization.

Altitude pre-exposure regimens in artificially hypoxic environments have been evaluated to facilitate acclimatization. Pre-exposure regimens lasting less than 8 to 12 hours appear to offer limited protection from subsequent altitude exposure.[16,17]

Mild to moderate exercise likely aids acclimatization; however, overexertion can contribute to the development of AMS. Maintaining adequate hydration—targeting relatively clear (dilute) urine and normal urine output—is also recommended. No data support recommendations for hyperhydration that is often promoted in the lay literature. In fact, consumption of excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness. Balanced electrolyte solutions are recommended (premixed or prepared with purified water).

The goal elevation, rate of ascent, and prior history of altitude illness should be considered in the assessment of the risk for development of altitude illness and the choice of prevention strategies (eTable 136.1). Individuals in low-risk situations should not need medications for prophylaxis. Ascent should be gradual to prevent illness. In some cases, such as arrival at a high-altitude airport or the immediate dispatch of rescue personnel to high altitude, a slow or staged ascent is impossible. Mountain climbers commonly ascend at rates that are higher than recommended, and some individuals continue to suffer AMS symptoms despite gradual ascent. Individuals who have a known susceptibility to the development of AMS and those for whom slow ascent is impractical fall into the moderate- and high-risk categories and should consider prophylactic medication in addition to gradual ascent.[2]

Numerous studies demonstrate the effectiveness of acetazolamide in prevention of AMS in adults.[18] Lower dosages provide prophylaxis similar to that of higher dosages with fewer adverse reactions. Many studies demonstrate that 250 mg twice daily starting 24 hours before ascent and continuing for the first 2 days at high altitude is effective. For avoidance of side effects, a dose of 125 mg given twice daily is effective.[2] Although it is unstudied, the recommended dosage of acetazolamide for AMS prophylaxis for children is 2.5 mg/kg/dose up to 125 mg total given twice daily, and this weight-based approach may reduce side effects in smaller adults. Ibuprofen compared with acetazolamide is equally efficacious in preventing headache.

Dexamethasone also prevents AMS. The lowest effective dosage is 2 mg every 6 hours or 4 mg every 12 hours.[2] Some patients experience the rapid onset of AMS after dexamethasone is discontinued. Dexamethasone does not facilitate acclimatization but rather reduces nausea and enhances mood. In most cases, dexamethasone use should be reserved for treatment of AMS rather than for prophylaxis. Military or rescue personnel rapidly ascending to high altitude and individuals with acetazolamide intolerance are candidates for prophylaxis with dexamethasone. The combination of acetazolamide and dexamethasone may be more effective than either drug alone.

Compelling data do not support the use of *Ginkgo biloba* for preventive therapy of AMS.

Oxygen is an effective prophylactic modality for rescue personnel. Adequate supplies should be available to ensure the safety of all team members for the entire duration of the rescue. Air drops of oxygen can be lifesaving when weather or terrain prevents the immediate arrival of rescue personnel.

HIGH-ALTITUDE PULMONARY EDEMA

Principles

HAPE is the most common fatal manifestation of severe high-altitude illness (Box 136.4). Although HAPE is uncommon below 10,000 feet, it can occur and even be fatal at altitudes below 8,000 feet. Episodes occurring between 8000 and 10,000 feet are usually related to heavy exercise; but at higher altitudes, pulmonary edema can also occur at rest or with light activity.

Some individuals are susceptible and experience HAPE with each ascent to altitude. Rarely, the congenital absence of a pulmonary artery exaggerates the pulmonary vascular response to hypoxia, resulting in recurrent HAPE at elevations lower than expected. Many patients, however, have a single episode of HAPE and subsequently are able to return to high altitude without a recurrence. Less commonly, those with multiple previously uneventful high-altitude exposures may still develop HAPE.

BOX 136.4

High-Altitude Pulmonary Edema

Incidence: 0.01% to 15%, varies with elevation and rate of ascent; rare below 8000 feet and more common above 14,500 feet; typically occurs 2 to 4 days after arrival at high altitude.
Symptoms and signs: Dyspnea at rest, cough, anorexia, cyanosis, rales, tachypnea, tachycardia.
Treatment: Patients with mild cases may recover with bed rest. Moderate cases can be treated with bed rest and supplemental oxygen if clinical monitoring is available. Severe cases require oxygen and descent; use hyperbaric therapy if available; if oxygen or descent is unavailable, then nifedipine 30 mg slow-release every 12 hours; consider acetazolamide (125–250 mg every 12 hours) and tadalafil 10 mg every 12 hours (unstudied).
Prevention: Gradual ascent and recognition of early AMS symptoms so that ascent is stopped before HAPE develops; with previous HAPE history, use nifedipine 30 mg slow-release every 12 hours during ascent, then continue for 3 days (monitor for hypotension).

AMS, Acute mountain sickness; *HAPE,* high-altitude pulmonary edema.

eTABLE 136.1

Risk Categories for Acute Mountain Sickness*

RISK CATEGORY	DESCRIPTION
Low	Individuals with no prior history of altitude illness and ascending to ≤9200 feet Individuals taking ≥2 days to arrive at 8200 to 9800 feet with subsequent increases in sleeping elevation <1600 feet per day
Moderate	Individuals with prior history of AMS and ascending to 8200 to 9200 feet in 1 day No history of AMS and ascending to >9200 feet in 1 day All individuals ascending >1600 feet per day (increase in sleeping elevation) at altitudes above 9800 feet
High	History of AMS and ascending to ≥9200 feet in 1 day All individuals with a prior history of HAPE or HACE All individuals ascending to >11,500 feet in 1 day All individuals ascending >1600 feet per day (increase in sleeping elevation) above >11,500 feet Very rapid ascents (eg, Mt. Kilimanjaro)

*Altitudes listed in the table refer to the altitude at which the person sleeps. Ascent is assumed to start from elevations <4000 feet. The risk categories described pertain to unacclimatized individuals.

AMS, Acute mountain sickness; *HACE,* high-altitude cerebral edema; *HAPE,* high-altitude pulmonary edema.

Modified from Luks AM, et al: Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. Wilderness Environ Med 21:146-155, 2010.

Individuals who have been residents at high-altitude locations for extended periods may have pulmonary edema develop on re-ascent from a trip to low altitude. This phenomenon has been termed *reentry HAPE*. The incidence of reentry HAPE is not established; however, there seems to be an increased risk for children and young adults. This apparent increased susceptibility among children for development of HAPE is probably the result of developmental changes in pulmonary vascular reactivity and tone.

Clinical Features

The initial symptoms of HAPE usually begin insidiously 2 to 4 days after arrival at high altitude. Most cases occur during the second night, but HAPE may develop rapidly, with early symptoms apparent after just a few hours at high altitude. Marked dyspnea on exertion, fatigue with minimal-to-moderate effort, prolonged recovery time, and dry cough are early manifestations of the disease. The symptoms of AMS usually occur concurrently with the development of HAPE.

As the HAPE patient deteriorates, usually through the night, the dyspnea intensifies with effort and is unrelieved by rest. Dyspnea at rest should be recognized as a red flag warning. The cough may become productive of copious amounts of clear, watery sputum. Hemoptysis may be seen in severe cases. As the condition intensifies, cerebral edema or simply severe hypoxemia causes central nervous system dysfunction, such as ataxia and altered mentation. Coma may follow and precede death in a few hours if immediate oxygen therapy and descent are not instituted.

The physical examination reveals a few rales in patients with mild HAPE, usually found in the region of the right middle lobe, progressing to unilateral or bilateral rales and then to diffuse bilateral rales and also rhonchi and gurgles audible without the stethoscope. Neck veins are not distended. Cyanosis of the nail beds alone may progress to severe central cyanosis. Tachypnea and tachycardia become more pronounced as severity increases. Elevated temperatures are common, and a concurrent respiratory tract infection is occasionally seen, especially in children.

Differential Diagnosis

It is prudent to maintain a wide differential diagnosis in assessing patients with acute dyspnea at high altitude (Box 136.5). Although HAPE occurs at high altitude, so do acute coronary syndrome, pulmonary embolism (PE), congestive heart failure (CHF), and pneumonia.

BOX 136.5

High-Altitude Pulmonary Edema Differential Diagnosis

- Carbon monoxide (CO) poisoning
- Pneumonia
- Pneumothorax
- Pleural effusion
- Pulmonary embolism (PE)
- Acute coronary syndrome
- Acute congestive heart failure (CHF)
- Acute exacerbation of preexisting pulmonary hypertension
- Acute flare of chronic obstructive pulmonary disease (COPD)
- Acute asthma flare
- Acute exacerbations of valvular disease (insufficiency and stenosis)

Pneumonia can be misdiagnosed in the setting of HAPE because the symptoms and signs of pneumonia are similar to those of HAPE. The incidence of pneumonia and the common organisms responsible for pneumonia at high altitude are unknown, but visitors to high altitudes may be predisposed to acquire bacterial infections because of impaired T-lymphocyte function. Patients who present with symptoms compatible with pneumonia at high altitude should be treated for HAPE. If any doubt exists about the diagnosis of HAPE versus pneumonia, empirical antibiotic therapy should be initiated. Because of decreased respiratory reserves and mild immunosuppression coincident with high-altitude exposure, the treatment of any serious pulmonary infection at high altitude requires oxygen, descent, and antibiotics.

High-altitude bronchitis and pharyngitis are common problems among climbers. They may result from the increased ventilation of cold, dry air across the upper airway mucosa, causing mucosal inflammation. Copious sputum production is sometimes seen, and antibiotic therapy is rarely helpful. Coughing spasms may be severe and require treatment with antitussives. Other therapeutic measures include hydration, lozenges, and steam inhalation.

Death from PE at high altitude is described. Given frequent travel involving long plane flights prior to many vacations at high altitude, patients may often have increased pre-test likelihoods of deep vein thrombus (DVT) and PE. Additional predisposing factors for DVT may include acute hyperviscosity due to increased hematocrit, dehydration, and forced stasis due to weather. The symptoms and signs of PE can mimic those of HAPE; however, embolic disease tends to have a more rapid onset, and pleuritic chest pain is a more prominent feature.

Diagnostic Testing

Ultrasonography

Ultrasound machines are portable, require limited training for effective use in this setting, and use non-ionizing radiation. As a result, serial assessments can easily be performed to gauge response to treatment. Given their portability, limited power requirements, and instant access to imaging, they are the preferred modality for many remote clinical settings.

Thoracic ultrasonography allows rapid, accurate assessment for acute pulmonary edema at the bedside (Fig. 136.4). The presence of "lung comet tails" (also called *B-lines*) on thoracic ultrasound indicated extravascular water, are reproducible, quantifiable and have been inversely correlated with oxygen saturation and clinical status in HAPE patients. The use of ultrasonography to estimate pulmonary artery pressure is an emerging modality in the early detection and diagnosis of HAPE. Demonstration of high pulmonary artery pressures with normal left ventricular function is associated with HAPE and HAPE susceptibility.

Chest Radiographs

Other thoracic imaging options include chest radiographs. In HAPE patients, chest films reveal alveolar infiltrates, patchy in distribution, with areas of clearing between the patches. Unilateral infiltrates may be present in mild cases; however, bilateral infiltrates are seen in more advanced cases, with involvement of the right mid-lung field being most common (Fig. 136.5). Pleural effusion is rare but may be present in severe cases. The extent of the edema on the chest radiograph roughly parallels the clinical severity. Of note, the radiographic findings of cardiomegaly, bat-wing distribution of infiltrates, and Kerley B lines, which are typical of cardiogenic pulmonary edema, are absent in cases of HAPE.

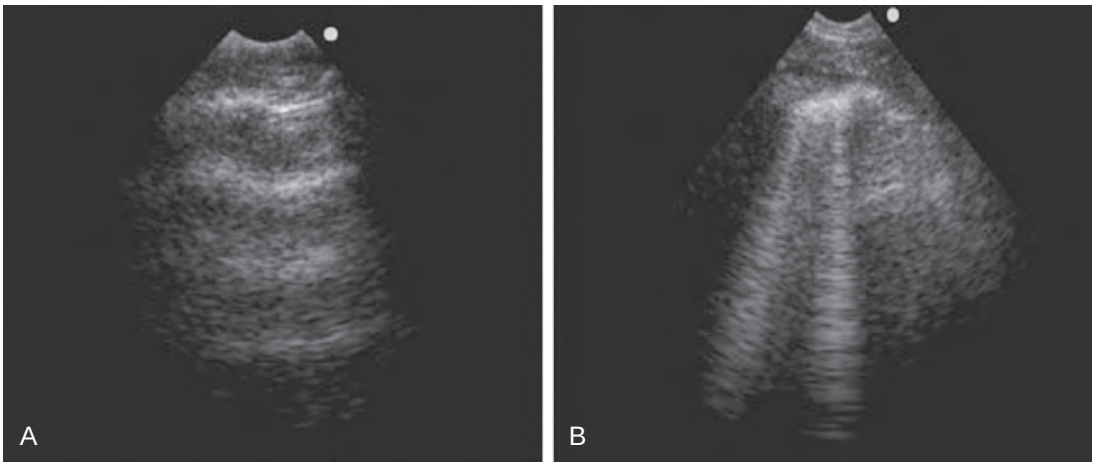

Fig. 136.4. Thoracic ultrasound of lung with high-altitude pulmonary edema (HAPE). **A,** Normal lung tissue is uniform "snowstorm." **B,** B-lines, also known as "comet tails," are present in this patient with HAPE. They are defined as echogenic, coherent, wedge-shaped signals with a narrow origin in the near field of the image, arising from the pleural line and extending to the edge of the screen. B-lines indicate pulmonary interstitial fluid (edema). Views obtained using *low* frequency, curved probe and B-mode imaging. (Courtesy American College of Chest Physicians.)

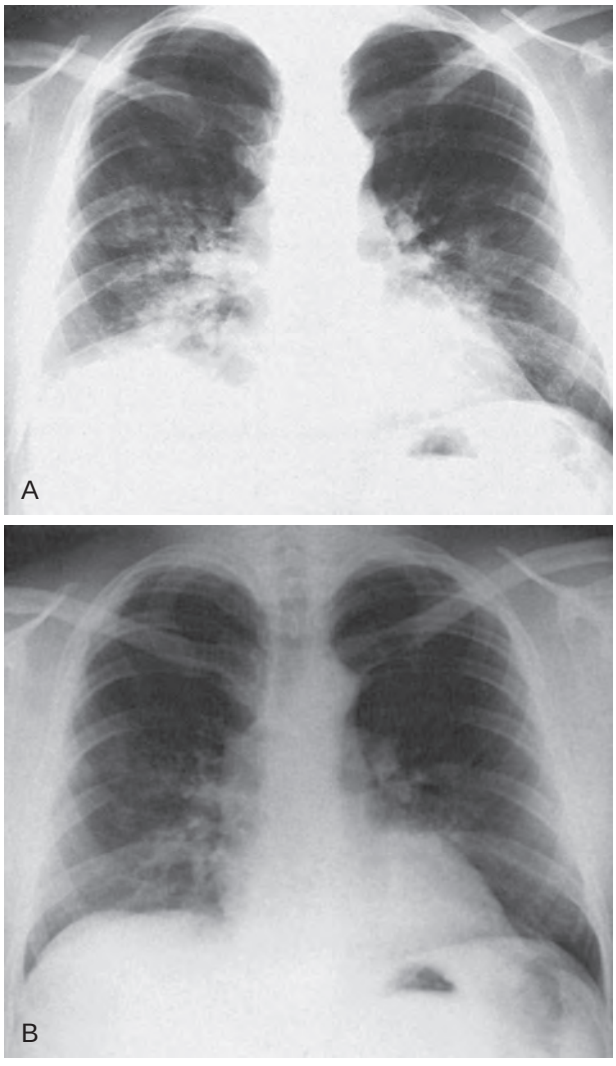

Fig. 136.5. Chest radiograph of a patient with high-altitude pulmonary edema (HAPE). **A,** Before treatment. **B,** After treatment. (Courtesy Richard Nicholas, MD.)

Radiographic evidence of HAPE clears rapidly after initiation of treatment; some mild cases may clear in 4 to 6 hours, and most clear by 24 hours. Radiographs of patients with severe HAPE may reveal infiltrates that persist for as long as 2 weeks, even though the clinical symptoms have resolved.

Electrocardiogram and Echocardiogram

An electrocardiogram reveals tachycardia and evidence of right-sided heart strain, including right axis deviation, P wave abnormalities, tall R waves in the precordial leads, and S waves in the lateral leads. Hemodynamic studies reveal increased pulmonary vascular resistance, elevated pulmonary artery pressures, and normal pulmonary wedge pressures. Echocardiographic studies demonstrate high estimated pulmonary artery pressures, pulmonary vascular resistance, and normal left ventricular function.

Management

In remote settings, where oxygen and medical expertise may be unavailable, immediate descent to treat HAPE may be lifesaving. Delay of descent (eg, waiting hours for rescue personnel to initiate evacuation) can lead to rapid HAPE progression and can prove fatal. Descents of 3000 feet are generally adequate for a rapid recovery; however, descent should continue until symptoms resolve.

Oxygen Therapy

To minimize cold- or exercise-induced pulmonary hypertension, HAPE patients should be kept warm and should minimize exertion (Fig. 136.6). Patient with mild cases of HAPE under expert supervision have been successfully treated at altitude with oxygen, medications, and 1 or 2 days of bed rest. Oxygen administration increases the rate of improvement. Moderate cases can be treated without descent if bed rest, experienced providers, and adequate supplies of supplemental oxygen are available. Any treatment plan that does not include descent necessitates serial examinations by clinicians with experience in management of high-altitude illness.

If difficult terrain or weather conditions hamper efforts to descend, oxygen administration (or hyperbaric therapy) can be a lifesaving measure. Rescue personnel should air drop oxygen

Fig. 136.6. High-altitude pulmonary edema (HAPE) patient being treated with immediate descent in rural Nepal. Patient is provided with oxygen and descending with minimal exertion. (Courtesy Lara Phillips, MD.)

Fig. 136.7. Gamow bag lightweight, portable hyperbaric chambers. Note the attached foot-operated pressure pump. (Courtesy Reuben Tabner.)

supplies if immediate evacuation to lower altitudes will be delayed. High-flow rates of oxygen (6 to 8 L/min) by mask should be delivered initially to victims with severe HAPE until improvement is seen. Flow rates can then be lowered until recovery or descent is completed. Delivery of oxygen with a continuous positive airway pressure mask is more efficacious than normal oxygen delivery and may improve alveolar fluid clearance.

Hyperbaric therapy simulates descent without the administration of supplemental oxygen. Several portable, lightweight (approximately 15 pounds), fabric hyperbaric chambers are available and pressurized manually (Fig. 136.7). These chambers generate 103 mm Hg (2 psi) above the ambient pressure. This simulates a descent of 4000 to 5000 feet at moderate altitudes, and at the summit of Mt. Everest it would simulate a descent of approximately 9000 feet. These devices can be lifesaving in patients with HAPE and HACE. Some non-ambulatory patients are able to descend under their own power after a few hours in hyperbaric chambers.

Nifedipine

Although oxygen and descent remain the mainstays in treatment of HAPE, medications that lower pulmonary artery pressure, pulmonary blood volume, and pulmonary vascular resistance or enhance alveolar fluid clearance may be useful adjuncts. Unlike pulmonary edema secondary to acute CHF, HAPE does not result from excessive intravascular volume or failed cardiac pump function. As such, diuretic therapy has no role in the treatment of HAPE and may further exacerbate volume loss in patients who are already intravascularly depleted.[19]

Many pharmacotherapies used for HAPE treatment derive their limited authority from their demonstrated abilities to prevent HAPE. One of the better studied agents for both prophylaxis and treatment of HAPE is the calcium channel blocker, nifedipine. Acting as a pulmonary vasodilator, nifedipine is especially useful when oxygen is unavailable or descent is impossible. Nifedipine does not improve pulmonary hemodynamics as much as oxygen or descent do, and it does not have an additive effect when it is administered with oxygen. Treatment with 30 mg of a slow-release nifedipine preparation administered twice daily is effective. Patients should be monitored for the development of hypotension during nifedipine administration.

Other Medications

Although phosphodiesterase type 5 inhibitors (including tadalafil and sildenafil) are known to be useful for HAPE prevention, are widely used, and are unlikely to cause acute harm in this indication, they remain unstudied for HAPE treatment. Alveolar fluid clearance is upregulated by beta-adrenergic agonists in animal models, and inhaled beta-agonists have been used anecdotally for therapy of HAPE (salmeterol 125 μg inhaled twice daily).

The mainstay of HAPE treatment remains immediate oxygen (if it is available) and descent. Should these treatments not be available, nifedipine should be initiated. No compelling evidence suggests the concurrent use of these medications with oxygen has additional benefit beyond the use of oxygen alone.

Disposition

Mild to moderate cases of HAPE can be treated with oxygen, rest, and careful monitoring. Experienced physicians in recreational areas at moderate altitudes (eg, Colorado ski resorts) administer oxygen and observe HAPE patients to ensure adequate oxygenation. These patients are then discharged to their hotel with supplemental oxygen and monitored for improvement or deterioration. In severe HAPE, or milder cases that do not improve with therapy, descent is warranted. Rapid recovery is usually seen after descent to lower altitudes, and observation of the patient in the emergency department to ensure adequate room air oxygenation is generally adequate. On occasion, admission to the hospital is indicated to maintain the Sao_2 greater than 90%. In the hospital, continuous positive airway pressure improves gas exchange in HAPE patients. Hypocapnia, alkalosis, and radiographic evidence of HAPE may persist for several days. Thoracic ultrasound allows for frequent reassessments and has been shown to closely follow resolving edema and increasing oxygen saturations.

After oxygen saturation remains greater than 90% on room air and clinical improvement is apparent, the patient can be

discharged. If the patient requires air travel to return home (cabin pressures equal approximately 8000 feet), additional recovery time before travel or arrangement for supplemental oxygen administration is advised. Detection of a heart murmur in a patient with HAPE should lead to an evaluation searching for cardiac structural anomalies that may increase pulmonary vascular resistance. An evaluation for underlying congenital heart disease is warranted after an episode of HAPE in a young child.

Patients may be able to re-ascend (generally in 2 to 3 days) when symptoms resolve and oxygen levels remain acceptable off supplemental oxygen at rest and with mild exercise. Re-ascent with pulmonary vasodilator medication may be considered.

Prevention

As with all forms of serious altitude illness, two key teaching points are the most effective means of prevention and must be understood by the patient: (1) a gradual or staged ascent to allow sufficient time to acclimatize is critical, and (2) immediate cessation of further ascent at the onset of symptoms can be lifesaving. Individuals with a prior history of HAPE should also avoid extreme exertion during the first 2 days at altitude. With a prior history of HAPE, prophylactic therapy should be considered. The preferred medication for HAPE prevention is the nonspecific pulmonary vasodilator nifedipine, 30 mg (controlled-release) two times daily before ascent and continued at altitude for 3 days. Less evidence exists to support the routine use of other pulmonary vasodilators for HAPE prevention.

Phosphodiesterase type 5 inhibitors are selective pulmonary vasodilators that increase cyclic guanosine monophosphate availability. Sildenafil (40 mg every 8 hours) and tadalafil (10 mg every 12 hours) are effective in preventing HAPE. The phosphodiesterase type 5 inhibitors have the added benefit that they are less likely than calcium channel blockers to induce systemic hypotension. A few additional medication options may be considered for prevention. Limited data suggest that dexamethasone (8 mg every 12 hours) started 2 days before ascent may prevent HAPE. Unpublished data from animal models revealed that dexamethasone decreases pulmonary capillary leakage through downregulation of the inflammatory cascade, decreasing alveolar fluid accumulation.[17] To enhance alveolar fluid clearance, salmeterol 125 µg inhaled twice daily may be used as an adjunct to nifedipine in patients with a history of HAPE, although side effects are common at this high inhaled dose. Finally, clinical experience suggests that acetazolamide aids in acclimatization and prevents HAPE, and it has utility in reduction of hypoxic pulmonary vasoconstriction.

HIGH-ALTITUDE CEREBRAL EDEMA

Principles

HACE is the least common but most severe form of high-altitude illness (Box 136.6). Death from HACE at as low as 8200 feet is reported, although most cases occur above 12,000 feet. Mild AMS can progress to severe HACE with coma in as few as 12 hours. Although severe symptoms usually develop within 1 to 3 days, they may not occur until 5 to 9 days.

Clinical Features

HACE is characterized by evidence of global cerebral dysfunction. The symptoms of severe AMS (headache, fatigue, and vomiting) as well as those of HAPE (cough and dyspnea) are often present. Patient with HACE almost inevitably have had prior, unheeded symptoms of worsening AMS over hours to days. HACE-specific signs include ataxia, slurred speech, and altered mental status, which can range from mild emotional lability or confusion, to hallucinations and worsening obtundation that may advance to coma and death. Less commonly, generalized seizures and rarely, focal neurologic deficits may occur.

Altered mental status and cerebellar ataxia are the most sensitive signs for early recognition of HACE. The early appearance of ataxia reflects the particular sensitivity of the cerebellum to hypoxia. Ataxia alone is an indication for immediate descent. Retinal hemorrhages are common and rarely of clinical significance. Papilledema and occasionally cranial nerve palsy also occur in the setting of increased intracranial pressure.

BOX 136.6

High-Altitude Cerebral Edema

Incidence: Lower than 1% or 2%, uncommon as a pure entity; usually associated with the presence of severe AMS and HAPE.
Symptoms and signs: Ataxia, severe headache, nausea and vomiting, altered mentation, seizures, coma.
Treatment: Immediate evacuation to a lower altitude; oxygen, bed rest, dexamethasone. Hyperbaric therapy if unable to immediately descend.

AMS, Acute mountain sickness; *HAPE,* high-altitude pulmonary edema.

BOX 136.7

High-Altitude Cerebral Edema Differential Diagnosis

- Acute cerebral vascular accident (CVA)/transient ischemic attack
- Intracranial hemorrhage
- Hypoglycemia
- Carbon monoxide (CO) poisoning
- Meningitis/encephalitis
- Hypothermia
- Intracranial mass
- Vertebral/carotid dissection or stenosis
- Acute toxidrome—alcohol, other
- Acute alcohol withdrawal/delirium tremens
- Seizure
- Transient global amnesia

Differential Diagnosis

Paroxysmal onset of symptoms should prompt consideration of other etiologies, such as hypothermia, hypoglycemia, CO poisoning, and acute cerebral vascular accidents (CVAs) (Box 136.7). A vascular lesion is suggested by abrupt onset, presence of a dense hemilateral palsy, a lack of preceding evidence of worsening high-altitude illness, or the persistence of signs despite adequate treatment of high-altitude illness.

Diagnostic Testing

Without advanced imaging, differentiating between HACE and acute CVA may be difficult. Although not common, the occurrence of cerebral thrombosis and transient ischemic attacks, in the absence of high-altitude illness, has been documented at high altitude. MRI of patients with HACE reveals white matter changes consistent with vasogenic edema (Fig. 136.8).

Management

Successful therapy for HACE requires early recognition and initiation of immediate descent. If available, high-flow oxygen should

be administered. Oxygen alone reduces intracranial blood flow at high altitude. Steroid therapy is recommended and may result in recovery from HACE without neurologic deficits. The initial dose of dexamethasone is 8 mg parenterally or orally in mild cases, followed by 4 mg every 6 hours.

Patients with severely altered levels of consciousness require tracheal intubation. All efforts should be made to increase oxygenation, both by increasing FiO_2 and barometric pressure by descent. Hyperventilation, diuretics (eg, furosemide), and hypertonic solutions (eg, mannitol) have been used to manage severely elevated intracranial pressure, but grave caution is warranted. Many patients with HACE are already volume depleted from poor fluid intake; diuretic use could compromise adequate intravascular volume and reduce cerebral perfusion pressure.

Hyperbaric treatment of HACE is also effective and may result in temporary improvement and allow self-rescue. Conversely, coma may persist for several days after descent to lower altitudes.

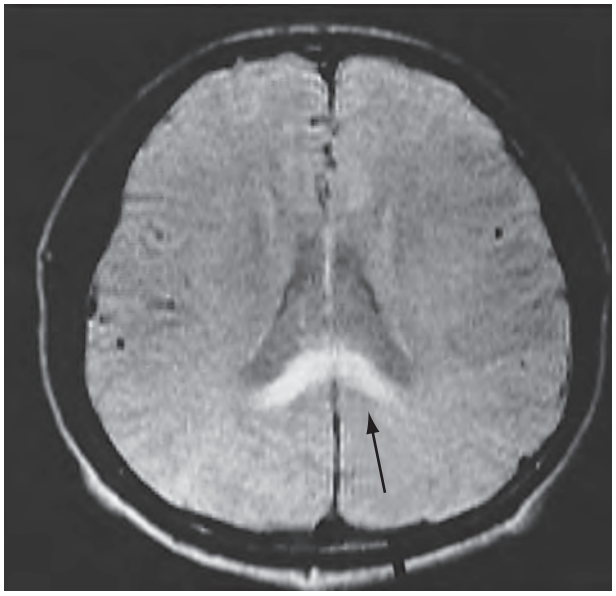

Fig. 136.8. Axial proton-weighted magnetic resonance image of a mountain climber with high-altitude cerebral edema (HACE). The *arrow* demonstrates the markedly increased signal (edema) in the splenium of the corpus callosum. (Courtesy Peter Hackett, MD.)

Disposition

Immediate descent should occur as soon as possible. Placing HACE patients in a hyperbaric device may only delay the more comprehensive care available in the hospital setting.

Long-term neurologic deficits including ataxia and cognitive impairment have been reported after recovery from acute episodes of HACE. Both transient and long-lasting neurobehavioral impairments can occur in mountaineers after climbing to extreme altitude without experiencing clinical HACE. Because of the potential for long-lasting neurologic injury, the clinician who treats high-altitude illness should be extremely sensitive to the early manifestations of HACE. Early treatment of HACE generally results in good outcomes, but after coma is present, the mortality rate exceeds 60%.

SPECIAL CONSIDERATIONS

High-Altitude Retinal Hemorrhage

High-altitude retinal hemorrhage (HARH) is the most common type of retinopathy in visitors to high altitude. These hemorrhages are common at altitudes above 17,500 feet, although they can occur at lower levels.

The exact incidence of HARH is unknown because most patients are asymptomatic, with HARH noted only on retinoscopy. HARH is not generally related to the presence of mild AMS but does seem to be related to strenuous exercise at high altitude. At any altitude, in the setting of severe HAPE or HACE, retinal hemorrhages are commonly noted, but the mechanism remains unclear.[20]

Hemorrhages usually spare the macula (Fig. 136.9) and most often resolve without treatment in 2 or 3 weeks. With macular involvement, central scotomas may be noticed and only gradually resolve. In some cases, these visual defects are permanent. HARH is more likely to occur among individuals with a previous history of such hemorrhages. The underlying risk remains unclear. They usually do not pose a contraindication to return to high altitude unless the macular region is involved. Altitude related changes in intraocular pressure are not associated with AMS.[21]

Carbon Monoxide Poisoning

CO poisoning can occur at altitude from the use of fires and combustion stoves to keep warm and to prepare food in the high-altitude environment. CO poisoning at altitude can be more

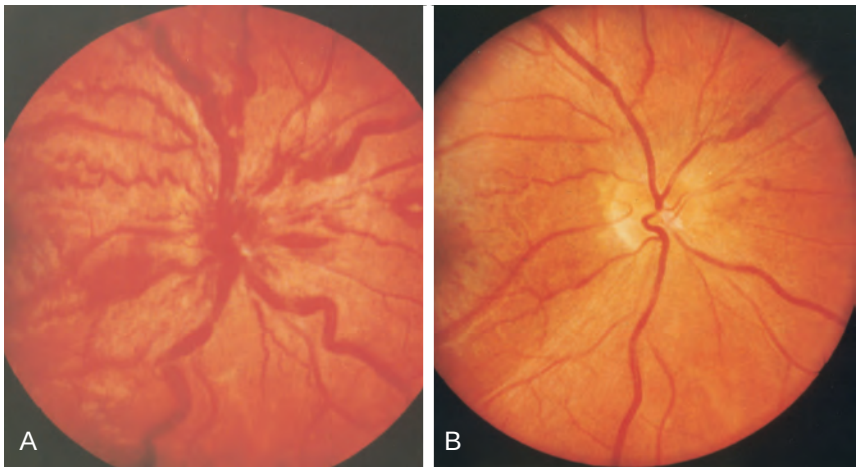

Fig. 136.9. High-altitude retinal hemorrhages (HARHs). **A,** Acute. **B,** After 1 week of resolution. (Courtesy Charles Houston, MD.)

devastating because of preexisting hypobaria-induced hypoxia. As CO avidly binds to hemoglobin, it prevents oxygen transport and so exacerbates tissue hypoxia. CO poisoning and AMS are easy to confuse because of similar symptoms and signs, including headache, nausea, dizziness, dyspnea, and lassitude. If suspected, immediate assay of carboxyhemoglobin levels using co-oximetry or lab testing is indicated. Importantly, empirical treatment with oxygen and hyperbaria will benefit both conditions. If CO poisoning is suspected, immediate testing of the patient's affected indoor space should occur before patient is discharged home. If testing is not available, the patient should leave the enclosed space and descend or use supplemental oxygen if it is available.

ALTITUDE AND UNDERLYING MEDICAL CONDITIONS

Individuals with preexisting diseases such as sickle-cell disease, moderate to severe chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) may have a more difficult time acclimatizing, because these disease states may be aggravated by the hypoxic atmosphere at higher elevations. eBox 136.1 describes the risk associated with travel to altitude in individuals with a variety of underlying comorbidities.

Respiratory Illnesses

Travelers with COPD to have underlying anatomic and physiologic changes that predispose them to development of hypoxemia, sleep apnea, pulmonary hypertension, and ventilation disorders at even moderate altitudes. COPD is a risk factor for the development of AMS. Although oxygen saturation remains more than 90% in a healthy, awake individual until an altitude of 8000 feet, patients with COPD may desaturate below 90% at lower altitudes. High altitude increases hypoxic pulmonary vasoconstriction and may potentiate the development of cor pulmonale, which is known to adversely affect survival at sea level. Individuals with chronic COPD should be advised of the potential need for oxygen supplementation when traveling to moderate altitude, especially if they are already using oxygen at sea level or if dyspnea or fatigue becomes worse. Use of a pulse oximeter can guide the need for increased oxygen supplementation.

Patients with asthma, on the other hand, may have fewer problems at altitude because of decreased allergens and pollutants and decreased airflow turbulence. Even those with exercise-induced bronchospasm do not have worsening symptoms while exercising at 5000 feet. In addition, AMS incidence is not increased in asthmatics. People with asthma traveling to higher elevations should continue their usual medications and carry a rescue supply of bronchodilators and steroids.

Patients who ascend to high altitude with preexisting primary or secondary pulmonary hypertension should be considered HAPE susceptible, and those with primary pulmonary hypertension should be considered at increased risk for HAPE. Patients with known pulmonary hypertension should be advised against travel to higher elevations. If travel cannot be avoided, supplemental oxygen should be used. Prophylactic sustained-release nifedipine, 30 mg twice daily for the duration of the stay at altitude, can prevent HAPE. Phosphodiesterase type-5 inhibitors and steroids may also be used.

Cardiovascular

Individuals with a history of CHF, CAD, dysrhythmias, or coronary bypass surgery are infrequently studied in the high-altitude setting. In theory, people with diseased myocardium should be advised to avoid high altitude because of decreased environmental oxygen availability. No studies report increased mortality in visitors to these locations. To the contrary, long-term residents at high altitude may be protected from coronary artery disease (CAD) by increased collateral vessel formation or a decrease in the development of atherosclerosis.

All travelers have increased sympathetic activity on initial exposure to high altitude. In patients with heart disease, the resultant increase in heart rate and blood pressure increases cardiac work and myocardial oxygen consumption, which could increase angina symptoms and dysrhythmias. Although both cardiac rhythm abnormalities and ST segment and T wave electrocardiographic changes are reported, none of these changes are associated with clinical evidence of myocardial ischemia. Limited data suggest no increased risk for sudden cardiac death or myocardial infarction at altitudes up to 8000 feet. When individuals with stable angina are exercised, there is conflicting evidence for the probability of inducing malignant dysrhythmias. Travelers with heart disease who ascend to moderate altitudes do not appear to have an increased incidence of AMS.

Travelers with mild stable CAD should be advised to ascend gradually, to limit activity especially in the first few days at elevation, and to continue anti-anginal and antihypertensive medications. Individuals who have more severe, symptomatic coronary disease or those in a high-risk group (low ejection fraction, abnormal stress test results, and high-grade ventricular ectopy) should avoid travel to high altitudes. Ascent to moderate elevations can be suggested on an individual basis with the previously mentioned precautions. Individuals with heart failure who travel to altitude may require increased use of diuretics to promote diuresis and acclimatization. Acetazolamide prophylaxis may be useful to speed acclimatization and to prevent AMS and its accompanying fluid retention.

Hypertension

High-altitude travel produces a rapid, mild increase in blood pressure and heart rate in healthy individuals because of increased sympathetic tone. This increase is maximal at 2 or 3 weeks, and returns to baseline values over time because of a downregulation of adrenergic receptors if one stays at high altitude or on descent to sea level. No studies demonstrate an increased predisposition for altitude illness in patients with underlying hypertension.

The incidence of hypertension in sea-level dwellers traveling to high altitude is 10% to 25%. On travel from sea-level to low altitudes (3000 feet), no differences are noted in either normotensive or hypertensive individuals. Above 9800 feet, more significant increases may occur. This suggests that people with severe hypertension should travel to high altitude only under careful monitoring. For individuals who have mild preexisting hypertension, additional treatment is not routinely necessary. Patients with moderate hypertension should be monitored frequently in the first few days at altitude and antihypertensive medications continued. For hypertensive patients with a rapid rise in blood pressure and who will be staying for several weeks, an alpha-blocker, nifedipine, or angiotensin-converting enzyme inhibitor should be considered.

Seizures

Numerous reports of altitude-provoked seizures exist, but epidemiologic data are lacking. Seizures attributable to high altitude are typically generalized tonic-clonic in nature.[89] A focal seizure at altitude should prompt a thorough evaluation for a space-occupying lesion. Several pathophysiologic mechanisms are implicated. These include sleep deprivation from periodic breathing, hyperventilation, and the direct effect of hypobaric hypoxia.[89] These mechanisms are postulated to induce a metabolic state that lowers the seizure threshold. Seizures not responding to

eBOX 136.1

Risk Associated With Travel to Altitude in Individuals With a Variety of Underlying Comorbidities

ADVISABILITY OF EXPOSURE TO HIGH ALTITUDE FOR COMMON CONDITIONS (WITHOUT SUPPLEMENTAL OXYGEN)

Probably No Extra Risk

Young and old
Fit and unfit
Mild obesity
Diabetes
Previous coronary artery bypass grafting (without angina)
Mild chronic obstructive pulmonary disease (COPD)
Asthma
Low-risk pregnancy
Controlled hypertension
Controlled seizure disorder
Psychiatric disorders
Neoplastic diseases
Inflammatory conditions

Caution

Moderate COPD
Asymptomatic pulmonary hypertension
Compensated congestive heart failure (CHF)
Morbid obesity
Sleep apnea syndromes
Troublesome arrhythmias
Stable angina or coronary artery disease (CAD)
High-risk pregnancy
Sickle cell trait
Cerebrovascular diseases
Any cause of restricted pulmonary circulation
Seizure disorder (not taking medication)
Radial keratotomy

Contraindicated

Sickle cell anemia (with history of crises)
Severe COPD
Symptomatic pulmonary hypertension
Uncompensated CHF

Modified from Hackett PH, Roach RC: High altitude medicine. In Auerbach P: Wilderness medicine, ed 6, Philadelphia, 2012, Elsevier.

supportive care can be treated with benzodiazepines. Should an epileptic who is already taking seizure medicine experience a breakthrough seizure at altitude, standard seizure evaluation is warranted, and acetazolamide at 125–250 mg twice daily may be added. Acetazolamide itself has antiepileptic properties and may ameliorate the altitude-related metabolic derangements.

Sickle Cell Disease

In patients with sickle cell disease, exposure to even low to moderate altitudes (4000 to 6500 feet) will provide additional hypoxia stress. Up to 20% of patients with hemoglobin sickle cell and sickle cell–thalassemia disease may experience a vaso-occlusive crisis, even under pressurized aircraft conditions. Oxygen is therefore advised for air travelers who have sickle cell disease.

Although most people with sickle cell trait remain asymptomatic, this subgroup can experience the development of left upper quadrant pain as a result of splenic ischemia or infarction. Nonblacks, usually of Mediterranean origin, who have sickle cell trait may be more prone to the development of splenic infarctions than are blacks.

Pregnancy

Studies of permanent high-altitude residents in Colorado and Peru show an increased incidence of complications in maternal, fetal, and neonatal life. Infants born at high altitude have a lower birth weight compared with infants born at sea level because of a combination of factors, including altitude-related effects on fetal growth, changes in uterine blood flow, and increased premature births.

Pregnancy-induced hypertension, proteinuria, and peripheral edema (manifestations of toxemia and preeclampsia) are more common at high altitudes and may also be related to maternal and uterine hypoxemia.[22] Although hypertension in pregnancy is more common at high altitudes, no evidence exists for an increase in spontaneous abortions, abruptio placentae, or placenta previa.

Travel by pregnant women to moderate altitudes appears to be safe, but caution is advised for lowland women with normal pregnancies who wish to travel above 13,000 feet, for pregnant women who wish to remain at high altitude for a prolonged period, and for women with complicated pregnancies.

Radial Keratotomy

Patient with a history of radial keratotomy may experience hyperopic (farsighted) visual changes with ascent above 9000 feet. This results from corneal swelling from ambient hypoxia because the cornea is markedly sensitive to both systemic and ambient oxygen tension.[23] In normal corneas, this swelling is uniform. After radial keratotomy, the swelling is exacerbated and inconsistent secondary to the pattern of the incisions. Photorefractive keratotomy and LASIK, which use laser techniques that do not produce incisions but instead shave the cornea and corneal stroma, respectively, do not result in similar problems.

ACKNOWLEDGMENT

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KEY CONCEPTS

- All forms of altitude illness can be treated with oxygen and rapid descent.
- The diagnosis of AMS requires the presence of headache in the setting of recent elevation change to greater than 8000 feet. Additional nonspecific symptoms may include nausea, anorexia, fatigue, and insomnia.
- Patients with AMS should not ascend further until symptoms improve. Patients with mild HAPE may be treated in place if experience providers and treatment options exist. Patients with moderate HAPE or HACE should descend immediately.
- Dyspnea at rest is an early symptom of HAPE. More advance findings of HAPE include marked rest tachypnea, cough productive of frothy sputum, and altered mentation. Immediate treatment with oxygen and descent are recommended.
- Altered consciousness and cerebellar ataxia are early signs of HACE. Failure to initiate immediate treatment with oxygen, descent, and dexamethasone can result in permanent disability or death.
- AMS may be prevented by using acetazolamide or dexamethasone. Symptoms can be controls with analgesia (ibuprofen and antiemetics). HAPE may be prevented using nifedipine, inhaled salmeterol, and phosphodiesterase type 5 inhibitors (sildenafil [40 mg every 8 hours] and tadalafil [10 mg every 12 hours]).[50,132-134] Temazepam (7.5 mg qhs) can safely improve sleep quality.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 136: QUESTIONS & ANSWERS

136.1. Which of the following individuals has the highest risk of developing high-altitude pulmonary edema (HAPE), assuming all are generally healthy, live at the same altitude, and travel to the same altitude?
A. A 16-month-old boy
B. A 19-year-old man
C. A 19-year-old woman
D. A 42-year-old man
E. A 42-year-old woman

Answer: B. Many factors contribute to the development of HAPE including total altitude, sleeping altitude, time at altitude, previous acclimatization, and the presence of comorbidities. However, in general, both females and the elderly are less likely to develop HAPE. Also, whereas younger males are more at risk, HAPE is extremely rare in individuals younger than 2 years old regardless of gender.

136.2. Which of the following symptoms must be present to establish a diagnosis of acute mountain sickness (AMS)?
A. Dizziness
B. Fatigue
C. Headache
D. Insomnia
E. Nausea

Answer: C. To diagnose AMS, a patient must have a recent gain in altitude, be at that altitude for several hours, and have a headache. In addition, at least one of the following must also be present: gastrointestinal upset, fatigue, dizziness or lightheadedness, or difficulty sleeping.

136.3. Which of the following medications used to treat acute mountain sickness (AMS) actually accelerates acclimatization?
A. Acetazolamide
B. Aspirin
C. Dexamethasone
D. Oxygen
E. Prochlorperazine

Answer: A. Acetazolamide is a carbonic anhydrase inhibitor and induces a metabolic acidosis that results in increased ventilation. Aspirin is an appropriate treatment for the headache associated with AMS. Dexamethasone and oxygen both improve all symptoms of AMS but do not aid acclimatization. Prochlorperazine is appropriate treatment for the gastrointestinal upset caused by AMS and is preferred over promethazine because it does not depress the respiratory centers.

136.4. Which of the following conditions occurs more commonly at high altitude?
A. Congestive heart failure (CHF)
B. Myocardial infarction
C. Pericarditis
D. Pneumothorax
E. Pulmonary embolism (PE)

Answer: E. Altitude causes hypercoagulability from hyperviscosity due to elevated hematocrit and dehydration. Venous stasis is also more common at altitude due to the relative immobility of sleeping in confined spaces (sleeping bags and small tents). Together, these facts lead to an increased risk of PE. Occasionally, PE may be misdiagnosed as high-altitude pulmonary edema (HAPE) and treated inappropriately.

136.5. High-altitude pulmonary edema (HAPE) can be difficult to distinguish from acute mountain sickness (AMS). Although the pathophysiology of each is similar, the treatment and prognosis are different. Which of the following features is indicative of HAPE as opposed to AMS?
A. Diuresis
B. Dyspnea at rest
C. Headache
D. Lower-extremity edema
E. Symptom onset soon after arrival at altitude

Answer: B. Dyspnea on exertion is nearly universal at altitude and is not indicative of a pathologic process, but dyspnea at rest is not normal and is an early symptom of HAPE. Cough is common at

altitude or any time when one breathes cold dry air. Fluid retention and peripheral edema are common manifestations of AMS, whereas a diuresis can be a sign of acclimatization. Neither AMS nor HAPE commonly occurs soon after arrival at altitude, with AMS usually occurring within 24 hours and HAPE usually occurring in 2 to 4 days.

136.6. The definitive treatment for high-altitude pulmonary edema (HAPE) is oxygen and descent to lower altitudes. Which of the following medications is also useful in the treatment of HAPE?
A. Hydrochlorothiazide
B. Metoprolol
C. Nifedipine
D. Nitroglycerin
E. Verapamil

Answer: C. Nifedipine is a nonselective pulmonary vasodilator and is useful in the treatment and prevention of HAPE. Sildenafil and tadalafil may also be useful in the prevention of HAPE. These phosphodiesterase–5 inhibitors increase cyclic guanosine monophosphate availability and result in pulmonary vasodilation.

136.7. Which of the following signs or symptoms is specific for high-altitude cerebral edema (HACE) as opposed to acute mountain sickness (AMS) or high-altitude pulmonary edema (HAPE)?
A. Ataxia
B. Dizziness
C. Dyspnea
D. Headache
E. Vomiting

Answer: A. Ataxia, seizures, slurred speech, focal neurologic deficits, and altered mentation are all specific to HACE. Dizziness, headache, and vomiting can all be seen in AMS. Dyspnea is nearly universal in HAPE.

136.8. You are the doctor on a group expedition to Denali. Recently, some of the climbers have complained of headaches, dyspnea, nausea, and difficulty sleeping. At breakfast this morning, one of the climbers is noted to have difficulty speaking and some slurred speech, which he attributes to a restless night's sleep. What treatment is appropriate for this patient?
A. 24 hours of rest before further ascent
B. Acetazolamide
C. Descent to lower altitude
D. Nifedipine
E. Oxygen

Answer: C. This patient has high-altitude cerebral edema (HACE). Any hard neurologic finding (ataxia, slurred speech, focal neurologic deficits, seizure, or altered mentation) at altitude is indicative of HACE. Unlike acute mountain sickness (AMS) or high-altitude pulmonary edema (HAPE), which can occasionally be treated without descent, descent is mandatory for all cases of HACE. Dexamethasone should also be given to all patients with HACE. The other treatments mentioned are all possible treatments for HAPE.

136.9. You are the doctor on a group expedition to Denali and are currently at an elevation of 10,000 feet. One of the members of the group experiences headache, lightheadedness, and nausea. You diagnose him with acute mountain sickness (AMS) and treat him with acetazolamide and oxygen. He wants to know when he can continue climbing the mountain. What do you tell him?
A. You may ascend if your oxygen saturation (as measured by pulse oximetry) is higher than 90%.
B. You may ascend when all your symptoms resolve.
C. You may never ascend any higher than this altitude.
D. You may not ascend any higher on this expedition but may try again in 1 or 2 months.
E. You may only sleep 1000 feet higher than your current altitude.

Answer: B. Management of AMS must adhere to the axiom, "After the symptoms of altitude illness occur, further ascent to a higher sleeping altitude is contraindicated."

CHAPTER 137

Drowning

David B. Richards

PRINCIPLES

Definitions

Traditionally, the terminology describing drowning injuries has been confusing and impractical. In the past, *drowning* referred to death within 24 hours of suffocation from submersion in a liquid, whereas *near-drowning* described victims who survived at least 24 hours past the initial event regardless of the outcome. In 2005 the World Health Organization (WHO) published a new policy defining drowning to clarify documentation and to better track drowning injuries worldwide. Drowning was defined as "the process of experiencing respiratory impairment from submersion/immersion in liquid." Furthermore, the WHO policy states, "Drowning outcomes should be classified as: death, morbidity, and no morbidity; the terms wet, dry, active, passive, silent, and secondary drowning should no longer be used." The term *near-drowning* should not be used, and the association of the term *drowning with a fatal outcome* should be abandoned.

Immersion syndrome refers specifically to syncope resulting from cardiac dysrhythmias on sudden contact with water that is at least 5° C lower than body temperature. The risk is proportional to the difference between body temperature and water temperature. Wetting of the face and head before entrance into the water may prevent the inciting sequence of events. Putative mechanisms for the syndrome are vagal stimulation leading to asystole and ventricular fibrillation secondary to QT prolongation after a massive release of catecholamines on contact with cold water. The resultant loss of consciousness leads to secondary drowning.

Epidemiology

Each year an estimated 350,000 people die of drowning worldwide, a rate of 40 individuals an hour, most of whom are children. Low- and middle-income countries account for more than 90% of all drowning deaths and a disproportionate share of years of life lost. Drowning is among the top ten causes of mortality for children and young people worldwide. In Bangladesh it accounts for 43% of deaths in children 1 to 4 years old.[1]

In the United States drowning is the tenth most common cause of unintentional death, accounting for 3391 deaths (1.1 per 100,000) in 2013. Among children 1 to 4 years old, drowning is the leading cause of injury mortality; for 5- to 14-year-olds, it is second only to motor vehicle crashes.[2]

The incidence of drowning with nonfatal outcomes is unknown. The Centers for Disease Control and Prevention (CDC) estimates that for every child who dies by drowning in the United States, another five receive emergency department (ED) care for a drowning event, and half of these children require hospitalization.[3] Among all age groups, an estimated one to four hospitalizations secondary to nonfatal drownings occur for every drowning death. The economic implications of drowning injuries are profound. In Australia, drowning has the highest average lifetime cost ($40,071 in US currency) of any injury type.

Drownings occur in domestic settings such as swimming pools, hot tubs, bathtubs, large buckets, and rainwater tanks and in all forms of natural bodies of water. A review of all drowning deaths among individuals younger than 20 years old in the United States during a 1-year period revealed that 55% of infants younger than 1 year old drown in bathtubs, and nearly 16% drown in large household buckets. Most (56%) children 1 to 4 years old drown in artificial pools, whereas most (63%) deaths among older children occur in natural bodies of fresh water.

Because of the recent natural disasters, the incidence of drowning injuries and fatalities is rising. In disasters such as floods and tsunamis, older populations are disproportionately affected. A study from hurricane Katrina found that 49% of fatalities were in people 75 years old or older.

Risk Factors

Age, gender, and race affect incidence of drowning. Toddlers and those over 75 years old are at greatest risk of death by drowning, with annual incidences of 2.1 and 1.3 per 100,000, respectively. Boys account for almost 80% of victims older than 1 year old.[2] American Indian and Alaska Native children between 1 and 4 years old have the highest annual incidence of drowning mortality (3.83 per 100,000), and black teenagers between 11 and 12 years old drown in swimming pools at ten times the rate of white children of the same age. The risk of death by drowning for all ages of the American Indian and Alaska Native population is 80% higher than the United States population as a whole.[4]

Ethanol consumption in proximity with water is a major risk factor for drowning. Acute ethanol intoxication may be a contributing factor in 30% to 50% of drownings among adults and adolescents. An association has established between blood ethanol concentration (BEC) and risk of death from drowning while using watercraft. The odds ratios of fatality from drowning follow a trend from 2.8 for a BEC of 1 to 49 mg/dL to 37.4 for a BEC of 150 mg/dL or greater compared with sober case controls.

Drowning in the United States follows clear temporal patterns. Two-thirds of pediatric deaths occur between May and August. Drowning injuries are 48% more likely to occur on weekends than weekdays and drowning victims older than 20 years old are most often participating in water sports or using watercraft.[5]

The relationship between swimming ability and the risk of drowning is unclear. No direct evidence exists to suggest that inexperienced swimmers are more likely to drown. On the contrary, skilled swimmers have greater exposure to water and may be more prone to drowning incidents.

Numerous medical conditions confer an increased likelihood of drowning injury. Seizure disorders increase the chance of drowning among children and adolescents nearly 20 times. Ten percent of deaths in a cohort of patients with seizures followed for 40 years were due to drowning.[6] Autism and other developmental and behavioral disorders increase risk in children as well. Immersion in cold water extends the QT interval, thus increasing the risk of dysrhythmias in individuals with prolonged QT syndrome at baseline.

Pathophysiology

Unexpected submersion triggers breath-holding, panic, and a struggle to surface. Air hunger and hypoxia develop, and the victim begins to swallow water. As breath-holding is overcome, involuntary gasps result in aspiration. The quantity of fluid aspirated, rather than the composition, determines subsequent pulmonary derangement.

The pathophysiologic differences between freshwater and saltwater aspiration with respect to resultant electrolyte imbalance, hemolysis, and fluid compartment shifting do not occur until the amount of aspirated water is significantly more than the typical drowning victim aspirates. In one review of the hospital treatment of drowning victims, no patient required emergent intervention for a significant electrolyte abnormality. Aspiration of 1 to 3 mL/kg of either fresh water or salt water destroys the integrity of pulmonary surfactant, leading to alveolar collapse, atelectasis, noncardiogenic pulmonary edema, intrapulmonary shunting, and ventilation-perfusion mismatch. Profound hypoxia and metabolic and respiratory acidoses ensue, leading to cardiovascular collapse, neuronal injury, and ultimately death.

The classic hypothesis was that 10% to 15% of drowning victims die without aspiration of a significant amount of water. Death from such *dry* drowning putatively results from severe laryngospasm causing hypoxia, convulsion, and death without entry of fluid into the lungs. An exhaustive review of the literature failed to corroborate this hypothesis. *Dry drownings* more appropriately reflect deaths from causes other than simple submersion.

Many factors may influence the pathophysiologic sequence of events in drowning and affect the chance of survival, including age, water temperature, duration and degree of hypothermia, diving reflex, and effectiveness of resuscitative efforts. Children have a lower ratio of body mass to surface area and, therefore, develop hypothermia more quickly and to a greater degree after immersion in cold water than adults do. Hypothermia lowers cerebral metabolic rate and is neuroprotective to some extent for victims of submersion injury. Despite dramatic case reports of patients surviving prolonged submersion in cold water with full neurologic recovery, hypothermia is generally a poor prognostic finding. Cold-water immersion speeds the development of exhaustion, altered consciousness, and cardiac dysrhythmia. The *diving reflex* may also play a protective role in infant and child submersions. Activation of the diving reflex by fear or immersion of the face in cold water shunts blood centrally to the heart and brain. Apnea and bradycardia ensue, prolonging the duration of submersion tolerated without central nervous system (CNS) damage. The proposed protective effect of cold water immersion was unfortunately not seen in a study of 1094 drowning victims of all ages, where water temperature had no correlation.[7]

CLINICAL FEATURES

History and Physical Examination

Many drowning episodes are witnessed. Toddler drownings are an important exception, however, often occurring because of a lapse in supervision. Signs of pulmonary injury may be obvious in a drowning victim who is hypoxic, cyanotic, and in respiratory distress or arrest. More subtle clues, such as increased respiratory rate and audible rhonchi, rales, or wheezes, should alert the clinician to evolving respiratory compromise. Drowning victims swallow a significantly greater volume of water than is aspirated, and gastric distention from positive-pressure ventilation during rescue is common. As a result, 60% of patients vomit after a drowning event. Aspiration of gastric contents greatly compounds the degree of pulmonary injury and increases the likelihood that acute respiratory distress syndrome (ARDS) will ensue. In addition, aspiration of particulate contaminants such as mud, sewage, and bacteria may obstruct the smaller bronchi and bronchioles and greatly increase the risk of infection (both bacterial and fungal in nature).

Victims with CNS injury may present with symptoms ranging from mild lethargy to coma with fixed and dilated pupils. CNS injury results from the initial hypoxic or ischemic insult and from the cascade of reperfusion injury that follows reestablishment of cerebral blood flow after an arrest. The release of inflammatory mediators and the generation of oxygen free radicals in the postresuscitative period contribute to cytotoxic cerebral edema, compromise of the blood-brain barrier, and increased intracranial pressure.

Cardiac dysrhythmias may incite drowning or develop as its consequence. Hypoxemia, acidosis, and, potentially, hypothermia are the primary factors responsible for dysrhythmias ranging from ventricular tachycardia and fibrillation to bradycardia-asystole. Electrolyte disturbances are rarely significant enough to be dysrhythmogenic.

Other clinical sequelae of drowning may include acute renal impairment, which is present on admission in approximately 50% of patients as the result of lactic acidosis; prolonged hypoperfusion; and, in some instances, rhabdomyolysis. Coagulopathy as a consequence of associated hypothermia or disseminated intravascular coagulation (DIC) may also occur.

Prognostic Factors

Many factors help predict patients who will survive a drowning injury neurologically intact. Hypoxia, which is usually dependent on submersion time, is the most important factor related to outcome and subsequent quality of life in drowning victims. Drowning victims who arrive in the ED alert with normal hemodynamics are unlikely to experience neurologic impairment. Circumstantial variables that portend a poor outcome include victim age younger than 3 years old, submersion for longer than 5 to 10 minutes, and initiation of cardiopulmonary resuscitation (CPR) more than 10 minutes after rescue. Adverse neurologic findings on initial presentation do not preclude full neurologic recovery, although in general, patients whose duration of submersion or resuscitation exceeds 10 minutes have an unfavorable outcome.[7] With the exception of victim age, however, such measurements are generally either unknown or inaccurately estimated at the time of a patient's arrival in the ED. On arrival, objective findings associated with an unfavorable prognosis include hypothermia, severe acidosis, unreactive pupils, a Glasgow Coma Scale score of 3, and asystole or the need for ongoing CPR. Neurologically intact survival is reported for individual patients even with several of these factors present; none of several proposed scoring systems using combinations of these variables has 100% predictive power.

Children who present with an abnormal head computed tomography (CT) scan (eg, intracranial bleed, cerebral edema) within the first 24 hours have a nearly 100% mortality rate. Furthermore, an abnormal head CT scan at any time is associated with poor outcome (death or persistent vegetative state).

DIFFERENTIAL DIAGNOSIS

The precipitants of a drowning, such as drug or ethanol intoxication, cardiac arrest, hypoglycemia, seizure, and attempted suicide or homicide, should be considered in patients found unresponsive in water. For pediatric victims, child abuse or neglect should also be considered a potential cause. Potential head or cervical spine injury is an important consideration in drowning associated with trauma.

DIAGNOSTIC TESTING

Cardiac monitoring and an electrocardiogram (ECG) should be obtained to determine the presence of significant dysrhythmias, QT prolongation, or ischemia. Pulse oximetry, capnography, and arterial blood gases should be monitored closely in all drowning victims for signs of hypoxemia, hypercarbia, and acidosis. Blood glucose, serum creatinine, and electrolyte values should be obtained, although serum creatinine concentration and electrolyte levels are usually normal on initial presentation. Similarly, complete blood count is often normal with the exception of leukocytosis. Serum ethanol levels and urine toxicology screening may be appropriate for illicit drugs, depending on the circumstances of the drowning. Subsequently, evidence of renal failure, hepatic dysfunction, and DIC may be noted on laboratory testing.

The initial chest radiograph is often unremarkable and may underestimate the severity of pulmonary injury. Infiltrates or pulmonary edema may be evident within hours; therefore, repeat radiographs are indicted with persistent respiratory symptoms. Initial chest radiographs are often unremarkable even in the setting of serious and evolving pathologic processes. In symptomatic patients, frequent arterial blood gas measurements are indicated to monitor rapidly changing respiratory function.

Electroencephalography should to assess for seizure activity should be considered in the obtunded drowning victim.[8] Cranial CT is rarely initially contributory unless significant trauma or other pertinent injury is suspected. Magnetic resonance imaging (MRI) of the brain may predict neurologic outcome after drowning, but its prognostic value is not optimal until 3 or 4 days elapse.

MANAGEMENT

Salient details of the events surrounding the incident should be ascertained rapidly. Resuscitation of pulseless and apneic patients should be attempted initially in most cases because bystander estimates of total submersion time are often inaccurate. The clinical presentation of severe hypothermia often mimics death, and functional recovery is possible for hypothermic individuals submerged for significant periods of time.

For a victim without vital signs, outcome depends on the interval preceding CPR. Because these are hypoxic driven cardiac arrests, this is one situation where compression-only CPR may not be as effective as CPR with assisted ventilation, although this has not been well studied. Mouth-to-mouth ventilation while in the water should be attempted but not at the cost of prolonging the extrication. Chest compressions are impractical before extrication but should be initiated as soon as the individual is placed on a solid surface, such as a poolside or beach.

Cervical spine injuries are rare in drowning victims. Patients more likely to have cervical spine injuries tend to have either clinical signs of serious trauma or a history of motor vehicle crash, fall from height, or diving into the water. Unless such factors are present, routine cervical spine immobilization for submersion victims is not warranted.

On arrival in the ED, cardiac monitoring and continuous pulse oximetry should be established. A core temperature obtained with a low-reading probe is indicated for any unstable or lethargic patient. Values obtained by use of infrared ear thermometry are unreliable in drowning victims.[9] Rewarming of a hypothermic patient may suffice for hemodynamic stabilization and improvement in mental status. A spontaneously breathing patient should be monitored for signs of developing pulmonary injury.

Clinical impression and objective determination of the adequacy of oxygenation and ventilation should determine the decision for tracheal intubation. Apparent or developing respiratory distress, absence of protective airway reflexes, and significant associated head or chest injuries are indications. A partial pressure of carbon dioxide in the arterial blood ($Paco_2$) greater than 50 mm Hg should prompt strong consideration of intubation and lung protective ventilation. Patients unable to maintain oxygen saturation greater than 90%, or with an oxygen in arterial blood (Pao_2) greater than 60 mm Hg on high-flow oxygen, require positive airway pressure to increase functional residual capacity, to decrease intrapulmonary shunting, and to reduce ventilation-perfusion mismatch. In awake patients, this may be accomplished by face or nasal mask (continuous positive airway pressure), but the risk of potential gastric distention, vomiting, and aspiration should be considered. Otherwise, tracheal intubation and lung protective ventilation with positive end-expiratory pressure are indicated. The hemodynamic consequences of positive end-expiratory pressure should be monitored carefully, because increased intrathoracic pressure may compromise venous return and cardiac output. Decreased cranial venous return may impede cerebral perfusion.

No consensus exists with regard to the appropriate length of resuscitative effort for hypothermic drowning victims in the ED. The safest parameter is to continue until the core temperature reaches at least 32°C to 35°C, because cerebral death cannot be diagnosed accurately in hypothermic patients with temperatures below this level. This parameter may not always be practical, however, because brain-dead patients are often poikilothermic.

The administration of corticosteroids in the setting of drowning and potential ARDS does not improve outcome. Barbiturate-induced coma, diuresis, neuromuscular blockade, and hyperventilation do not improve neurologic outcome and, particularly in the case of hyperventilation, may be harmful. Similarly, empirical antibiotics do not increase survival and should be administered only to the patient who was submerged in grossly contaminated water or who shows signs of infection or sepsis.

Interventions, such as induced or permissive hypothermia, aimed at attenuation of reperfusion injury after anoxic brain insult are the focus of intense investigative effort. Drowning victims in cardiac arrest are usually colder than 30°C and require warming. Comatose patients who have been resuscitated after reasonable submersion time regardless of rhythm should not be rewarmed above 34°C. Rewarming only up to 34°C followed by a 24-hour mild hypothermic treatment before normothermia is reached may be advantageous because of decreased pulmonary reperfusion injury and reduced secondary brain injury. Emerging resuscitation literature indicates an emerging role for therapeutic hypothermia in drowning victims.

DISPOSITION

Symptomatic patients should be admitted for treatment. Patients with a history of apnea, unconsciousness, intoxication, or hypoxia and any patients who manifest dysrhythmias or an abnormal chest radiographs also require admission. Patients who are asymptomatic on presentation to the ED, maintain normal room air oxygen saturation, and have no chest radiograph or arterial blood gas abnormalities can be discharged safely after an observation period of 6 hours. Careful instructions about symptoms or signs of delayed pulmonary complications are necessary, and the patient should be discharged in the care of a competent adult.

Preventive Efforts

The mortality rate from drowning has been decreasing since the 1990s in the United States.[2] A similar downward trend in submersion injuries is reported in Great Britain. In low income countries globlally, drowning deaths (particularly in children) are on the rise. Although the exact causes of this decline are unknown, an

increased public awareness of preventive measures and an emphasis on public education with regard to CPR and the dangers of ethanol use in conjunction with water-related activities are contributing significantly to the reduction in fatalities, in some locations by over 80%.

Parental education about the danger of pediatric drowning is an important focus of preventive efforts. Inadequate supervision of children playing in or near water is one of the most common causes of pediatric submersion death, underscoring the importance of increasing awareness of the need for constant oversight of children in this setting. Most pediatric submersion injuries in swimming pools occur at the victim's home. In most cases, the child is last seen in the house, is left unattended for a moment, and enters the pool on an unfenced side closest to the home with no audible splash or screaming. Adequate and fully circumferential fencing of residential pools is a current recommendation of the American Academy of Pediatrics (AAP). Drowning or submersion is 3.7 times more likely in a non-fenced pool than in a properly fenced pool. In Australia, safety legislation is associated with a 30% reduction in drowning rates in young children. Unfortunately, legislation requiring appropriate fencing is poorly adhered to, and only 40% of households are compliant.

Legislation requiring personal floatation device usage in recreational boaters in Australia resulted in a significant decrease in drowning deaths.[10]

Effective approaches to prevention efforts in low- and middle-income countries differ from those in high-income countries. Data from almost 100,000 children in Bangladesh either entered into swim lessons or kept in a common supervision area in the community showed relative risks of drowning of 0.072 and 0.181, respectively. Both interventions were found to be extremely cost effective.[11]

Medical care providers are a vital resource for enhancement of public awareness of the importance of these measures. The literature supports the concept that education in the ED about drowning prevention can have a positive impact on patient and family awareness of steps to lessen the likelihood of catastrophic drowning injury.

KEY CONCEPTS

- Drowning is a leading cause of death and loss of years of life with over 90% of cases occurring in lower- and middle-income countries. Cost-effective prevention strategies have been developed for settings where resources limit treatment for drowning victims.
- All significant drownings induce pulmonary injury and hypoxia by the amount of water aspirated and the duration of submersion.
- Pulmonary and neurologic support is essential to optimize the victim's chance of a favorable outcome from this hypoxic event.
- Electroencephalography may be indicated in obtunded drowning victims to assess for subclinical seizures.
- No prognostic scale or clinical presentation accurately predicts long-term neurologic outcome; normal neurologic recovery is documented in patients with prolonged submersions, persistent coma, cardiovascular instability, and fixed and dilated pupils.
- Hyperventilation, steroids, dehydration, barbiturate coma, and neuromuscular blockade do not improve outcome after resuscitation.
- Comatose patients who have been resuscitated after reasonable submersion time regardless of rhythm should not be rewarmed above 34° C.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 137: QUESTIONS & ANSWERS

137.1. Which of the following is the greatest risk factor for death from drowning?
- **A.** Ethanol
- **B.** Male gender
- **C.** Poor swimming ability
- **D.** Saltwater drowning
- **E.** Warm water

Answer: A. Ethanol is a major risk factor for drowning and for death from drowning. Ethanol is a contributing factor in up to 50% of drowning incidents among adolescents and adults. More males drown than females, but male gender alone does not increase the risk of death from drowning. No direct evidence exists relating swimming ability to risk of death from drowning. Although frequently cited in older literature, there is no significant difference between saltwater and freshwater drowning. Although case reports of good survival from cold-water drowning exist, overall mortality is greater in cold water than in warm water.

137.2. A 13-year-old boy is brought to the emergency department (ED) after an apparent drowning. Family and paramedics report the patient was submerged for approximately 4 minutes. Bystanders began cardiopulmonary resuscitation (CPR) immediately. Paramedics intubated the patient and continued CPR, which has now been ongoing for 10 minutes. On arrival in the ED, the patient has a Glasgow Coma Score (GCS) of 3, unreactive pupils, no pulse, and is in asystole on the cardiac monitor. What is the most appropriate next step?
- **A.** Cessation of treatment/pronounce death
- **B.** External cardiac pacing
- **C.** Induction of hypothermia
- **D.** Intravenous epinephrine
- **E.** Unsynchronized defibrillation

Answer: D. Although this patient will likely have a poor outcome, asystolic victims of drowning have a higher incidence of full neurologic recovery than patients with asystole from other causes. Poor prognostic indicators are age younger than 3 years old, submersion greater than 5 minutes, delay in initiation of CPR greater than 10 minutes, hypothermia, severe acidosis, unreactive pupils, GCS of 3, and asystole. The decision to cease care must be made on a case-by-case basis, but initial treatment of asystole should be begun in drowning victims following standard advanced cardiac life support (ACLS) protocols. Experiments with induction of hypothermia are ongoing in drowning victims, but the results are not definitive.

137.3. A 16-year-old boy presents with tachypnea and coughing. Family members state that they were swimming in a nearby lake when they noticed the patient with the previously mentioned symptoms. The patient is awake and alert but in obvious distress. He has a respiratory rate of 35 breaths per minute, with the remainder of his vital signs within normal limits. His oxygen saturation as measured by pulse oximetry is 84% while on high-flow oxygen. Pulmonary examination reveals diffuse rales. There is no evidence of trauma. In addition to intubation, which of the following is indicated?
- **A.** Administer intravenous diuretics.
- **B.** Administer intravenous steroids.
- **C.** Obtain an electrocardiogram (ECG).
- **D.** Perform maneuvers to remove fluid from the lungs.
- **E.** Place the patient in cervical spine precautions.

Answer: C. Dysrhythmias are frequently associated with drowning, especially when no obvious cause is found. ECGs should be performed on all drowning patients. Antibiotics, steroids, and diuretics have all been studied in drowning victims, and none show any benefit. Cervical spine precautions are often initiated in all drowning victims but are not needed unless the patient has clinical signs of trauma or a history of motor vehicle crash, fall from height, or diving into the water. Maneuvers to remove fluid from the lungs (Heimlich, Patrick) are ineffective and potentially dangerous.

137.4. An 18-year-old man is brought to the emergency department (ED) after submersion in his swimming pool. Per witnesses, once the patient was brought from the water, he initially had severe coughing and complained of shortness of breath. On arrival to the ED, the patient denies shortness of breath and is not coughing. Vital signs as well as oxygen saturation are all within normal limits. Electrocardiogram (ECG) and chest radiographs are normal. What is the appropriate disposition of this patient?
- **A.** Admission to telemetry for 23-hour observation
- **B.** Admission to the general hospital for 23-hour observation
- **C.** Admission to the intensive care unit for 23-hour observation
- **D.** Discharge home after observation in the ED for 6 hours
- **E.** Discharge home now

Answer: D. Any symptomatic patients or patients with a history of apnea, unconsciousness, or hypoxia should be admitted. Likewise, patients with dysrhythmias or abnormal chest radiographs should be admitted. Some effects of drowning can be delayed, so asymptomatic patients should be observed for 6 hours in the ED but can be safely discharged if they continue to be asymptomatic and can maintain normal room air oxygen saturation. They should be discharged in the care of a responsible family member or friend.

CHAPTER 138

Radiation Injuries

Daniel Hryhorczuk | Jillian L. Theobald

PRINCIPLES

Radiation

Overview

Radiation is energy that travels through space in the form of a particle or wave.[1] It is produced by radioactive decay of an unstable atom (radionuclide or radioisotope) or by the interaction of a particle with matter. *Particle radiation* consists of particles that have mass and energy, and may carry an electric charge. Examples of particle radiation include alpha particles (helium nuclei), protons, beta particles (electrons ejected from the nucleus), and neutrons. *Electromagnetic radiation* consists of photons that have energy but no mass or charge. Radiation can be either ionizing or nonionizing depending on its energy and ability to penetrate matter. Electromagnetic radiation varies by frequency and wavelength as shown in Figure 138.1.

Radioactive decay (radioactivity) is the process by which a nucleus of an unstable atom loses energy by emitting ionizing radiation in the form of high-energy particles or rays. Radioactive decay can emit particles such as those described earlier or rays such as gamma or x-rays. Gamma and x-rays are high-energy photons that differ in their place of origin: gamma rays are emitted from the nucleus, whereas x-rays are produced as the result of changes in the positions of electrons orbiting the nucleus.

The type and rate of radioactive decay varies by radionuclide. The rate of decay is measured by the *radioactive half-life* (the time for half the radioactive nuclei in any sample to undergo radioactive decay) and varies from a few microseconds to billions of years. Radiation exposure can be external (eg, exposure to x-rays) or internal, resulting from the inhalation, ingestion, or injection of radioisotopes.

Radiation Measurements

The four different but interrelated units for measuring radiation (radioactivity, exposure, absorbed dose, and dose equivalent) are shown in Table 138.1. These units are also commonly expressed as fractions of whole units using the terms and abbreviations, (eg, milli [m] [1/1000th] and micro [μ] [1/1,000,000th]).[1]

Radiation Protection

The principles of radiation protection include time, distance, shielding, and quantity. Reducing the time of radiation exposure will reduce the absorbed dose. The intensity of radiation is a function of distance from the source and follows the inverse square law: the intensity of radiation dose decreases inversely with the square of the distance. Shielding is the placement of an absorber (material that reduces radiation) between the person and the source. The effectiveness of shielding varies with the type of the radiation. For example, alpha particles can be stopped by a thin piece of paper or even the dead cells in the outer layer of the skin, whereas thick, dense shielding is necessary to protect against gamma rays. Limiting the quantity of radioactive material in the working area will also decrease exposure. National and international regulatory bodies set acceptable limits for occupational and population exposures to radiation.

Radiation Sources

Ionizing radiation and radioactive substances are natural and permanent features of the environment. The average annual radiation dose per person in the United States is 6.2 mSv (620 mrem). Fifty percent of this average dose comes from background radiation and 48% from medical procedures. The major sources of background radiation are radon and thoron (37%), cosmic radiation (5%), naturally occurring internal radioisotopes (eg, potassium-40 [5%]), and terrestrial background (3%). The major medical sources include computed tomography (CT; 24%), nuclear medicine (12%), interventional fluoroscopy (7%), and conventional radiography and fluoroscopy (5%). The remainder of the average annual radiation dose comes from occupational and consumer sources.[2]

Radon is a naturally occurring radioactive gas that is formed from the radioactive decay of uranium. Radon can accumulate in homes and is the second leading cause of lung cancer in the United States.[3] Radon exposure is estimated by measuring radon levels in the air using inexpensive and readily available kits. If indoor levels of radon are ≧4 pCi/L, then the US Environmental Protection Agency recommends that the homeowner consult a certified radon mitigation specialist to reduce radon air levels in the home.

Although radiation-related accidents are rare, the consequences of exposure or significant internal contamination can be fatal. The Radiation Emergency Assistance Center at Oak Ridge National Laboratory maintains a worldwide registry of serious radiation accidents. Between 1944 and 2012, there have been 454 radiation accidents recorded worldwide. The greatest numbers of serious accidents have occurred with sealed sources, which include brachytherapy sources used in radiation oncology and industrial radiography devices (n = 214), followed by x-ray devices (n = 86). Radioisotopes used in medical diagnosis and therapy have caused almost 11% percent of major radiation accidents.[4]

Serious nuclear power accidents include the Fukushima Daiichi disaster (2011), the Chernobyl disaster (1986), Three Mile Island (1979), and the SL-1 accident (1961). The radioisotopes most commonly released from nuclear reactor accidents include iodine, cesium, and strontium. Chernobyl had the largest number of radiation-related injuries. About 150 individuals who received very high whole-body doses were treated for acute radiation sickness; 28 of these died within a relatively short time, and approximately 20 more have since died from radiation-related diseases.[5] Radiation to the thyroid from radioisotopes of iodine released during Chernobyl accident has caused several thousand cases of thyroid cancer with children being the most susceptible population.

The detonation of nuclear bombs has the greatest potential to produce mass casualties. The acute and long-term effects have

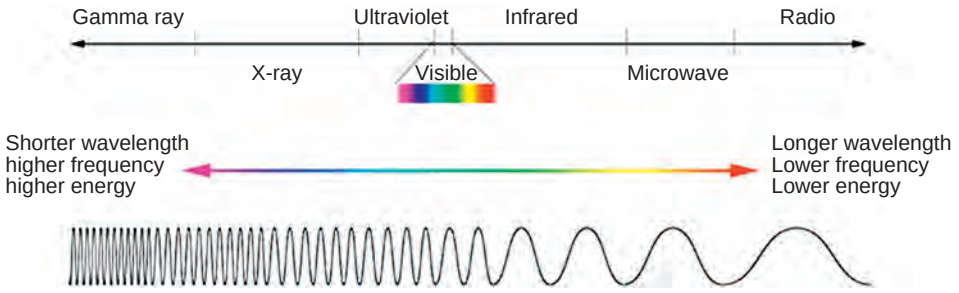

Fig. 138.1. Electromagnetic radiation varies by frequency and wavelength. (National Aeronautics and Space Administration: Imagine the universe: the electromagnetic spectrum. Available at: http://imagine.gsfc.nasa.gov/science/toolbox/emspectrum1.html.)

TABLE 138.1

Radiation Units Description and Conversion Factors

MEASURE	DESCRIPTION	UNITED STATES UNITS	INTERNATIONAL UNITS	CONVERSION
Radioactivity	Amount of ionizing radiation released by a material	Curie (Ci)	Becquerel (Bq)	1 Bq = 2.7×10^{-11} C
Exposure	Amount of radiation traveling through air	Roentgen (R)	Coulomb (C)/kg	1 C/kg = 3875.9 R
Absorbed dose	Amount of radiation absorbed by a person	Radiation absorbed dose (Rad)	Gray (Gy)	1 Gy = 100 rad
Dose equivalent (effective dose)	Combines the amount of radiation absorbed with the tissue damaging potential of the type of radiation	Roentgen equivalent man (Rem)	Sievert (Sv)	1 Sv = 100 rem

been well documented following the bomb blasts in Hiroshima and Nagasaki in 1945 (18 and 22 kilotons). Today's nuclear weapons are orders of magnitude more devastating. Another potential scenario is the detonation of a low-yield nuclear bomb by terrorists. A 10-kiloton nuclear detonation within a city in the United States would result in a zone of destruction of up to 2 miles from ground zero and would expose hundreds of thousands of people to radiation.[6] A more likely terrorist scenario is the explosion of a *dirty bomb*. A dirty bomb is the combination of a conventional explosive with a radioisotope illegally obtained from medical or industrial sources. The radioisotopes most likely to be used in a dirty bomb are cesium-137, cobalt-60, or strontium-90.[7] Although the acute radiation risks from a dirty bomb detonation are low, the localized residual radiation contamination would likely cause wide spread panic.

Pathophysiology

The biologic effects of radiation exposure are determined by the type of radiation, the total dose, the dose rate, the volume of tissue or anatomical body part irradiated, and individual susceptibility factors. The amount of energy released in matter (linear energy transfer) varies by type of radiation. Different types of radiation are assigned a quality factor (QF) based on their ability to produce biologic damage in exposed tissue. Gamma rays, x-rays, and beta particles have a QF of 1. Alpha particles (internal exposure only) have a QF of 20, whereas neutrons have a QF range of 3 to 20, depending on their energy.

Ionizing radiation includes particles and photons that have sufficient energy to produce ionization of the atoms that they encounter. Alpha particles, beta particles, and neutrons are examples of particle ionizing radiation. Only the high frequency portion of the electromagnetic radiation (gamma rays, x-rays, and far ultraviolet) has sufficient energy to produce ionization. Other frequencies and wavelengths (near ultraviolet, infrared, microwaves, radio waves, and very or extremely low frequency radiation) are *nonionizing*. The health effects of exposure to nonionizing radiation depend on the frequency and wavelength. For example, ultraviolet light can produce sunburns, visible light (eg, lasers) can produce corneal and retinal burns, and microwaves can produce heating of body tissues.

The effects of ionizing radiation on tissue can be *direct* or *indirect*. Direct effects include single- and double-strand DNA breaks. Indirect effects act through generation of free radicals that then attack other molecules in the cell. Cells vary in their sensitivity to radiation. In general, cells that are undifferentiated, divide quickly, and have high metabolic activity are most radiosensitive. Examples of these types of cells include bone marrow stem cells, lymphocytes, spermatogonia, intestinal crypt cells, and epidermal basal cells. The effects of radiation can be *deterministic* or *stochastic*. Deterministic effects are those in which the severity of injury is a function of dose (eg, bone marrow suppression). Stochastic or probabilistic effects are those in which the probability of an effect, rather than its severity, is a function of dose. An example of a stochastic effect is the development of radiation-induced cancer.

For external exposure, the site of the body that is irradiated (eg, bone marrow vs. upper extremity) is an important determinant of the resulting effects. For internal exposure, the biodisposition of the radioisotope, its radiologic and biologic half-lives, as well as the types of radioisotopes produced during radioactive decay are important determinants of the effects. The *effective half-life* reflects both the radiologic and biologic half-life and can be calculated as 1/effective half + 1/physical half-life.[8] For example, iodine-131 has approximate biological half-life of 57 days and a radiologic half-life of 8 days. The resulting effective half-life is approximately 7 days. *Biodisposition* refers to the absorption, distribution, metabolism, and excretion of a radioisotope. Radioisotopes will have their greatest effects at the sites in the body where they are concentrated. For example, radioiodine concentrates in the thyroid gland and the resulting effects, such as thyroiditis or thyroid cancer, occur at the site of concentration.

TABLE 138.2

Systemic Radiation Effects Based on Dose

Dose (gray)				
	12 +	→ Bone Marrow Suppression	Neurovascular syndrome onset	Multiple organ failure
	11			Probable death
	10			Consider stem cell transplants
	9			
	8			
	7			LD 50/60 with supportive care
	6		Gastrointestinal syndrome onset	
	5			LD 50/60 without treatment
	4			
	3			
	2			≈100% survival without treatment
	1		Hematopoietic syndrome onset	
	0			

Adapted from The Medical Aspects of Radiation Incidents; originally published by ORISE and REAC/TS under contract number DE-AC05-06OR23100 between the US Department of Energy and ORAU, 2013.

Routes of Exposure

An individual can be exposed to radiation through one or more of three processes: irradiation, incorporation, and contamination.

Irradiation occurs when an object or person is exposed to a radioactive source. An object doesn't become radioactive unless neutron activation occurs. So, when a person is irradiated, such as a patient who has just received a CT scan or x-ray, no hazard exists to medical personnel who come into contact with the patient.

Contamination is exposure to radioactive particulate matter (alpha and beta particles). Contamination usually occurs externally but may be internal if the radioactive material is inhaled and deposited in the lungs. Contamination is not an acute threat to the life of the patient or the provider, and its presence should not preclude institution of lifesaving measures. The radioactive particulate matter may emit radiation with an effect that is directly related to the time of exposure, distance from the source, and type of contamination.

Incorporation occurs when a radioactive material is taken up by a tissue, cell, or organ. This can occur through ingestion, inhalation, or absorption via an open wound.

Clinical Features

Acute Radiation Syndrome

Acute radiation syndrome (ARS) occurs after a patient is exposed to whole body radiation. ARS can result from external or internal exposure to radiation and varies in nature and severity by dose, dose rate, dose distribution, and individual susceptibility. This syndrome can result from external or internal exposure to radiation. The patterns of symptoms and signs of ARS overlap and the timing of the progression through the phases can be accelerated with increasing doses.[9] There are three phases to ARS: prodromal, latent, and manifest illness.

In the *prodromal phase,* initial symptoms are typically nonspecific and include anorexia, nausea, vomiting, and fatigue. This phase is useful to help predict the severity of the radiation injury. The presence, onset, and frequency of nausea and vomiting, although nonspecific, can serve as a prognostic factor. Early onset of nausea and vomiting, the persistence of it, and the presence of diarrhea indicates a severe radiation injury.[10]

The *latent phase* is a period of initial symptom improvement. Those with lethal radiation doses may not have a symptom free period and progress from the prodromal phase directly to the manifest illness phase.

The *manifest illness phase* has three sub-syndromes that may occur and overlap depending on the radiation dose received (Table 138.2). All organs are affected by radiation; however, the relative sensitivity of organ systems exposed to radiation determines the clinical symptoms. Tissues with greater rates of cellular division, particularly the hematopoietic and gastrointestinal systems, are most radiosensitive.

The hematopoietic sub-syndrome is the first sub-syndrome seen as the hematopoietic system is the most radiosensitive. This sub-syndrome can appear at doses greater than 1 Gy and typically results in bone marrow suppression. At doses less than 1 Gy (100 rem), most cells survive but may be susceptible to radiation-induced cancer.[11] Lymphocyte depletion is the first cell line to decrease and with high doses of radiation the drop will occur sooner and with greater severity.

The gastrointestinal sub-syndrome begins to occur at doses nearing 6 Gy about 1 week after exposure. Patients will display nausea, vomiting, gastrointestinal bleeding, malabsorption, and massive fluid loses potentially leading to hypovolemia and cardiovascular collapse. These symptoms are due to death of the intestinal epithelial precursor cells and resultant denuding of the intestinal epithelial surface. Thrombocytopenia and immunosuppression from the accompanying hematopoietic sub-syndrome predisposes patients to infection and bleeding.[12]

The neurovascular sub-syndrome results from doses greater than 10 Gy and is typically lethal. Patients will develop the following: irritability, altered mental status, seizures, prostration, ataxia, and hypotension. Coma and death usually occur within a few hours. Because of the high dose of radiation needed to produce these findings, patients often die before progressing to the latent phase.[13]

Local Radiation Injury

Cutaneous involvement can occur following a radiation exposure. It can be one component of ARS with other organ involvement or it can occur alone.[14] Radiation injury limited to the skin and the tissues located directly beneath the area of injury is termed a *local radiation injury (LRI).*[15] This injury typically happens after a patient handles or has close contact with an industrial radioactive source. LRI can also result from medical testing or therapy, such as fluoroscopy, nuclear medicine studies, and CT scans.[16] Inflammation, oxidative damage, and damage to the microvasculature are all involved in the pathophysiology of LRI.[17] Hair loss occurs after exposure to 3 Gy, erythema is seen after exposure to 6 Gy, wet desquamation occurs after 15 Gy, and necrosis occurs after 20 to 25 Gy of localized skin exposure (Table 138.3).[15,17,18]

TABLE 138.3

Local Irradiation Symptoms by Dose

THRESHOLD DOSE (Gy)	SYMPTOMS	TIME TO ONSET (DAYS)
3	Epilation	14 to 18
6	Early erythema	14 to 21
10	Dry desquamation	25 to 30
15	Moist desquamation	20 to 28
>20	Ulceration and necrosis	>21

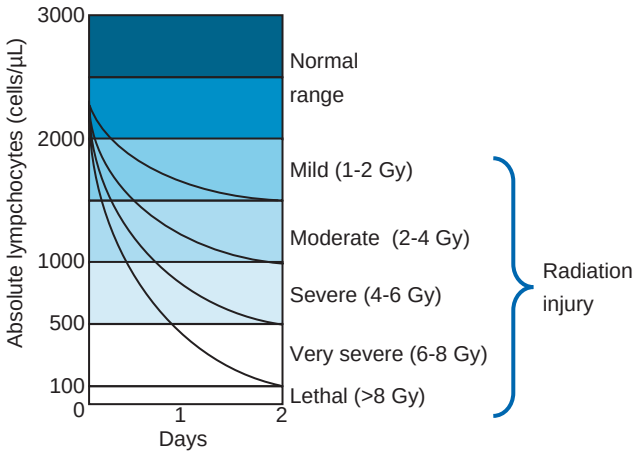

Fig. 138.2. Lymphocyte decrease over time following radiation injury. (Adapted from Andrews GA, Auxier JA, Lushbaugh CC: The importance of dosimetry to the medical management of persons exposed to high levels of radiation. In: Personal dosimetry for radiation accidents, Vienna, 1965, International Atomic Energy Agency.)

DIFFERENTIAL DIAGNOSES

The initial signs and symptoms following radiation exposure are nonspecific and include anorexia, nausea, vomiting, and fatigue. In the absences of an exposure history, these symptoms in the prodromal phase of acute radiation sickness can be confused for gastroenteritis with its long list of differential diagnoses. Neutropenia seen after whole body radiation exposure also has many other etiologies, including viral infections, medications, certain autoimmune disorders, and nutritional deficiency.

The severe symptoms following high-dose radiation injury resulting in the neurovascular sub-syndrome can occur with any catastrophic cardiovascular or neurological event. Local radiation injury can appear similar to thermal burns but differ in their progression over time.

DIAGNOSTIC TESTING

If contamination with radioactive material is a possibility, then the patient should be surveyed with a contamination survey instrument (eg, Geiger Muller detector). These very sensitive detectors measure the presence of radioactive material in counts per minute. There are a variety of other radiation detection devices that are designed to measure field strength in units of mrem/hour or μSv/hour. These latter types of instruments are most often used to measure radiation fields at the event scene. The hospital radiation safety officer should be consulted to assist in performing radiation surveys of potentially contaminated patients or objects.

Quantifying the absorbed dose of radiation can be challenging, especially in the emergency department (ED). Information on the radiation source, field strength, time of exposure, distance, shielding, and routes of exposure is often incomplete. Although radiation doses can be reconstructed at a later time by health physicists, emergency clinicians will most often rely on biodosimetric tools, such as time to vomiting and lymphocyte depletion kinetics. These online tools are available at www.remm.nlm.gov/ars_wbd.htm#vomit.

A baseline complete blood count (CBC) with differential and absolute lymphocyte count should be obtained and repeated every 6 hours for the first 24 hours and at least daily thereafter. The absolute lymphocyte count at 48 hours after exposure is a good predictor of radiation injury (Fig. 138.2). If the absolute lymphocyte count is greater than 1200 cells/μL, it is unlikely that the patient has received a clinically significant dose of radiation. If the absolute lymphocyte count falls between 100 and 500 cells/μL at 48 hours, a significant or even lethal dose of radiation should be suspected. A level in this range is an indication for neutropenic precautions.[19] Weeks later, thrombocytopenia and anemia may develop because these cell lines are more radioresistant. Serum lipase, liver function tests, and C-reactive protein (CRP) should also be obtained and repeated at least daily. If the patient has been exposed to radioisotopes, rather than just external radiation, obtain nasal and mouth swabs and collect 24-hour urine and feces specimens for radiation bioassay.[8] Hospital nuclear medicine departments may have equipment that can be adapted and used for the diagnosis of internal contamination (eg, thyroid scanners and gamma cameras).

MANAGEMENT

Prehospital Care

Information should be gathered regarding the exposure event: the numbers and types of patients potentially affected, the radionuclide involved, the route of exposure, and the estimated dose of radiation. Multiple triage guidelines exist to help guide transport and decontamination of individuals in the prehospital setting and are available to the public (Table 138.4).[20] Most communities will have a disaster plan for radiation incidents, which should be activated if a significant number of patients are involved.

Decontamination should be initiated at the scene. Patients with abnormal vital signs should have partial decontamination, such as clothing removal, at the scene before expeditious transportation to an ED. Unstable patients should be rapidly transported in lieu of decontamination measures. Radio contact with the receiving hospital should be provided to facilitate preparations. If the community disaster plan has a designated hospital for radiation-contaminated victims, patients should be transported directly to that facility, bypassing hospitals less equipped to care for these complicated patients.

Emergency Department

Preparation

The chaos that occurs following radiation exposure incidents suggests that a community disaster plan should be developed with a predetermined individual empowered to make decisions about evacuation and other issues concerning the at-risk population. On notification of the numbers and types of patients involved in a radiation exposure accident, a decision should be made about implementation of a full disaster plan versus a limited response. The hospital *radiation control officer*, usually a radiologist, toxicologist or pathologist, should be contacted immediately. The radiation

TABLE 138.4

Available Resources for Assistance and Consultation During a Radiation Incident and Informational Resources

ORGANIZATION	CONTACT	WEBSITE
CONSULTATIVE		
Radiation Emergency Assistance Center/Training Site (REAC/TS)	24-hour emergency number: (865) 576-1005	www.orau.gov/reacts
Armed Forces Radiobiology Research Institute	24-hour military emergency response resource: (301) 295-0530	www.usuhs.edu/afrri/
Chemical/Biological Hotline of the National Response Center	24-hour federal point of contact: (800) 424-8802	www.nrc.uscg.mil/
INFORMATIONAL		
US Department of Human and Health Services: Radiation and Emergency Medical Management		www.remm.nlm.gov/
Center for Disease Control and Prevention: Radiation Emergencies		http://emergency.cdc.gov/radiation/
World Health Organization: Radiation Emergencies		www.who.int/ionizing_radiation/a_e/en/

control officer should monitor all patients and medical personnel with a radiation counter and should supervise the "cleanup" and the routing of patients to minimize "tracking," or spread, of contamination. Information dissemination to the public is critical. Timely and accurate information and instructions should be given to a public relations person for dissemination to the news media to minimize the chaos and paranoia that inevitably result from such incidents.

External Contamination

Radiation contamination is not an acute threat to the life of the patient or the provider, and its presence should not preclude institution of lifesaving measures. If standard precautions are taken, the risk to the health care providers is minimal. This was true for the physicians caring for Alexander Litvinenko, a former agent of the Federal Security Service of the Russian Federation who was poisoned with a radioactive substance. It was 3 weeks before it was determined what he was internally contaminated with polonium 210.[21] Because the risk is minimal, care for life-threatening conditions and evaluation for severe traumatic injuries takes precedence over decontamination measures. A general approach to the patient exposed to radiation developed by the Radiation Emergency Assistance Center/Training Site of Oak Ridge Associates Universities is shown in Figure 138.3.

When a person is irradiated, such as in a patient who has just received a CT scan or x-ray, no hazard exists to medical personnel and the patient may be handled like any other emergency patient.

If a patient is determined to be contaminated with radioactive material by survey with a radiation counter (such as, a Geiger counter), then they require decontamination. Universal precautions, including rubber gloves, shoe covers, and respirators if airborne contamination is suspected, are effective in protecting personnel and the work area from contamination. The only variation is to wear two sets of gloves and to change the outer pair when appropriate to avoid cross-contamination.[22] The patient's clothing should be removed and placed in plastic bags. Removing a patient's clothing and shoes will remove about 90% of the radiation from the patient.[23] If possible, soap and water cleansing of exposed skin should be performed. All materials, including wash water, should be placed in containers and labeled as radioactive waste. After decontamination, the patient should be surveyed again. Decontamination should be repeated until the patient's radiation reading is only two times background radiation. If decontamination methods are causing damage to the skin, they should be discontinued regardless of the patient's radiation survey results.[8]

Wounds should be decontaminated with saline or water. High pressure irrigation is more important than the irrigation solution.[24] Foreign bodies should be removed and safely set aside for further analysis. Repeat survey of the wound for radiation should be done, and repeat irrigation may be needed. If further attempts at decontamination do not result in a decreased amount of radiation in the wound, then the wound should be treated as medically appropriate with surgical closure if needed. Attempts to surgically decontaminate the wound should be avoided because this will cause more localized damage.[23]

Internal Contamination

Assessing a patient for internal contamination can be difficult because most beta and alpha emitters will not be detectable with a handheld survey device. If a patient is externally contaminated, they have a higher risk of being internally contaminated. For internally contaminated patients, management should focus on decreasing absorption, enhancing elimination, and blocking distribution to target organs.[8] Treatment directed at internal contamination by particular radionuclides can include potassium iodide for radioactive iodine exposures, bicarbonate for uranium, Prussian blue for cesium and DTPA for plutonium and transuranics (Table 138.5).

Acute Radiation Syndrome

Hematopoietic Sub-Syndrome. Colony-stimulating factors (cytokines) that induce bone marrow hematopoietic cells to proliferate may have substantial benefit, with little risk in victims predicted to have moderate or severe bone marrow failure. Cytokine therapy should be started for the following reasons: greater than 2 Gy dose, decrease in lymphocyte count, and if leukopenia is expected to last more than 7 days. It should be started within 24 hours of exposure and continued until the absolute lymphocyte count is above 1000 cells/μL. Bone marrow transplant should be considered for patients who continue to have

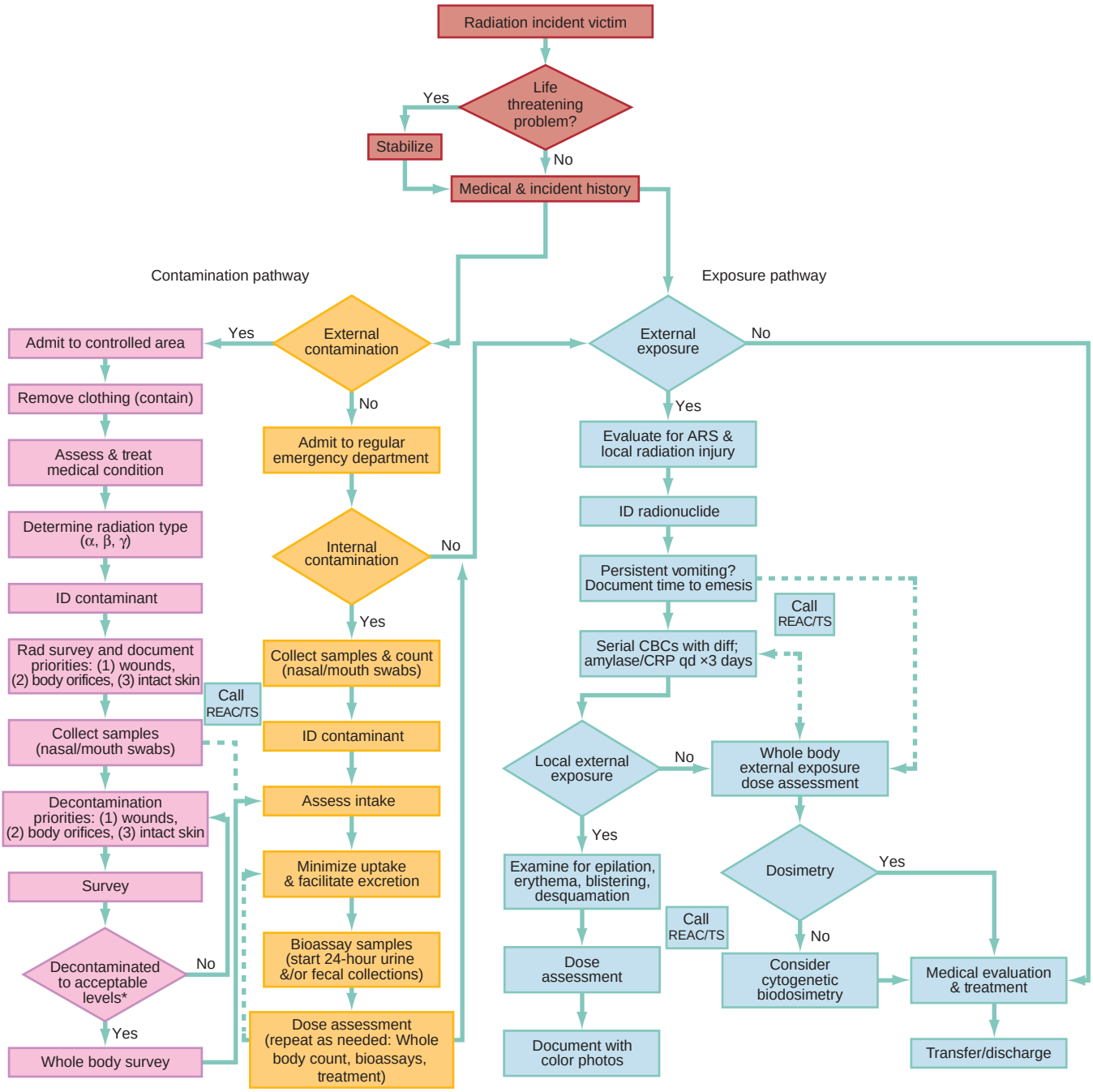

Fig. 138.3. Radiation patient treatment algorithm. *, <2-3X Natural background or no reduction in counts, medical priorities dictate stopping decontamination, health physics consultation warranted. *ARS,* Acute radiation syndrome; *CBC,* complete blood count; *CRP,* C-reactive protein; *diff,* differential; *ID,* identification; *qd,* on prescription; *REAC/TS,* Radiation Emergency Assistance Center/Training Site. (Used with permission and originally published by ORISE and REAC/TS under contract number DE-AC05-06OR23100 between the US Department of Energy and ORAU.)

prolonged leukopenia (2 to 3 weeks) in spite of cytokine treatment; however, the patients must not have other significant organ involvement.[19] Prophylactic antibiotics should also be given in accordance with the Infectious Disease Society of America recommendations for neutropenia.[25]

Gastrointestinal Sub-Syndrome. Treatment for the gastrointestinal sub-syndrome is largely supportive with antiemetics (preferably serotonin receptor antagonists), antidiarrheals, fluid resuscitation, antibiotics, and monitoring for signs of gastrointestinal perforation.

Neurovascular Sub-Syndrome. Patients who develop signs and symptoms consistent with this sub-syndrome within the first 24 hours should be provided comfort care, because they likely sustained a lethal dose of radiation.

Local Radiation Injury

Patients who sustained a LRI are managed in a manner similar to thermal burn patients.[15] Treatment at a burn center is preferred for débridement and wound care. Eventual amputation may be necessary in patients who present with symptoms such as pain

TABLE 138.5

Radionuclides of Interest, Primary Decay Pattern, Half-Life, Major Routes of Exposure, and Recommended Treatment

	NAME	ISOTOPE	DECAY	HALF-LIFE	ROUTE OF EXPOSURE	TREATMENT
University Five	Carbon 14	^{14}C	β	5700 years	Inhalation Ingestion	N/A
	Phosphorus 32	^{32}P	β	14 days	Inhalation Ingestion Skin	Phosphorus
	Iodine 125	^{125}I	γ	59 days	Inhalation Ingestion	KI
	Iodine 131	^{131}I	β, γ	8 days	Inhalation Ingestion	KI
	Californium 252	^{252}Cf	α, γ	2.6 years	Inhalation Ingestion	DTPA
Industrial Three	Iridium 192	^{192}Ir	β, γ	74 days	Inhalation Ingestion	DTPA
	Cesium 137	^{137}Cs	β, γ	30 years	Inhalation Ingestion	Prussian Blue
	Cobalt 60	^{60}Co	β, γ	5.3 years	Inhalation	DTPA
Military Five	Tritium	^{3}H	β	12 years	Inhalation Ingestion Skin	Water Diuresis
	Uranium 235	^{235}U	α	700 million years	Inhalation Ingestion	Bicarbonate
	Uranium 238	^{238}U	α	4.5 billion years	Inhalation Ingestion	Bicarbonate
	Plutonium 239	^{239}Pu	α	24,000 years	Inhalation	DTPA
	Americium 241	^{241}Am	α	430 years	Inhalation Skin	DTPA

DTPA, Diethylenetriaminepentaacetate; *KI,* potassium iodide.

and erythema shortly after radiation exposure. Due to the chronic vascular injury and the potential for even minor trauma to the area to recapitulate the injury, the following are important in the treatment of LRI: topical corticosteroids, hyperbaric oxygen (HBO) therapy, pentoxifylline and vitamin E therapy, and appropriate wound care.[23]

Psychological Consequences

The general public harbors a profound fear of radiation and its effects on the body. Radiation is one of the most dreaded components of a terrorist attack or industrial accident.[26] People are fearful of the long-term effects of radiation exposure such as cancer and also the effects on children. This fear can lead to ostracizing people or things associated with the area of the event or disaster. Furthermore, those who develop ARS or other illnesses related to radiation may have significant fear and depression requiring psychological post-traumatic support. Moreover, both health care providers and communities as a whole are also at risk. As a result, proper information dissemination to the public and incorporating behavioral health professionals into the disaster response is extremely important.

DISPOSITION

The disposition of the patient will depend in part on the scale of the event and the availability of medical resources. A mass casualty event may require disaster triage and resource rationing. Fortunately, large-scale radiation events are rare, and most radiation accidents have generated small numbers of patients requiring emergency or intensive care. The time of onset to vomiting can be useful in determining likelihood of survival. Patients who experience vomiting within 2 hours of exposure will require hospitalization and careful medical observation, because they are likely to have sustained life-threatening doses of radiation. Patients with severe burns and those requiring surgical management should be transferred to a burn unit, preferably within 72 hours from the time of radiation exposure.

ADDITIONAL RESOURCES

Many resources are available for both assistance in diagnosing and managing radiation injuries and for reporting of incidents. Table 138.4 lists resources that can help guide diagnosis and treatment of radiation emergencies and provide evidence-based information for those without formal radiation medicine expertise.

KEY CONCEPTS

- Patients contaminated with radiation pose very little risk to health care providers when appropriate precautions and decontamination procedures are employed.
- Decontamination should not delay or impede the stabilization of patients in radiation emergencies.
- Tissues with greater rates of cellular division, particularly the hematopoietic and gastrointestinal systems, are most radiosensitive.
- Vomiting and skin burns occurring shortly following radiation exposure are predictors of severe radiation injury.
- The 48-hour absolute lymphocyte count is the most important prognostic indicator and should be drawn on suspected radiation exposure patients.
- Most therapy is supportive and symptomatic except for exposures involving the ingestion or inhalation of radioactive material, when specific therapy with blocking or chelating agents may be indicated.
- Formal consultation at the hospital, regional, and national levels is available 24 hours a day and should be used for assistance when any patient with radiation injuries is evaluated.

The references for this chapter can be found online by accessing the cocompanving Expert Consult website.

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CHAPTER 138: QUESTIONS & ANSWERS

138.1. In the event of a nuclear power accident, which of the following radionuclides is most likely to pose the greatest hazard to the population living downwind from the reactor?

A. Carbon 14
B. Cobalt 60
C. Iodine 131
D. Plutonium 239
E. Uranium 235

Answer C. The radioisotopes most commonly released from nuclear reactor accidents include iodine, cesium, and strontium. Release of radioiodine from the Chernobyl reactor resulted in several thousand cases of thyroid cancer among the exposed population.

138.2. A worker in your hospital's blood bank comes into the emergency department (ED) complaining that he has been exposed to radiation on an ongoing basis for approximately 1 month. He reports his job duties include irradiating blood products to be used in the hospital and that he has not been wearing protective clothing. He reports a burning sensation in his hands. His physical examination is normal. What is the appropriate course of action?

A. Admit for observation
B. Decontaminate the patient, admit for observation
C. Decontaminate the patient, discharge home
D. Decontaminate the patient, place on isolation, admit for observation
E. Educate patient and arrange appropriate follow-up

Answer: E. This patient has been irradiated but not contaminated. Patients who are exposed to external beam radiation are not made radioactive and are not a hazard to others. Decontamination and isolation are not necessary. With a normal physical examination and minimal symptoms, this patient can be followed as an outpatient. The most important action in this instance is to educate the patient.

138.3. What is the most important laboratory test to be performed 48 hours after exposure in determining the prognosis of a patient exposed to a significant radiation source?

A. Absolute lymphocyte count
B. Absolute neutrophil count
C. Karyotype
D. Platelet count
E. Serum albumin

Answer: A. Monitoring the kinetics of lymphocyte depletion during the first 48 hours following a radiation exposure is very useful at estimating the radiation dose received. The 48-hour absolute lymphocyte count is the most important prognostic indicator and should be drawn on all suspected radiation exposure patients. Levels greater than 1200/μL indicate a clinically insignificant dose of radiation and an excellent prognosis. Levels less than 500/μL indicate a significant and possible lethal exposure. None of the other answer choices carry prognostic significance.

138.4. What organ system is the first to show signs and symptoms following a significant radiation exposure?

A. Central nervous
B. Dermatologic
C. Gastrointestinal
D. Genitourinary
E. Hematopoietic

Answer: C. The first signs and symptoms of acute radiation injury are nausea and vomiting. An earlier onset of symptoms indicates more severe exposure. Typically, exposure to a radiation dose of at least 1 Gy is necessary to produce symptoms.

138.5. A 45-year-old man is accidently exposed to a radiation field of 850 mSv/hour for 4 hours while working on the clean-up of a nuclear power plant accident. Other than general supportive care, which of the following medications may improve his survival?
A. Acyclovir
B. Colony-stimulating factor (cytokines)
C. diethylenetriaminepentaacetate (DTPA)
D. Erythropoietin
E. Potassium iodide

Answer: B. This patient's radiation dose is sufficient to produce the hematopoietic component of acute radiation syndrome (ARS). Cytokines or colony-stimulating factors have shown modest effects in improving survival. Irradiated patients may develop oral herpes, and acyclovir can be used for treatment but does not affect survival. Anemia is present is most irradiated patients but is usually not clinically significant, and erythropoietin has no role. DTPA is a chelating agent that can be used for patients with internal exposure to plutonium or transuranics. Potassium iodine is useful if a patient is exposed to radioactive iodine, because it will compete with the radioactive iodine for uptake into the thyroid gland, resulting in overall less radioactive uptake.

138.6. What type of radiation event is most likely to cause incorporation and internal contamination?
A. A portable x-ray machine
B. Detonation of a dirty bomb
C. Fluoroscopy
D. Proton-beam radiotherapy
E. Solar flare

Answer: B. A dirty bomb is the combination of a conventional explosive with a radioisotope illegally obtained from medical or industrial sources. Dispersal of the radioisotope is likely to produce incorporation of the radioisotope through inhalation and inadvertent ingestion. The other radiation sources listed result in external radiation.

CHAPTER 139

Approach to the Poisoned Patient

Timothy J. Meehan

PRINCIPLES OF TOXICITY

Most poisoned patients seen in the emergency department (ED) are adults with intentional oral drug overdoses. Other common clinical scenarios include accidental poisoning in children, which represent the majority of calls to regional poison control centers.[1] Illicit drugs of abuse; chronic poisoning from supratherapeutic pharmaceutical agents; environmental, industrial, and agricultural chemical exposures; envenomation; and medication interactions are other causes of toxicity. In the ED, it is important to evaluate and recognize scenarios where there may be immediate or delayed toxicity, as well as initiating decontamination, enhanced drug elimination, and administering more focused antidotal strategies, when indicated.

In regards to a specific patient with a particular ingestion, essential historical points include: the agent itself, the route of exposure, the amount ingested, possible co-ingestants, and the timing of the exposure. Knowing these facts can help make a determination regarding the expected course of care in the ED and help to mobilize resources.

CLINICAL FEATURES

Toxicologic History and Physical

Oftentimes, the poisoned patient may be altered or obtunded, or uncooperative with the examiner. This leaves the history limited to that which can be gleaned from witnesses, such as paramedics or family, and the information generated from the physical examination restricted to those functions over which the patient does not have conscious control.

Historical information must be pulled from all available sources.[2] A family member or friend may offer insight into the circumstances behind the patient's exposure, (eg, intentional or accidental). Information regarding what medications or substances were available to the patient, and the timing of ingestion also is important. Paramedics routinely will bring in all medication bottles present at the scene—not just the patient's prescribed medications or alleged ingestion. A patient attempting suicide may intentionally mislead the ED staff, or medications may have been stored in mislabeled containers. Other sources of potentially useful information include state controlled-substance registries, pharmacy records, and previous medical records. Accessing the patient's text-messaging history also may be helpful, if the patient or guardian consents to this.

For chemical exposures in either the home or workplace, avoid exposure to other individuals in the ED. Proper identification of the substance is important to initiate care and obtain product safety information, such as a Material Safety Data Sheet. Consequently, one could consider taking a picture of the label including any precise chemical numbers; if a substance is brought to the ED, then take appropriate steps to avoid further exposure, such as sealing in an airtight container.[3,4]

Poisoned patients are frequently unwilling or unable to participate in an interactive physical examination. The toxicologic physical examination, therefore, rests upon observing factors that do not require cooperation to elicit. Many ingestants can cause derangement of the pulse and respiratory rates, as well as blood pressure.[2] Thus, rapid and accurate recording of the patient's vital signs, including a rectal core temperature and pulse oximetry, should be done and repeated at appropriate intervals. The overall level of consciousness, pupillary size, and presence or absence of seizure activity may suggest a particular agent (Boxes 139.1 and 139.2). Examination of the skin and mucous membranes with particular attention toward discoloration and level of moisture may suggest poisoning by any of several agents (Box 139.3); it may also reveal evidence of injection drug abuse, such as "track marks" or ulcerations from "skin popping."[5] A careful neurologic examination focusing on the level of muscle tone, clonus, or hyperreflexia can assist in the diagnosis of serotonin syndrome or neuroleptic malignant syndrome (NMS).[6] Finally, certain intoxicants may have particular odors associated with them; the presence of such an odor ought alert the clinician to the possibility of poisoning by one of these agents (Table 139.1). However, the absence of a characteristic smell is not accurate in excluding poisoning.

Toxidromes

Toxidromes are constellations of signs and symptoms based on autonomic and neurochemical processes that can suggest a particular class of exposure and direct management and therapy.[6] The five traditionally described entities include the sympathomimetic, anticholinergic, cholinergic, sedative/hypnotic, and opioid toxidromes. In addition, serotonin syndrome and NMS have been well described.

Sympathomimetic

This toxidrome is defined by a state of sympathomimetic excess, typically causing those effects expected from the "fight or flight" reaction. Patients are often altered and may be delusional—especially with ingestion of substituted amphetamines, such as *N*-methyl-3,4-methylenedioxyamphetamine (MDMA).[7] Their vital signs are typically elevated, and present with hypertension, tachycardia, and tachypnea. They may also be hyperthermic as a consequence of an increased metabolic rate. Mydriasis and diaphoresis may also be present. In severe overdoses, derangement of

BOX 139.1

Agents Affecting Pupil Size

MIOSIS (COPS)
Cholinergics, clonidine, carbamates
Opioids, organophosphates
Phenothiazines (antipsychotics), pilocarpine, pontine hemorrhage
Sedative-hypnotics

MYDRIASIS (SAW)
Sympathomimetics
Anticholinergics
Withdrawal syndromes

BOX 139.2

Agents Causing Coma or Seizures

COMA (LETHARGIC)
Lead, lithium
Ethanol, ethylene glycol, ethchlorvynol
Tricyclic antidepressants, thallium, toluene
Heroin, hemlock, hepatic encephalopathy, heavy metals, hydrogen sulfide, hypoglycemics
Arsenic, antidepressants, anticonvulsants, antipsychotics, antihistamines
Rohypnol (sedative hypnotics), risperidone
Gamma-hydroxybutyrate (GHB)
Isoniazid, insulin
Carbon monoxide, cyanide, clonidine

SEIZURES (OTIS CAMPBELL)
Organophosphates, oral hypoglycemics
Tricyclic antidepressants
Isoniazid, insulin
Sympathomimetics, strychnine, salicylates
Camphor, cocaine, carbon monoxide, cyanide, chlorinated hydrocarbons
Amphetamines, anticholinergics
Methylxanthines (theophylline, caffeine), methanol
Phencyclidine (PCP), propranolol
Benzodiazepine withdrawal, botanicals (water hemlock, nicotine), bupropion, GHB
Ethanol withdrawal, ethylene glycol
Lithium, lidocaine
Lead, lindane

cardiac output can occur—decreased diastolic filling time coupled with arrhythmogenesis—resulting in circulatory collapse and shock, which may be refractory to fluid resuscitation and pressor agents.

Anticholinergic

Many pharmaceuticals have antimuscarinic properties, and thus this toxidrome is commonly encountered. By blocking normal cholinergic tone, an alteration in the normal homeostatic balance between the sympathetic and parasympathetic arms of the autonomic nervous system occurs. This allows the sympathetic side to function unopposed and generates a state of relative sympathomimesis. Therefore, many of the symptoms attributable to the anticholinergic toxidrome—delirium, hyperthermia, mydriasis, and cutaneous flushing—share similarity. In contrast, as the secretory glands of the skin and mucous membranes are cholinergically innervated, these systems are typically dry and not diaphoretic as found in the sympathomimetic toxidrome. The typical signs and symptoms can be recalled by the mnemonic "mad as a hatter, hot as a hare, blind as a bat, red as a beet, and dry as a bone."

TABLE 139.1

Agents With a Characteristic Odor

ODOR	POSSIBLE SOURCE
Bitter almonds	Cyanide
Carrots	Cicutoxin (water hemlock)
Fruity	Diabetic ketoacidosis, isopropanol
Garlic	Organophosphates, arsenic, dimethyl sulfoxide (DMSO), selenium
Gasoline	Petroleum distillates
Mothballs	Naphthalene, camphor
Pears	Chloral hydrate
Pungent aromatic	Ethchlorvynol
Oil of wintergreen	Methylsalicylate
Rotten eggs	Sulfur dioxide, hydrogen sulfide
Freshly mowed hay	Phosgene

BOX 139.3

Agents Causing Skin Findings

DIAPHORETIC SKIN (SOAP)
Sympathomimetics
Organophosphates
Acetylsalicylic acid or other salicylates
Phencyclidine (PCP)

DRY SKIN
Antihistamines, anticholinergics

BULLOUS LESIONS OR BLISTERS
Barbiturates and other sedative-hypnotics
Mustard gas
Snakes and spiders

FLUSHED OR RED APPEARANCE
Anticholinergics, niacin
Boric acid
Carbon monoxide (in morbid states)
Cyanide (rare)

CYANOSIS
Ergotamine
Nitrates
Nitrites
Aniline dyes
Phenazopyridine
Dapsone
Agent causing hypoxemia, hypotension, or methemoglobinemia

ACNEIFORM RASH
Bromides
Chlorinated aromatic hydrocarbons

Cholinergic

The cholinergic toxidrome results from overstimulation of the parasympathetic portion of the autonomic nervous system, which

BOX 139.4

Toxidrome Symptoms

CHOLINERGIC
Muscarinic (DUMBELLS)
Diarrhea, diaphoresis
Urination
Miosis
Bradycardia
Bronchorrhea
Emesis
Lacrimation
Lethargic
Salivation

Nicotinic: Days of Week
Mydriasis
Tachycardia
Weakness
Tremors
Fasciculations
Seizures
Somnolent

ANTICHOLINERGIC
Hyperthermia (HOT as a hare)
Flushed (RED as a beet)
Dry skin (DRY as a bone)
Dilated pupils (BLIND as a bat)
Delirium, hallucinations (MAD as a hatter)
Urinary retention (DRY as a bone)
Tachycardia

OPIOID
Miosis
Hypoventilation
Depressed mental status/coma
Withdrawal
Diarrhea
Mydriasis
Goose flesh
Tachycardia
Lacrimation
Hypertension
Yawning
Cramps
Hallucinations
Seizures (with ethyl alcohol [ETOH] and benzodiazepine withdrawal)

Sympathomimetic
Hyperthermic
Flushed
Diaphoretic
Mydriatic
Agitated
Tachycardic
Seizures

maintains the "rest and digest" functions. These patients typically have "fluids coming from every orifice" as a consequence of increased glandular secretion, and present with diaphoresis, urination, miosis, bronchorrhea, emesis, lacrimation, lethargy, and salivation (Box 139.4). Agents of concern are primarily anticholinesterase agents, such as organophosphates and carbamate insecticides. These substances are readily available as pesticides; but they have also been engineered as weapons of mass destruction, typically referred to as *nerve gases*. It is important to rapidly recognize this toxidrome because patients frequently die from excessive bronchorrhea, effectively drowning in their own secretions, unless timely antidotal therapy and cholinesterase regenerators can be given.

Nicotine poisoning from tobacco can occur in children who ingest detritus, such as used cigarettes or chewing tobacco, as well as liquids from electronic cigarettes.[8,9] Given the role of nicotine in both the central and peripheral autonomic nervous systems, the clinical picture in these poisonings may resemble both sympathomimetic and cholinergic toxidromes as noted in Box 139.4.

Sedative/Hypnotic

The hallmark of this toxidrome is sedation. This typically occurs on a spectrum depending on the particular ingestant, route, and potency. In severe ingestions, a state of general anesthesia may be reached with loss of tone and airway protective reflexes. In addition, it may cause hypothermia through suppression of muscle metabolism. It is well known in the ED, because ethanol intoxication is frequently seen. Other agents such as barbiturates and benzodiazepines will also cause a similar picture, as will illicit substances such as gamma-hydroxybutyrate (GHB). The coincidence of traumatic injuries may be high, and one should have a low threshold for evaluating to exclude their presence.

Opioid

Similar to sedative/hypnotics, the opioid toxidrome also involves sedation and a diminished respiratory drive. With the notable exception of pentazocine and propoxyphene, this toxidrome causes pupillary miosis. The diagnosis is confirmed by noting a response to naloxone, a direct opioid receptor antagonist. However, because certain opioids have higher potencies, a lack of response does not exclude opioid intoxication. Furthermore, this is a clinical diagnosis because not all opioids will be detectable by the standard drug screen (discussed later).

Serotonin Syndrome

A state of serotonergic excess defines this toxidrome, and it is often precipitated by the addition of a new serotonergic agent or a substance that interferes with the metabolism of a previously tolerated agent. Typically described with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), it has been reported with cyclic antidepressants and atypical antipsychotics. Consequently, serotonin syndrome typically occurs within hours to days of introduction to a new medication; although it has been described in a delayed fashion due to the prolonged half-lives of some antidepressants. The manifestations of serotonin syndrome include altered mental status, hyperthermia, and agitation; as well as hyperreflexia, clonus, and diaphoresis.

Neuroleptic Malignant Syndrome

Similar to serotonin syndrome, NMS also presents with altered mental status, hyperthermia, and agitation; however, unlike serotonin syndrome, peripheral muscular effects tend toward

rigidity and decreased reflexes rather than clonus and hyperreflexia. It is due to dopaminergic depletion due use of dopamine antagonists, such as antipsychotics.

DIFFERENTIAL DIAGNOSES

Frequently, poisoned patients have some level of delirium as part of their presentation. As such, excluding other causes of altered mental status while initiating appropriate toxicologic therapy should be considered (Box 139.5). Any "intoxicated" patient presenting to the ED should have the reversible causes of altered mental status excluded, such as hypoglycemia and nutritional deficiencies.[10] Trauma is frequently coincident with intoxication, so a careful unclothed examination looking for evidence of traumatic injury should be investigated as well.

BOX 139.5

Altered Mental Status

AEIOU
Alcohol/acidosis
Encephalopathy/electrolytes
Infection
Opioids/overdose
Uremia

TIPS
Trauma
Insulin (hypoglycemia/hyperglycemia)
Psychosis
Seizure/stroke

The thorough physical examination may also reveal findings that could suggest specific intoxicants, as noted in Box 139.6. The most important diagnostic approach is maintaining a broad differential diagnosis of both toxicologic and non-toxicologic causes for the patient's presentation, and avoiding premature conclusion. The differential diagnosis may be extremely broad, particularly when ingestion of a toxin is not known, or felt unlikely, or much more specific, when a certain agent, or class of agent is known to be involved.

DIAGNOSTIC TESTING

Diagnostic testing is guided by the clinical findings and suspected toxin(s) involved. When a patient presents with altered mental status and hyperthermia, testing may focus on differentiating a toxic cause from thyrotoxicosis or acute infectious disease. Patients with intoxication and evidence of trauma may require evaluation for head trauma as a cause of their altered mental status. In most instances, however, it is known that the patient has a potentially toxic exposure and some or all of the involved toxins have been implicated or identified. The approaches to individual toxins and syndromes are outlined in the relevant chapters. In the setting of an unknown overdose or exposure, a broad array of laboratory testing is often used to screen for abnormalities and potentially elucidate the clinical picture. The diagnostic studies routinely checked are: complete blood count, serum chemistry with renal function, liver function tests, urinalysis (with a pregnancy test if appropriate), urine toxicology screen, serum alcohol concentration, serum lactate, and a bedside glucose.[11]

Based on these results, or when the ingestion is known, other tests such as specific serum concentrations may be obtained; Box 139.7 lists those drug levels commonly available in most hospitals. When assays for a particular agent are not available, or are not

BOX 139.6

Predicting Toxicity From Vital Signs

BRADYCARDIA (PACED)
Propranolol (β-blockers), poppies (opioids), propoxyphene, physostigmine
Anticholinesterase drugs, antiarrhythmics
Clonidine, calcium channel blockers
Ethanol or other alcohols
Digoxin, digitalis

TACHYCARDIA (FAST)
Free base or other forms of cocaine, Freon
Anticholinergics, antihistamines, antipsychotics amphetamines, alcohol withdrawal
Sympathomimetics (cocaine, caffeine, amphetamines, phencyclidine [PCP]), solvent abuse, strychnine
Theophylline, tricyclic antidepressants (TCAs), thyroid hormones

HYPOTHERMIA (COOLS)
Carbon monoxide
Opioids
Oral hypoglycemics, insulin
Liquor (alcohols)
Sedative-hypnotics

HYPERTHERMIA (NASA)
Neuroleptic malignant syndrome (NMS), nicotine
Antihistamines, alcohol withdrawal
Salicylates, sympathomimetics, serotonin syndrome
Anticholinergics, antidepressants, antipsychotics

HYPOTENSION (CRASH)
Clonidine, calcium channel blockers
Rodenticides (containing arsenic, cyanide)
Antidepressants, aminophylline, antihypertensives
Sedative-hypnotics
Heroin or other opioids

HYPERTENSION (CT SCAN)
Cocaine
Thyroid supplements
Sympathomimetics
Caffeine
Anticholinergics, amphetamines
Nicotine

RAPID RESPIRATION (PANT)
PCP, paraquat, pneumonitis, phosgene
Acetylsalicylic acid (ASA) and other salicylates
Noncardiogenic pulmonary edema, nerve agents
Toxin-induced metabolic acidosis

SLOW RESPIRATION (SLOW)
Sedative-hypnotics (barbiturates, benzodiazepines)
Liquor (alcohols)
Opioids
Weed (marijuana)

BOX 139.7

Commonly Available Serum Drug Levels

Acetaminophen
Acetylsalicylic acid (salicylate)
Carbamazepine
Carbon monoxide
Digoxin
Ethanol
Ethylene glycol
Iron
Isopropyl alcohol
Lead
Lithium
Methanol
Methotrexate
Phenobarbital
Phenytoin
Valproic acid

BOX 139.8

Substances Causing Wide Anion-Gap Acidoses

A CAT PILES MUD
Alcoholic ketoacidosis
Cyanide,* carbon monoxide (CO),* colchicine*
Acetaminophen (large ingestions)
Toluene
Paraldehyde, phenformin
Isoniazid, iron,* ibuprofen (large ingestions)
Lactic acidosis
Ethylene glycol
Salicylates
Methanol, metformin,* massive ingestions
Uremia
Diabetic ketoacidosis

*These agents cause lactic acidosis.

performed on site, empirical treatment generally begins before these results are available.

If the blood gas shows the presence of a metabolic acidosis, calculating the anion gap can further refine the possible etiologies.

The calculation is: $[Na] - ([HCO_3] + [Cl])$. The normal range is 8 to 12 mEq/L.

Metabolic acidosis without an anion gap typically results from loss of bicarbonate (diarrhea, renal tubular acidosis) or gain of chloride-containing compounds (ammonia, calcium chloride). Metabolic acidosis associated with an anion gap results from an increase in unmeasured serum anions and suggests several specific toxins and disease states (Box 139.8).

When ingestion of a toxic alcohol (such as, methanol, ethylene glycol, or isopropanol) is suspected, calculating the osmole gap may be helpful; because early in the poisoning course the patient may be minimally or non-acidemic. Furthermore, urine fluorescence is not sufficiently sensitive to be reliable and its absence cannot be used to "rule out" said ingestion. The osmole gap is discussed in Chapter 141.

Toxicology "screens" may also be helpful in diagnosing an unknown ingestion, provided that the limitations of these panels are understood. Blood toxicology screens can be falsely negative if the ingested drug has a short half-life and the sample is not drawn soon enough after the exposure. Urine toxicology screens are more reliable, because they typically have a longer time period for positive detection, typically 24 to 72 hours. Urine toxicology screens typically include phencyclidine (PCP), cocaine, opioids, amphetamines, and cannabinoids; however, these can vary among institutions, so knowing what is available in one's facility is important in interpreting a positive or negative screen.[6] The urine screen is also a qualitative, not a quantitative test; as such, a positive result does not necessarily imply acute toxicity. A urine toxicology screen can be falsely positive due to cross-reactivity between agents (such as, a "positive" PCP screen in the setting of dextromethorphan ingestion). Alternatively, urine screens can be falsely negative if the substance ingested does not cross-react with the tested analyte—such as, the case with methadone, which will not cross react with the opioid component of the urine toxicology screen (Table 139.2). Ultimately, the diagnosis of intoxication is clinical; urine drug screening may be confirmatory but should not supplant clinical evaluation and judgment.

In addition to the blood work discussed earlier, one should obtain an electrocardiogram (ECG) if the patient is tachycardic or bradycardic, or may have ingested a cardiotoxic agent that can prolong the QRS or QT intervals, such as cyclic antidepressants and antipsychotic agents. Table 139.3 provides guidance regarding for which patients an ECG should be obtained.[12]

MANAGEMENT

The general management of a poisoned patient involves providing appropriate supportive care, undertaking decontamination or enhancing elimination if indicated, and providing specific antidotal therapy where an antidote exists and is indicated. Specific strategies will be discussed at length in the following chapters regarding specific poisons. However, the basic framework remains the same.

Antidotes do not exist for every potential poisoning, and thus supportive care is the cornerstone of managing the poisoned patient. Following the basic "ABCs" of resuscitation by ensuring airway protection and adequacy of ventilation while maintaining the circulatory status of the patient with fluid resuscitation and vasopressor support is the prime focus. If the airway is compromised or in danger of becoming so, or if the respiratory effort is insufficient to maintain appropriate ventilation, intubation is usually the preferred course (with special care in the situation of a salicylate poisoning, which is discussed in Chapter 144).

Vascular access needs to be obtained, with peripheral and central venous catheters well-known to practitioners. Intraosseous lines are also viable access points from the toxicologic perspective, because there are no known contraindications to antidotal therapy through this route.

Once supportive care has been initiated and the immediate threat to the ABCs has been stabilized, one should then progress to a systematic assessment of decontamination strategies, enhanced elimination, focused therapy (antidotes), and getting help (consultation).

Decontamination

Decontamination is the process of preventing systemic absorption into the body. In the case of ocular or dermal exposure, this is achieved by copious irrigation with water, after removal of contaminated clothing to expose the area. Water irrigation is not used for metallic potassium, magnesium, or sodium (such as, found in "tracer" ammunition), because these can ignite on contact with water. Instead, in these very rare exposures, the area should be covered with petroleum jelly or mineral oil.

TABLE 139.2

Urine Drug Screen Limitations

ASSAY	FALSE POSITIVE	TRUE POSITIVE (THERAPEUTIC USE)	FALSE NEGATIVE
Amphetamines	Many; some clinically relevant ones include: Amantadine Bupropion Labetalol Promethazine Ranitidine Trazodone	ADHD medications: Dextroamphetamine, methamphetamine Phenylephrine Pseudoephedrine	"Designer amphetamines"
Benzodiazepines	Sertraline Oxaprozin	Marijuana	Alprazolam Flurazepam Midazolam "Z" drugs (zolpidem, zaleplon, zopiclone, eszopiclone)
Cannabinoids	Dronabinol Efavirenz PPI		Synthetic marijuana: K2/Spice
Opioids	Dextromethorphan Diphenhydramine Quinolones		Synthetic opioids: Demerol, fentanyl, methadone, propoxyphene Semisynthetic opioids (may have some cross-reactivity): Hydrocodone, hydromorphone, oxycodone
Phencyclidine (PCP)	Dextromethorphan Diphenhydramine Ibuprofen Tramadol	Ketamine	
Cocaine	Coca leaf tea	Cocaine-containing anesthetics (topical TAC)	

ADHD, Attention deficit hyperactivity disorder; *PPI,* proton pump inhibition; *TAC,* tetracaine, adrenaline (epinephrine), and cocaine.

TABLE 139.3

Toxicologic Electrocardiogram Manifestations

SEGMENT/INTERVAL	APPEARANCE	AGENT(S)	SEGMENT/INTERVAL	APPEARANCE	AGENT(S)
P wave	Absent	Digoxin Cholinergics Hyperkalemia	QT/QTc	Prolonged	Antipsychotics (typical and atypical), citalopram, hydrofluoric acid, methadone, ethylene glycol (oxalate byproduct)
	Notched	Quinidine			
PR interval	Prolonged	Beta-antagonists, calcium-channel antagonists, magnesium	T wave	Peaked	Hydrofluoric acid (hyperkalemia)
				Flattened	Lithium
QRS interval	Prolonged	Type 1 antidysrhythmics, cocaine, diphenhydramine, tricyclic antidepressants	U wave		Barium, beta-agonists, lithium, methylxanthines (caffeine, theophylline), toluene
ST segment	Scooped	Digoxin ("Salvador Dali's moustache")			

SYRUP OF IPECAC

Inducing emesis with syrup of ipecac is not indicated in the care of any poisoned patient in the ED. Syrup of ipecac use is associated with significant side effects (eg, dehydration due to intractable vomiting) and complications (eg, aspiration pneumonitis, Mallory-Weiss tears, and gastric rupture). There are also insufficient data and evidence showing improvement in clinical outcomes.[13]

GASTRIC LAVAGE

Gastric lavage, the process of directly removing an ingested substance from the stomach using a 30 Fr or larger orogastric tube, also has little data or evidence showing its efficacy and should not be performed routinely for the treatment of poisoned patients. Given the risks of aspiration and esophageal trauma, the American Association of Poison Centers suggests it only be employed

"within an hour of ingestion of a potentially life-threatening poison which does not adsorb to activated charcoal or for which no antidote exists" and, even then, in a center with "sufficient expertise" to perform the procedure safely.[14] Only a rare overdose will meet all these criteria; and hence, despite its once widespread use, gastric lavage is mostly of historical interest only.

SINGLE-DOSE ACTIVATED CHARCOAL

Historically, single-dose activated charcoal (SDAC) has been the mainstay of gastric decontamination in medical toxicology.[15] Activated charcoal is a carbonaceous substance that has been exposed to high heat and steam, resulting in a large surface area to volume ratio, to provide ample surface space for ingested substances to adsorb, and thus decrease absorption into the body. Our current understanding of the role of activated charcoal in poison management is based on pharmaco-toxicologic data (lethality, availability of antidotes, or alternative detoxification therapies); pharmacokinetics (area under the concentration versus time curve in controlled volunteer studies); clinical trials in patients with overdose; and collective, empirical clinical experience.[16-21] Studies involving healthy volunteers ingesting small (safe) doses of various agents do not accurately replicate the overdose (large ingestion) situation, so are of limited value. In addition, there are very few appropriately designed clinical studies assessing the benefit from SDAC. Therefore, due to the lack of convincing evidence demonstrating benefit in clinical outcome in human overdose, we do not recommend the routine use of activated charcoal following ingestion.[15] We do, however, recommend its use in certain overdose scenarios.

Although few studies have shown a reduction of morbidity or mortality attributable to activated charcoal administration, and there have been reports of pulmonary aspiration of activated charcoal with serious patient harm, these aspiration events have occurred in a minority of patients receiving activated charcoal; and activated charcoal, accordingly, is considered a is a low risk intervention.[21] With certain toxic exposures, SDAC administration may be reasonable after a consideration of the risk versus benefit for the patient in the context of the quantity and toxicity of the ingested substance, the time elapsed between ingestion and treatment, and the availability of alternative antidotes or decontamination procedures (eg, hemodialysis). Benefits include decreasing primary absorption, or binding during enterohepatic recirculation of a potentially toxic xenobiotic. These benefits are more likely to occur if:

- The activated charcoal is administered within one hour post-ingestion, *and*
- The patient is alert, able, and willing to cooperate with administration, and anticipated to remain alert and protective of airway reflexes, *and either*
  - The substance ingested has high toxicity (eg, verapamil, colchicine), or is a toxic, sustained–release agent (eg, bupropion SR), *or*
  - There is evidence of a massive ingestion of a toxic agent (eg, salicylates)

If the patient is sedated, has an unprotected airway, or is unwilling to drink the charcoal suspension, administration is contraindicated. This may be particularly true for young children with limited ability to drink the slurry. Furthermore, one should not place a nasogastric tube solely to administer activated charcoal, because the risk of aspiration or direct instillation of activated charcoal into the lungs rises in these patients, thus tipping the risk-benefit ratio.

Considering all of this information, how does one decide whether activated charcoal is indicated in a specific overdose? First, the ingested drug must have a high potential for toxicity and lethality. These drugs are listed by class in Box 139.9. If the drug ingested has low toxicity (eg, ibuprofen, diazepam), or there is an effective antidote available (eg, *N*-acetylcysteine for acetaminophen, digoxin immune fab for digoxin), activated charcoal administration is not advised.[20]

Second, the ingestion must be recent. For most overdoses, this means that the activated charcoal is administered within 1 hour of ingestions. For certain overdoses (sustained-release products, anticholinergic agents, massive ingestions), either because of pharmacokinetics or the quantity ingested, activated charcoal may be given up to 2 hours after ingestion. Many patients arrive at the ED more than 2 hours after the ingestion, or ingest the drugs over a period of several hours, often with alcohol, and do not meet this time requirement. Third, the ingestion must be amenable to adsorption by activated charcoal. This eliminates rapidly absorbed toxins (eg, alcohols) and those agents listed in Box 139.10. Fourth, the patient must be alert and anticipated to remain alert and be willing to take the activated charcoal slurry voluntarily. An algorithm guiding the administration of activated charcoal is shown in Figure 139.1. We recommend consultation with a regional poison center or medical toxicologist if there is uncertainty regarding the indications for activated charcoal.

Activated charcoal historically has most often been given in a dose of 25 to 100 grams (10 to 25 grams or 0.5 to 1.0 gram/kilogram in young children), but we advise customizing the dose to the dose of the ingested agent by administering activated charcoal in a weight ratio of 10:1 (ratio of activated charcoal to drug).[20]

BOX 139.9

Potentially Lethal Toxins Where Early Activated Charcoal Administration May Be Indicated

THE KILLER CS

Cyanide
Colchicine
Calcium channel blockers
Cyclic antidepressants
Cardio glycosides
Cyclopeptide mushrooms *(Amanita phalloides)*
Cocaine
Cicutoxin (water hemlock)
Salicylates

BOX 139.10

Substances That Do *Not* Bind to Activated Charcoal

PHAILS

Pesticides
Heavy metals
Acids/alkalis
Iron
Lithium
Solvents

WHOLE BOWEL IRRIGATION

In certain ingestions such as extended-release preparations, illicit drug packets, or metals (eg, iron and lead), continuous whole-bowel irrigation may be indicated. Whole bowel irrigation (WBI) is performed with a balanced polyethylene glycol solution that

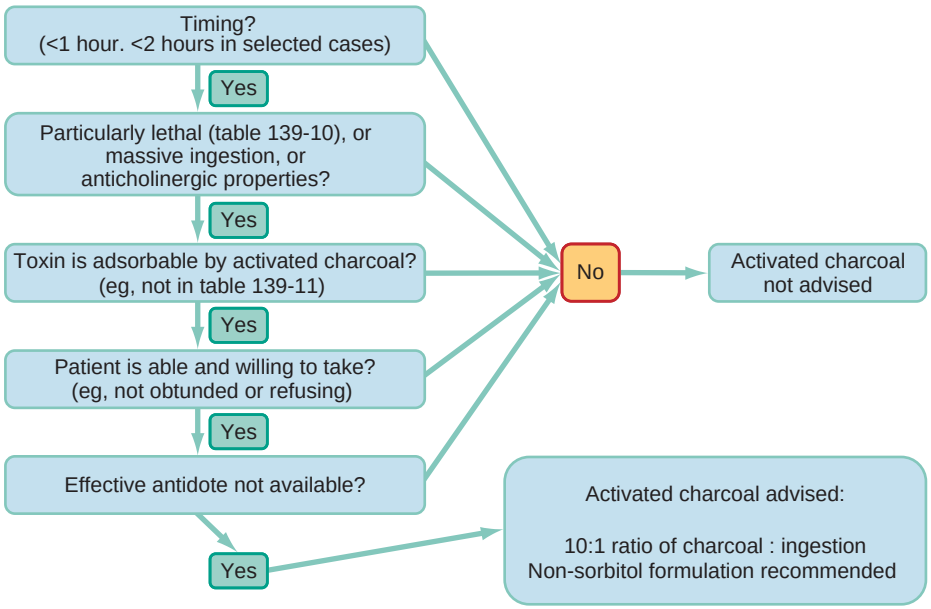

Fig. 139.1. Indications for early administration of activated charcoal 1 hour post-ingestion.

BOX 139.11

Dialyzable Toxins

STUMBLED
Salicylates
Theophylline
Uremia
Metformin/methanol
Barbiturates
Lithium
Ethylene glycol
Depakote (valproic acid—in massive overdose)

BOX 139.12

Substances Amenable to Multiple-Dose Activated Charcoal

ABCDQ
Aminophylline/theophylline
Barbiturates
Carbamazepine/concretion forming drugs (eg, salicylates)
Dapsone
Quinine

does not participate in fluid exchange nor become absorbed into the body. To be effective, it requires a rate of 2 liters per hour in an adult; consequently, this will require nasogastric tube placement.[22,23] However, if a patient is critically ill, has hypoperfusion of the gut, or has obstruction of the bowel, WBI is contraindicated because there have been reports of worsened morbidity and mortality in these clinical settings.[24]

Enhanced Elimination

Once a toxin has been absorbed into the body, it undergoes metabolism and elimination; typically via hepatic and renal pathways. Certain substances are amenable to enhancing these elimination pathways either ex vivo as is the case with hemodialysis and its related therapies, or in vivo as is the case with multiple-dose activated charcoal (MDAC) and urinary alkalinization.

Hemodialysis and its related therapies are best suited to remove poisons of low molecular weight, low protein binding, and high water solubility; examples include toxic alcohols, lithium, and salicylates, as listed in Box 139.11. All forms of extracorporeal removal have been studied and found to be efficacious; the selection of a specific type of elimination modality ought to be made based on patient-specific factors and early consultation with a nephrologist in conjunction with a toxicologist or poison control center.[25,26]

MULTIPLE-DOSE ACTIVATED CHARCOAL

Unlike preventing absorption of a drug as is the case for SDAC, MDAC is intended also to facilitate removal of a toxin that has already been absorbed. MDAC decreases xenobiotic absorption and elimination half-life when large amounts of the toxin are ingested and dissolution is delayed (eg, concretions, bezoars, or extended release formulations). It also is believed to create a hemoperfusion substrate for the gut wall microcirculation to permit "gastrointestinal dialysis," which generates a concentration gradient into the stool or certain poisons, which are then be eliminated by defecation.[16] In addition, certain drugs are excreted in the bile, then reabsorbed by the gut, only to be re-excreted in the bile, a process called *enterohepatic circulation.* MDAC also may interfere with reabsorption of these drugs by binding them during their transit of the gastrointestinal tract. Drugs with significant enterohepatic circulation are listed in Box 139.12. As with SDAC, MDAC administration may cause pulmonary aspiration and intestinal obstruction. Aspiration is best avoided by applying the same conditions for administration as for SDAC—ie, patient awake, alert, and cooperating and is anticipated to remain awake and alert. Obstruction is more difficult to predict and prevent, although avoidance in situations with delayed gut motility (eg, critical illness, opioid or anticholinergic effects) is recommended to reduce this risk.

When MDAC is indicated, the initial loading dose of an activated charcoal–to-xenobiotic ratio of 10:1, is followed by

subsequent doses of 50% of the initial dose every 4 to 6 hours for up to 24 hours.[21] MDAC may be discontinued when the patient's measureable serum levels are no longer considered in the toxic range.

SERUM ALKALINIZATION

Certain water-soluble ingestants such as salicylates, methotrexate, and phenobarbital will undergo ion-trapping and enhanced urinary elimination if the serum is sufficiently alkalinized. This is especially important with salicylate poisonings, because alkalinization not only promotes elimination but also prevents salicylate crossing the blood-brain barrier into the central nervous system (CNS). Monitor the serum pH and bicarbonate level, as well as the urinary pH, with the goal being a serum pH of approximately 7.5 and a urinary pH of approximately 8.0. Also ensure that the serum potassium level is normal, because alkalinization will cause an intracellular shift of potassium and consequently increase urine reabsorption of potassium by excreting hydrogen ions into the urine; this will eliminate the pH gradient and dissipate the benefits of this process. To accomplish this, combine 150 mEq (3 amps) of 8.4% sodium bicarbonate into a liter of dextrose 5% in water (D5W) and add potassium (20 to 40 mEq total) to the intravenous fluid as well, with a rate not to exceed 250 cc/hour.

INTRAVENOUS FAT EMULSION (INTRALIPID)

Intravenous fat emulsion (IFE) is a newly introduced therapy for poison-induced cardiogenic shock. This therapy was first described for treatment of toxicity from local anesthetics, such as bupivacaine. IFE is proposed to work primarily by two separate mechanisms: (1) the lipid sink and (2) enhanced cardiac metabolism.[27] The lipid sink theory posits that fat-soluble drugs are soaked up and removed from the site of toxicity, effectively increasing the volume of distribution for a fat-soluble drug. This is the predominant theory behind the use of IFE. A second theory involves optimization of cardiac metabolism. The heart under physiologic circumstances prefers free fatty acids; in times of stress, it switches to glucose metabolism for energy. A dose of IFE theoretically provides a large supply of free fatty acids to optimize energy use in the heart. In addition to providing supplemental energy for myocytes, IFE may also enhance activation of cardiac calcium channels.

Indications for IFE are not universally agreed upon. In addition to anesthetic agents, successful resuscitations have been described with refractory B-blocker overdose, calcium channel blockers, cyclic antidepressants, and bupropion and cocaine toxicity. Although originally described as a treatment for overdose patients in cardiac arrest, several reports now exist describing the successful use of IFE in critically ill patients prior to an arrest state with a pulse. Dosing for IFE also varies in the literature. If indicated, we recommend an initial bolus of 1.5 mL/kg of 20% lipid solution given over 2 to 3 minutes is most commonly recommended, followed by an infusion of 0.25 mL/kg/min. IFE should be used only in consultation with a medical toxicologist or poison center.

Despite recent enthusiasm for IFE, its use has associated complications, including extreme lipemia resulting in lab interference with blood tests (complete blood counts, chemistries, and coagulations studies), as well as acute pancreatitis, and acute respiratory distress syndrome.[28]

Focused Therapy

Although the majority of poisonings require supportive care alone, in selected ingestions specific antidotal therapy may be available. Evidence and experience support the use of several antidotes, which should be available either immediately (eg, stocked) or in a rapid fashion (eg, transported within a few hours). These antidotes and their indications can be found in Table 139.4, and their use is discussed in the relevant chapters.[29,30]

TABLE 139.4

Selected Antidotes and Their Indications

ANTIDOTE	INDICATION (POISON)
N-acetylcysteine	Acetaminophen
Fomepizole (4-MP)/ethanol	Methanol/ethylene glycol
Oxygen/hyperbarics	Carbon monoxide
Naloxone	Opioids
Physostigmine	Anticholinergics
Atropine/pralidoxime (2-PAM)	Organophosphates
Methylene blue	Methemoglobinemia
Nitrites/hydroxycobalamin	Cyanide
Deferoxamine	Iron
Dimercaprol (BAL)	Arsenic, lead
Succimer (DMSA)	Lead, mercury
CaEDTA	Lead
Fab fragments	Digoxin, crotalids
Glucagon	β-blockers
Sodium bicarbonate	Salicylates, tricyclic antidepressants
Calcium, insulin/glucose	Calcium channel antagonists
Dextrose, glucagon, octreotide pyridoxine (vitamin B_6)	Oral hypoglycemic agents Isoniazid (INH)
Intravenous fat emulsion	Local anesthetic systemic toxicity Certain fat-soluble medications

2-PAM, 2-pralidoxime; *4-MP,* 4-methylpyrazone; *BAL,* British antilewisite; *CaEDTA,* calcium ethylenediamine tetracetate; *DMSA,* dimercaptosuccinic acid.

Toxicology Consultation

Most poisoning cases are straightforward and are easily handled by the emergency clinician. When the poisoning is severe, high risk, involves unfamiliar or multiple toxins, or occurs in a patient with significant comorbidity, we recommend consultation with a Poison Control Center or, if available, a medical toxicologist. Consultation can assist the bedside clinician in the determination of an unknown ingestion, critical management decisions, or whether an antidote or invasive procedure, such as hemodialysis, is advisable.

In the United States, a national toll-free phone number has been set up that will route a practitioner to their nearest Poison Control Center. This number is 1-800-222-1222.[1]

DISPOSITION

Patients with severe toxicity (such as, seizures, persistent cardiovascular instability, airway compromise, or significant metabolic derangements) should be admitted to an intensive care setting. Patients who are asymptomatic on arrival but have ingested a potentially dangerous substance or an extended-release preparation that could cause significant deterioration in their clinical status, are admitted to either an inpatient setting or an observation unit for 24 hours, or until peak toxicity has obviously passed

and the patient is physiologically normal or near normal. For patients who are asymptomatic after an ingestion of a minimally toxic substance and for whom other ingestions and psychiatric issues have been addressed, discharge after the ED visit, which typically takes at least 4 to 6 hours, is appropriate.

If the motivation behind the ingestion, was suicidality, or self-harm, a psychiatric consultation is warranted. If a suicidal patient is to be admitted medically for observation, it is important to ensure that a sitter or other type of secure environment is available to prevent any further patient inflicted self-injury.

KEY CONCEPTS

- Toxidromes are constellations of signs and symptoms based primarily on vital signs and neuropsychiatric functions that are characteristic manifestations of certain toxic exposures. Recognition of the presence of a toxidrome can suggest a potential intoxicant and guide early interventions and management strategies. Examples of toxidromes include sympathomimetic, antimuscarinic, cholinergic, sedative-hypnotic, and opioid categories.
- Qualitative urine drug are inferior to quantitative serum levels in terms of guiding specific therapy.
- Syrup of ipecac is not indicated in the ED care of a poisoned patient. Gastric lavage is not part of routine care. When given in a timely fashion (1 hour post ingestion), activated charcoal may be indicated for potentially lethal agents in alert, cooperative patients as noted in Figure 139.1. Whole-bowel irrigation is rarely useful for management of poisoned patients but is potentially helpful for specific poisonings, such as metals, illicit drug packets, or sustained-release medications.
- Serum alkalinization enhances urinary drug elimination for certain drugs and is indicated for significant poisoning caused by salicylates, phenobarbital, and methotrexate.
- Hemodialysis is best suited to remove poisons of low molecular weight, low protein binding, and high water solubility; examples include methanol, ethylene glycol, lithium, and salicylates.
- Regional Poison Control Centers 1-800-222-1222 or a medical toxicologist can assist with antidotal therapy and may help facilitate patient disposition.
- If the motivation behind the toxic exposure was self-harm, a psychiatric consultation is warranted.

The references for this chapter can be found online by accessing the cocompanving Expert Consult website.

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CHAPTER 139: QUESTIONS & ANSWERS

139.1. A 23-year-old man presents with confusion. His vital signs are blood pressure 105/77 mm Hg, heart rate 69 beats per minute, respiratory rate 10 breaths per minute, temperature 37.0° C, and arterial oxygen saturation (SaO_2) 96% on 2 L NC. His eyes open only to pain, he localizes to pain, but he does not follow commands and his speech is confused. Otherwise, his physical examination is normal. After intravenous (IV) access is obtained and he is placed on continuous cardiac monitoring, what is the most appropriate next step?

A. Check arterial blood gases (ABG).
B. Check bedside serum glucose.
C. Give 50% dextrose 1 amp IV.
D. Give naloxone 2 mg IV.
E. Perform electrocardiogram (ECG).

Answer: B. All patients with altered mental status should have a rapid determination of their glucose. Although this patient has several abnormal vital signs, none necessitate immediate action. His Glasgow Coma Score (GCS) is 11, and it appears that his respiratory status is adequate. Dextrose should not be given unless hypoglycemia is documented. Naloxone is an opioid antagonist, and it could reverse the patient's confusion if it is caused by opioids. This drug could be considered once other more easily reversible causes of confusion (eg, hypoglycemia) have been ruled out. ABG and ECG are both occasionally needed in patients with altered mental status, but neither is as urgent as glucose testing.

139.2. The odor on a poisoned patient can provide clues as to the substance causing the poisoning. If a patient smells of garlic, what should you be concerned about?

A. Cyanide
B. Hydrogen sulfide
C. Methyl salicylate
D. Organophosphates
E. Toluene

Answer: D. Arsenic, dimethyl sulfoxide (DMSO), yellow phosphorus, selenium, and tellurium can also have a garlic odor. Odors associated with the other answer choices are as follows: cyanide, bitter almonds; hydrogen sulfide, rotten eggs; methyl salicylate, wintergreen; and toluene, glue. Odors can aid in making the diagnosis but should not be relied on as completely diagnostic. Also, the lack of odors cannot be used to rule out a poisoning resulting from that substance.

139.3. A 17-year-old girl presents with delirium, tachycardia, dry skin, flushed face, decreased bowel sounds, dilated pupils, and urinary retention. A friend states that the patient had recently ingested some unknown medications in a suicide attempt. Which of the following medications is most likely responsible for the constellation of signs?

A. Alprazolam
B. Clonidine
C. Diphenhydramine
D. Hydrocodone
E. Pseudoephedrine

Answer: C. The patient is expressing the signs of classic antimuscarinic poisoning. Central nervous system (CNS) effects include the delirium and typical "picking movements" of the fingers. Suppression of the cholinergic system results in tachycardia. All secretory functions are inhibited, causing the dry, flushed skin, decreased bowel sounds, and urinary retention. Unopposed sympathetic activity results in dilated pupils. Alprazolam, clonidine, and hydrocodone can all cause the sedative toxidrome.

Pseudoephedrine can lead to the sympathomimetic toxidrome, which typically has diaphoretic skin but can otherwise appear similar to an anticholinergic presentation.

139.4. What is the elimination half-life of naloxone?
A. 30 minutes
B. 1 hour
C. 2 hours
D. 4 hours
E. 6 hours

Answer: B. The exact elimination half-life of naloxone is closer to 1.1 hours (1 hour 6 minutes). This is markedly shorter than the half-life of almost all opioids. For comparison, morphine has a half-life of approximately 2 hours, hydrocodone has a half-life of approximately 4 hours, and methadone has a half-life up to 30 hours. This means that repeat dosing of naloxone is often necessary when treating opioid overdose. A drug similar in action to naloxone, nalmefene, has a half-life of 10 hours and may sometimes be useful.

139.5. You suspect a patient has a cholinergic syndrome. Which of the following, if found, would make you question your diagnosis?
A. Confusion
B. Diaphoresis
C. Diarrhea
D. Fasciculations
E. Mydriasis (dilated pupils)

Answer: E. The typical cholinergic patient is "wet." A common mnemonic used to remember the symptoms is SLUDGE—salivation, lacrimation, urination, defecation, gastrointestinal cramping, and emesis. Confusion can be present but is nonspecific. Frequently, cholinergic syndrome is caused by organophosphate poisoning, so fasciculations are common. Another common sign is miosis, not mydriasis.

139.6. Gastric decontamination with activated charcoal can decrease the absorption of certain toxins. However, before charcoal can be given, it must be determined that the risk of aspiration is low, the likelihood of reduction of toxicity or improved patient outcome is high, and that the ingestion occurred recently (within approximately 1 hour). Also, it must be determined that the substance ingested is actually adsorbed by charcoal. Which of the following substances is adsorbed by charcoal?
A. Gasoline
B. Hydrofluoric acid
C. Iron
D. Methanol
E. Metoprolol

Answer: E. Charcoal does not adsorb hydrocarbons (ie, gasoline), ionic substances (ie, strong acids or bases), metals (ie, iron), or alcohols. It does adsorb most therapeutic drugs with potential major toxicity, such as beta-blockers, calcium channel blockers, and cyclic antidepressants.

139.7. A 6-year-old boy is found playing with liquid pesticide by family members. The family states that he was drinking the solution. Paramedics find the child sitting in a puddle of liquid that smells strongly of pesticide. He is acting normally. En route to the hospital, the paramedics report that the child is now sleepier than previously but still easily aroused with a loud voice. His vital signs are within normal limits. They ask what they should do next. What do you advise?
A. Administer IV atropine
B. Administer oral activated charcoal
C. Administer naloxone
D. Perform rapid sequence intubation
E. Remove the child's clothing and wash the skin

Answer: E. This child's clothing has been impregnated with poison, and as long as the child is clothed, he will continue to absorb the poison. Ideally, all patients should be decontaminated on scene to expedite decontamination as well as to minimize the risk of contaminating others. Although this child may have ingested some poison, it is likely that far more is being absorbed from his skin than through his gastrointestinal tract. In addition, charcoal can cause complications, whereas removal of contaminated clothing is relatively safe. Although this child may eventually require intubation, he does not need it now. Most pesticides are organophosphates, so this patient may require atropine, but removal from the poison (taking off his clothing) will provide the greater immediate impact on his condition.

139.8. A patient suffering from serotonin syndrome will experience myriad physiologic abnormalities, including altered mental status, fever, agitation, tremor, and myoclonus. Many of the symptoms are nonspecific. Which of the following diagnoses is often mistaken for serotonin syndrome?
A. Anticholinergic syndrome
B. Brown recluse envenomation
C. Opioid withdrawal
D. Sepsis
E. Sympathomimetic overdose

Answer: E. Serotonin syndrome is characterized by altered mental status, fever, agitation, tremor, myoclonus, hyperreflexia, ataxia, incoordination, diaphoresis, shivering, and diarrhea. Similar symptoms are seen with overdoses of sympathomimetics, lithium, and monoamine oxidase inhibitors (MAOIs). Similar symptoms are also seen with neuroleptic malignant syndrome (NMS) and malignant hyperthermia. The antimuscarinic syndrome will give a "dry" patient without diaphoresis. Brown recluse envenomation produces local pain and possibly skin necrosis, as well as systemic symptoms of fever, nausea, and vomiting. Opioid withdrawal produces similar symptoms and will cause myalgias but without other musculoskeletal effects. Sepsis likewise can produce many of the systemic signs and symptoms seen in serotonin syndrome but without the musculoskeletal effects.

CHAPTER 140

Substance Abuse

Alicia B. Minns | Richard F. Clark

PRINCIPLES OF TOXICITY

The use and abuse of psychoactive substances are global and timeless. People used hallucinogenic plants to achieve altered states of consciousness in prehistoric times, and psychoactive substances have been used in all eras and cultures. As Osler remarked, "The desire to take medicine is, perhaps, the great feature which distinguishes man from other animals." The human cost of substance abuse is high, and deaths secondary to the use of psychoactive substances are common. In the United States, illicit drug use results in thousands of deaths each year (Box 140.1).[1]

A major barrier to appropriate recognition and treatment of substance abuse is the lack of a precise definition. The American Psychiatric Association defines it as a maladaptive pattern of drug use associated with some manifest harm to the user or others. Physicians have a difficult time recognizing such abuse, particularly in patients with chronic pain syndromes. Chronic pain may not manifest the typical overt sympathetic changes or physical findings of acute pain. Patients may seek treatment because of perceived failure of their outpatient regimen, an acute flare up, or because of abuse or addiction. Therefore, emergency clinicians constantly walk a tightrope between undertreating legitimate pain and inappropriately rewarding substance abusers with controlled medications.

EPIDEMIOLOGY

A variety of stereotypes come to mind in compiling the profile of a substance abuser. Adherence to a belief in these stereotypes is a dangerous trap for the clinician. Physicians are likely to discount the possibility of drug intoxication in the well-dressed professional or in those at the extremes of age, but drug use and abuse spans the spectrum of society.

A large 2013 survey of teenagers in grades 9 to 12 found misuse and abuse of prescription medications to be the third most prevalent drug abuse behavior among teens, trailing only use of marijuana and alcohol. Abuse of over-the-counter (OTC) cough medications is on par with or higher than the abuse of illegal drugs, such as ecstasy and cocaine.[2] Dextromethorphan abuse has become epidemic in the last decade. Increasing numbers of teens are ingesting dextromethorphan-containing OTC products, such as Coricidin HBP Cough & Cold tablets, known on the streets as triple Cs, red devils, red C, red box, or skittles.[3] Other dextromethorphan compounds include cough medicines, such as Nyquil and Robitussin DM, which provide the sought-after high known as the "robo-buzz." Adolescents may also abuse methylphenidate and related compounds used to treat obsessive-compulsive disorder and attention-deficit/hyperactivity disorder. Tablets can be abused orally, or they can be crushed and the powder injected or snorted. Despite its abuse potential, experts disagree about the extent to which methylphenidate is diverted from therapeutic use to abuse in preteens and adolescents.[4]

Numerous synthetic and naturally derived psychoactive substances ("legal highs") are easily obtained from Internet websites, "head shops," and local suppliers. One prevalent example is known as *bath salts.* These products are available in small quantities, with packaging that usually includes the disclaimer "not for consumption" to avoid regulation.[5] Bath salts contain synthetic cathinones, which are pharmacologically similar to methamphetamine and *N*-methyl-3,4-methylenedioxyamphetamine (MDMA) (ecstasy) and produce similar clinical effects.[6] A variety of adverse effects have been reported from cathinone derivatives, including tachycardia, hypertension, agitation, hyponatremia, hallucinations, paranoia, and suicide.[5-7] The legal status of these agents is in flux. The U.S. Department of Justice Drug Enforcement Administration has placed a number of the synthetic cathinones under Schedule I of the Controlled Substances Act; however, numerous other synthetic cathinones have been found in these products.[5]

Elders also abuse substances, and geriatric patients may suffer new-onset psychosis as a result of sympathomimetic abuse or drug withdrawal. Drug use also occurs in pregnant women, resulting in both maternal and fetal morbidity. Manifestations of abuse may be acute, as in abruptio placentae or premature birth, or insidious, producing growth restriction and birth defects. Drug problems are more prevalent among lower socioeconomic groups, which are disproportionately affected by drug-related problems, such as incarceration, unemployment, acquired immunodeficiency syndrome, hepatitis, and tuberculosis.

The drugs of misuse or abuse most commonly involved in deaths are cocaine, opioids, antidepressants, benzodiazepines, stimulants, and club drugs.[8]

Among prescription drugs, abuse of psycho-active drugs, especially anti-anxiety and insomnia medications, is rising. Additionally, there has been a dramatic increase in opioid prescriptions for non-cancer related pain. The increase in opioid prescriptions has resulted in an increase in misuse, abuse, diversion, overdose, and deaths. From 1999 to 2013, the death rate from opioid analgesics has nearly quadrupled. Many of these deaths involve another prescription medication, frequently a benzodiazepine.[9] Those individuals with chronic pain conditions who initiate opioid therapy with long-acting agents are at a higher risk of unintentional overdose as compared to those given shorter-acting agents. There has been a multifaceted approach to opioid abuse deterrence in the United States. In July 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for extended release and long-acting opioids. One element of REMS is the availability of voluntary training programs to licensed prescribers in the United States. There have also been changes to the labeling of extended release or long-acting products with an increase in information related to risk and precautions. Additional efforts to curtail opioid abuse and misuse include development of abuse-deterrent formulations of opioid analgesics, adoption of prescription drug monitoring programs, increased education for patients and health care providers, and cracking down on pill mills and doctor shopping.

PHARMACOLOGY

Knowledge of drug pharmacology, interactions, and expected clinical effects assists in the diagnosis and care of substance abuse victims. A careful medication history for all legal and illegal drugs,

BOX 140.1

Complications of Illicit Drug Use

INFECTIOUS
Hepatitis
Pneumonia
Skin abscess
Brain abscess or spinal epidural abscess
Endocarditis
Human immunodeficiency virus (HIV) infection
Osteomyelitis
Botulism
Gangrene

CARDIOVASCULAR
Cardiomyopathy
Aortic dissection
Myocardial infarction
Dysrhythmias
Pseudoaneurysms
Arteritis
Hypertension

NEUROLOGIC
Stroke
Drug-induced Parkinsonism
Dystonia
Vasculitis
Intracerebral hemorrhage
Cerebral atrophy
Radiculopathy
Leukoencephalopathy

PULMONARY
Chronic lung disease
Pulmonary hypertension
Pulmonary edema
Eosinophilic pneumonia
Pneumonitis
Barotrauma (pneumomediastinum)
Pulmonary fibrosis
Emphysema

PSYCHOSOCIAL
Unemployment
Inadequately treated depression
Conduct disorders
Hallucinations
Suicide
Homicide

MISCELLANEOUS
Dental caries and periodontal disease
Rhabdomyolysis
Thrombophlebitis
Tattooing
Placental abruption
Congenital malformations

including ethanol, may pinpoint the source of an adverse reaction. For example, a variety of agents can increase the effects of cocaine. The co-ingestion of ethanol and cocaine results in an active metabolite, cocaethylene, which can enhance and magnify cocaine's effects. Serotonin syndrome, manifested by muscle rigidity, hyperthermia, diarrhea, and seizures, may result when sympathomimetic drugs are taken concurrently with other serotonergic drugs, such as selective serotonin reuptake inhibitors. Amphetamines elevate serotonin either directly, by reversible inhibition of monoamine oxidase, or by inhibiting presynaptic catecholamine reuptake. Monoamine oxidase inhibitors can provoke hypertensive crisis in patients taking sympathomimetics. Interactions between medications commonly prescribed for patients with human immunodeficiency virus (HIV) infection and recreational drugs may be associated with serious clinical consequences because protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) can inhibit or induce the cytochrome P_{450} system, which could result in either drug accumulation or toxicity or withdrawal reactions.[10] For example, patients maintained with methadone who are subsequently treated with NNRTIs are at risk for development of methadone withdrawal by NNRTI-mediated enzyme induction.[10]

Household products and medications also have abuse potential. For example, dextromethorphan in common cough medications is converted into a substance (dextrorphan) similar to ketamine and phencyclidine (PCP) that causes dissociative effects by antagonizing the *N*-methyl-D-aspartate (NMDA) receptor. Recreational users describe mild hallucinations and an "out-of-body" state.[11] Some common chemicals in the home and workplace have an intoxicating effect that may be unexpected. Solvents, paint, lacquers, glues, aerosols, refrigerants, and other propellants (Fig. 140.1) are readily accessible for abuse among children and teens. Inhaled hydrocarbons, such as toluene, are rapidly absorbed and easily pass through the lipophilic blood-brain barrier to give an inexpensive high.

Fig. 140.1. Freon abuser. (Copyright Stephen A. Colucciello.)

Illicit drug laboratories have poor quality control, and many drugs are combined or "cut" with other substances to increase profits. Up to 50% of street samples lack the alleged drug. Some additives, such as local anesthetics or sugars, may be innocuous, but others, such as strychnine, may be lethal. Levamisole, a widely available anthelmintic agent, is now a common cocaine adulterant and can result in life-threatening agranulocytosis, leukoencephalopathy, and cutaneous vasculitides.[12] Other drugs, such as PCP, are misleadingly sold as a different drug, such as lysergic acid

diethylamide (LSD). Many doses of purported ecstasy (MDMA) actually contained amphetamine drug mixtures or even simple caffeine.[13] Drug combinations and unanticipated additives or substitutions may produce a clinical picture discordant with what the patient claims to have taken.

"Look-alike" drugs may also have toxic effects. Teens in particular may take look-alike or "knock-off" drugs that look like a desired product, such as Ritalin or Coricidin, in the hope of getting high, when in reality they may suffer unanticipated effects from an unrelated medication sold by an unscrupulous dealer.

CLINICAL FEATURES

History

Patients often present claiming a "drug reaction," but a drug history should be obtained from all patients presenting with altered mental status, acute anxiety or other psychiatric problems, and acute cardiopulmonary or neurologic symptoms. This information should include use of legal and illegal substances, prescription and OTC medications, vitamins, herbals, tonics, and potions. The clinician should distinguish recreational or regular use from suicidal intent.

Parents should be asked what is available in the house, or what they believe their son or daughter took, and when. There are numerous resources available, such as www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts, which is sponsored by the National Institute on Drug Abuse, to help decipher street jargon for various agents.[14] Poison centers also are good sources for the names given to various drugs of abuse. However, there is no guarantee that the purported ingestant is pure or unadulterated; therefore, a careful examination may provide the most reliable clues about the exposure. Prehospital personnel, family members, and friends may be able to offer additional information. Patients who are brought from the scene of a club, "rave," or circuit party with altered mental status may be under the influence of a club drug, such as MDMA (ecstasy), gamma-hydroxybutyrate (GHB), flunitrazepam (Rohypnol), or ketamine. Other club drugs, contain gamma-butyrolactone (GBL) or 1,4-butanediol (BD) and are sold on the Internet as precursor molecules to GHB.[15] "Grazing parties" are a social phenomenon in which teens attending these events bring several random pills from their home medicine cabinet, which are then placed in a large bowl or container. Willing participants at the party will then try various unidentified pills and compare clinical effects.

Injection drug abusers often have infectious complications, such as septic pulmonary emboli, skin or brain abscesses, endocarditis, and HIV or hepatitis-related disease.

Physical Examination

In addition to determination of vital signs, patients should be undressed and completely examined, with particular attention paid to the skin, pupils, and mental status, and evaluated for signs of trauma. Needle or track marks may be found in unusual areas, such as the supraclavicular space. Medicinal patches (eg, fentanyl) may be located under skin folds, or in the genital or rectal areas.

Physical examination includes evaluation for specific toxic syndromes. The presence of diaphoresis, mydriasis, tachycardia, hypertension, abnormal mental status, and urinary retention suggests sympathomimetic toxicity. In comparison, the anticholinergic (antimuscarinic) syndrome may have these same features along with dry mucous membranes. In addition, patients with antimuscarinic delirium tend to be less violent and paranoid than those with sympathomimetic toxicity. The mental status evaluation should address both the level of consciousness and appropriateness of affect. Specific physical findings, such as dental disease, skin abscesses, cardiac murmur, or focal neurologic abnormalities, such as tremor or ataxia, can assist in identification of chronic drug abuse (Table 140.1). Dental disease with extensive caries has traditionally been attributed to methamphetamine use, but it is common with other forms of chemical dependency.[16] The skin provides important clues to substance abuse, such as residue of chemicals or drugs on the hand or face or track marks from injection drug use.

COMPLICATIONS

Illicit drugs produce a wide variety of complications involving all major organ systems. Neurologic complications are especially prominent. A significant percentage of strokes are secondary to drug abuse.[17] Cerebral infarction, cerebral and cerebellar hemorrhage, and subarachnoid bleeding are often secondary to use of sympathomimetics and, occasionally, PCP or heroin. Single generalized tonic-clonic seizures are common with substance abuse, and status epilepticus can occur. Although sympathomimetics such as cocaine and amphetamines are responsible for the majority of seizures, heroin, tricyclic antidepressants, bupropion, and diphenhydramine are high risk. Withdrawal from benzodiazepines and alcohol can also result in seizures, including status epilepticus.

The dangers of substance abuse extend far beyond the toxic effects of a particular drug. Associated hazards include HIV infection, not only secondary to injection but also from the promiscuous lifestyle associated with the drug culture. The prevalence of HIV infection in injection drug users has been estimated at approximately 12% to 17%.

Recent declines in the incidence of HIV infection among injection drug abusers are encouraging, but resurgences have been associated with needle sharing and inadequate methadone treatment. Accompanying this phenomenon is a decrease in hepatitis B and hepatitis C among injection drug users in some cities in the United States. This is probably due to increases in preventive measures, such as needle-exchange programs, condom use, and vaccination for hepatitis B. Almost 20% of cocaine abusers have a positive tuberculosis skin test result. Sexually transmitted disease is common, especially in the sex-for-drugs culture of heroin and crack cocaine. Syphilis, in particular, is endemic among crack abusers.

The lungs are target organs for impurities in intravenous drugs, and pyrogens become trapped in this massive filter. This can produce "cotton fever," characterized by high fever, tachycardia, and tachypnea 10 to 20 minutes after injection. This is usually a self-limited illness in contrast with the long-term restrictive and obstructive lung diseases with the prolonged intravenous abuse of methylphenidate. Right-sided endocarditis is a frequent sequela of chronic injection drug abuse, and the nonspecific influenza-like symptoms that accompany this disease can mislead the clinician. In addition to endocarditis and HIV infection, injection drug abusers have septic pulmonary emboli, cellulitis, botulism, tetanus, and other infectious complications. They may have unusual sites of osteomyelitis or septic arthritis involving the spine or sternoclavicular or sacroiliac joints. A diagnosis of spinal epidural abscess, diskitis, or osteomyelitis should be considered in an injection drug user presenting with unexplained back pain.

Psychiatric complications of substance abuse are frequent and include anxiety, depression, suicidal ideation, mood swings, paranoia, and panic attacks. Paranoia and depression and associated suicide attempts are common among stimulant abusers, and hallucinations of parasites under the skin (formication) are frequent in those addicted to amphetamine derivatives and cocaine. Sympathomimetics are strongly associated with aggressive behavior and street crime. More than 50% of penetrating trauma from knife or gunshot wounds is now attributed to drug use

TABLE 140.1

Physical Examination Findings of Substance Abuse, the Agents Predominantly Involved, and the Proposed Mechanism

PHYSICAL FINDING OF SUBSTANCE ABUSE	SUBSTANCE INVOLVED	PROPOSED MECHANISM
Dental carries and gum disease	Amphetamine derivatives, predominantly methamphetamine	Unknown, possibly poor oral hygiene due to lack of attention
Skin abscesses	Intravenous and "skin popping" abuse of methamphetamine, heroin	Injection of drugs with non-sterile technique introducing bacteria into skin
Cardiac murmur	Intravenous heroin	Introduction of bacteria into bloodstream through non-sterile technique that embolized to the heart and adhere to valves leading to vegetations
Tremor, ataxia	All sympathomimetics, such as methamphetamine and cocaine; withdrawal from ethanol, benzodiazepines, and other sedatives; N_2O; toluene	Excessive stimulation of catecholamine receptors in the CNS with sympathomimetics and withdrawal syndromes; functional vitamin B12 deficiency with N_2O, cerebellar damage with toluene
Septic emboli, septic arthritis, osteomyelitis, spinal epidural abscess	Any intravenous drug but predominantly heroin	Introduction of bacteria into the bloodstream through non-sterile technique with resultant seeding of various tissues
Stroke	Sympathomimetic agents, predominantly methamphetamine or cocaine, or intravenously injected heroin	Vasoconstriction of cerebral vessels, or embolization of particulate matter
Cardiac dysrhythmias	Predominantly cocaine, but also methamphetamine and derivatives; methadone can cause QT interval prolongation	Cocaine blocks cardiac sodium channels leading to a prolonged QRS duration and ventricular dysrhythmias; methamphetamine can hyper-stimulate beta receptors on heart muscle cells; methadone affects cardiac myocyte repolarization
Convulsions	All sympathomimetics, bupropion, hypoxia related to sedatives or opioids; diphenhydramine, tricyclic antidepressants and other antimuscarinic agents; withdrawal from alcohol and other sedatives	Vasoconstriction, excessive release of brain catecholamines; hyperthermia related to antimuscarinic anhidrosis or CNS sodium channel blockade; excessive CNS catecholamine stimulation and GABA receptor changes
Coma	Sympathomimetics, ethanol, opioids, all sedatives	Depletion of brain catecholamines, excessive stimulation of GABA receptors in the CNS
Violent, paranoid behavior	Sympathomimetics, especially methamphetamine and derivatives, cocaine, PCP, and synthetic cannabinoids	Excessive dopamine or serotonin stimulation in the CNS; NMDA receptors may also be involved
Depression	Predominantly withdrawal from sympathomimetics	Possible depletion of CNS catecholamines or upregulation of receptors
Psychosis	All sympathomimetics, synthetic cannabinoids	Excessive dopamine or serotonin stimulation in the CNS

CNS, Central nervous system; *GABA,* gamma-aminobutyric acid; *N_2O,* nitrous oxide; *NMDA, N*-methyl-D-aspartate; *PCP,* phencyclidine.

(particularly methamphetamine) in some communities. Traumatic injuries from motor vehicle collisions are also endemic in substance abusers. Psychedelic drugs, such as LSD and PCP can prompt extreme behavioral changes and violence that can in turn lead to traumatic injuries. On occasion, trauma can be occult, and the unwary physician may overlook wounds in patients whose clinical picture is predominantly drug-induced agitation.

DIFFERENTIAL DIAGNOSES

Many serious illnesses can be confused with the effects of drug abuse, including sepsis, meningitis, encephalitis, head trauma, unintentional poisoning (eg, carbon monoxide), hypothermia, heatstroke, intracranial hemorrhage, complex seizures, and drug withdrawal. Hypoglycemia and other metabolic and endocrine derangements are important considerations. Similarly, drug intoxication should be considered in the differential diagnosis of altered mental status or abnormal vital signs regardless of age. Although patients with decompensated psychiatric disease can present similarly to those with drug intoxication, the hallucinations from psychiatric disease are usually auditory in nature, whereas hallucinations from drug intoxication or withdrawal tend to be visual hallucinations. There are other differences, as well, such as the maintenance of orientation with psychosis, but it nevertheless is difficult for the clinician to clearly differentiate between behaviors and agitation associated with drug abuse and those of decompensated psychiatric disease.

DIAGNOSTIC TESTING

All patients with acute alterations in mental status in whom hypoglycemia is possible require a point-of-care glucose test. Electrolytes and renal function are indicated for patients who are unstable or present with altered mental status. An electrocardiogram is indicated for patients with drug-related chest pain and will identify changes specific to certain drugs and medications, such as prolongation of the QRS or QTc interval in patients with significant toxicity. Arterial or venous blood gas analysis may be useful in assessment of presence of respiratory acidosis, as well as in measurement of oxygenation and ventilation, specifically if a

patient is sedated and hypoventilating. It may also be helpful if there is concern for a co-ingestant that can cause a metabolic acidosis such as salicylates or a toxic alcohol. Rhabdomyolysis, most often seen with psychostimulant abuse, drug-induced hyperthermia, or prolonged periods in the same body position after abuse of sedatives (eg, barbiturates), is best detected by measurement of serum creatine kinase or myoglobin.[18]

The use of qualitative toxicology screens is less important than the patient's history and clinical status. Although unsuspected drugs may be detected on a urine toxicology screen, this knowledge rarely affects acute management of the patient.[19] Quantitative levels of suspected substances, such as acetaminophen, acetylsalicylic acid, lithium, and certain anticonvulsants, may be valuable in certain circumstances. A new generation of rapid bedside "drug of abuse" urine toxicology screens utilizing newer techniques, such as liquid chromatography and mass spectrometry, may provide more accurate and timely information.[20] There are some special circumstances in which rapid qualitative urine toxicology screening may have some utility. For example, positive urine screens for sympathomimetics can occasionally be found in children presenting with bizarre or abnormal behavior or new-onset convulsions if they have been exposed to these substances in the home environment where they are being used or manufactured. These findings in older children may also assist parents in assessing changing behavior or school performance in some situations.

MANAGEMENT

Agitation

Few antidotes exist for psychoactive drug intoxication, and with a few notable exceptions, treatment is supportive. Violent or agitated patients require rapid sedation. Benzodiazepines are the preferred agents to treat anxiety and agitation, especially if caused by sympathomimetic or hallucinogenic drug intoxication. Treatment options include lorazepam 1 to 2 mg IV, repeated every 10 minutes until the patient is calm or diazepam 5 to 10 mg IV, repeated every 1 to 4 hours. More frequent dosing may be necessary in the setting of seizures or alcohol withdrawal. When the drug-induced agitation has not responded to what the clinician believes to be an adequate dose of a benzodiazepine, an antipsychotic medication should then be added. Butyrophenone antipsychotic agents such as haloperidol and droperidol, are rapidly effective and generally safe for all drug-induced psychosis or agitation states including sympathomimetics. Haloperidol, 2–5 mg IM, may be repeated every 20–30 minutes. Although not approved for intravenous use, this route it widely used and apparently safe. However, the FDA added a warning that "torsade de pointes and QT prolongation have been observed in patients receiving haloperidol, especially when the drug is administered intravenously or in higher doses than recommended." The sedative dose for droperidol is 2.5–5 mg IM. Droperidol has a box warning from the Food and Drug Administration (FDA) for QT prolongation and potentially torsade de pointes. Most reported cases of butyrophenone-induced dysrhythmias have been in individuals receiving large doses for prolonged periods, such as hours to days, or in elderly populations (older than 60 years of age). These medications lack the respiratory depression potentially caused by other agents and may be beneficial in some cases when sedation is required. For these reasons, the butyrophenones remain effective agents for treatment of drug-induced agitation. We do not recommend the routine use of second-generation or "atypical" antipsychotic agents, such as olanzapine, because there is no evidence for superiority of these agents over the "typical" antipsychotic medications, which have stood the test of time. In a patient felt inappropriate for a typical antipsychotic agent (eg, listed allergy, prolonged QT), the dose of olanzapine for agitation is 2.5 to 10 mg IM, given every 2 hours up to a maximum of 30 mg. We do not recommend the use of "first generation" phenothiazines, such as chlorpromazine, in the drug-intoxicated patient because of their strong anticholinergic effects and potential to produce hypotension and possibly lower the seizure threshold. Finally, temperature abnormalities, such as severe hyperthermia stemming from substance abuse with sympathomimetics, should be treated with sedation and rapid cooling measures.

Drug Seeker

As the front line in medical care, emergency departments (EDs) are frequently confronted by patients with drug-seeking behavior, typically for opioids or benzodiazepines. This drug-seeking behavior is described as a compulsion for seeking and taking drugs after prolonged use of a certain drug but also may be motivated by obtaining prescription drugs for the purposes of trafficking (selling) them. The street value of some prescription opioids, such as oxycodone, is greater than that of marijuana and heroin.

Self-admission of drug dependency would provide an excellent screening test, but 90% of patients who abuse opioids deny it.[21] A prior history of drug or alcohol abuse may identify patients at risk for abuse of opioids, the most commonly abused agents of the prescription drug seeker.[22] Repeated visits for the same complaint, rapid dose escalation, unusual and multiple allergies, and demands for specific agents (often in specific milligram amounts) are all warning signs of potential drug seeking.[23] Unfortunately, there is no reliable finding that can consistently identify drug seeking while not penalizing those in true need of analgesics.

Chronic or recurrent pain syndromes (with notable exceptions like renal colic occurring after an interval of months to years) are not acute problems amenable to treatment in, or from, the ED. Patients with these conditions require consistent outpatient treatment from a regular provider or a pain management center. Some hospitals and states are starting to track patients who repeatedly receive opioid prescriptions. The effectiveness of such programs is not yet clear. Some locales have had success with pain guidelines that restrict the use of opioids to proven conditions, with electronic flagging of habitual visitors who present for medical care.[23] Such approaches may work if they are done in conjunction with referral to chronic pain clinics or detoxification centers. A multifaceted approach combining counseling, denial of opioid or other psycho-active prescriptions in the ED, and referral to a single pharmacy may dramatically decrease ED visits by frequent users. Use of a prescription drug monitoring program, which is now available in many states, can also impact emergency clinician ability to recognize the substance abusing patient.[24]

Finally, pain contracts or explaining to the patient that opioids or other controlled substances are not appropriate may be helpful, but only if other physicians in the group or community agree on such a strategy for a particular patient.

DISPOSITION

After acute medical issues have been managed, substance abusers should be asked whether they would like help in overcoming their addiction. Studies show that intervention may be most successful for abusers of heroin, non-prescribed methadone, and benzodiazepines. Users of crack cocaine or methamphetamine appear to be more resistant to treatment. Offering symptomatic relief from withdrawal with short courses of medications, including antiemetics, antidiarrheals, and benzodiazepines, when indicated, may improve the patient's ability to sustain sobriety. Any patient with suicidal ideations or intent warrants immediate psychiatric evaluation. Those with a history of substance abuse requesting

assistance with sobriety should be given resources or a social work evaluation if available. If inpatient resources are not available or not deemed required, discharging the patient in the care of a family member or reliable friend is ideal.

Patients with acute intoxication and altered mental status that does not normalize after a period of observation would require admission or a prolonged observation period. Those under the influence of sympathomimetic drugs (such as, cocaine or methamphetamine) may develop delayed complications (such as, rhabdomyolysis) that warrant inpatient hospitalization. After the patients' acute intoxication has resolved, withdrawal symptoms may develop requiring hospitalization and adjunctive medications, such as benzodiazepines. Admission to the intensive care unit may be needed in certain situations, such as severe hyperthermia, intractable convulsions, respiratory depression necessitating airway support, myoglobinuric renal failure, severe metabolic acidosis, or severe agitation requiring large doses of sedatives.

KEY CONCEPTS

- Substance abuse can affect people from all socioeconomic groups and all ages.
- For the majority of patients with toxin-induced violent behavior, intramuscular butyrophenones (such as, haloperidol) are safe and rapidly effective sedating agents. With suspected sympathomimetic (eg, cocaine and amphetamines) intoxication, benzodiazepines (such as, lorazepam) should be used.
- Presentation to an ED with a complication of substance abuse may be a "teaching moment." Substance abusers should be offered drug treatment services.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 140: QUESTIONS & ANSWERS

140.1. The toxic syndrome for anticholinergic overdose is similar to sympathomimetic toxicity and includes all of the following signs with the exception of:

A. Altered mental status
B. Diaphoresis
C. Hyperthermia
D. Increased heart rate
E. Urinary retention

Answer: B. Anticholinergic (antimuscarinic) syndrome includes all of the signs above except for diaphoresis. Typically, anticholinergic poisoning presents with dry skin and mouth but otherwise has similar features to sympathomimetic toxicity. Sympathomimetic overdose often presents with diaphoresis. Anticholinergic patients are also less paranoid and violent.

140.2. What percentage of emergency department (ED) patients are in need of substance abuse treatment?

A. 1%
B. 10%
C. 25%
D. 50%
E. 75%

Answer: C. Approximately 1% of ED patients have a formerly recorded diagnosis of substance abuse, but about 25% are actually in need of substance abuse treatment. Many patients are in denial about their dependency or hiding their substance abuse problems and will avoid talking about this. Because substance abuse increases the risk for injury or illness, these patients are at much higher risk for the need for emergency care than the general population.

CHAPTER 141

Toxic Alcohols

Michael E. Nelson

Ethyl alcohol (ethanol) is ubiquitously consumed worldwide on a daily basis and contributes to a multitude of disease process, cancers, and traumatic events. Although ethanol certainly can be viewed as a toxic alcohol, its use, abuse, and related conditions are discussed in Chapter 142. This chapter will focus on methanol, ethylene glycol (EG), and isopropyl alcohol (isopropanol).

METHANOL

Methanol (methyl alcohol; CAS 67-56-1; H_3COH) is a clear, volatile, colorless, slightly sweet-tasting alcohol at room temperature. It is also known as wood alcohol due to being distilled from wood in the 1920s and 1930s. Methanol is mainly used as a solvent or octane booster in gasoline. It is manufactured frequently as an intermediate in chemical reactions. As a solvent, it is present in many items found in the home, including cleaning solutions, adhesives, enamels, stains, dyes, and paint removers. Methanol is also commonly found in windshield wiping fluid, antifreeze (particularly brake line antifreeze), embalming fluid, and fuel for camp stoves.

Many mass methanol poisonings have occurred throughout history, including recent outbreaks in Estonia (2001), Norway (2002–2004), the Czech Republic (2012), Libya (2013), and Kenya (2014).[1,2] Despite vast knowledge and experience with methanol, these outbreaks demonstrate the diagnostic challenge and difficulty in treating these patients. In 2013, 1747 single substance exposures to methanol were reported to US poison centers. The vast majority were unintentional exposures (88.7%), with few major complications (<1%) and only 8 deaths.[3] These data, however, rely on voluntary reporting and likely underrepresent the true burden of methanol exposures and mortality outcomes from forensic data in the United States.

Principles of Toxicology

Methanol is rapidly absorbed from the gastrointestinal (GI) tract, with an average absorptive half-life of 5 minutes, and reaches peak concentration in 30 to 60 minutes. Inhalation of methanol from carburetor cleaning fluid results in toxicity necessitating antidotal therapy and hemodialysis. Transdermal exposure can lead to significant methanol exposure and toxicity as well. High-risk occupations for exposure to methanol include painting, varnishing, lithography, printing, and glazing.

Methanol itself has very low toxicity, but its metabolism results in toxic metabolites, in particular formic acid, which dissociates into formate and hydrogen ions. Methanol is primarily metabolized in the liver by alcohol dehydrogenase (ADH) into formaldehyde. Formaldehyde is then metabolized by aldehyde dehydrogenase (ALDH) very rapidly, with a half-life of 1 to 2 minutes, into formic acid (Fig. 141.1). Formic acid can combine with tetrahydrofolate (THF) to form 10-formyl THF, which can be metabolized into carbon dioxide and water.

Elimination of methanol is mainly characterized via zero-order kinetics in the poisoned patient but does have first-order metabolism at very low concentrations, with an elimination half-life of about 2 to 3 hours. Small amounts of methanol are eliminated by the renal and pulmonary systems.

At toxic concentrations, the elimination half-life of methanol is nearly 24 hours. The metabolite, formic acid, has a half-life of nearly 20 hours. With ADH inhibition by concurrent consumption of ethanol or administration of fomepizole, the half-life of methanol extends upward to more than 50 hours.[4] With dialysis, the half-life of methanol is approximately 200 minutes.

Formic acid will accumulate due to its slower metabolism as it exceeds the elimination rate. Formic acid binds iron efficiently, resulting in mitochondrial cytochrome oxidase inhibition, and interferes with oxidative metabolism in a manner similar to that of cyanide, carbon monoxide, and hydrogen sulfide. The dissociation of formic acid into formate and hydrogen ions leads to acidosis. The interference of oxidative metabolism, combined with acidosis, further promotes lactate production and worsens the acidotic state. Decreasing pH promotes formic acid diffusion across cell membranes, in particular to the central nervous system (CNS). Also, inhibition of cytochrome oxidase by formic acid is potentiated with decreasing pH. The net effect of this vicious cycle is tissue hypoxia and inhibition of intracellular respiration. Further mechanisms of toxicity include free radical formation, lipid peroxidation, and impairment of antioxidant reactions.

Formic acid uniquely targets the optic disk of the retina and retrolaminar optic nerve, potentially due to the high amount of blood and cerebrospinal fluid (CSF) flow through the choriocapillaris. These cells are more susceptible to cellular hypoxia due to low levels of mitochondria and cytochrome oxidase. Inhibition of mitochondrial cytochrome oxidase results in decreased adenosine triphosphate (ATP) production, leading to myelin sheath damage and loss of vision. Worsening acidosis again potentiates these effects by enhancing the diffusion of formic acid across cell membranes into the neurons.

The basal ganglia and subcortical white matter are affected by formic acid in a similar manner to the ocular toxicity. Neuroimaging and autopsy findings classically demonstrate putamen hypodensity, with hemorrhages and necrosis.[4] Bilateral putamen changes are not specific to methanol toxicity and can be found in Wilson's disease, Leigh's disease, Kearns-Sayre syndrome, toxic encephalopathy (eg, 1,1,1-trichloroethane, carbon monoxide, cyanide, hydrogen sulfide), hemolytic-uremic syndrome, and hypoxic-ischemic injury. The severity of findings and extent of necrosis on imaging do not necessarily correlate with clinical outcome. The vulnerability of the basal ganglia to formic acid toxicity may be due to its high metabolic activity, with poor venous drainage and inadequate arterial flow.

Clinical Features

Clinical signs and symptoms of methanol intoxication typically involve the GI tract, CNS, and the eyes. Initially, patients present in a manner similar to other alcohol ingestions, with GI irritation, inebriation and CNS depression. Methanol has a less inebriating effect than ethanol but causes similar slurred speech, ataxia, confusion, and CNS depression.[4,5] Abdominal discomfort and

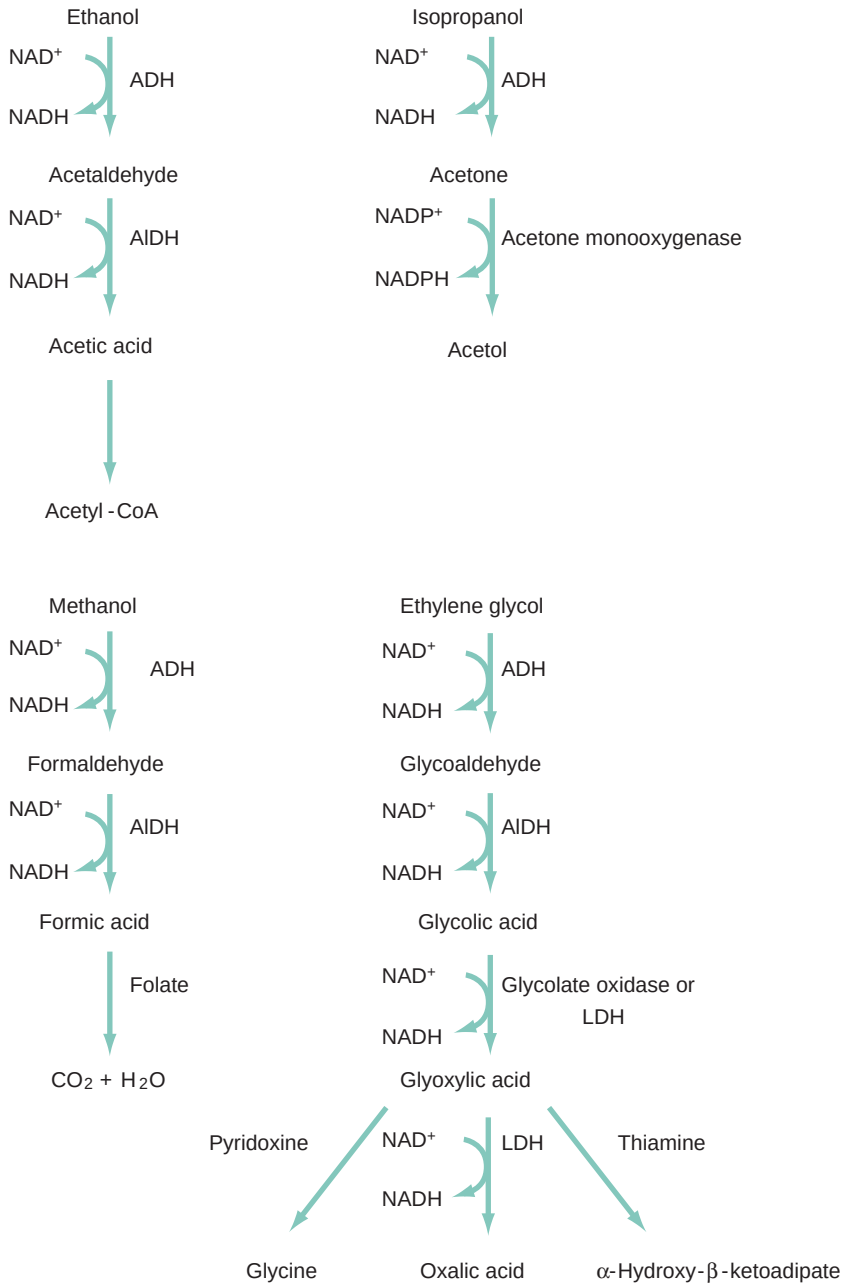

Fig. 141.1. Metabolism of alcohols. *ADH,* Alcohol dehydrogenase; *ALDH,* aldehyde dehydrogenase; *LDH,* lactate dehydrogenase, *NAD+,* nicotinamide adenine dinucleotide; *NADH,* reduced form of nicotinamide adenine dinucleotide.

vomiting occur from mucosal irritation, and patients can develop acute pancreatitis. Severe mucosal irritation can also result in hemorrhagic gastritis. A latency period, ranging from 1 to 72 hours, depending on the amount ingested, can occur with the improvement of inebriation symptoms and development of visual symptoms as methanol metabolizes and formic acid accumulates.[5]

As formic acid accumulates, the most characteristic feature is some degree of visual disturbance, including seeing spots with blurred vision (such as in a snowstorm), altered visual fields, and blindness.[5] Visual disturbances occur in 30% to 70% of patients.[4] Early ophthalmologic findings include reduced pupillary response to light and hyperemia of the optic disc. Peripapillary retinal edema and loss of optic disk cupping follow and often leads to decreased visual fields and central scotomata. Retinal dysfunction can be reversible. Blurred vision, with the sensation of being in a snowstorm from formic acid induced retinal injury, is typically transient, and vision recovers. Optic atrophy and optic neuropathy suggest a poor prognosis for visual recovery.[6] The incidence of ophthalmologic abnormalities correlates directly with the degree of acidosis.[7]

As acidosis progresses, a compensatory tachypnea develops.[4] Acidosis can be profound, with many patients presenting with an arterial pH less than 7 and serum bicarbonate level less than 10 mEq/L. Tachycardia is often noted, but patients rarely have significant cardiac dysrhythmias. Also, shock, seizures, myoglobinuria and rhabdomyolysis have been reported. Death typically results from respiratory failure and sudden respiratory arrest, with cerebral edema and multiorgan failure.[1,2]

Prognosis after methanol ingestion correlates with the degree of acidosis, time to presentation, and initiation of treatment. The strongest predictor of morbidity and mortality is the degree of acidosis, with high mortality rates observed at a pH less than 7. A

TABLE 141.1

Causes of Elevated Osmolar and Anion Gaps

OSMOLAR GAP	ANION GAP (*A CAT PILES MUD*)	DOUBLE GAP	DISTINGUISHING FEATURES
Methanol	***A***lcoholic ketoacidosis	Methanol	Vision loss—methanol
Ethylene glycol	***C***yanide, carbon monoxide, colchicine	Ethylene glycol	Hypocalcemia and calcium oxalate crystalluria—ethylene glycol
Isopropanol	***A***cetaminophen (large ingestion)	Diabetic ketoacidosis	Hyperglycemia, ketonuria—diabetic ketoacidosis
Ethanol	***T***oluene	Alcoholic ketoacidosis	Normal or low glucose level, ketonuria—alcoholic ketoacidosis
Mannitol	***P***araldehyde	Uremia	Positive blood cultures—septic shock
Acetone	Propylene glycol	Septic shock	
Glycerol	Phenformin	Multiorgan failure	
Propylene glycol	***I***soniazid, iron, ibuprofen		
Sorbitol	***L***actic acidosis (eg, sepsis, ischemia)		
Fructose	***E***thylene glycol		
Diatrizoate (IV dye)	***S***alicylates		
Acetonitrile	***M***ethanol, metformin		
Ethyl ether	***U***remia		
Hyperlipidemia	***D***iabetic ketoacidosis		
Hyperproteinemia			
Diabetic ketoacidosis			
Alcoholic ketoacidosis			
Uremia			
Multiorgan failure			
Septic shock			

comatose state at presentation also portends a worse outcome.[1,8] Patients that survive the acute toxicity of methanol can have permanent complications, including blindness and neurologic deficits. A Parkinson-like extrapyramidal syndrome, with bradykinesia, tremor, and dementia, can occur. These findings are generally associated with necrosis of the putamen and subcortical white matter on neuroimaging studies.[4] Other neurologic sequelae include polyneuropathy, encephalopathy, ataxia, and cognitive deficits.[9]

Diagnostic Considerations

Differential Diagnoses

The differential diagnoses for methanol intoxication is broad, making it difficult to detect, particularly at the initial presentation. The inebriated state of the patient can easily be confused with ethanol intoxication. Further causes of altered mental status (AMS) include hypoglycemia, hypoxia, carbon dioxide narcosis, infections, trauma, seizures, metabolic disturbances, endocrinopathies, and encephalopathy. Poisoning or intoxication by other substances, including opiates, carbon monoxide, sedative-hypnotics, and benzodiazepines, often presents with AMS. The GI irritation can occur with ethanol intoxication and with other intra-abdominal pathologies, such as gastritis and pancreatitis.

After ingestion of methanol, serum osmolality will be elevated and can lead to an elevated osmolar gap. Other substances contribute to an elevated osmolar gap. including EG, isopropanol, ethanol, mannitol, glycerol, propylene glycol, sorbitol, fructose, diatrizoate (IV dye), acetonitrile, and ethyl ether (Table 141.1). Additionally, hyperlipidemia and hyperproteinemia cause an increase in the osmolar gap by decreasing the measured sodium concentration.

As the parent compound methanol is metabolized, the production of formic acid results in an elevated anion gap (AG) acidosis. In addition to methanol, causes of AG acidosis include lactic acidosis of varying causes (eg, sepsis, ischemia), diabetic ketoacidosis, alcoholic ketoacidosis, uremia, inborn errors of metabolism, and toxins (eg, salicylates, isoniazid, iron, carbon monoxide, cyanide, metformin, toluene, paraldehyde, propylene glycol, and ethylene glycol; see Table 141.1). Worsening acidosis, despite adequate fluid hydration and no evidence of underlying ischemia producing lactic acidosis, should raise the concern for toxic alcohol ingestion.

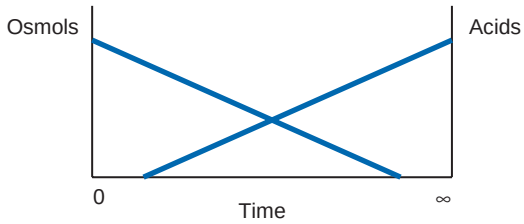

Fig. 141.2. Relationship of osmotically active substance to acid over time. (Adapted with permission from Mycyk MB, Aks SE: A visual schematic for clarifying the temporal relationship between the anion gap and the osmol gaps in toxic alcohol poisoning. Am J Emerg Med 21:333–335, 2003.)

The presence of a so-called double gap (elevated osmolar and anion gaps) is classically described for toxic alcohol ingestion. Many other situations, however, can cause a similar picture, including diabetic ketoacidosis, alcoholic ketoacidosis, renal failure, multiple organ failure, and septic shock (see Table 141.1). This double gap picture is also dependent on the timing of presentation because early presenters will have only an osmotically active parent compound and late presenters will have acidosis without an elevated osmolar gap[11] (Fig. 141.2).

The development of ocular manifestations with worsening acidosis is a strong indicator for methanol poisoning. Other toxins, however, can cause ophthalmologic conditions and blindness such as cinchonism with quinine intoxication, but this lacks the elevated osmolar and anion gaps. Cortical blindness can occur with various causes of toxic leukoencephalopathy, including carbon monoxide, hydrocarbons, steroids, metals (organic mercury), and various chemotherapeutic agents (eg, carboplatin, cisplatin).

Diagnostic Testing

The classically described presentation of toxic alcohol ingestion includes an anion gap metabolic acidosis and an elevated osmolar

gap. Due to the latency period of methanol metabolism, a normal anion gap does not exclude methanol ingestion. The anion gap is commonly calculated by the following equation:

$$AG = [Na^+] - ([HCO_3^-] + [Cl^-])$$

with a normal AG of 8 to 12 mEq/L. Decreased albumin can falsely elevate the AG; the AG can be corrected by using the Figge equation:

$$\text{AG corrected} = AG + (2.5 \times [4.4 - \text{measured serum albumin}])$$

Mortality correlates highly with the degree of acidosis and formate concentration rather than with a specific methanol concentration. Visual dysfunction occurs with a formate concentration greater than 20 to 30 mg/dL. Indicators for a poor prognosis include a formate concentration more than 50 mg/dL and a pH less than 7.[8]

Many formulas exist for calculating serum osmolarity but the most commonly used is the following:

$$\text{Calculated osmolarity (mOsm/kg)} = 2Na^+ + (\text{BUN}/2.8) + (\text{glucose}/18) + (\text{ethanol}/4.6)$$

where BUN is blood urea nitrogen and the ethanol concentration is in mg/dL. The difference between measured serum osmolality and calculated serum osmolarity is as follows:

$$\text{Osmolar gap} = \text{measured osmolality (mOsm/L)} - \text{calculated osmolarity (mOsm/kg)}$$

In systems using SI units, there are no corrections, and the various serum levels are simply added or subtracted. The normal osmolar gap has been arbitrarily defined as normal if it is less than 10 mOsm. However, a wide range of osmolar gaps occurs in the population, ranging from −15 to +10 mOsm. As a result, individuals who begin with a negative osmolar gap can have significantly elevated concentrations of toxic alcohols but have a so-called normal osmolar gap. Many other substances can contribute to an osmolar gap and can be misleading. Also, if patients are acidotic, the parent compound (methanol, ethylene glycol) has been metabolized into its respective acid and does not contribute to the osmotic load. Thus, a normal osmolar gap cannot exclude toxic alcohol ingestion. Methanol, however, is more likely than EG to have an elevated osmolar gap.

Neuroimaging with magnetic resonance imaging (MRI) and computed tomography (CT) can be performed for patients with altered mental status. The most consistent finding for methanol poisoning is bilateral necrosis of the putamen. However, this finding is not specific for methanol poisoning, and neuroimaging is typically normal in the first 24 hours after methanol exposure, because findings typically lag behind clinical symptoms. Patients with evidence of putaminal necrosis on imaging are at risk for a permanent, Parkinson-like extrapyramidal syndrome.

Ultimately, the definitive diagnosis requires laboratory confirmation of the presence of methanol. Once toxic alcohol ingestion is suspected, directly measure methanol and ethylene glycol concentrations and begin empirical therapy. Peak methanol concentrations less than 20 mg/dL are generally not associated with toxicity, but peak methanol concentrations greater than 50 mg/dL indicate significant and serious exposure. Peak methanol concentrations occur shortly after ingestion due to rapid GI absorption. Due to the variability of timing of patient presentation, the methanol level interpretation must be based on clinical (eg, altered mental status, vision complaints) as well as additional laboratory findings (eg, acidosis). Depending on the location of the practice and laboratory capabilities, specific serum concentrations of methanol or EG may not be readily attainable in most hospitals, and blood specimens may need to be transported to reference laboratories for emergent analysis.

Management

Alcohols are rapidly absorbed from the GI tract, so GI decontamination has limited to no value. Gastric suctioning via a nasogastric or orogastric tube may be considered in a large suicidal volume exposure (eg, an entire bottle of windshield washer fluid or antifreeze) in someone who presents immediately after ingestion, but there is no evidence to support routine use. Activated charcoal is not indicated for toxic alcohol ingestions. Aside from standard stabilization and resuscitation, the main priorities in toxic alcohol exposure are correction of acidosis, inhibition of the production of toxic metabolites, and elimination of the parent alcohol and its toxic metabolites. Therapy should be initiated based on strong clinical suspicion; treatment should not be delayed while waiting for specific serum concentrations to be determined.

Because the degree of acidosis correlates with severity and outcome, treat a serum pH less than 7.3 with intravenous (IV) sodium bicarbonate in and attempt to normalize it.[12] Worsening acidosis from formic acid accumulation potentiates mitochondrial cytochrome oxidase inhibition and anaerobic metabolism, also generating a lactic acidosis. Based on supporting patient data, correction of acidosis likely improves outcomes and ophthalmologic symptoms. Bicarbonate can be administered via intermittent boluses, combination of a bolus and infusion, or infusion alone, based on the severity of symptoms. Administer bolus sodium bicarbonate at 1 to 2 mEq/kg and infuse 150 mEq/L of sodium bicarbonate in 5% dextrose at 1.5 to 2 times the maintenance fluid rate until normalization of the serum pH (7.35–7.45). Large amounts of bicarbonate may be necessary for even partial correction of acidosis due to metabolism of the parent alcohol into its toxic acid. With bicarbonate administration, monitor for the development of hypernatremia and hypokalemia. The use of bicarbonate should not deter definitive elimination of the parent alcohol and its toxic metabolites via hemodialysis.

Prevent the further production of formic acid by inhibiting ADH with fomepizole (methylpyrazole, 4-MP) or ethanol. Fomepizole is preferable due to its safety profile and ease of administration, with a sevenfold reduction in adverse drug event rate versus ethanol.[4,12,13] No contraindication exists for fomepizole use except for a severe allergic reaction, but currently there have been no reported cases.[12] Specific indications for initiating ADH blockade are a documented methanol or EG concentration more than 20 mg/dL, documented history of methanol or EG ingestion with an osmolar gap more than 10 mOsm/L, or suspected methanol or EG ingestion with and arterial pH less than 7.3, serum carbon dioxide level less than 20 mmol/L, or oxalate crystalluria[12] (Box 141.1).

In clinical practice however, initiate fomepizole therapy with a strong clinical suspicion for serious ingestion, and send for confirmatory levels, because a delay in ADH blockade can lead to the development of acidosis and deleterious consequences. Fomepizole dosing involves a loading dose of 15 mg/kg followed by 10-mg/kg doses bid, up to 48 hours. After 48 hours, give 15 mg/kg bid because repeated dosing of fomepizole induces its own cytochrome P-450 metabolism.[10] The fomepizole dosing frequency does need to be adjusted with hemodialysis (Box 141.2). Side effects of fomepizole include headache, nausea, dizziness, phlebitis, and reversible liver transaminase level elevation. One case of hypotension and bradycardia due to the rapid infusion of fomepizole has been described.[11-13]

If ethanol is used to inhibit ADH, maintain serum ethanol concentrations between 100 and 150 mg/dL. The affinity of ADH for ethanol is 10 times greater than for methanol.[12] Ethanol dosing

BOX 141.1

Criteria for Initiation of ADH Blockade for Methanol or Ethylene Glycol Poisoning

Documented plasma methanol or EG concentration ≥20 mg/dL
or
History of ingestion of methanol or EG and an osmolar gap >10 mOsm/L
or
Strong clinical suspicion of ingestion of methanol or EG and at least two of the following:
1. Arterial pH < 7.3
2. Serum bicarbonate < 20 mEq/L (mmol/L)
3. Osmolar gap > 10 mOsm/L
4. Urinary oxalate crystals present (for EG ingestion)

EG, Ethylene glycol.

BOX 141.2

Fomepizole Dosing

- Loading dose—15 mg/kg IV
- Maintenance dose—10 mg/kg IV every 12 hr for up to 48 hr
- After 48 hr—15 mg/kg IV
- If undergoing HD—same doses as above, but start maintenance schedule 6 hr after loading dose and then administer every 4 hr thereafter

is complex and can cause worsening CNS and respiratory depression, with hypotension, vomiting, phlebitis, and hypoglycemia, particularly in children or malnourished individuals.[13] Given the widespread availability of fomepizole and its safety profile versus that of ethanol, the dosing of IV ethanol will not be discussed here because its routine use is not recommended. With ADH inhibition, the half-life of methanol is significantly extended upward of 50 hours.[4] Patients who present early after methanol ingestion without acidosis can potentially be treated with ADH inhibition alone, but may have prolonged hospitalizations due to the extended half-life of the parent compound.[12]

Elimination of the parent alcohol via hemodialysis (HD) is the mainstay of therapy in severe toxic alcohol ingestions, and consultation with a regional poison center or medical toxicologist will help determine whether the patient is a candidate. HD serves multiple purposes in that it removes the parent alcohol and its metabolites, corrects acidosis, and aids in fluid management and cardiovascular stabilization. Additionally, it can shorten the course of hospitalization, particularly in methanol ingestions, due to its long half-life.

HD is indicated for acidosis (pH < 7.3), renal failure, vision abnormalities with methanol exposure, electrolyte imbalances unresponsive to conventional therapy (ie, hyperkalemia), hemodynamic instability, and methanol or EG concentration more than 50 md/dL.[11] Traditional endpoints for discontinuing HD or ADH inhibition are a normal acid-base status and methanol-EG concentration less than 20 mg/dL.[11,12] Ophthalmologic disturbances are not an indication for continued dialysis after correction of the acid-base disturbance and removal of methanol. There is no specific treatment for methanol-induced persistent optic nerve injury.[12] Formic acid is converted to carbon dioxide and water via tetrahydrofolate synthetase, so folinic acid (leucovorin) may aid in formic acid elimination, but there have been no human trials to support its benefit.[1,12] The recommended dose is 50 mg of folinic acid IV every 4 to 6 hours until methanol has been eliminated and the acidosis resolves.[12] The use of folinic acid (leucovorin) should not deter emergent HD if indicated.

Disposition

Admission is generally necessary for patients being treated for methanol exposure. Consult with nephrology early for possible HD. If HD is not available, initiate ADH inhibition and transfer the patient to an institution where dialysis is available. Consult the regional poison center (1-800-222-1222) or a medical toxicologist to guide management. Consult an ophthalmologist to evaluate visual fields and the retina fully for methanol-induced ocular injury within 24 hours. Patients with a methanol concentration less than 20 mg/dL and no clinical symptoms or laboratory abnormalities may be discharged. If the patient has psychiatric issues or intent of self-harm, a psychiatric consultation is indicated.

ETHYLENE GLYCOL

Ethylene glycol (ethane-1,2-diol, CAS 107-21-1, $C_2H_6O_2$) is a colorless, odorless, sweet-tasting liquid. It is a common component of antifreeze and de-icing solutions because it lowers the freezing point of water. Additional sources of EG include hydraulic brake fluids, industrial solvents, foam stabilizer, paints, and cosmetics. Because EG has a sweet taste, it is often substituted for ethanol and has led to mass poisonings, including during World War II and the 1973 Arab-Israeli conflict. In 2013, 5956 single substance exposures to EG were reported to US poison centers. Most of these were unintentional (83%) but resulted in roughly 10% of patients having moderate to severe effects and a total of 16 deaths.[3] Like methanol, these data rely on voluntary reporting and likely underestimate the true burden of EG exposures and mortality outcomes.

Principles of Toxicology

Ethylene glycol is rapidly absorbed from the GI tract; peak blood levels occur within 1 to 4 hours after ingestion. EG is highly water-soluble and, unlike methanol or isopropanol, is not volatile at room temperature. Transdermal and pulmonary absorption of EG are extremely limited, and toxicity from these routes of exposure is not expected or observed.

Metabolism of EG primarily occurs in the liver via the conversion of ADH into glycoaldehyde, which is rapidly converted by ALDH into glycolate. Glycolate is further metabolized into glyoxylic acid (glyoxylate) and oxalic acid (see Fig. 141.1). The conversion of glycolate into glyoxylate is slow, and the accumulation of glycolate generates a profound metabolic acidosis. Pyridoxine and thiamine are cofactors in the metabolism of glyoxylate but, given the slow conversion of glycolate to glyoxylate, these cofactors likely do not contribute significantly to EG detoxification. A small amount of oxalate will precipitate with calcium to form calcium oxalate crystals. These metabolic oxidation steps result in the conversion of nicotinamide adenine dinucleotide (NAD^+) to nicotinamide adenine dinucleotide (NADH), which converts pyruvate to lactate and generates a lactic acidosis.

Calcium oxalate crystals precipitate in the proximal renal tubules and are the main contributing factor in the development of acute tubular necrosis and renal failure. Calcium oxalate deposits also occur in the brain, intestinal mucosa, lungs, heart, and spleen, although the contribution of these deposits to the clinical picture is less clear. Further findings of EG toxicity include diffuse petechial hemorrhages in the heart, lungs, and brain, as well as the development of cerebral edema. Myonecrosis and rhabdomyolysis can occur. The chelation of calcium by oxalate can lead to systemic hypocalcemia.

Elimination of EG occurs mainly in the liver but roughly 20% to 25% of EG is excreted unchanged in the urine. The reported half-life of EG ranges from 3 to 9 hours, but when metabolism is inhibited by ethanol or fomepizole, the half-life increases up to 20 hours.[12] With dialysis, the half-life of EG is about 2 to 3 hours, depending on flow rates.

Clinical Features

The clinical picture of EG toxicity is typically divided into three stages: (1) acute neurologic stage; (2) cardiopulmonary stage; and (3) renal stage. As with methanol, delayed neurologic sequelae are described. An extreme amount of clinical variability occurs, stages may overlap, and mortality may occur at any stage. Poor prognostic factors at admission include hyperkalemia, severe metabolic acidosis, renal failure, seizures, coma, and delays in treatment. Seizures are highly prognostic for death.[13] The co-ingestion of ethanol can delay the onset of symptoms.

EG is a gastric irritant and can produce nausea and vomiting shortly after ingestion. The acute neurologic stage occurs over 30 minutes to 12 hours after ingestion with EG, producing inebriation and euphoria similar to ethanol. In severe poisonings, CNS depression can progress to coma, hypotonia, and seizures. Additional findings include nystagmus, ataxia, and myoclonic jerks. Cerebral edema can develop from calcium oxalate crystal deposition and cytotoxic damage contributing to CNS depression.[5]

The cardiopulmonary stage occurs 12 to 24 hours after ingestion, with patients developing tachycardia with a severe metabolic acidosis and compensatory tachypnea. The acidosis occurs from the generation of glycolic acid. Hypoxia with pulmonary edema and acute respiratory distress syndrome (ARDS) can cause hypoxia. Multiorgan failure with circulatory collapse can occur, and most deaths ensue during this stage.[5]

The renal stage occurs 24 to 72 hours postingestion with the development of acute renal failure (ARF) from calcium oxalate crystal deposition. Conscious patients may complain of flank pain and have costovertebral tenderness. Hematuria and proteinuria can occur. Renal failure can be anuric, oliguric, or nonoliguric. Renal dysfunction frequently necessitates HD and, in some cases, for months after exposure. Renal function usually returns to normal following EG intoxication, but occasionally some renal damage can be permanent. Long-term hemodialysis is rarely necessary.[5]

Delayed neurologic sequelae commonly present as a bulbar palsy from 5 to 20 days after ingestion, with cranial nerve VII being most commonly implicated.[9] Other cranial nerve involvement has been documented; clinical findings include ophthalmoplegia, diplopia, nystagmus, facial droop, facial sensory loss, hearing loss, dysphagia, and vertigo.[5] The term *facial auditory nerve oxalosis* has been used to describe this delayed syndrome and its predilection to affect cranial nerves VII and VIII on autopsy. In addition to the cranial nerves, an autonomic nerve dysfunction has been described, with postural hypotension and gastroparesis.[14] The exact pathogenesis for these neurologic findings is unclear, but postulated mechanisms include calcium oxalate deposition resulting in mechanical nerve injury, inflammatory response causing nerve dysfunction, and depletion of thiamine and pyridoxine cofactors. Neuroimaging studies can demonstrate the focal infiltration of calcium oxalate with inflammation and necrosis of the basal ganglia.[9]

Diagnostic Considerations

Differential Diagnoses

The differential diagnoses for EG intoxication is broad and similar to methanol. See earlier, "Methanol: Differential Diagnoses," for a more in-depth explanation, especially regarding the initial presentation of inebriation and AMS, proceeding through elevated osmolar and anion gaps (see Table 141.1).

Unlike methanol, however, the hallmark of EG toxicity involves renal failure with calcium oxalate crystalluria. Many other substances cause ARF, including antimicrobials (eg, aminoglycosides, vancomycin, sulfa-based drugs, ciprofloxacin, penicillins, polymixins), nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, HMG-CoA reductase inhibitors, antivirals (eg, acyclovir, foscarnet, antiretrovirals), amphotericin B, chemotherapeutics (eg, methotrexate, cisplatin, ifosfamide), diethylene glycol (DEG), bisphosphonates, radiocontrast media, metals, proton pump inhibitors, lithium, and acetaminophen.[15] Calcium oxalate crystalluria is therefore not specific for EG and is only present in up to 50% of cases of EG ingestion. Healthy individuals with excess dietary intake of vitamin C or foods rich in oxalate (eg, garlic, tomatoes, spinach, rhubarb, and tea) may have incidental calcium oxalate crystalluria.

Xenobiotic-induced hypocalcemia can occur from proton pump inhibitors, bisphosphonates—and other phosphate-containing substances, such as laxatives and sodium phosphate)—loop diuretics, glucocorticoids, calcitonin, cisplatin, pentamidine, interferon-alfa, fluorides (eg, hydrofluoric acid), citrate, phenytoin, phenobarbital, carbamazepine, estrogens, and ethylenediaminetetraacetic acid. Hypocalcemia and calcium oxalate crystalluria, however, strongly suggests EG toxicity. Ultimately, the definitive diagnosis requires laboratory confirmation of the presence of EG.

Diagnostic Testing

Diagnostic testing for EG is similar to that for methanol; for a more detailed discussion of AG acidosis and elevated osmolar gap calculations, see earlier, "Methanol: Diagnostic Testing." The contribution of EG to the osmolar gap is relatively small compared to other alcohols, and an EG concentration of 50 mg/dL will only cause an 8- to 10-mOsm rise in the osmolar gap. Thus, an elevated osmolar gap can suggest EG ingestion, but a normal gap does not exclude it.

Calcium oxalate crystalluria can be of two major forms, needle-shaped calcium oxalate monohydrate or polyhedron-shaped calcium oxalate dihydrate crystals. The calcium oxalate monohydrate crystals may be mistaken for hippuric acid crystals.[5] Crystals can be found in the urine 4 to 8 hours after exposure. Additional urinary findings include hematuria and proteinuria. (Fig. 141.3).

Fluorescein dye is often added to antifreeze agents to assist in the detection of radiator leaks, so patients who ingest antifreeze

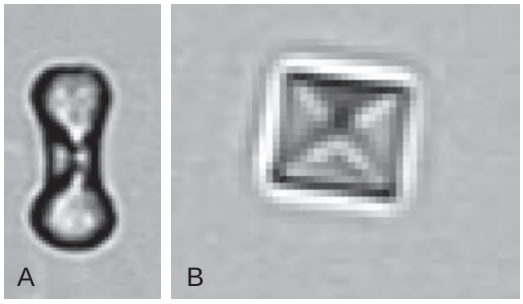

Fig. 141.3. Calcium oxalate crystals. Illustrated are calcium oxalate monohydrate (**A**) and dihydrate (**B**) crystals in the urine. The monohydrate whewellite crystals typically are needle-like or dumbbell-shaped and strongly birefringent, whereas the dihydrate weddellite crystals are octahedral, envelope-shaped, and weakly birefringent.

EG-containing agents may exhibit urinary fluorescence under a Woods lamp. Urinary fluorescence, however, is neither specific nor sensitive for diagnosing or excluding EG intoxication. The fluorescence of gastric contents soon after EG ingestion may be more definitive.

The EG concentration itself does not predict severity as much as it depends on the timing of presentation and initiation of intervention. Serum EG concentrations more than 50 mg/dL, however, are associated with serious ingestion and toxicity. The degree of acidosis (particularly a pH <7.2–7.3) does predict an increase in the creatinine level and mortality outcome.[16] A peak EG concentration less than 20 mg/dL is not associated with significant toxicity.

In EG intoxication, the serum glycolate concentration is the driving force for acidosis. Glycolate concentrations more than 10 mmol/L are strongly associated with severe CNS toxicity and mortality and have 100% sensitivity for predicting ARF. Patients with glycolic acid levels less than 8 to 10 mmol/L are unlikely to develop ARF. Serum glycolate concentrations, however, typically are not readily available in a timely fashion to aid in most clinical situations.

Management

Many of the management principles of EG toxicity overlap with those of methanol. See earlier, "Methanol: Management" for additional information. EG, like methanol, is rapidly absorbed from the GI tract; thus, gut decontamination has a limited to no role in EG ingestion. Correct metabolic acidosis with sodium bicarbonate (pH < 7.3) because this may increase the urinary excretion of EG and delay calcium oxalate–induced ARF. Initiate ADH blockade, preferably with fomepizole, as soon as possible to prevent the development of toxic metabolites (Boxes 141.1 and 141.2). Ethanol therapy can be used if fomepizole is unavailable, although its routine use is not recommended. Consider HD for the indications stated earlier, particularly for an acid-base imbalance and renal failure. EG, however, has a shorter half-life than methanol, and patients without acidosis or renal compromise can be managed with fomepizole alone, thus preventing the need for HD in adult and pediatric patients.[17] Continue treatment until EG concentrations are less than 20 mg/dL and a normal acid-base status is present.

Pyridoxine and thiamine are cofactors in EG metabolism. Pyridoxine aids in the conversion of glyoxylate metabolism to glycine. Thiamine stimulates conversion of glycolic acid to α-hydroxy-β-ketoadipate (see Fig. 141.1). No clinical data, however, support the effectiveness of the use of these cofactors in otherwise healthy patients with EG ingestion. These cofactors should be given to patients with vitamin deficiencies, such as alcoholics abd malnourished individuals. The recommend adult doses are thiamine, 100 mg qid, and pyridoxine, 50 mg qid, for 2 days. If patients have symptomatic hypocalcemia (interval changes on the electrocardiogram and dysrhythmias), replete with calcium gluconate or calcium chloride, as needed.

Disposition

Admission is generally necessary for patients being treated for EG exposure. Consult nephrology early for possible HD. If HD is not available, initiate ADH inhibition and transfer the patient to an institution where dialysis is available. Consult the regional poison center (1-800-222-1222) or a medical toxicologist to guide management. Patients with an EG concentration less than 20 mg/dL and no laboratory abnormalities or clinical symptoms may be discharged. If the patient has psychiatric issues or intent for self-harm, a psychiatric consultation is indicated.

ISOPROPYL ALCOHOL

Isopropyl alcohol (IPA; isopropanol, 2-propanol, CAS 67-63-0, C_3H_7OH) is a clear, colorless liquid with a fruity odor and slightly bitter taste. IPA is found in numerous household and commercial products, including rubbing alcohol, antifreeze, disinfectants, cleaning solutions, skin and hair products, and hand sanitizers. IPA is commonly used as a solvent for industrial applications. It is the second most commonly ingested alcohol after ethanol. Exposures to IPA reported to US poison centers have ranged from about 15,000 to 21,000 cases/year.[3,18] In 2013, 15,454 single substance exposures occurred, with 85% unintentional in nature, 4% having moderate to major effects, and three deaths, reflecting a low case-fatality rate.[3]

Principles of Toxicology

Isopropyl alcohol is rapidly absorbed from the GI tract; peak plasma concentrations occur within 30 minutes. Oral ingestion is the major route of exposure, but absorption can occur transdermally, rectally, or via inhalation. Children are especially susceptible to systemic symptoms from the dermal application of IPA used to reduce fever.

Metabolism occurs primarily in the liver by ADH into acetone. Acetone is metabolized to acetol (hydroxyacetone) by acetone monooxygenase (see Fig. 141.1). Further metabolic products include propylene glycol, methylglyoxal, lactate, formate, and acetate. Many of these minor metabolic products are then converted to glucose. Acetone reaches a peak plasma concentration from 7 to 30 hours postexposure and has a half-life of up to 24 hours. IPA follows first-order kinetics, with a half-life of 2.5 to 8 hours. ADH inhibition increases the half-life to 16 to 27 hours.[18] Elimination primarily occurs via the kidneys, with up to 20% of IPA excreted unchanged in the urine.

Isopropyl alcohol directly acts as a CNS depressant and is considered to be twice as inebriating as ethanol. Acetone can also contribute to CNS depression. A concomitant respiratory depression can occur with profound CNS depression. With larger doses, peripheral vasodilation and decreased cardiac inotropy can cause hypotension.[18] Topical exposure leads to corneal de-epithelialization, with dermal irritation.

Clinical Features

Isopropyl alcohol irritates mucosal surfaces, and GI effects typically occur early after ingestion. Nausea, vomiting, and abdominal pain typically ensue, but hemorrhagic gastritis, hematemesis, and significant blood loss can result with larger ingestions.[18] As with other alcohols, pancreatitis is a potential complication. Aspiration of IPA can cause hemorrhagic tracheobronchitis and pulmonary edema.

CNS depression ranges from lethargy to stupor or coma. Headache, dizziness, ataxia, hypotonia, hyporeflexia, dysarthria, and seizures have been reported.[18] Pupil size is variable, but miosis is commonly observed. Loss of consciousness is associated with respiratory depression, hypoxia, and aspiration pneumonitis. Hypotension and hypothermia can occur with very large ingestions. Hypotension signifies severe poisoning with increased mortality risk. Injuries from prolonged immobilization with CNS depression can lead to compartment syndrome and rhabdomyolysis. Myoglobinuria can cause ARF. Hypoglycemia has not been reported with IPA as it has for other alcohols. Dermal contact causes a defatting dermatitis with drying and cracking of the skin, and pediatric patients can sustain chemical burns. Ketosis without acidosis is a classic finding in IPA ingestion.

Diagnostic Considerations

Differential Diagnoses

Patients with significant IPA ingestion appear intoxicated. IPA will elevate the osmolar gap but, unlike methanol and ethylene glycol, not the anion gap. See earlier, "Methanol: Differential Diagnoses" for causes for AMS and an elevated osmolar gap. As IPA is converted to acetone, ketosis will occur. Ketosis is present in conditions such as diabetic ketoacidosis, alcoholic ketoacidosis, starvation ketosis, salicylism, and cyanide and acetone ingestion. ARF can develop from rhabdomyolysis but the differential for ARF is extensive (see earlier).

Diagnostic Testing

The most common laboratory abnormality is ketosis without acidosis and euglycemia. As IPA is metabolized, acetone accumulates. Acetone does not elevate the anion gap but IPA and acetone do contribute to the osmolar gap. Acetone can be detected within 30 minutes in serum and within 3 hours in urine postexposure.[18] Acetone can interfere with the assay for creatinine and cause a pseudo–renal failure measurement with an isolated elevated creatinine but normal blood urea nitrogen (BUN) level. If patients are hypotensive however, from a large IPA ingestion, a lactic acidosis can occur, which can then cause a confounding anion gap acidosis.

The measurement of the IPA concentration is the definitive method of diagnosis. Occasionally, IPA can be detected in patients with acetonemia not exposed to IPA because acetone is converted to IPA in vivo. Serum concentrations of IPA do not correlate well with clinical outcomes—deaths have been reported with concentrations as low as 20 mg/dL. The scant data available suggest that a concentration more than 50 mg/dL is associated with toxicity, and some authors have suggest HD for levels greater than 400 mg/dL although there has been no clear evidence for these recommendations.[18] The clinical status of the patient should direct the necessary care.

Management

Supportive care is the mainstay of therapy for IPA ingestion. There is no role for GI decontamination. Wash the skin with soap and water for dermal contamination. Provide proton pump inhibitors (eg, pantoprazole, 80 mg IV push and a drip at 8 mg/hr for 72 hours, or until the patient can tolerate oral foods and fluids) for hemorrhagic gastritis. Consult gastroenterology for endoscopy to exclude other causes of upper GI bleeding or to intervene for persistent bleeding causing hemodynamic instability, necessitating transfusion, or worsening clinical scenario. For deeply comatose patients, airway protection is indicated. Hypotension generally responds to IV crystalloid solution. For significant hypotension, initiate 1 to 2 L of normal saline as a bolus infusion, followed by repeated 500-mL boluses at 30-minute intervals until a mean arterial pressure (MAP) of 65 mm Hg is achieved. If the target MAP cannot be achieved or maintained with 4 L of normal saline boluses, start a norepinephrine infusion at 8 to 12 μg/min and titrate to the target MAP. Additional vasopressor support can be added with fluids and vasopressors, as needed. If the patient is persistently hypotensive, despite standard resuscitative measures, initiate HD. ADH blockade with fomepizole or ethanol is not indicated because this will only prolong the hypotensive and CNS depressant effects of IPA.[18]

Disposition

Due to IPA's rapid absorption on its onset of action, patients who are stable and alert 6 hours after ingestion are unlikely to develop significant complications and can be monitored until no longer clinically intoxicated for discharge from the ED. Patients with significant inebriation or altered mental status should be admitted as an inpatient or placed in an observation unit for 24 hours. Consult gastroenterology for patients with hemorrhagic gastritis for endoscopy. Consult nephrology for patients with a comatose state or refractory hypotension for HD. Consult the regional poison center (1-800-222-1222) or medical toxicologist to help guide management.

OTHER ALCOHOLS OF CLINICAL SIGNIFICANCE

Diethylene glycol (DEG) is an odorless, viscous, sweet-tasting liquid commonly used as a solvent. It is found in brake fluid, antifreeze, lubricants, wallpaper strippers, and artificial fog solutions. Most exposures to DEG occur in epidemics in which DEG is substituted in pharmaceutical preparations for more expensive glycols. The first epidemic occurred in the United States in the 1930s, with DEG being used as a solvent for sulfanilamide, and led to the passing of the 1938 Federal Food, Drug, and Cosmetic Act requiring drug manufactures to demonstrate product safety prior to marketing. Other epidemics include those in South Africa (1969), Spain (1985), Nigeria (1990), Bangladesh (1990–92), Haiti (1996), India (1998), Panama (2006), and Nigeria (2008). DEG toxicity resembles that of EG, with initial GI irritation and CNS depressant effects, and then a resultant metabolic acidosis. ARF without urinary calcium oxalate crystals occurs. Patients who survive ARF, unlike EG, typically require lifelong HD. Neurologic symptoms develop 5 to 10 days postingestion and can include lethargy, cranial neuropathies, peripheral polyneuropathies, and quadriparesis. DEG is metabolized into 2-hydroxyethoxyacetic acid and does not metabolize into EG, as once believed. Management is similar to that of methanol and EG and includes ADH blockade and early HD.

Propylene glycol (PG) is commonly used as a solvent in various pharmaceutical products and in antifreeze and hydraulic fluids. Common xenobiotics that use PG as a solvent include IV phenytoin, lorazepam, diazepam, etomidate, nitroglycerin, phenobarbital, hydralazine, and trimethoprim-sulfamethoxazole.[19] PG is metabolized to lactic acid and can produce a metabolic acidosis. Also, it can contribute to an elevated osmolar gap. Because PG has a short half-life, the osmolar gap rapidly returns to normal once it is discontinued. Underlying renal insufficiency and hepatic dysfunction increase the risk for toxicity. Case reports have noted acute kidney injury from proximal tubular necrosis with PG toxicity. Additionally, PG toxicity can mimic a systemic inflammatory response syndrome and cause a confounding picture, with an elevated osmolar and anion gap triggering exploration for methanol and EG exposure. Approximately 20% of intensive care unit patients on a lorazepam infusion can have some degree of PG toxicity. Treatment typically involves stopping the offending agent, but HD and ADH blockade can be considered for severe acidosis and metabolic abnormalities.

KEY CONCEPTS

- Serum osmolarity is calculated by the following equation:

$$\text{Calculated osmolarity (mOsm/kg)} = 2Na^{+} + (\text{BUN}/2.8) + (\text{glucose}/18) + (\text{ethanol}/4.6)$$

  The measured osmolar gap is the difference between the measured serum osmolality and calculated serum osmolarity, with a normal range of −15 to +10 mOsm.
- The classic finding of an elevated osmolar and anion gap should raise suspicion of methanol or ethylene glycol toxicity but may not be present, depending on the timing of ingestion. Early ingestion has a high osmolar gap without acidosis, and late ingestion has acidosis without an osmolar gap.
- A normal osmolar gap does not exclude toxic alcohol ingestion.
- Initiate therapy based on clinical suspicion of exposure to methanol or ethylene glycol. Block alcohol dehydrogenase preferably with fomepizole, but ethanol can be used if fomepizole is unavailable.
- The presence of acidosis indicates accumulation of the toxic metabolites of methanol (formic acid) and ethylene glycol (glycolic and oxalic acid). Consult nephrology for emergent hemodialysis to correct acid-base disturbances and remove the parent compound and its toxic metabolites.
- Severe acidosis is a poor prognostic factor, with high mortality rates in methanol and ethylene glycol ingestions. A comatose state at time of presentation also is associated with a higher mortality outcome.
- The main priorities in toxic alcohol exposure are correction of acidosis using bicarbonate solution and hemodialysis, inhibition of the production of toxic metabolites, and elimination of the parent alcohol and its toxic metabolites.
- The findings of an elevated osmolar gap with ketonemia or ketonuria and no development of acidosis indicates isopropanol ingestion. Patients can have a prolonged period of inebriation and can be comatose. Alcohol dehydrogenase inhibition is not indicated in these cases.
- Hypotension and GI bleeding are poor prognostic factors in isopropanol ingestion.
- Diethylene glycol can result in acidosis and renal failure and should be managed similarly to ethylene glycol poisoning with fomepizole and early hemodialysis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 141: QUESTIONS & ANSWERS

141.1. A 24-year-old man presents after an intentional methanol ingestion. The patient reports that 1 or 2 hours ago he drank approximately 8 ounces of windshield washer fluid in a suicide attempt. He is not sure of the product name. His only current complaint is slight nausea. His vital signs and physical examination are within normal limits. Serum chemistry reveals the following: sodium, 142 mEq/L, potassium, 4.5 mEq/L, chloride, 110 mEq/L, bicarbonate, 22 mEq/L, blood urea nitrogen (BUN), 18 mg/dL, creatinine, 1.5 mg/dL, and glucose, 111 mg/dL. Serum methanol levels are not obtainable at your hospital. The psychiatry service asks if the patient is medically cleared. Which of the following is the most appropriate response?

A. The patient is cleared; he has a normal anion gap, so no significant methanol ingestion occurred.
B. The patient is cleared; ingestion of 8 ounces is below the toxic level regardless of the concentration.
C. The patient is not cleared; he has an elevated anion gap and needs to receive treatment for methanol toxicity.
D. The patient is not cleared; he has evidence of renal failure and needs to receive treatment for methanol toxicity.
E. The patient is not cleared; not enough time has elapsed from the ingestion to determine if significant toxicity has occurred.

Answer: E. Windshield washer fluid can contain high concentrations of methanol. Methanol itself does not cause toxicity or an anion gap acidosis but its metabolites do, specifically formic acid. It can take 12 to 24 hours for acidosis to develop and even longer if a significant amount of ethanol has also been ingested. This patient should be observed and treated. This patient's anion gap is 10 mEq/L, which is within normal limits. Ingestion of very small amounts of methanol can be fatal or cause permanent neurologic or ophthalmologic damage. As little as 15 mL of 40% methanol can cause death in adults.

141.2. A 44-year-old woman complains of abdominal pain and headache. Her family reports that the patient drank "something" approximately 8 hours ago in a suicide attempt. The patient is sleepy but arouses with manual stimulation. Her speech is confused, but she follows all simple commands. Her vital signs are blood pressure, 124/82 mm Hg, heart rate, 108 beats/min, respiratory rate, 26 breaths/min, and temperature, 37.0°C (98.6°F). Her physical examination is unremarkable. Her serum chemistry reveals an anion gap of 24 mEq/L. Other laboratory work is pending. Which of the following treatments should be administered initially?

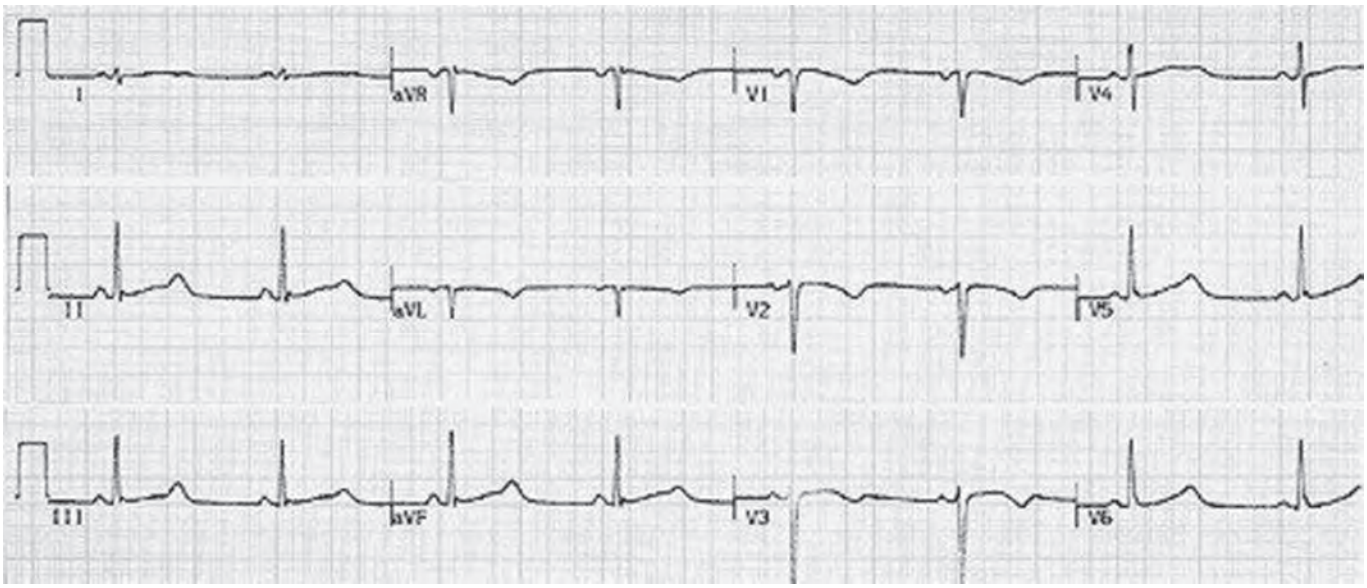
A. Diuresis
B. Hemoperfusion
C. Intravenous flumazenil
D. Intravenous fomepizole
E. Oral activated charcoal

Answer: D. Intravenous fomepizole should be administered. This patient has likely ingested methanol or ethylene glycol, both of which can cause these symptoms, as well as an anion gap metabolic acidosis. The definitive treatment for both ingestions is hemodialysis, which can take some time to arrange. Treatment should be started with fomepizole, even before a definitive diagnosis has been made. Fomepizole and ethanol act by inhibiting the conversion of methanol or ethylene glycol to toxic substances, thereby allowing elimination of the much less toxic original compounds. Diuresis and hemoperfusion are not effective for methanol or ethylene glycol. Flumazenil will reverse the effect of benzodiazepine but should always be used with caution so as not to induce seizure activity. Oral charcoal is not effective for methanol or ethylene glycol, especially after such a long delay.

141.3. A 20-year-old man presents after ingesting antifreeze. His electrocardiogram (ECG) is shown below. Which electrolyte abnormality is most likely responsible for the findings on the ECG?

A. Hypercalcemia
B. Hyperkalemia
C. Hypocalcemia
D. Hypokalemia
E. Hypomagnesemia

Answer: C. Hypocalcemia is a cause of QT prolongation. Ingestion of ethylene glycol can result in hypocalcemia, which is caused by calcium precipitation with oxalate. Although ethylene glycol ingestion can result in renal failure that can then cause hyperkalemia, it is not associated with QT prolongation. Hypokalemia and hypomagnesemia can both cause QT prolongation; neither is associated with ethylene glycol ingestion.



141.4. An otherwise healthy patient presents after a suicidal ethylene glycol ingestion. He is drowsy. His serum pH is 7.1. You have started treatment with fomepizole and have contacted the nephrologist to arrange dialysis. In the meantime, what should be done about the patient's acidosis?

A. Normal saline should be administered to facilitate clearance of the acid.
B. Nothing should be done; dialysis will correct the acidosis.
C. Nothing should be done; the fomepizole will correct the acidosis.
D. Nothing should be done; the patient is not truly acidotic, but ethylene glycol interferes with the laboratory determination of pH.
E. Sodium bicarbonate should be administered to neutralize the exogenous acid.

Answer: E. Unlike lactic acid, which will be metabolized to bicarbonate, the acidic metabolites of methanol and ethylene glycol cannot be metabolized to bicarbonate and can cause a severe acidosis if not treated. Dialysis will correct the acidosis, but early treatment of the acidosis can reverse some of the adverse effects of methanol or ethylene glycol poisoning. Fomepizole prevents the conversion of methanol or ethylene glycol into toxic metabolites but does nothing to the metabolites already produced. Forced saline diuresis in not beneficial and may increase the incidence of acute respiratory distress syndrome.

141.5. Which of the following is an indication for hemodialysis after methanol or ethylene glycol ingestion?

A. Acidosis
B. Blood level of 10 mg/dL
C. Elevated anion gap
D. Hypocalcemia
E. Hypokalemia

Answer: A. Metabolic acidosis, renal compromise, visual symptoms, deterioration despite intensive supportive care, and electrolyte abnormalities unresponsive to conventional therapy are all indications for hemodialysis. Although an anion gap is often associated with metabolic acidosis, an anion gap in and of itself is not an indication for hemodialysis. There is debate about the alcohol levels that indicate the need for hemodialysis. Recommendations have been made to dialyze patients with levels of methanol or ethylene glycol between 25 and 50 mg/dL.

141.6. Which of the following cofactors helps with the elimination of methanol and should be given to patients with methanol poisoning?

A. Folate (vitamin B_9)
B. Hydroxocobalamin (vitamin B_{12})
C. Niacin (vitamin B_3)
D. Pyridoxine (vitamin B_6)
E. Thiamine (vitamin B_1)

Answer: A. Folate is a cofactor in the degradation of formic acid to carbon dioxide and water, the final step in the metabolism of methanol. Folinic acid is recommended to be given 50 mg IV every 4 hours to adults with methanol poisoning. Thiamine and pyridoxine are both useful for patients with ethylene glycol poisoning and should be given. Niacin and hydroxocobalamin are antidotes but play no role in treatment for ethanol or ethylene glycol poisoning.

141.7. Which of the following statements comparing the effects of isopropyl alcohol and ethylene glycol is true?

A. Isopropyl alcohol causes less CNS depression and is less toxic than ethylene glycol.
B. Isopropyl alcohol causes less CNS depression and is more toxic than ethylene glycol.
C. Isopropyl alcohol causes more CNS depression and is less toxic than ethylene glycol.
D. Isopropyl alcohol causes more CNS depression and is more toxic than ethylene glycol.
E. Isopropyl alcohol has the same effects as ethylene glycol.

Answer: C. Isopropyl alcohol causes twice the central nervous system (CNS) depression of ethanol, which causes more depression than ethylene glycol. Isopropyl alcohol is metabolized to acetone, which also causes CNS depression but is relatively nontoxic, except in very high doses.

141.8. A patient presents with decreased mental status after drinking some homemade alcohol. Serum chemistry reveals sodium, 140 mEq/L, potassium, 4.5 mEq/L, chloride, 108 mEq/L, bicarbonate, 22 mEq/L, BUN,

28 mg/dL, creatinine, 1.0 mg/dL, glucose, 90 mg/dL, and serum osmolality, 320 mOsm/kg. Urinalysis is positive for ketones. Which of the following is the most likely alcohol ingested?

A. Ethanol
B. Ethylene glycol
C. Isopropyl alcohol
D. Methanol
E. On the basis of this information, the patient probably did not ingest an alcohol.

Answer: C. This patient has a normal anion gap of 10 but an elevated osmolal gap of 25. The osmolal gap equals the measured serum osmolarity minus the calculated serum osmolarity. The calculated osmolarity is

$$(\text{Sodium} \times 2) + (\text{BUN}/2.8) + (\text{glucose}/18)$$

In this case, it is 295 mOsm/kg. Ethylene glycol and methanol both cause a double gap or elevated anion and osmolal gaps. Ethanol and isopropyl alcohol generally elevate only the osmolal gap. Isopropyl alcohol ingestion causes more CNS depression than ethanol ingestion and results in ketonemia and ketonuria as it is metabolized to acetone.

CHAPTER 142

Alcohol-Related Disease

John T. Finnell

As eloquently stated by Paracelsus in the 16th century, "all substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."

PRINCIPLES OF TOXICITY

Alcohol is the most common recreational drug taken by Americans, and per capita consumption is increasing. Alcohol is the third leading cause of preventable death in the United States; alcoholism permeates all levels of society and is a preventable cause of morbidity and mortality.[1] The widespread incidence and disastrous effects of alcoholism are well known to the emergency clinician. Almost all societies that consume alcohol have related health and social problems. The tragic effects of alcohol not only affect the individual drinker but also have far-reaching implications for the family, community, and workplace.

Alcohol consumption is responsible for 3.8% of global mortality, 4.6% of every disability-adjusted life-year (DALY) lost due to premature death, and is projected to take on increasing importance over time.[2] Alcohol use and misuse also have social and financial costs, with estimates of the annual economic costs (eg, the costs of health care and lost productivity) to be over $800/person for the entire US population.[3] Alcohol contributes to 79,000 deaths and $223.5 billion in societal costs annually in the United States.[4] Harmful consequences and risk of disability exist on a continuum (Fig. 142.1).[4]

At-risk drinking is defined as heavy or problematic alcohol use that may lead to an array of negative consequences, including social, physical, psychological, legal, and financial problems. Across the United States, at least 24% to 31% of emergency department (ED) patients meet National Institute Alcohol Abuse and Alcoholism (NIAAA) criteria for at-risk drinking.[3] At-risk drinking is defined as an average of 15 or more standard drinks/week or 5 or more per occasion for men and 8 or more drinks weekly or 4 or more per occasion for women and people older than 65 years.[4]

The lifetime prevalence of alcohol use disorder (AUD) in the general population is nearly 20% and of dependence is 13%.[5] AUD consist of alcohol dependence, alcohol abuse, and dependence or harmful use. These disorders are common in all developed countries and are more prevalent in men than in women, with lower but still substantial rates in developing countries. However, most people with AUD are difficult to identify because they are likely to have jobs and families and to present with general complaints, such as malaise, insomnia, anxiety, sadness, or a range of medical problems. The prevalence of AUD is higher in specialized populations, affecting about 40% of patients presenting to the ED and 59% to 67% of trauma patients.[5] In response to the high prevalence of this disease, the American Medical Association has recommended screening patients for alcohol use problems in medical and surgical settings and EDs.[3]

Alcohol is a central nervous system depressant. Like benzodiazepines, barbiturates, and drugs that have similar action, it rapidly increases the release of γ-aminobutyric acid (GABA) in the brain, and it inhibits postsynaptic N-methyl-D-aspartate glutamate receptor activity.[6] Chronic alcohol consumption also affects central α-adrenergic and β-adrenergic receptors and dopamine turnover.[7]

Animal studies have suggested that in alcohol withdrawal, the balance of the neurotransmitters GABA and glutamate is altered. Decreased synthesis of GABA and increased synthesis of glutamate might be related to withdrawal symptoms experienced on brutal cessation of chronic alcohol intake.[8]

About 40% to 60% of AUD cases are explained by genes and the rest by environmental association. Polymorphisms in genes for enzymes that metabolize alcohol are generally associated with a lower risk of AUDs because they increase sensitivity to alcohol. One candidate gene and gene product that has been shown to contribute to the risk of drug abuse and addiction-related phenotypes is the mu opioid receptor (MOR; *OPRM1* gene).[9]

Metabolism of Alcohol

Ethanol is rapidly absorbed from the stomach and small intestine. It is distributed uniformly to all organ systems, including the placenta. Although 2% to 10% of alcohol is excreted through the lungs, urine, and sweat, most is metabolized to acetaldehyde, primarily by alcohol dehydrogenase (ADH). The oxidation of alcohol is a complex process involving three enzyme systems, all contained in the hepatocyte. Acetaldehyde is then quickly converted to carbon dioxide and water, primarily through aldehyde dehydrogenase (ALDH). The common forms of ADH decrease the alcohol concentration in blood by about 4.5 mmol/L ethanol/hr (the equivalent of about one drink/hr):

$$\text{Ethanol ADH} \xrightarrow[\text{NAD}\rightarrow\text{NADH}]{\text{Alcohol hydrogenase}}$$

$$\text{Acetaldehyde ADH} \xrightarrow[\text{NAD}\rightarrow\text{NADH}]{\text{Alcohol dehydrogenase}}$$

$$\text{Acetyl coenzyme A} \xrightarrow[\text{Cycle}]{\text{Critical acid}} CO_2 + H_2O$$

where NAD is nicotinamide adenine dinucleotide and NADH is reduced nicotinamide adenine dinucleotide.

At least two variations of ADH genes (*ADH1B*2* and *ADH1C*1*) produce a slightly more rapid breakdown of alcohol and therefore potentially faster production of acetaldehyde, which is rapidly metabolized by *ALDH2*. However, about 40% of Asian people (Japanese, Chinese, and Koreans) have an inactive *ALDH2* mutation that results in much higher acetaldehyde levels after drinking than normal. About 10% of people who are homozygous for this gene form cannot drink alcohol without becoming sick and have almost no risk of AUD, whereas those who are heterozygous have a relatively low rate of AUD.

An alternative pathway, the microsomal ethanol-oxidizing system (MEOS), is induced by chronic alcohol exposure. The primary component of the MEOS is the molecule cytochrome P_{450}, which exists in several variants. The variant most important for alcohol metabolism is cytochrome P_{450} 2E1 (CYP2E1). Many effects of alcoholism are produced by the toxic byproducts (hydrogen, acetaldehyde), acceleration of metabolism of other drugs,

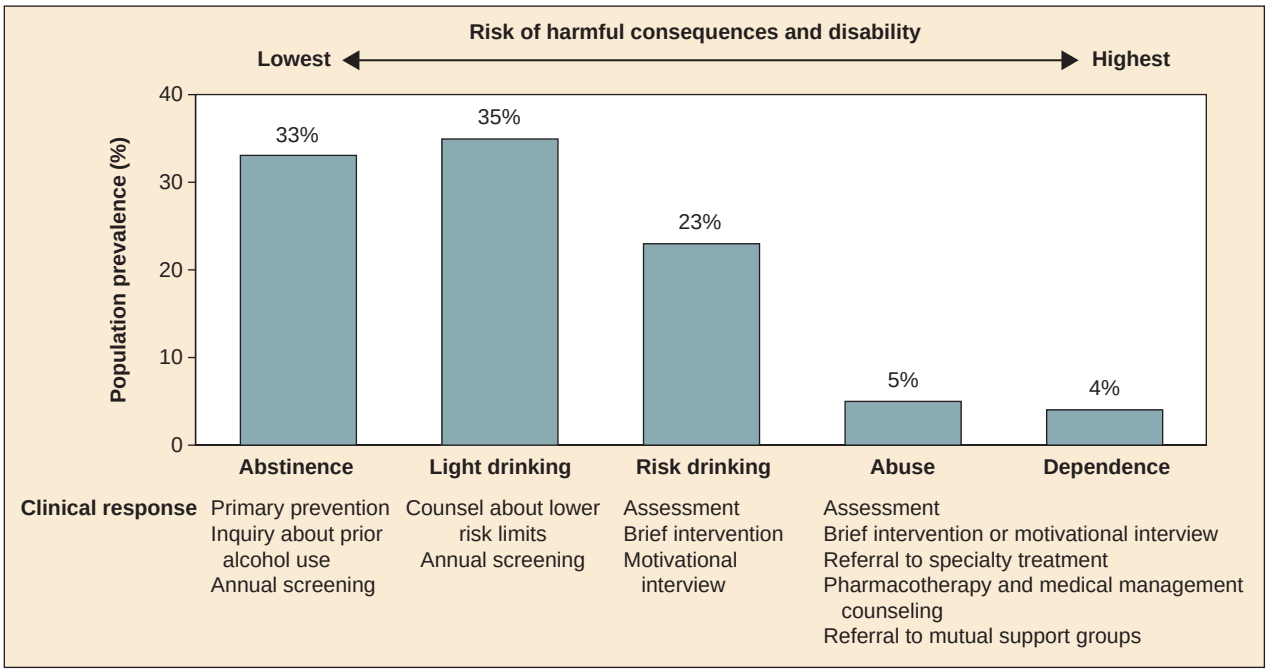


Fig. 142.1. Continuum of risk associated with alcohol use and possible clinical responses. Risk drinking is defined as an average of 15 or more standard drinks/week or 5 or more on occasion for men and 8 or more drinks weekly or 4 or more on occasion for women and people older than 65 years. Persons in remission from an alcohol use disorder remain at risk for recurrent drinking and adverse consequences.

and activation of hepatotoxic compounds by these metabolic pathways.

Although the liver is the major site of ethanol metabolism, other tissues contribute to its metabolism. ADH is found in the gastric mucosa, but the gastric metabolism of alcohol is decreased in women and those of Asian descent. This increased bioavailability of ethanol or decreased first-pass metabolism may explain the greater vulnerability of women to acute and chronic complications of alcohol.

Alcohol metabolism has two elimination rates. The alcohol elimination rate approximates zero-order kinetics (constant rate) for lower ethanol levels and first-order kinetics (amount of drug removed over time is proportional to the concentration of the drug) for higher levels, especially in chronic alcoholics; most likely, through induction of the MEOS pathway, the elimination rate is increased at higher blood levels.

The absorption and elimination rates of alcohol vary by individual and depend on many factors—diet, gender, body weight and habitus, speed of consumption, gastric motility, presence of food in the stomach, smoking history, age, whether the person is a chronic alcohol consumer with enzyme induction and high-activity MEOS, advanced cirrhosis, presence of ascites, and state of nourishment. There is enormous variation among patients in the rate of elimination of ethanol from the blood, ranging from 9 to 36 mg/dL per hour in published data. Although the clearance rate may be as high as 36 mg/dL/hr in some chronic drinkers, 20 mg/dL/hr is a reasonable rate to assume in a typical intoxicated ED patient. This holds true for adults, adolescents, and children, whether they are experienced or inexperienced drinkers.

Physiologic effects vary directly with the blood alcohol level (Table 142.1). Diminished fine motor control and impaired judgment appear with alcohol concentrations as low as 20 mg/dL (0.02 mg%), but wide individual variability exists. Chronic alcoholics can exhibit impressive tolerance. The blood alcohol concentration of a person cannot be accurately determined without quantitative testing. More than 50% of the adult population is obviously intoxicated with a level of 150 mg/dL (0.15 mg%). As the ethanol level rises, the patient's level of consciousness declines, eventually ending in coma. Death is caused by aspiration or respiratory depression.

Alcohol through passive diffusion will be present anywhere there is water in the body. Hence, expired breath alcohol or saliva can be used to obtain a reliable approximation of blood alcohol concentration in a cooperative patient. This value can be used as a rapid screen for alcohol intoxication.

TABLE 142.1

Physiologic Effects and Blood Alcohol Levels

BLOOD ALCOHOL CONCENTRATION (mg/dL)	EFFECTS[a]
20–50	Diminished fine motor control
50–100	Impaired judgment, impaired coordination
100–150	Difficulty with gait and balance
150–250	Lethargy, difficulty sitting upright without assistance
300	Coma in the novice drinker
400	Respiratory depression

[a]These effects are for the occasional drinker. Chronic drinkers can function at much higher alcohol concentrations because of tolerance. On the other hand, patients may become comatose with low levels of alcohol in mixed alcohol-drug overdose.

CLINICAL FEATURES

Alcohol Withdrawal Syndrome

The neurophysiology of alcohol withdrawal is complex and not fully understood. The hallmark of alcohol withdrawal is central

BOX 142.1

Dsm-V Criteria for Withdrawal Delirium (Delirium Tremens)

CRITERIA FOR ALCOHOL WITHDRAWAL

Cessation of or reduction in heavy and prolonged use of alcohol

At least two of eight possible symptoms after reduced use of alcohol:

- Autonomic hyperactivity
- Hand tremor
- Insomnia
- Nausea or vomiting
- Transient hallucinations or illusions
- Psychomotor agitation
- Anxiety
- Generalized tonic-clonic seizures

CRITERIA FOR DELIRIUM

Decreased attention and awareness

Disturbance in attention, awareness, memory, orientation, language, visuospatial ability, perception, or all these abilities that is a change from the normal level and fluctuates in severity during the day

Disturbances in memory, orientation, language, visuospatial ability, or perception

No evidence of coma or other evolving neurocognitive disorders

From American Psychiatric Association: Diagnostic and statistical manual of mental disorders, ed 5 (DSM-5), Washington DC, 2013, American Psychiatric Publishing.

TABLE 142.2

Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

COMPONENTS OF SCALE	MOST SEVERE MANIFESTATIONS
Nine items[a]	
• Nausea or vomiting	Constant nausea with vomiting
• Tremor	Severe tremor, even with arms extended
• Paroxysmal sweats	Drenching sweats
• Anxiety	Acute panic
• Tactile disturbances (eg, itching, numbness, sensation of bugs crawling on or under the skin)	Continuous hallucinations
• Auditory disturbances (eg, sensitivity to sound, hearing things that are not there)	Continuous hallucinations
• Visual disturbances (eg, sensitivity to brightness and color, seeing things that are not there)	Continuous hallucinations
• Headache, sensation of a band around the head	Extremely severe headache
• Agitation	Pacing during most of interview with clinician or thrashing about
One item—orientation and clouding of sensorium[b]	

[a]Scored on a scale ranging from 0 (no symptoms) to 7 (most severe symptoms).
[b]Scored on a scale ranging from 0 (no symptoms) to 4 (disoriented with respect to place or person).
Adapted from Sullivan JT, Sykora K, Schneiderman, J, et al: Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). Br J Addiction 84:1353–1357, 1989.

nervous system (CNS) excitation, with increased cerebrospinal fluid, plasma, and urinary catecholamine levels.

Alcohol withdrawal syndrome (AWS) is a continuum of syndromes that begins after a decrease in the amount of intake of ethanol. AWS is often divided into three sets of symptoms. The first set consists of autonomic hyperactivity, which appears within hours of the last drink and usually peaks within 24 hours. Common presenting characteristics include trembling, sweating, nausea, vomiting, anxiety, and agitation. The second symptom set includes additional neuronal excitation, with epileptiform seizures and global confusion, usually occurring within 24 to 48 hours of abstinence. The third feature set comprises delirium tremens or alcohol withdrawal delirium (AWD), with auditory and visual hallucinations, confusion and disorientation, clouding of consciousness, impaired attention, and pronounced autonomic hyperactivity.[8] The criteria for withdrawal delirium, as described in Box 142.1, are delirium and alcohol withdrawal.[6] Emergency clinicians should be familiar with a commonly used withdrawal rating instrument known as the Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar).[6] See Table 142.2.

Alcohol-Related Seizures

Among the many medical problems related to alcohol abuse, the differential diagnosis and management of seizures remain among the most challenging and controversial (Box 142.2). Patients presenting to the ED with seizures should be questioned about alcohol intake. Of seizure patients presenting to an ED, 20% to 40% will have their seizures related to alcohol use or abuse. Alcohol is a causative factor in 12% to 24% of patients with status epilepticus. In states where alcohol sales are restricted on Sundays, EDs see a spike in alcohol-related seizures on Mondays.

The primary consideration in the initial care of seizure patients who use alcohol is the recognition of treatable, life-threatening causes. These causes include but are not limited to CNS infection, metabolic disorders, and intracranial hemorrhage. Alcohol may act in one of several ways to produce seizures in patients with or without underlying foci—by its partial or absolute withdrawal after a period of chronic intake, by an acute alcohol-related metabolic disorder (eg, hypoglycemia, hyponatremia), creation of a situation leading to cerebral trauma, precipitation of seizures in patients with idiopathic or post-traumatic epilepsy, or lowering

BOX 142.2

Differential Diagnosis of Alcohol-Related Seizures

Withdrawal (alcohol or drugs)
Exacerbation of idiopathic or posttraumatic seizures
Acute intoxication (eg, amphetamines, anticholinergics, cocaine, isoniazid, organophosphates, phenothiazines, tricyclic antidepressants, salicylates, lithium)
Metabolic (eg, hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hepatic failure)
Infectious (eg, meningitis, encephalitis, brain abscess)
Trauma (eg, intracranial hemorrhage)
Cerebrovascular accident
Sleep deprivation
Noncompliance with anticonvulsants

of the seizure threshold in patients with prior existing intracerebral disease states. Moreover, alcoholics are more susceptible to other disorders associated with seizures, including neurosyphilis, acquired immunodeficiency syndrome (AIDS), brain abscess, and meningitis.

Alcohol Withdrawal Seizures

Seizures occur 6 to 48 hours after the cessation of drinking. Of patients with seizures, 90% have one to six generalized tonic-clonic seizures; 60% experience multiple seizures within a 6-hour period. The incidence of partial seizures, common with posttraumatic epilepsy, is increased in alcohol withdrawal. The term *alcohol withdrawal seizure* is reserved for seizures with these characteristics. The term *alcohol-related seizure* is used to refer to all seizures in the aggregate associated with alcohol use, including this subset of alcohol withdrawal seizure.

Cardiovascular Effects

Acute and chronic ethanol consumption can affect the mechanical function of the heart, produce dysrhythmias, and exacerbate coronary artery disease (CAD). It may alter myocardial function by direct toxic effects, by associated hypertension, or indirectly by altering specific electrolytes. Acute intoxication can decrease cardiac output in alcoholic and nonalcoholic patients with preexisting cardiac disease.

Studies have linked moderate alcohol consumption (two to four drinks/day in men and one or two/day in women) to a protective effect from CAD. Low to moderate alcohol consumption decreases platelet aggregation, raises plasma levels of endogenous tissue plasminogen activator, and lowers insulin resistance.

Studies have suggested that moderate alcohol consumption, through a reduced risk of CAD, may also protect individuals from congestive heart failure. All these beneficial effects are lost in heavy drinkers, in whom chronic alcoholism is associated with hypertension and congestive cardiomyopathy.

Heavy alcohol consumption has a detrimental effect on those with preexisting CAD. It can reduce exercise tolerance, induce coronary vasoconstriction, and raise heart rate and blood pressure. Additive cardiovascular effects of ethanol and nicotine contribute to dysrhythmias and sudden death in patients with CAD. There is an increased incidence of sudden death among heavy drinkers, regardless of concomitant CAD or smoking.

Supraventricular (usually atrial fibrillation) and ventricular (usually transitory ventricular tachycardia) dysrhythmias, labeled holiday heart, have been documented in alcoholic patients who have been drinking heavily. Tachydysrhythmias as a result of episodic drinking commonly revert to sinus rhythm with abstinence and do not require immediate intervention if the patient is hemodynamically stable.

Pulmonary Effects

Alcohol reduces the mobilization of alveolar macrophages and their bactericidal capacity. Their impairment is greatest in alcoholics with hepatic cirrhosis. There is evidence that chronic alcohol consumption decreases the level of glutathione, promoting inflammation and remodeling of the lung tissue. These effects, along with aspiration, decreased airway sensitivity, concomitant smoking, and malnutrition, probably account for the increased incidence of pneumonia, particularly lobar pneumonia, among alcoholic patients.

The high prevalence of respiratory disease in alcoholics is largely caused by smoking. Alcohol induces bronchospasm in some asthmatics and increases ventricular ectopy and sleep apnea in patients with chronic obstructive pulmonary disease.

Gastrointestinal and Hepatic Effects

Esophagus and Stomach

Alcoholic patients have a higher incidence of esophagitis, gastric cancer, and esophageal carcinoma than that in the general population. Acute alcohol ingestion also decreases lower esophageal sphincter pressure, delays gastric emptying, and disrupts the normal gastric mucosal barrier. Alcohol consumption, because of its inherent toxicity, has been shown to eliminate infection of the gastric mucosa by *Helicobacter pylori*.[5] Forceful or persistent emesis can lead to a Mallory-Weiss tear or Boerhaave's syndrome.

Gastrointestinal Bleeding

Alcohol is closely associated with gastrointestinal (GI) bleeding. Causes and contributing factors include Mallory-Weiss tears, esophagitis, esophageal varices, acute and chronic gastritis, thrombocytopenia, portal hypertensive gastropathy, qualitative and quantitative platelet disorders, and prolonged clotting times. Alcohol may exacerbate gastric mucosal damage when it is combined with nonsteroidal antiinflammatory drugs (NSAIDs), but ethanol itself is not a risk factor for peptic ulcer disease. Peptic ulcer disease is the most common cause of bleeding in alcoholic patients with upper GI hemorrhage, as well as in those who do not drink.

Liver Damage

Hepatic damage has been recognized for centuries as the hallmark of chronic alcohol abuse. The activation of the immune system with the production of cytokines such as tumor necrosis factor alpha is one of the earliest events in many types of liver injury. This cascade stimulates Kupffer cells and the production of other cytokines that together enlist inflammatory cells, kill hepatocytes, and initiate healing through fibrogenesis. There is no single test that can be used to diagnose alcoholic liver disease reliably. However, a ratio of aspartate transaminase (AST) to alanine transaminase (ALT) higher than 2 suggests that alcohol is the cause of liver injury. Alcoholic liver disease is the most common liver disorder in the West and, along with hepatitis C, is a leading cause of liver transplantation.

Alcoholic Hepatitis

Alcoholic hepatitis is more serious than fatty infiltration and develops in up to 35% of heavy drinkers. These individuals usually have right upper quadrant pain, a tender enlarged liver, fever, jaundice, leukocytosis, and altered liver function test results. AST levels are usually less than 400 IU/L, and ALT levels are typically less than half the AST level. Alcoholic hepatitis has a range of clinical manifestations, from mildly symptomatic hepatomegaly to fulminant hepatic failure. The severity of the disease can be estimated in the ED by a prolonged prothrombin time/international normalized ratio (INR) or with the use of the Maddrey discriminant factor. The ABIC (***a***ge, ***b***ilirubin, I***N***R, ***c***reatinine) score and model for end-stage liver disease (MELD) are also helpful in predicting mortality in these patients.

Alcoholic Cirrhosis

Cirrhosis is the disruption of the normal architecture of the liver by scarring and regenerating nodules of parenchyma. Alcoholism is the most common cause of cirrhosis in the United States and is responsible for approximately 50% of all cirrhotic deaths. Alcoholic cirrhosis usually requires 10 to 15 years of chronic drinking,

often punctuated by one or more episodes of acute alcoholic hepatitis. The clinical outcome is determined by the development of complications of portal hypertension and by hepatic dysfunction. It is unknown why hepatic damage develops in some alcoholic patients and not in others exposed to identical amounts of alcohol. The disorder was originally described as nutritional cirrhosis, but it has been shown that alcohol, independent of malnutrition, produces the liver damage. Alteration of the normal hepatic architecture by fibrosis and nodule formation may eventually lead to portal hypertension. Portal hypertension may be complicated by ascites and esophageal varices. Although cirrhosis is irreversible, its progression may be halted with abstinence.

No specific medical therapy exists for alcoholic liver disease other than abstinence, proper diet, and management of the subsequent hepatic decompensation (ie, ascites, encephalopathy). A decrease in the amount of alcohol consumed during 1 year is associated with a 60% decrease in mortality.

Pancreatitis and Malabsorption

The association of ethanol with acute and chronic pancreatitis is well established, but the exact pathogenesis is unclear. Hypotheses include reflux of duodenal contents and bile into the pancreatic duct, obstruction by a plug of pancreatic juice rich in proteins, and a direct toxic effect of ethanol.

The diagnosis of alcoholic pancreatitis can be difficult because asymptomatic alcoholics may have an elevated amylase level. Conversely, up to 30% of patients with acute alcoholic pancreatitis have an amylase value within normal limits. The serum lipase level rises after amylase, remains elevated longer, and is a more reliable indicator of alcoholic pancreatitis, especially when it is more than three times normal. Alcohol is the leading cause of chronic pancreatitis.

Diarrhea and impaired intestinal absorption are common problems of the chronic alcoholic. Alcohol increases small intestine transit time and decreases brush border enzyme activity. Thiamine, vitamin B_{12}, amino acids, folic acid, and glucose have impaired absorption in alcoholics. Dietary deficiencies in folic acid and protein, pancreatic insufficiency, abnormal biliary secretion, and direct toxic effects of ethanol on the GI tract contribute to malabsorption. Abstinence and adequate nutrition reverse the diarrhea and much of the malabsorption.

Neurologic Effects

Neuropathy

A symmetric sensorimotor polyneuropathy is common with chronic alcohol abuse, usually in the lower extremities. It is thought to be a combination of nutritional deficiency with thiamine or vitamin B_{12} deficit and a direct neurotoxic effect of alcohol. Burning pain and paresthesia are common complaints. Findings on physical examination include loss of light touch, decreased pinprick sensation, and reduced lower extremity deep tendon reflexes. Distal muscle weakness is a late finding. The neuropathy may lead to nonhealing ulcers on the feet. Treatment of alcoholic neuropathy is abstinence, adequate diet, and thiamine. Complete recovery is rare.

So-called Saturday night palsy or honeymooner's syndrome is a wrist drop caused by radial nerve compression. The patient usually has spent the night with his or her arm drooped over the back of a chair, bench, or companion, compressing the radial nerve against the humerus and producing a neurapraxia. Loss of function due to radial nerve neurapraxia usually returns after a few weeks to months.

Wernicke-Korsakoff Syndrome

Although they are similar pathologically and are caused by thiamine deficiency, Wernicke and Korsakoff syndromes are clinically distinct. Wernicke's encephalopathy, a medical emergency with a mortality rate of 10% to 20%, remains a clinical diagnosis and is often unrecognized. Contemporary criteria require two of these signs—dietary deficiencies, oculomotor abnormalities (nystagmus is most common), cerebellar dysfunction, and an altered mental state or mild memory impairment. Mental abnormalities include lethargy, inattentiveness, abulia, and impaired memory, progressing without treatment to coma.

Korsakoff's psychosis or amnesic state, also called alcohol-induced persisting amnestic disorder, is a disorder with recent memory impairment, inability to learn new information or recall previously learned information, apathy, and confabulation. Although it is common, confabulation is not essential for the diagnosis. Whereas 80% of patients with acute Wernicke's encephalopathy have Korsakoff's syndrome, age older than 40 years and many years of heavy alcohol use are additional risk factors.

Treatment of Wernicke-Korsakoff syndrome consists of abstinence, adequate diet, and thiamine. The ophthalmoplegia and nystagmus usually have a good response to thiamine within hours to days. The ataxia and mental changes may take days to weeks to improve and usually have a poorer prognosis. Less than 25% of patients show any real recovery, 50% show some recovery, and the remainder show no response, despite adequate thiamine replacement. Because magnesium is a cofactor for this enzyme system, its serum levels should be corrected. Patients with Wernicke's syndrome require admission and thiamine and magnesium repletion.

Movement Disorders

Alcohol withdrawal is associated with tremor, ataxia, and myoclonus. Acute alcohol consumption ameliorates essential tremor and myoclonus. Persistent tremor is occasionally seen in chronic alcoholism. This alcoholic tremor may persist up to 1 year after abstinence. Although the pathophysiologic mechanism is poorly understood, studies have confirmed that essential tremor and alcoholic tremor are distinct entities.

Alcoholic Cerebellar Degeneration

Characterized by ataxia of the extremities, cerebellar ataxia of alcoholism results in a wide-based stance and uncoordinated gait. Lower extremity involvement predominates, although the arms may rarely be involved. Pathologic changes consist of degeneration of elements in the cerebellum, especially the Purkinje cells. The diagnosis is based on history, physical examination, and findings on magnetic resonance imaging or computed tomography (CT), which shows severe cerebellar atrophy. Treatment consists of abstinence, adequate nutrition, and thiamine.

Infectious Disease

Chronic alcohol abuse causes immunosuppression. Neutropenia may be found in up to 8% of hospitalized alcoholics. Alcohol ingestion prevents the normal delivery (chemotaxis) of polymorphonuclear neutrophils to sites of bacterial infection. Chronic alcohol exposure depresses the development and expression of cell-mediated immunity. This depression may contribute to the high incidence of tuberculosis and head, neck, and upper GI cancers in alcoholics. The suppression of macrophage function by alcohol reduces the reticuloendothelial system's ability to clear particles. This may contribute to spontaneous bacteremia, spontaneous bacterial peritonitis, and pneumonia. Primary antibody

response to new antigens is also depressed. Malnutrition and liver failure also contribute to an immunocompromised state in the alcoholic.

The most common infection in alcoholism is pneumonia. Associated risk factors for pneumonia in alcoholics include smoking, decreased ciliary function, decreased surfactant production, depressed cough reflex, malnutrition, and poor oral hygiene. Although alcoholic patients may contract a variety of bacterial pneumonias, *Streptococcus pneumoniae* is still the most common organism. Periods of alcoholic stupor with incomplete glottic closure and subsequent aspiration can lead to aspiration pneumonia or lung abscess. *Klebsiella pneumoniae,* classically associated with alcoholism, is currently more common in patients with cytotoxic chemotherapy, hematologic malignant disease, and transplantation than in the chronic alcoholic. In addition, these infections now tend to be nosocomial rather than community-acquired.

Endocrine Effects

Alcohol dependence adversely affects many endocrine systems. Peripheral thyroid hormone dysfunction and central hypothalamic-pituitary-thyroid axis deregulation are seen. Male hypogonadism and feminism are seen in chronic male alcoholics. Alcohol's effects on the testes and hypothalamus decrease testosterone production in men. Alcohol may cause impotence by CNS sedation, secondary depression, or decreased testosterone production. Decreased testosterone, increased estrogen (in patients with liver disease), and increased prolactin levels can lead to decreased libido, feminization, and gynecomastia in male alcoholics and to abnormalities in lactation and menstruation in women. In female alcoholics, increased levels of testosterone and estrogen are found. Estrogen replacement therapy may increase hormonal levels threefold and thus increase the risk of cholelithiasis and breast cancer.

Metabolic Effects

Carbohydrates

Alcohol-induced hypoglycemia occurs in 1% to 4% of intoxicated ED patients. It is more frequently seen in chronic alcoholics. Coma, seizures, hemiparesis, and a variety of other neurologic signs have been described in patients presenting with alcohol-induced hypoglycemia. Starvation, depletion of liver glycogen stores, decreased plasma cortisol levels, impaired release of growth hormone, and inhibition of gluconeogenesis contribute to this phenomenon.

Hyperglycemia and diabetes may be found in chronic alcoholism. Alcohol abuse can lead to chronic pancreatitis, resulting in underproduction of insulin by the damaged pancreatic cells. Alcohol also impairs peripheral glucose utilization, causing a relative insulin resistance (similar to type 2 diabetes). In diabetic patients, alcohol can induce hypoglycemia and also mask the signs of hypoglycemia.

Lipids

A reversible hypertriglyceridemia occurs in many chronic alcoholics. Ethanol increases hepatic synthesis of triglycerides. Abstinence is necessary to reduce elevated triglyceride levels. Except for its relationship to fatty infiltration of the liver, the clinical significance of this hyperlipidemia is unknown.

Electrolytes

Ethanol has numerous effects on electrolytes and mineral metabolism, as summarized in Table 142.3. Hyponatremia and hypokalemia are common in active drinkers. Vomiting, diarrhea, magnesium depletion, malnutrition, and metabolic alkalosis contribute to these abnormalities.

TABLE 142.3

Effect of Ethanol on Mineral Metabolism

MINERAL	CAUSE OF DEPLETION	ADDITIONAL EFFECT OF COMPARTMENT SHIFTS	CONSEQUENCES
Magnesium	Alcohol diarrhea Poor intake Phosphate depletion Hyperaldosteronism	↓ Hyperventilation ↓ Free fatty acids	Pseudohypoparathyroidism Myopathy Potassium depletion Phosphate depletion Electrocardiographic abnormalities Seizures
Phosphorus	Poor intake Diarrhea Metabolic alkalosis Hypomagnesemia	↓ Metabolic alkalosis ↓ Respiratory alkalosis ↓ Glucose (refeeding) ↑ Hypoparathyroidism (secondary to hypomagnesemia) ↑ Rhabdomyolysis	Rhabdomyolysis Platelet dysfunction White blood cell dysfunction Central nervous system dysfunction Cardiac failure Renal tubular acidosis
Calcium	Poor intake Steatorrhea Hypovitaminosis K	↓ Hypoparathyroidism (secondary to hypomagnesemia) ↓ Rhabdomyolysis ↓ Hypovitaminosis D ↓ Hyperphosphatemia ↓ Pancreatitis ↓ Hypoalbuminemia ↑ Recovery from rhabdomyolysis	Tetany Seizures
Potassium	Poor intake Metabolic alkalosis Hyperaldosteronism Diarrhea	↓ Glucose (refeeding) ↓ Hyperventilation ↑ Rhabdomyolysis	Weakness Paralysis Myopathy Sudden death

↑, Into plasma; ↓, out of plasma.

Alcoholism is the most common cause of severe magnesium deficiency in adult outpatients. Magnesium deficiency is seen in 30% of alcoholics as a result of malabsorption, malnutrition, diarrhea, vomiting, and increased urinary losses. Oral magnesium supplementation in chronic alcoholics improves liver function test findings, electrolyte balance, and muscle strength. Multivitamin preparations may be considered for chronic malnutrition. Although their clinical benefit is not proved, they carry no significant risk or cost.

Hypocalcemia is common in alcoholic patients with magnesium depletion. The mechanism is related to diminished parathyroid hormone secretion, decreased tissue responsiveness to parathyroid hormone, decreased vitamin D metabolism, and decreased calcium release from bone, independent of parathyroid hormone. Correction of magnesium depletion is necessary to restore calcium to normal levels. Hypoalbuminemia, pancreatitis, or vitamin D deficiency also contribute to low serum calcium levels or low total body stores of calcium in alcoholic patients.

Hypophosphatemia is found in 30% to 50% of hospitalized patients with alcoholism. Phosphorus depletion results from malnutrition, vomiting, respiratory alkalosis, diarrhea, enhanced release of calcitonin, phosphate-binding antacids, and urinary loss (related to vitamin D deficiency and secondary hyperparathyroidism). Hypophosphatemic patients often have low magnesium levels. Rehydration, carbohydrate repletion, and parenteral alimentation further exacerbate phosphorus depletion. Glucose bolus and infusion have been shown to produce a significant fall in serum inorganic phosphate levels. Severe hypophosphatemia (<1 mg/dL) has been associated with acute respiratory failure, myocardial depression, dysfunction of erythrocytes, leukocytes, and platelets, CNS irritability, and rhabdomyolysis.

Although chronic alcoholics requiring admission often have potassium, magnesium, and phosphate depletion, empirical treatment with potassium and phosphate is discouraged. Serum levels and renal function should be determined. Unintended hyperkalemia and hyperphosphatemia can produce significant morbidity, and phosphate infusion exacerbates hypocalcemia, if present. Because most magnesium is intracellular, a normal serum magnesium level does not rule out decreased total body magnesium stores. If the serum level is normal, total body levels may still be low. As long as renal function is adequate, empirical magnesium treatment can be considered. Abstinence and a proper diet resolve electrolyte and nutritional deficiencies in the ambulatory alcoholic patient who is healthy enough to be treated as an outpatient.

Alcoholic Ketoacidosis

Alcoholic ketoacidosis occurs most frequently in severe chronic alcoholics who have had a recent binge followed 1 to 3 days later by protracted vomiting, decreased food intake, dehydration, and abstinence. Nausea, vomiting, and abdominal pain are common presenting complaints. These patients have tachypnea, dehydration, ketonuria, and little or no glucosuria. Serum glucose levels are usually less than 200 mg/dL. Normal blood pH may be found despite ketonemia because of coexisting respiratory alkalosis and metabolic alkalosis.

The exact mechanism responsible for the increase in ketone bodies is unclear. Acute starvation superimposed on chronic malnutrition, as well as release of an alcohol-induced block in ketogenesis, allowing marked ketosis, may explain the disorder. An increased ratio of NADH to NAD in the alcoholic predisposes to the accumulation of β-hydroxybutyrate and the inhibition of gluconeogenesis, which may underlie the common occurrence of hypoglycemia in alcoholic ketoacidosis.

The alcoholic patient with metabolic acidosis presents an interesting dilemma because most of these patients have an increased anion gap acidosis. Glucosuria may suggest diabetes, crystalluria can be seen in ethylene glycol poisoning, low specific gravity, proteinuria, and casts can be seen in renal failure, leukocytes and bacteria are present with urosepsis, and significant ketones in an otherwise normal urine may indicate starvation or alcoholic ketosis. Elevated levels or a very high osmolal gap (>25 mOsm/kg) is specific for methanol or ethylene glycol ingestion.

Treatment of alcoholic ketosis consists of the administration of normal saline, glucose, and thiamine and correction of hypokalemia. This can be accomplished with 5% dextrose in normal saline and 30 mEq of potassium chloride or 30 mEq of oral potassium. If no serious complicating illness is present, the ketosis is reversed in 12 to 24 hours with this treatment.

Hematologic Effects

The alcoholic presents with myriad hematologic abnormalities. The direct toxic effect of ethanol and its metabolites, secondary nutritional deficiency, and hepatic disease, individually or in combination, affect red blood cells, white blood cells, platelets, hemostasis, and the immune system. Macrocytosis is the most common hematologic manifestation of the chronic alcoholic. It may be caused by folate deficiency, reticulocytosis (the younger reticulocytes are larger), liver disease (producing an abnormal lipid coating of the red blood cell membrane), or vitamin B_{12} deficiency. The most common condition is idiopathic macrocytosis of alcoholism.

Anemia

Several mechanisms cause anemia, which is common in the alcoholic. Megaloblastic anemia resulting from folate deficiency is the most common anemia in alcoholics. The mean corpuscular volume (MCV) is typically increased but may be normal when iron deficiency coexists. Malnutrition, inability of the cirrhotic liver to store folate, excessive urinary loss, and malabsorption decrease folate stores. Alcohol accelerates the development of megaloblastic anemia in individuals with depleted folate stores (MCV > 100 fL) by a less clearly defined mechanism.

Iron deficiency anemia is common and is usually a result of blood loss from the GI tract. With iron deficiency anemia, the serum iron level is decreased, total serum iron-binding capacity is elevated, and serum ferritin level is decreased. Alcoholics frequently have chronic inflammatory diseases such as endocarditis, tuberculosis, empyema, lung abscess, malignant disease, and hepatic disease. These illnesses can produce the anemia of chronic disease, a mild microcytic or normocytic anemia in which the serum iron is low but, in contrast to iron deficiency, the total serum iron-binding capacity is low or low-normal, and the serum ferritin level is increased.

Ethanol also has a direct toxic effect on erythropoiesis. Bone marrow biopsies reveal vacuolization of erythroid precursors, resulting in decreased reticulocytosis and a reversible sideroblastic anemia. Sideroblastic anemia, which is usually seen in the presence of malnutrition with pyridoxine deficiency and folate deficiency, occurs in 25% to 30% of anemic alcoholics.

Leukocyte Abnormalities

Leukopenia is common in the alcoholic patient and has several possible causes. Sepsis, folate deficiency, and hypersplenism all lead to a decreased white blood cell count. Alcohol has a direct toxic effect on white blood cell production in the bone marrow. Granulocyte mobilization (chemotaxis) and adherence are also impaired, resulting in a decreased inflammatory response.

Platelet Disorders

Thrombocytopenia can occur with folate deficiency, marrow suppression, sepsis, disseminated intravascular coagulation, or splenic sequestration. The direct toxic effects of alcohol decrease measured survival time and impair production of platelets in the bone marrow, but marrow toxicity will rarely reduce the platelet count below 30,000/mm^3. Qualitative platelet function is also impaired. Binge drinking is associated with a reactive thrombocytosis potentially responsible for acute stroke and sudden death.

Hemostasis

Alcoholic patients have a bleeding diathesis for many reasons, including thrombocytopenia, qualitative platelet disorders, deficient production of hepatic clotting factors, GI variceal formation, and vitamin K deficiency. A complete blood count, peripheral smear, platelet count, reticulocyte count, thrombin time, prothrombin time and INR, and partial thromboplastin time help evaluate episodes of significant bleeding. Bleeding associated with coagulation abnormalities may require fresh-frozen plasma for the immediate correction of coagulation factor depletion; vitamin K (10 mg IV) takes 6 to 10 hours to reverse the vitamin K–dependent factors II, VII, IX, and X. Because of poor diet and impaired hepatobiliary function, alcoholics may have insufficient vitamin K storage and benefit from vitamin K delivery. However, alcoholic patients with profound liver failure are unable to produce the precoagulation factors II, VII, IX, X, and IV, so vitamin K therapy is futile. Platelet transfusions should be started in the ED for adult patients with active bleeding when the platelet count is less than 50,000/mm^3.

Oncologic Effects

Worldwide, 389,000 annual cases of cancer representing 3.6% of all cancers are alcohol-related.[10,11] Although alcohol itself is not carcinogenic, its metabolite, acetaldehyde, has emerged as an important contributor; it can form stable DNA adducts, trigger mutations in tumor suppressors and oncogenes, and interfere with DNA repair. Smoking certainly has an additional role as a cause of neoplasia and is difficult to isolate in these studies.

Chronic alcohol use is associated with an increased incidence of upper alimentary and respiratory tract cancers, with a clear dose-response relationship. Specifically, alcohol increases the risk of cancer of the mouth, pharynx, larynx, lung, esophagus, liver, and pancreas.[12] Chronic hepatitis B infection may sensitize the liver to alcohol, producing hepatocellular carcinoma. Women who drink two to five drinks/day have a relative risk of 1.41 for invasive breast cancer compared with nondrinkers. There is also a significant increase in endometrial cancer risk among postmenopausal women who consume more than two alcoholic drinks/day. Moderate alcohol consumption leads to an increased risk of colorectal and prostate cancer.

Hypothermia

Acute alcohol ingestion is one of the most common precipitating factors for accidental hypothermia and occurs in 33% to 73% of patients presenting with a core temperature below 35°C (95°F). Alcohol exacerbates hypothermia of other causes, with depressed hypothalamic thermoregulation, peripheral vasodilation producing heat loss, CNS depression, sepsis, inability to shiver, hypoglycemia, and increased risk of environmental exposure. Hypothermia may be the presentation of Wernicke's syndrome, possibly caused by lesions of the posterior hypothalamus, hypoglycemia, or sepsis. Intoxicated patients may have slower rewarming rates.

Psychiatric Effects

Of alcohol-dependent adults, 45% are diagnosed with one or more additional psychiatric conditions during their lifetime. Of alcoholic men admitted to a psychiatric ward, approximately 40% have another psychiatric disorder unrelated to substance abuse—in particular, antisocial personality disorder, schizophrenia, mood disorders, and anxiety disorders.

Depression and antisocial personality are the two most common psychiatric disorders that correlate with alcoholism, with a prevalence of 30% to 60% in most studies. Chronic alcohol use can produce an imbalance in the serotoninergic system. This imbalance may lead to increased anxiety, aggression, and depression. Interestingly, behavior is more strongly linked to depression than to alcohol dependence. Secondary depression may be caused by alcoholism, or the primary affective disorder may be present with secondary alcoholism. Mild depressive symptoms are also common in alcohol withdrawal. Antisocial individuals are at high risk for alcoholism and drug dependence, although an unstable, unhappy childhood environment appears to be more important than alcohol to the development of sociopathy. Alcohol increases the lifetime risk of suicide, with 17% of all alcoholics eventually dying by suicide. Alcoholism, major depression, and antisocial personality all predispose to suicide, and interaction among the three is particularly dangerous, but the acute risk on any particular day is difficult to assess.

Toxicologic Effects

Alcohol has long been known to have additive or even synergistic effects with several drugs. Acute intoxication decreases the rate of drug metabolism, which is at least partially explained by competition for the same enzymatic process in the liver. When cocaine and ethanol are taken concomitantly, the unique metabolite, cocaethylene, is a neurologically active compound that is significantly more toxic than cocaine to the heart, liver, and brain and more addicting and more lethal than cocaine alone. Cocaethylene produces a higher incidence of confusion, lower mean Glasgow Coma Scale (GCS) scores, a higher incidence of violent trauma and more often requires endotracheal intubation. Hemodynamically, these patients demonstrate an elevated heart rate (1.5–5 times normal) and higher blood pressure than with either drug alone. Sudden death is increased up to 25-fold above that associated with the use of cocaine alone. Plasma levels of cocaine in this combined group were higher than in those who used cocaine alone.

Ethanol increases aspirin-induced prolongation of bleeding time and reduces the metabolism of warfarin, leading to increased anticoagulant effects. There is an increased risk of upper GI bleeding when alcohol is combined with NSAIDs. This may be the most dangerous additive or synergistic effect of alcohol.

Disulfiram and Similar Reactions

Most patients pretreated with disulfiram (Antabuse) who then consume even small amounts of alcohol experience an extremely unpleasant reaction. These patients have a hypersensitivity to ethanol and experience a direct response within 15 minutes, lasting 30 minutes to several hours. The reaction consists of skin flushing on the head that spreads to the trunk, along with nausea, vomiting, headache, chest and abdominal discomfort, diaphoresis, vertigo, palpitations, and confusion. A severe reaction may produce hypotension, seizures, and dysrhythmias. The disulfiram-ethanol reaction is thought to occur by the accumulation of acetaldehyde secondary to inhibition of the aldehyde dehydrogenase enzyme, which may be deficient in many Asians, or another unknown toxic factor. This incapacitating reaction has been used to discourage chronic alcohol ingestion. Treatment for disulfiram

reaction is usually just observation, an antiemetic for symptoms, and intravenous (IV) fluids.

Profound hypoglycemia can occur when alcohol and oral hypoglycemic agents are combined. Patients taking metformin may have an increased risk for the development of lactic acidosis when it is combined with heavy drinking. A disulfiram-ethanol–like reaction has been described with many hypoglycemic agents.

Other Considerations

Patient Groups Affected

Adolescents. Alcohol is a common drug of abuse among adolescents and young adults. It is estimated that at least 50% of adolescents 12 to 20 years old have imbibed alcohol during any 30-day period. Alcohol is often associated with the three leading causes of death among youth—unintentional injury, homicide, and suicide.

Adolescent drinking is associated with many negative consequences, including deleterious effects on neurocognitive and hormonal development and cognitive and emotional abilities. Social conflicts, delinquency, and problems of academic adjustment are often associated with repeated episodes of heavy drinking, which also put youth at risk for the chronification of problematic substance use patterns into adulthood.[13]

Older Patients. Unhealthy drinking is found in up to 15% of older ED patients (>65 years). It has been estimated that 50% of older people drink alcohol, and 2% to 4% meet the criteria for alcohol abuse or dependence. Common screening tests (eg, the CAGE questionnaire) tend to be less sensitive in this age group. Alcohol may exacerbate underlying disease by masking anginal chest pain, worsening hypertension, and inducing dysrhythmias. However, older adults who consume low to moderate levels of alcohol may have a decreased risk for the development of dementia and heart failure. More than 90% of people aged 65 years or older use more than one prescribed medication. Aging alters GI absorption, lowers volume of distribution, diminishes homeostatic responses, and reduces renal and hepatic function. Older adults also demonstrate increased end-organ sensitivity, particularly involving the CNS, with concomitant drug use increasing their risk for alcohol and drug interactions.

Older patients are more likely to have neuropsychiatric complications of alcoholism, such as sleep problems, anxiety, depression, and dementia. Alcohol is involved in one third of suicides in older adults. Older subjects also perform less well than younger subjects on tests of perception and attention at all blood alcohol levels. This may result in an increased risk of fractures from falling and osteoporosis. However, evidence has suggested that compared with abstinence, consumption of up to one drink/day is associated with a decreased risk of osteoporotic hip fracture, and there is a beneficial effect of moderate alcohol consumption on bone density.

Pregnant Women. Many scientific reports confirm alcohol's teratogenic effects. According to the National Institute on Drug Abuse, nearly 20% of all children born in the United States have been exposed to alcohol during gestation. Pregnant women who report the use of any alcohol, binge drinking, or frequent drinking are more likely to be older than 30 years, employed, and unmarried.

Fetal alcohol syndrome is characterized by a triad of CNS defects, including mild to moderate mental retardation, dysmorphology, involving mostly facial structures, and growth deficiencies, usually consisting of short stature and microcephaly. Fetal alcohol syndrome is now considered the most common identifiable source of mental retardation. Children exposed to prenatal alcohol exhibit increased activity levels, cognitive and attention deficits, perseverative behavior, and language and motor problems, which persist into adulthood.

Ethanol rapidly diffuses across the placenta and is distributed to all fetal tissue, with a predilection for gray matter. Although infants of mothers who drink heavily have the poorest outcome, children of mothers who consume only two or three alcoholic drinks/day also display abnormalities. Even in the absence of growth retardation or congenital abnormalities, children born to women who consume excessive alcohol during pregnancy appear to be at increased risk for attention deficit disorders. These findings are referred to as fetal alcohol effects.

Whereas there is no known safe amount of alcohol consumption during pregnancy, an average of less than one drink/day in early or late pregnancy showed no measurable impact on a child's learning or cognitive functioning in a cohort study of more than 5000 patients observed for 14 years. Adverse outcomes in this study were associated with an average of more than one drink/day, binge drinking, and consumption of alcohol later in pregnancy. The American Academy of Pediatrics recommends abstinence from alcohol for women who are pregnant or who are planning a pregnancy.

Trauma

The single greatest contributor to alcohol-related mortality in the United States is unintentional injury, accounting for approximately 26,000 deaths/year. The importance of alcohol misuse as a precursor to serious injury is widely accepted enough that the American College of Surgeons Committee on Trauma requires screening for problem drinking for designation at a level I or II trauma center. In addition, level I trauma centers must provide an intervention for identified problem drinkers. Alcohol and trauma are inextricably linked. Independently, the tragic effects of each are numerous; in combination, they are staggering. Injury is a leading cause of death in those between the ages of 1 and 44 years, accounting for more than 50 million injuries/year. In the United States, alcohol is the major risk factor for virtually all categories of intentional and unintentional injury. In addition to increasing the frequency and severity of injury, alcohol significantly complicates management of the trauma victim. Alcohol intoxication often complicates the initial assessment of injury severity, resulting in an increased need for invasive diagnostic and therapeutic procedures (eg, intubation, CT, intracranial pressure monitoring).

Alcohol may diminish the patient's capacity to respond to hemorrhagic shock by altering hemodynamic effects and the acid-base balance. Volume depletion as a result of the diuretic effect of alcohol or vomiting can impair the reserve of the intoxicated trauma patient. Peripheral vasodilation caused by alcohol may contribute to hypotension and hypothermia. Although these effects may be minimal, they underscore the need for early and adequate fluid resuscitation in these patients. Intoxicated patients with severe nonneurologic trauma may have lower blood pressures and carbon dioxide levels, indicative of a compensatory hyperventilation, on hospital arrival compared with sober patients. More important, a poorly understood cardiac depressant effect also increases the depth of shock and volume requirements for resuscitation. Alcohol-induced skin vasodilation may be accompanied by an increase in skeletal muscle, mesenteric, and renal bed constriction and left ventricular stroke work. Thus, the overall effect on systemic vascular resistance and blood pressure may be balanced.

Intoxication renders the signs and symptoms of intra-abdominal and retroperitoneal injury less reliable than usual. If the risk of an intra-abdominal injury exists, further evaluation (eg, ultrasonography, CT) should be considered.

Alcohol intoxication predisposes to abdominal wall laxity and therefore less protection from blunt trauma. These patients are also likely to have full stomachs, increasing the risk of gastric injury after trauma and predisposing to vomiting and aspiration, especially during airway management. The fatty liver changes of alcoholism can result in hepatomegaly. Portal hypertension in alcoholics may produce splenomegaly. These organs can become more vulnerable to the effects of trauma because of their enlarged size, protrusion beneath the protection of the ribs, and increased intracapsular pressure.

No consensus exists on the indications for an emergency CT scan in patients with minor head injury (eg, loss of consciousness, posttraumatic amnesia, GCS score of 14–15, normal findings on neurologic examination). One disturbing prospective study has found that the GCS score and 1 hour of observation were unable to predict abnormal head CT scans in intoxicated patients with minor head trauma. Patients with signs of head trauma and focal or generalized seizures need an urgent CT scan. CT scans of the head should be performed for any patient with deteriorating mental status, focal neurologic findings, new-onset seizures, even without obvious signs of history of trauma, failure to improve over time, or mental status changes out of proportion to the degree of intoxication.

Alcohol Withdrawal Syndrome

Clinical Features

The severity of signs and symptoms of alcohol withdrawal syndrome depends on the dose and duration of ethanol consumption. The withdrawal syndrome may occur any time after the blood alcohol level starts to fall. Therefore, only a reduction, not the abrupt cessation, of ethanol intake may result in withdrawal.

Minor alcohol withdrawal occurs as early as 6 hours after cessation of or significant decrease in alcohol intake and usually peaks at 24 to 36 hours. It is characterized by mild autonomic hyperactivity—nausea, anorexia, coarse tremor, tachycardia, hypertension, hyperreflexia, sleep disturbances (eg, insomnia, vivid dreams), and anxiety.

Major alcohol withdrawal occurs after more than 24 hours and usually peaks at 50 hours after cessation of or significant decrease in alcohol intake but occasionally takes up to 5 days to be manifested after the decline or termination of drinking. The syndrome is characterized by pronounced anxiety, insomnia, irritability, tremor, anorexia, tachycardia, hyperreflexia, hypertension, fever, decreased seizure threshold, auditory and, more commonly visual hallucinations, and finally delirium.

Delirium tremens is a life-threatening manifestation of alcohol withdrawal and consists of gross tremor, frightening visual hallucinations, profound confusion, agitation, and a hyperadrenergic syndrome characterized by a temperature above 101°F (≈38.5°C), blood pressure higher than 140/90 mm Hg, and tachycardia. It seldom appears before the third postabstinence day. Only 5% of patients hospitalized for alcohol withdrawal have delirium tremens.

DIFFERENTIAL DIAGNOSES

Acute alcohol intoxication is a diagnosis of exclusion. Before it is assumed that a patient's behavior is caused only by alcohol, other conditions should be considered, particularly co-ingestants, head trauma, and infection. Hypoglycemia, hypoxia, carbon dioxide narcosis, mixed alcohol-drug overdose, ethylene glycol poisoning, isopropanol or methanol poisoning, hepatic encephalopathy, psychosis, severe vertigo, postictal state, and psychomotor seizures can be manifested in a manner similar to that of ethanol intoxication.

Alcohol withdrawal syndrome can initially be confused with acute schizophrenia, encephalitis, drug-induced psychosis, thyrotoxicosis, anticholinergic poisoning, and withdrawal from other drugs of the sedative-hypnotic type. It may be difficult to differentiate between alcohol withdrawal and alcohol-induced hypoglycemia.

Signs of alcohol withdrawal usually begin 6 to 24 hours after a decrease in the patient's usual intake of alcohol. If patients manifest withdrawal 3 to 4 days or more after their last drink, drugs with a longer half-life should be considered. Barbiturate and benzodiazepine withdrawal syndromes usually progress more slowly, with a higher frequency of seizures later (7 days vs. 2 days), and status epilepticus is more common than with alcohol withdrawal.

DIAGNOSTIC TESTING

Determination of a blood alcohol level is not routinely necessary in caring for the intoxicated patient when there is clear evidence of alcohol intake (eg, confirmation by the patient). When mental status is sufficiently altered that a good history cannot be obtained, there is evidence of head trauma, or the patient fails to improve (detoxify) as expected, determine the serum alcohol level or measure the alcohol level by breathalyzer. If the degree of obtundation is not commensurate with the measured (or breathalyzed) level, and other laboratory test results (eg, toxicology screen, electrolyte levels) do not explain the altered mental status, a head CT scan is indicated. Adequate history from paramedics, patient, and family, serial physical examinations (especially mental status), and bedside testing, such as glucose level and oximetry, can help clarify the clinical situation and guide testing.

Blood tests can be useful if the history is in doubt and can also help patients recognize that alcohol has adversely affected their health. Tests of liver function that measure AST and ALT levels can identify heavy drinking and AUDs with sensitivities of 25% to 45% and specificities as high as 90%. A ratio of AST to ALT higher than 2, especially if concentrations of these enzymes do not exceed 400 units/L, suggests alcoholic hepatitis (Table 142.4).

Laboratory Tests

In the apparently intoxicated patient with altered mental status, the serum glucose level, usually as a point of care test, should be measured to assess for hypoglycemia. In the alcoholic patient, electrolyte levels should be determined to look for hypomagnesemia, hypophosphatemia, hyponatremia, and acidemia. A complete blood count is obtained to evaluate for anemia, leukopenia, and thrombocytopenia and a serum lipase level to evaluate for pancreatitis if the patient has severe upper abdominal pain or tenderness, especially if accompanied by vomiting. Liver function tests are followed in a serial manner in cases of alcoholic hepatitis. An electrocardiogram (ECG) is indicated for tachydysrhythmias or chest pain (eg, holiday heart, acute ischemia). A CT scan of the head or cervical spine may be indicated if head trauma or seizures are suspected or confirmed or if the patient's mental status does not clear in step with the metabolism of alcohol. A chest radiograph is obtained to rule out cardiomyopathy or infectious pneumonia.

Alcohol Screening Questionnaires

Detection of risky drinking behaviors can be through clinical history or the administration of short alcohol screening tools in the ED setting, such as the Alcohol Use Disorders Identification Test (AUDIT), Fast Alcohol Screening Test (FAST), Paddington alcohol test (PAT), and CAGE questionnaires. Other questionnaires include the rapid alcohol problem screen (RAPS-4) and TWEAK (***t***olerance, ***w***orried, ***e***ye opener, ***a***mnesia, ***K*** [cut down]).

TABLE 142.4

Current Biomarkers for Alcoholism

MARKER	ABBREVIATION	HALF-LIFE ELIMINATION RATE	CLINICAL CHARACTERISTICS
Blood ethanol	EtOH	1 g/1 hr/10 kg	Levels exceeding 1.5% without evidence of intoxication or 3% at any time indicate EtOH tolerance typically found in alcohol abusers and alcohol-dependent patients; suitable for emergency clinics
γ-Glutamyltransferase	GGT	2–3 wk	Sensitive and inexpensive marker Age-dependent Specificity decreased by obesity, diabetes, nonalcoholic liver diseases, pancreatitis, hyperlipidemia, cardiac insufficiency, severe trauma, medications (eg, barbiturates, drugs for epilepsy, anticoagulants), nephrotic syndrome, renal rejection
Mean corpuscular volume of erythrocytes	MCV	2–4 mo	More sensitive in women Specificity decreased by vitamin B_{12} or folic acid deficiency, liver disease, hematologic diseases hypothyroidism, reticulocytosis, smoking
Carbohydrate-deficient transferrin (desialotransferrin)	CDT	2–3 wk	Most specific of currently available methods Specificity decreased by genetic variants of transferrin on rare occasions
GGT-CDT combination	GGT-CDT (γ-CDT)	2–3 wk	Mathematically formulated combination that is easy to manage in hospital laboratories Improves sensitivity without a loss of specificity Good correlation with t amount of recent ethanol intake Suitable for routine use
Aminotransferases—aspartate transaminase (AST); alanine transaminase (ALT)	AST, ALT	2–3 wk	AST/ALT ratio >2 suggests alcoholic cause in liver disease patients

From Niemelä O: Biomarkers in alcoholism. Clin Chim Acta 377:39–49, 2007.

The objectives of these screening tools vary; AUDIT and FAST are focused on the detection of recent hazardous or harmful alcohol consumption and associated problems, whereas CAGE is designed to detect lifetime alcohol dependence. The most sensitive screening tool appears to be FAST (93%–94%), which has a specificity of 86% to 88% and positive predicted value of 86% to 87%. Although FAST appears to be the best for accurately identifying alcohol misuse in ED patients, it was assessed as a universal screening tool and may not be feasible—in regard to time or cost—to screen all who present to this service. In contrast, PAT has been developed to be used on a select population in the ED and has already been shown to be cost-effective.[14]

As part of the initial assessment and in alignment with national recommendations, computerized screening programs could be used as an effective method for detecting at-risk alcohol use in ED patients.[15] Identification of AUD and brief advice in the ED can be an effective and cost-effective method to reduce levels of alcohol consumption and alcohol-related harm.[16]

MANAGEMENT CONSIDERATIONS

Comatose or stuporous patients may require intubation. If the bedside glucose level identifies hypoglycemia, IV glucose, as $D_{50}W$ or an infusion of D_5W, is indicated. Patients with evidence of poor nutrition should receive naloxone, 0.4 to 2.0 mg IV, before or early during administration of glucose to prevent Wernicke-Korsakoff syndrome. If an opioid overdose is suspected, IV naloxone, 0.8 mg, may be diagnostic and therapeutic. Because magnesium is a necessary cofactor for thiamine metabolism, consider administering magnesium, 2g IV. When possible, hypoglycemia should be documented before the empirical administration of glucose. With the airway maintained and respirations supported, the patient's liver eventually metabolizes the alcohol, and most patients recover.

Intoxicated patients who do not appear capable of appropriate decision making require evaluation and treatment in the ED, regardless of their willingness to cooperate. At the least, it is incumbent on the emergency clinician to establish that the patient understands the nature of the problem, whether intoxication alone or intoxication in the context of acute illness or injury, and is capable of making reasoned and responsible decisions about care. Inappropriate discharge and failure to diagnose are two common areas of liability in treatment of the alcohol-dependent patient. The theoretic liability for detention by reasonable restraint is less than the potential liability for injury sustained by the intoxicated patient or an innocent bystander after premature discharge. Discharge can be considered when a patient is clinically sober enough to be able to dress, walk, make reasonable decisions, and function independently, as judged and well documented by the treating emergency clinician. When possible, it is ideal to have another sober adult who is willing to take responsibility for and remain with the patient for the next 24 to 48 hours.

Alcohol Withdrawal Syndrome

Family, friends, bystanders, or paramedics often give more reliable historical data than the patient does. Accurate vital signs are essential; this may require a rectal temperature. Hyperthermia, hypothermia, tachypnea, or tachycardia may suggest serious disorders that often accompany the alcohol-dependent patient. These disorders should be considered during the initial assessment.

A rapid and thorough examination should be performed, with attention to the level of consciousness, signs of hepatic failure, or coagulopathy. Signs of trauma are sought, such as subcutaneous emphysema, ecchymosis, subconjunctival hemorrhage, hemotympanum, and Battle's sign, and palpation is done for occult injuries. The neurologic examination should search for focal

findings, including central facial nerve palsy, hemiparesis, and asymmetry of pupillary response.

The alcohol withdrawal syndrome should be promptly recognized and treated. The CIWA-Ar is a validated tool for symptom-based prescribing of chlordiazepoxide for alcohol withdrawal and is an alternative to traditional fixed-dose regimens, which may prolong length of stay for up to 5 days. Scores on the CIWA-Ar range from 0 to 67; scores lower than 8 indicate mild withdrawal symptoms that rarely require the use of medications, scores from 8 to 15 indicate moderate withdrawal symptoms that are likely to respond to moderate doses of benzodiazepines, and scores higher than 15 indicate severe syndromes that require close monitoring to avoid seizures and alcohol withdrawal delirium (delirium tremens).

In combination with appropriate chemical sedation, detention by reasonable restraint may be an option to prevent potential injury that patients may inflict on themselves or hospital staff. These appropriate measures need to be instituted; decision-challenged patients should not be permitted to sign an Against Medical Advice Form and be discharged.

Pharmacologic Treatment

Patients suffering from alcohol withdrawal should receive pharmacologic intervention along with supportive care. The ideal drug for alcohol withdrawal should have a rapid onset, wide margin of safety, metabolism not dependent on liver function, and limited abuse potential. Although no one drug class fits all these requirements, benzodiazepines are clearly the mainstay of treatment.

Benzodiazepines. The benzodiazepines have superior anticonvulsant activity, have the least respiratory and cardiac depressive effects of all the CNS depressants, and can be given parenterally to the uncooperative patient. By interacting with receptors linked to the GABA-associated chloride ion channel, benzodiazepines substitute for the withdrawal of the GABA-potentiating effect of alcohol and abate withdrawal signs and symptoms. Numerous benzodiazepines have been studied, but there is no evidence of the clear superiority of any one benzodiazepine.

Lorazepam has good bioavailability with the oral, intramuscular, and IV routes. It is rapidly and completely absorbed from intramuscular sites in agitated patients with no IV access. The half-life of lorazepam is intermediate (7–14 hours), and it reaches a steady state in 36 to 48 hours, without active metabolites. Excessive sedation, confusion, and ataxia are potential complications of all benzodiazepines with prolonged half-lives. Lorazepam is metabolized (conjugated) in the liver, yielding inactive products. Although the half-life of lorazepam increases in patients with cirrhosis or liver failure, it is much shorter than the increase with chlordiazepoxide. The elimination of lorazepam is only minimally altered in patients with renal failure and in older adults. Lorazepam may be given IV in a dose of 1 to 4 mg, depending on the severity of the withdrawal. Dosing can be repeated at 5- to 15-minute intervals for patients in severe withdrawal. Although it is not ideal, an intramuscular dose of 1 to 4 mg can be used every 30 to 60 minutes until the patient is calm and then every hour, as needed, for light somnolence. The oral schedule for moderate withdrawal is 6 mg/day in three divided doses, tapering the amount by 1 to 2 mg/day during 4 to 6 days.

As one dosing regimen, diazepam, 5 mg IV every 5 to 10 minutes (2.5 mg/min), can be given in major withdrawal until the patient is calm. The dose can be repeated in 5 to 10 minutes. If the second dose of 5 mg is not working, consider 10 mg for the third and fourth doses every 5 to 10 minutes. If this is not effective, consider 20 mg for the fifth and subsequent dose until adequate sedation has been obtained.

In patients who do not have a response to high doses of benzodiazepines (especially patients who are intubated), propofol may be administered (eg, 0.3 to 1.25 mg/kg of body weight, up to 4 mg/kg/hr, for up to 48 hours).[6]

Butyrophenones. Haloperidol, a dopamine antagonist, can be considered in patients with major alcohol withdrawal or delirium tremens not responding to IV benzodiazepines. Haloperidol has little effect on myocardial function or respiratory drive, and its safety and efficacy by the IV, intramuscular, or oral route in the ED have been established. Haloperidol has no anticonvulsant properties; however, extrapyramidal effects may be seen. Caution should be used in patients who may be susceptible to a prolonged QTc interval. Droperidol has effects similar to those of haloperidol. Despite the 2001 US Food and Drug Administration (FDA) black box warning for QTc interval prolongation and torsades de pointes after droperidol use, droperidol remains a relatively safe and effective treatment for agitated patients.

Other Agents. Patients being treated for major alcohol withdrawal may be given thiamine (100 mg IV) and magnesium (2 g IV). Although magnesium sulfate does not decrease the severity of withdrawal symptoms, incidence of delirium, or seizures, it carries no significant risk with adequate renal function.

If volume depletion is present, it can be corrected with normal saline. Reversal of electrolyte and metabolic disorders (eg, hypomagnesemia, hypophosphatemia, hypokalemia, acidosis) benefits the patient but does not abate the withdrawal syndrome.

Neurologic Examination

Normal Examination

New-Onset Seizures. Patients with new-onset, alcohol-related seizures should be thoroughly evaluated. This includes alcoholics who claim to have had seizures but for whom no documentation or appropriate evaluation is available. Metabolic disorders, toxic ingestion, infection, and structural abnormalities should be considered.

If the initial physical examination findings, imaging studies, and laboratory test results are within normal limits, patients who remain seizure-free and symptom-free, with no sign of withdrawal after 4 to 6 hours of observation, may be discharged. It may be unclear whether the patient has had a pure alcohol withdrawal seizure or a new-onset seizure disorder in the setting of alcohol ingestion. Long-term treatment with antiepileptic drugs is not useful in unprovoked new-onset seizures that have resolved or when a clear relation to alcohol consumption can be identified.

Optimal outpatient treatment includes follow-up and referral to a detoxification or rehabilitation program. Ideally, the help of a concerned family member or friend who is not a drinking partner and can remain with the patient for at least 1 or 2 days is helpful.

Prior History of Seizures During Withdrawal. The risk of seizure increases significantly in alcoholic patients with manifestations of alcohol withdrawal who relate a history of alcohol withdrawal seizure. Detoxification with benzodiazepines reduces alcohol withdrawal seizure and should be initiated early because most seizures occur within the first 24 hours after alcohol withdrawal. An initial dose of 2 mg of lorazepam or 5 mg of diazepam can be given IV. These doses frequently need to be repeated.

Abnormal Neurologic Examination

New-Onset Partial Seizures. Partial seizures account for up to 50% of alcohol-related seizures. Conversely, studies have

shown that approximately 20% of patients with partial alcohol-related seizure have structural lesions—hematomas, tumors, vascular abnormalities, or stroke. These primary causes of partial alcohol-related seizure, such as prior head trauma, may be easily missed in the history taking. As a result, an emergent CT scan is indicated to evaluate new-onset partial seizures. The patient with a history of a focal alcohol-related seizure who has been previously evaluated does not require an emergency CT scan provided a return to baseline occurs promptly.

Patients Taking Phenytoin Anticonvulsant

Phenytoin has no significant benefit over placebo in the prevention of recurrence of uncomplicated alcohol withdrawal seizure. Considering the risks of phenytoin and no demonstrated benefit in the setting of alcohol withdrawal seizure, it is not indicated for the treatment of alcohol withdrawal seizures. The sudden withdrawal of phenytoin may potentiate the convulsive effects of alcohol withdrawal.

A patient currently taking antiepileptic drugs for an antecedent seizure disorder who presents with a seizure while intoxicated falls into a different category. Such an episode could be an isolated event in a usually compliant patient without a history of chronic alcohol abuse. In this patient, a seizure in the setting of a subtherapeutic antiepileptic drug level may represent the consequences of noncompliance with antiepileptic medication or sleep deprivation versus alcohol withdrawal seizure.

DISPOSITION

Most patients with acute alcohol intoxication are managed in the ED or ED observation unit and then discharged home. Patients who achieve sufficient sobriety to be ready for discharge are offered detoxification or alcohol treatment. Most alcoholics suffer from a combination of medical, psychiatric, and social problems. Hospitalization may be necessary to diagnose and treat these multiple problems. Moreover, with alcoholics who are no longer able to care for themselves, hospitalization is often dictated for this reason alone. Unfortunately, many managed care and Medicaid plans limit or do not cover inpatient detoxification. In choosing medical versus psychiatric admission, a medical illness usually takes priority. Optimal outpatient therapy for chronic alcoholics includes the involvement of concerned family or friends to ensure that the patient takes his or her medications properly, keeps follow-up appointments, abstains from alcohol, and maintains an adequate diet. Alcoholic patients who undergo outpatient treatment need close supervision; therefore, a follow-up clinic appointment within 24 to 48 hours should be considered.

Acute Intoxication

Acute intoxication alone seldom requires admission. However, a combined alcohol-drug overdose or associated medical, psychiatric, or social problems may require hospitalization. Acute alcohol intoxication is a diagnosis of exclusion reached after adequate observation to ensure that the altered mental status resolves.

Alcohol levels that may be tolerated by an adult can be lethal in children. It is prudent to admit children with acute intoxication unless close psychosocial follow-up can be ensured. Children presenting with hypoglycemia or medical complications should be admitted. Child abuse or neglect should be considered.

Alcohol Withdrawal

Outpatient treatment consists of lorazepam, 1 to 2 mg tid tapered during 3 to 6 days, chlordiazepoxide, 25 to 100 mg tid tapered during 3 to 6 days, or diazepam, 30 mg once daily tapered during 5 days, depending on the severity of symptoms. Adequate diet, abstinence, and participation in a rehabilitation program in the community are also desirable. Any patient requiring 300 mg of chlordiazepoxide or 60 mg of diazepam/day to control withdrawal should be considered for admission.

Patients with signs of major withdrawal (fever, hallucinations, confusion, extreme agitation) require admission. Patients with mild alcohol withdrawal can be observed in the ED. After 4 to 6 hours of observation and treatment, the alert oriented patient whose vital signs, physical examination findings, and results of appropriate laboratory analysis are within normal limits may be released with appropriate medications and aftercare instructions. Nevertheless, the patient requires treatment for the underlying disease of alcoholism and should be advised or referred accordingly.

Seizures

The alcoholic patient with a first-time, alcohol-related seizure may be discharged to a suitable social situation in these situations: (1) when the patient's alcohol withdrawal is mild and controlled by supportive care or low-dose benzodiazepines; (2) the diagnostic evaluation, including a head CT scan, is unremarkable; (3) the patient has had fewer than two seizures; and (4) the patient has been observed to be alert and oriented, with normal vital signs, physical examination findings, and laboratory study results during the 6 hours since the last seizure, and appropriate outpatient follow-up can be ensured.

Patients with a documented history of alcohol-related seizures can be discharged if they have had no more than two alcohol-related seizures during a 6-hour period, with a lucid interval between seizures, and are observed to be seizure-free and at baseline mental and physical status for at least 6 hours after their last alcohol-related seizure. Three to five brief, self-limited seizures may occur with alcohol withdrawal seizure. We recommend prolonged observation in the ED or ED observation unit for patients with two or more seizures because of the potential for deterioration to status epilepticus. Such patients should be observed until at least 6 hours has passed since their last seizure and they have a normal neurologic examination, including normal mental status.

Patients with partial seizures or focal neurologic findings on physical examination require admission unless these findings have been previously documented. Patients with seizures associated with head trauma or mixed alcohol-drug withdrawal are admitted. Status epilepticus or recurrent seizures during ED observation indicate a lack of seizure control and also require hospitalization.

Psychiatric and Social Problems

Alcoholic patients requiring admission with acute intoxication, alcohol-related seizure, alcohol withdrawal, or medical or surgical disorders are usually best managed in acute care units rather than by a general psychiatric service. Some psychiatric and social conditions in the alcoholic can be better handled on a general psychiatric unit—psychosis, exacerbation of schizophrenia, depression with suicidal tendencies, any patient who is a danger to self or others, or alcoholic hallucinosis with an otherwise clear sensorium.

Patients who are no longer able to care for themselves may also require admission. Although these patients' ultimate destination is a rehabilitation center or a board and care program, hospitalization may be necessary to rule out medical or psychiatric illness and treat impending withdrawal symptoms. Patients who wish to stop drinking are usually referred to a detoxification unit for treatment of impending withdrawal. Data and interest are increasing for outpatient drug therapy for alcohol dependence. The FDA has

approved disulfiram, naltrexone, acamprosate, and topiramate for the treatment of alcohol dependence. There is growing evidence that patients with alcohol dependence who carry a particular variant of an opioid receptor gene are more likely to respond to naltrexone, raising the possibility that genetic tests may one day guide medication selection. Naltrexone, ondansetron, acamprosate, and acamprosate plus naltrexone have had mixed results facilitating abstinence. The role of medications in combination with behavioral therapy is being actively investigated.

Several other medications are under active study and are sometimes prescribed for alcoholism treatment on an unapproved or off-label basis. Baclofen, because of its anticraving action and safety, could have an important role for the treatment of alcohol-dependent patients with advanced liver disease. Gabapentin is used as monotherapy or as add-on pharmacotherapy in outpatient settings in the control of alcohol consumption and craving and in helping patients achieve abstinence. Ondansetron may show benefit in early-onset but not in late-onset alcoholics.

Brief intervention and screening (SBIRT—***s***creening, ***b***rief ***i***ntervention, and ***r***eferral to ***t***reatment) is valuable and is now recommended in the ED.[17,18] Internet-based interventions show promise for reducing alcohol consumption, especially among those meeting criteria for hazardous or harmful drinking. Telephone contact after the ED visit may be another effective tool to screen injured patients for hazardous drinking and offer a brief intervention while avoiding interruptions to patient flow. Most communities have an Alcoholics Anonymous (AA) chapter or treatment center for anyone who desires help with alcohol. In smaller communities, clergy or social workers can usually arrange rehabilitation.

KEY CONCEPTS

- Moderate alcohol consumption is defined as one or two drinks/day for men and one drink/day for women.
- Benzodiazepines are the main treatment of alcohol withdrawal and alcohol withdrawal seizures. Minor alcohol withdrawal occurs as early as 6 hours and usually peaks at 24 to 36 hours after the cessation of or significant decrease in alcohol intake.
- Major alcohol withdrawal occurs after 24 hours and usually peaks at 50 hours (but occasionally takes up to 5 days) after the decrease or termination of drinking.
- Delirium tremens is the extreme end of the alcohol withdrawal spectrum; it consists of gross tremors, profound confusion, fever, incontinence, and frightening visual hallucinations.
- Alcohol withdrawal seizures occur 6 to 48 hours after the cessation of drinking, with 60% of patients experiencing multiple seizures within a 6-hour period.
- Alcohol withdrawal should be assessed and managed using a validated scale, such as the CIWA-Ar scale.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 142: QUESTIONS & ANSWERS

142.1. A 56-year-old man presents with altered mental status. You recognize the patient as a frequent visitor to the emergency department (ED) for alcohol intoxication. He is drowsy but arousable to painful stimuli. He is confused. Vital signs are within normal limits, and there is no evidence of trauma. His blood glucose level is 30 mg/dL. Which treatment is indicated first?

A. Dextrose
B. Folate
C. Glucagon
D. Naloxone
E. Thiamine

Answer: A. Although alcohol intoxication clearly causes altered mental status (AMS), it should never be assumed that AMS is due to alcohol intoxication. Alcoholics are at risk for multiple medical and traumatic causes of AMS. Chronic alcoholics have decreased glycogen stores and frequently experience hypoglycemia. Because glucagon works by mobilizing glycogen stores, it is often not effective in alcoholics. Thiamine and folate stores are often depleted and can result in Wernicke's encephalopathy. However, hypoglycemia is much more common and can also result in permanent morbidity if untreated. Although the administration of thiamine and folate should be considered for alcoholics, their use should never delay treatment of hypoglycemia. Naloxone is an opioid antagonist and has no effect on alcohol metabolism or glucose levels.

142.2. A 62-year-old man presents with agitation, confusion, and fever. He is noted to experience visual hallucinations during your interview. His vital signs reveal hypertension, tachycardia, and fever. Physical examination is otherwise unremarkable. Diagnostic studies (including head CT and lumbar puncture) are nonspecific. Which diagnosis is most consistent with this patient's presentation?

A. Acute schizophrenia
B. Alcohol withdrawal
C. Anticholinergic poisoning
D. Opioid withdrawal
E. Thyrotoxicosis

Answer: B. Patients are often confused and agitated and exhibit autonomic instability, resulting in hypertension, tachycardia and, often, fever. Hallucinations are typically visual. Schizophrenia typically results in auditory hallucinations and, although patients are delusional, they are not typically confused. Patients with anticholinergic poisoning typically present with confusion but also have dry mouth, dry eyes, dry skin, hypoactive bowel sounds, and urinary retention. Patients with opioid withdrawal typically have gastrointestinal complaints and, although they may be agitated, they are seldom confused or febrile. Thyrotoxicosis is much more common in women, and patients can exhibit lid lag, tremor, and gastrointestinal complaints.

142.3. In addition to altered mental status (AMS), which of the following is a criterion for diagnosing Wernicke's encephalopathy?

A. Alcohol intoxication
B. Fever
C. Oculomotor abnormalities
D. Recent glucose administration
E. Seizure

Answer: C. Criteria to diagnoses Wernicke's encephalopathy require two of the following: (1) dietary deficiencies; (2) oculomotor abnormalities; (3) cerebellar dysfunction; and (4) AMS or mild memory impairment. Although it is most often diagnosed in alcoholics, alcohol consumption is not required. Treatment is with replacement of dietary deficiencies, particularly thiamine. Magnesium levels should be checked and treated if low. Magnesium is a cofactor for thiamine and is often depleted in chronic alcoholics.

CHAPTER 143

Acetaminophen

Robert G. Hendrickson | Nathanael J. McKeown

PRINCIPLES OF TOXICITY

Acetaminophen (better known internationally as paracetamol) is one of the most important toxins encountered in emergency care because of its ready availability, high lethality, and absence of clinical indications of ingestion until the time to administer the effective antidote has passed. Acetaminophen is found as an isolated product or in combination medications for the treatment of pain and febrile illness. An intravenous (IV) formulation is also available in the United States and Europe.[1,2] Given its widespread availability and occult clinical presentation, acetaminophen toxicity is a concern in the vast majority of intentional ingestions, as well as with repeated supratherapeutic dosing, prescription drug abuse, and use by alcoholic patients. Acetaminophen toxicity is one of the leading causes of hospital admission, antidote use, and fatalities from oral poisonings in the United States.[3]

Protocols have been established for the assessment and management of acute and chronic acetaminophen ingestion through decades of research and experience; however, controversy continues to exist, and with new formulations recently approved, the management of acetaminophen exposures continues to evolve.

Acetaminophen is absorbed rapidly, with peak plasma concentrations generally occurring within 1 hour and complete absorption within 4 hours. Once absorbed, acetaminophen inhibits prostaglandin E_2 (PGE_2) synthesis, leading to antipyresis and analgesia. Inhibition of PGE_2 synthesis is either by direct cyclooxygenase-2 (COX-2) inhibition or inhibition of membrane-associated prostaglandin synthase.

In therapeutic doses, acetaminophen is primarily metabolized by conjugation with glucuronide (40% to 67%) and sulfate (20% to 46%) into nontoxic metabolites that are excreted in the urine (Fig. 143.1).[4] A small percentage (<5%) is oxidized by cytochrome P_{450} 2E1 (CYP2E1) (and to a lesser extent 1A4 and 3A4) to a highly cytotoxic metabolic intermediary, *N*-acetyl-*p*-benzoquinone imine (NAPQI).[5] In therapeutic doses, NAPQI is short-lived, combining rapidly with glutathione and other thiol-containing compounds to form nontoxic metabolites that are excreted in the urine. With typical therapeutic acetaminophen dosing, glutathione stores and the ability to regenerate glutathione easily detoxify any NAPQI that is produced.

After large acute ingestions or repeated supratherapeutic ingestions, the amount of NAPQI produced begins to overwhelm glutathione stores and the liver's ability to regenerate glutathione, leading to unbound NAPQI. The highly reactive electrophile NAPQI covalently binds to cell proteins in the liver, which initiates a cascade of events that lead to hepatic cell death. Renal injury may also occur with or without liver injury and may be mediated by renal cytochrome P_{450} (CYP) enzymes or activation of prostaglandin synthase.

Acetaminophen-induced liver damage initially occurs in hepatic zone III (centrilobular) because oxidative metabolism is concentrated in this area. With severe toxicity, necrosis of the entire liver parenchyma may occur. The clinical effects of severe acetaminophen toxicity are the result of severe fulminant liver failure rather than a direct acetaminophen effect. These effects include multiorgan failure, systemic inflammatory response syndrome, hypotension, cerebral edema, and death.

The principal therapy for acetaminophen toxicity is *N*-acetylcysteine (NAC),[4] which is effective via two separate mechanisms. Soon after overdose, NAC serves as a glutathione precursor and a sulfur-containing glutathione substitute (see Fig. 143.1), binding to, and thereby detoxifying NAPQI and avoiding subsequent hepatotoxicity. In addition, NAC may decrease NAPQI formation by enhancing acetaminophen conjugation with sulfate to nontoxic metabolites.

Even after acetaminophen hepatotoxicity is evident, NAC acts as a free-radical scavenger and an antioxidant and alters hepatic microcirculation and oxygen delivery. In patients with acetaminophen-induced hepatic failure, IV NAC decreases the rates of cerebral edema, hypotension, and death even when no detectable acetaminophen remains in the serum.[6]

CLINICAL FEATURES

Early after acute acetaminophen ingestion, patients may be asymptomatic or have mild nonspecific symptoms (eg, nausea, vomiting, anorexia, malaise, and diaphoresis) (Table 143.1). Liver injury becomes evident after a period of 8 to 36 hours as an elevation in aspartate transaminase (AST).[7] Once liver injury has begun, patients may develop right upper quadrant (RUQ) pain or tenderness, vomiting, and jaundice. AST concentrations continue to rise rapidly and usually peak in 2 to 4 days, corresponding to maximal liver injury.[7] Alanine transferase (ALT), prothrombin time (PT), and bilirubin typically begin to rise and peak several hours after AST values. With severe toxicity, AST, ALT, and the PT may all be elevated within 24 hours (Fig. 143.2).[7] With maximal liver injury, patients develop signs and symptoms consistent with fulminant liver failure, including metabolic acidosis, coagulopathy, and hepatic encephalopathy. Death may occur from hemorrhage, adult respiratory distress syndrome, sepsis, multiorgan failure, or cerebral edema. The risk of renal injury increases with the severity of hepatic injury (hepatorenal syndrome), occurring in less than 2% of patients without hepatotoxicity and in 25% of patients with severe hepatotoxicity.

If patients recover, aminotransferases return to baseline concentrations over a 5- to 7-day period (see Fig 143.2), although complete histologic resolution of liver injury may take months. Once histologic recovery is complete, there are no long-term sequelae to the liver and patients are not at risk for chronic hepatic dysfunction.

DIFFERENTIAL DIAGNOSES

Acetaminophen poisoning should be on the differential diagnosis in patients with intentional oral overdoses regardless of whether they state that they ingested acetaminophen. In patients with elevations in aminotransferases, bilirubin, partial thromboplastin time (PTT)/international normalized ratio (INR), or creatinine, other

sources of injury should be considered, including acute tubular necrosis, rhabdomyolysis, ischemic hepatitis, alcoholic hepatic disease, cyclopeptide-containing mushroom toxicity, viral hepatitis, Wilson disease, and other hepatic toxicities (eg, valproic acid, isoniazid [INH], statins, herbal medications, vinyl chloride, and polychlorinated biphenyls).

DIAGNOSTIC TESTING

The goals of patient assessment after acetaminophen ingestion are (1) the determination of the patient's risk, (2) diagnostic testing, and (3) treatment with the antidote NAC when appropriate.

Acetaminophen exposures may be classified as acute or chronic, and each type requires different testing and risk assessment. An acute ingestion is generally considered to be a single ingestion or a series of ingestions that are arbitrarily defined to occur within an 8-hour period. All other ingestions, including accidental repeated supratherapeutic ingestions and intentional ingestions spread over longer than 8 hours, can be considered to be chronic.

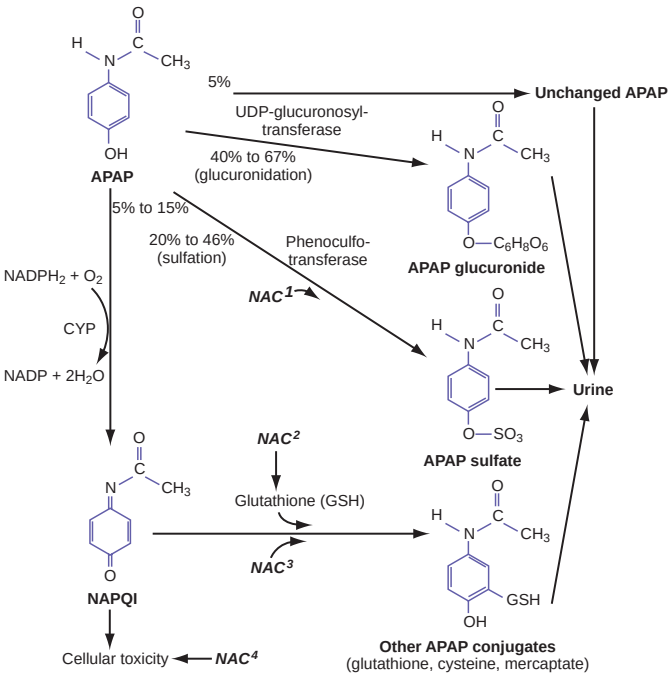

Fig. 143.1. Acetaminophen *(APAP)* metabolism and *N*-acetylcysteine *(NAC)* mechanisms of action. NAC^1 enhances sulfation; NAC^2 serves as a glutathione (GSH) precursor; NAC^3 is a GSH substitute; NAC^4 may reduce systemic toxicity. *CYP,* Cytochrome P_{450}; *NAPQI, N*-acetyl-*p*-benzoquinone imine; *UDP,* Uridine 5′-diphospho. (Modified from Hendrickson RG: Acetaminophen. In Hoffman RS, et al, editors: Goldfrank's toxicologic emergencies, ed 10, New York, 2015, McGraw-Hill Education, p 448.)

Risk Assessment With Acute Acetaminophen Ingestion

The initial diagnostic strategy of an acute ingestion is well established. The first step is to determine the patient's risk of acute acetaminophen exposure. Patients who report an acute intentional ingestion of acetaminophen should have laboratory risk stratification regardless of the reported amount ingested. In an adult patient, significantly greater than 10 grams in total or 150 mg/kg (approximately forty 325 mg [regular strength] or twenty-five 500 mg [extra strength] tablets for an 80 kg adult) in an acute ingestion is generally required before significant liver toxicity occurs; however, history alone may not be reliable. We recommend a serum acetaminophen concentration in any intentional overdose patient who admits to taking acetaminophen (regardless of the admitted dose) or had access to acetaminophen, even if they deny taking it. Acetaminophen is detected in the serum of up to 8% of patients with intentional ingestions who deny acetaminophen ingestion. Also there is a high prevalence (18%) of unrecognized acetaminophen toxicity among subjects presenting with indeterminate acute liver failure.[8]

When acute acetaminophen overdose is identified, the time of ingestion is established as accurately as possible using all available information. If no accurate time of ingestion can be determined, it is best to base further evaluation and therapy on a scenario that assumes the earliest possible time of ingestion.

A serum acetaminophen concentration 4 hours post-ingestion, or as soon as possible after 4 hours is needed to determine the need for antidotal therapy by plotting the serum acetaminophen concentration against the time since ingestion on the treatment

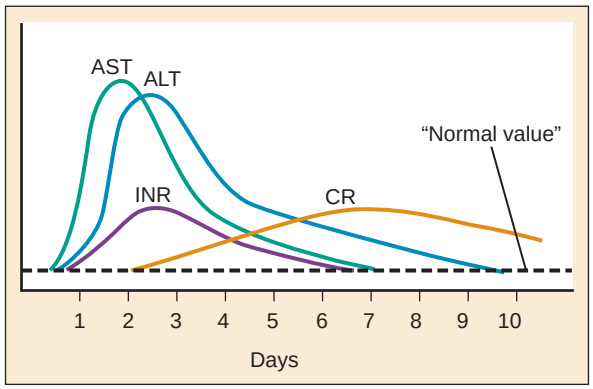

Fig. 143.2. A typical time course of rise, peak, and fall of laboratory values in patients with acetaminophen-induced hepatic dysfunction who survive. Peaks are not proportional. Not all laboratory abnormalities occur in all patients, and significant individual variation may occur. *ALT,* Alanine transaminase; *AST,* aspartate transaminase; *CR,* creatinine; *INR,* international normalized ratio. (Copyright Robert G. Hendrickson, MD.)

TABLE 143.1

Time Course and Clinical Stages of Acetaminophen Toxicity

STAGE	TIME COURSE	NAME	SYMPTOMS	SIGNS
1	0 to 12 (up to 24 to 36) hours	Preinjury	Nausea, vomiting, anorexia, malaise	Elevated serum acetaminophen concentration
2	8 to 36 hours	Liver injury	Nausea, vomiting, RUQ abdominal tenderness	Aminotransferase elevation (AST begins to rise 8 to 36 hours after ingestion)
3	2 to 4 days	Maximum liver injury	Liver failure (encephalopathy, coagulopathy, hemorrhage, acidosis)	Hemorrhage, ARDS, sepsis/SIRS, multiorgan failure, cerebral edema
4	>4 days	Recovery	None	Complete hepatic histologic recovery

ARDS, Acute respiratory distress syndrome; *AST,* aspartate transaminase; *RUQ,* right upper quadrant; *SIRS,* systemic inflammatory response syndrome.

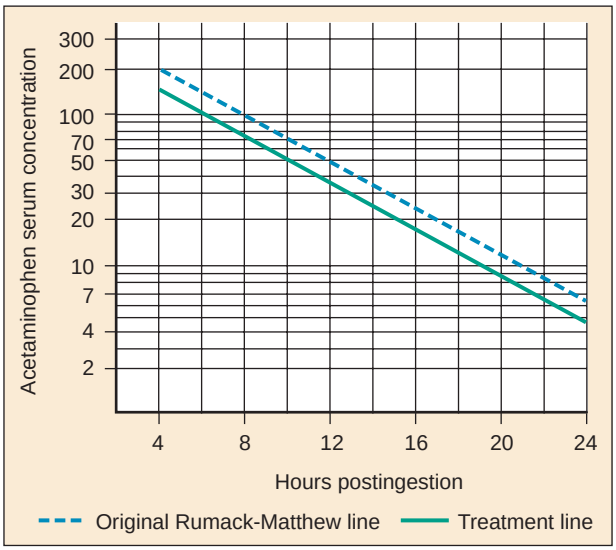

Fig. 143.3. Treatment nomogram for acute overdose. The lower treatment line should be used for treatment decisions. (Modified from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 55:871, 1975.)

TABLE 143.2

Indications for Initiating Testing for Serum Acetaminophen Concentration and Aspartate Transaminase in Chronic Acetaminophen Ingestions

Age ≥6 years old;	Ingestion of >10 g/d (or >200 mg/kg/d) (whichever is smaller) over a 24-hour period
or	Ingestion of >6 g/d (or >150 mg/kg/d) (whichever is smaller) over a 48-hour period or longer
or	Symptomatic (eg, RUQ pain/tenderness, jaundice, vomiting)
Children <6 years old;	Ingestion of >200 mg/kg/d over a 24-hour period
or	Ingestion of >150 mg/kg/d over a 48-hour period
or	Ingestion of >100 mg/kg/d over a 72-hour or longer period
or	Symptomatic (eg, RUQ pain/tenderness, jaundice, vomiting)

AST, Aspartate transaminase; *RUQ,* right upper quadrant.

nomogram (Fig. 143.3), an adaptation of the Rumack-Matthew nomogram. If the serum acetaminophen concentration is on or above the treatment line (that starts at 150 μg/mL at 4 hours and decreases to 4.7 μg/mL at 24 hours), this indicates the need for treatment with NAC. If the serum acetaminophen concentration is below the treatment line and the most severe possible scenario has been taken for the time of ingestion, then the patient requires no antidote. Use of the treatment line is a highly sensitive approach and may be used for patients presenting after acute ingestions. Alternative approaches in patients with alcoholism, patients with co-ingestions of antimuscarinic agents, patients with unknown ingestion times, and after IV formulations have been suggested, but these remain unsubstantiated.[9,10] We recommend adherence to the approach that is described earlier.

Measurement of serum acetaminophen concentration prior to 4 hours is not necessary. Although a serum acetaminophen concentration less than 10 μg/mL between 1 and 4 hours after ingestion likely excludes significant ingestion of acetaminophen, there are insufficient data on which to base this conclusion. Absorption of acetaminophen may not be complete prior to 4 hours, and any serum acetaminophen concentration greater than 10 μg/mL is difficult to interpret. Finally, serum acetaminophen concentrations measured prior to 4 hours cannot be plotted on the treatment nomogram. Fortunately, there is little need to treat patients prior to 8 hours after ingestion, because patients treated with NAC up to 8 hours after ingestion, even after very large doses, have no increased risk of hepatotoxicity regardless of their serum acetaminophen concentration.[11] For patients with potential hepatotoxicity due to the total amount ingested, or those with preexisting liver disease in whom a serum acetaminophen concentration cannot be obtained prior to 8 hours after ingestion, a loading dose of NAC should be given, or consultation obtained with a medical toxicologist or poison center.

Iatrogenic acetaminophen toxicity related to IV dosing is exceedingly rare. Pharmacokinetics are different after a large IV acetaminophen overdose, and the nomogram is based entirely on oral ingestion. When the extremely rare occurrence of acetaminophen toxicity related to IV administration is encountered, we recommend treatment with NAC if the patient received greater than 60 mg/kg IV acetaminophen in one dose or has a serum acetaminophen concentration greater than 50 μg/mL at 4 hours after the infusion stops.[10] Consultation with a regional poison center or medical toxicologist is advisable if there is uncertainty about whether to administer NAC.

Risk Assessment With Chronic Ingestion

With repeated or chronic exposure, risk assessment is more complex, and the treatment nomogram cannot be used. Determination of the need for NAC is based on assessment of the risk for hepatotoxicity and measurement of serum levels of acetaminophen and AST.

The risk of hepatotoxicity from chronic ingestion of acetaminophen increases with total dose of acetaminophen and the duration over which it has been ingested in supratherapeutic quantities. Laboratory testing for serum acetaminophen concentration and AST should be initiated in any patient who fits the criteria in Table 143.2.[10]

Ingestion of therapeutic amounts of acetaminophen appears to be quite safe. However, rare reports of aminotransferase elevation and liver injury during therapeutic dosing suggests that some patients may be at increased risk for liver injury, possibly due to genetic variation or to specific risk factors. Patients who chronically ingest INH or ethanol may have increased CYP2E1 activity and, theoretically, may be at higher risk for chronic acetaminophen toxicity. Similarly, patients who are malnourished or have severe dehydration may be at higher risk for hepatoxicity.

Once serum acetaminophen concentration and AST are obtained, further risk assessment is necessary. Conceptually, patients with chronic ingestions (ie, >4 grams/day over a period of several days) may benefit from antidotal therapy if they have evidence of liver injury (AST >2× normal, or 120 IU/L) *or* if they have evidence of acetaminophen excess (serum acetaminophen >30 mcg/mL) with a prolonged half-life that may lead to liver injury.[12] (Of note, after a typical therapeutic dose of acetaminophen, serum acetaminophen concentration peaks below 30 μg/mL and is less than 10 μg/mL at 4 hours.)

Risk Assessment in Pregnant Women

The risk assessment and diagnostic approach to pregnant women is the same as for nonpregnant women. In acute overdoses, a

serum acetaminophen concentration should be drawn and plotted on the treatment nomogram. NAC therapy should be initiated if the serum acetaminophen concentration plots above the treatment line. With chronic exposure, the same criteria strategy as outlined earlier should be instituted.

MANAGEMENT

Stabilization and Supportive Care

In addition to supportive care as needed, the mainstay of management is the initiation NAC therapy when indicated. Where doubt exists regarding initiation of NAC or there are confounding clinical issues present (eg, preexisting liver disease), clinicians may consult with a regional poison center (1-800-222-1222) or medical toxicologist for advice.[13] Supportive care includes management of co-ingestions, and the nausea and vomiting, hepatic injury, and renal dysfunction related to acetaminophen poisoning. Treatment of these problems is based on general treatment principles and is not acetaminophen-dependent (see Chapters 80 and 87).

Decontamination

Activated charcoal (AC) effectively binds acetaminophen in vitro, and some limited studies have suggested that early administration of AC (within 1 to 2 hours post-ingestion) may decrease the number of patients that require antidotal therapy. However, many patients have co-ingestions that may decrease mental status, and patients with severe acetaminophen poisoning often develop vomiting, thus increasing the risk for aspiration of AC. Therefore, use of AC should have no bearing on the determination of the need for NAC therapy. Given the lack of demonstrated efficacy in terms of improved outcome, and the risk of adverse outcome from aspiration of AC, we do not recommend the use of AC for acetaminophen overdose when NAC therapy is readily available within 8 hours following an acute potentially hepatotoxic ingestion.

Enhanced Elimination

Hemodialysis is not routinely used for acetaminophen overdose, because there is a highly effective antidote with good clinical outcomes when given within 8 hours of ingestion. However, hemodialysis may be helpful when the absorbed acetaminophen burden is sufficient to cause hepatotoxicity despite usual doses of NAC. We recommend consultation with a poison center or medical toxicologist for initiation of hemodialysis for patients presenting following an acute massive ingestion with the characteristics shown in Box 143.1. There is no definitive evidence regarding the efficacy of hemodialysis in this setting, but removal of excess acetaminophen may prevent hepatotoxicity by allowing the NAC to effectively deal with the reduced burden of toxin.[14,15]

Antidote Therapy

N-Acetylcysteine

When indicated, NAC should be administered as early as possible. Delay of NAC more than 8 hours after ingestion increases the risk of hepatotoxicity (Fig. 143.4).

NAC can be administered *per os* (by mouth; PO) or IV. Both methods are efficacious in most situations, with advantages and disadvantages for each. All formulations of NAC (PO or IV) are very effective when started within 8 hours of ingestion.[16,17] When administered early (<8 hours), NAC's main role is to prevent hepatotoxicity by detoxifying NAPQI and decreasing NAPQI production. The risk of liver injury (ie, AST >1000 IU/L) in patients treated with NAC within 8 hours is less than 4% and the mortality rate approaches zero (see Fig. 143.4).[16]

Both PO and IV NAC are equally effective in treating patients who present 8 to 24 hours after ingestion, although those patients with vomiting or hepatic encephalopathy may be unable to tolerate the oral formulation.

Once liver failure (eg, coagulopathy, encephalopathy, and so on) is evident, however, NAC is given intravenously.[6] IV NAC decreases the risk of hypotension, cerebral edema, and death in patients with acetaminophen-related hepatic failure.[6] Oral NAC should only be used if IV NAC is not available.

The main differences between IV and PO NAC are in their side effect profiles (Table 143.3).

Approximately 2% to 6% of patients treated with IV NAC develop significant anaphylactoid reactions, although rates of up to 30% have been reported in prospective trials. The majority of these symptoms are mild and consist of transient skin rashes and

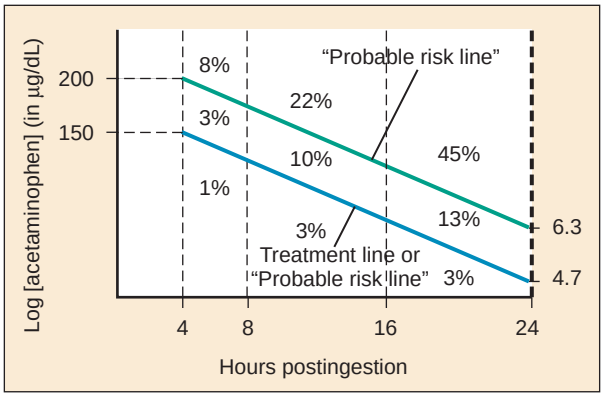

Fig. 143.4. Risk of liver injury (alanine transaminase >1000 IU) based on initial acetaminophen concentration and time to administration of oral *N*-acetylcysteine (NAC). (Adapted from Rumack BH: Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol 40:3, 2002.)

BOX 143.1

Indications for Emergent Hemodialysis Following Acute Acetaminophen Ingestion

Highly elevated serum acetaminophen concentration (>1000 mg/L) at 4 hours post-ingestion
Hepatorenal syndrome (Cr >3.5)
Metabolic acidosis with pH <7.30
Encephalopathy
Elevated lactate (>3.5 mmol/L)

TABLE 143.3

Side Effect Profile for *N*-Acetylcysteine Formulations

N-ACETYLCYSTEINE FORMULATION	COMMON SIDE EFFECTS	SEVERE SIDE EFFECTS
PO NAC	Vomiting (13%)	Very rare
IV NAC	Mild anaphylactoid reactions (eg, rash, flushing, pruritus, vomiting), 2% to 18%	Severe anaphylactoid reactions (eg, hypotension), <1%

IV, Intravenous; *NAC, N*-acetylcysteine; *PO, per os* (by mouth).

flushing. More severe reactions have been reported in less than 1% of patients and include angioedema, bronchospasm, hypotension, and rarely death. Symptoms typically occur within 30 minutes of the start of the loading infusion. These anaphylactoid reactions are dose, rate, and concentration-dependent.

Anaphylactoid reactions are much less frequent with PO NAC. Skin rash, serious systemic reactions, and anaphylactic reactions are rarely reported with the PO formulation. However, approximately 13% of patients receiving PO NAC vomit (versus 7% with IV NAC), delaying timely antidote delivery.[18] PO NAC is extremely unpalatable largely due to a sulfur or "rotten egg" odor and taste. Palatability may be improved by administering NAC diluted with either soda or juice and serving it in a covered container through a straw. Any dose that is vomited within 1 hour of administration should be repeated. If vomiting occurs, we recommend ondansetron in a 4 mg dose for adults. However, we do not recommend routine "prophylactic" use of antiemetics.

Anaphylactoid reactions to IV NAC are typically mild (eg, flushing) and occur during the initial 15- to 60-minute infusion. Mild reactions can be managed with parenteral diphenhydramine, 25 mg IV, without stopping the infusion. For more serious reactions, with hypotension, we recommend slowing or pausing the infusion, giving a 500 mL fluid crystalloid bolus, and administering diphenhydramine, 25 mg IV. For reactions persisting despite these steps, administer methylprednisolone 120 mg IV and take other actions as indicated for severe allergic reaction. Epinephrine is rarely required. Although these reactions require close observation and treatment, they do not preclude subsequent doses, but pretreatment with diphenhydramine is advised.[19]

Use in Pregnancy

Acetaminophen crosses the placenta, but the fetus in the first trimester of development is only at risk for injury if the mother suffers hepatoxicity because fetal CYP enzymes have not fully developed.[20,21] However, if the fetus is near-term (third trimester of development), there is a risk for direct fetal/neonatal hepatotoxicity, because the liver system is more developed at this stage. Treating the mother with NAC is safe and effective, and NAC effectively crosses the placenta. NAC is used with the same protocols as for the nonpregnant patient. Administration of IV NAC to the mother has the theoretical advantage of increased NAC delivery to the fetus compared to PO NAC. IV administration circumvents first-pass metabolism, presumably exposing the fetal circulation to higher maternal serum concentrations. Based on large published studies, we recommend 21 hours of therapy with the IV protocol following an acute ingestion, or alternatively, 72 hours with the oral protocol if the IV preparation is unavailable, as described later.

Duration of Therapy. There are two well-established protocols for NAC administration in cases of acute acetaminophen toxicity: a 21-hour IV protocol and a 72-hour PO protocol.[22] The standard IV NAC protocol in adults is a loading dose of 150 mg/kg up to a maximum of 15 gm in 200 mL of dextrose 5% in water (D5W) infused over 60 minutes followed by a first maintenance dose of 50 mg/kg (up to a maximum of 5 gm) in 500 mL D5W infused over 4 hours followed by a second maintenance dose of 100 mg/kg (up to a maximum of 10 gm) in 1000 mL D5W infused over 16 hours (6.25 mg/kg/hour).

When NAC is administered orally, the patient should receive a 140 mg/kg loading dose, either orally or by enteral tube. Starting 4 hours after the loading dose, 70 mg/kg should be given every 4 hours for an additional 17 doses (total treatment duration of 72 hours).

Several other regimens, including 48 hours IV, 36 hours IV, 36 hours PO, and 20 hours PO protocols are described; however, none of these has been adequately studied for general use.[17]

For delayed, chronic, or supratherapeutic toxicity, NAC therapy should continue until acetaminophen is undetectable in the serum (<10 mcg/mL) and any signs of liver injury have resolved (ie, encephalopathy has cleared, normalization of the coagulation profile, resolution of metabolic acidosis) and the AST is less than 1000 IU/L with demonstration of a downward trend.

DISPOSITION

Asymptomatic patients who fit the criteria for treatment should be treated with NAC, which can be administered in a medical inpatient unit or an emergency department observation unit. The motivation behind any ingestion needs to be evaluated, and psychiatric consultation is obtained when appropriate.

Patients showing evidence of severe hepatotoxicity and those at risk for fulminant hepatic failure may need to be admitted to a monitored bed or an intensive care unit. These patients require frequent neurologic checks, monitoring of vital signs, and repeated laboratory studies.

If a patient presents with established hepatotoxicity, transferring to a tertiary-care center that specializes in the management of patients with hepatic failure and have liver transplant capabilities is advisable. Clinical predictors of severe hepatic failure are listed in Table 143.4.

TABLE 143.4

Inpatient Predictors of the Severity of Illness in Patients With Acetaminophen Toxicity

SCORE	PREDICTIVE VARIABLES	OUTCOME PREDICTED	NOTES
Modified Kings College Criteria	pH <7.3 *or* *All three:* • Cr >3.3 *and* • INR >5 (or PTT >100s) *and* • Encephalopathy more than grade III (patient comatose)	Death or transplant	Arterial pH is measured *after* fluid resuscitation.
APACHE II	APACHE II score >20	Death or transplant	Confounders include co-ingested medications that may alter the APACHE II score.
Lactate	Lactate >3.5 mmol/L prior to resuscitation	Death or transplant	Lactate was drawn a mean of 55 hours after ingestion. The predictive ability of an early lactate draw is unknown.

APACHE II, Acute Physiology and Chronic Health Evaluation II; *Cr,* creatinine; *INR,* international normalized ratio; *PTT,* partial thromboplastin time.

KEY CONCEPTS

- Acetaminophen concentration should be measured in the vast majority of intentional oral overdoses. Acetaminophen is relatively clinically silent until serious hepatotoxicity ensues.
- Repeated supratherapeutic dosing of acetaminophen can lead to life-threatening toxicity.
- The acetaminophen concentration on the nomogram at 4 hours or more post-ingestion is used to determine whether NAC therapy is indicated for acute ingestions.
- IV NAC is preferable to PO NAC. When NAC is initiated, it is continued until the protocol is completed and there is no evidence of liver injury and clearance of acetaminophen. If there is evidence of liver injury or acetaminophen level remains >10 μg/mL, NAC is continued until acetaminophen is undetectable, clinical signs of liver injury have resolved, and liver enzymes are declining (AST <1000 IU/L).
- For maximum benefit, NAC treatment should not be delayed beyond 8 hours after ingestion. If more than 8 hours has passed since ingestion, treatment should be started with ongoing assessment of the amount of ingestion (with serial acetaminophen levels) and likelihood of hepatotoxicity (elevated transaminases, coagulopathy, and encephalopathy).
- Late or prolonged administration of NAC is beneficial even with low or absent acetaminophen concentrations if hepatotoxicity is evident.
- NAC is safe in pregnancy and is used in the same protocol as for the nonpregnant patient.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 143: QUESTIONS & ANSWERS

143.1. Which of the following is true regarding pregnant patients with an acute acetaminophen ingestion?

A. All pregnant women should be treated with *N*-acetylcysteine (NAC) after any known ingestion of acetaminophen
B. Pregnant women in the third trimester should be treated with NAC if their acetaminophen concentration is ever elevated above 50 μg/mL
C. Pregnant women should be treated with NAC if their acetaminophen concentration is above the Treatment Line on the nomogram
D. Pregnant women should be treated with NAC if they ingest >75 mg/kg PO acetaminophen over less than 8 hours
E. The Treatment Line on the nomogram is lowered to a line starting at 100 μg/mL at 4 hours after ingestion

Answer: C. Pregnant patients with an acute ingestion of acetaminophen should have the same initial treatment as nonpregnant patients. After measurement of an acetaminophen concentration, plotting of the acetaminophen concentration on the nomogram treatment with NAC should be given if the concentration is above the Treatment Line on the nomogram.

Both acetaminophen and NAC do cross the placenta, but the fetus is at risk only if the mother becomes ill. Patients with first trimester pregnancies are at risk of miscarriage if the mother becomes ill, and fetuses that are near-term may be at risk for fetal/neonatal hepatotoxicity.

143.2. A 3-year-old boy with intractable vomiting and fever is treated with intravenous (IV) acetaminophen. He is given a tenfold dosing error (150 mg/kg instead of 15 mg/kg). Which of the following is one of the current criteria for treatment of his overdose?

A. Treat with *N*-acetylcysteine (NAC) if the 4-hour acetaminophen concentration is above 50 μg/mL
B. Treat with NAC for any IV dose greater than 15 mg/kg
C. Treat with NAC for any IV dose greater than 4 grams
D. Treat with NAC only if the 2-hour acetaminophen concentration is above the Treatment Line
E. Treat with NAC only if the 4-hour acetaminophen concentration is above the Treatment Line

Answer: A. Although data is limited, the current recommendations for treatment with NAC of an IV acetaminophen overdose is (1) treat for any dose >60 mg/kg or (2) treat if the 4-hour acetaminophen concentration is >50 μg/mL.

143.3. A 30-year-old woman presents with drowsiness, nausea, and vomiting. She reports taking several pills in a suicide attempt. Despite your best efforts, she cannot describe what she ingested or how many she ingested. She states she took the pills "last night" and refuses to be more specific. Currently, it is 6 AM. A family member is present and found the patient vomiting at 4 AM, at which time she informed the family member she took some pills. The family member further states that the patient was in an argument with a friend at 12 PM and may or may not have ingested the pills at that time. The family was with the patient at 8 PM and is sure that she had not ingested the pills at that time. What time should be used as the time of ingestion?

A. 2 AM—the time that is 4 hours prior to presentation
B. 4 AM—the time the patient was found abnormal
C. 6 AM—the time of presentation
D. 8 PM—the time the patient was last seen and known to be prior to the ingestion
E. 12 PM—the time the patient was last seen prior to becoming symptomatic

Answer: D. If the exact time of ingestion cannot be determined, then the "worst case" scenario should be assumed. The longer a patient goes without therapy, the worse the outcome. Therefore, the time of ingestion should be assumed to be the last time the patient was seen normal prior to any possible ingestion.

143.4. A 20-year-old man is brought to the emergency department by family with a complaint of "overdose." The patient is drowsy but arousable. His vital signs are normal. His physical examination is normal except for appearing to be intoxicated. He has no complaints. The family reports the ingestion of unknown "pills" as well as alcohol and possibly "street drugs." The ingestion occurred approximately 6 hours ago after an argument. Routine supportive care is initiated. What test must be ordered on this patient because it may affect the immediate treatment plan?
A. Acetaminophen concentration
B. Chest radiograph
C. Head computed tomography (CT) scan
D. Serum alcohol concentration
E. Urine drug screen

Answer: A. The antidote is given as soon as possible after ingestion, but definitely within 8 hours to prevent toxicity.

143.5. What is the typical peak serum acetaminophen concentration after a therapeutic oral ingestion?
A. Undetectable
B. 10 µg/mL
C. 30 µg/mL
D. 50 µg/mL
E. 100 µg/mL

Answer: C. This concentration is typically reached approximately 1 hour after ingestion. Four hours after a therapeutic ingestion, the concentration is typically less than 10 µg/mL. Concentrations higher than this should lead one to consider the possibility of chronic ingestion or a person who does not properly metabolize acetaminophen.

143.6. Two 20-year-old patients present to the emergency department 1 hour after ingesting 15 grams of acetaminophen each in a suicide pact. You are confident of the time of ingestion and that time is confirmed by text messages sent by the patients. Patient A has a 4-hour acetaminophen concentration of 130 mg/dL. Patient B's 4-hour acetaminophen concentration is 170 mg/dL. What is the appropriate treatment for both patients?
A. Neither patient requires treatment because the acetaminophen concentrations are below the treatment cutoff.
B. Neither patient requires treatment because they received activated charcoal (AC).
C. Patient A should receive immediate *N*-acetylcysteine (NAC); patient B should *not* receive NAC.
D. Patient A should *not* receive NAC; patient B should receive immediate NAC treatment.
E. Both patients should receive immediate NAC therapy.

Answer: D. In this case, your confidence of the time of ingestion is high. The Treatment Line crosses 150 mg/dL at 4 hours. Therefore, if the 4-hour acetaminophen concentration is >150 mg/dL, treatment is indicated. In the case above, patient A does not require NAC therapy, but patient B does require treatment with NAC.

143.7. What is the antidote for acetaminophen ingestion?
A. Dimercaprol
B. Hydroxycobalamin
C. *N*-acetylcysteine (NAC)
D. *N*-acetyl-*p*-benzoquinone imine (NAPQI)
E. Succimer

Answer: C. Hydroxycobalamin is an antidote for cyanide; succimer is an antidote for lead; and dimercaprol is an antidote for arsenic, lead, and mercury. NAPQI is the toxic metabolite of acetaminophen.

143.8. A 42-year-old man presents to the emergency department with complaints of nausea and vomiting. He has no other complaints. His symptoms started approximately 12 hours ago. His history is significant for "back pain," which has been worse than normal recently. He states that he finished a bottle of 60 "pain pills" during the past 2 days. His vital signs are normal. Other than right upper abdominal tenderness, his physical examination is normal. Routine laboratory tests including complete blood count, chemistry, and liver panel are normal except an aspartate transaminase (AST) concentration of 265 IU/L. You are concerned for possible repeated supratherapeutic acetaminophen poisoning. What should you do next?
A. Admit the patient for observation and repeat AST testing; because this is a repeated supratherapeutic ingestion, treatment with *N*-acetylcysteine (NAC) is not beneficial.
B. Initiate treatment with activated charcoal (AC) now.
C. Initiate treatment with NAC now.
D. Obtain two serum acetaminophen concentrations 1 hour apart to determine the drug's elimination half-life to decide if treatment with NAC is indicated.
E. Plot the acetaminophen concentration on the acetaminophen treatment nomogram to determine if treatment with NAC is indicated.

Answer: C. Many prescription and nonprescription analgesics contain acetaminophen, so although a patient may deny use of acetaminophen, suspicion should remain high. A patient with chronic acetaminophen ingestion should have an AST and acetaminophen concentration checked. If either is abnormal, treatment with NAC should be initiated. Many patients with repeated supratherapeutic ingestion will not have a markedly increased acetaminophen concentration, and the treatment nomogram is not used with repeated supratherapeutic dosing. Regardless of how long ago the ingestion occurred, if a patient displays signs or symptoms of liver damage, NAC should be given because it will still have beneficial effects.

143.9. A 55-year-old man is taking 10 grams of acetaminophen per day over the last 8 days for a toothache. He arrives to the emergency department with severe right upper quadrant (RUQ) pain, jaundice, and hypoglycemia. His aminotransferases, bilirubin, and acetaminophen concentration are highly elevated, and he is resuscitated and started on intravenous (IV) *N*-acetylcysteine (NAC). Which of the following laboratory findings is a very poor prognostic indicator and indicates that he is a candidate for immediate liver transplant?
A. Aspartate transaminase (AST) >10,000 IU/L
B. Bilirubin >5 mg/dL
C. Lactate >5 mmol/L
D. Acetaminophen concentration >150mg/dL
E. pH <7.4

Answer: C. The patient has severe liver failure due to repeated supratherapeutic dosing of acetaminophen. Prognostic variables that are used to determine immediate hepatic transplant are the Kings College Criteria (a pH <7.3[or lactate >3.5 mmol/L] after resuscitation *or* the combination of Cr >3.3 and PTT >100s [or INR >5] and grade 3 or 4 encephalopathy). Other criteria that

indicate high mortality are the APACHE II score >20. If a patient in the emergency department meets these criteria, immediate consultation with a hepatic transplant surgeon is indicated.

143.10. A 27-year-old woman is brought to the emergency department by emergency medical service (EMS). The patient is lethargic and cannot provide a history. A suicide note indicates that she ingested 50 g of acetaminophen approximately 24 hours ago. The patient is noted to be jaundiced with right upper quadrant (RUQ) tenderness. General supportive care is initiated. Her aspartate transaminase (AST) is 1072 IU. A serum acetaminophen concentration is pending. Which of the following statements is true regarding treatment with *N*-acetylcysteine (NAC)?

A. Treatment with NAC should be delayed until the acetaminophen concentration is obtained.

B. Treatment with NAC should be initiated because an ingestion of 50 g of acetaminophen is potentially fatal.

C. Treatment with NAC should be initiated because the patient has liver injury secondary to acetaminophen poisoning.

D. Treatment with NAC will not alter the outcome; this patient will require a liver transplant.

E. Treatment with NAC will not be beneficial as the ingestion occurred more than 10 hours ago.

Answer: C. Ideally, NAC treatment is initiated within 8 hours of ingestion, but treatment with NAC is still beneficial even after hepatotoxicity has developed. An acetaminophen concentration should be obtained, but there is no reason to delay treatment. Ingestion of 50 g is potentially toxic, but decisions should be based on the patient's current condition. Occasionally, hepatotoxicity from acetaminophen is severe and liver transplant is required, but most cases of hepatotoxicity resolve with NAC treatment.

CHAPTER 144

Aspirin and Nonsteroidal Agents

Benjamin W. Hatten

ASPIRIN

Principles of Toxicity

Overview

Aspirin, or acetylsalicylic acid, is widely consumed for its analgesic, antiinflammatory, and antiplatelet effects. Although its therapeutic use is ubiquitous, salicylate toxicity is not a benign condition and causes a complex set of life-threatening metabolic derangements with significant morbidity and mortality.

Epidemiology

In 2013, 26 deaths were reported to United States Poison Control Centers due to aspirin alone.[1] This is consistent with reports to Poison Control Centers of 20 to 30 deaths per year for the last decade. Of note, elderly patients with chronic medical problems and young patients diagnosed with an acute illness are particularly at risk for delay in diagnosis with consequent severe clinical effects.[2]

Salicylate Containing Products

Aspirin is the most common salicylate-containing product. Other potential sources of salicylate toxicity include topical salicylates, oil of wintergreen, willow bark, and bismuth subsalicylate. Ingestion of oil of wintergreen is of particular concern given that 1 mL of 98% solution contains the equivalent salicylate of 1.4 grams of aspirin.[3]

Pathophysiology

Salts of salicylic acid are rapidly absorbed intact from the gastrointestinal (GI) tract, with appreciable serum concentrations occurring within 30 minutes of ingestion of a therapeutic dose and peak levels in 2 to 4 hours. Large ingestions frequently delay gastric emptying. In addition, aspirin, particularly enteric-coated preparations, tend to form concretions in the stomach. These properties often result in prolonged absorption with rising serum levels for 12 hours or more.[2]

In the intestinal wall, liver, and red blood cells, aspirin is hydrolyzed to free salicylic acid, which reversibly binds to albumin. Free salicylate is eliminated by renal excretion. At therapeutic salicylate concentrations, elimination follows first-order kinetics. Once serum salicylate concentrations are greater than 30 mg/dL, elimination follows zero-order kinetics. The metabolic pathways become saturated, and the pH-sensitive urinary excretion of salicylic acid determines the half-life, prolonging significantly (up to 15 to 30 hours) with large overdoses.[2]

The initial physiologic effect of salicylates is direct stimulation of the medullary respiratory center. In addition, they increase the sensitivity of the respiratory center to pH and partial pressure of carbon dioxide (P_{CO_2}). Hyperventilation develops early, subsequently becoming a compensatory mechanism for metabolic acidosis. Prolonged high serum concentrations eventually depress the respiratory center. Respiratory alkalosis is compensated by the buffering capacity of the hemoglobin-oxyhemoglobin system, the exchange of intracellular hydrogen ions for extracellular cations, and the urinary excretion of bicarbonate. Loss of bicarbonate decreases buffering capacity and intensifies the metabolic acidosis (Box 144.1).[2]

Toxicity results primarily from salicylate interference with aerobic metabolism by uncoupling of mitochondrial oxidative phosphorylation. Inhibition of the Krebs cycle increases production of pyruvic acid and increases conversion to lactic acid. Increased lipid metabolism generates ketone bodies. Metabolic rate, temperature, tissue carbon dioxide, and oxygen consumption are increased. Tissue glycolysis predisposes to hypoglycemia. Inefficiency of anaerobic metabolism results in decreased production of adenosine triphosphate, with energy released as heat causing the hyperthermia frequently seen in salicylate poisoning.

Only non-ionized particles can cross the lipophilic cell membrane and accumulate in the brain and other tissues. Because salicylic acid has a pK_a of 3.5, the majority of salicylate is ionized and unable to enter tissue at the physiologic pH of 7.4. However, as serum pH decreases, more particles become un-ionized and cross the cell membrane and blood-brain barrier, markedly increasing the movement of salicylate into the tissues and central nervous system (CNS).

The rapid depletion of potassium stores in salicylate toxicity is caused by multiple factors. These include vomiting, which is secondary to stimulation of the medullary chemoreceptor trigger zone; increased renal excretion of sodium, bicarbonate, and potassium as a compensatory response to the respiratory alkalosis; salicylate-induced increased permeability of the renal tubules with further loss of potassium; and intracellular accumulation of sodium and water. A final factor is inhibition of the active transport system, secondary to uncoupling of oxidative phosphorylation.[3]

Salicylate related decrease in renal blood flow or direct nephrotoxicity may cause acute non-oliguric renal failure. Drug induced secretion of inappropriate antidiuretic hormone may also affect renal function. The exact mechanism by which salicylates increase alveolar capillary membrane permeability is not clearly defined. Theories include inhibition of prostacyclin, changes in platelet-vessel interaction, and neurogenic influences.

In adults, risk factors for salicylate-induced pulmonary edema include age greater than 30 years old, cigarette smoking, chronic salicylate ingestion, metabolic acidosis, neurologic symptoms, and serum salicylate concentration greater than 40 mg/dL. Risk factors in children include high serum salicylate levels (>80 mg/dL), large anion gap, decreased serum potassium concentration, and low P_{CO_2}.

Salicylates severely affect the CNS in two ways. First, there is, a poorly elucidated aspect of toxicity that ultimately results in cerebral edema. This pathway is presumably related to increased energy requirements, acidemia, and direct cellular toxicity. Second, the consumption of glucose in the brain may outpace the supply. This occurs even in the face of normal serum glucose. One or both

BOX 144.1

Acid Base Disturbance and Progression of Toxicity in Acute Salicylate Overdose

Early (0 to 4 hours; level 20 to 60 mg/dL): Respiratory alkalosis with alkalemia; gastrointestinal (GI) distress, mild to moderate hyperpnea, tinnitus, lethargy

Moderate (2 to 12 hours; level 50 to 90 mg/dL): Respiratory alkalosis and metabolic acidosis with alkalemia or neutral pH; severe hyperpnea, lethargy or agitation, hyperthermia

Severe (6 to 24 hours: Level >80 mg/dL): Respiratory alkalosis or acidosis and metabolic acidosis with acidemia; severe hyperpnea, coma or acute delirium, hyperthermia, pulmonary or cerebral edema, seizure, cardiovascular collapse

of these mechanisms cause altered mental status, seizures, and coma.

At a moderate to high tissue burden, salicylates induce a classic finding of salicylate toxicity—tinnitus, or the sensation of ringing in the ears. This phenomenon is due to a combination of central and peripheral effects. Cochlear toxicity is thought to be the result of alterations in *N*-methyl-D-aspartate (NMDA) activity, decreased blood flow, and increased membrane permeability. Cochlear toxicity combines with hyperactivity in the auditory cortex to cause tonotopic shifts where upper and lower frequency sounds are perceived in the 10 to 20 hertz tinnitus range, and sounds within this range become hyperacute. Salicylate induced hearing disturbance may take days to resolve after the tissue burden normalizes.[4,5]

Physiologic changes of aging predispose elderly patients to toxicity from chronic therapeutic ingestion. Decreased liver blood flow limits biotransformation of salicylate, and decreased renal function reduces salicylate clearance. Chronic ingestion decreases albumin binding, increasing the free salicylate that can enter the cell, and allows salicylates more time to pass through the blood-brain barrier. A patient with chronic salicylate toxicity and a serum concentration of 40 mg/dL may be more ill than a patient with an acute ingestion and serum concentration of 80 mg/dL.

Clinical Features

Salicylate toxicity initially generates GI distress followed by tachypnea, tinnitus, and hearing disturbance due to concentration dependent reversible ototoxicity, diaphoresis, and an evolving anion gap acidosis. As the toxicity progresses, hyperthermia, coagulopathy, cerebral and pulmonary edema, cardiovascular collapse, and, ultimately, death occur. Chronic poisoning may be much more subtle, manifesting as a waxing and waning combination of the above features of toxicity.[3]

Differential Diagnoses

Salicylism mimics sepsis, CNS infection, withdrawal syndromes, and alcoholic or diabetic ketoacidosis. This is especially true in chronic toxicity given that the serum salicylate concentration is relatively low. Thus, the severity of poisoning is often not recognized or not fully appreciated. In addition, co-ingestion is common, so evaluation for other toxic exposures is warranted.

Other pain relievers and fever reducers such as acetaminophen and ibuprofen are often confused with aspirin by patients. Other toxins that cause a metabolic acidosis with an elevated anion gap include colchicine, iron, isoniazid, methanol, ethylene glycol, and cyanide.

Diagnostic Testing

The serum salicylate concentration, acid-base status, and potassium are key diagnostic studies. Be mindful of units when interpreting salicylate levels. Serum salicylate concentrations are reported as mg/dL, mg/L, or mmol/L by various labs but are listed in mg/dL in this text. The Done nomogram should not be used to determine prognosis or treatment of the salicylate-poisoned patient. Measure a salicylate concentration on arrival with a second sample obtained 2 hours later if the first level is detectable. If the second concentration is not substantially declining, obtain concentrations every 2 hours to monitor for continued absorption, which may be prolonged. Serum salicylate levels should be repeated every 2 hours until three consecutive levels are both <30 mg/dL and are decreasing by at least 10% to 20% on each measurement while no longer undergoing therapy to enhance elimination. Even in the face of an initial undetectable level, if the history suggests significant salicylate ingestion, then a second level should be performed 2 hours later to ensure that delayed absorption is not occurring.[4,5]

Acid-base status can change quickly, and monitoring of pH every 2 hours is important to guide treatment. Use early and frequent blood gas determinations in symptomatic patients to rapidly assess acid-base and compensatory status. Developing acidemia portends severe disease. The pH begins to drop when the patient is unable to compensate for acidemia. Lactic acid accumulates, and serum bicarbonate is consumed. When serum pH is less than 7.4 and both Pco_2 and bicarbonate level are low, hemodynamic instability rapidly develops.[3]

A metabolic panel is necessary to guide electrolyte replacement (focused on potassium) and to assess renal function and glucose metabolism. However, anion gap determination on a metabolic panel is not a substitute for obtaining a salicylate level or measuring pH. A serum acetaminophen concentration should also be obtained to screen for ingestion of this common, clinically occult analgesic. An electrocardiogram (ECG) is indicated in older patents with underlying cardiac disease that are on daily aspirin therapy.

Management

Stabilization and Supportive Care

Accurate ascertainment of vital signs is the initial step in assessment, including oxygen saturation, respiratory rate, and a reliable temperature. Chest auscultation provides evidence of pulmonary edema, and altered mental status may suggest CNS toxicity.

Dehydration occurs early in salicylate intoxication because of the hypermetabolic state and initial fluid requirements may be as high as 4 to 6 L. Fluid administration should be guided by the patient's apparent deficit to maintain urine output of 2 to 3 mL/kg/hr. Correct potassium depletion to maintain a serum level greater than 4.5 mEq/L.[3]

Unless the patient is decompensating, early mechanical ventilation should be avoided. Similar to diabetic ketoacidosis, it is difficult to artificially achieve adequate minute ventilation that sufficiently matches the patient's own respiratory compensation. In addition, the loss of ventilation during the intubation results in rapid loss of respiratory compensation and worsening acidemia. If the patient is sufficiently critically ill to require intubation, worsening of acidosis during apnea is potentially harmful. Thus we recommend administration of 50 to 100 mEq (1 to 2 amps) of sodium bicarbonate ($NaHCO_3$) immediately prior to the procedure irrespective of the serum pH. Attempt to adjust the tidal volume post-intubation to match the pre-intubation PCO_2 level. In addition, establish an elevated minute volume and obtain

frequent blood gases to guide ventilator management to maintain respiratory compensation.[3]

Decontamination

Activated charcoal (AC) has been shown to reduce salicylate absorption in both animal studies and human volunteer trials. Evidence in overdose is less clear. We recommend administering multiple-dose oral AC (25 to 50 gm) every 2 to 4 hours if the patient's GI, mental, and hemodynamic status tolerate, because large salicylate ingestions tend to form gastric concretions. AC is not used in chronic salicylate poisoning because the presentation occurs long after absorption.[3]

Enhanced Elimination

Specific treatment of salicylate toxicity has two objectives: (1) to correct fluid deficits and acid-base abnormalities and (2) to increase excretion (Box 144.2).

Because salicylates have a low pK_a and are renally excreted, alkaline urine traps the salicylate ion and increases excretion. Urine alkalinization is advisable in patients with salicylate levels greater than 30 mg/dL, significant acid-base disturbance, or increasing salicylate levels. This is most often achieved via administration of a bicarbonate drip: 132 to 150 mEq (three 50 mL ampules) of 7.5% or 8.4% $NaHCO_3$ in 1 L of dextrose 5% in water (D5W) + 40 mEq of potassium chloride (KCl) running at 2 to 3 mL/kg/hr. Salicylate clearance varies in direct proportion to flow rate but increases exponentially with pH. A urine pH of at least 7.5 to 8.0 is ideal to increase excretion. Urine alkalinization is difficult to achieve because the excretion of salicylic acid in the urine decreases urine pH. In addition, potassium depletion must be corrected to attain alkaline urine as the kidney exchanges hydrogen for potassium in the setting of hypokalemia, further acidifying the urine. In most patients, a serum pH of up to 7.55 is well tolerated. Forced diuresis should not be performed, because it does not significantly increase salicylate excretion and may potentiate cerebral and pulmonary edema.[2,3,6]

Hemodialysis is highly effective in resolving salicylate toxicity. It is indicated for patients with any of the following: serum salicylate levels greater than 100 mg/dL in acute and 40 mg/dL in chronic salicylate poisoning; altered mental status, including coma; seizure; endotracheal intubation (other than for coingestions); renal or hepatic failure; pulmonary edema; severe acid-base imbalance (pH <7.1 to 7.2); rapidly rising serum salicylate level; and failure to respond to more conservative treatment. Of note, the levels recommended here are for initiation of hemodialysis. Consultation with nephrology to prepare for hemodialysis should occur long prior to reaching a serum salicylate concentration of 100 mg/dL. A concentration of 80 mg/dL, or even lower if concentrations are rising rapidly, should prompt nephrology consultation or transfer to a higher level of care in anticipation of hemodialysis.[2,3]

Greater salicylate concentration on the fetal side of the placenta and relative fetal acidemia contribute to fetal distress from maternal salicylate poisoning. Salicylate poisoning during pregnancy is associated with fetal demise, and consultation with an obstetrician to facilitate delivery of the distressed fetus in the third trimester of pregnancy should be considered if the fetus is viable.[2]

Antidote Therapy

Central hypoglycemia may be responsible for altered mental status in the setting of salicylate toxicity. In all cases of altered mental status, even in the face of a normal serum glucose measurement, supplemental intravenous (IV) glucose (0.5 to 1 gm/kg) should be administered. Additional glucose supplementation may be required and should be administered in response to recurrent altered mental status.[3]

BOX 144.2

Treatment of Acute Salicylate Poisoning

Treat dehydration; maintain urine output at 2 to 3 mL/kg/hr.
Correct potassium depletion with goal serum level of 4.5 mEq/L.
Consider activated charcoal (AC); 25 grams every 2 to 4 hours for two to four doses if tolerated.
Alkalinize urine with goal urine pH of 7.5 to 8.0.
- Infuse bicarbonate drip: 132 to 150 mEq (three 50-mL ampules) of 7.5% or 8.4% sodium bicarbonate ($NaHCO_3$) in 1 L of dextrose 5% in water (D5W) + 40 mEq of potassium chloride (KCl) running at 2 to 3 mL/kg/hr.
- Allow serum pH up to 7.55.
- Do not attempt forced diuresis.

Initiate hemodialysis if any of the following occur:
- Altered mental status, coma, seizure
- Renal failure
- Hepatic failure
- Pulmonary edema or respiratory failure
- Severe acid-base imbalance (pH <7.1 to 7.2)
- Deterioration in condition
- Intubation
- Failure of urine alkalinization
- Rapidly rising salicylate level
- Serum salicylate concentration ≥100 mg/dL after acute ingestion
- Serum salicylate concentration ≥40 mg/dL after chronic ingestion

Administer intravenous (IV) dextrose 0.5 to 1 g/kg IV for any central nervous system (CNS) abnormalities (altered mental status, coma, agitation, seizure)

Disposition

In patients with acute intoxication, hospital admission to an intensive care setting is appropriate for pulmonary edema, CNS symptoms (other than tinnitus), seizures, pH <7.3, electrolyte disorders, dehydration, renal insufficiency, or increasing serum levels during serial testing. In patients with chronic intoxication, low serum salicylate concentrations (40 mg/dL) may accompany severe salicylism. These patients should be admitted to a monitored setting for observation, serial levels, and metabolic assessment. Consultation with a medical toxicologist may allow for emergency department (ED) observation management of the salicylate poisoned patient not requiring hemodialysis.

In patients with acute ingestion, repeated serum salicylate measurement is essential to determine that the serum concentration is decreasing before the patient is discharged. Serum salicylate levels should be repeated every 2 hours until three consecutive levels are both <30 mg/dL and are decreasing by at least 10% to 20% on each measurement while no longer undergoing therapy to enhance elimination. In addition, the patient should no longer be symptomatic at the time of discharge. With any case of intentional overdose, psychiatric evaluation is recommended.[2,3]

NONSTEROIDAL AGENTS

Principles of Toxicity

The nonsteroidal antiinflammatory drugs (NSAIDs) have analgesic, antiinflammatory, and antipyretic activities. Ibuprofen and

naproxen, both propionic acid derivatives, are available over the counter in the United States and are the most commonly encountered NSAIDs. The therapeutic antiinflammatory effect of the NSAIDs is achieved by inhibition of cyclooxygenase (COX) and consequent blockade of prostaglandin production.

NSAIDs are almost completely absorbed from the upper small intestine after oral administration. NSAIDs are highly bound to plasma proteins and therefore have small volumes of distribution (0.10 to 0.17 L/kg). They are eliminated by hepatic biotransformation. Metabolites are typically inactive with the notable exception of phenylbutazone. Plasma half-lives are short (1 to 4 hours), except for naproxen (12 to 15 hours), oxaprozin (25 to 50 hours), piroxicam (45 hours), and phenylbutazone (50 to 100 hours). Elimination half-lives are not substantially prolonged in overdose.[7]

Clinical Features

Most NSAID overdoses are asymptomatic or cause only minor symptoms. Ibuprofen is the most common NSAID ingested in overdose and most follow a benign, self-limited course. Symptomatic overdose occurs only after ingestion of at least 100 mg/kg, and symptoms develop within 4 hours of ingestion. Life-threatening toxicity is rare with most cases limited to mild GI disturbance that resolves in hours. Less common clinical effects include metabolic acidosis, muscle fasciculations, mydriasis, diaphoresis, hyperventilation, bradycardia, hypotension, dyspnea, tinnitus, and rash. Rare cases of coma, seizure, hypotension, and metabolic acidosis have been reported in massive overdoes (400 to 500 mg/kg).[7]

Renal dysfunction is seen only after large acute overdose and in association with a period of relative hypovolemia with hypotension. It is reversible and usually responds to supportive measures.

All propionic acid derivatives have been associated with sporadic cases of aseptic meningitis. This complication is most common with ibuprofen. It occurs in an idiosyncratic fashion—both in overdose and with therapeutic dosing.

Mefenamic acid, a fenamate, is associated with a relatively high incidence of seizures, which occur 2 to 7 hours after supratherapeutic ingestion. Rapid recovery is the rule with supportive care and IV benzodiazepines.

Phenylbutazone, a pyrazolone, is now rarely used because of its association with aplastic anemia and agranulocytosis. Although phenylbutazone overdose is rare, the course is much more severe than with other NSAIDs. Severely poisoned patients have early onset of GI distress, coma, seizure, hyperthermia, hyperventilation, alkalosis or acidosis, hypotension, electrocardiographic abnormalities, or cardiac arrest. Late sequelae of severe poisoning (2 to 7 days) include renal, hepatic, and hematologic dysfunction. The clinical course is prolonged compared with that of other NSAID poisoning, reflecting the elimination half-lives of phenylbutazone and its principal metabolite, oxyphenbutazone.

Differential Diagnoses

Given that nearly all NSAID overdoses are minimally symptomatic, the differential diagnosis should focus on toxicity due to possible co-ingestions. Patients often confuse NSAIDs with other pain relievers and fever reducers, including acetaminophen and salicylates.

Diagnostic Testing

Plasma NSAID concentrations are not clinically useful and are rarely available in the ED. With larger overdoses (>100 mg/kg), a complete blood count, metabolic profile, and assessment of renal function are recommended. Because patients often confuse and mix pain relievers, a screening serum acetaminophen and salicylate level is prudent.

Management

Stabilization and Supportive Care

The management of NSAID overdose is supportive, and there is no specific antidote. Pyrazolone (eg, phenylbutazone) and fenamate (eg, mefenamic acid) toxicity is associated with significantly higher morbidity (see earlier) and may require more supportive care measures, including control of seizures with benzodiazepines, fluid resuscitation, correction of electrolyte disturbances, and ventilatory support. Hypotension is managed with a 1 to 2 L bolus of normal saline or lactated Ringer's solution, which may be repeated or supported by infusions at two to three times maintenance rate. If perfusion compromise persists, initiate a vasopressor, such as norepinephrine, and titrate to maintain an adequate mean arterial pressure for perfusion. Although it is rarely indicated and not studied, extracorporeal membrane oxygenation has successfully managed refractory hypotension after massive ibuprofen overdose.

Decontamination

There is no evidence supporting the use of gastric emptying or AC in NSAID overdoses.

Enhanced Elimination

Because of high protein binding and rapid metabolism, enhanced elimination is not useful in most cases. In the rare case of a massive overdose with pH <7.1, hemodialysis should be considered to correct acidemia. In this situation, hemodialysis may also remove the free drug once protein binding is overwhelmed. Plasmapheresis has been attempted in severe phenylbutazone poisoning.

Antidote Therapy

There is no specific antidote for NSAID poisoning.

Disposition

Patients who are mildly symptomatic or asymptomatic for more than 4 hours after an NSAID overdose do not require further medical care. Patients who have ingested a pyrazolone or fenamate require observation for possible seizures until 8 hours after ingestion. Those with CNS symptoms, acidosis, or renal insufficiency and who require supportive care should be admitted for ongoing treatment. Patients with mild to moderate symptoms may be observed in the ED until they are asymptomatic or improving. Patients for whom the ingestion represents a suicidal gesture should undergo psychiatric assessment.

KEY CONCEPTS

- Salicylates are profoundly toxic and can be fatal. Salicylate overdose requires active assessment and treatment. The other NSAIDs generally have self-limited toxicity and respond to supportive measures only. There is no antidote for any of these drugs.
- Salicylism should be considered in the differential diagnosis of altered mental status in the elderly.
- Acidemia signifies loss of respiratory compensation and acceleration of toxicity.
- The Done nomogram should not be used in the evaluation and treatment of salicylate toxicity.
- Salicylate concentrations and blood gas draws should occur every 2 hours until salicylate level is less than 30 mg/dL and is falling at least 10% between assays in the absence of measures to enhance elimination.
- Potassium stores are rapidly depleted in patients with salicylate intoxication and should be repleted with a goal serum level of 4.5 mEq/L.
- Mechanical ventilation should be avoided if possible in cases of severe salicylate poisoning. Acidosis may rapidly worsen due to loss of ventilation during the intubation procedure, and it is difficult to maintain ventilation at the level of physiological hyperventilation.
- If intubation is necessary, a bolus of sodium bicarbonate (50 to 100 mEq) is given before intubation and post-intubation minute ventilation is increased to match pre-intubation respiratory compensation.
- Enhanced elimination through urinary alkalinization with a sodium bicarbonate drip should be initiated in acute toxicity with a level >30 mg/dL.
- Consultation with nephrology and preparation for hemodialysis should occur if the salicylate concentration is 80 mg/dL or is rising rapidly.
- Hemodialysis is recommended for signs of pulmonary or cerebral edema, coma, seizures, hepatic failure, renal failure, circulatory collapse, or refractory acidosis along with acute levels greater than 100 mg/dL and chronic levels of 40 mg/dL.
- Altered mental status in the setting of salicylate toxicity warrants IV glucose supplementation.
- Most NSAID overdoses are asymptomatic or cause only minor symptoms.
- Ibuprofen, along with other propionic acid derivatives, has been associated with sporadic cases of aseptic meningitis.
- The management of NSAID overdose is supportive, and there is no specific antidote. Hemodialysis is reserved for patients with massive overdose and pH <7.1.
- Patients who have ingested a pyrazolone or fenamate require observation for possible seizures until 8 hours after ingestion.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 144: QUESTIONS & ANSWERS

144.1. What type of acid-base disorder is caused by salicylate overdose?

A. Metabolic acidosis and respiratory acidosis
B. Metabolic acidosis and respiratory alkalosis
C. Metabolic alkalosis and respiratory acidosis
D. Metabolic alkalosis and respiratory alkalosis
E. No acid-base disorder

Answer: B. Early in overdose, salicylates stimulate the respiratory center, causing hyperventilation and a respiratory alkalosis. Later, salicylates inhibit mitochondrial oxidative phosphorylation, resulting in anaerobic metabolism and a metabolic acidosis. This is the classic situation but is later followed by respiratory compensation, resulting in the possibility of a triple acid-base disorder.

144.2. A 22-year-old man presents 6 hours after a suicide-related aspirin overdose. His only complaint is of tinnitus, and his vital signs and physical examination are normal. His salicylate level is 47 mg/dL. His serum pH is 7.3, with an anion gap of 18 and a serum bicarbonate level of 17 mmol/L. Which of the following is the most appropriate therapy?

A. Forced diuresis
B. Hemodialysis
C. Observation only
D. Oral-activated charcoal due to chronic poisoning
E. Urinary alkalinization

Answer: E. Salicylates are acidic compounds and therefore readily ionize in an alkali environment. Only in the non-ionized state can they traverse cell membranes. Thus, once ionized in the urine, they are effectively "trapped" and can be easily excreted. Urinary alkalinization is indicated in patients with a salicylate level greater than 30 mg/dL, significant acid-base disturbances, or increasing salicylate levels. Forced diuresis does not increase excretion, increases the risk for pulmonary and cerebral edema, and is never indicated. Hemodialysis is the ultimate treatment for salicylate poisoning but is generally reserved for patients with more severe signs or symptoms, more severe acid-base disturbances, or acute salicylate levels greater than 100 mg/dL. Observation alone would be indicated in a patient with a history of salicylate overdose but with no symptoms and normal laboratory values. AC can decrease the amount of salicylate absorbed if given within 1 hour of ingestion. Because large salicylate ingestions tend to form gastric concretions, multiple doses of AC may be indicated. AC is not used in chronic salicylate poisoning because the presentation occurs long after absorption.

144.3. Which of the following patients is at the highest risk of death?

A. A 9-year-old boy with chronic salicylate ingestion and salicylate level of 10 mg/dL
B. A 20-year-old pregnant woman with acute salicylate overdose and salicylate level of 100 mg/dL
C. A 24-year-old man with acute salicylate overdose and salicylate level of 110 mg/dL
D. A 30-year-old woman with chronic salicylate ingestion and salicylate level of 50 mg/dL
E. A 42-year-old woman with acute salicylate overdose and salicylate level of 90 mg/dL

Answer: D. The mortality rate for chronic salicylate ingestion is 25 times that of acute salicylate ingestion. Infants and the elderly, as well as patients with comorbidities, are also at greater risk of death. Salicylate poisoning can cause severe fetal distress and ultimate fetal demise, but the prognosis for the mother is not significantly changed. In otherwise similar patients, a higher salicylate level is associated with a worse prognosis.

144.4. A 41-year-old man presents after an accidental ibuprofen overdose. He complains of epigastric pain, nausea, and one episode of vomiting. He reports that approximately 2 hours ago he took four 800-mg ibuprofen tablets. (He meant to take four 200-mg ibuprofen tablets.) Which of the following is the appropriate next step?

A. Check electrocardiogram (ECG) to determine further treatment
B. Check serum chemistry and salicylate level to determine further treatment
C. Observation for resolution of symptoms
D. Oral activated charcoal (AC)
E. Urinary alkalinization

Answer: C. Nonsteroidal antiinflammatory drugs (NSAIDs) are generally safe in overdose. Specifically, ibuprofen overdose often results in mild self-limited gastrointestinal (GI) upset. Typically, at least 100 mg/kg of ibuprofen needs to be ingested to cause symptoms. Rare, but serious, symptoms include coma, seizure, hypotension, hypothermia, GI bleeding, acute renal failure, and metabolic acidosis. All symptoms are treated with supportive care. Symptoms almost always develop within 4 hours of ingestion. In general, patients may be discharged in cases of small overdoses (<100 mg/kg), once symptoms resolve or after a 4-hour period of observation.

CHAPTER 145

Anticholinergics

Andrew A. Monte | Jason A. Hoppe

PRINCIPLES OF TOXICOLOGY

Overview

Anticholinergic agents cause toxicity through inhibition of muscarinic, nicotinic, parasympathetic, or sympathetic acetylcholine receptors. Nicotinic receptor inhibition and ganglionic acetylcholine inhibition at parasympathetic and sympathetic locations is covered in Chapter 157. This chapter focuses on antimuscarinic effects and toxicity. The terms *anticholinergic* and *antimuscarinic* are commonly used synonymously, but the mechanism of toxicity is more accurately described by the term *antimuscarinic,* and thus that term is used in this chapter.

Antimuscarinic effects are due to inhibition of acetylcholine at muscarinic receptors. Muscarinic receptors are found on peripheral postganglionic cholinergic nerves in smooth muscle (intestinal, bronchial, and cardiac), the secretory glands (salivary and sweat), the ciliary body of the eye, and the central nervous system (CNS).

Antimuscarinic agents have been used medicinally from antiquity to present day. Mandrake plant remains were found in the casket of Tutankhamen, the Old Testament of the Bible references use as an aphrodisiac, and antimuscarinic plants were used as anesthetics in Greek and Roman settlements in the first century. Atropine, hyoscyamine, and scopolamine are naturally occurring tertiary amine antimuscarinic agents that remain in wide clinical use today. The tertiary amine structure allows the agent to cross the blood-brain barrier; and therefore, these agents may precipitate CNS toxicity. Quaternary amine antimuscarinic agents, such as glycopyrrolate, have been developed to mitigate CNS side effects due to their limited ability to cross the blood-brain barrier, although mild delirium may occur in the setting of a large overdose.

Clinical Features

Over 600 compounds contain antimuscarinic activity, including prescription drugs, over-the-counter medications, and plants. The effects of muscarinic receptor blockade are used for clinical purposes including pupillary dilation, antispasmodics, treatment of motion sickness, drying of airway secretions, reactive airways disease, treatment of bradycardia, treatment of Parkinsonism, and the management of urinary incontinence and bladder spasm. The agents that most commonly precipitate antimuscarinic toxicity, such as H1 antihistamines and some antipsychotics, often affect several neurotransmitters and receptor systems in addition to antagonism at muscarinic receptors. This may complicate the clinical presentation, and some clinical symptoms may be unique to the specific etiologic agent (Table 145.1).

Antimuscarinic toxicity has central and peripheral manifestations (Fig. 145.1 and Box 145.1). Peripheral muscarinic antagonism causes tachycardia, hypertension, hyperthermia, mydriasis, dry mouth, dry skin (lack of sweating), skin flushing, decreased bowel motility, and urinary retention. CNS blockade of muscarinic receptors may produce delirium characterized by confusion, mumbling speech, agitation, hallucinations, picking gestures, myoclonus, tremor, and coma. Seizures are not expected from pure muscarinic receptor antagonism but many antimuscarinic medications have activity at other receptors that may precipitate seizures. Diphenhydramine toxicity is a classic example of this; it causes significant antimuscarinic symptoms and may also cause seizures through sodium channel blockade. Manifestations of the toxidrome are frequently incomplete and either peripheral or central components may predominate depending upon the antimuscarinic agent, the dose, and the individual patient (see Table 145.1). Only about one-third of patients will manifest all three classic autonomic findings: tachycardia, dry skin/axilla, and mydriasis. Patients may demonstrate delirium as their only manifestation of toxicity. The duration of toxicity is dependent on the dose and is difficult to predict but is often prolonged (18 to 72 hours) due to delayed gastric emptying.

DIFFERENTIAL DIAGNOSES

The diagnosis of antimuscarinic poisoning is most often made by obtaining a history of exposure, either from the patient or someone who was present with the patient at the time. Antimuscarinic toxicity is an important consideration when there is altered mental status with a history of exposure or if physical examination is consistent with toxicity (Box 145.2). Altered mental status, mydriasis, and tachycardia are common antimuscarinic effects that are also seen with multiple conditions (eg, sympathomimetic toxicity, serotonin syndrome, alcohol withdrawal). However, dry axilla, decreased bowel sounds, and urinary retention are less common with adrenergic toxicity and more likely to be associated with antimuscarinic causes. Agitation occurs both with sympathomimetic and antimuscarinic toxicity, but severe agitation and combativeness are more likely to represent the sympathomimetic than antimuscarinic agents—the latter generally cause only mild to moderate agitation. Major medical emergencies should be considered early in the course to ensure timely management. Intracranial hemorrhage (ICH) may lead to altered mental status, hypertension, and dilated pupils, although unilateral pupillary dilation is more likely due to tonsillar herniation when ICH is the etiology of altered mental status. CNS infections or hyperthyroidism may similarly lead to altered mental status, hyperthermia, and hypertension. Failure of physostigmine to reverse the altered mental status should prompt evaluation for meningitis, encephalitis, and thyrotoxicosis.

DIAGNOSTIC TESTING

Laboratory

Patients with mild toxicity, a reliable history of exposure, and symptoms consistent with antimuscarinic toxicity do not require specific laboratory testing. Patients with an unclear history of exposure, other potential etiologies, moderate to severe toxicity, or hyperthermia should be evaluated for causes of altered mental status and end-organ toxicity, including serum glucose,

TABLE 145.1

Specific Antimuscarinic Agents and Their Unique Clinical Manifestations

ANTIMUSCARINIC AGENT	TOXIC DOSE	UNIQUE CLINICAL MANIFESTATIONS AND RECEPTORS ANTAGONIZED
Datura spp.	Seeds contain high concentrations of hyoscyamine and scopolamine. The toxic dose depends upon the species and the mode of ingestion. In general 5 to 10 seeds may be toxic.	Classic peripheral and central antimuscarinic features M_1
Diphenhydramine	2.5 mg/kg; >10 mg/kg may result in cardiovascular and neurologic toxicity.	CNS depression, QRS prolongation and ventricular dysrhythmias, seizures* M_1, H_1, Na^+ channels
Doxylamine	>20 mg/kg associated with rhabdomyolysis.	CNS depression, seizures, rhabdomyolysis† M_1, H_1
Tricyclic antidepressants (TCAs)	2.5 mg/kg, >10 mg/kg may result in cardiovascular and neurologic toxicity.	CNS depression, QRS prolongation, ventricular dysrhythmias, seizures, hypotension, antimuscarinic symptoms may manifest late in the course. M_1, H_1, α_1, Na^+ channels
Atypical antipsychotics	Varies depending upon agent.	CNS depression, hypotension, antimuscarinic symptoms may manifest late in the course.‡ M_1, H_1, α_1, D_2, 5-HT_{2A}

5-HT_{2A}, Serotonin; α_1, alpha adrenergic; *CNS*, central nervous system; D_2, Dopamine; H_1, histamine; M_1, muscarinic.
*Jang DH, Manini AF, Trueger NS, et al: Status epilepticus and wide-complex tachycardia secondary to diphenhydramine overdose. Clin Toxicol (Phila) 48:945-948, 2010.
†Kim HJ, Oh SH, Youn CS, et al: The associative factors of delayed-onset rhabdomyolysis in patients with doxylamine overdose. Am J Emerg Med 29:903-907, 2011.
‡Levine M, Ruha AM: Overdose of atypical antipsychotics: clinical presentation, mechanisms of toxicity and management. CNS Drugs 26:601-611, 2012.

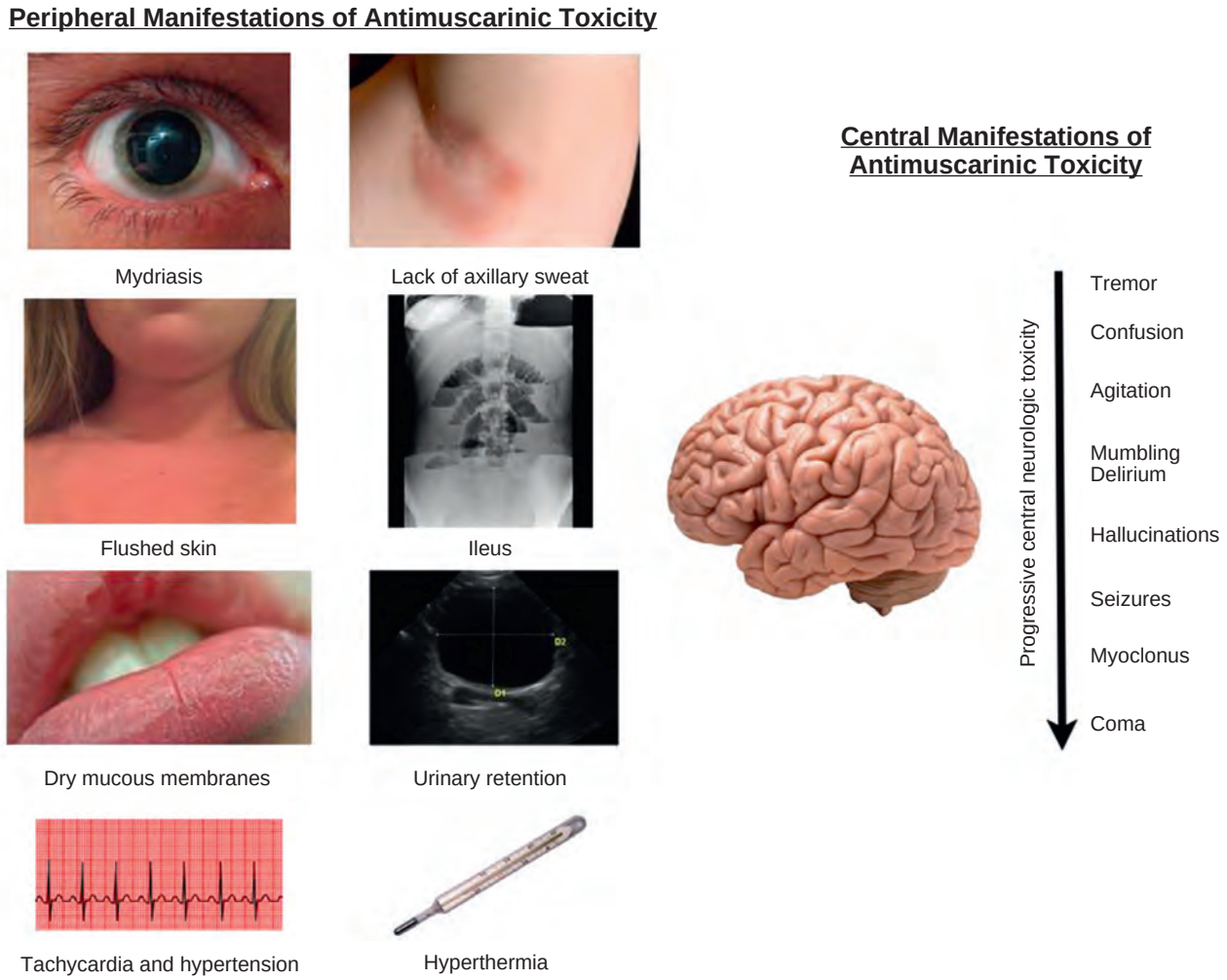

Fig. 145.1. Signs and symptoms of antimuscarinic toxicity.

BOX 145.1

Clinical Presentation of Antimuscarinic Toxicity

Mydriasis: "Blind as a bat"
Altered mental status: "Mad as a hatter"
Dry mucous membranes: "Dry as a bone"
Dry, flushed skin: "Red as a beet"
Hyperthermia: "Hot as Hades"
Urinary retention: "Full as a flask"
Decreased bowel sounds/ileus
Tachycardia

BOX 145.2

Common Differential Diagnosis Considerations With Overlapping Signs and Symptoms of Antimuscarinic Toxicity

DIFFERENTIAL DIAGNOSIS CONSIDERATIONS

Toxicological
Sympathomimetic toxicity
Serotonin toxicity
Neuroleptic malignant syndrome
Lithium toxicity
Antidepressant toxicity
Antipsychotic toxicity

Central Nervous System
Intracranial hemorrhage (ICH)
Seizure

Metabolic
Hyperthyroid
Encephalopathy

Infectious
Sepsis
Central nervous system (CNS) infections

electrolytes, cardiac biomarkers, renal function, and creatinine kinase (for rhabdomyolysis). Patients with an overdose of unclear history should be evaluated for co-ingestion, because antimuscarinic agents are often formulated with other potentially toxic agents. Acetaminophen and salicylate levels should be measured. Physostigmine may be used as a diagnostic test in some cases (see the Management section).

Electrocardiogram

An electrocardiogram (ECG) should be obtained in cases of suspected tricyclic antidepressant (TCA) or diphenhydramine toxicity to assess for possible sodium channel blockade (widened QRS interval or terminal R wave in lead AvR >3 mm). Presence of bradycardia or atrioventricular (AV) block contraindicates the use of physostigmine.

MANAGEMENT

Stabilization

Initial management should focus on evaluation and stabilization of cardiovascular and neurologic toxicity. An intravenous (IV) sodium bicarbonate bolus (50 mEq) should be given for evidence of sodium channel blockade with a QRS interval of more than 120 msec, and it may be repeated with a goal of QRS duration of less than 110 msec. Patients with recurrent seizures or agitation that place the patient or staff at risk should be treated with lorazepam (0.05 to 0.1 mg/kg), midazolam (0.05 to 0.1 mg/kg), or diazepam (0.1 to 0.2 mg/kg) boluses. These doses may be repeated every 5 to 15 minutes as needed to halt seizures and provide adequate sedation. When seizures are not present and agitation requires intervention, physostigmine treatment, which is both diagnostic and therapeutic, is preferred (see later discussion). Patients with drug-induced hyperthermia should be promptly treated to prevent progressive acidosis and subsequent organ failure. If evaporative cooling measures and sedation fail, progression to paralysis, ventilation, and airway control is necessary. The target temperature is 36° to 38° C.

BOX 145.3

Antimuscarinic Reversal Agent: Physostigmine

PHYSOSTIGMINE SALICYLATE
Indications: Diagnosis and treatment of antimuscarinic toxicity.
Contraindications: Narrow angle glaucoma, first degree atrioventricular (AV) blockade, bradycardia, and seizures due to current overdose.
Adverse effects: Bradycardia, seizure, vomiting.
Route: Intravenous (IV) or intramuscular (IM).
Kinetics/dynamics: Time of onset within 5 minutes following IV administration; 20 to 30 minutes following IM administration. Half-life: 16 ±3 minutes. Plasma cholinesterase inhibition 84 ±5 minutes.
Dosing: 1 to 2 mg bolus slowly (no faster than 1 mg/min). A drip (gtt) may be used. Start gtt at 1 mg/hour titrated every 30 minutes to effect.

Decontamination

Most patients with antimuscarinic poisoning do well with symptomatic care alone. There is no role for gastric lavage, whole bowel irrigation, or hemodialysis. Oral activated charcoal, similarly, is not indicated for the vast majority of antimuscarinic poisoned patients. However, oral activated charcoal may be used for symptomatic patients who have ingested a highly toxic quantity of antimuscarinic plant seeds only if the patient presents early after ingestion (<2 hours) and is anticipated to remain cooperative. Administering AC after antidote treatment with physostigmine has reversed delirium is a complex decision and is best made in consultation with a medical toxicologist or regional poison center.

Pharmacologic Intervention and Antidote Treatment

Control of delirium is the most common reason for emergency intervention in antimuscarinic poisoned patients. Sedation or antidotal treatment is indicated for patients whose delirium places them at risk of harming themselves or staff, requiring ongoing physical restraint, or interfering with effective treatment (eg, pulling out IV lines). Physostigmine is the preferred for treatment for antimuscarinic toxicity if no contraindications are present.

Physostigmine salicylate is a specific antidote for antimuscarinic toxicity (Box 145.3).

Physostigmine is safe and highly effective in reversing both agitation and delirium when used as treatment of delirium caused by antimuscarinic poisoning. In this specific setting, physostigmine is several-fold more effective than benzodiazepines, which control agitation in only about one-quarter of patients and have

no effect on delirium. Physostigmine use also seems to hasten recovery from the manifestations of antimuscarinic toxicity. Therefore physostigmine should be used early in the course of suspected antimuscarinic poisoning, because it is a more effective treatment of agitation and delirium and may limit additional unnecessary diagnostic testing and sedative requirements.

The drug is a tertiary amine carbamate that reversibly inhibits cholinesterases in the both peripheral nervous system and CNS. This allows for acetylcholine accumulation and subsequent competition with the antimuscarinic blocking agent occupying the receptor. Physostigmine has a short half-life, approximately 20 minutes. Although inhibition of the esterase, which yields the pharmacodynamic effects, last considerably longer with a half-life of 80 minutes. Accordingly, the clinical duration of physostigmine is 3 to 6 hours.

Physostigmine should be used to control symptoms of agitation or delirium potentially attributable to antimuscarinic toxicity. The initial dose of physostigmine is 1 to 2 mg IV over 5 minutes (see Box 145.3). If only a partial response is observed (the delirium is not completely reversed) at 10 minutes post administration, the same dose may be repeated. If agitation or delirium symptoms recur within 3 hours and the patient is again a risk to themselves or staff, repeat dosing of 1 to 2 mg IV over 5 minutes should be given.[4] If three or more administrations are necessary over a 6-hour period to control agitation or delirium, then an infusion should be started. A bolus of 1 to 2 mg IV should be given and the infusion started at 1 mg/hour.[5,6] If symptoms recur while on the infusion, the drip can be increased by 0.5 mg/hour every hour to maintain a normal mental status. The patient should be placed on a cardiac monitor to monitor for bradycardia during physostigmine administration. The infusion should be stopped every 12 hours to determine if the toxidrome has resolved. If symptoms recur during observation off physostigmine, the same bolus and infusion rate should be given. Patients may be considered medically cleared from antimuscarinic toxicity if symptoms do not recur within 6 hours of the last antidote dose.[4] If the patient develops side effects (vomiting, diarrhea, or bradycardia), the infusion should be stopped. Extended observation with repeated dosing and/or infusions may be required in very large overdoses or in antimuscarinic plant seed ingestions because ongoing absorption leads to prolonged symptoms.

When used diagnostically, near complete reversal of delirium over a matter of minutes is specific for antimuscarinic poisoning and may be used to defer additional testing, such as lumbar puncture or neuroimaging.

We do not recommend use of physostigmine in the treatment of acutely TCA poisoned patients with cardiovascular toxicity, specifically bradycardia or AV block. Physostigmine use in this context has been associated with ventricular tachycardia and cardiac arrest. TCAs have inherent cardiac toxicity, so it is not clear that physostigmine actually causes these adverse cardiac events. Many patients who received physostigmine without adverse effects were subsequently found to have ingested a TCA.[4] Further considerations regarding the use of physostigmine in patients with TCA toxicity are discussed in Chapter 146.

When physostigmine is contraindicated, sedation can be accomplished with IV benzodiazepines, as described earlier in this chapter.

Overall, physostigmine should be given as a diagnostic and therapeutic intervention, if the antimuscarinic-induced delirium places the patient or staff at risk, in patients without overdose-induced seizure, AV blockade, or bradycardia.

DISPOSITION

Most patients do well with supportive care (sedation, hydration, temperature control, and observation). Length of observation and need for admission depend on the agent, the dose, the intent, and the patient. Antimuscarinic agents slow gut motility, which increases the time to peak symptoms. As such, long-acting agents, plant seeds, or large ingestions should have extended observation up to 24 hours even if asymptomatic. Patients at extremes of age are at increased risk for toxicity and should be considered for observation. Patients with an unreliable history or concern for self-harm should have extended observation and psychiatric consultation.

Observation at Home

Asymptomatic, accidental exposures to a known, low dose, in patients with normal mental status and normal vital signs four hours after ingestion are safe to be observed at home by a trustworthy adult.

Emergency Department Observation

Patients with mild toxicity (normal mental status or slight drowsiness, normal vital signs, no ECG changes) and small ingestions should be observed in the ED until symptoms are clearly resolving (typically less than 6 hours). Patients treated with physostigmine who are asymptomatic 6 hours following physostigmine administration are considered clear of antimuscarinic toxicity and can be medically cleared.[1]

Hospital Admission

Patients with self-harm attempts and moderate to severe toxicity (abnormal vital signs, altered mental status) should have an extended observation period for progression of toxicity or until symptoms improve. Ingestion of large amounts of pills or plant seeds should be expected to require prolonged observation (24 to 48 hours) due to decreased gastrointestinal motility. Patients requiring more than three doses of physostigmine within 6 hours or who require an infusion of physostigmine should be admitted to a monitored setting, because the clinical course is likely to be prolonged.

Intensive Care Unit Admission

Patients with agitated delirium requiring physostigmine infusion, hyperthermia, dysrhythmia, or seizures will benefit from intensive care unit (ICU) admission for monitoring, frequent medications, and airway control if high doses of sedatives or additional physostigmine administration are necessary.

Consultations

Medical toxicology or poison center consultation should be considered when there are questions about exposure, diagnosis, or the appropriateness of antidotal therapy.

KEY CONCEPTS

- Symptoms of muscarinic receptor blockade may include delirium, mydriasis, a lack of sweating, dry mucous membranes, ileus, urinary retention, hyperthermia, tachycardia, and hypertension.
- Delirium may be the sole manifestation of toxicity and only one-third of patients manifest all of the classic autonomic findings of tachycardia, dry skin and axilla, and mydriasis.
- Physostigmine should be given to control severe agitation and delirium precipitated by muscarinic receptor antagonism.
- Physostigmine is relatively contraindicated in patients with bradycardia or AV block in the setting of possible TCA toxicity.
- Benzodiazepines should be used for symptom control when seizures occur or when physostigmine is contraindicated.
- Patients who develop hyperthermia despite treatment with evaporative cooling should be paralyzed, intubated, and cooled.
- Symptomatic patients should be observed until symptoms are clearly resolving. Accidental ingestion with mild symptoms can be expected to improve in less than 6 hours. Purposeful ingestions with mild to moderate symptoms will require admission to the hospital for extended observation (24 to 48 hours).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 145: QUESTIONS & ANSWERS

145.1. A 21-year-old man presents after drinking an "herbal tea" with some friends. He reports visual hallucinations. He has a resting tachycardia and a mildly elevated temperature. On physical examination, he is noted to have dry mucous membranes, dry and flushed skin, and absent bowel sounds. In addition to certain plants, which of the following medications can also cause these symptoms?

A. Amiodarone
B. Clonidine
C. Diphenhydramine
D. Lidocaine
E. Morphine

Answer: C. This patient is experiencing the antimuscarinic toxidrome. In addition to the signs and symptoms described here, patients may also have mydriasis and bladder distention. Mental status can be agitated or depressed. Myoclonus or choreoathetoid movements can also be seen. Amiodarone can cause hypothyroidism or hyperthyroidism and skin discoloration, as well as several other long-term effects. Clonidine can cause dry mouth, drowsiness, bradycardia, and hypotension. Lidocaine can cause headaches, dizziness, confusion, tinnitus, and tremor, as well as bradycardia and hypotension. Morphine can cause respiratory cerebral depression, as well as miosis, bradycardia, and hypotension.

145.2. Many signs and symptoms of the antimuscarinic syndrome are similar to those of other syndromes, including the sympathomimetic syndrome, serotonin syndrome, and neuroleptic malignant syndrome. Which of the following antimuscarinic findings is most likely to distinguish the antimuscarinic syndrome from the other syndromes listed?

A. Altered mental status
B. Altered movements
C. Dry skin
D. Fever
E. Mydriasis

Answer: C. All the other syndromes often have some degree of diaphoresis. Fever, altered mental status, and mydriasis can occur in all the named syndromes. Myoclonus can occur in the antimuscarinic syndrome, tremor in the serotonin syndrome, and rigidity in the neuroleptic malignant syndrome.

145.3. A 31-year-old woman presents with altered mental status after ingesting an unknown quantity of an unknown medication. Her vital signs are significant for tachycardia and fever. Her physical examination reveals mydriasis, dry mucous membranes, dry skin, decreased bowel sounds, and hypotension. Her electrocardiogram (ECG) reveals a wide QRS complex and prolonged QT interval. Which of the following medications is associated with this toxidrome?

A. Amitriptyline
B. Dextroamphetamine
C. Diphenhydramine
D. Fluoxetine
E. Lithium

Answer: A. This patient is experiencing many of the signs and symptoms of antimuscarinic syndrome. However, pure antimuscarinic rarely if ever cause cardiac dysrhythmias (other than sinus tachycardia). Tricyclic antidepressants (TCAs) frequently cause antimuscarinic signs and symptoms but also cause dysrhythmias. Although selective serotonin reuptake inhibitors, stimulants, and lithium can all cause similar signs and symptoms, electrocardiographic abnormalities such as those described here are rare.

145.4. Which diagnostic test should be performed in almost all patients presenting with the antimuscarinic syndrome?

A. Arterial blood gas analysis
B. Computed tomography (CT) scan of the brain
C. Electrocardiography
D. Electroencephalography
E. Urine drug screen

Answer: C. Patients with a clear presentation and mild symptoms do not necessarily require any diagnostic evaluation. However, patients with more severe symptoms should have measurements of serum electrolytes, renal function, creatine kinase, and glucose concentration performed. Electrocardiography is most helpful because cyclic antidepressants are a common cause of antimuscarinic symptoms and can cause fatal cardiac dysrhythmias. Arterial blood gas analysis might be helpful if the patient has respiratory depression. Head CT might be indicated in patients with altered mental status of unknown cause. Electroencephalography would be indicated only if there is a suspicion of unrecognized seizures. Urine drug screens are almost never helpful in determining treatment, especially in the case of antimuscarinic syndrome because they will not detect most of the medications responsible for this syndrome.

145.5. What is the best initial treatment of hyperthermia in patients with antimuscarinic syndrome?

A. Acetaminophen
B. Cooling blankets
C. Dantrolene
D. Evaporative cooling
E. Physical restraints

Answer: D. Evaporative cooling is the most effective and noninvasive way to decrease temperature. Death has occurred because of untreated hyperthermia in patients with antimuscarinic syndrome. Antipyretics such as acetaminophen are ineffective at reducing temperature because hyperthermia is not "fever." Dantrolene is useful in malignant hyperthermia but has no role in hyperthermia of other causes. Cooling blankets are ineffective. Physical restraints are likely to worsen the problem and to increase the risk of rhabdomyolysis and myoglobinuric renal failure. If a patient is dangerously agitated, physostigmine are the agents of choice to decrease agitation, muscle activity, and related metabolic activity that contribute to hyperthermia.

145.6. Which of the following medications crosses the blood-brain barrier and is potentially useful in the treatment of antimuscarinic syndrome?
A. Edrophonium
B. Metoclopramide
C. Neostigmine
D. Physostigmine
E. Pyridostigmine

Answer: D. Metoclopramide is an antiemetic and prokinetic medication that has no role in antimuscarinic syndrome. All of the other agents are acetylcholinesterase inhibitors, but only physostigmine crosses the blood-brain barrier and so it is the only drug that can reverse the central and peripheral effects of antimuscarinic medications. However, physostigmine can cause serious side effects and thus should be used carefully in patients with bradycardia and A-V block.

145.7. Which of the following is a contraindication to physostigmine use in a patient with antimuscarinic syndrome?
A. Altered mental status
B. Bradycardia and atrioventricular (AV) blockade
C. Coexisting myasthenia gravis
D. Hyperthermia
E. Seizure

Answer: B. Physostigmine is an acetylcholinesterase inhibitor that is useful to reverse the effects of antimuscarinic medications. However, it is contradicted with narrow angle glaucoma, AV blockade, bradycardia, and seizures due to the causal overdose. The main benefit of physostigmine is to reverse the altered mental status and agitation caused by the antimuscarinic medication. Physostigmine is occasionally used to treat myasthenia gravis. Hyperthermia and seizures can occur as part of the antimuscarinic syndrome, and although neither is directly treated with physostigmine, they are not contraindications to its use.

CHAPTER 146

Antidepressants

Michael D. Levine | Anne-Michelle Ruha

PRINCIPLES OF TOXICITY

Depression is one of the most common medical conditions in the United States, with a lifetime prevalence of nearly 20%.[1] Whereas many treatment strategies are used in the management of depressed patients, pharmacotherapy remains a cornerstone of modern practice. Modern antidepressant therapy hinges on the 60-year-old monoamine hypothesis, which suggests that depressive symptoms are mediated through an imbalance of the dopaminergic, noradrenergic, and serotonergic systems.[1] As a result, numerous antidepressant classes have emerged in an attempt to increase synaptic monoamine concentrations.

In the early 1950s, isoniazid and iproniazid were introduced for the treatment of tuberculosis. Shortly after, it was noted that these patients had improved mood, which was attributed to the ability of iproniazid to inhibit monoamine oxidase (MAO). Iproniazid, a derivative of isocarboxazid, subsequently became the first drug marketed specifically as an antidepressant.[2-3] This led to the advent of other monoamine oxidase inhibitors (MAOIs). In 1956, the antidepressant effect of imipramine, a tricyclic agent, was recognized, and it was marketed the following year. The MAOIs and tricyclic antidepressants (TCAs) became the mainstay for treatment of depression for several decades until the advent of the safer selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

The morbidity of antidepressants in overdose varies greatly by specific class. Overall, however, there were nearly 110,000 overdoses on antidepressants reported to United States poison control centers in 2013. Despite representing only 4% of calls, they accounted for 9% of fatalities.[4]

MONOAMINE OXIDASE INHIBITORS

MAO is located on the outer mitochondrial membrane and is responsible for breakdown of cytoplasmic catecholamines. Monoamine oxidase type A (MAO-A) primarily deaminates serotonin and norepinephrine; monoamine oxidase type B (MAO-B) primarily deaminates phenylethylamine.[5-6] Tyramine and dopamine are metabolized equally by both isoenzymes.[5-6] Whereas most tissues contain both isozymes, MAO-A is primarily found in the placenta, sympathetic nerve terminals, and intestinal mucosa; MAO-B is found primarily in platelets and the basal ganglia.

Drugs targeting the MAO system can act as specific or nonspecific inhibitors. The first-generation MAOIs are nonselective and irreversible. Drugs belonging to this class include phenelzine, isocarboxazid, and tranylcypromine. The second-generation MAOIs can preferentially inhibit either MAO-A or MAO-B.

MAOIs have fallen out of favor for treatment of depression due to side effects from adverse drug and food interactions. However, their use in treatment of Parkinson's disease is increasing. Drugs that selectively inhibit MAO-B disproportionately increase dopamine concentrations in the striatum.[6] Selegiline is an irreversible MAO-B inhibitor used in the treatment of Parkinson's disease. Importantly, the selectivity for MAO-B is only present at low doses.[7] Rasagiline is also an irreversible inhibitor of MAO-B and has similar clinical efficacy with selegiline.[8] Furthermore, unlike selegiline, which is metabolized to L-methamphetamine, rasagiline is not metabolized to an amphetamine derivative.[9] Table 146.1 Summarizes the MAO-inhibitors currently available for use in the United States.

In addition to its antibiotic properties, linezolid, an oxazolidinone class antibiotic, is a reversible inhibitor of MAO, producing significant inhibition of MAO-A.

As a class, MAOIs are rapidly absorbed from the gastrointestinal tract and are bound extensively to plasma proteins. With overdose, the MAOIs initially stimulate release of neurotransmitters from the presynaptic neuron but later inhibit their release.

Clinical Features

Patients have MAOI toxicity as a result of an acute overdose or as a consequence of a food or drug interaction. Depending on the scenario that leads to toxicity, the clinical presentation may differ. Obtaining a thorough medication history is key to establishment of the diagnosis of MAOI toxicity. After overdose, an asymptomatic period followed by delayed toxicity can be a diagnostic clue. Patients may be asymptomatic for up to 24 hours before significant, possibly life-threatening toxicity develops. After this asymptomatic period, hyperadrenergic symptoms, including tachycardia, hypertension, and hyperthermia, can develop. Seizures, rhabdomyolysis, coma, and ultimately cardiovascular collapse can occur once presynaptic catecholamines are depleted.

Patients who take nonselective MAOIs in therapeutic doses are at risk for food-drug interactions. Tyramine is an indirectly acting sympathomimetic amine that is present in aged cheeses, red wine, smoked or pickled and aged meats, and other foods. Usually, tyramine is metabolized in the gut and liver by MAO, rarely causing systemic effects. When MAO-A is inhibited, tyramine is absorbed systemically and enters presynaptic vesicles, ultimately causing release of norepinephrine and serotonin into the synapse, leading to a hypertensive crisis.[7] This tyramine syndrome, which can occur within minutes to hours of ingestion of foods with high tyramine content, is characterized by headache, hypertension, flushing, and diaphoresis. This syndrome can occur up to 3 weeks after discontinuation of a nonselective MAOI. Although it is theoretically possible, this syndrome is rare with therapeutic use of MAO-B inhibitors.[10] A drug-drug interaction may result when MAOIs are combined with other agents that have serotonergic effects. A variety of prescription and over-the-counter medications may interact with MAOIs to produce a constellation of symptoms referred to as *serotonin syndrome* (see later section). This syndrome may be life threatening, so use of medications with serotonin-potentiating activity should be avoided in patients taking MAOIs.

Differential Diagnoses

The differential diagnosis for MAOI toxicity includes sympathomimetic drugs of abuse such as cocaine and amphetamine derivatives, anticholinergic (or antimuscarinic) toxicity (eg,

TABLE 146.1

Summary of Monoamine Oxidase Inhibitor Agents Currently Available

GENERIC NAME	ROUTE	SELECTIVITY	FDA-APPROVED USES
Tranylcypromine	Oral	Nonselective	Depression
Phenelzine	Oral	Nonselective	Depression
Isocarboxazid	Oral	Nonselective	Depression
Selegiline	Oral or transdermal patch	MAO-B at lower doses; MAO-A at higher doses	Depression, Parkinson's disease

FDA, U.S. Food and Drug Administration; *MAO-A,* monoamine oxidase type A; *MAO-B,* monoamine oxidase type B.

diphenhydramine, cyclic antidepressants, anti-Parkinson drugs, and jimson weed), and methylxanthine toxicity (eg, theophylline and caffeine). Other toxicological considerations include acute withdrawal states (eg, ethanol and benzodiazepines), neuroleptic malignant syndrome (NMS) and the serotonin syndrome from other serotonergic drug combinations. Non-toxicologic causes to consider include environmental hyperthermia or heat stroke, febrile illness from infectious causes (eg, meningitis and encephalitis), pheochromocytoma, carcinoid syndrome, thyroid storm, and hypertensive emergency.

Diagnostic Testing

Laboratory abnormalities are nonspecific but can include hyperglycemia and leukocytosis, secondary to a hyperadrenergic state, and elevated creatine kinase due to rhabdomyolysis. Immunoassay urine drug screens that are commonly used in the emergency department do not detect MAOIs, and even gas chromatography–mass spectroscopy of urine may fail to detect the presence of an MAOI. Patients taking selegiline will test positive for methamphetamine because methamphetamine is a metabolite.

Symptomatic patients presenting after an MAOI overdose should have an electrocardiogram (ECG) to assess the QT and QRS intervals. Patients with chest pain should be evaluated for myocardial infarction. Measurement of serum glucose and electrolytes are indicated if the patient is obtunded. Because of the potential for intracranial hemorrhage in the setting of severe MAOI-induced hypertension, patients with a seizure or focal neurological deficit should undergo a non–contrast-enhanced head computed tomography (CT) scan.

Management

As with most intoxication, supportive care is paramount. Central nervous system (CNS) excitation should be treated with intravenous (IV) administration of benzodiazepines such as lorazepam and diazepam in usual titrated doses. Hyperthermia should be treated with external cooling using evaporative techniques and strategic ice packing. Hyperthermia that persists, despite administration of benzodiazepines and external cooling measures, may need intubation, ventilation, and chemical paralysis with a nondepolarizing neuromuscular blocker. Because typically only a single dose of a paralytic is required, the authors recommend rocuronium during rapid sequence intubation. The use of succinylcholine may incite hyperkalemia if rhabdomyolysis has occurred, and fasciculation from succinylcholine might further increase metabolic heat production. Furthermore, many of these patients are acutely hyperkalemic, which is a relative contraindication to succinylcholine. Mild hypertension should not be treated, but sustained severe hypertension (eg, systolic blood pressure exceeding 200 mm Hg or a diastolic exceeding 100 mm Hg) is best managed with a rapid, short-acting agent such as phentolamine (titrated slowly by repeated IV doses of 1 mg every 3 minutes) or nitroprusside (0.25 to 0.5 mcg/kg/min by IV infusion). Treatment should target a 25% reduction in the mean arterial pressure. Hypotension should first be managed by volume resuscitation with normal saline. Persistent or severe hypotension requires treatment with infusion of a direct-acting catecholamine such as norepinephrine or epinephrine. Because hypotension and cardiovascular collapse after MAOI overdose are due to catecholamine depletion, the use of indirect-acting agents such as dopamine is not likely to be beneficial. Extracorporeal elimination is also unlikely to be beneficial because of extensive protein binding and large volume of distribution of MAOIs.

Patients presenting with a tyramine reaction may have spontaneous resolution of symptoms during 6 hours. Severe hypertension higher than 200 mm Hg systolic with symptoms such as headache, flushing, or chest pain should be treated with phentolamine or nitroprusside. Patients with persistent severe headache and hypertension should have a head CT scan to assess for intracranial hemorrhage. Patients with chest pain should be evaluated for myocardial infarction (see Chapter 68).

Treatment of suspected serotonin syndrome is supportive (see later section) and consists primarily of the administration of benzodiazepines.

Disposition

Patients presenting with an MAOI overdose should be admitted to a monitored setting for 24 hours due to the risk of delayed, rapid deterioration and development of hyperadrenergic symptoms. Asymptomatic patients chronically taking an MAOI who present out of concern for a possible drug-food interaction can be discharged after 6 hours if no signs of toxicity develop over that period of time.

TRICYCLIC ANTIDEPRESSANTS

Principles of Toxicity

In the 1950s, imipramine became the first TCA used for the treatment of depression. Until the introduction of the SSRIs, TCAs remained the primary agents for treatment of depression. The therapeutic benefit of TCAs results from monoamine reuptake inhibition.[11] Whereas use of TCAs for treatment of depression has waned, use for other conditions, including treatment of migraines, various neuropathies, trigeminal neuralgia, and nocturnal enuresis has increased.

Clinical Features

Cyclic antidepressant toxicity can result from overdose of a TCA or drug interactions. Overdose is more commonly associated with life-threatening toxicity, but toxic effects can also occur when a TCA is combined with drugs that impair its metabolism through cytochrome P450. Tertiary amine TCAs such as amitriptyline, imipramine, and clomipramine are substrates of CYP2C19 and CYP1A2. Doxepin is also a substrate for CYP2D6. Drug-induced inhibition of these enzymes as well as genetic polymorphisms of these isoenzymes can decrease metabolism of these drugs, resulting in unexpectedly high serum concentrations and clinical toxicity. Conversely, inhibition of CYP2D6 and other P_{450} enzymes by these TCAs can also lead to increased serum concentrations of other drugs metabolized by the same enzymes. Because desipramine and nortriptyline are only weak CYP2D6 inhibitors, they cause fewer drug interactions. Another drug interaction that

occurs with TCAs is the serotonin syndrome, which can result when a TCA is combined with another serotonergic drug such as MAOI or SSRI.

After an overdose of a TCA, symptoms typically begin within 1 to 2 hours. With smaller ingested amounts, symptoms may be minimal and resolve quickly; patients who take large amounts may deteriorate rapidly soon after ingestion. Severely poisoned patients typically have symptoms within 6 hours of an overdose. Early cyclic antidepressant toxicity (within the first 2 hours) is primarily characterized by anticholinergic effects. These findings include dry mucosal membranes, urinary retention, and hot, dry skin. Despite having potent antimuscarinic properties, the pupils are often small due to *alpha* effects. Patients may be alert and confused, severely agitated, mute, hallucinating, or even deeply comatose. Speech is often rapid and mumbling in character. Seizures may occur and are likely to be multifactorial, resulting from increased synaptic monoamines, sodium channel inhibition, and gamma-aminobutyric acid (GABA) receptor antagonism. Early hypertension is common from the anticholinergic effects of the TCA and excess norepinephrine in the synapse from blockade of norepinephrine reuptake, but hypotension may also be due to alpha-receptor antagonism and also norepinephrine depletion. Later (2 to 6 hours post ingestion), myocardial depression resulting from severe sodium channel antagonism may also lead to hypotension and bradycardia.[12] Significant sodium channel blockade is associated with widening of the QRS interval. The degree of widening is prognostic. A QRS wider than 100 msec is associated with seizures, where as a QRS complex wider than 160 msec is associated with ventricular dysrhythmias. TCAs also block potassium efflux, which leads to a prolonged QT interval.[13] With severe poisoning, the combined effects of the TCA on various receptors and ion channels lead to depressed level of consciousness, seizures, hypotension, and wide-complex cardiac arrhythmias.

Chronic toxicity from drug interactions or decreased ability to metabolize the drug because of genetic polymorphism may be manifested in a more subtle fashion. Confusion, urinary retention, and prolonged corrected QT (QTc) interval are common. Chronic toxicity presents more gradually and should be considered in any confused patient taking therapeutic doses of a cyclic antidepressant.

Differential Diagnoses

Many agents with anticholinergic properties produce similar clinical features as TCAs. Diphenhydramine and carbamazepine, in particular, can also produce seizure and sodium-channel blockade. Agents that produce sympathomimetic toxicity (eg, cocaine) or serotonin syndrome (eg, SSRIs, MAOIs) should be included in the differential diagnosis. Other drugs with sodium channel blockade, and hence a wide QRS complex, includes the Vaughn-Williams class IA antidysrhythmics (eg, procainamide, disopyramide, quinidine) and class IC antidysrhythmics (eg, flecainide, encainide, and propafenone), along with amantadine, carbamazepine, cocaine, diphenhydramine, mesoridazine, and thioridazine. Propoxyphene and propranolol can also cause an intraventricular conduction delay by sodium channel blockade but typically cause a bradycardic rhythm rather than a tachycardic rhythm.

The constellation of early anticholinergic symptoms, decreased level of consciousness followed by seizures, wide QRS, and cardiovascular collapse is highly suggestive of acute TCA overdose.

Diagnostic Testing

After overdose, the ECG can yield prognostic information. Early anticholinergic effects cause sinus tachycardia, which occurs virtually uniformly before other effects. Whereas the serum tricyclic concentrations are not particularly beneficial in predicting adverse events, the ECG is prognostic. Historically, it is felt that QRS duration longer than 100 milliseconds is predictive of seizures, whereas QRS duration longer than 160 milliseconds is predictive of ventricular dysrhythmias, but hard evidence does not exist for either of these assertions. Additional findings on the ECG include a rightward shift of the terminal 40 milliseconds of the QRS complex seen as an R wave in augmented vector right (aVR) longer than 3 milliseconds. Figure 146.1 demonstrates lead aVR following a tricyclic ingestion. QT prolongation is less important clinically than the QRS duration.

Fig. 146.1. Augmented vector right *(aVR)* demonstrating tall R wave.

Urine drug of abuse screens commonly test for the presence of TCAs, but a positive test result suggests only use of a TCA or another xenobiotic that cross-reacts with the screen (eg, antipsychotic medications, antimuscarinic agents, carbamazepine, or the muscle relaxant cyclobenzaprine). Quantitative serum tricyclic levels do not correlate with severity of illness.

Management

Ensuring stability of the airway, with adequate ventilation, and volume repletion are of primary importance. There are no randomized controlled trials demonstrating improved patient-oriented outcomes and decreased mortality with activated charcoal in patients with cyclic antidepressant overdose. Nonetheless, because of the high lethality of the acute overdose, a patient who presents within 1 hour after an overdose and who is awake, alert, and cooperative and is not exhibiting any signs of toxicity (eg, no tachycardia or intraventricular conduction delay) can be given activated charcoal. However, due to risk of seizures with subsequent aspiration, activated charcoal is not routinely recommended, other than in the specific setting described. There is no role for gastric lavage.

Patients with sinus tachycardia alone do not need specific treatment but should be monitored to detect QRS widening early in the clinical course. Early hypertension should not be treated. Hypotensive patients should first receive fluid resuscitation with an isotonic crystalloid. Patients who remain hypotensive should be treated with direct-acting vasopressors such as norepinephrine and epinephrine.

Hypertonic sodium bicarbonate is given only to treat specific evidence of sodium channel blockade such as a wide QRS and ventricular dysrhythmias. Sodium bicarbonate should not be given strictly due to tachycardia. Recommendations regarding the specific administration of sodium bicarbonate vary. We recommend a conservative approach by administering a bolus of 1 to 2 mEq/kg hypertonic sodium bicarbonate intravenous push (IVP) if the QRS interval exceeds 100 milliseconds. This dose may be repeated in a few minutes if the QRS does not narrow. After IV bolus, a sodium bicarbonate infusion can be used to maintain a pH between 7.50 and 7.55. Such an infusion can be created by the addition of 150 mEq sodium bicarbonate, 40 mEq potassium, and 850 mL of dextrose 5% in water (D5W). The infusion should be created with a 5% dextrose solution, and not normal saline, due to the risk of hypernatremia with the latter. The infusion should be administered at twice the normal maintenance rate, titrating to QRS width and pH. Alternatively, infusions of 1 mEq sodium bicarbonate per milliliter of fluid may be used if volume overload is a concern. Additional IV boluses of sodium bicarbonate may be

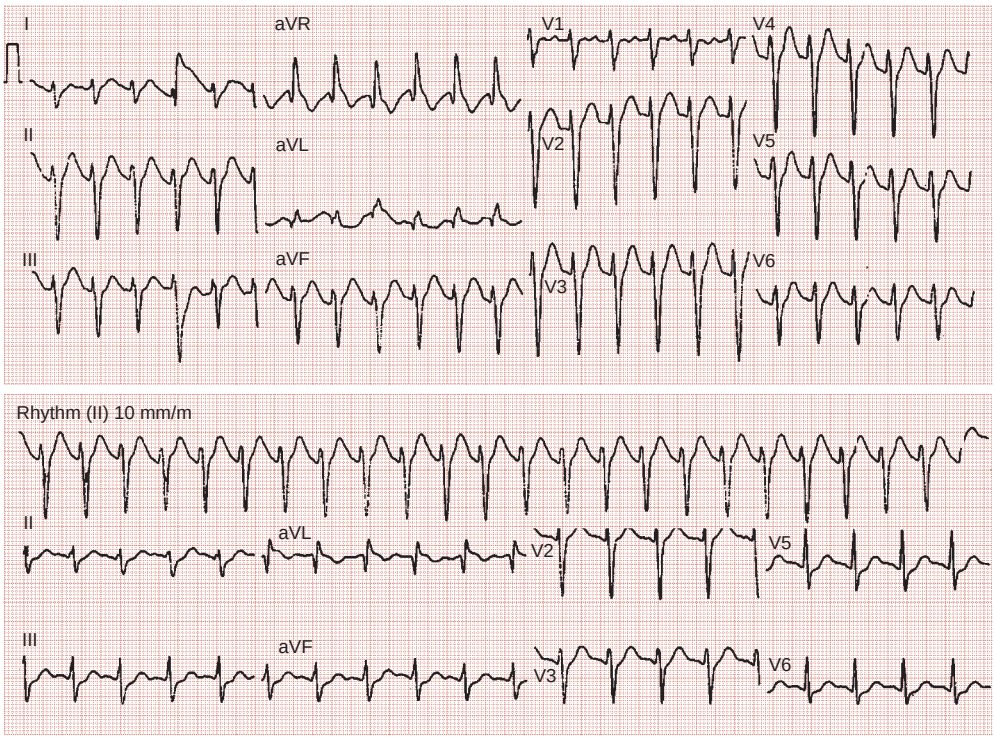

Fig. 146.2. *Top,* Initial 12-lead electrocardiogram (ECG) demonstrating substantial intraventricular conduction delay (QRS 146 milliseconds). *Bottom,* Repeated ECG after bicarbonate therapy. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right.

necessary if the QRS widens. Figure 146.2 demonstrates a 12-lead ECG from a patient poisoned with a TCA before and after sodium bicarbonate therapy. If ventricular dysrhythmias persist despite maximal alkalinization (pH > 7.55), 200 mL of 3% hypertonic saline (in an adult) can be used. Class Ia or Ic antidysrhythmics should be avoided. Seizures are best treated with an IV benzodiazepine (lorazepam 1 to 2 mg IVP; diazepam 5 to 10 mg IVP) along with sodium bicarbonate. Refractory seizures can be treated with phenobarbital (15 to 18 mg/kg IV loading dose). Because seizure leads to acidosis and worsens the cardiac status, seizing patients who do not respond quickly to benzodiazepines or phenobarbital should be rapidly paralyzed and intubated if necessary to prevent increasing metabolic acidosis.

Physostigmine, the antidote of choice for pure anticholinergic toxicity (see Chapter 145) is considered by many experts to be contraindicated in the management of TCA overdose. Asystole has been reported after physostigmine use in TCA toxicity, particularly in patients with bradycardia and A-V block. It is not advised to administer this agent to patients with QRS or QTc prolongation following TCA overdose. However, we recommend it be considered in patients with delirium of unknown etiology who are therapeutically taking anticholinergic agents and in whom toxicity is suspected, but only if the PR, QRS, and QTc intervals are normal. Physostigmine (1 to 2 mg slow IV infusion over 5 minutes in adults) should be given with caution in a monitored setting, because it may exacerbate bradycardia, AV block, and seizures related to the overdose (see Chapter 145).

Intravenous lipid emulsion (ILE) therapy has gained interest recently for reversal of toxicity caused by lipophilic drugs, including TCAs.[14-15] Although the exact mechanism of ILE is not clearly defined, it likely involves redistribution of a lipophilic drug from the tissue receptors back into the vascular compartment in the context of a large bolus of concentrated lipid solution, the so-called *lipid sink phenomenon.*[16] Other mechanisms such as enhanced cardiac metabolism are also possible explanations. Because not all studies reveal beneficial effects from ILE in the treatment of TCA toxicity and due to the potential for iatrogenic harm, its use is currently reserved for life-threatening toxicity that remains refractory to sodium bicarbonate administration.[17,18] ILE should be administered only on advice of a medical toxicologist or regional poison center. If ILE is to be administered, there are several different dosing strategies. We recommend 1.5 mL/kg of a 20% lipid solution over 2 to 3 minutes. This bolus can be repeated once in 5 minutes if there is no clinical improvement. If clinical improvement does occur, the bolus may be followed by an infusion of 0.25 mL/kg/min for 15 to 30 minutes.[19]

Despite recent enthusiasm for ILE, its use is not without associated complications, including extreme lipemia resulting in interference with laboratory blood tests (complete blood counts, chemistries, and coagulation studies), as well as acute pancreatitis, and acute respiratory distress syndrome.

Disposition

If the heart rate has not exceeded 100/minute for a period of at least 10 minutes, ECG intervals are normal, level of consciousness is normal, and no seizures have developed within 6 hours of a TCA overdose, it is unlikely that toxicity will occur.[20] The patient can be medically cleared from the emergency department for psychiatric evaluation and disposition if needed. Patients with signs of cyclic antidepressant cardiotoxicity, seizures, or coma should be admitted to an intensive care unit.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Principles of Toxicity

In recent years, the SSRIs have become the mainstay for treatment of depression. As implied by their name, these drugs prevent the presynaptic reuptake of serotonin without affecting the synaptic concentration of other monoamines. Some of the more commonly used SSRIs available today include escitalopram and

its enantiomer citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

SSRIs have a wide therapeutic index. Most SSRIs undergo hepatic metabolism. There is considerable variability in their half-life; however, paroxetine has one of the shortest half-lives (17 hours) compared with fluoxetine, which has one of the longest half-lives (53 hours for parent drug, 240 hours for active metabolite).

Clinical Features

Overdose of SSRIs is usually well tolerated and rarely fatal, with ingestions of up to 30 times the daily dose associated with few or no symptoms. Gastrointestinal upset and mild CNS depression can occur with large overdoses. Coma and seizures are rare, with incidences of approximately 2% for each. The incidence of serotonin syndrome after SSRI overdose is variable, up to 15%, but most other series report a much lower incidence.

Citalopram overdose deserves special mention because of a higher rate of QTc prolongation and seizures compared with other SSRIs.[21-22] There has been some suggestion that the QT prolongation may be delayed with citalopram ingestion. However, there is not convincing data to support this delayed onset of toxicity. The QT prolongation does, however, appear to be dose dependent.[23] Despite being the active enantiomer of citalopram, escitalopram appears to be less toxic than citalopram, with a lower incidence of seizure and QTc prolongation.[21]

Therapeutic administration of SSRIs may be associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[24] Most cases of hyponatremia develop shortly after commencing care. The overall incidence is not well documented. However, in one small study, 12.5% of elderly patients taking an SSRI had SIADH, with an additional 12.5% of patients having mild asymptomatic hyponatremia.

Differential Diagnoses

The differential diagnosis for SSRI toxicity includes cyclic antidepressants, MAOIs, sedative hypnotics (eg, benzodiazepines, barbiturates), SNRIs, neuroleptic agents, and atypical antipsychotics.

Diagnostic Testing

Diagnosis of SSRI toxicity is often dependent on obtaining a history of overdose. Clinical features of toxicity are similar to those seen after overdose of many other toxicants. An ECG can assess for conduction disturbances, especially QT prolongation. Specific SSRI levels are not performed by most hospital laboratories and do not influence management, although they may help confirm overdose retrospectively. A standard urine drug of abuse screen will not detect an SSRI.

Management

Treatment of an SSRI overdose is largely supportive. There is no role for activated charcoal or gastric lavage. Only rarely will patients require tracheal intubation because of loss of airway reflexes. For patients with a corrected QT interval greater than 500 msec, 2 grams of IV magnesium sulfate should be administered. IV administration of benzodiazepines (0.05 to 0.1 mg/kg of lorazepam via rapid IV bolus; or 0.1 to 0.2 mg/kg diazepam via rapid IV bolus) should be used to treat agitation and seizures.

Disposition

Patients who overdose with an SSRI who are asymptomatic after 6 hours of monitoring are unlikely to have toxicity. Some authors advocate for 12 hours of observation after the ingestion of more than 1000 mg of citalopram or escitalopram, although that recommendation is not universally accepted. If a patient with citalopram ingestion is to be cleared after 6 hours, a repeat ECG should be performed to assess the QT interval. Symptomatic patients should be admitted to a monitored care setting. Those patients with an intent of self-harm should be evaluated by a psychiatric service.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS AND NOREPINEPHRINE REUPTAKE INHIBITORS

Principles of Toxicity

Duloxetine, venlafaxine, desvenlafaxine, milnacipran, and levomilnacipran are collectively referred to as *serotonin-norepinephrine reuptake inhibitors (SNRIs).* All of these agents, except milnacipran, are approved for use in the United States for treatment of major depression. Milnacipran, despite being used as an antidepressant in Europe, is only approved for treatment of fibromyalgia in the United States. Some of these agents are also approved for other disorders. For example, venlafaxine can be used to treat panic disorder, generalized anxiety disorder, or social phobia, whereas duloxetine is also used to treat chronic musculoskeletal pain, diabetic neuropathy, fibromyalgia, and generalized anxiety disorder. Venlafaxine and its active metabolite desvenlafaxine are both available medicinally. The SNRIs may also produce dose-dependent inhibition of sodium channels. Reboxetine is an isolated norepinephrine reuptake inhibitor. It is also used for the treatment of depression.

Clinical Features

Unlike the SSRIs, which are relatively benign in overdose, ingestion of any of the SNRIs can be dangerous. Fatal ingestions have been described with virtually all of the SNRIs. All of these agents may produce hyperadrenergic symptoms, including tachycardia and hypertension. Rarely, hypotension can be observed after massive overdose.[25-26] It is hypothesized that the hypotension may be the result of an acute cardiomyopathy.[27,28-30] Seizures can occur following ingestion of the SNRIs.[31-32] Unlike bupropion, however, which can have delayed onset of seizures, the onset of seizures following an SNRI ingestion would be expected to occur within the first several hours post ingestion.

Rhabdomyolysis has been reported independent of seizure activity following ingestions of venlafaxine.[33] Venlafaxine and desvenlafaxine overdoses can result in cardiovascular toxicity, manifesting as intraventricular conduction delay and ventricular dysrhythmias.[28] Venlafaxine has also been associated with QT prolongation.[34] Lastly, based on their mechanism of action, serotonin syndrome may develop after ingestion of these agents.

Differential Diagnoses

The differential diagnosis for SNRIs toxicity includes cyclic antidepressants, MAOIs, sedative hypnotics, serotonin reuptake inhibitors, neuroleptic agents, and atypical antipsychotic medications.

Diagnostic Testing

Specific drug levels are not rapidly available and do not aid management. An ECG can detect QRS or QT interval prolongation. SNRIs are not detected by urine drug of abuse screens, but venlafaxine is associated with a false-positive phencyclidine screen.[35] In cases of a venlafaxine ingestion, a creatinine kinase and renal function tests should be obtained to assess for acute

rhabdomyolysis. As with any multidrug ingestion, serum acetaminophen and salicylate levels should be measured.

Management

Care of the patient with an SNRI overdose is supportive, with focus on ensuring airway patency and adequate ventilation. There is no role for activated charcoal or gastric emptying. Hypotension (systolic blood pressure <90 mm Hg) should first be treated with a 20 cc/kg bolus of 0.9% normal saline. This bolus can be repeated if necessary. If hypotension still persists, a direct-acting vasopressor (such as epinephrine or norepinephrine) should be used. Intraventricular conduction delay with a widened QRS on ECG should be treated with sodium bicarbonate infusions (as described in the Tricyclic Antidepressants section earlier). First-line treatment of seizures is the IV administration of a benzodiazepine such as lorazepam or diazepam.

Disposition

Patients who are asymptomatic with a normal 12-lead ECG after an observation period of 6 hours can be cleared for discharge after appropriate psychiatric consultation. Patients with an intentional ingestion who develop manifestations of neurologic or cardiovascular toxicity (such as sedation, hypotension, tachycardia, and so on) should be observed in an in-patient monitored setting. Those with profound CNS depression or hemodynamic instability warrant intensive care unit admission. Symptomatic patients should be admitted to a monitored care setting. Those patients with conduction delay and coma should be admitted to an intensive care unit.

MISCELLANEOUS ANTIDEPRESSANTS

Bupropion

Bupropion is a unique class of antidepressant, which is also used for smoking cessation.[36] The primary mechanism of action is inhibition of dopamine and norepinephrine reuptake, but it can also act as a noncompetitive inhibitor of nicotinic acetylcholine receptors.[37]

Seizure activity is a dose-dependent phenomenon and can occur with therapeutic dosing or overdose of bupropion.[38] Seizures are relatively common after overdose and occur in approximately 30% of cases, the majority of which are initially tachycardic.[38-39]

Sinus tachycardia, tonic-clonic seizures, and agitation are common after overdose. Unlike many agents that produce seizures acutely following overdose, ingestion of extended release bupropion can produce delayed onset seizures. Both QRS and QT prolongation can occur with toxicity. Treatment is primarily supportive. Activated charcoal or gastric emptying are not indicated. Patients with large overdoses may require endotracheal intubation because of CNS and respiratory depression. Lorazepam or diazepam is effective for terminating seizures. If seizures persist, phenobarbital or other GABA agonists may be used. Sodium bicarbonate (150 mEq IV or 3 mEq/kg for pediatric patients) should be administered for any QRS prolongation. Additional bicarbonate should be given based on subsequent ECGs. Resuscitative ILE therapy has been described in anecdotal case reports with severely poisoned patients refractory to standard management measures. ILE should be undertaken only on the advice of a medical toxicologist or regional poison center.

Trazodone

Trazodone is an atypical antidepressant with a mechanism of action that includes antagonism of the 5-hydroxytryptamine type 2A (5-HT_{2A}) receptor and alpha_1 receptor. In addition, it is a serotonin receptor antagonist and reuptake inhibitor. Its use as an antidepressant has been historically somewhat limited by adverse effects (such as orthostatic hypotension, priapism, and sedation), although once-daily formulation has recently been released.[40]

Priapism is probably a result of trazodone's alpha-antagonism, with an incidence of 1/100 to 1/10,000. Whereas many drugs are associated with priapism, particularly those with alpha-antagonism or inhibition of type 5 phosphodiesterase, trazodone is responsible for a disproportionate number of reported cases.

After overdose, sedation and hypotension due to vasodilation are expected. Priapism is not typically associated with overdose of trazodone. Prolongation of the QT interval may occur. Management is supportive, with airway protection, IV fluid resuscitation, and use of alpha-adrenergic agonists such as norepinephrine as needed for refractory hypotension. Activated charcoal and gastric emptying are not indicated.

Nefazodone

Nefazodone, a phenylpiperazine antidepressant, is structurally similar to trazodone. It acts as an antagonist at the 5-HT_{2A} receptor, and chronic administration is associated with receptor downregulation. Nefazodone is associated with weak inhibition of norepinephrine and serotonin reuptake. It is metabolized to several active metabolites. After overdose, most patients remain asymptomatic. Antagonism of the alpha_1 receptor is responsible for the orthostatic hypotension that can occur. Treatment is primarily supportive.

SEROTONIN SYNDROME

Principles of Toxicity

Serotonin syndrome is a potentially lethal condition resulting from excess serotonin accumulation in the synaptic cleft. This syndrome occurs after an isolated overdose of an SSRI, but it is more commonly a result of drug interactions, especially with drug combinations that raise synaptic serotonin concentrations by different mechanisms. Agonism of the 5-HT_{2A} receptor appears to be largely responsible for this condition in humans.[41]

Whereas numerous xenobiotics have been implicated in causing serotonin syndrome, some of the most common are the SSRIs, SNRIs, TCAs, MAOIs, dextromethorphan, amphetamines, and designer amphetamines, including methylenedioxymethamphetamine ("ecstasy"), cocaine, meperidine, lithium, tramadol, buspirone, lysergic acid diethylamide (LSD), and linezolid (Box 146.1). Serotonin syndrome is more likely to develop when drugs from different classes are combined, resulting in increased serotonin in the synaptic cleft from different mechanisms (eg, increased release and impaired uptake).

Clinical Features

Serotonin syndrome is described as a triad of mental status changes, autonomic instability, and increased neuromuscular activity, but the condition exists along a spectrum; some patients have only mild tremor and diarrhea, whereas others exhibit life-threatening manifestations. Clinical features may include tremor, akathisia, gastrointestinal illness, clonus (inducible or spontaneous), rigidity, fever, seizures, and autonomic instability. The clonus is typically more pronounced in the lower extremities than in the upper extremities. After an acute overdose of a serotonergic agent, symptom onset typically begins within several hours. With proper treatment, symptoms usually resolve within 24 hours but can persist for several days in severe cases.

BOX 146.1

Xenobiotics Commonly Implicated in Serotonin Syndrome

Analgesics: Tramadol, meperidine, pentazocine
Drugs of abuse: Cocaine, amphetamine derivatives (eg, methylenedioxymethamphetamine), lysergic acid diethylamide (LSD)
Monoamine oxidase inhibitors (MAOIs) (eg, isocarboxazid, linezolid, phenelzine, moclobemide, selegiline)
Miscellaneous: Dextromethorphan, lithium, metoclopramide, St. John's wort
Selective serotonin reuptake inhibitors (SSRIs) (eg, milnacipran, venlafaxine)
Serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
Tricyclic antidepressants (TCAs) (eg, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline)

BOX 146.2

The Hunter Criteria for Serotonin Syndrome

In the setting of exposure to a known serotonergic agent, serotonin syndrome can be diagnosed by the presence of any of the following:

- Spontaneous clonus
- Inducible clonus *and* agitation or diaphoresis
- Ocular clonus *and* agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonic with temperature >38° C *and* ocular clonus or inducible clonus

Differential Diagnoses

The differential diagnosis of serotonin syndrome includes NMS, malignant hyperthermia, sympathomimetic toxicity, anticholinergic toxicity, strychnine toxicity, bupropion toxicity, and GABA withdrawal. Non-toxicologic considerations include thyroid storm, meningitis, idiopathic seizure, intracranial hemorrhage, and hypoglycemia.

Diagnostic Testing

There is no "gold standard" for the diagnosis of serotonin syndrome. Laboratory studies cannot be used to confirm or to exclude the diagnosis of serotonin syndrome. Rhabdomyolysis and hyperkalemia can occur as a result of increased neuromuscular activity, and these should be screened for as indicated on the basis of the clinical examination.

The Sternbach criteria were developed in the 1990s and became the first widely used diagnostic algorithm. Additional criteria, including the Hunter criteria and the Boyer and Shannon criteria, have been developed. The Hunter criteria (Box 146.2) appear to be more sensitive than the Sternbach criteria, with fewer false positives.

In general, a history of overdose or of recently starting an additional serotonergic agent along with clinical findings consistent with this diagnosis should raise the concern for serotonin syndrome.

Management

Management is supportive, with removal of the offending agents being paramount. Mild cases may require only discontinuation of the offending agent and low-dose benzodiazepines (eg, 5 to 10 mg of IV diazepam) for rigidity. More severe cases may require IV fluid resuscitation and large doses (eg, 10 to 20 mg of IV diazepam, with titration in 10 mg aliquots) of benzodiazepines or other sedative-hypnotic agents to gain control of symptoms. Cyproheptadine, a 5-HT_{2A} antagonist, is an adjunctive therapy for more severe cases, but there are no randomized controlled trials demonstrating improved benefit with cyproheptadine over supportive care and benzodiazepines alone. If cyproheptadine is available, the syndrome is severe or refractory to treatment, and the clinician is confident with the diagnosis, we recommend a single dose of 12 mg of cyproheptadine for patients with serotonin syndrome. If anticholinergic toxicity remains on the differential diagnosis, cyproheptadine should not be given, because it can worsen anticholinergic toxicity. Patients with hyperthermia that does not respond promptly to sedation with benzodiazepines should receive a nondepolarizing neuromuscular blocking agent (eg, rocuronium) during rapid sequence intubation. Typically only a single dose of a long-acting neuromuscular blocking agent is required.

Disposition

Patients with all but the mildest forms of serotonin syndrome should be admitted to a monitored care setting. Those with unresponsiveness and rigidity should be admitted to an intensive care unit.

DISCONTINUATION SYNDROMES

After the abrupt discontinuation of certain antidepressants, patients can experience a withdrawal, or discontinuation, syndrome. Unlike potentially life-threatening GABA withdrawal from ethanol or benzodiazepines, the discontinuation syndrome from antidepressants is rarely life threatening but can result in significant discomfort. One notable exception involves neonates born to mothers using TCAs who can have serious, potentially life-threatening withdrawal.[42] Antidepressant discontinuation syndrome does not always develop, but when it does, it typically starts within the first 3 days after therapy is stopped. This syndrome is difficult to distinguish from recurrence of the underlying depression, which has overlap of some symptoms.

Antidepressant discontinuation syndrome occurs with all major classes of antidepressants. Withdrawal from SSRIs involves both physical and psychological symptoms, most commonly nausea, lethargy, headache, and dizziness. The symptoms can be divided into six general categories: dysequilibrium (eg, dizziness, ataxia), sleep disturbances, gastrointestinal symptoms, affective symptoms (eg, irritability, anxiety), sensory symptoms (eg, electric shock–like sensation, paresthesias), and general somatic symptoms (eg, headache, tremor, anorexia, diaphoresis). The syndrome is more common after discontinuation of drugs with shorter half-lives (eg, paroxetine) than of drugs with longer half-lives (eg, fluoxetine). TCA withdrawal is similar to SSRI withdrawal, although sensory abnormalities and equilibrium disturbances are rare with TCA discontinuation. Non–life-threatening arrhythmias are rare after discontinuation of the TCAs.

Patients with mild withdrawal symptoms do not require any specific therapy. For those patients with more severe symptoms, treatment involves restarting of the antidepressant, followed by a gradual tapering dose.

KEY CONCEPTS

- Although rarely used for depression, MAOIs are used in the treatment of Parkinson's disease.
- Because serious symptoms can occur after a lengthy latent period, patients with reported MAOI overdose should be admitted for 24 hours, regardless of symptoms. Symptoms are characterized by tachycardia, hypertension, and CNS changes, and later cardiovascular collapse.
- The primary manifestations of TCA toxicity are seizures, tachycardia, and intraventricular conduction delay. IV sodium bicarbonate should be administered for QRS prolongation.
- SSRIs are relatively benign in overdose.
- SNRI ingestions can result in seizures, tachycardia, and occasionally intraventricular conduction delay.
- The hallmark feature of serotonin syndrome is lower extremity rigidity with spontaneous or inducible clonus, especially at the ankles.
- Serotonin syndrome is primarily treated with supportive care, including discontinuation of the offending agent, and benzodiazepines.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 146: QUESTIONS & ANSWERS

146.1. A 42-year-old woman presents after ingesting an unknown number of pills in a suicide attempt. She does not know the name of the medication she ingested but knows it is an antidepressant. She denies taking any co-ingestants. Currently, she has no complaints; her vital signs, physical examination findings, and electrocardiogram (ECG) are normal. To receive a psychiatric evaluation, she must be transferred off-site. How long should she be observed in the emergency department before transfer to a psychiatric facility?

A. 1 hour
B. 2 hours
C. 6 hours
D. 12 hours

Answer: C. The most dangerous class of antidepressants is the cyclic antidepressants. Typically, peak plasma concentrations and therefore peak effect occur in 2 to 4 hours. However, in overdose, the anticholinergic effects of these agents may result in delayed gastric emptying and delay peak absorption to 6 hours. Most serious signs and symptoms occur within 30 to 60 minutes of ingestion. If the patient has tachycardia or seizure or decreased level of consciousness at 6 hours, she should be admitted for medical observation. If any of these pills were a monoamine oxidase inhibitor (MAOI), however, the patient should be admitted to the hospital for 24 hours.

146.2. After sinus tachycardia, what is the most common electrocardiographic abnormality seen in cyclic antidepressant overdose?

A. Left bundle branch block
B. PR prolongation
C. QRS prolongation
D. QT prolongation
E. Right bundle branch block

Answer: C. After sinus tachycardia, QRS prolongation of more than 100 milliseconds is the most common specific finding and results from sodium channel–blocking effects of the cyclic antidepressant. Prolonged PR and QT intervals, as well as a right bundle branch block, can also occur but are less common.

146.3. Which of the following treatment options would be the most appropriate to consider in the awake, asymptomatic

patient who presents within 1 hour of a large overdose of a tricyclic antidepressant (TCA)?
A. Activated charcoal
B. Endotracheal intubation
C. Gastric lavage
D. Physostigmine
E. Sodium bicarbonate

Answer: A. Physostigmine should never be prophylactically administered and its use in TCA overdose is generally considered contraindicated, particularly in patients with bradycardia, A-V block, and seizures related to the overdose. Sodium bicarbonate should not be prophylactically administered either, but it should be administered as an intravenous (IV) bolus for patients with intraventricular conduction delay and QRS widening. Endotracheal intubation is indicated for patients with significant central nervous system (CNS) depression who are not able to protect their airway. Gastric lavage is not routinely indicated. Activated charcoal can be considered in an awake individual. It should not be "forced" on someone who will not voluntarily drink it (eg, by placement of a nasogastric tube for the purpose of administering charcoal) because of the increased risk of aspiration and subsequent charcoal pneumonitis.

146.4. A 23-year-old man presents after an ingestion of a cyclic antidepressant. His initial vital signs are normal. During your initial evaluation, the patient begins to seize. Which agent should be administered first?
A. Lorazepam
B. Phenobarbital
C. Phenytoin
D. Propofol
E. Valproic acid

Answer: A. Lorazepam or any other benzodiazepine is the first-line treatment of toxin-induced seizures. Intravenous phenytoin can increase the incidence of ventricular tachycardia and is not generally effective in controlling toxin-induced seizures. Phenobarbital and propofol are effective but take longer to give and typically are used after benzodiazepines. Valproic acid is not likely to be effective.

146.5. A 57-year-old woman presents with altered mental status. A friend states that the patient takes antidepressant medications and has recently been complaining of symptoms of an upper respiratory tract infection. The patient is noted to have a temperature of 39.2° C and a pulse of 135 beats/minute. Otherwise, her vital signs are within normal limits. On examination, she has a tremor, myoclonus, and diaphoresis. Which of the following is the most consistent with this presentation?
A. Anticholinergic syndrome
B. Cocaine intoxication
C. Cyclic antidepressant overdose
D. Neuroleptic malignant syndrome (NMS)
E. Serotonin syndrome

Answer: E. Symptoms of serotonin syndrome include altered mental status, agitation, ataxia, diaphoresis, diarrhea, hyperreflexia, hyperthermia, myoclonus, shivering, and tremor. Many of the symptoms are similar to symptoms caused by NMS and sympathomimetic overdoses; however, myoclonus is unique to the serotonin syndrome. Additional historical features consistent with the serotonin syndrome are the fact that the patient is taking an antidepressant, possibly a selective serotonin reuptake inhibitor (SSRI), and has likely added an over-the-counter "cold" medication. Many of these medications contain dextromethorphan, which also decreases serotonin reuptake and can precipitate the serotonin syndrome in patients taking SSRIs.

146.6. A 24-year-old man presents after taking an overdose of his antidepressant. He does not know the name of the drug. He has no complaints, and his vital signs and physical examination findings are normal. Soon after completing your evaluation, the patient experiences a tonic-clonic seizure. Which of the following antidepressants is most likely to produce seizures without other symptoms of severe toxicity?
A. Amitriptyline
B. Bupropion
C. Fluoxetine
D. Phenelzine
E. Trazodone

Answer: B. Bupropion can induce seizures even at therapeutic levels. Other adverse effects include tachycardia, tremulousness, hallucinations, and QRS prolongation. Cyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (SSRIs; fluoxetine), and monoamine oxidase inhibitors (MAOIs; phenelzine) can also cause seizures but less frequently than bupropion and usually with other symptoms of serious intoxication such as central nervous system (CNS) depression or QRS prolongation.

146.7. A patient is prescribed a new medication that he takes each night. After 4 days, he is drowsy and noted to have orthostatic hypotension, nausea, vomiting, and priapism. What medication is most likely involved?
A. Amitriptyline
B. Bupropion
C. Fluoxetine
D. Phenelzine
E. Trazodone

Answer: E. Trazodone and nefazodone may cause orthostatic hypotension and lethargy. Priapism is a relatively unique complication of trazodone and is more common with therapeutic use rather than in acute overdose.

146.8. A patient presents after a substantial accidental overdose of her monoamine oxidase inhibitor (MAOI), which she confused with her megavitamin therapy. There is no need for psychiatric evaluation. She is asymptomatic and has normal vital signs and a normal physical examination. What is the appropriate disposition?
A. Admit to intensive care unit for a minimum of 24 hours of observation
B. Admit to ward for a minimum of 24 hours of observation
C. Discharge home
D. Observe for 6 hours, then discharge home
E. Observe for 12 hours, then discharge home

Answer: A. All patients who overdose on MAOIs should be admitted for at least 24 hours of observation because symptom onset is often delayed. In addition, the effects of overdose may be severe and require aggressive therapy.

CHAPTER 147

Cardiovascular Drugs

Jon B. Cole

Cardiovascular drugs are a common cause of poisoning in the United States; in 2013, 101,544 exposures to cardiovascular drugs were reported to United States poison control centers.[1] Cardiovascular drugs are the seventh most common cause of poisoning and the second most common cause of poisoning death in the United States, accounting for more than 10% of all poisoning fatalities. Of the plethora of cardiovascular drugs, three classes—cardioactive steroids (primarily digoxin), beta-adrenergic blockers, and calcium channel blockers—account for the majority of fatalities. Because the commonality between all three of these drug classes is a combination of bradycardia and hypotension, it is critical for emergency clinicians to be familiar with clonidine poisoning as well, because it may present in a similar fashion. In addition, familiarity with nitrates, their untoward effects and drug interactions, and the treatment of methemoglobinemia is critical for the emergency clinician.

CARDIOACTIVE STEROIDS (DIGOXIN)

Principles of Toxicity

Digoxin is derived from the Balkan foxglove plant, *Digitalis lanata* (Fig. 147.1), and the trade name for digoxin (Lanoxin) is derived from the Latin name of this plant. Digitoxin, which is no longer in clinical use in the United States, comes from *Digitalis purpurea*.[2] Despite centuries of experience with digitalis, chronic and acute poisonings still occur. Medication errors and toxic effects account for the most common causes (44%) of preventable iatrogenic cardiac arrests. Controversial or not, over 20 million digoxin prescriptions are still written in the United States annually.[3]

Pathophysiology

Digoxin is used therapeutically (1) to increase the force of myocardial contraction to increase cardiac output in patients with heart failure and (2) to decrease atrioventricular (AV) conduction to slow the ventricular rate in atrial fibrillation. The basis for its first effect is inhibition of membrane sodium-potassium–adenosine triphosphatase (Na^+,K^+-ATPase), which increases intracellular sodium and extracellular potassium concentrations. This increase in intracellular sodium concentration results in dysfunction of the sodium-calcium ion exchanger, which normally extrudes intracellular calcium after systole. This subsequent increase in intracellular calcium concentration results in a larger amount of calcium pumped into the sarcoplasmic reticulum so that on calcium-induced calcium release during subsequent action potentials, a larger amount of calcium is released into the cell, causing a more powerful contraction and thus increased cardiac output. Any molecule with this effect is classified as a cardioactive steroid. Cardiac glycosides (such as digoxin) are merely cardioactive steroids with additional sugar moieties attached to their steroid nucleus. At therapeutic doses, the effects of digoxin on serum electrolytes are minimal. With toxic concentrations, digoxin paralyzes the Na^+,K^+-ATPase pump, potassium cannot be transported into cells, and serum potassium concentration can rise as high as 13.5 mmol/L.

Digoxin exerts direct and indirect effects on sinoatrial (SA) and AV nodal fibers. At therapeutic concentrations, digoxin indirectly increases vagal activity. At toxic concentrations, digoxin can directly block the generation of impulses in the SA node, depress conduction through the AV node, and increase the sensitivity of the SA and AV nodes to catecholamines. Catecholamines, whether endogenous or administered to treat bradydysrhythmias or hypotension, play an important role in digoxin toxicity. Because bradydysrhythmias and tachydysrhythmias can appear and alternate in the same patient, administration of drugs to treat tachycardias may later contribute to more refractory bradycardias and AV block.

Digoxin also exerts three primary effects on Purkinje fibers: (1) decreased resting potential, resulting in slowed phase 0 depolarization and conduction velocity; (2) decreased action potential duration, which increases sensitivity of muscle fibers to electrical stimuli; and (3) enhanced automaticity resulting from increased rate of phase 4 repolarization and delayed after-depolarizations. These mechanisms account for an increase in premature ventricular contractions, which is the most common electrocardiographic manifestation of digoxin toxicity. At extremes of toxicity, these effects result in a dangerous sensitivity to mechanical and electrical stimulation. Interventions with pacemaker wires, catheters, and cardioversion can result in asystole, ventricular tachycardia, and ventricular fibrillation.

Unlike most cardiovascular drugs, digoxin can produce virtually any dysrhythmia or conduction block, and bradycardias are as common as tachycardias (Box 147.1). However, none is unique to digoxin, and because they can all occur in the setting of ischemic and other heart disease, digoxin toxicity remains a clinical rather than an electrocardiographic diagnosis.

The volume of distribution (V_d) of digoxin is 5 L/kg for adults but varies from 3.5 L/kg in premature infants to 16.3 L/kg in older infants. This indicates that only a small fraction of digoxin remains in the intravascular space, and the drug is highly concentrated in cardiac tissue. The myocardial-to-serum ratio at equilibrium ranges from 15:1 to 30:1. In contrast, the V_d for digitoxin is only 0.5 L/kg, giving it a different pharmacokinetic profile.

The elimination half-life of digoxin, which is primarily excreted in the urine, is 36 hours, and the half-life of digitoxin, which is metabolized in the liver, is 7 days. Whereas digoxin undergoes a small enterohepatic circulation, the circulation for digitoxin is large.

Protein binding varies from 20% to 30% for digoxin to 95% for digitoxin. The significant protein binding and large volumes of distribution of digoxin suggest that hemodialysis, hemoperfusion, and exchange transfusion are ineffective. The long half-lives have therapeutic implications for temporizing measures such as pacemakers, atropine, and antidysrhythmic drugs compared to the more definitive treatment of Fab fragments.

Multiple drugs and disease states can negatively alter absorption, V_d, protein binding, and elimination, rendering the heart

Fig. 147.1. The Balkan foxglove plant, from which digoxin is derived.

BOX 147.1

Dysrhythmias Associated With Digoxin Toxicity

NONSPECIFIC
PVCs, especially bigeminal and multiform
First-, second- (Wenckebach's), and third-degree AV block
Sinus bradycardia
Sinus tachycardia
SA block or arrest
Atrial fibrillation with slow ventricular response
Atrial tachycardia
Junctional (escape) rhythm
AV dissociation
Ventricular bigeminy and trigeminy
Ventricular tachycardia
Torsades de pointes
Ventricular fibrillation

MORE SPECIFIC BUT NOT PATHOGNOMONIC
Atrial fibrillation with slow, regular ventricular rate (AV dissociation)
Nonparoxysmal junctional tachycardia (rate 70 to 130 beats/min)
Atrial tachycardia with block (atrial rate usually 150 to 200 beats/min)
Bidirectional ventricular tachycardia

AV, Atrioventricular; *PVCs,* premature ventricular contractions; *SA,* sinoatrial.

more susceptible to digoxin toxicity. The factors listed in Box 147.2 are especially important risk factors in chronic intoxication.

Clinical Features

The symptoms and signs of chronic digoxin toxicity are nonspecific. The most common symptoms, in more than 80% of cases, are nausea, anorexia, and fatigue; but a variety of gastrointestinal, neurologic, and ophthalmic disturbances also occur (Box 147.3). Visual disturbances include decreased visual acuity, scotomata, photophobia, and chromatopsia (aberrations of color vision). Digoxin intoxication should be considered in any patient receiving maintenance therapy who has consistent symptoms, no matter how vague, particularly if presenting with new conduction disturbances or dysrhythmias.

There are significant differences between acute and chronic toxicity (Table 147.1). Chronic poisoning has an insidious onset

BOX 147.2

Factors Associated With Increased Risk of Digoxin Toxicity

Renal insufficiency
Heart disease
- Congenital heart disease
- Ischemic heart disease
- Congestive heart failure
- Myocarditis

Electrolyte imbalance
- Hypokalemia or hyperkalemia
- Hypomagnesemia
- Hypercalcemia

Alkalosis
Hypothyroidism
Sympathomimetic drugs
Cardiotoxic co-ingestants
- Beta-blockers
- Calcium channel blockers
- Tricyclic antidepressants

Drug interactions
- Quinidine, amiodarone
- Erythromycin
- Verapamil, diltiazem, nifedipine
- Captopril

Elderly woman

BOX 147.3

Noncardiac Symptoms of Cardioactive Steroid Intoxication

GENERAL
Weakness
Fatigue
Malaise

GASTROINTESTINAL
Nausea and vomiting
Anorexia
Abdominal pain
Diarrhea

OPHTHALMOLOGIC
Blurred or snowy vision
Photophobia
Chromatopsia (yellow, green, red, brown, blue vision changes)
Transient amblyopia, diplopia, scotomas, blindness

NEUROLOGIC
Dizziness
Headache
Confusion, disorientation, delirium
Visual and auditory hallucinations
Paranoid ideation, acute psychosis
Somnolence
Abnormal dreams
Paresthesias and neuralgia
Aphasia
Seizures

Fig. 147.2. Oleander *(Nerium oleander),* common to much of the Southern United States, contains oleandrin, a cardiac glycoside.

Fig. 147.3. Lily-of-the-Valley *(Convallaria majalis),* found in much of the Northern Hemisphere, contains convallatoxin, a cardiac glycoside.

TABLE 147.1

Chronic Versus Acute Digoxin Intoxication

CHRONIC	ACUTE
Higher mortality (LL_{50} 6 ng/mL)	Lower mortality
Ventricular dysrhythmias more common	Bradycardia and AV block more common
Usually elderly patients	Usually younger patients
Underlying heart disease increases morbidity and mortality	Absence of heart disease decreases morbidity and mortality

AV, Atrioventricular; LL_{50}, level with a 50% mortality.

and is accompanied by a higher mortality rate that is probably due in part to underlying heart disease and chronic accumulation of the toxin. In cases of chronic intoxication, the level with a 50% mortality (LL_{50}) is only 6 ng/mL. The LL_{50} for acute intoxication is not known, but it is much higher, especially in children. Although toxicity increases with greater body load, there is no clear correlation with amount ingested, especially in children, and many patients with large acute ingestions or high serum levels become only mildly symptomatic. The association of hyperkalemia with acute toxicity is obvious given the mechanism of digoxin; either hypokalemia or hyperkalemia may occur with chronic toxicity.

Differential Diagnoses

No sign or symptom, including dysrhythmia, is unique to digoxin poisoning, so the differential diagnosis is broad. Intrinsic cardiac disease as well as other cardiotoxic drugs should be considered. Cardioactive steroid poisoning from plants is rare, but presents similarly to digoxin toxicity. Common examples include oleander (*Nerium oleander;* Fig. 147.2) and lily-of-the-valley (*Convallaria majalis;* Fig. 147.3). Aconitine, a sodium-channel opening xenobiotic found in common Monkshood *(Aconitum napellus),* may also mimic digoxin poisoning. Central nervous system (CNS) depression or confusion may be due to various depressant drugs (opioids, major tranquilizers, sedative hypnotic agents) and toxins, as well as infection, trauma, inflammation, and metabolic derangements. Visual disturbances caused by digoxin are binocular and are often not reported by the patient; unfortunately, they are not specific to digoxin poisoning. Methanol, metformin, ethambutol, ethyl chloride, quinine, and other antimalarial medications are all capable of producing visual disturbances. Gastrointestinal disturbances are common and nonspecific and may be misdiagnosed as gastritis, enteritis, or colitis.

Diagnostic Testing

Diagnosis and management rely heavily on serum digoxin concentrations, but it is the steady state, rather than peak concentration, that correlates with tissue toxicity and is used to calculate antidote dosages. Peak concentrations after an oral dose of digoxin occur in 1.5 to 2 hours, with a range of 0.5 to 6 hours. Steady-state serum concentrations are not achieved until after alpha distribution, or 6 to 8 hours after a dose or overdose, and may be only one fourth to one fifth of the peak concentration. The ideal serum digoxin concentration for patients with heart failure is considered to be 0.7 to 1.1 ng/mL, although laboratory "normals" are often reported up to 2.0 ng/mL. Serum steady-state digoxin concentrations of 1.1 to 3.0 ng/mL are difficult to interpret; that is, concentrations as low as 1.1 ng/mL have been associated with toxicity, and patients with levels up to 3.0 ng/mL can be asymptomatic. The incidence of digoxin-incited dysrhythmia reaches 10% at a concentration of 1.7 ng/mL and rises to 50% at a concentration of 2.5 ng/mL. Determination of a serum digoxin concentration measured too soon after the last maintenance dose falsely suggests toxicity, especially in cases of chronic intoxication, in which significant morbidity and mortality can occur at levels of 2 to 6 ng/mL. After an acute massive overdose in a patient who is rapidly becoming symptomatic, however, it may be impractical to wait 6 to 8 hours for the first measurement. It is unlikely that early

concentrations exceeding 10 to 20 ng/mL will fade to clinical insignificance at 6 to 8 hours after ingestion.

Management

Fab Fragments (DigiFab)

The treatment of significant digoxin poisoning is the administration of digoxin-specific fragment antigen-binding (Fab) antibodies (DigiFab); all other interventions are considered complementary.

The mortality rate of digoxin poisoning before Fab fragment therapy was 23% despite all of the interventions described. Fab fragment treatment is well established in both chronic and acute poisonings, with a response rate approaching 90%. Nonresponders usually receive Fab fragments too late, have concomitant poisoning, or are compromised by underlying disease.

Digoxin antibodies are derived from sheep. Allergic reactions only occur in less than 1% of cases but are slightly more common in patients with asthma. Reactions have included erythema, urticaria, and facial edema, all of which are responsive to the usual treatment for allergic reactions. Other expected reactions when Fab fragments neutralize digitalis include hypokalemia, exacerbation of congestive heart failure, and increase in ventricular rate with atrial fibrillation all of which occur infrequently. Two Fab fragment preparations were previously available; however, Digibind has been discontinued, leaving DigiFab as the only available product in the United States. If vials of Digibind are still available at a given institution, they require a 0.22-μm membrane filter for proper use; such a filter is not required for DigiFab.

Fab fragment treatment is best reserved for cases of serious cardiovascular toxicity rather than for routine or prophylactic administration with higher than expected serum concentrations. In acute poisoning, Fab fragments should be used for a serum potassium level above 5.0 mEq/L or unstable dysrhythmias such as symptomatic sinus bradycardia, ventricular dysrhythmias, or second- or third-degree heart block unresponsive to atropine. Fab fragment therapy should be used before transvenous pacing, because the latter is believed to carry risk of ventricular dysrhythmia, although the evidence for this is mixed.

The median time to initial response is 19 minutes after completion of the Fab infusion, but complete resolution of digitalis toxic rhythms may require hours. Late administration of Fab fragments has resuscitated 54% of patients who have suffered cardiac arrest. Fab fragments should be administered whenever hemodynamic compromise occurs in the setting of a digoxin-induced toxic dysrhythmia or heart block; a full list of indications is included in Box 147.4.

Dosing of Fab fragments is based upon the patient's clinical status. If the patient is in cardiac arrest, the maximum number of vials of Fab fragments available (up to 10) should be administered undiluted as an intravenous (IV) bolus. If the patient is hemodynamically unstable, there is no time to assess serum digoxin concentration, and the ingested amount is also unknown, in acute toxicity 10 vials (if available) should be administered over 30 minutes, and three to six vials should be administered in chronic poisoning. In a hemodynamically unstable patient after an acute digoxin ingestion where the serum digoxin concentration is unknown but the amount of digoxin ingested is known, we recommend full reversal based upon the following concept: one vial of DigiFab contains 40 mg of Fab fragments, which bind 0.5 mg of digoxin or digitoxin (Box 147.5). If, in acute or chronic toxicity, the patient is hemodynamically unstable and the steady-state serum digoxin concentration is known, we recommend full reversal with Fab fragments based upon the digoxin concentration utilizing the formula in Boxes 147.6 and 147.7.

In hemodynamically stable patients, we recommend a more conservative dosing regimen of Fab fragments. The total body

BOX 147.4

Recommendations for Administration of Digoxin Antibody Fragments

ADULTS

1. Ventricular dysrhythmias more severe than premature ventricular contractions
2. Progressive and hemodynamically significant bradydysrhythmias unresponsive to atropine
3. Serum potassium concentration above 5.0 mEq/L
4. Rapidly progressive rhythm disturbances or rising serum potassium level
5. Co-ingestion of cardiotoxic drugs such as beta-blockers, calcium channel blockers, or tricyclic antidepressants with concomitant shock
6. Ingestion of plant known to contain cardioactive steroids *plus* severe dysrhythmias
7. Acute ingestion of more than 10 mg *plus* any one of factors 1 through 6 above
8. Steady-state serum digoxin concentration above 6 ng/mL *plus* any one of factors 1 through 6 above

CHILDREN

1. Ingestion of more than 0.1 to 0.3 mg/kg or steady-state digoxin concentration above 5 ng/mL *plus* rapidly progressive symptoms or signs of cardioactive steroid intoxication *or* potentially life-threatening dysrhythmias or conduction blocks *or* serum potassium concentration above 6 mmol/L
2. Co-ingestion of other cardiotoxic drugs with additive or synergistic toxicity
3. Ingestion of plant known to contain cardioactive steroids *plus* severe dysrhythmias

BOX 147.5

Sample Calculation of DigiFab Based on Ingested Dose of Digoxin or Digitoxin*

Case: A toxic-appearing 40-year-old woman has ingested fifty 0.25-mg digoxin tablets.

Body load = amount ingested
× 0.8 (bioavailability of digoxin tablets)
= 12.5 mg × 0.8 = 10 mg

Dose of digoxin Fab fragments (in vials) = 10 mg ÷ 0.5 mg bound per vial
= 20 vials

*Formula from GlaxoSmithKline, 2008.

BOX 147.6

Sample Calculation of DigiFab Based on Steady-State Digoxin Concentration*

Case: A toxic-appearing 4-year-old child weighing 20 kg has a digoxin level of 16 ng/mL 8 hours after ingestion of an unknown number of digoxin tablets.

Dose (in number of vials) = (serum digoxin concentration
× weight in kg) ÷ 100
= (16 × 20) ÷ 100
= approximately 3 vials

*Formula from GlaxoSmithKline 2008; assumes V_d = 5 L/kg.

BOX 147.7

Calculation of DigiFab Based on Steady-State Digitoxin Concentration*

Case: A toxic-appearing 70-year-old man weighing 80 kg has a digitoxin level of 200 ng/mL (therapeutic = 10 to 35 ng/mL).

$$\text{Dose (in number of vials)} = (\text{serum digitoxin concentration} \times \text{weight in kg}) \div 1000$$
$$= (200 \times 80) \div 1000$$
$$= 16 \text{ vials}$$

*Formula from GlaxoSmithKline 2008; V_d = 5 L/kg.

burden of digoxin is often overestimated.[4] Furthermore, the incidence of life-threatening dysrhythmias, even in reported large ingestions, is low, suggesting most patients do not require Fab fragments.[5] Pharmacokinetic modeling of digoxin toxicity suggests smaller doses of Fab fragments are adequate to reverse toxicity. Therefore, in acute digoxin poisoning, we recommend two vials, repeated as needed using clinical markers of toxicity such as evidence of shock or severe dysrhythmias. For chronic poisoning, we recommend one vial with a repeat dose at 60 minutes if the patient is still symptomatic. Repeat dosing sooner is reasonable if the patient becomes unstable.

Because most assays measure both bound and unbound drug, digoxin concentrations will be elevated for up to 1 week after Fab fragments administration, with values often greater than 100 ng/mL once Fab fragments have been administered. Measurement of free serum digoxin is possible in some institutions, but it is more meaningful to follow the patient clinically.

Electrolyte Correction

In cases of chronic toxicity, which may be exacerbated by hypokalemia, maintenance of the serum potassium level to at least 3.5 to 4 mEq/L is an important early treatment. Potassium can be administered orally (which is safer) or intravenously at a rate of less than 40 mEq/hr.

In acute poisoning, serum potassium concentration may begin to rise rapidly within 1 to 2 hours of ingestion. Potassium should be withheld, even if mild hypokalemia is measured initially. The initial serum potassium concentration may in fact be a better predictor of mortality than the initial digoxin concentration. Before Fab treatment was available, up to 50% of the patients with serum potassium concentrations between 5.0 and 5.5 mmol/L died. In the setting of digoxin toxicity, we recommend initiating Fab treatment based solely on, a serum potassium concentration greater than 5 mmol/L.

The decision to administer calcium to patients with hyperkalemia and digoxin poisoning represents a clinical dilemma. Classic teaching is that in the setting of the increased intracellular calcium concentration from digoxin poisoning, administration of exogenous calcium will result in "stone heart" from excessive intracellular calcium. This concept has been in the literature since 1927, based primarily on animal studies. Documented cases of cardiac arrest after calcium administration are exceedingly rare in the literature, and the temporal relationship is dubious. More recent human data indicate that the IV administration of calcium for hyperkalemia in the setting of digoxin toxicity is safe.[6] Unequivocally, however, the best treatment of hyperkalemia due to acute digoxin toxicity is Fab fragments. The treatment of hyperkalemia in a patient with chronic digoxin toxicity and renal failure is less clear; however, the evidence that calcium salts will be harmful in this scenario is lacking. Calcium salts should be administered over several minutes through a secure peripheral IV site or through a central venous catheter. Treatment of hyperkalemia related to digoxin toxicity is identical in indication and approach to that for hyperkalemia from other causes (see Chapter 117). Hypomagnesemia enhances the effects of cardioactive steroids.[7] Therefore, any patient with suspected poisoning should have serum magnesium concentrations measured. This is further supported by evidence of magnesium reversing digoxin-induced tachydysrhythmias. If significant magnesium depletion is present or suspected (eg, electrocardiographic changes such as QTc prolongation are present), 1 to 2 g of magnesium sulfate should be administered over 10 to 20 minutes (child: 25 mg/kg), followed by a constant infusion of 1 to 2 g/hr until magnesium concentrations are normal. Patients should be closely monitored for respiratory depression, which is usually preceded by progressive loss of deep tendon reflexes. Infuse magnesium slowly and pause the infusion if heart block or bradycardia develops. Avoid magnesium in patients with renal failure. We do not recommend administration of magnesium in bradydysrhythmias and conduction blocks, because hypermagnesemia can impair impulse formation and AV conduction.

Atropine

Atropine is generally used for severe bradycardia and advanced AV block. We recommend using atropine as a temporizing measure for patients with shock while Fab fragments are being administered. We also recommend atropine for bradycardia refractory to Fab fragments. Standard dosing (0.02 mg/kg in children with a minimum of 0.1 mg; 1 mg IV in adults) should be used. Doses can be repeated every 3 to 5 minutes. In general, an external or transvenous pacemaker should be readied once atropine has been administered.

Pacing and Cardioversion

Transvenous pacing has been a mainstay of treatment for several decades; however, there is some evidence that the catheter may induce ventricular tachydysrhythmias in a myocardium made irritable by digoxin, although convincing studies on this question are lacking. Iatrogenic accidents of cardiac pacing are frequent (36%) in one study and can be fatal (up to 13%). Transvenous pacing should be used only if external pacing fails. Pacing usually is required only temporarily while waiting for Fab fragments to take clinical effect. Cardioversion in the setting of digoxin poisoning should be reserved for life-threatening dysrhythmias such as tachydysrhythmias with profound refractory hypotension, unstable ventricular tachycardia, or ventricular fibrillation.

Phenytoin and Lidocaine

Digoxin immune Fab fragments are the preferred therapy for dysrhythmias, but a dysrhythmia may require intervention while Fab fragments are readied, or to begin to show effect after infusion.

Although both phenytoin and lidocaine are believed to be safe for control of tachydysrhythmias in the setting of digoxin toxicity, we prefer phenytoin. Indications for phenytoin include unstable tachydysrhythmias when Fab fragments are unavailable and unstable tachydysrhythmias that occur while waiting for Fab fragments to take effect. Phenytoin may enhance AV conduction. We recommend administering phenytoin in 100 mg boluses every 5 minutes until dysrhythmias improve or until the standard loading dose of 18 mg/kg is reached. No data exists to support or refute the substitution of fosphenytoin for phenytoin in this scenario. We recommend lidocaine only if the patient has a contraindication to phenytoin or if the maximum dose of phenytoin has been reached. When given, we recommend a loading dose of 1.5 mg/kg

TABLE 147.2

Age Differences in Digoxin Intoxication

ADULT	PEDIATRIC
Toxic at lower concentrations	Asymptomatic at higher concentrations
Nausea, fatigue, and visual disturbances most common	Obtundation and vomiting more common than in adults
Tachydysrhythmias as common as blocks and bradydysrhythmias	Bradydysrhythmias and blocks most common
Allergic reactions to Fab fragments uncommon (<1%)	Allergic reactions extremely rare
V_d less variable (5 to 7.5 L/kg)	V_d more variable (3.5 to 6.0 L/kg in premature infants, 8.0 to 16.3 L/kg in infants 2 to 24 months old)

IV push, followed by an infusion of 1 to 4 mg/min (30 to 50 μg/kg/min), started at 1 mg/min and titrated up based on response to therapy. Most other cardiac drugs (isoproterenol, procainamide, amiodarone, beta-blockers, calcium antagonists) may worsen dysrhythmias or depress AV conduction in digoxin poisoned patients and should not be used.

Pediatric Considerations

Children with healthy hearts can tolerate massive acute oral ingestions without Fab treatment.[8] This excludes therapeutic errors, children who are taking digoxin therapeutically, and children with heart disease.

Dosage calculation and administration errors account for more pediatric digoxin intoxication and death than accidental oral ingestion. Therapeutic errors, especially accidental IV overdoses, often result in death within 1 to 4 hours.

Signs and symptoms in children with digoxin poisoning are different than adults (Table 147.2). Vomiting, somnolence, and obtundation are more common than in adults.[8] Conduction disturbances and bradycardias are more common than ventricular dysrhythmias in children, especially with acute ingestion.[8,9]

Disposition

All patients who are symptomatic from digoxin toxicity with hyperkalemia, dysrhythmia, AV block, or significant comorbidity should be admitted to an intensive care or coronary care unit after treatment with Fab fragments. Asymptomatic patients reporting an acute ingestion of digoxin should be observed for at least 12 hours of continuous cardiac monitoring.

BETA-ADRENERGIC BLOCKERS

Principles of Toxicity

Beta-adrenergic blocking drugs became widely used in Europe in the 1960s for treatment of dysrhythmias. Their antihypertensive effects were later appreciated. By the 1970s, they were one of the most widely prescribed classes of drugs in the United States. Current indications include supraventricular dysrhythmias, hypertension (although the drugs have fallen out of favor for this indication), angina, thyrotoxicosis, migraine, and glaucoma. Of the numerous beta-blockers available, propranolol overdose is the most deadly. In 2013, United States poison centers received more than 24,000 calls regarding beta-blocker exposures.[1] Nearly 1000 of these calls were regarding patients with life-threatening symptoms.

BOX 147.8

Manifestations and Complications of Beta-Blocker Overdose in Order of Decreasing Frequency*

1. Bradycardia (65/90 cases)
2. Hypotension (64/90)
3. Unconsciousness (50/90)
4. Respiratory arrest or insufficiency (34/90)
5. Hypoglycemia (uncommon in adults)
6. Seizures (common only with propranolol, 16/90)
7. Symptomatic bronchospasm (uncommon)
8. VT or VF (6/90)
9. Mild hyperkalemia (uncommon)
10. Hepatotoxicity, mesenteric ischemia, renal failure (rare or single case reports)

VF, Ventricular fibrillation; *VT,* ventricular tachycardia.
*Intoxication with beta-sympatholytics.

Pathophysiology

Beta-blockers structurally resemble isoproterenol, a pure beta-agonist. They competitively inhibit endogenous catecholamines such as epinephrine at beta-adrenergic receptors, blocking the catecholamine effects of inotropy (increased myocardial contraction), dromotropy (enhanced cardiac conduction), and chronotropy (increased heart rate). These are all β_1 effects. Complex β_2 effects include vascular (smooth muscle relaxation and vasodilation), liver (glycogenolysis, gluconeogenesis), lung (bronchodilation), adipose tissue (release of free fatty acids), and uterus (smooth muscle relaxation) effects. Equally important properties, which vary from one beta-blocker to another, include cardioselectivity (β_1 selectivity), membrane-stabilizing effect (fast cardiac sodium channel blocking properties), lipophilicity, and intrinsic sympathomimetic activity (Table 147.3). Although cardioselectivity is lost in overdose, cardioselective beta-blockers such as atenolol, metoprolol, and esmolol still have a lower mortality rate than that of propranolol.[1]

Beta-blockers are rapidly absorbed after oral ingestion, with peak effects varying between drugs. Hepatic metabolism on first pass results in significantly less bioavailability after oral dosing than with IV injection (eg, 1:40 for propranolol, 1:2.5 for metoprolol). Because volume of distribution for most beta-blockers generally exceeds 1 L/kg, hemodialysis is not efficacious for most beta-blockers. Protein binding varies from 0% for sotalol to 93% for propranolol. Elimination half-lives vary from 8 to 9 minutes for esmolol to as long as 24 hours for nadolol (see Table 147.3).

Clinical Features

The most common initial sign remains bradycardia. Hypotension and unconsciousness are the second and third most common signs (Box 147.8). Much of propranolol's unique toxicity derives from its lipophilic nature, which allows it to penetrate the CNS, causing obtundation, respiratory depression, and—with large overdoses—seizures. Seizures probably result from a combination of hypotension, hypoglycemia, hypoxia, and direct CNS toxicity including sodium-channel blockade. Other beta-blockers are not lipophilic and do not have these effects. Of note, bronchospasm is rarely a problem in cases of beta-blocker overdose, even with nonselective beta-blockers. The few cases of symptomatic bronchospasm respond to the usual bronchodilator nebulizations.

Propranolol, nadolol, betaxolol, and acebutolol have a membrane-stabilizing effect that impairs SA and AV node

TABLE 147.3

Selected Characteristics of Common Beta-Blockers

	V_d (L/kg)	ISA	ELIMINATION HALF-LIFE (hr)	LIPOPHILIC	PROTEIN BINDING (%)	MSE	COMMENTS
NONSELECTIVE BETA-BLOCKERS							
Propranolol	4	0	4	+	93	+	Most fatalities
Nadolol	1.9	0	10–20	0	20	0	Dialyzable
Timolol	1.4–3.5	0	3–5	+	10	0	Dialyzable
Pindolol	3–6	+	3–4	+	51	+	
Labetalol	10	0	4–6	0	50	+	Alpha-blockade also
Oxprenolol	1.3	+	2	+	78	+	
Sotalol	1.6–2.4	0	7–18	+	0	0	Class III and class II antidysrhythmic; torsades de pointes; dialyzable
Carvedilol	1.5–2	0	6–10	+	95	0	
SELECTIVE BETA-BLOCKERS							
Metoprolol	5.5	0	3–4	+	12	0	
Atenolol	0.7	0	5–8	0	5	0	Dialyzable
Esmolol	2	0	0.13	0	55	0	
Acebutolol	1.2	+	2–4	+	26	+	QT prolongation, VT, dialyzable
Practolol	1.6	+	10–11	+	0		
Bisoprolol	2.9	0	10–12	0	30	0	
Betaxolol	5–13	0	12–22	0	55	0	

ISA, Intrinsic sympathomimetic activity; *MSE,* membrane-stabilizing effect; *VT,* ventricular tachycardia.

function and leads to bradycardia and AV block. Ventricular conduction is also depressed, leading to QRS widening, occasional ventricular dysrhythmias such as ventricular tachycardia and ventricular fibrillation, and cardiogenic shock. The intrinsic sympathomimetic activity of some beta-blockers such as pindolol, oxprenolol, acebutolol, and carteolol can lead to some unusual manifestations such as ventricular dysrhythmias and sinus tachycardia instead of bradycardia. Labetalol and carvedilol also block α_1-adrenergic receptors, giving an additional mechanism for hypotension and distributive shock. However, labetalol's beta-blockade is three (oral route) to seven (IV route) times more potent than its α-blockade. Carvedilol is even more beta-selective; it blockade of β_1 and β_2 receptors is 10 times more potent than α_1. Nebivolol is a cardioselective beta-adrenergic blocker that also causes vasodilation through a unique mechanism: induction of endothelium-dependent vasodilation by stimulation of nitric oxide bioactivity.

In contrast to digoxin, beta-blocker toxicity has a more rapid onset. Life-threatening CNS and cardiovascular effects can occur 30 minutes after oral overdose. Patients ingesting delayed-release preparations may remain asymptomatic for several hours, followed by a prolonged period of toxicity of up to 24 hours.

Differential Diagnoses

The combination of bradycardia and hypotension suggests beta-blockade, calcium channel blockade, or digoxin poisoning. Centrally acting α_2-adrenergic agonists such as clonidine and tizanidine or imidazoline receptor agonists such as tetrahydrozoline and oxymetazoline may also cause this constellation of symptoms. Without a history of beta-blocker ingestion, the diagnosis can be challenging, especially when non-cardiac effects such as CNS depression and seizures predominate. Sodium channel poisoning with QRS widening can occur, suggesting other antidysrhythmic drugs or cyclic antidepressants. The differential diagnosis also includes sedative-hypnotic drug overdose, hypoglycemic drug ingestion, opioid overdose, CNS injury or infection, endocrine-metabolic disorder, sepsis, and acute myocardial infarction.

Diagnostic Testing

Diagnosis and management depend entirely on the clinical picture, and the only mandatory testing is in the form of a 12-lead electrocardiogram (ECG) and continuous ECG monitoring for rate, rhythm, and intervals. Blood concentrations of beta-blockers correlate poorly with severity of intoxication and are not readily available. Most urine toxicology screens do not identify antidysrhythmic drugs and are not helpful. Hypoglycemia is more common in children, and bedside determination of glucose concentration should be done if CNS depression is noted. Known access of the patient to a beta-blocker and consistent clinical features such as bradycardia and hypotension should lead the clinician to consider beta-blocker intoxication and begin empirical treatment. Whereas some authors believe that a serum lactate concentration can help predict mortality in overdose patients, this has not held true in pure beta-blocker ingestions.[10,11]

Management

Immediate measures include IV fluids, supplemental oxygen, and monitoring of cardiac rhythm and respirations.

Whole-bowel irrigation is cumbersome; and because there is a lack of evidence for efficacy in clinical trials, we recommend against its use in beta-blocker poisoning.[12] The benefit of gastric lavage is also unproven, the procedure is cumbersome and benefit

likely is outweighed by procedural risks. Please see Chapter 139 for further information on gastrointestinal decontamination, including the use of activated charcoal.

Hypotension, Bradycardia, and Atrioventricular Block

The first step in the treatment of beta-blocker overdose is bolus administration of crystalloid fluids. In hypotensive patients, 20 to 40 mL/kg of normal saline or lactated Ringer's solution can be infused and repeated once. Further doses of isotonic fluids, however, can lead to pulmonary edema and should be avoided particularly in older patients with cardiac disease. Atropine at standard doses noted earlier may be used for bradycardia but is rarely effective. We recommend atropine for a heart rate of less than 50 beats per minute with concomitant hypotension and symptoms of severe bradycardia such as weakness, drowsiness, or obtundation. Infusion of more potent drugs or cardiac pacing is often necessary; in fact, we recommend atropine is best used as a temporizing measure to the therapies noted later.

Calcium

The final common pathway for stimulation of beta-adrenergic receptors is an increase in intracellular calcium concentration, and deleterious effects on calcium transport may contribute to beta-blocker toxicity. Therefore, IV administration of calcium can be used for treatment of hypotension. One gram of calcium gluconate contains 4.5 mEq of elemental calcium, whereas 1 g of calcium chloride contains 13.6 mEq. Calcium chloride is an acidifying salt and can cause significant tissue damage and necrosis if extravasation occurs. Thus it should be administered through a central venous catheter or a secure large-bore antecubital peripheral line if the patient is in extremis. Indications for calcium include hypotension unresponsive to crystalloid fluids and/or bradycardia; typically the heart rate should be less than 60 beats per minute, keeping in mind to consider if the patient has relative bradycardia. We recommend an initial dose of 13 to 25 mEq of calcium in adults (1 to 2 g calcium chloride, 3 to 6 g calcium gluconate) during 10 minutes. Patients in extremis may receive the initial dose during 1 minute. If a response is observed, repeated doses may be given in 20 minutes, and a constant infusion may be started at 20 mg/kg/hr of calcium chloride (60 mg/kg/hr of calcium gluconate). The total serum calcium level should be raised no higher than 14 mg/dL, which is the threshold of "severe" hypercalcemia. If ionized calcium is measured instead of total calcium, we recommend not to exceed 1.5 times the upper limit of normal. The serum calcium concentration can be as high as 18.2 mg/dL within 15 minutes after a bolus of just 5 mL of 10% calcium chloride, so calcium concentrations should be measured at least 30 minutes after bolus dosing has finished.

Glucagon

Glucagon has both inotropic and chronotropic effects and does not depend on beta-adrenergic receptors for its action; therefore, it has long been used for beta-blocker toxicity. It stimulates the production of intracellular cyclic adenosine monophosphate independently of the beta-adrenergic receptor. Furthermore, it helps counteract the hypoglycemia induced by beta-blocker overdose. Although not well studied, the initial dose of glucagon is a 5- to 10-mg IV bolus (0.05 to 0.1 mg/kg for children). If a response occurs to glucagon, specifically if heart rate, blood pressure, or symptom improvement is observed, the "response dose" should be started as an infusion at a rate of the response dose administered over 1 hour. We recommend glucagon for patients with bradycardia or hypotension not responsive to crystalloid fluids, atropine, and an initial bolus of calcium. Glucagon has a very short (20-minute) half-life, and its effect is often transient. Vomiting is a common complication of glucagon, particularly if administered too rapidly, so the airway should be secured or monitored closely to prevent aspiration. With cumulative large doses, glucagon should be diluted in 5% glucose in water for constant infusion. Side effects also include hypokalemia and allergic reactions. The response to glucagon alone is often inadequate, and glucagon is likely to be less effective than high-dose insulin (HDI) therapy. Furthermore, hospitals may not be adequately stocked for treatment beyond a few hours. From clinical experience, we find glucagon most useful as a transient therapy to bridge patients to HDI therapy.

High-Dose Insulin

Despite glucagon's longer history for treatment of beta-blocker toxicity, HDI is a superior therapy. HDI is not a vasopressor; it is a profound inotrope with vasodilating properties. The mechanism for HDI is not fully elucidated but probably involves both optimization of the use of carbohydrates for fuel by cardiac myocytes and modulation of intracellular calcium. HDI improves cardiac output significantly in beta-blocker toxicity from an increase in stroke volume more than heart rate.[13] Dosing of HDI is not agreed on; dosing in humans successfully treated with HDI has ranged from 0.5 to 22 U/kg/hr.[9] In the largest human case series to date, of patients receiving HDI, 11 of 12 patients survived.[14] Mean maximal HDI dosing in this series was 8.7 U/kg/hr. We recommend a bolus of 1 U/kg of regular insulin IV, followed by an infusion at 1 U/kg/hr titrated up by 2 U/kg/hr every 10 minutes until a maximum of 10 U/kg/hr is reached. Regardless of HDI dosing, we recommend that patients should receive a bolus of dextrose before insulin, and a dextrose infusion should be started thereafter such as a bolus of 25 g glucose (1 traditional "amp" of D50) if the serum glucose concentration is below 200 mg/dL (11.1 mmol/L) followed by concentrated dextrose solutions such as D25, D50, or even D70 through a central line because patients receiving HDI therapy are at risk of fluid overload. Glucose concentration should be monitored as frequently as every 15 minutes until a steady state of glucose use is achieved. Potassium concentration should also be monitored closely and potassium replaced as needed because patients may become hypokalemic. We recommend HDI for patients experiencing hypotension despite crystalloid fluid, atropine, and a single bolus of calcium and glucagon. We also recommend a central venous catheter and an arterial catheter be placed immediately upon the decision to initiate HDI.

Sodium Bicarbonate

Sodium channel blockade from beta-blockers with membrane-stabilizing activity such as propranolol occasionally causes QRS widening, which mechanistically should respond to sodium bicarbonate. Bicarbonate should be dosed at 1 to 2 mEq/kg IV as a bolus repeated every 3 to 5 minutes until the QRS narrows to less than 120 ms. It is our experience this is typically a late or even moribund finding in propranolol overdose. We recommend sodium bicarbonate for patients poisoned with a membrane-stabilizing beta-blocker who have an acute change in QRS duration to greater than 120 ms and demonstrate clinical signs of shock.

Vasopressors and Other Inotropes

Catecholamines are indicated when mean arterial pressure (MAP) cannot be maintained at 60 mm Hg or above, despite use of crystalloid infusion, calcium, atropine, glucagon, and HDI.

A single catecholamine of choice after HDI and glucagon has not emerged. Because norepinephrine appears to be superior to

dopamine for cardiogenic shock and does not carry any vasodilatory risk as many pure inotropes do, norepinephrine is our catecholamine of choice when HDI is inadequate in maintaining MAP.[15] In the selection of cardioactive medications to supplement HDI and glucagon, we recommend early assessment of cardiac contractility with bedside echocardiography. If contractility and heart rate is adequate, therapeutic focus should shift to providing support with vasopressors. Our second-line vasopressor of choice is vasopressin, dosed at a constant infusion of 0.04 U/min. If the clinical picture is still uncertain, systemic vascular resistance and cardiac output by either indirect or direct measurements is recommended to determine if either cardiogenic or distributive shock exists. We recommend third-line vasopressors be chosen based upon these measurements used along-side bedside echocardiography. Refractory cases of bradycardia may respond to an external or transvenous pacemaker. A pacemaker is particularly useful when cardiac contractility is vigorous but bradycardia is persistent.

Intravenous Fat Emulsion (Intralipid)

Intravenous fat emulsion (IFE) is a newer therapy option for poison-induced cardiogenic shock. This therapy was first described for treatment of toxicity from local anesthetics such as bupivacaine. The pharmacologic rationale for the use of IFE is discussed in Chapter 139. Of note, animal evidence exists to support the use of IFE for both lipid-soluble beta-blockers (such as propranolol) and non–lipid-soluble beta-blockers (such as atenolol). Human case reports of successful resuscitations of patients in extremis or arrest exist for propranolol, nebivolol, and metoprolol.[9,16,17] Indications for IFE are not universally agreed upon. Although originally described as a treatment for overdose patients in cardiac arrest, several reports now exist describing the successful use of IFE in critically ill patients that still retain a pulse. IFE is a reasonable therapy in beta-blocker overdose in patients with shock refractory to conventional treatments.[18] We recommend IFE in patients with persistent bradycardia or hypotension not responding to IV fluids, calcium, HDI, and at least three vasopressors or inotropes at maximum recommended infusion rates. Dosing for IFE is also not universally agreed upon. We recommend an initial bolus of 1.5 mL/kg of 20% lipid solution given over 2 to 3 minutes, followed immediately by an infusion of 0.25 mL/kg/min. Based on pharmacokinetic modeling, some authors recommend decreasing the maintenance infusion to 0.025 mL/kg/min to sustain lipemic serum for a longer period of time.[19] Such an approach, however, is not yet validated in human overdose patients. The 1.5 mL/kg bolus can be repeated up to two additional times for refractory shock or cardiac arrest, although clinicians should avoid exceeding the U.S. Food and Drug Administration (FDA) recommended lipid daily dose of 12.5 mL/kg unless hemodynamic compromise requires otherwise. Response, when it occurs, is typically within minutes of the bolus.

Despite recent enthusiasm for IFE, its use is not without associated complications, including extreme lipemia resulting in lab interference with blood tests (complete blood counts, chemistries, and coagulations studies), as well as acute pancreatitis, and acute respiratory distress syndrome.[20-22]

Ventricular Dysrhythmias

Although it is uncharacteristic, ventricular tachydysrhythmias can occur following beta-blocker toxicity. Cardioversion and defibrillation are indicated for ventricular tachycardia and ventricular fibrillation, respectively, following American Heart Association guidelines. Pulsatile ventricular tachycardia can most safely be treated with lidocaine. For dosing recommendations, please see the Management of Cardioactive Steroids section. Antidysrhythmic drugs, especially of classes IA and IC, should be avoided; they may potentiate AV block or be pro-dysrhythmic because of an additive membrane-stabilizing effect. Sotalol, unlike other beta-blockers, has class III as well as class II effects; that is, it prolongs the QT interval and can cause torsades de pointes and other ventricular dysrhythmias. Overdrive pacing with isoproterenol or a pacemaker and magnesium sulfate are specific therapies for torsades de pointes.

BOX 147.9

Beta-Blockers That May Be Amenable to Hemodialysis

- Sotalol
- Atenolol
- Timolol
- Acebutolol
- Nadolol

Extracorporeal Elimination and Circulatory Assistance

Hemodialysis or hemoperfusion may be beneficial for beta-blockers with lower V_d, lower protein binding, and greater hydrophilicity (Box 147.9).

Unlike overdoses of other drugs, toxicity from cardiovascular drugs do not destroy tissue, and if circulation can be supported, complete recovery can be expected. An intra-aortic balloon pump or cardiopulmonary bypass can be lifesaving in cases of hypotension refractory to HDI multiple vasopressors and IFE. A percutaneous left ventricular assist device, in addition to extracorporeal membrane oxygenation (ECMO), have also been used to successfully resuscitate beta-blocker poisoned patients though this combination of therapies is unproven.[23] ECMO alone is considered by some investigators to be a promising emerging therapy; however, no consensus guidelines exist.[8] We recommend ECMO in cases where patients have hypotension refractory to HDI, at least three catecholamines, and IFE, or in cases with bradycardia unresponsive to inotropes and a pacemaker.

Pediatric Considerations

Severe pediatric beta-blocker poisonings are rare. In the cases reported, CNS, cardiac, and metabolic toxicities are similar. Symptomatic hypoglycemia, however, is more common in children and occurs even after therapeutic doses. Therefore, serum glucose concentration should be measured in children. Risk factors include young age, fasting state, and diabetes mellitus. Obtunded children should receive empirical glucose, 1 to 2 mL/kg of 25% glucose IV. In general, 5% glucose infusions have been sufficient to maintain euglycemia, especially with concomitant use of glucagon and catecholamines, which stimulate glucose release.

Seizures also occur in cases of pediatric beta-blocker overdose, but hypoglycemia is probably an important contributing factor. They are more common with the lipid-soluble beta-blockers propranolol. Benzodiazepines are generally effective.

Children generally fare well after beta-blocker ingestion, with symptoms in only 2% of potential beta-blocker exposures in children.

Sequential Approach to Beta-Blocker Poisoning

The management of beta-blocker poisoning begins with a 20 mL/kg bolus of IV fluid, repeated once if needed (Box 147.10).

BOX 147.10

Treatment of Beta-Blocker Poisoning

PHASE 1 (RESUSCITATION)
Boluses of intravenous (IV) isotonic fluids, calcium, atropine, glucagon

PHASE 2 (STABILIZATION)
Infusions of:
- Glucagon
- High-dose insulin (HDI)/glucose
- Catecholamines (epinephrine, norepinephrine, isoproterenol, dobutamine, dopamine)
- Phosphodiesterase inhibitors (amrinone)

Early cardiac pacing if no prompt response to chronotropic or dromotropic drugs
Peripheral arterial and pulmonary artery catheter monitoring if refractory hypotension
Consider hemodialysis of hydrophilic beta-blockers with low protein binding and low V_d

PHASE 3 (SALVAGE THERAPIES)
Intravenous fat emulsion (IFE) (eg, Intralipid)
Intra-aortic balloon counterpulsation
Consider percutaneous left ventricular assist device or cardiac bypass

Symptomatic bradycardia, typically a heart rate of 60 bpm or less in adults, should be treated with atropine, 0.5 mg every 3 minutes up to total of 3 mg. If hypotension (a systolic pressure <90 mm Hg) persists, 3 to 6 g of calcium gluconate should be infused over 10 minutes. If hypotension persists after calcium infusion, HDI should be initiated. Glucagon, given as a 5-mg bolus, can be used to bridge to HDI. One "amp" of D50 should be administered followed by 1 U/kg of regular insulin as a loading dose. An infusion of 25 g/hr of concentrated glucose should be initiated in addition to an infusion of insulin at 1 U/kg/hr. The insulin infusion should be increased by 2 U/kg/hr every 10 minutes until hypotension resolves or a maximum rate of 10 U/kg/hr is reached. Glucagon may be repeated during HDI titration if hypotension persists. If HDI does not resolve hypotension, norepinephrine should be administered starting at 0.1 mcg/kg/min and titrated up until hypotension resolves or until a maximum dose is reached. After maximal norepinephrine is reached, the clinician should reassess using bedside echocardiography and measurement of cardiac output and systemic vascular resistance to determine if the patient needs additional inotropy, chronotropy, or vasotropy. If bradycardia is contributing to decreased cardiac output, we recommend a transvenous pacemaker. Additional inotropes and/or vasopressors such as vasopressin, phenylephrine, epinephrine, dopamine, or dobutamine should be selected and titrated up based upon the patient's cardiac output and systemic vascular resistance. We recommend vasopressin as the second-line vasopressor at a steady-state infusion of 0.04 U/min. Once the patient has reached maximal doses on HDI and three vasopressors or catecholamines, we next recommend IFE at 1.5 mL/kg IV of 20% lipid solution followed by an infusion of 0.25 mL/kg/min. The bolus may be repeated; however, a maximal dose of 1000 mL of lipid solution should not be exceeded. If the patient continues to have hypotension or bradycardia refractory to all the aforementioned therapies, extracorporeal support should be initiated. We recommend ECMO; although cardiopulmonary bypass, an intra-aortic balloon pump, or a percutaneous left-ventricular assist device would be reasonable if ECMO is not immediately available. Downward titration of infusions for beta-blocker poisoning rarely occurs in the emergency department.

Disposition

Patients who remain completely asymptomatic for 6 hours after an oral overdose of normal-release preparations can be safely referred for psychiatric evaluation. We recommend consultation with a poison control center or standard pharmacologic reference to confirm that peak effect of the beta-blocker in question has passed before psychiatric disposition. Patients ingesting sustained-release preparations should be admitted to a monitored bed; however, those who remain asymptomatic 8 to 12 hours after ingestion are very unlikely to have toxicity. Patients with second or third degree heart block, hypotension not responding to IV fluid administration, or who have hemodynamically significant dysrhythmias should be admitted to an intensive care unit.

CALCIUM CHANNEL BLOCKERS

Principles of Toxicity

Verapamil and nifedipine, the earliest calcium channel antagonists, were introduced in Europe in the 1970s and in the United States in the early 1980s. Calcium antagonists have found many clinical applications: angina pectoris, hypertension, supraventricular dysrhythmias, hypertrophic cardiomyopathy, and migraine prophylaxis. Most fatalities occur with verapamil, but severe toxicity and death have been reported for most drugs of this class. In 2013, United States poison control centers received more than 11,000 calls about calcium channel blockers.[1] Nearly 500 of these calls were regarding patients with life-threatening symptoms.

Pathophysiology

Calcium channel antagonists block the slow L-type calcium channels in the myocardium and vascular smooth muscle, leading to coronary and peripheral vasodilation. They also reduce cardiac contractility, depress SA nodal activity, and slow AV conduction. In cases of overdose, verapamil has the deadliest profile, combining severe myocardial depression and peripheral vasodilation. Both verapamil and diltiazem act on the heart and blood vessels, whereas dihydropyridine calcium channel blockers (such as nifedipine) cause primarily vasodilation and subsequent reflex tachycardia. As with beta-blockers, selectivity is lost after overdose, and toxicity is fourfold; the calcium antagonists have negative effects on heart rate, contractility, conduction, and vascular tone, with the exception of dihydropyridine calcium channel blockers, which tend to result in tachycardia even in severe toxicity.

All calcium channel blockers are rapidly absorbed, although first-pass hepatic metabolism significantly reduces bioavailability (Table 147.4). Onset of action and toxicity ranges from less than 30 minutes to 60 minutes. Peak effect of nifedipine can occur as early as 20 minutes after ingestion, but peak effect of sustained-release verapamil can be delayed beyond 12 hours. High protein binding and V_d greater than 1 to 2 L/kg make hemodialysis or hemoperfusion ineffective. With sustained-release preparations, their half-lives are relatively short, generally limiting toxicity to 24 to 36 hours.

Clinical Features

Severe calcium antagonism eventually affects multiple organ systems, but cardiovascular toxicity is primarily responsible for morbidity and mortality. Hypotension and bradycardia occur early, and other rhythm disturbances include AV block of all degrees, sinus arrest, AV dissociation, junctional rhythm, and asystole. Dihydropyridine calcium channel blockers (such as

TABLE 147.4

Selected Characteristics of Some Calcium Channel Blockers

	V_d (L/kg)	HALF-LIFE (hour[s])	PROTEIN BINDING (%)	COMMENTS
Verapamil	4	3–12	90	Most fatalities; impairs contractility and cardiac conduction more than most other calcium antagonists
Diltiazem	1.7–5.3	3–7.9	70-80	Suppression of atrioventricular (AV) node similar to verapamil; myocardial depression otherwise less
Nifedipine	1.4–2.2	1–5	92-98	Vasodilation greatest effect
Nicardipine	0.64	8–9	95	Vasodilation
Nimodipine	0.94–2.3	1–2	95	Vasodilation
Amlodipine	21	30–50	98	Vasodilation
Bepridil	8	33–42	99	Class I as well as class IV antidysrhythmic; prolongs QT: torsades de pointes
Felodipine	10	10	99	Vasodilation
Isradipine	3	1.9–16	95	Vasodilation
Nisoldipine	4–5	7–12	99	Vasodilation

amlodipine) often cause reflex sinus tachycardia from peripheral vasodilation. Calcium channel blockade has little effect on ventricular conduction; therefore, QRS widening is not seen early on. Ventricular dysrhythmias are also uncommon. A unique feature of calcium channel blocker poisoning is endocrine dysfunction. Like many drugs, calcium channel blockers lose specificity in overdose and thus interfere with other calcium channels within the body. As calcium influx triggers the release of insulin, patients poisoned with calcium channel blockers are often hyperglycemic. For additional clinical features, see Box 147.11.

BOX 147.11

Manifestations of Calcium Channel Blocker Poisoning

Cardiovascular: Hypotension, sinus bradycardia, sinus arrest, AV block, AV dissociation, junctional rhythm, asystole; ventricular dysrhythmias uncommon except with bepridil
Pulmonary: Respiratory depression, apnea; pulmonary edema; adult respiratory distress syndrome
Gastrointestinal: Nausea, vomiting, bowel infarction (rare)
Neurologic: Lethargy, confusion, slurred speech, coma; seizures (uncommon); cerebral infarction (rare)
Metabolic: Metabolic (lactic) acidosis; hyperglycemia (mild); hyperkalemia (mild)
Dermatologic: Flushing, diaphoresis, pallor, peripheral cyanosis

AV, Atrioventricular.

Differential Diagnoses

Differential diagnosis is similar to that of beta-blocker overdoses. Until characteristic rhythm disturbances supervene, many other toxic, metabolic, traumatic, and cardiovascular disorders can cause hypotension but less commonly bradycardia. The reflex tachycardia and distributive shock seen with dihydropyridine calcium channel blockers can mimic sepsis, volume depletion, or anaphylaxis.

As with beta-blockade, CNS depressive effects typically follow shock and include lethargy, confusion, and coma. Unlike beta-blockers, calcium antagonists are not associated with hypoglycemia or seizures. Pulmonary effects include non-cardiogenic pulmonary edema, respiratory distress, and apnea. As with cardioactive steroids (eg, digoxin) and beta-blocker overdose, nausea and vomiting are common (see Box 147.11).

Diagnostic Testing

Serum levels of calcium antagonists are not readily available, nor do urine toxicology screens reliably detect this class of drugs. Glucose and electrolytes (including calcium and magnesium) should be measured. Hyperglycemia secondary to insulin inhibition occurs, but the elevation is usually mild (150 to 300 mg/L) and usually short-lived (<24 hours). Hyperglycemia is a predictor of poor outcomes in verapamil and diltiazem toxicity. If hyperglycemia is present with concomitant hypotension, we recommend HDI. Please see specific dosing recommendations later. A metabolic (lactic) acidosis can occur with prolonged hypotension and hypoperfusion.

An ECG should be promptly obtained, with special attention to atrial and ventricular rates and PR, QRS, and QT intervals. The ECG is repeated when hemodynamic status changes.

Like the beta-blockers, calcium antagonists cause early toxicity, and symptoms can be expected within 6 hours of ingestion of normal-release preparations. Toxicity can be delayed 12 to 24 hours with sustained-release preparations.

Management

Initial management includes rapid establishment of vascular access, cardiac monitoring, and frequent blood pressure measurement. Please see Chapter 139 for further information on gastrointestinal decontamination, including the use of activated charcoal. For an algorithmic approach to management, see Box 147.12.

Hypotension and Bradycardia

Hypotension can be caused by myocardial depression, inadequate heart rate, or peripheral vasodilation. Atropine may be used for bradycardia but is rarely effective. We recommend atropine at the

BOX 147.12

Treatment of Calcium Channel Blocker Intoxication

PHASE 1 (RESUSCITATION)
Boluses of intravenous (IV) isotonic fluids, calcium, atropine

PHASE 2 (STABILIZATION)
Calcium infusion
High-dose insulin (HDI)/glucose infusion
Catecholamine infusions
Transcutaneous or transvenous cardiac pacing
Invasive monitoring

PHASE 3 (SALVAGE THERAPIES)
Methylene blue
Intravenous fat emulsion (IFE) (eg, Intralipid)
Intra-aortic balloon counterpulsation
Consider percutaneous left ventricular assist device or cardiac bypass

doses noted earlier for a heart rate of less than 50 beats per minute with concomitant hypotension and symptoms of severe bradycardia such as weakness, drowsiness, or obtundation. Atropine's effect has often been minimal and short-lived, and it is at best a temporizing intervention. A bolus of crystalloid fluid (20 to 40 mL/kg or more) should also be infused early; however, care should be taken to avoid fluid overload given the additional risk of pulmonary edema with calcium channel blocker poisoning particularly in older patients. Calcium salts, HDI, vasopressors, and inotropes should be administered in the same fashion as noted earlier for beta-blocker toxicity with one exception—we do not recommend glucagon in calcium channel blocker poisoning. It has no mechanistic advantage over epinephrine, and no good evidence exists to support its use in calcium channel blocker poisoning.

IFE (eg, Intralipid) has been described in the use of calcium channel blockers. The proposed mechanisms are discussed earlier with beta-blockers. Animal evidence exists that IFE may be effective especially for the treatment of verapamil toxicity. Human case reports exist of successful resuscitation of toxicity from diltiazem and verapamil. Dosing and indications are identical to those for beta-blocker toxicity. We recommend that IFE be used in patients with hypotension refractory to calcium, HDI, and three vasopressors.

Methylene blue is an emerging therapy for calcium channel blocker poisoning.[24] Although traditionally used as a reducing agent for the treatment of methemoglobinemia, methylene blue is also a vasoconstrictor. Specifically, it inhibits the enzyme guanylyl cyclase, resulting in decreased production of cyclic guanosine monophosphate (cGMP) and inhibition of endothelial smooth muscle relaxation, causing an increase in systemic vascular resistance.[25] Methylene blue is particularly intriguing to use in the treatment of amlodipine poisoning, because amlodipine specifically causes an increase in nitric oxide production, which leads to increased cGMP and vasodilation as noted earlier. Data are limited to a small number of animal studies and human case reports, and thus far suggest improvements more in hemodynamic parameters as opposed to mortality. We recommend the use of methylene blue only as an alternative salvage therapy to ECMO when HDI, catecholamines, and IFE have failed. Dosing involves a 1- to 2-mg/kg bolus of a 1% methylene blue solution followed by an infusion of 1 mg/kg for up to 6 hours.

Pediatric Considerations

Nifedipine, verapamil, and probably other drugs in its class join the short list of medications that can kill a child with ingestion of a single tablet. Seizures may be more common in children than in adults and should be treated with diazepam, lorazepam, or phenobarbital.

Overall, death after calcium antagonist ingestion in children is rare. The IV route of administration, as with digoxin, is much more dangerous. Even therapeutic doses of IV verapamil are considered contraindicated in infants with supraventricular tachycardia because of case reports of cardiovascular collapse and cardiac arrest after injection.

Hyperglycemia occasionally occurs in children, but the elevation is usually short-lived. Although insulin has been administered in a small number of cases, it is generally not necessary unless HDI is required for hemodynamic compromise, because the hyperglycemia usually resolves spontaneously within 24 to 36 hours.

Case reports of children in refractory shock secondary to drug toxicity have been treated with intra-aortic balloon counterpulsation or cardiac bypass. Circulatory support during the day or two required for hepatic or renal elimination of the drug is potentially beneficial for a drug that does not cause irreversible damage. Aside from the differences previously noted, the presentation in children is similar to that in adults: rapid onset of toxicity with CNS depression, bradydysrhythmias (except for dihydropyridine calcium channel blockers), and hypotension.

For an algorithmic approach to calcium channel blocker poisoning, please reference the sequential approach to beta-blocker poisoning earlier, with the following exceptions. Glucagon is not recommended, and methylene blue is recommended prior to initiation of ECMO.

Disposition

Because the peak effect of normal-release calcium channel blockers commonly occurs in 90 minutes to 6 hours, patients who are totally asymptomatic for 6 hours after an ingestion of immediate-release medication can be safely discharged according to psychiatric needs. Symptomatic patients or those who ingested delayed-release preparations should be admitted to a medical or toxicology service for at least 24 hours of continuous cardiac monitoring. Persistently hypotensive, bradycardic patients who do not respond to conventional therapy require intensive care monitoring.

CLONIDINE

Principles of Toxicity

Clonidine is a central acting α_2-adrenergic and imidazoline agonist initially approved by the FDA as a treatment for hypertension in 1974. Since that time, its use has expanded to treat conditions such as attention-deficit/hyperactivity disorder (ADHD), pheochromocytoma, and withdrawal from opioids, ethanol, and nicotine. It is also used in spinal and epidural anesthesia. Based on its mechanism of action, it mimics clinical features of both opioid poisoning and poisoning from digoxin, beta-blockers, or calcium channel blockers. In 2013 United States poison centers received over 9400 calls regarding clonidine exposures with over 1500 suffering life-threatening effects.[1]

Clinical Features

Clonidine exerts its effects by binding to pre-synaptic α_2-adrenergic receptors in the brain, inhibiting neurons in the nucleus tractus solitaries, causing decreased norepinephrine release. This leads to

bradycardia, hypotension, decreased mental status, miosis, and occasionally hypothermia. Clonidine is also an agonist at imidazole receptors; imidazoline receptors are located throughout the body, but their activation in the brain, specifically in the rostral ventrolateral medulla, causes unconsciousness, bradycardia, and hypotension, potentially exacerbating the α2-adrenergic effects of clonidine.[26]

Differential Diagnosis

There is great overlap between the clinical effects of central α_2-agonists such as clonidine and imidazole agonists. Individual drugs that are agonists at either or both receptors may belong to disparate classes. Therefore, antihypertensive medications (such as guanabenz and alpha-methyldopa, ADHD medications (such as guanfacine), muscle relaxers (such as tizanidine), and topical vasoconstrictors (such as tetrahydrozoline, oxymetazoline, and naphazoline) all have similar systemic effects in overdose. The presentation of miosis and obtundation may be mistaken for opioid or sedative-hypnotic overdose, and the combination of bradycardia and hypotension may mimic digoxin, beta-blocker, or calcium channel blocker poisoning. Pontine hemorrhage should also be considered in the differential diagnosis.

Diagnostic Testing

Clonidine and other similar drugs are not routinely screened for in most blood or urine drug screens. Clonidine poisoning is a clinical diagnosis. An ECG should be obtained to evaluate for heart block and to evaluate the QRS and corrected QT (QTc) intervals, and the patient should be placed on continuous cardiac monitoring and pulse oximetry. Small doses of naloxone may help differentiate clonidine poisoning from opioid poisoning; however if large doses are required, this may be less helpful diagnostically because large doses of naloxone have been reported to reverse clonidine toxicity.

Management

Supportive care is the mainstay of therapy for clonidine poisoning. Monitoring as described earlier is essential. Hypotension should be treated with boluses of 20 mL/kg of isotonic fluid. The concern for pulmonary edema is less than with beta-blocker or calcium channel blocker poisoning, thus the clinician should make more liberal use of IV fluids in clonidine poisoning. We recommend treating hypotension with up to 60 mL/kg of isotonic fluid. If hypotension is worsening or persistent at a level of inadequate organ perfusion despite adequate fluid resuscitation, a catecholamine is indicated. There are no human randomized trials comparing various catecholamines in clonidine poisoning; however, because the underlying pathophysiology is a lack of systemic norepinephrine, we recommend norepinephrine in this setting. Norepinephrine is initiated as 0.1 mcg/kg/min and titrated to a MAP of 60. When blood pressure stabilizes, downward titration of norepinephrine is initiated, with a goal to maintaining adequate organ perfusion with the least necessary dose, ultimately weaning the patient entirely.

Several authors have suggested naloxone may be a useful therapy in clonidine poisoning. As endogenous opioids do play a role in the central neurotransmission of norepinephrine, there is a physiologically plausible reason naloxone may be effective for clonidine poisoning. Although case reports of naloxone successfully reversing clonidine poisoning exist, they are rare. Our clinical experience is that naloxone is rarely effective for clonidine poisoning. Nevertheless, as side effects of judicious naloxone use are rare, steadily increasing doses of naloxone are a reasonable therapy for clonidine poisoning. If time and airway patency allows, we recommend escalating doses of naloxone of 0.1 mg, 0.4 mg, 2 mg, and 10 mg. Naloxone is indicated solely if the patient is obtunded or has an unprotected airway, and it should be administered in parallel with any necessary IV fluids or catecholamines.

Disposition

Clonidine's peak effects occur 2 to 4 hours post-ingestion. Its half-life is between 5 and 13 hours. Therefore patients with normal vital signs and mental status 4 hours post-ingestion may be discharged home or to an appropriate psychiatric facility. Patients with persistent vital sign abnormalities or altered mental status should be admitted to a unit capable of continuous cardiac and oximetry monitoring. Patients requiring vasopressor support or with severe obtundation should be admitted to a critical care unit.

NITRATES AND NITRITES

Principles of Toxicity

Nitrates (nitroglycerin, isosorbide mononitrate, and dinitrate) are widely used as vasodilators in the treatment of heart failure and ischemic heart disease. They augment coronary blood flow, as well as reduce myocardial oxygen consumption by reducing afterload. At lower doses nitrates primarily dilate veins, but at higher doses they also dilate arteries. In addition, many exposures occur in young adults, usually male, who inhale various alkyl nitrites (amyl, butyl, isobutyl, or ethyl nitrite) in the hope of enhancing or prolonging sexual pleasure. Because of the sound they make when broken open, these products are best known to abusers as "poppers."[27] The popularity of poppers has waned in recent years as sales of sildenafil and related products have soared.

Nitrates are occasionally found in rural well water contaminated by livestock or fertilizer runoff. Oral nitrates may be converted to nitrites in the gastrointestinal tract, especially in infants up to 4 months old. Nitrites, and to a lesser extent, nitrates themselves, have substantial oxidizing power and may oxidize the ferrous (Fe^{2+}) ion in hemoglobin to its ferric (Fe^{3+}) state causing methemoglobinemia. Methemoglobin is incapable of carrying oxygen, thus it alters the shape of the hemoglobin-dissociation curve shifting it to the left, causing functional anemia via impaired oxygen delivery.

Clinical Features

Hypotension is a common complication. Typically it is accompanied by reflex tachycardia unless the patient also has taken another agent such as a beta-blocker that slows chronotropy. Rapid dilation of meningeal arterioles causes headache.

Patients suffering methemoglobinemia have symptoms related to impaired oxygen delivery. The concentration of methemoglobin and the speed with which the condition is contracted are related to symptom severity. The higher the concentration of methemoglobinemia and the speed with which it is achieved are proportional to symptom severity. Cyanosis occurs commonly if the percentage of methemoglobin exceeds 10%. Inspection of the patient's blood upon venipuncture reveals "chocolate-colored" blood due to the spectrum of light absorbed by methemoglobin; this typically occurs at a methemoglobin concentration greater than 15%. Higher concentrations of methemoglobin may result in fatigue, dyspnea, weakness, dizziness, drowsiness, coma, seizures, and death.

Differential Diagnosis

The differential diagnosis of nitrate poisoning includes all other vasodilating drugs such as diuretics, angiotensin-converting

enzyme (ACE) inhibitors, and dihydropyridine calcium channel blockers, as well as oxidative phosphorylation uncouplers such as cyanide. Non-toxicologic conditions capable of mimicking nitrate poisoning include sepsis and anaphylaxis. The differential diagnosis of methemoglobinemia includes hypoxia, as well as other hemoglobinopathies such as sulfhemoglobinemia.

Diagnostic Testing

No specific diagnostic testing is recommended for nitrate poisoning. For patients with suspected methemoglobinemia, an oxygen challenge should first be attempted. If the patient is cyanotic and high flow oxygen at 15 L/min by non-rebreather mask does not improve cyanosis, blood co-oximetry should be performed to determine the percentage of methemoglobin in the blood. If methemoglobinemia is confirmed, a hemoglobin concentration should be obtained. If anemia is present, smaller concentrations of methemoglobin may be clinically significant because the functional anemia of methemoglobinemia is synergistic with absolute anemia. It should be noted most humans have, at baseline, a methemoglobin percentage of 1% to 3%. Symptoms do not typically occur until concentrations of 10% or more.

Clinicians should be wary of interpreting pulse-oximetry in the setting of methemoglobinemia. Pulse oximeters function by reading the absorbance of light at wavelengths of 660 and 940 nm, which are selected to separate oxy and deoxyhemoglobin. Methemoglobin absorbs light at both these wavelengths more than either oxy or deoxyhemoglobin. This results in unreliable pulse oximetry that typically reads between 75% and 85%, regardless of the patient's oxygenation status.[28]

Management

Nitrate poisoning usually responds to supine positioning, IV fluids, and reduction of dose or removal of the offending agent. Hypotension is usually transient. Low-dose vasopressors are occasionally needed, but it is best to avoid them in the setting of acute coronary syndrome.

Review of the therapeutic use of nitrates offers insight into poisoning. For example, IV nitroglycerin infusions are used commonly in patients with acute pulmonary edema for afterload reduction. Infusions are usually initiated at 5 to 10 μg/min, but rates as high as 200 to 300 μg/min may be used. These doses may be beneficial in patients with pulmonary edema accompanied by acute hypertension, but hypotension may develop suddenly. IV nitroglycerin has a rapid offset of action, so excessive fall in blood pressure usually responds to reduction or termination of the infusion. Use of nitrates is contraindicated in patients who have recently taken sildenafil (Viagra). Sildenafil and related drugs (vardenafil [Levitra] and tadalafil [Cialis]) inhibit type 5 phosphodiesterase, relaxing vascular smooth muscle. These agents can prolong and intensify the vasodilating effects of nitrates, resulting in severe hypotension. If blood pressure does not normalize with IV fluids and cessation of the nitrate infusion, norepinephrine should be cautiously titrated to a MAP of 60, beginning at 0.1 mcg/kg/min.

Treatment of patients with methemoglobinemia involves supportive care such as supplemental oxygen and IV fluids. More severely poisoned patients should be treated with IV methylene blue. Methylene blue is an oxidizing agent. However, in the presence of the red blood cell enzyme nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase, it is reduced to leukomethylene blue, which then reduces methemoglobin back to hemoglobin. We recommend an intravenous dose of 1–2 mg/kg of 1% methylene blue solution for patients with a methemoglobin concentration greater than 25% and any symptoms of functional anemia. The infusion should be given over 5 minutes to reduce pain at the IV site. A clinical response should occur within minutes of infusion. If cyanosis does not resolve in 1 hour, a second infusion of 1 mg/kg can be repeated. At doses exceeding 7 mg/kg, the oxidizing power of methylene blue becomes great enough that it may in fact worsen methemoglobinemia, thus patients receiving multiple doses should be monitored closely.

KEY CONCEPTS

Cardioactive Steroids

- Digoxin toxicity is often occult and should be considered in any patient who is on digoxin and presents with gastrointestinal or visual disturbance and a new dysrhythmia or conduction disturbance.
- Digitalis Fab is the specific antidote for digoxin toxicity and is dosed by body load of digitalis, not by body weight of the patient.
- Indications for digitalis Fab are summarized in Box 147.4, and Fab should be used before pacing or antidysrhythmic drugs.
- Hyperkalemia in acute digitalis toxicity is best treated with Fab fragments. Conventional treatment as for any other cause of hyperkalemia is also appropriate when Fab fragment preparations are not immediately available.

Beta-Adrenergic Blockers

- Beta-blocker intoxication usually causes bradydysrhythmias and occasionally AV block.
- Noncardiac symptoms such as obtundation, seizures, and hypoglycemia may occur, especially early in the course and particularly with propranolol.
- Volume expansion, atropine, calcium, and glucagon are early treatment measures, but absent a response, begin a HDI/glucose infusion.
- When using HDI/glucose infusions, concentrate glucose solutions to avoid fluid overload.

Calcium Channel Blockers

- Signs and symptoms of calcium channel blocker intoxication often occur early after overdose but may be significantly delayed with sustained release products.
- AV block and bradydysrhythmias predominate with verapamil and diltiazem; dihydropyridine calcium channel blockers often present with tachycardia.

Clonidine

- Clonidine poisoning may mimic opioid poisoning and is best treated with crystalloid fluids followed by an infusion of norepinephrine.

Nitrates, Nitrites, and Methemoglobinemia

- Nitrates are contraindicated in patients who have recently taken phosphodiesterase inhibitors for erectile dysfunction.
- Patients with a methemoglobin concentration of 25% and symptoms of anemia should be treated with methylene blue.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 147: QUESTIONS & ANSWERS

147.1. A 72-year-old man presents with a chief complaint of nausea. He also complains of blurred vision and general weakness. His vital signs and physical examination are normal. He has a past medical history significant for myocardial infarction, congestive heart failure, hypertension, and diabetes. He states that he takes all prescribed medications regularly and just took all of his medications as prescribed approximately 1 hour ago. Reviewing his medication list, you note that one of his medications is digoxin. Which of the following should be done?

A. Administer oral potassium.
B. Give digoxin-specific Fab fragment antibodies now.
C. Give digoxin-specific Fab fragment antibodies only if he has an abnormal electrocardiogram (ECG).
D. Obtain a serum digoxin level in 6 hours.
E. Obtain a serum digoxin level now.

Answer: D. The steady-state (as opposed to peak) digoxin level is most closely correlated with toxicity. Peak level is reached in 1.5 to 2 hours, whereas steady-state levels are not reached until 6 to 8 hours after ingestion. As long as a patient is stable and a chronic ingestion is suspected, digoxin levels taken soon after ingestion are not helpful. Other diagnostic studies should be undertaken while waiting for the digoxin level, including, but not limited to, an electrocardiogram (ECG) and serum electrolyte determination.

147.2. In a patient with a known digoxin overdose, which of the following is an indication for administration of digitalis antibody fragments?

A. Acute ingestion of 10 mg of digoxin
B. Atrial fibrillation with rapid ventricular response
C. First-degree heart block
D. Ingestion of oleander *(Nerium oleander)*
E. Serum potassium greater than 5 mEq/L

Answer: E. Hyperkalemia is an indication for treatment with digitalis antibody fragments. Other indications include severe ventricular dysrhythmias; hemodynamically significant bradydysrhythmias unresponsive to atropine; rapidly progressive rhythm disturbances or rising potassium level; co-ingestion of cardiotoxic drugs such as beta-blockers, calcium channel blockers, or cyclic antidepressants; or ingestion of a plant known to contain cardiac glycosides in the setting of severe dysrhythmias.

147.3. A 27-year-old man presents after ingesting 8 mg of digoxin in a suicide attempt. He has ventricular tachycardia on his electrocardiogram (ECG). His blood pressure is 93/54 mm Hg. Laboratory results are not available. You decide to treat with digitalis antibody fragments. How many vials should be given to bind the entire ingestion?

A. 2 vials
B. 4 vials
C. 8 vials
D. 16 vials
E. 20 vials

Answer: D. Each vial contains enough digitalis antibody fragments to neutralize 0.5 mg of digoxin; therefore the patient should be given 16 vials of Fab fragments to fully treat his ingested dose.

147.4. A 5-year-old girl presents after taking some of her grandmother's heart medications. She has sinus bradycardia and a slightly low blood pressure. The remainder of her vital signs and physical examination are nonspecific. A bedside glucose test reveals hyperglycemia. The child is not responsive to calcium therapy. The next

therapeutic intervention that is likely to treat both the endocrine and cardiovascular pathology would be:
A. Dobutamine
B. Epinephrine
C. High-dose insulin (HDI)
E. Intravenous fat emulsion (IFE)
E. Glucagon

Answer: C. Calcium channel blocker toxicity may result in bradycardia and hypotension, much like beta-blocker toxicity. Unlike beta-blocker toxicity, which can cause hypoglycemia, calcium channel blockers can cause hyperglycemia via blockade of calcium channels on beta islet cells. HDI therapy treats calcium channel blocker toxicity via increasing inotropy, as well as normalizing glucose.

147.5. A 60-year-old man has taken an overdose of his beta-blocker medication. He is awake and alert but has a pulse of 50 beats per minute and a blood pressure of 92/60 mm Hg. Which of the following is the most appropriate initial treatment?
A. Atropine, crystalloid fluids, calcium salts, glucagon
B. Atropine, crystalloid fluids, insulin
C. Atropine, dopamine, glucagon
D. Dopamine, crystalloid fluids, insulin
E. Dopamine, glucagon, insulin

Answer: A. Atropine, crystalloid fluids, calcium salts and glucagon are the initial treatments of choice for beta-blocker toxicity. If these agents are ineffective, high-dose insulin (HDI) is reasonable as next-line therapy for cardiogenic shock. If HDI is ineffective, catecholamines are a reasonable option. The catecholamine choice may vary depending on the type of shock the patient is in, and the dose needed for a response may be greater than for other conditions.

147.6. A patient presents after an apparent overdose of diltiazem. Which of the following findings would lead you to suspect a co-ingestant in addition to the calcium channel blocker?
A. Atrioventricular (AV) block on electrocardiogram (ECG)
B. Hyperglycemia
C. Metabolic acidosis
D. Prolonged QRS complex on ECG
E. Respiratory depression

Answer: D. Prolonged QRS and QT intervals are generally not seen in calcium channel blocker overdose and should prompt the search for co-ingestants. One exception is the calcium channel blocker bepridil, which can cause QRS or QT prolongation. All the other listed abnormalities are typical of calcium channel blocker overdose.

147.7. Treatment for an overdose of beta-blockers is most similar to the treatment for an overdose of which other class of medication?
A. Anticholinergics
B. Calcium channel blockers
C. Cyclic antidepressants
D. Digoxin
E. Nitrates

Answer: B. Symptoms from overdose of calcium channel blockers and beta-blockers are similar, as are the therapeutic strategies. Severe anticholinergic toxicity may respond to physostigmine administration, cyclic antidepressants to intravenous (IV) sodium bicarbonate boluses, digoxin poisoning to antibody Fab fragments, and nitrate toxicity to methylene blue therapy.

147.8. Which of the following drugs can kill a toddler with ingestion of a single tablet?
A. Atenolol
B. Chlorthalidone
C. Lisinopril
D. Nitroglycerin
E. Verapamil

Answer: E. Verapamil and other calcium channel blockers can kill a toddler with the ingestion of a single tablet. Appropriate medical treatment, however, is extremely effective, and very few children die from calcium channel blocker overdose. Although beta-blockers have the potential to cause serious toxicity, propranolol is the beta-blocker most likely to cause serious toxicity. Educating parents and caregivers of young children about the potential effects of these medications is important.

CHAPTER 148

Caustics

Christopher Hoyte

PRINCIPLES OF TOXICITY

Caustic or corrosive agents have the potential to cause tissue injury on contact with mucosal surfaces. Both strong acids and alkalis are capable of causing corrosive chemical injury. Alkalis are proton acceptors and result in the formation of conjugate acids and free hydroxide ions. Lye is an example of an alkali and refers to both sodium hydroxide (NaOH) and potassium hydroxide (KOH). Ammonia (NH_3) is another common alkaline corrosive. Acids are proton donors; they dissociate into conjugate bases and free hydrogen ions in solution. Acidic caustics include hydrochloric acid (HCl) and sulfuric acid (H_2SO_4). The injury from caustic agents typically increases with a pH below 3 or above 11. Other chemicals that have caustic properties include phenol, formaldehyde, iodine, and concentrated hydrogen peroxide. This chapter discusses oral exposure. Dermal and inhalational exposures are discussed in Chapter 57 and Chapter 153, respectively.

More than 40,000 exposures involving caustic agents occur in the United States every year.[1] Nearly 75% of reported caustic ingestions are intentional for the purpose of self-harm.[1] Accidental ingestions occur typically among pediatric and elderly populations. Transfer and storage of cleaners in alternative containers that may not be "child proof," such as jars, soda, and sports drink bottles, contribute to unintentional ingestion. Intentional ingestions may have a greater degree of oropharyngeal sparing because of rapid swallowing but have a higher likelihood of serious injury.

Some household products, such as liquid drain cleaners, continue to have high concentrations of alkali (30% KOH) or acid (93% H_2SO_4) (Table 148.1). These products often do not have concentration or content information available on the label, making it difficult for clinicians to determine the severity of exposure. Industrial, farm (dairy pipeline cleaners containing liquid NaOH and KOH in concentrations of 8% to 25%), and swimming pool chemicals also contain caustics in high concentrations.

Crystals and solid particles can have prolonged tissue adherence, causing more severe injury. These ingestions are limited by immediate oral pain, usually causing them to be spit out sooner than a liquid agent. The ingestion of granular automatic dishwashing detergents or brightly colored laundry detergent capsules or "pods" can be associated with devastating injuries.[2] Crystal drain cleaners have lye concentration as high as 74% NaOH and may cause proximal esophageal injury. Liquid dishwashing detergents and laundry detergents have a pH higher than 12, but because the titratable alkaline reserve is low, tissue equilibration occurs quickly, and there is less risk of injury after ingestion.

Liquid household bleach typically contains dilute (3% to 5%) sodium hypochlorite (NaOCl), and ingestion rarely causes consequential injury. Industrial-strength bleach, however, contains significantly higher concentrations of NaOCl, which are more likely to cause esophageal necrosis. Toilet bowl cleaners contain HCl as high as 26%. General-purpose anticorrosive cleaners, such as 31% muriatic acid (HCl), are sold in gallon containers for home use and as swimming pool cleaners.

The alkali powder in air bags can cause ocular burns. Perfume unintentionally sprayed into the eyes can be caustic. Cement is alkaline and causes topical burns, typically on the knees and hands. Although hair relaxer creams contain NaOH and have a pH of 11.2 to 11.9, injuries after ingestion are usually mild.

Caustic ingestions may occur when methamphetamine is produced from over-the-counter medications and household chemicals. H_2SO_4, HCl, NaOH, ammonium hydroxide, anhydrous ammonia, and metallic lithium are all used in the clandestine production of methamphetamine. Severe caustic injuries occurring from ingestion of these agents can cause stricture formation, esophageal resection, and the need for colonic interposition.

Many medication pills can cause injury when they come in contact with esophageal mucus for prolonged periods. Patients who take medications in the supine position or who take pills without water are at higher risk of pill esophagitis. The pills most likely to adhere are doxycycline, tetracycline, potassium chloride, and aspirin. Although uncommon, potassium chloride is particularly dangerous and can cause esophageal perforation with devastating communication with the aorta, left atrium, and bronchial artery.[3]

Factors that influence the extent of injury from a caustic exposure include type of agent, concentration of solution, volume, viscosity, duration of contact, pH, and presence or absence of food in the stomach. The titratable acid/alkaline reserve of an alkali or acid correlates with the ability to produce tissue damage. Concentrated forms of acids and bases generate heat, resulting in superimposed thermal injury.

Acidic compounds desiccate epithelial cells and cause *coagulation necrosis*. An eschar is formed that limits further penetration. Because acids tend to have a strong odor and cause immediate pain on contact, the quantity ingested is usually limited. Because of resistance of squamous epithelium to coagulation necrosis, acids are thought to be less likely to cause esophageal and pharyngeal injury, although severe esophageal and laryngeal injury still occur particularly with intentional ingestions.[4] In many case series, acid ingestion results in equal esophageal and gastric mucosal injury.[4] Acids can also be absorbed systemically, causing metabolic acidosis as well as damage to the spleen, liver, biliary tract, pancreas, and kidneys from perforation and direct local contact.

Alkaline contact, in contrast to acids, causes *liquefaction necrosis,* fat saponification, and protein disruption, allowing further penetration of the alkaline substance into the tissue. The depth of the necrosis depends on the concentration of the agent. A concentration of 30% NaOH in contact with tissue for 1 second results in a full-thickness burn. Alkalis are colorless and odorless, and unlike acids, they do not cause immediate pain on contact. Alkaline ingestions typically involve the squamous epithelial cells of the oropharynx, hypopharynx, and esophagus. The narrow portions of the esophagus, where pooling of secretions can occur, are also commonly involved. Alkalis may also cause gastric necrosis (Figs. 148.1 and 148.2), intestinal necrosis, and perforation. The esophagus can also be injured (Fig. 148.3). Burns below the

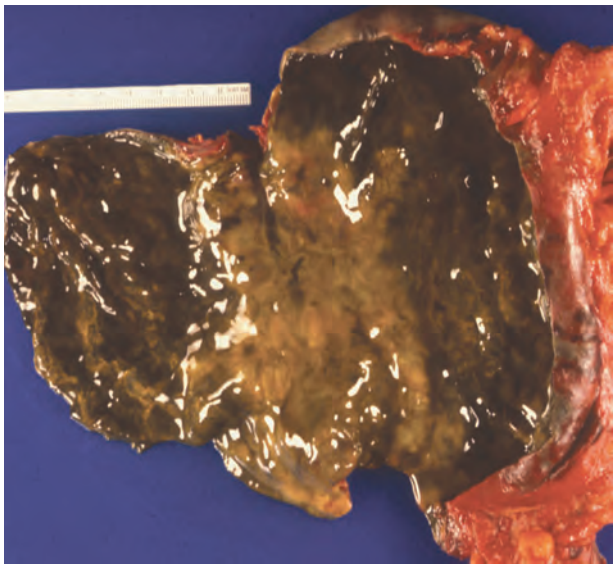

Fig. 148.1. Gastric mucosa after ingestion of 35% potassium hydroxide (KOH).

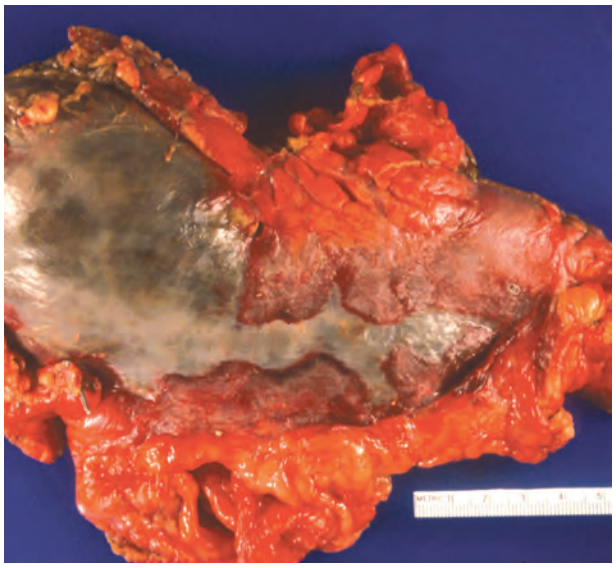

Fig. 148.2. Gastric serosa after ingestion of 35% potassium hydroxide (KOH).

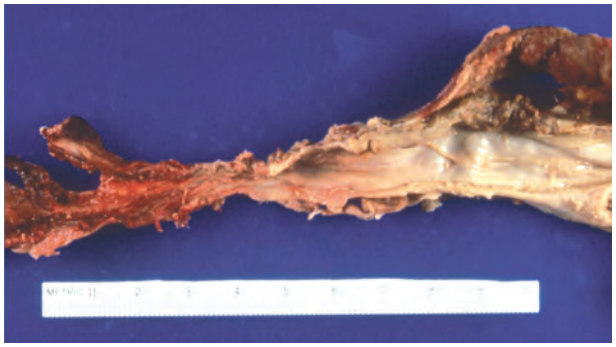

Fig. 148.3. Esophagus after ingestion of 35% potassium hydroxide (KOH).

TABLE 148.1

Household Cleaning Products That Contain Caustic Chemicals

APPLICATION	PRODUCT (MANUFACTURER), CHEMICAL
Drain cleaner, liquid	Heavy Duty Liquid Drain Opener (Share), H_2SO_4 93% Drain Out Extra (Iron Out), KOH 30% Liquid-Plumr (Clorox), NaOH 0.5% to 2%, NaOCl 5% to 10% Maximum Strength Drain Opener (Enforcer), KOH 1% to 10%, NaOCl <5% Drain Care Professional Strength Drain Opener, NaOH 5% to 15%
Drain cleaner, crystals	Heavy Duty Crystal Drain Opener (Roebic), NaOH 100% Crystal Drain Opener (Rohyme), NaOH 74% Crystal Drain Out (Iron Out), NaOH 30% to 60% Drano Pipe Cleaner (Johnson), NaOH 54%
Oven cleaner	Easy-Off Heavy Duty Oven Cleaner (Reckitt), NaOH 4% to 6%
Rust remover	Rust Remover/Carpet Care (Johnson Wax Professional), HCl 10% Rust Stain Remover (Whink), hydrofluoric acid 2.5% to 3% Rust Stripper (Certified), NaOH 50% to 75% Naval Jelly Rust Dissolver (Loctite), phosphoric acid 25% to 30%
Toilet bowl cleaner	Instant Power Toilet Bowl Cleaner (Scotch), HCl 26% Bowl and Porcelain Cleaner (Cleanline), HCl 0.10% Bowl/Tile/Porcelain Cleaner (Share), phosphoric acid 15% to 25% Husky 303 Toilet Bowl Cleaner, HCl 23% Misty Bolex Bowl Cleaner, HCl 26%
Swimming pool cleaner	Muriatic acid, Aqua Chem (Recreational Water), HCl 31%

H_2SO_4, Sulfuric acid; *HCl,* hydrochloric acid; *KOH,* potassium hydroxide; *NaOCl,* sodium hypochlorite; *NaOH,* sodium hydroxide.

pylorus carry a 50% mortality compared with 9% for burns above the pylorus.[5]

Caustic damage occurs in four phases. Initially, necrosis occurs, with invasion by bacteria and polymorphonuclear leukocytes. Vascular thrombosis follows, increasing the damage. During the next 2 to 5 days, superficial layers of injured tissue begin to slough. The tensile strength of the healing tissue may be low for up to 3 weeks after the caustic exposure, greatly increasing the chance of delayed perforation in some cases. Between 1 week and several months, granulation tissue forms, collagen is deposited, and reepithelialization occurs in the burn area. Esophageal stricture may form during a period of weeks to years from contraction of the scar.

Caustic injury is categorized as first, second, and third degree, similar to a thermal burn, by appearance on endoscopy. The initial depth of injury found on esophagoscopy correlates with the risk of stricture formation. Grade I injury consists of edema and hyperemia. Grade II injury can be further divided into grade IIa, which is non-circumferential, and grade IIb, which is nearly circumferential. Overall, grade II injuries are characterized by superficial ulcers, whitish membranes, exudates, friability, and hemorrhage. Grade III injury is associated with transmural involvement with deep injury, necrotic mucosa, or frank perforation of the stomach or esophagus. Although grade I injuries do not progress to stricture, 15% to 30% of all grade IIa injuries and up to 75% of circumferential grade IIb injuries of the esophagus develop strictures. With grade III injury, up to 90% result in

stricture. Recently, the formation of strictures is decreasing for both grade II and grade III injury, possibly because of the type and caustic intensity of the substance ingested.[4]

CLINICAL FEATURES

Airway edema and esophageal or gastric perforations are the most emergent issues. Laryngeal edema begins in minutes and occurs over several hours. Systemic toxicity, hypovolemic shock, and hemodynamic instability with hypotension, tachycardia, fever, and acidosis are ominous signs. Small ingestions of potent substances can be as serious as larger ingestions. More than 40% of patients reporting to have "only taken a lick or sip" have esophageal burns. Patients with acid or alkali ingestions present with similar initial constellation of signs and symptoms. Oral pain, abdominal pain, vomiting, and drooling are common. Patients can have wheezing and coughing, respiratory distress, hoarseness, odynophagia, dysphagia, stridor, and dysphonia. Chest pain is common. Visible burns to the face, lips, and oral cavity may be seen (Fig. 148.4), although these signs are not always clinically reliable.[5,6] Skin burns can occur from spillage or secondary contamination after vomiting. Peritoneal signs suggest hollow viscus perforation or contiguous extension of the burn injury to adjoining visceral areas. Tracheal necrosis is one of the most frequent causes of death after caustic ingestion.

Oropharyngeal burns alone are not predictive of more distal injury, but drooling, odynophagia dysphagia, vomiting, and stridor, especially in combination, are highly predictive of significant lesions.

Dysphagia usually subsides in 3 to 4 days. Patients with significant esophageal burns, particularly those that are circumferential, may develop esophageal stricture; 80% of strictures become apparent in 2 to 8 weeks. Symptoms include dysphagia and food impactions. Strictures that become symptomatic early are generally more severe. In one study of 86 adults admitted to the hospital after caustic ingestion, 18 had complications with strictures and six died.

Patients with significant esophageal injury have a thousandfold increase in esophageal carcinoma, which develops 40 to 50 years after the caustic ingestion. Long-term, 2% of patients who ingest caustics develop esophageal cancer and nearly 3% of esophageal cancer patients have a history of caustic ingestion.

Significant acid ingestions may be devastating and result in a higher mortality rate than alkali ingestions. The fulminant course of some acid ingestions may be due to systemic absorption of the acid, resulting in metabolic acidosis (which may also be the result of extensive tissue necrosis), hemolysis, and renal failure. Ingestion of glacial acetic acid (80% acetic acid) is common among certain ethnic populations as a suicidal gesture or accidental ingestion during food preparation, resulting in systemic complications, including renal and hepatic insufficiency, hemolysis, and disseminated intravascular coagulation. Ingestion of H_2SO_4 and HCl typically does not cause these systemic complications.

Fig. 148.4. Lip burn after exposure to 35% potassium hydroxide (KOH).

On clinical evaluation, the goal is to identify the extent and severity of the burn. In evaluation of a patient, the history should include the time, amount, type of product ingested, and presence of suicidal intent, if any. Patients who are suicidal may minimize their symptoms or understate the trauma. Physical examination addresses all of the above described features, so it focuses particularly on the oropharynx, supraglottic area, airway, and gastrointestinal (GI) tract.

DIFFERENTIAL DIAGNOSES

The ingestion of a caustic agent is usually clinically apparent upon presentation, most often by patient or family member report. When this is not known, the differential diagnosis is essentially that of abdominal discomfort, nausea, and vomiting, until typical mucosal injury becomes apparent. Mucosal injuries can be the result of various causes. The presence of early shock or altered mental status soon after ingestion of a caustic agent should prompt the search for other causes. Gastroenteritis from the ingestion of heavy metals (eg, iron, arsenic) and hydrocarbons can result in similar clinical effects as seen in caustic ingestions. Other GI conditions such as gastric perforation, esophageal rupture, esophagitis, and gastroesophageal reflux disease should be considered. Patients suffering from allergic reactions progressing to anaphylaxis can present with irritation and inflammation of the throat and larynx mimicking a caustic ingestion. Infectious sources such as aspiration pneumonitis, croup (laryngotracheobronchitis), and epiglottitis can present in a similar manner as well.

DIAGNOSTIC TESTING

Product labels are important in confirming the concentration of the chemical. If a sample is obtained, call the poison center for product information, look up the contents, or test the pH with litmus paper.

Evaluation of the severity of caustic ingestion and determination of the likelihood of deterioration or serious injury is based on examination of the upper airway, the esophagus, and the chest and abdomen. Examination of the oral pharynx is by direct visualization. Nasopharyngoscopy, after appropriate application of a vasoconstrictor (eg, Neo-Synephrine) and local anesthesia (eg, 4% lidocaine), determines the extent of injury and edema posterior to the tongue and in the supraglottic area and the glottis itself. Flexible endoscopy is used to evaluate the esophagus and stomach, after completion of the airway evaluation. Computed tomography (CT) scan is much more accurate than plain radiography for identification of perforation of the GI tract, and both chest and abdomen are scanned when there is concern for serious injury (see earlier criteria). CT of the chest and the abdomen are able to detect evidence of perforation, such as mediastinal and extraluminal air with high sensitivity.[7,8] Another benefit to CT is the ability to evaluate tissues unable to be directly visualized during endoscopy due to technical challenges or safety.[7,8] Although chest and abdominal radiography are often used in the early stages to determine whether perforation has occurred, they are insensitive and these tests are not indicated if CT scan is contemplated.

Patients with significant injury (such as grades IIb or III) may have perforations difficult to detect during endoscopic evaluation. Thus, delayed (approximately 24 hours post ingestion) esophagram with water soluble contrast medium may detect perforations by the presence of extravasation of contrast. If there is a high clinical suspicion, we recommend barium in the case of

a non-diagnostic water soluble contrast study that does not demonstrate leak because barium is more radiopaque. Esophageal dilation, widening of the pleuroesophageal line, and pleural reflection displacement all portend impending perforation.

Laboratory studies should evaluate for acidosis, coagulation profile, hemoglobin, and electrolyte derangement. Some ingested acids are absorbed from the gastric mucosa and subsequently hydrogen ion disassociation occurs. The accumulation of the anionic species in the vascular space contributes to an elevation in ion gap. Ingestion of acids such as HCl result in a non-anion gap metabolic acidosis because both the dissociated hydrogen and chloride ions contribute in the measurement of the anion gap. Typically, alkalis are not absorbed from the gastric mucosa into the vascular space. A lactic acidosis can result, however, due to esophageal or gastric injury and necrosis. Therefore, in the setting of significant acid or alkali ingestion, serum pH and chemistry for serum bicarbonate analysis are indicated to determine the degree of acidosis. In cases of intentional overdose, co-ingestants should be considered and measured diagnostically if levels are available and clinically indicated.

Hydrofluoric acid exposures, whether by inhalation, ingestion, or dermal contact (hand size or larger), are notorious for the effect of absorbed fluoride, resulting in hypocalcemia, and require immediate cardiac monitoring to assess for corrected QT (QTc) prolongation, torsades de pointes, or other ventricular dysrhythmias. Rapid cardiac deterioration can occur in these cases. Serum calcium, potassium, and magnesium levels should also be determined in these cases.[9]

The depth and extent of injury cannot be predicted based on signs and symptoms alone. Patients with signs and symptoms (vomiting, drooling, stridor, or dyspnea) of intentional ingestion should undergo endoscopy within 12 to 24 hours to define the extent of the disease.[10] Endoscopy is contraindicated, however, in patients with likely or known perforation. Endoscopy performed too early may miss the extent or depth of tissue injury. Wound softening in the subacute phase when the likelihood of perforation is greatest makes late endoscopy (after 24 hours) more hazardous. Wound strength is weakest between day 5 to day 14 and the time of greatest risk for perforation.[10] Early endoscopy has been studied and shown to be beneficial to patients. Early endoscopy and GI tract evaluation permits more rapid administration of nutritional support. However, the endoscopy should terminate at the level of the most proximal circumferential burn, particularly if the burn is severe, to avoid iatrogenic perforation. A soft feeding tube or silk string can be placed in the esophagus, when burns are present, for future dilation.

MANAGEMENT

Early and continuous hemodynamic monitoring is indicated. All contaminated clothing should be removed to prevent ongoing injury to the patient as well protection of healthcare care personnel. Appropriate personal protective equipment and hazardous waste disposal should be used.

After a caustic ingestion, little can be done to attenuate the severity of the tissue injury. Early endotracheal intubation or upper airway endoscopic examination is warranted when there are indications of upper airway injury on nasopharyngoscopy. If there are significant symptoms or signs, such as respiratory distress, stridor, or voice alteration (hoarseness, muffling), intubation is often necessary early in the course of evaluation, before edema and secretions both threaten the airway and make intubation difficult or impossible. For this reason, upper airway examination is often done with an intubating bronchoscope so that if significant injury and edema are identified, intubation can be accomplished during performance of the bronchoscopic examination. Blind nasotracheal intubation is contraindicated. When oral intubation is planned, a video laryngoscope should be used to provide optimal view with the least tissue trauma. If significant symptoms and signs are present, intubation can be anticipated to be difficult, and awake flexible endoscopy is the method of choice.

After the airway is secured, persistent hypoxia and an increasing arterial-alveolar gradient warrant early bronchoscopy. Patients should have intravenous fluid resuscitation (20 to 40 cc/kg 0.9 normal saline bolus). Oropharyngeal and GI injury secondary to caustic ingestion can result hypotension because of fluid shift from the intravascular to the interstitial space. Intravenous access should be established and a bolus of 20 mL/kg of isotonic crystalloid, usually normal saline, should be administered. Standard measures of resuscitative progress such as heart rate and urine output should be followed closely. In alert patients who are not vomiting and can tolerate liquids, small volumes (1 to 2 cups) of water or milk can be considered within the first 5 minutes after ingestion. Because injuries occur almost immediately, later dilution is not warranted. Forcing of fluids is never indicated. Attempts to neutralize the ingested corrosive with weak acids or alkalis can cause possible thermal reactions and worsen the injury.

GI decontamination after caustic ingestion is generally not indicated and can be hazardous. Inducing emesis is absolutely contraindicated given the risk of re-induction of the caustic agent into the esophagus, oropharynx, and airway. Activated charcoal is contraindicated as well, because it has little effect and will interfere with the endoscopist's view.

Careful nasogastric aspiration may decrease the amount of acid absorbed and may be useful in the setting of significant (massive) acid ingestions presenting 30 to 45 minutes after the event, given the ominous natural history of many of these cases and the lower risk of esophageal perforation compared with alkali ingestion.

Surgical consultation is indicated for free air, peritonitis, increasing and severe chest and abdominal pain, and hypotension.

Corticosteroid treatment does not significantly decrease stricture after grade IIa, IIb, or III esophageal burns, and it may increase risk for hemorrhage, infectious complications, severe esophagogastric necrosis, and prepyloric ulcer formation. Steroids can also mask early signs of inflammation and inhibit resistance to infection. Accordingly, they are not indicated to reduce the extent of esophageal injury. Controversy also surrounds the administration of steroids in patients with airway edema secondary to caustic ingestion. There are no controlled studies evaluating this practice, and the same downside risks exist as for steroid use for esophageal stricture. Airway edema can be fatal, however, and a single dose of a potent corticosteroid might mitigate some of the edema with minimal risk for the patient. We recommend 10 mg IV dexamethasone when there is indication of airway edema.

Prophylactic antibiotics are not indicated. Patients with proven perforation should have an emergent surgical consultation.

DISPOSITION

Asymptomatic patients can undergo endoscopy in the emergency department. Those patients with grades 0 or I injury may be discharged home with close follow-up monitoring with appropriate gastroenterology or otolaryngology consultants. They can have a liquid diet for 24 hours and then progress to soft food over the next 3 days and to full diet thereafter if all goes well.

Surgical intervention is required in cases of hollow viscus perforation; early exploration may also be warranted in cases of suggested full-thickness burns. Symptomatic patients, particularly those with potential for airway compromise, or high-grade esophageal or gastric injuries require admission to the intensive care unit. If endoscopy is unavailable, the patient should be

transferred to a facility where it can be performed. Psychiatric evaluation is indicated in patients with intentional ingestion.

SPECIAL CASES

Ocular alkali exposures are true ophthalmologic emergencies. Immediate irrigation with at least 2 L of normal saline per eye is indicated in almost all cases except frank perforation. Management is described in Chapter 61.

Dermal caustic exposures can also result in significant burn injuries (see Chapter 57). Clothing removal, copious irrigation, and local wound débridement are the most important initial treatment measures.

Povidone-Iodine

Povidone-iodine (Betadine) is used as a surgical scrub and is not a caustic agent, but ingestion of tincture of iodine can cause severe GI injury and is potentially life-threatening. Gastric irrigation with starch or milk in these cases may convert iodine to the much less toxic iodide. Either of these agents is most likely to be effective if administered within the first 30 to 45 minutes post ingestion. The goal is turning the gastric effluent dark blue or purple.

Phenol and Formaldehyde

Ingestion of phenol or formaldehyde can also cause severe caustic injury to the GI tract. Both phenol and formaldehyde are general protoplasmic poisons and can cause protein denaturation and coagulation necrosis. Systemic symptoms, including dysrhythmias, hypotension, seizures, and coma, may also result from phenol ingestion. Acidosis may be prominent after formaldehyde ingestion because of its metabolism to formic acid. Phenol is well absorbed through the skin, and dermal exposure may result in burns and systemic toxicity. Although dermal decontamination of phenol exposures with low–molecular-weight polyethylene glycol has been suggested, there is no evidence that it is superior to irrigation with water, which is more readily accessible.

Hydrogen Peroxide

Ingestion of concentrated (industrial strength) hydrogen peroxide (H_2O_2) may cause GI burn injury and the formation of gas emboli. Radiographic evaluation for the presence of gas in the chest or abdominal cavities, including the portal system, should be performed in symptomatic patients or those who ingest concentrated H_2O_2. Hyperbaric oxygen has been used successfully to treat gas emboli from H_2O_2 ingestion.

Button Batteries

Button (disk) batteries and conventional alkaline cylindrical batteries pose potential obstructive and chemical hazards if they are ingested. Ingestion of large 25-mm wafer-sized button batteries was a common problem in the past, but the smaller button batteries of today are less likely to cause esophageal obstruction. Button batteries are usually made of a metallic salt (lithium, mercury, nickel, zinc, cadmium, or silver) bathed in NaOH or KOH. Obstruction can cause pressure necrosis, caustic injury due to leakage of alkaline medium, or electrical injury. Caustic injury is much less common. Ulceration, perforation, and possible fistula formation occur but are uncommon. Heavy-metal toxicity in this setting has not been reported with newer disk batteries.

Evaluation of button battery ingestions includes radiography to assess the position of the foreign body. Batteries lodged in the airway or esophagus require expeditious removal. Gastric or intestinal batteries can be treated with watchful waiting. Checking the stool for passage of the batteries is recommended. Follow-up radiographs should be obtained in 1 week if the battery has not passed. If the patient becomes symptomatic with acute abdominal pain or exhibits GI bleeding, expedited reassessment is indicated.

KEY CONCEPTS

- Health care workers caring for patients with caustic exposures should adhere to universal precautions to prevent additional exposure.
- All symptomatic patients should undergo endoscopy and be considered for admission.
- Asymptomatic patients can undergo endoscopy in the emergency department or be discharged with close follow-up monitoring.
- Gastric emptying or GI decontamination is not indicated for the majority of caustic ingestions.
- Concentration and pH are the most important characteristics of a substance to predict esophageal and gastric injury.
- Button batteries lodged in the airway or esophagus require endoscopic retrieval.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 148: QUESTIONS & ANSWERS

148.1. A patient presents after the intentional ingestion of hydrochloric acid (HCl). He complains of mouth, throat, and chest pain, as well as painful swallowing and nausea. His vital signs are normal. Physical examination reveals oral burns without edema. The remainder of the examination is normal. You decide that in addition to psychiatric consultation, the patient should have upper endoscopy. What is the best time for the patient to have the endoscopy?

A. Immediately
B. In 2 to 4 hours
C. In 4 to 12 hours
D. In 12 to 24 hours
E. In 2 or 3 days

Answer: D. The ideal time for endoscopy is 12 to 24 hours. Endoscopy done too soon may miss the extent or depth of injury, whereas endoscopy after 24 hours is actually more likely to cause perforation because the wounds have softened. All patients with signs or symptoms of strong acid ingestion as well as patients with intentional ingestion should have endoscopy performed.

148.2. A patient presents immediately after the ingestion of bleach. The patient is awake and alert and complaining only of mouth pain. His vital signs and physical examination findings are normal. You consider having the patient drink fluids to dilute the bleach. Which of the following statements regarding this therapy is *true*?

A. Dilution is beneficial only if it is done very soon after ingestion.
B. In cases of alkali ingestions, dilution with a mild acid such as acetic acid is best.
C. Large volumes of fluid should be used.
D. Milk should always be used instead of water.
E. Patients should also be encouraged to eat solids.

Answer: A. Dilution, if it is done at all, should be done early because injuries from caustics occur almost immediately. Water and milk are equally beneficial and are the agents of choice. Weak acids or alkalis should never be used for dilution, because they can cause thermal reactions that worsen the injury. Small volumes up to approximately 500 mL should be used. Solids are not beneficial and can complicate the situation and increase the risk of aspiration.

148.3. A patient presents after an intentional caustic ingestion. She complains of hoarseness, with mouth, throat, and chest pain. Burns are present on her lips and oral mucosa and she is drooling. Her vital signs are normal, as is the remainder of her physical examination. Which of the following is the most appropriate treatment?

A. Administer 500 mL water orally
B. Administer intravenous Solu-Medrol
C. Endotracheal intubation
D. Obtain electrocardiogram
E. Upper endoscopy

Answer: C. Early intubation is indicated if there is any evidence of airway compromise, such as hoarseness, throat pain, drooling, or edema. Because edema and secretions can both increase rapidly and can make intubation difficult or even impossible, preparations should be made for a difficult airway. Fluids for oral dilution should not be given if the patient has difficulty swallowing. Corticosteroids have been studied to decrease the incidence of stricture formation, but evidence for their benefit is lacking and serious side effects can occur. With the exception of hydrofluoric acid, an electrocardiogram is not routinely needed for caustic ingestions, and endoscopy should be performed 12 to 24 hours after the ingestion and after the airway has been secured.

148.4. What empirical treatment is indicated to prevent systemic toxicity from hydrofluoric acid ingestions?

A. Calcium chloride
B. Magnesium chloride
C. Potassium chloride
D. Sodium bicarbonate
E. Sodium chloride

Answer: A. Calcium chloride is indicated in significant hydrofluoric acid exposures. Although hydrofluoric acid is a weak acid, the fluoride ion is extremely electronegative and will bind with multiple cations, specifically calcium and magnesium. Profound hypocalcemia is responsible for most deaths from hydrofluoric acid exposure and can occur before a serum calcium concentration can be measured.

148.5. A 3-year-old boy presents after swallowing a button battery. What is the most appropriate management?

A. Endoscopic removal
B. Inpatient observation
C. Radiograph to assess anatomic location
D. Surgical removal
E. Whole-bowel irrigation

Answer: C. Outpatient observation is warranted for button batteries that are located in the stomach or intestines, which can be assessed by plain radiographs. Batteries lodged in the esophagus require endoscopic removal. Examination of the stool for passage of the battery is recommended. If it is not passed in 1 week, repeated radiographs should be obtained. Inpatient observation is not needed as long as close follow-up can be ensured. Surgical removal and whole-bowel irrigation are not beneficial and are potentially deleterious.

CHAPTER 149

Cocaine and Other Sympathomimetics

Rama B. Rao | Robert S. Hoffman | Timothy B. Erickson

PRINCIPLES OF TOXICITY

Cocaine, amphetamines, and derivatives of amphetamines are called *sympathomimetics* (Box 149.1). These agents cause central nervous system (CNS) stimulation and a cascade of adrenergic physiologic effects. Cocaine is a naturally occurring plant-derived alkaloid that has been used for centuries as a medicinal product. In 1860, the pure alkaloid form was isolated and became a popular constituent of various beverages, pharmaceuticals, and therapeutic tonics, but it was banned from these products in the United States in 1914. As of 2012, there are roughly 17 million users worldwide.[1] Cocaine use in the United States peaked in the early 1990s at an estimated 5 million people with up to 1.6 million users of cocaine reported as of 2010.[2] Cocaine accounts for 40% of drug misuse related deaths and up to 40% of United States emergency department (ED) visits for illicit drug use.[3-5]

Amphetamines are stimulants originally designed for use as decongestants and dietary aids that became popular as recreational drugs in the mid-20th century. By modification of the amphetamine molecule, illicit "designer" amphetamines are inexpensively produced. The enhanced effects from these alterations add to the popularity of drugs, such as *N*-methyl-3,4-methylenedioxyamphetamine (MDMA) and methamphetamines. Estimates place the number of methamphetamine users in the United States at approximately 600,000.[2]

Cocaine Formulations

Unpurified cocaine paste is converted to more usable forms of cocaine. The crystallized freebase of the cocaine alkaloid is known as *crack cocaine.* It is inhaled with use of a special "crack pipe" designed to tolerate the high temperature required to volatilize pure cocaine. The high lipid solubility and rapid transport from the lungs into the brain contribute to crack's rapid onset of action (Table 149.1). The water-soluble salts of cocaine (cocaine hydrochloride and cocaine sulfate) are available as a white crystalline powder that is used intranasally or dissolved and injected intravenously. Oral administration is rare except for patients who are smuggling or concealing drugs.

Pathophysiology of Cocaine

Acute cocaine use causes release of dopamine, epinephrine, norepinephrine, and serotonin. These neurotransmitters act on different receptor subtypes to cause many effects, but the most important is adrenergic stimulation by norepinephrine and epinephrine (see Box 149.1). Norepinephrine causes vasoconstriction by stimulation of alpha-adrenergic receptors on vascular smooth muscle. Epinephrine increases myocardial contractility and heart rate through stimulation of $beta_1$-adrenergic receptors. In addition to catecholamine release, the reuptake of these stimulatory neurotransmitters from synaptic clefts is inhibited, altering the normal balance between excitatory and inhibitory tone in the CNS. Subsequent stimulation propagates peripheral catecholamine release (Fig. 149.1). Reuptake of serotonin is similarly inhibited and can cause serotonergic excess as well.

Cocaine also is a local anesthetic agent, slowing nerve impulses from neuronal pain fibers by blocking the inward movement of sodium across cell membranes (during phase 0 of the action potential). Sodium channel blockade across myocardial cells, similar to the class IA antidysrhythmics, is responsible for the occasional conduction abnormality that is noted in patients with acute cocaine toxicity.

Cocaine metabolism occurs in the liver and the plasma. In the liver, the drug is metabolized primarily to the active metabolite norcocaine, which potentiates the parent drug. In the plasma, cocaine is metabolized to ecgonine methyl ester through pseudocholinesterase (plasma cholinesterase). This difference may account for the differences in duration of action with different routes of administration. Ecgonine methyl ester may be protective because it is a vasodilator. Genetic differences in the phenotypic expression of plasma cholinesterases may account for individual differences in susceptibility to cocaine toxicity.

Benzoyl ecgonine, a metabolite found in the plasma, is produced primarily from nonenzymatic hydrolysis. It is the metabolite of cocaine identified by urine toxicology screens. Methylecgonidine and its metabolite ecgonidine are products of cocaine pyrolysis (crack). Although it is less commonly assayed, methylecgonidine also can be identified in the urine. The use of ethanol with cocaine forms cocaethylene, a metabolite that may potentiate the drug's stimulatory effects and lengthens the duration of effect.

CLINICAL FEATURES

The primary clinical effect of cocaine is the excitation of the sympathetic nervous system. Patients with moderate toxicity are alert and awake but may have diaphoresis, tachycardia, mydriasis, and hypertension without organ damage. A more severely toxic patient may be agitated, combative, and hyperthermic. End-organ damage is rare but may be manifested as an acute hypertensive emergency. Patients may present with focal acute pain syndromes, circulatory abnormalities, delirium, or seizures.

The clinical presentation depends on the dose, route of administration, and time to presentation after drug use. Additives, contaminants, or other drugs may alter the classic signs of acute cocaine toxicity. Patients who are "speed balling," using intravenous (IV) heroin and cocaine together, may be initially sedated, and administration of naloxone may precipitously reveal the underlying cocaine toxicity.

Death due to acute cocaine overdose is significantly higher on days with ambient temperatures higher than 88°F, possibly as a result of the individual's impaired ability to cool in warmer temperatures. The profound diaphoresis associated with cocaine may be absent or limited in cooler environments or if the patient is excessively salt and water depleted.

Initial assessment should focus on rapidly fatal complications, specifically hyperthermia, hypertensive emergencies, and cardiac dysrhythmias.

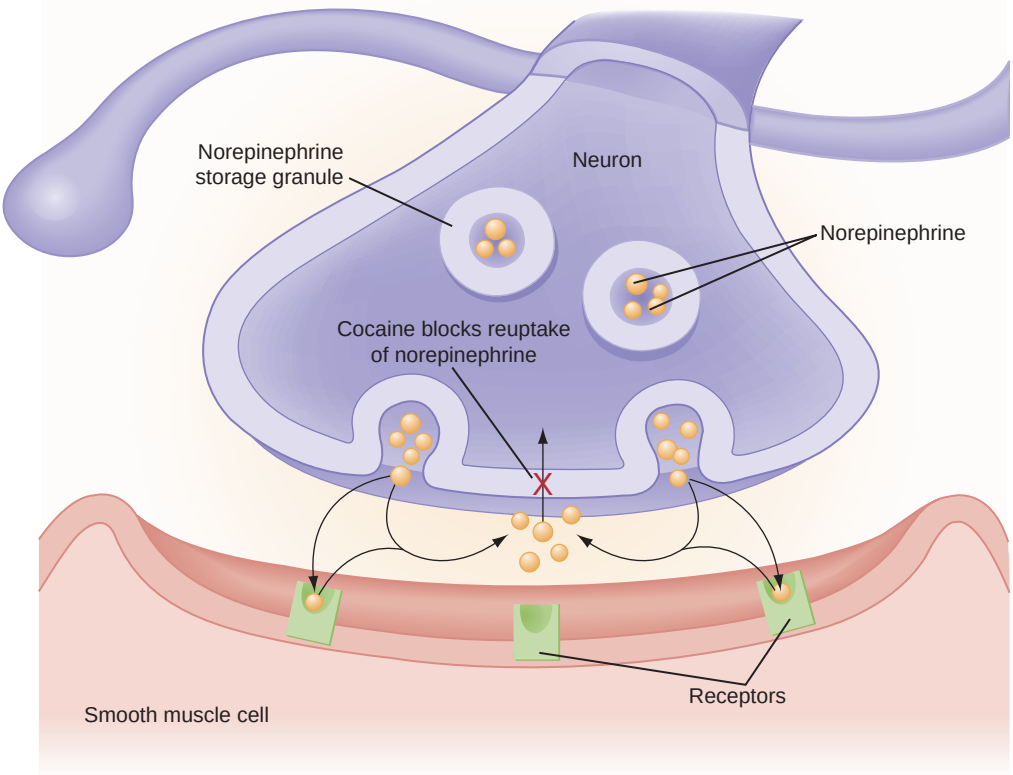

Fig. 149.1. How cocaine increases sympathetic tone by increasing neurotransmitters in the synapse.

TABLE 149.1

Cocaine Pharmacology by Route of Administration

ROUTE	FORMULA	ONSET OF ACTION	PEAK EFFECT	DURATION
Inhalation	"Crack"	8 s	2–5 min	10–20 min
Intranasal	Cocaine HCl	2–5 min	5–10 min	30 min
Intravenous	Cocaine HCl	Seconds	10–20 min	60–90 min
Oral	Cocaine HCl	30–60 min	60–90 min	Unknown
"Skin popping"	Cocaine HCl	Unknown	Unknown	Unknown

HCl, Hydrogen chloride.

BOX 149.1

Clinical Effects of Sympathomimetics

Central nervous system (CNS) excitation
Diaphoresis
Hypertension
Hyperthermia
Increased motor tone
Mydriasis
Tachycardia

Hyperthermia

Acute psychomotor agitation with delirium increases the risk of hyperthermia. Cocaine toxic patients have increased motor tone and generate excessive heat. Vasoconstriction and salt and water depletion can compromise cooling, resulting in life-threatening hyperthermia with core temperatures exceeding 106°F (41.1°C). Delay in recognition and management increases the likelihood of death. Even with a normal temperature, increased motor tone can release intramuscular (IM) creatine kinase (CK), with rhabdomyolysis and its attendant renal and electrolyte complications.

Hypertensive Emergencies

Acute cocaine-induced hypertension can cause serious injury to the cardiovascular and central nervous systems. Reported sequelae include aortic dissection, pulmonary edema, myocardial ischemia and infarction, intracranial hemorrhage, stroke, and infarction in the distribution of the anterior spinal artery. Vasospasm can also compromise perfusion to various organs. Intestinal infarctions and mesenteric ischemia can occur, particularly in body packers with large oral ingestions. Other local ischemic events include retinal vasospasm, renal infarctions, and placental insufficiency and infarction in the gravid uterus.

Cardiac Dysrhythmias

Although sinus tachycardia is the most common rhythm, atrial fibrillation and other supraventricular tachycardias can occur as a result of the surge in catecholamines. Life-threatening dysrhythmia may occur suddenly, heralded by abrupt diminution of cardiac output and loss of consciousness. Torsade de pointes from potassium channel blockade or wide-complex tachycardias from blockade of fast sodium channels on the myocardium may deteriorate into poorly perfusing or fatal ventricular rhythms. Transient conduction abnormalities consistent with a Brugada-type pattern are associated with cocaine. Hyperkalemia from rhabdomyolysis and myocardial ischemia can also cause dysrhythmias.

Other Complications

People who binge on repeated doses of cocaine for an extended time have a prolonged state of arousal, which causes catecholamine

depletion, salt and water depletion, and poor nutrition. After the acute effects of cocaine have subsided, these patients with "cocaine washout" are profoundly sleepy but arousable and oriented, with normal vital signs or a mild sinus bradycardia.

Patients are occasionally noted to be "crack dancing," which is defined as a transient choreoathetoid movement disorder probably related to abnormalities in dopaminergic tone.[6] Paranoia, either drug induced or from underlying psychiatric illness, may occur even after the acute effects of the drug subside. The neuropsychiatric effects of cocaine can alter behavior and judgment, increasing the risk of violent injuries.

Complications also arise from the route of administration of cocaine. Inhalation of crack cocaine may cause oropharyngeal burns from the high temperature required to volatilize the drug. Pneumothorax, pneumopericardium, and pneumomediastinum occur from inhalational barotrauma. Intranasal cocaine use is associated with sinusitis and nasopalatine necrosis or perforation. IV users have a high risk of infection with blood-borne viruses, local abscesses, and systemic bacterial infections, including botulism and endocarditis**.** Transdermal injection of cocaine, or "skin popping," has similar types of complications, especially skin abscesses. For chronic users, addiction or psychological dependence is mediated through specific dopaminergic neurotransmitter pathways. Although there are no well-defined syndromes constituting cocaine withdrawal, patients have strong cravings for the drug or a general feeling of dysphoria that is not physiologically life-threatening.

Over the last 10 years levamisole, a veterinary anthelminthic drug, has been increasingly used as an adulterant of cocaine. Levamisole was used historically to treat pediatric nephritic syndrome and rheumatoid arthritis before being withdrawn from the market due to its significant toxicity (ie, hematological complications and vasculopathy).[7] Agranulocytosis, vasculopathy with thrombosis, dermal ulcers, and purpura, often affecting the earlobes, occurred as a result of the unintentional exposure to levamisole.[8-10] The reason for this adulteration of cocaine with levamisole is still not clear but likely continues.

BOX 149.2

Differential Diagnosis of Agitated Delirium

- Endocrine disease
  - Thyrotoxicosis
- Heatstroke
- Infections
  - Bacterial or viral meningitis or encephalitis
- Psychiatric
  - Acute mania
  - Acute schizophrenia
- Metabolic causes
  - Electrolyte abnormalities
  - Hyperammonemia
  - Hypoglycemia
  - Hypoxia
  - Uremia
- Postictal state
- Structural lesions of the CNS
  - Hemorrhage
  - Mass
  - Stroke
  - Trauma
- Toxicologic causes
  - Amphetamines and derivatives
  - Anticholinergics
  - Caffeine
  - Cocaine
- Lithium
- Neuroleptic malignant syndrome (NMS)
  - PCP, ketamine
  - Sedative-hypnotic withdrawal
  - Serotonin toxicity
  - Sympathomimetics, stimulants
  - Synthetic cannabinoid receptor agonists

CNS, Central nervous system; *PCP,* phencyclidine.

DIFFERENTIAL DIAGNOSES

A thorough assessment of mental status, vital signs, and physical examination can help direct and narrow the differential diagnosis of cocaine toxicity. History may be particularly helpful in differentiating acute cocaine toxicity from the many causes of agitated delirium, including thyrotoxicosis, lithium toxicity, other toxins, and CNS infection. Thought disorders and auditory hallucinosis generally are not present, in distinction to acute psychosis from paranoid schizophrenia, or an acute manic episode in a patient with bipolar affective disorder (Box 149.2). Conditions that may be difficult to distinguish from cocaine toxicity include withdrawal from benzodiazepines, ethanol, and other sedative-hypnotics. A history of recent abstinence from these agents should be elicited.

Toxicity from other sympathomimetic agents such as amphetamines, amphetamine derivatives, and phencyclidine (PCP) can present in a fashion very similar to cocaine poisoning. Cocaine toxicity generally causes more frequent cardiotoxic effects (eg, acute myocardial infarction, cardiac dysrhythmia, aortic dissection) than amphetamines or PCP.[11] Important considerations in the differential diagnosis of a cocaine-induced wide-complex tachycardia include hyperkalemia, direct sodium channel blockade (eg, cyclic antidepressant toxicity), and myocardial ischemia. Designer amphetamines such as ecstasy are more likely than cocaine to cause hyponatremia, either from the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or excessive intake of free water. Patients abusing methamphetamine also tend to have more muscle wasting, malnutrition, and poor dental hygiene than chronic cocaine users. PCP toxicity may be distinguished by the presence of multidirectional nystagmus and highly combative behavior.

Like cocaine, patients with antimuscarinic poisoning (eg, diphenhydramine, atropine, and jimsonweed; see Chapter 145) often present with agitation, tachycardia, hypertension, and mydriasis, but unlike sympathomimetic agents, typically have acute urinary retention and dry skin.

The hyperthermic state induced by cocaine toxicity should be further differentiated from classic and exertional heat stroke. Heat stroke tends to have more ambient environmental factors, dehydration, and more profound changes in mental status than cocaine toxicity. Serotonin syndrome (SS) is often precipitated by the addition of a new serotonergic agent or a substance that interferes with the metabolism of a previously tolerated agent. Although by far most common with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), serotonin syndrome also has been reported with cyclic antidepressants and atypical antipsychotics. The manifestations of serotonin syndrome include altered mental status, hyperthermia, and agitation; as well as hyperreflexia, clonus, and diaphoresis. In addition, the agitation described with serotonin syndrome is less organized and the patient is unlikely to be ambulatory or severely combative. The onset is typically abrupt in the setting of serotonergic drug interactions or overdose. The finding of clonus is an important differentiating feature, because this is present in serotonin syndrome but absent in cocaine toxicity. Similar to serotonin syndrome, neuroleptic malignant syndrome (NMS) also presents with altered mental status, hyperthermia, and agitation; however,

unlike serotonin syndrome, peripheral muscular effects tend toward rigidity and decreased reflexes rather than clonus and hyperreflexia. This is due to dopaminergic depletion from the use of dopamine antagonists, such as the older or classic antipsychotic agents. Patients presenting with NMS generally have a gradual course of hypokinesis and increasing resting muscle tone in the setting of escalating antipsychotic use. The alteration in mental status is more commonly a catatonic state.

DIAGNOSTIC TESTING

Urine drug screening for cocaine is unlikely to change treatment, because it measures a cocaine metabolite (benzoyl ecgonine) that persists for at least 3 days after last use. In a few circumstances, however, urine drug screening may be beneficial to document possible abuse or neglect in a child with suggested exposure, to confirm cocaine as the unknown substance in body packers, and to differentiate paranoia from drug-induced or psychiatric causes. Urine drug screening may be informative in the evaluation of younger patients with chest pain syndromes. Although sensitivities for amphetamines may vary, therapeutic agents may be detected and confound interpretation. Other potent adrenergic synthetic stimulants may be undetectable on urine drug screening.

An electrocardiogram (ECG) screens for dysrhythmias and conduction abnormalities from ischemia, hyperkalemia, or, more precipitously, QRS prolongation from sodium channel blockade. This blockade slows myocardial depolarization and results in a wide-complex tachycardia. The axis may be indeterminate or have a terminal rightward axis deviation similar to cyclic antidepressant toxicity. Cyclic antidepressants and cocaine share class IA antidysrhythmic effects with QRS widening and resultant QT prolongation. Evaluation of chest pain is challenging, because ST segment elevation is confounded by the presence of early repolarization. Serial ECGs may be helpful and obtained with any change in status or every 6 hours during care. A chest radiograph may identify aspirated foreign bodies, pneumothorax, or pneumomediastinum from inhalational barotrauma, when these are suspected, but is not required in most cases.

CK, a nonspecific marker for muscle injury, is often elevated with cocaine use. The original data on cocaine related coronary syndromes used CK-MB as a cardiac marker; however, this is now supplanted by troponin I or troponin T levels, as for all patients evaluated for possible ischemic chest pain.

Most patients presenting with troponin elevation and chest pain after cocaine use had angiographically proven obstructive coronary disease, often of a single vessel, but almost 20% have normal angiography.[12]

Although the sensitivity and specificity of troponin cardiac markers are still being investigated for cocaine-related chest pain, we recommend that patients with cocaine use be evaluated for chest pain in a similar fashion to that for patients without cocaine use. Decisions regarding further investigation are based on the characteristics and course of the chest pain and results of serial troponin measurements and ECGs. Data regarding the role of coronary computed tomography angiography (CTA) to identify patients with cocaine-related coronary disease are evolving.[13] We do not recommend routine use of CTA in the evaluation of patients with chest pain in the context of acute cocaine use.

Severe, persistent headache despite normalization of blood pressure may be caused by a subarachnoid hemorrhage (SAH) and warrants evaluation as for any other patient suspected of acute SAH (see Chapters 91 and 93). A serum CK and urine for myoglobin should be checked to screen for rhabdomyolysis.

In the rare event that a patient presents with agranulocytosis or vasculopathy suggestive of the cocaine adulterant levamisole, a special laboratory evaluation for urine levamisole by gas chromatography–mass spectrometry may be requested.[7] The sample is ideally obtained within 48 hours after last use.[10]

BOX 149.3

Initial Evaluation of Patients With Sympathetic Stimulation

Rapid assessment of vital signs, especially core temperature
Exclude hypoxia, hypoglycemia, and hyponatremia
Pharmacologic sedation with benzodiazepines
Electrocardiogram (ECG)
Urinalysis
Serum creatine kinase (CK)

MANAGEMENT

A severely poisoned patient may be combative and unable to cooperate in assessment of vital signs. Actions taken during these first stages of the encounter are crucial (Box 149.3). Because the etiology of the patient's condition is often unclear, the initial priority is to recognize and treat the life-threatening agitated delirium.

Patients may transiently require physical restraints for complete vital signs to be obtained and IV access to be secured. If a chest restraint is used, a mesh vest is preferred to a jacket to help limit hyperthermia. The patient should have assessment with a bedside blood glucose monitor. Immediate pharmacologic sedation with IM or IV administration of benzodiazepines may be necessary (see next section), which, in adequate doses, restores inhibitory tone to the CNS and decreases excessive sympathetic outflow to peripheral tissues. Sedation also facilitates measurement of vital signs (particularly core temperature), continuous electrocardiographic monitoring, and completion of the physical examination.

Pharmacologic Sedation for Agitation

Benzodiazepines are the mainstay of treatment of cocaine-induced agitation. Diazepam, lorazepam, and midazolam have all been successfully used in this setting. Diazepam can be administered intravenously in increments of 5 to 10 mg every 5 minutes in adults until sedation is achieved.[11,14] Diazepam has a rapid onset of action, is easily titratable, and has active metabolites for a sustained effect. Lorazepam, 1 to 2 mg intravenously every 5 minutes is also an acceptable option. Persistently increased motor tone reflects an inadequate benzodiazepine dose, even if the patient appears sleepy. Additional doses of lorazepam or diazepam can be given, with close monitoring of the patient's respiratory status. For an adult patient in whom IV access is not possible because of agitation, IM midazolam 10 mg can be administered to facilitate subsequent interventions. Although lorazepam also can be given intramuscularly, it may take 15 minutes to reach peak sedation; and repeated doses given at more frequent intervals may accumulate, causing oversedation and respiratory depression. Because cocaine agitation can be indistinguishable or coexist with alcohol intoxication, the presence of alcohol can have synergistic depressant effects on the respiratory centers. In all patients, titration of the benzodiazepine is important, allowing the clinician to observe the effects of one dose (usually 5 minutes) before an additional dose is given. After sedation is achieved, the patient is closely observed to ensure that the patient's respiratory status is stable when peak sedation effect is reached.

Benzodiazepines also treat the choreoathetoid movements of crack dancing. Most cocaine toxic patients have salt and water depletion and require vigorous IV crystalloid replacement. If the

cause of delirium is unclear, careful attention to the patient's respiratory status avoids the respiratory depression caused by excessive benzodiazepine administration in the presence of other sedative-hypnotic agents, such as ethanol.

The vast majority of patients with cocaine-induced agitation respond clinically to adequate doses of benzodiazepines. Butyrophenone antipsychotic agents (such as, haloperidol and droperidol) are rapidly effective and generally safe for drug-induced psychosis or agitation states from sympathomimetic agents, including cocaine, amphetamines, and PCP when used in patients with normal vital signs (also discussed in Chapters 140 and 150). Haloperidol, 2 to 5 mg IM, may be repeated every 20 to 30 minutes with consideration of other agents after a total of 10 mg. Although not approved for IV use, this route is widely used and should only be considered in the psychotic patient with normal vital signs with close cardiac monitoring in 5-mg doses with a maximum dose of 15 mg. The sedative dose for droperidol is 2.5 to 5 mg IM. Droperidol has a box warning from the U.S. Food and Drug Administration (FDA) for QT prolongation and potentially torsade de pointes. However, most reported cases of butyrophenone-induced dysrhythmias have been in individuals receiving large doses for prolonged periods, such as hours to days, or in elderly populations (older than 60 years). These medications lack the respiratory depression potentially caused by other agents and may be beneficial in some cases when sedation is required. For these reasons, the butyrophenones remain effective agents for treatment of drug-induced agitation in carefully selected patients.

Hyperthermia

Cocaine-induced hyperthermia must be treated with rapid cooling (Box 149.4). Patients who sustain elevated core temperatures above 106°F (41°C) for more than 20 minutes are likely to subsequently have fatal multisystem organ failure, which is often heralded by disseminated intravascular coagulation. Patients should have continuous monitoring of core temperature with a rectal probe. Heat generated by agitation and increased muscle tone can be terminated by adequate use of benzodiazepines, as described earlier, with neuromuscular paralysis and intubation as required. Although cocaine use or intoxication, per se, is not a contraindication to use of succinylcholine for intubation, we recommend use of rocuronium, 1 mg/kg, when possible. Succinylcholine shares metabolism through plasma cholinesterase with cocaine, which may nominally prolong the effects of both drugs, succinylcholine also may precipitate hyperkalemia if rhabdomyolysis, which often occurs with cocaine use, is present. It is crucial to reduce core temperature to 102°F (38.8°C) as soon as clinically possible, ideally within 20 minutes or less. Cooling blankets are insufficient. Ice water submersion in a portable tub is preferred when available; although some favor wet sheets with large fans.[15] These patients require continuous temperature monitoring and fluid resuscitation as judged by standard measures. Invasive cooling techniques are often too delayed and inadequate against the vasoconstrictive effects of cocaine and other adrenergic agents.

BOX 149.4

Management of Stimulant-Induced Hyperthermia

COOLING

Early identification of elevated core temperature
Large-bore IV access with rapid infusion of crystalloid
Sedation and muscle relaxation with benzodiazepines
Rapid cooling within 20 minutes*
Paralysis and intubation if necessary

MONITORING AND DIAGNOSTICS

Urine output via Foley catheterization
Laboratory analysis for organ function
- Serum chemistries, creatinine, CK
- Liver function
- PT, PTT, fibrin split products
- Bacterial cultures†
- Urinalysis for myoglobinuria

Neuroimaging if etiology unclear

*Ideally with ice water immersion.
†Consider lumbar puncture or antibiotic therapy, especially in injection drug users.
CK, Creatine kinase; *IV,* intravenous; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

Acute Hypertensive Emergencies

The goal in acute hypertensive emergencies is to promptly reverse the vasoconstriction of norepinephrine at peripheral alpha-adrenergic receptors. Benzodiazepines restore the CNS inhibitory tone on the peripheral nervous system and are first line treatment, as outlined earlier for agitation. When ECG evidence of myocardial ischemia is present, IV nitroglycerin can be used, but control of the blood pressure by phentolamine, which we consider the drug of choice, usually will resolve the issue. Phentolamine, a direct alpha-adrenergic antagonist, can be titrated slowly by repeated IV doses of 1 mg every 3 minutes with blood pressure monitoring.[11] If adequate reduction in therapy by at least two-thirds of mean arterial pressure is not achieved after two doses, phentolamine dose can be escalated by 1 mg every 3 minutes up to 5 mg/dose until adequate vasomotor control is achieved. Phentolamine effect will last roughly 45 minutes. Supplies of phentolamine in the United States have been subject to shortage. If phentolamine is not available, other antihypertensives that can be used include hydralazine, nitroglycerin, and short-acting IV calcium channel antagonists like nicardipine or clevidipine (see Chapter 74). In contrast to chronic hypertension, individuals with acute cocaine hypertension often have a normal blood pressure in the absence of the drug, and unless the patient's history suggests otherwise, a normal systolic and diastolic blood pressure should be the endpoint of therapy. Shorter acting antihypertensive infusions offer an advantage in that they can be readily discontinued as the cocaine is metabolized and the vasomotor effect subsides.

Historically, it has been theorized that beta-adrenergic antagonists (beta blockers [BB]) may cause paradoxical hypertension with acute cocaine toxicity and should be avoided due to concerns of unopposed α-receptor activity, resulting in coronary artery spasm and hypertension.[16] Furthermore, patients undergoing cardiac catheterization show decreased coronary artery diameter in the presence of cocaine and beta-adrenergic antagonists.

In two retrospective studies, beta-blocker use was not associated with clinically significant hypertension, troponin elevation, or adverse events.[17,18] Despite this, we do not feel that their use provides a clinical benefit in this setting and do not recommend the routine use of beta-blocker therapy in patients presenting with cocaine-induced hypertension and chest pain.

The treatment of cocaine-induced SAH or aortic dissection differs from treatment of other causes of the same conditions. The combined use of phentolamine and beta-adrenergic antagonists may result in profound hypotension, and we therefore recommend initial administration of phentolamine only, in the manner described earlier, with close monitoring for sudden alterations in blood pressure. If phentolamine is unavailable, a short acting antihypertensive infusion can be used (eg, nitroglycerin, nicardipine, or clevidipine) combined with pain control and benzodiazepines to diminish adrenergic output.

Dysrhythmias

Dysrhythmias from cocaine may be atrial or ventricular. Atrial fibrillation and supraventricular tachycardias are likely to be due to sympathetic stimulation and often respond to benzodiazepines. Calcium channel blockers (eg, diltiazem) can be used if rapid atrial rhythms fail to respond to sedation, cooling, and volume resuscitation.

Important considerations in the differential diagnosis of a wide-complex tachycardia include hyperkalemia, direct sodium channel blockade (cyclic antidepressants and cocaine), and ventricular ischemia. In cocaine body packers or patients presenting with cocaine-induced adrenergic toxidrome, abrupt development of a wide-complex tachycardia with a pulse should be treated with empirical sodium bicarbonate, 1 to 2 mEq/kg IV bolus, with closely recorded cardiac monitoring to observe for QRS narrowing.[19,20] If the patient does not respond with both QRS narrowing and hemodynamic stabilization, lipid emulsion therapy may be attempted in consultation with a medical toxicologist, but there is no evidence to support its use.[21]

As with any dysrhythmia, fluid and electrolytes should be assessed and corrected as indicated. Close monitoring is required for patients with a Brugada-type conduction pattern. Data regarding the ideal antidysrhythmic agent in this setting are limited.

Cocaine-Related Chest Pain

The causes of cocaine-related chest pain are diverse (Box 149.5), including aspirated foreign bodies or pneumothorax or pneumomediastinum from inhalational barotrauma. Fever and shortness of breath should prompt consideration of pneumonia, pulmonary infarction, or endocarditis with septic pulmonary emboli in IV drug abuse.

Cocaine acutely induces coronary vasoconstriction while increasing myocardial oxygen demand. Platelet aggregation is enhanced through thrombogenic and antifibrinolytic pathways. These cumulative effects can result in coronary insufficiency. Cigarette smoking acutely exacerbates these conditions. Chronic cocaine use may accelerate atherogenesis and induce left ventricular hypertrophy. All of these factors contribute to myocardial ischemia or infarction. Of nonfatal myocardial infarctions in patients aged 18 to 45 years, 25% are attributed to cocaine, even after adjustment of other known cardiac risk factors.

BOX 149.5

Causes of Stimulant-Induced Chest Pain

CARDIAC CHEST PAIN

Coronary stent thrombosis
Endocarditis
Ischemia, infarction
- During acute intoxication
- After acute intoxication

Left ventricular apical ballooning
Pericarditis

NONCARDIAC

Aortic dissection
Foreign body aspiration
Infection
Pneumomediastinum
Pneumopericardium
Pneumothorax
Pulmonary infarction
Intestinal ischemia or infarct

Identification of a patient with a cocaine-related coronary syndrome is difficult. Patients may present hours to days after use, possibly because of vasoactive metabolites. The patient may deny drug use and have atypical chest pain. Almost one-third of cocaine-using patients with elevated serum enzymes have pleuritic chest pain. There are no clear predictors for patients at risk because the patient's age, route of drug use, time to presentation, and preexisting risk factors for coronary artery disease are inadequate to identify patients sustaining myocardial infarction. In the setting of cocaine-related chest pain, risk stratification by thrombolysis in myocardial infarction (TIMI) score may not adequately identify patients at risk for 30-day adverse outcomes. However, in one study, cocaine history alone in low-risk, asymptomatic patients assessed by coronary CTA is generally not associated with increased risk of coronary artery disease. Patients with positive serum enzymes for myocardial infarction often have significant angiographic stenosis. Of patients without positive serum markers, 18% still have significant disease by angiography. Other predictors of significant disease in this group included elevated cholesterol concentration and prior diagnosis of coronary disease or myocardial infarction. Patients with previous coronary stent placement are at a high risk of thrombosis with cocaine use.

As for most complications of cocaine use, benzodiazepines decrease myocardial oxygen demand by limiting peripheral stimulation and should be given early to patients presenting with cocaine-induced chest pain, especially when signs of adrenergic excess are present. Aspirin and nitrates should be administered as for any case of suspected ischemic chest pain. In patients meeting electrocardiographic criteria for myocardial infarction with persistent chest pain and hypertension and a clear history of acute cocaine intoxication, coronary vasodilation with IV phentolamine (1 mg) can be given slowly during 3 minutes if available. This dose can be repeated, if needed, as long as the patient's blood pressure remains stable. Morphine sulfate can be used to treat pain. Patients with persistent chest pain and ST segments strongly suggestive of myocardial infarction can be considered for percutaneous intervention or thrombolytic therapy, assuming there are no contraindications, such as uncontrolled severe hypertension.[11]

In contrast to non–cocaine-induced myocardial ischemia or infarction, beta-adrenergic antagonists, including labetalol, are generally not recommended during acute cocaine toxicity because coronary vasoconstriction may worsen.

In patients with cocaine-related coronary syndromes who are not acutely toxic, alpha-adrenergic vasoactive metabolites may be responsible. Outcomes of uncomplicated chest pain due to cocaine are very good. Current guidelines for care of the patient with an acute coronary syndrome that is unrelated to cocaine do not recommend immediate administration of beta-adrenergic antagonists, but rather within the first 24 hours.[22] As such patients with known or suspected cocaine-related myocardial infarction with or with ST segment elevation, there is little role for beta-adrenergic antagonists in the ED, and we do not recommend their routine use.[16,22] Such patients warrant a further evaluations of coexisting atherosclerotic heart disease and clinical reevaluation prior to consideration of this therapy. Administration of beta-adrenergic antagonists on discharge is controversial, especially if cocaine use is likely to continue, and we advise against this practice.[23]

Heparin can be given, but fibrinolytic therapy is not well studied. Some mechanisms of cocaine-induced myocardial infarction would be expected to respond to fibrinolytic agents. Patients failing to respond to treatment with nitrates and phentolamine who have known coronary artery disease or a previous ECG confirming new ST segment elevations are candidates for cardiac catheterization or fibrinolysis if necessary. The same contraindications apply as for non–cocaine-induced myocardial infarction. Nuclear imaging studies also may provide more diagnostic

information, but their use is best considered in consultation with cardiology. Patients presenting with chest pain after cocaine use and an ECG with definitive or new ST elevations should have prompt evaluation by a cardiologist for potential intervention when such services are available.

Antiplatelet and glycoprotein IIb/IIIa inhibitors and calcium channel antagonists seem to be of benefit to some patients with myocardial infarction or ischemia of atherosclerotic origin. Theoretically, these agents may counter some of the platelet aggregation enhanced by cocaine, but data investigating their use are lacking.

Patients with cocaine-related chest pain without other risk factors who have normal ECGs and cardiac enzymes are at low risk for myocardial infarction. The role of provocative testing in these patients is not well established.

In summary, cocaine-induced coronary ischemia is managed with benzodiazepines, nitrates and vasodilators, preferably phentolamine. As with non-cocaine using patients presenting with acute ischemic chest pain, we recommend use of aspirin, heparin, antiplatelet agents, and calcium channel blockers in conjunction with interventional therapy as indicated.[11]

Interventions to cease cocaine use are warranted. For patients with documented coronary artery disease, cessation of cocaine use is imperative. Cocaine users presenting with chest pain who subsequently continue cocaine use after ED discharge were more likely to have recurrent ED visits than were those who stopped subsequent use.

Cocaine Body Packers

Before crossing international borders, "body packers" ingest cocaine that has been wrapped tightly into condoms or other latex products and sometimes coated in wax. Each packet can contain approximately 10 g of cocaine, and packers may swallow as many as 150 packets. On arrival at the patient's destination, a cathartic is often taken to stimulate gastrointestinal passage of the contraband for subsequent delivery and distribution. Body packers are likely to know the exact number of packets they ingested but may be reluctant to share that information.

A body packer may present without symptoms to the ED. The patient should be placed immediately on continuous cardiac monitoring, with large-bore IV access. Diagnosis is made by history. An abdominal radiograph may confirm foreign bodies but cannot be used to count packets, because plain radiographs have limited sensitivity in detecting an isolated or small number of packets. When uncertainty persists, a CT scan or contrast study is warranted.[24]

Body packing also is used to transport heroin and other illicit substance. Although heroin body packing rarely requires surgical intervention, an asymptomatic patient may refuse to identify the packet's contents. A urine toxicology screen may be useful because small quantities of drug may be ingested in swallowing of the contraband. Rupture of a single cocaine packet can result in death, because each packet contains almost 10 times the lethal dose. Accordingly, cocaine body packers with retained packets should be admitted to a monitored setting with a plan to facilitated removal of the packets by whole bowel irrigation. Surgery should be consulted, and the operating room should be prepared in advance in the event that the patient develops acute toxicity. We recommend emergency surgical removal of all packets for patients with mechanical bowel obstruction or a leaking packet with symptoms suggesting a leaking packet.[24,25] Because of the large quantity of pure drug in one packet, patients with a ruptured or leaking packets are likely to die without prompt intervention. When evidence of cocaine toxicity is manifested, rapid surgical intervention may be the only way to save these patients. Benzodiazepines, neuromuscular blockade, or sodium bicarbonate administration (for wide-complex tachycardia) may be required preoperatively as described earlier for treatment of acute cocaine toxicity.

Because leaking of pure cocaine from packets is potentially lethal, we recommend whole-bowel irrigation with polyethylene glycol solution to facilitate gastrointestinal passage of the packets and preoperatively cleanse the bowel in the event of emergent surgery is required. Subsequent CT scans or contrast studies may be required to evaluate for remaining packets.[24] However, these radiographic studies may fail to detect isolated packets that contain potentially fatal quantities of cocaine. Patients stating that they swallowed a larger number of packets than are passed or who refuse to reveal the number ingested should have continued bowel irrigation, observation, and repeated studies. Endoscopic retrieval is generally discouraged because of concern for packet rupture during the procedure, but it has been done on occasion.[25]

All packets passed in the stool, through endoscopic procedures, or in the operating room should be counted carefully and promptly given to law enforcement officials. When law enforcement is not yet involved, hospital legal counsel or risk management and the hospital ethics committee may be helpful in determining the disposition of the packets and ultimately of the patient when he or she is medically cleared.

Body Stuffers

A "body stuffer" is an individual who attempts to conceal evidence of cocaine possession by internally concealing the drug while being pursued by law enforcement officials. This can be most commonly through ingestions, but it may also involve vaginal or anal concealment. These are usually unplanned events with generally small quantities of drug that were initially intended for personal use. The drugs are often swallowed in poorly sealed vials or glassine packets that may not be evident on radiographs. In general, patients ingest nonlethal doses and are asymptomatic. For cooperative, asymptomatic oral body stuffers, the role of gastric decontamination is not well studied. In this setting, if presenting soon after ingestion, we recommend administration of oral activated charcoal to adsorb any potential leaking cocaine from the packets in the GI tract. Monitoring, as described earlier with body packers, should be performed if the quantity ingested is of concern or if signs of toxicity develop. Due to lower doses and less potential lethality, the vast majority of body stuffers will not require whole bowel irrigation therapy as do body packers. Body stuffers rarely have fatal events, and these patients usually have symptoms in the first 8 hours. Asymptomatic patients who are unwilling to disclose events or cooperate with care should have monitoring in the ED regardless of status of police custody. However, if the patent is not under arrest, they are free to decline therapy and leave the ED against medical advice if they can demonstrate clear understanding of the risks, including sudden death, of leaving with retained packets. Although the ideal period of observation is uncertain, 8 to 12 hours is reasonable with admission if the patient develops signs or symptoms of toxicity. Patients with suspected vaginal or anal concealment who are asymptomatic and without signs of toxicity who refuse a physical examination should be assessed for capacity and observed in the ED as outlined earlier. Any judicial warrants for an invasive examination against patient's will should carefully involve risk management and hospital legal counsel, because these are forensic requests and not medically emergent in the asymptomatic patient.

Levamisole-Related Complications

Patients with agranulocytosis, vasculopathy, or other dermatologic manifestations require supportive care, evaluation for other potential causes, and abstinence from further levamisole exposure.[7,9] Reporting to the local department of health or poison control center can help track these cases.

BOX 149.6

Admission Criteria for Cocaine-Related Chest Pain

Cardiogenic shock
CHF
Dysrhythmias or conduction abnormalities
Electrocardiographic changes
Elevated myocardial enzymes
Multiple risk factors for CAD
Persistent chest pain, dyspnea or abnormal vital signs
Preexisting CAD or stent placement
Requiring vasodilating pharmacotherapy
Persistent symptoms

CAD, Coronary artery disease; *CHF,* congestive heart failure.

DISPOSITION

Acutely toxic patients who need only observation or who respond quickly to sedation and do not have complications can be discharged after the acute toxicity resolves. These patients may be extremely lethargic from catecholamine depletion, and it is best to discharge them with a responsible adult. Patients may be open to drug counseling and referral while in the ED.

Patients with chest pain (Box 149.6) who are acutely toxic and who show dynamic changes on the ECG, dysrhythmias, or congestive heart failure and patients requiring vasodilators or reperfusion should be admitted to a monitored setting or coronary care unit. These patients require further evaluation of the extent of preexisting reversible ischemia and intervention to encourage cessation of drug use.

The disposition of patients with chest pain who are not acutely toxic is less clear. Admission is warranted for patients with complications or electrocardiographic changes and patients requiring pharmacologic intervention with vasodilators. Other patients may be placed in an ED observation unit or discharged, depending on the level of concern about underlying coronary artery disease using standard screening for risk factors as with non-cocaine chest pain (see Chapters 23 and 68).

In symptomatic ED patients at low to intermediate risk of acute coronary syndrome, cocaine use is not associated with an increased likelihood of coronary disease after adjustment for age, race, sex, and other risk factors for coronary disease.[26] Serious complications such as congestive heart failure and ventricular dysrhythmias typically are manifested within the first 4 hours. Young patients who present after resolution of chest pain with normal and unchanging ECGs, no dysrhythmias, and few or no risks of coronary artery disease are likely to have a good outcome. Prior studies have demonstrated that these low- to intermediate-risk patients with cocaine-associated chest pain can be safely discharged after 9 to 12 hours of observation. The goal of a more recent study was to determine the safety of an 8-hour protocol for ruling out myocardial infarction in patients who presented with cocaine-associated chest pain. Application of an abbreviated cardiac enzyme protocol (at 0, 2, 4, and 8 hours) after presentation with continuous cardiac monitoring, resulted in the safe and rapid discharge of patients presenting to the ED with cocaine-associated chest pain.[27]

Body packers need to be observed until all packets have passed. Ideally, these patients have had several packet-free stools, a reliable packet count consistent with the ingestion, and a normal CT scan or contrast radiographic study. Body stuffers who receive activated charcoal, have normal ECGs, and remain asymptomatic with normal vital signs after 6 to 12 hours of observation may be discharged.

Other Stimulants

Amphetamines

Amphetamines enhance release of catecholamines from presynaptic nerve terminals by altering the pH of presynaptic vesicles. Amphetamines are usually taken as pills but are occasionally crushed and injected. The subsequent CNS stimulation results in sympathomimetic effects nearly identical to those from cocaine but not with the same frequency or intensity (see Box 149.1). Patients are at risk for hyperthermia, hypertensive emergencies, dysrhythmias, myocardial ischemia, and hyperkalemia associated with rhabdomyolysis.[28] In contrast to cocaine, amphetamines do not block sodium channels and only minimally affect presynaptic reuptake of catecholamines. Although urine drug screens can identify amphetamines, they are of little utility in treatment of a toxic patient. The management follows the same guidelines as for cocaine (see Box 149.3), although the duration of toxicity is longer for amphetamines. Phenylethylamines, which are closely related in molecular structure to amphetamines, include the "2C" and "NBOMe" drugs named for the location of specific structural elements.[29] These have powerful serotonergic, hallucinogenic effects; and patients can present with adrenergic toxicity and behavioral agitation. The brominated form (named "bromodragonfly" due to its structural similarity to a dragonfly in shape) is associated with a necrotizing angiitis that can compromise blood flow to limbs. Limb or digit pain in such patients warrants a comprehensive monitoring and evaluation for vasospasm and tissue ischemia.[30]

Methylenedioxymethamphetamine

Methylenedioxymethamphetamine (MDMA, ecstasy, XTC, Adam) is a chemically modified amphetamine originally taken orally at all-night dance parties or "raves."[31] Patients describe the euphoria allowing "closeness to others," so it is sometimes called the love drug. The molecular structure of MDMA confers some serotoninergic properties that may account for the "shimmering" (a sense of a flickering light) visual effects reported. The term *Molly* is often used to describe a product with a higher concentration of MDMA. Analysis of products sold as Molly often reveals substitute agents—some of which are inert and others may have adrenergic effects. User reports are, therefore, often unreliable in determining the true exposure.

Along with the usual complications of amphetamines, MDMA can precipitate a life-threatening hyponatremia. MDMA or its metabolite alter release of endogenous stores of vasopressin, which in the setting of high free water intake results in free water retention. Although the exact mechanism is not understood, patients with MDMA-induced hyponatremia have concentrated urine samples with a relatively high urine sodium concentration, similar to the SIADH. Unless seizures or other neurologic events are present, patients can be treated supportively with fluid restriction. Urine can be tested for specific gravity, and a sample should be sent to the laboratory for electrolyte analysis and osmolality. Normal saline or other crystalloids may worsen the hyponatremia, because these patients are likely to retain more free water than sodium. Their fluid intake should be restricted unless severe hypovolemia exists, and they should be treated with hypertonic saline for neurologic impairment. A newer treatment of hyponatremia includes vasopressin V_2-receptor antagonists, but it has not been described for these patients. In contrast to other amphetamines, chronic MDMA use causes potentially irreversible neurologic damage to serotoninergic neurons. Other MDMA variants,

such as 3,4-methylenedioxyethamphetamine (Eve), may cause similar complications.

Methamphetamine

Methamphetamine, known as crank and crystal meth, is a fat-soluble, smokable, designer amphetamine. Complications from methamphetamine use are similar to those from other sympathomimetics. The duration of action can be significantly longer, however, with some paranoid delusions persisting for 15 hours. The production of methamphetamines requires a variety of metal salts, and lead toxicity from inappropriately produced drug is reported. Injuries during illicit methamphetamine production or police raids include exposure to anhydrous ammonia, hydrochloric acid, sodium hydroxide, ether, and ephedrine, as well as burns and explosions.

Ephedrine and Ephedra

Ephedrine is another illicitly used amphetamine-like agent associated with complications of excessive sympathomimetic stimulation. Ephedra, a plant-derived product, also known as a Chinese herbal product, ma huang, has been associated with strokes and deaths in adolescent users. The FDA has banned all ephedra-containing dietary supplements.

Khat and Methcathinone

Khat is a stimulant agent naturally occurring in the leaves of the plant *Catha edulis*. These leaves are chewed to extract the active compounds, cathinone and methcathinone, which are stimulants with sympathomimetic effects. Management and disposition follow the same guidelines as for cocaine. Smoking of khat does not typically result in clinical effects, because the agent degrades with pyrolysis. Illicitly manufactured methcathinone is known as cat or qat. Some methcathinone users experienced an extrapyramidal syndrome associated with elevated manganese concentrations, probably resulting from an inadvertent contaminant during production or inadequate purification. The role of chelation therapy for elevated manganese concentrations is uncertain.

Bath Salts

Bath salts were first encountered in Japan in 2006. The ease of synthesis and modification of specific functional groups of the parent cathinone make these drugs particularly difficult to regulate.[32,33] Substances are vended as "bath salts" or "plant food" and labeled "not for human consumption." These synthetic cathinones sold unregulated over the Internet initially contained mephedrone, but their content rapidly changed to include methylone, ethylone, butylone, pyrovalerone, methylenedioxypyrovalerone (MDPV), methcathinone, and ethcathinone and their chemical variants. These substances are exploited for an adrenergic "high" but have no pharmacologically approved medical indications in the United States.[34,35] Bath salts may be ingested, inhaled, or injected and can result in severe agitation, sympathomimetic effects, hyperthermia, and rhabdomyolysis. Numerous fatalities have been reported, causing the U.S. Drug Enforcement Administration (DEA) to categorize these agents illegal and as Schedule I substances.[29,35] Synthetic cathiones are usually not detectable on routine urine drug screens. Treatment is similar to that of cocaine and amphetamine toxicity, including adequate dosing of benzodiazepines for agitation with diazepam, lorazepam, or butyrophenone antipsychotic agents, such as haloperidol and droperidol (see Management, Pharmacologic Sedation for Agitation section).

KEY CONCEPTS

- Rapid sedation with an IV benzodiazepine is the key for most symptoms from cocaine and other stimulants.
- Hyperthermia is a high-risk event, and body temperature must be reduced rapidly.
- Short-acting antihypertensive agents (such as, phentolamine, nitroglycerin, nicardipine, or clevidipine) are recommended for cocaine-induced hypertension, including in the presence of chest pain.
- Wide-complex rhythms secondary to cocaine may respond to IV sodium bicarbonate therapy.
- Cocaine body packers who develop symptoms of acute cocaine toxicity need emergent surgical intervention.
- Amphetamine symptoms and effects last longer than those produced by cocaine.
- Hyponatremia should be rapidly identified in patients with an altered mental status after use of illicit stimulants, most specifically MDMA.
- Synthetic cathinones or "bath salts" may be ingested, inhaled, or injected and can result in severe agitation, sympathomimetic effects, hyperthermia, and rhabdomyolysis. Fatalities have been reported.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 149: QUESTIONS & ANSWERS

149.1. How long does a typical urine drug screen result remain positive after use of cocaine?

A. 1 day
B. 3 days
C. 1 week
D. 2 weeks
E. 1 month

Answer: B. Urine drug screens detect the cocaine metabolite benzoylecgonine, which is typically present in the urine for 3 days after the last use.

149.2. A 24-year-old man is seen by police to be smoking crack cocaine on a street corner. On the way to jail, the patient reports a severe headache, so the police bring him to the emergency department (ED) for medical clearance. The patient is awake with normal mental status but continues to complain of diffuse head pain. His vital signs are blood pressure (BP), 195/99 mm Hg; heart rate (HR), 102 bpm; respiratory rate (RR), 18 rpm; and temperature, 37.2°C. His physical examination is normal. How should his headache be evaluated?

A. Acetaminophen administration, discharge if headache resolves
B. Blood pressure reduction, discharge if headache resolves
C. Head computed tomography (CT) scan, discharge if normal
D. Head CT scan, lumbar puncture if normal, discharge if both are normal
E. No evaluation needed; cocaine is not associated with headache

Answer: D. Cocaine is associated with subarachnoid hemorrhage (SAH). Patients complaining of a severe headache after cocaine use should receive a complete evaluation for SAH, including head CT and lumbar puncture. In addition, elevated blood pressure should be lowered while the evaluation is being performed.

149.3. What is the preferred primary method for controlling a combative patient suffering from a sympathomimetic overdose?

A. Chlorpromazine
B. Diazepam
C. Droperidol
D. Haloperidol
E. Physical restraints

Answer: B. Diazepam and other benzodiazepines are the best agents to sedate and establish control of an agitated patient. They cause sedation as well as decrease muscle tone, which can ameliorate hyperthermia. In addition, they can lower the acutely

increased blood pressure often seen with sympathomimetic use. In the agitated patient when intravenous (IV) access may be difficult to establish, lorazepam is more predictably absorbed than diazepam. Chlorpromazine can be given intramuscularly to provide rapid sedation, but is associated with anticholinergic effects that may exacerbate hyperthermia. Butyrophenone agents (eg, haloperidol and droperidol) are reserved for more severe agitation and are considered secondary methods of treatment after adequate doses of benzodiazepines. Also, they may have associated dysrhythmic effects that are additive to those of cocaine. Physical restraints may be necessary initially but are not desirable, because they can also increase the risk of hyperthermia as well as increase agitation, which is associated with sudden death.

149.4. A 27-year-old woman presents with severe chest pain that began soon after use of a large amount of cocaine. She describes the pain as "tearing from my chest to my back." Her vital signs are blood pressure (BP), 210/112 mm Hg; heart rate (HR), 142 bpm; respiratory rate (RR) 22 rpm; and temperature, 38.0°C. A BP measurement taken in the other arm is 147/86 mm Hg. An electrocardiogram (ECG) is normal. You are highly suspicious that the patient is suffering from an aortic dissection and order a transesophageal ultrasound examination while contacting the cardiothoracic surgeon. In the meantime, what should you use to lower her blood pressure?

A. Labetalol
B. Nitroglycerine
C. Nitroprusside
D. Phentolamine
E. Treatment should be withheld until a definitive diagnosis is made.

Answer: D. Phentolamine is a direct alpha-adrenergic antagonist and is the drug of choice for sympathomimetic-induced hypertension with end-organ damage. Labetalol and beta-blockers are not recommended, because they have little to no clinical benefit in this setting. Nitroprusside and nitroglycerine are acceptable agents if phentolamine is not available. Treatment should not be withheld, because rapid blood pressure control could be lifesaving.

149.5. A 35-year-old man presents with chest pain that started approximately 2 hours ago, soon after he smoked crack cocaine. The pain occurred with exertion and has not resolved. He has no previous medical history. His vital signs are blood pressure (BP), 182/99 mm Hg; heart rate (HR), 122 bpm; respiratory rate (RR) 18 rpm; and temperature, 38.2°C. His electrocardiogram (ECG) shows sinus tachycardia with ST depression in the anterior leads. The chest radiograph is normal. Laboratory results are significant for elevations in creatine kinase (CK), CK-MB, and troponin I. What is the likely explanation for his elevated serum cardiac markers?

A. He has a completely occluded coronary artery causing ischemia.
B. He has coronary artery spasm without ischemia.
C. He has coronary stenosis causing ischemia.
D. He has fever and rhabdomyolysis but no cardiac disease.
E. His elevated blood pressure is causing cardiac strain but not ischemia.

Answer: C. Although cocaine can cause coronary spasm with resultant chest pain, patients with positive serum markers are likely to have significant angiographic stenosis. Cocaine users who have complete coronary occlusion typically develop ST elevation just as non–cocaine users do. His elevated blood pressure and fever are certainly increasing the workload on the heart but are not causing his elevated cardiac markers. Cocaine patients may suffer from rhabdomyolysis, and although the resultant renal failure can slow the clearance of the cardiac markers, it does not cause the elevation.

149.6. A 24-year-old man is brought to the emergency department (ED) in police custody after he admitted to swallowing multiple packets of cocaine to smuggle them through an airport. The patient has no complaints. His physical examination is normal. An abdominal radiograph shows multiple slightly radiopaque areas consistent with packets of cocaine. An electrocardiogram (ECG) is normal. What is the most appropriate management of this patient?

A. Endoscopic removal of packets
B. No therapy needed; the patient may be discharged
C. Observation alone to watch for elimination of packets
D. Surgical removal of packets
E. Whole bowel irrigation to remove packets

Answer: E. Whole bowel irrigation with polyethylene glycol facilitates passage of the packets and is safe and effective. Endoscopic removal should be avoided, because there is increased risk of packet rupture. Emergent surgical removal is indicated if there is evidence of packet leak and the patient becomes symptomatic. The patient needs to be observed with cardiac monitoring at a center capable of emergent surgery until all packets have passed.

149.7. Which unique life-threatening electrolyte abnormality is seen with the use of *N*-methyl-3,4-methylenedioxyamphetamine (MDMA)?

A. Hyperkalemia
B. Hypernatremia
C. Hypokalemia
D. Hypomagnesemia
E. Hyponatremia

Answer: E. Hyponatremia can occur with MDMA use and can be severe and life-threatening. MDMA alters the release of vasopressin and will induce a clinical syndrome resembling the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The patients have concentrated urine with high urine sodium content. Seizures can occur and should be treated with hypertonic saline. In the absence of seizures or other life-threatening conditions, general supportive care with water restriction is adequate treatment.

CHAPTER 150

Hallucinogens

Janetta L. Iwanicki

The term *hallucinogen* is used to describe a variety of xenobiotics causing altered perception. A hallucination is defined as perception of an object or sensation that does not exist in reality. However, most drugs do not produce actual hallucinations. Drugs that are classified as hallucinogens are more likely to cause illusions, or misperceptions of real objects. Some hallucinogens are called psychedelics, a subset that alters cognition and perception. Hallucinogens may work by several different mechanisms, including stimulating the serotonergic 5-HT_{2A} receptor, hyperactivation of the dopamine D2 receptor, and blockade of the glutamate *N*-methyl-D-aspartate (NMDA) receptors.[1] This chapter describes serotonergic agents, dissociative agents, and selected plants and fungi. Sympathomimetic agents are discussed in Chapter 149.

SEROTONERGIC AGENTS

Principles of Toxicity

Serotoninergic agents are a broad category of compounds that share chemical similarities with serotonin (5-hydroxytryptamine [5-HT]) or enhance serotonergic tone within the body, predominantly by their action at the 5-HT_{2A} serotonin receptor subtype. These agents include various lysergic acid derivatives (lysergamides) and tryptamines (indolealkylamines). Serotonin-like agents produce changes in thought, mood, perception, and consciousness. Orientation to person, place, and time is usually preserved, but severe intoxication may cause delirium, disorientation, and altered levels of consciousness. Patients may present to the emergency department (ED) because of an acute panic reaction, massive ingestion, or accidental exposure (eg, children or adults who have ingested the drug unknowingly). There is no addictive component in psychedelics and no euphoria-dysphoria cycle, as occurs with sympathomimetic drugs such as cocaine. The rapid development of tolerance also limits the effect of repeated doses.

Lysergamides

Lysergic acid diethylamide (LSD), or acid, is a potent psychedelic drug. Doses of 1 to 1.5 µg/kg produce psychedelic effects. The typical dose taken for an acid trip is approximately 25 to 100 µg. LSD is sold in as a tablet (microdot), liquid, powder, gelatin square (windowpane), and blotter acid. Sheets of blotting paper are sprayed with LSD, dried, and perforated into small squares. Graphics are incorporated onto the blotting paper in designs that include cartoon characters (eg, Felix the Cat, Bart Simpson) and geometric designs (Fig. 150.1). Each sheet is composed of hundreds of squares that are placed sublingually or eaten whole. Massive ingestions are rare.

In addition to synthetic LSD, several plants contain lysergic acid amide (LSA) similar in structure and action to LSD. These plants include the Hawaiian baby wood rose (*Argyreia nervosa*), Hawaiian wood rose (*Merremia tuberosa*), morning glory (*Ipomoea violacea*), and ololiuqui (*Rivea corymbosa*). Intoxication may result after ingestion of the seeds or an extract.

Tryptamines

Tryptamines may be synthetic or natural compounds. For centuries, Native Central and South Americans have used tryptamine-containing beverages such as ayahuasca in their religious ceremonies. This beverage is brewed from a combination of plants containing dimethyltryptamine (DMT) and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), as well as harmine alkaloids with monoamine oxidase inhibitor effects that increase the bioavailability of orally ingested DMT. Ayahuasca has gained popularity in Europe and North America.

Psilocybin and psilocin are naturally occurring tryptamines found in some species of *Psilocybe* (Fig. 150.2), *Panaeolus,* and *Conocybe* mushrooms. Psilocybin remains active when the mushrooms are dried or cooked. Street psilocybin sold as pills or capsules is frequently substituted with phencyclidine (PCP) or LSD. Naturally occurring tryptamines are also found in the parotid glands of the *Bufo* toad species. The venom of the Sonoran Desert or Colorado River toad (*Bufo alvarius*) contains 5-MeO-DMT. Smoking of the dried venom results in psychoactive effects.

Designer tryptamines such as α-methyltryptamine, diisopropyltryptamine, and diisopropyl-5-methoxytryptamine (foxy, foxy methoxy) have been synthesized and are orally active.[2] The effects of these synthetic derivatives are similar to those of naturally occurring tryptamines.

Clinical Features

In Western society, psychoactive agents are taken for internal mental exploration or, more commonly, for recreation. Effects include loss of boundaries between the user and environment, the sensation that colors and sounds are distorted and intensified, and the perception that usual objects appear novel, fascinating, or awe-inspiring. Users are usually aware that they are under the influence of the drug. A sense of euphoria is typical, but it may alternate with an intense dysphoric experience that is accompanied by suffering (eg, that of dying or being born).

Acute panic reaction is a common adverse reaction to psychedelics. Paranoid delusions and fear of impending death may be present. Behavior may be agitated or withdrawn. Sympathomimetic effects include dilated pupils and moderate increases in blood pressure, heart rate and, rarely, temperature. Mydriasis seems to parallel the intensity of the trip. The individual's altered perceptions may result in lack of awareness of dangers in the environment, resulting in injury. Psychosis after LSD trips has been reported, and schizophrenia (overt or borderline) may worsen. Transient depression sometimes occurs after LSD use. Flashbacks, or posthallucinogen perceptual disorder, are transient episodes of altered consciousness that occur months or years after an LSD trip. Hyperactivity may also be seen, with marked auditory and visual hallucinations. Massive ingestions may result in coma and decreased responsiveness to painful stimuli. Fixed and dilated pupils, diaphoresis, vomiting, hyperthermia, rhabdomyolysis, coagulopathy, and seizures may result.

Euphoria and a distortion of reality usually occur after ingestion of one to five *Psilocybe cubensis* mushroom caps. In contrast

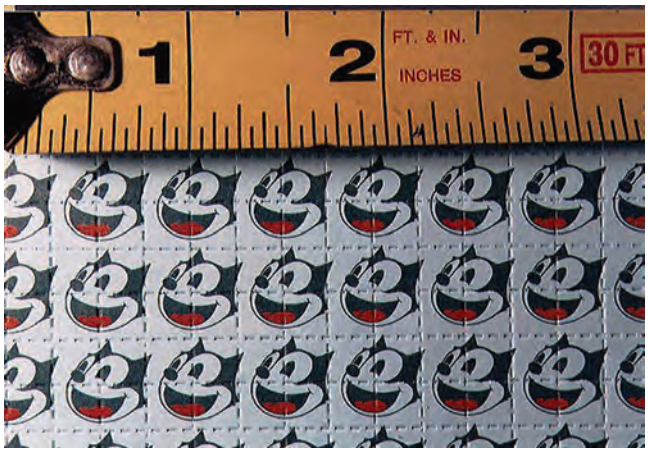

Fig. 150.1. LSD blotters (Felix the Cat). (Photo by Jon, copyright 2001, Blotterart.com. Accessed at www.erowid.org.)

Fig. 150.2. *Psilocybe cubensis* mushroom. (Photo by Gweedo, copyright 2003. Accessed at www.erowid.org.)

to peyote (discussed later), vomiting is unusual. Larger doses (5–20 *P. cubensis* mushrooms) produce visual hallucinations. Few adverse reactions occur, and the incidence of bad trips or panic reactions is lower than with LSD. Rarely, seizures, coma, and hyperthermia have been reported after psilocybin use.

Differential Diagnoses

Other drugs and mixed ingestion are a possible source of the patient's symptoms, especially with coma or marked physiologic changes. Cocaine, PCP, anticholinergic drugs, and amphetamines should be considered because their acute effects may require specific treatment. Acute psychosis may also appear, similar to a psychedelic reaction.

Diagnostic Testing

Often, patients are in a panic or are brought in by a worried companion, so the drug is usually known. Although mass spectrometry can identify psychedelics in serum, urine, or gastric contents, it is not available in the clinical setting, so diagnosis and treatment are based on clinical grounds. Most patients require no laboratory testing, but a basic metabolic profile and ethanol and serum glucose levels may be helpful in patients with unclear ingestions, co-ingestants, or underlying disorders.

Management

Reassurance and supportive care are the cornerstones of management. If the patient is a danger to himself, herself, or others, the patient may need to be sedated with benzodiazepines (see below) or restrained temporarily to permit sedation. There is no specific antagonist to the effects of serotonergic agents. Empathetic reassurance in a calm, quiet environment with decreased external stimuli is an effective therapeutic modality. The drug effects last for hours but, when it wears off, the patient feels normal again.

Benzodiazepines are the mainstay of treatment for hallucinogenic drug-induced agitation. Diazepam, lorazepam, and midazolam have all been successfully used in this setting. Diazepam can be administered via the intravenous (IV) route in increments of 5 to 10 mg every 5 minutes in adults until sedation is achieved. Diazepam has a rapid onset of action, is easily titratable, and has active metabolites for a sustained effect. Lorazepam, 1 to 2 mg IV every 5 minutes is also an acceptable option. Additional doses of lorazepam or diazepam can be given, with close monitoring of the patient's respiratory status. For an adult patient in whom IV access is not possible because of agitation, intramuscular (IM) midazolam, 10 mg, can be administered to facilitate subsequent interventions. Although lorazepam also can be given IM, it may take 15 minutes to reach peak sedation, and repeated doses given at more frequent intervals may accumulate, causing oversedation and respiratory depression. In all patients, titration of the benzodiazepine is important, allowing the emergency clinician to observe the effects of one dose (usually 5 minutes) before an additional dose is given. After sedation is achieved, the patient is closely observed to ensure that the patient's respiratory status is stable when the peak sedation effect is achieved.

The vast majority of patients with hallucinogen-induced agitation respond clinically to adequate doses of benzodiazepines. Butyrophenone antipsychotic agents, such as haloperidol and droperidol, are rapidly effective and generally safe for drug-induced psychosis or agitation states from other drugs, including cocaine, amphetamines, and phencyclidine (also discussed in Chapters 140 and 149). If needed, we recommend haloperidol, 5 to 10 mg IM or IV, which may be repeated every 20 to 30 minutes, as needed for clinical sedation. This medication lacks the respiratory depression potentially caused by other agents and may be beneficial in some cases when rapid sedation is required.

Disposition

Patients with anxiety or panic reactions are often easily talked down, with little clinical intervention. Acutely toxic patients who respond to sedation and do not have complications can be discharged after the acute toxicity stage resolves following a 4- to 6-hour observation period. We recommend discharging them accompanied by responsible family or friends, with drug counselling and referral. Patients who persist with confused or paranoid behavior should be observed until their mental status returns to baseline. Patients with altered mental status that does not normalize after 8 to 12 hours of observation in the ED, or who present after a massive ingestion with medical complications, require admission to a monitored setting for serial reassessments.

DISSOCIATIVE AGENTS

Principles of Toxicity

PCP and ketamine are the two main agents included in the class of dissociative agents. Dextromethorphan abuse may also

have a similar presentation, and methoxetamine has recently emerged as a new drug of abuse. They are similar in chemical structure and pharmacologic effects and cause dissociation of the patient from the environment. They have analgesic and amnestic activity but do not typically cause respiratory or cardiovascular depression.

Phencyclidine

PCP was initially marketed for use as a general anesthetic; however, severe emergence reactions rapidly led to its recall. In the 1960s, PCP was sold as the PeaCe Pill, which was consumed orally, but the effects were often unpredictable and unpleasant. In the mid-1970s, PCP was the most common cause of recreational drug–related emergencies. Its popularity decreased because of unpredictable effects, long clinical course, dysphoria, and association with violence; however, there has been a recent resurgence in popularity in some regions of the United States. In 1978, PCP was classified as a Schedule I drug.

Ketamine

Ketamine is known as vitamin K, special K, kit kat, and cat valium; however, preparations available on the street are often adulterated with various stimulants. The most common use of street ketamine is insufflation, but subcutaneous and IM injection and even rectal infusion are done to achieve a level of intoxication or high, known as the K-hole.

Methoxetamine

Methoxetamine is a derivative of ketamine known as special M, MXE, Mexxy, and ROFLcopter, and has been sold as a legal high and an alternative to ketamine, with reports of a lower risk of the urologic complications seen with chronic ketamine use.[3] Symptoms of intoxication are similar to those seen with ketamine, but may also have an increased risk of acute cerebellar toxicity.[4]

Dextromethorphan

Dextromethorphan is not truly a dissociative agent but does share a similarity in structure to PCP and its binding to the PCP site of the NMDA receptor. With the availability of concentrated pill formulations, abusers of dextromethorphan can ingest large doses without having to drink large volumes of the less palatable cough syrup formulation. Particularly popular in the adolescent community, dextromethorphan is known as DXM, robo, skittles, triple C, and red hots.

Despite being simple molecules, PCP, ketamine, and methoxetamine have a complex pharmacology, including the NMDA receptor, dopamine-norepinephrine-serotonin reuptake pump, sigma opioid receptor, and cholinergic receptors. PCP is well absorbed from any oral, nasal, or rectal mucous membrane and can be insufflated or smoked. It can be injected IM subcutaneously, or IV. Ingested PCP is well absorbed, with an onset of action between 15 and 60 minutes. When it is smoked, PCP produces symptoms within 5 minutes, with peak activity in 15 minutes. Intoxication with PCP usually lasts 8 to 16 hours but can be prolonged in chronic users. Although enterohepatic recirculation has been proposed, a more likely cause is gastrointestinal concretion or delayed release from lipid stores.

Ketamine is approximately 10% as potent as PCP. With ketamine, the intensity of intoxication is less pronounced, although in larger doses the effects may parallel those of PCP. Duration of action of ketamine is typically shorter, with symptoms lasting approximately 1 hour after insufflation but up to 4 to 8 hours after an oral dose. Methoxetamine appears to have a slower onset and longer duration of action than ketamine.[3] PCP and ketamine are highly lipid-soluble agents that undergo extensive metabolism in the liver and are eventually excreted in the urine.

Although dextromethorphan is typically classified as an opioid, it has a complex pharmacology. Dextromethorphan is the dextrorotatory isomer of the synthetic opioid levorphanol. At high dosages, dextromethorphan is an agonist at the sigma opiate receptor, and naloxone has been reported to reverse intoxication. Dextromethorphan antagonizes the NMDA receptor, which results in its dissociative effects. It also inhibits the uptake of serotonin, and drug interactions with selective serotonin reuptake inhibitors and monoamine oxidase inhibitors have been reported.

Clinical Features

Patients with PCP intoxication have a wide spectrum of findings, including sympathomimetic signs and symptoms. Behavior may be bizarre, lethargic, agitated, confused, or violent. A blank or catatonic stare is common. Pupils usually are midsized and reactive, although there may be miosis or mydriasis. Vertical and horizontal nystagmus are often present and considered a hallmark sign of PCP intoxication. Less commonly, rotary nystagmus may be noted with PCP toxicity and should be differentiated from that induced by head injury or brain lesions. Moderate hypertension and tachycardia may be present. Bizarre posturing, grimacing, and writhing may be seen.

Other variable findings include ataxia, muscle rigidity, increased deep tendon reflexes, increased secretions, bronchospasm, hyperthermia, and seizures. Up to 40% of PCP patients may be violent and combative, and control of these patients may be the most challenging problem in the ED. Superhuman strength is possible because of the dissociative and analgesic action of PCP. Rarely, severe hypertension with PCP overdose has caused intracerebral hemorrhage.

Hyperthermia can range from mild to life-threatening. High-output congestive heart failure has been reported. Acute rhabdomyolysis and acute myoglobinuric renal failure are also seen due to muscle damage from seizures, extreme muscle activity such as struggling against restraints, or prolonged immobility. Respiratory depression, apnea, and cardiac arrest have also been described.

Although dextromethorphan has activity at opioid receptors, the typical triad of opioid intoxication—miosis, respiratory depression, and mental status depression—is not generally encountered. Similar to meperidine, dextromethorphan may result in mydriasis through paralysis of the ciliary body with intoxication. Typical clinical findings include lethargy, agitation, slurred speech, ataxia, diaphoresis, hypertension, nystagmus, nausea, vomiting, and hallucinations.

Differential Diagnoses

PCP, ketamine, methoxetamine, and dextromethorphan intoxication can mimic such diverse entities as head trauma, meningitis, catatonia, and heat stroke. Sympathetically mediated vital sign changes can be found with numerous other agents, including cocaine, amphetamine, and LSD. Antimuscarinic compounds, such as diphenhydramine, benztropine, and tricyclic antidepressants, can also simulate the tachycardia and altered mental status found with PCP or ketamine. Salicylate poisoning, thyrotoxicosis, and sepsis should be considered. Meningitis, intracerebral hemorrhage, and viral encephalitis can be manifested, with altered mental status of unclear cause. Even with a urine screen positive for PCP, the diagnosis is not certain unless a definite history of recent PCP, ketamine, methoxetamine, or dextromethorphan use is obtained and other conditions have been eliminated.

Diagnostic Testing

Most hospital laboratories use radioimmunoassays that can detect urinary PCP with a detection limit of 5 ng/mL. Urine may be positive for PCP for 2 to 4 days after use and can be positive for more than 1 week. Serum screening for PCP is of little clinical benefit because levels correlate poorly with symptoms. Several substances, including dextromethorphan, may cross-react with urine screens for PCP because of their structural similarities. Chlorpromazine, methadone, mesoridazine, ketamine, diphenhydramine, venlafaxine, meperidine, and tramadol may also cross-react with some assays.[5] In some geographic regions, false-positive test results may be more common than true-positive test results. Because dextromethorphan is typically formulated as a hydrobromide salt, chronic use may result in spurious hyperchloremia with a low or negative anion gap due to interference of chloride analysis by the bromide ion in the laboratory autoanalyzer. Many dextromethorphan cough and cold preparations also contain acetaminophen; a serum acetaminophen level should be measured. If patients have not been hyperthermic and have no signs of trauma, laboratory or other diagnostic tests are generally not needed. With acutely symptomatic patients, a complete metabolic profile, renal function, and creatine phosphokinase (CPK), serum glucose, and ethanol levels should be measured.

Management

Life-threatening complications, such as apnea and seizures, should be stabilized before transport. The threat of violence to prehospital care providers from patients with PCP intoxication makes it dangerous for only two or three providers to restrain these patients until additional help arrives. Oxygen and glucose testing should be deferred until the patient is controlled. Patients with PCP toxicity can have unpredictable violent behavior, and may sustain traumatic injuries. Extreme agitation, although possible, is less common with ketamine and methoxetamine. Most patients with minor intoxication are alert, oriented, and neurologically normal after 4 to 6 hours. Patients with signs of trauma should be evaluated for injuries. Reliable assessments of these individuals are difficult, and sedation and restraint are often necessary before diagnostic tests or examinations can be performed.

Chemical sedation is preferred to physical restraint with PCP or ketamine intoxication, although temporary physical restraint may be necessary to ensure the patient's safety, establish IV access, and administer sedating medications. Butyrophenones such as haloperidol and droperidol can be given IM with a rapid response, avoiding the danger of IV establishment. Haloperidol, 5 to 10 mg IM or IV, is usually effective but can be titrated at 10- to 15-minute intervals until the patient is calm. The sedative dose for droperidol is 2.5 to 5 mg IM. These agents may antagonize the CNS receptor sites that are responsible for much of the violent behavior in these individuals. Droperidol has a black box warning from the US Food and Drug Administration (FDA) for QT prolongation and potentially torsade de pointes. However, the FDA added a warning that "torsade de pointes and QT prolongation have been observed in patients receiving haloperidol, especially when the drug is administered intravenously or in higher doses than recommended. Haloperidol is not approved for intravenous use." Most reported cases of butyrophenone-induced dysrhythmias have been in those receiving large doses for prolonged periods, such as hours to days, or in older adults (>60 years). These medications lack the respiratory depression potentially caused by other agents and may be beneficial in some cases when sedation is required. Thus, the butyrophenones remain safe and effective agents for the treatment of drug-induced agitation. Benzodiazepines, such as lorazepam, 2 to 4 mg IV or IM, or diazepam, 5 to 10 mg IV, may also be used to treat agitation (see Chapters 140, 149, and 189).

A well-coordinated team may be needed to apply restraints simultaneously to all four extremities and the body. Assessment of mental status may not be as reliable after chemical sedation, but the benefits of protecting the staff and patient far outweigh the disadvantages.

Hyperthermia is common in severe cases of PCP poisoning. All patients with significant symptoms, psychosis, or history of violent behavior should have their core temperature measured. Individuals with hyperthermia should be treated with rapid sedation to decrease neuromuscular hyperactivity and heat production, intubation if needed to allow for sufficient sedation, and active, evaporative cooling measures (see Chapter 133).

Renal status and the creatine kinase level should be monitored to detect rhabdomyolysis and myoglobinuric renal failure. Seizures should be treated with an IV benzodiazepine (see Chapter 92). Dextromethorphan poisoning can be managed with supportive care and measures to prevent injury to the patient. Sedation with a benzodiazepine may be used for agitation. Respiratory depression may respond to IV administration of naloxone; however, the dissociative effects do not typically respond to naloxone. The patient should improve during 4 to 6 hours postingestion.

Disposition

For nonviolent patients with dissociative agent intoxication, a quiet holding room is ideal for 4 to 6 hours of observation. Patients with violent behavior or obtundation often require admission to the hospital, where close observation and treatment of potential life-threatening complications can be accomplished. Many of these patients can be medically cleared the next day.

MARIJUANA AND SYNTHETIC CANNABINOIDS

Principles of Toxicity

Marijuana is the most common federally illegal drug in the United States. It was used medicinally in ancient times for conditions such as colic and asthma and has been federally illegal since 1937. However, as of 2015, four states (Colorado, Washington, Oregon, and Alaska) and the District of Columbia have passed legislation to legalize recreational marijuana, 20 states have legalized medical marijuana, and 4 states have decriminalized marijuana possession.

Cannabis sativa and *Cannabis indica* plants are some of the earliest plants grown by humans. Bioactive substances derived from these plants are collectively called cannabinoids. The seedless flowering tops of the female plant are referred to as sinsemilla and are the commonly grown form of marijuana in the United States. The resin from the flowers is made into hashish. Marijuana is smoked, vaporized, or eaten blended into foods. Δ^9-Tetrahydrocannabinol (THC) is the main psychoactive agent of the more than 61 cannabinoid compounds and approximately 300 other substances present in the cannabis plant, and cannabidiol (CBD) is the major nonpsychoactive component. THC has been associated with some of the adverse effects of marijuana use, including increased agitation, anxiety, and potential for psychosis. Neuroimaging studies have shown that co-ingestion with CBD may modulate and decrease some of these effects, leading to concerns that newer, high-potency, THC-predominant strains of cannabis may lead to a higher risk chemical profile of these plants.[6-7]

Synthetic cannabinoids have also become readily available. These products are often marketed as novelty herbal incense and labeled "not for human consumption." They typically come in resealable foil packages and contain various plant leaves sprayed with a solvent mixture of one or several synthetic cannabinoid

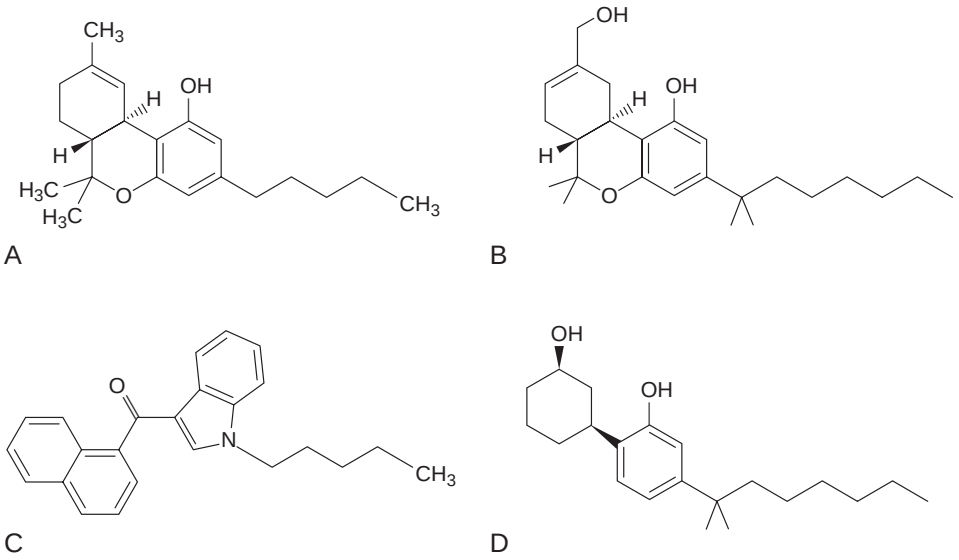

Fig. 150.3. Cannabinoid structures. **A,** Δ^9-Tetrahydrocannabinol. **B,** HU-210. **C,** JWH-018. **D,** CP-47,497.

compounds. Examples of products have names such as Spice, K2 Summit, Banana Cream Nuke, Yucatan Fire, Genie, Black Mamba, Crazy Clown, and many others. The Drug Enforcement Administration (DEA) issued an order in 2011 to list five synthetic cannabinoids—JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol—into Schedule I of the Controlled Substances Act (CSA) to avoid an imminent hazard to public safety.[8] Previously, only one synthetic cannabinoid (HU-210), a structural analogue of THC, was listed as such. In 2014, another four compounds—PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA—were also listed as Schedule I after outbreaks of severe illness in several states.[9] Because numerous synthetic cannabinoids are available, producers of spice products can simply replace a scheduled cannabinoid with others that remain supposedly legal, which minimizes the impact of scheduling by the DEA on long-term availability because the demand for the cannabinoid products remains high.

Cannabinoids act primarily at cannabinoid receptors CB1R, found mostly in the CNS, and CB2R, found primarily on peripheral immune cells. Discovery of these cannabinoid receptors and experiences in states with medical marijuana availability have led to interest in further exploration of the therapeutic potential of cannabinoids[10] (Fig. 150.3).

Clinical Features

Smoking marijuana leads to rapid and predictable signs and symptoms. Ingestion can cause delayed and sometimes unpredictable effects. The most common effects from smoking of marijuana include alteration of mood and usually relaxation and euphoria. The only reliable physiologic effects are a mild increase in heart rate and conjunctival injection. Other acute peripheral changes include urinary retention, decreased testosterone levels, and decreased intraocular pressure. Short-term memory is impaired, and the ability to perform complex tasks may be adversely affected. Many users report excessive appetite after marijuana use. Peak blood levels occur within 8 minutes of inhalation, with rapid distribution into tissues, especially tissues with a high lipid content. The duration of perceived effects is usually 2 to 4 hours when the drug is smoked.

Oral ingestion of marijuana edibles may be associated with longer duration of effect (≥6–12 hours), and patients with a massive oral marijuana ingestion may develop profound ataxia, vomiting, agitation, anxiety, and CNS depression requiring medical care.[11] Edible products often carry high concentrations of THC in relatively small portion sizes and, due to a delayed onset of effect up to 4 hours after ingestion, patients may ingest escalating amounts of product while awaiting the onset of psychoactive effects.[12]

Pediatric exposures to marijuana may lead to hypothermia, ataxia, nystagmus, tremor, tachycardia, injected conjunctiva, and labile affect. Oral ingestion of potent marijuana in children can produce rapid onset of drowsiness, hypotonia, and lethargy, which can lead to coma and airway obstruction and respiratory compromise requiring intubation and ventilatory assistance.[13]

Whereas intoxications with marijuana and synthetic cannabinoids may have some similarities, significant differences have been described.[14] First-generation synthetic cannabinoids such as JWH-018, JWH-073, HU-210, and CP-47 were commonly associated with tachycardia, agitation, nausea and vomiting, altered mentation, and hallucinations.[15] Seizures were also noted with this group of cannabinoids. Second-generation synthetic cannabinoids such as ADB-PINACA and AB-FUBINACA have been associated with more profound agitation and aggression, seizures, tachycardia followed by bradycardia and, less commonly, ischemic stroke and cardiac toxicity.[16]

Differential Diagnoses

The presentation that most closely resembles that of marijuana and synthetic cannabinoid intoxication is acute psychosis. Some individuals with underlying and preexisting psychiatric disorders may progress to overt psychosis after heavy or first-time marijuana use. Because marijuana is so readily available, it is commonly a co-intoxicant used with ethanol and other psychotropic agents. Pediatric patients with unknown unintentional exposures may appear similar to patients with sepsis, meningitis, or metabolic disorders. Rarely, marijuana can be adulterated with other substances, such as PCP and other illicit drugs used concomitantly.

Diagnostic Testing

Marijuana screening is rarely helpful in the ED. Urinary metabolites of THC are detectable within 1 hour after smoking of marijuana, but a positive urine test result does not correlate with acute intoxication. A single marijuana cigarette can be detected for 72

hours when a cutoff level of 100 ng/mL is used, and positive urine levels may persist for 3 months after chronic marijuana use. Inadvertent or passive exposure to large amounts of second-hand marijuana smoke in enclosed areas may produce positive urine test results, depending on cutoff levels used. False-positive urine screen results may be produced by efavirenz, ibuprofen, and naproxen. An exception to this is the utility of a urine drug screen for marijuana in pediatric patients with an unclear cause of altered mental status.

Of the synthetic cannabinoids, only HU-210 is expected to trigger a positive THC immunoassay screen as a result of structural homology. Many other synthetic cannabinoids are structurally distinct from THC and do not result in positive THC immunoassay screens.

Management and Disposition

Care of patients intoxicated from marijuana and synthetic cannabinoids consists of prevention of injury and reassurance for those who have panic reactions. An extremely agitated patient can be sedated with oral or parenteral administration of benzodiazepines or antipsychotics. Antiemetics (eg, ondansetron 4–8 mg IV, or metoclopramide, 10–20 mg IV) may be used to treat nausea and vomiting induced by the cannabinoid hyperemesis syndrome (CHS) associated with the synthetic cannabinoids and heavy, daily marijuana use. Hot showers are often recommended for patients suffering these symptoms. The precise mechanism whereby hot bathing produces a rapid reduction in the symptoms of CHS is unknown. It has been postulated that hot water may act by correcting the cannabis-induced disequilibrium of the thermoregulatory system of the hypothalamus.[17] Children who are significantly symptomatic may require admission for a 24-hour observation period.

Other Agents

Mescaline

Mescaline is a naturally occurring phenylethylamine usually consumed in the form of peyote buttons, which are derived from the small, blue-green cacti *Lophophora williamsii* and *Lophophora diffusa*[18] (Fig. 150.4). They grow in the deserts of the southwestern United States and Mexico.

Peyote has been used in religious ceremonies for 8000 years. Mescaline is also contained in the San Pedro cactus (*Trichocereus pachanoi*) of South America and is used ritualistically by Andean Native Americans. These cacti contain many other alkaloids, some of which are also psychoactive. The use of peyote is legal for members of the Native American Church in some states. Adverse reactions (eg, panic attacks) to peyote are rare in structured religious use. Mescaline has an onset of action of 45 to 60 minutes, with a duration of effect lasting 4 to 8 hours. The CNS and physiologic effects of mescaline use are similar to those of LSD, but more vivid hallucinations can occur. Nausea and vomiting are pronounced and almost always precede the hallucinogenic effects, which is an important aspect of the cleansing spiritual ritual.

Fig. 150.4. *Lophophora williamsii* (peyote cactus). (Photo by Christopher B., copyright 2000. Accessed at www.erowid.org.)

Nutmeg

Nutmeg is a spice derived from the seed of the nutmeg tree, *Myristica fragrans*. Use of nutmeg as a natural and legal psychotropic agent was popularized in the 1960s. Despite lack of any in vivo human studies, myristicin and elemicin have been suggested as the agents responsible for intoxication because their chemical structure resembles that of mescaline. Reports of intoxication are uncommon.[19] Ingestion of 5 to 30 g (1–4 tablespoons) of the spice is said to induce euphoria and hallucinations but is more likely to cause gastroenteritis.

Salvia

Salvia divinorum, a perennial herb cultivated outdoors in mild climates, is a member of the mint (Lamiaceae) family. Common names for *S. divinorum* are diviner's sage, mystic sage, magic mint, sage of the seers, Sally-D, ska, and Maria Pastora. Although the plant has been used for divination and shamanism by the Mazatec Indians of Oaxaca, Mexico, *S. divinorum* has become popular in the past 20 years for recreational purposes because of its recognized hallucinogenic properties. In 2004, the DEA listed *S. divinorum* as a "drug of concern" but, to date, *S. divinorum* and salvinorin A are not currently controlled under the CSA in the United States.[20] Several states, however, have instituted or are considering legislation making possession, cultivation, and use of *S. divinorum* or its extracts illegal.

The active ingredient in *S. divinorum* is salvinorin A, a neoclerodane diterpene with selective agonist activity for kappa opioid receptors. Salvinorin A appears to have no activity at delta or mu opioid receptors.[21] The threshold dose of salvinorin A to produce hallucinations is comparable to that of synthetic LSD. However, salvinorin A is distinct from more traditional hallucinogens because it does not bind to the 5-HT_{2A} serotonin receptors, as is the case with LSD.[22]

Salvia is usually chewed and spit out or swallowed, and it seems to be absorbed more readily from the oral mucosa than from the rest of the gastrointestinal tract. Effects produced as a result of oral mucosal absorption may persist for 1 hour. Dried leaves can also be smoked. Inhalation of smoke can produce symptoms within 1 minute that subside during 20 to 30 minutes. Sensations experienced are variable but include distortions of color and vision, uncontrollable laughter, and synesthesias, which are confusions of the senses, such as seeing sounds or smelling colors. Salvinorin A is not detected by typical drug screening tests and is not known to cause interference with routine drug screens used in the clinical setting. Management of intoxication from *S. divinorum* is mainly supportive, with emphasis on injury prevention. Use of naloxone, a nonspecific opioid receptor antagonist, may theoretically be helpful for the reversal of psychotropic manifestations.

Kratom

Mitragyna speciosa, or kratom, is a tree found in tropical and subtropical regions of Asia and Africa. The popularity of kratom

has grown because of reports of its successful use to attenuate symptoms of opioid withdrawal. Because kratom remains easily obtainable from Internet sources, individuals are able to self-administer the perceived remedy, obviating the need for physician supervision. The safety of such a practice is unknown.

Although kratom extract contains more than 25 alkaloids, mitragynine is the most abundantly found in the plant. Mitragynine is an indole alkaloid with structural analogy similar to that of yohimbine and has agonist activity at mu and delta opioid receptors, producing euphoric, analgesic, and respiratory depressant effects. The respiratory depressant effects are more likely to occur when combined with opioids or other respiratory depressants. Despite its structural similarity to yohimbine, a selective antagonist of presynaptic α_2-adrenergic receptors, animal studies have suggested that mitragynine is also an agonist at postsynaptic α_2-adrenergic receptors and blocks 5-HT_{2A} receptors.

Typically, kratom leaves are chewed, smoked, or brewed into a tea. The leaves may also be ingested in powder or capsule form. Psychotomimetic effects occur within 5 to 10 minutes of use and may persist for 1 hour, with stimulatory effects at lower doses and opioid effects at higher doses. Opioid properties include analgesic, antitussive, antidiarrheal, and emetogenic effects. Reports in the medical literature include intrahepatic cholestasis after abuse for 2 weeks.[23]

Currently, there are no clinical diagnostic tests available to detect the presence of kratom alkaloids. Treatment of intoxication is supportive. Although coma and opioid activity have been demonstrated with kratom,[24] the effectiveness of opioid antagonists in reversing its effects is inconsistent. A withdrawal syndrome characterized by anxiety, restlessness, and nausea treated with an opioid agonist and lofexidine (an α_2-agonist related to clonidine) has also been reported.[25]

Fig. 150.5. *Amanita muscaria* mushroom. (Photo by Mark Shubert, copyright 2004. Accessed at www.erowid.org.)

Ibogaine

Ibogaine is a naturally occurring indole alkaloid found in the roots of the African rain forest shrub *Tabernanthe iboga*. For many centuries, iboga has been ingested by the indigenous peoples of western Africa as a remedy for fatigue, hunger, and thirst and as a sacrament in religious ceremonies. As with many plant-derived agents, ibogaine's physiologic effects are highly complex and may involve opioid, dopaminergic, serotonergic, glutaminergic, γ-aminobutyric acid (GABA)–ergic, glutamatergic, adrenergic, and cellular ion channel signaling systems.

Although ibogaine is classified as a Schedule I drug, it is still sought after as a treatment to ease opioid withdrawal and diminish craving of other abused drugs. The intensity of visual hallucinations from ingestion of iboga, in contrast to other hallucinogens, are described to be more pronounced with closed eyes. Since the first report in 1990, there have been multiple reported fatalities due to sudden cardiac death within 72 hours of ibogaine use. The mechanism appears to be blockage of the hERG/IKr channel, leading to marked QT prolongation and tachyarrhythmias.[26] There are no specific detection tests for ibogaine, and diagnosis is dependent on a history of exposure because clinical findings are largely nonspecific. Management is predominantly supportive, although patients with markedly prolonged QT intervals and evidence of risk for torsades des pointes may require admission to a monitored setting, treatment with IV magnesium supplementation (magnesium sulfate, 2–4 g IV), electrolyte repletion, and possibly overdrive pacing in rare cases.

Isoxazole Mushrooms

Isoxazole-containing mushrooms include *Amanita muscaria*, *Amanita pantherina*, *Amanita gemmata*, and *Amanita cothurnata*. *A. muscaria* has a red or yellow cap, with white warty structures on its surface, and grows in forests of aspen, birch, fir, or pine trees (Fig. 150.5). It has been used in Siberia for centuries and is often described in folklore and fairy tales (also see Chapter 158).

The active ingredients are the isoxazole derivatives ibotenic acid and its decarboxylation product, muscimol, which are structural analogues of the endogenous neurotransmitters glutamic acid (excitatory) and GABA (inhibitory) and are thought to act at these respective receptor sites. The excitatory effects characterized by elation, giddiness, hyperactivity, muscle tremors, and distortion of space and time begin approximately 30 minutes to 2 hours after ingestion and are likely to be mediated by ibotenic acid. Following is a phase of tiredness and deep sleep, in which it may be difficult to arouse the patient. During this phase, vivid hallucinations and manic excitement may oscillate with periods of deep sleep. The duration of effect is up to 12 hours. Management of the excitatory phase is similar to that of other hallucinogens previously described in this chapter. Prolonged sleep with *A. muscaria* ingestion requires only observation and supportive care. Tonic-clonic seizures are reported, but occurrences are rare.

Because elements of isoxazole poisoning resemble manifestations of anticholinergic toxicity, these mushrooms have also been referred to as anticholinergic mushrooms; however, belladonna alkaloids are not present. Paradoxically, there has been a high incidence of mistreatment of *A. muscaria* ingestion with atropine because the name implies that it contains muscarine, a cholinergic toxin. However, the amount of muscarine is miniscule. Many texts recommend the use of atropine, but atropine may exacerbate the anticholinergic effects associated with isoxazole mushrooms. It is important to differentiate isoxazole-containing *Amanita* mushrooms from the deadly hepatotoxic cyclopeptide-containing *Amanita* mushrooms, of which *Amanita phalloides* is a member.

KEY CONCEPTS

- Hallucinogens include many types of drugs and chemicals with different associated effects, including action at serotonin receptors, dopamine receptors, and NMDA receptors.
- Diagnosis and management are based primarily on the history and physical examination, with hallmarks of therapy including supportive care, a calm quiet environment, and sedation with benzodiazepines such as diazepam or lorazepam. Severely agitated patients may benefit from butyrophenone antipsychotic agents such as haloperidol and droperidol.
- Screening tests for drugs of abuse are of limited value in the acute management of intoxicated patients.
- Novel synthetic hallucinogens continue to emerge and may have effects from hallucinogenic, serotonergic, and dissociative toxidromes. These drugs are rarely detected by screening tests, and cases of toxicity may occur in regional outbreaks.
- Patients with PCP toxicity can have unpredictable, violent behavior, and may sustain traumatic injuries. Extreme agitation, although possible, is less common with ketamine and methoxetamine.
- Extremely agitated, violent PCP-intoxicated patients may require rapid sedation to decrease danger to the patient and providers. For hyperthermic patients, sufficient sedation to decrease neuromuscular hyperactivity may require intubation, paralytics, and active external cooling to decrease the risk of multiorgan failure and mortality.
- The care of patients intoxicated from marijuana and synthetic cannabinoids consists of prevention of injury and reassurance for those who have panic reactions. An extremely agitated patient can be sedated with oral or parenteral administration of benzodiazepines or antipsychotics. High doses of antiemetics may be necessary to treat the nausea and vomiting associated with synthetic cannabinoids and heavy daily marijuana use—cannabinoid hyperemesis syndrome.
- The central nervous system and physiologic effects of mescaline use are similar to those of lysergic acid diethylamide (LSD) derivatives, but more vivid hallucinations can occur. Nausea and vomiting are pronounced and almost always precede the hallucinogenic effects.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 150: QUESTIONS & ANSWERS

150.1. Intoxication with morning glory seeds will mimic intoxication with which of the following hallucinogens?
- **A.** Ecstasy
- **B.** Ketamine
- **C.** LSD
- **D.** Marijuana
- **E.** PCP

Answer: C. Several plants contain alkaloids similar to LSD, including morning glory and Hawaiian baby wood rose.

150.2. A 14-year-old boy presents with altered mental status. On examination he has mydriasis, nystagmus, and lethargy. There is a history of exposure to skittles. His urine drug screen for drugs of abuse is presumptively positive for PCP. Which toxicant did he ingest?
- **A.** Dextromethorphan
- **B.** Ecstasy
- **C.** Ketamine
- **D.** Psilocybin
- **E.** Synthetic cannabinoids

Answer: A. Dextromethorphan presents with more of a dissociative clinical pattern than opioids. Skittles, red hots, and triple C are street names for over-the-counter tablets of dextromethorphan. Most immunoassays for PCP cross-react with dextromethorphan to give a false-positive PCP report. Ketamine can also give a similar clinical picture, so the history is also necessary to determine which is the most likely intoxicant in the differential.

150.3. Which of the following urine immunoassays is most likely to give a true-positive result for its class of compounds?
- **A.** Amphetamines
- **B.** Benzodiazepines
- **C.** Benzoylecgonine (cocaine metabolite)
- **D.** Phencyclidine
- **E.** Tetrahydrocannabinol (THC)

Answer: C. The immunoassay screen for cocaine detects its metabolite, benzoylecgonine. Unlike immunoassays for amphetamines, benzodiazepines, phencyclidine, and THC, which may be highly unreliable, inconsistent, or nonspecific, the immunoassay for benzoylecgonine does not typically result in false-positives or false-negatives. Detection of benzoylecgonine is a specific indication of cocaine use in the past 3 days.

150.4. Which of the following mushroom species has hepatotoxic but not hallucinogenic properties?
- **A.** *Amanita muscaria*
- **B.** *Amanita pantherina*
- **C.** *Amanita phalloides*
- **D.** *Conocybe smithii*
- **E.** *Psilocybe cubensis*

Answer: C. *A. phalloides* mushrooms do not have hallucinogenic properties. Their toxicity is mainly hepatic due to a number of cyclopeptide toxins contained in all parts of the mushroom. *C. smithii* and *P. cubensis* contain psilocybin and psilocin tryptamines. *A. muscaria* and *A. pantherina* contain the isoxazole compounds ibotenic acid and muscimol, which are analogues of glutamic acid (excitatory) and γ-aminobutyric acid (GABA; inhibitory) neurotransmitters, respectively.

CHAPTER 151

Iron and Heavy Metals

Jillian L. Theobald | Mark B. Mycyk

IRON

PRINCIPLES OF TOXICITY

Iron poisoning used to be the leading cause of poisoning death in children. However, in 1997 the U.S. Food and Drug Administration (FDA) required warning labels and implemented changes in the packaging of iron supplements after which there was an abrupt decrease in the number of poisonings and deaths. Although the FDA rescinded its strict packaging restrictions on iron supplements in 2003, iron poisoning currently remains relatively uncommon. In 2013, there were 5249 calls to poison centers concerning iron exposures, yet there were no deaths.[1]

Iron (periodic element 26) is an important metal that is essential to the function of hemoglobin, myoglobin, and many cytochromes and enzymes. Certain disease states result from too much or too little iron, such as hematochromatosis and anemia. Iron is absorbed mostly in the small intestine; depending on total body stores, as little as 10% or as much as 95% of the ingested iron is taken into the cell. In the cell, iron has three fates: storage bound to ferritin, transfer to the serum where it is bound to transferrin, or loss when the intestinal cell is sloughed off. Under normal conditions only 15% to 35% of the iron-binding capacity of transferrin is used. Normal serum iron concentrations range from 50 to 150 μg/dL. The total iron-binding capacity (TIBC), a crude measure of the ability of serum proteins (including transferrin) to bind iron, ranges from 300 to 400 μg/dL. When iron concentrations rise after a significant overdose, transferrin becomes saturated so that excess iron circulates free and unbound in the serum. Unbound iron is directly toxic to target organs.

Iron has two distinct toxic effects: (1) direct caustic injury to the gastrointestinal mucosa, and (2) impaired cellular metabolism, primarily of the heart, liver, and central nervous system (CNS). The caustic effects of iron on the gut cause the initial symptoms of vomiting, diarrhea, and abdominal pain. Hemorrhagic necrosis of gastric or intestinal mucosa can lead to bleeding, perforation, and peritonitis. Unbound iron moves into cells and localizes near the mitochondrial cristae, resulting in uncoupling of oxidative phosphorylation and impairment of adenosine triphosphate synthesis. Cell membranes are injured by free radical–mediated lipid peroxidation. Furthermore, iron increases capillary permeability and leads to both arteriolar dilation and venodilation, resulting in hypotension. Direct myocardial toxicity decreases cardiac output. Hydration of the iron molecule creates an excess of unbuffered protons, worsening metabolic acidosis. These effects, combined with severe gastrointestinal fluid losses, can lead to shock, cardiovascular collapse, and death.

In an iron overdose, determining the amount of *elemental* iron ingested is most important, because cellular toxicity depends on the effects of elemental iron. Different formulations of iron salts contain different percentages of elemental iron (Table 151.1). The total amount of elemental iron ingested can be approximated by multiplying the estimated number of tablets by the fraction of elemental iron contained in the tablet. Ingestions of less than 20 mg/kg of elemental iron usually cause no symptoms. Ingestion of 20 to 60 mg/kg results in mild to moderate symptoms, and ingestion of more than 60 mg/kg may lead to severe morbidity and mortality. Although the dose of elemental iron associated with 50% mortality (LD_{50}) is 200 to 250 mg/kg, doses as small as 130 mg of elemental iron have been lethal in children. Newer forms of iron are carbonyl iron and iron polysaccharide: both are non-ionic and associated with lower toxicity. Neither form is directly corrosive; and the conversion to the iron ion, which is responsible for toxicity, is very slow. There are no reported cases of serious toxicity or death from the ingestion of these compounds.

CLINICAL FEATURES

The clinical effects of acute iron poisoning have traditionally been divided into five stages (Table 151.2), but not every patient experiences the effects of every stage in the same time frame. The severity of phase IV features is primarily dose-related, and it is usually during this phase that fatality occurs.

DIFFERENTIAL DIAGNOSES

Many toxins are irritating to the gastrointestinal tract and can cause nausea, vomiting, and diarrhea. Hemorrhagic gastroenteritis in the setting of an ingestion history should raise suspicions for caustic ingestions, certain alcohols, colchicine, and other heavy metals, such as arsenic, inorganic mercury, and iron.

DIAGNOSTIC TESTING

The presence of gastrointestinal symptoms suggests a potentially serious ingestion, whereas absence of gastrointestinal symptoms is usually reassuring. A serum iron concentration measured at 3 to 5 hours after ingestion is the most useful laboratory test to evaluate the potential severity of an iron overdose. Sustained-release or enteric-coated preparations may have erratic absorption, so the serum concentration should be repeated at 6 to 8 hours after ingestion. Peak serum iron below 350 μg/dL is generally associated with minimal toxicity; 350 to 500 μg/dL, with moderate toxicity; and above 500 μg/dL, with severe toxicity. Because iron is rapidly cleared from the serum and deposited in the liver, the concentration of iron after a substantial ingestion may be deceptively low if it is measured many hours after its peak absorption. TIBC is an inaccurate test and is not useful to gauge the severity of iron poisoning.

A screening abdominal radiograph may also be helpful to confirm a recent large ingestion, and should be interpreted in the context of serum levels, as described later. Most tablets that contain a significant amount of elemental iron are radiopaque (Fig. 151.1), although false-negative radiographs may occur with chewable, liquid, and completely dissolved iron compounds. Repeated radiographs can also demonstrate the efficacy of gastrointestinal decontamination efforts.

MANAGEMENT

Decontamination

Activated charcoal does not bind iron. Both gastric lavage and ipecac are ineffective and not recommended. Symptomatic patients with iron toxicity generally present with vomiting early in the clinical course. Iron tablets clump together as their outer coatings dissolve, often forming large pharmacobezoars. Whole bowel irrigation (WBI) is generally the preferred method of decontamination for significant iron ingestions.[2] Early, rapid decontamination of the gastrointestinal system may obviate the need for or shorten antidotal therapy.

For significant ingestions, especially when the number of tablets identified by abdominal radiography indicates a likely toxic dose, WBI with a polyethylene glycol–electrolyte solution (PEG-ELS) should be initiated.[2] The solution should be administered through a small nasogastric tube. The recommended rate of administration of PEG-ELS is 500 mL/hr in children 9 months to 6 years old, 1000 mL/hr in children 6 to 12 years old, and 1.5 to 2 L/hr in adolescents and adults. WBI is continued until the rectal effluent is clear and there is no radiographic evidence of pill fragments.[2] This technique has been used in children, adolescents, and pregnant women without serious complications or electrolyte disturbances. Common side effects include nausea, vomiting, abdominal cramping, and bloating. WBI is contraindicated in the presence of bowel obstruction, perforation, ileus, or hemodynamic instability.[2]

TABLE 151.1

Common Iron Preparations

COMPOUND	PERCENTAGE OF ELEMENTAL IRON
IONIC COMPOUNDS	
Ferrous sulfate	20
Ferrous fumarate	33
Ferrous gluconate	12
NON-IONIC COMPOUNDS	
Carbonyl iron	100
Iron polysaccharide	46

Fig. 151.1. Radiopaque iron tablets *(arrow)* seen on abdominal radiograph. (From Craig SA: Radiology. In Ford MD, Delaney KA, Ling LJ, et al, editors: Clinical toxicology. Philadelphia, 2001, WB Saunders, p 62.)

TABLE 151.2

Clinical Manifestations of Iron Toxicity Following an Acute Overdose*

	PHASE	CLINICAL FEATURES	MECHANISM OF TOXICITY
1	Gastrointestinal (6 hours)	Vomiting Diarrhea Hematemesis Hematochezia	Corrosive effect of iron on the gastrointestinal mucosa
2	Latent (6 to 24 hours)	Resolution of gastrointestinal symptoms Tachycardia Acidosis Depressed mental status	Ongoing cellular toxicity and organ damage
3	Systemic (12 to 24 hours)	Return of gastrointestinal symptoms Acidosis Leukocytosis Coagulopathy Renal failure Lethargy or coma Cardiovascular collapse	Iron distributes to the tissues with worsening cellular toxicity and organ damage
4	Hepatic (2 to 5 days)	Fulminant liver failure Coagulopathy	Rapid absorption from portal system with resultant oxidative damage
5	Obstructive (3 to 6 weeks)	Pyloric or bowel scarring Obstruction	Healing of the injured gastrointestinal mucosa

*Typical duration of symptoms, post-ingestion is also given.

Enhanced Elimination

Hemodialysis and hemoperfusion are not effective in the removal of iron because of its large volume of distribution. On the other hand, early exchange transfusions have been used with some success for severely symptomatic patients. However, this should only be considered in patients who are not responding to standard therapy.

Antidotal Therapy

Deferoxamine is the specific antidote for iron toxicity. Deferoxamine chelates iron to form the water-soluble compound ferrioxamine, which is renally excreted. Deferoxamine binds to free iron and will not chelate iron from hemoglobin, transferrin, or ferritin. Patients with an iron concentration above 500 µg/dL and those who, regardless of level, are exhibiting severe signs and symptoms of iron toxicity (such as, metabolic acidosis, repetitive vomiting, toxic appearance, lethargy, hypotension, or signs of shock) require chelation. Pregnancy is not a contraindication to deferoxamine. However, the pre-pregnancy weight should be used to calculate the ingested dose. Because of its short half-life, deferoxamine is administered as a continuous intravenous infusion at 15 mg/kg/hr for up to 24 hours. The maximum rate of administration is 35 mg/kg/hr. More rapid administration of deferoxamine can lead to hypotension, which is managed by reducing the initial rate of the infusion and then slowly increasing it to the desired rate. Deferoxamine has been associated with acute respiratory distress syndrome and also with *Yersinia* sepsis. The pulmonary complications are usually related to high-dose deferoxamine for durations longer than 24 hours.

DISPOSITION

The asymptomatic patient who is reliably known to have ingested less than 40 mg/kg of elemental iron does not need additional therapy and can be discharged home after appropriate poison prevention counseling. In patients who ingest more than 40 mg/kg, an iron concentration should be obtained at 3 to 5 hours post-ingestion and also 6 to 8 hours post-ingestion. If peak iron remains less than 300 µg/dL, is not rising, and the patient is asymptomatic during 6 hours of observation, the patient can be discharged home. If the patient is exhibiting signs of severe toxicity, even if the ingested dose is unknown, or meets criteria for deferoxamine, admission to an intensive care unit and poison center or toxicologist consultation is advised. If indicated, a psychiatric consultation should be requested.

LEAD

PRINCIPLES OF TOXICITY

Lead poisoning remains one of the most common and preventable environmentally mediated problems in the United States. The elimination of leaded gasoline and the ban on leaded paint in households in the 1970s exponentially reduced the number of lead poisonings in the United States. However, the Center for Disease Control and Prevention (CDC) estimates that approximately 535,000 children, aged 1 to 5 years old, still have elevated blood lead levels (BLLs) from various environmental exposures.[3] Immigrant and refugee children are at much greater risk for lead poisoning than children born in the United States because of diet and other exposure risks prior to arrival in the United States.[4,5] The CDC also estimates 1.2 million adult workers have BLLs above 25 µg/dL based on a workplace surveillance program. Given the continued wide use of lead in industry, there are many potential sources of exposure (Table 151.3).

TABLE 151.3

Sources of Lead Exposure

CATEGORY	SOURCE
Pediatric	Lead dust Paint in old homes Parent's occupation Imported toys or candies Foreign body ingestion (fishing weights, toys)
Occupational	Construction, old home rehab Lead smelters Battery recycling, repair, and manufacturing Firing range instructors Automobile mechanics Plastics manufacturing
Recreational	Moonshine Ceramics Home and car remodeling Painting
Other	Herbal remedies Retained lead bullets

Most lead exposures occur by ingestion in children and workplace inhalation in adults. Dermal absorption may also occur but is much less significant. Children and pregnant woman absorb almost four times the amount of ingested lead than other adults. Once absorbed, lead is bound to red bloods cells and slowly distributes to the soft tissues where it is eventually stored primarily in bone. Lead easily crosses the placenta, and maternal blood levels correlate with cord blood levels.[6] Neonatal lead exposure also occurs through breast milk. The half-life of lead in the red blood cell is about 30 days, but once in the bone the half-life lasts decades. Most lead is excreted in the urine and bile.

There is no biological role for lead in the human body. Lead (periodic element 82) complexes with sulfhydryl groups of proteins, which can alter enzyme and receptor function and distort structural proteins. Lead is also structurally similar to calcium and interferes with calcium dependent cellular processes. Its toxic effects are most prominent in the hematopoietic and neurologic systems.

CLINCAL FEATURES

The clinical features of lead poisoning are broad and often nonspecific (Table 151.4). Symptoms depend on the BLL, whether the patient is an adult or child, and whether the exposure is acute or chronic. Although all organ systems are affected, the most sensitive are hematologic, vascular, and nervous systems. Because routine lead screening is done less commonly today, many cases are now identified as a result of an anemia evaluation. Through inhibition of heme biosynthesis, the classic manifestation of hematopoietic lead toxicity is anemia. Anemia may be either normochromic or hypochromic. Chronic kidney disease and hyperuricemic gout ("saturnine gout") can also result from elevated BLLs. Chronic kidney disease consequently may worsen underlying anemia. Lead poisoning has been shown to be associated with hypertension. In the peripheral nervous system, segmental demyelination and degeneration of motor axons result in peripheral neuropathy. Wrist-drop and foot-drop are characteristic of adult lead poisoning but rarely seen today.[7] Most importantly, lead toxicity causes many different neuropsychiatric disorders. Many are difficult to distinguish during an emergency department (ED) evaluation, so collaboration with a primary physician is

TABLE 151.4

Typical Blood Lead Levels and Correlative Signs and Symptoms in Children and Adults

LEVEL (μg/dL)	SYMPTOMS	
	ADULTS	CHILDREN
10	None	Decreased IQ Decreased hearing Decreased growth
20	Increased protoporphyrin No symptoms	Decreased nerve conduction velocity Increased protoporphyrin
30	Increased blood pressure Decreased hearing	Decreased vitamin D metabolism
40	Peripheral neuropathies Nephropathy Infertility (men)	Decreased hemoglobin synthesis
50	Decreased hemoglobin synthesis	Lead colic
70	Anemia	Anemia Encephalopathy Nephropathy
100	Encephalopathy	Death

IQ, Intelligence quotient.

essential to identify new deficits. In children, elevated BLL is associated with decreased intelligence quotient (IQ) scores, hyperactivity, decreased attention span, overaggressive behavior, learning disabilities, and criminal behavior.[8] Severely high BLLs may present with lead encephalopathy associated with increased capillary permeability and cerebral edema.

DIFFERENTIAL DIAGNOSES

The differential diagnosis of lead poisoning is broad, and because the symptoms of early poisoning are so nonspecific, lead poisoning today is often initially misdiagnosed. Lead poisoning could be confused for neuropathies (such as, carpal tunnel or Guillain-Barre syndrome) or abdominal pathologies (such as, gastroenteritis, nephrolithiasis, or appendicitis).[7,9,10] The subtle neuropsychiatric signs in children can also be misdiagnosed as attention deficit hyperactivity disorder or other behavioral disturbances. Therefore, it is necessary to consider lead poisoning in the appropriate circumstance, particularly where another diagnosis is not established as the cause of the presentation. Perform a careful and detailed neurologic examination, and evaluate patients for potential sources of exposure.

DIAGNOSTIC TESTING

Lead toxicity rarely presents primarily to the ED. Most patients encountered in the ED have been referred for management of an elevated screening BLL done in clinic or workplace surveillance program. Some patients may seek ED care following an ingestion of a leaded foreign body or with worrisome symptoms and an exposure history. Diagnostic testing should consist of a venous BLL, including those cases referred in for an abnormal screening test, because those screens may be falsely elevated. If the patient is symptomatic, other tests include a complete blood cell count, basic metabolic panel, liver functions tests, and urinalysis. A peripheral smear classically shows basophilic stippling, but that finding is relatively rare. Because lead-containing objects and paint chips are radiopaque, abdominal radiographs can confirm acute ingestion and determine the need for bowel decontamination. In cases of altered mental status, seizures, or coma, a computed tomography (CT) scan of the head may show cerebral edema associated with acute lead encephalopathy and rule out other causes of these neurologic signs. In children, plain radiographs of the wrist and knees classically demonstrate increased metaphyseal activity termed as "lead lines" that are characteristic of chronic exposures. However, such x-rays do not need to be routinely done in the ED.

MANAGEMENT

The most important treatment step in lead poisoning is removing the patient from the source. This is the only treatment needed in most cases of lead poisoning. However, determining the exact source often requires the collaborative assistance of a primary care physician, social workers, and the department of public health. Recent data suggest urban patients at risk for lead poisoning are also at risk for asthma—the environmental evaluation for lead and asthma risks is similar, so ensuring follow-up with a primary care provider to assess the risk for both problems is essential.

Decontamination

Activated charcoal does not bind lead. If an abdominal radiograph demonstrates lead within the gastrointestinal tract, particularly the stomach and small intestine, or a leaded foreign body or multiple foreign bodies are present, then bowel decontamination should be performed. This can be done with WBI or repeated polyethylene glycol administration (see the Iron section for dosing regimen).

Antidotal Therapy

Children

Treatment for lead toxicity rarely is commenced in the ED. Information on chelation therapy is provided here for reference. Evidence indicates no benefit from chelation for children with a BLL lower than 45 μg/dL. A BLL between 20 and 44 μg/dL in a patient who is asymptomatic or minimally symptomatic requires a medical and environmental evaluation to identify the source and stop further exposure. Children with lead levels of 5 to 19 μg/dL require caregiver education about worrisome symptoms and sources of lead exposure with close follow-up with a primary caregiver. An environmental evaluation can often be arranged with the local public health department.

Blood lead levels of 45 to 69 μg/dL in patients without vomiting or CNS symptoms can be managed in the outpatient setting with oral succimer (2,3-dimercaptosuccinic acid [DMSA]; Chemet). The initial dose of succimer is 10 mg/kg every 8 hours for 5 days, then 10 mg/kg every 12 hours for 14 days. The most common adverse reactions include nausea, vomiting, diarrhea, and transient elevations in liver transaminase levels. Although succimer has been FDA approved only for children, it is effective and also used for adults. Table 151.5 summarizes available chelating agents with indications and doses. Any patient treated on an outpatient basis should be discharged to a lead-free environment.

Patients with a BLL of 69 μg/dL or higher require hospitalization and parenteral chelation therapy, even if asymptomatic or minimally symptomatic. Evidence of encephalopathy also requires admission for parenteral chelation therapy. Consultation with a medical toxicologist, regional poison center, and pediatrician is indicated. Dimercaprol (or British anti-Lewisite [BAL]) should be given first at a dose of 75 mg/m^2 by deep intramuscular injection

TABLE 151.5

Chelators

CHELATOR	DOSAGE	INDICATIONS	CONTRAINDICATIONS
Deferoxamine	15 mg/kg/hr up to 24 hours (titrate up slowly because of hypotension)	*Iron* level >500 g/dL or systemic symptoms	
Dimercaprol (BAL)	*Lead encephalopathy:* 75 mg/m^2 deep IM injection every 4 hours for 5 days in children or 4 mg/kg every 4 hours for adults *Arsenic (severe):* No established regimen; consider 3 mg/kg IM every 4 hours for 48 hours, then twice daily for 7 to 10 days *Mercury:* 5 mg/kg IM first, then 2.5 mg/kg every 12 to 24 hours	*Lead* level >70 μg/dL or encephalopathy *Arsenic:* Symptomatic patient with known exposure *Mercury:* Inorganic	Peanut allergy Organic mercury poisoning
$CaNa_2EDTA$	1500 mg/m^2/day continuous intravenous infusion 50 mg/kg/day or 1000 mg/m^2/day in two to four divided doses for up to 5 days if less severe symptoms	*Lead* level of 70 μg/dL or encephalopathy (given after first dose of BAL)	
Succimer (DMSA)	10 mg/kg every 8 hours for 5 days, then every 12 hours for 14 days	*Lead* level of 45 to 69 μg/dL *Arsenic*: If tolerated orally for subacute and chronic toxicity *Mercury*: Acute and chronic	
D-Penicillamine	25 mg/kg every 6 hours for 5 days	*Lead* level of 45 to 69 μg/dL, succimer not tolerated *Arsenic*: Only if BAL and DMSA are unavailable *Mercury*: If BAL and DMSA are unavailable or not tolerated	Penicillin allergy
DMPS (investigational)	5 mg/kg/dose IM every 6 to 8 hours; day 1, every 8 to 12 hours; day 2, every 12 to 24 hours; day 3 and until 24-hour urine is <50 μg/L	*Lead* (chronic) *Arsenic* *Mercury*	

Note: Indications for chelation and dosing regimens may change. Consult with a medical toxicologist or regional poison center for the most up-to-date recommendations.
BAL, British anti-Lewisite; *$CaNa_2EDTA$,* calcium disodium ethylenediaminetetraacetic acid; *DMPS,* ***; *DMSA,* 2,3-dimercaptosuccinic acid; *IM,* intramuscular.

every 4 hours for 5 days for children or 4 mg/kg every 4 hours for adults. Adverse reactions to BAL include nausea, vomiting, urticaria, pyrexia, hypertension, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. Because BAL is diluted in peanut oil, it is contraindicated in patients allergic to peanuts. In cases of encephalopathy, intravenous calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) should be initiated with the second dose of BAL, because starting treatment with $CaNa_2EDTA$ may paradoxically increase lead transport across the blood brain barrier. The dosage of $CaNa_2EDTA$ for patients with acute lead encephalopathy is 1500 mg/m^2/day (approximately 50 to 75 mg/kg/day) given by continuous intravenous infusion also for 5 days. Adverse reactions include renal tubular injury and chelation of other metals, especially iron and zinc. $CaNa_2EDTA$ should be given only with adequate urine flow or with hemodialysis in the patient with renal failure. For patients with a BLL more than 69 μg/dL but no signs of encephalopathy, the dosage of $CaNa_2EDTA$ is 50 mg/kg/day or 1000 mg/m^2/day, given in two to four divided doses for up to 5 days without the need for concurrent BAL.

Adults

The treatment of adults with chronic poisoning is based primarily on symptoms and threshold treatment BLLs established by workplace regulatory agencies. In the asymptomatic adult or the adult with only mild clinical problems, the only intervention needed is cessation of exposure. According to the Occupational Safety and Health Administration (OSHA) lead standard, workers with serum lead levels above 40 μg/dL should be removed from work. If encephalopathy or severe symptoms are present, then hospitalization and chelation therapy with combined BAL and $CaNa_2EDTA$, as in children, are indicated. Pregnant women should be treated in accordance with adult treatment guidelines. Lead does cross the placenta and can accumulate in the fetus. The newborn may require chelation as well.

DISPOSITION

Families of asymptomatic children with BLLs less than 45 μg/dL and asymptomatic adults should be counseled on how to avoid further exposure and given close follow-up with their primary care provider for a repeat BLL and further exposure risk evaluation.

Patients who require oral chelation can be discharged home if they can tolerate succimer and if it can be ensured they do not return to a lead-contaminated environment. The health department should conduct an environmental assessment and other family member testing so that the primary source of lead exposure can be identified and further exposure prevented. Follow-up should be arranged with an experienced pediatrician, toxicologist, or occupational medicine physician.

Patients who are significantly symptomatic, have worrisome CNS symptoms, and any children with a BLL of 69 μg/dL or higher require hospitalization for environmental exposure evaluation and chelation therapy.

ARSENIC

PRINCIPLES OF TOXICITY

Arsenic (periodic element 33) has an infamous history as an agent of homicide and been implicated in mass environmental poisonings.[11] Currently, arsenic exposure is primarily environmental and occupational. Arsenic is found in smelters and electric power plants that burn arsenic-rich coal; in the production of glass and microcircuits; and in rodenticides, fungicides, insecticides, paint, tanning agents, defoliants in the cotton industry, and in wood preservatives. Arsenic is also still used for medicinal purposes in the treatment of trypanosomiasis, amebiasis, and leukemia. Importantly, significant concentrations of arsenic have been found as a contaminant in ayurvedic medications.[12] Arsenic has also been reported in low-income countries with large environmental poisonings via well water.

Arsenic exists in different forms: elemental, organic, inorganic, and gaseous. Elemental arsenic (As) is a metal that is poorly water soluble and is considered nontoxic. Organic arsenic, found in shellfish, is also generally non-toxic. Of the two inorganic forms, trivalent arsenite (As^{3+}) is more toxic than the pentavalent arsenate (As^{5+}) form.[13] Absorbed arsenic is bound by hemoglobin, leukocytes, and plasma proteins. It is cleared from the intravascular compartment within 24 hours and concentrates in the liver, kidneys, spleen, lungs, and gastrointestinal tract. Arsenic crosses the placenta and can also accumulate in the fetus. Inorganic arsenic interferes with normal cellular metabolic function, energy generation, and induces apoptosis. Arsenic also generates reactive oxygen species and induces oxidative damage in the cell.[13] Gaseous arsenic in the form of arsine (AsH_3) is colorless, almost odorless, and extremely toxic. It is immediately lethal at 250 ppm. The excretion of arsenic and its metabolites occurs mainly through the kidneys. Arsenic has no metabolic or biologic function.

CLINICAL FEATURES

Acute Arsenic Toxicity

Gastrointestinal effects including nausea, vomiting, abdominal pain, and diarrhea predominate as the initial manifestations of acute exposure to inorganic arsenic.[14] The diarrhea has often been described as "rice water-like" and difficult to differentiate from diarrhea induced by cholera infection. These symptoms can be so severe as to be manifested with hematemesis and hematochezia. The patient can also have encephalopathy with seizures and coma, respiratory failure associated with acute respiratory distress syndrome, and dysrhythmias associated with cardiac conduction disturbances, such as QT prolongation and torsade de pointes (Box 151.1). In cases of severe poisoning, cardiovascular collapse and death ensue. Early arsenic poisoning syndrome may be misdiagnosed as gastroenteritis or sepsis. For those who survive the initial gastrointestinal illness, chronic effects of arsenic poisoning appear weeks to months later. These include characteristic lines in the nails (Aldrich-Mees lines; Fig. 151.2), painful sensorimotor neuropathy, and hyperkeratosis of the palms and soles.

Fig. 151.2. Mees lines seen on the fingernails of a patient. (From Chauhan S, D'Cruz S, Singh R, et al: Mees' lines. Lancet 372[9647]:1410, 2008.)

BOX 151.1

Acute Effects of Arsenic Poisoning

GASTROINTESTINAL
Severe gastroenteritis; hematemesis or hematochezia
Jaundice
Pancreatitis
Dysphagia
Hepatomegaly

CARDIOVASCULAR
Third spacing with shock
Sinus or ventricular tachycardia
Prolonged QT interval, ST depression, T wave inversion
Torsades de pointes
Pericarditis

RESPIRATORY
Respiratory failure
Acute respiratory distress syndrome
Pulmonary edema
Pneumonia

RENAL
Proteinuria
Hematuria
Oliguria
Renal failure

NEUROLOGIC
Headache
Drowsiness
Delirium
Coma
Encephalopathy
Seizures

Chronic Arsenic Toxicity

Chronic exposure to arsenic, typically through contaminated drinking water or occupational exposure, is associated with cardiovascular disease, diabetes mellitus, and dermatological disease both malignant and nonmalignant.[15-17] Furthermore, patients chronically exposed to arsenic have an increased risk of bladder, kidney, liver, and lung cancer.[18,19]

Arsine Gas

Acute exposure to arsine gas is characterized by severe hemolysis that is also associated with renal tubular injury.[20] Signs of toxicity are usually evident within minutes to hours after exposure. Gastrointestinal symptoms are common, and CNS and liver dysfunction can occur.

DIFFERENTIAL DIAGNOSES

Acute arsenic poisoning is often misdiagnosed as some form of gastroenteritis or gastrointestinal bleeding. Hemorrhagic gastroenteritis in the setting of an ingestion history should raise suspicion for caustic ingestion, heavy metals, and iron. Obtaining an environmental and occupational exposure history is important to help discern the etiology of the patient's symptoms.

DIAGNOSTIC TESTING

To diagnose arsenic poisoning accurately, a 24-hour urine collection should be done. Spot urine samples are inaccurate and do not guide therapy. Normal arsenic concentrations are 5 μg/L or less in blood or less than 50 μg/day in a 24-hour urine collection. Any urine level above 100 μg/day or 50 μg/L necessitates treatment. Seafood contains arsenobetaine, which can significantly increase total urine arsenic concentrations, but arsenobetaine does not result in toxicity. For this reason, patients should refrain from eating seafood, specifically shellfish, before testing, and the laboratory should be asked to speciate the type of arsenic measured.[21] Most patients referred to the ED for management of abnormal urine arsenic tests today are not arsenic toxic; their urine tests are falsely abnormal because laboratories do not routinely differentiate between arsenobetaine and inorganic arsenic. In cases of chronic arsenic poisoning or remote exposure, the serum and urine arsenic levels may no longer detect abnormal concentrations of arsenic.

Other laboratory results may suggest arsenic poisoning. Anemia, leukocytosis or leukopenia, and erythrocyte basophilic stippling may be seen in the complete blood cell count. The results of renal function tests may be abnormal, demonstrating proteinuria, hematuria, and pyuria. The alanine transaminase, aspartate transaminase, and bilirubin levels may be elevated.

Arsenic in the gastrointestinal tract is radiopaque and can appear on a radiograph, although sensitivity is limited by its rapid absorption and the ensuing gastroenteritis.

MANAGEMENT

Initial management of arsenic poisoning should address life-threatening conditions with supportive care of shock, dysrhythmias, and seizures.

Decontamination and Enhanced Elimination

As is the case with other metals, activated charcoal does not adsorb arsenic and is not recommended. Hemodialysis may remove some arsenic in the setting of acute renal failure. Exchange transfusions or plasma exchange can be done early after a severe arsine exposure. These treatments should be initiated in the intensive care setting for critically ill patients and in consultation with a medical toxicologist.

Antidotal Therapy

Acute Arsenic Poisoning

With a confirmed history of exposure in a symptomatic patient, chelation should start as early as possible without waiting for laboratory confirmation. Intramuscular BAL is the preferred chelator in patients who are critically ill as described for lead poisoning. Succimer can be given orally, but its use is often limited by the severe gastroenteritis resulting from arsenic poisoning. D-Penicillamine has a high side effect profile and is much less effective than BAL or succimer, so it should be used only when BAL or succimer are unavailable. Table 151.5 summarizes available chelating agents with indications and doses. Chelation is not useful for arsine gas exposures. With arsine gas poisoning, exchange transfusion, continuous venovenous hemodialysis, and plasma exchange have been used to remove arsine, which is tightly bound to erythrocytes.[22] Fluid resuscitation helps kidney perfusion early after exposure.

Chronic Arsenic Poisoning

Treatment of chronic arsenic toxicity should begin in a symptomatic patient after confirmation of elevated urinary arsenic levels. Oral chelation with succimer is the treatment of choice. Workers should modify their habits to avoid further absorption, and repeated monthly 24-hour urine collections can follow arsenic excretion. Chelation treatment in patients with chronic exposure but no detectable arsenic in blood or urine has not been proven to be effective.

DISPOSITION

All patients who are severely ill and those receiving chelation for acute arsenic toxicity should be admitted. Chronic arsenic exposure in a mildly symptomatic patient can be discharged home after removal from the source of exposure and close follow-up with occupational medicine or a medical toxicologist is ensured. Those who are asymptomatic with normal physical examination and vital signs can be sent home.

MERCURY

PRINCIPLES OF TOXICITY

Mercury (periodic element 80) is a silver-white metal, familiar to most as one of the few metals that is liquid at room temperature in its elemental form. Others include bromine and gallium. It has a long history of medicinal uses as an antiparasitic, a diuretic, a cathartic, an antiseptic, and a preservative in many vaccines.[23]

Significant poisoning can occur in the home and also in the work place.[24] Mercury has many industrial uses that include the manufacture of fluorescent lights, batteries, polyvinyl chloride, and latex paint. Recently, artisanal small scale gold mining has become a significant source of global mercury pollution and toxicity.[25] For these reasons, mercury is a common pollutant of air and water.[26] This has led to restrictions in the consumption of fish caught in many local waters, especially by pregnant women and children.

Like other metals, mercury exists in different forms and toxicity depends on the form of exposure: elemental, organic, and inorganic. The most familiar form of mercury is elemental or "metallic" mercury, also known as *quicksilver*. A common route of exposure

to elemental mercury is the inhalation of volatilized vapor during mining or after vacuuming up a spill. After inhalation, metallic mercury is retained in the lung that can result in pneumonitis and acute respiratory distress syndrome; systemic absorption may also occur.[27] Subcutaneous and intravenous injections also cause poisoning from systemic absorption.[28] Aspiration of elemental mercury results in primary pulmonary toxicity in addition to CNS and renal toxicities.[29] Elemental mercury is not well absorbed by the gastrointestinal tract and toxicity is unlikely by this route.[30]

Inorganic mercury salts have two different valences: Hg^{1+} *(mercurous)* and Hg^{2+} *(mercuric)*. Ingestion of either salt leads to significant gastrointestinal and renal toxicity. Inorganic salts have a direct corrosive effect on the gastrointestinal tract with third spacing and hemorrhage.

The organic mercury compounds are categorized as either short chain *(alkyl)* or long chain *(aryl)*. The major route of exposure to this type of mercury is through ingestion, but these compounds are also readily absorbed through the skin. These organic forms classically result in delayed neurotoxicity, and most medical evidence about this form of toxicity comes from large population epidemics.[31] Recent concerns about mercury poisoning from excessive fish consumption are extrapolations from those epidemics.

Mercury has no known physiologic role. Mercury binds covalently to sulfhydryl groups, disturbing multiple cellular enzyme functions. Nephrotoxicity results from both direct damage and an immune reaction in the kidney.[32] Mercury exposure affects both the cardiovascular system and the CNS. Mercury may lead to hypertension and other cardiovascular problems. Mercury also inhibits microtubule organization in the nervous system, which is vital to its function. The mechanisms by which these effects occur are still being discovered.[33] Although mercury used to be a preservative in various vaccines, it is important to note the dose in those vaccines is relatively low, and mercury has not been confirmed to be a cause for autistic spectrum disease.

CLINICAL FEATURES

The clinical manifestations of mercury poisoning depend on the acuity of the exposure, the route of exposure, and the chemical form of mercury (Table 151.6).

DIFFERENTIAL DIAGNOSES

Hemorrhagic gastroenteritis in the setting of an ingestion history should raise suspicions for caustic ingestion, heavy metals, and iron. Respiratory distress from elemental mercury inhalation can also be mistaken for pneumonia, asthma, or influenza. Obtaining an environmental and occupational exposure history is important to help discern the etiology of the patient's symptoms.

DIAGNOSTIC TESTING

Measurement of 24-hour urine mercury concentration is the most helpful test in confirming exposure and monitoring the effectiveness of chelation. For organic mercury compounds, which undergo little urinary excretion, serum concentration should be used to confirm the diagnosis. "Normal" mercury is considered to be less than 10 µg/L in the blood or less than 20 µg/L in the urine. Blood concentration above 35 µg/L and urine above 150 µg/L require intervention. Fish can be contaminated with mercury, especially larger fish and those from certain bodies of water known by local health departments to be most polluted. Individuals eating these locally caught fish will have elevated mercury levels. Elemental (metallic) mercury is radiopaque on plain radiographs, which can be ordered in cases of injection or ingestion of elemental mercury (Figs. 151.3 and 151.4).[28]

TABLE 151.6

Mercury Poisoning and Clinical Manifestations Based on Route of Exposure and Form of Mercury

TYPE OF MERCURY AND ROUTE OF EXPOSURE	SIGNS AND SYMPTOMS
Inhalation of metallic mercury	Hypoxemia, dyspnea, chest tightness Fever, chills Burning in mouth and throat Nausea, vomiting, bloody diarrhea Renal tubular necrosis
Aspiration of metallic mercury	Aspiration pneumonitis, ARDS
Subacute or chronic inhalation of metallic mercury	Metal fume fever Neuropsychiatric symptoms Renal dysfunction Skin changes
Ingestion of inorganic mercury salts	Severe hemorrhagic gastroenteritis, shock, hypovolemia, third spacing Acute tubular necrosis
Subacute or chronic inhalation of mercury	Neurasthenia, erethism, acrodynia
Organic mercury exposure (methyl-, diethyl-)	Delayed neurologic problems (ataxia, tremor, dysarthria) Visual field constriction Hearing loss Spasticity Hyperreflexia

ARDS, Acute respiratory distress syndrome.

Fig. 151.3. Radiograph of the hand showing elemental mercury deposits in the subcutaneous tissue of a patient who was injecting chronically subcutaneously. (Courtesy Dr. Steven Aks.)

MANAGEMENT

Initial management in the acutely poisoned patient is supportive. Activated charcoal and other gastrointestinal decontamination strategies are not recommended.

For acute inhalational exposures, the patient should be removed from the source and supportive management provided. There is

Fig. 151.4. Radiograph of the chest showing elemental mercury deposits in a patient who was injecting chronically subcutaneously. (Courtesy Dr. Steven Aks.)

no role for prophylactic antibiotics or steroids. Suction and postural drainage are indicated in cases of acute aspiration of metallic mercury. Self-injection of metallic mercury may require surgical débridement of infiltrated tissue.[28]

BAL is used for clinically significant acute inorganic mercury intoxication. Because BAL may increase transport of mercury into the brain in patients with organic methylmercury poisoning, BAL is contraindicated for patients poisoned with organic mercury compounds.[34] Succimer has been used for both acute and chronic mercury poisoning and may be the best available chelator for methylmercury. D-Penicillamine may also be used but should be administered as long as no additional mercury is present in the gastrointestinal tract, because mercury absorption from the intestinal lumen may be enhanced by the penicillamines. Table 151.5 summarizes available chelating agents with indications and doses.

DISPOSITION

Ingestion of inorganic mercury in patients with any symptoms warrants admission for further evaluation and supportive treatment. Patients who self-inject metallic mercury may need surgical consult for surgical débridement; this may be done as an outpatient if no symptoms or abnormal signs are evident. Patients with signs of neurotoxicity from organic mercury need admission. Asymptomatic patients with exposure to any form of mercury warrant environmental counseling, and those with concerns from excessive fish consumption need primary care or medical toxicologist follow-up as outpatients for dietary counseling and testing if indicated.

KEY CONCEPTS

- Asymptomatic patients seeking ED care for an abnormal metal test need follow-up evaluation arranged with a medical toxicologist.
- Metal testing in the ED should only be ordered in consultation with a medical toxicologist or regional poison center.
- Acute ingestion of the salts of most metals causes rapid severe gastrointestinal pain and emesis.
- Any abnormal neurologic signs in a patient with any metal exposure warrants admission for further evaluation and chelation therapy.
- Acute iron poisoning can result in gastrointestinal symptoms, metabolic acidosis, and hepatoxicity. Serum iron levels at 3 and 6 hours after ingestion determine toxicity and need for therapy.
- The chelation agent of choice for severe iron poisoning is deferoxamine and is indicated for peak serum iron concentrations greater than 500 μg/dL and patients with severe signs and symptoms regardless of the iron level.
- The most important intervention for lead poisoning is removal from the source of exposure.
- The gastrointestinal decontamination method of choice for iron and lead toxicity with radiographic presence of pills or paint chips is WBI.
- The chelation agent of choice for acute arsenic poisoning is intramuscular British anti-lewisite (BAL) or oral succimer.
- Elemental mercury is nontoxic to the gastrointestinal tract but may cause pulmonary and CNS toxicity from inhalation of volatilized vapors.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 151: QUESTIONS & ANSWERS

151.1. Which of the following laboratory tests is most useful in a suspected iron overdose?
- **A.** Aspartate aminotransferase
- **B.** Ferritin
- **C.** Serum iron
- **D.** Total iron-binding capacity (TIBC)
- **E.** Transferrin

Answer: C. The serum iron level is most helpful when it is measured at its peak, 3 to 5 hours after ingestion, and is the most useful to predict toxicity. Levels below 350 µg/dL are generally safe, whereas levels above 500 µg/dL indicate the potential for severe toxicity. At levels in between, the severity of the symptoms guides treatment.

151.2. A 20-year-old man presents after an iron overdose. An abdominal radiograph shows many radiopaque objects in his stomach, consistent with iron tablets. You decide to try to decrease the gastrointestinal absorption of the iron. Which of the following methods is most effective?
- **A.** Activated charcoal
- **B.** Gastric lavage
- **C.** Surgical removal
- **D.** Syrup of ipecac
- **E.** Whole bowel irrigation (WBI)

Answer: E. WBI is the preferred method to minimize iron absorption. WBI should not be routinely used is small overdoses or with mild symptoms, but it should be considered when a significant ingestion is suspected or when multiple tablets are identified by radiography. Iron is not adsorbed to activated charcoal. Gastric lavage and syrup of ipecac do not remove significant amounts of iron. Open surgical removal of tablets has been used in the past and is effective, but it is obviously invasive and has a higher rate of adverse outcomes than WBI.

151.3. A 5-year-old boy presents with abdominal pain, nausea, vomiting, and bloody diarrhea. The boy was found rummaging through his grandmother's medicine cabinet and may have ingested some of her medications. His vital signs are significant for hypotension and tachycardia. An electrocardiogram (ECG) shows only sinus tachycardia. Laboratory tests are significant for an anion gap acidosis, hyperglycemia, and moderate leukocytosis. Which of the following medications did he most likely ingest?
- **A.** Digoxin
- **B.** Diltiazem
- **C.** Iron
- **D.** Metformin
- **E.** Metoprolol

Answer: C. Iron toxicity typically presents with gastrointestinal symptoms including occasional bleeding soon after ingestion. The previously mentioned laboratory findings are also typical. Digoxin toxicity can also be manifested with gastrointestinal symptoms, but there is usually no gastrointestinal bleeding and there are also typically ECG changes. Beta-blocker toxicity, such as with metoprolol, is manifested with hypotension and bradycardia, as well as

with hypoglycemia. Calcium channel blocker toxicity, such as with diltiazem, can be manifested with gastrointestinal symptoms, acidosis, and hyperglycemia. However, patients typically have bradycardia, and gastrointestinal bleeding is not expected. Metformin toxicity is manifested with gastrointestinal upset, typically without bleeding. Lactic acidosis can result, but the vital sign abnormalities and other laboratory results are not expected.

151.4. A 45-year-old man presents with difficulty walking and fatigue. His vital signs are normal. His physical examination is significant for pale conjunctiva and a foot-drop. Serum electrolyte values are normal. A complete blood count is significant for a hypochromic anemia. Which of the following metals is most consistent with these findings?
A. Arsenic
B. Iron
C. Lead
D. Mercury
E. Tin

Answer: C. Lead principally affects the hematopoietic, neurologic, and renal systems. Typically, there is a hypochromic or normochromic anemia. Peripheral neuropathies can occur and often result in a wristdrop or footdrop. Lead also causes neuropsychiatric changes. Arsenic typically affects the gastrointestinal, cardiovascular, respiratory, and renal systems. Iron typically affects the gastrointestinal system and causes liver and heart failure. Mercury often affects the neurologic, gastrointestinal, and renal systems. Tin does not have significant toxicity in humans.

151.5. Which of the following laboratory tests would you expect to have an abnormal result in a child with the radiograph shown here.
A. Calcium
B. Iron
C. Lead
D. Mercury
E. Parathyroid hormone

Answer: C. This radiograph illustrates "lead lines," which indicate increased metaphyseal activity. This finding is common in children suffering from chronic lead exposure.

151.6. A 24-year-old man presents after attempting suicide by ingesting approximately 10 g of mercury that he collected from thermometers. The ingestion occurred approximately 30 minutes ago. He has no complaints currently. His vital signs and physical examination findings are normal. An abdominal radiograph reveals a radiopaque mass in his epigastrium. Other than psychiatry consultation, what treatment is indicated?
A. Dimercaprol
B. Hemodialysis
C. No treatment
D. Succimer
E. Whole bowel irrigation (WBI)

Answer: C. Ingested metallic mercury is poorly absorbed and poses no health risk as long as it is passed from the body and not trapped in the appendix or a diverticulum. Inorganic mercury salts are quite toxic, and patients exposed to these should be treated with succimer or dimercaprol. Organic mercury is typically not acutely toxic but does cause significant chronic disability and should be treated with succimer because treatment with dimercaprol can actually increase levels of mercury in the central nervous system (CNS). Hemodialysis is not effective.

CHAPTER 152

Hydrocarbons

George Sam Wang | Jennie Alison Buchanan

PRINCIPLES OF TOXICOLOGY

Hydrocarbons are a diverse group of organic compounds that contain hydrogen and carbon (Table 152.1). Most hydrocarbons (eg, gasoline) are byproducts of crude oil and are therefore called *petroleum distillates.* Essential oils such as turpentine or wormwood are derived from plants and not petroleum. Hydrocarbons are used as solvents and diluents in many products, such as household cosmetics and chemicals, pesticides, fuels, and essential oils. The two main categories of hydrocarbons are aliphatic (straight chain structures, such as propane) and aromatic (cyclic structures, such as toluene). Hydrocarbons can also have multiple nonorganic side chains. For example, halogenated hydrocarbons usually will have at least one bromide, chloride, fluoride, or iodide moiety (eg, carbon tetrachloride). Finally, hydrocarbons are used as a solvent base for many toxic chemicals, such as insecticides, carburetor cleaner (methanol), and metals, which in turn can cause a separate distinct syndrome of poisoning. Although the range of toxicity of hydrocarbons can vary widely, the majority of human exposures are confined to petroleum distillates.

Human exposure, both intentional and unintentional, to hydrocarbons is a common problem. In 2012, U.S. poison centers reported over 36,000 exposures to hydrocarbons accounting for approximately 1.5% of all calls.[1] In the previous decade, there were approximately 40,000 pediatric exposures to hydrocarbons, and almost 10% were hospitalized.[2] It is estimated 9% of the United States population 12 years and older have used an inhalant for its psychoactive properties.[3] Exposures to hydrocarbons are typically via inhalation, ingestion (with potential aspiration), and dermal. Inhalational exposures are typically due to either intentional abuse of volatile hydrocarbons (huffing) or household and workplace exposures. Ingestions are mostly due to accidental pediatric exposures, which also can lead to aspiration and pneumonitis. Dermal exposures are from household or workplace exposures and rarely intentional.

Pathophysiology

Acute hydrocarbons toxicity usually affects three main target organs: the lungs, the heart, and the central nervous system (CNS). Most ingestions of hydrocarbons do not lead to serious systemic toxicity but localized gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea may occur. Exceptions include halogenated or aromatic hydrocarbons, hydrocarbons containing metals or pesticides. Despite the fact that there are thousands of different types of hydrocarbons, their potential for acute toxicity depends on just a few physical properties[4]:

- Viscosity is the capacity to resist flow or change. Low viscosity allows a substance to spread rapidly, and low-viscosity hydrocarbons spread easily into the airway and lungs. Low viscosity hydrocarbons, such as furniture polish, gasoline, and lamp oil, have the highest potential risk of aspiration. Lubricants and mineral oil, conversely, have high viscosity and low toxicity potential.
- Volatility is a measure of a liquid's ability to evaporate to a gas or vapor. Hydrocarbons with high volatility can displace alveolar oxygen and cause hypoxia. Butane and propane are examples of hydrocarbons with high volatility.
- Surface tension is the capacity for a liquid to adhere to a surface. Low surface tension, like low viscosity, enables a substance (eg, turpentine) to disperse easily and may lead to pulmonary toxicity.
- Chemical side chains or substitutions often increase potential toxicity. These include metals (eg, arsenic), halogens (eg, the chloride ions in carbon tetrachloride), and those found on aromatic structures (eg, the CH_3 group in toluene).
- Lipophilicity can enhance blood brain barrier penetration resulting in CNS effects.

Pulmonary Pathophysiology

The primary target organ for direct toxicity is the lung. Fatalities after ingestion usually occur with accompanying aspiration. Hydrocarbons with high volatility, low viscosity, and low surface tension are especially dangerous (Box 152.1).[4-6]

Hydrocarbons penetrate into the lower airways, producing bronchospasm and direct injury to pulmonary alveoli and capillaries leading to an inflammatory response and pneumonitis.[7-9] Hydrocarbons also impair surfactant lipid function, leading to alveolar instability and collapse, decreased compliance, and impaired gas exchange. These mechanisms lead to alveolar dysfunction, ventilation-perfusion mismatch, and hypoxemia, which can result in respiratory failure. Lipoid pneumonia can also rarely develop after hydrocarbons coalesce in alveoli and become encapsulated by fibrous tissue. This has been reported in adults siphoning gasoline and from fire-eating performances, also known as "fire-eater's lung."[10-12]

Central Nervous System Pathophysiology

Most inhalant forms of hydrocarbons cause CNS depression. Products used for recreational mood alteration include glues and adhesives, aerosols, anesthetics, cleaning agents, solvents, and gases.[3] After respiratory exposure, hydrocarbons passively diffuse through the pulmonary alveolus, absorbed in blood and tissues and cross the blood brain barrier. Experimental data suggest neuropharmacological targets of hydrocarbons include glutamate/*N*-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA), dopamine and opioid receptors.[3,4] Inhalation of these substances avoids hepatic first-pass metabolism and generates high concentrations in the CNS. With an isolated single exposure, these effects usually have a rapid onset of intoxication and short duration of effect. Chronic use of inhaled hydrocarbons can cause severe abnormalities in nervous system function, which include memory, attention and judgment deficits, peripheral neuropathy, cerebellar degeneration, neuropsychiatric disorders, chronic encephalopathy, and dementia. More than 50% of patients who abuse toluene for more than 10 years will have

TABLE 152.1

Spectrum of Hydrocarbon Toxicity

TYPE	EXAMPLE	USE	PATHOPHYSIOLOGY	COMMENTS
Aliphatic petroleum distillates	Methane, propane, butane, gasoline, kerosene, mineral spirits, mineral oil, naphtha, mineral seal oil, diesel oil, *n*-hexane	Fuels, liquid fuels, solvents, furniture polish, degreasers, multiple uses in chemical industry	Asphyxiants causing hypoxia and CNS depression Abused inhalants Pneumonitis when aspirated CNS depression *n*-Hexane causes peripheral neuropathy	Sudden death from inhalation abuse Viscosity and volatility determine spectrum of toxicity Mineral seal oil has high aspiration potential Poor gastrointestinal absorption
Aromatic petroleum distillates	Toluene, xylene, benzene	Used in plastics, pharmaceutical, rubber, chemical, and solvent industries, degreasers	Highly volatile, lung aspiration Absorbed from gastrointestinal tract Abused inhalants	Inhaled toluene causes renal tubular acidosis Benzene causes aplastic anemia, leukemia
Essential oils	Turpentine, pine oil, oil of wintergreen, pennyroyal	Solvents, household disinfectants, incense	Well absorbed from gastrointestinal tract	Gastrointestinal and CNS toxicity Wintergreen with methysalicylates Pennyroyal can lead to hepatotoxicity
Halogenated hydrocarbons	Methylene chloride, chloroform, carbon tetrachloride, trichloroethylene, Freon, methylbromide, lindane, DDT	Solvents cleaning fluids, degreasers, fire extinguishers, paint strippers, fumigants	Multisystem toxicity (CNS, renal, hepatic, cardiac) Inhalant abuse Highly lipid soluble	Methylene chloride metabolized to carbon monoxide after ingestion Carbon tetrachloride is radiopaque and can lead to hepatotoxicity Insecticides absorbed through skin
Related chemicals	Phenol, creosols	Disinfectants	Very corrosive	Phenol causes severe skin burns, and systemic toxicity including metabolic acidosis

CNS, Central nervous system; *DDT,* dichlorodiphenyltrichloroethane.

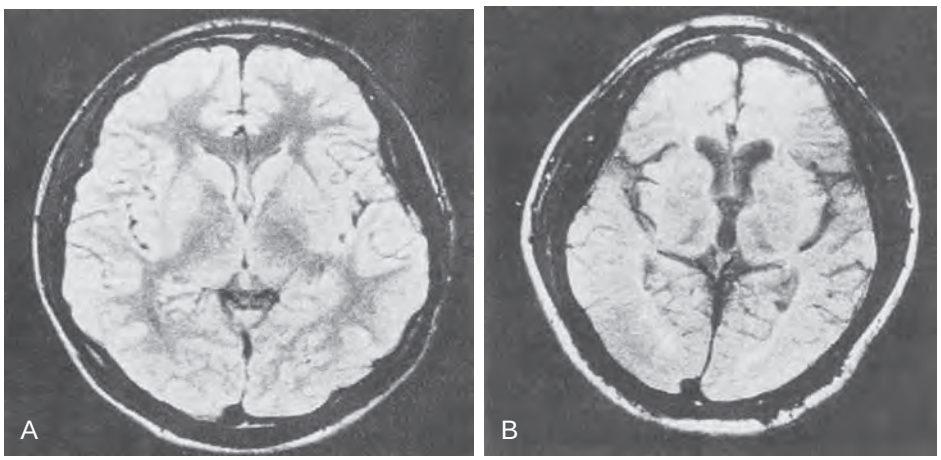

Fig. 152.1. Brain magnetic resonance imaging (MRI) of an individual with no history of inhalant abuse **(A)** and a patient with a history of chronic toluene abuse **(B).** (From NIDA Research Report [NIH 05-3818].)

BOX 152.1

Qualities of Hydrocarbon That May Lead to Aspiration and Pneumonitis

- High volatility
- Low viscosity
- Low surface tension

cerebral cortical atrophy (Fig. 152.1) with histologic changes that include loss of neurons, diffuse gliosis, and axonal degeneration.[4,13]

Cardiac Pathophysiology

Hydrocarbons can precipitate sudden death, usually in the setting of intentional inhalation. These compounds are thought to produce myocardial sensitization to endogenous and exogenous catecholamines by inhibition of calcium signaling, which precipitates ventricular dysrhythmias and myocardial dysfunction. Anoxia is also thought to be a contributing factor. Cardiac

Fig. 152.2. Angioedema resulting from huffing computer cleaner. (From Kurniali PC, Henry L: Inhalant abuse of computer cleaner manifested as angioedema. Am J Emerg Med 30:265.e3-5, 2012.)

Fig. 152.3. Presentation of paint sniffer ("huffer") with paint around the face and sedation. (Courtesy Chris Tomaszewski, MD.)

dysrhythmia occurs disproportionately among those using halogenated and aromatic hydrocarbons (eg, difluoroethane).[14] Halogenated hydrocarbons can be found in refrigerant propellants and air spray cleaners commonly used for computer keyboard cleaning. Prolonged use can lead to cardiac structural damage and may impede normal function.[4]

Other Organ Systems

Toxicity related to hydrocarbons also has been reported for other organ systems. Recognized syndromes include toluene-induced renal tubular acidosis, benzene-induced bone marrow toxicity and leukemia, methylene chloride–induced carbon monoxide poisoning, and chlorinated hydrocarbon–induced centrilobular hepatic necrosis, and renal failure.[4,15] Direct skin exposure of certain hydrocarbons can cause defatting dermatitis, allergic dermatitis, or chemical burns. Intentional intravenous injection of hydrocarbons such as kerosene has led to both localized caustic and necrotic effects, and systemic effects including renal or hepatic toxicity, systemic inflammatory response syndrome (SIRS), hemolysis, seizures, pulmonary injury, cardiovascular toxicity, and death.[4,16,17] Huffing can lead to localized increased vascular permeability, which can lead to angioedema, or localized frostbite when refrigerant is used (Fig. 152.2).[18,19]

CLINICAL FEATURES

After oral ingestion of hydrocarbons, severe poisoning is most often related to aspiration. This manifests with early respiratory symptoms, including cyanosis, coughing, grunting, noisy respirations, increased work of breathing or intractable vomiting. A patient may initially have mild symptoms and then develop tachypnea, dyspnea, bronchospasm, wheezing, rales, and fever after several hours.[4-6,9] A change in mental status can be a manifestation of hypoxia or hypercapnia, but it is also a direct effect of the hydrocarbon itself. In extreme cases, patients may have respiratory failure requiring prehospital intubation. Various additives or solutes can produce symptoms independently (eg, seizures from camphorated hydrocarbons, cyanosis from nitrite-induced methemoglobinemia, or delayed carbon monoxide poisoning from methylene chloride). Pesticides are often dissolved in a hydrocarbon base. With pesticide exposures, it can be difficult to distinguish acute respiratory distress syndrome induced by hydrocarbon aspiration from bronchorrhea induced by organophosphate toxicity (see Chapter 157).

Hydrocarbon solvent abuse is common and associated with various paraphernalia, such as plastic bags used for "bagging" (a method of pouring hydrocarbons in a bag or container and then inhaling deeply) and hydrocarbon-soaked cloth used for "huffing" (a method in which abusers inhale through a saturated cloth).[3,18,19] Patients often have the distinctive odor associated with organic hydrocarbons. A characteristic coloration from spray paint (usually silver or gold as these paint colors require higher concentrations of hydrocarbon) may be present over the mouth and nose or localized angioedema may occur, resulting in a "glue-sniffer's rash" (Fig. 152.3). These patients can also present to the emergency department (ED) with CNS intoxication with euphoria, agitation, hallucinations, confusion, or bizarre behavior. This may progress to CNS depression and seizures. In extreme cases, an individual who has inhaled solvents and then performed some type of physical exertion, such as an altercation, may suddenly collapse in cardiac arrest, likely due to cardiac sensitization by endogenous catecholamine with ensuing dysrhythmias.[4,14] Drug abusers who chronically inhale hydrocarbons may be brought to medical attention—not specifically for treatment of their drug use but rather for behavioral problems or nonspecific medical symptoms caused by their abuse. The long-term chronic abuser may clinically appear similar to the chronic ethanol user, with peripheral neuropathy, cerebellar degeneration, and encephalopathy.[4,13]

Another common scenario is the accidental dermal or inhaled (non-aspiration) respiratory exposure to hydrocarbons in the workplace or home. Such exposures are rarely life threatening. Most cases do not present for medical care.[1] The few patients who present to the ED typically will be asymptomatic or have transient nonspecific symptoms, such as headache, dizziness, or nausea. Those with significant respiratory exposure may have persistent pulmonary complaints and physical findings, such as coughing, wheezing, and cyanosis. Patients with significant acute dermal exposures may have pain and evidence of chemical burns consisting of erythema, swelling, angioedema, blistering, and dermal destruction (eg, exposure to phenol).[4,18,19]

In the absence of aspiration, large volume ingestion, or co-ingestion of another toxic substance, oral ingestion of most commonly available hydrocarbons is not associated with

significant morbidity or mortality. Cough may be an early sign of pneumonitis or aspiration.

DIFFERENTIAL DIAGNOSES

The history of exposure to a hydrocarbon, and the route or method of that exposure is usually straightforward. Additional history and examination should focus on possible aspiration especially if the agent is ingested. Symptoms include cough, dyspnea, and shortness of breath. Signs of significant exposure include tachypnea, tachycardia, wheezing, and hypoxemia. Differential diagnosis depends upon the route of exposure, which primarily include inhalation and ingestion. CNS depressants such as ethanol, sedative-hypnotics, can mimic the altered mental status of hydrocarbon ingestion. For hydrocarbon pneumonitis, pulmonary irritants; organophosphate, salicylate, and paraquat poisonings; and viral or bacterial pneumonia may all produce a similar clinical presentation, but the history usually will lead to the correct diagnosis. In the scenario of the recreational abuser inhaling a particular agent, multiple drugs of abuse are often present somewhat confounding the clinical evaluation. Furthermore, as previously mentioned, hydrocarbons may have other constituents leading to other toxicities. Behavioral disorders and confusion can be caused by hypoxia and respiratory compromise, as well as by the drugs themselves. Hypoglycemia, electrolyte abnormalities, and trauma should be considered as an etiology of altered mentation.

DIAGNOSTIC TESTING

The diagnosis is usually self-evident, supported by history of exposure and chemical odor. Ideally, the offending agent is brought to the ED. The local poison control center, medical toxicologist or material safety data sheet (MSDS) may identify and verify substances containing hydrocarbons. Hydrocarbons often are vehicles for other chemicals, and other exposures should be investigated.

CHAMP is a long-standing mnemonic used to help identify hydrocarbons and their additives with systemic toxicity[5] (Box 152.2).

Laboratory identification of hydrocarbons is difficult, time-consuming, and does not help ED management. Other laboratory tests including electrolytes, complete blood count, and liver function tests can be performed to assess for renal tubular acidosis, hypokalemia, bone marrow, or liver injury caused by various hydrocarbons.[4] We recommend an electrocardiogram (ECG) in patients with a history of use with halogenated hydrocarbons, dysrhythmias, syncope, or hemodynamic instability. Abnormal ECG findings may include dysrhythmias (ventricular fibrillation, ventricular tachycardia, premature ventricular contractions) or QTc interval prolongation.

Patients with pulmonary symptoms should have a chest radiograph taken and be observed for at least 6 hours with a repeat chest radiograph if there is worsening of their pulmonary status.[21,22]

BOX 152.2

CHAMP Mnemonic

*C*amphor, can cause neurotoxicity and seizures
*H*alogenated hydrocarbons, can cause dysrhythmias and hepatotoxicity
*A*romatic hydrocarbons, can cause bone marrow suppression and leukemia
*M*etals (eg, arsenic, mercury, and lead) can cause neurotoxicity
*P*esticides, can cause cholinergic crises, seizures, and respiratory depression

MANAGEMENT

Dermal exposures to hydrocarbons can cause extensive burns, and exposed patients require early decontamination. Contaminated clothing should be removed, and the skin should be washed with soap and copious lukewarm water. Burns are treated as described in Chapters 56 and 57. Gastrointestinal decontamination with gastric lavage or activated charcoal should be avoided. Most hydrocarbons are much more toxic to lungs than to the gastrointestinal tract, and emesis may lead to aspiration and pulmonary toxicity.

Cardiac abnormalities should be treated according to standard advanced cardiac life support (ACLS)/pediatric advanced life support (PALS) resuscitation algorithms. It is also postulated that catecholamines worsen or precipitate cardiac dysrhythmias and can be treated with short acting beta blockers, such as esmolol, which are presumed to be protective. Epinephrine should be avoided in the acutely intoxicated patient for concern of precipitating an arrhythmia.[20] Patients with any history or ECG abnormalities concerning for cardiac involvement should be monitored on cardiac telemetry until symptoms resolve.

Usually significant hydrocarbon toxicity leads to early and rapid decompensation of a patient's pulmonary, cardiac, and CNS functions. Intensive care monitoring should be used for patients with significant respiratory symptoms (respiratory distress, patient's with significant oxygen requirements, or requiring positive pressure or mechanical ventilation), cardiac involvement (arrhythmia or ECG abnormalities), or CNS depression. Patients with mild pulmonary symptoms (mild cough, minimal work of breathing, or low oxygen requirement) may be admitted to an inpatient ward for further observation. All other asymptomatic or minimally symptomatic patients should be in an observation unit with cardiac monitoring and pulse oximetry for minimum of 6 hours and until clinically well. Indications for positive pressure ventilation or mechanical ventilation include hypercarbia, severe respiratory distress, hypoxia unresponsive to noninvasive measures, and/or CNS depression. There are case reports, series, and animal models using high-frequency jet ventilation, and extracorporeal membrane oxygenation in severe cases of pneumonitis, but whether this is of benefit remains unknown.[4,6,8,9] Intrapulmonary administration of surfactant has been used successfully for severe hydrocarbon pneumonitis, using elevated oxygenation index, PaO_2/FiO_2 ratios, or poor lung compliance as indicators for use.[23,24] Corticosteroids and antibiotics have not been shown to improve outcomes and are not indicated.[4]

In most cases of hydrocarbon ingestion or inhalation, symptomatic care along with close observation and monitoring are the cornerstones of management.

DISPOSITION

Exposures to known, relatively benign hydrocarbons with minimal symptoms should have a 6-hour period of observation. If no signs of pulmonary or systemic toxicity develop during the observation period and the patient has a normal 6-hour chest radiograph, the patient may be discharged to home after appropriate psychiatric clearance if indicated. If pulmonary symptoms develop (tachypnea, hypoxia) and a chest radiograph shows evidence of pneumonitis (Fig. 152.4), patients will require hospital admission for at least 24 hours until symptoms have improved. Patients with CNS depression, history of dysrhythmia, significant respiratory distress or requiring more significant respiratory support should be monitored in the intensive care unit (Box 152.3).

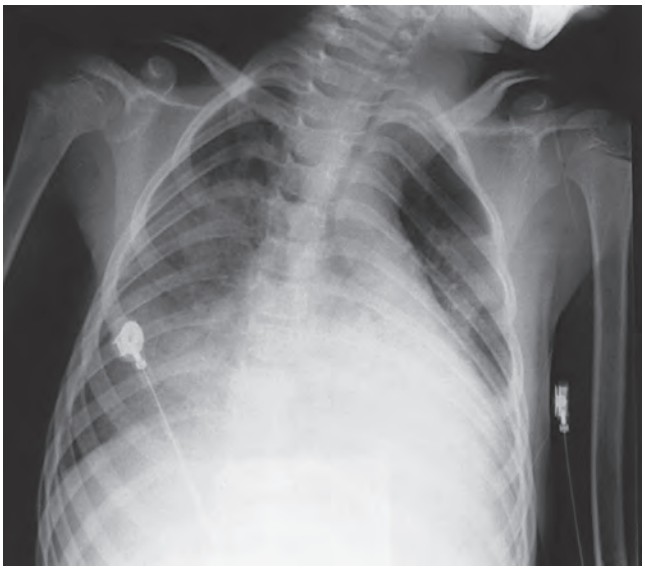

Fig. 152.4. Chest radiograph of a patient with hydrocarbon ingestion 6 hours after exposure.

BOX 152.3

Disposition

- Observation
  - All patients should be monitored for minimum 6 hours.
  - Discharge criteria: Asymptomatic without chest x-ray findings after 6 hours
- Inpatient admission
  - Mild CNS depression, tachypnea, hypoxia, chest x-ray findings not resolved after 6 hours
- Intensive care monitoring
  - Moderate to severe CNS depression
  - Significant respiratory distress
  - Significant hypoxia and/or hypercarbia
  - Requiring significant respiratory support (positive pressure ventilation/mechanical ventilation)
  - History of cardiac dysrhythmias
  - Hemodynamic instability

CNS, Central nervous system.

Recreational users via inhalation of hydrocarbons should be briefly observed until clinical symptoms are improving or resolved. In most cases if the patient is asymptomatic without complaints, they may be discharged after medical clearance for drug abuse counseling. Patients with concerning hydrocarbon exposures should be managed in conjunction with a poison control center and/or a medical toxicologist.

KEY CONCEPTS

- Aspiration is the major toxic risk of hydrocarbon poisoning.
- Hydrocarbons may cause systemic toxicity, burns, seizures, cardiac dysrhythmias, and altered mentation depending upon agent.
- Gastrointestinal decontamination is potentially harmful in cases of hydrocarbon ingestion and is contraindicated.
- Hydrocarbon inhalant abuse can cause CNS and cardiotoxic effects.
- Symptoms of toxicity, especially aspiration, can be delayed, so asymptomatic patients should be observed for 6 hours and given clear instructions to return if symptoms develop after discharge.
- In most cases of hydrocarbon ingestion or inhalation, symptomatic care along with close observation and monitoring are the cornerstones of management. Currently, there are no specific antidotes for hydrocarbons. Patients who have or develop pulmonary symptoms should have a chest radiograph performed.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 152: QUESTIONS & ANSWERS

152.1. Hydrocarbons can affect many organ systems, but derangements in which organ system most commonly lead to death after hydrocarbon exposure?
- **A.** Cardiac
- **B.** Gastrointestinal
- **C.** Nervous
- **D.** Pulmonary
- **E.** Renal

Answer: D. Most fatalities from hydrocarbon ingestion occur because of aspiration. Hydrocarbons cause direct lung injury, as well as displace oxygen and disrupt surfactant. Hydrocarbons can sensitize the myocardium to catecholamines, which can result in ventricular dysrhythmias and sudden death. Although an important consideration, death is more frequently caused by pulmonary complications. Gastrointestinal complications from hydrocarbon exposure are rare unless related to aspiration potential. Chronic hydrocarbon abuse or exposure causes nervous system dysfunction, including peripheral neuropathy, cerebellar degeneration, and neuropsychiatric disorders, but typically do not result in death. Several hydrocarbons cause renal failure, particularly toluene, but rarely result in death.

152.2. A healthy 20-year-old man presents after accidentally ingesting furniture polish that was stored in a plastic container that he mistook for a beverage. The ingestion occurred approximately 1 hour ago. He has no complaints. His vital signs and physical examination are normal. Which is the most appropriate course of action?
- **A.** Carbon monoxide level
- **B.** Careful gastric decontamination using nasogastric tube
- **C.** Drug screen
- **D.** Observe for 6 hours and discharge if condition does not change
- **E.** Serum electrolytes

Answer: D. Furniture polish is typically a mixture of nontoxic chemicals with a hydrocarbon base. The primary toxicity from hydrocarbon is from aspiration. Gastric decontamination is not recommended. Serum electrolytes and drug screens are rarely helpful in acute asymptomatic hydrocarbon exposures. Wood strippers often contain methylene chloride, which can cause carbon monoxide poisoning, but this chemical is not found in furniture polish.

158.3. A 4-year-old boy with a history of asthma is brought to the emergency department (ED) following an accidental hydrocarbon ingestion 2 hours ago. He initially was noted to be coughing. His vital signs are normal. His physical examination reveals mild bilateral wheezing but with good air movement. His oxygen saturation is 99% on room air. A chest radiograph is normal. The child is placed on a cardiac monitor and intravenous (IV) access is obtained. What is the most appropriate treatment plan?
- **A.** Admission and observation
- **B.** Endotracheal intubation
- **C.** Intravenous sodium bicarbonate
- **D.** Nebulized albuterol
- **E.** Oral activated charcoal

Answer: A. Hydrocarbons cause few symptoms when in the gastrointestinal tract, but they can be fatal when aspirated. Any therapy that risks inducing vomiting should be avoided (ie, gastric lavage and oral activated charcoal). This child likely has aspirated hydrocarbon and, although stable, could benefit from admission and observation. Endotracheal intubation may be warranted if symptoms worsen. Sodium bicarbonate has no role in hydrocarbon toxicity. Albuterol and other catecholamines can theoretically increase the possibility of ventricular dysrhythmias after hydrocarbon ingestion due to cardiac sensitization.

158.4. A 16-year-old male presents by emergency medical services (EMS) paramedics with sudden cardiopulmonary arrest after found unresponsive by friends at a high school beach party. In the emergency department (ED), he is unresponsive with no gag reflex. When you attempt to orally intubate the patient, you note gold metallic colorations inside his oral cavity. What else are you immediately concerned about clinically?
- **A.** Airway obstruction from anaphylactic shock
- **B.** Cardiac arrest from ventricular dysrhythmias
- **C.** Sedative hypnotic toxicity and respiratory arrest

D. Toxic alcohol poisoning and acute renal failure
E. Traumatic intracranial hemorrhage

Answer: B. This adolescent has likely abused a hydrocarbon (such as, toluene from gold spray paint) for recreational and euphoric reasons. Aside from pulmonary toxicity from aspiration pneumonitis, you are concerned about the possibility of direct cardiotoxicity from the inhaled hydrocarbon resulting in ventricular dysrhythmias and cardiac arrest.

CHAPTER 153

Inhaled Toxins

Lewis S. Nelson | Robert S. Hoffman

Inhalational exposure to systemic toxins can be covert and indolent (as in occupational exposure to irritant photochemical smog) or overt and fulminant. The circumstances of the exposure, the presence of combustion or odors, and the number and condition of victims assist in the management. Despite the array of possible toxic inhalants, identification of a specific inhalant is generally unnecessary because therapy is based primarily on the clinical manifestations (Table 153.1).

SIMPLE ASPHYXIANTS

Principles of Toxicity

Simple asphyxiants are inert and produce toxicity only by displacement of oxygen and lowering of the fraction of inspired oxygen (Fio_2). Exposed patients remain asymptomatic if the Fio_2 is normal. Carbon dioxide and nitrogen are exceptions in that both can produce narcosis at elevated partial pressures, even though their predominant toxicological effect is simple asphyxiation. Since the introduction of catalytic converters, most deaths from the intentional inhalation of automotive exhaust result from simple asphyxiation, due to hypoxia, and not from carbon monoxide (CO) poisoning.[1]

Clinical Features

Acute effects occur within minutes of onset of hypoxia and are the manifestations of ischemia. A fall in the Fio_2 from normal, 0.21 (ie, 21%), to 0.15 results in autonomic stimulation (eg, tachycardia, tachypnea, and dyspnea) and cerebral hypoxia (eg, ataxia, dizziness, incoordination, and confusion). Dyspnea is not an early finding, because hypoxemia is not nearly as potent a stimulus to the medullary respiratory center as are hypercarbia and acidemia. Lethargy from cerebral edema occurs as the Fio_2 falls below 0.1 (10%), and life is difficult to sustain at an Fio_2 below 0.06 (6%). Because removal from exposure terminates the simple asphyxiation and allows restoration of oxygenation and clinical improvement, most patients present with resolving symptoms. However, failure to improve suggests complications of ischemia (eg, seizures, coma, and cardiac arrest) and is associated with a poor prognosis.

Differential Diagnosis

Because the presenting complaints offered by most exposed patients are nonspecific (eg, dizziness, syncope, and dyspnea), the differential diagnosis is extensive. A consistent history, particularly of a setting in which asphyxia is expected to occur, an appropriate spectrum of complaints, and a rapid resolution on removal from exposure are generally sufficient to establish the diagnosis.

Diagnostic Testing

Minimally symptomatic or asymptomatic patients do not require chest radiography or arterial blood gas (ABG) analysis. There is no role for toxicology testing unless the asphyxiation was an act of deliberate self-harm, in which case we recommend selected screening for acetaminophen and any other relevant toxin implicated by history, physical examination, or observation. A definitive diagnosis ultimately requires scene investigation by a trained and suitably outfitted team. Determination of the exact nature of the gas is of limited clinical value but may have important public health implications.

Management

Management rarely requires specific therapy other than removal from exposure, supportive care, and administration of supplemental oxygen. Neurologic injury or cardiorespiratory arrest should be managed with standard resuscitation protocols. Psychiatric consultation is indicated when the exposure was an act of deliberate self-harm.

Disposition

Patients with manifestations of mild asphyxia who recover after removal from the exposure can be discharged after 6 hours of observation if they are asymptomatic or minimally symptomatic and improving. Patients at risk for complications of hypoxia, such as those presenting with significant signs or symptoms (eg, coma, chest pain, electrocardiogram [ECG] changes) or with exacerbating medical conditions (eg, cardiac disease), should be observed for 24 to 48 hours for the development or progression of post-hypoxic complications.

PULMONARY IRRITANTS

Principles of Toxicity

The pulmonary irritant gases are a large and diverse group of agents that produce a common toxicological syndrome when they are inhaled in moderate concentrations. Although many of these gases can be found in the home, significant poisoning from consumer products is uncommon because of restrictions designed to reduce their toxicity. However, catastrophes such as the 1984 release of methyl isocyanate in Bhopal, India, which resulted in more than 2000 fatalities and 250,000 injuries, remain as an environmental risk. On a different scale, industrialization has increased ambient concentrations of sulfur dioxide, ozone, and oxides of nitrogen. These irritant gases frequently exacerbate chronic pulmonary disease.

Irritant gases dissolve in the respiratory tract mucus and alter the air-lung interface by invoking an irritant or inflammatory response.[2] When these gases are dissolved, most of them produce an acid or alkaline product, but several generate oxygen-derived free radicals that produce direct cellular toxicity (Fig. 153.1). The clinical effects of pulmonary irritants can be predicted by their water solubility (see Table 153.1).

Clinical Features

Highly water-soluble gases rapidly impact the mucous membranes of the eyes (lacrimation) and upper airway (nasal burning, cough).

TABLE 153.1

Common Inhaled Toxins

INHALANT	SOURCE OR USE	PREDOMINANT CLASS
Acrolein	Combustion	Irritant, highly soluble
Ammonia	Fertilizer, combustion	Irritant, highly soluble
Carbon dioxide	Fermentation, complete combustion, fire extinguisher	Simple asphyxiant; systemic effects
Carbon monoxide (CO)	Incomplete combustion, methylene chloride	Chemical asphyxiant
Chloramine	Mixed cleaning products (eg, hypochlorite bleach and ammonia)	Irritant, highly soluble
Chlorine (Cl_2)	Swimming pool disinfectant, cleaning products	Irritant, intermediate solubility
Chlorobenzylidene malononitrile (CS), chloroacetophenone (CN)	Tear gas (Mace)	Pharmacologic irritant
Hydrogen chloride	Tanning and electroplating industry	Irritant, highly soluble
Hydrogen cyanide	Combustion of plastics, acidification of cyanide salts	Chemical asphyxiant
Hydrogen fluoride	Hydrofluoric acid	Irritant, highly soluble; systemic effects
Hydrogen sulfide	Decaying organic matter, oil industry, mines, asphalt	Chemical asphyxiant; irritant, highly soluble
Methane	Natural gas, swamp gas	Simple asphyxiant
Methylbromide	Fumigant	Chemical asphyxiant
Nitrogen	Mines, scuba diving (nitrogen narcosis, decompression sickness)	Simple asphyxiant; systemic effects
Nitrous oxide	Inhalant of abuse, whipping cream, racing fuel booster	Simple asphyxiant
Noble gases (eg, helium)	Industry, laboratories	Simple asphyxiant
Oxides of nitrogen	Silos, anesthetics, combustion	Irritant, intermediate solubility
Oxygen	Medical use, hyperbaric conditions	Irritant, free radical; systemic effects
Ozone	Electrostatic energy	Irritant, free radical
Phosgene	Combustion of chlorinated hydrocarbons	Irritant, poorly soluble
Phosphine	Hydration of aluminum or zinc phosphide (fumigants)	Chemical asphyxiant
Smoke (varying composition)	Combustion	Variable, but may include all classes
Sulfur dioxide	Photochemical smog (fossil fuels)	Irritant, highly soluble

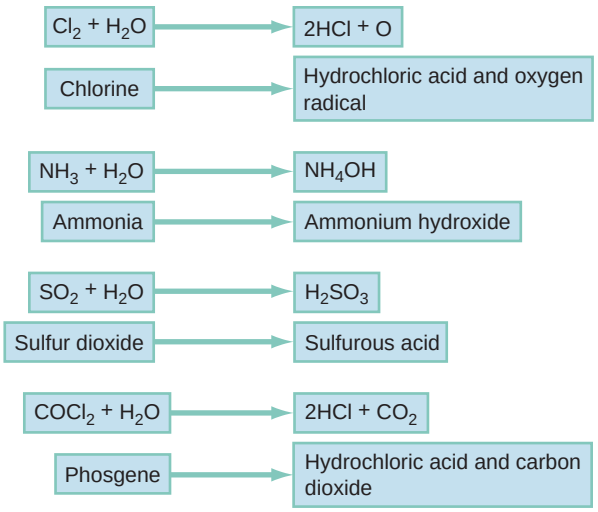

Fig. 153.1. Sample reactions of pulmonary irritants reacting with water in the lung. *Cl_2,* Chlorine; *CO_2,* carbon dioxide; *$CoCl_2$,* cobalt(II) chloride; *H_2O,* water; *H_2SO_3,* sulfurous acid; *HCl,* hydrochloric acid; *NH_3,* ammonia; *NH_4OH,* ammonium hydroxide; *O,* oxygen; *SO_2,* sulfur dioxide.

Although their pungent odors and rapid onset of symptoms tend to limit significant exposure, massive or prolonged exposure can result in life-threatening laryngeal edema, laryngospasm, bronchospasm, or acute respiratory distress syndrome (ARDS). In contrast, because poorly water-soluble gases do not readily irritate the mucous membranes at low concentrations and some have pleasant odors (eg, phosgene's odor is similar to that of hay), prolonged breathing in the toxic environment allows time for the gas to reach deep into the alveoli. Even moderate exposure causes delayed irritation of the lower airway, alveoli, and parenchyma after a 2- to 24-hour delay after exposure. Initial effects may be mild, only to progress to overt respiratory failure and ARDS during the ensuing 24 to 36 hours.[3] Gases with intermediate water solubility tend to produce syndromes that are a composite of the clinical features manifested with the other gases, depending on the extent of exposure. Massive exposure is most often associated with rapid onset of upper airway irritation and more moderate exposure with delayed onset of lower airway symptoms.

Differential Diagnosis

The typical symptoms of pulmonary exposure to irritant gas are bronchospasm, cough, a sensation of chest tightness, and acute conjunctival irritation, all of which may occur following allergen exposure, but the history generally confirms the exposure to the irritant. History may be particularly important if the patient

presents with severe or advanced findings, such as ARDS, which can occur after many physiologic insults, including trauma and sepsis.[4]

Diagnostic Testing

Inhalation of respiratory irritants may affect the upper airway, the lower airways and lungs, or both. Upper airway evaluation proceeds as described in the following Management section. Radiographic and laboratory studies are not useful in the evaluation of upper airway symptoms.

Oxygenation and ventilation are assessed by serial chest auscultation, pulse oximetry, and continuous capnography. Chest radiography is indicated for patients presenting with cough, dyspnea, hypoxia, or abnormal findings, such as rales or wheezes, on physical examination. ABGs are reserved for patients who are more severely symptomatic, have hypoxia, or do not improve readily with appropriate therapy.

In general, it is neither possible nor necessary to test for the specific agent. There are no clinical tests that will differentiate the irritant to which a patient was exposed, although testing at the site by public health authorities may be performed for epidemiologic purposes. Knowing that an agent was highly water soluble will shorten the observation period for symptom development, whereas patients exposed to poorly water soluble agents will require a more prolonged period of observation.

Management

Patients with no upper airway symptoms, normal voice, and no evidence of irritation (erythema) on examination of the oral pharynx require no further upper airway evaluation, but should be reexamined if symptoms or signs develop after the initial evaluation. Those with evidence of severe tissue irritation, such as oral or tongue edema, altered voice (raspy or muffled), or significant odynophagia or dysphagia should undergo early intubation, because progression of these injuries can be expected. Patients with significant erythema or pain in the oropharynx or nasopharynx and those with any evidence of alteration of voice, dysphagia or odynophagia, or stridor require early examination by laryngoscopy. Laryngoscopy may be performed using a flexible laryngoscope or rigid video or conventional laryngoscope with appropriate topical anesthesia and sedation as indicated (see Chapter 1). Patients with evidence of mild irritation of the larynx or supralaryngeal area (erythema, no edema, normal glottis) may be observed. Those with more severe findings considered not to require early intubation, such as erythema with mild edema, should undergo repeat examination 30 to 90 minutes after the initial examination or earlier, if symptoms or signs are worsening.

Bronchospasm generally responds to inhaled beta-adrenergic agonists in usual doses. There is no indication for ipratropium or a corticosteroid unless the patient has known underlying reactive airways disease.[3,5]

Patients exposed to chlorine or hydrogen chloride gas receive symptomatic relief from nebulized 2% sodium bicarbonate solution.[5] This solution is prepared by diluting a given volume of standard 8.4% sodium bicarbonate solution with three equivalent volumes of sterile water, and administering it with standard nebulizer equipment. There are no studies on the recommended dosing regimen, but if successful after its first use, providing it every 30 minutes as needed for symptom relief, for up to 6 hours, should be safe. Nebulized bicarbonate will not alter the inflammatory cascade, however, so it will not have significant effect on the progression of pulmonary injury.

ARDS, if identified, is managed as described in Chapters 22 and 67.

Disposition

Patients exposed to highly water-soluble gases (see Table 153.1) can be discharged if they are asymptomatic or symptoms are minimal and improving. After exposure to intermediate or poorly water-soluble gases, asymptomatic patients should be observed for increasing dyspnea for 6 hours before final disposition. Patients with prolonged gas exposure or exposure to highly concentrated gases, which may occur in a closed space, even if asymptomatic, or those in high-risk situations (eg, underlying pulmonary disease, extremes of age, and poor follow-up) should be observed in an inpatient setting or observation unit for 24 hours. Patients with upper airway findings on examination are observed in the emergency department (ED) or an intensive care unit (ICU) until there is clear evidence that the process is subsiding. All discharged patients should receive instructions for signs and symptoms of pulmonary deterioration.

SMOKE INHALATION

Principles of Toxicity

Annually, approximately 4000 people are injured or die in residential fires in the United States. Many of these casualties do not suffer serious cutaneous burns but rather die of smoke inhalation. This is a variant of irritant injury in which heated particulate matter and adsorbed toxins injure normal mucosa. In addition, CO and cyanide are systemic toxins often considered along with the smoke inhalation syndrome because of their common origin.

Even at temperatures between 350° and 500° C, air has such a low heat capacity that it rarely produces lower airway damage. However, the greater heat capacity of steam (approximately 4000 times that of air) or heated soot suspended in air (ie, smoke) can transfer heat and cause injury deep within the respiratory tract.

The nature of the fuel determines the composition of its smoke, and because fires involve variable fuels and burning conditions, the character of fire smoke is almost always undefined to the clinician. Irritant toxins produced by the fire are adsorbed onto carbonaceous particles that are deposited in the airways and damage the mucosa through mechanisms similar to those of the irritant gases.

Clinical Features

Thermal and irritant-induced laryngeal injury may produce cough, voice alteration, or stridor, but these findings are often delayed. Soot and irritant toxins in the airways can produce early cough, dyspnea, and bronchospasm. Subsequently, a cascade of airway inflammation results in ARDS with failure of pulmonary gas exchange. The time between smoke exposure and the onset of clinical symptoms is highly variable and dependent on the nature of the exposure. Deaths that occur rapidly after exposure are caused by asphyxia, airway compromise, or metabolic poisoning (eg, CO). Singed nasal hairs and soot in the sputum suggest substantial exposure, but significant exposure and injury can occur with neither of these being present.

Differential Diagnosis

With the obvious exposure history, the differential diagnosis is limited. Although it is often unclear whether inhalational injuries are thermal or irritant, the differentiation is clinically irrelevant. Concomitant physical injuries such as burns or trauma may complicate the metabolic picture.

Diagnostic Testing

Airway patency should be evaluated early. Airway management is as described earlier for inhaled pulmonary irritants. If evidence of significant airway exposure is present, such as carbonaceous sputum or hoarse voice, the airway should be examined by rigid or flexible laryngoscopy, and secured if signs of injury or compromise are noted. Pulmonary injury is assessed through auscultation and chest radiography for signs of alveolar filling or hyperinflation. Oxygenation should be assessed by co-oximetry, because blood gas analysis and pulse oximetry may be inaccurate in CO-poisoned patients (see discussion in the Carbon Monoxide section later). Co-oximetry will provide a blood carboxyhemoglobin (COHb) level, and we recommend testing for every patient, unless the smoke exposure was brief and in an open space. Metabolic acidosis, particularly when serum lactate concentration is greater than 10 mmol/L, suggests concomitant cyanide poisoning.[6]

Management

The acute management of smoke inhalation is identical to that of other irritant inhalational injuries. Early assessment of the airway and early intubation, as indicated, are critical because deterioration may be occult and rapid. Patients with no upper airway symptoms, normal oropharyngeal and nasopharyngeal examination, no voice alteration, and normal swallowing may be observed and reevaluated if symptoms, even mild symptoms, develop. Patients with symptoms or findings, though, are evaluated early by rigid or flexible laryngoscopy. Simply observing these patients for deterioration can result in airway compromise requiring rapid and, by then, difficult airway intervention. Despite a lack of evidence supporting their effectiveness, inhaled beta-adrenergics are widely used for patients with dyspnea or wheezing. Because these may provide benefit with little likelihood of harm, we recommend at least one dose of a beta-adrenergic agonist for patients with symptoms of bronchospasm. Both subjective (patient reported and findings on auscultation) and objective (respirometry) assessment may be used to determine whether these agents appear to benefit a particular patient and guide use of additional doses. Optimal supportive care and maintenance of adequate oxygenation (eg, suctioning and pulmonary toilet) are the most important aspects of care. Bronchoscopy with bronchoalveolar lavage is frequently recommended to clear debris and toxins from the distal airways. We do not recommend the use of corticosteroids, by inhalation or systemically, because there is no evidence of benefit and they are potentially harmful in patients with cutaneous burns. Ibuprofen, antioxidants, exogenous surfactant, and high-frequency ventilation yield variably improved survival in experimental and clinical trials; none is considered standard care.[7] Antibiotics should be used only in patients with suspected infection.

Disposition

Patients who are intubated should be admitted to the ICU or burn unit, depending on the extent of the cutaneous burns or respiratory tract injury. Patients with upper airway symptoms or signs, but without concerns for airway loss, should undergo repeat airway examination for 6 hours, preferably in an ICU. Patients with prolonged closed-space exposure or lower airway findings, such as rales or carbonaceous sputum, should be admitted to an ICU and observed for at least 24 hours while assessing for the development of signs of lower respiratory tract injury. Transfer to a higher level of care at another hospital or to a burn center should be based on local resources, consultation with the specialty center, an assessment of the risks of transfer, and existing protocols (see Chapter 56).

CYANIDE AND HYDROGEN SULFIDE

Principles of Toxicity

Instead of directly affecting the airway and lungs, these poisons cause effects at the cellular level. Hydrogen cyanide is a gas with many commercial uses, particularly in synthetic fiber manufacture and fumigation. Gaseous hydrogen cyanide is occasionally noted to have the odor of bitter almonds. Cyanide in its salt form (eg, sodium or potassium) is important in the metallurgy (eg, jewelry) and photography and is much safer to work with because of its low volatility. When cyanide salts are dissolved in water, hydrogen cyanide can leave the surface, particularly under acidic conditions. Cyanide is metabolically released in vivo from precursors (cyanogens) such as amygdalin, found in apricot and other *Prunus* species pits, and from nitriles, a group of chemicals with many commercial uses.

Hydrogen sulfide poisoning most often occurs in petroleum refinery and sewage storage tank workers. A recent Internet-derived means of suicide involves generation of hydrogen sulfide from sulfur-containing products, such as detergent, mixed with acids in an enclosed space, such as an automobile.[8] On occasion, well-intentioned but ill-prepared rescuers become victims, emphasizing the need for proper training and equipment. Hydrogen sulfide has a noxious odor similar to rotten eggs, which becomes unnoticeable with extremely high concentrations or prolonged exposure (a process called *olfactory fatigue*).

Gaseous cyanide is rapidly absorbed after inhalation and is immediately distributed to the oxygen-using body tissues. Inhibition of oxidative metabolism by binding to cytochrome c oxidase (or Complex IV) of the electron transport chain within mitochondria occurs within seconds. The poisoned tissue rapidly depletes its adenosine triphosphate reserves and ceases to function (Fig. 153.2). Cyanide has no evident effect on other oxygen-binding enzyme systems, most notably hemoglobin. This is probably explained by the oxidation state of its iron moiety; cyanide binds only to oxidized iron (Fe^{3+}), whereas deoxyhemoglobin contains reduced iron (Fe^{2+}).

Hydrogen sulfide exerts its toxic effects both as a pulmonary irritant and as a cellular poison.[9] Its deadly metabolic effects are produced by a mechanism identical to that for cyanide. However, hydrogen sulfide's spontaneous dissociation from the mitochondria is rapid, allowing many patients to survive after brief exposure.

Clinical Features

Tissue hypoxia occurs within minutes, with the exact onset dependent on the route, dose or concentration, and nature of the exposure. Dysfunction of the heart and the central nervous system—the organ systems most sensitive to hypoxia—is characteristic of cyanide poisoning, manifested as coma, seizures, dysrhythmias, and cardiovascular collapse. Metabolic acidosis develops as a result of diffuse cellular dysfunction and is associated with an elevated serum lactate concentration. Cyanosis is not a characteristic clinical finding. Given the extreme toxicity of cyanide, mild acute poisoning is uncommon. Patients with acute hydrogen sulfide poisoning have similar clinical manifestations, although many recover by the time of arrival in the ED.

Because cyanide and hydrogen sulfide prevent tissue extraction of oxygen from the blood, the oxygen content of venous blood remains high, approaching that of arterial blood. Clinically, this may appear as the "arterialization" or brightening of venous blood to resemble arterial blood. A comparison of the measured venous and arterial oxygen contents may assist in the diagnosis of cyanide poisoning. A low arterial-venous oxygen difference is suggestive

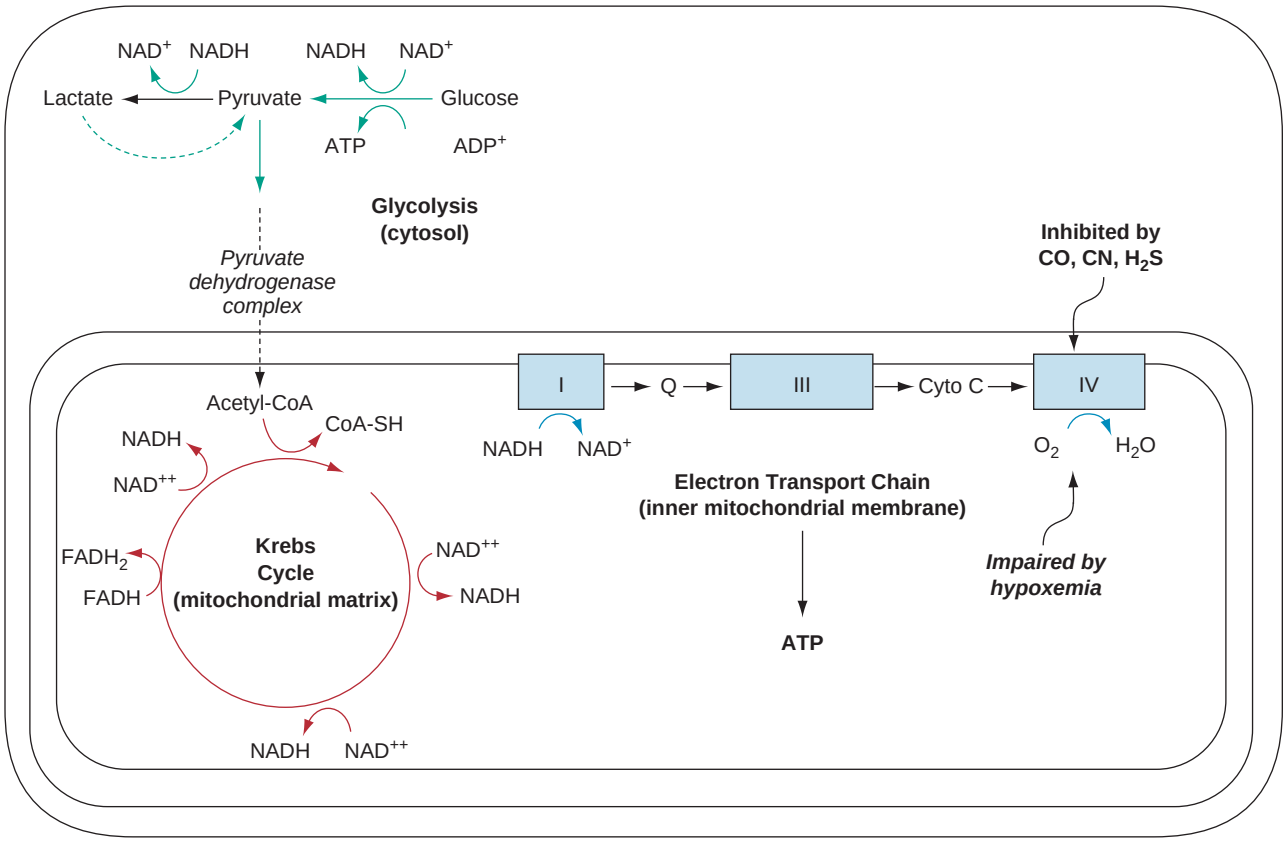

Fig. 153.2. The complete metabolism of a molecule of glucose to energy is complex but occurs in two broad steps. The first step, anaerobic glycolysis, which occurs in the absence of oxygen, generates pyruvate, nicotinamide adenine dinucleotide *(NADH),* and adenosine triphosphate *(ATP).* Pyruvate then enters the Krebs cycle to create potential energy in the second step, through the reduction of NAD^+ to NADH and flavin adenine dinucleotide *(FADH)* to $FADH_2$. Similarly, fatty acid metabolism and protein metabolism produce $FADH_2$ and NADH, which also requires conversion to ATP. These conversions occur in the mitochondrial membrane, where oxidative phosphorylation is linked to the electron transport chain, the last phase of which involves the transfer of electrons to molecular oxygen to form water. Cyanide *(CN),* hydrogen sulfide *(H_2S),* and carbon monoxide *(CO)* bind to and inhibit the last step, the Fe^{3+}-containing cytochrome-aa_3 oxidase in Complex IV, preventing further oxidation of NADH. This in turn hinders the Krebs cycle because the required regeneration of NAD^+ does not occur, and glucose metabolism is forced to end at pyruvate. For energy production to continue, NADH donates its electrons to pyruvate, creating lactate, and sufficient NAD^+ is regenerated for glycolysis to progress. Ultimately, energy failure and end-organ damage occur. *CoA,* Coenzyme A; *H_2O,* water; *IV,* intravenous; *O_2,* oxygen.

of cyanide poisoning but its absence is neither exclusionary nor its presence pathognomonic for the diagnosis.

Patients surviving cyanide or hydrogen sulfide poisoning may have persistent or delayed-onset neurologic syndromes identical to those noted in patients with CO poisoning or cardiac arrest.

Differential Diagnosis

In practice, rapid cardiovascular collapse, hypotension, bradycardia, ventricular dysrhythmias, and seizures in a fire victim should suggest cyanide poisoning, severe CO poisoning, or both.[6] In patients without an exposure history, the differential diagnosis is vast and includes CO poisoning, asphyxiants, cardiotoxins, cardiac dysfunction (dysrhythmia, myocardial infarction), and sepsis.

Diagnostic Testing

Unlike with CO poisoning, pulse oximetry and ABG analysis are accurate in cases of isolated cyanide or hydrogen sulfide poisoning. An increased anion gap metabolic acidosis and elevated serum lactate concentration are usually present. A lactate concentration greater than 10 mmol/L in a fire victim is highly predictive of cyanide poisoning.[6] CO and cyanide are fellow travelers, so an elevated COHb level in a fire victim warrants consideration of concomitant cyanide poisoning. The presence of severe clinical findings with a low COHb level is particularly concerning for cyanide poisoning. The result of a blood cyanide determination is usually too delayed to be of use in the ED, but it can be useful for confirmation and documentation purposes. Technology exists for immediate cyanide determination but is not widely available. Testing for hydrogen sulfide is not clinically available.

Management

The diagnosis of cyanide poisoning usually cannot be confirmed rapidly, and therapy is almost always empirical. Treatment should not be delayed pending the COHb level or other laboratory tests in patients with suspected acute cyanide poisoning. Patients removed from a fire environment who have cardiovascular instability, altered mental status, or a serum lactate greater than 10 mmol/L should receive cyanide treatment regardless of the COHb concentration.

Hydrogen Cyanide

The accepted goal of therapy is to reactivate the cytochrome oxidase system by providing an alternative binding site for the cyanide ion. There are two types of antidotal therapy for cyanide. The preferred antidote is hydroxocobalamin, which takes advantage of the high affinity of cobalt for cyanide. On binding of cyanide, cyanocobalamin, or vitamin B_{12}, is formed. The initial dose is 5 g intravenous (IV) over 15 minutes for adults and 70 mg/kg IV for children, up to an adult dose, and can be repeated once if an incomplete response is noted. Thiosulfate (see later), 12.5 g, can be administered concomitantly over 10 minutes through a separate IV. The known adverse effects of hydroxocobalamin are mild and include hypertension in those not cyanide poisoned and a bright red discoloration of the patient's skin. Inexperienced clinicians often mistake this side effect is as an "allergic" reaction to the drug. The drug's red color can interfere with certain spectrophotometric laboratory tests, including COHb and possibly serum lactate, and blood samples should be obtained before the administration of the first dose of hydroxocobalamin.[10]

The cyanide antidote kit is an alternative therapy for cyanide toxicity. The cyanide antidote kit produces a high-affinity source of ferric ions (Fe^{3+}) for cyanide to bind. The kit has three components (amyl nitrite, sodium nitrite, and sodium thiosulfate), and although the best results are likely to be attained when the entire kit is used, this may be impractical or dangerous, particularly for nonhospital providers. Because animal models and clinical evidence in humans demonstrate that sodium thiosulfate alone (the "third" component of the kit), in combination with oxygen, offers substantial protection, this should be the initial therapy administered by paramedics and during mass poisoning events in the absence of hydroxocobalamin. Antidotes should not completely replace other resuscitation measures, including high-flow oxygen and removal of the patient from the source of exposure.

Methemoglobin (MetHb) formation results from first two components of the kit. Inhaled amyl nitrite and IV sodium nitrite are both effective, but amyl nitrite should be administered to patients only before IV access. Caution should be taken to minimize the provider's exposure to the volatile amyl nitrite because dizziness, hypotension, or syncope may occur. The dose of sodium nitrite for a previously healthy adult is 300 mg (10 mL of a 3% solution) given during 2 to 4 minutes, and dosing instructions for anemic patients and children are supplied with the kit. Cyanide has a high affinity for MetHb and readily leaves cytochrome oxidase to form cyanmethemoglobin, which is metabolically inactive. Additionally, the nitrites are vasodilators, and this may be mechanistically important in their therapeutic effect by enhancing blood flow to the liver for clearance. However hypotension may complicate a rapid infusion.

Both free serum cyanide and cyanmethemoglobin are converted by sulfur transferase *(rhodanese)* to thiocyanate, which is renally eliminated. Because the rate of rhodanese function increases with the availability of sulfur donor, the third component of the antidote kit is the sulfur-containing compound sodium thiosulfate. The adult dose is 12.5 g IV, which is provided as 50 mL of a 25% solution (2 mL/kg of 25% sodium thiosulfate up to an adult dose in children). In general, few if any adverse effects are associated with proper doses. The nitrite components of the cyanide antidote kit should be avoided in fire victims with known or suspected simultaneous CO and cyanide poisoning because both CO and MetHb reduce oxygen delivery to the tissues. The use of the thiosulfate component alone in this subset of patients is recommended (Box 153.1).

There are insufficient clinical data to fully support the use of one cyanide antidote over the other. However, we recommend hydroxocobalamin, which is largely replacing the cyanide antidote kit because of its ease of use and presumed superior safety in CO-poisoned fire victims.[11] Direct comparison to thiosulfate alone in this population has not been and likely never will be performed, but animal models suggest that hydroxocobalamin is superior.[12] When possible, we recommend administering both hydroxocyanocobalamin and thiosulfate, with the priority given to hydroxocyanocobalamin, and never giving them through the same IV.

BOX 153.1

Cyanide Antidotes

HYDROXOCOBALAMIN*

Adults: 5 g IV over 15 minutes
Children: 70 mg/kg up to 5 g

CYANIDE ANTIDOTE KIT

1. MetHb inducers†
   Amyl nitrite (inhalational, prehospital) *or*
   Sodium nitrite ($NaNO_2$) 3% solution IV over 2 to 4 minutes IV
   Adults: 10 mL (300 mg)
   Children: See labeling information with kit
2. Cyanide detoxification
   Sodium thiosulfate (NaS_2O_3) 25% solution IV
   Adults: 50 mL (12.5 g)
   Children: 1.65 mL/kg up to 50 mL

IV, Intravenous; *MetHb,* methemoglobin.
*A second dose may be administered in patients with an incomplete response.
†Withhold nitrites if blood carboxyhemoglobin (COHb) is suspected to be present (eg, fire victims).

Hydrogen Sulfide

Because the bond between hydrogen sulfide and cytochrome oxidase is rapidly reversible, removal from exposure and standard resuscitative techniques are usually sufficient to reverse hydrogen sulfide toxicity. Use of the nitrite portion of the cyanide antidote kit is suggested to create MetHb for patients with severe or prolonged toxicity. Sodium thiosulfate is unnecessary because hydrogen sulfide is not detoxified by rhodanese. There is no defined role for hyperbaric oxygen (HBO) therapy in cases of hydrogen sulfide toxicity.

Disposition

Patients with symptomatic cyanide or hydrogen sulfide poisoning should be admitted to a critical care unit and observed for complications of tissue hypoxia. These patients should also be evaluated for delayed neuropsychiatric findings.

CARBON MONOXIDE

Principles of Toxicity

CO is the most common cause of acute poisoning death in developed nations and the most common cause of fire-related death.[13] CO is generated through incomplete combustion of virtually all carbon-containing products. Structure fires (eg, wood), clogged vents for home heating units (eg, methane), and use of gasoline-powered generators indoors are examples of the myriad means through which patients are poisoned by CO. Appropriate public health authorities (eg, fire department and Department of Health officials) should be informed immediately about any potential public health risks that are identified during the care of a CO-exposed patient.

CO interacts with deoxyhemoglobin to form COHb, which cannot carry oxygen. Hemoglobin binds CO tightly and forms a complex that is only slowly reversible. This allows the exposed individual to accumulate CO, even with exposure to low ambient concentrations. Although binding of hemoglobin is historically described as the mechanism of CO poisoning, it is relevant only in profoundly CO-poisoned patients because a simple reduction in oxygen-carrying capacity due, for example, to anemia would not cause similar symptoms. However, for pregnant patients, the fetus is at increased risk, because it is relatively hypoxic compared with the mother. Additionally, CO shifts the oxyhemoglobin dissociation curve to the left in such a way that even if oxygen is bound to hemoglobin, its unloading to tissues is impaired. In muscle, CO binds myoglobin, preventing its normal function, and this probably explains the development of atraumatic rhabdomyolysis.

Most importantly, CO affects cellular oxygen use at the tissue level. CO, similar to cyanide, inhibits the final cytochrome complex involved in mitochondrial oxidative phosphorylation. This results in a switch to anaerobic metabolism and ultimately in cellular death.

Delayed-onset neurologic complications may be a manifestation of the hypoxic insult, and reperfusion injury and lipid peroxidation related to platelet-induced nitric oxide release may play a significant role.[9] By alteration of the platelet-associated nitric oxide cycle, the microvascular endothelium of the central nervous system undergoes free radical–mediated injury, resulting in localized inflammation and dysfunction. Animal models and human reports suggest that loss of consciousness during CO exposure is a risk factor for the development of delayed neurologic sequelae.[14]

Clinical Features

Severe CO toxicity and cyanide poisoning have identical clinical presentations of chemical asphyxia: altered mental status, including coma and seizures; extremely abnormal vital signs, including hypotension and cardiac arrest; and metabolic acidosis. Unlike cyanide poisoning, however, mild CO poisoning occurs frequently, with headache, nausea, vomiting, dizziness, myalgia, and confusion as common presenting complaints. The neurological assessment in these patients may yield normal findings or may demonstrate focal findings or subtle perceptual abnormalities. The often-touted cherry-red skin color in patients with cyanide or CO poisoning is a postmortem finding and is not noted in living patients.

Delayed neurologic sequelae is a well-documented phenomenon after CO exposure; the frequency varies from 12% to 50%, depending on the definition and the sensitivity of the test used for their detection.[14] Patients have a variety of neurologic abnormalities after an asymptomatic period, ranging from 2 to 40 days. The delayed neurologic effects can be divided into those with readily identifiable neurologic syndromes (eg, focal deficits and seizures) and those with primarily psychiatric or cognitive findings (eg, apathy and memory deficits). Although the delayed neuropsychiatric sequelae require formal neuropsychiatric testing to be detected, the impact of these abnormalities on the patient's daily function may be significant. Risk factors that predict the development of delayed neurologic sequelae include extremes of age and loss of consciousness. Because most CO-poisoned patients reaching the ED survive with minimal intervention, prevention of delayed neurologic and neuropsychiatric sequelae is a major goal of therapy.

Differential Diagnosis

Mild to moderate CO poisoning is a difficult diagnosis to establish clinically, and patients are easily misdiagnosed as having a benign headache syndrome or viral illness. CO poisoning should be suspected in patients with persistent or recurrent headache, especially if a group of people have similar symptoms or if the headache improves soon after the person leaves an exposure site.

Patients with severe CO poisoning may present with coma or cardiovascular collapse, both of which have a broad toxicologic, metabolic, infectious, medical, and traumatic differential diagnosis. The medical history, physical examination, and standard laboratory testing are easily able to exclude many of these diagnoses. Given the relatively protean manifestations of CO poisoning and the potentially serious consequences of misdiagnosis, particularly if the patient returns to the contaminated environment, we recommend specific measurement of CO by co-oximetry of an arterial or venous blood sample when the clinician considers CO poisoning as a cause for the patient's presentation.

Diagnostic Testing

Suspicion of CO poisoning relies on the history and physical examination findings. Co-oximetry, an inexpensive and readily available spectrophotometric laboratory method that can distinguish between normal hemoglobin and COHb (and MetHb), confirms exposure to CO. Other laboratory tests only exclude other diagnoses. Severity of poisoning may not correlate with COHb levels because prolonged exposure to low levels can be fatal with a low measured COHb, but a brief, high-concentration exposure can produce a high COHb level with minimal symptoms.

The standard blood gas (ABG or venous blood gas [VBG]) analysis is a poor screening test for CO poisoning other than to identify the presence of a metabolic acidosis and a normal partial pressure of oxygen (Po_2). CO decreases oxygen bound to hemoglobin but does not affect the amount of oxygen dissolved in blood. Because the Po_2, a measure of dissolved oxygen, is normal in patients with CO poisoning, the calculated oxygen saturation will be normal even in the presence of significant CO poisoning. Most pulse oximeters are unable to detect CO poisoning because COHb essentially is misinterpreted as oxyhemoglobin. Newer pulse co-oximeters are capable of noninvasively detecting COHb as well as methemoglobinemia, but these instruments are not yet in common use.[15]

Management

Treatment begins with oxygen therapy, which serves two purposes. First, the half-life of COHb is inversely related to the Po_2; it can be reduced from approximately 5 hours on room air to 1 hour by providing supplemental 100% oxygen. HBO therapy (at 3 ATA) further reduces the half-life to approximately 30 minutes. Unfortunately, alteration of the kinetics of COHb is relevant only to patients with extremely elevated COHb levels (eg, 50%). Even then, only a minority of patients can be treated sufficiently rapidly for the HBO to be life saving. Second, a sufficient Po_2 can be achieved with HBO to sustain life in the absence of adequately functioning hemoglobin, but this is helpful only when the COHb is extremely elevated. Thus, the primary indication for HBO is not to prevent mortality but rather to prevent delayed neurologic sequelae.

There is controversy regarding the benefit of HBO because the effect is not immediate (as with life and death) and outcome assessment requires close follow-up and sophisticated testing. Several evidence-based reviews have asserted only a limited role for HBO, although this conclusion is disputed.[14,16] Evidence suggests that HBO helps prevent the development of delayed neuropsychiatric and neurologic sequelae after CO poisoning, with a decrease of delayed neurologic sequelae from approximately 12% to less than 1% with HBO. When HBO administration is delayed

BOX 153.2

Recommendations for Hyperbaric Oxygen

Carboxyhemoglobin (COHb) (varies by local standards) independent of clinical findings
- >25% with no clinical findings
- >15% in pregnancy or fetal distress

or an elevated COHb with one or more of the following findings:
- Syncope
- Coma
- Seizure
- Altered mental status (GCS <15) or confusion
- Abnormal cerebellar function
- Prolonged CO exposure with minor clinical findings ("soaking")

CO, Carbon monoxide; *GCS,* Glasgow Coma Score.

more than 6 hours after exposure, its efficacy appears to decrease, suggesting the need for rapid implementation. A randomized, double-blind study found that HBO therapy was superior to normobaric oxygen therapy at reducing the incidence of delayed neurologic sequelae at both 6 weeks and 1 year after poisoning.[17] However, another found no benefit of HBO on the development of delayed neurologic sequelae compared with extensive normobaric oxygen.[18] In the latter study, however, the majority of patients were suicidal and possibly depressed, which would interfere with performance on the neuropsychiatric testing needed to differentiate the two groups of patients. Another trial found that in comatose patients, one HBO session was superior to two sessions; however, in patients with transient loss of consciousness (ie, syncope), outcome after HBO therapy was equivalent to 6 hours of normobaric oxygen therapy.[13]

Given the implications of poor tissue oxygenation with COHb and the relative safety of HBO, a patient with a neurologic abnormality or cardiovascular instability (eg, syncope, altered mental status, myocardial ischemia, and dysrhythmias) is a candidate for HBO (Box 153.2). This should be tempered by the need for transport, often over long distances, for HBO therapy to be obtained. The decision about HBO therapy should not be strictly based on the COHb level, which correlates only weakly with toxicity. For example, patients with prolonged low-level exposure have a "soaking" phenomenon, in which extremely high tissue concentrations of CO occur with low COHb levels. Thus, patients with consequential clinical findings that are considered to be related to CO poisoning should receive HBO, even though their COHb level is relatively low.

In addition to use of HBO in patients with obvious signs of tissue hypoxia or syncope, we recommend referral for HBO for asymptomatic patients with a COHb level of 25%. The decision to perform HBO therapy should be made in the context of transport and other medical requirements, including need for transfer to a burn center. Where doubt remains, consultation with a medical toxicologist, poison center, or the HBO treatment specialist will guide decision-making. Because fetal CO poisoning is associated with dysfunction and death and HBO therapy appears to be safe in pregnancy, we recommend HBO therapy in a pregnant woman with a COHb level of 15% or greater regardless of symptoms. Further study is still needed to define the optimal duration, pressure, and frequency, as well as the cost-benefit and risk-benefit relationships of HBO therapy. At this time, discussion with a regional HBO center or poison control center is advisable. Patients with elevated COHb levels who do not require HBO should be treated with normobaric oxygen delivered by a tight-fitting non-rebreather face mask until the symptoms resolve and the COHb levels fall to normal.

Simultaneous Carbon Monoxide and Cyanide Poisoning (Fire Victims)

Concurrent toxicity from CO and cyanide is widely reported and a major factor in the mortality associated with smoke.[6] Smoke inhalation victims who present with coma and metabolic acidosis can have severe CO poisoning, cyanide poisoning, or both. Nitrite-induced methemoglobinemia, which further reduces the tissue oxygen delivery, may be detrimental to patients with elevated COHb levels or otherwise impaired oxygen delivery.

Sodium thiosulfate, administered without nitrites, or hydroxocobalamin should be given to all smoke inhalation victims with coma, hypotension, severe acidosis, or cardiovascular collapse in whom cyanide poisoning cannot be rapidly excluded.

Disposition

The decision to transfer a patient to an HBO facility should consider the time delay to therapy, patient issues (eg, burns and age), and potential transport-related complications. Patients with minor clinical effects that resolve can be discharged with follow-up, and those with signs of end organ effects, such as chest pain or altered mental status, if not transferred for HBO, should be admitted for observation. All patients exposed to CO require close follow-up for delayed neurologic sequelae.

KEY CONCEPTS

- An asphyxiant is any gas that displaces sufficient oxygen from the breathable air. Treatment consists of removal from exposure, supplemental oxygen, and supportive care.
- Highly water-soluble gases produce rapid irritation and predominantly upper respiratory tract symptoms, such as airway irritation. Poorly water-soluble gases often produce delayed lower respiratory tract findings, such as bronchospasm or acute respiratory distress syndrome (ARDS).
- CO poisoning is confirmed by co-oximetry measurement. Cyanide poisoning is treated empirically when cardiovascular instability (eg, hypotension), altered mental status, or a serum lactate greater than 10 mmol/L are present in a fire victim.
- Hydroxocobalamin is the preferred antidote for most cyanide poisoned patients due to its efficacy, ease of use, and safety in patient with concomitant CO poisoning. Sodium thiosulfate may be administered concomitantly and may provide additional benefit.
- Patients with hydrogen sulfide poisoning generally respond to removal from exposure and ventilatory support.
- Normobaric oxygen therapy is sufficient for many patients with CO poisoning, but we recommend consultation with a hyperbaric oxygen (HBO) facility, poison control center, or medical toxicologist for consideration of HBO therapy for patients with a COHb greater than 25% or any new neurologic or cardiovascular abnormality.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 153: QUESTIONS & ANSWERS

153.1. A laboratory worker is brought to the emergency department (ED) after being found unconscious. His colleague reports that the patient was found with his oxygen mask off while working in a room filled with carbon dioxide. The patient is now awake but reports feeling tired and confused. He has no other complaints. His vital signs and physical examination are normal. What toxin-specific diagnostics test should be ordered for this patient?

A. Carboxyhemoglobin (COHb)
B. Chest radiograph
C. Electrocardiogram
D. Methemoglobin (MetHb)
E. No tests are indicated

Answer: E. Carbon dioxide is primarily a simple asphyxiant, meaning that its major consequential adverse effects stem from its displacement of oxygen in the lungs. Once patients are removed from the source, they generally recover completely. Patients should be observed until this time. COHb measurement would be indicated if there is a suspicion of carbon monoxide (CO) exposure. Chest radiographs should be ordered if patients have pulmonary complaints after an unknown exposure. Electrocardiograms should be ordered if patients are exposed to known cardiac toxins. MetHb levels should be checked when there is suspicion for oxidative stress on the red blood cells.

153.2. A 32-year-old woman presents following exposure to an irritant gas at her job site. She reports cough, burning eyes, and shortness of breath. She has mild tachypnea, with the remainder of her vital signs within normal limits. Her oxygen saturation is 96% on room air. She is noted to have stridor on physical examination. What is the preferred method to evaluate her upper airway symptoms?

A. Arterial blood gas (ABG)
B. Chest radiograph
C. Computed tomography of the neck
D. Fiberoptic laryngoscopy
E. Soft tissue neck radiograph

Answer: D. Fiberoptic or direct laryngoscopy is the preferred method to evaluate upper airway symptoms after exposures to irritant gases. Radiographs and laboratory tests have no role and should not influence the decision to provide a definitive airway. Symptoms can progress rapidly, so patients with upper airway symptoms require either placement of a definitive airway or close observation with frequent serial examinations.

153.3. A 52-year-old man is brought to the emergency department (ED) after being rescued from a house fire. He has not suffered any cutaneous burns. He complains of a sore throat, hoarse voice, and cough. Vital signs are normal. Physical examination reveals soot in his oropharynx and carbonaceous sputum. What therapy should be instituted first?

A. Endotracheal intubation
B. Intravenous (IV) methylprednisolone
C. Nebulized albuterol
D. Nebulized sodium bicarbonate
E. Saline bronchoalveolar lavage

Answer: A. Endotracheal intubation should be performed early in patients with signs and symptoms of significant airway burns (as this patient has). Corticosteroids are not beneficial and can worsen associated injuries. Inhaled beta-agonists are commonly used, but there is no evidence of improved outcome. Inhaled sodium bicarbonate plays no role in the management of smoke inhalation. Bronchoalveolar lavage can be performed if there is suspicion of inhaled debris or toxins, but the airway should first be secured.

153.4. A 47-year-old woman is brought to the emergency department (ED) after being rescued from a house fire. She was found unconscious at the scene and intubated before arrival. Her vital signs are significant for hypotension and tachycardia. Physical examination is significant for soot in the oropharynx. No cutaneous burns are noted. You suspect that she is suffering from cyanide poisoning. What is the most appropriate immediate therapy?

A. Hyperbaric oxygen (HBO)
B. Intravenous (IV) hydroxocobalamin
C. IV methylene blue
D. IV sodium nitrite
E. Observation and supportive care

Answer: B. One of the two major treatments for cyanide poisoning is hydroxocobalamin (the other is the cyanide antidote kit). The nitrite compounds in the cyanide antidote kit convert hemoglobin to methemoglobin (MetHb), which in turn binds to cyanide. However, nitrites produce hypotension and the MetHb prevents proper oxygen deliver, which may compound the reduction in oxygen delivery associated with carbon monoxide (CO) poisoning. HBO has no role in acute cyanide poisoning. Methylene blue has been used for cyanide poisoning in the past but is not as useful as the cyanide kit. Its primary use is in treating methemoglobinemia. General supportive care is not appropriate because there is an antidote for this patient's poisoning.

153.5. A 22-year-old man is brought to the emergency department (ED) after being found unconscious in a car with an intentionally prominent suicide note visible in the window. By the time he arrives in the ED, he has regained consciousness and is complaining of headache and nausea. Paramedics report that the car engine was not running when the patient was discovered. His vital signs and physical examination are normal. Which of the following therapies should be instituted?

A. Hyperbaric oxygen (HBO)
B. Intravenous (IV) methylene blue
C. IV sodium nitrite
D. IV sodium thiosulfate
E. Observation and supportive care

Answer: E. This patient has been exposed to hydrogen sulfide (a common form of suicide in some parts of the world), which has similar effects on the mitochondria as cyanide. However, hydrogen sulfide is rapidly removed from the body; and as long as patients are recovering, removal from the source is usually all that is necessary. HBO and methylene blue have no role in hydrogen sulfide poisoning. Sodium nitrite can be used in patients who are not recovering once removed from the source or for severe exposures. Sodium thiosulfate is not necessary because hydrogen sulfide is detoxified by a different pathway than cyanide and does not need a sulfur donor.

153.6. A 51-year-old man is brought to the emergency department (ED) after being found unconscious and was intubated by emergency medical services (EMS) before arrival. His vital signs reveal hypotension but are otherwise normal. His physical examination is nonspecific. On 100% oxygen by endotracheal tube, his pulse oximetry reveals 100% saturation. Results of an arterial blood gas (ABG) are pH 7.05, partial pressure of carbon dioxide (Pco_2) 27 mm Hg, and partial pressure of oxygen (Po_2) 65 mm Hg. Which one of these findings is inconsistent with simple carbon monoxide (CO) poisoning?

A. Hypotension
B. Oxygen saturation 100%
C. Pco_2 27 mm Hg
D. pH 7.05
E. Po_2 65 mm Hg

Answer: E. Measurement of oxygen saturation and Po_2 values is complicated in CO poisoning. Carboxyhemoglobin (COHb) is essentially falsely read as oxyhemoglobin by pulse oximeters, so a high oxygen saturation is expected by pulse oximetry. Po_2 is a measurement of dissolved oxygen in the blood; this result is independent of CO exposure and is not useful in determining whether CO poisoning is present; thus it should be normal. Metabolic acidosis with an elevated lactate is common because CO impairs aerobic metabolism; respiratory compensation is appropriate.

153.7. What is the major benefit of hyperbaric oxygen (HBO) therapy for patients suffering from carbon monoxide (CO) poisoning?

A. Decreased rate of hospitalization
B. Improvement of 24-hour mortality
C. Improvement of 30-day mortality
D. Prevention of delayed cardiovascular complications
E. Prevention of delayed neuropsychiatric complications

Answer: E. There is controversy regarding the role of HBO therapy for patients with CO poisoning, but the best evidence suggests that it can significantly decrease the incidence of delayed neuropsychiatric complications. There is no change in rate of hospitalization, nor on overall mortality, either short term or long term. There are no delayed cardiovascular symptoms associated with CO poisoning.

153.8. Assuming that all patients have similar vital signs and complaints of headache and nausea, which of the following patients suffering from carbon monoxide (CO) poisoning should be considered highest priority for hyperbaric oxygen (HBO) therapy?

A. A 22-year-old otherwise healthy man with a carboxyhemoglobin (COHb) level of 30%
B. A 25-year-old otherwise healthy pregnant woman with a COHb level of 25%
C. A 30-year-old otherwise healthy man also suffering from cyanide poisoning with a COHb level of 15%
D. A 35-year-old otherwise healthy woman with second-degree burns to 20% of her body and with a COHb level of 20%
E. A 67-year-old asymptomatic woman with coronary artery disease and with a COHb level of 25%

Answer: B. Pregnant patients should be considered for HBO therapy. CO binds more strongly to fetal hemoglobin than to adult hemoglobin and can cause severe hypoxia to the fetus. There is controversy about an absolute level of COHb that requires HBO therapy. HBO does not benefit cyanide victims, nor is it indicated in uncomplicated burn patients or those with stable comorbidities.

CHAPTER 154

Lithium

Jillian L. Theobald | Steven E. Aks

PRINCIPLES OF TOXICITY

Lithium has been used therapeutically since the mid-1800s where it was initially prescribed to treat gout. Lithium compounds such as lithium bromide were historically used as a hypnotic, whereas lithium iodide was used to treat syphilis. Remarkably, lithium chloride was introduced as a table salt alternative for heart failure patients in the twentieth century until deaths led to its removal from the United States market. Lithium was approved for the treatment of bipolar disorder in 1970, and it remains one of the most effective agents for both depressive and manic symptoms.

Lithium is a monovalent cation with a narrow therapeutic range, and significant toxicity can result when outside of this range. Lithium largely has no effect when given in therapeutic doses to patients without mood disorders. In spite of long-term therapeutic use, the mechanism by which lithium acts is still not fully understood. Its efficacy in the treatment of psychiatric illnesses is thought to be due to the modulation of neurotransmitters, which has downstream effects through cell signaling and molecular mechanisms.[1,2]

Lithium is rapidly absorbed from the gastrointestinal tract and peaks in the serum 1 to 2 hours after ingestion of immediate release preparation and 4 to 5 hours with sustained release preparations. In overdose situations, absorption and peak concentrations may be delayed. Once absorbed, lithium enters the serum followed by a delayed distribution to the tissues. In therapeutic dosing, lithium reaches a steady state within about 6 hours after the last dose. Therefore, lithium levels must be interpreted in the context of the dosing. Sustained-release formulations or concretions formed in the gut may extend the time to peak absorption well beyond 6 hours in the overdose setting. Lithium is not metabolized and is excreted unchanged in the urine. Any changes in renal excretion due to conditions such as dehydration, hyponatremia, or renal dysfunction will lead to increases in serum lithium levels.

CLINICAL FEATURES

The classic presentation of significant lithium toxicity comprises altered mental status; tremors; hyperreflexia, clonus, or fasciculations; and vomiting or diarrhea. However, clinical features of lithium toxicity depend on whether it is acute or chronic in nature (Table 154.1). Thus, evaluation of the potentially lithium toxic patient requires knowledge of whether the patient was previously taking lithium, the timing of the last dose, and the amount of drug ingested. Acute toxicity usually follows a recent ingestion in a patient who is not therapeutically taking lithium. Acute toxicity typically manifests with gastrointestinal symptoms such as vomiting and diarrhea and can mimic many other disease states. Neurologic consequences of an acute lithium overdose (such as, altered mental status and seizures) occur several hours later after lithium redistributes to the brain, but in some cases where lithium has delayed-release properties, this can occur even 12 or more hours after ingestion. These consequences are similar to chronic lithium toxicity. Chronic toxicity is caused by an increase in serum levels of lithium in a patient who is regularly taking lithium. This can either be from reduced excretion, renal insufficiency, or dose adjustment (either by a clinician or by the patient). Chronic lithium toxicity causes predominantly neurological symptoms. Acute-on-chronic toxicity occurs when a patient with a stable steady-state lithium level takes a substantial additional amount of lithium, whether intentional or accidentally. These patients present with a combination of both acute and chronic toxicity signs and symptoms. Either acute or chronic toxicity can result in cardiac conduction abnormalities or bradycardia; however, these are uncommon.[3]

Long-term chronic use of lithium can lead to nephrogenic diabetes insipidus and hypothyroidism. Both of these conditions are reversible with discontinuation of the medication and respond well to conventional management.[4] Hypercalcemia and hyperparathyroidism also can occur and reverse upon discontinuation of lithium. Patients chronically taking lithium can develop the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). Patients with SILENT will often have persistent cerebellar and brain stem dysfunction, dementia, and extrapyramidal signs even after lithium use has been discontinued for more than 2 months. Use of lithium during early pregnancy may increase the risk for cardiovascular abnormalities in the fetus.[5] Women taking lithium who present to the emergency department (ED) with newly diagnosed pregnancy should follow up with an obstetrician for fetal evaluation and monitoring.

DIFFERENTIAL DIAGNOSES

Lithium toxicity is nonspecific and may present in a manner similar to many systemic and neurologic disorders, so obtaining a history of use or ingestion is critical to making the diagnosis. Nausea and vomiting is common with viral syndromes and also with ingestion of many pharmaceuticals, such as salicylates and iron. The neurological manifestations of lithium toxicity (such as, tremors, seizures, and altered mental status) may prompt consideration of withdrawal syndromes, such as from alcohol or benzodiazepines, sympathomimetic toxicities (cocaine and amphetamines), serotonin syndrome, and neuroleptic malignant syndrome.

DIAGNOSTIC TESTING

Lithium concentrations should be obtained in all patients who are taking lithium, or have access to lithium, and present with potential toxicity. Because of the insidious and nonspecific nature of chronic lithium toxicity, a serum lithium level is also advisable in patients who are on lithium maintenance, regardless of their reason for presentation (Box 154.1). Therapeutic serum concentrations of lithium are between 0.6 mEq/L to 1.2 mEq/L. Serum levels are in a steady state about 6 hours after ingestion of a therapeutic dose; however, in overdose, peak concentrations can occur beyond 6 hours. We recommend obtaining serial

TABLE 154.1

Clinical Features of Lithium Toxicity

CLINICAL FEATURES	TYPE OF TOXICITY	
	ACUTE	CHRONIC
Gastrointestinal[1]	Nausea Vomiting Diarrhea	Mild or nonexistent
Neurological[11,12]	Similar to chronic toxicity, occurs several hours after lithium distribution to the brain	Tremors Clonus Hyperreflexia Somnolence Extrapyramidal symptoms Coma Seizures
Cardiac[13-14]	Sinus node dysfunction AV blockade Brugada pattern on ECG Ischemic changes on ECG QTc prolongation	

AV, Atrioventricular; *ECG,* electrocardiogram.
Modified from references 1 and 10–14.

BOX 154.1

Diagnostic Testing for Lithium

Serum lithium level
Serum electrolytes
Electrocardiogram (ECG)
If the clinical picture dictates:
Acetaminophen/salicylate levels
Thyroid function tests

concentrations every 2 to 4 hours until a decline is observed. Serum electrolytes should be obtained because lithium can cause alterations in calcium and sodium, most commonly hypercalcemia and hypernatremia. If there is a clinical concern for thyroid dysfunction, then thyroid studies should be obtained. In patients presenting with an acute ingestion, both acetaminophen and aspirin levels should be sent to evaluate for possible co-ingestants. Finally, an electrocardiogram (ECG) should be obtained and cardiac monitoring initiated in patients presenting with an acute overdose. An ECG may also be indicated for patients on lithium chronically given the propensity of lithium to cause conduction abnormalities.

MANAGEMENT

No specific antidote exists for lithium toxicity, and activated charcoal does not bind lithium. Supportive care and enhanced elimination are the mainstays of treatment.

Because lithium is primarily excreted unchanged by the kidney, intravenous crystalloid should be administered early. Most patients who are lithium-toxic are dehydrated because of gastrointestinal losses in acute toxicity or from underlying dehydration leading to chronic toxicity. Crystalloid should be infused as a 1 L bolus followed by a continuous infusion at 150% of the calculated maintenance rate if there are no contraindications, such as congestive heart failure. Diuretics are contraindicated, because they can cause worsening dehydration and reabsorption of lithium. Electrolyte abnormalities, if significant, should be corrected.

We do not recommend the use of whole bowel irrigation (WBI) in routine lithium ingestions. Although a 2015 position paper suggests that WBI can be considered after massive overdose, there is only scant evidence that WBI can decrease the amount of lithium absorbed in non-toxic doses, and there no clinical evidence of benefit in overdose.[6] Similarly sodium polystyrene resins (eg, Kayexalate) have been proposed to assist in the elimination of lithium by sodium-lithium exchange; however, no studies demonstrate an actual impact on clinical outcome, and we do not recommend their use in lithium poisoning.[7]

Lithium is highly dialyzable and dialysis is indicated for patients exhibiting signs of severe lithium toxicity (Box 154.2). Patients with severe neurological toxicity (such as, seizures, clonus, and hyperreflexia) should be dialyzed to reduce serum lithium levels below 1.0 mEq/L.[8] Also, patients with impaired renal function or who cannot tolerate fluids will not be able to effectively eliminate lithium. In these patients, hemodialysis should be performed. The level of evidence for dialysis thresholds based solely on concentration is poor. We recommend, dialysis for serum levels above 4 mEq/L in acute toxicity and levels above 2.5 mEq/L in chronic toxicity regardless of symptoms.[9] Serum lithium concentrations can rise or rebound after dialysis sessions, and a steady state concentration should be determined at 6 hours post-procedure.

BOX 154.2

Indications for Dialysis in Lithium Poisoned Patients

Severely symptomatic patients
Unable to tolerate fluid hydration
Renal impairment
Acute toxicity: Levels above 4 mEq/L
Chronic toxicity: Levels above 2.5 mEq/L

DISPOSITION

Disposition depends largely on the extent of clinical toxicity and the psychiatric status of the patient. Patients manifesting clinical signs of neurotoxicity should be admitted. Patients with an acute overdose with significant cardiologic or neurologic symptoms and increasing lithium levels should be admitted to a hospital with hemodialysis capabilities. In these cases, we recommend consultation with a regional poison center or medical toxicologist. Patients with large ingestions of sustained release lithium should also be placed in observation status or hospitalized for serial monitoring of lithium concentrations until declining serum levels are documented. Patients with significant altered mental status, seizures, or requiring dialysis should be monitored in an intensive care or equivalent unit. Patients who are asymptomatic with normal physical examination findings 6 hours after ingestion of immediate release lithium preparations or 12 hours after a sustained release preparation can be discharged or cleared for psychiatric evaluation.

KEY CONCEPTS

- The clinical pattern of acute and chronic toxicity is different. Gastrointestinal symptoms occur early and neurological toxicity manifest late in acute toxicity. Neurological findings (such as, tremors, clonus, and somnolence) often are presenting signs of chronic lithium toxicity and gastrointestinal symptoms may be absent.
- Neither activated charcoal nor whole bowel irrigation (WBI) is indicated in the routine management of acute or chronic lithium toxicity.
- Serial lithium concentrations should be obtained every 2 to 4 hours initially to determine the peak level and the need for dialysis.
- Fluid hydration with crystalloid is essential to enhance the removal of lithium through the kidney. Diuretics are contraindicated.
- We recommend dialysis for acute lithium concentrations >4 mEq/L, and chronic lithium concentrations >2.5 mEq/L, or for patients with signs of severe neurological toxicity regardless of the concentration.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 154: QUESTIONS & ANSWERS

154.1. What are the two most common electrolyte abnormalities seen in chronic lithium toxicity—hypernatremia and hypercalcemia?

A. Hyperkalemia
B. Hypernatremia
C. Hypokalemia
D. Hypomagnesemia
E. Hyponatremia and hypercalcemia

Answer: E. Hyponatremia and hypercalcemia are frequently seen in cases of acute lithium overdose. Chronic lithium use can cause hypernatremia.

154.2. Which of the following conditions is most frequently seen in patients with chronic lithium use?

A. Anticholinergic syndrome
B. Diabetes insipidus
C. Hyperthyroidism
D. Hypoparathyroidism
E. Syndrome of inappropriate antidiuretic hormone

Answer: B. Diabetes insipidus commonly occurs in patients on chronic lithium therapy or with chronic overdose. Diabetes insipidus can cause dehydration and a further increase in lithium concentration and is a frequent contributory cause to chronic lithium toxicity. Rarely, hypothyroidism can also develop. Lithium use is also associated with neuroleptic malignant syndrome and serotonin syndrome but none of the other listed conditions.

154.3. Which of the following drugs should be used with caution in patients taking lithium?

A. Acetaminophen
B. Hydrochlorothiazide
C. Metformin
D. Metoprolol
E. Penicillin

Answer: B. Hydrochlorothiazide, other diuretics, angiotensin-converting enzyme (ACE) inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) can increase lithium levels and consequently cause chronic lithium toxicity by interfering with renal elimination. Lithium has also been implicated in serotonin syndrome when combined with other drugs, such as monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitor (SSRIs), dextromethorphan, and meperidine. None of the other drugs listed causes significant interactions with lithium.

154.4. A 26-year-old woman presents following a witnessed seizure. She was found with an empty bottle of lithium and a suicide note. Her vital signs reveal hypotension and tachycardia. She is lethargic, and her only response is to withdraw from painful stimuli. The remainder of her physical examination is normal. Laboratory tests including a serum lithium level are pending. Which of the following treatments is the most appropriate?

A. Activated charcoal
B. Forced diuresis
C. Hemodialysis
D. Urinary alkalinization
E. Whole bowel irrigation (WBI)

Answer: C. Hemodialysis is the most effective way to remove lithium. It can remove lithium at a rate five to seven times the rate of typical renal elimination. Common indications for dialysis include decreased level of consciousness and seizures. Activated charcoal does not adsorb lithium. Lithium overdose patients are often dehydrated and occasionally hyponatremic and should be fluid resuscitated, but once dehydration is corrected, forced diuresis is of no benefit and can be detrimental. Similarly, urinary alkalinization causes more harm than good and should be avoided. Because this patient has already experienced a seizure, the administration of WBI is not advised. In addition, the seizure suggests that the brain concentration of lithium is already toxic and this is not improved by WBI.

CHAPTER 155

Antipsychotics

Aaron B. Skolnik | Jessica Monas

PRINCIPLES OF TOXICITY

In 1950, promethazine was synthesized in an effort to develop antihistamines but proved to potentiate the effects of anesthetics and its use was widely adopted. An attempt to derive similar drugs led to the synthesis of chlorpromazine. It was discovered that patients treated with this drug became sedate and apathetic (*neuroleptic* effects), and chlorpromazine was first used successfully to treat a patient with psychosis in 1951. Antipsychotics were revolutionary because, prior to their development, pharmacotherapy for psychosis had focused on tranquilization rather than modification of disease.[1,2]

In 1956, clozapine was synthesized and demonstrated that a drug could treat psychosis without significant extrapyramidal effects at therapeutic doses. Agranulocytosis led to clozapine's withdrawal from the market in 1974. It was reintroduced with mandatory monitoring in 1990 because of its efficacy in treatment-resistant schizophrenia. Clozapine became the precursor of the *atypical* antipsychotics.[3,4]

The term *neuroleptic* has since been replaced with *antipsychotic,* because newer agents are less sedating. Antipsychotic medications are used to treat schizophrenia, schizoaffective disorders, mania, anxiety disorders, and psychoses (including those associated with substance use and withdrawal). In the last decade, antipsychotic prescribing has increased dramatically, including off-label and non-psychosis use.[5] In 2013, more than 45,000 exposures and 150 deaths attributable to antipsychotics were reported to poison control centers in the United States. In addition to sedatives and hypnotics, antipsychotics comprised the group of drugs with the greatest increase per year in serious adverse outcomes.[6]

All antipsychotics are dopamine receptor antagonists. Multiple schemas exist for classification of antipsychotic medications, including chemical structure, clinical effects, receptor affinities, and adverse effects. Commonly, antipsychotics are divided into typical, or first-generation antipsychotics (FGAs), and atypical, or second-generation antipsychotics (SGAs). This division is based on the premise that SGAs exhibit less extrapyramidal symptoms, treat negative symptoms of thought disorders, and typically have 5-hydroxytryptamine type 2A ($5\text{-}HT_{2A}$) serotonin receptor antagonism in addition to dopamine receptor antagonism. FGAs are sometimes also classified as low-potency or high-potency on the basis of their affinity for the dopamine D_2 receptor subtype (Box 155.1).[1,7] In general, low-potency FGAs are the most sedating. Movement disorders are significant adverse side effects of FGAs. Movement disorders also occur with SGAs but with lower frequency. Although neuroleptic malignant syndrome (NMS) can occur with all antipsychotic agents, it occurs with much less frequency with SGAs.[8]

Pathophysiology

Antipsychotic medications have both psychiatric and non-psychiatric clinical uses, and they are widely used and widely available. The antiemetic effects of prochlorperazine, promethazine, and droperidol are secondary to blockade of dopamine receptors in the chemoreceptor trigger zone of the medulla. Prochlorperazine and droperidol abort migraine headaches by preventing dopamine-mediated meningeal artery vasodilation. Chlorpromazine is the historical drug of choice for intractable hiccups, although other antipsychotics have since been used.[9,10] Haloperidol and pimozide are FDA-approved treatments for Tourette syndrome, although several SGAs have also been used experimentally.[11]

Toxicity of antipsychotic drugs can be broadly divided into three categories: exaggeration of pharmacologic effects (as occurs in acute overdose), undesired clinical effects occurring in therapeutic use such as extrapyramidal syndromes, and idiosyncratic effects such as NMS.

Most antipsychotics exert effects at other receptors and ion channels in addition to D_2 receptor antagonism. Common "off-target" effects include alpha-1 adrenergic receptor antagonism, muscarinic acetylcholine receptor antagonism, histamine H_1 receptor antagonism, fast voltage-gated sodium channel blockade, and delayed potassium rectifier channel blockade.

Alpha antagonism may result in orthostatic hypotension. Muscarinic antagonism can produce minor side effects in therapeutic use or frank anticholinergic toxicity in acute overdose. Many FGAs have other properties similar to antihistamines including sedation, both in therapeutic use and overdose.

Phenothiazine antipsychotics, including mesoridazine and thioridazine, are structurally related to tricyclic antidepressants (TCAs) and similarly exhibit sodium channel blockade that may lead to wide complex dysrhythmias. Many agents inhibit potassium rectifying currents resulting in QT prolongation and, potentially, torsades de pointes. The degree of prolongation varies between antipsychotics, increasing in a dose-dependent manner, and with concomitant use of other QT-prolonging drugs.[12] A direct correlation between degree of QT prolongation and risk of torsades de pointes has not been established, but antipsychotics are associated with increased risk of sudden death, particularly with comorbid cardiac disease and in elderly patients.[13,14] Psychotic disorders alone are also associated with increased risk of sudden death.[15] Clozapine can lead to myocarditis sometimes accompanied by eosinophilia and eosinophilic myocardial infiltrates in which a type I hypersensitivity mechanism has been proposed.[16]

Antipsychotic drugs distribute throughout the brain and block dopamine receptors in multiple regions. Mesolimbic D_2 blockade is desirable in reducing positive symptoms of schizophrenia. However, at similar degrees of D_2 receptor occupancy, blockade of D_2 receptors in the nigrostriatal pathway produces undesired extrapyramidal symptoms. Extrapyramidal symptoms can be immediate or delayed after initiation of drug therapy. Acute extrapyramidal symptoms include dystonia, akathisia, and drug-induced Parkinsonism. Second generation antipsychotics, in general, have lower affinity for the dopamine receptor and have serotonin receptor antagonism, both of which are believed to reduce extrapyramidal symptoms.[17,18] The propensity for antipsychotics to produce extrapyramidal symptoms is inversely proportional to the agent's muscarinic receptor antagonism.[18]

BOX 155.1

Classification of U.S. Food and Drug Administration Approved Antipsychotics*

LOW POTENCY (FIRST-GENERATION ANTIPSYCHOTICS)
Chlorpromazine (Thorazine)
Fluphenazine (Prolixin)
Perphenazine (Trilafon)
Promethazine (Phenergan)
Thioridazine (Mellaril)

HIGH POTENCY (FIRST-GENERATION ANTIPSYCHOTICS)
Droperidol (Inapsine)
Haloperidol (Haldol)
Loxapine (Loxitane)
Pimozide (Orap)
Thiothixene (Navane)
Trifluoperazine (Stelazine)

ATYPICAL (SECOND-GENERATION ANTIPSYCHOTICS)
Aripiprazole (Abilify)
Asenapine (Saphris)
Clozapine (Clozaril)
Iloperidone (Fanapt)
Lurasidone (Latuda)
Olanzapine (Zyprexa)
Paliperidone (Invega)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Ziprasidone (Geodon)

*Current as of March 2015.

BOX 155.2

Antipsychotics With Antimuscarinic Effects

TYPICAL ANTIPSYCHOTICS
Chlorpromazine (Thorazine)
Loxapine (Loxitane)
Mesoridazine besylate (Serentil)
Thioridazine (Mellaril)

ATYPICAL ANTIPSYCHOTICS
Clozapine (Clozaril)
Olanzapine (Zyprexa)
Quetiapine (Seroquel)

Data from Levine M, Ruha AM: Overdose of atypical antipsychotics: clinical presentation, mechanisms of toxicity and management. CNS Drugs 26:601-611, 2012; Richelson E: New antipsychotic drugs: how do their receptor-binding profiles compare? J Clin Psychiatry 71:1243-1244, 2010.

Rapid dissociation from the D_2 receptor is also hypothesized to reduce the risk of extrapyramidal symptoms, as in the case of clozapine.[19]

Tardive dyskinesia and tardive dystonia may develop after prolonged use of dopamine blocking medications and have been reported with all antipsychotics. One proposed pathophysiological mechanism for tardive dyskinesia is chronic dopamine receptor blockade in the nigrostriatal pathway leading to D_2 receptor upregulation and hypersensitivity to dopamine.[20]

The pathophysiologic mechanism of NMS, an idiosyncratic reaction to antipsychotic medication, is poorly understood. It is hypothesized that D_2 receptor blockade in the nigrostriatum and hypothalamus leads to rigidity and hyperthermia, respectively, with downstream dysregulation of the autonomic nervous system.[21]

The historical incidence of agranulocytosis in patients treated with clozapine was approximately 1%. With mandated white blood cell count monitoring, the incidence in the United States dropped to 0.38%.[3] Although the mechanism of agranulocytosis is unclear, research supports an immunogenic cause and direct cytotoxic effect on human bone marrow mesenchymal stromal cells.[22]

Therapeutic use of antipsychotics has been associated with weight gain, dyslipidemia, glucose intolerance, new-onset diabetes, and the metabolic syndrome.[23]

Antipsychotic drugs have been associated with an increased risk of venous thromboembolic (VTE) disease, primarily in observational and case-control studies. Multiple hypotheses have been proposed to explain the association, including metabolic effects and the possibility that thought disorders may predispose patients to VTE disease.[24] The risk of VTE disease may be highest with clozapine, olanzapine, and low-potency FGAs.[24]

CLINICAL FEATURES

Acute Overdose

In overdose, antipsychotics produce signs and symptoms that are exaggerations of their pharmacologic profile. Most patients develop symptoms within a few hours post-ingestion. Paliperidone has a unique delayed-delivery system and late onset of symptoms has been reported.[25] Central nervous system (CNS) depression is common, ranging from mild sedation to coma. Anticholinergic delirium and agitation may result from drugs with antimuscarinic effects (Box 155.2). Airway reflexes can be impaired and respiratory depression can occur after overdose. Pupils may be of variable size; anticholinergic effects promote mydriasis, whereas miosis, resulting from alpha-antagonism, may mimic opioid toxicity. Mild orthostatic hypotension is also a common finding from alpha-adrenergic blockade.[26]

Variable evidence suggests that antipsychotics lower seizure threshold; however, with the exception of clozapine, seizures rarely occur in overdose. Acute extrapyramidal symptoms have also been reported in overdose.[26,27]

Acute Extrapyramidal Syndromes

Acute dystonia presents with involuntary spasms of antagonistic muscle groups most often involving facial, neck, back, or limb muscles. This results in trismus, facial grimacing, dysarthria, tongue and lip distortion, torticollis, or oculogyric crisis. Half of patients who develop acute dystonia do so within 48 hours of receiving the implicated drug. Symptoms may develop rapidly or may be delayed hours to days, although most acute dystonias develop within 5 days of drug administration. Recurrent dystonic reactions may occur, even following a single dose of an antipsychotic.[28] *Laryngeal dystonia,* a rare but life-threatening form of dystonia, manifests as dyspnea, stridor, choking sensation, or respiratory distress and has been reported with both FGAs and SGAs.[29] Increased risk of death due to choking has been reported in patients treated for schizophrenia; a review of sudden deaths in schizophrenia patients listed airway obstruction as cause of death in 7.8%.[15,30]

Akathisia (from Greek, "*unable to sit*") is characterized by subjective feelings of internal restlessness associated with objective motor findings, including repetitive foot shuffling, truncal shifting, or pacing. Akathisia usually develops within hours to days of initiating or increasing the dose of an antipsychotic. One study reported that almost half of emergency department (ED) patients given 10 mg of intravenous (IV) prochlorperazine

developed akathisia within 1 hour. However, subsequent studies of ED patients have demonstrated markedly decreased incidence, ranging from 5% to 15%, with slower drug infusion.[31-33]

Drug-induced Parkinsonism manifest by bradykinesia, mask-like facies, shuffling gait, rigidity, and tremor may occur in up to 60% of patients treated with antipsychotics and frequently develops 2 to 4 weeks after initiating treatment. Ninety percent of cases develop within 3 months.[28]

Rabbit syndrome is a perioral, tongue-sparing dyskinesia in which rhythmic lip and nose movements resemble the chewing movements of a rabbit. Rabbit syndrome is also associated with prolonged antipsychotic therapy.[34]

Tardive Dyskinesia

Tardive dyskinesia is a chronic and sometimes permanently disabling movement disorder induced by prolonged use of dopamine antagonists, including antipsychotic medications. Typical signs of tardive dyskinesia include rapid, involuntary movements of the face (chewing, blinking, grimaces, and tongue movements). Tardive dyskinesia may also cause abnormal limb, truncal, or pelvic movements. The risk of tardive dyskinesia with sustained antipsychotic treatment is estimated around 5% per year and may be higher in the elderly. Prevalence is estimated at approximately 20% of psychiatric patients undergoing long-term treatment. Tardive dyskinesia is difficult to treat and is frequently permanent, with age and duration of treatment associated with irreversibility.[20] Reduction of the antipsychotic dose or a change to an alternative agent should be considered. Amantadine, levetiracetam, and clonazepam have improved symptoms in clinical trials.[35]

Respiratory dyskinesia is a variant of tardive dyskinesia that is characterized by orofacial dyskinesia, dyspnea, dysphonia, and respiratory alkalosis. This chronic disorder often goes undiagnosed and can cause repeated bouts of aspiration pneumonia.[36]

Neuroleptic Malignant Syndrome

NMS is a serious idiosyncratic drug reaction that is potentially life threatening. NMS typically develops during the first 2 weeks of therapy but has occurred during long-term drug regimens. The incidence of NMS in developed countries has been reported as approximately 2% of patients exposed to antipsychotics.[37,38] Risk factors include rapid dose escalation, cumulative drug dosage, high-potency antipsychotics, parenteral formulations, dehydration, preceding psychomotor agitation, prior brain injury, poorly controlled extrapyramidal symptoms, and previous episodes of NMS. Concomitant treatment with lithium increases the risk for NMS.[21,38-40] Abrupt withdrawal from dopaminergic agents used to treat Parkinson's disease may cause a syndrome clinically indistinguishable from NMS, termed *Parkinsonian-hyperpyrexia syndrome* or *neuroleptic malignant-like syndrome.*[41] All antipsychotic agents have been implicated in NMS, including SGAs.[8]

NMS is characterized by altered mental status, muscular rigidity, hyperthermia, and autonomic instability (Table 155.1). Other features of NMS may include sialorrhea, dysarthria, dysphagia, metabolic acidosis, elevated transaminases, sodium imbalance, dehydration, elevations in catecholamines, generalized slowing on electroencephalogram (EEG), coagulopathy, pulmonary embolism, and renal failure.[42,43]

Most patients have the cardinal features of altered mental status, muscle rigidity, hyperthermia, and autonomic instability within 1 to 2 weeks after starting an antipsychotic or abruptly increasing the dose.[44] However, the signs of NMS may develop gradually and in any order. Clinicians should discontinue antipsychotic drugs in patients with suspected NMS. Most episodes resolve with appropriate care within 2 weeks after cessation of the offending medication; symptoms may wax and wane for months.[45]

TABLE 155.1

Prevalence of Suggested Diagnostic Criteria for Neuroleptic Malignant Syndrome

CRITERION	PREVALENCE
Exposure to a dopamine antagonist or withdrawal of a dopamine agonist within 72 hours:	
Hyperthermia (>38° C) on at least two occasions, measured orally	98%
Rigidity	97%
Mental status alteration	97%
Creatinine kinase elevation (at least four times the upper level of normal)	95%
Sympathetic nervous system lability, defined as at least two of the following:	
Blood pressure elevation (SBP or DBP ≥25% above baseline)	61%*
Blood pressure fluctuation (≥20% DBP change or ≥25% SBP change in 24 hours)	
Diaphoresis	98%
Urinary incontinence	
Hypermetabolic state (heart rate ≥25% and respiratory rate ≥50% above baseline)	88%†
Negative evaluation for other toxic, metabolic, infectious, or neurologic causes	

*Elevated or labile blood pressure
†Tachycardia
DBP, Diastolic blood pressure; *SBP,* systolic blood pressure.
Modified from Gurrera RJ, et al: An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. J Clin Psychiatry 72:1222-1228, 2001.
Prevalence data from Caroff SN, Mann SC: Neuroleptic malignant syndrome. Med Clin North Am 77:185, 1993.

Cardiovascular Toxicity

The most common cardiac effect is sinus tachycardia with a normal QRS duration. A few FGAs can cause QRS prolongation; however, co-ingestions should be considered. QT prolongation should be considered a "class effect" of all antipsychotic medications. QT prolongation occurs during therapeutic dosing and in overdose of many antipsychotic agents. Therapeutic doses of thioridazine, followed by ziprasidone, prolong the QT interval more than risperidone, olanzapine, quetiapine, or haloperidol.[14] QT prolongation associated with torsade de pointes is a well-described adverse effect of thioridazine, mesoridazine, droperidol, haloperidol, chlorpromazine, sertindole, sulpiride, and pimozide.[14,46] Among SGAs, ziprasidone carries the greatest risk of QTc prolongation. SGAs, ziprasidone carries the greatest risk of QTc prolongation, and torsades de pointes has been reported with amisulpride overdose.[47-49]

Myocarditis has been reported in less than 1% of patients taking clozapine. The majority of cases develop in the first 2 months of treatment. A nonspecific, flu-like prodrome frequently precedes the onset of myocarditis by days to weeks. The spectrum of disease ranges from subclinical, asymptomatic disease to decompensated heart failure.[16,50]

Agranulocytosis

Clozapine can produce life-threatening agranulocytosis; most cases develop within 6 weeks to 6 months of starting the drug. With monitoring and treatment, attributable mortality is approximately 1 in 10,000.[3] Agranulocytosis has not been reported after acute clozapine overdose. Among other antipsychotics, the risk of

agranulocytosis is next greatest with chlorpromazine, followed by olanzapine, although agranulocytosis and neutropenia have been reported with many FGAs and SGAs. With early recognition, antipsychotic-induced neutropenia typically resolves within 3 to 4 weeks of discontinuing the drug.

Seizures

The incidence of new-onset seizures among patients treated with antipsychotics is higher than the background rate in the general population, suggesting antipsychotic medications can lower the seizure threshold.[51] Phenothiazines have been shown in observational studies to increase the risk of seizures.[52] However, antipsychotic-related seizures are rare in therapeutic use except for clozapine, which causes a dose-related increase in risk of seizures (up to 5% at high doses) and induces electroencephalographic abnormalities.[53] Antipsychotics can be prescribed for patients with a known seizure disorder.[54]

DIFFERENTIAL DIAGNOSES

The differential diagnosis of antipsychotic toxicity includes a broad list of agents and clinical conditions that produce altered mental status, orthostatic hypotension, anticholinergic toxidrome, seizure, QT prolongation, or torsades de pointes, such as TCAs. The differential diagnosis of NMS includes malignant catatonia, serotonin syndrome, heatstroke, sympathomimetic toxicity, acute salicylate poisoning, and other medical conditions (Table 155.2). Malignant hyperthermia should also be considered in patients receiving inhalational anesthetics or succinylcholine.

DIAGNOSTIC TESTING

Quantitative blood levels of antipsychotics are neither readily available nor helpful. As with any patient who presents with suspected drug toxicity, blood glucose concentration, serum acetaminophen level, and directed toxicologic screening are recommended. Aspiration is common among patients with depressed mentation; chest radiography should be performed in hypoxic patients.

An electrocardiogram (ECG) should be obtained in all patients with suspected overdose and in those taking antipsychotics therapeutically with symptoms concerning for cardiotoxicity. If QT prolongation is present, serum potassium, calcium, and magnesium levels should be measured.

Patients who have NMS, extrapyramidal symptoms with marked muscle rigidity, or prolonged seizures are at risk for rhabdomyolysis. In such patients we recommend serum creatinine kinase, assessment of renal function, and urine myoglobin measurements.

Patients who are severely hyperthermic (>40° C) are at risk for multi-system organ failure and disseminated intravascular coagulation. Because severe salicylate poisoning can cause CNS toxicity and hyperthermia due to uncoupling of oxidative phosphorylation, we recommend a serum salicylate level, in addition to serum transaminases and coagulation studies.

Patients taking clozapine, chlorpromazine, or olanzapine who present with infection or fever should be evaluated for neutropenia. We also recommend testing white blood cell counts in patients on other antipsychotics who present with unusual infections or fever without source.

Atypical antipsychotics have been associated with new-onset diabetes and diabetic ketoacidosis (DKA). This typically occurs soon after the onset of treatment and sometimes in the absence of weight gain.[55] Patients in whom DKA is clinically suspected should have blood pH measurement and serum or urine ketones. Salicylism can also produce a clinical picture that mimics DKA.

Other tests, such as brain computed tomography, lumbar puncture, and drug screens may be helpful in some cases to exclude other diagnoses or establish a comorbid condition, but are not indicated when the context and presentation support uncomplicated antipsychotic toxicity as the cause.

MANAGEMENT

General

Treatment of antipsychotic overdose is supportive. Endotracheal intubation and mechanical ventilation may be required due to CNS depression or to support respiration. Dextrose should be given to patients with hypoglycemia. Neither gastric emptying nor activated charcoal is indicated for antipsychotic toxicity. See Chapter 139 for a discussion of the roles of activated charcoal and other methods of gastric decontamination.[56,57]

If sedation and miosis suggest opioid intoxication, a trial of naloxone is warranted. We recommend administering naloxone 0.4 to 2.0 mg intravenous push (IVP) every 2 to 3 minutes and, if effective, titrating to return of normal respiratory rate, oxygenation, and ventilation.

Anticholinergic Toxidrome

Physostigmine has been used to treat anticholinergic (antimuscarinic) delirium from antipsychotic overdoses.[58,59] Contraindications to physostigmine include reactive airway disease and cardiovascular disease (including any intraventricular conduction delay, bradycardia, or heart block).[60] Physostigmine will usually cause a decrease in heart rate through enhanced vagal tone. We recommend avoiding its use in patients who present with seizures, because physostigmine may precipitate additional seizures. In adult patients who have obvious central anticholinergic delirium with agitation, we use physostigmine 1 to 2 mg IV, infused over 5 minutes in the absence of contraindications. In patients in whom agitated delirium is present but the toxidrome is unclear, we use lorazepam 1 to 2 mg IV every 10 to 15 minutes titrated to mild sedation. The delirium reversal effect of physostigmine is usually short-lived (45 to 60 minutes).[60] The use of physostigmine for reversal of anticholinergic delirium does not preclude the use of benzodiazepines for sedation and vice versa.

Seizures

Antipsychotic-induced seizures may be short, self-terminating, and not require pharmacologic treatment. For multiple seizures or status epilepticus, first line treatment is lorazepam 0.1 mg/kg (maximum 4 mg) given intravenously at a rate of 2 mg/min. This dose may be repeated in 5 minutes if seizures have not terminated. Refractory seizures unresponsive to lorazepam can be treated with phenobarbital (15 to 18 mg/kg IV loading dose). In patients who do not have a response to high doses of benzodiazepines (especially patients who are intubated), propofol may be administered (0.3 to 1.25 mg/kg of body weight, up to 4 mg/kg per hour). Use of propofol in this way generally requires intubation and initiation of continuous EEG monitoring if available.

Acute Extrapyramidal Syndromes

Dystonia will usually respond within 30 minutes to diphenhydramine 25 to 50 mg or benztropine 1 to 2 mg intravenously, intramuscularly, or orally. Lorazepam 1 to 2 mg IV may also be effective in patients who do not respond within 1 hour to diphenhydramine or benztropine. IV lorazepam may be repeated in 15 to 20 minutes if dystonia is not improved. Akathisia is treated

TABLE 155.2

Differential Diagnosis of Neuroleptic Malignant Syndrome*

DISEASE	PROPOSED MECHANISM	DIFFERENTIATING FACTOR	TIME COURSE	TREATMENT
Neuroleptic malignant syndrome (NMS)	Impaired thermoregulation in hypothalamus and basal ganglia due to due to dopamine blockade Downstream autonomic nervous system dysfunction	Antipsychotic use Muscle rigidity (see Table 155.2)	Gradual over several days Waxing and waning course	Stop offending medication Hydration Active cooling IV benzodiazepines Non-depolarizing neuromuscular blockade Limited evidence: Dantrolene Dopamine agonists (eg, bromocriptine) Consider ECT for refractory cases
Serotonin syndrome	Excess serotonin levels in CNS	Medications (usually a combination) that increase serotonin levels (eg, SSRIs, MAOIs, lithium, dextromethorphan, meperidine, tramadol) Muscle rigidity (lower > upper extremities) Muscular or ocular clonus	Usually rapid after introduction of new medication or increase in dose	Stop offending medication Hydration Active cooling IV benzodiazepines Cyproheptadine
Malignant or lethal catatonia	Severe manifestation of schizophrenia, mood disorders, other psychiatric disorders, or neurological conditions Multiple mechanisms proposed	Occurs in absence of antipsychotic administration May be clinically indistinguishable from NMS	Gradual, typically over several days	Hydration Active cooling IV benzodiazepines ECT
Sympathomimetic toxicity	Hyperadrenergic state Extreme psychomotor agitation	Occurs in absence of antipsychotic administration Cardiovascular toxicity may be prominent Muscular hyperactivity in lieu of rigidity	Subacute, typically over hours	Hydration Active cooling IV benzodiazepines Alpha-antagonists Vasodilators
Malignant hyperthermia	Mutations in ryanodine receptors or dihydropyridine receptors allow uncontrolled calcium release from sarcoplasmic reticulum	Occurs after administration of inhalational anesthetic or succinylcholine Muscle rigidity	Sudden Provoked by administration of anesthetic	Stop anesthetic Hyperventilation with 100% oxygen Active cooling Dantrolene
Heatstroke	Impaired physiologic mechanisms for heat dissipation (classical) Environment or exercise elevates body temperature beyond range of cooling mechanisms (exertional)	Environmental exposure History Muscle rigidity rare	Subacute, typically over hours	Hydration Active cooling Prevent shivering

*Other clinical entities to consider in the differential diagnosis of NMS include: CNS infection, status epilepticus (including nonconvulsive status), alcohol or sedative hypnotic withdrawal, hypocalcemia, hypoglycemia, hyponatremia, intracranial hemorrhage, other poisoning (eg, anticholinergics, nicotine, salicylates, strychnine, theophylline), sepsis, tetanus, thalamic infarct, thyroid storm, and psychotic agitation.
CNS, Central nervous system; *ECT,* electroconvulsive therapy; *IV,* intravenous; *MAOI,* monoamine oxidase inhibitor; *SSRI,* selective serotonin reuptake inhibitor.

similarly. Patients with akathisia who fail to respond to the above treatments can be given propranolol 10 mg by mouth twice daily until symptoms improve, although supporting evidence is limited.[61] Treatment of drug-induced Parkinsonism includes minimizing the effective antipsychotic dose. Acute therapy begins with an anticholinergic agent, dosed as for dystonia.[34]

Cardiotoxicity

Cardiac monitoring is recommended in patients who are symptomatic or those with ECG abnormalities until the symptoms are mild and resolving or ECG intervals have normalized. Sinus tachycardia with normal ECG intervals is expected in overdose and need not be treated unless secondary cardiac injury is present. Widening of the QRS due to sodium channel blockade is uncommon and is managed similarly to cyclic antidepressant toxicity. We recommend sodium bicarbonate 1 to 2 mEq/kg IVP, which may be repeated every 3 to 5 minutes until QRS narrowing (<114 msec) occurs. Boluses may be repeated or an infusion of 150 mEq/L of sodium bicarbonate in 5% dextrose in water may be infused at twice calculated maintenance rate and titrated to a goal blood pH of 7.5 to 7.55.[62]

Hypotension is generally mild and typically responds to IV sodium chloride bolus and infusion. We prefer sodium chloride as the crystalloid in these cases, because the sodium ion may be beneficial in the context of sodium channel blockade. If hypotension is severe, or persists after 2 L of isotonic crystalloid, a direct-acting vasopressor with alpha-adrenergic agonist is initiated. We recommend norepinephrine IV infusion, started at 1–2 mcg/min and titrated to maintain mean arterial pressure greater than 65 mm Hg.

Correction of hypokalemia, hypomagnesemia, and hypocalcemia shortens the QT interval. Adults with QTc greater than 500 msec or transient torsade de pointes should be given 2 to 4 g of magnesium sulfate IV.[63] Treatment of sustained torsades de pointes includes IV magnesium sulfate up to 4 g total, defibrillation, overdrive pacing, or isoproterenol (see Chapter 69).[64] Any drugs that prolong the QT interval should be avoided.

ED treatment of clozapine-induced myocarditis is supportive. Clozapine treatment should be stopped immediately when the diagnosis is suspected.[50]

Neuroleptic Malignant Syndrome

Treatment of NMS consists of supportive care and discontinuation of all dopamine-blocking medications. Agitation, psychomotor hyperactivity, and muscle rigidity should be treated with liberal doses of IV benzodiazepines. Lorazepam is administered as 1 to 2 mg IV every 5 to 10 minutes, until muscle rigidity improves. Refractory cases or patients at risk for aspiration can be managed with intubation and neuromuscular blockade with a *nondepolarizing* agent (eg, rocuronium). Hyperthermia should be managed with IV fluids and evaporative cooling. To facilitate evaporative cooling, the patient's bare skin is continually misted with water while a cooling fan blows air continuously across the skin surface. The goal of cooling is a reduction in core temperature to less than 39° C within 30 minutes. If rhabdomyolysis is present, it is treated as described in Chapter 119.

Bromocriptine, levodopa, amantadine, rotigotine, lisuride (available in EU, UK, and Canada), and apomorphine have all been tried for treatment of NMS but evidence of benefit is limited.[43,65] Bromocriptine is a dopamine agonist and increases serotoninergic transmission, so it risks exacerbating underlying psychiatric illness or serotonin syndrome. Dantrolene has also been successfully used for treatment of severe rigidity. As rigidity in NMS is believed to originate in the CNS rather than in myocytes, dantrolene offers no mechanistic advantage over benzodiazepines and nondepolarizing neuromuscular blockade. We do not recommend any of these agents as part of routine treatment of NMS.

Electroconvulsive therapy (ECT) may be used in cases of NMS refractory to pharmacologic treatment. Evidence for efficacy is limited, although it is proposed as a treatment of choice in malignant catatonia, which may be indistinguishable from NMS. We recommend ECT in cases of NMS that fail to demonstrate any improvement within 48 hours of benzodiazepine treatment and supportive therapies described earlier.[43,66]

VTE disease is a prominent cause of morbidity and mortality in NMS. Patients with NMS should receive pharmacologic VTE prophylaxis.

DISPOSITION

Patients with NMS and overdose patients with hypotension, coma, torsades de pointes, or airway compromise should be admitted to an intensive care unit. Patients with a prolonged QT interval of any magnitude should have at least 12 hours of cardiac monitoring to ensure that the interval prolongation is resolving and QTc is less than 500 msec. Patients with minimal signs of toxicity should be observed for at least 6 hours from the time of ingestion, with hospitalization for persistent or worsening signs and symptoms. Criteria for hospital discharge include return to normal mental status and resolution of any vital sign, metabolic, and electrocardiographic abnormalities. Psychiatric consultation may be necessary to assess the risk of suicide. Patients with acute dystonia resolved by diphenhydramine or benztropine should continue the drug for 48 hours to prevent recurrence. Patients with drug-induced Parkinsonism who must continue antipsychotic medications may need to use anticholinergic agents long-term. Such patients should be discharged with diphenhydramine 25 to 50 mg by mouth every 6 hours or benztropine 1 to 2 mg by mouth twice daily for at least 48 hours and should be referred to their treating physician, who may reduce the antipsychotic dose or change treatment regimens as necessary. Benztropine, diphenhydramine, and some antipsychotic medications cause anticholinergic effects, so combination therapy may worsen dry mouth, blurred vision, and urinary retention.

KEY CONCEPTS

- Extrapyramidal syndromes are a common complication of antipsychotic medications. First line treatment is benztropine or diphenhydramine. Lorazepam is used in refractory cases.
- The most common finding in antipsychotic overdose is CNS depression. Treatment centers on supportive care, airway management, and cardiac monitoring.
- QT prolongation and torsades de pointes are potential complications of many antipsychotic medications in overdose and can also occur with therapeutic doses.
- Clozapine is associated with potentially life-threatening agranulocytosis. Treatment includes stopping the drug, treating infections, and supportive care.
- The neuroleptic malignant syndrome (NMS) is characterized by altered mental status, hyperthermia, muscle rigidity, and autonomic instability. Supportive care includes airway management, benzodiazepines, treatment of muscular rigidity, and evaporative cooling.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 155: QUESTIONS & ANSWERS

155.1. A 24-year-old man presents with cough and fever. He has schizophrenia for which he takes haloperidol. You diagnose him with community-acquired pneumonia. Which of the following antibiotics could cause a life-threatening arrhythmia if administered to this patient?

A. Amoxicillin/clavulanic acid
B. Azithromycin
C. Cefpodoxime
D. Clindamycin
E. Doxycycline

Answer: B. Antipsychotics can cause QT prolongation, so other drugs that cause QT prolongation should be avoided. Macrolides, fluoroquinolones, and trimethoprim-sulfamethoxazole are common antibiotics that can all cause QT prolongation.

155.2. A 42-year-old man presents complaining that his neck is turned to the right. He states he cannot move his head and his neck hurts. He denies trauma and states that this has never happened before. He has schizophrenia but does not recall the names of his medications. His vital signs are normal and examination reveals palpable spasm of the right trapezius and sternocleidomastoid muscles. What is the most appropriate treatment?

A. Bromocriptine
B. Cyclobenzaprine
C. Diphenhydramine
D. Morphine
E. Prochlorperazine

Answer: C. This patient has an acute dystonic reaction to an antipsychotic medication best treated with an anticholinergic medication, such as diphenhydramine or benztropine. Bromocriptine is a dopamine agonist used to treat pituitary disorders and can worsen psychosis. Cyclobenzaprine can be used for typical muscle spasms but will not significantly improve acute dystonia. Morphine may help but does not resolve the underlying problem. Prochlorperazine is an antipsychotic that can induce acute dystonic reactions and should be avoided in this patient.

155.3. A 22-year-old man is brought to the emergency department (ED) by family because of a change in mental status. They report that 2 days ago the patient had his psychiatric medications adjusted and has been confused since then. The patient's vital signs are: blood pressure, 162/100 mm Hg; heart rate, 143 beats/min; respiratory rate, 22 breaths per minute; and temperature, 40.1° C. On physical examination, the patient is found to have muscle rigidity. Laboratory tests are pending. Intravenous (IV) access is obtained, and crystalloid fluids are started. Cool mist and fans are applied to the patient. What additional therapy is indicated?

A. Acetaminophen
B. Cyproheptadine
C. Dantrolene
D. Diphenhydramine
E. Lorazepam

Answer: E. Lorazepam or another benzodiazepine is indicated in neuroleptic malignant syndrome (NMS). Acetaminophen plays no role in treating the hyperthermia, which should be treated with active cooling measures. Cyproheptadine can be used in serotonin syndrome but does not improve NMS. Dantrolene can be used in malignant hyperthermia but does not improve NMS. Diphenhydramine is used for acute dystonia and does not affect the course of NMS.

CHAPTER 156

Opioids

Jenna K. Nikolaides | Trevonne M. Thompson

PRINCIPLES OF TOXICITY

Opiate is the term for natural agents derived from the poppy plant that have morphine-like pharmacological effects. Example opiates include morphine and codeine. *Opioid* is the more inclusive term, which refers to any synthetic, semisynthetic, or natural agent that has morphine-like properties. Some common semisynthetic opioids are heroin, hydrocodone, oxycodone, hydromorphone, oxymorphone, and buprenorphine. Some common synthetic opioids are fentanyl, methadone, and meperidine. Both *opiate* and *opioid* are terms derived from *opium,* which was the Greek word for the juice of the poppy plant *(Papaver somniferum)*.[1]

Opioids are among the world's oldest known drugs. The therapeutic use of opioids has been a practice since ancient times, with the primary goals being sedation and analgesia. Opioids act on receptors in the central nervous, cardiovascular, pulmonary, and gastrointestinal systems and can also be used therapeutically for their antitussive and antidiarrheal effects.

Pain is a common reason why patients present to the emergency department (ED). As much as 78% of ED visits are related to a painful condition.[2] Since the Joint Commission placed increased attention on pain management and hospitals increased their emphasis on patient satisfaction, there has been a proliferation in the amount of opioid prescriptions written by physicians, including emergency providers.[3] This trend has not led to an actual improvement in overall patient satisfaction but has led to a flood of available opioids into the wider population.[4] According to the Centers for Disease Control and Prevention (CDC), there has been a 300% increase in the sale of opioid analgesics from 1999 to 2011. In 2010 alone, enough prescription opioids were prescribed to medicate every American adult with 5 mg of hydrocodone every 4 hours for 1 month.[5] Consequently, the United States has seen a widespread rise in prescription opioid abuse, overdoses, and deaths. In 2010, approximately 12 million Americans, or 1 in 20, reported use of opioids without a prescription. Nearly 15,000 Americans die annually due to prescription opioid overdose, and overdoses overtook motor vehicle accidents as the number 1 cause of accidental death in 2010.[5,6]

There has been a concomitant resurgence in illicit heroin use. According to the CDC, the death rate from heroin overdose doubled across 28 states in just 2 years, between 2010 and 2012.[7] There has also been a change in demographics of heroin use. Formerly involving primarily inner-city minority populations, the practice has spread geographically beyond urban areas and to white men and women in their late 20s.[8] It is now believed that prescription analgesics are the gateway to heroin use, because the street price of heroin is often the cheaper option for opioid dependent patients.

The wider availability of opioids has affected every population group. This has been especially concerning for pediatric patients, because analgesic prescriptions written for adults can end up in the hands of children.[9,10] Recreational opioid use may be associated with the teenage and young adult population, but unintentional opioid overdose is also a growing concern among chronic pain patients, geriatric patients, and obese patients; because risk is increased by polypharmacy, medical comorbidities, and sleep apnea.

Opioids come in three forms: synthetic, semisynthetic, and natural opiates. There are prescription versions of all three forms, which are available in many different preparations, including tablets, liquids, patches, and even lollipops. Prescription opioids are commonly packaged as combination preparations with acetaminophen, ibuprofen, and aspirin and historically existed in combinations with atropine and camphor. Other prescription oral preparations are formulated with opioid-receptor antagonists, such as naloxone, which has little oral bioavailability to prevent illicit use and tampering for intravenous abuse. There are also prescription drugs that are not chemically classified as opioids, but which display μ opioid receptor agonist, such as tramadol and tapentadol.

Illicit opioids also exist in all three forms. Table 156.1 details some of the known street names for opioids sold illicitly.[11,12] Street names are often unreliable, however, because they are subject to dealers who may want to market or rebrand their product. Heroin (diacetylmorphine), a semisynthetic opioid, is the most widespread street preparation, but recent years have seen a rise in synthetics, such as fentanyl and fentanyl analogues, often mixed with or mislabeled as heroin.[13] Illicit opioid preparations can also be contaminated by the byproducts from the manufacturing process, adulterated with additives to change the preparation's pharmacological effects, and diluted with inert substances to increase bulk. The most common added substances are sugars, caffeine, over-the-counter medications, other drugs of abuse, heavy metals, and infectious agents.[14,15]

Toxicity can occur as a consequence of intentional overdose, intentional recreational abuse, or as an adverse effect of therapeutic use. Although different opioids have receptor preferences in therapeutic doses, this specificity is lost at higher doses.

Opioids are well absorbed via gastrointestinal, intravenous, intramuscular, mucocutaneous, and subcutaneous routes of administration. Depending on the lipid solubility of the specific opioid, they can also be absorbed through nasal, buccal, pulmonary, or transdermal routes. In general, toxicity is less pronounced but more prolonged when ingested than with parenteral administration. In therapeutic doses, an ingested opioid is absorbed in the small intestine within 1 to 2 hours. In toxic doses, delayed gastric emptying prolongs the absorption and clinical effects of the opioid.

Most opioids have a large volume of distribution. Different opioids and their metabolites cross into the blood-brain barrier due to variations in lipid solubility. All opioids undergo hepatic metabolism and renal elimination. Thus changes in hepatic or renal function will alter drug clearance, which could prolong clinical and toxic effects of the specific opioid.

CLINICAL FEATURES

The hallmarks of the opioid toxidrome are central nervous system (CNS) depression, respiratory depression, and miosis. Miosis is caused by stimulation of μ receptors in the Edinger-Westphal

TABLE 156.1

Street Names for Illicitly Obtained Opioids

OPIOID	STREET NAMES
Heroin	Dope, Smack, H, Horse, Junk, Skag, Skunk, Brown Sugar, White Horse, China White
Heroin + acetaminophen and diphenhydramine	Cheese
Codeine ± acetaminophen	Captain Cody, Cody, Lean, Schoolboy, T-threes, cough syrup
Codeine + promethazine + soft drinks and hard candy	Purple Drank, Sizzurp
Codeine + glutethimide	Doors & Fours, Loads, Pancakes and Syrup
Fentanyl	China White, China Girl, Apache, Dance Fever, Friend, Goodfella, Jackpot, Murder 8, Tango and Cash, TNT
Hydrocodone ± acetaminophen	Vike, Watson-387
Hydromorphone	D, Dillies, Footballs, Juice, Smack
Meperidine	Demmies, Pain Killer
Methadone	Dollies, Amidone, Fizzies
Methadone + MDMA	Chocolate Chip Cookies
Morphine	M, Morph, Miss Emma, Monkey, White Stuff
Oxycodone ± acetaminophen	O.C., Oxycet, Oxycotton, Oxy, Hillbilly Heroin, Percs
Oxymorphone	Biscuits, Blue Heaven, Blues, Mrs. O, O Bomb, Octagons, Stop Signs
Pentazocine	Yellow Footballs

MDMA, N-methyl-3,4-methylenedioxyamphetamine.

TABLE 156.2

Special Clinical Properties of Certain Opioids

EFFECT	OPIOID
QRS widening, sodium channel blockade	Propoxyphene
QT widening, potassium channel blockade	Methadone
Seizures	Propoxyphene, meperidine
Serotonin syndrome	Meperidine, methadone, tramadol, fentanyl
Hearing loss, ototoxicity	Methadone, hydrocodone, heroin
Spongiform leukoencephalopathy Parkinsonism	Heroin via "chasing the dragon" or inhalation of heroin vapor

nuclei of the third cranial nerve. This effect may be unreliable or masked by co-ingestants, and thus respiratory depression is the essential feature of opioid intoxication.[16] Respiratory depression is caused by opioids' effect on the medullary respiratory center via suppressing its sensitivity to hypercapnia and overriding the hypoxic drive. When combined with CNS depression, prolonged hypopnea can lead to hypoxia causing further neurologic complications. Long-term opioid use is known to cause dependence and appears to contribute to central sleep apnea, as well as structural and functional changes in the brain.[17,18]

Acute lung injury can be seen in opioid overdose, and pulmonary edema can cause a failure of oxygenation. This manifests as desaturations on pulse oximetry, despite an adequate respiratory rate, and rales on lung examination. The cause of acute lung injury in opioid overdose is not clearly elucidated but may be related to a capillary leak phenomenon.

Other signs and symptoms commonly associated with opioids include relative bradycardia, mild hypotension, pruritus, skin flushing, nausea, vomiting, and bowel dysfunction. Hypotension, pruritus, and flushing are caused by non-allergic histamine release; an effect more pronounced with morphine. Nausea and vomiting are frequently seen, even in therapeutic doses of opioids, and are responsive to antiemetics and more potent opioids. Decreased gastrointestinal motility, delayed gastric emptying, constipation, and ileus are all commonly seen and exist on the spectrum of opioid-induced bowel dysfunction.[19]

The skin should be examined in a patient exhibiting the opioid toxidrome, because it may give diagnostic clues as to which opioids have been used. Look for the presence of fentanyl patches over the entire body, including in the oropharynx and other bodily orifices. If marks or scars from "skin popping," a process where opioids are injected subcutaneously, are seen, this could be a sign of illicit opioid use.

Certain opioids have unique clinical findings due to their chemical structure or to their route of exposure (Table 156.2). Propoxyphene is associated with sodium channel blockade properties, causing QRS widening, in addition to PR and QT interval prolongation, which lead to its withdrawal from the market.[20] Methadone is known to block human ether-a-go-go related gene (hERG) potassium channels, causing QTc prolongation.[21] Propoxyphene and meperidine have been associated with hypertonicity, myoclonus, and seizures. Meperidine, methadone, tramadol, and fentanyl inhibit serotonin reuptake and are associated with serotonin syndrome.[22,23] Sensorineural hearing loss has been reported with both acute and chronic use of heroin, methadone, and hydrocodone, thought to be due to direct ototoxicity.[24,25] Heroin has also been found to be associated with Parkinsonian symptoms. A practice known as "chasing the dragon," wherein heroin is heated in aluminum foil and the vapor inhaled, has been found to be associated with spongiform leukoencephalopathy, with symptoms of psychomotor retardation, dysarthria, ataxia, and tremor.[26]

Patients who hastily ingest loosely packaged bags of illicit drugs are known as "body stuffers." Patients who internally conceal dense and meticulously packaged packets of illicit drugs for the purpose of trafficking are known as "body packers." Heroin is a common drug seen in both stuffers and packers. Both populations are at risk for severe and prolonged opioid toxicity if the packets leak or rupture.[27] However, heroin "stuffers" generally do not ingest enough to cause serious effects when compared to "packers" who may have lethal amounts of concentrated product in their gastrointestinal tract.

DIFFERENTIAL DIAGNOSES

The diagnosis of opioid intoxication is usually based on history, vital signs, and physical examination with recognition of its characteristic toxidrome: hypopnea, stupor, and miosis. All of these findings are not consistently present, and the clinical picture may be complicated by co-intoxicants. The essential finding in opioid intoxication is respiratory depression.[16] Other intoxications may present similarly, such as clonidine, guanfacine, valproic acid, gamma-hydroxybutyrate, ethanol, sedative hypnotics, and atypical antipsychotics. Non-toxicologic considerations include pontine stroke or hemorrhage.

DIAGNOSTIC TESTING

No laboratory test or drug screen should be relied upon by a clinician to make the diagnosis of opioid toxicity. The presence of the toxidrome and rapid response to naloxone are the two most important diagnostic clues. End-tidal carbon dioxide and oxygen saturation monitoring may be helpful for recognition of respiratory depression and hypoxia, but are not as necessary as observation of the patient's respiratory rate.

A 12-lead electrocardiogram is a useful diagnostic for identifying QRS widening, as seen in propoxyphene use, or for QTc prolongation, as seen in methadone use. If the patient has audible pulmonary rales on examination, then a chest radiograph is useful to evaluate for acute lung injury. If the opioid preparation is unknown, then acetaminophen and salicylate levels should be measured, because many prescription opioids are sold as combination preparations. Hypoglycemia is the only consistent laboratory abnormality found in opioid toxicity. It is generally mild but can contribute to the decreased level of consciousness seen in opioid overdose.

Opioids, such as morphine, codeine, and heroin, are reliably detected on most qualitative antibody-based enzymatic immunoassay urine toxicology screens. Some semisynthetic and synthetic opioids, such as hydrocodone, methadone, and fentanyl, however, are often missed on typical urine drug screens unless they are specifically measured. A urine test result can remain positive for up to 72 hours after last use, depending on the half-life of the drug used. A large poppy seed ingestion can lead to a positive opioid screen, although federal workplace testing guidelines have raised the confirmatory morphine concentration threshold to 2000 ng/mL to avoid positive screens for commonplace poppy seed ingestions.[28,29] Advanced screening methods detecting for 6-monoacetylmorphine, a specific metabolite of heroin, can be used to confirm heroin use.[30]

MANAGEMENT

Stabilization and Supportive Care

The ED physician should direct efforts at stabilizing the patient's airway, oxygenation, and ventilation. This can be accomplished with a combination of basic supportive measures and titrated use of antidotal therapy. Patients with acute lung injury may require oxygen and positive-pressure modalities, such as bi-level positive airway pressure, continuous positive airway pressure, or mechanical ventilation with positive end-expiratory pressure.

Decontamination

Because many opioids are extended-release preparations and also delay gastric motility, activated charcoal has been used in the past, but there are no data to support the effectiveness of this practice. Additionally, naloxone is an effective antidote for opioid overdose, and sedation from opioid intoxication could lead to charcoal aspiration. Gastric lavage similarly is not recommended because the risks outweigh the benefits. Whole bowel irrigation is not generally useful, but it can be considered for body packers (see Chapter 149).

Enhanced Elimination

There are no clinically effective techniques for enhanced elimination of opioids.

Antidote Therapy

Naloxone is a competitive opioid antagonist that rapidly reverses the effects of opioid intoxication. Because of the rapid clinical response, it can also aid in the diagnosis of opioid overdose. Naloxone is ineffective orally because its bioavailability is minimal due to first-pass metabolism. It is effective via intravenous, subcutaneous, intramuscular, inhalational, and endotracheal routes. It is indicated when an opioid intoxicated patient has significant CNS or respiratory depression.

In the ED, naloxone is usually administered intravenously with empirical dosing. The dose ranges from 0.04 mg to 15 mg, depending on the amount and formulation of the opioid taken, the patient's weight, and whether the patient is opioid dependent. In general, it is best to start with low doses and to increase doses as needed to alleviate respiratory depression. The exception to this is the arrest or near-arrest situation where opioids are the suspected cause. In this scenario, recommended starting doses are 0.4–2.0 mg. In chronic opioid users, the minimal effective naloxone dose should be used so as not to precipitate acute withdrawal. In this population, when respiratory status is adequate, we recommend starting with doses of 0.04 mg of naloxone, followed by titration of subsequent doses. Acute opioid withdrawal is unpleasant for the patient. Opioid withdrawal is not, in isolation, life-threatening, and naloxone has an excellent safety profile. The clinician should not be reluctant to dose naloxone as needed, even if opioid withdrawal symptoms develop.

Naloxone's onset of action, when administered intravenously, is less than 2 minutes, and the duration of action is anywhere between 20 minutes and 2 hours, which is shorter than the duration of action of most opioids. Reversal of respiratory depression usually occurs at low doses, but dosing is repeated until the desired effect is achieved. If respiratory depression is not reversed after the administration of high doses of naloxone (10 to 15 mg), then it is unlikely that opioid intoxication is the cause of the symptoms. If naloxone does reverse the symptoms but the patient later develops recurrent respiratory depression, then repeated naloxone doses, a continuous naloxone infusion, or endotracheal intubation should be considered. When starting a naloxone infusion, one-half to two-thirds of the bolus dose that effectively reversed intoxication is given hourly, although individual patient responses may vary depending on dose, tolerance, and dependency. This is usually enough to maintain respiratory effort without producing withdrawal.

In situations where intravenous access is not easily obtained, naloxone can also be given via intramuscular, intranasal, or nebulized routes. Intranasal naloxone has proved a viable, alternative to intravenous administration, especially for prehospital providers. Both 0.4 mg/mL and 1 mg/mL solutions of naloxone, delivered into each nare using an atomizer device, have been used.[31] Nebulized naloxone—2 mg of naloxone is mixed with 3 mL of saline—has also been shown to be a safe, effective, and gradual way to reverse opioid intoxication in both the ED and prehospital settings.[32,33] Care must be taken in selecting the optimal patient for nebulized naloxone. A patient with profound respiratory depression, such as a respiratory rate of less than six breaths per minute or cyanosis, will not receive enough naloxone to obtain the desired clinical effect.

Nalmefene and naltrexone are opioid antagonists with longer half-lives and duration than naloxone. Nalmefene's duration of action is 4 to 10 hours, and naltrexone's duration of action is 24 to 72 hours. These are generally not used in the ED because of concern for inducing a prolonged withdrawal state. Naloxone titration remains the treatment of choice for opioid reversal in the acutely intoxicated patient.

DISPOSITION

Patients who present with heroin toxicity can be successfully treated in the ED. Opioid-toxic patients who use longer acting opioids may require an observation admission. Body stuffers who remain asymptomatic after 6 hours of observation may be

discharged. Asymptomatic body packers, however, require admission until the packets have been passed or retrieved. If an overdose is severe, involves multiple drugs, requires multiple doses of naloxone, naloxone infusion, or endotracheal intubation, then intensive care unit (ICU) admission is appropriate.

The observation period following the administration of naloxone is dependent on the opioid implicated in the poisoning. Overdoses of long-acting opioids or sustained-released opioid preparations will require longer observation periods. In cases of heroin-only overdose, an observation period of up to 4 hours is generally sufficient. If there are no signs of recurrent toxicity after an appropriate observation period, the patient may be discharged, have a psychiatric evaluation, or be referred for substance abuse counseling and treatment depending on the clinical situation.

In recent years, as the opioid overdose epidemic has grown, there have been increased efforts to expand access to naloxone as a public health measure intended to save lives.[34] In many states, police officers have been added to the ranks of those trained to administer naloxone. There are also community- and hospital-based initiatives to educate users and bystanders on out-of-hospital naloxone use and then distribute or prescribe naloxone directly to patients or bystanders. Both intranasal and intramuscular auto-injector delivery methods have been used.[35] These programs are showing that providing opioid overdose education and out-of-hospital naloxone to drug users and to bystanders can help reduce opioid overdose mortality.[36]

Another emerging public health effort is the use of prescription drug monitoring programs, which are currently available in 49 states in the United States. To decrease the opioid burden in the community, the emergency provider can use these programs to access a patient's prescription opioid history prior to prescribing a new opioid upon discharge.[37] Currently, there is a policy under consideration to expand this database to the federal level to better monitor patients who cross state borders for multiple opioid prescriptions.

WITHDRAWAL

Withdrawal occurs in tolerant patients when opioids are stopped or an antagonist is administered. In withdrawal, the patient goes into a hyperadrenergic state. The symptoms include yawning, piloerection, CNS excitation, tachypnea, mydriasis, tachycardia, hypertension, nausea, vomiting, diarrhea, abdominal cramps, and myalgias. CNS excitation takes the form of restlessness, agitation, dysphoria, and insomnia. Cognition and mental status are usually unaffected. In general, opioid withdrawal is uncomfortable but not life-threatening. As with opioid toxicity, no diagnostic test exists for opioid withdrawal. It is diagnosed based on the patient's symptoms and signs.

Treatment for the withdrawing patient in the ED is supportive and symptom-based: intravenous fluids, electrolyte replacement, and antiemetics. Clonidine, an alpha$_2$-agonist, can be used to suppress sympathetic hyperactivity and shorten the duration of withdrawal. For long-term maintenance therapy, addiction clinics can provide or prescribe methadone, a long-acting opioid, as a replacement for heroin to both prevent withdrawal and treat addiction. Buprenorphine and buprenorphine-naloxone combined as a single product have recently been added to the outpatient treatment armamentarium for opioid abuse.[38] Opioid withdrawal alone typically does not require inpatient treatment. Some patients with severe symptoms may require admission.

KEY CONCEPTS

- The opioid toxidrome includes three prominent findings—CNS depression, miosis, and most importantly, respiratory depression—but presentations may be variable.
- A negative urine screen is unreliable, and absence of detection should not deter a diagnosis of opioid intoxication when clinical findings support it.
- Airway protection, oxygenation, ventilation, and early administration of naloxone are the cornerstones for management of patients with opioid toxicity.
- The duration of action of many opioids, especially after overdose, is significantly longer than that of naloxone. Patients responsive to naloxone should be observed for recurrence of respiratory depression, because they may require further doses of naloxone.
- Community naloxone programs and prescription drug monitoring programs are two new ways in which the medical profession is trying to curb the epidemic of opioid-related deaths.
- Opioid withdrawal syndrome does not include altered cognition. Patients with known or suspected opioid withdrawal who also have altered cognition should be evaluated for another cause of the altered cognition.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 156: QUESTIONS & ANSWERS

156.1. Most opioids cause mild hypotension related to histamine release and bradycardia. Which of the following opioids can also cause sodium channel blockade and QRS widening?

A. Hydromorphone
B. Meperidine
C. Morphine
D. Oxycodone
E. Propoxyphene

Answer: E. Propoxyphene and its metabolite norpropoxyphene can cause QRS widening. None of the other listed opioids has significant effects on the cardiac conduction system.

156.2. Which of the following laboratory abnormalities is most commonly seen in opioid overdose?

A. Hypocalcemia
B. Hypochloremia
C. Hypoglycemia
D. Hypokalemia
E. Hyponatremia

Answer: C. Hypoglycemia is the only consistent laboratory abnormality found in opioid overdose. It is generally mild but can contribute to the decreased level of consciousness seen in opioid overdose.

156.3. A 32-year-old man presents with confusion, nausea, vomiting, diarrhea, and abdominal pain. His friends report that he is withdrawing from heroin. Vital signs reveal mild hypertension, tachycardia, and tachypnea. Physical examination is significant for confusion, mydriasis, diaphoresis, lacrimation, piloerection, and mild diffuse abdominal tenderness. Which of the following signs and symptoms makes you concerned that this may not be a simple opioid withdrawal case?

A. Confusion
B. Diarrhea
C. Mydriasis
D. Piloerection
E. Tachycardia

Answer: A. Opioid withdrawal almost always causes restlessness, agitation, and anxiety. Cognition and mental status are not affected in simple opioid withdrawal and, if present, should prompt the clinician to search for other causes instead of or in addition to withdrawal.

156.4. A 20-year-old woman is brought to the emergency department (ED) after being found with decreased mental status at a club. Vital signs indicate mild hypotension and bradycardia. She is drowsy but

arousable, and she has an otherwise normal physical examination. Upon receiving naloxone 2 mg IV, her mental status immediately improves and soon thereafter she vomits. She now reports nausea but has no other complaints. She states she took some "pain pills" to get high but does not know what they were. What diagnostics tests should be performed?
A. Acetaminophen
B. Arterial blood gas
C. Chest radiograph
D. Lactate
E. Urine drug screen

Answer: A. Because many prescription opioid medications are combinations of an opioid and acetaminophen, ibuprofen, or salicylate, concentrations of acetaminophen and salicylate should also be ordered. Acetaminophen overdose might otherwise remain undiagnosed but, if identified, can be treated with an existing antidote, *N* acetylcysteine. The chest radiograph is not indicated unless a pulmonary complication is suspected. Lactate and a urine drug screen would not change patient management.

156.5. Which of the following medications can be used to treat opioid withdrawal?
A. Clonidine
B. Dextromethorphan
C. Diphenhydramine
D. Nalmefene
E. Valproic acid

Answer: A. Clonidine suppresses the sympathetic hyperactivity of opioid withdrawal. Dextromethorphan is an opioid derivative used as a cough suppressant, but it does not treat the symptoms of opioid withdrawal. Diphenhydramine and valproic acid have no role in opioid withdrawal. Nalmefene is an opioid antagonist similar to naloxone but with a longer duration of action. Administration of nalmefene would worsen opioid withdrawal symptoms.

156.6. A 14-month-old child is brought to the emergency department (ED) 4 hours after he was found with his grandmother's antidiarrheal medication bottle. A pill count identifies that only one Lomotil tablet is missing. The child is playful, has a normal respiratory rate and pattern, and has a soft abdomen with normal bowel sounds. Appropriate management includes which of the following?
A. Administration of activated charcoal
B. Administration of naloxone
C. Admission to a monitored unit
D. Discharge home
E. Gastric lavage

Answer: C. Activated charcoal and gastric lavage are means of gastrointestinal decontamination and are not routinely recommended in opioid toxicity. Opioid intoxicated patients with central nervous system (CNS) and respiratory depression should be treated with naloxone, but asymptomatic patients do not require antidote administration. Asymptomatic patients with known or suspected Lomotil (diphenoxylate/atropine) ingestion should be observed in a monitored setting for delayed onset of toxicity from the metabolite of diphenoxylate.

156.7. An 18-year-old male is driven to the emergency department (ED) by friends and carried into the triage area. He has agonal respirations and is cyanotic. Immediate resuscitative measures include bag-valve-mask (BVM) ventilation, establishment of an intravenous (IV) line, and administration of 0.4 mg of naloxone. The patient's respiratory status improves and although sleepy, he is able to answer some questions. During subsequent monitoring, the patient's respiratory status again declines, and he requires two additional doses of naloxone. Additional treatment should include which of the following?
A. Nalmefene
B. Naloxone infusion
C. Hemodialysis
D. Suboxone
E. Subutex

Answer: B. This patient likely has toxicity from a long-acting opioid agent, and a continuous infusion of naloxone will be necessary for ongoing reversal of toxicity. Nalmefene is a longer-acting opioid antagonist but is not preferred over naloxone infusion because naloxone allows for dose titration. Suboxone and Subutex are agonist agents used in the treatment of withdrawal. Opioids are not dialyzable due to large volumes of distribution.

156.8. A 26-year-old female is brought to the emergency department (ED) from the local airport by law enforcement. She is sleepy and mumbles incoherently in a foreign language. Vital signs include the following: blood pressure, 104/66; respiratory rate, 14 breaths per minute; and temperature, 98.6° F. Which of the following tests might identify the cause of this patient's symptoms?
A. Abdominal radiograph
B. Electrocardiogram (ECG)
C. Electroencephalogram (EEG)
D. Head computed tomography (CT)
E. Urine drug screen

Answer: A. An abdominal radiograph would likely reveal multiple packets of illicit opioid in the gastrointestinal tract of this body packer. One or more of the packets has leaked, producing the opioid toxicity. A urine drug screen may not identify an opioid but would not identify the internal packets. A head computed tomography (CT) scan would not be helpful unless associated head trauma is suspected. An EEG and ECG would not provide specific information to identify the internal packets.

CHAPTER 157

Pesticides

Katherine Welker | Trevonne M. Thompson

Pesticide is a general term that refers to all pest-killing agents, and so it includes insecticides, herbicides, rodenticides, and fungicides. In this chapter, several classes of pesticides will be discussed, as well as their importance in the emergency department (ED) setting (Table 157.1).

ORGANOPHOSPHATE INSECTICIDES

Principles of Toxicity

Organophosphates are a class of insecticide pesticides that work by inhibiting cholinesterases, including acetylcholinesterase and pseudocholinesterase. This is both the mechanism of their efficacy as insecticides as well as their toxicity in humans. Inhibition of cholinesterases result in accumulation of acetylcholine at multiple receptors within the autonomic nervous system, the sympathetic and parasympathetic ganglionic nicotinic sites, postganglionic cholinergic sympathetic and parasympathetic muscarinic sites, skeletal muscle nicotinic sites, and central nervous system sites (Fig. 157.1).

Organophosphates are lipid soluble and are absorbed through dermal, gastrointestinal, and respiratory routes. This can lead to deposition in fat tissues allowing for possible toxicity from acute and chronic, low-level exposures. Some organophosphates have active metabolites that can result in delayed toxicity.

Clinical Features

Organophosphate toxicity is represented by the "SLUDGE" or "DUMBELS" syndrome (these are mnemonics, which are explained in Box 157.1) manifested by accumulation of acetylcholine at receptor sites. The clinical features in any given case are attributable to the location of the receptors affected, the properties of the specific organophosphate product (predominance of nicotinic versus muscarinic effects), and the dose of the exposure. Muscarinic acetylcholine accumulation leads to salivation, lacrimation, urinary incontinence, defecation, emesis, bronchospasm, bronchorrhea, and bradycardia. Nicotinic acetylcholine accumulation leads to tachycardia, tachydysrhythmias, and skeletal muscle fasciculations.

At the neuromuscular junction, excess acetylcholine causes hyperstimulation of the muscles with secondary paralysis, and when the diaphragm is affected, cholinesterase poisoning leads to respiratory arrest. Sympathetic stimulation can lead to diaphoresis. A combination of sympathetic stimulation, involvement of the *N*-methyl-D-aspartate (NMDA) receptor, and enhanced acetylcholine concentrations can induce seizures.[1]

Pulmonary edema can occur in organophosphate poisoning and should not be confused with bronchorrhea or bronchospasm. Pulmonary edema results from many factors, including the release of inflammatory mediators and cells and increased vascular permeability. Bronchospasm and bronchorrhea are mediated by both central and local mechanisms involving acetylcholine. Pulmonary edema, bronchospasm, bronchorrhea, and the aforementioned respiratory muscle paralysis all contribute to respiratory failure.

Although the classic clinical picture of acute organophosphate poisoning is obvious, toxicity from gradual, cumulative exposure may be subtle. These patients commonly exhibit vague confusion or other central nervous system complaints; mild visual disturbances; or chronic abdominal cramping, nausea, and diarrhea.

A unique feature of organophosphate insecticides is the process called *aging*, the irreversible conformational change that occurs when the organophosphate is bound to the cholinesterase enzyme for a prolonged time. This causes the clinical effects to persist for periods of days to weeks. The time to aging varies by the specific product involved. Once an enzyme has aged, an oxime antidote (discussed later) cannot regenerate the cholinesterase.

Differential Diagnoses

The differential diagnosis for acetylcholinesterase inhibitor poisoning is limited. Carbamate pesticides, carbamate medications (such as, rivastigmine), nicotine and other nicotine alkaloids, and cholinomimetics (such as, pilocarpine) are xenobiotics that can cause a similar constellation of symptoms. There are few medical conditions included in the differential diagnosis: conditions causing exaggerated vagal response (such as, inferior wall myocardial infarction) and conditions that cause exaggerated sympathetic responses (such as, thyroid storm or pheochromocytoma).

Diagnostic Testing

Patients who present with the classic toxidrome should be treated empirically without waiting for laboratory confirmation of decreased cholinesterase activity. Known or suspected exposures to organophosphates can be evaluated by assessing plasma and erythrocyte (red blood cell [RBC]) cholinesterase concentrations. These concentrations are not generally available in real-time clinical settings.

In acute toxicity, plasma cholinesterase levels decrease first. In chronic, low-level exposure, however, plasma enzyme levels may be normal but RBC cholinesterase may still be decreased. This is because plasma cholinesterases can recover in 4 to 6 weeks, whereas RBC cholinesterases can take as long as 12 weeks to recover. Other laboratory studies should focus on the evaluation of pulmonary, cardiovascular, and renal function and fluid and electrolyte balance. A measurement of acid-base status should be performed, because patients with acidosis have higher mortality than those without.[2] Other prognostic tools such as the Glasgow Coma Scale or the Poison Severity Score vary by type of organophosphate and are generally of little utility.[3]

Management

Treatment of organophosphate poisoning is directed toward four goals: (1) decontamination, (2) supportive care with an emphasis on respiratory stabilization, (3) reversal of acetylcholine excess, and (4) reversal of toxin binding at receptor sites on the cholinesterase molecule. The severity of the patient's signs and symptoms guides management.

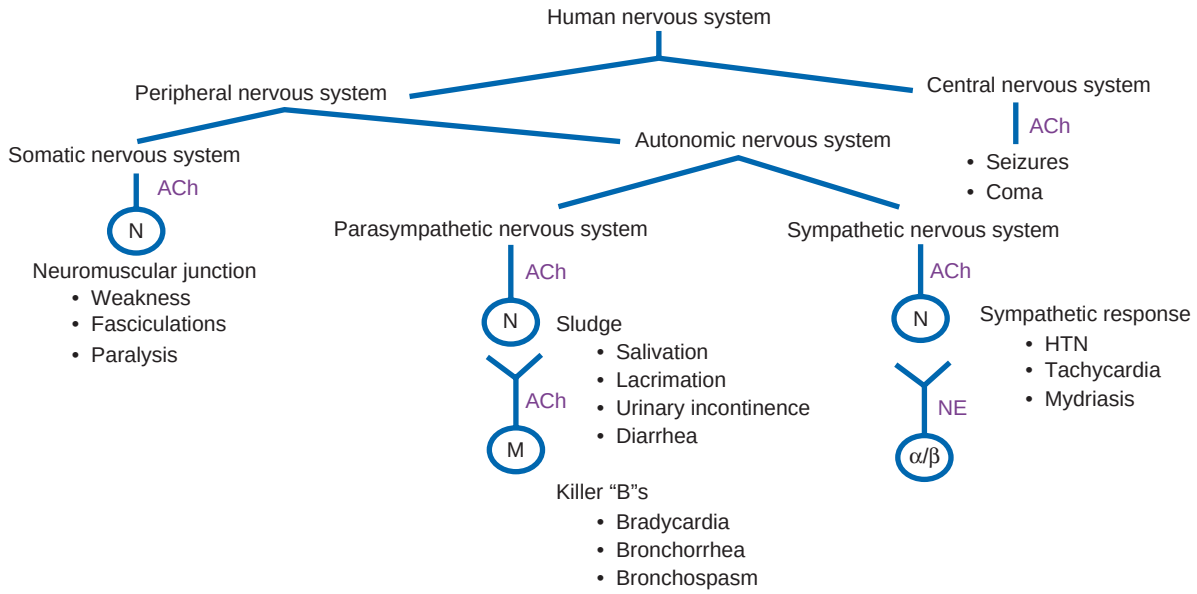

Fig. 157.1. Cholinergic effects on nervous system. *ACh,* Acetylcholine; *HTN,* hypertension; *M,* Muscarinic; *N,* nicotinic; *NE,* norepinephrine.

TABLE 157.1

Pesticide Classes and Examples

PESTICIDE CLASS	EXAMPLE(S)
Organophosphates	Parathion, malathion
Carbamates	Aldicarb, carbaryl
Chlorinated hydrocarbons	Dichlorodiphenyltrichloroethane (DDT), gamma-hexachlorocyclohexane (lindane)
Substituted phenols	2,4-dinitrophenol (DNP)
Chlorophenoxy pesticides	2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4-dichlorophenoxyacetic acid (2,4-D)
Bypyridyl pesticides	N,N′-dimethyl-4,4′-bipyridinum dichloride (paraquat), 1,1′-ethylene-2,2′-bipyridyldiylium dibromide (diquat)
Pyrethrins/pyrethroids	Permethrin
Glyphosate	N-(phosphonomethyl)glycine
Insect repellent	N,N-Diethyl-meta-toluamide (DEET)

BOX 157.1

Cholinergic Toxidrome

Salivation
Lacrimation
Urinary incontinence
Diarrhea
Gastrointestinal cramps
Emesis
Diarrhea/diaphoresis
Urination
Miosis
(Killer) **B**s: **B**radycardia/bronchorrhea/bronchospasm
Emesis
Lacrimation
Salivation

Decontamination

Decontamination begins in the out-of-hospital phase to prevent further absorption and subsequent toxicity and to protect care providers. Because dermal absorption is likely, removal and destruction of clothing and thorough flushing of exposed skin limits absorption and toxicity. Alternatively, dermal decontamination can be done with dry agents, such as military resins, flour, sand, or bentonite. Due to availability and ease of flushing, however, this is the method of decontamination we recommend, unless water is not available. Caregivers are at risk for contamination from splashes or handling of contaminated clothing. Personnel may be rotated to limit their exposure to encounters with either multiple contaminated patients or patients extensively contaminated (or contaminated with a high concentration product).[4] Caregivers should use universal precautions, including eye shields, protective clothing, and nitrile or butyl rubber gloves. In the case of ingestion, neither gastrointestinal decontamination procedures nor activated charcoal are of benefit. Anticholinergic agents are rapidly absorbed and profuse vomiting and diarrhea are seen early in ingestion, negating any beneficial effect of additional gastrointestinal decontamination.[5,6] Equipment, but not skin, may be washed with a 5% hypochlorite solution.

Stabilization and Supportive Care

Because death is a result of airway and respiratory failure, supportive care should be directed primarily toward airway management and include suctioning of secretions and vomitus, oxygenation, and, when necessary, ventilatory support. Succinylcholine, 1.5 mg/kg, is commonly used as a paralytic drug for emergency orotracheal intubation. Succinylcholine is metabolized by cholinesterases and may have a prolonged duration of effect (4 to 6 hours) in the setting of organophosphate poisoning. If succinylcholine is used as a paralytic drug, anticipate the need for prolonged sedation and ventilatory support. A nondepolarizing paralytic drug not metabolized by cholinesterases (such as, rocuronium, 1 mg/kg) is preferable. Tachycardia and tachydysrhythmia generally resolves by treating the underlying cholinergic excess and should not be treated symptomatically (eg, with beta blockers). Patients with agitation, seizures, and coma should be treated with

adequate doses of a benzodiazepine after the airway has been secured.

Enhanced Elimination

There is no role for enhanced elimination or hemodialysis in organophosphate poisoning.

Antidote Therapy

Definitive treatment for organophosphate poisoning is aimed at decreasing the amount and effect of acetylcholine at its various receptor sites. This begins with atropine. Atropine is a competitive inhibitor of acetylcholine at muscarinic receptors. The atropine dose for the treatment of organophosphate poisoning is 1 to 3 mg (0.05 mg/kg in children) intravenously with doubling of each subsequent dose every 5 minutes until there is control of the muscarinic effects, particularly reduction in airway secretions. Atropine may be initiated intramuscularly until intravenous or intraosseous access is obtained. Depending on the specific organophosphate product involved and the degree of poisoning, patients may require 200 to 500 mg of atropine during the first hour.[8] Once the patient has been stabilized with appropriate "atropinization," an infusion is initiated to provide 10% to 20% of the total cumulative dose needed to obtain symptom control per hour. Tachycardia and mydriasis may occur at these atropine doses but are not an indication to stop therapy; however, excessive administration of atropine may cause the typical symptoms of the anticholinergic toxidrome. The endpoint of atropinization is drying of respiratory secretions, easing of respiratory effort, and normalization of respiratory rate. Early and rapid atropinization is associated with better control of seizures and reduced mortality in animal models. The recommended atropine dosing regimen can easily exhaust available hospital supplies, and arrangements for this situation should be discussed with the appropriate hospital personnel early in the case of an organophosphate poisoning. Other anticholinergic medications, such as diphenhydramine and anticholinergic ophthalmic drugs, have been studied in rodents, and may be considered a "last resort" alternative in humans if intravenous atropine is scarce or exhausted.[9] Atropine is not active at nicotinic receptor sites and will not reverse skeletal muscle effects, such as respiratory muscle paralysis. The second part of the treatment of organophosphate poisoning is the use of an oxime to regenerate acetylcholinesterase function. Oximes bind to the organophosphate-cholinesterase complex causing a conformational change that allows for the cholinesterase to resume normal function. There are currently five oximes in common use worldwide: pralidoxime (2-PAM), trimedoxime (TMB-4), obidoxime chloride (Toxogonin), methoxime, and asoxime chloride (HI-6). Pralidoxime is the product commonly available in the United States. There are controversies regarding the use of oximes related to dosing, duration of treatment, time to therapy initiation, and effectiveness in treating neurologic symptoms. Despite these controversies, we recommend oximes for the treatment of moderate or severely poisoned patients, defined as those who require multiple, large doses of atropine. Indications for oxime treatment include respiratory depression or failure, muscle fasciculations, seizures, dysrhythmias, hemodynamic instability, or the use of large amounts or repeated doses of atropine to completely control signs and symptoms of organophosphate intoxication. We recommend administering pralidoxime as a 1 to 2 g bolus (25 to 50 mg/kg in pediatric patients) over 30 minutes, which can be repeated as needed (up to hourly) based on response (improved mental status, respiratory and heart rate, and decreased secretion). Even higher doses may be required. Alternative dosing options are: 2 g bolus over 20 minutes followed by an infusion of 500 mg/h for up to 7 days, 1 g/h every 4 hours, or 30 mg/kg followed by infusion of 8 mg/kg per hour (Table 157.2).[6,11]

Oximes can be given intravenously or intramuscularly (as evidenced by autoinjectors).

Novel treatments for organophosphate and nerve agent poisoning are under investigation. At present, pyridostigmine is the most commonly used prophylactic drug; other prophylactics include tablets containing pyridostigmine, trihexyphenidyl and benactyzine, as well as a transdermal patch containing H-series oximes (HI-6).[7]

Disposition

Most patients who present to the ED after significant organophosphate exposure should be admitted to a monitored setting. The effects of organophosphate intoxication can be prolonged. If plasma cholinesterase levels are available, they may be useful for treatment and disposition decisions. Asymptomatic or minimally symptomatic patients with normal or minimally depressed cholinesterase levels may be discharged after 6 hours with close outpatient follow-up to ensure that progressive toxicity does not occur. Patients who present with significant symptoms (acute respiratory compromise associated with depressed cholinesterase levels) require admission and close monitoring, usually in an intensive care unit (ICU). Patients may have rebound toxicity several days after apparently satisfactory response to initial treatment. This may occur for many reasons, including persistent release of organophosphates from lipid stores. Poisoning with fenthion is of particular concern, because initial symptoms could be mild and progress to life-threatening intoxication over time. Those patients with acts of self-harm or suicidal intent require psychiatric consultation once medically stabilized.

The intermediate syndrome (IMS) can occur after the acute intoxication from organophosphates has resolved. IMS is delayed muscle paralysis, including respiratory muscles, which can occur 24 to 96 hours after the resolution of the cholinergic crisis. The precise cause of IMS is not well documented. Finally, delayed peripheral neuropathy may occur 7 to 21 days after acute organophosphate intoxication. Therefore, close patient follow-up is important after stabilization.

Carbamate Insecticides

Carbamates are acetylcholinesterase inhibitors whose toxicological picture is similar to organophosphates. There are two

TABLE 157.2

Specific Treatment Dosing

AGENT	INDICATION	ADULT DOSE	PEDIATRIC DOSE	ROUTE	COMMENTS
Atropine	Organophosphate toxicity	1–3 mg	0.05 mg/kg	IV, IM	Double dose every 5 minutes until effect
Pralidoxime	Organophosphate toxicity	1–2 g bolus	25–50 mg/kg	IV, IM	Given over 30 minutes Dose can be repeated based on response

IM, Intramuscular; *IV,* intravenous.

important differences: (1) short duration of effect (minutes to 24 to 48 hours) and (2) the process of aging does not occur. Decontamination, supportive care, and atropinization are usually adequate for treating patients poisoned with these compounds. Severe toxicity, including respiratory depression and seizures, can occur. Because carbamates do not cross the blood-brain barrier as readily as organophosphates, neurotoxicity is less likely.[7] Dosing for atropine is the same as for organophosphates, but the duration of treatment is usually less. There is controversy regarding the use of oximes in carbamate poisoning. We recommend the use of oximes only when the poisoning is severe (as defined for organophosphates) and the provider cannot differentiate carbamate from organophosphate poisoning.

Chlorinated Hydrocarbons Insecticides

Dichlorodiphenyltrichloroethane (DDT) is the best-known example of chlorinated hydrocarbon insecticides. This class is also known as *organochlorine insecticides.* DDT was developed in the late 1800s and first used widely in World War II to prevent transmission of typhus and malaria. It was found to be effective and stable and led to the development of other similar insecticides that were used agriculturally, industrially, and residentially. Their widespread and indiscriminate use, long half-life, and persistence in the environment resulted in ecologic effects that lead to a ban on most chlorinated hydrocarbons. In the United States, gamma-hexachlorocyclohexane (also known as *lindane*) is a chlorinated hydrocarbon insecticide available as pharmaceutical drug for the second-line treatment of head lice and scabies. The state of California has banned lindane, and the state of Michigan has restricted its use to physician's offices only.[8,11]

Principles of Toxicity

Chlorinated hydrocarbon insecticides are highly lipid soluble. They are readily absorbed via dermal, respiratory, and gastrointestinal routes and are stored in fatty tissues. This storage allows for toxicity from repeated, low-level exposure. Lindane toxicity often occurs from excessive external (dermal) exposure or accidental oral exposure.

Chlorinated hydrocarbon insecticides affect neuronal voltage-gated sodium channels. They are also gamma-aminobutyric acid (GABA) antagonists. This results in hyperexcitability and irritability of both central and peripheral neurons. Chlorinated hydrocarbons also increase susceptibility to ventricular tachydysrhythmias because of increased myocardial sensitivity to circulating catecholamines.

Clinical Features

The primary clinical feature of chlorinated hydrocarbon insecticide toxicity is neurologic excitation. This includes muscle fasciculations, ataxia, tremors, delirium, weakness, paralysis, paresthesias, seizures, and death.[11] Mild premonitory symptoms are not always present prior to serious neurological manifestations that patients can present only with seizure activity. Hyperthermia can result from muscle fasciculations and seizures. Metabolic acidosis, respiratory failure, and acute renal failure can also occur. Chronic exposure can cause liver toxicity, arrhythmias, menstrual changes, and neuropsychological effects. The most important clue to diagnosing exposure to chlorinated hydrocarbons is a detailed history because there is no specific toxidrome.

Differential Diagnoses

The defining features of chlorinated hydrocarbon insecticide toxicity are neuro-excitation and seizure. The differential diagnosis is broad and includes any disorder or toxic exposure that can lead to seizures (eg, organophosphates, isoniazid, theophylline, sympathomimetic agents, lead, ethanol, and benzodiazepine withdrawal).

Diagnostic Testing

The diagnosis of chlorinated hydrocarbon insecticide poisoning is determined by history and clinical features. Some reference laboratories can measure chlorinated hydrocarbons from fat or plasma samples, but this will not be readily available during emergency treatment. An electrolyte panel, creatinine kinase, and blood gas are to be measured on patients with known or suspected acute poisoning.

Management

Decontamination

The first step in chlorinated hydrocarbon insecticide toxicity is decontamination. Remove all clothing and wash the skin and hair with soap and water. Ingested chlorinated hydrocarbons are rapidly absorbed by the gastrointestinal tract; therefore, decontamination with activated charcoal is of no use.

Stabilization and Supportive Care

The main objective in treating chlorinated hydrocarbon toxicity is cessation of seizures. Benzodiazepines and barbiturates are the mainstays of therapy to treat seizures. Chlorinated hydrocarbons can cause myocardial sensitization that can lead to ventricular tachydysrhythmias, which are most commonly seen around the time of seizure activity due to a catecholamine surge. Beta-adrenergic antagonists (such as, intravenous metoprolol, 5 mg boluses every 5 minutes) are recommended for treating any life-threatening tachydysrhythmias (such as, ventricular tachycardia and fibrillation) in this situation. Prolonged seizures can lead to hyperthermia. Seizure control with benzodiazepines and external cooling with evaporative cooling methods should be implemented if hyperthermia is present. Other complications such as metabolic acidosis, rhabdomyolysis, and acute kidney injury are treated with intravenous hydration and, in the case of rhabdomyolysis, alkalinization, as described in Chapter 119.

Enhanced Elimination

There is no role for enhanced elimination of chlorinated hydrocarbon insecticides in the ED.

Antidote Therapy

There is no antidotal therapy for chlorinated hydrocarbon insecticides.

Disposition

Patients who present symptomatic with chlorinated hydrocarbon insecticide poisoning require admission for evaluation, monitoring, and treatment of neurologic and metabolic derangements.

SUBSTITUTED PHENOLS

Principles of Toxicity

Dinitrophenol (DNP), pentachlorophenol, and dinitrocresol belong to a class of compounds called *substituted phenols* and have been used as dyes, wood preservatives, photograph developers,

TABLE 157.3

Differential Diagnosis for Substituted Phenol Poisoning

TOXICOLOGICAL	INFECTIOUS	ENVIRONMENTAL
Cocaine	Meningitis	Hyperthermia
Salicylates	Encephalitis	Heat stroke
Amphetamines/MDMA	Sepsis	
Caffeine		
Other sympathomimetics		

MDMA, N-methyl-3,4-methylenedioxyamphetamine.

and insecticides.[9] DNP was previously used as a weight loss medication but has not been available by prescription since 1938 because of fatalities associated with its use.[14] DNP is currently used as a weight loss supplement and is readily available over the Internet. It can be easily obtained from online nutritional supplement retailers and is available in powder, capsule, and crystalline form. The most common route of exposure is oral, but substituted phenols can also be absorbed dermally and can be inhaled.[14]

Substituted phenols uncouple oxidative phosphorylation. This results in decreased adenosine triphosphate (ATP) formation and increased heat generation, which is the mechanism of action for DNP in weight loss because calories are burned excessively. DNP also stimulates glycolysis, which, along with the uncoupling of oxidative phosphorylation, increases lactic acid production.

Clinical Features

Patients with acute toxicity from substituted phenols present with hyperthermia, tachycardia, diaphoresis, and tachypnea. Neurologic signs and symptoms include confusion, agitation, seizures, and coma. Rhabdomyolysis, myocardial injury, acute kidney injury, and hepatic damage can occur in acute toxicity. These patients can progress to cardiovascular collapse and death. Dermal exposure can cause a yellow discoloration and corrosive injury.[10]

Differential Diagnoses

Patients suffering from the toxic effects of substituted phenols will appear to have sympathomimetic excess. This leads to a broad differential diagnosis that includes toxicologic, infectious, and environmental considerations, such as cocaine toxicity, encephalitis, and heat stroke (Table 157.3; see Chapter 149). An accurate history is important to the diagnosis of substituted phenol intoxication.

Diagnostic Testing

Diagnostic testing focuses on the metabolic disturbances and potential organ damage associated with acute substituted phenol toxicity. Serum electrolytes and renal function are to be assessed. Liver studies should be performed, and creatinine kinase is measured to assess for rhabdomyolysis. An electrocardiogram (ECG) and laboratory assessment for myocardial injury with serial cardiac markers (troponin) is advised for any patient with symptoms consistent with myocardial ischemia.

Management

Decontamination

Patients who present with dermal exposure should have the clothing removed and skin washed with soapy water. Because of the potential lethality of phenol-containing compounds with no effective antidote, a patient who presents within 1 hour of an acute oral ingestion and who is alert and cooperative should be given oral activated charcoal (at least 100 g in adults).

Stabilization and Supportive Care

Supportive care is the mainstay of treatment for substituted phenol toxicity. Patients with hyperthermia (temperature >102.5° F) should be cooled with evaporative cooling, cooling blanket, cold intravenous fluids, ice packs, and whatever other methods available. All patients should be given adequate fluid resuscitation, and electrolyte derangements should be corrected. This is especially important in hyperthermic patients. Agitation and seizures treated with benzodiazepines, such as lorazepam (1 to 2 mg intravenous push [IVP]) or diazepam (5 to 10 mg IVP).

Enhanced Elimination

There is no known role for enhanced elimination in substituted phenol toxicity.

Antidote Therapy

There is no antidote for acute phenol poisoning.

Disposition

Patients who manifest symptoms after substituted phenol exposure should be admitted for intensive cardiac and neurologic monitoring and treatment. A patient who presents asymptomatically after an exposure is be observed for 8 to 12 hours and may be safely discharged if they remain asymptomatic over that period of time.[14]

CHLOROPHENOXY HERBICIDES

Principles of Toxicity

Chlorophenoxy compounds are effective herbicides for broadleaved weeds. This class of herbicides includes 2-methyl-4-chlorophenoxyacetic acid (MCPA), methylchlorophenoxypropionic acid (MCPP), and 2,4-dichlorophenoxyacetic acid (2,4-D). Chlorophenoxy herbicides are widely used in both commercial and residential settings.

Chlorophenoxy herbicides are absorbed through the gastrointestinal tract, skin, and respiratory tract. Most cases of toxicity, however, result from ingestion. Skeletal muscle is the primary organ of toxicity, although the exact mechanism of action is not well defined. Proposed mechanisms of action include direct cell membrane damage, forming analogues of acetyl-CoA and acting as false cholinergic messengers, and at high doses, uncoupling oxidative phosphorylation.[11]

Clinical Features

Ingestion of chlorophenoxy herbicides can result in gastrointestinal symptoms that include vomiting, abdominal pain, diarrhea, oropharyngeal burning, and gastrointestinal hemorrhage. Other symptoms include muscle fasciculations, weakness, myotonia, and decreased tendon reflexes. Myotonia and fasciculations may lead to rhabdomyolysis and metabolic acidosis.[10]

Differential Diagnoses

Severe toxicity from chlorophenoxy herbicides is rare. When symptoms are present, other possible diagnoses include other

causes of acute myopathy. When gastrointestinal symptoms are present, ingestion of caustic substances, organophosphate, and carbamate exposure are other considerations.

Diagnostic Testing

Testing for chlorophenoxy herbicides is not available in the emergency setting. Diagnostic testing should focus on assessing skeletal muscle damage and its consequences. Measurement of creatinine kinase, electrolyte profile, renal function, liver function, and acid base status are indicated.

Management

Decontamination

In the case of a dermal exposure, remove the clothing and wash the skin with soapy water. Because chlorophenoxy herbicides are rapidly absorbed via the gastrointestinal tract and vomiting may occur early, activated charcoal is not indicated.

Stabilization and Supportive Care

Supportive care with fluid resuscitation is the mainstay of treatment for patients symptomatic after chlorophenoxy herbicides.

Enhanced Elimination

In the rare event of a critically ill patient (patients requiring ventilator, hemodynamic support, and those with seizures, hyperthermia, or significant metabolic derangements) who presents after chlorophenoxy herbicide poisoning, urinary alkalinization or hemodialysis can be used to enhance elimination.[10]

Antidote Therapy

There is no antidote for chlorophenoxy herbicide toxicity.

Disposition

A patient who presents with muscular symptoms after chlorophenoxy herbicide toxicity should be admitted and carefully monitored for progression of symptoms. A patient who presents asymptomatic is monitored for 6 hours. If no symptoms develop, the patient can be safely discharged home.

BIPYRIDYL HERBICIDES

The bipyridyl (also called *dipyridyl*) herbicides, paraquat and diquat, are extremely effective contact herbicides that are widely used throughout the world. Paraquat is particularly toxic to humans and is under strict regulation in the United States. Diquat is less toxic and is subject to less regulation.

Principles of Toxicity

Paraquat causes the production of superoxides created during cyclic oxidation-reduction reactions in tissues. This causes oxygen radical damage that results in cell death.[11] Paraquat selectively concentrates in the lungs, regardless of the route of exposure, because of an uptake mechanism in alveolar cells. High concentration of oxygen in the lungs increases the extent of paraquat-induced oxygen radical injury; therefore, the lungs are the major target organs in paraquat poisoning. Paraquat exposure can lead to adult respiratory distress syndrome, progressive pulmonary fibrosis, and respiratory failure. Paraquat damages other organ systems by the same oxygen radical injury effect, including the liver, kidneys, heart, and central nervous system. Diquat has a similar mechanism of action but does not accumulate in the lung as does paraquat. Diquat concentrates in the kidneys and often results in renal failure. Paraquat is absorbed through the skin, gastrointestinal tract, and respiratory tract. Diquat is poorly absorbed through intact dermis.

Clinical Features

Paraquat and diquat are corrosive and can cause vomiting and caustic injury to the oropharynx, esophagus, and GI tract. Dermal exposure can cause corrosive injury to the skin. Systemic toxicity from both paraquat and diquat poisoning will often progress to multiorgan failure and death. This is especially true for paraquat, which can be fatal in small amounts. Patients who survive systemic toxicity from paraquat often develop a progressive pulmonary fibrosis 1 to 3 weeks after the exposure. The clinical course, however, is dependent on the dose of the exposure.

Differential Diagnoses

Bipyridyl herbicides are corrosive, and the differential diagnosis encompasses other caustic agents (such as, acids and alkalis), insecticides (organophosphates and carbamates), and pulmonary toxic chemotherapy agents (such as, bleomycin). The subsequent systemic toxicity and multiorgan failure with bipyridyl herbicide poisoning could be attributable to other sources of similar symptoms, such as sepsis and acute respiratory distress syndrome (ARDS).

Diagnostic Testing

The cornerstone of diagnosing bipyridyl herbicide poisoning lies in the history of exposure. There is a colorimetric urine test to detect diquat and paraquat in urine that can be useful but is not readily available in the United States. Serum concentrations of bipyridal herbicides can be measured but are generally not available in the timeframe useful in the ED; however, the concentration paired with the time of ingestion can be used for mortality prognostication.

Multiorgan failure is possible after bipyridal herbicide poisoning. Laboratory evaluation for respiratory, renal, hepatic, metabolic, and cardiovascular toxicity is indicated. Serial chest radiographs and arterial blood gases are recommended for symptomatic patients.

Management

Decontamination

Dermal exposure should be treated by removing soiled clothing and washing the skin with water. In general, gastrointestinal decontamination is not indicated in the case of caustic ingestions. Because bipyridyl herbicides, particularly paraquat, can cause systemic toxicity in small amounts, gastrointestinal decontamination may be warranted in these cases of ingestion. We recommend at least 100 g activated charcoal or Fuller's earth (in certain international settings) if the patient presents early within 1 hour of the ingestion, because this toxicity has high morbidity and mortality without any antidotal therapy.

Stabilization and Supportive Care

Upper airway corrosive injury can lead to an obstructed airway. Orotracheal intubation is necessary when there is any concern for such obstruction. Because of the oxygen radical damage, supplemental oxygenation should target oxyhemoglobin saturation of 95%, and excessive oxygenation should be avoided. Supportive care for multiorgan failure is indicated based on the clinical circumstances.

Enhanced Elimination

The use of hemodialysis to increase the elimination of paraquat or diquat is controversial. If renal failure, metabolic acidosis, or electrolyte imbalance develops as a result of the poisoning, dialysis is indicated.

Antidote Therapy

There is currently no specific antidotal therapy for bipyridal herbicide poisoning. Antioxidants, immune modulators, and corticosteroids have been incompletely evaluated as options for therapy to prevent the delayed pulmonary fibrosis. There is currently insufficient data to recommend specific antidotal treatment in the ED.

Disposition

Due to potential high lethality, patients presenting with bipyridyl poisoning require admission to an ICU setting.

PYRETHRIN AND PYRETHROID INSECTICIDES

Pyrethrins are naturally occurring insecticides derived from the chrysanthemum plant. Pyrethroids are synthetic derivatives of pyrethrins that are more stable in the environment.

Principles of Toxicity

In humans, pyrethrins block voltage-gated sodium channels, voltage-gated calcium channels, and the chloride channels on GABA receptors. Toxicity in humans, however, is not common. Pyrethrins and pyrethroids are used both as commercial insecticides and pharmaceutically to treat human infestations of scabies and lice (eg, permethrin). Pyrethrins and pyrethroids are poorly absorbed dermally but are well absorbed via gastrointestinal and respiratory routes.

Clinical Features

Toxicity from pyrethrins and pyrethroids is rare. Sensitivity reactions can be seen with exposure. Skin exposure can result in erythema. Inhalation can result in rhinitis, sneezing, oral mucosa irritation, cough, dyspnea, wheezing, and chest pain. Nausea, vomiting, abdominal pain, and diarrhea can occur after ingestion. With massive ingestions, the patient is at risk for neurological symptoms, such as numbness, tremors, ataxia, paralysis, or seizures.

Differential Diagnoses

Sensitivity reactions seen with exposure to pyrethrins and pyrethroids can mimic allergic reactions or contact dermatitis from other etiologies.

Diagnostic Testing

There are no laboratory or diagnostic tests specific to poisoning from pyrethrins and pyrethroids in the ED setting.

Management

Decontamination

In the case of dermal exposure, clothing should be removed and skin washed with water.

Stabilization and Supportive Care

Skin reactions should be treated symptomatically with histamine blockers, such as diphenhydramine. Wheezing should be treated with beta agonists. Neurologic symptoms can be treated with benzodiazepines as needed (lorazepam, 1 to 2 mg IVP; diazepam, 5 to 10 mg IVP).

Enhanced Elimination

There is no role for enhanced elimination in pyrethrin and pyrethroid poisoning.

Antidote Therapy

There is no antidotal therapy for pyrethrin and pyrethroid poisoning.

Disposition

Most cases of pyrethrin and pyrethroid exposure will not demonstrate signs of toxicity and can be safely discharged from the ED. Patients with massive ingestions should be observed for up to 24 hours for the development of neurologic symptoms. Any patient with neurologic symptoms should be admitted to a monitored setting.

GLYPHOSATE

Glyphosate (Roundup) is one of the most commonly used pesticides in the United States. It is a non-selective, contact herbicide that interferes with amino acid synthesis in plants but not in humans.

Principles of Toxicity

Glyphosate is poorly absorbed dermally. It is absorbed through the gastrointestinal tract. Concentrated solutions (41%) can cause mucosal injury. The residential concentration is 1%. Human acute toxicity is thought to be due to the surfactant included in the glyphosate preparation. Unintentional ingestion of glyphosate generally results in mild gastrointestinal symptoms. Hypotension, renal failure, respiratory distress, and death can occur from intentional, massive ingestions.

Clinical Features

Patients who present with dermal exposure to glyphosate will likely have no signs of toxicity. Most ingestions of dilute preparations cause only mild gastrointestinal symptoms. Patients ingesting large volumes of dilute solutions or moderate volumes of concentrated solutions may develop sore throat, nausea, vomiting, abdominal pain, hyperthermia, respiratory distress, acute lung injury, renal failure, and coma. Metabolic acidosis may develop as a result of cardiovascular compromise. Poor prognostic features include altered mental status, hyperkalemia, and renal failure.[12]

Differential Diagnoses

The differential diagnosis of glyphosate poisoning includes caustic ingestions and other causes of respiratory distress or cardiovascular compromise from other pesticides (such as, organophosphates and carbamates) and herbicides (such as, paraquat and diquat).

Diagnostic Testing

The key to the diagnosis of glyphosate poisoning is to obtain an accurate history of exposure. An electrolyte profile is suggested to

assess for hyperkalemia. A creatinine concentration assesses for renal injury. If respiratory distress is present, a chest radiograph should be performed. We recommend measuring acid-base status with a venous or arterial blood gas to assess extent of respiratory compromise and for comparison with future measurements to ascertain whether the patient is improving or deteriorating.

Management

Decontamination

With dermal exposure, remove the clothing and wash the skin with water. Gastrointestinal symptoms are generally present with significant ingestions, and activated charcoal is not indicated.

Stabilization and Supportive Care

The mainstay of management of acute glyphosate exposure is supportive care. Provide airway management and cardiovascular support as indicated by the symptom profile. Hyperkalemia can be managed by usual measures.

Enhanced Elimination

There is no role for enhanced elimination in the management of glyphosate poisoning.

Antidote Therapy

There is no antidote for glyphosate poisoning.

Disposition

Patients who demonstrate symptoms after glyphosate ingestion should be admitted for further management. Patients who present after unintentional exposures of small amounts or low concentrations of glyphosate can be discharged from the ED after a 6-hour observation period.

DEET

DEET, or N,N-diethyl-m-toluamide, is not technically a pesticide. It is the most widely used insect repellant used throughout the world. DEET is available in concentrations ranging from 5% to 100%, and it primarily repels mosquitoes.[13] The American Academy of Pediatrics recommends 30% as the maximum concentration for use in infants and children and does not recommend use of DEET in infants younger than 2 months old. It is available as lotions, aerosols, pump sprays, roll-on applicators, and impregnated towelettes. Concentrated DEET solutions (up to 100%) can cause plastic products, such as sunglasses, to melt on contact.

Principles of Toxicology

DEET is lipid soluble and is well absorbed when applied to the skin or ingested. Repeated exposure, skin wounds or abrasions, sweating, and elevated skin temperature increase absorption. DEET affects the central nervous system at the GABA receptors in humans.[12]

Clinical Features

Most exposures to DEET result in no or minimal symptoms. Prolonged skin contact may lead to contact dermatitis, and prolonged contact with higher concentrations can lead to skin blisters. Ingestion of DEET can result in nausea, vomiting, and oral mucosal irritation. Ingestion or excessive skin exposure can lead to headache, liver injury, lethargy, respiratory depression, seizure, and coma.[12]

Differential Diagnoses

The differential diagnosis for DEET poisoning includes any infectious, toxicological (pesticides, organophosphates, carbamates), metabolic, or neurologic abnormality that could cause seizures and depressed mental status.

Diagnostic Testing

There is no specific test for DEET poisoning that is useful in the ED.

Management

Decontamination

In patients with excessive or prolonged skin exposure to DEET, wash the skin with water. Gastrointestinal decontamination has no role in DEET ingestions because of rapid absorption and the potential for seizure activity.

Stabilization and Supportive Care

Supportive care is the mainstay of treatment for a DEET-poisoned patient. Seizures should be treated with benzodiazepines (lorazepam, 1 to 2 mg IVP; diazepam 5 to 10 mg IVP) and are generally self-limited.

Enhanced Elimination

There is no role for enhanced elimination with DEET exposure.

Antidote Therapy

There is no antidote for DEET poisoning.

Disposition

Any patient with acute neurologic symptoms after DEET exposure should be admitted. An asymptomatic patient after an oral ingestion or a patient with localized skin reaction can be discharged after a 6-hour observation period.

RODENTICIDES

There are hundreds of rodenticides available throughout the world with variable toxicity (Table 157.4). Rodenticides are implicated in self-harm attempts, malicious poisonings, and accidental ingestions. In the United States, anticoagulants, or superwarfarin- type are the most common (over 90% of exposures). They are long-acting anti–vitamin K anticoagulants. Examples are brodifacoum, diphacinone, bromadiolone, chlorophacinone, and difenacoum.[1]

Principles of Toxicology

Superwarfarins competitively inhibit vitamin K and hepatic synthesis of vitamin K–dependent coagulation factors II, VII, IX, and X. These anticoagulants can also damage capillary walls, increasing permeability and fragility, worsening any bleeding.[2] Effects are prolonged in these long-acting anticoagulants—half-life of 156 hours versus 17 hours in first generation warfarins, leading to toxic effects that can last for months. In overdose,

TABLE 157.4

Rodenticides (Mnemonic: RATS PANIC)*

R SUPER WARFARINS	AT FLUOROACETAMIDE	S STRYCHNINE	P PHOSPHORUS	A ALUMINUM[1]	NIC NICOTINAMIDE
Rodenticide	SMFA, fluoroacetamide 1080–1972; banned in 1972 Today: Sheep collars	Moles, gophers, pigeons Adulterant in heroin and cocaine	Yellow (white) phosphorus	Aluminum and zinc phosphide ("rice tablet")	Vacor: 2% PNU banned in 1979
Mechanism	Irreversible TCA cycle inhibitor (fluorocitrate is "suicide inhibitor")	Competitive inhibitor of glycine binding (increased neuronal excitability)	Corrosive, cellular poison Combusts at room temp	Unknown (inhibit electron transport chain, release phosphine gas with moisture and gastric acid)	Unknown (antagonizes nicotinamide axons and injures pancreatic cells)
Effects	GI: Nausea/vomiting/diarrhea/pain Respiratory distress Seizures Cardiotoxicity Hypotension	"Awake seizure" Risus sardonicus Opisthotonus Hyperthermia, rhabdomyolysis	Respiratory "Phossy jaw" GI ("smoking" stool), liver failure Neuro, cardio Eye Skin (burns)	Delayed pulmonary. edema, ARDS GI, neurologic, cardio, hepatic, adrenal Refractory hypotension Metabolic acidosis	Nausea/vomiting Orthostatic hypotension Diabetes mellitus Neuropathy, coma
Diagnosis	Electrolytes, BUN/Cr, calcium, LFTs ECG, MRI Levels not helpful acutely	Cramps, awake seizure, electrolytes, BUN/Cr, CPK, ABG, serum levels do not correlate with toxicity	Garlic odor Burns (skin fluoresces) BUN/Cr, calcium, LFTs UA ABG, chest x-ray, ECG	Fishy/garlic odor BUN/Cr, electrolytes, LFTs ABG, chest x-ray	History Sudden orthostatic hypotension or DM Electrolytes, glucose, BUN/Cr
Treatment	Decontaminate Activated charcoal Supportive care	Stabilization and supportive care Limit stimulation Benzodiazepines for seizures, analgesia	PPE Decontaminate Sand or water over solid phosphorus	Benzodiazepines for seizures, steroids for adrenal dysfunction, magnesium for refractory arrhythmia	IVFs, activated charcoal Nicotinamide Insulin Steroids
Disposition	ICU for CNS, CV symptoms—more than rapid death	ICU if symptomatic Symptoms several hours (supportive care)	Likely ICU admission if significant exposure Isolation (patient and secretions)	Observe at least 72 hours for delayed effects	Admit for delayed neurologic symptoms Neuropathy/DM after several days

*Modified from the original by Jack Snyder, MD.

ABG, Arterial blood gas; *ARDS,* acute respiratory distress syndrome; *BUN/Cr,* blood urea nitrogen/creatinine; *CNS,* central nervous system; *CPK,* creatine phosphokinase; *CV,* cardiovascular; *DM,* diabetes mellitus; *ECG,* electrocardiogram; *GI,* gastrointestinal; *ICU,* intensive care unit; *IVF,* intravenous fluids; *LFT,* liver function test; *MRI,* magnetic resonance imaging; *PNU,* N-3-pyridylmethyl-N′-*p*-nitrophenyl urea; *PPE,* personal protective equipment; *SMFA,* sodium monofluoroacetate; *TCA,* tricarboxylic acid; *UA,* urine analysis.

Hassan NAM, Madboly AG: Correlation between serum creatine phosphokinase and severity of acute organophosphorus poisoning: a prospective clinical study (2012-2013). IOSR Journal of Environmental Science, Toxicology and Food Technology 4(5):18-29, 2013.

elimination occurs via zero-order kinetics. Toxic effects can be seen in adults ingesting as little as 1 mg. All significant toxicological exposures are via ingestion, and all warfarins are well absorbed orally.

Clinical Features

Initially, patients can by asymptomatic and remain so as late as 72 hours after ingestion, even in large ingestions. Alternatively, signs of gastrointestinal irritation can predominate early in the course of poisoning, and symptoms appear as early as 8 hours after exposure. They can then present with bleeding anywhere, such as ecchymosis, epistaxis, hemarthrosis, gingival bleeding, dysmenorrhea, and hematuria. Life-threatening effects are massive gastrointestinal bleeding and intracranial hemorrhage.

Differential Diagnoses

Supratherapeutic doses of warfarin, advanced stages of hepatic failure, disseminated intravascular coagulation, hemophilia, and other bleeding disorders can present with similar bleeding symptoms.

Diagnostic Testing

With history, suspicion, or overt bleeding, measure hemoglobin/hematocrit, platelets, prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT), obtain blood type, and screen as well as crossmatch (if active bleeding). PT/INR might not be abnormal until 48 hours after ingestion; a normal INR at 48 hours essentially excludes a significant ingestion. Although most of these poisons are not commonly measurable,

brodifacoum level is available at many reference labs (<4 to 10 ng/mL is normal and should not cause coagulopathy).

Management

Decontamination

If a patient presents within 1 hour after reported massive ingestion of superwarfarin, we recommend oral activated charcoal in a 10:1 activated charcoal to poison ratio. If the dose ingested is unknown, 100 gm is an acceptable dose. Do not perform gastric lavage, because in addition to existing risks of this method of decontamination, severe gastrointestinal bleeding is added.

Stabilization and Supportive Care

With massive blood loss, fluid resuscitation and transfusion is necessary. RBCs to replace blood loss, fresh frozen plasma to improve coagulation profile, and four-factor prothrombin complex concentrate (PCC) are proven to be beneficial and are considered first-line treatment. Another option shown to be beneficial is recombinant activated factor VII.

Enhanced Elimination

There is no role for enhanced elimination in superwarfarin toxicity.

Antidote Therapy

Vitamin K_1, as opposed to K_3 or K_4, is the preferred antidote, or reversal agent, because other forms are not effective and have potential for toxicity. Although vitamin K_1 will reliably reverse anticoagulation, it should not be given prophylactically; toxicity is determined by derangement in INR. This therapy requires 6 hours to take effect and, therefore, is not used for immediate reversal. This pharmacokinetic principle is responsible for the usual vitamin K dosing regimen of every 6 hours. Prolonged treatment with doses as high as 800 mg daily have been required in massive overdoses.

Disposition

The majority of patients with small warfarin-based rodenticide ingestions (eg, children tasting 2 to 3 pellets) can be discharged home with outpatient follow-up in 48 to 72 hours. Patients presenting with reported large intentional ingestion of superwarfarins (ie, an entire box or bait tray) should be admitted for at least 48 hours, at which time an INR should be checked (minimum time after ingestion to check INR is 2 days). In patients with coagulopathy, admission is required until all bleeding has subsided and the patient is maintained on a vitamin K regimen for desired INR. (This depends on comorbid conditions.) On an outpatient basis, these patients may require monitoring of their coagulation profile for 4 to 6 weeks with the longer-acting superwarfarin products.

KEY CONCEPTS

- Organophosphates cause symptoms by accumulation of acetylcholine.
  - Treat cholinergic symptoms with atropine.
  - Reverse the inhibition of acetylcholinesterase with oximes.
- Aging, which results in prolonged toxicity, occurs with organophosphate poisoning, but not with carbamates.
- Chlorinated hydrocarbons can present with seizures and cardiac toxicity.
- Substituted phenols are found in weight loss products and exert their toxicity by uncoupling oxidative phosphorylation.
  - They can cause cardiac, liver, and renal injury.
- Chlorophenoxy compounds cause muscular injury.
  - Measure creatinine kinase; assess for acute rhabdomyolysis, kidney injury, and liver injury.
- Bipyridyl compounds cause pulmonary and renal injury.
  - Paraquat concentrates in lungs; limit supplemental oxygen therapy, because this will exacerbate pulmonary toxicity.
  - Diquat causes renal injury.
- Pyrethrins and pyrethroids cause local dermatologic symptoms.
- Glyphosate
  - Acute toxicity is likely related to the surfactant included in the product.
- DEET should not be used in infants younger than 2 months old.
- DEET in concentrations of more than 30% should not be used in children and may result in neurotoxicity and self-limited seizure activity if used in excessive amounts.
- Most rodenticide exposures will be superwarfarin compounds.
  - For large exposures, INR should be checked at a minimum of 2 days after ingestion.
  - Vitamin K should be used for reversal; blood products should be used for active bleeding.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 157: QUESTIONS & ANSWERS

157.1. A 37-year-old man arrives at the emergency department (ED) after exposure to an organophosphate. He is severely symptomatic, and atropine is given. When should atropine treatment be discontinued?

A. After 100 mg has been given
B. When fasciculations stop
C. When mydriasis occurs
D. When secretions have stopped
E. When tachycardia occurs

Answer: D. Patients with organophosphate poisoning may require very large doses of atropine (up to 500 mg). Proper dosing is 1 or 2 mg intravenously with doubling of the dose every 5 minutes until the drying of secretions. Atropine has no effect at the neuromuscular junction. Mydriasis may occur before secretions have dried. Tachycardia is likely, but it is not a contraindication for continued atropine treatment. The tachycardia often improves as the pulmonary status improves.

157.2. A 30-year-old agricultural worker arrives at the emergency department (ED) with confusion, abdominal pain, nausea, vomiting, and shortness of breath. His coworkers report that he was spraying plants with an insecticide. The patient's vital signs are significant for hypotension, bradycardia, and tachypnea. Physical examination reveals miosis, wheezing, vomiting, diarrhea, and urinary incontinence. Which of the following combinations of medications should be given to this patient?

A. Atropine and cyproheptadine
B. Atropine and physostigmine
C. Atropine and pralidoxime
D. Cyproheptadine and physostigmine
E. Physostigmine and pralidoxime

Answer: C. This patient has symptoms of the cholinergic syndrome (SLUDGE symptoms) and was likely exposed to an organophosphate or carbamate pesticide. Treatment for organophosphate and carbamate poisoning includes atropine to reverse the cholinergic effects and pralidoxime to restore cholinesterase activity. (Pralidoxime use for carbamate poisoning is controversial, but because it is often unclear what exact pesticide was used, treatment with pralidoxime is generally recommended.) Cyproheptadine is an antihistamine that can be used in serotonin syndrome. Physostigmine can be used as an antidote in anticholinergic syndrome.

157.3. A 4-year-old boy arrives at the emergency department (ED) after drinking a medication that was being used to treat his sister's head lice. An unknown amount was consumed, and the bottle is not available. The patient's only complaint is of nausea. Vital signs and physical examination findings are normal. Which of the following symptoms should be anticipated?

A. Gastrointestinal hemorrhage
B. Hallucinations
C. Hypotension
D. Paralysis
E. Seizure

Answer: E. Lindane is a chlorinated hydrocarbon insecticide that is used for the topical treatment of head lice and scabies. It is rapidly absorbed and can result in difficult-to-control seizures requiring high doses of benzodiazepines or barbiturates and that may require sedation, paralysis, and intubation. Because lindane is a hydrocarbon, it can sensitize the cardiac membrane and predispose to ventricular dysrhythmias. It can also cause pulmonary compromise if it is aspirated.

157.4. An 18-year-old woman arrives at the emergency department (ED) complaining of feeling generally weak. She reports reading online about a pesticide that can help in weight loss, and she has recently tried this. Her vital signs are: blood pressure, 110/70 mm Hg; heart rate, 121 bpm; respiratory rate, 22 rpm; and temperature, 104°F (40.0°C). Her physical examination reveals dry mucous membranes and yellow staining on her abdomen. Which of the following laboratory findings can you anticipate?

A. Hypoglycemia
B. Hypokalemia
C. Hyponatremia
D. Hypoxia
E. Methemoglobinemia

Answer: A. Substituted phenols, such as dinitrophenol, are pesticides that uncouple oxidative phosphorylation. This causes an increased metabolism, which in turn consumes glucose and generates heat, often causing an increased body temperature. For this reason, they have been used as diet aids. They can be applied topically, and the yellow skin staining is pathognomonic for nitrogen compounds. Treatment is supportive and should be aimed at stopping further exposure; providing the needed substrates of oxygen, water, and glucose; and applying active cooling measures.

157.5. What organ system is most affected by paraquat ingestion?
A. Cardiac
B. Gastrointestinal
C. Nervous
D. Pulmonary
E. Renal

Answer: D. Paraquat is concentrated in the lungs and directly damages the alveolar capillary membrane. This results in surfactant loss, adult respiratory distress syndrome, pulmonary fibrosis, and respiratory failure and is accelerated with supplemental oxygen. All the other organ systems listed are affected but to a much lesser degree.

157.6. A patient arrives at the emergency department (ED) after an intentional paraquat ingestion complaining of severe mouth, throat, and chest pain. What potentially fatal complication of paraquat ingestion should be suspected?
A. Aortic dissection
B. Esophageal rupture
C. Myocardial infarction
D. Pneumothorax
E. Pulmonary embolism

Answer: B. Paraquat is extremely corrosive and can cause severe burns to the oropharynx, as well as to the esophagus. Frequently, esophageal rupture occurs, leading to mediastinitis and death. None of the other listed conditions occurs with any frequency in paraquat poisoning.

157.7. How do pyrethrins cause toxicity?
A. Allergic reactions
B. Bone marrow suppression
C. Cardiovascular instability
D. Inhibition of coagulation
E. Uncoupling of oxidative phosphorylation

Answer: A. Pyrethrins are naturally occurring substances from the yellow chrysanthemum and commonly cause allergic reactions in humans. These reactions can be mild or life-threatening with bronchoconstriction and laryngeal edema. They also affect gamma-aminobutyric acid (GABA)-mediated chloride channels in the nervous system, but this typically results in only a mild headache and paresthesias.

157.8. DEET is a commonly used insect repellant that can cause contact dermatitis and more severe neurologic complications, including seizures with high doses that are absorbed through the skin. Which of the following methods will minimize DEET absorption through the skin?
A. Apply to skin at night
B. Cover skin with clothing
C. Expose skin to direct sunlight
D. Keep skin dry
E. Remove from skin with oil-based products

Answer: D. DEET absorption and toxicity increase with repeated applications, with increased ambient temperatures, with sweating, when it is applied to abraded or thin skin, and when it is covered with tight-fitting clothing. Oils or lipophilic substances applied to the skin also increase absorption of DEET.

CHAPTER 158

Plants, Mushrooms, and Herbal Medications

Christopher S. Lim | Steven E. Aks

PLANTS

PRINCIPLES OF TOXICITY

The nutritional, therapeutic, psychoactive, and toxic properties of botanicals have made their usage pervasive since antiquity. The earliest documented use of plants for medicinal purposes can be found in Sumerian clay tablets that describe the use of over 200 different plants in the treatment of various maladies. Ancient Greeks recognized the lethal effects of botanicals, sentencing Socrates to death by ingestion of a hemlock-based liquid. The recreational abuse and medicinal use of opium poppies highlight the wide-ranging role that plants have played throughout history.

Exposures to plants comprise over 45,000 calls nationally to United States poison centers, with approximately 65% involving patients younger than 6 years old. Over 85% of plant exposures are accidental ingestions. The overwhelming majority of plant exposures result in minimal toxicity and death is exceedingly rare.[1,2] Plant exposures reported to United States poison centers have been decreasing over the past three decades, ranking third and comprising 9% of all exposures in 1983, but ranking 17th and making up only 2.5% of all exposures in 2010.[3] The most common plant exposures resulting in severe and occasionally fatal poisonings involve those with anticholinergic, antimitotic, cardiotoxic, or convulsive properties.[2]

CLINICAL FEATURES

The vast majority of plants are considered non-toxic (Table 158.1). However, serious toxicity can result from certain plant exposure (Table 158.2). Toxicity does not correlate well with taxonomy, and plants within the same genera may have varying toxic profiles. Further complicating matters, the severity of exposure may depend on the method of ingestion (ie, chewed or swallowed) and which part of the plant was ingested.[4] For example, although all parts of the water hemlock plant are considered toxic, cicutoxin is most concentrated in the root of the plant. The majority of serious or fatal outcomes occur in the adult population intentionally ingesting botanicals for suicidal or recreational intent.[3] A focused history and physical examination should be aimed at identifying the involved plant and any toxidrome common to botanical exposures.

DIFFERENTIAL DIAGNOSES

Plant ingestions presenting with vomiting and diarrhea and should be differentiated from food poisoning, viral or bacterial gastroenteritis, and pesticide poisoning (often sprayed on plants). Those patients presenting with altered mental status should be differentiated from patients co-ingesting hallucinogenic, stimulant, or opioid drugs of abuse.

DIAGNOSTIC TESTING

Although measurement of specific concentrations of botanical toxins are not routinely available at most institutions, evaluation of electrolytes, complete blood count, liver transaminases, and renal function should be performed in patients with potentially toxic exposures. An electrocardiogram (ECG) and cardiac monitoring should be performed to identify any potential dysrhythmias specific to certain plant classes (eg, anticholinergic, cardiac glycosides). Efforts are made at botanical identification to determine potential toxicity. Patients should not be routinely relied upon for botanical identification. Mistaken identification by patients and family members is a frequent cause of accidental ingestions of toxic botanicals and can lead to inappropriate dispositions from the emergency department (ED).[5,6] Furthermore, most emergency medical staff struggle to correctly identify even common house plants. Instead, family members or friends should be asked to bring in or send digital photographs of the involved plant, which can then be compared to reliable reference photographs or referred to local botanical experts or poison centers for proper identification.[7,8]

MANAGEMENT

There is no role for gastric emptying in the ED management of botanical poisoning. There likewise is no evidence of clinical benefit from activated charcoal, and we do not recommend its routine use in the setting of botanical poisoning. A few exceptions can be made for those who present within 1 hour of ingestion of a potentially life-threatening exposure and can be found in Table 139.12.

There are few antidotes that have been shown to be effective in botanical poisonings. In most exposures, information and identification of the plant is not immediately known, and treatment should be focused on symptom-based, supportive care. This includes maintenance of a patent airway, intravenous (IV) fluids and vasopressors for hypotension, active cooling for hyperthermia, and benzodiazepines for agitation and seizures. Management of specific categories of botanicals is outlined in the following sections.

DISPOSITION

Any patient with signs of severe toxicity, especially those involving the cardiovascular and neurologic systems, should be managed in the ED until symptoms and signs are resolving, or admitted to an intensive care setting. Patients with exposure to unknown plants can be discharged after 6 hours of observation if they are hemodynamically stable and otherwise asymptomatic. This period of observation can be extended to as long as 24 hours if preexisting cardiovascular medical problems exists or an exposure to a plant of serious toxicity is suspected.[9]

Text continued on p. 1962

TABLE 158.1

Non-Toxic Plants

COMMON NAME	BOTANICAL NAME
Abelia	*Abelia* spp.
African daisy	*Gerbera jamesonii*
African violet	*Saintpaulia ionantha*
Aglaonema	*Aglaonema* spp.
Aluminum plant	*Pilea cadierei*
Alyssum	*Slyssum* spp.
Aralia	*Dizygotheca elegantissima*
Areca palm	*Chrysalidocarpus lutescens*
Artillery plant	*Pilea* spp.
Asparagus fern	*Asparagus setaceus*
Aspidistra	*Aspidistra* spp.
Aster	*Callistephus chinensis, Townsendia sericea*
Astilbe	*Astilbe japonica*
Baby's breath	*Gysophila paniculata*
Baby's tears	*Hypoestes phyllostachya, Soleirolia soleirolii*
Baby's toes	*Centaurea cyanus*
Bachelor's buttons	*Centaurea cyanus*
Balsam	*Impatients* spp.
Bamboo	*Phyllostachys aurea*
Basket vine	*Aeschynanthus* spp.
Beauty bush	*Kolkwitzia amabilis*
Begonia	*Begonia goegoensis, Cissus* spp.
Bird's nest fern	*Asplenium nidus*
Bleeding heart vine	*Clerodendrum* spp.
Blood leaf plant	*Iresine* spp.
Boston fern	*Nephrolepis* spp.
Bromeliad	*Vriesea hieroglyphica*
Brunch berry	*Cornus canadensis*
Butterfly bush	*Buddleia davidii*
Button fern	*Pellaea rotundifolia*
Calathea	*Calathea* spp.
Camellia	*Camellia japonica, Thea japonica*
Candle plant	*Plectranthus oetendahlii*
Cape primrose	*Streptocarpus* spp.
Cast iron plant	*Aspidistra elatior*
Cattail	*Typha latifolia*
China doll	*Leea* spp.
Chinese evergreen	*Aglaonema modestum*
Christmas cactus	*Cactaceae*
Coleus	*Coleus* spp.
Columbine	*Aquilegia* spp.
Coral bells	*Kalanchoe uniflora*
Cordyline	*Cordyline* spp.
Corn plant or cornstalk plant	*Dracaena fragrans*

TABLE 158.1

Non-Toxic Plants—cont'd

COMMON NAME	BOTANICAL NAME
Creeping Charlie (houseplant)	*Pilea nummulariifolia, Plectranthus australis*
Creeping Jennie	*Lysimachia nummularia*
Crocus (Spring only)	*Crocus* spp.
Dahlia	*Dahlia* spp.
Dandelion	*Taraxacum officinale*
Day lily	*Hermocallis* spp.
Donkey's tail	*Sedum morganianum*
Dracaena	*Dracaena* spp., *Cordyline* spp.
Dragon tree	*Dracaena draco*
Easter lily	*Lilium longiflorum*
Echeveria	*Echeveria* spp.
Emerald feather	*Asparagus densiflorus sprengeri*
Eugenia	*Eugenia cyanocarpa, Syzgium cuminii*
False aralia	*Dizygotheca elegantissima*
Fatsia	*Fatsia japonica*
Ferns	*Davallia canariensis, Davallia fejeensis, Rumohra adiantiformis, Asplenium* spp.
Ficus	*Ficus benjamina*
Fig	*Ficus carica*
Fingernail plant	*Aregelia* spp.
Firecracker flower	*Crossandra* spp.
Firecracker vine	*Menettia bicolor*
Fittonia	*Fittonia* spp.
Florida beauty	*Dracaena* spp.
Flowering quince	*Chaenomeles* spp.
Forsythia	*Forsythia* spp.
Friendship plant	*Billbergia* spp., *Pilea involucrate*
Fuchsia	*Fuchsia* spp.
Gardenia	*Gardenia jasminoides*
Gazania	*Gazania* spp.
Geranium	*Pelargonium* spp.
Glory tree	*Clerodendrum thomsoniae*
Gloxinia	*Gloxinia perennis, Sinningia speciosa*
Golddust plant	*Alyssum* spp., *Aucuba japonica*
Goldfish plant	*Hypocyrta* spp.
Hawthorn	*Crataegus* spp.
Hemlock tree	*Tsuga* spp. (not to be confused with *Conium* or *Cicuta* spp.)
Hens and chicks	*Echeveria* spp., *Sempervivum tectorum*
Hibiscus	*Hibiscus* spp.
Honey locust	*Gleditsia triacanthos*
Honeysuckle	*Lonicera fragrantissima*
Hosta	*Hosta* spp.
Hoya	*Hoya* spp.
Ice plant	*Aptenia cordifolia, Lampranthus* spp., *Mesembryanthemum cordifolium*

Continued

TABLE 158.1

Non-Toxic Plants—cont'd

COMMON NAME	BOTANICAL NAME
Impatients	*Impatients* spp.
Iron plant	*Aspidistra* spp.
Jade plant	*Portulacaria afra*
Janet Craig plant	*Dracaena deremensis*
Japanese aralia	*Fatsia japonica*
Japanese lantern	*Hibiscus schizopetalus*
Japanese snowbell	*Styrax japonica*
Kalanchoe	*Kalanchoe* spp.
King and queen fern	*Asplenium* spp.
Lavendar	*Lavandula officinalis*
Lilac	*Syringa* spp.
Linden tree	*Tilia americana*
Lipstick plant	*Aeschynanthus* spp.
Magnolia	*Magnolia* spp.
Maidenhair fern	*Adiantum decorum*
Maple tree	*Acer* spp.
Maranta	*Calathea* spp., *Maranta* spp.
Marigolds (except marsh marigolds)	*Calendula* spp.
Maternity plant	*Kalanchoe* spp.
Mexican snowball	*Echeveria* spp.
Mimosa	*Albizia julibrissin*
Mock orange	*Philadelphus* spp., *Pittosporum tobira*
Monkey plant	*Ruellia makoyana*
Mosaic plant	*Fittonia argyroneura*
Mother fern	*Asplenium* spp.
Mother of thousands	*Kalanchoe pinnata*
Mountain grape	*Mahonia* spp.
Mulberry tree or bush	*Morus* spp.
Nasturtium	*Tropaeolum* spp.
Neanthe bella	*Chamaedorea elegans*
Nerve plant	*Fittonia* spp.
Norfolk Island pine	*Araucaria heterophylla*
October plant	*Sedum sieboldii*
Old man of the mountains	*Hymenoxys grandiflora*
Orchid	*Cattleya* spp., *Cymbidium* spp., *Epidendrum* spp., *Oncidium* spp.
Painted lady	*Echeveria* spp.
Panda plant	*Kalanchoe tomentosa*
Parlor palm	*Chamaedorea elegans*
Passion vine, purple	*Gynura aurantiaca*
Patient Lucy	*Impatients* spp.
Peacock plant	*Calathea makoyana, Kaempferia* spp.
Peperomia	*Peperomia* spp.
Petunia	*Petunia* spp.
Phlox	*Phlox* spp.

TABLE 158.1

Non-Toxic Plants—cont'd

COMMON NAME	BOTANICAL NAME
Piggyback plant	*Tolmiea menziesii*
Pilea	*Pilea* spp.
Pine trees	*Pinus* spp.
Pitcher plant	*Darlingtonia californica*
Pittosporum	*Pittosporum* spp.
Plantago	*Plantago major*
Plush plant	*Echeveria* spp., *Kalanchoe* spp.
Pocketbook plant	*Calceolaria* spp.
Poinsettia	*Euphorbia pulcherrima*
Polka dot plant	*Hypoestes phyllostachya*
Pony tail plant	*Beaucarnea recurvata*
Potentilla	*Potentilla* spp.
Prayer plant	*Maranta leuconeura*
Pregnant plant	*Kalanchoe pinnata*
Propeller plant	*Crassula cultrate*
Purple passion	*Gynura aurantiaca*
Pyracantha	*Pyranchantha* spp.
Queen's tears	*Billbergia* spp.
Rabbit's foot	*Maranta leuconeura*
Rainbow plant	*Billbergia* spp.
Red bud	*Cercis canadensis*
Red hot poker	*Kniphofia* spp.
Resurrection plant	*Selaginella lepidophylla*
Rex-begonia vine	*Cissus discolor*
Ribbon plant	*Dracaena sanderiana*
Rosary vine	*Ceropegia woodii, Crassula rupestris*
Rose, rosehips	*Rosa* spp. (except *Rosa rugose*)
Rose of Sharon	*Hibiscus syriacus*
Rubber plant	*Ficus elastica*
Salvia	*Salvia* spp.
Sedum	*Sedum* spp.
Sensitive plant	*Mimosa pudica*
Sentry palm	*Howea forsterana*
Silk tree	*Albizia julibrissin*
Silver bell	*Halesia* spp.
Silver berry	*Elaeagnus* spp.
Silver dollar plant	*Astrophytum asterias, Crassula arborscens*
Silver evergreen	*Aglaonema* spp.
Silver king	*Aglaonema* spp.
Silver vine	*Actinidia polygama*
Snapdragon	*Antirrhinum majus*
Snowball bush	*Viburnum* spp.
Spider aralia	*Dizygotheca elegantissima*

Continued

TABLE 158.1

Non-Toxic Plants—cont'd

COMMON NAME	BOTANICAL NAME
Spider flower	*Cleome* spp., *Hermocallis* spp., *Tibouchina* spp.
Spiraea	*Astilbe japonica*
Spirea	*Spirea* spp.
Spruce tree	*Picea* spp.
Staghorn fern	*Platycerium* spp.
Starfish flower	*Stapelia* spp.
Stone face	*Lithops* spp.
String of buttons	*Crassula rupestris*
Striped inch plant	*Callisia* spp.
Swedish ivy	*Plectranthus australis*
Sword fern	*Polystichum munitum*
Teddy bear plant or vine	*Cyanotis kewensis*
Tiger lily	*Lilium* spp.
Tulip tree	*Liriodendron tulipifera, Spathodea campanulata*
Umbrella plant	*Eriogonum umbellatum*
Umbrella tree	*Magnolia tripetala*
Velvet plant	*Gynura aurantiaca*
Viburnum	*Viburnum* spp.
Wandering Jew	*Zebrina pendula*
Wax flower	*Stephanotis floribunda*
Wax plant	*Hoya* spp.
Wild strawberry	*Fragaria* spp.
Willow	*Salix* spp.
Yellow wood	*Cladrastis lutea, Rhodosphaera rhodanthema*
Yucca plant	*Yucca* spp.
Zebra plant	*Aphelandra squarrosa, Calanthea zebrina, Cryptanthus zonatus*
Zinnia	*Zinnia* spp.

PLANT CATEGORIES

Anticholinergics

Principles of Toxicity

Datura stramonium (Jimson weed, angel's trumpet) (Fig. 158.1) and *Atropa belladonna* (deadly nightshade) are the most frequently encountered plants with anticholinergic toxins. They contain scopolamine, hyoscyamine, and atropine. All parts of the plant contain toxic alkaloids, but they are most concentrated in the seeds of *D. stramonium* and the fruit and leaves of *A. belladonna*.

Clinical Features

Ingestion can cause an antimuscarinic syndrome of agitation, diminished gastrointestinal (GI) motility, dry skin, flushing, hallucinations, hyperthermia, mydriasis, tachycardia, and urinary

Fig. 158.1. *Datura stramonium* (Jimson weed). (Courtesy Steven Setzer.)

TABLE 158.2

Toxic Plants

COMMON NAME	BOTANICAL NAME	TOXIC EFFECTS
Ackee tree	*Blighia sapida*	Hypoglycemia, GI, neurologic
Almond, apricot, cherry, plum, peach	*Prunus* spp.	Cyanogenic
American mistletoe	*Phoradendron* spp.	GI
Angel trumpet	*Brugmansia suaveolens*	Anticholinergic
Autumn crocus, meadow or wild saffron	*Colchicum autumnale*	GI, multi-organ
Azalea	*Azalea* spp.	Cardiovascular
Betel nut	*Areca catechu*	Cholinergic
Bird-lime, blue thistle	*Atractylis gummifera*	Hepatic
Bitter orange	*Citrus aurantium*	Cardiovascular, neurologic
Black locust	*Robinia pseudoacacia*	GI
Buckeye	*Aesculus glabra*	GI, neurologic
Calabar bean	*Physostigma venenosum*	Cholinergic
Cassava	*Manihot exculentus*	Cyanogenic
Castor bean	*Ricinus communus*	GI, multi-organ
Cayenne pepper	*Capsicum* spp.	Dermatologic, mucosal irritant
Chrysanthemum, dandelion	*Chrysanthemum* spp.	Dermatologic
Cinchona	*Cinchona* spp.	Cardiovascular, cinchonism
Common, white or pink oleander	*Nerium oleander*	Cardiovascular*
Deadly nightshade	*Atropa belladonna*	Anticholinergic
Dumb cane, mother-in-law plant	*Dieffenbachia* spp.	Dermatologic, mucosal irritant
Elderberry	*Sambucus nigra*	GI, metabolic
Elephant ear, angel wings, heart of Jesus	*Caladium* spp.	Dermatologic, mucosal irritant
Ergot	*Claviceps purpurea*	Cardiovascular, neurologic, oxytocic
Eucalyptus	*Eucalyptus* spp.	Dermatologic, GI
European or true mandrake	*Mandragora officinarum*	Anticholinergic
Fava bean	*Vicia fava*	Hematologic
Foxglove	*Digitalis* spp.	Cardiovascular*
Glory lily	*Gloriosa superba*	GI, multi-organ
Golden chain or rain	*Laburnum anagyroides*	GI, neurologic
Grass pea	*Lathyrus sativus*	Neurologic, skeletal
Green tomato	*Lycopersicon* spp.	GI, neurologic, anticholinergic
Guarana	*Paullinia cupana*	Neurologic, cardiac
Henbane, hyoscyamus	*Hyoscyamus niger*	Anticholinergic
Holly	*Ilex* spp.	GI
Ipecac	*Cephaelis ipecacuanha, Cephaelis acuminata*	GI
Jequirity pea, rosary or prayer bead	*Abrus precatorius*	GI, neurologic
Jimson weed, angel's trumpet	*Datura stramonium*	Anticholinergic
Khat	*Catha edulis*	Cardiovascular, neurologic
Larkspur	*Delphinium* spp.	Cardiovascular, neurologic
Lily of the valley	*Convallaria majalis*	Cardiovascular*
Mad honey	*Rhododendron* spp.	GI, cardiac
Madagascar periwinkle, vinca	*Catharanthus roseus*	GI
Marijuana, hashish, pot	*Cannabis*	Neurologic

Continued

TABLE 158.2

Toxic Plants—cont'd

COMMON NAME	BOTANICAL NAME	TOXIC EFFECTS
Mayapple	*Podophyllum emodi, Podophyllum peltatum*	Multi-organ
Milkweed	*Asclepias* spp.	Cardiovascular*
Monkshood, wolfsbane	*Aconitum napellus*	Cardiovascular, neurologic
Nightshade (various), potato	*Solanum* spp.	Anticholinergic
Opium poppy	*Papaver somniferum*	Neurologic, respiratory
Peace lily	*Spathiphyllum* spp.	Dermatologic, mucosal irritant
Peyote, mescal	*Lophophora williamsii*	Neurologic
Philodendron	*Philodendron* spp.	Dermatologic, mucosal irritant
Pilocarpus	*Pilocarpus jaborandi, Pilocarpus pinnatifolius*	Cholinergic
Pink-eyed cerbera, sea mango	*Cerbera manghas*	Cardiovascular*
Poison hemlock	*Conium maculatum*	Neurologic, pulmonary
Poison ivy, poison oak, poison sumac	*Toxicodendron* spp.	Dermatologic
Pokeweed	*Phytolacca americana*	GI
Poplar	*Populus* spp.	Salicylism
Pothos	*Epipremnum aureum*	Dermatologic, mucosal irritant
Queen sago, indu	*Cycas circinalis*	Neurologic
Rattlebox	*Crotalaria* spp.	Hepatotoxic
Red squill	*Urginea maritima, Urginea indica*	Cardiovascular*
Spider plant	*Chlorophytum comosum*	Dermatologic, mucosal irritant
Tansy	*Tanacetum vulgare*	Neurologic
Tobacco	*Nicotiana* spp.	GI, neurologic
Tonka beans	*Dipteryx odorata, Dipteryx oppositifolia*	Hematologic
Tubocurare, curare	*Chondrodendron* spp., *Curarea* spp., *Strychnos* spp.	Neurologic
Tullidora, buckthorn	*Karwinskia humboldtiana*	Neurologic, respiratory
Umbrella tree	*Schefflera* spp., *Brassaia* spp.	Dermatologic, mucosal irritant
Water hemlock	*Cicuta maculata*	Neurologic
Water hemlock	*Oenanthe crocata*	Neurologic
White cedar	*Thuja occidentalis*	Neurologic
Wormwood, absinthe	*Artemisia absinthium*	Neurologic
Yellow oleander	*Thevetia peruviana*	Cardiovascular*
Yew	*Taxus* spp.	Cardiovascular

*Cardioactive steroid.
GI, Gastrointestinal.

retention.[10] *D. stramonium* is commonly abused for its hallucinogenic properties, whereas berries from *A. belladonna* have been mistaken for the common blueberry *(Vaccinium arctostaphylos),* resulting in poisonings.[11]

Differential Diagnoses

The differential diagnosis of antimuscarinic toxicity includes pharmaceutical agents, such as diphenhydramine, benztropine, cyclic antidepressants, antipsychotics, and antiparkinson medications. Sympathomimetic drugs such as cocaine and amphetamines will also cause similar toxic symptoms but typically present with diaphoresis instead of dry skin, which is typical of the anticholinergic toxidrome.

Diagnostic Testing

Symptomatic patients with altered mental status, hyperthermia, and tachycardia merit a screening ECG to assess corrected QT (QTc) and QRS intervals, serum electrolytes, glucose, creatine phosphokinase (CPK), and renal function.

Management

Management is based on supportive care, including active cooling for hyperthermia and benzodiazepines for agitation.[10] Recommended agents include diazepam, 5 to 10 mg IV, or lorazepam, 1 to 2 mg IV. Additional doses can be administered every 10 minutes until the patient is calm and able to cooperate with care. The use

of a cholinesterase inhibitor, such as physostigmine, is recommended for severe toxicity refractory to benzodiazepines (see Chapter 145).[12]

Disposition

Mildly symptomatic patients can be observed in the ED for 6 to 8 hours and discharged from the ED. Severely poisoned patients with refractory antimuscarinic symptoms should be admitted to a monitored setting for 24 hours.

Antimitotic Toxins

Principles of Toxicity

Colchicum autumnale is also known as autumn crocus, meadow saffron, or wild saffron, and contains the toxic alkaloid, colchicine. Colchicine inhibits microtubule formation, leading to disruption of mitosis, intracellular transport mechanisms, and cell structure. *C. autumnale* is often mistaken for *Allium ursinum* (wild garlic), leading to fatal, unintentional ingestions.[2] Pharmaceutical colchicine is most commonly used to treat acute gouty arthritis. Serious toxicity from pharmaceutical colchicine is seen at doses greater than 0.5 mg/kg, and it is invariably lethal at doses of 0.8 mg/kg.

Clinical Features

The clinical course of colchicine poisoning is typically divided into three phases of illness.[6,13] The first phase is marked by GI symptoms, such as severe vomiting, diarrhea, hypovolemia, electrolyte disturbances, and abdominal pain. Multi-organ failure ensues in the second phase, with manifestations of cardiac arrhythmia, adult respiratory distress syndrome (ARDS), pancytopenia, liver failure, rhabdomyolysis, and sepsis. Death usually occurs during this second phase. The third phase is recovery from the poisoning.

Differential Diagnoses

Patients presenting in the first phase of illness may be misdiagnosed as gastroenteritis or food poisoning. In the second phase, colchicine poisoning mimics many serious disorders and is treated similarly, with supportive interventions based on the type and severity of the patient's presentation. Obtaining a history of ingestion is critical to making the correct diagnosis but will not significantly alter the treatment plan. Patients with pancytopenia should be differentiated from patients with sepsis, leukemia, or oncological disorders—obtaining the history of ingestion may avoid invasive testing, such as a bone marrow biopsy.

Diagnostic Testing

Laboratory data should include a complete blood count to assess for pancytopenia. Additional laboratory tests include serum electrolytes, renal and liver function tests, as well as a screening ECG.

Management

There is no specific therapy for colchicine poisoning, and management consists primarily supportive care. There is no commercially available antidote for colchicine poisoning the the US, and supportive care is ineffective in those who ingest a lethal dose. Thus, efforts to prevent gastric absorption by administration of activated charcoal should be made for those who ingest a potentially lethal dose of colchicine and present within 1 hour of ingestion.

Disposition

Patients presenting with GI symptoms but normal laboratory testing may be discharged home after 6 to 8 hours of hydration and observation in the ED. Patients with cardiac dysrhythmias, pancytopenia, and/or liver or renal failure require admission to a monitored setting. Patients with pancytopenia require admission and isolation setting to avoid secondary nosocomial infections.

Cardiac Glycosides

Principles of Toxicity

Cardiac glycosides bind to cell transmembrane Na^+-K^+-ATPases, which, in turn leads to a rise in intracellular Ca^{2+} concentrations, causing decreased automaticity and increased contractility. Common plants that contain cardiac glycosides include *Convallaria majalis* (lily of the valley), *Digitalis spp.* (foxglove) (Fig. 158.2), *Nerium oleander* (common, pink or white oleander) (Fig. 158.3), and *Thevetia peruviana* (yellow oleander).

Clinical Features

Similar to digoxin poisoning, patients with exposure to cardiac glycosides can present with GI symptoms, generalized weakness, altered mental status, bradydysrhythmias and tachydysrhythmias, and hypotension. Toxicity and treatment of cardiac glycosides are also discussed in Chapter 147.

Differential Diagnoses

The differential diagnosis of cardiac glycoside plant poisoning is broad and includes pharmaceutical toxicity with digoxin, calcium channel blockers, beta blockers, and clonidine. Additionally, other cardiotoxic plants (discussed later) and other cardiogenic bradydysrhythmias (atrioventricular [AV] blocks and sick sinus syndromes) should be considered. Toxicologic causes of altered

Fig. 158.2. *Digitalis purpurea* (foxglove). (Courtesy Christopher Lim.)

Fig. 158.3. Nerium oleander. (Courtesy Steven Setzer.)

Fig. 158.4. *Taxus media* (yew). (Courtesy Christopher Lim.)

mental status include, but are not limited to, sedative-hypnotic, anticholinergic, and opioid poisoning. However, infectious, metabolic, traumatic, malignant, and endocrine etiologies can present in a similar fashion.

Visual disturbances can be seen with toxicity from methanol, ethambutol, ethyl chloride, and anti-malarial medications,

No sign or symptom, including dysrhythmia, is unique to digoxin poisoning, so the differential diagnosis is broad. Intrinsic cardiac disease, as well as other cardiotoxic drugs, should be considered. Cardioactive steroid poisoning from plants is rare but presents similarly to digoxin toxicity. Common examples include oleander (*Nerium oleander*, see Fig. 147.2) and lily-of-the-valley (*Convallaria majalis*, see Fig. 147.3). Aconitine, a sodium-channel opening xenobiotic found in common monkshood *(Aconitum napellus),* may also mimic digoxin poisoning. Central nervous system (CNS) depression or confusion may be due to various depressant drugs (opioids, major tranquilizers, sedative hypnotic agents) and toxins, as well as infection, trauma, inflammation, and metabolic derangements. Visual disturbances caused by digoxin are binocular and are often not reported by the patient; unfortunately, they are not specific to digoxin poisoning. Methanol, metformin, ethambutol, ethyl chloride, quinine, and other antimalarial medications are all capable of producing visual disturbances. GI disturbances are common and nonspecific and may be misdiagnosed as gastritis, enteritis, or colitis.

Diagnostic Testing

Patients should have an ECG obtained and serum electrolytes measured with attention to potassium because cardiac glycoside poisoned patients are susceptible to hyperkalemia. A serum digoxin concentration can be measured but correlates poorly with the degree of toxicity and should be used only to confirm exposure.

Management

The cornerstone of therapy is digoxin-specific antibody fragments and should be administered in any patient displaying serious toxicity (symptomatic bradycardia, sinus arrest or exit block, atrial tachydysrhythmia, ventricular dysrhythmia, second- or third-degree AV block, hypotension, and/or serum potassium level >5.0 mEq/L).[14] Administration of digoxin immune Fab is described in Chapter 147. Cardiac pacing, atropine, and beta-adrenergic agents are without demonstrated benefit and should only be considered adjunctive therapies.

Disposition

Symptomatic patients with bradycardia, hypotension, altered mental status, or hyperkalemia are admitted to a monitored setting. Those requiring digoxin-specific antibody fragments should be admitted to an intensive care setting with cardiology or medical toxicology consultation.

OTHER CARDIOTOXIC PLANTS

Rhododendron species contain grayanotoxin, which can be found in high levels in the honey that is produced from their nectar. Often referred to as "mad honey," poisonings can presents with GI symptoms, hypersalivation, diaphoresis, and cardiac effects.[14,15] Grayanotoxin binds to cell membrane sodium channels, preventing voltage-dependent inactivation, thereby holding cells in a depolarized state. This is thought to increase vagal tone. The cardiac manifestations mainly consist of bradydysrhythmias (including sinus bradycardia, AV blocks, and atrial fibrillation with slow ventricular response) and hypotension, leading to symptoms of dizziness and syncope.[14-19] It has even been implicated as a cause of myocardial infarction.[20-22] In addition to IV fluids for hypotension, atropine and cardiac pacing have been used successfully in the treatment of mad honey toxicity.[14,16]

Taxus species (Fig. 158.4), commonly known as yew, are coniferous trees and shrubs that are often cultivated for ornamental landscaping. They contain several toxic components, including taxine pseudoalkaloids that cause sodium and calcium channel blockade. The most serious effects are on the cardiovascular system, and manifestations include hypotension, dysrhythmias, and cardiac arrest.[23] Management of toxicity is largely supportive. The successful use of extracorporeal circulatory support for severe and refractory cardiotoxicity and hypotension has been reported.[24,25]

Aconitum spp. (monkshood, wolfsbane) contain aconitine and other related alkaloids. Similar to grayanotoxins, aconitine binds and prevents inactivation of voltage-gated sodium channels of

Fig. 158.5. *Cicuta maculata* (water hemlock). (Courtesy Steven Setzer.)

myocardial and neural cells. Thus, the main features of poisoning are neurological (paresthesias, weakness) and cardiovascular (hypotension, dysrhythmias).[26] Management includes supportive care and standard therapy for dysrhythmias.

Cicutoxin

Principles of Toxicity

Both *Cicuta spp.* (Fig. 158.5) and *Oenanthe crocata* are commonly known as water hemlock, and contain toxins responsible for the hallmark presentation of intractable and life-threatening seizure activity. Seizures are thought to occur from non-competitive gamma-aminobutyric acid (GABA) antagonism.

Clinical Features

Initial features of poisoning may include vomiting, abdominal pain, confusion, weakness, and dizziness. Prolonged seizures can further complicate the clinical course, leading to rhabdomyolysis, hyperthermia, acidosis, hypoxia, cerebral edema, and eventual cardiopulmonary arrest.

Differential Diagnoses

Water hemlock is often confused for edible plants, leading to unintentional poisonings.

Other neurotoxic agents should be considered including organophosphates, isoniazid (INH), tricyclic antidepressants, methyl xanthines, hypoglycemics, tramadol, sympathomimetic toxicity, and ethanol and benzodiazepine withdrawal. Seizure disorders, head trauma, and brain lesions are also diagnostic considerations.

Diagnostic Testing

History is essential to identify the toxin as the cause of the new onset seizure, thus obviating the need for further diagnostic testing. Serum electrolytes will exclude hypernatremia, hyponatremia, hypocalcemia, or hypoglycemia as a cause of the confusion or seizures and hypokalemia as a cause of the weakness. Serum creatine kinase (CK) and creatinine will evaluate for rhabdomyolysis and renal impairment. A toxicology screen, especially a serum ethanol level, also will help identify or exclude alternate causes of the confusion. An ECG should be performed to assess intervals if an electrolyte disturbance or overdose is suspected.

Fig. 158.6. *Conium maculatum* (poison hemlock). (Courtesy Steven Setzer.)

Management

The mainstay of management seizure control with benzodiazepines (lorazepam, 1 to2 mg IV, or diazepam, 5 to 10 mg IV, repeated every few minutes until seizure activity ceases). If seizure activity is not controlled with benzodiazepines, treatment is as for other toxicologic causes of status epilepticus (see Chapter 92).

Disposition

Patient with altered mental status and seizures should be admitted to an intensive care setting. Those who are asymptomatic after 6 to 8 hours observation the ED may be discharged home.

OTHER TOXIC PLANTS

Nicotinic Toxin

Conium maculatum (poison hemlock) (Fig. 158.6), *Nicotiana tabacum* (Fig. 158.7), and *Nicotiana glauca* (wild or tree tobacco) contain alkaloids capable of producing nicotinic-cholinergic poisoning. They contain the toxins coniine and coniceine *(C. maculatum),* and anabasine *(N. glauca)* that stimulate nicotinic acetylcholine receptors on the autonomic nervous system and neuromuscular junction.

Clinical effects can include hypersalivation, vomiting, diarrhea, muscle fasciculation, and agitation; toxicity can progress to profound weakness, paralysis, respiratory failure, hypotension, rhabdomyolysis, and renal failure.

There is no specific antidote, and treatment should be aimed at ventilatory support for those with respiratory distress or muscle fatigue and those who cannot adequately oxygenate. Treatment should be continued until resolution of respiratory muscle fatigue and the patient can adequately support their own respirations.

Raphides

Raphides are needle-shaped, calcium oxalate crystals and have been observed in over 200 plants.[27] Clinically common plants that contain calcium oxalate crystals include the species from the genera *Dieffenbachia* (dumb cane, mother-in-law plant)

Fig. 158.7. *Nicotiana tabacum* (tobacco). (Courtesy Christopher Lim.)

Fig. 158.8. *Dieffenbachia amoena* (dumb cane). (Courtesy Christopher Lim.)

(Fig. 158.8), *Philodendron*, *Spathiphyllum*, and *Brassaia*. *Dieffenbachia* is commonly found in homes and offices due to their attractive appearance, resistance to neglect, and relative inexpensiveness.[28]

Ingestions can result in vomiting, mucosal irritation, ulceration, and edema that can lead to compromise of the airway in severe ingestions.[28,29] Dermal exposures may lead to contact dermatitis.

Treatment is supportive, including maintenance of a patent airway. The use of corticosteroids and antihistamines are considered adjunctive therapies, but they have not been shown to improve outcomes in mild cases of exposure.[28,29] However, we recommend the administration of diphenhydramine (25 to 50 mg intravenous push [IVP]) and dexamethasone (4 to 8 mg IVP) for the rare case of respiratory distress with significant airway edema following ingestion of specific raphide plants.

Fig. 158.9. *Abrus precatorius* (jequirity pea or rosary pea). (Courtesy Steven Setzer.)

Toxalbumins

Abrus precatorius (jequirity pea, rosary or prayer bead) (Fig. 158.9) and *Ricinus communis* (castor oil plant) contain the toxins abrin and ricin, respectively, that inhibit ribosomal protein synthesis, leading to cell death. Seeds of *A. precatorius* are distinctive, bright red or orange seeds with black caps that are often used in jewelry or rosaries. Castor beans are light brown, mottled with dark brown spots. Seeds or beans swallowed whole with the hard outer shell intact typically prevent absorption of significant toxin.[30]

Chewed or crushed seeds or beans may release the toxin and cause local toxicity in the GI tract, leading to gastroenteritis, abdominal pain, dehydration, and electrolyte disturbances.[30,31] Rarely, abrin or ricin is absorbed systemically, and symptoms may progress to severe neurologic toxicity (seizure, coma, cerebral edema, demyelinating encephalitis), multi-organ failure, and death. Purified ricin derived from the castor bean is highly toxic and lethal in small doses. It has been used as a biologic weapon, implicated in the assassination of Bulgarian journalist Georgi Markov, and more recently, being discovered at a White House mail facility.

There is no effective antidote, vaccine, or other therapy for the treatment of prevention of abrin or ricin poisoning. Treatment consists of fluid resuscitation and correction of electrolyte imbalances with neurotoxic symptom precautions.

MUSHROOMS

PRINCIPLES OF TOXICITY

Mushrooms represent a wide range of species with regional variation. In this section, we consider the mushrooms of toxicologic significance. The categories of poisonous mushrooms are grouped

according to the types of illness or organ-specific toxicity. Another important perspective is that the most common species of toxic mushrooms belong to the GI irritant group and generally do not cause life-threatening illness.[32,33] Distinguishing the GI irritant group from the more serious groups is the challenge for the treating emergency clinician.

According to data from 2013 as reported to the American Association of Poison Control Centers, there were a total of 6575 mushrooms ingested. The majority of the ingested mushrooms were never identified (5517). Five mushrooms from the cyclopeptide group, five from the hallucinogenic group, and four from the muscimol-containing group resulted in major effects. There was only one fatality in this database, and it was an unknown mushroom.[1]

CLINICAL FEATURES

An important clinical consideration is the onset of symptoms caused by a mushroom. In general, the GI irritants will develop symptoms in the first 2 to 3 hours after ingestion. Some of the most lethal mushrooms will develop symptoms on a delayed basis, such as *Amanita phalloides*, or *Gyromitra esculenta,* at 6 to 8 hours after ingestion.[32] There are some exceptions that are mentioned later.

DIFFERENTIAL DIAGNOSES

Many mushrooms are edible and considered delicacies, such as puffballs or morels. However, there are many look-alikes, and foragers must be certain that they identify correct species to avoid illness. The differential diagnosis with mushroom poisoning includes gastroenteritis, pancreatitis, hepatitis, acute renal failure, hallucinogenic poisonings, anticholinergic and cholinergic poisonings, disulfiram toxicity, and food poisoning.

DIAGNOSTIC TESTING

Identifying the mushroom ingested is extremely helpful to the treating team. It is beyond a realistic scope for emergency clinicians to be able to identify mushrooms, and it is wise to coordinate with poison control centers and local mycologists to identify mushrooms in real time. Digital identification by sending images to mycologists via a poison control center model has been shown to be accurate in identifying mushrooms.[7] Attempts should be made to secure mushroom identification particularly after a delayed onset of GI symptoms.

Routine testing includes complete blood count, urinalysis, and basic metabolic profile with specific attention to renal function and measures of dehydration. Liver enzyme and tests of liver function should be obtained if cyclopeptide or gyromitrin poisoning is suspected.

MANAGEMENT

The general management of mushroom poisoning focuses on symptom-based, supportive care. Management for specific mushroom poisoning is discussed later.

There is no proven outcome benefit from administration of activated charcoal for patients with mushroom ingestion. We recommend activated charcoal only if the patient presents sufficiently rapidly for the activated charcoal to be given within 1 hour of the ingestion if the clinician suspects ingestion of a potentially life-threatening mushroom (eg, cyclopeptide or gyromitrin containing species). We do not recommend gastric emptying by any method. Because many toxic mushrooms can cause vomiting or diarrhea, it is important that these patients are fluid resuscitated and rehydrated until they can tolerate oral liquids and food.

DISPOSITION

Patients should be admitted for 24 hours when the ingestion of a potentially life-threatening mushroom poisoning has occurred. For suspected or confirmed GI irritant mushroom ingestion, the patient can be safely discharged home after the GI symptoms are controlled and oral fluids are tolerated.

MUSHROOM CATEGORIES

Hepatotoxic Mushrooms

Principles of Toxicity

The two major categories of mushrooms that can cause life-threatening hepatotoxicity include cyclopeptide-containing mushrooms, such as *Amanita phalloides,* and certain *Lepiota* species. The *Gyromitra* species also cause hepatotoxicity but have other symptoms distinct from the cyclopeptide-containing mushrooms.[33,34]

Clinical Features

The cyclopeptide-containing mushrooms will cause the onset of GI symptoms 6 to 8 hours after ingestion. This includes nausea, vomiting, diarrhea, and abdominal pain. Over the next 1 to 2 days, the patient will develop increasingly severe hepatic injury and encephalopathy.

Differential Diagnoses

In patients with cyclopeptide-containing mushroom toxicity with elevations in liver aminotransferases, bilirubin, partial thromboplastin time (PTT)/international normalized ratio (INR), or creatinine, other sources of injury should be considered, including acute tubular necrosis, rhabdomyolysis, ischemic hepatitis, alcoholic hepatic disease, viral hepatitis, and Wilson disease. Other hepatotoxic considerations include poisoning with acetaminophen, valproic acid, INH, statins, herbal medications, vinyl chloride, and polychlorinated biphenyls.

Diagnostic Testing

Evidenced by rising liver enzymes and worsening measures of liver function (rising bilirubin and increased INR). These markers should be followed serially during the hospital course. Also, because patients may develop a hepatorenal syndrome, renal function tests should be measured.

Management

Many therapies have been tried for cyclopeptide-containing mushrooms. Initial decontamination with oral active charcoal is recommended if the patient presents within 1 hour of ingestion and has not already vomited. Suggested therapies in the literature that may be immediately available include *N*-acetylcysteine (NAC), high dose penicillin, and early hemodialysis or hemoperfusion. NAC is thought to work via hepatoprotective effects, and animal studies indicate that amatoxins deplete glutathione stores. IV NAC dosing regimens are similar to those administered to acetaminophen poisoned patients (see Chapter 143). High-dose penicillin is thought to work by displacing amatoxin uptake by the hepatocytes. Experimental antidotes, such as thioctic acid, silibinin, and *polymyxin B,* have been more commonly used in Europe.[35,38,40] Silibinin is currently available as an investigational agent and can be accessed by calling the manufacturer at (866) 520-4412.[39] If a cyclopeptide-containing mushroom has been

ingested, we suggest mobilizing silibinin and calling your regional poison control center to coordinate management and prioritization of agents. Patients who progress to fulminant hepatic failure despite appropriate supportive care may ultimately require liver transplantation.[35,40] Early consultation with a transplant center should be initiated early in the course of management.

Disposition

Patients showing evidence of severe hepatotoxicity and those at risk for fulminant hepatic failure are admitted to an intensive care unit.[38] These patients require frequent neurologic checks, monitoring of vital signs, and repeated laboratory studies. If a patient presents with established hepatotoxicity, transferring to a tertiary-care center that specializes in the management of hepatic failure patients with liver transplant capabilities is advisable.

Gyromitrin-Containing Mushrooms

Principles of Toxicity

Gyromitrin-containing species are also known as the *false morel.*[33] Like the cyclopeptide-containing mushrooms, these can also cause significant hepatotoxicity but may also cause neurotoxic seizures. The mechanism for seizures is similar to INH by causing deficiency of pyridoxine and inhibiting the action of glutamic acid decarboxylase. This prevents the formation of GABA, an inhibitory neurotransmitter.[34] These mushrooms can also induce some degree of oxidant stress, which can clinically manifest as methemoglobinemia.

Clinical Features

Similar to the cyclopeptide-containing group, gyromitrin mushrooms can cause delayed nausea, vomiting, diarrhea, and hepatotoxicity, but they most notably manifest with generalized seizure activity.

Differential Diagnoses

The highly sought after "true" morel is a mushroom is an edible delicacy and is considered nontoxic. The false morel has a close resemblance and can found in similar regions. Other causes of seizures and neurotoxicity should be considered, including INH poisoning, sympathomimetic toxicity, intracranial bleeds, brain mass lesions, and underlying seizure disorders. Other causes of methemoglobinemia include nitrate and nitrate containing compounds, local anesthetic agents, dapsone poisoning, and inborn errors in metabolism.

Diagnostic Testing

In patients presenting with seizure activity, obtaining a history of toxic ingestion obviates the need for most diagnostic testing. Because there is potential for hepatoxicity, serial liver transaminases should be monitored. Serum electrolytes should be monitored for protracted vomiting or diarrhea. A screening methemoglobin level is also recommended.

Management

Management of gyromitrin-induced seizures should include IV pyridoxine, as one would for INH poisoning, with 5 g as an empirical dose (see Chapter 127). Clinically significant methemoglobinemia can be managed with methylene blue, although this is a rare occurrence. (See Chapters 57 and 153 for methylene blue dosing.)

Fig. 158.10. Coprinus atramentarius. (Courtesy Joe McFarland.)

Disposition

Patient with altered mental status and seizures requiring pyridoxine therapy should be admitted to an intensive care setting. Those who are asymptomatic after 6 to 8 hours observation in the ED may be discharged home.

OTHER MUSHROOM CLASSES

Cholinergic Agonists

True cholinergic agonists are rarely encountered in the clinical setting. *Clitocybe dealbata,* also known as "the sweater," is one of these mushrooms. If ingested, clinical symptoms of cholinergic excess may be seen.[36] Muscarinic effects recalled by the mnemonic SLUGBAM, can be useful. **SLUGBAM** stands for **S**alivation, **L**acrimation, **U**rination (excessive), **G**astrointestinal effects (nausea, vomiting, and diarrhea), **B**radycardia/bronchorrhea/bronchospasm, **A**bdominal cramps, and **M**iosis. Treatment is supportive, but atropine can be used for excessive cholinergic symptoms, precisely as described in Chapter 157. Unlike organophosphates, there is no role for oxime therapy.

Disulfiram Reaction-Inducing Mushrooms

Coprinus atramentarius and other *Coprinus* species contain the toxin coprine that can inhibit aldehyde dehydrogenase similar to disulfiram. If ingested along with ethanol, it can lead to a disulfiram-like reaction including nausea, vomiting, diarrhea, and flushing.[37] Treatment is generally supportive, including IV hydration and antiemetics, such as prochlorperazine, or ondansetron (Fig. 158.10).

Hallucinogenic Mushrooms

There are a wide variety of mushrooms that can lead to hallucinations. Some common examples include the *Psilocybe* and *Conocybe* species. These are direct hallucinogens and contain psilocybin and related compounds. Psilocybin is found in a wide range of mushrooms.[38] These are well known to be purchased online and in "grow at home" kits.

The ibotenic acid and muscimol containing mushrooms can also lead to hallucinations. *Amanita muscaria* is an important example of this class. Others include *Amanita pantherina* and *Gemmata* species. Ibotenic acid acts similar to glutamate and can have excitatory effects. Muscimol has inhibitory effects and works

as a GABA agonist. These mushrooms can be used for their hallucinogenic effect.

Overdose of these mushrooms can lead to dry mouth, dilated pupils, tachycardia, agitation, delirium, and seizures. The mainstay of treatment of hallucinogenic mushrooms is providing a low-stimulus environment where the effects can dissipate. Benzodiazepines are generally effective in treating the agitation and tachycardia (lorazepam, 1 to 2 mg IVP; diazepam, 5 to 10 mg IVP). Antipsychotic agents can be used for prolonged hallucinations not improved with benzodiazepines (eg, haloperidol, 2 to 5 mg).[39]

Gastrointestinal Irritants

There are hundreds of species of mushrooms that are GI irritants. These mushrooms cause irritation to the GI tract within 2 to 3 hours of ingestion.[33,34] Some commonly encountered species of GI irritants include *Boletus* spp., *Chlorophyllum molybdites, Lactarius* sp., and *Omphalotus* sp. Nausea, vomiting, diarrhea, and crampy abdominal pain will be the typical presenting symptoms. The course is generally self-limiting, but care should be taken to monitor patients with prolonged symptoms or with significant fluid losses.

Another consideration with mushrooms ingested that cause GI symptoms is that the mushroom may be contaminated with pesticides or metals. Therefore, the symptoms may not be from the mushroom itself but from the chemical contaminant.

Renal Insufficiency

Two species of mushrooms can potentially lead to direct renal toxicity. In Europe, the *Cortinarius* species of mushrooms have been associated with renal failure.[40] This effect commonly occurs on a delayed basis and as long as 2 weeks after ingestion. Similar to the deadly cyclopeptide and gyromitirin-containing mushrooms, symptoms will begin on a delayed basis. This mushroom is not generally found in the United States.

A more problematic mushroom that is found in the Pacific Northwest is the *Amanita smithiana* mushroom. The toxin contained in this mushroom is allenic norleucine. This mushroom leads to GI symptoms early after ingestion, and thus violates the general rule of thumb for serious poisoning follows delayed onset of GI symptoms. GI symptoms can begin between 2 and 12 hours after ingestion. Treatment is generally supportive, including fluid bolus followed by maintenance. However, with acute renal failure, metabolic acidosis, and electrolyte imbalances, hemodialysis may be required.

Rhabdomyolysis-Inducing Mushrooms

Another mushroom that can cause toxicity on a delayed basis is from *Tricholoma equestre* (commonly referred to as the "man on horseback" or "yellow knight" mushroom). It can cause weakness, fatigue, and muscle pain 24 to 72 hours after ingestion. This mushroom can cause clinically significant rhabdomyolysis. Serum CPK levels should be followed to monitor for rhabdomyolysis and development of renal failure. Treatment is supportive with IV hydration and alkalization therapy.

HERBAL MEDICATIONS

Although much of the world's population has used herbal products as medicine for centuries, its growing popularity in the United States is a relatively recent trend. Since the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994, the number of herbal products on the market has sharply increased over twentyfold to over 90,000 in 2014.[41] It is estimated that nearly 40 million adults in the United States use herbal products with sales exceeding $5 billion annually.[39]

PRINCIPLES OF TOXICITY

The DSHEA established herbal products as food; and unlike pharmaceuticals, they are not subject to rigorous regulations and do not need to demonstrate efficacy or safety for commercial sale. As a result, ingredients and their concentrations are often unknown, and controlled clinical trials and toxicologic testing are not routinely performed. Contrasting this, the consumer may believe that herbal medications undergo strict regulation and testing, and they are safer and more efficacious than pharmaceuticals. This misperception, combined with a lack of proper dosing and scheduling regimen, may lead to misuse and over-use of herbal medications. Factors that further contribute to adverse events include inherent toxicity, contamination and adulteration of products, and herb-drug interaction.[42,43] Studies show that most people who use herbal medications in addition to prescribed medications will do so without consulting or notifying health care providers.

Clinical research in the area of herb-drug interaction is lacking.[44] Most pharmaceutical drugs undergo hepatic biotransformation and inactivation via the cytochrome P450 enzymes. Herb-drug interactions typically stem from alteration of this system, leading to increased or decreased drug concentration. Herbal medications may also affect drug transporters, such a p-glycoprotein, and further modify pharmacodynamics. St. John's wort *(Hypericum perforatum)* (Fig. 158.11) induces cytochrome P_{450}, family 3, subfamily A (CYP3A), which metabolizes approximately 50% of available United States pharmaceuticals, leading to decreased drug concentrations.

CLINICAL FEATURES

Many herbal medications possess toxicity inherent to the botanical from which they are derived (Table 158.3). Adverse effects can range from allergic reactions to cardiovascular and hepatic toxicity. The U.S. Food and Drug Administration (FDA) banned the

Fig. 158.11. *Hypericum perforatum* (St. John's wort). (Courtesy Christopher Lim.)

TABLE 158.3

Mushrooms

CLINICAL CATEGORY/MUSHROOM GROUP	SYMPTOMS	TREATMENT
EARLY ONSET SYMPTOMS (FIRST 2 TO 3 HOURS)		
Clinical Category		
GI irritants (*Boletus* sp., *Chrlorophyllum* sp., *Lactarius* sp.)	Nausea, vomiting, diarrhea	Supportive care
Hallucinogens (*Psilocybe and Conocybe* sp.)	Agitation, hallucinations	Benzodiazepines Low stimulus environment
Disulfiram (*Coprinus* sp.)	Nausea, vomiting, diarrhea, abdominal cramping, flushing	Supportive care
Cholinergic (*Clitocybe* sp.)	SLUGBAM*	Atropine, supportive care
Renal *(Amanita smithiana)*	Renal insufficiency (GI symptoms early)	Supportive care, dialysis
LATE ONSET SYMPTOMS (>4 TO 5 HOURS)		
Mushroom Group		
Hepatotoxic cyclopeptide-containing (*Amanita phalloides, Lepiota* sp.)	Hepatic failure, symptoms begin 6 to 8 hours post-ingestion	Supportive care, NAC, dialysis, penicillin, thioctic acid, silibinin, liver transplant
Gyromitrin *(Gyromitra esculenta)*	Hepatic failure, seizures, methemoglobinemia methylene blue	Supportive care, vitamin B_6
Renal (*Cortinarius* sp.)	Delayed onset renal failure	Supportive care, dialysis
Rhabdomyolysis *(Tricholoma equestre)*	Muscle pain, weakness, fatigue	Supportive care, hydration, dialysis

*__SLUGBAM__ stands for **S**alivation, **L**acrimation, **U**rination (excessive), **G**astrointestinal effects (nausea, vomiting, and diarrhea), **B**radycardia/bronchorrhea/bronchospasm, **A**bdominal cramps, and **M**iosis.
GI, Gastrointestinal; *NAC, N*-acetylcysteine.

sale of Ma Huang *(Ephedra sinica)* in 2004 after reports of serious cardiovascular events and death related to its sympathomimetic effects.[52] Many herbal medications, including Germander *(Teucrium chamaedrys)*, Pennyroyal oil *(Mentha pulegium* and *Hedeoma pulegioides)*, and those containing pyrrolizidine alkaloids are associated with hepatotoxicity.[45] Most herbal medications that possess inherent toxicity can have adverse maternal-fetal effects, and we advise against the routine use of herbal medications during pregnancy.

Some herbal medications increase bleeding risk by altering the pharmacokinetics of anticoagulants, such as warfarin, or having a synergistic effect with antiplatelets and anticoagulants.[46,47] The concurrent use of several herbal medications, such as St. John's wort, with other serotonergic drugs can potentially contribute to the development of serotonin syndrome.[48] Kava-kava *(Piper methysticum)* and valerian *(Valeriana officinalis)* have been shown to potentiate GABA-mediated CNS depression of alcohol consumption.

DIFFERENTIAL DIAGNOSES

Due to the unregulated nature of herbal medications, contaminants and adulterants are often found and may contribute to toxicity. In addition to fillers and substituents, contamination with heavy metals, pesticides, and other harmful materials have been found in herbal medications. Certain metals are believed to have therapeutic properties.[42] Lead is the most commonly reported heavy metal contaminant, but arsenic, cadmium, and mercury poisoning after herbal medication use have been described as well.[49-51] Additionally, there are many examples reported in the literature of toxicity from herbal medications adulterated with pharmaceuticals.[52]

DIAGNOSTIC TESTING

Diagnostic studies in patients presenting with herbal medication toxicity include a complete blood count, coagulation profile, serum electrolytes, and glucose, hepatic, and renal function tests. In addition, acetaminophen and salicylate levels should be measured along with urinary heavy metal screens, targeting lead, arsenic, and mercury.

MANAGEMENT

Treatment is largely supportive with hydration, bleeding control if coagulopathic, cardiac dysrhythmia treatment, and targeted antidote therapy (eg, NAC, heavy metal chelation therapy; see Chapter 151).

DISPOSITION

The majority of patients with herbal medication toxicity will be mildly symptomatic with GI symptoms and normal diagnostic studies. These patients can be observed and hydrated in the ED and safely discharged home. Patients with systemic toxicity including hepatic, renal, cardiac, or multi-organ failure require admission for monitoring and consultation from appropriate specialty services.

KEY CONCEPTS

- Most botanical exposures result in minimal toxicity and management is largely symptom-based, supportive care.
- Most serious toxicity results from exposure to plants with anticholinergic, antimitotic, cardiovascular, or convulsive properties.
- Most cases in which gastrointestinal (GI) symptoms begin within the first 2 hours after an unknown mushroom ingestion will prove to involve a non–life-threatening substance.
- GI symptoms that onset in more than 6 to 8 hours suggest a potentially life-threatening ingestion, such as the cyclopeptide and gyromitrin groups.
- Use local poison control centers, mycologists, and botanists to help identify serious plants and mushrooms that have been ingested. We recommend digital photography with expert consultation.
- Herbal medications are unregulated and may have inherent toxicity, herb-drug interactions, or contaminants. Clinicians should advise against the routine use of herbal medications.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 158: QUESTIONS & ANSWERS

158.1. A 52-year-old man presents after ingestion of water hemlock complaining of nausea but no other symptoms. He reports that he ate the water hemlock in a suicide attempt but has since changed his mind. His vital signs and physical examination are normal. What is the most appropriate initial treatment of this patient?

A. General seizure precautions
B. Hemodialysis
C. Neutralization with milk
D. Supportive care only
E. Whole bowel irrigation

Answer: A. Water hemlock is very toxic with fatality rates as high as 70%. Because this patient is at risk for seizures, oral activated charcoal and gastric lavage are contraindicated. Hemodialysis, whole bowel irrigation, and milk are not beneficial. Supportive care is not adequate with water hemlock ingestion. Most deaths are caused by intractable seizures, so this complication should be anticipated.

158.2. Which toxidrome is seen after Jimson weed use?

A. Anticholinergic
B. Cholinergic
C. Opioid
D. Sedative/hypnotic
E. Sympathomimetic

Answer: A. Jimson weed contains atropine, hyoscyamine, and scopolamine, all of which have anticholinergic properties. In severe cases, physostigmine can be used to reverse effects.

158.3. Oleander contains cardiac glycosides similar to digoxin. Which of the following should be considered when treating oleander ingestion?
- **A.** Activated charcoal should be avoided.
- **B.** Serum digoxin levels correlate with degree of toxicity.
- **C.** Treatment is supportive.
- **D.** Treatment with digoxin-specific Fab fragments is beneficial, but a higher dose is necessary.
- **E.** Treatment with digoxin-specific Fab fragments is not beneficial.

Answer: D. Treatment is with digoxin-specific Fab fragments, but much higher doses are necessary compared with those needed to treat digoxin toxicity. Activated charcoal *may be* useful if the ingestion was recent. A serum digoxin level should be measured, but it is not a reliable indicator of level of toxicity. An elevated level confirms oleander ingestion, but a negative level cannot rule out ingestion.

158.4. A husband and wife present to the emergency department (ED) complaining of nausea and vomiting after eating mushrooms that they picked while hiking. They report eating the mushrooms on a salad approximately 1 hour ago. Each is complaining of severe nausea, vomiting, and diffuse abdominal pain. There is no hematemesis. Vitals signs and physical examination are normal. You inform them that they will be symptomatically treated and observed, but there is likely nothing to worry about. Why are you not concerned about their ingestion?
- **A.** Early onset of gastrointestinal (GI) symptoms
- **B.** No hematemesis
- **C.** No right upper quadrant tenderness
- **D.** Normal mental status
- **E.** Normal vital signs

Answer: A. The vast majority of severely toxic mushrooms have delayed onset of symptoms (>6 hours from ingestion). Occasionally, people will ingest two different types of mushrooms—one benign and causing early onset of symptoms and one more toxic. Therefore patients should be observed and rechecked.

158.5. What is the most common cause of death after mushroom ingestion?
- **A.** Gastrointestinal (GI) hemorrhage
- **B.** Heart failure
- **C.** Liver failure
- **D.** Renal failure
- **E.** Respiratory failure

Answer: C. The *Amanita* species of mushrooms are very toxic and cause fulminant liver failure often necessitating liver transplant. Mushrooms generally do not affect the other listed organ systems.

158.6. A 46-year-old man presents after waking in the night with headache and severe nausea and vomiting. For dinner the night before, he consumed some mushrooms that he had gathered from a nearby forest. He felt fine immediately after dinner. His vital signs are normal. While conducting your physical examination, he begins to seize. Benzodiazepines are administered without improvement. What treatment is indicated?
- **A.** Phenobarbital
- **B.** Phenytoin
- **C.** Propofol
- **D.** Pyridoxine
- **E.** Vecuronium

Answer: D. Most mushrooms do not cause seizures, but gyromitrin-containing mushrooms are an exception. They are commonly mistaken for edible morels, because they look quite similar. They contain an isoniazid (INH)-like toxin that causes seizures. Traditional seizure medications can be used (because they are typically more readily available), but seizures can be intractable until pyridoxine is given.

CHAPTER 159

Sedative Hypnotics

Leon Gussow | Andrea Carlson

BARBITURATES

Although barbiturates are still used for management of some seizure disorders, they have long been supplanted as sedatives by the benzodiazepines. Mortality from barbiturate poisoning declined from approximately 1500 deaths per year in the 1950s to fewer than five fatalities in 2013.[1]

Barbiturates are addictive, producing physical dependence and a withdrawal syndrome that can be life-threatening. Whereas tolerance to the mood-altering effects of barbiturates develops rapidly with repeated use, tolerance to the lethal effects develops more slowly, and the risk of severe toxicity increases with continued use.

Principles of Toxicity

Barbiturates depress the activity of all excitable cells, especially those in the central nervous system (CNS), by enhancing the activity of gamma-aminobutyric acid (GABA), the major central inhibitor. In acute overdose, barbiturates decrease neural transmission in autonomic ganglia, the myocardium, and the gastrointestinal tract and also inhibit the response to acetylcholine at the neuromuscular junction.

The $GABA_A$ receptor is a protein complex found on postsynaptic membranes in the CNS. Structurally, it consists of several distinct receptor sites surrounding a chloride ion (Cl^-) channel (Fig. 159.1). GABA opens the chloride channel. The resulting flow of Cl^- into the cell increases the negative resting potential, hyperpolarizing and stabilizing the membrane. There are separate receptor sites for barbiturates and for benzodiazepines and a third site that binds GABA, ethanol, and meprobamate. Although barbiturates and ethanol can directly increase Cl^- conductance, benzodiazepines require the presence of GABA to affect Cl^- flow, which may account for the relative safety of benzodiazepines in comparison with barbiturates.

Barbiturates produce dose-related depressive effects ranging from mild sedation to coma and fatal respiratory arrest. In the early stages of intoxication, some patients experience euphoria. Barbiturates have no analgesic effect and can paradoxically increase the reaction to pain at low doses.

Barbiturates act directly on the medulla to produce respiratory depression. In therapeutic doses, this respiratory depression mimics that of normal sleep. Starting with doses approximately three times therapeutic, the neurogenic, chemical, and hypoxic respiratory drives are progressively suppressed. Because airway reflexes are not inhibited until general anesthesia is achieved, laryngospasm can occur at low doses.

Therapeutic oral doses of barbiturates produce only mild decreases in pulse and blood pressure, similar to sleep. With toxic doses, more significant hypotension occurs from direct depression of the myocardium along with pooling of blood in a dilated venous system. Peripheral vascular resistance is usually normal or increased, but barbiturates interfere with autonomic reflexes, which then do not adequately compensate for the myocardial depression and decreased venous return. Barbiturates can precipitate severe hypotension in patients whose compensatory reflexes are already maximally stimulated, such as those with heart failure or hypovolemic shock. Barbiturates also decrease cerebral blood flow and intracerebral pressure. Although hypnotic doses of barbiturates do not affect gastric emptying, higher doses can decrease gastrointestinal smooth muscle tone and peristaltic contractions, delaying gastric emptying.

Barbiturates are classified according to their onset and duration of action (Box 159.1): ultra-short acting (onset immediate after intravenous dose, duration minutes), short acting (onset 10 to 15 minutes after oral dose, duration 6 to 8 hours), intermediate acting (onset 45 to 60 minutes, duration 10 to 12 hours), and long acting (onset 1 hour, duration 10 to 12 hours). Only long-acting preparations have anticonvulsant effects in doses that do not cause sedation. Short- and intermediate-acting preparations are almost completely metabolized to inactive metabolites in the liver, whereas 25% of a phenobarbital (long-acting) dose is excreted unchanged through the kidney.

Barbiturates cross the placenta with fetal levels approaching those of the mother. They are also excreted in low concentration in breast milk. Use during pregnancy is associated with birth defects (category D).

Clinical Features

Mild barbiturate toxicity manifests with drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional lability, and impaired cognition.

In severe acute intoxication, CNS depression progresses from stupor to deep coma and respiratory arrest. Although pupils are usually normal or small and reactive, concomitant hypoxia can cause pupils to be fixed and dilated. Corneal and gag reflexes may be diminished or absent, muscle tone flaccid, and deep tendon reflexes diminished or absent. Flexor (decorticate) and extensor (decerebrate) posturing can occur in patients comatose from barbiturate intoxication. These neurologic signs are variable and do not always correlate with severity of intoxication or depth of coma. A fluctuating level of consciousness is commonly seen. High barbiturate levels depress gastrointestinal motility, delaying drug absorption. As the drug is metabolized and blood levels drop, peristalsis and drug absorption may increase, causing drug levels to rise again.

The life threat in severe barbiturate toxicity is respiratory depression. Because respirations can be rapid but shallow, the degree of hypoventilation may not be apparent on clinical examination, and pulse oximetry or capnography may be needed to detect the ventilation compromise.

Hypotension is common in patients with severe intoxication, along with a normal or increased heart rate. Barbiturate overdose is associated with noncardiogenic pulmonary edema. Altered pulmonary capillary permeability can be caused by hypoperfusion, hypoxia, or a direct effect of the drug. Pneumonia due to aspiration may be delayed.

Barbiturate withdrawal syndrome includes tremors, hallucinations, seizures, and delirium (similar to the delirium tremens of

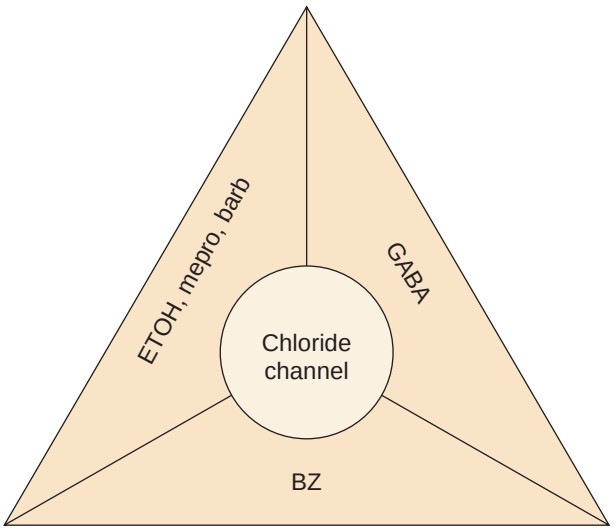

Fig. 159.1. The gamma-aminobutyric acid (GABA) receptor complex. *BZ,* Benzodiazepine binding site; *GABA,* GABA binding site; *ETOH, mepro, barb,* binding sites for ethanol, meprobamate, and barbiturates, respectively.

BOX 159.1

Barbiturates

ULTRASHORT ACTING
Methohexital (Brevital)
Thiopental (Pentothal)

SHORT AND INTERMEDIATE ACTING
Pentobarbital (Nembutal)
Secobarbital (Seconal)
Amobarbital (Amytal)
Aprobarbital (Alurate)
Butabarbital (Butisol)
Butalbital (Fiorinal)

LONG ACTING
Phenobarbital (Solfoton, Luminal)
Mephobarbital (Mebaral)

ethanol withdrawal). However, severe withdrawal occurs only after dependence on short- or intermediate-acting barbiturates (eg, pentobarbital, secobarbital, amobarbital, or butalbital). Because these drugs are not commonly used, this syndrome is now very rare.

Differential Diagnoses

Mild barbiturate toxicity mimics ethanol intoxication and that of other sedative hypnotic agents, such as benzodiazepines. Alcohol and benzodiazepine toxicity cause less hypotension and respiratory depression than barbiturates, whereas chloral hydrate overdose is marked by greater cardiotoxicity (see later in this chapter). Gamma-hydroxybutyrate (GHB) produces coma similar to that of barbiturates, but resolution of the coma occurs much more rapidly. Opioids cause similar sedation properties but with miosis, whereas barbiturates typically cause mydriasis when deeper stages of coma result in hypoxia. Other common antiepileptic agents (such as, carbamazepine, phenytoin, and valproic acid) will cause sedation similar to barbiturates with acute overdose. As with any patient exhibiting depressed mental status, metabolic causes (such as, hypoglycemia) and intracranial events (such as, cerebral ischemia or hemorrhage) should be excluded.

Diagnostic Testing

The therapeutic level of phenobarbital is 15 to 40 μg/mL (65 to 172 μmol/L). A serum level greater than 50 μg/mL can be associated with coma, especially in a patient who is not a chronic user. Levels greater than 80 μg/mL cause potentially fatal respiratory depression. Serial phenobarbital levels can monitor effectiveness of treatment. Other than phenobarbital, barbiturates have high volumes of distribution, so serum levels do not accurately reflect CNS concentrations or correlate with clinical severity. A positive urine screen establishes only qualitative exposure to a barbiturate but does not prove that the drug is present in toxic amounts and should not be relied on to explain decreased mental status.

Chest radiographs can detect noncardiogenic pulmonary edema or aspiration pneumonia. Computed tomography of the head may be helpful in comatose patients with evidence of trauma, focal neurologic signs, papilledema, or uncertain diagnosis to detect other causes of stupor and coma.

Because the electroencephalogram may be silent as a result of barbiturate overdose, no patient should be declared "brain dead" if barbiturates are present at therapeutic levels or higher.

Management

Because barbiturates have no specific antidote, the key to managing these patients is supportive care, particularly with respect to the cardiovascular and respiratory systems. Severely intoxicated patients are unable to protect their airway and have decreased ventilatory drive. Supplemental oxygen may suffice for patients with mild to moderate overdose, but intubation is often required. Long-term induced paralysis is rarely necessary, and additional sedation usually is unnecessary for mechanical ventilation. Careful fluid replacement should aim to maintain a systolic blood pressure above 90 mm Hg and adequate urine output. Patients should be monitored for fluid overload and pulmonary edema.

Gastrointestinal Decontamination

Gastric emptying by lavage is not indicated. High barbiturate levels depress gastrointestinal motility, delaying drug absorption. As the drug is metabolized and blood levels drop, peristalsis and drug absorption may increase, causing drug levels to rise. Although there is evidence that multidose activated charcoal increases clearance of phenobarbital and may shorten duration of clinical toxicity, there is no evidence it results in improved outcomes over supportive care alone.

Enhanced Elimination

Because phenobarbital is a weak acid (pK_a 7.2), alkalinization of the urine will increase the amount of drug present in ionized form, minimizing tubular reabsorption and increasing drug clearance. Other short- and intermediate-acting barbiturates are not significantly affected by pH changes in this range. Alkalinization may interfere with the ability of the drug to diffuse across intestinal mucosa from the blood into the gut. We agree with a comprehensive review that concluded that there is little clinical role for urine alkalinization in acute barbiturate poisoning.[2]

Although there are insufficient data to determine the true risk-benefit ratio of hemodialysis in acute barbiturate overdose, it remains a legitimate option for severe phenobarbital toxicity.[2-5] Because phenobarbital is 40% to 60% protein bound, in the past hemoperfusion was advocated over hemodialysis; however, newer

high-efficiency dialyzers using high blood flow rates provide drug clearance greater than that achieved by hemoperfusion. Although rarely indicated, we recommend hemodialysis for acute phenobarbital toxicity (serum levels over 100 mcg/mL) in the presence of refractory hypotension, renal or cardiac failure, acid-base or electrolyte abnormalities, or inadequate response to less invasive measures (as assessed by declining serum levels).[5]

Disposition

An asymptomatic patient who arrives in the emergency department (ED) after ingesting barbiturates should be observed for 6 hours after ingestion for mental status changes, slurred speech, ataxia, hypotension, and respiratory depression. Symptoms generally occur within 1 hour of ingestion. Patients who remain asymptomatic and have no significant complicating co-ingestants or medical problems can be discharged or referred for psychiatric care. Patients who are still symptomatic after 6 hours should be admitted to a monitored setting for observation and supportive care. Those with refractory hypotension, prolonged coma requiring intubation and ventilator support meet intensive care unit criteria for admission.

BENZODIAZEPINES

With the development of chlordiazepoxide in 1960 and diazepam in 1963, benzodiazepines, with their vastly superior safety profile, rapidly supplanted barbiturates and other non-barbiturate sedative-hypnotics as the principal agents for the treatment of anxiety and insomnia.

Benzodiazepines remain among the most widely prescribed class of drugs (Table 159.1) and are the most common prescription drugs used in suicide attempts. Pediatric patients comprise 10% of benzodiazepine overdose cases.

Principles of Toxicity

Most benzodiazepine overdoses follow a relatively benign clinical course. Benzodiazepines produce sedative, hypnotic, anxiolytic, and anticonvulsant effects by enhancing the inhibitory actions of GABA. Binding of a benzodiazepine to a specific benzodiazepine receptor potentiates GABA effects on the chloride channel at the $GABA_A$ receptor, increasing intracellular flux of chloride ions and hyperpolarizing the cell. The net effect is a diminished ability of the nerve cell to initiate an action potential, inhibiting neural transmission.

Three unique benzodiazepine receptors exist, distributed variably throughout the central and peripheral nervous systems. Classic benzodiazepines are nonselective, producing a broad range of clinical effects. Newer benzodiazepines interact selectively with a single receptor subtype to achieve a desired result, such as sedation, while minimizing unwanted effects.

Pharmacokinetics

Benzodiazepines are rapidly absorbed orally. Intramuscular use of chlordiazepoxide and diazepam is limited by erratic absorption, but lorazepam and midazolam are predictably absorbed after intramuscular injection. After absorption, benzodiazepines distribute readily and rapidly penetrate the blood-brain barrier. In plasma, benzodiazepines are highly protein bound.

All benzodiazepines are metabolized in the liver. Oxazepam, temazepam, and lorazepam are directly conjugated to an inactive, water-soluble glucuronide metabolite that is excreted by the kidney. Other benzodiazepines must first be converted by the hepatic cytochrome P_{450} system. Chlordiazepoxide, diazepam, flurazepam, and clorazepate are metabolized to active derivatives that are then slowly conjugated and excreted. The long elimination half-lives of these intermediates can cause accumulation in the body with repeated dosing. Triazolam, alprazolam, and midazolam are converted to hydroxylated intermediates that are active but rapidly conjugated and excreted and do not contribute significantly to the drug's overall effect.

Cytochrome P_{450} processes may be significantly impaired in elderly patients or those with liver disease, leading to prolonged elimination of some benzodiazepines. Co-ingestion of drugs that also undergo cytochrome P_{450} metabolism (eg, cimetidine, ethanol) prolongs the half-lives of these benzodiazepines.

TABLE 159.1

Benzodiazepines

NAME	USUAL DOSE	ORAL PEAK (hours)	HALF-LIFE (hours)	PARENT METABOLITE ACTIVITY
Alprazolam (Xanax)	0.25–0.5 mg	1–2	6–27	Inactive
Chlordiazepoxide(Librium)	5–25 mg	0.5–4	5–30	Active
Clonazepam (Klonopin)	0.25–0.5 mg	1–2	18–50	Inactive
Clorazepate (Tranxene)	7.5–15 mg	1–2	1–3	Active
Diazepam (Valium)	2–10 mg	0.5–1	20–50	Active
Estazolam (Prosom)	1–2 mg	2	8–28	Inactive
Flurazepam (Dalmane)	15–30 mg	0.5–1	2–3	Active
Halazepam (Paxipam)	20–40 mg	1–3	14	Active
Lorazepam (Ativan)	0.5–2 mg	2–4	10–20	Inactive
Midazolam (Versed)	0.025–0.1 mg/kg	1–2	1.5–3	Active
Oxazepam (Serax)	10–30 mg	2–4	5–20	Inactive
Quazepam (Doral)	7.5–15 mg	2	39–41	Active
Temazepam (Restoril)	7.5–30 mg	1–2	3–19	Inactive
Triazolam (Halcion)	0.125–0.25 mg	1–2	1.5–5.5	Inactive

Clinical Features

CNS depression, which is common in patients with benzodiazepine poisoning, ranges from mild drowsiness to coma. Cardiac effects and fatalities from pure benzodiazepine overdose are rare. Respiratory depression, although less severe than with barbiturates, is the most important clinical effect requiring intervention.[6] Upper airway obstruction and increased upper airway resistance from loss of muscle tone, rather than central apnea, are the main causes of respiratory compromise. Life-threatening respiratory depression is rare but can be seen with large oral overdoses or during intravenous procedural sedation, particularly when the benzodiazepine is combined with an opioid, such as fentanyl. Hypotension is uncommon. Other potential complications include aspiration pneumonia and pressure necrosis of skin and muscles.

Most children have symptoms within 4 hours of benzodiazepine ingestion. Ataxia is the most common sign of toxicity, occurring in 90% of pediatric patients. Respiratory depression occurs in fewer than 10% of pediatric cases, and hypotension has not been reported in children.

Prolonged or high-dose infusions of certain benzodiazepine preparations have been associated with the development of lactic acidosis. Intravenous solutions of diazepam and lorazepam contain propylene glycol, which is metabolized to lactate. Patients with renal or hepatic insufficiency are at increased risk for this complication.[7]

Differential Diagnoses

Benzodiazepine overdose is usually suspected or diagnosed by clinical presentation. Many patients are arousable and can provide supporting information. Atypical or focal findings suggest the presence of other conditions, such as intracranial events (eg, cerebral vascular accident [CVA], intracerebral hemorrhage). Profound coma or cardiopulmonary instability is rare with pure benzodiazepine overdose and should prompt the search for co-ingestants, such as phenobarbital, a cyclic antidepressant, or chloral hydrate. Non-toxicologic metabolic causes of CNS depression (such as, hypoglycemia) and endocrine issues (such as, hypothyroidism) should also be considered.

Diagnostic Testing

Any patient with altered mental status should have a blood glucose level rapidly determined. Qualitative immunoassays for benzodiazepines in urine are available, but do not aid management decisions. Because most of these screening tests detect only benzodiazepines that are metabolized to oxazepam glucuronide, some benzodiazepines (such as, clonazepam, lorazepam, midazolam, and alprazolam) will not show up on many urine drug tests. A positive urine drug screen for benzodiazepines indicates recent exposure but does not confirm intoxication or indicate a specific agent. Serum drug concentrations are not routinely available and do not correlate with clinical severity. A lack of alcohol odor or a negative breathalyzer or blood ethanol test result suggests benzodiazepine or another sedative as a possible cause.

The benzodiazepine antagonist flumazenil should not be routinely administered to patients with coma of unknown origin or suspected benzodiazepine overdose, for diagnostic purposes.[8,9]

Management

General

Initial stabilization, including endotracheal intubation, should not be delayed by the administration of an antidote. Most benzodiazepine overdoses can be managed expectantly with supportive care alone. Single dose or multidose activated charcoal, hemodialysis, and whole bowel irrigation are not effective in benzodiazepine overdose and therefore are not indicated.

Antidote

Flumazenil, a nonspecific competitive antagonist at the benzodiazepine receptor, can reverse benzodiazepine-induced sedation after general anesthesia, procedural sedation, and confirmed benzodiazepine overdose. However, when compared to placebo, the risks of flumazenil usually out-weigh the benefits in patients with toxicity, and flumazenil is not recommended for the routine reversal of sedative overdose in the ED.[8,9] Although theoretic benefits of flumazenil use include cost savings and avoidance of procedures and tests (such as, endotracheal intubation and lumbar puncture), several studies have not been able to demonstrate an actual benefit.[8,9] Seizures and cardiac dysrhythmias (principally paroxysmal supraventricular tachycardia [PSVT]) can occur after flumazenil administration, and fatalities have been reported. Flumazenil use can also precipitate acute withdrawal in patients who are chronically dependent on benzodiazepines. Similarly, this antidote is hazardous when it is given to patients who have co-ingested seizure-generating drugs (such as, cocaine, isoniazid, or a tricyclic antidepressant) because of loss of the benzodiazepine's protective anticonvulsant properties. Co-ingestants that cause dysrhythmias, such as carbamazepine and chloral hydrate, may increase the likelihood of cardiac effects. Other risk factors are summarized in Box 159.2. When nonbenzodiazepine-dependent patients ingest benzodiazepines alone in overdose (as might be expected in children), the risks associated with flumazenil are low.[9] In cases of benzodiazepine overdose by a non-benzodiazepine habituated patient, flumazenil use, combined with close monitoring and repeated or infusion-based dosing, may obviate the need for intubation and mechanical ventilation. We recommend basing this decision on a balance of risks/benefits for the particular patient and the reliability of the assessment that the patient is a novice benzodiazepine user.

BOX 159.2

Use of Flumazenil

INDICATIONS

Isolated benzodiazepine overdose in non-habituated user (eg, accidental pediatric exposure)
Reversal of conscious sedation

ABSOLUTE CONTRAINDICATIONS

Suspected co-ingestant that lowers seizure threshold (eg, tricyclic antidepressants, cocaine, lithium, methylxanthines, isoniazid, propoxyphene, monoamine oxidase inhibitors, bupropion, diphenhydramine, carbamazepine, cyclosporine, chloral hydrate)
Patient taking benzodiazepine for control of a potentially life-threatening condition (eg, seizures)
Concurrent sedative-hypnotic withdrawal
Seizure activity or myoclonus
Hypersensitivity to flumazenil or benzodiazepines
Patient with neuromuscular blockade

RELATIVE CONTRAINDICATIONS

Chronic benzodiazepine use, not taken for control of life-threatening condition
Known seizure disorder not treated with benzodiazepines
Head injury
Panic attacks
Chronic alcoholism

The initial adult dose of flumazenil is 0.2 mg given intravenously over 30 seconds. A second dose of 0.2 mg may be given, followed by 0.2-mg doses at 1-minute intervals to a total of 1 mg. In children, the initial dose is 0.01 mg/kg (up to 0.2 mg). Because the duration of action of flumazenil is short (0.7 to 1.3 hours), re-sedation occurs in up to 65% of patients and requires either re-dosing or continuous infusion (0.25 to 1.0 mg/hr).[9]

In summary, benzodiazepine overdose requires primarily supportive care (including, in some cases, intubation). Flumazenil may precipitate seizures or acute withdrawal and should be used only in highly selected cases (eg, to reverse procedural sedation, or to treat children with a clear history of inadvertent benzodiazepine ingestion). When flumazenil is used, close monitoring of oxy-hemoglobin saturation and overall status (ideally including end-tidal CO_2) is necessary because of the risk for recurrent respiratory depression or resedation.[9] Use of flumazenil has not been shown to alter outcome, complication rate, number of costly procedures performed, or duration of hospital stay in patients presenting to the ED with benzodiazepine overdose.

Disposition

Patients remaining asymptomatic after 4 to 6 hours of ED observation may be medically cleared. For cases of deliberate overdose, appropriate psychiatric consultation should be obtained. Patients presenting with respiratory depression and coma should be given oxygen, ventilatory support, and admission to a monitored setting.

Benzodiazepine Withdrawal Syndrome

Abrupt discontinuation of a benzodiazepine in a chronic user results in a characteristic constellation of symptoms similar to ethanol withdrawal (Box 159.3). Risk for withdrawal is a function of both the dose of benzodiazepine and the duration of its use. Continuous treatment for more than 4 months is generally required before a patient is at risk for withdrawal. With abrupt discontinuation of a benzodiazepine, the most severe withdrawal symptoms are expected within several days to a week. Treatment of withdrawal consists of restarting benzodiazepines.

SPECIAL CONSIDERATIONS

Flunitrazepam

Flunitrazepam (Rohypnol) has been used in Europe, Asia, and Latin America for insomnia and preoperative sedation since 1975. Although it has never been manufactured or sold in the United States, flunitrazepam has been documented in many sexual assault or "date rape" incidents. Flunitrazepam has been an active agent in the illicit drug market, where it is used to alter the effects of other drugs, including ethanol, heroin, and cocaine.[10]

Flunitrazepam has 10 times more affinity than diazepam for certain benzodiazepine receptors. CNS depression occurs within 30 minutes. The drug is most frequently ingested with alcohol, producing additional disinhibition and amnesia. Despite marked CNS depression, patients can usually be aroused with noxious stimuli. The half-life of the drug is 16 to 35 hours, but coma can be prolonged for up to 48 hours. Flunitrazepam is easily obtained outside the United States and on the Internet. The drug is not detected on routine urine drug screens, but if needed as evidence, a urine sample should be refrigerated or frozen and the local or state police crime laboratory contacted to arrange specific testing. Metabolites of flunitrazepam are detected in the urine up to 72 hours after exposure.

BOX 159.3

Benzodiazepine Withdrawal Symptoms

NONSPECIFIC
Anxiety, depression, insomnia, tremor, tachycardia, sweating

SEVERE (RARE)
Visual hallucinations, delirium, seizures

Buspirone

Buspirone (BuSpar) has been used for generalized anxiety since the 1980s. Unlike benzodiazepines, buspirone does not have any effect on GABA. It is, rather, a partial serotonin (5-hydroxytryptamine type 1A [$5\text{-}HT_{1A}$]) agonist. To a lesser extent, it also antagonizes dopamine (D_2) receptors. Buspirone has no hypnotic, anticonvulsant, or muscle relaxant effects.

Buspirone has several advantages over benzodiazepines. The drug causes minimal CNS depression, even in combination with ethanol. Dosage adjustment is not needed for elderly patients. A withdrawal state after discontinuation has not been reported.

Zolpidem, Zaleplon, and Zopiclone

Zolpidem (Ambien), zaleplon (Sonata), and zopiclone (Imovane) differ in structure from both the benzodiazepines and buspirone, and they are not detected on a benzodiazepine toxicology screen. They act selectively at a specific benzodiazepine receptor, producing sedation without many of the side effects seen with benzodiazepines. They have modest anxiolytic, muscle relaxant, and anticonvulsant properties. Significant drug interactions are rare. Compared with zolpidem, zaleplon causes less memory loss and sedation at therapeutic doses and is more rapidly eliminated.[11] Of the three "Z-drugs," zopiclone has the longest duration of action. Transient visual disturbances, transient global amnesia, hallucinations, and somnambulism can occur in patients with normal levels of consciousness with both zolpidem and zaleplon. Abuse of zolpidem is limited by vomiting, which may occur after a supratherapeutic dose. Both zolpidem and zaleplon are rapidly eliminated and lack active metabolites. A controlled-release formulation of zolpidem (Ambien CR) is also available. The dual-layered tablet releases an immediate dose of zolpidem, followed by a slow, extended release from the inner layer to maintain plasma zolpidem concentrations. Clinical experience thus far suggests that overdoses with the controlled-release formulation mirror those of the immediate-release preparation, with only small differences in the likelihood of drowsiness, hallucinations, and ataxia.

Patients with zolpidem overdose do well with supportive care alone. Fatalities from isolated zolpidem overdose are rare.[12] All published cases have involved individuals found dead at home and have been associated with co-ingestants, particularly other sedative-hypnotics or antipsychotics. Drowsiness is by far the most common symptom. Coma and respiratory failure are rare, despite overdoses of up to 40 times the normal dose, although intubation may be required, particularly if there are co-ingestants. Zolpidem overdose in children generally follows a similarly benign course. Drowsiness, ataxia, and hallucinations generally resolve within 8 to 10 hours.

Overdose information for zaleplon is limited. Patients generally experience CNS depression and mild hypotension. Arousal can be temporally associated with flumazenil administration, but routine use is not advised.[11] Adverse effects with therapeutic use include headache, anterograde amnesia, and transient visual hallucinations. The blue-green discoloration of gastric contents, mouth, and urine after zaleplon overdose is attributed to the indigo carmine dye present in zaleplon's capsule shell.

Eszopiclone

Eszopiclone (Lunesta) has been marketed in the United States for treatment of insomnia. It is the *S*-isomer of racemic zopiclone, which has been used for decades outside the United States. Eszopiclone has a structure unrelated to that of benzodiazepines or barbiturates.

The mechanism of eszopiclone's action involves a specific $GABA_A$ receptor close to or coupled with the benzodiazepine receptor. Eszopiclone is rapidly absorbed, with a peak serum level at 1 hour and a half-life of 6 hours. It is metabolized in the liver to minimally active metabolites. The usual bedtime dose is 3 mg. It is recommended that elderly patients and those with hepatic insufficiency be treated with a lower (1 mg) dose.

Adverse effects with therapeutic use of eszopiclone include drowsiness, dizziness, dry mouth, unpleasant taste, nausea, and vomiting. Auditory and visual hallucinations have been reported. Experience with eszopiclone overdose is limited. The key to treatment is supportive care. CNS depression may be prolonged and pronounced in elderly patients. A retrospective case review described over 500 eszopiclone ingestions; however, half of these patients had also ingested other drugs or chemicals. The ingestions involved eszopiclone doses up to 200 mg and had mild to moderate symptoms at most. Two deaths occurred, both involving significant co-ingestants.

CHLORAL HYDRATE

Principles of Toxicity

Chloral hydrate has a low therapeutic ratio and can produce significant, potentially fatal toxicity. Chloral hydrate is rarely used today but is still occasionally prescribed as a sedative in the elderly and for children undergoing hospital and outpatient procedures.[13] The hypnotic oral adult dose is 0.5 to 1.0 g. The toxic oral dose is approximately 10 g in adults and may be as little as 1.5 g in children.

The toxic effects of chloral hydrate include CNS depression, gastrointestinal irritation, cardiovascular instability, hepatitis, and proteinuria. The primary active metabolite of chloral hydrate, trichloroethanol, has a barbiturate-like effect on $GABA_A$ receptors and is responsible for most of the CNS depression seen with significant overdose.

Chloral hydrate is rapidly absorbed from the gastrointestinal tract and almost immediately metabolized to trichloroethanol by the enzyme alcohol dehydrogenase. Onset of action is 20 to 30 minutes. Trichloroethanol is long acting, and its half-life can be significantly prolonged after overdose as metabolic pathways become saturated.

Chloral hydrate and ethanol in combination (historically referred to as a "Mickey Finn") potentiate each other's action to produce rapid loss of consciousness. Chloral hydrate increases the half-life of ethanol by competitively inhibiting the enzyme alcohol dehydrogenase, and the metabolism of ethanol generates nicotinamide adenine dinucleotide (NADH), a cofactor for the conversion of chloral hydrate to trichloroethanol.

Clinical Features

Chloral hydrate toxicity causes CNS and respiratory depression, gastrointestinal irritation, cardiovascular instability, and dysrhythmias.[13] The combination of deep coma and cardiac dysrhythmia without hypoxia is characteristic of severe cases.

A pear-like odor to the patient's breath or gastric contents may suggest the diagnosis. Findings consistent with chloral hydrate toxicity include miosis, muscle flaccidity, diminished deep tendon reflexes, hypoventilation, hypotension, and hypothermia. Chloral hydrate is corrosive and causes nausea, vomiting, esophagitis, hemorrhagic gastritis, and, rarely, gastrointestinal perforation or necrosis. Transient hepatic or renal dysfunction can also occur.

Dysrhythmias from chloral hydrate toxicity can be fatal. Chloral hydrate decreases myocardial contractility, shortens the cardiac refractory period, and increases the sensitivity of myocardium to catecholamines. Dysrhythmias include atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, multifocal premature ventricular contractions, torsades de pointes, ventricular fibrillation, and asystole. Hypotension results from inhibition of central neurovascular regulatory centers and impaired myocardial contractility.

Differential Diagnoses

Mild chloral hydrate toxicity can mimic the effects of ethanol, benzodiazepines or barbiturates, with drowsiness, ataxia, and lethargy. Other agents to consider in the differential diagnosis of chloral hydrate toxicity include the anesthetic drugs ketamine, propofol, and etomidate. More severe toxicity mimics other cardiotoxic drugs, including tricyclic antidepressants, diphenhydramine, and cocaine. Torsades de pointes may suggest acute quinine or arsenic poisoning, as well as hypomagnesemia.

Management

The key to management is support of cardiorespiratory function. Intubation may be required for airway protection or to support ventilation and oxygenation. Avoid naloxone or flumazenil, which may precipitate ventricular dysrhythmias. Because chloral hydrate, like other chlorinated hydrocarbons, sensitizes myocardium to catecholamines, epinephrine and norepinephrine should also be avoided. Standard antidysrhythmic agents, such as lidocaine, do not appear effective against chloral hydrate–induced cardiac ectopy. The treatment of choice for chloral hydrate-induced dysrhythmias is a beta-blocker.[13] Intravenous propranolol can be given in adult doses of 0.5 mg until ectopy is suppressed, followed by an infusion of 1 to 2 mg/hr, titrated to a heart rate of 80 to 100 beats/minute. A short-acting agent, such as esmolol, can also be used. Torsades de pointes should be treated with intravenous magnesium or overdrive pacing, as described in Chapter 69. Type I antidysrhythmic agents, such as quinidine, should be avoided. Unstable patients not responding to conservative therapy can be treated with hemoperfusion or hemodialysis.

Disposition

Patients with acute chloral hydrate overdose, whether accidental, intentional or iatrogenic, should be observed in the ED until clinically stable, alert, oriented, and ambulatory. In cases of prolonged altered mental status, respiratory depression, hypoxia, or evidence of cardiotoxicity (ie, PSVT, QRS widening, QTc prolongation, torsades de pointes), the patient should be admitted to a monitored setting. If the intent of the overdose was self-harm, psychiatric consultation is indicated once the patient is medically stabilized.

OVER-THE-COUNTER SLEEP AIDS

Over-the-counter (OTC) sleep aids currently available in the United States contain either diphenhydramine or doxylamine. Many preparations also contain acetaminophen or aspirin, added to achieve nighttime pain relief. The availability and frequent use of these agents may explain why overdose is so common.

Principles of Toxicity

Diphenhydramine and doxylamine are antihistamines that also have hypnotic, antimuscarinic, and weak local anesthetic properties. They act as competitive antagonists of H_1 histamine receptors and cause sedation by inhibiting the actions of acetylcholine on muscarinic receptors in the CNS. Their toxicity is described in Chapter 145.

GAMMA-HYDROXYBUTYRATE

Originally synthesized in the 1960s as an anesthetic, GHB was later discovered to be a naturally occurring metabolite of GABA. Since 1970, GHB has been used to treat narcolepsy, alcohol addiction, opioid withdrawal, and depression.[14]

The sale and manufacture of GHB were banned in 1990; however, illicit use of GHB increased, along with its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD). There is a wide variety of "street names" that have been associated with GHB (Box 159.4). The FDA approved GHB for the treatment of narcolepsy under the trade name Xyrem (sodium oxybate, 0.5 mg/mL) as a schedule III drug in 2005.

GHB remains a popular drug of abuse. Some individuals take GHB for its purported muscle-building and fat-burning actions, others for its psychoactive effects. The drug's euphoria-producing properties make it popular at "raves" (large, crowded youth parties with energetic dancing to rhythmic music for many hours). Self-treatment of insomnia with GHB has been reported and can cause dependence. CNS depression, amnesia, and disinhibition caused by mixing of GHB with ethanol make this combination a potential agent in "date rape" situations. After overdose, a call for medical assistance is often delayed because of the false belief that victims need only "sleep off" their intoxications. Death occurs most often in the prehospital setting, both from direct effects of the drug and increased the risk for fatal accidents. Combined intoxication with ethanol occurs in 40% of fatal cases, but GHB is the sole intoxicant in one-third of deaths, underlining the lethal potential of the drug and its congeners.[15,16] Other common co-ingestants include amphetamines, cocaine and ketamine. Chemical precursors to GHB are also commonly abused. GBL is rapidly converted to GHB by plasma lactonases. 1,4-BD is metabolized to gamma-hydroxybutyraldehyde by the enzyme alcohol dehydrogenase and then to GHB by aldehyde dehydrogenase.

Principles of Toxicity

GHB binds to specific GHB receptors and at high concentrations also to $GABA_B$ receptors. The complex interaction between these two receptors may explain the sometimes paradoxical manifestations of GHB toxicity with somnolence alternating with agitation. Through its action on the $GABA_B$ receptor, GHB decreases release of dopamine.

As underground laboratories often synthesize liquid GHB by mixing and heating butyrolactone and sodium hydroxide, careless preparation can result in residual unreacted alkali, causing significant caustic injury when the liquid is ingested.

GHB is lipophilic and rapidly absorbed. Onset of symptoms occurs within 15 to 30 minutes, and peak plasma levels are reached within 20 to 60 minutes. Unlike GABA, GHB readily crosses the blood-brain barrier. The half-life of GHB is 27 minutes but may increase at high doses.

GBL is an industrial solvent that is rapidly absorbed after ingestion and metabolized within minutes to GHB by peripheral and hepatic lactonases.[17] Before conversion to GHB, GBL itself is inactive and has no sedating effects. It produces a clinical syndrome similar to that of GHB ingestion, but its effects are greater and more prolonged. In fact, after ingestion, GBL is more efficient at delivery of GHB to the CNS than GHB itself is. GBL is available under a number of street names (Box 159.5).

1,4-BD is converted after ingestion to GHB by the enzyme alcohol dehydrogenase. Like GBL, it is used as an industrial solvent. Unlike GBL, 1,4-BD itself has sedative-hypnotic effects. Clinical findings are similar to those of GHB. When 1,4-BD and ethanol are ingested together, ethanol acts as a competitive inhibitor of alcohol dehydrogenase, so the toxic effects of 1,4-BD are delayed and prolonged, and the risk of death is increased. 1,4-BD is available under a number of street names (Box 159.6).

Clinical Features

Diagnosis of GHB intoxication is based on the history and clinical course. Rapid recovery from coma, or periods of agitation alternating with periods of decreased level of consciousness, is characteristic. Hypothermia may occur with prolonged coma. In the presence of coma, bradycardia with or without hypotension can occur and may respond to stimulation alone. Miosis with or without nystagmus may be seen. Because emesis occurs in about 50% of cases, obtunded patients are at risk for aspiration pneumonitis. Apparent seizure activity may actually represent random myoclonic movements of the face and extremities. Severity is dependent on the dose and the concurrent use of alcohol or other psychoactive drugs.

BOX 159.4

Gamma-Hydroxybutyrate Street Names

Grievous bodily harm (GHB)
Georgia home boy (GBH)
Gib
Natural sleep-500
Gamma-OH
Gamma hydrate
Liquid X
Organic Quaalude
Liquid E
Liquid ecstasy
Liquid G
Somatomax
Soap
Salty water
Scoop
Sodium oxybate
Easy lay
Cherry menth
Fantasy
G-Riffick

BOX 159.5

Gamma-Butyrolactone Street Names

Blue Nitro
Blue Nitro Vitality
Enliven
Fire Water
Gamma G
GH Revitalizer
Growth hormone release extract (GHRE)
Nitro
NRG3
Remforce
RenewTrient
Revitalize Plus
Revivarant
SomatoPro
Verve 5.0

BOX 159.6

1,4-Butanediol Street Names

Blue Raine
Dream On
Fubar
Inner G
Pine needle extract
Pine needle oil
ReJuv@Nite
Revitalize Plus
Serenity
SomatoPro
Thunder nectar
Weight belt cleaner
Zen

Differential Diagnoses

The differential diagnoses of GHB intoxication is broad including other sedative hypnotics (such as, barbiturates or benzodiazepines), OTC sleep aids, antimuscarinic agents, opioids, ethanol, ketamine, chloral hydrate, and designer amphetamines.

Poisoning with other sedative-hypnotics can produce a similar clinical picture. Unique to GHB, however, is the relatively rapid resolution of symptoms. In the absence of a co-ingestant such as ethanol, most patients will be functionally awake within 3 to 4 hours. Nearly all patients recover fully within 8 hours. Prolonged coma should prompt a search for another toxicological or non-toxicological cause. Cardiac effects and refractory seizures are rare and suggest the presence of other agents or etiologies.

Diagnostic Testing

GHB is not detected on routine urine toxicology screens. If laboratory confirmation is required, specimens must be collected early and sent for gas chromatography–mass spectroscopy. The drug may be detected in urine up to 12 hours after ingestion.

Management

Because of the high incidence of emesis with GHB overdose, there is no indication for gastric decontamination. Intubation for airway protection may be required for patients with significant CNS depression or hypoxia. Treatment of isolated GHB ingestion is supportive. Although some authors suggest administering physostigmine to reverse GHB-induced coma, the efficacy and safety of this intervention have not been demonstrated, and physostigmine is not indicated or recommended.

Withdrawal

Patients who suddenly stop GHB or its precursors after chronic, frequent use can experience a severe and potentially life-threatening withdrawal syndrome.[18] Because of the short half-life of GHB, symptoms of withdrawal begin within several hours of the last dose. The typical patient will have been using these products for weeks or years, every 1 to 3 hours around-the-clock, to avoid withdrawal symptoms.

Mild withdrawal is manifested with anxiety, tremor, and insomnia. This can progress to confusion, delirium, overt psychosis, paranoid ideation, hallucinations (visual, aural, or tactile), and autonomic instability. Diagnosis relies on a history of symptoms beginning after abrupt cessation of use of these products. The differential diagnosis includes withdrawal from other sedative hypnotic agents, delirium tremens, sympathomimetic toxicity, serotonin syndrome, neuroleptic malignant syndrome, CNS infection, and thyroid storm.

Initial treatment begins with high-dose benzodiazepines (lorazepam 1 to 2 mg intravenous push [IVP] every 30 to 60 minutes as required for agitation). However, GHB withdrawal may involve depleted levels of GABA. Because the effect of benzodiazepines requires the presence of GABA, they may not be effective in control of GHB withdrawal. Barbiturates, such as pentobarbital or phenobarbital, which do not need GABA to be effective, are often required in cases of severe withdrawal. These patients often require admission to an intensive care unit for titrated sedation, as well as to monitor vital signs and observe for development of rhabdomyolysis or hyperthermia.

Disposition

Because of GHB's short half-life, symptoms generally resolve while the patient is still in the ED. The patient generally regains consciousness spontaneously within 3 to 4 hours. No delayed toxicity is expected unless co-ingestants have been taken. Patients should be counseled about the seriousness of GHB intoxication, withdrawal potential with chronic use, and discharged home with reliable caretakers.

KEY CONCEPTS

- Barbiturate intoxication is rare, and most patients recover with observation and supportive care alone. Hemodialysis is not indicated unless the patient remains hemodynamically unstable despite adequate supportive measures.
- A urine toxicology screen positive for barbiturates does not prove that the drug caused the patient's clinical condition. Serum barbiturate levels confirm the diagnosis, but do not correlate well with depth of coma or clinical outcome.
- Flumazenil is not indicated in the majority of benzodiazepine overdoses, particularly not in regular benzodiazepine users, in whom flumazenil can precipitate seizures. Because flumazenil's duration of action (about 1 hour) is much shorter than that of all commonly available benzodiazepines, if flumazenil is used patients should be monitored closely for recurrent respiratory depression or re-sedation.
- Chloral hydrate toxicity may result in sedation and cardiotoxicity, principally in the form of supraventricular tachycardias, which are best treated with a beta blocker.
- Endotracheal intubation to protect against emesis, aspiration pneumonitis, and hypoxia is often necessary for patients with significant CNS or respiratory depression from GHB overdose.
- Withdrawal from GHB or its precursors begins with anxiety, tremor, and insomnia, but it can progress to a severe syndrome characterized by delirium and autonomic instability. Management of this syndrome often requires high-dose benzodiazepine or barbiturate therapy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 159: QUESTIONS & ANSWERS

159.1. How do barbiturates affect peripheral and cerebral blood flow?

A. Decrease peripheral pressure and have no effect on intracranial pressure
B. Decrease peripheral pressure and increase intracranial pressure
C. Decrease peripheral and intracranial pressure
D. Increase peripheral and intracranial pressure
E. Increase peripheral pressure and decrease intracranial pressure

Answer: C. Barbiturates cause direct cardiac depression with decreased cardiac output. In addition, they cause venous pooling and blunt the normal compensatory increase in system vascular resistance that would occur with decreased cardiac output. They also decrease cerebral blood flow and lower intracranial pressure. These effects are particularly pronounced in individuals with an already low cardiac output, such as in congestive heart failure or hypovolemic shock.

159.2. Other than general supportive care, which of the following is most useful in the management of a severe phenobarbital overdose with hemodynamic instability?

A. Flumazenil
B. Hemodialysis
C. Multidose activated charcoal
D. Urinary alkalinization
E. Whole bowel irrigation

Answer: B. Although rarely indicated, hemodialysis is effective for acute phenobarbital toxicity (serum levels over 100 mcg/mL) in the presence of refractory hypotension, renal or cardiac failure, acid-base or electrolyte abnormalities, or inadequate response to less invasive measures (as assessed by declining serum levels). These patients often require mechanical ventilation, so the patient's airway should be secured prior. Although there is evidence that multi-dose activated charcoal (MDAC) increases clearance of phenobarbital and may shorten duration of clinical toxicity, there is no evidence it results in improved outcomes over supportive care alone. Flumazenil will reverse the effect of benzodiazepines but has no effect on barbiturates. Urinary alkalinization has traditionally been used to "trap" the acidic barbiturates in the urine to increase excretion, However, a recent comprehensive review concluded that there is little clinical role for urine alkalinization in acute barbiturate poisoning. Whole bowel irrigation is not beneficial.

159.3. All of the following patients have depressed mental status, decreased respiratory drive, and mild hypotension. Supportive care has been initiated. All of the patients have a confirmed benzodiazepine overdose by a reliable historian. For which patient is it most reasonable to consider the use of flumazenil?

A. A 5-year-old boy with no known medical problems who took his mother's medication
B. A 22-year-old woman with no known medical problems
C. A 30-year-old man who is known to abuse cocaine
D. A 43-year-old man with depression and anxiety
E. A 79-year-old woman with congestive heart failure, coronary artery disease, and diabetes who takes benzodiazepines for insomnia

Answer: A. Flumazenil variably reverses the effects of benzodiazepines but can cause dysrhythmias and intractable seizures. Contraindications for flumazenil include history or suspected chronic benzodiazepine use (which are the vast majority of benzodiazepine overdose patients), co-ingestants that lower the seizure threshold, tricyclic antidepressants, cocaine, history of seizure disorder, chronic alcoholism, and head trauma. Its use should be for a known non-habituated patient (eg, the pediatric patient described here). Because flumazenil's duration of action is short compared with the benzodiazepine and it has variability to reverse respiratory depression, patients require close, monitored observation, repeated dosing or continuous infusion, and preparations to manage the airway. Because benzodiazepine overdose is rarely lethal and patients recover with supportive care, using an antidote requires a careful benefit/risk analysis.

159.4. Which of the following sedative hypnotics is most likely to cause fatal cardiac dysrhythmias in overdose?

A. Buspirone
B. Chloral hydrate
C. Eszopiclone
D. Flunitrazepam
E. Zolpidem

Answer: B. Chloral hydrate sensitizes the myocardium to catecholamines and also independently induces dysrhythmias. Treatment of choice of dysrhythmias from chloral hydrate is beta-blockers. None of the other listed medications cause significant cardiac toxicity.

159.5. A 53-year-old woman presents with decreased mental status and mild hypotension. She is arousable to pain. Her husband reports that approximately 4 hours ago she had been complaining of insomnia and said she was going to take something to help her sleep. He then found her in her present state with an empty bottle of "sleeping pills" on the counter. He does not remember the name of the sleeping pills. Supportive care is initiated. Which of the following laboratory tests would be the most helpful to manage this patient?
A. Acetaminophen level
B. Arterial blood gas
C. Serum chemistry
D. Serum myoglobin
E. Urine drug screen

Answer: A. Many over-the-counter (OTC) sleep aids contain acetaminophen or salicylates. The active ingredient in OTC sleep aids is an antihistamine, typically diphenhydramine or doxylamine. Both have anticholinergic effects in addition to causing sedation. Toxicity is typically mild and can be successfully managed with supportive care. It is rare that an antihistamine overdose results in rhabdomyolysis, and a serum creatine phosphokinase level, urinalysis, and urinary myoglobin level can be checked if there is concern. Myoglobin is cleared rapidly from the serum and is not a useful diagnostic test. Arterial blood gases, serum chemistries, and urine drug screens can be ordered if there is a complicated clinical course—but only rarely alter treatment.

159.6. A 21-year-old woman is brought to the emergency department (ED) by her friends after they found her unconscious in the bathroom of a local bar. The friends report that she had only had one or two alcoholic drinks. The patient's vital signs show mild bradycardia, hypotension, and bradypnea. Physical examination reveals miosis and short periods of apnea. She wakens briefly to noxious stimuli. You suspect that she may be suffering from gamma-hydroxybutyrate (GHB) poisoning. What is the most appropriate next step in management?
A. Atropine
B. Electrocardiogram
C. Endotracheal intubation
D. Flumazenil
E. Naloxone

Answer: C. GHB frequently causes emesis and aspiration because patients are unable to protect their airways. Patients with significant GHB overdose should be intubated, but supportive care alone is all that is required for most GHB overdoses. The half-life is short, and many patients will return to baseline mental status in several hours. Bradycardia is common, usually mild, and does not typically require atropine, but this can be used if bradycardia is severe. GHB does not cause dysrhythmias. Neither flumazenil nor naloxone has any effect on GHB.

159.7. A 30-year-old man presents with anxiety and insomnia. He is agitated and has a tremor on physical examination. His vital signs are as follows: blood pressure, 200/124 mm Hg; heart rate, 123 beats/min; respiratory rate, 22 breaths per minute; and temperature, 37.5° C. On further questioning, he reports that he chronically uses gamma-hydroxybutyrate (GHB) for muscle building but has not been able to take any for approximately 24 hours. Lorazepam is given in two escalating doses without response. Which of the following should be given next?
A. A barbiturate
B. Additional lorazepam
C. Clonidine
D. GHB
E. Labetalol

Answer: A. GHB withdrawal is severe, and deaths have been reported. GHB acts as a central nervous system (CNS) depressant, so withdrawal causes CNS excitement and autonomic instability. Chronic GHB abuse can lead to GABA depletion in the CNS. Because benzodiazepines require the presence of GABA, they may not be effective. Barbiturates act independently of GABA and are therefore more effective in GHB withdrawal. Clonidine can be used in opioid withdrawal but is not useful in GHB withdrawal. Labetalol would improve the vital signs but would have no effect on the underlying cause of the autonomic instability.

CHAPTER 160

General Approach to the Pediatric Patient

Margaret G. Huang | Genevieve Santillanes

PRINCIPLES

Emergency clinicians assess and manage pediatric patients from newborns to adolescents. Of the 136 million annual US emergency department (ED) visits, 25 million (18%) are for children younger than 15 years.[1] Twenty-two percent of children have at least one ED visit per year.[2] Infants have higher per capita ED utilization than other age groups, with 87.3 visits/100 infants.[1] More than 80% of pediatric patients are seen in general EDs, requiring all emergency clinicians to be skilled in the assessment, treatment, and stabilization of pediatric illnesses and injuries.[3,4]

Children can present diagnostic and management challenges due to their anatomic, physiologic, and developmental differences from adult patients. Understanding these differences is crucial to the recognition and appropriate treatment of many pediatric emergencies. In addition, caring for the pediatric patient also involves active participation from caregivers.

Pathophysiology

Children exhibit different patterns of illness and injury because of their unique physiologic and anatomic characteristics. Illness and injury patterns not only differ between pediatric and adult patients, but also vary in children by age. In addition to changes in cognitive and behavioral development, temperature regulation, airway anatomy, cardiovascular physiology, immune function, and the musculoskeletal system all change as children grow. Furthermore, pediatric patients may present to the ED with previously undiagnosed congenital disorders. Drug dosing and choice of medications also depend on patient size and physiology.

Assessment should begin with a review of vital signs, evaluating for early signs of physiologic decompensation. Normal heart rate and respiratory rate vary by age (Table 160.1). Normal blood pressure also varies by age, height, and gender (Box 160.1; Table 160.2). Abnormal vital signs should be repeated and persistently abnormal vital signs quickly addressed.

Temperature Regulation

Infants and young children have a larger surface area–to–mass ratio, resulting in more heat loss to the environment than in adolescents and adults. Maintenance of a stable body temperature can be a significant metabolic demand for young infants, especially those stressed by injury or illness. Maintain a neutral thermal environment for children during the physical examination and while performing procedures. Patients exposed briefly for examinations and interventions should be covered as soon as possible to avoid excessive heat loss. Critically ill young infants should be placed under radiant warmers. Overhead warming lights are useful for older infants and children who require prolonged exposure for resuscitation and procedures.

Airway

The pediatric airway differs in a number of ways from an adult airway.[5,6] Compared to the adult airway, the pediatric larynx is more anterior and cephalad, and the epiglottis is composed of more flexible cartilage, making it floppy. The relatively larger occiput in infants and young children can cause neck flexion in the supine position, leading to potential airway obstruction. To open the airway, particularly during intubation attempts, a towel roll placed under the shoulders may be needed to align the laryngeal, pharyngeal, and oral airway axes (Fig. 160.1). Infants and young children also have relatively large tongues, which may lead to airway obstruction during periods of changes in muscle tone, such as during a seizure. Use of a nasopharyngeal airway can alleviate the obstruction by allowing a clear passage of inhaled gases. In addition, airways in children are much smaller in diameter and much more easily obstructed with secretions. Because young infants preferentially breathe through their noses, respiratory distress can develop from copious nasal secretions. Thus, suctioning the nose and upper airway can dramatically diminish an infant's work of breathing.

Cardiovascular System

Healthy children have compensatory mechanisms to maintain blood pressure, even when cardiac output is decreasing. Children have the ability to increase their heart rate and vasoconstrict peripherally to shunt blood centrally. Hypotension is a late finding of shock in previously healthy children, and interventions should ideally occur before the onset of hypotension.[7] The earliest sign of cardiovascular compromise in most patients is tachycardia. Unfortunately, tachycardia is nonspecific and may be due to fever, pain, or anxiety. Repeated assessment of the heart rate can be helpful. In a crying child, a true resting heart rate can be obtained by leaving the pulse oximeter on until the child is calm. Unexplained tachycardia in a calm or sleeping child is concerning. The quality of the pulse is also helpful. A thready peripheral pulse associated with tachycardia should be considered a sign of shock. Bradycardia in ill children is especially ominous and may signal impending cardiac or respiratory arrest.

Musculoskeletal System

Growing children have musculoskeletal injury patterns different from those of adults. Ligaments are stronger relative to the immature bone, so children are more likely to fracture bones than

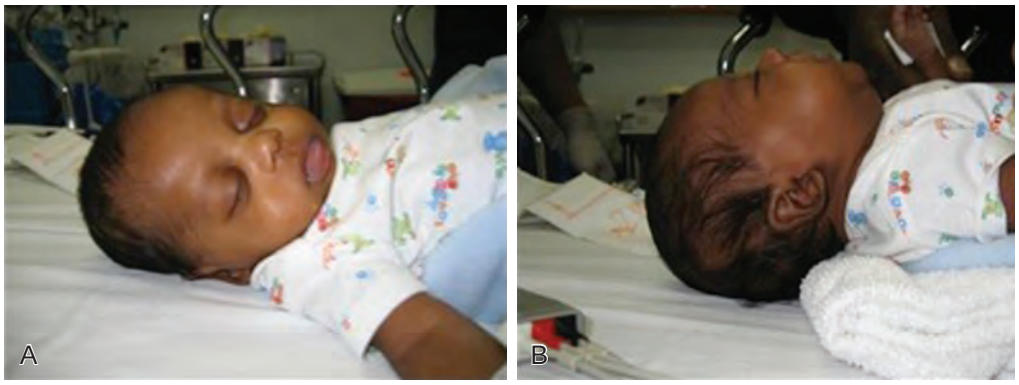

Fig. 160.1. Infant with neck in flexed position and after placement of a shoulder roll. (From Santillanes G, Gausche-Hill M: Pediatric airway management. Emerg Med Clin North Am 26:961–975, 2008.)

TABLE 160.1

Normal Pediatric Vital Signs

AGE (yr)	RESPIRATORY RATE (breaths/min)	HEART RATE (beats/min)
<1	30–60	100–160
1–2	24–40	90–150
2–5	22–34	80–140
6–12	18–30	70–120
>12	12–16	60–100

From Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric education for prehospital professionals, Sudbury, MA, 2013, Jones & Bartlett.

BOX 160.1

Lower Fifth Percentile of Systolic Blood Pressure

0–28 days: 60 mm Hg
1–12 months: 70 mm Hg
1–10 years: 70 mm Hg + (2 × age in years)

From American Heart Association: American Heart Association emergency cardiovascular care (ECC) guidelines, 2010. http://r.search.yahoo.com/_ylt=A0LEViv2_5xXGDQAthAnnIlQ;_ylu=X3oDMTEy NTY2dGRtBGNvbG8DYmYxBHBvcwM2BHZ0aWQDQjE4NjFfMQRzZWMDc3I-/RV=2/RE=1469935735/RO=10/RU=http%3a%2f%2fcpr.heart.org%2fAHAECC%2fCPRAndECC%2fResuscitationScience%2fGuidelines%2fUCM_473201_Guidelines.jsp/RK=0/RS=7d6mHtai64xX18.4XLFBMQl1fjg-.

TABLE 160.2

Pediatric Blood Pressure by Age[a]

AGE (yr)	50TH PERCENTILE (mm Hg)		HYPERTENSION–95TH PERCENTILE (mm Hg)	
	GIRLS	BOYS	GIRLS	BOYS
1	86/40	85/37	104/58	103/56
5	93/54	95/53	110/72	112/72
10	102/60	102/61	119/78	119/80
15	110/65	113/64	127/83	131/83

[a]For children at the 50th percentile for height.
Modified from The National High Blood Pressure Education Program Working Group on Children and Adolescents: The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. http://r.search.yahoo.com/_ylt =A0LEVjEL_pxXmVkA9ecnnIlQ;_ylu=X3oDMTEyMTlkcnI5BGNvbG8DYmYxBHBvcwMxBHZ0aWQDQjE4NjFfMQRzZWMDc3I-/RV=2/RE=1469935244/RO=10/RU=https%3a%2f%2fwww.nhlbi.nih.gov%2ffiles%2fdocs%2fresources%2fheart%2fhbp_ped.pdf/RK=0/RS=nLj248BF.zShav9t19Hzij4KyPU-

sprain ligaments. The weakest part of a growing child's bone is the physis, or growth plate. If tenderness is present on examination, physeal injuries should be considered in children with normal radiographs. Treatment of fractures in children should consider future growth potential. For example, certain physeal injuries can lead to long-term growth disturbances, whereas greater degrees of angulation are acceptable in many fractures due to the increased potential for bone remodeling.

Immunologic System

Due to their immature immune system, young infants are at increased risk of serious bacterial infections. Febrile infants younger than 1 month are a particularly high-risk group and have a 10% or higher rate of serious bacterial infection.[8-10] For this reason, the evaluation of infants with fever differs from the evaluation of older children and adults; the evaluation varies by age and vaccination status.

Pharmacologic Considerations

Medications for children are calculated using weight-based dosing, with attention to the maximum medication dose. Suggested safeguards to prevent calculation-based dosing errors in children include pharmacy review of medication orders, computerized order entry, use of templated order forms, and length-based resuscitation tapes to reduce calculation errors.[11,12] One easily remedied potential error is the inadvertent calculation of a drug dose on the basis of weight in pounds, not kilograms, leading to a more than twofold overdose. Therefore, ED scales and electronic charts should be programmed to report weight only in kilograms.

In addition to potential dosing errors, certain frequently used medications in older children and adolescents should not be given to young infants. For example, ceftriaxone is not recommended for infants younger than 28 days because it can displace bilirubin from albumin, leading to kernicterus or bilirubin-induced neurologic dysfunction (BIND). Although not well studied, the use of ibuprofen in infants physical examination younger than 6 months has not been approved by the US Food and Drug Administration because of the theoretical risk of kidney and liver injury.

TABLE 160.3

Developmental Milestones in Typically Developing Children Up to 2 Years of Age

AGE (mo)	GROSS MOTOR	VISUAL-MOTOR, SOCIAL, AND LANGUAGE
1	Raises head from prone position	Visually follows to midline, alerts to sound, regards face
2	Lifts chest off table	Smiles socially, recognizes parent, follows object past midline
4	Rolls over	Laughs, orients to voice
6	Sits unsupported	Babbles
9	Pulls to stand, cruises	Says "mama" and "dada" indiscriminately, plays games such as pat-a-cake
12	Walks alone	Two words other than "mama" and "dada"
15	Creeps upstairs, walks backward	Uses four to six words
18	Runs	Uses seven to ten words, knows five body parts
24	Walks up and down stairs independently	50-word vocabulary, two-word sentences

Adapted from Engorn B, Flerlage J: The Harriet Lane handbook, ed 20, Philadelphia, 2015, Elsevier Saunders.

Developmental Considerations

Assessment of pediatric patients requires an understanding of normal developmental milestones. Table 160.3 lists basic developmental milestones in the first 2 years of life. Variation in the rate at which children develop can be normal or may signal neurodevelopmental delays. Therefore, the parent's report of the child's developmental history and normal behavior is extremely important.

Young Infants

Infants younger than 2 months are especially challenging to assess because they have a limited behavioral repertoire. They may not make eye contact or have a social smile. Normal behavior includes sleeping, crying, quiet alert time, feeding, and stooling. A change in any of these activities may indicate serious disease. Increased sleeping or crying or decreased interest in feeding may herald a serious illness, such as sepsis or an underlying cardiac or metabolic disorder.

Infants (<12 Months)

Infants typically develop a social smile and track close objects by 2 months of age. After 6 months, infants may develop significant stranger anxiety, making the physical examination challenging. Whenever possible, examining the infant in the parent's lap, with the infant initially facing away from the examiner, will mitigate anxiety and facilitate physical examination. Bubbles or interactive toys can distract infants and may keep them calm.

Toddlers (1- to 2-Year-Olds)

Toddlers have variable reactions to a physical examination. A toddler may provide a limited history due to their narrow expressive language skills (eg, only pointing to the location of pain). Some are fearful and will not cooperate, whereas others are curious and cooperate more easily with the examination. In a stable patient, begin the encounter standing or sitting at a distance from the child while taking the history. Speaking in a soothing voice and distracting the child with toys or other interesting objects can facilitate the examination. Emergency clinicians should interact with the parents, because this will be perceived by the child as a sign of endorsement and indicate that the parents are involved with the emergency care. Conversely, toddlers will often negatively react to parental anxiety.

Preschoolers (3- to 5-Year-Olds)

Preschool-age children have increasing language skills. Like toddlers, their receptive language skills exceed their expressive language skills, and they often understand more than is realized. Preschoolers should be included in the conversation when possible. Providers should be cautious about talking to the parents about procedures or diagnoses in front of the preschool child, even if the child seems not to be paying attention or not to understand. Like toddlers, preschool children vary greatly in their cooperation with the physical examination. Providing limited options, such as sitting with the parent or on the gurney, or choosing which ear should be examined first, may give the child a sense of control and improve cooperation. Distraction with stories, videos, or games on a smartphone or other devices can also facilitate the physical examination. The young child will build up anxiety awaiting a procedure. For this reason, providers should provide children with simple concrete explanations of procedures only immediately before and during the procedure. Preschool children may perceive illness or painful procedures as punishment for their actions, making simple explanations of what and why it is occurring even more important.

School-Age Children

Some questions during the history should be directed at the school-age child, because many can provide much of the history themselves. At this age, children are often cooperative with the examination, but may regress when they are frightened or in pain. Additionally, children at this age become increasingly modest, and conscious attempts should be made to provide privacy.

School-age children may develop anxiety and attempt to negotiate or stall when a painful or unpleasant examination or procedure is planned, particularly if there is a long delay between the explanation and procedure. Firm but reassuring explanations of what will happen are important. Appropriate concrete explanations include the sequence of events and what physical sensations the patient will experience. It is also crucial to involve parents in the process to provide not only a candid explanation of the procedure itself, but also anticipated reactions from their child. When available, child life specialists are particularly helpful with this age

population, using play and education to prepare children for anxiety-provoking procedures.

Adolescents

Adolescents will be able to provide much, if not all, of the history. However, despite desired independence from their parents, adolescents may regress in times of stress. It is therefore important to elicit the concerns of the adolescent and parent and to ensure that both understand the diagnosis and plan. The adolescent should be given a chance to speak to the provider without the parent in the room. Any sensitive questions, such as those about drug use and sexual activity, should be asked privately.

Adolescents can generally be examined in a manner similar to that for adults. They may or may not prefer to have a parent present during the physical examination, and providers should clarify the patient's preference. Adolescents are often extremely modest, and attempts should be made to preserve privacy with the examination in a private room, when possible, and exposure of only the body part being examined.

EVALUATION

Triage

Pediatric-specific triage systems are important to avoid overtriage and undertriage of children. The application of adult-specific vital signs to children will lead to an inappropriate triage level classification. In addition, signs and symptoms of serious illness may be subtle in infants and very young children, requiring those providing the initial triage assessment to be familiar with normal pediatric physiology and development.

Triage systems with pediatric modifications include the Emergency Severity Index, Paediatric Canadian Triage and Acuity Scale, Manchester Triage System, and Australasian Triage Scale.[13] No triage system has been clearly demonstrated to be superior, and data on reliability and validity are limited for all triage systems. The Emergency Severity Index, Manchester Triage System, and Paediatric Canadian Triage and Acuity Scale have been demonstrated to be valid for pediatric patients.[14-16] Interrater reliability is good for the Manchester Triage System and moderate for the Emergency Severity Index and Paediatric Canadian Triage and Acuity Scale.[13-16] The Australasian Triage Scale appears to have lower reliability than the other triage systems.[13]

History

In critically ill or injured patients, the SAMPLE history can be used to obtain a focused history quickly (Box 160.2). The SAMPLE history reminds providers to ask for ***S***igns and symptoms, ***A***llergies, ***M***edications, ***P***ast medical history, ***L***ast meal, and ***E***vents surrounding the illness or injury.

BOX 160.2

Focused SAMPLE History

Signs and symptoms
Allergies
Medications
Past medical problems
Last food or liquid
Events leading to injury or illness

Adapted from Dieckmann R, Brownstein D, Gausche-Hill M, editors: Pediatric education for prehospital professionals, Sudbury, MA, 2013, Jones & Bartlett.

A more detailed history will be guided by the patient's presenting complaint. In preverbal children, symptoms will often be inferred by the caregiver based on the child's behavior. Parents are often very perceptive and may notice subtle changes in behavior that are not immediately evident to a healthcare provider.

Additional age-specific questions may be indicated. In neonates, pregnancy and birth history will help identify risk factors for conditions such as hyperbilirubinemia (eg, prematurity, ABO incompatibility), infection (eg, maternal fever during labor, early rupture of membranes, maternal group B streptococcus status), and respiratory illnesses (eg, prematurity, meconium aspiration, need for supplemental oxygen or mechanical ventilation). In infants and toddlers, urine output, quantified by the number of wet diapers, helps determine hydration status. This can be especially helpful in breast-feeding newborns, whose intake is difficult to quantify. Vaccination status is important in infants and children presenting with symptoms such as fever (eg, risk of bacteremia) and rash (eg, risk of varicella, measles). Drug and alcohol use, as well as the sexual history, become important in adolescents who have increased risk-taking behaviors and should be questioned in a private setting, not in front of the caregiver.

Pediatric Assessment Triangle

Rapid recognition of the critically ill child is a crucial skill. The pediatric assessment triangle (PAT) assists providers in assessing children quickly and is an orderly approach for formulating an initial impression of the child's overall status from the door of the examination room[17,18] (Fig. 160.2). The three components of the PAT are (1) appearance, (2) work of breathing, and (3) circulation. On the basis of the initial PAT, the emergency clinician can distinguish the "sick" from the "well" child rapidly. Table 160.4

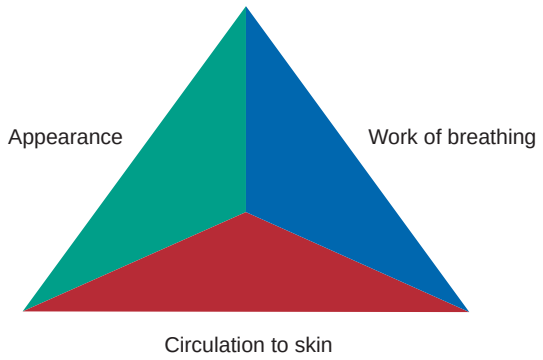

Fig. 160.2. Pediatric assessment triangle.

TABLE 160.4

Pediatric Assessment Triangle Findings

APPEARANCE	WORK OF BREATHING	CIRCULATION TO THE SKIN
Tone	Abnormal sounds—stridor, grunting, snoring, wheezing	Pallor
Irritable, interactive	Abnormal positioning—sniffing, tripoding, refusal to lie down	Delayed capillary refill time (>2 s) Mottling
Consolable	Retractions	Cyanosis
Look, gaze	Head bobbing	Petechiae
Speech, cry	Nasal flaring	

Adapted from Dieckmann R, Brownstein D, Gausche-Hill M, editors: Pediatric education for prehospital professionals, Sudbury, MA, 2013, Jones & Bartlett.

TABLE 160.5

Interpretation of the Pediatric Assessment Triangle

PHYSIOLOGIC STATE	APPEARANCE	WORK OF BREATHING	CIRCULATION TO THE SKIN
Respiratory distress	Normal	Abnormal	Normal
Respiratory failure	Abnormal	Abnormal	Normal-abnormal
Compensated shock	Normal	Normal	Abnormal
Decompensated shock	Abnormal	Normal-abnormal	Abnormal
Brain injury or dysfunction	Abnormal	Normal	Normal
Cardiopulmonary failure	Abnormal	Abnormal	Abnormal

Adapted from Dieckmann R, Brownstein D, Gausche-Hill M, editors: Pediatric education for prehospital professionals, Sudbury, MA, 2013, Jones & Bartlett.

summarizes the findings that may be noted on each of the three sides of the triangle, and Table 160.5 summarizes interpretation of the PAT.

Appearance

Observation of the child from a distance allows the provider to assess the patient's overall status without upsetting the child. The mnemonic TICLS (***t***one, ***i***nteractiveness, ***c***onsolability, ***l***ook and gaze, ***s***peech and cry) summarizes the components of the assessment of overall appearance. Observation of the infant or child interacting with his or her parents provides many clues about the child's overall status. An ill infant with a vacant or glazed look can be distinguished from an alert infant who responds to environmental stimuli. An infant who is awake but lying motionless on a gurney is much more concerning than an active infant who moves all the extremities. Irritability is an early sign of inadequate brain perfusion. This may be followed by lethargy and then coma as perfusion is further compromised.

The quality of the cry is another helpful clue. A persistently high-pitched or irritable cry is concerning for central nervous system disease, such as meningitis. A normal overall appearance suggests that oxygenation, ventilation, and perfusion are adequate.

Work of Breathing

The work of breathing should initially be observed from a distance because it is difficult to accurately assess work of breathing in a crying child. Infants and children with respiratory distress may assume the sniffing position in an attempt to decrease their work of breathing. The tripod position is an ominous sign of severe respiratory distress.

The quality of the voice or cry may be a clue to airway and respiratory disease or compromise. For example, children with croup have a hoarse voice, and children with peritonsillar abscesses may have a have muffled or so-called hot potato voice. Abnormal breath sounds may be audible without a stethoscope.

Signs of respiratory compromise include stridor, audible wheezing, retractions, grunting, and snoring respirations. To assess the presence of retractions and abdominal breathing, the infant or young child should be observed with the chest unclothed. Retractions may be seen in the suprasternal, supraclavicular, intercostal, and subcostal areas (Fig. 160.3). Nasal flaring is an attempt to decrease airway resistance (Fig. 160.4). Head bobbing (the use of neck muscles to assist respiration) and seesaw breathing (ineffective breathing pattern, in which the abdomen moves outward while the chest moves inward during inspiration) are signs of impending respiratory failure. As the child tires and nears complete respiratory failure, the respiratory rate falls and the work of breathing may diminish.

Fig. 160.3. Intercostal retractions in a child with respiratory distress.

Fig. 160.4. Nasal flaring in a child with respiratory distress from lower airway obstruction.

Normal pediatric respiratory rates are inversely related to age due to younger children's increased metabolic rates and lower tidal volume reserves. Because children normally function near their maximum tidal volume capacity, relatively small increases in metabolic demands (eg, fever) can result in an elevated respiratory

rate. As a result, abnormal respiratory patterns may provide clues about a nonrespiratory illness. Effortless tachypnea may be a sign of shock from any cause, whereas deep rapid breathing without other auscultative findings may be compensation for a metabolic acidosis. Children who are tachypneic despite normothermia must be evaluated for respiratory and nonrespiratory causes. Neurologic disorders may also lead to abnormal respiratory patterns (eg, bradypnea and respiratory irregularity in the setting of increased intracranial pressure).

Circulation

Visual inspection of the skin can provide clues to overall cardiovascular status. Early compensated shock is characterized by peripheral vasoconstriction and shunting of blood to the brain and other vital organs. At this stage, skin appears pale but remains warm to the touch with delayed capillary refill time (>2 seconds). If the shock state is not corrected, the patient may become mottled, with cold extremities (Fig. 160.5A). Mottling is a random pattern of vasoconstriction in adjacent capillary beds in the skin. This is not to be confused with cutis marmorata, a lacy pattern on the skin caused by vascular instability (see Fig. 160.5B). Cutis marmorata is a normal finding in young infants in a cool environment. In contrast to infants with mottling, infants with cutis marmorata will be otherwise well-appearing, and the skin findings will diminish or disappear if the infant is placed in a warm environment. Cyanosis may be present normally in children with congenital heart disease but, if cyanosis is a new finding for the patient, it is almost always indicative of respiratory failure or decompensated shock.

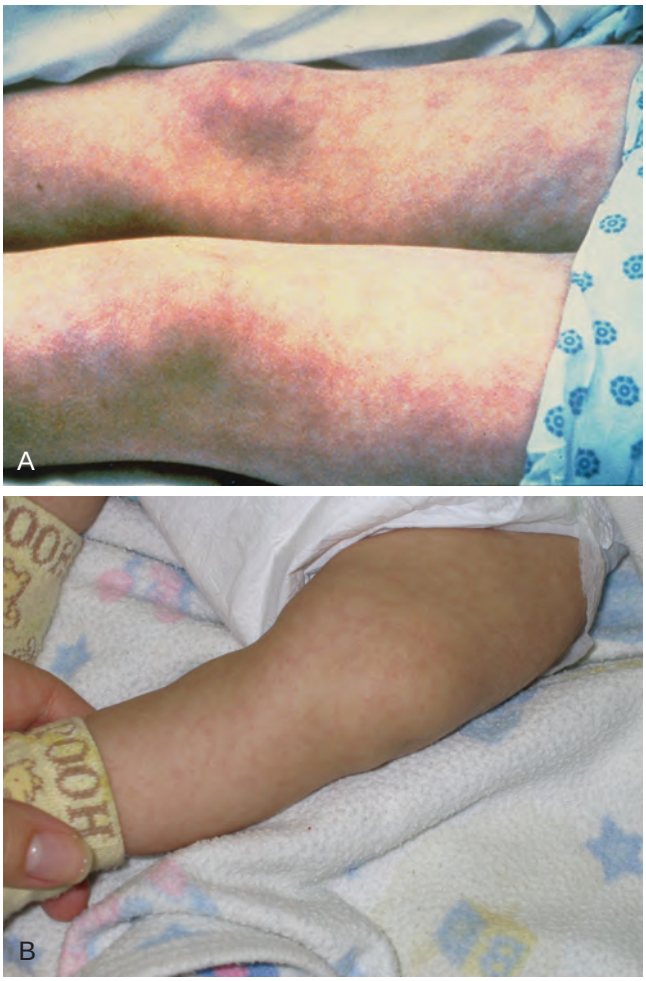

Fig. 160.5. Infant with skin mottling (**A**) and cutis marmorata (**B**).

Length-Based Resuscitation Tape

An accurate weight is often not available for critically ill children. Use of a color-coded, length-based resuscitation tape gives an estimate of the child's weight. Each color on the tape corresponds to a weight range that corresponds to an ideal body weight for length. Medication doses and appropriate equipment are listed on the tape for each weight range. Use of the length-based resuscitation tape avoids error-prone calculations of medication dosages and equipment sizes in the high-stress setting of a pediatric resuscitation. In addition, pediatric resuscitation equipment organized by weight ranges minimizes the need to search for appropriately sized equipment.

Physical Examination

As in adults, the physical examination in critically ill or injured children will focus initially on airway, breathing, and circulation, with abnormalities in these systems corrected before a complete physical examination is performed. In any infant or toddler with respiratory complaints, observing the child breathing with the shirt removed will allow the most reliable assessment of the work of breathing. The respiratory rate should be manually counted for a minimum of 30 seconds, due to periodic breathing, and also because the rate on the monitor can be unreliable. In infants and young children with some degree of respiratory distress, observation of respiratory status and pulse oximetry during feeding or sleeping can be helpful when deciding on further observation and admission.

In infants and young children, the physical examination should not be performed in a head to toe fashion. Auscultation of the heart and lungs and palpation of the abdomen should be performed before other more frightening or uncomfortable parts of the examination. Although, ideally, the physician should palpate the child's abdomen, occasionally a fearful child will cry so much it is impossible to determine if the child has abdominal tenderness or guarding. In these cases, observing the parent palpate the abdomen can be helpful. Although parents cannot be relied on to examine for masses or organomegaly, they can elicit pain with palpation and feel for guarding.

Examination of the ears, oropharynx, or area of injury should occur toward the end of the physical examination. Providers can try to ease a child's fear by first demonstrating the examination on a parent, older sibling, or stuffed animal. For the ear examination, the parent can hold the young child in his or her lap, with one arm around the head and one arm around the child's body and arms (Fig. 160.6). Young children can often be coaxed into opening the mouth wide enough for examination of the oropharynx without use of a tongue depressor. The examination can be turned into a game by asking the child to open his mouth and pant "like a puppy" or see if she or he can touch the tongue to the chin. When necessary, external examination of the vagina in young girls can be facilitated by having them sit in a frog leg position in the parent's lap. Children should be reassured of the safe environment with the provider and caregiver but also should be counseled to understand the difference between the examination and inappropriate touching by others.

SPECIFIC DISORDERS

The most common reasons for infants and children to present to EDs are respiratory illness, fever, and injury.[19] Causes of serious illness and injury vary by age. Respiratory illnesses are the most common reason for infant hospitalization after the

Fig. 160.6. Toddler being held for otoscopic examination of the ears.

immediate neonatal period.[20] Asthma and appendicitis are the most common reasons for hospitalization of school-age children, and affective disorders are the most common cause of adolescent hospitalizations.

This section focuses on complaints specific to the pediatric population and complaints in which the differential and approach vary significantly from those in adult populations.

Common Neonatal Complaints

Neonates may present with a variety of previously undiagnosed genetic, anatomic, and metabolic conditions. In addition to the very limited behavioral cues displayed by newborns, parents of newborns are frequently anxious and may not know what behaviors or patterns are normal.

Concerns about feeding are common. Neonates typically feed every 2 to 3 hours. Bottle-fed neonates take about 2 to 3 ounces per feed, whereas breast-feeding neonates typically spend 10 to 15 minutes on each breast each feed. Newborns, especially those who are exclusively breast-fed, can lose up to 10% of their birth weight during the first 7 days of life. Birth weight should be regained by day 10, with a subsequent weight gain of 20 to 30 g/day for the first 3 months of life. Providers should clarify feeding routines with caregivers. Infants with excessive weight loss or failure to gain weight may have underlying metabolic, cardiac, or infectious causes or be victims of abuse or neglect.

Small amounts of regurgitation of breast milk or formula are normal in infants and generally are not concerning if the amount is stable, the infant is gaining weight, and emesis is not bilious. Larger volume emesis must be evaluated. Common benign causes include overfeeding and inadequate burping, but providers should consider other serious causes, such as pyloric stenosis, volvulus, intussusception, and nonaccidental trauma (head or abdominal). Another common concern is the frequency and consistency of bowel movements. Although infants typically have soft stools multiple times a day, it can be normal for exclusively breast-fed infants to stool as infrequently as once every 5 to 7 days. Straining during a bowel movement is also commonly seen and may occur after transition from breast milk to formula. In infants presenting with constipation, a history of failure to stool in the first 24 hours of life is concerning for Hirschsprung's disease—aganglionic segments of the colon that fail to relax.

Neonatal Intensive Care Unit Graduate

Gestational rather than chronologic age is typically used for premature infants in whom development is often delayed. Due to their immature immune function relative to infants of the same chronologic age, premature infants are at increased risk for recurrent respiratory infections. Chronic lung disease is a common complication in extremely premature infants (gestational age < 28 weeks). Such infants frequently have a baseline tachypnea and increased work of breathing and may require supplemental home oxygen. Parental report of changes in work of breathing, activity, feeding pattern, and level of alertness can be clues to serious illness, such as sepsis or underlying metabolic abnormalities.

Respiratory syncytial virus (RSV) immunoglobulin (palivizumab) prophylaxis is recommended for certain high-risk infants during peak season.[21] During RSV season, the timing of the last RSV immunoglobulin injection given should be ascertained when a premature infant presents with fever, cough, or rhinorrhea. Palivizumab is administered monthly and, if a dose has been missed, the physician should have a higher level of suspicion for RSV infection.

Children With Special Health Care Needs

The assessment of children with chronic illnesses and other special health care needs is especially challenging. Parents or other daily caregivers can provide helpful information on baseline behavior and mental status, and the caregiver's input should be sought.

However, a parent's knowledge and recollection of detailed medical information may be limited, especially during times of high stress. Parents may forget medication names or concentrations, details of previous hospital admissions, and current treatment plans. An Emergency Information Form (EIF) that summarizes chronic medical conditions, medications, medical devices, and other critical information can be used for children with special health care needs (available at www.acep.org/clinical---practice-management/emergency-information-form-for-children-with-special-health-care-needs/).[22] These forms can quickly provide critical information to the ED provider, assisting in the early management and stabilization of the child until more detailed records are obtained. ED staff can request that specialists affiliated with their hospitals provide EIFs for complex patients to facilitate rapid and appropriate emergency treatment.

Child Abuse

Nonaccidental trauma should be a consideration for all patients presenting with injuries and complaints, such as altered mental status and apparent life-threatening events. Unfortunately, abusive injuries are frequently not recognized at the initial health care encounter, leaving children at high risk for future and more serious injuries and death.[23-25] Historical clues to nonaccidental trauma include mechanisms inconsistent with the injury pattern or a history inconsistent with the developmental level of the child (Box 160.3). Physical examination clues for abuse include presence of bruises in young precruising infants and unusual locations of bruises, such as the ear and trunk (Box 160.4).[26,27] Fractures in children younger than 12 months without a significant witnessed trauma mechanism are especially concerning.[28] For a more detailed description of the evaluation of suspected child abuse.[28a]

BOX 160.3

Historical Features Concerning for Child Abuse

History lacking in details
Inconsistency—details change with repeated questioning
History inconsistent with child's developmental status
Reported mechanism inconsistent with injury

BOX 160.4

Physical Examination and Radiologic Findings Concerning for Abuse

Any bruises in young precruising infants
Patterned ecchymosis, burns, or skin marks (abrasions, lacerations)
Bruises on the ears, trunk, inner thighs, neck, or groin
Posterior oropharynx bruising or lacerations
Posterior rib fractures
Classic metaphyseal fractures
Any fracture in a nonambulatory child
Fractures in different stages of healing

OTHER CONSIDERATIONS

Consent for Emergency Care

In general, parent or guardian consent is required for the evaluation and treatment of minors and emergency clinicians should attempt to notify parents or guardians and obtain consent. However, in emergent situations, evaluation and stabilization cannot be delayed while awaiting consent. The Emergency Medical Treatment and Active Labor Act has mandated that patients presenting for emergency care receive a medical screening examination and, if an emergency medical condition is identified, patients should receive the care required to stabilize the condition.[29] Thus, all minors presenting to the ED require an examination to determine if an emergency medical condition exists. If a condition that is threatening to life or health exists, treatment should be provided under the doctrine of implied consent. If an emergency medical condition is not suspected after a screening examination, nonemergent care should be delayed until guardian consent is obtained, unless the minor is legally able to consent for care.

The circumstances under which minors can consent for their own care vary from state to state, but minors can generally consent if they are emancipated or if they are seeking treatment for mental health issues, drug or alcohol abuse, contraception, pregnancy, or testing for or treatment of sexually transmitted infections.[29] Minors are generally considered emancipated if married, on active duty in the military, or living independently and economically independent from their parents. Some states recognize minors as emancipated if they are pregnant or a parent. Many states recognize that a mature minor, generally 14 years or older, can consent for care if sufficient intelligence and maturity is displayed to make a reasonable and voluntary choice. The process for determining mature minor status varies from state to state.

Pediatric-Ready Emergency Department

Preparation to care for infants and children of all ages involves not only ED staff training but also stocking pediatric medication formulations, equipment, and supplies in appropriate sizes for the premature neonate to the adult-sized adolescent. The American College of Emergency Physicians, American Academy of Pediatrics, and Emergency Nurses Association have developed joint guidelines for the care of children in the ED.[30,31] The guidelines include recommendations for necessary personnel, protocols, medications, equipment, and supplies. Surveys have found that EDs frequently lack the items recommended in the guidelines.[3,32] One strong recommendation in the guidelines is the appointment of physician and nurse coordinators for pediatric emergency care.[30,31]

Pediatric emergency readiness also requires a plan for continuing care of critically ill and injured children. Small community hospitals often do not have pediatric intensive care units or access to pediatric subspecialists. Therefore, a plan for transfer of patients whose needs exceed available resources is necessary. Receiving hospitals and a mechanism for transporting critically ill pediatric patients should be identified in advance.

Pediatric-Friendly Emergency Department

One topic that has received increasing attention is pain and anxiety management in pediatric patients. Procedural pain is frequently undertreated in infants.[33,34] Appropriate use of sedation, anesthesia, analgesia, and nonpharmacologic methods of pain management can increase the patient's cooperation and increase visit satisfaction for the child and parent. Children have significant anxiety and fear surrounding medical procedures, leading to additional challenges in performing procedures successfully. In addition to reducing pain and anxiety during the acute visit, adequate pain control is likely to have long-term benefits. Multiple studies have demonstrated that inadequate procedural pain control can lead to increased pain perception with future painful procedures.[35]

A variety of options are available to minimize pain associated with blood draws and intravenous line starts, including vapocoolants, topical anesthetics, and needle-free jet injection of anesthetics.[36] Topical anesthetics can also decrease the pain of an anesthetic injection before a lumbar puncture and other procedures. Topical application of a lidocaine, epinephrine, and tetracaine mixture has been shown to have comparable efficacy to injected anesthesia for facial and scalp lacerations.[37] The combination of sucrose and radiant warmth can provide effective analgesia to newborns.[38,39] Child life specialists are particularly helpful and, when available, should be used to provide play therapy and education to frightened children, allowing the provider to focus on the procedure singularly. Child life providers use nonpharmacologic distraction techniques such as bubbles, songs, books, videos, and video games to decrease anxiety, tools that can also be adopted by department staff.[36] In young children, the use of anxiolytic medications or procedural sedation may be appropriate for procedures that could be accomplished with local anesthesia in older patients.

Another shift in has been in regard to increased support for the family's presence during invasive procedures and resuscitations.[40] Children are stressed when separated from their parents, and one benefit of a family's presence is to reassure and calm the child. Studies have shown that a family's presence also decreases anxiety levels in family members.[41] Their presence during unsuccessful cardiopulmonary resuscitation is perceived by families as beneficial in the grieving process. Studies have shown that with well-implemented policies, a family's presence does not interfere with resuscitation.[40]

Families present during resuscitations should have a family support person assigned who can explain procedures and answer questions. Ideally, families are briefed on what to expect before entering the resuscitation room. Guidelines have been developed to assist emergency clinicians in implementing family presence protocols at their institutions.[42]

KEY CONCEPTS

- Patterns of illness and injury vary by age, and a number of anatomic and physiologic characteristics affect the presentation and management of pediatric emergencies.
- A basic understanding of normal development will aid the emergency clinician in assessment of the pediatric patient.
- The pediatric assessment triangle (PAT) can be used as a tool for rapid evaluation of the patient's overall status.
- Tachypnea in children must be evaluated relative to age norms and is often a sign of increased metabolic demands. A child with tachypnea despite normothermia should be evaluated for respiratory and nonrespiratory causes (eg, hypoperfusion, acidemia).
- Maintenance of a neutral thermal environment is necessary for critically ill infants.
- Child abuse should be considered when injuries are inconsistent with history, when details of the history change, or with certain injury patterns.
- A joint guideline of the American College of Emergency Physicians, American Academy of Pediatrics, and Emergency Nurses Association summarizes the role of pediatric emergency care coordinators, development of pediatric policies, and recommended equipment, supplies, and medications for EDs.
- The family's presence should be encouraged for pediatric procedures and resuscitations.
- A variety of pharmacologic and nonpharmacologic techniques are available to decrease procedural pain and anxiety.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 160: QUESTIONS & ANSWERS

160.1. Which of the following respiratory signs is characteristic of a child in compensated or decompensated shock?

A. Grunting with abnormal breath sounds
B. Tachypnea with nasal flaring
C. Tachypnea without aberrant breath sounds on auscultation
D. Tripoding with stridor
E. Wheezing with retractions

Answer: B. Effortless tachypnea, or rapid respirations with clear breath sounds, is characteristic of a child in compensated or decompensated shock. Grunting, nasal flaring, tripoding, stridor, wheezing, and retractions are all signs of increased work of breathing and would be more indicative of pulmonary or airway disease.

160.2. As the pediatric physician coordinator for your emergency department, you decide to institute new policies to prevent pediatric medication errors. Which of the following strategies will be most effective in decreasing risk of dosing errors?

A. Pharmacy review of medication orders
B. Use of length-based resuscitation tapes
C. Use of resuscitation calculators
D. Weighing and recording the weight in kilograms

Answer: D. Weights should be measured and recorded in kilograms, not pounds, to avoid inadvertent dosing calculations using pounds instead of kilograms. The use of length-based resuscitation tapes and resuscitation calculators and pharmacy review of medication orders have also been suggested to reduce medication

dosing errors, but the most effective measure is to weigh and record the weight in kilograms.

160.3. You have written an order for a blood draw and placement of an intravenous line in a nervous 3-year-old boy. Which of the following is least likely to be helpful in decreasing the patient's procedure-related distress?

A. Application of a lidocaine-epinephrine-tetracaine mixture

B. Having the patient blow bubbles prior to the needle stick

C. Needle-free jet injection of local anesthetic

D. Use of a vapocoolant

Answer: A. The formulation of lidocaine-epinephrine-tetracaine only works on broken skin (ie, lacerations). Unlike eutectic mixture of local anesthetic (EMLA) and 4% liposomal lidocaine preparations which are effective on intact skin, it will not work on intact skin. The use of vapocoolants and a needle-free jet infection of local anesthetic may decrease the patient's pain. Distraction techniques such as blowing bubbles, singing a song, or watching a video may relieve procedure-related anxiety.

CHAPTER 161

Airway Management for the Pediatric Patient

Joshua Nagler | Nathan W. Mick

PRINCIPLES

Although there are similarities in the skills required to perform endotracheal intubation in adults and children, anatomic and physiologic differences in children should be understood and mastered. These differences are most prevalent in the first 2 years of life and necessitate modifications to the intubation approach in older adolescents and adults. Additionally, because of the size and weight spectrum inherent in the pediatric patient population, there is a spectrum of equipment selection and medication dosages.

Management of the pediatric airway is a critical intervention, although infrequently required, making skill acquisition and retention difficult for emergency clinicians. Even in large children's hospitals, there are few opportunities to perform endotracheal intubation as part of clinical practice. Of 1000 pediatric emergency department (ED) patients, 1 to 3 will require intubation, compared to 1 out of 100 adults. Many providers will leave residency training with fewer than 10 pediatric intubations and will not routinely intubate children as part of their clinical practice after training.[1] At the same time, pediatric intubation success and skill mastery improves with increasing experience. Operating room studies demonstrate first-pass intubation success rates are less than 50% after 10 airways but rise to more than 90% after 50 intubation attempts. Fortunately, through experience with older patients, most emergency providers can recognize critical illness and have the skills necessary to manage the pediatric airway. These translational skills can be augmented using a simulated environment or with dedicated training in the operating room. Developing a systematic approach to pediatric airway management while recognizing the anatomic and physiologic differences in the young child will be critical to success and eliminate many of the anxieties associated with performing a time-dependent, infrequent critical action.

ANATOMY

There are several anatomic differences in pediatric patients which directly impact airway management (Table 161.1). These differences are most notable in the first 2 years of life; children 2 to 8 years old represent a transitional stage where the anatomy becomes more adult-like, yet variability with medication dosing and equipment size selection remain. Although infants and children are predictably different than the adult population, they are not inherently difficult with regards to airway management.

Aligning the oral, pharyngeal, and laryngeal axes is critical to visualization of the glottis during direct laryngoscopy, and correct positioning of the patient can facilitate alignment. The small infant has a relatively large head and occiput in relation to their body size. This can cause slight flexion at the neck when the patient is lying supine, impeding the ability to visualize the glottis. The patient should be positioned so that a line drawn through the external auditory canal and the anterior shoulder is horizontal and parallel to the bed (Fig. 161.1). In the infant (younger than 6 months old), this is accomplished by placing a towel roll under the patients shoulders, elevating the body, and overcoming the flexion associated with their large occiput. In the small child (6 months to 5 years old), correct positioning can likely be achieved without the need for support. In the older child/adolescent, the head is smaller in relation to the size of the body and the head may need to be elevated. As long as cervical spine injury is not suspected, correct positioning combined with slight extension at the neck will optimize the conditions for direct laryngoscopy.

Infants and children have large tongues relative to the size of their mouths and tend to have a large, floppy epiglottis. Because of these differences in anatomy, they are prone to obstruction when sedated or obtunded and manipulation of the epiglottis during direct laryngoscopy is frequently required to achieve intubation. Practically, these differences may necessitate the use of an oral or nasopharyngeal airway during bag-mask ventilator (BMV) ventilation to bypass the large tongue. Furthermore, a straight (Miller) laryngoscope blade may better manipulate the floppy epiglottis.

The vocal cords and glottic opening are situated at the level of the first cervical vertebrae in infants, gradually drop to the C3 to C4 level by age 7 and further descend to the C6 level by late adolescence. Therefore, the airway is higher and more anterior in small infants than what is encountered in adults, making correct positioning prior to direct laryngoscopy critical to ensure success of intubation (Fig. 161.2).

Historically the narrowest portion of the pediatric trachea was felt to be subglottic at the cricoid ring. Recent studies in anesthetized pediatric patients demonstrate anatomic narrowing at the level of the vocal cords and an elliptical-shaped subglottic region.[2] Because of the non-distensible nature of the cricoid cartilage, the subglottic region functionally remains the narrowest in the spontaneously breathing child.

The unique anatomy of the pediatric upper airway has led to the use of uncuffed endotracheal tubes (ETTs) in the small child. Support for uncuffed tubes came at a time when the cuffs were relatively stiff and there was not a reliable, easy way to identify high cuff pressures that can lead to subglottic tracheal injury. Current cuff technology can accurately measure cuff inflation pressures, and cuffed tubes may be preferred, particularly in instances of high airway pressures or poor compliance (eg, asthma, pneumonia, and acute respiratory distress syndrome [ARDS]). Utilizing a cuffed ETT may obviate the need to replace and upsize a tube when there is significant air leak that impacts ventilation.

The pediatric trachea is more flexible and prone to dynamic collapse. In addition to implications with positioning during assisted BMV and intubation, the trachea can collapse without complete obstruction with upper airway pathology (eg, croup, bacterial tracheitis). In cases of upper airway pathology, keeping

TABLE 161.1

Anatomic Differences in Pediatric Airway Management

ANATOMIC DIFFERENCE	IMPLICATIONS FOR AIRWAY MANAGEMENT	SOLUTION
Large occiput and head	Neck position flexed when laying supine and flat on stretcher	Shoulder roll required for optimal positioning of young infant
Large tongue	May occlude airway in the unconscious or obtunded patient	Jaw thrust and oral or nasopharyngeal airway useful adjuncts during airway management
High, anterior airway	Visualization of the vocal cords may be difficult	Correct positioning prior to laryngoscopy critical
Upper airway anatomy and narrow subglottic region	Upper airway prone to dynamic collapse and inflammation (eg, croup)	Utilization of uncuffed tubes Cuffed tubes safe as long as cuff pressure monitored
Large tonsils and adenoids	Prone to bleeding with manipulation	Blind nasotracheal intubation relatively contraindicated younger than 10 years old
Small cricothyroid membrane	Surgical cricothyrotomy difficult	Needle cricothyrotomy recommended in infants and young children
Large stomach, dependence on diaphragmatic excursion for ventilation	Insufflation of the stomach during BMV can compromise ventilation	Use orogastric or nasogastric tube for decompression

BMV, Bag-mask ventilator.

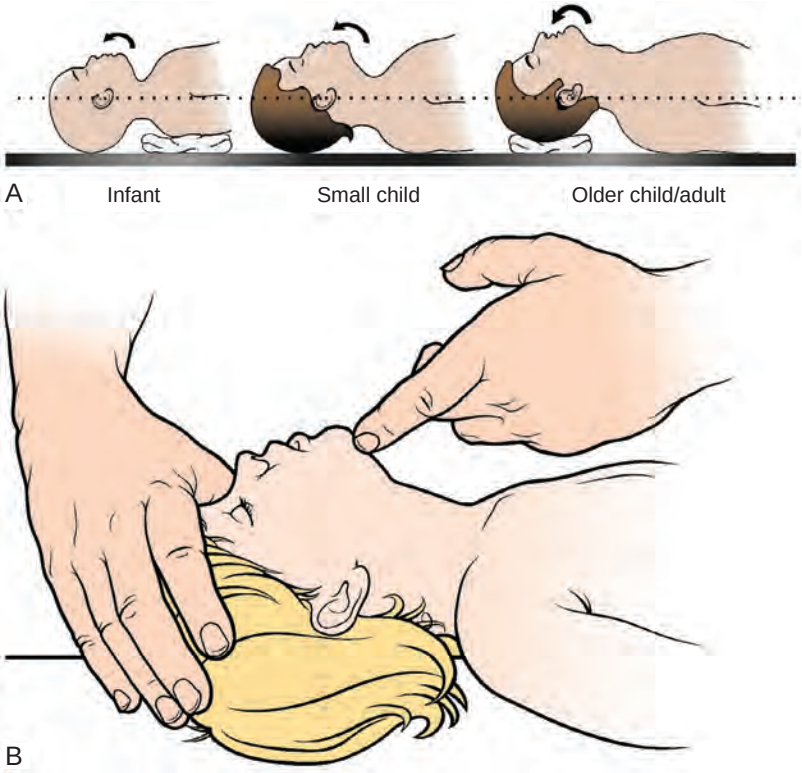

Fig. 161.1. Correct positioning of a pediatric patient to ensure optimal airway alignment utilizing a line passing through the external auditory canal and the anterior shoulder. **A,** The small infant requires a shoulder roll to achieve optimal positioning, the small child typically requires neither a shoulder roll nor head support, and the older child/adolescent may require head support. **B,** In this small child, a line drawn through the external auditory canal and the anterior shoulder reveals the child to be in good position without support. Slight extension of the head results in the achievement of the sniffing position. (Used with permission: Walls R, Murphy M: Manual of emergency airway management, ed 4, Philadelphia, 2012, Lippincott Williams & Wilkins.)

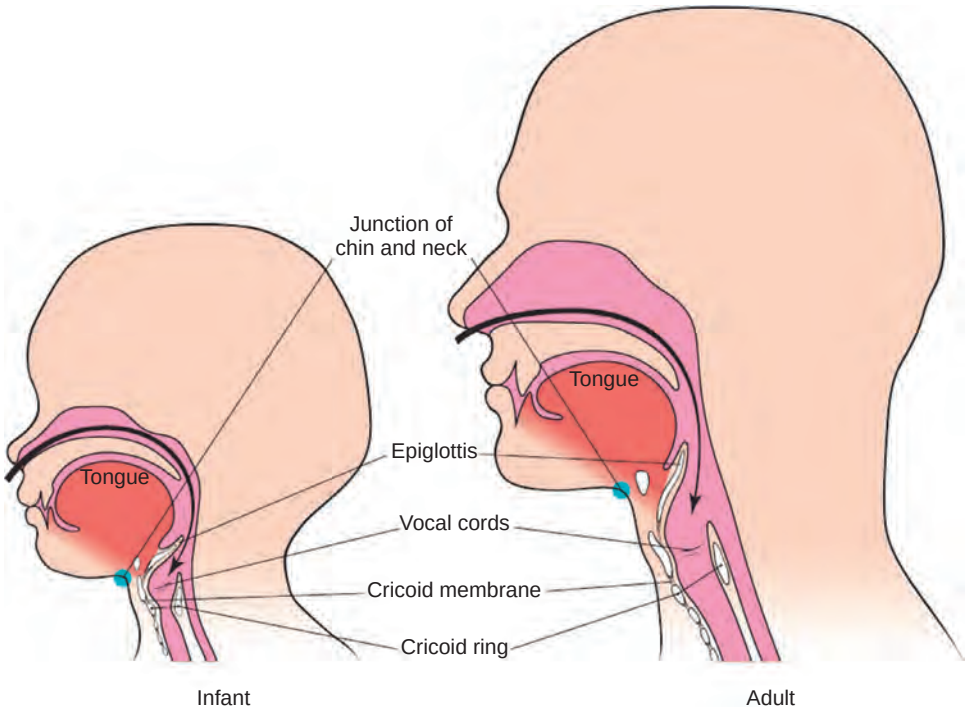

Fig. 161.2. High, anterior airway of the small child. Anatomic difference in the relation of the glottis in the small child compared with the adult.

the patient in a calm and quiet environment is important. Cases of "complete" upper airway obstruction in pediatrics often respond well to the addition of positive pressure via BMV, which can act to stent open the upper airway. Heliox, typically a 70% to 30% mixture of helium to oxygen, increases laminar flow in obstructed airways. A trial of heliox may be considered in cases of partial upper airway obstruction (eg, croup), although it has been found no more effective than racemic epinephrine or humidified oxygen in reducing the level of distress in these patients.[3]

The anatomic variations in children impact recommendations in pediatric airway management. Children have relatively prominent tonsillar and adenoidal tissue that is prone to bleeding with even minor trauma. Thus, blind nasotracheal intubation is relatively contraindicated and not routinely recommended in pediatric patients younger than 10 years old. Anatomical landmarks may be difficult in young infants and children with short necks with prominent soft tissue and with a small cricothyroid membrane, resulting in needle cricothyrotomy as the recommended invasive airway of choice rather than surgical cricothyrotomy.

Finally, small children are dependent on diaphragmatic excursion for ventilation and have relatively large stomachs and low gastroesophageal sphincter tone. They are predisposed to gastric insufflation during BMV attempts, which can impede diaphragmatic motion and compromise ventilation. Use of cricoid pressure in infants and young children is controversial and not well supported in the literature. If gentle cricoid pressure is used during BMV and chest rise is poor, we recommend release of cricoid pressure to see if effective ventilation can then be maintained. We recommend placement of a nasogastric or orogastric tube and aspiration of air immediately following endotracheal intubation or before intubation if the abdomen is becoming distended and impeding ventilation during BMV.

PHYSIOLOGY

Owing to a high metabolic rate and low functional residual lung capacity, young children are prone to quick desaturation once apneic, even with preoxygenation. Whereas a fully preoxygenated adult with healthy lungs may not desaturate below 90% for a full 6 minutes, a normal healthy 10-kg child may fall below 90% in half that time and a sick infant may desaturate in less than 1 minute. Thus, careful attention to preoxygenation is crucial. Additionally, use of high-flow nasal cannula (15 L/min for children and 5 L/min for infants) during the apneic period may help support oxygenation until intubation can be achieved. BMV should be provided between intubation attempts when oxygen saturation levels start to decline below 95%.

Children have a large extracellular fluid volume when compared with adults. Many of the drugs used to facilitate endotracheal intubation (sedatives and paralytics) need higher per kilogram doses; their duration of action may also be shorter when compared with adults.

EQUIPMENT

The cognitive burden that occurs when caring for a critically ill child is significant. Equipment selection and medication dosing must be calculated based on weight and size, which can vary tremendously across the spectrum of pediatric patients, from the 3 kg newborn to the 100 kg adolescent. Every ED that cares for pediatric patients should have airway equipment stocked, accessible, and organized by age and size to facilitate easy use. There are many systems, such as the Broselow-Luten system, to facilitate this organization (Fig. 161.3). Regardless of the system, elimination of the reliance on rote memorization lessens the cognitive burden of caring for pediatric patients across the age/size spectrum.

There are several "formulas" that are useful in selecting the appropriate equipment for pediatric patients. To determine ETT size, a number of methods are used. Measure the length of the child with a length-based resuscitation tape that has tube sizes based on length and weight recorded on the tape, or use of age-based formulas for a child older than 1 year old:

$$4 + (\text{age in years}/4)$$

Generic pediatric RSI

Zero – 10 min	**Preparation**	
Zero – 5 min	**Preoxygenation**	100% oxygen
Zero – 3 min	**Pretreatment**	Atropine*
Zero	**Paralysis with induction**	Etomidate SCh or rocuronium
Zero + 15 sec	**Positioning**	
Zero + 45 sec	**Placement with proof**	Intubate Confirm placement clinically and with $ETCO_2$ detection
Zero + 1 min	**Post-intubation management**	Sedation and analgesia Paralysis only if necessary

*Optional, used principally for infants younger than 1 year old.

The Broselow-Luten Zones for Pediatric Drugs and Equipment

the.difficult airway course™ EMERGENCY

Theairwaysite.com

Intubation considerations in children

Insertion depth - *see color chart*
Ventilator settings
- **FiO_2: 100%**
- **PEEP:** 5 cm H_2O initial
- **PIP:** 20–30 cm H_2O
- **Inspiratory time:** *see color chart*
- **Tidal volume* and RR:** *see color chart*

Post intubation - Secure tube at lip *and* stabilize neck

*Tidal volume of 6–10 mL/kg frequently used, but assess patient to determine there is chest rise and distal air entry on exam. Adequate tidal volume typically requires PIP of at least 15 cm H_2O if lung compliance is normal.

Zone	3 kg	4 kg	5 kg	Pink	Red	Purple	Yellow	White	Blue	Orange	Green
Length (cm)	46–52	52–57	57–61	61–67	67–75	75–85	85–97	97–109	109–121	121–133	133–146
Weight (kg)	3	4	5	6–7	8–9	10–11	12–14	15–18	19–23	24–29	30–36
Pretreatment											
Atropine	0.1 mg	0.1 mg	0.1 mg	0.13 mg	0.17 mg	0.2 mg	0.26 mg	0.33 mg	0.42 mg	0.5 mg	0.5 mg
Induction											
Etomidate[#]	0.9 mg	1.2 mg	1.5 mg	2 mg	2.5 mg	3.2 mg	4 mg	5 mg	6.3 mg	8 mg	10 mg
Ketamine	6 mg	8 mg	10 mg	13 mg	17 mg	20 mg	26 mg	33 mg	42 mg	53 mg	66 mg
Propofol	9 mg	12 mg	15 mg	20 mg	25 mg	32 mg	40 mg	50 mg	63 mg	80 mg	100 mg
Paralysis											
Succinylcholine	6 mg	8 mg	10 mg	13 mg	17 mg	20 mg	26 mg	33 mg	40 mg	53 mg	66 mg
Rocuronium	3 mg	4 mg	5 mg	7 mg	9 mg	10 mg	13 mg	17 mg	21 mg	27 mg	33 mg
Maintenance											
Vecuronium	0.3 mg	0.4 mg	0.5 mg	0.7 mg	0.9 mg	1 mg	1.3 mg	1.7 mg	2.1 mg	2.7 mg	3.3 mg
Lorazepam	0.15 mg	0.2 mg	0.25 mg	0.3 mg	0.4 mg	0.5 mg	0.6 mg	0.8 mg	1 mg	1.3 mg	1.6 mg
Equipment											
ETT (mm)	3.5 unc/3.0 cuff	3.5 unc/3.0 cuff	3.5 unc/3.0 cuff	3.5 unc/3.0 cuff	3.5 unc/3.0 cuff	4.0 unc/3.5 cuff	4.5 unc/4.0 cuff	5.0 unc/4.5 cuff	5.5 unc/5.0 cuff	6.0 cuff	6.5 cuff
Lip–tip (cm)	9–9.5	9.5–10	10–10.5	10–10.5	10.5–11	11–12	12.5–13.5	14–15	15.5–16.5	17–18	18.5–19.5
Suction	8 F	8 F	8 F	8 F	8 F	8–10 F	10 F	10 F	10 F	10 F	12 F
L–scope blade	1 St.	1 St.	1 St.	1 St.	1 St.	1 St.	2 St./Cvd.	2 St./Cvd.	2 St./Cvd.	2–3 St./Cvd.	2–3 St./Cvd.
Stylet	6 F	6 F	6 F	6 F	6 F	10 F	10 F	10 F	10 F	14 F	14 F
Oral airway	50 mm	50 mm	50 mm	50 mm	50 mm	60 mm	60 mm	60 mm	70 mm	80 mm	80 mm
NP airway	14 F	14 F	14 F	14 F	14 F	18 F	20 F	22 F	24 F	26 F	26 F
$ETCO_2$ detector	PED	PED	PED	PED	PED	PED	PED	Adult	Adult	Adult	Adult
BMV (min vol mLs)	450	450	450	450	450	450	450	450–750	750–1000	750–1000	1000
LMA	1	1	1	1.5	1.5	2	2	2	2–2.5	2.5	3
Ventilation											
Tidal volume mL	20–30	24–40	30–50	40–65	50–85	65–105	80–130	100–165	125–210	160–265	200–330
Frequency (bpm)	20–25	20–25	20–25	20–25	20–25	15–25	15–25	15–25	12–20	12–20	12–20
Insp time (sec)	0.6	0.6	0.6	0.6	0.6	0.7	0.7	0.7	0.8	0.8	0.8

[#]Midazolam is the same dose as etomidate.

Fig. 161.3. The Broselow-Luten zones for pediatric drugs and equipment. *BMV,* bag-mask ventilator; *$ETCO_2$,* end-tidal carbon dioxide; *ETT,* endotracheal tube; *FiO_2,* fraction of inspired oxygen; *LMA,* laryngeal mask airway; *NP,* nasopharyngeal; *PED,* pediatric; *PEEP,* positive end-expiratory pressure; *PIP,* peak inspiratory pressure; *RR,* respiratory rate; *RSI,* rapid sequence intubation; *SCh,* succinylcholine.

Example: 4-year-old patient

$$4 + (4 \text{ years}/4) = 5.0 \text{ uncuffed ETT}$$

or

4.5 *cuffed* ETT(subtract 0.5 from above formula for cuffed tube sizing)

ETT depth of insertion (lip to tip distance) can be estimated by use of the Broselow-Luten tape or by the following formula:

$$3 \times \text{uncuffed tube size} = \text{lip to tip distance (mid-trachea)}$$

Example: 5.0 ETT

$$3 \times 5.0 = 15 \text{ cm depth of insertion}$$

For a child who is effectively stabilized using noninvasive means (such as, BMV), the additional benefit of a secure airway needs to be weighed against the risk of potential difficulty or complications. The rapidity with which this decision needs to be made varies depending on circumstances. Failure to successfully oxygenate or ventilate a child by other means forces immediate action, whereas other conditions allow medical interventions and recurrent assessments over time to determine if advanced airway management is required.

Overall an equal number of pediatric intubations in the ED are performed on trauma and nontrauma patients. Indications for pediatric intubation can be placed into four categories: (1) inability to oxygenate and ventilate, (2) inability to maintain or protect the airway, (3) potential for clinical deterioration, and (4) facilitation of necessary diagnostic studies, procedures, or for patient transport.

Respiratory compromise is a leading contributor to morbidity and mortality in the pediatric population and more likely than a primary cardiac disease to be the cause of arrest. Respiratory failure can result from intrinsic pulmonary disease or from conditions with infectious, neuromuscular, traumatic, toxicologic, or environmental etiologies. Respiratory failure is a clinical diagnosis, identified by characteristic examination findings and supported by noninvasive measurement of oxygenation (pulse oximetry) and ventilation (capnography). Blood gas analysis can also be informative but should not be relied upon to determine need to perform necessary advanced airway management.

Signs of partial obstruction (sonorous or stridulous airway noises) or complete obstruction (inability to phonate or produce audible breath sounds in a patient with adequate respiratory effort) suggest an inability to maintain the airway and should prompt immediate basic airway maneuvers, including airway repositioning or oral and nasal airways used to help stent open the upper airways. Suctioning and removal of any foreign material might also be required. When these efforts are ineffective, patients may require an advanced airway. For patients with severely depressed mental status, the loss of protective airway reflexes necessitates airway control, regardless of the ability to maintain the airway. In fact, the use of a Glasgow Coma Score (GCS) of 8 or less is often cited as an indication for intubation in head-injured patients. Systemic illness, toxicologic exposure, and other etiologies of central nervous system (CNS) depression may also increase risk of aspiration, and the presence of a gag reflex correlates poorly with GCS and the risk of aspiration; thus testing for it is not recommended, because it may increase the risk of vomiting and subsequent aspiration.

When airway compromise is progressive (eg, from thermal injury or anaphylaxis), airway management should be initiated early to avoid respiratory embarrassment and increased difficulty later in securing the airway. Similarly, patients with systemic illnesses (such as, sepsis) may be intubated based on their anticipated course, as well as to maximize oxygen delivery and offload metabolic demands related to increased work of breathing.

Children often require sedation to perform diagnostic testing, such as computed tomography (CT), magnetic resonance imaging (MRI), or invasive procedures. The risk of airway compromise during procedural sedation is greater in patients with significant illness or medical instability. Therefore, securing the child's airway may be necessary to ensure safety during the procedure, particularly in circumstances where accessibility for assessment and intervention may be compromised, such as if a patient will be under surgical drapes or tunneled into a CT or MRI scanner. Because many acutely ill and injured children will require transfer to a pediatric tertiary care center, the stability of the patient's overall condition and risk of airway compromise should be carefully considered. Securing the airway prior to transfer can obviate the need for emergent advanced airway management in a less controlled setting.

MANAGEMENT

Rapid-Sequence Intubation

Rapid sequence intubation (RSI) is the preferred method to perform endotracheal intubation in children, provided no contraindications exist. There may be a temptation to attempt emergency pediatric endotracheal intubation with sedation only, but studies have demonstrated higher success and lower complications rates with RSI. A small number of medications are used for pretreatment, sedation/induction, and neuromuscular blockade during ED pediatric RSI (Table 161.2).

Pretreatment

The goal of pretreatment medications is to attenuate the physiologic responses to laryngoscopy and intubation, or to mitigate the adverse effect of pharmacologic agents used for sedation or neuromuscular blockade. It is important to note that data are limited with regard to the benefit of pretreatment medications in children. In addition, use of these agents needs to be weighed against the potential for procedural delays and drug errors that can occur with the administration of weight-based medications. This is particularly relevant during high stress situations, such as the management of critically ill children. Two drugs have been used for pretreatment in pediatrics: (1) atropine to prevent bradycardia related to vagal tone, and (2) lidocaine to attenuate the reflex sympathetic response in patients with concern for increased intracranial pressure (ICP); however, their use today is not routinely recommended.

Infants, particularly younger than 1 year old, have higher intrinsic vagal tone than older children or adults. Atropine serves as a vagolytic and can reduce the risk of bradycardia resulting from laryngoscopy in this age group. There is an association between the use of succinylcholine and bradycardia. Data suggest that this risk may be tied to use with select inhaled anesthetics (eg, halothane) and with newer induction agents the incidence of succinylcholine-related bradycardia is very low.[4] Given the limited available evidence, routine use of atropine for patients receiving succinylcholine during RSI is not necessary.[5] Atropine may be helpful for bradycardia that exists prior to the procedure, but it should not be administered until attempts are made to appropriately oxygenate the patient.

Data on the effectiveness of lidocaine in blunting the sympathetic response to laryngoscopy in patients with suspected elevated ICP is limited to case series and extrapolated from adult experience. Literature reviews have failed to identify a benefit in adult head injured patients, and no supporting data exist in pediatric

TABLE 161.2

Common Rapid-Sequence Intubation Medications in Children*

Medication	Dosage	Comments
PREMEDICATIONS		
Atropine	0.02 mg/kg	May have benefit in children less than 1 year old Not routinely required for use with succinylcholine Should be given for preexisting or peri-procedure bradycardia
Lidocaine	1.5 mg/kg	Very limited pediatric specific data to support use in increased ICP Needs to be given 3 minutes prior to laryngoscopy No data for bronchodilatory effect in children
INDUCTION AGENTS		
Etomidate	0.3 mg/kg	Rapid and reliable sedation Preserves hemodynamics Known to cause adrenal suppression even with single-dose, although limited data on impact on clinical outcome Consider stress dose hydrocortisone with use No analgesic properties
Ketamine	1 to 2 mg/kg	Causes release of endogenous catecholamines May support hemodynamics in hypotensive patients Beta-agonist effect may help with bronchodilatation, favoring its use in asthma Preserves airway reflexes and respiratory drive Can be used without NMBA for "awake sedated look" in suspected difficult airways
Propofol	1 to 2 mg/kg	Rapid onset, short acting May cause hypotension Apnea possible Higher dose recommended in infants No analgesic properties
PARALYTICS		
Rocuronium	1 to 1.2 mg/kg	Nondepolarizing agent Equivalent onset as succinylcholine but longer duration of action No specific contraindications in patients suitable for RSI
Succinylcholine	<10 kg: 2.0 mg/kg >10 kg: 1.5 to 2 mg/kg Double the dose when given IM	Fasciculations without clinical relevance in children Shorter duration than rocuronium Very low risk of bradycardia with IV induction agents used in ED (see earlier) Risk of hyperkalemia and arrest in patients with known and undiagnosed myopathies and neuromuscular disease

*RSI medications can be given intraosseous (IO) when IV access cannot be obtained.
ED, Emergency department; *ICP,* intracranial pressure; *IM,* intramuscular; *IV,* intravenous; *NMBA,* neuromuscular blocking agent; *RSI,* rapid sequence intubation.

populations. Therefore, we do not recommend the routine use of lidocaine.

Sedatives

Sedatives rapidly induce unconsciousness and facilitate intubation. Providers should choose sedatives based on their efficacy and adverse effect profile and matched to the clinical situation. In particular, providers should pay careful attention to the hemodynamic profile of these agents, to minimize the risk of clinical deterioration during RSI.

Etomidate is a common sedative used for pediatric RSI. It has reliable efficacy and pharmacokinetics and a stable hemodynamic profile. Etomidate may suppress adrenal corticosteroid synthesis. However, no convincing data exist to suggest that administration of a single dose during intubation influences clinical outcome. Pediatric advanced life support (PALS) guidelines have included precautions against "routine use" in septic shock and suggest consideration of stress dose hydrocortisone when etomidate is used.

Ketamine is a dissociative anesthetic with reliable and rapid onset, which is used frequently for procedural sedation and analgesia in pediatrics. It causes the endogenous release of catecholamines, making it appealing for patients with hypotension or shock. Adverse reactions to ketamine include vomiting, laryngospasm, myoclonus, and emergence phenomenon. Although ketamine is a known sialogogue, the co-administration of atropine is unlikely to be of help during RSI given that the onset of action for the drying effects of atropine may take up to 20 minutes. Ketamine has been shown to increase ICP, although the significance of this on clinical outcome is unclear. Controversy continues to exist as to whether head trauma and concern for increased ICP should be a relative contraindication to its use.[6-8] The catecholamine release may lead to beta-agonist effects resulting in bronchodilation, making it an ideal drug for patients with bronchoconstriction. This same benefit may not apply in conditions such as bronchiolitis, in which airway edema and debris are the primary etiology of airway obstruction. Ketamine is considered the sedative of choice for children in septic shock requiring RSI because of its ability to maintain mean arterial pressure.

Propofol has rapid and profound sedative properties, that when combined with its short duration of action, makes it an ideal induction agent. However, as a vasodilator and myocardial depressant, it should be used with caution in any patient with tenuous hemodynamics, including hypovolemia or shock. It may also

compromise cerebral perfusion if mean arterial pressure is rapidly reduced.

When benzodiazepines are used as an induction agent for RSI, they need to be given in higher doses than when used as anticonvulsants or during procedural sedation. Doses of midazolam (0.3 to 0.4 mg/kg) may be required to achieve sufficient sedation. Alternatively, they may be used in conjunction with opioids such a fentanyl, although the combination may compromise hemodynamics in some patients.

Neuromuscular Blocking Agents

The purpose of using a neuromuscular blocking agent (NMBA) is to relax airway musculature and to block airway protective reflexes during laryngoscopy and facilitate the passage of the ETT. The aim is rapid onset of action to limit the time without spontaneous or assisted ventilation. Succinylcholine and rocuronium are the most commonly used NMBAs for emergent pediatric RSI.[9] Understanding the specific benefits and risks of each is helpful in creating an airway management plan.

Succinylcholine has a rapid onset of action of 30 to 60 seconds and duration of action of 3 to 8 minutes. It is the oldest and often the most familiar NMBA for emergency clinicians and has a long track record of safe and effective use. Higher doses (2 mg/kg) are recommended in neonates and infants compared to 1.5 mg/kg for older children. Providers should be aware of several side effects and potential risks that exist with its use. Muscle fasciculations result from the depolarizing effect of this agent, although young children may not have large enough muscle mass for this to result in clinically observable effects. Use of succinylcholine can result in hyperkalemia, which can be fatal in a number of clinical conditions (see Table 161.2). In many patients, these diagnoses are known or suspected; however, published case series have described use in infants with undiagnosed myopathies leading to hyperkalemia arrest.[10] As a result, an U.S. Food and Drug Administration (FDA) Black Box warning exists for the use of succinylcholine in children, although given the rarity of these conditions, exception has been allowed for emergency use. Given this waiver, succinylcholine is still the most commonly used NMBA in pediatric emergency airway management. Other serious but rare adverse effects of succinylcholine use in children include masseter spasm and malignant hyperthermia, which are most commonly associated with halothane use.

Rocuronium is the most common nondepolarizing NMBA used in emergency airway management in children. Pediatric data suggest that rocuronium at a dose of 1.2 mg/kg has equivalent efficacy in time to intubation conditions as succinylcholine. The duration of action, however, is much longer with a time to return of spontaneous respirations of anywhere from 20 to 90 minutes. The primary advantage of nondepolarizing agents is the absence of the risks (eg, hyperkalemia) associated with depolarizing agents. The longer duration of action can be of concern if the airway cannot be secured or in patients in whom rapid return of examination findings (eg, neurological examination) is important. However, it may also have advantages if subsequent management may include imaging, additional vascular access, initial ventilator management, or other procedures. A reversal agent for rocuronium exists that can limit its duration of action to less than that of succinylcholine; however, it was only recently licensed for use in North America therefore clinical experience is limited.

DEVICES AND TECHNIQUES

Basic Airway Management

The priority in pediatric airway management is establishing effective oxygenation and ventilation. For children with hypoxemia but effective ventilation and without concern for increased work of breathing, passive supplemental oxygen delivery can be sufficient. For mild hypoxemia in children who will not tolerate a nasal cannula or facemask, "blow-by" oxygen using a mask, shovel, or a cupped hand or plastic funnel attached to oxygen tubing aimed toward the face are options. Nasal cannula can provide more consistent oxygen delivery, particularly in infants who are preferential nasal breathers. Simple facemasks can be used, whereas non-rebreather masks provide maximal passive oxygen delivery in spontaneously breathing patients.

When ventilation is of concern or a child's work of breathing is excessive, assisted ventilation may be required with a bag and mask. Effective assisted ventilation requires: (1) a patent airway and (2) an effective mask seal. Opening the airway is accomplished with positioning of the child, avoiding flexion of the neck from a large occiput or from downward pressure on the face when applying the mask. Application of basic airway maneuvers including a head tilt-chin lift maneuver or a jaw thrust can be of further help. Nasopharyngeal and oral airways can be of value when the airway is being partially or completely obstructed, often by the tongue or soft palate. Oral airways will only be tolerated in patients with depressed mental status, either pharmacologically induced or related to underlying pathophysiology. To create an effective mask seal, the provider first needs to select the appropriate size mask. An ideal fitting mask is large enough to cover the nose and open mouth but should not allow air leak across the bridge of the nose or off the base of the chin. Breaths should deliver an appropriate volume and pressure. There may be a tendency in an acute situation to deliver a much larger tidal volume than is appropriate for the size of the child, which may result in barotrauma. Gentle rise of the chest accompanied by clinical improvement are key clinical features of effective assisted BMV. The bag-mask device should be squeezed just until chest rise is initiated and then released. The emergency clinician may time ventilation by stating "squeeze, release," which slows ventilation rate and may reduce complications from hyperventilation and gastric insufflation during rescue ventilation. Cricoid pressure has little utility and should be used with caution in children. Too much cricoid pressure can compress the pliable pediatric trachea, leading to iatrogenic upper airway obstruction. Cricoid pressure should be lightened or released if felt to impede BMV.

Advanced Airway Management

Chapter 1 covers a detailed approach to RSI. The general approach to the procedure is identical to that of an adult, although there are several pediatric considerations worthy of mention.

Preparation

Passive oxygen delivery devices, self-inflating bags and masks, oral and nasal airways, laryngoscope blades, ETTs, stylets, and rescue devices all come in varying sizes to match the anatomy of the child. Generally having at least two sizes of ETTs (estimated size and a half size smaller) available during the procedure is prudent. Having a systemic approach to identifying the correct equipment prior to initiating the procedure can eliminate errors and failed attempts in critical situations. Potential resources include a length based resuscitation system (see Fig. 161.2), pediatric resuscitation cards, print or online textbooks, or mobile device applications.

Preoxygenation

As described earlier, young children desaturate much more quickly than adolescents or adults. In a patient with sufficient respiratory effort, preoxygenation with maximal passive oxygen delivery (ie,

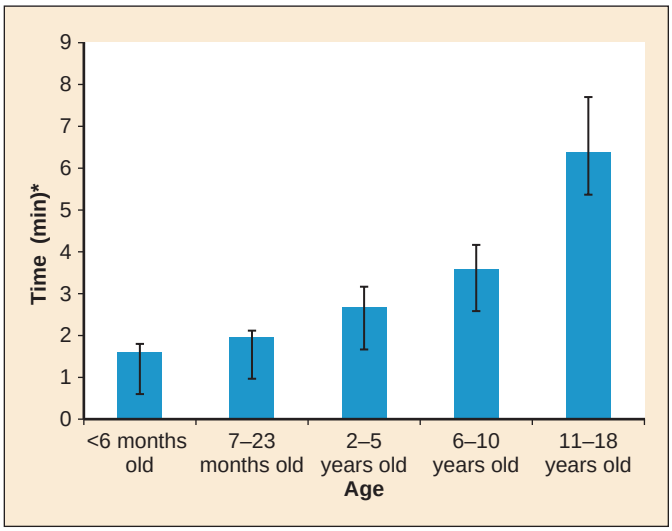

Fig. 161.4. Time to desaturation in preoxygenated healthy children. (American Society of Anesthesiologists Classification 1 [ASA 1] patients undergoing elective surgery.) *Time from administration of neuromuscular blocking agent (NMBA) to desaturation to 90%, with no ongoing supplemental oxygen or respiratory support. (Adapted from Patel R, Lenczyk M, Hannallah RS, et al: Age and the onset of desaturation in apnoeic children. Can J Anaesth 41:771-774, 1994.)

a non-rebreather mask) for 2 to 3 minutes may be sufficient in healthy children. However, patients requiring emergency intubation often have compromised pulmonary function or respiratory effort and may benefit from a more prolonged preoxygen delivery time. A technique of using vital capacity breaths for more rapid preoxygenation will be difficult to accomplish in children who may not be cooperative with this technique. Even with appropriate preoxygenation, a significant percentage of young children will desaturate during intubation attempts, particularly those with underlying respiratory illness or when intubation attempts are prolonged (Fig. 161.4).[10] Due to children's propensity to quickly drop oxygen saturations during intubation attempts, we recommend high flow nasal cannula oxygenation be performed during RSI. As a simplified approach in infants and children, we recommend 5 L/min for infants and 15 L/min for older children to prevent the drop in oxygen saturation during the apneic period of RSI. Positive pressure ventilation with bag-mask device should be considered at the first sign of desaturation, and absolutely initiated when oxygen saturation drops below 95%. Once oxygen saturation has improved, additional attempts can begin.

Positioning

As described earlier, age-appropriate positioning is required during laryngoscopy and endotracheal intubation. Alignment of the oral, pharyngeal, and tracheal axes greatly facilitates visualization. In neonates and infants, a shoulder roll is required, in toddlers and school age children, no roll is necessary; adolescents will often require elevation of the head similar to adults.

Placement of Tube

When performing direct laryngoscopy, straight blades are preferred in infants and younger children in whom the epiglottis is often larger and more likely to fall into the line of sight. In addition, young children may not have a well-developed hyoepiglottic ligament, which will inhibit elevation when a curved blade is placed in the vallecula. In younger children, there is a tendency to insert the laryngoscope blade too deeply, resulting in retroglottic or esophageal placement. With this in mind, emergency clinicians should start the intubation procedure by placing the laryngoscope blade just to the base of the tongue and lift up to view the airway anatomy. Identify structures from the mouth down, first directly identifying the base of the tongue and the epiglottis prior to insertion of the straight blade underneath the epiglottis to visualize the vocal cords. If no laryngeal structures are identified due to deep insertion, the blade should be slowly withdrawn, and the cords or the epiglottis will often fall into view.

Given the superior position of the larynx in children, use of a stylet is often helpful in guiding the ETT into the glottic opening. Given the relatively small size of the oropharyngeal cavity, the tube should be placed from the 3 o'clock position, often with an assistant applying lateral traction to the child's lip to provide more room for tube insertion.

There is a tendency to insert the ETT too far in the very young child in whom the distance from laryngeal cords to tracheal carina may just be a few centimeters. Right mainstem intubation is difficult to appreciate on auscultation, particularly in the infant whose breath sounds may be transmitted throughout the chest. Using a pediatric resuscitation resource as described earlier, or the formula (tube size × 3 = depth [cm] at the lip) can approximate insertion depth. Under direct visualization, the vocal cord markers on the tube should rest just below the glottic opening, or the cuff observed to pass just beyond the vocal cords.

Post-Intubation Management

Optimally, the ETT should be visualized to pass into the glottic opening. If vocal cords are not seen, passage of the tube below the epiglottis and above the posterior cartilages may indicate successful ETT placement but must be confirmed with clinical assessment in conjunction with other confirmatory tests. Visible chest wall rise, auscultation of breaths sounds in both axillae, absence of gurgling noise in the epigastrium (ie, absence of esophageal placement), and improving oxygenation are all used to confirm tube position. However, end-tidal carbon dioxide ($ETCO_2$) detection, either with a colorimetric device or capnography, is the most reliable and accurate measure of correct tube placement.[11]

Pediatric colorimetric $ETCO_2$ detectors are available for children weighing less than 15 kg in whom smaller tidal volumes may result in less apparent detection using adult-sized devices. Detection of $ETCO_2$ confirms the ETT is in the tracheobronchial tree; however, it does not preclude a right mainstem intubation. In patients in cardiac arrest, gas exchange in the lungs is markedly reduced, and CO_2 may not be detectable. Here, an esophageal detector device or bulb may be used to confirm tracheal placement in children who weigh more than 20 kg. Point-of-care ultrasound has been piloted as a real time modality for detecting bilateral lung sliding or diaphragm excursion.[12] However, a chest radiograph is still considered standard of care to confirm appropriate depth. Even small movements of the child's head can result in accidental displacement of the tube. Flexion of the neck advances the tube into a mainstem bronchus, whereas neck extension can lead to unintended extubation.[13] After intubation, the ETT should be secured and, as is possible, the child's head and neck kept still.

Most sedatives used for induction will wear off before rocuronium; therefore post-intubation sedatives should be administered after the airway has been secured. Table 161.3 lists common drugs used for post-intubation sedation in the pediatric population. Decisions regarding continued neuromuscular blockade can be made based on clinical context, including desire for return of clinical examination, ventilation management strategies, need for additional procedures or diagnostics studies, and need for interfacility transfer.

TABLE 161.3

Common Post-Intubation Sedation/Analgesia in Children

Medication	Bolus Dosing	Drip	Comments
Lorazepam	0.1 mg/kg		Long acting sedative/amnesic Often used in combination with analgesic
Midazolam	0.1 mg/kg	0.1 mg/kg/h	Short-acting sedative/amnestic Often used in combination with analgesic
Fentanyl	1 to 2 mcg/kg	1 mcg/kg/h	Short-acting analgesia Preserves hemodynamic stability
Morphine	0.1 to 0.2 mg/kg	0.1 mg/kg/hr	Longer-acting analgesic May cause histamine release
Ketamine		0.1 mg/kg/h	Bolus dosing not recommended for prolonged ongoing sedation May be helpful in status asthmaticus
Propofol		50 to 100 mcg/kg/min	No analgesic properties Prolonged infusion in children can lead to profound acidosis and rhabdomyolysis

Video Laryngoscopy

Video laryngoscopy is emerging as an approach to pediatric airway management. Much as in adults, data support improved laryngeal views with video laryngoscopes, with particular benefit in cases where there is difficulty visualizing the vocal cords or Cormick and Lehane grade 3 or 4 airways. In addition, video laryngoscopy allows for shared viewing by multiple providers, which permits real-time guidance and supervision during tracheal intubation. Currently, data on the use of video laryngoscopy in pediatric patients is limited to the anesthesia literature or performance in simulated scenarios. Although video laryngoscopy improves visualization, procedural performance metrics are not improved with its use.[14] However, video laryngoscopy has been shown to have a faster learning curve than direct laryngoscopy. This may be particularly important for airway management in children, given the infrequency with which pediatric airway management is performed in the ED.[15]

There are a number of video laryngoscopes available for use in pediatrics. Many are smaller adult models, which permit use in older children. Currently, only a few devices are available with a complete range of sizes that allow for use across all pediatric ages, from neonates through to adolescents. There are unique advantages, potential drawbacks, and subtleties in technique for using each (Table 161.4). The decision regarding which device to use is ultimately based on availability, operator preference, operator experience, and patient-specific attributes that may favor a given approach.

Airway Rescue Devices for Children

The overall success rate for advanced airway management in children is more than 99%. Therefore, the need for rescue device use is fortunately rare. Nonetheless, it is imperative to have a contingency plan for circumstances in which a provider cannot secure the airway. In most circumstances, effective BMV will be the mainstay for establishing adequate oxygenation and ventilation until additional personnel and resources are available to reattempt a definitive airway. Alternative strategies to manage the airway when intubation cannot be accomplished using traditional techniques include supraglottic devices (SGDs) or optical approaches to improve glottic visualization.

SGDs have been demonstrated to be a reliable way to establish oxygenation and gas exchange in the normal and difficult pediatric airway, as well as during resuscitation.[16] First generation devices have been used in anesthesia for more than 30 years, whereas second generation devices also include a gastric channel to allow gastric decompression. In addition to the gastric channel, newer versions of SGDs have alternative construction that may be advantageous in pediatrics. For example, the air-Q does not have aperture bars and uses a shorter wider tube to allow passage of an ETT through the lumen.[17] The I-gel uses a thermoplastic elastomer that molds to the airway as it warms from body temperature. This allows a tighter seal and avoids complications related to cuff hyperinflation.

In most cases, SGDs are easily and rapidly placed, with more than 90% success rate on first attempts; devices sized for neonates and young infants are the most difficult to place. Placement technique is similar to adults with two potential differences: (1) some studies have demonstrated improved placement success and fewer complications when using a rotational approach with traditional laryngeal mask airways (LMAs), and (2) insertion of the SGA with the cuff partially inflated may facilitate placement and help it mold to the shape of the pharynx.

Pharyngeal sealers, also called *esophageal blockers,* are double-balloon devices in which the tip is placed into the upper esophagus, and ventilation occurs between one balloon occluding the proximal esophagus and another occluding the airway above the glottis. The two most noted are the Combitube, which is available for use in children greater than 48 inches tall, and the laryngeal tube, which comes in a full range of pediatric sizes. Data regarding use in emergent pediatric airway management are limited. Given the entire spectrum of pediatric sizes and the ease of insertion and use, we recommend the laryngeal tubes for use in children.

A number of pediatric devices beyond video laryngoscopes are available to facilitate visualization and intubation in cases of difficult airways. Flexible fiberoptic scopes can be effective, although extensive experience is required. This approach is most commonly used by anesthesia or otorhinolaryngology, often in the operating room. Similarly, fiberoptic stylets are available in pediatric sizes to facilitate visualization with intubation. As with video laryngoscopes, gaining experience with the technique for a given device prior to use in the stressful scenario of a difficult or failed airway is critical.

Pediatric Surgical Airway Techniques

In the rare case of the "can't intubate, can't ventilate" child, a surgical airway represents the final airway option. This can occur if direct laryngoscopy/video laryngoscopy has failed and the emergency clinician is unable to maintain oxygenation and ventilation

TABLE 161.4

Video Laryngoscopy Devices for Use in Pediatrics

Device	Description	Monitor	Disposable	Recording	Sizes
C-MAC	Traditional Miller and Macintosh shaped blades Allows for direct or indirect (video projection) laryngoscopy	7″ LCD monitor or 2.4″ pocket monitor	Reusable blades or Disposable blades (adult sizes only)	SD card in 7″ monitor	Miller (size 0 and 1) Macintosh (size 2 to 4) D-Blade (pediatric and adult sizes)
GlideScope	Blades with 60-degree angulation Different models GVL, AVL (advanced video technology) AVL Preterm/small child, and ranger (improved portability)	7″ LCD monitor or 3.5″ portable screen	Reusable blades Video batons with single use blades	DVR or USB depending on model	GVL Blades (size 0, 1, 2, 2.5, 3, and 4) Macintosh blades (size 3 and 4)
Airtraq	Optical laryngoscope, no electronics Channeled device (provides guide for ETT to pass around curvature of airway)	Direct view eyepiece or 2.6″ camera hood with wi-fi capabilities	Disposable single use devices Reusable optics with disposable blades available in adult sizes only	Phone adapter or wi-fi camera	Size 0 (infant) Size 1 (pediatric) Size 2 (small) Size 3 (regular)

AVL, Advanced video laryngoscopy; *DVR,* digital video recording; *ETT,* endotracheal tube; *GVL,* GlideScope video laryngoscope; *LCD,* liquid crystal display; *SD,* secure digital; *USB,* universal serial bus.

via BMV or a rescue device, such as a SGD. In this case, direct access to the airway through the neck is the only option. Surgical techniques are challenged by optimal visualization or palpation of anatomical landmarks in infants and young children; therefore, we recommend needle cricothyrotomy in these children.

Experience in surgical airway techniques is limited in small children, with most of the published literature representing case reports, operating room experience, or animal studies. Needle-based rescue procedures should be considered an "oxygenation" strategy rather than a "ventilation" strategy, because progressive hypercarbia will inevitably ensue, limiting the utility of this technique for long-term use. Although human studies are limited, animal models suggest that a needle cricothyroidotomy will provide approximately 30 to 45 minutes of adequate oxygenation.

To perform a needle cricothyroidotomy, the provider places a large needle catheter (eg, 14-gauge) into the cricothyroid membrane. The needle is then removed, and the catheter can either be connected to a commercially available oxygen tubing set-up (eg, ENK modulator, Cook Inc.) with oxygen flow set at 1 L/min for every year of age, or to the adaptor from a 3.0 mm ETT, which is then connected to a standard bag-mask device. This technique is preferred to true "jet" ventilation, which uses a much higher-pressure oxygen source and has a greater potential for iatrogenic injury. Open surgical cricothyrotomy, performed in the same way as in an adult, is reserved for children *for which anatomical landmarks can be found* and in whom the cricothyroid membrane is larger. The literature does not support a specific age cutoff for needle cricothyrotomy versus surgical cricothyrotomy, but needle cricothyrotomy should be performed when indicated in infants and small children (<6 years of age or older depending on anatomical landmarks).

OUTCOMES

The majority of pediatric intubations performed in the ED are successful. Despite the relative rarity of the procedure, there is significant overlap in the techniques and strategies used in adult airway management. There are a limited number of anatomic and physiologic differences that can be learned and mastered. The cognitive burden associated with the procedure can be overcome by length/sized based systems to allow the clinician to focus on the critical actions necessary to successfully manage the airway.

KEY CONCEPTS

- Pediatric airway management is a relatively rare skill to perform in most emergency departments (EDs), and skill maintenance is difficult based solely on clinical practice.
- There are several anatomic differences that impact pediatric airway management, and these occur mostly in the very young child (<2 years old). Small infants have a large occiput and a high, anterior airway, which impacts positioning during intubation. They have a small, underdeveloped cricothyroid membrane, making needle cricothyrotomy the procedure of choice for surgical rescue of the failed airway. They are also more dependent on diaphragmatic excursion for ventilation, thus gastric insufflation can result in difficulty with providing rescue ventilation.
- Children are prone to desaturation due to their high metabolic rate and small functional residual capacity, making preoxygenation and maintenance of oxygenation during intubation crucial.
- The cognitive burden inherent in dealing with the large age/size spectrum in pediatrics can be overcome with reference aids that organize equipment selection and drug dosing based on length/age/size. Formulas have been developed to aid in selection of the correct endotracheal tube (ETT) size and determine appropriate depth of ETT

Continued

KEY CONCEPTS—cont'd

insertion. For estimation of uncuffed tube sizes in children older than 1 year old: ETT size = 4 + (age in years/4). Subtract 0.5 in size for cuffed tubes. To estimate the depth of ETT insertion (the so-called "lip to tip" distance), multiply the ETT size × 3 (eg, a 5.0 ETT would be inserted to 15 cm at the lip).

- Rapid sequence intubation (RSI) is the preferred method of airway management in the vast majority of pediatric cases in the ED.
- Compared to adults, children are more prone to desaturation over the time it takes for a neuromuscular blocking agent (NMBA) to take effect. Use of high-flow nasal cannula during the apneic period of RSI has not been well studied in children, but we recommend its use at 5 L/min for infants and 15 L/min for children and adolescents. Assisted ventilation (coordinated with the child's respiratory efforts) should only be used if oxygen saturation drops below 95%.
- Video laryngoscopy is an evolving technology for use in pediatrics and assists in visualization of the airway but prolongs time to intubation.
- Surgical airway techniques differ in infants and young children, necessitating a needle technique that is different from the older child or adult. This technique provides a mechanism to oxygenate the "can't intubate, can't ventilate" child, but should not be relied on as a definitive airway.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 161: QUESTIONS & ANSWERS

161.1. Which of the following is a correct formula?
- **A.** Cuffed ETT size (1 to 10 years old) = 4 + (age in years/2)
- **B.** ETT depth = 3 × ETT size
- **C.** ETT depth = 4 × ETT size
- **D.** Uncuffed ETT size (1 to 10 years old) = (16/age in years) + 4

Answer: B. Correct formulas are as follows:

Uncuffed ETT size = 4 + (age in years/4)
Uncuffed ETT size = 3.5 + (age in years/4) (or subtract 0.5 from the formula for uncuffed tubes)
ETT depth = 3 × uncuffed tube size

161.2. Which of the following should be used for proper positioning of the pediatric patient during endotracheal intubation?
- **A.** The chin should be tilted and the head lifted.
- **B.** The infant younger than 6 months old should have a towel role placed under his occiput to align the airway axes.
- **C.** The neck should be placed in slight flexion and the shoulders extended.
- **D.** The patient should be positioned so that a line drawn through the external auditory canal and the anterior shoulder is parallel to the bed.

Answer: D. The relatively large head and occiput of the infant results in slight flexion at the neck when supine, impeding the ability to visualize the glottis. The infant is correctly positioned so that a line drawn through the external auditory canal and the anterior shoulder is horizontal and parallel to the bed. In the infant (<6 months old), this is accomplished by placing a towel roll under the patients shoulders, elevating the body and overcoming the flexion associated with their large occiput. A head tilt-chin lift may open the airway.

161.3. Relative to rapid sequence intubation (RSI) in adults, children undergoing RSI:
- **A.** Are less affected by stomach pressures
- **B.** Are more likely to develop bradycardia in response to hypoxia
- **C.** Have less missed intubations
- **D.** Have less pliable airways
- **E.** Maintain their oxygen saturations longer after paralytics are administered

Answer: B. Children have a higher metabolic rate and thus a higher oxygen demand. In the absence of respiratory support, children will drop their oxygen saturations more quickly than adults due to their relatively greater consumption of oxygen. The more pliable pediatric thorax combined with children's lower ventilatory reserve make stomach inflation a significant impediment to effective respiratory support. Pediatric intubations are infrequent and multiple pediatric intubation attempts are more common in children than in adults.

161.4. Which of the following does *not* characterize the pediatric airway relative to adults?
- **A.** A straight blade is used to pick up the floppy epiglottis.
- **B.** Infants may require a shoulder roll to align airway axes.
- **C.** The airway is more pliable.
- **D.** The airway is more superior and posterior.
- **E.** The epiglottis is larger and omega-shaped.

Answer: D. Small infants have a large occiput and a high, anterior airway, which impacts positioning during intubation, often requiring a shoulder roll to align airway axes. The airway is also more pliable and the membranes thinner, necessitating needle cricothyroidotomy for surgical airways in children younger than 10 years old. Blade choice is age-dependent, and a straight blade is recommended in young children; this blade lifts the relatively larger epiglottis to visualize the vocal cords.

161.5. Following the administration of succinylcholine in a 7-year-old boy with respiratory distress, severe masseter spasm is noted. Which of the following medications should be administered to terminate this spasm?
- **A.** Diazepam
- **B.** Fentanyl
- **C.** Repeated dose of succinylcholine
- **D.** Rocuronium
- **E.** Thiopental

Answer: D. Masseter muscle spasm is a rare side effect of succinylcholine administration. It primarily occurs in pediatric patients and is typically terminated by the administration of a competitive neuromuscular blocking agent (NMBA), such as rocuronium, vecuronium, or pancuronium. Failure to respond to such therapy should prompt consideration of malignant hyperthermia.

CHAPTER 162

Procedural Sedation and Analgesia for the Pediatric Patient

Sharon E. Mace

SEDATION

PRINCIPLES

Sedation is a controlled reduction of environmental awareness. Sedation is a continuum that begins with minimal, next moderate, then deep sedation and proceeds to general anesthesia.

Definitions

- *Anxiolysis* is a state of decreased apprehension concerning a particular situation in which the patient's level of awareness does not change.
- *Analgesia* refers to the relief of pain without the intentional alteration of mental status, such as occurs in sedation. An altered mental state may be a secondary effect of the medications administered for this purpose.
- *Dissociation* is a trancelike cataleptic state induced by an agent such as ketamine and characterized by a profound analgesia and amnesia. Protective reflexes, spontaneous respirations, and cardiopulmonary stability are retained.
- *Minimal sedation* (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive functions and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
- *Moderate sedation/analgesia* (formerly called "conscious sedation") refers to a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. Reflex withdrawal from the painful stimulus is not considered a purposeful response. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is always maintained.
- *Dissociative sedation* is a trancelike cataleptic state induced by the dissociative agent ketamine and characterized by profound analgesia and amnesia, while protective airway reflexes, spontaneous respirations, and cardiopulmonary stability are maintained.
- *Deep sedation/analgesia* describes a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
- *General anesthesia* is a drug-induced loss of consciousness during which patients are not arousable, even with painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.
- *Procedural sedation and analgesia (PSA)* is a technique of administering a sedative or dissociative agent, usually along with an analgesic, to induce a state that allows the patient to tolerate unpleasant procedures while maintaining adequate spontaneous cardiorespiratory function. It is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently and continuously.

The goal of PSA is to alleviate the anxiety, pain, and suffering associated with medical procedures. PSA is an essential part of emergency medicine practice and part of the core curriculum for emergency medicine training programs. Providers should be prepared to intubate if sedation becomes deeper than expected. In the event the patient requires ventilatory support during PSA, providers should determine the patient's American Society of Anesthesiology (ASA) physical status classification (Table 162.1) and Mallampati score (see Chapter 1) to identify potential difficulties.

At least one provider, usually a nurse, should be available to document and monitor the patient.[1] Depth of sedation, heart rate, blood pressure, pulse oximetry, and capnography readings should be recorded at regular intervals. Although there are scales for assessing the depth of sedation in pediatric patients, continuous monitoring is more important than any specific measurement on a sedation scale. We recommend continuous cardiac rhythm monitoring, especially for high-risk patients (eg, preexisting cardiovascular disease or a history of dysrhythmias) or high-risk procedures (eg, cardioversion) because it has been useful in those with a cardiac history and older patients; although there is no evidence of benefit in young healthy individuals.

Providers administering procedural sedation should have training and skills in airway management. In addition to monitoring equipment and oxygen, age-appropriate suction, bag-valve-mask, and intubating equipment should be available and readied prior to administering medications. The SOAP-ME mnemonic provides an equipment checklist for pediatric sedation[2]:

Size-appropriate suction catheters
Oxygen supply
Airway: Size-appropriate airway equipment
Pharmacy: Advanced life support medications and antagonists
Monitors: Size-appropriate oximeter
Equipment or drugs for a particular case

Once the procedure is complete and the painful stimuli are removed, patients are at risk of hypoventilation or hypoxia. Monitoring should continue until the patient has met predetermined discharge criteria, which should include normal vital signs and baseline mental and physical status. Once fully awake, patients

TABLE 162.1

American Society of Anesthesiologists Physical Status Classification

CLASS	DESCRIPTION	EXAMPLES	SEDATION RISK
I	Normal and healthy patient	No past medical history	Minimal
II	Mild systemic disease without functional limitations	Mild asthma, controlled diabetes	Low
III	Severe systemic disease with functional limitations	Pneumonia, poorly controlled seizure disorder	Intermediate
IV	Severe systemic disease that is a constant threat to life	Advanced cardiac disease, renal failure, sepsis	High
V	Moribund patient who may not survive without procedure	Septic shock, severe trauma	Extremely high

should be discharged to the care of a responsible adult. Patients should receive predeveloped age-appropriate PSA discharge instructions.

MANAGEMENT

Table 162.2 details specific PSA sedative agents commonly used in infants and children. Patient age, preexisting conditions, and anticipated level of pain or anxiety should guide choice of sedative. Providers should administer drugs by slow intravenous (IV) titration to decrease the risk of adverse events, including hypotension and respiratory depression.

Preprocedural Fasting

The ASA has guidelines for preoperative fasting in healthy patients of all ages undergoing elective procedures. In patients undergoing PSA in the emergency department (ED), the evidence indicates that preprocedural fasting does not decrease the risk of emesis or aspiration as noted in the American College of Emergency Physicians (ACEP) clinical policy.[1] Therefore, adherence to the ASA preoperative fasting guidelines for procedures is not necessary in ED patients undergoing PSA.

Supplemental Oxygen and Capnography During PSA

Although supplemental oxygen does prevent hypoxemia in some patients, it may delay the recognition of hypoventilation or apnea and, therefore, should be available but not placed routinely. Hypoventilation, however, should be detected prior to any drop in pulse oximetry, irrespective of use of supplemental oxygen. We are in agreement with recent ACEP clinical policy recommendations that capnography should be routinely used to monitor ventilation in children undergoing PSA.[1,2]

Monitoring

Bispectral monitoring is a technology used during anesthesia that takes several electroencephalographic parameters and calculates a number from 0 to 100, which gives an indication of a patient's depth of anesthesia, with a bispectral index (BIS) between 40 to 60 appropriate for general anesthesia. The BIS does not correlate with the level of consciousness per se, but rather the effect of the drug on the cerebral cortex. The BIS is unreliable in infants with immature electroencephalogram (EEG) patterns, because the BIS was developed using adult EEG patterns. Although bispectral monitoring has been shown useful for monitoring the level of awareness in patients undergoing general anesthesia, its usefulness is yet unproven for differentiating levels of sedation (mild, moderate, or deep) during ED PSA.[3]

Specific Medications

Propofol

Propofol has several advantages for PSA; it has a rapid onset, is short acting, and has antiemetic properties. Its side effects include hypotension and respiratory depression, leading some to recommend limiting its use to the operating room. However, a large, prospective multicenter observational study found that propofol can be used safely and effectively in settings outside of the operating room, including the ED.[4] Although the dosing of propofol varies from 0.5 to 1.5 or even up to 2 mg/kg, an initial dose of 0.5 to 1.0 mg/kg should be administered and titrated to effect with additional doses, usually in increments of 0.5 mg/kg.

Ketamine

Ketamine, a dissociative anesthetic, has sedative, amnestic, and analgesic properties. Ketamine maintains cardiovascular and respiratory stability, has minimal respiratory depression, and maintains protective airway reflexes in patients with spontaneous respirations. Ketamine's sympathomimetic effects include increased blood pressure, heart rate, cardiac output, myocardial oxygen consumption, and bronchodilation, making it the preferred sedative in patients with severe asthma exacerbations.

Apnea is rare with ketamine (0.8% incidence), but has been associated with very high doses, rapid administration, and co-administration with respiratory depressants. Laryngospasm is also rare (0.3% incidence) and has been associated with high doses of the drug.[5] Laryngospasm is usually transient and responds to repositioning of the head, supplemental oxygen administration, and positive pressure ventilation with a bag-valve mask. Although rarely needed, the use of a paralytic at lower doses than required for intubation (eg, succinylcholine given at 10% of a paralytic dose) has been shown to break laryngospasm when the above measures fail. Rapid sequence intubation is rarely needed, but a last resort option to treat laryngospasm.

Ketamine may be given intravenously, intramuscularly, or *per os* (by mouth) (PO). For IV administration in pediatric patients, initial doses range from 1.0 to 2.0 mg/kg, with further bolus doses of 0.5 to 1 mg/kg titrated to desired effect. Intramuscular (IM) dosing is an option when IV access is unobtainable; dosing ranges from 4 to 5 mg/kg. The disadvantages of IM ketamine include a higher rate of vomiting, longer recovery time, and lack of IV access in the event of complications requiring IV medication administration (eg, paralytics). Ketamine can be given PO at a dose of 5–7 mg/kg, although PO is associated with an increased incidence of side effects, less predictable effect, and longer duration (up to 1 hour).

Use of Ketamine in Head Injury Patients. Studies from the 1970s on use of ketamine for rapid sequence intubation in surgical and neurologic patients, many of which had cerebrospinal fluid outlet obstruction, suggested that ketamine can increase intracranial pressure (ICP). However, since then, multiple studies have dispelled this association. A meta-analysis of randomized clinical trials found that ketamine does not increase ICP and therefore it can be used in patients with head trauma.[6]

TABLE 162.2

Commonly Used Sedatives for Procedural Sedation in Children and Infants

SEDATIVE[c]	ROUTE	DOSE[a]	USUAL DOSE[b]	MAXIMUM DOSE	ONSET	DURATION	SIDE EFFECTS	ADVANTAGES/COMMENTS[c]
Etomidate	IV	0.3 mg/kg	0.2 mg/kg PSA (0.3 mg/kg RSI)	0.6 mg/kg	<1 minute	3 to 10 minutes	Pain on injection, myoclonic movements, adrenal insufficiency (prolonged use)	Minimal CV/respiratory depression
Ketamine[d]	IV	1 to 2 mg/kg initial (repeat 0.5 to 1 mg/kg for longer procedures)	1.5 mg/kg initial PSA (2 mg/kg RSI)		1 minute	15 minutes	Sympathomimetic effects (↑HR, ↑BP) Nausea, vomiting Emergence reaction Laryngospasm (rare)	Also has analgesic effect CV/respiratory stability bronchodilator (use in asthmatics) Battlefield use/disasters
Ketamine	IM	4 mg/kg	4 mg/kg 2 mg/kg if <2 years old		5 minutes	30 minutes	(Same as above) Higher risk of nausea	(Same as above)
Midazolam[e]	IV	0.05 to 0.1 mg/kg (6 months to 5 years old or adult) 0.025 to 0.05 mg/kg (≥ 6 years old) If midazolam alone, 0.05 mg/kg IV unless at-risk patient	If giving with fentanyl, may dose at 0.02 mg/kg	6 mg/kg if ≤5 years old 10 mg/kg if >6 years old or adult	3 minutes	60 minutes	Paradoxical agitation, vomiting, coughing, hiccups, respiratory depression, apnea so use lower dose if given with other opioids or respiratory depressants, reversed by antagonist flumazenil	↑ Seizure threshold (used to treat seizure patients) ↓ ICP, CBF, ↓ LV filling pressure may benefit cardiac patients Mild CV effects unless hypovolemic Use in CAD patients
Midazolam	IM	0.05 to 0.1 mg/kg (6 months to 5 years old) 0.025 to 0.05 mg/kg (≥6 years old)	If giving with fentanyl, may dose at 0.02 mg/kg	6 mg/kg if ≤5 years old 10 mg/kg if >6 years old or adult	5 to 30 minutes	60 to 90 minutes	(Same as above)	(Same as above)
Midazolam	IN	0.3 to 0.5 mg/kg			3 to 5 minutes		(Same as above)	(Same as above)
Methohexital[f]	IV	1 to 3 mg/kg	1 to 1.5 mg/kg	3 mg/kg	1 minute	10 minutes	CV/respiratory depression, paradoxical agitation, extravasation can cause tissue necrosis Contraindication: Porphyria	↓ IOP, ↓ ICP (but don't use if patient has temporal lobe epilepsy) Use in head injury patients Can use if malignant hyperthermia

Continued

TABLE 162.2

Commonly Used Sedatives for Procedural Sedation in Children and Infants—cont'd

SEDATIVE[c]	ROUTE	DOSE[a]	USUAL DOSE[b]	MAXIMUM DOSE	ONSET	DURATION	SIDE EFFECTS	ADVANTAGES/COMMENTS[c]
Pentobarbital[g]	IV	1 to 6 mg/kg	2 mg/kg initial, titrate in increments of 1 to 2 mg/kg	6 or 200 mg/kg	5 minutes	15 to 60 minutes	CV/respiratory depression, paradoxical agitation, extravasation can cause tissue necrosis Contraindication: Porphyria	↓ IOP, ↓ ICP , used to treat status epilepticus Use in head injury/neurology patients Can use if malignant hyperthermia
Propofol	IV	0.5 to 1.5 mg/kg (repeat 0.5 mg/kg every 3 to 5 minutes for longer procedures)	Variable, may be 1.5 to 2 mg/kg	None	<1 minute	5 to 15 minutes (mean 8 minutes)	CV/respiratory depression Use with caution if shock/low BP/impaired cardiac function Don't use if allergy to eggs, soybean oil, EDTA	Rapid onset/recovery No dose change if renal or liver disease Can use if malignant hyperthermia
Nitrous oxide	Inhalation	Dose is 30% to 70% mixture	Commercially available in 50%:50% mixture	70%	1 to 2 minutes	15 to 20 minutes	Contraindications: Trapped air (bowel obstruction, pneumothorax, emphysema, air emboli)	Need a scavenger system and proper ventilation, potential for abuse, chronic exposure may have adverse effects

[a]Doses will vary with the individual patient; these are some generally recommended starting doses. Some patients will need greater than the typical maximum dose, whereas others may be sedated with less than the usual dose. So it is best to titrate the dose in all patients.
[b]Be especially cautious in at-risk patients. At-risk patients include those patients with significant heart disease, including heart failure or pulmonary hypertension, liver disease, renal failure, and patients at the extremes of age (infants, particularly neonates and the geriatric patient). It may be prudent in these patients, to "start low and go slow."
[c]Other agents used for sedation, eg, DPT (meperidine [Demerol], promethazine [Phenergan], and chlorpromazine [Thorazine]) IM should be avoided because there are better, newer agents for sedation with fewer side effects. Chloral hydrate has been used in the past but is used infrequently at present because there are other better options.
[d]Ketamine's effect on ICP is discussed in the text. Previously ketamine was thought to be contraindicated if there was an increase in ICP. However, recently, this concept has been challenged. If ketamine is given PO or PR, higher doses are needed with less predictable effect and increased side effects so PO and PR routes are not recommended.
[e]Midazolam may be given by several routes including IV, IM, IN, PO, and PR. The PO and especially PR routes of administration have more variable absorption and effects, so they are not commonly used.
[f]Methohexital can be given IM and PR with longer onset and duration and more variable effect, so these routes of administration are less commonly used.
[g]Pentobarbital can be given PO or PR or IM, but onset and duration are longer with more variable effect; so IV is preferred
BP, Blood pressure; *CAD,* coronary artery disease; *CBF,* cerebral blood flow; *CV,* cardiovascular; *EDTA,* ethylenediaminetetraacetic acid; *HR,* heart rate; *ICP,* intracerebral pressure; *IM,* intramuscular; *IN,* intranasal; *IOP,* intraocular pressure; *IV,* intravenous; *LV,* left ventricular; *PO, per os* (by mouth); *PR,* per rectum; *PSA,* procedural sedation and analgesia; *RSI,* rapid sequence intubation.

Recovery Agitation: Use of Benzodiazepines. Emergence reaction or recovery agitation refers to agitation (which may include hallucinations or delirium) that can occur after waking up or emerging from ketamine. In a large meta-analysis of pediatric ketamine sedations, the incidence of any recovery agitation was 7.4% and clinically important recovery agitation was 1.4% and was not significantly associated with age.[7] Emergence reactions occur more frequently in adolescents, adults, females, and individuals with psychiatric disorders, and can be treated with midazolam (0.03 mg/kg) up to a maximum of 6 mg for ages 6 months to 5 years old, 10 mg for children 6 years old and older and adults.[7,8]

The routine use of midazolam in adult patients receiving IV or IM ketamine was recently found to decrease the absolute risk of emergence reactions by 17%, with a number needed to treat of 6.[8] However, pediatric studies have not demonstrated the benefits with its routine use, likely due to midazolam's own adverse effects; although rare, midazolam can itself cause paradoxical agitation. As no pediatric studies to date have shown benefit, we do not recommend that midazolam be routinely given as an adjunct to ketamine in children. Providers should consider an alternate agent or ketamine plus midazolam for older teens and children with psychiatric illness.

Use of Anticholinergics. Ketamine stimulates tracheobronchial and salivary secretions. Except in young infants (eg, age younger than 3 months old due to age-related differences in airway anatomy/reactivity and laryngeal excitability) routine use of anticholinergics is probably not necessary. Providers may consider anticholinergics for children undergoing an airway examination (eg, fiberoptic laryngoscopy) to improve visibility, or in patients with clinically significant hypersalivation or an impaired ability to mobilize secretions.

Glycopyrrolate is the preferred anticholinergic over atropine; it is a more potent anti-sialagogue and has fewer tachydysrhythmias. Unlike atropine, glycopyrrolate does not cross the blood brain barrier, so has no central nervous system (CNS) side effects. CNS side effects of atropine range from drowsiness and coma and include headache, nervousness, insomnia, excitement, dizziness, disorientation, hallucinations, and ataxia. Headache is the only CNS side effect listed for glycopyrrolate.

Use of Antiemetics. The incidence of any vomiting with ketamine sedation is 8.4%.[7] It usually develops during recovery when patients are alert and can clear their airways. Risk is higher among adolescents and patients receiving high doses or IM administration. Although ondansetron is associated with a small decrease in the incidence of vomiting associated with ketamine sedation in children, ondansetron is associated with other adverse effects, including QT prolongation and serotonin syndrome. We recommend reserving treatment with ondansetron for patients who develop nausea and vomiting during recovery from ketamine.

Ketofol: Ketamine Plus Propofol

The combination of ketamine with propofol has the potential to provide benefits of both sedatives. The combination allows for lower doses of each medication, which may theoretically minimize adverse effects of either sedative alone. For example, the cardiorespiratory stimulatory effects of ketamine could offset the dose-related respiratory depression and hypotension from propofol. However, ketofol has not been shown to have fewer airway complications or incidences of respiratory depression than either sedative alone.[9,10]

Ketamine and propofol (ketofol) can be dosed at 0.50 mg/kg to 0.75 mg/kg for each drug. Ketofol can be administered via a 1:1 single–syringe mixture of 10 mg/mL of ketamine and 10 mg/mL of propofol (eg, 2 mL for a 20 kg child is equivalent to 0.50 mg/kg of each drug). For short procedures, re-dosing is usually not needed. For longer procedures, if the sedation is wearing off, then propofol is usually redosed (at a dose of 0.1 to 0.5 mg/kg IV) because of its shorter half-life.

OUTCOMES

Adequately treating the anxiety and pain that can occur with medical procedures results in greater procedural success rates, improved patient and caregiver satisfaction, decreased likelihood of the patient developing chronic pain, and improved patient outcomes. Patients at increased risk of adverse events during PSA include the following: the very young or very old, those with comorbidities (eg, cardiopulmonary diseases) or craniofacial abnormalities (eg, Down syndrome and Pierre Robin syndrome), the morbidly obese, and those with a higher ASA physical status classification (see Table 162.1).

PAIN MANAGEMENT

PRINCIPLES

Pain is defined as an unpleasant visceral or somatic experience or sensation associated with actual, potential, or perceived tissue damage. Pain receptors, termed *nociceptors,* are the free nerve endings of a sensory neuron that convert mechanical, thermal, or chemical stimuli into electrical activity, and initiates an impulse that travels along the neuron and then on to the dorsal horn of the spinal cord (Fig. 162.1). Input from various peripheral nerves and additional sensory stimuli are processed, undergoing integration and modulation in the dorsal horn of the spinal cord, and then transmitted up the spinal cord to the CNS (Fig. 162.2).

There are two types of pain: nociceptive or neuropathic. Nociceptive pain occurs when tissue injury or inflammation stimulates intact pain receptors. Nociceptive pain can be further divided into visceral pain (ie, of internal organs) and somatic pain (ie, of the skin, soft tissue, and musculoskeletal structures). Neuropathic pain occurs when there is abnormal functioning or stimulation of damaged sensory nerves. Children with severe developmental impairment may have central neuropathic pain or pain secondary to visceral hyperalgesia.

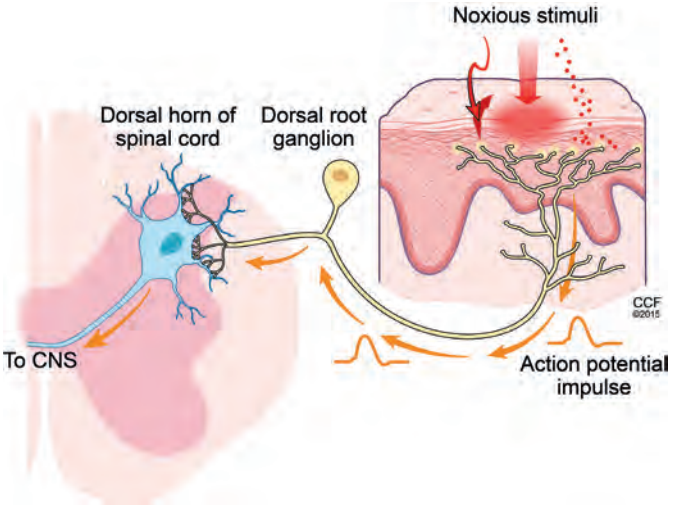

Fig. 162.1. Nociceptors. *CNS,* Central nervous system. (Figure illustration by Department of Medical Art and Photography—Cleveland Clinic and Mr. Dave Schumick with permission.)

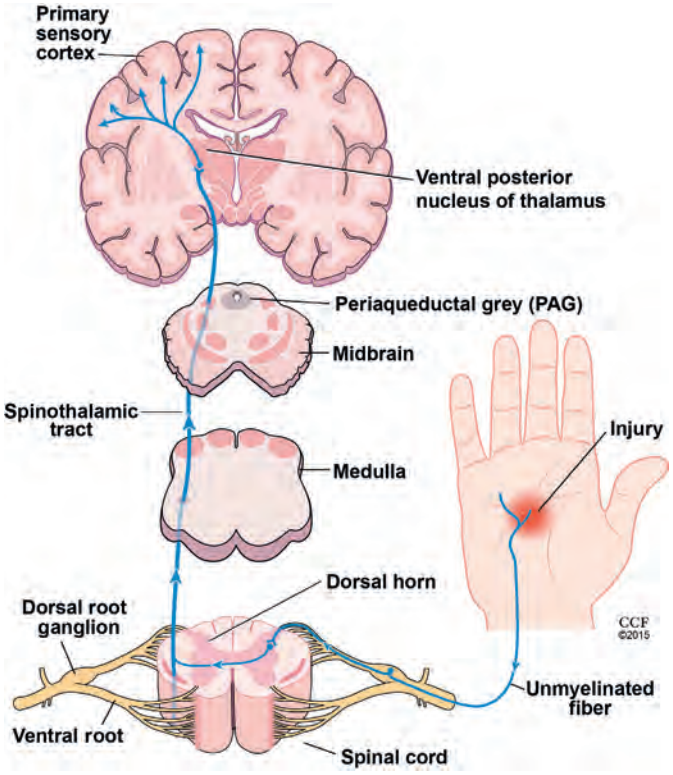

Fig. 162.2. Pain pathway. (Figure illustration by Department of Medical Art and Photography—Cleveland Clinic and Mr. Dave Schumick with permission.)

Neuropathic pain is typically burning, searing, tingling, shooting, or electric in quality. Nociceptive somatic pain is generally described as sharp and well localized. However, pain in deeper structures (eg, bones, joints, or tendons) can cause achy, diffuse, or radiating pain. Nociceptive visceral pain is typically poorly localized, deep, and aching. Chronic pain is a maladaptive response in which the pain persists after the original injury or illness has resolved.

MANAGEMENT

Pain Assessment

Patient self-report is the most accurate measure of pain severity. Pain assessments can be used to guide pain management. Pain scales should be age-specific; subjective or self-reporting scales can start being used at 3 years of age, depending on developmental level. Children younger than 3 years old do not have the cognitive or verbal skills needed to communicate levels of pain and, thus, require behavioral or psychological pain scales. Behavioral pain scales rely on the observation of specific child or infant behaviors. Some of the parameters used in behavioral pain scales include facial expressions, consolability, interaction level, limb responses, trunk motor responses, and verbal responses. Behavioral and physiologic pain scales combine behavioral observations and physiologic parameters (eg, vital signs) to obtain a score.

The numeric rating scale (NRS) and the visual analogue scale (VAS) are commonly used self-report scales that have been found to have reliability and validity. With the VAS, patients are asked to place a mark on a 10-cm line with descriptors along the line. With the NRS, patients are asked to rate their pain severity on a scale from 0 to 10 or 0 to 100, with 0 = no pain and 10 or 100 = worst pain possible. Horizontal lines are preferred rather than vertical lines because scores are more normally distributed. Patients with poor hand-eye coordination and visual acuity or hand dexterity, such as the cognitively impaired or geriatric patients, have difficulty completing the VAS (19% to 25% of the elderly fail to use the VAS correctly). Thus, the NRS is more commonly used and is preferred over the VAS.

As noted, the use of pain scales is based on age. Adolescents and adults can rate their pain using a NRS or VAS. Older children (8 to 11 years old) can also use a NRS or VAS. Younger children (3 to 8 years old) can quantify their pain using a faces pain scale, most commonly the Wong-Baker Faces Pain Scale in the United States and the Faces Pain Scale–Revised internationally. The Premature Infant Pain Scale (PIPP) is used to assess pain in premature infants. The Crying, Requires oxygen, Increased vital signs, Expressions, and Sleeplessness (CRIES) Scale is for infants. The Faces, Legs, Activity, Cry, Consolability (FLACC) Pain Scale can be used for infants and toddlers. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and the Observational Scale of Behavioral Distress (OSBD) may be used for toddlers and young children.

Nonverbal children with neurological impairment, irrespective of age, cannot self-report their pain. The child's caregiver generally knows his or her typical behavior patterns, both at baseline and in response to stimuli or needs. Behaviors that may indicate pain include facial expressions (eg, grimacing), vocalizations (crying or moaning), inconsolability, increased movement, increased tone or posture (eg, stiffening or arching), and uncharacteristic or atypical behaviors (eg, withdrawal, lack of expression, or even laughing). The revised FLACC (r-FLACC) scale is one pain scale designed for use in children with cognitive impairment.

Nonpharmacologic Techniques

Nonpharmacologic interventions should be used with pharmacologic therapy for pain management. Hypnosis is accepted by the American Medical Association as a medical therapy and has been used to treat anxiety, as well as acute and chronic pain. Children may be more easily hypnotized compared to adults. Studies indicate that hypnosis is efficacious in pediatric patients for painful medical procedures, headaches, sickle cell disease, chronic pain, and even in cancer treatment. Acupuncture and acupressure has been used as a nonpharmacologic method for pain management in non-ED settings.

Techniques that distract from pain should be culturally sensitive and may be low-tech or high-tech. Low-tech distractions include telling stories, reading a book, and playing cards or games. Kaleidoscopes have been successfully used as a distraction in children and adults to decrease the pain of phlebotomy. High-tech distractions involve more expensive electronic equipment, such as handheld computer games or virtual reality. Preliminary research suggests that the high-tech virtual reality that uses multiple sensory inputs may be effective in decreasing pain.

Educated in human growth, development, and psychology, child life specialists are invaluable team members of any pediatric ED. Child life specialists help children effectively cope with illness or injury through play, preparation, and education.[11] A study of children undergoing suturing in the ED found that having a child life specialist use low-tech distractions resulted in fewer fears than in the control group with no distractions.

Perhaps one of the most important and common nonpharmacologic methods for limiting the anxiety and pain of the child or infant is parental presence during the procedure. Techniques used in infants include nonnutritive sucking, breast feeding, skin-to-skin contact (kangaroo care), and sucrose. The use of sucrose water administered by pacifier or oral syringe been shown to effectively decrease pain in infants 3 months old and younger undergoing painful procedures.

Topical Anesthetics

Used in conjunction with other methods for decreasing pain, topical anesthetics may decrease the need for systemic analgesics or local anesthesia. Topical anesthetics can be used for venipuncture, IV cannulation, minor surgical procedures, wound care, suturing, and lumbar puncture. Topical anesthetics are painless to apply and do not distort tissue (eg, for cosmetically important facial lacerations). Needleless, they also avoid the risk of needle sticks.

Different topical anesthetics can be used on intact skin or broken skin (Table 162.3), as well as mucosal surfaces. Vasoconstrictors, such as epinephrine, increase anesthetic efficacy and duration of effect, but generally should not be used where there at an end-arteriolar blood supply (eg, fingertip). Common formulations used for intact skin (eg, prior to venipuncture), are eutectic mixture of local anesthetics (EMLA), liposome encapsulated lidocaine (LMX), and vapo-coolants. Lidocaine, epinephrine, and tetracaine (LET) and tetracaine, adrenaline (epinephrine), and cocaine (TAC) can be used for open wounds. Due to the potential for cocaine toxicity, we recommend using other topical anesthetics instead of TAC. EMLA has been associated with methemoglobinemia, seizures, and respiratory depression with excessive skin application. Methemoglobinemia is associated with the prilocaine component of EMLA and is more likely to occur in patients with glucose-6-phosphate dehydrogenase (G6PD) and those on methemoglobinemia-inducing medications.

The use of topical anesthetic agents (eg, lidocaine and benzocaine) on mucosal surfaces for teething pain or stomatitis has been associated with serious adverse events, including seizures, respiratory depression, cardiovascular toxicity, and death. This has led to a recent black box warning for viscous lidocaine, and the U.S. Food and Drug Administration (FDA) recommendation against using over-the-counter (OTC) topical anesthetics for teething pain. We recommend not using topical anesthetics on mucosal surfaces in infants and young children. For teething pain, use a chilled (not frozen) teething ring or have the caregiver gently massage the gums with a finger. Children with stomatitis can be treated with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs).

The topical vapo-coolants or refrigerant anesthetic sprays have similar uses to topical anesthetics (Table 162.4). Two commonly used vapo-coolants are ethyl chloride, which is flammable, and 1,1,1,3,3 pentafluoropropane/1,1,1,2 tetrafluoroethane, which is nonflammable and ozone friendly. To be effective, application should include correct distance 3 to 7 inches from the skin site, a steady spray covering the specific area (about as large as a quarter for a venipuncture or IV cannulation) and adequate spray time for 4 to 10 seconds or the skin begins to turn white, whichever comes first. Vapo-coolants have also been used to alleviate myofascial pain, muscle pain, and the musculoskeletal injury pain. Vapo-coolants have immediate onset. Although the anesthetic effect subsides within a minute, it can be reapplied.[12]

The J tip is a needleless jet injector that uses pressurized gas for the delivery of local anesthetic. J tip lidocaine delivery has been found effective in decreasing the pain of peripheral IV catheter insertion. In one study of pediatric ED patients, jet delivered lidocaine was no more effective in reducing pain than jet delivered normal saline; however, both were better than no pretreatment.[13] Devices used for injection of local anesthetics are often associated with minor local skin side effects (such as, erythema or bruising) and may produce an audible "pop" when used, which could frighten a young child. One study in pediatric patients found that a cold vibration device placed proximal to the venipuncture site decreased the pain of venipuncture when compared to standard care, which included the use of 4% liposomal lidocaine and vapocoolant.[14]

Local Anesthetics

Local anesthetics reversibly block sodium channels, which inhibits the propagation of nerve impulses (Fig. 162.3). Local anesthetics fall into one of two classes: amides and esters. Amides can be remembered as the prefix before the ending "caine" will have the letter "I" (eg, lidocaine and bupivacaine). Local anesthetics are also classified by duration of action. Local anesthetics that are tightly protein bound to a receptor in the sodium channel (eg, bupivacaine and tetracaine) have a longer duration of action than less tightly bound anesthetics (eg, procaine and prilocaine). Greater concentrations of the local anesthetic will also increase the duration of action.

Potency refers to the degree to which the individual local anesthetic blocks transmission in the neural tissue (Fig. 162.4). The nerve cell membrane consists of a lipoprotein matrix, so local anesthetics that are more lipid soluble (eg, tetracaine) are more potent than less lipid soluble local anesthetics (eg, procaine and prilocaine). Local anesthetics with low lipid solubility must be given in higher concentrations and higher doses to achieve the same efficacy.

When added to a local anesthetic, epinephrine lengthens the duration of the anesthesia, slows systemic absorption, and aids in controlling local bleeding. Clonidine added to a local anesthetic solution (10 μg = 0.1 mL clonidine added to 0.5 mL lidocaine 0.5%) has also been used to increase the duration of anesthesia. Although the risk is currently being questioned, epinephrine-containing local anesthetics should generally be avoided in

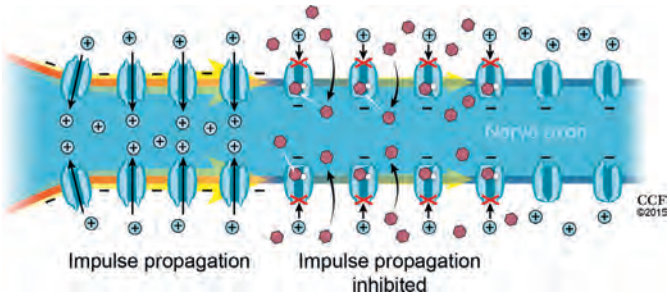

Fig. 162.3. Local anesthetics mechanism of action. Local anesthetics reversibly block sodium channels. (Figure illustration by Department of Medical Art and Photography—Cleveland Clinic and Mr. Dave Schumick with permission.)

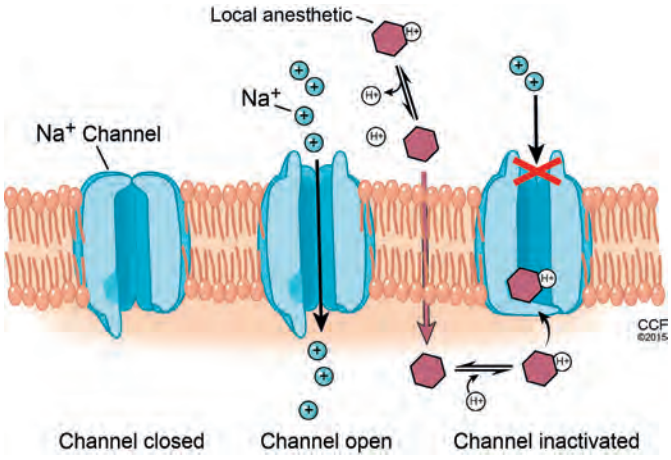

Fig. 162.4. Local anesthetics mechanism of action. Local anesthetics blocks transmission of nerve impulse by binding to the receptor within the sodium channel and inactivating it. *H^+,* Hydrogen ion; *Na^+,* sodium ion. (Figure illustration by Department of Medical Art and Photography—Cleveland Clinic and Mr. Dave Schumick with permission.)

TABLE 162.3

Topical Anesthetic Agents for Application to Intact Skin or Open Wounds

TOPICAL AGENT[b,c,d]	COMPOSITION	SITES	TIME TO EFFICACY	ADMINISTRATION	COMMENTS	CONTRAINDICATIONS
Eutectic mixture of local anesthetic agents (EMLA)	Lidocaine 2.5% Prilocaine 2.5% 1:1 mixture	Intact skin	Onset: 60 minutes Peak: 120 minutes	Apply 5 to 10 g in thick layer Cover with semiocclusive dressing	Dose[a]: 0 to 3 months old or <5 kg: maximum 1 g on ≤1 hr, 10 cm^3 3 to 12 months and >5 kg: maximum 2 g on ≤4 hours, 20 cm^3 1 to 6 years and >10 kg: maximum 10 g on ≤4 hours, 100 cm^3 7 to 12 years and >20 kg: maximum 20 g on ≤4 hours, 200 cm^3	Infants EGA <37 weeks, <1 year if susceptible to methemoglobinemia or on methemoglobin-inducing agents (sulfonamides, nitrates, primaquine, others) Use with caution if age <3 months old
Liposome encapsulated lidocaine (LMX)	Lidocaine 4% (LMX4) or 5% (LMX5) (previous name: ELA Max)	Intact skin	Onset: 30 to 60 minutes	Apply 2.5 grams in thick layer Cover with semiocclusive dressing		Same as for lidocaine
Lidocaine, epinephrine, and tetracaine (LET)	Lidocaine 4% Epinephrine 0.1% Tetracaine 0.5%	Open dermis	20 to 30 minutes	Apply 5 mL to gauze pad, place in wound, cover with semiocclusive dressing		Area of compromised blood supply, or end-arteriolar blood supply
Vapo-coolant (PainEase) (other common vapo-coolant is ethyl chloride)	1,1,1,3,3 pentafluoropropane, 1,1,1,2-tetrafluoroethane (nonflammable and ozone friendly so is preferred over ethyl chloride)	Intact dermis Open dermis	Almost instantaneously, 4 to 10 seconds	Hold the spray can 3 to 7 inches from site, spray for 4 to 10 seconds or until blanching occurs	Inexpensive Can use on intact or open dermis (such as, laceration) Must perform procedure quickly since effect wears off rapidly (within 1 minute) Can be reapplied	Area of compromised blood supply, insensitive skin cold intolerance or hypersensitivity

[a]The dose of EMLA® varies by age and weight, with the maximum amount of intact skin in cm^3 over which the cream can be applied and the length of time allowed for skin contact specified.
[b]Tetracaine, adrenaline (epinephrine), and cocaine (TAC) is a topical anesthetic used on open dermis, but because of the potential toxicity due to the cocaine component as well as for legal and regulatory issues, it has been replaced by other topical anesthetics.
[c]Tetracaine topical (Ametop) has been used in adults and reported in the literature in pediatric patients, but according to Pediatric and Neonatal Lexi-drugs for tetracaine topical under dosing, "Children: safety and efficacy has not been established" so it is not included in this list.
[d]Use of topical anesthetic agents on mucosal surfaces in infants and young children, as for teething pain or stomatitis, has been associated with serious adverse events, including seizures, respiratory depression, and death. So they are not included on this list. The American Academy of Pediatrics (AAP) recommends using a chilled (not frozen) teething ring or gently rubbing/massaging with the caregiver's fingers for teething pain. The U.S. Food and Drug Administration (FDA) recommends against using topical over-the-counter (OTC) medicines for teething pain. Such OTC products may contain up to 20% local anesthetic, such as 20% benzocaine, which is 200 mg/mL. This can be compared with the usual concentration of local anesthetics for subdermal injection for suturing, such as 2% lidocaine, which is 20 mg/mL for a tenfold increase to 200 mg/mL for 20% concentration.
EGA, Estimated gestational age.

TABLE 162.4

Common Local Anesthetics

LOCAL ANESTHETICS[a]	MAXIMUM DOSE[b]	ONSET	DURATION[c] (AVERAGE)	PROTEIN BINDING (%)	POTENCY[d]	LIPID SOLUBILITY[e]	pKa[f] (25° C)
AMIDES[g]							
Long Duration							
Bupivacaine (Marcaine)	3 mg/kg	10 minutes	200 minutes	96%	8	High	8.1
Etidocaine (Duranest)	3 mg/kg	3 minutes	200 minutes	94%	6	High	7.7
Moderate Duration							
Lidocaine (Xylocaine)	4 to 4.5 mg/kg	5 minutes	100 minutes	64%	2	Medium	7.9
Mepivicaine (Carbocaine)	4 to 4.5 mg/kg	3 minutes	100 minutes	78%	2	Low	7.6
Prilocaine (Citanest)	5 mg/kg	5 minutes	100 minutes	55%	2	Medium	7.9
AMIDES WITH EPINEPHRINE							
Lidocaine with epinephrine	7 mg/kg	5 minutes	120 minutes	64%	2	Medium	7.9
Mepivicaine with epinephrine	7 mg/kg	5 minutes	120 minutes	78%	2	Low	7.6
ESTERS[g]							
Short Duration							
Chloroprocaine (Nesacaine)	8 mg/kg	5 minutes	45 minutes	—	1	Low	8.7
Procaine (Novocain)	7 mg/kg	18 minutes	40 minutes	6%	1	Low	8.9
Long Duration							
Tetracaine (Pontocaine)	1.5 mg/kg	15 minutes	200 minutes	76%	8	High	8.5

[a]Use of commercially available brand names does not imply endorsement of any medication or product. They are included because individuals may be more familiar with commercial or brand names than the specific drug or category of drugs.
[b]Maximum dose is based on ideal body weight.
[c]Duration is affected by binding (eg, ↑ protein binding produces ↑ duration) and concentration (↑ concentration ↑ duration). 2% lidocaine has greater duration than 1% lidocaine.
[d]Potency is related to the ability of the local anesthetic to penetrate the lipid membrane of the nerve axon.
[e]Highly lipid soluble local anesthetics have greater potency (↑ lipid solubility leads to ↑ potency) (eg, tetracaine greater potency than procaine). To have the same efficacy, low lipid soluble anesthetics (eg, lower potency) must be given in higher concentrations and higher doses than local anesthetics with higher lipid solubility and thus, higher potency.
[f]Local anesthetics are weak bases. The onset is a function of the pKa, the pH at which there are equal percentages of the ionized and non-ionized forms (eg, 50% ionized, 50% non-ionized). The non-ionized form is able to easily transverse the neural membrane. Local anesthetics with a pKa close to the physiologic pH result in greater concentrations of the non-ionized form leading to a more rapid onset. pKa near physiologic pH: ↑ non-ionized base ↑ (faster) onset. However, once inside the nerve cell, the non-ionized base attains equilibrium with the ionized from. The ionized form (cation) binds to the receptor within the sodium channel and inactivates it (see Fig. 162.4).
[g]In case of a true immunoglobulin E (IgE) anaphylaxis, which is very rare, to one class of local anesthetics the other class may be used; eg, if allergy to esters, then one can use amides and vice versa. If an allergy to all "caines" (both amides and esters), then one can use benzoyl alcohol or diphenhydramine. Benzoyl alcohol is preferred over diphenhydramine.
Derived from multiple sources including Berde CB, Strichartz GR: Local anesthetics. In Miller RD, Cohen NH, Eriksson LI, et al, editors: Miller's anesthesia, ed 8, Philadelphia, 2015, Elsevier, pp 1028–1054.

end-arterial fields (eg, digits) and in patients with vascular pathology (eg, Buerger's disease, digital vascular injury) who are at high risk for ischemia. Techniques for decreasing injection pain are described in Box 162.1.

The vasoconstrictor reaction is the most common adverse reaction to a local anesthetic. It occurs when an epinephrine-containing local anesthetic is injected into a highly vascular space. The patient suddenly feels a rapid heartbeat and becomes anxious and panicky from rapid absorption of epinephrine. This reaction ends quickly and is not a true allergy.

True immunoglobulin E (IgE)-mediated anaphylaxis to local anesthetics is very rare, especially to the amide class. Reported allergies to amides are more likely to be a reaction to epinephrine or an allergy to one of the preservatives (eg, methylparaben). There is no cross-reactivity between amides and esters, and they contain different preservatives. For patients with a known true allergy to lidocaine, a benzoyl alcohol solution (made by adding 0.2 mL of 1:1000 epinephrine to a 20 mL vial of normal saline containing 0.9% benzoyl alcohol) can be used. Benzoyl alcohol is

BOX 162.1

Techniques to Decrease the Pain of Local Anesthetics

Use a topical agent prior to the injection
Use smallest gauge needle possible (generally, a 27- to 30-gauge needle)
Use warmed solution: Warmed to 98.6° to 102° F (37° to 39° C)
Inject slowly
Inject into the subcutaneous space, not the dermis
Minimize the number of punctures
Inject from within open wounds, do not inject through the adjacent intact skin
Buffer the local anesthetic: Mix 1% lidocaine with 8.4% sodium bicarbonate solution in a ratio of 9 parts lidocaine to 1 part sodium bicarbonate (Mixing bupivacaine with bicarbonate can cause precipitation of the anesthetic and is not recommended.)

preferable to diphenhydramine (4 mL normal saline:1 mL 5% diphenhydramine to make a 1% solution) as an alternative local anesthetic in patients with a true lidocaine allergy for several reasons. A randomized controlled trial of lidocaine, benzoyl alcohol, and diphenhydramine for local anesthesia found that the duration of analgesia was longest for lidocaine, and the highest median pain of infiltration occurred with diphenhydramine. Although diphenhydramine has been used as an effective local anesthetic; it can be absorbed systemically and cause sedation. More importantly, it is a tissue irritant, and hyperemia and tenderness at the injection site for several days is common; unpredictable local skin necrosis and sloughing has been reported. If diphenhydramine is used as a local anesthetic, it should be used in a 1% solution because lower concentrations (eg, <1%) may be less effective, and higher concentrations (eg, >1%) probably increase the risk of skin necrosis.

Serious toxicity from local anesthetics is due to their effects on the CNS and to the cardiovascular system (CVS). Early signs of toxicity include numbness or tingling of the lips, metallic taste, muffled hearing, and tinnitus. These symptoms often portend the onset of drowsiness, seizures, status epilepticus, and coma. Direct myocardial depression and pump failure can occur, especially if the patient is on beta blockers or calcium channel blockers; heart block and asystole can also occur. If cardiac arrest is known or presumed to be from local anesthetic toxicity, length of resuscitation should take into consideration time for the negative cardiac effects to wear off. Any of the local anesthetics can have these adverse effects, especially when exceeding recommended doses.

Compared to the amides, the esters have a higher incidence of allergic reactions. Procaine and benzocaine are metabolized to para-aminobenzoic acid (PABA), which has been associated with rare anaphylactic reactions. The metabolites of prilocaine and benzocaine have been associated with methemoglobinemia. Bupivacaine has a higher cardiac toxicity profile than other local anesthetics, but bupivacaine is still widely used and generally safe and effective when used as recommended. In general, the choice of local anesthetic depends more on duration and personal preference than a marked advantage of one specific drug or anesthetic class.

Nerve Blocks

A nerve block is regional anesthesia attained by the injection of a local anesthetic agent near a nerve, nerves, or nerve plexus supplying a particular area. There may be a fairly well circumscribed region of anesthesia (eg, a wrist or ankle block) or an entire limb, termed *major regional anesthesia.* Nerve blocks are often used to provide anesthesia prior to procedures (eg, reduction of fractures or dislocations and suturing large lacerations). This approach has the advantage of limiting the amount of lidocaine or other anesthetic needed, decreasing the possibility of reaching toxic levels of the local anesthetic. The use of ultrasound-guided nerve blocks in the ED has been increasing due to the increased safety and efficacy found with sonographic visualization of structures. Although there has been much literature on the use of nerve blocks for adults in the ED, there are relatively few studies dealing with the use of nerve blocks for pediatric patients in the ED.

Complications that can occur with any nerve block include needle breakage (more likely if very small and long needles or if needles are bent to perform the block; eg, posterior superior alveolar block), needle damage to anatomic structures (eg, nerves, vessels, viscera, pleura, other structures), neurotoxicity, vascular complications (eg, hematoma formation, intra-arterial injection), infection, and bleeding. With any nerve block, providers should review the appropriate anatomy (particularly if performed infrequently), be careful not to exceed maximum doses of anesthetics, and calculate the maximum dose based on actual not ideal body weight. Mixing lidocaine and bupivacaine will give both a rapid onset and longer duration nerve block.

Nonopioid Systemic Analgesics

Nonopioid systemic analgesics (Table 162.5) include acetaminophen (paracetamol), which has analgesic and antipyretic effects but does not have any anti-inflammatory effects. There is no need for any dosage change for mild renal or hepatic impairment. If therapeutic doses are used and there is no alcohol abuse or preexisting liver disease, then hepatic toxicity is rare. Acetaminophen is an excellent choice for the treatment of mild pain, in combination with opioids for moderate to severe pain, and has several methods of administration, including the IV route. Indications for the IV use of acetaminophen include patients with pain or fever who are unable to take oral medications and those who have impaired gastrointestinal (GI) absorption.

The NSAIDs have analgesic and anti-inflammatory properties. NSAIDs inhibit cyclooxygenase (COX)-1 and COX-2, which decreases the synthesis of prostaglandins, thereby elevating the threshold for nociceptor activation. Nonselective NSAIDs inhibit both COX-1 and COX-2. Side effects of COX-1 inhibition include GI bleeding, renal failure, and platelet dysfunction. In pediatric patients, ibuprofen is the NSAID of choice, because it has fewer side effects than other NSAIDs. NSAIDs may be more effective than acetaminophen at reducing pain from inflammation associated with tissue injury.

Aspirin has analgesic, antipyretic, and anti-inflammatory effects. However, aspirin is not recommended in children and infants due to risk of Reye syndrome, a rapid-onset encephalopathy associated with hepatic dysfunction; for this reason, aspirin should not be used in any individual with chicken pox or flu symptoms.

Opioid Analgesics

Opioids, previously termed *narcotics,* produce analgesia by binding to opioid receptors in the brain, brainstem, spinal cord, and peripheral nervous system. The main adverse effect of opioids is a dose-dependent respiratory depression with blunting of the responses to hypoxia and hypercarbia; this effect is potentiated when co-administered with other sedative medications. Other side effects are primarily GI (eg, constipation, nausea, vomiting), urinary retention, and pruritus.

There are many routes of administration of opioids. IM is not recommended secondary to injection pain and variable IM absorption. Codeine is a weak opioid that has an increased incidence of side effects compared to other opioids. Up to one-third of patients are considered codeine "non-responders," due to a genetic trait that interferes with codeine metabolism. As a result, they are unable to create the active metabolites responsible for codeine's analgesic effects. Meperidine is not recommended due its possible CNS toxicity (eg, seizures, hallucinations, and psychosis) at therapeutic doses and its risk of serotonin syndrome.

Opioid Prescribing and Use. Partially due to an increased focus on treating pain, there has been a tremendous increase in the prescribing of opioids by health care providers in recent years for both adults and pediatric patients. There has also been a concomitant increase in the untoward complications of opioid prescribing, including opioid abuse, addiction, overdose, and deaths.

Americans, with only 4.6% of the world's population, consume 80% of the global opioid supply, 99% of the global hydrocodone supply, and two-thirds of the illegal drugs.[15] According to the National Hospital Ambulatory Medical Care Survey, the overall use of opioid analgesics in pain-related pediatric ED visits

TABLE 162.5

Systemic Analgesics

SYSTEMIC ANALGESIC[d,e]	ROUTE[c,f]	DOSE (PEDIATRIC)[a]	DOSE (ADULT)[b]	MAXIMUM DOSE[c]	FORMULATIONS AND NOTES	COMMENTS
NONOPIOID[b]						
Acetaminophen (Paracetamol) (Tylenol)	PO	Child/infant 10 to 15 mg/kg dose every 4 to 6 hours Child 6 to 11 years old: 325 mg dose every 4 to 6 hours	≥12 years old/ adults 650 mg every 4 to 6 hours 1000 mg every 6 hours (maximum 4000 mg daily)	Child single dose 15 mg/kg Total daily dose: Lesser of 75 mg/kg or 4000 mg Not more than five doses daily	PO solution or suspension: 160 mg/5 mL, 500 mg/5 mL Tablets/gelcaps: 325 mg, 500 mg Chewable or ODT: 80 mg	Analgesic Antipyretic No anti-inflammatory effect Has been associated with liver failure Hepatotoxicity is usually associated with excessive dose Do not exceed maximum daily dose
	PR	20 to 30 mg/kg dose every 4 to 6 hours	650 mg every 4 to 6 hours	Total daily dose: 3900 mg	120 mg, 325 mg, 650 mg	(Same as above)
Acetaminophen (Ofirmev)	IV	<50 kg: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours	≥50 kg: 650 mg every 6 hours or 1000 mg every 6 hours	If <50 kg: Single dose 15 mg/kg, total daily dose <75 mg/kg/day ≥50 kg: Single dose 1000 mg daily: 4000 mg	10 mg/mL (100 mL vial)	(Same as above) More expensive, can be used in NPO patients
Aspirin (acetylsalicylic acid)	PO or PR	Weight <50 kg: 10 to 15 mg/ kg dose every 4, 6, or 8 hours	Weight ≥50 kg or ≥12 years old/ adults 325 to 650 mg every 4 to 6 hours	Total daily dose: Lesser of 120 mg/kg or 4000 mg	Tablets/caplets: 81 mg, 325 mg, 650 mg Chewable tablets: 81 mg	Analgesic Antipyretic Anti-inflammatory Avoid if recovering from chicken pox or flu symptoms due to association with Reye syndrome (has led to ↓ use)
Ibuprofen (Advil, Motrin)	PO	6 months old to 5 years old: 5 to 10 mg/kg dose every 6 to 8 hours	≥12 years old/ adults 400 to 600 mg every 4 to 6 hours or 800 mg every 8 hours	<12 years old Single dose: 400 mg Total daily dose: 40 mg/kg up to 1200 mg Adults: Total daily dose 3200 mg	Suspension: 100 mg/5 mL Tablets: 100, 200, 400, 600, 800 mg Chewable tab: 50, 100 mg	Analgesic Antipyretic Anti-inflammatory Side effects: GI bleeding, renal failure, and platelet dysfunction; most side effects occur with the chronic use of nonselective NSAIDs
Toradol (Ketorolac)	IV or IM	0.5 mg/kg dose every 6 to 8 hours	Child >50 kg and adult 30 mg	30 mg per dose Total daily dose: 120 mg	Doses up to 60 mg can be given but are not recommended because doses higher than 30 mg have no greater efficacy but have more incidence side effects	(Same as for ibuprofen) Therapy should not be more than 5 days
OPIOIDS: ORAL WITH OR WITHOUT ACETAMINOPHEN[b]						
Hydrocodone	PO	0.1 to 0.2 mg/kg dose every 4 to 6 hours Usual dose: 0.15 mg/kg	Child ≥50 kg and adult: 5 to15 mg every 4 to6 hours, usual dose 10 mg	No more than six doses per day 60 mg total daily dose	24-hour extended release tablets: 20, 30, 40, 60, 80, 100, 120 mg capsules 12-hour extended release tablets: 10, 15, 20, 30, 40, 50 mg	Weak opioid Preferred over codeine Generally hydrocodone is given in combination with acetaminophen

Continued

TABLE 162.5

Systemic Analgesics—cont'd

SYSTEMIC ANALGESIC[d,e]	ROUTE[c,f]	DOSE (PEDIATRIC)[a]	DOSE (ADULT)[b]	MAXIMUM DOSE[c]	FORMULATIONS AND NOTES	COMMENTS
Hydrocodone and acetaminophen[j] (Lorcet, Vicodin)	PO	0.1 to 0.2 mg/kg dose every 4 to 6 hours (based on hydrocodone component) Usual dose: 0.15 mg/kg	Child ≥50 kg and adult: 10 mg hydrocodone every 4 to 6 hours (10 mg hydrocodone is two tabs or 20 mL)	No more than six doses per day or recommended acetaminophen daily dose, 60 mg hydrocodone total daily dose	Solution: Hydrocodone 7.5 mg/acetaminophen 325 mg/15 mL Tablets: Hydrocodone 5 mg/acetaminophen 325 mg	Weak opioid Preferred over codeine Generally hydrocodone is given in combination with acetaminophen
Oxycodone	PO	0.1 to 0.2 mg/kg dose every 4 to 6 hours Usual dose: 0.15 mg/kg	Child ≥50 kg and adult: Immediate release: 5 to 10 mg every 4 to 6 hours	Initial: 5 mg/dose oxycodone	Solution: 5 mg/5 mL Concentrate: 100 mg/5 mL Capsule: 5 mg Tablets: 5, 10, 15, 20, 30 mg 12-hour extended release tablets: 10, 15, 20, 30, 40, 60, 80 mg	Strong opioid Preferred over hydrocodone Generally oxycodone is given in combination with acetaminophen Sustained release form is available but is usually not given for acute pain in the ED setting
Oxycodone and acetaminophen[j] (Endocet, Percocet, Roxicet)	PO	0.1 to 0.2 mg/kg dose every 4 to 6 hours Usual dose: 0.15 mg/kg (based on oxycodone component)	Child ≥50 kg and adult: Immediate release: 5 to10 mg every 4 to 6 hours	Initial: 5 mg/dose oxycodone Total daily dose: Based on acetaminophen component	Solution: Oxycodone 5 mg/acetaminophen 325 mg/5 mL (Roxicet) Tablets: Oxycodone 5 mg/acetaminophen 325 mg (Roxicet5)	Strong opioid Preferred over hydrocodone Generally oxycodone is given in combination with acetaminophen Sustained release form is available but is usually not given for acute pain in the ED setting
OPIOIDS: ORAL[b]						
Hydromorphone (Dilaudid, Exalgo)	PO	Child <50 kg: 0.03 to 0.08 mg/kg dose every 3 to 4 hours	Child ≥50 kg and adults: 2 to 4 mg every 3 to 4 hours	Varies: Depends on whether opioid naive or opioid tolerant	Oral liquid: 1 mg/mL Tablets: 2 mg, 4 mg, 6 mg	More potent (x5) than morphine No histamine release and fewer side effects than morphine
Morphine (Duramorph, Kadian, MS Contin)	PO	Child <50 kg: 0.3 mg/kg dose every 3 to 4 hours (immediate release)	Child ≥50 kg and adults: 15 to 20 mg every 3 to 4 hours	Infants: 2 mg/dose Ages 1 to 6 years old: 4 mg/dose Ages 7 to 12 years old: 8 mg/dose Usual adolescents and adults: 10 mg/dose but may go up to 15 to 20 mg/dose	Solution: 10 mg/5 mL Tablets: 15 mg, 30 mg Extended release tablets: 15 mg, 30 mg, 60 mg, 100 mg	Potent opioid Side effect: May cause histamine release (some prefer other opioids for this reason) May be the most commonly use opioid in pediatric patients Sustained release forms available but generally not given in the ED for acute pain in the ED
Tramadol (Synapryn, Ultram)	PO	Child ≥ 4 years old: 1 to 2 mg/kg dose every 4 to 6 hours	Adolescents and adults: 50 to 100 mg every 4 to 6 hours	400 mg total daily dose	Suspension: 10 mg/mL Tablets: 50 mg 24-hour extended release tablets or capsules: 100, 200, 300 mg	Weak opioid; related to codeine; preferred over codeine Less respiratory depression than other opioids Mechanism of action: Central inhibition of norepinephrine and serotonin reuptake, weak affinity for mu receptors

TABLE 162.5

Systemic Analgesics—cont'd

SYSTEMIC ANALGESIC[d,e]	ROUTE[c,f]	DOSE (PEDIATRIC)[a]	DOSE (ADULT)[b]	MAXIMUM DOSE[c]	FORMULATIONS AND NOTES	COMMENTS
OPIOIDS: PARENTERAL[b]						
Fentanyl (Abstral, Actiq, Duragesic, Fentora, Lazanda, Onsolis, Subsys)	IV	<50 kg: 0.5 to 1 μg/kg every 1 to 2 hours or 0.5 to 1.5 μg/kg/hr	Child ≥50 kg and adults: 25 to 50 μg/dose every 1 to 2 hours	0.05 mg/kg/dose Usually 50 μg/dose Infusion for PCA pumps is available (dose in μg/kg/hr) as well as bolus dosing (μg/kg/dose)	Note: Fentanyl is μg or micrograms/kg dose (unlike other opioids which are milligrams or mg/kg per dose), also shorter half-life so given more frequently	More potent (70 to 100x) than morphine Side effect: Chest wall rigidity with high doses given rapidly More rapid onset and shorter duration than morphine and other opioids
Hydromorphone (Dilaudid, Exalgo)	IV	<50 kg: 0.015 mg/kg every 2 to 4 hours or 0.002 mg/kg/hr	Child ≥50 kg: 0.015 mg/kg every 2 to 4 hours or 0.002 mg/kg/hr	Usual 2 mg May need higher doses in opioid tolerant patients	Infusion for PCA pumps is available as well as bolus dosing	More potent (x5) than morphine No histamine release and fewer side effects than morphine
Morphine (Duramorph, Kadian, MS Contin)	IV	<50 kg: 0.1 mg/kg/dose every 2 to 4 hours or 0.1 mg/kg/hr	Child ≥50 kg and adults: 2 to 8 mg every 2 to 4 hours	8 to 10 mg/dose	Infusion for PCA pumps is available (dose in mg/kg/hr as well as bolus dosing [mg/kg/dose])	IM is not recommended because of painful administration, variable absorption, and lag time to peak effect Repeated subcutaneous causes local pain, irritation and induration (see also PO)

[a]Typical common doses and maximums are listed. This may not apply to all individuals. Patients differ greatly in their responses to medications, especially opioids. Response may vary due to many factors including age (very young and elderly), previous or chronic exposure to opioids (opioid naive or opioid tolerant), and initial pain severity so opioids should be titrated to effect.

[b]Use of commercially available brand names does not imply endorsement of any medication or product. They are used because health care providers may be more familiar with brand names than the specific drug name or category or drugs.

[c]There are many routes of administration of opioids, but IM is not recommended, because the injection is painful and has variable absorption and, thus, variable efficacy and unpredictable side effects.

[d]Codeine and meperidine are not included in this table, because they are not preferred and other options are available with fewer side effects.

[e]Oral transmucosal fentanyl is not included in the table, because the fentanyl lollipop was associated high a high incidence of side effects, including nausea, vomiting, and respiratory depression; so it was removed from the market.

[f]Rectal suppositories available for hydromorphone but are not recommended due to variable absorption.

[g]Other analgesics, such as remifentanil, have been administered for analgesia as part of procedural sedation and analgesia (PSA) but has not yet gained widespread popularity so is not included in the table.

[h]Transdermal patches are available for various medications including lidocaine (Lidoderm) and opioids, fentanyl (Duragesic) and buprenorphine (Butrans), but these are generally for chronic pain. They may be encountered in patients with chronic pain, such as cancer patients, but are not generally used for the treatment of acute pain in the ED.

[i]If the hydrocodone or oxycodone or morphine are in the extended release or sustained form, which is for chronic pain, the tablets should be swallowed whole and should not be moistened, dissolved, cut, crushed, broken, or chewed, because this changes the formulation from sustained release to immediate-acting, which can lead to an acute overdose.

[j]Note: Both hydrocodone (Hysingla ER, Zohydro) and oxycodone (Oxecta, OxyContin, Roxicodone) are available in formulations without the acetaminophen component, with the same dosage of hydrocodone or oxycodone, respectively, as for the combinations with acetaminophen. However, they are not frequently prescribed in these formulations without the acetaminophen.

ED, Emergency department; *GI,* gastrointestinal; *IM,* intramuscular; *IV,* intravenous; *NPO, nil per os* (nothing by mouth); *NSAID,* nonsteroidal anti-inflammatory drug; *ODT,* orally disintegrating tablets; *PCA,* patient-controlled analgesia; *PO, per os* (by mouth); *PR,* per rectal.

significantly increased from 11.2% in 2001 to 14.5% in 2010. The use of Drug Enforcement Agency (DEA) schedule II agents doubled from 3.6% in 2001 to 7.0% in 2010, whereas there was no significant increase in the use of schedule III, IV, or V agents. In comparison, there was no significant increase in the use of nonopioid analgesics in pediatric ED patients. Increased opioid use was most striking in ED visits that involved adolescents.[16] A recent survey indicated that 10.4% of ED patients ages 14 to 20 years old reported nonmedical prescription opioid or sedative use.[17] Another report noted that 80% of America's high school students (11 million teens) and 44% of middle school students personally witnessed illegal drug use, illegal drug dealing, illegal drug possession, and other activities related to drug abuse on school grounds.[15]

Although there is no evidence based literature documenting a clear superiority of opioid versus nonopioid analgesics, there are multiple adverse effects and consequences for both the individual and the community associated with opioid use, misuse, and abuse. Thus, we recommend that opioids be reserved for more severe pain or pain refractory to other analgesics rather than be routinely prescribed. If opioids are indicated, they should be given at the lowest effective dose for a limited duration (eg, 1 week), and the

prescriber should consider the patient's risk for opioid use, abuse, or diversion.[18]

Low Dose Ketamine for Treatment of Pain

Low dose ketamine has been successfully used in adults and pediatric patients for the treatment of acute pain.[19] Pediatric studies are small case series in hospitalized patients (eg, non-ED setting) for the treatment of acute pain from cancer or sickle cell disease. Doses for the treatment of acute pain are lower than used for sedation and vary. A commonly used dose is 0.15 mg/kg (range 0.1 to 0.2 mg/kg). Higher doses (eg, 0.3 mg/kg) have been associated with a higher incidence of side effects. Continuous infusions have also been used, in the range of 0.1 to 0.2 mg/kg/hour. Adverse events noted with low dose (0.15 mg/kg) ketamine in one adult study include nausea (15%), vomiting (10%), dysphoria (10%), and an abnormal taste sensation (5%). One adult study reported an overall 6% incidence of side effects with low dose ketamine, which included a 3.5% incidence of dysphoria, 1.5% transient hypoxia, and 1% vomiting. Dizziness, fatigue, and headache have also been reported. Similar data is not yet available for pediatric patients.

Reversal Agents

Naloxone is used for the reversal of opioids effects on the mu receptors (eg, sedation and respiratory depression). Although the half-life is about 1 hour, the clinically effective duration of action may be much less (eg, 20 to 60 minutes). Due to longer half-lives of many opioids, re-dosing or an infusion of naloxone is often needed with opioid overdoses. The usual dose for full reversal of opioid intoxication is 0.1 mg/kg/dose with an initial maximum dose of 2 mg for infants and children 5 years old and younger or 20 kg and less; for children >5 years or >20 kg and adolescents, the dose is 2 mg. The dose may be repeated every 2 to 3 minutes if there is no response. The IV route is preferred, but intraosseous (IO) can be used if there is no IV line. It may also be given intramuscularly or subcutaneously, but the onset of action may be delayed, especially if there is poor perfusion. Naloxone may be administered intranasally at a dose of 2 mg (1 mg per nostril) for adolescents (13 years old and older), and is often given by emergency medical service (EMS) in the field or at home for acute opioid overdoses. Naloxone can also be administered endotracheally at 2 to 3 times the initial IV dose. For reversal of respiratory depression with therapeutic opioid doses, lower doses may be used with an initial dose of 0.001 to 0.005 mg/kg/dose with some recommending 0.001 to 0.015 mg/kg/dose intravenously, intramuscularly, or subcutaneously; with the dose titrated to effect or repeated every 2 to 3 minutes as needed until the desired response is obtained.

Flumazenil antagonizes the action of the benzodiazepines at the gamma-aminobutyric acid (GABA) receptor. It has a half-life of about 1 hour, but the clinically effective duration of action may be much less (20 to 60 minutes). Flumazenil can only be given intravenously. Flumazenil may be given when there is an overdose of benzodiazepines administered for clinical reasons and only in a patient who is not benzodiazepine habituated. In individuals who overdose on benzodiazepines, it is likely that they are habituated and on benzodiazepines chronically. In these cases, benzodiazepine withdrawal may be associated with status epilepticus and even death. Thus, except in the acute iatrogenic overdose setting, the use of flumazenil is not recommended. Patients who co-ingest benzodiazepines and tricyclic antidepressants may develop intractable seizures after flumazenil administration. Thus, use of flumazenil should be reserved for patients with an uncomplicated benzodiazepine overdose, no evidence of tricyclic antidepressants use (eg, no electrocardiogram [ECG] findings and no anticholinergic signs and symptoms), no history of seizure disorder, and no history of benzodiazepine habituation. For benzodiazepine reversal with procedural sedation or anesthesia, the initial dose of flumazenil for infants, children, and adolescents is 0.01 mg/kg (maximum 0.2 mg), which may be repeated after 45 seconds and then every minute up to 4 additional doses. The maximum total cumulative dose is 1 mg or 0.05 mg/kg, whichever is lower. In adults, the initial dose is 0.2 mg, which may be repeated for a total of 5 doses with a total cumulative dose of 1 mg. Flumazenil has a black box warning. In general, it is used infrequently and only for benzodiazepine reversal with procedural sedation or anesthesia.

OUTCOMES

There are moral, ethical, legal, and regulatory reasons to adequately treat pain. Oligoanesthesia, the failure to adequately treat pain, continues despite increasing literature demonstrating that pain is too often undertreated. Children and infants, the elderly, individuals with limited cognitive ability, and ethnic and social minorities have a greater risk of oligoanesthesia. The negative consequences of undertreating pain include increasing the patient's pain threshold and predisposing patients to developing chronic pain syndromes. Inadequate analgesia may lead to harmful physiologic consequences, including an increase in stress hormones and increased sympathetic outflow. This results in an increase in catabolism, myocardial oxygen consumption, production of carbon dioxide, and peripheral vascular resistance, as well as an impaired immune response.

The Joint Commission (TJC) mandates that hospitals adapt a pain management quality improvement program, which includes the measurement, documentation, and therapy for pain. Patient satisfaction and the patient experience are gaining greater importance, especially since the Centers for Medicare and Medicaid Services (CMS) and the National Committee on Quality Assurance require public reporting of patient satisfaction data for participating health plans. In the future, hospital and physician payment will be based on patient outcomes, as well as patient satisfaction. The positive relationship between adequate treatment of pain and patient satisfaction has been documented for all ages of patients, including children and infants. Eliminating or minimizing the pain of medical procedures can also lead to greater procedural success rates.

KEY CONCEPTS

- Patients of all ages experience pain, even infants, neonates, and premature babies.
- Oligoanesthesia, the inadequate treatment of pain, has many short-term and long-term consequences: worse patient outcomes, increase in patient's pain threshold, and development of chronic pain.
- Pain management may include a combination of techniques: analgesics, topical anesthetics, local anesthetic injections, and nonpharmacologic interventions.
- Nonpharmacologic interventions to decrease pain or anxiety include oral sucrose in infants; parental presence; physical measures, such as heat or cold therapy and splinting for musculoskeletal injuries; and behavioral or cognitive measures, such as distraction and play therapy.
- Topical anesthetics are recommended to decrease the pain of minor procedures, such as venipuncture or IV cannulation.
- Techniques for decreasing the pain of intradermal injections include topical agent prior to the intradermal injection; slowly injecting warmed, buffered local anesthetic solution from within the wound with the smallest gauge needle possible; and limiting the number of needle punctures.
- When using large amounts of local anesthetics in small children or infants, calculate the drug dose to avoid toxicity; a 1% solution = 1 g/100 mL or 10 mg/mL.
- Procedural sedation and analgesia (PSA) requires pre-sedation evaluation; sufficient monitoring (during and after the procedure) by qualified individuals capable of dealing with any adverse events that may occur; age-appropriate equipment (including airway equipment) and medications (including reversal agents and advance life support drugs); and discharge criteria for when the patient is fully awake, returns to baseline with stable vital signs, and is able to be discharged in the care of a responsible adult.
- Overall, preprocedural fasting is not necessary for most emergency patients, because large studies show no clinically significant differences with airway complications, emesis, or other adverse effects between groups of patients stratified by their preprocedural fasting status.
- Choice of sedative and analgesic for PSA depends on many variables including patient factors and the procedure to be done. Slow titration of medications can achieve the desired level of sedation and analgesia while minimizing risk of adverse events.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 162: QUESTIONS & ANSWERS

162.1. When do most adverse events associated with emergency department (ED) procedural sedation occur?

A. During the manipulation or intervention
B. 5 to 20 minutes after the last sedative dose
C. 20 to 30 minutes after the last sedative dose
D. 30 to 60 minutes after the last sedative dose
E. 60 to 90 minutes after the last sedative dose

Answer: B. High-risk times are 5 to 20 minutes after the last medication administration and at the completion of the procedure when there is no longer a painful stimulus but the patient remains sedated.

162.2. Which of the following modalities has proven most effective for monitoring patients undergoing procedural sedation?

A. Capnometry or capnography
B. Cardiac rhythm monitoring
C. Continual direct visual observation of qualitative clinical signs
D. Documented respiratory rate
E. Pulse oximetry

Answer: C. The patient's ability to follow commands in response to varied levels of stimulation and direct observation of the ventilatory status have been the most reliably documented methods of assessing the level of consciousness during procedural sedation. Pulse oximetry is a reliable adjunct, but it identifies hypoventilation late, especially when used with supplemental oxygen. Cardiac monitoring has been shown to be helpful in older patients or in those with a history of cardiac disease, but there is no evidence that it is of any benefit in young healthy patients. End-tidal carbon dioxide monitoring has been shown to be useful to detect inadequate ventilation earlier than oximetry, especially when direct observation of the patient is difficult, but no studies have demonstrated an effect on clinical outcome to date. Recently, the American Society of Anesthesiologists (ASA) updated its procedural sedation standards to include capnography during moderate or deep sedation, in addition to the continual observation of qualitative clinical signs. Respiratory rate alone is an insensitive indicator of adequacy of ventilation.

162.3. Which of the following agents is matched with the correct associated side effect?

A. Etomidate—limited (30-minute) duration of sedation
B. Ketamine—laryngospasm
C. Methohexital—venoirritation
D. Pentobarbital—seizures
E. Propofol—myoclonus

Answer: B. Ketamine has been associated with laryngospasm in children younger than 3 months old and those with a respiratory infection. The following are the other correct associations:

- Etomidate—myoclonus
- Methohexital—seizures
- Pentobarbital—30-minute duration
- Propofol—venoirritation

162.4. Which of the following statements regarding the use of ketamine is false?

A. Benzodiazepine coadministration has not been shown to reduce the incidence of emergence phenomenon in children.
B. Despite increased secretions, airway reflexes are generally well maintained.
C. Hypotension is common.
D. Profound analgesic and sedative effects occur with minimal respiratory depression.
E. Repeat doses are well tolerated in longer procedures.

Answer: C. Ketamine increases the release of catecholamines upon administration and supports blood pressure well. It also decreases smooth muscle tone in the bronchial tree and may have a benefit in patients with reactive airways disease. Several studies have failed to show benefit with the concurrent administration of low-to-moderate dosages of benzodiazepines in preventing emergence phenomenon in children. These studies have shown a slightly increased risk of side effects. Their routine use is discouraged and should be reserved for the actual treatment of severe emergency phenomenon.

162.5. Which of the following statements regarding the use of propofol is true?

A. Propofol has a long duration of action and provides significant analgesia.
B. Propofol has significant antiemetic properties.
C. Propofol is cerebroprotective.
D. Propofol is well tolerated in volume-depleted patients.
E. The use of "ketofol" (ketamine in combination with propofol) is clinically superior to the use of propofol alone.

Answer: B. Propofol is an ultra–short-acting, sedative-hypnotic, cerebroprotective agent with no analgesic but profound antiemetic properties. Its adverse effects include dose-dependent respiratory depression, apnea, hypotension, and pain on injection. Preload-dependent patients are particularly susceptible to hypotension. Its combined use with ketamine is common. The two agents are felt to have synergistic effects that balance each other's deficits. The combined use has been shown to improve provider satisfaction, sedation quality, and decrease emesis but has not been shown to be clinically superior to either agent used alone regarding respiratory depression, airway complications, or improved recovery times.

162.6. Which of the following statements is true regarding the need for fasting before procedural sedation?

A. A 6-hour period of fasting is required after the ingestion of liquids or solids before procedural sedation.
B. Preprocedural fasting is required in all circumstances.
C. The recommendation for preprocedural fasting is based on controlled trials involving patients undergoing procedural sedation.
D. The risk of vomiting and the loss of the airway protective reflexes is an extremely rare occurrence during procedural sedation.
E. There is an increased risk of aspiration during procedural sedation after a liquid or solid meal.

Answer: D. The American Society of Anesthesiologists (ASA) currently recommends a period of 2 hours after ingestion of clear liquids, a period of 4 hours after ingestion of breast milk, and a period of 6 hours after ingestion of other liquids or solids before the performance of procedural sedation. This recommendation is based on expert consensus and extrapolated from data on patients receiving general anesthesia and manipulation of the airway during intubation and extubation. There are no published studies showing increased risk of aspiration after a liquid or solid meal, nor benefits of fasting before procedural sedation. There are large studies showing no clinically significant differences with airway complications, emesis, or other adverse effects between groups of patients stratified by their preprocedural fasting status. Adherence to the ASA preoperative fasting guidelines for procedures is not necessary in emergency department (ED) patients undergoing procedural sedation and analgesia (PSA).

CHAPTER 163

Pediatric Resuscitation

Joshua Samuel Easter | Halden F. Scott

CARDIAC ARREST

Principles

Pediatric cardiac arrest is rare, but the consequences are dire when considering lost years of life and productivity. The incidence and survival for pediatric cardiac arrest varies with the location of the arrest, patient's age, and the mechanism. Most cardiac arrests encountered in the emergency department (ED) occur outside the hospital, from medical causes in infants and traumatic causes in older children.[1] Most infant arrests occur before 3 months of age, reportedly as a result of sudden infant death syndrome (SIDS).[2] The incidence of cardiac arrest in infants approaches the incidence of arrest in adults. The incidence of nontraumatic cardiac arrest in older children is 30 to 50 times less common than infants and adults.

Previous literature suggests survival following cardiac arrest in children is poor; however, this is largely based on studies that fail to differentiate survival among infants and older children. Infants survive infrequently (2% to 3%) but older children survive (9%) more commonly than adults (5%).[3] In addition, survival for all children following cardiac arrest has improved substantially over the last 30 years.[2] The frequency of survival with good neurologic outcome has been estimated at 1% to 12%.[4] These estimates arise largely from studies focusing on neurologic status at 1 month, yet children often continue to demonstrate improvements in their neurologic statuses for years.[4] Most traumatic arrests in children are often fatal; resuscitative thoracotomy in selected patients may improve survival.[1,5-8]

Pediatric resuscitations are relatively rare, limiting provider proficiency. In a recent retrospective review, less than half of emergency clinicians had completed any critical care procedures (eg, cardioversion, intubation, intraosseous line placement) on children in the ED in the preceding year.[9] Moreover, 75% of the procedures completed were intubations. Procedures that no providers in the study had performed included cardiac pacing, needle cricothyroidotomy, diagnostic peritoneal lavage, thoracentesis, arterial line placement, or venous cutdown line placement. This study was conducted at a busy children's hospital; the frequency of critical pediatric procedures is likely lower in general EDs.

Lack of experience limits provider proficiency.[10] In the absence of actual clinical experience, providers often rely on didactic resuscitation courses. However, knowledge retention after these courses is poor.[11,12] As a result, many providers remain uncomfortable managing critically ill children.[13] This discomfort can lead to insufficient interventions for fear of harming a child, or alternatively, excessive interventions unlikely to be of benefit.

Pathophysiology

Most nontraumatic cardiac arrests in children arise from respiratory etiologies, particularly drowning, asphyxia, and respiratory failure.[14] The typical progression is from respiratory failure to shock, and finally to bradycardia and loss of circulation. Pediatric advanced life support (PALS) guidelines have largely focused on the treatment of these respiratory emergencies. However, recent international population based studies suggest cardiac causes account for approximately a third of pediatric medical arrests.[3,15,16] Another 21% of pediatric arrests follow trauma. These frequencies are in stark contrast to adults, where two-thirds of arrests are attributed to cardiac etiologies and 5% to 10% are traumatic.[17,18] The differences in the etiology of arrests between adults and children have significant implications for management; arrests from respiratory causes require an emphasis on ventilatory support, oxygen delivery, and maintenance of perfusion, whereas arrests from cardiac causes require a more directed emphasis on restoring perfusion and treatment of underlying dysrhythmias.

The most common presenting pediatric arrest rhythm is asystole, occurring in two-thirds of children. Pulseless electrical activity and bradycardia are the next most common presenting rhythms. Unlike adults, ventricular fibrillation and tachycardia are rare, occurring in less than 10% of children.[19] These dysrhythmias become more common in adolescents, in children with congenital heart disease, and they also often arise during the course of prolonged resuscitations.

Clinical Features

The absence of a pulse, respiratory effort, and responsiveness constitute cardiac arrest. While identifying respiratory effort and responsiveness are relatively straightforward, detecting a pulse in a pediatric patient can prove difficult. Health care providers have been found to identify a pulse when not present in 26% of children undergoing extracorporeal membrane oxygenation (ECMO). Moreover, providers have been found to take an average of 9 (±6) seconds to detect a brachial pulse and 29 (±14) seconds to determine a pulse was not present in children.[20] Current guidelines suggest lay people should initiate cardiopulmonary resuscitation (CPR) in children without performing a pulse check; any child that is unresponsive and apneic should receive CPR. For emergency clinicians, a 10-second pulse check is appropriate. If no pulse is detected in 10 seconds, CPR should be initiated without delay. The adverse effects of delayed CPR outweigh the effects of CPR for an apneic, unresponsive child with a pulse.

Location to Perform Pulse Check

The ideal location for palpation of a child's pulse is unclear. There are few studies comparing sites, and they are conducted in the operating room with conflicting results. In infants, the carotid pulse can be difficult to detect compared to the brachial or femoral pulse. In adolescents, the carotid is the easiest location to identify a pulse. In children in cardiac arrest, auscultation of the heart or palpation of the apical impulse can be misleading; patients with pulseless electrical activity can have an apical impulse or auscultated heartbeat without central pulses or adequate perfusion. If ever in doubt about the presence of a pulse, providers should err on the side of initiating compressions.

Recognizing Imminent Arrest

Anticipating impending cardiac arrest allows for early interventions that may prevent progression. Abnormal vital signs, based on age-specific norms, are often the best indicator of imminent arrest in an ill child. These values can be difficult to remember, but providers can recognize several key features (Box 163.1).

Management

The paucity of pediatric out-of-hospital cardiac arrest results limits available evidence on its management. Most pediatric guidelines are consensus-based and much is extrapolated from adult data.[21-24] The American Heart Association (AHA) guidelines for management are illustrated in Figure 163.1. These pediatric guidelines are generally intended for use on children until puberty (ie, axillary hair in males and breasts in females).

Compressions-Airway-Breathing

During the initial no-flow state of cardiac arrest, the priority is initiation of flow. This priority has led to a change in the sequence of "airway-breathing-compressions (A-B-C)" to "compressions-airway-breathing (C-A-B)." CPR begins with compressions, rather than "look, listen, and feel" for respirations, to avoid delays in the initiation of blood flow. In addition, this approach may render bystanders to an arrest more likely to provide CPR, because compressions are prioritized over ventilations, which bystanders are more reluctant to provide. This is particularly helpful in children; bystander CPR improves pediatric survival but is infrequently administered.

There is debate about the true benefits of the C-A-B approach in children, where arrests are more commonly from a respiratory etiology, potentially requiring respiratory support to correct. However, no delays were found in the initiation of ventilations with the C-A-B approach compared to the A-B-C approach in simulated respiratory arrest in children.[25] Moreover, the C-A-B approach led to prompter recognition of cardiac arrest. Because multiple providers are available in the ED, initiation of compressions can and should begin concurrently with ventilations.

Compressions. High quality compressions improve outcomes but are rarely performed. When administered appropriately, compressions generate one-third of a child's normal cardiac output and a coronary artery perfusion pressure of 10 mm Hg. Compressions can improve blood pressure, return of spontaneous circulation, and survival.[26,27] Despite these findings, numerous studies have shown that inadequate compressions are the norm.[27] A prospective, observational study of in-hospital pediatric arrest found AHA guidelines for chest compressions were achieved in 54% and depth in 19% of children.[27] In an academic pediatric ED study, compression rates more than 100 per minute were observed in 87%, but recommended compression to ventilation ratios were achieved in only 40%, with frequent pauses in compressions.[28]

Compression technique influences cardiac output, and those over the lower part of the sternum improve cardiac output. This is particularly important in infants, whose hearts reside inferior to the lower third of their sternums. In these younger children, encircling the chest with both hands and compressing with the thumbs while squeezing the thorax with the remaining fingers yields greater cardiac output than compression with two fingers (Table 163.1). The AHA suggests utilizing the heal of one hand to administer compressions to children 1 to 8 years old, but a study of simulated compressions suggested a two-handed technique, identical to that performed on adults, is easier and generates higher pressures. When feasible, a resuscitation board should be placed under children receiving chest compressions; at a minimum, the child should be supine on a firm surface.

The ideal compression depth and rate is unknown, but the AHA recommends pushing "hard and fast." Compressions should be deep enough to achieve optimal cardiac output without being

BOX 163.1

Worrisome Vital Sign Findings in Children*

BLOOD PRESSURE
Systolic blood pressure <70 mm Hg + (2 × age in years) is hypotension (less than fifth percentile for age)

RESPIRATORY RATE
Respiratory rate >60 breaths per minute is tachypnea
Declining respiratory rate in previously tachypneic patient can represent improvement *or* fatigue and imminent respiratory failure

FEVER
Each 1° C (1.8° F) of fever increases heart rate by only 10 beats per minute and respiratory rate by 2 to 5 breaths per minute[124]*

END-TIDAL CARBON DIOXIDE
Progressive increase or decrease precede desaturation and respiratory failure

*These are guidelines only and should be combined with clinical signs, such as mental status and evidence of perfusion in assessing physiological status.
Nijman RG, Thompson M, van Veen M, et al: Derivation and validation of age and temperature specific reference values and centile charts to predict lower respiratory tract infection in children with fever: prospective observational study. BMJ (Clinical research ed.) 345:e4224, 2012.

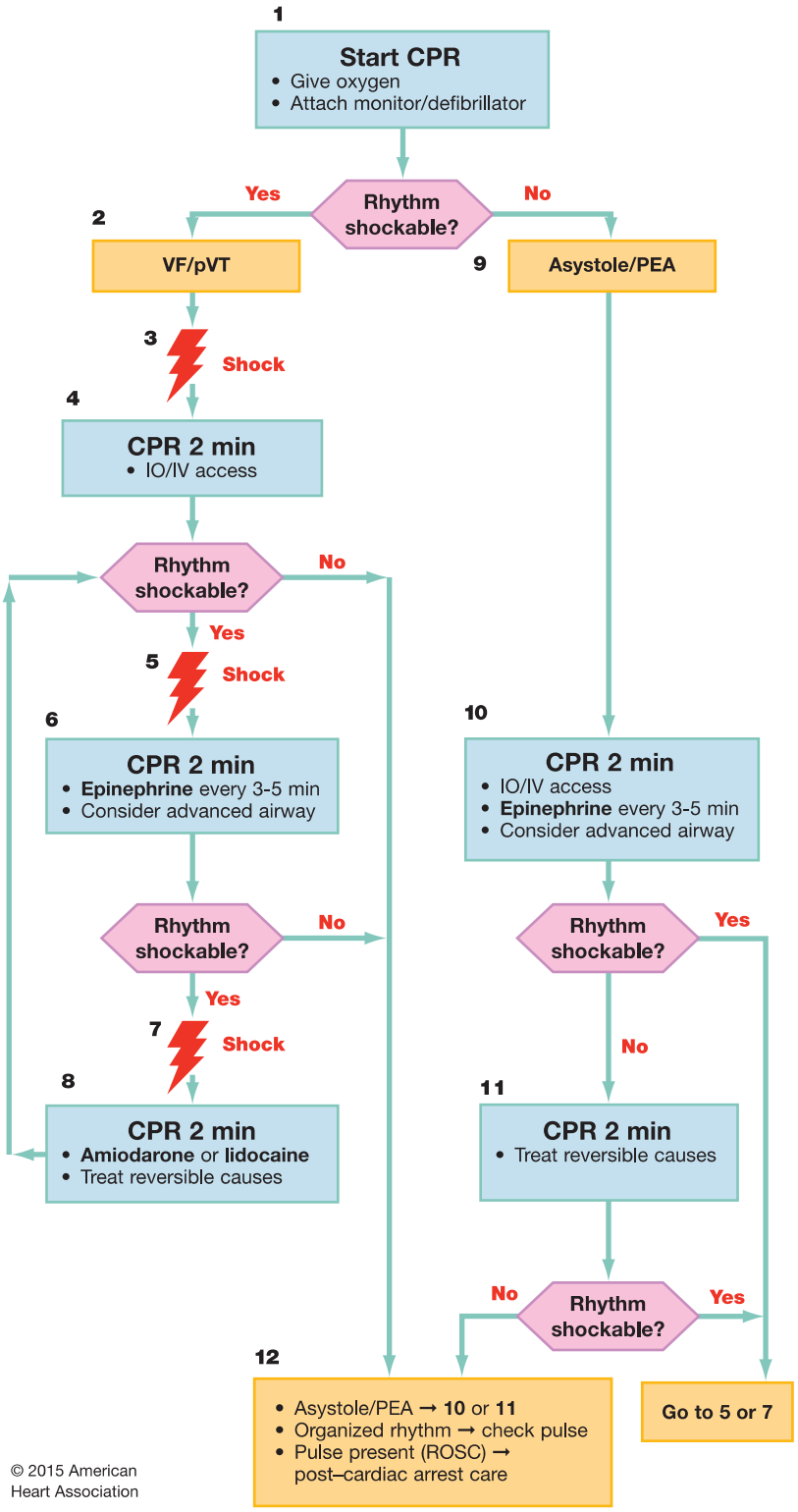
TABLE 163.1

Differences in Cardiopulmonary Resuscitation Between Infants, Children, and Adults*

	INFANTS	CHILDREN	ADULTS	ALL
Hands	Two thumbs, hands encircle chest	Two hands	Two hands	
Depth	1½ inches	2 inches	2 inches	
Rate				100-119/minute
Duration				Change providers every 2 minutes
Ratio (two rescuers)	15:2	15:2	30:2	
Assessment				$ETCO_2$ monitor ± accelerometer

*Recommendations listed are for the ED setting and not a single lay rescuer.
ED, Emergency department; *$ETCO_2$,* end-tidal carbon dioxide.

Pediatric Cardiac Arrest Algorithm – 2015 Update



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CPR quality

- Push hard (≥⅓ of anteroposterior diameter of chest) and fast (100-120/min) and allow complete chest recoil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Rotate compressor every 2 minutes, or sooner if fatigued.
- If no advanced airway, 15:2 compression-ventilation ratio.

Shock energy for defibrillation

First shock 2 J/kg, second shock 4 J/kg, subsequent shocks ≥4 J/kg, maximum 10 J/kg or adult dose

Drug therapy

- **Epinephrine IO/IV dose:** 0.01 mg/kg (0.1 mL/kg of 1:10 000 concentration). Repeat every 3-5 minutes.
  If no IO/IV access, may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of 1:1000 concentration).
- **Amiodarone IO/IV dose:** 5 mg/kg bolus during cardiac arrest. May repeat up to two times for refractory VF/pVT.
- **Lidocaine IO/IV dose:** Initial: 1 mg/kg loading dose. Maintenance: 20-50 mcg/kg per minute infusion (repeat bolus dose if infusion initiated >15 minutes after initial bolus therapy).

Advanced airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ETT placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of spontaneous circulation

- Pulse and blood pressure
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible causes

- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypoglycemia
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Fig. 163.1. The American Heart Association (AHA) guidelines algorithm for management of infants and children in cardiopulmonary arrest. *CPR,* Cardiopulmonary resuscitation; *ETT,* endotracheal tube; *IO/IV,* intraosseous/intravenous; *PEA,* pulseless electrical activity; *ROSC,* return of spontaneous circulation; *VF/pVT,* ventricular fibrillation/pulseless ventricular tachycardia.

so deep as to cause injuries to other vital organs. Attempts to increase depth excessively can result in leaning, which reduces coronary artery perfusion pressure and cardiac output.[29] Guidelines suggest compressing the chest half of the anteroposterior diameter of the child, but this estimate leads to relatively deeper compressions than recommended in adults, where guidelines provide an absolute depth for compression. Moreover, it can be extremely difficult to assess the proportion of anteroposterior compression depth during CPR. As a result, it is more practical to focus on absolute depths; we recommend 1½ inches in infants and 2 inches in older children.

Similarly, the exact rate of compressions to generate ideal cardiac output is unclear. Rates more than 100 compressions per minute improve cardiac output, coronary artery perfusion pressure, and survival compared with rates less than 90 compressions per minute in children.[26] However, attempts to exceed 120 compressions per minute likely diminish the quality of compressions. In adults, there is an association between survival and compression rates of 100 to 119 compared to faster or slower rates.[30] High quality compressions diminish after 2 minutes. At this point, providers may deny fatigue and be able to maintain the rate of compressions, but depth of compressions decreases substantially. This reduction in quality worsens with time.[31] Pauses in compressions to provide defibrillation or switch compressors create substantial drops in coronary artery perfusion pressure; in adults, pauses more than 20 seconds increase the odds of mortality by 50%.[32] Provider switches account for 57% of no-compression/no-flow time observed in CPR.

Finally, the appropriate ratio of compression to ventilations is unknown. Animal models indicate the amount of ventilation required during CPR is much lower than with a normal perfusing rhythm, likely due to the lower cardiac output in CPR. The AHA recommends 30:2 compressions to ventilations for single rescuers and 15:2 for two rescuers. However, the 15:2 ratio may yield insufficient compressions per minute in older children, and a 30:2 ratio may be considered. Over half of CPR observed in a study of pediatric arrest involved ventilations in excess of recommendations, with 20% over twice the recommended ventilation rate.[33] Once an advanced airway is in place, compressions should not be interrupted for ventilations delivered at 8 to 10 breaths per minute.

Notably, although resuscitation guidelines provide exact rates, depths, and ratios of compressions to ventilations, these recommendations are largely based on consensus. There are no randomized control studies comparing the impact of exact ratios, frequencies, or depths of compressions on survival. Rather than focusing on strict adherence to exact guidelines, emergency providers should focus on ensuring compressions are appropriately located and administered rapidly without interruptions.

Feedback improves the quality of compressions. Quantitative feedback is most helpful, because qualitative assessments by providers can be difficult. Accelerometers and force sensors provide real-time data on compression rate and force. These feedback devices improve adherence with compression guidelines amongst children in cardiac arrest.[27] Despite proven benefits, less than 5% of hospitals employ feedback devices regularly during resuscitation.[34] End-tidal carbon dioxide ($ETCO_2$) also serves as an adjunct measure of the adequacy of compressions.[35,36] In the low-flow state of CPR, the flow of venous blood to the lungs serves as the rate-limiting step for the elimination of CO_2 as opposed to ventilation. As a result, exhaled CO_2 increases with cardiac output. In animal models, using target $ETCO_2$ levels to guide compressions performs as well as using video and verbal feedback.[36]

Ventilation. Although life-threatening airway emergencies in children are rare, most critical illness in children stems from respiratory etiologies; therefore, emergency clinicians should be well versed in the management of the pediatric airway.[37] In a survey of pediatric ED directors, nearly two-thirds reported their ED had inadequate airway management opportunities to maintain provider proficiency; thus continuing education including skill practice is recommended to maintain skills. For an in-depth discussion of the management of the pediatric airway, see Chapter 161.

Bag-mask ventilation may be preferred over endotracheal intubation for inexperienced providers managing children in cardiac arrest. A randomized trial of intubation versus mask ventilation for out-of-hospital pediatric arrest supports this approach.[38] There was no difference in survival to hospital discharge or good neurologic outcome between tracheal intubation by emergency medical service (EMS) and bag-mask ventilation alone. Similarly, a recent population-based observational study in adults found survival was lower for out-of-hospital intubation (odds ratio [OR] 0.45; 95% confidence interval [CI], 0.37 to 0.55) compared to bag-mask ventilation.[39] Similar to out-of-hospital intubations, ED-based pediatric intubations that require multiple attempts are associated with adverse outcome. Under these circumstances, a focus on delivery of high quality bag-mask ventilation as opposed to endotracheal intubation should be considered.

Compression-Only Cardiopulmonary Resuscitation

For arrests secondary to ventricular fibrillation, patients often have a reservoir of oxygen in their lungs and can maintain adequate arterial partial pressure of oxygen (PaO_2) for 5 minutes with compressions alone. In contrast, animal studies of arrests from respiratory causes show that compression-only CPR leads to rapid depletion of oxygen reservoirs and increased CO_2 and lactate. In a non-randomized observational study of 5,170 children with out-of-hospital cardiac arrest, children with a non-cardiac etiology for their arrest receiving conventional CPR had a more favorable neurological outcome than compression-only CPR (OR 5.5; 95% CI, 2.5 to 17).[3] In children with a cardiac etiology for their arrest, conventional CPR and compression-only CPR performed similarly (OR for good neurologic outcome: 1.2; 95% CI, 0.6 to 2.7).

Compression-only CPR is better than no CPR. Bystander CPR improves outcomes but less than half of children receive it.[3] Bystanders may be more willing to perform compression-only CPR, and this should be encouraged compared to no CPR. In the ED, pediatric CPR should include compressions and ventilations.

Defibrillation. Although ventricular fibrillation and pulseless ventricular tachycardia are rarely the presenting rhythm in children, they arise at some point during 25% of pediatric resuscitations.[40] Children with these rhythms are more likely to survive than children or adults with other rhythms. The shorter the duration between onset of the rhythm and defibrillation, the greater the likelihood of achieving return of spontaneous circulation. No other procedures, including establishment of an airway, should delay defibrillation. While awaiting defibrillation, providers should focus on administering high quality compressions without interruptions until the defibrillator is in place and charged.

Defibrillation applies asynchronous current to the heart. Both paddles and pads provide adequate energy, assuming gel is placed on the paddles and pads are firmly attached to the chest wall. The largest pads available that fit on the child's chest without touching will decrease transthoracic impedance and provide greater energy to the heart. Anteroposterior and anterolateral positioning of pads provide equivalent energy to the heart.[41] When available, providers should use pediatric paddles for children younger than 8 years old. If not available, adult-sized pads can be employed with anteroposterior placement, minimizing contact between the pads. Currently, there is insufficient evidence to support the safety of

providers maintaining their hands on the chest to perform compressions during defibrillation.

Although the optimal energy dose for defibrillation in children is unclear, a prospective observation trial found no difference in return of circulation or survival between monophasic and biphasic defibrillation in children.[42] The AHA recommends administering 2 to 4 J/kg initially, whereas the European Resuscitation Council recommends 4 J/kg. The optimal dose depends on the child's transthoracic impedance and weight; however, the relationship between impedance and weight is not linear. As a result, dosing based strictly on weight often leads to lower than anticipated energy delivery. Higher doses per kilogram may overcome this variability and ensure adequate energy reaches the heart. A prospective multicenter study of pediatric arrest showed a trend toward increased survival with doses more than 2 J/kg.[43] A similar study failed to replicate this result; although, the results may have been confounded by providers administering higher defibrillation doses to sicker children.[44] The primary disadvantage of higher energy doses is damage to the myocardium, but animal studies suggest long-term myocardial necrosis only occurs with doses more than 10 J/kg. The only circumstance where providers would potentially encounter such high doses is when utilizing adult paddles on infants. However, when presented with an infant in ventricular fibrillation and no other options, utilization of the adult paddles is appropriate. We recommend starting defibrillation at 2 J/kg, increasing to 4 J/kg with the second defibrillation, and increasing to 10 J/kg for third and subsequent shocks. After a failed defibrillation attempt, compressions should immediately resume without stacked defibrillation attempts.

Medications for Cardiac Arrest. There are no high quality randomized control studies showing improvement in survival to hospital discharge or neurologic outcome with any medications administered during pediatric cardiac arrest.[45] Moreover, there is mounting evidence to suggest that certain commonly administered medications are associated with decreased survival and poorer neurologic outcome. Bicarbonate continues to be used routinely (68% of pediatric in-hospital cardiac arrests) despite little evidence supporting its use.[46] Similarly, calcium is administered in 45% of pediatric in-hospital cardiac arrests, despite an association with decreased survival and poorer neurologic outcome. These drugs should be reserved for specific indications (Table 163.2). The ideal drug for ventricular tachycardia and pulseless ventricular tachycardia remains unclear, and recommendations are primarily extrapolated from adult data. However, a recent retrospective study of in-hospital arrest from ventricular fibrillation or pulseless ventricular tachycardia in children found lidocaine was independently associated with improved return of circulation (OR 2.0; 95% CI, 1.4 to 3) and 24-hour survival (OR 1.7; 95% CI, 1.1 to 2.5), although not survival to hospital discharge.[47] The implications of this study for out-of-hospital cardiac arrest are uncertain. Without further evidence or consensus, amiodarone should remain first-line therapy.

Dosing of medications during pediatric cardiac arrest can be difficult; accurate administration requires correct estimation of weight, determination of weight-based dose, and conversion of weight to volume. Time spent on these tasks increases providers' cognitive load and errors. The Broselow-Luten tape estimates weight based on supine length and provides immediate access to drug doses and equipment sizing. Overall, such length-based methods of estimating weight are more accurate than age-based or appearance-based approaches.[48] However, they may not accurately estimate weight in certain cohorts, such as obese or emaciated children.[49,50] In the United States, where children are often obese, the tape may underdose medications.[51] Methods incorporating estimates of body habitus through visual provider estimates (PAWPER) or mid-upper arm circumference (Mercy TAPE) have yielded more accurate weight estimates than the Broselow method. However, the differences appear minimal and not likely to be clinically significant.[52,53] Regardless, these systems do not eliminate all dosing errors, because providers must still calculate the volumes of medications. Utilization of color coded, prefilled syringes corresponding to the weight based dosages provided on the Broselow tape can mitigate these dosing errors.[54]

Confirmation of weight estimates reduces errors. Often in the rush of resuscitation, inaccurately estimated weights result in inappropriate equipment and medications.[55] The finger counting method can be quickly employed to confirm an estimated weight.[56] The provider counts age on the left hand, starting with 1 on the thumb and counting by odd numbers to 9 on the small finger. Weight in kilograms is counted on the right hand, starting with 10 kg and counting by 5 kg to 30 kg on the small finger. Fingers are matched between hands to estimate weight. EMS should also have a system to estimate and report weight when transporting a critical child to allow ED providers to prepare appropriate equipment and medications.[57]

Vascular Access. The particular site of vascular access is less important than its timely acquisition. Obtaining central venous access is not crucial early in resuscitation, because peripheral venous and intraosseous drug administration produce similar onset of drug action and peak levels for the commonly administered resuscitation drugs.[58,59] Peripheral venous access, including the external jugular vein, is typically the easiest method. However, in children in arrest or imminent arrest, concurrent attempts at intraosseous access often save time.

Intraosseous access is typically more successful and faster with minimal complications compared to peripheral or central access in critically ill patients.[60-63] Long-term follow up has shown adverse impact on bone growth from intraosseous placement is rare. Directing the needle away from the growth plate during insertion reduces the risk of injury to the growth plate. Frequent checks around the insertion site are necessary, because excessive insertion of fluids into needles misplaced in the subcutaneous tissue can lead to compartment syndrome. Powered intraosseous insertion devices, such as the EZ-IO (Vidacare), decrease insertion times (77% in <10 seconds) and improve the frequency of successful insertion (>90%); although, other powered devices that require calibration, such as the Bone Injection Gun (WaisMed) may delay insertion and reduce the frequency of success.[55,64] Although studies in adults have demonstrated increased first pass success with placement in the tibia, they have not shown any clinically significant difference in performance compared to other sites.[65] In young children, the tibia and femur are preferred, because their marrow cavity is well developed. When administering fluid through an intraosseous line, manual pressure is helpful to overcome the resistance of the marrow cavity. Multiple injections of smaller (10 cc) syringes of normal saline (ie, "saline flushes") may be used to resuscitate infants and small children through an intraosseous needle. Surveys also suggest providers often unnecessarily delay attempts at intraosseous access while attempting peripheral or central access.[66,67] Central line access should be established for prolonged resuscitations requiring vasopressors or large volumes of fluid. The femoral vein is the easiest site of cannulation in young children and avoids interference with CPR.

Post-Arrest Care. Following initial resuscitation of a child in cardiac arrest, focus should shift to treating the underlying etiology of the arrest, minimizing brain injury, and improving end-organ perfusion. Post cardiac arrest patients develop a sepsis-like syndrome with elevations in inflammatory markers, myocardial dysfunction, systemic ischemia, and multiple organ dysfunction. Table 163.3 outlines several approaches to mitigate these effects.

TABLE 163.2

Medications for Pediatric Cardiac Arrest

MEDICATION	INDICATIONS	COMMENTS
Epinephrine	Asystole, PEA, bradycardia, VF, pulseless VT	0.01 mg/kg of 1:10,000 formulation Higher doses of epinephrine have no benefit and may decrease survival
Atropine	Bradycardia	Not for routine use in PEA, asystole[112] 0.02 mg/kg; no minimum dose is recommended Usually second line for bradycardia after epinephrine
Vasopressin	Refractory cardiac arrest	Mixed evidence but available as last resort[113-115]
Amiodarone	VF, VT, SVT	Unclear if superior to lidocaine for VF, VT
Lidocaine	VF, VT	Avoid in WPW
Procainamide	SVT refractory to adenosine, stable VT	First line for SVT in WPW May be more effective than amiodarone for SVT[116] Do not give in patients receiving amiodarone, torsades de pointes, or prolonged QT Can cause hypotension
Adenosine	SVT	First line therapy for stable SVT Avoid in WPW, wide complex tachycardia, long QT Potentially unreliable through IO route
Glucose	Hypoglycemia	D10W: 5 mL/kg, D25W: 2 mL/kg, D50W: 1 mL/kg Do not administer empirically
Calcium chloride	Hyperkalemia, hypocalcemia, calcium channel blocker overdose	Not for routine use Calcium chloride provides more bioavailable calcium but requires central line
Sodium bicarbonate	Hyperkalemia, TCA overdose	Not for routine use but recommended for indications listed
Magnesium	Torsades de pointes, hypomagnesemia	Not for routine use but recommended for indications listed

D10W, Dextrose 10% in water; *D25W,* dextrose 25% in water; *D50W,* dextrose 50% in water; IO, intraosseous; *PEA,* pulseless electrical activity; *SVT,* supraventricular tachycardia; *TCA,* tricyclic antidepressant; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White.Barrington KJ: The myth of a minimum dose for atropine. Pediatrics 127(4):783-784, 2011; Yilidzdas D, Horoz OO, Erdem S: Beneficial effects of terlipressin in pediatric cardiac arrest. Pediatr Emerg Care 27(9):865-868, 2011; Gil-Anton J, Lopez-Herce J, Morteruel E, et al: Pediatric cardiac arrest refractory to advanced life support: is there a role for terlipressin? Pediatr Crit Care Med 11(1):139-141, 2010; Carroll TG, Dimas VV, Raymond TT: Vasopressin rescue for in-pediatric intensive care unit cardiopulmonary arrest refractory to initial epinephrine dosing: a prospective feasibility pilot trial. Pediatr Crit Care Med 13(3):265-272, 2012; Chang PM, Silka MJ, Moromisato DY, et al: Amiodarone versus procainamide for the acute treatment of recurrent supraventricular tachycardia in pediatric patients. Circ Arrhythm Electrophysiol 3(2):134-140, 2010; Goodman IS, Lu CJ: Intraosseous infusion is unreliable for adenosine delivery in the treatment of supraventricular tachycardia. Pediatr Emerg Care 28(1):47-48, 2012.

Hypotension after return of circulation is a predictor of mortality. Although vasopressors can help maintain end-organ perfusion in the setting of post-arrest myocardial dysfunction, its use has not been associated with improved survival. There are no randomized studies of comparing the performance of particular vasopressors for pediatric cardiac arrest. In the absence of strong evidence, we administer norepinephrine, which has been shown to cause fewer arrhythmias than dopamine in adults. Concurrent administration of dobutamine may be necessary to achieve hemodynamic stability in patients with refractory cardiogenic shock. Hypercapnia and hypocapnia also increase mortality in the post-arrest period.[68] Ventilator settings should be titrated frequently in the post-arrest period to normalize carbon dioxide levels. To avoid free-radical generation from hyperoxia, ventilator settings should be adjusted to maintain oxygen saturations above 94%, while avoiding PaO_2 levels over 300 mm Hg.

Adult studies report conflicting results for induced hypothermia following arrest. In a randomized trial of 260 children, induced hypothermia (target temperature, 91.4°F [33°C]) demonstrated no difference from therapeutic normothermia (target temperature, 98.24°F [36.8°C]) in survival with good neurologic outcome.[69] In the absence of strong evidence, we recommend avoidance of hyperthermia as well as targeted temperature management to maintain a temperature of 89.6°F (32°C) to 96.8°F (36°C) for adolescents with return of spontaneous circulation after witnessed arrest with ventricular fibrillation. Moreover, avoidance of hyperthermia with cooling blankets and antipyretic medications is beneficial.

When readily available, providers should also consider ECMO early in an arrest course. Although initial studies suggested ECMO provided greater benefits primarily for patients with underlying cardiac disease, a recent retrospective analysis also identified benefits for children with non-cardiac etiologies for their arrest. Centers performing high volumes of ECMO or with rapid response teams to initiate timely cannulation have better outcomes.[70,71]

Disposition

Family Presence. We endorse the recommendation from the American College of Emergency Physicians (ACEP) and American Academy of Pediatrics (AAP) that family be given the option of being present during their child's resuscitation. The limited evidence to support this recommendation is primarily descriptive or survey-based. Most families want to be present for the resuscitation of their child, and when asked after being present, they report that they would repeat the experience, even in situations where their child died. Families report their presence comforts their children, helps them appreciate the efforts of providers, facilitates their understanding of the gravity of the situation, and promotes

TABLE 163.3

Post Cardiac Arrest Care in Children

	GOAL/EVIDENCE	ACTION
Oxygenation	Avoid hypoxemia and hyperoxemia[117]	Titrate oxygen to SpO_2 94% to 98% Avoid PaO_2 >300 mm Hg
Ventilation	Avoid hypercapnia and hypocapnia • Hypercapnia OR for death = 3.3 • Hypocapnia OR for death = 2.7	Maintain $PaCO_2$ of 35 to 50 mm Hg
Cardiovascular support	Avoid hypotension • 56% children have BP less than fifth percentile within 6 hours of ROC[118] • OR for death = 1.7 • OR for poor neurologic outcome = 1.8 • Only 41% with hypotension receive vasopressors	1. Maintain euvolemia with fluids 2. Supplement with norepinephrine if needed 3. Monitor lactate levels[119]
Temperature	Avoid hyperthermia • May be more beneficial than induced hypothermia[120] Consider induced hypothermia for specific cases • Few studies in pediatrics[121] • Mixed results in adults	1. Antipyretics and cooling blankets for fever 2. Consider induced hypothermia for comatose adolescents with ROC after witnessed VF arrest
Glucose	Maintain modest euglycemia • Association between hypoglycemia or hyperglycemia and mortality	1. Monitor glucose levels 2. No evidence to support tight glucose control, which may lead to increased hypoglycemia 3. Supplement glucose for hypoglycemia
Extracorporeal membrane oxygenation (ECMO)	Potentially more beneficial if: • Initiated rapidly • Underlying cardiac etiology • Arrest with environmental hypothermia <86° F (30° C)[122] • Hospital with high volume of ECMO patients	Consider when available, particularly for children with underlying cardiac disease or severe environmental hypothermia

BP, Blood pressure; *OR,* odds ratio; *$PaCO_2$,* partial pressure of carbon dioxide in the arterial blood; *PaO_2,* arterial partial pressure of oxygen; *ROC,* return of circulation; *SpO_2,* oxygen saturation as measured by pulse oximetry; *VF,* ventricular fibrillation.

Kilgannon JH, Jones AE, Shapiro NI, et al: Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 303(21):2165-2171, 2010; Del Castillo J, Lopez-Herce J, Matamoros M, et al: Hyperoxia, hypocapnia and hypercapnia as outcome factors after cardiac arrest in children. Resuscitation 83(12):1456-1461, 2012; Topjian AA, French B, Sutton RM, et al: Early postresuscitation hypotension is associated with increased mortality following pediatric cardiac arrest. Crit Care Med 42(6):1518-1523, 2014; Topjian AA, Clark AE, Casper TC, et al: Early lactate elevations following resuscitation from pediatric cardiac arrest are associated with increased mortality*. Pediatr Crit Care Med 14(8):e380-387, 2013; Nielsen N, Wetterslev J, Cronberg T, et al: Targeted temperature management at 33° C versus 36° C after cardiac arrest. N Engl J Med 369(23):2197-2206, 2013; Moler FW, Silverstein FS, Holubkov R, et al: Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 372(20):1898-1908, 2015; Scholefield B, Duncan H, Davies P, et al: Hypothermia for neuroprotection in children after cardiopulmonary arrest. Cochrane Database Syst Rev (2):CD009442, 2013; Turek JW, Andersen ND, Lawson DS, et al: Outcomes before and after implementation of a pediatric rapid-response extracorporeal membrane oxygenation program. Ann Thorac Surg 95(6):2140-2146; discussion 2146-2147, 2013; Skarda D, Barnhart D, Scaife E, et al: Extracorporeal cardiopulmonary resuscitation (EC-CPR) for hypothermic arrest in children: is meaningful survival a reasonable expectation? J Pediatr Surg 47(12):2239-2243, 2012; Freeman CL, Bennett TD, Casper TC, et al: Pediatric and neonatal extracorporeal membrane oxygenation: does center volume impact mortality?*. Crit Care Med 42(3):512-519, 2014.

the grieving process. In contrast, surveyed providers frequently are reluctant to have families present, often due to a mistaken assumption that parents will be critical of their work.[72] In the only randomized study of family presence during trauma resuscitations in the pediatric ED, 93% of physicians reported increased stress from family presence. However, the adverse effects of family presence seemed limited to stress on the emergency clinician, because no differences were detected in clinical care variables. Other studies have confirmed family presence rarely hinders care. Concerns about family presence prolonging resuscitation efforts also seem unfounded. In most situations, the benefits to the family of being present outweigh the increased stress on providers.

Structured programs for family presence during resuscitations are helpful. Families should be counseled on anticipated events prior to entering the resuscitation. They should be informed that their presence in the resuscitation is their decision; although, they can be asked to leave if they impede medical care. Designated nurses or social workers with training in grief counseling and free of clinical responsibilities can focus on the family, explaining steps in the resuscitation and answering questions.

Termination of Resuscitation. There are no universal criteria to guide the termination of a pediatric resuscitation. Providers are less comfortable terminating efforts in children than adults, often resulting in prolonged, futile resuscitations that increase stress on families and staff. There are numerous anecdotal reports of children surviving with good neurologic outcome after prolonged resuscitations, but these often involve in-hospital arrests or arrests with prompt access to ECMO.[71] Several variables, including length of resuscitation, unwitnessed arrest, initial cardiac rhythm, administration of multiple doses of epinephrine, administration of atropine, and $ETCO_2$ <10 mm Hg have been associated with poor survival and neurologic outcome.[14,73-75] However, none of these variables possess sufficient discriminative ability to provide absolute cutoffs for termination of resuscitation. Perhaps the most predictive variable is duration of resuscitation; a recent multicenter retrospective analysis indicated that for every additional minute of pediatric CPR, the frequency of survival decreased by 2.1% and favorable neurological outcome by 1.2%.[74] For traumatic arrest, guidelines suggest prehospital termination after 30 minutes of unsuccessful resuscitation.[76] Such guidelines

TABLE 163.4

Typical Patterns of Septic Shock Seen in Children

	HEMODYNAMICS	CLINICAL FINDINGS	TYPICAL POPULATIONS AND PATHOGENS	VASOPRESSOR OPTIONS
Warm	High cardiac output, low systemic vascular resistance	Widened pulse pressure, brisk capillary refill, warm extremities, bounding peripheral pulses	Hospital-acquired, central line; mixed gram-positive/gram-negative	Norepinephrine; dopamine
Cold	Low cardiac output, high systemic vascular resistance	Narrow pulse pressure, delayed capillary refill, cool/mottled extremities, weak peripheral pulses, cold extremities; congestive heart failure: rales, hepatomegaly, jugular venous distention	Community-acquired; gram-positive	Epinephrine; dopamine; dobutamine; milrinone

Note: Children frequently switch between categories, and repeated assessment of hemodynamics for adjustment of therapy is recommended.

do not exist for atraumatic arrest. Outside of family wishes and specific clinical situations where prolonged resuscitation may be beneficial (eg, hypothermia with drowning or electrocution, in-hospital arrest, or prompt access to ECMO), termination of resuscitation should be considered after 30 minutes for nontraumatic causes. This approach can minimize suffering for the patient, family, and caregivers.[77]

Providers have several responsibilities after the death of child in the ED. They should consider organ donation when a child dies. An organ procurement organization official accompanied by a social worker or chaplain should lead this discussion at a time removed from news of the child's death. Providers should contact the medical examiner for all deaths in the ED. Autopsy requirements for pediatric patients vary by state. With suspicious deaths, providers should limit manipulation of potential forensic evidence, while concurrently allowing family the opportunity to mourn their child's death. Attempts should also be made to inform the child's primary care physician of a child's death in the ED.

SEPTIC SHOCK IN THE PEDIATRIC PATIENT

Principles

Sepsis is the leading cause of death in children worldwide. A global point prevalence study showed that 8% of children in the intensive care unit (ICU) have severe sepsis.[78,79] Mortality estimates for severe sepsis in pediatrics are 9% to 25%, with variation in location and ascertainment methods accounting for this wide range.[78-80] Pediatric sepsis prevalence measured by the *International Classification of Diseases*, 9th edition, Clinical Modification code has increased in the last decade, whereas mortality has decreased.[78,80]

Decreasing mortality may be attributable to consensus recommendations from the American College of Critical Care Medicine (ACCM) and international experts.[81,82] Although increasingly supported by growing research in pediatric sepsis, the majority of recommendations for sepsis care in children are based on low-grade evidence.[83] Nonetheless, studies have demonstrated that adherence to the overall bundle of ACCM recommendations decreases mortality in children with severe sepsis and septic shock, and prospective ED implementation of sepsis treatment programs improves outcomes including hospital length of stay and mortality.[84-86] Variation and uncertainty exist in specific elements of ED care, particularly the optimal approaches to screening, diagnosis, fluid administration, and vasoactive therapy. Clinically, pediatric septic shock is identified by the presence of decreased perfusion or mental status in the setting of suspected infection.[87]

Pathophysiology

Shock represents the physiologic state of excess cellular oxygen demand for adenosine triphosphate (ATP). In septic shock, a pathogen initiates the shock state by triggering an inflammatory response in the host, and in toxin-mediated illness through direct effects on the host. The cytokine cascade promotes fever, leukocytosis, procoagulant effects, and increased vascular permeability.[88] Deleterious consequences include endothelial cell damage, capillary leak, microcirculatory shutdown, and hypovolemic shock with decreased tissue oxygenation and mitochondrial dysfunction. The inflammatory immune response also causes vasodilation, myocardial depression, activation of the complement system, disseminated intravascular coagulation, and increased production of nitric oxide. Left unchecked, this inflammatory cascade progresses to end-organ hypoperfusion and multisystem organ failure.[89]

Infants and children with sepsis exhibit variability in their hemodynamic profile in sepsis. Studies using invasive and noninvasive monitoring to categorize hemodynamic patterns of fluid-refractory pediatric septic shock have shown that 40% to 60% of patients are in cold shock with decreased cardiac output. Marked by relative hypovolemia, vasoconstriction, and myocardial failure, this "cold" shock is more common in children than in adults. Half of all children in fluid-refractory shock will have mixed hemodynamics or vacillate between cold and warm shock (Table 163.4).[90-92]

Clinical Features

The diagnosis of sepsis begins with suspicion for infection, either fever or hypothermia, or an infectious presentation, such as pneumonia. When coupled with hypotension, this constitutes decompensated shock and should prompt immediate resuscitation. The emergency clinician should also begin resuscitation in the absence of hypotension when there are signs of decreased perfusion, including altered mental status, abnormal capillary refill time, abnormal pulse quality, or cold mottled extremities. Other concerning signs include seizure, loss of consciousness, and increased respiratory effort. These signs distinguished sepsis from other febrile illness in children hospitalized in the United Kingdom.[93] The combination of hypotension and delayed capillary refill together portended the highest mortality in a large study of patients transported to a pediatric ICU (Fig. 163.2).

Unfortunately, many of the recommended physical examination findings suffer from modest inter-rater reliability and low sensitivity, as well as low positive predictive value. No prediction

Fig. 163.2. Measuring capillary refill time begins with applying pressure to the capillary nail bed until it blanches, as shown. Capillary refill time of 3 seconds or more has been associated with increased mortality in children with septic shock. (Courtesy Tia Brayman, Children's Hospital Colorado.)

Fig. 163.3. **A,** Using a 60-mL syringe with an inline three-way stopcock is an effective way to deliver rapid fluid boluses, particularly in patients less than 25 kg where a bolus is not easily dosed by a standard fluid bag. **B,** Rapid infusers and pressure bags rapidly deliver fluid boluses when a full bag is an appropriate dose. (Courtesy Tia Brayman, Children's Hospital Colorado.)

rules or scores exist to optimize their use in ED diagnosis of compensated septic shock.[94] Compounding this problem is that fever is among the most common chief complaints for children in an ED, often accompanied by tachycardia and tachypnea in non-septic patients. The diagnosis and treatment of pediatric septic shock is dependent on recognizing a syndrome of infection with decreased perfusion or altered mental status.

Laboratory testing and technologies to evaluate hemodynamics and vital signs show promise in sepsis diagnosis and monitoring but are not yet considered the standard of care.[81] Risk stratification of patients may include serum lactate level, procalcitonin, B-natriuretic peptide, markers of coagulopathy or disseminated intravascular coagulation, and heart rate variability.[95-98] Small studies suggest that, similar to adults, elevated serum lactate levels are associated with increased risk of organ dysfunction and death in children with sepsis. Although not an American Critical Care Medicine standard of care, we recommend that lactate levels be used in conjunction to the physical examination in diagnosing and monitoring treatment of pediatric septic shock. Risk-stratification strategies in a research setting include RNA expression profiling and novel serum biomarkers.[99] These techniques hold promise in the future for more objective and systematic assessment to enable providers to distinguish children with more benign febrile illness from those with early septic shock.

Management

The pillars of emergency treatment of pediatric sepsis are timely establishment of intravascular access; rapid fluid resuscitation titrated to patient condition; appropriate, broad-spectrum antibiotics; and individualized vasoactive agents directed to reverse shock. Initial stabilization also includes recognition and correction of hypoxia, hypoglycemia, and hypocalcemia, to which children are particularly prone.[82]

Timely and Appropriate Antibiotics

The Surviving Sepsis Campaign recommends antibiotic administration within 1 hour of recognition of septic shock.[83] Delays in appropriate antimicrobial therapy increase mortality and prolong organ dysfunction in pediatric patients with severe sepsis or septic shock.[100] Institutional antibiotic protocols can facilitate timely medication delivery; host factors, suspected source, and local susceptibility patterns should determine antibiotic selection.[101]

Fluid Resuscitation

Septic shock in children is most frequently marked by relative or absolute hypovolemia; outcomes from shock in children are improved when the shock state is reversed as early as possible. Fluid should be administered using a "push-pull" inline syringe, rapid infuser, or pressure bag to achieve a goal of administering each 20 mL/kg crystalloid fluid bolus over 5 to 15 minutes, followed by reassessment and potentially additional boluses (Fig. 163.3). Fluid resuscitation should continue until vital signs and signs of perfusion improve. Concomitantly, patients should be monitored for signs of fluid overload. Continued shock after administration of 60 mL/kg of isotonic fluid bolus, or signs of fluid overload, such as presence of rales or hepatomegaly, should

be treated with vasoactive agents.[82] We recommend that vasoactive agents be initiated in any pediatric patient with septic shock and hypotension lasting more than 1 hour, regardless of the amount of fluid delivered. In many patients in whom fluid resuscitation is achieved quickly, vasoactive agents may be required before 1 hour. Fluid status may be ascertained with clinical signs of shock, rales and hepatomegaly, as well as central venous oxygen saturation (SvO_2), bedside echocardiogram, serial serum lactate, and noninvasive cardiac output monitoring.

Cohort studies have demonstrated improved mortality and hospital length of stay in septic children with hypotension or organ dysfunction treated with 40 to 60 mL/kg of intravenous (IV) fluid in the first hour.[85] However, a large randomized controlled trial in African children with severe infection, but not hypotension, demonstrated increased mortality in patients receiving 20 to 40 mL/kg in the first hour compared to no fluid.[102] Although these results may be tied to the setting and large proportions of the study population with malaria and anemia, they have led to an increased focus on titrating IV fluid volume to the individual patient, and highlighted that IV fluid bolus should not be empirically given to every child with infection but not shock. Outcomes are similar for crystalloid versus colloid resuscitation, except in Dengue shock where colloid may lead to more rapid improvement.

Vasoactive Agents

Shock that persists despite fluid resuscitation should be treated with vasoactive agents. Dopamine, epinephrine, or norepinephrine may be used as a first-line agent in pediatric septic shock. Because the majority of children with septic shock have depressed cardiac output, dopamine or epinephrine is preferred due to their inotropic and peripheral vasoconstrictor effects. Dopamine has a long history of safety and efficacy in pediatric shock, but due to an association with increased risk of death in adult, epinephrine may be preferred. Norepinephrine is indicated for "warm shock" with high cardiac output.

Obtaining central venous access in an ill child is an uncommon procedure in most EDs, and it is a frequent source of delayed care in pediatric septic shock.[103] We recommend rapid vascular access in critically ill children with peripheral IV catheters or an intraosseous device preferred for initial access. Vasoactive infusions can be administered through a peripheral IV catheter to correct shock until a central venous catheter can be safely placed.[82]

Hemodynamic Monitoring to Direct Therapy

In addition to the clinical examination, assessment of cardiovascular hemodynamics and choice of vasoactive agents can be enhanced by use of bedside echocardiography, as well as invasive and noninvasive cardiac output monitors. Studies that have used devices, including ultrasonic cardiac output monitor, bedside ultrasound, and pulmonary artery catheter, have demonstrated discrepancies between clinicians' classification of hemodynamic states and those revealed by monitoring.[91,92] Although no recommendations can be made at this time, these studies suggest that the customization of therapy aided by hemodynamic monitoring may direct emergency clinicians in their management.

In studies in Brazil and India, central venous oxygen monitoring to direct IV fluid resuscitation has been associated with improved mortality.[104] SvO_2 should be titrated to 70% or more in patients with a central venous catheter.

Corticosteroids

Adrenal insufficiency in sepsis is moderately prevalent, but studies of hydrocortisone replacement in pediatric patients have yielded inconclusive results.[105,106] There is insufficient evidence to support or refute the use of exogenous corticosteroids in children with sepsis, nor is there consensus on the optimal method of diagnosis of adrenal insufficiency. In children in shock despite epinephrine or norepinephrine infusion, testing of a serum cortisol level and administration of hydrocortisone may be considered in those at risk of adrenal insufficiency, including known abnormalities of the hypothalamic pituitary adrenal axis, chronic illness, chronic steroid use, and purpura fulminans.

Glucose

Although children with sepsis may be prone to stress hyperglycemia like adults, they are also prone to hypoglycemia due to their limited glycogen stores. Tight and conventional glycemic control has shown equivalence in critically ill children; a large trial is currently underway to determine optimal glucose-control strategies.[107] We recommend correction of hypoglycemia when present, and cautious use of insulin and frequent glucose monitoring for blood glucose levels more than 180 mg/d.[81]

Impact of Bundled Sepsis Care

Institutional quality improvement programs have improved timeliness and decreased variation in sepsis care.[84,86,108] These programs decreased mortality and ICU and hospital length of stay.[84,86] Institutional care delivery bundles for recognition, resuscitation, and performance measurement are recommended to optimize care.

ACUTE LIFE-THREATENING EVENTS

Principles

An acute life-threatening events (ALTEs) is "an episode that is frightening to the observer" and characterized by a combination of apnea, color change, change in tone, choking, or gagging. Typically these children are younger than 1 year old with the most common presenting age between 2 to 4 months old. Children with ALTEs pose a challenge, because the causes range from minor to life-threatening; and commonly a definitive etiology is not identified. In the minority of cases where an etiology is identified, it is most typically gastrointestinal reflux, seizures, or respiratory illness. More critical causes of ALTEs include non-accidental trauma, congenital heart disease, bacterial infection, and neurologic or metabolic abnormalities.

Clinical Features

The infant (<12 months old) with a history of an ALTE often appears well on presentation. Nearly 50% of children brought to the ED after an ALTE have an entirely normal clinical examination, and the final diagnosis often correlates poorly with the presenting signs and symptoms, which can include cyanosis, breathing difficulties, abnormal movements, loss of consciousness, vomiting, pallor, and choking.

Diagnostic Testing

There is no evidence to support a standard set of tests that should be performed on all children with ALTE.[109] ED evaluation of children with ALTE may include the tests listed in Table 163.5. Routine testing on all patients is low yield, with only 3% of tests contributing to a diagnosis that is not already likely based on the history and physical examination. The risk of serious bacterial infections is similar to age-matched cohorts without ALTE, so evaluation for bacterial infection should proceed according to

TABLE 163.5

Emergency Department Studies for Acute Life-Threatening Event*

TEST	POTENTIAL ETIOLOGY DETECTED
CBC	Anemia
Viral and bacterial cultures, including RSV and pertussis	Infection
Urinalysis	Infection
Electrolytes	Dehydration
Glucose	Hypoglycemia
Liver enzymes	Metabolic disorder
Toxicology screen	Poisoning
Chest x-ray	Infection; cardiomegaly
Brain CT scan	Mass; hemorrhage
Skeletal survey	Non-accidental trauma
ECG	Arrhythmia Congenital cardiac abnormality

*There are no recommendations that apply to every patient, and diagnostic testing is based on the emergency clinician's assessment and the patient's clinical presentation.
CBC, Complete blood count; *CT,* computed tomography; *ECG,* electrocardiogram; *RSV,* respiratory syncytial virus.

TABLE 163.6

Potential Risk Factors for Serious Etiology Following an Acute Life-Threatening Event*

	ADMISSION TO HOSPITAL	INFECTION
Past medical history	Prematurity Comorbidities <1 month old[123] Prior ALTE	Prematurity
History	Color change to blue >1 event/24 hours Absence of choking Absence of URI symptoms	Fever
Physical examination	Abnormal findings in ED	Ill-appearing Fever

Note: Several clinical prediction rules have been proposed combining these elements to identify children at low risk of disease, who can be safely discharged from the ED.
*None of these rules have been externally validated.
ALTE, Acute life-threatening event; *ED,* emergency department; *URI,* urinary tract infection.
Mittal MK, Sun G, Baren JM: A clinical decision rule to identify infants with apparent life-threatening event who can be safely discharged from the emergency department. Pediatr Emerg Care 28(7):599-605, 2012; Kaji AH, Claudius I, Santillanes G, et al: Apparent life-threatening event: multicenter prospective cohort study to develop a clinical decision rule for admission to the hospital. Ann Emerg Med 61(4):379-387. e374, 2013; Claudius I, Keens T: Do all infants with apparent life-threatening events need to be admitted? Pediatrics 119(4):679-683, 2007.

usual clinical judgment. Other testing should also be tailored to the child's history and physical examination findings. Overall the highest yield tests, such as an upper gastrointestinal series, pertussis antigen, and pH probe, are not typically performed in the ED or do not result quickly.

Disposition

High risk and ill-appearing infants should be admitted, as should infants with more than one episode of ALTE or those requiring resuscitation. Some patients with ALTE may be appropriate for discharge with close follow-up (Table 163.6). Otherwise healthy infants with their first episode, particularly when associated with feeding and a normal physical examination may be discharged assuming close follow-up can be guaranteed and the patient undergoes a period of observation in the ED for 3 to 4 hours, to ensure that there are no signs of progressive disease. Clinical prediction models have been derived but demonstrate imperfect sensitivity for poor outcomes and have not been validated.[110,111] The outcome of an ALTE depends on the underlying cause. The majority of ALTE studies with complete follow-up demonstrate no deaths.[110]

KEY CONCEPTS

- Exact rates, depths, and ratios of compressions to ventilations in cardiopulmonary resuscitation (CPR) are not based on high quality evidence. It is most important to push fast, deep, and without interruptions. We recommend a depth of 1½ inches in infants and 2 inches in older children.
- Unlike in adults, conventional CPR versus compression-only CPR is recommended in most children, because children often arrest from respiratory causes. This is less important for the emergency department (ED) setting where compressions and ventilations should begin almost simultaneously.
- In pediatric arrest, timely acquisition of vascular access is much more important than the site of access; when access is needed, the intraosseous route is recommended.
- Central venous access is not required emergently in most pediatric arrests.
- The focus in pediatric cardiac arrest should be on providing high quality, uninterrupted compressions and ventilations, not medication administration.
- If defibrillation is indicated, begin at 2 J/kg, followed by 4 J/kg, and if needed increase to 10 J/kg for subsequent shocks.
- Unless specifically indicated, do not administer calcium or sodium bicarbonate in pediatric arrest of unknown cause.
- After return of circulation, focus on avoiding hypotension (intravenous [IV] fluids and vasoactive medications) and hyperthermia (antipyretics and cooling blankets).
- When death is likely, family presence at pediatric resuscitations provides significant lasting benefits for the family.
- There are no universal criteria to terminate resuscitation efforts in children. We recommend considering the termination of resuscitation after 30 minutes for unwitnessed out of hospital pediatric cardiac arrest.
- Due to the inherent risks associated with pediatric intubation, providers who lack extensive experience caring for critically ill children should focus on bag-mask ventilation, particularly for children in cardiac arrest or infants younger than 1 year old.
- Signs of sepsis overlap with the signs of many non-critical febrile illnesses in children.
- Treatment of pediatric sepsis in the United States should include rapid fluid boluses (total of 40 to 60 mL/kg for hypotension),

KEY CONCEPTS—cont'd

broad-spectrum antibiotics, early use of vasopressors for signs of poor perfusion, and close monitoring.
- Compared to adults, septic children more commonly display cold shock with hypovolemia and peripheral vasoconstriction.
- Most children with an acute life-threatening event (ALTE) do not require any diagnostic tests.
- Otherwise healthy children with a first ALTE occurring while feeding/choking, normal examination, prompt follow-up, and no high-risk features are candidates for discharge after a period of observation in the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 163: QUESTIONS & ANSWERS

163.1. A 3-year-old girl presents to the emergency department (ED) with fever, lethargy, and a petechial rash. Her initial vital signs are: heart rate, 186 bpm; respiratory rate, 60 breaths per minute; blood pressure, 62/21 mm Hg; and pulse oximetry, 92% on room air. She is listless and ill appearing, with pale, cool extremities, and a capillary refill time of 4 to 5 seconds. After application of 100% oxygen and obtaining vascular access, what treatment should the patient receive next?

A. Calcium gluconate 50 to 100 mg/kg by intravenous push (IVP)
B. Ceftriaxone 100 mg/kg by rapid IVP
C. Dopamine at 5 to 10 mcg/kg/minute continuous infusion
D. Glucose 0.5 g/kg by rapid IVP
E. Normal saline 20 cc/kg by rapid IVP

Answer: E. Septic shock in children presents most commonly as a physiologic state of hypovolemia and increased systemic vascular resistance. Immediate and rapid isotonic crystalloid administration is the initial step for all children in shock.

163.2. All of the following are correct features of cardiopulmonary resuscitation (CPR) in children in cardiac arrest *except:*

A. Complete release of chest wall between chest compressions
B. Compression:ventilation rate of 15:2 once airway is secured with an endotracheal tube (ETT)
C. Depth of at least one-third the anteroposterior chest diameter
D. Rate of at least 100 compressions/minute
E. Use of a backboard under patient

Answer: B. In the intubated patient, compressions should be administered continually at a rate of at least 100/minute and ventilations continuously at a rate of 8 to10 breaths/minute.

163.3. Which of the following statements best describes the practice of family presence in the emergency department (ED) for children?

A. Is not recommended; family presence sets up a medical legal minefield for the emergency clinician.
B. Is not recommended; providers perceive more stress, leading to clinical errors and family confusion.
C. Is recommended; although providers have been shown perceive more stress when parents are present, clinical care variables have not been shown to be impacted and families are more likely to effectively work through their grieving process.
D. Is recommended; providers do not perceive their presence, the grieving process is promoted, and clinical care variables are improved.

Answer: C. The American College of Emergency Physicians (ACEP) and American Academy of Pediatrics (AAP) recommend that family be given the option of being present during their child's resuscitation. Families report their presence comforts their children, helps them appreciate the efforts of providers, facilitates their understanding of the gravity of the situation, and promotes the grieving process. Physicians reported increased stress from family presence, but no differences were detected in clinical care variables.

CHAPTER 164

Neonatal Resuscitation

Ryan D. Kearney | Mark D. Lo

PRINCIPLES

Approximately 10% of newborns require some assistance at birth, with 1% requiring extensive resuscitative measures.[1] Knowledge of neonatal physiology, appropriate equipment, and procedural skills are essential to successful resuscitation. Preparation for neonatal resuscitation requires an understanding of how it differs from pediatric and adult resuscitation, primarily as follows:

1. Newborns have rapidly changing, dynamic cardiopulmonary physiology, with a unique range of normal vital signs.[2,3]
2. Neonatal resuscitation is almost entirely respiratory (not cardiac) management.[2]
3. Neonates require special and dedicated equipment.

PATHOPHYSIOLOGY

Transition From Fetal to Extrauterine Life

The successful transition from fetal to extrauterine life requires three major cardiorespiratory changes: (1) removal of fluid from unexpanded alveoli to allow ventilation; (2) lung expansion and establishment of functional residual capacity; and (3) redistribution of cardiac output to provide lung perfusion. Failed development of adequate ventilation or perfusion leads to persistent shunting, hypoxia and, ultimately, a deleterious reversion to fetal physiology.[2]

In utero, fetal nutrient and gas exchange is dependent on the placenta, a temporary organ with remarkably low vascular resistance, as well as the maternal circulation. As a result of its low resistance, the placenta receives approximately 30% of total fetal cardiac output between 18 and 41 weeks of gestation. In contrast, fluid-filled fetal alveoli have increased vascular resistance, leading to poor perfusion of the developing lung. The pulmonary arterial bed is so vasoconstricted that the fetal lung receives only 40% of right ventricular output and approximately 10% of total cardiac output; most of the right ventricular output is shunted from the pulmonary artery through the ductus arteriosus to the descending aorta.[4,5] An additional right to left shunting occurs at the level of the foramen ovale, with relatively oxygen-rich blood shunted from the right to left atrium. Reversal of these two shunts is essential to the successful transition into extrauterine life and is facilitated by the significant drop in pulmonary vascular resistance that occurs at birth. The first step in this process is alveolar fluid clearance.

Removal of this fluid is partially accomplished by vaginal delivery, which provides some compression of the fluid out of the alveoli into the bronchi, trachea, and pulmonary capillary bed. The remaining fluid is largely evacuated by the first few breaths, with the quality of the first few breaths crucial to establishing adequate ventilation. Alveolar expansion requires the generation of high intrathoracic pressures and the presence of surfactant to maintain alveolar patency. Because the lung is one of the last organs to reach structural and functional maturity, interruptions in this coordinated physiologic process, although rare, should be nonetheless anticipated in all deliveries, particularly those outside of the delivery room.[6]

After the first few breaths, pulmonary vascular resistance decreases as a result of alveolar oxygen exposure. Simultaneously, clamping of the umbilical cord removes the placenta from circulation, predictably increasing systemic vascular resistance. Shunting through the ductus arteriosus reverses as systemic vascular resistance increases; this usually ceases altogether by 15 hours of age as the ductus arteriosus also constricts. This reversal of flow redirects all right ventricular output to the lungs. However, hypoxia or acidosis can cause the pulmonary vascular bed to constrict again and, when severe or prolonged, recurrent pulmonary vascular constriction can cause the ductus arteriosus to reopen. The reinstitution of fetal circulation, with its attendant shunting, leads to ongoing hypoxia and is termed *persistent fetal circulation*.[2,5] When indicated, resuscitation facilitates the first few breaths, prevents and reverses ongoing hypoxia and acidosis, and assists the newborn in the transition to extrauterine life.

INDICATIONS FOR RESUSCITATION

At least one person, whose exclusive role is to ensure safe transition of the newborn, should be present for all deliveries, including those that occur outside the delivery room. Any infant born outside of a delivery room should be anticipated to need resuscitation.[1-3] Although minimal intervention may be required, a standardized approach should still be followed. Some specific conditions increase the likelihood that additional resuscitative efforts will be required.

Hypoxia

Even in the uncompromised newborn, it can take 10 minutes for blood oxygen saturation to reach normal extrauterine levels.[1] Pulse oximetry may assist in determining hypoxemia, but it may take several minutes for a reliable waveform to be achieved.[7,8] In utero or intrapartum asphyxia (pathologic lack of oxygen to the fetus before or during delivery) can precipitate a sequence of events that results in primary or secondary apnea. With initial hypoxia, rapid gasps are followed by cessation of respirations (primary apnea) and, if prolonged, decreased heart rate (HR). Ostensibly normal respiratory effort does not ensure adequate ventilation. However, bradycardia in the newborn (HR < 100 beats/min) almost always reflects inadequate ventilation and oxygenation. As such, bradycardia is a major indicator of hypoxia.[1,2] Simple stimulation is required at the onset of primary apnea to stimulate ventilation and reverse bradycardia. If asphyxia persists, the newborn takes several final deep, gasping breaths, followed by cessation of respirations (secondary apnea); this is accompanied by worsening bradycardia, refractory to simple stimulation, and eventually hypotension. For newborns with secondary apnea,

more vigorous and prolonged resuscitation is needed to restore ventilation and adequate circulation.[2]

Hypothermia

Drying and warming the newborn are vital to initial resuscitation because the newborn's inability to maintain normothermia (>36.5°C [97.7°F]) has potentially dire consequences. Newborns cannot generate heat by shivering, cannot retain heat due to low fat stores, and have excess heat loss due to their large surface-to-volume ratio. Exacerbating these challenges in the immediate postpartum period, newborns have an acutely elevated metabolic rate, are covered with amniotic fluid, and are suddenly exposed to a relatively cool environment. Body temperature rapidly decreases, with hypothermia accelerating metabolic acidosis, oxygen consumption, hypoglycemia, and apnea.[1-3] Prematurity and very low-birth-weight status exacerbate these consequences and require extra efforts to mitigate.[1]

Hypoglycemia

Poor glycogen stores, coupled with immature hepatic enzymes, place the normal newborn at increased risk for hypoglycemia. Hypoglycemia is particularly common in premature and small-for-gestational-age newborns, as well as those born to diabetic mothers. Hypoglycemia may also be a response to other factors, including respiratory illness, hypothermia, polycythemia, asphyxia, and sepsis. Hypoglycemia can be asymptomatic or may cause an array of symptoms, including apnea, color changes, respiratory distress, lethargy, jitteriness, seizures, acidosis, and poor myocardial contractility.[9,10] A low blood glucose level, particularly when prolonged, recurrent, or associated with hyperinsulism, has been associated with adverse neurologic outcomes[9]; correction of hypoglycemia, if detected expeditiously, improves outcomes.[11] Neonatal hypoglycemia is generally defined as a blood glucose level less than 40 mg/dL, although this number serves as more of a guideline than a strict cutoff. All newborns exhibiting signs of hypoglycemia, with glucose levels less than 40 mg/dL, should receive intravenous (IV) glucose. Of note, bedside glucometers generally underestimate plasma glucose levels by approximately 10 mg/dL.[10]

Hypovolemia

Clinically significant hypovolemia is rare and usually secondary to blood loss. Risk factors include known maternal hemorrhage during delivery, prematurity, newborns with overt shock, and initiation of CPR.[1-3,12] Hemorrhage can lead to respiratory depression and overt shock in the newborn, whether secondary to abruptio placentae, placenta previa, umbilical cord accident, or trauma. In the newborn, hemorrhage is one of the few situations in which fluid resuscitation and volume expansion improves outcomes. The following formula should be equivalent to gestational age in weeks:

$$\text{Newborn mean arterial pressure} \approx \text{diastolic pressure} + [\text{pulse pressure}/3]$$

where pulse pressure = systolic pressure − diastolic pressure. Examination findings consistent with hypovolemia or hemodynamically significant hemorrhage include pallor, despite oxygenation, weak pulses with a rapid HR, and poor response to resuscitation.[1-3,12]

Prematurity

Premature infants, especially those born before 34 weeks of gestational age, are uniquely at risk due to their pulmonary immaturity and susceptibility to hypothermia. Those requiring delivery room cardiopulmonary resuscitation (CPR) have increased risk of mortality, bronchopulmonary dysplasia, severe brain injury, pneumothorax, and intestinal perforation.[13] For these reasons, in utero transfer of high-risk pregnant women to tertiary centers possessing expertise and experience with premature infant resuscitation has been associated with improved neonatal outcomes.[14] Intubation should be performed for the premature newborn in respiratory distress, which is clinically suggested by retractions, desaturation, or tachypnea.[15] In certain cases, surfactant may be delivered via an endotracheal tube (ETT) shortly after birth.

Meconium-Stained Amniotic Fluid

Meconium-stained amniotic fluid (MSAF) indicates potentially significant newborn stress prior to delivery. Aspiration of meconium and its consequences can be avoided, or at least significantly limited, by rapid intervention. Previous recommendations stipulated suctioning meconium from the newborn's airway after delivery of the head but before delivery of the shoulders (intrapartum suctioning). However, there appears to be no benefit from intrapartum suctioning.[16,17] Therefore, current recommendations no longer advise routine intrapartum suctioning of newborns with MSAF. To prevent aspiration of meconium, previous recommendations also stipulated tracheal suctioning of all nonvigorous newborn with MSAF immediately on delivery and before any other resuscitative efforts (including drying and stimulation). However, routine endotracheal intubation in nonvigorous and vigorous term, meconium-stained newborns has shown no benefit, including the incidence of meconium aspiration syndrome (MAS), pneumothorax, oxygen need, stridor, seizure, or hypoxic ischemic encephalopathy.[18] Standard measures to support adequate ventilation and oxygenation should be initiated for all infants born through MSAF, with a small subset eventually requiring endotracheal intubation, as warranted.[1]

The most recent recommendations from the American Heart Association have changed the practice of tracheal suctioning after delivery for meconium aspiration. Indications for intubation in newborns born through MSAF are the same as those for all neonates; meconium aspiration should only be performed if indicated for signs of airway obstruction secondary to meconium that do not improve despite standard resuscitative measures, including warming and drying and initiation of effective positive-pressure ventilation (PPV). When performing tracheal suctioning, a meconium aspirator (Fig. 164.1) should be attached to the appropriate-sized ETT and connected to wall suction at 100 mm Hg or less. On intubation by direct laryngoscopy, the ETT is then withdrawn while suction is applied. Serial re-intubation with suctioning should be repeated to remove obstructing meconium or until the infant becomes vigorous, which is usually accomplished after two rounds. If bradycardia or apnea persists beyond two passes, ongoing resuscitation should include bag-mask ventilation (BMV) and consideration of endotracheal intubation to secure

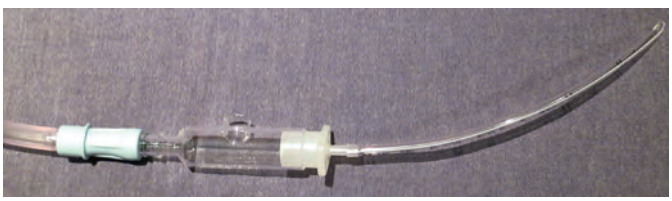

Fig. 164.1. Meconium aspirator with suction and 3.0 uncuffed ETT attached. (Courtesy Seattle Children's Hospital, Seattle, WA.)

the airway. In tertiary centers with skilled providers, lung lavage with dilute surfactant may be beneficial, particularly if prolonged intubation appears inevitable.[19]

Maternal Factors

Infection

Maternal infection (chorioamnionitis) is a particularly common trigger for premature delivery; premature infants are themselves more susceptible to infection. Therefore, IV antibiotics should be administered after obtaining blood cultures and a complete blood count should be carried out in all infants born before 37 weeks of gestation.

Medications

Medications provided to the mother during labor or illicit drugs taken before delivery, usually opioids, can augment newborn respiratory depression. Maternal opioid administration or antenatal drug abuse should be considered in any newborn with isolated respiratory depression that persists, despite a seemingly successful initial resuscitation. As in adults, opioid-induced respiratory depression could be reversed with naloxone.[1,20] However, naloxone may precipitate acute withdrawal and seizures in the newborn of an opioid-dependent mother; thus, naloxone is not recommended in the initial resuscitation of the newborn.[3,21] Suspected opiate toxicity in the newborn should be treated with support of oxygenation and ventilation rather than pharmacological reversal. This should include use of a bag-mask device and, if necessary, intubation.

Withholding and Discontinuing Resuscitation

No reliable and widely adopted set of parameters has been identified for newborns who should not receive resuscitative efforts.[23] Resuscitation is not currently recommended for neonates with a confirmed gestational age less than 23 weeks, those with birth weight less than 400 g, and those with confirmed anencephaly, trisomy 13, or trisomy 18.[23,24] Parental request has been shown to be the most important factor determining resuscitative efforts for newborns at 22 to 25 weeks of gestation; most neonatologists consider a gestational age more than 25 weeks of gestation as the cutoff for obligatory resuscitation, even with parental refusal.[25] In the setting of uncertain gestational age and unclear or conflicting parental wishes, the recommendation is to initiate resuscitation. Similarly, if prognosis is uncertain at the time of delivery, resuscitation should be attempted until additional data can be obtained that can inform prognostication and align with parental wishes. Outside the delivery room, every attempt should be made to stabilize the neonate until further resuscitation would clearly not improve the likelihood of survival with acceptable morbidity. Neonates with no signs of life (asystole, apnea), after 10 minutes of resuscitation, have high mortality or severe lifelong developmental delay, and resuscitation can be terminated.[24,26] This is a rare and inherently challenging decision to make and must account for availability of local resources and personnel skill, transportation needs and options, and parental preference. However, enhanced resuscitation techniques and postresuscitation therapeutic hypothermia have recently shown promise, even for neonates with a 10-minute APGAR score of zero,[27] highlighting the importance of dialogue with the parent(s) and acknowledgment of their feelings regarding the risks of morbidity. Parents should actively participate in the decision to continue or withdraw resuscitative efforts in cases in which there is prognostic uncertainty. For infants with a low 10-minute APGAR score but some signs of life, especially when aligned with parental preference, resuscitation efforts should continue until further prognostication can occur.

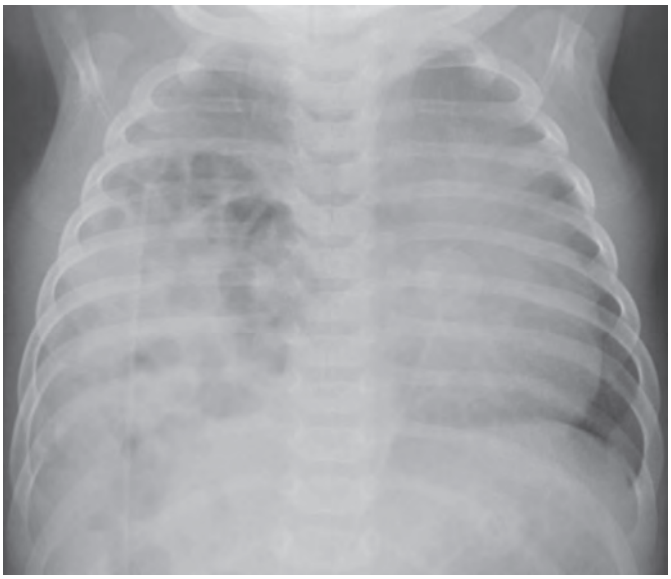

Fig. 164.2. Chest radiograph reveals right-sided congenital diaphragmatic hernia. (Courtesy Seattle Children's Hospital, Seattle, WA.)

SPECIAL ANATOMIC ANOMALIES

Diaphragmatic Hernia

In addition to pulmonary hypoplasia, neonates with diaphragmatic hernias have exquisitely reactive pulmonary vascular beds, predisposing them to potentially fatal pulmonary vasospasm in the immediate and late postnatal period.[28] Examination findings concerning for congenital diaphragmatic hernia include barrel chest, ipsilateral absence of breath sounds, tracheal or point of maximum cardiac impulse displacement, and scaphoid abdomen. Bag-mask ventilation will distend the stomach, which is usually intrathoracic, further worsening respiratory distress. The neonate should be emergently intubated if a prenatal diagnosis of diaphragmatic hernia is known or if a diaphragmatic hernia is diagnosed on the chest radiograph (Fig. 164.2).

Myelomeningocele and Omphalocele

Infants with myelomeningocele should never be placed supine but instead be placed prone or on the side to avoid pressure on the defect. Resuscitation should proceed from this modified position (Fig. 164.3). For unclear reasons, myelomeningocele is associated with an elevated risk for latex allergy, necessitating efforts to avoid latex sensitization in these neonates.[29] The spinal defect should be gently wrapped with sterile gauze pads soaked in warm sterile saline and enclosed with plastic wrap.[30] Infants with gastroschisis or omphalocele should be resuscitated as needed, and these defects should also be covered with an occlusive plastic wrapping to decrease water and heat loss.[31] These newborns often require parenteral maintenance fluid infusion, orogastric tube for gastric decompression, and antimicrobial prophylaxis with IV antibiotics.[31]

Choanal Atresia

Because newborns are obligate nose breathers, bilateral choanal atresia causes upper airway obstruction and often severe respiratory distress. Choanal atresia can be rapidly diagnosed by the

Fig. 164.3. Preoperative myelomeningocele, highlighting the obvious anatomic challenges and sensitivities required in resuscitation of neonates with this condition. (Courtesy Mandy Breedt, Division of Neurosurgery, Seattle Children's Hospital, Seattle, WA.)

inability to pass a catheter through either naris into the posterior oropharynx. An oral airway device can bypass the obstruction. Special attention should be paid to initial the physical examination of these children because these infants often have a multiple congenital anomaly syndrome.

Pierre Robin Sequence

The hallmark of this abnormality is profound micrognathia, resulting in glossoptosis (retraction or downward displacement of the tongue) and cleft palate. Pierre Robin sequence, therefore, confers a high risk for significant upper airway obstruction. A nasal or oral airway should be able to bypass the obstruction; if not, intubation may be necessary. Given the technical challenges of performing endotracheal intubation on a patient with Pierre Robin sequence, fiberoptic intubation is often needed, although prone positioning and a laryngeal mask airway (LMA) or other supraglottic airway device can be attempted to support ventilation.[32] Consultation with anesthesiology or otolaryngology may be required.

Congenital Cardiac Disease

Echocardiographic evidence of congenital heart disease (CHD) is as high as 5% for term newborns.[33] However, critical CHD, defined as requiring surgery or catheter-based intervention in the first year of life, accounts for only up to 50% of CHD cases.[33] Stereotypic examination findings seen in critical CHD include a blood pressure gradient between the upper and lower extremities, weak femoral pulses, central cyanosis, pathologic murmur, and hepatomegaly. These signs of cardiogenic shock in a newborn may be fairly indistinguishable from those of severe sepsis and respiratory failure. Resuscitation of a newborn with known or suspected critical CHD should therefore include standard ventilatory management, as well as empiric antimicrobial therapy. Cardiomegaly on a chest radiograph is more likely consistent with cardiogenic shock.[34] Some common laboratory findings include polycythemia and unexplained acidosis. Many newborns with critical CHD have a ductal-dependent lesion and are likely to experience profound physiologic decompensation—defined by severe metabolic acidosis, seizure, cardiac arrest, or renal or hepatic injury—on closure of the ductus arteriosus.[35] Prostaglandin E_1 (PGE_1) should be used in lesions with ductal-dependent systemic or pulmonary blood flow (Box 164.1).[36] In case of an uncertain diagnosis or in preparation for transport to a specialized facility, prostaglandin should be started via continuous IV infusion. A second peripheral IV is recommended to treat the possible adverse effects of prostaglandin, including hypotension, tachycardia, and apnea. Continuous PGE_1 should begin soon after birth,[36] with gradual dose titration to a maximum of 0.1 μg/kg/min. For a more in depth discussion on CHD, see Chapter 170.

BOX 164.1

Ductal-Dependent Congenital Cardiac Lesions

DUCTAL-DEPENDENT PULMONARY BLOOD FLOW:
Critical pulmonary stenosis, atresia
Severe tricuspid stenosis, atresia
Severe tetralogy of Fallot

DUCTAL-DEPENDENT SYSTEMIC BLOOD FLOW:
Hypoplastic left heart syndrome
Critical aortic stenosis
Interrupted aortic arch

BOX 164.2

Equipment Checklist for Neonatal Resuscitation

1. Gown, gloves, and eye protection (universal precautions)
2. Timing device
3. Blankets (to warm and dry infant)
4. Plastic wrap (for omphalocele, gastroschisis, possibly premature infant)
5. Radiant warmer
6. Bulb syringe
7. Suction and suction catheters (sizes 5, 8, and 10 Fr)
8. Self-inflating (450 and 750 mL) and flow-inflating (250 and 450 mL) bags
9. Masks (premature, newborn, and infant sizes)
10. Laryngoscope with straight blades (nos. 00, 0, and 1)
11. Endotracheal tubes with stylets (2.5, 3.0, 3.5, and 4 mm), uncuffed
12. Scissors and tape to stabilize endotracheal tube
13. Pediatric CO_2 detector
14. Meconium aspirator
15. Umbilical catheters (3.5 and 5 Fr)
16. Hemostats, sterile drapes and gloves, povidone-iodine solution, scalpel, umbilical tape, suture, and three-way stopcock for umbilical vessel catheterization

PREPARATION

To maximize the effectiveness of resuscitation, all emergency departments should have an age- and weight-appropriate prestocked drug pack, standardized equipment (Box 164.2), and staff trained on newborn resuscitation.[1,3] The pediatric length-based resuscitation tape (Broselow Luten tape) can be used to determine equipment size and drug dosages for newborn resuscitation of infants weighing 3 kg or more.[37,38] A dedicated neonatal resuscitation cart, organized according to the Neonatal Resuscitation Program (NRP) algorithm, increases the speed of equipment retrieval and is preferred by providers to other organizing schemes.[39] When available, additional maternal information (Box 164.3) can help anticipate resuscitation needs so that appropriate staff, equipment and disposition plans can be expeditiously managed.

Universal precautions, including gown, gloves, and eye protection, should be followed during neonatal resuscitations. An

Fig. 164.4. Appropriate self-inflating resuscitator with appropriate neonatal-sized mask attached. This device has additional functionality with manometer and single-use positive end-expiratory pressure (PEEP) valve attachments. (Courtesy Seattle Children's Hospital, Seattle, WA.)

TABLE 164.1

Endotracheal Tube Size by Birth Weight and Gestational Age

BIRTH WEIGHT (kg)	GESTATIONAL AGE (wk)	ETT TUBE SIZE (mm, uncuffed)	DEPTH OF INSERTION (cm)
<1	<28	2.5	7
1–2	28–34	3	8
2–3	34–38	3.5	9
3+	38+	3.5–4	10

ETT, Endotracheal tube.
Adapted from American Academy of Pediatrics; American Heart Association: neonatal resuscitation textbook, ed 6, Elk Grove Village, IL, 2011, American Academy of Pediatrics.

BOX 164.3

Maternal History Questions

1. What is the estimated gestational age?
2. Is this a multiple gestation?
3. Is meconium present?
4. Is there a history of vaginal bleeding?
5. Were medications given or drugs taken?
6. Was there documented maternal fever?
7. Did mother have routine prenatal care? If so, were any abnormalities seen on prenatal ultrasonography?

external heat source should be turned on early and the table warmed prior to the start of resuscitation. Hypothermia is an independent risk factor for neonatal mortality worldwide.[40,41] Similarly, hyperthermia is an effect modifier of neonatal encephalopathy and correlates with respiratory depression, cerebral palsy, and mortality.[42] Correct equipment size is essential; in particular, respiratory supplies are most likely to be used and are key to most resuscitative efforts. Appropriately sized self-inflating devices (Fig. 164.4) decrease complications from overventilation, prevent injury, and limit the inability to ventilate due to improper mask fit. When available, and in the hands of experienced providers, flow-inflating devices have the added ability to deliver continuous positive airway pressure (CPAP), control ventilation pressure with greater precision, and ensure a proper fit. Table 164.1 lists the recommended ETT sizes by birth weight and gestational age.

MANAGEMENT

As part of their shared NRP curriculum, the American Heart Association and American Academy of Pediatrics, with the International Liaison Committee On Resuscitation, have developed a newborn resuscitation algorithm (Fig. 164.5). This stepwise approach is detailed below.[1-3] However, if a term neonate is crying and appears to have good tone, she or he can be warmed, dried, and returned to the mother for ongoing care and evaluation, without any additional resuscitation efforts.[1]

Newborn Resuscitation Algorithm

Dry, Warm, Position, Suction, Stimulate, and Assess Need for Further Intervention

Hypothermia increases metabolic demand and oxygen consumption, which can render seemingly effective resuscitation efforts futile. To prevent these and more subtle sequelae of hypothermia, all newborns should be dried immediately on delivery and placed under a radiant heat source. In the case of crying term infants with normal tone, this may be accomplished by simple drying and skin to skin contact with the mother.[1] Wet blankets should be replaced with dry blankets and preferably warm linens, but the baby should be left uncovered to facilitate radiant warming and team access, when required. All resuscitation techniques are designed to be performed with these temperature-controlling efforts in place.[1] The supine neonate should be further positioned to maximize air entry and avoid obstruction of airflow. Due to a relatively large occiput and anterior glottic opening, airway patency is best achieved with the neck in slight extension. A slightly extended position that aligns the posterior pharynx, larynx, and trachea is best accomplished by placing a rolled diaper or small towel *under the infant's shoulders.* Placement under the neck is not useful. However, a towel that is too large and under the shoulders can also lead to airway occlusion due to hyperextension of the neck.

Only if meconium is present and the newborn has poor tone, poor respiratory effort, or bradycardia (HR < 100 beats/min) after 1 minute of appropriate PPV should the trachea be suctioned with an ETT and meconium aspirator attachment. Poor respiratory effort and obvious obstruction from secretions should otherwise be treated with bulb or mechanical suction (≈100 mm Hg wall suction). Upper airway suctioning, including that performed with a bulb syringe, should be reserved only for newborns with these signs because suctioning has been associated with decreased lung compliance, bradycardia, and lowered cerebral blood flow velocity.[1] In one randomized study comparing NRP-recommended bulb suctioning versus mouth wiping, there were no differences in mean respiratory rate, use of advanced resuscitation efforts, APGAR scores, neonatal intensive care unit (NICU) admission, and discharge oxygen saturation levels.[42] When suction is indicated, the NRP protocol should be followed, with the mouth suctioned first, followed by the nose. This sequence helps avoid aspiration of oral secretions if the neonate inspires after nasal suctioning. Overly vigorous or deep suctioning should be avoided because it can cause significant vagal stimulation and subsequent bradycardia or apnea.[2,43] Because NRP recommendations stipulate suctioning with less than 100 mm Hg, emergency clinicians should be judicious with syringe use because even standard delivery bulb syringes produce a modest negative pressure, which easily exceed this threshold.[43]

For most term neonates, these measures stimulate breathing sufficiently and may be all that is required to resuscitate a newborn. If adequate respirations are still not present, additional stimulation should be given. This is best done by flicking the soles of the feet and rubbing the back; more aggressive efforts could prove

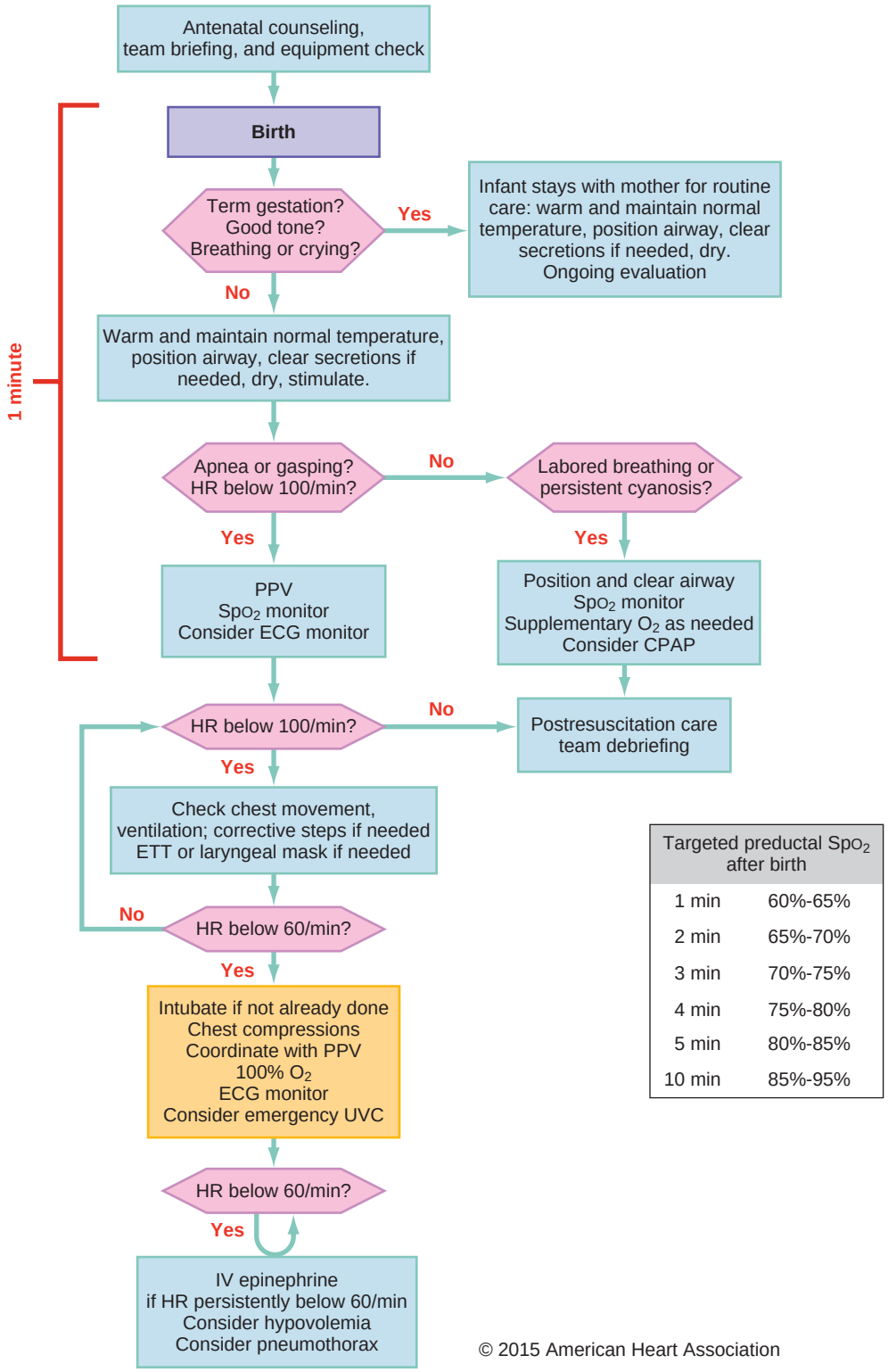

Fig. 164.5. Algorithm for neonatal resuscitation. *ECG,* Electrocardiogram; *ETT,* endotracheal tube; *HR,* heart rate; *PPV,* positive-pressure ventilation; *UVC,* umbilical vein cannula. (Adapted from Wyckoff MH, et al: Part 13: neonatal resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 132:S543–S560, 2015.)

harmful. If stimulation and warming efforts prove inadequate, PPV is required, followed by intubation, if necessary.

Time is an important component of NRP guidelines. Within the first 60 seconds of life, the newborn should be assessed with simultaneous warming, drying, and stimulation; if necessary, upper airway clearance should be performed (see Fig. 164.5). If the HR is below 100 beats/min, or if the newborn has primary apnea or respiratory distress, PPV and pulse oximetry should be initiated within the first minute of life. If bradycardia (HR < 60 beats/min) persists, despite adequate ventilation, chest compressions should be initiated. HR calculation can be manual—by palpation of the pulse at the base of the umbilical or auscultation

TABLE 164.2

APGAR Score[a]

	POINTS		
SIGN	0	1	2
Heart rate (beats/min)	Absent	Slow (<100)	≥100
Respirations	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Active, good flexion
Reflex irritability	No response	Grimace	Cough, sneeze
Color	Blue, pale	Pink body, blue hands and feet	Pink

[a]Calculate at 1, 5, and 10 minutes of life.

BOX 164.4

Intubation Corrective Action and Deterioration Mnemonics

MR SOPA
M: Mask adjustment
R: Reposition airway
S: Suction mouth and nose
O: Open mouth
P: Pressure increase
A: Airway alternative

DOPE
D: Displacement of ETT
O: Obstruction of ETT
P: Pneumothorax
E: Equipment failure

of cardiac sounds—with pulse oximetry, or with a standard electrocardiographic lead.[44] Persistent bradycardia is usually secondary to inadequate ventilation. Thus, intubation is recommended in the event that chest compressions are indicated.

Routinely counted at 1, 5, and 10 minutes of life, the APGAR score (Table 164.2) is a composite that reflects HR, respiratory effort, muscle tone, reflex irritability, and color. The score is primarily for assessing the need for (1 minute) and efficacy of (5 minute) ongoing resuscitative measures. In the setting of modern algorithm-based resuscitation, low 5- and 10-minute APGAR scores are associated with increased mortality because they identify infants who are failing medical management.[44] Muscle tone and reflex irritability do not significantly aid in the assessment of the newborn during resuscitation.[44,45] Instead, HR and respiratory effort are the important indicators and should be continuously monitored. Skin color is a poor indicator of oxyhemoglobin saturation during the first several minutes of life while the transition from fetal to infant circulation ensues.[46-48] In this brief period, pulse oximetry may be a useful tool to assess the oxygenation status of the newborn.[7,8,48] NRP guidelines specify pulse oximeter use in only a few select situations—anticipated resuscitation, prolonged PPV use, persistent cyanosis, and use of supplemental oxygen.[1]

Ventilation, Oxygen, Intubation

Any neonate with persistent cyanosis or signs of respiratory distress (eg, grunting, nasal flaring, tachypnea) should be assisted by CPAP or PPV. For apnea, severe respiratory distress, or an HR less than 100 beats/min, BMV (with a manometer, if available) should be initiated. The first breaths often require higher pressures (30–40 mm Hg) to remove lung fluid, with the adequacy of ventilation assessed by chest rise. An initial sustained breath of 2 to 5 seconds may further increase functional residual capacity (FRC) and promote clearance of lung fluid, but several clinical trials have yet to prove the efficacy and safety of this technique.[49-52] Subsequent breaths generally require 20 mm Hg of peak inspiratory pressure.[1,2] To minimize barotrauma and the incidence of pneumothorax, excessive pressures (defined as more than needed to achieve adequate chest rise) should be avoided. An appropriately sized mask with a tight seal (covering the mouth and nose, but not the eyes), proper positioning of the newborn, and use of pressure to attain correct chest wall movement are essential for effective ventilation. Unless otherwise dictated by blood gas levels, recommended ventilation rates are 40 to 60 breaths/min, aimed at achieving a heart rate above 100 beat/min. Current NRP guidelines recommend PPV, but do not delineate between CPAP and PEEP (positive end-expiratory pressure). However, preterm neonates (<33 weeks' gestation) receiving single-inflation CPAP (pressure-controlled inflation at 20 cm H_2O for 10 seconds) appear less likely to be intubated at 72 hours of age, receive more than one dose of surfactant, or develop bronchopulmonary dysplasia (BPD). When BMV is required for more than 2 minutes, an orogastric tube should be placed to prevent respiratory compromise from gastric distention.[2]

Resuscitation with 100% oxygen is no longer recommended.[53-56] There appears to be reduced mortality in infants resuscitated with room air, with no obvious evidence of harm.[56] Resuscitation-induced hyperoxia results in increased oxidative stress, including direct cardiac and renal injury.[57] Neurologic outcomes appear improved by resuscitation with room air versus 100% oxygen, likely due to a reduction in cerebral free radical generation.[1,3,5,56,58] Current NRP guidelines recommend initiating resuscitation with room air and then blending to increasing oxygen concentrations, as needed. Use of 100% oxygen for resuscitation should occur only if the newborn has persistent bradycardia below 60 beats/min bradycardia after 90 seconds. Attempts to restore adequate ventilation are more beneficial than increasing the oxygen concentration. There has been a growing body of literature suggesting that lower initial preductal oxygen saturation in healthy uncomplicated newborns may contribute to the appearance of cyanosis; oxygen saturation after birth may not reach 90% or more until 10 minutes of life.[46-48]

Endotracheal intubation is indicated at several points during neonatal resuscitation—tracheal suctioning for meconium in infants with failure to improve, despite effective PPV; if BMV is ineffective or prolonged; when chest compressions are performed; and for extremely low-birth-weight infants or infants with anatomic anomalies (eg, diaphragmatic hernia). Traditional direct laryngoscopy and videolaryngoscopy are both reasonable options, with video-assisted techniques consistently having improved views but slightly longer total intubation times.[59-61] Confirmation of proper ETT placement should include detection of expired carbon dioxide. Although ultrasonography can show appropriate ETT positioning in term and preterm infants, the gold standard remains plain radiography.[62-66]

If acute deterioration occurs shortly after intubation, equipment must be immediately checked. Consider the DOPE and MR SOPA mnemonics when trying to determine the cause of the deterioration (Box 164.4). In the absence of an obvious explanation, it is safest to extubate the newborn and promptly ventilate with a BMV device by an experienced provider. Needle aspiration

TABLE 164.3

Resuscitation Medications

MEDICATION	CONCENTRATION	DOSE	ROUTE	COMMENTS
Epinephrine	1:10,000	0.01–0.03 mg/kg (0.1–0.3 mL/kg)	IV (preferred) or ETT	
Dopamine	Varies	Continuous infusion at 5 µg/kg/min; increase to 20 µg/kg/min as needed.	IV	
Glucose	$D_{10}W$	2–4 mL/kg	IV	Avoid higher concentrations
Volume expanders	O-negative packed RBCs	10 mL/kg	IV	Give over 5–10 min for acute bleeding; repeat as needed
	Normal saline	10 mL/kg	IV	Give over 5–10 min; repeat as needed
	Ringer's lactate	10 mL/kg	IV	Give over 5–10 min; repeat as needed
Ampicillin	Varies	100 mg/kg	IV, IM	
Gentamicin	Varies	4 mg/kg	IV, IM	
Cefotaxime	Varies	50 mg/kg	IV, IM	

$D_{10}W$, 10% dextrose in water; *ETT,* endotracheal tube; *IM*, intramuscular; *IO*, intraosseous; *IV*, intravenous; *RBCs,* red blood cells; *SC*, subcutaneous.

of the chest may be considered for treatment of a possible pneumothorax, particularly if unequal breath sounds are appreciated upon extubation, ventillatory pressures are inexplicably high, or a neonate's condition fails to improve with effective ventilation.

If ETT intubation is indicated but is technically challenging, the LMA has been shown to be effective for ventilating full-term newborns.[67-69] However, there are limited data on LMA use in preterm infants (<2000 g or <34 weeks' gestation), in the setting of MAS or during cardiopulmonary resuscitation (CPR).

Chest Compressions

Bradycardia (HR < 100 beats/min) is a reliable indicator of clinically significant hypoxia. Fortunately, most neonates with bradycardia respond promptly to effective ventilation. If a neonate has an HR less than 60 beats/min, despite oxygen and adequate ventilation (good air movement and chest rise) for at least 30 seconds, chest compression should be started.[1,2,70] Compressions should be performed at a rate of 90/min, coordinated with 30 breaths/min for a total of 120 events/min. The preferred neonatal resuscitation compression-to-ventilation ratio is 3:1. If the provider is certain that the cardiac arrest has a primary cardiac cause, a compression-to-ventilation ratio of 15:2 may be considered.[1,3] The preferred method for performing chest compressions, the two thumb-encircling hands technique, is as follows: the fingers of both hands encircle the chest and support the back, with the thumbs of both hands placed side by side or one over the other on the sternum, just below the nipple line. The depth of compression is one-third the anteroposterior diameter of the chest.[2,71,72] Spontaneous respirations and HR should be assessed every 30 seconds, attempting to minimize interruptions, when possible, with coordinated chest compressions and ventilation continuing until the HR is at least 60 beats/min.[1,2] A yellow color change on a colorimetric CO_2 monitor during PPV administration often precedes a significant rise in HR and should be used, when available.[73]

Medications

Few neonates require pharmacotherapy during resuscitation.[12] Medications (Table 164.3) are primarily indicated for bradycardia or asystole unresponsive to effective ventilation and chest compressions, as well as hemorrhage (maternal, fetal, or placental) that necessitates fluid resuscitation.[1-3]

Vascular Access

The umbilical vein is the preferred route of immediate vascular access because it can be easily identified and cannulated. Umbilical vein access can have serious complications (eg, infection, portal vein thrombosis), so the umbilical vein cannula (UVC) should be removed by the accepting neonatologist after the infant has been stabilized and additional venous access has been obtained. Other vascular access routes include peripheral veins, peripherally inserted central catheters, and the femoral vein. Intraosseous (IO) access can be problematic in neonates (especially premature infants) because of bone fragility and the small size of the intraosseous space. However, in simulated resuscitation, placement of an IO line has been shown to be almost 1 minute faster than a UVC, even for skilled providers.[74] Preferred IO access sites in newborns include the proximal tibia (≈2 cm below the tuberosity and 1 cm medially on the tibial plateau) and distal femur (midline; ≈1 cm above the superior border of the patella, with the leg in extension). If vascular access cannot be achieved, certain drugs including epinephrine, can be given through the ETT, although this is not the optimal route.

Types

Epinephrine. Epinephrine is indicated for asystole and persistent bradycardia less than 60 beats/min despite effective ventilation with 100% oxygen and ongoing coordinated chest compressions. Although it may be given by ETT, the preferred epinephrine administration route is the IV route. The recommended IV dose is 0.01 to 0.03 mg/kg, or 0.1 to 0.3 mL/kg, of a 1:10,000 solution. Unlike epinephrine use in adult patients, weight-based dosing with no known minimum is required for neonates. Repeat doses may be given every 3 to 5 minutes.[1,2,75] If administered via an ETT, higher doses (0.05–0.1 mg/kg) with a 1:10,000 solution are indicated, but the safety and efficacy of this practice have not been rigorously evaluated.[1,2,75,76] Unlike many

adult resuscitations, sodium bicarbonate is not routinely used,[77,78] although it may be beneficial in the NICU setting when ventilation is known to be adequate.[1,79]

Volume Expanders. When indicated, volume expansion is accomplished with packed red blood cells (Rh-negative type O blood), normal saline or Ringer's Lactate solution given in IV boluses of 10 mL/kg over 5 to 10 minutes. During resuscitation of premature infants, rapid administration of volume expanders should be avoided because this practice has been associated with increased incidence of intraventricular hemorrhage.[2] Higher volume (eg, 20 mL/kg) fluid boluses are recommended for full-term infants. Boluses may be repeated several times, as indicated by the ongoing response to resuscitative efforts.

Antibiotics. Antibiotics are not indicated in the initial resuscitation phase, but may be required once the neonate has been stabilized. When suspected, sepsis should be treated aggressively with broad-spectrum antimicrobial therapy directed against the most likely pathogens. The most common bacterial pathogens implicated in early-onset neonatal sepsis are a heterogeneous group that includes group B *Streptococcus* (GBS), *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and *Listeria*. In the United States, where GBS and *E. coli* represent the most common newborn pathogens, a recommended empirical antibiotic regimen is ampicillin (100 mg/kg IV) plus an aminoglycoside (usually gentamicin, 4 mg/kg).[80] Reasonable alternative regimens include ampicillin with a third-generation cephalosporin, but there is evidence that several members of the latter group predispose a neonate to invasive candidiasis. Because ceftriaxone can increase the risk of kernicterus, cefotaxime (50 mg/kg IV) is preferred.[80]

Glucose. Concomitant hypoglycemia should be considered and promptly treated in a neonate requiring ongoing resuscitation. Hypoglycemia is most easily diagnosed by rapid bedside glucose testing or serum glucose level measurement. Neonates with a glucose level less than 40 mg/dL and with symptoms of hypoglycemia—irritability, tremors, jitteriness, apnea, tachypnea, seizures, cyanosis, lethargy, poor feeding—require treatment with IV glucose. Standard therapy is 2 mL of 10% dextrose in water ($D_{10}W$)/kg as well as starting a continuous infusion of $D_{10}W$ at 80 to 100 mL/kg/day.[10] Higher concentrations of glucose (eg, 25% dextrose in water, $D_{25}W$) are hyperosmolar and should be avoided. If the newborn can safely tolerate feeds, oral glucose solution, maternal breast milk, or formula should be given by mouth (PO) on demand. Repeat glucose measurement should be obtained 10 to 20 minutes after glucose administration. Asymptomatic neonates with hypoglycemia should be encouraged to feed more often and are treated with IV glucose only if glucose levels fall precipitously (<25 mg/dL at birth to 4 hours of age or <35 mg/dL at 4–24 hours of age).[10]

Dopamine. Dopamine is indicated only when signs of shock (eg, poor peripheral perfusion, weak pulses) are still present, despite adequate volume replacement. Given as a continuous infusion beginning at 5 µg/kg/min, dopamine may be increased to 20 µg/kg/min as necessary, before additional inotrope support is indicated.

Therapeutic Hypothermia

When moderate to severe hypoxic-ischemic encephalopathy is suspected, selective cerebral hypothermia in asphyxiated infants may protect against brain injury.[1,81-89] Therapeutic hypothermia of 33.5° to 34.5°C (92.3°–94.1°F) in this population can lower mortality and improve the likelihood of normal neurologic outcome at 18 months. Current NRP guidelines recommend therapeutic hypothermia for patients with suspected early neonatal asphyxia. Symptoms of possible evolving brain injury include abnormal levels of consciousness, seizures, hypotonia, and hyporeflexia.[90] Established protocols generally recommended the initiation of cooling within 6 hours of birth, for a total of 72 hours, followed by gradual rewarming over at least 4 hours. Neonates meeting eligibility criteria should be transferred to facilities capable of providing this specialized care. Emergency clinicians and families should be aware that the risks associated with therapeutic hypothermia include thrombocytopenia and hypotension.[81-88]

DISPOSITION

Early consultation with a neonatologist can assist in the resuscitation and postresuscitation phases of care. Once a neonate is stabilized, the monitoring of oxygenation, ventilation, perfusion, temperature, and glucose level continues. Neonates who require extensive resuscitation (ie, obtaining venous access, medication requirement, and/or endotracheal intubation) should be transported to an NICU by personnel skilled in neonatal resuscitation. If feasible and safe, parents should be allowed to see, touch, and hold the newborn before transport.

OUTCOMES

Safety

Advanced life support skills are critical for successful neonatal resuscitation, yet are far from routine for most emergency clinicians. For example, in a cohort of almost 5000 births at a tertiary level hospital, only 30 infants required intubation, 15 were given chest compressions, and only 10 received epinephrine or volume expanders.[90] An important step toward improving outcomes is team adherence to NRP guidelines. Highlighting the importance of safety, an essential component of the new NRP curriculum is the inclusion of simulation.[91] Simulation in neonatal resuscitation allows for a multidisciplinary team to practice behavioral and teamwork skills, not only individual technical skills, in a safe environment. Implementation of an integrated TeamSTEPPS (Team Strategies and Tools to Enhance Performance and Patient Safety) and NRP curriculum has been shown to result improved outcomes in regard not only to communication, but also to incorrect medication dosing and inadequate chest compression depth.[92] Furthermore, routine (and unannounced) simulation-based neonatal resuscitation training has been shown to improve provider self-confidence in addition to knowledge and technical and nontechnical skills.[93]

Effectiveness

In the hands of trained emergency clinicians, neonates requiring advanced resuscitative efforts receive improved PPV, decreased time to vascular access, and shortened time to first IV medication.[94] Deliberate training of emergency medicine residents has been shown to result in double their self-rated confidence scores and improved ability to perform the key first steps of resuscitation—dry, warm, position, stimulate.[95] These dramatic provider level improvements are seen worldwide with the implementation of guideline-based care. For patients, the results are just as profound. For example, implementing neonatal resuscitation practice protocols at county-level hospitals in China has been shown to decrease birth asphyxia from 8.8% to 6.0% and asphyxia-related deaths from 27.6 to 5.0/100,000.[96] Early analyses of the NRP program, which has now trained more than 5 million providers in the United States alone, have suggested that fewer high-risk infants experience a drop in APGAR score from 1 to 5 minutes, with many actually showing an improvement since

implementation.[97] However, resuscitation is not without potential pitfalls.

Complications

Relatively common complications post–neonatal resuscitation include hypoglycemia, transient tachypnea of the newborn, MAS, pneumothorax, hypermagnesemia, significant hyperbilirubinemia, and sepsis.[97] These conditions are associated with increased NICU admission rates, as well as morbidity and mortality.[98] Additional risk factors in infants requiring prolonged PPV at delivery that predict NICU stay for longer than 1 day include placental abruption, assisted delivery, small for dates, gestational age less than 37 weeks, low 5-minute APGAR score, and need for intubation at birth.[99]

Further Considerations

The need for chest compressions and CPR is a known prognostic marker for increased rates of morbidity and mortality in neonates. Undergoing CPR at delivery increases the likelihood of pneumothorax, grades 3 and 4 intraventricular hemorrhage, bronchopulmonary dysplasia, and death by 12 hours and 120 days after birth.[100] Unfortunately, these complications have also been associated with long-term neurodevelopment impairment (NDI), with less than 15% of infants with 5-minute APGAR scores lower than 2 surviving without NDI.[100] The implementation of a local neonatal resuscitation protocol appears to improve neurodevelopment outcome; follow-up data have suggested that the incidence of electroencephalographic abnormalities, cerebral palsy, and seizure disorders are all greatly reduced.[101]

KEY CONCEPTS

- Resuscitation should be anticipated for all neonates born outside the delivery room; 10% of newborns will require some resuscitation, and 1% will require advanced life support interventions after birth.
- Predictable indications for resuscitation include hypoxia, hypothermia, hypoglycemia, hypovolemia, prematurity, maternal infection, and adverse effects of maternal medication.
- Drying, warming, positioning, and stimulating the infant are sufficient resuscitative measures for most deliveries.
- Adequate ventilation will reverse most bradycardia whereas, in general, 100% oxygen is not indicated for most neonatal resuscitations.
- The NRP resuscitation algorithm provides a proven guide for management and its implementation has shown to improve short- and long-term outcomes, including neurodevelopment.
- Routine tracheal suctioning of vigorous and nonvigorous infants born through meconium-stained amniotic fluid is no longer recommended.
- Weight-based epinephrine and volume expanders are rarely required.
- Significant hypovolemia is rare in neonates. Hemorrhage is one of the few predictable situations in which volume expansion improves newborn outcome.
- Preterm infants and those born to mothers with suspected infection, including chorioamnionitis, should receive empirical antibiotic therapy. An acceptable regimen includes dual therapy with ampicillin and gentamicin.
- Any neonate with persistent cyanosis or signs of respiratory distress (eg, grunting, nasal flaring, tachypnea) should be assisted by CPAP or PPV. Endotracheal intubation should be performed in several situations, such as when bag-mask ventilation is ineffective or prolonged, chest compressions are performed, an extremely low-birth-weight infant is born, and tracheal suctioning for meconium in infants results in failure to improve, despite effective PPV.
- Chest compressions are rarely required because bradycardia generally responds to effective ventilation. However, compressions should be started for an HR less than 60 beats/min, despite oxygen and adequate ventilation for 30 seconds.
- The umbilical vein is the preferred route of immediate vascular access, followed by peripheral veins, peripherally inserted central catheter lines, and the femoral vein. IO line placement can be problematic in neonates.
- No reliable and widely adopted set of parameters has been identified for newborns who should not receive resuscitative efforts. Unless there is clear family, parent, and/or health care provider agreement, all resuscitation efforts should continue until further prognostication can occur.
- Infants receiving appropriate resuscitation efforts nonetheless showing no signs of life after 10 minutes may have further efforts withheld, particularly when this decision is in accord with parental preference.
- All newborns requiring IV placement, medication administration, chest compressions or endotracheal intubation should be transferred to an appropriate neonatal intensive care unit.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 164: QUESTIONS & ANSWERS

164.1. With most neonatal deliveries, which resuscitative measures are usually sufficient?
- **A.** Administer fluids.
- **B.** Administer glucose.
- **C.** Bag-mask ventilate.
- **D.** Intubate.
- **E.** Warm, dry, stimulate, and position.

Answer: E. Drying, warming, positioning, and stimulating the infant are usually sufficient resuscitative measures in most deliveries.

164.2. For a newborn with cyanosis, respiratory distress and a heart rate more than 100 beats/min, which of the following is not initially indicated?
- **A.** Apply 100% oxygen.
- **B.** Position airway.
- **C.** Suction.
- **D.** Ventilate with bag-mask with room air.
- **E.** Warm, dry, and stimulate.

Answer: A. 100% oxygen is no longer indicated for initial resuscitation; avoiding unnecessary supplemental oxygen is thought to minimize free radical creation in the brain and decreases the incidence of retinopathy of prematurity. Initial resuscitation with room air is recommended.

164.3. In a typical neonatal resuscitation, what is the preferred compression-to-ventilation ratio?
- **A.** 3:1
- **B.** 5:1
- **C.** 10:2
- **D.** 15:2
- **E.** 30:2

Answer: A. Unlike pediatric or adult cardiopulmonary resuscitation (CPR), neonatal CPR is performed at a ratio of three compressions to one breath, with a goal of approximately 90 compressions with 30 synchronized breaths (120 "events") per minute. If the cause of the bradycardia is known to be cardiac, a ratio of 15:2 is acceptable.

164.4. A nonvigorous and crying newborn is delivered with copious meconium-stained fluid. What is the correct recommended resuscitative measure?
- **A.** Bag-mask ventilate.
- **B.** Intubate.
- **C.** Intubate and suction.
- **D.** Suction at maternal perineum before cutting umbilical cord.
- **E.** Gentle mouth suctioning if needed, followed by warming, drying, and stimulation.

Answer: E. For infants born with meconium-stained amniotic fluid, routine intubation and endotracheal tube suctioning are no longer recommended because they have shown no consistent benefit. Vigorous and nonvigorous infants born through even thick meconium should instead have gentle mouth suctioning, if needed, followed by warming, drying, and stimulation.

164.5. After drying, stimulating, and bag-mask ventilation, what is the next step in resuscitation of a newborn that appears floppy and apneic and with a heart rate of 50 beats/min?
- **A.** Give a normal saline bolus of 20 mL/kg.
- **B.** Give epinephrine (1:10,000) intravenous (IV) at a dose of 0.1 mg/kg.
- **C.** Intubate.
- **D.** Start with a chest compression-to-ventilation ratio of 3:1.
- **E.** Suction.

Answer: D. With a heart rate less than 60 beats/min in a neonate, intubation may be considered, but compressions should be started. If the low heart rate persists, IV epinephrine (1:10,000) may be considered at a dose of 0.01 mg/kg.

CHAPTER 165

Pediatric Trauma

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PRINCIPLES

Trauma is the leading cause of death among children from 1 to 18 years old in the United States, with injuries accounting for more than 8 million annual emergency department (ED) visits.[1] Head injury is the most common cause of pediatric trauma deaths.[2] Motor vehicle collisions (MVCs) account for more than half of all pediatric trauma deaths, whereas nonfatal injuries are primarily due to falls.[1] Other nonfatal injuries vary by age. Young children (<4 years old) experience higher rates of animal bites and burns. School-age children (5 to 9 years old) are more likely to experience bicycle and pedestrian injuries. Older children (>9 years old) have high incidences of both fatal and nonfatal motor vehicle–related trauma and higher incidences of suicide and self-inflicted harm.

Anatomy and Physiology

Children have distinctive anatomy and unique physiology that impacts the evaluation and management of the pediatric trauma patient (Box 165.1). Force is more widely distributed through the body of a child, making multi-system injuries more likely in children. The younger a patient is, the greater their surface area to weight ratio, resulting in a greater potential for heat loss. Even mild to moderate hypothermia contributes to metabolic acidemia and has direct negative effects on cardiac inotropy, chronotropy, catecholamine responsiveness, platelet function, and drug clearance through both renal and hepatic routes. Therefore, maintenance fluid requirements, oxygen extraction and consumption, and glucose utilization are much higher per kilogram in infants and small children than in adults.

A child's physiologic response to injury is different from an adult's, depending on the age and maturation of the child and the severity of the injury. Children have a great capacity to maintain blood pressure despite significant acute blood losses constituting up to 30% of total blood volume.[3] A child's cardiac output is primarily determined by the heart rate and systemic vascular resistance. Compensated shock should be considered and promptly addressed when a child's heart rate is elevated, especially if the capillary refill time is delayed. Changes in heart rate, blood pressure, and extremity perfusion commonly precede cardiorespiratory failure and should be recognized and resuscitation initiated.

CLINICAL FEATURES

Initial Assessment Priorities and Primary Survey

The highest priority is ruling out the presence of life- or limb-threatening injuries. Treatment of these injuries precedes continuation of the physical examination. This initial assessment and necessary initial resuscitation efforts occur simultaneously. In general, the assessment and resuscitation phase of the evaluation should be addressed within the first 5 to 10 minutes. Any child with a potentially serious or unstable injury should have continual reassessment. The elements of the primary survey for pediatric trauma patients can be remembered by *A, B, C, D, E,* and *F.*

A—Airway and Cervical Spine Stabilization

Chapter 161 describes anatomic considerations that have implications in the management of the pediatric airway. Possible airway obstruction or inability of the child to maintain his or her own airway should be assessed. Spinal motion restriction should be maintained with significant mechanisms, increased risk of spinal injury with trauma (eg, Down syndrome), or signs of neurological injury post trauma. (Evaluation of the cervical spine in children is discussed later in this chapter.) The airway can be opened with a jaw-thrust maneuver. Gurgling or stridor may indicate upper airway obstruction. Maxillofacial trauma, loose teeth, blood, swelling, or vomitus may obstruct the airway, and efforts should be made toward clearing the oropharynx of debris. If an open airway cannot be maintained by noninvasive means, endotracheal intubation (ETI) will be required.

Indications for ETI in a pediatric trauma patient may include (1) inability to ventilate with bag-mask ventilation (BMV) or the need for prolonged control of the airway, (2) Glasgow Coma Score (GCS) of less than 9, (3) respiratory failure from hypoxemia or hypoventilation, and (4) the presence of decompensated shock resistant to initial fluid administration. Box 165.2 lists airway equipment sizes.

B—Breathing and Ventilation

Breath sounds and adequacy of chest rise should be assessed. In a young child, this rise occurs in the lower chest and upper abdomen. Both the chest and the abdomen should move concordantly. Discordant motion is referred to as *paradoxical breathing* and is a sign of impending respiratory failure. Respiratory rates that are too fast or too slow can also indicate impending respiratory failure; treatment is assisted ventilation. If assisted ventilation is necessary, BMV should be initiated. Only the volume necessary to cause the chest to rise should be provided. Excessive volume or rate of ventilation can lead to gastric distention (increasing the risk of vomiting and aspiration), which may lead to respiratory embarrassment and potential hypotension caused by decreased venous return and impaired diaphragmatic function. Gastric decompression may be performed in children who are intubated with an orogastric or, when deemed appropriate, a nasogastric tube.

Many factors may compromise ventilatory function in an injured child. These include depressed sensorium, occlusion of the airway, painful restriction of lung expansion, diaphragmatic fatigue, and direct pulmonary injury. Adequate ventilation is dependent upon airway patency and sufficient air exchange. Pulse oximetry measures adequacy of oxygenation but not ventilation. Continuous end-tidal carbon dioxide capnography can better inform ventilatory status. Table 165.1 describes priorities in the assessment of breathing in pediatric trauma patients.

BOX 165.1

Specific Anatomic Differences in Adults and Children: Implications for Pediatric Trauma Management

The child's head-to-body ratio is greater, the brain is less myelinated, and cranial bones are thinner, resulting in more serious head injury.
The child's internal organs are more susceptible to injury based on more anterior placement of liver and spleen, and less protective musculature and subcutaneous tissue mass.
The child's kidney is less well protected and more mobile, making it susceptible to deceleration injury.
The elasticity of the child's chest wall allows for pulmonary injury without skeletal injury.
Growth plates are not yet closed in pediatric patients, leading to Salter-type fractures with possible resultant limb-length abnormalities.
Children have a more tenuous spinal cord blood supply and a greater elasticity of the vertebral column, predisposing them to spinal cord injury without radiographic abnormality (SCIWORA).

BOX 165.2

Equipment Size Estimates for Pediatric Trauma

ENDOTRACHEAL TUBE SIZE ESTIMATES (SIZING IN MILLIMETERS INTERNAL DIAMETER) AND DEPTH

For children 1 to 10 years old, a length-based resuscitation tape may be used, or ETT size can be estimated by the following formulas:
Cuffed endotracheal tube size (mm) = (Age in years/4) + 3.5
Uncuffed endotracheal tube size (mm) = (Age in years/4) + 4
An ETT 0.5 mm larger and 0.5 mm smaller in internal diameter should also be ready at the bedside.
Depth of ETT (cm) = (tube size) × 3

LARGEST CHEST TUBE SIZE

Largest chest tube diameter = 4 × the endotracheal tube size

OROGASTRIC, NASOGASTRIC, OR FOLEY SIZE

Orogastric, nasogastric, or Foley diameter = 2 × ETT size

FEMORAL LINE SIZING ESTIMATES (WEIGHT BASED)

≥3 kg = 3 F
3–10 kg = 4 F
10–20 kg = 5 F
>20 kg = 6 F

ETT, Endotracheal tube.

C—Circulation and Hemorrhage Control

Shock is a state in which the body is unable to maintain adequate tissue perfusion. Maintenance of systolic blood pressure does not exclude the presence of shock. The pediatric vasculature has the ability to constrict, increasing systemic vascular resistance, in an attempt to maintain splanchnic perfusion. Signs of poor perfusion (cool distal extremities, decreases in peripheral versus central pulse quality, and delayed capillary refill time) are signs of pediatric shock, even when blood pressure is at normal levels. External hemorrhage should be sought and controlled with direct pressure. The assessment of circulation in pediatric trauma patients is described in Box 165.3.

TABLE 165.1

Breathing: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Respiratory rate	Fast rates may indicate impending respiratory failure and need for intubation, shock and need for fluid resuscitation, or pain and need for analgesics. Slow rates may indicate impending respiratory failure, head injury, or over-sedation.
Chest wall movements	Paradoxical breathing and flail segments may represent impending respiratory failure. 100% oxygen should be provided by non-rebreather mask, and intubation may be considered.
Percussion and breath sounds	Consider pneumothorax, hemothorax, or diaphragmatic rupture. For significant pneumothorax or hemothorax, place chest tube. A small pneumothorax in a spontaneously breathing patient may require only close monitoring and oxygen. For hemothorax, transfer to operating room if initial drainage >15 mL/kg or subsequent output >2 mL/kg/hr. For open pneumothorax, seal with three-sided occlusive dressing followed by tube thoracostomy, then seal the remaining side of the occlusive dressing. Diaphragmatic rupture requires surgical consultation.
Tracheal deviation	Tension pneumothorax: Needle decompression at second intercostal space, midclavicular line, followed by placement of chest tube; if a chest tube can be immediately placed, needle decompression is not needed.

BOX 165.3

Circulation Assessment and Treatment in Critical Pediatric Trauma Patients

ASSESSMENT

Increased heart rate, slow capillary refill, decreased peripheral pulses, and altered sensorium may indicate poor circulation.
Vital signs should be monitored every 5 minutes during the initial assessment.
Continuous oximeter and cardiac monitor.

TREATMENT AND INTERVENTIONS FOR HYPOVOLEMIC SHOCK FROM TRAUMA

Place two large-bore IV lines (above and below diaphragm when indicated).
Consider central line or intraosseous line placement if peripheral venous access is difficult.
Bolus with 20 mL/kg of warmed normal saline, and repeat if necessary.
Consider intubation and ventilation to decrease work of breathing.
Transfuse 10 to 20 mL/kg PRBC for decompensated shock secondary to blood loss.

IV, Intravenous; *PRBC,* packed red blood cells.

D—Disability Assessment

For assessment of patient disability, a rapid neurologic and mental status evaluation is needed. The assessment of disability in pediatric trauma patients is described in Box 165.4. The alert, verbal,

BOX 165.4

Disability: Neurologic Assessment and Treatment

ASSESSMENT

Level of consciousness: Use AVPU scale and age-appropriate Glasgow Coma Scale
Pupil size and reactivity
Extremity movement and tone
Posturing and reflexes

TREATMENT AND INTERVENTIONS

Stabilize spinal column with spinal motion restriction techniques.
If GCS <9: RSI.
If altered mental status, obtain a head CT scan and neurosurgical consultation as needed.
With signs of herniation, consider 3% hypertonic saline 6.5–10 mL/kg IV (or mannitol 0.25 to 0.5 g/kg IV), if possible elevate the head of the bed, keep the facing forward, and hyperventilate to a P_{CO_2} of 30 to 35 mm Hg.
Maintain CPP of at least 50 mm Hg in children and 70 mm Hg in adults.
Assess for signs of spinal injury, including respiratory failure and bulbocavernosus reflex or presence of anal wink.

AVPU, Alert, verbal, painful, unresponsive; *CPP,* cerebral perfusion pressure; *CT,* computed tomography; *GCS,* Glasgow Coma Score; IV, intravenous; P_{CO_2}, partial pressure of carbon dioxide, *RSI,* rapid sequence intubation.

painful, unresponsive (AVPU) system (Box 165.5) and the modified pediatric GCS (Table 165.2) are useful to the emergency clinician to assess level of consciousness as well as motor strength.

E—Events, Exposure, and Thorough Examination

The historical details of the trauma as well as initial response to the event are key to estimation of risk of injury. Type of force applied, secondary impacts, such as being struck and then ejected from a vehicle or thrown onto the ground, response to the trauma (ie, loss of consciousness, seizure, altered level of consciousness), and initial interventions by emergency medical service (EMS) personnel as applicable.

The trauma patient should be fully undressed to assess for hidden trauma. However, patients should also be kept normothermic, because metabolic needs are greatly increased by hypothermia. The environment of care for pediatric trauma patients should

BOX 165.5

AVPU System

A—*A*lert
V—Responds to *v*erbal stimuli
P—Responds to *p*ainful stimuli
U—*U*nresponsive

TABLE 165.2

Glasgow Coma Scale Modified for Pediatric Patients*

	EYE OPENING RESPONSE		
SCORE	**>1 YEAR OLD**	**<1 YEAR OLD**	
4	Spontaneous	Spontaneous	
3	To verbal command	To shout	
2	To pain	To pain	
1	None	None	
	MOTOR RESPONSE		
SCORE	**>1 YEAR OLD**	**<1 YEAR OLD**	
6	Obeys commands	Spontaneous	
5	Localizes pain	Localizes pain	
4	Withdraws to pain	Withdraws to pain	
3	Abnormal flexion to pain (decorticate)	Abnormal flexion to pain (decorticate)	
2	Abnormal extension to pain (decerebrate)	Abnormal extension to pain (decerebrate)	
1	None	None	
	VERBAL RESPONSE		
SCORE	**>5 YEARS OLD**	**2 TO 5 YEARS OLD**	**0 TO 2 YEARS OLD**
5	Oriented and converses	Appropriate words and phrases	Babbles, coos appropriately
4	Confused conversation	Inappropriate words	Cries but is consolable
3	Inappropriate words	Persistent crying or screaming to pain	Persistent crying or screaming to pain
2	Incomprehensible sounds	Grunts or moans to pain	Grunts or moans to pain
1	None	None	None

*Total score key: severe, <9; moderate, 9-13; mild, 14-15.

TABLE 165.3

Exposure: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Full examination	Fully undress. Look under collar and splints. Log roll and examine back. Perform rectal examination if indicated.
Imaging	Consider chest and pelvis radiographs. Consider additional imaging of any area of pain or trauma. Perform a bedside FAST examination.
Laboratory	Complete blood cell count, type and crossmatch, urinalysis, urine pregnancy test, urine drug screen.
Supportive interventions	For pelvic fracture, consider binding to decrease pelvic volume and aid hemostasis. For extremity fractures, consider reduction and splinting. Place urinary catheter and nasogastric or orogastric tube as indicated.
Medications	Provide analgesia with IV medications. Tetanus vaccine and tetanus immune globulin for appropriate cases. Antibiotics when indicated.

FAST, Focused assessment with sonography in trauma; *IV,* intravenous.

have an increased ambient temperature, and warmed humidified oxygen, warmed fluids, and warmed blood should be used to avoid heat loss as is possible. Head wraps, and convective warmers or radiant heat sources should be used as soon as possible in newborns and infants, as well as older children when their temperature is 95°F (35°C) or lower. The exposure phase of the survey is often the appropriate time to concurrently begin imaging and further diagnostic testing (Table 165.3).

F—FAST and Family

The focused assessment with sonography in trauma (FAST) evaluates for traumatic free fluid in the peritoneum and pericardial space and has proved to be useful in children.[4,5] In hemodynamically unstable children, a FAST may point to hemorrhage in the abdomen or the pericardial space and the need for intervention. In hemodynamically stable children, the FAST examination may indicate the need for computed tomography (CT) imaging, closer observation, repeat abdominal examinations, or repeat ultrasound examinations. The extended FAST (eFAST) examination incorporates the addition of lung views to evaluate for pneumothorax or hemothorax.

In the management of children, the family (caregivers) may be added to the primary survey, to remind emergency clinicians to rapidly inform the family of the evaluation and progress and address their concerns. Allowing family members to be present during resuscitations is acceptable and often preferred by families. Some family members choose not to be present, but they should have the choice. We recommend having a staff member dedicated to the family during the resuscitation: to explain treatments, answer questions, and provide emotional support.

Secondary Survey

After completion of the primary survey and requisite procedures, the secondary survey is performed. The secondary survey is an organized, complete assessment to detect additional injury. A more complete history and examination are obtained. Features of the history that need to be obtained can be remembered by the mnemonic *AMPLE* (Box 165.6). Ongoing assessment of the patient occurs after the secondary survey, and key points are summarized in Box 165.7.

BOX 165.6

AMPLE History

A—*A*llergies
M—*M*edications
P—*P*ast medical history
L—*L*ast meal
E—*E*vents and *E*nvironment

BOX 165.7

Tasks to Be Completed After the Secondary Survey

- Continuous monitoring of vital signs
- Provision of analgesia, and continuous reassessment of pain
- Antibiotics and tetanus as appropriate
- Ensure urine output of 1 mL/kg/hr
- If patient is intubated, ensure adequate sedation and analgesia
- If head injury is present, frequent neurologic assessment

MANAGEMENT AND DIAGNOSTIC TESTING

General Management Principles

In most cases of pediatric trauma, the child is stable and evaluation can proceed without need for intravenous (IV) access or laboratory evaluation. In pediatric patients who have sustained *major* trauma, they should be placed on cardiac and pulse oximetry monitoring, receive supplemental oxygen, and have continuous reassessment of vital signs. Vascular access is best obtained by accessing the upper extremity for the establishment of two large-bore IV lines. In the absence of available upper extremity peripheral sites, lower extremity sites may be used. Many emergency clinicians favor the femoral vein as a safe site for insertion of a central line; preferably under ultrasound guidance (see Box 165.2).

If vascular access is unobtainable or delayed, intraosseous access is a safe, quick, and reliable procedure to access the vascular space. Although most commonly started in the proximal medial tibia just below the growth plate, intraosseous access can be obtained in the proximal humerus, the flattened area of the anterior distal femur, the distal tibia, or even the sternum. Once intraosseous access is obtained, it should be stabilized and secured to ensure it is not accidentally displaced. More than one intraosseous needle may need to be placed (in separate bones), and IV access may be more easily inserted once fluids have been given. Intraosseous placement in a fractured extremity is contraindicated. Medications and blood products can be administered through an intraosseous line.

Other less commonly used vascular access techniques for trauma include venous cut-down and umbilical vein cannulation for neonates. Venous cutdown is a skill not often performed by emergency clinicians and is rarely needed to obtain vascular access in the pediatric trauma patient. If performed, the greater

saphenous vein at the ankle is the preferred site. Umbilical vein cannulation can be achieved in infants up to approximately 7 to 10 days old, as long as there is enough of an umbilical stump to perform the procedure.

Most hypovolemic pediatric trauma patients respond to 20 mL/kg boluses of isotonic crystalloid solutions. If 40 mL/kg has not reversed systemic signs of hypoperfusion, an additional 20 mL/kg bolus of crystalloid may be given, and an infusion of packed red blood cells (PRBCs) at 10 mL/kg should be given while investigating for potential sources of shock. In patients in decompensated hemorrhagic shock or cardiopulmonary failure secondary to hemorrhage, crystalloid and blood products should be administered simultaneously. With massive transfusion (blood product volume of ≥40 mL/kg), it is important to add platelets to correct coagulopathy.[6] We recommend plasma, platelets, and PRBCs given in a near 1:1:1 ratio if massive transfusion is expected. This is based predominantly on adult studies.[7-9]

In trauma, shock is most likely hemorrhagic in nature. Cardiogenic shock is rare. However, chest trauma associated with shock should alert the emergency clinician to the possibility of concomitant tension pneumothorax, myocardial injury, or pericardial tamponade. Neurogenic and spinal shock can also occur in traumatic injury and are discussed later in this chapter.

Physical Examination

After the primary survey, a head-to-toe examination is carefully performed. Specifics of the head examination include inspection and palpation of the skull and facial bones, assessment of pupil size and reactivity, and evaluation of extraocular movements. A funduscopic examination may be considered in cases of possible nonaccidental trauma. A fluorescein examination may reveal occult eye injury. Eye shields (not patches) should be used to protect eyes with possible globe rupture.

Assessment of the cervical spine is done carefully. The patient should be removed from the backboard with spinal motion restriction maintained if not clinically cleared or if at high risk for cervical spine injury. Backboards cause pain and with time skin breakdown at pressure points and should be removed as quickly as possible. There are no common indications to justify leaving children on backboards after their initial evaluation. When the patient is rolled to remove the backboard, palpation of the rest of the spine can take place with an emphasis on evaluating for ecchymosis, tenderness, and step-offs. Obtunded patients and those with signs or symptoms of thoracic or lumbar spine injuries should be carefully moved and positioned to protect them from possible further injury until imaging or return of consciousness allows more definitive assessment.

Assessment of the chest and internal structures involves inspection for wounds and flail segments; palpation for tenderness, crepitus, and point of maximal cardiac impulse; and auscultation for asymmetry or abnormal breath sounds.

The abdominal examination consists of inspection, palpation, and a FAST examination. A "seat belt sign" across the abdomen is a sign of potential serious traumatic injury. Palpation is best done on a cooperative patient but is an insensitive screening test for the presence of an injury.

A digital rectal examination should only be performed when its result has a reasonable chance of changing the patient's treatment.[10] It may provide information on sphincter tone in possible spinal injury and the presence of blood in penetrating trauma but otherwise we recommend it not be done routinely.

Although urethral injury is rare in children, all trauma patients should be assessed for perineal, scrotal, penile, or lower abdominal hematoma and blood at the urethral meatus. If there is concern for urethral injury, a retrograde urethrogram should be completed before the insertion of a urinary catheter.

Extremity examination evaluates for deformities, penetrations, neurologic deficits, and interruptions of perfusion. Fractures may be stabilized with splinting prior to definitive management. Careful and recurrent (especially after interventions such as splinting or reduction) vascular and neurologic examinations should be performed in all cases of extremity injury.

Reexamination of trauma patients throughout their time in the ED is important to ensure that their condition has not changed, that their pain is controlled, and that no injuries are overlooked. Ambulation as appropriate prior to discharge is helpful in uncovering additional injuries identified with previous examinations. Up to 70% of injuries with delayed diagnosis in pediatric trauma are orthopedic in nature.[6]

Pain Control

Pain control is an essential part of any trauma patient's management. Analgesic medications, immobilization of injured extremities, and nonpharmacologic techniques should all be considered. Please refer to Chapter 162.

Diagnostic Testing

Laboratory Studies

Blood sampling for a pediatric trauma patient is no different than that for an adult trauma patient; however, use of smaller blood collection tubes may be necessary in infants and small children.

In hypovolemic shock, hemoglobin alone is unreliable because equilibration will not have occurred at the time of presentation to the ED. Serial hemoglobin measurements may be useful to assess the possibility of ongoing bleeding.[11]

Children's glucose utilization and metabolic rate per kilogram are much greater than those of adults. Any child with a change in mental status after trauma should have a point of care glucose level checked immediately. Any child requiring dextrose owing to hypoglycemia will likely need an ongoing dextrose supply to prevent recurrence of hypoglycemia.

Older pediatric trauma patients should be assessed for substance abuse and depression as contributing factors to the traumatic event. Post-pubertal females or those girls Tanner stage 3 or greater should be tested for pregnancy.

Radiology

Chest and pelvic radiographs can assess for causes of respiratory failure, sites of blood loss, and causes of shock. In stable, alert children without distracting injuries, the pelvic film may be eliminated if no suggestion of sacral or pelvic fracture is found on thorough clinical examination.[12] Plain pelvic films have been shown to have limited sensitivity in children after blunt trauma.[13] In children with pelvic or sacral tenderness and negative plain radiographs, a CT scan should be strongly considered.

Other imaging is obtained based on the physical examination. For patients sustaining minor trauma, no imaging may be needed. Evaluation of suspected nonaccidental trauma is discussed in detail in Chapter 177.

SPECIFIC DISORDERS AND INJURIES

Head Injury

Principles

Traumatic brain injury is the leading cause of death and disability in children older than 1 year old in the United States.[14-16] Infants and toddlers are more prone to falls from their own height,

school-age children are involved in sports injuries and MVCs, and children of all ages are subject to the sequelae of abuse.

Important anatomic variations lead to differences in pediatric and adult head trauma. The cranial vault of a child is larger and heavier in proportion to the total body mass. This predisposes young children to high degrees of torque that are generated by forces along the cervical spine axis. Sutures within the pediatric skull are both protective and detrimental to the outcome of head injury. Although the cranium may be more pliable relative to traumatic insult, forces are generated internally that predispose the pediatric patient to parenchymal injury in the absence of skull fractures. The pediatric brain is less myelinated, with higher water content, predisposing it to shearing forces, further injury, and post-traumatic seizures.

Clinical Features

The mechanism of the head injury relates to the severity of injury. The height of the fall and the quality of the surface at the point of impact are particularly important with regard to the development of associated injury. Most children fall from their own height, and impact with an object increases the localized force even after a short fall. In MVCs, the type of restraint that was present at the time of the collision should be evaluated because unrestrained and improperly restrained children are more prone to serious injury.

It is also important to establish if alteration of consciousness occurred at the time of the injury event.[17] The behavior of a child after a traumatic event should be assessed with questions related to the presence or absence of irritability, lethargy, personality change, or other alterations in behavior. The prognostic significance of vomiting after pediatric head trauma is unclear. Recurrent vomiting is commonly seen in patients with significant head injury and is often considered in the decision to obtain a CT study; however, in the case of isolated vomiting without other clinical signs, a period of observation is an option.[18]

A brief seizure that occurs immediately after an insult (with rapid return to normal level of consciousness) is commonly called an *impact seizure*. The decision to scan should take into account the mechanism of injury and current neurologic status of the

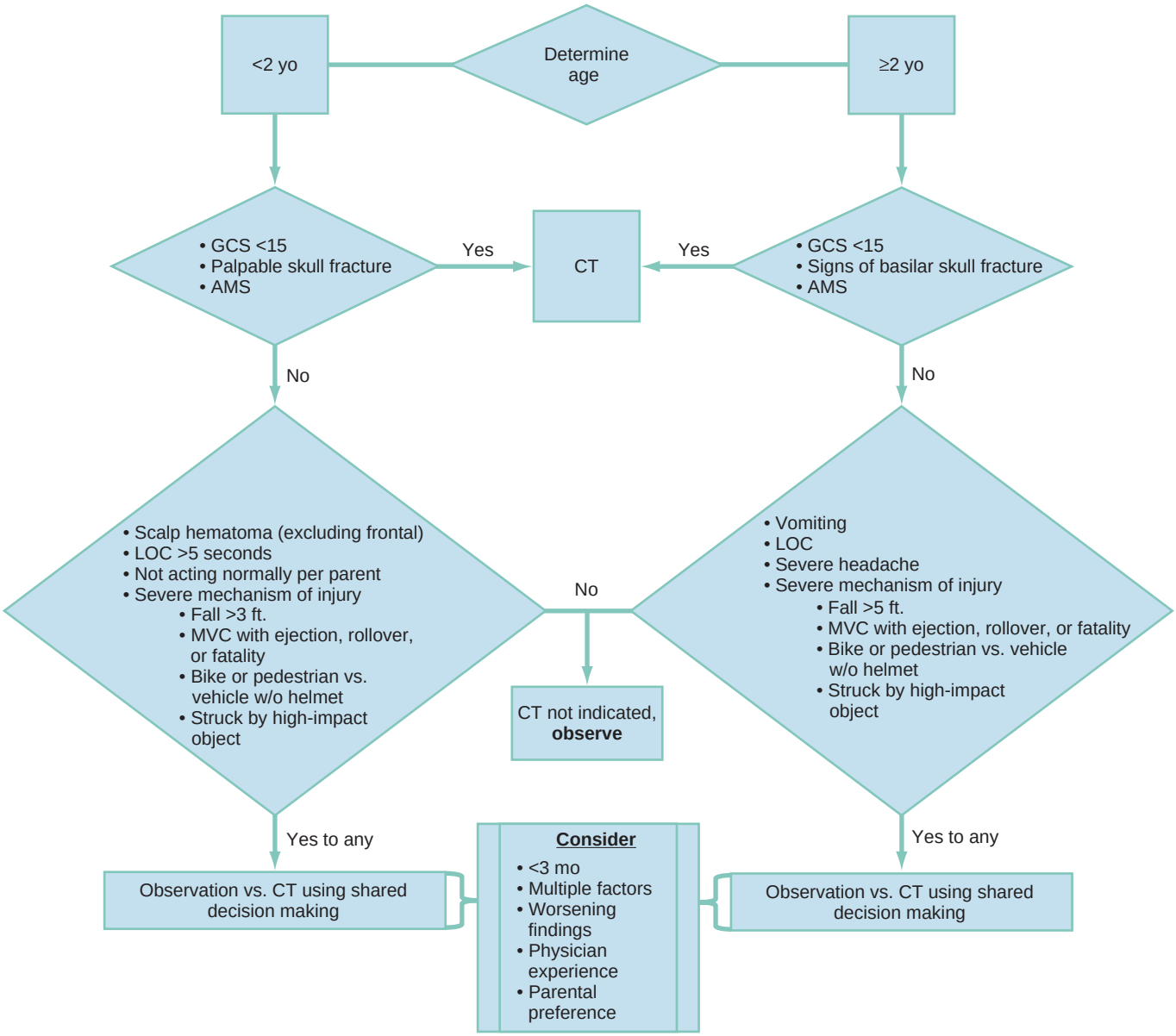

Fig. 165.1. Head injury rule chart. AMS, Altered mental status; CT, computed tomography; GCS, Glasgow Coma Score; LOC, loss of consciousness; MVA, motor vehicle collision.

child, but in most cases a CT scan is performed for post-traumatic seizure.[19] If a CT scan is not performed, a period of observation for at least 2 hours in the ED is prudent. Seizures that occur later (more than 20 minutes after the insult) herald a greater possibility of traumatic brain injury and the development of seizures at a later date. A CT scan is indicated for these later post-traumatic seizures. These patients may benefit from treatment with anticonvulsants as having one later seizure (nonimpact) raises the risk of subsequent additional seizures. Seizures also raise ICP, while often decreasing oxygenation and ventilation.

The examination of a head-injured child include strict attention to the ABCs (airway, breathing, and circulation). Because the pediatric brain is sensitive to decreases in oxygen, perfusion, and glucose, their maintenance reduces further brain insult and optimizes the chances of good recovery. Cerebral perfusion pressure (CPP) is adequate only in the face of a normal mean arterial pressure (MAP). Conceptually, CPP is equal to MAP minus ICP:

$$CPP = MAP - ICP$$

As MAP is reduced, so is CPP. Localized CPP at the site of injury and in the areas surrounding it may vary greatly from this formula's approximations. Pediatric patients with any form of head injury should have an evaluation of their cervical spine for injury.

Several methods are available for evaluating the mental status of head-injured patients, including the AVPU system and the GCS.[20,21] A commonly used modification of the GCS for children is shown in Table 165.2. A child with a head injury should have cranial nerve, motor, sensory, cerebellar, reflex, and memory testing. The most important aspect of motor and cranial nerve evaluation involves ruling out the presence of increased ICP. Common symptoms and signs of increased ICP in infants and children should be sought (Boxes 165.8 and 165.9).

BOX 165.8

Symptoms and Signs of Increased Intracranial Pressure in Infants

- Full fontanel
- Split sutures
- Altered level of consciousness
- Paradoxical irritability
- Persistent emesis
- "Setting sun" sign (bilateral downward gaze of the eyes with apparent inability to elevate the eyes superiorly in a normal manner leading to an area of sclera being seen between the iris and the upper palpebra)

BOX 165.9

Symptoms and Signs of Increased Intracranial Pressure in Infants and Children

- Headache
- Stiff neck
- Photophobia
- Altered state of consciousness
- Persistent emesis
- Cranial nerve involvement
- Papilledema
- Hypertension, bradycardia, and hypoventilation
- Decorticate or decerebrate posturing

Differential Diagnoses

Concussion. A *concussion* is a functional brain injury seen after a blow to the head or body, a fall, or another injury that shakes the brain within the skull.[22] Radiographic studies should be obtained if there are symptoms suggestive of intracranial hemorrhage. In concussions, structural radiographic studies are normal. Patients who sustain concussive insults may have somatic, cognitive, affective, and sleep symptoms. All children with concussive symptoms should be monitored for progression of symptoms by their primary care physician or a concussion recovery specialist. They should undergo both physical and cognitive rest until symptoms have resolved, then return slowly to their baseline activities.

Scalp Injuries. Bleeding from scalp wounds is often profuse and can lead to hemodynamic compromise in infants and small children if not quickly controlled. Scalp injuries in infants and children may also involve the development of three injury complexes. For these injury complexes to be better understood, the layers of the *s*kin, *c*onnective tissue, *a*poneurosis, *l*oose areolar tissue, and *p*eriosteum (SCALP) should be considered (Fig. 165.2). *Caput succedaneum* refers to a hematoma in the connective tissue layer. This is freely mobile and crosses suture lines. A *subgaleal hematoma* refers to a hematoma that is subgaleal within the loose areolar tissue above the periosteum. Lastly, *cephalohematoma* refers to a collection of blood under the periosteum. Because the periosteum adheres tightly to the various suture lines, the cephalohematoma does not cross them.

Skull Fractures. In children, skull fractures occur in many different configurations. Simple linear non-depressed fractures rarely require therapy and often are associated with good outcomes. Factors associated with poor outcomes include the presence of a fracture overlying a vascular channel (especially the middle meningeal artery), a depressed fracture, or a diastatic fracture. Diastatic fractures, or defects extending through suture lines, are different from simple linear fractures in that leptomeningeal cysts ("growing fractures") may develop at these sites.[23] Leptomeningeal cysts are more common in children younger than 3 years old and are the result of a dural tear and skull fracture. In "growing fractures," the leptomeninges herniate through the dural tear, causing bony erosion around the fracture site.

The presence of cerebrospinal fluid rhinorrhea and otorrhea has been associated with fractures of the skull base. Signs of basilar skull fractures in children are similar to signs in adults and include the presence of periorbital subcutaneous hematoma (raccoon eyes) and posterior auricular ecchymosis (Battle sign). It should be noted that these signs can take hours to days to develop, and therefore absence of these signs cannot rule out basilar skull fractures.

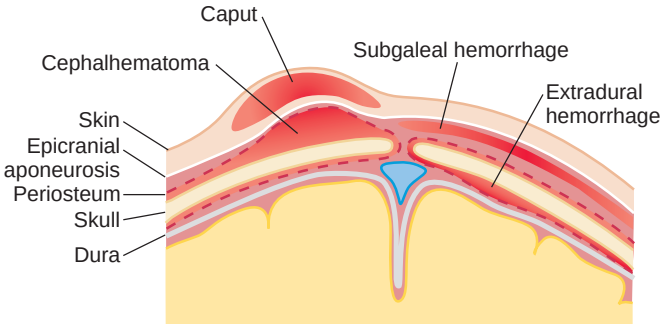

Fig. 165.2. Sites of extracranial hemorrhages in the infant. (From Volpe JJ: Neurology of the newborn, ed 4, Philadelphia, 2001, WB Saunders.)

Cerebral Contusions. Cerebral contusions are often the result of coup and contrecoup forces. Cerebral contusions may not be associated with any loss of consciousness at the time of insult. Patients often have associated symptoms, such as altered level of consciousness, severe headache, vomiting, or focal deficits on neurologic assessment. Contusions are clearly demonstrable on CT.

Epidural Hematoma. Epidural hematomas are typically caused by bleeding from the meningeal vessels and often associated with overlying fractures. Traditional teaching regarding the development of epidural hematomas involves the typical triad of head injury followed by a lucid interval, followed by rapid deterioration as intracranial hemorrhage worsens. After head trauma, guardians are informed of the delayed signs and symptoms that should prompt immediate reassessment.

Subdural Hematoma. Subdural hematomas are often secondary to the rupture of bridging veins. Less than half of pediatric cases have overlying fractures. Subdural hematomas most commonly occur in patients younger than 2 years old. Chronic subdural hematomas are associated with "shaken baby syndrome." This clinical complex involves forcible shaking of the child with accelerating and decelerating forces affecting the cranial vault. This syndrome is most often a result of nonaccidental trauma. Subdural hematomas at multiple sites, over areas other than the convexities, in the posterior fossa, or in the posterior interhemispheric fissure should suggest the possibility of nonaccidental trauma. These patients have nonspecific findings, such as vomiting, failure to thrive, change in level of consciousness, or seizures. See Chapter 177 for a more in-depth discussion on nonaccidental trauma.

Diagnostic Testing and Management

Serial examinations are the most reliable indicators of clinical deterioration. The presence of focal findings on neurological examination is a reliable indicator of a localized insult, whereas the absence of focality may be misleading. The classic Cushing response (bradycardia and hypertension) does not always occur in children; but when it occurs, it is often an ominous sign. If ICP elevation is suspected, emergency intervention and neurosurgical consultation are immediately warranted (Table 165.4).

The contents of the skull are composed of three main compartments: brain, cerebrospinal fluid, and blood. Because the cranial vault is a fixed volume, the Monroe-Kellie doctrine suggests the effects that changes within each compartment may have on the others. For example, in the presence of an intracerebral hemorrhage of significant volume, either cerebral spinal fluid or brain must leave the cranial vault. Similarly, if the brain swells, cerebral spinal fluid, blood, or both must leave the cranial vault. When this balance is disrupted and the autoregulatory system's capacity to adapt is exceeded, the ICP rapidly increases. ICP can quickly reach a level that is not conducive to localized brain survival or continued blood flow to the brain. If the condition is left untreated, herniation may occur.

TABLE 165.4

Emergent Management of Increased Intracranial Pressure

THERAPY	DOSAGE	MECHANISM OF ACTION
Head elevation (30 degrees)		Lowers intracranial venous pressure.
Head in midline		Prevents jugular vein compression.
Hyperventilation	Maintenance $Paco_2$ 38 to 42 mm Hg If acute increase in ICP, then reduce $Paco_2$ to 30 to 35 mm Hg	Promptly but temporarily decreases cerebral blood volume and thus intracranial pressure. Recommended only for short-term treatment of acute ICP elevation.
HYPEROSMOLAR AGENTS		
Mannitol 3% Hypertonic saline (HTS)	0.25 to 0.5 g/kg IV 6.5–10 mL/kg IV	Both agents effect rapid osmotic diuresis. Diuresis may decrease BP and CPP. Mannitol should be given through filter. Effect from osmotic and rheologic effects. Avoid dehydration.
Pentobarbital	5 to 10 mg/kg over 30 minutes, then 5 mg/kg/hr for 3 hours, then 1 mg/kg/hr Rarely indicated or started in ED	Thought to lower cerebral metabolism; also may have some effect on free radical formation. Other barbiturates (phenobarbital) have also been used. May decrease BP and CPP.
Decompressive craniotomy		Allows more space for swelling and decreases ICP.
Maintain euvolemia	Clinically or invasive monitoring	Maintenance of MAP.
Pressors if needed to maintain CBF	Depends on agent used	Maintain CBF and CPP by increasing MAP.
Neuromuscular blockade	Depends on agent used	Helps maintain lower ICP.
Sedation	Depends on agent used	Do not assume patient is completely incapable of response to noxious stimuli or situation.
Prevent fever	Acetaminophen 15 mg/kg orogastrically	Fever raises ICP and metabolic demand.
Treat seizure aggressively	Depends on agent used	Prophylactic treatment controversial. Treatment of seizure is not controversial and is aggressive to prevent increased ICP, hypoxia, hyperpyrexia, and hypercarbia.

BP, Blood pressure; *CBF,* cerebral blood flow; *CPP,* cerebral perfusion pressure; *ED,* emergency department; *ICP,* intracranial pressure; *IV,* intravenously; *MAP,* mean arterial pressure; *$Paco_2$,* arterial carbon dioxide partial pressure.

Most emergency clinicians favor early and controlled intubation in pediatric trauma patients with GCSs that are deteriorating or are less than 9. For the out-of-hospital phase of care, BMV ventilation is recommended over intubation for support of ventilation and oxygenation.[24] Isolated head injury is uncommon; a careful search for other injuries should be made.

The use of anticonvulsants after moderate to severe head injury in children is controversial. Early prophylaxis does not decrease the incidence of late seizures and is not recommended for this purpose. However, because early seizures after trauma are discordant with the management principles of acute brain injury, some guidelines suggest the use of prophylactic anticonvulsants (most often phenytoin or levetiracetam).[25,26] These decisions should be made in consultation with the neurosurgical service. If a seizure does occur, aggressive management is necessary.

Herniation syndromes in children are similar to those in adults. These are described in Chapter 34. Management of suspected acute herniation begins with immediate controlled hyperventilation.[26] Clinical endpoints of hyperventilation are improved patient status or constriction of dilated pupils. Subsequent management of herniation includes hyperosmolar agents, (mannitol or hypertonic saline) followed by other specific interventions in the intensive care unit (ICU).[26,27]

Radiology

Skull Radiographs. Possible indications for skull radiographs include the skeletal survey involved with the evaluation of child abuse, establishment of a functioning ventricular peritoneal shunt, some penetrating wounds of the scalp, or the suspicion of foreign bodies underlying scalp lacerations. In children requiring neuroimaging because of concern for intracranial injury, a noncontrast CT scan is the recommended test, because plain skull radiography lacks sufficient sensitivity to be used as a screening tool.[28] A recent retrospective cross-sectional study calls into the question the necessity of admission for otherwise neurologically normal children with isolated skull fractures and no concern for nonintentional trauma, because the cost is high and the incidence of neurosurgical intervention in these patients seems very low. In selected cases after neurosurgical consultation, discharge with close outpatient follow-up and return precautions may be acceptable.

Computed Tomography of the Head. There has been a considerable amount of research on the indications and relative value of CT scanning in pediatric head-injured patients. CT of the head when appropriately used can be lifesaving and of small individual risk even to children who generally have higher risk than adults due to higher radiation sensitivity, higher likelihood of future imaging studies, longer life expectancy, and the still prevalent higher than necessary radiation dose used for pediatric studies. Although based on extrapolations of data from atomic bomb related cancers, it is generally accepted that the lifetime risk of cancer to an individual due to a CT scan is on the order of one in 500 to 1000. Studies have shown various combinations of characteristics that make significant intracranial injury very unlikely but have provided less guidance in the selection of which patients actually need a head CT scan (high negative predictive value but low positive predictive value).[21,29-31]

As children of different ages manifest intracranial trauma differently, guidelines on CT imaging are age-based. In infants, suspicion of abuse should trigger strong consideration for head CT imaging if signs and symptoms warrant it. For children younger than 2 years old, head CT imaging should be performed in the presence of altered mental status, GCS of 14 or lower, or a palpable skull fracture. In the same age group, occipital, parietal or temporal scalp hematomas, a history of loss of consciousness 5 seconds or more, not acting normally per parent, or a severe mechanism of injury should lead to a period of observation in the ED or head CT. Children older than 2 years old with GCS of 14 or lower, altered mental status, or signs of basilar skull fracture should undergo head CT imaging. A history of loss of consciousness, vomiting, severe headache or severe mechanism of injury should prompt observation or a head CT.[29]

All children who sustain head injury, with or without diagnostic imaging, should be monitored closely for any signs of deterioration. Those with intracranial injury should be admitted to the hospital and seen by the neurosurgery service. Most patients with normal brain CTs or with isolated linear skull fractures in the setting of minor blunt head trauma who have a normal GCS, a stable examination, and no focal neurologic signs may be discharged home.[30] Reliable caretakers should be given specific return precautions for any focal deficit, lethargy, worsening of symptoms, or alteration of consciousness.

Spinal Injury

Principles

Spinal cord injury patterns vary with the age of the patient. Although cervical spinal injuries are less common in children than in adults, higher cord level injuries are more common in children and can lead to devastating outcomes. Fractures above the C3 level account for the majority of cervical spinal lesions in children younger than 8 years old, which differs dramatically from the patterns seen in older children and adults.[31,32] Anatomic features of the cervical spine approach adult patterns between 8 and 10 years old (Box 165.10). However, injury patterns identical to those of adults often do not fully manifest until 15 years old.

BOX 165.10

Anatomic Differences in the Pediatric Cervical Spine

- Cervical spine fulcrum changes from C2 to C3 in toddlers to C5 to C6 by 8 to 12 years old.
- Relatively larger head size, resulting in greater flexion and extension injuries.
- Relatively large occiput in children younger than 2 years old leads to flexion of cervical spine if they are laid flat on standard backboard without support under their scapula and pelvis.
- Smaller neck muscle mass with ligamentous injuries more common than fractures.
- Anterior wedge appearance of cervical vertebral bodies is common.
- Increased flexibility of interspinous ligaments.
- Flatter facet joints with a more horizontal orientation.
- Incomplete ossification, making interpretation of bony alignment difficult (synchondrosis).
- Uncinate processes do not calcify until approximately 7 years old.
- Basilar odontoid synchondrosis fuses at 3 to 7 years old.
- Apical odontoid epiphyses radiographically apparent at 7 years old but may not fuse until approximately 12 years old.
- Posterior arch of C1 fuses at 4 years old.
- Anterior C1 arch may not be visible until 1 year old and fuses at 7 to 10 years old.
- Neural arches fuse to body by approximately 7 years old.
- Posterior arches fuse by 3 to 5 years old.
- Epiphyses of spinous process tips may mimic fractures.
- Predental space 4 to 5 mm in those <8 years old and <3 mm in those ≥8 years old.
- Pseudosubluxation of C2 on C3 seen in 40% of children 8 to 12 years old.
- Prevertebral space size varies with phase of respiration.

The pediatric spine has greater elasticity of the supporting ligamentous structures than the adult spine. The joint capsules of the child have greater elastic properties, and the cartilaginous structures are less calcified than in adults. In the spine, there is a relatively horizontal orientation of the facet joints and uncinate processes, and the anterior surfaces of the vertebral bodies have a more wedge-shaped appearance. Compared with the adult, the child has relatively underdeveloped neck musculature and a disproportionately large and heavy head. These differences lead to an anatomic fulcrum of the spine in children that is at the level of the C2 and C3 vertebrae versus the lower cervical vertebrae as found in adults. These combined anatomic features lead to higher cervical cord injuries and an increased incidence of cord injury without bone injury.[31,32] Thus *s*pinal *c*ord *i*njury *w*ithout *o*bvious *r*adiographic *a*bnormality (SCIWORA) is more common in children. SCIWORA may be a misnomer in the era of magnetic resonance imaging (MRI), because most injuries traditionally described as SCIWORA are seen immediately on MRI, albeit not plain radiographs. Treatment and prognosis are based upon neurologic presentation and MRI findings.[33] Whenever a spinal injury is noted or suspected, careful attention should be paid to the entire spine as multilevel injuries are common.[34]

Clinical Features

Any patient with severe multiple injuries should be evaluated for spinal cord injury. Likewise, significant head, neck, or back trauma, trauma associated with high-speed MVCs or falls from a height onto the head should raise suspicions for spinal cord injury. The evaluation of a pediatric patient should begin with a primary survey to assess airway patency, ventilatory status, and perfusion. After initial evaluation and stabilization, the cervical region can be examined. Palpation of the neck for pain and bony deformity should be performed. Closely watching the patient's facial expression will often indicate more than asking, "Do you have pain?"

Tenderness or pain with palpation may be underappreciated in a child who is not yet old enough to talk. Similarly, patients with head injury, decreased level of consciousness, or distracting injury, and those who are intoxicated may not reliably localize pain; therefore, spinal motion restriction should be maintained to avoid potential additional injury.

The neurologic examination in a pediatric patient can be difficult, but several factors should be evaluated in a patient with suspected spinal cord injury. Paralysis, perceived paresthesias, ptosis, torticollis, and priapism are neurologic signs highly correlated with spinal cord injuries. Complaints of paralysis or paresthesias, even if completely resolved at the time of examination, should be considered an indication of possible spinal injury. Symptoms that resolve in the ED may be an indication of spinal cord injury from SCIWORA; deficits from an initial stretching of the cord with a rapid deceleration mechanism resolve, only to resurface (even days later) from subsequent cord edema.

Several characteristic spinal cord injury syndromes can be diagnosed on initial ED evaluation. Pediatric presentations of these syndromes are similar to adults and are detailed in Chapter 36. Spinal cord injuries are generally described as either complete or incomplete, depending on the presence or absence of sensory or motor function. Incomplete lesions have some preservation, even if slight, of sensory or motor function below the area of SCI. Incomplete SCI has a better prognosis for recovery of some motor function after spinal shock resolves. The determination of complete or incomplete lesions is not a one-time assessment and cannot be reliably made until after spinal shock has resolved, manifested by return of spinal cord reflexes.

Diagnostic Testing

Some pediatric trauma patients can safely avoid cervical spine imaging. Patients older than 3 years old do not require imaging if they are alert, have no midline tenderness, neurological deficit, painful distracting injury, unexplained hypotension, or intoxication. In addition to the aforementioned criteria, children younger than 3 years old generally do not require cervical spine imaging if their mechanism of injury is not a MVC, suspected nonaccidental trauma, or a fall from a height of more than 10 feet. Cervical spine imaging should be performed for children not meeting the aforementioned criteria.[35-37]

We recommend cervical spine CT for children with high clinical pretest likelihood for cervical fracture. In young children (<3 years old) at risk for cervical spine injury who are receiving a head CT scan for head injury, emergency clinicians should obtain a C-spine CT to the top of C3. In lower risk populations, plain radiographs should be performed.[37,38] When obtained, plain radiographic evaluation should routinely consist of a cross-table lateral and an anteroposterior view. In children older than 8 years old, an open-mouth odontoid view should also be performed.[36,37] The sensitivity of cervical spine plain radiographs is highly variable. Interpretation of plain cervical spine radiographs in children may be especially challenging because of the anatomic changes that occur with growth (see Box 165.10). In addition, pseudosubluxation of C2 on C3 is common on non-extended cervical spine radiographs in children up to adolescence, occurring in approximately 40% of patients. Pseudosubluxation and true subluxation on non-extended cervical spine radiographs can be distinguished through use of the posterior cervical line and the relationship of the spinolaminar line (also called the *line of Swischuk*) to the anterior cortical margin of the spinous process at C2 (Fig. 165.3). This line should maintain its integrity with no more than 1.5 mm of deviation. Exceptions to this guideline do occur, and the clinical scenario is taken into account before it is applied. Pseudosubluxation may be seen less commonly at C3 to C4.

An important criterion for radiographic clearing of the cervical spine is complete visualization of all seven cervical vertebral bodies on plain film down to and including the C7 to T1 interface. The predental space should be less than 5 mm in children younger than 6 years old, and the prevertebral soft tissue space should not be greater than normal (variable but generally one-third to one-half the vertebral body width through C4, and <14 mm at C6). The four cervical radiographic lines should be evaluated, and the atlanto-occipital alignment should be assessed for dislocation in this region. If there is any question of injury, thin-section CT and MRI can be used to delineate injury. If the dens cannot be adequately assessed by the open-mouth odontoid view, then a transoraminal view or CT scan should be used. Patients with high clinical suspicion for fracture but negative plain radiographs should be considered candidates for CT or MRI radiographic evaluation and specialist consultation.

The pretest likelihood of fracture is considered when decisions are being made regarding the removal of cervical immobilization in children with apparently normal imaging. Patients with continued neck pain despite negative radiographs or CT may require MRI evaluation.[39] Rare cases may necessitate evaluation by neurosurgery under fluoroscopy. The use of flexion-extension views in the ED is rarely indicated nor helpful. If ligamentous injury is suspected, a MRI should be obtained; and if MRI is not available, consider CT in consultation with neurosurgery.

Young children are at greater risk for upper cervical spine injury. Many occipital cervical junction injuries are immediately fatal. However, survival is possible in some cases. Early detection and immobilization is crucial. Occipital cervical junction injuries should be suspected in any pediatric pedestrian versus vehicle

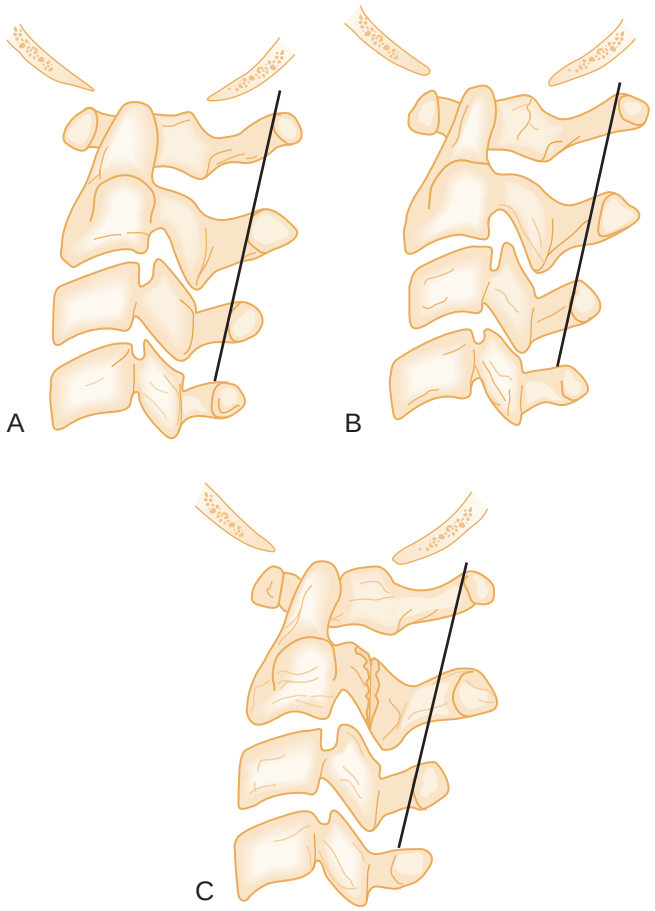

Fig. 165.3. Spinolaminar line. Use only to access anterior displacement of C2 on C3. A line is drawn from the cortex of the spinous process of C1 to the cortex of the spinous process of C3, and the relationship of the spinous process of C2 is noted. **A,** Normal line passing through the cortex of C2. **B,** Normal line passing within 1.5 mm of the cortex of C2. **C,** Abnormal line passing more than 1.5 mm anterior to the cortex of C2, suggesting underlying fracture of posterior elements of C2. (From American Academy of Pediatrics and American College of Emergency Physicians: APLS: the pediatric emergency medicine resource, ed 4, Sudbury, MA, 2004, Jones and Bartlett Publishers.)

accident, especially if the child has a laceration under the chin from a forward fall. In many fatal cases, distraction and displacement are obvious. However, in nonfatal cases, they can be subtle. A Power's ratio greater than 1 indicates an atlanto-occipital dislocation until proven otherwise (normal, approximately 0.77). Power's ratio is shown in Figure 165.4.

A traumatic or even sometimes nontraumatic atlantoaxial rotatory subluxation should be suspected in a child with a fixed rotatory cervical abnormality. Classically, this can be differentiated from a muscular torticollis in nontraumatic cases by the history, the time course, and the presence of palpable spasm of the sternocleidomastoid muscle on the side contralateral to the direction in which the chin is pointing in the case of torticollis. When atlantoaxial rotatory subluxation cannot be confidently ruled out clinically, plain radiographs or CT should be used.

In children with upper cervical spine tenderness, it is prudent to consider a fracture of the synchondrosis between the odontoid and C2. This can be difficult to diagnose on plain radiographs, but it is often recognized as a subtle anterior tilt to the odontoid on C2. A CT scan with sagittal reconstructions will clarify this entity.[40]

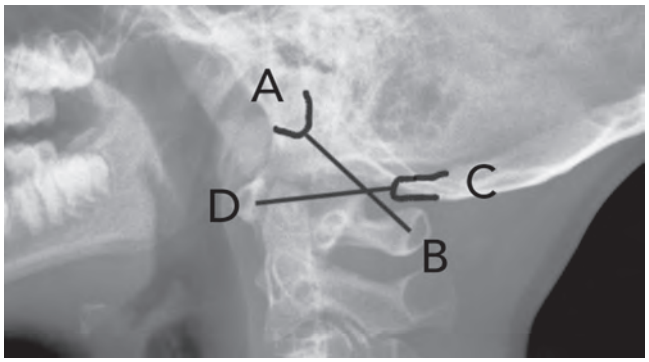

Fig. 165.4. Power's ratio is calculated as the ratio of the distance from the basion (midpoint of the anterior margin of the foramen magnum) *(C)* to the anterior cortex of the posterior arch of the atlas *(D)* divided by the distance from the opisthion (median (midline) point of the posterior margin of the foramen magnum) *(B)* to the posterior cortex of the anterior arch of the atlas *(A)*. A ratio of greater than 1 indicates an atlanto-occipital dislocation. The figure shows a normal Power's ratio.

Management

There are two phases of spinal cord injury. Direct injury (initial phase) results in largely irreversible injury to the spinal cord. Indirect injury results from preventable or reversible injury to the spinal cord secondary to ischemia, hypoxemia, and tissue toxicity. Resuscitation of a patient with injury to the cervical spine should focus on prevention or minimization of the indirect causes of injury to the cervical spine. Management of possible spinal cord or column injury should begin in the out-of-hospital phase of emergency care. Most injured children arrive at the ED with adequate immobilization. For transport, the child who requires spinal motion restriction should be immobilized with a stiff cervical collar, a rigid backboard, and external fixation by means of head blocks, cloth tape, or straps to provide adequate precautions. Appropriate padding should be placed under the shoulder blades of the patient to approximate neutral alignment of the cervical spine and help prevent pressure-related injury. Some out-of-hospital protocols call for small children to be immobilized in their car seats. In the hospital, spinal immobilization should be maintained throughout the evaluation. However, even when thoracic or lumbar fractures exist, patients should be expeditiously removed from the backboard to prevent discomfort and morbidity. Sliding boards (smooth movers) can be used to move patients onto scanner tables and back to their trauma beds.

Breathing should be assessed to determine the presence of hypoventilation. Patients with spinal cord injury may hypoventilate because of diminished diaphragmatic activity or intercostal muscle paralysis. Supplemental oxygen should be given routinely, and ventilatory assistance by BMV or definitive airway management should be considered in the presence of clinically significant hypoventilation.

Circulatory status should also be addressed early to prevent end-organ perfusion deficits. Hypotension can result from hypovolemia, neurogenic shock, spinal shock, or other less common causes. Spinal shock usually results from injury above the level of T1. It manifests with lower extremity findings of spinal cord injury, with flaccid paralysis of skeletal and smooth muscle leading to the appearance of a relative hypovolemia caused by diminished systemic vascular resistance. Spinal shock generally resolves in hours to approximately 1 day once some spinal level reflexes return below the site of injury. Neurogenic shock typically occurs after injury to the spinal cord above the level of approximately T6. Patients with neurogenic shock lose their

sympathetic tone and demonstrate hypotension in the face of unopposed parasympathetic action, such as bradycardia. In each case, fluid administration, parasympathetic receptor blocking agents (such as, atropine or glycopyrrolate) and vasopressors with chronotropic, vasoactive, and inotropic characteristics (eg, dopamine) are used. If spinal shock with normal chronotropy and inotropy is found, then fluids and agents with more peripheral vascular vasoconstrictive properties may be preferable, such as phenylephrine or norepinephrine. Spinal and neurogenic shock remain diagnoses of exclusion once hemorrhagic shock has been definitively eliminated.

Immediate evaluation by a spinal cord specialist should be sought for all children with spinal cord injury. In the absence of such a specialist, the patient should be transported to a center with adequate facilities to care for spinal cord–injured patients.

Cardiothoracic Injury

Principles

Most serious chest injuries in children are caused by blunt trauma and result from MVCs, pedestrian accidents, and falls. Isolated chest injury is a relatively infrequent occurrence considering the typical mechanisms of blunt trauma in the pediatric patient. Pediatric trauma patients with thoracic injury have a twentyfold increase in mortality over pediatric trauma patients without thoracic trauma.[41] Sequelae of blunt injury include pulmonary contusion, pneumothorax, hemothorax, myocardial injury, pericardial injury, vascular injury, and rib fractures.

Children subjected to penetrating trauma, in contrast to the injuries associated with blunt trauma, often die from the primary insult. Nationwide misuse of firearms has resulted in an increasing incidence of penetrating trauma, often with children as victims.

Specific clinical patterns should alert the emergency clinician to the potential for concurrent abdominal and thoracic injury. Any patient with penetrating trauma at or below the level of the nipples falls into this category. Apparent isolated thoracic trauma does not exclude abdominal injury.

It is important to understand the physiology of pediatric respiration in considering the potential for early decompensation after chest injury; any impairment of diaphragmatic mobility compromises ventilation. The presence of gastric distention elevates the diaphragm and severely diminishes the vital capacity of a child. In addition, the particular types of muscle fibers involved in the diaphragm of infants and young children predispose them to the sudden development of apnea when these muscles become fatigued. Unlike adults, whose thoracic wall musculature can pull the ribs up anteriorly to give a larger circumference to the chest wall, children's chest wall circumference does not change drastically during respiration, because a child's chest is barrel-like throughout the respiratory cycle. This also decreases the ability of children to increase their vital capacity. For these reasons, children will increase ventilation typically by increasing their respiratory rate. Most important, the presence of adequate oxygenation in a pediatric patient does not always ensure sufficiency of ventilation, necessitating confirmatory auscultatory. End-tidal carbon dioxide capnography can be very useful in this regard in both the intubated and the nonintubated trauma patient.

Infants and children are anatomically protected against blunt thoracic cage trauma because of the compliance of the rib cage. Compressibility of the rib cage dissipates the force of impact, which lessens the likelihood of bony injury. However, this protective mechanism may mask complex pediatric thoracic insults. The compliance of the rib cage allows significant injury to occur with little apparent external signs of trauma. Multiple rib fractures are a marker of serious injury in children. In addition, the pediatric mediastinum is mobile, which favors the development of rapid ventilatory and circulatory collapse in the presence of a tension pneumothorax.

Specific Disorders

Pneumothorax. The development of a traumatic pneumothorax is commonly associated with significant pulmonary injury. In contrast to spontaneous pneumothoraces, these insults do not resolve spontaneously and often are associated with the presence of a hemothorax. Signs and symptoms include external evidence of chest trauma, such as abrasion, contusion, or ecchymoses; tachypnea; respiratory distress; hypoxemia; and chest pain. Decreased breath sounds may not be appreciated in children with pneumothoraces because of the wide transmission of breath sounds in the chest and upper abdomen. Emergency clinicians should listen to the chest from the axilla in children; this location helps with lateralization to distinguish decreased breath sounds on one side compared with the other. Extended FAST procedure performed by the emergency clinician during the initial trauma evaluation, utilizing B mode and M mode ultrasound, have high sensitivity and accuracy for diagnosing pneumothorax. Plain radiography should be performed, however ultrasound of the chest has high sensitivity in detecting pneumothorax in a child and should be performed when a pneumothorax is suspected but not present on plain radiography.

Management of a hemopneumothorax includes the placement of a large-caliber chest tube (largest tube that can fit between the ribs; or estimated as four times the endotracheal tube size) far enough posteriorly, near the mid-axillary line, to prevent encroaching on more anterior soft tissue that will later become part of the breast. Chest tube size for hemopneumothorax management can be found in Box 165.2 or on a length-based resuscitation tape. A chest tube should be considered for any patient with a pneumothorax who will be undergoing mechanical ventilation. Some small (<20%) simple pneumothoraces without tension may be managed with observation and 100% oxygen supplementation in a child not being mechanically ventilated. Reassessment can be accomplished by repeat chest radiographs at selected intervals, or a pigtail catheter can be placed percutaneously.

Open Pneumothorax. An open pneumothorax exists when the chest wall is injured sufficiently to allow bidirectional flow of air through the wound. The patient is unable to expand the lung because of equalization of pressures between the atmosphere and the chest cavity. Ventilation and oxygenation are severely impaired.

Management of an open pneumothorax is dictated by the size of the defect and the amount of respiratory compromise. A simple, small, open pneumothorax in a breathing patient may be treated by covering the chest wall defect with occlusive dressing, such as sterile petroleum gauze, and performing a separate incision for a thoracostomy tube. Defects that are too large to seal adequately and patients with ventilatory failure are candidates for intubation.

In the out-of-hospital setting, a bandage applied over an open pneumothorax wound and taped on three sides as a temporizing measure may allow air to escape during expiration but not to enter during inspiration.

Tension Pneumothorax. Pulmonary air leaks that occur in a one-way valve arrangement favor the development of a tension pneumothorax. Increasing amounts of free air within the pleural cavity cause the mediastinal structures to shift toward the opposite side, compromising cardiac output. The final common pathway involves hypoxia, hypotension, and refractory shock. Most patients with tension pneumothoraces have severe respira-

tory distress, decreased breath sounds (often bilaterally), and a shift in the point of maximal cardiac impulse. In the worst scenario, there is mediastinal shift, contralateral tracheal deviation, and distention of the neck veins with decreased venous return to the thorax. In pediatric patients, signs of tension pneumothorax are often subtle. A short neck and increased soft tissue may make detection of tracheal deviation difficult. The emergency clinician should consider the diagnosis of tension pneumothorax and, if it is detected or strongly suspected, should treat with needle thoracostomy or chest tube decompression.

Immediate treatment includes needle thoracostomy placed in the second intercostal space in the midclavicular line or in the fourth intercostal space just above the rib and anterior to the mid-axillary line. The needle should be placed above the rib margin to avoid injuring the intercostal vessels. In the ED, definitive treatment involves the use of a large-caliber thoracostomy tube that favors drainage of the tension pneumothorax and any accompanying hemothorax.

Hemothorax. Significant bleeding may occur as a result of injury to intercostal vessels, internal mammary vessels, or lung parenchyma. Without an upright chest radiograph, it is difficult to quantify the degree of bleeding on plain films. The only sign of hemothorax on a supine radiograph may be a slightly less radiolucent appearance on the affected side of the chest. Clinically, patients have decreased breath sounds and dullness to percussion on the affected side. A pneumothorax may coexist with a hemothorax.

The treatment of hemothorax includes a tube thoracostomy. The tube needs to be large enough to occupy most of the intercostal space and should be placed laterally and directed posteriorly. In the supine patient with simple pneumothorax, chest tubes are directed superiorly; in hemopneumothorax, they are directed posteromedially. Repeat chest radiographs should be obtained to confirm tube position and document improvement in lung expansion.

Development of a massive hemothorax is rare in children and is associated most often with severe impact, such as that seen in high-velocity MVCs, falls from extreme heights, or the use of high-powered firearms. Any alteration in cardiovascular sufficiency should be treated with rapid fluid replacement with isotonic crystalloid solutions. The emergency clinician should also prepare for transfusion with the institution of red blood cell (RBC) replacement as necessary. Patients with profound shock may receive either type-specific or O-negative blood; crossmatched blood may be used for more stable patients. Many centers have the capability to salvage blood from hemothoraces and to reinfuse it through use of an autotransfusor. The emergency clinician is often able to stabilize the patient with RBC replacement until surgical intervention is achieved.

Indications for thoracotomy in an operating room include evacuated blood volumes exceeding 15 mL of blood per kilogram immediately after the placement of the chest tube, persistent blood loss (exceeding 2 to 4 mL/kg/hr over 3 hours), or continued air leak.

ED thoracotomy is reserved for patients with thoracic trauma who deteriorate to cardiopulmonary arrest despite maximal resuscitation in the out-of-hospital setting or ED. For both children and adults, it has been shown to be more effective in cases of penetrating trauma.[42-44] In patients with penetrating chest trauma and cardiopulmonary resuscitation (CPR) for less than 15 minutes, a left anterior thoracotomy may be warranted. Patients with blunt trauma should undergo rapid assessment by ultrasound for tamponade. If tamponade is present and CPR has been performed for less than 10 minutes, then a left anterior thoracotomy may be indicated.[45] Suggested contraindications to ED resuscitative thoracotomy after out-of-hospital CPR include (1) blunt trauma with CPR for longer than 10 minutes with asystole and no signs of life on presentation without ultrasound evidence of cardiac tamponade and (2) penetrating trauma with CPR for greater than 15 minutes and asystole with no signs of life on arrival without ultrasound evidence of cardiac tamponade.[45]

Pulmonary Contusion. Penetrating and blunt thoracic trauma may result in the development of a pulmonary contusion. The compliance of the rib cage in children renders them susceptible to the development of pulmonary contusion even in the absence of external signs of chest trauma. Injury to capillary membranes allows blood to collect within the interstitial spaces, resulting in hypoxia and respiratory distress. If bleeding is severe enough, oxygenation and ventilation are impaired. Initial chest radiographs may not show the classic findings of pulmonary consolidation. In addition, in the early stages of injury, blood gases may be normal.

Treatment of pulmonary contusions includes a careful evaluation for the presence of additional injuries because significant force is necessary to cause the contusions. Most patients may be treated with supplemental oxygen and close monitoring. Most pulmonary contusions resolve without sequelae. Rare cases are associated with the development of acute respiratory distress syndrome.

Traumatic Diaphragmatic Hernia. Children involved in MVCs who are wearing lap belts are predisposed to the development of diaphragmatic herniation. Mechanisms of injury involve sudden increases in intra-abdominal pressure. Patients initially are in stable condition, with the degree of respiratory distress directly proportional to the amount of abdominal contents that protrude into the pulmonary space. The presence of bruising from lap belt–only compression should alert the clinician to the possibility of diaphragmatic hernia and other intra-abdominal injuries (small bowel injury) and the possibility of associated thoracolumbar spinal insults, such as Chance fractures. Most commonly, the herniation occurs on the left side because the liver prevents herniation of bowel on the right.

Initial management for these patients involves placement of a nasogastric tube to decompress the stomach. In cases of severe respiratory distress, intubation is indicated. BMV is avoided whenever possible. Surgery is required for repair of the injury.

Cardiac and Vascular Injuries. Injuries to the heart and large vessels are uncommon in children and rarely happen in isolation. In cardiac and vascular injuries, an electrocardiogram may show tachycardia with low voltage (pericardial tamponade), findings consistent with acute myocardial ischemia, or a variety of other nonspecific abnormalities. Patients with dysrhythmias, ST-segment abnormalities, and hypotension (without another cause) should be admitted with a pediatric cardiologist consulted and undergo further testing (eg, echocardiogram).

The most common traumatic cardiovascular injury sustained by children is myocardial contusion. Patients often have chest wall tenderness or may report generalized chest pain. Tachycardia is the most common finding. Echocardiogram may be diagnostic. Patients with myocardial contusions should be monitored closely for the development of dysrhythmias and impaired myocardial function; however, in most cases of myocardial contusion, there are no long-term sequelae.

The most life-threatening scenario involving the cardiac structures is the development of cardiac tamponade. Penetrating wounds with myocardial penetration and tamponade are potentially survivable if recognized immediately. Extravasated blood fills the pericardial space and impairs cardiac filling during diastole. Clinically, patients demonstrate tachycardia, distant heart sounds, narrow pulse pressure, jugular venous distention, and

pulsus paradoxus. In the scenario of profound hypovolemia, venous distention is absent. The final common pathway involves the development of cardiopulmonary failure and pulseless electrical activity. Ultrasound can characterize cardiac tamponade in seconds and guide therapy.

Bedside ultrasound or echocardiography defines the degree of pericardial effusion present and the significance of any diastolic dysfunction present. Pericardiocentesis may be attempted, as treatment involves drainage of the fluid from the pericardial sac. However, significant hemodynamic compromise from an acute traumatic pericardial effusion is rarely adequately addressed with a needle pericardiocentesis, owing to the amount of cardiac bleeding and subpericardial clot. Performance of a thoracotomy or pericardial window is often necessary to evacuate the pericardium adequately.

Commotio Cordis. Commotio cordis is a disorder described in pediatric patients that results from sudden impact to the anterior chest wall (eg, when a child is struck in the chest with a thrown or hit baseball), which causes cessation of normal cardiac function. The patient may have an immediate dysrhythmia or ventricular fibrillation that is refractory to resuscitation efforts. Significant morbidity and mortality are associated with this disorder, and although most patients recover completely, some require extended treatment with antiarrhythmic agents, cardiac pacemaker placement, inotropic agents, or an intra-aortic balloon pump.[46] In patients with prolonged cardiac instability, cardiogenic shock and death may occur despite maximal therapeutic intervention.

Abdominal Injury

Principles

Abdominal trauma is the third leading cause of traumatic death in children after head and thoracic injuries.[1] Blunt trauma related to MVCs causes more than half of abdominal injuries in children and is the most lethal. "Lap belt" injury, including small bowel injury and Chance fractures, may occur in restrained children involved in MVCs.[47] Another common cause of abdominal injury involves handlebar injuries from bicycle crashes.[48-50] Often, the effects of bicycle injuries may not be seen on initial presentation, with the mean elapsed time to onset of symptoms being nearly 24 hours after injury. All children with epigastric pain after blunt trauma, especially when concentrated force has been applied in this area, should be considered to have a duodenal hematoma or pancreatic injury.

Sports-related injuries are another common cause of pediatric abdominal trauma. Sports-related injuries are associated most commonly with isolated organ injury as a result of a blow to the abdomen.[39,51] At particular risk are the spleen, kidney, and intestinal tract. Finally, abdominal injury is second only to head injury as a cause of death in child abuse cases. All abuse victims should be screened carefully for abdominal trauma (see Chapter 177).[52,53]

The anatomy of the child lends special protection from some abdominal injury patterns and predisposes the child to other types of injuries. Children have proportionally larger solid organs, less subcutaneous fat, and less protective abdominal musculature than adults. Therefore they have relatively more solid-organ injury. Children have relatively larger kidneys with fetal lobulations that predispose them to renal injury. Children also have a fairly flexible cartilaginous rib cage that allows for significant excursion of the lower chest wall, permitting compression of the internal organs. The combination of these factors provides the basis for the differences in abdominal injury patterns seen between children and adults.

Clinical Features

Pediatric patients with multiple injuries often have blunt abdominal injury. In children, history is often limited, traditional signs of decompensation are often not as evident, and physical examination can be difficult.

Signs and symptoms of abdominal injury in children include tachypnea from impaired diaphragmatic excursion, abdominal tenderness, ecchymoses, and signs of shock. Restrained children involved in MVCs with abdominal bruising are much more likely to have an intra-abdominal injury than those without bruising. Abdominal distention is a common nonspecific finding that is often the result of air swallowing subsequent to a painful event.

Children with hepatic and splenic injuries may have trouble localizing their pain. Kehr's sign (left shoulder pain with spleen injury) may be the only indication of an intra-abdominal injury. Any abdominal tenderness on examination should prompt further evaluation of the abdomen. Vomiting can be associated with duodenal hematoma or traumatic pancreatic injury but is usually a late sign. Signs of small bowel injury may be delayed and noted clinically only with serial examinations.

Pelvic bone stability should be assessed in cases of abdominal trauma, and a genital examination searching for signs of injury should be performed. Rectal examination is insensitive and nonspecific when used as a general screening test for all patients after serious trauma.[10] Rectal examination should only be performed in patients with concern for specific injuries: such as for rectal tone when there is concern for spinal injury, or to evaluate for blood in the case of penetrating colon injury.

Even minor falls can result in significant splenic injury. Repeated examination, prolonged observation, and close attention to vital signs are warranted for children who have sustained a direct blow to the abdomen. Any child with clinically suspicious abdominal examination findings or significant direct trauma should be evaluated further with additional radiologic and laboratory studies or admission for serial examinations.

Diagnostic Testing and Management

In patients with suspected abdominal injury, management and resuscitation must be rapid. In children who have undergone major trauma and have no evidence of urethral trauma, a urinary catheter should be considered for bladder decompression, evaluation for the presence of urinary retention, examination for the presence of blood in the urine, and monitoring of urine output. Urinary catheter size estimates are shown in Box 165.2.

A careful examination and diagnostic laboratory testing can be useful in identifying children at lower risk for intraabdominal injury. Intraabdominal injury is unlikely in the absence of the following: hypotension (age-adjusted), abdominal tenderness, a femur fracture, increased liver enzyme levels (serum aspartate aminotransferase concentration >200 U/L or serum alanine aminotransferase concentration >125 U/L), microscopic hematuria (urinalysis >5 RBCs/high powered field), or an initial hematocrit level less than 30.[54,55] Liver enzyme testing is particularly useful to risk stratify patients with equivocal examination finings. Victims of suspected child abuse should also undergo liver enzyme testing and those with transaminase levels more than 80 U/L should undergo CT of abdomen and pelvis to assess for abdominal injury.[52]

The diagnostic test of choice to assess intra-abdominal injury in stable patients at high risk for injury is abdominal CT. The FAST examination can be a useful adjunct.[4,5] The finding of intraperitoneal hemorrhage alone on ultrasound is not necessarily an indication for surgery in a stable pediatric patient; but when the FAST is positive, it will clarify the need for abdominal CT, close observation, and possible repeat ultrasound examinations.

BOX 165.11

Indications for Laparotomy

- Hemodynamic instability despite aggressive resuscitation and appropriate ED procedures (eg, a decompression hemothorax or tension pneumothorax)
- Hemodynamic instability despite resuscitative efforts and evidence of intraperitoneal free fluid on bedside ultrasound examination (FAST)
- Transfusion of ≥50% of total blood volume because of massive intraperitoneal bleeding
- Radiographic evidence of pneumoperitoneum, intraperitoneal bladder rupture, grade V renovascular injury
- Gunshot wound to the abdomen
- Evisceration of intraperitoneal or stomach contents
- Signs of peritonitis

ED, Emergency department; *FAST,* focused assessment with sonography in trauma.

In hemodynamically unstable children, FAST may point to the abdomen as the source of hemorrhage and may expedite the decision to operate.

Indications for laparotomy are listed in Box 165.11. Patients who remain hypotensive after adequate crystalloid infusion, have active arterial bleeding on CT scan, or have consistent decreases in their hemoglobin level are likely candidates for early invasive intervention. Exploratory laparoscopy or laparotomy is often required for these critically injured patients, but patients with a known source of bleeding may be appropriate candidates for arterial embolization in an angiography suite.[55]

Spleen Injury. Injuries to the spleen are the most common injuries in pediatric abdominal trauma. Children with injuries from MVCs, sudden deceleration injuries, and contact sports–related injuries may sustain splenic trauma. Typical findings include left upper quadrant abdominal pain radiating to the left shoulder. The abdominal examination may show evidence of peritoneal irritation in the left upper quadrant of the abdomen. Patients may be hemodynamically stable or, after significant splenic rupture or laceration, may be persistently hypotensive or in fulminant cardiovascular collapse. Stable patients may undergo CT for radiologic evaluation.

Most often with minor splenic trauma, bleeding is controlled spontaneously without operative intervention; however, all patients with a splenic injury should be evaluated by a surgeon. In patients with a contained splenic subcapsular hematoma, extracapsular bleeding may occur days after capsular rupture. Patients with splenic injury should be admitted to the hospital for close observation and repeated examinations. Because of the desire for splenic salvage to maintain immunocompetency, an injured spleen is often left in place as long as the patient can be resuscitated adequately with crystalloid and blood products.

Liver Injury. The liver is the second most commonly injured solid organ in the pediatric patient with abdominal trauma; however, it is the most common cause of lethal hemorrhage. Tenderness on palpation of the right upper quadrant of the abdomen, the complaint of abdominal pain in this region, and pain in the right shoulder are signs of possible liver injury. Patients managed conservatively with crystalloid and/or blood transfusion often do well. Once liver injury is detected on CT scan, close observation in the hospital, serial abdominal examinations, and serial hemoglobin measurements are recommended.

Renal Injury. The kidney is more susceptible to injury in children than in the adults due to the potential for remnant fetal lobules, increased organ mobility with rapid deceleration mechanisms, and lack of protective intraabdominal musculature; there is also a tendency for congenital renal abnormalities, which are susceptible to injury (eg, the horseshoe kidney) to be discovered at a young age after trauma. For these reasons, even though the kidney is less susceptible to trauma from forces applied to the anterior abdomen, it is often injured in the pediatric patient with multiple injuries.[56,57] Because this organ is retroperitoneal, signs and symptoms of kidney injury are often less obvious and more diffuse than signs and symptoms of other abdominal organ injuries. Often, dull back pain, ecchymosis in the costovertebral region, and hematuria are the only clues to renal injury. CT and renal ultrasound may be used in a stable patient to assess the degree of renal involvement. For most patients, initial CT scan of the abdomen to assess for genitourinary injury is indicated when there is gross hematuria, microscopic hematuria and shock, and penetrating injury to the abdomen with or without hematuria. Major deceleration injuries also pose a risk of genitourinary injury and low threshold for imaging in these cases even with microscopic hematuria should be exercised.

Other organs, such as the pancreas and gastrointestinal tract, are less frequently injured in pediatric patients but may have delayed presentations.

Penetrating Injury. Penetrating wounds to the abdomen usually require rapid evaluation by a surgeon and consideration of operative intervention. With hemodynamic instability, or peritonitis, urgent laparotomy is indicated. In the hemodynamically stable patient, further evaluation with a CT scan, local wound exploration, diagnostic laparoscopy, and observation may be warranted. Diagnostic peritoneal tap (DPT) and diagnostic peritoneal lavage (DPL) have been largely supplanted by other diagnostic modalities in modern practice, such as CT and diagnostic laparoscopy.[58] Children with a positive DPL should receive fluid and or transfusion in the ED, and children with a positive DPL do not necessarily require surgical intervention because of splenic salvage.

Radiology. Pediatric patients frequently sustain injury to the spleen, liver, kidneys, and gastrointestinal tract. CT of the abdomen with IV contrast can provide high sensitivity and specificity for identification of these injuries while being relatively noninvasive.[59] Abdominal CT has a high negative predictive value.[60] Oral contrast should not be used; it does not add to the accuracy of CT for trauma and can lead to a delay in evaluation, and risk of aspiration.

Although radiologic evaluation can provide important diagnostic information in a pediatric patient with possible abdominal trauma, any patient with unstable vital signs from an obvious surgically correctable cause should receive immediate operative intervention and not be subjected to delay while radiographic screening studies are obtained. Children with persistent or recurrent hypotension, continued abdominal pain, or persistent abdominal distention should undergo evaluation by a surgeon.

DISPOSITION

The primary role of the emergency clinician is to evaluate and stabilize the patient before admission or transfer to a facility with a higher level of care available. Infants and younger children who are moderately to severely injured have improved outcomes in pediatric specific ICUs.[61]

Before any transport, the patient should be maximally stabilized. This may include the involvement of general surgeons, definitive surgery, or temporizing surgery (such as, packing the abdomen). The emergency clinician should communicate directly with the accepting physician at the tertiary care center. In general, the emergency clinician should refrain from completing extensive radiologic testing in a facility that is potentially unable to manage

the injury being screened for, unless the clinician is confident that it will not delay the transfer to definitive care. All documents and test results should be sent with the patient. Parents should be informed of the reason for transfer and exact location to which the child is being taken.

Indications for admission include operative intervention and need for ongoing monitoring. The threshold for admission should be low in cases in which the health care team does not believe the child will have the social support or oversight necessary to be appropriately observed or to recover at home.

KEY CONCEPTS

- Trauma is the leading cause of death in children in the United States.
- Avoid hypoxia and hypotension by early administration of oxygen and assisted ventilation, and fluid resuscitation with crystalloid at 20 mL/kg increments. Initiate transfusion of 10 mL/kg of PRBCs if hypotensive or remains with signs of hypovolemic shock after 40 mL of crystalloid is infused.
- Key pediatric anatomic and physiologic differences include:
  - Children are smaller, so force is more widely distributed through the body of a child, making multi-system injuries more likely.
  - The infant's head-to-body ratio is greater, creating a relatively higher center of gravity. This combined with a less myelinated brain and thinner cranial bones may result in more serious head injury.
  - Children have a higher anatomic fulcrum in the cervical spine (C2 to C3 in children <8 years old). This leads to higher C-spine injuries.
  - Children have more lax ligaments of the cervical column. This leads to an increased risk of SCIWORA.
  - Children have more horizontally positioned ribs meaning that with inspiration, the ribs move only up and not out. This leads to a limited ability to increase tidal volume and risk for respiratory failure with chest or diaphragmatic injury.
  - Children have more elastic chest walls that allow for pulmonary injury without skeletal injury.
  - Children have thinner abdominal walls and have more anterior livers and spleens. This results in a greater chance of injury to those organs.
  - Children have excellent compensatory mechanisms. They can remain normotensive until they lose large amounts of intravascular volume. Hypotension is a very late sign.
- Continuous monitoring and reassessment of the trauma patient is essential to recognize early signs of deterioration and to discover all injuries.
- Most minor head trauma may be managed with observation and without CT imaging. Clinical decisions rules when applied may reduce imaging and exposure of children to ionizing radiation.
- In major trauma patients indications for intubation include respiratory failure or a GCS less than 9.
- Most cases of shock in trauma are due to hypovolemia so fluid resuscitation with normal sale is recommended, and the addition of packed cell transfusions should be initiated in a pediatric trauma patient with hypotension or with signs of shock after 40 to 60 mL/kg normal saline.
- The diagnostic test of choice for the evaluation of intra-abdominal injury in a stable patient with high suspicion for injury is CT of the abdomen.
- Splenic injuries are generally treated conservatively in children to ensure immunocompetence.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 165: QUESTIONS & ANSWERS

165.1. A 5-year-old male is struck by a car while riding a bicycle. On presentation, he exhibits hypotension, a normal heart rate, and quadriplegia. You suspect neurogenic hypotension secondary to spinal shock and attempt to correct the hypotension with fluids but are not successful. Which of the following should be your first choice for a vasopressor?
A. Dobutamine
B. Dopamine
C. Epinephrine
D. Phenylephrine

Answer: D. Spinal shock is related to decreased systemic vascular resistance (SVR). A pressor with primarily alpha vasoconstrictive effects, such as phenylephrine or norepinephrine, is the best choice for increasing SVR without having other physiologic effects.

165.2. A 6-week-old infant is brought to your emergency department (ED) by his mother after he reportedly fell 3 feet from his changing table approximately 45 minutes ago. His mother reports that the child did not lose consciousness and "seems fine." She is concerned, however, by a large scalp hematoma that developed almost immediately. What is your most important intervention at this point?
A. Consulting a social worker to help screen for child abuse
B. Head computed tomography (CT) scan
C. Ice packs for the scalp hematoma
D. Observation in the ED for 4 hours
E. Skull radiographs

Answer: B. A 6-week old infant is at high risk for intracranial injury given the softness/deformability of the skull. Scalp hematomas signify possible skull fracture and thus CT of the head is indicated.

165.3. Which of the following is the most commonly injured solid organ in pediatric patients with abdominal trauma?
A. Bladder
B. Duodenum
C. Kidney
D. Liver
E. Spleen

Answer: E. Injuries to the spleen are the most common injuries in pediatric abdominal trauma. Children involved in motor vehicle collisions (MVCs), sudden deceleration injuries, and contact sports–related injuries may sustain splenic trauma. Treatment includes fluid resuscitation and blood transfusion as needed. Splenic salvage is important for immunocompetence in children and operative intervention is avoided as long as the patient can be stabilized with fluid resuscitation.

165.4. A 4-year-old female is brought to your emergency department (ED) from the scene of an motor vehicle collision (MVC). Paramedics intubated the child in the field because she was unresponsive at the scene. On arrival, her vital signs are within normal limits. Before transport to the computed tomography (CT) scanner, however, you note that she is becoming mildly bradycardic and hypertensive. Her left pupil becomes dilated and nonreactive. Which of the following should be your next immediate action?
A. Hyperventilation to a carbon dioxide (CO_2) level between 30 and 35 mm Hg
B. Mannitol administration
C. Nicardipine infusion
D. Phenytoin administration
E. Proceed immediately to the CT scanner

Answer: A. The patient's sudden onset of dilated, nonreactive pupil, along with bradycardia and hypertension, is indicative of acute brain herniation. Immediate hyperventilation to a goal of CO_2 between 30 and 35 mm Hg has been shown to reduce brain injury. CT scanning should not be performed before this potentially lifesaving intervention. The administration of a hyperosmolar agent, such as mannitol or hypertonic saline, is indicated but should not take precedence over hyperventilation. Phenytoin is arguably indicated in this patient but not necessary in the acute setting. Nicardipine and other antihypertensive agents have no place in the management of a head-injured child. Her hypertension is a physiologic response to brain herniation, in which increasing mean arterial pressure (MAP) preserves cerebral perfusion pressure (CPP).

165.5. A 7-year-old girl is brought into the emergency department (ED) by emergency medical service (EMS) personnel from the scene of an motor vehicle collision (MVC). On your primary survey, she is noted to have a clear airway, decreased breath sounds in the right lung field, subcutaneous emphysema, and tracheal deviation to the left. She has thready distal pulses. What is your next step in stabilizing this patient?
A. Airway control with endotracheal intubation (ETI)
B. Bag-mask ventilation (BMV)
C. Immediate needle thoracostomy in the second midclavicular space on the right
D. Portable chest radiograph to confirm diagnosis

Answer: C. This patient is presenting with signs of tension pneumothorax. In this case, immediate decompression with a needle thoracostomy, followed by the placement of an appropriately sized chest tube or immediate chest tube placement is required to avoid cardiovascular collapse.

165.6. Which of the following statements regarding chest injuries in children is correct?
A. Aortic transection is more likely in a pediatric patient than in an adult patient.
B. Multiple rib fractures without significant underlying lung injury are common in children.
C. Penetrating chest trauma is more common than blunt chest trauma in pediatric patients.
D. Significant pulmonary contusions may be present in the absence of rib fractures in children.

Answer: D. The pediatric rib cage has more compliance than an adult rib cage. This makes children predisposed to pulmonary injury in the absence of bony injury. Rib fractures are more rare in the pediatric population because of this, and their presence is concerning for underlying lung injury. Blunt chest trauma is more common than penetrating chest trauma in pediatric patients and concurrent chest and abdominal injuries are common. Aortic transection is more common in adults.

165.7. A 12-year-old male fell while climbing over a 12-foot barbed-wire fence and sustained a deep 10-cm laceration to his medial left thigh. There is active bleeding from the laceration. What is the first step in the management of this patient?
A. Apply a tourniquet to the leg.
B. Begin with a primary survey and assess the patient's airway and breathing.

C. Obtain intravenous (IV) access and begin blood transfusion immediately.
D. Pack the wound to decrease hemorrhage.

Answer: B. The primary survey should quickly assess the airway, breathing, and circulation (ABCs). Initial wound management involves the application of direct pressure to the wound. Approaching trauma patients in a systemic fashion will ensure that large, obvious injuries do not distract from the detection of other injuries. Oftentimes multiple interventions would be done simultaneously. Jaw thrust to open an airway and then another health care providers quickly applying hemorrhage control. The child in the question also fell from a fence and may have other fall-related injuries.

165.8. Which of the following statements regarding imaging of a multi-trauma pediatric patient is correct?
A. A negative computed tomography (CT) scan of the cervical spine rules out spinal cord injury, and if normal, immobilization can be discontinued.
B. A negative focused assessment with sonography in trauma (FAST) examination rules out traumatic intra-abdominal injury, making a CT scan unnecessary.
C. In a hemodynamically stable pediatric trauma patient, CT imaging should be complete before transfer to a pediatric trauma facility, even if it delays transfer.
D. In a hemodynamically stable pediatric patient with a high level of concern for intra-abdominal trauma, CT scan is the imaging test of choice.

Answer: D. CT scan is the diagnostic test of choice for evaluation of intra-abdominal trauma in children. Spinal cord injury without radiologic abnormality (SCIWORA) is more common in pediatric patients, and normal cervical spine CT scan does not rule out spinal trauma. Although often a useful adjunct, a FAST examination does not rule out intra-abdominal injury. In a hemodynamically stable patient, CT imaging does not need to be complete before transfer to a pediatric trauma center and should not delay transfer. With clinical concern for elevated intracranial pressure (ICP), treatment (eg, hyperventilation, mannitol, or hypertonic saline) should be initiated immediately.

CHAPTER 166

Pediatric Fever

Nathan W. Mick

PRINCIPLES

Background

Fever is the most common chief complaint of pediatric patients presenting to the emergency department (ED). Most cases of fever are viral in origin, benign in course, and resolve spontaneously. Management of children with fever varies by the age of the child, with the following common divisions: 0 to 28 days old, 1 to 2 months old, 2 to 3 months old, 3 to 6 months old, 6 to 36 months old, and 3 years old to adulthood. These divisions reflect differing immunologic and vaccination milestones as well as a spectrum of age-specific pathogens.

Anatomy and Physiology

Fever is defined as any elevation in body temperature equal to or above 100.4°F (38.0°C). The most reliable method to measure temperature is with a rectal thermometer and is the preferred method of measurement in high-risk groups, such as infants 0 to 3 months old. However, the rectal route should not be used in patients who are potentially immunocompromised (eg, children with fever who are receiving cytotoxic chemotherapy) because of the risk of mucosal damage leading to bacteremia. The cutoff for a clinically significant fever (ie, one that may trigger a laboratory evaluation) varies with the age and immunologic status of the child. A rectal temperature of 100.4°F (38.0°C) is considered to be a clinically significant fever in an infant younger than 3 months, whereas a toddler with a temperature of 103.1°F (39.5°C) and an upper respiratory infection may not need any evaluation beyond a thorough history and physical examination.

Pathophysiology

Causes of fever vary with the age of the child (Table 166.1). The majority of pediatric fever is due to infections, and most infections are attributable to a viral source. Upper respiratory infections, viral gastroenteritis, croup, bronchiolitis, stomatitis, roseola, infectious mononucleosis, and varicella are all known causes of fever. Most viral illnesses are benign and self-limited, but infection with measles, herpes simplex virus (HSV), or respiratory syncytial virus (RSV), can lead to significant morbidity and mortality, particularly in the first month of life.

Bacterial disease is also an important cause of fever in children. Serious bacterial illness (SBI) is typically defined as the presence of pathogenic bacteria in a previously sterile site and includes urinary tract infection (UTI), bacteremia, meningitis, osteomyelitis, bacterial gastroenteritis, bacterial pneumonia, cellulitis, and septic arthritis. The risk of SBI in febrile infants younger than 3 months old with a temperature of 100.4°F (38.0°C) or greater to be between 6% and 10%; children younger than 28 days old have the highest incidence.[1] Pathogens change during early infancy, with vertical transmission of organisms such as group B streptococcus, *Listeria monocytogenes,* and HSV being more common in neonates. By 1 to 2 months old, organisms such as *Streptococcus pneumoniae, Neisseria meningitidis,* and urinary pathogens *(Escherichia coli* or *Enterococcus)* become more common. In all children younger than 3 months old, the urinary tract is the most common site of infection, followed by bacteremia and meningitis. UTIs are more common in white girls compared with other races and are of higher prevalence in patients in whom no source for infection is found and who have higher temperatures (ie, >102.2°F [39.0°C]).

Children younger than 3 months old may present with an apparent viral syndrome and still harbor SBI. Levine and colleagues studied 1248 infants younger than 60 days old who had temperatures above 100.4°F (38.0°C).[2] Of these children, 22% were positive for RSV. Although, overall, children with documented RSV had a lower incidence of concomitant SBI than did those without RSV (12.5% vs. 7%), there was no significant difference in rates of SBI in children younger than 28 days old (14.2% in RSV-negative neonates vs. 10.1% in RSV-positive infants). Most of the bacterial infections were UTIs.[2] Older children 3 to 36 months old with recognizable viral syndromes (eg, croup, bronchiolitis, varicella, stomatitis) have a very low incidence of bacteremia. In over 1300 patients with temperature above 102.2°F (39.0°C) who had a recognizable viral syndrome, the risk of bacteremia was 0.2%.

Occult bacteremia describes the presence of pathogenic bacteria in the bloodstream of a well-appearing febrile child in the absence of a focus of infection; it was first described as a clinical entity in the 1970s. The term typically refers to children 3 to 36 months old who are highly febrile (>102.2°F [39.0°C]) but appear well. Before the adoption of the conjugate vaccines against *Haemophilus influenzae* type b and *S. pneumoniae,* the incidence of bacteremia in this population was approximately 5%. Vaccination has proved remarkably effective, nearly eradicating *H. influenzae* type b as a significant pathogen and greatly reducing the burden of pneumococcal disease (Fig. 166.1).[3,4] Currently, the rate of occult bacteremia is less than 1%, with pathogens such as *N. meningitidis* becoming proportionally more prevalent. Urinary pathogens, occurring in 5% of febrile children younger than 2 years old, continue to be an important source of bacterial illness in infants and children. Risk factors include female sex, absence of another apparent source of infection, fever higher than 102.2°F (39.0°C), white race, and for boys, uncircumcised status.[5]

Bacterial illness in school-age children and adolescents includes focal infections, such as streptococcal pharyngitis, cellulitis, and pneumonia, as well as bacteremia and meningitis. *N. meningitidis* has a bimodal distribution, with the highest incidence in children younger than 12 months old (9.2/100,000 population). A second peak occurs during adolescence, when the rate of illness is 1.2/100,000 population, with a significant proportion of cases occurring in college students who reside in a dormitory setting (3.2/100,000 population).

Although it is much less common than in viral or bacterial infection, fever can also be a presenting sign of autoimmune diseases, such as juvenile rheumatoid arthritis or Kawasaki disease. Central nervous system (CNS) lesions such as brain tumors also can infrequently be manifested with fever.

TABLE 166.1

Etiology of Fever in Children

AGE	BACTERIAL CAUSES	VIRAL CAUSES	OTHER
0 to 28 days old	Group B streptococcus	HSV	Bundling*
	Listeria monocytogenes	Varicella	Environmental
	Escherichia coli	Enteroviruses	
	Chlamydia trachomatis	RSV	
	Neisseria gonorrhoeae	Influenza	
1 to 3 months old	*Haemophilus influenzae*	Varicella	
	Streptococcus pneumoniae	Enteroviruses	Environmental
	Neisseria meningitidis	RSV	
	E. coli	Influenza	
3 to 36 months old	*S. pneumoniae*	Varicella	Leukemia
	N. meningitidis	Enteroviruses	Lymphoma
	E. coli	RSV	Neuroblastoma
		Influenza	Wilms' tumor
		Mononucleosis	
		Roseola	
		Adenovirus	
		Norwalk virus	
		Coxsackievirus	
3 years old to adulthood	*S. pneumoniae*	Varicella	Leukemia
	N. meningitidis	Enteroviruses	Lymphoma
	E. coli	RSV	Neuroblastoma
	Group A streptococcus	Influenza	Wilms' tumor
		Mononucleosis	Juvenile rheumatoid arthritis
		Roseola	
		Adenovirus	
		Norwalk virus	

*Bundling may raise core temperature enough in some neonates to cause a fever; in older children, bundling raises skin temperature but does not raise core temperature appreciably. Care should be exercised in attributing a fever to bundling in any age group.
HSV, Herpes simplex virus; *RSV,* respiratory syncytial virus.

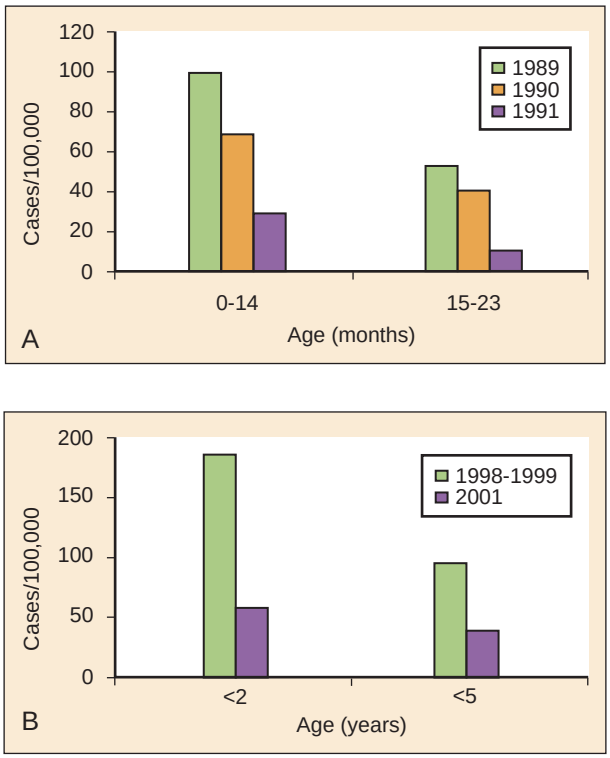

Fig. 166.1. Decline in incidence of occult bacteremia after the introduction of the conjugate vaccine against *Haemophilus influenzae* **(A)** and *Streptococcus pneumoniae* **(B).**

The body's ability to fight infection varies with age. Maternal antibodies confer some protection after birth, but the infant's immune system is initially inadequate, particularly T-cell function and the ability to mount an immunoglobulin G response to infection. The immature neonatal immune system as well as exposure to certain pathogens during the birthing process (eg, group B streptococcus, *Chlamydia trachomatis, Neisseria gonorrhoeae*) places the newborn at particular risk for SBI. Young infants are also at risk for disseminated infection, because they are unable to mount the immune response needed to prevent a localized infection from spreading. Thus a simple cellulitis, mastitis, omphalitis, or, rarely, gonococcal eye disease, can lead to sepsis or focal seeding of the CNS. Immune function improves during the first 2 to 3 months of life as does the ability to assess a child clinically. Infants begin the primary series of vaccinations against acquired infections, such as *S. pneumoniae* and *H. influenzae,* at 2 months old, which further provides protection against common bacterial pathogens. As a result, empirical testing and treatment give way to more selective evaluations above 2 to 3 months old.

Clinical Features

History taking should focus on the length of illness, presence of localizing symptoms (eg, headache and neck pain [meningitis or encephalitis] or ear pain [otitis media]), exposure to persons with serious illness, and any pertinent past medical history. For infants younger than 28 days old, document birth history, including the presence of potentially transmittable maternal infections (HSV or group B streptococcus). Document immunization status, sick contacts, use of antipyretics before evaluation, and prior use of antibiotics. Defervescence after acetaminophen administration has not been shown to reliably exclude bacteremia in children of any age. Prior antibiotic use may mask the classic findings in diseases, such as meningitis. Cough and congestion may suggest pneumonia or viral upper respiratory infection, whereas a harsh, barking, or seal-like cough is often a predominant complaint in viral laryngotracheitis (croup). Parents may report vomiting and diarrhea as a component of gastroenteritis or the presence of sore throat and lymphadenopathy with viral or streptococcal pharyngitis. Decreased oral intake or decreased urine output is a frequent complaint in gastroenteritis but may also be seen in patients with stomatitis, because the painful aphthous ulcerations in the mouth make fluid intake difficult. Any history of lethargy, irritability, or altered mental status can be elicited with severe dehydration but raises the specter of meningitis or encephalitis. A rash occurs in many viral illnesses (eg, roseola), but may be seen in life-threatening conditions, such as meningococcemia, Rocky Mountain spotted fever, and toxic shock syndrome (TSS).

The physical examination of the febrile child should begin with a complete set of vital signs, including pulse oximetry. Hypoxia or significant respiratory distress manifested by tachypnea, grunting respirations, nasal flaring, or retractions may accompany sepsis or

pulmonary infection. Stridor can be seen with croup but also with retropharyngeal abscess, epiglottitis, or bacterial tracheitis. Note signs of shock, such as hypotension and poor peripheral perfusion, should be noted. Children typically mount a tachycardic response to fever, and hypotension is often a late and dire finding. Tachycardia is often due to the fever itself, but tachycardia out of proportion to the degree of fever can be seen with early shock, myopericarditis, and dehydration. Estimations of heart rate increase based on fever in infants younger than 12 months old (ie, heart rate increases linearly by 9.6 beats/minute with each 1°C increase in body temperature) should be used with caution, and clinical signs of sepsis should be evaluated before attributing tachycardia to fever alone. Once oxygenation, ventilation, and perfusion have been assessed and deemed adequate, the physical examination should focus on a thorough search for focal infection. In young infants, particularly those younger than 3 months old, and in children who lack immunocompetence, fever may be the only presenting sign of SBI, including meningitis. The physical examination in this age group is sufficiently insensitive to exclude SBI, and emergency clinicians should not be falsely reassured by a normal physical examination in small children.

Diagnostic Testing

Numerous laboratory and radiographic studies can be used to evaluate the febrile child. In general, testing should be directed at identification of the source of infection or evaluation for complications. Several guidelines exist for the evaluation of febrile children, although there is marked variation in adherence to these guidelines. Office-based practitioners have been found to follow published guidelines only 42% of the time in the evaluation of febrile children. Clinicians with less experience and those based in the hospital tend to order more tests compared with more experienced clinicians and those practicing in an office setting. Use of institutional clinical decision rules and guidelines can help streamline appropriate testing.[6,7]

White Blood Cell Count

An elevated white blood cell (WBC) count (>15,000/mm^3) can be an indicator of bacteremia but is also present in many viral illnesses. Leukopenia (<5000/mm^3) can also be a sign of SBI or early sepsis. Pneumococcal infection is classically associated with leukocytosis, whereas infection with *N. meningitidis* and *H. influenzae* may be present even with normal WBC counts. Lee and colleagues found that the rate of pneumococcal bacteremia increased from 0.5% in highly febrile children (>102.2°F [39.0°C]) with a WBC count between 10,000 and 15,000/mm^3 to 3.5% if the WBC count was 15,000 to 20,000/mm^3 and up to 18% with a WBC count above 30,000/mm^3. More extreme leukocytosis is associated with an increased risk of bacterial infection, particularly lobar pneumonia and a WBC count of above 25,000/mm^3 should prompt consideration of a chest radiograph unless another definitive source is apparent.[8]

The WBC differential diagnosis has also been used to risk stratify febrile children in various models; an increase in polymorphonuclear leukocytes increases the risk of bacterial disease. A rise in polymorphonuclear leukocytes is also seen early in some viral infections. An absolute neutrophil count (ANC) above 10,000/mm^3 suggests increased risk of pneumococcal bacteremia in febrile children (0.8% for children with an ANC below 10,000/mm^3 vs. 8% for children with an ANC above 10,000/mm^3). Routine screening of all febrile children with bloodwork has not been shown to be cost effective in the post-vaccination era. The vast majority of acute febrile illness is due to self-limited viral infection. If the decision is made on clinical grounds to obtain a WBC and it is abnormal (<5,000/mm^3 or >15,000/mm^3) or the ANC is greater than 10,000/mm^3, then screening for occult bacteremia with a blood culture is advised, understanding that leukocytosis is neither perfectly sensitive nor specific for bacterial illness. Treatment of incompletely immunized children who have a WBC more than 15,000/mm^3 with parenteral ceftriaxone is appropriate.

Inflammatory Markers. Both C-reactive protein (CRP) and procalcitonin have been studies as markers of bacterial infection. The utility of the measurement of inflammatory markers is dependent on the cutoff level assigned for clinical significance with lower values having higher sensitivity but lower specificities. Both CRP and procalcitonin appear to be more sensitive and specific than the WBC alone, although the lack of widespread availability limits the usefulness of procalcitonin clinically at this time.[9-11]

Blood Culture

Many centers obtain blood for culture during intravenous (IV) catheter placement after sterile preparation of the skin has been performed. Although this technique has the advantage of eliminating a second venipuncture solely to obtain blood for culture, the rates of contamination with this technique have been shown to be higher than a sterile straight stick in children (9.1% vs. 2.8%). The risks of contamination should be weighed against the ability to obtain blood through a separate venipuncture. The yield of a single blood culture in infants and small children is actually good. The routine sending of more than one sample is generally not needed, and bacteremia is often accurately detected even if only 0.5 to 1 mL of blood is obtained. The advent of automated blood culture systems has led to the identification of true pathogens more quickly than by traditional methods, often within 24 hours. Pathogens isolated in the first 24 hours are more likely to be true pathogens than are bacteria isolated after 24 hours.[12]

Urinalysis and Urine Culture

UTIs are common causes of bacterial illness in febrile children, occurring in 5% of infants 2 to 24 months old with fever 100.4°F (38.0°C) or higher. Accurate documentation of UTI is imperative both to diagnose the cause of a fever and to identify those infants who need follow-up radiographic imaging to exclude anatomic abnormalities that will predispose them to further infection. It is currently recommended that febrile infants with documented UTIs undergo renal ultrasonography to evaluate for hydronephrosis or rare complications, such as renal or perirenal abscesses. Voiding cystourethrography is not indicated after the first febrile UTI in children unless renal ultrasonography reveals evidence of high-grade vesicoureteral reflux or scarring.[5]

The only reliable method to obtain urine in a non–toilet-trained child is bladder catheterization or suprapubic aspiration. Bladder catheterization is the preferred method in almost all cases. Bag collection of urine is notoriously unreliable; up to 85% of cultures from bag specimens will be falsely positive (defined as a culture growing a single organism with >10^5 colony-forming units [CFUs]/mL or a mix of two or more organisms), which then places these children at risk for unneeded, potentially painful, and expensive follow-up diagnostic testing and antibiotics. A clean catch urine specimen is appropriate for toilet-trained children.

UTI is defined as the combination of bacteriuria and pyuria. Bacteriuria in the absence of WBCs on microscopic examination represents asymptomatic bacteriuria. Urine is typically analyzed with a dipstick, followed by microscopic analysis of a centrifuged specimen of urine. An "enhanced" urinalysis, which is examination with a hemocytometer of an unspun specimen of urine for pyuria (defined as >10 WBCs per high-power field) or the

presence of any bacteria per high-power field in Gram stain of unspun urine has a negative predictive value of 99.8%, perhaps making urine culture unneeded if pyuria and bacteriuria are absent by use of the enhanced urinalysis method. However, many centers are not using this enhanced method. Because dipstick and microscopic analysis have lower sensitivities, most experts recommend sending urine for culture in high-risk groups (febrile girls <24 months old, uncircumcised boys <12 months old, and circumcised boys <6 months old).

A positive urine culture is defined as the growth of more than 50,000 CFU/mL of a single uropathogen in urine obtained via catheterization or suprapubic aspirate.

Lumbar Puncture

A sample of cerebrospinal fluid (CSF) should be obtained from any child with signs and symptoms of meningitis. Fluid should be obtained with the smallest pencil-point or noncutting spinal needle possible (typically a 22-gauge spinal needle) and sent for cell counts, manual differential diagnosis, Gram staining, culture, and measurement of CSF protein and glucose concentrations. Meningoencephalitis due to HSV is a potential cause of fever, particularly in children; if suspected, CSF should be sent for HSV polymerase chain reaction (PCR) testing. The CSF in bacterial meningitis typically contains more than 1000 WBCs/mL, although there is considerable overlap in the CSF profile of bacterial and viral meningitis, making a determination of viral or aseptic meningitis difficult on the basis of CSF parameters, such as cell count, protein, and glucose; thus, CSF culture of a pathogenic bacterium is the "gold standard." A prediction rule has been developed and validated to differentiate bacterial from aseptic meningitis in children 29 days to 19 years old who have CSF pleocytosis.[13] Children without any of the following criteria have a low risk (0.1%) of bacterial meningitis: positive CSF Gram stain, CSF ANC of 1000 cells/mL or more, CSF protein concentration of at least 80 mg/dL, peripheral blood ANC of 10,000 cells/mL or more, and history of seizure before or at the time of presentation. This may obviate the need for empirical antibiotic therapy and hospital admission in some children who are at low risk for bacterial meningitis.[14-16]

Contraindications to lumbar puncture include cellulitis over the proposed site of puncture, cardiopulmonary instability, bleeding diathesis, or platelet count below 50,000/μL, focal neurologic deficits, and signs of increased intracranial pressure, including papilledema. In these patients, lumbar puncture should be deferred until the child is stable, and blood should be obtained for culture while the child is treated empirically, recognizing that up to 50% of children with meningitis will not have bacteremia.

CSF contaminated by blood, or a traumatic lumbar puncture, can make interpretation of cell counts and differential diagnoses difficult.[17,18] In these cases, fluid should be obtained for Gram stain and culture and the child hospitalized and treated presumptively for meningitis until culture data are available. Risk factors for a traumatic lumbar puncture include operator experience, excessive patient movement during the procedure, multiple attempts, advancement of the needle with the stylet in place, and lack of local anesthesia.

Stool Studies

Stool studies are indicated in patients in whom bacterial gastroenteritis may be a cause of fever. A stool guaiac test for blood as well as Gram stain for WBCs should be performed. Presence of more than 5 WBCs per high-power field in the stool of a febrile child should trigger a culture of stool for *Salmonella, Shigella, Campylobacter,* enterotoxigenic *E. coli,* and *Yersinia* species. Patients with sickle cell disease are at particular risk for focal complications, such as osteomyelitis from *Salmonella* infection (see Chapter 171).

Chest Radiography

Chest radiographs may be useful in the evaluation of the febrile child and are indicated when hypoxemia, respiratory distress, tachypnea, or focal findings on lung examination are present. Children younger than 6 months old may present with tachypnea as the sole finding of bacterial pneumonia. Truly occult pneumonia can also occur in a small percentage of children, particularly in the highly febrile child (>102.2°F [39.0°C]) without apparent source of fever and an elevated ANC.[19] Studies done prior to universal vaccination against pneumococcus demonstrated a relatively high rate of pneumonia in highly febrile children who had leukocytosis more than 20,000/mm^3 (26%). Since the advent of universal vaccination, the number of occult pneumonias has declined (15% to 9%) but is not yet low enough to recommend not obtaining radiographs on highly febrile children with leukocytosis or elevated ANC and no other apparent source of infection.

Rapid Viral Antigen Testing

Many clinical laboratories have the ability to perform rapid viral antigen testing for such common pediatric viral illnesses as influenza A and B and RSV. The presence of a viral "source" for the fever in an ill child may obviate the need for expensive, painful, and lengthy diagnostic evaluations for bacterial processes.[20-22] Of patients aged 2 months to 21 years old who present with classic signs and symptoms of influenza, more than half have been shown to have positive rapid assays for influenza, leading to fewer antibiotics prescribed. A large multicenter trial of febrile infants 60 days old or younger revealed a decreased risk (2.5% vs. 11.7%) if the infant was influenza positive.

RSV is also a frequent cause of fever in children. As previously noted, RSV decreases but does not completely eliminate the risk of SBI in children. This is especially true of UTI in infants younger than 28 days old. Routine testing for RSV has not been shown to affect outcome at the individual patient level.[22a] Based on this data, it is reasonable to consider a selective, de-escalated evaluation (ie, urine and urine culture) of well-appearing infants who have positive viral testing in the ED given the exceedingly low rates of bacteremia and meningitis. Ill-appearing infants or neonates (28 days old and younger) should still undergo a full evaluation for SBI.

Approach to the Febrile Infant and Child

The initial approach to any child with a febrile illness is a rapid assessment for evidence of cardiopulmonary compromise or shock. Significant respiratory distress, hypoxemia unresponsive to supplemental oxygen, or altered mental status may necessitate intubation by rapid sequence induction and mechanical ventilation. Evidence of shock (poor perfusion, hypotension, altered mentation) should be aggressively treated with fluid resuscitation. An IV or intraosseous line should be placed, and the initial resuscitative fluid should be 20 mL/kg of isotonic crystalloid. This should be repeated to a total of 60 mL/kg over 60 minutes if signs of hypovolemia persist, after which vasopressor therapy (dopamine 1 to 20 μg/kg/min or norepinephrine 0.1 to 3 μg/kg/min titrated to blood pressure) should be considered.

Every effort should be made to obtain appropriate specimens for culture (blood and urine), even in the critically ill child, before antibiotic administration. Lumbar puncture may be deferred in the critically ill child until stabilization occurs. Empirical antibiotic therapy should be directed at the most likely causative

organisms based on age. Sterilization of the CSF starts to occur once antibiotic administration has been initiated—within 15 minutes to 2 hours in patients with meningococcal meningitis and within 4 to 10 hours in patients with pneumococcal meningitis. However, antibiotics should not be delayed awaiting successful lumbar puncture. Antibiotics will not affect PCR or bacterial antigen test results.

Infants 0 to 28 Days Old

Children presenting with temperature of 100.4°F (38.0°C) or higher who are younger than 28 days old are at particularly high risk for bacterial illness, with rates as high as 12%.[23] Often, fever is the only manifestation of potentially life-threatening disease, with other signs and symptoms may be exceedingly subtle. This has led to an aggressive approach to diagnostic testing, empirical antibiotic therapy, and hospitalization in this age group, even if the child appears well.

Children in this age group often present with nonspecific complaints, such as irritability, lethargy, poor feeding, and grunting. Besides fever, other signs of serious illness include a bulging fontanel, mottled extremities, petechiae, and tachypnea. Bacterial pathogens in this age group include group B streptococcus, *L. monocytogenes, N. meningitidis, S. pneumoniae,* and *E. coli*.[24] Viral pathogens, including RSV and HSV, are also important considerations. Neonatal HSV infection carries a high degree of morbidity and mortality and should be considered in any febrile neonate with a maternal history of genital herpes, or who appears ill, presents with fever and seizure, has cutaneous vesicles on physical examination, or evidence of transaminitis or coagulopathy. HSV meningoencephalitis should also be considered in patients with fever and CSF pleocytosis but a negative CSF Gram stain. The highest risk period for HSV disease is between 2 and 12 days old (Fig. 166.2). Other noninfectious causes of a septic-appearing neonate include the acute salt-wasting crisis associated with congenital adrenal hyperplasia and undiagnosed ductal-dependent congenital heart disease.

Because of the high risk of bacterial pathogens and the difficulty in clinical assessment of children younger than 28 days old (neonate), these patients require an aggressive diagnostic evaluation, including a complete septic evaluation. This consists of a complete blood count (CBC) with differential diagnosis, blood culture, urinalysis and urine culture, and lumbar puncture. Lumbar puncture is indicated in this age group even in the presence of a UTI because of the risk of concomitant meningitis. All neonates should be admitted to the hospital with empirical antibiotics until culture data become available. Appropriate parenteral antibiotic regimens include ampicillin (100 mg/kg/24 hours divided every 6 hours) plus either gentamicin (5 mg/kg/24 hours divided every 8 to 12 hours) or cefotaxime (150 mg/kg/24 hours divided every 8 hours). Ceftriaxone should be avoided in infants younger than 28 days old because of a theoretic risk of inducing acute bilirubin encephalopathy as ceftriaxone causes bilirubin to be displaced from its protein binding sites. Empirical acyclovir should be added if risk factors for HSV disease exist (60 mg/kg/24 hours divided every 8 hours).

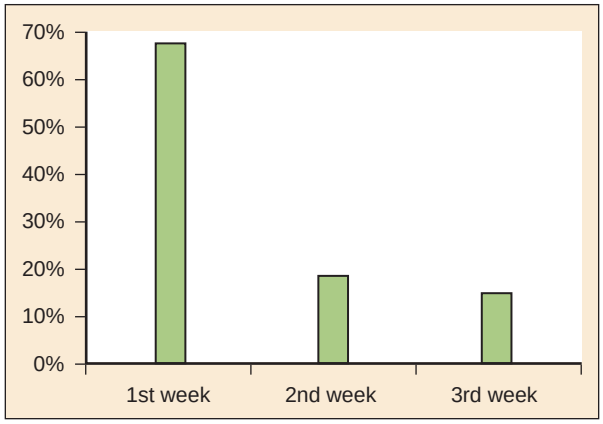

Fig. 166.2. Age at presentation for neonatal herpes simplex virus (HSV) infection.

Infants 29 to 90 Days Old

Although there is a relative consensus as to the evaluation and management of febrile infants younger than 28 days old, there is debate about the appropriate evaluation for the slightly older febrile infants. Ill-appearing children of any age should have a complete sepsis evaluation performed and be admitted to the hospital with empirical antibiotic therapy. Appropriate antibiotic therapy for high-risk children includes coverage of neonatal pathogens, such as *L. monocytogenes* and group B streptococci, as well as coverage against *H. influenzae, N. meningitidis,* and *S. pneumoniae*. Ampicillin, 50 to 100 mg/kg every 6 hours, plus cefotaxime, 50 mg/kg every 8 hours parenterally, is one option. Vancomycin, 10 to 20 mg/kg IV every 6 to 8 hours, should be considered if *S. pneumoniae* resistant to penicillins and cephalosporins is suspected.

Various strategies (herein referred to as the *Rochester, Philadelphia, and Boston criteria*) for the evaluation of well-appearing children have been reported, compared, and retested in the literature.[25-27] Each strategy has unique features, including the definition of fever (100.4°F [38.0°C] vs. 100.8°F [38.2°C]), the study population (0 to 3 months old, 1 to 2 months old, and 1 to 3 months old), the clinical and laboratory variables studied, and the disposition (hospitalization with or without antibiotics or outpatient treatment with or without antibiotics). Each strategy seeks to identify a set of low-risk criteria that, if met, will allow less aggressive treatment or the withholding of empirical antibiotic therapy. The three main strategies are highlighted in Table 166.2. Baraff synthesized the recommendations of the Rochester, Philadelphia, and Boston criteria into an algorithm for the management of the previously healthy febrile infant 29 to 90 days old[27a] (Fig. 166.3). To be low risk, the child had to have been previously healthy with an uncomplicated nursery stay, to be nontoxic clinically, and to have no focal source of bacterial infection. Low-risk laboratory criteria in this schema included a normal WBC count (between 5000 and 15,000 WBCs/mm^3), fewer than 1500 bands/mm^3, normal urinalysis (negative Gram stain and <5 WBCs per high-power field), and negative CSF Gram stain and cell counts (<8 WBCs/mm^3), if obtained. When diarrhea was present, fewer than 5 WBCs per high-power field was the threshold for low risk.

Once the child is deemed to be at low risk by these criteria, two options are available to the clinician on the basis of the Philadelphia and Boston criteria. One management strategy calls for a CBC, blood culture, urinalysis, and urine culture. If the results reveal the patient to be at low risk, the child may be discharged without antibiotics with close outpatient follow-up. If results are abnormal, the patient should receive a lumbar puncture and antibiotics. Another option, based on the Boston criteria, calls for a complete sepsis evaluation, including lumbar puncture, followed by empirical treatment with ceftriaxone (50 mg/kg IV or intramuscularly [IM]) and reevaluation within 24 hours. Overall, antibiotics should not be administered unless a complete sepsis evaluation is performed, including a lumbar puncture. Otherwise, if a lumbar puncture is not initially performed and the child returns for reevaluation and a lumbar puncture is subsequently performed with the finding of CSF pleocytosis, pretreatment

TABLE 166.2

Summary of Major Strategies for the Management of Febrile Infants Younger Than 3 Months Old

	PHILADELPHIA	ROCHESTER	BOSTON
Age	29 to 60 days old	<60 days old	28 to 89 days old
Temperature	>100.8° F (38.2° C)	>100.4° F (38.0° C)	>100.4° F (38.0° C)
Examination	Well, no focus	Well, no focus	Well, no focus
Laboratory values (define low risk)	WBCs >15,000/mm^3 Band/neutrophil ratio <0.2 UA <10 WBCs/hpf (negative Gram stain) CSF <8 WBCs/hpf (negative Gram stain) Chest radiograph normal, stool negative (if obtained)	WBCs 5000 to 15,000/mm^3 Absolute band count <1500 UA <10 WBCs/hpf Stool <5 WBCs/hpf (if obtained)	WBCs <20,000/mm^3 UA <10 WBCs/hpf CSF <10 WBCs/hpf Chest radiograph normal (if obtained)
High risk	Admission + IV antibiotics	Admission + IV antibiotics	Admission + IV antibiotics
Low risk	Home, no antibiotics	Home, no antibiotics	Home, empirical antibiotics
Performance	Sensitivity 98% (92% to 100%) Specificity 42% (38% to 46%) PPV 14% (11% to 17%) NPV 99.7% (98% to 100%)	Sensitivity 92% (83% to 97%) Specificity 50% (47% to 53%) PPV 12% (10% to 16%) NPV 98.9% (97% to 100%)	Sensitivity not available Specificity not available PPV not available NPV 94.6%

CSF, Cerebrospinal fluid; *IV,* intravenous; *NPV,* negative predictive value; *PPV,* positive predictive value; *UA,* urinalysis; *WBC,* white blood cell; *WBCs/hpf,* white blood cells per high-power field.

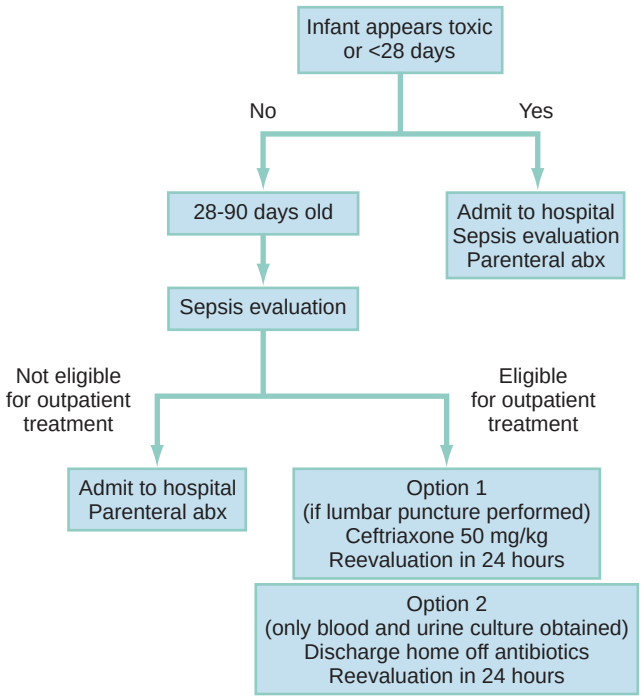

Fig. 166.3. Sample algorithm for the management of febrile infants younger than 3 months old. To be eligible for outpatient treatment, the following must be met: white blood cell (WBC) count 5,000 to 15,000 cells/mm^3, urinalysis is negative, lumbar puncture without pleocytosis or bacteria on Gram stain, able to return for care if necessary, reliable outpatient follow-up, no focal infection present (ie, cellulitis, omphalitis), and chest radiograph and stool studies negative if obtained. *abx*, Antibiotics.

with antibiotics makes interpretation of culture results difficult. Thus a child with a possible viral process may be subjected to inpatient admission and 14 days of parenteral antibiotic therapy. The various criteria developed to define low-risk populations of febrile young infants all perform similarly and emphasizing consistent use of a set of criteria is more critical than which set of criteria are used. Use of an evidence-based guideline to standardize the evaluation and disposition of young infants has been shown to reduce costs.[28-32]

Infants 3 to 36 Months Old

Most cases of fever in children 3 to 36 months old represent self-limited viral illnesses. Common causes of fever in this age group include viral upper respiratory infections, croup, bronchiolitis, stomatitis (typically caused by HSV or coxsackievirus), gastroenteritis, roseola, and fifth disease (parvovirus B19 infection). Focal infections, such as pyelonephritis, periorbital cellulitis, bacterial pharyngitis (group A streptococcus), septic arthritis, retropharyngeal abscess, meningitis, and bacterial pneumonia, also become common in this age group. Typically, these focal infections are apparent on the basis of history and physical examination findings, and diagnostic testing and treatment should be directed accordingly.

The history in this age group should focus on the duration of illness, associated symptoms that may focus the evaluation, immunization history (particularly vaccination for *H. influenzae* type B and pneumococcus), and sick contacts. A thorough physical examination is essential to rule out serious focal infection, such as meningitis. Young children may demonstrate inconsolable irritability or lethargy as the sole manifestation of meningitis; furthermore, classic meningeal signs, such as nuchal rigidity, are seen in less than 27% of infants (0 to 6 months old) with bacterial meningitis.

Prior research has focused on assessment of children in this age group for the presence of occult bacteremia. It was found that a small percentage of highly febrile children (>102.2° F [39.0° C]) 3 to 36 months old were bacteremic. These children were noted to be highly febrile but lacked any localizing signs of infection. No historical or physical examination findings were sufficiently sensitive or specific to identify cases of occult bacteremia, making universal diagnostic testing necessary. A typical evaluation included a CBC and blood culture, and empirical antibiotic therapy was prescribed for children with WBC counts above 15,000/mm^3. Empirical antibiotics were justified on the basis of studies that revealed treatment with antibiotics prevented focal sequelae of bacteremia, such as meningitis and shortened the duration of fever. Before the advent of almost universal immunization against

S. pneumoniae, the rate of occult bacteremia was approximately 3%, and although pneumococcal bacteremia resolved without therapy up to 75% of the time, a small proportion of children had sepsis or focal infections, such as meningitis. Pneumococcal meningitis has a high degree of morbidity and mortality, including permanent neurologic disability, hearing loss, and death.

Since the advent of PCV7 (conjugate pneumococcal vaccine) and most recently PCV13, the number of invasive pneumococcal infections caused by vaccine-serogroup isolates among eight children's hospitals in the United States has decreased more than 75% among children younger than 24 months old. Because of the decline in invasive pneumococcal disease brought on by vaccination, the cost-effectiveness of mandatory blood testing has been called into question. The cost-effectiveness of various management strategies have been evaluated: no evaluation, relying on clinical judgment, blood culture, blood culture plus empirical antibiotics, WBC count plus blood culture and empirical antibiotics, and WBC count plus selective blood culture for WBC counts above 15,000 and empirical antibiotics. For rates of pneumococcal bacteremia greater than 1.5%, obtaining a WBC count plus selective blood culture and empirical antibiotics has been shown to be the most cost-effective approach, whereas for rates of pneumococcal bacteremia less than 0.5%, strategies that use empirical testing and treatment have not been found cost-effective. They concluded that at lower rates of bacteremia, clinical judgment is more useful in selecting out high-risk populations who might benefit from selective testing and treatment.[5] Although the incidence of pneumococcal bacteremia has declined in infants 3 to 36 months old because of the aggressive campaign to vaccinate, infants 3 to 6 months old have not yet completed the primary series of immunizations against *S. pneumoniae* and to a lesser extent *H. influenzae*. Despite being "incompletely vaccinated" at this age, the rate of bacteremia is exceedingly low, arguing against routine screening in this age group. The 13-valent conjugate pneumococcal vaccine (PCV-13) for routine childhood vaccinations provides expanded coverage. The additional six serotypes included in PCV13 were responsible for more than 60% of the cases of invasive pneumococcal disease in the years preceding the release of the updated vaccine schedule.[33-38] Despite these vaccine advances, there are approximately 90 serotypes that are capable of infecting humans, and continued bacterial surveillance is necessary to ensure that other serotypes do not rise in incidence to fill the void left by vaccination. No clinical prediction algorithm correctly identifies all patients with meningococcal disease. Additional signs and symptoms that may suggest meningococcemia are purpuric rash, bandemia, limb pain, and exposure to a person with the disease. An appropriate flow diagram for the evaluation of febrile infants 3 to 36 months old is presented in Figure 166.4.

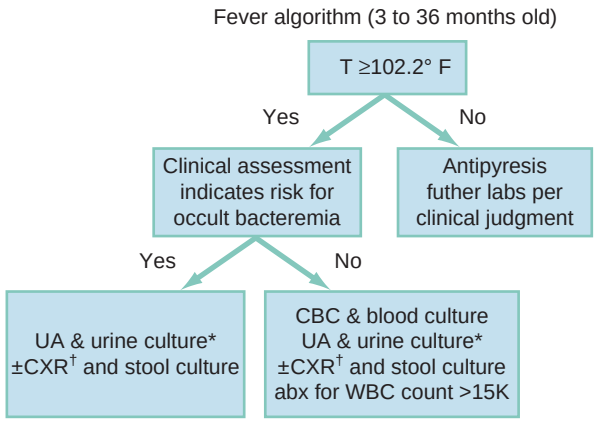

Fig. 166.4. Sample algorithm for the management of febrile infants 3 to 36 months old. *Females <24 months old; circumcised males <6 months old, uncircumcised males <12 months old. †CXR for symptoms or WBC >20,000/mm^3. *abx,* Antibiotics; *CBC,* complete blood count; *CXR,* chest x-ray; *T,* temperature; *UA,* urinalysis; *WBC,* white blood cell.

Children 3 Years Old to Adulthood

The incidence of occult bacteremia decreases after 3 years old. Focal infections such as streptococcal pharyngitis, septic arthritis, pneumonia, peritonsillar abscess (most often in adolescents), and cellulitis become more common. Viral pathogens are also common, such as infectious mononucleosis. Infection with atypical pathogens, such as *Mycoplasma pneumoniae,* should also be considered in children presenting with pneumonia. Skin infections secondary to community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) are also becoming more common. Community-acquired MRSA occurs in all age groups but has clustered among such children as wrestlers (associated with contaminated wrestling mats) and football players (infected equipment). This diagnosis should be considered in all children who present with pyogenic skin infection and skin abscesses. Appropriate therapy includes incision and drainage of the abscess cavity. Antibiotic therapy in addition to incision and drainage for simple abscesses has not been shown to hasten resolution of the infection but should be considered for patients with large abscesses (>5 cm), with cellulitis, or with fever. Antibiotic selections should be based on local resistance patterns, but could include trimethoprim-sulfamethoxazole or clindamycin for younger children and doxycycline for children 8 years old or older.

There is a second peak in incidence of meningococcal disease in adolescent children with an attack rate of 1.2 infections per 100,000 population. As opposed to infants, adolescents with meningococcal infection are more likely to present with meningococcemia (40% vs. 20%) and shock (69% vs. 27%) and to have a fatal outcome (22.5% vs. 4.6%). Meningococcal often manifests with one of three clinical syndromes: meningitis, bacteremia, or a combination of the two. College students residing in dormitories are at particular risk for infection, with attack rates of 3.2/100,000 population.

Meningococcal infection is often rapidly progressive, presenting with fever, headache, and a stiff neck. Shock, altered mental status or frank coma, petechiae or purpura, seizures, and myalgias are also seen. Some of the first signs of meningococcal infection include leg pain, cold hands and feet, and abnormal skin mottling. Children exposed to a patient with meningococcemia, particularly those with close contact with nasopharyngeal secretions, and who have any of the presenting signs should receive a full septic evaluation, admission to the hospital, and empirical treatment with antibiotics until results of blood and CSF cultures are known. Appropriate initial therapy for children suspected of having meningococcal infection is ceftriaxone 100 mg/kg IV.

In January 2005, the U.S. Food and Drug Administration (FDA) approved the quadrivalent meningococcal conjugate vaccine (Menactra) for use in adolescents. This vaccine is a polysaccharide-protein conjugate directed against the four serotypes that cause most cases of invasive meningococcal disease in humans. The Advisory Committee on Immunization Practices recommends vaccination of adolescents at their 11- or 12-year-old well-child checkup, and the American Academy of Pediatrics (AAP) has also advised that all college freshmen living in dormitories be vaccinated. Use of the vaccine is associated with a 67% decrease in invasive disease and a 66% decrease in carriage rates. Younger children with anatomic or functional asplenia, those with complement component deficiencies, and children who travel reside in other countries where the disease is hyperendemic should be vaccinated. Based on age, a number of vaccines for prevention of meningococcal disease are available (www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html).

Febrile Seizures

Febrile seizures are a common cause of convulsions in children younger than 5 years old. They are defined as a seizure accompanied by fever without the presence of CNS infection. They typically occur in infants and children 6 months to 5 years old. It is thought that the at-risk period is the rapid rise or defervescence of a fever, rather than the absolute height of the fever. Many parents worry about the subsequent risk of epilepsy after a febrile seizure, although studies have borne out that the risk is only slightly increased. The risk of epilepsy in the general population is thought to be 0.5% to 1%, whereas the risk in a patient who has had a febrile seizure is 1% to 2%. Although they are generally benign in course, febrile seizures can rarely be the presenting complaint of infants and children with CNS infection, such as meningitis. Febrile seizures are classified as either simple or complex. Simple febrile seizures are brief (<15 minutes), single, and nonfocal or generalized tonic-clonic. Complex febrile seizures are prolonged, recurrent (more than one within 24 hours), focal, prolonged, or occur outside the typical age range.

Differentiation of a benign febrile seizure from one that heralds CNS infection can be difficult. The AAP has published consensus guidelines for the evaluation and management of febrile seizures.[39] Laboratory and radiographic evaluation should be directed at finding the source of the fever, not driven by the seizure itself. The AAP suggests that a lumbar puncture be performed in any child with signs of meningeal irritation after the first febrile seizure and be considered in symptomatic children who are incompletely immunized or have received prior antibiotic therapy.

Routine referral for neuroimaging or electroencephalography is not indicated. There is also no role for antiepileptic therapy after a single febrile seizure. Retrospective studies have shown that the incidence of meningitis after the simple or complex febrile seizures is exceedingly low and that infants with meningitis will demonstrate signs of sepsis or meningitis after the seizure, making empirical lumbar puncture based solely on a febrile seizure unnecessary.[40]

Parents should be warned that recurrence is common and is inversely related to age of first febrile seizure and height of the fever. Overall 33% of children who have a febrile seizure will have another one, and that 75% of these will occur within a year. If the child is younger than 1 year old, the recurrence is 50%, and children presenting with temperatures of 101.3°F (38.5°C) has a 35% chance of recurrence versus 13% at 104°F (40°C).

Fever and Petechiae

The presence of a petechial rash in the setting of a febrile illness is concerning for the possibility of meningococcal infection, although the vast majority are due to a viral cause. The incidence of meningococcal infection has been found to be 7% to 11% in patients hospitalized with fever and petechiae. The rate of bacteremia of any cause was found to be much lower (1.9%) in an ED population. The differential diagnosis of fever and petechiae also includes disseminated intravascular coagulation, Rocky Mountain spotted fever, pneumococcal bacteremia, *Streptococcus pyogenes* infection, various viral infections, idiopathic thrombocytopenic purpura, Henoch-Schönlein purpura, and leukemia. Petechiae can also be caused mechanically from a tourniquet, retching, or violent coughing. Petechiae due to vomiting or coughing are typically confined to the skin above the nipple line, but petechiae caused by SBI can have any distribution.

Because of the risk of serious illness in children with fever and petechiae, blood should be obtained for CBC, CRP, and culture.[41] Patient with associated pharyngitis should undergo testing for group A streptococcus infection. Among patients presenting to a pediatric ED with temperature higher than 100.4°F (38.0°C) and petechiae, an abnormal WBC count (<5000 WBCs/mm^3 and >15,000 WBCs/mm^3) or abnormal coagulation studies have been shown to be predictive but not diagnostic of invasive bacteremia. Well-appearing children with normal WBC and coagulation studies were exceedingly unlikely to have invasive bacteremia. In their study, only two well-appearing children had bacteremia *(S. pneumoniae),* and this study was done in the pre-Prevnar era. It is recommended that children with fever and petechiae, and an elevated or depressed WBC, high band count, or elevated CRP be admitted and treated for presumptive bacterial infection until the results of the blood culture are available. Well-appearing children with normal laboratory parameters can be discharged without antibiotic therapy with close outpatient follow-up.

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

Kawasaki disease is one of the most common vasculitides in childhood and should be considered in any infant or child with prolonged fever (greater than 4 days). A more complete discussion of Kawasaki disease can be found in Chapter 170. Accurate diagnosis is important because the main complication of Kawasaki disease is the development of coronary artery aneurysms. Some patients will present with "incomplete Kawasaki disease," which occurs when not all diagnostic criteria are met. Despite the lack of classic findings, these children are still at risk for coronary complications. Laboratory abnormalities found in cases of Kawasaki disease include leukocytosis, thrombocytosis (platelet counts as high as 1,000,000/mm^3), and evidence of systemic inflammation with elevation in the erythrocyte sedimentation rate and CRP level.

Children with suspected Kawasaki disease should be hospitalized and receive therapy with intravenous immune globulin (IVIG; 2 g/kg infused during 10 to 12 hours) and aspirin (initial dose 80 to 100 mg/kg daily divided every 6 hours). Pediatric cardiology consultation for echocardiography is also indicated.

Toxic Shock Syndrome

TSS refers to the toxin-mediated clinical syndrome that occurs from *Staphylococcus aureus,* although a similar illness is caused by group A streptococcus. The toxin implicated in TSS is an exotoxin termed *TSS toxin 1.* The syndrome is classically associated with tampon use by menstruating women, although cases also occur in males and prepubertal girls from other sources of infection with *S. aureus*.

Clinical manifestations of TSS include fever (>102°F [38.9°C]), hypotension, diffuse erythroderma, and multisystem involvement. Patients may present with vomiting or diarrhea, severe myalgias, oropharyngeal hyperemia, or altered mental status. Laboratory abnormalities are common and include elevated creatine kinase, elevated blood urea nitrogen or creatinine, transaminitis, and thrombocytopenia. The Centers for Disease Control and Prevention (CDC) has developed a set of findings for case definition (Box 166.1).

Treatment of TSS involves fluid resuscitation, because these patients typically have immense requirements and antistaphylococcal antibiotic therapy with clindamycin (25 to 40 mg/kg per day in three divided doses) and vancomycin (40 mg/kg per day IV in four divided doses).

Fever in Children With an Underlying Chronic Medical Illness

Oncology Patients

Children with cancer, particularly those undergoing treatment with cytotoxic chemotherapy, are at particular risk for sepsis and

BOX 166.1

Centers for Disease Control and Prevention Case Definition for Toxic Shock Syndrome

Fever: Temperature >102° F (38.9° C)
Hypotension: Systolic blood pressure 90 mm Hg for adults or less than fifth percentile by age for children <16 years old; orthostatic drop in diastolic blood pressure by 15 mm Hg
Orthostatic syncope or dizziness
Diffuse erythroderma
Desquamation: 1 to 2 weeks after onset of illness, particularly involving palms and soles
Multisystem involvement (three or more of the following organ systems):
- Gastrointestinal: Vomiting or diarrhea at onset of illness
- Muscular: Severe myalgia or creatine kinase elevation more than two times the normal upper limit
- Mucous membranes: Vaginal, oropharyngeal, or conjunctival hyperemia
- Renal: Blood urea nitrogen or serum creatinine more than two times the normal upper limit, or pyuria (>5 WBCs/high-power field)
- Hepatic: Bilirubin or transaminases more than two times the normal upper limit
- Hematologic: Platelets <100,000/L
- CNS: Disorientation or alterations in consciousness without focal neurologic signs in the absence of fever and hypotension

Negative results on the following tests, if obtained:
- Blood, throat, or CSF cultures for another pathogen (blood cultures may be positive for *Staphylococcus aureus*)
- Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Criteria for a probable case include a patient with temperature >102° F (38.9° C), hypotension, diffuse erythroderma, desquamation (unless the patient dies before desquamation can occur), and involvement of at least three organ systems. A probable case is a patient who is missing one of the characteristics of the confirmed case definition.

CNS, Central nervous system; *CSF,* cerebrospinal fluid; *WBC,* white blood cell.

bacterial infection. These life-threatening infections are most common during periods of profound neutropenia. Neutropenia is defined as an ANC of less than 500/mL or an ANC of less than 1000/mL that is falling. Children with cancer also frequently have indwelling catheters, predisposing them to surgical line infections.

Causative organisms include both gram-positive and gram-negative bacteria. Staphylococci and streptococci as well as *Pseudomonas* are frequent pathogens. Often, patients with focal infection may not present with classic signs because of their leukopenia. Focal infections specific to cancer patients include stomatitis and typhlitis, which is a necrotizing enterocolitis of the terminal ileum and cecum.

Children presenting with fever and possible neutropenia require prompt evaluation with a goal of arrival to antibiotic therapy of less than 60 minutes.[42] Blood should be obtained for a CBC and manual differential diagnosis as well as culture. If a central line infection is suspected, a separate culture specimen from the line should be obtained. Once appropriate laboratory studies are obtained, empirical antibiotic therapy should be initiated without waiting for the laboratory results. Appropriate monotherapy antibiotic regimens include cefepime, 50 mg/kg IV every 8 hours, and ceftazidime, 50 mg/kg IV every 8 hours. Vancomycin, 10 to 20 mg/kg every 6 to 8 hours, should be added for antistaphylococcal coverage in children with suspected central line infections or skin and soft tissue infections. Children with fever and neutropenia are rarely treated as outpatients; if so, ceftriaxone 50 mg/kg IV should be give every 24 hours with close follow-up.

Patients With Acquired Immunodeficiency Syndrome

Children with the acquired immunodeficiency syndrome (AIDS) are at risk for bacterial infection due to a whole host of different organisms—some common, some uncommon. Infections specific to AIDS include cryptococcosis and infection with *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare,* and *Pneumocystis jiroveci (carinii)*. Viral infections, such as cytomegalovirus and Epstein-Barr virus infections, are also common.

Laboratory evaluation should be directed by the history and physical examination. Early initiation of broad-spectrum antibiotic therapy is warranted.

Sickle Cell Disease

Febrile children with sickle cell disease are at particular risk for overwhelming infection. In fact, infection is the most common cause of sickle cell–related death, occurring in up to 40% of patients with sickle cell disease who die. Recurrent episodes of splenic infarction lead to functional asplenia early in life. Thus, these patients are at particular risk for infection with encapsulated organisms, including *S. pneumoniae* and *H. influenzae*. Because of this risk of bacterial disease, it is recommended that all children with sickle cell disease be completely immunized. Prophylaxis with penicillin is recommended in children younger than 5 years old, after which it can be safely discontinued in children who have not had a prior severe pneumococcal infection or surgical splenectomy. The dose of penicillin is 125 mg orally twice daily until 3 years old (at about 14 kg) and 250 mg orally twice daily after 3 years old.

High-risk criteria for bacterial infection include toxic appearance, temperature higher than 104°F (40°C), abnormal WBC count (<5000 or >30,000 WBCs/mm^3), and noncompliance with penicillin prophylaxis. Sickle cell patients are at particular risk for *Salmonella* osteomyelitis. All patients presenting with a temperature higher than 100.4°F (38.0°C) and sickle cell disease should have a blood specimen drawn for CBC, reticulocyte count, and culture. A reticulocyte count is important, because many infections (eg, parvovirus B19) can induce life-threatening aplastic crisis. Infection also predisposes children with sickle cell disease to acute chest syndrome. Common causes of infection include *Chlamydia pneumoniae, M. pneumoniae,* RSV, *S. aureus,* and *S. pneumoniae*. Further laboratory and radiographic evaluation should be directed by the presenting history and physical examination findings.

As defined earlier, high-risk patients should be admitted for further evaluation and antibiotic therapy. Low-risk patients may be treated with a single dose of IV or IM antibiotics, typically ceftriaxone 50 mg/kg, and discharged to close outpatient follow-up. All patients should be reevaluated within 24 hours or sooner if the clinical condition deteriorates.

Osteomyelitis typically is manifested with fever and bone pain. As patients with sickle cell disease may have frequent bone pain due to vaso-occlusive crisis, the diagnosis often can be difficult. All patients should have a blood specimen drawn for CBC with differential diagnosis, erythrocyte sedimentation rate, and culture; a radionuclide bone scan or magnetic resonance imaging (MRI) may help localize the infection. If *Salmonella* infection is suspected, a stool sample should be sent for culture.

Congenital Heart Disease

Children with congenital heart disease are at high risk for cardiovascular complications in the setting of febrile illness. Often, relatively minor viral illness can produce significant changes in

BOX 166.2

Modified Duke Criteria for the Diagnosis of Infective Endocarditis

MAJOR CRITERIA

Blood cultures positive for IE
- Typical microorganism for IE from two separate blood cultures
  - Viridians streptococci
  - *Streptococcus bovis,* including nutritional variant strains
  - HACEK group: *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*
  - *Staphylococcus aureus*
- Community-acquired enterococci, in the absence of a primary focus; *or*
- Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood samples drawn more than 12 hours apart; *or*
- All of three or a majority of four or more separate blood cultures, with first and last samples drawn at least 1 hour apart
- Single blood culture positive for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1:800

Evidence of endocardial involvement

Echocardiogram positive for IE
- TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE (paravalvular abscess); TTE as first test in other patients[a]
- Definition of positive echocardiogram
- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; *or*
- Abscess; *or*
- New partial dehiscence of prosthetic valve

New valvular regurgitation (increase in or change in preexisting murmur not sufficient)

MINOR CRITERIA

Predisposition: Predisposing heart condition or injection drug use

Fever: 100.4° F (38.0° C)

Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions

Immunologic phenomena: Glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor

Microbiologic evidence: Positive blood culture but not meeting major criterion (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

[a]Echocardiographic minor criteria eliminated.

IE, Infective endocarditis; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography.

cardiac function or make it difficult for children to be compliant with their oral medications. Children with congenital heart disease are also at risk for infective endocarditis. Infective endocarditis is heralded by fever and possibly a changing or worsening cardiac murmur. The modified Duke criteria for the diagnosis of endocarditis are presented in Box 166.2.

Endocarditis is typically caused by *S. aureus,* viridans streptococci, *Streptococcus bovis,* enterococci, or infection with organisms from the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*). Children with suspected endocarditis should have blood culture specimens drawn and be admitted to the hospital for treatment and echocardiography. The American Heart Association recommends that initial antibiotic therapy be with ceftriaxone, 100 mg/kg IV or IM every 24 hours, or vancomycin, 40 mg/kg IV every 24 hours. Therapy is typically continued at least 4 weeks. Ceftriaxone can be combined with gentamicin, 3 mg/kg IV divided every 8 hours, if shorter treatment duration (2 weeks) is desired. See Chapter 170 for a more complete discussion.

Ventriculoperitoneal Shunts

Children presenting with fever in the setting of ventriculoperitoneal shunts are at risk for shunt infection. If shunt infection is suspected, based on the presence of altered mental status or signs of meningismus neurosurgical consultation should be obtained and a sample of CSF obtained. This is typically accomplished by sterile aspiration of fluid from the shunt reservoir. *S. aureus* and *Staphylococcus epidermidis* are the usual causative organisms. If altered mental status is present, a computed tomography (CT) scan should be obtained to assess ventricular size. Children with suspected shunt infection are typically managed as inpatients, and antibiotics should begin as soon as possible.

KEY CONCEPTS

- Fever is the most common complaint among pediatric patients presenting to the emergency department (ED), although rates of bacterial illness are lower since the advent of universal vaccination for *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, serious bacterial illness (SBI) must be considered in the undervaccinated or unvaccinated child
- Viruses cause the vast majority of childhood febrile illnesses and are generally self-limited and benign.
- SBI is growth of pathogenic bacteria in a previously sterile site, such as urinary tract infection (UTI), bacteremia, meningitis, osteomyelitis, bacterial gastroenteritis, bacterial pneumonia, cellulitis, or septic arthritis.
- The rate of SBI in infants younger than 3 months old presenting with fever is between 6% to 10%.
- Infants 28 days old and younger are at much higher risk for bacterial illness with fever because of their immature immune systems and incomplete vaccination status, making aggressive evaluation of these children important.
- Empirical treatment of febrile neonates is indicated and appropriate antibiotic regimens include ampicillin plus either gentamicin or cefotaxime, which cover the bacterial organisms likely in this age group.
- Empirical treatment for herpes simplex virus (HSV) should be considered in any neonate with a maternal history of genital herpes, who appears ill, presents with fever and seizure, has cutaneous vesicles on physical examination, or evidence of transaminitis or coagulopathy.
- The most common cause of SBI in children continues to be UTI, and the only reliable method to obtain urine in a non–toilet-trained infant is bladder catheterization or suprapubic aspiration when a catheter sample cannot be obtained.
- Bacterial meningitis can occur at any age but most commonly presents in a relatively small proportion of febrile infants younger than 3 months old (3/1000).
- Respiratory syncytial virus (RSV) and influenza are common viral causes of fever and respiratory distress in infants, although the presence of viral infection does not lower the risk of concomitant SBI in children younger than 28 days old.
- In older infants and children, the documented presence of RSV or influenza significantly reduces the incidence of SBI and can be used to modify the evaluation. Because UTI is still common in this population, a urinalysis should be obtained
- There are several risk-stratification strategies (ie, Boston, Rochester, and Philadelphia criteria) reported in the literature that have similar performance characteristics. All involve a laboratory evaluation designed to identify a subset of febrile infants younger than 3 months old that can safely be managed as outpatients with or without antibiotics.
- Standardization and adoption of a clinical practice guideline for the evaluation of the febrile infant has been shown to reduce variation and cost.
- Due to universal vaccination against pneumococcus, the evaluation of highly febrile children 3 to 36 months old has evolved from one of universal screening for occult bacteremia to one where clinical gestalt determines the need for bloodwork.
- Inflammatory markers, such as C-reactive protein (CRP) and procalcitonin, have been shown to predict bacterial illness in febrile children more accurately than the white blood cell (WBC) count but cannot be relied upon solely to rule-out SBI.
- Traumatic lumbar punctures occur relatively commonly in young infants and can make interpretation of cell counts difficult and use of various formulas to account for the protein and WBCs in the cerebrospinal fluid (CSF) after a traumatic tap should be used with caution.
- The risk of meningitis is exceedingly low in well-appearing children after a simple febrile seizure and lumbar puncture is not recommended.
- Children presenting with fever and petechiae are at risk for infection with meningococcus; blood should be obtained for complete blood count (CBC) and culture and if available CRP or procalcitonin. Children with abnormal CRP or elevated or depressed WBC count, or with bandemia should be treated with parenteral antibiotics and admitted. Lower risk, well-appearing children with normal laboratory parameters can be considered for close outpatient follow-up.
- Children with fever who also are receiving cytotoxic chemotherapy for cancer are at high risk for bacteremia and sepsis and should receive prompt broad spectrum antibiotic therapy after appropriate diagnostic evaluation (at the minimum, a CBC and blood culture).
- Patients with fever and a history of sickle cell disease are at risk for bacteremia from encapsulated organisms due to functional asplenia and should be considered high risk and should be admitted and treated.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 166: QUESTIONS & ANSWERS

166.1. Which of the following are appropriate methods to obtain urine as part of a fever evaluation in a non–toilet-trained child?

A. Catheterized specimen
B. Clean catch, midstream
C. Suprapubic aspiration
D. A and B

Answer: D. The only reliable method to obtain urine in a non–toilet-trained child is bladder catheterization or suprapubic aspiration if a catheter specimen cannot otherwise be obtained. Bag collection has a high rate of false-positive results and should not be used in a child who is not toilet trained.

166.2. Which of the following statements regarding occult bacteremia in children younger than 36 months old is *true?*

A. Children with no obvious source of fever and a temperature higher than 102.2°F (39°C) have an incidence of bacteremia of 5%.
B. Most patients appear toxic.
C. The most common pathogen is *Neisseria meningitidis*.
D. There has been a marked decrease in the incidence of occult bacteremia since the advent of universal vaccination against pneumococcus and *Haemophilus influenza* type B.
E. With pneumococcal bacteremia, most patients remain febrile until antibiotic therapy is initiated.

Answer: D. Children younger than 36 months old with fever higher than 102.2°F (39°C) and no obvious source have an incidence of occult bacteremia of less than 1%. Most patients appear nontoxic. The most common pathogen in positive cultures is *Streptococcus pneumoniae,* and the incidence of infection has dropped dramatically since the advent of universal vaccination. With pneumococcal bacteremia, most patients become afebrile in 3 or 4 days with or without antibiotic therapy.

166.3. A 3-year-old boy presents with fever of 103°F. His mother reports that the fever started approximately 5 days ago, and he has an associated maculopapular rash. On examination, you find the patient also has bilateral conjunctival injection, a strawberry tongue, and swelling of his hands and feet. Which of the following medications should be included in the treatment of this patient?
A. Aspirin
B. Clindamycin
C. Decadron
D. Penicillin G
E. Rocephin

Answer: A. This patient has Kawasaki disease. Treatment includes amelioration of symptoms and prevention of coronary aneurysms, which are normally treated with aspirin and immunoglobulin. There are no indications for antibiotics or steroids.

166.4. A 2-year-old presents with a high fever and vomiting. On examination, you find an irritable child with a rectal temperature of 102°F rectal and a stiff neck. The patient's past medical history is significant for hydrocephalus with a ventriculoperitoneal shunt placement. You suspect the patient has a ventriculoperitoneal shunt infection. Which of the following is the most likely bacterial pathogen?
A. *Haemophilus influenzae*
B. Neisseria meningitidis
C. Staphylococcus aureus
D. Staphylococcus epidermidis
E. Streptococcus pneumoniae

Answer: D. Patients with ventriculoperitoneal shunts and fever must be evaluated for shunt infection. The most common bacterial pathogen is *S. epidermidis.*

CHAPTER 167

Pediatric Respiratory Emergencies: Upper Airway Obstruction and Infections

Emily Rose

PRINCIPLES

Respiratory distress from upper airway obstruction is a rare but potentially catastrophic emergency in young children. Causes include acute infectious processes, congenital anomalies, or a foreign body in the airway or esophagus. Children are predisposed to respiratory failure due to increased airway resistance (small, compressible airway), low functional residual capacity, high oxygen metabolism, which leads to quicker fatigue, and shorter safe apnea time, with precipitous hypoxia.

Clinical presentations of children with upper airway disease vary with cause, predisposing factors, and age at presentation:

- Acute infections of the upper airway range from relatively mild distress and self-limited signs and symptoms to the abrupt onset of a rapidly progressive airway obstruction.
- Undiagnosed congenital anomalies of the airway and surrounding structures may be manifested as chronic or progressive stridor or simply difficulty with feeding.
- An infant with a congenital airway anomaly in whom an acute airway infection develops is at higher risk for decompensation and respiratory failure.
- Upper airway obstruction from a foreign body in the airway or esophagus can cause partial or complete airway obstruction and may require urgent, advanced, airway management skills.

CLINICAL FEATURES

Recent history and observation of the child typically provide clues to the cause of the airway obstruction. Important items to elucidate in the history include the following:

- Onset and duration (acute vs. chronic)
- Associated symptoms (e.g., respiratory distress, fever, toxicity, drooling, cyanosis, neck stiffness or torticollis)
- Progression with age (number of bouts and severity of "croup" with increasing age)
- Exacerbating factors (supine vs. prone position, upper respiratory infection [URI], crying)
- Feeding abnormality or dysphagia
- Prior airway procedures, such as intubation in the neonatal period
- Choking episode indicating possible foreign body aspiration
- Baseline noises, quality of cry and voice to assist the emergency clinician in pinpointing the location of obstructive lesion

Observation and physical examination should include vital signs (respiratory rate, heart rate, oxygen saturation) and indicators of increased work of breathing (retractions, flaring, grunting, stridor, wheezing) to gauge severity of the distress. Observe the character and timing of stridor and symmetry and quality of breath sounds. Respiratory failure is identified by the presence of extreme distress, hypoventilation or hyperventilation, altered mental status, pale, mottled or cyanotic skin color, and/or hypotonia. Stridor may not be present in respiratory failure due to lack of airflow.

Stridor (from the Latin, *stridulus*, indicating creaking, whistling, or grating) is the classic sound associated with upper airway obstruction.[1] Stridor is a harsh vibratory sound of variable pitch caused by partial airway obstruction or collapse and the resultant turbulent airflow through some portion of the airway, from the nose to the trachea. Stridor is described by timing in the respiratory cycle (inspiratory, expiratory, biphasic) and quality (coarse or high-pitched; Table 167.1). Inspiratory stridor is usually associated with obstruction above the glottis, expiratory stridor with intrathoracic obstruction, and biphasic stridor typically with a critical or fixed obstruction at any level. Stridor character differs by cause and anatomic location (Fig. 167.1).

Snoring or stertor is low-pitched inspiratory noise caused by nasal or nasopharyngeal obstruction. Stertor and stridor can coexist. Stridor from the pharynx, such as from a peritonsillar abscess, tends to have a sonorous, gurgling, and coarse quality. The voice may be altered and have a muffled or "hot potato" quality to it. High-pitched inspiratory stridor occurs in the supraglottic and immediate subglottic trachea, as in croup and laryngomalacia. The voice may sound hoarse or weak but a normal voice may be heard, even with a laryngeal cause of stridor.[2]

Biphasic stridor is heard with inspiration and expiration and usually suggests a fixed lesion. Examples include laryngeal webs and vocal cord paralysis. Stridor from the lower part of the trachea is usually expiratory such as in bacterial tracheitis or aspirated foreign bodies (Fig. 167.2).

DIAGNOSTIC CONSIDERATIONS

Diagnostic Testing and Management

Definitive airway management takes precedence in an acute airway emergency. In a stable patient with an uncertain diagnosis, an individualized diagnostic evaluation is undertaken. Lateral and anteroposterior radiographs of the soft tissues of the neck may be helpful to assess the adenoid and tonsillar size, contour of the epiglottis, thickness of the retropharyngeal soft tissue space, vallecula, aryepiglottic folds, and tracheal air column (Fig. 167.3). The child's head should be positioned in extension and film taken during inspiration. Chest views assess the heart size, trachea and bronchi, location of the aortic arch, and presence of other pulmonary pathologic processes.

Additional studies may be indicated in specific settings. Bedside fiberoptic nasopharyngoscopy allows for the visualization and assessment of the supraglottic structures and vocal cords. Fiberoptic-assisted intubation may occur through the nasopharyngoscope. Esophagography can define lesions compressing the airway and trachea; computed tomography (CT), magnetic resonance imaging (MRI), and/or bronchoscopy may be needed to evaluate the upper airway.

TABLE 167.1

Causes of Stridor: Anatomic Location, Sound, and Quality

FEATURES (STRUCTURES)	SUPRAGLOTTIC (NOSE, PHARYNX, EPIGLOTTITIS)	GLOTTIC (LARYNX, VOCAL CORDS)	SUBGLOTTIC TRACHEA (LOWER TRACHEA)
Sound	Sonorous (stertor) Gurgling Coarse Expiratory stridor	Biphasic stridor	High-pitched stridor Inspiratory stridor Expiratory stridor (if intrathoracic)
Congenital	Micrognathia Pierre Robin syndrome Treacher-Collins syndrome Macroglossia Down syndrome Storage diseases Choanal atresia Lingual thyroid Thyroglossal cyst	Laryngomalacia Vocal cord paralysis Laryngeal web Laryngocele	Subglottic stenosis Tracheomalacia Tracheal stenosis Vascular ring Hemangioma cyst
Acquired	Adenopathy Tonsillar hypertrophy Foreign body Pharyngeal abscess Epiglottitis	Papillomas Foreign body	Croup Bacterial tracheitis Subglottic stenosis Foreign body
Positional stridor	Micrognathia, macroglossia		Laryngomalacia

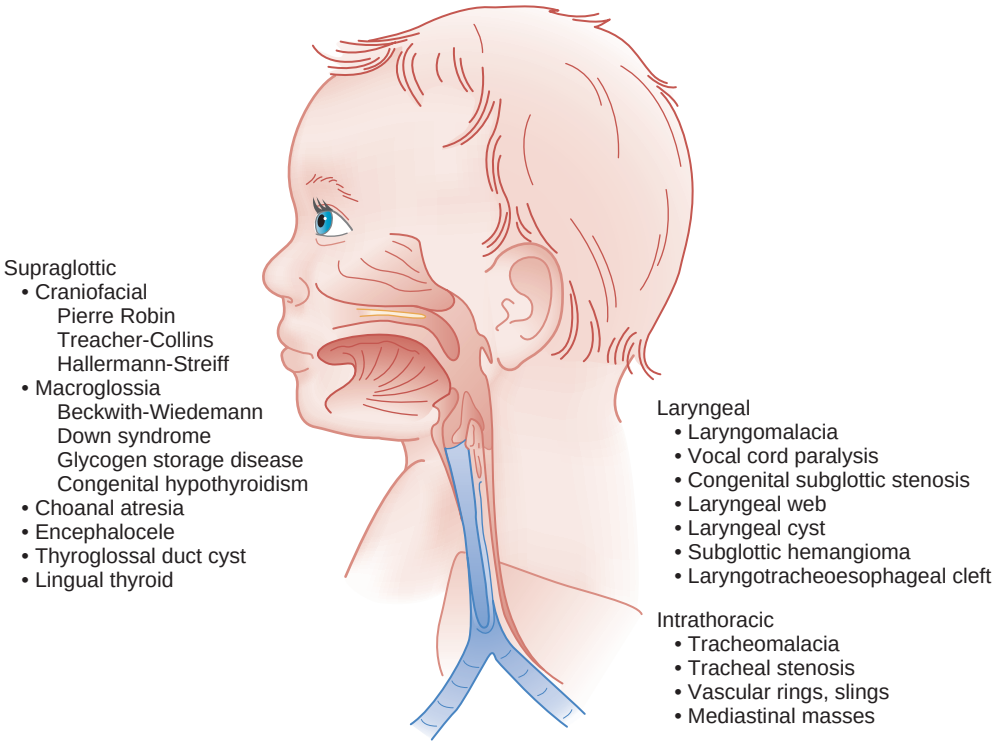

Fig. 167.1. Regions and associated diseases of the pediatric upper airway. (From Simon NP, Simon N: Evaluation and management of stridor in the newborn. Clin Pediatr [Phila] 30:211, 1991.)

Differential Diagnoses

Supraglottic Airway Diseases

The supraglottic portion of the airway includes the nose, pharynx, epiglottis, and surrounding structures. Diseases of the nose and pharynx are commonly associated with noisy congested breathing and respiratory distress. Congenital lesions involving these structures may cause mild symptoms at baseline but dramatic distress when there is a superimposed infectious process. Congenital lesions include choanal atresia, macroglossia, micrognathia, thyroglossal duct cyst, and lingular thyroid. Acquired causes of supraglottic disease include a nasal foreign body, nasal polyps, hypertrophic tonsils and adenoids, epiglottitis, retropharyngeal

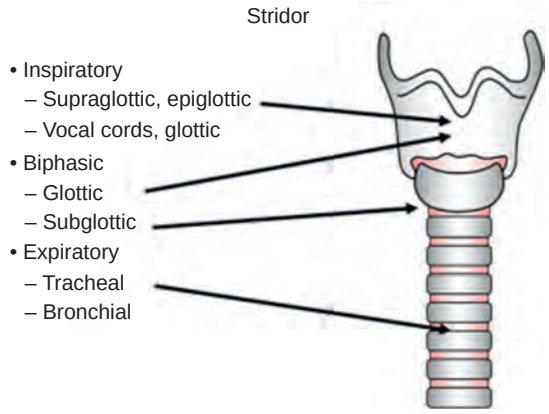

Fig. 167.2. Level of obstruction correlates with phase of stridor. (From Ida JB, Thompson DM: Pediatric stridor. Otolaryngol Clin North Am 47:795–819, 2014.)

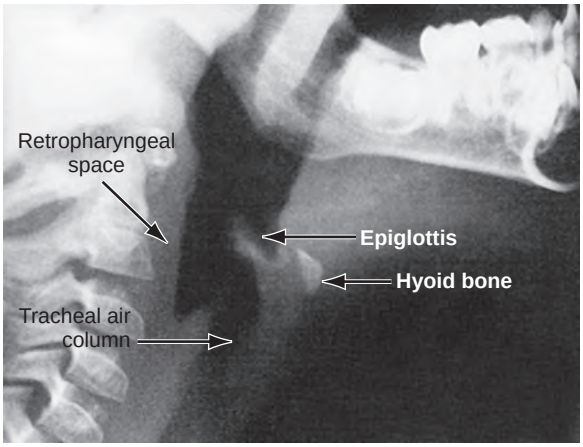

Fig. 167.3. Normal appearance of upper airway structures on a lateral neck radiographic study. Note the hyoid bone, epiglottis, retropharyngeal space, and tracheal air column.

abscess, peritonsillar abscess, pharyngitis, mononucleosis, and upper airway foreign body. The most common conditions are discussed in the following sections.

Congenital Lesions

Choanal Atresia. Choanal atresia, the most common congenital anomaly of the nose, is caused by persistence of the buccanasal membrane or a bony septum in the posterior naris. Infants are so-called obligate nose breathers because they breathe nasally when the mouth is closed at rest and to maintain breathing while feeding. The posterior aspect of the infant's soft palate extends downward and contacts the tip of the epiglottis. Bilateral choanal atresia is a life-threatening emergency that is identified early because neonates become acutely distressed and cyanotic at birth. Immediate airway management is with oral airway and definitive surgical correction of the obstructing membrane. Unilateral choanal atresia is often initially undetected. Infants may present in respiratory distress with a URI when the normal patent naris is obstructed by swelling or secretions. Immediate nasal suction should be performed along with referral for surgical repair.

Macroglossia. Macroglossia, an abnormally large tongue that protrudes posteriorly into the hypopharynx, is associated with conditions such as Down syndrome, glycogen storage disease, and congenital hypothyroidism. The increased secretions with a URI exacerbate underlying obstruction and may induce stridor or labored breathing. Good head positioning with nasal suctioning should be performed to relieve the obstruction.

Micrognathia. With micrognathia, an abnormally small mandible posteriorly displaces the normal-sized tongue (eg, Pierre-Robin and Treacher-Collins syndromes). Obstructive symptoms typically worsen when supine.

Retropharyngeal Abscess

A retropharyngeal abscess is a potentially life-threatening airway emergency resulting from infection of the retropharyngeal soft tissue space. The retropharyngeal space is a potential space between the posterior pharyngeal wall and prevertebral fascia that extends from the base of the skull to the level of T2. It is rich in lymph tissue that drains the nose, pharynx, sinuses, and ears. An abscess may result from direct trauma from a fall with an object in the mouth such as a toothbrush, suppuration of lymph nodes, contiguous spread of infection, or hematogenous seeding. It is usually a disease of infants and toddlers because the lymphatic chains are prominent in the young and atrophy before puberty. Approximately 50% of pediatric cases occur in children 6 to 12 months of age, most occur before 3 years of age, and 96% of all diagnosed pediatric retropharyngeal abscesses are seen before 6 years of age. These infections are commonly polymicrobial, with *Streptococcus* and anaerobes the most commonly isolated organisms. Consider methicillin-resistant *Staphylococcus aureus* (MRSA) in severe infections such as jugular venous thrombosis or mediastinal extension.[1]

Clinical Features. Retropharyngeal infections typically progress from cellulitis to organized phlegmon to mature abscess. Presenting symptoms may vary. Common signs and symptoms include fever, sore throat, neck stiffness or nuchal rigidity, torticollis, trismus, neck swelling, drooling, stridor, and muffled voice. Stridor and respiratory distress may occur if a large abscess compresses the trachea; the clinical appearance can resemble that of epiglottitis. Reluctance to extend the neck and an unwillingness to look side to side is often seen with retropharyngeal abscess and may help differentiate it from other supraglottic infections. With less obvious signs of airway obstruction, patients can exhibit a mixture of symptoms, including fever, neck stiffness, and generalized toxicity, which may suggest meningitis or sepsis. Other serious complications of retropharyngeal abscess include aspiration pneumonia, mediastinitis, and empyema.

Diagnostic Testing. Careful evaluation of airway patency takes precedence in the management of a child with a presumed retropharyngeal abscess. Examination of the pharynx may reveal bulging of the posterior pharyngeal wall. A soft tissue lateral view of the neck may be helpful to establish the diagnosis; in the normal patient, the width of the retropharyngeal space should not exceed the diameter of the adjacent vertebral body (Fig. 167.4). The soft tissue width should not be larger than 6 to 7 mm at C2, regardless of the patient's age. At C6, this distance should not exceed 14 mm in children younger than 15 years and 22 mm in adults. Most patients will demonstrate retropharyngeal thickening on the lateral neck radiograph. An air-fluid level may be present in perforation or anaerobic infections. Redundant soft tissue of the retropharyngeal space complicates the interpretation of lateral neck films in young infants with a retropharyngeal abscess. Artifactual widening of a normal retropharyngeal space is commonly seen when the radiograph is taken with the head and neck in flexion or during exhalation. CT scanning of the neck (thin cuts to T2) may be beneficial in delineating the size and extent of

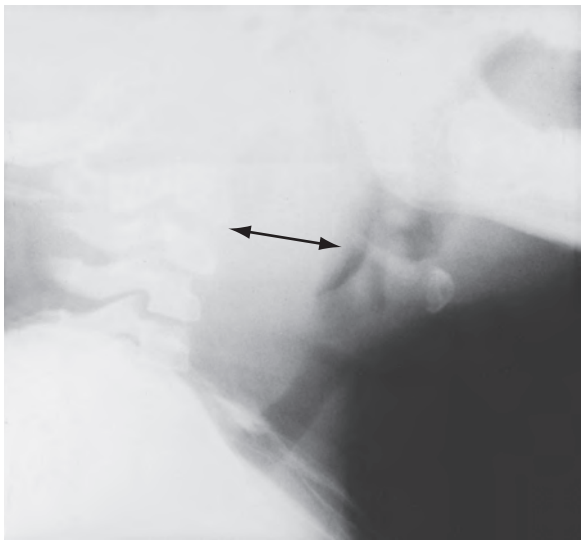

Fig. 167.4. Retropharyngeal abscess. Note the widened retropharyngeal soft tissue space (*double arrow*).

an abscess and determining possible impingement on airway structures. The ability to tolerate lying supine should first be assessed, and staff and airway equipment should be immediately available.

Management. The size of the abscess, degree of airway obstruction, and overall toxicity of the patient dictate management. The need for intubation or surgical drainage is determined on an individual basis, and these patients generally benefit from involvement of an otolaryngologist. Intubation can be complicated by distorted anatomy and can lead to abscess rupture. Some retropharyngeal infections respond to intravenous (IV) antibiotics and do not require surgical drainage. Features that suggest abscess and require surgical intervention include imaging findings of scalloping of the abscess wall, rim enhancement, and lesions larger than 2 cm. The decision to admit and provide a trial of antibiotic therapy should be made between the emergency clinician and otolaryngology consultant. Clindamycin and a third-generation cephalosporin are recommended antibiotic therapy.[1]

Peritonsillar Abscess

Peritonsillar abscess (PTA) is the most common deep neck infection and usually occurs in older children and teenagers. Drooling and a muffled, hot potato voice can occur, but severe respiratory distress is unusual. Peritonsillar abscess is associated with trismus, bulging or asymmetry of the tonsils, and deviation of the uvula away from the abscess side (in 50% of patients). Throat pain also may radiate to the ear. Treatment involves antibiotics and incision and drainage or needle aspiration. Antibiotics alone are insufficient management for an abscess but may resolve a phlegmon. Surgical intervention typically removes most of the pus, and antibiotics are recommended to clear the remaining infection.

PTAs are typically polymicrobial. Predominant bacterial species are *Streptococcus pyogenes* (group A streptococcus), *Staphylococcus aureus* (including MRSA), and respiratory anaerobes. Posterior pharynx ultrasonography can confirm the diagnosis and guide treatment. A CT scan may be indicated if extension of infection is suspected. Any drainage effort should take great care to avoid puncture of the carotid artery (the carotid artery lies 25 mm posterolateral to the tonsillar pillar in children >12 years). Approximately 10% to 20% of patients may have recurrent PTAs.

Mononucleosis

Infectious mononucleosis, caused by the Epstein-Barr virus (EBV), can lead to mucosal edema and an exudative pharyngitis. Uncommonly, massive tonsillar enlargement can occur and create upper airway distress. EBV IgM antibody is the preferred test for infective mononucleosis (>90% sensitive), particularly in children younger than 4 years who are less likely to generate heterophile antibodies with primary EBV infection. In older children and adults, the heterophile antibody is measureable in 50% of patients within the first week of illness and in 60% to 90% in weeks 2 and 3.

In addition to airway management and general supportive care, some studies have shown the benefit of steroids and racemic epinephrine in reducing tonsillar edema.[3] Although steroids decrease pharyngitis symptoms, it is important to consider an underlying lymphoid malignancy. Evaluate a child for diffuse lymphadenopathy, hepatosplenomegaly, and rash. The absence of these on the physical examination and a normal complete blood count makes a lymphoid malignancy unlikely. Treatment with glucocorticoids prior to the diagnosis of leukemia may delay leukemia diagnosis, increase the risk of tumor lysis syndrome, complicate risk stratification, and ultimately result in fatal complications.[4,5] Therefore, great caution should be exercised in using glucocorticoids in children and adolescents, and should be avoided in children younger than 14 years or in a child who has any signs of possible lymphoid malignancy.

Ludwig's Angina

Ludwig's angina is an aggressive, rapidly spreading, woody induration or brawny cellulitis of the sublingual, submandibular, and submaxillary spaces, with potential for airway obstruction. Most patients have dental sources of infection, which are usually polymicrobial. The spread of infection is direct and not via the lymphatics, so involvement is typically bilateral and without associated lymphadenopathy. Enlargement and elevation of the tongue above the lower teeth, a tender woody induration in the sublingual space, trismus, and odynophagia are hallmark signs. Ludwig's angina can create a functional upper airway obstruction or respiratory distress through significant swelling and direct airway compression. Subsequent abscess formation may occur. CT confirms the diagnosis—MRI may help delineate soft tissue involvement—and evaluates the extent of infection. Treatment involves broad-spectrum antibiotics with anaerobic coverage, airway support, and admission for close monitoring. Otolaryngology and anesthesia consultants may facilitate planning and support if an emergent airway is required.

Epiglottitis

Although still a feared pediatric emergency, acute epiglottitis has declined markedly in incidence since the widespread administration of *Haemophilus influenzae* type b vaccine in the 1980s.

Principles. Epiglottitis is an invasive bacterial disease that causes inflammation and edema of the epiglottis, aryepiglottic folds, arytenoids, and surrounding supraglottic tissues. As these structures become inflamed and distended, they protrude downward and over the glottic opening. Supraglottic swelling reduces the upper airway caliber and causes turbulent airflow during inspiration (stridor). The epiglottis may also act as a ball valve, obstructing airflow during inspiration but permitting exhalation. This traditional profile of *Haemophilus influenzae* type b (Hib) in young children has changed; the overall incidence has decreased, and now epiglottitis is relatively more common in older children and adults.[6] However, Hib is still the most common infectious

cause of epiglottitis in children and can occur in fully immunized children. Additional causes include other *H. influenzae* types (A, F, nontypeable), streptococci, and *Staphylococcus aureus* (including methicillin-resistant strains). Immunocompromised children may have other infections such as *Pseudomonas aeruginosa* and *Candida* spp. Noninfectious causes are rare and include thermal injury from swallowing of hot liquids, steam inhalation, caustic ingestions, allergic reactions, foreign body and irritant injuries, and lymphoproliferative disorders.

Clinical Features. Epiglottitis is classically acute in onset. It is marked by high fever, intense sore throat, toxicity, and rapid progression. Children with epiglottitis appear anxious and maintain a sniffing or tripod position, with the jaw jutting forward and the neck extended to maximize airway patency. As symptoms worsen, cough and phonation are usually absent. Drooling is prominent because of an inability to swallow. Toxicity, altered mental status, dyspnea, stridor, retractions, and fever are common initial symptoms; the diagnosis is often delayed and is associated with a significantly increased mortality rate. Croup is a common misdiagnosis made in young children and those without prominent drooling and difficulty swallowing. The older patient is less likely to show dramatic signs of upper airway obstruction compared with the younger child because the diameter of the airway is larger and thus takes a greater degree of swelling to produce symptoms. These patients often complain of a sore throat that is out of proportion to physical findings and may also exhibit tenderness on palpation of the anterior neck. Epiglottitis caused by bacteria other than *H. influenzae* tends to have a slower onset and is less likely to cause airway compromise.

Diagnostic Strategies. When epiglottitis is strongly suspected, a lateral neck radiograph can be helpful to confirm the diagnosis and should be evaluated for an enlarged epiglottis (thumbprint sign; Fig. 167.5), thickened aryepiglottic folds, lack of air in the vallecula, and dilated hypopharynx. However, up to 70% of all patients with epiglottitis have normal radiographic findings. Careful observation of a child in consultation with an otolaryngologist is essential, and clinicians skilled in airway management should accompany the patient at all times.

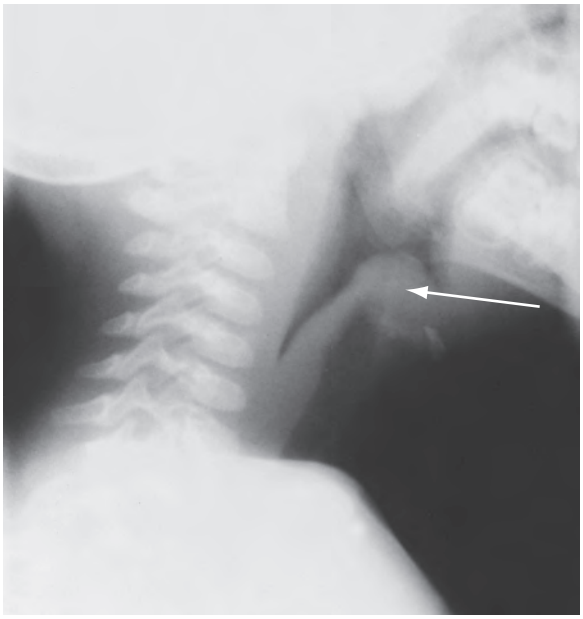

Fig. 167.5. Epiglottitis. Note the thumbprint sign of the epiglottis (*arrow*) and thickened aryepiglottic folds.

Management. For the younger child, the importance of securing the airway takes precedence over diagnostic evaluation. A stable patient who is maintaining a patent airway and adequate oxygenation should not be moved or repositioned for examination, laboratory tests, or radiography. Such patients should be carefully transported to a setting where definitive airway management can be achieved in a controlled fashion, generally the operating room. Adolescents with epiglottitis generally have signs and symptoms of adults and do not often require airway stabilization. These patients can be managed as inpatients in a pediatric intensive care unit (PICU) setting with IV antibiotics but do not require immediate airway management unless signs and symptoms dictate that this is the case.

Unstable patients with respiratory failure require assisted ventilation. Bag-mask ventilation should be attempted first and, if successful, continued until intubation can be performed. If neither bag-mask ventilation nor intubation is successful, more aggressive techniques, such as needle cricothyroidotomy or tracheostomy, may be indicated. Regardless of the approach to securing the airway, it is prudent for the emergency clinician to consult other experts in airway management rapidly, such as an anesthesiologist (fiberoptic intubation), otolaryngologist, or general surgeon (surgical approaches), so that a plan of approach can be made and morbidity minimized. Patients often remain intubated for 3 to 5 days in order for antibiotic therapy to reduce inflammation and surrounding tissue edema. A second- or third-generation cephalosporin is recommended.

Trauma and Burns

Thermal injury from facial burns and inhaled smoke or steam and trauma to the face and neck can create physical findings similar to those of infectious epiglottitis. Rapidly progressive stridor, drooling, an unwillingness to lie flat, and a swollen inflamed epiglottis may occur. Aspiration of hot liquids is the most common cause of airway burns in infants and young children.[7] Toddlers are particularly prone to inhalation of hot liquids because they can eat and drink independently without initially being attentive to temperature. The initial physical examination of the oropharynx may be relatively normal. Health care providers should electively secure the airway when laryngeal edema and progression of symptoms and edema are suspected. Bronchodilators may help with bronchospasm; steroids are not routinely recommended.

Allergic Reactions

Acute allergic reactions may cause supraglottic edema with respiratory distress and stridor. Food is the most common precipitant in infants and children. Children with peanut allergies and those with atopy and asthma have a higher mortality rates. The treatment of anaphylaxis is epinephrine. Intramuscular epinephrine (1 mg/mL solution) at 0.01 mg/kg up to 0.5 mg per dose is initial management and may be repeated twice. IV epinephrine (0.1 mg/mL solution) at a 0.01 mg/kg bolus followed by 0.1–1 mcg/kg/min up to 10 mcg/min may be necessary for patients in shock with anaphylaxis. IV fluids and oxygen should be administered. Nebulized epinephrine may be given to reduce airway edema and other bronchodilators may be given for epinephrine-resistant bronchospasm. H1 and H2 antihistamines and steroids are commonly given for symptomatic relief but do not aid in acute airway obstruction.[8-10] Intubation may be required and should be considered early. On discharge from the hospital, all patients with anaphylaxis should be given a prescription for an epinephrine autoinjector (0.15 mg for children <30 kg; 0.3 mg for older children) and instructed in its use. Follow-up with the primary care physician for allergist referral and a medical alert bracelet may also be recommended.

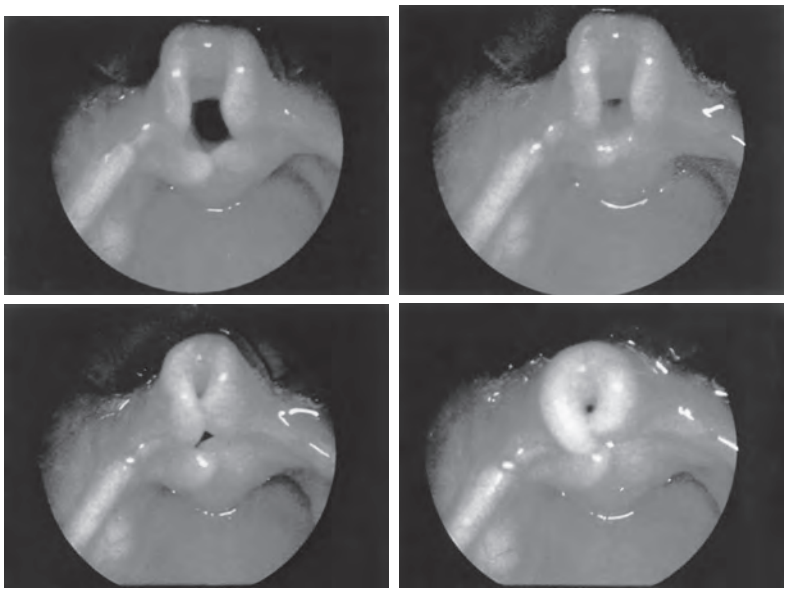

Fig. 167.6. Laryngomalacia. Note the progressive obstruction with inspiration as the epiglottis and surrounding structures collapse into the glottic opening.

Diseases of the Larynx

The larynx and vocal cords are commonly involved with obstructing airway disease. Many obstructing conditions are congenital lesions, including laryngomalacia, laryngeal web, and vocal cord paralysis. Acquired lesions include laryngeal papillomas.

Congenital Lesions. Laryngomalacia is the most common cause of chronic stridor in infants and accounts for 60% to 75% of congenital laryngeal anomalies. It is a result of incomplete development of the supporting cartilage of the larynx. With inspiration, the long floppy epiglottis, arytenoids, and aryepiglottic folds are drawn into the larynx and create a partial obstruction (Fig. 167.6). Baseline inspiratory stridor begins several weeks after birth and worsens with supine positioning, neck flexion, and increased respiratory effort (crying, URI). Laryngomalacia is rarely associated with significant respiratory distress, feeding difficulties, or failure to thrive. Most patients experience complete resolution of symptoms by 2 years of age and are treated conservatively. Fiberoptic bronchoscopy is used to confirm the diagnosis and identify the existence of coexisting or synchronous anomalies (eg, subglottic stenosis, tracheomalacia). Surgical intervention is warranted in severe cases in which the child suffers from apneic events, respiratory compromise, pulmonary hypertension, or failure to thrive.

Vocal cord paralysis is the second most common cause of chronic stridor in infants. Bilateral vocal cord paralysis results in severe respiratory distress and stridor and typically requires intervention for airway protection. It is often associated with serious central nervous system abnormalities, such as Arnold-Chiari malformations. Unilateral vocal cord paralysis is usually left-sided and related to traction on the left recurrent laryngeal nerve at birth or compression from mediastinal structures. Infants with unilateral vocal cord paralysis have a hoarse weak cry, feeding difficulties, and aspiration. Stridor often worsens with distress and improves with positioning the affected side down.

A laryngeal web results from failure of complete canalization of the airway. Most webs lie between the cords and appear as a partial anterior fusion (Fig. 167.7). The spectrum of symptoms reflects the size of the web. Small webs may cause a hoarse weak cry and mild stridor. Larger, more complete webs are associated with aphonia and severe respiratory distress.

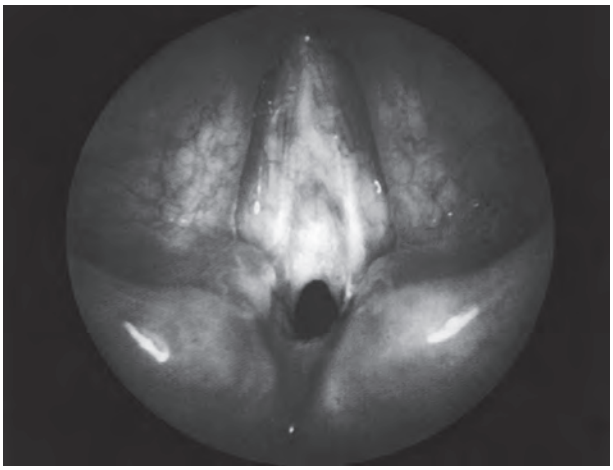

Fig. 167.7. Large laryngeal web.

Congenital laryngotracheal (subglottic) stenosis is a result of a congenital defect in canalization of the subglottic trachea. Deformity of the cricoid ring is usually seen. Infants with severe stenosis have stridor at birth. Milder lesions may be asymptomatic until additional obstruction from infection or inflammation occurs. Subglottic stenosis is also an acquired condition that occurs after prolonged intubation or blunt trauma to the neck.

A subglottic hemangioma is a less common cause of stridor and subglottic airway obstruction in infants. The infant is usually asymptomatic at birth, but stridor (which may be biphasic) and cough develop within the first few weeks to months of life. Symptoms generally peak at 6 months as a result of rapid growth of the infant and hemangioma during the first months of life. Respiratory symptoms worsen with crying and agitation. Cutaneous hemangiomas are seen in approximately 50% of cases (often in a beard distribution; Fig. 167.8). Hemangiomas of the airway may be seen on plain film as an asymmetric lesion along the tracheal air column. Endoscopy is diagnostic (Fig. 167.9).

Acquired Lesions

Laryngeal Papillomas. Laryngeal papillomas are the most common benign laryngeal neoplasm in children and the second

Fig. 167.8. 2-month-old infant with a facial hemangioma in the beard distribution. This patient was also found to have a subglottic hemangioma. (From: O-Lee TJ, Messner A: Subglottic hemangioma. Otolaryngol Clin North Am. 41:903–911, viii–ix, 2008.)

Fig. 167.9. Subglottic hemangioma seen on endoscopy. (From Ida JB, Thompson DM: Pediatric stridor. Otolaryngol Clin North Am 47:795–819, 2014.)

most common cause of hoarseness. They are typically acquired after exposure to human papillomavirus via vertical transmission from an infected mother. Multiple lesions are generally present and usually occur in the vocal cords, but may involve any part of the larynx. Hoarseness, abnormal cry, and inspiratory stridor commonly occur by 3 to 4 years of age. Symptoms can progress to severe respiratory distress as the lesions enlarge and obstruct the larynx.

Subglottic Tracheal Diseases. The subglottic trachea is the origin of the high-pitched inspiratory sound commonly associated with upper airway obstruction. The subglottic space is the narrowest part of the airway in children younger than 8 years and is completely surrounded by the cricoid ring. This anatomy predisposes this part of the airway to obstruction. Subglottic narrowing or stenosis can result from a congenital anomaly, inflammation from infection, and trauma associated with prolonged intubation.

Viral Croup

Principles of Disease. Croup (laryngotracheobronchitis) is the most common infectious cause of upper airway distress and obstruction in childhood. It accounts for more than 90% of all cases of stridor in children. It usually occurs between 6 and 36 months of age but can be seen from early infancy through school age. Parainfluenza virus accounts for 50% to 75% of cases; respiratory syncytial virus, influenza A and B viruses, and rhinovirus cause the remainder. The clinical picture of croup associated with influenza is more severe than with parainfluenza. Croup is caused by inflammation, exudates, and edema of the loosely adherent mucosal and submucosal tissues of the subglottic space. The inflamed mucosa expands into the airway lumen because the cricoid cartilage forms a complete cartilaginous (nonexpanding) ring in this part of the trachea.

Clinical Features. Croup is diagnosed clinically. A 1- to 3-day prodrome of mild fever and URI symptoms is followed by a fairly abrupt onset of barky cough, hoarse voice, and high-pitched inspiratory stridor. Croup symptoms typically resolve in 4 to 7 days.[11] A subset of children with croup has involvement of the lower airway and exhibit bronchoconstriction, lower airway edema, and atelectasis. A simplified clinical approach to the differential diagnosis for croup is shown in Fig. 167.10. Scoring systems have been developed for the assessment of croup; these include an evaluation of worsening stridor, retractions, cyanosis, heart rate, and respiratory rate. Although a formal croup score is often not assigned in many clinical settings, the determination of mild, moderate, or severe croup should be based on careful evaluation of these five signs as well as on mental status and air movement (Fig. 167.11).

Mild croup is characterized by an intermittent barky cough, stridor with agitation but not at rest, mild tachypnea, and tachycardia. A child with mild croup is minimally distressed and well hydrated and has normal mental status. Moderate croup is characterized by audible stridor at rest, worsening stridor with agitation, barky cough, and increased work of breathing (retractions, tachypnea, tachycardia). A patient with moderate croup may be fussy but is alert, interactive, and comforted by parents. Hypoxia is atypical in mild or moderate croup. When hypoxia is seen, it may signify concomitant lower respiratory disease, another disease process, or severe croup. Mild croup occurs in 85% of children; fewer than 1% of children have severe croup.[11,12] Laboratory tests are nondiagnostic, and radiographic studies of the neck do not change management nor are they sensitive or specific. The classic x-ray finding is a steeple sign—a tapered narrowing of the normal shouldered appearance of the subglottic trachea—which can be seen in those with croup and also in patients without the disease.

Management. Glucocorticoids reduce symptoms, decrease the need for aerosolized epinephrine, result in fewer readmissions to the ED, and shorter ED and hospital stays.[11-17] Oral dexamethasone in a dose as small as 0.15 mg/kg is as effective as higher doses in decreasing the duration of symptoms and hospitalization.[18,19] Inhaled budesonide (2 mg/dose) is as effective as oral dexamethasone (0.6 mg/kg) in decreasing the duration of hospital stay, improving clinical symptoms, and decreasing the ongoing requirement for aerosolized epinephrine.

Aerosolized epinephrine, which reverses edema and relieves acute symptoms through vasoconstriction in the subglottic

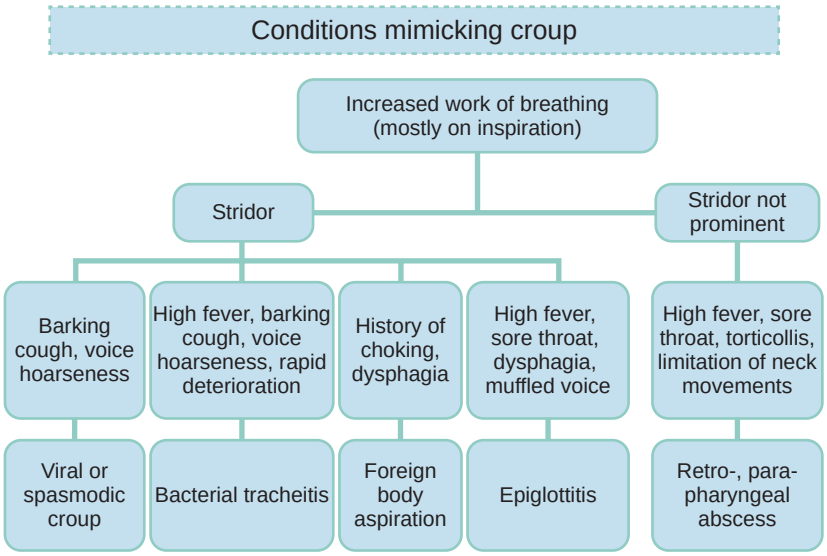

Fig. 167.10. Clinical approach to the differential diagnosis of croup with acute onset of symptoms. (From Petrocheilou A, Tanou K, Kalampouka E, et al: Viral croup: diagnosis and a treatment algorithm. Pediatr Pulmonol 49:421–429, 2014.)

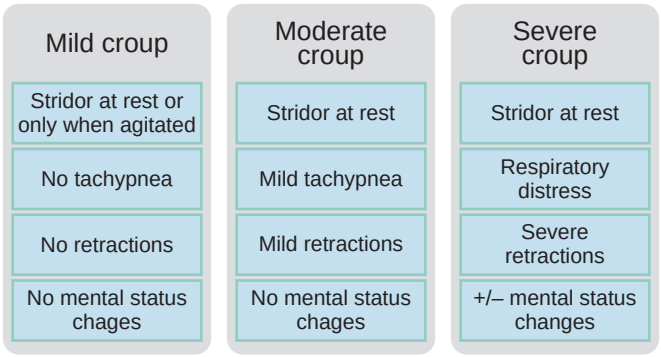

Fig. 167.11. Initial assessment of croup severity in the emergency department. (From Petrocheilou A, Tanou K, Kalampouka E, et al: Viral croup: diagnosis and a treatment algorithm. Pediatr Pulmonol 49:421–429, 2014.)

mucosa, should be given to children with stridor at rest. It is a temporizing measure with a quick onset of action (<10 minutes) and duration of 1 to 2 hours. The L form of epinephrine is the active isomer and has the same degree of safety and efficacy as racemic epinephrine; either form may be used.[20] Patients should be observed in the ED for 2 to 3 hours after epinephrine administration to ensure that stridor and respiratory distress do not recur.[20]

There is some evidence to suggest short-term benefit of heliox inhalation in moderate to severe croup; however, I cannot recommend its routine use.[21] Cool mist has not been demonstrated to improve outcomes but there is insufficient evidence to support its routine use.[11,12,14,22]

Most children with croup can be safely discharged, provided respiratory distress and stridor have resolved. A small percentage of patients with croup require admission. Several factors may impact the decision to admit a child with moderate croup, such as severity of symptoms at initial evaluation, persistence of respiratory distress, stridor at rest, hypoxia, poor response to treatment, dehydration, history suggesting airway disease or recurrent croup, young age (<6 months), high fever, and poor social support (Box 167.1).

Severe croup is rare (<1%) and associated with signs of impending airway obstruction and respiratory failure—fatigue, hypoxia, hypercapnia, abnormal mental status, and extreme respiratory distress. In the rare case in which intubation is required, an endotracheal tube at least a half-size smaller than expected for the child's size is often necessary. If the endotracheal tube that can be passed is too small to allow adequate ventilation, tracheostomy may be required.

BOX 167.1

Croup: Indications for Admission

Severe respiratory distress or failure
Unusual symptoms (hypoxia, hyperpyrexia)
Dehydration
Persistence of stridor at rest after aerosolized epinephrine and steroids
Persistence of tachycardia, tachypnea
Complex past medical history (prematurity, pulmonary, cardiac disease)

Spasmodic or Atypical Croup

Spasmodic or atypical croup is a somewhat indistinct clinical entity with many features that overlap those of viral croup. There is no consensus on the definition but the term *atypical croup* is often used to describe numerous recurrent episodes or croup in children outside the expected age group. An association with allergy, atopy, airway hyperreactivity, asthma, and gastroesophageal reflux has been described. Large airway lesions (usually subglottic stenosis) may be present and contribute to the pathophysiology.[23]

Diseases of the Trachea

Obstruction of the trachea distal to the subglottic space can be a result of congenital and acquired lesions.

Congenital Lesions. Tracheomalacia results from abnormally soft, undeveloped supporting cartilage of the tracheal rings. Primary or congenital tracheomalacia is seen in otherwise healthy term newborns, as well as in infants with conditions such as Down syndrome and DiGeorge syndrome. Healthy infants with isolated disease have a good prognosis because symptoms improve as the

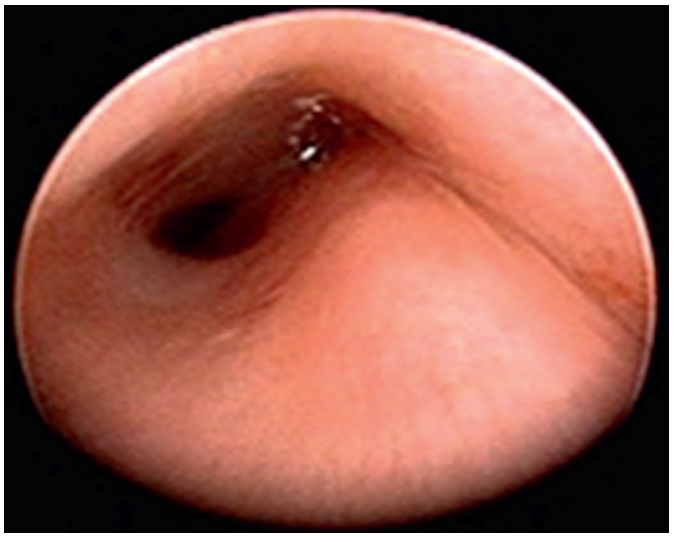

Fig. 167.12. External vascular compression of the trachea seen on endoscopy. (From Ida JB, Thompson DM: Pediatric stridor. Otolaryngol Clin North Am 47:795–819, 2014.)

cartilage strengthens with growth. Secondary disease is associated with extrinsic compression of the trachea (eg, vascular rings, tumor, nodes, cysts). Tracheomalacia should be suspected in patients with a history of stridor that increases during the first few weeks of life and worsens with agitation, supine positioning, and infection. Plain radiographs are usually nondiagnostic but dynamic studies, such as fluoroscopy, may be helpful. Referral to the patient's primary care physician for further evaluation after ED care should be done.

Tracheal stenosis is a congenital anomaly that results from complete tracheal rings. Infants have persistent stridor and respiratory distress. Because the tracheal diameter is fixed, symptoms worsen with agitation and age.

Tracheal compression may occur externally from vascular anomalies or mediastinal lesions (Fig. 167.12). A vascular ring is an anomaly of the aortic arch and related vessels in which a ring of vessels encircles the trachea, esophagus, or both. Examples of vascular rings include a double aortic arch, right aortic arch with a persistent left ligamentum arteriosum, anomalous innominate artery and anomalous left common carotid artery, left pulmonary artery, or aberrant right subclavian artery. Stridor, wheezing, dyspnea, and cough are common initial symptoms and are frequently mistaken as a URI. Many patients with vascular rings have additional cardiovascular anomalies. The association of congenital cardiac anomalies is a consideration in the evaluation of these patients. Other associated mediastinal lesions that can compress the trachea include esophageal duplication cyst, bronchogenic cysts, mediastinal cyst, teratoma, lymphoma, and lymphadenopathy.

Infants with vascular rings typically present with persistent, unexplained respiratory and feeding problems. A chest radiograph revealing an abnormal (right-sided) aortic arch may suggest the diagnosis in the ED; barium esophagography has traditionally been considered to be the single most important diagnostic procedure in patients with complete vascular rings (Fig. 167.13). The need for additional studies, such as CT, MRI, angiography, or bronchoscopy, should be individualized.

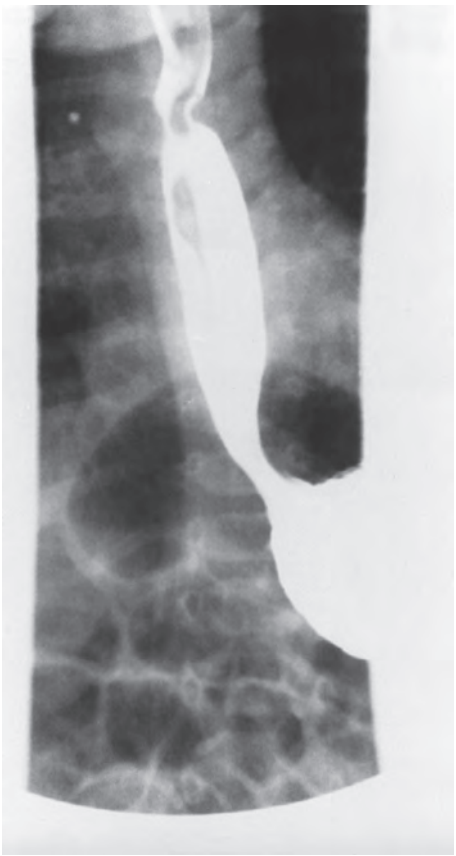

Fig. 167.13. Barium esophagogram. Note the indentation of the esophagus caused by an encircling vascular ring.

Bacterial Tracheitis

Principles. Bacterial tracheitis—membranous croup, bacterial croup, pseudomembranous croup—is a serious cause of stridor and airway obstruction in children. The epidemiology of upper airway infections has changed since widespread immunization for *H. influenzae* and the use of steroids for croup. This has increased the relative frequency of bacterial tracheitis as a cause of respiratory failure from upper airway infection. Bacterial tracheitis is three times more likely to cause respiratory failure than epiglottis and viral croup combined. Bacterial tracheitis usually affects younger children, but may occur at any age.

The pathogenesis of bacterial tracheitis is severe inflammation of the tracheal epithelium and production of thick mucopurulent secretions. The lining of the trachea forms a loosely adherent membrane that may become necrotic and slough, occluding the lumen. Microabscesses may be present in the tracheal mucosa. Perforation and pneumomediastinum have been described. Traditionally, *S. aureus* (including MRSA) has been the organism primarily responsible for bacterial tracheitis but many causative bacteria have been reported. Fungal tracheitis in immunocompromised individuals portends a grave prognosis.

Clinical Features. The classic presentation of bacterial tracheitis is a toxic child with high fevers and rapidly worsening stridor that fails to improve with racemic epinephrine. Symptoms may overlap with those of croup and epiglottitis (Table 167.2). Most patients experience a viral prodrome of fever, barky cough, and stridor. These symptoms typically intensify as the bacterial superinfection grows on damaged tracheal epithelium. The child appears toxic, and signs of airway obstruction and respiratory failure may develop acutely. Less commonly, primary bacterial tracheitis may occur with a fulminant onset and rapid progression to acute respiratory distress. Features that suggest bacterial tracheitis include a viral prodrome followed by acute decompensation, symptoms atypical for croup (eg, high fever, cyanosis, severe distress), poor response to usual treatment of croup (eg, steroids, aerosolized epinephrine), and inspiratory and expiratory stridor. Changes in bacteriologic profiles have produced less virulent but more prolonged infections, increasing the diagnostic challenge.[6]

TABLE 167.2

Comparison of Croup, Epiglottitis, and Bacterial Tracheitis

PARAMETER	CROUP	EPIGLOTTITIS	BACTERIAL TRACHEITIS
Peak age	6 mo–3 yr	5–7 yr, but can be seen throughout childhood	3–5 yr, but seen throughout childhood
Pathologic features	Subglottic inflammation, edema	Inflammation and edema of the epiglottis, aryepiglottic folds	Bacterial superinfection with inflammation of the tracheal mucosa, copious mucopurulent secretions obstructing the trachea
Organisms	Parainfluenza virus, RSV, adenovirus, influenza	*Haemophilus influenzae*, group A beta-hemolytic streptococcus, *Staphylococcus aureus, Streptococcus pneumoniae*	*S. aureus* or mixed flora
Clinical features	Onset follows URI prodrome consisting of croupy cough, hoarse voice, low-grade fever, inspiratory stridor	Rapid progression of high fever, toxicity, drooling, stridor	Several-day prodrome of crouplike illness progressing to toxicity, inspiratory and expiratory stridor, marked distress
Laboratory and radiographic findings	Steeple sign on PA view of the neck or normal	Thumbprint sign on lateral aspect of the neck, thickened aryepiglottic folds, loss of air in the vallecula	Normal upper airway structures, shaggy tracheal air column
Management	Steroids uncommon, aerosolized epinephrine	Intubation, antibiotics	Intubation common, antibiotics rare, intubation

PA, Posteroanterior; *RSV,* respiratory syncytial virus; *URI,* upper respiratory infection.

Diagnostic Strategies. The evaluation of a toxic-appearing child with bacterial tracheitis should be conducted expeditiously. Laboratory tests are nondiagnostic. The white blood cell count is often normal or slightly elevated, and blood cultures are rarely positive in bacterial tracheitis. Lateral and anteroposterior views of the neck and chest may be helpful. Findings on plain radiographs include subglottic narrowing, a ragged edge of the usually smooth tracheal air column, and a hazy density within the tracheal lumen, mimicking the appearance of airway foreign bodies. The epiglottis and supraglottic structures appear normal. In addition, the chest radiograph may reveal coexisting pneumonia. Bronchoscopy is diagnostic and therapeutic and should be performed emergently (Fig. 167.14). This procedure should allow visualization of the supraglottic structures and larynx, exclusion of other disease, suctioning of tracheal secretions and debris, and establishment of an artificial airway.

Management. Severe distress may rarely require immediate intubation and suctioning in the ED, although airway management in the operating room is preferred. Endoscopic tracheal débridement may result in significant clinical improvement and allow the child to be managed without intubation. Serial endoscopy may be needed to manage secretions. Endotracheal intubation is required in children with respiratory distress and hypoxia. Patients should be admitted and receive supplemental oxygen, fluid resuscitation, and broad-spectrum antibiotics.

Broad antibiotic coverage is recommended with an antistaphylococcal agent (eg, vancomycin, clindamycin) plus a third-generation cephalosporin (eg, cefotaxime, ceftriaxone). Alternatively, an antistaphylococcal agent plus ampicillin-sulbactam may be used. In penicillin-allergic patients, vancomycin or clindamycin plus a quinolone should be administered (ciprofloxacin if *Pseudomonas* is a concern or levofloxacin if *Streptococcus pneumoniae* is suspected). Although 7 to 10 days is usually sufficient, longer courses of antibiotics may be necessary for children with extratracheal infection of persistent tracheal inflammation. Complications of bacterial tracheitis include toxic shock syndrome, septic shock, renal failure, postintubation pulmonary edema, acute respiratory distress syndrome, and need for reintubation. Residual subglottic stenosis has been described.

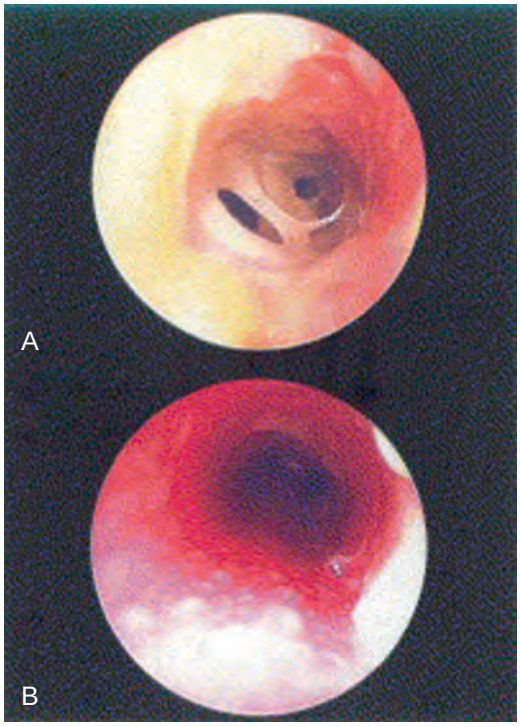

Fig. 167.14. Thick tracheal membranes seen on rigid bronchoscopy in bacterial tracheitis. **A,** Thick adherent membranous secretions. **B,** The distal tracheobronchial tree is unremarkable. (From Salamone FN, Bobbitt DB, Myer CM, et al: Bacterial tracheitis reexamined: is there a less severe manifestation? Otolaryngol Head Neck Surg 131:871–876, 2004.)

Foreign Bodies

Airway Foreign Body

Perspective. Asphyxia from airway obstruction by an airway or esophageal foreign body is a common cause of death in children. Round foods (eg, peanuts, grapes, raisins, hot dogs) are especially common. Conformable objects are the most difficult to

manage and remove, and balloons, including those made from examination gloves found in physicians' offices, are the objects most likely to result in death.

Large objects that lodge in the upper airway and trachea cause dramatic signs of upper airway obstruction (eg, dyspnea, drooling, stridor, cyanosis) and carry the worst prognosis. Objects that pass through the subglottic space typically will lodge in a bronchus, usually the right mainstem bronchus, or in a more terminal part of the airway.

Clinical Features. An upper airway foreign body can cause partial or complete obstruction. Clinical signs of complete obstruction include poor air exchange, ineffective cough, severe distress, and cyanosis. Foreign body aspiration that has settled in the lower airways may have subacute symptoms such as unilateral wheeze or may present later (days to years) as recurrent pneumonia. The sensitivity of a witnessed choking episode varies in the literature.

Diagnostic Testing. In a child with an aspirated foreign body in the upper airway, there is often no time, nor is it prudent, to perform diagnostic imaging. In a stable patient, a portable lateral neck radiograph and chest radiograph may be obtained as long as the patient is allowed to maintain a position of comfort. Radiographic findings suspicious for foreign body aspiration include radiopaque materials, mediastinal shift, emphysema, and atelectasis.[24] A normal chest radiograph cannot rule out a nonradiopaque foreign body.[25] CT scan and virtual bronchoscopy (a reformatted three-dimensional CT image that generates intraluminal views of the airway to the sixth- and seventh- generation bronchi) may be used to aid diagnosis in equivocal cases. Diagnostic flexible bronchoscopy is indicated with significant clinical suspicion of foreign body aspiration, despite normal imaging.[25,26]

Management. An acute obstructing upper airway foreign body requires emergent intervention with basic life support maneuvers. Choking infants younger than 1 year should be given five back blows delivered between the shoulder blades, followed by five chest thrusts with the head held below the trunk. Abdominal thrusts should not be performed in infants and may injure abdominal organs. Blind finger sweeps are no longer recommended and may push the object further into the airway.[27,28]

The Heimlich maneuver is used in conscious children younger than 1 year; chest compressions should be delivered to unconscious children. If there is no chest rise with assisted ventilation with a bag-mask device, advanced airway techniques are indicated. Laryngoscopy should be performed to attempt visualization and foreign body removal with pediatric Magill forceps. If the obstructing foreign body cannot be visualized, it may be pushed distally into the right mainstem bronchus with an endotracheal tube to ventilate the nonobstructed portion of the lung. Recruiting additional expertise from an otolaryngologist, anesthesiologist, or general surgeon may be valuable.

A patient who is adequately oxygenated and is moving air should be initially allowed to maintain a preferred position, continue coughing to clear the obstruction, and breathe spontaneously until operative management can be arranged. Paralysis with rapid sequence induction should be avoided if the patient is maintaining a patent airway; with paralysis, the airway tone may be lost, and a partial obstruction can become complete.

Can't Intubate, Can't Ventilate Scenario. Surgical cricothyrotomy is not recommended for infants and young children younger than 6 to 10 years. The anatomy changes with growth (ie, the larynx is high and cricothyroid membrane small), and it may be difficult to locate pertinent anatomy until a child is of school age. Tracheal compressibility also increases complication risk. Needle cricothyrotomy may also be used but significant CO_2 retention limits its effectiveness.

Commercial percutaneous transtracheal ventilation kits may be purchased but homemade kits can be constructed using tools readily available in the ED. A 14- to 18-gauge angiocatheter (the size of catheter does not affect the rate of turbulent gas flow) is inserted in the cricothyroid membrane and connected to a 3-mL syringe (without the plunger) to a 7.5-mm endotracheal tube (ETT) adaptor (or a 3.0-mm ETT connector directly to the angiocatheter). These homemade kits are rigid and may easily become dislodged. Alternative setups include using IV tubing—attaching IV tubing to the angiocatheter, cutting the tubing, and attaching a 2.5-mm ETT connector—or directly connecting oxygen tubing to the catheter with a Y connector or three-way stopcock. Bag-mask ventilation (recommended in children < 5 years) can be performed through the ETT adaptor at 10 to 12 breaths/min to minimize barotrauma by allowing for passive exhalation. Percutaneous transtracheal ventilation (in children ≥ 5 years) is given at an oxygen flow rate of 1 L/min/year of age with a 1 : 4 inspiration-to-expiration ratio (I:E). Adults should receive oxygen from the wall source at 15 L/min (50–58 psi) and children at a rate of 10 to 12 L/min (25–35 psi). Complete airway obstruction does not allow for passive exhalation and necessitates a reduction of bag-mask ventilation rate to five or six breaths/min or I : E ratio of 1 : 8 to 10 as a temporizing measure. Complications of needle cricothyrotomy include barotrauma and damage to adjacent structures.[29,30]

KEY CONCEPTS

Respiratory arrest precedes most pediatric cardiac arrests. Quick recognition of an airway problem and intervention in potentially life-threatening upper airway obstruction in children are critical.

Retropharyngeal Abscess

- This is a potentially life-threatening emergency in young children with signs of upper airway obstruction or meningismus; a retropharyngeal abscess is often related to oral trauma.
- Retropharyngeal abscess is most frequently caused by *Staphylococcus aureus,* group A streptococci, and anaerobes. Treatment is admission, IV antibiotics and, for more severe cases, surgical drainage.

Epiglottitis

- Epiglottitis may be caused by many bacteria or local injury. In the post–*H. influenzae* type b vaccine era, the typical profile of epiglottitis has changed to include older patients.
- Clinical features of epiglottitis are often subtle, such as in the older adolescent, (eg, sore throat out of proportion to physical findings, anterior neck tenderness), but may also be dramatic, as in infants and young children (ie, drooling, stridor, toxicity, severe respiratory distress).

Croup

- Viral croup is the most common infection of the upper airway in young children.
- Glucocorticoids (usually given as a single oral dose of dexamethasone) reduces symptoms, hospitalizations, and length of stay in the ED.
- Treatment of moderate to severe croup includes vaporized epinephrine in addition to glucocorticoids. These patients can be discharged from the ED after a posttreatment observation period of 2 to 3 hours if they remain free of stridor and distress and have access to follow-up care.

Continued

KEY CONCEPTS—cont'd

Bacterial Tracheitis

- Suspect bacterial tracheitis when a URI progresses to acute toxicity and marked respiratory distress and stridor. Standard treatment for croup should be initiated but does not improve the patient's symptoms. Antibiotic therapy should include a cephalosporin plus coverage for *S. aureus*, which is the most common cause of this infection.
- Bronchoscopy is diagnostic and therapeutic and should be emergently performed.

Airway Foreign Body

- Complete obstruction due to an airway foreign body requires emergent basic followed by advanced life support procedures for removal of the foreign body.
- Plain films may be negative in aspirated foreign bodies. Bronchoscopy should be performed with a clinical suspicion of aspiration.
- Emergency cricothyroidotomy may be required for obstructed patients who cannot be intubated or ventilated as a lifesaving temporizing measure; needle cricothyroidotomy is preferred for infants and young children because of the challenges in identifying landmarks and associated complications of surgical cricothyrotomy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 167: QUESTIONS & ANSWERS

167.1. Which of the following is the most common cause of upper respiratory obstruction in childhood?
- **A.** Airway foreign body
- **B.** Bacterial tracheitis
- **C.** Croup
- **D.** Epiglottitis
- **E.** Retropharyngeal abscess

Answer: C. Although all the choices may lead to symptoms of airway obstruction in children, the most common cause of upper airway obstruction is viral croup.

167.2. A 3-year-old girl presents at 2 AM with complaints of a barky cough, which started abruptly overnight. Vital signs are heart rate, 140 beats/min, respiratory rate, 40 breaths/min, and temperature, 100.1°F (38°C). She has no history of asthma or wheezing. She appears to be in moderate distress and has audible stridor. Indications for admission include which of the following?
- **A.** Low-grade fever
- **B.** Prior history of croup
- **C.** Pretreatment for tachycardia and tachypnea
- **D.** Pretreatment for stridor
- **E.** Severe dehydration

Answer: E. Indications for admission of patients with croup include severe respiratory distress or failure, unusual symptoms (hypoxia and hyperpyrexia), anything but mild dehydration, persistence of stridor at rest after aerosolized epinephrine and steroids, persistence of tachycardia or tachypnea, and complex medical history (eg, prematurity, pulmonary or cardiac disease).

167.3. A 5-year-old immunized boy presents with stridor, low-grade fever, and nasal congestion. His family reports a barky-sounding cough. After initiating vaporized epinephrine, he appears well and is in no distress. The parents are requesting discharge. Which of the following would be the most appropriate next step in management?
- **A.** Administer dexamethasone (Decadron), observe the patient for 2 hours, and discharge if well.
- **B.** Admit the patient for overnight observation.
- **C.** Allow the patient to go home.
- **D.** Allow the patient to go home with a prescription of steroids.
- **E.** Observe the patient for 2 to 3 hours and then discharge if well.

Answer: A. The child has croup and, after being treated with vaporized epinephrine, should be observed for rebound stridor for a minimum of 2 hours. If the child is well, is in no respiratory distress, has a good hydration status, and is able to access emergency and follow-up care, he or she can then be safely discharged.

167.4. What is the ideal head position to assess a pediatric soft tissue radiograph of the neck for an upper airway pathology?
- **A.** Extension
- **B.** Extension during inspiration
- **C.** Flexion
- **D.** Flexion during inspiration
- **E.** Neutral

Answer: B. Gentle extension of the head gives the most accurate images, avoiding the artificial soft tissue widening that can be seen in flexion. Inspiration, if possible, allows maximal distention of the pharynx and the best viewing of soft tissue structures defined by an air–soft tissue interface.

167.5. Which of the following factors is least consistent with the diagnosis of peritonsillar abscess?
- **A.** Muffled, hot potato voice
- **B.** Pain radiating to the ear

C. Patient 3 years of age
D. Patient 13 years old
E. Trismus

Answer: C. Peritonsillar abscess more commonly occurs in older children and teenagers, whereas retropharyngeal abscess is more common in a younger population. All the other signs or symptoms listed are consistent with peritonsillar abscess, along with deviation of the uvula away from the abscess side.

167.6. A 3-year-old immunized girl presents after a brief viral illness with progressive dyspnea, ill appearance, and high fever. The child is relatively still, appearing as if she is trying not to cough. Stridor is heard, and she does not respond to croup therapy. You notify the operating room, where the patient undergoes bronchoscopy, with suctioning and airway placement. Culture results are most likely to grow which of the following organisms?
A. *Bacteroides fragilis*
B. *Candida albicans*
C. Parainfluenza
D. *Staphylococcus aureus*
E. *Streptococcus pneumoniae*

Answer: D. The case described is consistent with bacterial tracheitis. Although *Candida,* parainfluenza, and *Streptococcus* have all been reported, *S. aureus* is most common. Broad-spectrum antibiotics are appropriate, with an emphasis on covering *S. aureus*.

CHAPTER 168

Pediatric Respiratory Emergencies: Lower Airway Obstruction

Richard J. Scarfone | Jeffrey A. Seiden

ASTHMA

Principles

Asthma is the most prevalent chronic disease of childhood, affecting almost 7 million children in the United States. In the past 3 decades, childhood asthma prevalence rates have more than doubled. In addition, there are important racial disparities among children with this condition. Compared with white children, African American children have a 60% higher prevalence rate, 260% higher emergency department (ED) visit rate, 250% higher hospitalization rate, and 500% higher death rate due to asthma.

Anatomy and Physiology

Asthma is a lower airway disease marked by bronchoconstriction, mucosal edema, and pulmonary secretions. Upper respiratory infections (URIs) associated with copious rhinorrhea, a common trigger of an asthma exacerbation, may significantly increase airway resistance in young children. Because children have compliant chest walls and horizontally located ribs, their ability to use the thorax to increase tidal volume is limited; thus, ventilation is highly dependent on diaphragmatic movement. Also, minute ventilation is largely rate-dependent and may quickly lead to fatigue. An infant younger than 12 months has an oxygen consumption index that is double that of an adult. Increased airway resistance and a compliant chest wall predispose infants to tachypnea, increased work of breathing, and increased oxygen consumption. As a result, the infant with respiratory distress may rapidly develop hypoxemia, bradycardia, and cardiopulmonary arrest.

Clinical Features

All acutely wheezing children arriving for ED care should be attached to a cardiorespiratory monitor and have oxygen saturation determined by pulse oximetry. If needed, supplemental oxygen should be provided. After this, the emergency clinician may begin the clinical assessment.

History

To determine the initial degree of illness and initiate appropriate therapy quickly, a concise initial history should be obtained, followed by a physical examination that focuses on the cardiopulmonary systems. After therapy has begun, a more comprehensive history and examination can be conducted. The initial history should include questions about the child's age, duration and severity of symptoms, recent medication use, and hospitalizations, including the need for intensive care unit (ICU) care or intubation. The parents should be able to relate how the severity of this attack compares with that of previous exacerbations. A history of difficulty sleeping, eating, or speaking suggests a moderate to severe exacerbation. Providers should note names, doses, and frequency of asthma medications, as well as preexisting conditions.

After initiating therapy, a more comprehensive history should include questions about asthma triggers, such as URIs, cigarette smoke, allergies, and exercise. Frequent ED visits or hospitalizations due to asthma may indicate poorly controlled asthma. The impact of asthma on the child's life may be gauged by the monthly frequency of daytime or nighttime symptoms, including cough, as well as missed days of school or restricted activity. A child with persistent asthma marked by frequent symptoms should receive daily antiinflammatory therapy; those older than 5 years should monitor symptoms with a peak flow meter. Family and social histories should focus on asthma, cystic fibrosis, or atopic disease and on the adequacy of support systems at home.

Physical Examination

The initial focused examination includes assessing vital signs, mental status, and cardiopulmonary systems. A child who is anxious, restless, or lethargic may be hypoxemic. No single asthma score has been universally adopted to assess the degree of illness or treatment responses. However, most scores include some combination of respiratory rate, degree of wheezing, inspiratory-to-expiratory ratio, use of accessory muscles, and oxygen saturation. These scores can assist in the assessment of the pretreatment degree of illness and tracking the response to therapy.

Assessing the work of breathing should include a careful inspection of the chest and neck; palpation of the chest and neck may reveal subcutaneous air associated with a pneumomediastinum or pneumothorax. Severely ill children may have wheezing that is audible without a stethoscope or no wheezing due to poor aeration. Asymmetric wheezing suggests pneumonia, pneumothorax, or a foreign body. More anxiety-provoking parts of the examination, such as otoscopy, should be delayed until treatment is well underway.

Diagnostic Considerations

Differential Diagnoses

The differential diagnosis for childhood asthma includes bronchiolitis, laryngotracheobronchitis (croup), pneumonia, and gastroesophageal reflux (Table 168.1). Bronchiolitis is the disease that is most commonly confused with asthma, and the two cannot be distinguished by examination findings alone.

Croup may have a viral or allergic cause and affects children from infancy through early school age. Clinical presentation is marked by an abrupt onset of a harsh barky cough and inspiratory stridor. Symptoms are typically worse at night. Asthma will not be manifested with stridor alone, but a subset of children with croup may present with stridor and wheezing. Children with

TABLE 168.1

Differential Diagnosis of Asthma

CONDITION	DISTINGUISHING CHARACTERISTICS
INFECTIOUS	
Bronchiolitis	Infant, preceding upper respiratory infection, seasonal, no history of atopy, no family history of asthma
Laryngotracheobronchitis (croup)	Inspiratory stridor, barky cough, fever, response to humidified air
Pneumonia	Focal wheezing, rhonchi, rales, grunting, fever
Tuberculosis	Diffuse adenopathy, weight loss, prolonged fever
Bronchiolitis obliterans	Prolonged cough or chest pain, inhalational exposure to toxin
ANATOMIC OR CONGENITAL	
Gastroesophageal reflux	Frequent emesis, weight loss, aspiration
Cystic fibrosis	Diarrhea, weight loss, chronic cough, salty sweat
Congestive heart failure	Rales, murmur, gallop, hepatosplenomegaly, cardiomegaly or pulmonary vascular congestion on chest radiograph
Tracheoesophageal fistula	Choking, coughing, cyanosis with feeds
Mediastinal mass	Chest pain, mediastinal density on chest radiograph
Vascular ring	Stridor, cyanosis, apnea, high-pitched brassy cough, dysphagia
ACQUIRED	
Foreign body aspiration	History of choking, toddler, asymmetric pulmonary examination, unilateral hyperinflation on chest radiograph
Anaphylaxis	Abrupt onset, urticarial rash, angioedema, history of allergies

pneumonia may sometimes present with a component of wheezing, although rales and rhonchi are the usual auscultative findings. Infants and young children with pneumonia may also have high fever, cough, grunting, nasal flaring, retractions, and an asymmetric lung examination.

Diagnostic Testing

The oxygen saturation of any child with respiratory distress should be determined soon after ED arrival, and supplemental oxygen should be provided if the oxygen saturation is 92% or less. Most children with wheezing are presumptively treated for an asthma exacerbation without imaging or laboratory studies. Adjunctive studies, such as arterial oxygen saturation measured by pulse oximetry, may assist in determining the initial degree of illness. Performing an arterial blood gas (ABG) analysis is rarely indicated for children with asthma but may be obtained in children with severe bronchospasm and signs of respiratory failure despite initial therapy. A high or apparently normal partial pressure of carbon dioxide ($Paco_2 \geq 40$ mm Hg) in a child with hypoxia and retractions indicates impaired ventilation and impending respiratory failure.

Measurement of the peak expiratory flow rate (PEFR) is a means of obtaining an objective assessment of exacerbation severity. However, up to two-thirds of children older than 5 years are unable to complete PEFR testing during an asthma exacerbation. When feasible, the PEFR should be measured with the child standing and the best of three attempts recorded.

URIs marked by low-grade fever and coughing are common triggers of asthma exacerbations. These signs overlap with those found among children with pneumonia, making it difficult to determine the necessity of obtaining a chest x-ray. No set of predictors has been found that can accurately identify children likely to have radiographic abnormalities. ED physicians frequently obtain a chest x-ray for children in the ED with asthma but rarely are pneumonia or other unsuspected diagnoses discovered, even if the child has never wheezed before.[1]

It should not be routine practice to obtain a chest x-ray for wheezing children, even for those who are febrile, wheezing for the first time, or requiring hospitalization. Performing chest radiography is indicated for those with a history of choking, focal chest findings, extreme distress, or subcutaneous emphysema. Reassessment after short-acting β_2-agonist (SABA) treatment to evaluate for resolution of focal findings may further decrease the need to obtain a chest x-ray.

Management

Children can be stratified by degree of illness based on the physical examination (Fig. 168.1).

Mild Exacerbation

A mild exacerbation is characterized by alertness, slight tachypnea, expiratory wheezing only, mildly prolonged expiratory phase, minimal accessory muscle use, and oxygen saturation of greater than 95%. Patients with a mild exacerbation will usually only require SABA therapy. We agree with the Expert Panel of the National Heart, Lung, and Blood Institute (NHLBI), which recommends that patients receive therapy every 20 minutes in the first hour of care. Children with mild exacerbations often improve promptly with just one or two SABA treatments and many are managed without systemic corticosteroids (CS). However, CS may be given to mildly ill children have received home SABA doses prior to presentation or to those who do not respond promptly to SABA therapy (see later, "Moderate Exacerbation").

Racemic albuterol has become the SABA of choice for treatment of children with acute asthma. Options for mode of delivery include a small-volume nebulizer (NEB) and metered-dose inhaler with a spacer (MDI-S). Most emergency clinicians use NEBs to administer SABA, regardless of illness severity. NEBs provide a passive means of receiving aerosolized medication because precise coordination between respiration and aerosol delivery is not needed; additionally anticholinergic medication and humidified oxygen may be delivered concurrently. However, delivery is inefficient, with only about 10% of the drug delivered to the small airways. Also administration takes about 10 minutes, increasing respiratory therapy time and costs.

On the other hand, spacers used with a MDI provide a reservoir of medication that is available to be inhaled. Therefore, precise coordination between actuation and inhalation is not needed, and there is no need for breath-holding. After each actuation, children should take five to eight breaths. Drug deposition in the oropharynx and systemic absorption are reduced with the use of a spacer, and decreased administration time may result in reduced costs.[2] Face mask–equipped spacers are available for children too young to use the spacer's mouthpiece, although mouthpieces are preferable for older children to decrease nasal filtering of the drug.

Numerous clinical trials and meta-analyses have consistently demonstrated that delivery by MDI-S is at least as effective as delivery by NEB. Among children 1 to 4 years old, MDI-S use was

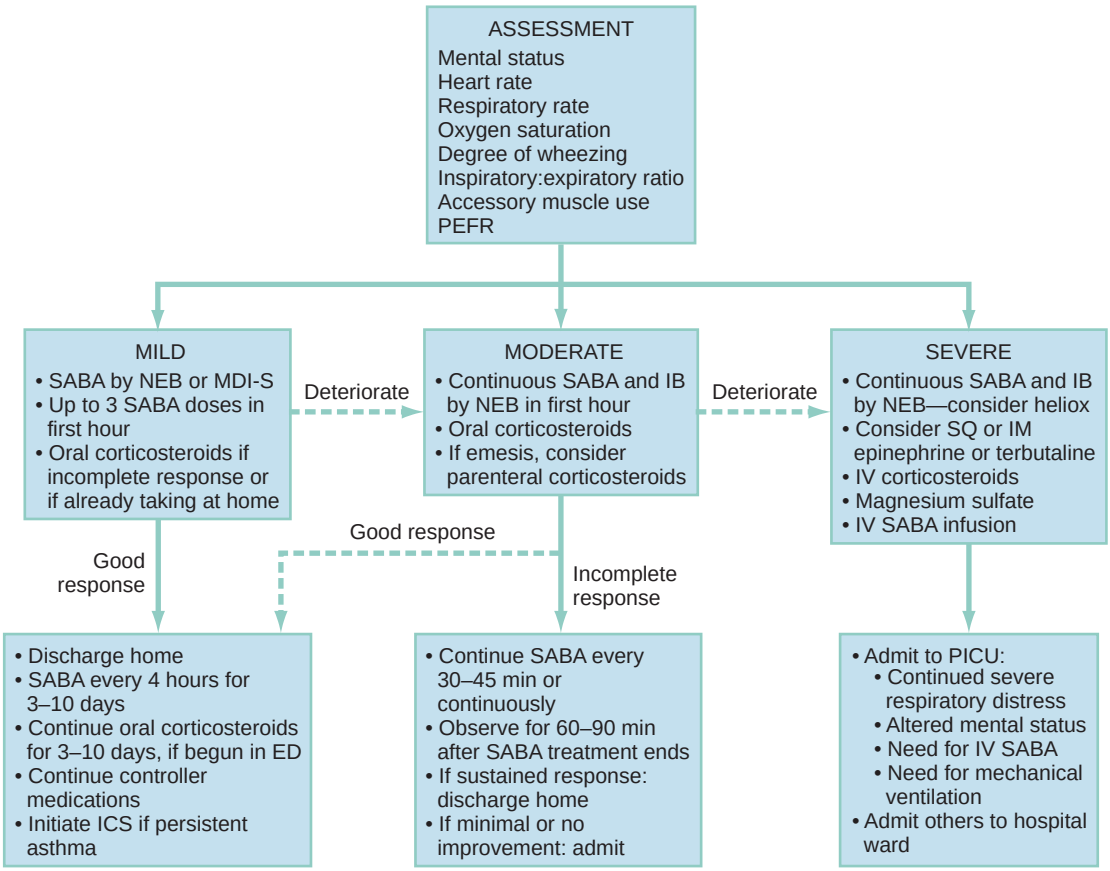

Fig. 168.1. Emergency department management of acute asthma. *ED,* Emergency department; *IB,* ipratropium bromide; *ICS,* inhaled corticosteroids; *IM,* intramuscular; *MDI-S,* metered-dose inhaler with spacer; *NEB,* nebulizer; *PEFR,* peak expiratory flow rate; *PICU,* pediatric intensive care unit; *SABA,* short-acting β_2-agonist: *SQ,* subcutaneous.

associated with a greater reduction in wheezing and lower hospitalization rates. One systematic review evaluated trials in which over 2000 children were randomized to receive SABA by one of these two methods. Those treated with MDI-S had a shorter ED length of stay and reduced hospitalization rate that was not statistically significant. The American College of Chest Physicians and American College of Asthma, Allergy, and Immunology have concluded that NEBs and the use of a MDI-S are appropriate for the delivery of SABA in the ED.

Nebulized racemic albuterol should be administered at a dose of 0.15 mg/kg with a maximum dose of 5 mg. Optimal dosing for albuterol administered by MDI-S is not as well defined. A review assessing 10 randomized controlled trials comparing MDI-S with NEBs has found a wide variability in MDI-S dosing. In some studies, up to seven times more drug was placed in the NEB's reservoir compared with that released by MDI-S, yet outcomes were similar. Multiple puffs of SABA delivered by MDI-S seem to be well tolerated, even by young children. In one trial, children 1 to 4 years of age treated with six puffs of albuterol by MDI-S had less tachycardia than those treated with 2.5 mg of albuterol by NEB. Per the 2007 NHLBI guidelines, a high dose (4–12 puffs) of a SABA MDI with spacer had "equivalent bronchodilation" to NEB treatment. We recommend two to eight puffs, depending on weight (Table 168.2).

Another consideration in the use of SABA is the potential role of levalbuterol. Racemic albuterol is an equal mix of the active *R*-albuterol and inactive *S*-albuterol. *R*-Albuterol produces bronchodilation as well as tachycardia and tremors, and *S*-albuterol was long thought to be inert. However, there is some evidence that *S*-albuterol may increase reactivity to histamine, have proinflammatory effects, and exhibit characteristics of a typical contractile agent. There is also preferential retention of *S*-albuterol in the lungs of healthy volunteers; this may account for diminished effectiveness with frequent dosing. Levalbuterol is pure *R*-albuterol without the *S* component. In theory, levalbuterol should be more effective than racemic albuterol at 50% of the dose (same amount of *R*-albuterol) because there are no competing harmful effects from the *S* isomer. However, studies assessing the use of levalbuterol for treatment of children with acute asthma have not consistently demonstrated this theoretic advantage.

In the first of these trials, 1.25 mg of levalbuterol was compared to 2.5 mg of racemic albuterol in the ED treatment of more than 500 children with acute asthma. The use of levalbuterol was associated with a decreased need for hospitalization. Subsequently, three other randomized trials comparing the ED use of the two drugs failed to find a levalbuterol benefit. Another trial failed to demonstrate benefit with continuously nebulized levalbuterol. The cost of levalbuterol is more than 10 times that of racemic albuterol. Until there are more compelling data to demonstrate conclusively that the additional costs of levalbuterol are offset by clinical benefits, racemic albuterol is the drug of choice for children with acute asthma exacerbations.

Children sustaining clinical improvement 60 minutes after the most recent SABA treatment may be discharged; SABA should be weaned over the next 3 to 7 days. If CS therapy was administered in the ED, it should be continued as 3 to 5 days of prednisone (1 mg/kg once or twice per day; maximum, 60 mg) or 1 or 2 days of dexamethasone (0.6 mg/kg once per day with a maximum 8 to 16 mg). Children should continue all other asthma controller medications, including inhaled corticosteroids.

For those who are not already receiving inhaled corticosteroids, it is unclear if prescribing them at ED discharge leads to improved short-term outcomes. Among adult asthmatics discharged from the ED, the addition of inhaled flunisolide did not lead to improved outcomes. On the other hand, adults randomized to inhaled budesonide after ED discharge had a marked decrease in relapse rates, frequency of SABA use, and asthma symptoms. One review has concluded that there is "insufficient evidence that ICS [inhaled CS] therapy provides additional benefit" when added to systemic CS at ED discharge. Emergency clinicians rarely prescribe ICS at ED discharge, even to children who have persistent asthma. Rather than preventing ED relapse, ICS should be prescribed to help achieve long-term goals for patients with persistent disease. These patients have frequent symptoms—coughing or wheezing, frequent exacerbations requiring the use of SABA, or recurrent visits to the ED. ICS are safe and well tolerated at recommended doses and may be given concurrently with systemic CS. Longitudinal studies have shown that daily use of inhaled corticosteroids may decrease growth velocity, but these changes are small and reversible.

In addition to prescribing medications, emergency clinicians should also provide asthma education at discharge. Some EDs provide standardized information to families with a video or DVD while they undergo ED therapy. Descriptions of how to identify and avoid asthma triggers, written asthma action plan explaining proper steps to take in response to an asthma flare, review of discharge medications, and instruction on proper MDI-S use should be included. Follow-up asthma care within 1 to 4 weeks should be arranged.

TABLE 168.2

Recommended Doses of Medications for Acute Asthma

MEDICATION	DOSAGE
Albuterol	0.15 mg/kg/dose (0.03 mL/kg/dose, max, 1.0 mL)
• ≤10 kg	2.5 mg (0.5 mL)
• 11–19 kg	3.75 mg (0.75 mL)
• ≥20 kg	5 mg (1.0 mL)
Continuous albuterol	1.0 mg/kg/hr by nebulization (max, 20 mg/hr)
• ≤10 kg	7.5 mg/hr (1.5 mL/hr)
• 10–20 kg	11.25 mg/hr (2.25 mL/hr)
• ≥20 kg	15 mg/hr (3 mL/hr)
Albuterol by metered-dose inhaler	Dose not well established
• ≤10 kg	2–4 puffs
• 11–19 kg	4–6 puffs
• ≥20 kg	6–8 puffs
Levalbuterol	Half the recommended albuterol doses
Ipratropium bromide	
• ≤20 kg	250 μg/dose
• >20 kg	500 μg/dose
L-Epinephrine (1:1000) or terbutaline (1.0 mg/mL)	0.01 mL/kg/dose SC or IM (max, 0.4 mL) 0.005 to 0.01 mL/kg/dose SC (max, 0.4 ml) every 15–20 min for two doses
IV terbutaline	10 μg/kg bolus during 10 min, then 0.1–0.3 μg/kg/min infusion Every 30 minutes, may increase infusion by 0.3 μg/kg/min to max of 5 μg/kg/min
Prednisone	2 mg/kg (max, 60 mg), in ED 1 mg/kg/dose bid (max, 30 mg/dose), home therapy
Dexamethasone	0.6 mg/kg PO, two doses 24 hours apart (max, 8–16 mg/dose)
IV methylprednisolone	1 mg/kg (max, 125 mg)
IV magnesium sulfate	50–75 mg/kg during 20 min (max, 2.5 g)

IM, Intramuscular; *IV,* intravenous; *PO,* by mouth; *SC,* subcutaneous.

Moderate Exacerbation

A moderate exacerbation is characterized by alert tachypneic children who have wheezing throughout expiration, an inspiratory-to-expiratory ratio of 1:2, and significant use of accessory muscles. Typically, the oxygen saturation will be 92% to 95% and the PEFR will be 41% to 70% of personal best. As with children experiencing milder attacks, the cornerstone of therapy is SABA therapy. Other medications include ipratropium bromide (IB) and CS.

IB, an anticholinergic agent, blocks reflex bronchoconstriction caused by stimulation of airway cholinergic receptors. It is available as an MDI and as a NEB solution for nebulization that may be mixed directly with albuterol. The use of a SABA with IB is more effective than an SABA alone. In a randomized controlled trial of children with severe acute asthma exacerbations, three doses of IB were shown to be superior to one dose or no dose of IB; all children also received three doses of albuterol. In another study of children with an initial PEFR below 50% predicted who all received albuterol and prednisone, those who also received IB had a significantly lower rate of hospitalization. A systematic review and meta-analysis of 16 trials found that combination therapy was associated with significantly lower hospitalization rates and improvements in asthma scores and pulmonary function test results.

The clinical benefits of IB may be delayed for up to 60 minutes. However, it is inexpensive and free of adverse effects, because less than 1% is systemically absorbed. IB should be given to children with moderate to severe exacerbations. Two to three doses may be mixed with three doses of albuterol and delivered continuously by NEB for 1 hour (Table 168.3). This means of administration,

TABLE 168.3

Short-Acting β_2-Agonists in Acute Asthma

	MILD	MODERATE	SEVERE
Delivery method	Intermittent NEB or MDI-S	Continuous by NEB for 1 hr, then reassess	Consider subcutaneous or intramuscular therapy; continuous by NEB
Comments	Most patients will need one or two treatments; allows MDI-S teaching; no IB needed	Not superior to MDI-S; easier to adhere to NHLBI guidelines for the first hour of therapy; concurrent IB therapy more easily delivered	Better outcomes in severe asthma

IB, Ipratropium bromide; *MDI-S,* metered dose inhaler with spacer; *NEB,* nebulizer; *NHLBI,* National Heart, Lung, and Blood Institute.

although not superior to delivery by MDI-S, will help in the delivery of three albuterol treatments in the first hour of care. Alternatively, four to eight puffs of IB may be given every 20 minutes in the first hour, along with albuterol via a MDI-S.

Moderately ill children who continue with dyspnea or significant work of breathing or poor aeration after 1 hour of continuous nebulized albuterol and IB should receive more prolonged, continuous, NEB therapy. These children treated with continuously nebulized SABAs have lower rates of hospitalization, greater improvements in PEFR, and similar rates of adverse events compared with those treated intermittently. Continuous NEB therapy will result in less respiratory therapy time and costs, has been shown to be safe, and may benefit the sickest patients the most.

The prompt use of CS can decrease the need for hospitalization and should be used routinely for patients with moderate disease. The most recent NHLBI guidelines recommend oral administration of CS; compared to intravenous (IV) or intramuscular injections, it is less invasive and benefits are equivalent. Oral CS therapy is inexpensive, with rapid gastrointestinal absorption. Children treated with frequent SABAs and oral prednisone have a reduced need for hospitalization.

A recent review of six randomized studies found similar efficacy for prednisone and dexamethasone.[3] Dexamethasone has the advantage of having a substantially longer half-life (36–72 hours) than prednisone (18–36 hours), permitting a shorter treatment course. Children treated with dexamethasone (0.6 mg/kg) plus 1 day of additional dosing or prednisone (2 mg/kg), followed by 4 days of additional dosing, were found to have no differences in hospitalization or relapse rates. More patients in the dexamethasone group were compliant with treatment, and fewer vomited the study drug in the ED.

Most children with a moderate asthma exacerbation can be managed without the insertion of an IV line. Intramuscular therapy is a reasonable option for children who vomit orally administered CS. The use of ICS for the ED treatment of acute asthma is an area of ongoing research. Although a handful of studies have suggested potential benefits of ICS, there is not enough pediatric literature to recommend their use. Secondary to greater bioavailability and proven benefits, all moderately ill children should receive systemic CS therapy.

Intermittent Versus Continuous Therapy. Children requiring very frequent, intermittently nebulized albuterol may benefit from receiving albuterol continuously instead. In one clinical trial of asthmatic children, patients were randomized to receive the same total dose of albuterol nebulized intermittently or continuously over 2 hours. Those in the continuous group had a greater mean improvement in their asthma scores and significantly less respiratory therapy time, although there were no differences in mean PEFR or admission rates. A systematic review found that those treated with continuously nebulized SABAs had lower rates of hospitalization, greater improvements in pulmonary function test results, and similar rates of adverse events compared with those treated intermittently.

Perhaps the greatest advantage of continuous over intermittent therapy is one of a practical nature. It allows greater compliance with the goal of delivering the equivalent of three intermittent albuterol treatments in the first hour of care. In addition, this method will result in less respiratory therapy time and costs; it has been shown to be safe and may benefit the sickest patients the most. On the other hand, young children may not tolerate a face mask for prolonged periods.

Many emergency clinicians find it helpful to determine the total dose of racemic albuterol that would be delivered if three treatments were to be given intermittently during 1 hour, place that total dose in the NEB reservoir, and administer it continuously during 1 hour. Alternatively, a dose range may be used on the basis of the child's weight (see Table 168.2).

A suggested approach to the management of children with moderately acute asthma is summarized in Fig. 168.1. After 1 hour of therapy, a clinical reassessment should be made; evaluation at this time is more accurate than the initial assessment at predicting the need for hospitalization. Children with decreased wheezing and work of breathing and improved aeration may be monitored without SABAs to assess their risk of clinical deterioration. Disposition decisions should be made after the child has been observed for 90 to 120 minutes from their last SABA dose. Disposition decision should take into consideration frequency of prior hospitalizations and ED visits and issues regarding compliance and support systems. ED discharge medications and education are the same as outlined for those with mild exacerbations.

Children who remain moderately ill after the first hour of continuous SABAs should remain on continuous or frequent intermittent therapy. These patients should also have received CS early in their course of treatment. If after 2 hours, the degree of respiratory distress is unchanged or worse, the patients should be hospitalized. There will be a subset of patients who demonstrate some degree of clinical improvement at the 2-hour assessment, but are not yet well enough to be sent home. One study found that among children treated with prednisone and 2 hours of SABA therapy, less than 50% were hospitalized when therapy was continued for an additional 2 hours, and none returned to the ED within 48 hours of discharge. To avoid unnecessary hospitalizations, we recommend observing patients who do not otherwise decline for a total of 3 to 4 hours prior to the decision to admit.

Severe Exacerbation

A severe exacerbation is characterized by restlessness or lethargy, extreme tachypnea and tachycardia, audible wheezing, inspiratory-to-expiratory ratio exceeding 1:2, significant use of accessory muscles, and oxygen saturation less than 92%. Some older children with a severe exacerbation may have bradypnea due to a prolonged expiratory phase, and auscultated wheezing may be absent with markedly decreased aeration. The PEFR will typically be less than 40% predicted, although most children will be too ill to use a peak flow meter.

Fig. 168.1 outlines the approach to management of severely ill children. They should be attached to a cardiorespiratory monitor and blood pressure cuff, with continuous monitoring of oxygen saturation by pulse oximeter. As with moderately ill children, supplemental oxygen and continuously nebulized albuterol and IB should be provided soon after arrival. Nearly all severely ill children will require more prolonged therapy with continuously nebulized albuterol, as outlined above. To achieve an oxygen saturation of 92% or greater, it may be necessary to use a non–rebreathing facemask. Severely ill children may be too sick to tolerate oral medications and may need an IV catheter. A dose of methylprednisolone should be given as soon as an IV line is established.

For children with very poor inspiratory flow, nebulized SABAs may not be effectively delivered to the smallest airways; short inspiratory time, low inspiratory pressures, and a prolonged exhalation phase will impair delivery of inhaled medications. In these cases, subcutaneous or intramuscular terbutaline or epinephrine should be used, especially if an IV line has not been established. Terbutaline has the advantages of being a more selective agent with fewer side effects, such as tremors, vomiting, or palpitations. This treatment can be of particular benefit for very ill and anxious young children who are uncooperative with the inhalation treatments. There are no data to suggest that one mode of administration is superior to the other, although intramuscular epinephrine therapy is recommended for children with

bronchospasm due to anaphylaxis. If it is more readily available, an epinephrine autoinjector is effective for this subset of patients. Subcutaneous or intramuscular therapy may be repeated every 10 to 15 minutes, as needed, in extreme cases.

Meta-analyses have determined that the use of magnesium sulfate results in improved outcomes for adults and children.[4] In two separate trials, children with a suboptimal response to initial SABA therapy who were randomized to receive magnesium had significantly greater improvements in pulmonary function compared with those treated with placebo. In contrast, magnesium was not found to be efficacious as a component of initial therapy for children with moderate to severe exacerbation when given prior to judging the response to early albuterol therapy.

Magnesium is inexpensive and has minimal adverse effects. It has been found to be efficacious when added to a regimen of SABA and CS therapy. Hypotension may be minimized by slowly infusing the dose over 20 minutes. Magnesium (50–75 mg/kg over 20 minutes; maximum, 2.5 g) should be given to moderately ill patients who have a suboptimal response to SABAs, IB, and CS, as well as for all severely ill children.

There are insufficient data to make recommendations for the use of IV SABAs; a systematic review of randomized controlled trials has failed to support this practice. Potential adverse effects from the use of IV SABAs are substantial and include dysrhythmias, hypertension, and hypokalemia. IV SABAs should not be used, except for impending respiratory failure, where the risk-benefit ratio shifts toward their use.

Heliox is a low-density mixture of helium and oxygen that results in less turbulent flow through narrowed airways. Theoretically, heliox may decrease the work of breathing, resulting in less respiratory muscle fatigue and lower likelihood of ventilatory failure. Heliox has not been found beneficial in all asthma exacerbations, but it may be considered for severely ill children who are not responding to more conventional therapy.

When making decisions about the need for mechanical ventilation of the severely ill patient, one should assess the entire clinical picture, including illness severity, response to therapy, and ABG results. However, the ABG results should not be used alone. The child with an initial pH of 7.10 and a $Paco_2$ of 55 mm Hg who shows marked improvement with IV SABA therapy may not require ventilatory assistance, whereas the child with a pH of 7.18 and $Paco_2$ of 50 mm Hg who appears fatigued and is not responding to therapy will likely need mechanical support. Ketamine is a bronchodilator and is the drug of choice for sedation and analgesia of the asthmatic child who requires intubation.

Mechanical ventilation can result in air trapping with resultant, and enough expiratory time must be allowed for air exit from the lungs. Permissive hypercapnia describes a strategy to prevent barotrauma. It minimizes tidal volumes and respiratory rates to decrease peak inspiratory pressures.

BRONCHIOLITIS

Principles

Bronchiolitis is an acute infectious disease that results in inflammation of the small airways in children younger than 2 years. This process is manifested clinically as wheezing and increased work of breathing, along with the typical signs and symptoms of a URI. Nearly all children are affected by the viruses that cause bronchiolitis at least once during their first 2 years of life, but it is more common for infants younger than 12 months to manifest clinical signs of bronchiolitis.

Bronchiolitis is a seasonal disease, with most cases occurring between November and April in temperate climates. It is rarely fatal, with an average mortality rate of 2.0/100,000 live births in the United States. Low birth weight (<2500 g), low 5-minute Apgar score, high birth order, and young maternal age are associated with an increased risk of death. Breast-feeding, on the other hand, appears to be associated with a less severe clinical course.[5]

Many viruses are implicated as the underlying cause of bronchiolitis. Respiratory syncytial virus (RSV), the most common agent identified in children diagnosed with this disease, is estimated to cause up to 70% of cases in previously healthy children. Other viruses commonly isolated are parainfluenza, human metapneumovirus, influenza, adenovirus, bocavirus, and rhinovirus.

Most respiratory viruses that cause bronchiolitis in children are transmitted from one host to another by fomites spread from hand to nose or by droplets produced by sneezing or coughing of respiratory secretions. Shedding of the virus often begins before the onset of significant clinical symptoms and can continue for 2 to 3 weeks in an immunocompetent infant. The typical incubation period is 2 to 8 days from the time of initial contact.

In an infected patient, viral replication often begins in the epithelial cells of the upper airway before spreading to the mucosal surfaces of the lower respiratory tract. The infected epithelial cells are generally destroyed by lysis or apoptosis, which results in the desquamation of these cells and release of host inflammatory mediators. Affected lungs demonstrate epithelial cell necrosis, monocytic inflammation and edema of the peribronchial tissues, and mucus and fibrin plugging of the distal airways on histologic examination. These findings translate into the clinical findings of wheezing and lower airway obstruction in an infant with bronchiolitis. Younger infants, whose distal airways are of smaller caliber and whose immune systems lack active immunity to most respiratory viruses, are prone to more severe clinical symptoms. Severe lower airway obstruction leads to air trapping and atelectasis, resulting in mismatched ventilation and perfusion and hypoxemia. In addition, younger infants are at increased risk for fatigue, leading to hypercarbia and respiratory failure.

Clinical Features

Infants with bronchiolitis are typically younger than 12 months and present during the winter months. The first symptoms are generally those of a URI, such as nasal congestion and copious rhinorrhea. This is followed within a few days by a tight cough, often associated with difficulty in feeding. Some parents will report audible wheezing as well. Approximately one-third of patients admitted with bronchiolitis will have fever. Very young infants may present with a history of apnea, which may precede the onset of typical symptoms of respiratory infection. The emergency clinician should ascertain information about the infant's hydration status, including the amount and frequency of oral intake, urine output, vomiting, and diarrhea.

Comorbidities, such as congenital heart disease, chronic lung disease, and prematurity, can have a significant impact on the clinical course of bronchiolitis. A past history or family history of wheezing or atopy may make the diagnosis of asthma more likely, particularly in the older infant; daycare attendance and household contacts with respiratory symptoms also favor a diagnosis of bronchiolitis.

Common vital sign abnormalities include fever, tachycardia, tachypnea, and hypoxia. Pulse oximetry is noninvasive and inexpensive and provides objective data about the degree of illness of a wheezing child. The oxygen saturation (Sao_2) of any moderately or severely ill infant should be obtained soon after ED arrival as an adjunct to the physical examination. With the use of pulse oximetry, an ABG analysis is generally unnecessary to assess a patient's oxygenation. Thus, carrying out ABG analysis should be reserved for those with severe disease and impending respiratory failure to measure the extent of hypercarbia and respiratory acidosis.

Nasal flaring and retractions are visible signs of respiratory distress. Lung auscultation often reveals decreased air movement,

TABLE 168.4

Suggested Bronchiolitis Assessment Tool

	DEGREE OF BRONCHIOLITIS		
PARAMETER	**MILD**	**MODERATE**	**SEVERE**
Feeding	Normal	Less	Poor
Sao_2 in room air	≥95%	92%–94%	<92%
Respiratory rate (breaths/min)	<60	60%–70%	>70
Retractions	None or minimal	Intercostal	Substernal
Accessory muscle use	None	None	Neck or abdominal
Wheeze	None or minimal	Moderate expiratory	Severe inspiratory-expiratory; audible without stethoscope
Air exchange	Good, equal breath sounds	Localized, decreased breath sounds	Multiple areas of decreased breath sounds

rales, rhonchi, wheezing, and an increased ratio of expiratory to inspiratory times. Irritability or lethargy, particularly in young infants, indicates more severe disease. Children can be stratified into mild, moderate, and severe categories based on the physical examination findings (Table 168.4). The combination of poor feeding and increased insensible fluid losses often has an impact on an affected infant's hydration status. A careful assessment of the anterior fontanel, mucous membranes, and skin turgor can help identify dehydration.

The worst phase of the illness generally occurs in the first few days, and children admitted for bronchiolitis have a median length of hospital stay of 2 to 3 days. However, the entire course of illness can last much longer, with a median duration of 12 days. Coughing and noisy breathing, in particular, can last for more than 4 weeks.

Acute bacterial otitis media is the most common associated illness, with a prevalence of up to 60%. The bacterial pathogens are similar to those recovered in other children with acute otitis media and should be treated accordingly. Other concurrent bacterial infections are rare. In one study of more than 2000 children hospitalized with RSV bronchiolitis, approximately 1% also had a urinary tract infection (UTI); no child had pathologic bacteremia or meningitis. Similar rates of UTI without bacteremia have been found in febrile children with clinical bronchiolitis, with or without documented RSV infection.

Infants younger than 8 weeks with fever and bronchiolitis present a unique dilemma for emergency clinician. The rate of serious bacterial infections (SBIs), defined as UTI, bacteremia, bacterial meningitis, or bacterial enteritis, among all febrile infants younger than 8 weeks is reported to be up to 12%. However, in infants with documented RSV infection or clinical bronchiolitis at the time of ED presentation, the incidence of an SBI is substantially lower. In a large prospective, multicenter study, 7% of febrile infants younger than 61 days who were RSV-positive had a concurrent SBI, compared with 12.5% of those who were RSV-negative. Of the patients with SBIs, most (82%) had a UTI. Bacteremia was rare and occurred only in infants younger than 1 month. None of the RSV-positive infants had bacterial meningitis. As a result, for infants between 1 and 2 months of age who are known to be RSV-positive or have clinical bronchiolitis, we recommend catheterized urinalysis and culture. Additional testing to obtain culture specimens of cerebrospinal fluid and blood may be done selectively. These infants may not require empirical antibiotic therapy for presumed SBIs; decisions to treat with antibiotics should be made on an individual basis, considering the degree of ill appearance and comorbidities. All febrile infants in the first month of life should undergo a complete laboratory evaluation for an SBI and be empirically treated with antibiotics, regardless of RSV status or presence of clinical bronchiolitis.

Apnea is commonly reported in young infants with bronchiolitis, especially those who are admitted for inpatient management. Of admitted patients, 12% have a reported history of apnea, and 5% will have apnea during the hospital stay. Risk factors for the development of in-hospital apnea include corrected age younger than 8 weeks, low birth weight, significant tachypnea or bradypnea, hypoxia, and history of apnea before admission.[6] The absence of all these risk factors has a high negative predictive value for the development of in-hospital apnea.

Diagnostic Considerations

Differential Diagnoses

Asthma is the condition that has the most clinical overlap with bronchiolitis. Physical examination findings alone cannot distinguish the two. Younger age, presentation during the winter months, antecedent URI symptoms, and absence of a prior or family history of atopic disease and wheezing suggest bronchiolitis as the cause of wheezing in an individual patient. Some infants will have clinical features consistent with both conditions. For example, a 12-month-old may present in July with a URI and wheezing for the first time. For this child, a clinician may choose to initiate therapy for acute asthma. Conditions that should be differentiated from bronchiolitis are summarized in Table 168.1.

Diagnostic Testing

Bronchiolitis should be diagnosed primarily on the basis of history and physical examination findings. In general, viral diagnostic testing is not warranted for patients well enough for outpatient management. If test results can be obtained rapidly, identification of a viral cause may eliminate the need for further laboratory evaluation in young infants with fever. (See Chapter 166 for a comprehensive overview of recommendations for pediatric fever.)

There is tremendous variability in the use of diagnostic imaging, with some centers reporting that chest radiographs are obtained for more than 70% of infants hospitalized with bronchiolitis. In children with clinical findings typical for bronchiolitis, radiographic imaging is rarely necessary. Hyperinflation, atelectasis, and peribronchial cuffing are the findings most commonly associated with this disease. In ambulatory patients with acute lower respiratory infections, obtaining a chest radiograph does

not affect the clinical outcome but has been associated with increased use of unnecessary antibiotics. Furthermore, the chance of identifying an alternative diagnosis from a chest x-ray is less than 1%. Diagnostic imaging may be helpful in patients with severe distress, significant hypoxia, or an atypical presentation. We agree with the clinical practice guideline published by the American Academy of Pediatrics in 2014, that "when clinicians diagnose bronchiolitis on the basis of history and physical examination, radiographic or laboratory studies should not be obtained routinely."[7]

Management

Whereas the diagnosis of bronchiolitis is fairly straightforward, the management of children with the disease often presents emergency clinicians with confusing and controversial dilemmas. The literature is often contradictory, making it difficult to reach a consensus. As a result, there is wide practice variation in the management of bronchiolitis. However, it is clear that a consistent, evidence-based approach to this disease can lead to more efficient and effective care. Supportive care, such as providing hydration and supplemental oxygen, is the cornerstone of therapy for affected children.[7] A management strategy, stratified by the patient's initial degree of illness, is outlined in Figure 168.2.

SABAs are the treatment of choice for children with wheezing due to asthma. However, the evidence supporting their use in wheezing caused by bronchiolitis is less favorable than for asthma. In a meta-analysis of 22 clinical trials, a small short-term benefit in clinical score was observed for children with bronchiolitis treated with SABAs. This treatment had no significant effect on rates or duration of hospitalization. Although rare, adverse effects such as tachycardia, decreased oxygen saturation, flushing, and hyperactivity occurred more frequently in children treated with SABAs.[8] Thus, the American Academy of Pediatrics does not recommend the routine use of SABAs for bronchiolitis[7]; instead, emergency clinicians should consider a trial of such medications to determine if a patient has a beneficial clinical response, especially if it is unclear whether the patient has asthma or bronchiolitis..

Similar controversy exists with respect to the use of nebulized epinephrine in the treatment of bronchiolitis. A meta-analysis of 14 studies has concluded that there is not enough evidence to support the use of epinephrine for inpatients because treatment does not decrease the rate of hospitalization or the length of hospital stay for admitted patients.[9] However, in countries where outpatient nebulized epinephrine is available, it has shown some short-term clinical benefit over other bronchodilators and placebo for outpatients. We recommend that a trial of nebulized epinephrine be considered for children with moderate to severe distress who might otherwise require more invasive interventions (eg, endotracheal intubation) secondary to disease severity. As with SABAs, nebulized epinephrine should be continued only for those patients who demonstrate a clinical benefit. There is currently no sufficient evidence to recommend the use of other bronchodilators, such as anticholinergic agents, for young children with wheezing and suspected bronchiolitis.

Many of the symptoms of bronchiolitis are a result of increased and thickened respiratory secretions. A great deal of literature supports the use of nebulized hypertonic saline in the treatment of cystic fibrosis, in which clearance of thickened secretions is vital. Although there is not yet enough literature to recommend its use in the ED definitively for bronchiolitis, several studies have suggested that nebulized hypertonic saline is a safe medication that reduces the length of stay for hospitalized children. Thus far, studies have not demonstrated any clinically significant benefits associated with its use in ED patients.[10]

Chest physiotherapy has also been examined as a means to clear respiratory secretions. A meta-analysis of three randomized controlled trials has revealed no improvement in clinical score, length of stay, or oxygen requirement after chest physiotherapy.[11]

Systemic CS are a well-established and effective treatment of wheezing due to acute asthma. Despite reports that more than 50% of infants may be prescribed CS when they are diagnosed with bronchiolitis, well-designed controlled trials have demonstrated no benefit for their use in terms of rate of admission, clinical score, or any other outcome. Specifically, Corneli and colleagues conducted a double-blind, randomized trial comparing oral dexamethasone with placebo in 600 children with acute moderate to severe bronchiolitis.[12] They concluded that oral dexamethasone has no significant effect on the rate of hospitalization, respiratory status after 4 hours of observation, or later outcomes, such as length of inpatient stay, repeated medical visits, and adverse events.[12] Although another multicenter trial did demonstrate a reduction in hospitalization rates in patients treated with the combination of oral dexamethasone and nebulized epinephrine,[13] it is not clear that this reduction is clinically significant nor that the routine use of systemic CS for bronchiolitis has a positive effect on clinical course.[14] Thus, our recommendation is that emergency clinicians not use CS for the treatment of bronchiolitis.

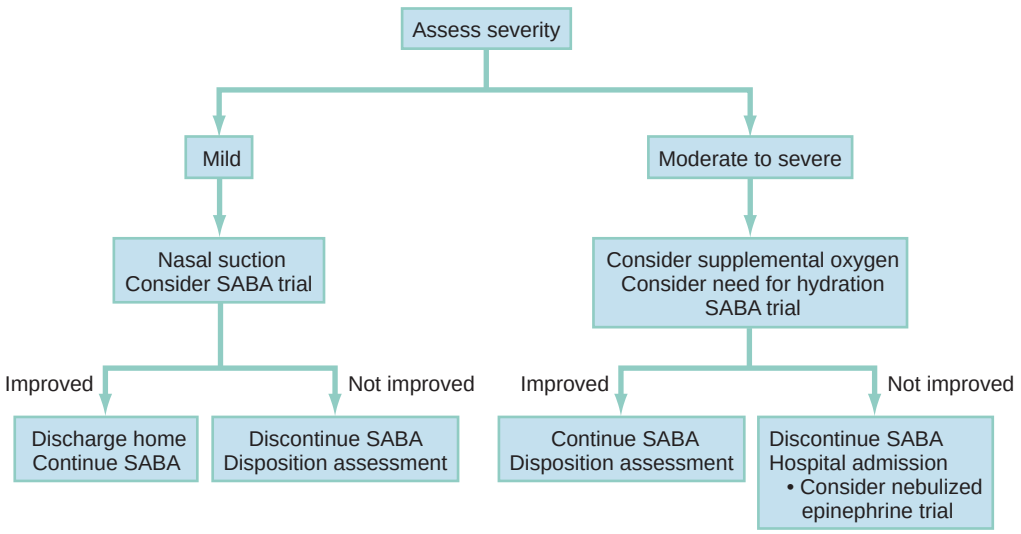

Fig. 168.2. Emergency department management of bronchiolitis. *SABA,* Short-acting β_2-agonist.

Whereas infants with severe bronchiolitis requiring intensive care and mechanical ventilation frequently have concurrent or secondary bacterial infections, this is an uncommon complication for most children. Despite some reports that clarithromycin may hasten recovery in RSV bronchiolitis, there is no evidence for the routine use of antibiotics for bronchiolitis, and they should be reserved for patients with identified bacterial infections.[15]

Prophylaxis

Although emergency clinicians generally do not have a role in the administration of preventive medications, they should be aware that selected infants will be receiving prophylactic management. Palivizumab (Synagis) consists of monoclonal antibodies against RSV. Whereas RSV-specific immune globulin is not effective for treating the acute disease process, palivizumab is effective in reducing hospitalization rates for RSV in certain high-risk populations. It is recommended for most children younger than 24 months with chronic lung disease, congenital heart disease, or prematurity and is administered as a monthly intramuscular injection during the high-prevalence months. The emergency clinician must be aware that although preventive treatment has been initiated, treated infants with signs of bronchiolitis may still have RSV infections.

Disposition

Because bronchiolitis is a dynamic disease, evaluations at a single point in time may not be sufficient to estimate its severity fully; thus, serial examinations are necessary. A number of demographic and clinical features have been associated with a severe clinical course. These factors include age younger than 12 weeks, history of prematurity, ill appearance, hypoxemia (Sao_2 < 95%), tachypnea (>70 breaths/min), and significant atelectasis on the chest radiograph (when obtained). In addition to younger age and prematurity, a history of hemodynamically significant congenital heart disease, chronic lung disease, and immunocompromised state have been associated with higher morbidity and mortality among inpatients.

Ultimately, the emergency clinician should assess more than just the child's degree of respiratory distress. Patients should be admitted if they are unable to maintain oral hydration due to respiratory symptoms difficulty with feeds due to increased work of breathing; or copious nasal secretions requiring frequent deep suctioning. The family or caregiver should be able to continue supportive measures at home and seek further medical care. Discharge instructions should include 24-hour follow-up with a primary care provider or emergency clinician for reevaluation. For children with a sustained clinical improvement to SABA therapy, this treatment should be continued at home every 4 hours, as needed. Although home oxygen therapy for selected patients with mild to moderate disease has demonstrated success in reducing inpatient hospitalization, primarily in high-altitude conditions, this practice requires careful coordination of care and resources, which may not be feasible in all practice settings. Furthermore, its application to children at sea level is still unclear and thus is not generally recommended. Parents should be instructed to seek immediate medical care for signs of worsening respiratory distress, including poor feeding, retractions, increased tachypnea, lethargy, and irritability.

KEY CONCEPTS

- An infant younger than 12 months has an oxygen consumption index double that of an adult. An infant with bronchospasm due to asthma or bronchiolitis may rapidly develop hypoxemia, bradycardia, and cardiopulmonary arrest.
- No single asthma score has been universally adopted to assess degree of illness or treatment responses. However, most scores include some combination of respiratory rate, degree of wheezing, inspiratory-to-expiratory ratio, use of accessory muscles, and oxygen saturation.
- It should not be a routine practice to obtain a chest x-ray for wheezing children, even for those who are febrile, wheezing for the first time, or require hospitalization. Chest x-rays are indicated for those with a history of choking, focal chest findings, extreme distress, or subcutaneous emphysema.
- Albuterol is the drug of choice in the ED treatment of acute asthma of any severity.
- Albuterol delivered by MDI-S is as effective as that delivered by nebulizer for children with acute asthma. The mode of delivery is largely chosen on the basis of cost and ability to adhere to the goal of three treatments within the first hour of care.
- Almost all children treated in the ED for asthma will require systemic corticosteroids. However, children with mild exacerbations who respond promptly to a single SABA treatment may be managed without systemic corticosteroids.
- To date, most studies have failed to demonstrate that levalbuterol leads to better ED outcomes compared with racemic albuterol. Racemic albuterol, at a substantially lower cost, should remain the drug of choice for children with acute asthma exacerbations.
- Continuously nebulized albuterol, CS, magnesium sulfate, and IV SABA are cornerstones of therapy for moderately to severely ill children with asthma.
- National guidelines recommend that emergency clinicians initiate controller therapy (eg, inhaled corticosteroids) for children with persistent asthma at ED discharge.
- Asthma is the condition that has the most clinical overlap with bronchiolitis. Physical examination findings alone cannot distinguish the two. Younger age, presentation during the winter months, antecedent URI symptoms, and absence of prior or family history of atopic disease and wheezing suggest bronchiolitis as the cause of wheezing in an individual patient.
- Bronchiolitis is a clinical diagnosis based on a history of prodromal URI symptoms in a young infant, followed by findings on physical examination of wheezing and increased work of breathing. The value of diagnostic imaging and laboratory evaluation is limited, and these measures should not be used routinely.
- A urinalysis and culture should be performed for febrile infants between 1 and 2 months of age who are known to be RSV-positive or have clinical bronchiolitis. The decision to obtain blood or cerebrospinal fluid cultures and give empirical antibiotics should be made on an individual basis.
- All febrile infants in the first month of life should undergo testing and evaluation for SBIs and be empirically treated with antibiotics, regardless of RSV status or presence of clinical bronchiolitis.
- The management of infants with bronchiolitis focuses largely on supportive measures, and most patients able to tolerate oral hydration can be managed as outpatients. There are currently no consistently effective pharmacologic therapies for bronchiolitis.
- Despite reports that more than 50% of infants may be prescribed corticosteroids when diagnosed with bronchiolitis, well-designed controlled trials have demonstrated no benefit for their use in terms of rate of admission, clinical score, or any other clinical outcome.
- Disposition from the ED for bronchiolitis depends on the assessment of multiple risk factors, including young age, prematurity, significant hypoxemia, and severe tachypnea, which may predict a more severe clinical course.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 168: QUESTIONS & ANSWERS

168.1. A 19-month-old girl with a history of asthma present with severe respiratory distress marked by wheezing, tachypnea, deep retractions, and an oxygen saturation of 92% in room air. She fails to improve 10 minutes after nebulized short-acting β_2-agonist (SABA) therapy and repeatedly tries to pull off her face mask. Which strategy is likely to produce the most rapid clinical benefits in this setting?

A. Administering IM terbutaline
B. Administering IV methylprednisolone
C. Administering the SABA via metered-dose inhaler (MDI) instead of by nebulization
D. Doubling the dose of SABA in the nebulizer reservoir
E. Taking off her face mask and holding it close to her face to reduce her agitation

Answer: A. This patient's degree of bronchospasm and lack of cooperation make it difficult to deliver aerosolized medication effectively. In this setting, IM terbutaline is most likely to result in rapid bronchodilation, making subsequent aerosolized therapy more effective.

168.2. A 4-month-old male infant presents to the ED with his father, who reports that the patient has been wheezing. His vital signs are temperature, 102.2°F (39°C), respiratory rate, 50 breaths/min, and oxygen saturation, 97%. On examination, you find diffuse wheezing and copious nasal secretions. While in the ED, the patient does not have a wet diaper, and his father reports that he has had decreased oral (PO) intake for the past 2 days. Which of the following findings with bronchiolitis is not associated with the need for admission?

A. Age
B. Decreased PO intake
C. Oxygen saturation
D. Respiratory rate
E. Temperature

Answer: E. Patients often in need of admission for bronchiolitis include those with respiratory rate more than 70 breaths/min, O_2 saturations of 95% or less, age younger than 3 months, and poor feeding.

168.3. Which of the following side effects are seen with the use of intravenous magnesium in the treatment of asthma in children?

A. Change in serum pH
B. Development of a prolonged QT interval on the electrocardiogram
C. Hypercalcemia
D. Hyperkalemia
E. Hypotension

Answer: E. Most patients who receive a magnesium infusion at the recommended dose will experience a clinically insignificant decrease in blood pressure. This may be minimized by infusing the medication over 20 minutes and by concurrently administering normal saline solution.

168.4. You are about to treat a child with acute asthma with albuterol. Which of the following factors is most important when considering the method of aerosolized drug delivery?

A. About 20% to 30% of nebulized drug reaches the alveoli.
B. Children receiving β-agonists by nebulizer (NEB) have similar outcomes compared with those using a metered-dose inhaler (MDI-S).
C. Children weighing > 20 kg should receive a maximum of four puffs of albuterol via MDI-S.
D. MDI-S therapy is more costly than NEB therapy.
E. The use of MDI-S for acute asthma is not supported by national guidelines.

Answer: B. Clinical trials and systematic reviews have repeatedly shown these two forms of therapy to be equivalent. With NEB treatment, less than 10% of nebulized drug reaches the alveoli. A recommended MDI-S dose for older children is eight puffs. Most studies demonstrate that MDI-S therapy is more cost-effective because of a slightly reduced need for hospitalization. National guidelines support the use of MDI-S to deliver albuterol to children with acute asthma.

168.5. A 7-month-old male infant was diagnosed 2 days ago with bronchiolitis. He continues to have wheezing and increased work of breathing, prompting his parents to bring him into the ED because of a new-onset fever. Which of the following is the most likely secondary bacterial infection in this infant with bronchiolitis?

A. Pneumonia
B. Acute otitis media
C. Meningitis
D. Urinary tract infection

Answer: B. Bacterial acute otitis media (AOM) is the most common condition associated with bronchiolitis, with a prevalence of up to 60%. The bacterial pathogens are similar to those recovered in other children with AOM; thus, it should be treated according to standard recommendations. Other concurrent bacterial infections are rare.

CHAPTER 169

Pediatric Respiratory Emergencies: Diseases of the Lungs

Genie E. Roosevelt

PNEUMONIA

Principles

Although most acute infections of the respiratory tract involve the upper respiratory tract, children frequently develop lower respiratory tract infections, most notably pneumonia and bronchiolitis. Bronchiolitis (see Chapter 168) is primarily seen in children younger than 2 years and defined as wheezing and congestion due to a viral infection. Pneumonia is an inflammation of the lung tissue that is most often due to an infection, but occasionally may follow a noninfectious insult. Although the diagnosis of pneumonia may be suggested by clinical signs and symptoms, pneumonia is typically diagnosed by an abnormal chest radiograph showing pulmonary infiltrates. The clinical picture of pneumonia is highly variable, ranging from a mild illness to life-threatening disease. Clinical and radiographic findings sometimes suggest a specific organism, but determination of a precise causative agent is not always straightforward given the limitations of diagnostic testing. Infection rates for pneumonia in children vary inversely with age, averaging 40/1000 in preschool-age children and decreasing gradually to 7/1000 in 12- to 15-year-olds, with a male predominance of 2:1. Three-fourths of all deaths from pneumonia result from bacterial infections.

The causative organisms also vary with the age of the child. The organism is not definitively identified in most pneumonia cases, so the true incidence of the specific causative agent is unknown. Overall, viral agents cause 60% to 90% of pneumonias and are more common in younger children. Bacteria predominate in neonates but are less frequent in toddlers and older children. Outside the neonatal period, the incidence of bacterial agents is stable throughout different age groups.[1] *Chlamydia trachomatis* is a unique cause of pneumonia in infants 3 to 19 weeks of age.[2] *Bordetella pertussis* classically occurs in infants younger than 1 year but may occur in older children and adolescents.[3,4] *Mycoplasma pneumoniae* is one of the most common causes of pneumonia among children older than 5 years and may play a role in younger children.[5,6] *Chlamydophila (*formerly *Chlamydia) pneumoniae* is more often seen in children older than 5 years, but may cause infection in younger children.[7,8]

Among bacteria, group B streptococci and gram-negative bacilli predominate in neonates. Although rare, *Ureaplasma urealyticum* and *Listeria monocytogenes* may cause illness in infants younger than 2 months. *Streptococcus pneumoniae* is the leading bacterial cause of pneumonia in all age groups beyond the newborn period; *Staphylococcus aureus* and *Haemophilus influenzae* are less common causative agents. The incidence of *H. influenzae* type b disease has decreased by 90% since the onset of immunization of infants and young children.[9] In 2010, the 13-valent pneumococcal vaccine (Prevnar 13, Wyeth Pharmaceuticals, NY) replaced the heptavalent pneumococcal conjugate vaccine Prevnar (Wyeth). Prevnar 13 is recommended for the primary series at 2, 4, and 6 months of age, with a fourth booster dose given at 12 to 15 months of age. Clinical trials have suggested 85% protection against serotype-specific cases of pneumococcal pneumonia.[10] Studies have also shown a decrease in carriage rates of the serotypes included in daycare settings. Pneumococcal vaccine has also been shown to provide some protection against viral pneumonia. One study found a 31% reduction in the incidence of pneumonia associated with seven respiratory viruses in hospitalized children, possibly due to frequent concomitant infection of viral pneumonia with pneumococcal infection.[11] Other, less common bacterial agents include group A streptococci, *Neisseria meningitidis,* and anaerobic bacteria, seen in the setting of aspiration pneumonia. Unusual causes of pneumonia include *Pseudomonas aeruginosa, Legionella pneumophila, Pneumocystis jiroveci,* and rickettsial infections. The incidence of *Mycobacterium tuberculosis* has been increasing in the United States, particularly in urban and low-income areas and among nonwhite racial or ethnic groups. Infants and adolescents are at highest risk in the United States.

Respiratory syncytial virus (RSV) and parainfluenza are the most frequent viral agents in infants younger than 1 year. Viruses that may be responsible for neonatal pneumonia include rubella, cytomegalovirus (CMV), and herpes simplex virus. Other viral agents include influenza, adenovirus, rhinovirus, enterovirus, measles, varicella, and Epstein-Barr virus. In addition, immunocompromised hosts are susceptible to mixed and opportunistic infections, including bacterial, viral (CMV, varicella), protozoan (*P. jiroveci*), and fungal disease.

Pathophysiology

The lung is protected from infection by a variety of local and systemic immune mechanisms. Passively acquired maternal antibodies are important in protection against *S. pneumoniae* and *H. influenzae* infections during the first few months of life. Children with altered protective mechanisms are at increased risk for development of pneumonia; this includes children with congenital anatomic abnormalities (eg, cleft palate, tracheoesophageal fistulas, pulmonary sequestration, congenital cystic adenomatoid malformation), immune deficiencies, neurologic alterations that predispose to aspiration (eg, coma, seizures, cerebral palsy, general anesthesia), and alterations in quality of secreted mucus (cystic fibrosis [CF]).

Bacterial pneumonia and mycoplasma infections are usually transmitted person to person by droplet aspiration. Asymptomatic upper airway colonization often occurs in children and may spread infection to other children. Much less commonly, bacterial pneumonia may result from hematogenous spread from a distant

focus or during primary bacteremia. Viral agents that cause pneumonia proliferate in the upper respiratory tract and spread contiguously to involve the lower respiratory tract. Viruses such as varicella, CMV, herpes simplex, Epstein-Barr, measles, and rubella also may infect the lungs through hematogenous spread.

Clinical Features

Clinical symptoms and signs of pneumonia in pediatric patients vary with patient age, specific pathogen, and disease severity. Infants younger than 3 months generally have respiratory symptoms, such as tachypnea, cough, retractions, and grunting, but may show only nonlocalizing symptoms, such as isolated fever or hypothermia, vomiting, poor feeding, irritability, and lethargy. Toddlers with *S. pneumoniae* infection may have nonspecific symptoms, such as high fever and lethargy, without significant respiratory symptoms. In general, with increasing age, signs and symptoms in children become more specific, although pneumonia in any child may have only subtle manifestations. General symptoms include fever and chills, headache, rigors, and malaise. Symptoms of lower respiratory tract disease may include cough and wheezing. Pleural irritation may cause chest, abdominal, or neck pain or result in neck stiffness. Vomiting (often posttussive) or poor oral intake is common.

Key historical factors include birth and immunization history (particularly pneumococcal and *H. influenzae* type b vaccination), sickle cell status, history of previous pneumonia or frequent infections, and presence of underlying chronic disease. Children with known respiratory (eg, bronchopulmonary dysplasia, CF) or cardiac disease tend to have more severe courses of illness; children with primary or acquired immunodeficiencies are also prone to more severe and fulminant disease from common, uncommon, and opportunistic pathogens.

The physical examination should begin with the general appearance and breathing pattern. Vital signs, including oxygen saturation, should be evaluated on arrival. Important findings include hydration status, perfusion, and level of alertness and interaction. Fever is often present with bacterial pneumonia, but may be of low grade or absent in neonates. Cardiovascular parameters may indicate dehydration or, rarely, shock. Tachypnea, although not universal, is the most sensitive indicator of pneumonia and may be the only manifestation in a young child. The World Health Organization (WHO) has published guidelines for the clinical diagnosis of pneumonia in developing countries and cites tachypnea and retractions as indicators of lower respiratory disease. Tachypnea is defined by WHO as a respiratory rate of greater than 50 breaths/min in infants younger than 1 year, more than 40 breaths/min in children 1 to 5 years of age, and more than 30 breaths/min in children older than 5 years[12] Other manifestations of lower airway disease may include cough, wheezing, nasal flaring, retractions, grunting, and accessory muscle use. The characteristics of the cough may aid in the diagnosis; a staccato cough in an infant may indicate pneumonia caused by *C. trachomatis* or *B. pertussis*. Auscultatory findings in an older child may include rales, wheezing, and/or diminished breath sounds. Although these may be present in younger children, the findings are much less consistent, and rales may be masked by poor inspiratory effort or noisy upper airway sounds.

Pleural irritation may cause abdominal tenderness or meningismus, and pulmonary hyperinflation may cause downward displacement of the liver and spleen. Extrapulmonary findings may include rhinorrhea, pharyngitis, or exanthems with viral infections, conjunctivitis with chlamydial disease, pharyngitis and exanthems with mycoplasmal pneumonia or extrapulmonary infections, such as soft tissue abscesses, otitis media, sinusitis, meningitis, and pericarditis, with bacterial pathogens.

Diagnostic Considerations

Differential Diagnoses

The major conditions to be differentiated in children with pneumonia include bacterial pneumonias, viral disease, other unusual infectious causes (mycobacterial, protozoal, fungal), and noninfectious pathologic conditions (Box 169.1). Certain features may help differentiate the common infectious causes (Table 169.1). Each disease entity has certain classic historical, clinical, and laboratory findings. However, the broad spectrum of illness for each condition may make an accurate diagnosis in an individual patient difficult. No specific feature reliably differentiates patients with bacterial infection from children with nonbacterial pneumonia. The health care provider should strongly consider a bacterial cause in a child with a temperature higher than 39°C (102.2°F), clinical toxicity, lobar infiltrate, or pleural effusions. Consideration of host factors, epidemiology, and the clinical picture, with judicious use of laboratory tests, generally points the emergency clinician toward the likely diagnosis and effective management.

Diagnostic Testing

Radiology. A chest radiograph is unnecessary in children without comorbid conditions who have no fever, unilateral wheezing, or tachypnea because they are unlikely to have pneumonia. A well-appearing child with cough and rales may be diagnosed clinically and treated with antibiotics as an outpatient. A child who appears ill or in whom the diagnosis is unclear requires radiographic evaluation. Radiographic findings in pneumococcal pneumonia may show an alveolar infiltrate in a patchy

BOX 169.1

Noninfectious Causes That May Present as Pneumonia

Radiologic technique
- Inadequate inspiration
- Breast shadow
- Thymus
- Uneven grid on film
- Underpenetrated film

Primary pulmonary
- Asthma
- Bronchiectasis
- Atelectasis
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Pulmonary sequestration
- Congenital cystic adenomatoid malformation
- α_1-Antitrypsin deficiency

Aspiration
- Foreign body
- Chemical
- Recurrent, caused by anatomic or physiologic disorders

Primary cardiac
- Congenital heart disease
- Congestive heart failure

Pulmonary infarction
- Sickle cell vaso-occlusive crisis
- Pulmonary embolism

Collagen vascular disorders
Acute respiratory distress syndrome
Pleural effusion
Neoplasm

TABLE 169.1

Pneumonia Syndromes

	INFECTIOUS CAUSE			
FEATURE	**BACTERIAL**	**VIRAL**	**CHLAMYDIAL**	**MYCOPLASMAL**
Historical				
or Age	Any	Any	4–16 wk	5–18 yr
or Fever	High (>39° C [102.2° F])	Low grade	Usually none	Low
or Onset	Abrupt, often after upper respiratory infection	Gradual	Gradual	Gradual
Cough	Productive	Nonproductive	Staccato	Hacking
Associated symptoms	Chest pain; focal infarct	Myalgias, rash, sore throat, coryza	Conjunctivitis	Headache, sore throat, rash
Physical	Toxic appearance			
Lungs	Confined rales	Diffuse rales, wheeze, stridor	Diffuse rales, rare wheeze	Unilateral rales
Chest radiograph				
Infiltrate	Lobar or segmental	Interstitial	Diffuse, interstitial	Lobar or diffuse
Pleural effusion	Occasional	Rare	None	Rare
Other	Pneumatocele; abscess	Hyperinflation, atelectasis	Hyperinflation	
Laboratory test results	Increased WBC granulocytosis	Normal or increased WBC count, lymphocytosis	Normal WBC count, eosinophilia	Normal WBC count
Pathogens (common)	*Streptococcus pneumoniae Haemophilus influenzae Staphylococcus aureus* <2 mo—group B streptococcus; gram-negative enterics; *Listeria monocytogenes*	RSV, parainfluenza, influenza, adenovirus, enterovirus	*Chlamydia trachomatis*	*Mycoplasma pneumoniae*

RSV, Respiratory syncytial virus; *WBC,* white blood cell.

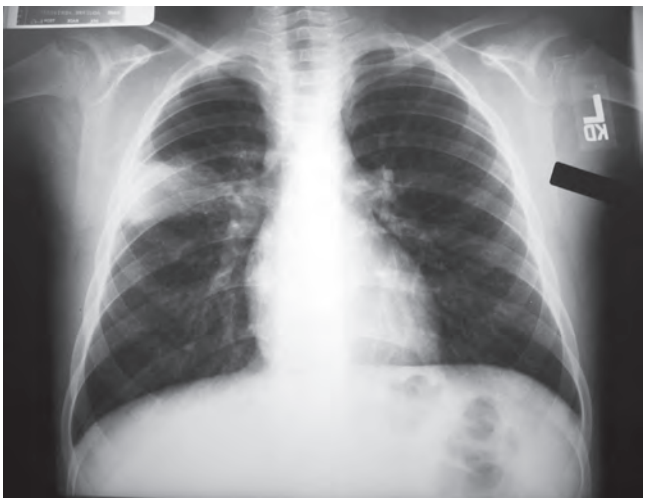

Fig. 169.1. Radiograph showing pneumococcal pneumonia, with infiltrate in the right upper lobe. (Courtesy Dr. Marianne Gausche-Hill.)

Fig. 169.2. Radiograph showing staphylococcal pneumonia, with empyema and abscess on the right. (Courtesy Dr. Brianna Enriquez and Dr. Marianne Gausche-Hill.)

or consolidated lobar (Fig. 169.1) or subsegmental distribution, although patients with bacterial pneumonia may have an interstitial infiltrate. Bilateral involvement, pleural effusion, pneumatocele, and pneumothorax may occur with more severe disease. Rarely, a dehydrated child with pneumonia may have a normal study, and the infiltrate becomes readily apparent only after rehydration.

Although great variability exists, bacterial pathogens classically produce alveolar infiltrates in a lobar distribution but may produce diffuse interstitial infiltrates. Viral and chlamydial infections tend to appear as diffuse interstitial infiltrates, commonly with hyperinflation and atelectasis. Chest radiographs also identify multilobar disease, pleural effusions, pneumatoceles, and pneumothorax (Fig. 169.2). Hilar adenopathy may indicate tuberculosis or malignant neoplasm.

Patients with pleural effusions should have lateral decubitus radiographs to assess effusion size and loculation. Computed tomography (CT) is useful to provide greater detail of effusions and lung abnormalities in critically ill children with complicated pneumonia. Routine CT of the chest to establish the diagnosis is not recommended.

Laboratory Studies

Any child with pneumonia is at risk for hypoxemia and should undergo pulse oximetry to determine oxygen saturation. A complete blood count (CBC) has a very limited role and is often not useful in differentiating between viral and bacterial pneumonia. A CBC should not be obtained unless the results will change management. A venous or arterial blood gas study is not needed in most patients, but may be considered in a child with severe respiratory distress to monitor the effectiveness of respiratory status or ventilation with therapy. In a well-appearing child with an uncomplicated pneumonia, a blood culture is unlikely to be helpful and should not be obtained.[13,14] Blood cultures should only be considered in ill-appearing hospitalized patients. Sputum cultures may be useful for adolescents, but are technically difficult in younger children.

Patients with pleural effusions that are enlarging or compromising respiratory function should undergo thoracentesis for diagnostic and therapeutic purposes.[15] Although parapneumonic effusions are most suggestive of bacterial infection, they also occur with mycoplasmal and occasionally with viral infections. The fluid should be sent for Gram staining and culture (anaerobic and aerobic bacterial), cell count and differential, total protein level, pH, and glucose concentration. Interpretation of pleural fluid in children follows adult guidelines (see Chapters 66 and 67). Cultures for rare pathogens may be considered if the initial assessment is not diagnostic. Bronchoscopy with bronchoalveolar lavage may be useful in a severely ill child.

Patients should not receive rapid antigen testing for viruses unless the result would change management (eg, risk stratification in a young infant with fever, consideration of using antivirals in influenza). Although most pediatric patients with tuberculosis do not have pulmonary symptoms, skin testing for tuberculosis should be considered for patients with lobar pneumonia, pulmonary effusions, or hilar adenopathy, especially in immunocompromised children or children who have recently emigrated from less developed countries. Acid-fast bacilli are more likely to appear on an early morning gastric aspirate.[16] Sputum specimens generally are not helpful in a child younger than 8 years because of contamination by organisms of the upper respiratory tract. Bacterial cultures of upper respiratory secretions usually grow normal flora or organisms that reflect only colonization. Although transtracheal sampling and direct aspiration from the lung may permit a more precise diagnosis, the invasiveness of these tests limits their usefulness.

Types of Pneumonia

Bacterial Pneumonia

S. pneumoniae is one of the most frequently seen bacterial agents that causes pneumonia in children.[17] Children with immunodeficiency, chronic renal disease, functional or anatomic asplenia, and Native Americans are at increased risk for *S. pneumoniae* infection. *S. aureus* pneumonia, although less common, tends to cause a more severe pneumonia. Children with foreign body aspiration, immunosuppression, or skin infections may be at increased risk for *S. aureus* pneumonia. Progression of the disease is rapid, and empyema (90%), pneumatocele (50%) and pneumothorax (25%) are common complications (Fig. 169.2).

Before widespread immunization, *H. influenzae* type b was the second most common bacterial cause of pneumonia. However, its incidence has decreased by 90% since the onset of effective immunization.[9] *H. influenzae* was previously considered a disease of younger children, but most cases now occur in older children.[17] Although clinically indistinguishable from *S. pneumoniae* pneumonia, *H. influenzae* pneumonia historically had a higher incidence of associated pleural effusions (25%–75%) and bacteremia (75%–95%).

Although still uncommon, the incidence of group A streptococcal pneumonia has increased since the 1980s. Group A streptococcal pneumonia may occur sporadically and may be a complication of varicella. It is typically a severe illness with abrupt onset, rapid progression to toxicity, and high fatality rate (30%–60% fatality rate reported in a study of all ages).

In bacterial pneumonia beyond the neonatal period, fever is almost universal (often >39°C [102.2°F]). Patients may or may not have a cough and often appear relatively toxic, with tachypnea disproportionate to fever. Confined rales or wheezes and localized decreased or tubular breath sounds commonly occur in older children, whereas the physical examination in a younger child may be completely unrevealing.

The outcome of otherwise healthy children with pneumonia secondary to resistant pneumococcus currently does not differ significantly from the outcome of children with pneumonia secondary to penicillin-sensitive pneumococcus.[18] Pneumonia caused by *S. pneumoniae* may be complicated by empyema, pleural effusion, lung abscess, and/or necrotizing pneumonia. Children who appear well can be treated with oral antibiotics. High-dose amoxicillin tid is recommended for the initial outpatient treatment of suspected pneumococcal pneumonia in otherwise healthy children, with a maximum daily dose of 2 g/day[1] (Table 169.2). Uncomplicated bacterial pneumonia often has a rapid response to antibiotics; a stagnant or worsening clinical picture should prompt further investigation.

Viral Pneumonia

Viral pneumonia occurs more commonly in the winter and generally has a gradual onset during several days, often with associated cough, congestion, and low-grade fever.[19] Tachypnea may be the only physical finding; however, retractions, rales, and wheezing are common. Grunting, cyanosis, lethargy, dehydration, and apnea are seen in more severely affected children. The diagnosis of viral pneumonia is often made clinically. A chest radiograph is usually not needed for the diagnosis of a child with viral pneumonia who presents during the winter months with fever, cough, congestion, and wheezing. Rapid antigen testing for RSV is not indicated unless the result would change management (eg, risk stratification in a young infant with fever). A real-time influenza polymerase chain reaction (PCR) assay may be helpful when the use of antivirals is being considered. However, children at risk (eg, children <2 years or those with significant comorbid disease) should be treated with antivirals empirically.

Radiographic findings typically include hyperinflation and peribronchial thickening, with a diffuse increase in interstitial findings. Patchy areas of consolidation may be present, representing lobular atelectasis or alveolar pneumonia. Although lobar consolidation and small pleural effusions may occur in viral pneumonia, these findings are more consistent with a bacterial cause.

Most viral pneumonias resolve without specific therapy. Because of the possibility of bacterial superinfection and the difficulty in differentiating between bacterial and viral pneumonia, antibiotics should be considered for a more severely ill child. Potential complications include dehydration, local progression of the disease, bronchiolitis obliterans, and apnea (usually in the first 3 months of life).

TABLE 169.2

Antibiotics for Treatment of Pediatric Bacterial Pneumonia

AGE GROUP	MOST FREQUENT PATHOGENS	OUTPATIENT TREATMENT	INPATIENT TREATMENT
Neonate (<4 wk)	Group B streptococcus, *Escherichia coli*, other gram-negative bacilli		Ampicillin + aminoglycoside *or* Ampicillin + cefotaxime Avoid ceftriaxone.[a]
3 wk–3 mo	*Streptococcus pneumonia, Haemophilus influenzae, Chlamydia trachomatis* (if afebrile)	Erythromycin estolate *or* Azithromycin (limited data)	Ampicillin + cefotaxime or ceftriaxone Erythromycin estolate *or* Azithromycin (limited data)
	Bordetella pertussis (if afebrile and prolonged cough)	Azithromycin	Azithromycin
3 mo–4 yr	*Streptococcus pneumonia, Haemophilus influenzae,* group A streptococcus	Amoxicillin *or* Amoxicillin–clavulanic acid *or* Cefuroxime *or* Cefprozil *or* Cefdinir	Ampicillin *or* Ampicillin-sulbactam *or* Ceftriaxone *or* Cefotaxime *or* Clindamycin-vancomycin for coverage of MRSA[b] or in critically ill patients
	Mycoplasma pneumonia	Azithromycin—only for coverage of atypical pneumonias *or* Clarithomycin	Azithromycin—only for coverage of atypical pneumonias *or* Clarithomycin
	Bordetella pertussis (if afebrile and prolonged cough)	Azithromycin	Azithromycin
≥5 yr	*Mycoplasma pneumoniae, Chlamydophila pneumoniae*	Azithromycin—only for coverage of atypical pneumonias *or* Clarithomycin	Azithromycin—only for coverage of atypical pneumonias *or* Clarithomycin
	Streptococcus pneumonia, Haemophilus influenzae	Amoxicillin *or* Amoxicillin–clavulanic acid *or* Cefuroxime *or* Cefprozil *or* Cefdinir	Ampicillin *or* Ampicillin-sulbactam *or* Ceftriaxone *or* Cefotaxime *or* Clindamycin-vancomycin for coverage of MRSA or in critically ill patients
	Bordetella pertussis (if afebrile and prolonged cough)	Azithromycin	Azithromycin

[a]Ceftriaxone is not preferred in neonates due to risk of hyperbilirubinemia, particularly in premature infants.
[b]*MRSA,* Methicillin-resistant *Staphylococcus aureus.*

Mycoplasma Pneumonia

Mycoplasma pneumonia accounts for 10% to 20% of all pneumonias and was traditionally thought to occur most commonly in 5- to 18-year-olds; however, it may also play a significant role in younger children, although still rare in infants younger than 1 year.[5] The onset is classically gradual and insidious, but some patients may present with an abrupt onset of symptoms.[5] Prodromal symptoms include fever, headache, and malaise, followed several days later by a nonproductive hacking cough. Patients may present with a pertussis-like illness. Other symptoms of infection may include hoarseness, sore throat, and chest pain; coryza is unusual.

Children with mycoplasma pneumonia generally appear nontoxic. Patients may have rales; wheezing occurs less often. Pharyngitis, cervical lymphadenopathy, conjunctivitis, and otitis media may occur occasionally. Rash is present in 10% of patients and may be urticarial, erythema multiforme, maculopapular, or vesicular. The course may be complicated by pneumatocele, pleural effusion, pneumothorax, or bronchiectasis. *Mycoplasma,* typically thought to be a benign and self-limited infection, has been shown to play a significant role in the exacerbation of asthma and may cause chronic pulmonary structural abnormalities.[20] Physical findings are generally less impressive than the radiographic picture; involvement is usually unilateral and in the lower lobes. The radiographic findings are wide-ranging, however, and may show lobar consolidation, scattered segmental infiltrates, or interstitial disease. Pleural effusions may occur but are uncommon. The WBC count is usually normal.

Infection often is diagnosed clinically and treated empirically. Bedside cold agglutination is rarely used today because it is not accurate, particularly in patients younger than 12 years. Diagnosis may be confirmed with acute and convalescent antibody titers; however, patients may take 4 to 6 weeks to seroconvert, and some patients may fail to mount an immune response.[5] Culture is not routinely available; PCR diagnosis is available only from research laboratories.[5] Complications are varied but unusual and include hemolytic anemia, hemolytic uremic syndrome, myopericarditis,

neurologic disease (eg, meningoencephalitis, Guillain-Barré syndrome, transverse myelitis, cranial neuropathy), rhabdomyolysis, arthritis, and rash.

Chlamydial Pneumonia

C. trachomatis is a common sexually transmitted organism that causes cervical infection in 2% to 30% of pregnant women.[2] It is transmitted from the genital tract of infected mothers to their newborn infants, resulting in conjunctivitis in 22% to 44% and pneumonia in 5% to 20%.[2] An infant with pneumonia caused by *C. trachomatis* presents at 3 to 19 weeks of age after colonization at birth. The illness usually begins with nasal congestion followed by cough. In 50% of cases, conjunctivitis precedes the onset of respiratory symptoms. The infant is often afebrile and alert but tachypneic, with a repetitive staccato cough that may interfere with feeding or sleeping. It can resemble the paroxysms of pertussis and occasionally precipitates episodes of alarming respiratory distress. Mild retractions and diffuse inspiratory crepitant rales may be noted on chest examination; expiratory wheezing is usually absent or minimal. Middle ear abnormalities are present in 50% of cases.

The radiograph usually shows hyperinflation with bilateral and symmetric, diffuse, interstitial infiltrates (Fig. 169.3). Nucleic acid amplification tests have replaced culture and nonamplified detection methods (eg, direct fluorescent antibody tests) because of their higher sensitivity and specificity. Chlamydial pneumonia is often a mild illness, but may rarely be complicated by apnea and hypoxemia. Treatment with erythromycin may shorten the course; however, the disease tends to be protracted, with cough and tachypnea often requiring weeks to clear, despite antibiotics.

*Chlamydophila (*formerly *Chlamydia) pneumoniae* is a species of *Chlamydia* that is antigenically, genetically, and morphologically distinct from other *Chlamydia* species. *C. pneumoniae* infection is transmitted from person to person, may play a role in respiratory tract infections in infants and young children, and may cause mild illness or asymptomatic infection in children and adults. Like *Mycoplasma, C. pneumoniae* may play a greater role in pediatric pneumonia than was previously thought. It has been reported to cause sore throat, fever, headache, pertussis-like cough, pneumonia, and influenza-like illness.[7,8] Outbreaks have been reported in schools, daycare centers, military camps, adolescents, and families. Infection with *C. pneumoniae* can trigger acute episodes of wheezing in children with asthma. There are no reliable diagnostic tests to identify the organism.

Fig. 169.3. Radiograph showing chlamydial pneumonia in an infant. Note the symmetric interstitial infiltrates. (Courtesy Dr. Michael Diament.)

Aspiration Pneumonia

Aspiration pneumonia may be due to mechanical, chemical, or bacterial causes. Bacterial aspiration occurs in children with anatomic abnormalities and central nervous system disturbances that impair normal swallowing or protective airway reflexes. Pulmonary damage results from chemical (eg, stomach acid) and bacterial (eg, gastrointestinal and upper respiratory organisms) insults. Within several hours of the aspiration, the child may have the onset of cough, tachypnea, and fever. Physical examination commonly reveals rales and wheezing with cyanosis as the disease progresses. Radiographic findings include localized (right middle lobe, right lower lobe) and diffuse, often bilateral, infiltrates.

Pneumonia in an Immunocompromised Host

Children with chronic disease and congenital, acquired, and iatrogenic immunodeficiencies are susceptible to the aforementioned respiratory pathogens and to a multitude of opportunistic organisms, including *P. jiroveci,* CMV, and fungi. Presenting symptoms may be similar to those in normal hosts; however, the course tends to be more rapid, severe, and fulminant. While awaiting organism identification and the results of culture, patients should be hospitalized for monitoring, supportive therapy, and treatment with intravenous antibiotics active against a broad spectrum of organisms. A tissue sample for diagnosis of potentially treatable organisms may need to be obtained if the patient fails to improve after initial therapy.

Complications

Several complications of pneumonia result from local and systemic effects of the infection. Pleural effusion or empyema usually accumulates with bacterial pathogens (notably *S. pneumoniae, H. influenzae,* and *S. aureus*) but are occasionally associated with mycoplasma, viral, and tuberculous pneumonia. Similarly, lung abscess, pneumatocele, and pneumothorax are local complications primarily seen with bacterial disease, particularly with *S. aureus*. Extensive pulmonary involvement of any cause may lead occasionally to hypoxia and progressive respiratory failure, with multiple organ failure. Apnea without other symptoms is usually seen in viral, chlamydial, and pertussis infections in infants younger than 3 months. The most common systemic complication of pneumonia is dehydration. Additional infectious foci may develop from concomitant bacteremia (eg, meningitis, epiglottitis, pericarditis, septic arthritis, soft tissue infections). Viral and bacterial pneumonia are rarely associated with meningitis, encephalitis, arthritis, rhabdomyolysis, and hemolytic uremic syndrome.

Management and Disposition

Infants Younger Than 2 Months

Treatment of pneumonia in a pediatric patient consists of appropriate antimicrobial use and supportive therapy (see Table 169.2). Because of the difficulty in identifying a causative agent, antibiotic choice is generally empirical. The three most important factors in directing management are the patient's age, likely pathogen, and degree of illness. An infant younger than 2 months with pneumonia should usually be admitted to the hospital. This age group is immunologically immature, and signs of sepsis may be subtle. Blood, urine, and cerebrospinal fluid cultures generally are indicated before the initiation of antibiotics. In infants younger than 1 month, ampicillin plus an aminoglycoside or cefotaxime, particularly in premature infants, would be appropriate choices; ampicillin and a third-generation cephalosporin should be used for infants 1 to 2 months of age. If *C. trachomatis* or *B. pertussis*

is suspected, the infant should also be treated with erythromycin, azithromycin, or trimethoprim-sulfamethoxazole. Given the association of erythromycin with infantile hypertrophic pyloric stenosis, azithromycin may be the most appropriate choice.

Infants 2 to 3 Months of Age

Blood and urine cultures should be obtained for infants 2 to 3 months of age. The decision to perform a lumbar puncture depends on clinical suspicion of central nervous system infection. Ampicillin and a third-generation cephalosporin should be given for an infant 2 to 3 months old. If *C. trachomatis* or *B. pertussis* is suspected, the infant also should be treated with erythromycin, azithromycin, or trimethoprim-sulfamethoxazole. Supportive therapy in this age group consists of fever control and hydration. All infants should be monitored with continuous pulse oximetry for signs of needed respiratory support; apnea and respiratory failure may be precipitous.

Infants and Children Older Than 3 Months

In an older child, pneumonia should be categorized into likely bacterial, viral, or mycoplasmal. The emergency clinician should base the presumptive causative diagnosis on clinical and radiographic findings. A toxic child with high fever and lobar consolidation is likely to have a bacterial process, whereas a child with a disease of gradual onset, low-grade fever, and interstitial infiltrate with air trapping is more likely to have a viral process.

A well-appearing infant or preschool-age child with isolated pneumonia may be treated with outpatient oral antibiotics. In an infant beyond the neonatal period or a preschool-age child, high-dose amoxicillin (90 mg/kg/day, divided tid) is the first-line agent and will treat intermediate susceptible *S. pneumonia*. Amoxicillin–clavulanic acid (90 mg/kg/day of the amoxicillin component, divided tid) is the second-line agent and includes some gram-negative and methicillin-sensitive *S. aureus* coverage. Oral cephalosporins are relatively poorly absorbed and are highly protein-bound, resulting in inferior pharmacokinetics as compared to amoxicillin; these should be reserved for penicillin allergic patients only. Cefpodoxime 10 mg/kg/day divided bid, cefprozil (30 mg/kg/day, divided bid), or cefdinir (14 mg/kg/day, divided bid) are other options. Azithromycin should not be used to treat *S. pneumoniae* because 40% of infections are predicted to be resistant, but it is appropriate therapy for presumed atypical pneumonias in this age group. Azithromycin (10 mg/kg on day 1, followed by 5 mg/kg once daily on days 2–5) is the antibiotic of choice in a school-age child or adolescent, in whom *M. pneumoniae* and *C. pneumoniae* are more common.[1] Every child with bacterial pneumonia treated as an outpatient should be reevaluated within 24 to 48 hours. In patients who are febrile, dehydrated, or not clinically improved, inpatient hospitalization for parenteral antibiotic therapy should be considered. A repeat radiograph to look for progression of disease or development of a pleural effusion should also be considered.

Indications for hospitalization at the time of diagnosis include toxic appearance, vomiting or dehydration, respiratory compromise (eg, distress, hypoxia, inadequate ventilation), multilobar disease, pleural effusions, impaired immune function, and unstable social environments (Fig. 169.4). Strong consideration should be given to hospitalization of children younger than 6 months because they are more prone to complications of bacterial pneumonia than older children. Supportive therapy for the inpatient should include maintenance of hydration, fever control, supplemental oxygen, ventilatory assistance, and pleural fluid drainage, as indicated. Parenteral antibiotic therapy should be administered until clinical improvement occurs.

Children with suspected bacterial pneumonia that is serious enough to warrant hospitalization should routinely be treated with parenteral antibiotics to provide reliable blood and tissue concentrations. Parenteral antibiotics for initial therapy should be considered for hospitalized patients with moderate to severe illness or those with vomiting, suspected decreased absorption, or systemic illness concerning for sepsis. For patients with mild illness, initial therapy with oral antibiotics may be considered. First-line parenteral therapy is ampicillin (150–200 mg/kg/day, q 6 hours). Ceftriaxone (100 mg/kg/day, every 12–24 hours) or cefotaxime (150 mg/kg/day q 8 hours) are second-line agents. Addition of azithromycin (10 mg/kg on day 1, followed by 5 mg/kg once daily on days 2–5) should be considered if *M. pneumoniae* is a possible causative agent. Vancomycin (40–60 mg/kg/day, divided every 6–8 hours) or clindamycin (40 mg/kg/day, divided every 6–8 hours) should be added if methicillin-resistant *S. aureus* is suspected.[1]

Fig. 169.4. Radiograph showing multilobar pneumonia in a child with respiratory distress. (Courtesy Dr. Marianne Gausche-Hill.)

Children with neurologic or anatomic abnormalities who aspirate oral or gastric contents are susceptible to pneumonia, predominantly from anaerobes. Penicillin and clindamycin are appropriate first-line antibiotic choices. In seriously ill patients or patients not responding, agents such as metronidazole and cefoxitin may be more useful. Nosocomial infections should be treated with antibiotics also active against aerobes and gram-negative bacilli. Children with significant aspiration should be admitted to the hospital, and supportive therapy should include hydration, supplemental oxygen, and oropharyngeal suctioning.

Long-term management of a child with pneumonia should include a clinical reevaluation 2 to 3 weeks after diagnosis. If the child had a prompt response to therapy and is well at the follow-up evaluation, a repeat radiograph is unnecessary. If the child has had a complicated course (eg, pleural effusion), residual symptoms, or if the illness is not the child's first episode of pneumonia, a chest radiograph should be obtained to ensure resolution. The follow-up radiograph should be performed 6 to 8 weeks after diagnosis.

The age of the child and clinical presentation often suggest the causative agent. The patterns of causative organisms have been changing. The spectrum of antimicrobial sensitivities also has changed, particularly with the emergence of penicillin-resistant *S. pneumoniae*.

OTHER RESPIRATORY EMERGENCIES

Pertussis

Pertussis, or whooping cough, is a respiratory tract infection usually seen in infants younger than 6 months (≈40% of cases are in children <6 months; 70% of cases are in children <5

years). The incidence of pertussis increased in the 1980s and 1990s, especially in adolescents and adults, despite high immunization rates.

The disease is characterized by three clinical stages—catarrhal stage, paroxysmal stage, and convalescent stage. Pertussis begins with mild upper respiratory tract symptoms and cough; this catarrhal stage usually lasts 1 to 2 weeks. The disease progresses to severe paroxysms of a staccato cough, followed by posttussive emesis, and may be accompanied by periods of cyanosis and apnea in infants younger than 6 months. The classic whoop is rare, occurring in only 6% of patients and generally seen in children older than 2 to 3 years. Fever is often absent, and the examination findings are remarkably normal between paroxysms. The paroxysmal stage lasts 2 to 4 weeks and is followed by a convalescent stage, during which symptoms gradually wane. The duration of the illness in more complicated cases may be 6 to 10 weeks. Immunization is only 80% effective in providing immunity after three doses, making pertussis possible in immunized infants. The WBC count is usually elevated, exceeding 15,000/mm^3 and occasionally 40,000/mm^3, often with a marked lymphocytosis. The chest radiograph may show a shaggy, right-sided heart border or have clear lung fields. *B. pertussis* is a fastidious organism, making culture difficult. The organism is most easily recovered in the catarrhal or early paroxysmal stages. Cultures may be negative during the first week or after the fourth week of illness in immunized patients or in patients treated with antibiotics.[4] The PCR assay has been increasingly used for the detection of *B. pertussis* because of its high sensitivity and more rapid turnaround time than culture.

Pertussis is a particularly severe disease in the first year of life; complications are common and include apneic episodes, seizures, secondary bacterial pneumonia, encephalopathy, and death. Pertussis has been increasing in incidence among immunized children and young adults who have waning immunity. Adults are believed to be the reservoir for disease. The illness in these patients does not follow the classic stages as described here. These patients have a mild but prolonged course. A dry cough is the predominant symptom, often lasting 3 weeks or more.

Because of the risk of apnea, all children younger than 6 months with presumed pertussis should be observed in the hospital for monitoring and supportive care and treated with erythromycin, azithromycin, or trimethoprim-sulfamethoxazole. Given the association of erythromycin with infantile hypertrophic pyloric stenosis, azithromycin may be the most appropriate choice. Antimicrobials have no effect on disease progression after the beginning of the paroxysmal stage but limit the spread of organisms. Vaccination of health care workers and the adult population with Tdap (tetanus, diphtheria, pertussis) has been shown to decrease rates of pertussis in infants.

Cystic Fibrosis

CF is an autosomal recessive disease caused by a mutation in the CF transmembrane conductance regulator (*CTFR*) gene. In whites, approximately 1 in 25 is a carrier, and the disease has an incidence of 1 in 2500 births.[21] The disease also is present (in decreasing incidence) in Hispanics, Native Americans, African Americans, and Asians. Progressive lung disease and infection account for most of the morbidity and nearly all the mortality in those with CF. Defects in chloride transport across the airway epithelium result in reduced ciliary clearance of thickened mucus, decreased antimicrobial effect of the airway surface, increased bacterial adherence, and innate secretion of inflammatory cytokines. All these factors result in a unique sensitivity to bacterial infection of the airway.

Chest radiographic findings of CF include emphysema, peribronchial thickening, bronchiectasis, and focal infiltration, which may be linear or nodular (Fig. 169.5). Crucial to the effective treatment of pulmonary infections in CF patients is identification of the pathogens involved, usually through sputum culture. Early childhood pneumonias in patients with CF are predominantly caused by *S. aureus* and *H. influenzae*.

With the emergence of methicillin-resistant *S. aureus* (MRSA), careful attention should be paid to antibiotic coverage. Patients receiving antistaphylococcal prophylaxis may be at increased risk for pseudomonal infections. By 18 years of age, 80% of patients

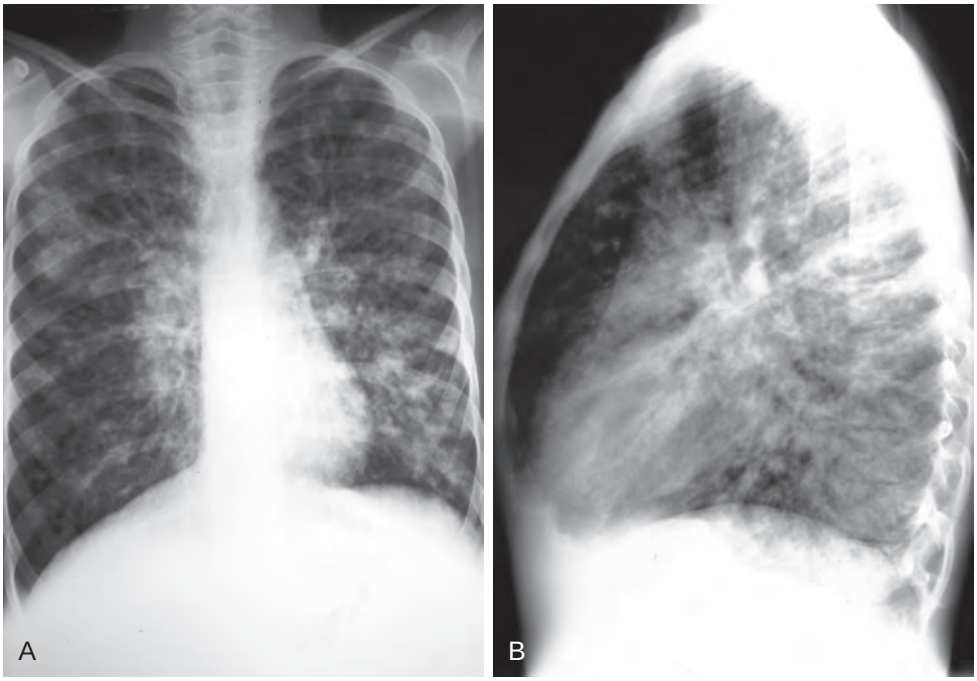

Fig. 169.5. Posteroanterior (**A**) and lateral (**B**) radiographs of a teenager with cystic fibrosis. Note emphysema and nodular infiltrates. (Courtesy Dr. Michael Diament.)

are permanently colonized with *P. aeruginosa*. Acute infective exacerbations generally are managed by oral and intravenous antimicrobial drugs, typically a penicillin (eg, ticarcillin, piperacillin) or ceftazidime combined with an aminoglycoside for purposes of synergy.[18] If a patient's previous sputum culture results are available, antibiotic coverage for the last known bacterial pathogen should be used. Resistant strains may benefit from imipenem or meropenem. Patients routinely are hospitalized for 10 to 14 days for the course of therapy. There has been emerging evidence that CF patients also are at increased risk for hospitalization with nonbacterial pathogens.[18]

Burkholderia cepacia, a significant pathogen in CF patients, has been associated with an accelerated decline in clinical status and increased mortality. In general, antimicrobial coverage is similar to that for *Pseudomonas*. Resistance is common, however, and the existence of differing colonization and resistance patterns of patients with CF necessitates respiratory isolation from other susceptible individuals.

Clearance of thick mucoid secretions is vital for treatment. Patients may respond favorably to bronchodilator therapy and to mucolytics, such as inhaled *N*-acetylcysteine, in the acute setting. Chest physiotherapy often is provided by a high-frequency oscillator device. A flutter valve or positive expiratory pressure mask also may be of assistance for improved mucoid clearance. Short-term control of inflammation may be obtained by inhaled corticosteroids.[22,23]

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is defined as the need for supplemental oxygen 28 days postnatally. BPD is a common cause of diffuse lung disease in infants.[24] Approximately 40% of children with a birth weight less than 1000 g will develop BPD.[25] The severity of disease is related to several factors, including degree of prematurity, use of peripartum steroids, damage incurred by ventilation in the neonatal period, and nutritional status.[26] Infants with BPD have greatly increased rates of hospitalization because of respiratory illness in the first year of life, approaching 65% in infants born weighing less than 1000 g.[25]

Immunizations are vital to the prevention of pneumonia in patients with BPD. All infants 6 to 23 months old should receive the influenza vaccine during the appropriate season. The 13-valent pneumococcal vaccine and *H. influenzae* type b vaccine are especially vital for the prevention of bacterial pneumonia. In addition, monthly prophylaxis against RSV is administered to carefully selected patients with the monoclonal immunoglobulin palivizumab, which reduces the incidence of RSV disease and risk of subsequent hospitalization.

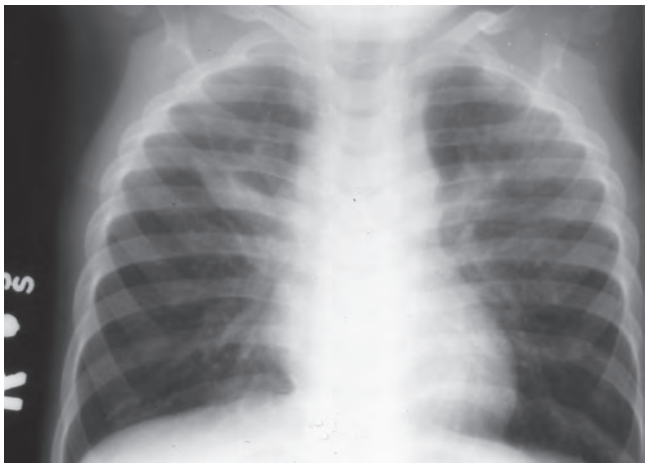

Fig. 169.6. Radiograph of a child with bronchopulmonary dysplasia showing findings of chronic lung disease and hyperinflation. (Courtesy Dr. Michael Diament.)

Patients with BPD have increased airway resistance, decreased lung compliance, and obstructive lung disease. Pneumonia in patients with BPD may be complicated by a reactive airway component. If complicated by pneumonia, radiographs show marked hyperinflation and infiltrates (Fig. 169.6). Inhaled bronchodilators may be efficacious, although these medications may worsen air exchange in patients with concomitant airway malacia. Hypoxia and hypercarbia are common, despite an increased respiratory effort. Patients with severe BPD may be receiving long-term diuretic therapy to improve lung mechanics; care should be taken not to confuse pneumonia with cor pulmonale, which can occur in younger infants with chronic supplemental oxygen requirements. Premature birth is a risk factor for reduced exercise capacity extending into adulthood.[27]

KEY CONCEPTS

- Determining the causative agent of pneumonia by clinical presentation and radiographic findings is not reliable; empirical treatment is based on likely pathogens.
- Infants and younger children with pneumonia may have subtle or nonspecific symptoms and signs on presentation.
- First-line therapy for the treatment of bacterial pneumonia in children is amoxicillin as an outpatient and ampicillin as an inpatient.
- Pertussis should be considered in a young infant with a staccato cough or episodes of cyanosis.
- *M. pneumoniae* and *C. pneumoniae* may play a role in pneumonia in a younger child.
- In patients with CF, defects in chloride transport across the airway epithelium result in reduced ciliary clearance of thickened mucus, which results in an increased likelihood for pneumonia, especially that caused by *P. aeruginosa*.
- CF may respond favorably to bronchodilator therapy and mucolytics, such as inhaled *N*-acetylcysteine.
- Patients with BPD have increased airway resistance, decreased lung compliance, and obstructive lung disease; reactive airway disease and pneumonia are common in these patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 169: QUESTIONS & ANSWERS

169.1. A 5-month-old boy presents with a cough. His parents report that for the past several weeks he has had mild respiratory tract symptoms and cough; however, during the past day, he has developed a severe paroxysm of staccato cough followed by posttussive emesis. What is the most appropriate antibiotic choice for this patient?

A. Amoxicillin
B. Ampicillin
C. Ceftriaxone
D. Erythromycin
E. Trimethoprim-sulfamethoxazole

Answer: D. This patient likely has pneumonia caused by *Bordetella pertussis*. All children younger than 6 months with presumed pertussis should be observed in the hospital for monitoring and supportive care and treated with erythromycin. Other macrolides and trimethoprim-sulfamethoxazole are other possible alternatives. Amoxicillin and ceftriaxone are used to treat other types of pneumonia.

169.2. Which of the following findings is necessary to make the diagnosis of pneumonia in children requiring admission to the hospital?

A. Abnormal chest radiograph showing pulmonary infiltrates
B. Fever and decreased breath sounds unilaterally
C. Fever and rales
D. Rales and tachypnea

Answer: A. A chest radiograph showing pulmonary infiltrates is necessary to make the diagnosis of pneumonia in children who are ill. The World Health Organization does allow for clinical signs and symptoms, such as tachypnea, for the diagnosis of pneumonia in resource-poor areas. However, in the United States with easy access to radiological services, children should have an abnormal radiograph showing pulmonary infiltrates prior to hospitalization for the diagnosis of pneumonia. Infectious Disease Society of America guidelines allow for the treatment of clinical pneumonia if community-acquired pneumonia (CAP) is strongly suspected and the child does not have respiratory distress.

169.3. Which of the following statements best describes the epidemiology of pneumonia in children?

A. *Bordetella pertussis* is the most common cause in infants.
B. *Haemophilus influenzae* type b is still an important pathogen.
C. *Listeria monocytogenes* may cause illness in children younger than the age of 5 years.
D. Viral agents are the most common cause of pneumonia in children overall.

Answer: D. Viral agents are the most common cause of pneumonia in children. Bacteria predominate in neonates but are less common causative agents in toddlers and older children. Although L. monocytogenes may cause pneumonia in infants, it is unusual after 3 months of age. H. influenzae type B has decreased by 90% since the onset of immunization of infants and young children.

169.4. What is the most common viral agent causing pneumonia in infants younger than 1 year?

A. Adenovirus
B. Enterovirus
C. Epstein-Barr virus
D. Respiratory syncytial virus (RSV)

Answer: D. RSV and parainfluenza are the most common viral agents in infants younger than 1 year. Viruses that may be

responsible for the other agents may also cause viral pneumonia but are not as common as RSV.

169.5. Which of the following conditions may predispose children to a bacterial pneumonia?
- **A.** All of these
- **B.** Cystic fibrosis
- **C.** Foreign body aspiration
- **D.** Immunosuppression

Answer: A. All these conditions predispose children to severe pneumonia—foreign body aspiration because of obstruction and resulting inflammation with secondary infection, immunosuppression with unusual organisms such as Pseudomonas, and cystic fibrosis, for the inability to clear mucus in the lung itself, resulting in increased risk of infection.

169.6. A 2-month-old presents with a persistent cough for 2 weeks and intermittent episodes of posttussive vomiting. Which of the following tests is the most accurate to establish a diagnosis?
- **A.** Blood culture
- **B.** Direct fluorescent antibody
- **C.** Polymerase chain reaction assay of nasal aspirate
- **D.** Sputum culture

Answer: C. This clinical scenario depicts a young infant with possible pertussis. Although culture may be highly specific, it often yields false-negative results. The most accurate test at this time is the polymerase chain reaction. Blood cultures are unreliable in cases of pertussis and are only positive in less than 10% of children with bacterial pneumonia overall.

169.7. Which of the following strategies has been shown to be most effective in decreasing the rates of pertussis in infants?
- **A.** Postexposure prophylaxis with a macrolide for family members of index cases
- **B.** Vaccination of all infants at 2 months of age
- **C.** Vaccination of health care workers in the adult population
- **D.** Vaccination of school-age children

Answer: C. Vaccination of health care workers in the adult population with Tdap (tetanus, diphtheria, pertussis) has been shown to decrease rates of pertussis in children. All other strategies have been less effective.

169.8. A 2-year-old presents with fever, cough and rales. Chest radiograph reveals right middle lobe pneumonia. Which of the following antibiotics would be recommended for outpatient treatment for this toddler who is not penicillin allergic?
- **A.** Amoxicillin
- **B.** Azithromycin
- **C.** Ceftriaxone
- **D.** Cephalexin

Answer: A. High-dose amoxicillin, 90 mg/kg/day, divided tid is the treatment of choice for children with pneumonia younger than 5 years. Once the child reaches school age, then macrolides (eg, azithromycin) are suggested as empirical therapy because of the increased risk of *Mycoplasma pneumoniae* infection.

CHAPTER 170

Cardiac Disorders

Timothy Horeczko | Alson S. Inaba

PRINCIPLES

Pediatric cardiac disease traditionally has been divided into congenital and acquired disorders, with a further subdivision of the congenital heart disorders into cyanotic and acyanotic lesions. From a purely clinical standpoint, however, children with cardiac disorders present to the emergency department (ED) in one of two scenarios. In the first scenario, the child has signs and symptoms that may represent an exacerbation or complication of an already known underlying cardiac disorder. In cases with a known underlying cardiac disorder, early consultation with the child's cardiologist along with comparisons of the child's previous and most recent diagnostic cardiac studies, such as chest radiographs, electrocardiograms (ECGs), and echocardiograms are very useful in the evaluation and management phases.

The second scenario represents more of a challenge to the emergency clinician: the child with an undiagnosed congenital or acquired cardiac disorder who presents with concerning signs and symptoms (Box 170.1). This chapter focuses on some of the more common and life-threatening cardiac disorders in infants and children who present to the ED, with an emphasis on rapid evaluation, stabilization, and management of these disorders.

Fetal and Neonatal Circulation

Some key features of fetal circulation that differ from that of the child are the presence of the ductus venosus, the ductus arteriosus, and a patent foramen ovale. During fetal development, blood oxygenated by the placenta flows to the fetus through the umbilical vein, bypasses the fetal liver through the ductus venosus, and returns to the fetal heart through the inferior vena cava. Blood returning from the inferior vena cava then enters the right atrium and is preferentially shunted to the left atrium through the patent foramen ovale (Fig. 170.1). Blood in the left atrium is then pumped from the left ventricle to the aorta. The oxygenated blood ejected through the ascending aorta is preferentially directed to the fetal coronary and cerebral circulations.

Deoxygenated blood returns from the superior vena cava to the right atrium and ventricle to be pumped into the pulmonary artery. Fetal pulmonary vascular resistance (PVR), however, is higher than fetal systemic vascular resistance (SVR); this forces deoxygenated blood to mostly bypass the fetal lungs (see Fig. 170.1). This poorly oxygenated blood enters the aorta through the patent ductus arteriosus and mixes with the well-oxygenated blood in the descending aorta. The mixed blood in the descending aorta then returns to the placenta for oxygenation through the two umbilical arteries.

Once the infant is delivered and the umbilical cord is cut, expansion and aeration of the lungs cause a decrease in PVR, which enhances pulmonary blood flow. Increased global oxygenation causes a physiologic closure of the umbilical arteries, umbilical vein, ductus venosus, and ductus arteriosus. Increasing pulmonary blood flow to the infant's left atrium promotes closure of the foramen ovale. Complete anatomic closure of the foramen ovale does not occur until about 3 months of age. Although the ductus arteriosus functionally closes at about 10 to 15 hours of life, complete anatomic closure does not occur until 2 to 3 weeks of life.

In the absence of any congenital cardiac defects, these transitional circulatory changes pose no physiologic problems to the infant. However, closure of the ductus arteriosus can cause life-threatening complications in neonates, with specific congenital cardiac defects, who are dependent on the patency of the ductus arteriosus for survival.

Pathophysiology of Cardiovascular Compensatory Responses

There are two fundamental and clinically useful physiologic formulas to keep in mind during the clinical assessment and management of cardiac disorders:

$$\text{Cardiac Output} = \text{Stroke Volume} \times \text{Heart Rate}$$

$$\text{Blood Pressure} = \text{Cardiac Output} \times \text{SVR}$$

The young myocardium is inefficient and unable to increase its contractility in response to demand.[1] When more cardiac output is needed, infants and children respond with an increase in heart rate. Therefore, bradycardia in infants and young children is an ominous sign that connotes a severely compromised cardiac output. Children develop the adult capacity to increase their stroke volume to improve overall cardiac output by 8 to 10 years of age.[2]

On the basis of the first physiologic formula, as stroke volume decreases, a compensatory increase in the heart rate will be necessary to preserve a normal cardiac output. A decrease in stroke volume can be caused by a weak "pump," decreased volume in the circulation, or both. The most common cause of decreased stroke volume in children is hypovolemia from dehydration. Other causes of decreased stroke volume in children are listed in Box 170.2.

Tachycardia is the first compensatory cardiovascular response when stroke volume is decreased. If tachycardia alone is not enough to maintain a normal cardiac output, the next compensatory physiologic mechanism to preserve perfusion is an increase in the SVR. This change in SVR is exhibited as an increase in the diastolic blood pressure, which in turn accounts for a narrowed pulse pressure. The clinical examination findings of the extremities of a child with an increased SVR include pallor, mottling, cool skin, delayed capillary refill time (>2 seconds), and weak or thready distal pulses.

Pathophysiology of Cyanosis

Cyanosis is a clinical sign caused by the presence of deoxygenated blood in the capillary beds, most readily observed in the mucous membranes, conjunctiva, nail beds, and skin. For cyanosis to be evident clinically, there must be at least 4 to 5 g/dL of deoxyhemoglobin admixed in the blood; this correlates with an oxygen

BOX 170.1

Common Presenting Signs and Symptoms of Cardiac Disorders in Infants and Children

GENERAL
Fussiness
Lethargy
Poor feeding (with or without associated diaphoresis)
Poor growth

RESPIRATORY
Respiratory distress
Wheezing
Apnea

CARDIOVASCULAR
Tachycardia
Shock
Paleness
Mottling
Cyanosis
Palpitations
Chest pain
Syncope
Various dysrhythmias

BOX 170.2

Causes of Decreased Stroke Volume in Infants and Children

Hypovolemia (most commonly secondary to dehydration)
Congestive heart failure (CHF; acquired or secondary to underlying congenital cardiac defects)
Myocarditis
Hypertrophic cardiomyopathy with decreased diastolic filling
Dilated cardiomyopathy with decreased systolic ejection
Pericarditis or pericardial effusion with cardiac tamponade
Tachydysrhythmias with decreased diastolic filling times

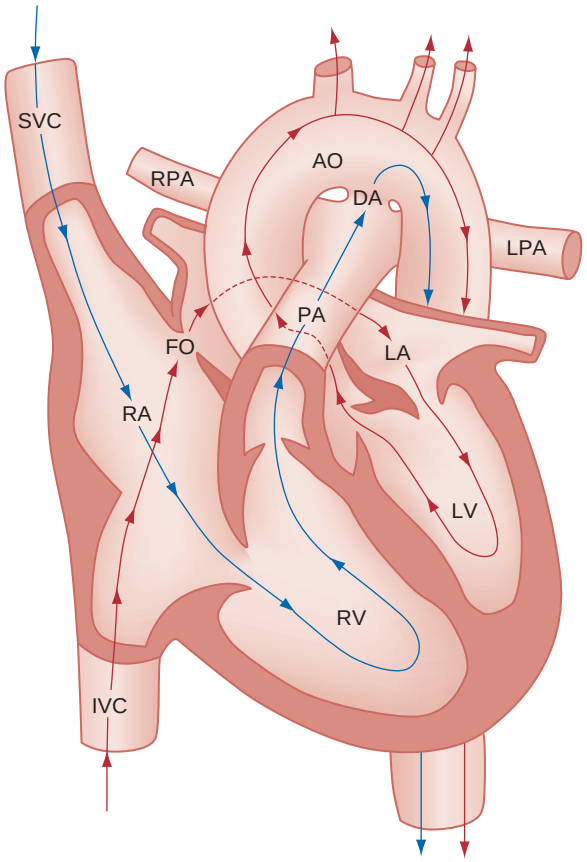

Fig. 170.1. Normal intracardiac fetal circulation: Physiologic shunting through the patent foramen ovale *(FO)* and the patent ductus arteriosus *(DA).* Oxygenated blood from the placenta *(red arrows)* reaches the right atrium *(RA)* through the inferior vena cava *(IVC).* This well-oxygenated blood is preferentially shunted from the RA across to the left atrium *(LA)* through the FO and is then ejected out the left ventricle *(LV)* to the ascending aorta *(AO).* Deoxygenated blood *(blue arrows)* returning from the superior vena cava *(SVC)* preferentially travels from the RA into the right ventricle *(RV)* and then out through the main pulmonary artery *(PA).* Because of the high pulmonary vascular resistance (PVR) in the fetal lungs, this deoxygenated blood bypasses lungs and enters the descending aorta through the DA. Thus the areas of the fetal body that are perfused by arteries proximal to the DA receive well-oxygenated blood, whereas those areas of the body that are perfused by arteries distal to the DA receive blood with a mixed oxygenation. *LPA,* Left pulmonary artery; *RPA,* right pulmonary artery.

saturation of approximately 80% to 85%.[3] That is, children with anemia—even if hypoxic—may not show overt signs of cyanosis (ie, the critical mass of deoxygenated hemoglobin is not met to manifest cyanosis clinically). Central cyanosis results from a decrease in pulmonary ventilation and oxygenation, a decrease in pulmonary perfusion, the shunting of deoxygenated blood directly into the systemic circulation, or the presence of abnormal hemoglobin. Cyanosis in the neonate may be due to a variety of cardiac, pulmonary, hematologic, or toxic causes. Cardiac causes of cyanosis include congenital lesions with right-to-left shunts and cardiac lesions with decreased or increased pulmonary blood flow. Common pulmonary causes of cyanosis include bronchiolitis, pneumonia, and pulmonary edema. Methemoglobinemia is one of the hematologic causes of cyanosis.

Clinical Features of Cyanosis

The region of the body that is cyanotic can provide important clinical clues to the cause of the cyanosis. Central cyanosis involves the lips, tongue, and mucous membranes, whereas peripheral cyanosis (acrocyanosis) involves the hands and feet. Acrocyanosis is a common finding in neonates caused by cold stress and peripheral vasoconstriction. Central cyanosis reflects a pathologic origin and is an ominous sign. Infants with cyanosis secondary to a congenital heart defect may not exhibit as much respiratory distress compared with the infant with cyanosis due to a pulmonary cause. Thus, a cardiac cause of central cyanosis should be suspected in a child who appears "comfortably blue." Another important clinical clue to the cause of central cyanosis is that cyanosis of cardiac origin usually worsens with crying, whereas cyanosis due to a pulmonary cause may improve when the infant cries.[4,5] Cyanotic congenital heart defects with right-to-left shunting will demonstrate a minimal improvement with supplemental oxygen, whereas cyanosis of a purely pulmonary origin typically exhibits a significant improvement with supplemental oxygen (Table 170.1).

CLINICAL FEATURES AND DIAGNOSTIC TESTING: THE CARDIAC EVALUATION

The key elements that should be elicited in the history of a child with a known underlying cardiac disorder are listed in Box 170.3.

TABLE 170.1

Clinical Clues to Help Distinguish Between Cardiac and Pulmonary Causes of Central Cyanosis*

	CARDIAC ETIOLOGY	PULMONARY ETIOLOGY
Respiratory status	May be "comfortably blue"	Respiratory distress
Response to crying	Worsening cyanosis	Improved cyanosis
Response to oxygen	Minimal or no improvement	Improvement with oxygen

*Cyanosis due to severe pulmonary disease (eg, severe pneumonia, tension pneumothorax, acute chest syndrome of sickle cell disease) may not show significant improvement with supplemental oxygen, but these children will also typically exhibit severe respiratory distress along with clinical cyanosis.

BOX 170.3

Key Elements to Elicit in the History of a Child With a Known Cardiac Disorder

CARDIAC DIAGNOSIS

Congenital or acquired disorder?
Any episodes of previous decompensation? (If so, are the current signs and symptoms similar to or different from those previous episodes?)

OXYGEN ISSUES

Currently receiving home oxygen supplementation (continuous or only during feedings and sleep)?
Baseline oxygen saturation (room air or while receiving home oxygen)?
Any recent need for increasing the amount of supplemental oxygen?

MEDICATIONS

Names and dosages of all current medications (cardiac and noncardiac medications)?
Were any of these cardiac medications stopped recently (by the cardiologist or parental noncompliance)?
Any recent increases in the cardiac medications (reasons for the increase, previous dosage versus the current dosage, and the date this dosage was increased)?
Any new cardiac medications added recently and the reason for these additions?
Recent digoxin level if the patient is receiving daily digoxin therapy?

RESULTS OF MOST RECENT STUDIES (CHEST RADIOGRAPH, ELECTROCARDIOGRAM, ECHOCARDIOGRAM, AND CARDIAC CATHETERIZATION)

When were the last studies performed, and what were the results?
Why were those studies performed (routine follow-up studies or obtained because of decompensation from baseline, or a planned evaluation for an upcoming surgical procedure)?

SURGICAL PROCEDURES

Previous procedures and complications?
Any future planned procedures?

Early consultation with the child's cardiologist or cardiac surgeon is extremely useful.

In addition to a well-focused history and physical examination, a chest radiograph and an ECG should be obtained for any child with a known or suspected cardiac disorder. Other useful ancillary studies include an arterial blood gas analysis, hemoglobin and hematocrit levels, digoxin levels in those patients receiving daily digoxin, serum electrolyte values in those patients receiving daily diuretic therapy, and the 100% oxygen (hyperoxia) challenge.

History

Certain maternal medical conditions are associated with a higher incidence of cardiac disorders, such as congenital heart blocks from maternal systemic lupus erythematosus and cardiomyopathy in infants of diabetic mothers.

Infants with an underlying congenital heart disorder may exhibit diaphoresis during feeds and poor weight gain secondary to congestive heart failure (CHF). The cause of the infant's hypoxia—cardiac or pulmonary—may be ascertained by the age at onset and the events surrounding a change in color. For example, an infant who sweats during feeding may exhibit a splanchnic steal from anomalous coronary arteries, causing transient ischemia, pain, color change, and diaphoresis that resolve after eating.[1] A child with an undiagnosed congenital heart defect resulting in CHF and pulmonary edema may take longer to feed, frequently pausing to catch his or her breath, with subsequent poor weight gain and gradually increased work of breathing. Respiratory tract infections are common during childhood and may cause an acute deterioration in a child with an underlying cardiac disorder. In turn, children with congenital heart disease (CHD) with large left-to-right shunts and increased pulmonary blood flow tend to have a higher incidence of lower respiratory tract infections. Acute respiratory distress in these patients may be from a combination of pulmonary and cardiac factors (eg, CHF).

Chest Pain

Common causes of pediatric chest pain are musculoskeletal chest wall pain, costochondritis, asthma exacerbation, pneumonia, pleurisy, gastritis, and gastroesophageal reflux. An often underdiagnosed cause of acute chest pain in the child or adolescent is precordial catch syndrome (also known as *Texidor's twinge*). The pain is sharp, non-radiating, and located in the left periapical area of the chest wall; it occurs suddenly, is often worsened by inspiration, and is not associated with dyspnea. The child may report that the pain "took my breath away" or that "I was afraid to move"; the pain typically resolves within a few minutes and is not associated with dysrhythmias or other sequelae. The pathophysiologic mechanism of precordial catch syndrome is unknown; the pain may originate from the parietal pleura or costal cartilage.[6] Patients often have some relief by taking a slow, deep breath, stretching, or massaging the chest wall. If an ECG and a chest radiograph are performed, findings are typically normal. The pain is fleeting but may recur at any time and at any age. Management includes administering pain control as needed and reassuring family members that their child's chest pain is not of cardiac origin.

Chest pain or syncope on exertion may be due to an underlying cardiac condition and deserve a more thorough investigation, especially if there is a positive family history of sudden unexplained death in young adulthood. Myocardial injury due to drug abuse (eg, stimulants such as cocaine, methamphetamines, synthetic or over-the-counter drugs of abuse) should be considered. Pulmonary embolism is a possible cause of chest pain, especially in pregnant adolescent girls, patients taking oral contraceptive agents, or those with blood dyscrasias. The rare though life-threatening condition of aortic dissection should be considered as a cause of chest pain in a patient with physical examination stigmata that are suggestive of a collagen vascular disorder, such as Marfan syndrome. Patients with a known congenital heart defect or an acquired cardiac disorder (eg, Kawasaki disease, acute rheumatic heart disease, myocarditis, pericarditis, cardiomyopathy) who present with chest pain or unexplained shortness of

breath prompt a more thorough diagnostic evaluation, including serial cardiac biomarkers and ECGs.

Physical Examination

General Appearance and Pulses

All four extremities should be palpated for the presence and quality of pulses. In infants, feel for the brachial and femoral pulses. Bounding pulses are typically present in infants with a patent ductus arteriosus. Coarctation of the aorta should be suspected in any child with strong or unequal pulses in the upper extremities and weak pulses in the lower extremities. The pulse may be weak and thready in all extremities in a child who presents with CHF and shock.

Vital Signs and Blood Pressures

A mild resting tachypnea or tachycardia may be the only clinical clue to an underlying cardiovascular disorder. A simplified table of normal pediatric vital signs may be used at the bedside (Table 170.2). Methods to calculate normal expected blood pressures and hypotensive blood pressures are also listed in Table 170.2.[3]

To measure blood pressure accurately, use a cuff that covers two-thirds of the upper arm or thigh. A cuff that is too narrow will overestimate the patient's true blood pressure; conversely, a cuff that is too large will underestimate the true blood pressure. Measure blood pressures in both arms in children with a suspected cardiac disorder. As an example, coarctation of the aorta (proximal to the origin of the left subclavian artery) may present with a left arm blood pressure significantly lower than the right arm. Measure blood pressures in the thighs in any child with a suspected aortic coarctation or with documented hypertensive blood pressures in the upper extremities. The mere presence of femoral pulses does not rule out clinically the possibility of a coarctation of the aorta. Even with an appropriately sized cuff, the blood pressures in the thighs can be 10 to 20 mm Hg higher than the blood pressures in the upper extremities because of the lack of well-designed blood pressure cuffs for the legs. Therefore, if the measured blood pressure in the lower extremities is lower than the blood pressure in the upper extremities, coarctation of the aorta should be suspected. Pulse oximetry readings that are lower in the legs than in the upper extremities are also suggestive of either a coarctation of the aorta or a right-to-left-shunt across a patent ductus arteriosus.[4]

TABLE 170.2

Pediatric Vital Signs and Pertinent Formulas for Estimation of Blood Pressure

SIMPLIFIED PEDIATRIC VITAL SIGNS

AGE GROUP	AVERAGE NORMAL HEART RATE (beats/min)	RESPIRATORY RATE (breaths/min)
Newborn to 1 year	140	40
1–4 years	120	30
4–12 years	100	20
>12 years	80	15

FORMULAS TO CALCULATE THE ESTIMATED NORMAL BLOOD PRESSURES IN CHILDREN 1 YEAR OLD AND OLDER

Estimated average systolic blood pressure (SBP): [age in years × 2] + 90 mm Hg
Estimated average diastolic blood pressure: ⅔ × [estimated SBP]

MINIMUM ACCEPTABLE SYSTOLIC BLOOD PRESSURE FOR AGE (LOWER FIFTH PERCENTILE)

Newborn to 1 month	60 mm Hg
1 month to 1 year	70 mm Hg
1–10 years	[Age in years × 2] + 70 mm Hg
>10 years	90 mm Hg

From Eerola A, Jokinen EO, Savukoski TI, et al: Cardiac troponin I in congenital heart defects with pressure or volume overload. Scand Cardiovasc J 47(3):154-159, 2013 and Thuny F, Grisoli D, Cautela J, et al: Infective endocarditis: prevention, diagnosis, and management. Can J Cardiol 30(9):1046-1057, 2014.

Cardiac Auscultation

The intensity and degree of splitting of the S_2 heart sound (closure of the pulmonic and aortic valves) are extremely important in a pediatric cardiologic evaluation. In normal children, both components (aortic closure and pulmonic closure) of S_2 should be heard along the left upper sternal border (the pulmonic area). A widely split and fixed S_2 suggests a physiologic problem resulting from either a constant volume overload to the right side of the heart (eg, atrial septal defect [ASD]) or a pressure overload to the right side of the heart (eg, pulmonic stenosis). An ASD classically presents as a widely split and fixed S_2. The intensity of the S_2 component may be louder than normal in the child with pulmonary hypertension.

The third heart sound (S_3) is best heard along the lower left sternal border or the apex and may be a normal finding in children and young adults. S_3 is produced by a rapid filling of the ventricles and is heard during early diastole, just after the S_2 sound. A loud S_3, however, is pathologic and due to dilated ventricles from volume overload (eg, CHF and large ventricular septal defects [VSDs]). The fourth heart sound (S_4) occurs late in diastole, just before the S_1 sound. The finding of an S_4 is due to a decrease in compliance of a stiff, hypertrophic ventricle, best heard at the apex with the patient in the left lateral decubitus position.

Cardiac murmurs are produced by turbulent blood flow through the heart. The presence of a cardiac murmur may not be associated with an underlying cardiac defect. The location, intensity, quality, timing, and radiation of the murmur determine whether the murmur is suggestive of an underlying cardiac pathologic condition. Although systolic murmurs can be present without any underlying anatomic abnormalities, diastolic murmurs are always considered pathologic in nature. Other criteria that suggest an underlying anatomic cardiac abnormality are listed in Box 170.4. Murmurs may be difficult to appreciate in the noisy ED setting, especially in tachycardic children. However, the location of the murmur may be a valuable clinical tool in determining the underlying anatomic origin of the murmur (Box 170.5).

Murmurs without any underlying anatomic abnormalities or hemodynamic significance are termed *innocent* or *functional murmurs.* All innocent murmurs are associated with normal ECGs and normal chest radiographs. Two of the most common innocent murmurs encountered in the pediatric population are the neonatal pulmonic flow murmur (peripheral pulmonic stenosis murmur) and Still's murmur. The pulmonic flow murmur of the neonate is due to the relatively thin walls and angulation of the right and left pulmonary arteries at birth. This systolic murmur is best heard at the left upper sternal border with radiation throughout the entire chest, axilla, and back. It usually disappears by 3 to 6 months of age. Persistence of a systolic murmur in the pulmonic area beyond this period should raise the possibility of a pathologic pulmonary arterial stenosis.

BOX 170.4

A Pathologic Etiology of a Heart Murmur Should Be Suspected With Any of the Following Criteria

Diastolic murmurs
Systolic murmurs that are louder than a grade 3/6, continuous, or associated with a thrill
Murmurs that are associated with abnormal heart sounds (clicks, rubs, or gallop rhythms)
Presence of cyanosis or respiratory distress
Bounding pulses or weak pulses
Abnormalities on the electrocardiogram (ECG)
An abnormal cardiac silhouette, abnormal pulmonary vascularity, or cardiomegaly on the chest radiograph

BOX 170.5

Auscultation Locations of Common Systolic Murmurs in Children

LEFT UPPER STERNAL BORDER (PULMONIC AREA)
Pulmonic valvular stenosis
Atrial septal defects (ASDs; due to an increased pulmonic flow)
Innocent pulmonic ejection murmur
Neonate pulmonic flow murmur
Patent ductus arteriosus (a continuous, "machinery" sounding murmur)

LEFT LOWER STERNAL BORDER
Innocent vibratory Still's murmur
Ventricular septal defects (VSDs)
Endocardial cushion defects
Tetralogy of Fallot
Hypertrophic cardiomyopathy

APEX
Innocent vibratory Still's murmur
Mitral regurgitation
Aortic stenosis
Hypertrophic cardiomyopathy

RIGHT UPPER STERNAL BORDER (AORTIC AREA)
Aortic stenosis
Coarctation of the aorta

Another common innocent murmur in children is Still's murmur, in children between 2 and 6 years of age. Best heard along the left midsternal border, this murmur has a vibratory, musical, or twanging quality resulting from turbulent flow. The distinct quality of Still's murmur distinguishes it from a VSD murmur, which has a harsher quality. The intensity of Still's murmur increases in the supine position, or with fever, excitement, exercise, or anemia; like most murmurs, it is best heard with the bell of the stethoscope.

Hyperoxia Test

The hyperoxia test is an important bedside diagnostic tool to help differentiate between cardiac and pulmonary causes of central cyanosis. This test consists of assessment of the rise in arterial oxygenation with the administration of 100% oxygen. An arterial blood gas is measured after several minutes on high-flow oxygen (100% oxygen). When the child is breathing high-flow oxygen, an arterial oxygen partial pressure (Pao_2) of more than 250 mm Hg virtually excludes hypoxia due to CHD—a "passed" hyperoxia test.[5] An arterial oxygen reading of less than 100 mm Hg (in a child without obvious pulmonary disease) is consistent with a right-to-left shunt and is highly predictive of CHD—a "failed" hyperoxia test.[5] Values between 100 and 250 mm Hg may indicate lesions with intracardiac mixing. Pulse oximetry is not an appropriate substitute for an arterial blood gas analysis; it is not sensitive enough to determine "pass or fail" of the test because a child breathing high-flow oxygen and registering 100% on pulse oximetry may actually have a Pao_2 anywhere between 80 and 680 mm Hg.[1] Prolonged administration of 100% oxygen may cause some theoretic problems, such as closure of the ductus arteriosus in those infants with critical left-sided heart obstructions or pulmonary vasodilation (which would potentially worsen pulmonary vascular congestion). Oxygen should not be initially withheld in critically ill infants based on this concern alone; rather, providers should closely monitor the response to oxygen in infants with suspected CHD.[1]

Arterial Blood Gas Analysis

Patients with CHF exacerbation may exhibit respiratory acidosis (low pH and high $Paco_2$) in addition to a low Pao_2 due to worsening respiratory fatigue, which initially may be subtle clinically. In contrast, children with compensated cyanotic congenital heart defects may have a normal pH despite a (chronically) low Pao_2. Chronic mild hypoxemia causes a chronic mild acid load on the respiratory, renal, and blood buffer systems; acute illness such as a respiratory infection can rapidly cause a decompensation in this fragile balance, resulting in a worsening acidosis. Patients with congenital heart defects who are not experiencing respiratory compromise are unlikely to exhibit elevation in $Paco_2$. Any cardiac condition that results in inadequate tissue perfusion (ie, any of the acyanotic congenital heart defects that result in CHF) will exhibit a metabolic acidosis with or without respiratory compensation.

Hemoglobin and Hematocrit Levels and Serum Electrolyte Values

The hemoglobin and hematocrit levels may reveal a compensatory physiologic elevation (ie, polycythemia) in children with cyanotic congenital heart defects. Any concurrent medical illness or blood loss could precipitate an acute deterioration by compromising the oxygen-carrying capacity in children with an underlying congenital heart defect. Hemoglobin and hematocrit levels are also helpful in evaluating whether a child's pallor is due to CHF or anemia. Serum electrolyte values may be helpful in the evaluation of children with acute dysrhythmias or suspected metabolic acidosis and those children who are receiving chronic diuretic therapy.

Chest Radiography

Three important features of the chest radiograph (Fig. 170.2) are the cardiac size (cardiothoracic ratio), the cardiac shape (silhouette), and the degree of pulmonary vascular markings. The easiest method to gauge heart size in children is to determine the cardiothoracic ratio: compare the largest transverse diameter of the cardiac shadow on the posteroanterior view of the chest radiograph with the widest internal diameter (measured from the inside rib margin at the widest point above the costophrenic angles) of the chest. The films should be obtained during maximal inspiration whenever feasible.

The normal cardiothoracic ratio in children is 50% to 55%.[6] The cardiothoracic ratio is not very accurate in preverbal children, in whom a good inspiratory view is rarely obtained.[6] A cardiac

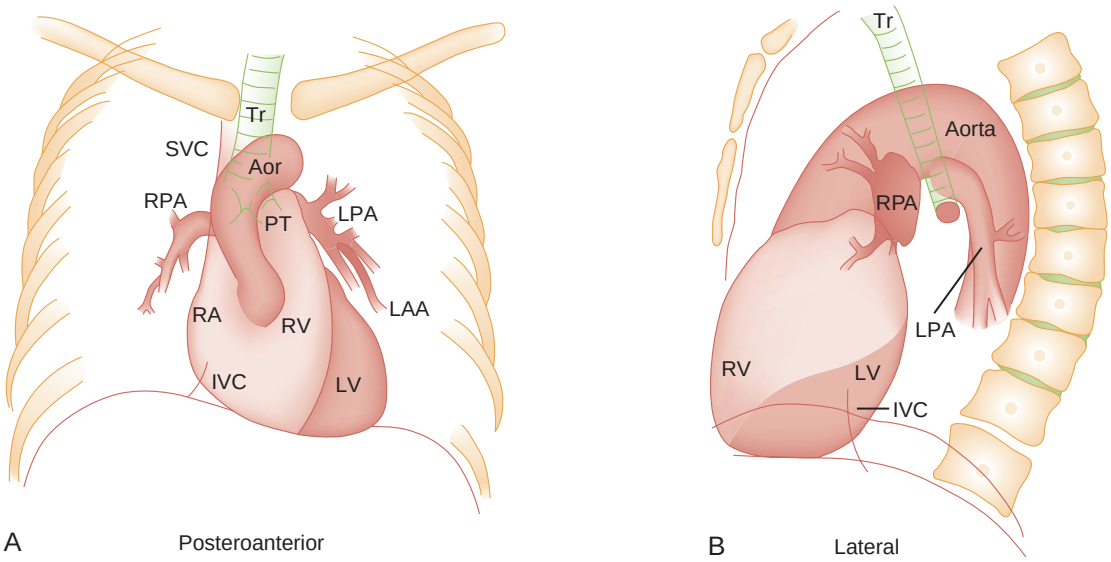

Fig. 170.2. Diagrammatic representations of the anatomy of the chest radiograph. **A,** Normal heart in a young man, posteroanterior projection. **B,** Right lateral projection of a normal heart in a young man. *Aor,* Aorta; *IVC,* inferior vena cava; *LAA,* left atrial appendage; *LPA,* left pulmonary artery; *LV,* left ventricle; *PT,* pulmonary trunk; *RA,* right atrium; *RPA,* right pulmonary artery; *RV,* right ventricle; *SVC,* superior vena cava; *Tr,* trachea.

silhouette that is larger than normal may be due to a shunt lesion, cardiomegaly, or pericardial effusion. An enlarged heart shadow on a chest radiograph more reliably reflects a volume overload rather than pressure overload. Evidence of volume overload seen on ECG include: right atrial enlargement (also seen with ASD, atrioventricular [AV] canal defects, tricuspid atresia, Ebstein's anomaly, and severe pulmonary stenosis); and right ventricular hypertrophy (also seen with pulmonary stenosis, tetralogy of Fallot, transposition of the great arteries, VSD with pulmonary stenosis or pulmonary hypertension, coarctation of aorta [CoA] in the newborn, pulmonary valve atresia, and hypoplastic left heart syndrome). The cardiac size can be falsely increased in infants by the presence of the thymus, seen in the mediastinum on the chest radiograph from birth until about 5 years of age. The thymic borders are typically wavy in appearance and sometimes can be seen as the classic "sail sign" along the superior right border of the heart (Fig. 170.3). The thymic shadow may not be visible radiographically in infants during times of physiologic stress but should reappear when the infant recovers.

The three classic cardiac silhouettes seen in patients with congenital heart defects are the "boot-shaped heart" of tetralogy of Fallot lot (Fig. 170.4), the "egg-on-a-string" silhouette of transposition of the great arteries, and the "snowman-shaped" or "figure-of-eight" heart of total anomalous pulmonary venous return.

The degree of pulmonary vascular markings is a key factor to consider in working through the differential diagnosis of congenital heart defects. Increased pulmonary vascularity is present when the pulmonary arteries appear enlarged and are visible in the lateral third of the lung fields or the lung apices. Another marker of increased pulmonary vascularity is seen on the posteroanterior view of the chest radiograph: the diameter of the right pulmonary artery in the right hilum is wider than the internal diameter of the trachea. The differential diagnosis of a cyanotic infant with decreased vascular markings includes tetralogy of Fallot, pulmonary atresia, and tricuspid atresia. The cyanotic infant with increased vascular markings may have transposition of the great arteries, total anomalous pulmonary venous return, or truncus arteriosus. Increased vascular markings in an acyanotic infant are

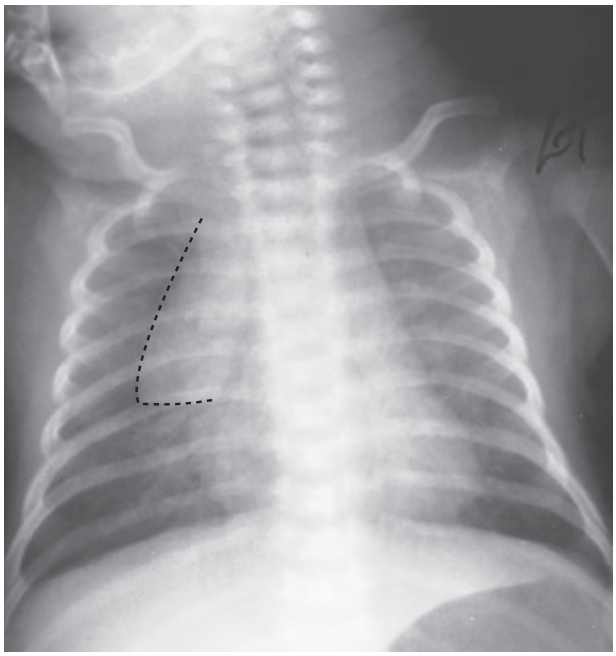

Fig. 170.3. Thymic shadow demonstrating the "sail sign" along the right cardiac border *(dotted line).*

suggestive of an endocardial cushion defect, VSD, ASD, or patent ductus arteriosus.

In a normal left-sided aortic arch, the aorta descends to the left of the midline and slightly displaces the tracheal air shadow toward the right of midline above the level of the carina. With a right-sided aortic arch, the tracheal air shadow may be midline or deviated toward the left. A right-sided aortic arch is found in up to 25% of the children with tetralogy of Fallot.[4] Rib notching secondary to increased collateral blood flow along the intercostal vessels can sometimes be appreciated between the fourth and eighth ribs in older children with undiagnosed coarctation of the

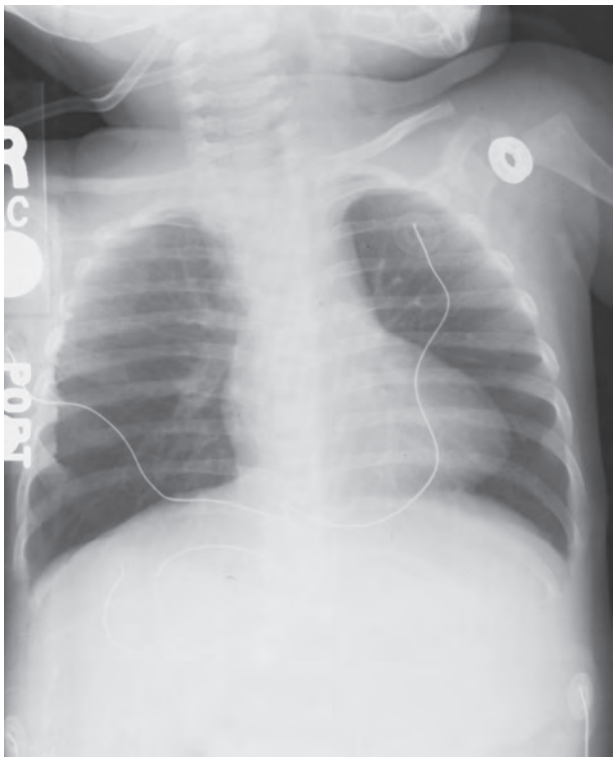

Fig. 170.4. The classic boot-shaped heart of tetralogy of Fallot.

aorta (Fig. 170.5) but is rarely visualized in children with coarctation of the aorta who are younger than 5 years old.

Electrocardiography

Electrocardiographic findings in infants and children change according to the child's age (Table 170.3).[3] At birth, the muscle mass of the right ventricle is greater than that of the left ventricle; this is demonstrated by right axis deviation on the neonatal ECG. By the end of the first month of life, the left ventricle assumes dominance. By 6 months old, the left ventricular to right ventricular mass ratio is 2:1, which then reaches the adult ratio of 2.5:1 by adolescence. The durations of the PR interval, QRS complex, and QT intervals increase with age.

Left axis deviation is present when the QRS axis is less than the lower limit of normal for the child's age; it occurs with left ventricular hypertrophy and left bundle branch block. Right axis deviation is present when the QRS axis is greater than the upper limit of normal for the child's age; it occurs with right ventricular hypertrophy and right bundle branch block. A "superior" QRS axis (0 to −180 degrees with an S wave in aV_F greater than the R wave) may be suggestive of an endocardial cushion defect or tricuspid atresia.

Some of the more common indications to obtain an ECG in a pediatric patient include chest pain, dyspnea, syncope, palpitations, suspected dysrhythmias, or an underlying cardiac disorder. A rare but potentially fatal congenital cardiac abnormality detected by ECG, anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA), will show ischemic changes. These infants have a history of poor feeding, irritability, and failure to thrive, then suddenly present with cardiogenic shock secondary to myocardial ischemia.

Biochemical Markers

As in adults, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are highly sensitive and specific in children for myocardial damage.[7,8] Reference values are slightly higher for neonates younger than 3 months; normal and indeterminate values will depend on the bioassay used. The indications for troponin testing in children include suspected cardiac ischemia (of any etiology), myocarditis, and myocardial dysfunction in sepsis syndrome. Several studies have supported the use of plasma B-type natriuretic peptide (BNP) levels in the assessment and management of CHF in adults. Elevated BNP levels have demonstrated a similar correlation in children with CHF. BNP levels also correlate with the clinical symptoms of heart failure and ejection fraction.[9,10]

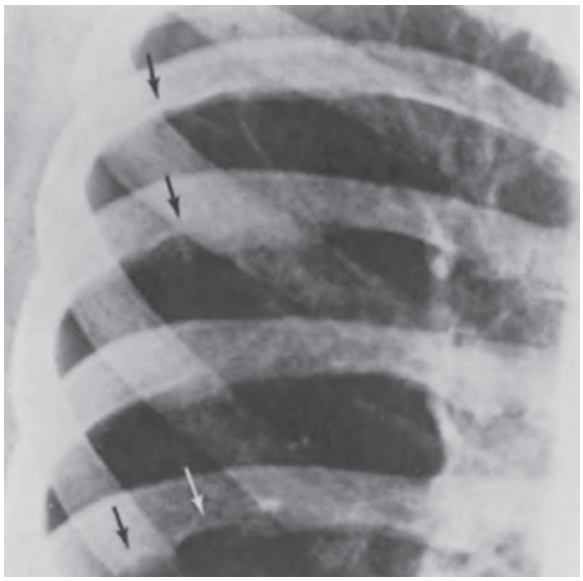

Fig. 170.5. Rib notching *(arrows)* in an 11-year-old girl with coarctation of the aorta. (From Park MK: Park's pediatric cardiology for practitioners, ed 6, Philadelphia, 2014, Elsevier/Saunders, pp 67–74. Figure 4-9 from Caffey J: Pediatric x-ray diagnosis, ed 7, Chicago, 1978, Mosby.)

SPECIFIC DISORDERS

Congenital Heart Disease

In the United States, the incidence of CHD has remained fairly constant at approximately 1%, or 8 to 10 cases per 1000 live births. This equates to approximately 32,000 infants born each year with some form of CHD (Table 170.4). Although a large percentage of CHD is now detected with prenatal sonograms, pulse oximetry before discharge from the nursery is an inexpensive screening tool for CHD, especially useful in resource-poor settings.[11-13]

Clinical Features

Age, severity of symptoms, and time of presentation of a child with CHD vary by the specific defect, complexity, severity, and timing of the normal physiologic changes that occur as the fetal circulation transitions to that of a neonate (Table 170.5). The more severe or complex CHD lesions may not be clinically apparent immediately after birth. As the ductus arteriosus begins to close in the first several weeks of life, cardiac defects with obstructive lesions of the pulmonary or systemic circulations will be unmasked, and these infants will present with acute cyanosis, shock, or both. In general, the more severe the anatomic defect is (ie, lack of pulmonary blood flow or lack of systemic blood flow), the earlier in life these conditions will be manifested with cyanosis and shock.

Many children with CHD do not fit neatly into a single pattern; some have mixed defects. The exact anatomic diagnosis of a CHD is dependent on echocardiography, cardiac catheterization, or

TABLE 170.3

Normal Electrocardiographic Values (PR, QTc, and QRS Axes) in Infants and Children

	PR INTERVAL	QRS DURATION
AGE	AVERAGE (UPPER LIMIT)	AVERAGE (UPPER LIMIT)
0–1 month	0.10 (0.12)	0.05 (0.07)
1 month to 1 year	0.10 (0.14)	0.05 (0.07)
1–3 years	0.11 (0.15)	0.06 (0.07)
3–8 years	0.13 (0.17)	0.07 (0.08)
8–12 years	0.15 (0.18)	0.07 (0.09)
12–16 years	0.15 (0.19)	0.07 (0.10)
Adult	0.16 (0.21)	0.08 (0.10)

The corrected QT (QTc) interval should not exceed:
- 0.45 second in infants <6 months old
- 0.44 second in children and adolescents

NORMAL QRS AXES IN INFANTS AND CHILDREN

AGE	MEAN DEGREES (RANGE)
1 week to 1 month	+110 (+30 to +180)
1–3 months	+70 (+10 to +125)
3 months to 3 years	+60 (+10 to +110)
>3 years	+60 (+20 to +120)
Adults	+50 (–30 to +105)

NORMAL T WAVE AXIS IN INFANTS AND CHILDREN

AGE	LEADS V_1 AND V_2	LEAD AV_F	LEADS I, V_5, AND V_6
Birth to 1 day	+/–	+	+/–
1–4 days	+/–	+	+
4 days to adolescent	–	–	+
Adolescent to adult	+	+	+

+, Upright T wave; –, inverted T wave.

TABLE 170.4

Incidence of Specific Congenital Heart Defects

DEFECT	PERCENTAGE OF CONGENITAL HEART DEFECTS
ACYANOTIC CONGENITAL HEART DEFECTS	
Ventricular septal defect (VSD)	20–25
Atrial septal defect (ASD)	5–10
Patent ductus arteriosus	5–10
Coarctation of the aorta	8
Pulmonic stenosis	5–8
Aortic stenosis	5
CYANOTIC CONGENITAL HEART DEFECTS	
Tetralogy of Fallot	10
Transposition of the great arteries	5
Tricuspid atresia	1–2
Total anomalous pulmonary venous return	1
Truncus arteriosus	<1
Pulmonary atresia	<1
Ebstein's anomaly	<1
Hypoplastic left heart syndrome	<1
Hypoplastic right heart syndrome	<1

TABLE 170.5

Symptomatic Presentation of Congenital Heart Defects and Time of Presentation

DEFECT	TIME OF PRESENTATION
CONGENITAL HEART DEFECTS THAT PRESENT WITH CYANOSIS	
Transposition of the great arteries	Birth to 2 weeks
Total anomalous pulmonary venous return	Birth to 2 weeks
Tricuspid atresia	Birth to 2 weeks
Ebstein's anomaly of the tricuspid valve	Birth to 2 weeks
Truncus arteriosus	Birth to 2 weeks
Pulmonary atresia	Birth to 2 weeks
Hypoplastic right heart syndrome	Birth to 2 weeks
Hypoplastic left heart syndrome	Birth to 2 weeks
Tetralogy of Fallot	Birth to 12 weeks
CONGENITAL HEART DEFECTS THAT PRESENT WITH SHOCK	
Coarctation of the aorta	From first week on
Aortic stenosis	From first week on
CONGENITAL HEART DEFECTS THAT PRESENT WITH CONGESTIVE HEART FAILURE	
Ventricular septal defects (VSDs)	From 4 weeks on
Patent ductus arteriosus	From 4 weeks on

advanced imaging; establishment of the exact anatomic diagnosis is seldom possible in the ED setting.

Diagnostic Testing

The emergency clinician should rely on several key elements of the clinical evaluation in addition to findings on the chest radiograph and ECG to narrow the diagnostic possibilities. Pattern recognition may be helpful (Box 170.6). For example, the presence of cyanosis, a grade 3/6 systolic ejection murmur best heard at the mid left sternal border, a boot-shaped heart, and a decreased pulmonary blood flow on the chest radiograph with evidence of right ventricular hypertrophy on the ECG suggest tetralogy of Fallot.

Management

The majority of children who present to the ED in shock are volume depleted or septic. These patients should receive rapid repeated fluid boluses of 20 mL/kg. Children with poor perfusion and suspected CHD, however, should receive smaller aliquots of 10 mL/kg to avoid precipitation or exacerbation of CHF. In this

BOX 170.6

Clinical Clues to Aid in the Diagnosis of Congenital Heart Disease

PRESENCE OR ABSENCE OF CENTRAL OR PERIPHERAL CYANOSIS?

Central cyanosis with minimal respiratory distress ("comfortably blue") is suggestive of CHD more than of a purely pulmonary etiology.

ABNORMALITIES IN CARDIAC AUSCULTATION?

Murmurs: Systolic versus diastolic, location, and radiation
Quality of S_1, S_2, and the presence of any clicks or gallops

CHANGE IN THE DEGREE OF CENTRAL CYANOSIS WITH CRYING?

Worsening of cyanosis with crying suggests a cardiac rather than a purely pulmonary etiology.

RESPONSE OF PAO_2 TO THE HYPEROXIA CHALLENGE (ADMINISTERING 100% OXYGEN)?

Purely pulmonary causes of cyanosis: Pao_2 should rise to levels above 250 mm Hg
Cyanotic CHD associated with an increased pulmonary blood flow: Pao_2 may occasionally reach as high as 150 mm Hg
Cyanotic CHD associated with a decreased pulmonary blood flow: Pao_2 will not rise above 100 mm Hg

CHEST RADIOGRAPH ABNORMALITIES?

Cardiac size and shape (one of the three classic cardiac silhouettes)?
- Boot-shaped heart: Tetralogy of Fallot
- Egg-on-a-string silhouette: Transposition of the great vessels
- Snowman-shaped or figure-of-eight heart: Total anomalous pulmonary venous return

DEGREE OF PULMONARY BLOOD FLOW?

Increased (acyanotic): ASD, Eisenmenger's syndrome, VSD, patent ductus arteriosus, endocardial cushion defects
Increased (cyanotic): Transposition of the great arteries, total anomalous pulmonary venous return, hypoplastic left heart syndrome, truncus arteriosus
Decreased or normal (acyanotic): Pulmonic stenosis, aortic stenosis, coarctation of the aorta
Decreased (cyanotic): Tetralogy of Fallot, severe pulmonic stenosis, Ebstein's anomaly, tricuspid atresia, pulmonary atresia, hypoplastic right heart syndrome

ELECTROCARDIOGRAPHIC ABNORMALITIES?

Evidence of chamber enlargement: right ventricular hypertrophy, left ventricular hypertrophy, biventricular hypertrophy, right atrial hypertrophy, or left atrial hypertrophy
An abnormal superior QRS axis is suggestive of endocardial cushion defect or tricuspid atresia.

ASD, Atrial septal defect, *CHD,* congenital heart disease; *PaO_2,* arterial oxygen partial pressure; *VSD,* ventricular septal defect.

case, give the initial 10 mL/kg bolus and assess for effect. If the child is improved or no worse, consider giving more fluids. Be judicious in suspected CHD and ready to provide ionotropic support and/or positive pressure ventilation, either by noninvasive or endotracheal means.

One unique pharmacologic intervention that can be life-saving in infants involves the use of prostaglandin E_1 (PGE_1) to maintain the patency of the ductus arteriosus. CHD that is manifested within the first 2 to 3 weeks of life with a sudden onset of cyanosis or cardiovascular collapse is typically due to ductal-dependent cardiac lesions (Box 170.7).

BOX 170.7

Ductal-Dependent Cardiac Lesions in the Neonate

CONGENITAL HEART DISEASES THAT REQUIRE A PATENT DUCTUS ARTERIOSUS TO PRESERVE BLOOD FLOW FROM THE AORTA TO THE PULMONARY CIRCULATION

Tetralogy of Fallot
Tricuspid atresia
Pulmonary atresia
Hypoplastic right heart syndrome
Transposition of the great vessels

CONGENITAL HEART DISEASES THAT REQUIRE A PATENT DUCTUS ARTERIOSUS TO PRESERVE BLOOD FLOW FROM THE MAIN PULMONARY ARTERY TO THE SYSTEMIC CIRCULATION

Severe coarctation of the aorta
Severe aortic stenosis
Hypoplastic left heart syndrome

Closure of the ductus arteriosus in these patients interrupts blood flow to the lungs, producing cyanosis (eg, tricuspid atresia), or disruption in blood flow to the systemic circulation and shock (eg, hypoplastic left heart syndrome). PGE_1 infusion is typically started at 0.05 to 0.1 μg/kg/min. A known adverse reaction to a PGE_1 infusion is apnea (30%). Assiduous monitoring of the child's respiratory drive is essential with PGE_1 administration. Although some small studies endorse the omission of endotracheal intubation of neonates on a PGE_1 infusion, endotracheal intubation should be considered for these infants, especially before inter-facility transport.

Children with cardiac conditions are at risk of post-intubation cardiovascular collapse due to positive pressure ventilation, increased intrathoracic pressures, and decreased venous return (eg, cyanotic heart disease is often preload dependent). To support cardiac output and SVR (which mitigates a right-to-left shunt), ketamine is the preferred induction agent along with a nondepolarizing metabolically neutral neuromuscular blocker, such as rocuronium. Not only will intubation provide a secure airway, but controlled ventilation will also help decrease the infant's work of breathing, shunting much needed cardiac output and metabolic demands from the overtaxed respiratory apparatus. Other adverse reactions to a PGE_1 infusion include fever, seizures, bradycardia, hypotension, flushing, and decreased platelet aggregation.

Acyanotic Congenital Heart Defect

Acyanotic CHD can be further subdivided (Fig. 170.6) into obstructive lesions (eg, pulmonic stenosis, aortic stenosis, coarctation of the aorta) and lesions characterized by left-to-right shunting with an associated increase in pulmonary blood flow (eg, VSDs, ASDs, patent ductus arteriosus, endocardial cushion defects). These acyanotic lesions usually present within the first 6 months of life with symptoms of CHF; however, ASDs can remain asymptomatic until adulthood.

Ventricular Septal Defect. VSD is the most common congenital cardiac defect and accounts for 20% to 25% of all cases of CHD. Spontaneous closure occurs in 30% to 40% of all VSDs overall and in 50% to 70% of smaller VSDs.[4]

Clinical Features. The degree of symptoms is dependent on the size of the VSD and the degree of peripheral vascular resistance (PVR). Most VSDs are clinically asymptomatic (minimal or no

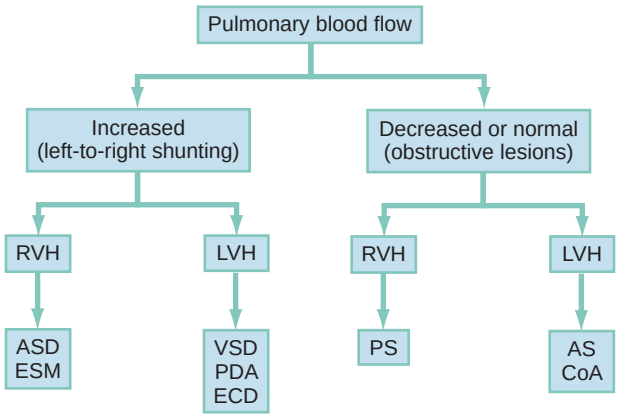

Fig. 170.6. Clinical clues to diagnosis of acyanotic congenital heart defects. *AS,* Aortic stenosis; *ASD,* atrial septal defect; *CoA,* coarctation of the aorta; *ECD,* endocardial cushion defect; *ESM,* Eisenmenger's syndrome; *LVH,* left ventricular hypertrophy; *PDA,* patent ductus arteriosus; *PS,* pulmonic stenosis; *RVH,* right ventricular hypertrophy; *VSD,* ventricular septal defect.

left-to-right shunting) immediately after birth because of the high PVR. When the PVR decreases to the normal levels at 6 to 8 weeks after birth, left-to-right shunting can then occur, and the typical systolic murmur of a VSD can be appreciated. Small VSDs may remain completely asymptomatic throughout childhood. Approximately 10% of the infants with large VSDs will eventually have signs and symptoms of CHF (eg, poor feeding and poor growth) by 2 to 3 months old because of the increased pulmonary blood flow. Older children with VSDs may have decreased exercise tolerance or recurrent pulmonary infections. If moderate to large VSDs are not surgically corrected, irreversible changes in the pulmonary vasculature may begin to occur as early as 6 to 12 months old, resulting in elevation of the PVR and pulmonary hypertension. This in turn can lead to a reversal of the shunt direction across the VSD: a new right-to-left shunt, Eisenmenger's syndrome, and resultant cyanosis.

Diagnostic Testing. The chest radiograph in children with small VSDs may be entirely normal, but cardiomegaly with increased pulmonary vascular markings is usually present with untreated moderate-to-large VSDs. The ECG of moderate-sized VSDs typically reveals left ventricular hypertrophy, but biventricular hypertrophy may be present in VSDS with large left-to-right shunting.

Management. All VSDs, regardless of the size of the defect, are at risk for bacterial endocarditis because of the high velocity of turbulent blood flow through them and thus should be repaired.

Traditional closure of VSDs required open heart surgery. Today, however, a transcatheter closure technique that avoids the inherent risks and complications of open heart surgery and cardiopulmonary bypass has supplanted traditional methods.[14,15]

Atrial Septal Defect.

ASDs account for 5% to 10% of all cases of CHD. The majority of infants and children with ASDs remain clinically asymptomatic until adulthood. Spontaneous closure has been reported in up to 40% of the cases within the first 5 years of life.[4]

Clinical Features. Large ASDs or those associated with comorbid conditions, such as bronchopulmonary dysplasia, can be manifested with symptoms of CHF and pulmonary overcirculation (eg, dyspnea with feedings, poor weight gain, and frequent lower respiratory tract infections). The majority of ASDs are discovered when a suspicious murmur is detected on a routine physical examination. A widely split and fixed S_2 is a characteristic finding of ASDs.

Diagnostic Testing. The chest radiograph of children with ASDs will reveal varying degrees of cardiomegaly, right atrial and right ventricular enlargement, and a prominent main pulmonary artery segment and increased pulmonary vascular markings. The ECG will reveal varying degrees of right axis deviation and right ventricular hypertrophy. All patients with unrepaired ASDs will have symptoms if pulmonary hypertension develops. Patients with large ASDs that are not detected and repaired are at risk for development of Eisenmenger's syndrome. Unlike VSDs, uncomplicated ASDs are not associated with high risk of bacterial endocarditis because of the lower turbulence and velocity of blood flow through the atrial defect.

Management. The traditional closure of ASDs required open heart surgery to place a patch over the septal defect. Newer therapies involving closures with septal occluder devices placed by the transcatheter approach have been described.[16] Antiplatelet therapy during the 6-month period after placement of the device is typically given and is safe and effective in preventing thrombus formation on the surface of the septal occluder device.

Eisenmenger's Syndrome.

Eisenmenger's syndrome can occur in any large left-to-right shunt defect that is not surgically corrected. Left uncorrected, irreversible changes in the pulmonary arterioles leads to pulmonary vascular obstruction and pulmonary hypertension. As the degree of pulmonary hypertension increases, the PVR may then begin to exceed the SVR. This causes right-sided pressures to exceed those on the left, causing right-to-left shunting. The reversal in the direction of shunt flow produces cyanosis. Other clinical features of patients who have Eisenmenger's syndrome include chest pain, dyspnea on exertion, and hemoptysis.[17,18]

Coarctation of the Aorta.

Coarctation of the aorta accounts for approximately 8% of all CHD, and up to 50% of patients with coarctation of the aorta also have an associated bicuspid aortic valve.[19] The area of coarctation can occur proximal to the insertion of the ductus arteriosus (preductal type) or distal to the insertion of the ductus arteriosus (most common, postductal type).

Clinical Features. The severity of the symptoms and the age at time of presentation are dependent on the location of the coarctation, the degree of narrowing, and the presence of any other associated cardiac defects. Infants with the rarer, preductal type of coarctation of the aorta may also exhibit differential cyanosis if the ductus arteriosus remains open. With differential cyanosis, the upper half of the body is perfused with well oxygenated blood supplied by the left ventricle and the ascending aorta. However, the lower half of the body will appear cyanotic, because it is largely perfused by right-to-left shunting of deoxygenated blood from the patent ductus arteriosus into the descending aorta. Infants with the preductal type of coarctation of the aorta will present with signs of circulatory failure and shock when the ductus arteriosus begins to close. The clinician should search for a "brachial-femoral delay" by palpating both pulses simultaneously.[20]

Most of the asymptomatic cases of the more common postductal coarctation of the aorta are diagnosed as a result of a cardiology referral for a systolic murmur or a hypertension evaluation, but infants with severe postductal coarctation of the aorta can also present during the first few weeks of life with signs of circulatory failure and shock. If a child is discovered to have hypertension on a routine physical examination, obtain blood pressure measurements in the lower extremities to assess the possibility of coarctation of the aorta. Systolic blood pressure in the legs is typically slightly higher than in the arms. Coarctation of the aorta should be suspected if the systolic blood pressure in the right arm is 15 to 20 mm Hg higher than that in the legs. If the systolic pressure

in the right arm is higher than that in the left arm, the area of coarctation is probably preductal and located proximal to the origin of the left subclavian artery.[20] In general, diastolic blood pressures are similar in the upper and lower extremities.

Diagnostic Testing. The chest radiograph will most often reveal a normal-sized cardiac silhouette and normal pulmonary vascular markings, but notching along the lower borders of the posterior fourth to eighth ribs due to the pressure of the dilated collateral vessels may be exhibited in children older than 5 years old. The ECG typically reveals a left axis and left ventricular hypertrophy. Suspected cases of coarctation of the aorta should be imaged with transthoracic echocardiography or cardiac magnetic resonance imaging to confirm and to define the coarctation.[20] In stable patients, this can be done on an outpatient basis.

Management. Definitive surgical repair of coarctation of the aorta involves angiography or stenting of the narrow aortic lumen; resection of the narrowed section of the aorta with an end-to-end anastomosis may be necessary.[21] Complications of undiagnosed cases are related to the resultant hypertension and can include heart failure, hypertensive encephalopathy, and intracranial hemorrhages.

Cyanotic Congenital Heart Diseases

Cyanotic CHDs are a result of either decreased pulmonary blood flow to the lungs or right-to-left shunting of desaturated blood directly into the systemic circulation (Fig. 170.7). The classic cyanotic CHD can be remembered by the five Ts: truncus arteriosus, transposition of the great arteries, tricuspid atresia, tetralogy of Fallot, and total anomalous pulmonary venous return. Other forms of cyanotic CHD include Ebstein's anomaly, pulmonary atresia, severe pulmonary stenosis, hypoplastic left heart syndrome, and hypoplastic right heart syndrome. Many of these cyanotic heart lesions are routinely detected either on prenatal ultrasound or in the nursery; only tetralogy of Fallot is covered in this section.

Tetralogy of Fallot. Tetralogy of Fallot accounts for approximately 10% of all cases of CHD and is the most common cause of cyanotic CHD beyond infancy. Tetralogy of Fallot is often associated with other cardiac defects, such as right-sided aortic arch (25% of patients), ASD (10% of patients), and anomalous origin of the left coronary artery. Tetralogy of Fallot arises from a single embryologic defect in which the subpulmonic conus fails to expand, resulting in the four abnormalities (Fig. 170.8): (1) right ventricular outflow tract obstruction; (2) large, unrestrictive, malaligned VSD; (3) over-riding aorta that receives blood flow from both ventricles; and (4) right ventricular hypertrophy secondary to the high pressure load placed on the right ventricle by the right ventricular outflow tract obstruction. These anatomic defects collectively result in decreased pulmonary blood flow and varying degrees of right-to-left shunting of deoxygenated blood across the VSD.

Clinical Features. The degree of cyanosis and the age at presentation are directly dependent on the degree of right ventricular outflow tract obstruction. Infants with tetralogy of Fallot typically have worsening of their cyanosis during crying and feeding. Older children with tetralogy of Fallot may have cyanotic exacerbations during periods of physical exertion. Infants with milder forms of right ventricular outflow tract obstruction may be acyanotic and are sometimes referred to as having a "pink" tetralogy of Fallot. Infants with severe right ventricular outflow tract obstruction exhibit profound cyanosis within the first few days of life and may even require PGE_1 infusion to preserve pulmonary blood flow by left-to-right shunting from the aorta

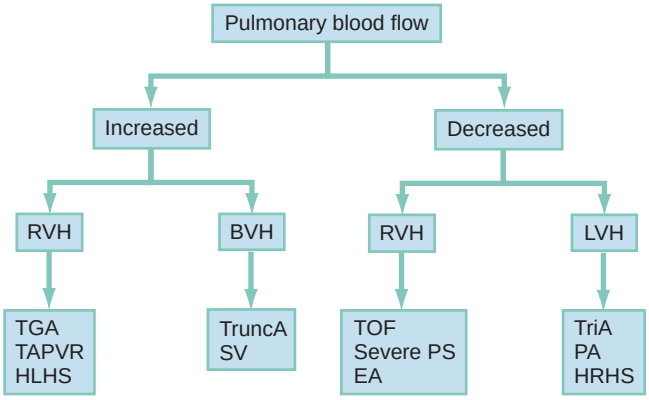

Fig. 170.7. Clinical clues to diagnosis of cyanotic congenital heart defects. *BVH,* Biventricular hypertrophy; *EA,* Ebstein's anomaly; *HLHS,* hypoplastic left heart syndrome; *HRHS,* hypoplastic right heart syndrome; *LVH,* left ventricular hypertrophy; *PA,* pulmonary atresia; *PS,* pulmonary stenosis; *RVH,* right ventricular hypertrophy; *SV,* single ventricle; *TAPVR,* total anomalous pulmonary venous return; *TGA,* transposition of the great arteries; *TOF,* tetralogy of Fallot; *TriA,* tricuspid atresia; *TruncA,* truncus arteriosus.

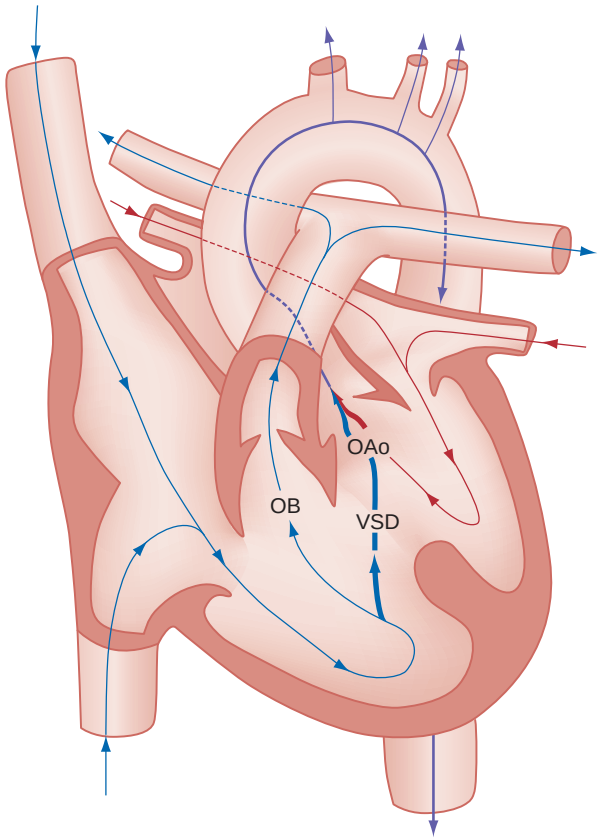

Fig. 170.8. Diagrammatic representation of the right-to-left shunting that occurs in tetralogy of Fallot. Some of the deoxygenated blood *(thick blue arrow)* in the right ventricle is shunted across the ventricular septal defect *(VSD)* into the left ventricle. This deoxygenated blood mixes with the well-oxygenated blood from the lungs *(red arrow).* The blood that is ejected out through the overriding aorta *(OAo),* therefore, contains blood of mixed oxygenation *(purple arrows).* The amount of deoxygenated blood that is shunted through the VSD *(thick blue arrow)* is dependent on a combination of factors, including the severity of right ventricular outflow tract obstruction *(OB),* the size of the VSD, and the degree of systemic vascular resistance (SVR). When the SVR falls (as occurs during a tet spell), more deoxygenated blood from the right ventricle will be shunted across the VSD into the systemic circulation, which results in hypoxia, metabolic acidosis, and worsening cyanosis.

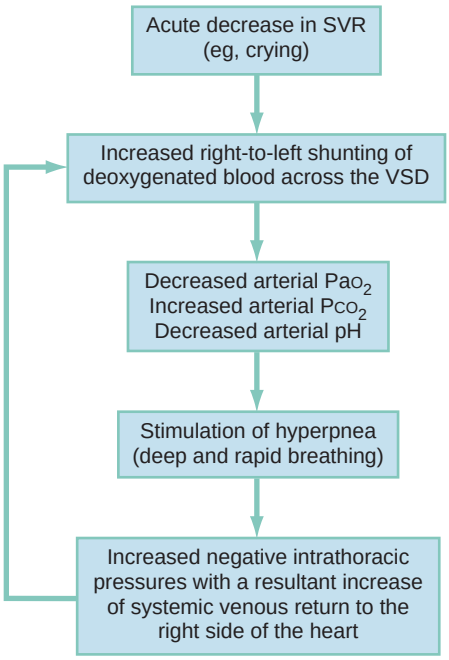

Fig. 170.9. Pathophysiologic mechanisms of a hypoxic (tet) spell. *PaO_2,* Arterial oxygen partial pressure; *PCO_2,* partial pressure of carbon dioxide in the arterial blood; *SVR,* systemic vascular resistance; *VSD,* ventricular septal defect.

into the main pulmonary artery through the patent ductus arteriosus.

The physical examination can reveal varying degrees of cyanosis and a systolic ejection murmur along the left sternal border. Chronic hypoxemia results in a compensatory polycythemia and varying degrees of clubbing of the fingers and toes.

Diagnostic Testing. The chest radiograph of a patient with cyanotic tetralogy of Fallot (see Fig. 170.4) shows decreased pulmonary vascular markings and a boot-shaped heart (secondary to a concave main pulmonary artery segment along the superior aspect of the left border of the heart). The heart size in tetralogy of Fallot is normal, and a right-sided aortic arch may be seen in 25% of the cases. The ECG of cyanotic tetralogy of Fallot reveals right ventricular hypertrophy and a right axis deviation. Children with pink tetralogy of Fallot may not initially exhibit any degree of right ventricular hypertrophy, but these acyanotic variations of tetralogy of Fallot gradually develop into the cyanotic form by 1 to 3 years old.

A potentially life-threatening complication of tetralogy of Fallot is the so-called *tet spell,* which is known as a hypercyanotic or hypoxic spell. These episodes occur most commonly in infants, with a peak incidence between 2 and 4 months old.

Any event that suddenly lowers the SVR, such as crying or defecation, and hypovolemia or tachycardia will produce a large right-to-left shunt across the VSD, beginning the vicious circle of a hypoxic spell. The large right-to-left shunt through the VSD bypasses the lungs, which then causes a decrease in the Pao_2, an increase in the Pco_2, and a fall in the arterial pH. These metabolic changes then stimulate the respiratory centers in the brain to produce hyperpnea (deep and rapid respirations), which increases the negative intrathoracic pressure during inspiration, causing an increase in the systemic venous blood return to the right side of the heart. This increased volume of blood in the right ventricle is then shunted through the VSD by the combination of the existing right ventricular tract outflow obstruction and the acute decrease in the SVR. This in turn further decreases the arterial oxygen saturation, perpetuating the hypoxic spell (Fig. 170.9).

BOX 170.8

Management of Tetralogy of Fallot Hypoxic Spells

Place the child in the knee-to-chest position to increase the systemic vascular resistance (SVR), which decreases the right-to-left shunt across the ventricular septal defect (VSD).
Provide supplemental oxygen (limited value by itself).
Morphine: 0.1 to 0.2 mg/kg IV or IM
Fentanyl: 1 µg/kg/dose IV or IM as an alternative to morphine
Fentanyl: 2 µg/kg/dose intranasally (anatomic limit of 1 mL solution per naris)
Midazolam: 0.2 to 0.3 mg/kg/dose intranasally (anatomic limit of 1 mL solution per naris)
Sodium bicarbonate: 1 mEq/kg IV if suspected or documented acidosis
Consider ketamine: 1 to 2 mg/kg IV or 3 to 5 mg/kg IM
Consider propranolol: 0.01 to 0.2 mg/kg IV
Consider phenylephrine: 0.01 to 0.02 mg/kg IV

IM, Intramuscular; *IV,* intravenous.

These hypoxic spells are characterized clinically by periods of hyperpnea, uncontrollable crying, and worsening cyanosis. Limpness, seizures, cerebrovascular accidents, and even death have been reported with more severe tet spells. During a tet spell, the intensity of the murmur decreases because of less blood flow through the right ventricular tract obstruction and more blood being shunted from the right ventricle to the left ventricle through the VSD.

Management. The overall treatment goals for tet spells are to increase the SVR, to abolish the hyperpnea, and to correct the metabolic acidosis (Box 170.8). Give supplemental oxygen and increase the child's SVR by placing him in a knee-to-chest position; older children may be placed in the squatting position, if tolerated. Both maneuvers are believed to increase SVR and to decrease the pathologic right-to-left shunting of blood. Analgesics should be given to calm the child, decrease the catecholamine surge, and decrease the respiratory rate. Morphine (0.1 to 0.2 mg/kg) intramuscularly has been a traditional option but has the possible untoward effect of systemic vasodilation (further decreasing the SVR) by endogenous histamine release. Fentanyl and midazolam are newer options without the potential risk of endogenous histamine release.[22] Both may be given via the intranasal route and may be less distressful than intramuscular morphine. Ketamine (1 to 2 mg/kg IV or 3 to 5 mg/kg IM) is a good choice for its analgesic and sedative effects; it is an excellent choice to improve SVR.[23-26] In the event of clinically suspected or documented (pH <7.4) metabolic acidosis, sodium bicarbonate (1 mEq/kg IV) may be given to break the cycle of hypoxemia, acidosis, and worsening hypotension and perfusion. Most infants respond to these measures and exhibit an improvement in their oxygenation and a decrease in their degree of cyanosis.

Infants whose condition does not improve with these measures may require a vasopressor (such as, phenylephrine) to increase the SVR and thereby to decrease the degree of right-to-left shunting across the VSD. An intravenous fluid bolus may also be considered to increase the volume of blood flow through the pulmonary artery. If the aforementioned pharmacologic interventions are not successful, consider propranolol (0.1 to 0.25 g/kg IV) administered slowly and repeated if needed every 10 to 15 minutes (possibly reduces infundibular spasm at the right ventricular outflow tract) or phenylephrine (5 to 20 mcg/kg IV) administered slowly and repeated if needed every 10 to 15 minutes (alpha-antagonist to increase SVR).

Palliative surgical procedures to increase the amount of blood flow temporarily to the pulmonary arteries are performed in infants with severe cyanotic tetralogy of Fallot. The most commonly performed procedure is the modified Blalock-Taussig shunt, in which an anastomosis is created between the subclavian artery and the ipsilateral pulmonary artery. Definitive surgical repair consists of closing the VSD and opening the right ventricular outflow tract obstruction by resection of the infundibular tissue. The mortality rate is 5% to 10% within the first 2 years after definitive surgical repair in uncomplicated tetralogy of Fallot cases. Complications that can occur after definitive surgical repair include complete heart block, ventricular dysrhythmias, and right bundle branch block (secondary to the right ventriculotomy).

Postoperative Complications of Congenital Heart Defects

A variety of postoperative complications can be seen in patients who present to the ED weeks to months after cardiac surgery: thrombosis of a shunt-conduit with decreased flow; increased shunt-conduit flow with resultant CHF; atrial and ventricular dysrhythmias; heart block; myocardial ischemia; and endocarditis. The size of the cardiac silhouette and the degree of pulmonary blood flow on the chest radiograph may provide valuable clues as to whether there is an increased or decreased blood flow through a surgical conduit that was created to provide an improvement in blood flow to the pulmonary system.[20,27] Comparison of the child's other postoperative chest radiographs can help determine whether there has been a change in the heart size and pulmonary vascularity.

The post-pericardiotomy syndrome is an inflammatory pericarditis that can occur 1 to 6 weeks after any surgical procedure that involved a pericardiotomy. An immunologic inflammatory response is believed to occur from blood in the pericardial sac. This syndrome is characterized by fever, chest pain, and pericardial effusion. A pericardial friction rub may be heard, depending on the amount of fluid that accumulates in the pericardial sac. The chest radiograph may reveal an enlarged cardiac silhouette, and the echocardiogram will confirm the diagnosis. Pericardiocentesis is rarely required but may be necessary if the amount of pericardial effusion is significant enough to cause a pericardial tamponade. The majority of cases will resolve within 2 to 3 weeks with bed rest and nonsteroidal antiinflammatory medication.

Respiratory Syncytial Virus Infections in Infants and Children With Congenital Heart Defects

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and children worldwide, with the majority of children infected at least once by 2 years of age. Reinfection occurs commonly throughout life.[27-30] Children with CHD who have RSV infections tend to have a higher rate of intensive care unit (ICU) admissions and require mechanical ventilation more frequently than those children who do not have CHD. Children with CHD who require hospitalization for RSV infection have a fatality rate that is two to six times greater than that of children without CHD.[29] RSV infection in a child with CHD carries a 40% mortality rate—70% in children with CHD *and* associated pulmonary hypertension. Therefore any infant with CHD and acute RSV infection should be admitted for observation (Box 170.9).

BOX 170.9

Conditions Associated With an Increased Risk of Severe or Fatal Respiratory Syncytial Virus Infections

Cyanotic or complex congenital heart defects
Pulmonary hypertension
Prematurity (especially those infants with bronchopulmonary dysplasia or chronic lung disease)
Immunodeficiency states

Congestive Heart Failure

Perspective

CHF is defined as a clinical syndrome in which the cardiac output is unable to meet the hemodynamic and metabolic demands of the body. Although there is a wide array of causes of CHF, the primary cause in infants and children is CHD, which results in volume or pressure overload. Other causes of CHF include the anomalous left coronary artery in infants, myocarditis, endocarditis, rheumatic heart disease, pericardial effusions, anemia, cardiomyopathies, systemic hypertension, hypothyroidism, hyperthyroidism, electrolyte imbalances, endocrine disorders, cardiac toxins, and dysrhythmias that compromise cardiac output.

CHF can result from a derangement in any of the four primary determinants of normal cardiac function: (1) excessive preload (eg, large left-to-right shunts and severe chronic anemia); (2) decreased cardiac contractility (eg, myocarditis); (3) excessive afterload (eg, left-sided obstructive lesions); and (4) rhythm abnormalities that compromise cardiac output or stroke volume (eg, paroxysmal supraventricular tachycardia and severe forms of heart block). The treatment of CHF depends on which of these four primary determinants of normal cardiac function are compromised. For example, inotropic agents and diuretics may be required in a child with volume overload and decreased cardiac contractility, whereas vasodilatory agents may be required in a child with CHF due to an increased afterload.

Clinical Features

Although the clinical manifestations of CHF depend on the exact pathophysiologic cause of the CHF, common presenting signs and symptoms include tachycardia, gallops (especially an S_3), tachypnea with rales, hepatomegaly, peripheral edema, and decreased peripheral perfusion of the extremities. Wheezing and a chronic cough may also be the presenting symptoms of CHF.

Diagnostic Testing

The chest radiograph typically reveals an enlargement of the cardiac silhouette and varying degrees of pulmonary congestion. An echocardiogram will be able to assess the ejection fraction, as well as to identify underlying anatomic defects. Plasma BNP may be helpful in differentiating cardiac from pulmonary causes of dyspnea in children.

Management

Acute stabilization of any child who presents with CHF includes administration of supplemental oxygen and agents to augment cardiac contractility and to improve cardiac output. Children with respiratory distress due to pulmonary congestion may benefit from elevation of the head and upper torso—if available, place the infant in his car seat. Continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BiPAP) ventilation via mask or nasal cannula (nasal CPAP) may be useful initially to

avert the need for endotracheal intubation.[31] Children who present in severe respiratory distress secondary to pulmonary edema may require intubation to support oxygenation and ventilation. Plasma BNP levels have been used also to monitor the response to treatment regimens in patients with CHF.[9,10]

Diuretics and inotropic agents may be considered. Furosemide (Lasix) in a dose of 1 mg/kg is the most common loop diuretic used to increase renal perfusion and to improve urine output. In contrast to adults, nitroglycerin is not first-line therapy for CHF in children. Children are much more sensitive to the drug's potent vasodilatory effects than adults, and they can experience profound and rapid hypotension with its administration.[32]

The best vasopressor for decompensated pediatric cardiogenic shock is currently under debate and investigation.[33] Traditionally, dopamine was administered for undifferentiated shock in children; however, other agents with less arrhythmogenic side effects are available.[34,35] Increasingly, guidelines advocate for an approach based on etiology and pathophysiology. Norepinephrine is a good choice as a first-line vasopressor for pediatric decompensated cardiogenic shock due to its effectiveness in supporting SVR.[33,34] Dobutamine may be added for its selective cardiac inotropic effects. Epinephrine is also potent inotrope and chronotrope that increases the SVR.

Amrinone and milrinone, most commonly used in the ICU setting, may be added to an inotrope to promote forward blood flow via peripheral vasodilatory effects.[35,36] These agents have been used to improve cardiac index in septic shock and to prevent low cardiac output states for children with CHD. Side effects of these medications include profound hypotension, dysrhythmias, hypersensitivity reactions, fever, hepatotoxicity, and thrombocytopenia.

Pediatric Dysrhythmias

The most common cause of cardiopulmonary arrest in infants and children is the untreated progression of respiratory failure or shock rather than a primary cardiac dysrhythmia. Accordingly, the most common arrest rhythm is asystole or bradycardia rather than ventricular fibrillation or ventricular tachycardia. Drugs of abuse (eg, cocaine and crystal methamphetamine, among others) and overdose of prescription medications (eg, cyclic antidepressants) should be considered in the evaluation of any previously healthy adolescent patient who presents with an acute dysrhythmia. Even medications used to treat underlying cardiac problems (such as, digoxin, amiodarone, and procainamide) can themselves precipitate dysrhythmias.

Pediatric dysrhythmias can be divided into three broad categories of rhythms by their effect on the child's pulse: *slow* (sinus bradycardia and heart blocks), *fast* (supraventricular tachycardia or ventricular tachycardia with a pulse), or *absent* (ventricular tachycardia without a pulse, ventricular fibrillation, pulseless electrical activity, or asystole).[37] The most common dysrhythmia in children is supraventricular tachycardia, which occurs most commonly in infants and young children. Although supraventricular tachycardia can spontaneously occur in infants without any underlying structural cardiac defects, ventricular tachycardias typically are due to an underlying myocardial abnormality.

Clinical Features

Rhythm disturbances in infants can be manifested with symptoms, such as fussiness, lethargy, poor feeding, pallor, respiratory distress, or cardiogenic shock. Older children present with chest pain, palpitations, difficulty in breathing, or syncope. The type and degree of severity of the presenting signs and symptoms should be taken into account in the evaluation and management of the specific dysrhythmia in each case (Box 170.10).

BOX 170.10

Conditions Associated With a High Risk for Development of Dysrhythmias

Congenital heart defects (uncorrected defects and postoperative complications)
Congenital complete heart blocks (eg, maternal systemic lupus erythematosus)
Myocarditis
Rheumatic heart disease
Kawasaki disease with involvement of the coronary arteries
Cardiomyopathy
Prolonged QT syndrome
Aberrant atrioventricular conduction pathways (eg, Wolff-Parkinson-White syndrome)
Electrolyte abnormalities (eg, potassium, calcium, and magnesium disturbances)
Commotio cordis
Profound hypothermia
Hypoxia

Management

Not every child who exhibits a rhythm disturbance requires emergency intervention. Emergency treatment and stabilization of any dysrhythmia depend on three key clinical questions:

1. Does the child have a pulse?
2. If a pulse is present, is it slow or fast?
3. Is the child hemodynamically stable or unstable?

Children who have a pulse with good perfusion parameters (ie, an alert child with strong distal pulses, warm extremities, and brisk capillary refill times) do not require emergency intervention unless they exhibit a rhythm that has the potential to rapidly degenerate into a more serious condition. Children who exhibit electrocardiographic evidence of conduction abnormalities (eg, Mobitz type II second-degree heart block, complete heart block, prolonged QT intervals, or aberrant conduction, such as the Wolff-Parkinson-White syndrome) may require emergent management, depending on symptoms and hemodynamic status.

Although some medications can be used to treat only atrial tachycardia (eg, adenosine for supraventricular tachycardia) or ventricular tachycardia (eg, lidocaine for ventricular tachycardia), amiodarone and procainamide can be used for an array of both atrial and ventricular dysrhythmias, including supraventricular tachycardia and ventricular tachycardia.[38-40]

Bradydysrhythmias

Sinus Bradycardia. Bradycardia is defined as a heart rate that is slower than the lower limit of normal for a child's age. According to the current definition by the American Heart Association (AHA) guidelines in pediatric advanced life support (PALS), clinically significant bradycardia in children is a heart rate slower than 60 beats/minute that is associated with poor systemic perfusion.[37] An athletic adolescent may have a resting baseline heart rate lower than 60 beats/minute, requiring no treatment if asymptomatic with good perfusion.

Bradycardia is poorly tolerated in infants and children because they are not physiologically capable of increasing their stroke volume to maintain an adequate cardiac output in the face of significant bradycardia. **The most common cause of symptomatic bradycardia in infants and children is hypoxia.** First, ensure adequate oxygenation and ventilation. Epinephrine is the first-line medication for treatment of symptomatic bradycardia in children

Fig. 170.10. An example of an electrocardiogram (ECG) showing a wide-complex supraventricular tachycardia at a rate of approximately 270 beats/minute in an infant with Ebstein's anomaly of the tricuspid valve. This infant was in supraventricular tachycardia for approximately 2 days and presented with an acute exacerbation of her congestive heart failure (CHF), as evidenced by the cardiomegaly on the chest radiograph (see Fig. 170.11). Note that the cardiothoracic ratio in this infant is approximately 70%.

that is not responsive to appropriate oxygenation and ventilation. If additional doses of intravenous or intraosseous epinephrine are required to treat symptomatic bradycardia, the dose should remain at standard dosing (0.01 mg/kg). Atropine is indicated for vagally-induced bradycardia or treatment of primary atrioventricular block. Atropine will have no effect on the denervated heart (e.g. after cardiac transplantation).[15] If vascular access is not available, both epinephrine and atropine can be administered through the tracheal tube, although the intravenous route is preferred.

Other causes of bradycardia include hypothermia, increased intracranial pressure, heart blocks (congenital and acquired), denervated heart status after cardiac surgery, hypothyroidism, sick sinus syndrome, and various medications and toxins (eg, digoxin, beta-blockers, calcium channel blockers, and cholinergic agents). Children with presyncopal or syncopal symptoms or poor perfusion with Mobitz type II second-degree atrioventricular block, complete third-degree heart block, or sick sinus syndrome should be paced.

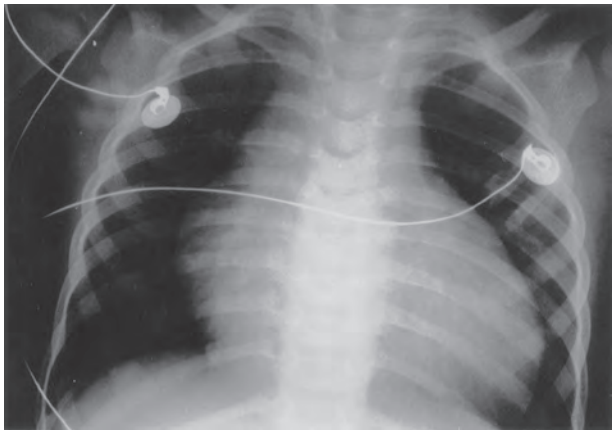

Fig. 170.11. Chest radiograph of same infant as in Figure 170.10.

Tachydysrhythmias

Supraventricular Tachycardia. Supraventricular tachycardia is the most common symptomatic dysrhythmia in infants and children. No cardiac abnormalities are found in approximately half of the cases; the Wolff-Parkinson-White syndrome is present in only 10% to 20%. The QRS complex is narrow (<0.08 second) in up to 90% of the cases of pediatric supraventricular tachycardia.[40] The type of supraventricular tachycardia that occurs most commonly in infants and children involves a reentrant mechanism that uses an accessory pathway and the atrioventricular node (ie, atrioventricular reentrant tachycardia [AVRT]). The *orthodromic* reentry phenomenon involves the normal antegrade conduction from the atria to the ventricles down the atrioventricular node with retrograde conduction back from the ventricles to the atria by the accessory pathway. Orthodromic conduction will produce a narrow–QRS complex supraventricular tachycardia. The less common reentry mechanism is the *antidromic* form in which conduction from the atria to the ventricles first goes antegrade down the accessory pathway then retrograde back to the atria by the atrioventricular node. Antidromic conduction will produce a wide–QRS complex supraventricular tachycardia. Supraventricular tachycardia in a child with a preexisting bundle branch block can also result in a wide-complex supraventricular tachycardia (Fig. 170.10). The ECG in Figure 170.10 reveals a case of a wide-complex supraventricular tachycardia in a child with Ebstein's anomaly of the tricuspid valve who also presented with CHF (Fig. 170.11).

Clinical Features and Diagnostic Testing. The width of the QRS interval in patients with pediatric supraventricular

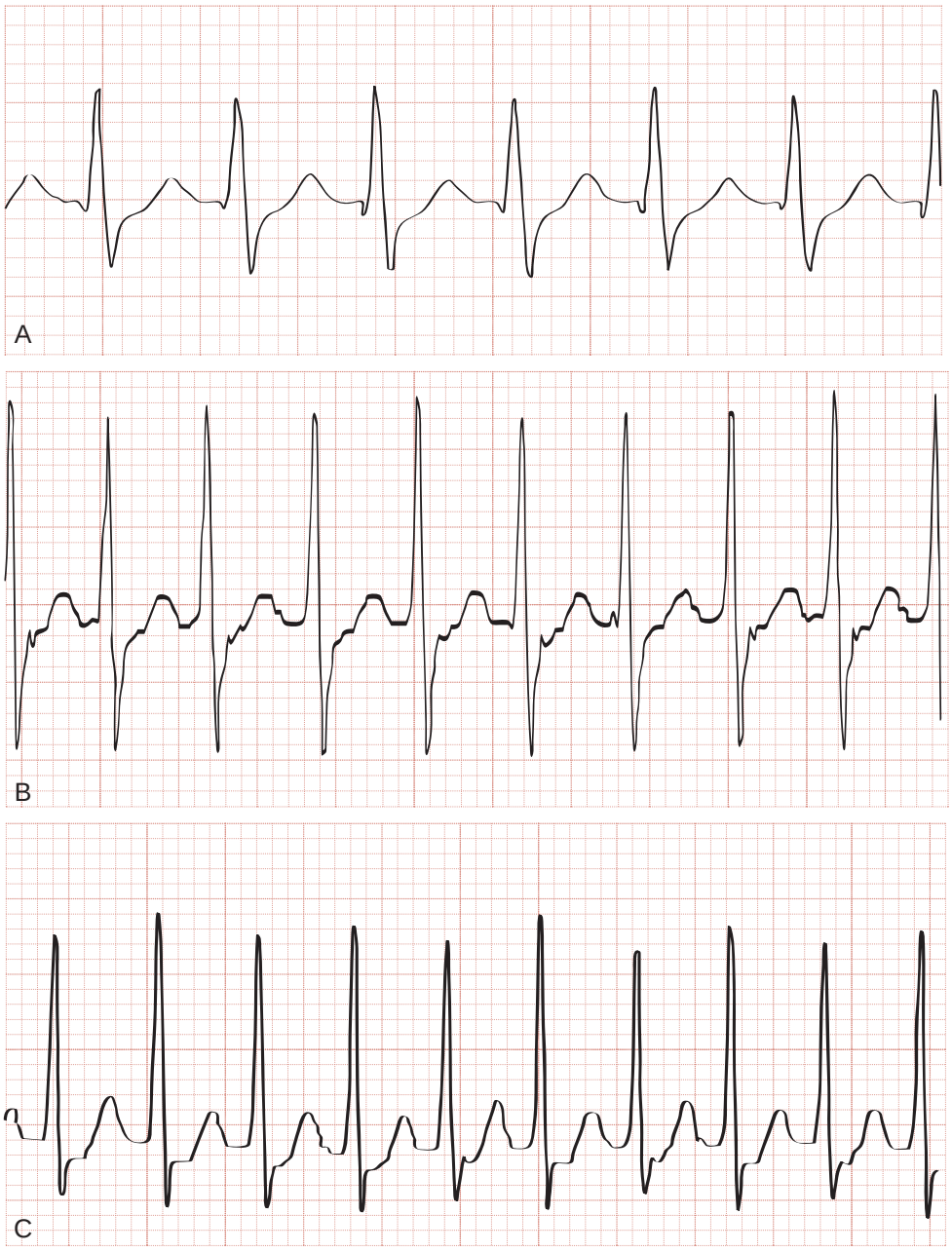

Fig. 170.12. Three electrocardiographic examples of classic narrow-complex supraventricular tachycardia in children. The heart rate is approximately 240 beats/minute in the first two examples **(A** and **B)** and approximately 270 beats/minute in the third example **(C).**

tachycardia is most commonly narrow complex, with heart rates in infants usually higher than 220 beats/minute (Fig. 170.12). It is sometimes difficult to distinguish between sinus tachycardia and supraventricular tachycardia (Table 170.6).

Although healthy infants can generally tolerate supraventricular tachycardia with heart rates approaching 300 beats/minute, supraventricular tachycardia may begin to produce signs of CHF and shock if it is left untreated. Older children with supraventricular tachycardia commonly present with palpitations, difficulty in breathing, and chest discomfort.

Management. The emergency clinician should immediate synchronized cardioversion (0.5 to 1 J/kg) for children in supraventricular tachycardia (SVT) with signs of poor perfusion, such as altered mental status, delayed capillary refill, pallor, cyanosis, or hypotension (ie, decompensated shock). If the child does not convert with this initial cardioversion attempt, the energy dose can be doubled up to 2 J/kg on subsequent attempts. If the child is hemodynamically stable, vagal maneuvers, then adenosine, may be attempted initially before cardioversion; a continuous rhythm strip should be run to document the response to each conversion attempt. Vagal maneuvers (eg, a bag containing a slurry of crushed ice and water to the face, blowing on an occluded straw, or blowing on the tip of a syringe) can be attempted before adenosine administration in the child with hemodynamically stable supraventricular tachycardia. Application of ice to the face has been demonstrated to be a fairly effective method of converting supraventricular tachycardia in infants and children. One method to perform this maneuver is to fill a plastic bag or surgical glove with a slurry of crushed ice and water, which is then placed over the infant's forehead, eyes, and bridge of the nose for 10 to 15 seconds. Placement of the ice bag should not occlude the nose or mouth. External ocular pressure should be avoided; it can be dangerous

in children because excessive pressure can lead to a ruptured globe. Carotid massage is less effective and is not recommended as a vagal maneuver in infants or children.[37]

The initial dose of adenosine in children is 0.1 mg/kg with a maximum initial dose of 6 mg. If this initial dose of adenosine fails to convert the supraventricular tachycardia, the dose is then doubled to 0.2 mg/kg with a maximum of 12 mg/dose. This 0.2 mg/kg dose of adenosine may be repeated once. Higher doses can be used in younger children (0.3 mg/kg) but doses should not exceed the adult maximum of 12 mg. Elective cardioversion with procedural sedation may be required in children who fail to convert with adenosine. Adenosine-induced wide-complex tachycardia (secondary to an occult accessory conduction pathway) is an uncommon complication (Fig. 170.13). Amiodarone may be given at a loading dose of 5 mg/kg over 60 minutes, then continued at 5 mcg/kg/min.[41] Verapamil should be avoided in infants and children younger than 2 years old because of the risk of profound hypotension and cardiovascular collapse in this age group.[42-44] Once the patient has converted to sinus rhythm, a 12-lead ECG should be obtained to assess for the possibility of Wolff-Parkinson-White syndrome or any other underlying conduction abnormalities that may have predisposed the child to development of the supraventricular tachycardia.

TABLE 170.6

Clinical and Electrocardiographic Features to Differentiate Sinus Tachycardia From Supraventricular Tachycardia in Children

	SINUS TACHYCARDIA	SUPRAVENTRICULAR TACHYCARDIA
Precipitating events	Dehydration, fever, pain	No precipitating event
P waves on electrocardiogram (ECG)	Present	Absent
Heart rate varies with activity	Yes	No
Beat-to-beat variability	Yes	Constant R-R intervals
Heart rate in infants (beats/minute)	Usually <220	Usually >220
Heart rate in children (beats/minute)	Usually <180	Usually >180

Atrial Flutter and Atrial Fibrillation. Both atrial flutter and atrial fibrillation are rare in children and are usually associated with underlying heart conditions (eg, CHD, status post–open heart surgical procedures that involved the atria, myocarditis, and digoxin toxicity). Hemodynamic stability of these two dysrhythmias depends on the rate of the ventricular response. As in adults, children with hemodynamically unstable atrial flutter or atrial fibrillation should be electrocardioverted. The initial treatment priority in patients with hemodynamically stable atrial flutter and atrial fibrillation is first to slow the rate of the ventricular response with medications, such as diltiazem, beta-blockers, or digoxin. Once the ventricular rate is controlled, the rhythm can then be

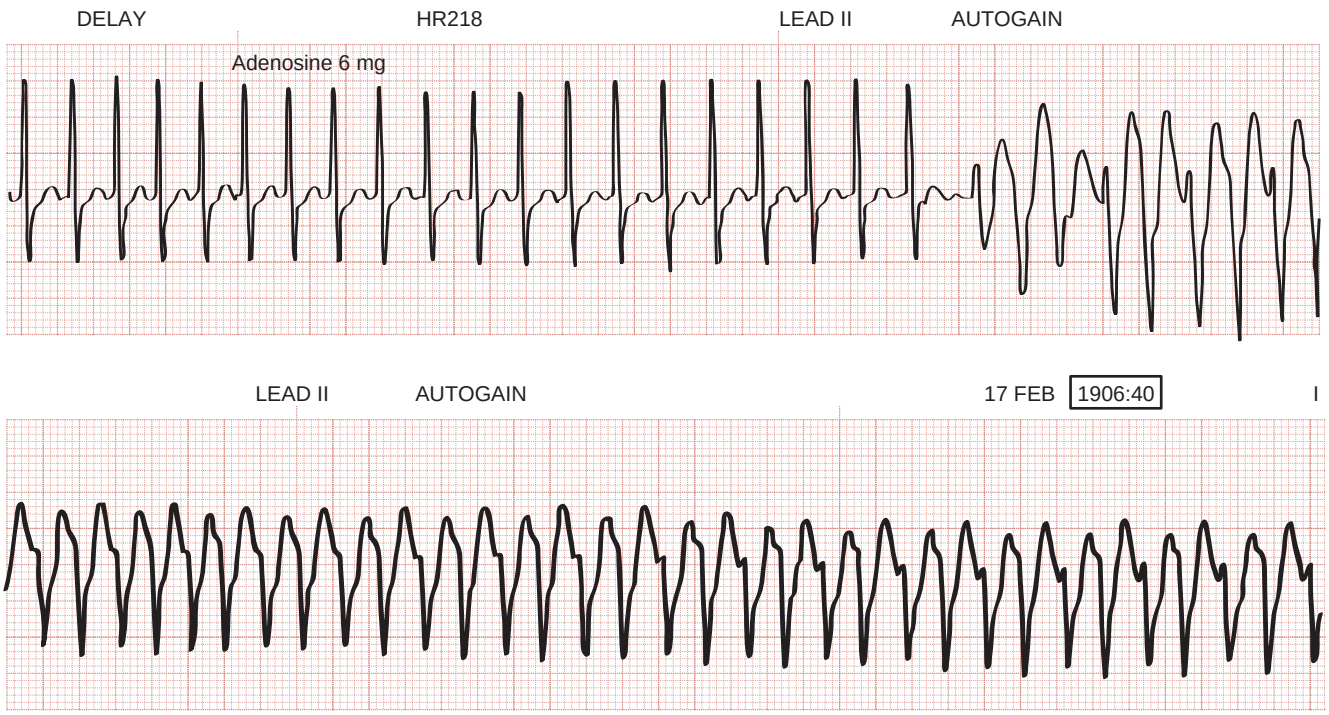

Fig. 170.13. An example of adenosine-induced wide-complex tachycardia. A dose of 6 mg of adenosine was administered to this previously healthy 15-year-old girl who presented with a 6-hour history of palpitations. She had no previous cardiac problems except for intermittent palpitations in the past that always resolved spontaneously without any medical interventions. Once adenosine blocked the conduction through the atrioventricular node, a wide-complex tachycardia appeared on the electrocardiogram (ECG), which was probably due to antegrade conduction through an accessory pathway. During the 30 seconds of this wide-complex tachycardia, the patient remained alert with excellent perfusion parameters. This wide-complex tachycardia then spontaneously converted to normal sinus rhythm. Although the patient's postconversion ECG did not reveal an accessory pathway, Holter monitoring 1 month later detected the classic electrocardiographic findings of Wolff-Parkinson-White syndrome.

converted and suppressed with amiodarone, procainamide, or elective cardioversion. If the patient who presents with atrial flutter or atrial fibrillation is known to have an underlying Wolff-Parkinson-White syndrome, the four medications that should be avoided are the A-B-C-D medications (adenosine, beta-blockers, calcium channel blockers, and digoxin); all of these medications preferentially block conduction down the atrioventricular node, leaving the accessory pathway open to conduct the atrial tachycardia to the ventricles at a potentially lethal rate.[37] Under these circumstances, physicians should use amiodarone, procainamide, or cardioversion as safer alternatives. Consultation with the cardiologist and initiation of anticoagulation should also be considered to prevent a thromboembolic complication before conversion of either of these atrial dysrhythmias in the hemodynamically stable patient believed to have the rhythm disorder within 48 hours prior of presentation.

Ventricular Tachycardia. Ventricular tachycardia is not a common dysrhythmia in children. The majority of children with ventricular tachycardia have an underlying condition, such as post–cardiac surgery status, myocarditis, prolonged QT syndrome, drug or toxin exposures (eg, cyclic antidepressants), or electrolyte abnormalities. The treatment of ventricular tachycardia will depend on hemodynamic status of the patient. Torsades de pointes is a unique type of polymorphic ventricular tachycardia characterized by QRS complexes that change in polarity and amplitude. Prolonged QT syndrome, underlying congenital cardiac defects, hypomagnesemia, and various medications (eg, cyclic antidepressants) have been identified as known causes of torsades de pointes. The treatment of choice is intravenous magnesium at an initial dose of 25 to 50 mg/kg, up to the adult dose of 2 g over 2 minutes. Class IA (ie, procainamide) and class III (ie, amiodarone) antidysrhythmic agents are contraindicated in the treatment of torsades de pointes because these antidysrhythmic agents are capable of prolonging the QT interval, which could then precipitate the degeneration of the torsades de pointes into a lethal rhythm.

Pulseless Rhythms

Ventricular Fibrillation and Pulseless Ventricular Tachycardia. Ventricular fibrillation and pulseless ventricular tachycardia account for approximately 9% to 10% of out-of-hospital cardiac arrest cases in which a terminal rhythm was recorded. The survival rate for out-of-hospital ventricular fibrillation and pulseless ventricular tachycardia can be as high as 30%, whereas the survival rate from asystolic cardiac arrest is less than 1%. In a study of in-hospital cardiac arrests, a shockable rhythm was present during some point of the resuscitation in 25% of children.[45] The survival rate of children who initially exhibited shockable rhythms was higher than for children with nonshockable rhythms. The use of automated external defibrillators (AEDs) is now acceptable in all age ranges, including infants and children. Pediatric pads (attenuating pads) should be used whenever possible for children 1 year to 8 years old (or less than 25 kg).[37,46,47] In infants younger than 1 year, manual defibrillation is preferred. If a manual defibrillator is unavailable or its use is delayed, an AED with a pediatric attenuator may be used; if neither is available, an AED without a dose attenuator may be used.[37]

Asystole and Pulseless Electrical Activity. Asystole is the most common rhythm found in out-of-hospital cardiac arrest in children and is associated with a less than 1% chance of survival. The key to survival from any pulseless electrical activity rhythm is the rapid identification and treatment of the underlying cause. The causes of pulseless electrical activity can be remembered by the six Hs and five Ts: hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia/hyperkalemia, hypoglycemia, and hypothermia; and toxins, tamponade, tension pneumothorax, thrombosis (pulmonary or coronary artery), and trauma.[37] The most common cause of pulseless electrical activity in children is profound hypovolemia. As such, an intravenous fluid bolus should always be considered as a therapeutic option during the treatment of pulseless electrical activity.

Special Resuscitation Situations in Children

Children with single-ventricle physiology (eg, hypoplastic left heart syndrome and double-outlet right ventricle physiology) after a palliative shunting procedure should be given standard resuscitation care.[37] Heparin may be used in the pre-arrest or arrest of infants with a systemic–to–pulmonary artery shunt or right ventricle–to–pulmonary artery shunt to halt thrombus propagation in this low circulatory flow state.[37] A target oxyhemoglobin saturation (Spo_2) of approximately 80% is preferred in these children. End-tidal carbon dioxide readings after resuscitation may lag behind as varying pulmonary blood flow changes that do not necessarily reflect cardiac output. The goal is to provide adequate preload with judicious fluids to balance systemic and pulmonary blood flow. If available, extracorporeal membrane oxygenation should be considered in these patients.[14,48-50]

Children with a history of pulmonary hypertension should also receive standard resuscitation management. Preload should be optimized with isotonic saline boluses. Inhaled nitric oxide in the ICU may be given to reduce PVR.[51] Early contact with the child's cardiologist and cardiothoracic surgeon is instrumental in the postresuscitative care of children with CHD.

Bacterial Endocarditis

Perspective

Bacterial endocarditis involves an infection of the endothelial surfaces of the heart with a propensity for the valves. The incidence of bacterial endocarditis in children may be increasing slightly because of the many advances in surgical technology that are now allowing many children with very complex congenital heart lesions to survive. Children with indwelling intravenous lines with or without underlying CHD are also at risk for development of bacterial endocarditis. Although bacterial endocarditis most commonly occurs in children with an underlying CHD or an acquired cardiac lesion (eg, acute rheumatic valvular heart disease), it can also occur in patients with no underlying anatomic defects of the valves or endocardium.[52,53]

Factors that predispose children with underlying anatomic cardiac defects to bacterial endocarditis include dental procedures and other surgical procedures involving the respiratory, gastrointestinal, or genitourinary tracts. Those cardiac lesions with a more turbulent blood flow or a higher flow velocity are more prone to development of bacterial endocarditis secondary to a greater risk of endothelial surface damage, which then increases the risk of platelet deposition and vegetation formation. Cardiac lesions that carry this higher risk include VSD, aortic valvular stenosis, tetralogy of Fallot, single-ventricle states, bicuspid aortic valves, prosthetic valves, and postoperative systemic-to-pulmonary shunts. Isolated secundum ASD carry a much lower risk for bacterial endocarditis because the shunt flow through the ASD is typically of a much lower velocity.

Clinical Features and Diagnostic Strategies

The early clinical manifestations of bacterial endocarditis may be nonspecific. The child may simply present with only fever and tachycardia. However, bacterial endocarditis should be suspected

in any child with an anatomic cardiac defect who presents with an unexplained fever. This diagnosis should always be considered in any child with a known CHD or an acquired cardiac lesion who presents with any of the conditions listed in Box 170.11. A new heart murmur is present in less than 50% of the bacterial endocarditis cases.[28,53] Common presenting signs are fever (99%), petechiae (21%), changing murmur (21%), dental caries (14%), and hepatosplenomegaly (14%). Less common signs are CHF (9%), splinter hemorrhages (5%), Roth's spots (5%), and Osler's nodes (4%).

In addition to vigilance for the diagnosis of infective endocarditis—especially in children with CHD—the emergency clinician should be aware of the indications for prophylaxis. The AHA in conjunction with the American Academy of Pediatrics (AAP) and the Infectious Diseases Society of America has published revised guidelines for the prevention of infective endocarditis.[54,55] The changes simplify and greatly narrow the recommendations to provide prophylaxis for only the higher risk patients and procedures (Box 170.12). For those children for whom prophylaxis is recommended, the indications are (1) all dental procedures and (2) any manipulation or perforation of the gingival or oral mucosa. Antibiotic prophylaxis for infective endocarditis is no longer recommended for gastrointestinal and genitourinary procedures (Box 170.13). The committee found that it is still reasonable to give prophylaxis for procedures on the respiratory tract, infected skin, or musculoskeletal tissue only for high-risk patients (Table 170.7).[54]

Diagnostic studies for a child with suspected bacterial endocarditis include a complete blood cell count, C-reactive protein (CRP) assessment, measurement of erythrocyte sedimentation rate (ESR), three blood cultures, chest radiography, and electrocardiography.[56-58] Cultures from scrapings of cutaneous emboli can also aid in the diagnosis. Although the definitive diagnostic study is the echocardiogram, it is only 80% sensitive in detecting the nidus of infection on the endocardium or valves. *Streptococcus viridans* and *Staphylococcus aureus* are the two most common offending organisms recovered from the blood cultures of children with bacterial endocarditis. Studies have shown that in children with CHD, 60% of the cases caused by staphylococcal species are methicillin resistant and associated with increased risk of mortality.

Management

Antibiotics should be started immediately after blood culture samples have been obtained. Although the choice of intravenous antibiotics depends on the suspected source of seeding and the child's immune status, a commonly recommended regimen includes an aminoglycoside plus a penicillinase-resistant penicillin, such as oxacillin. If methicillin-resistant staphylococcus is suspected, vancomycin should also be included in the initial empirical antibiotic regimen.[59]

An increase in antibiotic resistance to the three major causes of bacterial endocarditis—streptococci, staphylococci, and enterococci—has increased the mortality rate of bacterial endocarditis, now at 25% to 40%.[55] Complications of bacterial endocarditis include systemic septic emboli, pulmonary emboli, central nervous system emboli with resultant neurologic deficits, dysrhythmias, CHF, myocarditis, myocardial abscesses, and valvular obstruction and destruction. Despite appropriate antibiotic treatment, surgical intervention to remove septic vegetations or valve replacement is sometimes necessary.

Myocarditis

Myocarditis is an inflammatory condition of the myocardium with various infectious and noninfectious origins. In the United States, the most common cause is viral; coxsackievirus B and enteroviruses account for the majority of cases. Other viral causes

BOX 170.11

Clinical Conditions in Which Bacterial Endocarditis Should Be Suspected in a Child With an Underlying Anatomic Cardiac Defect

- Fever of unknown etiology
- A change in the quality of the preexisting heart murmur or the presence of a new heart murmur
- Development of a neurologic deficit (secondary to central nervous system emboli)
- New-onset microscopic hematuria
- Splenomegaly
- Petechiae
- Splinter hemorrhages involving the conjunctiva, nail beds, palms, or soles
- Myalgias

BOX 170.12

Cardiac Conditions for Which Endocarditis Prophylaxis Is Recommended

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Congenital heart disease (CHD)*
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device during the first 6 months after the procedure†
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device (which inhibit endothelialization)
- Cardiac transplantation recipients who have cardiac valvulopathy

From American Heart Association: Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation 116:1736, 2007.

*Except for those conditions above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

BOX 170.13

Procedures for Which Endocarditis Prophylaxis Is Recommended

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa*
- Consider prophylaxis for incisional procedures on the respiratory tract, infected skin, or musculoskeletal tissue only for high-risk patients

From American Heart Association: Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation 116:1736, 2007.

*The following procedures do not need prophylaxis: routine anesthetic injections through noninfected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.

TABLE 170.7

Regimens for Prophylaxis of Infective Endocarditis

		SINGLE DOSE 30 TO 60 MINUTES BEFORE PROCEDURE	
SITUATION	AGENT	ADULTS	CHILDREN
Oral	Amoxicillin	2 g PO	50 mg/kg PO
Unable to take oral medications	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin *or* Clindamycin *or* Azithromycin or clarithromycin	2 g PO 600 mg PO 500 mg PO	50 mg/kg PO 20 mg/kg PO 15 mg/kg PO
Allergic to penicillins or ampicillin—unable to take oral medications	Cefazolin or ceftriaxone *or* Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

Modified from American Heart Association: Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation 116:1736, 2007.
IM, Intramuscular; *IV,* intravenous; *PO, per os* (by mouth).

include echoviruses, influenza A and B viruses, adenovirus, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and hepatitis B virus. Bacterial causes include *Corynebacterium diphtheriae, Streptococcus pyogenes, S. aureus, Mycoplasma pneumoniae, Borrelia burgdorferi,* and meningococcus. Noninfectious causes include Kawasaki disease, acute rheumatic fever (ARF), collagen vascular disorders (eg, systemic lupus erythematosus), toxins (eg, cocaine and doxorubicin), endocrine disorders (eg, hyperthyroidism), and drug-induced hypersensitivity (eg, penicillins, sulfonamides, phenytoin, carbamazepine).

Clinical Features

Viral myocarditis usually has a gradual onset with preceding upper respiratory tract infection. Providers should consider myocarditis in infants and children with symptoms out of proportion to the typical course of a benign cause, such as a viral syndrome. In mild cases, the only sign of myocarditis may be tachycardia. Tachycardia that is disproportionate to the degree of fever should alert the emergency clinician to the possibility of myocarditis.[59] Other presenting signs and symptoms include fever, myalgias, fatigue, tachypnea, wheezing, abdominal pain, and chest pain. More severe cases of myocarditis can even have signs and symptoms of acute CHF and various dysrhythmias. The physical examination may reveal a new murmur, a gallop rhythm, or a pericardial friction rub with muffled heart tones (if the myocarditis is also accompanied by pericarditis and subsequent pericardial effusion). In general, these are sick children with vague symptoms.

Diagnostic Testing and Management

The evaluation and management of the child with myocarditis depend on the suspected cause and presenting signs and symptoms. Blood cultures and viral titers should be considered in infectious and post-infectious cases. Appropriate antibiotics should be initiated immediately in cases with suspected bacterial origin. The chest radiograph may be normal in very mild cases, but cardiomegaly will be evident in more advanced cases. The electrocardiographic findings are usually nonspecific and can include low-voltage, nonspecific ST segment abnormalities, T wave inversions, atrioventricular block, and various other dysrhythmias. Creatine kinase-MB, cTnT, cTnI, CRP, and ESR may be elevated.

Bedside echocardiography can evaluate for effusion, tamponade, and global function. The goal of treatment is to maintain adequate cardiac output and to control any associated dysrhythmias. Children who present in CHF with poor perfusion (such as, lethargy, delayed capillary refill, poor urine output, or hypotension) will likely require inotropic support, positive pressure ventilation, or diuretics. The use of beta-blockers is contraindicated, and the routine use of immunosuppressive agents remains controversial.[59-61] Although the majority of children with acute viral myocarditis make a full recovery, a few patients will progress to dilated cardiomyopathy, which is characterized by dilated ventricles and impaired systolic contractility.

Pericarditis

Pericarditis is an inflammatory process within the pericardial sac that may not be associated with a pericardial effusion. In the majority of cases, pericarditis in children is self-limited and follows a benign clinical course. A sudden increase or a large amount of fluid within this pericardial sac can cause a tamponade-induced decrease in stroke volume, resulting in diminished cardiac output and hypotension.

The most common causes of pericarditis include bacterial and viral infections; other causes are ARF, systemic lupus erythematosus, uremia, post-pericardiotomy syndrome, leukemia, lymphoma, and tuberculosis. Approximately 30% of pericarditis cases are due to bacteria, such as pneumococcus, *S. aureus,* meningococcus, and *Haemophilus influenzae.* Approximately 30% of the purulent bacterial pericarditis cases occur in children younger than 6 years old. Viral causes are most common, but a specific viral pathogen is recovered in only 20% to 30% of cases. Viral causes include coxsackieviruses, echoviruses, adenovirus, Epstein-Barr virus, and influenza viruses.[62]

Clinical Features

The presenting signs and symptoms of pericarditis depend on the cause of the pericarditis, as well as on the amount of fluid that has accumulated within the pericardial sac. Chest pain that varies with position is a common complaint with pericarditis; pain is exacerbated with inspiration and the supine position but relieved when the patient sits up or leans forward. Tachycardia is also a common finding in patients with pericarditis and may be the only clue to the diagnosis. Other findings include fatigue,

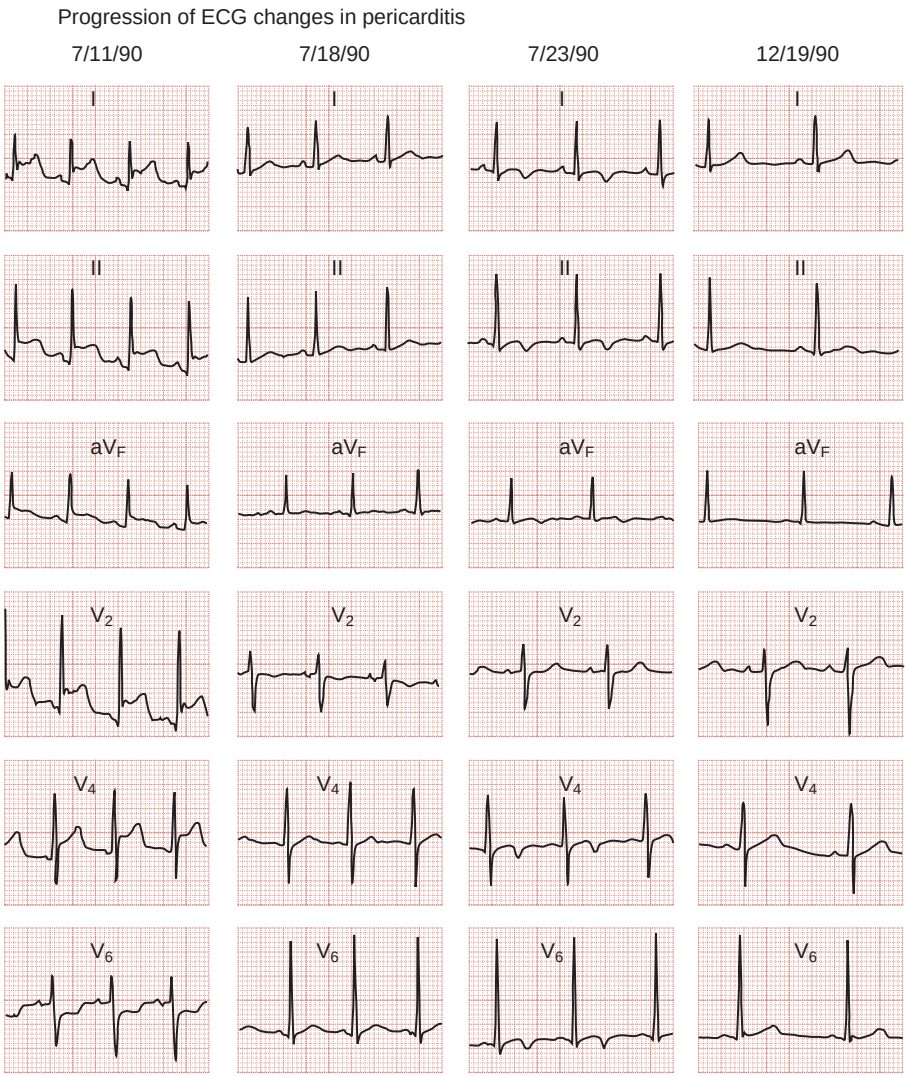

Fig. 170.14. The classic electrocardiographic progression of a patient with pericarditis. First phase: Diffuse ST segment elevation. Second phase: ST segments back to isoelectric but decreased T wave amplitude. Third phase: T wave inversion. Fourth phase: Complete resolution. Notice that the first three phases of the electrocardiographic abnormalities of pericarditis in this patient are evident during the first 2 weeks of his illness. A follow-up electrocardiogram (ECG) obtained 5 months later reveals a complete resolution of all the previous electrocardiographic abnormalities.

tachypnea, neck vein distention, pulsus paradoxus, hepatomegaly, lower extremity edema, and thready distal pulses if heart failure is present. Cardiac auscultatory findings can include a harsh-sounding friction rub or diminished or muffled heart tones if there is a significant amount of fluid within the pericardial sac. The pericardial friction rub, if present, is best heard when the patient sits up or leans forward. This friction rub of pericarditis can be distinguished from a pleural friction rub by having the patient hold his or her breath during auscultation. The friction rub of pericarditis will remain present during breath-holding; the pleural friction rub will no longer be heard while the patient holds the breath.

The chest radiograph in a child with pericarditis may not reveal an enlarged cardiac silhouette. If there is a large collection of fluid within the pericardial sac, the heart shadow on the chest radiograph will resemble a "water bottle" silhouette. Approximately 50% of pericarditis cases have some associated pleural effusion.[62,63]

The classic electrocardiographic findings of viral pericarditis include diffuse ST segment elevation and diffuse T wave inversions. The classic electrocardiographic changes associated with pericarditis evolve through four phases (Fig. 170.14). During the initial phase, there is diffuse ST segment elevation secondary to subepicardial inflammation; PR segment depression may also be seen. During the second phase, the previously elevated ST segments begin to return to isoelectric baseline, and the T wave amplitudes begin to decrease with flattening of the T waves. During the third phase, although the ST segments are now back to isoelectric baseline, the T waves are inverted. The fourth and final phase demonstrates complete resolution of the ST segment and T wave abnormalities. Diminished electrocardiographic voltages in all leads can also occur if there is a significant amount of fluid accumulated within the pericardial sac.

The diagnostic procedure of choice in any patient with suspected pericarditis is the echocardiogram; this study will confirm both the presence and the amount of accumulated fluid within the pericardial sac. Although echocardiography cannot accurately quantify the exact amount of fluid that has accumulated within the pericardial space, the presence of an anterior and posterior fluid collection is suggestive of a large collection.

Management

The management of a child with pericarditis depends on both the suspected cause, severity of symptoms, and amount of fluid that has accumulated within the pericardial space. Patients with fever, respiratory distress, or signs of CHF should be admitted and an echocardiogram emergently performed. An emergency pericardiocentesis is required in those patients with signs of acute cardiac tamponade. Any fluid that is aspirated from the pericardial space should be sent for routine cell counts, Gram's stain, and cultures. Antiinflammatory agents and appropriate antibiotics should be initiated on the basis of the suspected cause. Steroids are reserved for refractory cases that are not responsive to these agents and should be considered only after an infectious etiology is ruled out.[64,65]

Kawasaki Disease

Kawasaki disease, originally described as mucocutaneous lymph node syndrome by Dr. Tomisaku Kawasaki in 1967, has emerged as a significant cause of acquired cardiac disease in children in the United States. An estimated 3000 to 5000 cases of Kawasaki disease are diagnosed annually in the United States. Up to 20% of untreated children have some degree of coronary artery abnormalities.[66,67] This febrile, exanthematous, multisystem vasculitis is seen most commonly in children younger than 5 years old, with a male-to-female ratio of 1.5:1. Although the exact cause of this vasculitis of small- and medium-sized vessels remains unknown, early clinical recognition and initiation of high-dose aspirin and intravenous immune globulin (IVIG) improve the morbidity and mortality rates of Kawasaki disease in children.

Clinical Features

In addition to fever, the physical examination of a child with Kawasaki disease may reveal the typical findings as listed in Box 170.14 and illustrated in Figure 170.15. The classic features of Kawasaki disease may be manifested simultaneously or in series of days; a careful history and physical examination may elucidate the need for further testing. In addition, very young children may not have a classic presentation and require further investigation. All children with suspected Kawasaki disease, with either classic or incomplete features, should undergo echocardiography for detection of the presence and degree of coronary aneurysm.[66]

Incomplete Kawasaki Disease

The classic presentation of Kawasaki disease is a clinical diagnosis of four or more of the five criteria in a child who is febrile 5 days or more. However, these strict criteria may miss a substantial number of children who present with incomplete Kawasaki disease. Any child may have an incomplete presentation, but this is mostly seen in infants younger than 6 months old.

The AHA's Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease has published consensus guidelines on the approach to incomplete Kawasaki disease.[66,67] The more inclusive criteria recommend that in a child who is febrile 5 days or more, the presence of two or three criteria should prompt further testing. A CRP of 3 mg/dL or more or an ESR of 40 mm/hr or more should prompt further laboratory investigations; children with elevated inflammatory markers should be empirically treated (Box 170.15). During their hospital stay, children should receive an echocardiogram to assess for coronary aneurysms.

Children with a CRP of less than 3 mg/dL and an ESR of less than 40 mm/hr may be observed daily and reassessed without treatment; serial ESR and CRP should be should be obtained daily on an outpatient basis. Infants 6 months of age or younger are more likely to present with incomplete Kawasaki disease and are more susceptible to giant coronary artery aneurysm formation. For this reason, irrespective of general well appearance or lack of clinical findings, infants 6 months of age or younger with fever lasting for 7 days or more should undergo supplemental laboratory testing and undergo echocardiogram when inflammatory markers are abnormal. This underscores the current limits of diagnosis of Kawasaki disease, as well as the obligation to prevent the disastrous sequelae of aneurysmal development.

Differential Diagnoses

Measles can mimic Kawasaki disease (ie, a febrile illness with red eyes, a rash, and erythema of the oropharynx). The measles rash classically begins on the head and face and progresses caudally. The rash of Kawasaki disease typically begins on the trunk and then spreads to the face and extremities; it may be polymorphous, but not bullous or vesicular.

The palmar lesions of measles are discrete macular lesions (see Fig. 170.15, *F*), whereas the palmar finding in children with Kawasaki disease is diffuse erythema, which may later desquamate (see Fig. 170.15, *C*).

BOX 170.14

Diagnostic Criteria for Kawasaki Disease

- Fever for 5 days or more
- At least four of the five following physical examination findings:
  1. Bilateral, nonexudative bulbar conjunctival injection (bilateral scleral injection with perilimbic sparing)
  2. Oropharyngeal mucous membrane changes (pharyngeal erythema, red and cracked lips, and a strawberry tongue)
  3. Cervical lymphadenopathy (with at least one node >1.5 cm in diameter)
  4. Peripheral extremity changes (diffuse erythema and swelling of the hands and feet during the acute phase or periungual desquamation during the convalescent phase of the illness); this diffuse palmar erythema seen in Kawasaki disease is in contrast to the discrete macular lesions of various viral illnesses (eg, measles) that can sometimes be seen on the palms and soles
  5. A polymorphous generalized rash (non-vesicular and nonbullous); there is no specific rash that is pathognomonic for Kawasaki disease
- In a child with four or more criteria, the diagnosis may be made on day 4 of the fever.

Burke RJ, Chang C: Diagnostic criteria of acute rheumatic fever. Autoimmun Rev 13(4-5):503-507, 2014.

BOX 170.15

Supplemental Laboratory Criteria for Kawasaki Disease

Albumin ≤3 g/dL
Anemia for age
Platelet count of ≥450,000/mm^3
White blood cell (WBC) count ≥15,000 mm^3
Elevation of alanine aminotransferase
Sterile pyuria of ≥10 WBCs per high-power field

From Newburger JW, et al: Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 110:2747, 2004.

Fig. 170.15. Classic physical examination findings of Kawasaki disease. Note the bilateral nonexudative scleral injections **(A)** with perilimbic sparing (the thin margin of white sclera around the cornea), red and cracked lips with a strawberry tongue **(B),** diffuse palmar erythema **(C),** red soles **(D),** and polymorphous exanthem **(E).** The diffuse palmar erythema of Kawasaki disease **(C)** is distinct from the palmar findings seen in other viral illnesses, such as the discrete macular lesions on the palms in this child with measles **(F).**

Streptococcal disease, including pharyngitis and scarlet fever, can be confused with Kawasaki disease, but conjunctivitis and swelling of the hands and feet are unusual for streptococcal disease. Other infectious or autoimmune causes that mimic Kawasaki disease include Rocky Mountain spotted fever, leptospirosis, Stevens-Johnson syndrome, and juvenile rheumatoid arthritis.[66,67]

There are many imitators of Kawasaki disease. Conversely, this systemic vasculitis can affect any organ system and thus be misleading. For example, Kawasaki disease can present with nausea, vomiting, and abdominal pain in a febrile child, which may be mistaken for a surgical abdomen. In addition, a febrile irritable child with Kawasaki disease may have a cerebrospinal fluid pleocytosis and be misdiagnosed with viral meningitis. For this reason, Kawasaki disease should be included in the differential diagnosis of any child with several days of fever, rash, and nonpurulent conjunctivitis to avoid the pitfall of early diagnostic closure.

Clinical Course

Kawasaki disease is postulated to be caused by an infectious agent that enters the respiratory tract and initiates an oligoclonal immunoglobulin A response, which activates lymphocytes, cytokines, and proteinases that weaken vessel walls and predispose the entire circulation to aneurysms. Approximately 25% of patients have mild diffuse myocardial inflammation. This occurs during the acute febrile period and is characterized by tachycardia, a gallop, and nonspecific ST-T wave changes. Up to 5% of the children also exhibit some degree of CHF during this acute phase of their illness. This carditis usually resolves when the fever resolves. Pericardial effusions also occur in up to 20% to 40% of cases. Mild mitral and aortic regurgitation is also seen in 1% to 2% of untreated cases on echocardiographic examinations. This phase of the disease is mild and self-resolving.

Recognition of Kawasaki disease allows for prompt treatment, to prevent cardiac complications; these complications usually peak 2 to 4 weeks from the onset of the illness and are seen in 15% to 25% of untreated patients. These coronary aneurysms can lead to myocardial infarction, thrombosis, rupture, or dysrhythmias. Significant risk factors for coronary aneurysmal formation include male gender, age younger than 1 year old, or older than 8 years old, prolonged febrile period longer than 10 to 14 days, early myocarditis, anemia (hemoglobin <10 g/dL), white blood cell count more than 30×10^3/hpf, increased band count, elevated ESR, elevated CRP level, low serum albumin levels, aneurysms involving other arteries (renal, axillary, or iliac), and giant coronary aneurysms (>8 mm in diameter). Death from Kawasaki disease is primarily due to myocardial infarction secondary to coronary artery occlusion. Giant coronary artery aneurysmal rupture is rare. Although most of the fatalities of Kawasaki disease occur within 6 weeks from the onset of the illness, sudden death can occur many years after the illness. Prompt recognition and treatment have decreased this mortality rate from 2% to less than 0.01%.[37]

Management

The main goal of treatment during the acute febrile phase of Kawasaki disease is to provide supportive care and to decrease the inflammation of the myocardium and coronary arteries. IVIG and high-dose aspirin have an additive effect and—when initiated within 10 days from the onset of the illness—can substantially decrease the progression to coronary artery dilation and aneurysm formation compared with aspirin therapy alone.[68] The combination results in a more rapid resolution of fever and the other indicators of acute inflammation.[68] However, despite prompt treatment with IVIG and high-dose aspirin, 2% to 4% of children still have coronary artery abnormalities.[66]

The current IVIG regimen involves an infusion of 2 g/kg over 10 to 12 hours. Side effects of IVIG include hypotension, nausea, vomiting, headache, and seizures. Close cardiac monitoring during the IVIG infusion is recommended. The 5% to 10% of children who receive IVIG and experience a persistent or recurrent fever after the initial dose of IVIG may be given a second infusion at the same dose. Approximately two-thirds of children who fail to respond to the initial dose of IVIG will improve with the second infusion.

Aspirin is initiated at 80 to 100 mg/kg/day orally divided into an every-6-hour dosing regimen until the child is afebrile for 48 to 72 hours. This dose is then decreased to 3 to 5 mg/kg orally each day until the laboratory study results return to normal, which typically occurs 6 to 8 weeks after the onset of the disease.[68-70] Aspirin therapy is continued beyond this period only in those children in whom coronary artery abnormalities are present. Ibuprofen can antagonize the antiplatelet effects of aspirin and should be avoided during treatment.

The follow-up of children with Kawasaki disease depends on the degree and presence of carditis and coronary artery abnormalities detected on the initial echocardiogram. Other imaging modalities used to follow aneurysmal parameters include electron-beam computed tomography, coronary magnetic resonance angiography, and computed tomography. Those children with more severe cardiac abnormalities should have close follow-up by a cardiologist experienced in Kawasaki disease. Prompt diagnosis and treatment leads to rapid symptomatic improvement in 90% of cases and prevents coronary aneurysm formation in 95%.

Acute Rheumatic Fever

ARF, one of the most common causes of acquired heart disease in children, is the result of a delayed immune reaction to a group A streptococcal infection. In the United States, ARF most commonly occurs in children 5 to 15 years old, with an attack rate of 0.3% in children with an untreated streptococcal infection. Although this disease affects multiple organ systems, carditis is the most serious complication.

Clinical Features and Diagnostic Testing

The diagnosis of ARF is based on the Jones criteria (Box 170.16). In addition, there must also be evidence of an antecedent streptococcal infection, which can be documented by a positive throat culture, a positive rapid streptococcal antigen test finding, or an elevated antistreptolysin O (ASO) titer. The ASO titer begins to rise 1 to 3 weeks after streptococcal infection, peaks at 3 to 5 weeks, and reliably falls to baseline after 6 months. The streptozyme test is not as reliable and therefore should not be used as a definitive test for evidence of an antecedent group A streptococcal infection.[71] The diagnosis of ARF is made in a patient with a documented antecedent streptococcal infection who exhibits either two major criteria or one major plus two minor criteria.[71]

The most common presenting major criterion is the migratory polyarthritis, which commonly involves the larger joints of the

BOX 170.16

Jones Criteria for the Diagnosis of Acute Rheumatic Fever

The diagnosis of acute rheumatic fever (ARF) is based on the documentation of an antecedent streptococcal infection and (1) two major criteria or (2) one major criterion plus two minor criteria.

MAJOR CRITERIA

Carditis
Migratory polyarthritis
Erythema marginatum
Subcutaneous nodules
Chorea

MINOR CRITERIA

Clinical findings:
- Fever
- Arthralgia

Laboratory findings:
- Elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
- Prolonged PR interval

Supporting evidence of an antecedent group A streptococcal infection with either of the following:
- A positive throat culture or rapid streptococcal antigen test result
- An elevated antistreptolysin O (ASO) titer

extremities, as well as the smaller tarsal joints in the foot and the smaller carpal joints in the hand. The carditis of ARF most commonly involves valvulitis of the mitral and aortic valves, which clinically is manifested as occult mitral or aortic insufficiency. The murmur of mitral insufficiency is characterized as a holosystolic murmur best heard over the apex with radiation to the axilla. The murmur of aortic insufficiency is characterized as a diastolic murmur that is best heard over the base of the heart. Innocent murmurs that are normally exacerbated with fever can be mistaken for the murmurs of mitral or aortic insufficiency.

Other cardiac manifestations of ARF include CHF, pericarditis, and various degrees of heart block. The two dermatologic major criteria (erythema marginatum and subcutaneous nodules) and chorea occur less commonly than the migratory polyarthritis and carditis. Chorea may occur as the only manifestation of ARF. If arthritis is used as a major component, arthralgia cannot be used as a minor component to make the diagnosis. Likewise, if carditis is used as a major component, a prolonged PR interval cannot be used as a minor component.[71]

In addition to the ECG, CRP or ESR levels, and documentation of an antecedent streptococcal infection, the diagnostic evaluation of ARF should also include a chest radiograph, as well as an echocardiogram to evaluate the degree of cardiac involvement.

Differential Diagnoses

The differential diagnosis of ARF includes myocarditis, bacterial endocarditis, Lyme disease, systemic lupus erythematosus, juvenile rheumatoid arthritis, serum sickness, and septic arthritis.

Management

The acute management of ARF should focus on stabilization and treatment of any of the symptomatic cardiac manifestations of the illness, such as CHF or tamponade due to a pericardial effusion. Treatment should also include appropriate antibiotic therapy to eradicate the streptococcal infection, bed rest, and anti-inflammatory agents for arthritis. Steroids should be used in the treatment of carditis only under direction of a cardiologist. Monthly injections of benzathine penicillin G provide prophylaxis against recurrent attacks; alternative regimens include oral penicillin administered twice daily and, for penicillin-allergic patients, twice daily oral erythromycin. Prophylaxis is required until 18 years of age but can be continued for life, depending on the degree of cardiac involvement and risk of recurrence.[72]

Cardiac Causes of Sudden Death in Young Athletes

In a large registry study of 1866 sudden deaths in young athletes, 1048 (56%) were due to cardiovascular disease and 416 (22%) were due to direct blunt trauma.[73] The most common cardiovascular cause of sudden death in the athlete is hypertrophic cardiomyopathy, accounting for up to 36% of the cardiovascular-related cases (Box 170.17).[74]

Specific Disorders

Congenital Coronary Artery Anomalies. An additional 24% of the cases of sudden death are due to various anomalies of the coronary arteries.[49] Congenital coronary artery anomalies are difficult to detect from a clinical standpoint, but 37% of those individuals who died of congenital coronary artery anomalies exhibited previous symptoms of exercise-induced syncope or chest pain.[49,73] The exact pathophysiologic mechanism of sudden death in individuals with congenital coronary anomalies is unknown. Although there are a variety of congenital coronary artery anomalies, the most common potentially lethal lesion is the anomalous left coronary artery, in which the left main and right coronary arteries both arise from the right sinus of Valsalva. Individuals with this particular anomaly have a 46% incidence of sudden death, with more than 85% of the known cases of sudden death occurring during exercise.[73] Congenital coronary artery hypoplasia is another uncommon cause of exercise-induced sudden death. Any athlete with exertional syncope or chest pain should be evaluated by a cardiologist for the possibility of a congenital coronary artery anomaly. If an anomaly is detected and surgically corrected, the athlete may resume full activity and participation in competitive sports.

BOX 170.17

Cardiovascular Causes of Sudden Death in Young Athletes

Hypertrophic cardiomyopathy
Various congenital coronary artery anomalies
Prolonged QT interval syndrome
Various preexcitation syndromes (eg, Wolff-Parkinson-White syndrome)
Commotio cordis
Aortic rupture secondary to Marfan syndrome
Idiopathic dilated cardiomyopathy
Myocarditis
Coronary artery disease secondary to Kawasaki disease
Aortic stenosis
Mitral valve prolapse

Marfan Syndrome. Individuals with Marfan syndrome should be evaluated for potential cardiac abnormalities before being allowed to participate in competitive sports. Clinical manifestations of the disease include tall and slender habitus, striae atrophicae, disproportionately long extremities compared with the trunk, scoliosis, pectus excavatum or carinatum, and lens dislocation. Approximately 50% of patients with Marfan syndrome have cardiac manifestations, such as mitral valve prolapse or aortic dilation. The most serious cardiac complication of Marfan syndrome is the progressive dilation of the aorta with the potential risk of aortic rupture, which most commonly involves the descending portion of the aorta. Therefore, patients with Marfan syndrome should be prohibited from participation in contact sports. Those individuals who are known to have aortic dilation should also be prohibited from participation in any competitive sports regardless of the degree of contact involved. All patients with Marfan syndrome with or without cardiac involvement on their initial evaluation should be observed by a cardiologist with serial imaging studies of the aorta by echocardiography, magnetic resonance imaging, or computed tomography.

Hypertrophic Cardiomyopathy. Obstructive hypertrophic cardiomyopathy involves a thickened muscular intraventricular septum that bulges into the left ventricle and impedes forward flow, causing chest pain, shortness of breath, pre-syncope, or syncope. The nonobstructive form, which occurs when the thickened septum does not block forward flow, occurs in only 0.2% of the general population, yet it is the single most common cardiac cause of sudden death in the young athlete.[74] Sudden death in previously asymptomatic individuals with hypertrophic cardiomyopathy occurs during moderate or severe physical exertion. The proposed pathophysiologic mechanism of sudden death during exertion in these individuals is thought to be a transient decrease of blood flow out through the aorta or dysrhythmia originating from the hypertrophied ventricular myocardium.

Hypertrophic cardiomyopathy is a familial disease, inherited in an autosomal dominant fashion with variable penetrance. The hypertrophy of the left ventricle in this condition is idiopathic in nature and not due to chronic pressure overload conditions, such as systemic hypertension or aortic stenosis. The systolic left ventricular contractile function is vigorous, but the thickened muscle of the left ventricle is stiff, resulting in impaired ventricular relaxation and high diastolic filling pressures.

Clinical Features. Some individuals with hypertrophic cardiomyopathy have experienced previous "warning" episodes of chest pain, dyspnea, syncope, or palpitations during vigorous activities. A family history of sudden unexplained death in young adults should also alert the clinician to the possibility of hypertrophic cardiomyopathy. The majority of young athletes who die of this condition have the nonobstructive form of hypertrophic cardiomyopathy, and the classic loud systolic ejection murmur that is present with the obstructive form may not be heard during the routine pre-sports physical examination.[75,76]

If a systolic murmur along the lower left sternal border is heard on the routine screening physical examination of a young athlete, a Valsalva maneuver may help differentiate the murmur of aortic stenosis from the systolic murmur associated with the obstructive form of hypertrophic cardiomyopathy. During the Valsalva maneuver, the venous blood return to the heart is decreased, which in turn transiently reduces the left ventricular size. The transient reduction in the size of the left ventricle will increase the degree of obstruction and thus cause an increase in the intensity of the systolic murmur heard with the obstructive form of hypertrophic cardiomyopathy. In contrast to this, the systolic murmur of aortic stenosis will decrease in intensity during a Valsalva maneuver because of the transient reduction of blood flow through the stenotic aortic valve.

Current recommendations for pre-sports screening include a detailed family and personal history of known or suspected heart disease, physical examination, and 12-lead ECG.[77] If any suspicion remains, further evaluation (eg, echocardiography, Holter monitoring, other imaging studies) and referral to a cardiologist are indicated.[75]

Diagnostic Testing. The electrocardiographic findings in individuals with hypertrophic cardiomyopathy typically reveal various degrees of left ventricular hypertrophy and left atrial enlargement. Other electrocardiographic findings include prominent Q waves in the inferolateral leads and diffuse T wave inversions. The most accurate study for the diagnosis of hypertrophic cardiomyopathy is the echocardiogram, which will demonstrate various degrees of left ventricular hypertrophy and involving the ventricular septum in up to 90% of the cases. Patients with echocardiographic evidence of hypertrophic cardiomyopathy should receive serial echocardiographic examinations to monitor progression.[75]

Management. Beta-blockers are the mainstay of pharmacologic therapy (verapamil is second-line). Beta-blockers exert negative inotropic effects, attenuate adrenergic-induced tachycardia, improve myocardial oxygen supply-and-demand, and improve diastolic filling.[78] No pharmacologic therapy has been proven to prevent sudden death. The use of digoxin is contraindicated in patients with hypertrophic cardiomyopathy because its positive inotropic effect may worsen the left ventricular outflow obstruction. Sudden death in patients with hypertrophic cardiomyopathy is thought to be due to exertion-induced ventricular fibrillation or pulseless ventricular tachycardia. Therefore, all individuals diagnosed with hypertrophic cardiomyopathy, as well as those with an equivocal diagnosis of hypertrophic cardiomyopathy should not participate in vigorous activities and competitive sports.[75]

A transaortic septal myomectomy may be considered for patients with severe symptoms unresponsive to medical therapy. For suboptimal surgical candidates, implantation of a dual-chamber pacemaker may improve symptoms by decreasing the left ventricular outflow tract gradient.

Prolonged QT Syndrome. In 1957, Jervell and Lange-Nielsen first described the association of recurrent syncope, sudden death, and long QT interval in a series of deaf patients. Later, in 1963, Romano reported a similar association of symptoms with long QT intervals in patients with normal hearing. Both the Jervell–Lange-Nielsen and the Romano-Ward syndromes are inherited disorders with variable penetrance, characterized by a prolonged QT interval that has been associated with sudden death. The corrected QT (QTc) interval in normal individuals should not exceed 0.44 second in children or 0.42 second in adolescents. Individuals with QTc intervals longer than 0.55 second have a higher risk of sudden death. Prolongation of the QT interval predisposes the individual to ventricular tachycardia, torsades de pointes, and ventricular fibrillation, which is often initiated by a premature ventricular contraction occurring during the prolonged repolarization phase. In addition to the inherited syndromes of prolonged QT intervals, other causes of prolonged QT intervals include hypocalcemia, hypokalemia, hypomagnesemia, myocarditis, and medications (eg, procainamide, erythromycin, cyclic antidepressants, phenothiazines, quinidine, and organophosphates).

Clinical Features. Symptoms in the young athlete that are suggestive of QT prolongation include exercise-induced palpitations, chest pains, syncope, dizziness, and atypical seizures. The young athlete who has any of these symptoms should be evaluated by a cardiologist, especially if the family history is positive for sudden unexplained death, cardiac problems, syncope, or deafness. Any young athlete who has been diagnosed with a prolonged QT syndrome should be prohibited from participation in competitive sports and vigorous activities. The growing popularity and presence of AEDs in public places and at sporting events can potentially save the lives of those athletes who suddenly collapse because of an underlying prolonged QT syndrome–induced nonperfusing ventricular dysrhythmia.

Management. Treatment of a prolonged QT interval depends on the cause. Underlying metabolic disorders should be corrected, and medications that induce prolongation of the QT interval should be discontinued. Magnesium sulfate is the drug of choice in the treatment of torsades de pointes. Lidocaine is the safest medication for patients with prolonged QT interval–induced ventricular tachycardia or fibrillation. Anti-dysrhythmic agents that can prolong the QT interval, such as procainamide and amiodarone, should be avoided. Beta-blockers have been used to prevent sudden ventricular dysrhythmias in those patients with the familial forms of QT prolongation. Adjunctive treatment in these selected patients also includes the insertion of pacemakers or internal defibrillators.

Commotio Cordis. Commotio cordis occurs after a high-impact trauma to the chest, as in a high-speed motor vehicle collision or a baseball to the sternum. The impact occurs during the vulnerable repolarization period of the cardiac cycle, mechanically inducing ventricular fibrillation. This phenomenon most commonly occurs in children between 5 and 15 years old with no known predisposing cardiac conditions.[79,80] Although commotio cordis most commonly occurs in baseball, it has also been reported to occur in ice hockey, lacrosse, softball, and fist fights.[80] The majority of patients who sustain commotio cordis do not survive unless rapidly treated with defibrillation. If an AED is not immediately available and the patient is completely unresponsive with no pulse after sustaining a direct blow to the chest, a chest thump during CPR should be attempted.

KEY CONCEPTS

- The possibility of a congenital heart defect should be considered in an infant who presents with central cyanosis that does not respond to 100% supplemental oxygen (hyperoxia challenge).
- Neonates with ductal-dependent cardiac lesions typically present within the first 2 to 3 weeks of life with either acute cyanosis or shock. Initiation of a prostaglandin E_1 (PGE_1) infusion (0.05 to 0.1 μg/kg/min) will be lifesaving in these neonates.
- Treatment of a hypoxic tet spell first includes the placement of an infant in the knee-to-chest position or of an older child in a squatting position to increase systemic vascular resistance (SVR) and the provision of supplemental oxygen. Sedative agents can be used to decrease hyperpnea. Various medications can be used as adjunctive treatment to increase the SVR and thereby decrease the degree of right-to-left shunting across the ventricular septal defect (VSD).
- Prompt recognition of the clinical findings and symptoms of Kawasaki disease along with the rapid initiation of high-dose aspirin and intravenous immune globulin (IVIG) infusion can prevent the formation of coronary aneurysms.
- Acute bacterial endocarditis should always be considered in a child with a known congenital heart defect or an acquired cardiac defect who presents with fever of unknown origin, acute neurologic deficits, new-onset microscopic hematuria, myalgias, splenomegaly, petechiae, or other signs of systemic embolization.
- Oxygen, positive pressure ventilation (noninvasive or invasive), diuretics, and possibly inotropes are the main emergency department (ED) treatment of infants and children who present with congestive heart failure (CHF).
- If vagal maneuvers fail to convert stable paroxysmal supraventricular tachycardia in children, rapid adenosine administration (0.1 mg/kg for the first dose, followed by 0.2 mg/kg on repeated doses) is the treatment of choice. Verapamil should be avoided in children younger than 1 year old because of its profound hypotensive effects.
- Consider the use of lidocaine instead of amiodarone in cases of ventricular fibrillation or ventricular tachycardia due to medications (eg, cyclic antidepressants) or toxins that prolong the QT interval.
- Young athletes with a positive family history of sudden unexplained death or exertion-induced symptoms (such as, chest pain, dyspnea, palpitations, and syncope) should be evaluated by a cardiologist before their resumption of vigorous activity.
- The increased presence of automated external defibrillators (AEDs) in public places and at sporting events can potentially save the lives of more young athletes who suddenly collapse secondary to hypertrophic cardiomyopathy, prolonged QT syndromes, and commotio cordis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 170: QUESTIONS & ANSWERS

170.1. Which of the following congenital heart diseases (CHDs) requires a patent ductus arteriosus to preserve blood flow from the main pulmonary artery to the systemic circulation?
A. Pulmonary atresia
B. Severe aortic stenosis
C. Tetralogy of Fallot
D. Transposition of the great vessels
E. Tricuspid atresia

Answer: B. Pulmonary atresia, tetralogy of Fallot, transposition of the great vessels, and tricuspid atresia are also ductal-dependent lesions, but they require a patent ductus arteriosus (PDA) to preserve blood flow from the aorta to the pulmonary circulation.

170.2. Which of the following is considered a cyanotic congenital heart defect (CHD)?
A. Aortic stenosis
B. Atrial septal defect (ASD)
C. Coarctation of the aorta
D. Tetralogy of Fallot
E. Ventricular septal defect (VSD)

Answer: D. Aortic stenosis, ASD, coarctation of the aorta, and VSD are all considered acyanotic CHDs. The classic cyanotic CHDs can be remembered by the "five Ts": truncus arteriosus, transposition of the great vessels, tricuspid atresia, tetralogy of Fallot, and total anomalous pulmonary venous return.

170.3. Which of the following increases the systemic vascular resistance (SVR), thus producing a left-to-right shunt through the ventricular septal defect (VSD) associated with tetralogy of Fallot?
A. Acute hypovolemia
B. Crying
C. Defecation
D. Squatting
E. Tachycardia

Answer: D. Squatting or knee-to-chest positions increase the SVR, thus improving tet spells by producing the left-to-right shunt. Acute hypovolemia, crying, defecation, and tachycardia are all events that suddenly lower the SVR and produce large right-to-left shunts across the VSD, beginning the vicious cycle of a hypoxic ("tet") spell.

170.4. A 14-year-old girl presents to the emergency department (ED) with altered level of consciousness and trouble breathing. Her vital signs are blood pressure (BP), 72/39 mm Hg; heart rate, 240 beats/min; temperature, 99.6° F; respiratory rate, 60 breaths per minute; and oxygen saturation, 80%. An electrocardiogram (ECG) is performed, which shows supraventricular tachycardia. The patient weights 50 kg. Which of the following is the most appropriate initial treatment?
A. Adenosine 5 mg IV
B. Cardioversion with 50 J
C. Cardioversion with 200 J
D. Diltiazem 12.5 mg IV
E. Vagal maneuvers

Answer: B. This patient should be considered unstable supraventricular tachycardia (SVT), with trouble breathing, low O_2 saturation, and hypotension. In stable patients, vagal maneuvers may be appropriate to try first, followed by adenosine. Diltiazem may be used for rate control in patients with atrial flutter or atrial fibrillation. Cardioversion is the treatment of choice in patients with hemodynamic instability and SVT. The dose is 0.5 to 1 J/kg.

170.5. What is the most common cause of bradycardia in infants?
A. Complete heart block
B. Hypothermia
C. Hypothyroidism
D. Hypoxia
E. Medication induced

Answer: D. Although all of these may cause bradycardia in infants and children, the most common cause is hypoxia.

170.6. A 16-year-old boy presents with complaints of syncope during a basketball game. His mother reports a family history of sudden death in young adults, and you are concerned that the patient may have hypertrophic cardiomyopathy. Which of the following increases the murmur associated with this condition?
A. Hand grip
B. Methoxamine
C. Passive leg elevation
D. Squatting
E. Valsalva

Answer: E. During the Valsalva maneuver, the venous blood return to the heart is decreased, which in turn transiently reduces the left ventricular size. This transient reduction will increase the degree of obstruction and thus cause an increase in the intensity of the murmur. Hand grip, methoxamine, passive leg elevation, and squatting will increase return of blood to the heart and therefore decrease the murmur associated with hypertrophic cardiomyopathy.

170.7. A 3-year-old child (15 kg) is in pulseless ventricular tachycardia after being struck in the chest. The patient remains in pulseless ventricular tachycardia despite two doses of defibrillation, one dose of intravenous epinephrine, and high-quality cardiopulmonary resuscitation. The team leader prepares for the third dose of defibrillation to be delivered with a dose of amiodarone. What is the appropriate dose of defibrillation to deliver for this third defibrillation?

A. 15 joules
B. 30 joules
C. 45 joules
D. 150 joules

Answer: D. The first dose of defibrillation should be 2 joules/kg (which would be 30 joules in this 15-kg child). The second dose of defibrillation should be 4 joules/kg (which should be 60 joules in this 15 kg child). The new 2010 pediatric advanced life support (PALS) guidelines recommend that the third and subsequent defibrillation doses be 4 to 10 joules/kg. Therefore the third and subsequent defibrillation doses could be as high as 150 joules. Choice D of 150 joules is within the recommended range of 4 to 10 joules/kg.

In summary:

- First shock: 2 joules/kg
- Second shock: 4 joules/kg
- Subsequent shocks: 4 to 10 joules/kg up to maximum adult dose for the defibrillator

170.8. A 15-year-old boy is sent to the emergency department (ED) from his primary care doctor for further evaluation of "high blood pressure (BP)" recorded in the clinic today on a routine visit. He has no past medical history or symptoms. On examination, his BP is 150/90; when you palpate his radial and femoral pulses simultaneously, there is a marked pulse delay. Which of the following statements regarding this patient's most likely diagnosis is *true?*

A. On chest radiograph, the absence of rib-notching rules out the diagnosis.
B. This is an isolated congenital finding; there are no other structural or valvular lesions associated with this condition.
C. The majority of cases involve a lesion distal to the ductus arteriosus.
D. This is a normal variant, and referral back to his primary medical doctor for follow-up is indicated.

Answer: C. This boy has classic findings of asymptomatic coarctation of the aorta (CoA). Dilated collateral vessels are under pressure, causing notching of the posterior ribs, typically seen after 5 years of age. Their absence, however, does not rule out this diagnosis. Up to 50% of patients with CoA have an associated bicuspid aortic valve. Although the coarctation can occur proximal to the insertion of the ductus arteriosus or within the duct itself, the majority (89%) of cases are the postductal type. Weaker or delayed pulses in the lower extremities are common in CoA; BP measurements in all four extremities are indicated if there is any suspicion. This is not a normal variant, and this asymptomatic patient's evaluation should include an electrocardiogram (ECG; to assess left ventricular hypertrophy) and chest radiograph (to assess cardiomegaly, pulmonary vascular markings). Diagnosing the asymptomatic child with CoA and expediting definitive surgical repair can prevent the complications of severe untreated hypertension, including cardiomyopathy, heart failure, renal failure, and intracranial hemorrhage.

170.9. A 5-month-old girl presents with fever for a week, rash, and fussiness; reportedly yesterday her rash was faint throughout her body and has since resolved. On examination, she is febrile with otherwise reassuring vital signs; she is fussy and has conjunctival injection in both eyes. Her parents think she got sick from their other children. Which of the following statements regarding this patient's most likely disease is *true?*

A. If present, other systemic signs (such as, nausea, vomiting, and diarrhea) suggest an alternative diagnosis (such as, acute gastroenteritis).
B. Laboratory investigation in the emergency department (ED) will assist in her risk stratification.
C. Older children are at the highest risk for aneurysm formation.
D. She does not need further testing because she has only one of four criteria at the present.

Answer: B. Kawasaki disease is a systemic vasculitis, and gastrointestinal findings (nausea, vomiting, abdominal pain, diarrhea) and neurologic findings (irritability, positive pleocytosis on lumbar puncture if done) may mislead the clinician. Although she only has one criterion currently, signs of Kawasaki disease may occur in series or simultaneously over the course of the disease. With two or more signs in a child who is febrile for more than 5 days, markers of systemic inflammation (such as, C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) are indicated to determine the need for further laboratory testing (complete blood count, liver function tests [LFTs], albumin, urinalysis), imaging (echocardiography), or next day follow-up (with repeat laboratory tests). This child is at high risk because infants are more prone to vascular complications (such as, giant aneurysm formation); tragically they are also more likely to present with incomplete Kawasaki disease and may be overlooked. Accordingly, consensus guidelines recommend that all infants younger than 6 months old with fever of 1 week or greater (regardless of other findings) should undergo laboratory testing for markers of inflammation and, if positive, should have an echocardiogram performed emergently.

CHAPTER 171

Gastrointestinal Disorders

Patrick J. Maloney

PRINCIPLES

Gastrointestinal (GI) symptoms are common among pediatric patients presenting to the emergency department (ED). Unfortunately, the signs and symptoms commonly attributed to the GI tract, such as abdominal pain, nausea, anorexia, and vomiting, are often nonspecific and ill-defined because young children lack the social skills and vocabulary to describe and localize their symptoms. As a result, their evaluation and management may be challenging.

Pediatric GI disorders can be divided into different groups on the basis of their unique pathophysiologic mechanisms. Several disorders occur as a normal variant of early neonatal and infant development (eg, neonatal jaundice, gastroesophageal reflux, hypertrophic pyloric stenosis). Others result from congenital malformations (eg, malrotation, Meckel's diverticulum) or genetic abnormalities (eg, Hirschsprung's disease). Idiopathic or poorly explained disorders include necrotizing enterocolitis (NEC), intussusception, Henoch-Schönlein purpura (HSP), and inflammatory bowel disease (IBD). The child's age can also help identify common causes of abdominal pain. Infants, for example, may have disorders such as NEC, hypertrophic pyloric stenosis, or intussusception, whereas older children are more likely to present with appendicitis, pancreatitis, or biliary tract disease (Table 171.1).

SPECIFIC DISORDERS

Neonatal Jaundice

Principles of Disease

Bilirubin is formed by the breakdown of heme-containing proteins, primarily hemoglobin. Unconjugated bilirubin binds to albumin and is carried to the liver, where it is conjugated by glucuronyl transferase and excreted into bile. Hyperbilirubinemia and jaundice in the neonate usually result from a combination of three factors—increased production, decreased clearance and excretion, and increased enterohepatic resorption. Hyperbilirubinemia in the neonatal period is usually unconjugated. Conjugated hyperbilirubinemia, which is always pathologic, is less common.

Nearly every newborn develops an unconjugated serum bilirubin level greater than 1 mg/dL— the normal upper limit in adults—during the first week of life. Jaundice, the yellow discoloration of the skin and sclera, becomes clinically noticeable when the total bilirubin level rises above about 5 mg/dL. Jaundice during the newborn period is usually the result of a benign, self-limited process termed *physiologic jaundice of the newborn* and occurs in approximately 50% of normal newborns.

At levels greater than approximately 20 to 25 mg/dL, there is an increased risk of bilirubin-induced neurologic dysfunction (BIND). Acute bilirubin encephalopathy (ABE) refers to the early, potentially reversible, signs and symptoms, including somnolence, poor feeding, hypertonia or hypotonia, and a high-pitched cry associated with severe hyperbilirubinemia (>20 to 25 mg/dL). If untreated, symptoms progress to lethargy, hypertonia, backward arching of the neck (retrocollis) and trunk (opisthotonos), fever, irritability and, ultimately, apnea, seizures, and death. If treated, some or all these symptoms may be reversible. Kernicterus refers to the chronic, long-term neurologic sequelae of BIND. Symptoms include cerebral palsy, sensorineural hearing loss, and gaze abnormalities (usually upward gaze limitations). Management of neonatal jaundice is aimed at preventing the development of kernicterus.

Breast milk jaundice is the second most common cause of neonatal jaundice. The exact pathophysiology is uncertain, but it may be hormonally mediated or related to increased enterohepatic resorption of bilirubin. Other causes of jaundice vary significantly (Tables 171.2 and 171.3); although jaundice in adults is usually the direct result of primary liver disease, infantile jaundice is usually the result of extrahepatic causes—genetic, metabolic, infectious, and obstructive.

Risk factors for the development of hyperbilirubinemia in the neonate include prematurity, isoimmune-mediated hemolysis (ABO incompatibility), sepsis, cephalohematomas, dehydration, and inherited abnormalities, such as hereditary spherocytosis and glucose-6-phosphate dehydrogenase (G6PD) deficiency.[1] Unconjugated bilirubin crosses the blood-brain barrier, where it causes cell death.

Clinical Features

Healthy infants are born with normal bilirubin levels that gradually increase to a peak level of 6 mg/dL on the third day of life and then decline to normal levels within 2 weeks. Infants with hyperbilirubinemia usually begin life with similarly low bilirubin levels but exhibit a faster rise in bilirubin levels over the first few days of life. Physiologic jaundice is rarely present within the first 24 hours. Children with breast milk jaundice typically demonstrate the same gradual increase seen with physiologic jaundice, but levels continue to increase and peak at around 10 to 21 days of life. Elevated levels may persist for 3 to 10 weeks before gradually declining.

Toxic levels of bilirubin (dependent on age, but in general > 20 mg/dL) may be associated with neurotoxicity, encephalopathy, and the development of kernicterus. Kernicterus is characterized by yellow staining in areas of the basal ganglia. Clinical manifestations of BIND include poor feeding and lethargy and may progress to muscle rigidity, opisthotonos, seizures, and death. Survivors may have chronic, permanent coordination problems, hearing loss, and learning disabilities.

Diagnostic Considerations

Differential Diagnoses. The birth history may reveal a history of trauma that can cause cephalohematomas ,or a review of the maternal and infant perinatal records may identify maternal-child blood type and antibody testing. A detailed history of feeding patterns, urine output, and stool appearance may identify poor nutritional intake, poor weight gain, and dehydration. The family history may identify siblings or other relatives with a history of jaundice or genetic or metabolic

TABLE 171.1

Differential Considerations for Abdominal Pain by Age

CLASSIFICATION BY CAUSE	INFANCY	CHILDHOOD	ADOLESCENCE
Mechanical	Malrotation with midgut volvulus Intussusception Incarcerated hernia Meckel's diverticulum Hirschsprung's disease	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction
Inflammatory or infectious	Necrotizing enterocolitis	Gastroenteritis Appendicitis Henoch-Schönlein purpura Pancreatitis Gastritis Biliary tract disease	Gastroenteritis Appendicitis Henoch-Schönlein purpura Pancreatitis Gastritis Biliary tract disease
Genitourinary	Urinary tract infection	Urinary tract infection	Urinary tract infection Nephroureterolithiasis Pregnancy, ectopic Pelvic inflammatory disease Testicular or ovarian torsion
Other or atypical	Colic Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Pneumonia Diabetic ketoacidosis Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Pneumonia Diabetic ketoacidosis Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

BOX 171.1

Indications for Evaluation of Jaundiced Infants

Jaundice appearing within 24 hr of birth
Elevated direct (conjugated) bilirubin level
Rapidly rising total serum bilirubin unexplained by history or physical examination
Total serum bilirubin approaching exchange level or not responding to phototherapy
Jaundice persisting beyond 3 weeks of age
Sick-appearing infant

disorders. Tables 171.2 and 171.3 present differential considerations for jaundiced infants and children, respectively.

Diagnostic Testing. Although physiologic jaundice and breast milk jaundice are most common, pathologic causes and indications for evaluation of hyperbilirubinemia are listed in Box 171.1. Initial testing requires the determination of fractionated levels of total and direct bilirubin. Conjugated (direct) hyperbilirubinemia is always pathologic, resulting from biliary atresia, other biliary obstructive pathology, severe infections, toxins, and inborn errors of metabolism. Evaluation should include a complete blood count (CBC) with a peripheral smear and Coombs test to determine immune-mediated major blood group incompatibility. Diagnostic testing in ill-appearing infants includes finger stick blood glucose level measurement, electrolyte panel, urine assay for reducing substances, serum ammonia levels, and evaluation for infection.

Management

The treatment of infants with hyperbilirubinemia centers on the prevention of kernicterus. Guidelines for the use of phototherapy and exchange transfusion, based on age, risk factors for developing BIND, and bilirubin level, have been established and recommended by the American Academy of Pediatrics (Fig. 171.1).[2] Because oral intake stimulates enterohepatic circulation and decreases bilirubin levels, feeding (including breast-feeding) should be continued.

Infants with severely elevated bilirubin levels are at greatest risk for developing BIND. Indications for exchange transfusion include bilirubin level above age-specific threshold recommended by the American Academy of Pediatrics (see Fig. 171.1), failure of phototherapy (ie, the bilirubin level continues to rise despite intensive phototherapy), and jaundiced infants with signs and symptoms of BIND. Exchange transfusions are the most effective and rapid way to remove bilirubin. The procedure is time-consuming and should be performed in a pediatric or neonatal intensive care unit (NICU), where the infant's hemodynamic status may be closely monitored. A double-volume transfusion (180 to 190 mL/kg packed red blood cells) replaces approximately 85% of an infant's blood volume and reduces the total bilirubin level by at least 50%. It is performed by serially removing small aliquots of the infant's blood, typically no more than 5 to 10 mL/kg, and replacing it with a similar volume of packed red blood cells until the total transfusion volume is achieved.

Disposition

In general, infants with bilirubin levels greater than 18 to 20 mg/dL require hospital admission and phototherapy. All infants with direct hyperbilirubinemia require admission and evaluation.

Hypertrophic Pyloric Stenosis

Principles of Disease

Hypertrophic pyloric stenosis is the most common cause of infantile GI obstruction beyond the first month of life.[3] This

TABLE 171.2

Differential Considerations for Hyperbilirubinemia in Infants

CLASSIFICATION BY CAUSE	UNCONJUGATED (INDIRECT)	CONJUGATED (DIRECT)
Benign, physiologic	Physiologic jaundice of the newborn Breast milk jaundice	
Hemolysis	ABO incompatibility Physiologic breakdown of birth trauma hematoma (cephalhematoma) Intracranial/intraventricular hemorrhage Spherocytosis, elliptocytosis Sickle cell anemia Thalassemia Glucose-6-phosphate dehydrogenase deficiency Pyruvate kinase deficiency	
Infectious	TORCHS infections Urinary tract infection Sepsis	TORCHS infections Urinary tract infection Gram-negative sepsis Listeriosis Tuberculosis Hepatitis B Varicella Coxsackievirus infection Echovirus infection HIV infection
Obstructive	Meconium ileus Hirschsprung's disease Duodenal atresia Pyloric stenosis	Biliary atresia Choledochal cyst Bile duct strictures Inspissated bile syndrome Neonatal hepatitis Alagille syndrome Byler's disease Congenital hepatic fibrosis
Metabolic or genetic	Galactosemia Congenital hypothyroidism Crigler-Najjar syndrome Gilbert's syndrome	Galactosemia Tyrosinemia Glycogen storage disease type IV Niemann-Pick disease Wolman's disease Gaucher's disease Cholesterol ester storage disease α_1-Antitrypsin deficiency Cystic fibrosis Dubin-Johnson syndrome Neonatal hypopituitarism Zellweger's syndrome Donohue syndrome (leprechaunism) Rotor syndrome
Miscellaneous		Drugs and toxins Parenteral nutrition

CMV, Cytomegalovirus; *HIV,* human immunodeficiency virus; *TORCHS,* toxoplasmosis, other infections, rubella, CMV, herpes, syphilis.

condition occurs in 1 of every 250 live births, although rates and trends vary significantly by region. Boys are affected at four times the rate of girls. Approximately one-third of cases occur in first-born children. Prematurity and exposure to erythromycin or azithromycin are additional risk factors.[4] Hypertrophic pyloric stenosis tends to have familial patterns, but the exact pattern of inheritance is unclear.

Infants are born with a normal pylorus that enlarges as time progresses. The exact cause is unknown, although hypertrophy seems to be stimulated by feeding. As the pylorus enlarges, progressive gastric outlet obstruction develops, and vomiting ensues. Vomiting causes loss of fluid and hydrogen and chloride ions. As dehydration and electrolyte derangements worsen, the kidney attempts to retain hydrogen ions in exchange for potassium, resulting in the classic hypochloremic-hypokalemic metabolic alkalosis.

Clinical Features

Infants classically present at 2 to 6 weeks of chronologic age with gradually progressive vomiting that becomes projectile but remains nonbilious.[5] Early in the disease process, infants remain vigorous, with a ravenous appetite. They rapidly finish an entire feeding, only to regurgitate the entire volume in a projectile fashion. In the later stages of the disease, children may exhibit poor weight gain, clinical dehydration, and malnutrition, along with visible waves of abdominal peristalsis in response to intense contractions against the obstruction.

TABLE 171.3

Differential Considerations for Hyperbilirubinemia in Older Children

CLASSIFICATION BY CAUSE	UNCONJUGATED (INDIRECT)	CONJUGATED (DIRECT)
Obstructive		Gallstones Tumor Choledochal cyst Bile duct stricture
Infectious		Hepatitis Sepsis Urinary tract infection
Genetic	Sickle cell Thalassemia Spherocytosis, elliptocytosis Glucose-6-phosphate dehydrogenase deficiency Pyruvate kinase deficiency Crigler-Najjar syndrome Gilbert's syndrome	Dubin-Johnson syndrome Rotor syndrome Wilson's disease Cystic fibrosis α_1-Antitrypsin deficiency Glycogen storage disease
Other	Drug-induced hemolytic anemia Autoimmune hemolytic anemia Microangiopathic hemolytic anemia Hypersplenism	Cirrhosis Sclerosing cholangitis Cholestatic jaundice of pregnancy Drugs and toxins (acetaminophen, estrogens)

Diagnostic Considerations

Diagnostic Testing. Children may have a palpable pylorus in the right epigastrium on abdominal examination, commonly referred to as an olive. Because ultrasound is readily available in most US health centers, pyloric stenosis is generally diagnosed earlier compared to decades ago. As a result, the olive is now palpated in only a minority of infants. Laboratory derangements reflect a state of dehydration and electrolyte loss through vomiting—a hypochloremic metabolic alkalosis (serum bicarbonate [HCO_3] levels ≥ 29 mmol/dL and chloride levels ≤ 98 mmol/dL), although these abnormalities may be absent early in the disease course.

Hypertrophic pyloric stenosis may be confirmed by ultrasonography or upper GI series.[6] Ultrasonography is the diagnostic modality of choice because it is simple, readily available, without serious complications such as aspiration and, in skilled hands, may even be performed by the emergency clinician.[7] With both modalities, reported accuracy is greater than 95%. On ultrasound, the pylorus appears thickened (pyloric muscle thickness > 4 mm; pyloric diameter > 14 mm) and elongated (>19 mm), which is diagnostic.[6] A characteristic string sign, reflecting passage of contrast material through the narrowed pyloric sphincter, may also be evident. In advanced stages with complete obstruction at the pylorus; plain films may reveal a distended, air-filled stomach (Fig. 171.2).

Differential Considerations. Vomiting in infants is common, and the differential diagnosis is broad. Usually, infants present early in the disease progression and are well-appearing. In these infants, the common consideration is differentiating hypertrophic pyloric stenosis from gastroesophageal reflux. Reflux classically begins shortly after birth and remains relatively constant. Infant with pyloric stenosis typically have progressively worsening emesis beginning around 2 or 3 weeks of life. In advanced stages, it occurs with every feed and is often described as projectile.

Infants who present with sudden onset of severe vomiting and bilious emesis, or who are ill-appearing, should be evaluated for other surgical emergencies, including malrotation with midgut volvulus, duodenal atresia, and necrotizing enterocolitis. With reflux and pyloric stenosis, emesis is rarely bilious.

Many causes of vomiting do not have a true GI origin, including sepsis, metabolic disturbances (eg, diabetic ketoacidosis), increased intracranial pressure, middle ear disturbances, urinary tract infections, inborn errors of metabolism, pain, medications, and drug intoxications. Differential considerations for vomiting in children vary by age (Table 171.4).

Management

Treatment consists of fluid and electrolyte replacement and surgical consultation. Hypertrophic pyloric stenosis is not a true surgical emergency, but may be a fluid and electrolyte emergency. Fluid resuscitation should begin with repeated boluses of 20 mL/kg of normal saline as necessary to treat dehydration and hypovolemic shock. Potassium supplementation (KCl, 0.5 to 1 mEq/kg IV over 1 to 2 hours) is often necessary. Definitive management is surgery. The corrective procedure, called a pyloromyotomy, may be performed open, referred to as the Ramstedt pyloromyotomy, or laparoscopically.[8] Associated mortality is rare.

Disposition

Most children are best managed with hospital admission for rehydration and correction of electrolyte abnormalities in conjunction with urgent imaging and surgical consultation.

Malrotation With Midgut Volvulus

Principles of Disease

Malrotation occurs in 1 in 500 live births and has a male predominance of at least 2:1. Among infants with malrotation, symptomatic volvulus occurs in the first month of life in approximately one-third, in the first year of life in approximately half, and before the age of 5 years in 75% of children. Cases of adult midgut volvulus have been reported.[9,10] Bilious emesis is the hallmark presentation. Malrotation with volvulus carries a mortality rate of 3% to 15%.

During embryologic development, the GI tract rotates around the superior mesenteric artery. As it completes the rotation, the duodenum forms a C-loop and is fixed to the retroperitoneum in the left upper quadrant at the ligament of Treitz. The cecum becomes similarly fixed in the right lower quadrant. Thus, the duodenum and cecum normally come to lie widely separated and are firmly fixed in position by peritoneal attachments called Ladd's bands. They are only loosely connected by a broad-based mesentery. In cases of malrotation, the duodenum and cecum do not rotate completely, remain closely positioned, and are suspended in the midgut region by the mesenteric vascular stalk. This unusually close proximity results in a short stalk of mesentery that easily twists on itself, resulting in obstruction of the distal duodenum and bowel ischemia and necrosis secondary to compression of the superior mesenteric artery.

Clinical Features

Infants classically present with sudden-onset bilious emesis and abdominal distention. Any pigmented staining of the vomitus suggests the presence of bile. When bile is initially produced, it is bright yellow and turns green only with time and oxidative exposure. Differential coloring of bile-stained emesis, yellow versus green, is not predictive of a surgical condition. Infants usually appear quite ill and may present in shock.

Diagnostic Considerations

Diagnostic Testing. The diagnostic procedure of choice to identify midgut volvulus is a limited upper GI contrast series, which reveals an abnormal position of the duodenal C-loop (Fig. 171.3) and small bowel, with a characteristic corkscrew appearance (Fig. 171.4).[11]

Other diagnostic strategies may include plain films of the abdomen and ultrasonography. Findings on plain abdominal films may include air-fluid levels suggesting obstruction, abnormally dilated bowel loops overlying the liver, and a paucity of small bowel gas distally (Fig. 171.5). Ultrasonography, usually performed to evaluate for hypertrophic pyloric stenosis, may reveal an abnormal orientation of the superior mesenteric artery and vein (the vein is abnormally positioned anteriorly or to the left of the artery; Fig. 171.6) or a whirlpool sign caused by the vessels twisting around the mesenteric stalk, causing an echogenic twisting pattern.[12,13] The role of ultrasonography in the direct evaluation for midgut volvulus has yet to be determined. CT is usually not recommended as it carries the risk of additional radiation without benefit of improved diagnostic ability over upper GI series.

Differential Diagnoses. Vomiting in childhood is common and occurs across a wide spectrum of illnesses (see Table 171.3).

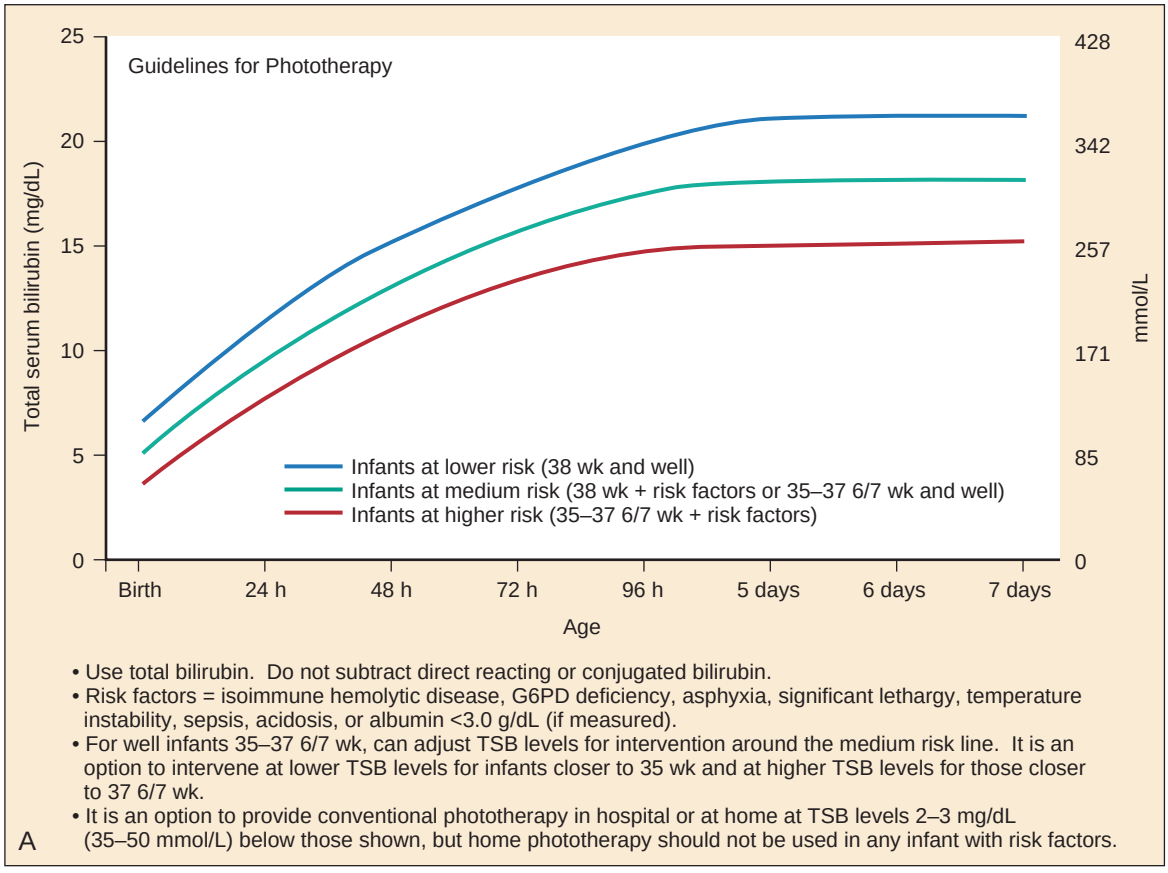
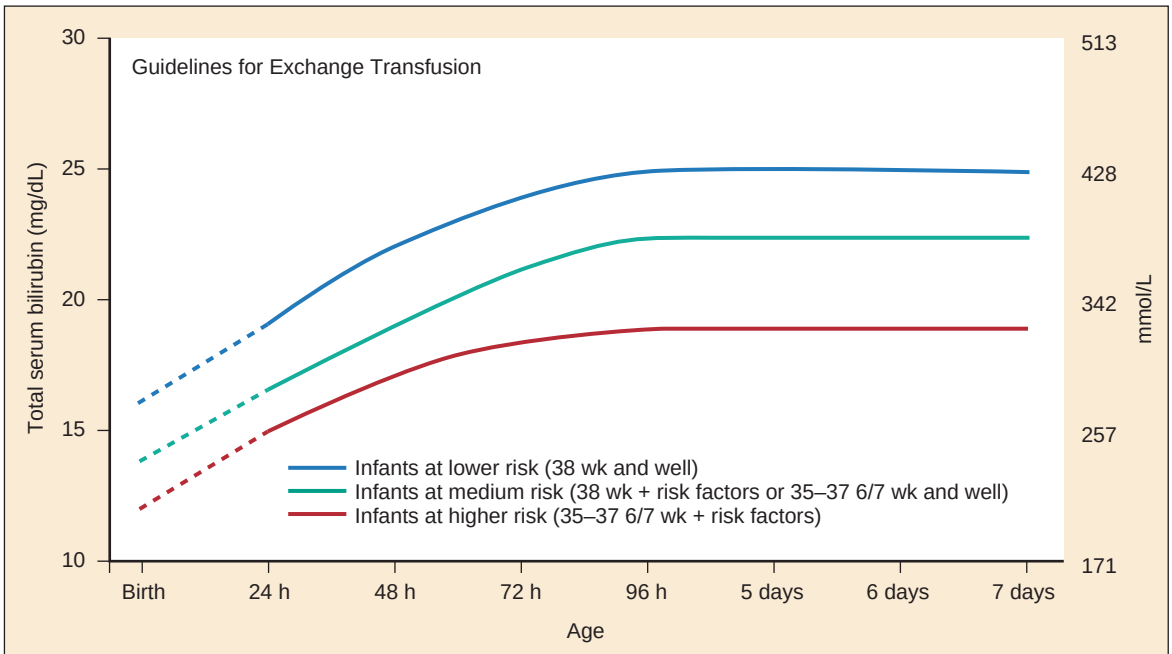


Fig. 171.1. A, Guidelines for phototherapy in hospitalized infants at 35 weeks or more of gestation. Note that these guidelines are based on limited evidence. The guidelines refer to intensive phototherapy, which should be used when the total serum bilirubin (TSB) exceeds the line indicated for each category. Infants are designated higher risk because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin.

Continued



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is 5 mg/dL (85 mmol/L) above these lines.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (see legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35–37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

B

Fig. 171.1, cont'd. B, Guidelines for exchange transfusion in infants at 35 weeks or more of gestation. Note that these suggested levels represent a consensus but are based on limited evidence. Exchange transfusion is recommended if the TSB continues to rise or remains above these levels, despite intensive phototherapy. B/A, Bilirubin/albumin; G6PD, glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 114:297–316, 2004.)

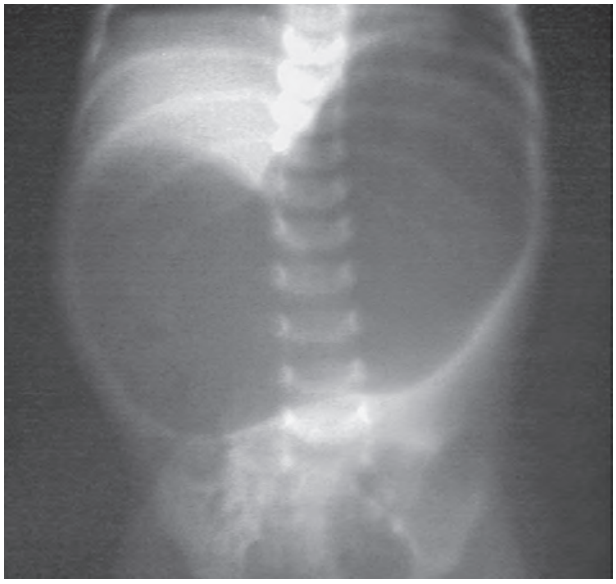


Fig. 171.2. Plain radiograph of the abdomen revealing enlargement of the body and pyloric portions of the stomach. This is seen in advanced stages of hypertrophic pyloric stenosis. (Courtesy Dr. Mark A. Hostetler.)

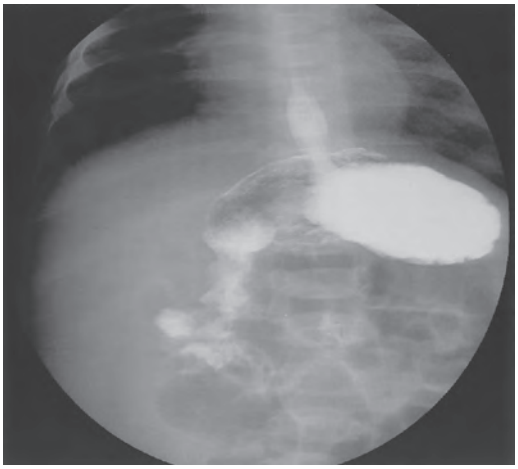


Fig. 171.3. Upright abdominal radiograph obtained in an infant with bilious vomiting illustrates dilated loops of small bowel and a paucity of bowel gas distally, consistent with proximal obstruction secondary to malrotation with midgut volvulus. (Courtesy Dr. Mark A. Hostetler.)

TABLE 171.4

Differential Considerations for Vomiting by Age

CLASSIFICATION BY CAUSE	INFANCY	CHILDHOOD	ADOLESCENCE
Mechanical	Gastroesophageal reflux Malrotation with midgut volvulus Pyloric stenosis Meckel's diverticulum Intussusception Bowel obstruction Incarcerated hernia Tracheoesophageal fistula	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction	Constipation Incarcerated hernia
Inflammatory or infectious	Necrotizing enterocolitis Gastroenteritis Sepsis Henoch-Schönlein purpura Meningitis Pneumonia Otitis media	Gastritis or gastroenteritis Otitis media Appendicitis Pancreatitis Henoch-Schönlein purpura Biliary tract disease	Gastroenteritis Appendicitis Pancreatitis Gastritis Biliary tract disease
Genitourinary	Urinary tract infection	Urinary tract infection	Urinary tract infection Pregnancy Testicular or ovarian torsion
Central nervous system	Hydrocephalus Intracranial hemorrhage Intracranial tumor	Migraine headache Hydrocephalus Intracranial hemorrhage Intracranial tumor Reye's syndrome	Migraine headache Hydrocephalus Intracranial hemorrhage Intracranial tumor Glaucoma
Metabolic	Diabetic ketoacidosis Congenital adrenal hyperplasia Urea cycle defects Organic acidurias Amino acidopathies Fatty acid oxidation disorders	Diabetic ketoacidosis Urea cycle defects Fatty acid oxidation disorders	Diabetic ketoacidosis
Other or atypical	Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

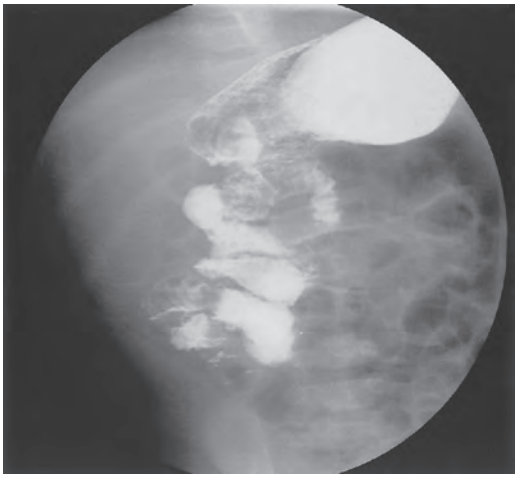


Fig. 171.4. Upper gastrointestinal film, obtained in the same infant as in Fig. 171.3, reveals abnormal positioning of the duodenal C-loop to the right of the spinal column, consistent with malrotation. (Courtesy Dr. Mark A. Hostetler.)

Causes vary by age, progression of symptoms, and vomitus appearance. Acute bowel obstruction usually causes sudden-onset vomiting, which is usually bilious. In a neonate, bilious vomiting may indicate malrotation with volvulus or other acute bowel obstructive process. Gastroesophageal reflux disease (GERD) and hypertrophic pyloric stenosis typically cause nonbilious emesis in relatively well-appearing infants. NEC may also present with obstructive signs and symptoms, including bilious emesis and abdominal distention but, unlike malrotation with volvulus, NEC is characterized radiographically by diffusely dilated loops of small bowel and the presence of air within the bowel walls, termed *pneumatosis intestinalis*.[14]

Management

Emergent pediatric surgical consultation should be obtained for any neonate or infant with bilious vomiting, even before diagnostic studies have been performed. In acute midgut volvulus, operative intervention must be rapid to save the bowel from necrosis.

Intravenous (IV) access should be obtained, and laboratory studies should include blood glucose level, a CBC with differential, electrolyte values, and renal and liver function tests. Repeated fluid boluses of 20 mL/kg of normal saline should be given until adequate circulation has been reestablished. Ill-appearing infants

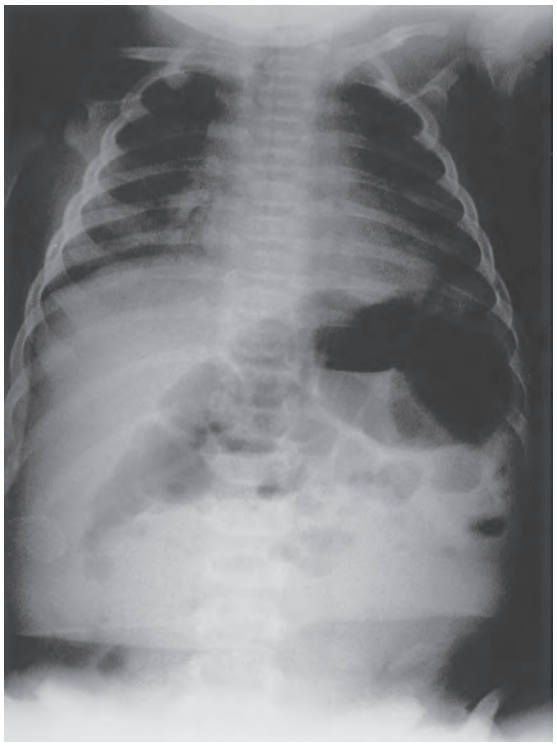


Fig. 171.5. Spot film from the upper gastrointestinal series obtained in the infant in Fig. 171.3. This radiograph shows the characteristic corkscrew appearance seen on small bowel follow-through in patients with malrotation. (Courtesy Dr. Mark A. Hostetler.)

should receive empirical, broad-spectrum antibiotic coverage. A nasogastric or orogastric tube should be placed. A limited upper GI series should also be emergently obtained, but should not delay resuscitation and surgical consultation.

Disposition

Patients with a confirmed or equivocal diagnosis should be admitted with emergent surgical consultation.

Necrotizing Enterocolitis

Principles of Disease

NEC, the most common GI emergency in neonates, affects up to 4000 US infants every year. NEC is also the most common cause of intestinal perforation during the newborn period.[15] Because most affected infants are premature and acquire the condition in the NICU, NEC usually is not considered a disease of the ED. NEC does occur in a small subset of late preterm and full-term infants, although most of them have other underlying illnesses and rarely are discharged from the NICU prior to the onset of disease. Complications in children who survive NEC include strictures, fistulas, and short gut syndrome.

The exact pathophysiologic mechanism of NEC is unclear but is likely multifactorial. Prematurity is the most common and universally accepted risk factor; 90% of all affected infants are born prematurely. The primary pathologic event may be inflammation or injury to the intestinal wall, beginning in the mucosa and extending transmurally.

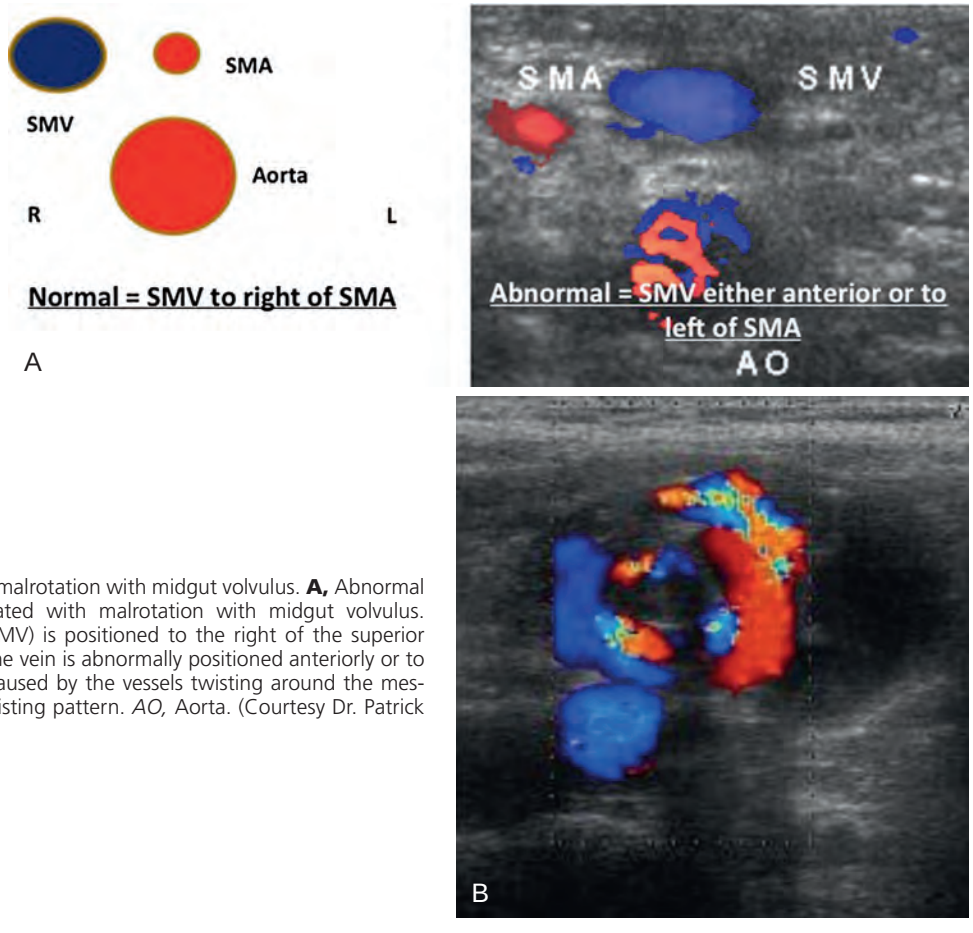


Fig. 171.6. Ultrasonographic findings in malrotation with midgut volvulus. **A,** Abnormal orientation of mesenteric vessels associated with malrotation with midgut volvulus. Normally, the superior mesenteric vein (SMV) is positioned to the right of the superior mesenteric artery (SMA). In malrotation, the vein is abnormally positioned anteriorly or to the left of the artery. **B,** Whirlpool sign caused by the vessels twisting around the mesenteric stalk, resulting in an echogenic twisting pattern. *AO,* Aorta. (Courtesy Dr. Patrick J. Maloney.)

Clinical Features

Infants with NEC first usually develop feeding intolerance and bilious or nonbilious emesis. In the more advanced stages of the disease, infants may appear extremely ill, with hematemesis, hematochezia, fever, and shock. Abdominal radiographs commonly show intestinal dilation, pneumatosis intestinalis, and perforation.

Diagnostic Considerations

Differential Diagnoses. Feeding intolerance and vomiting are common and nonspecific findings in neonates. Infants with NEC are usually quite ill-appearing. GERD classically begins shortly after birth and remains relatively constant in character. Pyloric stenosis–related vomiting does not begin until 2 to 3 weeks of age and then becomes increasingly severe and projectile. In neonates, bilious vomiting requires careful consideration to rule out other obstructive pathology, including malrotation with midgut volvulus. The appearance of the plain radiographs may help differentiate NEC and volvulus. Volvulus is associated with a paucity of small bowel gas, whereas the hallmark of NEC is diffusely dilated loops of small bowel and pneumatosis intestinalis.

Diagnostic Testing. Plain abdominal radiographs are the imaging study of choice in NEC. Radiographs may show nonspecific dilated loops of bowel, intramural air (pneumatosis intestinalis), which is pathognomonic for NEC (Fig. 171.7), air within the portal system and biliary tract, or pneumoperitoneum. Pneumatosis is present in 75% of patients with NEC. No individual laboratory test is diagnostic or specific for NEC, but may reflect dehydration, electrolyte derangements, and sepsis.

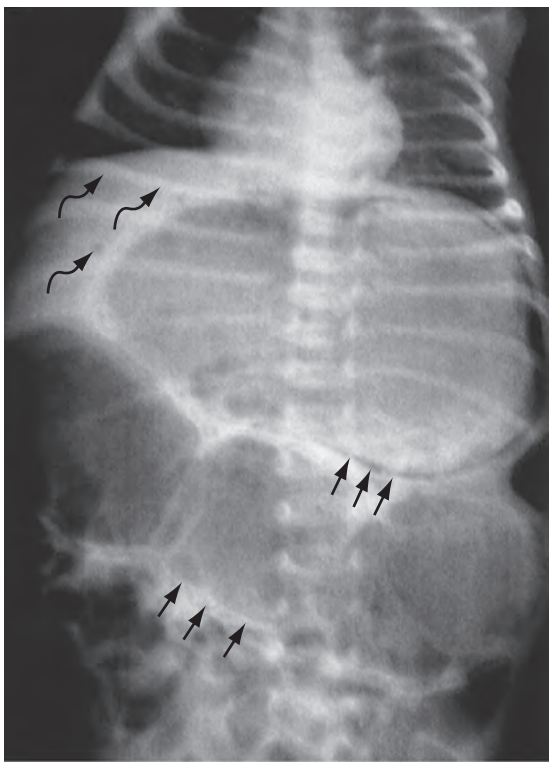


Fig. 171.7. Plain radiograph obtained in an infant with necrotizing enterocolitis. *Straight arrows* indicate air within the wall of the small bowel and gastric mucosa (pneumatosis intestinalis and gastralis). *Curved arrows* indicate air in the biliary tree (portal venous gas). (Courtesy Dr. Mark A. Hostetler.)

Management

Patients suspicious of having NEC should receive nothing by mouth (NPO), with placement of an orogastric or nasogastric tube for decompression of the stomach and small bowel. Because these patients are frequently hemodynamically unstable and may have periods of apnea or significant respiratory distress, the airway should be managed as indicated. IV or intraosseous access should be established; laboratory studies should include a CBC with differential, electrolyte panel, renal and liver function tests, and type and screen. A bedside blood glucose level should be determined. Blood and urine cultures should be obtained. Fluid resuscitation with 20 mL/kg boluses of normal saline should be repeated until adequate circulatory volume has been achieved. Vasoactive agents such as dopamine, epinephrine, or norepinephrine are indicated for patients in refractory shock. Broad-spectrum antibiotic coverage is indicated (Box 171.2). Emergent pediatric surgery consultation should be obtained in all cases because perforation and bowel necrosis may not be immediately evident on plain radiographs.[14]

Disposition

Children thought to have NEC require admission to an ICU and should have emergent pediatric surgical consultation.

Gastroesophageal Reflux

Principles of Disease

GERD, one of the most common causes of vomiting during infancy, refers to the regurgitation of stomach contents into the esophagus. GERD occurs as a result of an incompetent lower esophageal sphincter. Chronic reflux of gastric contents into the esophagus may result in esophagitis, aspiration, and failure to thrive if it is severe.

Clinical Features

GERD generally begins shortly after birth and resolves with time, usually by the age of 1 year. Clinical manifestations occur along a wide spectrum of disease, ranging from asymptomatic to occasional episodes of spitting up to severe persistent vomiting and

BOX 171.2

Empirical Antibiotic Regimens for Necrotizing Enterocolitis

REGIMEN

- Piperacillin-tazobactam + gentamicin
- Piperacillin-tazobactam + gentamicin + vancomycin
- Ampicillin + gentamicin + metronidazole
- Ampicillin + ceftriaxone + metronidazole
- Meropenem

DOSING

- Piperacillin-tazobactam: 25 mg/kg IV qid
- Gentamicin: 2.5 mg/kg IV tid
- Ampicillin: 50 mg/kg IV qid
- Vancomycin: 15 mg/kg IV qid
- Metronidazole: 10 mg/kg IV tid
- Ceftriaxone: 100 mg/kg IV once daily
- Meropenem: 20 mg/kg IV tid

failure to thrive.[16,17] Sandifer's syndrome, although rare, refers to the stereotypical opisthotonic movements highly suggestive of severe GERD. GERD may occasionally be associated with brief periods of apnea and pallor, apparent life-threatening events, or respiratory symptoms, including chronic coughing, recurrent stridor, and persistent wheezing.

Diagnostic Considerations

Differential Diagnoses. Children with GERD exhibit nonbilious emesis that begins shortly after birth and is relatively constant over time. Unlike pyloric stenosis, vomiting is usually neither progressive nor projectile. Most children with GERD of milder severity continue to gain weight.

Diagnostic Testing. In the ED, the diagnosis of GERD is typically made on the basis of the history and physical examination. However, ill-appearing infants in whom the diagnosis is uncertain may benefit from diagnostic studies; these tests, such as esophageal pH probes, barium swallow studies, and direct visualization by endoscopy, should be conducted in consultation with a pediatric gastroenterologist.

Management

Most infants respond to conservative lifestyle modifications, such as smaller feedings, frequent burpings, formula thickened with cereal, and a semiupright position after feeding.[18] Pharmacologic regimens are not recommended for infants with uncomplicated reflux (so-called happy spitters). Although lacking supportive evidence, acid suppression can be used, but should be reserved for those with more severe symptoms, such as esophagitis, weight loss, or significant irritability, in whom more conservative lifestyle modifications have failed. Severe and refractory cases occasionally require Nissen fundoplication.

Disposition

Most children may be discharged home safely with conservative measures. Children with more severe symptoms or poor weight gain should be referred to a pediatrician or pediatric gastroenterologist for testing and additional pharmacologic management. Those with severe dehydration, weight loss, or failure to thrive should be admitted.

Intussusception

Principles of Disease

Intussusception refers to the invagination of part of the intestine into itself. It is the most common cause of intestinal obstruction in children younger than 2 years, occurring most frequently in infants 5 to 12 months of age. In contrast to adults, most cases of intussusception in children are idiopathic, occurring in healthy children.

The exact cause of intussusception is unclear, but the most prevalent theory relates to a lead point that causes telescoping of one segment of the intestine into another. Bowel wall edema develops, resulting in mechanical obstruction and vascular compromise. The end result is bowel wall ischemia and necrosis.

Intussusception may occur at any point along the GI tract. Ileocolic intussusceptions are most common. In younger children, lead points are usually the result of enlarged Peyer's patches secondary to a recent viral infection. Approximately 75% of cases, especially in children older than 5 years, have a pathologic lead point; lesions include HSP vasculitis, Meckel's diverticulum, lymphoma, polyps, postsurgical scars, celiac disease, and cystic fibrosis. Ileoileal intussusception occurs more frequently in children with HSP.

Clinical Features

The classic triad of clinical findings in intussusception consists of abdominal pain, a palpable sausage-shaped abdominal mass, and bloody stools, described as currant jelly. All three features are present in a minority of patients, however. Abdominal pain is the most common symptom. The child experiences cyclic episodes of severe abdominal pain as waves of peristalsis cause bowel dilation adjacent to and proximal to the involved bowel. These episodes typically last 10 to 15 minutes and occur in intervals of 15 to 30 minutes. During the painful episode, the child may be irritable and inconsolable, often described as drawing the legs up to the abdomen and screaming in pain. Vomiting may be present. Blood, gross or occult, may be present in the stool. Diarrhea containing mucus and blood constitutes the classic currant jelly stool, a relatively infrequent and late finding. Occasionally, children present with atypical symptoms, including altered level of consciousness and profound lethargy, rather than the more typical abdominal pain syndrome.

Diagnostic Considerations

Differential Diagnoses. Differential considerations for abdominal pain in children by age are listed in Table 171.4. A slow progressive onset of pain is more likely to be associated with appendicitis, constipation, or pancreatitis. A sudden onset of severe pain is usually associated with acute obstruction or vascular occlusion, as seen with intussusception, volvulus, or torsion of the testicle or ovary. Children with intussusception classically have severe intermittent colicky pain. Children with ischemic pain exhibit symptoms out of proportion to the physical examination findings.

Diagnostic Testing. Initial screening radiographs of the abdomen may be obtained, but findings are usually nonspecific. Images should be examined for evidence of a soft tissue mass or mass effect, dilated loops of small bowel and a paucity of gas in a decompressed colon suggesting obstruction, a target sign (representing air in the intussusceptum as it telescopes into adjacent bowel), meniscus sign (representing air compressed like a meniscus from invaginating bowel), and free air (Fig. 171.8).[19] Rarely, normal radiographs can likely exclude the diagnosis of intussusception, revealing complete visualization of the entire colon, with the presence of air throughout, including in the cecum. Indeterminate or nonspecific findings are common and do not exclude the diagnosis.[20]

Ultrasonography is the diagnostic imaging modality of choice. In skilled hands, it is highly sensitive and specific. The classic finding is a target sign (also referred to as a bull's eye or doughnut sign), visualization of the telescoping intestinal wall in the transverse or cross-sectional view. When visualized in the longitudinal plane, it is referred to as the pseudo–kidney sign (Fig. 171.9).[20-22] Contrast enemas have the advantage of being diagnostic and therapeutic. Occasionally, in children with the triad of paroxysms of pain, vomiting, and blood in the stool, contrast enemas may be safely done as first-line therapy (Fig. 171.10). Air-contrast enemas are equally efficacious.[21] Either type of enema requires readily available backup by a pediatric surgeon in case of the bowel to reduce or iatrogenic perforation.[23]

Management

IV fluids should be given in repeated boluses of 20 mL/kg of normal saline until adequate intravascular volume has been

Fig. 171.8. Plain radiograph obtained in a child with crampy abdominal pain and vomiting, later confirmed to have intussusception. Findings include a poorly defined soft tissue density in the right upper quadrant, obscuration of the liver edge, and focally dilated loops of small bowel, consistent with an acute obstructive process (intussusception). (Courtesy Dr. Mark A. Hostetler.)

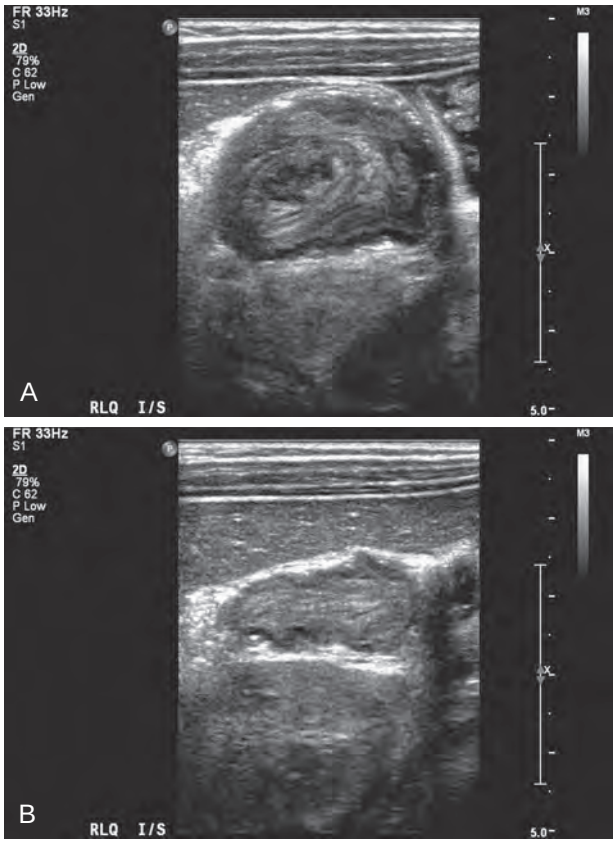


Fig. 171.9. Abdominal ultrasound examination in a child with colicky abdominal pain and vomiting, later confirmed to have intussusception. **A,** On the transverse view, findings include a complex mass with a multilayered or rolled appearance. **B,** In the long view , the ileum can be seen protruding up into the cecum, forming the intussuscipiens-intussusceptum complex. (Courtesy Dr. Mark A. Hostetler.)

achieved. Children should be maintained on NPO status. Prompt surgical consultation is required. Diagnostic and therapeutic interventions depend on the location and resources available. Patients may undergo an initial ultrasound examination or, if history and plain film findings are highly suggestive of intussusception, may go directly to a pneumatic or hydrostatic enema.

The overall success rate for an air-contrast enema or barium enema approaches 90%. Surgical intervention is indicated in cases of prolonged intussusception with signs of perforation or shock or if enema reduction is unsuccessful. A severe, acutely life-threatening complication of air enema reduction is tension pneumoperitoneum.[23] Intussusception recurs in approximately 12% of radiologic reductions.[24] Less than 50% of these recurrences occur within the first 48 hours postreduction. Although admission for observation after reduction has traditionally been recommended, a shorter observation period (6 hours) is safe, and children who are able to tolerate oral fluids may be discharged home.[25]

Disposition

Children with suspected intussusception require definitive imaging with ultrasonography or contrast enema. Confirmed intussusception requires reduction with enema or surgery.

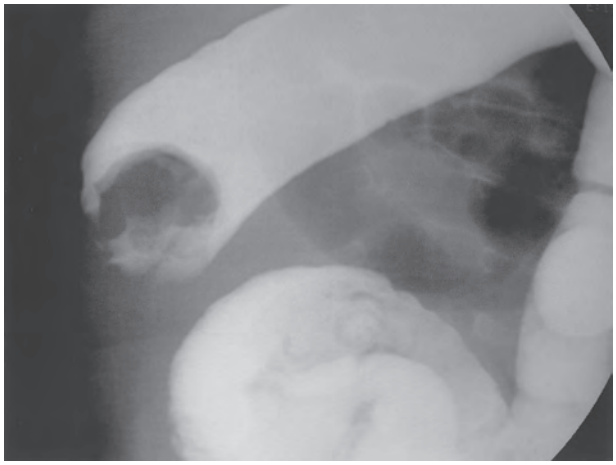


Fig. 171.10. Contrast enema image obtained in a child with intussusception shows a sharp cutoff where the contrast material meets the intussusceptum and acute obstruction. (Courtesy Dr. Mark A. Hostetler.)

Hirschsprung's Disease

Principles of Disease

Hirschsprung's disease accounts for approximately 20% of cases of partial intestinal obstruction in early infancy. Hirschsprung's disease occurs at a rate of 1 in 5,000 live births and is four to five times more common in boys. Cases are usually sporadic in occurrence but may be associated with Down syndrome or other congenital anomalies.

Hirschsprung's disease refers to congenital aganglionosis of the colon—that is, an absence of ganglion cells in the myenteric plexus of the distal colon. The anus is invariably involved, with aganglionic bowel usually extending proximally 4 to 25 cm. The absence of colonic ganglion cells interferes with that segment's ability to relax, creating a functional obstruction. Stool

accumulates proximal to the level of obstruction and produces dilation of the colon (ie, megacolon).

Clinical Features

Neonates with Hirschsprung's disease often present in the nursery with failure to pass meconium; however, a spectrum of disease is recognized, and presentation may be later in life. Infants brought to the ED usually have a history of chronic constipation. Vomiting, irritability, poor weight gain, failure to thrive, and abdominal distention may be present. Children who appear ill, with fever, should be evaluated for enterocolitis and toxic megacolon.[26]

Diagnostic Considerations

Differential Diagnoses. Constipation is one of the most common causes of abdominal pain and vomiting in children. Infants during the first few months of life may have normal stool frequencies that range from one per feeding to one every few days, with breast-fed infants having more frequent stools than formula-fed infants. Truly pathologic causes of constipation are uncommon. In addition to Hirschsprung's disease, considerations include cystic fibrosis, infantile botulism, and hypothyroidism.

Diagnostic Testing. Plain films of the abdomen are usually nonspecific and may reveal evidence of fecal impaction with proximal obstruction, air-fluid levels, and a dilated colon. Barium enema studies revealing a narrowed aganglionic segment with proximal dilation is highly suggestive of Hirschsprung's disease. The diagnosis is confirmed by biopsy or manometry.

Management

Initial management is focused on ensuring adequate fluid and electrolyte status. Abdominal films should be obtained. With evidence of acute obstruction, such as marked bowel dilation, decompression with a rectal tube may be necessary. Children who appear ill, with fever, should be evaluated for enterocolitis and toxic megacolon or bowel perforation. Definitive therapy of Hirschsprung's disease is surgical, with resection of the aganglionic segments.[26]

Disposition

Unless a child appears ill, most constipated children may be managed safely on an outpatient basis.

Meckel's Diverticulum

Principles of Disease

Meckel's diverticula are remnants of the omphalomesenteric duct and contain bowel wall, with 60% containing heterotopic tissue, usually gastric mucosa. Bleeding occurs when acid secretion from the ectopic gastric mucosa causes ulceration and erosion. Meckel's diverticulum is the most common congenital malformation of the small intestine.

Meckel's diverticula traditionally follow so-called the rule of 2's. The diverticulum is 2 cm wide, 2 cm long, and located within 2 feet of the ileocecal valve. Moreover, the condition occurs in 2% of the population, and only 2% of affected patients ever become symptomatic. Of symptomatic patients, 50% manifest symptoms by the age of 2 years, and most present by the age of 20 years.

Clinical Features

Patients classically present with massive, painless rectal bleeding. Some children may have complaints of abdominal cramping. The abdominal examination is usually benign. The blood is often described as brick red, but may range from melena to bright red. Complications may include intussusception, obstruction, perforation, and peritonitis.

Diagnostic Considerations

Differential Diagnoses. Massive GI bleeding is uncommon in childhood. Children commonly eat or drink substances containing red dyes that lead to changes in the stool's color that may be mistaken for hematochezia. In addition, bismuth subsalicylate (eg, Pepto-Bismol), iron, and spinach may cause black stools falsely appearing melanotic. A simple Hemoccult test of stool or Gastroccult test of emesis can confirm the presence or absence of hemoglobin.

Similar to adults, the location of bleeding may be theorized on the basis of appearance of the blood. Hematemesis suggests bleeding proximal to the ligament of Treitz. Melena results from bleeding beyond the ligament of Treitz but proximal to the ileocecal valve. Hematochezia implies bleeding from the colon. Occasionally, in young children, GI transit time may be rapid enough to cause an upper GI source to cause hematochezia.

In neonates, the cause of GI bleeding is usually never identified. In young breast-fed neonates, an Apt test may be performed to differentiate fetal from swallowed maternal blood. Nursing mothers should be asked about cracked bleeding nipples. Milk protein allergy is another common cause of GI bleeding in infancy. Affected children are typically younger than 6 months, with a history of sudden-onset, mucoid, blood-streaked stools. Table 171.5 lists the differential considerations for GI bleeding in children by age.

Diagnostic Testing. A technetium-99m (^{99m}Tc) scan, also known as a Meckel's scan, is the diagnostic modality of choice and has an accuracy of 90% when ectopic gastric mucosa is present; ^{99m}Tc has an affinity for gastric mucosa.[27] A computed tomography (CT) scan of the abdomen may be performed to look for signs of inflammation or obstruction. Definitive diagnosis is confirmed by laparoscopy or laparotomy.

Management

Management of GI bleeding begins by assessment of circulatory status and volume resuscitation, as indicated. In cases of minimal or mild bleeding in otherwise healthy and well-appearing children, laboratory studies are unlikely to be useful. When there is concern for more serious disease, screening laboratory studies should include a CBC, coagulation studies (eg, prothrombin time, partial thromboplastin time), and typing and screening; a pediatric surgeon should be consulted.

Disposition

Children with massive GI bleeding suspicious for Meckel's diverticulum should undergo a Meckel's scan.[27] Children with minor bleeding may be discharged home with close follow-up. Children with ongoing active bleeding should be hospitalized.

Henoch-Schönlein Purpura

Principles of Disease

HSP, also known as anaphylactoid purpura, is a hypersensitivity vasculitis with immune complex deposition with immunoglobulin A; it mainly affects the arterioles and capillaries. Although it is most well-known for its characteristic petechial to purpuric rash, HSP is a systemic vasculitis affecting any vessels.

TABLE 171.5

Differential Considerations in Gastrointestinal Bleeding by Pediatric Age Group

CLASSIFICATION BY CAUSE	INFANCY	CHILDHOOD	ADOLESCENCE
Factitious	Swallowed maternal blood Dyes in foods and beverages Vaginal origin Urinary origin	Dyes in foods and beverages Swallowed nasopharyngeal blood Vaginal origin Urinary origin	Dyes in foods and beverages Swallowed nasopharyngeal blood Vaginal origin Urinary origin
Upper gastrointestinal tract	Necrotizing enterocolitis Intussusception Gastroenteritis Gastritis	Esophagitis Gastroenteritis Gastritis Peptic ulcer disease	Esophagitis Gastroenteritis Gastritis Peptic ulcer disease
Lower gastrointestinal tract	Necrotizing enterocolitis Intussusception Gastroenteritis Milk allergy Vascular malformation	Gastroenteritis Intussusception Meckel's diverticulum Inflammatory bowel disease Vascular malformation Henoch-Schönlein purpura Hemolytic-uremic syndrome Colitis	Gastroenteritis Intussusception Meckel's diverticulum Inflammatory bowel disease Vascular malformation Henoch-Schönlein purpura Hemolytic-uremic syndrome Polyps Colitis
Rectal	Rectal fissure	Rectal fissure	Rectal fissure Hemorrhoids Trauma
Other or atypical	Bleeding dyscrasia Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Bleeding dyscrasia Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Bleeding dyscrasia Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

HSP is commonly associated with abdominal pain, palpable purpuric rash, arthralgias, and renal disease. It is most common in children 4 to 11 years of age and occurs during the spring season following viral upper respiratory infections.

Clinical Features

Symptoms include abdominal pain, nausea, vomiting, and diarrhea. Patients are usually diagnosed clinically on the basis of the classic palpable purpura located on the buttocks and lower extremities (Fig. 171.11). Up to 70% of patients have GI complaints, including bleeding and ileoileal intussusception. Microscopic hematuria occurs in 50%. The syndrome is often relapsing and remitting for several weeks and may be associated with arthralgias. Neurologic involvement is less common in children.

Diagnostic Considerations

Differential Diagnoses. The most important entity in the differential diagnosis for a petechial or purpuric rash is meningococcemia. Patients with meningococcemia are typically febrile and ill-appearing. The classic triad of palpable purpura, abdominal pain, and hematuria in an otherwise well-appearing and afebrile child is more likely to be HSP.

Diagnostic Testing. Patients are usually diagnosed clinically on the basis of the classic rash. All children with clinically diagnosed HSP should have a urinalysis for evaluation of renal involvement—white cells, red cells, casts, and protein. Those with apparent renal involvement should have serum electrolyte and creatinine levels measured. Patients with an uncertain diagnosis should have a CBC with differential, coagulation studies, blood culture, and sedimentation rate. Patients with HSP do not have thrombocytopenia. Children diagnosed with HSP who have worrisome abdominal pain should be evaluated for intussusception.

Fig. 171.11. Henoch-Schönlein purpura in a 7-year-old child. Note the typical red-purple rash on the lower extremities. (Courtesy Dr. Marianne Gausche-Hill.)

Management

Most children with HSP require only supportive management. Mild and moderate pain is usually well-controlled with

nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen. Management of HSP with glucocorticoids is controversial. Glucocorticoids have been shown to reduce pain associated with HSP, but have not been shown to affect the other disease complications, including nephropathy.[28,29] Prednisone, at a dose of 1 mg/kg/day (maximum, 60 mg), is reserved for patients with severe symptoms, including severe abdominal pain, GI bleeding, hematuria, or severe arthralgias, usually in consultation with a rheumatologist.

Disposition

Most patients can be managed symptomatically with close outpatient observation and follow-up. Indications for hospital admission include uncertain diagnosis to exclude the possibility of meningococcemia, severe abdominal pain, and intractable vomiting. Additionally, a set of six criteria, with the presence of at least one of these criteria, predicts the need for hospitalization— orchitis, moderate or severe abdominal pain, polyarthritis, GI bleeding, and inability to ambulate.[30] Those with compromised renal function should have a nephrology consultation and also should be considered for admission, particularly if presenting with hypertension.

Inflammatory Bowel Disease

Principles of Disease

Approximately 20% of patients with IBD develop symptoms before the age of 20 years. Most patients do not experience symptoms until adolescence. IBD is rare in children younger than 1 year.[31]

Ulcerative colitis is an inflammatory disease primarily involving the mucosa and submucosa of the rectum and distal colon. Crohn's disease is a transmural inflammatory disease that may involve any portion of the intestinal tract. Chronic inflammation may result in the formation of an abscess, fistula, or stricture. Crohn's disease is commonly associated with extraintestinal manifestations, especially in children.

Clinical Features

Although patients experiencing complications frequently present to the ED, the diagnosis is rarely made in this setting. Usually, children with known disease present in the midst of an acute flare, usually with increased frequency of diarrheal stools, bloody diarrhea, abdominal pain, and occasionally fevers. Patients with toxic megacolon or perforations are usually febrile and volume-depleted and demonstrate significant abdominal tenderness. There are also extraintestinal manifestations and include fever, anemia, oral ulcerations, erythema nodosum, pyoderma gangrenosum, uveitis, liver dysfunction, and failure to thrive.

Diagnostic Considerations

Diagnostic Testing. Acute IBD flares are usually diagnosed clinically. Patients who appear ill may require plain films to evaluate for toxic megacolon or bowel perforation. Screening laboratory studies should include a CBC with differential and platelet counts, typing and screening, and electrolyte panel. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels may also be beneficial in the diagnosis and management because most patients have elevated levels at the time of diagnosis, as well as with acute flares.

Differential Diagnoses. There are a large number of differential considerations for abdominal pain and GI bleeding (see Tables 171.4 and 171.5). Gastroenteritis is the most common consideration in this clinical scenario. Children experiencing their first episode of IBD and children outside the usual age at presentation are much more likely to be misdiagnosed with acute gastroenteritis.

Management

Management in the ED begins with attention to volume status and resuscitation with repeated boluses of 20 mL/kg of normal saline until the volume status is adequate. Acute exacerbations should be treated in conjunction with a gastroenterologist. Corticosteroids (eg, prednisone, 1 mg/kg/day; maximum dose, 60 mg/day) are usually recommended for mild to moderate exacerbations. Other agents commonly used include sulfasalazine and azathioprine, along with other immunosuppressive agents.[32,33] Patients with suspected toxic megacolon require IV broad-spectrum antibiotic therapy and surgical consultation.

Disposition

Children not diagnosed with IBD but who have recurrent GI symptoms or a family history of IBD should be referred to a pediatric gastroenterologist for further evaluation. With acute flares, indications for admission include dehydration, toxic or ill appearance, and inability to tolerate oral fluids. Children with evidence of toxic megacolon should have a surgical consultation.

Gastrointestinal Foreign Bodies

Principles of Disease

GI foreign bodies usually are seen in children younger than 5 years and in those with developmental delays. Coins, small toys, magnets, batteries, and jewelry are the most common esophageal foreign bodies in children, compared to food boluses in adults. Most ingestions in children are accidental.

Most swallowed foreign bodies pass through the entire GI tract without complications. However, foreign bodies commonly become lodged in one of three areas of normal physiologic narrowing—upper esophageal sphincter (cricopharyngeus muscle), thoracic inlet (C6-T1); aortic arch, tracheal bifurcation (T4-6); and lower esophageal sphincter, diaphragmatic hiatus (T10-11).[34] Of objects that have made it into the stomach, 80% to 90% are passed without complications.

Clinical Features

Many accidental ingestions go unwitnessed. Children may gag as they attempt to swallow the object. Objects aspirated into the respiratory tract generally produce persistent coughing, wheezing, and increased work of breathing. Children who swallow objects into the GI tract may remain asymptomatic or develop a wide spectrum of symptoms, including food refusal, persistent gagging, drooling, continuous dry heaves, or wheezing.[35] Larger foreign bodies may compress the airway and cause respiratory distress.

Complications are more likely to occur when foreign bodies have been impacted for an extended period of time. Progressive dysphagia, pain, respiratory distress, or fever is suspicious for esophageal or intestinal perforation.

Swallowed button batteries warrant special mention. Button batteries lodged in the esophagus cause severe mucosal erosions, severe burns, and mediastinitis in as little as 2 hours, most likely as a result of the electrical current discharged from lithium batteries. GI consultation for emergent foreign body removal is necessary. Button batteries in the stomach usually pass without complications and do not require removal unless they fail to pass

the pylorus within 48 hours of ingestion.[35,36] The National Capital Poison Center operates a 24/7 website (www.poison.org/battery) and hotline (202-625-3333) for battery ingestion cases.[37]

On occasion, objects pass into the stomach that are too large to pass through the pylorus. As a general rule, objects longer than 5 cm and wider than 2 cm are less likely to pass the pylorus spontaneously. Persistent vomiting may herald obstruction. If not removed, foreign bodies may, over time, result in erosion, perforation, infection, stricture, or fistula formation.

Diagnostic Considerations

Diagnostic Testing. Plain radiography is the most common method of diagnosing and locating foreign bodies. Classically, coins in the esophagus project en face (round) in the frontal (coronal) view (Fig. 171.12). When coins are lodged in the upper airway, they will project on end in the frontal view. Occasionally, it may be difficult to differentiate the appearance of a coin from a button battery radiographically. A button battery will typically have a distinctive double-rim contour on radiographs[36,37] (Fig. 171.13).

Differential Diagnoses. Not all foreign bodies are radiopaque and visible with standard radiography. Patients who remain symptomatic require further contrast-enhanced imaging or direct visualization.

Management

Most GI foreign bodies will spontaneously pass without complications. In general, if the object has made it into the stomach, further treatment or routine serial imaging is unnecessary. Patients with button batteries located in the stomach represent an exception in that they require repeated films to ensure passage

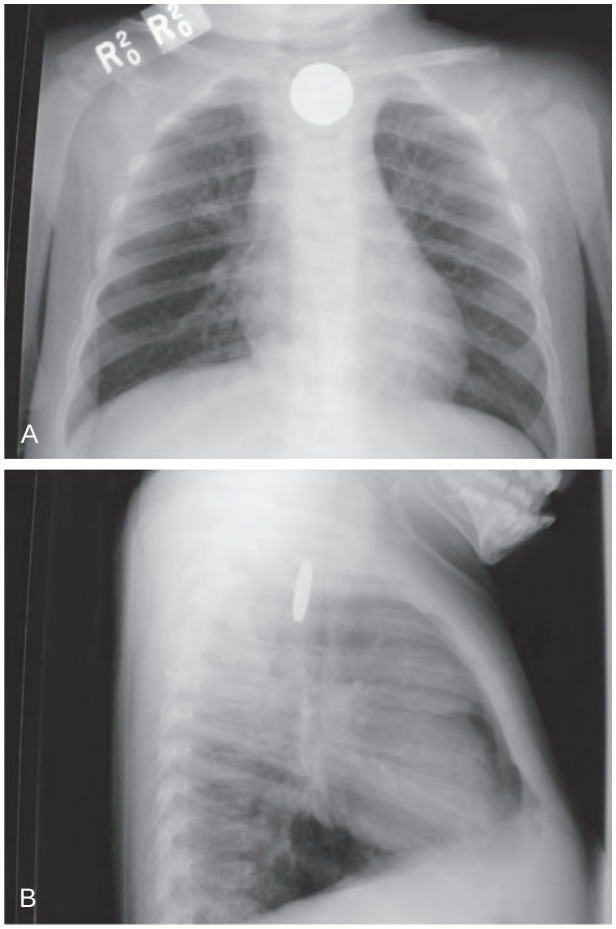


Fig. 171.12. Plain radiographs obtained in a child with an esophageal coin foreign body. Posteroanterior (**A**) and lateral (**B**) views show the expected orientation for a coin lodged in the esophagus. (Courtesy Dr. Mark A. Hostetler.)

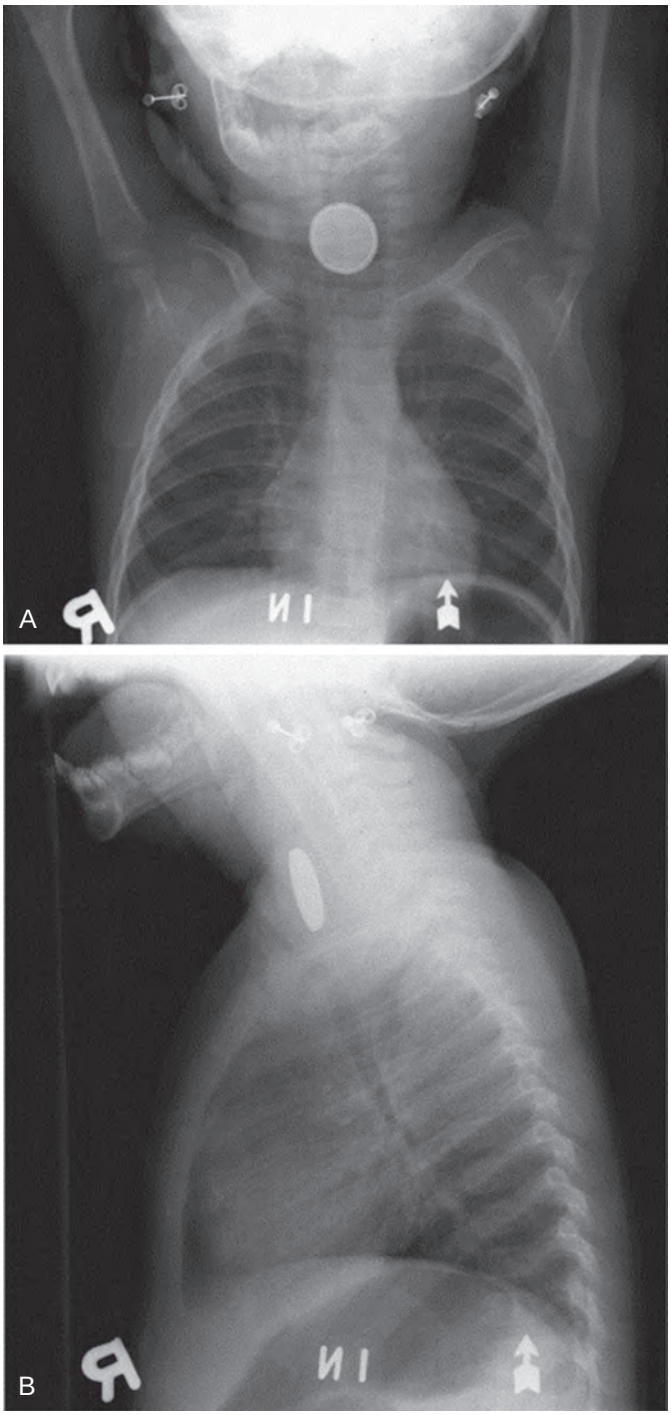


Fig. 171.13. Esophageal button battery. It may be difficult to differentiate the appearance of a coin from a button battery radiographically. However, a button battery will typically have a distinctive double-rim contour on radiographs, as seen in this posteroanterior radiograph. (From: Lin VYW, Daniel SJ, Papsin BC: Button batteries in the ear, nose and upper aerodigestive tract. Int J Pediatr Otorhinolaryngol 68:473–479, 2004.)

BOX 171.3

Indications for Emergency Removal of Gastrointestinal Foreign Bodies

- Signs of respiratory distress
- Evidence of esophageal obstruction (inability to swallow secretions)
- Button batteries in the esophagus
- Sharp or long (>5 cm) objects in the esophagus or stomach
- High-powered magnets (buckyballs)
- Signs or symptoms of intestinal inflammation, obstruction or perforation
- Esophageal foreign bodies impacted for >24 hr or for an unknown amount of time

beyond the pylorus. Asking parents to check the child's stool for a passed foreign body is rarely productive.

The timing of intervention for foreign body removal is based largely on the type of object, location, duration, and symptoms. With the exception of button batteries, which should be removed emergently within 2 hours, esophageal foreign bodies may be removed urgently within 24 hours. Blunt objects such as coins in the esophagus of asymptomatic children may be observed for 12 to 24 hours because many of them will pass spontaneously into the stomach. Indications for more emergent removal are listed in Box 171.3.

The preferred method to remove esophageal foreign bodies varies by institution; flexible endoscopy is most common and has a high success rate.[38] Other options include fluoroscopic Foley catheter removal, bougie advancement into the stomach, and removal by rigid bronchoscopy under general anesthesia in the operating room.

Disposition

Esophageal foreign bodies require removal, as described previously. Once foreign bodies have passed into the stomach, most pass without complications, and no specific follow-up is usually necessary. Abdominal pain, food aversion, and intractable vomiting may suggest a retained gastric foreign body warranting repeat radiography. Button batteries in the stomach constitute the exception and necessitate follow-up films in 24 hours to document passage beyond the pylorus, even in asymptomatic children.

Appendicitis

Principles of Disease

Appendicitis is the most common surgical condition involving the abdomen and the most common nontraumatic surgical emergency in children. Appendicitis develops in approximately 1 of every 15 people sometime during their lifetime. The peak age of incidence is between 9 and 12 years, and it is uncommon in children younger than 5 years.

The appendix is a blind pouch that may become obstructed, resulting in edema, vasocongestion, inflammation, ischemia, infarction, necrosis, and perforation. In adults, a thicker appendiceal wall resists perforation, and a well-developed omentum aids in walling off the infection to prevent its diffuse spread. Children have neither, so rupture tends to occur earlier, and diffuse peritonitis develops more readily.

Morbidity and mortality related to acute appendicitis increase significantly if the appendix ruptures prior to operative management. Therefore, the goal of management is diagnosis and operative management prior to appendiceal perforation. Perforation seems to be directly related to the duration of symptoms. In children, the rate of appendiceal perforation varies inversely with age. Perforation is highest among children younger than 5 years, among whom more than 50% are ruptured at the time of surgery.[39] This likely reflects, at least in part, the fact that preschool children have a limited ability to describe their symptoms.

Clinical Features

Patients classically present with a constellation of symptoms that includes abdominal pain, nausea, vomiting, and anorexia. Symptoms are gradually progressive over the first 24 hours. Abdominal pain is usually first described as vague, crampy, and periumbilical. Pain becomes more severe, constant, and localized to the right lower quadrant as the disease progresses. Fever usually develops later or not at all. Patients may have a multiphasic course to their illness, with symptom resolution followed several days later by the development of fever, chills, and abdominal pain. This likely represents spontaneous appendiceal rupture and formation of an abscess.

The physical examination may reveal several typical findings. In patients with inflammation surrounding the appendix, peritoneal findings that localize to the right lower quadrant are typical. Pain occurs with movement; patients may be unwilling to jump up and down, and tapping their heels may cause abdominal pain. Bowel sounds are usually decreased or absent. Rebound tenderness may be elicited in the right lower quadrant. The Rovsing, psoas, and obturator signs are difficult to assess in young children and should not be relied on due to their poor sensitivities and specificities. The absence of the classic signs and symptoms of appendicitis does not exclude the diagnosis, especially in younger children.

Diagnostic Considerations

Diagnostic Testing. Appendicitis may be diagnosed clinically on the basis of the history and physical findings alone in children with a classic constellation of findings. Patients with an equivocal presentation should undergo a diagnostic evaluation. There are no sufficiently sensitive or specific laboratory tests that alone can confirm or exclude the diagnosis of acute appendicitis. Screening studies may include a CBC with differential, CRP, urinalysis, electrolyte levels, and renal and liver function testing. Pregnancy testing, vaginal wet mount, and gonorrheal and chlamydial testing should be considered in postpubertal females. Most children with acute appendicitis have an elevated white blood cell count (>10,000 $\times$ 10^6/L) or absolute neutrophil count.[40] Because it is neither sensitive nor specific enough, an elevated white blood cell count should not be exclusively used to diagnose or exclude appendicitis. An elevated CRP level (>0.6 mg/dL) has been shown to correlate with acute appendicitis, especially when symptoms have been present for longer than 24 to 48 hours.[41] Acute appendicitis occasionally causes a mild sterile pyuria (<5 to 10 white blood cells/high-power field and an absence of bacteria) related to local inflammation of the right ureter.

Several clinical scoring systems have been developed to assist in the evaluation of appendicitis. The most widely studied prospectively include the Alvarado score, Pediatric Appendicitis Score, and Refined Low-Risk Appendicitis Rule.[42,43] Each system relies on a combination of clinical factors and laboratory values to risk-stratify children into low-, moderate-, and high risk categories for acute appendicitis. Unfortunately, none of these have been shown to be sensitive and specific enough to be recommended alone for widespread clinical use.

Diagnostic imaging options include plain films of the abdomen, ultrasonography, and CT. Plain films have limited value in appendicitis and are not recommended in the routine evaluation of

appendicitis. Occasionally, an appendiceal fecalith will be evident (Fig. 171.14). Although the presence of an appendicolith in a child with acute abdominal pain is essentially pathognomonic for acute appendicitis, it is present in only 10% of cases.

Ultrasonography is routinely recommended as the first-line imaging modality in suspected appendicitis. It has the advantages of a lack of ionizing radiation and the ability to evaluate ovarian anatomy. Ultrasonographic findings consistent with appendicitis include an enlarged, noncompressible appendix (wall thickness > 2 mm; total appendix diameter > 6 mm) that is painful during scanning (Fig. 171.15A, B).[44] Appendiceal ultrasound studies have reported sensitivities and specificities of more than 90% when the appendix is successfully visualized. Unfortunately, the ability to visualize the appendix adequately with ultrasound is limited in obese children and is highly user-dependent.[45]

Fig. 171.14. Fecalith in a child with appendicitis. (Courtesy Dr. Marianne Gausche-Hill.)

In the child in whom the appendix is not visualized or findings are equivocal with ultrasonography, clinical observation with serial examinations or CT imaging may be undertaken. CT in general has high sensitivity and specificity for unruptured and ruptured appendicitis, and the use of IV contrast seems to improve sensitivity slightly. Limited appendiceal CT protocols decrease the ionizing radiation exposure without sacrificing sensitivity or specificity. The increased use of CT has been shown to reduce the negative laparotomy rate without increasing the risk of perforation.

Differential Diagnoses. Differential considerations for abdominal pain by age are listed in Table 171.4. Mesenteric adenitis is the most common imitation of appendicitis. Similar to appendicitis, it often is associated with significant diffuse tenderness that may localize in the right lower quadrant. Children with mesenteric adenitis lack true peritoneal signs, however. Mesenteric adenitis usually follows a viral illness and results from nonspecific inflammation of the mesenteric lymph nodes.

Girls of reproductive age merit consideration of gynecologic pathology, including ectopic pregnancy, ovarian torsion, ovarian

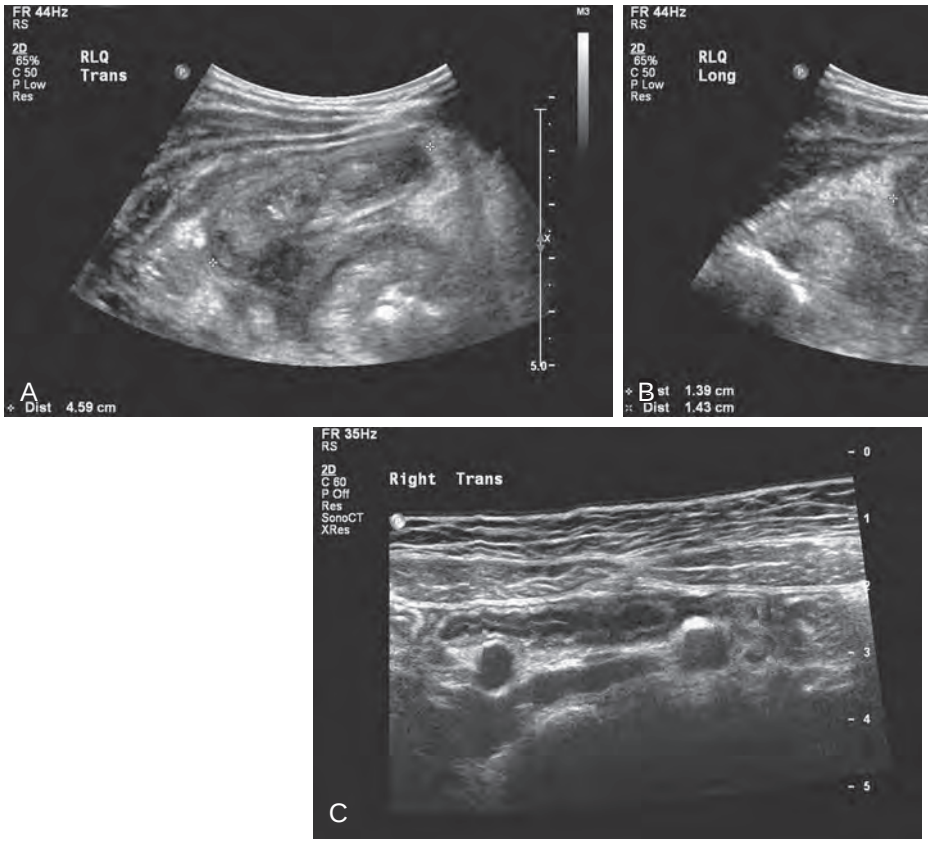


Fig. 171.15. Ultrasound images obtained in children with appendicitis. Findings include an enlarged, noncompressible, tubelike structure in the longitudinal view with an appendicolith (**A**), an enlarged noncompressible structure seen in cross section (**B**) and, in another patient, an enlarged, poorly compressible structure with a moderate amount of free fluid consistent with acute perforation (**C**). (Courtesy Dr. Mark A. Hostetler.)

cyst, pelvic inflammatory disease, and tubo-ovarian abscess. Testicular torsion may manifest with nausea, vomiting, and abdominal pain, but the testicular examination is usually grossly abnormal in these boys. Boys with abdominal pain on the side of an undescended testis should be evaluated for torsion of an intra-abdominal testicle. Group A streptococcal pharyngitis may also present with abdominal pain.

Management

Definitive management of acute appendicitis is open or laparoscopic appendectomy. The exact timing of surgery is controversial but should optimally be performed within 12 to 24 hours of diagnosis.[46,47] Most patients benefit from IV fluids and parenteral administration of opioid pain medications and antiemetics. Narcotics are safe and effective and should not alter the diagnostic accuracy of the physical examination. Patients with a nonperforated appendicitis should receive a single dose of parenteral antibiotics (Box 171.4) 30 to 60 minutes prior to surgery to decrease the risk of wound infection and intra-abdominal abscess formation.[48,49] It is not necessary to continue antibiotics postoperatively in those with a nonperforated appendicitis. Patients with suspected perforation, signs or symptoms of sepsis, or unusual delay in surgical management should receive IV antibiotics in the ED and continued postoperatively.[48,49]

Disposition

Children with appendicitis should be hospitalized for appendectomy. Patients with nonspecific signs and symptoms in whom imaging studies are nondiagnostic should be observed for a period of 12 to 24 hours with serial exam examinations or, with adequate family and social support, discharged home, with careful instructions to return for reexamination.

Pancreatitis

Principles of Disease

Pancreatitis is uncommon in childhood, especially in children younger than 10 years. In adults, pancreatitis is usually caused by alcohol abuse and biliary tract disease. In children, pancreatitis is usually associated with trauma, infection, structural anomalies, systemic disease, and drugs or toxins. Idiopathic causes account for 30% of cases. Biliary obstruction should be considered in the adolescent.

The common pathophysiologic pathway of acute pancreatitis is inflammation, edema, and autodigestion of pancreatic tissue by pancreatic enzymes. In severe cases, the inflammatory cascade may progress to necrotizing or hemorrhagic pancreatitis. Other complications include the formation of abscesses, pseudocysts, and fistulas.

Clinical Features

Abdominal pain in the hallmark of pancreatitis in adults and children. Patients typically present with complaints of severe, constant epigastric pain that worsens gradually and radiates to the back. Nausea, vomiting, diarrhea, fevers, irritability, and lethargy are also described. Patients have significant abdominal tenderness in the epigastric area.

Diagnostic Considerations

Diagnostic Testing. Screening laboratory studies reveal elevations in the serum lipase level. The degree of elevation or serial changes are not always directly related to disease severity. Evidence of liver inflammation (elevated aspartate transaminase and alanine transaminase levels) and elevated bilirubin and alkaline phosphatase levels may be seen in patients with biliary obstruction. Plain films of the abdomen commonly show an ileus pattern, often with a sentinel loop of dilated small bowel in the left upper quadrant. An ultrasound study or CT may be helpful to evaluate anatomy for congenital malformations, biliary tract disease, pseudocyst, or abscess formation.[50] In patients with respiratory distress, a chest radiograph may identify a secondary pleural effusion.

Differential Diagnoses. Slow progressive onset of pain is more likely to be associated with appendicitis, constipation, and pancreatitis. Sudden onset of severe pain is usually associated with acute obstruction or vascular occlusion, as seen with intussusception, volvulus, or torsion. Differential considerations for abdominal pain in children by age are listed in Table 171.4.

Management

Patients should receive volume replacement and electrolyte correction and maintained on an NPO status. IV fluids are given in repeated boluses of 20 mL/kg of normal saline until adequate vascular volume has been established. Patients should receive adequate symptomatic relief with parenteral narcotics and antiemetics. Steroids and antibiotics are not indicated.

Disposition

Children with acute pancreatitis require hospitalization. Children with known or recurrent disease, are able to self-hydrate, and have adequate analgesia may be managed as outpatients.

Biliary Tract Disease

Principles of Disease

Biliary tract disease is uncommon in childhood and has causes differ from those in older individuals. Cholestasis in the neonatal period is usually associated with biliary atresia, biliary cysts, infections, and other metabolic and genetic disorders. Gallstones in children are usually associated with hemolytic disease (eg, sickle

BOX 171.4

Empirical Antibiotic Regimens for Acute Appendicitis

REGIMEN

- Cefoxitin
- Ceftriaxone + metronidazole
- Cefotetan
- Gentamicin + clindamycin or metronidazole (penicillin-allergic patients)
- Piperacillin-tazobactam

DOSING

- Cefoxitin: 40 mg/kg IV; maximum dose, 2000 mg
- Ceftriaxone: 50 mg/kg IV; maximum dose, 1000 mg
- Metronidazole: 10 mg/kg IV; maximum dose, 500 mg
- Cefotetan: 40 mg/kg IV; maximum dose, 2000 mg
- Gentamicin: 2.5 mg/kg IV
- Clindamycin: 10 mg/kg IV; maximum dose, 900 mg
- Piperacillin-tazobactam: 25 mg/kg IV

cell disease), cystic fibrosis, total parenteral nutrition, sepsis, and dehydration. Ceftriaxone has been associated with sludging and biliary disease, particularly in neonates. Acute acalculous cholecystitis has been associated with Rocky Mountain spotted fever and a variety of bacterial infections, including those due to *Salmonella* and *Shigella* organisms. Hydrops of the gallbladder (ie, fluid distention of the gallbladder from chronic cystic duct inflammation or obstruction without inflammation or infection) is associated with viral upper respiratory or GI infections, Kawasaki disease, streptococcal pharyngitis, mesenteric adenitis, nephrotic syndrome, and leptospirosis.

Pigment gallstones stones are more common in childhood; cholesterol stones are uncommon prior to adolescence. Pigment stones result from the excess breakdown of red blood cells and are usually seen in those with hemolytic anemia, such as sickle cell disease and spherocytosis. Adolescents may form cholesterol gallstones in association with oral contraceptives, pregnancy, or obesity.

Clinical Features

Similar to adult patients, pediatric patients usually present with postprandial right upper quadrant pain associated with fever, nausea, and vomiting. Jaundice occurs in one-third of patients.

Diagnostic Considerations

Diagnostic Testing. Biliary tract disease is usually associated with elevations in alkaline phosphatase, liver enzyme, and bilirubin levels; however, absence of elevations does not exclude the diagnosis. Elevated white blood cell counts are nonspecific. Although only 15% of gallstones in adults are calcified and visible on plain radiographs, 50% of stones in children are radiopaque. Ultrasonography is the imaging modality of choice. It cannot only determine the presence of gallstones, dilation of the gallbladder and common bile duct, gallbladder wall thickness, and pericystic fluid, but can reproduce pain on compression of the gallbladder (sonographic Murphy's sign). When ultrasound findings are equivocal or normal, and clinical suspicion is high, cholescintigraphy biliary tract imaging (HIDA [hepatobiliary iminodiacetic acid] scan) can further assess the functional status of the gallbladder. Although its role in children is unclear, magnetic resonance cholangiopancreatography can assess the intrahepatic and extrahepatic ducts.

Differential Diagnoses. Pediatric biliary tract disease is uncommon in children and requires consideration of an underlying or coexistent disease. Differential considerations are listed in Table 171.4.

Management

Asymptomatic patients with incidental findings of gallstones require no further therapy in the ED and may be referred to a surgeon for outpatient care. Febrile patients require hospital admission, fluid resuscitation, IV antibiotics, and surgical consultation. Laparoscopic cholecystectomy is considered safe and effective in children.

Disposition

Indications for hospital admission for biliary disease include pain control, need for IV hydration, fever, and need for operative management.

KEY CONCEPTS

- Physiologic jaundice of the newborn and breast milk jaundice are the most common causes of jaundice in the neonatal period.
- Direct hyperbilirubinemia in infants is always pathologic and requires a detailed evaluation.
- Hypertrophic pyloric stenosis is associated with gradually progressive nonbilious emesis that becomes projectile.
- Hypochloremic-hypokalemic metabolic alkalosis is the classic electrolyte derangement associated with hypertrophic pyloric stenosis.
- Bilious vomiting in the neonate should initiate a diagnostic evaluation for possible malrotation with volvulus or other intestinal obstructive pathology.
- Toxic-appearing infants with bilious emesis should receive an emergent surgical consultation.
- Necrotizing enterocolitis occurs more commonly in premature infants, but 10% of affected infants are full term. Pneumatosis intestinalis—intramural air seen on x-ray—is pathognomonic for NEC.
- Gastroesophageal reflux (GERD) is very common in infants and is usually benign and self-limited. Occasionally, GERD may cause more severe symptoms, including irritability, respiratory distress, and failure to thrive. GERD usually responds to conservative measures (eg, positioning, thickening of formula, smaller and more frequent feedings); pharmacologic interventions are seldom needed.
- The classic clinical triad of intussusception includes colicky, intermittent abdominal pain, a palpable sausage-shaped abdominal mass, and bloody stools; however, the triad occurs in less than one-third of patients.
- Children with intussusception may present atypically, with an altered level of consciousness (eg, lethargy) rather than abdominal pain.
- Hirschsprung's disease is a common cause of constipation in the neonate and usually manifests as delayed passage of meconium. Occasionally, children may present later in life with symptoms of chronic constipation. Toxic megacolon is the most serious complication.
- Meckel's diverticulum classically manifests in children younger than 5 years, with massive, painless, brick red rectal bleeding.
- More than 90% of GI foreign bodies pass without complications
- Button batteries lodged in the esophagus may cause serious burns, erosions, and perforations within as little as 2 hours. Of all foreign bodies, button batteries require the most expeditious removal, usually by endoscopy.
- Appendicitis is the most common surgical disease in children. Diagnosis depends on a combination of clinical factors, including history, physical examination, laboratory values, and imaging studies. The ideal diagnostic algorithm remains elusive.
- Effective imaging strategies for children with suspected appendicitis include initial ultrasound examination followed by CT scanning of the abdomen for those with equivocal findings.
- Causes of pancreatitis in children include viruses, trauma, drugs, and toxins.
- Biliary disease in children is more commonly caused by cholestasis rather than biliary obstruction.
- Pigment gallstones are more common than cholesterol stones in children. Biliary tract disease is usually diagnosed with right upper quadrant ultrasound imaging; management strategies are similar to those for adults.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 171: QUESTIONS & ANSWERS

171.1. What is the most common cause of jaundice in the newborn?

A. Breast milk jaundice
B. Crigler-Najjar syndrome
C. Gilbert's syndrome
D. Physiologic jaundice of the newborn
E. Toxoplasmosis, other (congenital syphilis and viruses), rubella, cytomegalovirus, and herpes simplex virus (TORCH) infection

Answer: D. Although each of these may be a cause of hyperbilirubinemia in the newborn, the most common cause of jaundice is physiologic jaundice of the newborn.

171.2. A 4-week-old white infant presents with projectile vomiting. The mother denies that the patient has a history of fevers, irritability, or signs suggestive of abdominal pain. On physical examination, you palpate an olive in the patient's right epigastrium. Which of the following laboratory abnormalities would you expect to find?

A. Hyperchloremia and hypokalemia
B. Hyperglycemia and hypokalemia
C. Hypernatremia and hyperkalemia
D. Hypochloremia and hypokalemia
E. Hyponatremia and hyperkalemia

Answer: D. This patient likely has pyloric stenosis. As vomiting continues, the infant loses hydrogen and chloride ions through emesis of gastric juices. As this metabolic derangement worsens, the kidney attempts to retain hydrogen ions by substituting potassium, resulting in a hypochloremic-hypokalemic metabolic alkalosis.

171.3. An 11-month-old infant presents with vomiting. The patient's mother reports that he has been crying out in pain intermittently throughout the day, at which times he brings his knees to his abdomen. In between these episodes, the patient acts normally and plays. He has not had a fever, but the mother complains that his stool earlier looked like currant jelly. On examination, you find a playful afebrile patient, with a soft nontender abdomen. Which of the following may be used as an initial screening examination?

A. Air contrast enema
B. Barium enema
C. Computed tomography scan of the abdomen-pelvis
D. Ultrasound
A. Upper endoscopy

Answer: D. The initial screening examination for intussusception is abdominal ultrasonography. Although each of the other imaging modalities may be useful to exclude other diagnoses or identify intussusception, ultrasonography has high sensitivity and specificity and is the screening modality of choice.

CHAPTER 172

Infectious Diarrheal Disease and Dehydration

Patricia Padlipsky | Taylor McCormick

PERSPECTIVE

Diarrheal disease is responsible for approximately three quarter million deaths worldwide, 72% of which occur in children younger than 2 years old.[1,2] Diarrheal diseases account for one in nine pediatric deaths worldwide and is the second leading cause of death in children younger than 5 years old.[2,3] The rotavirus vaccine has markedly reduced pediatric diarrhea-associated emergency department (ED) visits and hospitalizations.[4,5] Acute diarrhea is defined as the abrupt onset of abnormally high fluid content in the stool with increased volume or frequency. As supported by the World Health Organization (WHO), "acute" diarrhea has a sudden onset and lasts no longer than 14 days; "chronic" or "persistent" diarrhea lasts longer than 14 days. This classification is important for epidemiologic studies and to identify the most likely offending organism. Protracted diarrhea has different causes, poses unique problems in management, and has a prognosis different from that of acute diarrhea. Acute infectious diarrhea can occur with or without vomiting. When it occurs with vomiting, it is often referred to as *acute gastroenteritis (AGE)*.

Principles of Disease

Up to 9 L of exogenous fluid and endogenous secretions enter the adult proximal bowel each day, and proportionally even more in children. Ninety percent of fluid is absorbed in the small bowel and the remainder in the large bowel. Water follows osmotic gradients created by active and passive transport of electrolytes, sugars, and amino acids into the bloodstream by the following mechanisms:

- Sodium chloride absorption in the small bowel, with an exchange of cations (Na^+/H^+) and anions (Cl^-/HCO_3^-)
- Electrogenic sodium absorption in the colon but also in the small intestine, wherein Na^+ enters the cell through an electrochemical gradient; this mechanism is often damaged in acute diarrhea
- Sodium co-transport mechanism in the small bowel

Na^+ absorption is coupled with the absorption of glucose, amino acids, and peptides. This mechanism often remains intact during acute diarrhea illness, making oral rehydration possible.[6]

Pathophysiology

Infectious agents cause diarrhea by adherence, mucosal invasion, enterotoxin production, and cytotoxin production. Under normal circumstances, the absorptive processes for water and electrolytes predominate over secretion, resulting in net water absorption. Diarrhea occurs when this balance is disrupted, either as a result of increased secretion from the gastrointestinal tract, decreased absorption of fluids, or from inflammation.

Secretory diarrhea is the result of increased intestinal secretion of water into the gut lumen or an inhibition of absorption. For example, *Vibrio cholera* produces an enterotoxin, resulting in increased chloride and bicarbonate secretion. Secretory diarrhea is characterized by the absence of expected reduction in stool volume with fasting, a stool pH above 6, and the absence of reducing substances in the stool. Other bacteria that produce enterotoxins include *Salmonella, Shigella, Escherichia coli,* and *Clostridium difficile*.

Osmotic diarrhea is caused by the presence of poorly absorbed solutes from altered bacterial gut flora, damage to the mucosal absorptive surface, or ingestion of substances. These substances create an osmotic gradient across the bowel lumen, resulting in intraluminal movement of water and electrolytes. Typical acute viral gastroenteritis produces injury to the small bowel epithelium with consequent disruption of microvilli, decreasing the absorptive area, and preventing normal fluid, electrolyte, and nutrient absorption. The illness is compounded if the colon is unable to compensate for the large fluid volume. Osmotic diarrhea is often characterized by diarrhea that decreases or stops with fasting, a stool pH below 6, and the presence of reducing substances in the stool.

Inflammatory processes can cause destruction of villous cells or dysfunction of cellular transporters, leading to loss of fluids and electrolytes, as well as mucus, proteins, and blood in the intestinal lumen. *Dysentery,* diarrhea associated with blood and mucus in the stool, implies a compromised bowel wall. Acute inflammation, caused by enteroinvasive organisms such as *Salmonella, Shigella,* and *Campylobacter,* leads to infiltration of the gastrointestinal tract by neutrophils, which release a host of enzymes and factors causing both increased secretion and decreased absorption by the intestinal tract. Although blood loss may be clinically appreciable, it is usually less significant than fluid and electrolyte losses. Infectious diarrhea can present with significant signs of dehydration and electrolyte abnormalities.

The pediatric patient has several physiologic factors that predispose them to more severe complications from vomiting and diarrhea. As a result of their relatively larger extracellular fluid compartments, children can lose proportionately more fluids through the gastrointestinal tract. Furthermore, the turnover of fluids and solute in infants and young children can be three times that of adults. This rapid turnover of fluids is the result of higher metabolic rates, increased body surface area to mass index, and higher body water content. Children also have limited stores of metabolic substrates such as fat and glycogen, limited ability or desire to access fluids when ill, and a more limited ability to conserve water through their kidneys compared to adults. These factors make children more susceptible to large fluctuations in fluid, electrolytes, and nutrients, resulting in hypoglycemia, electrolyte abnormalities, dehydration, and shock.

Some groups are at higher risk for developing serious complications of infectious diarrhea (eg, invasive disease, bacteremia, and sepsis). These include premature infants, very low birth weight infants (up to a year), young infants (younger than 3 months old), immunosuppressed or malnourished children, and those with chronic underlying conditions. Recent hospitalization, treatment with broad-spectrum antibiotics, and travel to developing countries are additional risk factors. Risks factors for death from diarrhea include age younger than 1 year; birth weight less than 2500 g; malnourishment; African American, Hispanic American, or American Indian ethnicity; immunocompromise; and illness during winter months.

Clinical Features

Infectious diarrhea can present with diarrhea alone or accompanied by vomiting (ie, AGE). Signs and symptoms usually begin 12 to 72 hours after contracting the infectious agent. If due to a viral agent, the condition usually resolves within 1 week.[7] See Box 172.1 for a list of common signs and symptoms. The history and physical examination should help differentiate acute infectious diarrhea from other causes of vomiting and diarrhea (see Tables 172.8 and 172.9) and help estimate the degree of dehydration. History and physical examination can sometimes aid in determining the type of pathogen responsible, although this will rarely affect management. Box 172.2 summarizes important information to gather from the history.

Vital signs should be assessed relative to age norms. The evaluation of the child should begin with looking at the child from across the room in a position of comfort, noting the patient's overall appearance, responsiveness, activity, and work of breathing (see Chapter 160). A head-to-toe physical examination of the patient should focus on signs of dehydration that may indicate another cause for the diarrhea (eg, otitis media, pyelonephritis, appendicitis, diabetic ketoacidosis), or signs that indicate the disease may have become extra-intestinal or systemic—bone pain (osteomyelitis), altered mental status (meningitis), petechiae (hemolytic-uremic syndrome [HUS]).

Acute infectious diarrhea in developed countries is often self-limited. The clinical presentation, course of illness, and treatments depends on the etiology of the diarrhea and the host. In the United States, viruses are responsible for most cases of acute infectious diarrhea, with bacteria causing only 7% to 10% of cases in children. Parasites are uncommon in the immunocompetent patient unless they have traveled to endemic areas. Table 172.1 lists the most common viruses, bacteria, and protozoa that can cause acute infectious diarrhea in children in the United States.[8-10]

BOX 172.1

Common Signs and Symptoms in Patients With Acute Infectious Diarrhea

Diarrhea—frequent, loose, watery, mucousy, bloody, and/or foul smelling
Nausea
Decreased appetite
Weight loss
Vomiting
Headache
Abdominal pain and/or cramps
Fever
Malaise
Signs of dehydration (see Dehydration section)

Specific Etiologies

Viruses

In the United States and Europe, the majority of cases of diarrhea are caused by viral pathogens, with incidence peaking in the winter. The most common of these are rotavirus and norovirus. See Table 172.2 for presentation and associated characteristics.

Rotavirus is the leading cause of diarrhea worldwide among children younger than 5 years old.[9] Neurologic symptoms, most commonly seizures, occur in 2% to 3% of children with rotavirus infection.[11] The chronically ill or malnourished child often fails to repair damaged intestinal epithelium post rotavirus infection, leading to a vicious cycle of malnutrition and progressive epithelial injury.

Prior to the release of the 2006 and 2008 vaccines, rotavirus was responsible for over 600,000 office and ED visits and up to 77,000 hospitalizations each year. An effective vaccine against

TABLE 172.1

Common Causes of Childhood Infectious Diarrhea in Developed Countries

VIRUSES (70% to 80%)	BACTERIA (10% to 20%)	PROTOZOA (<10%)
Rotavirus	*Salmonella* species	*Cryptosporidium*
Norovirus and Sapovirus	*Shigella* species	*Giardia intestinalis*
Astrovirus	*Campylobacter jejuni*	*Entamoeba histolytica*
Adenovirus	*Yersinia enterocolitica*	
	Escherichia coli; ETEC,	
	Clostridium perfringens	
	Clostridium difficile	
	Staphylococcus aureus	
	Vibrio cholera	
	Vibrio parahaemolyticus	

ETEC, Enterotoxigenic *E. coli.*

BOX 172.2

Patient History

- Behavior: Weight loss, amount and frequency of feeding, level of thirst, level of alertness, level of activity, lethargy, irritability, quality of crying, presence or absence of tears with crying, frequency of wet diapers in infants or urination in children
- Orthostatic symptoms
- Diarrhea: Duration, frequency, and amount of stools; consistency and content of stool; watery, blood, mucus
- Vomiting: Duration, amount and quality of the vomitus, time since last vomited
- Abdominal pain: Location, quality, radiation, severity per parent and child
- Signs of infection: Fever, chills, myalgia, rash, rhinorrhea, sore throat, cough
- Symptoms in relationship to eating and drinking
- Similar symptoms in other household members or school
- Similar episodes in the past
- Food history
- Water exposure and recent camping
- Travel to endemic or epidemic areas
- Household pets
- Past medical history; chronic medical problems, recent hospitalizations; vaccine status
- Current/recent antibiotic

TABLE 172.2

Viruses Causing Diarrheal Illness: Characteristics and Associated Symptoms

	AGE	SEASON	LASTS	INCUBATION PERIOD	HOW SPREAD	LENGTH OF EXCRETION	ABDOMINAL PAIN	NAUSEA/ VOMITING	FEVER	DIARRHEA CHARACTERISTICS	DIAGNOSTIC TESTS
Rotavirus	<5 years old	Winter and spring	4 to 8 days	1 to 3 days	Fecal-oral or respiratory secretions	Up to 21 days	±	++	± Low grade	Watery; large volume	ELISA and latex agglutination most commonly used; PCR most sensitive
Norovirus	<5 years old	Anytime; colder months	2 to 3 days	12 to 48 hours	Fecal-oral; contaminated food and water	5 to 7 days after onset of symptoms; up to 3 weeks	++	++	±	Abrupt onset; watery	RT-PCR testing available
Astrovirus	<4 years old	Late winter; early spring	2 to 5 days	1 to 4 days	Fecal-oral	Few days after symptoms resolve	±	+	++	Watery; large volume	No commercial tests available in United States
Adenovirus	<4 years old	All year	5 to 12 days	3 to 10 days	Fecal-oral	Most contagious first few days; asym excretion for months	±	+	Low grade	Watery	Commercial test available

Key: ++, common; +, occurs; ±, variable.
ELISA, Enzyme-linked immunosorbent assay; *PCR,* polymerase chain reaction; *RT-PCR,* reverse transcription polymerase chain reaction.
Data from: World Gastroenterology Organization: World Gastroenterology Organisation global guidelines: acute diarrhea in adults and children: a global perspective. Available at: www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english; and Pickering LK, Baker CJ, Long SS, editors: Red Book: 2012 report of the Committee on Infectious Diseases, ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics.

rotavirus was available for a short time (1998 to 1999) until it was noted to be associated with increased risk of intussusception. This vaccine was subsequently withdrawn from the United States market. Two live rotavirus oral vaccines, RotaTeq (RV5) (Merck & Co., Inc.) licensed in 2006 and Rotarix (RV1) (GlaxoSmithKline Biologicals) licensed in 2008 are now approved for prevention of rotavirus gastroenteritis.[12] Millions of infants in the United States have received the rotavirus vaccine since 2006. Each year, the vaccine prevents up to 50,000 hospitalizations of infants and young children in the United States. Rotavirus illness has also decreased among older children and adults that are not vaccinated, likely a result of community ("herd") immunity.[5]

The current rotavirus vaccines were not associated with intussusception in large pre-licensure trials. However, a post-licensure study done by Vaccine Safety Datalink found a slight increase in rates of intussusception in children vaccinated with the RV1 vaccine but not with the RV5 vaccine.[13,14] The U.S. Food and Drug Administration (FDA) found up to 1.5 excess cases of intussusception per 100,000 vaccinated infants in the United States within 21 days following first dose of RotaTeq.[15] Other international studies have also found a slight increase in the risk of intussusception.[16] Although there may be a slight increased risk of intussusception following the oral vaccines, the Centers for Disease Control and Prevention (CDC) still recommends the rotavirus vaccine due to its benefits far outweighing the risks.

Human Caliciviruses (Norovirus and *Sapovirus*). Norovirus accounts for approximately 12% of severe gastroenteritis among children younger than 5 years old. As the number of rotavirus cases decreases, norovirus is becoming the most common cause of infectious diarrhea in children.[17] In the United States, norovirus accounts for more than 90% of community outbreaks (cruise ships, schools, and hospitals) and is responsible for more than 250,000 ED and clinic visits and 23,000 hospitalizations for children younger than 5 years old.[18-21] Norovirus AGE is associated with more frequent and prolonged vomiting, but less fever, than AGE caused by rotavirus.[22] Seizures are the most common central nervous system (CNS) complication, whereas encephalopathy is possible but rare.[23] Clinical manifestations for *Sapovirus* are similar to those of norovirus.[24]

Astrovirus accounts for approximately 5% to 9% of cases of infectious diarrhea in children. In healthy children, it is an illness of short duration, although asymptomatic shedding continues up to several weeks after symptom resolution.[25]

Adenovirus is well known for causing infections of the respiratory tract along with pharyngitis, otitis media, and pharyngoconjunctival fever. Enteric adenovirus serotypes cause gastroenteritis, accounting for 2% to 4% of cases of acute infectious diarrhea in children. Asymptomatic shedding of the virus for months is common.[26]

The mainstay for treatment of viral enteritis is supportive care with rehydration and electrolyte correction.

Bacteria

The common bacterial organisms causing acute diarrhea in American children along with their presentations and associated characteristics are listed in Table 172.3, and their treatment is listed in Table 172.4.

Nontyphoidal *Salmonella* accounts for more than 98% of the cases of *Salmonella* in the United States. Infection can result in an asymptomatic carrier state, AGE, bacteremia, invasive disease, or a disseminated abscess syndrome. *Salmonellae* invade the mucosa of the distal small intestine and the colon; they produce a cholera-like enterotoxin and a cytotoxin, which can cause significant diarrhea and fluid and electrolyte abnormalities similar to patients with documented cholera. Sustained or intermittent bacteremia can occur and should be suspected in any patient with prolonged fever (fever in nontyphoidal *Salmonella* usually lasts about 48 hours). Patients with *Salmonella* bacteremia are at increased risk for developing extraintestinal infections. (These are seen in up to 10% of patients with *Salmonella* bacteremia.) Extraintestinal sites of infection can result in endocarditis, vascular infections, cholecystitis, hepatic and splenic abscesses, urinary tract infections, pneumonia, meningitis, septic arthritis, and osteomyelitis.[20]

Although it is uncommon, *Salmonella* serotype *typhi* is only found in humans and can cause a bacteremic illness often referred to as *enteric* or *typhoid fever.* Although uncommon in the United States, *S. typhi* is endemic in many other countries. Typhoid fever may be acquired during international travel and appear as a nonspecific febrile illness in young children in whom sustained or intermittent bacteremia may occur. Constipation can be the presenting symptom and is often seen early in the course of the disease, but diarrhea can also occur.[20]

Treatment of nontyphoidal *Salmonella* infection is usually supportive. However, for children with *S. typhi* infection, antibiotics are recommended. Relapse of enteric fever occurs in up to 15% of patients and requires retreatment. Treatment failures have occurred in people treated with cephalosporins, aminoglycosides, and furazolidone despite in vitro testing indicating susceptibility.[20]

Among *Shigella* isolates reported in industrialized nations, including the United States, most isolates found were *Shigella sonnei* (86%). *Shigella flexneri, Shigella boydii,* and *Shigella dysenteriae,* in descending order, make up the remainder of isolates.[21] *S. sonnei* is the most common cause of dysentery in the United States. Extraintestinal symptoms and signs are relatively common in children with *Shigella* infection and may include hallucinations, confusion, and seizures. Reactive arthritis (Reiter's syndrome) can occur weeks after the infection. Rare complications of *Shigella* infection include bacteremia, HUS, toxic megacolon, pseudomembranous colitis, and encephalopathy (Ekiri syndrome). The risk of septicemia increases in neonates, malnourished children, and infection with *S. dysenteriae.* There is some evidence that treatment is effective in shortening duration of diarrhea and hastening eradication of organisms from feces.[21] Drug-resistant *Shigella* has been increasing since 2006. According to CDC surveillance data from 2011, resistance to traditional first-line drugs, ampicillin and trimethoprim-sulfamethoxazole, has become so high that physicians must rely on alternative drugs like ciprofloxacin and azithromycin.[27,28] The CDC is starting to see the emergence of resistance to ciprofloxacin and azithromycin (1.6% and 3%, respectively).[28]

Campylobacter species cause a significant proportion of diarrheal disease worldwide, with 2.4 million cases yearly in the United States. According to data from the CDC, there has been a 30% decline in the incidence of infection since 1996.[29] Of the five types, *C. jejuni* and *C. coli* are the most common.[29,30] In neonates and young infants, bloody diarrhea without fever can be the only manifestation of infection. Febrile seizures can occur in young children before any gastrointestinal symptoms are present. The clinical presentation may be similar to acute appendicitis or intussusception. Severe or prolonged disease can mimic inflammatory bowel disease. Bacteremia is uncommon but can occur in children, including neonates. Immunocompromised hosts can have prolonged, relapsing, or extraintestinal infections. Antibiotic treatment is recommended, but most children will recover without treatment.[30] *Yersinia enterocolitica* is a relatively uncommon cause of simple self-limited diarrhea and vomiting in the United States. According to the CDC, the mean annual incidence is 0.3 per 100,000 people. However, for children younger than 5 years old, the incidence is 1.9 per 100,000.[29] As many as 6% of older children and adults may present with an appendicitis-like illness with right lower quadrant tenderness, usually as a result of

Text continued on p. 2153

TABLE 172.3

Bacteria Causing Diarrheal Illness: Characteristics and Associated Symptoms

	WHO AFFECTED	INCUBATION (RANGE)	DURATION OF ILLNESS	HOW SPREAD	LENGTH OF EXCRETION	ABDOMINAL PAIN	NAUSEA/ VOMITING	FEVER	DIARRHEA CHARACTERISTICS	OTHER CHARACTERISTICS	DIAGNOSTIC TESTS
Salmonella species	<4 years old	12 to 36 hours (6 to 72 hours)	2 to 7 days	Foods from animals; contaminated water; infected reptiles, amphibians, rodents, and mammals	Up to 12 weeks in children <5 years old	++	+	++	Mild to severe; can have blood and/or mucus	Bacteremia can occur, focal infections in 10%	Stool culture
Salmonella typhi	Travelers	7 to 14 days (3 to 60 days)	Requires antibiotics	Contaminated food or water	Chronic carriers	++	+	++	Not main problem; mild diarrhea	Gradual onset; HA, malaise, anorexia; HSM, rose spots, dactylitis, ams	Blood, bone marrow, or bile culture
Shigella species	≤5 years old	1 to 7 days	48 to 72 hours	Fecal-oral, contaminated food/ water, objects	1 to 4 weeks with or without antibiotics	++	++	++	Mild to severe: watery to mucoid with or without blood	Can have systemic symptoms; neurological symptoms; tenesmus Fecal PMNs often positive	Stool culture; improved with fresh stool
Campylobacter	<4 years old	2 to 5 days	5 to 7 days; can relapse	Ingestion of contaminated foods; fecal-oral in the very young; greatest in acute phase	2 to 3 weeks without treatment 2 to 3 days with treatment	+ +	+	++	Watery to mucoid/ bloody	Malaise; can have febrile symptoms before GI symptoms Infants may have bloody diarrhea and no fever Can mimic acute inflammatory bowel disease	*C. jejuni* and *C. coli* from stool culture
Yersinia enterocolitica	Median age, 6 years old	4 to 6 days (1 to 14 days)	Variable; usually few days	Contaminated food or water; contact with animals, person to person is rare	Average 42 days	+	±	++	Often with blood and mucus	Pseudoappendicitis syndrome Fecal PMNs often positive Bacteremia; <1 year old, excessive iron storage, immunosuppressed	Stool culture; need to specify

Continued

TABLE 172.3

Bacteria Causing Diarrheal Illness: Characteristics and Associated Symptoms—cont'd

	WHO AFFECTED	INCUBATION (RANGE)	DURATION OF ILLNESS	HOW SPREAD	LENGTH OF EXCRETION	ABDOMINAL PAIN	NAUSEA/ VOMITING	FEVER	DIARRHEA CHARACTERISTICS	OTHER CHARACTERISTICS	DIAGNOSTIC TESTS
Clostridium difficile	>24 months	5 to 10 days after starting antibiotics	Variable	Fecal-oral or environment	Unknown	+	–	+ Low grade	Mild: watery diarrhea to pseudomembranous colitis; mucus in stool		EIA detection of toxins NAAT good sensitivity and specificity
Clostridium perfringens	Any age	8 to 12 hours (6 to 24 hours)	24 hours	Catered foods	As long as illness persists	++	–	–	Sudden onset; watery diarrhea	Common is healthy people's stool Treatment not necessary; short course	High spore count in stool Commercially available kits
Staphylococcus aureus	Any age	2 to 4 hours (30 minutes to 8 hours)	1 to 2 days	Contaminated food that remains at room temperature for hours	Short time	+	+	± Low grade	Watery	Violent onset of nausea/vomiting; can have mild hypothermia	Culture stool or vomitus EIA or PCR detect enterotoxin
Vibrio cholera	Traveled to endemic area	1 to 3 days (hours to 5 days)	3 to 7 days	Contaminated food and water (shellfish; raw vegetables)	Short time	±	±	±	Large amounts watery diarrhea; stool colorless with flecks of mucus	Dehydration, hypokalemia, metabolic acidosis and shock within 4 to 12 hours; coma, seizures, hypoglycemia	Stool culture; need to request
Vibrio parahaemolyticus	All ages	23 hours (5 to 92 hours)	2 to 5 days	Seawater; undercooked seafood	Not excreted	++	± ⅓	± Low grade	Acute onset Watery stools	Liver disease, low gastric acidity, immunosuppressed increased risk	Lab needs to be notified when test; can test stool, blood, or wounds
E. coli (STEC)	All ages	3 to 4 days (1 to 8 days)	Usually 7 days	Contaminated food or water with human or animal feces; person to person occurs		++	+	– <⅓	Bloody or nonbloody	Stool become bloody after 3 to 4 days; can cause HUS Shiga toxin produced	Stool culture; must request test for *E. coli* O157 EIA for Shiga toxin if available

E. coli (EPEC)	<2 years old; RLAs and travelers	10 hours to 6 days	Usually few days but variable	Contaminated food or water with human or animal feces	–	–		Watery, usually mild	Can become chronic and cause growth retardation No toxin produced	Not widely available
E. coli (ETEC)	Infants in RLAs and travelers of all ages	10 hours to 6 days	1 to 5 days	Contaminated food or water with human or animal feces; person to person occurs	+	–	±	Watery	Uncommon in the United States Enterotoxin produced	Not widely available
E. coli (EIEC)	All ages	10 hours to 6 days	Variable	Contaminated food or water with human or animal feces	±	–	+	Usually watery without blood or mucus; dysentery can occur	Related to *Shigella* can cause similar dysenteric illness	Not widely available
E. coli (EAEC)	All ages	10 hours to 6 days	Variable	Contaminated food or water with human or animal feces	±	–	±	Watery, occasionally bloody	Enterotoxin and cytotoxin Associated with prolonged diarrhea; becoming more common in United States	Not widely available

Key: ++, common; +, occurs; ±, variable; –, not common.
EAEC, Enteroaggregative *Escherichia coli; EIA,* enzyme immunoassay; *EIEC,* enteroinvasive *E. coli; EPEC,* enteropathogenic *E. coli; ETEC,* enterotoxigenic *E. coli; HA,* headache; *HUS,* hemolytic-uremic syndrome; *GI,* gastrointestinal; *NAAT,* nucleic acid amplification test; *PCR,* polymerase chain reaction; *PMN,* polymorphonucleocyte; *RLA,* resource limited area; *STEC,* Shiga toxin–producing *E. coli.*
Data from: World Gastroenterology Organization: World Gastroenterology Organisation global guidelines: acute diarrhea in adults and children: a global perspective. Available at: www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english; and Pickering LK, Baker CJ, Long SS, editors: Red Book: 2012 report of the Committee on Infectious Diseases, ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics.

TABLE 172.4

Treatment Recommendations for Common Bacteria Causing Acute Infectious Diarrhea in Children

	ROUTINE TREATMENT	TREATMENT INDICATED—HIGH RISK GROUPS	ANTIBIOTIC	COMMENTS
Salmonella non-typhi	No; treatment prolongs excretion; does not shorten disease	Infants <3 months old, prolonged illness, chronic GI disease, neoplasms, hemoglobinopathies, HIV, immunosuppression, localized invasive disease (osteomyelitis, abscess, meningitis) or bacteremia	**Susceptibility is known** Oral: Amoxicillin 25–50 mg/kg divided every 8 hours IV: Ampicillin 200 mg/kg divided every 6 hours Oral: TMP-SMX 10 mg/kg divided every 12 hours **Susceptibility not known or areas of high resistance or invasive disease or bacteremia** IV or IM: Ceftriaxone 100 mg/kg every day or divided every 12 hours or Oral or IV: Azithromycin 10–20 mg/kg or Oral: *Ciprofloxacin 500 mg/kg divided every 12 hours Ciprofloxin: 20 mg/kg divided every 12 hours IV: Cefotaxime 150 to 200 mg/kg divided every 4 to 6 hours (maximum 12 g/day)	Bacteremia: Treat for 10 to 14 days Localized invasive disease: Treat for 4 weeks (6 weeks if meningitis) and begin with IV medications Aminoglycosides not recommended for invasive disease Drug of choice, route of administration, and duration of therapy based on susceptibility of organisms, site of infection, host and clinical response
Salmonella typhi	Yes	All patients with enteric fever Delirium, stupor, coma, or shock	**Start with IV medications; change to oral when susceptibility is known** Ceftriaxone 100 mg/kg every day or divided every 12 hours or Cefotaxime 200 mg/kg divided every 4 to 6 hours (maximum 12 g/day) or *Ciprofloxacin 20 mg/kg divided every 12 hours	Multidrug resistance is common 10- to 14-day treatment Check susceptibilities Azithromycin for uncomplicated disease Consider: Dexamethasone IV 3 mg/kg, followed by 1 mg/kg every 6 hours for 48 hours
Shigella species	No; usually self-limited but treatment decreases diarrhea and eradicates organism from stool	Severe disease, bacteremia, dysentery, immunosuppression Less ill and able to tolerate PO	IV: Ceftriaxone 50–100 mg/kg for 5 days or *Ciprofloxacin (>17 years old or ceftriaxone contraindicated) 20 mg/kg divided every 12 hours or Azithromycin 10 mg/kg for 3 days Oral: Azithromycin 12 mg/kg for first day, then 6 mg/kg for days 2 to 5 or *Ciprofloxacin 20 mg/kg divided every 12 hours for 5 days	Oral route preferred when possible and disease is not serious TMP-SMX and ampicillin only if isolated strain is susceptible because of high resistance Amoxicillin less effective because of rapid absorption from GI tract
Campylobacter jejuni	Yes	Usually recommended for all infections; most children will resolve on own	Oral: Azithromycin 10 mg/kg for 3 days or Erythromycin 40 mg/kg divided every 6 hours for 5 days	Shorten duration of illness and excretion of organisms and prevent relapse if given early Resistance to fluoroquinolones is frequent
Yersinia enterocolitica	No	Septicemia or extra intestinal sites of infection; immunocompromised host	Oral: TMX-SMX 10 mg/kg divided every 12 hours or Oral or IV *Fluoroquinolone: Ciprofloxacin 20 mg/kg divided every 12 hours or IV: Ceftriaxone 50 to 100 mg/kg divided every day or every 12 hours or Cefotaxime 150 to 200 mg/kg divided every 4 to 6 hours (maximum 12 g)	Usually resistant to penicillin and first generation cephalosporins Antibiotics do decrease the duration of fecal excretion but do not decrease length of diarrhea Extraintestinal disease treat for 4 weeks
C. difficile	Yes	Symptomatic patients Severe disease, underlying intestinal tract disease, and those who don't respond to oral metronidazole use vancomycin	**Stop antimicrobial therapy** Oral or IV: Metronidazole 30 mg/kg divided every 6 hours for at least 10 days (maximum dose 2 g/day) or Oral: Vancomycin 40 mg/kg divided every 6 hours for at least 10 days (maximum dose 2 g/day)	25% relapse after treatment; infection usually responds to second course IV vancomycin is not effective Do not give antimotility agents

TABLE 172.4

Treatment Recommendations for Common Bacteria Causing Acute Infectious Diarrhea in Children—cont'd

	ROUTINE TREATMENT	TREATMENT INDICATED—HIGH RISK GROUPS	ANTIBIOTIC	COMMENTS
Vibrio cholera	No	Patients with moderate to severe disease	Oral: Doxycycline 4–6 mg/kg or Azithromycin 20 mg/kg single dose or Tetracycline 25 to 50 mg/kg divided every 6 hours (maximum dose 3 g) for 3 days	Susceptibility testing recommended Treatment decreases duration of diarrhea and eradicates bacteria from stool
V parahaemolytica	No	Severe diarrhea, septicaemiae Patients <8 years old	Third-generation cephalosporin and doxycycline* (patients ≥8 years old) TMX-SMX and aminoglycoside	
E. coli	No for STEC infection	Severe watery diarrhea in a traveler to RLA	Azithromycin or fluoroquinolone*	Treating patients with STEC may increase risk for HUS

*Fluorquinolone: Tetracycline is not recommended in children younger than 8 years old because of teeth staining, but the benefit of using the drug may outweigh the risk of teeth staining. Each case is considered separately. Ciprofloxin recommended for greater or equal to 17 years unless benefits outweigh the risks.

GI, Gastrointestinal; *HIV,* human immunodeficiency virus; *HUS,* hemolytic-uremic syndrome; *IM,* intramuscular; *IV,* intravenous; *PO, per os* (by mouth); *RLA,* resource limited area; *STEC,* Shiga toxin–producing *E. coli, TMP-SMX,* trimethoprim-sulfamethoxazole.

Data from Pickering LK, Baker CJ, Long SS, editors: Red Book: 2012 report of the Committee on Infectious Diseases, ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics; and Engorn B, Flerlage J, editors: The Harriet Lane handbook: a manual for pediatric house officers, ed 20, Philadelphia, 2015, Saunders.

reactive mesenteric adenitis.[31] Antibiotics are indicated for the immunocompromised patient with enterocolitis and in cases of septicemia or extraintestinal infections. Isolates are often resistant to first-generation cephalosporins and most penicillins.[31]

Thought to be brought on by the change in the gut flora from antibiotics, *C. difficile* infections among hospitalized children have been increasing since 1997.[32] However, there are an increasing number of cases in children who have not been hospitalized or received antibiotics. *C. difficile* infections cause a spectrum of illnesses ranging from asymptomatic to watery diarrhea to pseudomembranous colitis.[33] Clinical illness is rare before 12 to 24 months old. Asymptomatic infants can be colonized with *C. difficile*; carriage rates average 37% to 50% for neonates, 30% for infants 1 to 6 months old, 14% for infants 6 to 12 months old, and by age 3 years old the rate of colonization is similar to that of nonhospitalized adults (<3%).[33,34] Thus, the presence of *C. difficile* toxin cannot be assumed to be a causative agent in young children. *C. difficile* should be considered in children 1 to 3 years old, but only after other causes of diarrhea (particularly viral) are excluded.[35] Endoscopic findings of pseudomembrane and friable rectal mucosa are sufficient to diagnose *C. difficile* at any age. This is helpful when trying to determine if a child younger than 3 years old is colonized or has disease. The endoscopic findings are diagnostic of disease. Complications include toxic megacolon and intestinal perforation. Severe or fatal disease is more common in neutropenic patients with leukemia, infants with Hirschsprung's disease, and patients with inflammatory bowel disease.[33,35]

See Tables 172.3 and 172.4 for presentation and associated characteristics and treatment recommendations for *Clostridium perfringens, Staphylococcus aureus, V. cholera,* and *Vibrio parahaemolyticus.*[36-38]

E. coli, part of the normal flora in the lower gastrointestinal tract, includes five species types recognized to cause acute diarrheal disease.[39] The enterohemorrhagic *E. coli* (EHEC) strain is also known as Shiga toxin–producing *E. coli* (STEC); *E. coli* O157:H7 is the prototype and most virulent of the EHEC. Outbreaks have been linked to ground beef, petting zoos, contaminated apple cider, raw fruits and vegetables, and ingestion of water in recreational areas. The infectious dose is low, and person-to-person transmission can occur.[39] There are an estimated 265,000 cases of STEC infections per year; 36% are caused by *E. coli* O157.[40] HUS, the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency, is a serious complication of EHEC infection and occurs in up to 15% of children with *E. coli* O157:H7.[39] The overall incidence of HUS caused by a diarrheal pathogen (usually STEC) is estimated to be 2.1 cases per 100,000 persons per year, with a peak incidence in children younger than 5 years old (6.1 cases per 100,000 per year). HUS typically develops as diarrhea that is resolving, usually 7 days but up to 3 weeks after the onset of the illness.[39] Patients often present with pallor, weakness, irritability, and oliguria or anuria. Patients with HUS can develop neurologic complications, such as seizures, coma, and cerebral vessel thrombosis. Approximately 50% of patients who have HUS will require dialysis, and 3% to 5% die. Patients with white blood cell counts greater than 20,000, hematocrit less than 23%, and oliguria are at increased risk for poor outcome. A serious risk posed by hemorrhagic colitis is the rapid loss of fluids, which can cause electrolyte abnormalities and result in poor perfusion, leading to end-organ damage. Patients should receive adequate amounts of intravenous (IV) fluids (or by mouth if able to take in enough) to restore intravascular volume (monitor urine output, capillary refill time, blood pressure, pulse, and mental status), and electrolyte abnormalities should be corrected. Fluids should be continued and ongoing losses replaced. Consideration of admission to the hospital with fluid resuscitation, ongoing monitoring of electrolytes, complete blood cell count, blood urea nitrogen (BUN), and creatinine are imperative.

Controversy exists about the indications for antibiotic treatment of *E. coli* diarrhea. Early data indicated that antimicrobials offer no substantial benefit and may increase the risk for development of HUS. In addition, in vitro studies have shown that sub-inhibitory antibiotic concentrations can increase toxin production.[41] Most recently, in 2012, a study showed an increased risk of developing HUS if a child with STEC is treated with antibiotics (36% versus 12%, P = 0.001). This risk was seen across all antibiotic classes.[42] Therefore, we recommend that empirical antibiotics should not be administered because of the potential risk of HUS—except in cases when a child is extremely ill or in septic shock.

Protozoa

Protozoa can also cause diarrhea in children but are responsible for less than 1% of all cases of acute infectious diarrhea in the United States (Tables 172.5 and 172.6). The most common

TABLE 172.5

Protozoa: Presentation and Associated Characteristics

	WHO AFFECTED	INCUBATION	HOW SPREAD	LENGTH OF EXCRETION	ABDOMINAL PAIN	NAUSA/ VOMITING	FEVER	DIARRHEA CHARACTERISTICS	OTHER CHARACTERISTICS	DIAGNOSTIC TESTS
Cryptosporidium hominis	All ages	3 to 14 days	Contaminated water; fecal-oral	Immunocompetent: up to 2 weeks Immunosuppressed: Months	±	+	±	Frequent, nonbloody, diarrhea	Fatigue, anorexia and weight loss	DFA for detection of oocysts in stool
Giardia intestinalis	1 to 9 years old	1 to 3 weeks	Fecal-oral, contaminated water or food	Weeks to months	++	+	–	Acute watery diarrhea; foul smelling, flatulence	Can be protracted, abdominal distention, anorexia; FTT, anemia	EIA and DFA tests available; EIA with high sensitivity and specificity
Entamoeba histolytica	Immigrants or visitors to endemic areas	2 to 4 weeks (few days to months)	Fecal-oral; contaminated food or water; sexual transmission	Can excrete for years if untreated	+	±	< ½	Colitis to dysentery	Gradual onset of symptoms over 1 to 3 weeks; tenesmus; weigh loss is common	Trophozoites or cysts in stool; serial specimens often necessary; EIA commercially available

Key: ++, common; +, occurs; ±, variable; –, not common.
DFA, Direct fluorescent antibody; *EIA,* enzyme immunoassay; *FTT,* failure to thrive.
Data from: World Gastroenterology Organization: World Gastroenterology Organisation global guidelines: acute diarrhea in adults and children: a global perspective. Available at: www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english; and Pickering LK, Baker CJ, Long SS, editors: Red Book: 2012 report of the Committee on Infectious Diseases, ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics.

TABLE 172.6

Treatment Recommendations for Common Protozoa Causing Infectious Diarrhea in Children

	TREATMENT ROUTINELY RECOMMENDED	WHEN TREATMENT INDICATED—HIGH RISK GROUPS	ANTIBIOTIC INDICATED	COMMENTS
Cryptosporidium	No	If treat: Children >1 year old	Nitazoxanide for children 1 to 3 years old: 100 mg divided every 12 hours for 3 days 4 to 11 years old: 200 mg divided every 12 hours for 3 days 12 years old and older: 500 mg every 12 hours for 3 days	
		HIV-positive and >12 years old	Nitazoxanide: Oral, two times per day; 14 days	
Giardia intestinalis	Yes	Most require treatment	Oral: Metronidazole 15 mg/kg/day divided every 8 hours for 5 to 10 days (maximum 250 mg every 8 hours)	Symptom recurrence attributed to reinfection, lactose intolerance, immunosuppression, insufficient treatment or drug resistance
		Children >1 year old	Nitazoxanide: oral use same doses as for Cryptosporidium	Second course with same drug should be effective
		Children ≥3 years old	Tinidazole 50 mg/kg single dose (maximum 2 g/dose)	
Entamoeba histolytica	Yes	Asymptomatic excreters	Oral: Drug of choice: Iodoquinol 30 to 40 mg/kg/day divided every 8 hours for 7 days (maximum 2 g) or Paromomycin 25 to 35 mg/kg/day divided every 8 hours for 7 days	Do not give antimotility agents or corticosteroids Iodoquinol and paromomycin should be taken with meals
		Mild to severe intestinal or extraintestinal disease	Drug of choice: Metronidazole 35 to 50 mg/kg/day divided every 8 hours for 7 to 10 days (max dose 750 mg/dose) or Tinidazole (>3 years old) 50 mg/kg/day for 3 days or 5 days for severe disease followed by Iodoquinol 30 to 40 mg/kg/day divided every 8 hours for 20 days (maximum 2 g) or Paromomycin (same dose as above)	

Data from Pickering LK, Baker CJ, Long SS, editors: Red Book: 2012 report of the Committee on Infectious Diseases, ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics; and Engorn B, Flerlage J, editors: The Harriet Lane handbook: a manual for pediatric house officers, ed 20, Philadelphia, 2015, Saunders.

protozoa causing diarrhea are *Cryptosporidium, Giardia intestinalis,* and *Entamoeba histolytica*.

Cryptosporidium hominis is the most common of the *Cryptosporidium* species to infect humans. In the immunocompromised patient, chronic, severe diarrhea can develop and result in malnutrition, dehydration, and death. Because shedding can be intermittent, at least three stool specimens collected on separate days should be examined before considering test results to be negative. Treatment is usually supportive. However, the FDA has approved a 3-day course of nitazoxanide oral suspension for the treatment of immunocompetent children older than 1 year old.[43]

Infection with *Giardia intestinalis* is limited to the small intestine and biliary tract. Asymptomatic infection is common. Humans are the main reservoir, although it has been found in the stool of dogs, cats, beavers, and other animals.[44] These animals can contaminate water with stool containing cysts that are infectious for humans. Epidemics from person-to-person transmission occur in childcare centers and in institutions for people with developmental delay. Treatment includes correction of dehydration and electrolyte abnormalities and antibiotics. If therapy fails, a course can be repeated with the same drug. Relapse is common in the immunocompromised host, who often requires prolonged treatment. Patients with hypogammaglobulinemia or lymphoproliferative disease are at higher risk of giardiasis, and they are more difficult to treat. Patients with acquired immunodeficiency syndrome (AIDS) often respond to standard therapy. Treatment of asymptomatic carriers is not recommended except in households of patients with hypogammaglobulinemia or cystic fibrosis.[43,44]

E. histolytica can be found worldwide but is more prevalent in the lower socioeconomic population and in developing countries, where the prevalence of amebic infection may be as high as 50% in some communities. Symptoms can become chronic and may mimic inflammatory bowel disease. Complications include fulminant colitis, toxic megacolon, and ulceration of the colon and perianal area, rarely with perforation. Complications are more common in patients treated inappropriately with corticosteroids or antimotility drugs. Ultrasonography, computed tomography, and magnetic resonance imaging can identify liver abscesses and other extraintestinal sites of infection. Follow-up stool examination is recommended after completion of therapy, because complete eradication of intestinal infection is difficult. Asymptomatic household members with stools positive for *E. histolytica* should also be treated.[45]

See Tables 172.2, 172.3 and 172.5 for common signs and symptoms of the different viruses, bacteria, and protozoa discussed.

Complications

The complications of acute diarrheal illness are reflected primarily in abnormalities of fluid, electrolytes, and acid-base status and in systemic involvement (bacteremia, osteomyelitis, polyarthritis,

and HUS). Hypoglycemia and metabolic acidosis are common in younger children, yet manifested with nonspecific signs and symptoms, such as tachypnea and decreased activity. With severe illness or illness superimposed on underlying chronic conditions, children may arrive at the ED in extremis. Children may present with weakness, lethargy, respiratory distress, shock, anuria, cardiac dysrhythmia, seizure, or coma. It is vital to recognize early signs of shock (such as, persistent tachycardia, hyperpnea, irritability, and lethargy) and to restore intravascular volume before decompensation.

Diagnostic Strategies

Acute diarrhea in children usually results in self-limited mild disease; it can, however, cause significant fluid and electrolyte abnormalities with serious consequences. Indications for medical evaluation of children with diarrhea have been proposed (Box 172.3). The principal goals of the ED evaluation are to identify and to correct fluid, electrolyte, acid-base, and nutrient deficits that may result from vomiting, diarrhea, or decreased oral intake and to determine which children would benefit from prolonged management.

Children who present with mild to moderate disease often require no diagnostic testing and can often rehydrate orally. Children assessed to have moderate to severe dehydration from acute diarrhea with or without vomiting requiring IV fluids should have baseline serum electrolyte levels, bicarbonate, urea/creatine, and glucose concentration assessed. Studies evaluating the use of laboratory tests to estimate hydration status have found testing helpful only when results are markedly abnormal, with no single test definitive for dehydration. Children who are critically ill or hemodynamically unstable should have a fingerstick blood glucose and serum electrolytes measured.

Testing for fecal leukocytes may be useful to support a diagnosis of invasive disease and should be considered in children with diarrhea who are febrile or have mucus or blood in their stool. Many children with acute diarrhea caused by *Salmonella* or *Shigella* organisms will have fecal leukocytes in the stool. Fecal leukocytes are also found in patients with *Campylobacter* organisms, *Y. enterocolitica*, invasive *E. coli*, and *V. parahaemolyticus*. Although a negative test does not rule out invasive disease, a positive test (more than five fecal leukocytes per high power field) increases the likelihood of an invasive pathogen and should be followed with a stool culture.

Stool culture is not indicated in most cases of uncomplicated AGE. Stool cultures should be obtained when needed to guide specific therapy, hospitalization, or infection control measures. Stool cultures should also be considered in patients with systemic involvement or underlying chronic medical conditions, if the illness involves dysenteric features, or if it lasts longer than 2 weeks. Many hospital laboratories do not include testing for *E. coli* O157:H7 or *Y. enterocolitica* in their routine stool culture; thus the emergency clinician must order these tests separately. According to the CDC, all stools submitted for testing for *Salmonella, Shigella,* and *Campylobacter* (routine stool culture) should be cultured for *E. coli* O157:H7. These stools should also be simultaneously assayed for non-O157 STEC with tests that detects the Shiga toxins or the genes encoding these toxins.[46] In immunosuppressed patients, patients with chronic disease, infants younger than 3 months, or children with possible bacteremia or localized invasive disease, a complete blood count, stool studies, blood and urine cultures, chest x-ray, and lumbar puncture should be considered.

For patients with more than 2 weeks of watery diarrhea, consider sending stool for enzyme-linked immunoassay for rotavirus and ova and parasites in those with a history of travel to an endemic area.

Consideration of Differential Diagnoses

Most children with diarrhea or vomiting have a relatively benign cause of their illness. However, other, more sinister diagnoses should be considered and ruled out. A few disorders causing diarrhea may be life-threatening in children: intussusception, HUS, pseudomembranous colitis, appendicitis, toxic megacolon, and in very young infants, the congenital secretory diarrheas. See Tables 172.7 and 172.8 for other conditions that may cause vomiting and diarrhea.

Management

The American Academy of Pediatrics (AAP), The European Society of Pediatric Gastroenterology and Nutrition, and the WHO all recommend oral rehydration solution as the treatment of choice for children with mild to moderate dehydration (see the Dehydration section). In addition to fluid resuscitation, the

BOX 172.3

Indications for Medical Evaluation of Children With Acute Diarrhea

- Young age (eg, <6 months old or weight <8 kg)
- History of premature birth, chronic medical conditions, or concurrent illness
- Fever to ≥38° C for infants <3 months or ≥39° C for children 3 to 36 months old
- Visible blood or mucus in stool
- High output, including frequent and substantial volumes of diarrhea
- Persistent vomiting
- Caregiver's report of signs consistent with dehydration (eg, sunken eyes or decreased tears, dry mucous membranes, or decreased urine output)
- Change in mental status (eg, irritability, apathy, or lethargy)
- Suboptimal response to oral rehydration therapy (ORT) already administered or inability of the caregiver to administer ORT

Modified from King CK, et al: Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 52:1, 2003.

TABLE 172.7

Common Causes of Vomiting in Children

ETIOLOGIC CATEGORY	CLINICAL SYNDROMES
Central nervous system (CNS)	Infections, space-occupying lesion
Gastrointestinal	Obstruction, peritonitis, hepatitis, liver failure, appendicitis, pyloric stenosis, midgut volvulus, intussusception, inborn errors of metabolism
Drug	Ingestion, overdose, drug effect
Endocrine	Addisonian crisis, diabetic ketoacidosis, congenital adrenal hyperplasia
Renal	Urinary tract infection, pyelonephritis, renal failure, renal tubular acidosis
Cardiac	Congestive heart failure of any cause
Infection	Pneumonia, acute otitis media, sinusitis, sepsis
Other	Psychogenic, respiratory insufficiency

TABLE 172.8

Common Causes of Diarrhea in Children

ETIOLOGIC CATEGORY	CLINICAL SYNDROMES
Gastrointestinal	Malabsorption (eg, milk intolerance, excessive fruit juice), inflammatory bowel disease, irritable bowel syndrome, short gut syndrome
Drug	Ingestion, overdose, drug effect
Endocrine	Thyrotoxicosis, addisonian crisis, diabetic enteropathy, congenital adrenal hyperplasia
Renal	Urinary tract infection, pyelonephritis
Infection	Pneumonia, acute otitis media, sinusitis, sepsis
Other emergencies	Intussusception, appendicitis, hemolytic uremic syndrome (HUS), pseudomembranous colitis, toxic megacolon, and in very young infants, the congenital secretory diarrheas
Other	Parental anxiety, chronic nonspecific diarrhea

priorities in ED management of children with diarrhea are to consider and rule out potential causes of diarrhea other than infectious diarrhea; to assess for and treat underlying fluid and electrolyte deficits and potential complications; to determine which patients require prolonged treatment or hospitalization; and, when necessary, to arrive at a microbiologic diagnosis. Tables 172.4 and 172.6 list the common infectious agents of diarrhea and their recommended treatment.

Antibiotics are not needed in viral gastroenteritis or in most cases of uncomplicated bacterial gastroenteritis. Antibiotics are routinely recommended *for Campylobacter, C. difficile, Giardia intestinalis,* and *E. histolytica* and can be considered in *Cryptosporidium*. Premature babies (younger than 1 year old), neonates, young infants, and patients with immunosuppression, chronic diseases, and articular or valve prostheses are at increased risk for developing complications (bacteremia, sepsis, invasive disease, extraintestinal disease) from pathogens causing acute diarrhea. Antibiotics should be considered in these populations based on severity of presentation and in consultation with appropriate specialists (eg, pediatric oncologist or cardiologist). Children with bloody diarrhea are at higher risk for complications, including sepsis and other systemic diseases; and should therefore be considered for admission to the hospital for close observation. In the majority of cases, empirical antimicrobial agents should not be administered while awaiting culture results. Antimicrobial therapy may not be indicated, even when culture results are positive, and antibiotics may increase the risk for developing HUS if the offending agent is STEC. For severe watery diarrhea in a traveler to a developing country, azithromycin or a fluoroquinolone may be considered.[39]

Antidiarrheal compounds that impair gastrointestinal motility, such as loperamide (Imodium), diphenoxylate, and atropine (Lomotil), can prolong and exacerbate disease, and thus have no role in the treatment of acute infectious diarrhea in young children. The agents may also cause lethargy, paralytic ileus, toxic megacolon, CNS depression, coma, and even death.[47]

Probiotics have been studied extensively over the past several years for the treatment of acute infectious diarrhea. In large clinical trials, *Lactobacillus reuteri, Lactobacillus rhamnosus,* and *Saccharomyces boulardii* reduced mean duration and frequency of watery diarrhea and number of watery stools per day, and improved stool consistency.[48] A recent randomized double blind study, which was carried out in three Italian pediatric centers, showed that *L. reuteri,* taken together with a standard oral rehydration solution, significantly reduced the duration of watery diarrhea compared with placebo (2.1 ± 1.7 days versus 3.3 ± 2.1 days, P <0.03).[49] On days 2 and 3 of treatment, watery diarrhea persisted in 82% and 74% of the placebo and 55% and 45% of the *L. reuteri* recipients. Studies have also reported that *L. rhamnosus* is the most effective at doses greater than 10^{10} colony-forming units.[48] Probiotics also seem to be more effective when given early in the course of diarrhea and are most helpful for otherwise healthy infants and young children with watery diarrhea secondary to viral gastroenteritis but not invasive bacterial infections.[50,51] The European Society of Gastroenterology, Hepatology, and Nutrition, the National Institute for Health and Clinical Excellence, and the AAP all agree that when used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration of and reducing stool frequency in acute infectious diarrhea. More research is needed to determine appropriate doses for different strains of probiotics.[51-53]

Zinc deficiency is common in developing countries and occurs in most parts of Latin America, Africa, the Middle East, and south Asia. During the past 10 to 15 years, studies have shown that zinc supplementation given to children living in developing countries has decreased the duration and severity of diarrhea illness.[54] A recent Cochrane review looked at 24 published studies and found zinc supplementation may be effective in reducing the duration of diarrhea in children older than 6 months in areas where zinc deficiency and moderate malnutrition is prevalent.[55] The WHO recommends zinc supplementation (10 to 20 mg/day for 10 to 14 days) for all children younger than 5 years old with AGE, although few data exist to support this recommendation for children in developed countries.[56]

Disposition

Most cases of childhood diarrhea can be managed on an outpatient basis by continuing breast-feeding, routine formula, or diet specific for age. Supplemental maintenance electrolyte solutions may be given or recommended to purchase over the counter. Before discharge from the ED, careful and specific instruction about the signs and symptoms of expected improvement or complications should be given to the parents or caregiver. Instructions should address proper hygiene and handwashing techniques to prevent others from contracting the illness. Follow-up by the patient's primary care physician should be timely and address concerns of worsening of the condition and potential complications. Hospitalization should be considered in children at high risk for complications: infants, especially those younger than 3 months old, very-low-birth-weight infants, and children with chronic medical problems, children with electrolyte abnormalities who require IV repletion, children with severe dehydration, and children with dysentery. Hospitalization may also be warranted in cases of protracted vomiting, diarrhea with losses in excess of fluid administration, worsening clinical status despite therapy, presence of an underlying condition that would complicate therapy, or suspected systemic involvement. Very-low-birth-weight infants, because of low physiologic reserve and immature immune system, are at the highest risk for complications of AGE in the first year of life.

DEHYDRATION

Perspective

Dehydration, defined as a decrease in total body water, is a common complication seen in the ED. In severe cases, early detection and rehydration are vital to prevent progression to tissue

hypoperfusion and end-organ damage. Oral rehydration for mild to moderately dehydrated children has been identified as one of the American College of Emergency Physicians' Choosing Wisely Campaign's top five ways to improve the value of emergency medicine encounters. Dehydration (loss of free water) can be distinguished from volume depletion (decrease in effective circulatory volume), but because most relevant research does not make this distinction, the terms are often used interchangeably. Broadly speaking, dehydration occurs by three general mechanisms: (1) decreased intake (eg, stomatitis), (2) increased output (eg, diarrhea and diabetes), and (3) increased insensible losses (eg, fever). Most commonly, dehydration in children is due to volume losses from AGE, but many principles discussed here apply to other disease processes leading to dehydration.

Principles of Disease

Anatomy and Physiology

The average adult male and female bodies are comprised of approximately 60% and 50% water, respectively. Total body water is divided between the extracellular ($\frac{1}{3}$) and intracellular compartments ($\frac{2}{3}$). The extracellular compartment is further divided into interstitial fluid ($\frac{3}{4}$) and plasma ($\frac{1}{4}$). Interstitial fluid serves as a reservoir to replenish intravascular plasma volume in hypovolemia. Water makes up over 70% of an infant's total body weight; the majority of this "extra" fluid resides in the extracellular compartment. Because infants excrete far more water than adults per body weight (100 mL/kg versus 40 mL/kg daily), they require far more water per body weight to maintain homeostasis. As a result, infants and children are more vulnerable to rapid volume depletion from decreased water intake or increased output.

Pathophysiology

Isonatremic volume depletion (130 to 150 mEq/L) is the most common form of volume depletion and results from relatively equal losses of sodium and water from the extracellular space and therefore intravascular volume. There is no change in body fluid tonicity or redistribution of fluid between the extracellular and intracellular fluid spaces. Gastrointestinal fluid loss, with or without decreased intake or increased urine loss, is the most common cause. *Hyponatremic* volume depletion (<130 mEq/L) results from sodium loss in relative excess of free water loss. Free water then moves intracellularly from the extracellular space to maintain osmolarity, leading to a decrease in intravascular volume and potential hemodynamic compromise. This type of volume depletion is often caused by gastrointestinal fluid loss replaced by free water, although other etiologies, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), should be considered. Infants and children with hyponatremic volume depletion are often more ill-appearing than fluid losses would indicate. *Hypernatremic* volume depletion (>150 mEq/L) arises from the loss of relatively more free water than sodium and is observed less commonly than hyponatremic or isonatremic dehydration. This can occur if a child with diarrhea is given hypertonic fluid (eg, soup, improperly mixed formula, water with baking soda) to replace fluid losses, or if the illness is complicated by excessive insensible losses from fever of hyperventilation. Intracellular free water shifts to the extracellular compartment to maintain osmolarity, resulting in relatively preserved intravascular volume, and often underestimation of volume depletion. Hypernatremic dehydration is usually associated with at least a 10% free water deficit. Both hyponatremic and hypernatremic dehydration can lead to severe CNS effects: cerebral edema in the case of hyponatremic dehydration due to free water movement into neurons, and cerebral shrinkage in the case of hypernatremic dehydration due to free water movement out of neurons. Similarly, rapid correction of either condition can cause dangerous fluid shifts across the blood-brain barrier and should be avoided.

Metabolic acidosis often accompanies pediatric dehydration due to AGE through several mechanisms: bicarbonate loss in the stool, starvation causing ketone production, decreased tissue perfusion leading to anaerobic metabolism and lactic acid production, and decreased hydrogen ion excretion from poor renal perfusion. For the majority of patients, the acidosis is easily reversed by oral or parenteral volume replacement.

Clinical Features

The severity of dehydration is usually measured as the acute weight (presumably fluid) loss as a percentage of pre-illness total body weight. Dehydration of 3% to 5% or more is considered significant and can often be identified by history and physical examination (Table 172.9). Because pre-illness weights are generally not available or reliably reported, the clinician should rely on historical information and physical examination findings to assess the severity of dehydration. Parental reports of decreased oral intake, urine output, and tear production are of significant value, with good sensitivity in detecting dehydration. In a child who is dehydrated, initial physical examination may reveal an activity level lower than expected for age. The child may also appear weak or lethargic. If the fontanel is still open, it may be sunken. The eyes may appear sunken and the mucous membranes dry. However, if the child has recently had something to drink, the mucous membranes may falsely appear moist. Tachycardia and hyperpnea may be present. The skin over the trunk should be examined for tenting (Fig. 172.1) (suggesting hyponatremia) or a doughy texture (suggesting hypernatremia). The three most useful signs to determine dehydration of more than 5% are prolonged capillary refill time, abnormal skin turgor, and abnormal respiratory pattern. However, clinical signs and symptoms of dehydration are variable and often subtle, and determining the severity of dehydration is an ongoing challenge for emergency clinicians. Because individual signs are often inadequate for accurately diagnosing dehydration and estimating severity, most recent research has

TABLE 172.9

Clinical Assessment of Degree of Dehydration

	MILD (3% to 5%) (30 to 50 ml/kg)	MODERATE (5% to 10%) (60 to 100 ml/kg)	SEVERE (>10%) (90 to 150 ml/kg)
SIGNS AND SYMPTOMS			
Dry mucous membrane	±	+	+
Reduced skin turgor (pinch retraction)	–	±	+
Depressed anterior fontanel	–	+	+
Mental status	Alert	Irritable	Lethargic
Sunken eyeballs	–	+	+
Hyperpnea	–	±	+
Hypotension (orthostatic)	–	±	+
Increased pulse	–	+	+
Capillary refill	<2 seconds	>2 seconds	>2 seconds

+, Present; –, absent; ±, variable.
Adapted from Barkin RM, Rosen P: Emergency pediatrics, ed 5, St Louis, 1999, Mosby.

focused on noninvasive methods of dehydration assessment, including clinical scoring systems, bedside ultrasound, and laboratory testing.[57]

Clinical scoring systems have been developed by combining historical features and examination findings in an effort to better predict the presence and severity of pediatric dehydration. The Clinical Dehydration Score (CDS) and the Gorelick scale (Table 172.10) are the most widely used and well-studied.[58,59] In 2015, a meta-analysis found both the CDS and Gorelick scale improve diagnostic accuracy over unstructured physician assessment. However, with only approximately 80% accuracy, neither can definitively rule in or out dehydration in infants and children.[57]

Diagnostic Strategies

The role of beside ultrasound in the assessment of volume depletion in children is uncertain. Although inferior vena cava (IVC) collapsibility has not been shown to correlate with hydration status, an IVC to aorta ratio of 0.8 or less has been found to improve diagnostic accuracy.[60,61] However, because the test characteristics of bedside ultrasound (sensitivity 67% to 86%, specificity 56% to 71%) offer little to no advantage over clinical scores, and correlation between IVC to aorta ratio and intravascular volume depletion have been questioned, routine application of bedside ultrasound for this purpose is not recommended.[57,62]

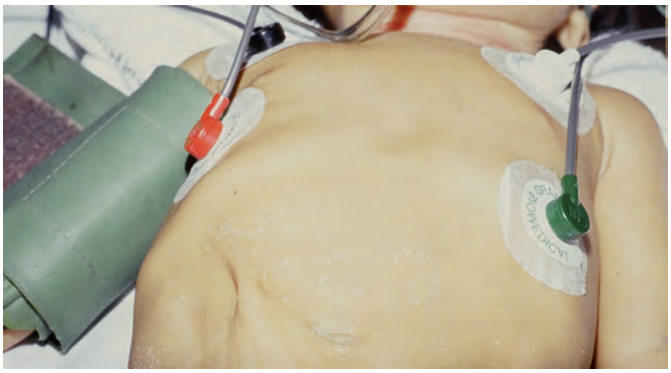

Fig. 172.1. Skin tenting. (Image courtesy of Dr. Stanley Inkelis.)

Laboratory tests are of little diagnostic value in the mildly dehydrated child, but they may be helpful in the severely dehydrated or ill-appearing child to assess etiology, severity, and complications of dehydration. A serum electrolyte panel and BUN, serum creatinine, and blood glucose level are most likely to be clinically useful. Sodium concentration is important in identifying isonatremic, hyponatremic, and hypernatremic states for appropriate choice of therapy. A low serum bicarbonate level may indicate loss of bicarbonate loss in the stool or may reflect poor tissue perfusion. Children with dysentery, characterized by fever, bloody stools, and abdominal cramping, should have BUN and serum creatinine concentrations measured and stool culture specimens sent and examined for *E. coli* O157:H7 to identify potential cases of HUS. Serum glucose level is important because hypoglycemia is not uncommon in young children with AGE, and this test may help identify children with previously undiagnosed fatty acid oxidation disorders or other inborn errors of metabolism (eg, galactosemia). Urine specific gravity and ketones are neither sensitive nor specific and should not be used in the assessment of pediatric dehydration.

Consideration of Differential Diagnoses

Most commonly, dehydration in children results from diarrhea and vomiting caused by infectious gastroenteritis. Table 172.11

TABLE 172.10

Clinical Dehydration Scale

	0	1	2
	0: NO DEHYDRATION (<3%)	1–4: SOME DEHYDRATION (≥3% to 6%)	5–8: MODERATE DEHYDRATION (≥6%)
General appearance	Normal	Thirsty, restless, or lethargic but irritable when touched	Drowsy, limp, old, sweaty, or comatose
Eyes	Normal	Slightly sunken	Very sunken
Mucous membranes	Moist	"Sticky"	Dry
Tears	Present	Decreased	Absent

	GORELICK SCALE	
	NO OR MINIMAL DEHYDRATION	MODERATE TO SEVERE DEHYDRATION
General appearance	Alert	Restless, lethargic, unconscious
Capillary refill	Normal	Prolonged or minimal
Tears	Present	Absent
Mucous membranes	Moist	Dry, very dry
Eyes	Normal	Sunken, deeply sunken
Breathing	Normal	Deep, rapid
Quality of pulses	Normal	Thready, weak or impalpable
Skin elasticity	Instant recoil	Slow recoil, recoil >2 seconds
Heart rate	Normal	Tachycardia
Urine output	Normal	Reduced

Four-point scale (italics): Two signs or more ≥5%; three signs or more ≥10%.
Ten-point scale (including all): Three signs or more ≥5%; seven signs or more ≥10%.
Adapted from Jauregui J, Nelson D, Choo E, et al: External validation and comparison of three pediatric clinical dehydration scales. PLoS One 9(5):e95739, 2014.

TABLE 172.11

Differential Diagnosis of Volume Depletion

FLUID LOSS CATEGORY	POTENTIAL ETIOLOGIC DISORDERS OR CONDITIONS
Renal	Diuretics, renal tubular acidosis, renal failure, urinary tract obstruction, diabetes insipidus, diabetes mellitus, hypothyroidism, adrenal insufficiency, renal trauma, salt-wasting nephritis
Extrarenal	Third spacing (pancreatitis, peritonitis, sepsis), skin loss (burns, cystic fibrosis), lung loss, congestive heart failure, liver failure, hemorrhage

BOX 172.4

Principles of Appropriate Treatment of Children With Diarrhea and Dehydration

Oral rehydration solutions should be used for rehydration.
Oral rehydration should be performed as rapidly as possible.
Unrestricted diet is recommended as soon as dehydration is corrected.
For breast-fed infants, nursing should be continued.
For formula-fed infants, diluted formula is not recommended. Special formula is not necessary.
Additional oral rehydration solution should be administered for ongoing diarrheal losses.

Modified from King CK, et al: Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 52:1, 2003.

lists some other causes of dehydration that should be considered when the gastrointestinal tract is not primarily involved.

Management

Oral Rehydration Therapy

Oral rehydration therapy (ORT) is a safe and effective treatment of infants and children with mild to moderate dehydration.[63,64] ORT may be instituted even if the patient continues to vomit or has diarrhea. Children with severe dehydration, shock, lethargy, acute abdomen, suspected intestinal obstruction, sodium derangement, or significant underlying illness should be identified by means of a thorough history and physical examination and laboratory tests and be excluded from ORT. Some of these principles are illustrated in Box 172.4.

The ORT period in the ED may span 4 to 8 hours and provides an opportunity to educate the family in skills of evaluating and treating childhood diarrhea. A number of oral rehydration solutions have been shown to be effective. The main ingredients are water, glucose, sodium chloride, and bicarbonate in various concentrations. In most situations, rehydration can be accomplished without the risk of causing hyponatremia or hypernatremia.

In infants and children with minimal dehydration, treatment should be directed at maintaining hydration and nutrition with an age-appropriate diet. Fluid intake should be increased, or oral rehydration solution can be administered to cover maintenance and to replace losses. Losses can be replaced at 10 mL/kg for each stool and 2 mL/kg for each emesis. Diet should not be restricted.[65]

Children with mild to moderate dehydration should have their estimated fluid deficit replaced, often started in the ED and continued at home. The volume of ORT is calculated in the following manner:

1. Estimate the degree of volume depletion as mild or moderate with information from the history, clinical signs, and physical examination findings (see Tables 172.9 and 172.10).
2. Calculate the desired volume of oral rehydration solution as 30 to 50 mL/kg for mild (3% to 5%) and 60 to 80 mL/kg for moderate (6% to 9%) volume depletion.
3. Administer 25% of the volume of oral rehydration solution to be replaced each hour for the first 4 hours.
4. Continue to replace ongoing losses as described above.
5. Monitor progress hourly and reevaluate frequently.

This technique requires that the ED have the facilities and personnel to observe and to monitor the patient for an extended time to determine the success or failure of ORT. The parent or other caregiver must be taught to administer ORT. Nursing personnel should instruct the parent in observation skills, methods of administration of the fluid, and types of fluid that are considered appropriate for children with vomiting and diarrhea. During the monitoring period, a child who is unable to tolerate intake of the prescribed volume of fluid at the expected rate should receive IV fluids. It is important to determine whether the failure is the result of the child's inability to ingest the fluid, excessive fluid loss through vomiting or diarrhea, or poor technique or motivation on the parent's part. It usually is possible to maintain the fluid administration rate in children who continue to vomit by administering small volumes frequently. This may require, for instance, use of a spoon or syringe to slowly drip the fluid by hand. Some success has been obtained with the use of nasogastric tubes. The patient is reassessed at the end of the first few hours. If the clinical examination indicates adequate volume repletion, the child may be discharged home with further specific instructions for parents about maintenance fluid requirements with oral rehydration solution. If the child still exhibits mild or moderate volume depletion on clinical examination but no deterioration in status has occurred, another 2- to 4-hour trial may be warranted. If the child is unable to ingest the appropriate volume to keep up with ongoing losses, or if volume repletion is not adequate at the end of 8 hours, IV therapy and admission are required.

In the last several years, ondansetron has become a useful adjunct in the treatment of AGE in the ED. Ondansetron, a selective 5-hydroxytryptamine type 3 receptor antagonist, acts at chemoreceptors in the peripheral and CNS to alleviate nausea. Ondansetron has been shown in numerous well-designed studies in children to reduce episodes of vomiting in the ED, improve oral intake in the ED, reduce the need for IV fluid rehydration, and reduce admissions.[66,67]

Intravenous Therapy

Some dehydrated children brought to the ED may not qualify for ORT, and others may fail to improve with ORT. These patients include those with shock, severe dehydration, increasing deficit or clinical deterioration during ORT, intractable vomiting, hypoglycemia, or electrolyte derangements.

Patients are evaluated in accordance with their immediate (emergency phase), short-term (repletion phase), and long-term (early refeeding phase) needs.[68] During the *emergency* phase, the aim of fluid resuscitation is to restore circulatory volume. Fluid needs to be administered rapidly to prevent tissue hypoperfusion, end-organ damage, and death. During the *repletion* phase, fluid and electrolyte derangements are reversed, and ongoing losses are replaced. This phase lasts 24 hours. In the *early refeeding* phase, long-term needs are addressed in the next few days, during which the body recovers fluid, electrolyte, and nutritional homeostasis. Immediate and short-term therapies are initiated in the ED, with subsequent phases carried out in the inpatient setting or at home

as managed by the primary care physician. In clinical practice, this algorithm represents a continuum of care and not three distinct, separate phases. Monitoring of serum electrolyte, BUN, and blood glucose concentrations is indicated for patients receiving IV fluid therapy.

Emergency Resuscitation Phase. Rapid reexpansion of the intravascular space is the goal of immediate resuscitation and can be achieved with an isotonic crystalloid solution. Administration of 20 mL/kg of 0.9% saline (or other appropriate isotonic crystalloid solution) intravenously at a rapid rate should result in reversal of signs of shock within 5 to 15 minutes. In critical situations, intraosseous routes should be used if venous access is not immediately available. Patients should be reevaluated periodically, and those with excessive deficits should receive repeated boluses of 20 mL/kg until clinical improvement occurs. Signs of recovery include normalization of blood pressure measurements, improvement of mental status, improvement of tachycardia and capillary refill time, and production of urine. Volume requirements greater than 60 mL/kg without signs of improvement warrant investigation for other conditions, such as septic shock, hemorrhage, capillary leak with third-space fluid sequestration, and toxic shock.

A rapid determination of serum glucose is important. Children require glucose as an energy substrate and often have marginal stores available in illnesses. If the serum glucose concentration is low (<50 mg/dL), dextrose 0.25 to 0.5 g/kg should be rapidly administered intravenously or intraosseously. Glucose can be administered per the "rule of 50," whereby the percent dextrose multiplied by the number of mL per kilogram equals 50. For neonates, a 10% dextrose solution should be given at approximately 5 mL/kg. Children 1 month old to approximately 8 years old or 25 kg should be given 2 mL/kg of 25% dextrose. In children older than 2 years old, 1 mL/kg of 50% dextrose can be used. Glucose levels should be monitored (every 30 to 60 minutes until stable) to ensure improvement and to identify ongoing needs. Repeated episodes of hypoglycemia should raise concern for sepsis, fatty acid oxidation defects, or other inborn errors of metabolism.

Dehydration due to AGE in children often leads to metabolic acidosis and ketosis, in part due to reduced carbohydrate intake leading to free fatty acid breakdown. It has been hypothesized that the addition of dextrose to initial IV rehydration fluids in moderately to severely dehydrated children will stimulate insulin release, reduce free fatty acid breakdown and ketone production, and reduce ketone-induced nausea and vomiting. This theory has been tested in small studies and produced mixed results. Levy and colleagues conducted a randomized controlled trial of 5% dextrose in normal saline compared with normal saline for initial fluid resuscitation in 188 children.[68] There was no difference in the primary outcome of hospitalization rates between groups, but they did find a greater reduction in serum ketone levels in the dextrose group. Further research focusing on patient-oriented outcomes is needed to determine whether dextrose should be included in the optimal rehydration regimen for moderately to severely dehydrated children requiring IV hydration.[69]

Repletion Phase. Appropriate fluid therapy for the patient should be determined after immediate resuscitation. Some patients may tolerate ORT after initial resuscitation; others may require ongoing parenteral hydration with 5% dextrose in half-normal normal at a weight-appropriate maintenance volume (Table 172.12), compensating for ongoing losses (10 mL/kg and 2 mL/kg for each diarrhea and vomiting episode, respectively). Potassium may be added to maintenance fluids once urine output is established and serum potassium levels are within a normal range. Overly rapid correction of serum sodium levels (>0.5 to 1 mEq/hr or >12 to 24 mEq/day) can lead to central pontine myelinolysis in hyponatremia and cerebral edema in hypernatremia. Neurologic status and serum sodium concentration should be closely monitored and the amount of sodium content of repletion fluid adjusted to maintain a slow correction. Ongoing sodium losses should also be replaced. In addition to oral, IV, intraosseous, and nasogastric routes of fluid delivery, hyaluronidase-facilitated subcutaneous hydration (hypodermoclysis) offers yet another alternative for treatment of dehydration. Hyaluronidase breaks down hyaluronic acid, an extracellular matrix that holds body tissues together and would otherwise prevent subcutaneous fluid from diffusing into tissues and capillaries.[70] Early studies of this method have found it to be safe, quick, cost-effective, and noninferior to IV hydration in terms of volume of fluid infused in the ED.[71,72] While awaiting further investigation into its widespread use in varied clinical settings, subcutaneous hydration should be considered in mildly to moderately dehydrated children who are unable to tolerate oral fluids and who have difficult IV access.

TABLE 172.12

Maintenance Fluid and Electrolytes

	WATER		ELECTROLYTES
BODY WEIGHT	ML/KG/DAY	ML/KG/HR	MEQ/100 ML H_2O
First 10 kg	100	4	Na^+ 3 mEq
Second 10 kg	50	2	Cl^- 2 mEq
Each additional kg	20	1	K^+ 2 mEq

Modified from Engorn B, Flerlage J, editors: The Harriet Lane handbook: a manual for pediatric house officers, ed 20, Philadelphia, 2015, Saunders.

Hospital-Acquired Hyponatremia. IV rehydration can lead to hyponatremia in children. This rare complication can lead to significant neurologic morbidity, including seizures, coma, and brain herniation or even death; children receiving IV fluids should have their neurologic status closely monitored. For acute hyponatremia to occur, two conditions have to be met: (1) an exogenous source of free water must be available, and (2) secretion of antidiuretic hormone must occur. For this reason, isotonic saline (rather than hypotonic saline) is the preferred IV fluid in hospitalized children.[73]

Disposition

Children with severe dehydration, intractable vomiting, inability to maintain oral hydration, severe metabolic acidosis or sodium derangement, or whose caregivers are unable to provide adequate care at home should be hospitalized. Observation status is often suitable for severely dehydrated children showing signs of improvement during their ED course.

KEY CONCEPTS

Identification of Pathogen

- Stool studies are not indicated in most uncomplicated cases of acute gastroenteritis (AGE). Exceptions are those cases in which specific treatment, specific prophylaxis, or health precautions are required, or in which the patient has systemic involvement, underlying medical complications, or the illness involves dysenteric features.
- Antibiotics are not required for most cases of uncomplicated acute bacterial enteritis. Antibiotics are recommended routinely for *Campylobacter, C. difficile, Giardia intestinalis,* and *E. histolytica.* Antibiotics can be considered for *Cryptosporidium,* traveler's diarrhea, and *Shigella* (because antibiotics have been shown to decrease diarrhea and eradicate organisms in the stool).
- Patients with Shiga toxin–producing *E. coli* (STEC) should not empirically receive antibiotics, because they may increase the risk of hemolytic-uremic syndrome (HUS).
- Testing for fecal leukocytes is a useful initial test because it may support a diagnosis of invasive disease. This test should be considered in children with diarrhea who are febrile or have mucus or blood in the stool. If the test result is positive, stool culture is indicated to further guide management.

Oral Rehydration

- Most patients with mild to moderate dehydration can be treated with oral rehydration therapy (ORT). Resumption of feeding with age-appropriate diets should begin as soon as vomiting subsides. Routine fasting with infectious diarrhea is not recommended.

Dehydration Assessment

- The degree of volume depletion is estimated from the history and physical examination findings. The desired volume of oral rehydration solution is calculated as 30 to 50 mL/kg for mild dehydration and 60 to 80 mL/kg for moderate dehydration; 25% of the volume of oral rehydration solution is to be replaced every hour (100% over 4 hours). Continue to replace ongoing losses with 10 mL/kg for each diarrheal stool and 2 mL/kg for each vomiting episode.

Severe Dehydration

- In severe dehydration, 20 mL/kg of 0.9% saline (or other appropriate isotonic crystalloid solution) given intravenously at a rapid rate should reverse signs of shock within 5 to 15 minutes. Repeated boluses of 20 mL/kg are indicated until clinical improvement occurs, but volume requirements greater than 60 mL/kg without signs of improvement suggest other conditions, such as septic shock, hemorrhage, capillary leak with third-space fluid sequestration, and heart failure.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 172: QUESTIONS & ANSWERS

172.1. A 5-month-old male infant presents in December with a 1-day history of fever to 38.3° C, emesis, and multiple episodes of foul-smelling, greenish, watery diarrhea. Physical examination reveals an awake but tired baby with a sunken fontanel, dry mucous membranes, decreased skin turgor, and irritated skin in the diaper area. What is the most likely cause of this patient's gastroenteritis?
A. *Astrovirus*
B. *Escherichia coli*
C. Norwalk virus
D. *Rotavirus*
E. *Salmonella* spp.

Answer: D. The child described most likely has diarrhea caused by rotavirus. *Rotavirus* is the most common cause of acute diarrheal illnesses in infants and toddlers. Norwalk virus and *E. coli* are not common causes of diarrhea in young infants. *Astrovirus* is a cause of diarrhea in children younger than 4 years old, but most of the infections are asymptomatic. *Salmonella* spp. also causes diarrhea in infants, but it is much less common.

172.2. For which of the following patients should the emergency clinician not obtain diagnostic testing of the stool?
A. 1-month-old with fever to 38° C with bloody diarrhea
B. 8-month-old with sickle cell disease with fever and diarrhea
C. 12-month-old, well-appearing child with 2 days of watery diarrhea
D. 2-year-old with nephrotic syndrome on prednisone with diarrhea and fever for 3 days
E. Community outbreak of diarrhea

Answer: C. Most children with uncomplicated gastroenteritis or acute diarrhea do not need laboratory studies. Stool cultures are useful and important to obtain in febrile infants and children with blood in their stools, in community outbreaks, and in the immunosuppressed.

172.3. A 4-year-old child presents with moderate dehydration from gastroenteritis. He is still actively vomiting. Which of the following statements regarding this patient's rehydration is correct?
A. A nasogastric tube should be placed for rehydration.
B. Oral rehydration should not be started.
C. Oral rehydration success can be determined in 2 or 3 hours.
D. Oral rehydration target volume is 80 mL/kg.
E. Target oral rehydration volume should be administered over 2 hours.

Answer: D. Oral rehydration can be effective even in the face of vomiting in cases of mild or moderate dehydration. Target oral volumes are 60 and 80 mL/kg, respectively. Nasogastric tubes may occasionally be useful but should not be used unless oral rehydration therapy (ORT) fails. The target oral volume should be given in doses of 25% of total replacement per hour over 4 hours.

172.4. A 9-year-old child with a history of sickle cell disease presents for evaluation of fevers, diarrhea, and vomiting. The parents say the patient has not had a sickle cell crisis in almost a year. On examination, the vital signs are stable and the child is nontoxic appearing with mild dehydration. His abdominal examination is benign. In addition to rehydration, which of the following would be the most appropriate management and disposition for this child?
A. Obtain blood cultures and admit for observation.
B. Obtain cultures (stool and blood), begin antibiotics, continue hydration, and admit for observation.
C. Obtain electrolytes; and if he has a normal bicarbonate level, then discharge home.
D. Perform a stat rotazyme assay; and if negative and patient tolerates oral intake, then discharge home
E. Provide oral rehydration therapy (ORT); and if successful, then discharge home.

Answer: B. Patients with sickle cell disease are more susceptible to *Salmonella* infections and are at increased risk for complications. It has been shown that giving antibiotics to patients with nontyphoidal *Salmonella* has been ineffective in shortening the duration of symptoms and prolonging the carrier state. Therefore antibiotics are generally not recommended for asymptomatic cases or for uncomplicated cases. However, antibiotic treatment is indicated in infants younger than 3 months old or those with complications, such as failure to improve within 5 to 7 days; bacteremia; focal infection in the central nervous system (CNS), bone, joint, kidney, or pericardium; or those with immunosuppressive conditions, hemoglobinopathies, malignant neoplasms, human immunodeficiency virus (HIV), or chronic gastrointestinal disease. The recommended antibiotics are for unknown susceptibility or in areas of high resistance to use ceftriaxone or cefotaxime until susceptibility is known. Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) may also be effective, but they should only be used in high-risk individuals once susceptibility is known.

CHAPTER 173

Genitourinary and Renal Tract Disorders

Maureen McCollough | Emily Rose

Genitourinary and renal tract disorders have unique presentations in children based on congenital and acquired disease. Morbidity and mortality risk vary with age, as do presenting signs and symptoms. This chapter outlines the common and serious pediatric genitourinary disorders presenting to emergency clinicians.

PRIAPISM

Principles

Priapism is the engorgement of the dorsal corpora cavernosa, resulting in dorsal penile erection lasting more than 4 hours (Fig. 173.1). Low-flow (also called anoxic or veno-occlusive) priapism is the most common form and occurs secondary to decreased venous outflow. Stuttering priapism is recurrent episodes of ischemic priapism, most lasting less than 4 hours. Episodes may increase in frequency and duration, with potential to develop into a major episode. High-flow (also called arterial or congenital) priapism is usually painless and is typically associated with trauma to the cavernosal artery, congenital anomaly, or fistula, resulting in excessive inflow of arterial blood and corporal engorgement. Oxygenation is maintained and emergent intervention is not typically necessary. Neurogenic priapism is not related to blood flow occlusion.

Clinical Features

Priapism can present at any age, including the neonate.[1] Sickle cell disease (SSD) is responsible for most cases in children, with nearly 50% of all males with SSD having at least one episode of priapism.[2] Other causes of priapism include malignancy, immunosuppressive disorders, medications,[3] drugs of abuse, and toxin exposure.[4] Complications include penile fibrosis, urinary retention, and impotence.

Diagnostic Considerations

Diagnostic Testing

Priapism is a clinical diagnosis. A complete blood count (CBC) and reticulocyte count are useful in sickle cell cases and hemoglobin electrophoresis if the hemoglobin S status is unknown. Rarely, a CBC may reveal an undiagnosed leukemia. In undifferentiated cases, a corporal cavernosal blood gas may differentiate the type of priapism, ischemic versus nonischemic, and color duplex ultrasonography can evaluate intracorporal blood flow (Table 173.1). Angiography may localize the site of arterial bleeding for embolization in high-flow priapism.

Differential Diagnoses

The differential diagnosis for priapism in children differs from that in adults. Penile erection from sexual arousal, erectile dysfunction medication, urethral foreign bodies, Peyronie's disease, spinal cord injury, and penile implants occur more commonly in adults than children.

Management

Ischemic or low-flow priapism is a compartment syndrome of the penis and requires emergent treatment. Management includes hydration, pain control, relief of urinary obstruction, and treatment of underlying conditions. Local anesthesia by a dorsal nerve block or ring block should be performed prior to aspiration, followed by intracavernous injection (ICI) of sympathomimetic drugs (Fig. 173.2).[2,5] Phenylephrine is the preferred agent, but epinephrine or ephedrine may also be used.

To perform aspiration, place an 18-gauge angiocatheter (smaller in young children) percutaneously into the lateral aspect of the penile shaft entering the corpus cavernosum. Aspirate and evacuate blood from the corpora cavernosa. Next, irrigate with normal saline (NS) or in combination with an ICI of an α-adrenergic sympathomimetic agent. Instill 1 mL of dilute phenylephrine (100–500 μg phenylephrine/mL of NS) into the corpus cavernosum every 3 to 5 minutes for up to 1 hour. If these measures fail to resolve the priapism, emergent urologic consultation should be obtained for possible surgical shunt placement. Prolonged episodes (>48 hours) are associated with a high likelihood of erectile dysfunction, irrespective of clinical management.[5,6]

Treatment in nonischemic priapism is observation, because over two-thirds of cases resolve spontaneously. Refractory cases may require cavernosal artery embolization or arterial ligation, although those procedures have high complication rates. Stuttering priapism has no evidence-based preventive treatment.[2,5,6]

PHIMOSIS

Principles

Phimosis is a constriction of the foreskin that prevents retraction of the prepuce from the glans. Most cases are physiologic, represent normal development, and do not require intervention. Four percent of newborns, 25% of 6-month-olds, 50% of 1-year-olds, 80% of 2-year-olds, and 90% of 4-year-old boys have fully retractable foreskins. Trauma, infections, chemical irritation, poor hygiene, congenital abnormality, or a complication of circumcision may contribute to the development of phimosis.

Clinical Features

The foreskin is not retractable on history, with narrowing or diversion of the urinary stream and foreskin bulging with urination. Phimosis may be accompanied by pain, hematuria, urinary obstruction and, rarely, glans ischemia and infarction.

Management

Gentle retraction and good hygiene are mainstays of management. Retraction of the prepuce should not be forced, because this can lead to future adhesions and strictures. A 6- to 8-week course of topical corticosteroids (eg, 0.1% triamcinolone topical cream), applied to the outlet twice daily, may expedite the development of retractable foreskin. With vascular compromise of the glans, a

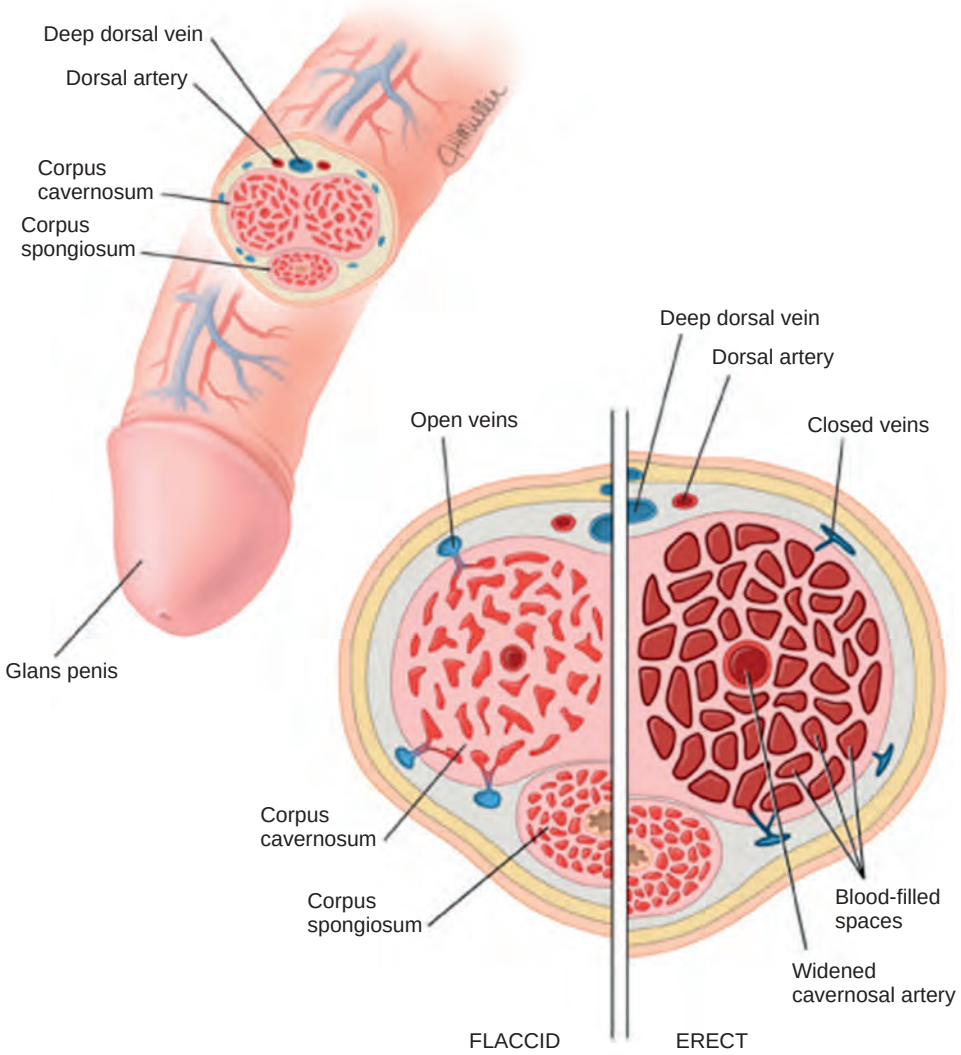

Fig. 173.1. Anatomy of the penis. (Reproduced with permission from Field JJ, Vemulakonda VM, DeBaun MR: Diagnosis and management of priapism in sickle cell disease. www.uptodate.com/contents/diagnosis-and-management-of-priapism-in-sickle-cell-disease.)

TABLE 173.1

Pathophysiologic Criteria of Priapism

VARIANT	PENILE BLOOD APPEARANCE	PENILE ARTERIAL BLOOD GAS FINDINGS	COLOR DUPLEX ULTRASONOGRAPHY FINDINGS
Ischemic priapism	Corpus cavernosum testing—blood hypoxic, dark in color	Blood gases • Pao_2 < 30 mm Hg • $Paco_2$ > 60 mm Hg • pH < 7.25	Minimal or absent blood flow
Nonischemic priapism	Corpus cavernosum testing—blood is oxygenated, red	Blood gases • Pao_2 > 90 mm Hg • $Paco_2$ < 40 mm Hg • pH = 7.40 (similar to normal arterial blood)	Blood flow normal to high in velocity
Stuttering (recurrent) priapism	Corpus cavernosum testing—blood hypoxic, dark in color	Blood gases • Pao_2 < 30 mm Hg • $Paco_2$ > 60 mm Hg • pH < 7.25	Minimal or absent blood flow during acute priapism; normal blood flow otherwise

$Paco_2$, Partial pressure of carbon dioxide; *Pao_2*, partial pressure of oxygen.
From Levey HR, Segal RL, Bivalacqua TJ: Management of priapism: an update for clinicians. Ther Adv Urol 6:230–244, 2014.

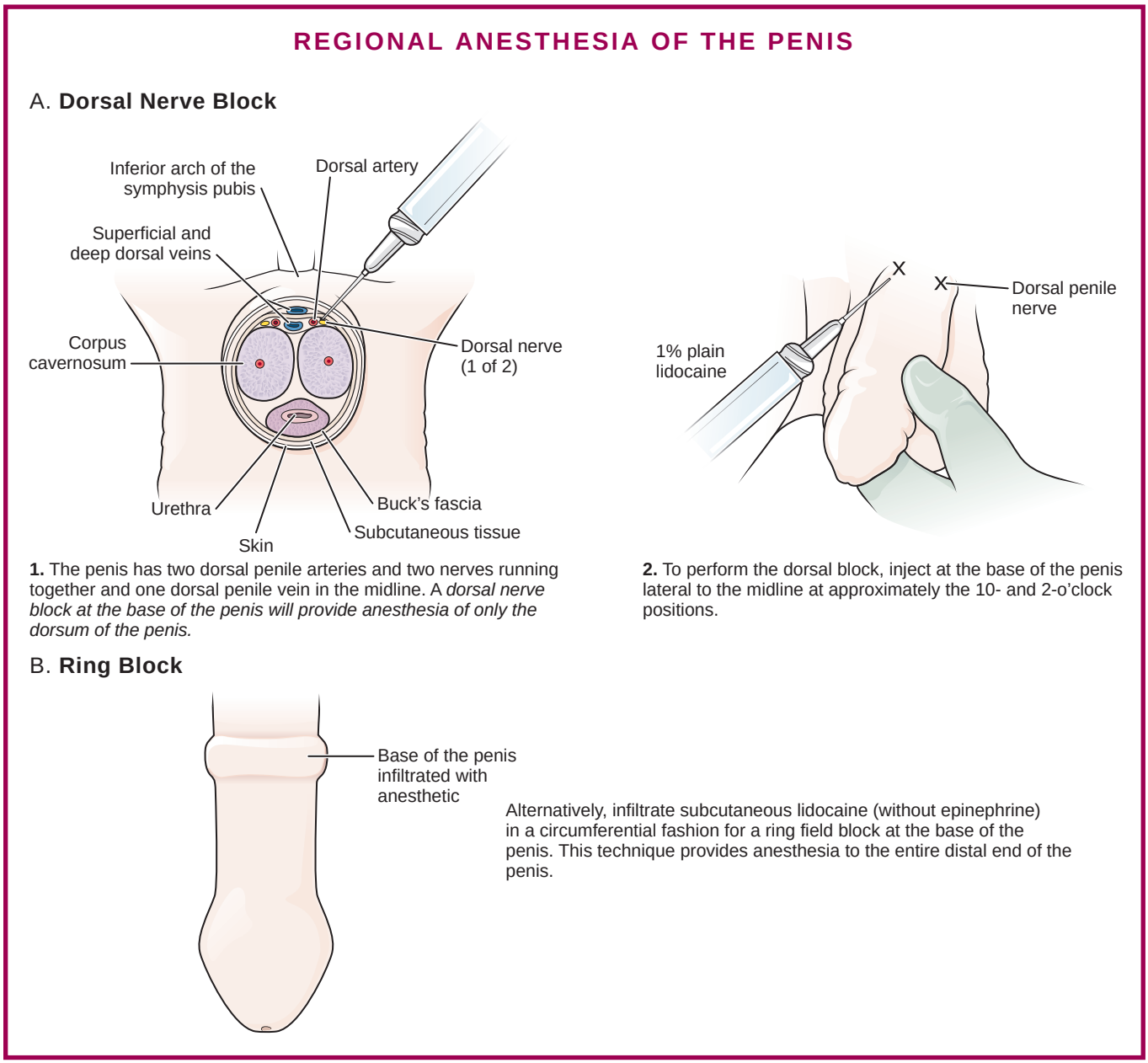

Fig. 173.2. Penile analgesia. (From Davis JE, Silverman MA: Urologic procedures. In Roberts JR, Custalow CB, editors: Roberts and Hedges' clinical procedures in emergency medicine, Philadelphia, 2014, Elsevier Saunders, pp 1113–1154.)

dorsal split procedure, circumcision, preputial plasty, or balloon dilation may be necessary. Obstructive uropathy can occur secondary to severe stenosis.

Disposition

Patients who are able to urinate and have no evidence of infection or ischemia can be discharged from the emergency department (ED) with outpatient urologic follow-up.

PARAPHIMOSIS

Principles

Paraphimosis is a pathologic condition in which the proximal foreskin cannot be returned to its anatomic position covering the glans penis, resulting in distal venous congestion. Paraphimosis can be caused by infection, masturbation, trauma, hair or clothing tourniquets, or failure to reduce the foreskin after a medical examination or procedure. Paraphimosis is a urologic emergency with potential for arterial compression, penile necrosis, gangrene, and/or autoamputation.

Clinical Features

The history often reveals that the parent or patient retracted the foreskin and then could not replace it over the glans (Fig. 173.3). Physical examination reveals a flaccid proximal penis with erythema and engorgement distal to the obstructing retracted foreskin. The health care provider should verify that the patient is uncircumcised, because hair tourniquet syndrome may mimic paraphimosis.

Fig. 173.3. Paraphimosis in a 4-year-old uncircumcised boy. (Courtesy Dr. Marianne Gausche-Hill.)

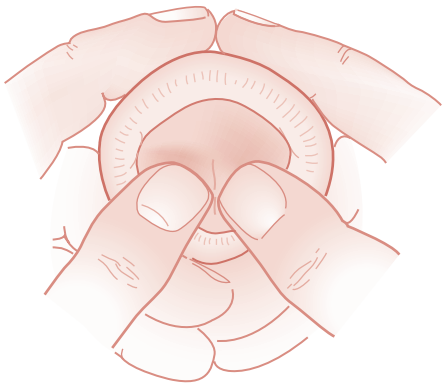

Fig. 173.4. Paraphimosis reduction. (Courtesy P.P. Kelalis.)

Management

Pain should be controlled topically, parenterally, and/or with a local dorsal penile nerve block or ring block (see Fig. 173.2) or procedural sedation. Edema should be reduced with manual compression of the penis via a provider's or parent's hand holding constant pressure, with a flexible self-adhering bandage or ACE wrap.[7] Compression is often required for several minutes to achieve adequate reduction of edema. Other methods to decrease edema include placing the finger of a rubber glove filled with ice water over the glans and foreskin, sprinkling granulated sugar over the edematous tip, and injection of hyaluronidase into the edematous prepuce.

Paraphimosis may spontaneously reduce as the edema resolves, but additional reduction is often required. If not, manual reduction should be attempted, with application of gentle steady pressure on the glans with both thumbs while the shaft is pulled straight (Fig. 173.4). If this is unsuccessful, the edematous foreskin may be punctured several times circumferentially with an 25-gauge needle to decrease edema further.[7] Dorsal band traction can be performed with Adson forceps applied directly to the band formed by the retracted foreskin and application of traction and countertraction to loosen the constriction.

An emergency dorsal slit should be performed when these measures fail to reduce the paraphimosis. Two straight hemostats are applied to crush the foreskin at the 12 o'clock position perpendicular to the corona. After 2 minutes, the prepuce between the hemostats is sharply incised, releasing the constricting band of tissue. The incisions are approximated with 4-0 absorbable sutures. Circumcision should be performed at a later date.

Fig. 173.5. Balanoposthitis in an 8-month-old boy caused by candidal infection. (Courtesy Dr. Marianne Gausche-Hill.)

Disposition

Patients can be discharged home with urologic follow-up after reduction if they are able to void spontaneously. Any evidence of cellulitis or necrosis warrants hospital admission, intravenous (IV) antibiotics, and urologic consultation.

BALANOPOSTHITIS

Principles

Balanoposthitis, an inflammation that involves the glans and foreskin, occurs in approximately 5% of uncircumcised males.[8] Balanitis involves the glans penis only. Balanoposthitis is usually secondary to poor hygiene, infection (bacterial and fungal), contact dermatitis, chemical irritation, or local trauma. Less commonly, a drug eruption, scabies infection, sexually transmitted infection (STI; eg, human papillomavirus [HPV], herpes), or nummular eczema may cause inflammation. Infectious organisms are gram-negative and gram-positive, including group A beta-hemolytic streptococci and, rarely, *Neisseria gonorrhoeae* and *Chlamydia*.

Clinical Features

Physical examination reveals penile erythema, edema, and occasionally discharge (Fig. 173.5). Streptococcal balanoposthitis is characterized by a fiery red surface and moist exudate under the prepuce. The patient may have a concomitant or recent streptococcal infection in other locations. Candidal balanoposthitis is associated with generalized erythema, fissuring, eroded papules, and a whitish discharge. Characteristic satellite lesions may be present.

Management

Providers should emphasize adequate hygiene with sitz baths to reduce inflammation. Irritants should be avoided. Painful micturition can be addressed by having the child urinate while in a warm water bath. Antibiotic ointments should be used for bacterial superinfection (eg, Polysporin [bacitracin and polymyxin B],

bacitracin, mupirocin). Topical corticosteroids (eg, hydrocortisone, 0.5%–1%) may help inflammation due to contact irritation. Candidal infections should be treated topically with antifungals (eg, clotrimazole, miconazole, nystatin). A blood glucose test should be considered in patients presenting with recurrent candidal balanoposthitis.

Disposition

Systemic antibiotics are indicated in severe infections or when an STI is suspected. Circumcision is recommended for recurrent disease.

COMPLICATIONS OF CIRCUMCISION

Principles

Circumcision prevents phimosis, paraphimosis, recurrent balanoposthitis, and decreases urinary tract infections, sexually transmitted disease transmission (including human immunodeficiency virus [HIV]), and penile cancer. An American Academy of Pediatrics task force has concluded that the benefits of circumcision outweigh the risks.[8] The most common complication is minor hemorrhage. Significant bleeding may indicate a blood dyscrasia. Local, systemic, or urinary tract infection also can occur.

Management

Postoperative pain usually resolves within 12 to 24 hours. Occlusive dressings can contribute to urinary retention and edema and should be removed. Children may develop urethral meatal stenosis from adhesions of the healing glans. Pain with urination, bloody discharge resulting from an inflamed meatus, high-velocity stream, and the need to sit while voiding indicate adhesions. Postcircumcision phimosis may result if excess foreskin remains, requiring surgical revision.

PENILE ENTRAPMENT AND TOURNIQUET INJURIES

Penile rings, string, wire, and human hair tourniquets can result in penile venous and arterial occlusion.[9] The patient presents with swelling of the glans, wherein the offending agent may be difficult to visualize because of edema of the coronal sulcus. The neurovascular supply can be occluded. Hair tourniquets may be removed with a depilatory agent. The foreign body can be cut with surgical scissors or removed with the string technique (Fig. 173.6). Metal

Fig. 173.6. String technique for penile ring removal. (From Dong C, Dong Z, Xiong F, et al: Successful removal of metal objects causing penile strangulation by a silk winding method. Case Rep Urol 2013:434397, 2013.)

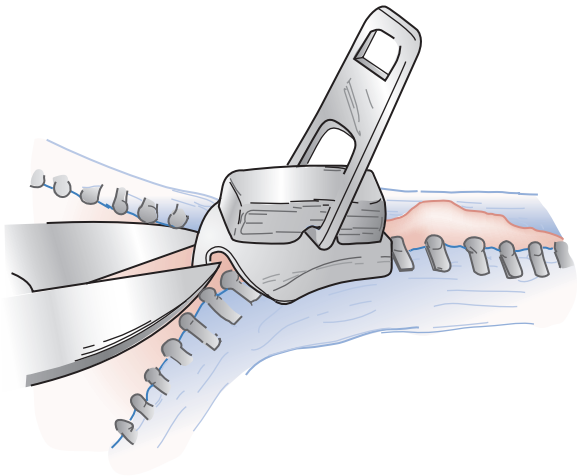

Fig. 173.7. Release of zipper entrapment by cutting of the median bar. (From Snyder HM III, et al: Genitourinary trauma. In Fleisher GR, Ludwig S, editors: Textbook of pediatric emergency medicine, ed 4, Philadelphia, 2000, Lippincott Williams & Wilkins.)

Fig. 173.8. Epididymitis in a 5-year-old boy; note mild swelling and erythema on the *left*. (Courtesy Dr. Marianne Gausche-Hill.)

bands may require ring cutters or a saw—cooling of ring will be required during the procedure to avoid penile burns.[9] Providers should document that patients can void once the constriction is relieved. Urethral obstruction can be evaluated with retrograde urethrography. Urologic consultation should be obtained emergently if penile arterial flow is disrupted, the constricting object cannot be removed rapidly, or there are signs of necrosis.

Zipper entrapment of the foreskin typically occurs in children between 2 and 6 years of age. Local anesthesia or sedation may facilitate removal. The zipper can be removed with bone or metal cutters or a mini-hacksaw to cut the median bar of the zipper (Fig. 173.7). The foreskin is freed once the zipper falls apart. Application of mineral oil to the penis may ease zipper removal. Additional methods to release the foreskin under the zipper mechanism include cutting the zipper below the entrapment and pulling the two halves of the zipper apart, cutting the zipper teeth above and below the entrapment and, with pliers, squeezing the median bar to allow more room to disengage the trapped prepuce, and insertion of a flat screwdriver between the face plates of the zipper mechanism to pry open the face plates and allow the prepuce to be released.[10]

EPIDIDYMITIS

Principles

Epididymitis is inflammation of the epididymis. Infectious causes vary by age. Young children commonly have viral infections. Bacterial epididymitis in prepubertal boys is associated with structural anomalies of the urinary tract. *N. gonorrhoeae* and *Chlamydia trachomatis* are common causes in adolescents. Risk factors include heavy physical exertion, direct trauma, and sexual activity.

Clinical Features

Patients present with a painful edematous scrotum and tenderness at the epididymis (Fig. 173.8). A urethral discharge may be present, particularly when the condition is secondary to an STI. Nausea, vomiting, fever, and lower abdominal, scrotal, or testicular pain may be present. Infants and young children may present with isolated fever. As the edema increases, obliteration of the sulcus between the testis and epididymis occurs, making differentiation from testicular torsion difficult. Relief of pain with scrotal elevation (Prehn's sign) is unreliable and should not be used to make the diagnosis.[11]

Diagnostic Considerations

Diagnostic Testing

Urinalysis and urine culture should be part of the ED evaluation for all infants and children younger than 2 years. In children older than 2 years, urine culture should be performed only if the urinalysis results indicate urinary tract infection. Lack of pyuria does not rule out epididymitis; up to 50% of patients have normal urinalysis. Direct urethral evaluation for *N. gonorrhoeae* and *C. trachomatis* is unnecessary because urine specimens are as sensitive with improved rapid nuclear acid amplification testing. Ultrasonography may be indicated in undifferentiated cases to exclude torsion. Increased vascular flow toward the side of the inflamed epididymis may be seen.

Management

Scrotal elevation, ice packs to the scrotal area, and pain medications are useful to control pain and inflammation. If urethral discharge is present, sexually active adolescents should be treated presumptively for both *N. gonorrhoeae* and *C. trachomatis*. Ceftriaxone (250 mg intramuscularly) and doxycycline (100 mg bid for 10 days) is preferred treatment. To increase compliance, azithromycin (1 g once) may be used instead of doxycycline, although there are little data on the use of azithromycin for chlamydial epididymitis. Follow-up for resolution of symptoms should occur if azithromycin used. In children, non–sexually acquired epididymitis without evidence of a urinary tract infection may be managed expectantly without antibiotics.[12] Infants with or without positive findings on urinalysis and young children with positive urinalysis findings may be treated with cephalexin tid if a bacterial urinary tract infection is suspected. *Mycoplasma genitalium* and *Ureaplasma urealyticum* may cause chronic epididymitis, and erythromycin, clarithromycin, or azithromycin may be used if symptoms persist.

Disposition

Patients with systemic symptoms and toxicity should be admitted for IV antibiotic therapy with ceftriaxone or cefotaxime. Follow-up with the pediatrician or urologist is needed to evaluate for contributing anatomic abnormalities and ensure symptom resolution.

ORCHITIS

Principles

Orchitis is a result of a bacterial or viral testicular infection leading to diffuse edema, pain, and discoloration of the scrotum. Paramyxovirus is most common, associated with mumps. Other causes include *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus* or *Streptococcus* spp., Epstein-Barr virus, coxsackievirus, arbovirus, enterovirus, *Brucella,* granulomatous disease, and filariae.[13]

Clinical Features

During the course of mumps, orchitis usually develops after the first week and is manifested with tenderness and edema of the testis, with discoloration of the scrotum. Bilateral cases are relatively rare, occurring in 2% to 5% of affected patients. If epididymitis coexists, a urethral discharge may be present. Bacterial orchitis can result in scrotal abscess formation.

Diagnostic Considerations

Diagnostic Testing

Doppler ultrasound imaging may be necessary to distinguish orchitis from testicular torsion.

Management and Disposition

Treatment of viral orchitis is aimed at pain control (scrotal elevation, nonsteroidal antiinflammatory drugs [NSAIDs], and possibly narcotics). When the diagnosis is unclear or when concurrent epididymitis is suspected, treat with oral antibiotics covering gram-negative bacteria (eg, a third-generation cephalosporin). A urologist should be urgently consulted for a scrotal or testicular abscess. Most cases can be managed on an outpatient basis.

TESTICULAR TORSION

Principles

Testicular torsion is the most concerning cause of an acutely painful scrotum. Delay in diagnosis and treatment can result in loss of spermatogenesis and, in severe cases, necrotic gangrenous testes. Testicular salvage rates are time-dependent. Nearly 100% of testes can be saved if detorsed within 4 hours of symptom onset. This decreases to less than 10% if there is more than a 24-hour delay to treatment. Testicular torsion can occur at any age. A small incidence peak occurs in the neonatal period but most cases occur in those from 12 to 18 years of age.[14]

Typically, the tunica vaginalis attaches to the posterior wall of the hemiscrotum and superior pole of the testis to achieve testicular fixation. If the tunica completely covers the testis and attaches higher up on the spermatic cord (bell clapper deformity), proper testicular fixation does not occur, and there is a predisposition to torsion (Fig. 173.9). In intravaginal torsion, the testicle may rotate within the tunica vaginalis, thereby constricting the arterial blood flow. Extravaginal torsion can occur antenatally and is most common in premature neonates.

Clinical Features

Patients present with acute scrotal pain and swelling, an elevated testicle and, typically, absence of the cremasteric reflex. This reflex can be demonstrated by lightly stroking the skin of the inner thigh

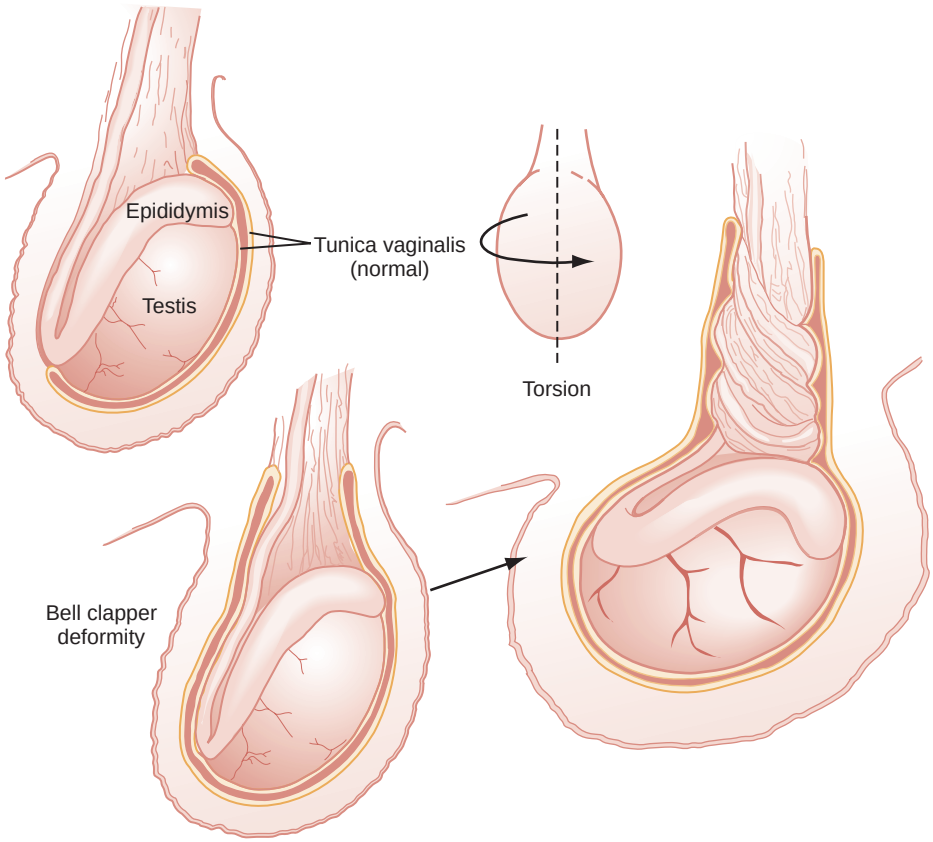

Fig. 173.9. Anatomy of testicular torsion. (From Snyder HM III, et al: Pain—scrotal. In Fleisher GR, Ludwig S, editors: Textbook of pediatric emergency medicine, ed 4, Philadelphia, 2000, Lippincott Williams & Wilkins.)

downward from the hip toward the knee. The cremaster muscle on the ipsilateral side rapidly contracts and elevates the testicle. Although absent in the vast majority of cases, the presence of the cremasteric reflex does not preclude testicular torsion.[11,14,15] Abnormal (high-riding and transverse) epididymal and testicular position may also be noted, with left-sided torsions slightly more common than right. Pain is typically constant, and the patient may have a history of a similar prior episode. Up to 90% of patients have associated nausea and vomiting. Cryptoorchism (one or both testes are undescended) increases the risk of torsion and may present with abdominal or inguinal pain.[14,16,17] Familial history and recent trauma may increase the risk of torsion.[14] Because adolescent males may be embarrassed to report testicular or scrotal pain, all males with abdominal pain should have their testes examined.

Diagnostic Considerations

Diagnostic Testing

Emergent urologic consultation should be obtained for patients with suspected testicular torsion. In undifferentiated cases, Doppler ultrasonography is indicated.[11,14] Ultrasound sensitivity is 85% to 98% (although operator-dependent), with specificity close to 100%. Scintigraphy and magnetic resonance imaging (MRI) are less commonly used imaging options, but may be considered for indeterminate ultrasound results. Homogeneous echotexture on ultrasound is predictive of testicular viability and justifies emergent surgical exploration. Heterogeneous parenchymal echotexture indicates testicular nonviability in the setting of prolonged symptoms.

Management

Immediate surgical exploration is indicated with clinical suspicion of torsion (particularly within 12 hours of symptom onset) and should not be delayed for diagnostic studies. Detorsion of the affected testicle is surgically performed, followed by an elective orchiopexy of the contralateral side to avoid recurrence. Approximately 40% of patients have a bell clapper deformity of the contralateral testicle. Bedside manual detorsion may be performed with analgesia if operative repair is delayed. The testicle is rotated in an open book fashion as viewed from below, from medial to lateral, until detorsion is complete. Torsion may cause ischemia at 180 degrees of rotation but typically occurs with 360 degrees of twisting. Up to one-third of patients may torse laterally; in these cases, manual reduction worsens torsion and its symptoms, and the procedure should be halted. After a successful detorsion, a postprocedure testicular compartment syndrome may occur secondary to testicular edema within the tight tunica albuginea. Elective (rather than emergent) orchiectomy with contralateral orchiopexy may be indicated for a patient with prolonged symptoms and an ultrasound consistent with testicular nonviability. Caution must be exercised in these cases because intermittent torsion can occur. This decision should be made by discussion with the consulting urologist and emergency clinician.

Both the appendix of the testis and appendix of the epididymis can torse, although the former is much more common. Patients with appendiceal torsion present with moderate pain of sudden onset localized to the involved hemiscrotum. The pathognomonic blue dot sign (<3 mm bluish hue in the upper lateral hemiscrotum—a cyanotic appendage) is present in less than 25% of cases.[15] Color Doppler ultrasound should be performed when the diagnosis is uncertain and will reveal normal or increased flow to the affected testicle.[18] Conservative therapy with analgesics and scrotal support is indicated; the involved appendage undergoes autoamputation within 1 week, accompanied by resolution of symptoms.[11,18]

VARICOCELE

A varicocele is a collection of venous varicosities of the spermatic veins in the scrotum caused by incomplete drainage of the pampiniform plexus. Varicoceles occur in 10% to 20% of males but are rare in children younger than 10 years. Most are left-sided.

The dilated venous collection may be tender on physical examination. It can be palpated superiorly and posteriorly to the testis. Patients should be examined in the supine and upright positions; varicoceles are more pronounced when upright. Varicoceles are described as a "bag of worms" in appearance and on palpation. Patients with varicoceles that are sudden in onset, right-sided, or do not diminish in the supine position should undergo imaging (eg, ultrasonography, computed tomography [CT], or MRI) to evaluate for a retroperitoneal neoplasm. Surgical correction may be required if the patient becomes symptomatic or has bilateral varicoceles.

IDIOPATHIC SCROTAL EDEMA

Idiopathic scrotal edema is erythema and induration of the scrotum that is typically painless but my be pruritic. There is no clear cause.[19] Most cases are unilateral and usually occur in prepubertal boys 5 to 11 years of age. There is minimal tenderness on physical examination, but the edema and erythema may extend to the phallus, groin, and abdomen. Examination of the testes and epididymis reveals no palpable masses. Systemic signs and symptoms are rare. Ultrasonography typically demonstrates thickening of the scrotal wall and increased peritesticular blood flow.[19] Patients can be discharged home with outpatient follow-up after an acute pathologic process has been ruled out. Most cases resolve spontaneously within a few days. NSAIDs and scrotal support may alleviate symptoms. Recurrences are typically more severe and occur in up to 21% of patients.[19]

HYDROCELE

A hydrocele is a collection of fluid that accumulates in the tunica vaginalis. Communicating hydroceles have an open tract between the peritoneum and scrotum. The tract is closed in noncommunicating hydroceles. Most hydroceles are right-sided. Hydroceles are common in newborns and most resolve spontaneously within 1 year. Hydroceles persistent beyond 1 year of age will often require surgical repair. In older children and adolescents, they may occur secondary to epididymitis, orchitis, testicular torsion, appendix testis or epididymis torsion, trauma, or tumor.

Examination with transillumination reveals enlargement of the scrotum. Color flow Doppler ultrasonography may be necessary to determine the cause of the hydrocele and exclude an acute pathologic process in patients with acute symptoms of pain. Asymptomatic patients can be discharged home with urologic follow-up for further evaluation and management.

INGUINAL HERNIA

Principles

Inguinal (direct and indirect) hernias are more common in males, with bimodal peaks before 1 year of age and after the age of 40 years. Infants are anatomically at risk for an inguinal hernia secondary to a short inguinal canal that crosses the abdominal wall perpendicularly, as opposed to obliquely in adults. Premature birth doubles the risk of inguinal hernia, likely in association with conditions that increase intra-abdominal pressure, such as mechanical ventilation. Infants often present with incarceration. Although hernias are more common in infant males, incarceration is more common in girls. Additionally, girls are more likely

to have an incarcerated ovary rather than bowel. Concomitant ovarian torsion may occur with inguinal hernias and should be suspected with continued irritability after successful hernia reduction. Patients should receive a urgent surgical referral because reduced incarcerated hernias commonly recur within days. See Chapter 89 for a further discussion of inguinal hernias.

TESTICULAR CARCINOMA

Principles

Testicular and scrotal cancers represent approximately 1% of solid tumors in children. Testicular cancer is one of the most curable solid tumors, particularly when diagnosed early. Cryptorchism increases the risk of testicular cancer in the undescended testicle and contralateral descended testicle. Tumor types include teratomas, embryonal carcinomas, yolk sac tumors, choriocarcinomas, Leydig cell tumors, and Sertoli cell tumors. Lymphoma and leukemia can also metastasize to the testicle.

Clinical Features

Patients typically present with a painless unilateral mass palpated separately from the testis or may describe a feeling of fullness, tugging, or increased weight of the scrotum and testicular enlargement. A reactive hydrocele may be present in 7% to 25% of patients and may contribute to diagnostic delay. The physical examination reveals a firm mass, smooth or nodular, that cannot be transilluminated. A complete physical examination looking for lymphadenopathy, petechiae, abdominal mass, hepatosplenomegaly, or gynecomastia should be performed. Diagnostic evaluation includes a CBC, urinalysis, urine human chorionic gonadotropin (produced by germ cell tumors) assay, and ultrasonography of the testis.

URINARY TRACT INFECTIONS

Principles

A urinary tract infection (UTI) is a common cause of fever in young children. Neonatal boys are more susceptible than girls but, beyond that, females are at higher risk. Vesicoureteral reflux from the bladder into the ureter is a common cause of recurrent urinary infections, including pyelonephritis. Resultant renal scarring may increase the risk of hypertension or lead to renal failure later in life.[20]

The baseline incidence of asymptomatic bacteriuria in young children is 1%.[21] The diagnosis of a UTI in children requires urinalysis results suggesting infection (pyuria, bacteriuria, or both) and the presence of at least 50,000 colony-forming units (CFU) per milliliter of a uropathogen cultured from a urine specimen.[22] *E. coli* is the predominant cause of UTIs in children; *Klebsiella* species are more likely in newborns. Other pathogens include *Enterobacter, Proteus, Morganella, Serratia,* and *Salmonella* spp. *Lactobacillus*, coagulase-negative *Staphylococcus*, and *Corynebacterium* are not considered clinically relevant pathogens in otherwise healthy children.[22] UTIs in infants younger than 3 months are associated with bacteremia in up to 50% of cases and 5% in older children.

Clinical Features

Approximately 5% of children younger than 2 years with a temperature above 39°C (102.2°F) and without a source for the fever have an occult UTI[22]; approximately 75% of children younger than 5 years with a febrile UTI have pyelonephritis. Girls younger than 2 years and uncircumcised boys younger than 12 months are at higher risk for UTI. Fever duration correlates with the prevalence of UTIs, with 2 days of fever more likely than 1 day of fever to be associated with a UTI.[23]

UTIs in children younger than 2 years often present with nonspecific symptoms, such as decreased oral intake, lethargy, jaundice, fever, vomiting, abdominal pain, and irritability. Children older than 2 years may have local symptoms of cystitis such as suprapubic tenderness or dysuria. Systemic symptoms of pyelonephritis include fever, costovertebral angle tenderness, abdominal pain, vomiting, and ill appearance. New-onset bedwetting also may be a sign of a UTI.

Diagnostic Considerations

Diagnostic Testing

Sterile urethral catheterization is the preferred method of urine collection.[24] In infants, chances of a full bladder improve if 45 to 60 minutes have elapsed since the last diaper change; ultrasound enhances the probability of obtaining urine. Bagged urines have false-positive rates of 12% to 83% due to contamination by periurethral flora and should not be used.[22] Because urethral catheterization is almost always successful, suprapubic aspiration is rarely needed.

Nitrite and leukocyte esterase markers have the highest combined sensitivity and specificity; the false-positive rate is less than 4% when both are positive.[25] A Gram stain of the urine increases the sensitivity to 93%, but has not been shown to change ED management.[25,26] In children younger than 2 years, urinalysis alone is not adequate to rule out a UTI. The nitrite test measures conversion of nitrates to nitrites by gram-negative bacteria, but this may not occur in young infants who urinate frequently. Leukocyte esterase requires the presence of leukocytes. Sensitivities of both tests remain low enough that urine cultures should be ordered on children younger than 2 years old.[22] Renal function test results are rarely abnormal but should be obtained in children with hypertension, proteinuria, or signs of dehydration. Blood cultures are not indicated in well-appearing children because the true-positive rate is low, and the organism identified is invariably the urinary pathogen.

Differential Diagnoses

Underlying renal disease or urinary tract abnormality should be considered in children presenting with hypertension, hematuria, elevated blood urea nitrogen (BUN) or creatinine level, electrolyte abnormalities, or acidosis.

Diabetes may present with urinary frequency, mimicking a UTI. Other causes of dysuria in children include irritants such as bubble bath or soaps, retained vaginal foreign bodies, and pinworms (Box 173.1). The possibility of sexual abuse should be considered in any child with a history of multiple UTIs without a cause, such as vesicoureteral reflux.

Management

Younger Than 2 Months

Infants younger than 2 months are more at risk for sepsis. It was formerly recommended that young infants receive a full sepsis evaluation and admission to the hospital for IV antibiotic therapy (eg, with gentamicin or cefotaxime and ampicillin). However, studies have shown it may be safe to treat a subset of young infants (29-60 days of age) with UTIs on an out-patient basis if they appear well in the ED and have good follow-up[27-29]

BOX 173.1

Cause of Dysuria in Children

INFECTION
Urinary tract infection, including cystitis and pyelonephritis
Vaginitis resulting from *Gardnerella, Trichomonas, Candida,* or sexually transmitted organisms
Pinworms
Balanitis

IRRITATION
Bubble bath, new soaps, or douches
Vaginal foreign body, such as retained toilet paper

TRAUMA
Sexual or physical abuse
Straddle injury (unintentional)
Self-stimulation or masturbation

OTHER
Labial adhesions
Renal stones or hypercalciuria

2 Months to 2 Years

Well-appearing children, 2 months to 2 years old, without signs of toxicity may have the UTI managed on an outpatient basis.[30] Oral antibiotic therapy is as effective as initial parenteral therapy[31]; health care providers should be familiar with their local antibiotic resistance patterns, because rates of *E. coli* resistance to trimethoprim-sulfamethoxazole can be as high as 20% to 30%.[32] Lower rates of resistance for first-generation cephalosporins (eg, cephalexin, amoxicillin-clavulanate), third-generation cephalosporins (eg, cefixime, cefpodoxime, cefdinir, cefotaxime, ceftriaxone), and aminoglycosides (eg, gentamicin) have been reported. Antibiotics that are excreted in the urine but do not reach sufficient levels in the bloodstream, such as nitrofurantoin, should not be used.[22]

Because UTIs in this age group are considered to be upper tract disease processes, a 7- to 14-day course of antimicrobials is indicated.[22] Patients should be followed clinically over the first 3 days of treatment until culture results provide antibiotic sensitivities. Follow-up imaging such as renal and bladder ultrasound looking for evidence of anatomic abnormalities or renal scarring may be completed on an outpatient basis.[22]

Older Than 2 Years

Children older than 2 years with simple cystitis should be treated with a short 3-day course of antibiotics, such as cephalexin or amoxicillin-clavulanate. Courses shorter than 3 days result in higher failure rates and are not recommended. Older children with pyelonephritis should receive a 7- to 14-day course of antibiotics.[22] Fluoroquinolones are not recommended for children due to possible musculoskeletal toxicity.

Disposition

Children with signs of toxicity, urinary obstruction, or inability to take oral medications should be hospitalized to receive IV antibiotics.[30] The discharged patient should receive instructions to return if he or she is not able to take orals or symptoms worsen. Even with appropriate treatment, children with UTIs may remain with lower grade fevers for 48 hours, despite clinically improving.

BOX 173.2

Cause of Hematuria in Children

EXTRARENAL
Trauma
Meatal stenosis or posterior urethral valves
Exercise
Menstruation or rectal bleeding
Foreign bodies
Cystitis, urethritis, or epididymitis

INTRARENAL
Pyelonephritis
Renal or bladder stones or tumors
Poststreptococcal or idiopathic glomerulonephritis
Acute interstitial nephritis
Acute tubular necrosis
Basement membrane glomerular disease
Renal vein or artery thrombosis
Recurrent familial hematuria
Polycystic kidney disease

SYSTEMIC
Alport syndrome nephritis
Henoch-Schönlein purpura
Systemic lupus erythematosus
Hemolytic-uremic syndrome
Infectious mononucleosis
Sickle cell disease or other hemoglobinopathies
Bacterial endocarditis or artificial cardiac valves
Bleeding disorders, warfarin, or aspirin
Medications such as amitriptyline or chlorpromazine, radiocontrast dyes
Munchausen syndrome or factitious

HEMATURIA

Principles

Red blood cells (RBCs) can enter the urinary tract from inflammation, infection, trauma, or anatomic abnormalities, anywhere from the glomerulus to the urethra. Microscopic hematuria is defined as more than 5 RBCs/mm^3; macroscopic or gross hematuria is the presence of blood or clots visible to the naked eye. The causes of hematuria can range from simpler factors, such as exercise or a UTI, to more serious factors, such as glomerular disease.

Clinical Features

The history and physical examination (including genital examination) should focus on signs of infection, trauma, or bleeding disorders. Providers should look for signs of renal disease (eg, glomerulonephritis), including hypertension, facial edema, rales, and cardiac murmurs.

Diagnostic Considerations

Differential Diagnoses

The causes of hematuria can be divided into extrarenal, intrarenal, and systemic illnesses (Box 173.2). Urine with lysed RBCs or myoglobin from muscle breakdown tests positive for hemoglobin, yet will not contain RBCs. Certain drugs or foods, such as phenothiazines, ibuprofen, beets, and blueberries, can cause reddish urine. In neonates, urate crystals can cause a benign red-tinged urine in the diaper, also termed *brick dust urine*.

Diagnostic Testing

A urinalysis with more than 5 RBCs per high-power field or gross blood indicates hematuria. The presence of white blood cells (WBCs) or leukocyte esterase indicates infection. Associated RBC casts, large proteinuria, hypertension, or renal insufficiency may indicate glomerular pathology. With hematuria, the urine dipstick may be positive for protein, but should not exceed 2+ (100 mg/dL) if hematuria is the only cause of the proteinuria. If glomerular disease is suspected, especially in the setting of a recent pharyngeal or skin infection, a throat culture, antibody test for *Streptococcus,* and complement studies should be ordered. Complement levels are lowered in poststreptococcal glomerulonephritis. If the patient has signs of hypertension, edema, weight gain, or proteinuria, nephrotic syndrome should be considered, and laboratory tests for electrolytes, total protein, and albumin should be ordered. The erythrocyte sedimentation rate and antinuclear antibody assay are indicated if diseases such as systemic lupus erythematosus are possible. Hypercalciuria is a common cause of microscopic and gross hematuria; urine and plasma calcium levels should be measured if no other cause of the hematuria is found. It has been theorized that microcalculi produced by the hypercalciuria cause irritation of the uroepithelium.

Management

Disposition will be depend on the underlying cause for the hematuria. Well-appearing children with no identifiable cause of hematuria should follow up with a primary care provider for a 24-hour urine collection to measure creatinine and protein levels.

RENAL STONES

Principles

Renal stones in children have been increasing in incidence.[33] Calcium-containing stones are responsible for approximately 60% of all cases, followed by struvite, uric acid, and cystine stones. Congenital abnormalities, trauma, or infection also can be an inciting cause. Renal stones are three to four times more common in white children, and a family history increases the risk.[33] In younger children, renal stones predominate over ureteral stones.

Clinical Features

Older children typically have colicky flank pain, vomiting, and hematuria. Younger children with renal stones can present with less specific complaints, such as nontender abdominal pain, vomiting, or malaise, and sometimes only isolated hematuria. History should include prior UTIs (*Proteus* species may potentiate struvite stones), family history of renal stones, and diet (including excessive vitamin use) and fluid intake. Toxins have also been associated with the development of renal stones.[34]

Diagnostic Considerations

Diagnostic Strategies

Urine should be checked for hematuria and evidence of infection, such as positive leukocyte esterase or nitrites, leukocytes, and bacteria. CBC, electrolyte panel, BUN and creatinine levels, and urine culture should be ordered, especially for the first episode of renal stones. Additional laboratory testing such as calcium or uric acid levels can be ordered during follow-up with a pediatric urologist.

Non–contrast-enhanced helical CT has high sensitivity and specificity for the detection of calculi as small as 1 mm and can identify associated processes, such as obstruction, hydroureter, hydrocalyx, and renal abscess. Ultrasonography is often an alternative first choice in young patients to avoid radiation because renal stones predominate over ureteral stones in this population. Sensitivity of ultrasonography with experienced ultrasonographers is up to 90% for renal stones but much lower for ureteral stones.[33] If the results of the ultrasound are equivocal, CT imaging should be considered, especially for presumed first-time renal stones.

Differential Diagnoses

Gastroenteritis and constipation are more common causes of colicky abdominal pain in young children. Intermittent abdominal pain associated with intussusception usually occurs in children younger than 2 years. In adolescents, biliary colic and intermittent gonadal torsion should also be considered.

Management

Management of pediatric nephrolithiasis is similar to that for adults (see Chapter 89). Children with normal renal function and adequate pain control, without signs of toxicity or renal infection, can be safely discharged home, with good follow-up. Stones 5 mm or smaller appear to pass safely in pediatric patients.

RENAL TUMORS

Principles

Renal tumors in children range from the benign cystic nephroma to the more aggressive malignant rhabdoid tumor. Most abdominal masses in infants are benign renal tumors or cysts.

Clinical Features

The most frequent presentation for a child with a renal tumor is that of an abdominal mass found by the parent while bathing or dressing the child. Hematuria or pain is a less common presenting manifestation than in the adult population.

Diagnostic Considerations

Diagnostic Testing

Because most abdominal masses are renal cysts, renal ultrasonography, which exposes the child to no radiation, is the initial imaging study of choice. Laboratory tests should include CBC, platelet count, BUN and serum creatinine levels, urinalysis, and urine catecholamine levels, which are increased in 95% of patients with neuroblastoma but normal in those with with Wilms' tumor. Once a solid mass is found on ultrasonography, CT should be performed to define the mass better. If the mass appears malignant on the CT scan, additional imaging (eg, CT brain or positron emission tomography [PET] scan) will identify metastases.[35]

Differential Diagnoses

Differential diagnosis for a renal mass includes cystic lesions, such as those of polycystic kidney disease, and severe hydronephrosis resulting from obstruction or severe reflux. Solid masses include Wilms' tumor, neuroblastoma, renal cell carcinoma, mesoblastic nephromas, and cystic nephromas.

Disposition

A preliminary diagnosis of the cause of the mass should be obtained before discharge of the child from the ED. Well-appearing

children with normal renal function for whom close follow-up can be ensured may be managed on an outpatient basis. A preliminary diagnosis of a renal tumor may require admission for coordination of continued evaluation and final diagnosis.

PROTEINURIA

Principles

Trace to mild proteinuria (1+ to 2+) is a common laboratory finding in young children and can represent benign conditions, such as exercise or mild dehydration, or more serious causes, such as nephrotic syndrome.[36] Albumin, a high-molecular-weight protein, does not pass through the glomeruli into the urine; low-molecular-weight proteins, however, do pass through the glomeruli and are reabsorbed in the proximal tubule. Proteinuria can result from increased passage of protein molecules such as albumin through the glomeruli or decreased reabsorption by the tubules. In most cases, proteinuria is benign and asymptomatic. If the amount of protein lost is significant, such as in nephrotic syndrome, the resultant hypoalbuminemia (albumin level < 2 g/dL; protein level < 4 g/dL) may cause ascites and generalized edema.

Clinical Features

The presenting symptoms in children depend on the cause of the proteinuria. Patients may have hypertension, edema (often facial), ascites or, in infants, palpable kidneys. Recent pharyngitis or the presence of hematuria may indicate an inflammatory renal process such as poststreptococcal glomerulonephritis. Changes in weight, urine output, or family history of proteinuria may indicate nephrotic syndrome. A butterfly rash of systemic lupus or the purpuric rash of Henoch-Schönlein purpura may also indicate the underlying cause of proteinuria.

Diagnostic Considerations

Differential Diagnoses

Causes of proteinuria can be glomerular or tubular. Glomerular causes include nephrotic syndrome, glomerulonephritis, and posttransplantation rejection. Transient causes of altered glomerular function include exercise, extreme cold or heat, fever, seizures, and stress. Tubular causes of proteinuria include heavy metal poisoning, urinary tract infections, and diabetes, as well as an asymptomatic tubular proteinuria.[36,37] Urinary dipstick testing can lead to a false-positive result for proteinuria when the urine is alkaline or contains mucus, blood, vaginal secretions, semen, or a significant number of inflammatory cells. In addition, dilute urine (specific gravity < 1.010) can lead to a false-negative result.

Orthostatic proteinuria is a benign condition characterized by protein in the urine collected with the patient in an upright position but not in samples collected from a supine child. Proteinuria that is persistent or associated with hematuria or other signs of renal disease such as an elevated BUN or creatinine level usually is a sign of a more serious condition.

Diagnostic Testing

Mild proteinuria (≦2+; equivalent to ≦100 mg/dL) requires no further investigation. Evidence of a UTI, such as WBCs or a positive leukocyte esterase or nitrite level, should be treated. Patients with moderate proteinuria (≧3+; equivalent to ≧300 mg/dL) should have additional testing, including the total serum protein, albumin, electrolyte, BUN, and creatinine levels, and urine culture. A random urine protein-to-creatinine ratio (urine Pr/Cr, expressed in mg/dL) correlates strongly with the protein levels found in a 24-hour urine collection. The normal urine Pr/Cr value in children older than 2 years and adults is less than 0.2 mg/dL; the normal value for children 6 months to 2 years of age is less than 0.5 mg/dL. A urine Pr/Cr more than 3.0 mg/dL correlates to nephrotic syndrome. Children with elevated urine Pr/Cr levels should be referred to a nephrologist for a 24-hour urine collection for protein.

An antistreptolysin O (ASO) titer can identify a previous streptococcal infection as the cause of the proteinuria. In young children, renal ultrasonography detects polycystic disease or anatomic abnormalities, but may be deferred as an outpatient study if the patient is being discharged. Children with proteinuria should be referred to their primary care physician, or a follow-up with a pediatric nephrologist is indicated. Indications for renal biopsy may include increased creatinine levels, low complement levels, and hematuria.

Disposition

A child with significant edema and ascites, significant hypertension (>99th percentile for age and height) resulting from glomerulonephritis, or marked impairment of renal function (>50% over normal) should be hospitalized. Consultation with a pediatric nephrologist may be beneficial in deciding whether to discharge a child home. Well-appearing children can be discharged home, with close follow-up.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Principles

Poststreptococcal glomerulonephritis (PSGN) is one of the most common glomerulonephritides. PSGN is a sequelae of streptococcal pharyngitis and, less commonly, streptococcal skin infections. PSGN is believed to result from the deposition of circulating immune complexes in the kidney. How those immune complexes develop is not completely understood. These immune complexes result in decreased glomerular filtration, allowing proteins to flow freely into the urine.

Although PSGN remains more of a cause of morbidity and mortality in developing countries, its overall incidence has been declining in industrialized countries.[38] Antibiotics for streptococcal pharyngitis have not been definitively shown to prevent PSGN. However, there is some evidence that prophylactic treatment of at-risk individuals in developing countries can curtail epidemics.[38]

Clinical Features

PSGN usually occurs in children 3 to 7 years of age, usually with a history of pharyngitis, with fever 2 weeks before the onset of glomerulonephritis (or up to 6 weeks after skin infections).[38] Symptoms can be localized to the urinary tract, manifested as hematuria or flank pain, or may be less specific, with lethargy or generalized edema. Some children may present with pulmonary edema, cardiac arrhythmias, or hypertension. Renal failure is found in 2% of these patients.[38] Delay in the diagnosis of PSGN may occur with a negative infection history and absence of gross hematuria.

Diagnostic Considerations

Diagnostic Testing

In PSGN, urinalysis will show significant blood and protein, with RBC casts in 60% of cases. Other findings may include pyuria, with granular or hyaline casts. The BUN level will be elevated;

hyponatremia and hyperkalemia may be present.[38] An ASO titer and immunoglobulin G levels are also elevated in PSGN. Total complement levels, especially C3 and C4, are decreased in most patients during the first 2 weeks of the illness. The complement levels should return to normal within 3 to 4 weeks in PSGN; with membranoproliferative glomerulonephritis, complement levels remain depressed longer.

Differential Diagnoses

Other primary causes of glomerulonephritis include immunoglobulin A (IgA) nephropathy typically seen with a simultaneous upper respiratory or gastrointestinal infection. Goodpasture's disease may present with chest pain or hemoptysis, and Wegener granulomatosis may present with sinusitis, epistaxis, cough, or dyspnea. Family history or hearing loss is common in Alport syndrome. Secondary causes and their manifestations include Henoch-Schönlein purpura with purpuric rash and arthralgias, hemolytic-uremic syndrome (HUS) and diarrhea or hematochezia, and systemic lupus erythematosus and oral ulcers or malar rash.[38]

Management

Management of PSGN includes restriction of fluid and salt intake. Diuretics should be given in consultation with a pediatric nephrologist; thiazides are first-line treatment, followed by loop diuretics for more significant disease. PSGN is a sequelae of a poststreptococcal infection typically seen weeks after the acute infection; therefore, treatment with antibiotics is not indicated for PSGN. Significant hypertension should be treated as outlined later (see "Hypertension"). Calcium channel blockers or beta blockers are usually considered first-line therapy for hypertension associated with PSGN.

Disposition

A child with significant hypertension (>99th percentile for age and height), congestive heart failure, or uremia requires hospitalization for inpatient management. Children with mild symptoms in whom good follow-up can be ensured can be managed on an outpatient basis.

NEPHROTIC SYNDROME

Principles

Nephrotic syndromes are kidney diseases that result in significant proteinuria, hypoproteinemia, and edema. Although hypoalbuminemia defines the diagnosis of nephrotic syndrome, levels of other important proteins such as immunoglobulins can also be reduced by the disease. From one to seven cases of nephrotic syndrome/100,000 children are discovered each year[39]; boys are affected twice as often as girls.

Primary nephrotic syndromes commonly occur in children younger than 5 years. Of children with nephrotic syndrome, 90% have the primary type, the vast majority due to minimal change nephrotic syndrome. Secondary nephrotic syndrome usually occurs in older children and results from a systemic illness, such as PSGN or lupus nephritis.[39]

Clinical Features

Characteristics of nephrotic syndrome include edema, hypoalbuminemia, proteinuria, and hyperlipidemia. The onset of edema may be insidious, beginning with periorbital edema. As weight increases, pants and shoes may not fit. The edema progresses, but the child usually does not appear ill unless she or he has pulmonary edema or ascites. Other features may include anorexia, nausea, and vomiting secondary to edema of the intestine. Hypertension, hematuria, or oliguria may be present. Acute renal failure is rare in primary nephrotic syndrome.

Nephrotic children are at increased risk for thrombosis, with 2% developing thromboembolic complications. Renal veins are particularly vulnerable to thrombosis, leading to flank pain, hematuria, and impaired renal function. Children with nephrotic syndrome who are taking corticosteroids are at greater risk for side effects of the steroids. Health care providers should counsel families on the possibility of acute mood changes, from depression to mania, with steroid use. Steroid therapy and decreased levels of immunoglobulins put nephrotic children at risk for bacterial infections, resulting in *Streptococcus pneumoniae* peritonitis as well as gram-negative, typically *E.coli*, infections and staphylococcal cellulitis.[39]

Diagnostic Considerations

Diagnostic Testing

Nephrotic-range proteinuria is a daily excretion of more than 3.5 g of protein/1.73 m^2 *or* more than 50 mg/kg, corresponding to 3+ or 4+ on the urine dipstick. The specific gravity may be high, and microscopic hematuria may be present. The total serum protein is usually low, 4.5 to 5.5 g/dL, and the serum albumin level is usually less than 3 g/dL and can be markedly decreased.

A random urine Pr/Cr, expressed in mg/dL, correlates strongly with the protein levels found in a 24-hour urine collection. The normal urine Pr/Cr value in children younger than 2 years and adults is less than 0.2 mg/dL; the normal value for children 6 months to 2 years of age is less than 0.5 mg/dL. A urine Pr/Cr more than 3.0 mg/dL correlates to nephrotic syndrome. Children with elevated urine Pr/Cr values should be referred to a nephrologist for a 24-hour urine collection for protein.

Complement levels should be normal. For reasons not completely understood, but triggered by changes in oncotic pressure, patients with nephrotic syndrome can develop hyperlipidemia. Hyponatremia may be present, but other electrolyte levels are usually normal. If an elevated cholesterol level is present, the lowered sodium level may be a combination of true hyponatremia and pseudohyponatremia. BUN and creatinine concentrations are usually normal, and hemoglobin and hematocrit levels may be elevated because of hemoconcentration.

Chest radiographs may show pleural effusions or pulmonary edema. The heart appears normal or small because of hypovolemia. An abdominal radiograph may reveal ascites; ultrasonography is usually nonspecific but may show abnormalities such as enlarged kidneys due to edema or small kidneys due to chronic disease. Renal biopsy facilitates diagnostic and therapeutic decisions and is indicated for patients with evidence of hematuria, elevated BUN level, or persistent hypertension or in whom renal dysfunction fails to respond to steroids.

Differential Diagnoses

Other renal diseases that cause edema include glomerulonephritis and renal failure; signs of these diagnoses would include gross blood or RBC casts in the urine, hypertension, or elevated creatinine level. Gastrointestinal disorders that cause hypoproteinemia include cirrhosis, cystic fibrosis, and protein-losing enteritides.

Management

Despite their edema, children with signs of hypovolemia or shock should be resuscitated with crystalloid. Patients with a

presumptive diagnosis of primary nephrotic syndrome (no gross hematuria or elevated creatine level, normal complement levels, and no evidence of extrarenal causes such as a malar rash) may be treated with corticosteroids.[39,40] After the initial evaluation is completed, patients should receive prednisone, 2 mg/kg/ 24 hours orally (PO), divided tid, with continued dosing determined by a pediatric nephrologist. Relapses or steroid resistance may necessitate a second course of steroids. Minimal change disease, the most common form of primary nephrotic syndrome in children, is usually very responsive to steroid treatment.

Patients should receive a diuretic (eg, furosemide, 1 to 2 mg/kg/24 hours) PO or IV, for respiratory distress or severe ascites. Salt restriction may be required. Fluid should be restricted if edema is present despite salt restriction or in the setting of hyponatremia.

Because they are relatively immunocompromised, nephrotic children with fever should likely be admitted to the hospital, have blood cultures, and receive antibiotic therapy with activity against *S. pneumoniae* and *E. coli*.[39] An intercurrent infection, even if viral, can also put the nephrotic child at risk for relapse, so admission may also be advised by the nephrologist.[40] Paracentesis should be performed on children with ascites and peritoneal signs; fluid should be sent for cell and differential counts, Gram staining, and culture.

Disposition

Newly diagnosed children with nephrotic syndrome are often hospitalized to facilitate initial evaluation, treatment, and education of the child and parents. Patients with signs of shock or respiratory distress should be admitted to the hospital after initial stabilization. Other patients with suspected bacterial infection, peritonitis, edema refractory to therapy, or evidence of renal insufficiency should also be hospitalized.

ACUTE KIDNEY INJURY

Principles

Acute kidney injury, previously known as acute renal failure, results from impaired glomerular filtration rate and may affect blood pressure, acid-base balance, removal of nitrogen waste, and fluid management. Acute kidney injury can be divided into three categories—prerenal, which involves decreased renal perfusion; renal (intrarenal), caused by parenchymal damage; and postrenal, which involves obstruction of the urinary tract (Box 173.3).[41]

Clinical Features

Children with acute kidney injury can present with hypertension, edema, decreased urine output, and microscopic or gross hematuria. Other signs or symptoms are related to the underlying cause—for example, heart failure, poststreptococcal glomerulonephritis, or a vasculitis such as Henoch-Schönlein purpura. Acute kidney injury can result in life-threatening complications, including severe hyperkalemia, hyponatremia, pulmonary edema or fluid overload, hypertensive encephalopathy, septic shock from renal obstruction and infection, and seizures from metabolic abnormalities or encephalopathy.

Diagnostic Considerations

Diagnostic Testing

Preliminary laboratory tests should include CBC, electrolyte, calcium, phosphorus, BUN, and creatinine levels, and urinalysis with microscopy and culture. Additional diagnostic studies may include ASO titer (for acute PSGN), C3 complement (for lupus), total serum albumin, cholesterol level, and albumin-to-globulin ratio and urine Pr/C ratio (for cirrhosis and nephrotic syndrome). RBC casts in the urine indicate glomerulonephritis. WBC casts indicate an infective cause, whereas hyaline casts suggest dehydration or acute tubular necrosis.

Ultrasonography is indicated to evaluate obstructive causes of renal failure. Ultrasonography may also reveal small kidneys due to congenital hypoplasia or the parenchymal loss of chronic kidney disease. Voiding cystourethrography shows extrinsic pressure on the bladder by the posterior urethral valves.

Differential Diagnoses

Causes of prerenal injury include hypovolemia (eg, dehydration, burns, hemorrhage), shock (eg, sepsis, anaphylaxis), and congestive heart failure (eg, decreased cardiac output; see Box 173.3). Obstruction of the renal artery or thrombosis of the renal vein can also cause acute kidney injury.

Intrarenal causes involve damage to the nephron. Glomerular damage can occur from PSGN (usually), systemic lupus erythematosus, HUS, and sepsis with hypoperfusion. Tubular damage can result from heavy metal poisonings or myoglobin from a crush injury, burn, or hemolytic crisis. Dehydrated children taking NSAIDs can also develop kidney injury.

Postrenal injury resulting from an obstruction in the urinary tract may be caused by infection, tumor, renal stones, or posterior urethral valves. Bilateral obstruction of the kidneys can lead to frank renal failure.

BOX 173.3

Cause of Acute Renal Failure in Children

PRERENAL
- Decreased intravascular volume or dehydration
  - Burns or hemorrhage
  - Third spacing
  - Sepsis
- Decreased cardiac output
  - Cardiac shock
- Decreased renal artery blood flow

INTRARENAL
- Glomerular disease
  - Poststreptococcal and other glomerulonephritis
  - Pyelonephritis
- Systemic causes
  - Hemolytic-uremic syndrome
  - Henoch-Schönlein purpura or other vasculitides
  - Systemic lupus erythematosus
  - Sepsis or other causes of prolonged decreased perfusion
- Toxins
  - Heavy metal poisonings, such as lead and gold
  - Myoglobin or hemoglobin deposits
  - Antibiotics such as aminoglycosides
  - Anticonvulsants such as phenytoin
  - Radiocontrast dyes

POSTRENAL
- Obstructive lesions
- Nephrolithiasis or tumor
- Posturethral valves
- Intra-abdominal tumor obstructing urinary flow
- Infection
- Renal vein thrombosis

Management

Patients with hypovolemia resulting in prerenal acute kidney injury should be rehydrated with a 20-mL/kg bolus of crystalloid to prevent progression to acute tubular necrosis. If no urinary response is obtained after two boluses of crystalloid, there is no evidence of obstruction, and the patient is otherwise euvolemic, we recommend diuretics, such as IV furosemide, 1 mg/kg/dose every 2 to 6 hours. Bumetanide may be considered in consultation with a pediatric nephrologist. Mannitol, 0.75 g/kg/dose IV qid, is the third-line option, but is contraindicated with obstruction.

If the child is considered euvolemic and has no urine output despite diuretic therapy, renal dose dopamine should be initiated (2–5 μg/kg/minute) in consultation with a pediatric nephrologist. Patients with hypertensive encephalopathy should receive IV blood pressure agents such as nicardipine or labetalol to achieve a controlled 10% to 20% reduction in blood pressure. Further discussion of hypertensive emergencies and treatment can be found in Chapter 74.

Acute kidney injury can lead to seizures secondary to hypertensive encephalopathy or a metabolic derangement. Intractable hyponatremic seizures may necessitate the use of hypertonic saline (3% sodium chloride, 3–5 mL/kg), with each 1 mL/kg increasing the serum sodium level by approximately 1 mEq/L. Once the seizures have ceased, sodium correction should continue more slowly to minimize the risk of central pontine myelinolysis. Correction should occur no faster than 10 to 12 mEq/L in the first 24 hours and no more than 18 mEq/L in the first 48 hours. Hemodialysis or peritoneal dialysis is indicated for symptoms of uremia (protracted vomiting), refractory fluid overload, congestive heart failure with pulmonary edema, electrolyte disturbances (severe hyperkalemia, hyponatremia or hypernatremia), or metabolic acidosis.[42]

Disposition

All children with acute renal failure should be admitted to the hospital. Any child with signs of congestive heart failure, pulmonary edema, significant hyperkalemia, or acidosis should be admitted to a monitored bed and receive emergent dialysis.

HYPERTENSION

Principles

Hypertension is defined as a systolic or diastolic blood pressure higher than 2 standard deviations (SDs) above the mean for age and gender (Table 173.2). Blood pressure readings should be taken on more than one occasion with appropriately sized cuffs. A child who is in pain or agitated may have falsely elevated blood pressure readings.

Hypertension is seen in boys and girls, occurring more often in African American children. Predisposing factors include obesity, physical inactivity, and family history. A history of umbilical artery catheterization increases the risk of developing hypertension from renovascular disease. Metabolic syndrome, a combination of insulin resistance, hypertension, and hyperlipidemia, may affect up to 50% of overweight adolescents.

Primary or essential hypertension is unrelated to a second systemic disease. Children diagnosed with primary hypertension are more likely to become adults with hypertension. Secondary hypertension results from endocrinologic, cardiac, neurologic, or other factors, such as exposure to certain drugs or poisons (Box 173.4). Children with significant hypertension will usually have an underlying renal (as in glomerulonephritis) or renovascular cause.

TABLE 173.2

Blood Pressure Limits in Children

	BLOOD PRESSURE: UPPER LIMIT (mm Hg)	
AGE (yr)	Systolic	Diastolic
0–2	110	65
3–6	120	70
7–10	130	75
1–15	140	80

From Daniels SR: Consultation with the specialist. The diagnosis of hypertension in children: an update. Pediatr Rev 18:131–135, 1997.

Clinical Features

There are a variety of clinical presentations of hypertension in children. Asymptomatic or mildly symptomatic hypertension may show up in routine vital signs measured in children in the ED for unrelated illnesses. Symptomatic children may have headaches, abdominal pain, irritability, or nosebleeds. Patients may have personality changes or difficulties in school.

Hypertensive pediatric patients may present with a variety of signs and symptoms. Health care providers should ask about joint pain or swelling (Henoch-Schönlein purpura), palpitations (electrolyte abnormalities), weight loss (hyperthyroidism), flushing of the skin (pheochromocytoma), and drug ingestion (cocaine, methamphetamines). Patients with a renal cause of hypertension may have peripheral edema, palpable kidneys, abdominal or flank bruit, or a UTI.

Severe elevations in blood pressures by age include a systolic blood pressure of 160 mm Hg or higher and diastolic blood pressure of 105 mm Hg or higher in children younger than 10 years, and systolic blood pressure 170 mm Hg or higher and diastolic blood pressure 110 mm Hg or higher in children older than 10 years. (Children with hypertension from coarctation of the aorta will have a blood pressure differential in their extremities; see Chapter 170.)

Children with hypertensive emergencies have evidence of end-organ damage, including acute neurologic changes or encephalopathy, pulmonary edema, myocardial ischemia, and proteinuria. The electrocardiogram may show signs of ischemia or ventricular hypertrophy. Chest radiography may reveal cardiomegaly or pulmonary edema. Although hypertensive emergencies require prompt treatment, overaggressive treatment can lead to worsening neurologic deficits due to relative hypotension.

Hypertensive encephalopathy symptoms include headache, vomiting, altered mental status, visual disturbances (including blurry vision and diplopia), and seizures or stroke. Papilledema, decreased retinal venous pulsations, and cranial nerve palsies may be found on examination. The diagnosis is confirmed when the symptoms and signs subside rapidly after the blood pressure is lowered. Headache alone, without any other associated symptoms or signs, generally is not considered to represent a hypertensive emergency.[43]

Diagnostic Considerations

Diagnostic Testing

Laboratory and radiologic studies performed in the ED can determine the cause of the hypertension and presence of a hypertensive emergency (Box 173.5). Initial laboratory tests should

BOX 173.4

Causes of Hypertension in Children

PRIMARY
Essential hypertension

SECONDARY

Renal
Glomerulonephritis
Henoch-Schönlein purpura
Pyelonephritis
Obstruction or reflux
Polycystic kidney disease
Diabetic nephropathy
Trauma
Renal transplant or hemodialysis
Tuberous sclerosis
Systemic lupus nephritis

Endocrine
Pheochromocytoma
Cushing's syndrome
Congenital adrenal hyperplasia
Corticosteroid treatment
Hyperthyroidism
Neuroblastoma
Ovarian tumor

Cardiac
Congestive heart failure
Coarctation of the aorta

Vascular
Hemolytic-uremic syndrome
Kawasaki syndrome
Renal artery thrombosis or stenosis

Neurologic
Central nervous system tumor or infection
Central nervous system trauma or abuse
Increased intracranial pressure
Guillain-Barré syndrome

Neoplastic
Neuroblastoma
Wilms' tumor
Pheochromocytoma
Adrenal carcinoma

Drugs
Corticosteroids
Cocaine
Sympathomimetics
Oral contraceptives
Phencyclidine
Beta-blocker or clonidine withdrawal
Lead, mercury

Others
Iatrogenic fluid overload
Volume overload from end-stage renal disease

BOX 173.5

Diagnostic Evaluation in Hypertensive Emergencies[a] in Children

History of medications or drugs, or family history of cardiovascular disorders
Symptoms of severe headache or chest pain
Physical examination focused on acute neurologic changes, funduscopic abnormalities, pulmonary edema
Urinalysis for significant protein
Chest radiography for cardiomegaly or congestive heart failure
Electrocardiography for ventricular hypertrophy

LABORATORY AND RADIOLOGIC TESTS TO CONSIDER
Urinalysis and urine culture
Urine catecholamine assay
Complete blood count with platelet count
Blood smear
Measurement of sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, magnesium, uric acid levels
Blood urea nitrogen and creatinine determinations
Serum C3 complement assay, antistreptolysin O titer, antinuclear antibody assay
Plasma renin level
Computed tomography urography or IV pyelography
Voiding cystourethrography
Renal ultrasound scan
Renal arteriography

[a]Evidence of end-organ damage.

include a CBC, electrolyte, BUN, and creatinine levels, urinalysis, urine culture, chest radiography, and electrocardiography.

Differential Diagnoses

See Box 173.4 for causes of pediatric hypertension. Disorders with presentations similar to hypertensive encephalopathy include meningitis, brain tumor, intracerebral hemorrhage, stroke, and uremia. These conditions, however, generally produce only a mild increase in the systolic blood pressure; CT or lumbar puncture can also help identify other disorders.

Management

The management of hypertensive emergencies is discussed in Chapter 74. The goal of treatment is to reduce the mean arterial blood pressure by 10% to 20% over several minutes to hours. Patients with headache and vomiting should have their blood

TABLE 173.3

Medications Used in Hypertensive Emergencies

MEDICATION	DOSE	TIME TO REPEAT DOSE	DURATION OF EFFECT	SIDE EFFECTS
Nicardipine[a]	0.2–0.5 μg/kg/min (max, 3 μg/kg/min)	15–20 min	During infusion	Tachycardia
Hydralazine[b]	0.1–0.2 mg/kg IV (max, 20 mg), slowly during 15 min	10–20 min	4–12 hr	Tachycardia, skin flushing, headache, vomiting, diarrhea, hypotension
Labetalol[c,d]	May bolus 0.2–1 mg/kg IV (max, 20 mg), then 0.4–1 mg/kg/hr IV (max, 3 mg/kg/hr)	10 min	6 hr, but variable	Gastrointestinal upset, headache, sedation
Esmolol[e-g]	Load 100–500 μg/kg IV during 1–2 min, then maintenance, 25–100 μg/kg/min	10 min	During infusion	Similar to labetalol
Phentolamine	0.1 mg/kg/dose IV (max, 5 mg)	30 min	30–60 min	Tachycardia, abdominal pain
Nitroprusside	0.3–0.5 μg/kg/min IV (max, 10 μg/kg/min)	30–60 min	During infusion	Headache, abdominal pain, chest pain, gastrointestinal upset, seizures, thiocyanate and cyanide toxicity[h]

[a]Use with caution in liver patients.
[b]Use with caution in renal patients.
[c]Avoid in asthma, pulmonary edema, and heart block.
[d]Avoid in second and third trimesters of pregnancy.
[e]With inadequate response, re-administer loading dose or increase maintenance dose by 25–50 μg/kg/min every 5–10 min.
[f]Usual maintenance range: 50–500 μg/kg/min.
[g]Morphine may increase esmolol levels.
[h]Avoid in pregnancy.

pressure lowered over several hours, whereas those with intracranial bleeding or herniation should be lowered over minutes. We recommend IV medications that provide tight blood pressure control: first-line agents include nicardipine, labetalol, and esmolol[43] (see Table 173.3).

Patients with persistently severe hypertension, but without evidence of end-organ damage, should be started on an antihypertensive agent in consultation with the child's primary care physician or a pediatric nephrologist. Angiotensin-converting enzyme inhibitors (eg, 0.3–0.5 mg/kg/dose (>12 months of age); maximum, 6 mg/kg/day) or calcium channel blockers (eg, nifedipine ER, 0.25–0.5 mg/kg/day; maximum, 3 mg/kg/day, up to 120 mg/day) are useful as first-line agents and usually are well tolerated. The child may be observed for 4 to 6 hours after administration of the medication for evaluation of effectiveness or complications.

Disposition

Otherwise asymptomatic well-appearing children without severely elevated blood pressure can be referred without treatment to their primary care physician for further evaluation and management. A child with evidence of a hypertensive emergency (ie, acute end-organ damage) should be admitted for vital sign monitoring, further evaluation, and treatment of hypertension.

HENOCH-SCHÖNLEIN PURPURA

Principles

Henoch-Schönlein purpura (HSP) is an immunoglobulin A–mediated systemic vasculitis involving the small blood vessels of the skin, gastrointestinal tract, and joints. Immune complex deposition results in a systemic vasculitis, with up to 33% of patients experiencing recurrences.[44] The peak incidence for HSP is between 4 and 7 years of age, with an overall occurrence rate of 13.5 episodes/100,000 children annually. Approximately 50% of affected children have a history of previous upper respiratory tract infection, and as many as 75% have group A beta-hemolytic streptococci cultured from the oropharynx. Other theorized predisposing factors include exposure to cold weather, certain foods, drugs, and insect bites. Other possible precipitants include varicella-zoster virus, *Mycoplasma* species, parvovirus, *Campylobacter enteritidis,* parvovirus B19, and Epstein-Barr virus.

Clinical Features

The hallmark of HSP is a palpable, purpuric, or petechial rash. The rash is seen in the vast majority of patients and is most prominent on the lower extremities, starting at the lateral malleoli and extending to the buttocks. Arthralgia and arthritis are common, usually involving the knee and ankle joints. Dull periumbilical pain resulting from bleeding into the intestinal wall occurs occurs in at least 50% of patients.[44] In up to 50% of patients, abdominal pain or arthritis can be the only initial complaint.[45] A self-limited glomerulonephritis will develop in 25% to 50% of children, manifested by hematuria with or without red blood cell casts. Children with acute renal failure, nephrotic syndrome, or hypertension are at higher risk of persistent renal manifestations. Testicular involvement occurs in up to 35% of male patients and may present with severe scrotal edema that resembles acute testicular torsion.

Diagnostic Considerations

Diagnostic Testing

The classic HSP rash is usually diagnostic. Urinalysis should be ordered to screen for hematuria, RBC casts, and proteinuria; BUN and creatinine levels should be ordered if the urinalysis is significantly positive. CBC and coagulation studies should be considered in patients with severe skin involvement or distribution atypical for HSP. Patients with significant abdominal pain, especially with signs of obstruction or peritonitis, should undergo abdominal ultrasound to evaluate for intussusception; ultrasound findings may include intraluminal hematomas, duodenal wall thickening, and peritoneal fluid.

Differential Diagnoses

Purpura may also be seen in meningococcemia, Rocky Mountain spotted fever, HUS, and other vasculitides. Polyarticular joint swelling can be seen with juvenile rheumatoid arthritis and systemic lupus erythematosus.

Management

The treatment of HSP is controversial because most cases resolve spontaneously and do not require therapy. NSAIDs can be used to treat joint pain, but renal function should be monitored. Corticosteroids have been shown to be effective in reducing the time to resolution of severe abdominal pain (eg, prednisone, 1–2 mg/kg/day; maximum, 60–80 mg/day). Corticosteroids do not reduce the risk of abdominal or renal complications.[46-48]

Disposition

Patients with only the skin manifestations of HSP can be discharged home, with close follow-up. NSAIDs or acetaminophen are recommended for joint pain and malaise. Patients with moderate to severe abdominal pain, multiple joint arthritis or inability to ambulate, proteinuria or evidence of gastrointestinal bleeding, or renal involvement should be admitted.[49]

HEMOLYTIC-UREMIC SYNDROME

Principles

HUS, a microangiopathic hemolytic anemia, is one of the most common causes of acute kidney injury in children. HUS is rare after 5 years of age, but recurrent HUS is more common in older children and is associated with a 30% mortality rate. In the United States, the most common cause is Shiga toxin (verotoxin)–producing *E. coli* (STEC), specifically serotype O157:H7.[50] Transmission is through person to person contact or exposure to contaminated food, such as unpasteurized dairy products or beef.

HUS can be classified as primary (or atypical) HUS, caused by compliment dysregulation, and secondary HUS, caused by infections (eg, STEC, *Shigella* organisms, *S. pneumoniae, Aeromonas,* or HIV), drugs (eg, chemotherapeutic or transplant antirejection drugs), or other idiopathic causes (eg, pregnancy, lupus). UTIs have also been implicated.

Renal compromise is due to renal vascular endothelium injury, often induced by viral or bacterial agents. RBCs are injured within narrowed blood vessels, resulting in a microangiopathic hemolytic anemia. Platelets, complement, and fibrin are deposited in the glomerular lumen, resulting in thrombocytopenia, a decrease in the glomerular filtration rate, and renal failure.

Clinical Features

Secondary HUS due to STEC presents with watery diarrhea, crampy abdominal pain, and occasionally fever. Within days of symptom onset, patients experience increasing abdominal pain, with 50% to 85% developing bloody stools. Patients may also develop toxic megacolon, ischemic colitis, intussusception, perforation, or delayed colonic stricture. Patients with a pneumococcal cause for the HUS typically present with pneumonia or, less commonly, meningitis, bacteremia, sinusitis, or otitis media.

Up to 10% of patients will experience the triad of sudden onset hemolytic anemia, thrombocytopenia, and acute renal insufficiency, with possible progression to renal failure. Up to 60% of diarrhea-associated HUS cases require dialysis, and death or end-stage renal disease was found to occur in 12%. Dehydration on admission increases the risk of renal failure.[51]

Pancreatic insufficiency resulting in insulin-dependent diabetes mellitus is a less common complication. Patients may develop central nervous system irritability; 40% develop seizures. Hypertension occurs in up to 50% of patients and may contribute to the development of encephalopathy.

Diagnostic Considerations

Diagnostic Testing

A family member with a concurrent history of HUS suggests an infectious source; a remote family history of HUS or previous episode of HUS suggests a genetic or complement-mediated source. Initial diagnostic laboratory tests include CBC, peripheral blood smear, urinalysis, and electrolyte, C-reactive protein, BUN, and creatinine levels. Leukocyte counts and C-reactive protein levels are significantly higher in patients with Shiga toxin–producing *E. coli* O157:H7. The peripheral blood smear shows microangiopathic changes such as schistocytes, teardrop cells, helmet cells, microspherocytes, and burr cells. WBC counts may be elevated, and the platelet count may be less than 50,000/μL. The hemoglobin level is typically less than 8 g/dL but can be as low as 5 g/dL as a result of the rapid hemolysis that occurs. Renal involvement can range from simple hematuria and proteinuria to severe renal failure, with elevated BUN and creatinine levels. Additional testing may include coagulation studies to differentiate other diagnoses (eg, disseminated intravascular coagulation [DIC]), Shiga toxin testing of stool, stool culture, and serologic studies for STEC serotypes.

Differential Diagnoses

The differential diagnosis of HUS includes systemic vasculitides, thrombocytopenic thrombotic purpura (rare in children), DIC, and nonmicroangiopathic causes of hemolytic anemia.

Management

With supportive therapy and early peritoneal dialysis, current mortality rates are less than 5%. Patients with evidence of dehydration should be resuscitated with NS, looking for improvement in mental status, heart rate, peripheral perfusion, and metabolic acidosis. Hyperkalemia is common and should be treated based on the potassium level and electrocardiographic findings (see Chapter 117). Patients with severe hyperkalemia, hyperphosphatemia, or severe metabolic acidosis should undergo dialysis.

Patients should receive packed RBCs (5 mL/kg during 4 hours) if the hemoglobin level falls below 6 g/dL. Platelet transfusions should be given for life-threatening bleeding or before an invasive procedure. Hypertension is responsive to calcium channel blockers (eg, nifedipine ER, 0.25–0.5 mg/kg/day PO; maximum, 3 mg/kg/day, up to 120 mg/day), beta blockers (eg, labetalol, 1–3 mg/kg/day, divided bid (maximum dosing 12 mg/kg/day up to 1200 mg/day), or nitroprusside (0.3–0.5 μg/kg/min IV; maximum, 10 μg/kg/min) for refractory cases. Seizures typically respond to benzodiazepines and phenytoin, but may require 3% saline (3–5 mL/kg) if secondary to hyponatremia. Antimotility agents may lead to toxic megacolon and should not be used. Antibiotics have not been shown to prevent HUS.[52] In STEC, antibiotics may enhance the release of verotoxin from bacteria and should be avoided. Pneumococcal-associated HUS often presents with pneumonia and should be treated with appropriate antibiotics (eg, ceftriaxone, 50 mg/kg IV q24h; maximum, 2 g/dose; and vancomycin, 15 mg/kg IV qid; maximum, 2 g/dose). Hyperglycemia, ketonemia, and acidosis secondary to pancreatic islet cell necrosis are managed with insulin therapy.

Although of unproven benefit, plasmapheresis may be used for patients with severe neurologic involvement (eg, stroke). Renal dialysis and renal transplantation may be required, although primary HUS can recur in the transplanted kidney.

Patients with primary HUS renal damage appear to see improvement in their renal function when treated with the complement inhibitor eculizumab.[53]

Disposition

Patients with HUS should be admitted to the hospital, with pediatric nephrology consultation. Early dialysis and supportive therapy result in return to baseline renal function in up to 90% of patients with acute renal failure.[52]

KEY CONCEPTS

Priapism

- **In low-flow priapism, cavernosal aspiration plus irrigation has been effective when performed within the first 48 hours, and preferably within a few hours, of symptom onset. Phentolamine, phenylephrine, ephedrine, or 1:1,000,000 epinephrine** can be added to the irrigation solution used in performing corporal aspiration.

Phimosis and Paraphimosis

- Steroid cream is first-line therapy for phimosis. In paraphimosis, most can be reduced utilizing a number of techniques, only in severe cases involving vascular compromise of the glans penis, may a dorsal slit procedure may be necessary.

Testicular Torsion

- Delay in diagnosis and treatment can result in loss of spermatogenesis and, in severe cases, a necrotic, gangrenous testis.
- Color Doppler ultrasonography is the test of choice, but false negatives due occur.
- Testicular salvage rates are 96% if detorsion is performed less than 4 hours after symptom onset; with more than a 24-hour delay, the salvage rate falls to less than 10%.

Varicoceles

- Left-sided varicoceles account for 85 to 95% of the cases.
- Right-sided varicoceles are often caused by inferior vena cava thrombosis or compression by tumors.

Urinary Tract Infections

- In children younger than 2 years, a urinalysis alone is inadequate to rule out a urinary tract infection; urinalysis yields false-negative results in 10%–50% of patients. Urine cultures should be sent in children less than 2 years of age.
- Girls less than 2 years old, and boys, uncircumcised, less than 1 year, and circumcised less than 6 months are at higher risk for UTIs.
- Children less than 2 years old should be considered to have upper tract disease and receive antibiotic treatment for 7–14 days.

Renal Stones

- Renal stones are more common than ureteral stones in younger children.
- Older children can present with classic renal stones signs and symptoms; younger children may present with more non-specific symptoms, such as malaise and non-tender abdominal pain.
- Ultrasound should be the first–line imaging modality used in children with suspected renal stones.

Poststreptococcal Glomerulonephritis

- Patients will present with a history of a pharyngeal or skin infection in the previous 2–6 weeks; clinical findings are usually limited to the urinary tract including hematuria, flank pain or sometimes generalized edema.
- Diagnostic testing will show blood, protein, and RBC casts in the urine; evidence of renal dysfunction (elevated BUN) and low complement levels will also be found.
- Treatment includes restricting fluid and diuretics for more significant disease.

Nephrotic Syndrome

- Albumin and immunoglobulin levels are typically both decreased in nephrotic syndrome.
- Clinical signs include periorbital edema, weight gain, and more serious signs such as pulmonary edema or ascites.
- Children with nephrotic syndrome are at increased risk for thrombosis and bacterial infections, especially *Streptococcus* and *E.coli*.
- Treatment includes corticosteroids and diuretics.

Henoch-Schönlein Purpura (HSP)

- HSP is an immunoglobulin A-mediated systemic vasculitis that involves the skin, GI tract, joints, and kidneys.
- Urinalysis may be positive for blood and RBC casts.
- Corticosteroids can be useful for severe abdominal pain.

Hemolytic-Uremic Syndrome (HUS)

- HUS is a microangiopathic hemolytic anemia found in young children. In the U.S., it is typically related to Shiga-toxin producing *E.coli* (STEC), presenting with abdominal pain and bloody diarrhea. *Streptococcus pneumoniae* has also been implicated.
- Renal vascular endothelium injury results in renal insufficiency and damage to RBCs; glomerular damage occurs due to platelet, complement, and fibrin deposits.
- Peripheral smear will show damaged RBCs and typically thrombocytopenia; renal involvement ranges from hematuria to elevated BUN and creatinine.
- Stool cultures and Shiga toxin testing should be sent in diarrhea-associated cases.
- Antibiotics are not indicated in HUS unless a concurrent presumptive pneumococcal infection such as pneumonia is present.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 173: QUESTIONS & ANSWERS

173.1. A 12-year-old boy presents with engorgement of the dorsal corpora cavernosa. You expect to elicit which of the following in his history?

A. Early sexual intercourse
B. Recent trauma
C. Sexual abuse
D. Sickle cell disease
E. Testicular mass

Answer: D. Priapism is the engorgement of the dorsal corpora cavernosa, resulting in dorsal penile erection and ventral penile flaccidity. Sickle cell disease and leukemia are responsible for most cases in children.

173.2. A 17-year-old uncircumcised adolescent presents complaining of pain and swelling of his penis. On physical examination, you find a grossly edematous glans and distal shaft, with a retracted prepuce that is unable to be reduced. There is evidence of cellulitis. Compression and manual reduction have been unsuccessful. What is the next step in the management of this patient?

A. Administer local anesthesia, lubrication, and forceful reduction.
B. Perform a dorsal slit followed by admission to the hospital.

C. Prescribe oral antibiotics and follow-up in 24 hours.
D. Prescribe topical antibiotics and antifungal agents and follow-up in 1 week.

Answer: B. Paraphimosis is the inability to retract the foreskin over the glans and represents a true urologic emergency. Ice, circumferential compression, and manual reduction are all ways to reduce the foreskin. If all attempts fail, urologic consultation and circumcision or a dorsal slit procedure may be necessary. Any evidence of cellulitis or necrosis warrants admission to the hospital, intravenous antibiotics, and urologic consultation. To achieve pain control using a local procedure, a dorsal penile nerve block should be attempted. Injection of anesthetic to the glans will add to the swelling and difficulty with reduction.

173.3. A 5-year-old boy presents with pain, swelling, and redness of his penis. You note inflammation of the glans and foreskin. Which of the following is indicated?
A. Antibiotics, sitz baths, and hydrocortisone cream
B. Complete blood count with differential, blood cultures, and urine cultures
C. Incision and drainage
D. Topical antibiotics and wet to dry dressing
E. Urinalysis and urethral swab

Answer: A. Balanoposthitis is an inflammation that involves the glans and foreskin, whereas balanitis is just involvement of the glans. Infectious organisms include gram-negative and gram-positive organisms, including group A beta-hemolytic streptococci and, rarely, *Neisseria gonorrhoeae* and *Chlamydia.* Management includes emphasis on adequate hygiene with sitz baths to reduce inflammation. In patients with cellulitis, treatment against *Staphylococcus aureus* and *Streptococcus pyogenes* is recommended.

173.4. A 13-year-old boy presents with pain, swelling, and discoloration of his left testicle. Prior to the testicular changes, he had a fever and mild facial swelling. What is the most appropriate next best step in the management of this patient?
A. Admission for antibiotics and serial examinations
B. Color flow Doppler ultrasound
C. Inquiry about sexual encounters
D. Pain management and reassurance
E. Urology consult for surgical management

Answer: B. During the course of mumps, orchitis usually develops after the first week and presents with tenderness and edema of the testis, with discoloration of the scrotum. With the limited information in this case, it is not clear that this patient does not have testicular torsion. Doppler ultrasound may be necessary to distinguish orchitis from testicular torsion. For patients with a clear viral origin such as mumps, treatment is aimed at pain control (eg, scrotal elevation, nonsteroidal antiinflammatory drugs, possibly narcotics).

173.5. Which of the following statements about testicular torsion is false?
A. Indeterminate ultrasound requires urology consult.
B. Intravaginal torsion results from rotation of the testis inside the tunica vaginalis.
C. Most patients with testicular torsion are infants.
D. Predilection for torsion exists if the tunica vaginalis completely covers the testis.
E. The presence of the cremasteric reflex does not preclude torsion.

Answer: C. Most patients are adolescents, although testicular torsion can be seen at any age. If the tunica completely covers the testis and attaches higher up on the spermatic cord, proper testicular fixation does not occur and there is a predisposition to torsion. In intravaginal torsion, the testicle may rotate within the tunica vaginalis and thereby constrict the arterial blood flow. The presence of the cremasteric reflex does not preclude testicular torsion. Results of a urinalysis are rarely helpful because pyuria can be seen in cases of testicular torsion and epididymitis. In cases of indeterminate ultrasound results, the urology consultant should be notified for disposition decisions.

173.6. A mother brings in her 2-year-old child after she noticed a pink tinge on the diaper when she was changing her child. Which of the following is not part of the differential diagnosis?
A. Blueberry ingestion
B. Henoch-Schönlein purpura
C. Red apple ingestion
D. *Serratia marcescens*
E. Urate crystals

Answer: C. Not all red urine contains blood. Certain drugs or foods, such as phenothiazines, ibuprofen, beets, and blueberries, can cause reddish-colored urine; apples, however, do not. In neonates, urate crystals can cause red-tinged urine in the diaper. *Serratia marcescens,* a fecal pathogen, can cause a red pigmentation when left in the diaper. Bleeding from the vagina or rectum can sometimes be mistaken for blood in the urine. Systemic illnesses such as Henoch-Schönlein purpura and hemolytic-uremic syndrome can cause hematuria.

173.7. A 5-year-old boy presents with flank pain and hematuria. He was recently treated with penicillin for a throat infection. Urinalysis demonstrates blood, protein, and red blood cell casts. Which test will be most helpful in establishing a diagnosis in this patient?
A. ASO titer
B. Complement levels
C. Hyaline casts
D. Serum sodium and osmolarity
E. Urine electrolytes

Answer: A. This is likely poststreptococcal glomerulonephritis. The ASO and immunoglobulin G levels should be elevated. Total complement levels, especially C3, are decreased in most patients during the first 2 weeks of the illness. The complement levels should return to normal within 3 or 4 weeks. The blood urea nitrogen (BUN) level is elevated; hyponatremia and hyperkalemia may also be present.

173.8. A 5-year-old girl presents with the complaint of a rash and knee pain. She has a palpable purpuric rash on both her lower extremities to her buttocks. Her knees are minimally swollen, with no increased warmth or limited range of motion. What is the most appropriate disposition for this patient?
A. Admission for parenteral corticosteroids
B. Admission for plasmapheresis
C. Admission if there is severe renal involvement for immunoglobulin administration
D. Admission to the hospital for observation and intravenous doxycycline
E. Supportive treatment and peritoneal dialysis at home

Answer: C. Henoch-Schönlein purpura is an immunoglobulin A–mediated systemic vasculitis involving the small blood vessels supplying the skin, gastrointestinal tract, and joints. The hallmark of Henoch-Schönlein purpura is a palpable, purpuric, or petechial rash most prominent on the lower extremities, starting around

the lateral malleoli and extending to the buttocks. Therapy for patients with severe renal involvement also includes intravenous immunoglobulins, although promising results have also been seen in patients with severe abdominal pain.

173.9. A 3-year-old girl presents with watery diarrhea and crampy abdominal pain. Her vital signs are blood pressure 130/80 mm Hg, heart rate 100 beats/min, respiratory rate 13 breaths per minute, and temperature 38.0° C (100.4° F). The diarrhea has been present for a number of days and has just turned bloody, which prompted the visit today. Laboratory assessment reveals hemoglobin, 6 g/dL, potassium, 6.1 mEq/L, blood urea nitrogen, 40 mg/dL, and creatinine, 2.5 mg/dL. Which of the following tests is most likely to aid in the diagnosis of this patient?

A. Blood cultures
B. Leukocytosis
C. Peripheral smear with schistocytes
D. Stool cultures
E. Thrombocytosis

Answer: C. The patient has hemolytic-uremic syndrome, which is one of the most common causes of acute renal failure in children. It usually involves infants and children, with a mean age at presentation of 3 years, but is rare after 5 years of age. The peripheral blood smear shows microangiopathic changes such as teardrop cells, helmet cells, microspherocytes, and burr cells.

CHAPTER 174

Neurologic Disorders

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Acute presentations of neurologic dysfunction reflect a primary nervous system abnormality or a secondary manifestation of underlying disease. In children, associated history and physical examination findings, as well as diagnostic considerations, are unique and often markedly different than those in adults. This chapter is directed at understanding the pathophysiology and significant clinical features of major neurologic presentations in children. Information will be organized by the most salient clinical manifestations of pediatric neurologic disorders—altered mental status, seizures, headache, ataxia and derangements of balance, and motor dysfunction (Table 174.1).

ALTERED MENTAL STATUS

Principles

Altered mental status is a common and often puzzling pediatric presentation. Groupings of possible causes include vascular events (eg, stroke, arteriovenous malformation with bleed), infection (eg, meningitis, sepsis, encephalitis), trauma, toxic ingestion, anatomic or structural abnormality (eg, intracranial mass or tumor), metabolic derangements, intussusception, or seizures, which may be subclinical. Individual diagnoses associated with altered mental status will not be explored in full detail in this chapter. However, a guideline for approaching and managing patients in the emergency department (ED) with altered mental status will be presented.

Clinical Features

Altered mental status in children has a varied spectrum of clinical presentations and may include abnormalities in cognition, behavior, or memory. In children, these are manifested as an altered level of consciousness, excessive sleepiness, irritability, lethargy, or abnormal behavior. The nature of the altered mental status, as well as the time course and concurrent findings, such as fever or focal neurologic signs, are pivotal in evaluating these patients. Information obtained in the history may be critical to diagnoses of trauma, toxic ingestion, atypical migraine, or infection.

During the initial assessment of an altered infant or child, vital signs can be essential to understanding the underlying diagnosis. Heart rate, blood pressure, and respiratory rate, for example, may provide information about conditions such as toxic ingestion, elevated intracranial pressure (ICP), or metabolic derangements such as diabetic ketoacidosis. Level of consciousness may be readily assessed using the AVPU scale: ***a***lert (alert and spontaneously interactive), ***v***erbal (responds to verbal cues), ***p***ainful (responds only to painful stimuli), ***u***nresponsive (unresponsive to all external stimuli). Additionally, identifying focal neurologic deficits and the presence or absence of fever promptly will aid the health care provider in the diagnostic evaluation.

Special consideration should be given to meningitis in the altered infant or child because presenting signs of meningitis vary widely by age and classic symptoms (eg, vomiting, headache, bulging fontanel, nuchal rigidity) may not be sufficient to guide diagnostic evaluation.[1] Neonates, for example, may or may not have a fever—the absence of fever does not eliminate the possibility of a serious bacterial illness because more than 50% of neonates with meningitis are afebrile or exhibit hypothermia—and often demonstrate vague findings such as poor feeding and increased sleepiness and fussiness in addition to abnormal vital signs. Tachycardia, bradycardia, tachypnea, or apnea are not uncommon. Older infants may show more visible signs of behavioral changes, including decreased social interaction. In children, common findings include fever, headache, vomiting, stiff neck, lethargy, and obtundation. Skin findings of diffuse petechiae and purpura in the ill-appearing pediatric patient should raise a high clinical suspicion for bacterial meningitis. In the ill-appearing or altered infant younger than 3 months, clinical signs are often nonlocalizing and can therefore present a diagnostic challenge. In this age group, there are few distinguishing features to differentiate sepsis from meningitis, metabolic derangements, or an acute abdomen.

Diagnostic Considerations

Differential Diagnoses

The breadth of differential diagnoses associated with altered mental status in children, by definition, involves a broad spectrum of potential management interventions in the ED. The mnemonic AEIOUTIPS, as outlined in Box 174.1, can assist the emergency clinician in the differential diagnosis and determining priorities for management.

Diagnostic Testing

After evaluation and stabilization of the airway, breathing, and circulation, priorities of the emergency clinician include obtaining a bedside glucose test, rapid IV access, and laboratory values, including a full panel of electrolytes. Rapid bedside testing, such as with iStat, can be performed to assess for abnormalities in sodium, potassium, and lactate levels and determine pH. A complete blood count (CBC) and blood culture may also be sent if an infectious cause is suspected, and determining venous blood gases and lactate level can be helpful in assessing acid-base status. Toxicology screens may be warranted in many cases. The decision to obtain head imaging—by computed tomography (CT) or magnetic resonance imaging (MRI)—rapidly in the ED is made based on the presence of focal neurologic deficits, in conjunction with a history and examination suggestive of an acute intracranial process.

Special consideration should be made regarding the need for more invasive diagnostic procedures such as lumbar puncture (LP) in this setting. Bacterial meningitis is a medical emergency that may present with altered mental status, and all children with suspected bacterial meningitis should have a lumbar puncture performed unless it is contraindicated. Contraindications to an LP include signs of elevated ICP, focal neurologic deficits on examination, and underlying coagulopathy. Antibiotic therapy for

TABLE 174.1

Common Pediatric Presentations and Associated Differential Diagnoses

PEDIATRIC PRESENTATION	UNDERLYING DIAGNOSES TO CONSIDER
Altered mental status	Vascular event (stroke, arteriovenous malformation, intracranial bleed) Infection (meningitis, sepsis, encephalitis) Trauma Ingestion (toxin, medication) Seizures (clinical or subclinical) Structural/anatomical (intracranial mass/tumor, hydrocephalus) Metabolic derangements (eg, diabetic ketoacidosis, hypoglycemia, urea cycle defect) Intussusception
Seizure	Infection (meningitis, sepsis, encephalitis) Metabolic derangement Ingestion Trauma Intracranial mass Antiepileptic dose or medication effect (in patient with known seizure disorder)
Headache	Nonpathologic: due to stress, inadequate sleep, dehydration, fever, viral infection Migraine Trauma, concussion Intracranial mass Infection (eg, meningitis, sepsis, encephalitis)
Ataxia/disorders of balance	Postviral, postinfectious syndrome Intracranial mass Ingestion Metabolic disorders
Motor dysfunction, weakness	Vascular event (stroke) Spinal cord dysfunction (eg, secondary to trauma, infection, autoimmune disorder) Infection-related (eg, Guillain-Barré syndrome, Lyme disease, botulism) Idiopathic (Bell's palsy)

BOX 174.1

AEIOU TIPS Mnemonic for Altered Mental Status in Children

A–**a**mmonia, **a**lcohol, **a**typical migraine, **a**buse
E–**e**lectrolytes, **e**pilepsy, **e**ncephalitis
I–**i**nsulin (hypoglycemia), **i**ntussusception, **i**nborn errors of metabolism
O–**o**xygen (hypoxia), **o**piates, **o**verdose
U–**u**remia
T–**t**rauma, **t**umor
I–**i**nfection
P–**p**oisoning, **p**sychiatric
S–**s**eizure, **s**epsis, **s**ubarachnoid hemorrhage

the patient with suspected bacterial meningitis should not be delayed by an LP.

Due to the difficulties in assessing ill-appearing infants younger than 3 months, a broad initial evaluation may be necessary for altered mental status in this population, including CBC, chemistries, LP, and pan cultures (blood, urine, and cerebrospinal spinal fluid [CSF]). It is important to note that in the case of the ill-appearing infant, blood cultures and LP should be undertaken concomitantly due to the increased risk of serious bacterial infection in this population, including bacteremia and meningitis. For older infants and children, the risk of bacterial meningitis may be evaluated using clinical prediction rules based on laboratory results.[2] Additionally, if the history or physical examination raises any concern for an acute abdominal process, abdominal ultrasound should be performed to evaluate for intussusception because its presentation is often nonspecific and can resemble that of meningitis or sepsis.

Management

After the initial resuscitation, including stabilization of the airway, breathing, and circulation, data obtained by the history, physical examination, and early laboratory values often dictate the first steps in management. If there is a known toxic ingestion, efforts will quickly be directed at the correction of perturbations associated with the offending agent and, if indicated, toxin removal. If initial laboratory values indicate hyperglycemia, hypoglycemia, or other electrolyte imbalances, early measures should be aimed at correcting these. The abdominal examination may reveal a surgical abdomen as the cause of altered mental status, necessitating the need for ultrasound, CT, or direct surgical consultation. Head imaging, if performed, may also guide early management steps further.

A lumbar puncture is indicated in any child for whom bacterial meningitis is suspected. Antibiotic therapy in the ED should not be delayed by an LP in a case of highly suspected bacterial meningitis.[3] Additionally, initial antibiotic coverage should be broad and guided by the most likely pathogens in the patient's age group (Tables 174.2 and 174.3). Pretreatment with antibiotics in patients with bacterial meningitis is associated with higher CSF glucose levels and lower CSF protein levels, but does not alter the CSF white blood cell count, absolute neutrophil count, or polymerase chain reaction (PCR) results. Over time, antibiotics will affect sensitivity of CSF cultures, but this does not justify treatment delay. The role of steroids, particularly dexamethasone, in conjunction with antibiotic therapy for the treatment of acute bacterial meningitis, is controversial. It is therefore best to adhere to the latest recommendations of the American Academy of Pediatrics (AAP) and limit the use of dexamethasone to the presumptive treatment of pneumococcal meningitis in infants older than 6 weeks after consideration of the potential benefits and risks. The AAP has suggested that dexamethasone may also be beneficial for infants and children with *Haemophilus influenzae* meningitis to decrease the risk of neurologic sequelae, including hearing loss, if is given before or concurrently with the first dose of an antimicrobial agent.[3,4] In this setting, a child's immunization history, as well as the CSF Gram stain results, may serve to guide the appropriate use of steroids.

When bacterial meningitis is in the differential diagnosis of altered mental status, but not highly suspected, it is reasonable to consider risk stratification of the patient to determine if antibiotics can be withheld until further information (eg, CSF white cell count) is obtained. Finally, acyclovir should be administered to an

TABLE 174.2

Bacterial Meningitis: Common Causative Pathogens by Age

AGE GROUP	PATHOGENS
Newborns	Group B *Streptococcus, Escherichia coli* (most common), *Listeria monocytogenes*
Infants and children	*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae* type B
Adolescents and young adults	*N. meningitidis, S. pneumoniae*

Adapted from Greenhow TL, Hung YY, Herz AM, et al: The changing epidemiology of serious bacterial infections in young infants. Pediatr Infect Dis J 33:595–599, 2014.

TABLE 174.3

Bacterial Meningitis: Initial Empirical Antibiotic Coverage by Age

AGE	ANTIBIOTIC
0–28 days	Ampicillin *plus* gentamicin *or* cefotaxime
28 days–3 mo	Ampicillin or vancomycin (if s. pneumoniae suspected) *plus* cefotaxime *or* ceftriaxone
≥3 mo	Cefotaxime *or* ceftriaxone *plus* vancomycin

Adapted from Kim KS: Acute bacterial meningitis in infants and children. Lancet Infect Dis 10:32–42, 2010.

ill or febrile infant with a history of maternal herpes simplex virus (HSV) infection, presence of vesicles on the skin, seizures, or focal neurologic signs.

Disposition

All patients with altered mental status should be admitted to the hospital for evaluation for the cause. In selected cases, when the cause of the altered mental status is self-limiting, such as a febrile seizure, the patient may be observed and discharged home once the mental status normalizes.

SEIZURES

Principles

Seizures are the most common pediatric neurologic disorder; up to 10% of children suffer at least one seizure in the first 16 years of life, most of which are febrile seizures. A seizure is defined as a paroxysmal event characterized by temporary involuntary changes in the patient caused by abnormal and excessive activity of a group of cortical neurons. The clinical manifestations of the seizure depend on the location and extent of brain involvement and may include alterations in behavior, motor activity, level of consciousness, or autonomic function. Seizures are classified as provoked or unprovoked. Provoked seizures are caused by an identifiable trigger and stem from a broad array of disturbances, including fever, metabolic derangements, and trauma. Unprovoked seizures have no clear immediate precedent. Epilepsy is commonly defined as the occurrence of two or more unprovoked seizures.

The underlying pathophysiologic feature of all seizures is excessive, synchronous electrical neuronal discharge. Infants and children younger than 5 years are thought to be more susceptible to seizures due to an immature nervous system, in which excitatory neuronal activity predominates and inhibitory systems are undeveloped. A paucity of synaptic connections and alterations in the synthesis of neurotransmitters may play a role in a child's susceptibility to seizures.

TABLE 174.4

Classification of Seizures

TYPE	TYPE
Generalized	Tonic clonic Absence Myoclonic Clonic Tonic Atonic
Focal	Simple partial (normal mental status) Complex partial (altered mental status)
Unknown	Epileptic spasms

Clinical Features

In the presence of ongoing seizure activity, resuscitation measures to ensure a patent and protected airway, stable circulation, and seizure control should be initiated. To determine whether an event was truly a seizure, the initial assessment should include an effort to obtain a description from an eyewitness. The history should include any known risk factors for epilepsy or prior seizures, details leading up to the event, a full description of the episode itself (including nature of body movements, duration, and associated symptoms, such as urinary incontinence), and characterization of the moments immediately following the event, with special attention to mental status, event recall, and lethargy or confusion. If the patient has a known seizure disorder, recent medication changes—including new medications as well as dose or interval adjustments of existing medications—should be identified, as well as missed or extra doses.

The physical examination should concentrate on signs of systemic disease that can cause seizure, including evidence of meningitis, trauma, drug ingestion, dehydration, hypertension, and heart disease. Skin lesions, such as café au lait spots or hypopigmented nevi, may indicate a neurocutaneous disorder. An abnormal head circumference may indicate hydrocephalus or abnormal brain growth. A careful neurologic examination should assess for signs of increased ICP and focal neurologic deficits.

If the presenting signs and symptoms are consistent with seizure activity, the seizure can then be classified by type and a cause pursued. Seizures are classified into two main types, partial (consciousness is maintained) and generalized (consciousness is lost; Table 174.4).

There are two types of partial, or focal, seizures, complex and simple. In complex partial seizures, the patient experiences a change in level of awareness and may exhibit bizarre behaviors, including staring, lip smacking, wandering, or picking at clothing. In simple partial seizures, the patient experiences no change in mentation. An important subcategory of focal seizures is composed of benign focal epilepsies of childhood, which are functional in nature; that is, they do not result from abnormalities in brain structure or injury to the brain. Benign focal epilepsies spontaneously resolve over time; benign childhood epilepsy with centrotemporal spikes (also called benign rolandic epilepsy) is most common and represents 10% to 20% of all childhood epilepsies.[5,6]

Generalized seizures may be convulsive or nonconvulsive. A convulsive seizure may start focally and generalize secondarily.

TABLE 174.5

Causes of Acute and Remote Symptomatic Seizures

CAUSE	EXAMPLES
Fever (febrile seizure)	
• Infectious process	Meningitis, encephalitis, brain abscess
• Traumatic lesions	Cerebral contusion, hemorrhage (subdural, epidural, subarachnoid, intraparenchymal), impact seizure
Toxic conditions	Drug intoxication, drug withdrawal
Metabolic disturbances	Hypoglycemia, hyponatremia, hypernatremia, hypomagnesemia, hypophosphatemia, hepatic or renal disorder, inborn errors of metabolism (eg, aminoacidurias, organic acidurias, mitochondrial disease)
Neoplastic disease	
• Vascular disorders	Arteriovenous malformation, subarachnoid hemorrhage, intraparenchymal hemorrhage, cerebral venous thrombosis, ischemic infarct, hypertensive encephalopathy
• Neurocutaneous disorder	Neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome
Neurodegenerative disorders—miscellaneous	Hypoxia, ventriculoperitoneal shunt malfunction, cerebral palsy, cerebral dysgenesis, primary epilepsy

The most common type of generalized nonconvulsive seizures is absence seizures. Absence seizures are marked by a brief arrest of consciousness and movement, typically lasting 5 to 30 seconds; no postictal drowsiness occurs. It may be difficult to differentiate a brief complex partial seizure, in which a child may stare and not respond, from an absence seizure.

The frequency of seizures is higher in the first month of life than at any other time in childhood. Neonatal seizures may be subtle; apnea, sustained eye deviation, chewing, or limb bicycling movements may be the only apparent signs. There is a high incidence of subclinical electroencephalographic seizures in this population. Focal clonic movements are often associated with an underlying structural lesion. Although there are many causes of neonatal seizures, relatively few account for most cases. These include hypoxic-ischemic encephalopathy, intracranial infection, congenital brain malformation, cerebrovascular events, electrolyte disturbances, metabolic derangements, and nonaccidental trauma.

Seizures can be further divided into three main categories—acute symptomatic, remote symptomatic, and idiopathic seizures (Table 174.5). Acute symptomatic seizures are provoked by an acute event such as fever. Remote symptomatic seizures are due to a preexisting or remote central nervous system (CNS) lesion such as cerebral palsy or a congenital brain malformation. Idiopathic seizures have no identifiable cause.

Categories of Seizures

Acute Symptomatic Seizures

Fever is the most common cause of acute symptomatic seizures affecting up to 5% of children. A febrile seizure is defined as a seizure occurring in the presence of fever without CNS infection or other cause. A simple febrile seizure is generalized, lasts less than 15 minutes, and occurs in a neurologically and developmentally normal child between 6 months and 6 years of age.

Simple febrile seizures typically occur early in the course of illness. Temperature does not need to be markedly elevated; almost 50% of children with a febrile seizure have a documented temperature below 39°C (102.2°F). Complex febrile seizures are diagnosed when multiple seizures occur during the same illness, the seizures are longer than 15 minutes, or the seizures have a focal component.

Meningitis should be considered in any patient with seizures and fever, although a child whose mental status is normal before and after the seizure is very unlikely to have meningitis. We recommend evaluation and treatment for meningitis in infants younger than 3 months presenting with febrile seizures. They are not only at higher risk for serious bacterial infections, including meningitis, but their mental status is difficult to assess accurately.

Inborn errors of metabolism and metabolic or electrolyte derangements are also a common cause of seizures in children. Hypoglycemia, hyponatremia, and hypernatremia are associated with seizures. Dehydration is the most common cause of hypernatremia. Hypocalcemia and hypomagnesemia may lead to muscle spasms, paresthesias, hyperactive reflexes, weakness, tetany, or seizures. Hypocalcemic seizures are a common cause of neonatal seizures.

Posttraumatic seizures occur in as many as 15% of children after head injury. Impact seizures, occurring within 1 hour of a head trauma, are not associated with significant injury or with the development of epilepsy. It may be difficult to distinguish these from seizures associated with intracranial injury, and a CT scan of the head without contrast enhancement should be considered. Early posttraumatic seizures, occurring within the first week of injury, may arise from cerebral edema or intracranial hemorrhage or contusion.

Brain tumors cause a wide variety of symptoms, depending on their location and type of tumor. Infratentorial tumors, the most common location in the pediatric population, do not typically cause seizures.

Although rare, a seizure may be the presenting sign of stroke. Congenital heart disease, sickle cell anemia, moyamoya disease, and homocystinuria are some of the major risk factors for ischemic stroke in children. Vascular malformations, such as arteriovenous malformations, may cause hemorrhagic stroke or subarachnoid hemorrhage.

Numerous drugs are known to cause seizures. Cyclic antidepressants, cocaine and other stimulants, antihistamines, and isoniazid are the most common agents of drug-induced seizures. Seizures may occur during drug withdrawal, usually within 48 hours of drug cessation. Withdrawal of benzodiazepines and barbiturates leads to an abstinence syndrome similar to ethanol withdrawal.

Reflex seizures are precipitated by a specific, identifiable stimulus. For example, flashing lights on television or video games may induce seizures in photosensitive children.

Convulsive status epilepticus is a true neurologic emergency. It is associated with high morbidity and mortality rates that increase with the duration of seizure activity. For clinical practice purposes, status epilepticus is typically defined as 5 minutes or more of continuous seizure activity (clinical or electroencephalographic) or recurrent seizure activity without return to baseline between seizures. Although the diagnosis of convulsive status epilepticus usually is obvious, the duration of the seizures is often underestimated because the intensity of the jerking tends to diminish with time.

Status epilepticus occurs significantly more frequently in children than in adults, particularly in those younger than 1 year[7]; febrile illness is the most common precipitant of status epilepticus in

TABLE 174.6

Episodic Disorders That May Mimic Seizures

AGE GROUP	FEATURES
Neonates	Jitteriness Benign neonatal sleep myoclonus Nonepileptic apnea Opisthotonos Normal movement
Nonneonates	Breath-holding spells Rigors or chills Gastroesophageal reflux (Sandifer's syndrome) Migraine Benign paroxysmal vertigo of childhood Syncope Neurovascular event Sleep disorders Sleep myoclonus Narcolepsy Nightmares, night terrors, somnambulism Movement disorders Tics or stereotypies Infantile shuddering attacks Paroxysmal choreoathetosis or dystonia Psychological Psychogenic seizures Panic attack

children. Medication change (often antiepileptic medications), toxic ingestion, idiopathic epilepsy, metabolic derangements, and congenital abnormalities are the next most common. Nonconvulsive status epilepticus is marked by an altered mental status. Patients may demonstrate confusion, unresponsiveness, abnormal motor movements, twitches, lip smacking, or automatisms. An electroencephalogram (EEG) can confirm the diagnosis and should be obtained if nonconvulsive status is suspected.

Remote Symptomatic Seizures

Causes of remote symptomatic seizures include congenital brain malformations, neurocutaneous disorders, cerebral palsy, and neurodegenerative disease.

Diagnostic Considerations

Differential Diagnoses

Paroxysmal events that affect children and involve alterations in level of consciousness or motor activity may be confused with seizure activity (Table 174.6). Syncope is most commonly mistaken for a seizure; it is characterized by a sudden loss of consciousness and motor tone caused by a transient, global cerebral hypoperfusion. The patient will often complain of lightheadedness and blurry vision and may appear pale and sweaty prior to losing consciousness. Brief jerking movements are possible with syncopal events, but should not be prolonged. Postictal confusion does not occur, but trembling and stiffening are common. Vasovagal syncope is common in otherwise healthy children and does not warrant further evaluation unless recurrent. Cardiogenic syncope, such as prolonged QTc syndrome, is potentially fatal. Syncope should be considered if there is no postictal period or tonic-clonic activity, if the event occurred during exercise, or if palpitations were present.

Breath-holding spells occur in up to 5% of children and are triggered by pain or emotional upset. The first episode usually occurs between the ages of 6 and 18 months, with episodes lasting up to 6 years of age. After a trigger, the child becomes pale or cyanotic and may lose consciousness, sometimes with a brief period of clonic movements or opisthotonos. The average attack lasts approximately 40 seconds. A history of recurrent episodes associated with crying may be helpful in distinguishing these from seizures or other apparent life-threatening events (ALTEs).

Migraines may mimic seizures, particularly when they are accompanied by an aura, motor dysfunction, clouding of consciousness, or vomiting.

Disorders of sleep are distinguished by excessive daytime sleepiness or by disordered nighttime sleep. In narcolepsy, daytime sleep attacks, sleep paralysis, hypnagogic hallucinations (vivid hallucinations while falling asleep), and cataplexy (sudden loss of motor tone) occur. Cataplexy may be mistaken for atonic or absence seizures. Nocturnal enuresis may raise concern for an unwitnessed nighttime seizure associated with incontinence. In night terrors (pavor nocturnus), the child suddenly wakens, crying inconsolably, and is relatively unresponsive. The child returns to sleep and does not typically recall the event. Sleepwalking (somnambulism) and sleeptalking (somniloquy) are common among school-age children.

Movement disorders may mimic seizures. Tics are rapid, repetitive, brief involuntary movements that occur intermittently and in flurries. Those most commonly seen are eye blinking and head shaking. Patients do not lose consciousness. Sydenham's chorea is an autoimmune-mediated systemic inflammatory response that occurs in association with a group A streptococcal pharyngitis infection. It typically manifests with irregular, nonrhythmic, involuntary jerking of the extremities and face and may present during the acute phase of the streptococcal infection or as a latent manifestation months after the initial illness. Shudder attacks are uncommon but are easily mistaken for seizures. The movement is that of the chill experienced when cold water runs down the back. Paroxysmal choreoathetosis is an abnormal motor movement that may be spontaneous or triggered by the child's movement.

Behavioral or psychiatric disturbances can produce behaviors that may appear epileptic. Panic attacks may be mistaken for complex partial seizures. The patient has a sudden sensation of intense fear accompanied by shortness of breath, dizziness, palpitations, sweating, choking, chest discomfort, and fear of dying. Psychogenic seizures are involuntary events that mimic seizures. Many children with psychogenic seizures also have epileptic seizures. Prolonged electroencephalographic monitoring may be necessary to differentiate an epileptic seizure from a psychogenic seizure.

Infants with gastrointestinal reflux may exhibit Sandifer's syndrome, characterized by episodes of abnormal posturing, arching of the back, and torticollis.

Management

The initial management of any actively seizing child involves ensuring patency of the airway, adequate oxygenation and ventilation, and support of circulation. Oxygen should be applied via cannula or face mask and intravenous (IV) or intraosseous (IO) access quickly obtained. Monitoring end-tidal carbon dioxide may be helpful to assess ventilatory status. Patients with ongoing convulsions are at risk for hypoventilation and apnea, and preparations should be made to assist ventilation. The administration of IV fluids should be approached cautiously, given the potential risk for increased ICP.

Hypoglycemia causing seizures in infants and children is treated with an IV bolus of 10% dextrose, 2 mL/kg, with repeat boluses as needed to normalize the serum glucose level. Severe symptomatic hyponatremia may be treated with the administration

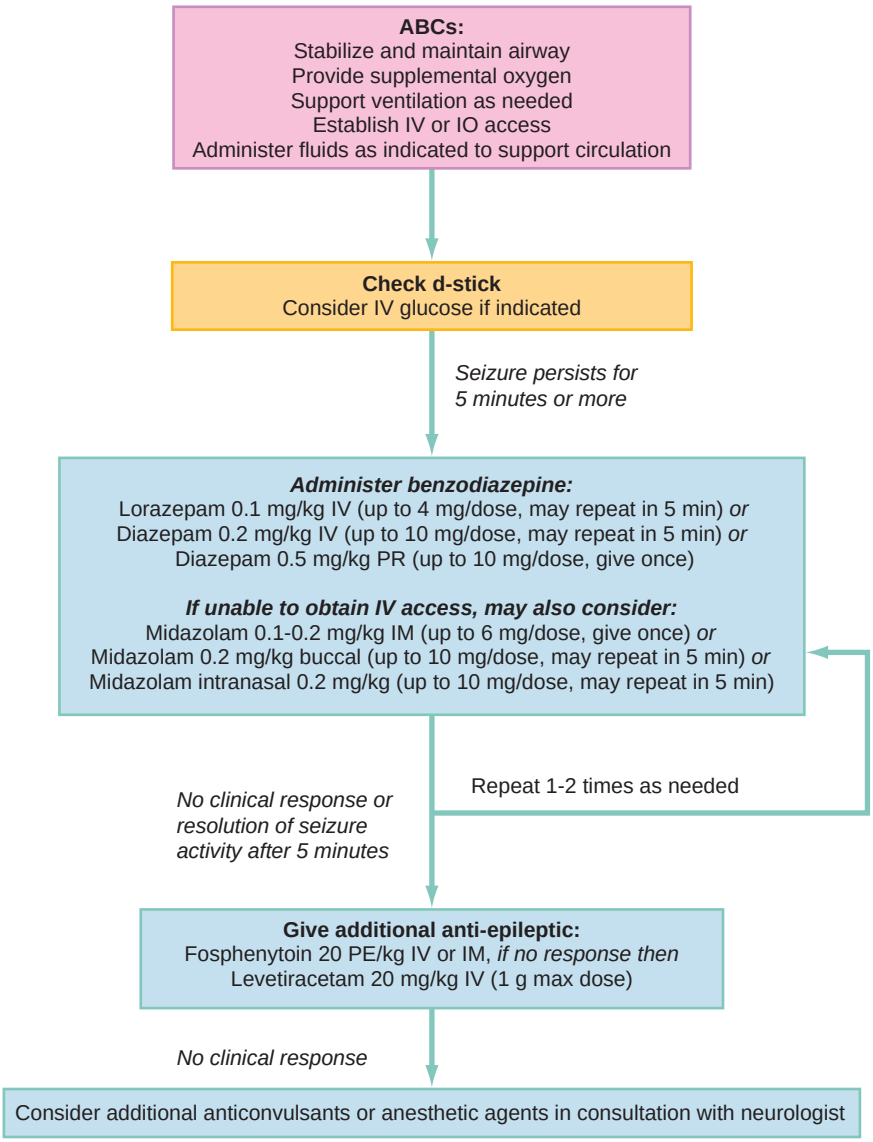

Fig. 174.1. Management of status epilepticus in infants and children. *IO,* Intraosseous; *IV,* intravenous. (Adapted from Chapman MG, Smith M, Hirsch NP: Status epilepticus. Anesthesia 56:648–659, 2001.)

of 3% saline (2 mL/kg IV infused over 30 minutes) to raise the serum sodium level by 3 to 7 mEq/L. The remainder of the correction should occur slowly during the next 24 hours or more with the goal of correcting serum sodium levels by 6–8 mEq/L per 24-hour period. Hypernatremia is corrected slowly during 48 hours. Hypocalcemia is treated with 10% calcium gluconate, 100 mg/kg IV; the patient should be on a cardiac monitor during the infusion. Toxic ingestions are treated based on the specific toxin involved. Seizures caused by isoniazid (INH) poisoning are particularly resistant to standard seizure treatment, yet respond to pyridoxine. The dose of pyridoxine is 1 g IV for every gram of INH ingested. When the quantity of INH ingested is unknown, 5 g IV may be administered to an adult and 70 mg/kg (maximum, 5 g) to a child.

Status Epilepticus

Status epilepticus is a true medical emergency. The patient should be positioned to maximize ventilation and prevent aspiration. The cervical spine should be protected in a case of suspected trauma. Oxygen should be administered by nasal cannula or face mask. A large suction catheter should be available to suction oropharyngeal secretions. In younger patients, the tongue may obstruct the airway; a nasopharyngeal airway will keep the tongue forward and improve respiratory status. If facial trauma is present, a nasopharyngeal airway may be contraindicated.

If there is evidence of increased ICP, the airway is compromised, or respiratory failure occurs, the patient should be intubated. When clinically appropriate, short-acting neuromuscular blockers should be used to permit continued monitoring of seizure activity.

Heart rate, blood pressure, respiratory rate, and pulse oximetry should be monitored and hyperthermia treated with antipyretics and cooling blankets. An IV line should be placed and blood samples sent for electrolyte values, glucose concentration (including rapid blood glucose test), calcium and magnesium levels, renal function tests, liver function tests, antiepileptic levels (if indicated), and CBC. Urine should be sent for toxicology. Metabolic abnormalities should be corrected.

Anticonvulsant treatment should begin as quickly as possible (Fig. 174.1).[8,9] Benzodiazepines, particularly lorazepam and diazepam, are the initial drugs of choice in the treatment of status epilepticus; they diffuse quickly into the CNS, rapidly terminating seizure activity 70% of the time. Hypotension,

respiratory depression, and impaired consciousness may occur. Rectal diazepam may be used if IV or IO access cannot be obtained. The dosage is 0.5 mg/kg (maximum, 20 mg). If Diastat, a rectal preparation of diazepam, is not available, the IV preparation may be instilled through a lubricated feeding tube inserted 4 to 6 cm into the rectum. Often, IV access is difficult; in such cases, intramuscular, intranasal, or buccal midazolam may also be effective.[10-13] Recommended doses for these non-IV preparations are shown in Fig. 174.1.

If the seizure continues for 5 minutes or more, or if there is cardiorespiratory compromise with the continued seizure activity, give a second dose of benzodiazepine. If the seizure persists after 5 minutes of giving the second benzodiazepine dose, administer a third benzodiazepine dose or load with fosphenytoin; use phenytoin if fosphenytoin is not available. Patients who already are receiving phenytoin should receive phenobarbital, 20 mg/kg, instead. Fosphenytoin is a water-soluble phosphate ester of phenytoin that is rapidly converted in plasma to phenytoin. Unlike phenytoin, fosphenytoin can be administered intramuscularly and with common IV solutions and is substantially less cardiotoxic and less sclerosing to the vasculature. In addition, it can be given three times more rapidly than phenytoin. Fosphenytoin produces plasma concentrations similar to those achieved for phenytoin in the same time. The standard loading dose of fosphenytoin is 20 PE (phenytoin equivalent)/kg at 3 PE/kg/min (maximum, 150 PE/min). The loading dose of phenytoin is 20 mg/kg at a rate of 1 mg/kg/min (maximum, 50 mg/min). If the seizure continues after administration of fosphenytoin, a third drug is loaded. The most commonly used drug is phenobarbital at a loading dose of 20 mg/kg at a rate of 2 mg/kg/min (maximum dose, 60 mg/min).

Because phenobarbital can cause apnea, depressed consciousness, and hypotension, all of which are more pronounced in the presence of benzodiazepines, continuous cardiorespiratory monitoring is imperative. Other options for the third medication have begun to take precedence. These include valproate sodium and levetiracetam. Valproate sodium is contraindicated in the presence of liver disease, thrombocytopenia, or possible metabolic disease. If the seizure continues, a different third-line medication such as midazolam is used or a pharmacologic coma may be induced, with continuous, concurrent, electroencephalographic monitoring after establishing a definitive airway.

Refractory status epilepticus poses a great challenge to the emergency clinician and should be managed in conjunction with a neurologist and electroencephalographic monitoring, if possible. Additional agents that may be helpful in the management of status epilepticus refractory to midazolam or pentobarbital infusions include general anesthetics such as propofol. Nonconvulsive status epilepticus is more difficult to recognize and often requires electroencephalography for diagnosis. Treatment is with benzodiazepines or IV valproic acid. Once the seizure has been effectively terminated, neuroimaging and lumbar puncture are often indicated to elucidate the cause of the seizure further.

Febrile Seizures

Children with simple febrile seizures do not require blood and urine testing other than as needed for the evaluation of fever source. According to newer AAP recommendations, LP is not necessary in children older than 12 to 18 months in whom clinical findings are not suggestive of meningitis. In immunized infants 6 to 18 months of age with a first-time simple febrile seizure, LP can be avoided if the child is not ill-appearing, has returned to baseline, and there are no clinical signs of meningitis.[14] Additional consideration of the need for LP should be made for children between 6 and 12 months of age whose vaccination status for *H. influenzae* type b or *Streptococcus pneumoniae* is incomplete and in children who have been pretreated with antibiotics. Electroencephalography and neuroimaging generally are not required after a first simple febrile seizure.

Afebrile Seizures

In many cases, the history and physical examination alone will serve to guide further testing. For infants and children older than 6 months who have had a first-time nonfebrile seizure and have returned to baseline, laboratory testing should be pursued in a targeted manner, based on clinical and historical findings. A seizure in the setting of recent diarrhea may warrant examination of serum chemistries for possible electrolyte abnormalities. All pediatric patients with a first-time afebrile seizure should have toxicology screening performed unless the history or examination strongly excludes this possibility.[15,16] A lumbar puncture should be considered for patients presenting with unprovoked seizures who demonstrate persistent abnormal mental status, do not return to baseline, or show signs of meningitis.[7,16] An outpatient EEG may be appropriate in well-appearing children who have returned to baseline.

Emergent neuroimaging should be performed in patients with new focal neurologic deficits, persistent altered mental status, recent trauma, persistent headache, or partial seizures.[16] Infants and children who present in status epilepticus not related to fever should have neuroimaging.[17] Children with generalized unprovoked seizures and normal examination findings on presentation do not necessarily require acute imaging. A focal abnormality on follow-up EEG may indicate a need for neuroimaging, which can be done on an outpatient basis. Children with a history of epilepsy do not need neuroimaging unless there is a change in clinical status.

If imaging is indicated in the acute period, CT or MRI may be used. Although MRI provides superior anatomic detail, sedation is commonly needed for the pediatric patient, impeding assessment of the patient's mental status. Therefore, CT, which provides rapid imaging and is highly sensitive for the detection of acute blood and fractures, is often the initial imaging study of choice.

Neonatal Seizures

The common underlying causes of neonatal seizures differ from those in older children and adults (Box 174.2). In addition to congenital abnormalities, metabolic derangements, and birth-related injuries, neonatal seizures may be the only presenting sign of nonaccidental trauma. Diagnostic assessment of neonatal seizures is broad and includes metabolic testing (blood and urine), CSF analysis, and neuroimaging. Glucose, calcium, magnesium, and electrolyte levels (basic chemistry, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen [BUN] and creatinine), and CBC should be obtained; lactic acid, ammonia, and pH determinations should be considered. Because clinical assessment for meningitis is not reliable in young infants, lumbar puncture should be performed and fluid sent for cell, protein, and

BOX 174.2

Common Causes of Neonatal Seizures

Hypoxic ischemic encephalopathy
Central nervous system infection
Intracranial hemorrhage
Trauma (accidental and nonaccidental)
Cerebral infarction
Chromosomal or congenital brain abnormalities
Inborn errors of metabolism or other metabolic derangements
Drug withdrawal or intoxication

glucose determinations, culture, and herpes simplex PCR assay. Head CT or MRI should also be performed. In the unstable neonate, a head ultrasound may be performed at the bedside to evaluate for a neurosurgical emergency until more definitive imaging can be obtained.

Empirical antibiotic therapy should be started in infants with suspected meningitis (see previous section). Acyclovir (20 mg/kg/dose IV tid) is initiated if herpes encephalitis is a clinical concern—CSF pleocytosis, continued seizures with no other clear cause, or concerning maternal history; CSF red cells are a late and ominous finding.

Electrolyte abnormalities, including hypoglycemia, hypomagnesemia, and hyponatremia, should be promptly corrected. Hypoglycemia is treated with 2 mL/kg of 10% dextrose solution IV. Hypocalcemia is corrected with 10% calcium gluconate (1 mL/kg over 5 to 10 minutes, with monitoring of the heart rate and infusion site) or calcium chloride (0.2 mL/kg). Caution should be used when administering calcium chloride because it can be highly caustic to peripheral veins. Hypomagnesemia, which may be associated with hypocalcemia, is treated with a 0.25-mL/kg dose of 50% solution magnesium sulfate injected intramuscularly (to avoid arrhythmias associated with intravenous administration).

Phenobarbital is the usual drug of choice for neonatal seizures. A loading dose of 20 mg/kg should be given; additional doses of 5 mg/kg may be given every 15–30 minutes up to a maximum of 30 mg/kg, if needed. It may be necessary to support respirations with additional doses. If seizures continue, fosphenytoin, 20 PE/kg, may be loaded. Lorazepam, 0.1 mg/kg IV, may be useful but is associated with hypotension and respiratory depression. Refractory seizures may be treated with a midazolam infusion.[18] At this point, continuous electroencephalographic recording should be instituted. If seizures are refractory to medical treatment, empirical treatment with pyridoxine, 100 mg IV, should be considered.

Disposition

Hospitalization is unnecessary for most patients after a first unprovoked seizure as long as the neurologic examination is normal and follow-up evaluation arranged. Electroencephalography and imaging studies can be performed on an outpatient basis. Children with simple febrile seizures can almost always be sent home. Guidance for families should include likelihood of recurrence, development of afebrile seizure, fever control, and emergency measures for seizure. For the child who has had a prolonged febrile seizure or cluster of seizures, a prescription for rectal diazepam can be given for outpatient use after consultation with the child's neurologist or primary care physician. Parents should give Diastat only if a seizure continues beyond 5 minutes.

Children who have had a prolonged seizure or who are not back to their baseline within a few hours should be admitted to the hospital. Hospitalization should also be considered if adequate follow-up evaluation cannot be arranged or in the case of extreme parental anxiety.

Neonates with seizures require admission and continuous cardiorespiratory monitoring.

Anticonvulsant Therapy at Discharge

The decision to start anticonvulsant prophylaxis should balance the risk for the recurrence of seizures against the potential complications associated with long-term medication use and should be done in consultation with a pediatric neurologist. Side effects of medications are common and include sedation, dizziness, blurred vision, ataxia, gastrointestinal disturbances, and cognitive and behavioral changes. Idiosyncratic reactions include hepatotoxicity, agranulocytosis, aplastic anemia, rash, Stevens-Johnson syndrome, and serum sickness.

TABLE 174.7

Commonly Used Anticonvulsants in Children

DRUG	SEIZURE TYPE	TYPICAL DAILY DOSE (mg/kg)[a]	THERAPEUTIC LEVEL (μg/mL)
Carbamazepine (Tegretol)	Partial, GTC	10–20 (max 1000 mg/day)	6–12
Ethosuximide (Zarontin)	Absence	15–30 (max 1500 mg/day)	40–100
Phenobarbital	Partial, GTC	3–6	15–40
Phenytoin (Dilantin)	Partial, GTC	4–10	10–20
Valproic acid (Depakene, Depakote)	Atonic, GTC	15–40	40–120
Lamotrigine (Lamictal)	Partial, GTC, absence, Lennox Gastaut syndrome	5–15 (1–5 if taking valproic acid)	Not routinely measured
Levetiracetam (Keppra)	Partial, GTC, myoclonic	20–40	Not routinely measured
Topiramate (Topamax)	Partial, GTC, myoclonic, Lennox Gastaut syndrome	5–9	Not routinely measured
Clonazepam (Klonopin)	GTC, atonic, myoclonic	0.05–0.2	Not routinely measured

[a]Starting doses for each drug may be lower than typical daily dose, and typical daily doses may fall outside the ranges noted in accordance with the child's underlying medical conditions and other medications.
GTC, Generalized tonic-clonic.

Two-thirds of children with a first unprovoked seizure never experience a recurrence.[19] The risk for recurrence is increased with the presence of neuroimaging or electroencephalographic abnormalities, developmental delay, family history of epilepsy, remote symptomatic seizure, first seizure occurring during sleep, or Todd's paralysis. If none of these risk factors is present, the 5-year recurrence risk is only 21%. There is no evidence that early treatment with anticonvulsant medications after a single seizure alters the risk of epilepsy, nor is there evidence to show that a single self-limited seizure causes neurologic sequelae. In light of these considerations, anticonvulsants are generally started after a second unprovoked seizure.

Patients with acute symptomatic seizures associated with a risk factor for recurrence, such as cerebral hemorrhage, meningitis, or contusion, should be treated in the hospital with prophylactic anticonvulsants, such as phenytoin or fosphenytoin. The decision to continue treatment should be made once the patient is stable.

The choice of medication is dictated by the seizure type and syndrome and the side effect profile of the agent (Table 174.7). Drug levels should be monitored with many anticonvulsants. Of the older medications, phenytoin, phenobarbital, valproic acid, and carbamazepine are all excellent medications for the treatment of generalized or partial seizures. However, phenytoin is a poor long-term choice for children because of the development over time of hirsutism, gum hyperplasia, and facial coarsening. Phenobarbital is rarely used in children older than 2 years because of

the high rate of hyperactivity, sleep disturbances, and lowered intelligence quotient (IQ). Because of its consistent absorption and excellent safety profile, phenobarbital is frequently used in neonates and young infants. Carbamazepine, an older medication, is the first choice for the management of partial epilepsy. (Of note, carbamazepine and phenytoin can worsen absence and myoclonic seizures.) Valproic acid is a first-line treatment for primary generalized epilepsy and is particularly useful for myoclonic and absence seizures. Because valproic acid has a relatively high incidence of hepatotoxicity, particularly in children younger than 2 years, as well as significant teratogenicity, newer anticonvulsants are often used first. Ethosuximide is the drug of choice for absence seizures, but is not effective for convulsive seizures.

Additional anticonvulsants include gabapentin, felbamate, lamotrigine, topiramate, zonisamide, oxcarbazepine, levetiracetam, vigabatrin, lacosamide, rufinamide, and clobazam. Their role in the management of various types of pediatric epilepsy has become increasingly important and should be coordinated at the time of discharge with the patient's pediatric neurologist.

HEADACHES

Principles

Headache is an extremely common problem in children and adolescents. Studies of schoolchildren have indicated that 40% of children will experience a headache by 7 years, and 75% by 15 years of age. Migraine, one of the most common causes of headache in childhood, with notable associated morbidity, has a prevalence of 8% to 23% by 15 years of age.[20] Although most pediatric patients have benign causes of headaches, a thorough history and physical examination can evaluate for serious underlying pathology and decide if further studies, such as neuroimaging, are necessary.

Migraine headaches are multifactorial in cause, with environmental end genetic contributions likely. The principal mechanism of migraine headaches is thought involve a primary dysfunction of the brain in which a wave of spreading cortical neuronal depression is accompanied by vascular changes. Derangement of the trigeminovascular reflex results in alterations of regional blood flow, and this neurovascular interaction is thought to contribute to neurogenic inflammation and the development of migraine headaches. Serotonin (5-hydroxytryptamine [5-HT]) may be a key mediator in this cascade of events. Serotonin agonists have been shown to relieve migraine pain.[21]

Clinical Features

Headaches can be classified into five temporal patterns—acute, acute recurrent, chronic progressive, chronic nonprogressive, and mixed. An acute headache is new in onset and different from previous headaches; it can herald a broad range of conditions, ranging from a viral illness to subarachnoid hemorrhage. Acute recurrent headaches can be expressed as periodic events separated by pain-free intervals. Chronic progressive headaches occur over weeks to months. They can signify serious medical disorders, such as brain tumors or arteriovenous malformations. Chronic nonprogressive headaches usually occur for years and are classified as primary headaches (as opposed to secondary symptomatic headaches, which are caused by an underlying medical problem). Mixed headaches are acute recurrent headaches (migraine) superimposed on a pattern of daily chronic nonprogressive headaches.

The primary goal of the ED evaluation is to differentiate life-threatening causes of headaches from primary headaches, such as migraine or tension headaches. The child's history is the most important component to an accurate diagnosis. The patient and family members should be asked about specific factors related to the headache, such as time of onset, duration, location, laterality, quality (sharp, dull, throbbing, aching), relieving and exacerbating factors, precipitating factors (poor sleep, hunger, specific foods), and associated symptoms, such as nausea, vomiting, or photophobia.

TABLE 174.8

Differential Diagnosis for Secondary Headache

CAUSE	FEATURES
Trauma	Intracranial bleed Concussion Skull fracture
Structural	Neoplasm Arteriovenous malformation Congenital malformation Hydrocephalus
Systemic	Hypertension Metabolic (eg, diabetes and ketoacidosis)
Infection	Meningitis Abscess Encephalitis Sinusitis Influenza Pyelonephritis Group A streptococcal pharyngitis
Toxic	Medication Ingestion

In addition to the important questions in Table 174.8, the emergency clinician should focus on a detailed history of the neurologic system to identify any related symptoms (eg, vomiting, lethargy, ataxia, seizures, weakness, visual disturbances) and a general review of other organ systems. Warning signs of secondary headaches include sudden onset, occurrence with straining or exertion, association with neurologic symptoms, change in headache pattern, nocturnal awakening, and bilateral occipital headaches. Additional information related to the past medical history (eg, history of recent head trauma, neurologic or psychiatric disorders, hospital admissions, medications) should also be obtained.

The physical examination should begin with vital signs.. Height, weight, and head circumference should be compared with standard percentiles and the child's previous growth history; a change in the rate or direction of head growth may indicate an intracerebral mass or hydrocephalus. The blood pressure should be carefully measured, with the use of age-appropriate cuff size and percentiles for age; hypertension may be a sign of increased ICP. An infant's fontanelle should be auscultated for bruits associated with arteriovenous malformations, and a skin examination should be performed to look for stigmata of neurocutaneous disorders, such as neurofibromatosis (cafe-au-lait spots; Fig. 174.2) or tuberous sclerosis (ash leaf spots; Fig. 174.3). The neurologic examination should begin with assessment of the child's mental status and overall development. For infants, observing their level of alertness, age-appropriate social interaction, overall tone, and general vigor is an essential component of the initial neurologic evaluation. Nonspecific findings such as irritability, fussiness, or poor feeding may be the only presenting signs in infants with headache. The neurologic examination should include a complete assessment of cranial nerves, gait analysis, cerebellar, sensory, and motor function testing, and evaluation of deep tendon reflexes. The ophthalmologic examination should

Fig. 174.2. Café au lait spots as seen with neurofibromatosis. (From Boyd KP, Korf BR, Theos A: Neurofibromatosis type I. J Am Acad Dermatol 61:1–16, 2009.)

Fig. 174.3. Ash leaf spots as seen in tuberosclerosis. (From Jindal R, Jain A, Gupta A, Shirazi N: Ash-leaf spots or naevus depigmentosus: a diagnostic challenge. BMJ Case Rep 2013:2013.)

include pupillary reactivity, visual acuity, extraocular movements, and funduscopy to evaluate for papilledema and retinal hemorrhages. Observation of interactions between the patient and family may provide clues to potential family problems, depression, or anxiety.

Diagnostic Considerations

Differential Diagnoses

Headaches may be primary (migraines, cluster headaches) or secondary to an underlying disease process. The list of differential considerations for secondary headaches is extensive and should be considered in the context of the child's history and physical examination (see Table 174.7).

Acute Headache. The acute headache is a common problem in children and adolescents and accompanies many infectious processes. In the absence of other signs of CNS involvement (eg, nuchal rigidity, alteration in level of consciousness, focal neurologic findings), headaches in febrile children usually do not constitute evidence of CNS infection. Nonspecific viral illnesses represent most diagnoses in children presenting to the ED with an acute headache.

Although far less common, arteriovenous malformations can be a trigger for a new severe headache. Intracranial arteriovenous malformations are structurally unstable and thus susceptible to spontaneous rupture. In children, the abrupt onset of a severe headache in the absence of trauma (especially when accompanied by focal neurologic findings) suggests an acute intracranial bleed, and a head CT should be performed after stabilization of the airway, breathing, and circulation. Localized acute headaches without focal neurologic findings commonly are due to sinusitis, otitis media, dental disorders, or traumatic head injury. Headache associated with trauma should be carefully investigated for the possibility of subdural or epidural hematomas, fractures, and leptomeningeal cyst (a "growing" skull fracture, usually in a child <3 years of age, with a history of recent trauma). Ophthalmologic problems, such as astigmatism, refractory errors, eye strain, and squint, are occasionally responsible for headaches in children.

Chronic Progressive Headache. Chronic progressive headaches in children often signify underlying pathology that is evolving to cause increasingly severe headaches over time. The development of increased ICP can be caused by brain tumors, pseudotumor cerebri, hydrocephalus, brain abscess, or intracranial bleeding. Headache that awakens the child from sleep, is present on first awakening, or is associated with morning emesis is a classic symptom of increased ICP and is often due to an intracranial mass or hydrocephalus. In the setting of an abnormal intracranial entity, such as a mass or CSF obstruction, impaired venous outflow in the supine position leads to excess volume inside the skull, generating elevated pressure. The physical examination may show signs of increased ICP—vital sign changes, including hypertension, bradycardia, and irregular respirations; papilledema; brisk reflexes; cranial nerve deficits; positive Babinski sign; and decreased level of consciousness—as well as focal symptoms related to the location of the lesion (eg, hemiparesis, ataxia, visual field deficits).

Headaches are more likely to be the first symptom of a brain tumor in older children. Frequently, there are associated symptoms, such as nausea, vomiting, visual effects, problems with walking, weakness, loss of developmental milestones, changes in personality or school performance, and/or speech changes. Often, the diagnosis of a brain tumor is made after one or more clinical visits for headache as the symptoms progress and evolve. Neurologic findings in children newly diagnosed with brain tumors may include papilledema, abnormal eye movements, ataxia, abnormal tendon reflexes, and abnormalities on the visual examination.

Clinical findings of pseudotumor cerebri (idiopathic intracranial hypertension or benign intracranial hypertension) are secondary to the increased ICP and include papilledema, sixth cranial nerve palsy, and visual field obstruction. Pseudotumor cerebri is more common in females and obese individuals. In younger children it is associated with medications (eg, vitamin A, steroids, birth control pills, tetracycline), and obstruction of the major venous sinuses. By definition, neuroimaging findings are normal. The LP usually demonstrates elevated pressure, often higher than 20 cm H_2O, and normal CSF protein and glucose levels. Neuroimaging should precede LP when increased ICP is suspected from mass or injury. Treatment can include repeat LP alone or with diuretics and LP for therapeutic removal of CSF. Hydrocephalus may be related to a previous episode of meningitis, subarachnoid hemorrhage, or head injury or may be congenital.

Brain abscess can result from meningitis, head trauma, chronic otitis media and sinusitis, or septic embolization in children with congenital heart disease. Focal neurologic signs, as well as fever and headache, may be present, but the patient may look surprisingly well. CT of the head without contrast enhancement is not sufficiently sensitive when an abscess is considered

in the differential but may be obtained; CT with and without contrast enhancement or MRI should be performed. CSF findings (performed only after neuroimaging) usually include a mild leukocytosis (10–200 leukocytes/mm^3), slightly elevated protein level, and normal glucose level. The CSF smear and culture usually do not reveal any organisms.

A subdural or epidural hematoma is associated with head trauma. Headaches in these patients may evolve and progress over a relatively short time period. Symptoms include those associated with increased ICP, seizures, and focal neurologic deficits. The diagnosis is confirmed by neuroimaging.

Chronic progressive headache also can be a symptom of systemic diseases, such as hypertension, collagen vascular disease, hypothyroidism, Lyme disease, mononucleosis, or inborn errors of metabolism.

Migraine Headache. The diagnosis of migraine is based on symptoms of recurrent headaches separated by pain-free intervals. A revised classification of migraine syndromes has been developed for pediatric migraines.[22] Pediatric migraines may last 2 to 72 hours and are more often bilateral compared to unilateral, which is more common in adults. Photophobia and phonophobia may be more difficult to assess in the young child or infant. Occipital headaches are rare and should raise clinical suspicion for an underlying diagnosis other than migraine.

Migraine headaches are classified primarily into migraine with and without an aura. Migraine without an aura, also known as common migraine, is the most frequent type of pediatric and adolescent migraine and includes the following criteria—more than five attacks that last 2 to 72 hours (untreated or unsuccessfully treated), accompanied by nausea, vomiting, photophobia or phonophobia—and including a minimum of two of the following criteria—unilateral or bilateral location, pulsing quality, moderate to severe intensity, and aggravated by routine physical activities.

Migraine with an aura, previously known as classic migraine, is diagnosed when at least two attacks fulfilling the diagnosis of migraine occur accompanied by a variety of sensory warning symptoms, such as flickering lights, loss of vision, and tingling or numbness. The aura typically develops over 5 or more minutes and completely resolve within 60 minutes.[22]

Migraine variants or atypical migraines are more common in children. Hemiplegic migraine is characterized by the sudden onset of hemiparesis or hemiplegia, along with headache in the contralateral hemisphere. Even though symptoms usually last for hours or even days, patients are rarely left with permanent deficits. Ophthalmoplegic migraine is characterized by severe unilateral eye pain and headache, followed by ipsilateral third nerve palsy of variable degree. Rarely, the fourth or sixth cranial nerve, rather than the third nerve, may be affected. Basilar artery migraine, also common in children, is manifested with a combination of visual symptoms (eg, transient bilateral blindness, blurred vision) and visual hallucinations, vertigo, ataxia, loss of consciousness, and drop attacks. An acute confusional state can be associated with migraines and is characterized by changes in personality, orientation, or behavior. The so-called Alice in Wonderland syndrome includes perceptions of distortion in body images and shapes; objects appear much larger (macropsia) or smaller (micropsia) before, during, or after the headache.

Migraine variants are not uncommon and can be misdiagnosed. Abdominal migraine is characterized by recurrent abdominal pain, nausea, vomiting, and recurrent headaches. Benign paroxysmal vertigo of childhood (distinct from benign paroxysmal positional vertigo) is manifested as headache accompanied by the sudden onset of vertigo, pallor, and nystagmus. Paroxysmal torticollis is defined as recurrent episodes of head tilt associated with headache, nausea, and vomiting. Of note, this is a diagnosis of exclusion; a child with a head tilt, vomiting, and headache should first be evaluated for a posterior fossa lesion. Ocular migraine is characterized by transient monocular visual blurring to blindness with bright flashes of light.

The incidence of seizures is higher in patients with migraine than in the general population. Although epilepsy and migraine headache are distinct clinical syndromes, they share several characteristics, such as aura, vertigo, nausea, pallor, loss of consciousness, drowsy postictal state, confusion, and transient focal neurologic deficits. Headache as the sole manifestation of a seizure is uncommon; however, headaches frequently follow tonic, tonic-clonic, and brief complex partial seizures. Bilateral frontal throbbing headaches may follow episodes of status epilepticus. Further neurologic evaluation, including electroencephalography, may occasionally be necessary to distinguish between these two syndromes.

Chronic Nonprogressive Headache. Chronic nonprogressive headache is commonly seen in the adolescent population. Included in this category are muscle contraction and conversion headaches. The International Headache Society classification of headaches refers to these types of headaches as tension headaches. This type of headache includes the following symptoms: bilateral or unilateral, nonthrobbing, pressing, or bandlike tightness of mild to moderate intensity, and the absence of nausea, vomiting, and aura. Tension headaches are further classified as episodic (10–15 episodes/month lasting 30 minutes to 7 days) or chronic (>15 episodes/month for more than 6 months).[22]

Cluster Headache. Cluster headache is a distinctive headache syndrome that is more common in males and rare in those younger than 10 years. Cluster headache is characterized by one to several attacks recurring each 24 hours, during several weeks to months. Headache-free periods between clusters may last months to years. The pain is throbbing, severe, and unilateral; occurs over the same orbitotemporal region, and is associated with ipsilateral scleral injection, lacrimation, nasal stuffiness, and sometimes a partial Horner's syndrome (enophthalmos, ptosis, miosis, and anhidrosis, unilateral, affecting sympathetic innervation of the eye). The pain lasts 30 minutes to several hours and can occur at any time of day or night.

Diagnostic Testing

Although most patients presenting to the ED do not require neuroimaging or laboratory evaluation, if neuroimaging is obtained, MRI provides superior anatomic detail compared with CT and is particularly useful in the detection of abnormalities in the sella turcica, posterior fossa, and cervicomedullary junction. MRI is also better for detecting arteriovenous malformations and low-grade tumors. CT scanning, however, is superior to MRI for the detection of acute blood and skull fractures and therefore is often the modality of choice in the ED if neuroimaging is emergently required. Indications for the use of neuroimaging are presented in Box 174.3.[23]

An LP is indicated for the diagnosis of an infectious process, subarachnoid hemorrhage not detected by CT, or idiopathic intracranial hypertension. If a mass lesion is suspected (eg, early-morning headaches and vomiting, progressively worsening headaches, or focal neurologic findings), radiologic imaging should precede an LP.

Chronic progressive headaches may be a symptom of a systemic disease. Guided by the history and physical examination, laboratory tests may include CBC, urinalysis, erythrocyte sedimentation rate, antinuclear antibody testing, liver function studies, thyroid function studies, serum lipid assay, serum magnesium, lactate, and pyruvate concentrations, and Lyme disease titers.

BOX 174.3

Indications for Radiologic Imaging in Patients With Headache

STRONGLY INDICATED IF:

Abnormal neurologic examination findings
Signs and symptoms of elevated intracranial pressure
Meningeal signs plus focal neurologic findings or altered mental status
Progressive or new focal neurologic signs
Significant head trauma
Severe nocturnal headaches that awaken the patient from sleep or are present on awakening
Severe (characterized by patient as "worst headache of my life") headaches; new or of increasing frequency and duration
Presence of ventriculoperitoneal shunt
Chronic progressive headache

CONSIDER IF:

Headache or vomiting on awakening
Unvarying location of headache, especially occipital
Persistent headache plus no family history of migraine
Neurocutaneous syndrome
Age < 3 years (limited verbal skills)

Data from Qureshi F, Lewis D: Managing headache in the pediatric emergency department. Clin Pediatr Emerg Med 4:159, 2003.

Management

Treatment of primary childhood headaches requires attention to initial pharmacologic management as well as reassurance, removal of potential triggers, and initiation of a behavioral management program.[24] The most important aspect of management is a thorough history and physical examination, past medical history of migraines or systemic disease, and targeted diagnostic evaluation for potentially life-threatening causes.

In addition to the use of standard oral analgesics, selective abortive treatment for children with migraine headaches has been recommended.[24] There is little evidence to support precise medication regimens but, for the initial management of children with severe migraines presenting to the ED, management generally involves IV fluid hydration with a normal saline bolus, nonopioid analgesic such as IV ketorolac, and antiemetic such as procholorperazine.[20,24]

Disposition

Children with primary headaches are not hospitalized for care unless the diagnosis is uncertain and a serious cause of secondary headache is being considered. On discharge from the ED, patients may be given a variety of treatment recommendations (discussed below) while stressing the importance of close follow-up with a primary care provider for ongoing management of migraines.

Nonmedical interventions may have some impact and should be strongly considered. These include avoidance of triggers, placement of the child in a darkened room, with minimal or no extraneous noise, avoidance of hypoglycemia by feeding during a migraine, avoidance of caffeinated beverages (except for possible use as a migraine medication during an episode), application of a cool compress on the forehead, use of a gentle fan, and breathing exercises and relaxation techniques.[21] A headache diary can help identify potential triggers and effects of medications. Common triggers include reduction in sleep, perimenstrual stress, missed meals, and certain foods (eg, chocolate, processed meats, alcohol, hard cheeses, red wine, monosodium glutamate, yeast extracts, nuts, figs, aspartame, sauerkraut).

In general, there are several outpatient treatment options available for acute migraine headaches in children. For many patients, symptom relief can be achieved by oral analgesics such as acetaminophen or ibuprofen, along with rest and avoidance of triggers. In other cases, additional agents are needed, such as vasoconstrictors, sedatives, triptans, and antiemetics. Some children may respond well to small doses of caffeine.

Vasoconstrictor drugs are used less commonly in the pediatric than in the adult population. Antiemetic agents are often given include and include dopamine receptor antagonists such as metoclopramide, promethazine, and prochlorperazine as well as the serotonin receptor antagonist ondansetron. Sumatriptan, a selective 5-HT_1 receptor agonist that can mediate cerebral vasoconstriction and block inflammatory response, may also be used in this setting, although a review of medication trials of triptans in children with migraine highlighted the important finding that randomized clinical trials found no difference in outcome between the control and experimental groups.[24] Sumatriptan can be administered orally, intranasally, or subcutaneously.

Combination medications, such as Fiorinal (butalbital, aspirin, and caffeine), Fioricet (butalbital, acetaminophen, and caffeine), and Midrin (isometheptene, acetaminophen, and dichloralphenazone) may be effective but should not be first-line treatment. In addition to producing an analgesic effect, these medications may produce alterations of emotional state, sedation, and psychological dependence.

The use of pharmacologic agents for prophylaxis in children with migraine headache requires careful observation and follow-up evaluation by the child's primary care physician or a neurologist. Although controlled studies are extremely limited, current indications for these medications include more than two or three headaches per week and interference with lifestyle, particularly missed school days or inability to participate in social activities. In keeping with or perhaps reflecting the high spontaneous remission rate of childhood migraine, the placebo effect of many medications is high. Steroids may have a role in preventing recurrence after an ED visit for migraine. Medications that have been used include propranolol, amitriptyline, calcium channel blockers, anticonvulsants (particularly valproic acid), cyproheptadine, and naproxen sodium. Cyproheptadine, valproic acid, and naproxen are available in liquid form. Amitriptyline may be useful for adolescents with a diagnosis of migraine and muscle contraction headaches and for depressed children with headaches.

DISORDERS OF BALANCE

PEDIATRIC ATAXIA

Principles

Ataxia comes from the Greek word *ataktos,* meaning "lacking order," and describes a pathologic abnormality of organization or modulation of movement. Congenital ataxia is associated with CNS abnormalities. Acquired ataxia can be acute, episodic, or chronic. The chronic ataxias are usually caused by inherited metabolic or genetic disorders. Usually, ataxia is caused by cerebellar dysfunction, but lesions in the corticospinal tract or dorsal columns of the spinal cord may also be causative.

Clinical Features

Most children with ataxia are seen in the first few days after onset, usually because of a refusal to walk, unsteadiness of arm movements, or sudden development of a wide-based so-called drunken gait. The history should identify any recent infection, injury, inadvertent drug ingestion, or other family members with similar symptoms. Mental status is usually normal in cases of

BOX 174.4

Causes of Childhood Ataxia

Acute cerebellar ataxia
Acute postinfectious demyelinating encephalomyelitis
Brainstem encephalitis
Drug ingestion
Guillain-Barré syndrome
Metabolic disorders
Aminoacidopathies
Mitochondrial disorders
Organic acidopathies
Urea cycle disorders
Migraine headaches
Multiple sclerosis
Neoplasm
Opsoclonus-myoclonus syndrome
Recurrent and chronic genetic ataxias
Seizures
Stroke
Vertebral artery dissection

Adapted from Ryan M, Engle E: Acute ataxia in childhood. J Child Neurol 18:309–316, 2003.

postinfectious ataxia; if abnormal, the possibility of ingestion, acute disseminated encephalomyelitis, or stroke should be considered. Nystagmus is common if the cerebellum is affected. Papilledema or cranial nerve palsies suggest hydrocephalus or a CNS lesion.

Diagnostic Considerations

Differential Diagnoses

In children, 40% of ataxia cases are caused by acute cerebellar ataxia. Box 174.4 delineates common causes of pediatric ataxia. Boys are more commonly affected, with the highest incidence at the ages of 2 to 4 years. A history of recent illness with multiple causative agents is seen in 70% of patients, but varicella virus is the most common, associated with up to 26% of cases. The disease is thought to be due to an autoimmune phenomenon leading to cerebellar demyelination. Symptoms and signs are maximal at the onset, with the extremities more seriously affected than the trunk, and range from unsteadiness and wide-based gait to complete inability to walk. Mental status is normal, and nystagmus is common. Fever and seizures are uncommon outcomes.

Acute postinfectious demyelinating encephalomyelitis can also cause ataxia and occurs in the recovery phase of a viral illness or vaccination. It is distinguished from acute cerebellar ataxia by alteration in consciousness and multifocal neurologic deficits, as well as by fever and frequent occurrence of seizures. Brainstem encephalitis can involve the cerebellum, causing ataxia in association with focal neurologic abnormalities and respiratory irregularities. Causative agents include Epstein-Barr virus, *Listeria monocytogenes,* and enteroviruses.

Up to 32% of cases of acute childhood ataxia are due to drug toxicity, usually anticonvulsants, benzodiazepines, alcohol, or antihistamines or, less commonly, from exposure to organic chemicals or heavy metals. The ataxia is usually accompanied by lethargy, confusion, and inappropriate speech or behavior. Nystagmus may be present.

Approximately 45% to 60% of all childhood brain tumors arise in the brainstem or cerebellum and can be manifested with slowly progressive ataxia. Acute decompensation can occur, with the development of hydrocephalus or hemorrhage into the lesion.

Head injuries with cerebellar contusion or hemorrhage can cause ataxia. Posterior circulation strokes are rare in children but should be considered after neck trauma, with possible vertebral artery dissection as a cause of the ataxia.

The opsoclonus-myoclonus syndrome consists of ataxia, rapid, chaotic, multidirectional eye movements, and myoclonic jerks of the extremities, head, trunk, and face. This is usually a presenting manifestation of neuroblastoma or ganglioneuroblastoma, in which the ataxia is thought to be due to a paraneoplastic autoimmune phenomenon involving cross-reactivity of tumor and cerebellar antigens. Spontaneous vertebral artery dissections also have been reported in children.

Ataxia can be seen in patients with basilar migraine and can be associated with vertigo, hemiparesis, cranial nerve dysfunction, nausea, vomiting, and/or headache. Loss of sensory input to the cerebellum can cause a sensory ataxia. Clinical manifestations include a Romberg sign, decreased deep tendon reflexes, and impaired proprioception and vibration sense. Of patients with Guillain-Barré syndrome (GBS), 15% have sensory ataxia. In the Miller Fisher variant of GBS, the triad of ataxia, areflexia, and ophthalmoplegia of vertical gaze is characteristic.

Transient ataxia can be present in the ictal or postictal phase of seizures. Repeated attacks of ataxia can be the presenting manifestation of multiple sclerosis. Inborn errors of metabolism can also manifest with ataxia, acutely or intermittently, depending on dietary intake or the presence of other illness. Inborn errors of metabolism should be considered when ataxia is accompanied by lethargy, encephalopathy, vomiting, diarrhea, loss of muscle tone, or unusual body odor, as in urea acid cycle defects (aminoaciduria) or defects in pyruvate and lactate metabolism. Ataxia is associated with other inherited diseases such as Niemann-Pick, Tay-Sachs, and Wilson's diseases.

The two most common genetic disorders associated with ataxia are Friedreich's ataxia and ataxia-telangiectasia. Friedreich's ataxia is a disorder of autosomal recessive inheritance characterized by progressive gait and limb disturbance. Affected patients demonstrate dysarthria, lower limb areflexia, proprioceptive sensory loss, and high-arched feet (pes cavus). Ataxia-telangiectasia is a disorder of recessive inheritance manifested as a truncal ataxia in infancy that leaves most patients wheelchair-bound by the age of 12 years. Oculocutaneous telangiectasias usually appear by the age of 3 to 5 years. These patients also demonstrate dysarthria, nystagmus, dystonic posturing, myoclonic jerks, and accelerated aging.

Diagnostic Testing

An accurate diagnosis for pediatric ataxia is dependent on a complete history and thorough physical examination, including testing of gait and cerebellar function. Urine and serum toxicology studies are the highest yield laboratory studies. CT and MRI findings are usually normal in patients with postinfectious ataxia, but demyelination, tumor, hydrocephalus, or traumatic injuries may be identified. CSF analysis may show mild pleocytosis or lymphocytosis in acute postinfectious ataxia; findings are normal in most other cases.

Electroencephalography is recommended for patients with altered consciousness and fluctuating clinical signs. A pattern of epileptiform discharges or slowing is seen in 66% of children with acute cerebellar ataxia. Electroencephalography can diagnose nonconvulsive or convulsive seizures. The electroencephalographic pattern is normal in the opsoclonus-myoclonus syndrome. Electromyography may be helpful if sensory ataxia is suspected and may help diagnose GBS, although this is less feasible in the ED setting. Urinary catecholamine levels can be assayed for diagnosis of neuroblastoma. Testing for inborn errors of metabolism includes a CBC, liver function tests, glucose, ammonia lactate, pyruvate,

and ketone levels, and determination of acid-base status. The four most high-yield tests are for levels of glucose, lactate, ketones, and ammonia. If all four of these are normal, it is unlikely that there is an inborn error. Any other laboratory tests should be ordered in consultation with a geneticist and may include plasma and urinary amino acid, urine organic acid, and CSF lactate assays and determination of the serum biotinidase level.

Management

Most children with acute postinfectious cerebellar ataxia recover completely, and treatment is supportive in nature. Improvement is seen within 1 week, and the vast majority recover completely within 2 to 4 weeks. Some children exhibit persistent gait disturbances, ataxia, and delayed speech development.

Disposition

Children with ataxia usually require hospital admission and consultation with a pediatric neurologist for patients in whom the cause of the ataxia is not evident on the ED evaluation.

PEDIATRIC VERTIGO

Principles

Vertigo, also discussed in Chapter 16, is defined as an illusion of movement, a sensation that the external world is revolving around an individual (objective vertigo) or that the affected person is revolving in space (subjective vertigo). Vertigo is well recognized to occur in the pediatric age group and has many potential causes. Disease processes that affect the balance of the vestibular, visual, and proprioceptive systems can cause vertigo by impairing the neural activity of the vestibular nucleus. Diseases of the ear, eighth cranial nerve, neck, brainstem, or eye can lead to vertiginous symptoms. Vertigo is characterized as central or peripheral, depending on whether the cause is in the CNS.

Clinical Features

Vertigo is often described as dizziness. There may be a history of sudden falls, grasping for support, or unwillingness to move. A review of systems should include those related to the ear, such as otalgia, hearing loss, and tinnitus. Other important historical features that should be determined include headache, loss of consciousness, head trauma or barotrauma, and family history of migraine or seizure disorders.

Diagnostic Considerations

Diagnostic Testing

Patients can be divided into those who have hearing loss and those who have normal hearing. In the group with hearing loss, further characterization of the loss as conductive or sensorineural (using the Weber and Rinne tests) can help localize the peripheral lesion from the middle ear, labyrinth, or eighth cranial nerve.

Differential Diagnoses

Although vertigo is not as common in the pediatric age group as in adults, it has many potential causes (Box 174.5). It usually is helpful to separate conditions that cause vertigo into those with and without associated hearing loss.

Benign paroxysmal vertigo of childhood is defined by the repeated occurrence of vertiginous episodes lasting seconds to minutes, with occasional vomiting. In addition to being pale and diaphoretic, preverbal children may appear fearful, grasping onto a caregiver's leg for stability. This entity usually remits spontaneously within months to years. The most frequent cause of benign paroxysmal vertigo of childhood is a migraine headache, with vertigo occurring as the aura of an episode.

Patients with basilar artery migraines also present with vertigo, hemiparesis, ataxia, palsies of the third, sixth, or seventh cranial nerve, drop attacks, and blindness in various combinations, followed by migraine headache. Children with benign paroxysmal vertigo of childhood or basilar migraines usually have a family history of migraine headaches.

Benign paroxysmal positional vertigo is rare in children, but can occur spontaneously as well as after trauma. The earliest age at which it has been reported is 11 years. It is believed to be due to otoliths that have moved out of their normal positions in the utricle and is corrected by canalith repositioning maneuvers (eg, Epley maneuver).

Ménière's disease, a syndrome with a combination of vertigo, fluctuating hearing loss, and tinnitus, is responsible for 1.5% to 4% of cases of pediatric vertigo. Vestibular neuronitis, thought to be caused by viral infections, is manifested as vertigo without hearing loss. A preceding cold is found in 60% of patients. It is manifested with severe vertigo that resolves in a few days, after which the child

BOX 174.5

Causes of Pediatric Vertigo

CENTRAL VERTIGO

Atrioventricular malformations
Brain abscess
Chiari malformations
Demyelinating disorders
Encephalitis
Meningitis
Migraine headaches
Neoplasm
Seizures
Trauma

PERIPHERAL VERTIGO

Alport syndrome
Benign paroxysmal torticollis
Benign paroxysmal vertigo of childhood
Benign positional vertigo
Cholesteatoma
Diabetes mellitus
Labyrinthine dysplasia or aplasia
Labyrinthine concussion
Labyrinthitis
Lyme disease
Otitis media, suppurative and serous
Ototoxins
Ocular disorders
Pendred syndrome
Perilymphatic fistula
Stenosis of the internal auditory canal
Syphilitic inner ear disease
Thyroid disease
Trauma
Usher syndrome
Vestibular neuronitis
Waardenburg syndrome (genetic disorder associated with deafness, wide-spaced eyes)

Adapted from Rudolph C, Rudolph A, editors: Rudolph's pediatrics, ed 21, New York, 2003, McGraw-Hill, p 1248.

will have vertigo only with rapid head movements, which persists for weeks or months until central compensation occurs.

Labyrinthitis is an inflammatory process involving the inner ear membranous labyrinth; it manifests with vertigo, hearing loss, and tinnitus. Cytomegalovirus, rubella virus, and rubeola viruses are common causative agents. Bacterial labyrinthitis usually occurs in association with meningitis and should be suspected in any ill child with vertigo and high fevers, especially in combination with a perforated tympanic membrane. Neurofibromatosis can be manifested with vertigo if it involves the superior vestibular nerve. Other genetic syndromes such as Alport syndrome are also associated with vertigo (see Box 174.5).

Ototoxic drugs, such as aminoglycosides and chemotherapeutic agents, can cause vertigo, usually in association with hearing loss. Cerebellar and brainstem lesions can also cause with vertigo. Cranial nerve deficits associated with vertigo may indicate a brainstem lesion or tumor. Vertigo is the presenting symptom in 5% to 12% of cases of multiple sclerosis.

For most patients, the cause of vertigo cannot be made in the ED. A complete physical examination, including an otologic and neurologic evaluation, should be performed, including nystagmus and cerebellar testing. Having the child hop and stand from a seated position on the floor, with eyes open and closed, can reveal vestibular dysfunction. Signs of other disease processes, such as café au lait spots in neurofibromatosis, may aid in the diagnosis.

Laboratory tests in the vertiginous patient should be dictated by the history and physical examination and may include glucose and electrolyte level assessment, thyroid function tests, and viral titers or serologic studies (eg, for Lyme disease or syphilis). CT or MRI is indicated for patients for whom an underlying CNS abnormality (central vertigo) is suspected.

Management

Management of the vertiginous patient depends on the underlying cause, which may not be evident in the ED. For acute symptomatic relief, vestibular suppressants such as meclizine and diazepam may be helpful.

Disposition

Patients with suspected CNS infection, focal neurologic deficits, abnormal mental status, or inability to ambulate or tolerate oral medication should be admitted. Patients should follow-up with a neurologist or otolaryngologist for follow-up testing.

MOTOR DYSFUNCTION

Acute weakness or motor abnormalities in the pediatric patient can result from pathology at a variety of levels in the neural axis. A complete neurologic assessment can indicate the location of pathology—upper motor neuron (motor neurons originating in the cerebral cortex or brainstem) or lower motor neuron (the spinal cord anterior horn cells, peripheral nerve, neuromuscular junction, and the muscle itself). Upper motor neuron pathology generally creates spasticity, increased tone, hyperreflexia and no fasciculations. Lower motor neuron abnormalities demonstrate decreased tone and reflexes, with fasciculations.

STROKE

Principles

Although less common in children than adults, pediatric strokes are important to recognize and treat promptly. Stroke is characterized by the acute onset of focal neurologic deficit lasting more than 24 hours. Underlying conditions that predispose children to stroke include sickle cell disease, structural cardiac anomalies, and moyamoya disease (Box 174.6).[25] Because stroke mimickers (eg, migraines) are much more common than strokes in pediatric populations, the diagnostic evaluation may be erroneously delayed.

Strokes are classified as ischemic or hemorrhagic in nature. In ischemic stroke, there is an interruption of blood supply to a particular area of the brain, resulting in hypoxic injury. In hemorrhagic stroke, the rupture of a blood vessel or an abnormal vascular structure causes focal damage. Hemorrhagic strokes are more common in children than adults and often stem from unstable arteriovenous malformations.

Clinical Features

Manifestations of stroke in infants and children are widely variable due to the potential affected areas of the brain, as well as the child's age and development. Common presenting features of stroke include hemiparesis and facial weakness. In addition to focal motor findings, children may also present with headache, seizures, or altered level of consciousness. The middle cerebral and anterior cerebral arteries are usually affected in children with stroke, generating upper extremity hemiplegia and lower extremity weakness, respectively. The posterior circulation, although less commonly involved, may produce ataxia, nystagmus, or vertigo, along with hemiparesis and hemianopsia.

Diagnostic Considerations: Diagnostic Testing

Imaging of the brain can confirm the diagnosis of stroke in infants and children. A noncontrast head CT scan can reveal the presence of a bleed, but may not show evidence of ischemia if the stroke took place in the preceding 24 hours. Early consultation with a pediatric neurologist or neurologist is prudent. Urgent MRI and MR angiography (MRA) are indicated if there is no evidence of hemorrhage on head CT and clinical suspicion for stroke remains high. If the child does not have a predisposing condition for stroke, additional laboratory evaluation may be helpful, including a CBC and coagulation studies, inflammatory markers, chemistry and lipid panels, and toxicology screen. Electrocardiography and echocardiography can reveal structural abnormalities associated with intracardiac clots.

Management

Initial pediatric stroke management is directed at stabilization of the airway, breathing, and circulation and controlling any seizure activity. To prevent secondary brain injury, hypoxemia and hypotension should be avoided. When present, hypertension should be managed with consideration of possible increased ICP, particularly in the setting of a hemorrhagic stroke. Blood pressure should be slowly reduced while maintaining cerebral perfusion pressure. The metabolic demands of the brain should be minimized by controlling fevers, pain, and agitation. Any hyperglycemia or hypoglycemia should be corrected, particularly in the setting of an ischemic stroke.

Additional therapy and definitive treatment of stroke in children are ultimately dictated by the type and extent of the stroke. In the case of hemorrhagic stroke, neurosurgical intervention is often required for intracranial decompression, blood evacuation, or control of active bleeding. For children with sickle cell disease, an urgent blood transfusion should be considered to decrease the circulating level of hemoglobin S. Although well studied and implemented in adults, thrombolytic therapy for stroke in children has not been well examined. Thrombolytics, however, have increasingly been used for children with ischemic stroke. We recommend rapid transfer to a pediatric stroke center, when feasible.

BOX 174.6

Risk Factors for Pediatric Stroke

CARDIAC
Congenital heart defects
Valvular heart disease
Right-to-left shunts
Cardiomyopathy
Endocarditis, myocarditis
Arrhythmia
Cardiac tumors
Cardiac surgery

HEMATOLOGIC DISORDERS AND COAGULOPATHIES
Anemia
Sickle cell disease
Dehydration
Idiopathic thrombocytopenia purpura (ITP)
Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS)
Thrombocytosis
Polycythemia
Disseminated intravascular coagulation
Leukemia or other neoplasm
Congenital and acquired coagulation disorders
Pregnancy and the postpartum period
Vasculitis, vasculopathies
Systemic lupus erythematosus
Polyarteritis nodosa
Takayasu arteritis
Kawasaki disease
Moyamoya syndrome, disease

INFECTION
Meningitis, encephalitis
Mastoiditis, otitis media
HIV
Varicella
Syphilis
Tuberculosis
Systemic infection

METABOLIC, MISCELLANEOUS
Homocystinuria
Fabry disease
Organic acidemia
Hyperlipidemia
Mitochondrial encephalopathy with lactic acidosis and strokelike episodes syndrome
Menkes disease

OTHER VASCULAR
Vasospasm (subarachnoid hemorrhage)
Migraine
Carotid ligation (eg, extracorporeal membrane oxygenation)
Fibromuscular dysplasia
Cervicocephalic arterial dissection
Arteriovenous malformation
Arteriography
Hereditary hemorrhagic telangiectasia
Sturge-Weber syndrome
Intracranial aneurysm

TRAUMA (INCLUDING NONACCIDENTAL)
Blunt and penetrating cervical trauma

BRAIN TUMOR
DRUGS
Cocaine
Amphetamines
Oral contraceptives
L-asparaginase

Adapted from Freundlich CL, Cervantes-Arslanian AM, Dorfman DH: Pediatric stroke. Emerg Med Clin North Am 30:805–828, 2012.

DISORDERS OF THE SPINAL CORD

Principles

Disorders of the spinal cord may arise from within the spinal cord itself or from extrinsic causes, such as trauma or malignancy. Acute compression of the spinal cord is a medical emergency; rapid accurate assessment of children with acute spinal cord abnormalities can directly affect patient outcomes. Trauma, spinal masses, and infection or inflammation can all cause acute spinal cord compression. The mechanism of compression may be due to direct mass effect (eg, from a tumor) or related to edema or hemorrhage from infection or trauma. Epidural abscesses are a common infectious cause of acute spinal cord compression and are typically caused by hematogenous spread of bacteria.

Infection or inflammation may also affect the spinal cord intrinsically. Transverse myelitis is an inflammation of the full width of the spinal cord (involving variable lengths of the cord) that manifests with demyelinating lesions at any level of the cord. It is thought to be autoimmune-mediated, often following a recent infection. Transverse myelitis typically evolves over hours to days, but may develop over a few weeks. Specific infections associated with transverse myelitis include Epstein-Barr virus, cytomegalovirus, measles, *Campylobacter jejuni,* and *Mycoplasma pneumoniae.*

Clinical Features

Regardless of the cause of acute spinal cord dysfunction, patients will present with certain characteristic findings, including paraplegia, hyporeflexia, and sensory deficits (complete sensory loss or paresthesias) below the level of the spinal cord lesion(s). Also, if the distal portion of the cord is affected, patients will have bowel and bladder incontinence. In the case of transverse myelitis, the thoracic region is usually affected. Children may demonstrate lower extremity paresthesias or pain with progressive weakness, which may be asymmetric, over a period of hours to days, and possibly urinary retention. There is often a history of a recent viral-like illness. An acute onset of local back pain with neurologic deficits suggests spinal cord compression due to a bleed, trauma, or infection. With infectious causes, pain may be the first sign, before fever, neurologic deficits, or other systemic signs. With oncologic processes such as spinal tumors, children may have a more insidious onset of symptoms and have evidence of spinal cord compression in the absence of pain.

Diagnostic Considerations: Diagnostic Testing

Diagnosing children with acute spinal cord compression requires a high level of clinical suspicion based on history and physical examination. A careful neurologic examination should include

strength, deep tendon reflexes, sensation, and evaluation of anal sphincter tone. In suspected spinal cord compression, priority should be on emergent neuroimaging with MRI of the spine while immobilizing the patient. CT is less helpful, and plain spine radiographs are of little value. An LP should not be performed when spinal cord compression is suspected. LP can be helpful in evaluating transverse myelitis, but should be performed only after confirmed by MRI.[26,27]

Management and Disposition

Initial management steps for the patient with spinal cord trauma include immobilization of the spine and immediate neurosurgical consultation. Steroids are no longer routinely recommended for spinal cord trauma. Children with an epidural abscess identified on MRI should be promptly treated with IV antibiotics and neurosurgical consultation for decompression or drainage. Antibiotic coverage should be tailored to match local bacterial resistance patterns. Generally, antistaphyloccocal coverage, including methicillin-resistant *Staphylococcus aureus* (MRSA), is recommended. Patient-specific conditions such as recent surgery may warrant additional coverage. Administration of corticosteroids for epidural abscesses is controversial because evidence is lacking for routine use. Corticosteroids should be administered only in select cases and in conjunction with neurosurgical consultation.

S. aureus is the most common pathogen associated with epidural abscesses; thus, initial IV antibiotic therapy in the ED should include vancomycin to cover MRSA (in addition to methicillin-sensitive *S. aureus* [MSSA]) and coverage of gram-negative bacilli with a third- or fourth-generation cephalosporin, such as ceftazidime or cefepime. Consideration of additional anaerobic coverage is warranted for higher risk individuals (eg, associated sinus disease).

Surgical drainage in conjunction with IV antibiotic therapy is the mainstay of treatment of epidural abscesses. For spinal masses, surgical intervention is needed to decompress the cord and further elucidate the diagnosis. Supportive care is the underpinning of treatment for transverse myelitis; these children should be hospitalized for observation, IV corticosteroid therapy, and consideration of additional immunotherapy.[26] Initiation of IV corticosteroid therapy in the ED and its specific dosing for children with transverse myelitis should be discussed with a neurologist. Although there are no randomized controlled trials to demonstrate the efficacy of IV corticosteroids in transverse myelitis, consensus favors their use; timing and optimal initial dosage should be determined in consultation with a neurologist.

GUILLAIN-BARRÉ SYNDROME

Principles

GBS is an acute, demyelinating polyneuropathy that typically presents as transient, symmetric, ascending paralysis in the setting of a recent infection. It is thought to be autoimmune-mediated and classically causes demyelination of motor and sensory nerves.

Children of all ages may be affected; however, it is uncommon in young toddlers and infants. Often, there is a history of a preceding minor viral or gastrointestinal illness in the weeks prior to presentation. *Campylobacter jejuni* is the most common infectious agent associated with GBS.[28] The differential diagnosis for GBS is broad; a careful history and detailed neurologic examination will help localize the pathology to the peripheral nerves rather than to the brainstem, brain, spinal cord, neuromuscular junction, or muscle itself.[28] The relatively acute and typically symmetric nature of GBS paralysis helps distinguish this diagnosis.

The primary mechanism of GBS is an immune-mediated attack on the myelin of peripheral nerves. It typically occurs in an ascending pattern and affects distal limbs initially. The process is thought to be mediated by an antecedent infection triggering an immune response, which, in turn, provokes the acute peripheral nerve demyelination.

Clinical Features

Lower extremity pain, paresthesias, and weakness in any combination may be the initial presenting symptoms of GBS, followed by progressive ascending weakness of the lower extremities.[28] The weakness may progress rapidly over hours to involve the trunk and, importantly, the muscles of respiration. Deep tendon reflexes are typically diminished or absent at the time of presentation. Cranial nerve abnormalities may also be present; in the Miller-Fisher variant of GBS, they represent the main findings, with oculomotor palsies, ataxia, and areflexia in the absence of extremity weakness.

Diagnostic Considerations: Diagnostic Testing

The diagnosis of GBS is largely clinical; however, a lumbar puncture can be helpful. CSF typically reveals an elevated protein level, with normal glucose and protein levels and white blood cell count, known as albumin cytologic dissociation.

Management and Disposition

Given the potential risk of respiratory compromise or failure associated with progressive demyelination and weakness, patients with GBS should be admitted to the hospital for monitoring and supportive care. Bedside respiratory evaluations, such as forced vital capacity and negative inspiratory force, may be very useful in predicting respiratory compromise. Treatment with plasma exchange and IV immunoglobulin may be used in severe cases.[28]

INFANT BOTULISM

Principles

Infant botulism typically affects infants younger than 6 to 8 months. It results from intestinal colonization with *Clostridium botulinum*. A neurotoxin produced by *C. botulinum* impairs acetylcholine release from the presynaptic membrane, thereby affecting skeletal muscle, smooth muscle, and autonomic function. Infants develop constipation and poor feeding, with subsequent hypotonia and weakness (Fig. 174.4), which may require respiratory support.[29] Most US cases of infant botulism are thought to arise from ingestion of environmental dust particles containing *C. botulinum* spores and may be associated with active construction areas in which there is disruption of the ground. Honey is also a potential reservoir for *C. botulinum* spores.

Clinical Features

Infant botulism typically has an insidious onset of symptoms, commonly starting with constipation. Over time, infants develop poor feeding, lethargy, hypotonia, and weakness. On examination, infants may have decreased deep tendon reflexes, cranial nerve findings such as poor suck and gag, weak pupillary reflexes, and/or ptosis.

Diagnostic Considerations: Diagnostic Testing

The diagnosis of botulism may be confirmed through isolation of botulinum toxin in the stool; however, this process may be delayed because infants are often constipated and laboratory processing times may be hours to days. As such, treatment should be initiated

Fig. 174.4. Infant with hypotonia, as seen with botulism. (From Arnon SS, Schechter R, Maslanka SE, et al: Human botulism immune globulin for the treatment of infant botulism. N Engl J Med 354:462–471, 2006.)

while awaiting confirmation of the toxin in a stool sample. Characteristic electromyography (EMG) findings of low-amplitude motor potentials of reduced duration may rapidly suggest the diagnosis.

Management and Disposition

Infants with botulism require admission to the hospital for supportive care, mechanical ventilation for depressed respiratory reflexes, and possibly nasogastric feeding. Botulism immune globulin is safe and effective and should be given IV as early as possible when the diagnosis is highly suspected, without awaiting confirmatory stool sample results.[29] Initial dosing for botulism immunoglobulin in infants less than 1 year of age is 50 mg/kg of body weight in a single IV infusion.

MYASTHENIA GRAVIS

Principles

Myasthenia gravis is an autoimmune disorder characterized by autoantibodies directed against the acetylcholine receptor of the neuromuscular junction. This action produces intermittent and fatigable weakness. Myasthenia gravis is usually seen in adults; however, there are three types that affect children—neonatal (transient), congenital, and juvenile. The juvenile form of myasthenia gravis presents similarly to the adult form and will be discussed here. Children with juvenile myasthenia gravis are more commonly female and of early school age.

Clinical Features

Patients typically have waxing and waning weakness of the skeletal and facial muscles, exacerbated by repetitive use of these muscles. Facial weakness with bilateral ptosis that fatigues throughout the day is a common initial presenting sign. Oculomotor, truncal, and extremity weakness may also be seen.

Diagnostic Considerations: Diagnostic Testing

A history of fatigable weakness with predominantly facial muscle findings should raise a high clinical suspicion for myasthenia gravis. The Tensilon test may be used in the ED to confirm the diagnosis. Edrophonium (Tensilon), an acetylcholinesterase inhibitor, is administered IV. By blocking the action of acetylcholinesterase at the neuromuscular junction, the presence of acetylcholine is prolonged, and muscle weakness transiently improves. Atropine should be available during the administration of edrophonium to treat possible cholinergic reactions (eg, bradycardia).

Management and Disposition

Myasthenia gravis may be life-threatening. Ventilatory support should be provided in the event of marked truncal weakness and respiratory compromise or failure, particularly in the setting of an intercurrent illness, which can exacerbate myasthenia gravis symptoms. In patients without risk of respiratory failure, treatment can often occur on an outpatient basis, with close symptom monitoring and oral cholinesterase inhibitor therapy.

KEY CONCEPTS

- Causes of altered mental status in children include vascular events (eg, stroke, arteriovenous malformation with bleed), infection (eg, meningitis, sepsis, encephalitis), trauma, toxic ingestion, anatomic or structural abnormality (eg, intracranial mass or tumor), metabolic derangements, intussusception, or seizures, which may be subclinical.
- Altered mental status in children has a varied spectrum of clinical presentations, and may include any of the following: altered level of consciousness, excessive sleepiness, irritability, lethargy, and abnormal behavior.
- Signs and symptoms of bacterial meningitis vary by age and can include nonspecific manifestations in infants and young children, such as irritability and lethargy.
- Antibiotic therapy for the patient with suspected bacterial meningitis, should not be delayed by an LP. Initial antibiotic coverage should be broad and guided by the most likely pathogens in the patient's age group.
- A careful and detailed history is instrumental in determining whether an event was a seizure. If the event was a seizure, the history should delineate which type of seizure occurred (partial or generalized) and whether the clinical event fits into a known epilepsy syndrome.
- Status epilepticus constitutes a neurologic emergency that carries high morbidity and mortality rates. Initial treatment is typically with IV lorazepam, followed by fosphenytoin.
- A simple febrile seizure is generalized, lasts less than 15 minutes, and occurs in a neurologically and developmentally normal child between 6 months and 6 years of age.
- Children with simple febrile seizures do not require blood and urine testing, other than as needed for the evaluation of fever source. In immunized infants 6 to 18 months of age with a first-time simple febrile seizure, a lumbar puncture (LP) can be avoided if the child is not-ill appearing, has returned to baseline, and there are no clinical signs of meningitis.
- The possibility of provoked seizures should be considered because many causes are treatable.
- Breath-holding spells occurs in children 6 months to 6 years of age, and are triggered by pain or emotional upset. After a trigger, the

Continued

KEY CONCEPTS—cont'd

child becomes pale or cyanotic and may lose consciousness, sometimes with a brief period of clonic movements or opisthotonos.
- Most headaches in children have benign causes that usually can be diagnosed by a careful history and physical examination. Radiologic evaluation by CT, MRI, or both may be necessary to rule out secondary causes of headache such as intracranial hemorrhage, subarachnoid hemorrhage, brain tumor, or brain abscess.
- Warning signs of secondary headaches include sudden onset, occurrence with straining or exertion, association with neurologic symptoms, change in headache pattern, nocturnal awakening, and bilateral occipital headaches.
- In children, 40% of ataxia cases are caused by acute cerebellar ataxia.
- A toxicology screen is the test with the highest diagnostic yield for acute-onset ataxia in children.
- Approximately 45% to 60% of all childhood brain tumors arise in the brainstem or cerebellum and can be manifested with slowly progressive ataxia.
- The cause of vertigo with hearing loss is significantly different from that of vertigo with no hearing loss. This differentiation can be helpful in guiding the diagnostic evaluation.
- When assessing an infant or child with motor weakness, it is important to distinguish presentations consistent with upper motor neuron pathology from lower motor neuron processes.
- Strokes are less common in children than in adults. They represent a neurologic emergency and may be hemorrhagic or ischemic in nature. Imaging with CT and/or MR can help confirm the diagnosis of stroke. An important component of stroke management involves the prevention of secondary brain injury.
- Spinal cord compression is a medical emergency regardless of cause and requires prompt diagnosis and treatment. It may arise from trauma, infection and inflammation, or malignancy.
- The diagnosis of Guillain-Barré syndrome (GBS) is largely clinical, although LP may be helpful in confirming the diagnosis. Patients with GBS are at risk for respiratory compromise and should be admitted to the hospital for observation and supportive care.
- The diagnosis of infant botulism is largely clinical. If there is high clinical suspicion, treatment should be initiated promptly, without awaiting laboratory confirmation. Given the risk of respiratory compromise, infants with botulism should be admitted to the hospital for observation and supportive care.
- Diagnosis of myasthenia gravis in the ED may be confirmed with the Tensilon test. The disorder can often be treated on an outpatient basis, but patients with truncal involvement and concern for respiratory compromise should be admitted to the hospital for observation and supportive care.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 174: QUESTIONS & ANSWERS

174.1. Which of the following is the most common cause of neonatal meningitis?
- **A.** *Escherichia coli*
- **B.** Group B streptococci
- **C.** *Haemophilus influenzae*
- **D.** *Listeria monocytogenes*
- **E.** *Neisseria meningitidis*

Answer: A. *E. coli* is the most common cause of neonatal meningitis. The incidence of Group B streptococcal meningitis has declined with changes in prenatal screening, as well as with infant immunizations.

174.2. Which of the following clinical findings of bacterial meningitis is more common in newborns compared with infants and children?
- **A.** Hypothermia
- **B.** Neck ache
- **C.** Rash
- **D.** Shaking chills
- **E.** Tachycardia

Answer: A. Hypothermia is more commonly found in newborn infants with bacterial meningitis compared with older infants and children with a similar disease.

174.3. A 15-month-old child is seen with a history of one 10-minute tonic-clonic event, which was nonfocal and accompanied by a temperature of 39°C (102.2°F). Two hours after the event, the child is still unresponsive to external stimulation. Which of the following is the next step in the management of this child?
- **A.** Admit to the inpatient service for antibiotics after blood cultures are drawn.
- **B.** Admit to the inpatient service for continued observation.
- **C.** Carry out imaging by obtaining a magnetic resonance image (MRI) of the brain.
- **D.** Obtain a complete blood count (CBC) and urinalysis if the child does not improve in 1 hour.
- **E.** Order a lumbar puncture, complete blood count, and blood and urine cultures.

Answer: E. According to American Academy of Pediatrics recommendations, lumbar puncture is not necessary in children older than 12 to 18 months in whom the clinical findings are not suggestive of meningitis. Because this child has exhibited a prolonged postictal period, a more serious illness is suggestive.

174.4. What is the appropriate treatment for a 12-year-old boy with a history of epilepsy who is brought from home by emergency medical services to the emergency department (ED), with multiple seizures within the 15 minutes. The child is still unconscious and seizing. Which of the following is the next step in the management of this child?
- **A.** Benzodiazepine; if seizures continue, fosphenytoin
- **B.** Electroencephalography (EEG) and computed tomography (CT) scan of the head
- **C.** Intubation using etomidate and vecuronium

D. Methohexital
E. Propofol infusion

Answer: A. If the airway cannot otherwise be maintained, there is respiratory failure, or there is evidence of increased intracranial pressure, the patient should be intubated. Do not paralyze the patient unless absolutely necessary. If needed, consider short-acting neuromuscular blockers such as succinylcholine and vecuronium. The three most commonly used agents to treat convulsive status epilepticus are benzodiazepines, fosphenytoin, phenytoin, and barbiturates. Methohexital actually lowers the seizure threshold. Propofol infusions should be used with great caution in children.

174.5. A 3-year-old boy is seen for seizure-like activity at home. He has no prior history of epilepsy and no family history of seizures. His fever has been as high as 39°C (102.2°F), and his parents have been watching him at home. The history and physical examination are normal, and the child is fully immunized for age. Which of the following statements is not consistent with appropriate counseling of parents regarding their 3-year-old?
A. Although acetaminophen may make him feel better, it will not prevent recurrence.
B. He is at high risk for developing epilepsy later in life.
C. It is safe for him to go home with the parents.
D. Seizures with fever are common in young children and do not lead to brain damage.
E. There is no need to start any antiepileptic medication.

Answer: B. In general, a child between 6 months and 5 years who has a normal neurologic examination and has had a brief seizure in the setting of fever can be assumed to have a simple febrile seizure. Future epilepsy is not predicted and is unlikely in children with simple febrile seizures.

174.6. Which one of the following statements best describes the signs and symptoms associated with pediatric brain tumors?
A. At the time of diagnosis, most patients with brain tumors have associated symptoms, such as nausea, vomiting, visual effects, problems with walking, weakness, changes in personality or school performance, or speech changes.
B. Headaches are never the first symptom of a pediatric brain tumor.
C. Most pediatric brain tumors are diagnosed within the first month after symptom onset.
D. Papilledema is one of the least common neurologic findings in children with brain tumors.

Answer: A. Of patients with brain tumors, most have some of the associated signs or symptoms noted in choice A. Headaches may be the first symptom of a pediatric brain tumor, although the frequency of this presentation increases with age. Papilledema is one of the more common neurologic findings, along with abnormal eye movements, ataxia, abnormal tendon reflexes, and abnormalities on the visual examination. CT scanning is usually not performed with the first sign of a headache unless clinically indicated.

174.7. A 10-year-old boy is brought in by his mother for gait imbalance. He is alert and oriented to person, place, and time, and he has a negative drug or alcohol screen. He has a wide-based gait. What should be the next step in management?
A. Admission and neurologic evaluation
B. Discharge home if CT scan is negative
C. Perform a lumbar puncture
D. Reassurance and primary care referral
E. Start sepsis evaluation

Answer: A. Most children with ataxia are seen in the first few days after onset, usually because of a refusal to walk, unsteadiness of arm movements, or the sudden development of a wide-based "drunken" gait. History should include recent infection, injury, inadvertent drug ingestion, or other family members with the same problem. Children with ataxia usually require admission for a complete evaluation. Consultation with a pediatric neurologist should be sought for patients in whom the cause of the ataxia is not evident on ED evaluation.

174.8. A 14-year-old girl with a history of migraines presents to the ED with the complaint of being unable to move her left side following a severe right-sided headache. Which of the following statements best describes her management?
A. Imaging, analgesics, and admit to the hospital because symptoms may last for days.
B. Immediate thrombolytics
C. Inpatient vasculitis evaluation is indicated.
D. She can be safely discharged home, and the symptoms will resolve in an hour.

Answer: A. Hemiplegic migraine is characterized by the sudden onset of hemiparesis or hemisensory loss followed by headache in the contralateral hemisphere. This type of migraine is seen more frequently in children than adults. Although symptoms usually last for hours or days, affected individuals are rarely left with permanent deficits.

174.9. A mother brings in her 4-year-old son for periods of lip smacking that occur multiple times per week and last several minutes. During these episodes, he may turn his head to her when she calls, but he does not speak. You suspect which of the following condition?
A. Complex partial seizure
B. Generalized seizure
C. Infantile spasm
D. Lennox-Gastaut syndrome
E. Simple partial seizure

Answer: A. In complex partial seizures, the patient has a change in level of awareness and may exhibit bizarre behaviors including staring, lip smacking, wandering, or picking at clothing. In simple partial seizures, the patient has no change in mentation. Lennox-Gastaut syndrome is characterized by mental retardation, multiple seizure types, and a classic EEG pattern of slow spike and wave. Infantile spasms manifest during the first year of life and consist of rapid, jackknife flexor or extensor spasms that appear in clusters.

CHAPTER 175

Musculoskeletal Disorders

Kemedy K. McQuillen

PRINCIPLES

Anatomy and Physiology

Several factors distinguish the pediatric musculoskeletal system from that of the adult. The most striking difference is the presence of the physis (the growth plate), made up of proliferating cartilage cells between the metaphysis and epiphysis. The physis is the weakest part of the bone and more likely to separate before the adjacent tendon or ligament tears, making sprains less frequent and physeal injuries common.

Children also have a thick, physiologically active periosteum, which is easily stripped from the bony cortex. The periosteum acts as a tether to reduce the amount of fracture displacement and, when it remains intact, aids in fracture reduction. The great bone-forming potential of the periosteum also facilitates the healing process. As a result, callus formation is vigorous, and nonunion almost never occurs. Growing bone is more porous, more pliable, and less dense than adult bone, making children more susceptible to fractures. Although less force is required to cause deformation, pediatric bone is more likely to buckle when it is compressed or bow when it is bent. Finally, because the bones are still growing, the potential for remodeling is greater. Growth can often compensate for postreduction imperfections in apposition and alignment, with deformities occurring in the plane of motion having the greatest potential for remodeling.

Fracture Patterns

Pediatric fracture descriptions include bone location (diaphysis, metaphysis, physis, or epiphysis), relationship of fracture fragments to one another (angulation and displacement), and relationship of fracture fragments to adjacent tissue (open or closed). Children develop fracture configurations not found in the adult population. Pediatric fractures can be classified as follows:

- Plastic deformation. Bone is bowed, with no obvious cortical disruption.
- Torus fracture (buckle fracture). Buckling of bone without cortical disruption tends to occur from compression failure at the metaphyseal-diaphyseal junction (Fig. 175.1). Distal radius buckle fractures may be immobilized with a Velcro wrist splint.[1-3] These can be removed by the family or primary care provider in 3 to 4 weeks.
- Greenstick fracture. The bone is disrupted, along with one cortex; the periosteum on the fracture's compression side remains intact (Fig. 175.2). In the emergency department (ED), minimally angulated (<10 degrees) distal radius greenstick fractures can be immobilized with a splint[4] and patients referred to an orthopedic specialist within 1 week.
- Complete fracture. The fracture propagates completely through the bone involving both cortices; these include fractures that are transverse (Fig. 175.3), spiral (Fig. 175.4), oblique, and comminuted (Fig.175.5).

Although injuries to the physis can occur at any age, they are more common during rapid skeletal growth. The Salter-Harris classification system is the most frequently used tool to describe physeal injuries. This classification system is based on the extent of involvement of the physis, epiphysis, and joint (Table 175.1). Types I and II Salter-Harris fractures (Figs.175.6 and 175.7) do not involve the germinal layer of the growth plate, making the risk for growth arrest small. In general, the higher the Salter-Harris classification (Salter-Harris types III–V), the greater the damage to the growth plate, and thus the greater the likelihood of growth arrest or limb length abnormalities (Figs. 175.8 to 175.10). Type II fractures account for approximately 75% of all growth plate injuries.

SPECIFIC DISORDERS

Clavicle Fracture

The clavicle is a frequently broken bone in children. The physis of the clavicle does not close until the third decade (someone in their 20s) and is at risk for injury until that time. Midshaft fractures account for approximately 85% of all clavicle fractures. The usual mechanism of injury is a fall on the shoulder or, less commonly, direct trauma to the bone itself. The child typically supports the affected side with the other hand and tilts the head toward the side of the fracture. Physical examination reveals point tenderness at the fracture site, with or without an obvious bone deformity. Pain usually limits range of motion of the shoulder.

Although complications are rare, due to the proximity of the clavicle to the great vessels and brachial plexus, a thorough neurovascular evaluation should be performed. Posterior sternoclavicular displacement can cause injury to the trachea, esophagus, and subclavian vessels, whereas lateral clavicular displacement can result in injury to the brachial plexus. Middle third fractures have been associated with neurovascular bundle injuries, pulmonary injury, and pneumothorax.

An anteroposterior (AP) radiograph of the clavicle (Fig. 175.11) confirms the diagnosis. If clinical suspicion is high, and the AP view does not reveal a fracture, a 30-degree cephalic view can be helpful. With proximal fractures or posteriorly displaced fractures or dislocations, associated neurovascular injuries may be identified by computed tomography (CT) or duplex ultrasonography.

Clavicle fractures do not usually require anatomic reduction for healing or function; treatment should be directed at maintenance of comfort with splinting, ice, and analgesics. Figure-of-eight splinting is not recommended due to a risk for brachial plexus palsy with long-term use. A sling with or without a swath should be used to provide comfort by supporting the upper extremity and providing the suspensory forces usually maintained by the clavicle. Most clavicle fractures heal without complications, except for the development of bony callus at the fracture site; the younger the patient, the greater the potential for remodeling of this deformity. Younger children generally require shorter periods of immobilization (2–4 weeks) than adolescents and adults (4–8 weeks).

Rehabilitation includes early range of motion and strengthening of the rotator cuff. Immediate orthopedic consultation should be obtained for clavicle fractures that are open or associated with

Fig. 175.1. Buckle fracture of the distal end of the radius. Treatment consists of immobilization for 3 to 6 weeks.

Fig. 175.3. Transverse fractures of the radius and ulna.

Fig. 175.2. Greenstick fracture of the radius. This fracture may need to be completed for an anatomic reduction to be achieved.

Fig. 175.4. Spiral fracture of the femur.

neurovascular compromise or for fractures associated with more than 100% displacement of the fracture fragment, with skin tenting. Distal clavicular fractures and middle clavicular fractures that are comminuted or displaced more than 2 cm may require surgical management; an orthopedic surgeon should see these patients within 72 hours. High-level athletes should also be referred to an orthopedist for surgical evaluation because surgical repair may expedite a return to sports.

Clavicle fractures can occur during childbirth and represent more than 90% of obstetric fractures. Displaced clavicle fractures are identified by crepitus, edema, lack of movement of the affected extremity, asymmetric bone contour, and crying with passive motion. Nondisplaced fractures may not be noticeable until a bony callus becomes apparent at 10 days of age. The presence of a clavicle fracture should prompt further investigation for accompanying brachial plexus injury.

Fig. 175.5. Comminuted fractures of the tibia and fibula.

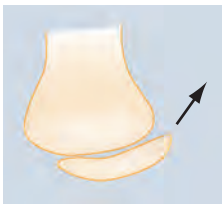
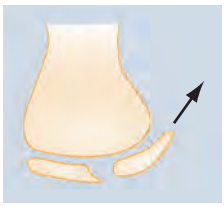
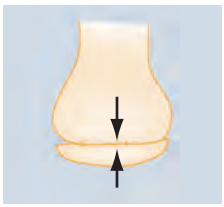
Fig. 175.6. Salter-Harris type I fracture of the fibula. The only finding on examination was point tenderness over the distal end of the fibula. Radiographic findings include soft tissue swelling over the growth plate and minimal physeal widening.

Supracondylar Fractures of the Humerus

Supracondylar fractures represent the most common elbow fractures in children younger than 8 years.[5] Until that age, the tensile strength of the ligaments and joint capsule is greater than that of the bone itself, and the weaker bones yield to the stronger ligament complex around the joint.

TABLE 175.1

Salter-Harris Fracture Classification

TYPE	DESCRIPTION	
I	Fracture extends through the physis (see Fig. 175.6)	
II	Fracture extends from the physis into the metaphysis (away from the joint space) (see Fig. 175.7)	
III	Fracture extends from the physis into the epiphysis (toward the joint space) (see Fig. 175.8)	
IV	Fracture extends from the physis into the metaphysis and epiphysis (see Fig. 175.9)	
V	Crush injury of the physis (see Fig. 175.10)	

Supracondylar fractures are classified according to mechanism of injury as flexion or extension injuries. The extension type of injury constitutes 95% of all supracondylar fractures and typically results from a hyperextension injury incurred from a fall onto the outstretched arm. This mechanism results in failure of the anterior cortex and displacement of the distal fragment posteriorly. With extension-type fractures, the degree of displacement and continuity of the cortex are defined by the Gartland classification (Table 175.2). In the less common flexion type of supracondylar fracture, the elbow is flexed when it hits the ground. This mechanism results in a supracondylar fracture with anterior displacement of the distal fragment and failure of the cortex posteriorly.

Children with supracondylar fractures may present with anything from mild swelling and elbow pain to a grossly displaced humerus. Due to the risk of neurovascular damage, manipulation of the elbow should be avoided. Children with extension-type supracondylar fractures hold the affected arm in extension with an S-shaped configuration of the elbow and exhibit a prominence at the olecranon. Children with flexion-type supracondylar fractures hold the arm in flexion and exhibit an empty space where the olecranon should be. Motor and sensory functions should be

Fig. 175.7. Salter-Harris type II fracture of the radius. The triangular piece of the metaphysis is referred to as the Thurston-Holland segment.

Fig. 175.9. Salter-Harris type IV fracture of the proximal phalanx.

Fig. 175.8. Salter-Harris type III fracture of the middle phalanx.

Fig. 175.10. Salter-Harris type V fracture of the distal end of the radius. The crush injury has obliterated the physis.

evaluated by assessing the radial, ulnar, and median nerves (Table 175.3). Two-point discrimination of more than 5 mm on the fingers indicates a deficit. Vascular assessment should include evaluation of the radial and brachial pulses and capillary refill of the hand. Due to risk of compartment syndrome of the forearm, patients with pain on flexion or extension of the fingers, forearm swelling, tenseness or tenderness, or pain that is disproportionate to the injury should have compartment pressures measured. Unrecognized ischemic injury can result in Volkmann's ischemic contracture, characterized by fixed elbow flexion, forearm pronation, wrist flexion, metacarpophalangeal joint extension, and interphalangeal flexion. A complete examination of the upper extremity should be completed because concomitant injuries involving the wrist or forearm occur in approximately 10% of patients.

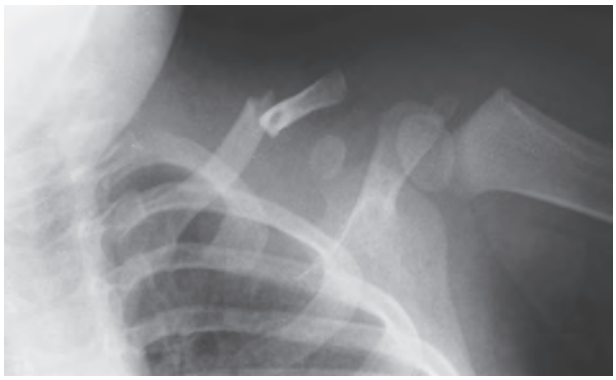


Fig. 175.11. Fracture of the middle third of the clavicle.

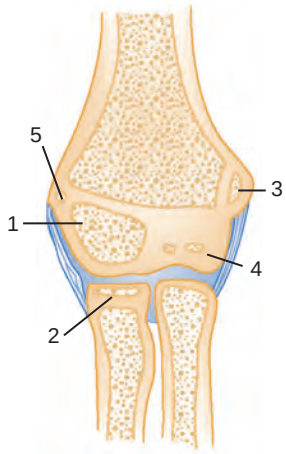


Fig. 175.12. Ossification centers of the elbow. *1,* Capitellum; *2,* radial head; *3,* medial epicondyle; *4,* trochlea; *5,* lateral epicondyle. (From Connolly JF: DePalma's management of fractures and dislocations, Philadelphia, 1981, WB Saunders.)

TABLE 175.2

Gartland Classification of Extension-Type Supracondylar Fractures

TYPE	DESCRIPTION
I	Nondisplaced fracture
II	Displaced fracture with intact posterior cortex
III	Displaced fracture with no cortical contact
IIIA	Posteromedial rotation of the distal fragment
IIIB	Posterolateral rotation of the distal fragment

Adapted from Gartland JJ: Management of supracondylar fractures of the humerus in children. Surg Gynecol Obstet 109:145, 1959.

TABLE 175.3

Neurologic Examination of the Distal Upper Extremity

	EXAMINATION COMPONENT	
NERVE	Motor	Sensory
Radial	Wrist extension	Thumb and first finger web space
Ulnar	Wrist flexion and adduction	Little finger
Median	Wrist flexion and abduction	Thumb, index, and middle fingers
Thumb opposition	Radial aspect of palm of hand	
Anterior interosseous	Distal phalanx flexion (thumb and first finger)	None

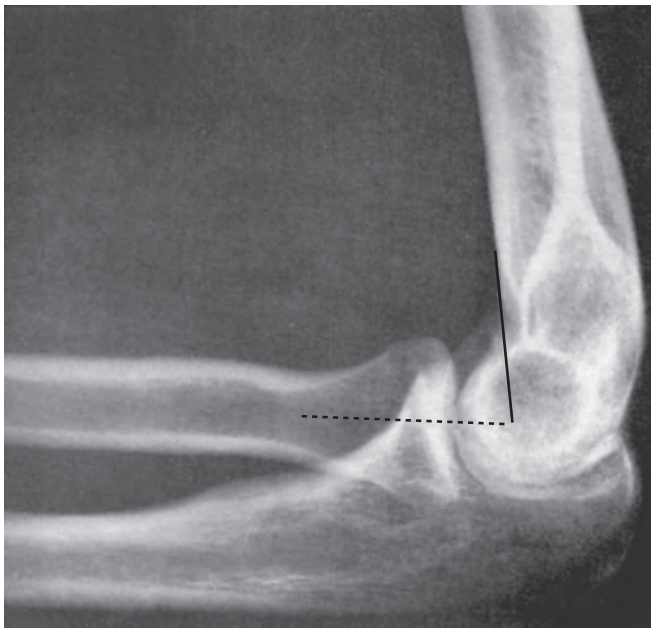


Fig. 175.13. Lateral radiograph demonstrating the bone relationships in a normal elbow. The anterior humeral line (*solid line*) and proximal radial line (*dashed line*) bisect the capitellum. (From Weissman BN, Sledge CB: Orthopedic radiology, Philadelphia, 1986, WB Saunders.)

Radiographic evaluation of an elbow injury includes an AP view of the extended elbow, oblique view, and lateral view of the flexed elbow. The elbow is largely cartilaginous during early childhood, and the six secondary centers of ossification around the elbow can camouflage or be mistaken for fractures (Fig. 175.12). These ossification centers can be remembered by the mnemonic CRITOE—***c***apitellum, ***r***adius, ***i***nternal (medial) epicondyle, ***t***rochlea, ***o***lecranon, and ***e***xternal (lateral) epicondyle. The approximate ages at which these sites ossify are 1, 3, 5, 7, 9, and 11 years, respectively (Table 175.4).

Bone relationships are helpful in the evaluation of a radiograph for a supracondylar fracture (Fig. 175.13). A true lateral view should demonstrate a figure-of-eight appearance of the distal humerus, with bisection of the capitellum by the anterior humeral

TABLE 175.4

Sequence of Ossification Around the Elbow: CRITOE

OSSIFICATION CENTER	AGE AT APPEARANCE	AGE AT CLOSURE (yr)
Capitellum	6–12 mo	14
Radial head	4–5 yr	16
Medial (***I***nternal) epicondyle	5–7 yr	15
Trochlea	8–10 yr	14
Olecranon	8–9 yr	14
Lateral (***E***xternal) epicondyle	9–13 yr	16

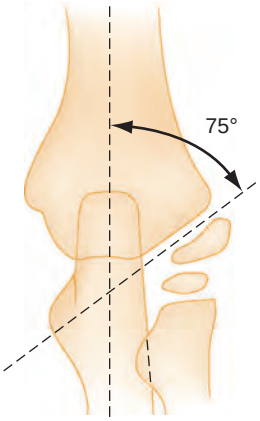


Fig. 175.14. Baumann's angle in a normal elbow (anteroposterior radiograph). (From Worlock P: Supracondylar fractures of the humerus: assessment of cubitus varus by the Baumann angle. J Bone Joint Surg Br 68:755, 1986.)

Fig. 175.15. Lateral radiograph of a supracondylar fracture with an anterior fat pad sail sign and posterior fat pad.

line. If the capitellum falls posterior to this line, an extension-type supracondylar fracture is likely. In all views, the proximal end of the radius and radial neck should point to the capitellum. Baumann's angle is helpful in diagnosing a subtle supracondylar fracture (Fig. 175.14). This angle is formed by a line drawn to follow the growth plate of the capitellum transected with a line that runs perpendicular to the axis of the humerus. The angle should be approximately 75 to 80 degrees. Baumann's angle should be the same in both elbows; differences between elbows can be used to detect subtle supracondylar fractures. In children younger than 3 years, difficult to distinguish bone landmarks limit the utility of Baumann's angle.

Fat pads also provide a means for the detection of occult supracondylar fractures. A lateral radiograph with the elbow flexed at 90 degrees is useful for evaluating anterior and posterior fat pads. An anterior fat pad protruding from the coronoid fossa is normal unless the pad is bulging or in the shape of a ship's sail (the so-called sail sign). The posterior fat pad sits snugly within the olecranon fossa and should never be seen; the presence of a posterior fat pad suggests an occult fracture around the elbow. Patients with a posterior fat pad, but no obvious fracture (Fig. 175.15) should be splinted and given a 1-week orthopedic follow-up. After plain radiography, if the diagnosis remains in question, ultrasound imaging may be useful in infants, and magnetic resonance imaging (MRI) may be useful in older children.

ED treatment of supracondylar humeral fractures is determined by the degree of displacement and neurovascular status. A patient with a pale, pulseless cold hand should receive emergency consultation with an orthopedic surgeon. If an orthopedic surgeon is not immediately available, and the vascular supply has not been restored, reduction should be attempted (Fig. 175.16), taking care not to entrap the brachial artery and median nerve. If the hand does not become warm and pink, the reduction may be attempted a second final time. If perfusion is not reestablished after a second attempt, the child should receive emergent operative intervention. A supracondylar fracture with a pulseless hand that is warm and pink does not need to be reduced immediately. The arm should be splinted as it lies to prevent further vascular compromised.

Gartland type I fractures can be splinted in the ED, with the arm maintained in 90 degrees of flexion and neutral rotation. Gartland type III fractures require immediate orthopedic consultation and should be treated in the operating room by closed reduction and percutaneous pinning or open reduction and internal fixation. Treatment of type II fractures is controversial. Some surgeons operatively reduce and pin, whereas others perform closed reduction and cast.

Neurovascular compromise complicates 11.3% of displaced supracondylar fractures—the anterior interosseous branch of the median and radial nerves are at risk of damage in extension- type injuries; the ulnar nerve is damaged in flexion-type injuries.[6] Most nerve injuries are neurapraxias that resolve spontaneously. Although motor function usually returns within 12 weeks, sensory function may not return for 6 to 12 months. Brachial artery injuries, including arterial entrapment, laceration, intimal tears, thrombosis, and compression from compartment syndrome, occur in approximately 40% of patients. Fortunately, the brachial artery has many branches around the elbow, allowing flow to the forearm and hand when the brachial artery is injured. Untreated vascular injury can also result in Volkmann's ischemic contracture and permanent limb disability. Some supracondylar fractures heal with a gunstock deformity with varus, hyperextension, and medial rotation of the limb.

Monteggia's Fracture-Dislocation

Monteggia's fracture-dislocations are characterized by a fracture of the proximal third of the ulna plus dislocation of the radial head. The radiographic evidence can be subtle, with only a minor greenstick fracture or bowing of the ulna. Isolated ulna fractures are rare in children; therefore, with all such fractures, a dislocation of the radial head should be excluded (Fig. 175.17). Radiographs should be examined for the ulnar bow sign. This is found when any portion of the ulna lies anterior to a line drawn along the posterior cortex of the ulna on the lateral view.

Immediate orthopedic consultation should be obtained for closed reduction of the radial head dislocation and repair of the ulna fracture. Complications include permanent radial head dislocation, valgus deformity of the arm, loss of pronation, and late radial nerve palsy.

Nursemaid's Elbow

Radial head subluxation, also known as annular ligament displacement or nursemaid's elbow, has been estimated to represent about 1% of injury-related ED visits. It typically occurs when axial traction is placed on an extended and pronated arm, as when the child is pulled up or swung by the arms. It also may occur when the child falls onto the outstretched arm, sustains minor direct trauma to the elbow, or simply twists the arm. Subluxation occurs

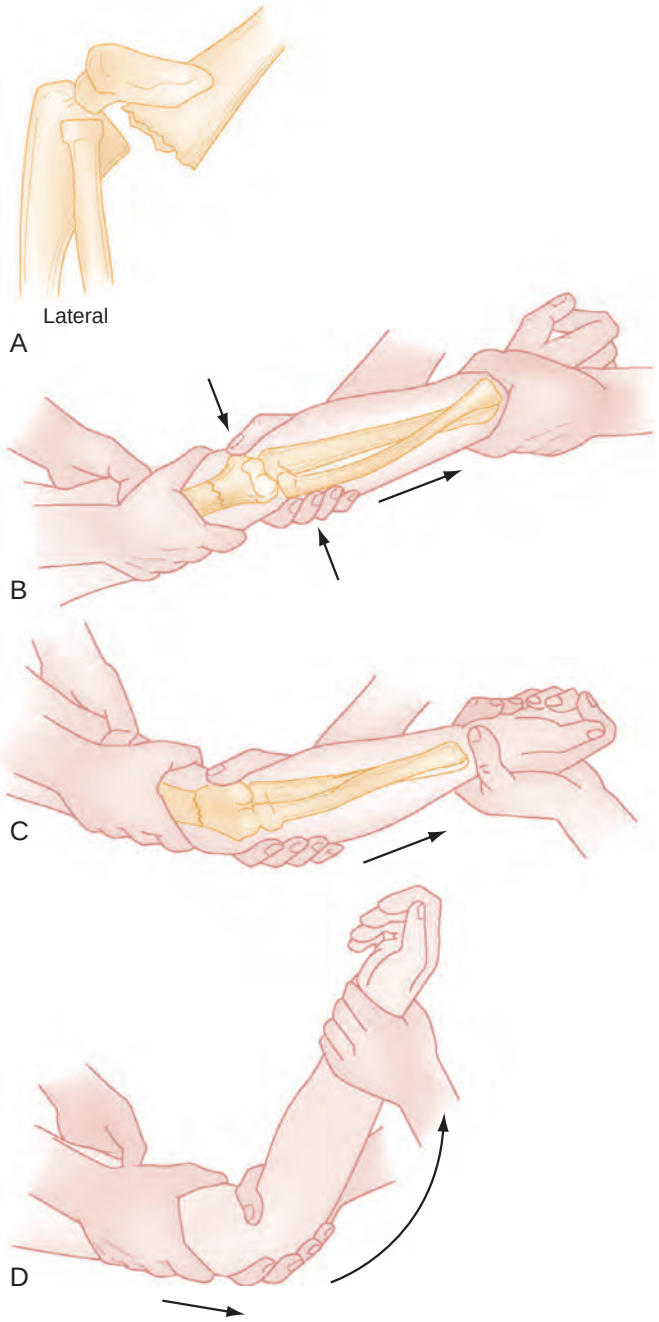


Fig. 175.16. Steps in reduction of a displaced supracondylar fracture. **A**, **B,** The assistant fixes the arm of the patient while the emergency clinician grasps the patient's wrist and applies steady traction in line with the long axis of the arm while keeping the forearm in the neutral, thumb-up position. **C,** If the distal fragment is displaced laterally, it is pushed inward with the emergency clinician's other hand. If it is displaced medially, it is pushed outward. Throughout manipulation, traction is maintained. **D,** After length is restored and the medial and lateral displacement is corrected, the emergency clinician's thumb is placed over the anterior surface of the proximal fragment, with the fingers behind the olecranon, and the elbow is gently flexed. The arm is then immobilized with the forearm pronated; laterally displaced fractures are immobilized with the forearm supinated. (From Geiderman JM, Magnusson AR: Humerus and elbow. In Rosen P, Barkin R, editors: Emergency medicine: concepts and clinical practice, ed 4, St. Louis, 1998, CV Mosby.)

when the radial head slips out of the annular ligament, trapping the ligament in the radiocapitellar joint (Fig. 175.18).

Nursemaid's elbow occurs in children a few months to 5 years of age and has a peak incidence between 2 and 3 years. Children present with the acute onset of arm pain that may or may not be localized to the elbow. The affected arm is typically held against the body, with the elbow slightly flexed and the arm pronated. Physical examination is significant for lack of swelling, erythema, ecchymosis, or deformity. Examination may reveal mild tenderness of the radial head. Pain is elicited with supination, pronation and elbow flexion. The diagnosis of nursemaid's elbow is made clinically, and imaging is not necessary. Radiographs should be obtained for significant point tenderness, swelling, or ecchymosis. Ultrasound imaging may demonstrate a widened space between the radial head and the capitellum.

Radial head subluxation is easily reduced without sequelae. With the flexion-supination technique, the affected elbow is gripped with the emergency clinician's thumb over the radial head and, with the other hand, the emergency clinician flexes and supinates the patient's arm. As the radial head relocates, the emergency clinician feels it click or clunk under his or her thumb. Using the hyperpronation technique, the child's affected elbow is held with the emergency clinician's thumb over the radial head, and the forearm is hyperpronated. Success rates are approximately 85% with supination and 95% with hyperpronation. Pronation may be less painful to the patient and is the reduction method of choice. After successful reduction, the child typically uses the arm normally within 10 to 20 minutes. This may be delayed in younger children or when the injury occurred more than 4 to 6 hours before reduction. Neither splinting nor orthopedic referral is required after a successful reduction. Recurrence is common, and parents should be cautioned to avoid traction on the forearm.

Failure to reduce a nursemaid's elbow may result from improper reduction technique, edema, or disruption of the annular ligament. If two attempts at reduction are unsuccessful, a posterior splint should be applied, with the elbow kept at 90 degrees and the forearm in supination. Orthopedic follow-up should be arranged for the next day.

Toddler's Fracture

Toddler's fractures are oblique nondisplaced fractures of the distal tibia caused by low-energy torsional forces applied to the porous bone of infants and young children. The peak incidence is between 9 and 36 months of age but it can occur in children as old as 6 years. The mechanism of injury can be as mild as the child's twisting on the leg while walking or a fall from an insignificant height; the mechanism may even be unknown. The child will limp or may refuse to walk on the affected leg. Some children will revert to crawling and can crawl without pain. Examination may show mild swelling of the lower leg and point tenderness along the tibia. Gentle twisting of the lower part of the leg may elicit pain.

AP and lateral radiographs may reveal a spiral or oblique fracture extending downward and medially through the distal third of the tibia (Fig. 175.19). An internal oblique radiograph is helpful if evidence of fracture is absent on the AP or lateral view. If no fracture is apparent, the child should be splinted for comfort and radiography repeated in 10 days, at which time periosteal new bone or sclerosis of the fracture edges will make the fracture visible. If findings on these radiographs are normal and the child is still limping, further imaging should be undertaken to rule out osteomyelitis and malignant neoplasm. Ultrasonography can be considered for the detection of occult fractures in toddlers and in older children.[4,7] Treatment of a toddler's fracture consists of a long leg cast with the knee flexed for approximately 3 weeks.

Developmental Dysplasia of the Hip

Principles

Developmental dysplasia of the hip (DDH), formerly known as congenital dislocation of the hip, denotes a wide spectrum of

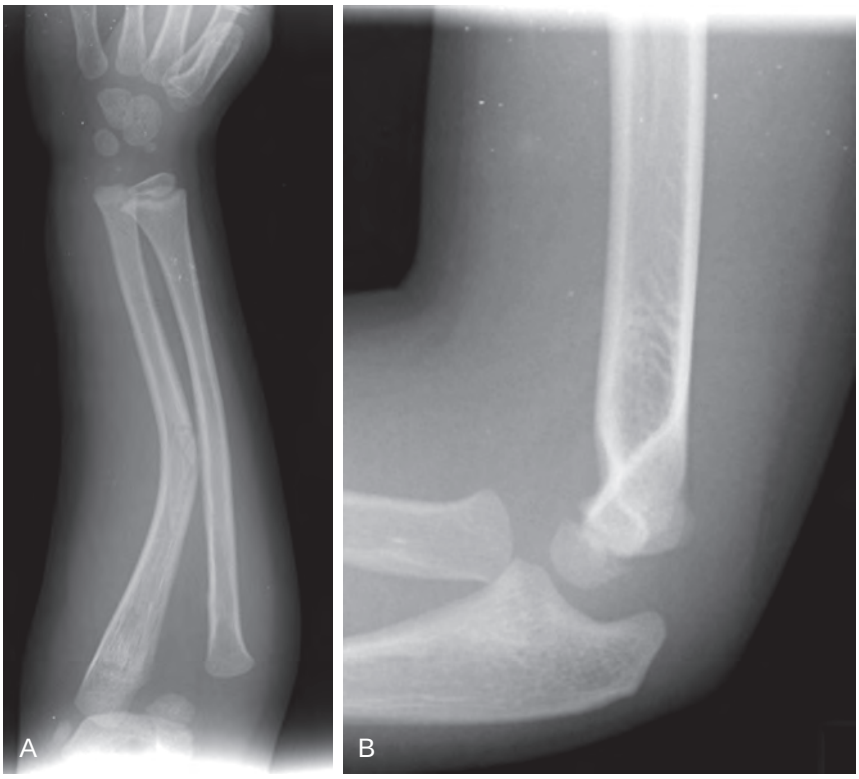


Fig. 175.17. **A,** Anteroposterior view of elbow revealing a distal ulna fracture with radial head dislocation. The radial head should align with the capitellum in all views. **B,** Lateral view of the elbow demonstrating poor alignment of the radial head, with the capitellum consistent with Monteggia's fracture-dislocation. (Courtesy Dr. Michael Diament, Pediatric Radiology, Harbor-UCLA Medical Center, Torrance, CA.)

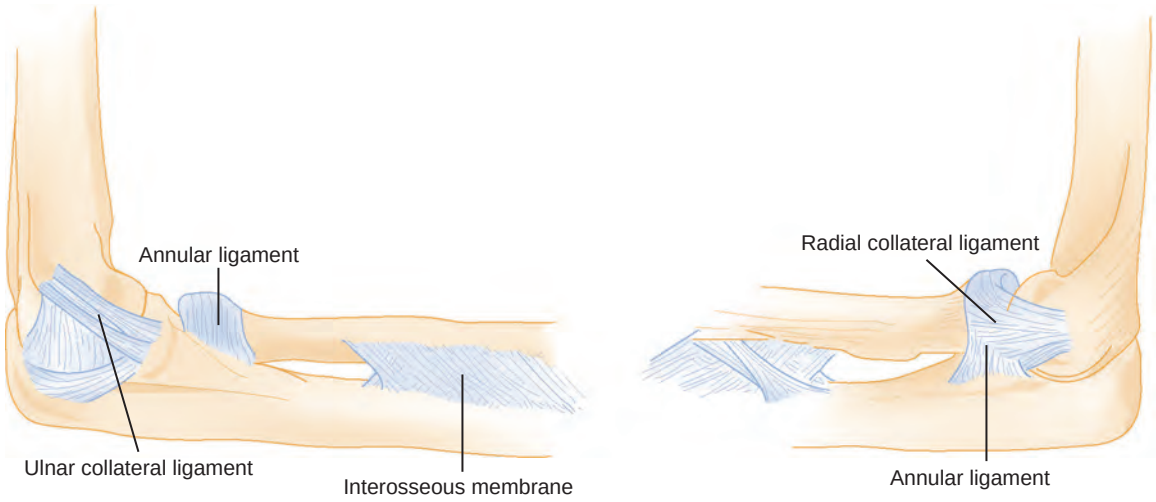


Fig. 175.18. Nursemaid's elbow. In a nursemaid's elbow injury, the annular ligament around the radial head is dislodged as an axial force is applied. The ligament is then partially dislocated into the radiocapitellar joint when the arm is released. (From Simon R, Koenigsknecht S: Emergency orthopedics: the extremities, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

physical and imaging conditions ranging from subtle acetabular dysplasia to irreducible hip dislocations.[8] The incidence of DDH ranges from 1.5 to 25.0/1000 and varies based on diagnostic criteria, population studied, and screening method. Risk factors for DDH include breech presentation, female gender, and family history.[8] Other associations include oligohydramnios, primiparity, high birth weight, postmaturity, and infant swaddling.[9] DDH is more common in whites and Native Americans and less common in African American, Korean, and Chinese populations. DDH is usually unilateral (80%). The cause of DDH is not entirely clear.

Clinical Features

DDH may be diagnosed at birth or, despite frequent and appropriate physical examinations, may not be discovered until later in life. The clinical manifestations of DDH vary with the severity of the dysplasia and the progressive changes that occur over time. Up to 6 months of age, the diagnosis of DDH is based on physical examination findings, including leg length, skinfold, and range of motion asymmetry, and abnormal findings on the Barlow provocative test and Ortolani reduction maneuver. Skinfold asymmetry can be

Fig. 175.19. Toddler's fracture.

Fig. 175.20. A 21-month-old child with right hip dislocation. Note the asymmetric skinfolds in the upper thigh *(arrow)*. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310–1316, 2006.)

noted in the groin, below the buttock, and along the thighs (Fig. 175.20). Although not pathognomonic for DDH, because it can be present in 30% of normal infant hips, skinfold asymmetry is sensitive; the diagnosis of DDH is unlikely in infants with normal skinfold symmetry. Patients with concerning skinfold asymmetry or asymmetry in hip flexion, abduction, and external rotation should be referred for orthopedic consultation.

Fig. 175.21. A 3-year-old child with a left hip dislocation. Note the limited abduction. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310–1316, 2006.)

BOX 175.1

Ortolani and Barlow Maneuvers

ORTOLANI (REDUCTION) MANEUVER

1. Stabilize the pelvis with one hand.
2. With the other hand, slightly abduct the infant's hip.
3. With the index and long fingers over the greater trochanter, pull up the thigh to gently reduce the hip.

BARLOW (PROVOCATIVE) TEST

1. Stabilize the pelvis with one hand.
2. Place the thumb on the inner aspect of the thigh near the lesser trochanter.
3. Adduct the hip.
4. Exert downward pressure on the thigh with the thumb and push it into the table.

Cornerstones for diagnosing DDH in young infants are the Ortolani reduction maneuver and Barlow provocative test. The Ortolani reduction maneuver is performed in an attempt to reduce a dislocated hip into normal position, and the Barlow provocative test detects a lax (subluxable) or easily dislocated hip (Box 175.1). Abnormal findings are the presence of a clunk with the Ortolani test and any abnormal movement between the femoral head and acetabulum with the Barlow maneuver.

After approximately 4 to 6 months of age (ie, when soft tissue contractures have developed), the Ortolani and Barlow tests are less reliable, and range of motion abnormalities become more apparent. Parents may notice limited or asymmetric leg movements or difficulty with diapering. Findings on examination include limited abduction (Fig. 175.21), relative shortening of the ipsilateral femur (Galeazzi's sign; Fig. 175.22), and skinfold asymmetry.

With the onset of walking, gait asymmetry or asymmetrical in-toeing or out-toeing is a clue to the presence of DDH. Adduction and flexion contractures, Galeazzi's sign, hyperlordosis, and waddling gait are common features. Patients may exhibit Trendelenburg's sign—while standing, the patient lifts one leg up at a time and, because the gluteal muscles are weakened on the affected side, the pelvis drops to the opposite side.

Diagnostic Testing

Radiographs of infant hips are extremely difficult to interpret. Before the femoral head ossifies at 3 to 6 months of age, an

Fig. 175.22. Galeazzi's sign in a 7-month-old girl with left hip dislocation. Apparent inequality of femur length is manifested as asymmetry in the level of the patient's knees. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310–1316, 2006.)

abnormal relationship between the upper end of the femur and acetabulum may not be apparent. In infants with unstable but nondislocated hips, radiographs will show the hips in normal position. Before femoral head ossification, a better diagnostic test is ultrasonography. Nondislocated but unstable hips can have ultrasound screening delayed until 4 to 6 weeks of age, when the normal laxity of the hip resolves. Children with dislocated hips, however, should undergo an immediate ultrasound examination. Plain radiographs are useful when the femoral epiphysis ossifies. A standard AP radiographic view of the pelvis with both legs extended in neutral abduction is sufficient for diagnosis. Radiographic findings may include displacement of Shenton's line—a curvilinear line defined by the medial border of the femoral neck and superior border of the obturator foramen—and a widened acetabular angle. Angles greater than 30 degrees are abnormal, and those greater than 40 degrees indicate dislocation (Fig. 175.23).

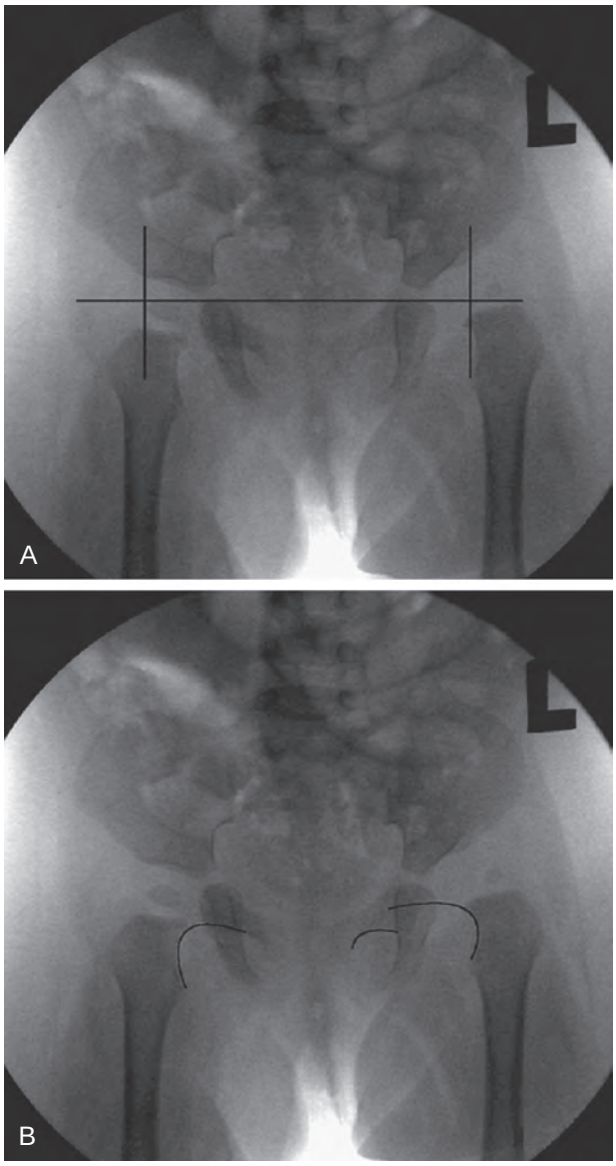


Fig. 175.23. Anteroposterior radiographs obtained in a 7-month-old girl with developmental dysplasia of the left hip. **A,** The horizontal line is Hilgenreiner's line; the vertical lines are Perkin's lines. Note that the femoral head on the right (normal) side lies in the inferomedial quadrant formed by those lines. The left hip is dislocated; its femoral head lies in the superolateral quadrant. **B,** Shenton's line is disrupted on the left (dislocated) hip. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310–1316, 2006.)

Management

Treatment of DDH is most successful when begun early. Patients with untreated abnormalities of the hips that persist beyond the newborn period are at risk for osteoarthritis, pain, abnormal gait, leg-length discrepancy, and decreased agility. Thus, all children who are seen in the ED should have their hips examined until they are able to walk. Neonates who have a dislocated hip at birth should be referred to a pediatric orthopedist immediately. When a newborn has a loose but nondislocated hip, referral can be made within 2 weeks, because most ultrasound and physical examination abnormalities detected in the neonatal period resolve by 2 to 4 weeks of age. Children with loose hips who are seen after the newborn period should be promptly referred to an orthopedic surgeon.

The goal of treatment of DDH is concentric reduction and stabilization of the hip and resolution of dysplastic features of the bone and cartilage. The two most important complications are failure to achieve these goals and aseptic necrosis of the femoral head. In the first 6 months of life, use of the Pavlik harness is the mainstay of treatment. This harness is a dynamic splint that allows movement while preventing hip extension or adduction. Other treatment options include the von Rosen and other similar splints.[9] If these modalities are unsuccessful, application of a hip spica cast is considered. If DDH is diagnosed after 6 months of age, the use of a hip spica cast or fixed orthosis is often required. Most children older than 18 months require surgical reconstruction. Beyond the age of 6 years in bilateral cases and 8 to 10 years in unilateral cases, repair is not usually attempted, because the risks of aseptic necrosis and treatment failure are too high.[9]

Pediatric Hip Pain

Principles

Hip pain in children is an extensive topic, with myriad causes (Box 175.2). The extensive differential diagnosis precludes an in-depth review of the topic in this chapter, but an overview of some of the more common causes of hip pain in children is presented.

BOX 175.2

Causes of Hip Pain in Children

TRAUMA
Hip or pelvis fractures
Overuse injuries

INFECTION
Septic arthritis
Osteomyelitis
Myositis
Lyme disease

INFLAMMATION
Transient synovitis
Juvenile rheumatoid arthritis
Rheumatic fever

NEOPLASM
Leukemia
Osteogenic or Ewing's sarcoma
Metastatic disease

HEMATOLOGIC DISORDERS
Hemophilia
Sickle cell anemia

MISCELLANEOUS
Legg-Calvé-Perthes disease
Slipped capital femoral epiphysis

Specific Disorders and Injuries

Transient Synovitis. Transient synovitis is one of the most common causes of hip pain in childhood, occurring in up to 3% of children. It is a self-limited condition caused by a nonpyogenic inflammatory response of the synovium. The cause of transient synovitis is unknown. Some have hypothesized an association with active or recent infection, trauma, or allergic hypersensitivity. It can occur in infants, adolescents, and adults; its peak incidence is between 3 and 9 years of age. Boys are affected more commonly than girls, and there is a slight predilection for the right side. Less than 5% of cases are bilateral. Its onset may be acute or insidious. Transient synovitis may affect the hips or the knees.

Patients commonly report pain in the hip or groin, but pain can also refer to the knee (femoral nerve), medial thigh (obturator nerve), or buttock (sciatic nerve). Affected patients may walk with a limp or may refuse to walk at all. The leg is held in flexion, with slight abduction and external rotation. On examination, passive movement may be pain-free, with a slightly decreased range of motion with extreme internal rotation or abduction. Most children with transient synovitis are appear well, although some have a low-grade fever and malaise.

The diagnosis of transient synovitis is one of exclusion and relies on the history and physical examination, in combination with limited laboratory testing and AP and frog leg lateral radiographs of the pelvis. Laboratory tests are used to help distinguish children with transient synovitis from those with septic arthritis. In transient synovitis, laboratory values may be normal or may reveal mild elevations in the white blood cell (WBC) count, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR), consistent with a nonspecific inflammatory process.

Multiple studies have attempted to define criteria to help differentiate transient synovitis from septic arthritis. Four independent multivariate predictors of septic arthritis have been found (Kocher criteria)—fever, inability to bear weight, ESR of 40 mm/hr or higher, and serum WBC count higher than 12,000 cells/μL. Patients with three of the four predictors had a 93% chance of having septic arthritis, and those with all four had a 99% likelihood. A subsequent study to validate these findings showed that patients with none of these predictors had a 2% probability of septic arthritis, with one predictor, a 9.5% probability, with two predictors, a 35% probability, with three predictors, a 73% probability, and with all four predictors, a 93% probability of septic arthritis.[10] When this algorithm was tested at another institution, however, the presence of all four Kocher criteria predicted septic arthritis only 59% of the time. A CRP level can also help risk-stratify children for septic arthritis. In a study of children with hip effusions, children with the ability to bear weight combined with CRP values lower than 20 mg/L had less than a 1% risk of septic arthritis. Children unable to bear weight with CRP values higher than 20 mg/L had a 74% probability of having septic arthritis.[11] Thus, in children who are able to ambulate, have minimal pain after treatment with nonsteroidal antiinflammatory drugs (NSAIDs), and have normal inflammatory markers, outpatient management with close primary care follow-up is reasonable.

Radiographs of the hip and pelvis may be normal or nonspecific with transient synovitis but are helpful in excluding other diseases. Radiographic findings consistent with transient synovitis include medial joint space widening, accentuated pericapsular shadow, and Waldenström's sign, which is lateral displacement of the femoral epiphysis, with surface flattening secondary to effusion. However, these findings also are apparent in Legg-Calvé-Perthes disease and, if present, need close follow-up or further investigation with MRI. If joint aspiration is necessary to clarify the diagnosis, ultrasonography can be used. Effusions are present in 60% to 70% of cases of transient synovitis; however, this is a nonspecific finding, and the presence of an effusion on ultrasonography cannot be used to distinguish transient synovitis from other causes of hip pain.

A complete blood count, CRP level, and ESR should be determined, and radiography should be performed. Unless the diagnosis is in question, there is no need to aspirate the joint. Patients with severe symptoms—absent range of motion, ill-appearing, or inability to bear weight—fever higher than 38.5°C (101.3°F), and elevated ESR (≥40 mm/hr) or CRP (>2.0 mg/dL or >20 mg/L) should undergo joint aspiration.

Most cases of transient synovitis can be managed at home with close follow-up by the child's primary care provider within 24 hours. Treatment of transient synovitis is directed at rest of the affected joint and NSAIDs. Temperatures should be monitored and any fever reported to the physician. Children are allowed a gradual return to activity as the pain subsides, and full activity is permitted when the hip is completely pain-free, with no evidence of a limp.

The prognosis for children with transient synovitis is excellent; 75% have complete resolution of pain within 2 weeks and 88% within 4 weeks. The remainder may have less intense but persistent pain for up to 8 weeks. Relapse is infrequent and long-term sequelae rare. A small number (2%) of cases of transient synovitis follow a clinical and radiographic course consistent with that of Legg-Calvé-Perthes disease. Children with persistent symptoms should undergo ultrasonography to evaluate for the presence of an effusion; persistent joint effusion beyond 6 weeks may be associated with the subsequent development of Legg-Calvé-Perthes disease.

Acute Septic Arthritis. Septic arthritis refers to microbial invasion and infection of the joint space. Bacterial pathogens are common in patients with acute septic arthritis, whereas fungal and mycobacterial pathogens tend to be associated with a more indolent septic arthritis. Acute septic arthritis occurs in all age

groups but is more common in children; 70% of cases occur in children younger than 4 years, with the peak incidence between 6 and 24 months. Boys are affected twice as frequently as girls. Predisposing factors include preceding viral infection, trauma, immunodeficiency, hemoglobinopathy, hemophilia with recurrent hemarthroses, diabetes, injection drug abuse, rheumatoid arthritis, and intraarticular injections or operations. Septic arthritis involves the lower extremities in 75% of cases, with the knee the most commonly involved and the hip second most commonly involved. More than 90% of the cases are monoarticular. A history of trauma is elicited in one-third of cases.[12]

Most cases of acute septic arthritis are spread hematogenously, although infection can result from direct inoculation or spread from adjacent tissues. After bacteria enter the joint space, they bind to bone and cartilage, initiating an inflammatory response that breaks down the joint by two mechanisms—directly through the effects of proteolytic enzymes and indirectly through pressure necrosis caused by accumulation of purulent synovial fluid.

Contiguous spread of infection from osteomyelitis to the joint space occurs in approximately 10% of cases and is more common in newborns and young infants. In these children, blood vessels cross the physis, thereby connecting the metaphysis and epiphysis and allowing bacteria direct access into the joint space. Additionally, the joint capsules of the hip and shoulder overlie the bony metaphyses of the femur and humerus, facilitating direct extension of osteomyelitis into the joint spaces. Contiguous septic arthritis with *S. aureus* osteomyelitis has also been documented in older children without these structural differences.[13]

The most common bacterial causes of septic arthritis are listed in Table 175.5. Overall, *S. aureus* is the most common cause of septic arthritis and infection in children; community-acquired, methicillin-resistant *S. aureus* (MRSA) accounts for up to 65% of *S. aureus* infections.[14] Patients with MRSA osteoarticular infection have a more acute onset of illness, with higher fever and a more severe and complicated clinical course. In neonates, group B streptococci and gram-negative organisms are common causes. In addition to the organisms listed in Table 175.5, other causative organisms include *Neisseria gonorrhoeae* in neonates and sexually active adolescents, *Pseudomonas aeruginosa* and *Candida* spp. in injection drug abusers, *Salmonella* spp. in children with sickle cell disease, and gram-negative bacteria in immunosuppressed children.

Kingella kingae, a fastidious gram-negative coccobacillus that colonizes the respiratory and oropharyngeal tracts in children, has been implicated as a common cause of osteoarticular infections in young children. In one study, *K. kingae* was found to be the causative agent in 82% of osteoarticular infections, with the authors reporting a more benign presentation than is seen with other pathogens.[15] *K. kingae* is susceptible to a wide array of antibiotics, including the third-generation cephalosporins that are given empirically to young children with suspected septic arthritis.

The clinical picture of septic arthritis varies with age. Infants tend to have fever, failure to feed, lethargy, pseudoparalysis of the extremity, and pain when being handled. Most older children have systemic signs and symptoms of fever, malaise, poor appetite, and irritability, as well as localized symptoms of pain and refusal to move the affected joint. If the lower part of the body is involved, patients may limp or refuse to walk. The physical examination reveals local erythema, warmth, and swelling. If the hip is affected, it often is held in flexion, abduction, and external rotation. Range of motion is decreased because of pain and muscle spasm, and passive joint movement is painful. In infants, joint dislocation may be observed.

Laboratory evaluation of septic arthritis should include a WBC count, ESR and CRP levels, blood cultures, and evaluation of joint fluid. (Use of the WBC count and ESR was discussed earlier in the section on transient synovitis.) The ESR rises 24 hours or longer after the onset of signs and symptoms of infection, so it may not be helpful during the first day of illness. The CRP level rises more quickly than the ESR, typically is elevated at the time of the initial evaluation and, with appropriate therapy will normalize within 1 week; by contrast, the ESR will not normalize for more than 1 month. As such, CRP is a better marker for response to treatment.

In patients with septic arthritis, the peripheral WBC count and ESR and CRP levels are generally elevated, although WBC counts and acute-phase reactants may be normal, especially with *K. kingae* infection.[15,16] Yagupsky and colleagues have found that the clinical and laboratory features in young children (6–27 months of age) with *K. kingae* septic arthritis and transient synovitis were so similar that the Kocher algorithm was not helpful and, even without fever or leukocytosis, they recommended blood cultures and nucleic acid amplification.[17] For patients without fever who are able to ambulate and have normal inflammatory markers, we recommend further testing, such as a polymerase chain reaction (PCR) assay of the blood or joint fluid, if symptoms worsen or persist beyond 3 days.

Blood cultures should be included in the evaluation of a child with suspected septic arthritis. Although cultures are positive in less than 50% of cases, positive cultures can help direct antibiotic treatment. If *N. gonorrhoeae* infection is suspected, special media are required for cultures of joint fluid, blood, pharynx, skin lesions, cervix, urethra, vagina, and rectum. Urine, urethral, cervical, and vaginal specimens also can be obtained for nucleic amplification testing. If the patient has signs or symptoms of pharyngitis, a throat swab should be sent for culture of *Streptococcus pyogenes*. Patients with *K. kingae* musculoskeletal infection tend to have oropharyngeal colonization and culture or PCR assay of the oropharynx should be performed.[18,19]

If septic arthritis is being considered, joint aspiration should be performed without delay and the synovial fluid sent for Gram staining, aerobic and anaerobic cultures, cell count with differential count, glucose determination, and PCR assay.[20] The synovial fluid in patients with septic arthritis tends to be turbid or grossly purulent, with a WBC count higher than 40,000 cells/μL and a

TABLE 175.5

Septic Arthritis Pathogens and Treatment

AGE	ORGANISM	TREATMENT
Birth–2 mo	Group B streptococci *Staphylococcus aureus* Gram-negative rods *Neisseria gonorrhoeae*	Nafcillin, 50 mg/kg, and cefotaxime, 50–75 mg/kg
2 mo–5 yr	*S. aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* *Kingella kingae* *Haemophilus influenzae*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg[a]
5 yr–12 yr	*S. aureus* *S. pyogenes*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg[a]
>12 yr	*S. aureus* *N. gonorrhoeae*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg[a]

[a]Consider vancomycin, 15 mg/kg, if methicillin-resistant *S. aureus* (MRSA) accounts for >10% local *S. aureus* isolates. Clindamycin can be substituted for vancomycin if local *S. aureus* resistance to clindamycin is <10%.

Adapted from Liu C, Bayer A, Cosgrove SE, et al: Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis 2011; 52:285.

TABLE 175.6

Synovial Fluid Findings in Different Types of Arthritis

CONDITION	FEATURE	WBC COUNT (cells/μL)	PMNs (%)	OTHER
Normal	Clear; yellow	<200	<10	
Juvenile rheumatoid arthritis	Turbid	25–50,000	50–70	50% with decreased complement
Reactive arthritis	Cloudy to turbid; may be clear	1000–150,000	50–70	Increased complement
Lyme arthritis	Turbid	500–100,000	>50	
Septic arthritis	Turbid; white-gray	10,000–250,000	>75	Low glucose High lactate

PMNs, Polymorphonuclear leukocytes (neutrophils); *WBC,* white blood cell.

predominance of polymorphonuclear cells (Table 175.6). Synovial WBC counts are suggestive of but not conclusive for the presence or absence of bacterial infection. Heyworth and associates have found that 48% of patients with synovial WBC counts of 50,000 cells/mm^3 or more had septic arthritis, as did 17% of those with synovial WBC counts less than 50,000 cells/mm^3.[21] The synovial glucose concentration may be low (synovial fluid glucose/blood glucose ratio < 0.5) and protein and lactate levels elevated. Because of the intrinsic immunoglobulins in the synovial fluid, cultures will be positive in less than 50% of cases. Joint fluid should be inoculated directly into blood culture bottles to enhance identification of fastidious organisms, such as *K. kingae*. Culture specimens may need to be incubated for 1 week or longer.

In septic arthritis of the hip, plain radiographs may be normal or may show periarticular soft tissue swelling, widening of the joint space, obliteration or displacement of the gluteal lines, and asymmetric fullness of the iliopsoas and obturator soft tissue planes. Late in the course of infection, radiographs may reveal subchondral bone erosions and narrowing of the joint space. Ultrasonography is much more sensitive than plain radiography for the detection of hip effusion and provides direct visualization during joint aspiration. MRI is the optimal imaging modality for bone and joint infections because it can assess osseous, articular, and surrounding structures without radiation exposure. In addition to establishing a diagnosis, it can identify adjacent intramuscular or subperiosteal abscesses or associated osteomyelitis.[22,23] Septic arthritis with adjacent osteomyelitis has been found in 59% to 68% of patients and more likely if three or more of the following were present: age older than 3.6 years, CRP level more than 13.8 mg/L, symptoms for more than 3 days, platelets less than 314,000/μL, and absolute neutrophil count (ANC) more than 8.6 × 10^3 cells.[22,23]

Septic arthritis requires hospital admission, antibiotics, and surgical intervention. Surgical options range from needle aspiration to open surgical drainage. Indications for surgical drainage in children with septic arthritis include involvement of the hip joint, presence of large amounts of pus or debris in the joint, loculated fluid, recurrence of joint fluid after four or five aspirations, and lack of clinical improvement within 3 days of the initiation of appropriate therapy.

Empirical antibiotic therapy for septic arthritis is directed against the most likely organisms, as dictated by the patient's age and comorbid conditions[24] (see Table 175.5). To maximize culture results, antibiotics should not be given until a specimen of joint fluid is obtained. The emergency clinician must weigh the stability of the patient and possible risk of sepsis with the time needed to obtain synovial fluid. If the child is septic, empirical antibiotics should be given, even if prior to aspiration of fluid. Initial treatment should be parenteral to ensure adequate serum antibiotic concentrations. In addition to antibiotics, a 4-day course of intravenous dexamethasone (0.15 mg/kg qid for 4 days) may be given before or within 2 hours of antibiotics because it can provide symptom relief with less fever and local inflammation, fewer acute-phase reactants, and shorter intravenous treatment time without increased sequelae.[25]

The mortality rate associated with septic arthritis has fallen to less than 1%, but the morbidity remains significant. Sequelae include leg-length discrepancy, persistent pain, limited range of motion and ambulation, and ischemic necrosis of the femoral head.

Legg-Calvé-Perthes Disease. Idiopathic avascular necrosis of the proximal femoral head, also known as Legg-Calvé-Perthes disease, is named after the men who independently described it in the early 1900s. The cause remains unclear; theories are myriad and research results conflicting. It usually occurs in those between the ages of 3 and 12 years, with the peak incidence between the ages of 5 and 7 years. Legg-Calvé-Perthes disease has been reported in teenagers as well as in children as young as 2 years. Boys are affected more frequently than girls, it is bilateral in up to 20% of cases, and it is familial approximately 10% of the time. It is least common in African Americans and East Asians and most common in whites. There is increased incidence at higher latitudes.[26-28]

Children with Legg-Calvé-Perthes disease initially exhibit a limp of insidious and stuttering onset. Pain tends to be localized to the groin or referred to the anteromedial aspect of the thigh or knee region and is worse with activity, relieved by rest, and worse at the end of the day. There is limited hip motion, particularly abduction and internal rotation. Trendelenburg's sign may be present (see earlier, "Developmental Dysplasia of the Hip") accompanied by thigh, calf, and buttock atrophy secondary to disuse. Advanced disease with femoral head collapse results in a limb-length discrepancy.

Laboratory evaluation in Legg-Calvé-Perthes disease is useful in ruling out other causes of hip pain (eg, septic arthritis) and evaluating potential hormonal, metabolic, or genetic causes in patients with bilateral hip involvement.

Legg-Calvé-Perthes disease is diagnosed and staged by AP and frog leg lateral radiographs. Radiographs show the extent of epiphyseal involvement and stage of disease. Radiographic "head at-risk" signs associated with poor results include a radiolucent, V-shaped, osteoporotic defect in the lateral epiphysis (Gage's sign), speckled calcification lateral to the capital epiphysis, diffuse metaphyseal reaction (metaphyseal cysts), lateral capital femoral epiphysis subluxation, and a horizontal physis. MRI can provide earlier and comprehensive information regarding the extent of femoral head necrosis, as well as the anatomy of the head and labrum. The addition of gadolinium enhancement shows femoral head perfusion and provides additional prognostic information. Arthrography is useful in evaluating the relationship between the femoral head and acetabulum and aids in the assessment of range of motion.[26,27]

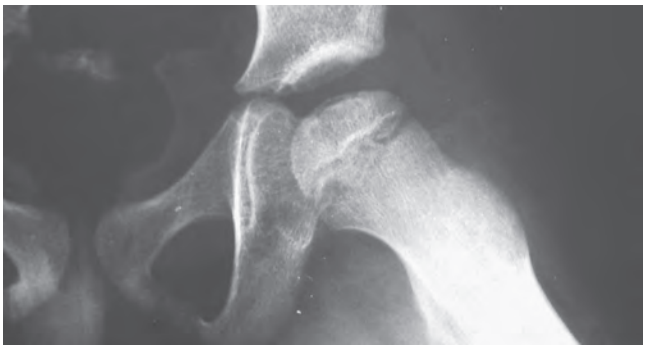


Fig. 175.24. Crescent sign (subchondral lucent zone) in early Legg-Calvé-Perthes disease. (Courtesy Dr. Marianne Gausche-Hill.)

There are four radiographic classification stages of Legg-Calvé-Perthes disease—initial, fragmentation, reossification, and healed. Radiographic findings in the initial stage include a femoral head that appears smaller than the opposite unaffected femoral head, widening of the medial joint space, subchondral lucent zone, subchondral collapse causing the crescent sign (Caffey's sign; Fig. 175.24), irregular physeal plate, and blurry and radiolucent metaphysis. In the fragmentation phase, the repair aspects of the disease become more prominent. The epiphysis begins to fragment, and there are areas of radiolucency and radiodensity as new bone forms. During the reossification stage, the repair process continues as normal bone density returns, radiodensities replace radiolucencies, and alterations in the shape of the femoral head and neck become apparent. The healed stage is the final radiographic stage of Legg-Calvé-Perthes disease, and radiographs of the proximal third of the femur will demonstrate residual deformities. Multiple prognostic classification systems of Legg-Calvé-Perthes disease have been devised; a poor prognosis is associated with greater degrees of deformity of the femoral head and acetabulum at maturity, disease onset in children 6 years or older, female gender, and prolonged duration of disease.

Children diagnosed with Legg-Calvé-Perthes disease should have an orthopedic consultation. Goals in the treatment of Legg-Calvé-Perthes disease are to improve range of motion, prevent deformity, limit growth disturbance, and prevent degenerative joint disease. Treatment is recommended for patients who have clinical and radiographic findings suggestive of a poor prognosis, and it should be started in the initial or fragmentation phase of the disease. The cornerstone of treatment of Legg-Calvé-Perthes disease is containment of the femoral head within the acetabulum to equalize pressure on the head and mold it to the acetabulum. Containment can be achieved nonoperatively or operatively and is determined on a case by case basis. Residual deformities resulting from Legg-Calvé-Perthes disease include morphologic changes in the femoral head (coxa magna, coxa brevis, and coxa irregularis), osteochondritis desiccans, femoroacetabular impingement, and early- or late-onset arthritis. Most patients develop osteoarthritis in their 30s and 40s, with the likelihood of arthritis linked to the sphericity of the femoral head.[29]

Slipped Capital Femoral Epiphysis. A slipped capital femoral epiphysis (SCFE) involves posterior and inferior slippage of the proximal femoral epiphysis on the metaphysis. The femoral head sits securely in the acetabulum and separates from the femoral neck through the growth plate. The average annual incidence of SCFE ranges from 0.71 to 10.8/100,000 children, with rates affected by several factors: (1) race—higher prevalence in African Americans, Hispanics, and Pacific Islanders than whites; (2) geography—higher rates north of 40-degree latitude and in the northeastern and western United States; (3) gender—boys are affected twice as frequently as girls; and (4) underlying medical conditions—more frequent with endocrinopathies, renal osteodystrophy, and radiation therapy.[30,31] The peak incidence is during the adolescent growth spurt, boys between 12 and 16 years of age (mean, 13.5 years) and girls between 10 and 14 years of age (mean, 11.5 years). The age at diagnosis decreases with increasing obesity. Most children with SCFE have delayed skeletal maturation. SCFE is bilateral in up to 80% of cases, although 30% to 40% of these cases are asymptomatic and discovered only on screening radiographs. In unilateral cases, the left hip is affected twice as often as the right.

Although SCFE is associated with endocrine disorders, renal osteodystrophy, and radiation therapy, most cases are idiopathic and associated with obesity. The cause of SCFE is unknown but is likely to be related to biomechanical and hormonal factors. Obesity results in increased shear forces across a more vertically and posteriorly oriented growth plate that has been weakened by architectural irregularities and hormonal changes of puberty. The consequence is slippage of the epiphysis inferiorly and posteriorly in the direction of the weight-bearing force.

Classification of SCFE is based on stability. With or without crutches, in stable SCFE, ambulation is possible, whereas in unstable SCFE, ambulation is not possible. This classification system is preferred to the traditional classification because it does not rely on patient or parent recall for duration of symptoms and provides information about prognosis.[32]

Approximately 90% of all cases of SCFE are stable, and children present with intermittent limp and pain for weeks to months. The pain of SCFE may be localized to the hip, thigh, groin, or knee. Atypical manifestations of SCFE include weakness and easy fatigability of the affected limb and limping on exertion. With continued slippage, there is progressive external rotation and shortening of the involved extremity, with subsequent difficulty in daily activities, such as tying shoes. On examination, children initially have a slight loss of internal rotation and experience pain only at the extremes of motion. As the slip becomes more severe, the gait becomes more antalgic, internal rotation is lost, abduction and flexion of the hip increase, thigh and gluteal muscle atrophy is more pronounced, and leg-length discrepancy develops. Drehmann's sign can be elicited during passive flexion of the affected hip when the patient is supine; as flexion is increased from an extended position, the thigh abducts and rotates externally.

Unstable SCFE in children typically is noticed after a sports-related injury or fall with a twisting injury. These children experience an acute onset of extreme pain, hold the hip in flexion, external rotation, and abduction, and resist any type of movement. Passive movement may result in further displacement of the epiphysis and should be avoided.

The diagnosis of SCFE is made with AP and lateral radiographs of both hips. With stable slippage, AP and frog leg lateral pelvic radiographs should be obtained. When an unstable slip or minimal slip is suspected, a cross-table lateral radiograph replaces the frog leg lateral view. Early in the course of SCFE, the initial slippage is posterior, so the AP view is normal in appearance or shows widening of the physis; the slip is better seen on the lateral projection (Fig. 175.25). Early findings on lateral radiographs include a minimal posterior step-off at the anterior physeal plate and widening of the growth plate. On AP radiographs, signs of slippage include Klein's line and the blanch sign of Steele. Klein's line is a line drawn along the superior margin of the femoral neck. With a normal hip, the line intersects with or falls within the epiphysis, whereas in a hip with a slipped epiphysis, the line does not come into contact with the epiphysis.

Because early slips may not be seen on the AP radiograph, and Klein's line has been shown to miss up to 61% of early slips, it has been recommended that a modified Klein's line be used to

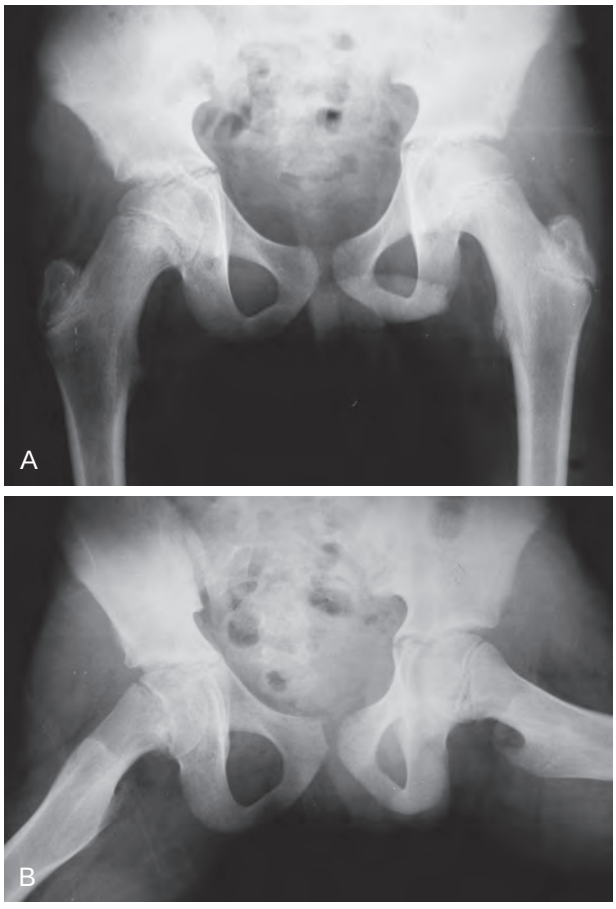


Fig. 175.25. A, Anteroposterior radiograph of the pelvis with a unilateral slipped capital femoral epiphysis. Note widening of the physis on the right compared with the left. **B,** Early inferior and posterior slippage is evident on the lateral view. (Courtesy Dr. Marianne Gausche-Hill.)

Fig. 175.26. Anteroposterior radiograph of the pelvis with a slipped capital femoral epiphysis. Note widening of the physis on the left and a greater distance from the lateral edge of the femoral epiphysis to Klein's line on the right than is seen on the left. A difference of more than 2 mm is diagnostic.

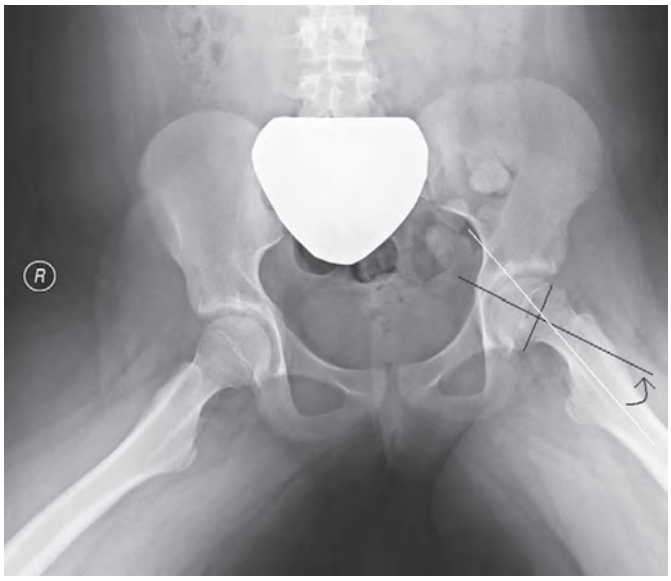


Fig. 175.27. Epiphyseal shaft angle of Southwick. On a lateral radiograph, a line is drawn from the anterior to the posterior epiphyseal edges and a second line is then drawn perpendicular to this line. A third line is drawn down the femoral diaphysis. The intersection between the perpendicular line and femoral shaft line is the epiphyseal shaft angle. The magnitude of slip displacement is the angle of the involved hip minus the angle of the normal hip. (From Pinkowsky GJ, Hennrikus WL: Klein line on the anteroposterior radiograph is not a sensitive diagnostic radiologic test for slipped capital femoral epiphysis. J Pediatr 162:804–807, 2013.)

evaluate for slippage (Fig. 175.26). The modified Klein's line is a comparison of the amount of epiphysis lateral to the Klein line on the symptomatic side compared with the same measurement on the asymptomatic side, with a difference of 2 mm being significant.[33] Even with the modified Klein's line, 13% of SCFEs were missed, highlighting the need for a lateral film.[34] The blanch sign of Steele, another SCFE finding seen on the AP radiograph, is a crescent-shaped area of increased density in the proximal portion of the femoral neck created by superimposition of the posteriorly displaced epiphysis on the femoral neck.

As the slip continues, the femoral metaphysis is more laterally displaced from the medial wall of the acetabulum, and the epiphysis continues to be displaced inferiorly and posteriorly relative to the metaphysis. Over time, remodeling smooths away the superior and anterior portions of the femoral neck and, in an attempt to buttress the slippage, a callus is formed at the inferior and posterior portions of the femoral neck. Acute unstable slips will not show any bone healing or remodeling. MRI can be used to confirm epiphyseal displacement in patients who have symptoms but no radiographic findings suggestive of SCFE; findings include widening of the physis, bone marrow edema of the metaphysis, joint effusion, and synovitis.

Slip severity is described in either of two ways. The simplest classification describes the amount of displacement of the femoral head on the femoral neck. In mild SCFE, the amount of displacement of the femoral head is less than one-third, in moderate SCFE, between one-third and one-half and, in severe SCFE, the femoral head is displaced more than half the width of the femoral neck. A more accurate description of the magnitude of slippage is obtained by measurement of the epiphyseal shaft angle of Southwick (Fig. 175.27). On a frog leg lateral radiograph of the pelvis, a line is drawn between the anterior and posterior tips of the epiphysis at the physeal plate level. A second line is then drawn perpendicular to the epiphyseal line. Next, a line is drawn along the midshaft of the femur. The epiphyseal shaft angle is formed by the intersection of the perpendicular and femoral shaft lines. The magnitude of slip displacement is the angle of the involved

hip minus the angle of the normal hip. Mild SCFE involves displacement of less than 30 degrees, a moderate slip is between 30 and 50 degrees, and severe displacement is more than 50 degrees.[31]

Children diagnosed with SCFE should be non–weightbearing. An urgent orthopedic consultation should be obtained. For a stable slip, definitive treatment is best performed within a few days. Unstable slips may require immediate fixation. The goals of treatment are to prevent further slippage, achieve physeal stability, avoid complications, and maintain adequate hip function. The vast majority are fixed surgically.

The most worrisome short-term complications of SCFE are avascular necrosis and chondrolysis. Avascular necrosis occurs in 10% to 15% of children with SCFE. The risk is higher with unstable SCFE,[30-32,35] greater degrees of slippage, and multiple attempts at reduction. Chondrolysis occurs in approximately 5% of patients with SCFE and may develop before or as a result of treatment. There is an increased incidence in children with greater degrees of slippage or with penetration of the screw into the joint space.[35]

Other complications of SCFE include nonunion, premature closure of the epiphyseal plate, and degenerative changes. Degenerative hip arthritis develops over decades and has an earlier onset, with more severe degrees of slippage.

Apophyseal Injuries

Principles

The apophysis is a cartilaginous structure that serves as a site for insertion of tendons on the growing bone. It has its own growth plate, with a slower rate of growth than the nearby epiphyseal plate. Apophysitis is unique to patients with skeletal immaturity and involves inflammation of this actively growing bone prominence, which is under great tensile stress. Apophysitis may be secondary to a single episode of macrotrauma or may follow repetitive microtrauma. Common apophyseal injuries include medial epicondylitis, Osgood-Schlatter syndrome, and Sever's disease.

Specific Disorders

Osgood-Schlatter Syndrome. In 1903, Osgood and Schlatter independently reported traumatically induced apophyseal injury to the tibial tubercle in adolescents. This entity, now known as Osgood-Schlatter syndrome, is the most common of the apophyseal disorders. It is most common in boys between 10 and 15 years and in girls between 8 and 13 years. It is bilateral up to 30% of patients.

Children with Osgood-Schlatter syndrome have tenderness, pain, and swelling at the site of insertion of the patellar tendon on the tibial tubercle. The tibial tubercle may be prominent and the quadriceps tight. Pain is worsened with activities that cause the quadriceps to contract and stress the tubercle, such as running and jumping. Extension of the knee against resistance causes pain, but resisted straight leg raises are painless. Osgood-Schlatter syndrome is a clinical diagnosis, and radiographs are not indicated. If radiographs are obtained, lateral views of the tibial tubercle may appear normal or may show an enlarged, fragmented, and irregular tibial tuberosity, with or without an overlying bony ossicle. These findings are nonspecific and are not diagnostic on their own. Ultrasonography may reveal pretibial swelling, fragmentation of the ossification center, insertional thickening of the patellar tendon, and/or excessive fluid collection in the infrapatellar bursa.

Treatment of Osgood-Schlatter syndrome includes ice and modification of activity, with or without NSAIDs. The use of a patellar strap may help relieve symptoms. After the acute inflammatory process has resolved, treatment focuses on strengthening and stretching of the quadriceps muscles. Mild pain during activity is permissible. With more severe symptoms, the risk of avulsion of the tibial tubercle should be weighed against the benefits of competing. In rare cases, conservative therapy is insufficient, and a 2- to 3-week trial of crutches is appropriate. Steroid injections are not recommended due to the risk of patellar tendon rupture. Complete recovery without residual pain or weakness is typical. Recovery usually occurs within weeks but, in some cases, may not be complete until the underlying growth plate has closed.

Sever's Disease. Sever's disease is an apophysitis of the calcaneus due to traction by the gastrocnemius-soleus complex. It initially was described in 1912 and manifests as posterior heel pain in an 8- to 13-year-old athlete. It is bilateral in 60% of cases. As with other apophyseal injuries, pain is exacerbated by activity. Sever's disease can be associated with growth or tight heel cords. Impact sports, especially those that involve running, and sports in which cleats are worn are implicated in the development of Sever's disease.

Patients have pain at the insertion site of the Achilles tendon and plantar fascia on the calcaneus. Tenderness is elicited when the calcaneus is squeezed bilaterally. Dorsiflexion of the ankle is restricted by tight heel cords. Radiographs may be normal in appearance or may show partial fragmentation and increased density of the calcaneal apophysis, although these findings can be normal.

Treatment of Sever's disease consists of ice, massage, stretching of the plantar fascia and involved muscles (gastrocnemius-soleus complex and ankle invertors and evertors), NSAIDs, and shock-absorbing shoe inserts. Heel cups can be beneficial if their use is accompanied by stretching to avoid exacerbation of the calf muscle contracture. Patients in whom conservative management fails should be evaluated for calcaneal stress fractures. Modification of activity and a trial of crutches for 3 to 4 weeks may be necessary.

Little League Elbow. *Little League elbow* is a term used to describe a group of injuries of the elbow, including apophysitis, medial epicondylitis, and osteochondritis dissecans of the radial head and capitellum. The injury involves an overuse phenomenon resulting in inflammation at the origin of the forearm flexors. It generally affects overhand athletes, including baseball pitchers and tennis players, most commonly preadolescents.

Examination reveals localized tenderness and swelling over the medial epicondyle and pain with resisted flexion of the wrist. There may be a slight flexion contracture. Radiographs may be normal in appearance or may show fragmentation, sclerosis, and widening of the medial epicondylar apophysis. Treatment consists of ice, NSAIDs, and modification of activity. Throwing is restricted until the symptoms have resolved. After resolution of the pain, the patient can begin a program of muscle stretching and strengthening, with a gradual return to throwing. Recovery usually takes 4 to 6 weeks. Patients with persistent pain, locking or decreased range of motion of the joint, or lateral elbow pain should be evaluated for avulsion fractures, loose bodies, and osteochondritis dissecans.

Apophysitis of the Hip. Apophyseal injuries of the hip occur where major abdominal and hip muscles originate or insert, such as the anterior superior iliac spine, anterior inferior iliac spine, iliac crests, and ischial tuberosities. Dancers and distance runners are most commonly affected. Patients experience dull pain near the hip that is related to activity. Treatment includes strengthening and stretching of the abdominal and hip muscles and restriction of activity.

Avulsion Fractures. Any patient with sudden onset of apophyseal pain after an acute traumatic event should be evaluated for an avulsion fracture of the apophysis or adjacent bone. Such fractures occur when the muscle attachments to the apophyses are pulled off during strong active contractions against resistance. Examination will reveal localized tenderness and swelling. Plain films are usually diagnostic (Fig. 175.28). Ultrasonography may play a role when the diagnosis is in question. Findings include a hypoechogenic zone, increased distance to the apophysis, dislocation of the apophysis, and mobility of the apophysis on dynamic examination. Treatment of an avulsion fracture is based on the degree of separation; displacement less than 2 cm with a hip avulsion and less than 5 mm with a medial epicondyle avulsion can be immobilized for 4 to 6 weeks, with subsequent slow resumption of activities. Widely separated avulsion fractures are treated surgically.

Fig. 175.28. Avulsion of the inferior iliac spine in a child with hip pain after kicking a soccer ball. (Courtesy Dr. Marianne Gausche-Hill.)

KEY CONCEPTS

- The growth plate is the weakest part of the bone and is more likely to separate before the adjacent tendon or ligament tears, thereby making sprains uncommon.
- Of supracondylar fractures, 95% are of the extension type. Displaced fractures are at risk for neurovascular injury and compartment syndrome; the anterior interosseous branch of the median nerve and the brachial artery are most commonly involved.
- Developmental dysplasia of the hip affects 1% of children; all children who are not yet walking should have a thorough hip evaluation, including Ortolani and Barlow testing.
- Transient synovitis presents between 3 and 9 years of age and usually involves the hip. It can be differentiated from septic arthritis and other causes of hip pain with a thorough physical examination and directed laboratory and radiographic evaluation.
- The peak incidence of septic arthritis is between 6 and 24 months of age. Patients presents with pain, fever, and decreased use of the involved limb. The knee is usually involved, followed by the hip. Inflammatory markers tend to be elevated, although they may be normal in young children with *Kingella kingae* infection. Blood and synovial fluid cultures are positive less than 50% of the time. *Staphylococcus aureus* is a frequent culprit. Treatment consists of joint drainage and empirical antibiotics (eg, nafcillin and ceftriaxone, with or without vancomycin).
- Examination of the hip is warranted in all patients with knee pain.
- Legg-Calvé-Perthes disease is an idiopathic avascular necrosis of the hip that has a peak presentation between 5 and 7 years of age. It is bilateral in 20% of cases.
- A slipped capital femoral epiphysis (SCFE) is a posteroinferior slippage of the proximal femoral epiphysis on the metaphysis. It is more common in boys than girls, more common with obesity, and bilateral in 80% of cases. It is best seen on a cross-table or frog leg lateral view radiograph; 90% are stable.
- Osgood-Schlatter disease is the most common form of apophysitis. The onset is insidious, and treatment is conservative and symptomatic. A sudden onset of apophyseal pain is more suggestive of an avulsion fracture.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 175: QUESTIONS & ANSWERS

175.1. A 7-year-old boy presents with left elbow pain following a fall. He has a moderately swollen left elbow and holds his elbow in extension. He has pain and crepitus at the distal humerus, with anterior fullness. Which of the following statements regarding this patient's most likely injury is true?

A. An anterior fat pad may be normal.
B. An elbow flexion mechanism is likely.
C. Brachial artery injuries occur in less than one-third of cases.
D. The external epicondyle should be ossified on a radiograph.
E. The most commonly injured nerve is the radial nerve.

Answer: A. Supracondylar humerus fractures involve an extension mechanism 95% of the time. On plain films, an anterior fat pad may be normal as long as it is not bulging or sail-shaped. A posterior fat pad is never normal and warrants further imaging. The CRITOE mnemonic is useful to recollect that the external (lateral) epicondyle is the last elbow ossification center to ossify (age 11 years). Neurovascular injuries are common, with brachial artery injuries in up to 40% of cases. The median nerve is most commonly injured.

175.2. Which of the following statements regarding nursemaid's elbow is true?

A. After reduction, normal use should be observed by 4 to 6 hours.
B. Peak incidence is between 6 and 8 years of age.
C. Pronation is the reduction technique of choice.
D. Radiographs are necessary before reduction.
E. Swelling and ecchymosis are common.

Answer: C. Pronation is associated with success rates equal to those for supination and is associated with less pain**.** Normal use should be observed within approximately 10 to 30 minutes. Radiography is not indicated unless there is swelling, erythema, ecchymosis, or deformity. The peak incidence is age 2 or 3 years, with a slight female predominance.

175.3. A 21-month-old presents after a fall from standing. Since the fall, he has refused to walk or put weight on his left leg but is able to crawl without difficulty. Anteroposterior (AP) and lateral views of the left lower extremity are normal. Which of the following statements regarding this patient's most likely injury is true?

A. If not seen on routine radiographs, internal oblique radiographs may reveal the injury.
B. It requires a high-energy mechanism of injury.
C. Nonaccidental trauma should be considered in all children with this injury.
D. Peak incidence is between 6 and 8 months of age.
E. Treatment consists of a below-knee walking cast and immobilization.

Answer: A. Toddler's fractures are oblique nondisplaced fractures caused by low-energy torsional forces applied to the porous bone of infants and young children. The peak age of presentation is

between 9 and 36 months of age. The mechanism of injury can be as mild as the child's twisting on the leg while walking or a fall from an insignificant height. AP and lateral radiographs may reveal a spiral or oblique fracture extending downward and medially through the distal third of the tibia. An internal oblique radiograph is helpful if evidence of fracture is absent on the AP or lateral view. Treatment of a toddler's fracture consists of a long leg cast for approximately 3 weeks.

175.4. A 14-year-old obese male presents with progressively worsening left knee pain. On examination, he has full range of motion of the knee but is unable to move his left hip due to severe pain and is unable to bear weight. This patient's most likely injury would cause which of the following findings on routine radiographs?

A. Fragmentation of the femoral head
B. Inferiorly and posteriorly displaced femoral epiphysis relative to the metaphysis on a cross-table lateral view of the hip
C. Inferiorly and posteriorly displaced femoral epiphysis relative to the metaphysis on a frog leg view of the hip
D. Medial joint space widening on hip or pelvis radiographs

Answer: B. This patient's history is consistent with an unstable slipped capital femoral epiphysis (SCFE). The diagnosis of SCFE is made with AP and lateral radiographs of both hips. With stable slippage, AP and frog leg lateral pelvic radiographs should be obtained. When an unstable slip or a minimal slip is suspected, a cross-table radiograph replaces the frog leg lateral view. Fragmentation of the femoral head is seen in Legg-Calve-Perthes disease. Widening of the medial joint space is suggestive of a joint effusion and can be seen in Legg-Calve-Perthes disease, transient synovitis, or septic arthritis.

175.5. Which of the following statements regarding apophyseal disorders is true?

A. The age of onset tends to be younger in females than in males.
B. The first-line treatment is casting and immobilization.
C. They are extremely rare.
D. They only occur in mature skeletons.
E. They usually occur in adolescents older than 16 years old.

Answer: A. Apophysitis is unique to patients with skeletal immaturity and involves inflammation of the cartilaginous structure that serves as a site for insertion of tendons on the growing bone. Growth contributes to the development of apophysitis; females mature at a younger age than males and are affected earlier in life. Apophysitis is common and is estimated to occur in 18% of pediatric patients. Children between 8 and 15 years of age are most frequently affected, with different apophyseal centers affected at different ages.

CHAPTER 176

Drug Therapy for the Pediatric Patient

Maryann Mazer-Amirshahi | Matthew D. Wilson

PRINCIPLES

Background

Emergency clinicians are tasked with treating not only a wide age range of pediatric patients but also a wide spectrum of disease.[1,2] Nearly 75% of visits are associated with some form of pharmacotherapy during the visit or in the form of a prescription at discharge. Children may present to the emergency department (ED) with an acute-life threatening illness or injury. Although many children presenting for emergency care are otherwise healthy, children with complex medical needs and chronic illness account for a major portion of ED encounters.[2] This is further complicated by the fact that despite significant need for appropriate pharmacotherapy for pediatric ED patients, there is a relative paucity of data regarding the safe and effective use of medications in this population.

Historical Perspective

The sulfanilamide disaster of the 1930s resulted in the deaths of several children and led to the passage of the Food, Drug, and Cosmetic Act of 1938; however, significant disparities in pediatric pharmacotherapy were largely precipitated by the thalidomide disaster of the 1960s.[3] Thalidomide was widely marketed outside the United States as an antiemetic for pregnant women suffering from morning sickness until severe teratogenic effects, such as phocomelia, were discovered. Lessons learned from experience abroad stimulated legislative efforts to promote safer medication use in vulnerable populations. In 1962, the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act were passed, which essentially excluded children and women of childbearing age from clinical trials.[3] This resulted in a general lack of clinical pharmacology data in the pediatric population, drug labeling that often advised against the use of many medications in children due to insufficient data, and high rates of off-label prescribing.

Recent Legislative Efforts

It had long been recognized that children had essentially become so-called therapeutic orphans, but it was not until the mid-1990s that legislative efforts began to focus on correcting this disparity.[4,5] The US Food and Drug Administration (FDA) Pediatric Labeling Rule, passed in 1994 and promulgated in 1998, allowed for pediatric labeling based on the extrapolation of adult data if the course of disease was similar in both populations.[5] In 1997, the FDA Modernization Act was passed, which provided for an extension of market exclusivity for manufacturers that performed pediatric clinical trials.[6]

A major stride toward therapeutic equity was made when the Best Pharmaceuticals for Children Act (BPCA) was passed in 2002. The goal of the BPCA was to promote clinical trials of pharmaceuticals in children that would generate safety and efficacy data, leading to more pediatric drug approvals and expanded labeling.[7,8] This was followed by the Pediatric Research Equity Act (PREA) in 2003. PREA mandated that manufacturers conduct clinical trials in children for drugs under development that have the potential for pediatric use and expanded existing labeling for drugs that were already commonly used in children.[7,9] Further progress was made in 2012 with the passage of FDA Safety and Innovation Act (FDASIA), which permanently reauthorized the BPCA and PREA. In addition, the FDASIA strengthened FDA authority over pediatric clinical trials and promoted studies in underserved populations, specifically neonates.[7,10] Although progress in encouraging pediatric drug research has been gradual, the eventual increase in governmental regulation and engagement of manufacturers is shown in Table 176.1, which summarizes the significant legislation affecting research in pediatric pharmacology.

Current Landscape

This legislation has resulted in significant advances in pediatric pharmacotherapy, with over 500 drugs with new or expanded pediatric labeling as of late 2014.[10] At the same time, there is still a lack of high-quality pediatric data for many drugs currently on the market and high rates of off-label use of therapeutics in children continue.[11] In addition, labeling information for children was lacking in the package inserts for over 70% of newly approved pharmaceuticals over the past decade, and pediatric labeling revisions were fewer and took longer than their adult counterparts.[12] Even when there are adequate pediatric data for a particular drug, there may not be a specific formulation suitable for pediatric use.[13]

There are several reasons that therapeutic equity continues to elude the pediatric population, including ethical and practical considerations when performing pediatric trials, pharmaceutical market factors, and limitations to current legislation. Ultimately, a multifaceted approach engaging stakeholders from industry, government, health care systems and clinicians, and patient advocacy groups will be required to ensure safe and effective pharmaceuticals for children.[14]

PHARMACOKINETIC CONSIDERATIONS IN CHILDREN

Absorption

Physiologic differences in children can affect drug absorption, particularly for enteral administration, the major route of administration in children. However, these effects are rarely clinically significant in the ED. Fig. 176.1 illustrates many of the key factors that account for pharmacokinetic differences between children and adults. For example, in gastric absorption, young children have higher gastric pH levels, which affect the bioavailability of acid-labile drugs, and they have decreased gastric emptying times, which prolongs exposure to medications before they pass the pylorus. Variations in the intestinal tract also result in pharmacokinetic differences. The activity of drug-metabolizing enzymes on the intestinal border vary as development occurs, and differences in gut flora can affect drug absorption in young infants. One commonality between children and adults is that drug absorption is often impaired in the setting of critical illness.

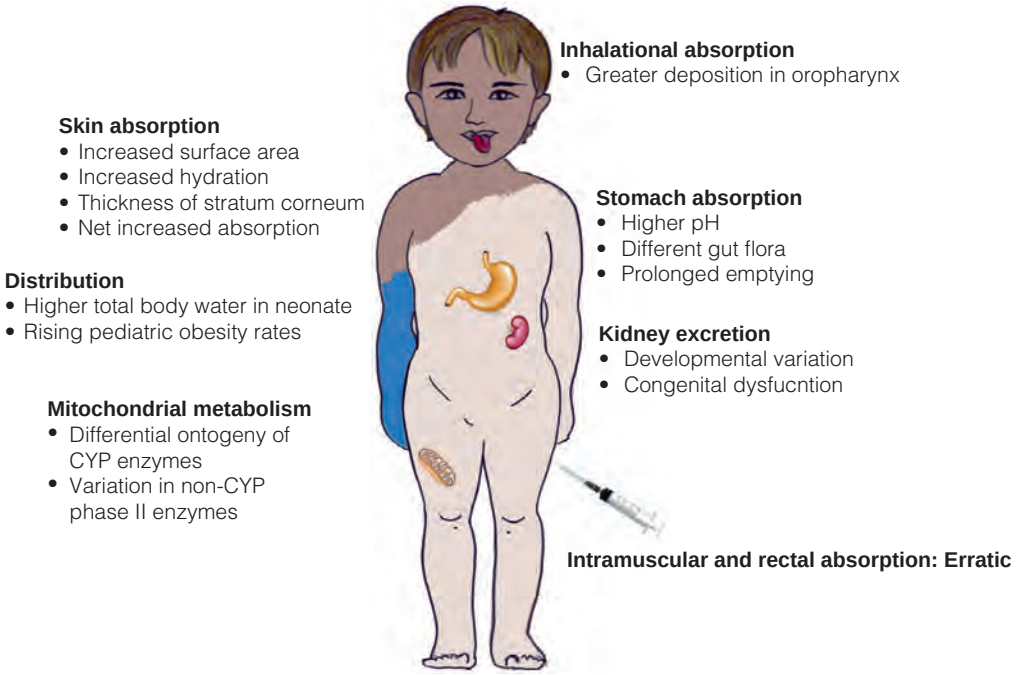

Fig. 176.1. Major Pharmacokinetic Considerations in the Pediatric Patient. (Courtesy Voyo Wu.)

TABLE 176.1

Selected Legislative Milestones Affecting Pediatric Drug Research and Manufacturing

YEAR	ACT
1938	The federal Food, Drug, and Cosmetic Act was passed in response to pediatric fatalities from "elixir of sulfanilamide," requiring manufacturers to prove a drug's safety.
1962	Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act were passed excluding children from clinical trials.
1983	The Orphan Drug Act was passed to promote research of drugs for rare diseases.
1994	The US Food and Drug Administration (FDA) Pediatric Labeling Rule allowed for pediatric labeling based on comparable adult data.
1997	The FDA Modernization Act (FDAMA) provided market exclusivity for manufacturers who conducted pediatric drug trials.
2002	The Best Pharmaceuticals for Children Act (BPCA) was passed to promote pediatric drug trials and expand current labeling.
2003	The Pediatric Research Equity Act (PREA) mandated that manufacturers conduct pediatric trials for drugs under development with potential pediatric use.
2007	The BPCA and PREA were reauthorized.
2012	The FDA Safety and Innovation Act (FDASIA), permanently reauthorized the BPCA and PREA and expanded research for underserved populations.

Absorption of drugs via a non–oral route can vary significantly in children compared to adults. The topical route can result in increased absorption in children due to their relatively larger body surface area. Additionally, children's skin contains more water and has a thinner stratum corneum. These factors make children more prone to systemic toxicity from dermally applied drugs. Intramuscular administration of medication is less common in young children because absorption is erratic; however, over time, drug absorption becomes more efficient via this route in older children. Absorption of rectally administered medications also varies widely, depending on the age of the child and chemistry of the drug involved. However, this route can be used for medications when children are unable to tolerate or are refusing oral administration, such as for the antipyretic acetaminophen and the antiepileptic diazepam. The ability to administer medications via the pulmonary route is particularly desirable in pediatric populations, given the high prevalence of respiratory conditions, such as reactive airway disease. At the same time, children are less able to coordinate the use of a metered-dose inhaler to deliver these medications properly; parental assistance and adjunct devices such as spacers should be used to maximize efficacy by minimizing drug deposition in the oropharynx.

Distribution

Distribution of drugs can differ significantly in children, which has important clinical implications. For example, neonates and infants have higher total body water and larger volumes of distribution; therefore, dosing of medications such as aminoglycosides will differ in this age group, and drug concentrations should be closely monitored. Free drug concentrations are also affected by the relatively lower concentrations of plasma proteins in infants and young children. A consideration specific to neonates is the displacement of bilirubin from protein-binding sites by drugs such as ceftriaxone, which can lead to kernicterus. Consequently, these medications should be avoided until the blood-brain barrier matures. Table 176.2 presents examples of other commonly used medications in the practice of emergency medicine that carry pediatric-specific toxicities as a result of pharmacokinetic and other idiopathic differences.

Childhood obesity has reached epidemic proportions in the United States and worldwide, resulting in more children being placed on medications for chronic conditions, such as antihypertensives.[15,16] Because these medications have been traditionally prescribed for adults, there is a significant paucity of safety and efficacy data in children, which could predispose them to adverse drug events. Increased body fat content can alter the distribution

TABLE 176.2

Common Emergency Department Medications With Pediatric-Specific Toxicities

MEDICATION	PEDIATRIC-SPECIFIC TOXICITY
Codeine	Ultrarapid CYP2D6 metabolism implicated in deaths in posttonsillectomy patients and from breast milk excretion in infants
Antipyretics	Dosing errors—led to 2011 US Food and Drug Administration (FDA) guidelines to reduce confusing labeling and package directions
Aspirin	Reye's syndrome associated with use during viral illness
Cough and cold medicines	FDA and Joint Advisory Panel warning for children <2 yr; expanded to 2–4 yr and still controversial for 4–6 yr
Phenothiazines	Apnea risk (severe respiratory depression at wide range of doses)
Ceftriaxone	Calcium precipitation in patients <28 days, kernicterus
Doxycycline	Tooth discoloration
Trimethoprim-sulfamethoxazole	Bilirubin displacement—may result in kernicterus in patients <2 mo

of lipophilic drugs, leading to the accumulation of these medications and potentially resulting in adverse effects. At the same time, there is a lack of guidelines for appropriate dosing of most medications in obese adults, let alone in the pediatric population.[17]

Metabolism

Drug metabolism in neonates and infants is diminished because of immature drug-metabolizing enzymes. Lower or less frequent dosing may be required to prevent toxicity in this age group. An example of toxicity due to differences in drug-metabolizing enzymes is the neonatal gasping syndrome. Benzyl alcohol, a common preservative for parenteral medications, is metabolized to benzoic acid, which is detoxified by glycine conjugation. Glycine conjugation is decreased in neonates and benzoic acid accumulates, leading to metabolic acidosis, respiratory distress, and cardiovascular collapse. Between the ages of 1 and 6 years, children may have increased drug-metabolizing activity compared to adults and may require higher relative doses. As children approach adolescence, drug metabolism is generally the same as in adults.

Elimination

The kidney is the primary route of elimination for many parent compounds and active metabolites. In the neonate and infant, glomerular filtration is decreased for the first 6 months of life, and tubular secretion is decreased for the first year. To avoid toxicity, maintenance doses should be decreased or dosing intervals extended. An important example in the ED is gentamicin, where it has been demonstrated that using dosing regimens designed for older children and adults has resulted in significant toxicity.[15]

OTHER CONSIDERATIONS

Drug Therapy in the Neonate

Neonates are the subgroup of pediatric patients that differ the most with regard to physiology and drug disposition; however, there is also the greatest paucity of pharmacologic data in this population.[12] Emergency clinicians caring for neonates should consult drug references for specific prescribing information because dosing recommendations, administration, and contraindications differ in this age group. Early consultation with a neonatologist may be warranted, depending on the clinical scenario.

Neonates can also be exposed to and experience subsequent toxicity from pharmaceuticals via lactation. For example, the postpartum use of codeine in lactating mothers has been associated with toxicity in the newborn. This phenomenon has been linked to maternal CYP2D6 polymorphisms, which result in ultrarapid metabolism of codeine to morphine. High concentrations of morphine are excreted in the breast milk, which can cause toxicity in the infant. Although many medications are safely administered during breast-feeding, this underscores the importance of obtaining a complete maternal medication history when evaluating a breast-fed infant, as well as consulting a lactation reference when prescribing medications to nursing mothers. This can be difficult because there are limited human data regarding medication use in pregnancy, and multiple factors need to be considered, including maternal comorbidities, therapeutic alternatives, and the benefits of continued breast-feeding, when possible.[18]

Use of Antipyretics in Children

Fever is one of the most common presenting complaints for pediatric ED and urgent care visits. Fever is a common physiologic response to illness, which is rarely harmful, and likely serves a beneficial role as part of the immune response. At the same time, many parents and clinicians still aggressively treat even slight elevations in temperature with antipyretics. This practice has not been proven to be beneficial and may even be harmful, because therapeutic errors while administering antipyretics are common.[19] One study has demonstrated that parents administer antipyretics incorrectly up to 50% of the time, which can lead to overdose and subsequent toxicity. Recently, manufacturers have moved to one standardized concentration of acetaminophen for infants and children in an effort to prevent dosing errors.

Current recommendations focus on maintaining patient comfort and not normalizing temperature. When dosed appropriately, acetaminophen and ibuprofen are equally effective for the management of fever.[19] Ibuprofen should be avoided in infants younger than 6 months because of pharmacokinetic differences and ongoing renal development in this age group. Combined regimens or alternating therapy with acetaminophen and ibuprofen may be slightly more effective; however, this approach is also more complicated and may predispose to medication errors, with little clinical benefit.[19] Emergency clinicians should focus on patient comfort when prescribing antipyretics in the ED and counsel parents regarding the safe and appropriate use of these medications on discharge. Table 176.3 presents manufacturer-recommended dosing for commonly used antipyretics and analgesics; Box 176.1 provides counseling points for parents regarding fever and antipyretic use.

Over-the-Counter Cough and Cold Medications

Cough and cold symptoms are complaints commonly encountered in pediatric ED patients. Until recently, over-the-counter (OTC) cough and cold medications containing various combinations of antitussives, antihistamines, decongestants, expectorants, and antipyretics were in widespread use for symptomatic relief in children. In 2007, a series of initiatives was launched to curb the use of these medications in young children due to a lack of efficacy data and mounting safety concerns, including therapeutic errors, unintentional ingestions, and adverse drug effects.

TABLE 176.3

Common Antipyretics and Analgesics

AGENT	INDICATION	DOSE	MAXIMUM
Acetaminophen	Analgesic, antipyretic	15 mg/kg PO, PR, q6–8h	75 mg/kg/day, never to exceed 3 g
Ibuprofen	Analgesic, antiinflammatory, antipyretic	10 mg/kg PO, q8h	40 mg/kg/day, never to exceed 3200 mg; not recommended for children <6 mo
Morphine	Analgesic	0.1 mg/kg IV, IO, IM, SC	Dosing recommended for children >6 mo
Codeine	Analgesic	0.5 to 1 mg/kg PO	60 mg; only used if benefit outweighs risk
Fentanyl	Analgesic	1 to 3 μg/kg IV, IO, IM, SC	N/A

IM, Intramuscular; *IO,* intraosseous; *IV,* intravenous; *PO,* orally, *PR,* per rectum; *SC,* subcutaneous.

BOX 176.1

Counseling Tips for Parents and Caregivers for Safe Antipyretic Use

- Fever is a clinical sign that the body may be fighting infection and children should be monitored for signs of serious illness.
- Be sure the child maintains adequate hydration during febrile illness.
- Antipyretics should be given to minimize discomfort; maintaining a normal body temperature is less important.
- The use of combination products and alternating use of antipyretics can lead to dosing errors and therapeutic duplication.
- Do not use ibuprofen in children younger than 6 months.
- Do not use aspirin in children younger than 15 years due to the risk of Reye's syndrome.
- Counsel caregivers and parents regarding appropriate weight-based dosing for the child.
- Recommend use of a calibrated measuring device to avoid dosing errors.
- Store antipyretics and all medications out of the reach of children.
- Do not use isopropyl or ethyl alcohol to cool the skin because it may result in toxicity from topical absorption.

In October 2007, a joint panel meeting of the FDA's Nonprescription Drugs and Pediatric Advisory Committees convened to advise against the use of OTC cough and cold medications in children younger than 6 years.[20] Later that month, the Consumer Healthcare Products Association (CHPA) issued a position statement and voluntarily withdrew OTC cough and cold products marketed for use in children younger than 2 years.[21] In January 2008, the FDA formally recommended against the use of OTC cough and cold medicines in children younger than 2 years.[22] The CHPA subsequently issued additional warnings against the use of these medications by children younger than 4 years.[23] Currently, the American Academy of Pediatrics (AAP) advises against the use of OTC cough and cold medications in children younger than 6 years, and the FDA continues to review available data in consideration of changing the labeling for OTC cough and cold medications for all children aged 2 to 6 years.[24]

Since these initial labeling changes were instituted, there has been a decrease in therapeutic errors and unintentional ingestions of OTC cough and cold medications reported to US poison centers. In addition, there was a decrease in ED visits, health care utilization, and fewer severe and fatal adverse medical outcomes.[25-29] At the same time, to date, these initiatives have not resulted in a significant decrease in the use of OTC cough and cold medications in pediatric ED patients; however, there has been an overall decrease in prescription cough and cold medication use in this age group.[30] Emergency clinicians should be cognizant of current recommendations to avoid these medications in young children and educate parents regarding the dangers of OTC cough and cold medications, also keeping in that mind prescription cough and cold alternatives have similar safety and efficacy concerns. Parents should also be counseled regarding alternative therapies, such as nasal suctioning, honey in children older than 1 year, and use of a humidifier.[24,31] Table 176.4 presents manufacturer-recommended dosing for commonly used medications in pediatric respiratory emergencies.

Phenothiazines

Phenothiazine medications such as promethazine were frequently used in pediatric patients, primarily in cough and cold preparations, for sedation, and as antiemetics. Since promethazine was approved in the early 1950s, there have been multiple cases of respiratory depression, apnea, and death in children. Due to these mounting safety concerns, the AAP has recommended against the use of phenothiazines for sedation in children. In 2000, the FDA also issued similar warnings, but continued reports of pediatric toxicity prompted the addition of a formal black box warning recommending against the use of promethazine in children younger than 2 years in 2004. In 2009, another black box warning was added, highlighting the risks of inappropriate parenteral use of promethazine resulting in severe tissue necrosis.[32] Since these recommendations, the use of phenothiazines for sedation and vomiting and as an antihistamine has declined, likely as a result of warnings and increased availability of safer therapeutic alternatives.

Opioid Analgesics

Pain in pediatric ED patients has been historically poorly assessed and undertreated.[33] Over the past 2 decades, there has been an emphasis on the identification and treatment of pain, and opioid analgesic use in pediatric ED patients has increased substantially.[34] Opioid analgesics can be used safely and effectively in children for the management of moderate to severe pain in the ED and should not be withheld when indicated.[33] At the same time, there are safety concerns regarding the use of opioid analgesics in pediatric patients of which emergency clinicians should be cognizant to minimize the potential of adverse drug events.

The toxicity of codeine in breast-fed infants whose mothers are CYP2D6 ultrarapid metabolizers has been discussed previously. Toxicity, including death, has also been documented in children who received codeine after a tonsillectomy and/or adenoidectomy for postoperative pain management. Children who are predisposed to codeine toxicity include those with obstructive sleep

TABLE 176.4

Common Pediatric Emergent Respiratory Medications

AGENT	INDICATION	DOSE	MAXIMUM
Diphenhydramine	Allergy	1–2 mg/kg PO, IV, IM	50 mg/dose
Prednisolone	Asthma, allergy	2 mg/kg PO	60 mg/dose
Methylprednisolone	Asthma, allergy	1 to 2 mg/kg IV	125 mg/dose
Dexamethasone	Croup	0.15–0.6 mg/kg PO, IV, IM	16 mg/dose
Albuterol	Asthma	0.15 mg/kg INH q1h	Continuous dosing: • ≤10 kg: 7.5 mg/hr • 10–20 kg: 11.25 mg/hr • ≥20 kg: 15 mg/hr
Ipratropium	Asthma	250 μg INH if <20kg	500 μg INH if >20 kg
Racemic epinephrine	Croup	0.25–0.5 mL of 2.25% solution; as needed up to q30min	N/A
Magnesium	Severe asthma	50–75 mg/kg IV over 20 min	2 g/dose
Terbutaline	Severe asthma	0.01 mg/kg SC	0.4 mg/dose

IM, Intramuscular; *INH,* isoniazid; *IV,* intravenous; *PO,* orally, *SC,* subcutaneous.

apnea and those who are CYP2D6 ultrarapid metabolizers.[35,36] In 2013, a black box warning was added to the labeling of codeine products contraindicating the use of codeine for postoperative pain in pediatric patients who have undergone tonsillectomy and/or adenoidectomy. It is unclear how this risk translates to the pediatric ED population. With regard to codeine use for other painful conditions, it is recommended that emergency clinicians only use codeine if the anticipated benefits outweigh the risk. The FDA continues to review safety data pertaining to codeine use in children.[37]

In recent years, there has been a dramatic increase in the use of opioid analgesics that has been paralleled by rising rates of misuse, abuse, and related-fatalities.[33,38] This phenomenon is not isolated to adult patients. There has been a significant rise in opioid analgesic use in pediatric ambulatory care and ED patients, with the greatest increases in use seen in adolescent patients. The most common medications prescribed for adolescent ED patients are hydrocodone and oxycodone products, which are also commonly abused for nonmedical purposes.[33]

There have been profound increases in nonmedical use and subsequent morbidity and mortality related to these agents among adolescents and young adults. This may be due to the fact that adolescents may be more likely to engage in risk-taking behavior, and opioid analgesics have become easier to obtain.[39] One study found that nearly 13% of high school seniors reported nonmedical use of a prescription opioid.[39] Prescription opioids are the second most commonly abused substance by adolescents in the United States, surpassed only by marijuana.[40] Additionally, up to 80% of nonmedical users obtained the drug from a previous medical prescription or from a relative or friend.[39,41] Increased availability of prescription opioids to adolescents has led to overdoses, medical complications, and long-term addiction.[42] Even more disturbing is the fact that opioid-related fatalities in adolescents have more than doubled in the past 25 years.[43,44]

It is important for emergency clinicians to balance adequate analgesia with the risks associated with the use of prescription opioids. Clinicians should determine whether an opioid is indicated, guided by evidence-based practice guidelines whenever possible. Nonopioid alternatives (eg, nonsteroidal antiinflammatory drugs) should be used as primary therapy or as an adjunct to minimize the dose of opioids. When an opioid is clearly indicated, it is important for clinicians to follow institution-based protocols for dosage and administration to avoid adverse drug events. Additionally, it is recommended that clinicians follow safe prescribing practices for opioid analgesics, as presented in Box 176.2, particularly for adolescent patients.[44,45]

BOX 176.2

Best Practices for Prescribing Opioid Analgesics in the Emergency Department

- Assess if there is an indication for an opioid analgesic; nonopioid therapies should be optimized and used as adjuncts, whenever possible.
- Perform a risk assessment for nonmedical use, particularly in adolescent patients.
- Consult state prescription drug monitoring programs and prior medical and pharmacy records if there is concern for nonmedical use.
- Short-acting opioids are preferred versus extended-release formulations.
- Use caution when combining opioid analgesics with other central nervous system depressants, such as benzodiazepines.
- Limit the duration of therapy to avoid having leftover doses.
- Provide instructions for the safe disposal of any unused medication.
- Arrange for close outpatient follow-up.
- Counsel parents and caregivers regarding signs of prescription drug abuse.

Medication Safety and Adverse Drug Events

Children are not only at an increased risk of medication-related injury—some have estimated up to threefold the inpatient risk of adults—for pharmacokinetic reasons but are also susceptible to other contributing risk factors. Because of the aforementioned legislative restrictions in pediatric drug research, many medications are used off label, with dosing based on experience and susceptible to error. Even when a medication has pediatric data shown in the drug labeling, this information is often not clearly presented and may offer little guidance to the prescriber. For example, the age range for which a medication is formally approved is often not listed in the indications section of the labeling. Approved pediatric-specific dosing information, when

TABLE 176.5

Selected Pediatric Drug References[a]

REFERENCE	DESCRIPTION	EXAMPLES
App store	Apps with calculators for common pediatric dosing; dosing recommendations provided for reference only	PediStat, palmPEDi, EMRA Pediatric Airway, PediCalc
Web-based	Web-based clinical information suites with medication dosing and company-provided evidence-based recommendations	Micromedex, Epocrates
EHR-based	Decision support tools and institutional guidelines incorporated into CPOE	Cerner, Epic, Allscripts
Reference text	Classic bedside reference texts for decision support and dosing information	Redbook, Harriet Lane, Tarascon, Broselow Tape

[a]This list is not all inclusive, nor does it carry a formal endorsement.

available, is listed in another section of the label. The results of pediatric-focused studies are commonly found in yet another section, under special populations.[14]

The lack of pediatric-specific formulations is also a contributor to adverse drug events and poor patient adherence. This is further complicated by the fact that there is little financial incentive for manufacturers to develop pediatric-specific formulations. Because pediatric formulations are not available for many medications, parents and clinicians may have to split fixed-dose adult tablets, or liquid formulations may need to be extemporaneously compounded, which introduces the potential for therapeutic errors. In addition, the poor palatability of adult formulations can lead to noncompliance; oral solutions, suspensions, and rapidly disintegrating and chewable tablets are preferred. Parents should be counseled regarding proper measurement and administration of prescribed medications, and a dosing syringe should be provided.

There are other factors that contribute to adverse drug events in children. Weight-based dosing and calculations required for many pediatric medications can present an additional step particularly prone to error in the delivery of emergent medications. Also, formulas used to calculate pediatric dosing derived from adult reference values are often inaccurate. Medication reconciliation in pediatric patients is also often inaccurate, which can contribute to suboptimal therapy and adverse drug events. Parents and caregivers should be specifically asked about all prescription medications, OTC medications, homeopathic preparations, and dietary supplements. Details regarding dosage and schedule should also be obtained. Very young children are nonverbal and cannot communicate allergies or current medications. In addition, they are less able to verbalize adverse effects when they do occur. Even when adverse drug events are identified, they are often underreported.[46] This is further complicated by the fact that there is a significant lag time between when a specific toxicity is noted and when labeling revisions occur.[47]

Ongoing attempts to mitigate these risks include the use of clinical pharmacists in the ED, separation of pediatric and adult care locations, and increased use of human factors and information technology solutions. There are also well-demonstrated bedside dosing reference guides for emergency pediatric medications, such as the Broselow and Mercy tapes.[48] The advent of hand-held wireless technology and gradual adoption of inpatient electronic health record (EHR) systems have generated many new reference options for pediatric pharmacology. It is thought that new decision support tools in the EHR system, such as computerized physician order entry, will help decrease adverse events, because many are related to weight-based dosing errors. Although calculation errors (eg, decimal point entry) still occur in computer-based systems, it is thought that decision support for infusions, maximum doses, and HER-linked medication reconciliation will contribute to a decrease in medication errors. At the same time, EHRs can also precipitate errors when clinicians "copy and paste" without critically evaluating data.[49] The ultimate responsibility for medication dosing rests with the ordering clinician, dispensing pharmacist, and administering nurse. Table 176.5 presents a selection of different types of decision support tools that can serve as a reference to emergency clinicians.

In recent years, prescription drug shortages have emerged as a threat to public health. Drug shortages can lead to delayed treatment or no treatment when indicated. This is best exemplified during past influenza seasons, when there were critical shortages for the pediatric formulation of osteltamivir. Sometimes, alternative medications should be substituted that may be more toxic or less effective, and medication errors can occur when emergency clinicians are forced to use therapeutic alternatives with which they are less familiar.[50,51] The reasons for the rising rates of prescription drug shortages are multifactorial, and it is anticipated that shortages will continue as a problem in the foreseeable future, despite mitigation efforts. Emergency clinicians should be cognizant of current drug shortages that may affect their practice and work to design protocols for the ethical distribution of available supplies of medications in short supply, as well as for safer use of therapeutic alternatives.[51]

KEY CONCEPTS

- Recent legislative efforts have begun to remove regulatory hurdles in closing the therapeutic gap between adult and pediatric patients.
- Awareness of differences in pediatric pharmacokinetics and specific drug toxicities is of critical significance for the safe and effective use of medications in children.
- Avoid prescription and OTC cough and cold medications in children younger than 6 years because these agents have limited efficacy data and may cause harm.
- Counsel parents about the management of fever and appropriate indications for and proper use of antipyretics.
- Perform a risk assessment prior to prescribing opioid analgesics and, when indicated, use safe prescribing practices and monitor for signs of prescription drug abuse.
- A multifaceted approach using clinical support systems and readily available reference tools are essential for the delivery of optimal emergent pediatric care.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 176: QUESTIONS & ANSWERS

176.1. A 15-year-old girl presents to the emergency department (ED) for arm pain with an old thumb spica splint and states that she ran out of her oxycodone prescription for a possible fracture and has been unable to follow-up with her orthopedist. Vital signs, examination, and radiographs are unremarkable. Which of the following is a best practice option for ED opioid prescribing?

A. Avoiding confusion by minimizing adjunct medication options

B. Consulting state prescription drug monitoring programs and prior medical and pharmacy records

C. Encouraging the parents of adolescents to maintain a central location in the house to store old and unused prescriptions
D. Working independently of outpatient providers to avoid undertreating chronic pain

Answer: B. Perform a risk assessment prior to prescribing opioid analgesics and, when indicated, use safe prescribing practices and monitor for signs of prescription drug abuse. Although parents should help with an adolescent's medications, unused prescriptions should be properly disposed of instead of maintained in the household, where they will be susceptible to future unintended misuse. Chronic pain management requires a multifaceted approach with emergency providers who are aware of an individual's pain management contract so as not to contribute to overuse. Adjunct medications such as nonsteroidal antiinflammatory drugs or neuroactive agents can help reduce overall opioid requirements. Prescription drug monitoring programs should be used, when possible, to limit the overprescribing of opioids from the emergency department.

176.2. Which of the following factors contributes to the relatively fewer number of pediatric-specific drugs and formulations compared to the adult population?
A. Ethical and institutional considerations of pediatric trials
B. FDA rules prohibiting extrapolation of adult data to pediatric labeling
C. Inability to use drugs approved for adults that are off label for children
D. Lack of federal mandate that manufacturers conduct clinical trials in children for drugs under development that have the potential for pediatric use

Answer: A. Recent legislative efforts have begun to remove regulatory hurdles in closing the therapeutic gap between adult and pediatric patients. The Pediatric Research Equity Act (PREA) in 2003 mandated that manufacturers conduct clinical trials in children for drugs under development that have the potential for pediatric use. The FDA Pediatric Labeling Rule in 1994 allowed for pediatric labeling based on extrapolation of adult data if the course of disease was similar in both populations. There are high rates of off-label use for many drugs used in children. These federal regulations and more were put in place to encourage pediatric research, despite the ethical and institutional considerations of pediatric trials, which can prove more difficult to surmount than in the adult population.

176.3. A healthy, fully vaccinated 11-month old male infant presents to your department for evaluation of a fever of 38.4°C (101.1°F) this morning that responded to a dose of acetaminophen. The physical examination reveals a well-appearing, afebrile infant with clear lungs. The patient has an unremarkable evaluation and, during the discharge process, his parents ask for advice regarding fever management. Which of the following statements is correct?
A. Aspirin should not be used in children younger than 15 years because of the risk of Reye's syndrome
B. Cool water baths and creams should be used to supplement antipyretics, even if they cause some discomfort to the patient.
C. Ibuprofen cannot be used in this age group because of ongoing renal development.
D. Over-the-counter (OTC) antipyretics are standardized, contain similar products and formulations, and are thus interchangeable.

Answer: A. Counsel parents and caregivers about the management of fever and appropriate indications for and proper use of antipyretics. There is no need to cause discomfort with external cooling methods for fever control. Ibuprofen should not be used in children younger than 6 months because of ongoing renal development. The formulations and dosing of OTC antipyretics are varied and cannot be used interchangeably. The correct answer is A because of the risk of Reye's syndrome with aspirin administration during a viral illness in children younger than 15 years.

176.4. Which of the following statements regarding pediatric pharmacokinetics is correct?
A. A thinner stratum corneum and increased body surface area contribute to a greater risk for systemic toxicity from dermally administered drugs.
B. An immature blood-brain barrier can result in kernicterus after ceftriaxone administration in neonates, resulting in increased bilirubin production.
C. Because of minimal differences in the volume of distribution and renal development, weight-based dosing of gentamicin without attention to age is sufficient.
D. Quicker gastric emptying and decreased gastric pH in neonates increase systemic absorption of enterally administered medications.

Answer: A. Awareness of differences in pediatric pharmacokinetics and specific drug toxicities is of critical significance for the safe and effective use of medications in children. The dosing of gentamicin needs to account for age-based differences in renal development in addition to weight-based differences in distribution volume. Decreased gastric emptying times and an increased pH can prolong exposure to medications before they pass the pylorus. An immature blood-brain barrier can result in kernicterus from bilirubin displacement by ceftriaxone. The correct answer is that a thinner stratum corneum and increased body surface area contribute to a greater risk for systemic toxicity from dermally administered drugs.

176.5. Which of the following steps can be taken to reduce pediatric dosing errors?
A. Adoption of electronic health records to decrease weight-based dosing errors
B. Calculation of weight-based dosing for all emergent medications administered in code situations as opposed to using a validated quick reference guide
C. Limiting hospital pharmacist presence in the emergency department to avoid delays in bedside care
D. Medication reconciliation should occur with just the patient present to limit primary caregiver influence

Answer: A. A multifaceted approach using clinical support systems and readily available reference tools are essential for the delivery of optimal emergent pediatric care. Caregivers are an integral part of medication reconciliation. ED pharmacists have been proven to increase departmental accuracy in pediatric medication management. Validated quick reference guides for code drug administration have been shown to decrease errors and improve efficiency.

CHAPTER 177

Child Abuse

Daniel Lindberg

Child maltreatment is an all-encompassing term that includes all forms of child abuse: physical abuse, sexual abuse, emotional abuse, child neglect (physical, emotional, educational), and medical child abuse (previously known as *Munchausen syndrome by proxy*).

PHYSICAL ABUSE

PRINCIPLES

Child physical abuse is a leading cause of death and disability for young children. In the United States, estimates suggest that more than 120,000 children are victims of physical abuse with more than 550 deaths each year, many of which are preventable.[1] Physical abuse is also commonly missed—approximately 30% of abusive head trauma and 20% of abusive fractures are missed on initial presentation.[2,3] Abuse is especially difficult to identify, because it is overwhelmingly a problem that affects pre-verbal children, particularly infants younger than 6 months old.[1,4] Not surprisingly, caregivers frequently omit or obscure the true history. Key portions of the physical examination (eg, neurological and musculoskeletal examinations) are limited; early recognition of abuse often depends on identifying subtle, minor, or self-limited injuries.[5] With these challenges, current practices are highly variable, and children are frequently returned to abusive environments.[2,6-9] Current practice also shows signs of reporting bias; testing and reporting for abuse are disproportionately high for African-American and poor families, whereas missed abuse is higher for affluent or white families.[10,11]

Overcoming these challenges is essential for abused children and their families. Because violence is a disease that affects entire households, recognition of abuse is important for not only for the children themselves but also for siblings and parents.[12-14] For abuse survivors and those who share a violent household, the long-term health effects of toxic stress are severe, diverse, and widespread.

Role of the Emergency Clinician

It is rarely possible and almost never necessary to definitively diagnose abuse in the emergency department (ED). Care of abused children requires the cooperation of medical, social, and law-enforcement agencies over weeks and months. Emergency clinicians are responsible for raising the initial concern for abuse and working with other professionals, including general pediatricians, child protective services (CPS) agencies, and child abuse pediatricians to stratify the risk for abuse and to arrange for ongoing care.

Inevitably, some children who are evaluated for abuse will ultimately be determined to have an innocent explanation for their injuries. Most injuries in childhood are not the result of abuse, and unusual events may produce unusual or unusually severe injuries.[15] To facilitate the evaluation and to preserve the doctor-patient relationship, emergency clinicians should maintain a routine and standardized approach to abuse evaluations.[16] Non-accusatory statements can explain the need for testing while minimizing conflict (Box 177.1).

CLINICAL FEATURES

Social and Demographic Risk Factors

Although social and demographic risk factors (eg, poverty, intimate partner violence, substance use, and the presence of an unrelated caregiver in the home) have been associated with increased risk for abuse, these are relatively insensitive and nonspecific and should not be used to confirm or exclude abuse.[13,17,18] Serious physical abuse has been reported in every socioeconomic setting; even in households with several risk factors, the vast majority of caregivers do not physically abuse their children.

History

Abuse is challenging to recognize when a child presents with nonspecific symptoms and without a recognized traumatic injury. Occult traumatic brain injury can present with irritability, difficult arousal, seizure, or prolonged vomiting, usually without fever or diarrhea. Fractures, abdominal injuries, and mild brain injuries can have a smoldering course of mild symptoms, such as irritability or decreased appetite or activity.[19] In these cases, identifying abuse is difficult and usually involves prolonged symptoms, additional clues on physical examination, known social risk factors, or prior concern for abuse.

Although still nonspecific, certain chief complaints should prompt consideration of abuse. A small percentage of children presenting with an apparent life-threatening event (ALTE) will have retinal hemorrhages or other abusive injuries.[20,21] Occult fracture should be considered in young or pre-verbal children who present with decreased use of an extremity, fussiness, and localized tenderness or refusal to bear weight.

Regardless of the injury, an unexplained delay in seeking care should prompt concern for abuse or neglect. There is no precise time period that defines "unexplained delay in care." Physicians should take into account the child's symptoms and progression of disease. Even without abuse, a delay of several hours is not uncommon for children with both fractures and abdominal injuries.[19,22] Conversely, even a brief delay can be concerning in a child who is limp, not breathing, actively seizing, has substantial burns, or has other obvious signs and symptoms.

Serious injury with a history of only minor trauma, or when there is no history of trauma, should raise concern for abuse. Intracranial hemorrhage is extremely uncommon from short falls (eg, from a bed or a couch) and does not result from choking on formula or saliva. Intra-abdominal and intrathoracic injuries do not commonly result from household falls, even with increased height or falls down stairs. Children with serious injuries attributed to siblings or pets should be evaluated carefully for other signs of abuse. Children who present for injuries sustained as a result of violence between their caregivers should also be evaluated for abuse.

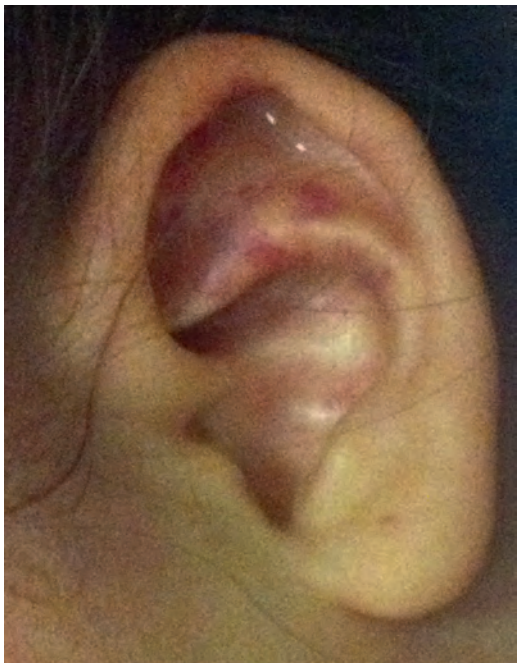

Fig. 177.1. Bruising to the helix of the ear is very concerning for abuse. (Courtesy Daniel Lindberg, MD.)

Fig. 177.2. Subtle bruising behind the child's ear can represent direct trauma or traction injury and should raise the level of concern for abuse. (Courtesy Daniel Lindberg, MD.)

BOX 177.1

Non-Accusatory Statements of Concern

- The injuries we've identified are more than we would expect from the event you've described.
- Whenever we see injuries like this, we test for other injuries or medical conditions to be sure we're not missing something that could affect your child's health.
- I want to make sure that your child is safe/that no one is hurting your child.
- Have you ever been concerned that someone might have been rough with or might have injured your child?

Physical Examination Findings

To identify subtle signs of abuse, infants should be completely undressed during physical examination. The fontanel, scalp, ears, oropharynx, skin, and genitalia should be specifically examined. If a growth chart is available, sudden increase in head circumference can be a sign of intracranial injury.

The most commonly identified abusive injury is bruising.[23] Although bruises are very common in ambulatory children, *any* bruising in a child that is not yet able to ambulate with assistance or "cruise" is highly concerning for abuse. Less than 1% of non-cruising children have bruises noted on routine physical examination. Of children younger than 6 months old referred for an abuse evaluation with apparently isolated bruises, 50% will have an additional injury (fracture, brain injury, abdominal injury) identified.[24]

Even in children old enough to cruise, bruises to the abdomen, neck, genitalia, or ears should raise concern (Figs. 177.1 to 177.3). The TEN-4 rule (bruising to the *T*orso, *E*ar, or *N*eck or bruising *anywhere* in children younger than 4 months old) has been shown to have 97% sensitivity and 84% specificity for abuse in a pediatric intensive care unit (PICU) population.[25]

Certain patterned injuries raise the likelihood of abuse (eg, bruises in the shape of a cord, belt, or hand) (Figs. 177.4 to 177.6).

Fig. 177.3. Bruising to the neck and under the chin of an abused child. (Courtesy Carol Berkowitz, MD.)

Human bite marks are patterned bruises in circular or paired semilunar rows (Fig. 177.7) and can be caused by adults or children; a maxillary intercanine distance of more than 3 cm is more likely to be from an adult. In cases concerning for abuse, human bite marks should be swabbed to identify assailant DNA. Forensic evidence collection kits used for sexual assault (ie, rape kits) can be used to obtain, document, and store this evidence for law enforcement.

Abusive burns generally fall into three categories: immersion burns, contact burns, and cigarette burns. Immersion burns should be distinguished from pull-down scalds, which are very common in toddlers. Although pull-down scalds principally involve the upper body, immersion burns tend to involve the perineum or have a symmetric, stocking/glove distribution (Fig. 177.8). Abuse should also be considered when scalds affect a large

Fig. 177.4. Facial bruising of an abused child. The parallel, linear bruising results when capillaries rupture outward between fingers—a slap mark. (Courtesy Daniel Lindberg, MD.)

Fig. 177.5. Loop marks demonstrate contact injury from a looped cord. (Courtesy Marianne Gausche-Hill, MD.)

Fig. 177.6. Patterned bruising from a woven belt. (Courtesy Daniel Lindberg, MD.)

Fig. 177.7. Human bite mark. (Courtesy Carol Berkowitz, MD.)

Fig. 177.8. Immersion burn. (Courtesy EMSC Slide Set, National EMSC Resource Alliance.)

body surface area, sparing patterns suggest that the child was held in place, or when the incident is reported in the context of a toileting accident.[26] For scald burns, CPS or law enforcement can measure the home's peak water temperature and the delay until peak temperature occurs. Although it takes several minutes to sustain a partial thickness burn from water at 120° F, the same burn can occur in seconds at 150° F.

As with bruises, emergency clinicians should consider abuse for young children with burns that take on the shape of an implement (eg, hair curler, grate, or lighter). Cigarettes can cause accidental or inflicted burns. Because the burning end of a cigarette can be more than 1000° F, inflicted burns are rarely superficial, and commonly result in crusted or ulcerated lesions between 8 to 10 mm. Glancing or *accidental contact* with a cigarette can also cause superficial, linear burns (Fig. 177.9).

Oropharyngeal injuries are also concerning in young children without a history of trauma to the mouth or throat (Fig. 177.10).[27] Tears of the lingular or labial frenula have been cited in several case series of children with missed abuse, as have unexplained injuries to the lips, teeth, or soft palate. When identified in the course of evaluation of children with other concerns of abuse, these injuries should increase concern.

Red-Flag Injuries

For many children, the concern for abuse is first raised by the unexpected or incidental identification of a traumatic injury. There are several injuries where abuse should routinely be

Fig. 177.9. Cigarette burns. (Courtesy EMSC Slide Set, National EMSC Resource Alliance.)

Fig. 177.10. Torn upper labial frenulum and bruising to the right, mucosal surface of the upper lip. (Courtesy Daniel Lindberg, MD.)

considered unless there is an independently verifiable history of major trauma (eg, a motor vehicle collision).

Serious traumatic brain injury should prompt a concern for abuse in children younger than 3 years old. In one series of children admitted to the intensive care unit (ICU) with traumatic brain injuries not known to be the result of a motor vehicle collision, 43% were victims of abuse.[28] Subdural hematomas and multifocal injury are especially concerning for abuse, whereas epidural hematomas and intraventricular hemorrhage are more likely to be non-abusive.[29]

Similarly, intra-abdominal injuries in young children are concerning for abuse if not sustained as a result of motor vehicle collision, accidental direct blow, or significant fall. In children who sustain short falls in hospitals or other witnessed settings, intra-abdominal injuries are vanishingly rare. Although hepatic injuries are the most common abusive injury identified, small bowel perforation and pancreatic injury are especially specific for abuse.[30]

Long-bone fractures of any type are concerning in children younger than 12 months old. Administrative data from the United States show that abuse is diagnosed in 30% to 60% of infants with fractures of the radius, ulna, tibia, fibula, femur, or humerus. Rib fractures (Fig. 177.11) were even more concerning, being associated with abuse in 69% of children younger than 12 months old

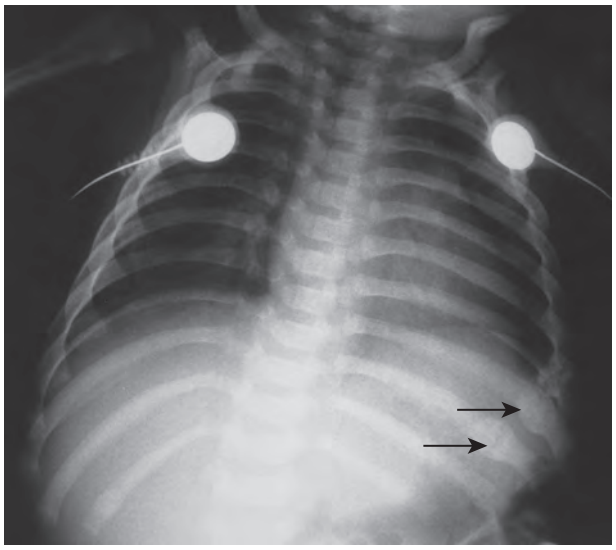

Fig. 177.11. Lateral rib fractures. Robust callus demonstrates healing fractures. (Courtesy Sara T. Stewart, MD, MPH.)

and approximately 27% of children 12 to 36 months old. Less common, fractures to the hands, feet, spine, pelvis, sternum, or scapula should be considered highly concerning for abuse in young children without a specific, independent history of significant trauma.[31-34]

Perhaps no fracture is more specific for abuse than the classic metaphyseal lesion (CML). Histologically, these lesions are planar fractures that extend through the primary spongiosa on the metaphyseal side of the growth plate. Radiographically, these lesions appear as chips or bucket handle lesions around the growth plate and are most commonly seen at the distal femur, proximal humerus, and proximal and distal tibia of infants with severe physical abuse (Figs. 177.12 and 177.13).[35,36] The identification of a CML in an infant should prompt a thorough abuse evaluation.

Skull fractures in infants commonly raise the concern for abuse but, relative to the injuries listed earlier, are much less specific. Even in infants, linear, parietal skull fractures can result from very short falls. Because skull fractures do not show signs of healing, birth-associated skull fractures can be both clinically subtle and difficult to differentiate from acute injury. Several series have examined rates of additional fractures in infants presenting with apparently isolated skull fractures. Rates of occult fracture ranged from just over 1% to approximately 5%.[37,38] Complex skull fractures—multiple fracture lines, fractures that cross suture lines, and those with substantial depression or widening—require more force or multiple impacts and are therefore more concerning. It is possible, however, for bilateral parietal fractures to result from a single impact to the cranial vertex.

Although spiral fractures were once thought to have high specificity for abuse, available data do not support this.[39] Spiral fractures of the tibia *in children learning to walk* (toddler's fractures) are among the few fractures in young children that do not require routine skeletal survey, even without a clear mechanism of trauma.[40]

DIFFERENTIAL DIAGNOSES

Because the diagnosis of abuse has a profound impact on a child, his or her family, and the alleged abuser, a variety of traumatic and medical conditions have been used to explain signs and symptoms of physical abuse. These range from sincere attempts

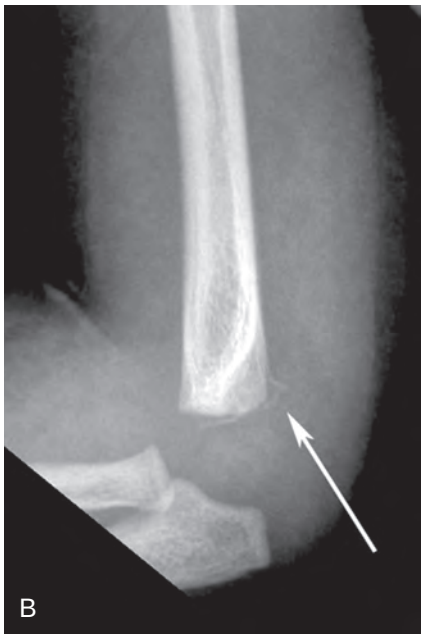

Fig. 177.12. A, Classic metaphyseal fracture. In this anteroposterior view, the fracture assumes the "bucket handle" conformation. **B,** In the lateral projection, the classic metaphyseal fracture appears as a chip. (Courtesy Daniel Lindberg, MD.)

Fig. 177.13. Healing classic metaphyseal fracture—the periosteal reaction on the lateral humerus demonstrates healing of the fracture. (Courtesy of Daniel Lindberg, MD.)

to distinguish abuse from rare but well-described medical entities to the invention of new medical entities, which are invoked only in legal settings or the lay press when there is a concern for abuse.[16,41-46] It is usually beyond the scope of an emergency clinician to test for such rare diseases or hypothetical entities unless there are specific signs or symptoms (eg, the blue sclera of osteogenesis imperfecta) or a specific family history.

The most common entity to be differentiated from abuse is accidental injury. With few exceptions (eg, the CML), most traumatic injuries that have been reported in the setting of abuse can also be seen with other severe forms of trauma.[28] Isolated injuries reported in the context of an accidental trauma mechanism should be evaluated on a case-by-case basis to determine whether the identified injury matches the reported mechanism. Young children who have started to cruise or walk frequently may have unobserved short falls from standing, beds, or couches less than 3 feet high. Although the vast majority of these falls are benign, they can produce isolated bruising to shins, elbows, or other hard body surfaces; linear skull fractures; buckle fractures of the distal femur; and clavicle fractures.

In the youngest infants, injuries from birth should be considered, because symptoms may only be recognized weeks after the child is discharged from the hospital. Skull fractures, cephalhematomas, and clavicle fractures are the most commonly identified, whereas asymptomatic subdural hematomas, rib fractures, and other extremity fractures are rarer.

Bone fragility disorders should be considered in children with exclusively bony injuries.[42] O*steomalacia of prematurity* occurs in roughly 30% of extremely low birth weight infants and is commonly associated with fractures in the absence of significant trauma. Risk factors include exposure to prolonged parenteral nutrition, steroids or furosemide, and those with cholestasis or chronic lung disease.[47] Minor forms of *osteogenesis imperfecta* can present with multiple-unexplained fractures. Although the diagnosis can be made early in children with a family history or severe disease, some cases are only diagnosed in the course of an

evaluation for abuse.[16,41] Be alert for blue-grey sclera, especially if they persist beyond infancy, family history of unexplained fractures, fragile teeth, congenital hearing problems, or short stature.

In children whose injuries are confined to problems of bruising or bleeding, emergency clinicians should consider an undiagnosed coagulopathy.[43] The American Academy of Pediatrics (AAP) has published guidelines for coagulopathy testing that will identify the vast majority of bleeding disorders.[48] Briefly, these children should have prothrombin time and international normalized ratio (PT/INR), partial thromboplastin time (PTT), Factors VIII and IX, and complete blood count (CBC). Children who present with bruising should also have testing for von Willebrand antigen and activity. Those with intracranial hemorrhage should have testing for D-dimer and fibrinogen. Because coagulopathy testing can take weeks or months, and because abuse is the more common etiology in children with isolated bruising and concern for abuse, the coagulation evaluation should not delay the evaluation for abuse, reporting to CPS, or safety planning.[24]

DIAGNOSTIC TESTING

Protecting a child from an abusive caregiver can require proving that the child's injuries are the result of abuse. Identification of additional traumatic injuries suggests abuse, particularly when not explained by the initial history. Although concomitant injuries may not require medical treatment, they have *forensic* significance. The clinical examination is insensitive, especially in very young children, for forensically significant injuries, such as healing fractures, CMLs, abdominal injuries, and even milder abusive head trauma.[2,49] To decrease testing disparities and improve abuse recognition, we recommend a routine testing strategy (outlined later) based on the level of concern for abuse and the child's presenting injuries.[9,40,49]

Skeletal Survey

The radiographic skeletal survey is the oldest and most commonly used diagnostic test to identify occult traumatic injuries in children with concern for abuse. Depending on the population studied, skeletal surveys performed in cases of suspected abuse identify additional fractures in approximately 10% to 25% of cases.[32,35,36,50] As occult fractures are more likely in young children, guidelines recommend skeletal survey for all children younger than 24 months old with abusive or suspicious injuries.[51,52] In children 24 to 60 months old, the skeletal survey is still a reasonable option, especially for those with limited mobility, decreased ability to communicate, and those 24 to 36 months old.[35,52] The skeletal survey is rarely useful for children older than 60 months old.

To avoid over- or under-diagnosis, proper technique for a skeletal survey requires at least 21 separate films (including oblique views of the ribs) and interpretation by an experienced radiologist.[53,54] A child should be transferred to an experienced center for skeletal survey rather than have an incomplete or inadequate series. There is no role for a single exposure "baby-gram" to identify occult fractures.[15] A follow-up skeletal survey, repeated after at least 14 days, frequently identifies additional missed fractures and can clarify indeterminate findings (Box 177.2).[55,56]

Although once commonly used to identify occult fractures, technetium 99 (^{99}Tc) bone scans have largely been replaced by the skeletal survey and follow-up skeletal survey due to their limited sensitivity for metaphyseal and rib fractures. However, newer sodium fluoride ($Na^{18}F$) bone scans have improved resolution and can be useful in children with indeterminate skeletal survey findings, especially when timely results are needed to determine if a child should be removed from the home.[57,58]

BOX 177.2

The Complete Skeletal Survey

APPENDICULAR SKELETON
Humeri (AP)
Forearms (AP)
Hands (PA)
Femurs (AP)
Lower legs (AP)
Feet (AP)

AXIAL SKELETON
Thorax (AP, lateral, L and R obliques)
Pelvis (AP)
Lumbosacral spine (lateral)
Cervical spine (lateral)
Skull (frontal and lateral)

AP, Anteroposterior; *L,* left; *PA,* posteroanterior; *R,* right.

Neuroimaging (Computed Tomography or Magnetic Resonance Imaging)

Abusive head trauma is the leading cause of death and disability in abused children. Head computed tomography (CT) scan or magnetic resonance imaging (MRI) should be undertaken in children with signs of brain injury—decreased mental status, external signs of impact to the head, bulging fontanel, seizure, coma, or focal neurological findings. However, occult head injury should also be considered. In one series, patients younger than 2 years old admitted with concern for abuse routinely underwent neuroimaging if they were younger than 6 months old or had facial bruising, rib fractures, or multiple fractures; 37% of those without other signs of head injury had an occult brain injury.

CT is the current criterion standard to diagnose abusive head trauma, because it is widely available, fast, and accurate. Head CT should routinely include three-dimensional reformatting to identify subtle skull fractures that may be missed in the plane of the scan. These reformats do not require additional radiation exposure, but they do require reformatting before data is expunged. An MRI of the brain is frequently performed several days after the initial CT scan to further delineate and assess the progression of injury. Some centers have also begun to use faster, more motion-tolerant MRI sequences (fast MRI) in place of CT as the initial test for abusive head trauma.[59] Cranial ultrasound is not sufficiently sensitive to identify occult abusive injuries and is not recommended as an initial study for children with concern for abuse.

Retinal Examination

Retinal hemorrhages identified in a child with head injury can significantly affect the recognition of abuse. Hemorrhages that are numerous (>20), multilayered and that extend to the retinal periphery, or those associated with macular retinoschisis are strongly associated with severe traumatic brain injury and abusive head trauma (Fig. 177.14).[60-63] Dedicated retinal examination by an experienced ophthalmologist is recommended for all children with concern for abusive head trauma to characterize the hemorrhages and improve sensitivity.[64] Conversely, without radiographic evidence of brain injury, significant retinal hemorrhages are rare, and transfer or referral for specialty retinal examination should be considered optional in this group.[52,64-66] Even in severe cases of abusive head trauma, retinal hemorrhages are absent in

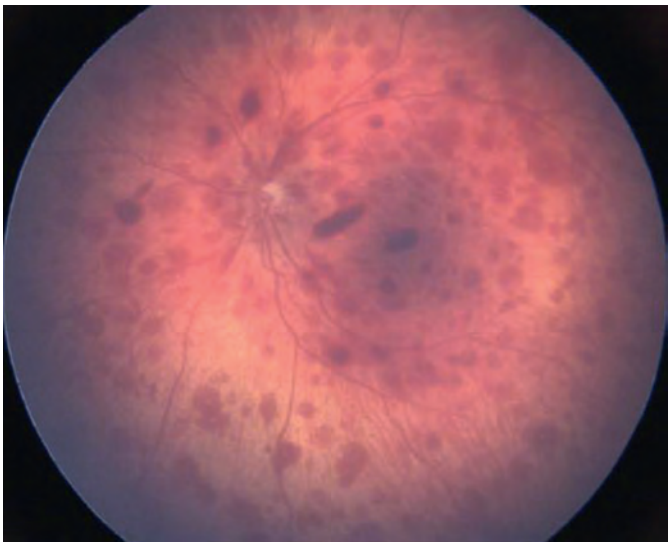

Fig. 177.14. Too numerous to count retinal hemorrhages in all layers that extend to the periphery—characteristic of abusive head trauma. (Courtesy of Daniel Lindberg, MD.)

approximately 15% of cases; retinal examination should therefore not be used as an initial screening test to determine the need for neuroimaging.[64]

Abdominal Injury Testing

Intra-abdominal injuries, ranging from obviously life-threatening to completely asymptomatic, are present in approximately 3% of children evaluated for physical abuse. Abdominal bruising, tenderness, or distention are present in approximately 50% of abusive abdominal injuries. In two large series of children younger than 60 months old evaluated for abuse, those who had either aspartate transaminase (AST) or alanine transaminase (ALT) >80 IU/L had at least 20% post-test probability of an intra-abdominal injury identified by CT scan or other definitive testing.[67] Amylase and lipase have been recommended by some authors to increase sensitivity for abdominal injuries but have not been shown to significantly improve yield beyond clinical examination plus AST and ALT.[67] Although ultrasound can identify abdominal injuries, it is relatively insensitive; CT should be used to characterize injuries identified by ultrasound. In children without obvious evidence of abdominal injury or history of trauma to the abdomen, we recommend routine AST and ALT testing and an abdominal CT scan with intravenous (IV) contrast for those with AST or ALT >80 IU/L. Because AST and ALT rapidly normalize, even in children with hepatic lacerations, trending of transaminases should not be used to determine the need for imaging. For this reason, it is also important that testing be completed during the initial evaluation.

Household Contacts

Violence is a disease that affects an entire household.[4,13] In cases with concern for abuse, emergency clinicians should determine if other children share the child's home, daycare, or care environment. CPS or the child's primary pediatrician can help arrange physical examination and/or skeletal survey for contact children. In one series of children with high likelihood of abuse and at least one serious injury, household contacts younger than 24 months old had occult fractures on skeletal survey in 12% of cases; for twins the incidence were dramatically increased risk (odds ratio [OR], 20).[4,13,68] In cases where there is significant concern for genetic diseases that mimic abuse, evaluation of biological siblings can improve diagnosis (Table 177.1).

TABLE 177.1

Recommendations for Occult Injury Testing

DIAGNOSTIC TEST	INDICATIONS (WITH CONCERN FOR ABUSE)
Skeletal survey	All patients <24 months old Consider in 24- to 60-month-olds
Neuroimaging (CT or MRI)	Signs/symptoms of traumatic brain injury History of assault to head or violent shaking Asymptomatic and any of the following: • <6 months old • Facial bruising • Rib fractures • Multiple fractures
Retinal examination	For patients with traumatic brain injury
AST/ALT	All patients <60 months old
Abdominal CT	History of assault to abdomen Signs/symptoms of abdominal injury AST or ALT >80 IU/L
Siblings and contacts	Skeletal survey for <24-month-old contacts of injured, abused children

ALT, Alanine transaminase; *AST,* aspartate transaminase; *CT,* computed tomography; *MRI,* magnetic resonance imaging.

Timing

Determining the age of an injury can affect the plausibility of an offered history and can assist law enforcement in identifying the perpetrator. In young children, multiple injuries of different ages are highly concerning for abuse. In many cases, the best way to determine the timing of an injury is based on when the child developed symptoms, or independent witness reports of when cutaneous injuries were first visible.

The best evidence for injury dating comes from fractures of endochondral bones (most bones except the skull). Signs of healing (eg, periosteal reaction and callus formation) are rarely evident before 7 days and commonly seen within 10 to 14 days.[69] Experienced radiologists can sometimes offer more nuanced estimates of fracture age.

Conversely, emergency clinicians should be cautious not to estimate the age of bruises based on their appearance. One widely cited dating system is based on scant data and had poor accuracy when prospectively used to estimate bruise ages in children with known times of injury.[70] Similarly, the appearance on CT of subdural hematomas or other intracranial hemorrhages is of limited utility in estimating the age of injury. Although hyperdense "bright" blood is often thought to signify acute hemorrhage (and vice-versa), hyper-acute bleeding, re-bleeding and mixing of blood and cerebrospinal fluid (CSF) probably account for their poor accuracy.[71,72] Mixed density subdural hematomas have been described in several cases with a single traumatic episode and therefore are not strong evidence for multiple episodes of trauma. In cases of severe traumatic brain injury, the onset of a child's symptoms is probably the most useful determination of timing of injury.[73]

MANAGEMENT

Compared to children with nonabusive traumatic brain injury, as a group, children with abusive head trauma tend to have more severe injury, longer ICU stays, and higher mortality.

Non-convulsive seizures are identified in more than 30% of children with abusive head trauma, prompting some to recommend routine electroencephalogram (EEG) monitoring.[74] Otherwise, medical management of children with abusive traumatic injuries is generally the same as for non-abused children. Beyond the management of the acute injuries themselves, management of abuse largely consists of secondary prevention—protecting the child from further abuse.

Mandated Reporting

In the United States, Canada, and several other jurisdictions, emergency clinicians are mandated to report a reasonable concern of child maltreatment to public CPS agencies or law enforcement. These reports can mobilize social resources for family, expand the investigation of abuse beyond the hospital, and facilitate testing or protection for other children in the abusive environment. A final diagnosis of abuse is not required to trigger the mandate, and reporters generally have legal protection for reports made in good faith, even if a child is ultimately determined not to have been abused. In cases where there is reasonable concern for abuse but where the final diagnosis is pending, clinicians should be reassured that a mandated report need not automatically trigger the removal of a child from their home or the instigation of criminal proceedings. In many jurisdictions, the mandate to report can be satisfied by reporting to a designated child protection team who will complete the evaluation and determine the need for reporting.

Hospital social workers can assist with the reporting process. The exact procedure for reporting varies by jurisdiction, but instructions are usually accessible by in any Internet search engine searching for "report child abuse [location]." In preparing to report, gather the child and family's contact information, the identity of any other children in the home, and the location where the abuse occurred to determine which agency has jurisdiction.

DISPOSITION

Many children with physical abuse will require hospital admission for treatment and stabilization of their injuries or identification of a safe environment. Children with concern for physical abuse may be discharged if (1) injuries have been medically stabilized, (2) reasonable concerns for abuse have been reported as required by statute, and (3) a safe environment has been identified. In children who are otherwise stable for discharge, CPS can work with families to establish a temporary safety plan in which the child is placed in the care of a friend or family member.

SEXUAL ABUSE

PRINCIPLES

Sexual abuse of children is common and under-recognized. Among 17-year-olds, a history of sexual abuse was self-reported in 26% of girls and 5% of boys with the highest rates occurring in adolescence.[75] These are likely under-estimates given the limitations of self-reporting. Perpetrators of sexual abuse are overwhelmingly male and can include family members, acquaintances, or strangers.

As with physical abuse, the bulk of the investigation in cases with concern for sexual abuse can occur outside of the ED. Urgent interventions include stabilization of medical injuries, evidence collection or post-exposure prophylaxis (PEP), arrangement of a safe environment, and reporting. Evaluation of children more than 72 hours after possible abuse (or another period if mandated by law) can be deferred from the ED to an outpatient setting.[76] Completion of a full evidence collection kit can require more than an hour of undivided attention, and emergency clinicians responsible for multiple potentially unstable patients may benefit in partnering with a sexual assault nurse examiner (SANE) program or subspecialty child abuse pediatrician.

Misconceptions about normal pediatric female genital anatomy (Fig. 177.15) are widespread among both patients and emergency clinicians. Normal configurations for the pediatric hymen include annular or ring-shaped, crescent-shaped and tulip-shaped, among others. Although imperforate hymens exist and can cause symptoms in pubertal children, this is a rare abnormality.

CLINICAL FEATURES

In contrast to physical abuse, most sexual abuse evaluations will be prompted by a patient or caregiver report. Genital bleeding or discharge should prompt consideration of sexual abuse in preverbal children or those who do not report sexual abuse. Pregnancy or sexually transmitted infections (STIs; gonorrhea, chlamydia, syphilis, trichomonas, or human immunodeficiency virus [HIV]) provide evidence of sexual contact.[76,77] Identification of pregnancy in a young adolescent should prompt nonjudgmental questions about the girl's sexual partners; some victims perceive abuse as consensual sexual activity with a "boyfriend."

Caregivers sometimes bring children for evaluation based on concern for abnormal appearance of a child's genitalia (redness, size, or shape of vaginal or rectal orifices). Without other indications of abuse, these findings are extremely nonspecific and do not increase the likelihood of abuse. In young children (2 to 6

KEY CONCEPTS

- The emergency department (ED) evaluation should focus on identifying and treating medical injuries, recognizing patterns suspicious for abuse, and establishing a safe disposition for the child. The ultimate determination of whether abuse has occurred can require days or weeks.
- Maintain an objective, matter-of-fact manner when evaluating children for abuse.
- Social factors are not sensitive or specific for abuse and may be hidden from the emergency clinician. Consider abuse routinely for serious injuries in young children without an independently-witnessed traumatic mechanism.
- Completely undress infants and pre-verbal children for the physical examination; pay particular attention to the skin, ears, mouth and oral cavity, scalp and fontanel, and genitalia.
- Without an independently witnessed severe trauma, injuries that should routinely prompt an evaluation for abuse include bruising in infants younger than 6 months old; bruising on the torso, ears, or neck; unexplained oral injuries; patterned cutaneous injuries; subdural hematoma; long-bone fractures in infants; intra-abdominal injuries; and rib fractures.
- Diagnostic testing should identify both clinically and forensically significant injuries and for physical abuse should include a skeletal survey in children younger than 2 years old.
- Emergency clinicians in the United States and Canada are legally mandated to report reasonable concerns for abuse.

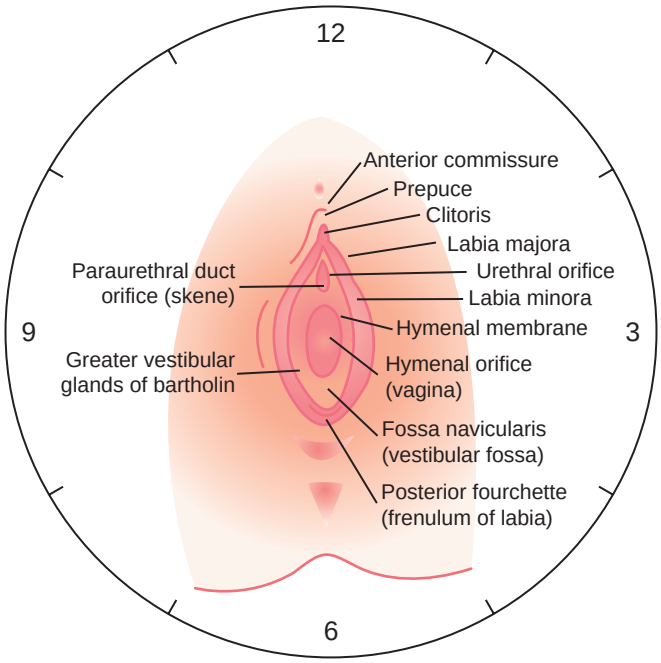

Fig. 177.15. Female pediatric genital anatomy. This area is best visualized by applying gentle outward (toward the examiner) traction on the labia. (Adapted from Groth SJ, et al: Handbook: evaluation and management of the sexually assaulted or sexually abused patient, Dallas, 1999, American College of Emergency Physicians.)

years old), some sexual behaviors that are concerning to caregivers (eg, touching genitals in public) are part of normal development, whereas others (eg, inserting objects into the genitals) should prompt concern for sexual abuse. The AAP has published guidelines for the evaluation of several such sexual behaviors. In general, behaviors are less concerning if they are transient, few, and distractible, and more concerning if they are persistent and resistant to parental distraction. When children engage in sexual actions or activity with each other, sexual abuse should be distinguished from sexual play by the presence of a significant difference in age or development, or the presence of coercion. Laws defining the age of consent for sexual activity and the age difference that constitutes statutory rape differ by jurisdiction.

Most cases of sexual abuse do not have diagnostic findings on physical examination, laboratory testing, or forensic evidence collection. A child's history is therefore often the most important factor to determine social or legal interventions in cases of alleged sexual abuse. Forensic interviews, conducted by CPS, law enforcement, child advocacy centers, or child protection teams, are conducted to avoid suggestive or coercive questions. In most cases, these forensic interviews can take place after the initial ED evaluation, allowing emergency clinicians to limit their history to the information needed to identify medically significant injury or illness. In cases where caregivers present with concerns for abuse, emergency clinicians should obtain the caregiver's history separated from the child. Document whether the child reported abuse; and if so, whether the report was spontaneous, or in response to questioning by the caregiver. If interviewing a child, avoid leading questions, and document both the question asked and the child's response. Interviews should be conducted at an appropriate developmental level; most children younger than 4 years old will have limited ability to participate in the interview. Younger school-aged children may have difficulty with "when" questions, limiting the ability to determine the time elapsed from the last episode of abuse. This also limits the ability to determine the need for several interventions, such as evidence collection or HIV PEP. Consider asking "where," "what," or "who" questions to understand the timeline. For example, a child who does not know what time or day something occurred may know whether it was day or night, it was a school day or a weekend, or whether it occurred during a specific holiday or event. It may be helpful to elicit the terms used by the child to describe different body parts.

Because forensic interviewing requires substantial training and ongoing peer review, and due to concern that repeated interviews could "contaminate" evidence, parents and caregivers should be counseled not to question the child before the formal forensic interview. However, they should also provide a safe, supportive, listening environment *if the child approaches them* with information or questions. Outcomes for sexually abused children are improved when they are believed and supported by their caregivers.

Most children who present to the ED with concern for sexual abuse should undergo dedicated physical examination of the genitalia and rectum. With proper preparation, this examination need not be painful or distressing to the child. Conducting the examination on the lap of a trusted caregiver and in the context of other painless examination maneuvers (inspecting the nose, heart, and belly-button) can reassure the child. Informing the child that this examination "is okay because I am a doctor, because Mom is here, and because Mom says it's okay" helps distinguish the examination from inappropriate sexual contact.

During puberty, the hymen develops from a thin, smooth rim of tissue to a thicker, redundant mucosal ridge. The pre-pubertal (non-estrogenized) hymen is exquisitely sensitive; touching it will almost certainly end the useful portion of your examination. For this reason, a speculum examination should not be conducted in a pre-pubertal child. To avoid additional trauma, a genital examination should never be forced on a reluctant child. In most cases, a child can return for an outpatient examination after food, rest, and preparation. In the rare cases of substantial bleeding or concern for a medically unstable injury, a gynecologist should perform an examination under anesthesia.

To best expose the hymen and other relevant anatomy, pull the labia majora out (off the table or toward the examiner—not laterally) with the same force you would use to retract the cheek to examine the teeth. The posterior hymen, if not sufficiently visualized in this position, can sometimes be better seen in the "knee-chest" position, where the child is placed in a prone position on the examination table with their hips flexed so that their knees and chest are resting on the table. The posterior hymen is then visualized by laterally retracting the buttocks.[76,78]

If manipulation of the hymen is absolutely necessary, consider using the mucosal surface of the contralateral labia to manipulate the hymen. Alternatively, a few drops of sterile saline can be used to "float" the posterior rim of the hymen and expose an area of interest. A colposcope can be useful to magnify, illuminate, and document examination findings. Data do not support the use of toluidine blue to identify mucosal injuries not apparent to the naked eye.[76,78]

Although the vast majority of physical examinations will be normal, even when performed soon after acute sexual assault, a normal examination does not exclude abuse. Children and families can be reassured that they are healthy and normal and that no one in the future (eg, doctors, spouses) will know from looking at them that abuse has occurred. Some families have concern for an anatomic definition of virginity, although they are reluctant to broach the issue. Providers should emphasize that the child is anatomically normal and that the definition of virginity should depend on when someone *chooses* to have intercourse.

A wide array of nonspecific findings (eg, erythema, periurethral bands, and bumps and notches of the hymen) should not be confused with evidence of sexual contact. Injuries that are indicative of trauma include bruising, petechiae, or abrasions on the

Fig. 177.16. Bruising to an estrogenized, pubertal hymen. Indicative of acute sexual contact. (Courtesy of Daniel Lindberg, MD.)

Fig. 177.17. Acute injury to the fossa navicularis in a pre-pubertal girl. The hymen is not well visualized. (Courtesy of Daniel Lindberg, MD.)

hymen; acute lacerations of the hymen; vaginal lacerations; or complete transection of the hymen between 4 o'clock and 8 o'clock (Figs. 177.16 and 177.17). In adolescents capable of consensual sexual activity, no examination finding can distinguish consensual sexual activity from assault or rape (Table 177.2).

DIFFERENTIAL DIAGNOSES

Strep infection of the perineal skin and genitalia can produce redness, inflammation, and fissures. Vaginitis from infection or poor hygiene can result in vaginal discharge or dysuria. Isolated vaginal bleeding can be the result of urethral prolapse (beefy red protrusion inferior to clitoral hood) or lichen sclerosis (pale, irritated, thin, hypopigmented skin surrounding the genitalia; Figs. 177.18 and 177.19). Straddle injuries can produce bruising of the external genitalia (labia, perineum, and peri-urethral tissues) and are usually accompanied by a history of injury. In boys who are toilet training, a falling toilet seat can produce dorsal and ventral penile bruising similar to a bite mark. Many laxatives are skin irritants, and diapered children who are treated for constipation may develop erythema or blistering if stool remains in contact with the skin.

Fig. 177.18. Urethral prolapse. (Courtesy Carol Berkowitz, MD.)

DIAGNOSTIC TESTING

The goal of diagnostic testing in the ED is to identify transient evidence of sexual assault or sexually transmitted diseases. Beyond the history and physical examination, a forensic evidence collection kit ("rape kit") can provide evidence of sexual contact and identify the assailant if DNA is isolated. Evidence is more likely to be obtained soon after the assault with the majority of positive kits obtained within 24 hours.[79,80] Forensic evidence collection is recommended for cases of assault with possibility of DNA transmission (semen, blood, or saliva) up to 72 hours from the assault, although some practitioners or jurisdictions are moving to a threshold of up to 7 days based on newer polymerase chain reaction (PCR)-based techniques. Beyond 24 hours, specimens from the child's clothing are the most likely to retain evidence. Obtaining the child's underwear (even if not worn at the time of the assault) can recover DNA evidence beyond 24 hours and is relatively noninvasive. Although many kits require documentation of whether a child has eaten, defecated, urinated, or wiped prior to evidence collection, these should not impact the decision to collect evidence.

Pregnancy testing is routinely obtained in pubertal females because levonorgestrel (Plan B) is ineffective for established pregnancies. STI testing is undertaken for symptomatic patients or in cases with potential for subacute or chronic abuse. Determining which tests to obtain depends on the details of the child's

TABLE 177.2

Significance of Genital Findings for Abuse

NORMAL FINDINGS	CONDITIONS MISTAKEN FOR ABUSE	FINDINGS CAUSED BY TRAUMA AND/OR SEXUAL CONTACT
• Normal hymen variants (annular, crescentic, imperforate, micro-perforate, septate, redundant, with tissue tags, with bumps or mounds) • Hymenal notches or clefts between 3 and 9 o'clock • Superficial notches below 3 and 9 o'clock • Periurethral bands • Intravaginal ridges or columns • External hymenal ridge • Linea vestibularis • Diastasis ani • Perianal skin tags • Hyperpigmentation of the skin of the labia minora or perianal tissues in children of color • Dilated urethral orifice Findings commonly caused by other medical conditions: • Erythema • Increased vascularity • Labial adhesions • Friability of posterior fourchette • Vaginal discharge • Molluscum contagiosum • Anal fissures • Venous pooling	• Urethral prolapse • Lichen sclerosus • Vulvar ulcers • Erythema, inflammation or fissures from bacterial, viral, fungal, parasitic infection • Perineal groove • Rectal prolapse • Anal dilatation from constipation, anesthesia, impaired muscular tone or post mortem	• Acute laceration(s) or bruising of labia, penis, scrotum, perianal tissues, or perineum • Acute laceration of the posterior fourchette or vestibule • Perianal scar • Scar of posterior fourchette or fossa • Bruising, petechiae, or abrasions on the hymen • Acute laceration of the hymen • Vaginal laceration • Perianal laceration with exposure of tissues below the dermis • Healed hymenal transection/complete hymen cleft—a defect in the hymen between 4 and 8 o'clock that extends to the base of the hymen with no hymenal tissue discernible at that location • A defect in the posterior (inferior) half of the hymen wider than a transection with an absence of hymenal tissue extending to the base of the hymen • Gonorrhea (genital, rectal or pharyngeal) • Syphilis • Chlamydia (genital or rectal) • Trichomonas • HIV (excludes transmission from blood transfusion) • Pregnancy • Semen found by forensic specimens

HIV, Human immunodeficiency virus.
Adapted from Adams JA, Kellogg ND, Farst KJ, et al: Updated guidelines for the medical assessment and care of children who may have been sexually abused. J Pediatr Adolesc Gynecol 29(2):81-87, 2016.

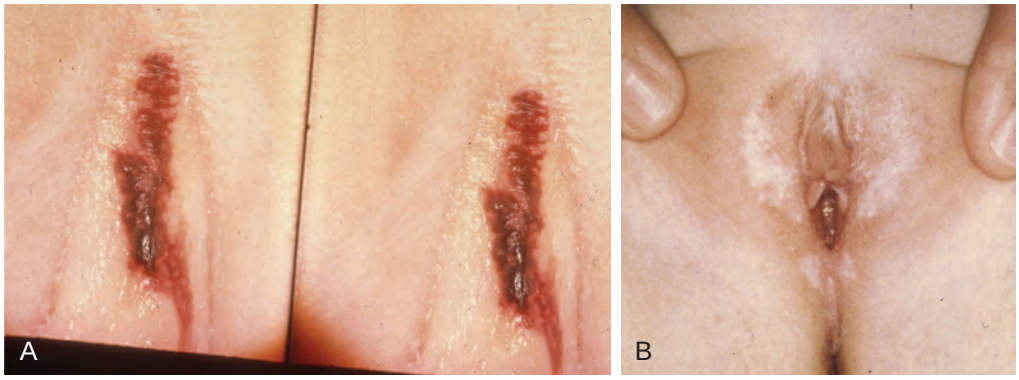

Fig. 177.19. A and **B,** Lichen sclerosis. (Courtesy Carol Berkowitz, MD.)

potential exposure and their physical examination, as well as local disease prevalence, patient and parent preferences, and the availability of timely follow-up. Emergency clinicians may benefit from case-by-case consultation with child abuse pediatrics or infectious disease colleagues.

Although STI transmission in pediatric assault is uncommon (5% to 8%), the advent of nucleic acid amplification testing (NAAT) in place of a culture has expanded the use of testing for gonorrhea, chlamydia, and trichomonas; NAAT has improved sensitivity, lower cost, and can be collected more easily.[77] NAAT testing has been endorsed by the Centers for Disease Control and Prevention (CDC) for urine or vaginal specimens in girls.[76,77] Based on CDC recommendations from 2010, we recommend testing children for sexual abuse when there are symptoms of STI, there is a known STI or risk factors for STI in the alleged perpetrator, an STI has been identified in a contact of the patient, physical examination findings show evidence of sexual contact or ejaculation, and when requested by the patient or the parent when there is reasonable concern for sexual abuse.[81,82]

Currently, there are no guidelines to direct testing for syphilis, hepatitis B or C, or HIV in children following sexual assault. We recommend testing in children with absent or incomplete hepatitis B vaccination, symptoms or diagnosis of another STI, known STI or risk factors in the alleged assailant, STI in a sibling or contact, or with patient or parent request when there is reasonable concern for abuse. Initial screening for syphilis should be by rapid plasma regain (RPR); hepatitis B screening should include hepatitis B surface antigen and hepatitis B virus (HBV) immunoglobulin M (IgM) core antibody. Testing for HIV and hepatitis B and C should be repeated 6, 12, and 24 weeks after sexual contact.[77]

MANAGEMENT

ED management should focus on the most time-dependent interventions, mandated reporting, and PEP for pregnancy and HIV. When there is a reasonable concern for sexual abuse, reporting to CPS is mandatory for physicians in the United States, Canada, and many other countries. Some caregivers may strongly desire reporting to children's services, even when the findings do not meet the threshold of a reasonable concern for abuse (as when the child presents for isolated nonspecific redness of the genitalia without a disclosure of abuse). Should the emergency clinician opt not to report these cases, caregivers can be advised that they have the option to report their concerns to CPS directly, independent of the health care provider.

Levonorgestrel (Plan B) should be offered to pubertal females within 120 hours (5 days) of sexual assault. When taken within 72 hours, it can prevent up to 50% of pregnancies, although there is some potential to prevent pregnancy up to 120 hours after sexual assault. Because it works by suppressing ovulation, patients can be reassured that it will not terminate an established pregnancy.

The decision to offer PEP for HIV is complex and depends on the nature, timing, and likelihood of the sexual assault; local prevalence of HIV; and likelihood that the perpetrator is HIV positive. Although rates of HIV transmission in the course of sexual abuse are probably low, cases of HIV in children whose only risk factor is abuse have been reported.[77] The CDC maintains a national telephone consultation service (1-800-933-3413) to provide real-time expert consultation to emergency clinicians with questions about HIV PEP.

Prophylaxis or empirical treatment for gonorrhea, chlamydia, or trichomonas may be offered to pubertal children but should be deferred for pre-pubertal children. In pre-pubertal children, consensual sexual activity is impossible by definition, rates of STD are low, ascending infection is very uncommon, and follow-up is usually obtainable. For these reasons, the medical consequences of delayed treatment are low, but the forensic significance can be profound. Because infection with gonorrhea, chlamydia, or trichomonas is usually strong evidence of sexual abuse in pre-pubertal children, proof of infection can be essential to ensure the child's protection from ongoing abuse. Treatment prior to obtaining proof of infection can limit confirmatory testing and thwart protection efforts (Table 177.3).

TABLE 177.3

Indications for Testing and Treatment in Cases With Concern for Sexual Abuse

TEST/INTERVENTION	INDICATION
Pregnancy testing	Pubertal females
Levonorgestrel (Plan B)	Non-pregnant, pubertal females <120 hours from assault
Gonorrhea/chlamydia/trichomonas testing	Symptoms of STI Known STI in suspected assailant STI in a contact child Patient or parent request Physical examination findings of sexual contact or ejaculation
Empirical treatment for gonorrhea/chlamydia/trichomonas	Pubertal children Avoid treatment in pre-pubertal children without confirmation of infection
HBV, HCV, HIV, syphilis testing	No clear guidelines, we recommend testing for: • Patient/parental request • Identification of another STI • Known STI in suspected assailant • STI in contact child
HIV PEP	No clear guidelines Depends on local prevalence
Forensic evidence collection	<72 hours from assault with potential DNA transmission (blood, saliva, semen)
Report to children's services	Reasonable concern for abuse

HBV, Hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *PEP,* post-exposure prophylaxis; *STI,* sexually transmitted infection.

DISPOSITION

The vast majority of children evaluated for sexual abuse in the ED can be discharged to follow-up as outpatients. Medically stable patients can be discharged to a safe environment after obtaining appropriate testing and evidence collection. When the alleged assailant is a member of the child's household, CPS can arrange safety planning to ensure that a child has a safe place for discharge or that the alleged assailant is removed from the child's home.

KEY CONCEPTS

- Emergency department (ED) evaluation of pediatric sexual assault should focus on time-dependent medical treatment and evidence collection. Ultimate determination of the likelihood of sexual assault can be deferred pending outpatient resources including forensic interview.
- A normal examination neither confirms nor excludes the possibility of abuse, but patients may be reassured that their body is normal and healthy.
- A genital examination should not be forced on a child.
- Likelihood of obtaining forensic evidence decreases with time from assault. Evidence collection may be performed up to 3 to 7 days after sexual assault, depending on jurisdiction. After 24 hours, non-body specimens (such as, undergarments) are most likely to have evidence.
- Emergency contraception should be offered to pubertal females up to 120 hours after sexual assault.
- Prophylactic or empirical treatment for gonorrhea, chlamydia, and trichomonas are not recommended for pre-pubertal children. Treatment should be deferred until infection is confirmed.
- When an investigation for sexual abuse is ongoing, caregivers should be counselled to provide a believing, supportive environment if their child reports abuse or has questions, but caregivers should not attempt to conduct their own interview of the child.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 177: QUESTIONS & ANSWERS

177.1. A 12 month-old girl is referred to the emergency department (ED) because her daycare noticed that she cried whenever she is picked up and crepitus in the left side of the chest. They deny any witnessed trauma in the daycare facility. The mother arrives and appears concerned. On physical examination, you find some circular contusions on the inner aspects of both her upper arms. The mother states this occurred from a fall a week ago. Which of the following should be the next step in the patient's management?

A. Conduct a skeletal survey, and call child protective services (CPS) as a mandated reporter.
B. Discharge the patient if a thorough physical examination is normal.
C. Determine whether the arm contusions are of the same age.
D. Perform a dedicated retinal examination to determine if the child has retinal hemorrhages and, if she does, perform a head computed tomography (CT) scan.
E. Perform a humerus x-ray to determine if there is a humerus fracture.

Answer: A. Contusions on the inner aspect of the upper arm are atypical injuries in light of the mother's claim of a fall for the child. This pattern of injury is often related to being held tightly around the arm. Chest wall pain in a child could indicate a rib fracture. Chest x-ray is insensitive for rib fractures, which are very uncommon at this age unless caused by inflicted trauma. This should raise your suspicion of child physical abuse. In general, children younger than 2 or 3 years old with suspected inflicted injuries should be evaluated with a skeletal survey.

177.2. In a 12 month-old, which of the following fractures are very concerning for abuse?

A. Metaphyseal fracture of the radius
B. Occipital skull fracture
C. Spiral fracture of the tibia (toddler's fracture)
D. Both A and B
E. All of the above

Answer: D. A toddler's fracture, also referred to as a *CAST* (*c*hildhood *a*ccidental *s*piral *t*ibial) *fracture,* occurs when there is a twisting injury to the tibia as the child falls on it. In toddlers, this is usually an accidental injury. In particular, metaphyseal fractures, rib fractures, scapula fractures, and certain types of skull fractures should raise concern about inflicted trauma.

177.3. An 8-year-old girl presents after sexual assault in which she reports penile-vaginal penetration 8 hours prior to presentation. Which of the following is not indicated?

A. Consideration of human immunodeficiency virus (HIV) post-exposure prophylaxis (PEP) based on local disease prevalence, other risk factors, and patient preferences
B. Genital examination
C. Prophylactic/empirical treatment for gonorrhea and chlamydia
D. Report to child protective services (CPS) and/or law enforcement
E. Testing for gonorrhea and chlamydia

Answer: C. Prophylactic/empirical treatment for gonorrhea andchlamydia is not recommended in the emergency department (ED) for pre-pubertal children because the forensic significance of these diseases far outweighs their clinical significance. Gonorrhea and chlamydia very rarely ascend to the upper genital tract in pre-pubertal children, and the risk of long-term complications of deferred treatment is therefore low.

177.4. Which of the following is not a finding suggestive of an underlying medical condition?

A. Blue sclera, brown discolored teeth, and frequent fractures
B. Bruises on both buttocks and flanks after jumping off the bed
C. Dark discoloration in the shape of a hand after making lemonade in the sun
D. Dark discoloration over lower spine present since first week of life
E. Osteopenia in a premature infant

Answer: B. Non-inflicted bruises are usually unilateral, occurring on the side where a fall or collision with a solid object has occurred. Bruises on the buttocks and flank must be explained by the mechanism of injury and are unusual in non-inflicted trauma. Phytophotodermatitis may be mistaken for bruises. This is a condition that develops on sun-exposed areas of the body that have been in contact with certain fruits or juices, such as lime or lemon juice. Premature infants may experience osteopenia of prematurity. Osteogenesis imperfecta, a brittle bone disease, is associated with other clinical findings, such as blue sclerae and brown discoloration of the teeth (dentinogenesis imperfecta). Dermal melanocytosis (Mongolian spots) are bluish discolorations that are seen normally over the buttocks and lower spine in children with darker complexions.

177.5. An otherwise healthy 3-month-old boy is brought to the emergency department (ED) in a deep coma.

Caregivers report that he was completely normal until 30 minutes prior to arrival when he suddenly seized. He is obviously ill with a pediatric Glasgow Coma Score (GCS) of 3. A head computed tomography (CT) scan shows bilateral subdural hematomas. Which other testing is *not* indicated to determine the likelihood of abusive injury?

A. Aspartate transaminase (AST)/alanine transaminase (ALT) with abdominal CT if these are abnormal
B. Dedicated retinal examination by an ophthalmologist
C. Determine whether there are other children in the home
D. Skeletal survey when the child is clinically stable
E. Testing for osteogenesis imperfecta

Answer: E. Osteogenesis imperfecta is an important consideration in children when the concern for abuse is based exclusively on bony injuries (fractures). It does not cause traumatic brain injury. All Children with concern for abusive head trauma should have a dedicated retinal examination to determine whether there are retinal hemorrhages or other retinal findings of abuse. Testing for abdominal injuries or fractures can identify additional abusive injuries. Young children (<24 months old) who share a home with an abused child are at high risk for abuse, especially twins.

177.6. In a 2-week-old infant that is not yet crawling, which of the following is most highly concerning for abuse?

A. Clavicle fracture with callous
B. Lateral rib fracture with obvious callous
C. Parietal skull fracture without callous
D. Torn lingual frenulum with scant bleeding
E. All of the above

Answer: D. Lingual frenulum tears are very concerning for abuse in pre-mobile infants. These injuries heal quickly, and the presence of bleeding excludes the possibility of birth injury. Several self-limited injuries can result from the birth process, even in deliveries that are not recognized as particularly traumatic. These injuries can be clinically subtle and are not-uncommonly missed in the newborn nursery. Rib fractures are uncommonly seen from birth and are more common in larger infants or difficult deliveries. The presence of obvious callous on the rib fractures is consistent with a fracture that is at least 7 to 14 days old. Clavicle and skull fractures are not uncommon parturitional injuries. Unlike other fractures, skull fractures do not develop callous and their age cannot be estimated.

177.7. Which of the following can be used to estimate the age of an injury?

A. Color can be used to estimate the age of a bruise within 12 to 24 hours.
B. Density on computed tomography (CT) scan can be used to estimate the age of subdural hematomas within 1 to 2 days.
C. Intensity on magnetic resonance imaging (MRI) can be used to estimate the age of subdural hematomas within 1 to 2 days.
D. The presence of periosteal reaction can be used to estimate the age of a fracture within 1 to 2 weeks.

Answer: D. Several studies have demonstrated that periosteal reaction and callous begin to become visible after 1 to 2 weeks. Conversely, neither color of bruising nor appearance of subdural hematomas on CT scan or MRI has been shown to reliably correlate with timing. The age of retinal hemorrhages cannot be precisely determined by their appearance.

177.8. Which injury is most concerning in light of the reported mechanism?

A. A 6-month-old with a linear, parietal skull fracture after a 3-foot fall from a bed to a hardwood floor
B. A 13-month-old, unrestrained passenger in a high-speed motor vehicle collision who has a large subdural hematoma and a few retinal hemorrhages around the optic nerve
C. A 27-month-old who with a small bowel perforation and pancreatic laceration after a fall down eight steps
D. An 18-month-old who presents with a spiral tibia fracture and no history of trauma
E. A 10-year-old who presents with a spiral femur fracture after a crash while skiing

Answer: C. Intra-abdominal injuries of any kind are uncommon after short falls or stairway falls. Hollow-viscus ruptures and pancreatic injuries are particularly concerning for abuse. Although spiral fractures have been thought to be particularly concerning for abuse, more recent data has not supported this. Spiral tibia fractures (toddler's fractures) are common among children learning to walk, and spiral femur fractures are plausible from injuries if there is sufficient energy and a torqueing mechanism. Too numerous to count retinal hemorrhages in multiple layers and throughout the retina are relatively specific for abusive head trauma, but severe non-inflicted head injuries can also result in retinal hemorrhages that are few, and localized to the posterior retina. Linear, parietal skull fractures can result from relatively minor trauma.

177.9. A 13-month-old girl with an abusive femur fracture and a small abdominal bruise is found to have AST 475 and ALT 300. The next most appropriate step to identify an abusive abdominal injury is:

A. Abdominal computed tomography (CT) scan with intravenous (IV) contrast
B. Amylase, lipase, urinalysis, and white blood cell count
C. Focused abdominal sonography in trauma (FAST) ultrasound
D. Formal abdominal ultrasound
E. Repeat aspartate transaminase (AST)/ alanine transaminase (ALT) in 6 to 12 hours to determine whether values are worsening

Answer: A. Abusive abdominal injuries can be clinically subtle, and even small injuries that are clinically self-limited can have important forensic significance. Children with severe abusive injuries should have hepatic transaminase testing to identify occult abdominal injuries and those with clinical signs of abdominal injury or with elevated transaminases (>80 IU/L) should undergo abdominal CT scan with IV contrast. Other laboratory tests and ultrasound are relatively insensitive for traumatic intra-abdominal injuries. Whether or not there is an injury, elevated hepatic transaminases almost always normalize quickly over time.

177.10. A 10-year-old, pre-pubertal girl presents to the emergency department (ED) at midnight after reporting to her parents that she was sexually abused 2 weeks ago while at summer camp. The patient is tired and irritable at the time of presentation. Which of the following are indicated in the ED?

A. Human immunodeficiency virus (HIV) post-exposure prophylaxis (PEP)
B. Obtain a detailed history of the assault including the time, place and circumstances of all sexual contact
C. Pregnancy prophylaxis with levonorgestrel (Plan B)

D. Report to child protective services (CPS)
E. Urgent genital examination

Answer: D. For sexual abuse that has occurred more than 1 week prior to presentation, ED management should include fulfilling the mandate to report to CPS and ensuring that the child has a safe place for discharge. A genital examination may be attempted in a cooperative patient and can assist in assuring the child that they are normal and healthy, but the examination should not be forced on the child if they are reluctant; and it is unlikely to identify transient evidence of sexual contact at this time. The detailed forensic interview should be conducted by a trained interviewer and may be deferred until the patient is rested. Plan B and HIV PEP are unlikely to be effective 2 weeks after the assault, and pregnancy prophylaxis is not indicated for prepubertal children.

CHAPTER 178

Acute Complications of Pregnancy

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Acute complications of pregnancy can appear in all trimesters and pose challenges in diagnosis and management for the emergency clinician. Life-threatening disorders, such as ectopic pregnancy in early pregnancy, pregnancy-induced hypertension in mid to late pregnancy, and abruptio placentae in late pregnancy, are relatively common. Emergency clinicians must consider the signs and symptoms, stage of pregnancy, and hemodynamic stability of the patient in developing diagnostic and treatment strategies.

PROBLEMS IN EARLY PREGNANCY

Miscarriage

Miscarriage, the most common serious complication of pregnancy, is defined as the spontaneous termination of pregnancy before 20 weeks of gestation. Fetal demise after 20 weeks of gestation or when the fetus is more than 500 g is considered premature birth. Loss of early pregnancy, defined as the detection of human chorionic gonadotropin (hCG) within 6 weeks of the last normal menstrual period, occurs in approximately 20% to 30% of pregnancies. Embryonic and fetal loss after implantation occur in up to one-third of detectable pregnancies. The risk of miscarriage rises with increasing maternal age (a fivefold increase in those >40 years compared with those 25–29 years), increasing paternal age, alcohol use, increased parity, history of prior miscarriage, poorly controlled diabetes mellitus and thyroid disease, obesity, low prepregnancy body mass index, maternal stress, and history of vaginal bleeding.[1,2] Approximately 80% of miscarriages occur during the first trimester; the rest occur before 20 weeks of gestation.

Approximately 25% of clinically pregnant patients experience some bleeding. It is estimated that up to 50% of all women who have bleeding during early pregnancy miscarry, although the risk is probably higher in the emergency department (ED) population.[3] Patients who have a viable fetus visualized on ultrasound examination have a much lower risk of miscarriage (3%–6%), although vaginal bleeding is a high-risk indicator, even when a viable fetus is present.[4] Those with a history of bleeding who do not miscarry may have otherwise normal pregnancies, although they have an approximately twofold increased risk of premature birth and low-birth-weight infants.[5]

Pathophysiology

Most miscarriages are due to uterine malformations or chromosomal abnormalities, which account for the majority that occur within 10 weeks of gestation. In some cases, the ovum never develops (anembryonic gestation). In most early miscarriages, fetal death precedes clinical miscarriage, often by several weeks. Although clinical symptoms of miscarriages are most common between 8 and 12 weeks of gestation, sonographic evidence in most cases demonstrates death before 8 weeks; if fetal viability can be demonstrated by cardiac activity and a normal sonogram, the subsequent risk of fetal loss decreases significantly.

Maternal factors that increase the risk of miscarriage include congenital anatomic defects, uterine scarring, leiomyomas, and cervical incompetence. Other conditions associated with increased miscarriage rates include toxins (eg, alcohol, tobacco, and cocaine), autoimmune factors, endocrine disorders including luteal phase defects, a prior history of miscarriage, and occasional maternal infections.[6]

Terminology

Miscarriage can be broadly divided into three categories. The first is a threatened miscarriage, in which the patient presents with vaginal bleeding but is found to have a closed internal cervical os. The risk of miscarriage in this population is estimated at 35% to 50%, depending on the patient's risk factors and severity of symptoms.[7] If the internal cervical os is open, the miscarriage is considered inevitable. If products of conception are present at the cervical os or in the vaginal canal, the miscarriage is termed *incomplete,* the second classification of miscarriage. The third classification is a termed a *completed* miscarriage, which occurs when the uterus has expelled all fetal and placental material, the cervix is closed, and the uterus is contracted. Establishing the diagnosis of completed miscarriage in the ED is difficult. A gestational sac should be visualized for diagnosis because the cervix may close after an episode of heavy bleeding and clot passage without or after only partial expulsion of the products of conception. Unless an intact gestation is passed and recognized, a completed miscarriage should be diagnosed only after dilation and curettage (D&C), with pathologic confirmation of gestational products, demonstration by sonography of an empty uterus with a prior known intrauterine pregnancy (IUP), or reversion to a negative pregnancy test result. This may take up to several weeks after the initial presentation.

Missed abortion is a relatively obsolete term referring to the clinical failure of uterine growth over time. The terms *anembryonic gestation* (when no fetus is visualized on ultrasound), *first-* or *second-trimester fetal death* (failure to see fetal cardiac activity with at least a 5-mm crown-rump length), and *delayed miscarriage* are more appropriate.

Clinical Features

Patient history should include the estimated length of the gestation, time since the last menstrual period, symptoms of pregnancy,

including evolution or loss of pregnancy symptoms, degree and duration of bleeding, presence of cramps, pain, or fever, and attempts by the patient to induce miscarriage. Although the history is important, it is not helpful in the classification of the type of miscarriage. In addition, the severity of symptoms does not correlate well with the risk of miscarriage, although cramping and passage of clots are thought more likely to occur as the miscarriage becomes inevitable.

The assessment of the patient who experiences first-trimester vaginal bleeding includes a careful abdominal examination to evaluate for tenderness or peritoneal irritation from a potential ectopic pregnancy and to determine the size of the uterus, which should not be palpable abdominally. A pelvic examination should be performed to evaluate whether the cervix is closed or open, look for clots or the products of conception, and determine the degree of vaginal bleeding, as well as uterine size and tenderness. The cervix should be gently probed with a ring forceps (not a cotton-tipped applicator) to determine whether the internal os (1.5 cm deep to the external os) is open or closed. This is unnecessary in the patient who has a clearly open os or visible products of conception but can be safely performed during the first trimester as long as the forceps are used gently and do not penetrate the cervix more than 2 or 3 cm. In the patient with second-trimester bleeding, probing should not be done because the uterus is more vascular, and the organized placenta may overlie the cervical os. Parous women normally have an open or lax external os, a finding of no significance. The adnexa may be enlarged, often unilaterally, because the corpus luteum is cystic or because the pregnancy is ectopic. Significant adnexal or uterine tenderness should always raise the possibility of an ectopic pregnancy. Much less commonly, pelvic infection can cause uterine and adnexal tenderness during early pregnancy.

Diagnostic Testing

A hemoglobin level is useful to provide a baseline measurement and evaluate the degree of blood loss in women whose bleeding persists. In addition, the Rh type should be determined. Ultrasonography is the primary means of evaluating the health of the fetus as well as its location (Table 178.1). Because historical and clinical estimations of gestational age are often inaccurate, ultrasonography is useful to provide an accurate measure of fetal age and viability (Box 178.1).

In the stable patient with threatened miscarriage, expectant management may be sufficient to determine when intervention is needed, as long as ectopic pregnancy has been excluded. Serial quantitative hCG levels are used to assess the health of the fetus if sonographic findings are indeterminate or if the gestational age is less than 6 to 7 weeks. The sonographic discriminatory zone is defined as the quantitative hCG level at which a normally developing IUP should reliably be seen. Discriminatory levels are operator- and equipment-dependent and vary by individual patient characteristics, but are usually considered to be 6500 mIU/mL for transabdominal ultrasonography and 1000 to 2000 mIU/mL for transvaginal ultrasonography.[8,9] Ultrasonography can be performed or repeated when hCG levels rise to 1500 to 3000 mIU/mL. If hCG levels are flat or decline, or if sonographic criteria for fetal demise are demonstrated (see Box 178.1), the patient should be referred to an obstetrician for follow-up to ensure miscarriage completion and to rule out subsequent complications.

Differential Diagnosis

Ectopic pregnancy can masquerade as a threatened miscarriage in the early stages of pregnancy and should always be considered in the differential diagnosis. Even in the patient with painless vaginal bleeding, the diagnosis of ectopic pregnancy must be considered. Early ultrasonography is imperative to locate the pregnancy in the patient who has bleeding or pain.

Other diagnoses should also be considered. A small amount of bleeding occurs at the time of implantation of the blastocyst into the endometrium and, occasionally, at the time of the first missed menses. Molar pregnancy is also characterized by vaginal bleeding, usually during the late first trimester or second trimester. This condition can be identified by ultrasonography. Cervical and vaginal lesions can also cause local bleeding and can usually be seen on vaginal inspection.

Management

After assessment of hemodynamic status and management of blood loss, a patient with a threatened miscarriage requires very little specific medical treatment. Anti-D immune globulin should be administered if the patient is Rh-negative. A 50-μg dose is used during the first trimester and a full 300-μg dose after the first trimester. Once ectopic pregnancy has been excluded, ultrasonography can be scheduled more routinely at a later time for the patient without significant pain. However, the patient should be made aware that the potential for ectopic pregnancy exists until it is excluded by identification of an IUP. In the patient who is planning pregnancy termination, prompt referral should be encouraged and chorionic villi confirmed at the time of uterine evacuation.

Unless an IUP is diagnosed, the patient with threatened miscarriage should be given careful instructions on discharge to return if she has signs of hemodynamic instability, significant

TABLE 178.1

Landmarks for Gestational Age and β-hCG Level by Transvaginal Ultrasonography

FINDING	WEEKS FROM LMP	β-hCG (mIU/mL)
Gestational sac (25 mm)	5	1000
Discriminatory zone	5–6	1000–2000
Yolk sac	6	2500
Upper discriminatory zone	6–7	3000
Fetal pole	7	5000
Fetal heart motion	6–7	7000

β-hCG, Beta subunit of human chorionic gonadotropin; *LMP*, last menstrual period.
Adapted from Ramsey E, Shilitto J: How early can fetal heart pulsations be detected reliably using modern ultrasound equipment? Ultrasound 16:193–195, 2008.

BOX 178.1

Sonographic Criteria for Abnormal Pregnancy With Transvaginal Ultrasonography

No gestational sac at β-hCG level of 3000 mIU/mL
No yolk sac with gestational sac of 13 mm (or at 32 days since last menstrual period)
5-mm crown-rump length, with no fetal heart tones
No fetus, with gestational sac of 25 mm mean diameter
No fetal heart tones after gestational age of 10–12 wk

β-hCG, Beta subunit of human chorionic gonadotropin.
Adapted from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310–320, 1999.

pain, or other symptoms that might indicate ectopic pregnancy (so-called ectopic precautions). In conjunction with gynecologic colleagues, an ED protocol is useful to determine when follow-up sonographic evaluation and serial hCG measurements should be obtained, because ultrasonography can be an inaccurate diagnostic tool if the hCG level is below 1500 mIU/mL, vaginal bleeding is significant, or sonographic findings do not include a fetal pole or yolk sac.[10,11]

Although 50% or more of women with threatened miscarriage who are seen in the ED ultimately miscarry, treatment to prevent miscarriage is not useful because most fetuses can be shown to be nonviable 1 to 2 weeks before symptoms occur. In most cases, spontaneous miscarriage is the body's natural method of expelling an abnormal or undeveloped (blighted) pregnancy. Thus, a major goal of early management should be patient education and support. Patients should be advised that moderate daily activities do not affect the pregnancy. Tampons, intercourse, and other activities that might induce uterine infection should be avoided as long as the patient is bleeding, and she should return immediately for fever, abdominal pain, or a significant increase in bleeding. Cramping from a known IUP can be safely treated with oral synthetic narcotics, if needed. If the patient passes tissue, it should be brought to a provider to be examined for products of conception because differentiation of fetal parts or villi from decidual slough or casts is difficult.

Patient counseling is paramount with threatened miscarriage.[12,13] Determination of fetal viability can be helpful in reassuring the mother or preparing her for probable fetal loss.[14] Miscarriages are associated with a significant grieving process, which is frequently more difficult because early pregnancy is unannounced, and early fetal death is not publicly recognized. Because many women consider that minor falls, injuries, or stress during the first trimester can precipitate miscarriage, patients should be reassured that they have done nothing to cause miscarriage. It is important to make them aware that miscarriage is common, grieving is normal, and counseling may be beneficial.[15,16] A follow-up appointment should be scheduled after miscarriage to support the patient in resolving such issues.

Treatment of the patient with incomplete miscarriage includes expectant management, medical management with misoprostol, or surgical evacuation.[15] When the miscarriage is incomplete, the uterus may be unable to contract adequately to limit bleeding from the implantation site. Bleeding may be brisk, and gentle removal of fetal tissue from the cervical os with ring forceps during the pelvic examination often slows bleeding considerably.

Management of patients with presumed completed miscarriage is more complicated. If the patient brings tissue with her, this should be sent to the pathology department for evaluation. Unless an intact gestational sac or fetus is visualized, it is rarely clear clinically whether miscarriage is complete. Studies have shown that in women with a history consistent with miscarriage who have minimal remaining intrauterine tissue as determined by ultrasonography, expectant management is safe, but only if ectopic pregnancy can be excluded.[17] If endometrial tissue is not seen with ultrasonography, bleeding is mild, and gestational age is less than 8 weeks, curettage is frequently unnecessary, and the patient can be safely observed by a gynecologist for serial hormonal assays. Up to 80% of women with first-trimester miscarriage complete the miscarriage without intervention.[17] However, the need for later visits and procedures may be decreased by uterine curettage, particularly if the fetal pole or a gestational sac is visible on the sonogram at the time of evaluation. Medical management with misoprostol instead of D&C is also an option and has a success rate of up to 96%.[15] The patient should be instructed to return if uncontrolled bleeding, severe pain or cramping, fever, or tissue passage occurs. Follow-up is recommended in 1 or 2 weeks to ensure that the miscarriage is complete.

After miscarriage, the patient should be advised that fetal loss, even during the first trimester, can cause significant psychological stress. Follow-up in 1 or 2 weeks with a gynecologist should be provided. Some physicians prescribe antibiotics after D&C or miscarriage (usually doxycycline or metronidazole), although there is no conclusive evidence to support this practice, and some evidence has suggested that the side effects of treatment may outweigh any potential benefit.[18,19] Ergonovine or methylergonovine (0.2 mg orally bid) can be used to stimulate uterine involution. The patient should be advised to return if signs of infection (eg, fever, uterine tenderness) occur, bleeding resumes, or further tissue is passed.

Ectopic Pregnancy

Principles

Ectopic pregnancy, or pregnancy implanted outside the uterus, is an increasingly frequent problem that poses a major health risk to women during the childbearing years. It is the third leading cause of maternal death, responsible for 4% to 10% of maternal mortality.[20] Ectopic pregnancy is estimated to account for approximately 2% of all pregnancies, although national estimates of incidence are difficult to determine.[21] Although the incidence of ectopic pregnancy is highest in women aged 25 to 34 years, the rate is highest among older women and women belonging to minority groups. Simultaneous intrauterine and extrauterine gestations (heterotopic pregnancy) have historically been rare, occurring in approximately 1 in 4000 pregnancies; more recently, women who have undergone assisted reproduction techniques with embryo transfer have a demonstrated risk of 4% or higher of one of the pregnancies being ectopic. The incidence of ectopic pregnancy among women presenting to the ED with vaginal bleeding or pain in the first trimester is consistently approximately 10%, but may be as high as 16%.[20]

Pathophysiology

Implantation of the fertilized ovum occurs approximately 8 or 9 days after ovulation. Risk factors for an abnormal site of implantation include prior tubal infection (50% of cases), anatomic abnormalities of the fallopian tubes, assisted reproduction (especially multiple embryo transfers), and abnormal endometrium (host factors). These result in failure of the embryo to implant in the endometrium. The risk of ectopic pregnancy increases approximately threefold after a patient has had pelvic inflammatory disease (PID). In recent studies, 25% of patients with ectopic pregnancies were found to have had tubal surgery, including tubal sterilization or removal of ectopic pregnancy.[22] If the patient is currently using an intrauterine device (IUD), increased risk can occur from a complicating PID or from failure of the IUD to prevent pregnancy while preventing endometrial implantation. All forms of contraception, except the IUD and tubal sterilization, decrease the incidence of ectopic pregnancy. After an ectopic pregnancy, the risk of a subsequent ectopic pregnancy can be as high as 22%, depending on the characteristics and treatment of the ectopic pregnancy (eg, location of implantation, surgical vs. medical management; Box 178.2).[22]

When abnormal implantation occurs in the fallopian tubes, on the ovaries, or in the cervix, the pregnancy usually grows at a less than normal rate, which can result in abnormally low or declining hCG production. Even if exceedingly low, there is no value in using a single hCG measurement to exclude the diagnosis of ectopic pregnancy. Blood leaks intermittently through the tubal wall or out the fimbrial ends, with spillage into the peritoneal cavity. Bleeding and other symptoms are usually intermittent. Three outcomes are possible—spontaneous involution of the

BOX 178.2

Risk Factors for Ectopic Pregnancy

Tubal surgery (for tubal sterilization or ectopic pregnancy)
Pelvic inflammatory disease
Smoking
Advanced age
Prior spontaneous abortion
Medically induced abortion
History of infertility
Intrauterine device

Adapted from Bouyer J, Coste J, Shojaei T, et al: Risk factors for ectopic pregnancy: A comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol 157:185–194, 2003.

BOX 178.3

Sonographic Findings in the Patient With Suspected Ectopic Pregnancy

DIAGNOSTIC OF INTRAUTERINE PREGNANCY
"Double" gestational sac
Intrauterine fetal pole or yolk sac
Intrauterine fetal heart activity

DIAGNOSTIC OF ECTOPIC GESTATION
Pregnancy in fallopian tube (see Fig. 178.1)
Ectopic fetal heart activity (see Fig. 178.2)
Ectopic fetal pole

SUGGESTIVE OF ECTOPIC GESTATION
Moderate or large cul-de-sac fluid without intrauterine pregnancy
Adnexal mass without intrauterine pregnancy[a]

INDETERMINATE
Empty uterus (see Fig. 178.3)
Nonspecific fluid collections (see Fig. 178.4)
Echogenic material
Abnormal sac (see Fig. 178.5)
Single gestational sac

Adapted from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310–320, 1999.
[a]A complex mass is the most suggestive of ectopic pregnancy, but a cyst can also be seen with ectopic pregnancy.

pregnancy, tubal abortion into the peritoneal cavity or vagina, or rupture of the pregnancy with internal or vaginal bleeding. Implantation in the uterine horn (cornual pregnancy) is particularly dangerous because the growing embryo can use the myometrial blood supply to grow larger (10–14 weeks of gestation) before rupture occurs.

Clinical Features

The classic clinical picture of ectopic pregnancy is a history of delayed menses, followed by abdominal pain and vaginal bleeding in a patient with known risk factors. Unfortunately, this history is neither sensitive nor specific. Risk factors for ectopic pregnancy are absent in almost half of patients. Of patients with symptomatic ectopic pregnancy, 15% to 20% have not missed a menstrual period, and occasionally the patient has no history of vaginal bleeding. Abdominal pain is usually severe, peritoneal in nature, and constant. Shoulder pain implies free fluid in the peritoneal cavity and is suggestive of an ectopic pregnancy with significant hemorrhage. The pain of ectopic pregnancy can also be crampy, intermittent, or even absent.

The physical findings in ectopic pregnancy are likewise variable. Vaginal bleeding, uterine or adnexal tenderness, or both in the patient with a positive pregnancy test result should trigger consideration of ectopic pregnancy. Tachycardia is not always present, even with significant hemoperitoneum; the hemoglobin level is usually normal, and hypotension may be seen. The presence of peritoneal signs, cervical motion tenderness, or lateral or bilateral abdominal or pelvic tenderness indicates an increased likelihood of ectopic pregnancy. If significant peritoneal irritation is present, pain can preclude an accurate bimanual examination. Adnexal masses are felt in only 10% to 20% of patients with ectopic pregnancy. Vaginal bleeding is often mild. Heavy bleeding with clots or tissue usually suggests a threatened or incomplete miscarriage, although the patient with an ectopic pregnancy who has decreasing hormonal levels may experience endometrial sloughing, which can be mistaken for passage of fetal tissue. Passed tissue should be examined, as with cases of miscarriage, in tap water or saline (or under low-power microscopy). Unless fetal parts or chorionic villi are seen, ectopic pregnancy should not be excluded in the patient with bleeding or passage of tissue.

Diagnostic Testing

Because the history and physical examination of the patient with ectopic pregnancy are insensitive and nonspecific, ancillary studies are essential to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result. Technologic advances have allowed accurate detection and exclusion of ectopic pregnancy in the assessment of the woman with first-trimester vaginal bleeding or pelvic pain. Ultrasonography and hormonal assays are the most commonly used ancillary tests. Laparoscopy may be the most efficient diagnostic tool in the hemodynamically unstable patient.

Ultrasonography. Ultrasonography is the primary method used to locate early gestation, establish gestational age, and assess fetal viability. Transabdominal ultrasonography is most useful for identification of IUPs with fetal cardiac activity and exclusion of ectopic pregnancy, except in patients at high risk for heterotopic pregnancy because of infertility procedures. Transvaginal ultrasonography is more sensitive, recognizes IUP earlier than transabdominal ultrasonography, and is diagnostic in up to 80% of stable patients presenting in the first trimester.[23]

Sonographic findings in the patient with suspected ectopic pregnancy are listed in Box 178.3 and illustrated in Figures 178.1 to 178.5. In general, an indeterminate ultrasound study usually does not result in a diagnosis of normal pregnancy.[23] In one series of more than 1000 pelvic ultrasound examinations, 53% of indeterminate ultrasound studies resulted in a diagnosis of embryonic demise, 15% were ectopic pregnancies, and only 29% had an IUP. However, correlation of sonographic results with quantitative hCG measurements can add to the predictive value.[24] With hCG levels less than 1000 mIU/mL, the risk of ectopic pregnancy increases fourfold, and ultrasonography is still diagnostic in approximately one-third of these patients with ectopic pregnancy. Normal pregnancy is unlikely if no gestational sac is seen by transvaginal ultrasonography with an hCG level higher than 1000 to 2000 mIU/mL, depending on the institution's discriminatory zone, but the differential diagnosis includes miscarriage and ectopic pregnancy. Unfortunately, levels of approximately 1500 mIU/mL develop in only approximately 50% of patients with ectopic pregnancies (see Table 178.1).

Indeterminate sonograms, which demonstrate neither an IUP nor extrauterine findings suggestive of ectopic pregnancy, occur in approximately 20% of ED evaluations of women with

Fig. 178.1. Pregnancy in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

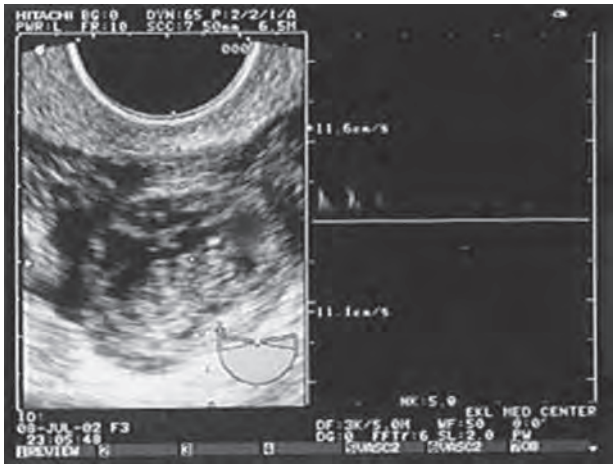

Fig. 178.2. Fetal heart movements detected by ultrasonography in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

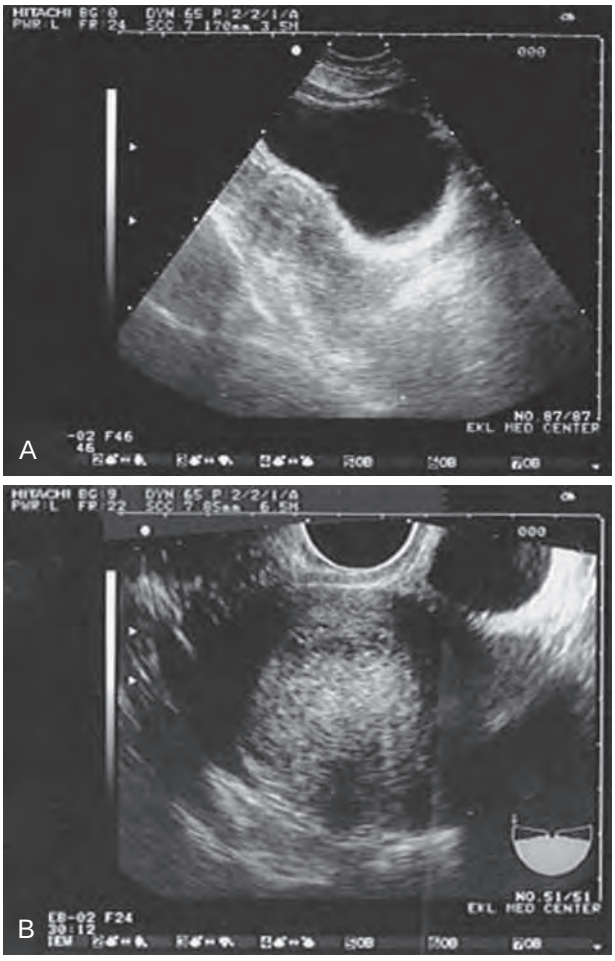

Fig. 178.3. Ultrasonogram showing an empty uterus, indeterminate for diagnosis of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

Fig. 178.4. Ultrasonogram showing fluid around the fallopian tube. (Courtesy Dr. Mary Ann Edens.)

first-trimester bleeding or pain. Ectopic pregnancy is more likely among this subgroup with indeterminate sonograms if the hCG level is less than 1000 mIU/mL and the uterus is empty. Endometrial debris and fluid in the uterus do not exclude ectopic pregnancy.[25]

Use of bedside ultrasonography in the ED for the diagnosis of IUP and exclusion of ectopic pregnancy has shown good sensitivity and negative predictive value in ruling out ectopic pregnancy, but it requires significant operator training.[26-28] In addition to operator-based limitations, the use of ultrasonography is also limited by device availability and quality.

Hormonal Assays. Quantitative hCG levels serve two primary functions—serial levels can be used in the stable patient who can be observed as an outpatient, and a single level can be correlated with sonographic results for improved interpretation. Serum hCG levels normally double every 1.8 to 3 days for the first 6 or 7 weeks of pregnancy, beginning 8 or 9 days after ovulation. An initial quantitative level can be measured at the time of the ED visit, particularly if the sonogram is indeterminate or gestational age is estimated as less than 6 weeks. A repeated level should be measured 48 to 72 hours later. Levels that fall or rise slowly are associated with abnormal pregnancy, intrauterine or ectopic. Of women with an ectopic pregnancy, 21% in one series had an initial rise in hCG at a rate consistent with an IUP.

Single quantitative hCG levels can also be useful in conjunction with ultrasonography; normal IUPs should be visible transvaginally at 1000 to 2000 mIU/mL hCG or higher (see Table 178.1). A benign course for ectopic pregnancy cannot be assumed with low hCG levels. Ruptured ectopic pregnancies requiring surgery have been reported with very low or absent levels of hCG.

Serum progesterone levels have been studied as an additional or alternative marker to determine which patients need further

Fig. 178.5. Ultrasonogram showing a gestational pseudosac. (Courtesy Dr. Mary Ann Edens.)

evaluation and follow-up for possible ectopic pregnancy. The progesterone level rises earlier than hCG level in normal pregnancy and plateaus with levels higher than 20 ng/mL, so measurement of serial levels over time is not necessary. Levels below 5 ng/mL exclude viable IUP—with rare exceptions—and could be useful when the hCG levels are low, ultrasonography is indeterminate, and the emergency clinician is considering D&C or laparoscopy. The ability of a progesterone level to differentiate ectopic pregnancy from a failed IUP is limited, and it is not a standard tool for ED evaluation.

Other Studies. Dilation and evacuation can be used in patients without a viable IUP or ectopic pregnancy on ultrasonography to differentiate intrauterine miscarriage from ectopic pregnancy. Identification of chorionic villi in endometrial samples is seen in approximately 70% of patients and excludes ectopic pregnancy, except in patients undergoing assisted reproduction. Identification of chorionic villi can be made, even in 50% of women with an empty uterus on ultrasonography, and limits the need for laparoscopy to exclude ectopic pregnancy in this population.

Although it is invasive, laparoscopy is extremely accurate as a diagnostic (and therapeutic) procedure for possible ectopic pregnancy. It is the diagnostic treatment of choice in the unstable first-trimester patient with peritoneal signs and is also indicated in patients with significant peritoneal fluid or an ectopic gestation in the pelvic cavity. Medical alternatives for the management of ectopic pregnancy have resulted in decreased indications for laparoscopy in stable patients.[24]

Differential Diagnosis

The spectrum of clinical presentations in ectopic pregnancy is wide, so the differential diagnosis includes essentially all first-trimester complications. Threatened miscarriage, the most common alternative diagnosis, can be recognized by sonographic evidence of an IUP, healthy or failed. Hypovolemia may be seen, particularly in incomplete miscarriage, but hypotension without significant vaginal hemorrhage is highly suggestive of ectopic pregnancy. Identification of fetal parts or chorionic villi in tissue expelled or obtained during D&C is useful to confirm a complication of IUP, although this is not sufficient to exclude ectopic pregnancy in the patient with an increased risk of heterotopic gestation, such as the patient undergoing assisted reproduction treatment.

A ruptured corpus luteum cyst should also be considered in the patient who has first-trimester bleeding associated with peritoneal pain or irritation. The corpus luteum normally supports the pregnancy during the first 7 or 8 weeks. Rupture causes pelvic pain and peritoneal irritation. Ultrasonography is helpful if it reveals an IUP (except in patients with in vitro fertilization). During early gestation, when ultrasonography is nondiagnostic, free fluid is usually visible by ultrasonography, and serial observation may be required (see Fig. 178.4). If the patient is unstable, especially if an IUP cannot be identified by ultrasonography, laparoscopy or, rarely, laparotomy may be required to differentiate between the two conditions.

Management

Classically, approximately 20% of women with ectopic pregnancies manifest signs and symptoms warranting immediate intervention. This includes patients with significant hypovolemia, large amounts of peritoneal fluid, or an open cervical os. For patients with significant signs of hypovolemia, rapid volume resuscitation should be instituted with intravenous (IV) fluids and blood products as necessary, and a baseline hemoglobin level and type and crossmatch should be obtained. A D&C or evacuation procedure with examination of the endometrial contents for products of conception can be performed urgently in the unstable patient with an open cervical os.

If the patient remains unstable, immediate surgery is warranted. Laparoscopy may be indicated for patients who stabilize with treatment or those who are hemodynamically stable but exhibit significant peritoneal signs on abdominal examination. One study has reported that identification of free fluid in Morison's pouch on bedside ultrasonography predicts the need for operative intervention in most cases in patients with suspected ectopic pregnancies. All patients with ectopic pregnancy who are Rh-negative should be given Rh immune globulin, 50 μg intramuscularly.

Most patients who seek treatment for bleeding or pain during the first trimester of pregnancy are stable. In these patients, the goal should be to exclude ectopic pregnancy in a timely manner. In the patient with significant pain by history or examination or significant risk factors for ectopic pregnancy, ultrasonography should be performed before discharge. If the results are indeterminate, a quantitative hCG level may be helpful in determining the patient's risk for ectopic pregnancy.

In low-risk patients with only minor symptoms or bleeding, ectopic pregnancy is still a possibility. Two general outpatient approaches can be considered. In most institutions, ultrasonography is the initial screening tool (Fig. 178.6). If an IUP is not seen, quantitative hCG levels help risk stratify these patients. In all cases, if the patient is discharged, careful instructions are given for symptoms that would require her earlier return (ectopic precautions). An alternative strategy uses hCG levels first. However, waiting times for the serum assay can increase ED length of stay. In addition, ultrasonography is usually diagnostic of IUP or ectopic pregnancy, even if the hCG level is less than 1000 mIU/mL. In most cases, the initial sonogram provides more rapid and accurate information.

A significant minority of patients have indeterminate sonographic results and hCG levels below 1000 mIU/mL. When the hCG levels never rise to the discriminatory zone, the differential diagnosis includes intrauterine fetal demise and ectopic pregnancy. Early D&C with identification of the products of conception can be useful in the patient with nonrising hCG levels to detect chorionic villi and confirm a failed IUP or strongly suggest ectopic pregnancy. Alternatively, hCG levels can be followed until they reach zero, particularly if initial levels are low.

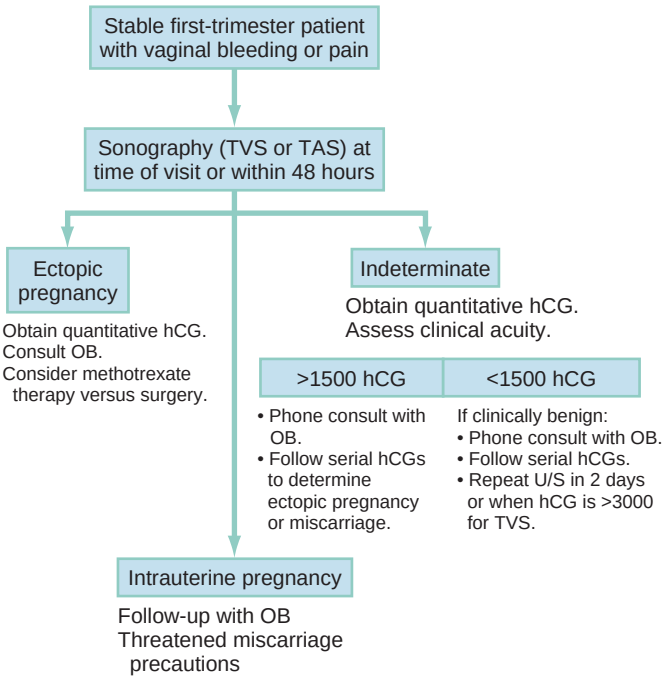

Fig. 178.6. Management of vaginal bleeding or pain in the stable first-trimester pregnant patient. *hCG,* Human chorionic gonadotropin; *OB,* obstetrics specialist; *TAS,* transabdominal sonography; *TVS,* transvaginal sonography; *U/S*, ultrasonography.

Although laparotomy may be required for patients who have an ectopic pregnancy, an increasing number of surgeries are being performed through the laparoscope. Salpingostomy is preferred to salpingectomy if the patient is stable and the procedure is technically feasible. Overall, the advent of transvaginal ultrasonography has resulted in a decreased number of surgeries and a trend toward nonoperative management.

Medical management is a safe and cost-effective treatment for the stable patient with minimal symptoms, especially when future fertility is desired.[22,29] Methotrexate is the drug most commonly used to treat early ectopic pregnancy. It interferes with fetal DNA synthesis and causes destruction of rapidly dividing fetal cells and involution of the pregnancy. Medical treatment is used most often for patients who are hemodynamically stable, with a tubal mass smaller than 3.5 cm in diameter, no fetal cardiac activity, and no sonographic evidence of rupture. Although there is no agreed on hCG cutoff for single-dose methotrexate, studies have suggested that increasing hCG levels are significantly correlated with methotrexate failure. Medical therapies are associated with an 85% to 93% success rate, with no significant difference between single- and multiple-dose protocols. Pelvic pain is common in patients receiving methotrexate (60%), even when it is used successfully. Indications of methotrexate failure and need for rescue surgery include decreasing hemoglobin levels, significant pelvic fluid, and unstable vital signs. All patients receiving methotrexate require close follow-up until the hCG level reaches 0, which may take 2 or 3 months.

Molar Pregnancy

Molar pregnancy, also known as a hydatidiform mole, comprises a spectrum of diseases characterized by disordered proliferation of chorionic villi. In the absence of fetal tissue, the pregnancy is termed a *complete hydatidiform mole*. Complete moles are caused by the fertilization of an ovum without maternal DNA and the subsequent duplication of the haploid genome. The term *incomplete mole* refers to a mole that is caused by the fertilization of a normal ovum by two sperm. The duplication of the triploid karyotype causes some fetal tissue to be present, along with focal trophoblastic hyperplasia. In approximately 19% of molar pregnancies, neoplastic gestational disease develops, with persistence of molar tissue after the pregnancy has been evacuated.[30] Metastatic disease can develop, requiring chemotherapy and intensive oncologic management.

Early molar pregnancy is usually not clinically apparent. The most well-described risk factor for the development of a molar pregnancy is extreme maternal age.[31] Many patients present with abdominal pain, nausea and vomiting, or vaginal bleeding, and it may be difficult to differentiate these patients from those with threatened miscarriage or ectopic pregnancy by historical features alone. Patients sometimes seek treatment for apparent persistent hyperemesis gravidarum from high circulating levels of hCG, bleeding or intermittent bloody discharge, or respiratory distress; failure to hear fetal heart tones during the second trimester is the usual initial clue to diagnosis. If molar pregnancy spontaneously aborts, it is usually in the second trimester (before 20 weeks), and the patient or physician may note the passage of grapelike hydatid vesicles. Uterine size is larger than expected by date (by >4 weeks) in approximately 30% to 40% of patients. Theca lutein cysts may be present on the ovaries as a result of excessive hormonal stimulation, and torsion of affected ovaries can be seen.

The characteristic sonographic appearance of hydropic vesicles within the uterus, described as a snowstorm appearance, is highly suggestive of a diagnosis of molar pregnancy (Fig. 178.7). Alternatively, cystic changes are seen in partial molar pregnancies. In some cases, a partial molar pregnancy is detected only on pathologic examination of abortion specimens. Complications of molar pregnancy include preeclampsia or eclampsia, which can develop before 24 weeks of gestation, respiratory failure or distress from pulmonary embolization of trophoblastic cells, hyperemesis gravidarum, and significant uterine bleeding, acute or chronic. Ultrasonography usually provides the diagnosis of a complete molar pregnancy in the second-trimester patient who has "threatened miscarriage" or during sonographic assessment for fetal well-being and size. However, ultrasonography is only 58% sensitive, and diagnosis of a partial mole is made in 17% of cases.[31] Up to two-thirds of molar pregnancies are diagnosed by pathologic specimens after miscarriage.

Following evacuation of a molar pregnancy, patients must be monitored in the outpatient setting for trophoblastic sequelae. Patients are at increased risk of an invasive mole, a benign tumor that invades the uterine wall and metastasizes to the lungs or vagina, or choriocarcinoma, a malignant tumor that invades the uterine wall and disseminates to the lungs, brain, and liver via the patient's vasculature. Patients who present to the ED with complications of bleeding metastases are managed with a combination of chemotherapy, radiation, and surgery.[32]

COMPLICATIONS OF LATE PREGNANCY

Vaginal Bleeding in Later Pregnancy

Bleeding during the second half of pregnancy occurs in approximately 4% of pregnancies. Only 20% of miscarriages occur after the first trimester, and the most important differential diagnoses after 12 to 14 weeks of gestation are abruptio placentae and placenta previa. The cause is often not determined, although occult marginal placental separations, which can be recognized only by placental inspection at delivery, are believed to come from a common source of bleeding above the cervix. Other causes of late

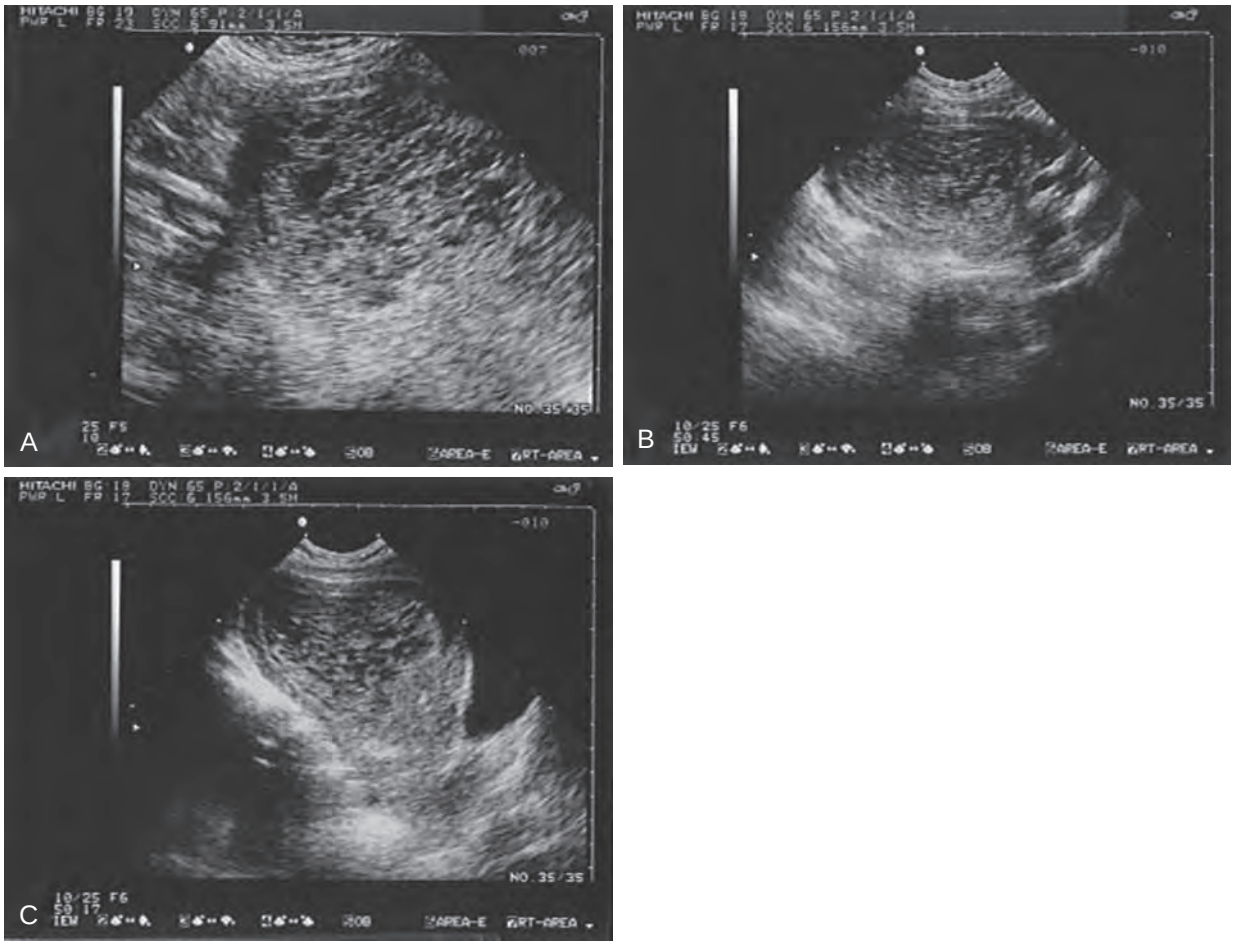

Fig. 178.7. Ultrasonogram showing molar pregnancy. (Courtesy Dr. Mary Ann Edens.)

vaginal bleeding include early labor, various cervical and vaginal lesions, lower genital tract infections, and hemorrhoids.

Bleeding during the second trimester before the fetus is potentially viable (14–24 weeks) is not benign. One-third of fetuses are ultimately lost when maternal bleeding occurs. Management is supportive and expectant because fetal rescue is impossible at this level of fetal immaturity. In the third trimester, vaginal bleeding is still associated with significant morbidity in approximately one-third of women; treatment includes consideration of urgent delivery.[33]

Abruptio Placentae

Abruptio placentae, or separation of the placenta from the uterine wall, is believed to account for approximately 30% of episodes of bleeding during the second half of pregnancy, 10% of preterm births, and 10% to 20% of perinatal deaths.[25] Small subclinical or marginal separations may go undetected until the placenta is examined at delivery and probably account for many of the other self-limited episodes of bleeding for which no diagnosis is made. In cases of nontraumatic abruptio placentae, apparently spontaneous hemorrhage into the decidua basalis occurs, causing separation and compression of the adjacent placenta. Small amounts of bleeding may be asymptomatic and remain undetected until delivery. In other cases, the hematoma expands and extends the dissection. Bleeding may be concealed or may be clinically apparent if dissection occurs along the uterine wall and through the cervix. Placental separation may be acute or may be an indolent problem throughout late pregnancy.

Abruptio placentae is most clearly associated with maternal hypertension and preeclampsia. It is also more common with maternal age younger than 20 or 35 years of age or older, parity of three or more, unexplained infertility, history of smoking, thrombophilia, prior miscarriage, prior abruptio placentae, and cocaine use.[25,34] Placental separation can also be associated with blunt trauma to the abdomen. In such cases, the cause appears to be shearing of a nonelastic placenta from the easily distorted elastic uterine wall at the time of traumatic impact. Women who reported physical violence during pregnancy were found to be twice as likely as women who did not report violence to have an abruption.[35]

Clinical Features. Vaginal bleeding occurs in 70% of patients with abruptio placentae. Blood is characteristically dark and the amount is often insignificant, although the mother may have hemodynamic evidence of significant blood loss. Uterine tenderness or pain is seen in approximately two-thirds of women; uterine irritability or contractions are seen in one-third. With significant placental separation, fetal distress occurs, and the maternal coagulation cascade may be triggered, causing disseminated intravascular coagulation (DIC).[33]

There is a wide spectrum of severity of symptoms and risk in placental separation. Up to 20% of women will have no pain or vaginal bleeding.[36] Assessment is generally based on clinical features, coagulation parameters, and signs of fetal distress. Slight vaginal bleeding, little or no uterine irritability, absence of signs of fetal distress, and normal coagulation characterize mild abruption. As the separation becomes more extensive, it is associated

with more vaginal bleeding (or hidden maternal blood loss), increased uterine irritability, with or without tetanic contractions, declining fibrinogen levels, and evidence of fetal distress and maternal tachycardia. In severe abruptio placentae (15% of cases), the uterus is tetanically contracted and very painful, maternal hypotension results from visible or concealed uterine blood loss, fibrinogen levels are less than 150 mg/dL, and fetal death can occur. Ultrasonography is insensitive in the diagnosis of abruptio placentae, often because the echogenicity of fresh blood is so similar to that of the placenta. Symptomatic or even fetus-threatening abruption can occur in the presence of a normal sonogram.[36]

Fetal distress and death occur in approximately 15% of patients with abruptio placentae by interruption of placental blood and oxygen flow. Risk of fetal death increases in proportion to the percentage of the placental surface involved and rapidity of separation. Fetal distress may result from the loss of placental blood flow, associated maternal hemorrhage (into the uterine cavity or externally), increased uterine tone, or resultant DIC. Maternal death can result, usually from coagulopathy or exsanguination. Fetomaternal transfusion occurs in a significant minority of patients. Placental separation also predisposes the mother to amniotic fluid embolism.

Differential Diagnosis. The main alternative diagnosis in the woman with late-pregnancy bleeding is placenta previa, which is usually associated with painless, bright red bleeding and is excluded with ultrasonography. Lower genital tract or rectal lesions and bloody show (blood-tinged cervical mucous plug) are also considerations.

In the patient with abdominal pain but no vaginal bleeding, abruptio placentae with concealed hemorrhage must be distinguished from other causes of abdominal pain in later pregnancy—complications of preeclampsia, pyelonephritis, various liver diseases, gallbladder disease, appendicitis, and ovarian torsion. Uterine irritability caused by abruptio placentae can also be confused with early labor; in one series, almost 25% of patients were misdiagnosed as having premature labor until fetal distress occurred. If the patient has acute catastrophic hypotension, amniotic fluid embolus, with or without abruptio placentae, and uterine rupture must be considered.

Placenta Previa

Placenta previa, or implantation of the placenta over the cervical os, is the other major cause of bleeding episodes during the second half of pregnancy. The risk of placenta previa is increased with maternal age, smoking, multiparity, cesarean section, prior miscarriage or induced abortions, and preterm labor.[37,38] Bleeding occurs when marginal placental vessels implanted in the lower uterine segment are torn, either as the lower uterine wall elongates or with cervical dilation near the time of delivery. Early bleeding episodes tend to be self-limited unless separation of the placental margin is aggravated by iatrogenic cervical probing or the onset of labor.

Clinical Features. Painless, fresh vaginal bleeding is the most common symptom of placenta previa. In approximately 20% of cases, some degree of uterine irritability is present, but this is generally minor. Vaginal examination usually reveals bright red blood from the cervical os. All patients with painless, second-trimester vaginal bleeding should be assumed to have placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis is excluded via ultrasound. Injudicious vaginal examination can precipitate severe hemorrhage in the patient with an asymptomatic or minimally symptomatic placenta previa. Speculum examination of the vagina and cervix should be performed only in those settings in which obstetric consultation is not readily available. It should be limited to an atraumatic partial speculum insertion to identify whether the bleeding is coming from the cervical os (and a presumed placenta previa), hemorrhoids, or a vaginal lesion that might not require urgent management.

Most cases of placenta previa identified during the midtrimester resolve by the time of delivery as the lower uterine segment elongates and the placenta no longer overlaps the cervical os. Central or total previa, which occurs in approximately 20% of cases, can, however, cause severe hemorrhage, with the risk of exsanguination for the fetus and mother.

Diagnostic Testing. Ultrasonography is the diagnostic procedure of choice for localization of the placenta and diagnosis of placenta previa. Accuracy is excellent, but visualization of the placenta and of the internal cervical os is required. The bladder should be emptied before examination for suspected placenta previa to avoid overdiagnosis of placenta previa. Transvaginal ultrasonography is safe and even more accurate for visualization of the relationships between the placenta and internal os.[38]

Management. Patients who experience vaginal bleeding during late pregnancy should have immediate obstetric consultation and arrangements for safe transfer to an appropriate obstetric facility. Initial management consists of maternal stabilization, with establishment of two large-bore IV lines and fluid resuscitation, as well as continuous fetal monitoring, if available. A baseline hemoglobin level should be determined, and blood should be sent for type and crossmatch. Baseline coagulation studies, including platelet count, prothrombin time, and partial thromboplastin time, should be performed, and the fibrinogen level and presence of fibrin split products should be determined. The normal fibrinogen level in pregnancy is 400 to 450 mg/dL; values below 300 mg/dL indicate significant consumption of coagulation factors.

Blood loss requiring transfusion can occur in patients with placenta previa or abruptio placentae. Fresh-frozen plasma or fresh whole blood may be needed because of the coagulopathy associated with significant abruptio placentae. Fetomaternal hemorrhage can occur with abruption. If the Rh-negative patient has not yet received her routine Rh immune globulin prophylaxis at 28 weeks, 300 μg of Rh immune globulin should be administered within 72 hours. Transfer to the obstetric unit should be expedited if the patient is stable, or it should be done after initiation of resuscitation if she is unstable. If transfer to another hospital is required, a high-risk transfer team should be used if bleeding is significant or the fetus is in distress. Although the bleeding source may not be identified or may be relatively benign, assessment is best accomplished by obstetricians who are accustomed to the evaluation of late-pregnancy complications and who can perform emergent cesarean section, if needed.

In the obstetrics unit, fetal monitoring is continued. Ultrasonography is used primarily to locate the placenta and diagnose placenta previa, but it may not be reliable in confirming the diagnosis of abruptio placentae. On occasion, subplacental hemorrhages of abruptio placentae can be seen, and changes in size of the collection can be monitored. If evidence of placenta previa is absent or equivocal, a vaginal examination is performed in the delivery suite, where an emergency cesarean section can be performed if uncontrolled bleeding is encountered.

Patients who have significant abruptio placentae may require early delivery—vaginal or surgical, depending on fetal status. If placenta previa is diagnosed or if abruptio placentae is considered mild, the patient is admitted for close monitoring. The goal is to support the patient, ideally until fetal maturity is demonstrated and a successful delivery can be accomplished.

Pregnancy-Induced Hypertension (Preeclampsia and Eclampsia)

Hypertension is observed in up to 8% of pregnancies and is generally divided into several categories[39,40]:

- Gestational hypertension occurs during pregnancy, resolves during the postpartum period, and is recognized by a new blood pressure reading of 140/90 mm Hg or higher.
- Preeclampsia is gestational hypertension with proteinuria (>300 mg/24 hr).
- Eclampsia is the occurrence of seizures in the patient with signs of preeclampsia. Progression of preeclampsia to eclampsia is unpredictable and can occur rapidly.
- Pregnancy-aggravated hypertension is chronic hypertension, with superimposed preeclampsia or eclampsia.
- Chronic or coincidental hypertension is present before pregnancy or persists more than 6 weeks postpartum.[40]

Approximately 2% to 7% of pregnancies are complicated by pregnancy-induced hypertension. The incidence of actual eclampsia has progressively declined but is still one of the major causes of maternal mortality. The risk of pregnancy-induced hypertension is greatest in women younger than 20 years, primigravidas, those with twin or molar pregnancies, those with hypercholesterolemia, pregestational diabetes, or obesity, and those with a family history of pregnancy-induced hypertension.[40]

Pathophysiology

Gestational hypertension or preeclampsia is a vasospastic disease of unknown cause unique to pregnant women. Vasospasm, ischemia, and thrombosis associated with preeclamptic changes cause injury to maternal organs, placental infarction and abruption, and fetal death from hypoxia and prematurity. The cause of eclampsia is unknown, but recent studies have centered on vascular responsiveness to endogenous vasopressors in the preeclamptic woman. Vascular responsiveness is normally depressed during pregnancy, which is a high-output, low-resistance state. Gestational hypertension is characterized by an even greater elevation in cardiac output, followed by an abnormally high peripheral resistance as clinical manifestations of the disease develop. In patients with preeclampsia, the cardiac output eventually drops as peripheral resistance rises.[41] The cause of these changes is not known, but endothelial dysfunction is purported to release vasoactive mediators and result in vasoconstriction. Antiplatelet agents during pregnancy have been reported to reduce the risk of development of preeclampsia, supporting the premise of an imbalance between levels of thromboxane and prostacyclin in preeclampsia.[42]

The vasospastic effects of gestational hypertension and preeclampsia are protean. The intravascular volume is lower than in normal pregnancy, central venous pressures are normal, and capillary wedge pressures are variable. Liver effects are believed to be due to hepatocellular necrosis and edema resulting from vasospasm. Renal injury causes proteinuria and may result in decreased glomerular filtration. Microangiopathic hemolysis may result from vasospasm, causing thrombocytopenia. Central nervous system (CNS) effects include microvascular thrombosis and hemorrhage, as well as focal edema and hyperemia.[40]

Clinical Features

Signs and Symptoms. The patient with gestational hypertension has mild systolic or diastolic blood pressure elevation, no proteinuria, and no evidence of organ damage. Mental status assessment, testing of reflexes, abdominal examination, liver function studies, and coagulation studies yield normal results. Preeclampsia is associated with kidney changes and, in severe cases, other end-organ symptoms. Edema is often difficult to assess because pregnancy is normally associated with excess extracellular fluid and dependent edema, and it is no longer used as a criterion for preeclampsia. Proteinuria (300 mg/24 hr) is variable at any given time and may not be detectable in a random urine specimen.[39]

In cases of severe preeclampsia, the diastolic blood pressure can exceed 110 mm Hg, proteinuria is more severe, and there is evidence of vasospastic effects in various end organs. CNS effects commonly include headache or visual disturbances. Thrombocytopenia may be present, liver function test findings may be elevated, and the liver is often tender. Renal dysfunction may be indicated by oliguria and elevated creatinine levels in addition to proteinuria.

Complications

The HELLP syndrome, a particularly severe form of preeclampsia that develops in 5% to 10% of women who have preeclamptic symptoms, is characterized by ***h***emolysis, ***e***levated ***l***iver enzyme levels (alanine transaminase [ALT] and aspartate transaminase [AST] > 70 U/L), and ***l***ow ***p***latelet count (<100,000/mL). Prothrombin time, partial thromboplastin time, and fibrinogen level are normal, and blood studies reveal microangiopathic hemolytic anemia. Other complications of preeclampsia include spontaneous hepatic and splenic hemorrhage and abruptio placentae.

The most dangerous complication is eclampsia, which is the occurrence of seizures or coma in the setting of signs and symptoms of preeclampsia. Warning signs for the development of eclampsia include headache, nausea and vomiting, and visual disturbances. Elevated total leukocyte count, and creatinine and AST levels are also predictive of increased morbidity for the patient with severe preeclampsia. Particularly in early eclampsia before 32 weeks of gestation, seizures may develop abruptly, and hypertension may not be associated with edema or proteinuria.[40] In postpartum women who have eclampsia, more than half (55%) have not been previously diagnosed with preeclampsia, and patients may present with headache, vision changes, elevated blood pressure, and/or seizures up to 4 weeks after delivery.[43] After 48 hours postpartum and without predelivery signs of preeclampsia, other diagnoses, such as intracranial hemorrhage, should be considered. Maternal complications of eclampsia include permanent CNS damage from recurrent seizures or intracranial bleeding, renal insufficiency, and death.

The maternal mortality rate from eclampsia has been reduced to less than 1% with modern management. Perinatal mortality has also decreased, although it remains at 4% to 8%.[40] Causes of neonatal death include placental infarcts, intrauterine growth retardation, and abruptio placentae. In addition, fetal hypoxia from maternal seizures and the complications of premature delivery contribute significantly to fetal morbidity and mortality.

Diagnostic Testing

The patient who has severe preeclampsia should have an IV line and fetal monitoring initiated. Blood testing should include complete blood cell count, renal function studies, liver function tests, platelet count, and coagulation profile. A baseline magnesium level should also be determined. In the patient with actual seizures, the serum glucose concentration should be determined. If a history of preeclampsia is not obtained or the symptoms are refractory to magnesium sulfate therapy, a computed tomography (CT) scan of the head should be performed to exclude cerebral venous thrombosis or an intracranial bleed, either of which can occur in pregnancy—with or without pregnancy-induced hypertension—and may require specific treatment. CT scan abnormalities can be seen in 50% of patients with eclampsia. Patchy hemorrhage and microinfarcts of the cortex are

characteristic and may be due to loss of cerebral autoregulation in patients with severe pregnancy-related hypertension. Diffuse cerebral edema can also be seen.

Differential Diagnosis

Peripheral edema is common in normal pregnancy, and it may be difficult to differentiate normal edema from that of early preeclampsia. Differentiation of gestational hypertension from preexistent hypertension is often impossible if no record of normal blood pressure is available. Seizures during pregnancy may be due to epilepsy as well as other intracranial catastrophes, such as thrombosis or hemorrhage.

Management

The management of patients with mild preeclampsia includes documentation of blood pressure and reflexes, weight, and testing to ensure normal end-organ function. Accurate determination of gestational age by ultrasonography is needed to allow optimal management if symptoms progress. Limitation of physical activities, including bed rest, is the only demonstrated means of reducing blood pressure and allowing the pregnancy to be sustained longer. Definitive treatment is delivery of the fetus, although expectant management is standard in women at less than 34 weeks of gestation. Arrangement for close follow-up is important for patients who are not hospitalized.

Hospitalization is usually required for patients with sustained hypertension above 140/90 mm Hg and signs of severe preeclampsia. Baseline laboratory studies should be carried out to identify end-organ effects in the liver, kidney, and hematologic systems. Both diuresis and antihypertensive therapy have been remarkably unsuccessful in improving fetal outcome and/or prolonging pregnancy. Admission does, however, allow the obstetrician to assess fetal age and well-being accurately, maternal organ function, and effect of bed rest on blood pressure before the optimal timing of delivery is decided.[39]

Fulminant or severe preeclampsia, with marked blood pressure elevation (≥160/110 mm Hg) associated with epigastric or liver tenderness, visual disturbance, or severe headache, is managed in the same way as eclampsia (Box 178.4). The goal is prevention of seizures and permanent damage to maternal organs. Magnesium sulfate is given for seizure prophylaxis.

BOX 178.4

Management of Eclampsia and Severe Preeclampsia

Control seizures with magnesium sulfate.
Control hypertension after seizure control if diastolic blood pressure >105 mm Hg.
Obtain initial laboratory studies to assess organ injury:
- Complete blood count and platelet count
- Liver function tests
- Blood urea nitrogen, creatinine

Monitor urine output; maintain at <25 mL/hr.
Limit intravenous fluid administration unless significant losses occur.
Avoid diuretics and hyperosmotic agents.
Perform a computed tomography scan of the head if consciousness is decreased or seizures persist, lateralizing signs are present, or there are other concerns.
Initiate steps to delivery.

Adapted from Pritchard JA, Cunningham FG, Pritchard SA.: The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol 148:951–963, 1984.

Seizures and coma are the hallmarks of eclampsia, the ultimate consequence of preeclampsia. As in all seizure patients, hypoglycemia, drug overdose, and other causes of seizures should be excluded with appropriate tests. Eclamptic seizures are controlled in almost all patients by adequate doses of magnesium sulfate, although the mechanism of action remains elusive. Magnesium has little antihypertensive effect but is the most effective anticonvulsant, preventing recurrent seizures while maintaining uterine and fetal blood flow. The goals of magnesium sulfate therapy are to terminate ongoing seizures and prevent further seizures. An IV loading dose of 4 g magnesium, followed by 2 g/hr IV, is recommended. Magnesium administration should be accompanied by clinical observation for loss of reflexes (which occurs at ≈10 mg/dL) or respiratory depression (which occurs at levels of 12 mg/dL, although actual serum magnesium levels are rarely monitored). The infusion should be stopped if signs of hypermagnesemia are seen, because such patients may require assisted ventilation. IV calcium gluconate, 1 g given slowly, will reverse the adverse effects of hypermagnesemia.[40]

Despite ongoing controversy, the familiarity with magnesium sulfate and its physiologic advantages to the fetus, wide margin of safety, and high success rate in controlling seizures make it the first-line drug in patients with eclampsia. A Cochrane review has found that magnesium sulfate is more effective than other anticonvulsants and diazepam for prophylaxis against or treatment of eclamptic seizures, more than halving the risk.[44] If seizures persist after the recommended doses of magnesium sulfate have been administered, diazepam or phenytoin may be given as alternative regimens in conjunction with obstetric consultation, and a careful search for other causes of seizures (eg, hypoglycemia and intracranial bleed) should be instituted.[45]

Although magnesium sulfate is not a direct antihypertensive, the hypertension associated with eclampsia is often controlled adequately by stoppage of the seizures. Rapid lowering of blood pressure can result in uterine hypoperfusion, so specific antihypertensive treatment is initiated only if the diastolic blood pressure remains above 105 mm Hg after control of seizures. Many patients do not require specific antihypertensive treatment after treatment with magnesium sulfate. The antihypertensive used most often by obstetricians is hydralazine, 5 mg IV, with repeated doses of 5 to 10 mg IV every 20 minutes as needed to keep the diastolic blood pressure below 105 mm Hg. Nimodipine and labetalol have also been reported to be safe and effective, although they are less widely used. Other antihypertensive agents have not been well studied in this population because there are specific risks to uncontrolled lowering of blood pressure and loss of uteroplacental blood flow.

Although total body water in the eclamptic patient is excessive, intravascular volume is contracted, and the eclamptic patient is sensitive to further volume changes. Hypovolemia results in decreased uterine perfusion. Thus, diuretics and hyperosmotic agents should be avoided in these patients. Invasive monitoring has demonstrated that vasospasm is not reversed with IV fluid administration. Rather, excessive IV fluids increase extravascular fluid stores that are difficult to mobilize postpartum, resulting in a higher incidence of pulmonary edema in patients treated aggressively with fluid therapy. Invasive pulmonary artery pressure monitoring may be required for accurate fluid management in the eclamptic patient.

Amniotic Fluid Embolus

Amniotic fluid embolus is the release of amniotic fluid into the maternal circulation during intense uterine contractions or uterine manipulation at areas of placental separation from the uterine decidua basalis (abruptio placentae), triggering a rapidly fatal, anaphylactoid-type maternal response. Although amniotic

fluid embolus usually occurs during labor, with the maternal mortality rate at 25% or higher, it can also occur after induced abortions and miscarriages and spontaneously during the second and third trimesters. Amniotic fluid embolus can also occur after amniocentesis or in association with abruptio placentae after abdominal trauma. Although it is a rare syndrome, amniotic fluid embolus is the leading cause of cardiovascular collapse during labor.[46]

Clinical Features

Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden hypotension, hypoxia, and coagulopathy. The embolization of amniotic fluid and the particulate matter suspended in it triggers a profound immunologic response when it enters the maternal circulation. The list of proposed mediators is extensive and includes histamine, endothelin, and leukotrienes.[46] In survivors, DIC, acute respiratory distress syndrome, and left ventricular dysfunction develop. An initial seizure is seen in approximately 20% of patients. Bleeding diathesis may be the initial sign in some women, and DIC occurs in approximately 50%.

Diagnostic Testing

When amniotic fluid embolus is suspected, a complete blood cell count, coagulation studies, arterial blood gas analysis, and chest radiograph should be obtained. Urine output should be monitored after urinary catheter placement. The diagnosis is usually made with certainty only at autopsy, with the finding of fetal hairs, squamous cells, and debris in the maternal circulation. Because squamous epithelial cells can be seen normally in the maternal pulmonary circulation, the typical clinical syndrome is also required for diagnosis.

Differential Diagnosis

Catastrophic pulmonary embolus, drug-induced anaphylaxis, and septic shock must be considered in the differential diagnosis. Seizures occur in patients with eclampsia, but hypertension rather than cardiovascular collapse is usually observed in that condition. Coagulopathy may be seen in patients with preeclampsia (HELLP syndrome), abruptio placentae, or other chronic coagulopathies seen in the nonpregnant patient.

Management

Amniotic fluid embolus is uncommon, so treatment recommendations are anecdotal and have been based on animal studies. The most helpful modalities appear to be high-flow oxygen, support of ventilation and oxygenation with intubation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy. Adequate treatment usually requires invasive hemodynamic monitoring in an intensive care unit.

Rh (Anti-D) Immunization in Pregnancy

Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. Small numbers of fetal cells enter the maternal circulation spontaneously throughout pregnancy, but the maternal immune system is triggered only by significant loads of fetal cells, which can occur during the third trimester and at delivery. Sensitization occurs in up to 15% of Rh-negative women carrying Rh-positive fetuses. To prevent this, anti-D immune globulin (RhoGAM) is routinely administered to Rh-negative mothers—if the father is Rh positive or his status is unknown—at approximately the 28th week of gestation to protect the mother from spontaneous sensitization, which occurs during the third trimester. Transplacental hemorrhage can also occur during uterine manipulation, threatened miscarriage (even without fetal loss), spontaneous miscarriage, surgery for ectopic pregnancy, and amniocentesis, although the risk is not clear. Anti-D immune globulin should be administered when these events occur. A dose of 50 μg can be used if the patient is at less than 12 weeks of gestation, although many pharmacies carry only the 300-μg dose, which can also be given. After 12 weeks, a 300-μg dose should be given. The half-life of immune globulin is 24 days, and it needs to be administered within 72 hours of a sensitization event to prevent antibody development.

The Kleihauer-Betke test of maternal blood has been used to detect fetal cells in the maternal circulation. Unfortunately, the test is difficult to perform, not immediately available in most emergency laboratories, and only sensitive enough to detect 5 mL of fetal cells in the maternal circulation. Because only 0.1 mL of fetal cells is required to sensitize the mother, routine immune globulin administration has been recommended in situations likely to result in sensitization. Patients with third-trimester bleeding are not at increased risk of sensitization compared with patients with normal pregnancy. Thus, RhoGAM should be administered only if the patient did not receive her prophylactic dose at 28 weeks. In cases of significant blunt trauma to the uterus, the Kleihauer-Betke test should be ordered to detect the rare, large fetal transfusions that may require specific fetal blood therapy or administration of additional immune globulin to the mother. The standard dose (300 μg) is sufficient to prevent maternal immunization for fetal transfusions of up to 15 mL of red blood cells or 30 mL of whole blood.

MEDICAL AND SURGICAL PROBLEMS IN THE PREGNANT PATIENT

Clinicians should be aware of a variety of illnesses, related and unrelated to pregnancy, that may have altered symptoms, risk, and treatment in the pregnant patient (Tables 178.2 and 178.3). See also Chapter 179.

Abdominal Pain

Appendicitis

Appendicitis is the most common surgical emergency in pregnant patients. The incidence of appendicitis in pregnant patients is the same as that in nonpregnant patients, but delays in diagnosis contribute to an increased rate of perforation, which results in significant fetal mortality and maternal morbidity.[47] There is also an increased rate of complications of appendicitis in pregnancy. A large, population-based study has found an almost twofold increase in sepsis and septic shock, transfusion, pneumonia, bowel obstruction, postoperative infection, and length of stay longer than 3 days.[48] During the first half of pregnancy, diagnostic findings are usually similar to those in the nonpregnant woman, but the clinical picture becomes more atypical during the second half of pregnancy.

Traditionally, the appendix was thought to be displaced counterclockwise out of the right lower quadrant after the third month of gestation, with its ultimate location deep in the right upper quadrant, superior to the iliac crest (Fig. 178.8). However, one study has found that in only 23% of pregnant patients does the location change from the right lower quadrant, even in the third trimester. Displacement of the abdominal wall away from the abdominal viscera can result in difficulty in palpation of organs and loss of signs of parietal peritoneal irritation. The physiologic

TABLE 178.2

Differential Diagnosis of Abdominal Pain in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
GYNECOLOGIC		
Miscarriage	<20 wk; 80% <12 wk	Ultrasonography to confirm location
Septic abortion	<20 wk	Fever, uterine tenderness
Ectopic pregnancy	<14 wk	Must always be considered in first trimester until intrauterine pregnancy confirmed
Corpus luteum cyst	<12 wk	Sudden focal peritoneal pain; no fever
Ovarian torsion	Especially <24 wk	Ischemic pain
Pelvic inflammatory disease	<12 wk	Very rare
Chorioamnionitis	>16 wk	Tender uterus, fever; amniocentesis reveals white blood cells
Abruptio placentae	>16 wk	Focal uterine tenderness, fetal distress, variable bleeding
Preeclampsia	>20 wk	Hypertension, proteinuria, edema, right upper quadrant pain
NONGYNECOLOGIC		
Appendicitis	Throughout	Guarding may be less prominent; location changes
Cholecystitis	Throughout	Confirm with ultrasonography
Hepatitis	Throughout	Confirm with liver function tests
Pyelonephritis	Throughout	Flank pain, fever, positive catheterized urinalysis

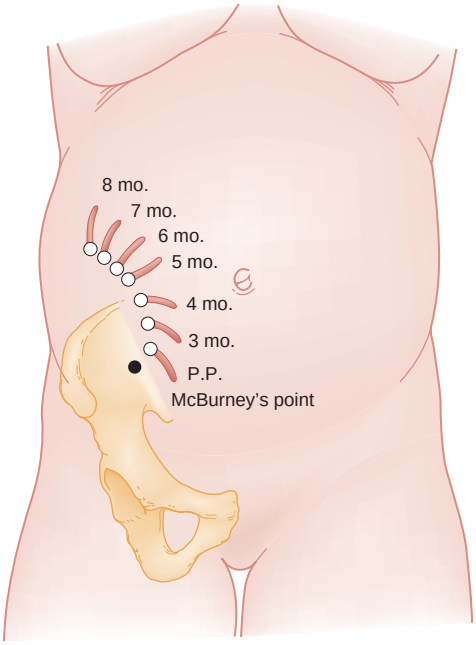

Fig. 178.8. Locations of the appendix during succeeding months of pregnancy. In planning an operation, it is better to make the abdominal incision over the point of maximal tenderness unless there is great disparity between that point and the theoretic location of the appendix. *P.P.,* postpartum. (From Gabbe SG, Niebyl JR, Simpson JL, Galan HL: Obstetrics: normal and problem pregnancies, New York, 2007, Churchill Livingstone.)

increase in white blood cell count and erythrocyte sedimentation rate in pregnancy should also be considered in the evaluation of the patient with possible appendicitis because these may confuse the overall clinical picture.

Clinical Features. The gastrointestinal symptoms of appendicitis, such as anorexia, nausea, and vomiting, mimic those of pregnancy, particularly during the first trimester, making such symptoms relatively nonspecific. Right-sided abdominal pain is the most constant finding, although this is less reliable later in pregnancy. Peritoneal signs are also most common during the first trimester. The absence of fever, leukocytosis, or tachycardia has been reported. The lack of these clinical findings in pregnant patients with appendicitis may be the result of a blunted inflammatory response caused by elevated maternal levels of pregnancy-related steroids. Pyuria without bacteriuria is seen in up to 58% of patients.

Because of confounding factors, the misdiagnosis rate for appendicitis is 30% to 35% overall in pregnancy, with a 40% to 50% rate of removal of normal appendix during the third trimester. In contrast to the relative safety of performing an exploratory laparotomy or laparoscopy during pregnancy, the risk of fetal loss and maternal morbidity from failure to diagnose appendicitis and perforation is considerable, so clinical vigilance is required, even in the absence of classic signs. In later pregnancy, when peritoneal signs are often absent and the uterus obscures normal physical findings, diagnosis is frequently delayed, and the perforation rate may approach 25%.

Differential Diagnosis. Pyelonephritis, cholecystitis, nephrolithiasis, and pregnancy-related diseases such as ectopic pregnancy, broad ligament pain, corpus luteum cyst leakage, and ovarian torsion should be considered in the patient who has right-sided abdominal pain. Pyelonephritis is the most common condition that is confused with appendicitis. During its migration, the appendix is located very near the kidney, resulting in a high incidence of pyuria and flank pain (see Fig. 178.8). In cases of appendicitis, unless there is coincident urinary tract infection, the urine is free of bacteria, a feature distinguishing it from pyelonephritis. Salpingitis, another common misdiagnosis, is very rare in pregnancy, although it can occur before 12 weeks of gestation.

Diagnostic Testing. Leukocytosis is common in pregnant patients with appendicitis, although it is rarely high enough to distinguish it from the physiologic leukocytosis of pregnancy. Pyuria in a catheterized urine specimen suggests pyelonephritis,

TABLE 178.3

Differential Diagnosis of Common Symptoms in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
VAGINAL BLEEDING		
Miscarriage	<20 wk	Usually no fetal heart activity at 8 wk; decreasing hCG level
Ectopic pregnancy	<14 wk	Evaluate with ultrasonography
Molar pregnancy	12-24 wk	No fetal heart tones, characteristic sonogram
Cervical lesions	Throughout	Perineal and vaginal inspection
Vaginitis, cervicitis	Throughout	White blood cells on wet mount, with culture
Placenta previa	>16 wk	Ultrasonography to localize placenta
Abruptio placentae	>16 wk	Ultrasonography to exclude previa; fetal distress, tenderness
SEIZURE		
Eclampsia	>24 wk	Blood pressure > 140/90 mm Hg; usually history of PIH, edema, proteinuria
Amniotic fluid embolus	>12 wk	Hypotension, respiratory distress, DIC
Epilepsy	Throughout	History; lack of PIH findings
DYSPNEA		
Pulmonary embolus	Especially 6 wk prepartum and postpartum	Usual diagnostic studies
Dyspnea of pregnancy	>24 wk	Exclude other causes
Pulmonary infection	Throughout	Examination; radiography
Amniotic fluid embolus	>12 wk	Uterine manipulation, bleeding diathesis, hypotension
JAUNDICE		
Cholestasis of pregnancy	>24 wk	Well patient; itching and jaundice
Hepatitis	Throughout	Abnormal liver function test results
Acute fatty liver	>24 wk	Rapid liver failure; coma, seizures, hypoglycemia
BLEEDING DIATHESIS		
Eclampsia	>24 wk	Blood pressure > 140/90 mm Hg; proteinuria, edema, HELLP syndrome
Amniotic fluid embolus	>12 wk	Respiratory distress, cardiovascular collapse
Abruptio placentae	>20 wk	Uterine tenderness; vaginal bleeding; fetal distress

DIC, Disseminated intravascular coagulation; *hCG,* human chorionic gonadotropin; *HELLP,* hemolysis, elevated liver enzyme levels, low platelets; *PIH,* pregnancy-induced hypertension.

but it is also seen in 20% of patients with appendicitis. Bacteriuria is uncommon. Ultrasonography with a graded compression technique may reveal a noncompressible tubular structure in the right lower quadrant consistent with appendicitis. Studies of the diagnostic value of ultrasonography in the diagnosis of appendicitis are limited but have suggested that it has a high positive predictive value but a low negative predictive value.[49] Butala and colleagues have recommended abdominal ultrasonography as the first imaging modality, followed by CT when ultrasound findings are inconclusive.[50] Surgical, obstetric, and radiologic society guidelines agree.[49] When available, magnetic resonance imaging (MRI) is also useful in the evaluation of pregnant patients with suspected appendicitis (see Chapter 83). Otherwise, laparoscopy or laparotomy is the diagnostic procedure of choice in the pregnant patient thought to have appendicitis. Early exploration is highly encouraged in pregnant patients because of the variability of clinical signs and increased fetal risk if diagnosis is delayed.

Management. The pregnant patient with suspected appendicitis should be hospitalized after appropriate consultation with a surgeon and obstetrician. Ultrasonography, MRI, or CT scan are diagnostic options. The patient should be kept on nothing by mouth (NPO) status, with IV fluid hydration to maintain intravascular volume. Although prompt surgery is required if the diagnosis is clear, in unclear cases the patient should undergo observation to allow for clarification of signs and symptoms.

Gallbladder Disease

Cholelithiasis is present in approximately 5% of pregnant women and is the second most common nonobstetric surgical condition in pregnant patients. The natural history of asymptomatic cholelithiasis is believed to be similar to that in nonpregnant women, with less than 50% of patients with gallstones developing symptoms.

Changes in gallbladder kinetics are believed to be due to high pregnancy-related steroid levels. Progesterone decreases smooth muscle tone and induces gallbladder hypomotility and cholestasis, causing an increased risk of stone formation. In addition, pregnancy induces changes in bile composition and increased cholesterol secretion, thus increasing the incidence of cholesterol stone formation.

Clinical Features

The signs and symptoms of acute cholecystitis during pregnancy are the same as those in nonpregnant women. Epigastric or right upper quadrant pain and tenderness and nausea predominate. Leukocytosis must be interpreted carefully because of the increased white blood cell count seen normally in pregnancy. Likewise, a slightly elevated amylase level can be normal during pregnancy, and alkaline phosphatase, which is produced by the placenta, may be twice the nonpregnant level. A history of self-limited pain episodes associated with food intake suggests the diagnosis.

Diagnostic Testing

Ultrasonography is a reliable means of recognizing stones in the gallbladder, although it may not differentiate symptomatic from asymptomatic stones. In the patient with right upper quadrant pain, simultaneous sonographic evaluation of the liver is useful but technically difficult, particularly during the third trimester, when subcapsular liver hematomas and other intrinsic hepatocellular disease can occur but the liver may be obscured under the ribs.

Differential Diagnosis

Pyelonephritis should be considered in the patient with right upper quadrant pain, with or without fever. During the third trimester, appendicitis can also be associated with right upper quadrant pain. Hepatitis and fatty liver infiltration occur in pregnancy; liver distention and inflammation associated with pregnancy-induced hypertension can also cause right upper quadrant pain. In addition, spontaneous intrahepatic bleeding can occur during late pregnancy, mimicking cholecystitis. Because of the potential for other serious diseases, diagnostic studies should be performed to verify a clinical diagnosis of symptomatic cholelithiasis and cholecystitis in pregnancy.

Management

The patient who has fever, leukocytosis, prolonged pain, or evidence of cholecystitis should be made NPO and given IV fluid hydration, adequate pain control, and broad-spectrum antibiotics. Some patients with uncomplicated cholecystitis can be managed medically. Patients with obstructive jaundice, gallstone pancreatitis, sepsis or failure to respond to conservative management are candidates for surgery (optimally, during the second trimester, if possible[51]).

Discharge should be considered only for patients with uncomplicated and sonographically proven cholelithiasis who are not otherwise candidates for admission after consultation with an obstetrician. Pregnant patients with symptomatic cholelithiasis have a high rate of symptomatic relapse and increased severity of disease with each relapse. Early follow-up should be arranged, and the patient should be given careful instructions to return if she experiences fever, vomiting, or persistent pain. In one study, patients who were observed during pregnancy had a higher rate of pregnancy-related complications (36%) in contrast to much lower rates of complications in those who had a laparoscopic cholecystectomy.[52]

Liver Disorders

Pregnancy is associated with several unique liver abnormalities in addition to more usual hepatic diseases. Emergency clinicians should recognize the various symptoms of liver disease during pregnancy, as well as the hepatic diseases unique to pregnant women. Liver metabolism increases during pregnancy, but hepatic blood flow is unchanged, and little change occurs in liver function. Bilirubin, transaminase, and lactate dehydrogenase levels and prothrombin times are unchanged from those in the nonpregnant state. Albumin levels decrease secondary to an increase in maternal circulating plasma volume. Alkaline phosphatase levels may be up to double the nonpregnant values, and amylase levels may also be slightly elevated.

Hepatitis

Hepatitis is the most common cause of liver disease in pregnancy, accounting for 40% of cases of jaundice in pregnancy. Management and treatment are supportive and unchanged from those for nonpregnant patients. Hepatitis E, however, has been reported to have a more aggressive course in pregnancy, with an increased maternal mortality rate and rate of fetal loss.[53] Maintenance of adequate nutrition is a priority. Vertical transmission of hepatitis B can occur if the disease is not recognized. Pregnant women should be vaccinated. Prophylaxis should be administered to the newborn.[54]

Acute Fatty Liver

Acute fatty liver of pregnancy is a disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. The disease is rare, occurring most often in primiparous patients and patients with twin gestations.

The cause of acute fatty liver of pregnancy is unknown, although studies have suggested that a deficiency in the fetus's fatty acid metabolism leads to an accumulation of hepatotoxic metabolites in the maternal circulation. On microscopic examination, fatty infiltration of the hepatocytes with edema and vacuolization can be seen, but there is no necrosis or inflammation. Liver function returns to normal after delivery if the patient can be supported through the acute phase. Although up to 50% of patients have signs of preeclampsia, the two are not clearly related. The diagnosis must be differentiated from viral hepatitis and HELLP syndrome, which have similar disease presentations and laboratory findings but, again, are not clearly related.

Clinical Features. Nausea and vomiting associated with malaise or jaundice during the third trimester should trigger consideration of a diagnosis of acute fatty liver.[55] The right upper quadrant or epigastrium is usually tender. The disease may progress to coagulopathy, jaundice, seizures, DIC and hepatic encephalopathy. Hemorrhage from coagulopathy is the most common complication at delivery.[56] The diagnosis is often delayed secondary to the multiple differential considerations.

Diagnostic Testing. Typically, leukocytosis is present, the platelet count and fibrinogen level are low, prothrombin and partial thromboplastin times are elevated, and fibrin split products are present. In a series of 11 patients, increased transaminase and serum bilirubin concentrations were found in all patients, hypoglycemia was found in 18%, and hypoproteinemia was found in 46%.[55,56] In contrast to Reye's syndrome, the serum ammonia level is only mildly elevated. Hyperuricemia is usually present. The bilirubin level is elevated late in the course of the disease. The CT scan and sonogram may be normal, so liver biopsy is used to make the definitive diagnosis.

Differential Diagnosis. Liver tenderness and coagulopathy usually suggest preeclampsia during the third trimester. Jaundice and increases in the ALT level are distinguishing features because they are unusual in cases of liver disease associated with pregnancy-induced hypertension. Similarly, rapid progression of hepatic failure, hypoglycemia, and coagulopathy is unlikely in cases of

preeclampsia. Elevations in the creatinine level are more common in acute fatty liver of pregnancy.[56] The patient with viral hepatitis is likely to have more marked elevations in transaminase levels. Drug-induced hepatic failure should be excluded by history and toxicologic screening for acetaminophen or other toxins, if appropriate. Cholecystitis may be distinguished by ultrasound examination, but may also be characterized by right upper quadrant pain; it is not associated with coagulopathy or progressive liver failure.

Management. The patient with acute fatty liver of pregnancy may require acute stabilization for seizures or coma. Hypoglycemia may occur, which should be rapidly corrected with dextrose. Coagulation parameters should be assessed. Fluid resuscitation and replacement of clotting factors may be required, and the patient should be admitted to an obstetric service capable of managing this serious disease. The diagnosis is usually made with liver biopsy if the disease has not progressed to severe coagulopathy. Rapid delivery is usually advisable when the diagnosis has been established. Fresh-frozen plasma, platelet transfusions, and glucose may be needed to sustain the patient until delivery can be accomplished.

Intrahepatic Cholestasis

Intrahepatic cholestasis of pregnancy, also termed *idiopathic jaundice of pregnancy*, *icterus gravidarum*, or *pruritus gravidarum*, is a rare syndrome that occurs during the third trimester of pregnancy. It is the second most common cause of jaundice in pregnancy, after hepatitis. On histologic examination, the disease is characterized by cholestasis and dilated canaliculi in the biliary tree. The liver is normal. It is more common with increasing maternal age, with multiple gestations, and in the winter months.

Clinical Features. Generalized pruritus and mild jaundice are the hallmarks of intrahepatic cholestasis of pregnancy. Only 20% of patients present with this combination, however, and 80% present with pruritus alone. The pruritus usually begins in the palms and soles and ascends to the trunk. Although insomnia and fatigue occasionally accompany the pruritus, the patient appears nontoxic, without fever, vomiting, diarrhea, or significant malaise. The bilirubin level is rarely above 5 mg/dL, the alkaline phosphatase level can be elevated sevenfold to tenfold, and transaminase levels are in the normal range. Resolution occurs when the woman delivers. Although maternal outcome is favorable, women with intrahepatic cholestasis of pregnancy are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.

Differential Diagnosis and Management. Exclusion of more serious entities, such as viral hepatitis, acute fatty liver, drug-induced cholestasis, and complicated cholecystitis, is required. Outpatient management is appropriate, provided the diagnosis is clear and the patient has close obstetric follow-up. Some have advocated aggressive fetal surveillance and delivery after fetal lung maturity to improve the fetal outcome. Symptomatic treatment with antihistamines, ursodeoxycholic acid, bile salts, guar gum, benzodiazepines, and other medications has been tried, with variable success.[57]

Nausea and Vomiting

Normal Pregnancy

Nausea and vomiting are common in pregnancy, particularly from 6 to 20 weeks of gestation. Symptoms are usually self-limited and often resolve with lifestyle changes, such as diet modification and avoidance of environmental triggers. Although evidence supporting nonpharmacologic agents is mixed, in several randomized trials ginger has been found to be effective.[58,59] Treatment is recommended at a dose of 250 mg qid, in capsule or syrup form.

In women who fail conservative management, pharmacologic therapy may be initiated. The American College of Obstetricians and Gynecologists has recommended Diclegis,[60] a delayed-release combination of doxylamine, 10, mg and pyridoxine, 10 mg (vitamin B_6), as the first-line pharmacologic agent for the treatment of nausea and vomiting in pregnancy.[58,61] A combination of the same medications, known as Bendectin, was previously available from 1976 to 1983, but was voluntarily withdrawn from the market due to financial repercussions of litigation alleging the teratogenicity of the drug.[62] Multiple studies and the Centers for Disease Control and Prevention (CDC) Birth Defect Monitoring Program data have since demonstrated the safety of the drug. Diclegis is now approved by the US Food and Drug Administration (FDA) for use in pregnancy.

If there are circumstances preventing the prescription of Diclegis, or in case of treatment failure, other antiemetics may be considered. Although the FDA has not explicitly approved metoclopramide or promethazine for the treatment of nausea and vomiting in pregnancy, both drugs have been widely used and are generally considered safe.[63-65] Ondansetron has been widely used for the treatment of nausea and vomiting in pregnancy. However, recent studies have suggested that ondansetron may be associated with an increased risk of fetal anomalies.[61,66] Some experts recommend that ondansetron be used only when alternative antiemetics have failed.[59]

Hyperemesis Gravidarum

Hyperemesis gravidarum occurs in approximately 1% of pregnant patients and is defined by nausea and vomiting that cause starvation metabolism, weight loss greater than 5% of total body weight, dehydration, and prolonged ketonemia and ketonuria.[62] Without treatment, there is an increased risk of micronutrient deficiency and their respective sequelae to the patient (eg, vitamin B_1 deficiency, Wernicke encephalopathy) and fetus (eg, vitamin K deficiency, bleeding diatheses).[58,67,68]

The cause of hyperemesis gravidarum is not clear; associations have been made with increasing estradiol and hCG levels, as well as with maternal cytokines. Several studies have suggested an increased infection rate with *Helicobacter pylori* in patients with hyperemesis gravidarum; a nonteratogenic regimen for *H. pylori* treatment has been shown to decrease vomiting in hyperemesis patients.[69] Studies have also suggested that early treatment of nausea and vomiting of pregnancy may prevent progression to hyperemesis gravidarum.[58]

Diagnostic Testing. Laboratory studies should assess volume status and reversible electrolyte abnormalities. A urinalysis should look for the presence of ketosis, elevated specific gravity, and infection. Serum chemistry should be tested to assess the presence of hypokalemia, contraction alkalosis, elevated anion gap, and/or other metabolic abnormalities. Bilirubin and alkaline phosphatase levels can be mildly elevated but should return to normal after delivery. Hyperemesis may be complicated by liver disease and abnormal liver function test results, which are expected to resolve with supportive treatment.

Management. Initial management involves rehydration with IV fluids, antiemetics, and demonstration of ability to take oral hydration. Expert consensus favors the addition of dextrose and vitamins to IV fluids and the administration of thiamine before dextrose to prevent progression to Wernicke encephalopathy.[58] Antiemetics may be used, as for nausea and vomiting in pregnancy. A short course of oral prednisolone has been reported

to be therapeutic for intractable hyperemesis; however, it is considered a last-line agent and its risk profile should be weighed carefully before administration.[58]

In women who cannot maintain their weight despite medical therapy, enteral nutrition via a nasogastric (NG) tube should be considered.[58]

Thromboembolic Disease

Thromboembolic disease accounts for almost 20% of obstetric mortality, making it the leading cause of death in pregnancy.[70] Pregnancy is a hypercoagulable state, with increased coagulation factors and stasis as pregnancy progresses and significant vascular trauma at the time of delivery. The risk of venous thrombosis increases during pregnancy to five or six times that of nonpregnant women. Although the risk is increased throughout pregnancy, it is highest during the puerperium. Risk factors include smoking, obesity, age older than 35 years, hypercoagulable state, varicose veins, and prior superficial venous thrombosis. Women who deliver prematurely or have postpartum hemorrhage are also at higher risk.[71,72]

Clinical Features

As in nonpregnant patients, clinical signs of pain, tenderness, and swelling are poor predictors of deep venous thrombosis (DVT) in pregnancy. The clinical diagnosis of pulmonary embolus (PE) is also difficult. Although tachypnea, tachycardia, dyspnea, and pleuritic pain are commonly associated with PE, the symptoms are nonspecific and may be associated with such diverse diseases as hepatic inflammation, pyelonephritis, and diaphragmatic impingement from a normal gravid uterus.

Diagnostic Testing

Deep Venous Thrombosis. Because of its widespread availability, Doppler ultrasonography is the first-line test for the diagnosis of DVT. An abnormal study result is usually sufficient reason to treat the pregnant patient. However, normal leg study results can be seen with isolated iliac vein disease, which is common in pregnancy and requires imaging with MRI or CT for diagnosis. If thromboembolic disease is suspected, serial indirect Doppler testing or CT may be required.[72] The risk of anticoagulation usually outweighs the risk of definitive studies when the diagnosis is equivocal.

Pulmonary Embolism. Currently, studies do not support D-dimer tests in pregnancy to exclude the diagnosis of PE because this test may lack sufficient sensitivity in pregnant patients.[72,73] Imaging with lung scintigraphy or CT angiography is recommended. Both have comparable performances for PE diagnosis during pregnancy, although CT angiography delivers a higher maternal radiation dose.[74] Pulmonary angiography may be required if the diagnosis of PE is unclear after less invasive studies have been performed.

Chest radiography (shielding the pelvis and uterus) should be performed to exclude other disease processes that may mimic a PE. The diaphragm is normally symmetrically elevated during late pregnancy.

Management

Warfarin (Coumadin) is contraindicated during pregnancy because of its teratogenic effects, high risk of abortions, and fetal hemorrhage. Heparinoids are used to treat thromboembolic disease during pregnancy.[72] Unfractionated heparin carries a poorly understood risk of fetal osteoporosis, thrombocytopenia, prematurity, or miscarriage. In general, acute anticoagulation with IV heparin is followed by subcutaneous heparin bid, usually continued for 3 to 6 months postpartum in patients who have DVT or PE during pregnancy. Patients receiving this treatment require laboratory testing every 1 or 2 weeks, and the efficacy of anticoagulation may be variable during pregnancy. Low-molecular-weight heparin is considered safe in pregnancy and offers several advantages over unfractionated heparin, including decreased bleeding risk, reliable pharmacokinetics, decreased risk of heparin-induced thrombocytopenia, fixed dosages, less frequent dosing, and decreased risk of osteoporosis and thrombocytopenia. In patients with a history of DVT or PE, prophylaxis for subsequent gestations is usually recommended.

Genitourinary Infections

Urinary Tract Infection

Asymptomatic bacteriuria in pregnancy predisposes the patient to the development of symptomatic lower and upper tract genitourinary infections. This has led to the US Preventive Services Task Force recommendation to screen for asymptomatic bacteriuria with urine culture in pregnant women at 12 to 16 weeks' gestation or at the first prenatal visit, if later (grade A recommendation). Uterine pressure exerted on the bladder and ureters, poor emptying of the bladder with voiding, and progesterone-induced smooth muscle relaxation that inhibits ureteral peristalsis appear to contribute to an increased risk of infection during pregnancy.

Prenatal screening of patients with asymptomatic bacteriuria in early pregnancy identifies approximately 95% of those at risk for subsequent bacteriuria during the pregnancy. Because up to 30% of women who have asymptomatic bacteriuria will have pyelonephritis if they are untreated, the treatment of bacteriuria is cost-effective and important.

Clinical Features and Diagnostic Testing. The pregnant patient who presents with lower urinary tract symptoms (eg, dysuria, frequency, urgency) or upper tract symptoms (eg, fever, malaise, back pain) should have a pelvic examination and evaluation of an uncontaminated urine specimen, preferably catheterized. There is a predominance of right-sided symptoms during pregnancy, probably the result of increased mechanical forces on the right ureter, but left-sided flank pain or bilateral symptoms may be caused by pyelonephritis. Rarely, urinalysis may yield normal results or cultures may produce negative findings because of failure to report lower colony counts or because of complete obstruction of the involved ureter.

The major risk of asymptomatic and lower urinary tract infection is spread to the renal parenchyma. Acute pyelonephritis carries considerable morbidity in pregnancy, including maternal sepsis, permanent renal injury, and premature labor. The risk of prematurity can be minimized by effective treatment and continued monitoring for recurrence. The development of premature labor in the woman who has pyelonephritis is ominous; it can be prevented only by aggressive recognition and treatment earlier in pregnancy.

Differential Diagnosis. Vaginitis, herpes genitalis, chlamydial infection of the urethra, and ovarian torsion can masquerade as urinary tract symptoms. A history of external dysuria (burning at the perineum with urination) suggests herpes or vaginitis. A pelvic examination should be performed to obtain cervical culture specimens and identify perineal or vaginal causes of dysuria. Appendicitis, cholecystitis, pancreatitis, and liver diseases in pregnancy must be considered in the differential diagnosis of an upper urinary tract infection. Back pain may also be a sign

of premature labor. Careful evaluation of an uncontaminated catheterized urine specimen is essential to the correct diagnosis.

Management. Patients with asymptomatic bacteriuria or lower urinary tract signs and symptoms should be treated with 7 to 10 days of an antibiotic that is active against usual urinary pathogens and safe in pregnancy. The most common choices are a cephalosporin, such as cephalexin, 500 mg orally qid for 3 to 7 days); nitrofurantoin, 100 mg orally bid for 3 to 7 days; or a sulfonamide, such as trimethoprim-sulfamethoxazole, 800/160 mg bid for 3 days (except during the third trimester). Emergency clinicians should consider factors such as cost, local availability, and side effects when selecting the best treatment option.[75,76]

Patients with fever, back pain, and evidence of acute pyelonephritis in pregnancy are usually admitted for IV antibiotic administration, although outpatient parenteral therapy can be effective and safe in selected patients.[77] In such cases, aggressive IV hydration, obstetric consultation, and testing of urine cultures should be initiated. At least one parenteral dose of antibiotics should be given, with antibiotic coverage guided by known organism susceptibilities in a given hospital. Because the resistance of *Escherichia coli* to ampicillin is considerable in most regions, a cephalosporin, such as ceftriaxone, 1 g IV bid, is usually administered. Culture testing must be performed to ensure that the original choice of antibiotic was correct, and the patient must have a repeated culture and be observed closely after treatment.

Vaginitis

Bacterial Vaginosis. Bacterial vaginosis (formally known as *Gardnerella* vaginitis or *Haemophilus vaginalis* vaginitis) is an overgrowth of multiple endogenous vaginal bacteria, in some cases producing excessive discharge and vaginal malodor. Prevalence rates for bacterial vaginosis in pregnancy are estimated at 15% to 20%. Bacterial vaginosis is associated with an increased risk of chorioamnionitis, subclinical PID, premature rupture of membranes, fetal prematurity, and postpartum endometritis after vaginal delivery. However, treatment of bacterial vaginosis is directed toward symptomatic relief for the patient and does not necessarily improve fetal outcomes. Management includes a 7-day course of metronidazole or 7-day course of clindamycin. Intravaginal treatment is not recommended in pregnant patients.[78]

***Candida albicans* Vaginitis.** The incidence of vulvovaginal candidiasis is increased during pregnancy by high levels of estrogen and other steroids. Oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes. Treatment with vaginal azoles for 7 days during pregnancy is considered safe, with an estimated 85% to 100% cure rate.[78] Recurrent disease may require a vaginal culture to confirm diagnosis and identify unusual candidal species (eg, *Candida glabrata*) that may be resistant to conventional treatment. Longer treatment or treatment of a potential *Candida* reservoir in the patient's sexual partner(s) may also be required. However, there is no association of *Candida* colonization with adverse pregnancy outcomes, and treatment is for relief of symptoms only.

***Trichomonas* Vaginitis.** Trichomoniasis is a sexually transmitted vaginitis caused by a protozoan parasite, *Trichomonas vaginalis*. Of patients who have trichomoniasis, 50% are asymptomatic. Symptoms include vaginal itching, malodorous discharge, and vaginal irritation. Diagnosis is made by direct visualization or protozoans on wet mount. The recommended treatment is metronidazole, a one-time dose of 2 g, for symptomatic patients only.[78] Although trichomoniasis has been associated with increased prematurity, treatment with metronidazole has not been shown to improve fetal outcomes, so emergency clinicians should counsel patients and consider deferment of treatment in asymptomatic pregnant women until after 37 weeks' gestation.

Sexually Transmitted Disease

Sexually transmitted diseases are treated in pregnant patients according to the latest CDC guidelines. In general, the tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important in preventing preterm labor and decreasing transmission to the infant.

Chlamydia trachomatis. *Chlamydia trachomatis* infection is the most common sexually transmitted disease in the United States and worldwide. Its prevalence is currently three to five times that of *Neisseria gonorrhoeae* infection. Clinical diagnosis is difficult during pregnancy because cervical mucus is usually cloudy and contains white blood cells, but urine sampling can be done and is equivalent to endocervical sampling in pregnancy infections.[79] Routine chlamydial screening during pregnancy is important to prevent complications of preterm labor and postpartum endometritis, both of which are more common in patients who have chlamydial cervical infections. Chlamydial infections of infants born to infected mothers include conjunctivitis and pneumonitis. Treatment during pregnancy or breast-feeding is azithromycin (single 1-g dose), which improves compliance and decreases gastrointestinal side effects; a 7-day course of amoxicillin is an acceptable alternative.[78]

Herpes Simplex. Herpes simplex virus infections pose a significant risk in pregnancy to the mother and newborn. Women who have genital herpes during the third trimester have a 30% to 50% increased risk of transmission compared with women with herpes simplex virus infection in the first trimester (1%). The virus can be transmitted prenatally through transplacental infection or ascending vaginal infection and by vaginal delivery, particularly when herpetic lesions are present. Infections in the neonate often are disseminated or involve the CNS, causing significant morbidity and mortality. In the ED, culture of new suspected herpetic lesions of the cervix, vagina, or perineum identifies patients at risk for perinatal complications. Although the risk of oral acyclovir and valacyclovir use in pregnancy is not well known, it is recommended for first-episode genital herpes. Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital herpes simplex occurred during pregnancy but may not eliminate the need for cesarean section in women with recurrent herpes simplex. Treatment should be undertaken with obstetric consultation and careful patient monitoring.

Neisseria gonorrhoeae. Gonococcal infection of the cervix occurs during pregnancy in 1% of women. Symptoms are similar to those in nonpregnant women. Salpingitis is rare but may develop during the first trimester from upper genital extension of cervical infection. Some practitioners believe that the incidence of the disseminated infection is increased in pregnant patients because of elevated progesterone levels and increased vascularity in the area of the cervix. Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy; treatment includes cephalosporins or azithromycin.[78] Treatment of possible coexistent chlamydial infection is recommended for pregnant and nonpregnant women. The major complications of third-trimester gonococcal infection are neonatal gonococcal ophthalmia and sepsis.[78,80]

Upper Genital Tract Infection

Pelvic Inflammatory Disease. PID is very rare in pregnancy and does not occur after the first trimester. The differential diagnosis includes ectopic pregnancy, septic abortion, and appendicitis, all of which are more common. In the patient with suspected infection, smears or cultures for *Chlamydia* and gonorrhea should be performed. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospitalization and IV antibiotics.[78]

Chorioamnionitis. Chorioamnionitis is the infection or inflammation of the placenta and fetal membranes. After 16 weeks of pregnancy, the chorioamniotic membranes adhere to the cervical os and may become infected. The risk is increased in women with preterm labor. Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy.[81] Leukocytosis can be suggestive of chorioamnionitis but is not diagnostic. Patients should have blood specimens drawn for culture. Vaginal and cervical culture specimens for group B streptococci, *E. coli,* chlamydia, and gonorrhea should also be obtained. Urgent obstetric consultation should be obtained, and hospitalization for IV administration of antibiotics is required. Patients are usually treated with IV ampicillin and gentamicin. In addition, a study has reported that antenatal steroids may reduce adverse neonatal outcome after a preterm birth associated with chorioamnionitis.[82]

Thyroid Disorders

Thyroid disorders are common in women of childbearing age. During pregnancy, however, this is associated with a range of adverse maternal and fetal outcomes, including spontaneous miscarriage, preeclampsia, heart failure, preterm delivery, intrauterine growth restriction, and stillbirth.[33,83] The evaluation and management of pregnant women with thyroid dysfunction parallel those of nonpregnant women, but require attention to the physiologic changes to the thyroid gland that occur during pregnancy.

Normal pregnancy exerts a significant amount of stress on the thyroid gland. During pregnancy, the thyroid gland increases in size, requires more iodine, and produces more thyroid hormone than in the nonpregnant state. Moreover, maternal and fetal thyroid function are strongly linked, with maternal thyroxine accounting for a substantial portion of fetal thyroid function at birth.[33] Thyroid dysfunction in pregnancy can occur during pregnancy or the postpartum state.

Hyperthyroidism, characterized by suppressed TSH levels, elevated T_4 and/or T_3 occurs in only 0.1 to 0.4% of all pregnancies.[84] Hyperthyroidism in pregnancy can be a result of any cause, but Graves' disease and hCG-mediated hyperthyroidism are the most common causes. Graves' disease is an autoimmune process associated with thyroid-stimulating antibodies and usually becomes less severe during the later stages of pregnancy.[33] hCG, which is homologous to thyroid-stimulating hormone (TSH), has some thyroid-stimulating activity and may transiently cause hyperthyroidism in the first half of gestation. hCG-mediated hyperthyroidism is typically less severe than Graves' disease–associated hyperthyroidism.

Hypothyroidism complicates 2% to 3% of pregnancies. Although nutritional iodine deficiency is a common cause of hypothyroidism globally, it is rare in the United States. When US women are diagnosed with hypothyroidism, the most common cause is Hashimoto's (autoimmune) thyroiditis, in which autoantibodies cause destruction of the thyroid gland. Hypothyroidism is associated with adverse pregnancy effects, including preeclampsia, placental abruption, low birth weight, and an increased risk of stillbirth.

Postpartum thyroiditis is characterized by transient hyperthyroidism and/or hypothyroidism in the postpartum period. It is estimated that 5% to 10% of women have postpartum thyroiditis. Most women return to a euthyroid state within 1 year postpartum, but approximately 25% of these women develop permanent hypothyroidism in the subsequent 10 years. The diagnostic triad consists of the lack of previous history of thyroid disorder, an abnormal TSH concentration during the first postpartum year, and the absence of TSH receptor antibodies (Graves' disease) or a toxic nodule.

Clinical Features

The diagnosis of thyroid dysfunction during pregnancy is difficult because pregnancy itself can mimic the findings in mild to moderate hypothyroidism and hyperthyroidism.

Hyperthyroidism in pregnancy should be suspected when the patient exhibits disproportionate tachycardia, thyromegaly, exophthalmos, weight loss, or inadequate weight gain during pregnancy. Hyperthyroidism may be associated with a hydatidiform mole and usually resolves with evacuation of the mole. Patients may present with signs of thyroid storm, including altered mental status, severe tachycardia, and signs of high-output heart failure (eg, edema, dyspnea, orthopnea).

Like hyperthyroidism, hypothyroidism in pregnancy is difficult to diagnose. Signs such as edema, fatigue, and/or weight gain may be attributed to the pregnancy rather than thyroid dysfunction. Enlargement of the thyroid gland may be absent depending on the cause of the hypothyroidism. The diagnosis of hypothyroidism during pregnancy should be suspected when the patient exhibits edema, dry skin, hair loss, and a prolonged relaxation phase of deep tendon reflexes.

Patients with postpartum thyroiditis classically present with thyrotoxicosis 6 weeks to 6 months postpartum, followed by a hypothyroid state lasting up to 6 months. A euthyroid state returns by the end of the first postpartum year. However, most patients present with hyperthyroidism alone or lone hypothyroidism. The recurrence rate in subsequent pregnancy is estimated at 69%, and 25% of women eventually develop permanent hypothyroidism.

Diagnostic Testing

Normal values of thyroid hormones vary based on stage of pregnancy. The diagnosis of hyperthyroidism is confirmed by a low (<0.1 mU/L) or undetectable (<0.01 mU/L) serum TSH level and levels of free triiodothyronine (T_3) and thyroxine (T_4) that exceed the normal range for pregnancy. Confirmation of hypothyroidism is based on an elevated serum TSH level, relying on trimester-specific TSH reference ranges.[83] Overt hypothyroidism is defined as an elevated trimester-specific TSH, along with a decreased, trimester-specific free T_4 concentration. Subclinical hypothyroidism is defined as an elevated trimester-specific serum TSH concentration and a normal free T_4 concentration.

Differential Diagnosis

Thyroid dysfunction should be considered in the patient with nonspecific symptoms, including fatigue, anxiety, depression, and unexplained weight loss or weight gain. When a diagnosis of hypothyroidism or hyperthyroidism is recognized, their respective causes and differential diagnoses should be considered (see Chapter 120 for more detailed information).

Management

No treatment is usually required for hCG-mediated hyperthyroidism. Treatment of pregnant women with overt hyperthyroidism due to Graves' disease is of utmost importance because good fetal and maternal outcomes depend on controlling the mother's hyperthyroidism. Although thyroid ablation with radioactive iodine is contraindicated in pregnancy, medical treatments are available. Propylthiouracil (PTU) is the preferred treatment of hyperthyroidism in the Unites States. Methimazole is equally effective at treating hyperthyroidism in pregnancy but may be associated with fetal anomalies such as aplasia cutis, esophageal atresia, and choanal atresia. It is therefore not recommended as first-line treatment for hyperthyroidism in pregnancy.

Patients with symptoms of thyroid storm should be managed in an intensive care setting. Treatment with PTU should be initiated early. Dexamethasone is recommended to block the peripheral conversion of T_4 to T_3.[33] Beta blockers should be considered to control tachycardia; labetalol, esmolol, and propranolol have been used intrapartum.[33] A subtotal thyroidectomy may be considered once the symptoms of thyrotoxicosis are managed medically.

Hypothyroidism in pregnancy is managed with levothyroxine supplementation (2 μg/kg/day). Patients in the hypothyroid phase of postpartum thyroiditis require levothyroxine when they have a TSH level higher than 10 mU/L or between 4 and 10 mU/L with symptoms or active pregnancy attempt. The hyperthyroid phase of postpartum thyroiditis is usually managed with limited course of beta blockers.

Disorders of the Hypothalamic-Pituitary Axis

The pituitary is normally enlarged in pregnancy due to estrogen stimulation. Disorders of the hypothalamic-pituitary axis may increase the incidence of maternal and fetal morbidity and mortality.

Pregnancy profoundly affects the hypothalamic-pituitary axis, resulting in increased circulating levels of cortisol and adrenocorticotropic hormone due to increased estrogen production. In contrast, levels of growth hormone decrease in pregnancy. Disorders of the hypothalamic-pituitary axis in pregnancy can result in adrenal insufficiency, Cushing's syndrome, acromegaly, diabetes insipidus, and prolactinomas. Although these disorders are rare, they are associated with maternal morbidity (eg, hypertension, hyperglycemia, eclampsia) and up to 20% fetal mortality.

Clinical Features

Disorders of the hypothalamic-pituitary axis usually present as an insidious set of chronic symptoms, many of which can mimic normal pregnancy, making diagnosis difficult. Symptoms vary depending on the specific disease but include fatigue, malaise, vomiting, weight gain or loss, amenorrhea, galactorrhea, and hyperprolactinemia. Normal pregnancy can be associated with slight decreases in the serum sodium level; more severe decreases in the serum sodium level may be signs of diabetes insipidus or adrenal insufficiency.

Diabetes insipidus may also be caused by pituitary infarction in the setting of severe obstetric hemorrhage (Sheehan's syndrome). Advancements in the management and resuscitation of obstetric hemorrhage have made Sheehan's syndrome increasingly rare, but it remains an important clinical consideration. The symptoms of Sheehan's syndrome are dependent on the degree of the patient's hypopituitarism. Patients present with signs and symptoms that vary, according to the deficient hormones. The failure of postpartum lactation and resumption of normal menstruation are strongly suggestive of Sheehan's syndrome.[85] Following postpartum hemorrhage, patients may have persistent tachycardia, hypotension, and latency between hemorrhage, and the onset of symptoms can vary, from months to years after pregnancy.[33]

Diagnostic Testing

Diagnostic considerations vary according to the patient's presentation. Growth hormone levels are elevated in patients with acromegaly. Patients with adrenal insufficiency may present with hyponatremia and hyperkalemia, although these may be absent in many patients. MRI is helpful in the detection of prolactinoma or Sheehan's syndrome.

Differential Diagnosis and Management

Stabilization consists of treatment of serious manifestations, such as hyperkalemia, tachycardia, and hypotension. Outpatient management is appropriate in the stable patient, provided there is urgent endocrinology follow-up.

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KEY CONCEPTS

Ectopic Pregnancy

- An ectopic pregnancy can masquerade as a threatened miscarriage in the early stages of pregnancy and should always be considered in the differential diagnosis.
- Because the history and physical examination of the patient with ectopic pregnancy are insensitive and nonspecific, pelvic ultrasonography and determination of serum hCG levels are essential to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result.

Bleeding in Late Pregnancy

- Bleeding during the second trimester (14–24 weeks) is not benign and is associated with a 33% risk of fetal loss. Management is supportive and expectant because fetal rescue is impossible at this level of fetal immaturity.
- The major conditions associated with vaginal bleeding in the second half of pregnancy include abruptio placentae and placenta previa. Patient history, physical examination, and results of ultrasonography can be used to distinguish them.
- All patients with painless, second-trimester vaginal bleeding should be assumed to have placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis has been excluded via ultrasound.
- Abruptio placentae has consists of a wide spectrum of severity of symptoms and risk. Up to 20% of women will have no pain or vaginal bleeding. Assessment is generally based on clinical features, coagulation parameters, and signs of fetal distress.

KEY CONCEPTS—cont'd

Hypertension in Pregnancy

- Gestational hypertension occurs during pregnancy, resolves during the postpartum period, and is recognized by a new blood pressure reading of 140/90 mm Hg or higher.
- Preeclampsia is gestational hypertension with proteinuria (>300 mg/24 hr); eclampsia is the occurrence of seizures in the patient with signs of preeclampsia.
- The HELLP syndrome is a particularly severe form of preeclampsia characterized by ***h***emolysis, ***e***levated ***l***iver enzyme levels (ALT and AST > 70U/L), and ***l***ow ***p***latelet count (<100,000/mL).
- Because progression of preeclampsia to eclampsia is unpredictable and can occur rapidly, blood pressure control in the pregnant patient is of utmost importance.

Amniotic Fluid Embolism

- Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden hypotension, hypoxia, and coagulopathy.
- Treatment of amniotic fluid embolus consists of support of oxygenation and ventilation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy.

Rh Immunization

- Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. To prevent this, a dose of 50 μg of Rh immune globulin can be used if the patient is at less than 12 weeks of gestation. After 12 weeks, a 300-μg dose should be given.

Abdominal Pain in Pregnancy

- Appendicitis is the most common surgical emergency in pregnancy. Clinical presentations may be atypical, leading to a misdiagnosis rate of 30% to 35% in pregnant patients. Right lower quadrant pain is the most common finding, especially early in pregnancy. Ultrasound, CT, and MRI are useful for the diagnosis.
- Cholelithiasis presents with similar symptoms to those in nonpregnant women and is similarly diagnosed through ultrasound. Surgery, if required, is optimally done during the second trimester.
- During pregnancy, albumin levels decrease while alkaline phosphatase levels may increase up to double; amylase levels may also be slightly elevated.
- Hepatitis is the most common cause of liver disease in pregnancy; the increased incidence of hepatitis E has increased maternal mortality and rate of fetal loss.
- Acute fatty liver of pregnancy is a rare disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. Coagulopathy, jaundice, seizures, DIC, and hepatic encephalopathy may also result.
- Intrahepatic cholestasis of pregnancy typically presents with generalized pruritus and mild jaundice. Resolution occurs with delivery. Women are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.

Nausea and Vomiting in Pregnancy

- Nausea and vomiting in pregnancy is common and may be treated with conservatively with diet modification and avoidance of environmental triggers. If conservative measures fail, Diclegis, a delayed-release combination of doxylamine, 10 mg, and pyridoxine (vitamin B_6), 10 mg, is the first-line pharmacologic agent for the treatment of nausea and vomiting in pregnancy.
- Hyperemesis gravidarum is defined as nausea and vomiting that cause starvation metabolism, weight loss, dehydration, and prolonged ketonemia and ketonuria. Initial management involves rehydration with IV fluids, antiemetics, and demonstration of ability to take oral hydration.

Thromboembolism in Pregnancy

- Thromboembolic disease accounts for almost 20% of obstetric mortality, making it the leading cause of death in pregnancy.
- Doppler ultrasonography is the first-line test for the diagnosis of DVT. CT angiography and lung scintigraphy are used for the diagnosis of PE.
- Low-molecular-weight heparin is preferred for anticoagulation.

Vaginal and Urinary Tract Infections

- Asymptomatic bacteriuria in pregnancy predisposes the patient to the development of symptomatic lower and upper tract genitourinary infections. Because up to 30% of women who have asymptomatic bacteriuria will have pyelonephritis if they are untreated, treatment of bacteriuria is cost-effective and important.
- Treatment of bacterial vaginosis is directed toward symptomatic relief for the patient and does not necessarily improve fetal outcomes. Management includes a 7-day course of metronidazole or 7-day course of clindamycin.
- For the treatment of vulvovaginal candidiasis, oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes. Treatment with vaginal azoles for 7 days during pregnancy is considered safe, with an estimated 85% to 100% cure rate.
- Of patients who have trichomoniasis, 50% are asymptomatic. Diagnosis is made by direct visualization of protozoans on wet mount. The recommended treatment is metronidazole, a one-time dose of 2 g, for symptomatic patients only.
- Regarding the treatment of sexually transmitted diseases, in general, the tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important for preventing preterm labor and decreasing transmission to the infant.
- *Chlamydia trachomatis* infection is the most common sexually transmitted disease in the United States and worldwide. Treatment during pregnancy or breast-feeding is azithromycin (single 1-g dose); a 7-day course of amoxicillin is an acceptable alternative.
- Women who have genital herpes during the third trimester have a 30% to 50% increased risk of transmission compared with women with herpes simplex virus (HSV) infection in the first trimester (1%).
- Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital HSV occurred during pregnancy.
- Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy; treatment includes cephalosporins or azithromycin.
- PID is very rare in pregnancy and does not occur after the first trimester. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospitalization and IV antibiotics.
- Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy. Patients are usually treated with IV ampicillin and gentamicin.

Thyroid Disease

- During pregnancy, the thyroid gland increases in size, requires more iodine, and produces more thyroid hormone than in the nonpregnant state.
- Hyperthyroidism, characterized by suppressed TSH levels and elevated T_4 and/or T_3 levels occurs in only 0.1% to 0.4% of all pregnancies. Graves' disease and hCG-mediated hyperthyroidism are the most common causes.
- When US women are diagnosed with hypothyroidism, the most common cause is Hashimoto's (autoimmune) thyroiditis.
- Postpartum thyroiditis is characterized by transient hyperthyroidism and/or hypothyroidism in the postpartum period. Approximately 25%

Continued

KEY CONCEPTS—cont'd

of these women develop permanent hypothyroidism in the subsequent 10 years.
- Hyperthyroidism may be associated with a hydatidiform mole and usually resolves with evacuation of the mole.
- The diagnosis of hyperthyroidism is confirmed by a low (<0.1 mU/L) or undetectable (<0.01 mU/L) serum TSH level and levels of free T_3 and T_4 that exceed the normal range for pregnancy.
- Confirmation of hypothyroidism is based on an elevated serum TSH level, relying on trimester-specific TSH reference ranges.
- Propylthiouracil (PTU) is the preferred treatment of hyperthyroidism in the Unites States. For thyroid storm, dexamethasone and beta blockers are added, with the patient under observation in the intensive care unit.
- Hypothyroidism in pregnancy is managed with levothyroxine supplementation (2 μg/kg/day).

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CHAPTER 178: QUESTIONS & ANSWERS

178.1. An 18-year-old G1P0 at 8 weeks of gestation presents with abdominal pain and vaginal bleeding for 1 day. Her serum human chorionic gonadotropin (hCG) level is 3,700 IU/L. Transvaginal ultrasonography does not reveal an intrauterine pregnancy (IUP) or mass. The pelvic examination is remarkable for a closed cervical os and a small amount of blood. Which of the following should be the next step?
A. Coagulation panel
B. Gynecologic consultation
C. RhoGAM, 300 μg intramuscularly
D. Repeat hCG in 2 days
E. Serum progesterone level

Answer: A. Ultrasonographic detection of an IUP is likely at hCG levels higher than 1500 to 2000 IU/L. A negative ultrasound, with an hCG level of 3700 IU/L, is concerning for an ectopic pregnancy or miscarriage. β-hCG levels should peak at the 7- to 10-week range, with mean values of 50,000 IU/L. A persistently low hCG level is even more suspicious for ectopic pregnancy, and gynecologic consultation is warranted.

178.2. A 36-year-old G3P2 presents with painless vaginal bleeding during the past hour. She is at 33 weeks of gestation, and her pregnancy has been uncomplicated. Her bleeding lasted approximately 20 minutes. Appropriate management includes all of the following except which one?
A. Baseline hemoglobin level and platelet count
B. Immediate complete pelvic examination
C. Immediate obstetric consultation
D. Intravenous fluid resuscitation
E. Transvaginal ultrasound

Answer: B. Painless late pregnancy bleeding is placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis is excluded via ultrasound. An injudicious vaginal examination can precipitate severe hemorrhage in the patient with an asymptomatic or minimally symptomatic placenta previa.

178.3. In pregnancy, treatment is indicated in each of the following sexually transmitted diseases except which one?
A. *Chlamydia trachomatis*
B. Herpes simplex virus
C. *Neisseria gonorrhoeae*
D. Pelvic inflammatory disease (PID)
E. *Trichomonas vaginalis*

Answer: E. Although trichomoniasis has been associated with increased prematurity, treatment with metronidazole has not been shown to improve fetal outcomes, so emergency clinicians should counsel patients and consider deferring treatment in asymptomatic pregnant women until after 37 weeks' gestation.

178.4. A 28-year-old G3P0 at 34 weeks of gestation presents with new-onset seizures. The patient has multiple seizures in the emergency department (ED) and is noted to be hypertensive at a blood pressure of 164/87 mm Hg. Which of the following should be administered next?
A. Benzodiazepines
B. Calcium gluconate
C. Labetalol
D. Magnesium sulfate
E. Pralidoxime

Answer: D. Magnesium sulfate has little antihypertensive effect but is the most effective anticonvulsant, preventing recurrent seizures while maintaining uterine and fetal blood flow. A loading dose of 4 g intravenous (IV) magnesium, followed by 2 g IV/hr, is recommended.

178.5. A 36-year-old G5P4 at 8 weeks of gestation presents to the ED with painless vaginal bleeding. Ultrasonography shows products of conception in the uterus. The pelvic examination shows a dilated cervix and a moderate amount of blood in the vaginal vault. Which of the following is appropriate management?
A. All of these
B. Expectant management
C. Medical management with misoprostol
D. None of these
E. Surgical evacuation

Answer: A. All of these are appropriate management options for an incomplete miscarriage.

178.6. Which of these is the most commonly observed surgical emergency in pregnancy?
A. Abruptio placentae
B. Appendicitis
C. Cholecystitis
D. Ovarian torsion
E. Ruptured peptic ulcer

Answer: B. Appendicitis is the most common surgical emergency in pregnancy. Clinical presentations may be atypical, particularly during the second half of pregnancy.

178.7. For the treatment of nausea and vomiting in pregnancy, which of the following has been found to have some associated risk of fetal abnormalities?
- **A.** Diclegis (delayed-release combination of doxylamine and pyridoxine)
- **B.** Ginger
- **C.** Metoclopramide
- **D.** Ondansetron
- **E.** Promethazine

Answer: D. Ondansetron has been shown in studies to be linked with fetal cardiac abnormalities, as well as cleft lip and palate. Diclegis is first-line pharmacologic treatment of nausea and vomiting in pregnancy; metoclopramide and promethazine are alternatives if it fails. Ginger, a nonpharmacologic treatment, has been shown to be safe and effective at a dose of 250 mg qid.

178.8. Which of the following is not considered a normal physiologic change in pregnancy?
- **A.** Decreased albumin level
- **B.** Increased D-dimer level
- **C.** Increased serum amylase level
- **D.** Increased serum bilirubin level
- **E.** Increased WBC count

Answer: D. Bilirubin, transaminase, and lactate dehydrogenase levels and prothrombin times are unchanged from the nonpregnant state. Albumin levels decrease secondary to an increase in maternal circulating plasma volume. Alkaline phosphatase levels may be up to double the nonpregnant values, and amylase levels may also be slightly elevated. The D-dimer level can be substantially elevated, even in normal pregnancy.

CHAPTER 179

Comorbid Medical Emergencies During Pregnancy

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PRINCIPLES

The physiologic changes that occur in pregnancy may exceed the patient's underlying compensatory mechanisms, resulting in initial symptom onset or rapid decompensation of medical illness during pregnancy. Certain chronic medical conditions also pose a serious threat to the mother's health or result in a poor fetal outcome. Finally, some medical illnesses result in a difficult delivery or the need for special resuscitation measures in the neonate.

The incidence of pregnancy in chronically ill patients has been increasing because of improved survival of patients with diseases such as diabetes, epilepsy, renal failure, obesity, and various cancers. Also, the demographics of pregnancy are changing in that maternal age at the time of first pregnancy is increasing. Advances in assisted reproduction, including in vitro fertilization and oocyte donation, have made it possible for older women—including those who are postmenopausal—to become pregnant. Older pregnant women experience an increased rate of antepartum and intrapartum complications and are more likely to have comorbid conditions such as cardiovascular disease.

The recognition of an unexpected or even expected pregnancy may occur in the setting of the emergency department (ED), and many interventions are time-sensitive, mandating treatment in the ED. All emergency clinicians should have an understanding of critical diagnostic and treatment possibilities when encountering a pregnant patient with a preexisting illness.

ASTHMA

Asthma is one of the most common chronic medical problems in pregnancy, with a prevalence of between 3.7% and 9.4 %.[1] Maternal asthma is associated with an increased risk of preeclampsia or eclampsia, premature contractions, cesarean section, low birth weight, and small-for-gestational-age status.[1,2] The risk of such complications varies with the severity of the disease and degree of control during pregnancy. Adverse perinatal outcomes increase with the severity of asthma during pregnancy. Controlling asthma during pregnancy leads to less intrauterine growth retardation and fewer adverse perinatal outcomes.[1-3] It has been well documented that asthma may worsen, improve, or remain the same during pregnancy, but no studies have examined whether this is caused by changes in asthma treatment, severity, or sudden asthma attacks.[4]

Maternal respiratory function changes can make it more difficult to recognize the decompensating pregnant asthmatic patient. Tidal volume and minute ventilation increase by 45% over the course of pregnancy resulting in an average P_{CO_2} of 32 mm Hg. The kidneys compensate and maintain an average bicarbonate level of 19 mEq/mL, which results in a compensated respiratory alkalosis with a serum pH between 7.40 and 7.45.

Many adverse perinatal outcomes caused by asthma are thought to be due to fetal hypoxia. Thus, the overall goal of treatment is maintaining maternal oxygen saturations above 95%. Both the American College of Obstetrics and Gynecology (ACOG) and National Asthma Education and Prevention Program have clearly stated that it is safer to use asthma medications to treat pregnant women than to allow severe asthma symptoms and exacerbations to occur during pregnancy.

The standard treatment for a pregnant asthmatic patient is the same as that for a nonpregnant patient with an asthma exacerbation. After history and the performance of a physical examination, the peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV_1) should be measured. Patients with an FEV_1 or PEF less than 50% of their predicted maximum are classified as having a severe exacerbation. An initial fetal assessment should be performed, including fetal heart tones and continuous electronic fetal monitoring with a biophysical profile if the pregnancy has reached viability. Supplemental oxygen should be given to all mothers with oxygen saturation below 95%.

Inhaled short acting β_2-agonists are the first-line treatment for an asthma exacerbation and can be given continuously, if needed, for a severe exacerbation (Table 179.1). Long-acting selective β_2-agonists and inhaled corticosteroids, with budesonide being the preferred agent, can be added as controller medications on discharge from the ED. Multiple studies have shown no increased risk of adverse perinatal outcomes.[3-5] Nonselective β-agonists such as epinephrine are generally avoided because of concern for their effect on placental blood flow. It is important to note that β-agonists are tocolytics and will often halt labor.

Oral corticosteroids are indicated for use in moderate to severe asthma exacerbations and should be prescribed for the same indications as in nonpregnant asthmatics. Despite these recommendations, in multiple studies in the acute care setting, pregnant women with asthma exacerbations were between 17% and 21% less likely to be treated with oral corticosteroids than nonpregnant controls.[6,7] Reasons for this treatment disparity may be due to evidence that oral corticosteroid use increases the risk of preterm delivery and low-birth-weight infants; there is also conflicting evidence of an increased risk of orofacial clefts.[2-4] However the benefits of oral corticosteroid use for avoiding fetal hypoxia outweighs the risk of adverse perinatal outcomes.

Second-line agents for asthma control (eg, cromolyn sodium) are considered safe in pregnancy. In limited studies, magnesium has been shown to improve respiratory function in pregnant females with severe asthma exacerbations without adverse fetal outcomes.

CARDIOVASCULAR DISORDERS

Principles

Heart disease complicates more than 1% of pregnancies in the United States and leads to 20% of nonobstetric maternal deaths.[8-11] Hypertensive disorders are the most frequent cardiovascular events, occurring in 6% to 8% of pregnancies.[12] The

TABLE 179.1

Drugs Used to Treat Acute Asthma Exacerbations During Pregnancy

PHARMACOLOGIC CLASS	EXAMPLES	DOSAGE	COMMENTS
Inhaled beta agonists	Albuterol Levalbuterol	2.5–5 mg every 20 min 1.25–2.5 mg every 20 min	Inhaled beta agonists first-line therapy May also be administered by metered-dose inhaler; up to three doses in first hour; continuous use in severe exacerbations
Injectable beta agonists	Epinephrine Terbutaline	0.3–0.5 mg SC (1:1000 or 1 mg/mL) every 20 min 0.25 mg SC (1 mg/mL) every 20 min	No proven benefit over inhaled dosing; up to three doses in first hour
Systemic corticosteroids	Prednisone Prednisolone Methylprednisolone	Dosage applies to all preparations Initial inpatient therapy: variable dosing; need at least 120–180 mg/day Outpatient burst therapy—40–60 mg/day for 3–10 days	No benefit of intravenous dosing over oral except in patients with impending respiratory failure who cannot take oral medications
Inhaled anticholinergics	Ipratropium bromide	0.5 mg every 20 min	Not first-line therapy; should be used with beta agonists Consider for use in patients with severe exacerbations
Smooth muscle relaxants	Magnesium sulfate		Limited data on use for asthma in pregnancy

SC, Subcutaneous.

Adapted from National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program Asthma and Pregnancy Working Group: NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment—2004 update. J Allergy Clin Immunol 115:34–36, 2005.

proportion of maternal deaths due to cardiovascular disease has increased as pulmonary hypertension, cardiomyopathies, aortic dissection, and myocardial infarction have become leading causes of death.[11] The increase in blood volume due to pregnancy, along with the increases in preload, cardiac output, and oxygen consumption, can worsen or reveal cardiac disease in pregnant women. Because the signs and symptoms of acute coronary syndromes and heart failure (eg, shortness of breath, mild chest pain, edema) can be seen in normal pregnancies, these entities are especially difficult to diagnose.[10,12]

Chronic Hypertension and Hypertensive Emergencies

Hypertension commonly affects pregnant women, causing complications in 12% of pregnancies and 18% of maternal deaths in the United States. Chronic hypertension in pregnancy significantly increases the risk of superimposed preeclampsia, preterm delivery, intrauterine growth restriction, and cesarean section.[13] Chronic hypertension is defined as hypertension (>140 mm Hg systolic or >90 mm Hg diastolic) diagnosed prior to pregnancy or before 20 weeks' gestation (Table 179.2).

Many women have mild hypertension of pregnancy (defined as systolic blood pressure of 140–159 mm Hg or diastolic blood pressure of 90–109 mm Hg). Medical treatment of uncomplicated chronic hypertension in pregnancy without evidence of end-organ damage has demonstrated no benefit in reducing adverse perinatal outcomes as compared to placebo in multiple studies. Additionally, antihypertensive medications pose a risk of hypotension and decreased fetal blood flow.[14,15] Thus, the ACOG recommends that antihypertensive treatment should be started when blood pressures are consistently higher than 160 mm Hg systolic and/or higher than 105 mm Hg diastolic.[14] The major risk posed by severe chronic hypertension is a progression to preeclampsia, which occurs in 25% of these pregnancies. Antihypertensive drugs have proven to be effective in preventing this progression.[15]

The first-line oral agents for the treatment of chronic hypertension in pregnancy are listed in Table 179.3. The ACOG defines a hypertensive emergency as acute-onset persistent hypertension with systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 110 mm Hg. In these cases, parenteral therapy is indicated, with a target blood pressure range of 140 to 150 mm Hg systolic and 90 to 100 mm Hg diastolic, to prevent loss of cerebral autoregulation.[8,9] Therapy with intravenous (IV) labetalol is preferred, although hydralazine and oral nifedipine are also considered firs-line treatment (Table 179.4).[8,9,16] Although labetalol is recommended by the ACOG, it should be noted that regular beta blocker use during the first trimester has been associated with small-for-gestational-age newborns.[17]

In 2013, the ACOG changed its diagnostic criteria for preeclampsia to no longer requiring proteinuria. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in the presence of thrombocytopenia, impaired liver function, pulmonary edema, visual disturbances, and/or the development of renal insufficiency.[14]

Cardiac Disorders

Acute Coronary Syndromes

Pregnancy-related acute myocardial infarction (AMI) occurs in 6.2 of every 100,000 deliveries. The mortality rate in pregnant women who have had an AMI is from 5.1% to 7.2 %. Pregnant women are two to four times more likely to have an AMI as compared to age-matched nonpregnant individuals. As the number of women becoming pregnant who are older than 35 years increases, it is important to recognize that pregnant women aged 40 years or older have a 30-fold greater risk for acute coronary syndrome (ACS) than pregnant women 20 years of age or younger.[18] The incidence of AMI is highest during the last trimester and peripartum period.

Multiple factors are hypothesized to increase the risk of AMI in pregnancy, including a prothrombotic state, increased myocardial oxygen demand secondary to increased cardiac output and heart rate, and decreased oxygen-carrying capacity secondary to

Text continued on p. 2266

TABLE 179.2

Hypertensive Disorders of Pregnancy

	CHRONIC HYPERTENSION	GESTATIONAL HYPERTENSION	PREECLAMPSIA	CHRONIC HYPERTENSION WITH SUPERIMPOSED PREECLAMPSIA
Definition	Hypertension that antedates pregnancy[a]	Hypertension diagnosed after 20 wk of gestation in the absence of proteinuria or other evidence of preeclampsia	Hypertension that begins after 20 wk of gestation in association with new-onset proteinuria (>300 mg/24 hr) or symptoms below in the absence of proteinuria	Hypertension that antedates pregnancy in association with new-onset proteinuria
	Hypertension diagnosed before 20 wk of gestation		Decreased platelets, elevated liver transaminase levels, renal insufficiency, pulmonary edema	Sudden increase in proteinuria in woman with chronic hypertension[a] and proteinuria before 20 wk of gestation Hypertension that antedates pregnancy in association with sudden increase in blood pressure
	Comment—rarely, preeclampsia presents before 20 wk of gestation	Comment—may progress to preeclampsia; may also represent previously undiagnosed hypertension		Hypertension that antedates pregnancy in association with decreased platelets, elevated liver transaminase levels, renal insufficiency, pulmonary edema, or cerebral or visual symptoms

[a]Defined as blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic.
Adapted from Nishimura RA, Otto CM, Bonow RO, et al; ACC/AHA Task Force Members: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129:e521–e643, 2010.

TABLE 179.3

Gestational Effects and Treatment of Medical Illnesses During Pregnancy

ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Asthma	Fetal—IUGR, PTD, hypoxia, meconium-stained amniotic fluid, fetal loss Maternal—preeclampsia, gestational hypertension, gestational diabetes, hyperemesis gravidarum, need for labor induction	Good prenatal outcomes seen in well-controlled asthma Treatment of acute exacerbations is the same as for the nonpregnant patient with the goal of keeping maternal oxygen saturations >95% to prevent fetal hypoxia. Fetal monitoring is recommended for exacerbations during the third trimester, even in the absence of maternal hypoxia. Maintenance therapy also is unchanged, with the following precautions: • Corticosteroids—inhaled agents preferred, but oral route may be necessary with acute exacerbations or severe, persistent disease; patients receiving long-term steroids require "stress dose" hydrocortisone during labor and delivery. • Methylxanthines—safe but debatable benefit; use only in refractory disease; reduced clearance during pregnancy may result in maternal toxicity and fetal tachycardia. • Leukotriene receptor antagonists—avoid zileuton.
Acute coronary syndrome	Fetal—perinatal death, PTD Maternal—uterine hemorrhage, abruption (related to use of antiplatelet, antithrombotic, fibrinolytic agents)	Standard medical therapy is the same as for the nonpregnant patient, although antiplatelet, antithrombotic, and fibrinolytic agents are best avoided when delivery is imminent. Avoid maternal hypotension when nitrates are used; they may result in fetal distress. Avoid beta blockers in the first trimester because they may cause fetal growth restriction. Coordinate definitive care (fibrinolytics vs. percutaneous coronary intervention) with cardiologist.

Continued

TABLE 179.3

Gestational Effects and Treatment of Medical Illnesses During Pregnancy—cont'd

ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Valvular heart disease	Fetal—perinatal death, PTD Maternal—heart failure, thromboembolism, death	Appropriate antithrombotic therapy is indicated for patients with prosthetic valves and atrial fibrillation (see text). Mitral stenosis—diuresis and beta blockade; avoid volume depletion when diuretics are used; valvuloplasty or open cardiac surgery for severe symptomatic disease; consider early pregnancy termination in women with severe stenosis. Mitral and aortic regurgitation—diuresis in patients with pulmonary congestion; surgical therapy for acute regurgitant lesions. Aortic stenosis—avoid hypotension and supine hypotensive syndrome; vigorous fluid replacement during delivery; valvuloplasty or open cardiac surgery for severe symptomatic disease; consider early pregnancy termination with severe symptoms despite therapy.
Hypertension	Fetal—perinatal death, IUGR, PTD Maternal—progression of target end-organ damage, superimposed preeclampsia, abruption, cardiac decompensation	Most perinatal complications occur in patients with preeclampsia or secondary causes of hypertension; outcomes are usually good with mild essential hypertension, and ACOG does not recommend treatment for blood pressures <160 mm Hg systolic or <10 mm Hg diastolic. The major risk posed by chronic hypertension in pregnancy is progression to preeclampsia, which occurs in 25% of these pregnancies. The most commonly used agents include methyldopa (preferred agent), labetalol, and hydralazine. Avoid beta blockers in the first trimester because they may cause fetal growth restriction and may also decrease placental blood flow. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are teratogenic. Fetal cyanide poisoning might develop after several hours of sodium nitroprusside. Avoid prolonged infusions; use as agent of last resort.
Iron deficiency anemia	Fetal—low birth weight, PTD, low fetal iron stores, fetal loss (with severe anemia) Maternal—preeclampsia, high-output heart failure (rare); effects on maternal mortality unclear	Oral iron supplementation is indicated for patients with iron deficiency anemia. Recent evidence also supports prophylactic iron supplementation in pregnant patients. Several over-the-counter preparations are available. There is a delay from onset of therapy to an increase in the serum hemoglobin level. Parenteral iron replacement is safe and effective, although rarely required. Transfusion is rarely required but is a consideration for fetal well-being in mothers with severe anemia.
Sickle cell anemia	Fetal—fetal loss, IUGR, PTD, premature rupture of membranes Maternal—↑ need for cesarean section, preeclampsia, infection, heart failure, pulmonary infarction, ↑ incidence of painful crises; maternal mortality low with treatment; false-positive Apt and Kleihauer-Betke test results secondary to persistent hemoglobin F	Management of pain crises and infections is the same as for the nonpregnant patient, with rest, hydration, narcotic analgesia, supplemental oxygen, and antibiotics, as indicated. Narcotic analgesics should not be withheld, but the need for neonatal respiratory support should be anticipated if delivery is imminent. Prophylactic transfusion is not indicated. Fetal monitoring and assessment of fetal well-being are indicated for viable pregnancies. Chronic maintenance care includes pneumococcal vaccination and supplemental folate. Hydroxyurea has been discouraged during pregnancy, but few adverse fetal effects have been reported in humans.
Epilepsy	Fetal—various congenital malformations associated with AEMs, fetal hypoxia and bradycardia, fetal loss Maternal—variable changes in seizure frequency; alterations in AEM levels; increased seizure frequency secondary to voluntary medication noncompliance; abruption, anemia, hyperemesis gravidarum, preeclampsia, possible need for labor induction and cesarean section, premature rupture of membranes	Management of status epilepticus is the same as for the nonpregnant patient. Maintenance therapy should be coordinated by the patient's neurologist (or primary care practitioner) and obstetrician. In general, a single AEM given at the lowest effective dose is recommended. The newer AEM levetiracetam has demonstrated a lower incidence of birth defects and has equal to better efficacy as older AEMs. Folate supplementation (at least 0.4 mg/day) is indicated for patients taking AEMs. Consider administration of oral vitamin K to the mother during the last month of pregnancy and parenteral vitamin K to the newborn.

TABLE 179.3

Gestational Effects and Treatment of Medical Illnesses During Pregnancy—cont'd

ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Myasthenia gravis	Fetal—transient neonatal myasthenia syndrome Maternal—variable changes in disease severity; arrest of labor; disease exacerbation in postpartum period	Management is the same as for the nonpregnant patient. Ventilatory support is the most important aspect of therapy. Note that patients with myasthenia gravis are relatively resistant to depolarizing paralytic agents; higher doses may be required. Pyridostigmine therapy can be continued; intravenous therapy is recommended during labor. Patients receiving maintenance corticosteroids require "stress dose" hydrocortisone during labor and delivery. Plasmapheresis is safe during pregnancy.
Renal (chronic kidney disease)	Fetal—IUGR, low birth weight, polyhydramnios, fetal loss, increased NICU utilization, preterm birth Maternal—placental abruption, preeclampsia, increased need for cesarean section	Aggressive hypertension control Monitoring of proteinuria Treating worsening kidney dysfunction as if preeclampsia Beta blocker, calcium channel blocker, or hydralazine use with salt restriction Avoid ACE inhibitors.
Diabetes mellitus—insulin-dependent diabetes mellitus (IDDM), non–insulin-dependent diabetes mellitus (NIDDM), and gestational diabetes mellitus (GDM)	Fetal—congenital malformations; macrosomia; IUGR; fetal loss; neonatal hypoglycemia, jaundice, hypomagnesemia, and hypocalcemia Maternal—preeclampsia, "brittle" diabetes, ↑ need for cesarean section	Every attempt should be made to maintain maternal serum glucose concentration of 100 mg/dL; note that insulin requirements decrease during immediate postpartum period, the mother may not need insulin for 24–48 hr after delivery; insulin therapy, with intermittent dosing or continuous subcutaneous infusion, is standard care for patients with IDDM and NIDDM. Management of diabetic ketoacidosis is the same as for the nonpregnant patient, with the addition of an assessment of fetal well-being and continuous fetal heart monitoring; blood glucose concentration may be normal or only slightly elevated.
Obesity	Fetal—infant death, immune dysregulation and increased risk of neonatal asthma Maternal—excess gestational weight gain, increased risk of postterm delivery, failure to progress, preeclampsia, cesarean section, complications associated with cesarean section	Control of maternal gestational weight gain Monitoring for progression of gestation post-dates
Hyperthyroidism	Fetal—preterm birth, low birth weight, fetal thyroid dysfunction (leading to clinical picture of irritability, tachycardia, goiter, cardiomegaly, CHF, premature craniosynostosis, failure to thrive), fetal loss Maternal—preeclampsia, heart failure	Management of thyroid storm is the same as for the nonpregnant patient and includes a search for the underlying precipitant. Therapy for hyperthyroidism in the absence of thyroid storm: • Reversal of sympathetic effects— propranolol in standard doses is useful until thyroid hormone synthesis has been blocked by thioamides. • Thioamides—propylthiouracil (PTU) and methimazole at the lowest effective dose are acceptable; PTU is preferred. • Surgical therapy: thyroidectomy is useful in refractory cases. • Other—avoid iodide if possible; hydrocortisone decreases peripheral conversion of T_4 to the more active T_3 and can be used during pregnancy. Radioactive iodine is absolutely contraindicated.
Hypothyroidism	Fetal—congenital malformations, low birth weight, fetal loss, fetal thyroid dysfunction, and goiter Maternal—preeclampsia, abruption, postpartum hemorrhage, ↑ need for cesarean section	Maintenance therapy includes levothyroxine, 0.15 mg/day. Appropriate treatment prevents adverse obstetric and fetal outcomes. Myxedema coma is rare, but when present, treatment is the same as for the nonpregnant patient.

Continued

TABLE 179.3

Gestational Effects and Treatment of Medical Illnesses During Pregnancy—cont'd

ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Tuberculosis	Fetal—fetal loss, low birth weight, PTD; fetal and neonatal tuberculosis Maternal— preeclampsia; potential for delayed diagnosis and treatment out of concern for fetus	Positive response to purified protein derivative (PPD), normal chest radiograph—6- to 9-mo course of isoniazid (starting after the first trimester) for patients with recent conversion (<2 yr); patients who have been PPD-positive >2 yr may defer treatment until after delivery but should still be offered a course of isoniazid because it is safe in pregnancy. Increased index of suspicion in HIV-positive mothers with moderate to severe anemia. Active tuberculosis—9-mo course (starting immediately) of isoniazid plus rifampin or ethambutol (all three agents in combination recommended by American Thoracic Society). Multidrug-resistant tuberculosis warrants aggressive therapy, without regard to potential teratogenicity. Pyridoxine is indicated for all patients receiving isoniazid.
HIV/AIDS	Fetal—HIV infection, PTD, low birth weight, fetal loss; neonatal abstinence syndrome if mother uses injection drugs, teratogenicity associated with efavirenz (EFV) use Maternal—postpartum endometritis, uterine bleeding (in the setting of thrombocytopenia), progression of HIV disease in absence of HAART therapy	Antiretroviral therapy— • Highly active antiretroviral therapy (HAART) should be offered to all pregnant patients with HIV infection and viral load >1000 copies/mL. The HAART regimen should include zidovudine (AZT) to prevent vertical transmission of the virus. • There are specific HAART drug-related concerns during pregnancy; decisions about therapy are best made by appropriate specialists. • AZT monotherapy is not recommended except for those patients with a low viral load who do not wish to take HAART. In these cases, AZT is appropriate to reduce disease transmission. Cesarean section is recommended with viral load >1000 copies/mL. Opportunistic infections require standard therapies despite the potential fetal effects.
Syphilis	Fetal—congenital syphilis, fetal loss, PTD, IUGR, nonimmune hydrops	Primary, secondary, early latent (<1 yr)—benzathine penicillin G, 2.4 million units IM × one dose Late latent (>1 yr or unknown duration) — benzathine penicillin G, 2.4 million units IM weekly × three doses Neurosyphilis—aqueous penicillin G, 2–4 million units IV q4h × 10–14 days, or procaine penicillin G, 2.4 million units IM, and probenecid, 500 mg PO q6h × 10–14 days
Systemic lupus erythematosus (SLE)	Fetal— PTD, IUGR, fetal loss, cesarean section Maternal—SLE flare, worsening of renal dysfunction, thrombocytopenia, anemia, preeclampsia, subclinical coronary vascular disease	Initiation of aspirin therapy post–16 wk for decreasing preeclampsia risk. Close monitoring of SLE nephritis via decreasing C3 and C4 levels and elevated anti-DNA antibodies, monitoring of proteinuria. Markers of disease activity via increased lupus anticoagulant levels and antiphospholipid antibody levels Natural disease hiatus during pregnancy
Rheumatoid arthritis	Fetal—IUGR Maternal—increased flare within 1 yr of pregnancy	Aspirin after 16 wk EGA Azathioprine as a safer alternative to cyclophosphamide or methotrexate in first and second trimesters
Eating disorders (anorexia nervosa, bulimia nervosa [BN])	Fetal—miscarriage, low birth weight, preterm birth, congenital malformations (neural tube defects) Maternal—cesarean section, depression	Restoration of normal physiologic parameters (electrolyte replacement and clearance of ketosis) Antidepressants for BN
Alcohol	Fetal—IUGR, low birth weight, miscarriage, IUFD, fetal alcohol spectrum disorders Maternal—increased risk of unintended pregnancies, alcohol withdrawal	Any gravid patient with signs of active withdrawal should be considered for inpatient management.
Smoking	Fetal—miscarriage, IUFD, preterm birth, IUGR, SIDS, congenital deformities (clubfoot) Maternal—decreased risk of preeclampsia	Behavioral and cognitive treatment for cessation Nicotine patches in second and third trimesters appear safe in limited studies.
Opioids	Fetal—IUGR, SIDS, narcotic abstinence syndrome, NICU admissions Maternal—increased risk of unintended pregnancies, withdrawal, endocarditis	Close monitoring of fetal depression peripartum Management of methadone maintenance to decrease risk of IV drug injection complications

ACOG, American College of Obstetrics and Gynecology; *AEM,* antiepileptic medicine; *CHF,* congestive heart failure; *EGA,* estimated gestational age; *IUFD,* intrauterine fetal demise; *IUGR,* intrauterine growth restriction; *NICU,* neonatal intensive care unit; *PTD,* preterm delivery. *SIDS,* sudden infant death syndrome; T_3, triiodothyronine; T_4, thyroxine.

TABLE 179.4

Antihypertensive Agents for Hypertensive Emergencies

DRUG	ROUTE	STARTING DOSE	TITRATION DOSE	MAXIMUM DOSAGE	MODE OF ACTION	ONSET OF ACTION	DURATION OF ACTION	ADVERSE EFFECTS	COMORBID INDICATIONS
Hydralazine	IV (intermittent)	5 mg IV push or IM	5–10 mg IV every 20–40 min	30 mg	Direct smooth muscle relaxation	10 min	12 hr	Headaches, aggravation of angina, tachycardia, nausea, flushing, hypotension, lupus-like syndrome	Preeclampsia, eclampsia (first line)
Labetalol	IV (intermittent)	10–20 mg IV (over 2 min)	20–80 mg IV, every 20–30 min	300 mg	α_1-agonist + nonselective beta blockade	5–10 min	2–6 hr	Fetal, maternal bradycardia, heart block, postural hypotension, cold extremities, sleep disturbances, rebound hypertension, bronchospasm, masking of hypoglycemia	Preeclampsia, eclampsia (first line); acute pulmonary edema, diastolic dysfunction; acute myocardial infarction; hypertensive encephalopathy; aortic dissection; hypertensive encephalopathy; ischemic or hemorrhagic stroke
	IV (infusion)	1–2 mg/min	Increase by 1 mg/min every 10 min	300 mg					
Esmolol	IV (infusion)	Bolus—500 μg/kg Maintenance—50 μg/kg/min	Increase by 50 μg/kg/min every 4 min	300 μg/kg/min	Beta blockade	<1 min	15–30 min	First-degree heart block, maternal bradycardia, congestive heart failure, bronchospasm; crosses the placenta; may cause fetal bradycardia, persistent fetal beta blockade	Acute myocardial infarction; aortic dissection
Nifedipine[a]	Oral	10–20 mg	Repeat in 30 min if needed	30 mg	Calcium channel blocker	5–10 min	2–4 hr	Uncontrolled hypotension, stroke, myocardial infarction, flushing, headache, reflex tachycardia	
Nicardipine	IV (infusion)	5 mg/hr	Increase by 2.5 mg/hr every 5–15 min	15 mg/hr	Calcium channel blocker	1–5 min	4–6 hr	Tachycardia, flushing, and headache	Preeclampsia, eclampsia (first line); acute pulmonary edema, systolic dysfunction; hypertensive encephalopathy; acute renal failure; ischemic or hemorrhagic stroke
Sodium nitroprusside	IV (infusion)	0.25 μg/kg/min	Increase by 0.25–0.5 μg/kg/min every 2–3 min	5 μg/kg/min	Nonselective direct NO inhibitor	<1 min	2–3 min	Nausea, vomiting; potential risk for maternal and fetal cyanide and thiocyanate toxicity if used for >4 hr	Aortic dissection; acute pulmonary edema; left ventricular dysfunction

[a]Theoretical risks with simultaneous administration of magnesium (eg, severe hypotension, myocardial depression, potentiation or prolongation of neuromuscular blockage).
IM, Intramuscular; *IV,* intravenous; *NO,* nitrous oxide.
From Too GT, Hill JB. Hypertensive crisis during pregnancy and postpartum period. Semin Perinatol 37:280–287, 2013.

physiologic anemia, which may precipitate angina.[19,20] Hypertension, thrombophilia, anemia, diabetes, advanced maternal age, multiparous state, and smoking increase the risk of pregnancy-associated AMI.[19]

Approximately 13% to 25% of pregnant patients diagnosed with ACS have normal coronary arteries.[20] In one study, 43% of patients diagnosed with AMI had atherosclerosis, with or without thrombus, 21% had coronary thrombus, and 16% had dissection.[19] AMI with normal coronaries tends to occur during the peripartum period. Other causes such as coronary artery dissection and vasospasm are more likely to occur in otherwise normal vessels, whereas atherosclerotic disease causes most AMIs in the antepartum period. Pulmonary embolus, reflux esophagitis, biliary colic, and aortic dissection are all more common than myocardial ischemia during pregnancy and should be considered in the differential diagnosis of the pregnant patient who presents with chest pain. Initial signs and symptoms of AMI, such as chest pain and shortness of breath, are often attributed to the normal physiological changes of pregnancy.[18,20,21]

The diagnosis of ACS is similar to that in nonpregnant patients, with certain exceptions. Electrocardiographic changes sometimes occur in normal pregnancies and delivery. These include T wave flattening, T wave inversion (mainly in lead III), and nonspecific ST changes during pregnancy, as well as ST depression during labor induction for cesarean section.[20] As a result, an additional evaluation may be necessary. Echocardiography is useful in the correlation of suspicious electrocardiographic findings with wall motion abnormalities. The enzymatic diagnosis of myocardial infarction is unchanged, except during and immediately after delivery; the troponin level is preferred to the creatine kinase level because it rises above baseline during this time. The United Kingdom's Saving Mother's Lives Report has found that in gravid women who died from cardiac ischemia, care was substandard in 46% of cases. Key diagnostic and management issues include the following[21,22]:

- Ischemic cardiac disease as a cause of symptoms should be considered.
- Asymptomatic pregnant patients with ischemic cardiac disease may have a normal electrocardiogram (ECG), so evaluation for chest pain should include serial ECGs and troponin levels.
- A normal echocardiogram does not exclude myocardial infarction (non–ST segment elevation MI).
- Cardiologists are reluctant to perform coronary angiography because of pregnancy.

Treatment of AMI during pregnancy is similar in most respects to treatment of the nonpregnant patient, with survival of the mother as the goal (see Table 179.3). Standard treatments including antiplatelet agents, nitroglycerin, and beta blockers: antithrombotic agents are considered safe during pregnancy but the decision to use them should be made jointly by emergent consultation with a cardiologist.[18,21] Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone antagonists, and statins are not advised until the postpartum period. Aspirin is the first-line antiplatelet agent. Clopidogrel and eptifibatide have been studied in case reports, with no adverse fetal outcomes, and the benefit of their use outweighs any risks.[21] Heparin has long been the antithrombotic of choice for pregnant patients, although low-molecular-weight agents such as enoxaparin also do not cross the placenta and are considered efficacious and safe in pregnancy.[18]

Cardiac catheterization with stenting is the treatment of choice for AMI in the pregnant patient and, with shielding, exposes the fetus to less than 1 radiation-absorbed dose (rad).[18] When a catheterization laboratory is unavailable, lifesaving thrombolytic therapy should not be withheld. Although thrombolytics do not cross the placenta, there is an increased risk of maternal hemorrhage and, in the setting of AMI caused by coronary dissection, thrombolytic use can worsen the dissection.[20,21] Because thrombolytic therapy precludes major surgery and epidural anesthesia in the hours to days immediately after administration, one must carefully consider whether to use these agents in pregnant women who are close to term, especially if the need for cesarean delivery is anticipated.

In the setting of peripartum AMI, labor should be conducted with continuous monitoring of the mother's hemodynamic status and fetal well-being. Assisted vaginal delivery is preferred unless there is an indication for cesarean section. Cesarean section avoids prolonged exertion by the mother but can subject the patient to general anesthesia if the use of antithrombotic agents precludes epidural catheter placement.

Valvular Heart Disease and Pulmonary Hypertension

Principles. The European Registry on Pregnancy and Heart Disease has reported that mitral stenosis and regurgitation are the most common types of valvular disease (63%), followed by aortic valve disease (23%).[23,24] The ability of patients to tolerate pregnancy without significant adverse effects depends on the type and severity of the lesion. Mild to moderate lesions (New York Heart Association [NYHA] classes I and II) are often associated with good outcomes for the mother and fetus. On the other hand, mitral stenosis (beyond class I), advanced aortic stenosis, and aortic and mitral lesions associated with moderate to severe ventricular dysfunction or pulmonary hypertension, as well as mechanical prosthetic valves requiring anticoagulation, can result in significant maternal mortality and require directed therapy and expert cardiology consultation (Table 179.5).[10,12,23,25]

Heart failure is the most common maternal complication in pregnancy with valvular heart disease.[23,24] In the European Registry on Pregnancy and Heart Disease, hospital admissions occurred in 38% of pregnant patients with valvular heart disease. Diagnosing heart failure is challenging because women in the last months of pregnancy experience symptoms such as dyspnea on exertion,

TABLE 179.5

Risk Classification in Women With Cardiac Disease[a]

LOW RISK	HIGH RISK
Aortic stenosis with ejection fraction >50% and mean gradient <25 mm Hg, asymptomatic	Severe aortic stenosis, regardless of symptoms
Aortic or mitral regurgitation, asymptomatic or mild symptoms	Aortic or mitral regurgitation, NYHA class III–IV
Mitral valve prolapse with mild or moderate regurgitation and ejection fraction >50%	Severe left ventricular dysfunction with ejection fraction <40%
Mild mitral stenosis without severe pulmonary hypertension	Symptomatic mitral stenosis, NYHA class II–IV
Mild to moderate pulmonary valve stenosis	Severe pulmonary hypertension (pulmonary artery pressure >75% of systemic pressure) Marfan syndrome Mechanical valve

[a]Maternal and fetal risk classification in women with cardiac valve disease according to the American College of Cardiology, American Heart Association, and European Society of Cardiology.

NYHA, New York Heart Association.

From Pessel C, Bonanno C: Valve disease in pregnancy. Semin Perinatol 38:273–284, 2014.

paroxysmal nocturnal dyspnea, orthopnea, and pedal edema that are identical to those of heart failure.[26] Normal B-type natriuretic peptide (BNP) levels can be used to rule out heart failure in pregnant females but, because BNP levels are higher in pregnant females, an elevated BNP level can be difficult to interpret.[27]

Pulmonary Hypertension. Pregnancy is poorly tolerated by patients with pulmonary hypertension because the pulmonary circulation cannot cope with the increased stroke volume and cardiac output of pregnancy, causing pulmonary pressures to rise. This causes dyspnea, heart failure, and syncope. Mortality in pregnant women with pulmonary hypertension has been reported to be as high as 50%, although a more recent study has demonstrated a mortality of 25% likely due to improvements in recognition and treatment.[28] Pregnancy is contraindicated, and patients early in pregnancy should be counseled about elective pregnancy termination.[29]

The treatment of the pregnant patient with pulmonary hypertension focuses on diuresis and pulmonary vasodilation. Diuretics are indicated for the management of volume overload, and common diuretics—with the exception of spironolactone—are considered safe, although limited data exist regarding their effect on the fetus.[29] Specific agents for treating pulmonary hypertension include endothelin receptor agonists (ERAs), phosphodiesterase inhibitors, and prostanoids. Phosphodiesterase inhibitors such as sildenafil and tadalafil, as well the prostacyclin derivatives epoprostenol and treprostinil, have not been shown to be fetotoxic in animals and are regularly used in pregnancy. ERAs such as bosentan and ambrisentan are teratogenic.

Mitral Stenosis. Mitral stenosis is the most commonly encountered valvular lesion in pregnancy and is also the most important lesion to detect in early pregnancy because it can cause maternal mortality.[10,12,23] The increased resting heart rate and stroke volume in normal pregnancy increase the pressure gradient across the mitral valve and can cause symptoms of left heart failure, as well as atrial arrhythmias such as atrial fibrillation.[10] The likelihood of maternal symptoms and worsening of cardiovascular status is directly related to the severity of disease. Pregnancy in women with mild mitral stenosis is generally well tolerated.

Beta blockers are the mainstay of treatment for patients with symptomatic mitral stenosis. Diuretics may also be used for patients with symptoms of heart failure[10,12,23,25] (see Table 179.3). Surgical intervention is indicated for patients with refractory symptoms despite optimal medical management and in patients with pulmonary hypertension.[12,25]

Aortic and Mitral Regurgitation. Mitral valve prolapse is the most common cause of mitral regurgitation in developed countries, whereas rheumatic heart disease is the most common cause worldwide.[23] In most cases, chronic regurgitation lesions are well tolerated during pregnancy and may even improve because the reduced systemic vascular resistance of pregnancy allows more forward and less regurgitant flow. In addition, this effect is aided by the increase in heart rate and shortened diastole that occur in pregnancy.[23] When necessary, medical therapy consists of diuresis, digoxin, and vasodilators.

Aortic Stenosis. Symptomatic aortic stenosis during pregnancy usually occurs in the setting of a congenital bicuspid valve. Patients with mild to moderate aortic stenosis tend to have uncomplicated pregnancies; conservative management is often possible, especially if the aortic valve area is greater than 1.0 cm^2. Patients with symptomatic aortic stenosis may respond to bed rest or preload reduction with diuretics. Severely symptomatic patients may need percutaneous valvotomy and surgical replacement.[23,24]

Prosthetic Heart Valves. Pregnancy is a hypercoagulable state and leads to an increased risk of thromboembolic events, especially in patients with prosthetic valves or underlying valvular disease.[23,24] Pregnant patients with prosthetic heart valves who are not anticoagulated have a maternal mortality as high as 5%, and thromboembolic events can occur in up to 24% of cases.[25] Warfarin is the most effective anticoagulant in preventing maternal thromboembolic events.[12] However, warfarin is considered teratogenic in the first trimester. Neither unfractionated heparin (UFH) nor low-molecular-weight heparin (LMWH) crosses the placenta and are not teratogenic. However, their use throughout pregnancy is not recommended due to the increased risk of thromboembolic events as compared to using UFH or LMWH in the first trimester, followed by warfarin for the remainder of pregnancy.[12,25]

Current anticoagulation recommendations in pregnant patients with prosthetic heart valves are to continue using warfarin until pregnancy has been achieved. If an international normalized ratio of 2.5 to 3.5 can be achieved with a warfarin dose less than or equal to 5 mg, warfarin may be used throughout pregnancy after a full discussion with the patient about the benefits and risks of the therapy. If a dose more than 5 mg is required, UFH or LWMH should be used in the first trimester, with warfarin being resumed for the second and third trimesters.[12,25] Warfarin should again be replaced by UFH or LWMH several weeks before delivery.

HEMATOLOGIC DISORDERS

Anemia

Anemia is the most common medical complication of pregnancy. Recent research has indicated that anemia may be associated with maternal mortality, perinatal mortality, preterm birth, low birth weight, and small-for-gestational-age infants.[30] The classic clinical presentations of anemia include pallor, fatigue, and shortness of breath.[31] Most anemia, however, is asymptomatic. The hemoglobin threshold for severe anemia requiring blood transfusions is typically considered to be less than 7 g/dL for gravid patients and less than 8 g/dL for postpartum patients.[31] There are several types of anemia exist, but four types predominate: dilutional anemia, iron deficiency, folate deficiency, and sickle cell hemoglobinopathy.

Dilutional Anemia

Dilutional anemia differs slightly from the other three. Where iron deficiency, folate deficiency and sickle cell hemoglobinopathy anemias are complications of pregnancy, dilutional anemia is a normal process associated with pregnancy. In preparation for blood loss at delivery, blood volume increases by nearly 50% between weeks 6 and 34. This rapid blood volume increase, accompanied by a lag in red blood cell (RBC) production, results in a dilution of hemoglobin. The result is that the threshold for anemia in gravid patients is slightly lower (11 g/dL) than in nongravid patients (12 g/dL). Pregnant patients with hemoglobin values typically considered normal in the nongravid patient have an increase in adverse outcomes such as preeclampsia, intrauterine growth retardation, and preterm birth, and the emergency clinician should consider that gravid patients with hemoglobin values of 13 to 15 g/dL have inadequate expansion of their plasma volume.[32]

Iron Deficiency Anemia

Iron deficiency anemia is common, occurring in approximately 20% to 25% of pregnancies in industrialized countries.[33] The risks of adverse pregnancy outcomes (see Table 179.3) have been noted

to relate to the severity of the anemia. Studies have indicated a higher risk of preterm birth and low birth weight in patients with mild to moderate anemia,[30,34] whereas severe anemia (<6 to 7 g/dL or 60–70 g/L) is associated with increased fetal mortality, abnormal fetal oxygenation, premature rupture of membranes, gestational hypertension, and reduced volume of amniotic fluid.[35] The diagnosis is made most accurately in the very early stages of pregnancy because serum ferritin, the most sensitive and specific (and preferred) test, is affected by the dilution effect of increased plasma volume occurring later in pregnancy. Other supporting laboratory evidence includes low plasma iron levels, increased free erythrocyte protoporphyrin, and elevated total iron-binding capacity.

The ACOG has developed guidelines for the management of iron deficiency anemia. Patients with an uncomplicated physiologic anemia who are not iron-deficient can be expected to have good obstetric outcomes without therapy and do not require treatment. Patients presenting with iron deficiency anemia should be treated with non–enteric-coated supplemental iron. The use of prophylactic supplementation in women with normal hemoglobin levels (>11 g/dL [110 g/L]) and normal iron stores (ferritin > 20 mg/dL [20 µg/L]) to prevent anemia in late pregnancy is controversial. However, recent studies and meta-analyses have demonstrated that prenatal iron supplementation significantly reduces the risk of anemia at term by 70% and the risk of iron deficiency anemia at term by 57% to 66%.[36-39] The dose of iron recommended by the World Health Organization (WHO) is 60 mg/day, but the Institute of Medicine has suggested an upper limit of 45 mg/day due to the gastrointestinal side effects of higher doses.

Folate Deficiency

Folate is critical to several intracellular processes associated with cell growth. However, due to the 5- to 10-fold increase in folate requirements during pregnancy, gravid patients are at risk for folate deficiency.[40] Folate deficiency is one of a number of causes of megaloblastic anemia, which is the second most common anemia.[41] The incidence of folate deficiency in pregnancy is low in developed countries but remains higher in other populations. The risk for development of folate deficiency is increased in patients with multiple gestations, short interpregnancy intervals, preexisting malnutrition, hyperemesis gravidarum, malabsorption syndromes, alcoholism, use of certain antiepileptic drugs, and diets lacking green leafy vegetables and animal protein. Low maternal folate stores have, most importantly, been linked to increased risk of neural tube defects, as well as increased risk of placental abruption, preterm birth and low birth weight, preeclampsia, and spontaneous abortion.[41,42] As is the case for iron deficiency, effects on the fetus depend on the degree of anemia.

Iron deficiency and folate deficiency anemias often coexist, making the peripheral blood smear difficult to interpret. In cases of suspected folate deficiency, the measurement of serum and RBC folate levels is indicated. However, the serum folate level is noted to exhibit a rapid response to folate intake, and low levels may normalize within days after a folate-rich meal. The serum folate level is also affected by the hemodilution of pregnancy. Oral folate supplementation with 0.4 mg daily is routinely recommended for all women before conception, and 0.4 to 0.8 mg is recommended during pregnancy as the requirement for this micronutrient increases during gestation. The ACOG recommends 1.0 mg for those women who have a known pregnancy-related folate deficiency.[21] Women at higher risk for neural tube defects (eg, neural tube defects in prior pregnancy) are advised to take much higher doses of folate, 4 mg daily, under close supervision of their obstetrician.[43] ACOG advises continuing oral folate supplementation throughout the second and third trimesters.[41]

Sickle Cell Anemia

Sickle cell disease (SCD) is one of the major sources of maternal and fetal complications in the United States. The details of the pathophysiologic mechanism and genetics of SCD are discussed in Chapter 112, but it is useful to review the most common phenotypes that affect pregnancy. The sickle gene can be homozygous (hemoglobin *SS* or *SCD*), and this form of the disease is responsible for most pregnancy complications. The sickle gene can also be heterozygous with normal hemoglobin A (sickle cell trait, or hemoglobin SA), in which case symptoms are rare, except under extreme environmental conditions. Hemoglobin S can also be heterozygous with a large number of abnormal hemoglobins, such as hemoglobin C, several variants of thalassemia, and other rare hemoglobin variants; each variant has its own complication profile. Of these, the most relevant in terms of pregnancy complications is hemoglobin SC.

Patients with SCD are subject to many chronic medical problems secondary to a variety of pathophysiologic mechanisms, including sickling of RBCs, anemia, immunosuppression caused by autosplenectomy, and repeated transfusion. Median life expectancy is in the fifth decade for both genders affected by SCD, and female fertility is generally unaffected, so it is likely that the emergency clinician will encounter pregnant patients with the disease. Maternal complications are common in patients with SCD; these include preterm labor, eclampsia, premature rupture of membranes, maternal infections, more frequent pain crises, thrombosis, preeclampsia, and increased need for cesarean delivery.[44-46] Despite these complications, the maternal mortality rate is less than 1% with current treatment.

SCD also results in adverse effects on the fetus (see Table 179.3). Placental infarction and insufficiency are common, and the incidence of premature labor, small-for-gestational-age infants, and low-birth-weight infants is significantly increased in SCD pregnancies compared with normal controls. The reported perinatal mortality rate varies but is low in the setting of appropriate maternal and neonatal care.[44-46]

Vasoocclusive crises and anemia occur more often in pregnancy and are the most common complications of SCD in pregnancy.[45,47] There have been no good randomized trials studying the management of SCD during pregnancy, so recommended treatment is similar to that for the nonpregnant patient (see Table 179.3). Hydroxyurea is not recommended for use in pregnancy because of potential teratogenicity, and nonsteroidal antiinflammatory drugs (NSAIDs) are avoided after 30 weeks of gestation. General anesthesia can result in an increase in postpartum sickling complications, so regional anesthesia is preferred in the case of cesarean delivery. The use of supplemental iron and transfusion is controversial because of the potential for iron overload, alloimmunization, volume overload, and hyperviscosity syndrome. Therapeutic transfusions should be given to patients with severe disease manifestations such as symptomatic anemia, cardiopulmonary instability, acute chest syndrome, intrapartum hemorrhage, and preeclampsia.[45,46,48] In general, the goal with transfusion or exchange transfusion is to lower the percentage of hemoglobin S to 40% and achieve hemoglobin values of approximately 10 g/dL (110 g/L). Transfusions aimed solely at secondary prevention of adverse events such as pain crises have not shown improvement in pregnancy outcomes.[45,47,48]

NEUROLOGIC DISORDERS

Epilepsy

Epilepsy is the most common neurologic complication of pregnancy but remains relatively rare, affecting less than 1% of all

gestations. Epilepsy refers to a broad spectrum of seizure disorders that range from relatively benign and infrequent seizures to a disabling condition with daily, poorly controlled generalized convulsions; therefore, care is individualized. The treatment of epilepsy during pregnancy entails balancing the risk of increased frequency and duration of seizures to the mother and fetus against the teratogenic risks of antiepileptic drugs (AEDs).

The effect of pregnancy on epilepsy is variable. Most epileptic patients (50%–76%) experience no change in their seizure frequency, whereas approximately 15% experience more frequent seizures.[49] Delivery and the first 24 hours postpartum are the most likely times for a seizure to occur, with a ninefold greater incidence of seizure than during pregnancy in general. A decrease in plasma drug concentrations is expected with certain AEDs, such as phenytoin, lamotrigine, oxcarbazepine, and levetiracetam.[50] Many authors have recommended that maternal plasma drug levels should be monitored and compared to prepregnancy levels.[49,50] Antiepileptic medications also increase the clearance of medications, including oral contraceptives, making unintentional pregnancy a possibility.

Gravid patients with epilepsy may be at increased risk for cesarean section, postpartum hemorrhage, and other adverse outcomes (see Table 179.3).[33] Patients who have nonconvulsive seizure disorders or who are seizure-free for a sufficient period of time before conception are candidates for nonpharmacologic observation because the risk of treatment with AEDs can outweigh the benefit.[49] This decision should be deferred to the patient's primary physician or neurologist. However, there are significant obstetric complications related to prolonged seizure activity, and long-term treatment with an AED for most patients with seizures is warranted (see Table 179.3).

The primary complication of AED use in pregnancy is congenital malformations. Of primary concern is the risk for neural tube defects, facial clefts, cardiac anomalies, and cognitive defects with the older generation agents (eg, valproate, carbamazepine, phenytoin) and the newer generation agents (eg, lamotrigine, topiramate, levetiracetam). There is a two- to three-fold increase in the incidence of serious congenital malformations in offspring of epileptic mothers taking these agents. The risk is greatest with valproate and is also increased with AED polypharmacy and increased dose of individual agents.[50,51-53] Of all the older agents, carbamazepine appears to be the safest for use as monotherapy.[50,53] Recent studies have looked at the risk of major congenital malformations of the newer AEDs and have found that in monotherapy with lamotrigine or levetiracetam, the risks are lower than those in the older agents.[49,51,52] Specifically, the United Kingdom and Ireland Epilepsy and Pregnancy Registry has found a rate of major congenital malformations of 0.7% for women receiving levetiracetam monotherapy; the North American AED Pregnancy Registry found a rate of 2.4%.[52,54] Both these rates are significantly below those of other AEDs.

When compared to the older AEDs, levetiracetam performed as well at controlling seizures when used in monotherapy. However, lamotrigine and topiramate, when used in monotherapy, showed worse seizure control.[55] Because phenytoin, carbamazepine, valproate, and possibly other AEDs interfere with folate metabolism, oral supplementation with at least 0.4 mg/day is recommended for all women of childbearing age taking these drugs to help prevent congenital malformations such as neural tube defects. Enzyme-inducing AEDs such as carbamazepine, phenytoin, and phenobarbital have been reported to cause neonatal vitamin K deficiency and neonatal hemorrhage, but the American Academy of Neurology and American Epilepsy Society have noted that there is inadequate evidence to determine a definitive relationship.

Any potential cause of seizure, including eclampsia, may result in status epilepticus. Despite this, status epilepticus in pregnancy is relatively rare, and limited data are available about its occurrence and therapy. Observations from the European Epilepsy Pregnancy Registry have noted that status epilepticus may occur at any time during gestation and even at delivery. It may also occur in patients who have been seizure-free throughout pregnancy, and no specific risk factors for its occurrence have been identified. Older reports noted a high fetal and maternal mortality, but recent data support a much lower complication rate.

The risk of untreated status epilepticus to the mother and fetus clearly outweighs the potential for adverse teratogenic effects, and standard resuscitative measures, as well as drug therapy, are indicated. Continuous fetal monitoring should be instituted as soon as possible to observe for signs of fetal hypoxia, and the mother should be positioned in the left lateral decubitus position to avoid the supine hypotensive syndrome.[49]

Multiple Sclerosis

Multiple sclerosis (MS) affects approximately 400,000 Americans and is twice as common in women as in men. The peak age at onset is 20 to 35 years, which overlaps peak childbearing years. The disease is characterized by intermittent episodes of central nervous system (CNS) demyelination, with consequent neurologic impairment that follows a relapsing-remitting course. Progressive neurologic deficits and permanent disability develop in certain patients.

The impact of pregnancy on the course of MS has been closely studied in various cohorts and, as in other autoimmune diseases, the frequency and severity of exacerbations of MS improve because of the immunosuppressant effects of pregnancy. This effect is most pronounced in the third trimester. During the 3 months after delivery, the rate of relapse increases and then returns to the prepregnancy baseline.[56,57] Relapses are more likely in MS patients with higher disability at the time of pregnancy onset. However, it does not seem that postpartum relapses are related to the duration of disease or total number of relapses before conception.[56,57]

MS patients with disease exacerbation are often treated with immunomodulators such as intravenous immune globulin (IVIG), corticosteroids, glatiramer acetate, and interferon beta. Small studies in gravid patients have shown that the use of IVIG during pregnancy and in the postpartum period is safe and may decrease the relapse rate.[57] Likewise, the use of intermittent steroids in the postpartum period may decrease the likelihood of disease relapse. Although the evidence is not conclusive, it is currently not recommended to treat MS exacerbations during pregnancy with interferon beta or glatiramer acetate based on evidence that they may cause adverse fetal effects.[58,59]

Spinal Cord Injury

Because spinal cord injury (SCI) occurs mainly in young people and usually does not impair fertility, there is a relatively large population of paraplegic and quadriplegic patients who become pregnant.[60] Pregnant women with SCI are twice as likely to have preterm labor and are at increased risk of having a low-birthweight infant.[61] Although many of these pregnancies are uneventful, these patients are at risk for certain complications.

The hypercoagulable state of pregnancy, combined with chronic immobilization, results in an increased incidence of thromboembolic disease, with the incidence of deep vein thrombosis (DVT) reported as high as 8% in pregnant women with SCI.[60] The incidence of urinary tract infection is also markedly increased as a result of neurogenic complications and the need for catheterization.[60] Infections are even more likely during pregnancy and may progress to pyelonephritis, with the subsequent increased risk of fetal loss, prematurity, and maternal sepsis.

Autonomic dysreflexia is the most serious complication of SCI and occurs in up to 85% of women with high lesions (above T5-T6); it occurs with increased frequency during pregnancy.[60] Autonomic dysreflexia is manifested as severe paroxysmal hypertension, headache, tachycardia, diaphoresis, piloerection, mydriasis, and nasal congestion. It is often precipitated by afferent stimuli from the hollow viscus such as the bladder, bowel, or uterus. Symptoms of autonomic dysreflexia often occur with uterine contractions during labor. However, labor may be difficult to detect because patients with spinal cord lesions below T10 to T12 have an intact uterine nerve supply and will experience labor pains; however, with lesions above T10, labor may be imperceptible or experienced as only mild abdominal discomfort. Pregnant patients with SCI with symptoms of autonomic dysreflexia should be assessed for cervical dilation and have uterine contractions monitored. ED treatment is directed at the restoration of normal blood pressure with standard agents. Definitive therapy is with regional anesthesia. Spinal anesthesia and epidural anesthesia obliterate and prevent this response and should be used as soon as possible during labor for all women with SCI. Finally, it can be difficult to differentiate between the symptoms of autonomic dysreflexia and preeclampsia. In autonomic dysreflexia, symptoms such as hypertension will resolve once the stimuli to the skin or hollow viscus have been relieved; in preeclampsia, the symptoms and laboratory abnormalities are more likely to persist.[60]

Myasthenia Gravis

Myasthenia gravis is a rare disorder in which autoimmune destruction of the postsynaptic cholinergic receptor results in profound muscle fatigability. The effect of pregnancy and postpartum state on myasthenia gravis is unpredictable in the individual patient, but overall, approximately 25% to 40% of patients experience exacerbation of disease, with the remainder having improvement or no change in disease severity.[62-64] Disease exacerbations are most likely in the first trimester or puerperium, with improvement in symptoms often seen in the second and third trimesters due to the hormone-mediated immunosuppression of pregnancy.[63] Because of weight gain, anemia, and other physiologic adjustments of pregnancy that may result in fatigue, the distinction between normal pregnancy symptoms and myasthenia may be difficult. Also, these changes, along with the nausea and vomiting of normal pregnancy, may result in a need to adjust medication dosage requirements.[63]

Most deliveries are accomplished vaginally without complication in adequately treated patients; assisted and surgical delivery in these women is indicated mainly for obstetric reasons rather than for specific myasthenia-related care.[62] Up to 30% of neonates born to mothers with myasthenia gravis have a transient neonatal myasthenia syndrome through the placental transport of acetylcholine receptor antibodies.[63,64] There is no correlation between the severity of maternal disease and occurrence of neonatal myasthenia.[63] The onset of neonatal myasthenia is typically within the first hours of life but may be delayed by a period of days. Manifestations include poor feeding and suck, diminished reflexes, hypotonia, and bulbar and respiratory muscle weakness. As in adults, the symptoms respond to cholinesterase inhibitors, but treatment should be carried out in an intensive care unit setting.[64]

Myasthenia crises during pregnancy present with typical symptoms of painless fluctuating weakness of skeletal muscles. With extraocular muscle involvement, diplopia and ptosis are the most common early symptoms.[63] When exacerbations do occur, treatment is no different from the treatment of nonpregnant patients (see Table 179.3). Acetylcholine esterase inhibitors, corticosteroids, azathioprine, IVIG, and plasmapheresis are all considered safe for the mother and fetus.[64] Assessment of pulse oximetry, forced vital capacity, and arterial blood gas parameters will guide respiratory therapy. For patients presenting with weakness, an edrophonium (Tensilon) challenge test to distinguish myasthenia from cholinergic crisis is appropriate after the initiation of appropriate ventilatory support. Standard medical treatment is continued during labor and delivery to maximize motor strength. Epidural anesthesia is also recommended to reduce pain and fatigue. The emergency clinician should be aware that 30% of patients experience an exacerbation during the postpartum period as the protective immunosuppressant effect of pregnancy dissipates.[63,64]

RENAL DISORDERS

Chronic kidney disease (CKD) can be silent well into its disease course and is more difficult to diagnose in pregnancy because of expected decreased blood urea nitrogen (BUN) and creatinine levels during pregnancy. For women with known renal disease, including end-stage renal disease, on hemodialysis, pregnancy rates are 1% to 7%. For those post–renal transplantation, fertility rates return to prerenal failure levels within 1 to 6 months post-transplantation, so pregnancy is not an uncommon finding in posttransplantation women of childbearing age.

CKD in and of itself is an independent risk factor for maternal and fetal complications. The degree of underlying renal dysfunction is a strong determinant of morbidity associated with pregnancy. Patients with moderate to severe renal dysfunction have a much higher risk of further decline in renal function, as well as adverse obstetric outcomes, including preeclampsia, placental abruption, fetal loss, preterm delivery, low birth weight, polyhydramnios, and increased need for cesarean section and neonatal intensive care.[65,66] Despite this, 80% of pregnancies with a maternal BUN level higher than 60 mg/dL ended in the delivery of live births. Worsening of underlying renal function is more likely in patients with a decreased glomerular filtration rate who also have associated proteinuria or hypertension. Because worsening renal function is manifested by hypertension and proteinuria, differentiation from preeclampsia can be difficult. In this setting, it is best to treat the patient for presumed preeclampsia, with the caveat that magnesium administration should be performed judiciously on the basis of serum magnesium levels.

Pregnant women with chronic renal failure require aggressive and timely management to optimize their chances for a successful gestation without causing further deterioration in renal function. One of the most successful tenets of CKD management in pregnancy is close control of blood pressure and monitoring for proteinuria. Treatment regimens are the same as those outlined earlier (see "Chronic Hypertension and Hypertensive Emergencies").

Evidence of renal function deterioration or the development or exacerbation of hypertension warrants admission for specialized inpatient care. Hemodialysis is indicated for creatinine levels above 3.5 to 5 mg/dL (266.9–381.3 μmol/L). Pregnancy in women who are already dialysis- dependent has been associated with poor outcomes, and pregnancy has previously been discouraged in these patients. However, studies including small numbers of women have noted live birth rates approaching 60% to 85% when mothers receive specialized prenatal care.[65,66] Such care includes correction of anemia, appropriate antihypertensive therapy, and more aggressive dialysis with more frequent or prolonged sessions.[66]

METABOLIC AND ENDOCRINE DISORDERS

Diabetes

Three types of diabetes affect pregnant patients—type 1, or insulin-dependent diabetes mellitus (IDDM); type 2, or

non–insulin-dependent diabetes mellitus (NIDDM); and gestational diabetes mellitus (GDM). Although risk factors for GDM can be identified prepregnancy, it is not classified as a preexisting medical condition and will not be considered in this discussion. However, the considerations for glycemic control in GDM are the same as those for IDDM and NIDDM. Although NIDDM is sometimes considered a more benign form of disease, the risk of pregnancy complications and fetal malformations is, at best, the same for NIDDM and IDDM. Some studies have shown that complications, maternal and fetal, are actually greater for NIDDM.[67]

This represents a distinct medical challenge, given the ever-increasing prevalence of NIDDM and the generally lower rates of glycemic control and preconception planning in this patient population. In general, maternal and fetal complications relate to inadequate glycemic control and to the presence of vascular complications or severe renal insufficiency more than to the type of diabetes. Glycemic control is incrementally more challenging during pregnancy because of complexities in glucose regulation precipitated by hormonal changes. Specifically, in early pregnancy and again in the peripartum period, hyperglycemia is common and is caused by increased insulin resistance, even in IDDM patients. Obesity and preexisting insulin resistance in NIDDM can further complicate efforts of glucose control.[68] Ideally, hemoglobin A_{1c} (HbA_{1c}) values should not be higher than 6% (see Table 179.3); the best outcomes occur when tight glycemic control is achieved for at least 4 months preconception.[69] Experts have recommended that NIDDM patients taking oral agents be transitioned to insulin during pregnancy.[69] The predisposition to develop diabetic ketoacidosis (DKA) throughout pregnancy has been well documented; this is attributable to hormonal changes. An increased risk of significant hypoglycemic episodes stems from attempts at very tight glucose regulation, but is also caused by diminished glucagon response to hypoglycemia, emesis, and increased metabolic demands of the placenta and growing fetus.

Maternal Complications

The effects of pregnancy on underlying diabetes vary by organ system. The data are limited, but pregnancy is not advised for diabetic patients with significant coronary artery disease because of the cardiovascular demands of pregnancy and high mortality of AMI during pregnancy. Given the likelihood of silent ischemic events in the diabetic population, atypical or vague presentations of angina or MI, including new-onset congestive heart failure should be carefully evaluated in those with preexisting known coronary artery disease, but also in any diabetic mother.[70]

Patients with diabetic nephropathy are at increased risk for preeclampsia and the subsequent requirement for preterm delivery. Following progression of nephropathy closely in conjunction with aggressive blood pressure control and optimizing protein intake are strongly recommended.

Retinopathy worsens acutely in 77% of pregnancies, and those at greatest risk for this are patients with high HbA_{1c} levels, hypertension, nephropathy, and active nonproliferative or proliferative retinopathy. Laser therapy of preexisting retinopathy is recommended before conception, as well as for pregnant patients with severe disease.[71-73] Patients with known proliferative retinopathy should be counseled to avoid excessive, aggressive Valsalva maneuvers during labor to minimize the risk of retinal hemorrhages.[70]

Autonomic neuropathy does not accelerate during pregnancy, with the exception of a possible increase in symptomatic severity of gastroparesis.

DKA occurs in up to 9% of diabetic patients during pregnancy and may be the initial presentation of diabetes. DKA is usually seen in patients with IDDM but also complicates pregnancies in women with NIDDM and GDM. Common precipitating events include the typical factors seen in nonpregnant patients, such as insulin noncompliance and infection. Other pregnancy-specific factors are increased insulin resistance, hyperemesis, use of beta-mimetic medications for tocolysis, and use of corticosteroids to hasten fetal lung maturity. The serum pH may be deceptively normal in a pregnant patient with DKA because the initial pH tends to be higher in pregnancy as a result of physiologic hyperventilation. In addition, the serum glucose concentration may be normal or only moderately elevated. Therefore, screening for DKA is indicated in gravid diabetics with nausea, vomiting, malaise, or headache or in those with persistent hyperglycemia. Maternal mortality is rare in those with appropriately treated DKA. Fetal mortality rates are relatively high, ranging from 10% to 35%.[74]

Fetal Complications

Diabetes has many deleterious effects on the fetus (see Table 179.1). The risk of congenital anomalies in infants of diabetic mothers (IDMs) is as high as 10%.[74] The rate of congenital malformations in patients with prepregnancy diabetes is increased threefold or fourfold compared with the nondiabetic population, with anomalies being more likely in pregnant women with poor glycemic control.[69,74,75] Macrosomia is the most likely factor leading to the need for cesarean section and has been associated with shoulder dystocia. Conversely, preeclampsia and placental infarction secondary to vascular disease may result in impaired fetal development and stillbirth.[76] Diabetic patients are also at increased risk of spontaneous preterm delivery and labor-induced preterm deliveries.[76] Neonatal complications seen at increased rates in IDMs include transient tachypnea of the newborn, neonatal hypoglycemia, hypocalcemia in the peripartum period, hyperbilirubinemia, polycythemia, cardiomyopathy, and respiratory distress as a result of fetal hyperinsulinemia.

Management

Early management of diabetes in pregnancy in the ED requires the careful management of hyperglycemia or hypoglycemia because congenital abnormalities can occur in the first trimester. Treatment of NIDDM and IDDM requires individualized and carefully adjusted insulin administration, with the goal of maintaining strict glycemic control while avoiding hypoglycemia.

Treatment of DKA in pregnancy generally follows the same principles as those in nonpregnant patients, except that fluid resuscitation and insulin therapy should be maintained in the presence of normoglycemia until bicarbonate levels return to normal, indicating that any lagging acidemia has cleared. Fetal viability and well-being should be assessed in all cases of maternal DKA.

The timing and mode of delivery depend on whether obstetric or maternal complications exist. In the absence of suspected problems, vaginal delivery at term is recommended. Elective delivery is indicated in the setting of poor metabolic control, significant diabetic complications, and fetal macrosomia with suspected birth weight more than 4500 g.[75]

OBESITY

It is well documented that the incidence of obesity is increasing.[77] Obesity has been found to be an independent risk factor for poor predictors of pregnancy outcome, even without the comorbid conditions of diabetes, vascular disease, or hypertension.[78] Maternal risks include an increased incidence of gestational weight gain and increased risk of postterm delivery, preeclampsia, and inadequate contraction patterns in labor, leading to failure to progress. This is thought to be caused by an independent influence of obesity on myometrial activity.[79] The increased risk of undergoing

cesarean section is 3.2-fold of that seen in the nonobese population,[80] and postsurgical complications of hematoma, seroma, abscess formation, and wound dehiscence all increase in obese postpartum, cesarean section mothers.[81] Meta-analysis has shown obesity to be an independent risk factor for infant death and neonatal asthma; this risk is proportional to increased body mass index (BMI).[82] Obesity has not been associated with increased rates of shoulder dystocia, congenital malformations, or low 5-minute Apgar scores, however.[78,80] The BMI does not appear to be correlated with postpartum hemorrhage requiring intervention, severe maternal morbidity or maternal mortality, or spontaneous preterm delivery before 32 weeks of gestation.[78]

THYROID DISORDERS

The peak incidence of thyroid disease is in women of childbearing age. Hypoactivity and hyperactivity of the thyroid gland lead to obstetric complications and warrant specific therapy.

Hyperthyroidism

The most common cause of hyperthyroidism is Graves' disease, in which autoimmune thyroid-stimulating immunoglobulin results in increased production and release of thyroid hormone. Because the symptoms of hyperthyroidism resemble the physiologic changes expected during pregnancy in many respects, the diagnosis may not be immediately evident. Patients with Graves' disease have disease-specific findings, including a diffusely enlarged, soft, mildly tender thyroid gland, exophthalmos, and dermopathy. Other symptoms, such as dyspnea, heat intolerance, hyperemesis, tachycardia, palpitations, systolic flow murmurs, increased appetite, and fatigue, are common to both conditions. Therefore, clinically differentiating Graves' disease from non–Graves'-associated hyperthyroidism can be difficult. In cases of suspected hyperthyroidism, thyroid function studies and antibody assays are indicated and will confirm the presence of disease.

There are several obstetric concerns for the mother and fetus in the setting of untreated clinical hyperthyroidism (see Table 179.3). Thyroid storm is the most serious manifestation of the disease. It may be precipitated by stressors such as infection and delivery; it is manifested by fever, dysrhythmias, myocardial dysfunction, and circulatory collapse. The most helpful differentiating symptoms between thyrotoxicosis and thyroid storm is markedly altered mental status in the presence of thyroid storm. Untreated, mortality approaches 100%, but prompt recognition and aggressive therapy have lowered mortality to 20% to 30%.[83] In addition to the more general complications stemming from thyroid hormone excess, early (spontaneous abortion) and late (stillbirth) fetal loss are more common in hyperthyroid patients than in the general population.[84] Graves' disease places the fetus at risk for autoimmune-mediated thyroid dysfunction through placental transfer of maternal thyroid-stimulating immunoglobulins. Up to 20% of neonates of mothers with Graves' disease and positive thyroid-stimulating immunoglobulin values have transient hyperthyroidism lasting 3 to 12 weeks.[85] The condition gradually clears as maternal antibodies are metabolized. Manifestations are potentially severe and include irritability, tachycardia, goiter, cardiomegaly, congestive heart failure, premature craniosynostosis, low birth weight, and failure to thrive.[86]

The mainstay of treatment of hyperthyroidism (see Table 179.3) consists of antithyroid drugs. Propylthiouracil has been recommended as being preferred to methimazole because of an increased potential for adverse congenital drug effects from methimazole.[87] Most patients respond to pharmacologic manipulation, although thyroidectomy may be considered in severe cases in which patients cannot tolerate antithyroid medication or in the setting of medication failure. Use of iodine-131 radionuclide to ablate the maternal thyroid is contraindicated because it will also destroy the fetal thyroid gland.

Additional therapy with beta blockade to mitigate the hemodynamic effects of sympathetic stimulation may be required in certain cases pending adequate disease control with antithyroid medications. Iodide is considered class D in pregnancy because of fetal thyroid sensitivity to the medication; its use should be reserved for severe cases, with duration of therapy limited to days. As with other autoimmune conditions, transient improvement of Graves' disease during pregnancy is common, with rebound and clinical deterioration occurring in most patients after delivery.

Hypothyroidism

The most common cause of hypothyroidism worldwide is iodide deficiency. In iodine-replete areas, the most common cause is post autoimmune thyroiditis, such as Hashimoto's thyroiditis. Overt hypothyroidism is often associated with infertility, so most cases seen during pregnancy are less severe. Subclinical disease forms can also be seen or may occur in patients already undergoing levothyroxine therapy for known disease. Undiagnosed subclinical hypothyroidism may become clinically apparent as the metabolic demands of pregnancy unmask deficient thyroid hormone levels. When signs and symptoms do occur, they are generally the same as those in the nonpregnant state. Myxedema coma is extremely rare but should be considered along with other causes of coma in a pregnant patient. As with hyperthyroidism, there is an increased incidence of adverse maternal and fetal effects in women with clinical hypothyroidism (see Table 179.3).[88]

Most patients who are already undergoing treatment for hypothyroidism will require an increased dosage of levothyroxine during pregnancy, especially during the first trimester, in which average increases are from 20% to 30%.[89] Approximately 3% to 5% of women of childbearing age have subclinical hypothyroidism, as defined by an elevated thyroid-stimulating hormone (TSH) level and normal thyroxine (T_4) level. It has been noted that clinical and subclinical hypothyroidism result in adverse perinatal outcomes and adverse neurologic outcomes for affected infants. Compared with euthyroid status, subclinical hypothyroid pregnancy is associated with higher rates of gestational hypertension, premature rupture of membranes, intrauterine growth restriction (IUGR), and low-birth-weight infants.[90]

SYSTEMIC INFECTIONS

Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

Human immunodeficiency virus (HIV) infection is one of the leading health problems in pregnancy. In 2008, 25% of reported cases of HIV infection and acquired immunodeficiency syndrome (AIDS) in the United States were in women, with a significant percentage being in women of childbearing age.[91] Estimates of the seroprevalence of HIV infection in pregnant women vary on a regional basis. In the United States, the overall prevalence and number of perinatally infected infants are low but also vary according to the population, with increased rates seen in the southern states and in black and Hispanic populations.[91] Worldwide, vertical transmission of HIV remains a significant problem.

The mechanism of vertical transmission is multifactorial. Most cases are thought to occur during delivery through exposure to maternal blood and secretions; other infants are likely to be infected in utero or through breast-feeding. Various factors influence the rate of transmission. The most important is maternal viral load, although infection can occur even with a low maternal viral load.[92,93] Other contributing factors for transmission include inadequate prenatal care, vaginal infections, injection drug use,

premature delivery, low birth weight, and prolonged rupture of membranes.[92-94] Vertical transmission of HIV in the United States and other developed countries has declined significantly since its peak in the early 1990s because of the implementation of a number of interventions, including routine voluntary testing, highly active antiretroviral therapy (HAART), use of elective cesarean section, and avoidance of breast-feeding. However, vertical transmission remains a concern in women without adequate prenatal care and is a global concern. It is estimated that perinatal infection occurs in approximately 20% of deliveries if the mother is untreated, whereas the interventions noted have reduced this rate to less than 1%. Because of this beneficial effect, it is recommended that all pregnant women undergo screening for HIV. Rapid HIV screening is recommended for women in labor whose HIV status is unknown.[92,95]

Treatment of the pregnant patient with HIV infection includes appropriate HAART and standard therapy for opportunistic infections (see Table 179.3).[96,97] There are limited data on specific therapy for opportunistic infections during pregnancy, but the emergency clinician should take into account the fact that medication clearance may be affected by various pregnancy-related changes, including increased renal clearance, dilutional anemia, and fetal metabolism of medications.[98]

Optimal therapy to prevent vertical transmission includes three stages—antepartum administration of HAART, intrapartum intravenous zidovudine dosing, and treatment of the infant with 4 to 6 weeks of zidovudine.[92,99] The specific HAART regimen to follow depends on a number of variables. In patients who are already taking HAART with good disease control (viral load <1000 copies/mL) at the time of pregnancy diagnosis, the current medication regimen should be continued. Efavirenz (EFV) has teratogenic risks, with neural tube defect abnormalities prior to 6 weeks' gestation, so HIV-positive women planning to become pregnant should have this regimen changed. If a woman previously on EFV becomes pregnant, current recommendations are to continue the therapy, because most pregnancies are not diagnosed prior to 6 weeks, when the potential teratogenic effects of the medication have already been sustained.[92] Women who have never received any form of antiretroviral therapy are started on a standard multidrug HAART regimen that avoids the use of EFV in the first trimester. Delayed initiation of HAART until the second trimester may be considered in women if the only goal of therapy is to prevent mother to child transmission (maternal viral load < 1000 copies/mL).[92,99] In HIV-infected mothers without prenatal care, intrapartum HAART followed by postexposure zidovudine treatment of the infant reduces the likelihood of infection but is less effective than the recommended three-stage regimen.[92,100] Elective cesarean section is recommended in mothers with a viral load greater than 1000 copies/mL.[92] It is reasonable to present cesarean delivery as an option for patients with lower viral loads, although the benefit for these lower risk mothers is uncertain, and the risk of mother to child transmission by vaginal delivery is very low when mothers have received effective HAART.[92,101]

Whereas breast-feeding is associated with mother to child transmission of HIV infection and is not recommended in urban areas with access to formula preparations, it remains the preferred mode of feeding in resource-poor areas where formula use is not possible. WHO now encourages breast-feeding exclusively in women when adequate and safe formula feeding is not possible.[102]

The preferred means of diagnosis of perinatal HIV infection is by the use of assays to detect viral RNA or DNA. Two negative viral assays, with at least one after 4 months of age, means that the infant can be labeled seronegative. In addition, two negative tests after 6 months of age, with the absence of other clinical symptoms or suggestive laboratory findings, can be used to rule out infant disease. Infants with AIDS typically present with recurrent bacterial infections, *Pneumocystis* pneumonia, encephalopathy, extrapulmonary tuberculosis, and generalized wasting.

The effects of pregnancy in women with symptomatic HIV infection include an increased incidence of infant mortality, prematurity, stillbirth, and low birth weight, delivery by cesarean section, and gestational diabetes.[103-105] Seropositive mothers who undergo cesarean delivery generally have an uncomplicated postoperative course, although some studies have noted a slightly increased risk of postpartum endometritis and other maternal infections, with the highest rate of infection seen in women who have low CD4+ cell counts.[106] It is also important to consider the effect of HAART on pregnancy outcomes. Overall, however, most antiretroviral medications are considered safe in this regard. Several large studies have noted no increase in adverse outcomes in women taking HAART,[107] with the possible exception of preterm delivery, although this remains controversial.[108-110]

In the absence of retroviral therapy, HIV disease progression during pregnancy is moderate, and the risk of HIV negative outcomes increases. When HAART is used in pregnancy, there appears to be no increased risk of disease progression.[111]

Tuberculosis

It is estimated that tuberculosis (TB) complicates in excess of 200,000 pregnancies worldwide annually.[112] Most of these occur in Africa. The acquisition and presentation of TB are unchanged during pregnancy, but the effect of TB on pregnancy is unclear. Preconception, active genital TB disease increases the risk of an ectopic pregnancy.[113] Accurate assessment of the risk of maternal and neonatal morbidity has been difficult to ascertain,[114] but there seems to be consensus that complications are more likely in patients with inadequate or delayed diagnosis and treatment and in those with extrapulmonary (extranodal) tuberculosis. Delayed diagnosis is common in pregnancy because TB symptoms are atypical during gestation.[115,116] This is an even greater challenge in those patients co-infected with HIV who will likely fail WHO screening guidelines on surveillance for pulmonary TB (16% vs. >90% compared to nonpregnant women).[117] Neonatal tuberculosis acquired by exposure to undiagnosed and untreated active disease places infants at significant risk for acquiring tuberculosis during the first year of life, with significant mortality. In addition, congenital tuberculosis is possible after the fetus becomes infected through the placenta or via aspiration of infected amniotic fluid. The latter is rare if the mother has received appropriate therapy.

Definitive treatment is indicated in all pregnant patients with confirmed tuberculosis as well as in those high-risk women with suspected disease (see Table 179.3). Moderate to severe anemia, particularly in HIV-positive mothers, has a strong association with undiagnosed TB and should prompt screening.[118] Isoniazid, ethambutol, and rifampin in their usual doses have not been shown to be teratogenic to human fetuses and are acceptable during pregnancy and breast-feeding. Standardized, second-line treatment for multidrug resistant TB appears to be safe in pregnancy.[119]

Syphilis

The incidence of primary and secondary syphilis among US reproductive age women has steadily increased since the late 1990s, when there were hopes of eradicating the disease. Significant differences in ethnic distribution of the disease have been noted, with current rates of 4.5/100,000 in African Americans, 2.5/100,000 in Hispanics, and 1.0/100,000 in whites.[91] Unfortunately, the incidence of congenital syphilis has shown a similar increase from 2005 to 2008, with a current rate of 8.2/100,000 live births.[120]

Syphilis causes numerous gestational complications (see Table 179.3), but its most significant sequela is congenital syphilis. This syndrome is characterized by hepatosplenomegaly, osteochondritis, jaundice, rash, lymphadenopathy, rhinitis, Hutchinson's teeth, and anemia. Infant mortality for cases within the last decade was 6.5%.[120] Fetal ultrasonography before the 20th week of gestation is indicated to assess for abnormalities consistent with congenital syphilis.[71,72,95] Sonographic signs of fetal syphilis confer a higher risk of congenital syphilis at delivery, and few of these completely regress after sufficient treatment.[72]

Treatment is identical to that given to nonpregnant patients, with the use of benzathine penicillin G appropriate for the disease stage[71] (see Table 179.3). Penicillin-allergic patients are sometimes treated with macrolides. However, it is preferable that these patients undergo skin testing and desensitization if the skin test result is positive because alternative therapies are not reliably effective in preventing congenital syphilis.[95] Treatment failures are rare with appropriately administered penicillin, but do occur. Failures leading to congenital syphilis are more likely in mothers with secondary syphilis, high Venereal Disease Research Laboratory or rapid plasma reagin test levels, and an interval from treatment to delivery of less than 30 days.[95]

Viral Hepatitis

Hepatitis B

There are 43,000 new cases of Hepatitis B reported annually in the United States, but this is likely an underestimation of disease burden, given the absence of symptoms in early infection.[121] From 800,000 to 1.4 million people in the United States have chronic hepatitis B. The prevalence of hepatitis B virus (HBV) infection among pregnant women varies by the population studied, with the highest rates seen in Asians and women of African descent.[122] Perinatal transmission is approximately 10% to 20% in women seropositive for HBV surface antigen (HBsAg) alone but approaches 90% in mothers who are seropositive for HBsAg and HBV envelope antigen (HBeAg); it is also more likely if the mother has acute infection during the third trimester. Of infants who have HBV infection, up to 90% become chronic carriers as adults and are at risk for complications such as cirrhosis and hepatocellular carcinoma.

Studies have suggested that lamivudine given in late pregnancy to women with high viral loads of HBV DNA reduces viral transmission when given in conjunction with HBV vaccine and immune globulin.[123] Infants of HBsAg-positive mothers should receive hepatitis B immune globulin and the first dose of vaccine within 12 hours of birth. Two additional doses of vaccine are administered at a later date.[73]

Hepatitis C

The worldwide prevalence of hepatitis C virus (HCV) infection in pregnant women is estimated to be between 1% and 8%.[124] As with HBV, the prevalence of hepatitis C virus (HCV) infection among pregnant women varies by geographic location and ethnic subculture within a population, ranging from less than 1% to approximately 4%, with white mothers having higher infection rates than black or Hispanic mothers. Vertical transmission is rare in mothers with anti-HCV antibodies and no circulating HCV RNA. However, perinatal transmission is significantly increased by the presence of HCV viremia, occurring in approximately 4% to 6% of cases. The transmission rate is even higher in the setting of co-infection with HIV; the rates of HCV co-infectivity with HIV are about 10-fold higher than that seen in non–HIV-infected mothers. Perinatal transmission is now the leading cause of HCV transmission to children in developed countries. Cesarean delivery has not been shown to prevent HCV transmission.[95,125] There is no available vaccine or immune globulin to prevent hepatitis C, and routine prenatal screening is not indicated.[95,125]

INFLAMMATORY DISORDERS

Rheumatic diseases or collagen vascular diseases are characterized by sterile inflammation in multiple anatomic sites. The most common rheumatic diseases encountered in pregnancy are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Gravid patients with collagen vascular disease may have preexisting cardiovascular or renal compromise and may not tolerate the increased intravascular volume and other physiologic changes that occur during pregnancy.

Systemic Lupus Erythematosus

SLE primarily affects women of reproductive age, but fertility is usually unaffected. The disease course during pregnancy varies, but studies have indicated that acute flares occur in less than one-third of patients in clinical remission at the time of conception.[126-128] Disease activity tends to involve the skin and musculoskeletal system, although renal involvement is not uncommon, especially in patients with active lupus nephritis.[129,130] The gestational effects of SLE also depend on the underlying severity of disease. Patients with active disease at pregnancy onset with symptoms of hypertension, thrombocytopenia and, especially those with preexisting lupus nephritis, have a higher incidence of disease flares and pregnancy complications.[126,128,130,131] Many patients have acceptable outcomes, but lupus pregnancies are associated with an increased maternal mortality and increased rate of other complications, including preterm delivery, thrombocytopenia, anemia, intrauterine growth retardation, fetal loss, and need for cesarean section.[126,132]

The risk of preeclampsia is increased up to 14% in lupus-related pregnancies; initiation of low-dose aspirin therapy prior to 16 weeks' gestation decreases the risk of preeclampsia.[133] The development of preeclampsia in women with a history of SLE seems to have a predictive association with subclinical coronary vascular disease.[134] This should prompt consideration of less exertional delivery methods as well as drive postpartum medical decision making to evaluate for coronary artery disease.

Other comorbid conditions that adversely affect pregnancy, such as diabetes and thrombophilia, are also seen more commonly in SLE patients. The risk of preeclampsia is especially increased in those with active lupus nephritis.[128,130] As with other renal disease, increasing proteinuria warrants a careful evaluation to distinguish between lupus glomerulonephritis and preeclampsia. The presence of abnormal urine sediment, increasing titers of anti-DNA antibody, and decreasing levels of C3 and C4 suggest lupus nephritis.

Neurologic disease in SLE may be manifested as psychosis, seizures, chorea, or peripheral neuropathy. The incidence of these complications is low during pregnancy, although the occurrence of seizures in late pregnancy in patients with coexistent hypertension and renal insufficiency may pose a diagnostic dilemma between the neurologic effects of SLE and signs of eclampsia. Elevated levels of lupus anticoagulant and antiphospholipid antibodies have emerged as markers of disease activity and are good predictors for adverse pregnancy outcomes.[135]

Rheumatoid Arthritis

RA is characterized by chronic, destructive, symmetric joint inflammation. Less common manifestations include the development of subcutaneous nodules, neuropathy, pleuropericarditis, and vasculitis. Systemic symptoms, including weight loss,

lymphadenopathy, and fatigue, are common. Because the median age at onset is later with RA, this disorder is seen less frequently than SLE in the pregnant population. Immune tolerance mechanisms are upregulated in pregnancy to decrease fetal rejection. In rheumatic diseases, this typically results in disease improvement, which has been estimated to occur in approximately two-thirds of patients with RA.

Patients with RA tend to have good pregnancy outcomes in the setting of well-controlled disease. Women with active disease are more likely to have small-for-gestational-age infants, possibly as a result of underlying vasculopathy and associated effects on the placenta.

Treatment

Corticosteroids are the mainstay of therapy for most rheumatologic complications or exacerbations. Aspirin has been advocated for all lupus-related pregnancies of more than 16 weeks' gestational age, and other NSAID regimens remain useful treatments for inflammatory flares. A full discussion on fetal teratogenicity and fetal complications of these agents can be found in Chapter 180.

Second-line therapy for rheumatic diseases can include cytotoxic agents such as cyclophosphamide and methotrexate. These are both potent teratogens and abortifacients and should be avoided, especially in the first trimester. Azathioprine is a cytotoxic agent that appears to be much better tolerated in pregnancy.[135,136]

PSYCHIATRIC DISORDERS

Eating Disorders

The peak incidence of eating disorders matches that of those in the prime childbearing age range, so the likelihood of anorexia nervosa (AN) or bulimia nervosa (BN) complicating a pregnancy is high. The overall prevalence of AN is 0.5% to 1% of young adult women, with a mean age of onset of 17 years, and an overall prevalence of BN of 1% to 3% in the same population.[137] Of all eating disorders, 90% begin before the age 25 years, and there has historically been an increased incidence of all eating disorder diagnoses in the past decade. The high incidence of amenorrhea in AN makes pregnancy less likely than in BN. Medical complications of AN include bradycardia, hypotension, orthostatic changes, hypothermia, mitral valve prolapse, and symptoms associated with electrolyte imbalance. Anemia and transaminitis are also seen.

Pregnancy can frequently precipitate a subclinical eating disorder or exacerbate a condition in remission. The loss of control of body image and weight gain are frequent inciting features for recurrence. Adverse pregnancy outcomes include increased rates of miscarriage, low birth weight, preterm birth, congenital malformations, and increased likelihood of cesarean section births.[138] Inappropriate dieting, with subsequent folate deficiency, increases the rate of congenital neural tube defects. In the postpartum period, depression risk is increased threefold in mothers with a history of eating disorders.

Treatment of any eating disorder during pregnancy is aimed at the restoration of normal physiologic parameters, electrolyte replacement, and correction of ketosis. There are no recommended pharmacologic interventions for AN by the US Food and Drug Administration, but antidepressant therapy may be beneficial in those with exacerbations of BN.[139]

Substance Abuse

The prevalence of substance abuse in pregnancy has been increasing, with major societal and personal costs. Substance abuse is frequently not identified during pregnancy unless self-reported, or an unplanned pregnancy is discovered during the evaluation of the mother for a substance-related disorder. This is particularly common in the ED, where women of childbearing age are seen frequently for associated complications and pregnancy is coincidentally identified during the visit.

The overall rate of substance use and abuse in pregnancy is approximately 15%. The rate has been steadily increasing in the last 3 decades, with roughly 225,000 infants annually exposed to illicit drugs in utero.[140] Drug use and dependence afflict women, regardless of socioeconomic status, ethnicity, or age. Although illicit drug use is more common in African Americans, alcohol, cannabis, and prescriptive drug use are most commonly seen in white women.

The impact of substance abuse on pregnancy is determined by the following: (1) specific exposure (mono- vs. polysubstance abuse); (2) gestational timing; (3) duration of exposure; (4) dosing of exposure; and (5) other maternal comorbid conditions (eg, smoking, general nutritional status). There is a strong association of substance abuse with psychiatric conditions, particularly depression and psychosis.

Within this context, the terms *abuse* and *dependence* will be used synonymously, although they are different clinical entities. Both conditions have the same impact on maternal and neonatal health and pregnancy-related complications.

Alcohol

Of women of childbearing age, 51% self-identify as alcohol users and 15% are binge drinkers.[141] Nearly 2 million women annually are at risk for alcohol-exposed pregnancies, defined as women who are not using birth control, currently drinking, and are sexually active with a man.[142] Once pregnancy has been identified, the rate of active alcohol consumption in gravid women drops to 7%, and binge drinking to lower than 2%.[143]

There is no clear safe threshold for alcohol intake during pregnancy, with intake as little as one drink/day being associated with increased rates of IUGR and low birth weight. Heavier consumption of alcohol at more than three drinks/day increases the rate of miscarriage, and more than five drinks/day significantly increases the risk of intrauterine fetal demise (IUFD) two to three times that of nondrinking mothers. Alcohol consumption in pregnancy is the most preventable cause of mental retardation, with alcohol-exposed children having a 1.7-fold greater relative risk of mental retardation and a 2.5 times greater risk of delinquent behaviors.

Congenital abnormalities associated with in utero alcohol exposure can be characterized within the fetal alcohol spectrum disorders. Fetal alcohol syndrome, the most severe of these, has a prevalence of up to 1/1000 births.[143] It is characterized by at least one of a series of morphologic abnormalities in association with a history of heavy alcohol use (>three drinks/day), including midfacial hypoplasia, flat philtrum, low nasal bridge, epicanthal folds, shortened palpebral fissure, low-set ears, and microcephaly. It can also have ocular, cardiac, and skeletal manifestations.

Screening is imperative to identify at-risk pregnancies, and the most successful screening tools assume the presence of alcohol intake. This approach yields more honest reporting from the patient.[144]

Treatment of an alcohol-dependent mother is difficult. As with nonpregnant patients, withdrawal symptoms are likely to manifest 6 to 24 hours after last alcohol consumption. Any signs of withdrawal should prompt admission and continued management in an inpatient setting. There is a paucity of data on the risk of delirium tremens and major withdrawal in pregnant versus the nonpregnant population. There are also little data on the safety profiles of medications used to ameliorate withdrawal

symptoms.[145] The use of naltrexone, acamprosate, or disulfiram or the long-term use of benzodiazepines has not been studied in pregnancy.

Smoking

The long-term deleterious effects of smoking on fetal growth and development have been well documented, up to and including the risk of sudden infant death syndrome (SIDS).[146] Chronic placental insufficiency and vasoconstriction lead to an increased risk of miscarriage, IUFD, preterm birth, IUGR, and clubfoot.[147] Conversely, smoking decreases the risk of preeclampsia.[148]

Treatment for tobacco addiction in pregnancy is largely behavioral and cognitive. Nicotine patches have not been associated with adverse maternal or newborn consequences when used in the second and third trimesters.

Cannabis

Cannabis is the most commonly used illicit drug in pregnancy.[149] Although marijuana use in pregnancy is not associated with any major congenital malformations or increased risk of IUFD, infants born to cannabis-using mothers show increased tremulousness, exaggerated startle responses, and high-pitched cries. These are some of the same features associated with neonatal abstinence syndrome (NAS) discussed later in more detail (see "Opioids"). Cannabis is excreted in breast milk and has been associated with neurologic impairment during continued exposure.[149]

Cocaine and Methamphetamines

Maternal cocaine and methamphetamine use is independently linked to IUGR from impaired placental circulation and preterm birth (PTB) less than 36 weeks' gestation, preeclampsia, IUFD, and increased incidence of cesarean section, gestational hypertension, and GDM.[149,150] Cocaine use also increases the risk of placental abruption and infarction. Infants of methamphetamine- addicted mothers have lower Apgar scores and increased rates of neonatal mortality and jaundice.[150] The potential for adverse outcomes is increased in the presence of polysubstance abuse or other confounding maternal risks, such as poor nutrition. Neonatal congenital abnormalities do not seem to be significantly increased with cocaine use, although there is a slight increased risk of cleft palate with cocaine exposure.

Treatment of a gravid patient who is acutely intoxicated with cocaine or methamphetamine should involve the judicious use of benzodiazepines and antipsychotics, weighing the risk-benefit ratio for treatment against the medical and psychiatric instability of the patient. Methamphetamine is excreted in breast milk, so infant exposure continues after pregnancy.[150]

Opioids

Roughly 1% of pregnant patients report opioid use during pregnancy, but drug testing proves this number to be higher, around 4%. In general, usage rates have been significantly increasing,[151,152] which has created a downstream effect of large numbers of addicted infants requiring neonatal intensive care. There is a significant risk of unintended pregnancy among opioid-addicted women, close to 90%, compared to the unintended pregnancy rate in the general population of 40%.[153] The ED is a likely site of entrance of the opioid-addicted gravid patient to the health care system.

There are no well-identified syndromes, congenital abnormalities, or teratogenic effects in infants of opioid-dependent mothers, but maternal risks of postpartum hemorrhage, PTB, and increased rates of cesarean section have been documented.[154] Neonatal risks include IUGR, specifically symmetric smallness and small head circumference,[155] and an increased risk of SIDS.[156] The major complication in infants of opioid-addicted mothers is NAS, a constellation of physiologic and neurobehavioral changes noted in newborns of addicted mothers secondary to a sudden discontinuation of fetal exposure to abused substances. There has been a 10-fold increase in NAS within the last decade.[157] These infants have a 97% admission rate to neonatal intensive care units.

The syndrome is characterized by the following: (1) CNS disturbances, including excessive or continuous high- pitched crying, shortened postprandial sleep pattern, hyperactive newborn reflexes, tremulousness, and increased muscle tone, myoclonic jerks, or frank convulsions; (2) metabolic and respiratory abnormalities (eg, sweating, hyperthermia, yawning, mottling, sneezing, nasal flaring, tachypnea); and (3) gastrointestinal disturbances (eg, increased sucking, poor feeding, regurgitation or projectile vomiting, loose or watery stools). The Finnegan scale, developed in the 1970s, is still the mainstay of neonatal assessment for NAS. Treatment of NAS is supportive.

KEY CONCEPTS

- The physiologic demands of pregnancy may cause previously occult medical conditions to become apparent and known problems to deteriorate rapidly.
- The physiologic adjustments of pregnancy alter the normal ranges for certain laboratory values. The adjusted values need to be considered in the interpretation of results.
- The possibility of pregnancy should be considered in the differential diagnosis of certain conditions, including new-onset seizures or status epilepticus (eclampsia), glucose intolerance (GDM), persistent vomiting (hyperemesis gravidarum), and thyroid disorders.
- The immunosuppressive effects of pregnancy may cause temporary improvement in inflammatory and autoimmune conditions. This beneficial effect is lost in the postpartum period, resulting in exacerbations of asthma, thyroid disorders, and myasthenia gravis.
- Medication requirements can change drastically during pregnancy and the postpartum period.
- Certain medical conditions in the mother result in neonatal complications that require special resuscitative measures. This is particularly true of many chemical dependency states, and anticipatory management of these patients is essential.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 179: QUESTIONS & ANSWERS

179.1. A 28-year-old G2P1 at 26 weeks of gestation presents with a recurrent asthma flare. Vital signs are temperature, 36°C, heart rate, 110 beats/min, blood pressure, 120/60 mm Hg, respiratory rate, 28 breaths/min, and O_2 saturation, 96%. She has diffuse expiratory wheezes. Arterial blood gas reveals Po_2 = 90 mm Hg, Pco_2 = 40 mm Hg, and pH = 7.34. Which of the following statements best describes the issues in management with this patient?

A. Corticosteroids are contraindicated.
B. Inhaled β-agonists are first-line therapy.
C. Most patients with asthma improve during pregnancy.
D. She has a metabolic acidosis.
E. Treatment and discharge are likely.

Answer: B. β-Agonists followed by corticosteroids are the mainstay of asthma therapy during pregnancy. During pregnancy, one-third of asthmatics worsen, one-third improve, and one-third stay the same. Blood gas interpretation must take into account the so-called normal alkemia of pregnancy, with a Pco_2 of 30 to 32 mm Hg and a compensatory HCO_3 level of 18 to 20 mEq/L. This patient has a relative hypoventilation and may indeed need admission for close observation.

179.2. Which of the following statements best describes treatment for hypertension in pregnancy?

A. Angiotensin-converting enzyme inhibitors are second-line agents.
B. Diuretics are contraindicated in the third trimester.
C. Hydralazine is a useful venodilator.
D. Labetalol is a first-line oral agent.
E. Sodium nitroprusside is the parenteral agent of choice.

Answer: D. First-line oral and parenteral agents are hydralazine and labetalol. The former is an arterial dilator. Most antihypertensives are useful in pregnancy; angiotensin-converting enzyme inhibitors and receptor blockers are the exception. Diuretics are second-line agents. Nitroprusside is a second-line agent due to concerns for fetal cyanide toxicity.

179.3. Which of the following statements best describes risk factors for acute myocardial infarction (AMI) and pregnancy?

A. Anemia is not a risk factor.
B. Gestational diabetes does not increase risk.
C. Hypotension is an important risk factor.
D. Maternal age is inversely associated with risk.
E. Maternal smoking increases the risk.

Answer: E. Maternal smoking increases the risk. AMI is rare but may occur. Up to 29% of cases have normal coronaries one their angiogram. Risk factors are anemia, diabetes, hypertension, old age, thrombophilia, and smoking. Atherosclerotic lesions are the more likely cause antepartum, whereas coronary dissection and vasospasm are more likely causes postpartum.

179.4. Which of the following statements best describes issues in the evaluation of diabetes mellitus in pregnancy?

A. Diabetic ketoacidosis (DKA) in pregnancy always presents with hyperglycemia and a low pH.
B. Patients with gestational diabetes usually require medical therapy to achieve adequate glycemic control.
C. Standard management of non–insulin-dependent diabetes in pregnancy is with continued use of oral medications.
D. The American Congress of Obstetricians and Gynecologists recommends universal screening for gestational diabetes.
E. The risk of malformations and pregnancy complications is significantly increased in patients with insulin-dependent disease as opposed to those with pregravid, non–insulin-dependent diabetes.

Answer: D. The American Congress of Obstetricians and Gynecologists recommends universal screening for pregnant women to achieve prompt diagnosis and minimize related complications. Insulin-dependent diabetes mellitus (IDDM) and non–insulin-dependent diabetes mellitus (NIDDM) place the gravida at increased risk for poor pregnancy outcomes, with the risk being related to inadequate glycemic control. Although patients with

IDDM and NIDDM are typically managed with insulin during pregnancy, patients with gestational diabetes often achieve adequate control of their blood glucose level with diet alone. DKA is a potential complication of all forms of diabetes during pregnancy and may present with euglycemia and a minimal change in pH.

179.5. Which of the following statements best describes issues in the management of the pregnant patient with human immunodeficiency virus (HIV)?

A. Antiretroviral therapy is not appropriate in the first trimester of pregnancy with the exception of efavirenz, which is contraindicated.

B. Elective cesarean section is not indicated for all gravidas with HIV and a viral load greater than 1000 copies/mL.

C. Postnatal zidovudine therapy in the infant is necessary when the mother has received appropriate antepartum and intrapartum antiretroviral therapy and has a viral load less than 1000 copies/mL.

D. The risk of perinatal transmission of HIV is high in the setting of routine screening, intrapartum antiretroviral therapy, and elective cesarean section for patients with a viral load greater than 1000 copies/mL.

Answer C. Recommended care for HIV during pregnancy includes intrapartum antiretroviral therapy, postnatal zidovudine prophylaxis, standard treatment for opportunistic infections, and cesarean section for all patients with a viral load greater than 1000 copies/mL. It is appropriate to begin antiretroviral therapy during the first trimester, although it is recommended that these patients be managed by an infectious disease specialist. Postnatal zidovudine is recommended for all infants born to mothers with HIV.

CHAPTER 180

Drug Therapy in Pregnancy

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PRINCIPLES

Background

More than 90% of women take at least one prescription or over-the-counter medication during pregnancy, and overall medication use during pregnancy has increased in the last 3 decades.[1-3] One study revealed that only 22% of reproductive-aged women have pregnancy testing done when administered or prescribed US Food and Drug Administration (FDA) category D or X medications in the emergency department (ED).[4] Unfortunately, research in the use of medications in pregnancy is currently insufficient to determine reliable and accurate risks to the mother and fetus. Only a few medications have been tested specifically for safety and efficacy during pregnancy and current methods to assess teratogenicity are limited in determining drug safety especially for newer agents. Prescribing medications during pregnancy is challenging and must account for the physiologic changes associated with pregnancy as well as the benefits and risks to the mother and to the developing fetus using all available data.

The fetal age at exposure is crucial in determining its impact on the pregnancy. The fetus is most vulnerable to toxic insults during the time of organogenesis (days 21–56 of fetal life). Exposure during this period may result in major anatomic defects. Exposure after the period of organogenesis may affect the growth and development of the fetus. Functional development of the central nervous system (CNS) is affected when it is exposed to a CNS teratogen during the 10th to 17th weeks of pregnancy.[5]

Major birth defects affect 3% to 5% of all live births. Most are of unknown cause, but 1% to 3% of these are thought to be due to pharmaceutical or environmental agents. A teratogen is any chemical, pharmacologic, environmental, or mechanical agent that can cause disruptive development of the conceptus. Included in this definition are functional impairment, growth restriction, and congenital malformations. These may range from subtle neurobehavioral effects to devastating physiologic effects and physical deformities, including fetal death.[5]

The process of establishing teratogenicity is tedious and often flawed. Animal research, although valuable in determining risk initially, is not always applicable to humans, and controlled prospective human studies are generally not performed for ethical reasons. As a result, much of our current knowledge on teratogenicity has been derived from less rigorous studies, which are inherently weak in establishing a causal relationship between a specific exposure and malformations. The genetic background of the fetus, timing and duration of the exposure, environmental factors, multiple exposures, nutritional deficits, maternal illness, and illicit drug use all contribute to the outcome of pregnancy. Large population studies are needed to understand the connection between the outcome of a pregnancy and in utero exposures. Finally, as in the case of diethylstilbestrol, teratogenicity may not be apparent for years after birth.

Classification of Teratogenic Risk

To aid physicians in determining the teratogenic potential of a particular medication, the US Food and Drug Administration (FDA) had assigned one of five letters—A, B, C, D and X—to the drug, depending on the strength of evidence for its safety or teratogenicity (Box 180.1). This classification system has been criticized as overly simplistic and perhaps inaccurate.[6] Many believed that the classification system conveyed the incorrect impression that there is a gradation of reproductive risk from exposure across categories (ie, that risk increases from A to B to C to D to X) and that the drugs within a given category present similar reproductive risks.[7] Efforts have been made to address these concerns and other significant gaps in knowledge.[8-11] More than 90% of newly introduced drugs in the United States are assigned to class C, an undetermined teratogenic risk. The FDA issued a final rule for drug labeling during pregnancy, called the Pregnancy and Lactation Labeling Rule (PLLR), effective June 2015, to address these concerns. The PLLR changes the content and format for prescription drug labeling to help health care providers assess the benefits and risks in counseling pregnant and nursing women who are taking medications. The rule requires the removal of letter categories and mandates labeling that includes a summary of risks of drug use during pregnancy and lactation, a discussion of the data supporting that summary, and any relevant information to help health care providers make informed decisions and counsel patients. Drugs already approved before this rule will be phased in gradually.[12] Currently, a number of clinical teratology resources that assign risk are available online, such as Clinical Pharmacology, TERIS, and Micromedex REPRORISK (Shepard's *Catalog of Teratogenic Agents*).

Drug Transfer Across the Placenta

Drug transfer across the placenta usually occurs by simple passive diffusion or protein transport. A thin layer of trophoblastic cells is all that separates maternal from fetal circulation. The degree to which a drug gains access to fetal circulation depends on molecular size, ionic state, lipid solubility, and extent of protein binding. Drugs with a molecular mass of less than 5 kDa readily diffuse. Anionic substances diffuse through the lipid layer more readily than ionized forms. Free drug diffuses more readily than a protein-bound drug. Because fetal pH is slightly more alkalotic than maternal pH, weak organic acids may become ion-trapped in the fetal circulation, increasing fetal exposure.

Drug Transfer During Lactation

Generally, drugs that are ingested or injected by the mother diffuse passively into milk and then back into the maternal circulation for excretion.[13,14] The amount of drug diffusing into milk depends on many factors. Lipid-soluble and nonionic substances diffuse more readily, and highly protein-bound substances diffuse less

BOX 180.1

US Food and Drug Administration Classification for Teratogenic Risk of Drugs

Class A: Controlled studies have shown no risk. Adequate well-controlled studies in pregnant women have failed to show risk to fetus.
Class B: No evidence exists of risk for humans. Animal studies show risk or are negative, but no human studies have been done.
Class C: Use may engender risk for fetus. Human studies are lacking, and animal studies may be positive or lacking. Potential for benefit may outweigh potential for harm.
Class D: Positive evidence of risk is based on studies or postmarketing data. Potential for benefit may outweigh potential for harm.
Class X: Drugs are contraindicated in pregnancy on the basis of human or animal studies or postmarketing reports that indicate benefit is clearly outweighed by risk.

readily. Whether a substance is concentrated in maternal milk or not, the neonate generally is able to detoxify it with no adverse effects, and only a few drugs pose a serious danger to a breast-feeding infant.[15] The interruption of breast-feeding should not be advocated except in rare situations of known drug toxicity to the infant and in all cases of maternal critical illness.

Drug Therapy During Pregnancy

In general, the health of the fetus is directly related to the health of the mother. Physicians should not withhold lifesaving medications from pregnant patients because of a reported risk to the fetus and should resuscitate pregnant patients according to advanced life support guidelines. Physicians may also prescribe any agent when the maternal benefits outweigh the risks to the fetus. Included in this category are therapeutic medications for asthma, arrhythmias, status epilepticus, life-threatening overdoses, and human immunodeficiency virus (HIV) infection. When prescribing drugs to pregnant and lactating women, one must weigh the benefits of treatment against the inherent risks of treatment or disease, consider the pharmacokinetics of the drug during pregnancy and lactation, choose the drug with the lowest known toxicity, and use the lowest effective dose.

PHARMACOLOGIC THERAPY

Analgesic Agents

Over-the-counter analgesics are used commonly during pregnancy, with acetaminophen being used by at least two-thirds of pregnant women.[1,2,16] New evidence has been emerging that calls for a reassessment of the safety of these medications in pregnancy.[15] Several studies have reported increasing use and adverse pregnancy outcomes with opioid use, such as neonatal abstinence syndrome and birth defects (Table 180.1).[17-23]

Acetaminophen

Acetaminophen (paracetamol) is widely used during pregnancy and has not been associated with congenital malformations.[15,24-26] In a population-based, case-control study, acetaminophen was associated with a decreased risk of certain craniofacial malformations when it was used for febrile illnesses in the first trimester. Maternal acetaminophen use has recently been associated with a higher risk for hyperkinetic disorders and attention-deficit hyperactivity disorder–like behaviors in children, possible increased risk of cryptorchidism with early gestational exposure, and increased risk of childhood asthma with exposure in the first trimester.[27-42] Acetaminophen is safe during lactation.[15]

Nonsteroidal Antiinflammatory Drugs

Prostaglandin synthesis inhibitors, such as nonsteroidal antiinflammatory drugs (NSAIDs), taken in the first trimester, have been linked to an increased risk of spontaneous abortions and a slight increase in cardiac septal defects, oral clefts, and gastroschisis (an abdominal wall defect).[15,24,26,43,44] When used in the third trimester, NSAIDs inhibit labor and have been used as tocolytic agents for premature labor. When used in the latter part of pregnancy, NSAIDs have been linked to a number of negative effects on the neonate, most notably premature closure of the ductus arteriosus, leading to neonatal pulmonary hypertension, and death. Recent studies have shown a potential association of exposure during pregnancy with an increased risk of asthma.[35,45,46] An increased incidence of fetal periventricular hemorrhages, fetal nephrotoxicity, oligohydramnios, and neonatal gastrointestinal (GI) hemorrhage has also been reported.[15,24,47] Use in the latter part of pregnancy is therefore discouraged. NSAIDs in general appear to be safe during lactation.

Aspirin

Chronic or high doses of aspirin during pregnancy should be avoided and may affect maternal and newborn hemostasis, leading to increased perinatal morbidity and mortality.[15,44] Aspirin use may increase the risk of gastroschisis in the first trimester, intrauterine growth retardation (IUGR), and fetal and maternal hemorrhage in the third trimester. Aspirin use has been associated with postmaturity, prolonged labor, neonatal hypoglycemia, neonatal metabolic acidosis, premature closure of the ductus arteriosus causing primary pulmonary hypertension in the newborn, and neonatal death.[15,24] Low doses of aspirin may be beneficial in pregnancies complicated by systemic lupus erythematosus with antiphospholipid antibodies and those at risk for gestational hypertension and preeclampsia, as well as fetuses with IUGR. Aspirin is excreted into breast milk and its use is discouraged during breast-feeding.[15]

Opiate Analgesics

In general, short-term, episodic use of opiates such as oxycodone, hydrocodone, morphine, and fentanyl appears to be safe in pregnancy. Their use near term, however, may result in severe respiratory depression of the neonate. In addition, prescribing of narcotics for long periods can lead to fetal addiction, low birth weight, and neonatal abstinence syndrome.[21,24,44,48,49] Neonatal abstinence syndrome is characterized by CNS hyperirritability, autonomic nervous system dysfunction, and higher infant mortality.[7,4,50,51]

The short-term use of opiates during lactation appears to be safe, but nursing infants should be closely monitored for respiratory depression.[15]

Rapid Sequence Intubation Agents

Data regarding the use of these agents during pregnancy is limited and has primarily been obtained from animal studies and retrospective human data. None of the agents has been consistently associated with congenital malformations.[7,15] The effects of nondepolarizing neuromuscular blocking agents on organogenesis in humans are not known, but are not thought to pose a significant teratogenic risk because very little of the maternal dose crosses the placenta (Table 180.2).[15,24]

TABLE 180.1

Analgesic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Acetaminophen	B most formulations C in parental (IV) route	Compatible, excreted in breast milk	CP, NHT; increased risk of attention-deficit/hyperactivity-hyperkinetic disorder, cryptorchidism with first- and second-trimester use, childhood asthma with first-trimester use
Ibuprofen	C in first and second trimesters D in third trimester	Compatible, excreted in breast milk	CP, association with structural cardiac and other defects; risk in third trimester of premature closure of ductus arteriosus and subsequent primary pulmonary hypertension; potential increased risk of asthma with use in pregnancy
Aspirin	C in first and second trimesters D in third trimester	Potential toxicity	CP; avoid chronic or high doses in pregnancy; high doses may increase perinatal mortality, teratogenic effects; increased risk of gastroschisis in first trimester; increased risk of IUGR and fetal and maternal hemorrhage in third trimester; risk in third trimester of premature closure of ductus arteriosus and subsequent primary pulmonary hypertension; near-term use may prolong gestation, labor
Codeine	C	Potential toxicity Use with caution Excreted in breast milk, metabolized to morphine	LHS; first-trimester exposure and congenital defects have been described; some association with preterm and poor fetal outcomes; avoid prolonged use or high doses near term; may develop respiratory depression and/or withdrawal symptoms, neonatal abstinence syndrome
Oxycodone	B	Potential toxicity Use with caution Potential for SAR	LHS; use during organogenesis associated with low absolute risk of congenital birth defects; may result in preterm birth, poor fetal outcomes, NOWS
Morphine	C	Potential toxicity Usually compatible for short-term use Use with caution	CP; use during organogenesis associated with low risk of CBD; may result in preterm birth and poor fetal outcomes; prolonged maternal use during pregnancy may result in NOWS

CBD, Congenital birth defects; *CP,* crosses placenta; *FDA,* US Food and Drug Administration; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity; *NOWS,* neonatal opioid withdrawal syndrome; *SAR,* serious adverse reactions.

Anticoagulants

Low-molecular-weight-heparin (LMWH) is preferred over unfractionated heparin and warfarin when indicated in pregnancy for therapeutic and prophylactic anticoagulation. Warfarin has the highest teratogenicity of the anticoagulants. The heparins, as a class, do not cross the placenta. All three anticoagulants are considered compatible with breast-feeding. Early reports on the use of heparin for the prevention or treatment of venous thromboembolism during pregnancy have noted an increased risk of prematurity, stillbirth, and fetal hemorrhage. However, these risks were recently attributed to the underlying maternal condition, rather than to heparin (Table 180.3).[24,25,27,28,52-54]

Thrombolytic Agents

Alteplase, reteplase, urokinase, and streptokinase have been used successfully in pregnant women in cases of life-threatening pulmonary embolus, myocardial infarction, ischemic stroke, thrombosis of cardiac valve prosthesis, and deep venous thrombosis.[52-61] Complication rates when used for these indications were similar compared to nonpregnant patients, and none of the live-born children had permanent defects. Experience with these agents during pregnancy, however, remains limited. To date, no teratogenic effects have been reported in humans, but intrapartum maternal hemorrhage has been reported with alteplase and urokinase.[24,25] Most thrombolytics are thought to be compatible with breast-feeding (Table 180.4).[15,24]

Antidotes

There are limited human data on the risks of antidote use during pregnancy. Generally, antidotes should be used when there is a clear maternal indication to reduce the morbidity and mortality from the poisoning (Table 180.5).

N-Acetylcysteine

N-Acetylcysteine has been used successfully and without untoward effects in pregnant women who have overdosed on acetaminophen. No teratogenic effects have been reported, and pregnant patients who overdose on acetaminophen should be treated the same as nonpregnant patients.[15,24,25] It is most likely safe during lactation because it has been used in neonates without untoward effects.

Deferoxamine

Deferoxamine has been associated with developmental effects on ossification in some animal species. Experience in humans is

TABLE 180.2

Rapid Sequence Intubation Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Fentanyl	C	Compatible; may cause sedation or respiratory depression	CP; associated with congenital birth defects; may cause neonatal respiratory depression, transient neonatal muscular rigidity, NOWS
Etomidate	C	Probably compatible	CP; animal studies suggest risk of embryonic, fetal death but no teratogenicity; transient decrease in newborn cortisol levels of unknown clinical significance; LHS not harmful when used as induction agent
Propofol		Probably compatible, but not recommended	CP; animal studies show no malformations, LHS with no data on use in first and second trimesters; use at term appears to be safe, but high doses may be associated with neonatal CNS, respiratory depression
Thiopental	C	Probably compatible; use with caution	CP; LHS; animal studies show no congenital defects, even with high doses; may cause respiratory depression
Ketamine	Not classified; LHS; low risk	Probably compatible; plasma levels undetectable after 12 hr	CP; used frequently in obstetrics, not associated with fetal developmental malformations; dose-dependent oxytocic effect; in high doses (>2 mg/kg), associated with uterine tetany; may increase maternal blood pressure and heart rate; may increase neonatal muscle tone or cause apnea and depression of the newborn, SAR usually dose-related
Midazolam	D	Use with caution Avoid with other CNS depressants	CP; animal studies show no congenital effects, even with high doses; LHS, human observational studies show no malformations, no data on use in first and second trimesters; use near term has resulted in adverse neonatal neurobehavior, respiratory depression
Succinylcholine	C	Probably compatible because of rapid hydrolysis	Not embryotoxic or teratogenic in animals; may result in neonatal apnea and partial or complete newborn paralysis in neonates with pseudocholinesterase deficiency
Rocuronium	C	Probably compatible; LHS	CP; LHS; animal data suggest low risk; newborn neuromuscular blockade is potential complication but probably rare, may have prolonged blockade when used with magnesium
Vecuronium	C	Probably compatible	CP; LHS; use late in gestation appear to carry little if any risk to the newborn; use lower doses if administering magnesium sulfate

CNS, Central nervous system; CP, crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies; *NHT,* no human teratogenicity; *NOWS,* neonatal opioid withdrawal syndrome; *SAR,* serious adverse reactions.
Additional data adapted from ref. 103.

limited, but it does not appear to affect the fetus. The effects of deferoxamine on the nursing infant are not known, but are probably compatible.[15,24]

Digoxin Immune Fragment

There are very few case reports of the use of digoxin immune fragment (Fab) during pregnancy, so effects on the fetus are inconclusive. In cases of life-threatening digitalis overdose with arrhythmias, the benefits of treatment of the mother outweigh the risk to the fetus. Fab is probably safe for use during lactation.[15,24]

Dimercaprol

Dimercaprol, or British antilewisite, is teratogenic in mice and has been associated with increased mortality, growth restriction, cleft facial features, cerebral herniation, and abnormal digits, but experience in humans is limited. In general, with heavy metal poisonings, the maternal benefits of treatment will outweigh the potential risks to the fetus. Breast-feeding is contraindicated in patients poisoned by heavy metals.[15,24]

Flumazenil

No teratogenic effects have been reported with flumazenil in animals, and there is limited human data. Its use in pregnancy and lactation depends on the potential maternal benefit compared with possible risks to the fetus and nursing infant. Because it has a short half-life, breast-feeding may resume after a few hours.[15,24]

Fomepizole

Fomepizole use during pregnancy has not been studied in animals or humans. Its safety during pregnancy is not known. In cases of

TABLE 180.3

Anticoagulant Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Warfarin	X	Compatible; however, caution advised when breast-feeding premature infants due to increased risk for intraventricular hemorrhage	CP; known dose-dependent teratogen affecting 4%–5% of exposed fetuses; greatest risk at gestational wk 6–9; fetal warfarin syndrome associated with corpus callosum agenesis, hypoplasia of nasal bones, midline dysplasia, optic atrophy and blindness; also associated with fetal osteogenesis, CNS malformations, fetal intraventricular hemorrhage, stillbirths, spontaneous abortions, abnormal development of bones, stippled epiphyses; school-age children exposed in utero had increased incidence of mild neurologic dysfunction
Heparin (UFH)	C	Compatible	DNCP; associated with maternal osteopenia, immune-mediated thrombocytopenia, maternal hemorrhage at delivery, requiring careful monitoring; has reduced bioavailability, shorter half-life, lower peak plasma concentrations during pregnancy; risk of antepartum bleeding ~1%
Low-molecular-weight heparin	B	Compatible	DNCP; lower risk of osteoporosis than UFH has reduced bioavailability, shorter half-life, lower peak plasma concentrations during pregnancy; lower rate of bleeding, HIT, lower allergic response versus heparin; recommended over UFH for VTE

CP, Crosses placenta; *DNCP,* does not cross placenta; *HIT,* heparin-induced thrombocytopenia; *UFH,* unfractionated heparin; *VTE,* venous thromboembolism.
Additional data adapted from refs. 104–107.

TABLE 180.4

Thrombolytic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Alteplase	C	Compatible Unknown if excreted in breast milk	Embryocidal, not teratogenic, in animal studies; LHS; use if benefits to mother outweigh risks; risk of hemorrhage at any time in gestation
Anistreplase, streptokinase	C	Use with caution; unknown safety	Use with caution; streptokinase (component of anistreplase) CP in minimal amounts; no fetal abnormalities reported; antistreptokinase antibodies cross the placenta
Reteplase	C	Probably compatible Use with caution Unknown if crosses into breast milk	Unknown if CP; risk for bleeding during labor and delivery; abortifacient, but no teratogenicity in animals; LHS; one report of use at 30 wk without sequelae
Tenecteplase	C	Hold breast-feeding Unknown safety	Unknown if CP; use with caution, safety unknown; risk of bleeding during labor and delivery; toxicity to mother in animal studies; LHS
Urokinase	B	Probably compatible Unknown if excreted in breast milk	Probably acceptable in pregnancy; not fetotoxic or teratogenic in animal studies; unknown if CP; placental hemorrhage and separation may occur; increased risk of bleeding during pregnancy; LHS

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.

toxic alcohol poisoning, the benefits of treatment of the mother outweigh the possible risks to the fetus or nursing infant. Use of ethyl alcohol in these situations may be considered.[15,24] Breast-feeding is not expected to continue during acute toxic alcohol poisoning.

Hydroxycobalamin

The effects of hydroxycobalamin on human pregnancy have not been studied, but benefits of its use in cyanide poisoning outweigh any risk to the fetus. Studies in animals do not reveal an association with any developmental abnormality. Breast-feeding is not expected to continue during cyanide poisoning but hydroxycobalamin, like its related compounds, is considered compatible with breast-feeding.[15,24]

Methylene Blue

Historically, methylene blue was injected into the amniotic sac to identify twins and detect rupture of the membranes, but these practices were associated with hemolytic disease in the newborn, hyperbilirubinemia, and deep blue staining of the newborn. Methylene blue in pregnancy has also been associated with an increased incidence of intestinal obstruction and atresia in the newborn. The effects of methylene blue on the nursing infant are expected to be minimal.[15,24]

TABLE 180.5

Antidotes

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
N-Acetylcysteine	B	Probably compatible unknown if excreted in milk so consider waiting 30 hr for elimination	CP; not teratogenic or embryotoxic in animal studies; LHS; no adverse fetal outcome when administered IV as antidote in acetaminophen overdose
Deferoxamine	C	Probably compatible Unknown if excreted in breast milk	LHS; no adverse toxic or teratogenic effects seen; animal studies show toxicity and teratogenicity (delayed ossification, skeletal anomalies)
Digoxin immune fragment	C	Probably compatible Unknown if excreted in breast milk	Unknown if CP; LHS; no adverse outcomes in fetus or newborn
Dimercaprol	C	Contraindicated Unknown if excreted in breast milk	Animal studies show teratogenicity; safety in pregnancy unknown; LHS
Flumazenil	C	Probably compatible Unknown if excreted in breast milk	Unknown if CP, but may occur; animal studies show no teratogenicity or impaired fertility; LHS
Fomepizole	C	Hold breast-feeding	No animal or human studies; safety unknown
Hydroxocobalamin	C	Probably compatible, but monitoring of infant recommended	Limited animal and human studies; safety unknown
Methylene blue	X	Probably compatible Unknown if excreted in breast milk	Epidemiologic evidence of teratogenicity; diagnostic intraamniotic injection resulted in hemolytic anemia, hyperbilirubinemia, methemoglobinemia, jejunal-ileal atresias
Naloxone	B	Probably compatible Unknown if excreted in breast milk LHS	CP; animal studies show no teratogenicity, no adverse fetal outcomes in human studies
Physostigmine	C	Probably compatible but safety unknown	Rarely used in pregnancy; no reports linking it with teratogenicity; safety unknown
Pralidoxime	C	Hold breast-feeding for 6 to 7 hr after dose	Rarely used in pregnancy; safety unknown; limited human case reports, with no adverse outcomes
Pyridoxine	A	Compatible	High doses appear to pose little risk to the fetus; no increased risk of malformations in first trimester in human trials
Succimer	C	Contraindicated Heavy metals may be excreted in breast milk, cause harm to newborn	Teratogenic and fetotoxic in animals; avoidance in first trimester recommended for pregnant women unless severe symptoms; LHS

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.
Additional data adapted from refs. 108–110.

Naloxone

Naloxone readily crosses the placenta. Although it has not been associated with reproductive abnormalities, its use during pregnancy results in increased fetal wakefulness, increased fetal movement, and increased heart rate, effects attributable to the antagonism of fetal endorphins. In addition, its use in opiate-addicted mothers may precipitate withdrawal in mother and term fetus. It is compatible with breast-feeding.[15,24]

Physostigmine

Experience during pregnancy is limited, and its effects on the developing fetus are unknown. Use of physostigmine at term has been associated with only mild decreases in Apgar scores at 1 and 5 minutes.[15,24,62] Physostigmine is thought to be probably compatible with breast-feeding.

Pralidoxime

Experience with pralidoxime in pregnancy is limited, and its effects on fetal development are not known.[15,62-64] In cases of organophosphate poisoning, the benefits to the mother generally outweigh the possible risk to the fetus. Breast-feeding can be resumed after 6 to 7 hours after the last dose.[24]

Pyridoxine

Pyridoxine has not been associated with any adverse developmental effects when given in high doses, and it is safe in lactation.[15,24]

Succimer

Succimer has been linked to congenital defects in animal models, possibly because of its negative effects on zinc and copper metabolism. Experience with the use of succimer in human pregnancy is limited to case reports, and adverse effects are unknown. Breast-feeding is contraindicated in heavy metal poisoning.[15,24]

Antiinfective Agents

Infections during pregnancy have the potential to affect outcomes as well as fetal development adversely. In the first trimester,

infections are a common cause of spontaneous abortion and, in the second or third trimester, they are the most common cause of preterm labor and delivery. Antimicrobial agents may also adversely affect the pregnancy. Aminoglycosides, for example, may be nephrotoxic and ototoxic to the mother and newborn, tetracyclines may result in dental staining of the developing fetus, and lincosamides may be skeletotoxic.[15,24] The penicillins, cephalosporins, and macrolide antibiotics remain the drugs of choice for infections during pregnancy. Alternative classes of antibiotics are prescribed only if these have failed to control the infection or in cases of severe maternal intolerance to these drugs. The choice of antimicrobial therapy will depend on the gestational age of the pregnancy, severity of infection, and maternal tolerance for the drug used. Many drugs are secreted into breast milk. Potential problems for the neonate include direct effects on the neonate, changes in bowel flora, diarrhea, and potential interference with culture results (Table 180.6).

Antibiotics

Aminoglycosides

The association of aminoglycosides such as gentamicin, streptomycin, tobramycin, and neomycin with nephrotoxicity and ototoxicity is well known in the literature and in practice.[15,24] Aminoglycosides, however, do not appear to have any structural teratogenic effect in humans, but kanamycin and streptomycin have been reported to cause ototoxicity in the mother and her offspring. There are no reports definitively linking in utero exposure to gentamicin, streptomycin, tobramycin, and neomycin with ototoxicity or nephrotoxicity.[1,27] Aminoglycosides are probably compatible with breast-feeding.

Cephalosporins

The first- to fourth-generation cephalosporins appear to be safe during pregnancy, although there have been no controlled studies examining their safety.[15,24] Some cephalosporins are excreted into breast milk and may interfere with culture results in the evaluation of neonatal sepsis.

Chloramphenicol. Chloramphenicol has been associated with bone marrow suppression and aplastic anemia, which may be fatal. Apart from these complications, its use during pregnancy appears to have no effects on the developing fetus. However, it is contraindicated at birth because chloramphenicol has been associated with cardiovascular collapse in the neonate, the so-called gray baby syndrome.[15,24] The safety of chloramphenicol during breast-feeding is unknown. It is secreted into the breast milk, however and, because of its potential for bone marrow suppression and its association with gray baby syndrome, it is not recommended for use during lactation.

Clindamycin. Clindamycin has not been associated with birth defects in humans or in animal studies. The American Academy of Pediatrics (AAP) considers clindamycin to be compatible with breast-feeding, although there is a rare association with bloody diarrhea in nursing infants.[15,24]

Fluoroquinolones. Fluoroquinolones have been linked to numerous toxic effects on bone and cartilage growth in animal models and are discouraged from use during pregnancy, particularly during the first trimester. A number of observational studies, however, have failed to demonstrate such a toxic effect on the human fetus. Furthermore, a meta-analysis did not reveal any increase in the rates of spontaneous abortions, birth defects, prematurity, or low birth weight in women exposed to fluoroquinolones in the first trimester. The AAP considers ciprofloxacin to be compatible with breast-feeding.[15,24] Data are inconsistent for other quinolones, and they are best avoided in lactation.

Linezolid. Linezolid has been linked to embryonic death, decreased weight, and abnormalities in cartilage and ossification in animal studies, but human data are lacking. Its use in pregnant women should be limited to cases in which the maternal benefits outweigh possible risks to the fetus.[15,24] Linezolid is likely compatible with breast-feeding.[27]

Macrolides. Erythromycin, azithromycin, and clarithromycin are considered safe for use in pregnancy and compatible with breast-feeding, although there are no well-controlled studies examining their effects on the fetus. Some reports have linked erythromycin to pyloric stenosis, but the studies were not controlled.[15,24] The estolate salt of erythromycin has also been associated with the development of hepatotoxicity in pregnant women and should be avoided. Clarithromycin has been associated with an increased risk of fetal and embryonic death, as well as with congenital malformations in animal species. This has not been shown in humans. In a prospective, controlled, multicenter observational study comparing the outcomes of pregnancies exposed to new macrolides (including clarithromycin) with matched controls, no difference in the types or patterns of malformations between the groups was found. Azithromycin is poorly concentrated in breast milk and may be the preferred agent in lactating mothers.

Metronidazole. Metronidazole is mutagenic and carcinogenic in mice and rats. In humans, a number of studies have failed to demonstrate a clear association between metronidazole and congenital malformations when used in the first trimester of pregnancy. Metronidazole has been used during the second and third trimesters to treat bacterial vaginosis, with no untoward effects. However, because of its effects in mice, many physicians avoid prescribing it at all during pregnancy. The use of metronidazole during lactation is discouraged because of its potential mutagenic and carcinogenic effects in rats and its slow elimination from infants.[15,24]

Nitrofurantoin. Nitrofurantoin has traditionally been considered safe for use throughout pregnancy, except near term. However, a population-based, multicenter, retrospective case-control study associated its use in the first trimester to a number of congenital abnormalities. This association with congenital abnormalities has been refuted, however, and there are no confirmatory studies that show teratogenicity. Its use near term has been associated with hemolytic anemia in the newborn.[15,24]

Penicillins. The first- to fourth-generation penicillins and their derivatives (including procaine, benzathine, clavulanate, sulbactam, and tazobactam) are considered safe for use in pregnancy, as is oral probenecid.[15,24,] Penicillins are considered safe during breast-feeding, but their use may interfere with culture results if evaluation is required for a neonatal fever.

Sulfonamides. Sulfamethoxazole is commonly combined with trimethoprim and has traditionally been contraindicated in pregnancy because of an increased risk of neural tube defects and other congenital abnormalities, such as cleft palate. A number of observational studies have demonstrated an increased risk of cardiovascular and urinary tract malformations in the offspring of women treated with trimethoprim-sulfamethoxazole in the first trimester. Sulfonamides are contraindicated near term because of their association with kernicterus; they are excreted in

TABLE 180.6

Antiinfective Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Aminoglycosides	D; human data suggest risk	Probably compatible Excreted in breast milk Oral absorption poor	No definable structural risk of any aminoglycoside when exposed in utero; streptomycin—low incidence of ototoxicity with careful dosing
CEPHALOSPORINS			
• First generation	B	Compatible	CP; NHT (most studies); conflicting studies on risk of congenital defects in first trimester
• Second generation	B	Compatible	CP; immune hemolytic reactions observed, especially with cefotetan
• Third generation	B	Compatible	CP; immune hemolytic reactions observed
• Fourth generation	B	Compatible	CP; LHS
Chloramphenicol	Use with caution Unknown risk Likely compatible	Potential toxicity (LHS) Excreted in breast milk	CP; may cause grey baby syndrome; idiosyncratic bone marrow suppression
Clindamycin	B	Compatible Excreted in breast milk	CP; no reports of fetal toxicity or malformations
Fluoroquinolones	C	Compatible Excreted in breast milk	Ciprofloxacin, ofloxacin, and levofloxacin CP; few reports of arthrotoxicity; risk of major malformations low; caution use during first trimester, risk of cardiac defects
Linezolid	C	Potential toxicity (LHS) Excreted in breast milk	No studies in pregnancy Use with caution
Macrolides	B	Compatible Excreted in low concentrations in breast milk	Estolate salt—may induce hepatotoxicity in pregnant patients; no risk of congenital heart malformations or pyloric stenosis, but use of erythromycin in infancy associated with pyloric stenosis
Metronidazole	B	Compatible Excreted in breast milk—but AAP recommends cessation of breast-feeding during use	CP; in vitro mutagen; NHT
Nitrofurantoin	B	Compatible	Caution advised with G6PD deficiency—may cause hemolytic anemia; limit use in later pregnancy
Penicillins	B	Compatible Small amount excreted in breast milk	CP; long-standing safety data
Sulfonamides	D	Compatible Excreted in breast milk Caution in newborns, infants with known G6PD deficiency	CP; adverse effects rare; most reports fail to demonstrate congenital malformations; concern for jaundice, hemolytic anemia, kernicterus; trimethoprim is folate antagonist—use with caution
Tetracyclines	D	Compatible Excreted in breast milk	CP; doxycycline poses little teratogenic risk; adverse effects on fetal bone development; discoloration of adult teeth; oxytetracycline shows neural tube defects, cleft palate, cardiac defects
Vancomycin	B (oral) C in parenteral (IV) route	Compatible IV form found in breast milk, but, no oral absorption	No toxicity or teratogenicity found
ANTIFUNGAL AGENTS			
Clotrimazole	B (Vaginal and topical) C (oral lozenge)	Compatible	Systemic absorption from skin minimal; NHT; avoid vaginal use during first trimester; some reports suggest increased risk of spontaneous abortions
Fluconazole	C (vaginal) D (other indications)	Compatible	High dose in first trimester associated with malformations
Ketoconazole	C	Compatible Excreted in breast milk	NHT, but teratogenicity seen in animal studies

TABLE 180.6

Antiinfective Medications—cont'd

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Nystatin	A (vaginal) C (other preparations)	Compatible Not excreted in breast milk	Poorly absorbed systemically; often first-line therapy in pregnancy
Terbinafine	B	Potential toxicity Excreted in breast milk	LHS
ANTITUBERCULOUS AGENTS			
Isoniazid	C; maternal benefit outweighs fetal risk	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risks; NHT
Ethambutol	B	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risks; no adverse effects seen
Rifampin	C	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risk; hemorrhagic disease of newborn
ANTIHERPETIC AGENTS			
Acyclovir	B	Compatible Excreted in breast milk	CP—found in higher concentrations than in maternal blood; systemic use should be avoided unless benefits outweigh the risks; NHT
Valacyclovir	B	Compatible Excreted in breast milk	CP; LHS
Famciclovir	B; LHS suggest caution	Potential toxicity	Unknown if crosses placenta or enters breast milk; LHS
ANTIINFLUENZA AGENTS			
Amantadine	C	Potential toxicity (LHS) Excreted in breast milk	CP; teratogenicity in animals; associated with cardiac malformations.
Oseltamivir	C	Compatible Excreted in breast milk but in low concentration	Benefits of treatment during gestation likely greatly outweigh risks; no congenital malformations identified

AAP, American Academy of Pediatrics; *CP,* crosses placenta; *FDA,* US Food and Drug Administration; *G6PD,* Glucose-6-phosphate dehydrogenase; *LHS,* limited human studies; *LS,* limited studies; *NHT,* no human teratogenicity,
Additional data adapted from refs. 111 and 112.

breast milk and generally tolerated by a healthy neonate.[11,12,15,24] They should be avoided, however, in ill or premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency.

Tetracyclines. Tetracycline and doxycycline readily cross the placenta. Tetracycline has been associated with the development of fatal fatty liver in pregnant women. It chelates calcium, causing abnormalities in bone growth and staining of decidual teeth. It has been associated with fetal genitourinary anomalies, inguinal hernias, and limb abnormalities. Tetracycline should therefore be avoided during pregnancy. Doxycycline, conversely, does not bind to calcium and is associated less with stained teeth than tetracycline. In addition, it does not appear to cause an increase in any type of congenital malformation. Despite these findings, doxycycline is not recommended in pregnancy.[15,24]

Because tetracycline binds to breast milk calcium, only a small amount reaches the nursing infant, and it may be used for short periods (<10 days) during breast-feeding. Doxycycline does not bind to breast milk calcium and is present in greater quantities in breast milk. This could theoretically increase its side effects in the newborn. Its use in nursing infants is best avoided.[15,24]

Vancomycin. Vancomycin has not been linked to birth defects in animals or in humans. Reports of auditory abnormalities and renal insufficiency in neonates of mothers treated with vancomycin are believed to be false-positives because these abnormalities were resolved on retesting. Vancomycin is excreted into milk but not well absorbed by the GI tract. Its effects on the nursing infant have not been studied.[15,24]

Antifungals

Nystatin has a long safety profile during pregnancy and lactation. It is poorly absorbed from skin, mucous membranes, and the GI tract and is considered the antifungal agent of first choice for the treatment of mucocutaneous fungal infections. Clotrimazole, miconazole, and ketoconazole appear to be safe during pregnancy and lactation because they have not been associated with major birth defects. However, a minor increase in the incidence of hypoplastic left ventricle was reported in one case-control study. In addition, ketoconazole is teratogenic in rats. For these reasons, clotrimazole, miconazole, and ketoconazole are considered second-line treatment of fungal infections in pregnancy. Fluconazole is teratogenic in high doses (>400 mg/day) and has been associated with an increased incidence of craniofacial and cardiovascular defects in offspring and multiple abnormalities of the skeleton and cartilage. However, these anomalies were not noted when lower doses were used or with single-dose therapy (150 mg) for vaginal candidiasis.[15,24]

Ketoconazole, fluconazole, and itraconazole are excreted into breast milk. Because of the safe use of ketoconazole in neonates and the lack of negative reports, it is considered compatible with breast-feeding (see Table 180.6).[15,24,65]

Antituberculous Agents

Untreated tuberculosis places the mother and fetus at greater risk than the use of antituberculous medications. Isoniazid, ethambutol, and rifampin cross the placenta and, in a review of antituberculous treatment during pregnancy, no association was found between these medications and major congenital malformations. Rifampin has been associated with hemorrhagic disease of the newborn.[3] Despite this adverse effect, it is considered first-line therapy for the treatment of tuberculosis. All three antituberculous medications are considered compatible with breast-feeding (see Table 180.6).[15,24,65]

Antiviral Agents

Antiherpetic Drugs

Acyclovir readily crosses the placenta and reaches higher concentrations in fetal circulation than in maternal circulation. Neither acyclovir nor valacyclovir has been associated with congenital malformations or adverse effects on the offspring.[66] Intravenous (IV) acyclovir is the drug of choice for life-threatening maternal herpes simplex virus infections, such as disseminated disease, herpes encephalitis, and varicella pneumonia, which carries a maternal mortality of 44% if untreated.[67] For non–life-threatening genital herpes infection in pregnant women, acyclovir or valacyclovir may be used. Experience with famciclovir is limited and therefore is not recommended for use in pregnancy. Because there are no reported adverse outcomes in infants of mothers taking acyclovir or in infants treated with acyclovir for disseminated herpes, it is considered safe during breast-feeding (see Table 180.6).[15,24]

Antiinfluenza Drugs

Influenza in pregnancy carries a high risk of morbidity and mortality. During the 2009–2010 H1N1 pandemic, 6% of confirmed H1N1 deaths in the United States occurred in pregnant women.[68] Antiviral therapy with M2 ion channel inhibitors, such as amantadine and rimantadine, or neuraminidase inhibitors, such as oseltamivir and zanamivir, is associated with improved maternal and pregnancy outcomes.[69] Whereas amantadine had been linked to various malformations, including cardiac defects in humans, and is considered teratogenic and embryotoxic in rats, a cohort study found that neither class of antiinfluenza drugs was associated with an increase in malformations or stillbirths.[15] There was, however, an increase in the incidence of necrotizing colitis in premature newborns exposed to either of these classes of drugs. Oseltamivir appears safe in lactation. In addition to antiviral therapy, the Centers for Disease Control and Prevention (CDC) has also recommended that pregnant women receive the inactivated influenza vaccine at any point during pregnancy (see Table 180.6).[70]

Anti-HIV Drugs

No specific pattern of birth defects has been described with the use of anti-HIV drugs, but the drugs' mutagenesis and carcinogenesis and their long-term effects on the liver, heart, and reproductive system are yet to be determined.[15,24]

Animal and human data suggest that didanosine, lamivudine, stavudine, zidovudine, and zalcitabine present a small risk of structural malformations and mitochondrial dysfunction in the developing fetus, but no specific pattern of birth defects has been described with protease inhibitors, such as ritonavir and nelfinavir. Despite potential risks, it is thought that the benefit from HIV treatment far outweighs the risk of these drugs and should not be withheld. In addition, zidovudine has been shown to reduce vertical and perinatal transmission of HIV from the mother to the fetus significantly.[15,24,67] Because of the risk of postnatal HIV transmission through milk, the CDC advises against breast-feeding by HIV-positive mothers.

Cardiovascular Agents

Antidysrhythmics

Atrial and ventricular arrhythmias are common during pregnancy. Most are benign; however, malignant degeneration occasionally occurs. All unstable tachycardias should be treated with electrical cardioversion and advanced cardiac life support guidelines. Stable patients may be treated medically, but the choice of drugs needs to be modified to protect the patient as well as the fetus from the drug's harmful effects[71-73] (Table 180.7).

Adenosine. Adenosine has been used safely throughout pregnancy and is the drug of choice for termination of maternal supraventricular tachycardia. Adenosine has also been used safely for termination of incessant tachycardia in the fetus.[15,24,71-73] Adenosine is safe in lactation.

Amiodarone. Amiodarone is a class D agent containing large amounts of iodine and has been associated with congenital goiter and transient neonatal hyperthyroidism and hypothyroidism.[71-75] Amiodarone has been linked to many congenital abnormalities, including growth restriction, structural cardiac abnormalities, corneal deposits, and developmental delay. It should be used only in refractory cases of supraventricular or ventricular tachycardias in the mother and incessant tachycardias in the fetus.[6] Because of its high iodine content, excretion into milk, and long elimination half-life, amiodarone should not be used in nursing mothers.[15,24]

Digoxin and Quinidine. Digoxin and quinidine are considered safe for use during pregnancy and lactation. Neither has been linked to congenital defects in humans or animals, and they are first-line agents for the treatment of significant maternal dysrhythmias. They have also been successfully used in fetal tachycardia.[71,73] During lactation, digoxin appears compatible with breast-feeding; there is very little information about quinidine's use in breast-feeding.[15,24]

Lidocaine. Lidocaine rapidly crosses the placenta and becomes ion-trapped in the fetus. There is no evidence of a link between the use of lidocaine in the first trimester and any fetal developmental malformations. However, high doses used near term are associated with neonatal CNS depression, apnea, hypotonia, seizures, and bradycardia.[15,24,71,72] Lidocaine is considered compatible with breast-feeding.

Procainamide. Procainamide has been safely used in the treatment of stable, wide-complex tachydysrhythmias during pregnancy. It has not been associated with fetal developmental abnormalities and appears well tolerated when used for a short duration.[71-73] It has been associated with a high incidence of maternal antinuclear antibodies and the occurrence of a lupus-like reaction in humans. During lactation, procainamide and its metabolite, *N*-acetylprocainamide, have been found in breast milk and, although the AAP considers its short-term

TABLE 180.7

Antidysrhythmic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Adenosine	C	Compatible	Many reports show compatibility during pregnancy; LHS; effects on fetus unknown, but teratogenicity or malformations not expected
Amiodarone	D	Contraindicated excreted in breast milk Concern for hypothyroidism	CP; linked to many congenital abnormalities; thyroid abnormalities, congenital goiter have been observed; contains high concentration of iodine; use only in refractory tachydysrhythmias
Digoxin	C	Compatible excreted in breast milk	CP; NHT; one of the safest antiarrhythmics during pregnancy
Quinidine	C	Probably compatible (LHS) Excreted in breast milk	CP; no teratogenic effects in humans reported; LHS
Lidocaine	B	Compatible excreted in breast milk	CP; animal studies—no harm; high doses near term associated with neonatal CNS depression, hypotonia, seizures, bradycardia
Procainamide	C	Probably compatible (LHS) Excreted in breast milk	LHS
Flecainide	C	Compatible Concentrated in breast milk	LHS; animal data suggest possible teratogenicity
Ibutilide	C	Probably compatible (LHS)	Unknown if CP; animal studies show teratogenicity, embryocidal events
Sotalol	B	Potential toxicity (LHS) Concentrated in breast milk. Conflicting reports	CP; may cause fetal bradycardia and/or IUGR

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity.

use compatible with breast-feeding, other authorities do not recommend it.[15,24]

Flecainide. Flecainide has been used safely to terminate maternal and fetal tachycardia,[5] but it has been associated with fetal hyperbilirubinemia, hepatotoxicity, and loss of fetal heart rate variability. Flecainide has also been found to be teratogenic in some animal species, resulting in cardiac and musculoskeletal abnormalities.[15,24,71-73] The AAP considers flecainide compatible with breast-feeding, despite limited experience.

Ibutilide. There are only a few case reports of the successful and safe use of ibutilide during the latter part of pregnancy in humans.[71-73] In animals, however, ibutilide was found to be teratogenic and caused cardiac septal defects as well as skeletal dysgenesis in rats, especially when high doses were given. Ibutilide should be reserved for refractory cases in which the benefits of therapy outweigh any fetal risk.[15,24]

Sotalol. Sotalol has been used in pregnant women to treat atrial arrhythmias successfully and safely, as well as hypertension. It has also been successfully used to terminate fetal atrial tachycardias.[71-73] It does not appear to have teratogenic effects in animals. Some of the negative effects of sotalol include bradycardia in the newborn, persisting for 24 hours. Sotalol is concentrated in milk but does not appear to result in bradycardia or hypotension in the nursing infant and, according to the AAP, it is compatible with breast-feeding.[15,24]

Antihypertensives

Labetalol is the agent of choice for hypertensive emergencies in pregnancy (Table 180.8).

Angiotensin-Converting Enzyme Inhibitors. Angiotensin-converting enzyme (ACE) inhibitors, classified as category D drugs, are contraindicated for use during pregnancy.[74] Furthermore, ACE inhibitors are embryocidal in animals and increase the rate of stillbirths in some animal species. In humans, the most significant adverse fetal effects occur when used in the second and third trimesters.[75,76] These include oligohydramnios, anuria, renal agenesis resulting in death, increased risk of stillbirth, intrauterine growth restriction, fetal skull abnormalities, pulmonary hypoplasia, respiratory distress syndrome, and fetal and neonatal hypotension.[77] Captopril and enalapril are considered compatible with breast-feeding.[15,24]

Angiotensin II Receptor Antagonists. Angiotensin II receptor antagonists should be avoided during pregnancy because their use has been reported to result in fetal abnormalities similar to the abnormalities seen with ACE inhibitors, including renal agenesis, neonatal anuria, oligohydramnios, intrauterine growth restriction, persistent patent ductus arteriosus, abnormal ossification, and death.[15,24,75,76] Their safety in lactation is unknown.

Beta Blockers. Beta blockers have become a first-line treatment of hypertension in pregnancy. They have not been associated with fetal malformations and appear to be safe when used for short periods. Adverse fetal effects include intrauterine growth restriction and a low placental weight. Beta blockers lacking intrinsic sympathomimetic activity, such as acebutolol, atenolol, nadolol, and propranolol, are more likely to be associated with these adverse effects. When beta blockers are given near term, they have been associated with persistent beta blockade in the newborn. Nonselective beta blockers, such as propranolol, also have resulted in neonatal hypoglycemia, respiratory depression, and hyperbilirubinemia in the newborn. These adverse effects

TABLE 180.8

Antihypertensive Medications

DRUG(S)	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists	D	Probably compatible, but variable safety	Use in second and third trimesters may cause teratogenicity, severe fetal/neonatal toxicity; reduce fetal renal function; associated with anuria, PDA, IUGR, prematurity, abnormal bone, lung development, renal failure, death
Esmolol	C	Safety unknown Appears to be low risk	LHS; not thought to cause structural anomalies; may result in persistent beta blockade of fetus or newborn[a]
Labetalol	C	Probably compatible Low excretion in breast milk	LHS; little risk to fetus except possibly in first trimester; most studies found no effect on fetal growth; IUGR and RPW may occur if used near delivery; newborn should be monitored for 24–48 hr for symptoms of beta blockade[a]
Metoprolol	C	Conflicting reports Concern for toxicity Excreted in breast milk	CP; LHS; no animal teratogenicity; may cause IUGR, RPW, and persistent beta blockade in newborns[a]
Propranolol	C	Conflicting reports Concern for toxicity	CP; NHT; fetal and neonatal toxicity may occur; may cause IUGR and RPW if used near delivery; newborn should be monitored for 24–48 hr for symptoms of beta blockade[a]
Amlodipine	C	Probably compatible, but safety unknown Neonatal myocardium sensitive to changes in calcium status Caution during breast-feeding	LHS; animal studies demonstrated fetotoxicity; safety unknown; case reports of IUGR, fetal death, neonatal rash
Diltiazem	C	Probably compatible, but safety unknown Neonatal myocardium sensitive to changes in calcium status Caution during breast feeding	LHS; animal studies demonstrate fetotoxicity, teratogenicity; safety unknown
Nicardipine	C	Probably compatible but safety unknown LHS	Dose-related embryonic toxicity but not teratogenicity in animals; LHS; neonatal hypotension and acidosis reported, but safety unknown; causes hypotension, reflex tachycardia, PPH, tocolysis, headache, nausea, dizziness, flushing in pregnancy
Nifedipine	C	Probably compatible but safety unknown Advised to delay breast-feeding for 3–4 hr	LHS; safety unknown; NHT; has been used as a tocolytic agent; may potentiate neuromuscular blocking action of magnesium
Verapamil	C	Probably compatible	CP; animal studies show adverse effects on fetal growth and fetotoxicity, LHS; appears to be low risk during any stage of pregnancy
Furosemide	C	Probably compatible Caution advised May suppress lactation	CP; LHS; fetotoxic and teratogenic in animals; no significant alteration of amniotic fluid volume; monitor fetal growth because may cause higher birth weight
Hydrochlorothiazide	B (class D in women with reduced uteroplacental perfusion)	Compatible Excreted in breast milk May suppress lactation	CP; NHT; risks to fetus and newborn include hypoglycemia, thrombocytopenia, hyponatremia, hypokalemia, death; may inhibit labor by direct effect on smooth muscle
Nitroglycerin	B to C depending on the product	Probably compatible Monitoring infants recommended	LHS; no adverse effects in animal studies; safety unknown, but appears safe; tocolytic
Nitroprusside	C	Potential toxicity	CP; LHS; adverse effects in animal studies, caution advised; transient fetal bradycardia noted; accumulation of cyanide in fetus may occur
Clonidine	C	Probably compatible May alter prolactin and oxytocin levels, affecting lactation	CP; LHS; safety unknown; no observed adverse fetal effects in humans; may develop sleep disorders later in life with prolonged use during pregnancy

TABLE 180.8

Antihypertensive Medications—cont'd

DRUG(S)	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Hydralazine	C	Probably compatible LHS Excreted in breast milk	CP; use with caution, no known congenital defects, but fetal toxicity associated with third-trimester use; meta-analysis on use in preeclampsia demonstrated more hypotension, placental abruption, cesarean section, maternal oliguria, adverse fetal heart rates, lower Apgar scores compared with labetalol or nifedipine
Methyldopa	B	Probably compatible	Long history of safety and efficacy in pregnancy

[a]Beta blockade = bradycardia, respiratory depression, and hypoglycemia.
CP, Crosses placenta; *FDA,* US Food and Drug Administration; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity; *PDA,* patent ductus arteriosus; *PPH,* postpartum hemorrhage; *RPW,* reduced placental weight.

are less common when a cardioselective beta blocker, such as atenolol or metoprolol, is used. Esmolol has been associated with fetal bradycardia, neonatal bradycardia and hypotonia, and fetal distress requiring emergent cesarean section.[75,76] Beta blockers have variable effects on the nursing infant, and close monitoring of the infant for adverse effects is recommended.[15,24]

Calcium Channel Blockers. Calcium channel blockers have been used for the treatment of hypertension and the termination of supraventricular rhythm disturbances during pregnancy.[78] IV verapamil has also been used to terminate fetal tachycardia, and IV nicardipine has been used for severe preeclampsia. In addition, some calcium channel blockers, such as nifedipine and diltiazem, have been used as tocolytic agents. In laboratory animals, use of calcium channel blockers in the first trimester was associated with a dose-dependent increase in embryonic mortality and skeletal abnormalities. To date, however, these abnormalities have not been seen in humans, although data remain limited. Some complications of calcium channel blocker use during pregnancy include maternal hypotension, tachycardia, and fetal distress, especially pronounced when sublingual nifedipine or IV nicardipine is used.[15,24] The AAP considers these drugs compatible with breast-feeding.

Diuretics

Loop diuretics such as furosemide are indicated in the treatment of pulmonary edema due to congestive heart failure. In laboratory animals, furosemide has been linked to renal and skeletal abnormalities when used in pregnancy. These effects have not been seen in humans, but a slightly increased risk of hypospadias has been reported. Furosemide is secreted into breast milk but is considered compatible with breast-feeding.[15,24]

Thiazide diuretics have been associated with hypoglycemia and electrolyte abnormalities in neonates when given near term and with an increase in meconium staining and perinatal mortality. Moreover, thiazide diuretics may have a direct effect on smooth muscle and inhibit labor. In general, these agents are considered safe during breast-feeding.[15,24]

Nitrates. Nitroglycerin has not been shown to cause fetal harm in animal studies. Limited reports in humans have not shown any major effects on the fetus or neonate. Nitroglycerin is rarely used during pregnancy, but it appears to be a safe, effective, rapidly acting, and short-acting agent.[79] Nitroprusside for the treatment of hypertensive emergencies in pregnancy has the same advantages and disadvantages as in nonpregnant patients. During prolonged administration of high doses, nitroprusside may result in cyanide toxicity and severe acidosis. It readily crosses the placenta, and fetal levels of cyanide can increase as high as twice maternal levels. Standard doses do not seem to subject the fetus to a major risk of toxicity but, with the availability of safer alternatives, notably labetalol, nitroprusside is considered a last resort agent.[15,24,79] No data are available on its use during lactation, but breast-feeding is not expected to continue during a critical illness.

Clonidine. Clonidine has been safely used throughout pregnancy, but experience during the first trimester remains limited. It does not appear to be teratogenic in laboratory animals and does not increase fetal mortality. Transient neonatal hypertension has been reported in neonates.[80] Its effects on breast-feeding neonates are unknown, but it is considered compatible with breast-feeding.[15,24]

Hydralazine. Hydralazine use has been associated with higher rates of maternal hypotension, placental abruption, and neonatal distress compared with labetalol. It is therefore no longer recommended as a first-line agent in the treatment of severe acute hypertension in pregnancy. It may still be used as a second-line agent. Hydralazine is considered compatible with breast-feeding.[15,24]

Methyldopa. Methyldopa has been safely used throughout pregnancy, and most reviews have not linked it to any teratogenic effects on the offspring or adverse effects on the pregnancy. Many emergency clinicians continue to prescribe it as first-line therapy for hypertension during pregnancy. Methyldopa is compatible with breast-feeding.[15,24]

Vasopressors

Vasopressors all have the potential to increase uterine vascular resistance, resulting in a proportional decrease in placental blood flow. At this time, on the basis of its safety profile, phenylephrine appears to be the vasopressor of choice in the treatment of vascular collapse during pregnancy (Table 180.9).[79,81]

Endocrine Agents

Diabetes Medications

Diabetes mellitus is associated with a number of congenital malformations involving multiple organ systems, as well as with a significant increase in perinatal morbidity. Glycemic control in

TABLE 180.9

Vasopressors

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Dobutamine	B	Probably compatible (LHS)	CP; LHS; animal data suggest low risk; no adverse effects on human fetuses found
Dopamine	C	Probably compatible (LHS)	LHS; used in maternal shock, including spinal shock due to spinal anesthesia; low-dose dopamine can be used to improve cardiac and urine output in patients with preeclampsia and oliguria, but has not been shown to improve mortality or renal function; animal studies suggest maternal toxicity, but no fetal teratogenicity found; decreases uterine blood flow
Epinephrine	C	Potential toxicity (LHS)	CP; NHT; preferred treatment agent for anaphylaxis, used for status asthmaticus and shock during pregnancy; associated with fetal anoxic injury, intracranial hemorrhage, and increased incidence of inguinal hernias; decreases uterine blood flow, which may lead to fetal anoxia
Norepinephrine	C	Potential toxicity (LHS)	CP; animal studies demonstrate malformation—situs inversus, cataracts, hemorrhages, bone abnormalities; increased incidence of cerebral hemorrhage; decreased placental flow and fetal anoxia, but overall effects unknown
Ephedrine	C	Potential toxicity	CP; NHT; effective in treatment of shock in pregnancy; compared to phenylephrine, ephedrine associated with higher heart rates, gastric upset, increased incidence of fetal acidosis; no major or minor malformations shown
Phenylephrine	C	Probably compatible (LHS)	Preferred agent to treat shock during pregnancy; severe hypertension during delivery when reacting to oxytocics or ergots; malformations when used in first trimester; use during late pregnancy, labor, or cesarean section may cause fetal anoxia, bradycardia due to uterine contractions, decreased uterine blood flow

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies; *NHT,* no human teratogenicity.
Additional data adapted from ref. 113.

pregnancy is therefore important and should be accomplished in a controlled manner, because hypoglycemia is also associated with adverse pregnancy outcomes. Insulin is considered the drug of choice for diabetes mellitus types 1 and 2 in pregnancy and gestational diabetes, if treatment is needed. Metformin has been associated with serious adverse effects in adults, including life-threatening metabolic acidosis and hepatotoxicity. It has not been associated with fetal malformations in animals and humans (Table 180.10).[15,24,81]

Thyroid Medications

Maternal hyperthyroidism is associated with an increased risk of spontaneous abortion, preterm labor, placental abruption, and maternal congestive heart failure. Effects of the disease on the offspring include intrauterine growth restriction, intrauterine fetal death, and neonatal goiter. Propylthiouracil (PTU) is the drug of choice during pregnancy. There does not appear to be an increase in the risk of congenital defects with PTU. Other drugs used to control hyperthyroidism in pregnancy include methimazole and carbimazole, both of which have been associated with abnormal development of the skin, albeit inconsistently. Hypothyroidism in pregnancy may result in an increased risk for spontaneous abortion, intrauterine growth restriction, placental abruption, and fetal demise and has been associated with severe neurologic impairment of the offspring.[15,24] Levothyroxine is the treatment of choice for hypothyroidism in pregnant women (Table 180.11).

Gastrointestinal Agents

Gastroesophageal reflux disease (GERD) occurs in up to 80%, of pregnancies and peaks in the third trimester. The exact mechanism and pathogenesis of this condition associated with pregnancy is likely multifactorial (Table 180.12).[82]

Antacids

H2 Receptor Antagonists. Antacids are commonly prescribed throughout pregnancy. None of the H2 receptor antagonists has been linked to congenital malformation, and they all appear to be safe for the nursing infant. There are multiple reports in the literature, however, linking in utero gastric suppression to an increased incidence of asthma and allergies during childhood, which require confirmation.[15,24,83]

Proton Pump Inhibitors. Studies on proton pump inhibitor (PPI) use in pregnancy are limited but several studies and a meta-analysis have found no association with an increased risk for major congenital birth defects, spontaneous abortions, or preterm delivery.[82,84,85] Esomeprazole, lansoprazole, pantoprazole, and rabeprazole may be used during pregnancy. There are reports, however, of an increased incidence of GI, hepatic, and thyroid cancers in rats and mice. Several studies have demonstrated a possible link between in utero exposure to gastric acid suppressors and childhood allergic disorders and asthma.[15,24,83,86,87] There are no human data studying the effect of PPIs on nursing infants.

Antiemetic Medications

Nausea and vomiting occur in up to 80% of all pregnant women between 6 and 12 weeks of gestation, but these symptoms are usually self-limiting. One-third of women with nausea and vomiting of pregnancy have clinically significant symptoms, and 1% will progress to hyperemesis gravidarum, which poses health risks

TABLE 180.10

Diabetic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Insulin	B	Compatible Degraded by infant's GI tract	Maternal hypoglycemia; DNCP; no observable effects found
Sulfonylureas	B	Compatible	Minimal amounts found in fetal circulation; no greater risk of adverse effects compared with insulin therapy; infant 200 g heavier with use of sulfonylureas; stop ≈2 wk before birth to prevent neonatal hypoglycemia
Metformin	B	Compatible Excreted in breast milk Monitoring advised	CP; NHT Less likely to experience maternal and neonatal hypoglycemia

CP, Crosses placenta; *DNCP,* does not cross placenta; *FDA,* US Food and Drug Administration; *GI,* gastrointestinal; *NHT,* no human teratogenicity.
Additional data adapted from refs. 113 and 114.

TABLE 180.11

Thyroid Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Levothyroxine	A	Compatible Excreted in breast milk	Minimal transfer across placenta; treatment of choice for hypothyroidism in pregnancy; minimal side effects; maternal benefits outweigh risks to fetus
Potassium iodide	D	Compatible Excreted in breast milk	CP; reserved for thyrotoxic patients; easily taken up by fetal thyroid, resulting in prolonged fetal hypothyroidism and goiter
Propylthiouracil (PTU)	D	Compatible Excreted in breast milk	CP; causes fetal goiter, hypothyroidism, hepatic injury, death; preferred drug for hyperthyroidism in pregnancy; maternal benefits outweigh risk to fetus
Methimazole	D	Compatible Excreted in breast milk	CP; may cause a methimazole embryopathy—congenital skin defects, umbilical defects

CP, Crosses placenta; *FDA,* US Food and Drug Administration.
Additional data adapted from ref. 115.

to the mother and fetus.[88] Despite these symptoms being common in pregnancy, there is a lack of high-quality evidence to support any particular intervention (Table 180.13).[89]

Pyridoxine (Vitamin B_6), Doxylamine-Pyridoxine Combination. Pyridoxine has been used alone and in combination for the treatment of nausea and vomiting of pregnancy. Combination therapy of doxylamine and pyridoxine was recently approved by the FDA for the treatment of nausea and vomiting of pregnancy after having been taken off the market. Doxylamine is an antihistamine. Positive associations with congenital malformations have been observed but are not thought to be causal in nature.[15,88,90]

Phenothiazines. Phenothiazines, such as metoclopramide, prochlorperazine, and promethazine, are dopamine antagonists commonly used in the treatment of nausea and vomiting during pregnancy. Although there have been reports of increased risk of cardiac defects, these reports did not consider other factors, such as the mother's health, when the drug was reviewed. The bulk of evidence does not support a link to congenital abnormalities.[24,91] The AAP cautions against their use in nursing mothers because they may cause sedation and other untoward effects.[15]

Serotonin 5-HT_3 Receptor Antagonists. Dolasetron, granisetron, and ondansetron have not been linked to any fetal malformations, although experience with the newer agents remains limited.[15,24] Recent studies of ondansetron have suggested a low teratogenic risk; however, an increased risk for a cardiac septum defect is possible, but data are inconsistent,[92] but this has not been confirmed in other studies.[93] The AAP considers these agents compatible with breast-feeding.[15]

Neurologic Agents

Anticonvulsants

Anticonvulsants are known teratogens, and 30% of neonates exposed to commonly used anticonvulsants exhibit congenital anomalies.[15,24] The risks for birth defects increase with the duration of exposure and with the number of agents used. Valproate is associated with the most frequent serious adverse effects on the pregnancy and fetus (20.3% incidence of serious adverse outcomes) compared with phenytoin, carbamazepine, and lamotrigine (10.7%, 8.2%, and 1.0%, respectively). Despite the risks, most practitioners believe that it is important to control seizures during pregnancy. Generalized seizures during pregnancy are associated with an increased risk of spontaneous abortion, hypoxic injury to the fetus, and impaired neuropsychological functioning.

Monotherapy is the most appropriate option and is recommended at the lowest effective anticonvulsant dose. Dividing the

TABLE 180.12

Gastrointestinal Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Famotidine	B	Probably compatible Secreted less than other H2 blockers Considered low risk	CP; no fetal toxicity or teratogenicity in animal studies[a]
Ranitidine	B	Probably compatible Considered low risk	CP; no toxicity or teratogenicity in animal studies; considered H2 blocker of choice due to efficacy and safety data; ranitidine-induced anaphylactoid shock has been reported[a]
Cimetidine	B	Compatible Has antiandrogenic activity, so use with caution	CP; no toxicity in animal studies, has some weak anti-androgenic activity that could result in feminism of male fetuses but no documented cases in humans[a]
Omeprazole	C	Potential toxicity LHS	CP; animal data show dose related embryonic and fetal mortality; low risk of fetal harm or teratogenicity; overall slightly higher rates of congenital malformations and stillborns after exposure in first trimester of pregnancy, but studies limited/unconfirmed[a]
Esomeprazole	B (esomeprazole magnesium) C (esomeprazole strontium)	Potential toxicity LHS Wait 5–7.5 hr after dose for breast-feeding to limit exposure Strontium formulations—should not be used	CP; LHS; some changes in bone morphology observed in animal studies; should be used with caution[a]
Lansoprazole	B	Potential toxicity Should be avoided	Unknown whether CP but likely; carcinogenic in animals; LHS; should be avoided in first trimester[a]
Pantoprazole	B	Probably compatible Potential for tumorigenicity and carcinogenicity in animals Caution advised	Animal and human data—suggest low risk in pregnancy[a]

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.
[a]Several studies have shown a possible link between in utero exposure to gastric acid suppressors and childhood allergy and asthma.
Additional data adapted from ref. 116.

daily dose to decrease peak plasma levels may be considered. Adjustment of the dosage upward is often required to maintain adequate seizure control.[15]

Classic Anticonvulsants. The classic anticonvulsants are considered class D agents and are teratogenic. Carbamazepine has been linked to an increased risk of craniofacial defects, neural tube defects, and developmental delay. Phenobarbital has been associated with a slightly increased risk of congenital heart disease and cleft lip or palate. In addition, its chronic use during pregnancy has been associated with neonatal withdrawal. Phenytoin use during pregnancy has been associated with the fetal hydantoin syndrome, which affects 5% to 10% of pregnancies. This syndrome is characterized by varying degrees of ossification abnormalities of the extremities and digits, craniofacial abnormalities, including cleft lip and palate, impaired growth, delayed neurologic development, and multiple cardiovascular anomalies. Valproic acid is associated with multiple facial anomalies, neural tube defects, strabismus, and congenital heart defects.[15,24]

Carbamazepine, phenobarbital, and phenytoin have also been associated with hemorrhagic disease of the newborn, presumably because they competitively inhibit placental transport of vitamin K.[15,24]

Carbamazepine, phenytoin, and valproic acid are considered compatible with breast-feeding. Phenobarbital, on the other hand, has been associated with neonatal sedation and toxicity and is not advised during breast-feeding.[15,24]

Newer Anticonvulsants. Newer anticonvulsants, such as lamotrigine, levetiracetam, and topiramate, have been associated with a slightly increased incidence of major birth defects, such as oral clefts, skeletal abnormalities, and hypospadias. The incidence of these birth defects increases significantly when these substances are combined with other anticonvulsants, such as valproic acid.[15,24] These findings, however, were not seen in two studies comparing the newer anticonvulsants. In the lamotrigine pregnancy registry,[94] a study conducted by the manufacturer of lamotrigine, and in an observational study from Denmark,[95] first-trimester exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam was not associated with an increased risk of major birth defects.

These agents also appeared to be well tolerated by the nursing infant, except for topiramate, which caused excess sedation.[15]

Antipsychotics

These agents sometimes cause extrapyramidal side effects of the infants when exposed in utero.[15,24] These effects are seen with use of the first- and second-generation antipsychotics. Haloperidol has been shown to cause some limb defects when the mother is exposed during the first trimester. However, this effect is not seen with other first-generation antipsychotics.[15] Most second-generation antipsychotics do not show teratogenicity. However, there are insufficient data for all antipsychotics (Table 180.14).

Migraine Medications

Ergot Alkaloids

Neither ergotamine nor dihydroergotamine has been associated with teratogenic effects but are contraindicated in pregnancy

TABLE 180.13

Antiemetic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Pyridoxine	A	Compatible Excreted in breast milk	High doses pose little risk to fetus; vitamin B_6 deficiency common during pregnancy—pyridoxine required for good maternal and fetal health
Doxylamine, pyridoxine	A (FDA-approved for use in nausea, vomiting in pregnancy)	Probably compatible, but sedative and antihistamine actions are potential concern	Safe in pregnancy, including first trimester; several meta-analyses demonstrated no increased risk of malformations, fetal abnormalities
Metoclopramide	B	Potential toxicity Concern for CNS effects but data lacking	CP; no association with adverse fetal and neonatal outcomes while with used during all stages of pregnancy
Prochlorperazine	C	Potential toxicity Use caution—may cause sedation, lethargy in infant	CP; LHS; fetal toxicity, teratogenicity in animals; adverse effects of extrapyramidal effects, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, feeding disorder reported in infants exposed during third trimester; isolated reports of congenital defects when exposed in utero; considered low risk for mother and fetus if used occasionally in low doses
Promethazine	C	Probably compatible May cause sedation in infant	CP; LHS; reports of embryonic and fetal harm may be considered low risk for embryo, fetus; may cause platelet aggregation in newborn if given within 2 wk of delivery, of unknown clinical significance
Ondansetron	B	Probably compatible Unknown safety	CP; animal, human data suggest low risk of birth defects; studies show increased risk of cardiac anomalies—therapy recommended only after 10 wk of gestation

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.
Additional data adapted from refs. 117–120.

TABLE 180.14

Antipsychotic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
FIRST GENERATION			
Haloperidol	C	Potential toxicity (LHS) Excreted in breast milk	CP; antipyramidal symptoms can be seen in infants exposed in utero; limb defects seen with first-trimester exposure
Droperidol	C	Potential toxicity (LHS)	CP; no effect on respiratory drive when given perinatally; no observed fetal or maternal SAR
SECOND GENERATION			
Olanzapine	C (insufficient data)	Potential toxicity (LHS) Concentrated in breast milk	CP; no teratogenicity or mutagenicity in animal studies; extrapyramidal effects noted in infants exposed in third trimester
Risperidone	C (insufficient data)	Potential toxicity (LHS)	CP; extrapyramidal effects noted in infants exposed in third trimester

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies; *SAR,* serious adverse reactions.

because of their oxytocic effects and effects on uterine blood flow. In a number of animals, these alkaloids have been associated with intrauterine growth restriction, probably because of reductions in uteroplacental blood flow. They are also contraindicated during breast-feeding because of possible ergot poisoning of the nursing infant manifested by convulsions and gastrointestinal symptoms.[15,24]

Triptans

Triptans have been found to be teratogenic in a number of animal species, but recent human studies appear to favor their safety during pregnancy.[15,24] Sumatriptan is considered compatible with breast-feeding, especially if the breast milk is not used for 8 hours after the last dose.

Respiratory Agents

Antihistamines

Approximately 10% to 15% of women reportedly take an antihistamine during pregnancy. Chlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, and meclizine have been safely used for the treatment of allergic reactions during pregnancy and as

TABLE 180.15

Antihistamine Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Chlorpheniramine	C	Probably compatible; use with caution: may cause sedation, irritability, disturbed sleep, hyperexcitability, excessive crying	LHS; no known congenital defects, low risk in pregnancy; recommended antihistamine in pregnancy, especially in first trimester[a]
Diphenhydramine	B	Probably compatible; use with caution, can be sedating; parenteral use contraindicated	LHS; animal and human studies demonstrate safety in pregnancy; association with cleft palate in one study; drug of choice if parenteral antihistamine is indicated[a]
Hydroxyzine	X first trimester only; C in second and third trimesters	Probably compatible, LHS; not recommended with breast-feeding: may interfere with establishment of lactation	Likely CP; teratogenic in animals, with high doses associated with developmental toxicity; low potential risk for fetus in humans; withdrawal or seizures noted in newborn exposed near term; possible increased risk of oral clefts, but limited data[a]
Meclizine	B	Probably compatible Safety unknown Occasional dose should not pose risk	Teratogenic in animals but not in humans; frequently used as antiemetic; considered low risk in pregnancy[a]
Cetirizine	B	Probably compatible Excreted in breast milk Not recommended—safety unknown	Animal studies—no teratogenicity; LHS; no evidence of increased risk of adverse fetal outcomes; may be used as alternative to oral first-generation antihistamine
Fexofenadine	C	Probably compatible excreted in breast milk	Animal studies—embryonic and fetal toxicity; no human studies available
Loratadine	None	Probably compatible considered antihistamine of choice in breast-feeding	Unknown if CP, but expected; no evidence of teratogenicity in animals or humans

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.
[a]H1 blockers are not recommended for use in last 2 wk of pregnancy due to association with retrolental fibroplasia in premature neonates.
Additional data adapted from refs. 121 and 122.

antiemetics in the treatment of nausea and vomiting during pregnancy. This has been further confirmed in meta-analyses involving more than 200,000 patients. First-generation antihistamines are not recommended during breast-feeding because they are thought to inhibit lactation.[15,24] In addition, serious adverse CNS effects, including seizures, have been reported to develop in neonates receiving antihistamines, especially when they are premature.

The newer generation antihistamines, such as cetirizine and loratadine, also appear safe during pregnancy. They may be acceptable alternatives for severe allergies if the first-generation antihistamines are not tolerated.[24] The AAP has classified these drugs as compatible with breast-feeding (Table 180.15).[15]

Asthma Medications

The prevalence of asthma in pregnancy is estimated at 8.8%,[96] and one-third of pregnant asthmatics experience a worsening of their asthma that may progress to a critical asthma syndrome, including status asthmaticus and near-fatal asthma. Pregnant women with asthma are at risk for neonatal death, preterm birth, low-birth-weight infants, preeclampsia, and small-for-gestational-age infants.[97,98] Asthmatic mothers may also have a higher rate of chorioamnionitis, hypertensive disorders of pregnancy, cesarean section, and prolonged hospital stay compared with control mothers. Better asthma control has been associated with an improved outcome.

Albuterol is the most commonly prescribed and is the treatment of choice in asthma. It appears safe, even when used long term.[99] None of the β-adrenergic medications has been linked to fetal or congenital malformations, but some have been associated with significant cardiovascular and metabolic effects, which are transient and generally well tolerated by the fetus. Transient hyperglycemia followed by insulin secretion may also occur, resulting in neonatal hypoglycemia, especially in diabetic patients. Terbutaline, when used IV or orally in pregnant women, may result in significant maternal and fetal arrhythmias, maternal pulmonary edema, and death. The FDA has recommended a label change to add a warning against its use in preterm labor because safer β_2-agonists and tocolytic agents are available.[100] Long-acting beta agonists also appear to be safe during pregnancy. Albuterol is compatible with breast-feeding.[15,24]

Ipratropium has not been found to be teratogenic in numerous animal models, but there are few data regarding its safety in human pregnancy.[15,24] It is considered compatible with breast-feeding.

Cromolyn sodium has not been associated with any significant risk of birth defects or negative perinatal outcomes.[15,24] It is considered compatible with breast-feeding (Table 180.16).

Corticosteroids

Inhaled corticosteroids are the main therapy for the prevention of asthma exacerbations during pregnancy. Oral corticosteroids are the mainstay of therapy for acute exacerbations of asthma. Although they are not considered human teratogens, there may be a slightly increased incidence of orofacial clefts when oral steroids are used during the first trimester.[101] Furthermore, their use in the third trimester has been linked to an increased incidence of preterm delivery, low birth weight, preeclampsia, and cataracts in the newborn. Other authors have also raised concerns about the development of congenital adrenal hyperplasia in newborns.[15,24] Prednisone is considered safe during breast-feeding.

Data on the use of leukotriene antagonists in pregnancy are limited. One study has found no association with congenital abnormalities, but there was a slight increase in intrauterine

TABLE 180.16

Asthma Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Ipratropium	B	Probably compatible, LHS May appear in breast milk	LHS; NHT; no teratogenicity in animals; recommended for use in severe asthma as additional therapy
Albuterol	C	Probably compatible, LHS Unknown if excreted in breast milk	May act as tocolytic; drug of choice for treatment of asthma; association with functional and neurobehavioral toxicity with prolonged use; may cause maternal and fetal tachycardia, hyperglycemia
Epinephrine	C	Potential toxicity, LHS Not known if excreted in breast milk	CP; teratogenic in animals; avoid during active labor and delivery—can delay labor progression; may lead to decrease in uterine blood flow with placental, uterine vasoconstriction
Terbutaline	C	Probably compatible Excreted in breast milk in small amounts	CP; NHT; may act as tocolytic; association with autism spectrum disorders (if used >2 wk); cardiac defects in first trimester; fetal tachycardia and hypoglycemia after parenteral use; avoid in early gestation, continuous use in second and third trimesters; may cause serious maternal cardiovascular events (eg, increased heart rate, hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and MI), death; black boxed warnings against use for prevention or prolonged use (beyond 2–3 days) of preterm labor

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies; *MI,* myocardial ischemia; *NHT,* no human teratogenicity.

growth restriction. However, these results should be interpreted with caution because of the small sample size of the study. Zileuton is mutagenic in animal studies and should be avoided during pregnancy and lactation.[15,24]

Decongestants

Decongestants with strong vasoconstrictive properties, such as phenylpropanolamine, phenylephrine and pseudoephedrine, cause placental vasoconstriction and are not recommended during pregnancy. There are limited data suggesting that their use in the first trimester may result in an increased incidence of abnormalities typically associated with placental vascular disruption, such as gastroschisis and intestinal atresia.[15,24] Recent evidence has supported the association of phenylephrine and endocardial cushion defect, phenylpropanolamine and ear defects, and phenylpropanolamine and pyloric stenosis with oral and intranasal decongestion use in the first trimester.[102] The risk, however, appears to be low. The AAP classifies pseudoephedrine as compatible with breast-feeding.

KEY CONCEPTS

- Chemically induced birth defects are believed to be responsible for approximately 1% to 3% of anomalous births.
- Gestational age is crucial in determination of the impact of any given exposure, especially during organogenesis (days 21–56 of fetal life), when major body organs are formed.
- Human data on teratogenicity and fetal toxicity of medications is often limited, and causal associations are difficult to determine, especially with newer medications.
- In general, the health of the fetus is directly related to the health of the mother, and drugs should be given when the maternal benefits outweigh the risks to the fetus.
- Certain medications should be avoided during pregnancy, if possible, because they are known teratogens or cause potential toxic effects in the newborn; these include anticonvulsants, warfarin derivatives, NSAIDs, sulfonamides, fluoroquinolones, and ACE inhibitors.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 180: QUESTIONS AND ANSWERS

180.1. A 42-year-old woman who is 7 months pregnant presents with severe, pressure-like chest pain that occurred while she was washing her clothes. The pain radiates to both shoulders and is associated with dyspnea and dizziness. Vital signs show heart rate, 92 beats/min, respiratory rate (RR), 22 breaths/min, blood pressure (BP), 134/70 mm Hg, and O_2 saturation, 97% on room air. She appears pale and diaphoretic and has a subdued affect. Lung examination reveals equal breath sounds without rales, rhonchi, wheezes, or friction rubs. Cardiac examination reveals a regular rhythm at 92 beats/min. There were no murmurs, gallops, or rubs appreciated. An electrocardiogram (ECG) shows ST elevations in leads I, aVL, and V_2–V_6, with reciprocal T wave inversions. Of the following, which would be the most appropriate?

A. Administer beta blockers.
B. Administer heparin drip, and admit the patient to the critical care unit.
C. Administer thrombolytic therapy.
D. Schedule the patient for computed tomography (CT) angiography of the chest STAT.

E. Start nonsteroidal antiinflammatory drugs (NSAIDs), and schedule the patient for two-dimensional echocardiography.

Answer: C. The patient has an acute myocardial infarction (MI) and requires immediate reperfusion therapy. This may be accomplished by thrombolytic therapy or by performing a percutaneous coronary intervention (PCI). Of the choices given, only C provides reperfusion therapy. In this case, treatment of the life-threatening MI in the mother outweighs the possible dangers to the embryo or fetus.

180.2. A 23-year-old woman who is 6 months pregnant was well until earlier in the morning, when she experienced sudden onset of shortness of breath and right-sided sharp chest pain. The pain is worse on inspiration and is not related to exertion, although her dyspnea becomes worse with any activity. She is alert and appears in distress. Her pulse is 112 beats/min, RR, 32 breaths/min, and BP, 98/48 mm Hg. Her temperature is 100.8°F (32°C), and O_2 saturation is 92%. Lung examination reveals splinting of the respirations, with rales and wheezing on the right. Cardiac examination reveals tachycardia. No murmurs, gallops, or rubs were noted. Chest radiograph reveals elevated right hemidiaphragm but no infiltrates. ECG reveals generalized T wave inversions. Of the following, which would be most appropriate?

A. Administer a low-molecular-weight heparin subcutaneously, as well as oral warfarin sodium (Coumadin).
B. Administer intravenous ceftriaxone and azithromycin for clinical pneumonia.
C. Administer nebulized bronchodilators, and start prednisone.
D. Administer oxygen, schedule for a diagnostic study, and start heparin.
E. Place a central line, and start early goal-directed therapy for sepsis.

Answer: D. On the basis of the information provided, the patient most likely has a pulmonary embolus. The patient is hypoxic and requires oxygen administration and anticoagulation. This may be accomplished with heparin and Coumadin. Coumadin, however, is teratogenic and is contraindicated in pregnancy. The patient has no symptoms of an infectious process; choices B and E are therefore not appropriate. Bronchodilators and steroids are indicated for asthma but not for thromboembolic disease. Choice C is therefore not appropriate.

180.3. In determining a causal link between a specific drug and congenital malformations, which of the following may be viewed as confounding factors?

A. All of these
B. Genetic background of the fetus
C. Maternal illicit drug use
D. Presence of maternal illness
E. Presence of nutritional deficits

Answer: A. The process of establishing teratogenicity of a substance is often flawed. Much of our current knowledge on teratogenicity has been derived from case reports, case-controlled studies, and cohort studies, which are inherently weak in establishing a causal link. These reports are often complicated by a number of confounding factors, which make a causal link difficult to establish. The presence of any of the listed choices may confound results. In the presence of maternal illness, for example, the outcome of pregnancy may be related to the medical condition and not the medication.

180.4. Which of the following drugs is a known teratogen?

A. Acetaminophen
B. Hydroxycobalamin
C. Levothyroxine
D. Penicillin VK
E. Phenytoin

Answer: E. Phenytoin or diphenylhydantoin is an anticonvulsant that is a class D agent and is highly teratogenic. It is associated with the fetal hydantoin syndrome, which is characterized by abnormal ossification of the digits, craniofacial clefts, multiple cardiovascular abnormalities, and impaired neurologic development. It affects 5% to 10% of pregnancies and should be used only if other, safer anticonvulsants fail to control convulsions. The other drugs listed are safe during pregnancy.

180.5. Which of the following drugs may be associated with complications in the newborn when used at term?

A. All of these
B. Nitrofurantoin
C. Nonsteroidal antiinflammatory drugs
D. Propranolol
E. Sulfonamides

Answer: A. All the choices have been associated with complications in the newborn when used at term. Sulfonamides compete with bilirubin for protein-binding sites, leaving large amounts of free bilirubin to diffuse freely into the brain. This results in bilirubin deposition in the infant's brain, thus causing kernicterus. Nitrofurantoin at term has been associated with hemolytic disease of the newborn. Nonsteroidal antiinflammatory drugs are associated with premature closure of the ductus arteriosus. Propranolol at term has been associated with neonatal hypoglycemia, respiratory depression, and neonatal jaundice.

180.6. Which of the following antiarrhythmic agents is a known teratogen?

A. Adenosine
B. Amiodarone
C. Digoxin
D. Lidocaine
E. Procainamide

Answer: B. All the listed antiarrhythmics are safe for use in pregnancy and have not been associated with structural effects except for amiodarone. Amiodarone is a class D agent. It contains a large amount of iodine and may result in congenital goiter and neonatal thyroid abnormalities. In addition, it has been linked to a number of congenital abnormalities affecting growth, cardiac, ophthalmic, and neurologic development. It should only be used for patients who are refractory to other drugs.

CHAPTER 181

Labor and Delivery and Their Complications

Veronica Vasquez | Shoma Desai

PRINCIPLES

Births in the emergency department (ED) are rare. In most cases, patients in labor are triaged directly to the obstetric suite for urgent management, maintaining a continuum of care with their primary providers. Because some births are precipitous and obstetric resources may not be immediately available, the emergency clinician must possess the basic skills for intrapartum management of normal and abnormal deliveries. In addition, a general knowledge of postpartum care is required in case of the occasional out-of-hospital delivery.

Limitations of the Emergency Department

The ED is a suboptimal location for the management of a complicated delivery. Unlike the obstetric suite, the ED may be lacking in appropriate resources, such as tocodynamometry, intrauterine pressure monitors, vacuum extractors, and forceps. In addition, the obstetrician typically has prenatal care information, including accurate gestational dates, presence of placental anatomy, and prior documented obstetric complications, which helps optimize maternal and fetal outcomes. It is difficult, if not impossible, to obtain these data in the ED while preparing for imminent delivery. Finally, cesarean section may be indicated to ensure a successful delivery. This option is not performed in the ED except in dire perimortem circumstances.

Epidemiology of Emergency Delivery

In 2011, the perinatal mortality rate in the United States was 6.26/1000 live births at 28 weeks of gestation or more.[1] Delivery complications and mortality occur with greater frequency in the ED, where the perinatal mortality rate is approximately 8% to 10%. There are multiple features of the high-risk ED delivery profile. The ED as a care environment is often selected by an obstetric population that subsequently may have unexpected complications. Psychosocial factors, such as drug or alcohol abuse, domestic violence, and lack of access to medical care, contribute to precipitous deliveries in pregnant women with little or no prenatal care. Antepartum hemorrhage, premature rupture of membranes (PROM), eclampsia, premature labor, abruptio placentae, malpresentation, and umbilical cord emergencies are overrepresented in the ED population.

Patient Transfer Considerations

Because of the high risk associated with ED delivery, patients should be transported to a facility that has obstetric and neonatal resources whenever possible. The transfer of a woman with an impending high-risk delivery to such a facility should be based on sound clinical and medicolegal judgment. Transfer, with an en route delivery, cannot only be disastrous for the mother and fetus, but also violates federal law. Further consideration should be given to the type of nursery and level of care that the neonate will require after delivery, particularly in preterm (<36 weeks of gestation) deliveries, in which interval transfer for a higher level of care may be necessary.

NORMAL DELIVERY

Initial Presentation

Although the epidemiology and high complication rate associated with ED births demand caution, most are normal deliveries. Knowledge of normal labor and delivery mechanics aids safe vaginal delivery and facilitates the identification of complications.

Whenever a woman in the third trimester of pregnancy seeks treatment in the ED, the possibility that she is in labor must be considered. A wide array of nonspecific symptoms may herald the onset of labor. Abdominal pain, back pain, cramping, nausea, vomiting, urinary urgency, stress incontinence, and anxiety can be symptoms of labor. After 24 weeks' gestation, any medical assessment should include the mother and fetus because fetal viability becomes established near that time.

Distinguishing False From True Labor

Braxton Hicks contractions, or false labor, must be differentiated from true labor. After 30 weeks of gestation, the previously small and uncoordinated contractions of the uterus become more synchronous and may be perceived by the mother. Braxton Hicks contractions do not escalate in frequency or duration, in contrast to the contractions of true labor. By definition, these contractions are associated with minimal or no cervical dilation or effacement. Examination should also reveal intact membranes. Care not to rupture the membranes is important to avoid inducing labor prematurely. If the diagnosis remains in doubt, external electrical monitoring of uterine activity can rule out true labor. Any discomfort associated with false labor is usually relieved with mild analgesia, ambulation, or change in activity.

Unlike false labor, true labor is characterized by cyclic uterine contractions of increasing frequency, duration, and strength, culminating in delivery of the fetus and placenta. In contrast to Braxton Hicks contractions, true labor causes cervical dilation to begin, marking the first stage of labor.

Bloody Show

At the onset of labor, the cervical mucous plug may be expelled, resulting in what is termed a *bloody show*. The bleeding associated with this process is slight (usually only a few dark red spots admixed with mucus) and is due to the increase in cervical vascularity that occurs in pregnancy. Bloody show is not a contraindication to vaginal examination for the determination of cervical

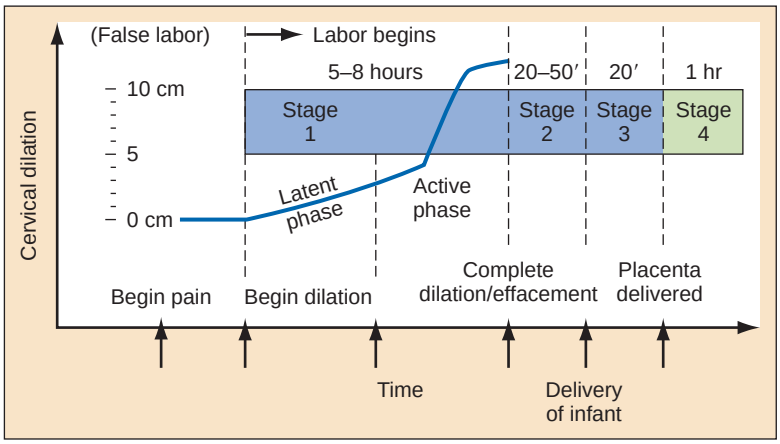

Fig. 181.1. Stages of labor and delivery. Stage 1, cervical stage; stage 2, fetal expulsion; stage 3, placental expulsion (20 minutes); stage 4, uterine contraction (1 hour postpartum).

effacement and dilation. If bleeding continues or is of a larger volume, more serious causes should be suspected, such as placenta previa and placental abruption, which are contraindications for a vaginal examination.

Stages of Labor

First Stage of Labor

The first stage of labor is the cervical stage, ending with a completely dilated, fully effaced cervix. It is divided into a latent phase, with slow cervical dilation, and an active phase, with more rapid dilation. The active phase begins once the cervix is dilated to 3 cm. Most women who deliver in the ED arrive while in the active phase of stage 1 or early stage 2 labor (Fig. 181.1). The duration of the first stage of labor averages 8 hours in nulliparous women and 5 hours in multiparous women. During this time, frequent assessment of fetal well-being is important, and continuous external electrical monitoring may help identify fetal distress, allowing for appropriate intervention.

The maternal examination provides a rough guide to gestational age. At 20 weeks' gestation, the uterine fundus reaches the umbilicus. Approximately 1 cm of fundal height is added per week of gestation until 36 weeks. At that time, the fundal height decreases as the fetus drops into the pelvis (Fig. 181.2). These estimates help establish gestational age rapidly.

The abdominal examination with Leopold's maneuvers may confirm the lie of the fetus (Fig. 181.3). After labor has begun, Leopold's maneuvers may not easily distinguish the lie due to uterine contractions. Other modalities of assessing the lie, such as ultrasonography, may be necessary if presentation remains in question.

The determination of the stage of labor depends on examination of the cervix. A sterile approach using sterile gloves, sterile speculum, and povidone-iodine solution is indicated to prevent ascending infection. On pelvic examination, the clinician should determine the following:

- Effacement refers to the thickness of the cervix. A paper thin cervix is 100% effaced.
  Dilation indicates the diameter of the cervical opening in centimeters. Complete, or maximum, dilation is 10 cm.
- Position describes the relationship of the fetal presenting part to the birth canal. The most common position of the head is occiput anterior.
- Station indicates the relationship of the presenting fetal part to the maternal ischial spines (Fig. 181.4).

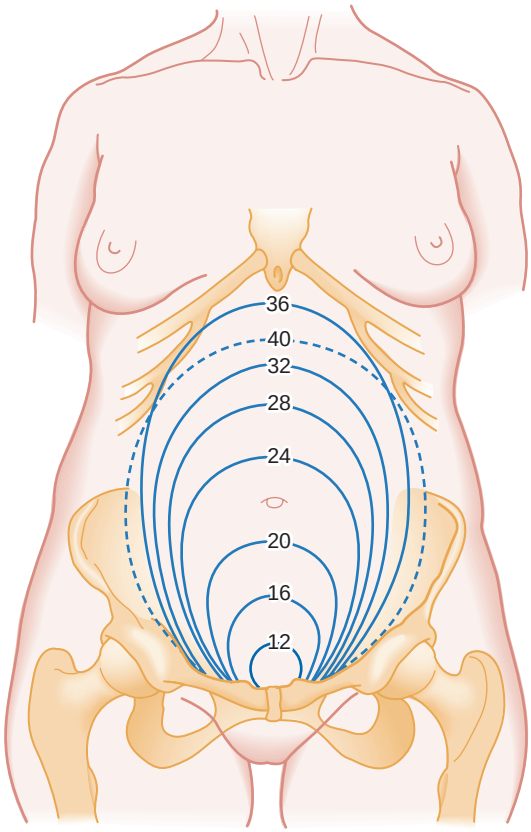

Fig. 181.2. Height of fundus by weeks of normal gestation with a single fetus. The dotted line indicates height after lightening. (Adapted from Barkaukas V, et al: Health and physical assessment. St. Louis, 1992, Mosby.)

- Presentation specifies the anatomic part of the fetus leading through the birth canal.

In 95% of all labors, the presenting part is the occiput, or vertex. On digital examination, a smooth surface with 360 degrees of firm bony contours and palpable suture lines is noted. Palpation of the suture lines and the fontanels where they join allows the examiner to determine the direction the fetus is facing. Three sutures radiate from the posterior fontanel, and four radiate from the anterior fontanel (Fig. 181.5). The lateral margins are examined carefully for fingers or facial parts that indicate compound or brow presentations.

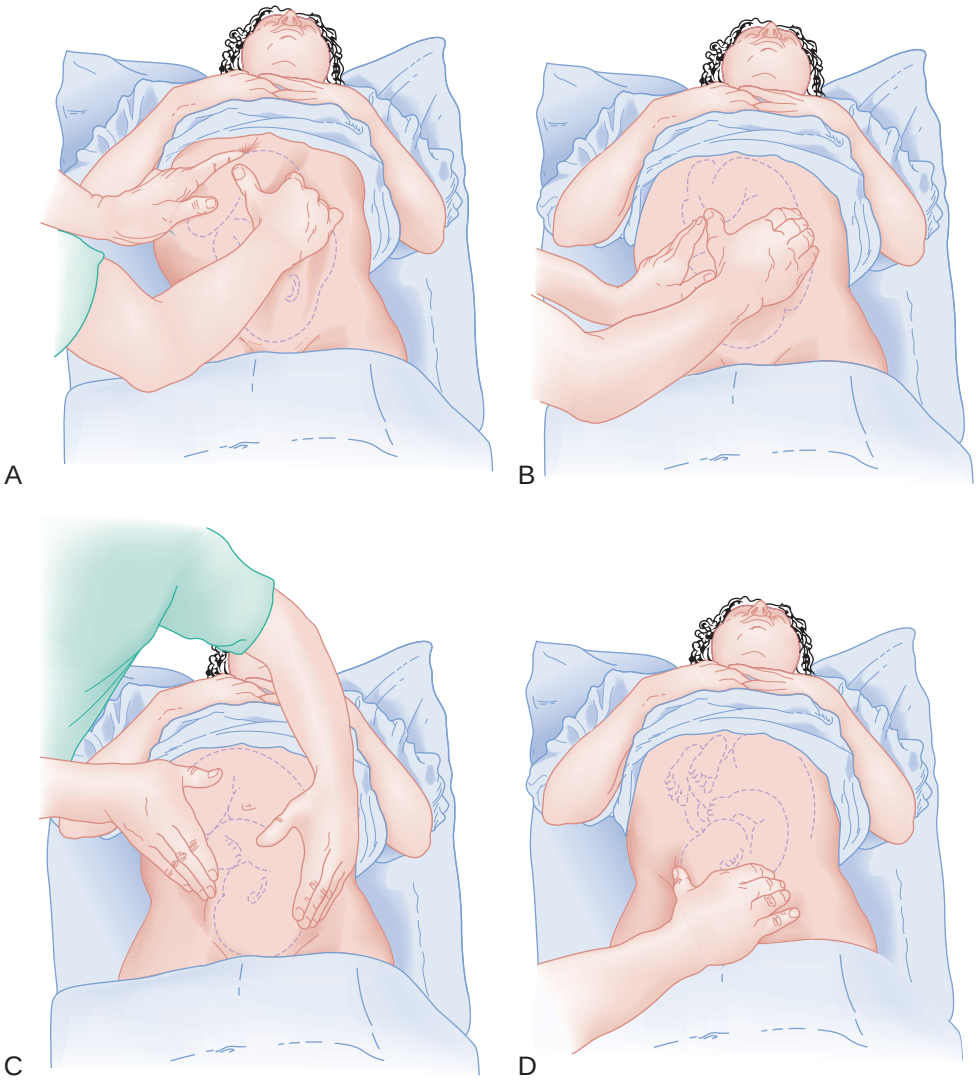

Fig. 181.3. Leopold's maneuvers. **A,** The first Leopold maneuver reveals which fetal part occupies the fundus. **B,** The second Leopold maneuver reveals the position of the fetal back. **C,** The third Leopold maneuver reveals which fetal part lies over the pelvic inlet. **D,** The fourth Leopold maneuver reveals the position of the cephalic prominence (Adapted from Willson JR, et al: Obstetrics and gynecology, ed 9, St. Louis, 1991, Mosby.)

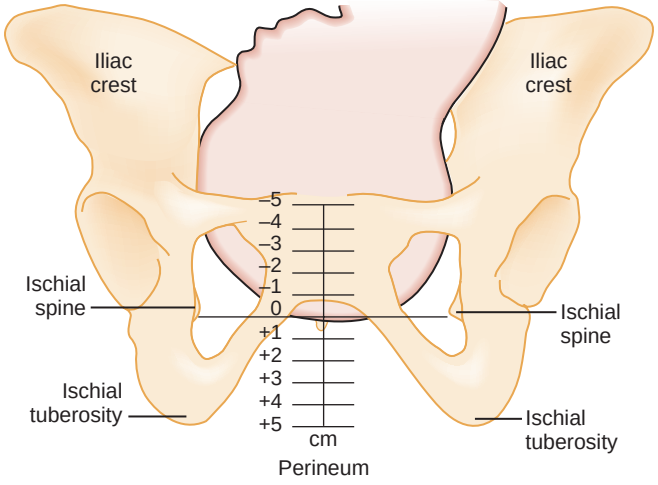

Fig. 181.4. Fetal stations. The level of the ischial spines is considered 0 station. The silhouette of the infant's head is shown approaching station +1. (Courtesy Ross Laboratories, Columbus, OH.)

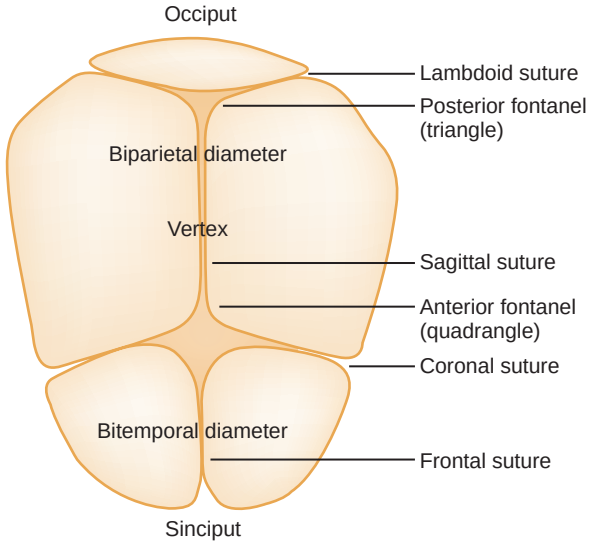

Fig. 181.5. Bony landmarks of the fetal skull. (Adapted from Willson JR, et al: Obstetrics and gynecology, ed 9, St. Louis, 1991, Mosby.)

When the clinician suspects rupture of membranes, a sterile speculum examination is performed. This may reveal pooling of amniotic fluid, a fernlike pattern when the fluid is allowed to dry on a microscope slide, and the use of Nitrazine paper, which should turn blue, indicating an alkaline amniotic fluid (pH > 6). Although vaginal blood, cervical mucus, semen, and infection can interfere with results, sensitivities of Nitrazine paper and ferning for the detection of amniotic fluid are nearly 90%.

Of note, if vaginal bleeding is evident, digital and speculum examination of the pelvis should be deferred until an ultrasound study can be obtained to rule out placenta previa.

Second Stage of Labor

The second stage of labor is characterized by a fully dilated cervix and accompanied by the urge to bear down and push with each uterine contraction. The median duration of this stage is 50 minutes in nulliparous women and 20 minutes in multiparous women, with the anticipation of a more rapid progression for low-birth-weight premature infants. A prolonged second stage of labor is associated with an increase in maternal complications, including postpartum hemorrhage, infection, and severe vaginal lacerations.

Antenatal Fetal Assessment. During labor and delivery, the identification of fetal distress and appropriate intervention can reduce fetal morbidity and mortality. There are currently three methods of assessing a fetus in utero: (1) clinical monitoring; (2) electrical monitoring; and (3) ultrasonography. External electrical monitoring and ultrasonography merit consideration for use in the care of women laboring in the ED. Both modalities provide real-time information that is helpful for the diagnosis of fetal distress and assistance with intrapartum decision making.

Electronic Fetal Monitoring. Electronic fetal monitoring uses tracings of the fetal heart rate and uterine activity. Documentation of organized cyclic uterine contractions helps confirm true labor and may help diagnose fetal distress. In combination with clinical data, this can portend fetal distress due to hypoxia and provide a window for intervention.

Uterine activity is measured transabdominally by a pressure transducer, creating a recording of the contraction frequency. Because the measurements are indirect, the strength of the contractions correlates poorly with the tracing. The tracings are position and placement sensitive.

Fetal heart rate tracings have several components that can be assessed—baseline heart rate, variability, accelerations, decelerations, and diagnostic patterns.

Baseline Heart Rate. This is the average fetal heart rate during a 10-minute period (in the absence of a uterine contraction) and is the most important aspect of fetal heart rate monitoring. Fetal bradycardia is defined as a baseline rate of less than 110 beats/min; fetal tachycardia is defined as a baseline rate of more than 160 beats/min.[2]

Variability. This can be instantaneous (beat to beat) or long term (intervals ≥ 1 minute). Both types of variability are indicators of fetal well-being. Accelerations occur during fetal movement and reflect an alert mobile fetus. Decreased variability may indicate fetal acidemia and hypoxemia or may be a side effect of a wide array of drugs, including analgesics, sedative-hypnotics, phenothiazines, and alcohol.

Decelerations. Decelerations in fetal heart rate are more complicated and should be interpreted according to the clinical scenario. There are three types of deceleration—variable, early, and late (Fig. 181.6). These terms refer to the timing of the deceleration relative to the uterine contraction.

Variable and early decelerations are common and normally represent physiologic reflexes associated with head compression in the birth canal or intermittent cord compression. Variable decelerations that are persistent and repetitive usually indicate repeated episodes of umbilical cord compression. The resultant hypoxia and acidosis may cause fetal distress. Attempts to shift maternal and fetal weight off the umbilical cord by changing position are indicated. If variable decelerations continue, the situation warrants efforts to hasten the delivery or, if obstetric backup becomes available, to perform an emergency cesarean section.

Late decelerations are more serious and most often indicate uteroplacental insufficiency. The tracing contours are generally smooth, with the heart rate nadir occurring well after a maximal uterine contraction (typically, ≥30 seconds afterward).[2] The lag, slope, and magnitude of late decelerations correlate with increasing fetal hypoxia. Late decelerations are particularly ominous in association with poor variability, nonreactivity, and baseline bradycardia. When these findings are present, immediate obstetric consultation for delivery is indicated to prevent further hypoxia.

Diagnostic Patterns. Finally, the emergency clinician should be aware of the significance of sinusoidal tracings. Tracings of this type have low baseline heart rates and little beat to beat variability. The sinusoidal tracing is an ominous finding that is often premorbid. The differential diagnosis includes erythroblastosis fetalis, placental abruption, fetal hemorrhage (trauma), and amnionitis.

Ultrasonography. In the third trimester or during labor, ultrasonography can provide crucial information pertaining to impending delivery. When a technician and radiologist are available, and if time permits, the gestational age, biophysical profile, amniotic fluid index, and a survey of fetal and placental anatomy may be obtained. The American College of Obstetricians and Gynecologists (ACOG) has published recommendations regarding the indications for ultrasonography in the third trimester (Box 181.1). The parameters of immediate interest in the ED are fetal viability (specifically in utero gestation and fetal heart rate), lie, and presentation. The use of bedside transabdominal ultrasonography by emergency clinicians to evaluate such parameters expeditiously continues to rise as this modality becomes increasingly available and operator skill improves.[3] Transvaginal ultrasonography is relatively contraindicated in the peripartum period, particularly in the cases of PROM and placenta previa.[4]

Delivery. As stage 2 of labor progresses, preparation for delivery should be under way. A radiant warmer should be available and heated. Neonatal resuscitation adjuncts should be available, including a towel, scissors, umbilical clamps, bulb suction, airway equipment (oxygen, bag-mask device with appropriate-sized masks, and tools for endotracheal intubation), and equipment to achieve vascular access. Most deliveries require only basic equipment to cut and clamp the umbilical cord, suction the

BOX 181.1

Third-Trimester Ultrasonography: Possible Indications

Determine number of fetuses.
Establish fetal presentation.
Identify fetal heart motion.
Locate placenta.
Measure amniotic fluid.
Determine gestational age.
Survey fetal anatomy.
Diagnose cord prolapse.
Diagnose cause of third-trimester bleeding.
Rule out placental abruption.

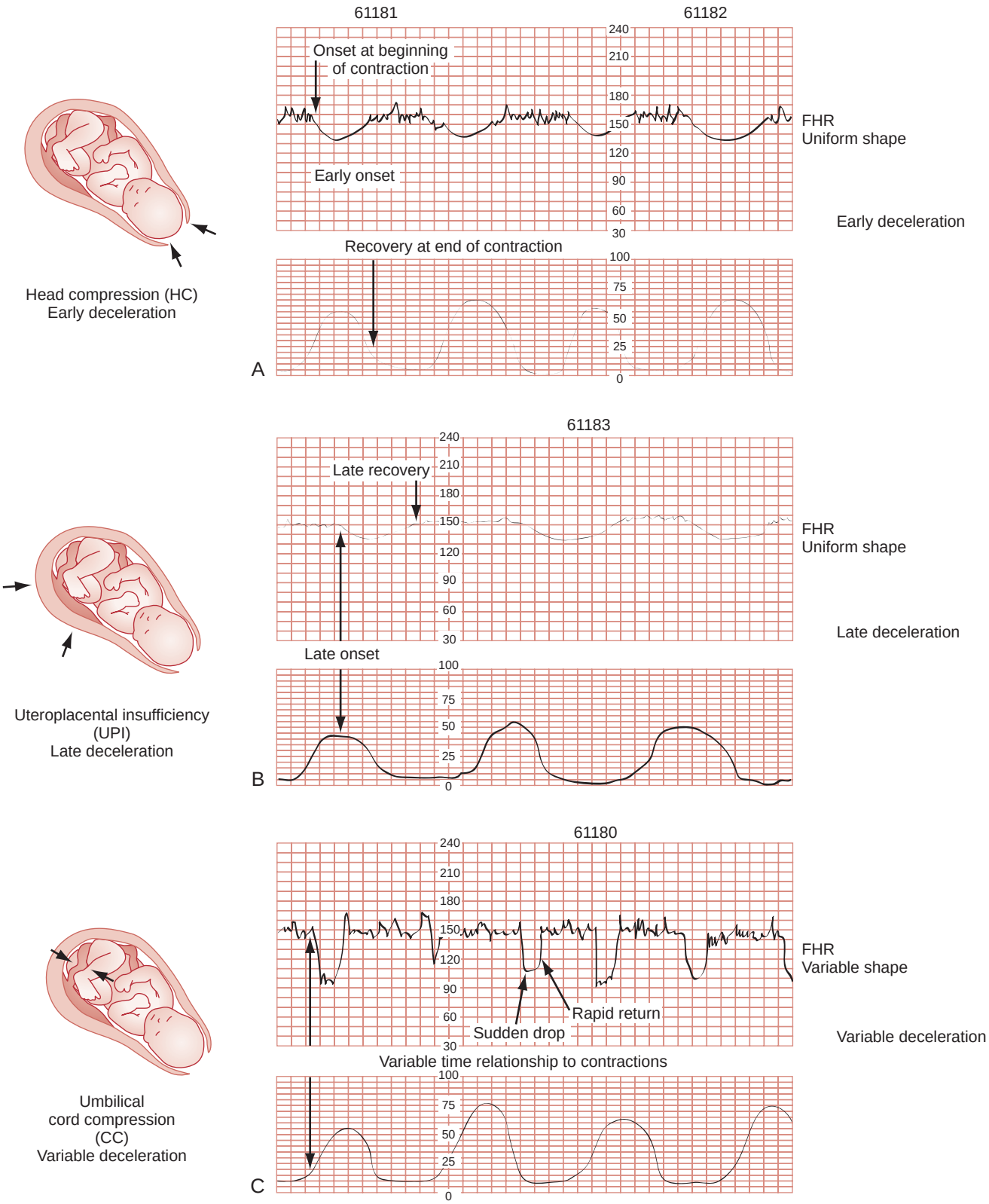

Fig. 181.6. Deceleration patterns of the fetal heart rate (FHR). **A,** Early deceleration caused by head compression. **B,** Late deceleration caused by uteroplacental insufficiency. **C,** Variable deceleration caused by cord compression. (Modified from Lowdermilk DL, et al: Maternity and women's health care, ed 6, St. Louis, 1997, Mosby.)

mouth and nose, and dry and stimulate the infant. A nurse should be at the bedside to coach and provide reassurance to the mother.

The mother is placed in the dorsal lithotomy position and prepared for delivery. The Sims position, or left lateral position with knees drawn toward the mother's chest and back to the physician, is also an acceptable position. The vulva and perineum are cleared and gently scrubbed with sterile water or saline. A repeated sterile examination to assess labor progression and confirm presentation may be performed. Firm digital stretching

of the perineum, particularly posteriorly, may prevent tears and lacerations later in delivery.

Controlled coordinated expulsion with coaching to sustain each push aids with crowning and delivery of the head. The most vulnerable moment is when the fetal head begins to stretch and distend the perineum. Instructing the mother to pant and not push slows the passage of the head and shoulders. The modified Ritgen maneuver may be used to support the perineum and prevent maternal injury. In this technique, a towel-draped, gloved hand is used to stretch the perineum and gently exert pressure on the chin of the fetus. The second hand places pressure on the occiput superiorly, guiding the head into slight extension and positioning it so that its smallest diameter passes through the pelvic outlet. Calm communication between the physician and mother is the best way to maintain control of the delivery.

After the head is delivered, the physician allows the head to rotate toward the maternal thigh and clears the fetal face and airway. Next, the shoulders, usually anterior shoulder first, clear the perineum. The shoulders often deliver spontaneously, with little effort by the physician. Gentle downward traction on the head promotes delivery of the anterior shoulder. A subsequent upward motion pulls the posterior shoulder through the pelvic outlet. If delay occurs in delivery of the shoulders, the potential for shoulder dystocia should be considered.

As the infant clears the perineum, attention focuses on the umbilical cord. The infant should be kept low or at the level of the perineum to promote blood flow into the infant from the placenta. The cord is clamped and cut. Clamps should be placed 4 or 5 cm apart, with the proximal clamp 10 cm from the infant's abdomen. An adequate umbilical stump is important for venous access if the neonate requires resuscitation. Suctioning of the nose and mouth at this time may reduce secretions that can cause increased airway resistance.

The infant is now clear of the mother and can be wrapped in towels and moved to the warmer. Gentle drying with a towel and suctioning usually provide adequate respiratory stimulation. If not, flicking the soles of the feet and rubbing the back are other modalities. Apgar scores at 1, 5, and 10 minutes after birth should be documented.

Episiotomy. With a controlled delivery, routine performance of an episiotomy is not recommended. It should be performed only for specific indications, such as shoulder dystocia or breech delivery. An episiotomy should be done before excessive stretching of the perineal muscles occurs but near the time of delivery to avoid excessive bleeding. Common practice is to cut the episiotomy when the head is visible during a contraction and the introitus opens to a diameter of 3 or 4 cm. The literature currently recommends a mediolateral incision to avoid perineal tears and rectal involvement (Fig. 181.7).

Third Stage of Labor

The third stage of labor involves the delivery of the placenta and frequent checks of the tone and height of the uterine fundus. Signs of placental separation include the following: the uterus becomes firmer and rises; the umbilical cord lengthens 5 to 10 cm; or there is a sudden gush of blood.

These signs usually occur within 5 to 10 minutes of the delivery of the infant but may extend to 30 minutes. Beyond 18 minutes, the risk of postpartum hemorrhage increases and is up to six times more likely after 30 minutes. Although the placenta may be delivered expectantly, active management reduces the length of the third stage of labor and thereby decreases the risk of postpartum hemorrhage. Active management includes the administration of uterotonic gentle traction of the clamped umbilical cord with mild pressure applied above the symphysis pubis and uterine massage after delivery. Any attempt to deliver the placenta before it separates is contraindicated.

Examination of the umbilical cord and placenta is an essential part of the delivery process and any abnormalities should be noted at this time. The umbilical cord is normally a three-vessel structure, with two umbilical arteries on either side of the single umbilical vein. A two-vessel cord (one umbilical artery) occurs in 1 of 500 deliveries and is more prevalent in African Americans. Common abnormalities of the placenta include accessory lobes and abnormal cord insertion. Visible clots adherent to the uterine aspect may indicate placental abruption and the discovery of an incomplete placenta or membranes should alert the emergency clinician to the possibility of postpartum complications.

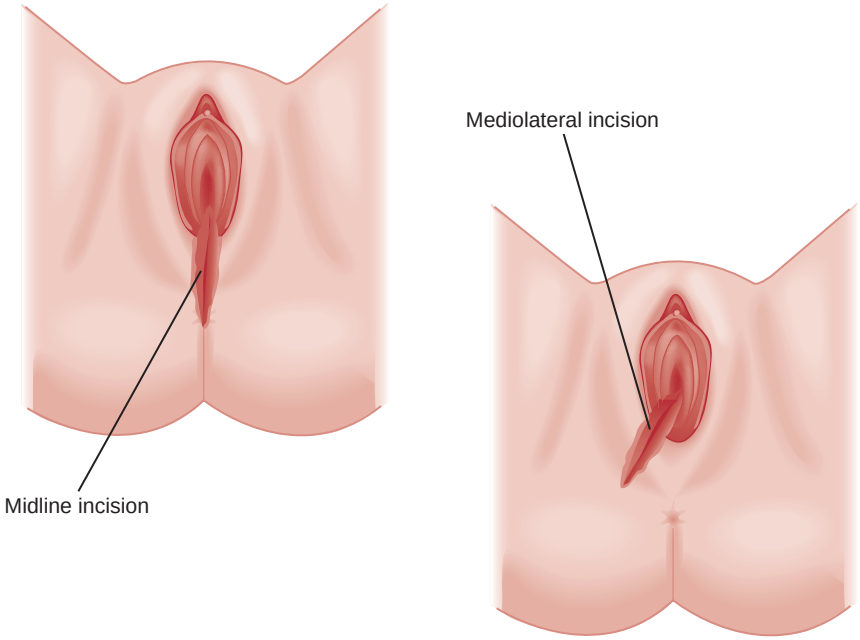

Fig. 181.7. A mediolateral episiotomy incision is preferred to a strictly midline incision. (Adapted from www.aurorahealthcare.org/healthgate/images/exh44028a_ma.jpg.)

Fourth Stage of Labor

The fourth stage of labor refers to the first hour after delivery of the placenta and is a critical period during which postpartum hemorrhage is most likely to occur. The cervix and vaginal fornices should be inspected for deep lacerations as a result of delivery, and repair of any vaginal lacerations should be performed at this time.

Finally, oxytocin is infused to promote contraction of the uterus and control hemorrhage. The uterus is evaluated frequently for tone and massaged transabdominally if any sign of relaxation exists. Oxytocin should not be given before delivery of the placenta because this could result in the trapping of placental fragments or may hinder the delivery of an undetected twin.

THIRD-TRIMESTER COMPLICATIONS ASSOCIATED WITH DELIVERY

Obstetric problems in the third trimester often result in the initiation of labor. Premature labor, PROM, and third-trimester bleeding are relatively common complications. The fundamental question to be addressed in these settings is whether the fetus would fare better in utero or delivered.

Premature Labor

Premature or preterm labor and fetal immaturity are the leading causes of neonatal mortality. Preterm labor is defined as uterine contractions with cervical changes before 37 weeks of gestation. Many underlying conditions result in preterm labor, which is associated with 5% to 18% of all pregnancies and is the leading cause of neonatal death.[5] Factors linked to this problem include substance abuse, history of preterm delivery, multiple gestations, placental anomalies, infections, and lifestyle or psychosocial stressors (Box 181.2). The unexpected nature of premature labor often results in an ED visit. When delivery is not imminent, the patient can be moved to the obstetrics unit for further care.

BOX 181.2

Factors Linked to Preterm Labor

DEMOGRAPHIC AND PSYCHOSOCIAL
Extremes of age (>40 yr, teenagers)
Lower socioeconomic status
Tobacco use
Cocaine abuse
Prolonged standing (occupation)
Psychosocial stressors

REPRODUCTIVE AND GYNECOLOGIC
Prior preterm delivery
Diethylstilbestrol exposure
Multiple gestations
Anatomic endometrial cavity anomalies
Cervical incompetence
Low pregnancy weight gain
First-trimester vaginal bleeding
Placental abruption or previa

SURGICAL
Prior reproductive organ surgery
Prior paraendometrial surgery other than genitourinary (appendectomy)

INFECTIOUS
Urinary tract infections
Nonuterine infections
Genital tract infections (bacterial vaginosis)

Clinical Features

The diagnosis of preterm labor requires the identification of uterine activity and cervical changes before 37 weeks of gestation. Early maternal signs and symptoms include an increase or change in vaginal discharge, pain resulting from uterine contractions (sometimes perceived as back pain), pelvic pressure, vaginal bleeding, and fluid leak.

Diagnostic Testing

If uterine contractions and cervical changes are present, and the estimated fetal weight on ultrasonography is less than 2500 g, the diagnosis of premature labor is likely. The differentiation of false labor from true labor is best done by electrical monitoring. The initial evaluation of a woman with possible preterm labor includes urinalysis, complete blood count, and pelvic ultrasonography. If delivery is not imminent, these studies can be performed under monitoring in the ED or obstetrics area. Whenever possible, these patients should be transferred to a perinatal center with an associated intensive care unit.

Management

A viable fetus and healthy mother are indications for medical management directed toward the prolongation of gestation. Preterm labor should not be postponed with medical management in the cases of fetal compromise, major congenital anomalies, intrauterine infection, placental abruption, eclampsia, significant cervical dilation, or PROM.

The treatment of preterm labor involves multiple modalities and is usually performed outside the ED. Tocolytics and fetal maturation therapy combined with bed rest and hydration are used with the hope of prolonging pregnancy (Box 181.3). When tocolytics are indicated, they should be used in coordination with an obstetric consultant because their initiation may arrest premature labor, delaying delivery for 48 to 72 hours.[6] These patients optimally should be transferred to an appropriate center before delivery, whenever possible, because medical management fails in more than 25% of preterm patients for whom it is attempted. It is important to review the contraindications to tocolytics before initiation of these therapies (Box 181.4). Any patient receiving tocolytics should be monitored for signs of fetal distress.

BOX 181.3

Commonly Used Tocolytic Agents

Magnesium sulfate
- 4–6 g IV bolus over 20 min
- 2–4 g/hr IV infusion

Terbutaline
- 5–10 mg PO q4–6h
- 0.25 mg SC q20min
- 10–80 μg/min IV

Ritodrine[a]
- 10 mg PO q2–4h
- 10 mg IM q3–8h
- 0.05–0.35 mg/min IV infusion

Isoxsuprine
- 20 mg PO q6h
- 0.2–0.5 mg/min IV infusion

[a]Ritodrine and Isoxsuprine have been discontinued in the United States.

BOX 181.4

Contraindications to Tocolysis

ABSOLUTE

Acute vaginal bleeding
Fetal distress (not tachycardia alone)
Lethal fetal anomaly
Chorioamnionitis
Preeclampsia or eclampsia
Sepsis
Disseminated intravascular coagulopathy

RELATIVE

Chronic hypertension
Cardiopulmonary disease
Stable placenta previa
Cervical dilation > 5 cm
Placental abruption

Premature Rupture of Membranes

Clinical Features

PROM is defined as rupture of the amniotic and chorionic membranes before the onset of labor. It affects 3% of all gestations. During pregnancy, the chorionic and amniotic membranes protect the fetus from infection and provide an environment that allows fetal growth and movement. The amniotic fluid is constantly exchanged by fetal swallowing and urination and umbilical cord transfer.

The word *premature* in PROM refers to rupture before labor, not to fetal prematurity. In 8% of PROM cases, the fetus is at or near term, and PROM may result in normal labor. When PROM occurs before 37 weeks, it is called preterm PROM and is associated with significant fetal morbidity and mortality. PROM is the inciting event in one-third of all preterm deliveries.

After the membranes rupture, the period from latency to the onset of labor varies. Longer latent periods are common earlier in pregnancy, and the latency shortens as gestational age increases. At term, labor is a desirable result of PROM, but with fetal immaturity, delivery would result in fetal complications.

Diagnostic Testing

The diagnosis of PROM can be established by the history and physical examination. In most cases, the patient suggests the diagnosis and usually is correct. The patient typically describes a spontaneous gush of watery fluid, followed by a mild persistent seepage. Urinary incontinence or excess vaginal or cervical secretions are occasionally confused with PROM.

Examination of women with potential PROM is performed under sterile conditions to prevent ascending infection. Direct digital examination of the cervix is avoided. The identification of amniotic fluid was previously discussed. Table 181.1 summarizes the bedside testing modalities available to confirm the diagnosis of PROM. Visualization of the cervix for a prolapsed cord or small fetal part is performed during the evaluation for effacement and dilation. Culture specimens for group B streptococci, *Chlamydia trachomatis,* and *Neisseria gonorrhoeae* should be obtained.

TABLE 181.1

Bedside Testing for Premature Rupture of Membranes

METHOD	RESULT
Nitrazine	Amniotic fluid (pH > 6.5) will turn nitrazine paper blue; normal vaginal secretions (pH < 5.5) leave nitrazine paper yellow
Ferning	Amniotic fluid crystallizes
Smear combustion	Amniotic fluid, when flamed, turns white and crystallizes; vaginal secretions caramelize, turn brown

Management

When the diagnosis of PROM is established, management depends on several factors, including the gestational age and fetal maturity, presence of active labor, presence or absence of infection, presence of placental abruption, and degree of fetal well-being or distress. In all cases, fetal heart rate monitoring, obstetric consultation, and admission are indicated. In the immature fetus (24–31 weeks of gestation), the initiation of specific treatment decisions aimed at accelerating fetal maturity should be made in coordination with the receiving obstetrician. This includes the possible administration of corticosteroids to promote pulmonary maturation. Patients with PROM between 31 and 33 weeks' gestation are usually managed expectantly and those at or beyond 34 weeks of gestation are generally delivered.

All patients with PROM should be assessed for intraamniotic infection. Infectious complications should be diagnosed and treated before the mother demonstrates overt clinical signs. Preterm PROM is generally treated with intravenous ampicillin, clindamycin, or erythromycin.[7] Treatment of term PROM is indicated when the patient is positive for group B streptococcus or has not been tested.

Chorioamnionitis

Chorioamnionitis occurs when vaginal or cervical bacteria ascend into the uterus, instigating an inflammation of the chorion and amnion layers of the amniotic sac. It occurs in 1% to 10% of all pregnancies; risk factors include prolonged labor, PROM, excessive vaginal examinations, and recent amniocentesis. Box 181.5 summarizes the findings and evaluation of chorioamnionitis. Chorioamnionitis may result in prolonged first- and second-stage labor and decreased responsiveness to oxytocin. Early aggressive treatment, even before evidence of infection occurs, decreases neonatal morbidity and delays delivery, allowing more time for fetal maturation.

Vertical Transmission of Human Immunodeficiency Virus

ED deliveries may involve women who are known to be positive for human immunodeficiency virus (HIV), in addition to women who are infected but have never been tested. The latter group generally includes pregnant women with little or no prenatal care who are at risk for precipitous delivery. In 2005, between 215 and 370 infants were born in the United States with HIV infection. Of these, approximately 30% were born to mothers undiagnosed with HIV infection before delivery.[8] Transmission may occur in the antepartum, intrapartum, or postpartum (breast-feeding) period. Because intrapartum transmission accounts for up to 75% of vertically transmitted HIV infections, antiretroviral therapy on presentation, even while labor progresses, can decrease vertical HIV transmission. Risk factors for transmission include high viral loads, prolonged rupture of membranes, maternal drug use, vaginal delivery, and breast-feeding.

BOX 181.5

Chorioamnionitis Evaluation

FLUID IN VAGINAL VAULT
Phosphatidylglycerol

CERVICAL CULTURES
Escherichia coli and other gram-negative bacteria
Neisseria gonorrhoeae

VAGINAL CULTURES
Chlamydia spp.
Mycoplasma hominis
Group B streptococci
Ureaplasma urealyticum

AMNIOCENTESIS STUDIES
Gram stain (group B streptococci)
Culture
Glucose
Lecithin to sphingomyelin ratio

MATERNAL SIGNS AND SYMPTOMS
Premature rupture of membranes
Uterine tenderness
Fever
Tachycardia (maternal or fetal)
Malodorous vaginal discharge
Leukocytosis

FETAL SIGNS AND SYMPTOMS
Decreased activity
Abnormal biophysical profile (ultrasonographic examination)
Fetal tachycardia
Decreased variability of fetal heart rate

Advances in point of care testing for HIV has resulted in the ability to make a preliminary diagnosis in a a patient with HIV in the ED. In November 2002, the US Food and Drug Administration approved the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Bethlehem, PA).[9] With a median turnaround time of 45 minutes, this test realistically allows an emergency clinician to initiate intrapartum and neonatal antiretroviral therapy when the test result is positive. Serologic confirmation is recommended, but emergent interventions can proceed on the basis of the bedside result. It has been shown that immediate treatment during labor can significantly decrease vertical transmission to the newborn. Moreover, a positive HIV test result may, in some cases, allow a change in the method of delivery, because cesarean section decreases the rate of HIV transmission compared with vaginal delivery methods.[10] Decisions regarding initiation of antiretroviral therapy, as well as mode of delivery, should be made in consultation with an obstetrician and neonatologist, when available.

COMPLICATED DELIVERY

Background

Complicated deliveries, involving dystocia, malpresentation, and multiple gestations, are potentially life-threatening emergencies. The emergency clinician cannot solve these obstetric problems with cesarean section and will therefore face the prospect of an extremely high-risk vaginal delivery. As expected, these abnormal deliveries increase the risk of fetal and maternal complications. Aggressive attempts to obtain obstetric, neonatal, and anesthesia support are warranted. If the delivery proceeds in the ED, preparations for maternal and neonatal resuscitation should be made rapidly.

Knowledge of abnormal labor and its anatomy and physiology is important for the emergency clinician facing a complicated delivery. Intrapartum management skills will enable him or her to proceed with delivery in an efficient and capable manner.

TABLE 181.2

Relative Incidence of Malpresentations

MALPRESENTATION	INCIDENCE
Breech presentation	1/25 live births
Shoulder dystocia	1/300 live births
Face presentation	1/550 live births
Brow presentation	1/1400 live births

Dystocia and Malpresentation

Dystocia, or abnormal labor progression, accounts for one-third of all cesarean sections and half of primary cesarean sections. Because rapid surgical resolution is unavailable to the emergency clinician, intrapartum management skills are important.

Dystocia can be divided into three categories of causative factors. Labor fails to progress when there are problems related to: the pelvic architecture (the passage), fetal size or presentation problems (the passenger), and inadequate uterine expulsive forces. Although it is useful to consider these causes independently, dystocia is usually caused by a combination of factors. Presentation problems are particularly important because they become apparent during stage 2 of labor and require immediate action.

In order of increasing incidence, brow, face, shoulder, and breech presentations are the most common malpresentations (Table 181.2). True fetopelvic disproportion is much less common. Cesarean section is indicated when labor arrest or cord prolapse coexists with these presentations.

Breech Delivery

Breech is the most common malpresentation, occurring in just less than 4% of all deliveries. Three types of breech presentation exist—frank, incomplete, and complete (Fig. 181.8; Box 181.6). The main mechanical problem with breech presentations is that the buttocks and legs do not provide a sufficient wedge, hindering cervical accommodation of the relatively larger head. In addition, because the presenting part does not occlude the cervical opening completely, umbilical cord prolapse may occur.

By convention, the presentation (frank, incomplete, and complete) is followed by the relationship of the fetus to the birth canal, with the fetal sacrum as a reference point. Correlated with this abnormal presentation are several factors, such as prematurity, multiparity, fetal abnormalities, prior breech presentation, polyhydramnios, and uterine abnormalities.

Overall, one-third of breech fetal deaths are believed to be preventable. Asphyxia is often due to umbilical cord prolapse or entrapment of the head. Other complications include labor arrest or brachial plexus injuries, and fetal head and neck trauma can occur if inappropriate delivery techniques are used. Scheduled cesarean section for these patients reduces the potential for an ED presentation. However, emergency clinicians should be prepared for vaginal delivery of breech presentations in the event of premature or unforeseen labor in the absence of immediate surgical services.

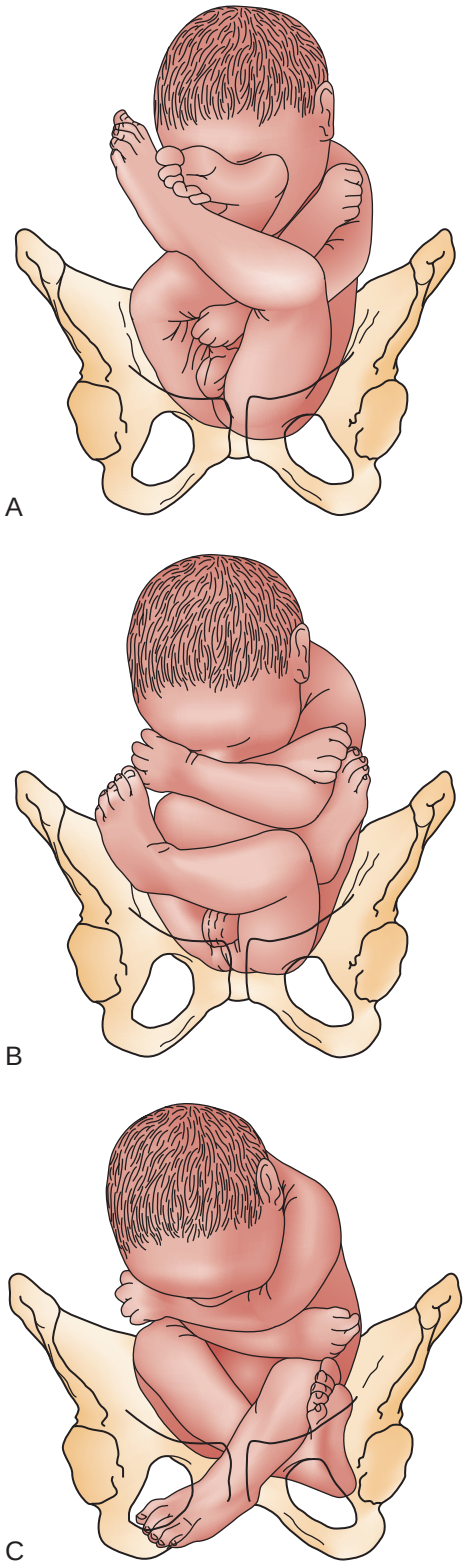

Fig. 181.8. Breech presentations. **A,** Frank breech presentation. **B,** Complete breech presentation. **C,** Incomplete breech presentation. (Adapted from Cunningham FG, et al: Williams obstetrics, ed 19, Norwalk, CT, 1993, Appleton & Lange.)

Diagnostic Testing

Before labor, Leopold's maneuvers facilitate the diagnosis of breech presentation. For the emergency clinician, however, active labor restricts the use of Leopold's maneuvers, and a vaginal examination is required. The differentiation of a vertex presentation from a breech presentation by tactile vaginal exam may be difficult. Whenever a fontanel is not identified on examination, a breech presentation should be suspected. It is helpful to remember that the face and skull have a complete circle of bone, whereas the anus is flanked by bone on only two sides.

If time permits, an ultrasound examination is indicated to distinguish the type of breech presentation, gestational age, fetal weight, and position of the fetal arms and neck. If the fetus has a hyperextended neck, vaginal delivery is associated with a high incidence of spinal cord injuries. If possible, labor should be delayed to allow cesarean section. Similarly, if the arms are over the head, they increase the dystocia when the head enters the birth canal.

BOX 181.6

Breech Presentations

FRANK BREECH
60%–65% of all breech presentations
Hips flexed, knees extended
Buttocks act as good dilating wedge
Incidence of cord prolapse ≈ 0.5%

COMPLETE BREECH
Least common; occurs in ≈5% of all breech presentations
Hips and knees flexed
Buttocks act as good dilating wedge
Incidence of cord prolapse is 5%–6%

INCOMPLETE BREECH
25%–35% of all breech presentations
Incomplete hip flexion, single or double footling
Poor wedge
Increased incidence of prolapsed cord (15%–18%)

Management

Premature infants in the breech position often deliver spontaneously without difficulty. As the infant comes to term, dystocia becomes increasingly common. With commitment to a vaginal delivery, knowledge of breech dystocia mechanics may allow atraumatic delivery. The key goals are to maximize the size of the passage and to minimize the dystocia of the after-coming head. Box 181.7 summarizes the actions associated with successful vaginal breech delivery.

The Mauriceau maneuver is the use of the fetal oral aperture to flex the fetal neck and draw in the chin. Because fetal neck extension is associated with cord injuries and worsening dystocia, this maneuver is useful to ensure a successful vaginal delivery. This maneuver should only be attempted once the fetal elbows and chin have entered the pelvic inlet to avoid inducing the Moro reflex, in which fetal head flexion results in the arms being suddenly extended. During this maneuver, the fetal pelvis should be supported to avoid abdominal injuries. A generous episiotomy may be necessary to facilitate the maneuver in a full-term infant. If the after-coming head cannot be delivered quickly, the chances of good fetal outcome are poor.

Shoulder Dystocia

Shoulder dystocia is the second most common malpresentation, occurring in 1.4% of all deliveries.[11] In contrast to a breech presentation, which may be diagnosed in the antepartum period, shoulder dystocia develops in the intrapartum period. Maternal and fetal factors are associated with shoulder dystocia. Maternal

BOX 181.7

Vaginal Breech Delivery

ACTIONS TO DO AS ABLE

Monitor fetal heart rate.
Obtain a focused history.
Diagnose a breech lie.
Determine cervical dilation and station.
Obtain an ultrasound or plain radiographic study.
Evaluate for prolapsed cord if there is spontaneous rupture of membranes.
Perform an episiotomy.
Flex knees and sweep out legs.
Pull out a 10- to 15-cm loop of cord (room to work) after the umbilicus clears the perineum.
Use the bony pelvis as a means of holding the infant.
Keep face and abdomen away from the symphysis and use rotation to deliver the more accessible arm.
Perform the Mauriceau maneuver.

ACTIONS TO AVOID

Inappropriate transfer with delivery en route
Misdiagnosis of cervical dilation
Iatrogenic rupture of membranes (cord prolapse)
Moving of patients or leaving them unmonitored
Traction on the fetus during delivery
Grasping of the fetus by the waist, causing abdominal organ injury
Arm entrapment over head
Neck hyperextension

factors include diabetes, obesity, and precipitous or protracted labor; fetal factors include macrosomia, postmaturity, and erythroblastosis fetalis. Shoulder dystocia responds well to a variety of intrapartum maneuvers; therefore, the skill involved during delivery is an important determinant of fetal outcome.

The consequences of shoulder dystocia can be devastating. As with a breech presentation, infant complications are more common and severe than maternal complications. Traumatic brachial plexus injuries, clavicular fractures, and hypoxic brain injury are all well-documented complications. Maternal complications are related to traumatic delivery and include vaginal, perineal, and anal sphincter tears, as well as urinary incontinence.

Diagnostic Testing

Shoulder dystocia is diagnosed clinically by the inability to deliver either shoulder. The fetal head may appear to retract toward the maternal perineum, otherwise known as the turtle sign. Traction on the head extends and abducts the shoulders, increasing the bisacromial diameter and worsening the dystocia. Fig. 181.9 shows the normal and abnormal relationship of the shoulders to the birth canal and illustrates why the bisacromial diameter is an important element of fetal biometry.

Normally, the shoulders negotiate the maternal pelvis in sequential fashion, anterior shoulder first. With shoulder dystocia, both shoulders attempt to clear the maternal pelvis simultaneously. In addition to the turtle sign, examination often reveals that the fetal shoulders are on a vertical axis, rather than oblique. These findings, in combination with an arrested delivery, confirm the diagnosis of shoulder dystocia.

Management

When shoulder dystocia becomes evident, knowledge of intrapartum delivery maneuvers can be lifesaving. Successful vaginal

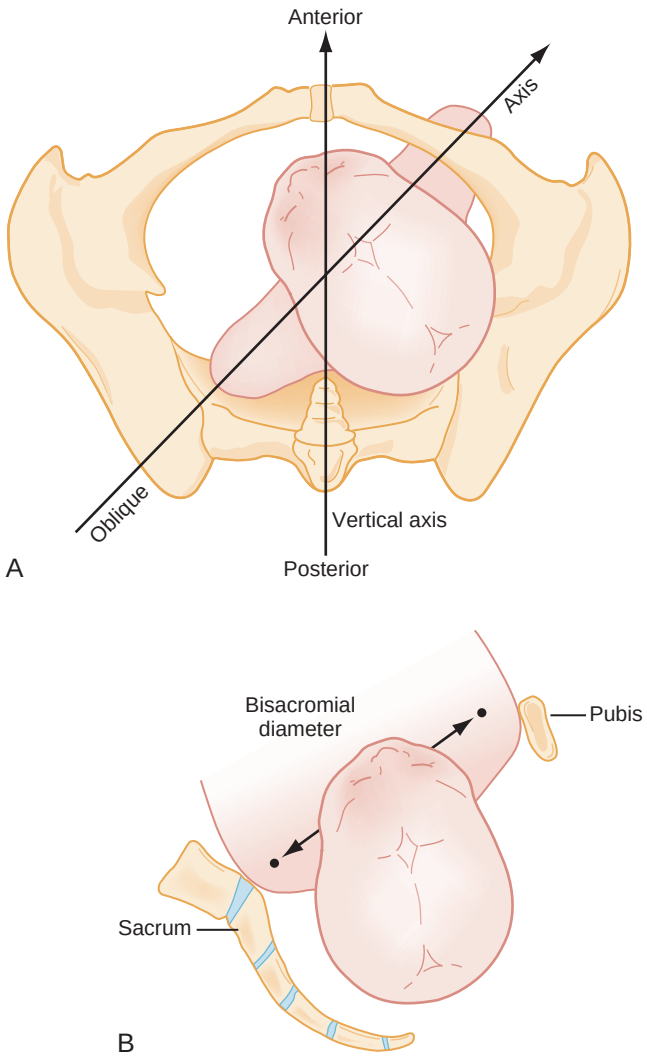

Fig. 181.9 **A,** Normal delivery. As the fetal head rotates, the shoulders assume an oblique position and enter the pelvis one at a time. **B,** Shoulder dystocia. Both shoulders attempt to clear the pelvis simultaneously, forcing the bisacromial diameter into the opening.

delivery is most likely when a directed sequential approach to each maneuver is used. A rapid resolution of shoulder dystocia is important to avoid fetal asphyxia and resultant central nervous system injury. Obstetric and neonatology assistance may improve the outcome, and aggressive attempts to obtain assistance are warranted.

Initial attempts to resolve shoulder dystocia involve increasing the anteroposterior diameter of the passage. An episiotomy may be used for fetal maneuvering by allowing access to the posterior shoulder. Anteriorly, draining the bladder with a Foley catheter can generate room.

The most important first step is to use McRoberts' maneuver (Fig. 181.10). Maternal leg flexion to a knee-chest position may disengage the anterior shoulder, allowing rapid vaginal delivery to follow. This maneuver "walks" the pubic symphysis over the anterior shoulder and flattens the sacrum, helping the fetus pass through the birth canal, one shoulder at a time. This method, although requiring very little effort, is often successful in alleviating shoulder dystocia.

If McRoberts' maneuver fails to free the anterior shoulder, the application of suprapubic pressure may accomplish this by forcing the anterior shoulder to slip beneath the pubis or posterior shoulder to retreat into the hollow of the sacrum. Digital pressure

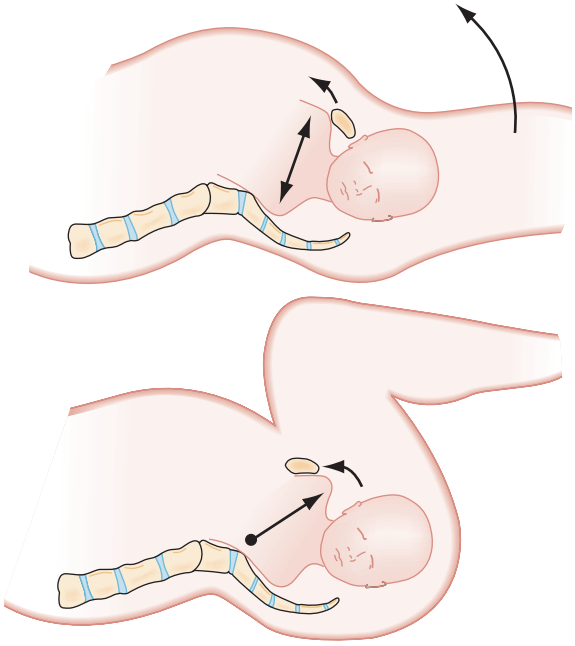

Fig. 181.10. McRoberts' maneuver. *Top,* Bisacromial diameter pinned behind pubic symphysis. *Bottom,* Removing the maternal legs from the stirrups and putting the knees up to the chest act as a fulcrum to the pubic symphysis over the impacted anterior shoulder.

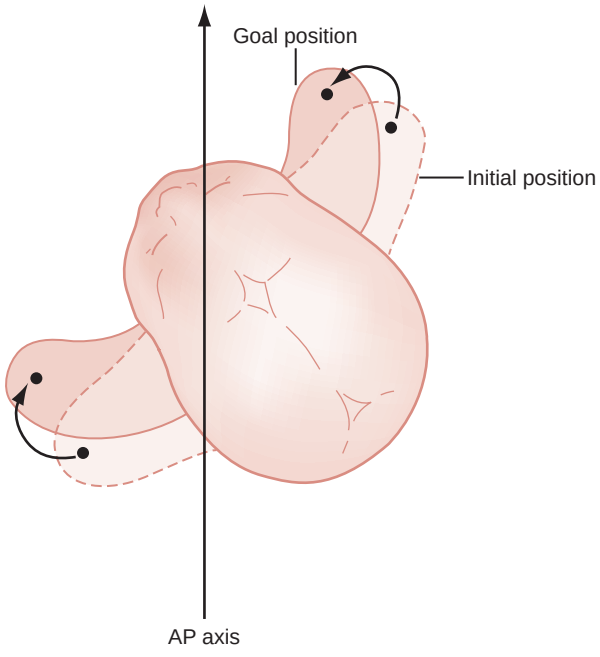

Fig. 181.11. Rubin's maneuver decreases the bisacromial diameter. *AP,* Anteroposterior.

on the posterior shoulder (through the episiotomy) may help facilitate posterior shoulder retreat. The use of the McRoberts' maneuver and suprapubic pressure resolve most cases of shoulder dystocia.

If delivery is still impossible, the next step is to attempt Rubin's maneuver (Fig. 181.11). The goal of this maneuver is to decrease the bisacromial diameter by pushing the most accessible shoulder toward the fetal chest. Often, both shoulders assume the same attitude, decreasing the bisacromial diameter and allowing delivery. Attempts to manipulate the shoulders for Rubin's maneuver may be transabdominal, through the introitus (anterior shoulder), or through the episiotomy (posterior shoulder).

If the shoulders remain undeliverable, the next step is to use Wood's corkscrew maneuver. In this process, the impacted shoulders are released through rotation of the fetus 180 degrees. Fetal rotation is achieved by pushing the most accessible shoulder in toward the chest. The fetal axilla can be snared with a digit, or a hand can be slid in along the fetal spine to sweep the hips and generate rotation. Wood's corkscrew maneuver is difficult to perform but should be attempted before reaching for an arm.

If the fetus remains trapped and several attempts have failed to yield delivery, consideration of delivery of an arm is appropriate. A hand is introduced along the posterior aspect of the posterior shoulder. The posterior arm is swept across the chest, bringing the fetal hand up to the chin. Attempts to splint the humerus may prevent fractures and brachial plexus injuries. The fetal hand is grasped and pulled out of the birth canal across the face, delivering the posterior shoulder.

The mnemonic HELPER (Box 181.8) has been proposed to help keep these steps organized and facilitate a sequential approach. These steps successfully deliver almost all cases of shoulder dystocia.

BOX 181.8

HELPER Mnemonic for Shoulder Dystocia

Help—obstetrics, neonatology, anesthesia
Episiotomy—generous, possibly even episioproctotomy
Legs flexed—McRoberts' maneuver
Pressure—suprapubic pressure, shoulder pressure
Enter vagina—Rubin's maneuver or Wood's maneuver
Remove posterior arm—Splint, sweep, grasp, and pull to extension.

Face, Brow, and Compound Presentations

Face and brow presentations yield a larger engaging aspect of the fetal head and predispose to labor arrest. Although these abnormal presentations can be diagnosed with ultrasonography or Leopold's maneuvers, most are discovered during labor by vaginal examination. Approximately 50% are discovered during the second stage of labor.

The engaging diameter of the head in vertex position is approximately 0.8 cm less than a face presentation and 1.5 cm less than a brow presentation. Face presentations are described with the chin as a reference point (eg, mentum anterior). Face presentation is managed expectantly. The obstetric adage—"if a face presentation is progressing, leave it alone"—is based on the fact that mentum anterior presentations usually deliver vaginally, and mentum transverse presentations frequently rotate to become mentum anterior. Brow presentations, occurring when the fetal head is partially flexed, also spontaneously convert to a vertex or face presentation in more than 50% of cases.

A persistent mentum posterior face and brow presentation cannot be delivered vaginally if the fetus is full term. The resultant labor arrest requires symphysiotomy or cesarean section. Prolongation of the second stage is the most common outcome of both these malpresentations at term. For the emergency clinician, this prolonged second stage may provide a window during which obstetric help may arrive.

Compound presentations are those in which an extremity enters the birth canal with the head or breech. Small and premature fetuses generally proceed to vaginal delivery without incident.

Labor arrest and umbilical cord prolapse are accepted indications for cesarean section in the setting of face, brow, and

compound presentations. Manipulation of a compound presentation, including attempts to reduce the hand or arm, increases the rate of cord prolapse. Therefore, manipulation attempts are contraindicated. Cord prolapse rates are 10% to 20%, even without manipulation. Close monitoring and careful examination are indicated.

MULTIPLE GESTATIONS

Due to the increasing use and availability of fertility treatments, the incidence of multiple gestation pregnancies has been increasing. In 2013, twin deliveries accounted for 33.7/1000 births in the United States. Because multiple gestation deliveries have a higher incidence of preterm labor and low birth weights, maternal and fetal complication rates are correspondingly increased.[12]

Diagnostic Testing

Most women with multiple gestations have the situation identified well before the third trimester. In patients who have had little or no prenatal care, bedside ultrasonography allows for a rapid diagnosis. The stages of labor for twins and other multiple gestations are similar to the stages for a singleton. Of importance to the emergency clinician is a relatively short latent phase of labor, with rapid progression to the active phase. The active phase is usually longer, however, and may allow time for obstetric assistance to arrive.

Vertex twin A and vertex twin B occur in approximately 42% of deliveries. One of the twins presents in a nonvertex position in approximately 35% to 40% of cases.[13]

Management

The presentation of twins is an important determinant for the safety of vaginal delivery. Twins who are vertex-vertex can be delivered vaginally, barring any other obstetric complication. If twin B is nonvertex, many obstetricians recommend cesarean section to prevent delivery-related complications for twin B. External cephalic version and breech extraction are possible maneuvers to facilitate precipitous vaginal delivery. Generally, if twin A is nonvertex, cesarean section is preferred. In such cases, efforts should be made to delay delivery until an operative approach can be used. Proceeding vaginally can result in the interlocking of twins, associated with a high mortality.[13]

The interval between the delivery of twin A and twin B is variable. In most cases, twin B delivers in minutes. When twin B does not follow rapidly, in utero assessment is important to document fetal well-being. If fetal heart tracings are reassuring, the delivery of twin B (especially nonvertex) should not be hastened. Repeated ultrasonographic evaluation may also be used to confirm twin B's presentation and well-being.

After every ED delivery, particularly deliveries that are precipitous or that occur in the out-of-hospital setting, the mother should be examined for the possibility of twins. Ongoing labor may be confused with postpartum cramping, only to have twin B and all the potential complications surprise the emergency clinician. This is particularly relevant for women with inadequate prenatal care and low-birth-weight infants.

UMBILICAL CORD-RELATED EMERGENCIES

Umbilical cord–related complications can occur in normal and abnormal deliveries. Immediate intervention is required to prevent fetal morbidity and mortality. The spectrum of cord-related emergencies includes prolapsed cord, nuchal loops of the umbilical cord, body coils, cord knots, and entangled cords in monoamniotic twins. The cord length is believed to be proportional to fetal activity in utero during the first and second trimesters. Excess cord length increases the potential for umbilical cord complications of all types. Because the umbilical cord supplies the fetus with all its oxygen, interruption of cord circulation before establishment of fetal respiration is a life-threatening emergency. Fetal asphyxia caused by cord circulation compromise is potentially preventable with appropriate delivery interventions.

Umbilical Cord Prolapse

Clinical Features

Umbilical cord prolapse occurs when the umbilical cord precedes the fetal presenting part or when the presenting part does not fill the birth canal completely. Most cases of cord prolapse are unexpected and develop during the second stage of labor.

Cord prolapse has a variable rate of association with different fetal presentations. Compound, shoulder, and breech presentations yield gaps and a relatively poor dilating wedge. Table 181.3 summarizes the rates of umbilical cord prolapse with various fetal presentations. Malpresentations account for 50% of all cord prolapse cases and the prolapsed cord itself may be the first indication of a malpresentation. The reported incidence of cord prolapse ranges from 1.4 to 6.2/1000 deliveries, and associated perinatal mortality is estimated to be just below 10%.[14]

Diagnostic Testing

Umbilical cord prolapse may be overt or occult, requiring a pelvic examination to reveal the umbilical cord lying beside the presenting part. The diagnosis may also be made with Doppler ultrasonography. In most cases, the diagnosis is obvious, and the cord is encountered at the perineum or introitus.

Management

When a prolapsed cord occurs with a viable infant, cesarean section is the delivery method of choice. If surgical delivery is available, maneuvers to preserve umbilical circulation should be instituted immediately. The mother should be placed in the knee-chest position, with the bed in the Trendelenburg position, because the presenting part is manually elevated off the umbilical cord. It is crucial that the mother be instructed to refrain from pushing to avoid further compression of the cord. Placement of a Foley catheter and instillation of 500 to 750 mL of saline into the bladder may help lift the fetus off the cord, particularly during the first stage of labor.[14]

Preparation for an emergency cesarean section should be under way. The time from prolapse to surgical intervention is an

TABLE 181.3

Conditions Associated With Umbilical Cord Prolapse

PRESENTATION	INCIDENCE (%)
Vertex	0.14
Breech	2.5–3.0
Frank breech	0.4
Complete breech	5
Incomplete breech	10
Shoulder	5–10
Compound	10–20
Face or brow	Rare

important factor in fetal outcome. Perinatal mortality rates are significantly higher for out-of-hospital cases versus those within a monitored setting, and outcomes correlate with time from diagnosis to delivery.

If timely surgical delivery cannot be performed, funic reduction—manual replacement of the cord into the uterus—and rapid vaginal delivery may be necessary. The same maneuvers to decrease cord compression should be used, pushing gently on the cord in a retrograde fashion, above the presenting part. Manipulation and cord trauma should be kept to a minimum because resultant vasospasm can cause fetal hypoxia. After funic reduction, the development of umbilical cord body coils or nuchal loops is common and should be anticipated.[14]

Cord Entanglement

The umbilical cord can also become entangled with itself, spontaneously knotting. Umbilical cord knots are related to intrauterine movements early in pregnancy. Approximately 5% of stillbirths are found to have knots that are believed to have caused fetal demise. Despite this association, cord knots can persist without problems as long as perfusion is maintained.

Loose umbilical cord knots pulled tight at delivery may cause fetal distress. As with cord prolapse, this situation must be resolved quickly to prevent fetal asphyxia. Rapid delivery with avoidance of further cord traction optimizes fetal outcome. No specific interventions have been identified to deal with this problem.

Long umbilical cords are associated with true knots, as well as with entanglements and prolapse. Umbilical cord loops can be single or multiple and can occur around the neck or body. Because the fetal limbs are short and flexed in most presentations, they are rarely involved. Although generally benign, umbilical cord loops may result in fetal complications, such as nonreassuring fetal status and respiratory distress.

During delivery, loose nuchal cords should be reduced at the perineum. Loose body coils usually disentangle spontaneously. The reduction process may be aided by slipping them over the extremities or forward over the head. On occasion, loops are tight enough to impede delivery and cannot be reduced. The solution is to cut the clamped cord and deliver the infant rapidly. The high frequency of nuchal loops (one in five births) means that the emergency clinician should expect to encounter this problem.

MATERNAL COMPLICATIONS OF LABOR AND DELIVERY

Maternal complications of labor and delivery include postpartum hemorrhage, uterine inversion and rupture, amniotic fluid embolism, and infections. Although some are managed medically, severe complications threaten the reproductive future and life of the mother, thereby requiring emergent surgical intervention.

Postpartum Hemorrhage

Clinical Features

Postpartum hemorrhage is the most common complication of labor and delivery. Defined as hemorrhage of more than 500 mL after vaginal delivery, it affects 5% to 10% of all deliveries and accounts for up to 25% of obstetric deaths. Postpartum hemorrhage is divided into two categories; the primary category includes blood loss that occurs within the first 24 hours, and the secondary category is hemorrhage 24 hours to 6 weeks after delivery. The clinical picture is as expected with any type of hemorrhage although, because of maternal adaptations during pregnancy, the patient may not show signs of shock until more than 1500 mL of volume has been lost.

Differential Diagnosis and Management

The differential diagnosis of primary postpartum hemorrhage includes uterine atony, genital tract trauma, retained placental tissue, and coagulopathies, or the "four Ts"—***t***one, ***t***rauma, ***t***issue, and ***t***hrombin.

Uterine Atony. Accounting for 75% to 90% of cases, the most common cause of serious immediate postpartum hemorrhage is laxity of the uterus after delivery. Normally, postpartum bleeding from the placental implantation site is limited by contraction of the myometrium, constricting the spiral arteries. If the uterus does not contract, ongoing hemorrhage will occur. Predisposing factors include overdistention of the uterus (eg, multiple gestations, fetal macrosomia, polyhydramnios), prolonged labor, chorioamnionitis, use of tocolytics, and general anesthesia with halogenated compounds. As a diagnosis of exclusion, a physical examination to rule out obstetric trauma and retained products of conception should be performed before the diagnosis is reached. On examination, the uterus is palpable as a soft boggy mass.

After other causes have been excluded, therapy to augment myometrial contractions is instituted to prevent further hemorrhage. A two-handed uterine massage may stimulate uterine contractions. One hand exerts pressure transabdominally while the other supports the uterus through the introitus. Uterotonic in conjunction with massage usually provide enough stimuli to control bleeding. Blood is typed, crossmatched, and available for resuscitation should these measures fail.

Maternal Birth Trauma. Maternal birth trauma is the second most common cause of postpartum hemorrhage, accounting for up to 20% of cases. Associated factors include uncontrolled delivery, macrosomia, episiotomy, nulliparity, maternal coagulopathy, operative delivery, prolonged second stage of labor, preeclampsia, and malpresentation. Tears and lacerations may involve the perineum, rectum, cervix, vagina, vulva, and urethra. Blood vessels beneath the vulvar or vaginal epithelium can also be injured without frank hemorrhage, resulting in the formation of large contained hematomas. These hematomas may go unrecognized for hours, gradually enlarging and possibly resulting in hemorrhagic shock. Delayed postpartum hemorrhage at these sites can also occur and is often a diagnostic challenge. The physical examination may reveal uterine displacement (lateral or cephalad), and confirmation by radiologic means may be used in stable patients. Management, decided in conjunction with specialists, may be expectant, involve bedside repair with absorbable suture, or require vascular embolization or surgical intervention, depending on the severity of clinical presentation.

Tears are classified by depth. First-degree tears involve the perineal skin and vaginal mucous membranes only. Second-degree tears extend through the skin into the fascia and muscles of the perineal body. Third-degree tears extend into the anal sphincter, whereas fourth-degree tears extend through all layers, including the rectal mucosa. Third- and fourth-degree tears should be repaired by an obstetrician in the operating room.

Retained Products of Conception. Approximately 10% of postpartum hemorrhage cases are due to retained placental tissue. Normally, the plane of cleavage between the zona basalis and zona spongiosa results in a clean separation of the placenta from the uterus. When this occurs, the placental tissue delivers as a single unit, without evidence of fragmentation. Any placental defect or evidence of accessory placental tissue may signify a retained cotyledon (part of the embryo). Retained fragments prevent myometrial constriction and result in hemorrhage. Aggressive traction on the placenta during stage 3 of labor can

result in retained products of conception, which may cause immediate or delayed postpartum hemorrhage. Ultrasound may reveal an expanded endometrium or solid echogenic mass within the uterus, providing evidence of retention.

Treatment requires removal of the remnant placental tissue. Digital uterine exploration with blunt dissection of the fragments from the myometrium will also facilitate myometrial contractions. Abnormally adherent tissue will not be freed by this maneuver.

The terms *placenta accreta*, *placenta increta*, and *placenta percreta* describe various degrees of abnormal placental attachment to the uterus. When the placenta adheres to the myometrium without the intervening decidua basalis, it is termed *placenta accreta*. In placenta increta, the villi extend into the myometrium. In placenta percreta, the placenta penetrates the full thickness of the myometrium.

The current incidence of placenta accreta is approximately 3/1000 deliveries, a relative increase from past decades. Associated risk factors include multiparity, prior cesarean sections, placenta previa, previous curettage, and uterine anomalies.[15]

Coagulopathies. All women with severe postpartum hemorrhage should be evaluated for disseminated intravascular coagulation (DIC). DIC can occur as a consequence of placental abruption, eclampsia, amniotic fluid embolism, postpartum infections, and dilution of clotting factors caused by aggressive volume resuscitation. Also, retained products of conception and dead fetal tissue contain excess thromboplastin, which can precipitate DIC. As with DIC from nonobstetric causes, bleeding is associated with hypofibrinogenemia, thrombocytopenia, and elevated levels of fibrin split products and D-dimer.

Appropriate management entails hemodynamic support and correction of coagulopathies. Recent investigations have reported the successful use of recombinant factor VIIa for severe cases of postpartum hemorrhage.

Uterine Exploration and Removal of the Placenta. In the presence of ongoing hemorrhage and retained products of conception, attempts to remove the placenta manually are indicated. The procedure entails risk of infection, perforation, and increased hemorrhage but may be the most expeditious way to control bleeding. Before beginning, the patient is placed on a monitor, good vascular access is established, and blood products are available. Also, a Foley catheter may be placed to reduce bladder distention and monitor urinary output.[16] The umbilical cord is traced through the cervical os to the placenta, allowing the identification of a placental margin. The placental membranes are digitally perforated, and the placenta is gradually divided from the myometrium. After removal of the placenta, the uterus is explored for retained cotyledons. Removal of fragments that are still present may require curettage of the uterine cavity by an obstetrician. Placenta accreta, percreta, and increta may be diagnosed in this way because they are not digitally dissectible.

Once it is emptied, the uterus should be stimulated to contract with uterine massage, oxytocin, and prostaglandins. Prophylactic antibiotic administration at the time of manual placenta extraction has been debated somewhat in the literature. If used, a single dose of metronidazole and ampicillin or cefazolin may be given.[16]

Uterine Packing. For the emergency clinician, this technique may be used to create tamponade, preventing further blood loss. The procedure has limited morbidity and is straightforward. The emergency clinician introduces 15 to 20 yards of 4-inch gauze with a ring forceps and packs it into the uterus by a layering technique. Another option is to place a Foley catheter or Sengstaken-Blakemore tube into the uterus and instill the balloon with saline.[16]

Opponents of packing have pointed out that an atonic uterus may accommodate a large volume of packing without effective tamponade. Packing may also increase the risk of postpartum infection, even when prophylactic antibiotics are given. As with all uterine manipulation and instrumentation, some risk of perforation also exists. Because pelvic embolization and hysterectomy sometimes are not immediately available to the emergency clinician, the importance of uterine packing as a temporizing measure is increased.

Pelvic Vessel Embolization. Pelvic bleeding postpartum can be difficult to control. Hysterectomy as a solution results in infertility and brings with it all the complications of general anesthesia and major surgery. Embolization of bleeding vessels by an interventional radiologist is another option. The procedure does not require an anesthesiologist, operating room, or obstetrician and may be readily available on an emergent basis. Reported success rates of embolization in control of postpartum hemorrhage range from 95% to 100%.[16] Common sites of bleeding include the uterine artery, pudendal artery, and hypogastric artery. Because only the smallest involved branches are embolized, and recanalization usually occurs, future reproductive capability is generally preserved.

Uterotonic Agents. Although they are commonly applied on delivery of the placenta, uterotonic agents also have special application in the case of a postpartum hemorrhage. Uterotonics such as oxytocin, ergot alkaloids, and prostaglandins control bleeding by inducing myometrial contractions. Oxytocin is considered to be first-line treatment, given intramuscularly or intravenously. Ergot alkaloids, such as methylergonovine and ergotamine, may induce hypertension and are therefore contraindicated in patients with preeclampsia or other comorbid conditions. Finally, prostaglandins may also be used (eg, misoprostol), although they have shown no clear advantage over oxytocin or ergot alkaloids in published reports.[16]

Hysterectomy. Rarely, hemorrhage continues, despite the interventions outlined. In the case of life-threatening obstetric bleeding, an emergency hysterectomy should be performed.

Uterine Inversion

Perspective

Uterine inversion is an uncommon but serious complication of delivery that occurs during stage 4 of labor. The resultant postpartum hemorrhage can be severe and life-threatening, accounting for a maternal mortality rate of up to 15%. Uterine inversion complicates 1 in 2000 deliveries. Risk factors include excessive fundal pressure during delivery, forceful traction on the umbilical cord (especially in conjunction with a fundal placenta), placenta accreta, maternal congenital abnormalities of the uterus, use of magnesium sulfate in the antepartum period, and primiparity.

Clinical Features

The patient will complain of sudden, severe abdominal pain. The abdominal examination reveals tenderness and an absence of the uterine corpus, which is potentially visualized at the cervical os or bulging from the introitus. Profuse bleeding with hemodynamic instability can also occur. Ultrasound may assist in the diagnosis.

Management

Once uterine inversion is identified, the appropriate mobilization of resources should begin simultaneously with efforts to

reestablish the correct anatomic position of the uterus. As with other causes of postpartum hemorrhage, initial management involves aggressive fluid resuscitation.

The highest likelihood for successful repositioning of the inverted uterus is immediately after inversion occurs. If the placenta is still adherent, it should not be removed until after repositioning. Removal of the placenta while the uterus is inverted is associated with excessive blood loss. The initial attempt to reposition the uterus should be to push the fundus upward through the introitus. Contraction of the cervical uterine segments can create a muscular ring, preventing repositioning. Therefore, all uterotonic agents should be withheld immediately on diagnosis of uterine inversion.

If initial attempts fail and a cervical ring develops, pharmacologic attempts to relax the uterus with sedation and tocolytics are indicated. Terbutaline and magnesium sulfate have been used successfully to relax cervical rings. When the uterus has been repositioned, the muscle relaxants should be halted, and oxytocin and prostaglandin therapy should be initiated. Firm manual pressure through the introitus should be maintained until the cervical ring contracts. If all these measures fail, and surgical backup becomes available, halogenated anesthetics may be used to induce relaxation of the cervical rings, with or without an attempt at surgical repair. Once uterine inversion has resolved, an assessment must be made to screen for uterine perforation, adherent placenta, and vaginal lacerations.

Uterine Rupture

Criticism of the high rate of cesarean delivery in the United States has led to an advocacy of vaginal birth after cesarean (VBAC). The high success rate and relative safety of VBAC are countered partly by the risk of uterine rupture. Dehiscence of a surgical scar occurs in 0.3% of VBAC deliveries.[17] As more women have an VBAC, emergency clinicians can expect to encounter uterine rupture, which is associated with high morbidity and mortality rates.

Clinical Features

Uterine rupture occurs late in pregnancy or as stage 1 of labor transitions to the active phase. Defined as a full-thickness uterine wall perforation, the severity of rupture ranges from simple scar dehiscence to complete fetal extrusion. It may be spontaneous but is most often linked to previous uterine surgery. Other risk factors for uterine rupture include multiple gestation, trauma, and prostaglandin administration.[17] Minimal fetal extrusion results in a perinatal mortality rate of less than 1%, whereas complete extrusion results in a 10% to 20% mortality rate. Maternal death is rare, but significant hemorrhage complicates one-third of cases.

Diagnostic Testing

The diagnosis of uterine rupture may be difficult because pain is not always present. In fact, clinical presentation of uterine rupture ranges from nonreassuring fetal heart rate patterns to frank maternal hemorrhagic shock. Prolonged fetal heart rate deceleration, indicating fetal distress, is the most reliable sign of fetal extrusion. Ultrasound may reveal a protruding amniotic sac, hemoperitoneum, or the myometrial defect; however, good sensitivity data are lacking.

Management

If uterine rupture is suspected, delivery should be hastened to limit fetal hypoxia. Emergency cesarean section is the best method to speed delivery and repair the injury. ACOG guidelines for uterine rupture identify a 30-minute window of opportunity that maximizes fetal outcome. Note that uterotonic agents may exacerbate the rupture and are contraindicated.

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare and catastrophic complication of labor and delivery. The incidence rate is 1.9 to 6.1/100,000 maternities.[18] Although the mechanism is not well understood, it is thought to involve the spread of amniotic fluid through the maternal vasculature, activating a complement or anaphylactic cascade. Cesarean delivery, forceps- or vacuum-assisted delivery, uterine rupture, eclampsia, placenta previa, and placental abruption have been found to have a significant association with amniotic fluid embolism. The diagnosis is clinically evident during labor, during delivery, or within 48 hours of delivery. It is characterized by the sudden onset of hypoxia, coagulopathy or hemorrhage, seizure, fetal compromise, or cardiovascular collapse. DIC occurs in approximately 50% of cases, and maternal and fetal mortality rates are high. Treatment is generally supportive and may include assisted ventilation, central hemodynamic monitoring, vasopressors, and the administration of blood products.[19]

Postpartum Endometritis

Puerperal infections affect 5% of all vaginal deliveries and 10% of all cesarean sections. Operative delivery, prolonged rupture of membranes, lack of prenatal care, prolonged stage 2 labor, use of intrauterine monitoring, and frequent vaginal examinations have been linked to these ascending gynecologic infections. It is estimated that sepsis results in up to 15% of maternal deaths worldwide.[20] Causative organisms for these infections include gram-positive cocci and gram-negative coliforms and, less commonly *Chlamydia* and *Mycoplasma* spp.

Endometritis is the most common puerperal infection, usually developing on the second or third day postpartum. Typically, the lochia has a foul odor, and the white blood cell count is elevated. Fever and abdominal pain indicate greater severity of infection, often warranting inpatient care and intravenous antibiotics. A coexistent surgical wound infection is often present. A search for retained products of conception is indicated, particularly if bleeding is ongoing.

Treatment is empirical and is directed at gram-positive, gram-negative, and anaerobic organisms. A combination of clindamycin and an aminoglycoside is recommended.[21] Most patients with postpartum endometritis require admission.

POSTPARTUM PROBLEMS

Peripartum Cardiomyopathy

For unclear reasons, the peripartum period is associated with the relatively sudden onset of cardiomyopathy in healthy women without evidence of prior cardiac disease. Estimates indicate that peripartum cardiomyopathy (PPCM) occurs in 1 of 2229 pregnancies; reported risk factors include advanced maternal age, preeclampsia, gestational hypertension, multiparity, and being African American. The cause is unknown.[22]

Onset usually occurs days to weeks after delivery; symptoms range from mild fatigue to florid pulmonary edema. PPCM is often unrecognized in its milder form, leading to the consensus that the condition may be more prevalent than reported. Dyspnea on exertion, orthopnea, and fatigue may be easily misinterpreted as normal in the postpartum period. The emergency clinician should not dismiss these symptoms because severe congestive heart failure, thromboembolism, and dysrhythmias may ensue.

Treatment includes the use of diuretics, vasodilators, and oxygen. Angiotensin-converting enzyme inhibitors are contraindicated

if PPCM occurs during the last month of pregnancy owing to teratogenicity but should be considered a mainstay of treatment postpartum. Hydralazine may be used before delivery to reduce afterload. Bromocriptine and pentoxifylline may also have roles in the treatment of PPCM.[23]

Cardiac function returns to normal in 23% to 32% of patients with PPCM during the following 6 months. Complications result in a mortality rate of approximately 15% worldwide.[23]

Postpartum Depression

Considered underdiagnosed, postpartum depression is estimated to affect 10% to 15% of new mothers. Although often self-limited, the condition has been recognized as having important consequences for the mother, infant, and family. Risk factors include previously diagnosed depression, inadequate spousal support, adverse socioeconomic factors, life stressors, and emergency delivery.

Clinical Features

Postpartum depression patients present similarly to those with other major depressive disorders. Symptoms include depressed mood, anhedonia, loss of appetite, insomnia, fatigue, decreased concentration, feelings of guilt and worthlessness, and suicidal ideation. Most women with postpartum depression do not have vegetative signs or symptoms. Symptoms peak at 10 to 12 weeks postpartum, although some cases are diagnosed up to 1 year after delivery. When postpartum depression is unrecognized, these women are at high risk for suicide and may come to the ED with overdoses or other manifestations of a suicidal attempt.

Management

Early identification and referral are the key components of therapy. Dismissal of postpartum fatigue as normal, without consideration of the diagnosis of postpartum depression, can be disastrous. Not only does this condition contribute to marital discord, maternal risk for suicide, and even infanticide, but studies have shown that children of depressed mothers have an increased incidence of delayed cognitive, psychological, neurologic, and motor development.

KEY CONCEPTS

- All ED deliveries should be considered high risk. Antepartum hemorrhage, PROM, eclampsia, premature labor, precipitous delivery, malpresentation, and umbilical cord emergencies are overrepresented in emergency deliveries.
- Women in labor who present to the ED are generally best cared for in the obstetric suite. Women with the urge to push or with the head of the infant crowning are at imminent risk of delivery, which should take place in the ED. The benefits of transfer of a woman with an impending high-risk delivery to a perinatal center must be carefully weighed against potential clinical adverse events and possible subsequent medicolegal judgments.
- Most ED deliveries require only basic equipment to cut and clamp the umbilical cord and dry and suction the infant. However, the ED should have additional equipment and trained staff available to care for a newborn requiring further resuscitation.
- Maternal complications of labor and delivery include obstetric trauma, postpartum hemorrhage, uterine inversion and rupture, amniotic fluid embolism, coagulation disorders, and infections. Many of these problems can initially be managed nonsurgically in the ED.
- Deliveries complicated by dystocia, malpresentation, or multiple gestations are life-threatening emergencies. The emergency clinician should develop strategies to treat each of these potential complications of delivery.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 181: QUESTIONS & ANSWERS

181.1. A 23-year-old G2P1 at term presents to the ED with contractions. She has received no prenatal care. She is in moderate distress and feels the urge to push. Which of the following is indicated?

A. Emergent delivery
B. Emergent transfer to the obstetrics suite
C. Formal abdominal ultrasound
D. Magnesium sulfate 2 g intravenously
E. Nitrazine testing of pooled vaginal fluid

Answer: A. Women with the urge to push or with the head of an infant crowning are at imminent risk of delivery, which should take place in the ED. Women in labor who present to the ED and are not at risk for imminent delivery are best cared for in the obstetrics suite.

181.2. A 28-year-old G3P3 presents 2 weeks after delivery with increasing dyspnea on exertion, pedal edema, orthopnea, and easy fatigue. Which of the following statements is true?

A. Angiotensin-converting enzyme (ACE) inhibitors are contraindicated.
B. Cardiac function returns to normal in 50% of cases.
C. Treatment differs from ischemic cardiomyopathy.
D. Onset is usually gradual.

Answer: B. Postpartum cardiomyopathy is associated with a fairly sudden onset of symptoms days to weeks after delivery. It may begin to occur during the end of pregnancy, at which time ACE inhibitors are contraindicated, but these agents are cornerstones of therapy after delivery. Fifty percent of patients will return to normal cardiac status. Mortality is high for those who do not.

181.3. Which of the following statements regarding uterine rupture is true?

A. Emergency ultrasonography has little value.
B. Emergent vaginal delivery is indicated.
C. Maternal mortality is high.
D. Pain is not always present.
E. The absence of vaginal bleeding precludes rupture.

Answer: D. Pain is not always present with uterine rupture, nor is vaginal bleeding always associated. Women at risk are those with a prior classic cesarean section incision or who have had three or more cesarean deliveries. Emergency ultrasonography may show a protruding amniotic sac, hemoperitoneum, or the site of myometrial rupture. Emergency cesarean delivery within 30 minutes is the indicated treatment. Maternal mortality rates in developed countries is less than 1%.

181.4. Which of the following statements is not associated with shoulder dystocia?

A. Fetal complications include clavicular fractures and hypoxic brain injury.
B. Shoulder dystocia can be overcome by placing traction on the fetal head.
C. Signs of shoulder dystocia include the turtle sign and the presentation of fetal shoulders in a vertical axis.
D. The McRoberts' maneuver frees the anterior shoulder by flexing the mother's legs to a knee-chest position.

Answer: B. Traction on the fetal head will extend and abduct the shoulders, which increases bisacromial diameter, thereby worsening the dystocia.

181.5. A 33-year-old G1P0 female at 38 weeks by dates presents to the ED with a chief complaint of "my water broke." The patient reports feeling a gush of fluid several hours earlier but has not yet had any contractions. Which of the following statements best describes issues important in the evaluation and management of this patient?

A. Fetal tachycardia may be indicative of chorioamnionitis.
B. Nitrazine paper applied to the patient's pooled vaginal fluid will confirm the presence of amniotic fluid by turning yellow.
C. Steroids should be given to the mother without delay to accelerate fetal lung maturation.
D. Tocolytics are indicated and should be administered if the patient develops contractions while in the ED.

Answer: A. This patient presents with premature rupture of membranes. Assuming that the fetal gestational age of 38 weeks is confirmed by ultrasound, steroids are unnecessary because fetal lung maturity has already taken place. The incidence of infection may be increased with steroid administration, so it should not be given in this case. Tocolytics are not clearly indicated in this patient because she is at term (ie, fetal lung maturity has taken place), and there is as yet no evidence of chorioamnionitis. Tocolytic use should be discussed with the obstetric consultant. Nitrazine paper should turn blue when it comes into contact with amniotic

fluid, indicating a pH over 6.5. Fetal tachycardia and decreased variability of fetal heart rate are both signs of chorioamnionitis.

181.6. Which of the following statements regarding fetal heart tracings is false?

A. Accelerations of heart rate occur during fetal movement.

B. Baseline heart rate is determined with a 10-minute tracing in the absence of contractions.

C. Late decelerations rarely result in suboptimal infant outcomes.

D. Persistent variable decelerations may indicate the need to hasten delivery.

Answer: C. Late decelerations indicate uteroplacental insufficiency and should prompt immediate obstetric consultation. Overall, 70% of infants with late decelerations have underlying pathologic conditions or hypoxia.

CHAPTER 182

Trauma in Pregnancy*

Valerie A. Dobiesz | Daniel W. Robinson

PRINCIPLES

Background

Trauma occurs in up to 8% of all pregnancies and is the leading non-obstetric cause of maternal death.[1-5] The most common causes of injury in pregnancy are motor vehicle collisions (MVCs), interpersonal violence, and falls.[2,4,6-8] The major determinant of obstetrical outcomes after trauma is the severity of the injury.[4] Trauma in pregnancy increases the risk of spontaneous abortion, preterm rupture of membranes, preterm birth, uterine rupture, cesarean delivery, placental abruption, and stillbirth.[4] A significant number of pregnant women admitted to a trauma center do not yet know that they are pregnant.

Commonly used thresholds of fetal viability are an estimated gestational age of 24 to 26 weeks or an estimated fetal weight of 500 g. Only viable fetuses are monitored, because no obstetric intervention will alter the outcome with a previable fetus. Counseling on proper seatbelt and alcohol use and screening for interpersonal violence may help to reduce the morbidity and mortality rates for pregnant patients. Although the essential principles of trauma management remain unchanged in the pregnant patient, a number of special points need to be considered because a gravid uterus does alter the pattern of injury. Pregnancy causes alterations in physiology and anatomy that affect multiple organ systems. Although there are two lives involved, maternal life takes priority and fetal outcomes are directly correlated with early and aggressive maternal resuscitation.[5]

ANATOMY AND PHYSIOLOGY

Anatomic Changes in Pregnancy

The uterus remains an intrapelvic organ until approximately the 12th week of gestation. It reaches the umbilicus by 20 weeks and the costal margins by 34 to 36 weeks. At term, the uterus has often enlarged by 30 cm and has increased fifteen fold in weight, which alters the normal anatomic location and function of multiple structures. The diaphragm progressively rises in pregnancy with compensatory flaring of the ribs, which may predispose to pneumothorax and a faster progression to tension pneumothorax. A thoracostomy done in the third trimester requires that the chest tube be placed one or two interspaces higher than the usual fifth interspace site to allow for diaphragm elevation.

Abdominal viscera are pushed upward by the enlarging uterus and can alter the location of perceived pain. The gravid uterus itself tends to protect abdominal organs from trauma but substantially increases the likelihood of bowel injury from penetrating trauma to the upper abdomen. Conversely, the upward displacement of the bowel makes it less susceptible to blunt trauma. The stretching of the abdominal wall as pregnancy nears term modifies the normal response to peritoneal irritation (blunting of muscle guarding and rebound) potentially underestimating the extent and severity of maternal trauma despite significant intra-abdominal bleeding and organ injury.

In the first trimester, the bony pelvis shields the uterus. After the third month, the uterus rises out of the pelvis and becomes vulnerable to direct injury. The bladder is also displaced into the abdominal cavity beyond 12 weeks' gestation, thereby becoming more vulnerable to injury. Like the uterus, the bladder becomes hyperemic, and injury may lead to a marked increase in blood loss compared with similar injury in a nonpregnant patient. Ureteral dilation secondary to smooth muscle relaxation or from compression by the gravid uterus is often found on imaging studies but is not necessarily pathologic. The ligaments of the symphysis pubis and sacroiliac joints are loosened during pregnancy. As a result, a baseline diastasis of the pubic symphysis may exist that can be mistaken for pelvic disruption on a radiograph.

Physiologic Changes

Cardiovascular

The normal cardiovascular changes of pregnancy can alter the clinical presentation and may either mimic or mask the recognition of shock or exacerbate the effects of traumatic hemorrhage (Table 182.1). Blood pressure declines in the first trimester, levels out in the second trimester, and then returns to nonpregnant levels during the third trimester. The decline in systole is small, 2 to 4 mm Hg, whereas diastole falls 5 to 15 mm Hg. Heart rate increases in pregnancy but does not rise by more than 10 to 15 beats per minute above baseline (mean of approximately 90 beats/min).

A major contributor to maternal hypotension is the supine hypotensive syndrome. After 20 weeks' gestation, the enlarging uterus has risen to the level of the inferior vena cava, resulting in compression when the mother is supine. Caval obstruction diminishes cardiac preload, which can decrease cardiac output and systolic blood pressure. In late pregnancy, it is common for the inferior vena cava to become completely occluded when the pregnant patient is supine. Hemodynamic improvement occurs when compression is relieved. In determining whether observed hypotension is related to positioning, the pregnant woman's pelvis can be tilted so that the uterus is displaced from the inferior vena cava (ie, tilt the patient onto her left side unless prevented by other injuries). The uterus can also be manually displaced to the left using two hands and pushing the uterus toward the patient's head. Maintaining a position between 15 and 30 degrees is optimal. Elevating the patient's legs will improve venous return. Inferior vena caval compression can also lower central venous pressure (CVP) in the last two trimesters. Normal CVP during pregnancy is approximately 12 mm Hg. Blood volume gradually increases during pregnancy, starting at 6 to 8 weeks' gestation, to as much

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TABLE 182.1

Hemodynamic Changes of Pregnancy (Mean Values)

PARAMETER	NONPREGNANT	TRIMESTER 1	TRIMESTER 2	TRIMESTER 3
Heart rate (beats/min)	70	78	82	85
Systolic blood pressure (mm Hg)	115	112	112	114
Diastolic blood pressure (mm Hg)	70	60	63	70
Cardiac output (L/min)	4.5	4.5	6	6
Central venous pressure (mm Hg)	9.0	7.5	4.0	3.8
Blood volume (mL)	4000	4200	5000	5600
Hematocrit without iron (%)	40	36	33	34
Hematocrit with iron (%)	40	36	34	36
White blood cells (cells/mm^3)	7200	9100	9700	9800

Data from de Swiet M: The cardiovascular system. In Hytten F, Chamberlain G, editors: Clinical physiology in obstetrics. Oxford, UK, 1980, Blackwell Scientific Publications, pp 3–42; Colditz RB, Josey WE: Central venous pressure in supine position during normal pregnancy. Comparative determinations during first, second and third trimesters. Obstet Gynecol 36:769, 1970; Letsky E: The haematological system. In Hytten RF, Chamberlin G, editors: Clinical physiology in obstetrics. Oxford, UK, 1980, Blackwell Scientific Publications, pp 43–78; and Cruikshank DP: Anatomic and physiologic alterations of pregnancy that modify the response to trauma. In Buchsbaum HJ, editor: Trauma in pregnancy. Philadelphia, 1979, WB Saunders, pp 21–39.

as 45% above normal, peaking at 32 to 34 weeks' gestation. Blood volumes become increasingly larger for multigravidas and for twin, triplet, and quadruplet gestations. With this increased circulatory reserve, clinical signs of maternal hypotension from acute traumatic bleeding may be delayed. Up to 35% of circulating blood volume may be lost before an injured pregnant patient exhibits signs or symptoms of shock.[5] By the beginning of the second trimester and throughout the remainder of pregnancy, cardiac output is increased 40% to 6 L/min. Blood flow to the uterus increases from 60 mL/min before pregnancy to 600 mL/min at term. This hyperdynamic state is needed to maintain adequate oxygen delivery to the fetus. Because the mother's total circulating blood volume flows through the uterus every 8 to 11 minutes at term, this can be a major source of blood loss if injured. By the third trimester, there is also marked venous congestion in the pelvis and lower extremities, increasing the potential for hemorrhage from both bony and soft tissue pelvic injuries.

Compression of the lower abdominal venous system by the gravid uterus increases peripheral venous pressure and volume in the legs, creating the potential for brisk blood loss from leg wounds and can exacerbate bleeding from attempts at central venous catheter placement.

Pulmonary

The pregnant woman at term has a significantly reduced oxygen reserve due to a reduction in functional residual capacity caused by diaphragm elevation and an increase in oxygen consumption related to the growing fetus, uterus, and placenta. Mean arterial oxygen tension drops by 29% in pregnant women at term during 60 seconds of apnea compared with 11% in nonpregnant women. Labor further accelerates this decline. In addition, minute ventilation and tidal volume increase, leading to hypocapnia. Therefore a partial pressure of carbon dioxide in the arterial blood ($Paco_2$) of 35 to 40 mm Hg may indicate inadequate ventilation and impending respiratory decompensation in the pregnant patient. Maternal hypoxia rapidly leads to fetal hypoxia, distress, and possibly demise. There are no contraindications to rapid sequence intubation during pregnancy. Bag-valve-mask ventilation is more difficult in the pregnant patient. The incidence of difficult or failed intubations in obstetric anesthesia is four times higher than in surgical non-obstetric patients.[8]

Gastrointestinal

Gastroesophageal sphincter tone and gastrointestinal motility are decreased in pregnancy, thus increasing the possibility of aspiration in patients with altered level of consciousness, such as during intubation. Early gastric decompression should be performed in these circumstances.

SPECIFIC DISORDERS

Blunt and Penetrating Trauma

Physical examination is unreliable in predicting adverse outcomes in the pregnant woman with blunt trauma. Risk factors predictive of the onset of contractions or preterm labor include gestational age greater than 35 weeks, assaults, and pedestrian collisions. In gravid patients, penetrating trauma of the abdomen increases the likelihood of injury to the bowel, liver, or spleen.

Fetal mortality can be as high as 40% after maternal trauma, with most likely causes of fetal death occurring from placental abruption, maternal shock, and maternal death, in order of decreasing incidence. Risk factors significantly predictive of fetal death include ejection, motorcycle and pedestrian collisions, maternal death, maternal tachycardia, abnormal fetal heart rate, lack of restraints, and an injury severity score greater than 9.

Unbelted or improperly restrained pregnant women are twice as likely to experience excessive maternal bleeding and increased maternal death with fetal death being three times more likely to occur.[2,4,9,10] For low- to moderate-severity crashes (constituting 95% of all MVCs), proper restraint use, with or without air bag deployment, generally leads to acceptable fetal outcomes. For high-severity crashes, even proper restraint does not improve fetal outcome.

Pregnant crash-test-dummy trials show that improper placement of the lap belt over the pregnant abdomen causes a threefold to fourfold increase in force transmission through the uterus. The lowest force transmission readings through the uterus occur when a three-point seat belt is used properly. For correct position, the lap belt should be placed under the gravid abdomen, snugly over the thighs, with the shoulder harness off to the side of the uterus, between the breasts and over the midline of the clavicle. Women

who receive information on seat belt use during pregnancy from a health care worker are statistically more likely to use seat belts and to use them properly than uninformed controls.

Interpersonal Violence

Physical abuse from husbands or boyfriends compromises a woman's health during pregnancy, as well as her likelihood of carrying a child to term and the health of her newborn. Women experiencing abuse in the year before or during a pregnancy were 40% to 60% more likely than non-abused women to report high blood pressure; vaginal bleeding; severe nausea; kidney or urinary tract infections; and hospitalization during that pregnancy. Abused pregnant women are more likely to deliver preterm, and children of abused pregnant women are more likely to be born underweight. Children born to abused mothers are more likely than other children to require intensive care at birth. Physicians detect only a minority of interpersonal violence cases in pregnant women, which supports the need for routine screening for interpersonal violence in this population.

Falls

Falls become more prevalent after the 20th week of pregnancy and at least one in four pregnant women will fall at least once while pregnant.[4,6] Protuberance of the abdomen, loosening of pelvic ligaments, strain on the lower back, and fatigability are contributory factors. In a given pregnancy, about 2% of pregnant women sustain repeated direct blows to the abdomen from repetitive falls. Although repeated falls often trigger premature contractions, they seldom result in immediate labor and delivery.

Penetrating Trauma

The gravid uterus affects the injury pattern seen with penetrating trauma to the upper abdomen with the probability of harm to the bowel, liver, or spleen at almost 100%. When the entry site is anterior and below the uterine fundus, visceral injuries are less likely.[4] Although the enlarging uterus can act as a shield against intra-abdominal injuries in the mother, it makes the fetus more susceptible to injury. A high fetal death rate from penetrating trauma to the uterus has been reported and is lower for maternal injuries above the uterus.

Fetal Injury

There is a high risk of fetal loss in the pregnant trauma patient. Poor fetal outcome is predicted by maternal hypotension and acidosis (hypoxia, lowered pH, lowered bicarbonate) and a fetal heart rate of less than 110 beats/min.[7] When the mother sustains life-threatening injuries, there is a 40% chance of fetal demise, compared with a less than 2% chance in cases of non–life-threatening maternal injuries. Disseminated intravascular coagulation (DIC), which may be caused by placental products entering the maternal circulation, is a significant predictor of fetal mortality. The American College of Obstetrics and Gynecology recommends a minimum of 2 to 6 hours of fetal monitoring after maternal trauma; cardiotocographic monitoring for a minimum of 4 hours is useful in predicting fetal outcome.[4]

Fatal fetal injuries from blunt trauma are usually the result of intracranial hemorrhage and skull fractures secondary to fractured maternal pelvic bones striking the fetal skull as a result of vertex lie. Pelvic and acetabular fractures during pregnancy are associated with a high maternal (9%) and a higher fetal (38%) mortality rate. Both gunshot wounds and stab wounds to the uterus produce substantial morbidity and mortality to the fetus.

Placental Injury

The leading cause of fetal death after blunt trauma is placental abruption.[11] Placental separation results when the inelastic placenta shears away from the elastic uterus during sudden deformation of the uterus. Because deceleration forces can be as damaging to the placenta as direct uterine trauma, abruption can occur with little or no external sign of injury to the abdominal wall. Placental abruption inhibits the flow of oxygen to the fetus and causes in utero carbon dioxide (CO_2) accumulation, resulting in hypoxia and acidosis and leads to fetal distress. Sustained uterine contractions induced by intrauterine hemorrhage also inhibit uterine blood flow, further contributing to fetal hypoxia.

The diagnosis of abruption is made on clinical grounds; ultrasonography and the Kleihauer-Betke test are of limited value. Classic clinical findings of abruption are vaginal bleeding, abdominal cramps, uterine tenderness, maternal hypovolemia (up to 2 L of blood can accumulate in the gravid uterus), or a change in the fetal heart rate; but many cases of placental abruption after trauma present without vaginal bleeding.

The most sensitive indicator of placental abruption is fetal distress, which can be detected with prompt fetal monitoring. Increased frequency of contractions is associated with abruption. Ultrasonography has poor sensitivity for detection of placental abruption (24% sensitivity; 96% specificity).[2] If the abruption bleeds externally, there may be an insufficient quantity to be detected sonographically. Even with significant intrauterine blood accumulation, accurate ultrasonography diagnosis may be difficult because of placental position (ie, posterior) and confounding uterine or placental structural conditions.

Placental abruption is associated with an increased risk of stillbirth (>20 weeks) and preterm delivery (before 37 weeks) even with minor abruption. The extent of placental separation is correlated with the rate of stillbirth.

A trial of expectant management with ongoing maternal and fetal monitoring is appropriate when mother and fetus are stable and with partial placental abruptions of less than 25%. This usually applies to fetuses of less than 32 weeks' gestation in which the likelihood of morbidity and mortality associated with prematurity makes delivery management risky. Expectant care in stable patients may allow further fetal maturation and improved outcome. An immediate cesarean section should be available in case of fetal distress from further placental separation. After 32 weeks' gestation, the risk of further placental separation outweighs the benefits of further fetal maturation, so intervention is indicated.

Women with placental abruption are more likely to have coagulopathies than those without abruption. The injured placenta can release thromboplastin into the maternal circulation, resulting in DIC, whereas the damaged uterus can disperse plasminogen activator and trigger fibrinolysis. The precipitation of DIC is directly related to the degree of placental separation. Severe clotting disorders rarely occur unless separation of the placenta is significant enough to result in fetal demise.

Uterine Injury

The most common obstetric problem caused by maternal trauma is uterine contractions. Myometrial and decidual cells, irritated by contusion or placental separation, release prostaglandins that stimulate uterine contractions. Progression to labor depends on the extent of uterine damage, the amount of prostaglandins released, and the gestational age of the pregnancy. The routine use of tocolytics for premature labor has come under question because most contractions stop spontaneously. Contractions that are not self-limited are often induced by some pathologic condition, such as underlying placental abruption, which is a contraindication to

tocolytic therapy. Older studies describe this risk as relative and have used tocolysis successfully with careful evaluation and intensive monitoring to continue the pregnancy and enhance fetal maturity. The option to use tocolytics ends when cervical dilation reaches 4 cm.

Uterine rupture is a rare event. It is most often caused by severe vehicular crashes in which pelvic fractures strike directly against the uterus. Uterine rupture may occur from stab wounds and gunshot injuries, but this is rare. Maternal shock, abdominal pain, easily palpable fetal anatomy caused by extrusion into the abdomen, and fetal demise are typical findings on examination. Diagnosing uterine rupture can be difficult. A fractured liver or spleen can produce similar signs and symptoms of peritoneal irritation, hemoperitoneum, and unstable vital signs. Optimal treatment, between suturing the tear or performing a hysterectomy, depends on the extent of uterus and uterine vessel tears and the importance of future childbearing.

DIAGNOSTIC TESTING

All women of childbearing age presenting with trauma should be assessed for possible pregnancy.

CHANGES IN LABORATORY VALUES WITH PREGNANCY

Increases in plasma volume and red blood cells cause physiologic anemia of pregnancy (hematocrit 32% to 34% by the 32nd to 34th week). Despite the lower hematocrit, there is an overall increase in oxygen-carrying capacity because of an increased total red blood cell mass. Placental progesterone directly stimulates the medullary respiratory center, producing a lower $PaCO_2$ (30 mm Hg) from the second trimester until term. The subsequent compensatory lowering of serum bicarbonate slightly reduces blood-buffering capacity during conditions of physiologic stress. A $PaCO_2$ of 40 mm Hg in the latter half of pregnancy reflects inadequate ventilation and potential respiratory acidosis that could precipitate fetal distress.

Electrocardiographic changes include a left-axis shift averaging 15 degrees, caused by diaphragm elevation. Consequently, flattened T waves or Q waves in leads III and augmented voltage unipolar left limb lead may be seen.

Laboratory

Laboratory tests for a pregnant patient with trauma should include a blood type with Rh status, arterial blood gas, and coagulation studies. Patients who appear to be stable but have a low serum bicarbonate level may have occult maternal shock. Interpretation of bicarbonate results requires consideration of the physiologic changes that occur in the later stages of pregnancy as a result of respiratory alkalosis. Coagulation studies are important in directing management of patients with multisystem trauma or when the diagnosis of placental abruption is considered.

Kleihauer-Betke Test and Fetomaternal Hemorrhage

Fetomaternal hemorrhage (FMH), the transplacental bleeding of fetal blood into the normally separate maternal circulation, is a unique complication of pregnancy. MVCs, anterior placental location, and uterine tenderness are associated with an increased risk of FMH. Massive fetomaternal transplacental hemorrhage causes alloimmunization in Rh incompatibility but also endangers the fetus by causing severe fetal anemia, fetal distress, and possible exsanguination. ABO incompatibility causes less severe disease.

In theory, it is possible that trauma can result in FMH as early as the fourth week of gestation, when the fetal and placental circulations first form. In practice, FMH is usually of more concern after 12 weeks' gestation, when the uterus rises above the pelvis and becomes susceptible to direct trauma.

The Kleihauer-Betke test quantifies the amount of FMH. Most laboratories screen for FMH of 5 mL or more, even though the amount of FMH sufficient to sensitize most Rh-negative women is well below this 5-mL sensitivity level. Therefore it is advisable that all Rh-negative mothers who have a history of abdominal trauma receive one prophylactic dose of Rhesus immune globulin (RhIG) within 72 hours of injury. Trauma patients at risk for massive FMH will have major injuries or abnormal obstetric findings, such as uterine tenderness, contractions, or vaginal bleeding. Rarely, the amount of FMH will exceed that covered by the maximum RhIG dose (300 μg). Because RhIG can effectively prevent Rh isoimmunization when administered as late as 72 hours after antigenic exposure, the results of the Kleihauer-Betke test are not immediately needed in the emergency department (ED).

Radiography

Plain Radiographs

Adverse effects to the fetus are unlikely if radiation exposure is less than 50 mGy.[12] Less than 1% of trauma patients are exposed to more than 30 mGy. Sensitivity to radiation is greatest during intrauterine development when the embryo undergoes organogenesis in weeks 2 to 15.[12] However, the risk to the fetus of a 10 mGy exposure is thousands of times smaller than the spontaneous risks of malformations, abortions, or genetic disease. Intrauterine exposure to 50 mGy does not appear to cause a significant increase in congenital malformations, intrauterine growth retardation, or miscarriage but is associated with a 2% increase in the risk of cancer.[12] Pathologic conditions more readily appear with intrauterine radiation doses of 150 mGy or greater (at this point, a therapeutic abortion may be considered).[12]

Providing information on radiation exposure from diagnostic radiographs is difficult. Fetal dose from computed tomography (CT) scans depends on many factors, but the type of equipment used, the abdominal girth of the mother, and the fetal distance from the maternal skin are important factors.[12] Diagnostic radiographic studies should be performed with regard for fetal protection, but necessary diagnostic studies of the traumatized pregnant patient should not be withheld out of concern for fetal radiation exposure.[12] When appropriate, fetal irradiation should be minimized by limiting the scope of the examination and using technical means, such as shielding and collimation. Table 182.2 provides estimated radiation doses from various types of examinations.

Ultrasonography

Ultrasonography is the best modality for simultaneous assessment of both the mother and the fetus. In the pregnant patient, it is most useful in detecting major abdominal injury, establishing fetal well-being or demise, gestational age, and placental location.[4,13] However, ultrasonography has low sensitivity (24%) but high specificity (96%) for placental abruption.[2,4] Ultrasonography can obviate more hazardous tests, such as CT, cystography, and diagnostic peritoneal lavage (DPL) when a pregnant trauma patient requires an objective evaluation of the abdomen. Limitations in accuracy include operator experience, patient obesity, the presence of subcutaneous air, and a history of multiple abdominal surgeries. If ultrasound findings are equivocal and the patient is hemodynamically unstable, DPL performed in an open

TABLE 182.2

Estimated Fetal Radiation Dose From Conventional Radiographic and Computed Tomography Examination

IMAGING STUDY	ESTIMATED FETAL DOSE (mGy)*
RADIOGRAPHY	
Cervical spine (AP, lateral)	<0.001
Extremities	<0.001
Chest (PA, lateral)	0.002
Thoracic spine	0.003
Abdomen (AP) (21-cm patient thickness)	1
Abdomen (AP) (33-cm patient thickness)	3
Lumbar spine (AP, lateral)	1
COMPUTED TOMOGRAPHY	
Head	0
Chest (routine)	0.2
Chest (pulmonary embolism protocol)	0.2
Abdomen	4
Abdomen and pelvis	25
CT angiography of the aorta	34
CT angiography of the coronary arteries	0.1

*The naturally occurring background radiation dose during pregnancy is 0.5 to 0.1 mGy.
AP, Anteroposterior; *CT,* computed tomography; *PA,* posteroanterior.
From Raptis CA, Mellnick VM, Raptis DA, et al: Imaging of trauma in the pregnant patient. Radiographics 34(3):748–763, 2014.

and supra-uterine fashion is indicated. Diagnostic peritoneal aspiration (DPA) may be considered in conjunction with a trauma surgeon; however, this procedure also poses risks.

Computed Tomography and Magnetic Resonance Imaging Scans

CT and, increasingly, magnetic resonance imaging (MRI) studies are used in evaluating abdominal trauma in pregnancy. If ultrasonography is indeterminate and the patient's condition is stable, CT and MRI can identify specific organ damage. They are particularly useful in assessing penetrating wounds of the flank and back. CT can miss diaphragm and bowel injuries. Both of these studies carry the risk of moving the patient from the closely monitored environment of the ED to a distant radiography suite.

Radiation from CT is a concern in the pregnant trauma patient. However, with shielding, fetal exposure from head and chest CT scans can be kept below an acceptable 1-rad limit. CT of the abdomen can be done with 4 mGy of exposure to the fetus.[14] Abdomen and pelvic CT produces about 25 mGy of radiation to the fetus, which is well below the 50 mGy level, where a 2% increase in risk of cancer is seen without evidence of malformation to the fetus.[12,14] Radiation exposure ultimately depends on the patient, scanner, and technique used in performing the study (see Table 182.2). MRI scanners use no radiation and have not been associated with significant fetal disease or disability.

SPECIAL PROCEDURES

Diagnostic Peritoneal Lavage

In unstable trauma patients with equivocal or negative findings on ultrasonography, DPL can be done in any trimester by an open technique above the uterus after placement of a nasogastric tube and a Foley catheter. The gravid uterus, in the later trimesters, makes the procedure more risky and technically challenging. In blunt trauma, the gravid uterus does not compartmentalize intraperitoneal hemorrhage and does not reduce the accuracy of DPL for identifying patients who need operative intervention for intra-abdominal bleeding. DPL is limited in detecting bowel perforations and does not assess retroperitoneal and intrauterine pathology.

MANAGEMENT

Depending on mechanism, maternal condition, and gestational age, the emergency clinician should consider early notification or consultation with an obstetrician, neonatologist, or pediatrician (or all three). A fetal monitor, portable ultrasound, and neonatal resuscitation equipment should be immediately available. Tetanus toxoid and immune globulin have no detrimental effect on the fetus. The World Health Organization (WHO) specifically recommends vaccination during pregnancy.[15] To prevent alloimmunization of an Rh-negative mother, administer one 50-µg dose of RhIG in the first trimester. It is sufficient because total fetal blood volume is only 4.2 mL by 12 weeks' gestation, and a 50 µg-dose covers 5 mL of bleeding. During the second and third trimesters, a 300-µg dose of RhIG is given, which protects against 30 mL of FMH. Beyond 16 weeks' gestation, the total fetal blood volume reaches 30 mL or more. Massive FMH likely exceeds the efficacy of one 300-µg dose of RhIG, so the Kleihauer-Betke test can be used to guide effective dosing.

Maternal Resuscitation

Primary Survey

The primary survey focuses on the mother. However, because two patients are present, it is reasonable also to gather preliminary information about the fetus at this time (Fig. 182.1).

Airway and Breathing. Oxygen therapy should be instituted early. Because of reduced oxygen reserve and increased oxygen consumption, the traumatized pregnant woman can quickly become hypoxic. The fetus is very vulnerable to any reduction in oxygen delivery. Supplemental oxygen should be continued throughout maternal resuscitation and evaluation.

A secure airway enables proper oxygenation and negates the higher risk of aspiration in pregnancy. Rapid sequence intubation is recommended. Pre-oxygenation of the pregnant patient is described in Chapter 1. Mechanical ventilation settings need to be adjusted for increased tidal volumes and respiratory alkalosis, which is consistent with the physiologic $Paco_2$ of 30 mm Hg in the last stage of pregnancy.

Circulation. Intravenous access above the diaphragm is preferred.[8] Maternal blood pressure and heart rate are not consistently reliable predictors of fetal and maternal hemodynamic stability. Due to an expanded circulating volume, the mother can hemorrhage but not show early signs of hypotension. Uterine blood flow is markedly reduced when maternal circulation is compromised. As a result, after an acute blood loss, uterine blood flow can be substantially decreased while maternal blood

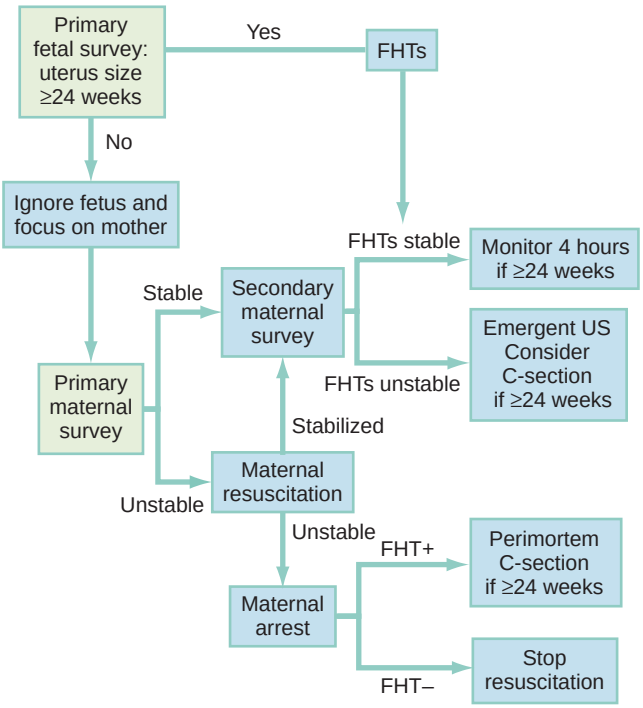

Fig. 182.1. Decision-making algorithm in emergency obstetric care. *C-section,* Cesarean section; *FHT,* fetal heart tone; *US,* ultrasonography.

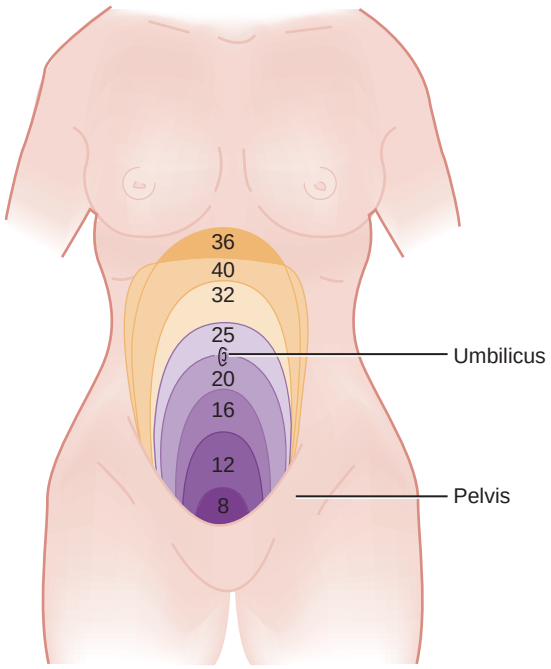

Fig. 182.2. Uterine size at different weeks of gestation. (From Kravis TC, Warner CG, editors: Emergency medicine: a comprehensive review. Rockville, MD, 1979, Aspen Publishers.)

pressure remains normal. Consequently, the pregnant woman with borderline hemodynamic stability probably already has a jeopardized fetus. When traditional signs of shock appear, fetal compromise may be far advanced. Vasopressors should be avoided, because they produce fetal distress by further decreasing uterine blood flow.

Beyond 20 weeks' gestation, tilting the patient to approximately 30 degrees to the left on a backboard or elevating the right hip reduces the compression on the inferior vena cava caused by the gravid uterus. Tilting to the right is less effective in removing the uterus from the inferior vena cava; manually displacing the uterus upward and leftward is more effective.

For severe injuries, a CVP line is helpful in assessing cardiac preload. CVP pressures decline as pregnancy progresses because of inferior vena caval compression by the gravid uterus. Therefore correction to nonpregnant normal pressures may be unnecessary. Instead, it is more valuable to focus on trends of how the CVP responds to fluid resuscitation. A Foley catheter for measuring urine output provides further information on circulatory volume status.

With trauma in pregnancy, the primary survey is modified to assess uterine size and the presence of fetal heart tones if the patient is severely injured. Otherwise, this assessment belongs in the secondary survey. Uterine size, measured from the symphysis pubis to the fundus, is the quickest means of estimating gestational age. This distance in centimeters equals the gestational age in weeks (eg, 24 cm = 24 weeks), which allows some early indication of fetal viability if delivery is necessary (Fig. 182.2). Usually, 24 to 26 weeks is used as the cutoff point for fetal viability (Table 182.3). As a rough guide, the fetus is potentially viable when the dome of the uterus extends beyond the umbilicus. Fetal heart tones can be detected by auscultation at 20 weeks' gestation or by Doppler probe at 10 to 14 weeks. If either the uterus is less than 24 cm in size or fetal heart tones are absent, the pregnancy is probably too early to be viable, and treatment is directed solely at the mother.

TABLE 182.3

Fetal Viability

WEEKS OF GESTATION	6-MONTH SURVIVAL (%)	SURVIVAL WITH NO SEVERE ABNORMALITIES (%)
22	0	0
23	15	2
24	56	21
25	79	69

Data from Morris JA Jr, et al: Infant survival after cesarean section for trauma. Ann Surg 223:481, 1996.

Secondary Survey

The secondary survey involves a detailed examination of the patient but is also modified to gather additional information about the maternal abdomen and the fetus. Physical examination of the abdomen, frequently unreliable in the nonpregnant patient, is even more inaccurate with changing organ position, abdominal wall stretching in advancing pregnancy, and uterine contraction pains. Still, valuable information can be gathered about uterine tenderness, contraction frequency, and vaginal bleeding.

Pelvic examination begins with sterile speculum examination to allow direct visualization to enable detection of possible trauma in the genital tract, the degree of cervical dilation, and the source of any observed vaginal fluid. Vaginal bleeding suggests placental abruption, and a watery discharge suggests rupture of the membranes. If a vaginal fluid sample placed on a slide dries and crystallizes in a ferning pattern, it is amniotic fluid and not urine. Cervical cultures for group B streptococci, *Neisseria gonorrhoeae,* and *Chlamydia* should be performed if there is evidence of amniotic fluid leak. Bimanual examination should be limited to assessing for pelvic bone injury or progression of advanced labor. If the mechanism of injury is significant enough and the fetus is judged

to be viable, early involvement of an obstetrician may enhance the fetal outcome.

Fetal Evaluation. Fetal evaluation in the secondary survey focuses on the fetal heart rate and detection of fetal movement. When the presence of fetal heart tones has been confirmed, intermittent monitoring of fetal heart rate is sufficient for the previable fetus. If the fetus is viable (ie, 24 weeks or more), continuous external monitoring initiated quickly and maintained throughout all diagnostic and therapeutic procedures may be useful in directing management. Such monitoring can also benefit the mother, because fetal hemodynamics are more sensitive to decreases in maternal blood flow and oxygenation than are most measures of the mother. Fetal distress can be a sign of occult maternal distress. However, fetal distress and even demise can occur with seemingly minor maternal trauma. Signs of fetal distress include an abnormal baseline heart rate, decreased variability of heart rate, and fetal decelerations after contractions.

The normal fetal heart rate ranges from 120 to 160 beats/min; rates outside or trending toward these limits are ominous. Heart rate variability has two components. Beat-to-beat variability measures autonomic nervous function, whereas long-term variability indicates fetal activity. Heart rate variability increases with gestational age. The loss of beat-to-beat and long-term variability warns of fetal central nervous system depression and reduced fetal movement caused by fetal distress (Fig. 182.3).

Late decelerations are an indication of fetal hypoxia. These decelerations are relatively small in amplitude and occur after the peak or conclusion of a uterine contraction. By comparison, early decelerations are larger, occur with the contraction, and recover to baseline immediately after the contraction. Early decelerations may be vagally mediated when uterine contractions squeeze the fetal head, stretch the neck, or compress the umbilical cord. Variable decelerations are large, occur at any time, and are possibly caused by umbilical cord compression (Fig. 182.4).

Mother Stable, Fetus Stable

Minor trauma does not necessarily exempt the fetus from significant injury. It is estimated that up to 3% of all minor trauma results in fetal loss, typically from placental abruption. Therefore, once the traumatized mother is stabilized, the focus of care is directed toward the fetus. For the viable fetus (greater than 24 weeks' gestation), monitoring is the next step. Continuous monitoring maintained throughout all diagnostic and therapeutic actions is advisable. Because direct impact is not necessary for fetoplacental pathology to occur, the traumatized pregnant woman with no obvious abdominal injury still benefits from monitoring.

The recommended 4 hours of cardiotocographic observation of the viable fetus is extended to 24 hours if at any time during the first 4 hours there are more than three uterine contractions per hour, uterine tenderness persists, results on a fetal monitor strip are worrisome, vaginal bleeding occurs, the membranes rupture, or any serious maternal injury is present. Most cases of placental abruption after maternal trauma are detected within the first 4 hours of monitoring.

On discharge from the hospital, the pregnant woman should be instructed to record fetal movements during the next week. If fewer than four movements per monitored hour are noted, the patient should see her obstetrician immediately and a nonstress test is warranted. The occurrence of preterm labor, membrane rupture, vaginal bleeding, or uterine pain also necessitates prompt reevaluation. Serial ultrasound and fetal heart rate tests on viable fetuses a few days after maternal trauma and periodically throughout the remaining portion of the pregnancy are helpful in monitoring fetal well-being.

Mother Stable, Fetus Unstable

Fetal death rates after maternal trauma are three to nine times higher than maternal death rates.[5] If a viable fetus remains in distress despite optimization of maternal physiology, cesarean section should be considered.

Although fetal viability is first reached at 24 weeks, the ultimate determinant of the age of fetal viability is the level of neonatal care provided by the intensive care nursery unit in each hospital or accessible regional facility. Determining gestational age for fetuses of less than 29 weeks may be difficult. Emergency decisions on fetal viability are therefore made on the basis of the best ultrasonography and gestational age information available.

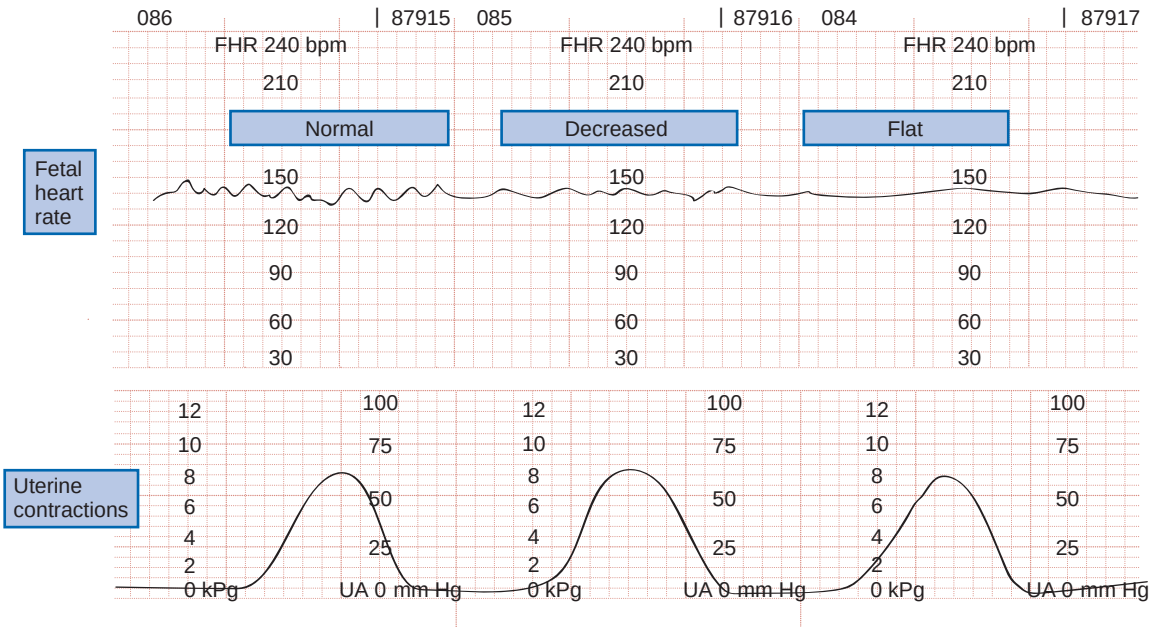

Fig. 182.3. Types of fetal heart rate variability. *bpm,* Beats per minute; *FHR,* fetal heart rate; *UA,* uterine activity.

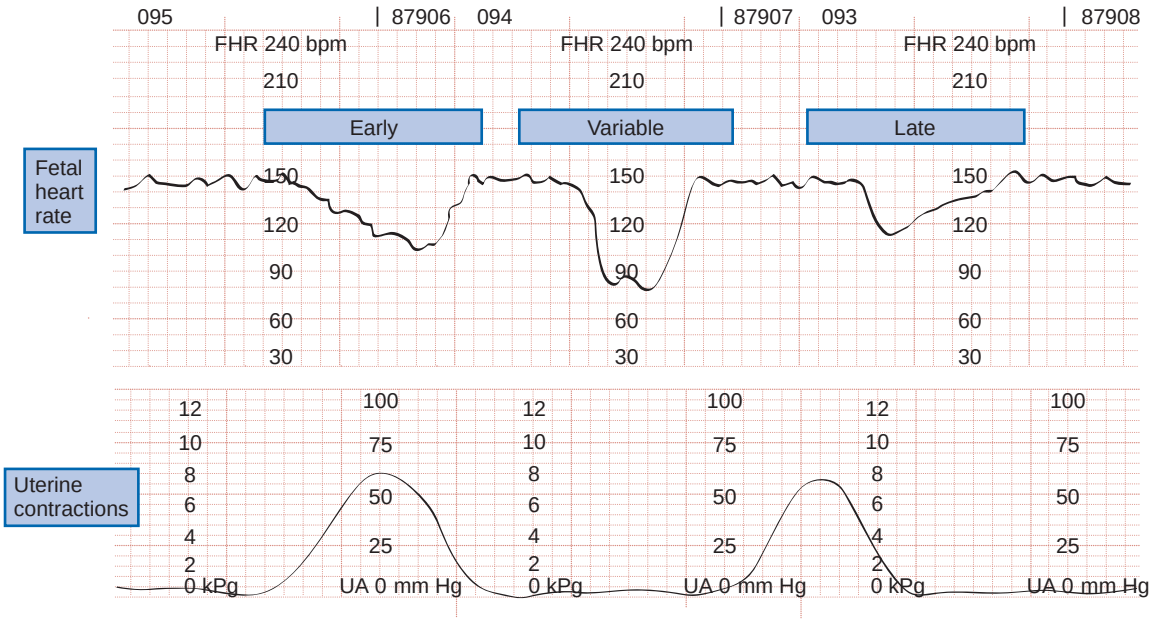

Fig. 182.4. Types of fetal heart rate decelerations. *bpm,* Beats per minute; *FHR,* fetal heart rate; *UA,* uterine activity.

The presence of fetal heart tones is an important survival marker for fetuses about to undergo emergency cesarean section. The fetal survival rate is zero if there are no fetal heart tones present when emergency cesarean section commences. If fetal heart tones are present and the gestational age is 26 weeks or more, then infant survival rate may be as high as 75%.

Besides fetal distress, other reasons for a cesarean section include uterine rupture, placental rupture with significant vaginal bleeding, fetal malpresentation during premature labor, and situations in which the uterus mechanically limits maternal repair. Fetal demise without any of the aforementioned conditions is not an indication for cesarean section, because most will pass spontaneously within 1 week.

Mother Unstable, Fetus Unstable

If the mother's condition is critical, primary repair of her wounds is the best course. This may apply even when the fetus is in distress, because a critically ill mother may not be able to withstand an additional operative procedure such as cesarean section, which prolongs laparotomy time and likely substantially increases blood loss. The best initial action on behalf of the fetus is early and aggressive restoration of normal maternal physiology. If it is felt that the unstable mother can tolerate an emergency cesarean section, it should be considered for the distressed, viable fetus.

As with nonpregnant patients, operative intervention for blunt trauma and above-the-uterus stab wounds is dictated by clinical findings and diagnostic testing results. Above-the-uterus intraperitoneal gunshot wounds require exploration. In situations of severe maternal hemorrhage, massive transfusion protocols should be initiated with fresh frozen plasma, platelets, and red blood cells in a 1:1:1 ratio to lower the rate of coagulopathy and improve survival.[4] There is little evidence to support a definitive management strategy for penetrating trauma to the gravid uterus. In situations of a hemodynamically stable mother, expectant management has been recommended. However, no prospective study has verified this. Damage to the uterus alone can be quite devastating because of its increased circulation. Without exploration, it is impossible to know the occurrence, size, or depth of uterine penetration, and there are no guidelines indicating whether a uterine wound can be left unsutured without incurring an increased risk of infection or delayed uterine rupture. Laparotomy or laparoscopy seems to be the safest means of managing penetrating uterine wounds, because missed maternal injuries can quickly compromise the fragile fetus.

Defibrillation

Electrical flow that bypasses the fetus has little effect on the pregnancy. Maternal elective and emergent cardioversion has been performed safely for cardiac dysrhythmias in all three stages of pregnancy. Energies up to 300 Joules have been used without affecting the fetus or inducing premature labor.[16] Although the amount of energy reaching the fetal heart is thought to be small, it is advisable to monitor the fetal heart during maternal cardioversion.

Perimortem Cesarean Section

Restoration of maternal and thus fetal circulation is the optimal goal with maternal hemodynamic instability. However, extended and exclusive attention to the mother in cardiopulmonary arrest may prevent recovery of a potentially viable fetus. During maternal resuscitation, adequate oxygenation, fluid loading, and a 30-degree left tilting position or manual displacement of the gravid uterus, may improve maternal circulation. If there is no response to advanced cardiac life support, a decision for perimortem cesarean section, also referred to as *resuscitative hysterotomy,* should be made within 4 minutes.[2,17,18] Perimortem cesarean section in the ED should be considered only if uterine size exceeds the umbilicus. Time since maternal circulation ceased is the critical factor in fetal outcome. Delivery increases venous return and cardiac output by 25% to 30% and may lead to survival benefit for mother.[8,19] Published reports support but fall short of proving that perimortem cesarean delivery should be initiated within 4 minutes of the onset of maternal cardiac arrest and no return of spontaneous circulation.[8,17,19-22] Beyond 20 minutes, there is virtually never survival or favorable neurologic outcome for either mother or fetus.[2]

In the event of maternal cardiopulmonary arrest, perimortem cesarean section may be indicated. The most experienced physician available should perform the procedure as cardiopulmonary resuscitation (CPR) is continuing. A midline vertical incision is made from the epigastrium to the symphysis pubis. The uterus is then entered with a midline vertical incision. If necessary, the placenta is incised to reach the fetus; once the fetus has been delivered, the cord is clamped and cut. Maternal revival after delivery of the fetus has been reported in a few perimortem circumstances, presumably because vena caval compression is relieved.

DISPOSITION

Any pregnant woman at 24 or more weeks of gestation who has sustained blunt trauma should undergo at least 4 hours of fetal monitoring even if she looks well. In general, pregnant women who sustain minor trauma have a favorable pregnancy outcome.[3] Other admission and operative criteria are similar for pregnant and nonpregnant trauma patients. The emergency clinician should consider the stability of the mother and the viability of the growing fetus when making management and disposition decisions.

KEY CONCEPTS

- Management of life- and limb-threatening injury in the mother comes first. Saving the mother provides the best chance of saving the baby.
- Even in the stable pregnant trauma patient, the fetus is at increased risk of morbidity and mortality.
- The fetus is viable at 24 weeks' gestation. This usually corresponds to when the fundus is at or above the umbilicus.
- Alterations in anatomy and physiology that occur during pregnancy may alter clinical findings related to blood loss and may mask injuries, making methodical assessment essential.
- Stable pregnancies with a viable fetus should be monitored continuously for a minimum of 4 hours after trauma.
- Keeping the mother tilted 30 degrees to the left or manually displacing the uterus may alleviate hypotension and improve perfusion for the mother and fetus.
- Perimortem cesarean section should be initiated for a viable fetus within 4 minutes of no spontaneous return of circulation.
- The use of ionizing radiation to the pregnant patient, including CT and plain radiography, should be minimized, but imaging should not be withheld if it may provide significant diagnostic information. Often, ultrasound, MRI, or a period of observation can preclude the need for ionizing radiation.

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CHAPTER 182: QUESTIONS & ANSWERS

182.1. In cases involving minor trauma to pregnant women, which of the following is a predictor of fetal outcome?
- **A.** Abdominal tenderness
- **B.** Cardiotocographic monitoring for 4 hours
- **C.** Maternal blood count and arterial blood gas results
- **D.** Maternal vital signs
- **E.** Ultrasonography

Answer: B. For women with mild trauma, fetal outcome is not predicted by maternal vital signs, abdominal tenderness, blood tests, or ultrasound results. Only cardiotocographic monitoring for a minimum of 4 hours is useful to predict fetal outcome.

182.2. Which of the following factors is most concerning in the presentation of a pregnant trauma patient?
- **A.** Diastasis of the symphysis pubis
- **B.** Electrocardiogram (ECG) findings of Q waves in III and aV_F
- **C.** Hematocrit 34% in third trimester
- **D.** Hypotension in the third trimester
- **E.** Respiratory alkalosis in the third trimester

Answer: D. Blood pressure declines in the first trimester, levels out in the second trimester, and then returns to nonpregnant levels during the third trimester. In pregnancy, minute ventilation increases, leading to hypocapnia. Therefore a partial pressure of arterial carbon dioxide ($Paco_2$) of 35 to 40 mm Hg may indicate inadequate ventilation and impending respiratory decompensation. The physiologic anemia of pregnancy, resulting from a 48% to 58% increase in plasma volume and only an 18% increase in red blood cells, results in hematocrits of 32% to 34% by gestational age of 32 to 34 weeks. Electrocardiographic changes include a left-axis shift averaging 15 degrees, caused by diaphragm elevation. Consequently, flattened T waves or Q waves in leads III and aV_F may be seen.

182.3. A 26-week gravid woman presents to the emergency department (ED) after a moderate-speed motor vehicle collision (MVC). The patient is without complaints, and her vital signs are as follows: blood pressure, 100/60 mm Hg; heart rate, 100 beats per minute; and respiratory rate, 18 breaths per minute. Ultrasound examination shows good fetal movement, with a fetal heart rate of 150 beats per minute. What is the appropriate disposition for this patient?
- **A.** Consult obstetrics for a minimum of 4 hours of cardiotocographic monitoring.
- **B.** Consult obstetrics for 1 hour of cardiotocographic monitoring.
- **C.** Consult trauma and obstetrics for admission and serial examinations.
- **D.** Consult trauma and obstetrics for clearance to discharge patient.
- **E.** Discharge the patient with close follow-up with obstetrics.

Answer: A. Placental abruption results when the inelastic placenta shears away from the elastic uterus during sudden deformation of the uterus. Because deceleration forces can be as damaging to the placenta as direct uterine trauma, abruption can occur with little or no external sign of injury to the abdominal wall. For the viable fetus (more than 24 weeks' gestation), monitoring is the next step.

182.4. A 33-year-old pregnant patient complains of abdominal cramping after a trip and fall accident at home. After 4 hours of cardiotocographic monitoring, the patient was admitted to the obstetric service for further evaluation. What was the least likely reason for the admission?
- **A.** Late decelerations on fetal monitoring strip
- **B.** Leakage of clear fluid from the os
- **C.** Maternal pulmonary contusion
- **D.** Persistent uterine tenderness
- **E.** Two uterine contractions per hour

Answer: E. The recommended 4 hours of cardiotocographic observation of the viable fetus should be extended to 24 hours if at any time during the first 4 hours there are more than three uterine contractions per hour, persistent uterine tenderness, a worrisome fetal monitor strip, vaginal bleeding, rupture of the membranes, or if any serious maternal injury is present.

182.5. A 26-year-old, 30-week gestation woman presents unresponsive with cardiopulmonary resuscitation (CPR) in progress after a high-speed motor vehicle collision (MVC). On ultrasonography, the fetal heart beat is noted at a rate of 130 beats per minute. The patient lost her vital signs 3 minutes before arrival in the emergency department (ED). What is the most appropriate next step in the management of this patient?

A. Perimortem cesarean section in the operating room by obstetrics
B. Perimortem cesarean section with horizontal suprapubic incision
C. Perimortem cesarean section with vertical incision
D. Thoracotomy with cardiac massage
E. Thoracotomy with cross-clamping of the aorta

Answer: C. In the event of maternal cardiopulmonary arrest, perimortem cesarean section is indicated. The most experienced physician available should perform the procedure.

CHAPTER 183

Approach to the Geriatric Patient

Jennifer C. Chen

PRINCIPLES

Epidemiology and Demographics

The current growth in the population of older adults is unprecedented in the history of the world, driven by longer life expectancies in developed countries. In the United States, the additional demographic contribution of the aging of the large baby boomer generation (about 10,000 boomers will turn 65 years old every day for the next 15 years) makes those aged 65 years and older the fastest growing segment of the US population (Fig. 183.1).[1] From 2010 to 2050, the population of US older adults will more than double, and those aged 85 years and older will more than triple.[2]

Causes of death in adults older than 65 years have shifted from infectious diseases and acute illnesses to chronic diseases as the leading causes of death in older Americans,[3] with associated declines in functional status, cognition, and social supports. These demographic changes—the increasing burden of chronic diseases, and financial, transportation, and functional limitations unique to older adults—translate into older people presenting to emergency departments (EDs) in greater numbers and at higher rates than any other age groups.[4] Older patients have the greatest degree of resource use, longest length of stay, and highest admission rates of any age group. Older adults are also at high risk of adverse health outcomes after an ED visit; within the first 3 months after ED discharge, approximately 5% of older people will die, 20% will be hospitalized, and 20% will have a return outpatient ED visit.

Assessing the Older Patient

Obtaining a detailed history remains a mainstay of clinical care in older adults. However, older patients more often have cognitive, functional, and sensory impairments or depression that limit their ability to communicate.[5] These syndromes, associated with aging complicate, the evaluation and management of older adults in the ED and may be underappreciated and underrecognized by emergency clinicians. History taking may need to expand beyond just asking the patient to include caregivers and institutions such as nursing home. Patients and caregivers may have difficulties recalling all the details of a long and complex history or multiple medications; therefore, careful review of medical records and medication lists are important adjuncts to the history.

Routine performance of a cognitive assessment in older patients has been identified as a geriatric quality indicator for EDs.[6] Patients with cognitive dysfunction, which includes mild cognitive impairment, dementia, and delirium, are less able to provide an accurate reason why they are in the ED and less able to comprehend discharge instructions.[7] Early performance of cognitive assessment in the evaluation of the older patient can improve quality of care and disposition planning.

Delirium, an acute confusional state with alterations in cognition and attention, occurs in around 10% to 20% of older ED patients. Unfortunately, emergency clinicians miss recognizing delirium up to 75% of the time, especially with the hypoactive subtypes of delirium. There are several brief assessment tools available, including the Confusion Assessment Method (CAM; Fig. 183.2). Delirium is generally caused by decreased neurologic reserve plus one or more acute precipitants, such as infection, metabolic abnormalities, and acute coronary syndromes. Delirium and dementia are sometimes difficult to distinguish from one another, but the distinction is important because the presence of delirium should lead to concern for a potentially life-threatening medical emergency. Older ED patients with delirium have higher intensive care unit (ICU admission, 30-day mortality and 30-day readmission rates.[8]

Studies that have universally screened older ED patients found rates of dementia of about 35%, mostly previously undiagnosed.[9,10] *Dementia* is an umbrella term for chronic disorders that result impairment in two or more cognitive domains, including memory loss, language, motor activity, object recognition, and disturbance of executive function. Although dementia would ideally be diagnosed by primary care physicians, this is not the norm. Detection of dementia by emergency clinicians allows a baseline cognitive status to be documented in the record and prompts patient and family to seek definitive evaluation for prognosis and planning. Most importantly, early recognition prompts additional history seeking from family and other collateral sources to reevaluate the chief complaint, which ultimately saves time and improves diagnostic accuracy.

Functional assessments, including activities of daily living (ADLs) and instrumental activities of daily living (IADLs), are important (Table 183.1). Functional decline can provoke ED presentation and may be the only manifestation of serious underlying disease. Functional impairment is relevant to disposition and predicts short-term repeat ED visits.[11]

Routine evaluation of cognitive and functional status can be time-consuming. Given the emphasis on efficiency in the ED, appropriate identification of high-risk older adults may help emergency clinicians target patients for more detailed evaluation in the ED or for some other intervention. Recently published geriatric emergency department guidelines also recommend screening for high-risk patients. The Identification of Seniors at Risk (ISAR) tool is a recommended screening tool that incorporates elements of cognitive impairment and functional decline together to estimate risk (Box 183.1).[10] Screening tools such as the ISAR highlight the interplay between cognitive impairment and

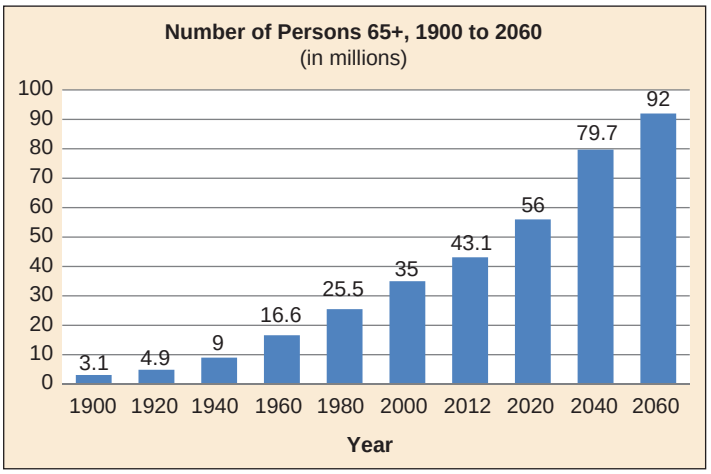

Fig. 183.1. Aging population. (Adapted from Administration on Aging, Administration for Community Living, U.S. Department of Health and Human Services: A profile of older Americans: 2013. nutritionandaging.org/profile-older-americans-2013.)

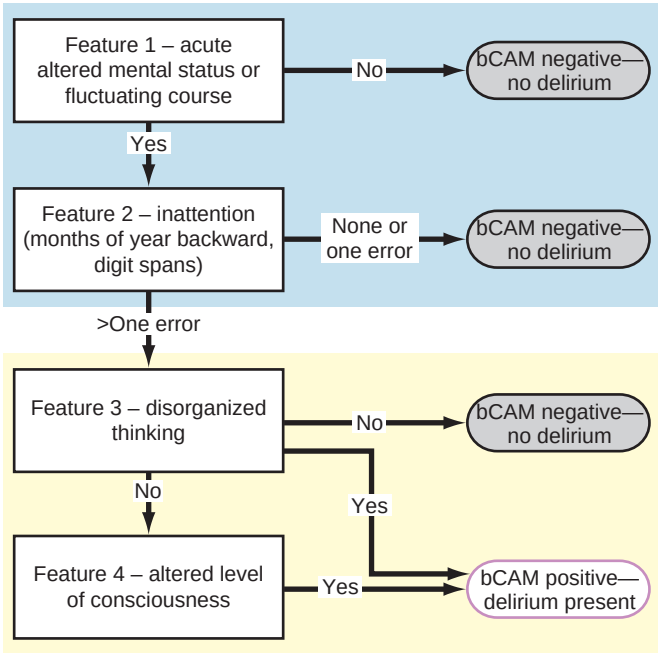

Fig. 183.2. Brief Confusion Assessment Method (bCAM)—screening tool for delirium. The results are positive if both features 1 and 2 and feature 3 or 4 are positive, with a 94% sensitivity and 89% specificity. (From Hospital Elder Life Program: Confusion assessment method (short CAM). www.hospitalelderlifeprogram.org/delirium-instruments/short-cam/short-cam-instrument. © 2016. All rights reserved.)

TABLE 183.1

Functional Assessment

ACTIVITIES OF DAILY LIVING	INSTRUMENTAL ACTIVITIES OF DAILY LIVING
Bathing	Telephone
Dressing	Shopping
Toileting	Food preparation
Transferring	Housekeeping
Continence	Laundry
Feeding	Transportation
	Medication management
	Ability to handle finances

Adapted from Temel JS Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733–742.

BOX 183.1

Identification of Seniors at Risk (ISAR) Tool

1. Before the illness or injury that brought you to the emergency department, did you need someone to help you on a regular basis? (yes)
2. Since the illness or injury that brought you to the emergency department, have you needed more help than usual to take care of yourself? (yes)
3. Have you been hospitalized for one or more nights during the past 6 months (excluding a stay in the emergency department)? (yes)
4. In general, do you see well? (no)
5. In general, do you have serious problems with your memory? (yes)
6. Do you take more than three different medications every day? (yes)

Each "yes" response counts as 1 point, for a total score ranging from 0 to 6. A patient is considered at high risk when the score is 2 or more.
Adapted from McCusker J, Bellavance F, Cardin S, et al: Detection of older people at increased risk of adverse health outcomes after an emergency visit: the ISAR screening tool. J Am Geriatr Soc 47:1229–1237, 1999.

functional decline. Further work is needed on the development and validation of brief screening instruments.[12]

Adapting Fundamental Principles of Geriatrics to the Emergency Department

Emergency clinicians should adapt fundamental principles of geriatrics for emergency practice such as shared decision making, a focus on risks and benefits of therapy, a focus on quality of life considerations, and interdisciplinary care. In contrast to a more holistic approach, traditional organ system or illness-based approaches will lead to greater intensity of service,[5,13] with resulting increases in crowding, medical spending, and iatrogenic harm. The ED will need to be not only a critical care safety net but also a partner in managing care coordination. Care coordination can be defined as the conscious effort by two or more health care professionals to facilitate and coordinate the appropriate delivery of health care services for a patient—for example, when the emergency clinician speaks by phone with the primary care physician to discuss follow-up needs to ensure a safe discharge.

Transitions in Care

Transitions in care, particularly from nursing home to ED, ED to inpatient, and ED discharge to home or nursing home setting, are

potentially high-risk events. Omissions in documentation and lack of direct communication may lead to information gaps, particularly in the transition from nursing home to ED. Transitions in care may be riskier for older patients due to the complexity of their medical problems, usage of multiple medications, and cognitive and/or hearing impairment that may limit the patient's ability to participate in history taking and disposition planning. Transitions in care may negatively affect older patients as a result of medication errors, adverse drug events, unnecessary treatments and hospitalizations, and lack of timely coordination of follow-up care.[14,15] A number of groups, including the American College of Emergency Physicians, have identified management of transitions in care as a quality gap in emergency medicine and have advocated for greater vigilance around these transitions.[10] Effective transitions in care for older patients requires communication between transferring and receiving providers, sharing of relevant information about patient preferences and clinical status, robust medication reconciliation, and detailed discharge planning, with the consideration of palliative care when appropriate.

Goals of Care and Palliative Care

Older patients with advanced and end-stage disease frequently present to the ED. A recent study examining ED use in the last months of life for older adults has found that 75% visited at least once during their last 6 months of life, and 51% visited the ED in the last month of life, with repeat visits and in-hospital death as common outcomes.[16] For patients with advanced life-limiting disease, the role of the emergency clinician is a combination of curative care, such as infection management, and palliative care, meaning a patient-centered focus on quality of life, particularly symptom management. For patients for whom the focus may be on symptom management for end-of-life care, frequent complaints include agitation and delirium, anxiety, constipation, dyspnea, pain, pruritus, excessive oral secretions, stomatitis and nausea, vomiting, and diarrhea.

Prognostication in the ED setting is challenging, as is communication with patients and families regarding goals of care in an inherently fast-paced ED environment. However, these interventions are nonetheless necessary because benefits of palliative care include improved patient satisfaction, reduced length of stay, cost savings, and improved outcomes.[17] Even if the interdisciplinary staff (eg, social worker, clergy, hospice case manager, palliative care specialist) are not immediately available in the ED, the role of ED staff must be facile in addressing end-of- life issues, including assisting in the transition to palliative care or hospice.[17]

SPECIFIC DISORDERS AND CHIEF COMPLAINTS

The most common chief complaints in older ED patients are chest pain, shortness of breath, and abdominal pain.[4] A major challenge in caring for older patients is that disease in old age—presentation, clinical course, response to treatment, outcomes—is usually modified by interaction with age-related changes. For example, atypical presentations may be due to a combination of age-related physiologic changes, age-related loss of physiologic reserve, interactions of chronic conditions with acute illnesses, and underreporting of symptoms.

Another challenge in caring for older patients is that chronologic age and physiologic age are not synonymous. There is great variability in senescence among older adults, so establishing baseline functional status is critical in shared decision making with the patient and family. Regardless, older patients are more susceptible to disease due to so-called homeostenosis, a diminished ability to maintain homeostasis under stress.

Acute Coronary Syndrome

Cardiovascular heart disease is the leading cause of death in men and women older than 65 years.[18] Many physiologic changes of aging occur in the cardiovascular system (see Table 183.2). Atypical presentations of acute coronary syndrome (ACS) occur more often in older patients. Chest pain at presentation occurs in only about 50% of patients with ST elevation myocardia infraction (STEMI) who are 85 years or older. Although chest pain may be absent, only 2% to 6% of older patients with ACS are actually asymptomatic. Other presenting symptoms may include dyspnea, syncope, shoulder or back pain, abdominal pain, weakness, fatigue, and delirium. One-third of women older than 65 years with acute myocardial infarction present with abdominal pain alone. Many of these presenting symptoms are nonspecific and are common to many other disease processes. As a result, the diagnosis of ACS may be delayed, and older patients may present instead with delayed complications, such as acute congestive heart failure.

Acute heart failure at presentation occurs in nearly 50% of STEMI patients 85 years or older compared to only 1.7% of STEMI patients younger than 65 years. Myocardial ischemia impairs left ventricular relaxation, which leads to an increase in left ventricular end-diastolic pressure (LVEDP). This increased LVEDP, superimposed on age-related decreases in left ventricular compliance, frequently results in elevated pulmonary capillary wedge pressure and heart failure.

Older patients with ACS have higher associated mortality. However, older patients often do not receive as aggressive treatment, in terms of referral for cardiac catheterization, as their younger counterparts,[19] even though current American Heart Association (AHA) guidelines recommend no absolute age restrictions in revascularization therapy for non-STEMIs and STEMIs.[20] Another factor that supports cardiac catheterization in older adults is that there is an age-related increase in complications with thrombolytic medications, particularly intracerebral hemorrhage and free wall rupture. For older patients with acute myocardial infarction complicated by cardiogenic shock, recent AHA guidelines now recommend early revascularization across all age groups.[21,22]

Abdominal Pain

Older ED patients with acute abdominal pain have about a sevenfold mortality risk compared to younger patients, and about

TABLE 183.2

Age-Related Changes to the Cardiovascular System

AGE-RELATED CHANGE	CLINICAL CONSEQUENCE
Decreased arterial compliance	Increased afterload, left ventricular hypertrophy, hypertension
Myocardial cell hypertrophy, interstitial fibrosis, drop out of cardiac myocytes	Decreased left ventricular compliance, increased contribution of atrial contraction to left ventricular end-diastolic volume (LVEDP)
Apoptosis of sinoatrial pacemaker cells, fibrosis and loss of His bundle cells	Slower intrinsic heart rate, varying degrees of heart block
Decreased responsiveness to β-adrenergic stimulation and reactivity to baroreceptors and chemoreceptors	Increased circulating catecholamines
Fibrosis and calcification of heart valves	Aortic valve sclerosis and stenosis

30% will require surgery. Atypical presentations are common. Several factors can complicate the ability to make a diagnosis based on the history and physical examination alone, including altered pain perception, aging effects on the immune system, medications that limit tachycardic response to stress, and decreased ability to mount a febrile response to infection. Sometimes, older patients will present only with generalized symptoms such as delirium, malaise, or dizziness when the cause is an acute abdominal condition. Laboratory values are frequently normal, despite the presence of surgical disease. Imaging studies, particularly computed tomography (CT), are often appropriate to facilitate diagnosis and are highly diagnostic in an older patient population.[23]

Consideration of intra-abdominal vascular catastrophe is important because the incidence of vascular disease increases with age. Vascular emergencies remain some of the most time-sensitive and highly morbid causes of abdominal pain in the older patient and should always be considered first, particularly for abrupt onset symptoms.[24] Although the diagnosis of a ruptured abdominal aortic aneurysm (AAA) may be fairly straightforward in the older patient who has abdominal pain, hypovolemic shock, and a pulsatile abdominal mass, most patients lack this triad at presentation. AAA is commonly misdiagnosed as acute renal colic, and any older patient presenting with symptoms of new-onset nephrolithiasis should have imaging to evaluate the aorta for AAA.

Appendicitis is the third most common indication for abdominal surgery in the older patient population. Older patients have a higher incidence of perforation and mortality due to much higher rates of delayed diagnoses and/or presentations. Cognitive issues, altered pain perception, high stoicism, and transportation barriers may be factors in regard to a delayed presentation. Appendicitis historically has been misdiagnosed half of the time in older adults because many patients lack fever, anorexia, or leukocytosis. One-quarter of older patients have no right lower quadrant pain at all.

Biliary tract disorders are the most common cause of abdominal pain in the older adult, with the incidence of gallstones increasing with age. Cholecystitis is the most common indication for abdominal surgery in the older patient. About one-third of older patients with cholecystitis have no fever or leukocytosis. Additionally, about one-third of older adults with acute cholecystitis will present with minimal abdominal pain and an absence of peritoneal signs. Due to the poor vascularity of the gallbladder, older patients are at increased risk of complications such as perforation and emphysematous cholecystitis.

Generalized Weakness

Nonspecific complaints such as generalized weakness are consistently among the top ten presenting complaints for older ED patients.[4] These poorly defined, nonspecific complaints have been variously described as dizziness, frailty, failure to thrive, generalized weakness, malaise, and fatigue. One study has found that 58% of older ED patients presenting with nonspecific complaints such as weakness developed a serious condition within 30 days.[25] Important historical features include timing and focality of symptoms (Fig. 183. 3).[26] Neuroimaging can be helpful if the weakness is acute or localized because around 75% of the subset of older weak patients with acute focal or localized weakness are ultimately found to have stroke or intracranial hemorrhage. Research suggests that three categories of illness—infections, metabolic abnormalities, and malignancies—were found in almost all patients presenting with nonspecific complaints of weakness.[25]

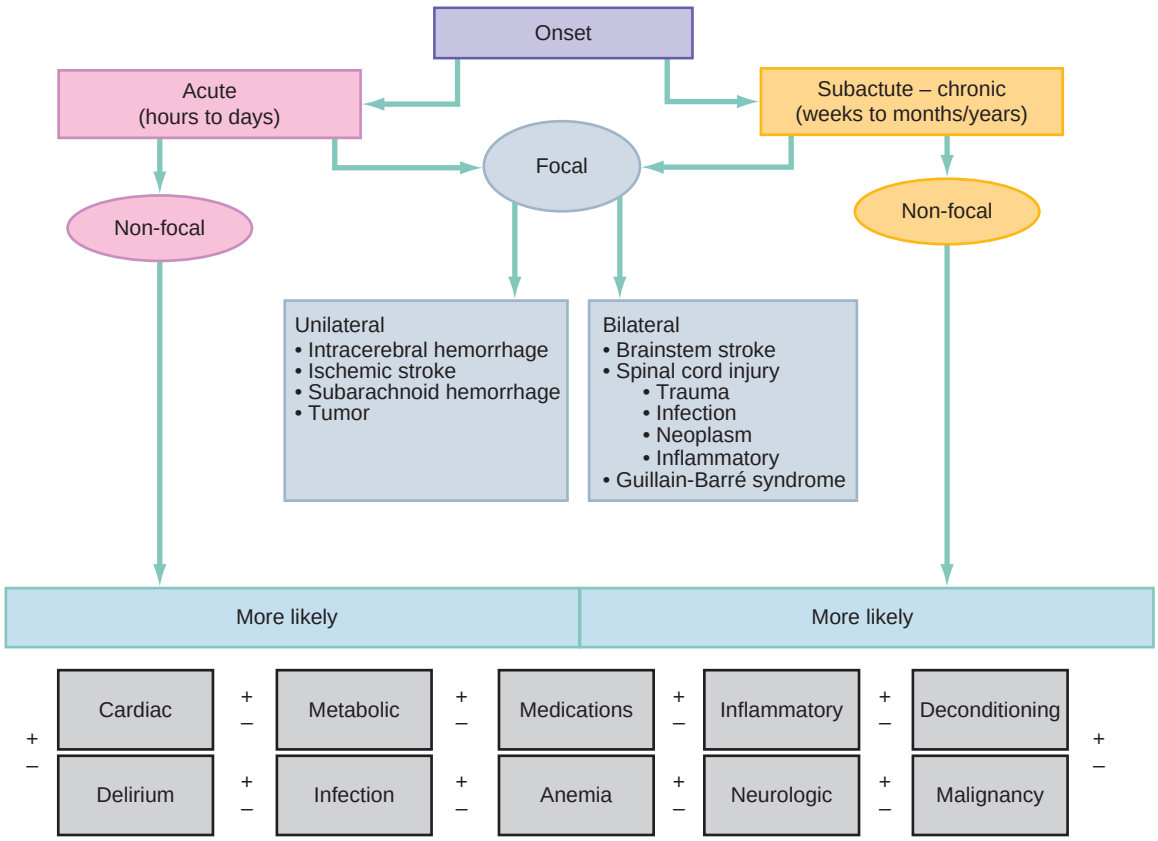

Fig. 183.3. Diagnostic approach to weakness by onset and focality. (From Anderson RS, Hallen SAM: Generalized weakness in the geriatric emergency department patient: an approach to initial management. Clin Geriatr Med 29:91–100, 2013.)

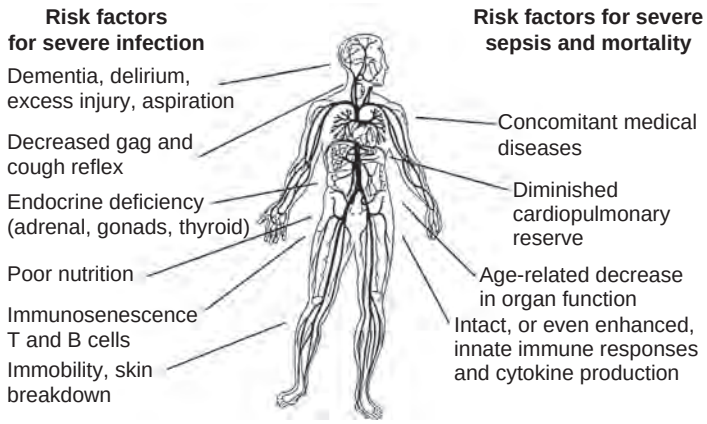

Fig. 183.4. Predisposing factors for sepsis in older individuals. (From Girard TD, Opal SM, Ely EW: Insights into sepsis in older patients: from epidemiology to evidence-based management. Clin Infect Dis 40:719–727, 2005.)

Infections

Older patients experience an increased incidence of severe infection and severe sepsis with advanced age. Mortality from sepsis approaches 40% for patients older than 85 years. Aging effects on immunity include a decline in cell-mediated immunity and antibody production.. Older patients may also have multiple risk factors for sepsis (Fig. 183.4) including comorbid diseases, exposure to instrumentation, malnutrition, and institutionalization. For example, studies have shown that an increasing chronic disease burden correlates with increasing hospitalization rates for community-acquired pneumonia in older adults.

With aging, the ability to generate a fever response in response to pyrogens (bacterial endotoxins) is decreased. Because of this blunted fever response, and because medication use or cardiac disease may limit tachycardic response to infection, older patients may have systemic inflammatory response syndrome (SIRS)–negative sepsis. Research has shown that abnormal triage vital signs in adults 75 years and older have poor sensitivity (73%) and specificity (50%) for predicting death or ICU admission.[27] It is important that emergency clinicians look more broadly than just the typical SIRS criteria to suspect and diagnose sepsis accurately. For example, in the long-term care population, in whom there are particularly high rates of cognitive impairment, Current Infectious Diseases Society of America (IDSA) guidelines define suspected infection as fever plus a decline in functional status—confusion, incontinence, falls, decreased mobility, reduced food intake, failure to cooperate with staff.

Management of suspected sepsis in older patients is similar to that for younger patients, with an emphasis on early identification of sepsis, fluid resuscitation, and early and appropriate antibiotics Just as with younger adults, older patients with sepsis have improved mortality with comprehensive sepsis treatment.[28] Older patients are more dependent on having an adequate preload to increase cardiac output in response to sepsis because the ability to raise the heart rate is blunted. However, aging-associated diastolic dysfunction is common, and fluid resuscitation goals may need adjustment if patients develop hypoxia or hypervolemia. In regard to the choice of empirical antibiotics, sepsis in older patients compared to younger patients is more likely to be due to respiratory (relative risk [RR], 1.29) or genitourinary (RR, 1.38) infections, with pneumonia as the single most common cause of sepsis. Management of suspected sepsis in older patients, particularly in those with a poor prognosis, also includes consideration of patient and family preferences and goals of care.

KEY CONCEPTS

- We are in the midst of a silver tsunami, with 10,000 Americans turning 65 every day. Older ED patients have the greatest resource use, longest lengths of stay, and highest admission rates of any age group.
- Delirium is underrecognized by emergency clinicians; recognition of delirium should prompt investigation for life-threatening emergencies, including infection, metabolic abnormalities, and acute coronary syndrome (ACS).
- Many older patients with ACS present without chest pain, especially females and patients older than 85 years. ACS in older adults is more often complicated by acute heart failure due to age-related decreases in left ventricular compliance. Recommendations regarding medical and revascularization therapy in those with non-STEMI and STEMI have no age limitations.
- Almost one-third of older ED patients presenting with abdominal pain are ultimately found to have a surgical condition causing the abdominal pain. Biliary tract disorders are the most common cause of abdominal pain in the older adult.
- Nonspecific complaints such as generalized weakness are among the top ten presenting complaints for older ED patients. Acute onset and focality of symptoms increase the likelihood of stroke or intracranial hemorrhage.
- Mortality from sepsis approaches 40% for patients older than 85 years, with respiratory and genitourinary infections being the most common sources. Older adults with serious infection may have SIRS-negative sepsis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

REFERENCES

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CHAPTER 183: QUESTIONS & ANSWERS

183.1. The presentation of infection in older patients differs from the presentation in younger patients. Older patients are more likely to have which of the following?

A. Benign clinical course
B. Elevated inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein
C. Fever
D. Left shift of the white blood cells
E. Normal white blood cell count

Answer: E. Older patients are more likely to have a normal white blood cell count, as well as a normal differential. They are less likely to have fever and signs or symptoms from the infection process. They are more likely to have complications and suffer long-term morbidity or mortality.

183.2. Which of the following statements is true regarding acute myocardial infarction (AMI) in older adults?

A. Atypical presentations portend a more benign course.
B. Atypical presentations increase with age.
C. Painless AMIs occur more commonly in men.
D. The absence of chest pain is rare.
E. Up to 50% of older patients with AMI are asymptomatic.

Answer: B. Atypical presentations of AMI increase with age and are of equal severity as typical cases. Although atypical cases are frequent, only 2% to 6% are asymptomatic. Women have painless presentations more than men, and present with abdominal pain almost one-third of the time. The absence of chest pain is not uncommon.

183.3. A 74-year-old man with a history of hypertension and hyperlipidemia presents to the ED with acute onset of severe, nontraumatic, left flank pain. His vital signs include a heart rate of 72 beats/min and blood pressure of 120/70 mm Hg. Which approach to his care would be most appropriate?

A. Arrange for him to be in the observation unit overnight for serial abdominal examinations to help clarify his diagnosis.
B. Consider abdominal aortic aneurysm only after the patient's urinalysis and renal ultrasound are negative for nephrolithiasis.
C. Diagnose him with nephrolithiasis without any further testing.
D. Evaluate for a possible abdominal aortic aneurysm.

Answer: D. Vascular disease prevalence increases with age. Vascular emergencies remain some of the most time-sensitive and highly morbid causes of abdominal pain in the older patient and should always be considered first, particularly for abrupt-onset symptoms.

183.4. Which of the following statements is true about complaints of nonspecific weakness in older ED patients?

A. Admission to a skilled nursing facility for failure to thrive should be the rule.
B. Emergency clinicians should assume that the weakness is a stroke until proven otherwise.
C. The most common underlying causes of complaints of nonspecific weakness are infection, metabolic derangements, and malignancy.
D. Weakness is a part of natural aging.

Answer: C. With nonspecific weakness, infections, metabolic abnormalities, and malignancies are the most common findings in older patients. Nonspecific complaints such as generalized weakness are consistently among the top ten presenting complaints for older ED patients. Important historical features include timing and focality of symptoms. If patients have acute focal weakness, a stroke or intracranial hemorrhage is very likely. However, in the absence of focal weakness, medical causes are more likely.

183.5. How does the presentation of abdominal pain in older adults differ from that in younger adults?

A. Bedside abdominal palpation and examination is the emergency clinician's most sensitive tool.

B. Older patients are less likely to have a surgical emergency.

C. Older patients often have delayed presentations.

D. Older patients uniformly mount a febrile response when they have a surgical emergency.

Answer: C. Older patients often have delayed presentations of abdominal emergencies. Cognitive issues, altered pain perception, high stoicism, and transportation barriers may be factors in delayed presentation. Older patients are more likely to have a surgical cause of their abdominal pain. Imaging studies, particularly computed tomography, are often appropriate to facilitate diagnosis and are highly diagnostic in the older patient population.

CHAPTER 184

Geriatric Trauma

Jeremiah D. Schuur | Zara Cooper

PRINCIPLES

Older adults make up a growing proportion of trauma patients in emergency departments (EDs). US trauma systems and management principles were developed in the 1970s and were based primarily on advances from military medicine and designed to serve younger adult patients. Although the general principles of trauma care for younger adults apply to older adults, there are special considerations for the older trauma patient. This chapter focuses on evaluation and management decisions for trauma in older patients that may differ from those in younger adults.

Background and Importance

There is no standard definition of the term *geriatric trauma* in the literature; studies include patients older than 45 to 65 years. Risk-adjusted analyses have demonstrated patients older than 55 years to be at higher risk of mortality, and some studies further stratify older adults into the oldest old group, those older than 80 or 85 years. In this chapter, unless noted, we are referring to patients 65 years and older. The literature on trauma in older adults has several limitations. Older adults are frequently excluded from clinical trials, a limitation in considering high-risk interventions such as surgery or invasive hemodynamic monitoring. Furthermore, studies conducted using trauma databases include only trauma center patients evaluated by a trauma team; the results may not be generalizable to non–trauma center ED populations.

Demographics and Epidemiology

The US population is aging, and older adults are living more independently and have more active lifestyles, which explains the dramatic rise in geriatric trauma. More than one in eight Americans were aged 65 years or older in 2012, whereas by 2030 one in five will be 65 years or older.[1] In 2011, US adults aged 65 and older accounted for almost 13% of all injury-related ED visits, and this percentage is expected to increase with the aging of the population.[2]

Older trauma patients have increased morbidity and mortality owing to the severity of injury, presence of comorbid conditions, and independent effects of age. In similar accidents, older adults sustain more severe injuries than younger adults, a strong predictor of mortality. In 2010, unintentional injury was the ninth leading cause of death among those older than 65 years.[3] Older adults are more likely to have significant underlying medical conditions that limit their physiologic response to injury and increase the risk of death after trauma, especially in less severe injuries.[4] Age is independently predictive of morbidity and mortality, even when controlling for comorbidities and the Injury Severity Score (ISS).[4]

Age as a Trauma Triage Criterion

Age should be considered in determining criteria for transfer to a trauma center and for activation of a trauma team. Traditional triage criteria based on mechanism and vital signs miss many older adults with major injuries.[5-7] Fewer older patients are transported to trauma centers despite meeting trauma center criteria, and older adults are less likely to be admitted to trauma centers than younger adults.[8] Ohio has developed and implemented additional prehospital triage criteria for geriatric trauma that trigger automatic transport to a trauma center (Box 184.1). Applying these triage criteria to a statewide database increased sensitivity for severe injury by 32% while decreasing specificity by 12%.[9] An Eastern Association for the Surgery of Trauma guideline does not give level I support for age as an independent criterion for trauma center referral or activation, but found less robust evidence to support using advanced age (≥65 years) in patients with comorbidities or severe anatomic injuries as a criterion for transfer to a trauma center, respectively.[10] The Advanced Trauma Life Support (ATLS) program recommends that emergency medical services (EMS) use age older than 55 years as a criterion for transfer to a trauma center.[11] However, the effect of trauma center care on older adults is not clear; several studies have shown that older patients with severe injuries have better outcomes when treated at a trauma center[12,13]; however, a larger study of 69 hospitals in 14 states found no survival difference. At trauma centers, age is often a criterion for trauma team activation, and single-center studies have shown decreased mortality after trauma team activation criteria were changed to include age older than 65 or 70 years.[14] We recommend using age of 70 years and older and the Ohio state criteria listed in Box 184.1 as criteria for trauma center referral and trauma team activation.

Mechanisms of Injury

Falls are the leading mechanism of injury and the leading cause of injury-related death in patients older than 65 years.[15] In 2013, there were 2.5 million ED visits for falls among those 65 years and older, and one-third were hospitalized. Up to one-third of older adults sustain a significant fall each year, and serious injuries occur in up to 25%. Most falls are from standing and occur at the older adult's place of residence. Risk factors for falling include, in decreasing relative risk, weakness, balance or gait deficit, visual deficit, mobility limitation, cognitive impairment, impaired functional status, and postural hypotension. Up to 10% of those who fall sustain a major injury, with head injury being the most frequent.[16] Although the height of the fall is associated with severity, falls from standing carry significant risk for older adults; same-level falls result in serious injury (ISS > 15) 30% of the time in older patients, and peri-injury mortality from low falls is up to 10%.[17]

Motor vehicle accidents (MVAs) and pedestrians struck by a motor vehicle are the second and third most frequent causes of trauma in older adults.[18] Older adults are more likely than younger adults to be involved in daytime crashes occurring close to home. A detailed crash history is important, and single-vehicle crashes should raise the suspicion that a medical problem caused the crash (eg, syncope, myocardial infarction, stroke), and an evaluation for coincident events leading to trauma should be undertaken

BOX 184.1

Ohio Prehospital Geriatric Trauma Triage Indicators

- Trauma patients ≥70 years are defined as having suffered geriatric trauma.
- If an injured older adult has any of the geriatric indicators, he or she must be transported directly to a trauma center.

GERIATRIC ANATOMIC INDICATORS
- Injury sustained in two or more body regions

GERIATRIC PHYSIOLOGIC INDICATORS
- Glasgow Coma scale score <15 with a known or suspected traumatic brain injury
- Systolic blood pressure < 100 mm Hg

GERIATRIC MECHANISM INDICATORS
- Fracture of one or more proximal long bones (humerus or femur) sustained in a motor vehicle accident
- Pedestrian struck by a motor vehicle
- Falls from any height—including standing—with evidence of a traumatic brain injury

Adapted from State of Ohio, State Board of Emergency Medical Services, Trauma Committee: Geriatric trauma task force report and recommendations. www.publicsafety.ohio.gov/links/ems_geriatric_triage.pdf.

during the trauma management process. Older adults are more likely to be struck by a motor vehicle than younger pedestrians because of poor eyesight, limited mobility, and slower reaction time. Pedestrians who are struck sustain significant injury patterns and have the highest fatality rate of all geriatric injuries, 30% to 55%.

Thermal injuries, self-injury, and elder abuse are less common but important injury patterns in older adults. Thermal injuries such as burns and smoke inhalation occur more frequently and are more severe in older adults owing to decreased mobility and physiologic skin changes.[19] Older adults have a lower likelihood of attempting self-injury but a higher likelihood of completing suicide attempts than any other age group, with men at higher risk. Elder abuse is a complex problem that can involve psychological, social (eg, financial), and physical abuse. Studies have found that around 5% of older adults self-report abuse in the previous month, although lower rates of physical abuse are reported to protective services. All older adults with injuries should be asked if they feel safe at home and if there is anyone in their life who is threatening or injuring them.

Anatomy and Physiology

Older adults are more vulnerable to trauma owing to age-related changes in anatomy, physiology, and pathophysiology. Aging's main effects on human physiology are decreased functional reserve, seen across organ systems, due to reductions in the volume of viable tissue and intrinsic function of the tissues. Older adults are more likely to have comorbidities and to be taking multiple medications that affect their likelihood to get injured and their response to injury. The assessment of the geriatric trauma patient should be informed by these important differences.

Pathophysiology

Due to decreased functional reserve, older adults are less able to compensate for physiologic demands of hypovolemia and stress resulting from hemorrhage associated with trauma. Although older adults in a good state of health have sufficient reserves to accomplish activities of daily living, when they are stressed by acute trauma and the subsequent response to injury, the decrease in physiologic reserve can lead to a more rapid progression to tissue hypoperfusion and organ failure, a common cause of death in older trauma patients.

Comorbidities

Older adults are likely to have significant comorbidities at the time of injury. The percentage of older adults experiencing at least one of five chronic diseases—arthritis, stroke, chronic lower respiratory tract disease, coronary heart disease, and diabetes mellitus—varies from 15% to 47%, with only 33% of men and 25% of women having none of these comorbidities.

Effect of Medications

Medication use is common in older adults. A representative survey of community-dwelling US adults (aged 57–85 years) has found that 81% use at least one prescription medication, and 29% use five or more prescription medications. Approximately 5% of older adults are on warfarin, a growing number are on novel oral anticoagulants, and more than 30% are on an antiplatelet agent, increasing the likelihood and severity of hemorrhage. Medications increase the likelihood of older adults experiencing a traumatic accident (eg, sedative-hypnotics causing falls). Some, such as beta blockers, affect the physiologic response to trauma. Medications' effect on vital signs should be considered during the primary survey, and a full medication history should be taken early in the secondary survey.

CLINICAL FEATURES

Modifications to the Trauma Assessment of Older Adults

A systematic trauma assessment, including a primary and secondary survey and resuscitation, should be conducted in older adults (see Chapter 33). However, many signs and symptoms of injury in the younger adult, such as hypotension, tachycardia, and pain, will be mild or absent in many older adults. Normal vital signs should not be reassuring because significantly injured older adults often display delayed hemodynamic signs of injury, such as tachycardia or hypotension.[20]

Primary Assessment and Resuscitation

Airway

Establishing and maintaining a patent airway is the primary objective. Because older patients are likely to have multiple risk factors for a difficult airway, emergency clinicians should perform a systematic airway assessment, focusing on the ability to mask-ventilate, endotracheal intubation, and a cricothyrotomy. Early intubation is indicated for unstable patients, as defined by signs of shock, altered mental status, and significant chest trauma. Because direct laryngoscopy is more difficult in older adults because of limited cervical mobility and less mobility at the temporal mandibular joint, the use of videolaryngoscopy is recommended.[21] Cricothyrotomy is more likely to be complex in older adults because they are more likely to have had scarring from neck surgery, radiation, or neck tumors, which distort normal anatomy. Older patients are also more likely to be anticoagulated. Finally, rapid sequence intubation (RSI) medications should be tailored to the older adult (see Chapter 1).

Breathing

High-flow supplemental oxygen should be initially applied to all patients, including those with chronic pulmonary disease. The short-term benefits of avoiding hypoxia and increasing oxygen reserves are important because older adults have a reduced pulmonary reserve, which can cause systemic pulmonary injuries to overwhelm the ability to oxygenate and ventilate. The respiratory rate should be closely followed because older adults are more likely to tire and can rapidly decompensate as a result of pulmonary injuries or aggressive fluid resuscitation.

Circulation

Older patients are particularly vulnerable to shock because their blunted response to stress and limited physiologic reserve increase the risk of organ dysfunction. The assessment of circulatory status is complicated because responses to hypovolemia, such as tachycardia and hypotension, are reduced by physiologic changes and medications (eg, beta blockers). Vital signs are insensitive because normal blood pressure does not reliably exclude significant hemorrhage or shock. Systolic hypertension is common among older adults, so normotension may indicate significant hypovolemia. It is important to remember that the therapeutic window for cardiac preload is narrow, and inadequate monitoring of fluid status may lead to errors in volume resuscitation. Vitals signs should be frequently reassessed; in older trauma patients, trends are more important than specific cutoffs.

First, life-threatening bleeding should be identified and controlled. This includes external bleeding, such as hemorrhage from scalp injuries, which can be significant in older adults. The focused assessment with sonography in trauma (FAST) modality has emerged as an important adjunct to the primary survey but has not been specifically studied in older patients. A urinary catheter can be placed to monitor urine output, although this is a less sensitive predictor of renal blood flow than in younger patients. Invasive hemodynamic monitoring is appropriate for some severely injured older adults such as those with shock and poor ejection fraction, but routine use is not justified.

Fluid resuscitation should balance the risk of hypoperfusion with the unclear benefit of fluids and blood. We recommend beginning initial resuscitation with blood in the patient with significant bleeding, signs of hemodynamic instability, or significant injuries (eg, unstable pelvic fracture) because older adults do not tolerate large-volume resuscitation well and can easily become fluid-overloaded. In patients in whom there is no obvious source of blood loss, incremental boluses (eg, 500 mL) of warmed isotonic crystalloid should be used for resuscitation. The hemodynamic status should be reassessed frequently after small fluid boluses to avoid causing pulmonary edema and respiratory failure from fluid overload.

Prompt reversal of anticoagulation is important because a significant number of older patients are on warfarin, and others may have pathologic coagulopathy. Specific considerations for reversing coagulation abnormalities in older trauma patients are the volume of reversal agents required and the corresponding risk of fluid overload. Prothrombin complex concentrates (PCCs) require minimal volume compared with fresh-frozen plasma (FFP) but are more costly. We recommend early use of vitamin K and a PCC in older adults with major injuries who are on warfarin. In EDs that do not have rapid availability of PCCs, FFP should be given.

Disability

Evaluation of older adults for disability includes examination for traumatic brain injury (TBI), spinal cord injury (SCI), and vertebral fractures and injuries. The primary neurologic examination of older adults should focus on mental status, verbal responsiveness, pupil responsiveness, and gross motor examination. The Glasgow Coma Scale (GCS) is often used to detect mental status changes after TBI but was not designed for this purpose and lacks sensitivity for mild injuries. Any GCS score less than 15 is concerning for TBI, and a GCS score below 8 is highly predictive of a poor outcome. Subtle changes in mental status such as confusion or decreased alertness or symptoms such as headache may be the only signs of TBI. The mental status examination in older adults is complicated by comorbidities such as previous stroke and the increasing prevalence of cognitive impairment in older adults, including dementia and delirium. Delirium can be the cause of traumatic injury, such as falls, or can be the result of traumatic injuries. Abnormal pupillary responsiveness or motor function should raise concerns for significant intracranial hemorrhage (ICH), with associated increased intracranial pressure (ICP). Ultimately, no combination of historical features and physical findings has been shown to reliably predict the absence of intracranial injuries in the older trauma population. Brain computed tomography (CT) is indicated for older adults with head trauma, significant multisystem trauma, or symptoms or signs of TBI, because no clinical decision rule has been validated in older trauma patients.

Older adults are at higher risk of vertebral fractures, and cervical fractures in particular, and they are more likely to sustain SCI as a result of trauma. Clinical decision tools that are available for cervical spine imaging in trauma are not recommended for older adults. The Canadian C-Spine Rule (CCR) classifies all patients 65 years and older as inherently high risk, requiring radiography; the derivation study found that age older than 65 years had an odds ratio of 3.7 (95% confidence interval [CI], 2.4–5.6) for clinically significant cervical spine injury. The National Emergency X-Ray Utilization Study (NEXUS) included all ages but found that patients aged 65 years and older had a relative risk of 2.1 (CI, 1.8–2.6) for clinically significant cervical spine injury. Other studies have shown that only 45% of older patients with cervical spine fractures had cervical spine tenderness on examination; therefore, the absence of tenderness cannot be used to rule out cervical spine injury in older patients. Older adults are also at increased risk of thoracic, lumbar, and sacral vertebral fractures, for which CT is more sensitive than the physical examination or plain radiography.

Exposure

Older trauma patients are more likely to develop hypothermia because of physiologic changes and mechanisms of injury. Because the skin thins with aging, and muscle and fat mass decrease, normal thermoregulatory mechanisms are no longer intact. Prolonged immobilization with exposure to the elements is common when older adults fall and are unable to get back up, leading to hypothermia, dehydration, and renal insufficiency. A rectal temperature should be routinely taken, and hypothermia should be rapidly treated. Because skin breakdown and relatively minor wounds can cause serious complications in older patients, older adults should be removed from backboards as soon as possible and examined for pressure ulcers. Older patients are more likely to require a tetanus booster, and older trauma patients should receive tetanus immunization if it is not up to date.

Secondary Assessment

The stable geriatric trauma patient requires a thorough secondary assessment. A complete history should be obtained from the patient or a care provider, with particular emphasis on corroborating the accident history, past medical history, medications and

allergies, and social history, including baseline functional status and living arrangements. Patients should be screened for alcohol and substance abuse and elder abuse.[22]

Laboratory Testing

We recommend the following routine laboratory tests: complete blood count, comprehensive metabolic profile, coagulation studies (international normalized ratio [INR]), lactic acid level, base deficit, urinalysis, cardiac enzyme levels, and toxicology. An elevated lactic acid level and base deficit, which can signal tissue hypoxia and organ dysfunction, are predictive of mortality and can help determine the prognosis in older adults with normal vital signs. Electrocardiography and cardiac monitoring are advised because many older patients have cardiac causes or complications of their traumatic event.

Imaging

Older trauma patients deemed unstable should undergo portable plain radiography of the chest and pelvis. CT is the imaging modality of choice for stable older trauma patients; plain radiography is less sensitive. Older adults have less additional lifetime risk from the radiation associated with CT scans than younger adults owing to their lower life expectancy, but they are at greater risk from contrast-introduced nephropathy. When possible, intravenous (IV) contrast should be avoided, and renal protective strategies should be used, including IV fluids, bicarbonate, and *N*-acetylcysteine.

SPECIFIC DISORDERS

Traumatic Brain Injury

TBI is common in older adults, can occur with minimal head trauma, and can be asymptomatic. Overall mortality rates among older patients with TBI range from 30% to 80%, and increasing age is an independent predictor of disability and mortality in patients with TBI. Physiologic changes of aging and the frequent use of anticoagulant and antiplatelet medications increase the likelihood and severity of TBI in older adults. With aging, the size of the brain decreases by 10% on average, resulting in less tortuous bridging veins and increased intracranial free space. The atrophied brain is more mobile within the skull, and trauma is more likely to shear bridging veins, leading to ICH.

Differential Diagnosis

If there is concern for intracranial injury, cranial CT is indicated, regardless of reported loss of consciousness. Diagnosis of TBI is more difficult in older adults because cognitive impairment is more common and increased intracranial free space can allow the accumulation of blood without changes in mental status. Clinical variables alone are insufficient to identify all cases of significant intracranial injury reliably following trauma in older patients; both the New Orleans Criteria (exclude age >60 years) and Canadian Head CT Rule (excludes age ≥65 years) exclude older adults.

Management

Treatment of TBI includes supportive care, rapid reversal of anticoagulation, and evaluation for decompressive surgical intervention. Supportive care aims to avoid cerebral hypoxia and hypoperfusion, which are significant predictors of adverse outcomes. All patients should initially receive high-flow oxygen to maintain high oxygen saturation. Patients with hypercarbic respiratory conditions (eg, chronic obstructive pulmonary disease) require an individualized determination of the appropriate oxygen saturation. Preventing cerebral hypoperfusion requires close monitoring of hemodynamic parameters, including blood pressure and urine output; individual patients may benefit from invasive hemodynamic monitoring. Early neurosurgical consultation is indicated to assess the need for and usefulness of surgical ICP monitoring and decompression. Current guidelines for ICP management have not been studied in older adults with TBI.

Prompt reversal of anticoagulation with a PCC, or FFP if PCC is unavailable, is indicated for older adults taking warfarin. The evidence supporting PCCs has shown that immediate administration of PCC is associated with more rapid reversal and less hematoma growth than vitamin K and FFP, including one study of years trauma patients.[23] To date, however, there have been no prospective randomized studies demonstrating better outcomes.[24] Treatment or reversal of antiplatelet agents and other anticoagulants, including low-molecular-weight heparins and novel oral anticoagulants, is based on expert opinion rather than clinical trial data. Thus, EDs should determine local practice in coordination with their trauma and neurosurgery consultants.

Disposition

TBI in older adults is associated with significant morbidity and mortality, but ED prognosis is not precise. Negative prognostic factors include increasing age, anticoagulation,[17] use of antiplatelet medications, greater severity of TBI, and lower GCS score.[25] Although many patients with severe injuries, significant comorbidities, or anticoagulation have no chance of a meaningful outcome, others can return to living in the community.[26] Patients with moderate or severe TBI, or any TBI and anticoagulation, require neurosurgical consultation and intensive care in which frequent neurologic checks and rapid reversal of anticoagulation can be accomplished. This is problematic for emergency clinicians at hospitals without neurosurgical coverage because it requires transferring patients with a grave prognosis, potentially for long distances. When an older adult with TBI is being transferred, reversal of anticoagulation and prevention of hypoxia and hypotension are important early management steps. Older patients with isolated head trauma, normal cranial CT, and normal INR are generally safe for discharge if they have a safe environment, responsible care provider, and reliable follow-up.[27]

Vertebral Fractures and Spinal Cord Injuries

Age-related changes to the vertebral bones, intervertebral disks, and spinal canal place older adults at greater risk of vertebral fractures, result in a greater likelihood of SCI, and make physical examination and diagnostic imaging results less accurate. Based on radiologic studies, approximately 25% of patients older than 65 years have cervical stenosis, and 90% of men older than 50 years and 90% of women older than 60 years have evidence of degenerative changes in the cervical spine. These changes have the effect of creating leverage on the spinal column when an external force is applied, such as in a fall with an impact to the head, concentrating force on weakened bone and increasing the risk of fracture and SCI.

Differential Diagnosis

Spinal canal stenosis and the resulting spinal cord compression are clinically manifested as a myelopathy, with impairment of coordination, gait, bowel or bladder function, and motor or sensory function, or both. Geriatric patients with vertebral injuries and SCIs are more likely to sustain incomplete neurologic

injuries of lesser severity than younger patients, largely because they have lower force injuries.

In cases of suspected vertebral fracture or SCI, continued immobilization, spine surgery consultation, and admission are indicated. Older adults are at higher risk for SCI without obvious radiographic abnormality owing to spinal cord stenosis and cervical kyphosis. Evaluation for ligamentous injury and SCI with magnetic resonance imaging (MRI) is appropriate in patients with focal neurologic deficits. Most geriatric vertebral fractures and SCIs are represented by three types of injuries: (1) central cord syndrome; (2) cervical extension-distraction injuries; and (3) odontoid fractures.

Central Cord Syndrome. Central cord syndrome (CCS) is characterized by weakness disproportionately greater in the arms than in the legs after a hyperextension injury. Most cases of CCS in older adults are the result of hyperextension injuries in patients with canal stenosis and no bony fracture. In CCS, injury may result from anterior compression of the cord by osteophytes or pinching of the cord posteriorly by the ligamentum flavum, resulting in bleeding into the central part of the cord or with axonal disruption in the lateral columns of the spinal cord. Injuries associated with CCS syndrome are typically stable and require immobilization with a hard collar. Surgical decompression may be indicated. Patients with symptoms concerning for CCS and without fracture should undergo MRI.

Cervical Extension-Distraction Injury. Cervical extension-distraction injury occurs in the patient with reduced cervical range of motion. A hyperextension injury of the cervical spine and external signs of trauma to the forehead or face in an older adult should raise suspicion for an extension-distraction injury. The patient may report that she or he is able to touch the pillow on the bed with the back of the head, which she or he was unable to do before the injury. This is a result of the fracture, which opens and lengthens the anterior column of the spine, resulting in the term *open book fracture*. Clinical symptoms can range from nerve root compression to severe SCI. These fractures are typically unstable and require surgical fixation.

Odontoid Fractures. Fracture of the C2 vertebral body, specifically the odontoid process, is usually the result of a fall with impact to the head, resulting in anterior or posterior displacement of the odontoid process. Although most odontoid process fractures are displaced, less than 10% cause neurologic deficits. Type II odontoid fractures, at the base of the dens at its attachment to the body of C2, are the most common C-spine fracture in older trauma patients. There is no agreement on the best approach to manage type II odontoid fractures[28]; types I and III fractures are typically managed nonoperatively with neck immobilization.

Thoracic Trauma

Older adults are at increased risk of rib and sternal fractures, pulmonary contusions, and their complications with low-force injuries. More than 50% of older patients admitted to hospital with rib fractures sustained them during a fall, and a significant number occurred during low- or moderate-speed MVAs.

Differential Diagnosis

The risk of pneumonia and complications increases with the number of ribs fractured.[29] Pulmonary contusions are more frequent with minimal trauma, even without accompanying rib fractures, and can cause significant morbidity and mortality in older adults.

Diagnostic Testing

Chest CT is recommended for older patients with significant chest trauma, multiple rib fractures by plain film, or respiratory complications from trauma.

Management

Patients with significant chest trauma require airway monitoring, with consideration of early intubation to anticipate their clinical course, pulmonary therapy, and pain control. Pain control is of particular importance because rib fractures will lead to splinting and atelectasis and increase the risk of pneumonia.[30] Analgesia can be administered with epidural analgesia, paravertebral analgesia, or opioids orally or with patient-controlled analgesia.

Disposition

Geriatric trauma patients with severe pain from rib fractures should be hospitalized to manage pain adequately and safely. Those with flail segments, multiple rib fractures, or pulmonary contusions may require intensive care unit admission.

Abdominal Trauma

Older adults are more likely to sustain intra-abdominal injuries and have higher mortality from such injuries. The general management principles are similar to those in younger adults, although there is less clinical evidence supporting nonoperative management (NOM) and angiographic embolization of solid organ injuries.

Differential Diagnosis

The focus of the emergency clinician is on the early diagnosis of intra-abdominal injuries, vigilant hemodynamic monitoring, and early resuscitation. Clinical manifestations of serious abdominal injury in older patients are often minimal. Reliance on the abdominal examination may lead to missed abdominal injuries, and the emergency clinician should use a low threshold of suspicion to carry out imaging.

Diagnostic Testing

The FAST examination should be part of the initial evaluation and can be repeated as part of ongoing hemodynamic monitoring, although it is insensitive for solid organ injuries. Older patients with abdominal tenderness, significant multisystem trauma, or hemodynamic instability should undergo CT scanning. Angiography is a reasonable option for the older trauma patient with solid organ injury and a blush or extravasation on CT.

Management

Although advanced age was initially an exclusion from NOM of solid organ injuries, there is more than a decade of evidence showing that carefully selected older adults are candidates for NOM. In several case series, approximately 80% of older adults with splenic injuries were successfully managed nonoperatively, with the caveat that grade III injuries were more likely to fail NOM, and all geriatric patients with grade IV or V injuries required an operation. There are limited data on NOM of liver injuries in older adults.

Extremity Injuries

Fractures are the most common injuries in older adults with trauma due to osteopenia. Fractures that affect mobility and the

ability to live independently, such as hip fractures, are associated with significant perioperative and 1-year mortality in older adults.

Differential Diagnosis

The most common fractures sustained by older adults, in order of frequency, are distal radius fractures (Colles' fractures), proximal humerus fractures, and elbow fractures, which usually occur during a fall onto an outstretched arm. Older adults with proximal humoral fractures can have remarkably few symptoms.

The most common lower extremity fractures in older adults are ankle fractures, hip and pelvic fractures, and tibial plateau fractures. Pelvic fractures can occur with relatively little force in older adults and fracture patterns are similar between older adults and younger adults, with lateral compression fractures more common than anteroposterior fractures. In older adults, both fracture types are associated with significant hemorrhage. Overall pelvic fracture mortality is 9% to 30% and up to 81% in older patients with open pelvic fractures. Emergent treatment of pelvic fractures consists of hemodynamic monitoring, resuscitation with blood, stabilization of the fracture with wrapping or external fixation, and control of bleeding, with consideration of embolization to treat retroperitoneal hemorrhage.[31] Hip fractures are common in older adults, occurring annually in approximately 1% of men and 2% of women. Whereas isolated hip fractures are not associated with significant immediate hemorrhage or mortality, such as seen in pelvic fractures, they are associated with an 8% to 30% 1-year mortality.

Diagnostic Testing

Hip fractures are usually seen on plain x-ray films (sensitivity ≅ 90%) and CT scans, but occult fractures are a well-described phenomenon in older adults. Patients with the inability to ambulate or who have persistent pain after trauma require further evaluation; MRI and bone scanning are useful imaging studies to delineate the pathology. Ultrasound-guided femoral nerve block or fascia iliaca compartment block can improve analgesia and reduce the use of opioids in the ED.[32]

Management

Older adults with fractures have better outcomes with early surgery (<72 hours) and care in a distinct orthogeriatric service.[33,34] Emergency clinicians should consider transferring older adults with hip fractures to hospitals with such services.

DISPOSITION: END-OF-LIFE CONSIDERATIONS

Emergency clinicians are faced with difficult decisions regarding prognosis, the effectiveness of aggressive care, and end-of-life decisions in geriatric trauma. Older trauma patients have a uniformly worse prognosis than younger adults. Several factors that portend a grave prognosis from the ED include a GCS score of 3, a GCS score below 8 with anticoagulation, and hemodynamic instability from internal hemorrhage with anticoagulation. However, initial injury in the ED does not predict an individual patient's long-term prognosis perfectly, and emergency clinicians have not traditionally withheld trauma care, including transfer to a trauma center and involvement of trauma surgeons. Emergency clinicians should discuss end-of-life decisions, such as intubation, cardiopulmonary resuscitation, transfer, and surgery, with patients, family members, caregivers, and surgical consultants. Although age alone is not an indication to withhold aggressive treatment, comfort measures may be more appropriate than transferring patients to a trauma center in select cases with a grave prognosis and when the patient's goals of care are known.

KEY CONCEPTS

- We recommend that advanced age (≥70 years) be used as triage criteria for transfer to a trauma center and activation of a trauma team.
- Emergency clinicians should consider shock in all older trauma patients. Because vital signs, including tachycardia and hypotension, are unreliable to detect hemodynamic instability in older adults, emergency clinicians should closely follow alterations in mental status, urine output, and skin perfusion.
- Older adults are at significant risk from shock, yet they are also at risk from aggressive resuscitation. Resuscitation should be rapid but should also include frequent reassessments of vital signs, respiratory status, and other potential indicators of shock. Start resuscitation with blood in the patient with significant bleeding, signs of hemodynamic instability, or significant injuries (eg, unstable pelvic fracture).
- Older patients are at high risk of hypothermia and develop pressure ulcers more rapidly. They should be removed from backboards as soon as possible, and rectal temperature should be routinely checked in the secondary survey.
- Clinical decision tools for radiographic imaging have generally excluded older patients. A low threshold for imaging should be used for older adults with trauma, and CT should be used as the primary modality, except for extremity imaging.
- Falls are the leading cause of injury-related death in older adults , and ground-level falls can result in major injuries. Although there is debate about the effectiveness of interventions for secondary prevention of falls, we advise that emergency clinicians assess gait and notify the primary care physician, and we recommend close follow-up at a minimum. Engaging social services, including arranging a home safety visit, may be beneficial.
- Among patients with TBI or hemorrhagic injuries, anticoagulation predicts poor outcome. Rapidly reverse warfarin with a PCC or FFP if a PCC is unavailable.
- Rib fractures and pulmonary contusions are associated with poor outcomes in older patients. Patients with flail chest, two or more rib fractures, or pulmonary contusions should be hospitalized for monitoring, pulmonary care, and analgesia.
- Older adults with hip fractures have improved survival on a dedicated orthogeriatric service. Consider transfer of patients to hospitals with this service available.
- Routinely screen for elder abuse. A valid screening question is: "Has anyone close to you tried to hurt you or harm you recently?"

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 184: QUESTIONS & ANSWERS

184.1. A 76-year-old man is brought to the emergency department (ED) after a fall at home. The paramedics tell you that he slipped in the shower and struck his head on a tile floor. The patient is awake and alert. He is unsure if he lost consciousness and complains of headache. When you obtain a computed tomography (CT) scan of his head, it reveals evidence of a cerebral contusion. The paramedic tells you that he has a history of severe congestive heart failure (CHF) and takes warfarin and furosemide daily. When he returns from CT, he seems slightly confused. Laboratory tests are pending. What is the best initial treatment?

A. Administer a prothrombin complex concentrate (PCC).
B. Administer desmopressin (DDAVP) intravenously (IV).
C. Administer protamine sulfate IV.
D. Transfuse 2 units fresh frozen plasma.
E. Transfuse one bag of platelets.

Answer: A. Prompt reversal of anticoagulation is important because approximately 5% of older adults is on warfarin, and others have pathologic coagulopathy. Specific considerations for reversing coagulation abnormalities in older trauma patients are the volume of reversal agents required and corresponding risk of fluid overload. PCCs require minimal volume compared with fresh-frozen plasma (FFP) but are costly. To reverse anticoagulation fully, 1 to 2 L of FFP may be required, presenting a limitation to rapid reversal in older patients at risk of fluid overload. Platelets, protamine, and DDAVP will not reverse the elevated international normalized ratio caused by warfarin.

184.2. Which of the following is the most common cervical spine fracture in geriatric trauma patients?

A. Anterior wedge fracture
B. Compression fracture
C. Jefferson fracture
D. Spinous process fracture
E. Type 2 odontoid fracture

Answer: E. Because of the relative immobility of the cervical spine related to degenerative joint disease, the most common level of cervical spine injury in older adults is C1 to C3, a higher level than in younger patients. Among these upper cervical spine fractures, the most common is a type 2 odontoid fracture.

184.3. An 80-year-old woman presents after a motor vehicle accident (MVA). Her vital signs on arrival are as follows: heart rate of 112 beats/min, blood pressure of 88/65 mm Hg, respiratory rate of 18 breaths/min, and oxygen saturation measured by pulse oximetry (Spo_2) of 98%. The paramedic tells you that she has a history of CHF and takes furosemide daily. The primary survey does not reveal an obvious source of bleeding. Which of the following treatments is most appropriate to address the patient's tachycardia and hypotension while searching for its cause?

A. Give a bolus of 500 mL warmed normal saline.
B. Give 2 units of non–crossmatched type O blood.
C. Run an infusion of warm normal saline wide open.
D. Start dopamine at a low dose.
E. Type and match and wait for type-specific blood.

Answer: A. The most prudent approach in the hypotensive older trauma patient is controlled boluses of warmed isotonic fluids, with frequent assessment of physical examination, vital signs, pulse oximetry, and urine output. Resuscitation with crystalloid may correct the patient's hypotension, obviating the need for transfusion. The patient's hypotension must be addressed immediately, and treatment should not be delayed for type-specific blood. Given her history of CHF, a wide open infusion of normal saline without an endpoint should not be administered. Vasopressors such as dopamine should not be given to any trauma patient, except in extreme circumstances. If the patient had an obvious source of hemorrhage, use of non–crossmatched type O blood would be appropriate as a first step, and starting with 1 unit would be appropriate.

184.4. A 76-year-old man presents after slipping and falling down several stairs at home. The patient is awake and alert and unsure if he lost consciousness after the fall. He complains of chest pain and has left chest wall tenderness and crepitance on examination. When you obtain a CT scan of his chest, it reveals four contiguous lateral rib fractures. The patient's pain is only moderately relieved by 0.15 mg/kg of morphine sulfate IV. What is the most appropriate disposition for this patient?

A. Admission for pain control with IV opioids
B. Admission with anesthesia consultation for pain management
C. Continued observation in the ED for 6 additional hours of IV opioid management, followed by reassessment
D. Discharge home with oral opioids

Answer: B. Geriatric trauma patients with severe pain from rib fractures often require hospitalization to allow adequate and safe pain management, and those with flail segments or larger numbers of rib fractures may require intensive care unit admission. Pain control is of particular importance because rib fractures will lead to splinting and atelectasis and increase the risk of pneumonia. Analgesia can be administered with IV opioids via patient-controlled analgesia or an epidural analgesic. An anesthesia consultation is appropriate for the older rib fracture patient without pain relief from parenteral opioids.

CHAPTER 185

Drug Therapy in the Geriatric Patient

Asad E. Patanwala | Arthur B. Sanders

PRINCIPLES

There are approximately 20 million annual visits to US emergency departments (EDs) by older adults.[1] This is expected to increase disproportionately compared to the general population based on estimates from the US census.[2] Results of a survey of emergency clinicians indicated a lack of confidence in managing older ED patients and a desire for additional training. Drug therapy issues are particularly challenging in older adults because of altered pharmacokinetics and pharmacodynamics compared to younger adults. In addition, they take more medications, have more comorbidities, and are at increased risk for adverse drug effects because of the physiologic changes with aging than younger adults. As a result, medication selection and dosing need to be age-adapted for optimal patient outcomes. Also, compared to younger adults, there is less high-quality evidence for many drug therapy interventions in older adults. In those who are 80 years of age or older, there is even less evidence, making extrapolation from studies and evaluating risks versus benefits for pharmacologic options more difficult.

Most developed countries have adopted the chronologic age of 65 years to define the geriatric or older population.[3] The United Nations does not have a standard definition, but generally uses the age of 60 years or older to refer to older persons.[3] This categorization may be overly simplistic, and stratification, such as young old (60–69 years), middle old (70–79 years), and very old (≥80 years), is more suitable and medically useful. From a drug therapy perspective, physiologic age is more indicative of the therapeutic or toxicologic effect. However, there are no physiologic markers that define the aging process or that can be routinely used in clinical practice.[4] Most studies evaluating medication use in older adults have used a cutoff value of 65 years, and this serves as basis for recommendations from the American Geriatrics Society.[5] Thus, in this chapter, we refer to older adults as those with a chronologic age of 65 years or older. However, from an emergency clinician's perspective, this is an arbitrary value for making drug therapy decisions. In addition to chronologic age alone, an overall assessment that incorporates organ function, comorbidity, functional status, and lifestyle is a better determinant of drug therapy selection and dosing. This should also be considered when interpreting recommendations for older adults, such as what is considered to be an inappropriate medication. This chapter reviews aspects of pharmacology for older adults and the clinical implications in emergency medicine.

Pharmacokinetics

The time course of drug exposure is a function of absorption, distribution, metabolism, and elimination. The drug effect is primarily determined by this exposure, which can be quantified by serum concentrations over time. It is assumed that increased exposure is also more likely to result in toxic medication effects. Thus, an understanding of pharmacokinetic changes in older adults is useful for determining risks of adverse drug reactions and helps guide medication selection and dosing.

The effect of changes in the absorption of drugs is important for orally ingested medications and can be affected by changes in gastric pH, gastric emptying, splanchnic blood flow, bowel motility, and absorptive capacity. For example, the increase in gastric pH associated with older adults can decrease the dissolution and absorption of medications that are weak bases. However, age-related changes in the gastrointestinal system can have a varied effect on drug absorption, leading to an increase or decrease in drug concentrations. As an example, decreased absorptive capacity coupled with decreased bowel motility can increase transit time, leading to a net neutral effect on drug exposure. Gastrointestinal and other comorbidities can have a greater effect on absorption than age alone. Given these considerations, it would be prudent in the ED to use the intravenous route for acute conditions, when rapid drug absorption is needed to achieve a therapeutic concentration.

Age-related changes in body composition have an effect on the distribution of drugs. There is an increase in total body fat and a decrease in relative skeletal muscle mass in older adults compared to young adults. This change in body composition accelerates between 60 to 75 years and then may start to decline. Lipophilic medications have a greater volume of distribution with increasing adiposity, whereas the opposite is true for hydrophilic medications. Opioid analgesics such as fentanyl and most sedatives (eg, benzodiazepines, propofol) are very lipophilic, so there is distribution and accumulation of the drug within adipose tissue. With prolonged use, this can lead to an increased duration of effect due to redistribution of drug from tissue to serum and central nervous system. Conversely, hydrophilic medications such as digoxin would require lower loading doses in older adults to achieve similar serum concentrations due to a smaller volume of distribution. This has the potential for drug toxicity if not dosed appropriately for age.

Most drugs require biotransformation into polar metabolites before final elimination. This primarily occurs in the liver via phase 2 metabolism by cytochrome P450 enzymes (oxidation) or phase 2 (conjugation, acetylation, sulfation) reactions. With advanced age, hepatic blood flow and mass may decrease by up to 40%, which reduces the delivery of medications to the liver and their subsequent metabolism. This decrease in first-pass metabolism improves drug bioavailability and efficacy and increases potential toxicity. Drugs with a high extraction ratio are more dependent on liver blood flow, and the decrease in liver metabolism with age has mainly been related to changes in phase 1 pathways. For example, morphine is a high–extraction ratio drug and would lead to greater drug exposure with decreased liver blood flow. Commonly used benzodiazepines in the ED also vary in their metabolic pathways. Midazolam undergoes phase 1 metabolism, and hepatic impairment would lead to drug accumulation, especially with repeated or prolonged use. Conversely, lorazepam undergoes conjugation and is preferred in patients

BOX 185.1

Equations to Estimate Glomerular Filtration Rate (GFR, in mL/min)

COCKROFT-GAULT EQUATION

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine}} \times (0.85 \text{ if female})$$

Use ideal body weight (IBW). If patient is obese, use adjusted body weight.

$$\text{IBW (male)} = 50 + [2.3 \times (\text{height in inches} - 60)]$$

$$\text{IBW (female)} = 45.5 + [2.3 \times (\text{height in inches} - 60)]$$

$$\text{Adjusted body weight} = \text{IBW} + [0.3 \times (\text{actual weight} - \text{IBW})]$$

MODIFICATION OF DIET AND RENAL DISEASE EQUATION

$$\text{GFR} = 175 \times \text{serum creatinine}^{-154} \times \text{age}^{-0.203}$$
$$(\times 1.212 \text{ if patient is black}; \times 0.742 \text{ if patient is female})$$

TABLE 185.1

Pharmacokinetic Changes in Older Adults

PARAMETER	CHANGE	COMMENTS
ABSORPTION		
Gastric pH	↑	Net absorption may be increased or decreased.
Gastric emptying	↓	Peak effect will likely be delayed.
Splanchnic blood flow	↓	The intravenous route is preferred in the ED for rapid and predictable effect
Bowel motility	↓	
Absorptive capacity		
DISTRIBUTION		
Adipose tissue	↑	Lipophilic medications will accumulate with repeated dosing, which increases duration of effect.
Total body water	↓	Hydrophilic medications will have a lower volume of distribution, requiring lower loading doses.
METABOLISM		
Phase 1 metabolism	↓	Medications with phase 1 metabolism are more likely to accumulate than those metabolized via phase 2 pathways.
Phase 2 metabolism	↔	
Liver blood flow	↓	
ELIMINATION		
Glomerular filtration rate	↓	This is the most important consideration for drug dosing. Calculate creatinine clearance using the equations in Box 185.1 and adjust dosing. First doses of antibiotics and most one-time doses do not require adjustment.

with hepatic impairment. The effect of aging on phase 1 metabolism via CYP3A4 is controversial. This enzyme represents the metabolic pathway for most medications, and studies have shown no significant differences between younger and older populations.

Renal blood blow, renal mass, and the number of nephrons decrease with age, leading to a decrease in renal function. In a longitudinal study, renal function decreased by approximately 10% for each decade between 30 and 80 years of age. This decrease was independent of comorbid conditions, and was attributed to aging alone. Although this decline is likely to occur in most patients, up to one-third may have no decline, and some may have an increase in renal function. Kidney function is expressed as the glomerular filtration rate (GFR) and is routinely estimated by the Cockcroft-Gault equation. However, this equation may not accurately estimate the GFR, so the modification of diet and renal disease (MDRD) equation has been suggested as a more accurate estimation.[6] Common equations used to calculate creatinine clearance and estimate GFR are in Box 185.1. Discordance in drug doses selected may occur 10% to 40% of the time when comparing the two equations, and there has been considerable debate regarding the most appropriate equation to use in practice.[7,8]

Historically, drug dosing in manufacturer's labeling per the US Food and Drug Administration is based on creatinine clearance determined by the Cockroft-Gault equation; most pharmacists continue to use this equation for drug dosing because of ease of calculation compared to the MDRD. One approach is to calculate estimated GFR based on both equations and evaluate if there is a discrepancy in dosing recommendations. A lower or higher dosing strategy can be based on the individual clinical situation. In general, a low-dose approach should be used for medications with a narrow therapeutic index, particularly when the risk of toxicity is high and serum concentration monitoring is not available. In general, medication dosing should be higher in the ED when the implications for therapeutic failure warrant such an approach, and the medication has a broader safety margin. An example would be the use of antibiotics for a patient with sepsis or febrile neutropenia. Thus, clinical circumstances may override drug dosing recommendations, especially when there is discordance between equations, and professional judgment is always required. These equations use the serum creatinine level to estimate creatinine clearance, which is affected by muscle mass. Therefore, although serum creatinine values may be normal, they may not accurately estimate renal function in some older adults, especially those with less musculature. For all older patients, some providers routinely round serum creatinine values less than 1 mg/dL up to 1 mg/dL to account for reduced muscle mass. However, this should be avoided in calculations because it has been shown to underestimate clearance.[8]

In the ED, most medications are dosed just once or may be repeated a few times, and the possibility of drug accumulation, even with hepatic or renal impairment, is unlikely to be clinically meaningful. If, however, several doses of a medication are administered in the ED, especially when patients are boarded, drug toxicity or prolonged effects may be clinically important. In general, a start low and go slow approach is prudent in older patients. The risks versus benefits of drug therapies generally increase with age, suggesting that a lower dose approach is warranted. Pharmacokinetic changes in older adults are listed in Table 185.1.

Pharmacodynamics

At similar plasma concentrations, drugs may have altered effects in older adults, perhaps because of changes in the number and sensitivity of receptors, signal transduction, and reduction in homeostatic processes that help maintain equilibrium. Thus,

physiologic mechanisms that help restore function are attenuated, leading to an exaggerated or relatively unopposed pharmacologic effect. Pharmacodynamic changes in older adults that are most relevant to consider in the ED include those that pertain to the cardiovascular, central nervous, and coagulation systems. For example, there is a decreased response to both β-adrenergic receptor agonists and antagonists. Conversely, there is no age-related change in α_1-adrenergic receptor sensitivity. Calcium channel blockers cause a greater drop in blood pressure and heart rate in older adults compared to younger adults, so the risk for postural hypotension is higher in older adults. The diminished inotropic response to catecholamines contributes to this risk. In the ED, non–dihydropyridine calcium channel antagonists such as diltiazem or verapamil are commonly used for patients with supraventricular tachycardias. Lower doses are appropriate in older adults, especially when the patient has tenuous blood pressure.

There is increased sensitivity to benzodiazepines in older adults, and lower doses are needed to obtain similar sedative-hypnotic effects. This is because of changes in the structure, composition, and function of the γ-aminobutyric acid (GABA) receptor complex. Similarly, in one investigation, older patients required less propofol for the induction and maintenance of sedation during procedures in the ED.[9] The dose required for induction was 0.5 mg/kg less than in the cohort of young adults. In older adults, it is more suitable to start with a 0.5-mg/kg rather than the 1-mg/kg bolus that is recommended initially. Some studies have shown that older patients have increased sensitivity to opioids. Pharmacodynamic effects in these studies were measured in terms of electroencephalographic readings, which do not reliably indicate the presence of pain. However, the risk of adverse effects and interactions due to the use of concurrent medications is likely increased in older adults, suggesting that a cautious approach is appropriate when dosing opioids. There is an age-related decrease in dopamine content in the central nervous system, which predisposes patients who are given neuroleptics and other dopamine antagonists to extrapyramidal symptoms. Similarly, there is a decrease in acetylcholine synthesis in older adults, which increases the risk for anticholinergic neurotoxicity with commonly used antihistamines, antispasmodics, and antiparkinson agents.

Bleeding is a potentially life-threatening consequence of anticoagulants. Warfarin is the most commonly used oral anticoagulant, although, more recently, newer oral agents such as direct thrombin and factor Xa inhibitors have become available. At similar warfarin plasma concentrations, there is greater vitamin K inhibition in older adults. Thus, it is recommended that warfarin should be initiated at a daily dose of 5 mg or less for older adults, when indicated. In the ED, this may occur for patients discharged after a venous thromboembolism in conjunction with low-molecular-weight heparin as bridge therapy. Newer oral anticoagulants do not have pharmacodynamic considerations in older adults. However, dosing adjustments are needed based on renal function because they undergo renal elimination. The other primary anticoagulant used in the ED is intravenous heparin for acute coronary syndrome or venous thromboembolism. Patient age does not correlate with heparin dose requirements, so no heparin dose adjustments are required based on patient age.

SPECIFIC DISORDERS

Polypharmacy and Drug Interactions

The term *polypharmacy* is used to describe the use of multiple medications. There is no standard definition or consensus regarding the number of medications that serves as a cut point for this term. Many studies have considered five or more medications as defining polypharmacy.[10] Older patients are particularly prone to polypharmacy because they have a greater number of comorbidities and conditions requiring treatment for medications.[11] In one national estimate of community-residing older adults, close to one-third of the population took five or more medications, and approximately half also took over-the-counter medications and dietary supplements. Polypharmacy may result in adverse drug effects, drug interactions, and functional and cognitive impairment and lead to falls, resulting in injury.[10,12] Approximately 10% of ED visits by older adults may be due to an adverse drug-related event.

An important consequence of polypharmacy is drug interactions, which occur more commonly in older adults. A drug interaction occurs when there is an alteration in the effect of a drug (object) due to the coadministration of another (precipitant). The alteration could be the increase in effect, leading to toxicity, or a decrease in effect, resulting in therapeutic failure. The mechanism of interaction could be pharmacokinetic, which is primarily due to the inhibition or induction of drug-metabolizing enzymes such as the cytochrome P450 system or alterations in drug transporter activity. Alternatively, the interaction could be pharmacodynamic, in which the change in effect is unrelated to pharmacokinetic mechanisms. This primarily occurs due to the pharmacologic effects of drugs, which may be additive or antagonistic. For example, the use of a benzodiazepine with an antibiotic that inhibits its metabolism would be a pharmacokinetic interaction, whereas the use of a benzodiazepine with an opioid, leading to additive central nervous system depression, would be a pharmacodynamic interaction.

There are thousands of possible drug-drug interactions, which increase exponentially with the number of medications that a patient is taking. Clinical decision support systems integrated with electronic medical records may provide a useful mechanism to reduce this risk. However, there are several challenges that need to be overcome in the ED setting so that providers than make the best possible decisions. The identification of an interaction is dependent on an accurate medication history, which is often difficult to obtain from older adults. Clinical decision support systems identify many drug interactions that are not clinically meaningful, leading to alert fatigue. It is estimated that providers override more than 80% of alerts, even when the interactions are significant.[13] Furthermore, most interactions are based on preclinical studies during drug development, have a theoretical basis, and often lack high-level evidence. This leads to discrepancies in major drug information systems, and there is no standard classification to guide decisions.

A prudent approach is to focus on the most common drug interactions that have been known to result in patient harm and that may be most applicable to the emergency clinician. Single doses of drugs administered within the monitored setting of the ED are less likely to lead to harm than those prescribed on discharge and used for several days. Adverse events can be narrowed down to several interactions that resulted in hospitalization from hyperkalemia, hypotension, fractures, hypoglycemia, bleeding, and specific drug toxicities.[14] The object drugs involved in these interactions should serve as important flags to alert prescribers when giving a new medication (Table 185.2). Most of these adverse events are seen to occur when new antibiotics are prescribed. Thus, antibiotics prescribed to patients need to be considered carefully for potential interactions, especially when patients are taking a medication such as one mentioned earlier. However, there are many other high-risk medications, such as antidepressants, neuroleptics, and antiepileptics, that are also known to have several drug-drug interactions. Ideally, consultation with a pharmacist is helpful in identifying and determining the risk of potential drug interactions and selecting appropriate alternatives, if necessary.

TABLE 185.2

Harmful Drug Interactions From Studies in Older Patients

OBJECT DRUG	ADVERSE EVENT	COMMENTS
ACE inhibitor or ARB	Hyperkalemia	Avoid potassium sparing diuretics or TMP-SMX
Benzodiazepines and sedative-hypnotics	Fractures, falls	Interacts with macrolides and has additive effect with other CNS depressants
Calcium channel blockers	Hypotension	Interacts with macrolides
Digoxin	Toxicity	Interacts with macrolides
Lithium	Toxicity	Interacts with diuretics, ACE inhibitors and NSAIDs
Phenytoin	Toxicity	Interacts with TMP-SMX
Sulfonylureas	Hypoglycemia	Interacts with TMP-SMX, fluconazole, macrolides and fluoroquinolones
Theophylline	Toxicity	Interacts with ciprofloxacin
Warfarin	Bleeding	Interacts with most antibiotics and antifungal agents. Increased risk with NSAIDs

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *CNS*, central nervous system; *NSAID*, nonsteroidal antiinflammatory drug; *TMP-SMX*, trimethoprim-sulfamethoxazole.

TABLE 185.3

Most Common Beers List Medications Prescribed to Patients Discharged From the Emergency Department

RANK	INAPPROPRIATE MEDICATION[a]
1	Promethazine
2	Diphenhydramine
3	Diazepam
4	Hydroxyzine
5	Amitriptyline
6	Cyclobenzaprine
7	Clonidine
8	Indomethacin

[a]Propoxyphene is not included because it is no longer available.

Potentially Inappropriate Medications

Beers Criteria

In 1991, Beers and colleagues developed explicit criteria defining inappropriate medication use in older adults. It is now known as the Beers criteria and is periodically updated by the American Geriatrics Society.[5] At that time, it was observed that residents of skilled nursing facilities were prescribed eight medications on average; more than 50% of them received a psychoactive medication. The Beers criteria were applied to the older residents in nursing homes, representing the frailest of the population. Inappropriate medications were defined by an expert panel as those that should be avoided, except under unusual clinical circumstances. This was because of the lack of effectiveness, risks outweighing the benefits, or safer alternatives that were available. The criteria were developed so that they could be assessed from easily identifiable pharmacy records using minimal clinical data. This made it feasible for use for the quality improvement initiatives in skilled nursing facilities. The Beers criteria were subsequently updated so that they could be applied to all older patients, regardless of the place of residence. The most recent version from the American Geriatrics Society was developed by an 11-member panel with expertise in geriatric medicine, nursing, pharmacy, research, and quality measures.[5] Each criterion for medication or class includes a quality of evidence rating and strength of recommendation, serving as a valuable resource for clinicians involved in the care of older adults.

However, important questions remain regarding the applicability of the Beers criteria to practice in the ED. For example, promethazine is considered to be an inappropriate medication for older adults because of its anticholinergic and central nervous system effects, and avoiding this agent was given a strong recommendation based on high-quality evidence by the expert panel. Although the chronic effects of promethazine, such drug-related falls, constipation, and dry mouth, are not of particular concern in the ED, promethazine-induced confusion or sedation may be problematic in patients presenting with altered mental status. A safer alternative for nausea or vomiting in this latter circumstance would be a 5-HT_3 receptor antagonist, such as ondansetron. However, even ondansetron has been associated with QTc interval prolongation, which could be concerning in older patients who are already taking QTc-prolonging medications, leading to a potentially severe drug interaction.[15] These nuanced therapeutic decisions require emergency clinicians to consider patient-specific parameters and realize that a "one size fits all" approach may not be appropriate.

Medications provided on discharge create another challenge. Although a one-time dose in the ED is less likely to be problematic, medications prescribed on discharge must be given cautiously. Medications given to older patients on discharge should be prescribed for a limited period of time until follow-up by a primary care provider. In this setting, the Beers criteria may provide important guidance. For example, the Beers criteria expert panel has recommended that benzodiazepines should be avoided for the treatment of insomnia in older adults. This is because of the increased risk for cognitive impairment, delirium, falls, fractures, and motor vehicle collisions. Even short-term use of benzodiazepines after ED discharge could be associated with these adverse effects. In one randomized controlled trial, the use of a clinical decision support system in the ED was able to reduce the prescribing of potentially inappropriate medications in patients being discharged from the ED. Interestingly, the study targeted only a few medications, which accounted for 80% of the inappropriate medications prescribed on discharge. These medications, listed from the most to least commonly used, are in Table 185.3. Each institution should periodically evaluate trends in medications being prescribed and assessed for appropriateness because this can vary by center.

STOPP and START Criteria

In 2008, the STOPP (***S***creening ***T***ool of ***O***lder ***P***eople's Potentially Inappropriate ***P***rescriptions) and START (***S***creening ***T***ool to ***A***lert doctors to ***R***ight ***T***reatment) tools were developed and validated. These screening tools built on the Beers criteria to overcome some of its limitations and further help clinicians determine when indicated medications should be prescribed. The Beers criteria accounts for only a small subset of medications that are prescribed

TABLE 185.4

Top 10 STOPP Criteria

RANK	CRITERIA
1	Long-term use of benzodiazepines
2	Duplicate prescriptions from the same drug class
3	Proton pump inhibitor for peptic ulcer disease at full dose for >8 wk
4	NSAIDs in patients with moderate to severe hypertension
5	Long-term use of opioids—first-line treatment for mild to moderate pain
6	Aspirin without adequate cardiovascular risk
7	Warfarin and NSAID used together
8	Beta blocker in patients with chronic obstructive pulmonary disease
9	Prolonged use of first-generation antihistamines
10	NSAID use in patients with chronic renal failure

NSAID, Nonsteroidal antiinflammatory drug; STOPP (***S****creening* ***T****ool of* ***O****lder* ***P****eople's Potentially Inappropriate* ***P****rescriptions).*

inappropriately to older adults. In one national estimate of ED visits for adverse drug events in older adults, medications on the Beers criteria accounted for only 3.6% of visits. Approximately one-third of total visits were from only three medications—warfarin (17.3%), insulin (13.0%), and digoxin (3.2%). In addition, many of the medications in the Beers criteria may not be available in European countries or are seldom prescribed. In the ED setting, tools incorporating potentially inappropriate medications can be used to identify drug-related presentations, determine if medications are suitable to be used in the ED during acute illness, and guide medication prescribing on discharge. Even if a presentation is not drug-related, assessment in the ED is an opportunity to identify medications that may be problematic and lead to future admissions. In this regard, the STOPP screening tool was able to identify more patients than the Beers criteria for potentially inappropriate medications (35% vs. 25%) who presented to the ED of a university teaching hospital. The STOPP-related medications also contributed to twice the number of admissions (12% vs. 6%). The most recent version includes 80 STOPP and 34 START criteria.[16] The top 10 criteria that identified the most patients with inappropriate medications are listed in Table 185.4.

Anticoagulation and Bleeding

Oral anticoagulation use is common for age-related conditions such as atrial fibrillation. Warfarin has been used for several decades but is less than ideal because it has a narrow therapeutic range. Routine laboratory monitoring is required, and numerous drug and food interactions lead to an unpredictable response, often resulting in bleeding. Of all drug-related presentations to the ED, warfarin-induced bleeding has been shown to be the most common in older adults.

More recently, newer oral anticoagulants have become available that do not require routine laboratory monitoring and have fewer drug interactions. These include a direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban). High-quality randomized clinical trials of these new oral anticoagulants have shown them to be equivalent or superior to warfarin with regard to stroke prevention and bleeding occurrence for patients in atrial fibrillation.[17-19] New agents account for over 60% of new anticoagulation prescriptions for atrial fibrillation.[20] Postmarketing surveillance data are emerging suggesting that the new agents may be associated with a greater risk of bleeding, especially in those with renal impairment.[21,22]

One drawback of these agents is that they undergo renal elimination, and patients with severe renal impairment were excluded from major trials. Although dosing adjustment is recommended based on creatinine clearance, the fluctuating course of renal function in older adults during an acute illness may contribute to accumulation and bleeding. Furthermore, routine laboratory testing does not quantify the level of anticoagulation. For warfarin-induced bleeding, reversal is achieved when the international normalized ratio (INR) is less than 1.5. The new oral anticoagulants increase prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time, but these measures do not reliably estimate the level of anticoagulation and thus have limited ability to guide therapy. Laboratory parameters such as ecarin clotting time, diluted thrombin time, and chromogenic antifactor Xa assay may be potentially useful, but these tests are not widely available.[23]

Guidelines from the American College of Chest Physicians have recommended that four-factor prothrombin complex concentrate (PCC) is preferred over fresh-frozen plasma infusions for warfarin-induced bleeding, although this was given a weak recommendation grade based on low-level evidence.[24] Four-factor PCC contains clotting factors II, VII, IX, and X. In older patients who are volume-restricted, the use of concentrated factor products is more appealing than fresh-frozen plasma because the usual volume of plasma needed for effective reversal can be 2 L, which can be problematic in frail older adults. The volume of four-factor PCC depends on the dose and product used, but is usually less than 100 mL. Vitamin K is also recommended in a dose of 5 to 10 mg to be given via the intravenous (IV) route for life-threatening bleeding.[24] Although the onset of effect of IV vitamin K is not apparent for several hours, there will be a rebound increase in the INR during hospitalization if patients are not given vitamin K initially. This would require the provision of additional clotting factor, which increases the risk for thromboembolism, as well as drug cost to the institution.

No consensus recommendations or high-quality evidence is available for reversal of the new oral anticoagulants. There is some evidence to suggest that four-factor PCC is also effective for the factor Xa inhibitors but less effective for dabigatran.[25] In dabigatran-induced bleeding, an activated four-factor PCC (FEIBA) that contains the same clotting factors but in activated form may be more effective.[26] Dabigatran is also removed by dialysis because it has low protein binding, whereas factor Xa inhibitors are highly protein-bound and will not be removed by dialysis. Nonetheless, this may be impractical when rapid bleeding cessation is required. Because routine laboratory tests do not quantify the level of anticoagulation, clinical judgment is useful to determine if bleeding has stopped or if additional interventions are needed.

Neurologic Conditions

Altered mental status is a common chief complaint of older patients presenting to the ED. Although its cause may include a number of factors, medications need to be considered in the differential diagnosis for this presentation. Many of the medications on the Beers list are known to cause adverse neurologic effects. Medications with anticholinergic properties, in particular, are commonly associated with delirium. Avoidance of anticholinergic agents was given a strong recommendation based on moderate- to high-quality evidence by the American Geriatrics Society.[5] There are numerous medications with anticholinergic effects, and toxicity is often due to a cumulative anticholinergic burden. Treatment

is supportive, along with discontinuation of the offending medications. Benzodiazepines may be used for agitated delirium after nonpharmacologic options have been exhausted. In a systematic review, there was moderate-quality evidence that benzodiazepine also contributed to delirium, and they should be used cautiously in the ED.[27] When agitation is due to underlying psychiatric illness, neuroleptic agents such as haloperidol or an atypical antipsychotic may be used. Haloperidol has the least anticholinergic effect. However, doses given to older adults should be low (eg, ≤5 mg IM [intramuscular] or IV) to avoid the risk of extrapyramidal symptoms.[28] Large dose of haloperidol given via the IV route have been associated with QTc interval prolongation, so monitoring of the electrocardiogram (ECG), if possible, is important, especially if repeated doses are needed.

There are also differences in the pharmacologic management of some key neurologic emergencies in older adults. In patients with community-acquired bacterial meningitis, the Infectious Disease Society of America has additional recommendations for older adults compared to young adults. In older adults, ampicillin is recommended in addition to the standard empirical regimen for coverage of *Listeria monocytogenes*. Thus, patients would receive a triple regimen of vancomycin, ceftriaxone, and ampicillin. However, the cutoff value for age is 50 years rather than the traditional age definitions for older adults. Similarly, there are differences in the eligibility criteria for thrombolytic therapy for ischemic stroke based on age. The most recent guidelines for stroke from the American Heart Association extend the time window for the provision of thrombolysis, from 3 to 4.5 hours after onset of symptoms.[29] However, in addition to other criteria, patients older than 80 years are not eligible for this extended window. This is similar to the exclusion criteria of the trial on which this recommendation was based. The recommendation was based on lack of data rather than evidence of harm.

Analgesia

In a national survey of US EDs, geriatric patients with pain-related complaints were less likely to receive any analgesics than young adults.[30,31] The risk for poor pain management in older adults is multifactorial and increases with logistic constraints, such as ED crowding. Pain perception and susceptibility to adverse drug effects of analgesics is also different in older patients. Dosing of opioids should be cautious, and monitoring for respiratory depression needs to be vigilant. It is difficult to anticipate how much opioid would be required for pain control in the ED. Instead of large single doses, a lower dose with titration consistent with pharmacokinetic and pharmacodynamic characteristics of the opioid is ideal. For example, morphine and hydromorphone have their peak analgesic effect at approximately 15 minutes. Thus, redosing every 1 to 2 hours is an unnecessarily long time and leads to suboptimal pain control. One strategy that has been successfully used in older patients for severe pain in the ED is a two-step hydromorphone protocol.[32] Patients are given 0.5 mg IV hydromorphone, which is repeated in 15 minutes if the patient desires another dose when asked, "Do you want more pain medication?" However, previous opioid exposure needs to be considered to determine appropriate dosing. For example, in some older cancer patients with chronic opioid consumption, doses will likely need to be escalated for pain control.

Meperidine use should be avoided in older patients. It has a neurotoxic metabolite that accumulates with renal impairment common in these patients. Given the availability of alternative opioids, there is little reason to use this medication in the ED, and it is also listed on the Beers criteria. Ketorolac is a valuable alternative to opioids in the ED, and single doses have been shown to be as effective as opioids for pain related to certain indications, such as renal or gallbladder stones. However, it is a potent nonsteroidal antiinflammatory drug (NSAID) with the possibility of causing renal failure or gastrointestinal hemorrhage. This is less likely to occur with isolated doses in the ED setting. Nonetheless, a reduced dose is recommended for older adults (15 mg IV or 30 mg IM), which is half of the usual adult dose.[33] This is done to minimize the possibility of these adverse effects.

Clinical Pharmacy Services

There are a growing number of institutions that have pharmacists who practice in the ED. The American Society of Health-System Pharmacists has published guidelines regarding pharmacy services to be provided to the ED, with one of the essential roles being monitoring and ensuring patient safety.[34] In geriatric EDs, there is a great opportunity to integrate pharmacists, given the myriad drug therapy issues that can lead to suboptimal care.[35] Older adults have more medications prescribed, which increases the risk for medication errors.[36] Pharmacists are able to intercept these errors, preventing patient harm.[37] Given the possibility of drug-induced admissions, pharmacy services can be used to identify medications that may have contributed to an ED presentation. However, resource constraints make it difficult for pharmacists to evaluate each geriatric patient, especially in EDs with large bed capacities.

Obtaining an accurate medication list is necessary for determining the cause of an adverse effect, but this often requires phone calls to multiple pharmacies and physicians' offices. One option is the use of pharmacy technicians who are also able to perform this function with similar accuracy.[38] Patients can also be referred to the pharmacist based on variables that have been associated with adverse drug events.[39] One clinical decision rule was able to identify 96% of patients with adverse drug events by limiting referral of less than half of patients to a pharmacist so that a full review could be conducted. This decision rule is shown in Fig. 185.1.

Even if the presentation is unrelated to an adverse drug event, clinical pharmacists can be used to identify potentially inappropriate therapies that the patient is taking to minimize the possibility for readmissions. For example, it is possible that a patient may

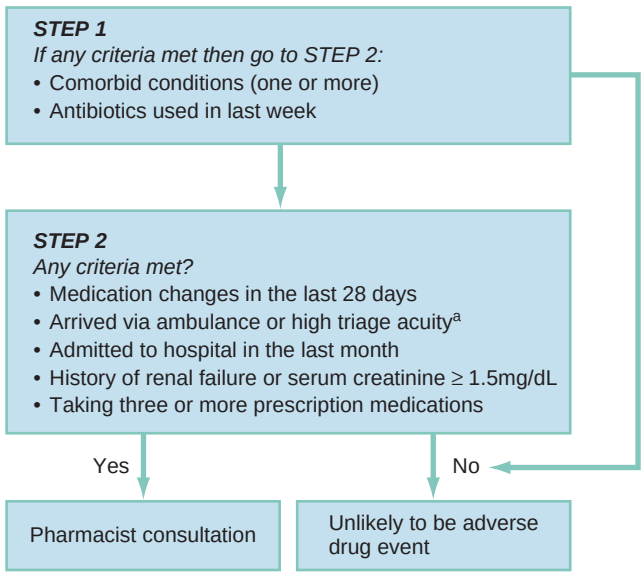

Fig. 185.1. Decision rule to identify adverse drug events. [a]Triage acuity was determined by the Canadian Triage Acuity Scale. A score of 1 to 3 was considered high acuity. This includes patients with at least urgent or emergent conditions who need to be seen by a physician within 30 minutes.

be taking two medications from the same drug class prescribed by two different physicians. Applying the Beers, START, and STOPP criteria, the anticholinergic burden and other opportunities for drug therapy optimization can be assessed. Finally, pharmacists serve as an important safety net for drug therapy prescribed by ED clinicians, both within the ED and on discharge. Setting up a system whereby the pharmacist can be consulted and is available to review these medication orders for potential harm is a risk mitigation strategy that may help reduce readmissions by older adults.

KEY CONCEPTS

- Those with a chronologic age of 65 years or older are commonly referred to as older adults (or the elderly), but physiologic age is more indicative of a drug's therapeutic or toxicologic effect. Besides age, overall patient assessment should include organ function, comorbidity, and functional status to guide drug dosing.
- Pharmacokinetic and pharmacodynamic changes that occur with age need to be considered to optimize drug dosing and minimize toxicity in older adults. In most cases, a start low, go slow approach is recommended. Multiple or repeated dosing is more likely to lead to drug accumulation compared to single doses in the ED.
- Polypharmacy is common in older adults, predisposing them to adverse drug effects, drug interactions, and functional and cognitive impairment. Some of these medications do not have legitimate indications or may be inappropriate.
- There are published lists of potentially inappropriate medications, such as the Beers list and the STOPP and START criteria, but there are limited studies to enable extrapolation to the ED setting.
- Of all drug-related presentations to the ED, warfarin-induced bleeding has been shown to be the most common in older adults. However, the use of newer oral anticoagulants, such as direct thrombin inhibitors and factor Xa inhibitors, has been increasing. These newer agents undergo renal elimination; thus, drug accumulation is a concern in older adults.
- Older adults often present to the ED with altered mental status. Drug-related causes such as anticholinergic medication burden should be considered in the differential diagnosis.
- Geriatric patients with pain-related complaints are less likely to receive analgesics in the ED compared to younger adults, placing them at risk for poor pain control. Dosing of opioids should be cautious, with frequent monitoring and titration. Given the availability of alternative opioids, the use of meperidine should be avoided.
- A growing number of institutions have pharmacists practicing in the ED. In geriatric EDs, there is a great opportunity to integrate and consult with pharmacists, given the myriad drug therapy issues that can lead to suboptimal care.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 185: QUESTIONS & ANSWERS

185.1. Which of the following pharmacokinetic change in older adults is associated with increased plasma concentration of drug?

- **A.** Decrease in absorptive capacity in an orally administered medication
- **B.** Decreased glomerular filtration rate in a renally eliminated medication
- **C.** Increase in gastric pH in a medication that is a weak base
- **D.** Increased liver blood flow in a high–extraction ratio medication
- **E.** Increased total body water in hydrophilic medications

Answer: B. Decrease in glomerular filtration rate is common with age. This leads to decreased elimination and increased plasma concentration of a drug. All other options listed would lead to decreased plasma drug concentrations. Liver blood flow, glomerular filtration rate, total body water, and absorptive capacity decrease with age. However, gastric pH increases.

185.2. Which of the following is the most appropriate strategy for analgesic provision in an older patient with renal insufficiency and severe abdominal pain in the emergency department?

- **A.** Hydromorphone 0.5 mg IV, followed by the same dose in 15 minutes, if needed
- **B.** Ketorolac, 30 mg IV qid
- **C.** Meperidine, 50 μg IV every 2 hours
- **D.** Morphine, 4 mg IV every 2 hours
- **E.** Oxycodone/acetaminophen, 5/235 mg orally every 2–4 hours

Answer: A. One strategy that has been used successfully in older adults is a two-step hydromorphone protocol. Patients are given 0.5 mg IV hydromorphone, which is repeated in 15 minutes if the patient desires another dose when asked, "Do you want more pain medication?" Hydromorphone does not have active metabolites that would accumulate with renal insufficiency, so it would be an appropriate option for severe pain. Ketorolac should be avoided

in older adults with renal insufficiency because the inhibition of prostaglandins can decrease renal blood flow. Meperidine use is no longer recommended because of a neurotoxic metabolite and accumulation in renal insufficiency. Morphine has an active metabolite that also accumulates in renal insufficiency. Oxycodone-acetaminophen given orally is not appropriate for severe acute pain due to delayed onset of effect. Bioavailability of oral medications may further be delayed in older adults.

185.3. Which of the following statements is true regarding reversal of anticoagulation in older adults who are bleeding?

A. Intravenous vitamin K can be avoided if factor concentrates are provided.
B. Dabigatran is not removed by hemodialysis because of high protein binding.
C. Prothrombin complex concentrate is preferred to plasma transfusion.
D. Plasma transfusion is preferred to prothrombin complex concentrate.
E. Factor Xa inhibitors can be removed by hemodialysis because of low protein binding.

Answer: C. Prothrombin complex concentrate has a lower volume of administration, which is beneficial for volume-restricted older adults. It is preferred to plasma transfusion based on low-level evidence. Intravenous vitamin K should be given with factor concentrates to sustain the reversal of anticoagulation. Dabigatran has low protein binding and thus can be removed by prolonged hemodialysis, but this is often not practical when emergent bleeding cessation is required. Factor Xa inhibitors are highly protein-bound and are not removed by hemodialysis.

185.4. Which of the following medications prescribed on discharge is most likely to interact in an older patient taking warfarin?

A. Albuterol inhaler for asthma
B. Ciprofloxacin for urinary tract infection
C. Insulin NPH for hyperglycemia
D. Oxycodone for fracture pain
E. Promethazine for nausea

Answer: B. Studies of harmful drug interactions in older adults have shown that the initiation of antibiotics in patients taking warfarin can lead to bleeding. Ciprofloxacin can lead to an elevation in the international normalized ratio (INR) due to disruption of vitamin K synthesis in patients taking warfarin. Thus, more frequent monitoring is required when ciprofloxacin is initiated. The other options listed do not interact with warfarin. However, oxycodone and promethazine can be harmful because of central nervous system effects, potentially leading to falls.

185.5. Which of the following statements is true regarding neurologic emergencies in older adults?

A. Ampicillin is added for the treatment of bacterial meningitis for additional coverage against *Enterococcus faecalis.*
B. Anticholinergic medication use is not associated with delirium.
C. Haloperidol, 10 mg IV, is recommended for acute agitation due to underlying psychiatric illness.
D. In patients with ischemic stroke who are older than 80 years, alteplase may be administered up to 4.5 hours after the onset of symptoms, according to guidelines.
E. Large doses of haloperidol given via the IV route have been associated with QTc interval prolongation

Answer: E. There is a US Food and Drug Administration (FDA) black box warning regarding the use of haloperidol and QTc interval prolongation. This risk is increased with large doses given intravenously. Polypharmacy in older adults also puts them at risk for drug interactions due to concomitant QTc-prolonging agents. Doses of haloperidol should be less than 5 mg in most older adults. Ampicillin is added for bacterial meningitis to cover *Listeria monocytogenes.* Although recent evidence has extended the 3-hour time window to 4.5 hours for receiving alteplase after the onset of stroke in a small subset of patients, those older than 80 years are not eligible, according to guidelines. Anticholinergic medications are known to be associated with delirium and sedation.

CHAPTER 186

Abuse and Neglect of the Geriatric Patient

Tony Rosen | Michael E. Stern

PRINCIPLES

Background

Elder abuse and neglect encompasses a wide variety of behaviors perpetrated upon an older person that can have serious medical and social consequences. There are no universally accepted definitions of elder abuse and neglect, but most include the concept, initially developed by a 2002 National Academy of Sciences panel, that elder mistreatment involves *a trusting relationship between an older person and another individual in which the trust has been violated in some way*. The definition that likely best captures current understanding is that which was developed for the 2014 Elder Justice Roadmap, a report prepared by a large, multidisciplinary team of stakeholders inside and outside the United States government, defining elder abuse as:

> *Physical, sexual, or psychological abuse, as well as neglect, abandonment, and financial exploitation of an older person by another person or entity that occurs in any setting (eg, home, community, or facility), either in a relationship where there is an expectation of trust and/or when an older person is targeted based on age or disability.*

This elder mistreatment may include physical abuse, sexual abuse, neglect, emotional/psychological abuse, abandonment, financial/material exploitation, and self-neglect (Table 186.1). Many victims may suffer concurrently from multiple types of abuse.

Epidemiology and Scope of the Problem

Elder abuse and neglect is common and can have a profound impact. Recent prevalence studies suggest that as many as 10% of community dwelling older adults experience some form of abuse, neglect, or exploitation each year.[1-3] Multiple smaller studies suggest that nearly 50% of dementia sufferers are victims of mistreatment by caregivers.[2,4] In prevalence studies, psychological/emotional abuse (4.6% to 12.9%), financial mistreatment (3.5% to 6.6%), and neglect (5.1% to 5.4%) are most commonly reported, with physical mistreatment (0.2% to 2.1%) and sexual abuse (0.3% to 0.6%) less frequently reported.[3,5] In a study of substantiated elder abuse cases from the United States, 58% involved neglect, 15% financial exploitation, 15% emotional abuse, 11% physical abuse, and 1% sexual abuse.

Elder abuse is strongly associated with adverse health outcomes, including increased emergency department (ED) usage, hospitalization, dementia, depression, nursing home placement, and dramatically increased mortality. The annual direct medical costs in the United States associated with violent injuries to older adults are estimated at $5.3 billion. This large disease burden and cost are likely to increase significantly due to anticipated geriatric population growth, particularly among the "oldest old" aged 85 years or older, who are the fastest growing segment of the adult population and are particularly vulnerable to the effects of abuse and neglect.

Despite its frequency and potential for significant harm, elder abuse and neglect is under-recognized and under-reported, with many sufferers enduring it for years before discovery. Studies suggest that as few as 1 in 24 cases of elder abuse is reported to the authorities, and much of the associated morbidity and mortality is likely due to this delay in identification and intervention.[1,2]

Many factors likely contribute to the occurrence of elder abuse and neglect. Several theories have been proposed to describe the underlying causes of elder mistreatment (Table 186.2). Although none of these theories alone fully explains this complex phenomenon, each offers insights into aspects of elder mistreatment and thus suggests potential targets for interventions to manage confirmed cases.

Recent research has focused on identifying risk factors for becoming a victim or perpetrator of elder abuse and neglect. Findings have been inconsistent and difficult to interpret, with some studies suggesting that older age (>80 years old) increases risk of victimization, whereas others correlate higher risk with younger age (<70 years old).[3,6] This inconsistency is likely partly due to the significant methodological limitations of current studies and the heterogeneity of elder mistreatment cases. Despite these limitations, potential risk factors for becoming a victim or perpetrator based on existing evidence are described in Box 186.1. Many cases of elder mistreatment occur in the absence of risk factors, however, and the phenomenon crosses ethnic and socioeconomic boundaries, so emergency clinicians should be vigilant in assessing older adult patients.

Identifying Elder Abuse and Neglect in the Emergency Department

The ED visit is an important and often underutilized opportunity to identify elder abuse or neglect, which may otherwise remain undiscovered. For many older adults, assessment by health care providers is their only contact outside the family. Emergency clinicians, therefore, have a unique opportunity to diagnose and report suspected elder abuse and initiate further evaluation by elder abuse teams and adult protective services (APS). Emergency clinicians, who typically manage acute injuries and illnesses, are particularly well-positioned to identify abuse. Despite this, only 1.4% of cases reported to APS come from emergency clinicians, and, in a survey of APS workers, of 17 occupational groups, physicians were among the least helpful in reporting abuse. Several reasons exist for this missed opportunity, including lack of awareness, inadequate training, insufficient information about available resources, lack of time to conduct a thorough evaluation

TABLE 186.1

Types of Elder Abuse and Neglect

TYPE	DEFINITION	EXAMPLES
Physical abuse	Intentional use of physical force that may result in bodily injury, physical pain, or impairment	• Slapping, hitting, kicking, pushing, pulling hair • Use of physical restraints, force-feeding • Burning, use of household objects as weapons, use of firearms and knives
Sexual abuse	Any type of sexual contact with an elderly person that is non-consensual or sexual contact with any person incapable of giving consent	• Sexual assault or battery, such as rape, sodomy, coerced nudity, and sexually explicit photographing • Unwanted touching, verbal sexual advances • Indecent exposure
Neglect	Refusal or failure to fulfill any part of a person's obligations or duties to an elder, which may result in harm—may be intentional or unintentional	• Withholding of food, water, clothing, shelter, medications • Failure to ensure elder's personal hygiene or to provide physical aids, including walker, cane, glasses, hearing aids, dentures • Failure to ensure elder's personal safety and/or appropriate medical follow-up
Emotional/psychological abuse	Intentional infliction of anguish, pain, or distress through verbal or nonverbal acts	• Verbal berating, harassment, or intimidation • Threats of punishment or deprivation • Treating the older person like an infant • Isolating the older person from others
Abandonment	Desertion of an elderly person by an individual who has assumed responsibility for providing care for an elder or by a person with physical custody	
Financial/material exploitation	Illegal or improper use of an older adult's money, property, or assets	• Stealing money or belongings • Cashing an older adult's checks without permission and/or forging his or her signature • Coercing an older adult into signing contracts, changing a will, or assigning durable power of attorney against his or her wishes or when the older adult does not possess the mental capacity to do so
Self-neglect	Behavior of an older adult that threatens his/her own health or safety—excluding when an older adult who understands the consequences of his or her actions makes a conscious and voluntary decision to engage in acts that threaten his/her health or safety	• Refusal or failure of an older adult to provide him or herself with basic necessities, such as food, water, shelter, medications, and appropriate personal hygiene • Disregard for maintenance of safe home environment and/or hoarding

Adapted from National Center on Elder Abuse: Types of abuse. Available at ncea.acl.gov/faq/abusetypes.html.

TABLE 186.2

Selected Theories of the Underlying Causes of Elder Abuse and Neglect

THEORY	DESCRIPTION
Transgenerational violence	Family violence is a learned behavior, and abused children grow up to potentially abuse not only their own children but also perhaps parents
Psychopathology of the abuser	Mental health issues of the abuser, including personality disorders, poorly treated mood disorders or schizophrenia, alcoholism, and other substance abuse problems, lead to abusive behavior
Dependency	Increasing frailty, including functional and cognitive disability result in overwhelming care needs that leave an older adult vulnerable to abuse by an overburdened caregiver
Stressed caregiver	A caregiver who has become increasingly stressed (from caregiving or other causes) may be more likely to be abusive
Isolation	Greater social isolation due to disability, illness, and age increases an older adult's vulnerability to abuse or neglect

Adapted from Jones JS, Holstege C, Holstege H: Elder abuse and neglect: understanding the causes and potential risk factors. Am J Emerg Med 15:579–583, 1997.

for abuse, misinterpretation of the sequelae of elder abuse or neglect as the result of accidental injury or illness, concern about involvement in the legal system, and desire to protect clinician-patient confidentiality. Despite these challenges, it is critical that emergency clinicians explore the potential for elder abuse and neglect when assessing older adult patients.

CLINICAL FEATURES

Screening

The American College of Emergency Physicians and American Medical Association have recommended that all EDs and all

BOX 186.1

Potential Risk Factors for Elder Abuse

FOR BECOMING A VICTIM

Functional dependence or disability
Poor physical health
Cognitive impairment/dementia
Poor mental health
Low income/socioeconomic status
Social isolation/low social support
Previous history of family violence
Previous traumatic event exposure
Substance abuse

FOR BECOMING A PERPETRATOR

Mental illness
Substance abuse
Caregiver stress
Previous history of family violence
Financial dependence on older adult

Acierno R, Hernandez MA, Amstadter AB, et al: Prevalence and correlates of emotional, physical, sexual, and financial abuse and potential neglect in the United States: the National Elder Mistreatment Study. Am J Public Health 100:292–297, 2010; Amstadter AB, Zajac K, Strachan M, et al: Prevalence and correlates of elder mistreatment in South Carolina: the South Carolina elder mistreatment study. J Interpers Violence 26:2947–2972, 2011; Pillemer K, Burnes D, Riffin C, et al: Elder abuse: background paper for the world report on ageing and health. Geronotologist 56(Suppl 2):S194–205, 2016; Gibbs LM: Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med 30:687–712, 2014.

BOX 186.2

Elder Abuse Suspicion Index

Questions 1 through 5 are answered by the patient. Question 6 is answered by the physician. The patient can answer "yes," "no," or "unsure." A response of "yes" on one or more of questions 2 through 6 should prompt concern for abuse or neglect.

1. Have you relied on people for any of the following: bathing, dressing, shopping, banking, or meals?
2. Has anyone prevented you from getting food, clothes, medication, glasses, hearing aids, or medical care or from being with people you wanted to be with?
3. Have you been upset because someone talked to you in a way that made you feel shamed or threatened?
4. Has anyone tried to force you to sign papers or to use your money against your will?
5. Has anyone made you afraid, touched you in ways that you did not want, or hurt you physically?
6. Doctor: Elder abuse may be associated with findings such as poor eye contact, withdrawn nature, malnourishment, hygiene issues, cuts, bruises, inappropriate clothing, or medication compliance issues. Did you notice any of these today or in the last 12 months?

Data from Yaffe MJ, Wolfson C, Lithwick M, et al: Development and validation of a tool to improve physician identification of elder abuse: the elder abuse suspicion index (EASI). J Elder Abuse Negl 20:276–300, 2008.

BOX 186.3

Indicators From the Medical History of Possible Elder Mistreatment

Poor living conditions according to paramedics or others
Unexplained injuries
Past history of frequent injuries
Delay between onset of medical illness or injury and seeking of medical attention
Recurrent visits to the ED for similar injuries
Using multiple physicians and EDs for care rather than one primary care physician ("doctor hopping or shopping")
Noncompliance with medications, appointments, or physician directions
Patient or caregiver reluctant to answer questions
Strained patient/caregiver interaction
Inconsistent history of injury mechanism between the patient and caregiver
Elderly patient referred to as "accident prone"
Caregiver not able to give details of the patient's medical history or routine medications
Caregiver answers the questions regarding the patient
Abandonment of the patient in the ED by the caregiver

ED, Emergency department.

health care providers routinely ask older patients about mistreatment. The identification of and intervention in abuse are considered by many to be a professional responsibility for emergency clinicians and are an accreditation requirement for hospitals. In the United States, the Joint Commission requires that EDs screen all patients for abuse or neglect.

Several screening tools have been devised to aid in the detection of elder abuse, but they are not applicable to all clinical environments, and few have been validated in primary care settings. The Elder Abuse Suspicion Index (EASI) is a short screening instrument that is easy to use in the ED and has been validated for cognitively intact patients in family practice and ambulatory care settings. It is detailed in Box 186.2.

Medical History

Obtaining an accurate and thorough medical history is critical to effectively assess for elder mistreatment, although this may be challenging for ED staff. Potential historical indicators of elder mistreatment are listed in Box 186.3. Because older adults are four times more likely to be brought in by ambulance to the ED than younger patients, paramedics and emergency medical technicians, who typically have the opportunity to evaluate patients in their home, may have critical information about the home situation and family dynamics that may inform the ED assessment. Emergency clinicians should seek out prehospital personnel and inquire about unusual family interactions, cleanliness and upkeep of the home, the availability of food, medications, heat, and sanitation, and the safety of the home for the older patient.

When initially assessing an older adult with a caregiver present, the emergency clinician should carefully observe their interaction, identifying any clues of a strained relationship. History should be taken from the patient in as private a setting as possible, without caregivers or family present. If a translator is needed, someone other than a family member or the caregiver should be used. The assessment for elder mistreatment should be incorporated into the routine evaluation. The emergency clinician may ask in detail about the reason for the ED visit and then inquire about the patient's health in general, focusing on the safety of the home environment and any need for support or assistance. A clinician may follow up about specific types of abuse suspected as appropriate. Box 186.4 suggests potential questions to screen for abuse. If the older adult is presenting with any injury, the emergency clinician should question the patient about how the injury occurred, including directed questions regarding whether anyone has hit, punched, pushed, tripped, or kicked the patient.

Unfortunately, obtaining a reliable history from victims of elder abuse and neglect is often difficult. Many older adults have advanced dementia or cognitive impairment that prevents them

BOX 186.4

Questions for Use in Asking Patients About Elder Abuse

GENERAL
Do you feel safe where you live?
Are you afraid of anyone where you live?
Who assists you if you need help?
Who makes your meals?
Who helps you take your medications?
Who manages your checkbook?
Do you have frequent arguments with your family or caregiver?
What happens when you argue?

PHYSICAL ABUSE
Have you been hit, slapped, or kicked?
Have you ever been locked in a room?
Have you ever been tied down?
Have you ever been forced to eat?

SEXUAL ABUSE
Has anyone ever touched you sexually without your consent?

PSYCHOLOGICAL OR EMOTIONAL ABUSE
Do you feel alone?
Are you yelled at where you live?
Has your family or caregiver ever threatened to punish you or have you put in an institution?

NEGLECT
Are you left alone often at home?
Do you need to use hearing aids, glasses, dentures, or a walker or a cane? Are they readily accessible to you?
Does your family or caregiver ever fail to help you when you need help?

FINANCIAL OR MATERIAL ABUSE
Has anyone ever taken anything from you without asking?
Have you been forced to sign a will, power of attorney, or any documents that you did not understand?
Does your family or caregiver rely on you for housing or financial support?

BOX 186.5

Physical Signs Suspicious for Potential Elder Abuse or Neglect

PHYSICAL ABUSE
Bruising in atypical locations (not over bony prominences/on lateral arms, back, face, ears, or neck) (see Fig. 186.1)
Patterned injuries (bite marks or injury consistent with the shape of a belt buckle, fingertip, or other object) (see Fig. 186.2)
Wrist or ankle lesions or scars (suggesting inappropriate restraint) (see Fig. 186.3)
Burns (particularly stocking/glove pattern suggesting forced immersion or cigarette pattern) (see Fig. 186.4)
Multiple fractures or bruises of different ages (see Fig. 186.5)
Traumatic alopecia or scalp hematomas
Subconjunctival, vitreous, or retinal ophthalmic hemorrhages
Intraoral soft tissue injuries

SEXUAL ABUSE
Genital, rectal, or oral trauma (including erythema, bruising, lacerations) (see Figs. 186.6 and 186.7)
Evidence of sexually-transmitted disease

NEGLECT
Cachexia/malnutrition
Dehydration
Pressure sores/decubitus ulcers (see Figs. 186.8 to 186.10)
Poor body hygiene, unchanged diaper
Dirty, severely worn clothing
Elongated toenails (see Fig. 186.10)
Poor oral hygiene (see Fig. 186.11)

Gibbs LM: Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med 30:687–712, 2014; Palmer M, Brodell RT, Mostow EN: Elder abuse: dermatologic clues and critical solutions. J Am Acad Dermatol 68:e37–42, 2013; Chang AL, Wong JW, Endo JO, et al: Geriatric dermatology: Part II. Risk factors and cutaneous signs of elder mistreatment for the dermatologist. J Am Acad Dermatol 68:533 e1–10, 2013; Speck PM, Hartig MT, Likes W, et al: Case series of sexual assault in older persons. Clin Geriatr Med 30:779–806, 2014.

from providing an accurate medical history. Even in these cases, an emergency clinician should consider attempting to interview the patient, because recent research suggests that older adults with cognitive impairment can often relate how an injury occurred.[7] Whenever an older adult is unable to provide history, additional information should be sought from others besides the caregiver who may have knowledge of the patient, such as other family members, the primary care physician, neighbors, or visiting nurses. Mistreated elders may be motivated to conceal abuse or neglect, due to a desire to protect the abuser (often a spouse or child), dependency on the caregiver, shame, cultural or ethnic beliefs, or a fear of retaliation or institutionalization. Emergency clinicians should, therefore, assess for behavioral signs and symptoms suggestive of potential elder mistreatment, including depression, withdrawal, confusion, poor eye contact, fear, anxiety, low self-esteem, and helplessness. When exhibited or expressed by the patient, these may provide clues to the presence of elder abuse or neglect.

A separate interview of the caregiver or suspected abuser is often useful. It may reveal important discrepancies from the patient's history. In addition, a caregiver who is unfamiliar with an older adult's routine medications and necessary medical care may be neglecting them. The emergency clinician should be careful to conduct this interview in a nonthreatening and nonjudgmental manner, because the goal is not to accuse the caregiver but rather to obtain information. Verbal expressions of sympathy, explicit recognition of the challenges, and demonstrations of support can be beneficial for the caregiver and also promote information sharing. Questions should also explore whether any important changes or recent stresses have occurred in the household, whether the caregiver feels that the patient is a burden, the caregiver's other dependents and responsibilities, and whether any respite services or other home help services have been made available.

Physical Examination

Many clues to the presence of elder physical abuse, sexual abuse, or neglect may be present on physical examination (Box 186.5 and Figs. 186.1 to 186.11), and emergency clinicians should evaluate older adults thoroughly and carefully. When an older adult presents with an acute injury (such as, a fall), consider whether the reported mechanism is consistent with the injuries suffered. Particular attention should be given to a full skin examination, which may reveal important findings that might otherwise be missed. Unfortunately, it can be difficult to distinguish between elder abuse or neglect and the sequelae of accidental trauma and acute or chronic illness. This is made more challenging by the

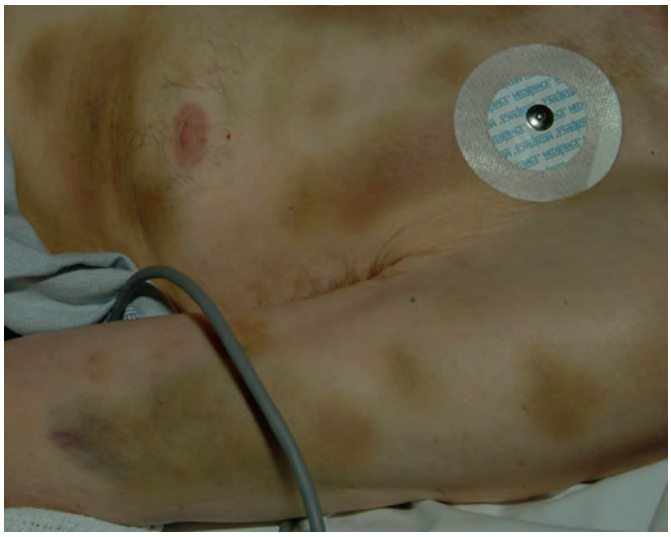

Fig. 186.1. Atypical bruising of the chest in a case of substantiated abuse. (From Gibbs LM: Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med 30:687–712, 2014.)

Fig. 186.2. Pattern bruise on the left buttock from unknown object. (From Gibbs LM: Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med 30:687–712, 2014.)

Fig. 186.3. Pattern bruising on lower leg from a ligature. (From Gibbs LM: Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med 30:687–712, 2014.)

Fig. 186.4. Burn injuries on the back and buttocks from scalding water. (From Gibbs LM: Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med 30:687–712, 2014.)

Fig. 186.5. A 70-year-old man was brought from his caregiver's home to the emergency department (ED) by police after his daughter found him severely bruised. He had multiple contusions at varying stages of healing on his chest and arms, as well as a linear patterned injury across his left anterior chest. The central and bilateral locations of the contusions, varying colors, and linear pattern of the bruise on the left side of his chest are highly suggestive of physical abuse. (Courtesy Dr. D.C. Homeier.)

normal physiologic changes that occur with aging, such as osteopenia, thinning of the skin, and easy bruising. Emergency clinicians should, therefore, consider elder mistreatment in the differential diagnosis of many conditions that occur frequently in older adults. Geriatric patients with multiple suspicious clinical findings may be more likely to be victims of elder abuse or neglect than those with isolated findings.

DIFFERENTIAL DIAGNOSES

Though under-recognized, sexual assault of older adults occurs and should be considered by emergency clinicians. If sexual abuse is suspected or reported and a genitourinary examination reveals evidence of trauma or vaginal bleeding, emergency clinicians should conduct a complete sexual assault examination, as in cases with younger victims. This evaluation should include evidence

Fig. 186.6. A 65-year-old woman in a nursing home with posterior fourchette and perineum laceration from rape by resident. (From Speck PM, Hartig MT, Likes W, et al: Case series of sexual assault in older persons. Clin Geriatr Med 30:779–806, 2014.)

Fig. 186.8. Case of elder neglect showing moisture-associated skin damage (MASD) and ulcers in the sacrum, buttocks, and thighs. (From Gibbs LM: Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med 30:687–712, 2014.)

Fig. 186.7. A 69-year-old woman with severe dementia who resided in a skilled nursing facility was brought to the emergency department (ED) after her daughter noticed that the patient had bruises on her bilateral inner thighs. When the daughter inquired about the bruises, she was told by the facility staff that the patient had fallen. These bruises are in a location that raises suspicion for sexual abuse. The emergency clinician consulted the hospital's adult protection team, which contacted local law enforcement; the long-term care ombudsman was also notified for further investigation. The hospital's sexual assault response team was consulted and conducted a sexual assault forensic examination for evidence collection. (Courtesy Dr. D.C. Homeier.)

Fig. 186.9. A 65-year-old developmentally delayed but ambulatory woman was brought to the emergency department (ED) by her family on account of "unruly behavior." Examination of her left heel revealed a pressure ulcer, and her left ankle revealed an erythematous rash in a circumferential pattern. This may represent the use of a restraint, resulting in the pressure ulcer. (Courtesy Dr. D.C. Homeier.)

collection by a forensic examiner with appropriate training and expertise.

Recent research has begun to systematically explore whether injury patterns exist that are pathognomonic for elder mistreatment (analogous to findings in child abuse, such as shaken baby syndrome and bucket-handle metaphyseal fracture). One recent study compared bruises in 67 elder abuse victims to older adults with accidental trauma, finding that victims of elder abuse had bruises that were more often large (>5 cm) and found on the face, lateral right arm, or posterior torso. A literature review identified 839 reported cases of physical elder abuse and found that two-thirds of injuries that occur in elder abuse are to the upper extremity and maxillofacial region.[8] More systematic research into clinical features distinguishing between elder abuse and accidental injury or illness is critically needed.

DIAGNOSTIC TESTING

No laboratory tests exist to definitively detect abuse, but medical and laboratory findings may suggest elder mistreatment. These include malnutrition, dehydration, anemia, hypothermia/hyperthermia, and rhabdomyolysis. In addition, serum or urine drug levels may be useful, because undetectable levels of prescribed medications may indicate that a caregiver is intentionally or neglectfully withholding. Perpetrators may divert controlled substances, such as narcotic pain medications, for their own use or to sell. Elevated serum levels of prescription medications may suggest intentional or unintentional overdose, and the presence of toxins or drugs that have not been prescribed may indicate poisoning. Platelet count and coagulation studies may helpful in ruling out a medical etiology for unexplained or abnormal bruising.

MANAGEMENT

When elder abuse or neglect is identified or suspected, management should include treating acute medical and psychological

Fig. 186.10. A 72-year-old woman was brought to the emergency department (ED) by paramedics for "not eating for 5 days" according to her family. The paramedics noted she was covered in urine and feces. The following signs were of concern for neglect: elongated toenails **(A),** pressure sores **(B),** poor hygiene, and a delay in seeking medical care. (Courtesy Dr. D.C. Homeier.)

Fig. 186.11. Poor dentition in a substantiated case of dependent adult neglect. (From Gibbs LM: Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med 30:687–712, 2014.)

issues, ensuring patient safety, and proper reporting to the authorities.

Traumatic injuries and metabolic abnormalities including dehydration are common and should be stabilized and treated. Management of worsening chronic medical conditions may be required due to an abuser's failure to provide appropriate care. In some circumstances, hospitalization may be necessary to provide extended treatment and observation.

If a mistreatment victim is in immediate danger, the patient should be prevented from having any contact with the suspected abuser. In some cases, the suspected abuser may be the patient's official health care proxy. In extreme cases, this may require security watch for the patient and even having the abuser removed from the ED and law enforcement, hospital social workers and administrators should be alerted. Alternate living arrangements may need to be arranged for the patient, with a reliable family member or friend or in an appropriate emergency shelter. If none of these options are available, the patient may require hospital admission to ensure safety.

If the patient refuses intervention, the emergency clinician must determine whether the patient has the capacity to make this decision. A psychiatric consultation may be helpful. The wishes of an older adult with decision-making capacity who desires to return to an abusive situation must be respected, as in cases of intimate partner violence among younger adults. If possible, the emergency clinician should educate the patient about the potential for escalation in violence and abuse and provide appropriate referral materials for future use.

In suspected cases of elder mistreatment without an imminent threat to a patient's safety, interventions are individualized. If the patient wants to return home and may be safely discharged, the emergency clinician should coordinate with the patient's primary care physician to ensure an appropriate longitudinal follow-up plan. Social workers may be able to offer resources to both the patient and the caregiver, including senior centers, medical transportation services, Meals-on-Wheels, adult day care, respite care, and substance abuse treatment. Ideally, elder mistreatment cases are managed in the community by a multidisciplinary team and involve home visits and advocacy.

Documentation

Accurate and thorough documentation of the history and physical examination findings is critical in cases of suspected elder mistreatment. The emergency clinician should document the history in the patient's own words if possible. Pertinent social history (eg, patient's functional status, caregiver's relationship to patient, living arrangements) should be included. The clinician should describe the patient's general appearance, including signs of potential neglect, such as a soiled diaper, inappropriate or dirty clothing, or dirt under nails. Injuries of any type (eg, fractures, lacerations, and contusions) should be described, including their number, size, location, and stage of healing and comment about whether the injuries are consistent with the reported mechanism. If possible, photographs of all injuries should be obtained and added to the medical record. The results of laboratory investigations and imaging studies should also be recorded. Careful documentation of interventions, follow-up plans, and referrals should be made. In cases of suspected elder abuse that result in legal action, thorough documentation may be critical to ensure justice for the victim.

Reporting Requirements

Although all states in the United States have laws on reporting and investigation of elder abuse, the definitions of elder abuse and requirements of the laws vary. In most states, emergency clinicians

are mandated to file a report if they know or reasonably suspect that elder abuse has occurred. Many of the states with mandatory reporting requirements grant immunity to emergency clinicians who report. Most state laws also have a penalty for failure to report, which may include a fine, a prison sentence, or both. A clinician does not have to confirm that abuse or neglect has occurred to report; a legitimate suspicion is all that is required to prompt a more thorough investigation. In most states, APS is the agency responsible for receiving and investigating all reports of suspected elder abuse. In some states, emergency clinicians are also required to report to law enforcement. Emergency clinicians should become familiar with state laws pertaining to elder abuse and their duty to report in the state in which they practice. The Administration of Aging's National Center on Elder Abuse website (https://ncea.acl.gov) is the most comprehensive online resource available on elder abuse and neglect.

SPECIFIC DISORDERS

Elder Mistreatment in Institutions

Residents of skilled nursing facilities account for over 2.2 million ED visits annually in the United States.[9] This currently represents 11% of all visits by patients aged 65 years old or older and is rising.[10,11] Elder abuse and neglect may also occur in these institutions. Emergency clinicians may play an important role in identifying this elder mistreatment, because each nursing home resident presents to the ED an average of 1.6 times every year.[9]

Over the last several decades, increased regulatory scrutiny has improved care and reduced staff mistreatment of older adults in skilled nursing facilities. In the 1970s, the Long-Term Care Ombudsman Program was created nationally to monitor nursing homes and to investigate cases of suspected elder abuse and resident complaints. Mandatory criminal background checks of all employees were established. The Nursing Home Reform Act in 1986 included provisions for residents' rights, which incorporated minimizing the use of restraints. The current prevalence of elder mistreatment in institutions is not well known, but research suggests it may still be common. In a recent study, 24% of family members of nursing home residents reported at least one incident of physical abuse against their elderly family member by nursing home staff.[12] Forensic analysis of 2400 deaths in in nursing homes found 50 suspected cases of fatal elder abuse or neglect. Poor working conditions, low wages, low staff-to-patient ratio, and inadequate training or supervision may increase the likelihood of nursing home staff members mistreating residents.

In addition to staff abuse and neglect of nursing home residents, resident-to-resident elder mistreatment has been recently identified as important problem. The prevalence of this phenomenon is unknown, but, given that dementia and associated behavioral disturbance in long-term care facilities is high, aggressive behavior can occur between residents. Additional research is needed to improve recognition of this type of elder mistreatment. When abuse or neglect of any kind in patients from nursing homes is identified or suspected, emergency clinicians should report to APS or the long-term care ombudsman in their state (www.ltcombudsman.org/) for further investigation.

Self-Neglect

Self-neglect includes behaviors in which an older adult threatens his/her own health or safety by failing to perform or refusing assistance with essential self-care. This may include malnutrition due to not eating, failure to take necessary medications, inattention to personal hygiene, hoarding, and not maintaining safe home environment. Often, patients with self-neglect suffer from an underlying mental disorder, including mild cognitive impairment, depression, psychosis, or substance abuse disorders that prevents them from understanding that their health and safety are at risk and that they need to seek assistance. Self-neglect is associated with increased mortality.[13]

Emergency clinicians frequently encounter patients who suffer from self-neglect, because it is the most common form of elder mistreatment reported to social services, with reports rising.[13] As with other types of elder mistreatment, recognition by an emergency clinician of this condition is critical, because many of these older adults have virtually no other contact outside the home. Prehospital personnel, who may note an empty refrigerator, expired pill bottles, or vermin infestation, are critical in identifying patients at risk.

DISPOSITION

Although evidence-based strategies for intervention have not been established, a reasonable approach for an emergency clinician includes laboratory assessment for metabolic and nutritional abnormalities and social work evaluation to offer resources and services. Many of these patients will require hospital admission, because it will be impossible to establish a safe discharge plan. If the patient refuses hospitalization, as is common, the clinician must determine whether the patient has the capacity to make this decision. A formal decision-making capacity evaluation by a psychiatrist may be helpful. In a patient with decision-making capacity, it is important to provide, whenever possible, education and resources as the patient leaves the ED. Also, when possible, contacting the patient's primary care physician and family members or friends who can check on the patient may help ensure safety.

KEY CONCEPTS

- Elder mistreatment, which includes physical abuse, sexual abuse, neglect, emotional/psychological abuse, abandonment, financial/material exploitation, and self-neglect, is common and may have serious medical and social consequences.
- Elder mistreatment is significantly under-recognized by emergency clinicians and under-reported to the authorities.
- Signs suggestive of potential elder abuse and neglect that should be recognized by emergency clinicians may exist in the medical history, physical examination, and medical/laboratory markers.
- Emergency clinicians should be vigilant in assessing for the possibility of elder abuse or neglect and routinely ask elderly patients about mistreatment, even in the absence of signs and symptoms.
- Emergency clinicians should hospitalize elderly patients who are in immediate danger or implement a care plan that prevents them from having any contact with the suspected abuser(s).
- Emergency clinicians must respect the wishes of an older adult with decision-making capacity who refuses interventions and desires to return to an abusive situation. If possible, the clinician should provide education and give information about available resources.
- The wishes of a competent elderly patient are required to be respected, even if the patient is not willing to accept interventions.
- Emergency clinician should always strongly consider reporting known or suspected cases of elder abuse or neglect to the authorities, and, in most states, emergency clinicians are mandated reporters.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 186: QUESTIONS & ANSWERS

186.1. A 70-year-old man who lives alone but has 12 hours per day of a home attendant is brought to the emergency department (ED) by his daughter, who found him in his caregiver's home with severe bruising. On examination, he had multiple bruises at varying stages of healing on the chest and arms, as well as a possible pattern injury—a bruise in the shape of a rectangle—across his left chest. What should you do?

A. Ask the daughter to make a report to adult protective services (APS), because she is the one who found him.
B. Contact the long-term care ombudsman.
C. Do not make a report because he has a long history of falls.
D. File a report with APS or law enforcement if your suspicion for abuse is high.
E. Interrogate the caregiver. If she denies abuse, do not report it.

Answer: D. The patient should be asked questions in a nonthreatening atmosphere, separate from the caregiver. If a clinician still has high suspicion, a report should be made to APS and/or law enforcement. The physician has the obligation to make the report. The long-term care ombudsman should be contacted only if the suspected abuse occurs in a facility, such as a nursing home.

186.2. A 72-year-old female is brought to the emergency department (ED) by paramedics for "not eating for 5 days" according to her family. The paramedics noted that she was covered in urine and feces and that the house was filthy, and she was found lying on the floor. On examination, she is noted to have a stage 4 pressure ulcer on her sacrum, which appears infected. Which of the following concerning for neglect?

A. Delay in seeking care
B. Evidence of dehydration
C. Poor hygiene
D. Pressure ulcer
E. All of the above

Answer: E. All of the above signs are potential markers for neglect.

186.3. A 69-year-old man with dementia presents to the emergency department (ED) with pneumonia and delirium. He is very confused, and his cognition is markedly worse than his baseline. You are called to the bedside because his adult daughter is at the bedside asking him to sign a legal form giving her the deed to his house. What should you do?

A. Perform an assessment of cognition and capacity and document it on the chart.
B. Request that the hospital lawyer and notary be present.
C. Tell her that there must be two witnesses present for the form to be legal.
D. Tell the daughter that if there are other children, they must be present for the form to be valid.
E. Tell the daughter that she must be the health care proxy for the form to be legally binding.

Answer: A. When an elderly patient has delirium or is confused because of another medical condition, he or she may lack the capacity to enter into a legal agreement or sign a legal document. The patient described is clearly too confused to understand all of the ramifications of signing his home over to another person. Confusion resulting from delirium or dementia is a risk factor for elder financial abuse.

186.4. An 85-year-old female with dementia, who lives in a skilled nursing facility, presents with bruises on her bilateral inner thighs. The facility staff states that she sustained these while being lifted from her bed to a chair. Who should you notify?

A. Adult protective services (APS)
B. Law enforcement
C. Sexual assault response team
D. The long-term care ombudsman
E. All of the above

Answer: E. The physical findings are concerning for sexual abuse. Therefore law enforcement and APS should be called, as well as the sexual assault response team to collect forensic evidence. Because the patient lives in a facility, the long-term care ombudsman should also be called to investigate the possible abuse.

CHAPTER 187

The Immunocompromised Patient

Michael J. Burns

PRINCIPLES

As greater numbers of immunocompromised persons present to the emergency department (ED), it is essential that emergency clinicians possess the knowledge and skills to recognize and treat infectious complications of cancer, organ transplantation, diabetes, renal failure, cirrhosis, asplenism, human immunodeficiency virus (HIV) infection, and other immunosuppressive conditions. These include infectious complications of immunosuppressive and immunomodulating medications used for a wide variety of disorders.

Compared with individuals with an intact immune system, infections in immunocompromised patients are more common, progressive, and severe, and they are caused by a wider variety of microorganisms. Immunocompromised persons who present with acute infections may appear deceptively benign initially. They may present with symptoms and signs that mimic noninfectious complications, only to deteriorate rapidly if they are not evaluated and treated urgently. Many interrelated factors cause patients to become immunocompromised and predispose them to the development of infections with potentially pathogenic microorganisms. These include disruption of the body's protective surfaces, such as skin and mucosal barriers (oral and respiratory mucosa and intestinal and genitourinary surfaces); disorders that directly impair the function of the body's immune system (eg, lymphoma, asplenism, and myeloma); drugs and irradiation that suppress or alter immune function; alterations in body substances (hyperglycemia) or solid organ function (kidney and liver failure); and malnutrition, aging, and exposure to antimicrobial agents that inhibit the normal protective resident bacterial flora.

Immunity and Immune Deficiency

The body's defense mechanisms consist of surface barriers, such as skin, enzymes, and mucus, as well as innate (natural) and acquired (adaptive) responses. Innate responses occur to the same extent regardless of how often the body encounters the infectious agent, whereas acquired responses improve on repeated exposure. Innate immunity is activated immediately on exposure to an infecting agent, rapidly controlling replication and allowing the requisite 3 to 5 days for the adaptive component to clone sufficient T and B cells to respond more specifically.[1]

Non–Microbe-Specific Immunity

Physical Barriers. Physical barriers, the first line of defense against microorganisms, consist of intact skin, gastrointestinal and respiratory mucosa, cilia, biofilm, gastric acid, antibacterial substances in pancreatic and biliary secretions, antimicrobial peptides and proteins on skin and mucous membranes, and resident microflora.[2] In the respiratory tract, mucociliary transport and the cough reflex remove particulate matter and microbes. This mechanism is impaired with smoking and pulmonary disease. Mechanical ventilation or tracheostomy introduces large numbers of microbes that often overwhelm natural clearance. Gastric acid and pancreatic enzymes have antibacterial properties that prevent overgrowth in the upper gastrointestinal tract. Normal peristalsis and mucosal shedding help maintain normal gut flora. Alterations in these factors increase susceptibility to infection. Broad-spectrum antibiotics alter normal flora, permitting overgrowth of pathogens, such as *Candida* species, multiantibiotic-resistant bacteria, and *Clostridium difficile.*

Initial Inflammatory Response and Innate Immunity. The intial inflammatory response to microbial invasion acts to promote phagocytosis and microbial killing and to activate the immune system. Sentry cells detect pathogens, immediately triggering inflammation. This innate immune response is not dependent on prior exposure to the pathogen. The initial inflammatory response factors, mainly produced in the liver, activate many cell types to synthesize and to release cytokines, chemokines, and "trigger molecules" that kill the invading organism.[1] This response delivers humoral and cellular immune components to sites of inflammation and initiates antibody responses. Cytokines, platelet-activating factor, and hormone-like proteins, including interferons, are secreted from various immune cells and play important roles in mediation of this response. Cytokines cause migration and adhesion of polymorphonuclear leukocytes and monocytes to sites of bacterial invasion. These cells release granules of substances that mediate vasodilation and increased vascular permeability, leading to edema, warmth, and redness, but also allow both phagocytic cells and humoral components to be concentrated at the site of infection.

A family of distinct transmembrane proteins, called *Toll-like receptors,* are found on many cell types, including macrophages, neutrophils, dendritic cells, mucosal epithelial cells, and endothelial cells. They recognize molecular patterns associated with microorganisms even in the absence of prior exposure, alert the host to the presence of the infectious agent and rapidly initiate a cascade of processes to activate innate immune responses, and help bridge innate and adaptive immune responses.[1,2]

Reticuloendothelial System. The reticuloendothelial system, composed of tissue macrophages and their blood-borne counterparts, monocytes, removes particulate matter, including microbes, from the lymph and blood. The tissue component is concentrated in the lymph nodes, spleen, liver, marrow, and lung and has particular affinity for encapsulated bacteria, such as

pneumococci, meningococci, and *Haemophilus influenzae*. The vital importance of this non–microbe-specific system is demonstrated by the overwhelming sepsis from encapsulated organisms in patients with asplenia.

Adaptive (Microbe-Specific) Immunity

Humoral Immunity

Antibodies. Antibodies are produced by B lymphocytes, and each B cell produces a single microbe-specific antibody type. Stimulation by an antigen (or microbe) causes proliferation of this particular B cell so that large quantities of a specific circulating antibody can be produced. Furthermore, B cells are active in presenting antigens to T lymphocytes, which promotes cell-mediated immunity (CMI).

Immunoglobulins. Immunoglobulin M (IgM) is the first immunoglobulin to appear in response to a new antigen. Although it has less affinity at binding antigens than immunoglobulin G (IgG) does, IgM provides some recognition of antigens and begins B-cell proliferation before the subsequent development of IgG.[3] IgM is detectable earlier in serum than IgG and serves as a marker for a patient's early response to acute infection.

Secretory immunoglobulin A (IgA) is the predominant immunoglobulin present in gastrointestinal fluids, nasal and oral secretions, tears, and other mucous fluids. IgA inhibits cell adherence of viral, bacterial, and protozoan pathogens and therefore prevents invasion by organisms through the respiratory or gastrointestinal tract.

Immunoglobulin E (IgE), which is expressed in high concentration on the surface of mast cells and basophils, is responsible for immediate-type hypersensitivity responses. Mast cells and IgE are important in defense against helminthic pathogens.

IgG, widely distributed in tissues, accounts for 75% of the total immunoglobulin mass. It crosses the placenta and provides fetal immunity during the first 6 months of life. Congenital or acquired deficiencies of IgG lead to infection with encapsulated organisms because the predominant subtype (IgG2) has affinity for the dense polysaccharides of bacterial cell capsules, such as those of *Streptococcus pneumoniae* and *H. influenzae*.

Complement. The complement cascade, a complex interaction of 30 proteins, is another crucial component of humoral response. Complement is important in producing inflammation and leukocytosis and in recruiting leukocytes to sites of infection by production of chemoattractants. Complement also neutralizes viruses, enhances opsonization of bacteria, and produces bacterial cell wall and membrane lysis.

Both IgG and IgM, when they are in contact with an antigen, activate the classical pathway, whereas molecules with repeating chemical structures (eg, bacterial cell walls and capsules) activate the cascade through the alternative pathway. Components of C3, the merging point of the classical and alternative paths, provide opsonization and modulate the response of lymphocytes (CMI). Opsonization is important in defense against infection with *S. pneumoniae, Streptococcus pyogenes, H. influenzae*, and *Staphylococcus aureus.* The terminal leg of the cascade, C5 through C9, forms the membrane attack complex, which inserts into cell walls and membranes and leads to cell death.

Individuals with inherited complement deficiencies are predisposed to frequent and recurrent infections with *S. pneumoniae, H. influenzae,* and especially *Neisseria meningitidis* and *Neisseria gonorrhoeae.* The risk of meningococcal infection is increased several thousandfold and most often develops in people deficient in C3 and in late complement components (C5 to C8). Paradoxically, the disease is usually milder with complement deficiency, and mortality is likewise reduced fivefold to tenfold. This suggests that the host response may be, in part, responsible for the severity of disease in normal individuals and is attenuated in complement deficiency. People with meningococcemia should be tested for inherited complement deficiencies, because they may benefit from immunization. Acquired deficiencies of complement function may develop in people with rheumatologic diseases, especially systemic lupus erythematosus (SLE). Approximately 40% of patients with SLE have an inhibitor of C5a-derived chemotaxis in their serum that results in enhanced susceptibility to infection.

Cell-Mediated Immunity. CMI includes immune responses that are mediated by T lymphocytes, natural killer (NK) cells, and mononuclear phagocytes. CMI is vitally important in the control of infections caused by microbes that survive and replicate intracellularly, including most viruses and some bacterial (obligate and facultative intracellular types), fungal, and protozoan pathogens.

Only 5% of lymphocytes are in circulating blood. Most mature and are active in the marrow, thymus, spleen, and lymph nodes. The last two sites expose T cells to circulating antigens from invading microbes.[2] Specialized antigen-presenting cells in the lymphoid system sequester antigen and antigen-antibody complexes and present them to T cells. This process involves internalization and processing of the antigen, followed by formation of peptides that bind to a cell surface molecule called the *major histocompatibility complex (MHC).* Only with this specific presentation can a T lymphocyte become activated against a particular antigen.

Two major types of T lymphocytes are CD4 (helper cell) and CD8 (suppressor cell), corresponding to type II and type I of MHC, respectively. CD4 lymphocytes provide help for other cells in the immune system, including enhanced B-cell antibody production and production of cytokines. CD8 lymphocytes are generally cytotoxic and mediate the eradication of virally infected target cells and certain tumors. A decline in the number of CD4 cells, with predominance of CD8 cells, is responsible for the increased susceptibility to infection in patients with acquired immunodeficiency syndrome (AIDS).[2] Despite the cytotoxicity of CD8 cells, immunity is reduced without adequate numbers of CD4 cells.

Patients with defects in CMI are at increased risk for disseminated infection with intracellular bacteria, such as *Mycobacterium tuberculosis, Listeria monocytogenes,* and *Salmonella* species. The DNA viral infections, such as cytomegalovirus, herpes simplex, and varicella-zoster, also affect these patients more severely, as do fungal infections with *Candida, Cryptococcus, Mucor, Aspergillus,* and *Pneumocystis*. Finally, some protozoa are pathogenic in patients without intact CMI, such as *Toxoplasma gondii*. Some infections are seen only below a certain CD4 cell count. *Pneumocystis* pneumonia, for example, is seen almost exclusively in patients with counts below 200 cells/mL (2×10^5 cells/L), whereas almost all patients with toxoplasmosis or cryptococcal meningitis have counts below 100 cells/mL (1×10^5 cells/L).

NK cells, closely related to lymphocytes but neither B nor T cells, are important in the innate immune response and are found in high concentrations in blood and spleen.[1,2] NK cells recognize infected cells and respond by directly killing these cells, and they secrete cytokines that activate macrophages to destroy phagocytosed microbes. NK cells are important in defense against intracellular microbes, particularly viruses and intracellular bacteria such as *L. monocytogenes*.

Granulocytic Phagocytes. Granulocytic phagocytes are the cellular effectors of microbe killing, engulfing them and enzymatically lysing their cell membranes or walls. Two major types are polymorphonuclear leukocytes (neutrophils) and macrophages (the tissue version of circulating monocytes). Macrophages have surface receptors that recognize nonvertebrate carbohydrates, such as mannose, which form the cell wall of some microorganisms. Hence, they can identify and attack "invaders" rather than "self."

Two other types of granulocytes, eosinophils and basophils, are less involved in the ingestion of organisms. Eosinophils mediate the destruction of certain parasitic helminths through release of toxic proteins. Normally only 3% of total granulocytes, this cell type can reach 20% during times of high parasite load. Basophils (rare in circulation) and their tissue counterparts, mast cells, have high affinity for IgE. On exposure to antigens, they release granules with histamine, prostaglandins, and leukotrienes, which affect the allergic-inflammatory response with increased vascular permeability, bronchospasm, and vasodilation.

Neutrophils constitute 90% of circulating granulocytes and spend only 6 to 8 hours of their average 4-day life in circulation (the remainder in tissues). Effective antibacterial activity depends on the ability of neutrophils to travel to sites of infection, a process known as *chemotaxis*. The locomotion of neutrophils along vascular endothelium is facilitated by adherence to cell surface proteins whose production is enhanced in the initial inflammatory response.

Half of all neutrophils that leave the bone marrow circulate in the plasma. The other half become marginated, adhering to endothelium, primarily in the lungs, liver, and spleen. During periods of stress or with endogenous or exogenous catecholamines or corticosteroids, these neutrophils demarginate and enter the circulation. As long as the patient is not neutropenic, demargination causes an increased peripheral neutrophil count composed of mature cells, whereas with bacterial infection, an increased proportion of immature (band) forms and is more typically seen.

Neutrophils (and macrophages in tissue) bind to and ingest bacteria through phagocytosis. This process is enhanced by proteins called *opsonins* that bind to bacterial surfaces. C-reactive protein, one of the initial inflammatory response proteins, fulfills this function for certain bacteria, including *S. pneumoniae*. IgG and complement protein C3b also opsonize bacteria, again illustrating the interdependence of the immune system. Actual killing takes place within granulocytes when cytoplasmic granules enzymatically produce potent oxidants. Granulocytes further control bacterial proliferation at the site of infection by elaborating lactoferrin, which locally binds free iron necessary for bacterial replication.

In addition to phagocytosis, macrophages (located in the spleen, alveoli, liver, and lymph nodes) modulate the immune response by presenting antigens to lymphocytes and releasing cytokines and complement components. Activation of macrophages to ingest bacteria depends on interaction with interferon-γ, a cytokine manufactured by T cells.[2] Thus the once clear demarcation between cellular and humoral immunity is breaking down as more is understood about the interdependent immune system.

SPECIFIC DISORDERS

Solid Organ Transplants

For specific issues regarding medication induced immunocompromised states in solid organ transplant patients, refer to Chapter 188.

Cancer

Patients with cancer frequently have multiple immune defects, such as neutropenia and impaired function of T and B cells, induced by cancer chemotherapy or by the disease process itself, which predisposes them to infection. Other factors leading to infection are defects in physical barriers (skin and mucous membranes), including cytotoxic effects of chemotherapy on cells lining the gastrointestinal tract. In addition, splenic dysfunction or splenectomy, use of long-term intravascular catheters, frequent use of complex invasive diagnostic and therapeutic procedures, toxic effects of radiation therapy, and frequent colonization with antimicrobial-resistant pathogens are predisposing factors to immune system compromise. Cancer treatments (eg, allogeneic bone marrow and autologous stem cell transplantation, platelet transfusion, granulocyte colony-stimulating factor) increase survival during episodes of profound immunosuppression, allowing patients to receive more intense cytotoxic cancer chemotherapy regimens. These therapies enhance long survival of patients with neoplastic diseases that were formerly rapidly fatal. Despite many advances in supportive care, infections continue to result in serious morbidity and mortality. Furthermore, increasing resistance to antimicrobials is occurring among common pathogens along with the emergence of new opportunistic pathogens. Infection is much more common in patients with acute leukemia and lymphoma (75% of patients) and multiple myeloma (50% of patients) than in those with solid tumors.[3] Immune system defects in the immunocompromised patient and the most common pathogens associated with each defect are listed in Box 187.1.

Neutropenia

Background

Neutropenia is defined as a neutrophil count of less than 500 cells/mL (5×10^5 cells/L), including band forms, or less than 1000 cells/mL (1×10^6 cells/L) and expected to fall to less than 500 cells/mL.[4] It usually results from cytotoxic chemotherapy or radiation therapy or the disease process, especially in hematologic malignant neoplasms. In addition, cancer chemotherapeutic agents and radiation therapy can cause functional defects in granulocytes. The risk of febrile neutropenia and mortality is higher in the first one or two cycles of multicycle cytotoxic chemotherapy regimens. In a large nationwide study in the United States of febrile neutropenia among patients with metastatic solid tumors, febrile neutropenia occurred in 13% to 20% of patients during their chemotherapy course with a mortality of 4% to 10%, depending upon cancer type, and most often occurred in the first chemotherapy cycle.[5]

The incidence and severity of infection in cancer patients with neutropenia are inversely proportional to the absolute neutrophil count and directly proportional to the duration of neutropenia. Although the incidence begins to rise as the neutrophil count falls below 500 cells/mL (5×10^5 cells/L), most severe infections and almost all bacteremias occur when the neutrophil count is less than 100 cells/mL. Fever in the neutropenic patient is defined as a single temperature of 38.3° C (101° F) or higher or a temperature of 38.0° C (100.4° F) or higher during 1 or 2 hours.[4] In neutropenic patients, the temperature should be measured orally or tympanically, not rectally. Although fever can be suppressed or lessened by immunosuppressive agents such as corticosteroids and nonsteroidal antiinflammatory drugs, most cancer patients with infection manifest fever despite the use of these agents. Also, although uncommon, immunocompromised patients can have serious local or systemic infections without fever. These infections may be manifested by unexplained tachypnea or tachycardia, mental status changes, metabolic acidosis, increased volume requirements, rapid changes in serum glucose or sodium concentration, or acute abdominal pain. Because the onset of life-threatening infections can be rapid in cancer patients with severe neutropenia or a history of splenectomy, urgent evaluation and initiation of antimicrobial therapy are essential. A prospective multicenter observational study of febrile neutropenic cancer patients in EDs in France found that high-risk critically ill patients were poorly recognized and undertreated, low-risk patients were overtreated, and compliance with established guidelines was low.[6]

BOX 187.1

The Immunocompromised Patient: Immune System Defects Predisposing to Infection and the Most Common Pathogens Associated With Each

NEUTROPENIA

Bacteria

Gram-negative bacilli
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Enterobacter* sp.
- *Serratia* sp.
- *Citrobacter* sp.
- *Proteus* sp.
- *Acinetobacter* sp.
- *Stenotrophomonas maltophilia*

Gram-positive cocci
- *Staphylococcus epidermidis*
- *Staphylococcus aureus* including methicillin-resistant strains
- *Viridans streptococci*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Enterococcus sp.,* including vancomycin-resistant strains

Gram-positive rods
- *Corynebacterium* sp.
- Less common: *Bacillus* sp.

Fungi

Candida sp.
Aspergillus sp.
Less common: *Mucor* sp., *Rhizopus* sp., *Trichosporon beigelii, Fusarium* sp., *Pseudallescheria boydii*

CELLULAR IMMUNE DYSFUNCTION

Bacteria

Listeria monocytogenes
Salmonella sp.
Mycobacterium tuberculosis
Mycobacterium avium-intracellulare
Legionella sp.
Nocardia sp.

Fungi

Cryptococcus neoformans
Histoplasma capsulatum
Coccidioides immitis
Candida sp.
Aspergillus sp.
Pneumocystis jiroveci (formerly *carinii*)

Viruses

Herpes simplex
Varicella zoster
Cytomegalovirus
Epstein-Barr
Less common: Measles, adenovirus

Parasites

Toxoplasma gondii
Cryptosporidium sp.
Strongyloides stercoralis

HUMORAL IMMUNE DYSFUNCTION (ANTIBODY DEFICIENCY)

Bacteria

S. pneumoniae
Haemophilus influenzae
Neisseria meningitidis
S. aureus

SPLENECTOMY OR FUNCTIONAL ASPLENIA

Bacteria

S. pneumoniae
H. influenzae
N. meningitidis
Capnocytophaga canimorsus
Bordetella holmesii

Parasites

Babesia sp.

COMPLEMENT DEFICIENCY

Bacteria

N. meningitidis
S. pneumoniae
H. influenzae

The most common sites of infection in neutropenic patients are the lung (25%); mouth and pharynx (25%); gastrointestinal tract (15%); skin, soft tissue, and intravascular catheters (15%); perineum and anorectal area (10%); urinary tract (5%); and nose and sinuses (5%). Pneumonia and anorectal infection are more likely to be associated with bacteremia. Bacteremia may occur without an obvious source despite intensive investigation. The most important bacteria producing infection in neutropenic patients are three gram-negative bacilli—*Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*—and four gram-positive cocci—*Staphylococcus epidermidis,* viridans group streptococci, *Enterococcus* species, and *S. aureus.* An increase in formerly uncommon gram-negative infections caused by *Enterobacter, Citrobacter,* and *Serratia* species has occurred, and infections caused by gram-negative organisms resistant to cephalosporins, extended-spectrum penicillins, and carbapenems are occurring more frequently. Anaerobes are uncommon but may be important in certain mixed infections (eg, mouth, abdominal, and perianal).

Infections caused by gram-positive organisms (eg, coagulase-negative staphylococci, *S. aureus,* viridans streptococci, and *Enterococcus* species) are now the leading cause of bacterial infection (50% to 70% at some centers) in febrile neutropenic cancer patients in the United States, Canada, and western Europe. Gram-negative organisms still predominate in developing countries. With the exception of viridans streptococci, most of these gram-positive organisms do not produce immediately life-threatening infections compared with the rapid lethality of many gram-negative infections. Life-threatening bloodstream infections caused by viridans streptococci (especially *Streptococcus mitis*), which can result in rapid development of a shock syndrome and/or acute respiratory distress syndrome, are now common in many cancer centers and often respond poorly to penicillins and cephalosporins. Risk factors for serious viridans streptococcal infections include aggressive cytoreduction therapy for acute leukemia or allogeneic bone marrow transplantation (especially after high-dose cytosine arabinoside treatment), profound neutropenia, and severe oral mucositis. Other factors include prophylactic use of

trimethoprim-sulfamethoxazole or fluoroquinolones, use of antacids or H_2 receptor antagonists, and childhood.[7]

Aspergillus and *Candida* species are the most common fungi producing infection in cancer patients with fever and neutropenia.[4] Infection is most likely to develop in neutropenic patients treated with broad-spectrum antimicrobials and in those whose fever persists for more than 7 days. *Aspergillus* species usually produce necrotizing infections in the lung or sinuses. Pulmonary aspergillosis often is manifested with pleuritic pain, hemoptysis, and localized wheezing. The chest radiograph demonstrates pleural effusion or focal infiltrates. Computed tomography (CT) is more sensitive in detection of pulmonary infiltrates compatible with aspergillosis, and it may demonstrate a distinct halo of low attenuation surrounding a pulmonary infiltrate. This pattern is highly suggestive of invasive aspergillosis, although mucormycosis and other disorders may mimic the halo. Invasive aspergillosis originating in the paranasal sinuses may extend to the surrounding bone and brain. Often, an initial red-purple lesion on the nasal turbinate or palate turns pale and then black as vascular invasion produces infarction of the mucosa and bone. The black eschar on the nose or palate is easily misdiagnosed as dried blood. Patients presenting with head or facial pain or swelling, or proptosis, should be rapidly evaluated for invasive aspergillosis and zygomycosis (formerly mucormycosis). *Candida* species produce infections of the skin, oral cavity, and esophagus, as well as fungemia. The sudden onset of generalized rash consisting of pink-purple, nontender subcutaneous nodules is characteristic of candidemia.

Less common fungi producing infection in these patients include *Mucor* and *Rhizopus* species (necrotizing pneumonia and sinusitis), *Trichosporon* species (pneumonia and fungemia), and *Pseudallescheria boydii* (soft tissue infection). Other than *Candida* species, these fungi are rarely found in blood cultures. Specific diagnosis requires biopsy.

Certain clinical findings are characteristic of specific pathogens (Table 187.1). Noninfectious causes of fever also need to be considered, such as drug toxicity, drug allergy, transfusion reactions, and pulmonary emboli.[3] Fever is frequently the only sign of infection, because these patients are unable to mount a full inflammatory response at a site of infection. Usual symptoms and signs of infection may not be present, especially when the neutrophil count is less than 100 cells/mL (1×10^5 cells/L). When pneumonia develops, purulent sputum may be absent, and the initial chest radiograph may not show an infiltrate but will be more likely found by CT scan. Pyuria may be absent in patients with urinary tract infection. Areas of cellulitis may have minimal induration and redness and little or no purulent drainage. Tenderness may be the only finding in perineal and anal infections. The neutropenic patient with a documented infectious cause of fever may be difficult to distinguish from the patient with fever not caused by infection. The neutropenic patient with a localized infection may have shaking chills and a toxic appearance, without localized findings, and may not have demonstrated bacteremia. Only 20% of febrile neutropenic patients have a clinical focus of infection identified at presentation, and only 30% of patients have positive blood cultures.

Mucositis involving the mouth and other mucous membranes is a painful and debilitating condition that commonly occurs in cancer patients receiving intense chemotherapy. It is a frequent prelude to viridans streptococcal bacteremia, which can produce sudden onset of acute respiratory distress syndrome, a toxic shock–like syndrome, rash, and pneumonia.

TABLE 187.1

Characteristic Clinical Findings in Neutropenia That May Be Associated With Infection With Specific Pathogens

CHARACTERISTIC CLINICAL FINDINGS	SUSPECT PATHOGENS
Ulcerative lesions in the mouth	Viridans streptococci, herpes simplex, *Candida,* anaerobes
Necrotizing skin lesions	*Pseudomonas aeruginosa, Aeromonas hydrophila, Aspergillus, Mucor*
Nontender subcutaneous nodules	*Nocardia, Cryptococcus*
Nontender pink skin papules	*Candida*
Black eschar of nose or palate	*Aspergillus, Mucor*
Generalized macular red rash	Viridans streptococci
Right lower quadrant abdominal pain, tenderness, distention, bloody diarrhea	Typhlitis (neutropenic enterocolitis) caused by *Pseudomonas aeruginosa, Escherichia coli, Clostridium septicum*
Perineal pain and tenderness without inflammation or abscess	Gram-negative bacilli, anaerobes
Redness or pain at vascular catheter sites	Coagulase-negative staphylococci, *Corynebacterium, Bacillus* species

Evaluation and Management

Box 187.2 describes a step-by-step approach to the evaluation and management of the adult patient with febrile neutropenia.

Antibiotic Therapy. Broad-spectrum antimicrobial therapy should be initiated promptly in the febrile neutropenic patient.[4] Moreover, even afebrile neutropenic patients who have symptoms and signs (eg, abdominal pain and tenderness) compatible with an infection should be treated empirically (Table 187.2).

Use of a single antimicrobial agent is preferred in most patients, because there is no conclusive evidence of a benefit from multiple drugs.[4,8] Antimicrobial resistance varies widely; and in the absence of a written hospital-specific protocol, immediate consultation with an oncologist or an infectious diseases specialist may be of great assistance.

Monotherapy with intravenous cefepime (favored at most cancer centers), meropenem, imipenem, or piperacillin-tazobactam is preferred, with an aminoglycoside (gentamicin, tobramycin, or amikacin) added for the more seriously ill patient.[4] Monotherapy, without an aminoglycoside, may be advantageous in the patient with mild to moderate renal dysfunction or for patients receiving nephrotoxic agents, such as cisplatin, cyclosporine, or amphotericin B. Empirical use of ceftazidime is not recommended.[8] None of these antimicrobial agents are active against vancomycin-resistant *Enterococcus* species or methicillin-resistant staphylococci.

For patients who are allergic to β-lactam antibiotics (eg, penicillins, cephalosporins, meropenem, and imipenem), coverage of gram-negative bacilli, including *P. aeruginosa,* can be provided by aztreonam. Because aztreonam is not active against gram-positive organisms, it should be combined with vancomycin. If anaerobes are suspected (ie, oral, abdominal, or perianal infection) in the β-lactam–allergic patient or in the patient receiving cefepime monotherapy, an antianaerobic drug (such as, clindamycin or metronidazole) should be administered. Empirical treatment with intravenous fluoroquinolones is not recommended in the febrile neutropenic cancer patient because of frequent prophylactic use of these agents in the cancer patient, risk for rapid emergence of

BOX 187.2

Evaluation and Management of the Adult Cancer Patient With Febrile Neutropenia in the Emergency Department

- Fever or history of fever is present, or patient has symptoms/signs of acute infection without fever.
- Complete blood count shows neutropenia (neutrophil count <500 cells/mL, including band forms, or <1000 cells/mL and expected to fall to <500 cells/mL).
- Careful monitoring of vital signs, including pulse oximetry; intravenous fluids as required.
- Obtain blood for measurement of electrolytes, renal and hepatic function, and serum lactic acid.
- Obtain blood cultures from each lumen of any existing central venous catheters and from at least one peripheral site, or two blood cultures from separate venipunctures of peripheral veins if no central venous catheter is present.
- Careful history and examination to search for subtle symptoms or signs of infection, with particular attention to the mouth, nose and sinuses, lower esophagus, lung, and skin, including nails, perineum including anus, bone marrow aspiration sites, and vascular catheter sites.
- Obtain chest radiograph if symptoms or signs of respiratory disease are present.
- Obtain urinalysis and urine culture if symptoms or signs of urinary tract infection are present.
- Obtain stool for culture for routine pathogens and PCR testing for *Clostridium difficile* if acute diarrhea or if acute abdominal pain without diarrhea is present.
- Obtain specimens for culture from any site of inflammation, including inflamed or draining catheter exit sites.
- If severe mucositis, obtain herpes simplex culture (or PCR testing) if not receiving antiherpes prophylaxis, and obtain smear (Gram stain) for *Candida* pseudohyphae.
- Lumbar puncture is not recommended as a routine procedure unless subtle symptoms or signs of meningitis are present.
- Consider ultrasonography over a subcutaneous tunneled catheter track and its vein of insertion, which may reveal the presence of an abscess or infected thrombus.
- Assess for risk of complications: High risk includes patients with hypotension, pneumonia, new onset abdominal pain, neurologic changes, or other acute organ dysfunction (especially renal or hepatic disease, or active COPD).
- Calculate the MASCC score if outpatient therapy is being considered in a stable patient.
- Initiate empirical intravenous antimicrobial monotherapy with an anti-pseudomonal beta-lactam agent (cefepime, meropenem, imipenem-cilastatin, or piperacillin-tazobactam) as soon as possible after cultures are obtained.
- Other antimicrobials (such as, an aminoglycoside and/or vancomycin) may be added for hypotension or pneumonia (ie, azithromycin) or if antimicrobial resistance is suspected.
- For suspected polymicrobial anaerobic infections (such as, intra-abdominal or perianal source), add an anaerobic drug (metronidazole or clindamycin) if cefepime is used as the beta-lactam agent.
- For patients with a minor penicillin allergy, empirical treatment with cefepime, meropenem or imipenem-cilastatin can usually be given safely.
- For patients with history of severe penicillin allergy, consult an infectious diseases specialist, or initiate empirical therapy with aztreonam and vancomycin, and add clindamycin or metronidazole if anaerobic infection is considered. Avoid empirical use of a fluoroquinolone as coverage for gram-negative bacilli in penicillin-allergic patients.
- Empirical use of vancomycin is not routinely indicated for all febrile neutropenic patients, but should be considered if there is suspicion for serious catheter-related infection; known colonization with MRSA or penicillin-resistant pneumococci; known isolation of a gram-positive organism before final identification and susceptibility is known; presence of shock; severe mucositis; prior fluoroquinolone prophylaxis; and institutions in which MRSA, vancomycin-susceptible enterococci, and *Streptococcus mitis* (viridans streptococcus group) are frequent pathogens.
- Empirical antifungal therapy is only rarely indicated in the ED and should not be initiated by the emergency clinician without consultation with an infectious diseases specialist.
- Urgent CT scanning may be indicated:
  - If the chest radiograph is normal or inconclusive in a patient with acute respiratory symptoms/signs, consider obtaining a high resolution CT scan of the chest without contrast enhancement.
  - If facial pain or swelling is present, consider obtaining a CT scan of the sinuses without contrast enhancement.
  - In patients with abdominal pain and tenderness, obtain a CT scan of the abdomen and pelvis with intravenous contrast.
- Administration of empirical antimicrobial therapy should not be delayed while waiting for CT scanning or other diagnostic testing (other than cultures) to be performed.
- Contact the patient's oncologist early in the evaluation of these patients.
- Do not initiate outpatient therapy in low-risk patients without contacting the patient's oncologist and/or an infectious diseases specialist.
- Patients being considered for early discharge and outpatient management should have a MASCC score ≥21 and have no other high risk features; and they should be observed for at least 4 hours after the initial antibiotic dose to monitor for stability. Low-risk patients may be monitored in an ED observation unit where they can be evaluated by an oncologist and/or infectious diseases specialist to determine whether early discharge to home is feasible. Avoiding an inpatient admission is advantageous for the stable low-risk patient because hospitalization exposes the patients to potential iatrogenic complications and antimicrobial-resistant nosocomial pathogens, and outpatient admission allows an improved quality of life.

COPD, Chronic obstructive pulmonary disease; *CT,* computed tomography; *ED,* emergency department; *MASCC,* Multinational Association for Supportive Care in Cancer; *MRSA,* methicillin-resistant *Staphylococcus aureus; PCR,* polymerase chain reaction.

Data from method of the author and Freifeld AG, Bow EJ, Sepkowitz KA, et al: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52(4):e56-93, 2011; Flowers CR, Seidenfeld J, Bow EJ, et al: Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 31(6):794-810, 2013; National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections, version 2. 2014. Available at: www.nccn.org/professionals/physician_gls/pdf/infections.pdf; Vidal L, Ben dor I, Paul M, Eliakim-Raz N, et al: Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. Cochrane Database Syst Rev (10):CD0023992, 2013; and Gea-Banacloche J, Segal BH: Infections in the cancer patient. In DeVita VT, Lawrence TS, Rosenberg SA, editors: DeVita, Hellman, and Rosenberg's cancer: principles and practice of oncology, ed 9, Philadelphia, 2011, Wolters Kluwer Health/Lippincott Williams & Wilkins, pp 2262-2299.

TABLE 187.2

Selected Antimicrobial Agents Useful in the Immunocompromised Patient

DRUG	DOSAGE		PRECAUTIONS AND COMMENTS
	ADULT	CHILD (AGE >28 DAYS)	
AMINOGLYCOSIDES			
Gentamicin or tobramycin	2 mg/kg loading dose, then 5 mg/kg/day IV every 8 to 12 hours, *or* 5 to 7 mg/kg IV once daily	Same as adult	Decrease maintenance dose in elderly or with renal dysfunction
Amikacin	10 mg/kg/day loading dose, then 15 mg/kg/day IV every 12 hours or once daily	Same as adult	Only active against aerobic gram-negative bacilli Some gram-negative bacilli may resistant to gentamicin and tobramycin
EXTENDED-SPECTRUM PENICILLINS AND β-LACTAMASE INHIBITORS			
Piperacillin-tazobactam	4.5 g IV every 6 hours	240 to 400 mg/kg/day IV every 6 hours	Broad activity against gram-positive organisms, *Pseudomonas aeroginosa,* and anaerobes
CEPHALOSPORINS			
Cefepime	1 to 2 g IV every 8 hours	150 mg/kg/day IV every 8 hours	Active against many gram-positive organisms, *P. aeruginosa* and many resistant gram-negative bacilli, but not anaerobes
CARBAPENEMS			
Imipenem-cilastatin	0.5 to 1 g IV every 6 hours	60 to 100 mg/kg/day IV every 6 hours	Adjust dose in elderly or with renal dysfunction
Meropenem	0.5 to 1 g IV every 8 hours	60 to 120 mg/kg/day IV every 8 hours	Seizures are associated with imipenem May be cross-allergenic with penicillin Broad-spectrum activity against gram-positive and gram-negative organisms, including *P. aeruginosa* and anaerobes
OTHER			
Aztreonam	1 to 2 g IV every 8 hours	120 mg/kg/day IV every 6 hours	Active against gram-negative bacilli including *P. aeruginosa* Not active against gram-positive organisms or anaerobes Safe in penicillin-allergic patient
Vancomycin	15 mg/kg IV every 12 hours	40 mg/kg/day IV every 6 to 12 hours	Infuse during 2 hours (flushing, hypotension with rapid infusion)
Amphotericin B	0.5 to 1.5 mg/kg/day IV once daily	Same as adult	Refer to infectious disease or pharmacology text
Acyclovir			Infuse during 1 hour
Herpes simplex, mucocutaneous*	5 mg/kg IV every 8 hours *or* 400 mg PO three times a day	250 mg/m^2 IV every 8 hours *or* 15 mg/kg/day PO every 4 hours	
Herpes zoster			
Not severe†	800 mg PO five times a day	20 mg/kg PO four times a day	
Severe	10 mg/kg IV every 8 hours	500 mg/m^2 IV every 8 hours	Elderly: 7.5 mg/kg IV every 8 hours
Primary varicella	10 mg/kg IV every 8 hours	500 mg/m^2 IV every 8 hours	

*Alternative for herpes simplex: valacyclovir 1 g two times a day PO.
†Alternative for herpes zoster: valacyclovir 1 g three times a day PO.
IV, Intravenous; *PO, per os* (by mouth).

resistance in gram-negative bacilli, and predisposition to *C. difficile* infection.[4]

When a focus of infection is identified, empirical therapy should cover the most likely pathogens causing infections at the site. Patients with pneumonia may need coverage for *Legionella* (azithromycin or a fluoroquinolone), *Pneumocystis* (trimethoprim-sulfamethoxazole), or fungi (amphotericin B) in addition to standard antibacterial coverage. Agents effective against anaerobes (clindamycin, metronidazole, meropenem, imipenem, or piperacillin-tazobactam) should be considered for patients with perianal or oral infection and those with abdominal pain, who may have appendicitis, diverticulitis, or typhlitis (neutropenic enterocolitis). Acyclovir should be considered for patients with ulcerative or vesicular lesions who may have herpes simplex or varicella-zoster virus infections. In patients with severe mucositis and febrile neutropenia, meropenen, imipenem, or piperacillin-tazobactam, often combined with vancomycin, is preferred for empirical treatment because of superior efficacy against viridans streptococci.[4]

"Routine" empirical use of vancomycin for all febrile neutropenic cancer patients is not recommended because of concern about the development of vancomycin-resistant organisms.[4,9]

Randomized clinical trials show no survival advantage when vancomycin is used as the initial therapy for neutropenic patients, even those with indwelling catheters. Because most infections with gram-positive bacteria are indolent, vancomycin therapy can be safely delayed for 24 to 48 hours in most patients until a vancomycin-requiring gram-positive infection is identified.

Indications for initial empirical vancomycin therapy include serious catheter-related infections, known colonization with penicillin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus* (MRSA), and positive blood culture for gram-positive organisms before final identification and susceptibility testing. Other indications include shock; severe mucositis; prior fluoroquinolone prophylaxis; and institutions in which MRSA, vancomycin-susceptible enterococci, and *S. mitis* are frequent pathogens.[4] Patients previously colonized or infected with MRSA, vancomycin-resistant enterococci, extended-spectrum β-lactamase–producing gram-negative bacteria, and carbapenemase-producing organisms may require modifications to initial empirical therapy.[4]

Amphotericin B (and its lipid formulations) is the drug of choice for treatment of invasive fungal infections in patients with neutropenia.[4,10] Up to one-third of febrile neutropenic patients not responding to 1 week of antibiotics have systemic fungal infections, usually *Candida* or *Aspergillus*. Antifungal agents (such as, caspofungin, voriconazole, or posaconazole) may be indicated in selected cases. Empirical use of fluconazole is not recommended because of lack of activity against *Aspergillus* and some *Candida* species.

Cell Stimulation Therapy. For prevention of chemotherapy-related neutropenia, some centers routinely use human recombinant hematopoietic or colony-stimulating growth factors (granulocyte colony-stimulating factor: filgrastim, pegfilgrastim; granulocyte-macrophage colony-stimulating factor: sargramostim) to stimulate the proliferation and maturation of bone marrow progenitor cells and to increase the number and function of these committed cell populations. They are safe and well tolerated but very expensive. Treatment with these agents after chemotherapy shortens the duration of neutropenia, may reduce the hospital stay and the duration of fever, and may reduce mortality in those at highest risk (elderly, comorbid conditons, multiorgan failure, recurrent febrile neutropenia), but current evidence does not support their use for all patients.[4,11]

Risk Assessment and Disposition

Febrile neutropenic cancer patients can be classified into high-risk and low-risk groups. Factors associated with high-risk include the following: status as inpatient when fever and neutropenia develop; presence of comorbid medical conditions; uncontrolled cancer; acute leukemia; hemodynamic instability; evidence of organ failure; presence of pneumonia, severe soft tissue infection, infection of a central line, abdominal pain, or neurologic or mental status abnormalities; and neutropenia expected to last more than 10 days. These patients should be treated in the hospital with intravenous antibiotics.

Outpatient empirical antibiotic therapy has been shown to be safe and efficacious in carefully selected febrile neutropenic adults who are not at high risk for medical complications.[4,12-14] The Multinational Association for Supportive Care in Cancer (MASCC) risk index score (available at www.mascc.org/mascc-fn-risk-index-score) is an easy to use, validated clinical prediction rule for classification of low risk adults (Table 187.3, Box 187.3) but should not be used as the sole factor to decide on low-risk status or outpatient management.[15] Three clinical practice guidelines, those of the Infectious Diseases Society of America, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network, as well as the Cochrane Database of Systematic Reviews, support outpatient or short-stay oral antibiotic therapy in carefully selected low-risk patients with neutropenic fever.[4,12-14] The only oral antibiotic regimen that is recommended is ciprofloxacin or levofloxacin *plus* amoxicillin-clavulanate (or *plus* clindamycin in penicillin-allergic patients).[4,12]

TABLE 187.3

Multinational Association for Supportive Care in Cancer Scoring System to Identify Patients With Cancer and Febrile Neutropenia at Low Risk of Medical Complications

CHARACTERISTIC	WEIGHT*,†,‡
Burden of febrile neutropenia with mild or no symptoms	5
No hypotension (systolic blood pressure >90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age younger than 60 years old	2

*Maximum score is 26. Higher score is better.
†Scores ≥21 indicate a low risk for medical complications.
‡Burden of febrile neutropenia: The general clinical status of the patient as influenced by the febrile neutropenic episode is evaluated on the following scale: No or mild symptoms (score of 5), moderate symptoms (score of 3), severe symptoms or moribund (score of 0). Choose only one score for burden of febrile neutropenia symptoms (5, 3, or 0).
Adapted from Flowers CR, Seidenfeld J, Bow EJ, et al: Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 31(6):794-810, 2013; Klastersky J, Paesmans M: The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer 21:1487-1495, 2013; and Multinational Association of Supportive Care in Cancer (MASCC): Identifying patients at low risk for FN complications: development and validation of the MASCC Risk Index Score. Available at: www.mascc.org/mascc-fn-risk-index-score.

Children With Cancer and Febrile Neutropenia

Box 187.4 lists unique considerations in the evaluation and management of children with cancer and febrile neutropenia.[16,17]

Non-Neutropenic Conditions in the Cancer Patient

The Solid Organ Cancer Patient Without Neutropenia

Most solid organ cancer patients who have fever and infection are not neutropenic. Infections in these patients may occur after surgical procedures and can include wound infection, deep abscess, or perforated viscus. Infections may be associated with central venous or urinary catheters, stents, and prosthetic devices. In addition, solid tumor patients with large tumor lesions may have obstructive infections (of bronchus, bile duct, or ureter). The spectrum of microorganisms includes a wide variety of community acquired organisms (bacterial, fungal, and viral), as well as nosocomial multiantibiotic-resistant pathogens.

Prompt initiation of antimicrobial therapy in the febrile non-neutropenic solid cancer patient is not always indicated. Rapid

BOX 187.3

Considerations for Outpatient Management of Cancer Patients With Febrile Neutropenia

Adult patients may be considered for outpatient therapy if:

- Patient should have a MASCC score ≥21.
- Patient is medically stable without acute or chronic organ dysfunction or comorbid conditions and does not have acute leukemia.
- No focus of infection identified: Patient does not have pneumonia, infection of a central line or a severe soft tissue infection, and does not have acute abdominal pain or an intra-abdominal infection.
- Patient has access to a telephone and transportation to return to hospital available 24 hours a day and has a caregiver at home.
- Patient has a history of compliance with follow-up and treatment protocols.
- Patient is not on fluoroquinolone prophylaxis and there is a low prevalence of fluoroquinolone-resistance in the community.
- Patient's oncologist agrees to outpatient management.
- The emergency clinician should contact the patient's oncologist and/or an infectious diseases specialist before considering outpatient therapy.

Patients being considered for outpatient therapy should be observed for at least 4 hours in the ED (or in an ED observation unit) after the initial antibiotic dose, which should be administered intravenously as soon as possible after initial cultures are obtained.

The only recommended outpatient oral antimicrobial therapy for these patients is ciprofloxacin or levofloxacin *plus* amoxicillin/clavulanate (or *plus* clindamycin for those with penicillin allergy).

ED, Emergency department; *MASCC,* Multinational Association for Supportive Care in Cancer.

BOX 187.4

Unique Considerations for Evaluation and Management of Children With Febrile Neutropenia and Cancer

- Because intravenous catheter infections are a common source of fever in children, obtain blood cultures from *all* lumens of indwelling central venous catheters.
- Obtain a peripheral vein blood culture if possible (may not be possible in small children).
- Obtain urinalysis and urine culture, because urinary tract infections are frequent causes of fever in neutropenic children.
- Obtain chest radiograph only in children with symptoms or signs of respiratory disease.
- Initiate monotherapy with an anti-pseudomonal beta-lactam or carbapenem as empirical therapy (cefepime, meropenem, imipenem-cilastatin, or piperacillin-tazobactam) as soon as cultures have been obtained. Avoid empirical use of ceftazidime monotherapy.
- Some low risk children with febrile neutropenia who have access to close follow-up may not require hospital admission and may be discharged home after a period of observation, but this should only be attempted after consultation with the patient's oncologist and/or an infectious diseases specialist.
- Transfer of the pediatric cancer patient with febrile neutropenia to a hospital experienced in the management of children with cancer is recommended.

Lehrnbecher T, Philips R, Alexander S, et al: Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol 30(35):4427-4438, 2012; Downes KJ, Zauotis TE, Shah SS: Guidelines for management of children with fever and neutropenia. J Pediatric Infect Dis Soc 2(3):281-285, 2013.

surgical intervention may be more important than the urgent initiation of empirical antibiotics. In febrile non-neutropenic cancer patients who are not ill-appearing and have no identified focus of infection, it may be appropriate to obtain culture specimens and to observe the patient. After consultation with an oncologist, some patients can be discharged home with close follow-up. Indications for urgent antibiotics include signs of sepsis, mental status changes, lactic acidosis, shock, abdominal pain, history of splenectomy, and identification of a focal site of infection.[18]

Impaired Cell-Mediated Immunity

The T-cell defects resulting from impaired CMI in cancer patients usually result from cancer chemotherapy or corticosteroid treatment. The cancer itself impairs CMI in patients with Hodgkin's disease, non-Hodgkin's lymphoma, and hairy cell leukemia.

Bacterial Infections. *L. monocytogenes* is one of the more common bacterial organisms infecting cancer patients with impaired CMI. *Listeria* infection is also seen in patients with organ transplants, diabetes, cirrhosis, AIDS, late pregnancy, and in those receiving high-dose corticosteroids or biologic therapies (infliximab and related drugs). No early characteristics distinguish *Listeria* infection from bacteremias caused by other organisms. Meningitis, which may be accompanied by cerebritis or brain abscess, is the most common focus of infection and may be manifested with personality changes or focal neurologic signs. Cerebrospinal fluid examination frequently does not reveal the organism on Gram's stain, but protein is elevated and pleocytosis is present. Treatment should be with ampicillin and gentamicin. Trimethoprim-sulfamethoxazole is the alternative drug for patients with penicillin allergy. Vancomycin is not effective in treatment of *Listeria* infections even when in vitro susceptibility is shown. Cephalosporins, such as ceftriaxone and cefotaxime, are not active against *Listeria*.

Infections caused by *Salmonella* species are common in patients with impaired CMI and usually are manifested with fever with or without enteritis. Bacteremia can result in infection of bones, joints, central nervous system, and endovascular devices.[19] Multidrug-resistant *Salmonella* species are increasing. Treatment usually includes a third-generation cephalosporin or a fluoroquinolone, because many isolates are resistant to ampicillin and trimethoprim-sulfamethoxazole.

Patients with solid tumors, lymphoma, and leukemia (especially hairy cell leukemia) are at increased risk for pneumonia from *Legionella* species, with the highest risk in cancer patients receiving high-dose corticosteroids. Non-*pneumophila* species of *Legionella* (eg, *Legionella micdadei* and *Legionella bozemanii*) are particularly common in these patients. Clinical and radiographic manifestations of *Legionella* infection in the immunocompromised patient often differ from those in the immunocompetent host.[20] For example, pleuritic chest pain may be a prominent symptom in the immunocompromised patient and may mimic pulmonary embolism. These patients can have fever without any other symptoms of pneumonia despite the presence of radiographic pulmonary infiltrates. In addition, the chest radiograph may reveal an expanding pulmonary nodule or cavitation of a nodule or infiltrate rather than the usual lower lobe alveolar filling defects. Hyponatremia (serum sodium <130 mEq/L [mmol/L]) is particularly common. Although gastrointestinal and neurologic symptoms and elevated serum transaminase levels are common in patients with *Legionella* infections, these are not more common in patients with *Legionella* than in those with other causes of pneumonia. The treatment of choice for immunocompromised patients with suspected *Legionella* infection is a respiratory fluoroquinolone or azithromycin.

Nocardiosis is an uncommon but often severe bacterial infection caused by a weakly acid-fast gram-positive branching filamentous rod. It occurs in cancer patients, in those receiving high-dose corticosteroids, and in others with defective CMI.[21,22] Subacute pneumonia with nodular infiltrates is the most common manifestation, usually without fever, but *Nocardia* may also produce cellulitis, subcutaneous abscesses, meningitis, and brain abscess. Diagnosis requires biopsy, tissue stains, and culture. Treatment is with sulfonamides often combined with other agents.

Mycobacterial Infections. Tuberculosis and other mycobacterial diseases may produce severe disease in those with defective CMI and be manifested as fever of undetermined origin, pneumonia, lymphadenopathy, or skin lesions. It is easily mistaken for signs caused by the patient's underlying disease or treatment. Disseminated nontuberculous mycobacterial infections are more common in patients with hairy cell leukemia or chronic myelogenous leukemia.

Fungal Infections. Infections with *Cryptococcus neoformans* and *Cryptococcus gattii* occur in patients with Hodgkin's and non-Hodgkin's lymphoma, chronic myelogenous leukemia, and chronic lymphocytic leukemia, especially those taking high-dose corticosteroids.[23] Patients with HIV infection, solid organ transplants, diabetes, renal insufficiency, and cirrhosis are also at risk, as are patients receiving prolonged high-dose corticosteroids for connective tissue diseases. Meningitis is the most common manifestation, often with the insidious onset of low-grade fever and subacute (and often intermittent) headache. Many other organ systems can become infected, including the lung, skin, bones, and joints. Diagnosis is made by measurement of cryptococcal antigen *(not antibody)* in serum and cerebrospinal fluid and by fungal cultures and tissue biopsy.

Impaired CMI may result in reactivation of *Histoplasma capsulatum* and *Coccidioides immitis* with resultant disseminated disease. Infections with *Candida* species are also common in cancer patients with defective CMI, but disseminated disease is less likely than in patients with neutropenia. Invasive aspergillosis may develop in cancer patients receiving high-dose corticosteroids but not as commonly as in those with organ transplants or prolonged neutropenia. *Pneumocystis jiroveci* (formerly *carinii*) pneumonia is most common in patients with AIDS, leukemia, and lymphoma and in patients with solid tumors taking high doses of corticosteroids.

Parasitic Infections. Reactivation of central nervous system infection with the protozoan *T. gondii* occurs most often in cancer patients with lymphoma and leukemia as well as in HIV infection. *Strongyloides stercoralis,* an intestinal nematode, is the only helminthic organism producing severe infection in patients with deficient CMI, almost exclusively in those receiving high-dose corticosteroids.[24] Larvae of the parasite disseminate from intestine to lung and other organs, including central nervous system and skin, causing the *Strongyloides* hyperinfection syndrome, with very high mortality. Wheezing, cough, dyspnea, hemoptysis, and hemorrhagic rash are common. Chest radiographs may show focal or diffuse infiltrates. Dissemination is often accompanied by bacterial infection, usually caused by enteric gram-negative bacilli carried by the parasites from the intestinal tract. Diagnosis is made by examination of stool, sputum, tissue or fluid (obtained by bronchoscopy or endoscopy), or cerebrospinal fluid for larvae of the parasite. The treatment of choice is oral ivermectin.

Viral Infections. The most common viruses producing serious infections in cancer patients with defective CMI are varicella-zoster, herpes simplex, and cytomegalovirus. Visceral dissemination is common in primary varicella (chicken pox) in nonimmune immunocompromised children and adults, with development of pneumonia, encephalitis, hepatitis, and hemorrhagic lesions.[25] When a nonimmune immunocompromised child or adult is exposed to varicella, varicella-zoster immune globulin (VariZIG in the United States) should be administered as soon as possible after exposure, up to 10 days postexposure, to ameliorate the disease.[26] Herpes zoster infection is common in cancer patients, particularly those with Hodgkin's and non-Hodgkin's lymphoma and leukemia. Disease usually remains localized to the primary dermatome, but dissemination occurs in approximately 11% of patients. Dissemination is usually limited to the skin, but visceral involvement (lung and liver) occasionally occurs. Skin lesions in primary varicella or zoster often become hemorrhagic in these patients.

Reactivation of herpes simplex virus is common, resulting in severe mucocutaneous infection in oral or genital areas. Spread may occur to the esophagus, lungs, or other organs. Herpetic lesions in cancer patients tend to be larger and deeper than those in the immunocompetent patient. Acyclovir given intravenously is the treatment of choice for varicella-zoster and herpes simplex infections in immunocompromised patients, but some stable patients may be treated with oral valacyclovir.

Cytomegalovirus infection may occur in cancer patients treated with corticosteroids. Measles virus, although uncommon, may produce severe infection in those with defective CMI. Fever, rash, pneumonia, and encephalitis are common manifestations. Immune serum globulin may be given after exposure to ameliorate disease. Common community respiratory viruses, such as respiratory syncytial virus, influenza, and adenovirus, may produce severe or fatal pneumonia.

Humoral Immune (B-Cell) Defects

Hypogammaglobulinemia is common in patients with chronic lymphocytic leukemia and myeloma. Low immunoglobulin levels predispose to infections with encapsulated bacteria, such as *S. pneumoniae, H. influenzae,* and *N. meningitidis.*[27] Pneumonia is the most common manifestation, but sepsis, otitis media, cellulitis, and urinary tract infection may occur. After receiving cytotoxic agents and corticosteroids for treatment, these patients become susceptible to infections associated with impaired CMI, as well as bacterial infections caused by *S. aureus* and gram-negative bacilli, often with high mortality. Regular infusions of intravenous immune globulin may decrease the incidence of infection but do not prolong survival. Patients should receive pneumococcal vaccine, but many do not respond.

Disruption of Natural Barriers

Disruption of natural anatomic barriers (eg, mucous membranes and skin) by ulcerating tumors, chemotherapy, radiation therapy, diagnostic and therapeutic procedures, and catheters can lead to infection by gram-positive and gram-negative organisms, including anaerobes. Oral mucositis, a debilitating and intensely painful condition associated with radiation therapy and high-dose chemotherapy, frequently results in serious local and systemic infections, including life-threatening sepsis with viridans streptococci.[28] Cancers may cause partial or total obstruction of body lumens and cavities, as does swelling and scarring from radiation therapy. Bronchial obstruction by tumor can lead to pneumonia. Obstruction of the urinary tract may result in infection. Gastrointestinal tract obstruction can lead to perforation and peritonitis.

Opportunistic Infections Mimicking Neoplasm

Infectious agents can produce laboratory, radiologic, or physical findings that resemble those caused by the spread of tumor. For

example, mass lesions in the brain caused by *Nocardia* or *Toxoplasma* can be mistaken for cancer metastases. *Aspergillus, Mucor, Rhizopus,* and related fungi invade blood vessel walls and produce thrombosis, which may result in Budd-Chiari syndrome (hepatic vein obstruction), nephrotic syndrome, or oculomotor palsy that may be misattributed to the spread of tumor. Renal vein thrombosis can be caused by infection with gram-negative bacilli. *Candida* fungus balls may develop in one or both ureters, producing a picture of postrenal obstructive uropathy. *Histoplasma, Pneumocystis, Legionella, Aspergillus, Nocardia,* and other organisms can produce pulmonary nodules and be mistaken for pulmonary metastases.

Pulmonary Infections in the Immunocompromised Patient

In neutropenic cancer patients, pneumonia is commonly caused by gram-negative bacilli early in neutropenia and by fungal organisms such as *Aspergillus* after prolonged neutropenia. In those with impaired CMI, cytomegalovirus, *Pneumocystis, Legionella, Nocardia,* mycobacteria, and fungal organisms predominate. Pneumococcal pneumonia is most common in patients with impaired humoral immunity. Patients with primary lung cancer or with pulmonary metastases from other cancers may develop postobstructive pneumonia, lung abscess, and empyema related to *S. aureus,* gram-negative bacilli, and anaerobes. Conditions mimiking pneumonia in the immunocompromised host include pulmonary emboli and infarction, congestive heart failure, metastatic or primary carcinoma, lymphangitic spread of carcinoma, alveolar hemorrhage, leukoagglutinin reactions, and radiation- and drug-induced pneumonitis. An acute presentation of "pneumonia" suggests bacterial pneumonia, pulmonary emboli, congestive heart failure, or pulmonary hemorrhage. Subacute presentations may suggest a fungal, nocardial, mycobacterial, or viral etiology (Table 187.4).

TABLE 187.4

Pulmonary Infiltrates in the Immunocompromised Patient: Common Patterns of Disease and Differential Diagnosis

DIFFUSE BILATERAL INFILTRATES	FOCAL OR PATCHY INFILTRATES
Viruses Cytomegalovirus Respiratory syncytial virus Influenza, parainfluenza Adenovirus Varicella	Bacterial pneumonias, including *Legionella* Fungi Invasive pulmonary aspergillosis Zygomycosis (mucormycosis) *Fusarium* *Pseudallescheria*
Pneumocystis jiroveci	Tuberculosis
Fluid overload and pulmonary edema	Nontuberculous mycobacteria
Acute lung injury due to transfusion of blood products	Nocardiosis Pulmonary embolus
Radiation damage	
Chemotherapy-induced toxicity	
Acute respiratory distress syndrome due to viridans streptococcal bacteremia	
Bronchiolitis obliterans	
Pulmonary hemorrhage	
Progression of disease (lymphangitic spread of carcinoma, leukemic infiltrates)	

Diabetes

Diabetic patients have increased susceptibility to infection because of defects in immune function, excess substrate for fungal and bacterial growth, vascular insufficiency related to microangiopathy and atherosclerosis, and sensory neuropathy that leads to wound neglect. Neutrophil and monocyte-macrophage functions are also impaired in diabetic patients, including adherence to bacteria, chemotaxis, neutrophil degranulation, phagocytosis, and intracellular killing. These defects are exacerbated by hyperglycemia and improved by tight glucose control. Hyperglycemia disrupts C-type lectin function, which is an essential component of the immune system's response to microbial invasion.[29] Although decreased lymphocyte proliferative responses to phytohemagglutinin and certain pathogens are described, cellular immunity appears normal or only minimally affected by diabetes. Humoral immunity is normal in diabetics.

Infections seen with increased frequency in diabetic patients include rhinocerebral zygomycosis (formerly mucormycosis) caused by *Rhizopus* and *Mucor* species; malignant (or necrotizing) otitis externa caused by *P. aeruginosa;* pneumonia caused by *S. aureus* and gram-negative bacilli; tuberculosis, emphysematous cholecystitis, and urinary tract infections including emphysematous cystitis and pyelonephritis; polymicrobial necrotizing fasciitis involving the perineum (Fournier's gangrene) and lower extremities; and psoas abscess, spinal epidural abscess, foot infections with osteomyelitis, and postoperative surgical site infections. Diabetics who inject insulin are frequently colonized in the nares and skin with *S. aureus* that may predispose to skin infections with transient bacteremia, which can seed distant sites. Women diabetics with hyperglycemia are predisposed to vulvovaginal candidiasis. Diabetics are not more likely to have pneumococcal pneumonia but are more likely to become bacteremic and to have a higher mortality rate.

Alcoholism and Cirrhosis

Alcohol consumption predisposes to infection through direct suppression of the immune system, alterations in blood flow, depression of mental status, and delay in seeking medical care. With alcoholic cirrhosis, there is deficient hepatic clearance and killing of bacteria by reticuloendothelial cells, as well as splenic hypofunction. Complement deficiency occurs because the liver is the primary site of C3 synthesis. Neutrophils show impaired recruitment to infective sites and defective chemotaxis and phagocytosis. Cellular immune deficiency occurs and is exacerbated by malnutrition. Bactericidal activity of IgM antibody against gram-negative pathogens such as *E. coli* and *H. influenzae* is decreased.

Acute ethanol intoxication is associated with granulocytopenia and diminished leukocyte mobilization that is reversible with abstinence. Ethanol intoxication interferes with most respiratory tract defense mechanisms, resulting in alterations of normal flora, impaired mechanical and cellular clearance because of a suppressed cough reflex, decreased ciliary motility, and resultant aspiration. These effects are often compounded by malnutrition, cigarette smoking, and chronic lung disease. Alcoholics exhibit an increased incidence of oropharyngeal colonization by gram-negative bacteria (35% to 59% of ambulatory alcoholic patients) compared with control subjects (14% to 18%). Alcoholics are also more likely to aspirate because of loss of reflex glottic closure associated with acute intoxication, withdrawal seizures, and encephalopathy.

Common infections in patients with cirrhosis include spontaneous bacteremia and sepsis caused by *E. coli, K. pneumoniae, Salmonella,* streptococci, *Vibrio vulnificus,* and *Aeromonas;* spontaneous bacterial peritonitis, usually caused by *E. coli, K. pneumoniae, S. pneumoniae,* or enterococci; pneumonia related to pneumococci, gram-negative bacilli *(E. coli, K. pneumoniae,* and *H. influenzae),* and anaerobes; tuberculosis; meningitis caused by *S. pneumoniae* and *L. monocytogenes;* and skin and soft tissue infections with *S. aureus,* streptococci, and gram-negative bacilli. Nasopharyngeal and cutaneous diphtheria also occurs. Cirrhotic patients who present to the ED after a recent prior hospitalization often have health care–associated infections including catheter-related and *C. difficile* infections, spontaneous bacteremia, urinary tract infections, and pneumonia, often with high mortality.[30]

Renal Failure

Infections are a major cause of death in patients with chronic renal failure and are the second most common cause of mortality after coronary artery disease. These patients are often diabetic, which increases their risk for serious morbidity and mortality from infections. Disruption of cutaneous barriers at vascular access sites and peritoneal dialysis catheter sites and numerous immune system defects are responsible for the increased incidence of infection. Uremic pruritus with excoriation, epidermal and sweat gland atrophy, dryness, and vesicular eruptions also compromise the cutaneous barrier. Reduced renal clearance of unknown toxins, nutritional deficiencies, and administration of immunosuppressive medications lead to aberrant immune regulation early in the course of renal failure.

Chronic kidney failure leads to a state of generalized immune hyporesponsiveness. Neutrophils show reduced mobility, chemotaxis, adherence, phagocytosis, and intracellular bactericidal activity, and leukopenia is commonly present. CMI is severely impaired, with decreased activation and proliferation of T lymphocytes and reduced NK cell activity, which cannot be reversed by hemodialysis. Furthermore, humoral immunity is adversely affected, resulting in deficient production of certain IgG subclass antibodies. Poor response to vaccines is common but can be improved by reinforced vaccination schedules, increased vaccine dosage, and adjunct immunomodulators. Additional predisposing factors to infection in uremic patients include low serum albumin, iron overload, increased intracellular calcium, circulating low-molecular-weight uremic toxins, metabolic acidosis, circulating inhibitors to chemotactic factors, decreased production of endogenous pyrogens, and invasive vascular procedures for dialysis access.

Severe infections with antibiotic-resistant bacteria (health care–associated infections) are common, and empirical therapy for a suspected serious infection should include broad-spectrum antimicrobials active against MRSA and antibiotic-resistant gram-negative bacilli. Skin and soft tissue infections, especially those caused by *S. aureus,* are particularly severe in diabetics and in those with peripheral vascular disease or peripheral neuropathy. Vascular access site infections are usually caused by *S. aureus* but occasionally by gram-negative bacilli and enterococci. Patients using central venous catheters for dialysis have much higher rates of sepsis compared with fistulas or grafts. Infections of dialysis access sites, often due to *S. aureus,* are life threatening and frequently associated with hematogeneous seeding of infection to distant sites, including osteomyelitis (usually involving the ribs or thoracic vertebrae), endocarditis, meningitis, epidural abscess, and septic arthritis. Pneumonia may be severe, and there is an increased incidence of *Legionella* pneumonia. Pneumonia may be difficult to diagnose by chest radiograph in these patients due to changing pulmonary fluid dynamics. Because mortality is high, early antimicrobial treatment should be administered if acute pneumonia is being considered after appropriate cultures have been obtained, with consideration of antimicrobial coverage for health care–associated pathogens. Tuberculosis and fungal infections caused by *Candida* species, *Cryptococcus, Histoplasma,* and *Coccidioides* occur with increased frequency. Diagnosis of tuberculosis may be difficult because of nonspecific symptoms and increased incidence of extrapulmonary disease.[31] In addition, *C. difficile* infection occurs more frequently and is more severe with high mortality.[32] Infections of the urinary tract are more prevalent, with urinary bladder catheterization the most frequent predisposing factor. There is a poor correlation between the presence of pyuria and urinary tract infection in these patients. *Candida* infection of the urinary tract may develop in patients with chronic renal failure treated with broad-spectrum antibiotics.

Up to two-thirds of patients receiving chronic peritoneal dialysis have peritonitis in their first year, and one-third may be forced to discontinue dialysis because of recurrent infections. *S. aureus* and *S. epidermidis* predominate, followed by streptococci, gram-negative bacilli, and *Candida* species. Fortunately, peritoneal dialysis patients have much lower rates of sepsis than those on hemodialysis.

Splenectomy, Hyposplenia, and Functional Asplenia

The spleen is the most important organ in the reticuloendothelial system and is the primary site for IgM synthesis, which is the first early immune response of the body. Opsonin production in the spleen facilitates phagocytosis of bacteria by intracellular macrophages. Patients without a spleen also have decreased production of neutrophils, NK cells, and immunomodulating cytokines.

The spleen is the principal site of clearance of *S. pneumoniae* from the blood. Splenectomy or functional asplenia predisposes to overwhelming pneumococcal infection and fulminant infection with other encapsulated organisms (*H. influenzae, N. meningitidis,* and *Capnocytophaga canimorsus* after dog bites) and gram-negative bacilli *(E. coli* and *P. aeruginosa).*[33,34] Asplenic patients who become infected with *Babesia microti,* a malaria-like protozoan transmitted by tick bite in the United States, may develop severe and often fatal hemolysis. Human granulocytic anaplasmosis (formerly ehrlichiosis), another tick-borne infection, is severe and sometimes fatal in asplenic patients. In addition, the gram-negative coccobacillus *Bordetella holmesii* produces a non–life-threatening acute febrile illness with bacteremia in patients with asplenia. Pneumococcal sepsis represents 50% to 90% of cases. Most healthy adults who die after fulminating pneumococcal sepsis have had a splenectomy or have a congenitally small or abnormal spleen.

The incidence of overwhelming postsplenectomy sepsis in these patients is low; but when it occurs, the mortality rate is high—especially in children with hematological disorders.[35] The risk is greater in children than in adults, with children younger than 2 years old at greatest risk. The risk is highest in the first few years after splenectomy but persists throughout life into old age. People undergoing splenectomy for a hematologic disorder or lymphoma are at much higher risk for overwhelming postsplenectomy infection than are those undergoing splenectomy for trauma. This is probably because of the occurrence of splenic implants (splenosis) or accessory spleens in traumatized patients. Patients with functional asplenia from sickle cell anemia or thalassemia major are at high risk for overwhelming bacterial infections as well.

Functional hyposplenism occurs in a variety of conditions besides sickle cell disease, including sickle cell–hemoglobin C disease, ulcerative colitis, celiac disease, sarcoidosis, amyloidosis, rheumatoid arthritis, and SLE. The presence of anatomic or functional hyposplenism may be recognized by the finding

of Howell-Jolly bodies in red blood cells on a peripheral blood smear.

When overwhelming postsplenectomy infection occurs, often no obvious source of infection is found. Prodromal symptoms (such as, fever, rigors, malaise, myalgias, headache, vomiting, and diarrhea) may be present for 1 or 2 days. Patients seen at this time may be misdiagnosed as having a viral illness, gastroenteritis, or food poisoning. Abrupt deterioration then occurs over hours, with rapid progression to septic shock with disseminated intravascular coagulation, purpura, and multiorgan dysfunction. The mortality rate is high (50% to 70%), with younger children having the highest mortality rate. In addition, meningitis without overwhelming infection or shock is a common presentation of pneumococcal infection in asplenic patients. When fever develops in a person at risk for this disorder, treatment with an antimicrobial agent effective against *S. pneumoniae* should be initiated without delay. After blood culture is performed, adults and children should receive ceftriaxone or cefotaxime at meningitis doses, with addition of vancomycin in areas where penicillin resistance is prevalent. Clindamycin, levofloxacin, or moxifloxacin are alternatives for patients with serious penicillin allergy. Children with a history of serious penicillin allergy should receive vancomycin plus levofloxacin.

Use of pneumococcal vaccine in patients at risk is especially important now that antimicrobial-resistant *S. pneumoniae* is prevalent, but the efficacy of this vaccine in these patients is unclear. Persons with functional hyposplenism related to serious underlying diseases often respond poorly to pneumococcal vaccine. Asplenic people should be immunized against pneumococcus, *H. influenzae* type b, *N. meningitidis,* and influenza virus. Children should receive prophylaxis with oral penicillin or amoxicillin up to the age of 5 years and for at least 1 or 2 years after splenectomy (but this is not evidence-based), provided they have not had an invasive pneumococcal infection and have received pneumococcal immunizations. Long-term antimicrobial prophylaxis is generally not recommended in adults. These patients should have standby oral antibiotics at home (amoxicillin-clavulanate, levofloxacin, or moxifloxacin) with instructions to self-administer at the first sign of infection, and they should be provided with information and a medical alert bracelet. Fatal pneumococcal infection has occurred in patients immunized with pneumococcal vaccine who were also taking penicillin.

IMMUNOSUPPRESSIVE THERAPY

Corticosteroids

High doses of corticosteroids alter the distribution and function of neutrophils, monocytes, and lymphocytes. Corticosteroids suppress inflammation and enhance susceptibility to infection by impairing the mobilization and function of neutrophils and mononuclear cells at sites of primary lodgment of microorganisms in tissues. Corticosteroids inhibit neutrophil adherence to endothelium, decrease chemotaxis of neutrophils and monocytes, and inhibit phagocytosis and intracellular killing of microorganisms. Corticosteroids also severely impair CMI, probably a result of inhibition of the migration of lymphocytes to the site of antigen challenge, inhibition of lymphokine production, and consequent inhibition of lymphocyte proliferation. They also inhibit both classical and alternative pathways of complement activation. The hyperglycemia that occurs with corticosteroid use also contributes significantly to infection risk. Moreover, patients receiving high-dose corticosteroids have infection risks related to anatomic abnormalities of the underlying disease, treatment with other immunosuppressive agents, cancer chemotherapeutic agents, radiation therapy, and implantation of foreign bodies.

Acute administration of corticosteroids produces marked alterations in circulating leukocyte numbers. Basophils, eosinophils, and monocytes decrease, whereas neutrophils are increased. These changes occur within 4 to 6 hours and abate by 24 to 48 hours after a single steroid dose. There is a redistribution of lymphocytes, predominantly T cells, out of the circulation, resulting in lymphocytopenia. Acute or chronic corticosteroid therapy has little effect on serum immunoglobulin levels.

The most common infections occurring in patients receiving high-dose corticosteroids are those caused by pyogenic bacteria (*S. aureus,* streptococci, and gram-negative bacilli). Despite the profound depression of CMI that occurs in patients taking corticosteroids, these patients generally have few infections commonly recognized as associated with defective CMI. The most common are tuberculosis and severe or disseminated infections caused by varicella-zoster and herpes simplex viruses. Patients receiving moderate doses of corticosteroids for asthma and other disorders are at increased risk for lethal primary varicella infection. Other infections seen with corticosteroid use include those caused by *Listeria, Salmonella, Legionella, Nocardia, Candida, Aspergillus, Cryptococcus, Histoplasma, Coccidioides, Pneumocystis, Toxoplasma, Cryptosporidium,* and *Strongyloides*. Patients with neurologic diseases have much higher rates of infectious complications than do patients with intestinal, hepatic, or renal disease. The infectious complications related to corticosteroid use increase with doses of prednisone equivalents of more than 20 mg/day in adults, with total doses of more than 700 mg, and with treatment longer than 30 days. The risk of adrenal suppression can be decreased by use of prednisone doses less than 7.5 mg/day, administration of doses early in the day, avoidance of split doses, and use of alternate-day dosing.

Corticosteroids decrease leukocyte accumulation at inflammatory sites, and the whole cascade of responses leading to local manifestations of infection is slowed. These effects result in delayed presentation of serious infections. In addition, prolonged administration of corticosteroids results in delayed wound healing. For example, skin sutures should be left in place 50% to 100% longer than in normal patients. Short-term treatment has little effect on wound healing.

Use of corticosteroids greatly increases the risk of hospital admission for complications of diverticular disease.[36] The diagnosis of peritonitis resulting from perforation of colonic diverticula, appendicitis, peptic ulcer, or another primary intra-abdominal condition is particularly difficult. These patients have abdominal discomfort, but they may have few abdominal findings and need rapid investigation for life-threatening abdominal disease. CT scan of the abdomen and pelvis and surgical consultation may be needed emergently in these patients. Broad-spectrum antimicrobials to cover for gram-negative enteric bacilli and anaerobes should be administered without delay.

Other complications unrelated to the effects on the immune system include iatrogenic Cushing's syndrome, peptic ulcer disease, pancreatitis, benign intracranial hypertension (pseudotumor cerebri), psychosis, glaucoma, posterior subcapsular cataract, poor wound healing, sodium retention, hypertension, vascular thrombosis, hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state, avascular necrosis of bone (especially the femoral and humoral heads), myopathy, and osteoporosis, resulting in vertebral compression fractures and other spontaneous fractures. In addition, adrenocortical insufficiency may occur on withdrawal of therapy.

Other Immunosuppressive Medications

Commonly used immunosuppressives include cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine, methotrexate, and cyclophosphamide. They treat a wide variety of conditions,

including rheumatoid arthritis, psoriasis, nephrotic syndrome, and inflammatory bowel disease, and they are used in the prevention and treatment of organ transplant rejection. These drugs depress immune function, especially CMI. In addition, they have a narrow therapeutic window, wide-ranging toxic side effects, and many significant drug-drug and drug-food interactions. Patients may present for evaluation of symptoms caused by an adverse drug reaction or an infection. Before altering current medications, the physician needs to check carefully for drug interactions.

Immunomodulating agents are available for treatment of a variety of immune-mediated inflammatory diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease. Some of these drugs include inhibitors of tumor necrosis factor alpha (infliximab, adalimumab, certolizumab, golimumab, etanercept), inhibitors of interleukins (tocilizumab, anakinra), inhibitor of pyrimidine synthesis (leflunomide), and inhibitor of T-cell activation (abatacept). These agents, particularly the tumor necrosis factor inhibitors, are associated with increased susceptibility to infection, particularly disseminated infection with various intracellular pathogens.[37,38] Reactivation of latent infection with *M. tuberculosis*, nontuberculous mycobacterial infection, histoplasmosis, and coccidioidomycosis is frequently disseminated and extrapulmonary at presentation. Additional infections seen at increased frequency include cryptococcosis, listeriosis, legionellosis, salmonellosis, aspergillosis, candidiasis, and pneumocytosis. The clinician should be alert to unusual manifestations of infection in patients taking these agents as misdiagnosis and delayed diagnosis increase mortality. These drugs may also cause impaired wound healing, so skin sutures should be left in place for a longer time than is usual.

KEY CONCEPTS

- Immunocompromised persons who present with acute infections, especially those that are neutropenic, may appear deceptively benign initially, their symptoms and signs often mimicking noninfectious complications, only to deteriorate rapidly if they are not evaluated and treated urgently. Early use of broad-spectrum antibiotics is indicated after obtaining appropriate cultures of all potential sites of infection, including intravascular catheters.
- Immunocompromised patients can have serious local or systemic infections without fever, which may be manifested by unexplained tachypnea or tachycardia, mental status changes, metabolic acidosis, increased volume requirements, rapid changes in serum glucose or sodium concentration, or acute abdominal pain.
- In neutropenic cancer patients, most severe infections and almost all instances of bacteremia occur when the neutrophil count is less than 100 cells/mL.
- In neutropenic patients, the temperature should be measured orally or tympanically, not rectally.
- In neutropenic cancer patients, pneumonia and anorectal infection are more likely to be associated with bacteremia than other localized infections.
- Gram-positive organisms are responsible for most serious infections in neutropenic cancer patients, but infections due to gram-negative organisms are more rapidly lethal.
- Neutropenic cancer patients with chemotherapy-induced oral mucositis can develop rapid onset of fever with shock, acute respiratory distress syndrome and rash due to viridans streptococci.
- If the chest radiograph is normal or inconclusive but there is still suspicion for pneumonia, CT of the chest without contrast should be obtained because pneumonia is often detected by chest CT in febrile neutropenic patients with normal findings on the chest radiograph.
- Broad-spectrum intravenous antimicrobial therapy with cefepime, meropenem, imipenem, or piperacillin-tazobactam, should be initiated promptly in the febrile neutropenic patient, with an aminoglycoside added for the more seriously ill patient. Aztreonam *plus* vancomycin should be administered to those with serious penicillin-allergy. Empirical fluoroquinolone therapy should be avoided except for specific indications.
- Some low-risk febrile neutropenic patients may not require admission to the hospital, but can be managed in a short stay observation unit or be discharged home from the ED.
- Patients with cell mediated immune deficiency including those on high dose corticosteroids may develop life-threatening infections with intracellular bacteria (*Listeria*, *Salmonella*, tuberculosis), fungi (*Cryptococcus*, *Coccidioides*, *Histoplasma*), herpes simplex virus, and varicella-zoster virus.
- Patients with end stage renal disease on hemodialysis who develop pneumonia, *C. difficile* disease, or infections of dialysis access sites have high mortality.
- Functional or surgical asplenia predisposes to fulminant infection with pneumococci and other encapsulated organisms (*H. influenzae*, *N. meningitidis*, and *Capnocytophaga canimorsus* after dog bites) and, when seen early, may be misdiagnosed as a viral illness, gastroenteritis, or food poisoning.
- High doses of corticosteroids cause profound dysfunction of neutrophils and mononuclear cells and impair cell-mediated immunity (CMI), resulting in an increase in infections caused by pyogenic bacteria, varicella-zoster and herpes simplex viruses, tuberculosis, and a wide variety of other bacteria, fungi, and parasites.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 187: QUESTIONS & ANSWERS

187.1. What is the most common site of infection in febrile neutropenic patients?

A. Gastrointestinal tract
B. Perineum and anorectal area
C. Respiratory tract
D. Skin and soft tissue
E. Urinary tract

Answer: C. The respiratory tract is the most common site of infection, with 25% of infections in the lung and another 25% in the mouth or pharynx (and an additional 5% in the nose or sinuses). Still, all neutropenic patients with fever need to have a thorough physical examination because an undiagnosed infection can cause severe morbidity or mortality.

187.2. A 49-year-old diabetic male who has been receiving chemotherapy for non-Hodgkin's lymphoma presents with fever and facial pain. Six weeks ago, he was treated with broad-spectrum antibiotics for fever but had negative cultures of blood and urine. He is taking ciprofloxacin as prophylaxis against infection. Examination is normal except for a purple-black lesion on his hard palate that looks like dried blood. A complete blood count shows severe neutropenia. In addition to blood cultures and chest radiography, what action should be taken immediately?

A. Administer intravenous clindamycin or ampicillin-sulbactam.
B. Administer intravenous levofloxacin.
C. Observe in the emergency department (ED) because he may be a candidate for home antibiotic therapy if other laboratory tests are normal, if he appears stable after an initial dose of antibiotics, and if his oncologist agrees.
D. Obtain a computed tomography (CT) scan of the paranasal sinuses and initiation of intravenous antifungal therapy in the hospital.
E. Undertake coagulation tests to check for a bleeding disorder induced by chemotherapy.

Answer: D. This patient has invasive aspergillosis or mucormycosis until proven otherwise. These fungi invade tissues and produce life-threatening necrotizing infections in cancer patients with neutropenia, as well as in diabetic patients, especially those who have received broad-spectrum antibiotics. CT scan will often show deep extension of the infection into the sinuses, orbit, or brain. The initial lesion in the palate or nose is often mistaken for a benign process. The antibiotics listed in A and B are incorrect. The

most appropriate empirical antibiotic regimen is cefepime or piperacillin-tazobactam, with or without an aminoglycoside, in addition to antifungal therapy. He is not a candidate for home therapy.

187.3. A 27-year-old male presents to the emergency department (ED) with acute onset of fever, chills, headache, myalgias, vomiting, mild abdominal cramping, and diarrhea for 8 hours. A splenectomy was performed 15 years earlier when he was treated for lymphoma, which has been in remission since then. He is not taking any medications and has been well. Vital signs are as follows: pulse, 125 beats/min; blood pressure, 110/60 mm Hg; respiratory rate, 20 breaths/min; and temperature, 39.5° C. His mental status is normal, and he has mild generalized abdominal tenderness. What is the most appropriate treatment for this patient at this time?

A. Blood cultures followed by immediate administration of ceftriaxone or cefotaxime, with or without vancomycin.
B. Hydration, antipyretic, antiemetic, and observation in the ED.
C. Immediate hospital admission with observation and frequent abdominal examinations.
D. Lumbar puncture.
E. Stool testing for occult blood and fecal leukocytes.

Answer: A. This patient is at high risk for overwhelming postsplenectomy sepsis, usually caused by *Streptococcus pneumoniae.* Persons who have undergone splenectomy for a hematologic disorder or lymphoma are at much higher risk for overwhelming postsplenectomy infection than are those undergoing splenectomy for trauma. The initial prodromal symptoms may be misdiagnosed as a viral illness, gastroenteritis, or food poisoning before there is abrupt deterioration with development of septic shock with disseminated intravascular coagulation, purpura, and multiorgan dysfunction. After blood cultures are obtained, he should immediately receive antimicrobials active against pneumococci, meningococci, and *Haemophilus influenzae.* He can be investigated for other possible etiologies of his symptoms after this initial critical action is taken.

187.4. Which answer is correct regarding diagnosis and management of patients on long-term high-dose corticosteroid therapy?

A. Acute, short-term administration of high-dose corticosteroids, but not long-term administration, can make the diagnosis of peritonitis particularly difficult.
B. After laceration repair, sutures should left in place for 50% to 100% longer than is usual.
C. Complications of chronic corticosteroid use include pancreatitis, pseudotumor cerebri, avascular necrosis of bone, cataracts, myopathy, spontaneous vertebral fractures, psychosis, and hypoglycemia.
D. Long-term corticosteroid use is frequently accompanied by peripheral blood neutrophilia.
E. Most serious infections in these patients are caused by organisms associated with defective cell-mediated immunity (CMI), such as severe or disseminated varicella-zoster and herpes simplex infections, tuberculosis, *Listeria, Cryptococcus,* and histoplasmosis.

Answer: B. Corticosteroids interfere with wound healing, so sutures need to remain in place longer than is usual for the type of laceration. Despite the profound defect in CMI that occurs with long-term corticosteroid use, infections with organisms associated with defective CMI are unusual. Most serious infections in these patients are caused by pyogenic bacteria, such as *Staphylococcus aureus,* streptococci, and gram-negative bacilli. Both short-term and long-term administration of corticosteroids interfere with the diagnosis of peritonitis. These patients will have poorly localized abdominal discomfort with minimal findings on examination. All the conditions listed in B are associated with chronic corticosteroid use—except hypoglycemia. Corticosteroid use is associated with hyperglycemia, hyperosmolar nonketotic diabetic coma, and diabetic ketoacidosis.

CHAPTER 188

The Solid Organ Transplant Patient

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PRINCIPLES

Solid organ transplantation for end-stage renal, hepatic, cardiac, and pulmonary failure has made significant advances since the first successful kidney transplant in 1956. In 2009, over 29,000 kidney, liver, pancreas, heart, and lung transplants were performed.[1] Because 1-year survival rates for all solid organ transplants exceed 80% and many patients survive much longer, increasing numbers of transplant patients are being seen in the emergency department (ED) with illnesses that can be complicated by their history of transplantation. Emergency clinicians should have a basic knowledge of organ transplant pathologies, an understanding of the initial approach to their management, and an appreciation of the utility of prompt consultation with transplant surgeons or oncologists.

Pathophysiology

Transplanted organs have surgical anastomoses to a variety of structures, including vessels, bronchi, ureters, intestines, and even the bladder. They are devoid of their native innervations and thus pain is an unreliable sign of underlying disease. Furthermore, the normal inflammatory and immunologic responses to infection and malignant disease are impaired. Subtle symptoms and signs may be the harbingers of serious complications, and each complaint merits careful investigation. Even in the most advanced stages of severe disease, patients may have few specific complaints and physical findings. The baseline physiologic capacity of the allograft will aid in interpretation of chief complaints in the context of possible organ failure. Subtle changes in allograft function may be a harbinger of an episode of rejection.

Transplant organ complications can generally be classified into one of four categories: anatomy, rejection, infection, and drug toxicity. The time since transplantation will help narrow the differential diagnosis; however, the exact etiology is often not determined until the patient is admitted to the hospital. It is also important to consider the risk of infection associated with immunosuppression and potential for drug toxicities when patients present with issues unrelated to their transplant.

Anatomy

Anatomic complications of solid organ transplants can be categorized into three groups: vascular, nonvascular anastomosis, and complications related to surgery. These are often manifested early in the post-transplantation course prior to initial discharge from the hospital, but delayed presentations can occur.

Vascular complications can include both arterial and venous structures, including thrombosis, stenosis, arteriovenous fistula, and pseudoaneurysm formation. Acute thrombosis of arteries may lead to fulminant organ failure. Arterial stenosis may also develop later in the course, with its effects typically determined by the degree of blood flow restriction. Pseudoaneurysms may develop and quickly lead to hemorrhagic shock if they rupture.

Nonvascular organ anastomoses may include bile ducts, bronchi, and ureters. Complications related to these structures include anastomotic leaks and obstructions from scarring, migration of stents, or stone development that may lead to acute graft dysfunction, infection, and abscess formation. Early identification is vital to salvage of the graft, and the evaluation includes laboratory investigation of graft function, cultures, imaging, and prompt consultation of transplant specialists.

Rejection

Rejection involves a complex set of T-cell receptor mediated pathways that lead to cytotoxic activity, B-cell memory and antibody formation, and cell death of the transplant allograft.[2] Each transplant patient typically has a lifelong course of a waxing and waning immune response to the allograft, mandating ongoing surveillance of allograft function. Differentiation of infection and rejection is often difficult and the determination is often made only after biopsy of the transplanted organ or positive culture results are identified.

Rejection typically occurs in three phases: hyperacute, acute, and chronic. *Hyperacute rejection* occurs with preformed antibodies against major histocompatibility complex or ABO blood type antigens. It is rare with careful donor-recipient matching, and typically occurs in the immediate perioperative period. *Acute rejection* occurs over days to weeks after transplantation. The patient presents with constitutional symptoms and signs of transplant organ insufficiency. Expeditious laboratory assessment, imaging, and possible allograft biopsy can confirm the diagnosis of rejection. If immunosuppression is stopped, acute rejection may occur at any time.

Chronic rejection, now referred to as *chronic graft dysfunction,* has a time course of months to years and results in the gradual failure of the transplanted organ over time. Each organ presents slightly differently, with interstitial fibrosis and tubular atrophy causing dysfunction in kidneys; inflammation causing airway obstruction in lungs; fibrosis of bile ducts, veins, and arteries in liver; and arteriosclerosis, or chronic allograft vasculopathy (CAV) in the heart.[3]

Infection

Infection is the primary cause of mortality after transplantation. Deaths from infection occur in 13% to 16% of kidney and heart transplants, 15% in liver, and 21% in lung transplants.[4] Signs of infection in this population of patients are often blunted by immunosuppression. Vague complaints of malaise and fatigue or the chief complaint of a fever in an afebrile patient may herald a severe infection. Any new headache with or without visual changes may be the first symptom of meningitis or brain abscess. All transplant patients with fever should be aggressively evaluated. The diagnostic evaluation includes blood and urine cultures, computed tomography (CT) scan or ultrasound, and lumbar puncture. In addition, complete blood count, glucose

concentration, serum chemistries, blood urea nitrogen and creatinine concentrations, chest radiography, and electrocardiography are recommended. Aggressive management usually translates into increased patient survival and graft function.[4] Broad spectrum antibiotics, antiviral agents, and antifungal medications should be considered, with awareness of nephrotoxicity and drug-drug interactions.

The timing of infection can be separated into three periods: first month after transplantation, between 1 and 6 months after transplantation, and more than 6 months after transplantation. These distinctions help predict the etiologic agents of the infection (Box 188.1).

First Month After Transplantation. The majority of infections occurring in the first month after transplantation are preexisting, donor derived, or nosocomial. Both donor and recipients undergo extensive serologic testing, but preexisting viral infections such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) no longer preclude transplantation. Donor derived infections complicate about 1% of transplants,[4] with the risk of transplant transmitted HIV infection reported to be 1 out of 50,000 and transplant-transmitted HCV infection to be 1 out of 5000.[5] Bacterial transmission can occur, especially latent tuberculosis; and fungal donor-to-recipient transmissions usually involve candida, cryptococcosis, aspergillosis, and endemic mycoses.[4] Nosocomial infections are similar to other postsurgical patients including bacteremia, ventilator-associated pneumonias, surgical site infections, and catheter-associated urinary tract infections.[6]

BOX 188.1

Infectious Pathogens in Transplant Patients

EARLY POST-TRANSPLANTATION (0 TO 1 MONTHS)

Preexisting in transplant patient: Bacterial colonization *(Pseudomonas aeruginosa, Mycobacterium tuberculosis);* viral (HIV, HBV, HCV, EBV, CMV, HSV, VZV); fungal (Candida species, *Cryptococcus neoformans, Aspergillus, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis*)

Donor-derived: Bacteria from transplant bacteremia, fungal (*Candida* species), rarely *Trypanosoma cruzi,* HCV, HIV, West Nile virus, lymphocytic choriomeningitis virus, *Legionella* species, *H. capsulatum, Strongyloides stercoralis, C. neoformans, Schistosoma species, Toxoplasma gondii,* and *M. tuberculosis*

Nosocomial: Bacteremia, surgical site infection, ventilator-associated pneumonia, urinary tract infections, *Clostridium difficile,* MRSA, VRE, respiratory viruses, *Legionella* species

INTERMEDIATE POST-TRANSPLANTATION (1 TO 6 MONTHS)

Viral infections: CMV, EBV, HBV, HCV, BK virus, respiratory viruses, HSV, VZV

Opportunistic infections: *Listeria monocytogenes, Nocardia* species, *C. neoformans, Mycobacterium* species, *Candida* species, *Aspergillus, H. capsulatum, B. dermatitidis, C. immitis, Pneumocystis jiroveci* (carinii), *T. gondii, S. stercoralis*

LATE POST-TRANSPLANTATION (MORE THAN 6 MONTHS)

Community-acquired pathogens: Respiratory viruses, community-acquired pneumonia, urinary tract infection

Chronic viral infection: CMV, EBV, HBV, HCV, BK virus

Opportunistic infections: In patients remaining on high dose immunosuppression

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *MRSA,* methicillin-resistant *Staphylococcus aureus; VRE,* vancomycin-resistant enterococci; *VZV,* varicella zoster virus.

Modified from Bowden R, Ljungman P, Snydman D, editors: Transplant infections, Philadelphia, 2010, Lippincott Williams and Williams.

1 to 6 Months After Transplantation. The period of 1 to 6 months after transplantation is a very high risk period for transplant patients. Infections occurring during this time are divided into two general types: immunomodulating viral infections and opportunistic infections.

Cytomegalovirus (CMV) is the most important and prevalent immunomodulating viral infection during this period. It may be asymptomatic; manifest as fever, malaise, and leukopenia; or present with symptoms specific to invasive disease of the lungs, liver, or gastrointestinal (GI) tract. CMV pneumonitis presents with fever, hypoxia, and diffuse infiltrates on chest x-ray. CMV GI disease causes ulcerations that can present with abdominal pain, diarrhea, bleeding, or perforation. CMV hepatitis can present with microabscesses in the liver. Definitive diagnosis is made by bronchoalveolar lavage or biopsy of lung, intestine, or liver, and patients often need admission for intravenous (IV) ganciclovir.

Furthermore, CMV has been shown to have multiple negative indirect effects in the solid organ transplant patient because of its immune-modulating properties, including increased risk of bacterial and fungal infections, opportunistic infections, acute or chronic organ rejection, and even increased mortality.[7] CMV has been linked to glomerulopathy and graft dysfunction in renal allograft recipients, recurrent HCV in liver transplantation, and acute cardiac dysfunction and accelerated coronary artery atherosclerosis in heart transplants.[8]

With the advent of prophylaxis for CMV disease, the average risk of CMV disease has decreased from 30% to 12%.[9] Most transplant centers employ prophylactic therapy with valganciclovir for high risk patients for 3 to 6 months. Future research is focused on effective CMV vaccines, which are currently in phase II clinical trials.[10]

Epstein-Barr virus is another significant immune-modulating virus that causes infections during the first 4 months of transplant.[4] Epstein-Barr virus infection may cause a mononucleosis-like syndrome (fever, malaise, pharyngitis, lymphadenopathy), or hepatitis, pneumonitis, and GI complaints.[11] The other feared complication of Epstein-Barr virus is post-transplant lymphoproliferative disorder (PTLD), which can present in varying ways including a viral mononucleosis syndrome, plasmacytic hyperplasia, B-cell infiltration of organs, or lymphoma. Treatment depends on type and extent of PTLD but includes reduction in immunosuppression, monoclonal B-cell antibody therapy (rituximab), and cytotoxic chemotherapy.[11]

BK virus is a polyomavirus that is common and asymptomatic in healthy subjects but pathologic in solid organ transplant patients.[12] BK virus resides in the kidneys, and it can progress from viruria to viremia to nephropathy, graft dysfunction, and graft loss in renal transplants.[13] There have also been case reports of BK nephropathy in heart, lung, and pancreas transplants. Diagnosis is by urine or serum viral loads and biopsy, and patients typically require reduction in immunosuppression to treat the disease.[13]

Hepatitis B and C may recur after transplantation. Hepatitis B–positive donors are being used more frequently now that prophylaxis with lamivudine, tenofovir, or entecavir are effective.[14] Hepatitis B reactivation usually presents mildly with fatigue, malaise, jaundice, and elevation in serum transaminases, but it causes fulminant hepatitis in 12% to 20% of cases with cholestasis, hypoprothrombinemia, and rapid deterioration.[4]

Other viral infections such as human herpes virus 6, primary varicella zoster virus infection, or reactivation of varicella zoster virus with shingles are common in transplant patients. Primary varicella infection may be life threatening with pneumonia, pancreatitis, hepatitis, encephalitis, and disseminated intravascular

coagulation. Treatment includes IV varicella-zoster immune globulin and IV acyclovir. Reactivation varicella zoster virus is usually confined to a single dermatome. Facial zoster involving the cornea and disseminated infections in more than one dermatome are indications for admission, although consultation with a transplant specialist for any episode of shingles is advised.[4]

Opportunistic pathogens in this time period are more common given the high level of immunosuppression. Listeria typically presents with fever, abdominal pain, and diarrhea in the immunocompetent patient, but it may cause bacteremia and meningoencephalitis in the solid organ transplant patient.[15] Treatment includes high dose penicillin or ampicillin and an aminoglycoside, although nephrotoxicity must be considered.

Nocardia infection is highest in lung and heart transplant patients and lower in kidney and liver transplant recipients. It typically presents with fever, cough, dyspnea, and hemoptysis, but it can progress to disseminated infection with central nervous system (CNS) abscess, skin and soft tissue abscess, osteomyelitis, or septic arthritis. *Nocardia* may be seen on gram stain as classic beading and branching gram-positive bacilli, although culture can take weeks. First line treatment is usually with trimethoprim-sulfamethoxazole (TMP-SMX), although other options include minocycline, amikacin, imipenem, cefotaxime, and ceftriaxone.[15]

Mycobacterial disease may manifest as opportunistic reactivation or a primary infection. Immunosuppressed solid organ transplant patients may not present with classic pulmonary tuberculosis, although they can present with cavitary or military tuberculosis (Fig. 188.1). They may present with nonspecific systemic symptoms, meningitis, peritonitis, pericarditis, liver abscess, renal tuberculosis, or disseminated disease. Treatment is complex because of drug interactions and graft dysfunction; however, it usually includes isoniazid (INH) with or without rifampin and ethambutol or pyrazinamide.[16]

Invasive candidiasis can present with fungemia, urinary tract infection, peritonitis, pleural empyema, or intra-abdominal abscess. Aspergillosis most frequently presents in the lungs as pulmonary nodules with or without cavitation but may disseminate to any organ system, including the CNS. Treatment is with antifungal agents, such as amphotericin B, azoles (fluconazole, voriconazole), or echinocandins (caspofungin, micafungin).[4]

Endemic mycosis such as histoplasmosis, blastomycosis, and coccidiomycosis should be considered based on geographic location and exposure, although histoplasmosis is the most commonly reported.[17] They all typically manifest with fever and respiratory symptoms and varying infiltrates on chest radiographs. Amphotericin B is usually first line therapy.

Pneumocystis jiroveci (carinii) pneumonia manifests subacutely with fever, nonproductive cough, progressive dyspnea, and an interstitial infiltrate on the chest radiograph (Fig. 188.2). Fortunately, its incidence is reduced with prophylactic low-dose TMP-SMX. Differentiation from CMV pneumonia is difficult without bronchoscopic confirmation. Treatment of *Pneumocystis* pneumonia includes IV TMP-SMX and steroids, depending on the degree of hypoxia.

Toxoplasmosis can occur as primary infection, but more commonly it is a reactivation of latent infection, resulting in pneumonia, hepatosplenomegaly, myocarditis, brain abscesses, or diffuse encephalitis. Typically, treatment of toxoplasmosis is a combination of IV sulfadiazine and pyrimethamine, although TMP-SMX has been used with some success in acquired immunodeficiency syndrome (AIDS) patients.

Cryptococcus neoformans may present in the intermediate or late period in solid organ transplant patients. Patients may present with meningoencephalitis and up to one-third have lesions apparent on imaging. Diagnosis is confirmed by lumbar puncture or serum cryptococcal antigen. Initial therapy is with amphotericin B and flucytosine.

Strongyloides stercoralis is an intestinal nematode that can present with hyperinfection syndrome, causing a necrotizing hemorrhagic enterocolitis and hemorrhagic pneumonia. Disseminated strongyloidiasis causes severe abdominal pain, obstructive symptoms, hemorrhage and secondary peritonitis, sepsis, meningitis, and pneumonia. Treatment of disseminated strongyloides is with thiabendazole, although mortality approaches 70%.

Each transplant center will have different prophylaxis guidelines, but overall prophylaxis with TMP-SMX for pneumocystis pneumonia (which also covers *Nocardia, Listeria,* and urinary tract infections), fungal prophylaxis with fluconazole, and CMV prophylaxis with ganciclovir when indicated have decreased the effect of classic opportunistic offenders.

Fig. 188.1. A 22-year-old man with a kidney transplant who presented with fever and a cough was diagnosed with reactivated tuberculosis by sputum analysis.

6 Months After Transplantation

Six months after organ transplantation, solid organ transplants can be categorized into three groups relative to infection

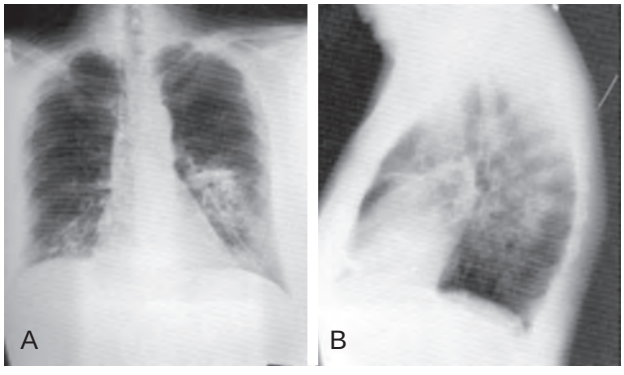

Fig. 188.2. **A** and **B,** Bilateral perihilar and lower lobe alveolar infiltrates in a cardiac transplant recipient from *Pneumocystis jiroveci*. (From Tewari S, Maurer J: Pulmonary considerations of organ transplantation. In Ginnes LG, Cosimi AB, Morris PJ, editors: Transplantation, Malden, MA, 1999, Blackwell Science, p 617.)

susceptibility: healthy transplant, chronic viral infection, and chronic rejection.

Healthy Transplant. Healthy transplant patients have no chronic immunomodulating viral infections and a functioning allograft; they are maintained with low doses of immunosuppressant medications. They have a mildly increased susceptibility to normal community-acquired infections, such as influenza, urinary tract infection, and pneumococcal pneumonia.

Chronic Viral Infection. Progressive disease may develop as a result of the combination of viral immunomodulating infections and long-term immunosuppression. Hepatitis B and C may cause progressive liver disease or hepatocellular carcinoma (HCC). CMV may present in this time period after prophylaxis is discontinued. Epstein-Barr virus–associated PTLD can occur late as well. Herpes simplex virus (HSV) reactivation is common after solid organ transplantation and can be manifested as oral or anogenital lesions, more often ulcers than vesicles.

Chronic Rejection. Patients with chronic rejection require ongoing aggressive immunosuppressive treatment to protect the allograft and are at higher risk of late infections. These patients are at the highest risk for life-threatening opportunistic infections, as well as standard nosocomial infections.

Drug Toxicity

Immunosuppressive therapy requires correctly timed drug combinations to establish a delicate balance between immunosuppression, rejection, and susceptibility to infection. Regimens are transplant center specific, but most include a calcineurin inhibitor, an antimetabolite, and varying dosages of steroids. Recognition of the side effects, toxicities, and potential drug interactions of immunosuppressant medications is an important component in the care of any transplant patient (Table 188.1).

Induction Agents. Induction agents may be used to initiate immunosuppression in the pre- or peri-transplant period. Antithymocyte globulin (ATG) or alemtuzumab are depletional agents that target lymphocyte production. These drugs induce cytolysis and apoptosis with a depletional effect on B cells and natural killer cells, which contribute to their efficacy. Alemtuzumab has a fairly low side effect profile and has been hailed as an agent that decreases the need for one or more maintenance agents.[18]

Basiliximab and muromonab-CD3 (OKT3) are monoclonal antibody preparations that suppress immune responses without depleting lymphocyte count. Basiliximab is a monoclonal antibody targeting IL-2, but is limited to relatively low-risk patients. OKT3 is used as an induction agents and in short courses to help reverse allograft rejection. OKT3 toxicity is common because of T-cell activation and lymphokine release, causing chills, fever, hypotension, and headache. The biggest side effects of induction agents are due to the long-term consequences of chronic lymphodepletion, including increased risk of opportunistic infections and PTLD.[19] Pulmonary edema may develop in overhydrated, oliguric patients. Aseptic meningitis may occur in 10% to 14% of patients treated with OKT3 approximately 6 to 10 days after therapy but may be difficult to differentiate from other causes by cerebrospinal fluid analysis alone.[4]

Calcineurin Inhibitors. The implementation of cyclosporine and tacrolimus in transplantation medicine has significantly improved the outcomes of organ transplantation. However, both drugs have narrow therapeutic indices, variable pharmacokinetics, and are associated with adverse side effects.[20] Serum levels should be checked in patients with worsening renal function.

Cyclosporine. Cyclosporine inhibits both cellular and humoral immunity by binding to a family of proteins called *cyclophilins,* which inhibit lymphocyte signal transduction. This results in immunosuppression of helper-inducer T cells, which are responsible for antibody recognition and production by B cells.

TABLE 188.1

Common Immunosuppressant Medications and Toxicities

DRUG	LEVEL	METABOLISM	TOXICITY
CALCINEURIN INHIBITORS			
Cyclosporine	25 to 200 ng/mL*	Hepatic cytochrome P_{450}	**Nephrotoxicity**, **hypertension**, tremor, hyperkalemia, hyperuricemia, glucose intolerance, hyperlipidemia, GI upset, gingival hyperplasia
Tacrolimus	5 to 10 ng/mL*	Hepatic cytochrome P_{450}	**Nephrotoxicity**, **neurotoxicity** (tremor, headache), hypertension, hyperlipidemia, glucose intolerance, GI upset, hypokalemia, alopecia
MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS			
Sirolimus	4 to 15 ng/mL*	Hepatic cytochrome P_{450}	**Nephrotoxicity**, hyperlipidemia, **impaired wound healing**, edema, GI upset, **pneumonitis**, anemia, stomatitis
ANTIMETABOLITES			
Azathioprine	Not sent, monitor CBC	Hepatic	**Hepatotoxicity**, **bone marrow depression,** GI upset
Mycophenolate mofetil (MMF)	Not sent, monitor CBC	Hepatic and GI	**Hepatotoxicity, bone marrow depression**, GI upset
CORTICOSTEROIDS			
Prednisone	Not sent	Hepatic cytochrome P_{450} (minor)	**Glucose intolerance**, GI bleeding, **osteoporosis**, myopathy, cataracts

*Appropriate levels vary based on time since transplantation, level of rejection, and concurrent toxicity and medications.
CBC, Complete blood count; *GI,* gastrointestinal.

The side effects of cyclosporine can be severe, with the most important one being nephrotoxicity. Cyclosporine causes renal tubular injury and direct renal artery vasospasm in a dose-dependent manner, leading to systemic hypertension in many recipients. This is especially precarious when used with other drugs typically used after transplantation, such as amphotericin B, aminoglycosides, and high-dose TMP-SMX. Cyclosporine can also cause hepatotoxicity, hyperlipidemia, hyperuricemia, hyperkalemia, hirsutism, tremor, and gingival hyperplasia. Rarely, cyclosporine toxicity can result in a neurotoxic syndrome of seizures, confusion, cortical blindness, and quadriplegia, progressing to coma if left untreated.

Cyclosporine levels are altered by many common post-transplantation medications (Table 188.2). Drugs that inhibit cytochrome P_{450} metabolism, such as erythromycin and ketoconazole, produce elevated cyclosporine levels and enhanced toxicity. Drugs that upregulate cytochrome P_{450} may decrease cyclosporine levels and possibly trigger episodes of organ rejection.[18]

Tacrolimus. Tacrolimus is a macrolide compound that binds to lymphocyte proteins and inhibits cytokine synthesis. Although it is chemically different, it has similar biological properties to cyclosporine. Because of an improved side effect profile and more effective immunosuppression, tacrolimus is used more frequently than cyclosporine as either primary or rescue therapy for allograft rejection in all types of solid organ transplants.

Tacrolimus can cause nephrotoxicity, as well as neurotoxicity. In combination with steroids, tacrolimus can lead to hyperglycemia and diabetes. Tacrolimus can also cause anorexia, diarrhea, dyspepsia, and nausea. Macrolide antibiotics should not be prescribed to patients receiving tacrolimus because they augment tacrolimus levels.

Mammalian Target of Rapamycin Inhibitors. Sirolimus and everolimus are two drugs in the mammalian target of rapamycin (mTOR) class. mTOR is key in the pathway for T-cell clonal activation.

Sirolimus was originally used as an anti-fungal agent but was later found to have immunosuppressive and antiproliferative properties. Initially, there was great hope for sirolimus in reducing risk of malignancy in solid organ transplants; however, results have been mixed.[21] Sirolimus has shown promise in reducing mortality in liver transplants with HCC and some benefit in decreasing vasculopathy in cardiac transplants.[22-24] Important side effects include nephrotoxicity and delayed wound healing, especially when used with cyclosporine.[18] Other side effects include hyperlipidemia, anemia, thrombocytopenia, proteinuria, stomatitis, and diarrhea.[25]

TABLE 188.2

Drug Interactions With Cyclosporine, Tacrolimus, and Sirolimus

AGENT	PHARMACOKINETIC ACTION	EFFECT
Carbamazepine Nafcillin Phenobarbital Phenytoin Rifampin	Induce cytochrome P_{450} enzymes	Decreased half-life and immunosuppressive effect, potential for acute rejection
Colchicine Diltiazem Fluconazole Fluoroquinolones Ketoconazole Macrolide antibiotics Oral contraceptives Verapamil	Inhibit cytochrome P_{450} enzymes	Increased half-life and potential drug toxicity or immunosuppression
Aminoglycosides Amphotericin B Cimetidine Nonsteroidals Sulfur	Interact at a glomerular or tubular level	Increased nephrotoxicity

Antimetabolites

Azathioprine. Azathioprine is an antimetabolite derivative of 6-mercaptopurine. One of the first immunosuppressive drugs for solid organ transplants, azathioprine inhibits both deoxyribonucleic acid and ribonucleic acid synthesis, resulting in a suppression of lymphocyte proliferation. Azathioprine works as a bone marrow toxin, so patients may exhibit dose-related neutropenia. Hepatic dysfunction and other GI disturbances may also occur.

Mycophenolate Mofetil. Mycophenolate mofetil (MMF) is an antimetabolite with more potent and selective inhibition of lymphocyte proliferation, so it has largely replaced azathioprine. It reduces the incidence of acute rejection, but it does not significantly improve long-term survival of transplant recipients or their allografts.

MMF has the advantage of a low side effect profile. The mostly mild effects resulting from its GI and hematologic toxicity include abdominal pain, nausea, diarrhea, gastroenteritis, leukopenia, and thrombocytopenia. Because magnesium and aluminum antacids interfere with the absorption of MMF, care should be exercised in treatment of the GI symptoms.

Corticosteroids. Corticosteroids have a wide range of effects on the immune system, specifically the T lymphocytes. Because of the significant long-term toxic effects associated with chronic glucocorticoid administration, every effort is made to minimize glucocorticoid use.

Long-term corticosteroid therapy causes osteoporosis, cataracts, GI bleeding, glucose intolerance, skeletal myopathy, bone disease, and adrenal suppression (Fig. 188.3). Acute administration may lead to glucose and electrolyte abnormalities, as well as altered mental status. Acute withdrawal or severe illness may lead to an Addisonian crisis.

SPECIFIC DISORDERS

Heart Transplant

In 2009, 2241 heart transplants were performed in the United States.[1] The overwhelming majority of heart transplants are performed for cardiomyopathy and coronary artery disease, with less common reasons being congenital heart disease, valvular pathology, or retransplant.[26] The 1-, 5-, and 10-year graft survival rates for heart transplants are reported to be 88.6%, 73.1%, and 53%, respectively.[1] Infection and rejection are the leading causes of mortality in the first year, with overall causes of mortality being graft failure (22%), infection (14%), malignancy (14%), cardiac allograft vasculopathy (CAV; 10%), multiorgan dysfunction (10%), acute rejection (4%), and renal failure (4%).[26,27] In one study of 131 ED visits by heart transplant patients, the most common complaints were fever (37%) and shortness of breath (13%), and 60% of the patients were admitted.[28]

Anatomic Considerations

The majority of orthotopic (same anatomic site of the original organ) heart transplants now being performed in the United States are bicaval, where there is a single left atrial anastomosis,

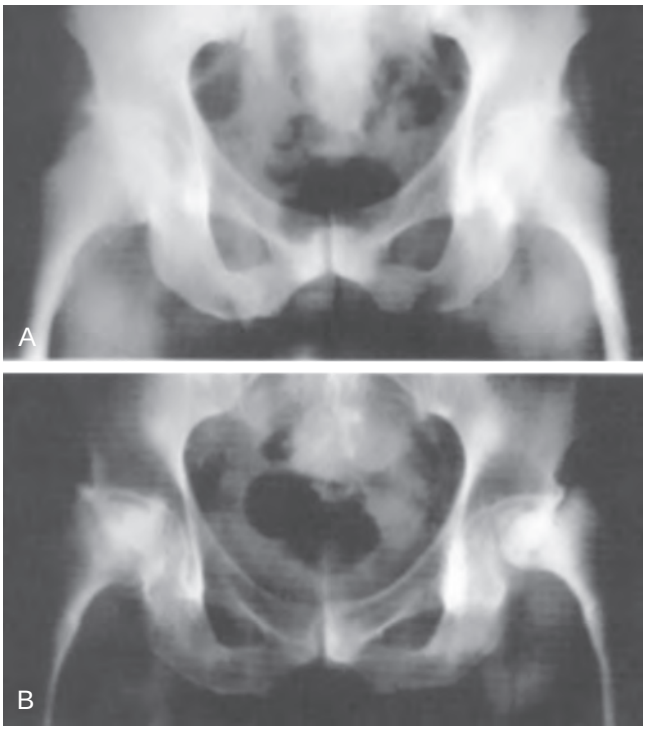

Fig. 188.3. Radiographic appearance of a 24-year-old renal transplant patient with early **(A)** and late **(B)** findings consistent with avascular necrosis from chronic steroid use. (From Walker RG: Steroids and transplantation. In Ginnes LG, Cosimi AB, Morris PJ, editors: Transplantation, Malden, MA, 1999, Blackwell Science, p 121.)

two caval anastomoses, and aorta and pulmonary artery anastomoses. The other method of orthotopic heart transplantation is biatrial, where the recipient right atrium connected to the vena cava is left intact, so the right and left atria, aorta, and pulmonary artery are anastomosed (Fig. 188.4).[29]

The transplanted heart is denervated, which causes clinically important physiologic changes. Without parasympathetic tone, the resting heart rate in a transplant patient varies from 95 to 110 beats/minute. Medications affecting the autonomic nervous system, such as atropine for bradycardia, will not have an effect on the denervated heart.[30] The transplanted heart rate can increase with exercise or stress through the effects of endogenous catecholamines, up to 70% of the maximum heart rate for age, and exogenous pressor agents are effective in the transplanted heart. Upregulation of beta-adrenergic receptors appears to occur in the graft, with a slightly enhanced response to norepinephrine and isoproterenol. Beta-blockers can worsen autonomic dysfunction and exercise tolerance, so they are typically avoided in treating hypertension in post-transplant patients but may be used to treat acute supraventricular tachyarrhythmias.[31,32] The transplanted heart is sensitive to adenosine, so the dose should be reduced by half. Lastly, heart transplant recipients often do not experience classic anginal symptoms with ischemia, but rather they have silent myocardial infarctions or present with heart failure symptoms or sudden cardiac death.

The most common electrocardiogram (ECG) abnormalities after heart transplant are incomplete right bundle branch block (RBBB), and repolarization abnormalities, although these changes are not felt to be of clinical significance. With the biatrial technique, the electrocardiogram may demonstrate two P waves (one from the native recipient sinus node and one from the donor sinus node; Fig. 188.5). The PR, QTC, and QRS intervals are usually normal. Patients with symptomatic bradycardia should be admitted and may need pacemaker implantation. New onset tachyarrhythmias (aflutter and atrial fibrillation) are concerning for potential rejection or CAV.[32] Most heart transplant patients with brady or tachyarrhythmias should be admitted for further evaluation and management.

Rejection

Etiologies of acute rejection include medication noncompliance, drug-drug interactions, or concurrent CMV infection. Approximately 25% of heart transplant patients will have an acute rejection episode between initial hospital discharge and 1 year, and the risk is highest in the first 3 months.[27,33] Acute rejection is often asymptomatic, although patients may present with fatigue, fever, dyspnea, signs of heart failure, or hypotension. Dyspnea is one of the most sensitive clinical criteria for rejection, so this complaint must be taken seriously. Other rare presentations of acute rejection are pericardial effusions or atrial arrhythmias.

Appropriate diagnostic tests include electrocardiogram, complete blood count, electrolytes, creatinine, troponin, cultures, chest x-ray, and echocardiogram, if possible. Patients who present with signs and symptoms concerning for acute rejection should be admitted for further evaluation and care. Endomyocardial biopsy is the gold standard for diagnosing acute rejection, and grading and treatment regimens are based on the results.[30] Patients must follow a strict regimen of endomyocardial biopsies at decreasing intervals to monitor for rejection. A new blood test to monitor for rejection with gene expression profiling of leukocytes (AlloMap) has some promise, although use varies based on transplant center.[30,33]

Acute rejection is treated with IV corticosteroids with or without OKT3 or ATG. If antibody mediated rejection is diagnosed, treatment also includes plasmapheresis, IV immunoglobulin, or adjuvant therapy with the anti-CD20 monoclonal antibody, rituximab (Rituxan).

CAV is associated with chronic rejection, immunosuppressant toxicities, and CMV infection and is a major determinant of morbidity and mortality for heart transplant patients. It is seen in 40% to 50% of transplants at 5 years. CAV is diagnosed via cardiac angiography with characteristic diffuse, concentric narrowing of coronary arteries rather than the eccentric focal narrowing caused by classic cardiac atherosclerosis. Like acute rejection, CAV is often asymptomatic, but it may present with new onset heart failure, myocardial infarction, arrhythmias, or sudden cardiac death. The only definitive treatment for documented CAV is retransplantation, so focus is on prevention with traditional risk factor management (hypertension, hyperlipidemia, diabetes mellitus [DM], obesity) and early recognition. mTOR inhibitors (such as, everolimus and sirolimus) have exciting implications for cardiac transplantation, including prevention of CAV and withdrawal of cyclosporine in setting of renal toxicity without increased risk of rejection.[24,25,30]

Drug Toxicity

Calcium channel blockers and amiodarone can increase cyclosporine, tacrolimus, or sirolimus levels. Statins have increased drug levels when taken concurrently with cyclosporine, so the statin side effects of rhabdomyolysis and myopathy may be seen.

Infection

Infections are a major cause of mortality in the first year after transplantation. Bacterial pneumonias, urinary infections, herpes virus infections, and invasive fungal infections have been noted as the most common infections in heart transplants.[4] Mediastinitis is a feared complication of heart and lung transplant patients. It is usually caused by staphylococci, although aspergillus and

Nocardia are important opportunistic infections. Toxoplasmosis is more common in heart transplant patients, because the organism may be encysted in the myocardium of donor. Chagas' disease is an important reason for heart transplantation in South America, and about one-fourth of patients with Chagas' pre-transplantation will undergo reactivation and acute disease. Reactivation can be asymptomatic or may cause myocarditis, subcutaneous nodules, or disseminated disease. Treatment is with benzidazole.[34] Because of the attendant risk of endocarditis, antibiotic prophylaxis should be provided for invasive procedures likely to cause bacteremia.

Liver Transplant

In 2009, 6320 liver transplants were performed in the United States. Unfortunately, 12,454 patients were on the transplant waiting list, and the waiting list mortality exceeds 20%. The most common indication for liver transplant is hepatitis C infection. Liver transplants have 1-, 5-, and 10-year graft survival rates of 85%, 67%, and 51%, respectively.[1] Complications are common, and loss of function of the graft organ is rapidly life-threatening. In one study of over 1200 solid organ transplant patients presenting to the ED, liver transplant patients most commonly presented with abdominal pain or GI symptoms, infections were the most common ED diagnosis, and 67% were admitted to the hospital.[35]

Anatomic Considerations

The orthotopic liver transplant (OLT) is connected to its host through five anastomoses (Fig. 188.6). The vessels are connected first, then the biliary system is reconstructed and often stented with a T-tube to prevent stenosis. The T-tube is left in place for up to 3 months. Anatomic complications are related to anastomosis and graft function.

Hepatic artery thrombosis (HAT) is the most common vascular complication and is devastating, because it is the only arterial blood supply to the transplanted liver. Patients usually present during the first month of transplantation with jaundice, right

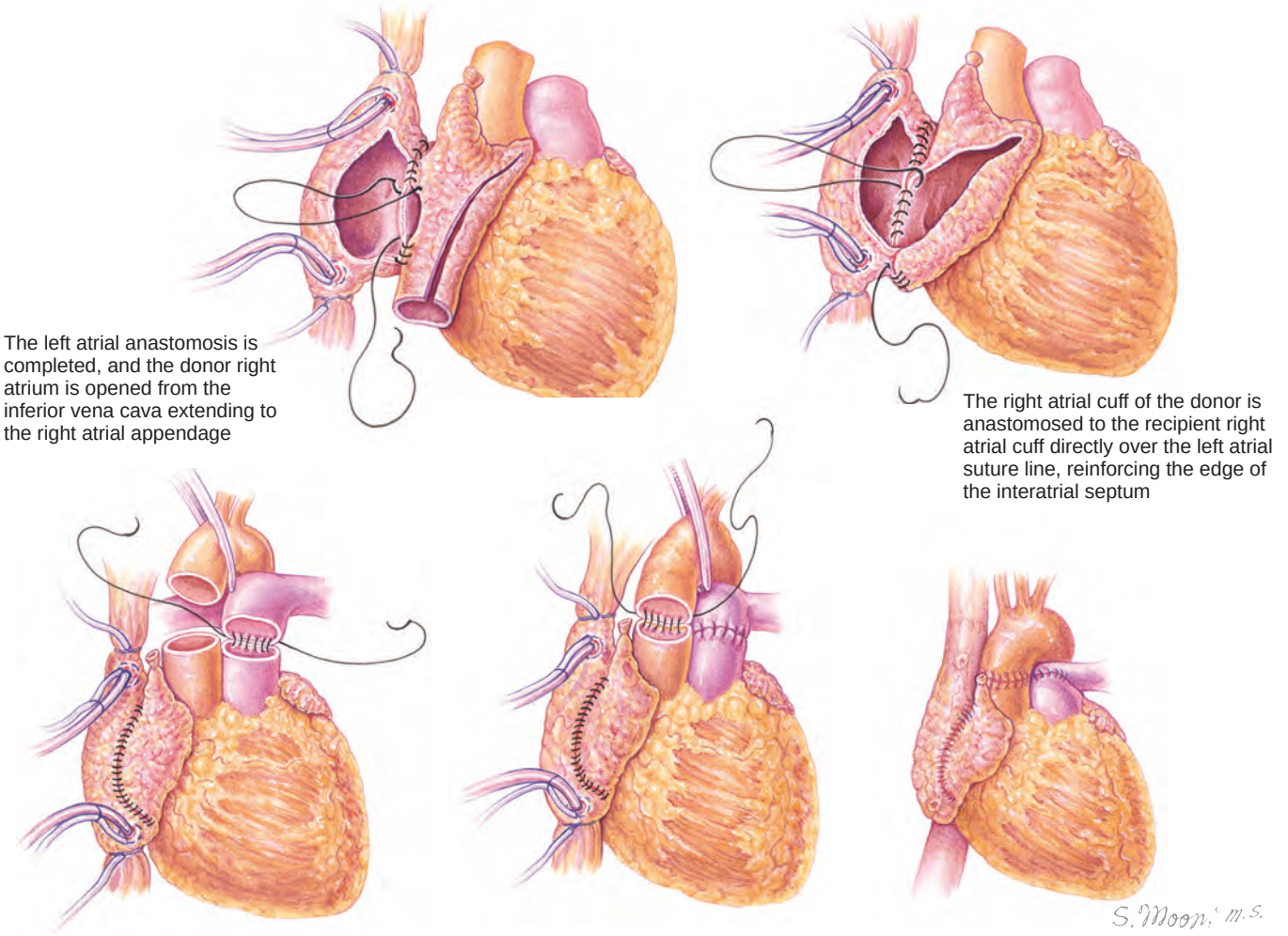

Fig. 188.4. Typical anastomoses of an orthotopic heart transplant. Biatrial anastomosis **(A)** and bicaval anastomosis **(B).** (Copyright 2017 Elsevier Inc. All rights reserved. www.netterimages.com.)

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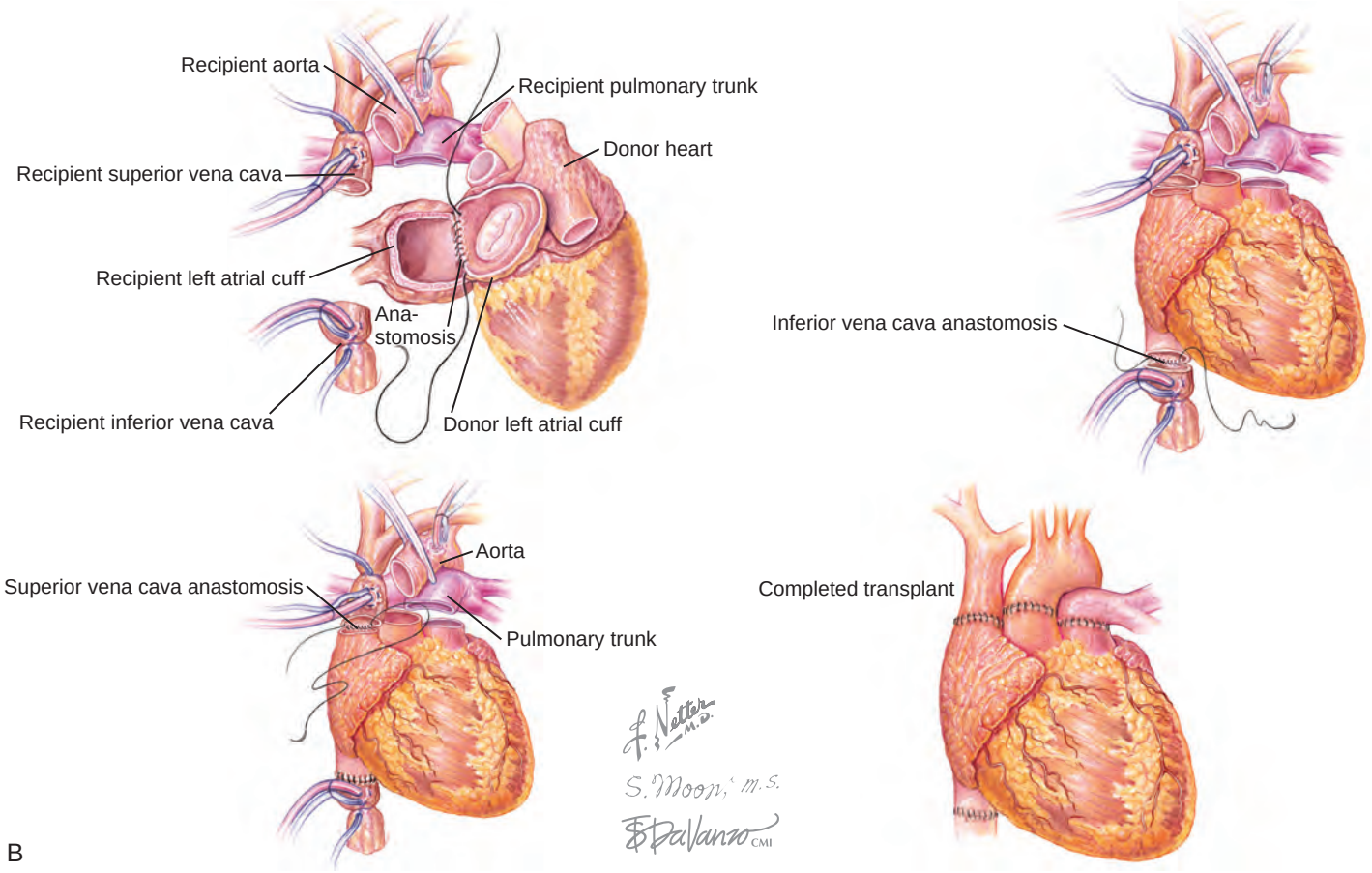

Fig. 188.4, cont'd.

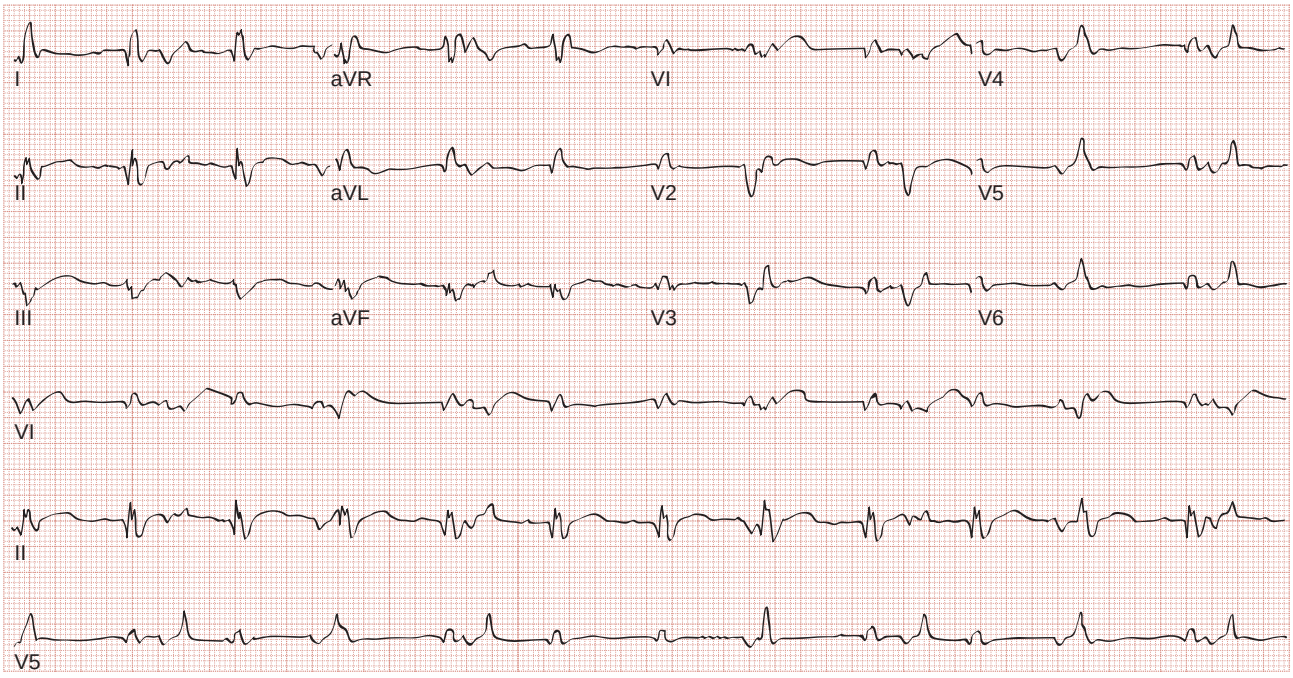

Fig. 188.5. A 68-year-old man status post heterotopic heart transplantation; native heart rate of 55 beats/minute and donor heart rate of 75 beats/minute.

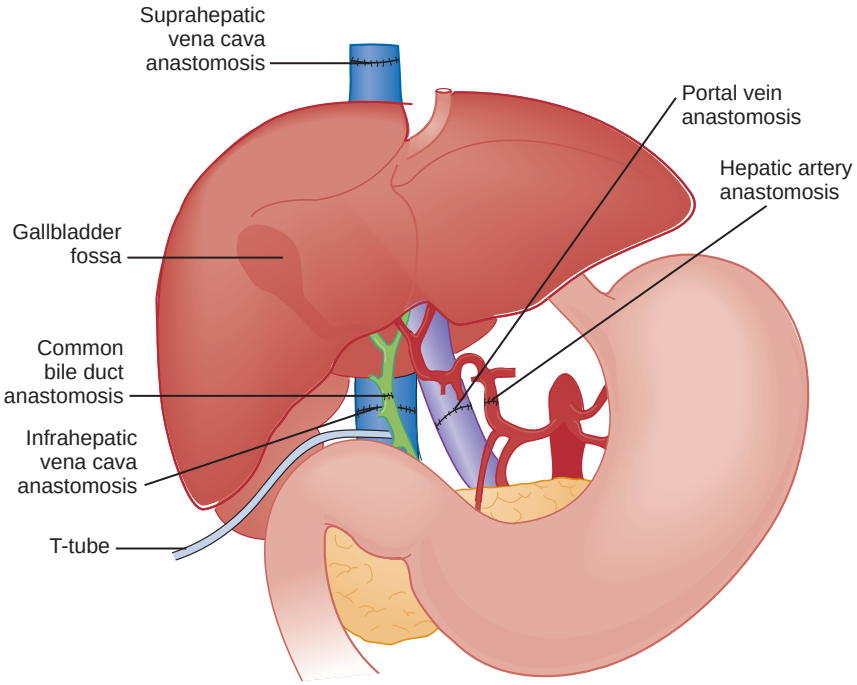

Fig. 188.6. Typical anastomoses of an orthotopic liver transplant (OLT). (From Powelson JA, Cosimi AB: Liver transplantation. In Ginnes LG, Cosimi AB, Morris PJ, editors: Transplantation, Malden, MA, 1999, Blackwell Science, p 352.)

upper quadrant pain, and fever associated with elevated liver enzymes and bilirubin. Diagnosis is made by Doppler ultrasound, helical CT scan, or arteriography. HAT can cause graft dysfunction, bile necrosis leading to leaks, abscess formation, and sepsis.[36] Treatment involves thrombectomy, either surgical or via interventional radiology.

Hepatic artery rupture is uncommon. It is usually caused by bacterial arteritis, and patients will present in hemorrhagic shock. Portal vein thrombosis occurs in up to 3% of liver transplants.[36] When acute, it presents as graft failure with encephalopathy and refractory ascites. Later presentations include portal hypertension and its sequelae.

Biliary complications including leaks, obstruction, and strictures are additional anatomical complications. Leaks will present with abdominal pain and peritonitis. Obstructions may be caused by migrating stents or stone formation. Diagnosis is made with ultrasound or CT imaging. ED care should involve broad spectrum antibiotics (gram positive, negative, and anaerobe coverage) and early consultation, because definitive care often requires percutaneous drainage or surgical intervention. Biliary strictures present within the first 6 months with a cholestatic picture. The vast majority are treated with endoscopic dilatation and stenting, although 18% to 30% of patients will have a recurrence.[36,37]

Rejection

Acute rejection occurs frequently despite immunosuppressive therapy, with 60% to 80% of patients experiencing at least one episode. Rejection often begins 1 or 2 weeks after surgery, with fever, right upper quadrant pain, malaise, and elevated bilirubin and transaminase levels. Leukocytosis may occur but is nonspecific. Related conditions that simulate graft rejection are mechanical biliary obstruction, infection, ischemia from thrombosis of vascular anastomoses, viral infections, drug toxicity, and recurrent primary disease. Definitive diagnosis is made by allograft biopsy.

As soon as transplant rejection is suspected, hospitalization and treatment with high-dose methylprednisolone and optimization of immunosuppression should begin. If steroids fail, OKT3 monoclonal antibodies are used in addition to polyclonal antilymphocyte globulin.[37] Treatment is usually successful, with 90% of patients responding to corticosteroids.[38]

Chronic rejection occurs in up to 4% of liver transplant patients. Chronic rejection may be asymptomatic early on, or present with a more indolent course of features similar to acute rejection including malaise, jaundice, right upper quadrant pain.[36] Laboratory investigations show elevated transaminases, and diagnosis is made by biopsy. Although chronic rejection may not respond to increases in immunosuppression, some centers may switch to tacrolimus, increase the dose, or add a third agent.[38]

Drug Toxicity

The most common cause of renal failure after liver transplant is calcineurin inhibitor toxicity. In the event of worsening renal dysfunction, calcineurin inhibitor doses may need to be reduced or treatment changed to MMF or sirolimus.[39] Over 75% of centers are using tacrolimus and MMF, and only 30% of patients require ongoing corticosteroids beyond 1 year after transplant.[1] As with any transplant, careful consideration of drug-drug interactions must be made before prescribing new medications.

Infection

Patients with liver transplants have a higher incidence of infection than those with kidney or heart transplants, with the most common source being abdominal and biliary tract infections. Bacterial infections and sepsis are common given the severity of illness pre-transplant, and over 50% occur within the first 2 weeks.[4] Patients presenting with abdominal pain in the first month should undergo laboratory evaluation, culture, and imaging to evaluate for cholangitis, peritonitis, liver abscesses, and abdominal abscesses. These are most commonly caused by gram-negative enteric bacilli, enterococci, and anaerobes, although staphylococcus and candida can also be culprit agents.[4]

OLT patients are particularly susceptible to fungal infections; candida is most common, but invasive aspergillosis occurs in up to 8% of patients.[4]

Hepatitis B and C are issues in the long term for liver transplant patients. Hepatitis B virus (HBV) infection may occur with hepatitis B surface antigen (HBsAg) positive or HBV naive recipients. Graft reinfection by HCV positive recipients is almost certain. Treatment with interferon alpha and ribavirin may be successful in delaying fibrosis in some patients, although 10% to 30% of HCV positive recipients develop cirrhosis in 5 years.[39]

Kidney Transplant

Kidney transplants have the most successful survival rates of the solid organs. The 1-, 5-, and 10-year graft survival rates are reported to be 92%, 70%, and 43%, respectively.[1] Due to increased survival rates and improved immunosuppressive pharmacotherapy, both the numbers of living transplant recipients and those waiting for transplants continue to grow. To address a chronic shortage, kidneys from older donors, those with a previous hepatitis, and even those with acute kidney injury have been used to increase the donor pool.[40]

Anatomic Considerations

The location of the transplanted kidney is most commonly in the iliac fossa. Donor renal vessels are anastomosed to recipient iliac vessels, and the donor ureter can be anastomosed directly to the recipient's bladder or native ureter, with J stents left in place for 6 weeks. Vascular complications such as bleeding and thrombosis can occur. A hematoma can form up to a week after the procedure and cause urinary obstruction and hydronephrosis. Renal artery and vein thrombosis is less common but will present with oliguria, anuria, and rising creatinine. Late vascular complications are due to arterial stricture or stenosis. Ureteric complications occur in up to 15% transplants and include ureteric leak, stent migration, or stricture.[41] Doppler ultrasound of the transplanted kidney can often identify anatomic issues with the allograft.

Infection

The most common source of infection is the urinary tract and is most commonly caused by *Escherichia coli.* Atypical pathogens such as urinary tract tuberculosis, mycoplasma hominis, and adenovirus can lead also lead to cystitis and graft failure.[4,42] The use of prophylactic TMP-SMX has been shown to decrease the incidence of pyelonephritis in these patients.[1] Oral antibiotics are adequate to treat patients with uncomplicated cystitis.

Graft pyelonephritis occurs in up to 13% of renal allograft patients. Patients with graft pyelonephritis may present with rigors, fevers, and pain over the implant site, although acute rejection may present similarly. Ultrasound should be performed to exclude partial obstruction in the early postoperative patient and in patients with incomplete bladder emptying, nephrolithiasis, or recurrent infections. Blood and urine cultures should be obtained routinely. Patients with graft pyelonephritis are typically admitted for treatment with IV antibiotics.

Chronic viral infections are important determinants in morbidity. BK nephropathy occurs in up to 10% of renal transplant patients.[43] HCV is a common cause of recurrent and chronic infection in renal transplant patients, with liver disease developing in approximately 50% of seropositive patients.[4]

Rejection

Acute rejection is a common complication of kidney transplantation, with 1-year rates of 10% to 11% and an associated reduced graft survival.[1,44] Clinically, renal graft rejection is manifested with fever, hypertension, edema, tenderness over the allograft, and decreased urine output. A subtle rise in serum creatinine concentration should prompt great concern. Renal ultrasound examination with color flow Doppler study should be performed to rule out obstruction, abscess, vascular thrombosis, and perirenal collections of blood, pus, or lymph. Early consultation with the transplant nephrologist is prudent, and definitive diagnosis is made with biopsy. Treatment is with high-dose IV methylprednisolone, with or without plasma exchange if antibody mediated rejection is suspected.[45]

Chronic transplant rejection occurs after long-term loss of adequate function due to nephrosclerosis or fibrosis of the blood vessels. This process involves proliferation of the vascular intima of renal vessels with marked decrease in the lumen size. Systemic hypertension ensues as the graft fails from ischemia, with resultant tubular and glomerular atrophy. Chronic allograft nephropathy is caused by immune and non-immune mechanisms and presents with proteinuria, hypertension, and graft dysfunction.

Lung Transplant

Although lung transplantation is still rare due to lack of donor tissue availability, it is increasing in frequency; more than 1600 are performed annually in the United States.[1] Common indications include chronic obstructive pulmonary disease, cystic fibrosis, and pulmonary fibrosis. There has been a shift from single to double lung transplantation due to its impact on long-term outcomes and quality of life. Although there is compelling data documenting the beneficial impact of lung transplantation on functional status and hemodynamics, the data are less convincing for a survival benefit.[46] Survival rates for lung and heart-lung transplant lag behind the other solid organ transplants with a 1-year graft survival of 80% and 89% and patient survival of 82% and 90%, respectively.[1]

Anatomic Considerations

Single or bilateral lung transplantation requires anastomosis of the main bronchi, pulmonary veins to left atrium, and pulmonary arteries. Any of these anastomoses may break down and cause ischemia, prolonged air leak, or mediastinitis.[28] Bronchial anastomotic complications such as stenosis, tissue degeneration, and dehiscence can also occur in up to 15% patients. Acute pleural complications and reperfusion edema can be seen within 1 week of transplant. Pneumothorax, hemothorax, pleural effusion, empyemas, and persistent air leaks can occur in roughly 20% of patients.

Rejection

Approximately 25% of lung transplant patients will have acute rejection in the first year.[1] An episode of acute rejection can occur as early as a few days after transplantation or as late as several years after. Clinically, the patient presents with cough, dyspnea, fatigue, and fever. Rales and rhonchi are heard, with deterioration in oxygenation and pulmonary function. Early rejection is often accompanied by infiltrates on the chest radiograph. When rejection occurs more than a month after transplantation, 75% of radiographs are normal or unchanged. The diagnosis of rejection is made by transbronchial biopsy showing lymphocytic infiltration. Suspected episodes of acute rejection are treated with high-dose corticosteroid therapy with OKT3 in refractory cases.

Chronic lung transplant rejection is caused by scarring or fibrosis of the airways and prolonged deterioration of lung function. Chronic rejection usually results from repeated infection and episodes of acute rejection, and it is a leading cause of late

morbidity and mortality.[27] On pathologic examination, vascular sclerosis and progressive limitation to airflow occur from obliterative bronchiolitis. Rejection can occur several years after transplantation, but the mean time to onset is 8 to 12 months. Clinically, this rejection mimics an upper respiratory infection or bronchitis. If dyspnea is a component of the presenting complaint, a search for transplant rejection should be initiated. Chronic rejection is treated with high-dose corticosteroids. Antilymphocyte antibodies are used as well, but relapse of the rejection episode is common.

Infection

Infections account for up to 20% deaths in lung transplant patients.[4] Transplanted lungs are highly susceptible to pneumonia, because they can be colonized by bacteria during the ventilator stage of the brain-dead donor. After transplantation, diminished mucociliary clearance, decreased cough reflex due to denervation, and defective function of alveolar macrophages are present. The most common infections are caused by gram-negative bacteria such as *Pseudomonas* and by *Staphylococcus aureus*. Influenza and respiratory viruses are the major cause of morbidity and mortality for lung transplant patients.[1,47,48] Antibiotic and antiviral therapy should be aggressively directed toward any pathogenic bacteria or virus cultured from the tracheobronchial tree.[4]

CMV pneumonia is the most common opportunistic pulmonary infection after lung transplantation. Patients are at highest risk between 3 weeks and 4 months. Clinically, CMV infection closely resembles transplant rejection, so tissue biopsy and culture are required to differentiate the two entities. Treatment with an antiviral agents such as ganciclovir is effective but is often required long term (>12 months). Colonization by *Candida* is common, but invasive diseases with *Aspergillus* and *Candida* provides the most significant fungal threat to the transplanted lung.[47] Invasive species can cause bronchiolitis obliterans syndrome by inflammation and obstruction of the bronchioles, which increases the risk of graft failure.[48] Although reactivation of tuberculosis is rare, pulmonary non-tuberculosis mycobacterial infections are relatively common.[49]

Pancreas Transplant

Approximately 1300 pancreas transplant operations are performed in the United States annually, singly or in combination with a kidney. Pancreas transplants typically occur secondary to long-standing diabetes. Isolated pancreatic transplants have a high complication rate, with 1-year graft survival rates as low as 72%. Kidney-pancreas transplants have better outcomes, with a 1-year graft survival rate of 93%, and a 1-year patient survival rate of 96%.[1]

Islet cell transplantation is under investigation as a treatment of diabetes mellitus. Although the procedural complication rate is significantly less compared with a whole pancreas transplant, islet transplantation requires several donors for adequate islet cell mass to achieve insulin independence. In addition, there is an increased attrition of islet graft function that occurs during the first few years compared with whole pancreas transplantation. These factors have made whole pancreas transplantation the most commonly performed type of beta cell replacement therapy.[50]

Anatomic Considerations

Pancreas transplant surgeries vary widely based on surgeon and institution. Arterial perfusion is usually via the iliac vessels, venous revascularization may be systemic or portal, and exocrine function may be drained into the small intestine (80%) or bladder (20%).[51] When drained into the bladder, patients develop a chronic non–anion gap acidosis caused by loss of bicarbonate into the bladder. Vascular thrombosis can be seen very early after transplant, typically within the first 48 hours. This is usually due to venous thrombosis of the pancreatic portal vein. Bleeding at the anastomotic site can result in an intra-abdominal hematoma. Pancreatitis is expected but should be closely monitored. Duodenocystostomy fistulas may form in the early post-transplantation period. Intra-abdominal abscess may form anytime but most commonly 1 to 6 months post-transplant. The clinical findings are abdominal pain, tenderness, hyperamylasemia, leukocytosis, and elevated serum creatinine.

Rejection

One year acute rejection rates for pancreas transplant have been reported from 16% to 25%.[1] Early acute pancreatic transplant rejection occurs when exocrine cell function is compromised. Patients present with pain around the graft due to peritoneal irritation. Serum lipase, amylase (or urinary amylase if patients are bladder drained), will be elevated. Destruction of beta cells occurs late, following injury of exocrine tissue; therefore, hyperglycemia is a late and often irreversible finding. The gold standard for diagnosing rejection is a pancreas graft biopsy, and treatment includes high dose corticosteroids with or without anti-lymphocyte immunotherapy.

Infection

The infection rate and pathogen type are highly specific based on the type of mechanisms used to drain exocrine secretions from the pancreas. Urinary tract infections are common in bladder drained transplants, although sterile cystitis may occur as well. In small bowel drained pancreas transplants, intra-abdominal infections with aerobic and anaerobic infections cause significant morbidity. CT imaging is used to diagnose leaks, abscesses, and fistulas that may be causing infection. Candida is also a common pathogen.[4]

Other Considerations

Trauma

The management of organ transplant trauma patients is generally no different than that of other trauma patients. One study of 50 solid organ transplant patients presenting to a single institution with trauma found that outcomes were no worse than the general trauma population, but trauma may precipitate episodes of rejection.[52] Other small studies have found a higher incidence of fractures but no increased rate of infection compared to general trauma population.[53]

There are a few specific instances where trauma care does differ for transplant patients. When possible, leukoreduced and CMV negative blood is preferred for patients on full immunosuppression. Heart transplant patients may have clinical tamponade from scarring and adhesions, even in the absence of a pericardium. Pleural adhesions may complicate chest tube placement in a lung transplant patient. Traumatic injury of the transplanted kidney and pancreas are rare, despite its location in the anterior pelvis.

Psychological Aspects

Transplant programs widely use psychosocial selection criteria. In general, the cardiac programs have the most stringent criteria. The side effects of lifelong immune suppression or steroid withdrawal can include anxiety, depression, and insomnia. On the other hand, successful transplantation often improves psychological well-being. Transplant social workers can provide awareness of and access to the social network that should surround each transplant

recipient. Long-term compliance with all aspects of treatment will minimize graft rejection.

DISPOSITION

Patients with solid organ transplants presenting to the ED have a much higher than average rate of hospitalization, with infection being the most common cause.[35] The insidious nature of the diseases affecting this immunosuppressed population necessitates a thorough structured approach to evaluation. If organ rejection, infection, or drug toxicity is suspected, local transplantation specialists should be consulted. Physicians without significant transplant experience should contact the patient's transplant center to obtain consultation and to coordinate follow-up care. Patients who are discharged require careful instructions, medication reconciliation to avoid toxicities, and close follow-up.

KEY CONCEPTS

- The possibility of organ rejection, infection, or drug toxicity should be considered in all organ transplant patients who present to the ED, because the presentations can be subtle.
- Anatomic issues related to solid organ transplantation are specific to the organ transplanted and time since transplantation but generally involve thrombosis, stricture, or breakdown and leak of the anastomoses.
- Timing since surgery, state of immunosuppression, exposures and risk factors, and graft function should be taken into account at each ED evaluation.
- Differentiation of infection and rejection is often difficult in the ED. Determination is often made only after biopsy of the transplanted organ or positive culture results are identified.
- Infections that occur 1 to 6 months after transplantation are generally immunomodulating viral infections, such as with CMV, or opportunistic infections.
- A patient's inability to take oral immunosuppressants for even a single day should be considered an emergency condition.
- When prescribing new drugs, care should be taken to avoid drug interactions and toxicity of immunosuppressants.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 188: QUESTIONS & ANSWERS

188.1. A 42-year-old man presents with fever, cough, and shortness of breath. He reports a history of renal transplant approximately 2 months ago. He denies surgical site pain or changes in urine output. Chest radiograph reveals a diffuse interstitial pattern. Although concerned that his fever could be caused by acute organ rejection, you are also concerned about pneumonia. What is the most likely cause of his pneumonia?

A. Cytomegalovirus (CMV)
B. Herpes simplex
C. *Klebsiella pneumoniae*
D. *Listeria monocytogenes*
E. *Staphylococcus aureus*

Answer: A. CMV is the most prevalent cause of pneumonia in the solid organ transplant patient. Infection typically occurs 1 to 6 months after transplant. Infections are serious and often fatal, but aggressive supportive care, as well as treatment with ganciclovir and CMV-specific immunoglobulin, improves outcome. *Pneumocystis jiroveci* pneumonia is also common and can be indistinguishable from CMV except by bronchoscopy. All infections are more common in immunocompromised individuals, with herpes and *Listeria* particularly more common in solid organ transplant patients. *Klebsiella* is typically seen in alcoholics, but it can occur in any patient population. *Staphylococcus* pneumonia is typically severe and can cause abscess formation or empyema.

188.2. Cyclosporine and tacrolimus are both commonly used immunosuppressant medications in solid organ transplant recipients. Unfortunately, both of them can cause significant side effects. Which organ is most at risk of toxicity from these medications?

A. Brain
B. Heart
C. Kidney
D. Liver
E. Lung

Answer: C. Both exhibit dose-related nephrotoxicity. Tacrolimus has an improved side effect profile over cyclosporine, but it can still cause significant adverse effects. Both exhibit significant drug interactions, and care should be taken when adding or subtracting medications because drug levels can be altered easily, resulting in either toxic or subtherapeutic levels.

CHAPTER 189

The Combative and Difficult Patient*

Jason D. Heiner | Gregory P. Moore

THE COMBATIVE PATIENT

Principles

Combative patients are among the most difficult patients emergency clinicians encounter. Often brought in against their will, they can be agitated, confrontational, nearly impossible to examine, and they may physically harm themselves or others. The emergency clinician should seek to control the patient and the situation, diagnose and treat reversible causes of violence, and protect the patient and staff from harm.

The emergency department (ED) is a volatile environment because of high stress, illness, prolonged waiting times, and frequent lack of communication. The 24-hour open door policy, availability of potential hostages, and widespread accessibility of drugs and weapons compound the potential for violent behavior. The assault-injury rate of health care support occupations is nearly 10 times that of the general sector, and over half of all health care providers will be victims of forms of violence during their careers.[1]

Emergency care providers throughout the world are more likely than other health care providers to experience violent events, such as verbal threats, physical assaults, and confrontations outside the workplace.[1-6] A 2011 survey of 263 emergency clinicians found that 78% reported at least one workplace act of violence within the past year, with 21% reporting more than one episode.[4] A 9-month prospective 2013 study of ED health care workers reported an average of over four violent events per health care worker during the study period.[1] From a growing body of literature, similar rates of violence and aggression toward physician and nursing staff are typically observed, and both men and women generally appear to be at comparable risk.[1,4] Violent incidents are far more likely to be verbal threats and acts of intimidation than physical assaults and, in the ED, may be acted out by patients, as well as their family and other visitors.[1-6] The actions of combative patients have consequences that extend beyond the physical injury of ED caregivers, such as provider post-traumatic stress disorder symptoms and lost provider work productivity.[1,6,7]

Presentation

Patient Characteristics

The pathogenesis of violent behavior is conjectural. Potential causes include environmental, historical, interpersonal, biochemical, genetic, hormonal, neurotransmitter, and substance abuse disorders.[8-12] Psychiatric illness is also a risk factor, with schizophrenia, personality disorders, mania, and psychotic depression most frequently associated with violence.[8-12] Delusional schizophrenic patients become violent, believing that others are attempting to harm them. They may also have auditory hallucinations commanding harm to others. The patient with acute mania is unpredictably dangerous because of emotional lability, a situation in which pleasantness can quickly turn to aggression. Substance abuse disorders and drug-seeking behavior are consistently associated with violent behavior in both psychiatric and nonpsychiatric populations.[12-14] Biologically, the serotonin system largely controls aggression and inhibition, with diminished serotonergic function possibly disinhibiting aggression against self and others.[14-16] Generalized brain dysfunction may predispose patients to violence by disruption of the regulation of aggression, particularly in the prefrontal and temporal cortex.[16-19] Cerebral imaging documents both functional and structural impairments in violent criminals and antisocial patients.[20-24]

Violent behavior also occurs in association with head trauma, hypoxia, hypoglycemia, electrolyte imbalance, infections (particularly herpes encephalitis), drug intoxication or withdrawal or adverse reaction, and metabolic and endocrine derangements. Uncommon organic causes include seizures (eg, temporal lobe), tumors (particularly those in the limbic system), limbic encephalitis, multiple sclerosis, porphyria, Wilson's disease, Huntington's disease, sleep disorders, hyperparathyroidism, and vitamin and mineral deficiencies (eg, folate, vitamin B_{12}, niacin B_2, and pyridoxine vitamin B_6). Although drug or ethanol intoxication and withdrawal are the most common diagnoses in combative ED patients, the mnemonic FIND ME (*f*unctional [ie, psychiatric], *i*nfectious, *n*eurologic, *d*rugs, *m*etabolic, *e*ndocrine) helps organize consideration of the many important causes of violence (Box 189.1).

Identification of potentially violent patients is more difficult; male gender, prior history of violence, and drug or ethanol abuse have historically been positive predictors, whereas ethnicity, diagnosis, age, marital status, and education have been unreliable identifiers. Overall, the most accurate tools for predicting acute violent behavior likely relies largely on current observed concerning behaviors and clinical observations of patients in the context of past patterns of violence when known or previously documented.[25-27]

Emergency Department Influences

An annual ED census over 50,000 patients, an average waiting time over 2 hours, and ED crowding are associated with an increased incidence of violence.[2,28] The risk of workplace assault in the ED, however, exists across hospitals of all sizes and reflects the rate of violence in the community. Despite these risks, health care providers are typically not trained in the identification and management of combative patients.[1,4,6]

Patients armed with lethal weapons pose a serious threat to staff and the potential risk posed by concealed weapons exists in all settings including pediatric EDs. The carriage of weapons in the ED population has previously been estimated at approximately 4% to 8% and up to 27% of major trauma patients; however, only a minority of EDs screen for weapons or use metal detectors.[4] Unfortunately, prediction of weapons carriage in any particular

*Disclaimer: The views expressed herein are solely those of the authors and do not represent the official views of the Department of Defense or Army Medical Department.

BOX 189.1

Selected Problems Associated With Violence

PSYCHIATRIC
Schizophrenia
Paranoid ideation
Catatonic excitement
Mania
Personality disorders
- Borderline
- Antisocial
- Delusional depression
- Post-traumatic stress disorder
- Decompensating obsessive-compulsive disorders

SITUATIONAL FRUSTRATION
Mutual hostility
Miscommunication
Fear of dependence or rejection
Fear of illness
Guilt about disease process

ANTISOCIAL BEHAVIOR
Violence with no associated medical or psychiatric explanation (these patients may be managed by the police or security)

ORGANIC
Diseases
Delirium
Dementia
Trauma
Central nervous system infection
Seizure
Neoplasm
Cerebrovascular accident
Vascular malformation
Hypoglycemia
Hypoxia
Acquired immunodeficiency syndrome (AIDS)
Electrolyte abnormality
Hypothermia or hyperthermia
Anemia
Vitamin deficiency
Endocrine disorder

Drugs
Unanticipated reaction to prescribed medication (especially sedatives in brain-injured or elderly patients)
Alcohol (intoxication and withdrawal)
Amphetamines
Cocaine
Sedative-hypnotics (intoxication or withdrawal)
Phencyclidine (PCP)
Lysergic acid diethylamide (LSD)
Anticholinergics
Aromatic hydrocarbons (eg, glue, paint, gasoline)
Steroids

patient is impossible, and it is therefore prudent to assume that all violent patients are armed until it is proved otherwise, especially those presenting with major trauma.

The deleterious effects of violence in the ED can be minimized by employing certain preventive measures and by training staff in techniques to de-escalate and limit violent behavior when it occurs (Box 189.2).

Initial Patient Evaluation

Evaluation of the combative patient begins with attention to safety measures. All patients should be screened for weapons before the interview. The use of metal detection is ideal before ED entry, and additional attention may be needed for patients brought to the ED by ambulance and thereby bypassing routine security booths and metal detectors. The practice of undressing patients and placing them in a gown is useful as a non-confrontational search for weapons that discourages fleeing and aids in identification if the patient escapes from the ED.

The ideal setting for the patient interview emphasizes privacy without isolation. The ideal setting is a seclusion room specifically designed for the interview of potentially dangerous patients. Prior to the medical interview, security should be stationed nearby and the door left open to facilitate both intervention and escape for the provider. The patient and interviewer may be seated roughly equidistant from the door, or the interviewer may sit between the patient and the door. Blocking of the door, however, poses a risk of harm to the clinician if the patient feels the urge to escape. Ideally, examination room doors should swing out, and more than one exit should be available. The clinician should have unrestricted access to the door and never sit behind a desk. The room should not contain heavy or potentially dangerous objects that may be thrown. There ideally should be a mechanism to alert others of danger, such as a panic button or a code word or phrase that summons security (eg, "I need 'Dr. Armstrong' in here."). For personal protection of the provider, earrings, necklaces, and neckties should be removed. Personal accessories that may be used against the caregiver, such as a stethoscope or scissors, should also be removed. The physician should be aware of any objects within the room or on the patient's body that might be used as weapons, such as pens, watches, necklaces, key chains, cell phones, or belts.

Violence risk assessment of a potentially combative patient can be difficult. Violence often erupts after a period of mounting tension. The astute practitioner may identify verbal and nonverbal cues and subsequently have the opportunity to defuse the situation. In a typical scenario, the patient first becomes angry, then resists authority, and finally becomes confrontational and violent. When physicians have a "gut feeling" that a dangerous situation may be developing, they should take appropriate precautions. Violent behavior may also erupt without warning, especially in patients with an organic brain syndrome, so clinicians should not feel overly confident in their ability to sense impending danger. An obviously angry ED patient should be considered potentially violent. Patients with a history of violent behavior are more likely to inflict serious injury, and certain patient behaviors may suggest impending violence (Box 189.3).[26,27]

To prevent escalation, the patient should be removed from contact with other agitated accomplices, as well as from other provocative patients. A quiet area enabling direct observation is optimal. As increased waiting times correlate positively with violent behavior, consider evaluating the potentially violent patient expeditiously to prevent escalation of aggression. When feasible, moving these patients up in line when triaging care may avoid the challenging consequences of violence for the patient at hand, the ED staff, and the care of other ED patients in the triage area and waiting room. Often, the perception of preferential treatment alone may aid to defuse the patient's anger.

BOX 189.2

Emergency Department Preparedness and Prevention of Violence

GENERAL EMERGENCY DEPARTMENT PREPAREDNESS CONSIDERATIONS

Physical and system factors to minimize ED violence risk:

1. Prominently displayed warning signs prohibiting weapons and alerting entering individuals that they may be screened for weapons
2. Nondiscriminatory inquiry about weapon carriage and searches of individuals for weapons with clear local policies for staff about searches and contraband disposal
3. A tiered alarm system with panic buttons in each room to activate a central buzzer in the department
4. ED placement of at least one telephone with a direct line to police or security to request additional personnel if needed
5. Control flow into the ED by limiting access to one or two entrances and consider buzzer access systems, bulletproof glass, and metal bar barriers to protect the physical structure
6. A secure examination room with shatterproof ceiling lights, solid ceiling, heavy indestructible chairs, well-secured restraint bed, two outward swinging doors that can be locked from the outside, an emergency distress button that can be activated unobtrusively, and consideration of a video monitoring system

PRIMARY PREVENTION

Control factors encouraging the development of frustration and aggression:

1. Minimize long waiting times
2. Optimize waiting room environment
3. The presence of visible surveillance cameras
4. The presence of a trained visible security force reflecting both hospital needs and anticipated violence based on local community prevalence

SECONDARY PREVENTION

Response to pre-violent agitation and aggression:

1. Recognition of risk (pre-violent patients and their companions)
2. Implementation of de-escalation techniques
3. Minimize treatment delays of pre-violent individuals
4. Ongoing staff training in violent management techniques to increase caregiver confidence and comfort while decreasing the rate of aggressive incidents

TERTIARY PREVENTION

Limitation of the actual act of violence once it has occurred:

1. Use of physical and chemical restraints
2. Appropriate security and police intervention
3. Apply familiar protocols for dealing with the violent individual

ED, Emergency department.

BOX 189.3

Patient Behaviors Suggesting Impending Violence

Provocative behavior
Angry demeanor
Loud, aggressive speech
Tense posturing (eg, gripping arm rails tightly, clenching fists)
Pacing or frequently changing body position
Aggressive acts (eg, pounding walls, throwing objects, hitting oneself)

BOX 189.4

Ten Elements for Verbal De-Escalation

1. Respect personal space: Maintain a distance of two arm's lengths and provide space for easy exit for either party.
2. Do not be too provocative: Keep your hands relaxed, maintain a non-confrontational body posture, and do not stare at the patient.
3. Establish verbal contact: The first person to contact the person should lead the effort.
4. Use concise, simple language: Elaborate and technical terms are hard for an impaired person to understand.
5. Identify feelings and desires: "What are you hoping for?"
6. Listen closely to what the patient is saying: After listening, restate what the patient said to improve mutual understanding (eg, "Tell me if I have this right …").
7. Agree or agree to disagree: (a) Agree with clear specific truths; (b) agree in general (eg, "Yes, everyone should be treated with respect."); (c) agree with minority situations (eg, "There are others who would feel like you.").
8. Lay down the law and set clear limits: Inform the patient that violence or abuse cannot be tolerated.
9. Offer choices and optimism: Patients feel empowered if they have some choice in matters.
10. Debrief the patient and staff: Be sure to include an opportunity for the patient and staff to speak.

Adapted from the American Association for Emergency Psychiatry De-escalation Workgroup consensus statement: Richmond JS, Berlin JS, Fishkind AB, et al: Verbal de-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA De-escalation Workgroup. West J Emerg Med 13:17-25, 2012.

Therapeutics

Verbal Management Techniques

Consideration of verbal de-escalation techniques should be given to agitated or violent patients prior to implementation of physical restraints or chemical sedation. The agitated but cooperative patient may be amenable to verbal de-escalation techniques alone. This verbal interaction provides an opportunity to assess the patient's mental status and comprehension, as well as perception of the current situation. However, the uncooperative actively violent patient or potentially violent patient may warrant immediate restraint without the risk to the patient and ED staff of verbal techniques. If the patient remains resistant or violent after verbal techniques, or incapable of interacting appropriately, then restraint is necessary.

Successful verbal management techniques include an effort to make the patient as comfortable as possible, being honest and straightforward during the medical interview, adopting a non-confrontational demeanor, and being an attentive and receptive listener without conveying weakness or vulnerability (Box 189.4).[29,30] The interviewer should respond verbally in a calm and soothing tone of voice. It is also important to stand at least an arm's length away and to avoid prolonged direct eye contact, approaching the patient from behind, or sudden movements. In some cases, an agitated patient may be aware of the impulse control problem and welcome limit setting by the clinician (eg, "I can help you with your problem, but I cannot allow you to continue threatening me, the emergency department staff, or other patients."). The interviewer should act as an advocate for the patient. Offering a soft chair or something to eat or drink (not a hot liquid, which may be used as a weapon) may help establish trust, and many patients relax from this attention to basic human needs.

A key mistake in interviewing a potentially violent patient is failing to address the issue of violence directly. The patient should be asked relevant questions about suicidal or homicidal ideations or plans, possession of weapons, history of violent behavior, and current use of intoxicants. Acknowledgment of the obvious (eg, "You look angry.") may help the patient to begin sharing emotions. If the patient becomes more agitated, it may be helpful to speak in a conciliatory manner and to offer supportive statements (such as, "You obviously have a lot of will power and are good at controlling yourself.") to help defuse the situation. If this is not successful, a respectful offer of medication or restraints to the patient may prevent further escalation.

Counterproductive approaches to the combative patient include arguing, machismo ("mano a mano"), threats, deception, and condescension.[29,30] These inappropriate strategies fail to build rapport and may challenge patients to "prove themselves." An open threat to call security personnel also invites aggression. Clinicians should be aware of their own reactions to such patients and avoid transference of anger. The deception of a patient (eg, "I am sure you will be out of here in no time.") may serve to invite violent consequences once the false promise is uncovered and an unsuspecting nurse or colleague who follows the interviewer may be victimized. Do not deny or downplay threatening behavior, and if verbal techniques are unsuccessful and escalation of violence occurs, the physician should leave the room and summon help.

Physical Restraints

Physical restraints should be considered when verbal techniques prove unsuccessful. The use of restraints can be humane and effective in facilitating diagnosis and treatment of the patient while preventing injury to the patient or medical staff. Generally speaking, the liability one incurs for restraining a patient against his or her will is negligible compared with the potential liability for allowing a patient to lose control and cause physical harm to themselves or others. Restraints should not be applied for convenience or as a punitive response for disruptive behavior and should be removed as soon as possible, usually once adequate chemical sedation is achieved.

Indications for emergency seclusion and restraint include the prevention of imminent harm to the patient, others, or the immediate environment, and as part of an effective ongoing behavior treatment program.[30] These patients can typically be broadly classified into three categories: (1) those with an organic disorder for whom restraints facilitate evaluation, (2) those with functional psychosis for whom verbal techniques are less effective and restraints facilitate administration of neuroleptics, and (3) those with personality disorders prohibiting the usefulness of verbal techniques. Seclusion or restraint may be contraindicated because of the patient's clinical or medical condition. Seclusion should not be used in an unstable patient who requires close monitoring and should be avoided when the patient is suicidal (unless adequate continuous observation can occur), self-abusive or self-mutilating, or has had an intentional ingestion of drugs or poisons. The indications for the use of restraints should be documented. Specific statements (such as, "I restrained Mr. Smith because he told me he was going to beat me up and then took a swing at me.") are preferable to general statements (such as, "I restrained Mr. Smith because he was violent.").

The implementation of restraints should be systematic and ideally follow a predetermined ED protocol that is implemented when the examiner leaves the room after verbal techniques are unsuccessful. It may be helpful to consider the application of restraints as a procedure analogous to running an advanced cardiac life support code. Whenever possible, the treating physician should not actively participate in restraint application to preserve the physician-patient relationship. The restraint team ideally consists of at least five people, including a team leader. The leader, whether a physician, nurse, or security officer, is to be the only person giving orders and should be the person with the most experience in implementing restraints. Before entering the room, the leader outlines the restraint protocol and warns of anticipated danger (eg, the presence of objects that may be used as weapons). All team members should remove personal objects that the patient could use against them. If the patient is female, at least one member of the restraint team should ideally be female to potentially mitigate allegations of sexual assault.

The team enters the room in force and displays a professional rather than threatening attitude. Many violent individuals calm down at this point as a large show of force protects their ego (eg, "I would have fought back but there were too many against me."). The leader speaks to the patient in a calm and organized manner, explaining why restraints are needed and what the course of events will be (eg, "You require a medical and psychiatric examination, as well as treatment."). The patient is instructed to cooperate and to lie down to have restraints applied. Some patients are relieved at the protection to self and others afforded by restraints when they feel themselves losing control. Even if the patient suddenly appears less dangerous, however, once the decision to restrain is made, continue the process and do not negotiate with the patient at this point.

If physical force becomes necessary, one team member restrains a preassigned extremity by controlling the major joint (knee or elbow). The team leader controls the head. If the patient is armed, two mattresses can be used to charge and immobilize or sandwich the patient. Restraints are applied securely to each extremity and tied to the solid frame of the bed (not side rails, as later repositioning of side rails also repositions the patient's extremity).

Leather is the optimal type of restraint, because it is a physically stronger material and less constricting than typical soft restraints. For this reason, gauze should not be used. Soft restraints may help restrict extremity use in the semi-cooperative patient but are likely to be less effective in the truly violent patient who is continuing to struggle and attempt escape. If chest restraints are used, it is vital that adequate chest expansion for ventilation is ensured. The application of a soft Philadelphia collar to the patient's neck may minimize head banging and biting. While restraining patients on their sides helps prevent aspiration, we recommend the supine position with the head elevated, because it is more comfortable and allows a more thorough medical examination while providing some protection against aspiration. Once the patient is immobilized, announcing "the crisis is over" will have a calming effect on the restraint team and the patient.

We recommend avoiding the prone restraint position when possible and employing chemical sedation when a patient continues to struggle against physical restraints. Sudden unexpected deaths have been reported in such patients, particularly if left unattended during busy shifts or between multiple sign-outs with various treating physicians. Although healthy volunteers, when restrained and undergoing physical exertion, do not appear to experience clinically significant positional asphyxia, combative ED patients often suffer from other conditions that may predispose to increased morbidity. Patients using cocaine or other stimulants who are restrained in the prone position appear to be uniquely at risk because increased sympathetic tone and altered pain sensation allow exertion beyond normal physiologic limits and sympathetic-induced vasoconstriction may impede clearance of metabolic waste products and induce hyperthermia and rhabdomyolysis.[31] Alteration of respiratory mechanics in an acidemic patient resulting from the position of restraint can be a contributing factor by impairment of respiratory compensation.

After restraints are successfully applied, the patient should be monitored frequently and positions changed to prevent neurovascular sequelae, such as circulatory obstruction, paresthesias, and

rhabdomyolysis associated with continued combativeness. Standardized documentation is recommended for this monitoring to include the specific indication for restraint and, ideally, other colleague agreement that restraints are necessary. Basic patient needs must be met (eg, hydration, toileting needs) and physical restraints should be removed as soon as possible. Review of restraint team performance and critical discussion may reveal opportunities for improvement. Education and rehearsal by staff can improve and maintain restraint skill and improve comfort and confidence with this skill.

Chemical Restraints

Chemical sedation alone or in conjunction with physical restraint may assist in the safe management of an agitated or violent patient unresponsive to verbal de-escalation techniques. Chemical restraints subdue patients who may otherwise harm themselves or others and facilitate their medical evaluation and treatment. Clinical and administrative guidelines for their use are similar to those for the use of physical restraints. The use of medication to calm a patient may obscure the mental status examination and clinical diagnosis. This should be weighed, however, against the increased risk that both the patient and staff may face if such medication is withheld.

The ideal agent for controlling combative patients should be effective, safe and well tolerated, free of significant side effects and drug interactions, rapid in onset, titratable, and available through multiple routes of administration. Several pharmaceutical agents can quickly achieve safe behavioral control, or "rapid tranquilization," without oversedation. However, they should be used with caution and close patient monitoring, because there is a paucity of rigorous clinical studies of chemical sedation in unique settings, such as acute delirium, the underlying comorbid or primary conditions of violent ED patients are often unknown, and a degree of individual variation to response to any medication should be anticipated.

Three primary classes of medication commonly used in the ED for chemical sedation are benzodiazepines, first-generation (typical) antipsychotics, and second-generation (atypical) antipsychotics.[32,33] With these medications, we suggest a patient-based approach to chemical sedative selection based on suspected or known clinical features (Box 189.5).

Benzodiazepines and antipsychotics (also known as *neuroleptics*) are commonly used either alone or in combination for rapid tranquilization. Chemical restraints should ideally be taken voluntarily by a patient, because the offer of voluntary administration may restore some feeling of control and ease escalating agitation. The intramuscular (IM) route is often advantageous in the uncooperative and dangerous patient refusing an oral medication or an intravenous (IV) catheter. As with physical restraints, it is imperative that these patients be evaluated regularly for changes in their clinical status.

BOX 189.5

Suggestive Patient-Based Approach to Chemical Restraint

THE SEVERELY VIOLENT PATIENT
Droperidol 2.5 to 5 mg IM/IV, titrate as needed
or
Midazolam 2.5 to 5 mg IM/IV, titrate as needed
or
Midazolam 2.5 to 5 mg IM/IV with droperidol 2.5 to 5 mg IM/IV, titrate either as needed
or
Haloperidol 2. 5 to 5 mg IM/IV with lorazepam 2 mg IM/IV, titrate either as needed

THE UNDIFFERENTIATED SEVERELY AGITATED PATIENT OR WITH STIMULANT INTOXICATION
Lorazepam 2 to 4 mg IM/IV
or
Midazolam 2.5 to 5 mg IM/IV
or
Haloperidol 5 mg IM/IV with lorazepam 2 mg IM/IV

THE PATIENT INTOXICATED WITH A CENTRAL NERVOUS SYSTEM DEPRESSANT (EG, ALCOHOL)
Haloperidol 2.5 to 5 mg IM/IV
or
Droperidol 2.5 to 5 mg IM/IV

THE PATIENT WITH A KNOWN PSYCHOTIC/PSYCHIATRIC DISORDER
Haloperidol 2.5 to 5 mg IM/IV
or
Droperidol 2.5 to 5 mg IM/IV
or
Haloperidol 2.5 to 5 mg IM/IV with lorazepam 2 mg IM/IV
or
Ziprasidone 20 mg IM*
or
Olanzapine 10 mg IM*

THE COOPERATIVE BUT AGITATED PATIENT
Lorazepam 2 to 4 mg PO
or
Risperidone 2 mg PO*
or
Olanzapine 5 to 10 mg PO*

THE ELDERLY PATIENT
Reduce above medication dose by half*

IM, Intramuscular; *IV*, intravenous; *PO, per os* (by mouth).
*The safety of atypical antipsychotics in geriatric patients remains somewhat uncertain.

Benzodiazepines. Benzodiazepines, particularly lorazepam (Ativan) and midazolam (Versed), are often used in the ED for rapid tranquilization of an agitated or violent patient. Benzodiazepines enhance the activity of the major inhibitory neurotransmitter γ-aminobutyric acid to cause anxiolytic, anticonvulsant, and sedative effects. These agents are particularly preferred for the management of agitation caused by ethanol or sedative-hypnotic drug withdrawal, as well as cocaine, amphetamines, and sympathomimetic drug ingestions. Benzodiazepines may be more effective than antipsychotics in reducing delirium and mortality and are useful in patients at risk for seizure or when antipsychotic associated akathisia must be avoided. For these reasons, we prefer the use of benzodiazepines when sedating the patient with agitation from an unknown cause. Although they are generally well tolerated, side effects of benzodiazepines include excessive sedation, ataxia, confusion, nausea, and respiratory depression, which may be amplified in the presence of concurrent alcohol and other depressant use.

Lorazepam is frequently preferred to other benzodiazepines because of its rapid onset of action, short half-life, route of elimination with no active metabolites, and effectiveness by oral, IM, or IV routes of administration. Recommended initial oral, IM, or IV doses of lorazepam range from 0.5 mg to 4 mg. Typical doses for chemical restraint in the ED begin at 1 mg to 2 mg increments IM or IV with upward titration as needed. The onset of action after administration of lorazepam is generally 5 to 20 minutes if

it is given IV or 15 to 30 minutes if it is given IM, with a duration of action of 6 to 8 hours.

Midazolam is also an effective benzodiazepine for achievement of mild sedation and has a more rapid onset of action and a shorter duration of clinical effects than lorazepam. The IM route is used widely to calm the agitated patient with a typical initial dose of 2.5 mg to 5 mg IM. When it is administered IM, the medication usually takes effect in about 15 minutes with a mean duration of 2 hours. In a comparison of midazolam 5 mg IM, lorazepam 2 mg IM and the antipsychotic haloperidol 5 mg IM to sedate violent and agitated patients, all three showed similar efficacy, but midazolam demonstrated a more rapid onset of action and shorter duration of activity than the other medications.[33] The choice of midazolam versus lorazepam may in part be guided by the duration of sedation desired.

Antipsychotics. Antipsychotic medications also play a prominent role in the chemical restraint of the violent ED patient. These medications include the older "typical" (or "classic") antipsychotics and the newer "atypical" antipsychotics. Although the precise mechanisms of action are unclear, typical antipsychotics appear to strongly block brain dopamine receptors, whereas the atypical antipsychotics less strongly and more specifically antagonize dopamine and serotonin receptors.[34,35] Both classes of antipsychotics have variable effects on other receptors, such as the adrenergic, cholinergic, and histaminic receptors. The typical antipsychotics can be categorized in terms of their "potency," a description referring to the relative dosing of the medication and generally predictive of its side effect profile. The incidence of sedation, hypotension, and anticholinergic side effects is higher with the low-potency antipsychotics, whereas the incidence of extrapyramidal symptoms is greatest with the high-potency antipsychotics. Low-potency antipsychotics include chlorpromazine (Thorazine) and thioridazine (Mellaril), medium-potency antipsychotics include loxapine (Loxitane) and molindone (Moban), and high-potency antipsychotics include haloperidol (Haldol) and droperidol (Inapsine).

Of the older typical antipsychotics, the butyrophenones—haloperidol and droperidol—have been widely used in the emergency setting. Haloperidol is the most frequently administered antipsychotic to control the agitated ED patients.[36] It is available in oral, IM and IV preparations, although the commonly used IV route of administration is not approved by the U.S. Food and Drug Administration (FDA). Haloperidol is generally given in 2.5 mg to 10 mg IM doses (often 5 mg IM for the severely agitated average sized adult), with half doses administered to elders followed by repeated dosing every 20 to 60 minutes as needed. Effects are usually seen within 30 minutes by the IM route, and the average patient typically requires fewer than three doses for the desired clinical effect.[37]

Droperidol has been commonly used at doses of 2.5 to 10 mg IM and 2.5 to 5 mg IV in a manner similar to haloperidol to control the agitated or combative patient.[38] Compared with haloperidol, droperidol appears to more rapidly reduce agitation at equal IM dosing, has a shorter duration of effect, more sedation, a larger incidence of orthostatic hypotension, and a lesser incidence of extrapyramidal symptoms. When compared with midazolam 10 mg IM, droperidol 10 mg IM appears to have an equally rapid onset of action and requires fewer additional doses for sedation.[39] The clinical use of droperidol decreased markedly after it was given a controversial black box warning in 2001 by the FDA for concern of QTc prolongation and torsades de pointes.

Haloperidol is also associated with QTc prolongation and torsades de pointes. Given the effectiveness and overall safety of these medications and the unclear risk association of potential QTc prolongation, we recommend the cautious use of both haloperidol and droperidol when these medications are administered to patients with other identified risk factors or the known presence of existing QTc prolongation secondary to other antipsychotic agents or methadone.[40] We also recommend obtaining an electrocardiogram or placing the patient on a cardiac monitor before drug administration if possible.[40] If this is precluded by poor cooperation of the violent or agitated patient, we recommend obtaining electrocardiogram as soon as possible once the patient becomes more cooperative.

Common side effects of haloperidol and droperidol are sedation, orthostatic hypotension, and extrapyramidal symptoms. Extrapyramidal symptoms are thought to be due to mesolimbic dopamine receptor blockade. They are not dose related and may occur immediately or days after medication administration.[34,35] Patients can have akathisia (extreme restlessness) and uncoordinated involuntary movements known as dystonia, including of the muscles of the mouth (buccolingual), neck (torticollis), back (opisthotonos), eyes (oculogyric crisis), and trunk (abdominopelvic). Treatment includes diphenhydramine 25 mg to 50 mg IV or IM or benztropine 1 mg to 2 mg IV or IM acutely and extended for 3 days to minimize symptom recurrence. Both haloperidol and droperidol do have minimal anticholinergic properties and are often coadministered with diphenhydramine or benztropine, so they should not be used to control agitation in a patient with known anticholinergic intoxication. Haloperidol and droperidol should also be avoided in patients with alcohol, benzodiazepine, or other sedative withdrawal syndromes, patients with known seizure disorders, and when possible avoided in pregnant or lactating females and patients with phencyclidine overdoses.

Neuroleptic malignant syndrome is a rare and potentially lethal idiosyncratic reaction estimated to occur in 0.01% to 0.04% of patients receiving antipsychotic medications.[41] Characteristic symptoms include autonomic instability, hyperthermia, "lead-pipe" muscle rigidity, and altered mental status. If neuroleptic malignant syndrome occurs, further antipsychotics should be withheld, and we recommend initiation of supportive treatment and rapid external cooling (see Chapter 155).

Chemical restraint with newer atypical antipsychotics (such as, olanzapine, ziprasidone, and aripiprazole) is generally safe and effective in the treatment of agitated patients, although their role in the treatment of the ED patient is still evolving because most of this research has been done in patients with known psychiatric disorders and not undifferentiated violent behavior.[32-34,42,43] Compared with the typical antipsychotics (such as, haloperidol), these medications appear to provide more tranquilization than sedation, have increased efficacy on both positive and negative symptoms in the outpatient, and have fewer extrapyramidal side effects.[32-34,42,43] Their use in the ED is facilitated by IM and oral dissolving tablet formulations that may assist in a smoother transition to oral dosing in those patients requiring ongoing antipsychotic therapy. Although the clinical significance is uncertain, atypical antipsychotics carry a black box warning associating their use with an increased risk of death in elders with dementia-related psychosis and may also cause some degree of QTc prolongation.[40] As a result, we recommend employing the same precautions used with the typical antipsychotics. Because ED experience with these agents is limited, we prefer the use of benzodiazepines and first-generation antipsychotics in cases of severe agitation or violence, pending the completion of more rigorous trials in the undifferentiated ED patient population.

Olanzapine (Zyprexa) is readily available in IM, oral, and oral-dissolving tablet formulations; and it has a reported distinct "calming" effect in clinical practice. It has FDA-approved indications for the treatment of agitation associated with bipolar I mania and schizophrenia. IM olanzapine has an onset of action of 15 to 45 minutes after initial administration and is typically administered as an initial dose of 2.5 mg to 10 mg followed by one or two subsequent doses every 2 to 4 hours for a total

maximum dose of 30 mg.[37] Although generally well tolerated, side effects include sedation (which may be unexpectedly additive in the setting of concomitant benzodiazepine use), mild hypotension, and anticholinergic properties that can exacerbate existing anticholinergic intoxication.[37] Olanzapine has minimal QTc-prolonging effects and a lesser occurrence of acute dystonia and akathisia compared with haloperidol.

Ziprasidone (Geodon) is FDA approved for treatment of the agitated schizophrenic and bipolar manic patient. Typical dosing is 10 mg IM every 2 hours or 20 mg IM every 4 hours (not to exceed 40 mg/day) with an onset of action of 15 to 30 minutes. Ziprasidone is generally well tolerated, although side effects such as somnolence, dizziness, and headache are common, and it appears to have potentially notable QTc-prolonging effects.

Aripiprazole (Abilify) has FDA-approved indications for the treatment of agitation associated with the schizophrenia or bipolar disorders. Recommended doses for the acutely agitated patient are 5.25 to 15 mg IM (often 9.75 mg) every 2 hours as needed (to a maximum daily dose of 30 mg).[37] Aripiprazole IM (9.75 and 15 mg) may have comparable efficacy to lorazepam 2 mg IM with a low risk of oversedation.

Risperidone (Risperdal) is typically used for schizophrenia and available in an oral and IM depot form with typical dosing of 1 mg to 2 mg. The medication's time to peak concentration is shorter than some oral second-generation antipsychotics and may be useful when rapid control of agitation is needed and an oral medication is to be given. Orally, risperidone appears to be as effective and tolerable as IM administration of haloperidol.[44] In a randomized trial of 42 agitated patients with psychosis and blinded raters, IM olanzapine, oral disintegrating olanzapine, and oral risperidone solution were found to be as effective as IM haloperidol for the treatment of acute agitation.[44]

Benzodiazepines and typical antipsychotics are commonly used in combination to chemically restrain the agitated or violent patient. Previously demonstrated effective combinations have included midazolam (5 mg IV or IM) with droperidol (5 mg IV or IM) and lorazepam (2 mg IV or IM) with haloperidol (5 mg IV or IM). When given together, lorazepam and haloperidol appear to be more rapidly sedating than either medication alone, have fewer adverse effects, and are compatible within the same syringe for up to 16 hours. Half doses should be administered to otherwise appropriate elders. If additional medication is immediately needed, we recommend consideration of additional midazolam every 3 to 5 minutes or lorazepam every 10 to 20 minutes. Although more investigations are needed to assess the efficacy and safety of the combination therapy of benzodiazepines with second-generation antipsychotics in the treatment of acute agitation in the ED, one multicenter, randomized, double-blind controlled trial found combination of either droperidol (5 mg IV) and midazolam or olanzapine (5 mg IV) and midazolam provided more rapid sedation of acutely agitated ED patients than midazolam (2.5 to 5 mg IV) alone with a mean time to sedation of 14 minutes for the olanzapine group.[45]

Ketamine. Ketamine is a dissociative anesthetic with a good safety profile used to manage the violent and acutely agitated patient in the hospital and prehospital setting, including after treatment failure with benzodiazepines and antipsychotics.[46-48] Although its use in agitated delirium in young adults is increasingly described, we recommend avoiding its use in elders with acute agitated delirium, patients at increased risk for heart disease, and patients with schizophrenia, because it can exacerbate this condition. For the treatment of acute violent agitation in the ED patient, we recommend an initial dose of 1 to 2 mg/kg IV or 4 to 5 mg/kg IM. The onset of drug action is typically 1 to 2 minutes after IV use and often 4 minutes or longer after IM administration, with duration of action of approximately 20 minutes. Notable side effects include hypertension and tachycardia (usually mild and transient), drooling, laryngospasm and other respiratory complications (uncommon), emesis, and emergence reactions.

Post-Restraint Medical Evaluation

Once combative patients are controlled, they require evaluation for organic causes of their agitated behavior. Separation of functional (psychiatric) from organic (medical) disease is a challenging task complicated by the fact that many patients with psychiatric disorders suffer from organic medical disorders that may worsen their symptoms. Patients who exhibit violent behavior that is caused or exacerbated by an organic problem may rapidly deteriorate if the medical issues are not addressed in a timely fashion. A focused history and physical examination assist the physician in differentiating functional from organic illness.

Historical features may distinguish functional from organic illness (Table 189.1). Patients older than 40 years old who have a new onset of psychiatric symptoms are more likely to have an organic cause. Elders are at higher risk for organic delirium from medical illness or adverse medication reactions. Patients with a history of drug or ethanol abuse may exhibit violent behavior as a manifestation of an intoxication or withdrawal syndrome. The acute onset of agitated behavior, as well as behavior that waxes and wanes over time, suggests an organic origin. Most psychiatric

TABLE 189.1

Distinguishing Organic From Functional Causes of Violent Behavior

CLINICAL FEATURE	ORGANIC		FUNCTIONAL
	DELIRIUM	DEMENTIA	
Onset	Acute	Gradual	Gradual
Age at onset	Any	>50 years old	<40 years old
Alertness	Altered	Normal	Normal or hyperalert
Orientation	Impaired	Normal	Normal
Hallucinations	Common; can be visual, auditory, or tactile	None	Auditory in schizophrenia, otherwise uncommon
Symptom picture	Fluctuating	Stable	Stable
Abnormal vital signs	Common	Uncommon	Uncommon
Psychiatric history	No	No	Yes

TABLE 189.2

Vital Signs and Toxic Syndromes

TOXIN	BLOOD PRESSURE	PULSE	RESPIRATORY RATE	TEMPERATURE	PUPIL SIZE	SKIN	EXAMPLE
Sympathomimetic	↑	↑	↑	↑	↑	Wet	Cocaine
Anticholinergic	↑/↓	↑	↑/↓	↑	↑	Dry	Diphenhydramine
Cholinergic	↑/↓	↑/↓	—	—	↓	Wet	Pesticides
Opioids	↓	↓	↓	↓	↓	—	Morphine
Sedatives	↓	↓	↓	↓	↑/↓	—	Lorazepam
Withdrawal (ethanol, sedative-hypnotics)	↑	↑	↑	↑	↑	Wet	Benzodiazepine withdrawal

patients are alert and oriented and have known psychiatric conditions.

The history should include psychiatric, medical, family, and social information, including suicidal ideation, drug and alcohol use, medication use, and any recent changes to prescribed medications. Family and friends can often provide valuable details, because the agitated patient may be unreliable. When they are available, they should be interviewed independently from the patient.

The violent patient should be asked for permission to perform a thorough physical examination to search for an organic cause of violent behavior and to uncover any resulting injury. Restraint of the patient may be necessary to accomplish even the most rudimentary physical examination, including obtaining accurate vital signs. Patients with persistently abnormal vital signs, a clouding of consciousness, or focal neurologic findings are more likely to suffer from organic disease and require further diagnostic evaluation. A careful examination should be mindful of the patient's general appearance (eg, hygiene, nourishment, tremors), vital signs, evidence of trauma or needle tracks, characteristic odors, neurologic and mental status, and signs of a possible toxidrome (Table 189.2).

In general, we recommend tailoring diagnostic studies on the basis of clinical findings.[49-52] When safe to do so, an initial rapid blood glucose determination and pulse oximetry should be obtained for all combative patients. Patients younger than 40 years old with a prior psychiatric history, normal physical examination, calm demeanor, normal orientation, and no physical complaints are likely to require no further diagnostic testing.[49-52] Additional studies that may be useful in selected patients include serum electrolyte values, blood and urine toxicology screening, serum ethanol level, thyroid function panel, cranial imaging, and electroencephalography. A lumbar puncture may be performed if a central nervous system infection is suggested if the patient is cooperative or properly sedated. Specific medication levels may be determined when toxic levels would affect therapy. An electrocardiogram may be useful in elders and in the setting of a suggested intentional ingestion. Patients who may have intentionally ingested a toxic substance should also have aspirin and acetaminophen level measurements, because these potentially fatal ingestions may be difficult to diagnose clinically.

Although serum ethanol and toxicology screening may not significantly influence a patient's ED treatment, the psychiatrist may use them to assess the degree to which ethanol or drug use contributes to the patient's behavioral issues. Ideally, an agreement on a diagnostic strategy should be reached between the psychiatrist and emergency clinician before referral. Unnecessary diagnostic testing prolongs ED length of stay and delays definitive psychiatric care.[49]

Disposition and Medical Clearance

The emergency clinician often provides "medical clearance" for the psychiatric or combative patient brought to the ED in police custody or after being placed on a psychiatric hold in the prehospital setting. "Medical clearance" is a misnomer, because a patient is not "cleared" of all possible medical conditions on completion of the ED evaluation; additionally, there is no standard process for the provision of what may be more accurately termed a "focused medical assessment." A better phrase in this setting is "medically stable for psychiatric evaluation." Few patients with primary psychiatric complaints are likely to have emergent complications of chronic disease or medical problems contributing to their violent behavior.[49-52] However, misattribution of aberrant organic behavior in a patient with known psychiatric disease is a common cause of litigation, and most psychiatrists rely on the emergency clinician's medical assessment of the patient.

Aspects of medical screening evaluations including specific laboratory tests are often influenced or dictated locally by the policies of the requesting or receiving entities of the patients following ED evaluation. When feasible, we believe that patients with known psychiatric disease who are deemed to be at low risk for active or complicating organic medical conditions can be rapidly referred for psychiatric evaluation once they are calm and cooperative with a therapeutic psychiatric interview. Patients at higher risk for an acute organic illness require further diagnostic studies. Potential high-risk considerations in the prehospital or ED setting include altered mental status, ingestion, hanging, rape, traumatic injury, or unrelated medical complaint.[49,50] The medical screening evaluation findings should ideally be communicated to the consulting psychiatrist or other mental health provider and the medical record reflect that the evaluation shows no evidence that an acute medical condition is contributing to the patient's behavior. When the cause of the patient's violent behavior is drug or ethanol intoxication, further observation may reasonably be achieved in the ED or another facility where the patient can be safely observed until the effects of the intoxicants have abated and any further warranted mental health examination can occur.

Assault and Hostage Situations

Interventions to prevent assault and hostage situations, such as optimization of ED security and general preparedness (see Box 189.2), are paramount when considering these violent events, because the rates of extreme hospital and ED violence have increased over time.[53,54] Unfortunately, physical assault may occur despite appropriate precautions and interventions. The victim of physical assault or threat of harm with a weapon can take steps to

BOX 189.6

Protective Responses to Physical Assault or Weapon Threat

If physically assaulted:
1. Immediately summon help (via panic button if possible).
2. Maintain a sideward posture, and keep arms ready for self-protection.
3. Use an arm or leg to deflect a punch or kick.
4. If choked, tuck in the chin to protect the neck, carotid circulation, and ability to breathe.
5. If bitten, do not pull away—push toward the assailant's mouth and hold the assailant's nares shut.

If threatened with a weapon:
1. Appear calm, adopt a nonthreatening posture, and avoid sudden movements.
2. Do not reach for the weapon.
3. Comply with demands, and avoid arguing, despair, or whining.
4. Do not bargain, make promises, or lie.
5. Attempt to establish a human connection with the hostage taker.
6. Appear less expendable by offering to administer aid to other hostages.
7. Reassure the hostage taker that a person of authority will arrive promptly to hear their complaints or demands.
8. If a weapon is put down, do not reach for it—instead attempt verbal resolution of the crisis while awaiting security.
9. Request a hostage negotiator from legal authorities if needed.

protect both themselves and other potential victims in the ED (Box 189.6).

The frequency of hospital-based shootings has more than doubled over the past decade to about 16 typically deadly incidents per year that commonly involve prisoners brought under guard for treatment, as well as disgruntled, demented, and mentally ill patients.[53,54] Each hospital should have a plan of action for cases of extreme violence. The plan should include prevention and safety measures, a means for rapid notification of security and police personnel, evacuation plans, medical treatment, and crisis intervention. Scenario-based training drills for medical personnel and dedicated multidisciplinary hospital violence management teams may help optimize an ED's readiness and management of extreme patient aggression.[55]

BOX 189.7

Factors Impacting the Difficult Patient-Physician Interaction

EMERGENCY DEPARTMENT FACTORS
Lack of patient choice of facility or physician
Time constraints, frequent interruptions, other priorities of care
Suboptimal patient privacy or comfort (eg, hallway examinations)
Long waiting times, department crowding
Negative non-physician bias toward the patient (eg, by prehospital team, nursing)

PHYSICIAN FACTORS
Poor communication
Difficulty expressing empathy or becoming easily frustrated
Personal negative bias and prejudices toward conditions and interactions
Limited knowledge of the patient's condition or psychosocial situation
Overly rigid medical agenda or interaction
Outside stresses affecting work
Emotional burnout or insecurity
Personal health issues
Situational stressors and perceived time pressure
Sleep deprivation or shift fatigue

PATIENT FACTORS
Behavioral issues (eg, argumentative, manipulative, medical noncompliance)
Fear of abandonment
Psychiatric conditions
Low literacy
Financial constraints
Chronic pain syndromes
Multiple complaints
Beliefs or goals of care foreign to the physician
Unrealistic expectations
Substance use disorder
Past or current physical, emotional, or mental abuse
Life stress or social disarray

Cannarella Lorenzetti R, Jacques CH, Donovan C, et al: Managing difficult encounters: understanding physician, patient, and situational factors. Am Fam Physician 87:419-425, 2013; Breen KJ, Greenberg PB: Difficult physician-patient encounters. Intern Med J 40:682-688, 2010.

THE DIFFICULT PATIENT

Principles

The difficult patient is one who is perceived to interfere with the physician's ability to establish a normal patient-physician relationship. Difficult patients are experienced across medical specialties and may represent 15% to 30% of physician-patient encounters.[56-60] Such patients have been described as invoking feelings such as "heart sink," dread, anxiety, and dysphoria in their caregivers, causing chaos in the medical setting, and they may carry a number of pejorative labels.[56-60] High frequencies of difficult patient encounters appear to be associated with physician dissatisfaction and burnout.[56,58]

The difficult patient-physician relationship is a consequence of aspects of the ED environment, physician characteristics, patient factors, and the complex dynamic interaction of these elements (Box 189.7).[56,61] These elements can act in concert to perpetuate a cycle of impaired patient-physician interactions, which may dominate the clinical encounter with negative effects on both the patient and provider. This can be particularly problematic in the case of patients with maladaptive patterns of behavior in the presence of unrecognized physician bias or poor communication. Physicians may react negatively to perceived difficult or unreasonable patients, which may summon fear of abandonment in such patients. In response to this perceived threat, the patients may attempt to sustain the patient-physician relationship through escalation of the actions that were originally perceived negatively by the physician. The subsequent physician reaction may be even greater in magnitude and result in even further escalation by the patient as the cycle continues. Ultimately, the patient may feel dissatisfied with care, diagnoses may be missed or made incorrectly due to the dysfunctional interaction, and discharge from the ED may be made prematurely by either the patient or provider. Following such encounters, the physician may experience frustration, exhaustion, a sense of failure or defeat, and fear of litigation. Also, unconstructive patient stereotypes or unrecognized prejudices may develop or perpetuate.

To every patient encounter the ED physician brings personal and professional experiences, bias, personality, and interpersonal skills. Some physicians appear to have a greater number of difficult encounters than other physicians, and similar interactions or

patients may not be perceived as "difficult" by different physicians.[57,59,61] Younger physicians, physicians who are more uncomfortable with diagnostic uncertainty, and physicians with poorer communication skills and psychosocial orientation are all more likely to have difficult patient encounters.[57,59,61] Within the complex difficult patient encounter, the physician has the greatest opportunity to positively alter aspects of his or her contribution to interaction. When recognized, strategies exist to help the physician manage negative reactions to difficult patient experiences (Box 189.8).[56] Communication is a critical aspect of the patient encounter affecting medical care, patient satisfaction, and overall patient perception of the experience—some general concepts of communication can aid the difficult patient interaction (Table 189.3).[56,59]

BOX 189.8

Tools for Managing Negative Reactions

MAINTAIN APPROPRIATE EMOTIONAL DISTANCE
Avoid reciprocating hostile behaviors while maintaining a sense of empathy for the patient

UNDERSTAND NEGATIVE BEHAVIOR AS A SYMPTOM
View the patient as a victim of their circumstances

LOOK FOR COGNITIVE DISTORTION
Be cautious not to overly-stereotype and cloud clinical judgment and avoid perpetuating negative labels

VIEW NEGATIVE REACTIONS IN CONTEXT
Recognize when one feels overwhelmed by the expectations of the emergency department (ED) work environment to gain perspective on personal reactions

Cannarella Lorenzetti R, Jacques CH, Donovan C, et al: Managing difficult encounters: understanding physician, patient, and situational factors. Am Fam Physician 87:419-425, 2013.

Specific Disorders

The primary characteristic of a difficult patient is an ability to frustrate or trigger a negative emotional response in the physician.[56] Difficult patients are more likely to be older, widowed or divorced, and have more acute or chronic medical problems. They are more likely to have notable psychiatric, substance or alcohol use disorders, and social issues such as homelessness.[56] Rather than a diagnosis or demographic, it is typically the behaviors of these patients and subsequent therapeutic dynamic that characterize the difficult encounter. Categorizing potentially difficult patients based on four common dominant behavior types—dependent clinger, entitled demander, manipulative help rejecter, and self-destructive denier—allows a structure for the physician to approach and manage challenges that may arise (Table 189.4).[57,59]

The Dependent Clinger

The "dependent clinger" may have associated personality disorders (dependent, borderline, or histrionic), may be malingering, or possess somatoform disorders or other chronic psychiatric diagnoses. The patient is characterized in part by an excessive need for attention with an initial extreme delivery of gratitude, which the physician may welcome. However, as the amount of care that the patient receives grows, so does their needs and demands. This cycle continues to often leave the physician frustrated and exhausted and eager to discharge or refer the patient to another physician.

When such patients are identified, the physician should carefully establish reasonable expectations and limits before the cycle

TABLE 189.3

Communication Strategies for the Difficult Patient Encounter

GOAL	PHYSICIAN ACTION	EXAMPLE
Structure the interview	Set time limits and expectation that interruptions may occur	"Thank you for your patience. I may have to excuse myself to care for another patient, but if we are interrupted, I will return to pick up where we left off and provide you with the care you need."
Set limits	Establish ground rules for behavior	"We want to help you, but your language and behavior is offending other patients—making it difficult to care for you and other patients. Please be mindful of your remarks or you may need to be escorted out."
Active listening to improve understanding	Allow the patient to talk without interruption, summarize concerns, and recognize that anger is usually a secondary emotion	"Help me to understand what is upsetting you so much right now."
Understand the patient's agenda	Nonjudgmentally inquire about the patient's primary needs, concerns, expectations, and so on	"What is the most important thing that we can do to help you right now?"
Validate emotion and empathize	Disarm intense emotion by attempting to name the patient's emotional state and express concern and empathy	"You seem upset." "You are right. It is frustrating to wait a long time to be seen."
Redirect the interview	Avoid pursuing trivial, chronic, or tangential complaints by redirecting focus	"I think I can help you most right now if we focus on your main concern first."
Take a time out	Leaving a patient's room and returning after both parties have regained composure is prudent if unable to contain one's frustration	"Thank you for your openness. I need to step out, and I will be back to see what we can do to help you."

Cannarella Lorenzetti R, Jacques CH, Donovan C, et al: Managing difficult encounters: understanding physician, patient, and situational factors. Am Fam Physician 87:419-425, 2013; Breuner CC, Moreno MA: Approaches to the difficult patient/parent encounter. Pediatrics 127:163-169, 2011.

TABLE 189.4

Approaches to Challenging Patient Behavior Types

PATIENT TYPE	CHARACTERISTIC OF PHYSICIAN RESPONSE	SUGGESTED STRATEGIES
DEPENDENT CLINGER		
• Excessive need for attention and reassurance • May use helplessness and seduction • Worried about abandonment • Escalating requests and demands	• Physician may initially feel special and welcome the patient's praise • As patient demands increase and physician time and energy commitment increases, a feeling of frustration, exhaustion, and resentment dominate	• Recognize the inflated positive self-esteem feeling that is being cultivated • Maintain a professional demeanor • Establish boundaries of care early and maintain them • Crisis intervention may be needed • Involve the patient in decision making including appropriate follow-up
ENTITLED DEMANDER		
• Uses intimidation, hostility, name dropping, blame, and threats • May refuse necessary steps of assessment or treatment • Behavior caused by fear of loss of power or physician abandonment	• Initial desire may be to engage in the patient's conflict • Physician may feel intimidated, inadequate, or fear litigation	• Resist urge to enter into conflict and avoid power struggles • Reinforce concept that the patient is entitled to good medical care while setting limits on unreasonable demands and behavior • Allow the patient to choose between reasonable treatment options • If a specific emotion is evident, recognize it and address it with the patient
MANIPULATIVE HELP REJECTER		
• Excessive need for attention through multiple visits and unsolvable problems • Rejects the possibility that any treatment will help	• Physician may feel frustrated and overlook real significant illness, but also may share the patient's pessimism and fear that serious illness has been missed	• Be mindful of cognitive distortions that may obscure real illness • Set limits on expectations while being supportive
SELF-DESTRUCTIVE DENIER		
• Disregard for own health with repeated self-destructive behaviors • Feels helpless or hopeless about changing the situation	• Physician may feel frustrated, helpless, or guilty for lack of empathy • Physician may avoid being available for the patient and unconsciously provide poor care	• Be mindful of one's own feelings and keep appropriate emotional distance • Set realistic expectations and provide appropriate care • Search for signs of mental health or social needs and consider referral or consultation as needed

From Cannarella Lorenzetti R, Jacques CH, Donovan C, et al: Managing difficult encounters: understanding physician, patient, and situational factors. Am Fam Physician 87:419-425, 2013; Breuner CC, Moreno MA: Approaches to the difficult patient/parent encounter. Pediatrics 127:163-169, 2011.

of "need" has set into motion. Importantly, these patients are especially likely to seek care in the ED during times of personal crisis. Structuring the encounter to be particularly attentive to the underlying crisis may provide the opportunity to address the underlying problem, rather than the patient's perceived needs. This scenario is often encountered with patients exhibiting drug-seeking behavior.

The Entitled Demander

The "entitled demander" can include very important persons (VIPs) or other well-informed successful professionals, substance abusers, or personality disorders, such as narcissistic or paranoid. Their behavior is often hostile, intimidating, and threatening, and they may have endless needs and unreasonable demands. These patients fear being helpless in the context of their medical needs, and behaviors that have promoted success in their professional lives become maladaptive behaviors of entitlement to protect themselves from their own insecurity.

The behavior of these patients can evoke feelings of anger and antagonism and a desire to engage in debate and conflict. These power struggles are often counterproductive and only escalate the maladaptive behavior. A physician can address the underlying insecurity and fears by maintaining a supportive relationship. Limit setting is important to curb escalation of unreasonable demands. Physicians may preserve the patients' sense of autonomy and control in situations where they otherwise feel helpless by engaging them to participate in the selection of reasonable recommended options of care.

The Manipulative Help Rejecter

The "manipulative help rejecter" is largely characterized by desperate and numerous repeat ED and other medical visits despite expressed certainty that past visits have been failures. Behaviors may appear entitled, manipulative, and self-defeating. These patients may have borderline or antisocial personality disorders and may be malingering. Their complaints are often vague and defy diagnosis, and physicians may feel a sense of futility or failure. The behavior of these patients often stems from a need for physician connection and relationship in the setting of a fear of rejection, and these patients are also at risk for unrecognized depression.[56,59]

The physician is at risk of both prematurely dismissing the patient's complaint due to a pattern of frequent visits and medical noncompliance or prematurely beginning an extensive investigation from fear that diagnoses have been missed. Awareness of one's own cognitive distortions and personal biases can aid in avoiding

inappropriate premature discharge, and seeking collateral information from previous medical records may reveal additional information that can help limit the evaluation and help coordinate ongoing consistent medical care. Although clarifying expectations and limit setting is important, support and empathy can be particularly valuable in these encounters, because expressed lack of concern and dismissal of the patient's fears may feed an underlying sense of rejection within the patient and fuel the maladaptive behavior.

The Self-Destructive Denier

The "self-destructive denier" may appear hopeless and helpless and in profound denial of their self-destructive and neglectful behaviors. These patients may be violent, chronically suicidal, substance abusers, or have borderline personality disorders. Untreated anxiety or depression may be present. These patients may not personally seek help but instead be referred for care by others. ED care may result in addressing immediate needs (such as, food or shelter), but despite adequate medical intervention, it is likely that the patient's often very serious problems will persist.

These self-destructive patients can be challenging to treat, because ED staff may feel frustration or even loathe or disgust toward the patient and minimize contact with them. Consequently, the physician and others may unconsciously provide substandard care. By recognizing one's own feelings and setting realistic expectations of care, the ED care team can avoid poor medical care and may discover patient needs, including mental health conditions or crises or unrecognized social needs.

KEY CONCEPTS

- The ED should have a written plan of action to deal with violence that integrates the activities of ED staff, hospital administration, security, and local authorities.
- ED staff should be trained to recognize potentially violent individuals and to intervene with verbal de-escalation techniques prior to physical or chemical restraint when possible.
- The emergency clinician should be familiar with the use of physical and chemical restraints and the breadth of options for chemical sedation, as well as situations suggesting use of particular medications. For the undifferentiated severely agitated patient requiring rapid tranquilization, we recommend a benzodiazepine (such as, lorazepam) either alone or with a first-generation antipsychotic (such as, haloperidol).
- The possibility of an organic (medical) cause of aggressive behavior should be considered in all violent patients, even those with known psychiatric disease.
- The negative reactions from difficult patient encounters may result in undesirable implications for both patients and their ED caregivers, including compromised patient care, compassion fatigue, and professional burnout.
- Management of the difficult patient can be optimized by understanding the multiple issues contributing to the impaired physician-patient relationship, including factors of the ED setting (such as, time constraints and lack of privacy), individual physician influences (such as, personal bias and poor communication), and patient contributions to the interaction, including behavioral, social, and substance use issues.
- Pejorative stereotypes of difficult patients should be avoided—to aid in physician strategies for these challenging encounters one should instead aim to characterize the patient's primary difficult behaviors, such as dependent clinger, entitled demander, manipulative help rejecter, and self-destructive denier.
- Strategies, including understanding one's own biases and reactions and optimizing communication, are helpful in dealing with the impaired physician-patient relationship.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 189: QUESTIONS & ANSWERS

189.1. Which of the following is a positive predictor of violent behavior in patients?
- **A.** Age
- **B.** Ethnicity
- **C.** Gender
- **D.** Level of education
- **E.** Marital status

Answer: C. Identification of potentially violent patients is difficult, with male gender, prior history of violence, and drug or ethanol abuse the only positive predictors. Ethnicity, diagnosis, age, marital status, and education are not reliable identifiers.

189.2. Which of the following medications is associated with the highest incidence of sedation, hypotension, and anticholinergic symptoms?
- **A.** Droperidol
- **B.** Haloperidol
- **C.** Loxapine
- **D.** Molindone
- **E.** Thioridazine

Answer: E. Antipsychotics can be divided into low potency (including chlorpromazine and thioridazine), midrange potency (such as, loxapine and molindone), and high potency (such as, haloperidol and droperidol). The incidence of sedation, hypotension, and anticholinergic symptoms is highest in the low potency group, and the incidence of extrapyramidal symptoms is greatest in the high potency group.

189.3. Which of the following antipsychotic medications is associated with the highest incidence of extrapyramidal symptoms?
- **A.** Chlorpromazine
- **B.** Haloperidol
- **C.** Loxapine
- **D.** Molindone
- **E.** Thioridazine

Answer: B. Antipsychotics can be divided into low potency (including chlorpromazine and thioridazine), midrange potency (such as, loxapine and molindone), and high potency (such as, haloperidol and droperidol). The incidence of extrapyramidal symptoms is greatest in the high potency group, and the incidence of sedation, hypotension, and anticholinergic symptoms is highest in the low potency group.

189.4. Which of the following disorders is best defined as a pattern of instability of interpersonal relationships, self-image, and affect and marked impulsiveness that begins by early adulthood and presents in a variety of contexts?
- **A.** Antisocial personality disorder
- **B.** Borderline personality disorder
- **C.** Dependent personality disorder
- **D.** Histrionic personality disorder
- **E.** Paranoid personality disorder

Answer: B. Borderline personality disorder is a pattern of instability of interpersonal relationships, self-image, and affect and marked impulsiveness beginning by early adulthood and present in a variety of contexts. It may be indicated by five or more of the following:
1. Frantic efforts to avoid real or imagined abandonment
2. A pattern of unstable and intense interpersonal relationships characterized by alternating extremes of idealization and devaluation
3. Identity disturbance: Markedly and persistently unstable self-image or sense of self
4. Impulsiveness in at least two areas that are potentially self-damaging (eg, spending, sex, substance abuse, reckless driving, and binge eating)
5. Recurrent suicidal behavior, gestures, threats, or self-mutilating behavior
6. Affective instability caused by a marked reactivity of mood (eg, intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
7. Chronic feelings of emptiness
8. Inappropriate, intense anger, or difficulty controlling anger (eg, frequent displays of temper, constant anger, and recurrent physical fights)
9. Transient, stress-related paranoid ideation, or severe dissociative symptoms

189.5. A patient demonstrates inappropriate sexually seductive behavior while being interviewed by her physician. This characteristic is most consistent with which of the following personality disorders?
- **A.** Antisocial personality disorder
- **B.** Borderline personality disorder
- **C.** Dependent personality disorder
- **D.** Histrionic personality disorder
- **E.** Paranoid personality disorder

Answer: D. Histrionic personality disorder is a pattern of excessive emotionality and attention seeking beginning by early adulthood as indicated by five or more of the following:
1. Is uncomfortable in situations in which the center of attention is someone else
2. Interaction with others often characterized by inappropriate sexually seductive or provocative behavior
3. Displays rapidly shifting and shallow expression of emotions
4. Consistently uses physical appearance to draw attention to self
5. Has style of speech that is excessively impressionistic and lacking in detail
6. Shows self-dramatization, theatricality, and exaggerated expression of emotion
7. Is suggestible (ie, easily influenced by others or circumstances)
8. Considers relationships to be more intimate than they actually are

CHAPTER 190

Emergency Medical Services: Overview and Ground Transport

Thomas H. Blackwell

PRINCIPLES

Background and Importance

Development of Emergency Medical Services

Before the advent of civilian ambulance services, the sick and injured were transported by any means available, including passerby motorists, wagons, farm machinery, delivery carts, buses, and taxicabs. Figure 190.1 depicts the early Larrey ambulance used during the Napoleonic Wars, the Rucker wagon used during the American Civil War, and a modern ambulance used today. In 1865, the Commercial Hospital in Cincinnati established the first hospital-based ambulance service. Four years later, the first city service began at New York's Bellevue Hospital.

In 1965, the President's Commission on Highway Safety recommended the National Accident Response Program to decrease death and injury from highway accidents.[1] Results from a second national survey by the National Academy of Sciences–National Research Council were used to draft a white paper entitled *Accidental Death and Disability: The Neglected Disease of Modern Society*.[2] Published in 1966, this document described the hazardous conditions of emergency care provision at all levels and outlined the necessary building blocks for future maturation of emergency medical services (EMSs). These national efforts were the impetus for congressional legislation that directed the U.S. Department of Transportation (DOT)–National Highway Traffic Safety Administration (NHTSA) to develop a program for improving emergency medical care.

During the mid-1960s, out-of-hospital cardiac care included field defibrillation programs in Belfast, Northern Ireland, and cardiac arrest research in several United States cities. In 1969, the first National Conference on EMS convened, resulting in the development of a curriculum, certification process, and national registry for the emergency medical technician–ambulance (EMT-A). By 1972, the U.S. Department of Labor recognized the EMT as an occupational specialty. Interested physicians and nurses later provided advanced educational courses and practical experiences for the EMTs and thus began the paramedic providers.

Additional programs prompted Congressional passage of the EMS Systems Act of 1973 (P.L. 93-154), which authorized funding that dramatically improved the development of comprehensive regional EMS delivery systems. Efforts to improve pediatric emergency care occurred in 1984 when Congress adopted the Emergency Medical Services for Children (EMS-C) initiative through the Health Services, Preventive Health Services, and Home Community Based Services Act of 1984 (P.L. 98-555).[3] An Institute of Medicine (IOM) study, released in 1993, promoted the integration of EMS-C not just into existing EMS systems but into comprehensive systems of care provision, including injury prevention, primary and definitive care, and rehabilitation services.[4]

In 1996, the NHTSA published *Emergency Medical Services Agenda for the Future,* which broadly outlined the principles required for future EMS development.[5] All components of an EMS system, both operational and clinical, were identified and discussed. This document has been used by many individuals and organizations as valuable reference material for planning, administration, and forecasting of the future of EMS delivery. More than 40 years after the 1966 white paper publication, the IOM released a report on the status of emergency care entitled *The Future of Emergency Care in United States Health System*. The report focused on three separate yet related topics: (1) emergency care: at the breaking point, (2) EMSs at the crossroads, and (3) emergency care for children: growing pains.[6-8]

A major focus included the need to strengthen the integration of EMS into the entire health care system because lack of such coordination often results in patients being diverted to inappropriate or distant facilities. The recommendation was to ensure that emergency medical and trauma care is organized into a coordinated, regional system such that patients receive care at the most appropriate facility on the basis of their injury or illness. Additional recommendations included national accreditation for paramedic educational programs, adoption of a national certification system for individual state licensure, and adoption of common levels of EMS certification across the United States.

The concern for inadequate funding for EMS systems operations and disaster response was also addressed. In addition to recommending that Congress develop regionally funded, multiyear demonstration projects that provide seamless systems of care, workforce strengthening, evidence-based practices, and disaster preparedness, the IOM recommended that an advisory committee be created to work with the Centers for Medicare and Medicaid Services to improve reimbursement.

Finally, because it is difficult for prehospital providers to maintain the knowledge and skills necessary to care for critically ill or injured children, the IOM report recommended that the care of children be integrated into the overall EMS system, with pediatric emergency care competencies being defined and training enhanced to maintain those competencies. Additionally, a pediatric coordinator should be included in all EMS systems to ensure that equipment, medications, training, and protocols are appropriate for children.

Each of the three IOM reports supported the federal government's objective to develop national standards for emergency care performance indicators and evaluation and protocols for triage, treatment, and transport of patients. Although debate exists as to whether EMS should remain under the NHTSA, a lead federal agency should be identified. The parent organization should

Fig. 190.1. Larrey's flying ambulance **(A),** Letterman's Rucker wagon **(B),** and the modern ambulance used today **(C).** (**A,** Courtesy the National Library of Medicine, History of Medicine Division. **B,** Courtesy the Library of Congress, Prints and Photographs Division, LC-88171-2585 DLC.)

ensure that research is supported to improve the knowledge base and evidence for the practice of prehospital medical care.

Specific Issues

Emergency Medical Service Systems

Multiple EMS system designs exist, all predicated on the type of community served. Whereas this is a local decision, all states incorporate an administrative office that governs or oversees the provision of EMS activities. The role of the state office of EMS is not to direct any individual service but to assist in planning, licensing services, and establishing or enforcing the scope and standards for practice. Other functions may include training, examining, certifying, and recertifying providers; record keeping; data collection; and auditing or investigating programs. A description of systems for the 200 most populous cities in the United States is periodically published in the *Journal of Emergency Medical Services.*[9] For simplicity, the following categorization of systems is used: private and public agencies; basic life support (BLS) and advanced life support (ALS) services; and single-tiered, multitiered, and first responder systems.

Private and Public Agencies

Where local government has not assumed primary responsibility for EMS services, communities may depend on private providers. Financial responsibility varies but usually depends on federal reimbursement (Medicare or Medicaid) and user fees. A local government subsidy may or may not supplement the operation. If multiple providers are serving one jurisdiction, calls may be allocated by rotation or specified zone coverage. Dispatching varies by the system but may be by the provider or by a central agency. Medical direction is often provided by a contracted physician or physician oversight board.

Hospital-based EMS systems are few in number and may be managed by a single hospital or hospital corporation. Not all hospital-based EMS programs are considered private, in that the hospital may be a division under local or state government or operate under a public authority. As in private models, financial responsibility is usually paid in the form of user fees, with or without additional subsidies. Dispatching may be provided by a local public safety agency that may also be responsible for police and fire communications. An emergency clinician from a sponsor or base hospital typically provides medical direction for these systems.

A public utility model is a hybrid between private and public design that allows local government to contract with a private or public provider. The successful bidder for service becomes a contracted entity that agrees to provide the specified services (ALS, BLS, or both) to the catchment area and, depending on the arrangement, bill the patient directly or receive uniform reimbursement. Depending on local structure and interagency agreement, dispatching may be performed by an existing public safety organization or by the parent company. Medical direction is usually performed by a specified individual subject to contractual terms.

When government officials were faced with planning and establishment of EMS systems many decided that the fire department was the logical choice to incorporate EMS. Fire stations were strategically located throughout the community, and personnel were already used to providing emergency response. Firefighters could be cross-trained as a firefighter-paramedic or dedicated to either fire or EMS function. Public EMS systems that were not incorporated into fire departments evolved into their own separate entity, referred to as a *municipal third-service system.* Such agencies are operated by local municipalities and are endorsed and supported by local government. Many cities have been successful in combining police, fire, and EMS under a global public safety agency, with all department heads or chiefs reporting to one manager or administrator. Financially, public EMS systems may be supported by a tax base, which may or may not be supplemented by user fees. Regardless of design, medical oversight for a municipal EMS system may be provided by a physician appointed and contracted by a local government, a local hospital, an advisory council, or a medical oversight board.

Basic Life Support and Advanced Life Support Service

BLS describes the provision of emergency care without the use of advanced therapeutic interventions. Skills include airway

management (oral and nasal airways, bag-mask ventilation), cardiopulmonary resuscitation (CPR), hemorrhage control, fracture and spine immobilization, and childbirth assistance. Defibrillation with an automated external defibrillator (AED) is often included by many BLS systems. Services are provided by emergency medical responders (EMRs) or emergency medical technicians (EMTs).

BLS systems may be associated with poor survival rates from out-of-hospital cardiac arrest, especially those not incorporating AED technology.[10,11] Few urban communities across the United States operate solely at the BLS level. Many rural and some suburban EMS services rely on volunteers who may not wish to become advanced-level providers. Because these services may have low call volumes, it becomes difficult for personnel to maintain advanced skills. Also, such communities may not have access to medical supervision or hospital sponsorship for ALS care.

The effectiveness of ALS, however, for medical and traumatic emergencies is debatable, although systems categorized as ALS offer a more comprehensive level of service by highly educated providers, usually certified at the advanced emergency medical technician (AEMT) or paramedic level. Provider skills include advanced airway interventions, intravenous line placement, medication administration, cardiac monitoring and manual defibrillation, and certain invasive procedures. Most EMS systems in urban cities operate at the ALS level of care.

The number of paramedics in any jurisdiction has come under scrutiny, in that cities with more paramedics per capita tend to have lower survival rates. Although this may seem implausible, one explanation might be that the number of patient encounters per paramedic decreases and skills degrade when that community is saturated with paramedics.

Single-Tiered, Multitiered, and First Responder Systems

In a single-tiered system, every response regardless of the call type receives the same level of personnel expertise and equipment allocation (all BLS or ALS). Multiple-tiered systems use a combination of ALS and BLS levels, depending on the nature of the call. Differences in cost and effectiveness between a mixed ALS-BLS service and an all-ALS service have been debated. A single-tiered ALS response may prove to be cost-effective in specific locales, ensures the capability of providing a consistent advanced level of care to all patients regardless of illness or injury severity, and obviates the potential for undertriage or overtriage by 9-1-1 telecommunicators. Alternatively, a multitiered system may meet the needs of individual communities. This design often increases employee satisfaction and has the potential to preserve ALS resources for higher priority calls, because BLS transport of nonurgent patients allows ALS ambulances to be available for potential critical responses.

Regardless of single- or multiple-tier design, EMS systems usually include first responder services as part of their structure. The first responder, usually a police officer or firefighter, is the non-transport BLS or ALS provider who responds to the scene of an emergency to provide initial care before definitive medical care and transportation assets arrive. The first responder quickly assesses the scene and patients, determines whether additional resources are required, initiates patient care, and provides advance information to responding personnel.

The design of an EMS system is targeted toward providing quality patient care in the briefest time after unexpected injury or illness. A desirable and cost-effective design might include BLS non-transport first responders with short response times (average 2 to 4 minutes), having the capability of providing early defibrillation and airway support, coupled with ensuing ALS care and transport services.

Levels of Provider and Scope of Practice

At the federal level, the NHTSA is responsible for development of the education standards and scope of practice for the different certification levels. The National EMS Education Agenda and the National EMS Scope of Practice Model now define the curriculum, education content, and core competencies for each level of providers.[12,13] Individual state legislation dictate the provider levels recognized, initial and continuing medical education requirements at each level, testing, and time intervals for course completion and recertification. The following sections outline the new suggested levels of provider and incorporated skills. Suggested hours of training are listed in Table 190.1.

Emergency Medical Responder

The EMR, formerly referred to as *first responder,* is typically the first to arrive on the scene of an incident. Initial scene and patient assessment along with limited lifesaving interventions is the primary function.[14] Along with CPR and basic airway management skills, the EMR should be able to control hemorrhage and initiate spinal immobilization.

The four elements referred to as the chain of survival by the American Heart Association (AHA), which decrease mortality from out-of-hospital cardiac arrest, are immediate recognition of cardiac arrest and EMS activation, CPR, rapid defibrillation, and ALS. The 2010 resuscitation guidelines of the AHA recommended the addition of a fifth link, post-cardiac arrest care in a regional center.[15] Because early defibrillation may improve the odds of survival of out-of-hospital cardiac arrest, the use of an AED should be a mandatory procedure for the EMR.

Emergency Medical Technician

The EMT, formerly referred to as the *EMT-Basic,* is the minimum level required to staff a BLS ambulance and is commonly used for nonemergency and convalescent transport services. In addition to the skills of the first responder, the EMT is also involved with triage, more detailed patient assessment, and transportation.[16] Like first responders, EMTs should have the capability of providing early defibrillation.

In 1995, the NHTSA released the revised EMT curriculum to include 46 lessons, each with cognitive, effective, and psychomotor objectives. Many states expanded the course to include more skills, such as AED use, epinephrine autoinjections, albuterol administration by handheld nebulizer or metered-dose inhaler, and use of adjunctive airway devices, such as the extraglottic airway.

Advanced Emergency Medical Technician

The AEMT, formerly referred to as the *EMT-Intermediate,* was established to allow a more comprehensive approach to care when paramedic services are unavailable or unobtainable. Many states recognize the AEMT certification, but others designate alternative but comparable levels, depending on specific skills and procedures.[17] This level is useful for rural systems, because it provides some ALS care for less cost and educational time expended. The scope of practice for the AEMT varies across the United States. Most systems allow the AEMT to establish an intravenous line, to manually defibrillate, and to administer limited medications.

Paramedic

The most advanced of the prehospital providers, paramedics have the capability to address most prehospital emergencies. Their scope of practice includes a wide variety of therapeutics and

TABLE 190.1

Emergency Medical Services Provider Level Training and Skills

PROVIDER LEVEL	COMMISSION ON ACCREDITATION OF ALLIED HEALTH EDUCATION PROGRAMS RECOMMENDED HOURS OF TRAINING	SKILL SET
Emergency medical responder (EMR)	Initial: 40 didactic and laboratory hours	Initial scene and patient assessment and stabilization Basic airway skills CPR Control hemorrhage Spinal immobilization
Emergency medical technician (EMT)	Initial: 110 hours that include didactic, laboratory, clinical, and field experience	First responder skills plus: Triage and detailed patient assessment AED May assist in some systems, such as use of epinephrine autoinjectors for anaphylaxis and albuterol for wheezing
Advanced emergency medical technician (AEMT)	Initial: 200 to 400 hours that include didactic, laboratory, clinical, and field experience	EMT skills plus: Endotracheal intubation Manual defibrillation Intravenous line placement Limited pharmacologic treatments May assist in some systems, such as laryngeal mask airway
Paramedic	Initial: 1000 or more hours that include didactic, laboratory, clinical, and field experience	AEMT skills plus: Cardiac rhythm recognition Expanded pharmacologic treatments Needle decompression of a tension pneumothorax Needle or surgical cricothyrotomy Transthoracic cardiac pacing

AED, Automated external defibrillator; *CPR,* cardiopulmonary resuscitation.

procedures, including cardiac rhythm recognition, expanded pharmacologic treatments, and advanced airway interventions.[18] Other important invasive procedures include needle decompression of a tension pneumothorax, needle or surgical cricothyrotomy, and transthoracic cardiac pacing.

The initial training course for the paramedic includes didactic, clinical, and field education. All course content focuses on technical and professional competencies. Additional modules are included that allow programs to incorporate an expanded scope of practice. With the expansion of EMS technology and management career options, many paramedic educational programs have advanced from 1-year certificate curriculums to 2-year associate or 4-year baccalaureate degrees. The National EMS Education Standards document recommends that all paramedic education programs be accredited in the future by the Commission on Accreditation of Allied Health Education Programs.[12]

Future

To complement many of the educational issues addressed in the EMS Agenda for the Future document and at the request of the National Association of State Emergency Medical Service Officials (NASEMSO), the NHTSA along with the Health Resources and Services Administration under the Department of Health and Human Services published the *Emergency Medical Services Education Agenda for the Future: A Systems Approach.*[19] Setting forth the processes required to improve EMS education delivery similar to what is realized with other allied health care professions, this document aims to increase instructor flexibility and EMS adaptation to community needs and resources, and to standardize levels of certification across the United States. Since publication of this document, the National EMS Core Content, a National EMS Scope of Practice Model of minimum competencies, and the 2009 National EMS Education Standards, which replaces the current National Standard Curricula for each level of provider, have been published.[12,13,20] The NASEMSO has been collaborating with multiple EMS stakeholders and the federal partner organizations to assist states in implementing this agenda, including the National Registry of Emergency Medical Technicians, which has revised their examinations. Future goals include the establishment of a national EMS certification program, the requirement for educational programs to be nationally accredited, and the limitation of examinations only to those graduates who completed these accredited programs.

In keeping with the spirit of the EMS Agenda for the Future, which specifically calls for integration of health services and prevention attributes, some systems have implemented programs that engage interprofessional health providers into the existing structures of care. Examples include embedding a nurse triage system at the 9-1-1 access level, where low acuity complaints as determined by vetted algorithms are transferred to alternate call center nurses who determine and arrange appropriate care at a clinic or facility other than an emergency department.[21] Another example that is becoming popular is having prehospital providers, usually at the paramedic level, provide patient evaluation services to pre-identified patients with chronic conditions, such as hypertension, diabetes, congestive heart failure, and substance abuse. These programs, referred to as *community paramedics, mobile integrated health,* or *advanced practice paramedics* among others, are designed to prevent or reduce the need for EMS calls and to decrease emergency department utilization for targeted patients or frequent users.

Material Resources

Before the mid-1960s, few if any regulations governed system design, operations, and equipment. As EMS development progressed, guidelines for emergency vehicle specifications were

adopted by the DOT and equipment lists were proposed. Today, collaborative efforts from multiple professional organizations continue to publish documents that recommend design, equipment, and medications for ambulances.[22]

Medications

During the 1980s, many believed that prehospital drug administration was unjustified and simply delayed hospital transport. Moreover, although there was a profound paucity of outcomes-based research into the use of various medications and practices in the prehospital environment, this has improved in recent years.[23] There is significant evidence for early defibrillation and certain advanced cardiac life support medications, which are carried by most ALS services. The wide variety of alternative medications is less uniform. This includes respiratory and anaphylaxis medications, preparations for altered mental status, analgesics, and antiemetics. Medications are traditionally administered in the field by the parenteral route, but the intranasal route is becoming popular. The beneficial aspects are that absorption is rapid with an onset of action similar to that of parenteral administration. Medications that are commonly administered intranasally are naloxone for narcotic overdose, midazolam for pediatric seizure, and fentanyl for pain control.[24-26]

Equipment

Basic ambulance equipment should include items necessary for emergency procedures (ie, airway support, hemorrhage control, fracture and spine immobilization, childbirth), personal protection, patient movement, and basic rescue procedures. Additional patient care equipment is predicated on the level of provision outlined by the system design. Many ALS systems have adopted the equipment necessary for the acquisition of prehospital 12-lead electrocardiograms to provide earlier diagnosis of acute myocardial infarction. This information often guides destination protocols to deliver these patients directly to acute care facilities that incorporate 24-hour cardiac catheterization laboratories with staff to facilitate emergent percutaneous coronary interventions.

Ambulances

Three basic ambulance vehicle designs are recognized by the DOT: type I, type II, and type III. Both type I and type III ambulances incorporate a modular patient compartment mounted on a conventional truck and van chassis, respectively. The type II vehicle is a standard van. The larger medium-duty vehicle, mounted on a business-class chassis, has become popular in recent years. This configuration requires less periodic maintenance and offers extended service time. Each ambulance manufacturer promotes various interior cabinetry and all include sufficient lighting, outlets for 110-volt equipment, suction, oxygen systems, and external audible and visual warning devices. The six-pointed blue star, or Star of Life, surrounding the staff of Aesculapius is recognized worldwide as the standard symbol for EMS.

Communications

Integral to out-of-hospital care systems, EMS communications involve multiple components, all interlinked to support expedient patient care. Effective communication systems include public information and education programs regarding general access to care, technology to ensure simplified access, a means of call prioritization and management of available resources, protocols for providing emergency patient care instructions before EMS arrival, ability to communicate with allied agency and hospital personnel, educational opportunities for telecommunicators, and quality improvement processes.

Access

Since 1973, the 9-1-1 universal emergency access telephone number has been adopted by many communities throughout the United States. Basic 9-1-1 service simply connects a caller to a central communications center or public safety answering point (PSAP). Most primary PSAPs are under the domain of law enforcement. Although many of these handle all public service (police, fire, and EMS) calls, many larger cities have secondary PSAPs for fire and EMS. Enhanced 9-1-1 provides additional information by immediately displaying the caller's telephone number and address.

Emergency Medical Dispatch

Dispatching encompasses multiple elements that assist patients in receiving expeditious medical care. There are several recognized programs with varying sensitivities and specificities that assist call-takers in identifying a patient's acuity level on the basis of the caller's information.

The emergency medical dispatcher (EMD) is responsible for ascertaining the primary medical condition and severity. Communication centers that model their dispatch response protocols by priority use a finite list of common chief complaints, each having associated predetermined questions. Answers to these questions ultimately dictate a predefined response mode. Depending on the response assigned and system configuration, an ambulance (BLS or ALS) and possibly a first responder resource is dispatched to respond in an emergency or nonemergency mode. When critical conditions are identified, the EMD may proceed to give specific pre-arrival instructions to assist the caller in providing critical interventions before EMS arrival. These include procedures, such as opening and clearing an airway, performing CPR, controlling hemorrhage, and assisting with childbirth. Such assistance dramatically narrows the response time interval for receiving emergency medical care.

Systems Status Management and Flexible Deployment

Depending on system size, population served, and resources available, systems status management has proved beneficial. On the basis of historical data, high-performance or peak-demand periods of the day coupled to service areas or call location can be identified so that coverage plans or posting assignments may be instituted. Such mechanisms place ambulances at predetermined locations where potential calls are likely to occur. Response vehicles may be equipped with an automatic vehicle locator that functions as a telemetry unit or a global positioning satellite system that provides a site interface with the computer-aided dispatch system. This site information is helpful in the staging or redeployment of vehicles during periods of high call volume or when resources are limited. To stage and identify closest resources to the callers, technologically advanced agencies are using new programs that incorporate additional factors, such as traffic patterns based on time of day and street configurations.

Field Communications

At the scene or during transport, EMTs usually have the capability of communicating with hospital staff. A consultative patient report may be given to receive medication or intervention orders or simply for arrival notification. Additional information resources may include cardiac telemetry or transmission of a 12-lead electrocardiogram. EMS providers should also have the capability of

communicating with all allied public safety agencies for mutual aid purposes, mass casualty situations, or disaster responses. If air medical services are available, EMS and fire personnel should have the capability of communicating with the helicopter pilot and crew members. In addition to providing a preliminary patient report to the medical crew, scene personnel should relay landing zone information and potential hazards to the pilot.

OVERSIGHT

Federal

Various federal agencies participate in the oversight of EMS development and refinement. Specifically, the lead agency in the federal government is the EMS Division of NHTSA under the DOT. In 2007, the National EMS Advisory Council was formed to provide advice and recommendations from consumers, advocates, and stakeholders regarding EMS to the NHTSA. Additional federal support comes from the EMS for Children Program under the Maternal and Child Health, Department of Health and Human Services. In an effort to better coordinate federal agencies involved with state, local, tribal, or regional EMS, Congress formed the Federal Interagency Committee on EMS in 2005. The purpose of this organization is to simplify the processes and efforts by which federal agencies support EMS by identifying state and local EMS needs and recommending the addition, expansion, or improvement of programs. Although it is not regulatory, the National Association of EMS Physicians is an international organization of physicians and prehospital professionals interested in promoting research, innovation, and excellence in prehospital care delivery.

State

Each state incorporates a governmental agency that oversees EMS. Duties typically include enforcement, regulation, and implementation of EMS rules adopted by the state and possibly a medical board, licensing services, and certifying providers. The NASEMSO assists in developing policy, providing insight, and ensuring leadership and resources for EMS development at the state, regional, and local levels.

Local

Emergency Medical Services Medical Director

An EMS medical director is a physician with specialized interest and knowledge of patient care activities unique to the out-of-hospital environment. Medical oversight must extend from the communications center through all components of field care. Typically, a contractual arrangement for services provides the physician with administrative authority to implement patient care protocols, to interact with all aspects of the system, and to remove a provider from practice if medical care or behavior is substandard. Published guidelines describing the activities and performance of an EMS medical director have been prepared by the National Association of EMS Physicians, and the NASEMSO.[27] On September 23, 2010, the American Board of Medical Specialties approved EMS medicine as the sixth subspecialty available to the American Board of Emergency Medicine (ABEM) diplomates with the first certification examination being administered in October 2013. The Core Content of EMS Medicine is available on the ABEM website.

Medical direction consists of off-line (indirect) and on-line or on-scene (direct) control. Off-line medical control includes protocol development, personnel education, prospective and retrospective patient care review, and other quality improvement processes. Direct medical control concerns real-time interaction between a physician or designee and the field provider.

Indirect Medical Control

Medical accountability for patient care activities is the basis for indirect medical control and functions either before a patient is encountered (prospective) or after hospital transport has occurred (retrospective). Patient care guidelines and protocol development for EMTs and EMDs, continuing medical education, medical-legal policies, and quality and performance improvement processes are important elements.

Perhaps the most important duty of the medical director is to develop patient care protocols, which are preestablished practice guidelines that define the standard of care for most illnesses or injuries encountered in the out-of-hospital setting. Operational issues, such as hospital designation and destination policies, termination of resuscitation, and patient transport refusal, may be included. Depending on state regulations, protocols may include standing orders for particular clinical situations in which EMTs may perform certain procedures or administer medications for predefined patient conditions before communication with hospital personnel. Protocol development should be driven by published evidence, system resources, and patient needs, and it should include guidelines for triage and care of specific populations of patients, including trauma patients, newborns, and children.[28]

Regardless of local communication protocols, out-of-hospital providers should always be able to discuss a case with a physician for clarification or guidance when clinical questions or controversial situations arise. Furthermore, hospital notification is important when critical patients are being transported.

Medical directors should be familiar with and actively involved in local or regional educational programs for initial and continuing education courses for all levels of EMT certification. Course curriculum development and administration, evaluation, and revision processes should be understood. Systems that incorporate their own educational programs allow modifications that reflect intrinsic needs of the system and the providers.

Field personnel and telecommunicators should be given regularly scheduled courses that improve competency in knowledge and skills. Instructional formats and resources to accomplish educational objectives may include didactic classroom lectures, skill laboratories, direct field observation, and distance learning models for self-paced opportunities. Standardized core content is important for consistency and quality of care.

Once patient care protocols are developed and implemented, there must be mechanisms, such as retrospective patient care report review or direct field observation, for evaluation of individual and system performance and patient outcome. Deviations from specific protocols may reflect problems with individual EMTs, medical control personnel, or the protocol itself, each requiring education and reevaluation. Deficiencies, both operational and clinical, should be identified for appropriate remediation, which may be in the form of counseling, educational instruction, or revisions of system design or patient care protocols.[28] Competency, knowledge retention, and skill performance are measurable parameters. Time standards (eg, out-of-chute time [time from ambulance notification to deployment], response time, and scene time) are equally important measures.[29,30]

Direct Medical Control

Direct medical control is the concurrent direction of EMTs providing patient care. This may be in the form of radio or telephone communications or by direct scene observation and may be considered centralized or decentralized. In a centralized system, a selected hospital is designated the lead facility (base station

hospital, resource hospital, or sponsor hospital) and is responsible for providing all direct medical control orders and notification regardless of the receiving facility. In a decentralized system, each hospital functions as a base station, providing direction to EMTs transporting patients to its facility.

Personnel responsible for direct medical control must be knowledgeable about the entire EMS system, receiving facilities, protocols, medication formulary and equipment, administrative and operational issues, and medical-legal implications for certain presenting situations. Systems whose protocols include standing orders may require direct communication only for specific reasons. Thus, whereas these medical and administrative protocols may guide EMTs through most circumstances, medical control consultation may assist with medical-legal issues, problems at the scene, patient non-transport, or ethical dilemmas that may be encountered. Furthermore, direct medical control is usually invaluable for notification and staff preparation when critical or potentially critical patients are being transported.

Table 190.2 lists the various levels of EMS oversight, and Table 190.3 lists contacts for agencies and organizations involved in EMS development.

TABLE 190.2

Emergency Medical Services Levels of Oversight

LEVEL	ORGANIZATION
Federal	Department of Transportation–National Highway Traffic and Safety Administration–EMS Division Department of Health and Human Services–Health Resources and Services Administration–Maternal and Child Health–EMS for Children
State	State regulatory office for EMS
Local	County, region, jurisdiction, territorial direct and indirect medical direction

EMS, Emergency medical service.

TABLE 190.3

Emergency Medical Services Resource and Contact Information

RESOURCE	URL
Advocates for EMS	www.advocatesforems.org
American Ambulance Association	www.the-aaa.org
American College of Emergency Physicians	www.acep.org
Centers for Disease Control and Prevention	www.cdc.gov
Commission on Accreditation of Ambulance Services	www.caas.org
EMS Division, NHTSA	www.nhtsa.dot.gov/people/injury/ems
Maternal and Child Health, EMS-C	www.ems-c.org
National Association of EMS Educators	www.naemse.org
National Association of EMS Physicians	www.naemsp.org
National Association of EMTs	www.naemt.org
National Association of State EMS Officials (NASEMSO)	www.nasemso.org
National Registry of EMTs	www.nremt.org

EMS, Emergency medical service; *EMS-C,* Emergency Medical Services for Children; *EMT,* emergency medical technician; *NHTSA,* National Highway Traffic Safety Administration.

OUT-OF-HOSPITAL MEDICAL CARE AND CONTROVERSIES IN MANAGEMENT

Airway Support and Respiratory Emergencies

Interventions

Respiratory complaints account for a significant number of EMS responses. Basic measures to control and support a patient's airway include manual maneuvers (eg, chin lift or jaw thrust), oral and nasopharyngeal devices, and bag-mask ventilation. At a more advanced level, interventions may include use of supraglottic airway devices (eg, Combitube, laryngeal mask airway, or laryngeal tracheal airway), which have been shown to enable faster and more successful placement than traditional endotracheal tube insertion.[31] Similar studies have demonstrated that paramedics are more successful when using supraglottic airways than endotracheal intubation.[32]

Commonly used by air medical services, drug-assisted intubation (DAI) and rapid sequence intubation (RSI) procedures are well established in ground transport services, despite a lack of supporting evidence. Although many services routinely perform intubation, the effectiveness of out-of-hospital intubation has been challenged, particularly in view of an alarming incidence of esophageal intubation in some systems and poor outcomes with the use of RSI for head-injured patients.[33-35] Although controversy exists and the debate will continue, most would agree that to have a successful airway management program, the educational and quality management component must be meaningful and should be as comprehensive as possible. For programs using DAI or RSI procedures, the experiential component should include operating room time and/or simulator sessions. Ideally, training would also occur in an ED setting where patients requiring emergent intubation would potentially have the full complement of confounding variables (eg, combative status, full stomachs, blood and vomit in the airway). Such training may be difficult or impossible to achieve, particularly ongoing maintenance of skills, especially in rural communities. Unless EMS systems perform a large number of intubations, with at least several intubations per provider per year, use of an extraglottic device for tracheal intubation should be strongly considered.[31]

Traditionally used in the hospital, prehospital continuous positive airway pressure (CPAP) has been shown to decrease intubation rates and improve patient outcome.[36,37] Out-of-hospital use requires strict protocols that outline variables, such as indications and contraindications, clinical applications, mental status assessment, hemodynamic status, and mechanisms for transfer of the patient and devices upon arrival at the hospital.

Medications

Most advanced programs have adopted the use of clinically proven medications for bronchospasm, chronic obstructive pulmonary disease, and anaphylaxis, but no studies have demonstrated benefit to administration of these medications in the out-of-hospital environment. Whereas some studies might be considered unethical (eg, an out-of-hospital study of epinephrine for anaphylaxis), others (eg, out-of-hospital use of beta$_2$-agonists or steroids for asthma, or loop diuretics for pulmonary edema) could easily be performed. Pending further studies, most systems have adopted the position that these medications do not harm patients in the out-of-hospital setting, may be helpful, and may provide comfort and clinical improvement for most patients experiencing varying degrees of respiratory distress. The overhead for training and maintenance of knowledge related to these medications is rarely considered.

Cardiovascular Emergencies

Interventions

Early research demonstrated the effectiveness of early defibrillation for termination of ventricular fibrillation and improvement of survival rates from sudden cardiac death. Advances in technology have improved such that defibrillators, traditionally used by paramedics, are now used by a variety of public safety responders and bystanders. Public access defibrillation programs are continuing to be implemented throughout the country, with devices being placed in high-volume, populous, and secluded areas, such as airports and airplanes, casinos, churches, office buildings, and other locations identified as high risk for resuscitation.[38] The acquisition and transmission of out-of-hospital 12-lead electrocardiograms is becoming more prevalent as well. Although it is expensive to implement, several studies have revealed minimal delays in scene time while the prehospital electrocardiogram is obtained and a shorter time to intervention (thrombolytic administration or catheterization laboratory admission).[39,40]

A factor now recognized to improve survival from cardiac arrest is uninterrupted or minimally interrupted chest compressions. Each interruption of compressions (eg, while intubating, checking for pulses, analyzing rhythms) decreases coronary perfusion pressure, which in turn decreases cellular respiration.[41] Additionally, more bystanders may be willing to perform continuous chest compressions if artificial ventilations are discarded.

Although the statistics for cardiac arrest survival across the United States are dismal, those who survive may suffer some degree of hypoxic encephalopathy. Recent evidence supports inducing hypothermia of patients who achieve a spontaneous return of circulation after cardiac arrest, especially with ventricular fibrillation as the initial rhythm, as higher survival rates and level of neurologic functioning are achieved.[42] International guidelines now call for the institution of hypothermia for patients who are resuscitated from cardiac arrest, and many out-of-hospital systems have implemented protocols that may include administration of chilled saline, sedation, or neuromuscular blockers in coordination with receiving hospital EDs.

Medications

Traditional cardiac medications recommended by advanced cardiac life support are used by most ALS systems. A multi-center investigation involving amiodarone as an out-of-hospital agent to terminate refractory ventricular fibrillation and improve survival is ongoing and should provide valid recommendations for future resuscitation guidelines.[43] Whether amiodarone should replace lidocaine for out-of-hospital ventricular fibrillation requires further investigation. The use of out-of-hospital fibrinolytic agents for acute ST elevation myocardial infarction has not gained wide acceptance and may be a useful intervention only for systems having prolonged transport times or if hospitals may not have catheterization or intervention facilities available. Future recommendation for out-of-hospital use of these agents remains speculative.

Traumatic Emergencies

Interventions

Interventions for specific medical emergencies, such as cardiac arrest (ie, defibrillation, intubation, intravenous line, and medication administration), may be effectively performed while on the scene or before hospital transport. Alternatively, it is widely accepted that most interventions for traumatic injuries should be performed en route to the hospital, and all efforts should be extended to reduce on-scene time. Only two interventions should be considered for critical injuries: (1) control of the airway to reverse hypoxemia and to prevent aspiration and (2) stopping of uncontrolled hemorrhage. Although it is a routine part of prehospital trauma care, tracheal intubation is not known to be beneficial for severely injured patients.[44] There are many potential drawbacks to prehospital intubation for major trauma. To be successful, paramedics should rapidly place the endotracheal tube correctly, assess and confirm the placement, and secure the tube to prevent displacement. In addition, providing the correct minute and tidal volumes is equally important. Inadvertent hyperventilation may impair cardiac output and cause further tissue damage. Patients sustaining blunt head injury pose special problems that should be expeditiously addressed and resolved. Intubation is but one means of providing ventilatory assistance and airway protection, but misadventure, complications, and improper post-intubation care may negate these potential benefits. Attempting to intubate head-injured patients may result in dental or soft tissue damage in those patients with clenched teeth, and intracranial pressure may be exacerbated from an intact gag reflex or from subsequent regurgitation. Studies on the use of RSI in head-injured patients reveal that patients experience significant hypoxia and bradycardia during the procedure, and outcome is actually worse.[29] Thus the role of RSI in prehospital airway management in trauma patients is in question, just as it is for medical patients. The use of extraglottic airway devices may be a promising addition to prehospital airway management. Routine use of prehospital intubation is not recommended unless the system can ensure that its providers meet the standards previously outlined.

Emergent hemorrhage control is also essential in reducing mortality in severe trauma. For internal bleeding, limiting of total prehospital time and transfer to definitive surgical care are paramount. Recent evidence on the battlefield has demonstrated the effectiveness of tourniquet application to extremity wounds.[45] These devices may have application in the civilian setting, are quick and easy to apply, and do not result in the complications once thought to exist.

The issue of intravenous fluid administration has gained controversy over the years. Traditionally, high-volume intravenous fluid for hemodynamic instability resulting from traumatic injury was the accepted standard. However, there has been a paradigm shift to restrictive or hypotensive resuscitation for penetrating truncal injuries, because there is evidence that restoration of hemodynamic stability with fluid resuscitation before definitive surgical hemostasis may lead to increased morbidity.[46]

INTERFACILITY AND SPECIALIZED TRANSPORTS

Transportation between health care facilities may occur for several reasons, including patient preference, unavailable diagnostic or therapeutic resource availability at the transferring facility, and managed care requirements that patients be cared for in predesignated hospitals after stabilization. Hospital corporations engaged in networks or alliances that share resources and services depend on interhospital transport systems to convey patients to allied institutions for specialized tests or procedures. Likewise, critical patients admitted to less specialized facilities may need to be transferred to tertiary care or designated trauma centers. Whereas long-distance transports may be best accomplished by air medical services, regional or local transports should use ground systems.[47] These may be provided by either local EMS resources or those owned and operated by the hospital.

Interfacility transfer of patients that is medically indicated must fall under a set of requirements referred to as the Emergency Medical Treatment and Active Labor Act (EMTALA).[48] Although the EMS system providing the transport plays a key role, these guidelines primarily involve particular information and

obligations that must be satisfied by the transferring and receiving facilities before transfer. An unstable patient should not be transferred to another facility unless the transferring hospital is incapable of providing standard care and the receiving hospital does have the capability to manage the condition and foreseeable complications. Box 190.1 lists various requirements that should be completed before a patient is transferred to another facility.

Depending on the patient's condition, specialized transport services may function at the BLS or ALS level, providing emergency or nonemergency transportation. Patient transfers considered ALS may include interhospital (either ED or intensive care unit) neonatal or high-risk infant, critical cardiac, and trauma transports. Personnel configuration depends on system design and level of care provided. Many programs use a nurse-paramedic combination. Patients requiring specialized care may need the services of specifically trained individuals, such as respiratory therapists, neonatal nurses, or other specialized critical care personnel. The presence of a physician is not mandatory but may be useful in selected cases.

BOX 190.1

Emergency Medical Treatment and Active Labor Act Requirements for Patient Transfers

Complete certification (risks and benefits) of transfer
Informed consent obtained from the patient or family
Appropriate transportation (equipment and personnel) arranged
Treatment and stabilization performed
Acceptance from receiving facility ensured
Appropriate patient care data sent (fax or with patient)

As with any EMS activity, all interfacility transports should be reviewed for appropriateness of transfer and medical care provided. In 2013, the American College of Emergency Physicians updated the policy statement on EMTALA and patient transfers.[49]

KEY CONCEPTS

- Published in 1966, *Accidental Death and Disability: The Neglected Disease of Modern Society* by the National Academy of Sciences–National Research Council was instrumental in EMS maturation in the United States.
- There are multiple system designs for EMS systems, including public and private services, those operating at basic and advanced levels of care, and those that include single or multiple tiers of response capability.
- There are four levels of prehospital providers recognized nationally—emergency medical responder (EMR), emergency medical technician (EMT), advanced emergency medical technician (AEMT), and paramedic, which is the most advanced level.
- The community paramedic provider focusing on population health issues, such as access, chronic disease, and decreasing utilization, and readmission is now being considered by many communities.
- Advances in emergency medical dispatching and positioning resources at locations and during specified times where expected call volumes are prevalent are innovations that are being implemented to decrease response times and improve outcomes.
- Regulatory oversight for EMS systems lies at the individual state level, and medical direction for individual public or private services resides at the local level.
- Direct medical oversight involves real-time interaction with the prehospital providers via face-to-face or by radio communications. Indirect medical direction involves off-line processes such as protocol development, quality improvement, and education.
- Advances in prehospital care of medical patients have included analgesics and anxiolytics that can be administered intranasally negating intravenous routes, noninvasive measures to support patients in respiratory distress, alternative adjuncts in place of endotracheal intubation for managing airways, and tourniquets for controlling hemorrhage.
- More advanced diagnostics (such as, 12-lead electrocardiography and use of stroke screens) have assisted in transporting patients to appropriate facilities based on their illness and acuity.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 190: QUESTIONS & ANSWERS

190.1. Which of the following is not an Emergency Medical Treatment and Active Labor Act (EMTALA) requirement for patient transfer?

A. Acceptance from receiving facility ensured
B. Appropriate patient care data sent
C. Appropriate transportation arranged
D. Complete certification of transfer
E. Medical or surgical stabilization

Answer: E. Box 190.1 provides a list of EMTALA requirements for patient transfer.

190.2. Which of the following is not included in the skill set of an advanced emergency medical technician (AEMT)?

A. Cardiac rhythm recognition
B. Endotracheal intubation
C. Intravenous line placement
D. Laryngeal mask airway
E. Manual defibrillation

Answer: A. Cardiac rhythm recognition is in the authorized skill set of a paramedic. See Table 190.1.

190.3. Which of the following best defines Direct Medical Control in the prehospital setting?
A. Concurrent direction of EMTs providing patient care
B. Development of prehospital care policies
C. Implement quality improvement program
D. Use of prehospital patient care protocols
E. Use of standing field treatment protocols

Answer: A. Direct medical control is the concurrent direction of EMTs providing patient care, which can be at the scene or online over radio or cell phone.

190.4. Public access defibrillation programs have been successful in all but which of the following locations?
A. Airports
B. Casinos
C. Churches
D. Office buildings
E. Schools

Answer: E. Public access defibrillation programs have been successful in high-volume, populous areas where large numbers of adults gather; schools generally have younger persons who are relatively healthy, so public access defibrillation programs there have not been cost effective.

190.5 Which of the following prehospital interventions has been shown to improve patient outcome?
A. Defibrillation
B. Endotracheal intubation for children
C. Endotracheal intubation for severe head trauma
D. Intraosseous needle placement
E. Needle cricothyrotomy

Answer: A. Rapid defibrillation has been shown to improve outcomes for patients in cardiopulmonary arrest; other interventions have not shown proven benefit in the prehospital setting.

CHAPTER 191

Air Medical Transport

Ira J. Blumen | Howard Rodenberg

PRINCIPLES

Background and Importance

Air medical transport (AMT) dates back more than a century to World War I. As early as 1915, the French evacuated soldiers from Serbia using airplanes as ambulances. In 1918, the United States military converted an airplane for the first recorded United States air ambulance to accommodate a litter patient in the rear cockpit. During World War II, more than 1.1 million sick and wounded soldiers were airlifted to the United States during the last 3 years of the war. The Korean War introduced the helicopter to AMT, and more than 20,000 battlefield medical evacuations were flown during the conflict. Utilizing the Bell 47 helicopter, wounded soldiers were strapped to litters outside the aircraft and transported from battalion aid stations to waiting hospital units. During the Vietnam War, Operation Dustoff transported nearly 1 million of the injured from the front lines to care in larger helicopters staffed with medics, to initiate care en route.

AMT had a significant impact on the wounded soldier when considering transport times and mortality. World War I saw battlefield transport times between 12 and 18 hours. Of those surviving transport, mortality was 20%. During World War II, the average time from injury to definitive care was 6 to 12 hours, with a mortality rate of 5.8%. In Korea, the time was 2 to 4 hours, with a 2.4% mortality rate. In Vietnam, no soldier was more than 35 minutes from definitive care, and overall mortality was of 2.6%.

Encouraged by the military experience, United States civilian AMT began in 1969 with a hospital-sponsored fixed-wing air medical program. The first civilian helicopter emergency medical services (HEMS) program in the United States was established in 1972. In 2015, the Federal Aviation Administration (FAA) determined that the term *HEMS* was obsolete, replacing it in official FAA documents with *helicopter air ambulance (HAA)*. Their rationale was that although a critical life and death medical emergency may exist, air ambulance flights are not operated as emergencies.

Aviation Physiology

A working knowledge of aviation physiology is vital to understanding of the effects of AMT on pilots, medical personnel, and patients.

Gas Laws

There are four gas laws important to aviation physiology: Boyle's law, Charles' law, Dalton's law, and Henry's law (Tables 191.1 and 191.2). The cornerstone of aviation physiology begins with Boyle's law, which describes the effect of gases in an enclosed space. Boyle's law also is a contributing factor to hypoxia along with Dalton's law. No one is exempt from the effects of hypoxia at altitude, and the most threatening feature is its insidious onset and the knowledge that the onset and severity of symptoms may vary with individuals.

Additional Stresses of Flight

Other stresses of flight that can affect the patient or crew include temperature fluctuations, dehydration, noise, and vibration. Temperature changes may produce increases in metabolic rate and oxygen consumption.

As altitude increases and the air cools, the amount of moisture in the air decreases significantly. To prevent dehydration during AMT, fluid intake (oral or intravenous) must be monitored carefully, and all patients should receive humidified medical oxygen. Noise and vibration may represent the most ubiquitous stresses encountered in AMT, and both may interfere with patient care or the function of medical equipment. Hearing protection should be worn at all times during aircraft operations by patient and crew. Prolonged exposure to environmental extremes may result in fatigue, motion sickness, disorientation, ear damage, and deterioration in task performance.

SPECIFIC ISSUES IN AIR MEDICAL TRANSPORT

Administrative Structure of Air Transport Systems

Air medical services may take the form of several business models, and it has resulted in tremendous growth of medical helicopters in the United States. In 2015, there were 220 dedicated HEMS HAA programs flying more than 860 dedicated aircraft throughout the nation. From 1990 to 2014, there has been more than a 260% increase in the number of dedicated HEMS aircraft. Over the past 13 years alone, the number has doubled. During that time, what had been the most common HEMS business model in the United States changed. The original and "traditional" non-profit hospital-based operation, sponsored by a single hospital or a consortium of institutions is now less common than the for-profit community-based programs or hybrid programs. Nearly 70% of the helicopters are for-profit ventures, operated by privately owned or publically traded companies. Public service agencies may also sponsor air medical services or partner with private companies; vehicles used by these programs are often multifunctional aircraft that serve in medical, search and rescue, fire suppression, and law enforcement roles. The Military Assistance to Safety and Traffic (MAST) program operated by the United States Armed Forces provides additional HEMS resources to civilians, but in recent years their role for civilian support has been generally limited to Hawaii and Alaska.[1] Together, the public service and MAST helicopters supply more than 110 additional aircraft for patient transport. There is no accurate accounting of the number of fixed-wing air ambulance companies or airplanes. Although some hospitals sponsor fixed-wing AMT, it is more common for these programs to be private fee-for-service operations.

Types of Missions

Air medical missions may involve primary or secondary response. Primary responses ("scene flights") are when the aircraft responds directly to the scene of an accident or illness and transports the

TABLE 191.1

The Gas Laws

GAS LAW	PRINCIPLE	CLINICAL IMPLICATION
Boyle's law	The volume of a unit of gas is inversely proportional to its pressure. As altitude increases and atmospheric pressure decreases, the molecules of gas grow apart, and the volume of gas expands. With descent (increasing atmospheric pressure), the molecules are condensed, and gas volumes contract. The result is the expansion and contraction of gases within the closed spaces of the body.	Squeeze injuries from contraction of air and associated soft tissues can occur on descent, resulting in barotitis, barosinusitis, and toothache. Reverse squeeze injuries occur on ascent, leading to an increased volume of the air trapped within the space. Examples include the conversion of a simple pneumothorax into a tension pneumothorax and rupture of a hollow viscus. Medical equipment containing closed air spaces, such as IV tubing and pumps, air splints, ventilators, and endotracheal tube and laryngeal airway cuffs, may also be affected by altitude. Responsible in part for hypoxia at altitude due to fewer molecules of oxygen present per volume of inhaled gas.
Charles' law	As the volume of a unit of gas rises, the temperature of that volume falls.	Explains why the ambient temperature decreases with increased altitude.
Dalton's law	The total barometric pressure at any given altitude equals the sum of the partial pressures of gases in the mixture. Oxygen still constitutes 21% of the atmospheric pressure at altitude.	A decrease in arterial oxygen tension with increasing altitude, resulting in hypoxia. Initial physiologic responses to hypoxia include tachypnea and tachycardia. Initial physiologic responses to hypoxia include tachypnea and tachycardia. With prolonged exposure, cerebral hypoxia causes headache, nausea, drowsiness, fatigue, unconsciousness, and death.
Henry's law	The mass of gas absorbed by a liquid is directly proportional to the partial pressure of the gas above the liquid.	Sudden decompression at altitude may result in dysbaric injuries. In scuba diving, rapid ascent can result in gas to come out of solution within the bloodstream, resulting in decompression sickness.

IV, Intravenous.

TABLE 191.2

Effects of Altitude on Oxygenation

ALTITUDE (ft)	BAROMETRIC PRESSURE (mm Hg)	P_{O_2} (mm Hg)	P_{AO_2} (mm Hg)	P_{aCO_2} (mm Hg)	OXYGEN SATURATION (%)
Sea level	760	159.2	103.0	40	98
8000	565	118.4	68.9	36	93
10,000	523	109.6	61.2	35	87
15,000	429	89.9	45.0	32	84
18,000	380	79.6	37.8	30.4	72
20,000	349	73.1	34.3	29.4	66
22,000	321	67.2	32.8	28.4	60

P_{AO_2}, Partial pressure of alveolar oxygen; P_{aCO_2}, partial pressure of arterial carbon dioxide; P_{O_2}, partial pressure of oxygen.

patient to an appropriate receiving facility. Aircraft involved in secondary responses—interfacility transport—move patients from outlying hospitals to facilities offering higher levels of care. AMT missions may also be classified according to the level of care provided. This may be critical care transport, specialty care transport, or advanced or basic life support.

Air Medical Aircraft

Although ground ambulance remains the primary means of out-of-hospital and interfacility patient transport, AMT has a definite role in the healthcare delivery system. However, no one aircraft is ideal for the needs of all air medical programs or patients.

Helicopters (Rotor-Wing Aircraft)

An estimated 300,000 patients are flown each year by United States HEMS operations. The helicopter offers several advantages over other transport vehicles. Traveling "as the crow flies" at speeds of 120 to 180 mph, helicopter transport time is often 75% less than that for an equivalent distance by ground. The service area of helicopter programs is generally up to 150 to 200 miles from its base of operations, but average transports can be significantly fewer miles. Rotor-wing aircraft have the ability to avoid common traffic delays and ground obstacles and can fly into locations that may be inaccessible to other modes of travel. Helicopter landing zone requirements are a disadvantage compared with ground ambulances but offer an advantage over airport requirements.

Disadvantages to HEMS include noise, vibration, thermal variances, and other stressors on patients and crew exaggerated by rotor-wing flight. Weather considerations may at times significantly limit the availability of helicopter transport. In smaller helicopters, cramped spaces and weight limitations may limit the number of patients, transport personnel, or equipment that can be carried. This may sometimes compromise optimal patient care in the transport environment (Fig. 191.1).

Many helicopter programs permit flight only under visual flight rules. When the weather conditions (ceiling and visibility) fall below established program minimums, a flight request may

Fig. 191.1. Confined spaces within helicopters may make it more challenging to perform procedures. (Courtesy University of Chicago Aeromedical Network [UCAN], University of Chicago Medicine.)

be declined for safety reasons. However, an increasing number of programs are equipping their helicopters and training their pilots for instrument flight rules (IFRs) to allow safe travel in less favorable weather conditions. IFR flight may facilitate use of fixed locations such as hospital helipads that have developed IFR approaches, but it does not facilitate travel to the scene of illness or injury.

Airplanes (Fixed-Wing Aircraft)

Although rotor-wing missions attract more media attention, fixed-wing flights constitute a significant portion of AMT operations. Fixed-wing aircraft provide increased range, greater speed, and often more patient, crew, and equipment capacity than rotor-wing vehicles. The decreased cabin noise and turbulence creates fewer patient management problems and pressurization combats the physiologic impact of altitude and the physiologic gas laws. Fixed-wing operations are limited, however, to areas that have airports with runways of appropriate length and airports with refueling facilities. During fixed-wing transports, patient transfers require multiple vehicles for each leg of the transport (ie, hospital to ground ambulance to airplane).

Various fixed-wing aircraft are available for medical transport. These range from unpressurized light planes with single- or twin-piston engines to pressurized turboprops and jets. The selection of the ideal aircraft depends on the nature of the air medical mission.

Air Medical Flight Crew

Air medical crew members represent the broad spectrum of health care providers. AMT services that provide critical care transport, advanced life support, or specialty care transport must staff the vehicle with a minimum of two medical personnel to provide direct patient care.[2] The majority of AMT programs in the United States provide critical care transport teams composed of one registered nurse and an additional crew member (paramedic, second nurse, respiratory therapist, or emergency clinician); most common is the nurse/paramedic crew. AMT crew configuration may also be mission dependent. Some programs will use specialty teams to transport pediatric, neonatal, or high-risk obstetrics patients. Other programs will add a specialty care provider to their "routine" team for these transports. Certain flight conditions and situations may also necessitate consideration of heat, humidity, altitude, distance, fuel on board, and weight of the patient.

Flight nurses generally have extensive experience in intensive care units (ICUs) or emergency departments (EDs). They may be specialized within the transport team to care for adult, pediatric, or neonatal patients. Paramedics often make their greatest contribution in the transport of critical patients from the scene of illness or injury. Respiratory therapists bring expertise in airway and ventilator management and oxygen delivery systems. Flight physicians may be residents or attending physicians. Much of the early research in AMT crew composition focused on the need for the flight physician. However, only 5% of the United States HEMS programs currently use a resident or attending physician as a dedicated or alternate member of the flight crew.

The AMT environment imposes unique considerations on the air medical flight crew. Human factors work has shown that most medical care procedures are more difficult to perform in an AMT vehicle than in other ground-based settings. Auscultation of the heart and lungs, palpation of pulses, performance of cardiopulmonary resuscitation, endotracheal intubation, radio communications while using a respirator or face mask, and recognition of visual alarms may all be impaired.[3] In addition, fatigue, motion sickness, exposure to engine exhausts, an erratic pattern of work activity, and the high risk involved in AMT operations may affect task performance.[4-6] Seizures from photic stimuli associated with rotor motion ("flicker illness") have also been reported. High-fidelity simulation of air medical missions can acquaint flight crew to the novel environment, but fiscal and personnel costs may be prohibitive.

Medical Direction

All air medical services require the active involvement of a physician as medical director, responsible for supervising, evaluating, and ensuring the quality of medical care provided by the AMT team. Emergency clinicians play a significant role, with nearly 70% of all United States air medical directors having a background in emergency medicine, according to a 2007 survey done by the Air Medical Physician Association (AMPA). The medical director must have the final authority over all clinical aspects of the air medical service and should ensure that the flight crew has adequate training and qualifications to optimize patient care. Medical care policies and procedures should be established, including specific provisions for on-line and off-line medical control. AMPA and the National Association of Emergency Medical Service Physicians (NAEMSP) have established guidelines for the medical director of an air medical service.

Safety

Safety is the predominant concern of air medical operations, and ensuring safe flight is a fundamental responsibility of every flight program. Safety must also be an overriding consideration in weighing the risks and benefits of AMT. The role of aircraft pilots and mechanics is essential to the airworthiness of the vehicle, and medical personnel must also be proficient in both routine and emergency operations in and around the aircraft. Checklists will aid in safe practices but alone may not detect significant operational concerns. Crew fatigue and other self-imposed stresses that could affect safety (such as, the use of prescription or over-the-counter medications, tobacco, and alcohol) must be scrupulously avoided.

Weather requirements ("minimums") must be strictly enforced. On receipt of a flight request, the pilot must verify the weather conditions and the condition of the aircraft. To ensure impartiality, the pilot should not be told of the patient's condition or acuity. The pilot maintains the unquestioned right to decline a mission because of aircraft or weather considerations. These decisions should not be questioned or influenced in any way by

administrators, flight crew, or other parties. In one witnessed event, a referring facility repeatedly called an HEMS program insisting that they come get their patient because their smartphone weather app showed them that the weather was "good enough to fly."

The practice of "helicopter shopping" has been a major factor in a number of fatal HEMS events. *Helicopter shopping* refers to the practice of a requesting emergency medical services (EMS) agency or hospital calling numerous HEMS programs until one agrees to accept a flight without disclosure to the accepting HEMS operator that other programs were called and declined the flight because of bad weather or other safety concerns.[7,8] The practice was so common that in 2006, the FAA issued a letter to all state EMS directors describing helicopter shopping and requesting that they take action to prohibit this practice.[9] Although there may be circumstances when a subsequent program called can safely undertake and complete the flight, it is essential that they are made aware of all of the facts surrounding the request.

The risk of an accident and patient safety is often a concern when considering HEMS transport for a patient. Cost-benefit analysis, however, has demonstrated that the risk of crash-related patient mortality is so low that the impact on calculations of HEMS use and overall effectiveness is minimal.[10] In addition, available data suggest that after adjustment for patient acuity, transport by HEMS is associated with lower risk of adverse events than transport by ground ambulance.[11]

Landing Zones

Helicopter landing zones are inherently dangerous places. The most obvious risk of injury is impact with rotor blades. This danger is heightened during ground operations, because the blades dip lowest to the ground at the slower rotor speeds associated with engine start-up and shutdown. Injuries also may occur as a result of debris being propelled through the air by "rotor wash," increased noise levels and an inability to hear warnings, and slippery surfaces found on exposed landing sites.

Many hospitals have designated landing areas that are appropriately lit and secured (Fig. 191.2), with fixed coordinates and predesignated liftoff and approach patterns. However, most primary (scene) responses occur at unmarked sites. Ground personnel must be trained to designate and secure a safe landing zone for helicopter operations. AMT programs have an obligation to help train ground staff on proper landing zone setup and conduct (Boxes 191.1 and 191.2).

Helicopter flights, which go directly to the scene of an accident, pose unique risks to AMT from hazards near the landing zone. This risk is heightened at night. In response to this concern, out-of-hospital care providers and flight programs have found it beneficial and safer to use a hospital helipad for rendezvous. This practice raised concerns about Emergency Medical Treatment and Active Labor Act (EMTALA) responsibilities to provide a medical screening examination for these patients. In May 2004, the Centers for Medicare and Medicaid Services (CMS) resolved this issue, noting that the use of a helipad on hospital property does not trigger EMTALA provisions as long as the helipad is being used only as a stopping place for EMS personnel to rendezvous with AMT, to facilitate transport of a patient to the closest appropriate facility.

Other adjuncts to landing zone safety and night operations in general are night vision goggles (NVGs) and terrain avoidance warning systems. A 2014 survey of 22 HEMS operators found that more than 95% of their helicopters were equipped with NVGs.

Fig. 191.2. Landing zone safety is paramount to delivery of patients to hospitals. (Courtesy Dan Lemkin, MD.)

Integration of Air Medical Transport Within Emergency Medical Service Systems

AMT should be an integral resource within a comprehensive EMS system. Integration begins with the establishment of geographic service areas. Service areas may be determined on the basis of program mission description, aircraft range and speed, placement of specialty centers and receiving facilities, and population densities. As a general rule, helicopters are generally less useful in urban settings because of the proximity of health care facilities and a lack of open and safe landing zones. Paramedics, emergency medical technicians, and other public safety personnel should be provided with guidelines specifying when AMT should be considered.

BOX 191.1

Landing Zone Safety

Vehicles and personnel should be kept at least 100 ft from the landing zone.
Spectators should be kept at least 200 ft from the landing zone.
No smoking or running is permitted within 50 ft of the helicopter.
All items (eg, intravenous lines, poles) should be kept below shoulder height.
The flight crew opens and closes aircraft doors.
The flight crew directs and supervises the loading and unloading of the patient and equipment.
Ground personnel should use eye and ear protection.
Approach the helicopter *only* when signaled to do so by the pilot or an onboard crew member.
Approach and depart the helicopter *only* forward of the rear cabin door and in a crouched position with your head down.
Never approach or depart from the rear of the helicopter.
Stay clear of the tail rotor; it is virtually invisible and extremely dangerous.
If the aircraft is parked on a slope, approach and depart on the downhill side (greatest clearance under the blades).
Keep the landing zone clear of (or hold on to) all loose articles (eg, hats, scarves, sheets, pillows).
Protect patient from the dust and debris.
Follow the flight crew's instructions at all times.
In disaster situations and mass casualty incidents, victims, witnesses, and spectators may become hysterical or exhibit signs of an acute situational reaction. These individuals must be kept clear of the landing zone and helicopter at all times. Injured victims who exhibit this behavior should not be triaged for helicopter transport, or they should be transported only with adequate physical or chemical restraints in use.
If you do not know, ask.

Courtesy University of Chicago Aeromedical Network (UCAN), University of Chicago Medicine and Illinois Association of Air and Critical Care Transport (IAACCT), 2015.

BOX 191.2

Landing Zone Requirements for Air Medical Transport

LANDING AREA
Landing zone should be as close as possible to the scene or hospital entrance but not so close that it may interfere with ground operations or patient care.
Landing zone should be at least 100 × 100 ft.
Landing zone should be as flat and level as possible.
Landing zone *must* be clear of debris.

HAZARDS AND OBSTRUCTIONS
Identify all potential hazards that may be on the ground or near the approach/departure path of landing zone.
Landing zone should be clear of wires, poles, trees, buildings, vehicles, and spectators.
Road cones, ropes, tape, and barricades are *not* recommended for use near landing zone.
Perimeter of landing zone should be at least 50 ft away from potential obstructions and hazards.
Landing zone should be located *upwind* from any hazardous material incident.

APPROACH AND DEPARTURE PATH
Path should point into the wind and be free of obstruction to an altitude of 500 ft above the surface.
Path should *not* pass over command posts, treatment areas, or operationally congested areas on the ground.

DAY OPERATIONS
Use radio communications and hand signals.
Stand with your back to the wind.

NIGHT OPERATIONS
Use radio communications and lighting to designate landing zone.
Spotlights should be directed at the top of possible hazards, *not* toward the approaching or departing aircraft.
Position a portable light, vehicle headlights, emergency vehicle flashing lights, flare, or chemical stick at each corner, with a fifth light upwind.
Nonessential lights should be turned off.

LIGHT SOURCES
Lights *must* be clear of landing zone.
If portable, lights *must* be well secured.
Never point lights toward an approaching or departing helicopter.

WIND INDICATOR
Indicator may be a wind sock, flag, flare, or smoke.
Indicator *must* be clear of landing zone.
If portable, indicator *must* be well secured.

Courtesy University of Chicago Aeromedical Network (UCAN), University of Chicago Medicine and Illinois Association of Air and Critical Care Transport (IAACCT), 2015.

BOX 191.3

Criteria for Air Medical Transport

Distance to the closest appropriate facility is too great for safe and timely transport by ground ambulance.
Patient's clinical condition requires that the time spent in transport be as short as possible.
Patient's condition is time critical, requiring specific or timely treatment not available at the referring hospital.
Potential for transport delay associated with ground transport is likely to worsen the patient's clinical condition.
Patient requires critical care life support during transport that was not available from the local ground ambulance service.
Patient is located in an area inaccessible to regular ground traffic, impeding ambulance egress or access.
Local ground units are not available for long-distance transport.
Use of local ground transport services would leave the local area without adequate EMS coverage.
For interfacility medical transport, the requesting physician based on his/her best medical judgment and information available at that time of transport determined the need for AMT.
For scene medical transport, the requesting authorized out-of-hospital provider based on applicable policy, his/her best medical judgment and information available at that time of transport determined the need for AMT.

AMT, Air medical transport; *EMS,* emergency medical service.
Courtesy University of Chicago Aeromedical Network (UCAN), University of Chicago Medicine, 2015. Based on Association of Air Medical Services: Position paper on the appropriate use of emergency air medical services. J Air Med Transp 9:29, 1990; and Determination of medical necessity for air and critical care medical transportation. Position statement of the Air Medical Physician Association. Revised April 13, 2002. In: Blumen IJ (ed): Principles and direction of air medical transport. Salt Lake City, Utah, 2006, Air Medical Physician Association.

These protocols are best developed by EMS medical directors in close collaboration with their air medical colleagues.

CLINICAL CONCEPTS AND PATIENT CARE

Although virtually all types of patients have been transported by air medical services, available data do not allow prospective, identification of which patients will benefit from flight. Many questions about the triage of patients to air or ground transport, the efficacy of air medical care, and the precise effects of AMT on morbidity and mortality in medical and surgical conditions remain unanswered. There are many studies indicating which patients *can* be cared for in the air medical environment, what skills and equipment *can* be used, and that medical flight is generally associated with safe patient care and a low incidence of adverse effects. Unfortunately, there is a relative paucity of clinical investigation addressing potential solutions to the problems of triage and appropriate use. In an effort to ensure that AMT resources are used wisely, AMPA has established a detailed medical condition list for the appropriate use of AMT. A more general approach to the need for AMT is illustrated in Box 191.3.

In response to the controversy over whether HEMS transport improves patient outcomes, the NAEMSP Air Medical Services Task Force began in 2000 to annotate HEMS outcomes studies published since 1980. This ongoing project has been updated every 3 to 5 years through the Critical Care Transport Collaborative Outcomes Research Effort (CCT CORE).[12,13] Annotated reviews of HEMS outcomes research from 2014 forward are available on the CCT CORE's website: www.cctcore.org.

Trauma

Most trauma studies have addressed HEMS use for scene response.[14] Methodological heterogeneity precludes formal meta-analysis of the AMT outcomes data. However, existing data consistently show significant improvement in trauma outcomes with AMT.[14-20] These data support an estimated 20% to 35% improvement in survival rates compared to ground transport, or the saving of three to six lives (fewer for pediatric patients) per 100 air medical trauma flights.[13,21] As demonstrated by a large 2011 study assessing nearly 75,000 secondary HEMS transports, interfacility air transport of the more seriously injured patient (but not those with lesser severity) is also associated with improved

outcomes. Two studies also found improved outcomes with seriously injured patients transported by HEMS while also concluding that stable patients may be transported from outlying hospitals to definitive care by ground with equal effect.[19] Noting that HEMS represents the *only* modality by which nearly 28% of United States residents have timely (within 1 hour) access to level I or level II trauma centers emphasizes the vital role of AMT in the care of the injured patient. Studies have also suggested lack of HEMS benefit for the trauma victim, but these studies represent a minority and are limited by confounding factors, such as inclusion of transports to nontrauma centers. Caution should be exercised in definitive statements about the criteria for and the value of AMT, because such statements can be interpreted only in light of the overall local environment in which the transport system exists. HEMS functions best as a part of a comprehensive trauma system and not as an isolated entity.[22,23]

Work in HEMS casts doubt on the logistical advantages of the helicopter itself. Faster times to trauma centers are not required for better outcomes. It is true that in some studies, subgroup analyses suggest improved trauma outcomes due to HEMS scene response for the more severely injured. However, studies conducted in regions as disparate as California and The Netherlands demonstrate HEMS mortality benefit but find similar scene–to–trauma center times for ground and air transports. For many patients, factors other than speed (such as, the provision of advanced levels of care over that provided by ground personnel) are hypothesized to be responsible for AMT's benefits.

Studies suggest that most trauma victims transported by air have non–life-threatening injuries. Still, the best large-scale population analysis of more than 40,000 HEMS transports from the 2007 American College of Surgeons National Trauma Data Bank, clearly demonstrated that HEMS-transported patients are indeed of much higher acuity than ground-transported patients.[14] The median Injury Severity Score of HEMS patients exceeded the commonly used "severe injury" cutoff of 15; HEMS patients also had a 43% rate of ICU admission.[14] More specifically within the trauma population, data from Pennsylvania and California of head injury patients undergoing out-of-hospital intubation demonstrate HEMS-associated improvements in both morbidity and mortality.

AMT is unlikely to improve outcome in those whose injuries are either trivial or grave. Therefore, the decision to request HEMS needs to be based upon the clinical and logistical considerations consistent with recommended guidelines for HEMS dispatch.[24] If the Injury Severity Score is collapsed into five ordinal categories, a significant association between helicopter transport and improved mortality is found in the middle three categories (survival odds ratios range from 2.1 to 2.6). Other work has also found that AMT shows benefit over ground transport only for those more seriously injured patients in both rural and urban environments.[18] In all these cases, it remains uncertain if improvements in outcome are related to the provision of improved on-scene care or the integration of HEMS into a comprehensive trauma system as opposed to the air transport itself.

Over utilization of HEMS is a significant concern as is over triage to trauma centers. After decades of studies looking at trauma triage, even the best guidelines have trauma center over triage rates as high as 50%.[16] The "problems" with trauma triage has a direct impact on the issue of HEMS "overuse." If it's not possible to predict with accuracy which patients need to be transported to a trauma center, it is not possible to identify with any greater certainty which patients should be flown. Fortunately, even the acknowledged imprecision of triage to HEMS does not preclude "real-world" identification of AMT-associated trauma outcomes benefit. In a 2010 population-based study in Canada, patients were entered into the study if HEMS services were requested, and outcomes were compared between those who actually underwent AMT and those who went by ground because of the unavailability of HEMS. The study identified a benefit of HEMS, compared with ground transport, of 5.6 more lives saved per 100 transports.[18]

AMT of injured patients by airplane has also been reviewed in the literature with the focus on longer distance transport. In general, fixed-wing AMT is determined to be beneficial when transporting patients hundreds or even thousands of miles to definitive trauma care.[25-27]

Cardiac Disorders

Most AMT studies on cardiovascular disease focus on ST-elevation myocardial infarction (STEMI) patients because these represent the largest group of nontrauma air transports. The ability to study HEMS-related outcomes benefit in acute coronary syndrome (ACS) is limited by the lack of validated scores that can be used to stratify risk and predict outcome. Helicopter transport extends the geographic referral base of primary angioplasty centers, and outcomes of patients flown from a distance for definitive care equal outcomes of patients presenting directly to the referral center. AMT systems have been shown to be able to safely transport complicated cardiovascular patients with conditions such as ACS, STEMI, and aortic aneurysm.[11,28,29]

HEMS could conceivably shorten door to percutaneous coronary intervention (PCI) time by transporting patients with STEMI rapidly from hospitals without PCI capability to a referral center. In many circumstances, however, the patient will not have angioplasty of the infarct-related vessel performed within the recommended window and would be best served by receiving thrombolytic therapy at the initial hospital and then being transported in a less emergent fashion. AMT might therefore be better used for transport of critical cardiology patients who require emergent care, such as bypass surgery or balloon pump support that is beyond the capability of the sending hospital. There is also evidence to support HEMS dispatch to rural or wilderness areas for field-diagnosed STEMIs.[30,31] One study has found HEMS saves at least 30 minutes over ground ambulance transport in nearly 80% of cases. Based on time savings alone then, a conservative estimate suggests that properly used HEMS can save one to two lives per 100 STEMI missions.[32]

Stroke

Acute stroke patients can be just as time-critical as trauma or ACS cases. With the advent of time-critical therapy for ischemic stroke, HEMS has played an increasing role in the regionalization of acute neurologic care. Early studies demonstrating safety of transport of post-thrombolysis stroke patients have been complemented by case series illustrating the increasing use of helicopter interfacility transport for stroke.

Although it is more common for flight programs to transport patients from smaller hospitals to regional stroke centers, case reports and series have demonstrated the utility of air medical dispatch for primary (scene) transport of patients with strong suspicion of stroke. In both of these scenarios, it has been demonstrated that HEMS can make important contributions when "time is brain."

Ground EMS can effectively triage and identify patients who would likely benefit from HEMS scene response. Over-utilization is rarely a problem because triage criteria include only the more severe strokes as candidates for HEMS scene response. In one region, ground EMS providers accurately identified stroke, and helicopter-transported patients composed nearly 25% of the stroke center's thrombolytic volume. The use of strict triage definitions kept inappropriate calls for AMT to acceptably low levels while allowing a significant extension of the geography served by

a stroke center. Performance measurement programs can monitor the efficacy of the AMT service. Considering the improved outcomes that are possible with rapid transport to appropriate specialty care centers, HEMS transport of stroke patients has significant potential.[33]

High-Risk Obstetric Patients

With appropriate triage, the speed of air transport of the high-risk pregnancy to an obstetric referral center can counter the risk of delivering an infant in an aircraft's confined space. Case series demonstrate that high-risk obstetric patients transported by air from distant hospitals have outcomes equal to patients presenting directly to an obstetric referral center.[34,35] Common reasons for obstetric transport include preterm labor and premature rupture of membranes.

Neonates and Children

The use of AMT to extend the geographic reach of neonatal care centers is reported from many settings. AMT allows infants with medical complications born in remote areas to achieve outcomes equal to those of infants born in urban centers. Although neonates are vulnerable to physiologic deterioration, specialty team air transport is associated with no more derangement in oxygenation and ventilation than transport by ground vehicle. As in the case of trauma, the question remains if the advantage of AMT is related to the use of air transport or specialty services brought to the patient's side.

Many areas depend on AMT to deliver critically ill or injured children to regional pediatric centers. Although speed of transport may be important, for neonates, the emphasis is often more on the transport *team* than on the *mode* of transport. Experienced pediatric transfer teams often bring a level of expertise unavailable to the pediatric patient in the outlying hospital and are noted to have fewer adverse events during transport than non-specialty teams. Appropriate training, experience, and competency are essential. AMT has been shown to be safe for the transport of even the most critical children requiring extracorporeal membrane oxygen support.[36]

EFFICACY AND COST-EFFECTIVENESS

Cost-benefit is an on-going issue for AMT. However, when no other option is available, fixed-wing transport is employed, essentially eliminating the question of cost-effectiveness. For HEMS, however, there is much more debate.

The crux of the problem lies in the inability to precisely identify in a prospective manner which patients will truly benefit from fixed-wing or rotor-wing flight, especially when outcome improvements are part of regionalized specialty care systems. As a result, in many cases there is little if any guidance regarding when air medical dispatch is indicated. With use of endorsed guidelines (such as, those endorsed by AMPA) for air medical dispatch, EMS regional authorities should collaborate to generate the best criteria for their own systems, with constant refinement guided by rigorous review. However, in practice, the lack of clear indications and guidelines means that AMT often acts more as a "taxi service" responding to the needs of referring clinicians, hospitals, and EMS services. There is a strong economic argument to be made for maintaining this "looseness" of service, because flight revenues keep AMT services available for those truly in need.

Compared with the cost-benefit ratios of other medical interventions, AMT is well within the accepted range per quality-adjusted life-year saved. One Scandinavian study concluded that the benefits of ambulance missions flown by helicopters exceed the costs by a factor of almost six. Another group from the region estimated that HEMS contributes to the cost-effectiveness of primary PCI, and other investigators have demonstrated the favorable cost-effectiveness of HEMS as part of overall care systems for trauma and stroke patients.[32,37-40] HEMS transport of the head-injured patients has been associated with improved outcomes, translating into lower long-term costs for survivors. However, none of these results can be taken as definitive statements, applied universally, because any cost-benefit calculation is applicable only to the system under study.[41]

Cost-effectiveness determinations are not straightforward. It is difficult to calculate true cost-effectiveness for transports that are not likely to occur (as with high-risk obstetrics cases at risk of precipitous delivery) or that would deliver patients outside critical time windows (as for stroke or cardiac transports) in the absence of AMT. Cost-efficiency is also difficult to demonstrate when there are no comparison options (such as, transport from coastal islands or locations without road access) or when integrated ground and air transport systems have already become established in ways that effectively prohibit head-to-head comparisons of risks and outcomes (as is true in most of the United States). If we accept that HEMS represents the only mechanism by which more than 80 million American citizens have timely access to mortality-improving high-level trauma center care, it is obvious that some form of air transport is a "must-have" for some EMS regions, and calculations of cost-efficiency fall away in favor of service provision.

Although transport by air is nearly always more expensive than that by ground, the costs of air medical flight should be viewed in contrast with the "real-life" alternative mode of transport. In many cases, and especially where time and distance are significant factors, the total fiscal and opportunity costs of AMT are arguably less expensive than the alternative. Unfortunately, the work of assessing the cost-effectiveness of AMT is complicated by extremely limited information on the cost-effectiveness of ground-based modes of transport. Although the available data do not enable rigorous meta-analysis, most investigations demonstrate that appropriately used HEMS are cost-effective.

FUTURE OF AIR MEDICAL TRANSPORT

AMT faces many challenges. The dramatic increase in the number of medical helicopters in the United States since the late 1990s has heightened concerns for their inappropriate use. AMT works best and provides the most benefit when it is integrated into an overall system of out-of-hospital care and interfacility transport and when systems are in place to educate requesting agencies and professionals about the appropriate use of available air and ground resources.

Currently, the major challenge facing helicopter transport outcomes researchers is to identify triage variables that can prospectively (ie, at the time of transport vehicle selection) guide use of air medical resources. Advances in ground-based EMS and the availability of critical care ground ambulances for interfacility transports are beginning to offset many of the assumed benefits of AMT. Nonetheless, the regionalization of specialty services, development of new therapies that are highly time-sensitive, and inflexible geography mean that there will always be a role for AMT in emergency care. Thus, the major challenge for the AMT community is to determine not *whether* but rather *in whom* there is benefit to air medical flight.

Although appropriate use and outcomes research remain important, the safety of AMT, especially HEMS, must be the highest priority. AMT programs, aviation operators, air medical associations, and regulatory agencies continue to address this issue. However, it is important to recognize the significant role that requesting and receiving personnel can also play with regard to AMT safety.

KEY CONCEPTS

- Boyle's law and Dalton's law have the greatest impact and explain the development of hypoxia and most common altitude-related symptoms. Other stresses of flight that can affect the patient or crew include temperature fluctuations, dehydration, noise, and vibration.
- The helicopter emergency medical service (HEMS) industry continues to grow; however, the business models are changing with the majority of helicopters operated by privately owned or publically traded for-profit companies rather than non-profit hospitals.
- Although most flight programs do both primary (scene flights) and secondary (interfacility) response, ground ambulance remains the primary means of out-of-hospital and interfacility patient transport.
- The helicopter offers several advantages over other transport vehicles, including reducing travel time by up to 75%, ability to avoid common ground delays (traffic, obstacles, and so on), and ability to fly into locations that may be inaccessible to other modes of travel.
- All air medical services require involvement of a medical director responsible for supervising, evaluating, and ensuring the quality of medical care.
- As a general rule, helicopters are less useful in urban settings because of the proximity of health care facilities and a lack of open and safe landing zones.
- Helicopter emergency medical service (HEMS) represents the only modality by which nearly 28% of American residents have timely (within 1 hour) access to level I or level II trauma centers, and the research supports an improvement in trauma survival rates compared to ground transport.
- HEMS may benefit in other time-critical situations, including ST-elevation myocardial infarction (STEMI) patients going to a catheterization laboratory and acute stroke patients going to regional stroke centers.
- Safety is the predominant concern of air medical operations. The practice of a requesting EMS agency or hospital calling numerous HEMS programs after other programs have declined the flight because of bad weather, must be avoided.
- Essential considerations for landing zone safety are as follows: vehicles and personnel should be kept at least 100 ft from the landing zone; spectators should be kept at least 200 ft from the landing zone; helicopters should only be approached when signaled to do so by the pilot or an onboard crew member; never approach or depart from the rear of the helicopter; and if the aircraft is parked on a slope, approach and depart on the downhill side (greatest clearance under the blades).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 191: QUESTIONS & ANSWERS

191.1. Which of the following statements is true regarding air medical transport (AMT)?

A. AMT improves outcomes when used for acute coronary syndrome (ACS) transport.

B. AMT of neonates is associated with more frequent oxygenation/ventilation derangements than ground transit.

C. AMT use after acute stroke is limited by emergency medical service (EMS) provider inaccuracy in stroke patient identification.

D. Faster times to a trauma center are not required for outcomes benefit from AMT.

E. Outcomes after AMT of high-risk obstetric cases are superior to those of patients presenting primarily.

Answer: D. Factors other than speed seem to be responsible for AMT benefit. No certain benefit for use during ACS has been demonstrated because most patients would benefit from thrombolysis at the outside hospital followed by advanced capability ground transportation. EMS personnel are able to identify stroke cases with reasonable accuracy. AMT transport of high-risk obstetric cases has outcomes equal to those of patients presenting primarily. Neonates do not suffer greater pulmonary derangements during or after AMT.

191.2. Which of the following statements is true regarding air medical transport (AMT)?

A. If the patient's condition is severe, it is prudent to request service from several AMT providers in the face of marginal weather.

B. Spectators should be kept at least 200 feet away from the landing zone.

C. The pilot should be briefed on the patient's acuity.

D. The use of a hospital helipad for emergency medical service (EMS) rendezvous triggers the Emergency Medical Treatment and Active Labor Act (EMTALA).
E. Vehicles and personnel should be kept at least 50 feet away from the landing zone.

Answer: B. See Box 191.1 for safety of personnel approaching and disembarking a helicopter. To maintain weather and equipment objectivity, the pilot has no need to know anything about the patient. "Helicopter shopping" between services is strictly discouraged by the Federal Aviation Administration (FAA). The use of a hospital helipad for EMS rendezvous does not trigger EMTALA for that hospital.

191.3. Which of the following statements is correct regarding the aviation physiology gas laws?
A. Boyle's law explains the physiologic effects of expansion and contraction of gases within the closed spaces of the body that may occur with altitude change.
B. Charles' law can be shown as Pt = P1 + P2 + P3 … Pn.
C. Dalton's law accounts for the gas changes that result in decompression sickness.
D. Henry's law explains why the ambient temperature decreases with increased altitude.

Answer: A. Boyle's law states that the volume of a unit of gas is inversely proportional to the pressure on it. As altitude increases, atmospheric pressure decreases, the molecules of gas grow apart, and the volume of the gas in an enclosed space expands. On descent, there is an increase in atmospheric pressure and gas volumes contract. Dalton's law states that the total barometric pressure at any given altitude equals the sum of the partial pressures of gases in the mixture (Pt = P1 + P2 + P3 … Pn). Charles' law notes that as the volume of a unit of gas rises, the temperature of that volume falls and explains why the ambient temperature decreases with increased altitude. Henry's law states that the mass of gas absorbed by a liquid is directly proportional to the partial pressure of the gas above the liquid. Rapid ascent from depth causes the gas to come out of solution within the bloodstream, resulting in decompression sickness.

191.4. Which of the following statements is correct with regard to landing zone safety?
A. During night operations, spotlights should be toward the approaching aircraft.
B. If the aircraft is parked on a slope, approach and depart on the downhill side.
C. In a rear-loading helicopter, it is safe to approach or depart from the rear of the helicopter.
D. It is safe to approach the helicopter when signaled to do so by trained ground personnel.
E. Vehicles and personnel should be kept at least 50 ft from the landing zone.

Answer: B. When the aircraft is parked on a slope, approach and depart on the downhill side where there is the greatest clearance under the blades. Vehicles and personnel should be kept at least 100 ft from the landing zone. Approach the helicopter only when signaled to do so by the pilot or an onboard crew member. Never approach or depart from the rear of any helicopter. Approach and depart the helicopter only forward of the rear cabin door. During night operations, spotlights should be directed at the top of possible hazards, not toward the approaching or departing aircraft.

CHAPTER 192

Disaster Preparedness

Carl H. Schultz | Kristi L. Koenig

PRINCIPLES

Disasters occur in all areas of the world and cause harm to populations, property, infrastructure, economies, and the environment. Harm to populations includes death, injury, disease, malnutrition, and psychological stress. Recent catastrophes include earthquakes in China (2008) and Haiti (2010) (Fig. 192.1); devastating tsunamis in the Indian Ocean (2004) and Japan (2011); severe flooding in Australia (2011); tornadoes in Arkansas, Tennessee, and Kentucky (2008); hurricanes in the United States (2012) and the Philippines (2013), and the Ebola outbreak in West Africa (2014). Increasing population density in floodplains and in earthquake- and hurricane-prone areas and the effects of climate change point to the probability of future catastrophic disasters with large numbers of casualties.

Factors that indicate an increasing probability of mass casualty incidents include terrorist activity; increasing population density in floodplains, seismic zones, and areas susceptible to hurricanes; production and transportation of thousands of toxic and hazardous materials; risks associated with fixed-site nuclear and chemical facilities (illustrated by damage to the Fukushima nuclear power plants after the 2011 Japan earthquake and tsunami); the possibility of catastrophic fires and explosions; and climate change. As an example, the United States Geological Survey has identified volcanoes in the western United States and Alaska that are likely to erupt in the future, including Mt. Hood, Mt. Shasta, and the volcano underlying Mammoth Lakes in California. Because of the rising population density in these areas, hazards from volcanic activity are increasing. Ash from the 2010 Eyjafjallajökull eruption in Iceland grounded aircraft in Europe for weeks.

Given this probability and the increasing role of emergency medicine in disaster mitigation, preparedness, response, and recovery, this chapter discusses disaster planning and operations with emphasis on the role of the emergency clinician. The emergency clinician has extensive responsibilities for community disaster preparedness and disaster medical services, including response to terrorism. In position and policy documents, the American College of Emergency Physicians (ACEP) outlines the scope of emergency medicine's involvement in preparedness and response to disasters and terrorism, stating that "emergency clinicians should assume a primary role in the medical aspects of disaster planning, management, and patient care." In addition, ACEP facilitated creation of national disaster and terrorism-related core competencies for emergency department (ED) personnel and emergency medical service (EMS) professionals through a grant from the Robert Wood Johnson Foundation.[1,2]

A committed ED alone is insufficient to provide hospitals with a successful disaster preparedness program. Institutional commitment by every hospital department and the administration is necessary to coordinate effectively with system-wide resources for disaster management. An integrated comprehensive health care system response is especially critical for providing care when demand exceeds available resources, a concept referred to as *hospital surge capacity.* A partial listing of sources for general disaster medicine information can be found in Table 192.1.

Surge Capacity

The concept of surge capacity has emerged as a way to manage an event that produces a sudden influx of casualties with medical and health needs that exceed current hospital resources. This can be due to either the volume or types of victims. The three basic components of the surge capacity system are commonly referred to as the three Ss: *s*taff (hospital personnel), *s*tuff (supplies and pharmaceuticals), and *s*tructure (physical location and management infrastructure). A complete discussion of surge capacity is beyond the scope of this chapter but has been published elsewhere.

Within the context of surge capacity, new protocols are being developed that address allocation of resources when the medical and health needs of a population exceed current inventory. The issues involve creation of an equitable system for scarce resource allocation strategies, including, but certainly not limited to, the assignment to an intensive care unit. Although no universally accepted approach currently exits, the Institute of Medicine has published a consensus based document that suggests approaches to optimize patient outcomes in a resource-constrained environment.[3]

Definitions

One of the challenges facing those responsible for disaster preparation is that no standard definition of *disaster* exists. In the most general terms, one might define a disaster as a severe supply and demand mismatch where the need for resources exceeds the supply. This suggests that a disaster is defined more by the resource and need discordance than the actual size of the event. For example, many would consider a plane crash a disaster, yet it may not even approach overwhelming of the resources of the local responders. Because disaster medicine is multidisciplinary and depends on the integration of multiple levels of responders, the use of a common, precise terminology is essential.

In general terms, an event can be considered a disaster when it overwhelms response capabilities. These response capabilities can change in diverse environments or even in the same location at different times of the day or days of the week. A multiple-vehicle collision with 6 critically injured patients and 12 patients with minor injuries could overwhelm both the EMS system and the hospital in a small rural community. In an urban area with multiple hospitals that participate in a trauma system, however, this same event could be managed with routine resources. Thus it is the functional impact on the specific entity that is the key concept in determining whether a disaster exists.

Classic Terminology

The words *internal* and *external* refer to a hospital setting to help distinguish whether an event has occurred within the hospital grounds (internal) or in the community (external). This concept distinguishes between preparing for casualties to arrive at the hospital and managing casualties or resources within the hospital.

Fig. 192.1. Large-scale catastrophes, such as this earthquake in Haiti (2010), have the potential to cause much injury and psychological stress.

TABLE 192.1

List of Disaster Medicine Resources

ORGANIZATION	WEBSITE
The Joint Commission	www.jointcommission.org
American College of Emergency Physicians (ACEP)	www.acep.org
Centers for Disease Control and Prevention (CDC)	www.cdc.gov
FEMA National Preparedness Directorate	training.fema.gov
National Response Framework	www.fema.gov/national-response-framework
Agency for Healthcare Research and Quality	archive.ahrq.gov/prep
Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices (Cambridge University Press)	www.cambridge.org
World Association for Disaster and Emergency Medicine	www.wadem.org

This geographic distinction between internal and external may be useful, but it has severe limitations. Many events can be both internal and external to the facility at the same time (eg, major earthquake or hurricane). Furthermore, simply identifying the location of the event does not answer the critical question: How are response capabilities affected?

An etiologic descriptor for an event is another customary classification. However, it does not matter whether a disruption in the ability of the hospital to respond is caused by nature or by humankind. The key consideration is what actions are required to mitigate and then to rectify the situation. Although the terms *natural* and *man-made* are prevalent disaster descriptors, they generally do not add anything of value, and therefore some experts have advocated removing them from the disaster lexicon, particularly because the etiology of the event may be unclear in its initial aftermath. A biological event initially considered as a natural occurrence may only much later be identified as terrorism.

Some definitions have been based on the number of casualties. As previously described, the absolute number of patients is much less important than whether their medical and health needs exceed the resources to care for them at a given point in time. The attack on the World Trade Center in 2001 (Fig. 192.2) illustrated this point. Although over 2000 victims died in the collapse of the twin towers, the actual impact on the overall health system of New York City was relatively mild. The capacity of the system to care for citizens living in New York remained intact. In contrast,

Fig. 192.2. The World Trade Center attack of 2001 overwhelmed local resources and necessitated state and federal help.

Hurricane Katrina in 2005 resulted in a similar number of deaths, but caused such massive destruction, including the loss of medical and health infrastructure, that federal disaster medical assistance teams (DMATs) were deployed to Louisiana to provide medical personnel and supplies.

One proposed model for what is common disaster vernacular eliminates the word *disaster* and replaces it with *potential injury-creating event (PICE)*. The PICE nomenclature is an attempt to resolve the challenges associated with diverse meanings for *disaster*. This model is referenced in the Joint Commission standards and in publications from several countries. The PICE system is discussed here to help clarify important concepts in describing an event.

Potential Injury-Creating Event Nomenclature

The acronym PICE and its modifiers concisely describe the critical features of most types or degrees of disaster. The same occurrence can have different effects at different points in time; thus, as an event evolves over time, its description may change.

Modifiers are chosen from a standardized group of prefixes along with a stage to indicate the need for outside medical assistance (Table 192.2). The first prefix (column A) describes the potential for additional casualties. The second prefix (column B) describes whether local resources are overwhelmed and, if so, whether they should simply be augmented (disruptive) or whether they require total reconstitution (paralytic). The third prefix (column C) shows the extent of geographic involvement. Column C refers strictly to the affected region and not to the location that sends assistance. Rather, The "stage" rating scale defines the likelihood that outside medical assistance will be needed either to augment or to completely reconstitute resources. Stage 0 means that there is little or no chance. Stage I means that there is a small chance and requires placing outside medical help on alert. Stage II means that there is a moderate chance and outside help should be placed on standby. Stage III means local resources are clearly overwhelmed and require the dispatch of outside resources and

TABLE 192.2

Potential Injury-Creating Event (PICE) Nomenclature

PREFIX			PROJECTED NEED		
A	*B*	*C*	PICE STAGE	FOR OUTSIDE AID	STATUS OF OUTSIDE AID
Static	Controlled	Local	0	None	Inactive
Dynamic	Disruptive	Regional	I	Small	Alert
	Paralytic	National	II	Moderate	Standby
		International	III	Large	Dispatch

TABLE 192.3

Potential Injury-Creating Event Nomenclature Examples

World Trade Center attack, September 11, 2001	Dynamic, paralytic, local, PICE stage III
Los Angeles civil disturbance	Dynamic, paralytic, regional, PICE stage I
Northridge earthquake	Dynamic, disruptive, regional, PICE stage II
Oklahoma City bombing	Dynamic, disruptive, local, PICE stage I

PICE, Potential injury-creating event.

commitment of personnel. For example, a multivehicle collision with a dozen injuries and several deaths in a large city would be a stage 0, whereas in a small rural town it might be a stage III (Table 192.3).

A PICE can be either static or dynamic. *Dynamic* implies an evolving situation in which it is too soon after the incident to determine the numbers and types of casualties and the impact on the hospital. Alternatively, a *static* situation results if 10 people are injured in an incident and little potential for further harm exists.

In some situations, enhancement of routine operations is not sufficient or possible. A PICE can completely overwhelm the capability to mount a normal response so that a substitute plan for recovery should be used. Situations that require significant reconstitution of critical resources are termed *paralytic.* Within the hospital, there are six critical elements necessary to manage a PICE (Box 192.1). If one or more of these resources are compromised, they require reconstitution or that a substitute be found and implemented. Such paralytic events can be either destructive or nondestructive (Box 192.2).

Hazard Vulnerability Analysis

An important consideration in disaster planning is an awareness of the types of events for which the hospital or community is vulnerable. The classic example is the monumental risk from earthquakes in the central United States resulting from the combination of the New Madrid fault and the limited seismic safety requirements for buildings in that area. The planner needs to learn what types of support are available from outside agencies (eg, hazardous materials decontamination from fire departments, and information from poison control centers). Although awareness of such resources is critical, contingency plans should be available when such assistance is not accessible.

After performing a hazard vulnerability analysis (www.calhospitalprepare.org/hazard-vulnerability-analysis), emergency planners should consider the most probable events and prepare for them. Although the approach to preparedness is generic, specific environments require special preparation, and there should also be planning for events that, although rare, result in catastrophic consequences.[4] The major peacetime threat to life and limb in the United States is probably a large earthquake in a densely populated area or a terrorist attack, although the threat from flooding is increasing. The disaster planner should prospectively identify all such hazards and prepare contingency plans for each.

BOX 192.1

Six Critical Substrates for Hospital Operations

Physical plant
Personnel
Supplies and equipment
Communication
Transportation
Supervisory managerial support

BOX 192.2

Examples of Paralytic Potential Injury-Creating Event

DESTRUCTIVE
Bomb explosion
Earthquake
Fire
Civil unrest

NONDESTRUCTIVE
Snowstorm
Employee strike
Power failure
Water supply cutoff

SPECIFIC ISSUES IN DISASTER MANAGEMENT

TRIAGE

The term *triage* derives from the French verb *trier,* meaning "to sort." The concept of triage was used as far back as Napoleon's time to assign priorities to treatment of the injured when resources were limited. Priority is given to the most salvageable patients with the most urgent conditions. Some EDs continue to use triage in the hospital setting, although this daily practice has little in common with triage during disaster conditions. For those EDs that continue to use standard triage, it is intended to identify the most seriously ill patients with time-dependent conditions and to

ensure that they receive rapid care. The goal of disaster triage is clearly different, that is, "to do the most good for the most people." In other words, there is a shift from focus on individual patients to focus on the entire affected population. It can be difficult for physicians to realize that to achieve the goal of maximizing benefit to an entire population of patients they may need to let some patients die with comfort care only. Under true disaster conditions, cardiopulmonary resuscitation should not be performed.

Routine Multiple-Casualty Triage

To assist in the understanding of triage techniques, it is useful to consider a routine out-of-hospital event with multiple casualties (eg, a multivehicle collision). In such situations, rescue personnel often use a simple triage and rapid treatment (START) technique that depends on a quick assessment of respiration, perfusion, and mental status.[5] These three assessments can be remembered by the mnemonic RPM (*r*espirations, *p*erfusion, and *m*ental status). Initially, all victims who are able to walk are asked to move away from the incident area. These patients are classified as green, or "walking wounded," and are reassessed after the more immediately critical patients are triaged.

The Pediatric Triage Tape (PTT) and JumpSTART have been proposed for the triage of children. JumpSTART is a modification of the START triage protocol that includes an additional step of five rescue ventilations for children presenting apneic and modification of criteria for hypoventilation and tachypnea, as well as for a decrease in mental status. The PTT uses criteria that change in proportion to increasing victim size. The parameters for a child 50 to 80 cm in length are illustrated in Figure 192.3. When comparing sensitivity and specificity of PTT to JumpSTART in pediatric trauma patients, the PTT demonstrated superior outcomes. Both START and the PTT appear to be useful tools, but only START has been evaluated in a disaster situation.[6]

As illustrated in Figure 192.4, a rescuer can assess each patient in seconds, quickly checking respiratory rate, pulse, and ability to

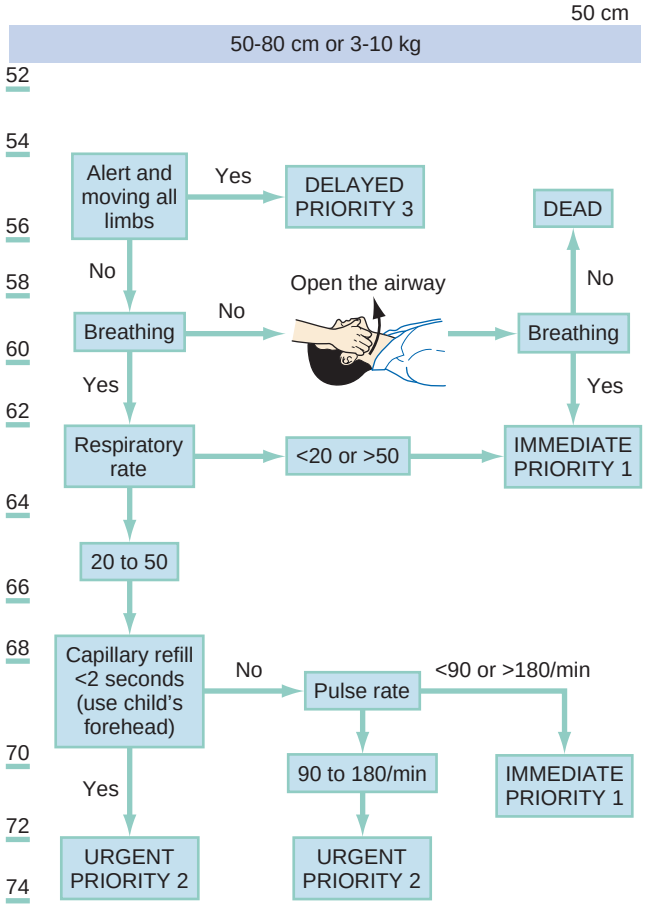

Fig. 192.3. Pediatric Triage Tape (PTT) algorithm for a child 50 to 80 cm in length.

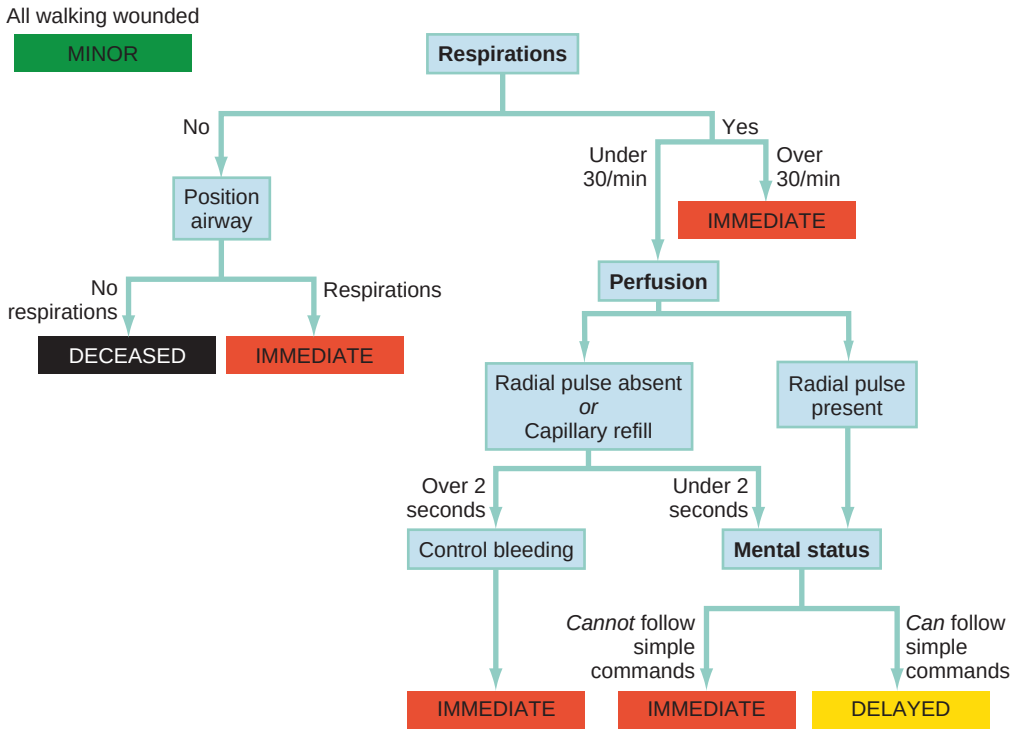

Fig. 192.4. Simple triage and rapid treatment (START). Victims who can walk are identified first and triaged into the "minor" category. Those remaining are triaged using the algorithm. (Modified from Triage—START and SAVE. In: Medical disaster response training course syllabus, Dana Point, CA, 1993, Medical Disaster Response.)

follow commands (mental status), and divide the patients into the remaining three categories: red (immediate), yellow (delayed), and black (deceased). The only patient care interventions provided during this process are the opening of an obstructed airway and direct pressure on obvious external hemorrhage. At this point, patients are generally transported to a hospital for definitive care. Most often, patients arrive with a color-coded triage tag and are reassessed and re-triaged by the hospital staff (Fig. 192.5). An outcomes-based evaluation of the performance of START triage in an actual disaster (2002 Placentia Linda train crash) demonstrated acceptable levels of under triage (100% sensitivity of the red category and 90% specificity of the green category). However, significant amounts of over triage occurred. Use of START also appropriately prioritized the transport of victims, with patients triaged as red arriving at hospitals earlier than patients triaged as yellow or green.

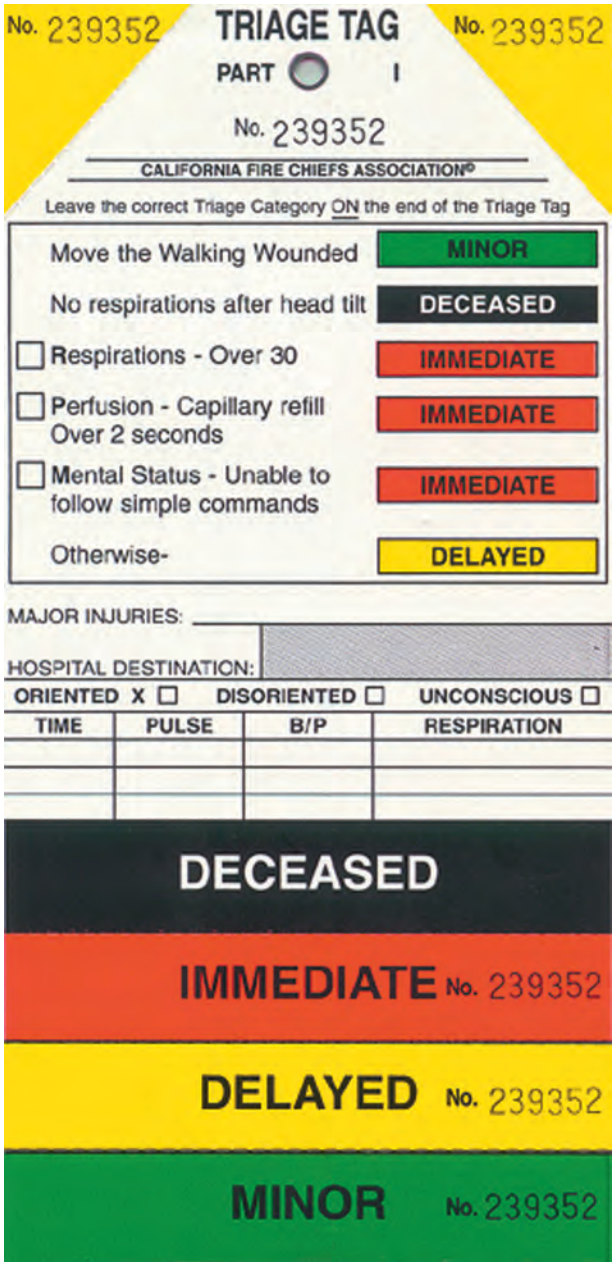

Fig. 192.5. Triage tag to be used in multi-casualty or disaster patient assessments.

A multidisciplinary group proposed a potential national triage system for the United States. The result, derived by consensus of opinions, was referred to as *SALT* (*s*ort, *a*ssess, *l*ifesaving interventions, and *t*reatment or transport). It differs from START mainly in the assessment of respirations (ie, relies on a qualitative evaluation of respiratory distress rather than a number), the requirement for performance of certain emergent interventions (chest decompression), and an unstructured estimate of survivability. The algorithm is more complicated than START, and no current data exist evaluating its sensitivity, specificity, or other performance characteristics after use in an actual incident. As such, it is not currently possible to make recommendations for its use.

Catastrophic Casualty Management

Triage during a widespread, catastrophic disaster differs from triage performed in routine out-of-hospital and hospital settings. The number of victims is vastly increased, while medical resources are severely limited or even initially absent. Patients may remain on scene for an extended period and should be frequently reassessed. If hospitals remain accessible, patients tend to seek care at the closest one, a phenomenon known as *convergence*. Hospitals close to the disaster scene are overwhelmed, whereas hospitals located only a few miles away may receive few if any patients. The triage process will then be decentralized, occurring at multiple sites, or compartments, simultaneously throughout the disaster zone. Rather than a single scene or localized disaster, this can be thought of as a compartmentalized disaster.

To address this situation, researchers developed the Secondary Assessment of Victim Endpoint (SAVE) system of triage. The SAVE triage system is designed to identify patients who are most likely to benefit from care available under austere field conditions in a resource-poor environment. When it is combined with the START protocol, SAVE triage is useful for any scenario in which multiple patients experience a prolonged delay in accessing definitive care.

The SAVE methodology is designed for use by health care providers under two conditions: (1) for those working within the disaster zone that begin caring for patients immediately but may not be able to transport patients to a definitive care facility for days and (2) for those caring for patients within hospitals where demand for resources exceeds supply. This second situation can occur as hospitals attempt to increase surge capacity. It is immediate and dynamic rather than delayed and static. Although there are many elements in common with other triage systems, rapid transport to a functional medical center within the "golden hour" may not be possible.

The SAVE triage methodology divides patients into three categories: (1) those who will die regardless of care, (2) those who will survive without care, and (3) those who will benefit from austere field interventions. Only those patients expected to improve receive care beyond basic or comfort measures. The decision to place patients in a particular group is based on field outcome expectations derived from existing survival and morbidity statistics. An example is a situation in which three victims require chest tubes (two victims require one tube each and one victim requires two tubes), but only two chest tubes are available. The SAVE principles guide providers to place their last two chest tubes into the two victims who need it rather than into the single victim requiring two tubes.

During the triage process, individuals who would most benefit from early transport should be marked as "first out" in case an evacuation opportunity occurs. These would be victims with medical problems readily treatable at a hospital or facility with equivalent capabilities but untreatable and fatal in the field. A patient requiring surgery for intra-abdominal hemorrhage is a common example.

Since nuclear, biologic, and chemical terrorism has become a threat, triage systems have been modified to address these situations. These systems attempt to incorporate the added threats from exposure and contamination into the triage process. One such method for biologic casualties triages many individuals to home observation rather than hospitalization to optimize resource use and to minimize the spread of the infectious agent. In addition, responders need to be protected from secondary contamination or exposure; therefore, part of the triage algorithm should include a risk assessment and determination of whether and what type of personal protective equipment should be donned before patients are assessed. This was illustrated during the 2014 Ebola outbreak when health care providers initiated Ebola exposure screening procedures during initial patient contact before engaging in patient evaluation and treatment. In a "combined event" scenario, such as an incident involving a radiologic dispersion device, rapid patient assessment is critical to prevent patient deaths from traumatic injuries while awaiting medical care from responders concerned about their own health and safety. Also associated with terrorism incidents are large numbers of *psychological casualties,* those who believe they were exposed but actually were not and those at risk for post-traumatic stress disorder. The emergency plan should include a mechanism to assess and to sort these individuals to assure that they have access to mental health care and also so as not to overwhelm the emergency medical capacity. While performing triage, the emergency clinician should consider the effects of extreme age, underlying disease, and multiple injuries when assessing the potential prognosis for a given patient. Treatment of many nontraumatic emergencies can be accomplished with field interventions that do not consume extensive resources. Therefore, patients with such illnesses should usually be triaged to the treatment area.

Vulnerable Triage Populations

Certain groups of patients, such as children, the elderly, the disabled, and homeless persons, may have special needs that present challenges to routine triage. For example, if a person is too young to follow commands or is deaf, the individual would not be able to respond to a command to walk away from an incident site for reasons that may not indicate severe injury. Triage schemes should attempt to accommodate language and cultural barriers, as well as physical and psychological limitations that result in social or medical vulnerabilities.

Special Triage Categories

To maximize human resources, disaster victims who would normally be triaged to the observation area can be triaged to the treatment area if they possess special skills valuable to the medical team (eg, medical expertise and translation skills). By the increase in the number of functional team members, the effectiveness of the overall response will improve. The guiding principle supports the disaster triage goal of maximizing benefit to the most people.

CARE OF POPULATIONS WITH FUNCTIONAL OR ACCESS NEEDS

Within the general population, groups of unique individuals exist that are at greater risk for injury, death, and property loss resulting from a disaster. These vulnerable populations include children, the elderly, racial and ethnic minorities, the disabled, those residing in institutions such as skilled nursing facilities, and the mentally ill. Challenges in the management of these populations with functional or access needs during a disaster include lack of mobility, tracking of victim movement during evacuations and issues of reunification with responsible family members, inability to understand English or to comprehend instructions issued by local authorities, and poor access to transportation resources. A detailed discussion on the disaster management of these populations is beyond the scope of this chapter but available elsewhere.[7] Those responsible for disaster planning should ensure that policies and procedures are developed that address the unique needs of such groups.

OUT-OF-HOSPITAL RESPONSE

Emergency Medical Services System Protocols

To prepare adequately, hospitals should be familiar with and involved in the development of county or regional plans. For example, some EMS systems use automatic systems such that each hospital may be expected to accept a fixed number of critically ill or injured and minor patients without advanced notification.

Physicians working at hospitals should be familiar with and involved in community disaster management operations, including the function of the emergency operations center. Mutual aid agreements with other hospitals or regions should be considered for situations in which current hospital capacity is exceeded or evacuation is necessary.

Incident Command System

Some form of an incident management system is a standard component of emergency command and control throughout the United States. It provides a flexible management structure on which to organize a response.[8] The federal version, known as the *National Incident Management System,* is incorporated into the National Response Framework and provides strategic guidance on the United States government's involvement in disaster response. All states must use an incident management system compliant with the National Incident Management System.[9] By standardizing an organizational structure and using a common vernacular, an incident command system provides a management configuration that is adaptable to events involving a multiagency or multijurisdictional response. At the most basic level, there are five functional elements in the organizational structure: incident command, operations, planning, logistics, and finance. The principles of an incident command system can also be applied to the hospital setting through implementation of a Hospital Incident Command System. With this type of organizational infrastructure and the flexibility to expand and to collapse functions as needed, an orderly and efficient response to any incident can be accomplished. Because hospitals cannot anticipate every contingency, a system such as the Hospital Incident Command System assists with planned improvisation. The Joint Commission standards require use of an incident management system in health care facilities.

Incident Command

The incident commander has overall management responsibility for the incident. Physicians should understand that they are not in charge at the scene of an out-of-hospital incident.[9] In general, nonhospital providers can manage the scene, and physicians should remain at the hospital to provide definitive care. When a physician is on scene, the best way to assist is to ask the incident commander where medical help is most needed.

The incident commander may choose to appoint a command staff to manage public information, safety, and interagency coordination.[8] When an event involves multiple jurisdictions, a unified command is established that coordinates a common and consistent action plan to make the best use of available resources.

Operations Section

The operations section has a chief who is responsible for the management of all incident tactical activities.[8] This section can be expanded and subdivided into branches (eg, law, fire, and medical) and divisions. The operations section also manages the resources assigned to staging areas. For events with a discrete scene, ambulances, personnel, and supplies should be staged outside the perimeter and directed in as needed rather than converging on the disaster site, potentially disrupting activities and blocking the exodus of patients. It is under the operations section that all medical triage and care is provided.

Planning Section

The planning section collects, evaluates, and disseminates information about incident operations and the status of resources. This section also develops incident action plans and conducts planning meetings.[8]

Logistics Section

The logistics section's chief is responsible for providing facilities, services, and material in support of the incident. This includes procuring equipment and supplies, providing food and medical support, and meeting transportation needs.[8]

Finance Section

The finance section is responsible for maintaining records on personnel and equipment, providing payments to vendors for supplies and use of equipment, and determining the cost of various alternatives for strategic planning.

Organization of the Out-of-Hospital Disaster Scene

The disaster site is organized into several distinct areas. The command post is the nerve center of the operation and contains the incident commander and section chiefs. A staging area for incoming personnel and equipment should be established on the outer perimeter. If air evacuation is needed, a safe landing zone must be identified. A casualty collection point and morgue should be designated. In conjunction with an incident command system, this structure brings order to the response.

PLANNING AND HOSPITAL RESPONSE

Comprehensive Emergency Management

The comprehensive emergency management all-hazard approach to disaster preparedness has been a Joint Commission requirement since January 2001. Comprehensive emergency management consists of four phases: mitigation, preparedness, response, and recovery.[10,11] *Mitigation* involves taking actions to reduce the impact of identified hazards. Enhancing the seismic structural design of hospitals is one strategy to mitigate the impact of large earthquakes on the health care system. Training, drills, and cataloging of resources are examples of *preparedness* activities. *Response* includes assessment of the situation and coordination of resources. Finally, *recovery* consists of a return to normal operations and debriefing to critique the response and to provide long-term psychological support to the victims and rescuers.

As required by The Joint Commission, a hospital's disaster or "emergency management" plan needs to address events that occur both inside (internal) and outside (external) the institution.[11] Because some incidents affect both internal and external operations, a hospital emergency management program should contain plans that address all circumstances.

Hospital Disaster Response Plan

A disaster event can disrupt daily, routine hospital functions. This can represent an infrastructure failure (eg, loss of electric power and water) or a threat to the safety of patients and hospital personnel (eg, labor dispute or approaching hurricane). Because the response varies from postponement of elective surgery to facility evacuation, every hospital department needs to participate in the planning process. At a minimum, the disaster plan should clearly delineate the circumstances in which the plan is activated; identify the command structure with defined lines of authority and responsibility; describe a response strategy for each anticipated incident; estimate an incident's impact on safety and hospital function, providing for evacuation if necessary; and list essential information, such as critical telephone numbers (eg, elevators, key personnel, and pay telephones), community agencies (EMS, police, and public health), and sources of vital supplies (water, oxygen, and drugs).

After plan activation, the primary role of the ED is to assess and to treat individuals with illness or injury. In the absence of casualties, other hospital departments primarily manage disasters that disrupt hospital operations. Nevertheless, the medical director of the ED should continuously monitor the response process.

In the unlikely event that evacuation of the ED is necessary, evacuation routes and relocation destinations that have been planned in advance maximize safety and efficiency. When resources are plentiful, ED patients in critical condition are assigned the highest priority for evacuation and transport. Less ill patients receive a lower priority. When resources are limited (eg, in the event of a large-magnitude earthquake), the reverse strategy applies. The least critically ill patients receive the highest priority for evacuation.

Another scenario would be an event occurring in the community that results in a sudden influx of patients requiring emergency care at hospitals. This type of incident has no direct impact on hospital structural integrity or function. However, the need to rapidly increase surge capacity may require implementation of different patient management strategies (ie, temporary creation of alternate care sites on hospital grounds). Participation in the planning and execution of the hospital disaster response is an important administrative responsibility. Available data guiding development of disaster strategies are incomplete, but an effective disaster response can be created by reviewing the essential components of disaster plans and the previous experience of hospitals.[12] A member of the ED must have a leadership role in the planning and implementation of the disaster plans.

Basic Components of a Hospital Comprehensive Disaster Response Planning Process

Interdepartmental Planning Group

The interdepartmental planning group has the responsibility for hazard identification and disaster preparedness activities. The process of conducting a hazard vulnerability analysis is complex, but templates such as the one created by the Kaiser Foundation Health Plan may be informative. Frequently referred to as the *disaster* or *emergency preparedness committee*, it is composed of representatives from all departments vital to the hospital's response, including administration, medical staff, nursing, safety, security, ED, and engineering. Additional input may occasionally be necessary from outside agencies (eg, fire department, hospital suppliers of goods and services, and EMS agency).

The committee should be structured to ensure that the plan is properly constructed, tested, and executed. Hospital resources are needed to support the planning process and testing of the plan, and a detailed educational program should exist for all affected hospital staff.[11,13]

Resource Management

A full inventory of the hospital's resources is necessary. In addition to equipment, space, and personnel within the institution, potential support from outside the hospital should be sought. It is also necessary to develop contingency plans to compensate for lost resources (eg, failure of hospital computers during a power outage or cyber-attack). Augmentation of such resources is critical to the successful increase of the hospital's surge capacity.

Strong relationships with community agencies (eg, fire department and regional EMS system) are important to ensure a coordinated disaster response. Hospitals located near companies using large amounts of hazardous materials are required by Title III of the Superfund Amendments and Reauthorization Act to participate in local emergency planning committees (LEPCs).[14]

Command Structure

An organized system establishing lines of authority and decision responsibility should be in place. This system needs to designate a command center where the disaster response can be coordinated and create a clear chain of command. This prevents confusion if certain individuals are missing, a common situation on nights and weekends or in cases of a community-wide disaster during which hospital personnel may become victims. The command center should contain sufficient equipment to support command and control functions, even if the center must be moved as a result of hospital damage. Implementation of the Hospital Incident Command System or similar management structure will support all such requirements.

Media

The media can be an important source of information but can also significantly disrupt the hospital's disaster response. Therefore, arrangements should be made in advance for a designated individual to coordinate all media interactions and for these briefings to occur in a designated location. Frequently referred to as the *public information officer (PIO),* media coordinators should inform reporters of the time they will receive their next update so that they do not intrude on response operations while trying to obtain information. A strong media liaison can facilitate dissemination of important information to the public, such as that no blood shortage exists so that individuals refrain from coming to the hospital to donate blood. In fact, crisis and emergency health risk communication is now an important part of managing the disaster response and can have a significant impact on the public's perception of events. Individuals designated the media coordinator should be familiar with the basic principles of emergency health risk communication. Security should be involved in managing the media response to the hospital and in preventing media from interfering with triage and treatment of patients.

Communication

Communication systems are probably the most important but also most vulnerable component of a disaster plan. Redundant systems are essential. Those responsible for mobilizing the emergency response require access to at least one other communication system besides the telephone (which is frequently one of the first systems compromised during a disaster). Two-way radios are often used, as are pay telephones, independent fax lines, and cellular phones. Another option is the use of satellite phones and wireless handheld devices to transmit email messages. Recent advances in communication technology exemplified by Facebook and Twitter show promise. Survivors of the 2011 Japan earthquake used these techniques to provide early information to the outside world on conditions within the disaster zone.[15] Runners are also useful for intrahospital communication if all else fails.

Personnel

The disaster plan should include a roster of all critical positions and personnel and establish a reliable method for their mobilization. Several individuals should be assigned to each position in case some personnel cannot be reached. A protocol for managing volunteers is also crucial. A large group of uncontrolled volunteers descending on a hospital ("convergent volunteerism") can be as disruptive as the disaster.

Credentialing of volunteer health professionals in a timely manner so hospitals can use their services during a disaster remains a challenge. A federally supported program known as the *Emergency System for Advance Registration of Volunteer Health Professionals (ESAR-VHP)* attempts to address this problem. It will provide a system for credentialing of volunteer health care providers in advance of a disaster so that they will have emergency privileges should the need for their services arise. There remain significant challenges with such a system, including whether sufficient numbers of providers will participate, how fast they can deploy, how well qualified they will be, and whether they will have competing obligations during a disaster. An alternative system that permits hospitals to recognize each other's credentialing process through a shared database shows promise and has been endorsed by a publication from the Agency for Healthcare Research and Quality. Not only will this alternative system facilitate participation by most health care providers, but it also permits hospitals to grant emergency privileges within minutes after a disaster.

Patient Management

A systematic approach to patient management is necessary to maximize resources. This includes protocols for decontamination, triage, patient prioritization, evacuation, and control of patients' families. Alternative use of hospital facilities should be anticipated, such as the conversion of a parking lot into a clinic area for suturing of lacerations or a decontamination zone. Provisions for patient identification and treatment documentation are also important to facilitate federal and third-party reimbursement at the conclusion of the disaster.

Training Exercises

Disaster exercises are one of the more effective ways of familiarizing hospital staff with their responsibilities. All hospital departments should participate, and community agencies should be involved. The Joint Commission requires two drills a year; these should mimic incidents that are likely to occur. Methods to assess the effectiveness of these exercises as measures of overall hospital disaster preparedness are improving.[16]

REVIEW OF HOSPITAL AND COMMUNITY DISASTER RESPONSE EXPERIENCE

Disaster plan implementation is complex and difficult. Knowledge can be gained from review of previous disaster response experiences and publications, resulting in improved implementation strategies. The following discussion highlights potential challenges.

Focal Disasters

Most disasters experienced by hospitals are focal in nature. Hospital function is typically unimpaired. The majority of problems encountered relate to creating surge capacity for the sudden increase in volume and acuity of arriving patients, or for those with illnesses not usually treated at that facility (eg, burns, radiation exposure, and severe acute respiratory syndrome).

Hospitals frequently experience difficulty in effectively using and interfacing with community resources. Field triage should allocate patients rationally, and transfer agreements must be in place to facilitate interhospital movement of patients and evacuation of patients to alternate care sites.

Media access must be controlled. During the Loma Prieta earthquake in 1989, a news helicopter occupied a nearby community hospital's only landing zone, preventing the possibility of landing a medical helicopter.

Redundant communication systems must be in place. Typical backup systems to the telephone are radios and cellular phones, but the frequencies can be overloaded in both systems. Use of cellular phones for text communication may offer another solution. Two-way radios are reliable and should be part of the communications network. Satellite phones are also an option.

Catastrophic Disasters

In a large-scale disaster, paramedics may be unavailable to assist in patient transfers or hospital evacuations. DMATs and urban search and rescue teams will deploy, but their time to arrival on scene may be variable. Each individual hospital may need to remain self-sufficient for 48 to 72 hours or longer.[12] Generator problems are frequent; they either fail altogether (as they did during the Loma Prieta earthquake) or supply insufficient power to meet emergency needs (as during the Northridge earthquake). Evacuation plans must not require elevators for this reason. Telephone service will cease as lines are disrupted or deliberately restricted by the phone company. Cellular phones may function within a local area, but failure is likely if more distant sites within the city are dialed. Hospital radios designated for disaster use should have the hardware secured to prevent earthquake damage.

Under catastrophic conditions, mobilization of personnel is more difficult. Because telephone communication is unreliable, at least one additional system to contact personnel at home should be in place. An alternative is to institute an automatic response system, in which personnel report to the hospital or another location when communications are impaired.

After earthquakes or explosions, immediate access to structural engineers is important. In the Northridge earthquake, eight hospitals in the Los Angeles area sustained enough damage to force evacuation of at least one patient. Four institutions completely evacuated their facilities in the first 24 hours, including two hospitals that met the most current structural earthquake standards. Further structural damage was subsequently identified, and two additional hospitals were forced to evacuate completely in the next 2 weeks. Ultimately, four of these hospitals were permanently closed and demolished.

Hospitals are also vulnerable to hurricanes. In a study of hurricane Rita's (2005) impact on regional hospitals in Texas and Louisiana, seven hospitals were forced to evacuate patients.[12] Significant problems included prolonged loss of power, potable water, and staff. It was also difficult to obtain vehicles for transportation of patients to other facilities. Nonmedical vehicles were sometimes used to evacuate stable patients.

Catastrophic earthquakes can cause extensive casualties, including large numbers of patients with crush syndrome and lacerations. Up to 90% of victims with serious but survivable injuries are rescued by local responders and volunteer citizens in the first 24 to 48 hours. Therefore, special medical teams, such as DMATs and urban search and rescue teams, may not significantly affect survival from acute injuries if they arrive after more than 48 to 72 hours. The traditional view holds that deploying field hospitals to distant disaster zones does not improve outcomes. The results reported by the Israeli Field Hospital after deployment to the Haitian Earthquake may change this.[17] If hospitals are not functional and no backup plan exists, immediate advanced medical care will not be available, and many people will die. Therefore, planners should include a backup system to provide medical care at alternate nonhospital care sites.

Need for Local Response

Currently, it is not possible for outside assistance to arrive in force during the crucial first 48 hours after the event. Therefore, an alternative source of rapidly available, sophisticated medical care is necessary. It appears this is best provided by local responders who can begin caring for patients soon after the event. The Medical Disaster Response Project is the most advanced model of a local medical response to such a disaster. Developed by emergency clinicians in southern California, the Medical Disaster Response Project has two components: (1) training of health care providers in the management of disaster victims under austere conditions and (2) placement of sophisticated medical supplies at designated sites within the community. Under this plan, victims could receive rapid, advanced medical care from surviving volunteer health care providers even if hospitals were destroyed. The current Strategic National Stockpile is modeled after components of this plan. In addition, it was used as a major source document for the development of the Medical Reserve Corps.

Toxic Disasters (Hazardous Material)

Hospitals in the vicinity of major chemical industries, transportation corridors, or probable terrorist targets (eg, major theme parks or nationally symbolic buildings) should be aware of potential hazards from incidents involving chemical and radioactive substances. Such facilities should be prepared to decontaminate large numbers of individuals exposed to these hazardous substances. Effective decontamination of victims and the need for safety measures on the part of rescue personnel to prevent secondary contamination are critical. Decontamination equipment should be stored near the ED and the staff trained in its use. This location should be known to personnel. When such an emergency occurs, there is little time to search the hospital for the necessary supplies.

Ideally, patients contaminated with hazardous chemicals should first be brought to a designated decontamination area containing a warm-water shower with a container to hold drainage water. Victims should remove all clothing. Clothing and valuables are bagged, identified, and stored. Contaminated patients should never be brought into regular patient care areas due to the danger of contaminating other patients, hospital staff, and equipment. In 1994, paramedics unsuspectingly transported a patient contaminated with a degradation product of dimethyl sulfoxide to an ED in Riverside, California. Before the presence of the hazardous material was detected, six health care workers were exposed, including an emergency clinician. The emergency clinician experienced a near-fatal exposure and required intubation and an extensive stay in the hospital's intensive care unit. Uncontrolled spread of the toxin resulted in evacuation and temporary closure of the ED.

Closing off air intake vents by hospital personnel is appropriate for rooms containing contaminated patients so that toxic products do not enter the ventilation system and circulate to other areas of the hospital. Rescue personnel and hospital staff should be

protected by gowns, gloves, and masks and, if necessary, supplied air respirators. The goals are to reduce the initial level of external contamination, to contain the contamination that remains, and to prevent further spread of these potentially dangerous substances to other patients and staff members (secondary contamination).

CHEMICAL, BIOLOGIC, RADIOLOGIC, NUCLEAR, AND EXPLOSIVE TERRORISM

In addition to the familiar threat from hazardous materials, there is another challenge: a potential attack by terrorists using biologic, radiologic, or chemical weapons (see Chapter 193). Although somewhat similar to hazardous materials situations, management of patients exposed to weapons of mass destruction (WMD) requires additional knowledge and skills. Expertise in the management of patients attacked with unconventional weapons is important, but emergency clinicians should also be familiar with treatment of blast injuries. High-explosive events, including suicide bombers, remain the most probable type of terrorism.

The most likely radiation source used by terrorists will probably not come from the detonation of a nuclear weapon. Instead, simple radiologic devices, such as those used by hospitals for radiation therapy, are believed to be the source of choice. They do not explode and give no warning of their presence. Terrorists can also dismantle such devices and incorporate the radioactive source into an explosive radiologic dispersion device ("dirty bomb"). Therefore, providers should recognize the presentation of patients suffering from radiation exposure to make the diagnosis. In addition to damage from radiation, these casualties may also suffer blast injuries. Initial treatment of such victims, if they are critically injured, should address stabilization of the blast injuries first before the radiation exposure is considered. Patients who are irradiated but not externally or internally contaminated pose no threat to ED personnel.

One of the greatest challenges with respect to WMD is the detection of biologic weapons. Patients exposed to biologic agents often initially present with vague symptoms associated with influenza-like illnesses. Decontamination is not a priority unless the exposure is immediate; standard precautions are generally sufficient.

Unlike radiologic or biologic weapons, chemical agents produce symptoms quickly. The challenge is decontamination and treatment. Approximately 80% of mass casualty decontaminations are performed at hospitals. Therefore, hospitals should be prepared to decontaminate patients outside the ED. Personal protective equipment is also essential for responders and hospital "first receivers" due to the risk of exposure during the decontamination process.

DISASTER STRESS MANAGEMENT

Emergency health care providers experience high levels of stress when responding to the needs of disaster victims. If this excessive stress exceeds the capacity of normal coping mechanisms, it can potentially interfere with job performance and produce symptoms, including depression, sleep disturbances, increased use of alcohol and drugs, irritability, and anxiety. Post-traumatic stress disorder can result. In an attempt to reduce the psychological impact of these events on medical responders, various therapeutic techniques have been introduced throughout the years and are collectively known as *critical incident stress management.* This formal process of resolving emotional conflict using mental health professionals is now widely practiced.

In general, the longer the delay between exposure to the critical incident and subsequent psychological intervention, the smaller is the chance for a successful outcome. Therefore, the critical incident stress management process is designed for rapid implementation. During the incident, stress management staff or even a colleague can provide on-scene intervention. The goal is to assist the health care worker in regaining emotional control by facilitating communication of feelings and reactions through listening and support.

If a critical incident has profoundly affected participants and if symptoms are still present many hours later, urgent assistance is provided in the form of defusing. The critical incident defusing process is coordinated by mental health and peer support staff and focuses on information and venting of emotions. This process often takes place away from public view to protect confidentiality. If the psychological stress is severe, the process transitions to formal care provided by psychiatrists or psychologists. Data from previous experiences suggest that such intervention can assist providers in maintaining job performance and satisfaction.

In addition to disaster health care providers, the victims themselves can suffer significant psychological trauma. Rapid identification of such individuals is a priority and can be facilitated by use of a recently developed psychological triage algorithm known as PsySTART. The tool itself has been previously validated and, in a recent trial, appears to assist health care workers in rapidly identifying patients who may benefit from acute psychological intervention.[18]

DISASTER MANAGEMENT AND RESPONSE ORGANIZATIONS WITHIN THE UNITED STATES GOVERNMENT

Department of Homeland Security

The Department of Homeland Security (DHS), a cabinet-level department formed after the terrorist attacks of September 11, 2001, is the federal government's lead organization for emergency management activities in the United States. The Federal Emergency Management Agency (FEMA) was incorporated into DHS and retained its name. DHS has a coordinating responsibility for the entire spectrum of disasters irrespective of their size or etiology. DHS assists state and local organizations to mitigate, to prepare for, to respond to, and to recover from emergencies and is a source of funding for these endeavors. In 2003, the President directed that DHS develop a National Incident Management System and a National Response Plan. Existing federal plans, including the National Response Plan, were then incorporated into the National Response Framework. The National Response Framework includes 15 Emergency Support Functions (ESFs). Each has a primary (lead) federal agency and many supporting agencies. ESF #8 is entitled Public Health and Medical Services and is of key importance to the health care community. The primary agency is the Department of Health and Human Services (DHHS). Examples of functions within ESF #8 include coordination of health care personnel, supplies, pharmaceuticals, surveillance and reporting, and mass fatality management.

Urban Search and Rescue (ESF #9 of the National Response Framework)

When a building collapses because of an earthquake, terrorist bombing, structural failure, or other reason, various challenges confront rescue and medical personnel. Some victims require field amputations to facilitate extrication, and use of urban search and rescue teams and effective emergency medical care may improve the outcomes of such lifesaving efforts. The role of urban search and rescue teams has recently been questioned and the cost effectiveness of their interventions remains unclear.[19] This national system of multidisciplinary task forces is designed for rapid deployment to the sites of collapsed structures. The medical team's responsibilities include caring for task force members,

victims recovered by search and rescue activities, and the search team's dogs. There are also WMD urban search and rescue teams trained by FEMA to respond to nuclear, biologic, and chemical terrorist attacks.

Department of Health and Human Services

On December 19, 2006, the President signed the Pandemic and All-Hazards Preparedness Act (S. 3678) into law and created a new position, the Assistant Secretary for Preparedness and Response (ASPR), within DHHS. The office of the ASPR oversees the department's responsibilities for emergency preparedness and response activities, including the National Disaster Medical System (NDMS) and the Hospital Preparedness Cooperative Agreement Program, the coordination of the Medical Reserve Corps, ESAR-VHP, the Strategic National Stockpile, and the Cities Readiness Initiative.

National Disaster Medical System

NDMS is a federally coordinated initiative designed to augment the emergency medical response capability of the United States in the event of a catastrophic disaster. This system is a cooperative program of four departments in the federal government: the Department of Defense (DoD), DHHS, DHS, and the Department of Veterans Affairs (VA). Although oversight of NDMS has moved between federal departments, DHHS currently has the lead for this program. NDMS provides an interstate medical mutual aid system linking the federal government, state and local agencies, and private sector institutions to address the medical needs of victims of catastrophic disasters. The three distinct NDMS elements focus on field medical response, patient transport, and definitive care. Its field medical response element includes dozens of volunteer civilian DMATs that supplement the local medical infrastructure, as well as disaster mortuary operational response teams (DMORTs), veterinary medical assistance teams (VMATs), and various specialty teams (eg, surgical teams).

In a disaster, NDMS is activated when state resources are overwhelmed and the governor makes a request for federal assistance. The DMATs and other teams must meet specific NDMS standards. Throughout the NDMS, emergency clinicians are taking key roles in defining training standards, the deployment of clinical services, and the administration of field operations and in developing the concept of a civilian-federal disaster response capacity during national emergencies. DoD manages patient transfers and provides patient transport from an impacted area to a designated definitive care site. The VA and DoD's Federal Coordinating Centers (FCCs) manage the provision of definitive care by directing patients requiring treatment to health care facilities that have Memoranda of Understanding with NDMS.

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC), based in Atlanta, is a United States federal agency under DHHS. Its major responsibilities include preparing for and responding to public health emergencies (eg, disasters) and conducting investigations into the health effects and medical consequences of these events. The major aims of CDC researchers are to assess the risks of death and injury and to develop strategies to prevent or to mitigate the impact of future disasters. Other responsibilities of CDC staff in the area of emergency preparedness and response include rapid assessment of the health and medical needs of disaster victims in the immediate postdisaster period; development and maintenance of national systems for acute environmental hazard surveillance; and provision of epidemiologic, sanitary, laboratory, and other relevant scientific support services to agencies involved in disaster planning and response. CDC played a major role in helping United States hospitals to prepare for identification and management of Ebola patients, including PPE training, during the 2014 outbreak.

Department of Veterans Affairs

VA has not traditionally been regarded as a disaster response entity. However, one of VA's four legally mandated missions is emergency management. A unique feature of VA is that its facilities and personnel are situated nationwide, and these are used to support federal health and medical assistance to state and local governments during disasters. VA has highly trained specialty personnel who can support disaster medical activities. In addition to the vast pool of human resources, VA provides large amounts of the pharmaceuticals and expendable supplies for on-site disaster support. VA support is coordinated through DHS and DHHS, as the lead federal agency for health and medical response. In addition to VA's role in the federal response to disasters, as the largest integrated health care system in the nation, it has a well-developed hospital emergency management program. Professional emergency managers are located at VA medical centers throughout the country. They also manage the majority of NDMS FCCs. The VA develops a number of emergency management planning and operations tools. Many of these are open source and available to the public.[20]

Department of Defense

On April 17, 2002, Secretary of Defense Donald Rumsfeld announced the formation of the Northern Command, or NorthCom, to assume responsibility over all military forces that operate within the United States in response to external threats and in support of civil authorities. The stated purpose of NorthCom is to assist the DoD to better manage natural disasters, attacks on American soil, or other civil difficulties. It provides for a more coordinated military support to civil authorities, such as the Federal Bureau of Investigation (FBI), FEMA, and state and local governments. Another important asset at the state level is the National Guard. Each governor has authority to activate the National Guard for its disaster response and recovery missions. National Guard assets also include WMD civil support teams (CSTs). CSTs provide significant capabilities to advise civilian authorities and assist local and state agencies that may be overwhelmed by a large-scale terrorist attack or where specific technical capabilities to identify WMD materials are required. CSTs are federally funded National Guard units established under Presidential Decision Directive 39.

FUTURE DIRECTIONS

The field of disaster medicine has become a major subspecialty within emergency medicine, and standing committees and membership sections for disaster medicine are now organized within the ACEP and the Society for Academic Emergency Medicine. There are also numerous national and international forums for the presentation of disaster medical research results. Since the ACEP first defined a disaster medicine curriculum suitable for residencies and fellowships, a number of disaster medicine fellowships and advanced degree programs have been established in the United States and elsewhere.[21] Standardized all-hazard disaster core competencies and associated curricula are being developed and promulgated.[2] Disaster medicine textbooks and journals are increasing. In the 21st century, disaster medicine will continue to develop as a professional activity and unique academic specialty. Increasing and enhancing disaster medicine research activity will be crucial to sustaining this trend. Finding sustainable funding sources remains one the most significant challenges.

KEY CONCEPTS

- Comprehensive emergency management consists of four phases: mitigation, preparedness, response, and recovery.
- Mass casualty planning should account for the fact that traditional transport and communications systems will break down.
- Field personnel should be specifically trained in mass casualty triage and stabilization because austere field conditions change management strategies.
- All plans must protect caregivers and rescue personnel.
- Critical incident stress management may be highly desirable after an event and should be planned for in advance. Psychological triage tools, such as PsySTART, may help.
- Planners should establish and exercise a hospital-based incident management system.
- Disaster planning needs to include policies to address the needs of vulnerable populations, such as children, disabled, and the elderly.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 192: QUESTIONS & ANSWERS

192.1. Which of the following statements is true regarding applications of Secondary Assessment of Victim Endpoint (SAVE) triage guidelines?

A. It is applicable to day-to-day hospital operations.
B. Outcome expectations are theoretically based.
C. Patients are sorted into one of four categories.
D. The system provides detailed management of psychogenic cases.
E. Triage decisions are based on field outcome expectations.

Answer: E. The SAVE system is designed specifically for care in an austere environment. It triages patients into (1) those who will die regardless of treatment, (2) those who will live regardless of treatment, and (3) those who would benefit from austere intervention. The triage decisions are based on field outcome expectations from existing survival and morbidity statistics.

192.2. Which of the following best describes the National Disaster Medical System (NDMS)?

A. It does not include private sector institutions.
B. It does not involve the Department of Veterans Affairs (VA).
C. It is military based.
D. The Department of Health and Human Services (DHHS) has oversight.
E. The medical response element consists of Department of Defense (DoD) personnel.

Answer: D. The NDMS is a federally coordinated initiative that is a cooperative program between the DoD, VA, DHHS, and Department of Homeland Security (DHS) with oversight provided by DHHS. The NDMS provides a system of coordinated mutual aid agreements among federal, state, local, and private institutional entities for resource and personnel provision in times of disaster. The medical response element includes dozens of volunteer civilian medical teams that supplement the local medical infrastructure.

192.3. Which of the following statements is true regarding disaster response?

A. Critical incident stress debriefing is best conducted 1 or 2 weeks after the event.
B. Medical resupply systems are the most vulnerable component of a disaster plan.
C. One of the Department of Veterans Affairs (VA) system's four legally mandated missions is emergency management.
D. The Federal Emergency Management Agency (FEMA) has a coordinating responsibility for the entire spectrum of disasters.
E. The Joint Commission mandates deal only with disasters within the hospital.

Answer: C. One of the VA health system's four mandated missions is emergency management. Although controversy exists, critical incident stress debriefing, if used, should be implemented as early as possible. The Department of Homeland Security (DHS) has full-spectrum disaster coordinating responsibility. Communications systems are likely the most vulnerable systems. The Joint Commission mandates deal with plans and preparations for disasters within the entire community as well as within the hospital.

192.4. Which of the following statements is *not* a feature of emergency management?

A. During simple triage and rapid treatment (START) triage, two interventions may be performed: opening an airway and controlling external hemorrhage.
B. Health care facilities should perform a hazard vulnerability analysis to assess community risks.

C. PICE is a conceptual framework to describe disasters and stands for "potential injury-creating event."
D. The four phases of comprehensive emergency management (CEM) are pre-event, event, post-event, and baseline.
E. Worldwide morbidity and mortality from disasters is increasing, in part due to increases in population density.

Answer: D. The four phases of CEM are mitigation, preparedness, response, and recovery. These phases represent a continuum over time, and more than one phase may be in effect at the same time (eg, even during the response phases, recovery actions may take place.)

CHAPTER 193

Weapons of Mass Destruction

Carl H. Schultz | Kristi L. Koenig

PRINCIPLES

Besides managing the injuries and illnesses from common disasters such as earthquakes and airplane crashes, emergency clinicians should also have competence in treating victims generated by terrorist attacks with nuclear, biologic, chemical, or high-energy explosive weapons. Conventional explosives remain the most common weapon used by terrorists; however, the risk from nuclear, biologic, and chemical agents may increase over time. The nomenclature for these weapons is not standardized. The military uses the acronym CBRNE, pronounced "see-burn-ee," referring to *c*hemical, *b*iologic, *r*adiologic, *n*uclear, and *e*xplosive agents. This chapter uses *weapons of mass destruction (WMD)* because of its wide acceptance and familiarity.

The results of an attack with WMD, although admittedly of low probability, are potentially catastrophic. According to a World Health Organization (WHO) estimate, 50 kg of anthrax spores aerosolized above a city of 5 million people would result in 100,000 deaths, with an additional 150,000 people seriously infected. The cost of managing 100,000 cases of anthrax exposure is estimated at between $6.4 and $26.2 billion. These types of estimates have led to authorities establishing emergency preparedness as a priority.

Children are particularly vulnerable to these weapons.[1] They breathe at a faster rate than adults do, increasing their relative exposure to aerosolized agents.[2] Some chemicals, such as sarin, are heavier than air, so they tend to accumulate at the level where children are more likely to inhale them. Children have a greater surface area–to–volume ratio and their skin is thinner. This makes them more susceptible to agents that act on or through the skin. They have smaller fluid reserves and higher metabolic rates. Therefore, they are more vulnerable to dehydration from vomiting and diarrhea and suffer increased toxicity from a given exposure, such as to radioactive iodine (^{131}I).

The use of biologic and chemical agents dates to biblical times, although the threat from radiation and nuclear detonation is relatively new.[3] Assyrians poisoned the wells of their enemies with rye ergot in the 6th century BC. The Mongols catapulted bodies infected with bubonic plague over the walls of Kaffa in the 14th century. The British Army gave American Indians blankets taken from individuals infected with smallpox during Pontiac's Rebellion in 1763. During World War I, the Germans effectively used chlorine and mustard agent against the advancing Allied armies. The Japanese killed hundreds to thousands of Chinese citizens with bubonic plague during World War II by spraying towns with fleas infected with *Yersinia pestis*. Saddam Hussein used a mustard agent against the Iranians during the Iran-Iraq War in the 1980s. Most recently, the Syrian government attacked cities within its own country using chemical nerve agents.

The use of WMD has been predominantly by the military during times of conflict. Toward the end of the twentieth century, however, the use of these agents has taken an ominous turn. Nonaffiliated groups have begun using WMD directed at civilians to achieve political ends. The Bhagwan cult sprayed salad bars in Oregon with *Salmonella* in an attempt to influence an election in 1984. The Aum Shinrikyo used the nerve agent sarin in an unsuccessful 1994 assassination attempt on three judges in Matsumoto, Japan. This same group used sarin again in the 1995 Tokyo subway attack that killed 11 people.[4] The United States experienced multiple anthrax hoaxes during 1997 and 1998, motivated by personal or political agendas. Terrorists initiated an actual anthrax attack using the United States mail in 2001 that resulted in 11 deaths.[5] No one has yet used radiologic or nuclear devices in a successful mass terrorist attack, but at least one attempt has occurred. In addition, several highly radioactive sources have been stolen from American medical facilities, and a Russian dissident, Alexander Litvinenko, was assassinated with a radiologic agent (polonium-210) in 2006.

Many agents are potential candidates for weaponization, and some represent a substantial risk (Box 193.1). Management strategies for patients exposed to WMD are frequently similar to strategies for hazardous materials exposure. However, several features associated with WMD make these events unique (Box 193.2). Additional knowledge and skills are required in the evaluation and treatment of WMD victims. These plans represent only one small part of an overall comprehensive emergency management strategy for all hazards (see Chapter 192). Names of departments, bureaus, and agencies that can assist with planning and response to WMD events are listed in Table 193.1.

SPECIFIC DISORDERS

NUCLEAR AND RADIOLOGIC DEVICES

Principles

Terrorists selecting radiation as a means to inflict casualties are unlikely to use nuclear weapons. These devices are heavily guarded, difficult to move because of their size and weight, and easy to detect. Although Russia acknowledges that 50 to 100 of its 1-kiloton "suitcase" nuclear weapons are missing, the problems of purchasing, moving, and detonating these devices are formidable. Sabotage at nuclear power stations is possible, but given tight security, multiple safety systems, and thick concrete housings surrounding the reactors, the threat is probably low.

Instead, simple radiologic devices, such as those used by hospitals for radiation therapy, are thought to be the source of choice. These sources are plentiful. They do not detonate on their own and give no warning of their presence unless they are dispersed by a conventional explosive (radiologic dispersal device). Thefts of radiotherapy sources have occurred in the United States. Accidental dispersion from a stolen hospital therapy source in Brazil resulted in the screening of 112,000 people for contamination. A total of 249 people were found to be exposed—four of whom ultimately died. Placement of such a device at an information kiosk in a crowded mall during a busy holiday shopping season would silently expose countless persons to significant radiation.

TABLE 193.1

Resources and Contacts for Planning and Response to Events Involving Weapons of Mass Destruction

ORGANIZATION	WEBSITE	TELEPHONE
Radiation Emergency Assistance Center/Training Site (REAC/TS)	orise.orau.gov/reacts/	Daytime: 865-576-3131 Emergency: 865-576-1005
State and local health departments Association of State and Territorial Health Officials (ASTHO) Public Health Resources: State or Territorial Health Departments	 www.astho.org/statepublichealth/ www.cdc.gov/mmwr/international/relres.html	
Centers for Disease Control and Prevention (CDC)	www.cdc.gov	800-CDC-INFO
Federal Bureau of Investigation (FBI)	www.fbi.gov	
Federal Emergency Management Agency (FEMA)	www.fema.gov	800-621-FEMA
U.S. Army Medical Research Institute of Chemical Defense	https://usamricd.apgea.army.mil/	

BOX 193.1

Potential Agents of High Concern for Use as Weapons of Mass Destruction

CHEMICAL
Nerve agents
- Sarin
- Soman
- Tabun
- VX

Mustard agent

BIOLOGIC
Anthrax
Plague
Smallpox
Botulism
Viral hemorrhagic fever
Tularemia

RADIOLOGIC
Simple device
Dispersal device

BOX 193.2

Features of Weapons of Mass Destruction Threat

Fear of unknown or unfamiliar
Lack of training for hospital personnel
Lack of equipment, including personal protective equipment (PPE) and diagnostic aids
Potential for mass casualties
Psychological casualties
Crime scene requiring evidence collection and interaction with law enforcement
Potential for ongoing morbidity and mortality (dynamic situation)

Clinical Features

Ionizing radiation, regardless of its type, causes injury at the cellular level, usually by damaging DNA. Rapidly dividing cells are the most sensitive. Patients have symptoms within hours to days, depending on the dose. Common syndromes associated with radiation exposure include dermal burns, bone marrow failure, and gastrointestinal dysfunction (eg, vomiting and gastrointestinal bleeding) (see Chapter 138). Reviews of medical treatment for radiologic casualties can be found elsewhere.[4]

Management

A basic emergency department (ED) radiation protocol should address decontamination, triage, staff safety, personal protective equipment (PPE), and diagnostic procedures that emphasize radiation monitoring. Victims presenting to the ED will suffer from three types of exposure: irradiation, internal contamination, and external contamination. Irradiated victims have been exposed to a beam of radiation, similar to someone undergoing a chest x-ray examination. They are not radioactive and pose no threat to ED personnel.

Contaminated patients are more challenging, and early involvement of the radiation safety officer is critical. This individual evaluates the degree of the victim's contamination and monitors radioactivity levels throughout the decontamination process. Internally contaminated patients present a therapeutic challenge because they have radioactive material inside their bodies (eg, lungs and gastrointestinal tract) or incorporated into their cells. They should be placed in an isolation room where all secretions and body fluids can be collected. Various medications are available for administration to internally contaminated patients and can limit uptake or facilitate removal of certain radioactive elements. These medications include Prussian blue (Radiogardase) for cesium and thallium ingestions and diethylenetriaminepentaacetic acid (DTPA) for plutonium exposure. Health care providers can receive assistance by calling the Radiation Emergency Assistance Center/Training Site (REAC/TS; http://orise.orau.gov/reacts/) at 865-576-3131 (emergency number: 865-576-1005).

Externally contaminated victims have radioactive material on their skin or clothing and are decontaminated by removal of clothing and washing with soap and water. Washing by protected personnel should continue until monitoring by the radiation safety officer demonstrates the absence of radioactivity. If wounds are present, they are decontaminated first. After the wounds are covered with a sterile, waterproof dressing, the remaining skin is washed. Hospitals should be prepared to decontaminate patients because historical data suggest that up to 80% of patients do not receive this intervention before arrival. Decontamination before hospital entry is crucial because these individuals can expose caregivers to radiation and contaminate the entire hospital through the ventilation system. Removal of clothing and covering

of the head with a surgical cap can reduce contamination by 80% to permit stabilization in the decontamination unit, but complete decontamination should occur before exposure of unprotected staff if the patient's medical condition permits.

Initial triage of radiation casualties is based on their overall pathologic condition, not on exposure.[4] Even patients who have received a lethal dose of radiation do not die immediately as a consequence of the ionizing exposure. Therefore, a patient in acute distress from a myocardial infarction or urosepsis would be triaged ahead of a radiation victim with stable vital signs, regardless of the dose received. If a radiation casualty also suffers a severe injury or illness, immediate intervention is required. Most of the immediate morbidity and mortality associated with a radiologic dispersion device is related to traumatic injuries from the explosion and not to radiation exposure.

In addition to contaminated patients, the radiation safety officer is responsible for monitoring of the exposure of hospital staff. All personnel involved in the care of contaminated patients should wear dosimeters, which measure the amount of radiation received by the wearer. The safety officer tracks the amount of radiation received by each staff member and can remove a health care worker from the area if the exposure is too high. Radiation monitoring is complex, and the radiation safety officer should be involved as early as possible. Hospitals should consider conducting disaster drills that include casualties suffering radiation injuries.

Although many radioactive elements are candidates for use in a terrorist attack, ^{131}I and related isotopes deserve additional discussion because of heightened interest. ^{131}I is found only after a nuclear detonation or in reactor fuel rods. Although it is not impossible, the probability that terrorists could tap either of these sources is very small. The use of ^{131}I in a radiologic dispersal device is unlikely because of its short half-life (8 days). Even if such a device could be made, it is extremely unlikely that the radiologic dispersal device could disperse sufficient radioactive material to pose an acute health hazard. Given these facts, the probability that any significant exposure of the population (especially children) to ^{131}I will occur is equally small. The large number of childhood thyroid cancers that occurred after the accident at the Chernobyl nuclear power plant resulted, to a significant degree, from situations that will not occur in the United States. These include delayed reporting of a breach in the reactor containment vessel preventing timely evacuation of all exposed populations, failure to effectively quarantine contaminated milk and vegetables, and significant iodine deficiency in the exposed population. The risk to children in communities surrounding the Fukushima nuclear power plant is also an issue that will require long-term monitoring. Nonetheless, concern about treatment to prevent thyroid cancer after potential exposure to ^{131}I remains. Current recommendations for treatment with potassium iodide, which blocks uptake of ^{131}I by the thyroid, are listed in Table 193.2. Caveats for use of this table include increasing the amount of potassium iodide for adolescents approaching 70 kg to the adult dose (130 mg) and monitoring thyroid-stimulating hormone and free thyroxine (T_4) levels in neonates when possible. Non-pregnant adults older than 40 years old are unlikely to benefit from this intervention.

TABLE 193.2

Treatment With Potassium Iodide for Radioactive Iodine Exposure

SUBPOPULATION	PREDICTED EXPOSURE (cGy)	POTASSIUM IODIDE DOSE (mg)	NUMBER OF 130-mg TABLETS
Adults >40 years old	>500	130	1
Adults 18 to 40 years old	≥10	130	1
Pregnant and lactating women	≥5	130	1
Children 3 to 18 years old	≥5	65	½
Children 1 month to 3 years old	≥5	32	¼
Neonates, birth to 1 month old	≥5	16	⅛

BOX 193.3

Signs Suggesting Biologic Weapon Deployment

SYNDROMES
Pulmonary symptoms, pneumonia
Rashes
Sepsis syndrome
Influenza symptoms

EPIDEMIOLOGY
Multiple, simultaneous events
Dead animals
Large numbers of patients with high toxicity and death rate

BIOLOGIC WEAPONS

Principles

By convention, biologic weapons are divided into three groups: bacteria, viruses, and toxins. A characteristic shared by these agents is their ability to be dispersed as an aerosol. Because this is the most effective means to expose a large population, aerosol dispersal is the route that terrorists would most likely use to deploy such weapons. Victims, unaware of the exposure to a biologic weapon, present to the ED with nonspecific influenza-like respiratory signs and symptoms. Dermal contact and ingestion are also potential pathways for exposure, and some agents are effective by these routes. People infected in the 2001 United States anthrax attack were inoculated through aerosol and dermal exposures.[5] However, it is logistically more difficult to produce large casualty numbers by nonrespiratory portals of entry, so agents spread primarily by injection or through the gastrointestinal tract are less likely candidates for wide deployment. If the goal is to disrupt the economy or to spread fear among the population, then almost any type of release will suffice, whether or not people actually die.

Clinical Features

Patients exposed to biologic agents usually present with vague symptoms associated with an influenza-like illnesses.[7,8] Unless a biologic attack is announced or suspected, the ED staff may not realize that they are treating victims. It is not always possible to distinguish natural occurrences from engineered outbreaks of diseases. Examples of non-terrorist related occurrences of anthrax include cutaneous disease in intravenous heroin users in Europe, an outbreak of cutaneous anthrax in Bangladesh in 2010 with more than 400 cases, and isolated infections in drum makers after using contaminated animal hides. Because of the challenges in identifying the true etiology of acute events, personnel should be vigilant and at least consider the possibility, especially when warning signs are present (Box 193.3). For example, large numbers

of patients suddenly presenting with "the flu" not during influenza season should cause concern. For these reasons, health surveillance will be paramount in identifying agents and potential sources. The ED should have a working relationship with local and state health departments as well as with local law enforcement and stay apprised of Centers for Disease Control and Prevention (CDC) and Department of Homeland Security guidelines.

Management

Several infectious agents with potential for use as biologic weapons can spread in a hospital environment. Examples include Ebola and smallpox. Hospitals need protocols for PPE and patient isolation to ensure a safe environment. Fortunately, such protocols are similar to those applied to other infectious diseases (Box 193.4) in non-terrorist events (eg, the 2014 Ebola outbreak). For example, implementation of such precautions is credited with halting of the in-hospital spread of the Ebola virus in the 1995 Zaire outbreak. Decontamination is not a priority unless the exposure is acute. Standard precautions are usually sufficient, and special suits (eg, levels A and B) are generally unnecessary.

Whereas the CDC lists six Category A (high threat) agents (anthrax *[Bacillus anthracis]*, botulism [*Clostridium botulinum* toxin], plague *[Yersina pestis]*, smallpox [variola major], tularemia *[Francisella tularensis]*, and viral hemorrhagic fevers [filoviruses (eg, Ebola, Marbug)] and arenaviruses [eg, Lassa, Machupo]), this chapter focuses on three biologic agents—anthrax, plague, and smallpox—that represent the greatest interest.[7,8]

Anthrax

Principles

Bacillus anthracis, a gram-positive spore-forming bacterium, is the causative agent of anthrax ("woolsorter's disease"). The spores are extremely hardy and can survive for years in the environment. The disease is caused by exposure to the spores, not the bacilli in their vegetative state. It is normally a disease of sheep, cattle, and horses and is rarely seen in developed countries because of animal and human vaccination programs. Disease in humans can occur when spores are inhaled, ingested, or inoculated into the skin. The spores germinate into bacilli inside macrophages. The bacteria then produce disease by releasing toxins (eg, protective antigen, edema factor, and lethal factor) that cause edema and cell death.

Russia and the United States have developed anthrax into a biologic weapon. The effectiveness of this agent was clearly demonstrated by two events: an accidental release of spores from a biologic weapons facility in the former Soviet Union town of Sverdlovsk in 1979 and the intentional distribution of anthrax spores through the mail along the eastern seaboard of the United States in 2001.[5] After the Sverdlovsk release, at least 66 people died downwind from the compound during the next several weeks, and animal cases of anthrax were reported 30 miles away. The ability of non–state-sponsored terrorist groups to develop anthrax as a weapon is uncertain. The Japanese organization Aum Shinrikyo made several attempts to disperse anthrax throughout Tokyo without success. The individual believed responsible for the United States anthrax attack was not a foreign national. This is consistent with the fact that the strain of anthrax used in the attack (Ames strain) was developed by the United States government.

Inhalational anthrax is the most lethal form of the disease and is caused by inhalation of spores into the lungs. The mortality rate was thought to exceed 90%. However, data from the 2001 anthrax exposure call this figure into question (5 deaths in 11 cases). Although the actual mortality rate is unknown, and would depend on availability of intensive care resources, it is probably in the 50% range. The minimum number of spores required to produce disease is unknown. The original number quoted in the literature—1000 spores—appears high given the experience following the 2001 anthrax event.

Clinical Features

After phagocytosis by macrophages, the spores germinate and are transported to the tracheobronchial lymph nodes, where the bacteria multiply. During the next 2 to 10 days, patients have an influenza-like illness, with malaise, fever, and nonproductive cough. This initial phase can be delayed for more than 1 month in some patients. Within 24 to 48 hours, abrupt deterioration occurs, with overwhelming sepsis, shock, hemorrhagic mediastinitis, dyspnea, and stridor. A chest radiograph obtained at this time may show a widened mediastinum and hilar adenopathy, but typical radiographic findings are not dramatic and could be missed (Fig. 193.1). Computed tomography (CT) scanning of the

BOX 193.4

Recommendations for Prevention of In-Hospital Transmission of Contagious Agents

Isolate patient in single room with adjoining anteroom.
Have handwashing facilities and personal protective equipment (PPE) available in anteroom.
Use negative air pressure if possible.
Use strict barrier precautions: PPE, gowns, gloves, high-efficiency particulate air (HEPA) filter respirators, shoe covers, protective eyewear.
Alert hospital departments that generate aerosols: Laboratory (centrifuges), pathology (autopsies).

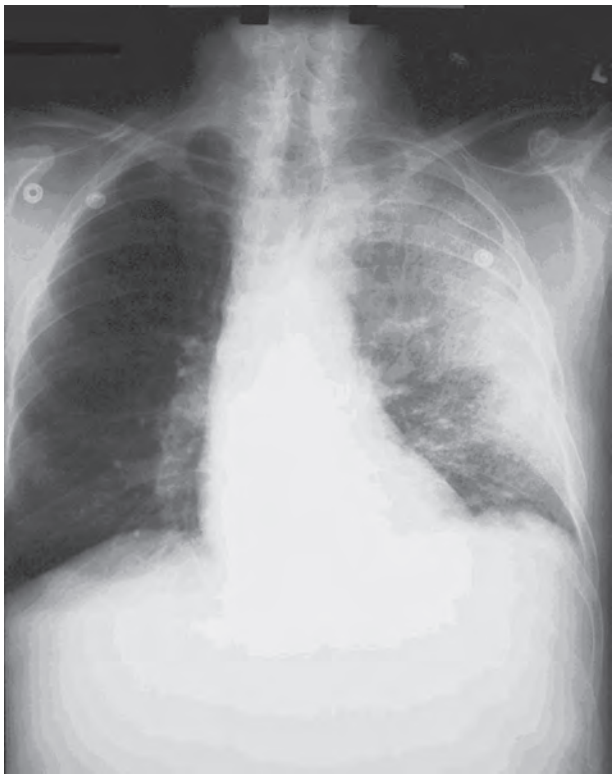

Fig. 193.1. Chest radiograph of anthrax patient showing diffuse left lung consolidation consistent with pneumonia. There is no mediastinal widening. (Courtesy Centers for Disease Control and Prevention [CDC].)

Fig. 193.2. Chest computed tomography (CT) scan of an anthrax patient showing pulmonary consolidation and effusions. (Courtesy Centers for Disease Control and Prevention [CDC].)

Fig. 193.3. Adult with cutaneous anthrax. (Courtesy Centers for Disease Control and Prevention [CDC].)

chest is more sensitive and should be performed if the disease is suspected. Bloody pleural effusions can also occur, and examination of the lung fields frequently reveals consolidation. This can easily be confused with pneumonia (Fig. 193.2). Death usually results within 3 days, and 50% of patients have hemorrhagic meningitis. Human-to-human transmission has not been reported with inhalational anthrax.

Initial diagnosis is generally made clinically on the basis of an influenza-like or septic illness; a suspicious chest radiograph or CT scan demonstrating hilar adenopathy, infiltrates, or pleural effusions; and a reason to consider anthrax in the first place (eg, current outbreak or warning from authorities). Several clinical algorithms exist that attempt to separate patients with influenza from those with anthrax. As these are based on a handful of anthrax cases, their usefulness remains in doubt. Sputum culture, Gram's stain, and blood cultures are not helpful until late in the course of the disease. Tests to confirm the diagnosis of inhalational anthrax include the polymerase chain reaction for identification of anthrax markers in pleural fluid, serologic detection of immunoglobulin to protective antigen, and immunohistochemical testing of biopsy specimens.

In addition to inhalational anthrax, cutaneous anthrax can occur in any area where large numbers of spores are released, as was the case in the United States in 2001. This form of the disease occurs when spores are introduced into the skin, usually through open wounds or abrasions. The mortality rate is approximately 20% without treatment and 1% with treatment. After an incubation period of 1 to 5 days, a papule develops, progressing to form a large vesicle during the next several days. Severe edema occurs around the lesion and is associated with regional lymphadenitis. The lesions are not tender, and the patient may or may not be febrile (Fig. 193.3). After approximately 1 week, the lesion ruptures, forming a black eschar (thus the name *anthrax,* from the Greek word for "coal"). In the next 2 or 3 weeks, either the eschar sloughs off and the illness is over or the organism disseminates and the patient dies. Antibiotics do not affect the course of local disease but are used to prevent dissemination and death. As with inhalational anthrax, the diagnosis is predominantly clinical. Confirmation is established by culture of the lesion, punch biopsy, or serologic testing. A total of 11 cutaneous anthrax cases occurred in the United States after the 2001 attack.

A few cases of gastrointestinal anthrax and oropharyngeal anthrax are also possible after a terrorist attack. These rare manifestations usually occur with the ingestion of insufficiently cooked, contaminated meat. The mortality rate is approximately 50%. After ingestion, the spores are transported to regional lymphatic tissue, where symptoms develop after a 2- to 5-day incubation period. Patients with oropharyngeal anthrax present with sore throat and neck swelling from cervical and submandibular lymphadenitis. The tonsils are also frequently involved, and symptoms are associated with fever and toxicity. Dysphagia and respiratory distress often follow. Gastrointestinal anthrax begins with nausea, vomiting, and fever associated with mesenteric lymphadenitis. Patients then experience severe abdominal pain, hematemesis, ascites, and bloody diarrhea and may present with an acute abdomen.

Management

Traditional treatment of anthrax infection has been penicillin. However, weapons-grade anthrax is probably resistant to penicillin (although this was not the case with the United States attack). Current treatment recommendations reflect this fact (Box 193.5). These consensus recommendations include fluoroquinolones and tetracycline for all children, regardless of age. Balancing the potential risks of such drugs against the consequences of infection by drug-resistant anthrax strains, the benefits justify the recommendations. Nontoxic victims with cutaneous anthrax can be treated as outpatients with oral ciprofloxacin or doxycycline for 7 to 10 days. Doxycycline is equally effective and may be better tolerated (less diarrheal side effects) than ciprofloxacin. Victims with inhalational, cutaneous, or gastrointestinal disease and toxicity require intravenous therapy with ciprofloxacin or doxycycline plus at least one other antibiotic (eg, linezolid, clindamycin, or an aminoglycoside) that inhibits protein synthesis. If meningitis is present, a third antibiotic is added that can penetrate the central nervous system (meropenem). Patients can be switched to oral antibiotics when toxicity resolves. Other modalities that may be helpful include chest tube drainage of pleural effusions, addition of antibody-based therapies (raxibacumab and anthrax immune globulin), and possibly tracheal intubation and mechanical ventilation.[5] Surprisingly, the latter intervention did not improve

BOX 193.5

Treatment of Anthrax

CUTANEOUS ANTHRAX *WITHOUT* TOXICITY

Adults

Ciprofloxacin, 500 mg PO bid; *or* doxycycline, 100 mg PO bid; *or* amoxicillin, 500 mg PO tid

Children

Ciprofloxacin, 20 to 30 mg/kg/day PO divided bid (maximum 1 g); *or* doxycycline, 4.4 mg/kg/day PO divided bid (maximum 200 mg); *or* amoxicillin, 20 to 40 mg/kg/day PO divided tid (maximum 1500 mg)

All doses are given for 7 to 10 days.

INHALATIONAL, CUTANEOUS, OR GASTROINTESTINAL ANTHRAX *WITH* TOXICITY

For adults and children, consider the antibody-based therapies raxibacumab and anthrax immune globulin in addition to IV antibiotics.

Adults

Ciprofloxacin, 400 mg IV every 12 hours; *or* doxycycline, 100 mg IV every 12 hours; *or* penicillin G, 4 million units IV every 4 hours

For patients without meningitis, add a second drug that inhibits protein synthesis, such as linezolid or clindamycin. For patients with meningitis, add a third drug to this regimen that penetrates the CNS, such as meropenem.

Children

Ciprofloxacin, 20 mg/kg/day IV divided every 12 hours (maximum 800 mg); *or* doxycycline, 4.4 mg/kg/day IV divided every 12 hours (maximum 200 mg); *or* penicillin G, 250,000 to 400,000 units/kg/day IV divided every 4 hours (maximum 24 million units)

For patients without meningitis, add second drug that inhibits protein synthesis, such as linezolid or clindamycin. For patients with meningitis, add a third drug to this regimen that penetrates the CNS, such as meropenem.

All doses are given until toxicity resolves, then switch to oral form. Treat for 60 days or until the patient receives three doses of vaccine.

POSTEXPOSURE PROPHYLAXIS

The same drugs and dosage are prescribed as for cutaneous anthrax without toxicity. Treat for 60 days or until the patient receives three doses of vaccine.

CNS, Central nervous system; *IV,* intravenous; *PO, per os* (by mouth).

mortality. All patients intubated after the United States anthrax attack died.

Treatment is to continue for 60 days or until the patient has received three doses of the anthrax vaccine, given on days 0, 14, and 28. The complete vaccine course requires 18 months. This treatment regimen is also recommended for children and pregnant women. If the anthrax strain proves susceptible, patients can be switched to intravenous penicillin or oral amoxicillin. In vitro studies suggest that ofloxacin or levofloxacin can be substituted for ciprofloxacin.

For postexposure prophylaxis, oral ciprofloxacin (500 mg) or doxycycline (100 mg) twice a day is recommended. Amoxicillin can be substituted if sensitive strains are identified. Antibiotic prophylaxis is to continue for 60 days or until patients have received at least three doses of the vaccine. The vaccine is approved by the U.S. Food and Drug Administration (FDA) for adults but not for children. However, it could become available for use in the pediatric population under the Investigational New Drug process if needed. A review by the Institute of Medicine (IOM) found the vaccine both safe and effective for prophylaxis against inhalational anthrax in adults.

Fig. 193.4. Child with bubonic plague demonstrating axillary bubo. (Courtesy Frederick M. Burkle, Jr., MD, MPH.)

Plague

Principles

Plague has been a human pathogen since antiquity. Many regions of the world, including Asia and India, are currently witnessing the third pandemic of plague, and this affliction is endemic in the western half of the United States. Plague is caused by *Yersinia pestis,* a gram-negative bacillus. It is normally a disease of rodents that is transmitted to humans through the bite of an infected flea or by inhalation. Three forms of the disease exist: pneumonic, bubonic, and septicemic plague. The bacteria do not form spores and die rapidly in the environment. However, they are viable for days in dry sputum, flea feces, and human remains. Dogs are relatively resistant to infection, but cats are highly susceptible and could form a reservoir for maintaining the disease in a human population. Recovery is followed by temporary immunity.

Clinical Features

Primary pneumonic plague results when bacilli are inhaled into the lungs. The mortality rate approaches 100% if it is not treated early. Pneumonic plague will be the most frequently encountered form of the disease because terrorists are likely to use aerosolization as the method of dispersal. After an incubation period of 2 or 3 days, victims have sudden onset of fever, chills, and an influenza-like illness. This is followed within 24 hours by a fulminant pneumonia associated with hemoptysis, systemic toxicity, respiratory failure, circulatory collapse, and death. The pneumonia is classically lobar, but any x-ray pattern is possible, including acute respiratory distress syndrome. Six percent to 10% of victims have plague meningitis. Coagulation abnormalities and hepatocellular injury occur. The coagulopathy is characterized by ecchymoses, disseminated intravascular coagulation, and acral gangrene ("black death"). The gangrene is caused by bacterial production of the coagulase enzyme in areas of the body where the temperature drops below 98.6° F (37° C). This induces blood to clot in fingers, toes, and the nose, with resultant infarction and gangrene. If the victims survive, long-term rehabilitation is required. Pneumonic plague is transmissible human to human.

Bubonic plague occurs when organisms are inoculated into the skin, usually from a flea bite. During the 2- or 3-day incubation period, the bacilli migrate to regional lymph nodes, where they multiply and cause inflammation and necrosis of lymphatic tissue, resulting in large, tender nodes, or buboes. Typically, buboes develop in the groin, axilla, or cervical region and are so painful that the patient will refrain from moving the affected area (Fig. 193.4). Individuals experience fever, chills, and weakness. In approximately 25% of patients, vesicles or ulcerations occur at the

site of the flea bite. The buboes are usually nonfluctuant but rarely can suppurate. Organisms can be aspirated from the nodes for diagnosis, but incision and drainage are not recommended because the lymphadenitis resolves with antibiotic treatment, and practitioners could become infected if they are exposed during the procedure.

During the next week or more, the bacteria disseminate in approximately 50% of patients with bubonic plague. These victims have septicemic plague or secondary pneumonic plague and die if they are untreated. Those with septicemic plague experience endotoxemia, shock, disseminated intravascular coagulation, and coma. If bacteremia does not occur, most victims recover. A small percentage of those infected by fleas have septicemic plague without detectable buboes. Direct human-to-human transmission does not occur with bubonic or septicemic plague. However, both of these conditions can lead to secondary pneumonic plague, which is communicable. Therefore, initial isolation (for the first 48 hours) is recommended for all patients with plague.

Differential Diagnosis

The preliminary diagnosis of plague is clinical. Few diseases other than plague cause fulminant gram-negative pneumonia associated with hemoptysis in previously healthy individuals. Other diseases cause lymphadenopathy and the differential diagnosis for such conditions includes cat-scratch disease, tularemia, and staphylococcal or streptococcal infections. However, the extremely tender nature of the lymphadenopathy and the toxicity of the patient strongly suggest plague. Once the disease is suspected, Gram's stain and culture of sputum, blood, cerebrospinal fluid, or lymph node aspirate are helpful. State health departments or the CDC can test specimens for the presence of the capsular antigen by direct fluorescent antibody staining. Polymerase chain reaction also holds promise. Because all laboratory tests require several days to complete, initial management decisions are based on clinical findings.

BOX 193.6

Treatment of Plague

PARENTERAL THERAPY

Adults
Streptomycin,* 1 g IM bid
Gentamicin, 5 mg/kg once daily IM or IV
Doxycycline, 100 mg IV bid
Ciprofloxacin, 400 mg IV bid
Chloramphenicol, 25 mg/kg IV qid

Children
Streptomycin,* 15 mg/kg IM bid (maximum 2 g/day)
Gentamicin, 2.5 mg/kg IM or IV tid
Doxycycline, 2.2 mg/kg IV bid (maximum 200 mg/day)
Ciprofloxacin, 15 mg/kg IV bid (maximum 800 mg/day)
Chloramphenicol, 25 mg/kg IV qid

Pregnant Women
Same as above but exclude streptomycin and chloramphenicol

ORAL THERAPY

Adults
Doxycycline, 100 mg bid
Ciprofloxacin, 500 mg bid
Chloramphenicol, 25 mg/kg qid

Children
Doxycycline, 2.2 mg/kg bid (maximum 200 mg/day)
Ciprofloxacin, 20 mg/kg bid (maximum 1 g/day)
Chloramphenicol, 25 mg/kg qid

Pregnant Women
Same as above but exclude chloramphenicol

*Although streptomycin is recommended as first-line treatment, it may not be readily available.
IM, Intramuscular; *IV,* intravenous.

Management

Antibiotic treatment is essentially identical for all three types of plague (Box 193.6). The same caveats for the use of fluoroquinolones and tetracycline in children with anthrax apply to plague. In the case of pneumonic and septicemic plague, treatment should be started within 24 hours of symptoms for outcome to be improved. Antibiotics are given for a minimum of 10 days. As patients improve, oral antibiotics are substituted for intravenous therapy to complete the course. Respiratory isolation of patients with pneumonic plague is necessary for 4 days after beginning of antibiotics to guarantee sterilization of sputum. Patients with septicemic and bubonic plague require isolation for 48 hours. If they do not have pneumonia or draining lesions during this time, isolation can be discontinued. Nonseptic patients with mild bubonic plague can be treated at home with oral doxycycline or tetracycline for 10 days.

The mainstay of prophylaxis against plague remains oral antibiotics. A vaccine exists but has no value in an acute outbreak. It is effective only against bubonic disease and takes several months to impart immunity. The drugs for prophylaxis are tetracycline, doxycycline, ciprofloxacin, chloramphenicol, and possibly trimethoprim-sulfamethoxazole for children.

Smallpox

Principles

Smallpox was eradicated in 1980. The only known repositories of the variola virus, the etiologic agent of smallpox, are in the United States and Russia. However, Russia was successful in weaponizing the virus, which may have been sold or smuggled out of the country. The effectiveness of Russia's weaponized strain was demonstrated in 1971 when an individual became infected while traveling on a ship 15 km downwind from a Soviet bioweapons test site (Vozrozhdeniye Island in the Aral Sea). Furthermore, in July 2014, several vials of smallpox were discovered in an unused storage room at the National Institutes of Health in Bethesda, MD, raising serious concerns about the security of the virus. In addition, most of the world's population is no longer fully immune to infection because vaccination against smallpox ceased approximately 40 years ago in nonmilitary personnel. Given its high infectivity and lethality, this makes smallpox an excellent biologic weapon.

The variola virus is spread as an aerosol. It can survive for 24 hours, and possibly 48 hours, in the environment. The occurrence of smallpox in hospital employees whose only exposure was handling of laundry from infected people is testimony to its viability. Approximately 30% of exposed people become ill. One infected person has the potential to infect up to 20 other individuals. People are infectious from the time the rash first appears until the scabs fall off (1 or 2 weeks). Anyone exposed to smallpox should be closely monitored by public health authorities for 17 days to rule out infection.

Clinical Features

The disease is manifested clinically in several forms. Variola major and variola minor represent 90% of the cases. Variola major is the

Fig. 193.5. Man with smallpox. (From the Centers for Disease Control and Prevention [CDC] Public Health Image Library.)

classic form, a more severe illness with a mortality rate of 30%. Variola minor is a milder form, with less toxicity, fewer pox, and a mortality rate of 1%. Two other forms of the disease, hemorrhagic and malignant (or flat) smallpox, are seen in 10% of cases; the mortality rate is greater than 90%. Patients with hemorrhagic smallpox have symptoms earlier and become toxic quickly. Instead of pox, their rash is characterized by petechiae and hemorrhage. Death occurs in 5 or 6 days. Those with malignant smallpox have a similar course, but their rash is characterized by soft, flattened lesions that do not progress to pustules. If they survive, the lesions resolve without forming scabs.

The infection begins when the virus is inhaled. After migrating to regional lymph nodes, the virus replicates for 3 or 4 days and then asymptomatically spreads to the spleen, bone marrow, other lymphoid tissue, and liver. A second viremia occurs 8 to 12 days later and is associated with fever, prostration, and headache. Mental status changes can occur. During this phase, which lasts 2 or 3 days, the virus localizes to the skin and pharyngeal mucosa. A maculopapular rash soon appears, which becomes vesicular and finally pustular. In contrast to chickenpox, the rash first appears on the face and forearms, later spreading to the legs and trunk. All the lesions in any one area of the body are at the same stage (Fig. 193.5). During the next 8 to 14 days, the pustules crust over and separate from the skin, leaving pitted scars.

A clinical algorithm developed by the CDC can assist in assessing the probability that an individual has smallpox.[7] It relies on three major and five minor criteria. The major criteria are a febrile prodrome, classic smallpox lesions, and lesions in the same stage of development. The minor criteria are centrifugal distribution of pustules; first lesions on the oral mucosa, face, or forearms; toxic appearance; slow evolution of lesions; and pustules on the palms and soles. A patient with all three major criteria is at high risk and should be isolated and reported to public health authorities and law enforcement agencies as soon as possible. Patients with the febrile prodrome and either four minor criteria or one other major criterion are at moderate risk. Emergency clinicians should consult with infectious disease and dermatology specialists and order tests to confirm varicella. If smallpox cannot be ruled out after these interventions, the patient should be treated as high risk. If a patient does not have the febrile prodrome or has the prodrome but no other major criteria and has fewer than four minor criteria, the individual is at low risk for smallpox. These patients can be managed as clinically indicated.

Differential Diagnosis

As with anthrax and plague, the initial diagnosis of smallpox is clinical. Other illnesses resembling smallpox include chickenpox, herpes simplex, and monkeypox. Unlike with variola, the rash associated with chickenpox (varicella) is seen first on the trunk and then spreads to the extremities and face. In addition, the pustules are in different stages of evolution in any one area of the body. If the first case seen is hemorrhagic or malignant smallpox, the diagnosis will probably be missed until more typical cases present.

Diagnostic Testing

For confirmation of the diagnosis, vesicular fluid or scabs are sent for electron microscopic examination or tissue culture. Polymerase chain reaction techniques are also useful for rapid viral identification, with sensitivities and specificities in the 98% range.

Management

No effective therapy exists for victims infected with smallpox who become symptomatic. However, potential antiviral agents, such as tecovirimat and cidofovir, show promise. In mice exposed to a lethal cowpox challenge, administration of an oral lipid prodrug of cidofovir in modest doses once a day for 5 days produced 100% survival. Vaccinia immune globulin (VIG) has no role in the treatment of active disease. Some practitioners suggest that most smallpox patients should be isolated at home or other nonhospital facilities because the virus spreads easily in a hospital environment and the disease is currently untreatable.

The best strategy for containment of the disease is vaccination of the susceptible population. Vaccination of an immunocompetent individual within 3 days of exposure will prevent or significantly ameliorate illness. Vaccination up to 7 days after exposure may prevent death. Complications from vaccination with vaccinia virus occur and can be fatal. Groups at risk for these adverse consequences include pregnant women and people with eczema, human immunodeficiency virus (HIV) infection, and immunosuppressive conditions (eg, malignant disease, chronic steroid use, and hereditary immunodeficiencies). Given the seriousness of the disease, the current recommendation is to vaccinate these individuals if there is risk of exposure and simultaneously administer 0.3 mL/kg of VIG intramuscularly. For people who have complications from the vaccine (eg, progressive vaccinia, ocular autoinoculation, and eczema vaccinatum), the dose of VIG is 0.6 mL/kg intramuscularly and is divided during 24 to 36 hours. Ribavirin can be administered but is considered experimental. VIG is not indicated for vaccinia-associated encephalitis.

The smallpox vaccine supply situation has improved dramatically in the United States. The CDC has replaced the traditional smallpox vaccine (Dryvax) with a next generation product, ACAM2000, in sufficient quantity to immunize the United States population. A British company developed the second-generation vaccine from the same vaccinia virus used in Dryvax but grown in cell cultures. As a consequence, its use can still produce the same adverse reactions as Dryvax. To improve the vaccine's safety profile, work has commenced on production of an improved vaccine based on a different vaccinia strain. Two new candidate vaccines, LC16 and Modified Vaccinia Ankara, show promise. Preliminary studies demonstrate safety and immunogenicity in populations for whom the traditional vaccine is contraindicated. The virus used in the modified vaccinia Ankara vaccine is so attenuated that it does not replicate in a human host. This may make it safe for administration to immunocompromised individuals.

CHEMICAL WEAPONS

Unlike victims of biologic weapons, casualties exposed to chemical agents manifest symptoms quickly, from acutely to a few hours after chemical contact.[3] Therefore, surveillance and recognition

BOX 193.7

Emergency Department Preparedness for Chemical Weapons of Mass Destruction

Community-based hospital planning
Personnel trained in recognition, mass casualty triage, and treatment
Decontamination facility with protocols (eg, runoff water, warm water)
Personal protective equipment (PPE) readily accessible and compliant with regulations
Rapid access to antidotes, cyanide kits, and anticonvulsants
Hospital incident management system in place
Knowledge of how to access experts quickly

are less problematic. The challenge is decontamination and treatment.

Terrorism with chemical weapons produces casualties similar to those seen in hazardous materials incidents, and medical management is comparable. However, the unique features of such events, including the volume of patients and the risk of hospital contamination, necessitate additional preparation. For example, the Tokyo subway attack with use of sarin in 1995 resulted in 11 deaths and more than 5000 patients converging on local EDs. Although the majority of these patients had subclinical exposure or psychological symptoms alone, the health care system was severely stressed. Secondary contamination by direct contact or vaporization occurred in ambulances and at the hospitals.

Health care facilities should have protocols in place to deal with the eventuality of chemically contaminated patients (Box 193.7). Current recommendations for levels of PPE and types of decontamination facilities necessary in a hospital setting have been advanced, but evidence-based recommendations remain inconclusive. Collection of waste water from the decontamination process in a containment vessel is ideal but not required if this would impede necessary and appropriate actions to protect human life (https://nepis.epa.gov/Exe/ZyNET.exe/P1002ZKP.txt).

The four basic classes of chemical compounds are nerve agents, vesicants (blistering), cyanides (previously referred to as *blood agents*), and pulmonary intoxicants (previously referred to as *choking agents*). Although all have potential for use as weapons, the nerve agents and vesicants are thought to represent the greatest threat.

Nerve Agents (Sarin, Tabun, Soman, and VX)

Principles

Nerve agents are organophosphates. They inhibit the enzyme acetylcholinesterase, blocking the degradation of acetylcholine at the postsynaptic membrane. Acetylcholine accumulates, resulting in overstimulation of muscarinic and nicotinic receptors.

Clinical Features

Symptoms are receptor dependent. Stimulation of muscarinic receptors produces miosis, salivation, rhinorrhea, lacrimation, bronchorrhea, bronchospasm, vomiting, and defecation. The major life threat associated with this syndrome is ventilatory compromise from profound bronchorrhea and bronchoconstriction. Stimulation of nicotinic receptors produces muscle fasciculations, flaccid paralysis, tachycardia, and hypertension. Unlike with typical organophosphates, exposure to nerve agents has not been associated with urination. In addition, bradycardia is rare, and miosis does not respond to systemic therapy.

Nerve agents also cause direct central nervous system toxicity that is manifested as seizures, coma, and apnea. In survivors, residual central nervous system effects are manifested as psychological changes that can last 4 to 6 weeks. These manifestations are caused by chemical effects, not stress.

BOX 193.8

Type and Degree of Nerve Agent Exposure

VAPOR EXPOSURE (SARIN)
Mild: Rhinorrhea and miosis
Moderate: Mild symptoms plus increased secretions, wheezing or dyspnea, muscle weakness or fasciculations, or gastrointestinal effects
Severe: Apnea, seizures, loss of consciousness, flaccid paralysis, or major involvement of two organ systems

LIQUID EXPOSURE (VX)
Mild: Localized sweating and fasciculations where a drop touches the skin; no miosis; may be delayed for 18 hours
Moderate: Gastrointestinal effects; miosis uncommon; may be delayed for 18 hours
Severe: Apnea, seizures, loss of consciousness, flaccid paralysis, or major involvement of two organ systems; occurs in less than 30 minutes at or above median lethal dose (LD_{50})

A preliminary diagnosis of nerve agent exposure is based on clinical findings. Important features include muscle fasciculations and miosis, which are sufficient to justify treatment pending further evaluation. Diagnosis is confirmed by measurement of red blood cell cholinesterase levels. This test may not be readily available, and results are difficult to interpret without a baseline level as significant variation exists within normal populations. Therefore, treatment is to begin before test results are known.

Terrorists are most likely to use the nerve agents sarin (designated GB) and VX. Sarin exists as a liquid at room temperature but represents primarily a vapor threat because of its high volatility. Symptoms occur within seconds after inhalation of vapor and peak at 5 minutes. There are no delayed effects; patients remaining asymptomatic 1 hour after possible chemical contact have not received a clinically significant exposure. They can be sent home. VX is a thick liquid with low volatility. It represents a liquid threat only. In general, victims have symptoms after skin exposure. The median lethal dose (LD_{50}) for VX is 10 mg, a droplet slightly larger than a pinhead. Death from doses of this size occurs in less than 30 minutes. Delayed symptoms occur, so individuals should be observed for 18 hours before potential intoxication can be ruled out.

Management

Decontamination of victims exposed to sarin vapor requires removal of clothing. People contaminated with VX or liquid sarin should have their clothing removed and then be decontaminated by using showers. When the level of exposure or the involved agent is uncertain, full decontamination is prudent. Responders caring for patients in the presence of liquid sarin exposure may require level A or B protective suits.

The treatment of nerve agent victims depends on the form (liquid or vapor) and level of exposure (mild, moderate, or severe) (Box 193.8). Three drugs are the mainstay of treatment: atropine for the muscarinic effects (improves ventilation), pralidoxime chloride (2-PAM) for the nicotinic effects (reverses paralysis), and diazepam for the prevention and treatment of seizures (Box 193.9). The dose of atropine is titrated to the drying of respiratory secretions and not to heart rate or pupil size. 2-PAM is most effective if it is administered within 4 to 6 hours of sarin exposure. After this period, the drug's impact wanes because of "aging,"

BOX 193.9

Treatment of Nerve Agent Exposure*

VAPOR

Mild: *Observe for 1 hour,* then release; no treatment
Moderate: One or two Mark I kits IM; *or* atropine, 2 to 4 mg IV, may repeat every 5 to 10 minutes as needed; *and* 2-PAM, 1 g IV during 30 minutes, may repeat every hour as needed
Severe: Three Mark I kits IM and one diazepam autoinjector IM; *or* atropine, 6 mg IV, may repeat 2-mg boluses IV every 5 to 10 minutes; *and* 2-PAM, 1 g IV during 30 minutes, repeat every hour for total of 3 g; *and* midazolam or diazepam, 5 mg IV, or midazolam 10 mg IM, may repeat as needed

LIQUID

Mild: One Mark I kit IM; *or* atropine, 2 mg IV; *and* 2-PAM, 1 g IV during 30 minutes
Moderate: Same as for vapor
Severe: Same as for vapor

PEDIATRIC DOSES

Atropine, 0.02 mg/kg IV
2-PAM, 20 to 40 mg/kg IV during 20 to 30 minutes
Midazolam, 0.15 mg/kg IV; *or* diazepam, 0.2 to 0.3 mg/kg IV

*Give atropine before attempting intubation. Otherwise, airway resistance will inhibit ventilation. Continue atropine until secretions are dry (usually 20 mg). In hypoxic patients, IV atropine has been reported to cause ventricular fibrillation, so consider use of IM atropine.
IM, Intramuscular; *IV,* intravenous.

defined as the permanent attachment of sarin to the acetylcholinesterase enzyme. Hypertension can occur during 2-PAM administration and is controlled by intravenous phentolamine, 5 mg for adults and 1 mg in repeated doses for children. In 2009, investigators published data that question the efficacy of oximes in the treatment of commercial insecticide exposure. In one study, the use of oximes did not improve clinically important outcomes.[9] Whether these results apply to nerve agents remains uncertain. Midazolam may be a more effective benzodiazepine for control and prevention of seizures, and it may replace diazepam as the drug of choice for treatment of severe nerve agent toxicity in future guidelines.[10,11]

An autoinjector kit (Mark I) approved by the FDA consists of two cartridges, one containing atropine (2 mg) and the other 2-PAM (600 mg). Mark I kits are available as part of civilian pharmaceutical caches strategically located throughout the United States. A newer version with both drugs combined in a single autoinjector (Antidote Treatment Nerve Agent Auto-Injector referred to as *DuoDote*) will gradually replace the Mark I kits. An autoinjector containing 10 mg of diazepam is an additional option if intravenous access is not possible. Doses should be adjusted for pediatric and geriatric patients. Atropine autoinjectors are manufactured in three doses (2 mg, 1 mg, and 0.5 mg) for these groups. Use of the Mark I kits to treat children and the elderly can be problematic because of difficulty in adjusting the dose. An alternative solution is to inject the medication into a sterile vial. The drug can then be re-aspirated in an appropriate amount for the patient's weight or age and administered.

Vesicants (Mustard)

Principles

Vesicants (blistering agents) are chemical warfare agents that induce blister formation on contact with skin. Terrorists could use several of these compounds, but sulfur mustard is considered the most likely. Mustard is a liquid at room temperature but has both liquid and vapor toxicity. Injury from mustard exposure occurs in 1 or 2 minutes, but symptoms do not develop for 4 to 8 hours.

Clinical Features

The exact mechanism is unknown, but the agent damages DNA, causing eventual cell death. These effects are similar to radiation exposure and often described as "radiomimetic." Mustard has both local and systemic toxicity. Local effects occur from direct exposure to the skin, eyes, and airway. Systemic effects result from the impact of absorbed mustard on the bone marrow.

Management

Treatment is supportive and includes decontamination (to prevent secondary contamination) and airway maintenance. No specific antidote for mustard is currently available. A topical iodine preparation showed promise in initial trials but did not demonstrate efficacy in larger studies.

Eye damage from mustard exposure varies from conjunctivitis to corneal ulcer and perforation; however, only 1% of patients have permanent eye damage. Ninety percent of ocular injuries will heal within 2 weeks to 2 months of exposure without sequelae. Severe pain is frequently associated with mustard injury and causes significant blepharospasm. Irrigation is beneficial if it is performed within minutes of exposure but ineffective once symptoms occur. Standard treatment includes mydriatics, topical antibiotics, oral analgesics, and petroleum jelly applied to the lids to prevent adhesions. Commercially available topical antibiotic/glucocorticoid ophthalmologic ointments have demonstrated efficacy when applied early in animal models. Application of this drug combination in the first few hours to days of exposure appears to reduce inflammation and subsequent injury. Continued use of topical steroids should occur under the supervision of an ophthalmologist.

The hallmark of mustard injury is skin blisters resembling second-degree burns. Within 4 to 8 hours of exposure, erythema and burning occur, followed by vesicle and bulla formation. Most vapor injuries do not involve the entire dermis, so wounds will not require skin grafting. If liquid exposure occurs to skin, full-thickness burns may result. The patient should be decontaminated by removal of clothing and washing with water or a dilute bleach (1:10 hypochlorite) solution. More concentrated bleach solutions are contraindicated, because they can cause skin damage. Decontamination immediately after exposure, ideally at the scene, prevents further injury to the patient, but delayed decontamination is indicated to protect staff. Treatment is supportive and includes standard burn wound management, analgesia, and tetanus prophylaxis. An important exception is fluid resuscitation. Fluid losses from mustard injury are much less than those associated with thermal burns. Therefore, standard burn formulas for fluid administration do not apply, and caution should be used to avoid overhydration.

The degree of airway injury after mustard exposure is dose dependent. Mild exposure causes irritation of the nose, sinuses, and pharynx and can be treated with cool, humidified mist. Moderate exposure extends to the larynx and upper trachea and may require treatment with oxygen, continuous positive airway pressure, or even intubation. Severe exposure involves the lungs, producing hemorrhagic necrosis of the bronchioles. Pulmonary edema is rare. Intubation is usually required, and patients may benefit from positive end-expiratory pressure and inline bronchodilators. Steroids are of questionable benefit, and antibiotics should be given only for established infection. Recent trials of inhaled tissue plasminogen activator in a rat model of sulfur mustard pulmonary injury show promise.[12]

Systemic toxicity from mustard is caused by bone marrow suppression. Absorbed mustard kills stem cells, causing the white blood cell count to decline after 3 to 5 days. Survival is rare if the white blood cell count falls below 200, which generally occurs when more than 50% of the total body surface area is involved from exposure to liquid agent. Death after mustard exposure usually results from secondary infection and respiratory failure.

Cyanides (Blood Agents)

Principles

Cyanide molecules, most typically hydrogen cyanide or cyanogen chloride, bind to cytochromes within mitochondria and inhibit cellular oxygen use.

Clinical Features

Low-dose exposures result in tachypnea, headache, dizziness, vomiting, and anxiety. Symptoms subside when the patient is removed from the source. At higher doses, the symptoms progress to seizures, respiratory arrest, and asystole within minutes of exposure.

Management

Victims should be removed from the area, have their clothing discarded, and receive oxygen. If no improvement occurs, the cyanide antidote is given. This has traditionally been the sequential administration of amyl nitrate, sodium nitrite, and sodium thiosulfate. However, the FDA has approved intravenous hydroxocobalamin for treatment of cyanide exposure. The initial dose is 5 g and can be repeated if necessary.[13-15]

Pulmonary Intoxicants (Phosgene and Chlorine)

Pulmonary or choking agents cause an inflammatory reaction when they come into direct contact with the eyes and upper airway. They can be life-threatening if inhaled. No specific antidote exists. Treatment is mainly supportive and consists of removal of the patient from the source, decontamination, airway maintenance, bronchodilator administration, and eye irrigation.

KEY CONCEPTS

- Emergency department (ED) preparedness for a radiation incident should address decontamination (an external freestanding decontamination unit is best), triage, staff safety, personal protective equipment (PPE), and diagnostic procedures that emphasize radiation monitoring. It is important that emergency personnel know their radiation safety officer.
- Management of acute life-threatening conditions takes priority over radiation-associated issues.
- Aerosol dispersal is a likely route that terrorists may use to deploy biologic weapons, so victims will present primarily with respiratory complaints.
- In addition to "flulike" symptoms, anthrax typically causes mediastinal widening, pulmonary consolidation, and pleural effusions best seen on chest computed tomography (CT) scans.
- Smallpox can spread in a hospital environment; thus patients thought to have smallpox should be admitted to locations separated from the rest of the hospital.
- Decontamination is a key activity in the management of patients exposed to chemical agents, and hospitals should provide this intervention.
- Nerve agents are organophosphates, and patients exposed to these agents are treated with large doses of atropine (repeated frequently), pralidoxime, and benzodiazepines.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 193: QUESTIONS & ANSWERS

193.1. Three patients arrive at triage simultaneously: One has received a 4 Gray work-related irradiation exposure from a food sterilizer but no other injury, one is experiencing an acute ST elevation myocardial infarction (MI), and one likely has urosepsis but with a stable blood pressure and heart rate of 105 beats/min. Which of these patients should receive your attention first?

A. Activate the cardiac catheterization team.
B. Decontaminate the irradiated victim before placing him in a room.
C. Initiate intravenous (IV) fluid bolus and prepare for intubation of the radiation-exposed patient.
D. Place a central venous catheter in the urosepsis patient.
E. Place the irradiated victim in an isolation room.

Answer: A. Even patients who have received a lethal radiation dose do not die quickly as a consequence of the ionizing exposure. Patients should still be triaged according to severity of the medical conditions and/or vital sign derangements. Here, the patient with the MI is most acute and should be treated first by activating the cardiac catheterization team. The radiation-exposed patient was not contaminated, just irradiated. As such, decontamination and isolation are not necessary. Although the victim has received the $LD_{50/60}$ dose of ionizing radiation, no significant injury will result just after exposure, so this patient does not take priority over the MI patient at this point and intubation is not indicated. The septic patient is not critically ill and should not be treated ahead of the MI patient.

193.2. Which of the following statements best describes issues in management of anthrax infection?

A. Antibiotics do not change the mortality of cutaneous disease.
B. Cutaneous anthrax lesions are nontender.
C. Doxycycline or ciprofloxacin is the single-agent treatment for symptomatic inhalational anthrax.
D. Intubation/mechanical ventilation clearly improves mortality from inhalational anthrax.
E. Sputum culture and Gram's stain obtained early in the disease help differentiate inhalational anthrax.

Answer: B. Cutaneous anthrax causes a severe, although nontender, peripheral vesicle and then eschar with regional adenopathy. Antibiotics lower the mortality from cutaneous anthrax twentyfold. For inhalational, gastrointestinal, and cutaneous anthrax with toxicity, intravenous (IV) treatment is with ciprofloxacin or doxycycline plus at least two other agents. Regarding inhalational anthrax, mechanical ventilation may not improve mortality, and sputum cultures and Gram's stains are not helpful until late in the disease.

193.3. Several children ages 5 to 8 years old have definitely been exposed to anthrax spores. Health department officials have brought these children to the emergency department (ED). They are all ambulatory with normal vital signs and without symptoms. Which of the following is the most appropriate management?

A. Admission for parenteral penicillin G
B. Doxycycline for 5 days
C. Observation
D. Outpatient ciprofloxacin for 60 days or until the children have received three doses of vaccine
E. Penicillin VK for 7 to 10 days

Answer: D. See Box 193.5. For children without toxicity, ciprofloxacin, doxycycline, or amoxicillin orally is indicated for a minimum of 60 days or until the child has received three doses of vaccine. The vaccine has not been approved for children but may be indicated to reduce the long-term exposure to antibiotics. Note that weaponized anthrax may be penicillin resistant.

193.4. An individual is exposed to sarin vapor. She presents complaining of difficulty with vision, salivation, vomiting, and the urge to defecate. The most appropriate treatment for this patient is which of the following?

A. 5 mg diazepam intravenous (IV)
B. 6 mg atropine IV and 1 g 2-PAM IV every hour for a total dose of 3 g
C. 10 mg diazepam intramuscular (IM) via auto-injector
D. Observation for 6 hours and then discharge if she does not develop new symptoms
E. One or two Mark 1 kits IM

Answer: E. The victim described would be characterized as a moderate exposure to sarin vapor. As such, treatment is indicated with one or two Mark 1 auto-injectors IM. Observation would not be appropriate. Diazepam is not indicated for moderate exposures. If an IV is established, the initial treatment is atropine 2 to 4 mg IV and 2-PAM 1 g IV.

CHAPTER e1

Forensic Emergency Medicine*

Adedamola A. Ogunniyi | *Andrea W. Wu*

PERSPECTIVE

FORENSIC ASPECTS OF GUNSHOT WOUNDS

Background

Epidemiology

Clinical Features

Diagnostic Testing

Differential Diagnosis

Management and Disposition

FORENSIC ASPECTS OF PHYSICAL ASSAULT

Perspective

Blunt Force Pattern Injuries

Sharp Force Pattern Injuries

Thermal Pattern Injuries

Chemical Injuries

FORENSIC ASPECTS OF MOTOR VEHICLE TRAUMA

Perspective

Motor Vehicle Collisions

Motorcycle Collisions

Evaluation of Motor Vehicle Collisions

Evaluation of Pedestrian Collisions

Law Enforcement Exemptions to the Health Insurance Portability and Accountability Act

KEY CONCEPTS

- Knowledge of wound mechanics and production, as well as wound appearance, can provide practicing emergency clinicians with important clues regarding the forensic interpretations of injuries.
- Wounds and injuries should be diagrammed and photographed.
- The medical record should accurately document objective findings associated with a patient's wounds. Emergency clinicians should not speculate about their mechanism or cause.
- Any evidence collected during the course of treatment must be documented in the medical record, including to whom the evidence was given, for the chain of custody to be preserved.

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

CHAPTER e1

Forensic Emergency Medicine

Adedamola A. Ogunniyi | Andrea W. Wu

PERSPECTIVE

Clinical forensic emergency medicine is the application of forensic medical knowledge, techniques, and procedures to the management of live patients in the emergency department (ED).[1] It is a key link through which patients or victims of violence can receive recourse for the actions against them. Emergency clinicians are in the unique position of being the first contact for most of these patients and play a crucial role in this process. They are also the clinicians who have the most contact with law enforcement, and are therefore well suited to aid in evidence conservation.[2] However, many emergency clinicians have limited training in clinical forensic emergency medicine and, as such, critical information or data can be missed during these interactions.[1]

All patients who are victims of physical or sexual assault, abuse, or trauma have forensic needs. When treating injuries without consideration of their forensic significance, emergency clinicians may misinterpret wounds, fail to recognize victims of abuse or domestic violence, and inadequately describe the physical appearance of the wounds. During the provision of patient care, evidence that can be of critical significance to criminal or civil proceedings can be lost, discarded, or inadvertently washed away,[3] despite requirements by The Joint Commission to "preserve evidentiary materials and support future legal actions." Prior studies have shown that evidence may be accidentally discarded during the initial evaluation and that injuries are also improperly documented.

Emergency medicine programs have identified and described the need for forensic training in their residency curricula. The American College of Emergency Physicians established the Forensic Medicine Section in 2006 to provide emergency clinicians with additional forensic resources and training. Unfortunately, however, no formal training programs currently exist. In contrast, the British Royal College of Physicians established the Faculty of Forensic and Legal Medicine (FFLM) in 2006 as the authoritative body on clinical forensic medicine in the United Kingdom. The FFLM has created training and certification programs and board-type certification examinations after 2 years of forensic practice for British physicians.[4]

There are a number of important ways to address this gap through training and exposure to clinical forensic emergency medicine. Forensic examinations should be conducted with the consent of the patient, legal guardian, or court or by implied consent. The evaluation should include a history and physical examination in which all wounds are documented and described in as much detail as possible, as well as photographs and anatomic diagrams.[1] Even simple findings, such as contusions or ecchymoses with associated injuries may serve as important clues as to how the injury was sustained[5] and may be invaluable in future legal proceedings. Evaluations of gunshot and stab wounds, physical or sexual abuse, domestic violence, and motor vehicle–related trauma should also be adequately documented for possible use as evidence. Documentation should include digital photographs as well as a narrative and diagrams.

Evidentiary material, such as clothing, bullets, and shrapnel, should be collected.[1] Clothing should be stored in a paper bag; bullets and other metallic foreign bodies should be handled minimally and with gloved hands. Contact with metal instruments should also be avoided because these can alter the markings present.[1]

When physical injuries are misinterpreted, and these misinterpretations are entered into the medical record, or when valuable evidence is lost or destroyed in the process of providing patient care, there are consequences for the legal proceedings that may follow.[4] These acts of omission or commission may deny patients their deserved redress in the justice system. To protect the interests of patients, EDs should implement protocols for wound documentation and evidence collection.[3] A proper understanding of the forensic relevance of certain observations is the key to protecting the rights of victims of assault.[2]

FORENSIC ASPECTS OF GUNSHOT WOUNDS

Background

Ballistics

Ballistics is the science of the motion of projectiles in flight.[6] In relation to firearms, it is the study of the interaction of a bullet (or missile) from when it leaves the gun cartridge until it makes contact with tissue. Ballistic physics is broken down into three parts, based on the material with which the bullet interacts:

1. Internal ballistics, which pertains to the projectile while in the firearm
2. External ballistics, or the path of the projectile from when it leaves the firearm until it reaches the target
3. Terminal (or wound) ballistics[7,8]

Internal ballistics factors in the design of the firearm and how the combustion of gunpowder within the firearm generates the pressure that subsequently projects the missile. External ballistics takes into consideration the effects of gravity and drag on the missile and how that affects the distance travelled and the accuracy with which it hits the intended target.[7,8]

Wound ballistics is the most clinically relevant because it is the study of the effects of penetrating projectiles on the body. Tissue disruption (wound severity) is directly related to the amount of kinetic energy ($KE = \frac{1}{2} mv^2$ [m = mass; v = velocity]) transferred to it, not to the total amount of kinetic energy possessed by the bullet.[7,9,10] There are two broad categories of weapons based on the amount of potential kinetic energy that can be transferred from the missile to the tissue:

1. High-velocity weapons, which generate velocities from 1500 to 4000 ft/s (or >600 m/s).[9] Examples of these are rifles or military weapons. Consequently, bullets fired from such weapons possess a higher kinetic energy and, therefore, theoretically have a greater wounding capacity.
2. Low-velocity weapons, which generate velocities ranging from 700 to 1600 ft/s (or <600 m/s).[9] These weapons include handguns and air rifles (BB guns).

Rifle bullets have more kinetic energy and a theoretically higher wounding potential, but energy transfer (and, by extension, wound severity) is the result of multiple variables. The most

are bullet type (eg, weight, deforming type, fragmenting type), bullet velocity, and the characteristics, location, and nature of the impacted tissue itself (tissue over bone or tissue over organs).[8,9,11] Interestingly, high-velocity bullets tend to travel straight through tissue, with minimal energy dissipation. The formula $KE = \frac{1}{2} m(V_1 - V_2)^2$ better reflects the actual energy transfer occurring during tissue penetration and wounding.[11]

The principal mechanism for tissue damage by bullets is crushing. A bullet traveling through tissue generates two cavities, one permanent and the other temporary. The size of the permanent cavity varies with the size, shape, and configuration of the bullet. A hollow point bullet that mushrooms can increase its diameter 2.5 times on impact and will increase the area of tissue crush 6.25 times compared with a nondeformed bullet. The temporary cavity results from a shock wave generated as the bullet enters the tissue, which results in a brief distortion or stretching of the tissue.[7,10] This tissue distortion lasts for a brief amount of time, 5 to 10 milliseconds from its generation until its collapse, and leaves behind the permanently crushed tissue and permanent cavity.[7,9,10] The effect of the temporary cavity depends on the elasticity of the tissue traversed: solid organs such as the liver, bone, or kidneys do not tolerate this temporary deformation as well as more elastic tissue (eg, lungs, skeletal muscle, skin), and therefore sustain more damage.[9] Secondary wounding can occur in situations in which the bullet hits a target (usually bone) and fragments disperse, resulting in further tissue damage.[7]

Forensic Evaluation of Handgun Injuries

The Weapon. Handguns are the most common firearm available. There are four categories of handguns: (1) the single-shot weapon (usually a target pistol); (2) the derringer (a small, concealable weapon, usually with two barrels); (3) the revolver (a weapon with a rotating cylinder that advances with the pull of the trigger); and (4) the semiautomatic pistol (which fires with each pull of the trigger). The semiautomatic handgun is the most popular because its magazine, or clip, can hold up to 17 cartridges, whereas revolvers hold five or six cartridges.

Handgun Ammunition. The cartridge, or round, is composed of the primer, cartridge case, powder, and bullet (Fig. e1.1). The bullet is the projectile that is propelled out of the muzzle. The primer is a small explosive charge in the base of the cartridge that ignites the gunpowder. The primer may contain lead, barium, or antimony. These materials may be deposited on the hands of the shooter, on the victim of a close-range assault, or on objects within a room in which the weapon was discharged.

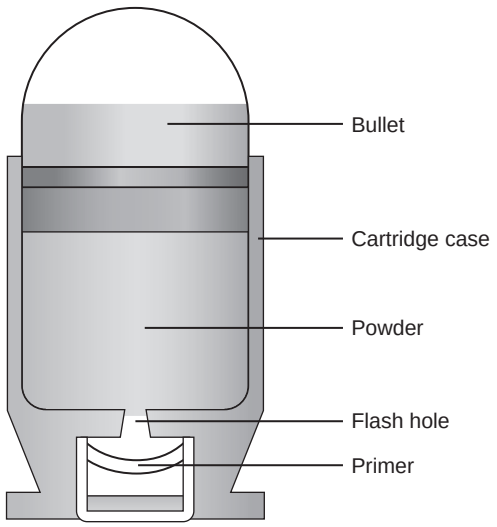

Fig. e1.1. A cartridge consists of several distinct components—bullet, cartridge case, gunpowder, flash hole, and primer.

The cartridge case is typically made of brass, although other materials may be used. The function of the cartridge case is to expand slightly, sealing the chamber against the escaping gases and propelling the bullet down the barrel. On detonation, a cartridge case is imprinted with unique microscopic marks that are valuable evidence and should be preserved for law enforcement.

The gunpowder found in all commercial cartridges except blanks is smokeless powder made with a single base (nitrocellulose) or a double base (nitrocellulose and nitroglycerin). When a weapon is discharged, not all the gunpowder is consumed. A percentage of the unburned or partially burned gunpowder will travel out of the end of the muzzle for a short distance (<48 inches). The distance depends on the physical characteristics and shape of the powder and the weapon's barrel length.

Blank cartridges, muzzleloaders, and other antiques or replicas may use black powder. Black powder—a combination of potassium nitrate, charcoal, and sulfur—does not burn as efficiently as the smokeless powder and results in a large flame and white smoke. It is black powder that produces powder burns by igniting clothing.

The bullet is the projectile that is propelled down the gun barrel at velocities ranging from 700 to 1600 ft/s. The higher velocities are achieved by the inclusion of supplemental gunpowder in the cartridge case (a magnum load; hence, a .357 magnum). The diameter of the bullet's base is termed its *caliber.* Bullet caliber is described in hundredths of an inch or millimeters. Handgun bullets range from .22 caliber, or 5.56 mm, to .45 caliber, or 11.3 mm. A bullet's weight is measured in grains, with 7000 grains/lb.

The most common bullet types are the round nose, full metal jacket, hollow point, wad cutter, and semi–wad cutter. Bullets generally are a solid core of lead or steel. If a jacket covers the bullet core, the jacket's metal is usually copper or aluminum. If the jacket covers only a portion of the core, the bullet is said to be semijacketed. If the core is completely covered, it is said to have a full metal jacket. Some bullets have a hole in the tip and are called hollow points. The hole causes the bullet to expand on contact, which significantly increases the damage to tissue.

Forensic Aspects of Rifles

Rifles are shoulder-fired weapons designed to generate significant pressures in the muzzle and, as such, result in firing of ammunition at high speeds.[7] Centerfire rifle bullets, .223 to .308 caliber, are similar in diameter to handgun ammunition but, based on the formula for kinetic energy ($KE = \frac{1}{2} mv^2$), their wounding potential is greatly enhanced by the higher velocity of the round. Injuries result from the transference of energy from the projectile to tissue, organs, and bony structures. With medium-velocity rounds (2000–3000 ft/s) and high-velocity rounds (>3000 ft/s), a temporary cavity is formed along the wound tract, which may be 11 or 12 times the diameter of the bullet. High-velocity rounds can also cause tissue damage away from the physical tract taken by the projectile. Because of the amount of energy possessed and transferred to underlying tissue, exit wounds associated with centerfire rifles, in contrast to those associated with handguns, are generally larger than their corresponding entrance wounds (Fig. e1.2).

Forensic Aspects of Shotguns

Shotguns are similar to rifles, but the missiles are multiple small projectiles, all of which have the potential to cause severe injury.[7] Shotguns have the barrel length of rifles but can discharge pellets or single slugs down a smooth bore barrel. The caliber of a shotgun

is defined by the term *gauge*. Historically, the gauge of a gun referred to the number of lead balls of the given bore diameter that make up a pound—for example, 12 lead balls to make 1 lb. A shotgun cartridge may contain only a single slug or may contain hundreds of pellets (Fig. e1.3A). Pellets range in diameter from 0.05 inch (#12 birdshot) to 0.36 inch (000 buckshot). A shotgun cartridge is made of several components that will be of forensic value and should be collected in the ED (see Fig. e1.3B).

Shotgun slugs are single projectiles that may weigh 200 times more than handgun ammunition—for example, a 12-gauge slug weighs 547 g, and a .22 long rifle bullet weighs 2.6 g (see Fig. e1.3B). The velocities of shotgun slugs are in the range of 1500 to 1800 ft/s.

Fig. e1.2. This patient sustained a high-velocity gunshot wound to the forehead. High-velocity rifle rounds, due to their kinetic energy, can cause massive damage when the energy is transferred to underlying tissue.

Forensic Aspects of Air Rifles

Air rifles work very similarly to traditional firearms and generate comparable muzzle velocities as low-velocity weapons.[12] As such, they possess enough kinetic energy to cause severe injuries because they can penetrate tissue, and particularly because they are often fired at close range.[12]

Epidemiology

According to data from the Centers of Disease Control and Prevention, there were 921,163 firearm injuries from 2001 to 2013; firearms accounted for 31,672 fatalities in 2010 alone and represent the second leading cause of injury-related deaths in the United States after motor vehicle trauma.[13] Many studies have suggested that the number of firearm injuries have stabilized in recent years, but a few recent studies have noted a decline in the number of firearm injuries while the mortality rate has largely remained unchanged.[14-16]

Firearm injuries occur predominantly in males between the ages of 15 and 45 years old, particularly in those of African American ethnicity.[16] Suicides are more common than homicides, and the incidence of the latter appears to be decreasing. Suicides accounted for 60.5% of all firearm fatalities from 2002 to 2012.[16] In a recent study, firearm homicide was the leading cause of death in African American males from aged 15 to 34 years in 2012 and was the second leading cause of death for whites or Hispanic males of the same age range. Firearm violence was the second leading cause of death in females aged 15 to 24 years.[16] In contrast, suicide rates were higher in white males, and the divergence increased with age, starting in adolescence. Hospitalizations for nonfatal firearm injuries have followed the same trend.[17] Stray bullet injuries are also important because they frequently affect females, children, or older adults,[18] who may not have any relation to the associated violence.

Firearm injuries are not limited to adults. Firearm homicide is a leading cause of death in African American youth aged 14 to 24

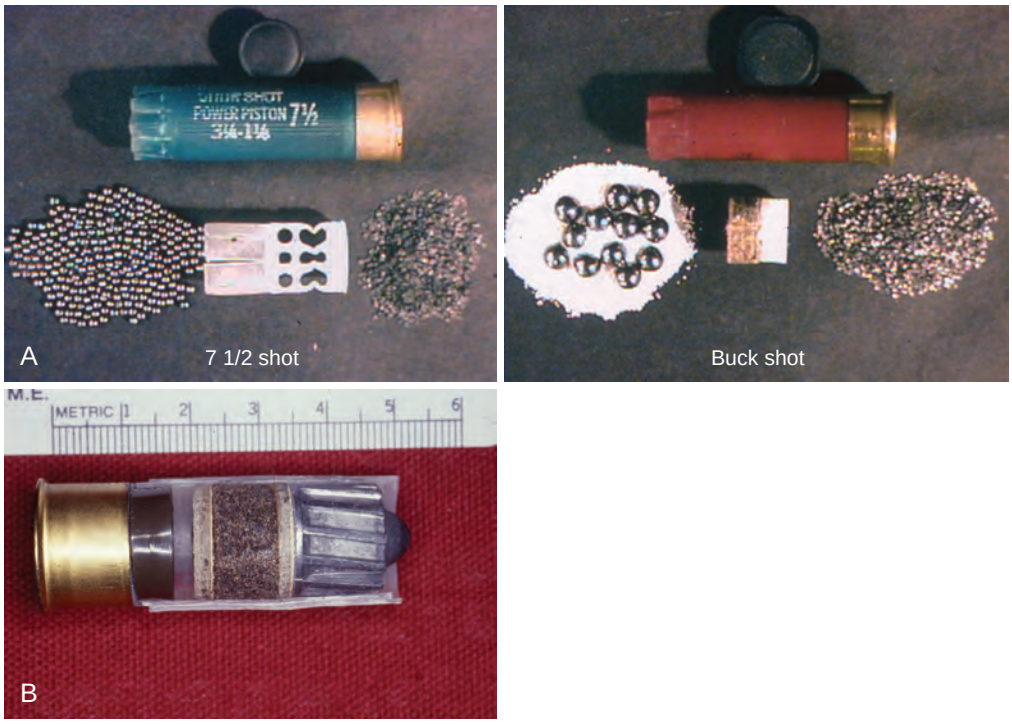

Fig. e1.3. **A,** Shotgun cartridges may contain eight to hundreds of pellets. **B,** A single shotgun slug and components of the cartridge.

years and the second leading cause of death in other youth, regardless of age or race.[19] Over 15,500 children aged 20 years and younger were treated for nonfatal firearm injuries in the United States in 2010, with 703 firearm unintentional fatalities in children aged 14 years and younger from 2000 to 2010.[15] Adolescents aged 15 to 19 had a nonfatal firearm injury rate three times that of the general population.[15] The medical impact is significant. One recent study noted that there were an estimated 322,730,927 emergency and outpatient visits for children and adolescents aged 1 to 19 years between 2001 and 2010, with an average incidence of 19,897 firearm injuries/year.[20] These patients were more likely to be male, aged 12 to 19 years, African American, and uninsured.[20,21]

Air rifles also contribute to the prevalence of firearm injuries. About 14,000 shootings occur annually, predominantly in males and in those younger than 19 years, with the highest incidence in children between the ages of 10 and 14 years.[12] Therefore, it is critical to understand and be well versed in the management of such injuries.

To manage patients with firearm-related injuries properly, it is also important to have a thorough understanding of the pathophysiology involved. Several misconceptions exist in the management if these injuries, such as a poor understanding of wound sterility following gunshot injuries,[22] the need for wound débridement, and the necessity for prophylactic antibiotics.[11] A study published in 2015 showed that such misconceptions were prevalent and were not influenced by prior Advanced Trauma Life Support (ATLS) training.[11] As such, focused training in forensic medicine is necessary to improve knowledge and the ability to treat these patients adequately.

Clinical Features

Errors of Interpretation and Terminology

The emergency clinician is in the ideal position to evaluate and document the state of a gunshot wound because he or she sees and explores it before it is disturbed, distorted, or destroyed by surgical intervention.[1,3] Documentation of gunshot wounds should include the anatomic location of the wound as well as its, size, shape, and distinguishing characteristics, and digital photographs of the wound should be taken. Wounds should be described according to the standard anatomic position, with the arms to the sides and palms facing forward.

Emergency clinicians should not describe wounds as "entrance" or "exit" but, using appropriate forensic terminology, should document a detailed description of the wound, including its appearance, characteristics, and location, without attempting to interpret the wound type or bullet caliber.[1] Exit wounds are not always larger than entrance wounds, and wound size does not consistently correspond to bullet caliber.[1]

The size of any wound (entrance or exit) is determined by five factors—the size, shape, configuration, or angle and velocity of the projectile at the instant of impact with tissue and the physical characteristics of the impacted tissue itself. If the projectile is slowed and its shape unchanged on exiting the skin, the exit wound may be the same size as or smaller than the corresponding entrance wound. If the projectile increases its surface area by fragmenting or changing its configuration while maintaining a substantial velocity, the exit wound may be significantly larger than the entrance wound. If the bullet strikes bone, fragments may extrude from the exit wound and contribute to the size and shape of the wound. Tissue elasticity also affects wound size so that entrance or exit wounds may be smaller, equal to, or larger than the projectile that caused them. Wounds on the palm or sole may appear as slits and can be easily mistaken for stab wounds.

A treating emergency clinician may be requested to render factual testimony, expert testimony, or both in a criminal case. Expert forensic testimony rendered without an appropriate forensic examination or adequate forensic training may mislead participants in the criminal justice system (eg, "the exit wound is always larger than the entrance wound"). Opinions related to entrance versus exit wounds or the range of fire can affect the determination of innocence or guilt.

The subsequent sections highlight the clinical features of entrance and exit wounds that result from the use of different types of firearms. This information is provided to make emergency clinicians aware of the varying presentations, depending on the distance from the target. Again, however, they should refrain from speculating on the type of wound and simply document the findings noted on examination.

Handgun Entrance Wounds

Range of fire is the distance from the muzzle to the victim and can be divided into four general categories: contact, near-contact or close range, intermediate or medium range, and indeterminate or distant range (Table e1.1). The size of the entrance wound does not correlate with the caliber of the bullet because the entrance wounds over elastic tissue will contract around the tissue defect and have a diameter much less than the caliber of the bullet.

Contact Wounds. There are three subcategories of contact wounds: (1) tight contact, in which the muzzle is pushed hard against the skin; (2) loose contact, in which the muzzle is incompletely or loosely held against the skin; and 3) contact through clothing.

In a tight contact wound, all material—the bullet, gases, soot, the incompletely burned pieces of gunpowder, and metal fragments—is driven into the wound. These wounds can vary from a small hole with seared blackened edges from the discharge of hot gases and an actual flame to a gaping stellate wound (Fig. e1.4). Large wounds occur when the wound is inflicted over thin, inelastic, or bony tissue, and the injected hot gases cause the skin to expand until it stretches and tears. These tears will have a triangular shape, with the base of the triangle overlying the entrance wound. Tears are generally associated with .32 caliber or greater, or with magnum loads. Large stellate contact wounds are easily misinterpreted as exit wounds if the determination is based solely on their size (see Fig. e1.4B).

Stellate tears are not pathognomonic for contact wounds, however. Tangential wounds, ricochet or tumbling bullets, and some exit wounds may also be stellate. These wounds' appearance differs from that of tight contact wounds by the absence of soot

TABLE e1.1

Range of Fire

RANGE	INCHES (BARREL TO SKIN)	PHYSICAL PROPERTIES
Contact	0	Soot, seared skin, triangular tears
Close	0–6	Soot, abrasion collar (abrasion collar may be obscured by soot)
Intermediate	<48	Tattooing, abrasion collar
Distant or indeterminate	Any distance	Abrasion collar (intermediate objects will prevent soot and gunpowder from contacting the skin)

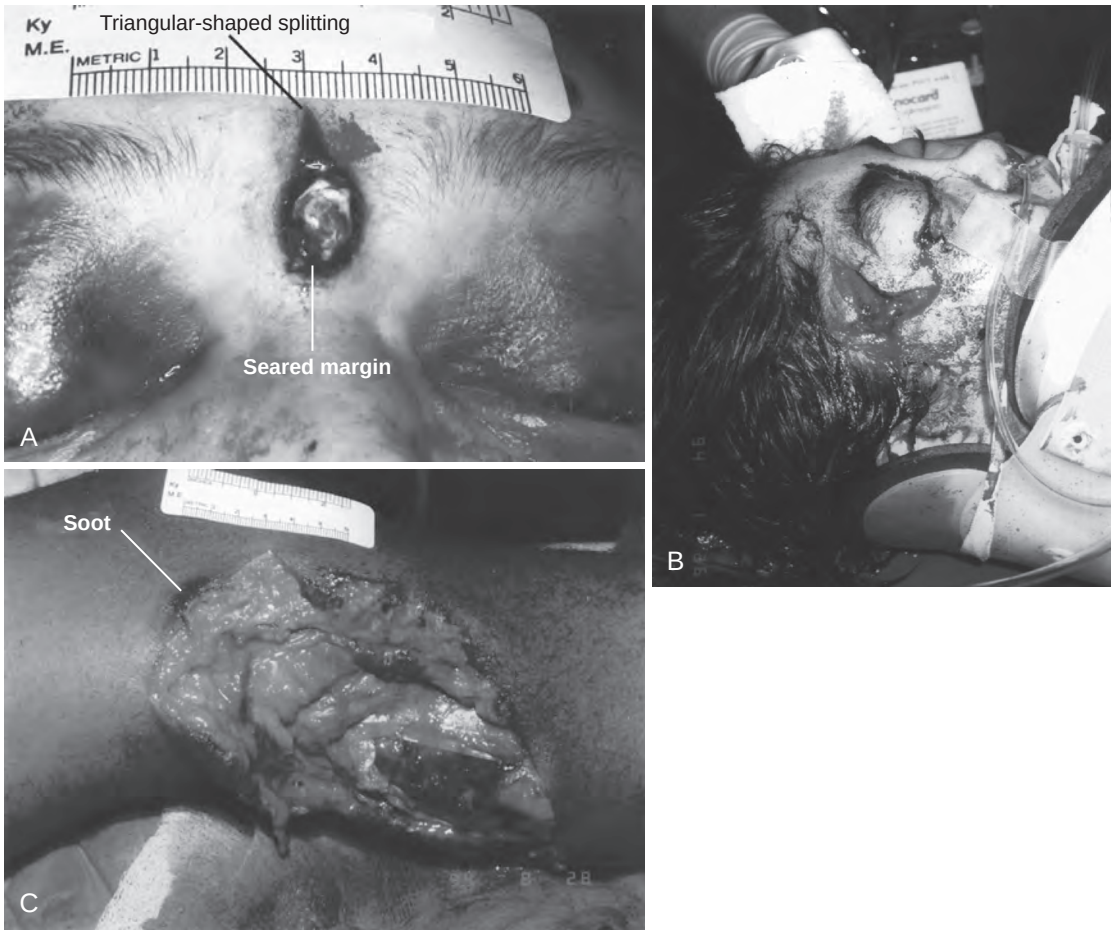

Fig. e1.4. **A,** Tight-contact entrance wound from a .38-caliber revolver. The wound margins are seared from the discharge of hot gases and an actual flame from the end of the barrel. The triangular tear is the result of tissue expansion from the discharge of gases into the tissue. **B,** Tight-contact entrance wound with large stellate tears from a .380 semiautomatic pistol. The large triangular tears are the result of rapid expansion of gases under the skin. **C,** Tangential-contact wound from a 9-mm pistol on the medial aspect of the left calf. The presence of soot at the superior aspect indicates a close range of fire. The patient initially reported that he was shot from a distance of 3 or 4 feet and later admitted that he had accidentally shot himself while withdrawing his pistol from his boot. Large wounds, as seen in **B** and **C,** may be misinterpreted as exit wounds because of their size.

and powder within the wound and a lack of seared wound margins.

In some tight contact wounds, expanding skin is forced back against the muzzle of the gun, leaving a characteristic muzzle abrasion or muzzle contusion (Fig. e1.5). Patterns such as these should be documented before wound débridement or surgery because they are helpful in determining the type of weapon used (revolver vs. semiautomatic).

When a gun's muzzle or barrel is in loose contact with or is angled to the skin, the soot and gunpowder residues are present within and surrounding the wound. The angle between the muzzle and skin determines the soot pattern. A tangential, loose, or near-contact wound produces an elongated searing and soot deposit surrounding the wound.

Discharge of a weapon in contact with clothing results in the gases and soot being deposited between the garment and skin. This results in a diffuse pattern of soot surrounding a wound, with seared margins (see Fig. e1.4C).

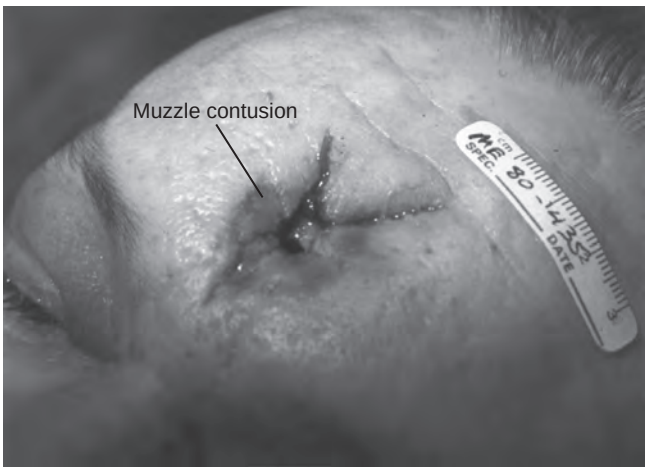

Fig. e1.5. A muzzle contusion is a contusion caused by skin expansion against the barrel of the weapon. Muzzle contusions are associated with contact wounds.

Close-Range Wounds. Close range is the maximum range at which soot is deposited on the wound or clothing. The muzzle to target distance is usually less than 6 inches but may be as much as 12 inches. Beyond 6 inches, most of the soot usually falls away

and does not reach the skin or clothing. The concentration of the soot varies inversely with the muzzle to target distance and is influenced by the type of gunpowder and ammunition used, length of the weapon's barrel, and caliber and type of weapon itself (Fig. e1.6). A precise range of fire (eg, 2 vs. 5 inches) cannot be determined from examination of the wound alone. Because soot can be removed with débridement or wound cleansing, its presence and configuration around the wound should be noted and photographed before débridement unless the patient's clinical condition precludes this attention to detail.

Intermediate-Range Wounds. Tattooing, or stippling, is pathognomonic for an intermediate-range gunshot wound. Tattooing appears as punctate abrasions and is caused by contact with partially burned and wholly unburned pieces of gunpowder (Fig. e1.7). Tattooing or stippling cannot be wiped away. Tattooing rarely occurs on the palms of the hands or soles of the feet because of the thickness of the epithelium.

Tattooing may occur as close as 1 cm to and as far away as 1.3 m from the weapon but is generally found at distances of 60 cm or less. The density of the tattooing and associated pattern depend on the length of the barrel, muzzle to skin distance, type of gunpowder, presence of intermediate objects, and caliber and type of ammunition. Clothing, hair, or other barriers may prevent tattooing from occurring. The presence of partially or entirely unburned pieces of gunpowder and gunpowder residues on clothing or skin aids in determining the range of fire. On rare occasion, pieces of gunpowder can penetrate thin clothing and leave punctate abrasions (Fig. e1.8).

Long-Range Wounds. The distant or long-range wound is inflicted from far enough away that only the bullet makes contact with the skin. There is no tattooing or soot. As the bullet penetrates the skin, the skin is indented, resulting in the creation of an abrasion collar, also termed an *abrasion margin*, *abrasion rim*, or *abrasion ring* (Fig. e1.9). This collar is an abraded area of tissue that surrounds an entry wound as the result of friction between the bullet and epithelium. The width of the abrasion collar varies

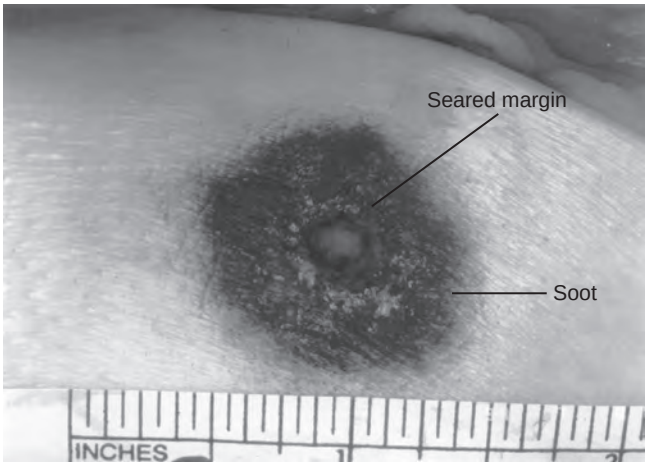

Fig. e1.6. Close-range wound with soot deposition. Soot is associated with a range of fire of 6 inches or less.

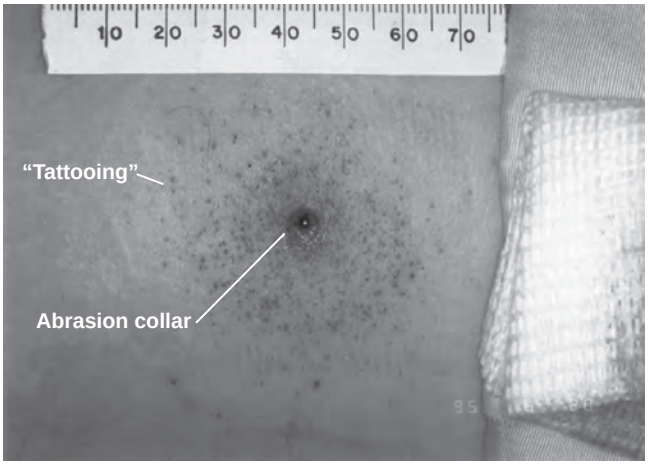

Fig. e1.7. Tattooing results from contact with pieces of unburned gunpowder. These punctate abrasions are associated with an intermediate range of fire, generally less than 36 inches. The density of these abrasions depends on the length of the gun's barrel, distance from the muzzle to the skin, type of gunpowder used, and presence of any intervening objects.

Fig. e1.8. Gunpowder can penetrate thin clothing and deposit tattooing on the skin. A 3-year-old was shot with a .45-caliber round at close range, and pieces of gunpowder passed through the T-shirt.

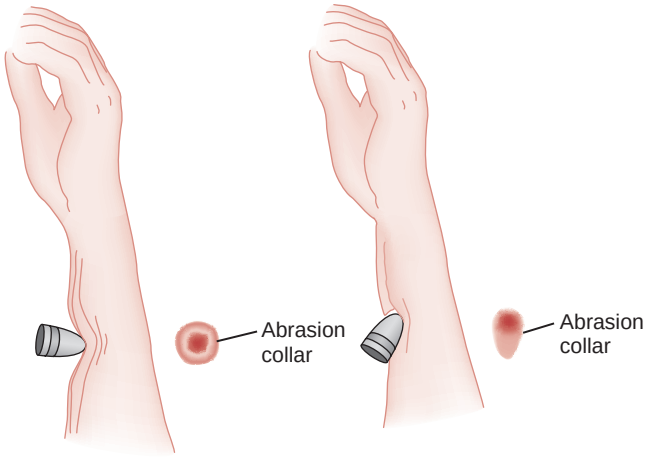

Fig. e1.9. An abrasion collar is the abraded area surrounding the entrance wound created by the bullet when it indents and passes through the epithelium. The collar or rim is the result of friction between the bullet and the epithelium. The width of the abrasion collar will vary with the angle of impact.

with the angle of impact. Most entrance wounds will have an abrasion collar. Entrance wounds on the palms and soles are exceptions because these wounds usually appear slitlike.

The abrasion collar is secondary to friction and is not the result of thermal changes associated with a hot projectile. The abrasion collar of a contact or close-range wound may be undetectable because hot gases and a flame have seared the tissue. When an abrasion collar is the only visible superficial clinical finding present, the term *indeterminate range* describes the range of fire. A wound inflicted from 10 feet will appear the same as a wound inflicted from 100 feet. An exact range cannot be determined with a distant wound.

Determining the range of fire may be complicated when clothing prevents the deposition of soot and powder on the skin. Without the overlying clothing or without information regarding the crime scene, the wound may appear to be from a distant range of fire. In reality, the range may have been close or intermediate. Conversely, a projectile discharged from a distant range of fire may mimic an intermediate range if it strikes an object, such as glass, that fragments. As with unburned gunpowder, when the glass fragments strike the skin, they may also cause punctate abrasions, resulting in pseudotattooing (Fig. e1.10).

Atypical Entrance Wounds. Atypical entrance wounds occur when a bullet encounters an intermediate object, such as a window, wall, or door, before striking the victim. The intermediate object may change the bullet's size, shape, or path. Such changes can result in entrance wounds with large stellate configurations that mimic close-range or contact wounds (Fig. e1.11). Ricochet bullets may also cause atypical entrance wounds. Graze wounds are atypical wounds from tangential contact with a passing bullet.

Handgun Exit Wounds

Exit wounds are the result of a bullet pushing and stretching the skin from the inside out. The skin edges generally are everted, with sharp but irregular margins.

The size of the exit wound is determined by the energy transferred from the bullet to underlying tissue and by the bullet's size and configuration as it exits the skin (Fig. e1.12). When a bullet enters the skin, its configuration may change from its usual nose-first attitude owing to tumbling and yaw. A bullet that exits the skin sideways, or one that has increased its surface area by mushrooming or transferring its energy to underlying bone, will have an exit wound larger than its entrance wound.

Atypical Exit Wounds. A shored exit wound is a wound that has an associated false abrasion collar. If the skin is pressed against or supported by a firm object or surface at the moment the bullet exits, the skin can be compressed between the exiting bullet and supporting surface (Fig. e1.13). Examples of supporting structures include belts, floors, walls, doors, chairs, and mattresses.

Fig. e1.10. Pseudotattooing, or punctate abrasions from glass fragments, not unburned gunpowder, on the medial aspect of the thigh associated with a gunshot wound. The leg was showered with glass fragments after the round penetrated the window pane.

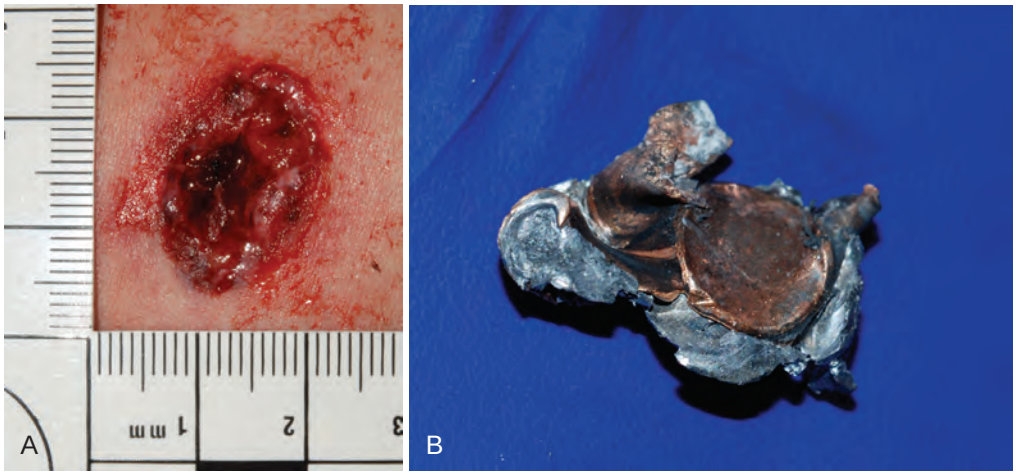

Fig. e1.11. **A,** An atypical entrance wound from impact with a .40-caliber bullet. **B,** The projectile was deformed as it penetrated a windshield.

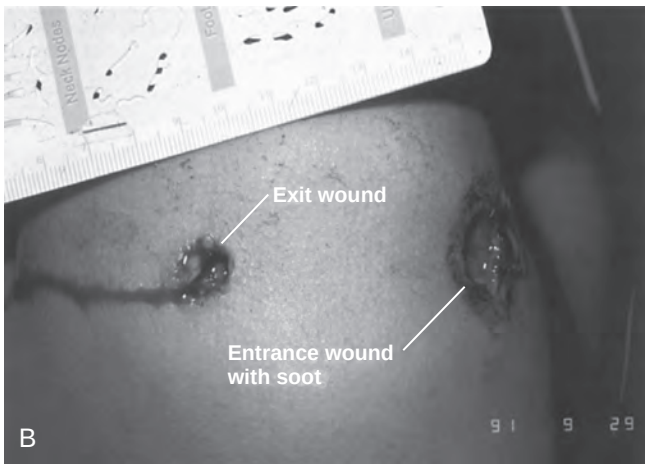

Fig. e1.12. **A,** Slitlike exit wound from a .22-caliber bullet. **B,** Perforating gunshot wound to the left deltoid area, with soot deposition around the larger entrance wound. No soot is present around the smaller exit wound. Exit wounds are not consistently larger than their corresponding entrance wounds.

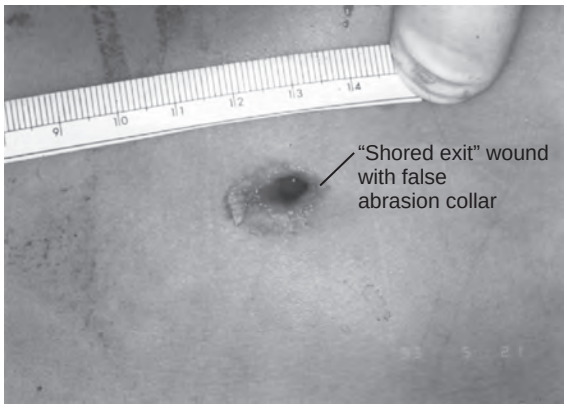

Fig. e1.13. Shored exit wound with a false abrasion collar. This type of wound occurs when the skin in the region of the exiting bullet is in contact with a supporting structure (eg, wall, floor, mattress). The skin is slapped against the supporting structure, which results in a false abrasion collar.

Centerfire Rifle Wounds

Projectiles discharged from centerfire rifles have the potential to inflict massive tissue damage (see Fig. e1.2). Entrance wounds associated with high-velocity, centerfire projectiles do not significantly differ from those of handguns. Entrance wounds will generally exhibit abrasion collars or microtears on the skin surface (Fig. e1.14). Wounds will also have associated soot deposition and tattooing but, because of a number of variables, such as muzzle length, amount of power in a given cartridge, muzzle configuration, and type of gunpowder, the range of fire in rifle wounds is not as clearly defined as in handgun wounds. The determination of an exact range of fire for rifles and shotguns is best established through controlled testing performed by a firearms examiner at a crime laboratory.

High-velocity bullets with jackets and lead cores generally break up into hundreds of fragments, termed a *lead snowstorm*, on entering tissue, resulting in significant tissue damage (Fig. e1.15). If the tissue penetrated is deep, the bullet fragments may fail to exit and remain embedded. It is therefore possible to sustain an injury from a high-velocity round and not exhibit an exit wound. High-velocity rounds with steel cores will almost uniformly exit intact.

Shotgun Wounds

The massive damage caused by slugs may obliterate the abrasion collar usually associated with entrance wounds. Shotgun slugs will almost uniformly exit the body with large exit wounds.

Clinical Features

Patients with firearm injuries have varying presentations, depending on the anatomic location of the injury and type of weapon used. It is important to identify all wounds to guide the determination of the potential missile trajectory and anticipate the other possible injuries. It is also important to consider how the

Fig. e1.14. **A,** An exit wound from a high-velocity rifle round. Exit wounds from high-velocity rounds are generally larger than their corresponding entrance wounds. The large size is a result of energy transfer from the projectile to underlying tissue, with the expelling of tissue, principally bone. **B,** An entrance wound from a high-velocity rifle round. Entrance wounds of high-velocity projectiles will also display an abrasion collar.

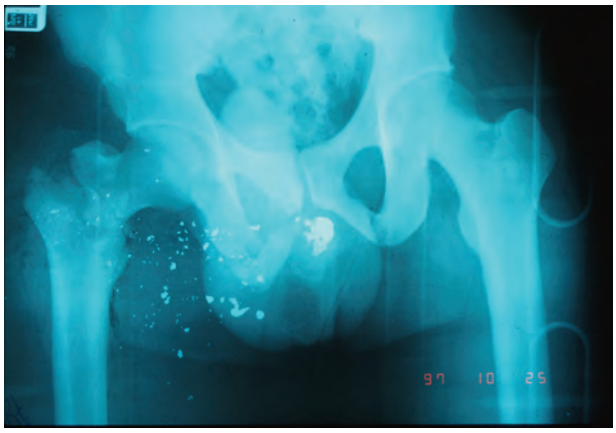

Fig. e1.15. A lead snowstorm from a high-velocity rifle round. High-velocity projectiles have a tendency to fragment into hundreds of tiny particles on contact with bone. This fragmentation contributes to the massive tissue damage associated with these projectiles.

temporary and permanent cavities may manifest anatomically to guide imaging and management.

Patients with injuries to the head and neck often present in critical condition due to the abundance of vital neurovascular structures in this area. Head-injured patients can present in extremis with altered mental status and signs of impending herniation, in which case emergent airway management and resuscitation are necessary. Emergent airway management may also be required in cases with intraoral involvement or a need for operative intervention for other reasons (eg, laparotomy).[23] Neck injuries can present with a multitude of symptoms, depending on the structures affected. Symptoms can run the gamut from asymptomatic to active bleeding (from trauma to the vasculature), dysphonia or hoarseness (due to pharyngeal or tracheal injuries), or hemiplegia or hemiparesis (if the internal carotids are disrupted). Again, urgent airway and bleeding control are required in these cases unless the patient is clinically stable.[23]

Gunshot injuries to the thorax can result in damage to the cardiac musculature, cardiac tamponade, pneumothoraces or hemothoraces, or other mediastinal pathology. Clinical symptoms include shortness of breath, chest pain, tachypnea, hypotension, and altered mental status.

In general, extremities are the most commonly injured anatomic region with nonfatal firearm injuries.[24] Injuries to the extremities could result in fractures, vascular or nerve injury, and compartment syndrome, because bullet tracts do not necessarily decompress fascial compartments.[22] Fractures are associated with vascular and nerve injuries, with isolated fractures increasing the risk for compartment syndrome. Vascular injuries alone are also associated with an increased risk of compartment syndrome and deep vein thrombosis. A combination of fractures and vascular injuries has been shown to increase the risk of wound infection.[24]

Gunshot wounds to the perineum should raise concern for bowel or bladder injury. Patients may not necessarily complain of any symptoms, but findings of gross hematuria or gross blood on rectal examination should indicate that such injuries have occurred.

Again, air rifle injuries deserve a special mention. Although they may seem innocuous, injuries to areas containing vital structures should prompt further investigation because air rifle pellets can cause significant tissue damage. Two recent case series have shown that shots fired from air rifles result in cardiac injury and traumatic brain injury.[12,25]

Diagnostic Testing

The imaging modalities used will differ, depending on the location of the injury. Details of the appropriate diagnostic strategies are outlined in the chapters on trauma (Part II of this text). In brief, most injuries will require computed tomography (CT) imaging to delineate the extent of tissue damage. A noncontrast CT scan of the head can show associated skull fractures, intracranial hemorrhages, or retained missiles. A CT angiogram of the neck is useful to evaluate for injuries to essential neurovasculature or aerodigestive structures.[9] Patients with persistent pain to the posterior neck with negative CT imaging may require magnetic resonance imaging (MRI) to evaluate further for ligamentous pathology. Thoracic injuries often mandate a CT chest scan to assess for injuries to the lungs, heart, and mediastinum, as well as to define the bullet trajectory.[8] Chest x-rays are sensitive for pneumothoraces but are not sensitive or specific for mediastinal injury, which requires more advanced imaging.[8] X-rays can also be used to diagnose diaphragmatic injuries when specific findings are present, such as a visualized herniated viscus (the collar sign) or a nasogastric tube in the stomach above the diaphragm.[8] However, a negative x-ray cannot rule out diaphragmatic injury, and CT imaging is more sensitive and specific.[8] Abdominal or genitourinary injuries will also require CT of the abdomen and pelvis to identify the tissues injured. It is important to keep in mind that thoracic and abdominal injuries occur concurrently in 6% to 42% of cases, with diaphragmatic injuries in 59%, and evidence of trauma to one body cavity should encourage imaging

of the other.[9] A CT urogram or cystogram may be indicated if there is a concern for upper tract or bladder injury respectively. Spinal cord or vertebral injuries are well visualized by MRI or CT, respectively—but note that the metallic nature of most bullets may preclude imaging with MRI.

Differential Diagnosis

There is a limited differential diagnosis for firearm injuries because the mechanism is usually known, often prior to the patient's arrival to the ED. However, patients may sustain multiple injuries, so it is important to be vigilant to avoid missing subtle or smaller concomitant injuries. It is also critical to realize that bullets and bullet fragments may travel, embolize, or cause damage by way of the temporary cavity, so a change in the patient's clinical condition should be trigger an appropriate reevaluation. For example, one case series has shown that an air rifle pellet embolizes to the internal carotid artery, resulting in stroke like symptoms.[26] Another study has shown that delayed stroke symptoms could occur from thrombosis of the internal carotid artery due to the temporary cavity following a gunshot wound.[27] These symptoms are often delayed (in the latter case, the patient was initially asymptomatic), so frequent reevaluation of these patients is valuable.

Management and Disposition

Again, management of patients with gunshot injuries varies by injury location. Resuscitation is key, with immediate and judicious use of crystalloid and/or blood as needed, as well as stabilization of the airway and actively bleeding wounds.

Head and Neck Injuries

In addition to resuscitative measures,, it is important to limit hypoxia and hypotension in head- injured patients with a traumatic brain injury (TBI). Emergent operative procedures may be required to evacuate intracranial hematomas in patients in whom there is significant mass effect, shift, or other evidence of increased intracranial pressure.[9] Neck injuries are managed with emergent intubation, as needed, and control of active hemorrhage. Vessel ligation might also be required if unable to control the hemorrhage with direct pressure.[9] Damage to vital structures may necessitate emergent operative intervention. Patients with penetrating injuries to the neck may also require endoscopy, esophagoscopy, and/or bronchoscopy, depending on the path of the missile.

Thoracic Injuries

Decompression of pneumothoraces, hemothoraces, and hemorrhagic pericardial effusions is usually emergently required. An ED thoracotomy is performed for patients who present in cardiac arrest within 15 minutes of their injury or on arrival to the ED. Tension pneumothoraces or pericardial tamponade should be decompressed emergently, prior to advanced imaging. Mediastinal and aerodigestive injuries should be elucidated by esophagoscopy, bronchoscopy, and possible angiography.[9] Suspected diaphragmatic injuries should also be evaluated with laparoscopy because patients may initially be asymptomatic but may develop bowel herniation and eventual strangulation of the herniated tissue even years later.[8,9]

Abdominal Injuries

Gunshot wounds to the abdomen can be managed expectantly if the patient is stable with no injuries to the peritoneal cavity or with moderate solid organ injuries (grades 1–3 liver or splenic lacerations). However, unstable patients or those with concomitant bowel injuries (including evisceration) or severe splenic or liver lacerations (grade 4 or 5) will require emergent exploratory laparotomy. Genitourinary injuries are often managed after other life-threatening injuries have been addressed, aside from severe renal lacerations (grade 4 or 5), which may require nephrectomy. Urethral injuries are managed with Foley catheter placement before or after the appropriate diagnostic modalities have been performed (retrograde urethrography or retrograde cystourethrography). Intraperitoneal bladder injuries are managed operatively, whereas extraperitoneal injuries are managed with Foley catheter placement and decompression.

Extremity Injuries

Management of these injuries involves irrigation, débridement of devitalized tissue, and traction or splinting of broken extremities.[10,28] Bullet removal is only required in certain cases. It is required for missiles in contact with synovial fluid or within intervertebral disks, given the potential for dissolution and resulting systemic symptoms.[7,11,22] Patients should also be monitored for compartment syndrome, vascular, or neurologic injuries, especially following high-energy injuries.[9,24] Operative intervention is required for patients with unstable fractures, fractures with exposed bone, compartment syndrome, or vascular injuries requiring repair.[22] Transabdominal injuries with pelvic fractures also mandate prophylactic antibiotics.[22,28]

High-energy gunshot wounds with associated fractures are treated as open fractures and are generally treated with prophylactic antibiotics because contaminants can be sucked into the wound due to cavitation.[10,22,28] Low-energy injuries can be managed as closed fractures with superficial débridement and prophylactic antibiotics, although the literature suggests that there are low infection rates with or without antibiotics.[22,28] Intraarticular fractures also appear to warrant débridement.[28]

Soft Tissue Injuries

Soft tissue wounds are managed with irrigation, but wounds are left open. Prophylactic antibiotics are not routinely recommended.[9] However, because high-energy injuries and shotgun wounds produce a significant amount of devitalized tissue, they often require operative ddébridement.[9] Aggressive débridement along the wound tract or path of the projectile is not routinely recommended.[9,11]

Tetanus vaccinations should be updated and tetanus immunoglobulin given to those without prior immunity. Bullet removal is also only indicated for certain extremity injuries (see earlier), for missiles with the potential to embolize, or for those in the myocardium.[11] Prophylactic antibiotics are also not routinely recommended, despite the fact that bullets wounds are not sterile.[11] Indications for prophylactic antibiotics are grossly contaminated wounds, abdominal wounds with hollow viscus injury, intraarticular injuries, intracranial injuries, and high-energy gunshot injuries.[9]

Evidence

A victim's clothing may yield information about a bullet's range of fire and help distinguish entrance from exit wounds.[3] Clothing fibers will deform in the direction of the passing projectile. Gunpowder residues and soot will deposit on clothing as they do on skin. Residue may be invisible to the naked eye, but nitrites and vaporized lead can be visualized with standard forensic staining techniques. Some bullets, as they make initial contact with clothing, leave a lead or lubricant residue that is termed *bullet wipe.*

Articles of clothing removed from a wounded patient need to be placed in separate paper bags to avoid cross-contamination of evidence.[3]

The bullet, bullet jacket, and cartridge case are invaluable for identifying or excluding a suspect weapon. When a weapon is discharged, the discharge imprints multiple microscopic marks on the side of the bullet and on the bottom or side of the cartridge case. The markings result from the bullet's contact with the tool marks, or rifling, in the gun's barrel. These marks are unique to each barrel and are reproducible. These marks are the gun's fingerprint, so to speak. Cartridge case marks are from contact with the firing pin, breech lock, magazine of semiautomatic weapons, and extractor and ejector mechanisms. These microscopic fingerprints can be obliterated by removing a bullet with hemostats or pickups.[3] Therefore, as mentioned earlier, bullets should be handled with gloves, and the tips of surgical instruments should be covered with gauze (Figs. e1.16 and e1.17) or plastic tips (so-called suture booties) to ensure the preservation of these microscopic marks. It is not necessary to place initials or other markings on the bullet if adequate notes are made in the patient's medical record regarding the chain of custody.[3]

Fig. e1.16. To determine whether a projectile was discharged from a specific weapon, firearms examiners use microscopic marks on the surface of the bullet.

Fig. e1.17. Hemostats should be covered with gauze or plastic tips when bullets are being removed. Metal-to-metal contact destroys the microscopic marks used to identify the weapon from which the bullet was discharged.

Radiographs also help locate retained projectiles and may be of evidentiary value in determining the number of projectiles and the direction of fire. It is important to maintain a chain of custody to preserve as much evidence as possible. This should also be documented, ideally on a chain of custody form.[1] There is a new trend of forensic care programs in EDs to facilitate this process.[1] It uses a concept similar to that of sexual assault nurse examiner programs, in which a dedicated forensic staff member is responsible for evidence collection,[1] which should theoretically improve documentation and collection due to her or his specialized training.

Conclusions

The impact of firearm injuries cannot be understated, and it is a tremendous public health issue.[29] Not only do firearms result in significant injuries or fatalities, but they can also have a significant impact in other areas, such as the number of productive years lost for adults and missed school for children and adolescents. They also contribute to health disparities.[21] One study has found that a disproportionate amount of resources is required for gunshot wound patients who require emergency medical services activation.[30] Economically, the estimated lifetime costs for firearm-related injuries (resulting in death, hospitalization, or ED evaluation alone) amounted to over $45 billion in 2010.[13] This does not take into consideration the emotional impact that fatalities have on families and communities as a whole. Therefore, the focus should be on prevention as much as possible to avoid incurring such costs.

A number of organizations, including the American College of Emergency Physicians, American College of Physicians, American Pediatric Surgical Association, and American Academy of Pediatrics have all noted that firearm violence is a significant public health problem and, as such, have advocated for a public health approach to reduce the burden of firearm-related injuries and deaths. Measures suggested include stricter background checks, stronger legislation regarding illegal firearm sales, and limitation of access to children[31] and those with a history of mental illness or substance abuse, as well as patient education about firearm injury prevention, especially in patients at risk.[15,32-36] There is also support for using the ED or outpatient visit following nonfatal injuries as teachable moments to educate patients about future firearm violence.[19] Education of emergency clinicians about appropriate counselling methods may be beneficial, as shown in one recent study with a pediatric training program.[37] Such a public health approach has been successful in reducing the fatalities from motor vehicle trauma and may be a good model to apply to firearm injuries to reduce the burden on society.

FORENSIC ASPECTS OF PHYSICAL ASSAULT

Perspective

Interpersonal violence is a leading cause of death in the United States, particularly among children, adolescents, and young adults. Annually, in the United States, there are more than 16,000 homicides and 1.6 million nonfatal assault injuries requiring treatment in the ED.[38] Rates of violence vary by age, gender, ethnicity, and geographic location. Homicide is the leading cause of death for non-Hispanic blacks from age 1 through 44 years, whereas it is the fifth most common cause among non-Hispanic whites in the same age group. The high rate among African Americans is primary driven by the remarkably high rates among males between

the ages of 15 and 34 years. Differences in child maltreatment rates, as well as other forms of violence, are attributable to underlying risk factors, such as poverty.[13] Urban areas have higher homicide rates than suburban or rural areas. Overall, the proportion of assaults resulting in death has declined markedly since the 1960s, thought to be due to the availability of organized trauma care.[38] It is the emergency clinician's responsibility not only to care for these patients clinically, but also to assist law enforcement with thoughtful documentation of injuries, evidence preservation, and collection.

Accurate documentation of the anatomic location of the injuries makes it easier to determine the implement, tool, or weapon responsible for producing each wound. Descriptions of wounds should include their shape, precise body location, and measured size. Specific characteristics should be noted, such as the presence of other materials, coloration, and patterned injuries. Such pattern injuries of abrasions or contusions may retain some features of the impacting object, possibly allowing it to be identified. Every weapon leaves a mark, design, or pattern stamped or imprinted on or just below the epithelium. The epithelial imprints of these weapons, termed *pattern injuries,* are consistently reproducible. These injuries are classified into major categories according to their source—blunt force, sharp force, thermal, and chemical.

Correct terminology is also important when describing wounds. When referring to blunt force wounds, these injuries are termed *lacerations* caused by blunt force trauma, as opposed to an incised wound or cut, which is the violation of epidermis caused by a sharp instrument that is longer than it is deep. Stab wounds are deeper than they are wide. Also, wounds and bruises should be described as they are seen, and no comment on age or time of occurrence should be documented.

When cutting clothes, avoid cutting through defects caused by sharp force injuries. Clothing items should be placed into paper bags, labeled, sealed, and then turned over to law enforcement. Plastic bags retain moisture and promote the growth of bacteria, which could degrade DNA evidence. Sharp force weapons that are recovered should be wrapped in craft paper or cardboard to protect them from causing injury and sealed for evidence collection.

Conclusions regarding the alleged perpetrator and the mechanism of injury should generally be avoided.

Blunt Force Pattern Injuries

The most common blunt force injury is the contusion, along with abrasions and lacerations. A weapon with a unique shape or configuration may stamp a mirror image of itself on the skin (Box e1.1).

Pattern Contusions

A blow from a linear object leaves a contusion that is characterized by a set of parallel lines separated by an area of central clearing (Fig. e1.18). The blood underlying the striking object is forcibly displaced to the sides, which accounts for the pattern's appearance (Fig. e1.19).

Circular or linear contusions suggest abuse or battery. Circular contusions 1.0 to 1.5 cm in diameter are consistent with fingertip pressure and grab marks (Fig. e1.20). One commonly overlooked anatomic location for fingertip pressure contusions is the medial aspect of the upper arm. The sole of a shoe from a kick or stomp may also leave a pattern contusion that can assist in identifying the assailant (Fig. e1.21).

Some injuries allegedly occur during police custody. Specific pattern contusions can include parallel contusions from a flashlight or night stick. Handcuff or shackle marks are narrow parallel contusions or abrasions on the wrists or ankles. Handcuff and shackle marks are generally more prominent on the lateral aspects of the extremity.

BOX e1.1

Commonly Inflicted Pattern Injuries

Slap marks with digits delineated
Looped or flat contusions from belts or cords
Circular contusions from fingertip pressure
Parallel contusions with central clearing from linear objects
Contusions from shoe heels and soles
Semicircular contusions and abrasions from bite marks

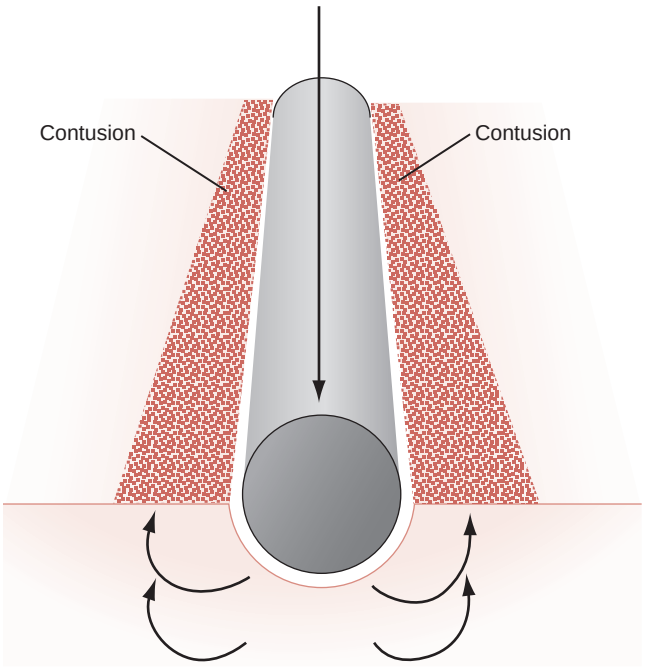

Fig. e1.18. A direct blow from a linear object results in a pattern contusion with central clearing surrounded by parallel linear contusions. The blood directly beneath the impacting object is displaced laterally and accounts for the distinctive contusion.

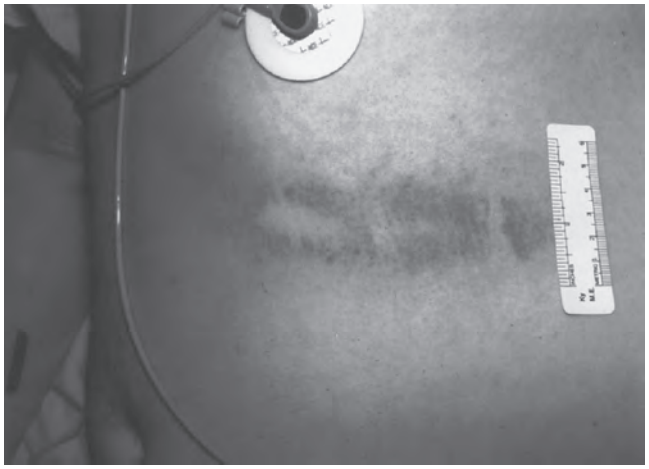

Fig. e1.19. Pattern contusion with parallel lines and central clearing from contact with a baseball bat.

Fig. e1.20. Circular contusions documented on the medial aspect of the upper arm. These injuries resulted from fingertip pressure applied during an assault.

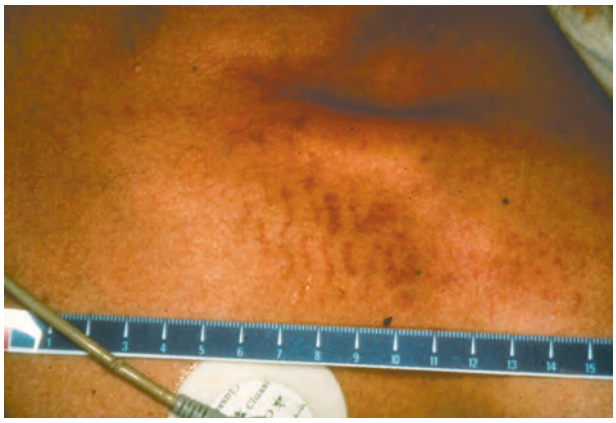

Fig. e1.21. Pattern contusion on the patient's upper chest from the sole of a tennis shoe after a kick. This type of pattern injury can assist in the identification of a suspect and provides a physical connection between the victim and the attacker.

A bite mark may appear as a pattern contusion, abrasion, or combination of both (Fig. e1.22). Bite marks vary greatly in the quality of their identifiable features, depending on the location of the bite and motion of the teeth relative to the skin. Some bite marks may not be readily identifiable as such and may appear as nonspecific contusions, abrasions, or contused abrasions. Generally, adult mikes have an interdental distance of more than 3 cm.

When an acute bite mark is identified, care should be taken not to wash away potential evidence. The skin surface should be swabbed with a sterile cotton-tipped applicator moistened with sterile saline. DNA from buccal cells may also be deposited over an acute bite mark.[3]

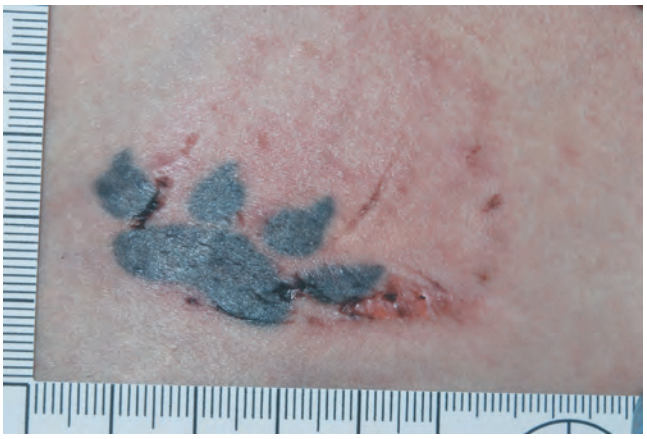

Fig. e1.22. Bite marks may display characteristic arches or appear as a pattern abrasion. A bite mark can be used to identify the assailant if the injury is correctly documented by a forensic photographer or forensic odontologist.

Fig. e1.23. A laceration is the result of blunt trauma and characteristically displays tissue bridges and crushed wound margins.

The emergency clinician should not render an opinion on the age of a contusion. The development of a contusion is based on a number of variables, such as the amount of blunt force applied to the skin, vascularity of the tissue, oxygenation of the extravasated hemoglobin, depth of the hematoma, skin tone, and amount of blood that escapes into the surrounding tissue. As a result, no reproducible standard for the dating of a contusion is possible based on its color.

Pattern Abrasions and Lacerations

A pattern abrasion is a rubbing or scraping away of the superficial layers of the epidermis, which is not important for treatment but may be invaluable from a forensic and injury reconstruction perspective.

A laceration is defined as a tear in the skin produced by blunt trauma and should not be confused with an incised wound produced when a sharp-edged implement (eg, knife, scalpel, piece of glass) is drawn across the skin. A laceration has characteristically abraded or crushed skin edges and unique so-called tissue bridges (Fig. e1.23).

Sharp Force Pattern Injuries

An incised wound is longer than it is deep, and a stab wound is defined as a puncture wound that is deeper than it is wide. The

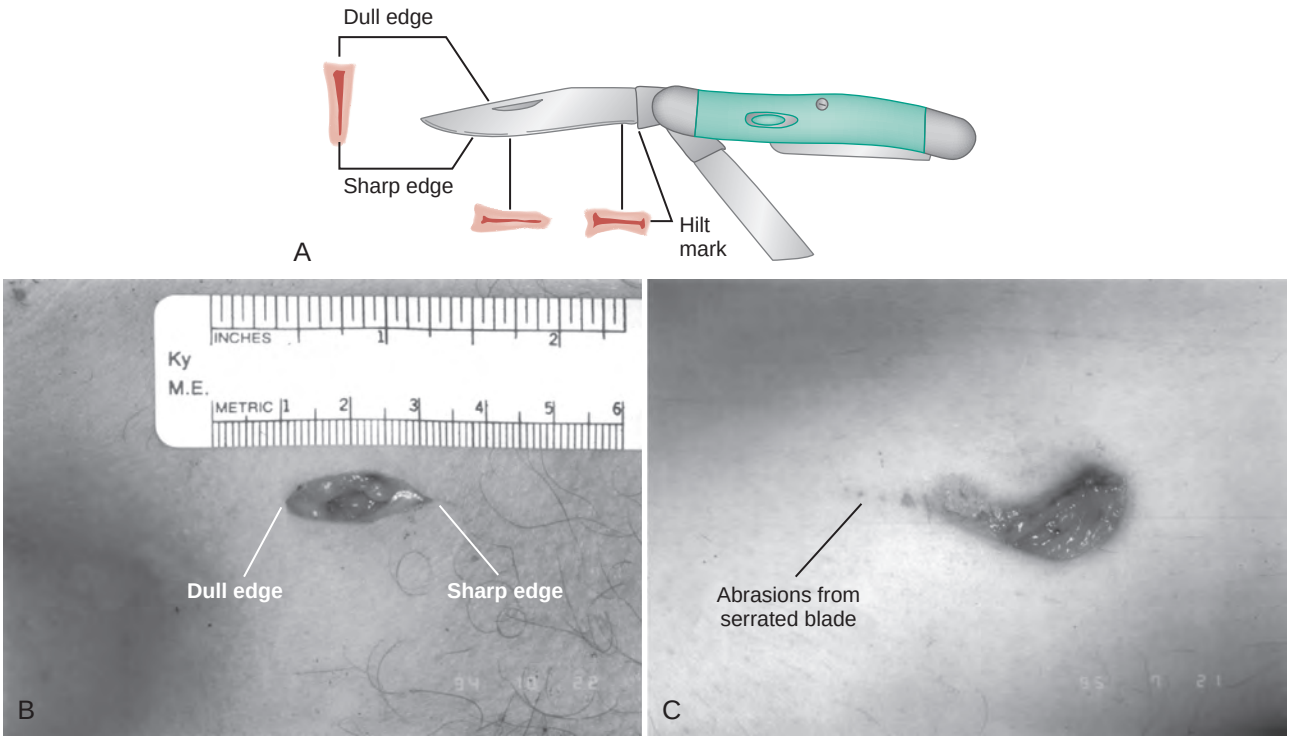

Fig. e1.24. **A,** A single-edged knife blade will cause a wound to be formed with a sharp edge and a dull edge. If the blade penetrates to its hilt, a hilt mark may be seen overlying the sharp edge. **B,** Single-edged stab wound. **C,** Single-edged stab wound made by a serrated blade. Abrasions from the blade's serrated edges are seen on the left margin of the wound.

wound margins of sharp force injuries are clean and lack the abraded edges and tissue bridges of injuries resulting from blunt forces.

Forensic information can be gathered during the examination of a stab wound. Some of the characteristics of a knife blade, single-edged or double-edged, can be determined from visual inspection (Fig. e1.24A, B). Additional blade characteristics, such as serrated versus sharp, can be seen if the blade was drawn across the skin during its insertion or withdrawal (see Fig. e1.24C).

Patients with self-inflicted wounds may visit the ED claiming an accident, self-defense, or assault. When the patient history, injuries, and forensic evidence are not consistent, the forensically informed emergency clinician is in a unique position to extrapolate the truth. With an understanding of how to identify the patterns of self-inflicted knife wounds, the emergency clinician can provide appropriate referrals, conserve resources, and assist law enforcement in the investigation of an alleged crime.

When a patient claims to have been assaulted as the victim of a crime, his or her injuries become physical evidence. It is important for the treating emergency clinician, who may be called as an expert witness, to recognize patterns of self-inflicted injury and to distinguish self-inflicted wounds from those sustained during an assault (Fig. e1.25; Box e1.2). One study of sharp force fatalities that were autopsied has shown that certain patterns may be used to distinguish these injury patterns. Homicide cases show other associated stab and cut wounds or defensive wounds, whereas self-inflicted cases predominantly show isolated cut wounds or associated superficial hesitation marks. Defense injuries most frequently present as cuts on the hands, followed by the forearms, typically on the extensor sides of the forearms and hands, as well as the flexor sides of fingers.[39] Wounds located at the head, limbs, hand, neck, or back are predictive of a homicide, whereas wounds located solely at the anterior parts of the trunk, neck, or forearms are more likely to be self-inflicted. The presences of bone or

Fig. e1.25. The presence of multiple, parallel, superficial incised wounds, sometimes termed *hesitation marks*, are indicators of self-inflicted wounds.

BOX e1.2

Characteristics of Self-Inflicted Knife Wounds

Multiple superficial incisions located on the anterior trunk, arms, and face
Multiple superficial stab wounds located on the anterior trunk, arms, and face
Parallel incisions, in close proximity to each other, on the nondominant side of the body
Sparing of sensitive body areas
Linear or curved incisions toward the hand inflicting the wound
Intact clothing covering the wound
Evidence of prior wounds in repeat offenders

cartilage wounds is predictive of homicide, and their absence is predictive of self-infliction.[40]

Thermal Pattern Injuries

A thermal pattern injury is a common form of abuse or battery, particularly in pediatric patients. They comprise about 5% to 22% of all physical abuse,[41] and pediatric burns represent 6% to 20% of all abuse cases.[42] The history should include the position of the patient relative to the thermal source. This information will help determine whether the injury was intentional or accidental. The location of the burn may also be helpful in delineating the intent of the burn; burns to the gluteal area or perineum are very rarely accidental, whereas burns to the hands and upper trunk are common with unintentional injuries.[41]

Intentional burns tend to be deeper and well demarcated and are often due to hot objects, such as curling irons, cigarettes, or hot liquids.[41] A sharp or clear line of demarcation between burned and unburned tissue characterizes immersion or dipping burns. In contrast, splash burns are characterized by an irregular or undulating line or by isolated areas of thermal injury, usually round or oval in shape, caused by droplets of hot liquid.

The severity of thermal or scald injury depends on the length of contact time and the temperature. Skin damage can result from a number of different mechanisms whereby temperatures in excess of 49° C (120° F)causes cellular damage but, again, the exact temperatures required depend on contact time.[42] Law enforcement routinely measures the household's or institution's water temperature in any investigation involving a scald injury.

It is important to be attentive to concomitant injuries in burn patients, particularly those who are victims of significant violence. These patients may sustain associated injuries, such as fractures, that need to be addressed emergently.[43]

Chemical Injuries

Chemical injuries are a rare means of assault in the United States and Europe but have been noted in countries such as Bangladesh and Jamaica. The victims tend to be female, often following domestic disputes.[42] The most commonly used agents are those found around the home, such as car battery acid, which is usually thrown at the victim. The head, face, and neck are predominantly affected but the fluid may spread to the chest and trunk as well.[42] Patients develop findings consistent with burns from acids or alkalis because cellular damage results from coagulative or liquefactive necrosis, respectively.

Primary management is similar to that for other chemical injuries and consists of prompt removal of contaminated clothing or other materials as soon as possible and irrigation of the affected area with copious amounts of water; tap water has been shown to be adequate for this purpose. Patients may also require rapid resuscitation with intravenous fluids and pain control, with or without airway management. These patients may also develop a significant electrolyte abnormality, such as metabolic acidosis or hypocalcemia, which require close monitoring and treatment.

FORENSIC ASPECTS OF MOTOR VEHICLE TRAUMA

Perspective

Globally, road traffic injuries are estimated to be the eighth leading cause of death.[44] Half of the world's road traffic deaths occur among so-called vulnerable road users, which are motorcyclists (23%), pedestrians (22%), and cyclists (5%), compared with 31% of deaths among car occupants.[45] In vulnerable road users struck by motor vehicles, there is evident gender disparity, with more males affected. In addition, infrequent helmet use, riding against traffic, and use of electronic devices while driving are important factors.[46] In high-income countries, the proportion of deaths in those older than 70 years is noticeably greater than in low- and middle-income countries, likely due to longevity, combined with the greater risks posed by reduced mobility and frailty. Young adults between 15 and 44 years account for 59% of global road traffic deaths, with 77% of those deaths occurring in men.[45] Substance abuse and distracted driving, particularly with cell phone use, are dominant patterns seen in high-risk behavior in motor vehicle crashes (MVCs) and not wearing a motorcycle helmet is deadly for victims of motorcycle crashes. Devastating brain injuries are the leading cause of mortality in MVCs and motorcycle-related deaths.[47-49] For pedestrians and bicyclists, the collision speed of the vehicle and protective devices are obvious factors that influence injury outcome.[50-52] Patterns of injury differ according to the mechanism of injury.

Motor Vehicle Collisions

In MVCs, the head and thorax are the most frequently injured body regions.[53,54] MVCs are associated with approximately 60% to 70% of all cases of blunt chest trauma and are the most common cause of pulmonary contusions.[55] Occupants impact against the dashboard and steering wheel and are more likely to sustain torso injuries.[56] Frontal and near-side crashes are most frequently associated with pulmonary contusion. Occupant weight, body mass index, and number of rib fractures are positively correlated with pulmonary contusion volume. The initial mechanical insult to the chest is followed by a secondary inflammatory response that extends the injury and has been shown to be predictive of ventilatory support, acute respiratory distress syndrome, and pneumonia.[55] Although women are less often involved in MVCs when compared to men, it has been shown that belt-restrained female drivers involved in an MVC are more susceptible to severe injuries, particularly of the chest and spine, when compared to male drivers.[57]

Motorcycle Collisions

In the United States, there has been an overall decrease in the injuries sustained by young adult motorcyclists and an increase in the injuries sustained by middle-aged and older adult motorcyclists. Older adult motorcyclists had the highest rates of hospitalization, followed by middle age, than younger adults. Similarly, older adult motorcyclists had high injury severity scores compared to younger adults.[58] Older adults and middle-aged adults were more likely to sustain internal organ injuries, with head and chest injuries associated with the lowest rate of survival.[52]

Evaluation of Motor Vehicle Collisions

Law enforcement officials investigating an incident involving serious or fatal injuries from a motor vehicle or pedestrian collision may benefit from information regarding injury patterns and the collection of trace evidence from the victim. This information can help determine whether an occupant was a driver or passenger. It may help identify a suspect vehicle involved in a hit and run pedestrian collision or a pedestrian's position (standing or lying) when struck in the roadway.

Determination of a vehicle occupant's role may be simple (eg, if the driver is pinned behind the steering wheel) or complex (eg, if the vehicle's occupants are ejected). Many impaired drivers claim to be passengers. Short-lived evidence or pattern injuries that might be destroyed or altered in the delivery of patient care should optimally be preserved and photographed.

An opinion on an occupant's position should be avoided because an occupant's role is difficult to determine based solely

on history and physical findings in the ED. Such an opinion is best rendered by someone who has examined the scene, vehicle, other occupants, and trace evidence, has reviewed postmortem examinations, and has had the collision reconstructed to determine vehicle dynamics (Box e1.3).

Pattern Injuries

Matching pattern injuries with components within a vehicle often reveals an occupant's position during a portion of the vehicle's collision sequence. Common pattern contusions, abrasions, and lacerations are seen from steering wheels, air bags, air bag module covers, window cranks, radio knobs, door latches, dashboard components, and front and side window glass. An occupant's movement and subsequent contact with a vehicle's components are dictated by the forces applied to the vehicle through its interaction with the environment. Vehicle occupants, restrained or unrestrained, will initially move toward the primary area of impact.

A deployed air bag may induce a pattern abrasion to the face, cornea, forearms, or other exposed tissue. Pattern lacerations, specific fracture patterns, and amputations are seen when the deployed air bag module cover impacts the hand or forearm (Fig. e1.26). The correlation of these injuries and transfer of DNA from the driver or passenger to the deployed air bag are helpful in assessing an occupant's role as driver or passenger.

Laminated glass (windshields) and tempered glass (side and rear windows) produce pattern injuries. The windshield has two layers of glass laminated together with a thin layer of clear plastic sandwiched between. Laminated glass breaks into shards on impact and causes linear incised wounds. Tempered or safety glass is a single layer of glass that breaks into small cubes when fractured, imparting a dicing pattern to the skin (Fig. e1.27).

Trace Evidence

Clothing, shoes, and biologic standards (eg, hair, tissue, blood) may determine an occupant's role. The soles of leather shoes may reveal the imprint of the gas or brake pedal (Fig. e1.28). Preservation of clothing permits the comparison of clothing fibers with

BOX e1.3

Evidence Collection—Driver Versus Passenger

VICTIM

Examine for Pattern Injuries
Steering wheel contusion
Radio knob contusion
Window crank contusion
Striated incised facial wounds
Dicing wounds

Examine Clothing for Transferred Material[a,b]
Glass (front and side windows)
Fibers
Pedal imprint on shoe
Dashboard components

Collect Biologic Standards[b]
Hair
Blood

Collect Clothing Standards[b]
Damage

VEHICLE

Examine for Pattern Damage
Steering wheel
Radio, knobs, dashboard
Window crank, side door
Windshield (laminated glass)
Side and rear window (tempered glass)

Collect Standards
Glass
Carpets and seats
Gas and brake pedals
Broken dashboard components

Examine for Transferred Material of Pedestrian
Hair on windshield and components
Blood on windshield and components

Examine for Transferred Material on Car Occupants
Fabric fibers
Imprinted fabric pattern

[a]Each article of clothing should be collected in a separate paper bag. This avoids cross-contamination, and wet material will dry. Do not collect evidence in plastic bags because moisture will condense within the bag and may degrade biologic material.
[b]Each article should be marked with the patient's name, item collected, date and time collected, location of collection, name of the collector, and name of law enforcement official to whom the evidence was given. This information will preserve the chain of custody.

Fig. e1.26. A traumatic partial amputation of the hand resulted from contact with a deploying air bag module cover.

Fig. e1.27. Sliding skin contact with the tempered glass found in a side or rear window creates dicing lacerations.

those fibers transferred to vehicle components during the collision. Imprints of fabric may also be transferred to components within the vehicle, including the steering wheel. Contact with the windshield often transfers hair and tissue to the glass. Glass collected from within a patient's wound can be matched with a particular window within the vehicle. Air bags can be an excellent source of trace evidence. Examples of transferred evidence include skin, blood, makeup, and hair (Fig. e1.29).

Evaluation of Pedestrian Collisions

Pedestrians impact against various parts of the vehicle and ground and therefore sustain injuries to their arms and legs.[52,56] The injury severity of pedestrians increases exponentially with increased impact speed of the offending vehicle.[52] Crossing at uncontrolled midblock locations results in greater injury severity compared with crossing at a signalized intersection.[59] Alcohol use is a significant risk factor for pedestrians stuck by motor vehicles because these patients are more likely to cross the street in an unsafe manner and sustain more serious injuries.[60] In pedestrians who were seriously injured or killed, driver failure to yield and driver inattention were cited as significant contributing factors.[61] Pedestrians are at high risk for severe TBI, specifically intracranial hemorrhages and contusions and significant skull fractures.[49]

Fig. e1.28. Imprint of a brake pedal on a leather-soled shoe. This information will assist in determining the occupant's role and whether the patient's foot was on the brake or accelerator pedal at the moment of impact.

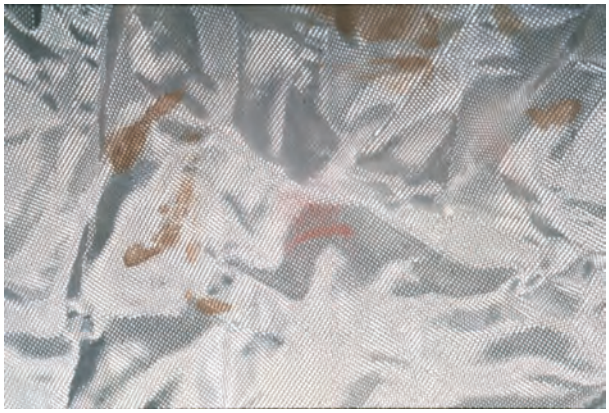

Fig. e1.29. Occupant contact with the air bag often results in the transfer of trace evidence. The presence of blood, tissue, hair, and makeup will assist in the determination of the seating arrangement of a particular occupant.

Pattern Injuries

When struck by the front of a vehicle, a standing adult will sustain bumper injuries, which include open and closed fractures of the tibia and fibula, soft tissue damage, and pattern injuries from vehicle components and hardware.

The height of bumper injuries, measured from the heel and including the height of the patient's shoe, can be correlated with the height of the vehicle's bumper to determine whether the vehicle was braking at the moment of impact. Application of the brake results in the dipping of a vehicle's front end. The presence or absence of braking may help determine the driver's intent. The presence of bumper injuries at one height on one leg and at another height on the other may indicate that the pedestrian was walking or running at the moment of impact, with one leg elevated. Examination may show lateral striations or abrasions when a patient has been dragged.

A victim who is struck from behind may have pattern contusions on the calf or thigh (Fig. e1.30), whereas pattern contusions from a grill on the anterior aspect of the thigh indicate that the

Fig. e1.30. **A,** A pattern imprint contusion on the posterior aspect of a pedestrian's right thigh was the result of contact with the vehicle's grill. The location of the contusion provides information about the configuration of the patient at the moment that the car struck him. The patient was struck from the rear. **B**, The grill of the striking vehicle.

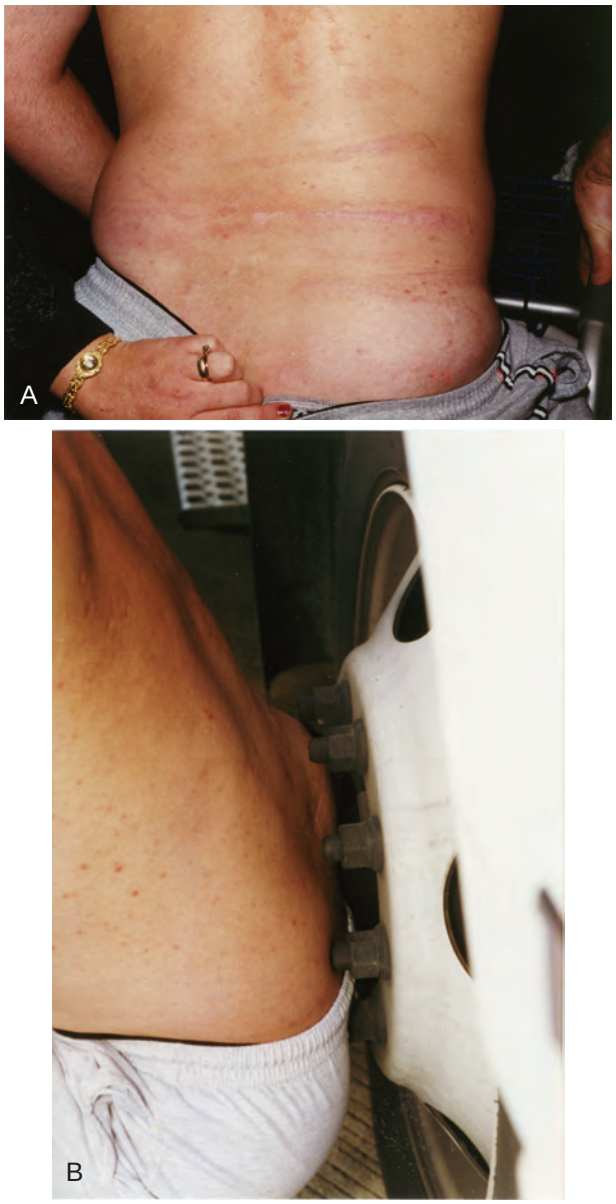

Fig. e1.31. **A,** Three horizontally oriented wounds were noted on the back of a pedestrian struck by a semi–tractor trailer on a highway while changing a flat tire. **B,** The pattern injury was matched to the lug nuts of the front right wheel.

pedestrian was standing and facing the vehicle. Pedestrians struck by a glancing portion of a vehicle may also display a pattern injury (Fig. e1.31). Victims who are run over may display a tire tread pattern (Fig. e1.32). Tire marks and the absence of bumper injuries suggest that the patient was supine or prone in the roadway before he or she was run over (Box e1.4).

Law Enforcement Exemptions to the Health Insurance Portability and Accountability Act

Title 45, Part 164, of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 permits hospitals to disclose

Fig. e1.32. Tire tread imprints on the skin indicate that this victim of a hit and run collision was on the ground when he was hit.

to investigating law enforcement agencies specific information regarding a victim or suspect, without patient consent. Section 45 CFR 164.512 permits the release of protected health information, without a court order, "in response to a law enforcement official's request for such information for the purpose of identifying or locating a suspect, fugitive, material witness, or missing person."[62] A hospital or emergency clinician may disclose the information listed in Box e1.5 only to an investigating law enforcement officer.

KEY CONCEPTS

- Knowledge of wound mechanics and production, as well as wound appearance, can provide practicing emergency clinicians with important clues regarding the forensic interpretations of injuries.
- Wounds and injuries should be diagrammed and photographed.
- The medical record should accurately document objective findings associated with a patient's wounds. Emergency clinicians should not speculate about their mechanism or the cause.
- Any evidence collected during the course of treatment must be documented in the medical record, including to whom the evidence was given, for the chain of custody to be preserved.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

BOX e1.4

Evidence Collection—Pedestrian Collisions

VICTIM

Examine for Pattern Injuries
Height of bumper injuries
- Contusion
- Fracture
- Head and neck injuries
- Crush injuries

Examine Clothing for Transferred Material[a,b]
Paint
Glass (windshield, headlight)
Oil or grease

Collect Biologic Standards[b]
Hair
Blood or tissue

Collect Clothing Standards[b]
Damage or tears

VEHICLE

Examine for Pattern Damage
Bumper height and damage
Specific components
Windshield damage
Wheels and undercarriage

Collect Standards
Paint
Glass
Oil or grease

Examine for Transferred Material of Pedestrian
Hair
Blood or tissue

Examine for Transferred Material on Vehicle
Fabric fibers
Imprinted fabric pattern

[a]Each article of clothing should be collected in a separate paper bag. This avoids cross-contamination, and wet material will dry. Do not collect evidence in plastic bags because moisture will condense within the bag and may degrade biologic material.
[b]Each article should be marked with the patient's name, item collected, date and time collected, location of collection, name of the collector, and name of law enforcement official to whom the evidence was given. This information will preserve the chain of custody.

BOX e1.5

Law Enforcement Exemptions to the Health Insurance Portability and Accountability Act (HIPAA)[a]

- Name and address
- Date and place of birth
- Social security number
- ABO blood type and Rh factor
- Type of injury
- Date and time of treatment
- Date and time of death, if applicable
- Description of distinguishing physical characteristics, including height, weight, gender, race, hair and eye color, presence or absence of facial hair (beard or moustache), scars, and tattoos

[a]45 CFR 164.152.

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CHAPTER e1: QUESTIONS & ANSWERS

e1.1. When documenting a gunshot wound, it is important to do which of the following?
- **A.** Describe the appearance, physical characteristics, and location of wounds.
- **B.** Describe the bullet trajectory.
- **C.** Determine the type of bullet used.
- **D.** Estimate the caliber of the bullet.
- **E.** Interpret the wounds as "entrance" or "exit."

Answer: A. Emergency clinicians should not identify wounds as "entrance" or "exit." Instead, their charting should include a detailed description, using appropriate forensic terminology, of the wound's characteristics and location without speculating about its function or the caliber or type of bullet (projectile) used to create it.

e1.2. A young woman presents with a gunshot wound to her arm. She has good pulses and sensation distal to the wound. On inspection of the wound, you notice a black material, which can be wiped away, surrounding the wound. This most likely indicates which of the following?
- **A.** The barrel of the gun was between 12 and 24 inches (intermediate range) away.
- **B.** The barrel of the gun was within 6 inches (close range) of the skin.
- **C.** The distance between the barrel of the gun and the skin cannot be determined.
- **D.** The patient was initially wearing a dark shirt.
- **E.** This is an exit wound.

Answer: B. In close-range wounds (6 inches or less), the carbonaceous material created from the burning of gunpowder will deposit on skin and clothing. The carbonaceous material is called soot and can be easily wiped away from wounds.

e1.3. Tattooing, associated with a gunshot wound of entrance, is pathognomonic for which of the following?
- **A.** Close-range wound
- **B.** Contact wound
- **C.** Distant-range wound
- **D.** Indeterminate-range wound
- **E.** Intermediate-range wound

Answer: E. Tattooing, or stippling, is pathognomonic for an intermediate-range gunshot wound. It appears as punctate abrasions and is caused by contact with partially burned and wholly unburned pieces of gunpowder. Tattooing or stippling cannot be wiped away and will gradually resolve over several days. Intermediate range is defined as 48 inches or less.

e1.4. A 23-year-old woman presents after having been physically and sexually assaulted by an unknown assailant. In addition to multiple abrasions and brown contusions, she has a bite mark on her left shoulder. Which of the

following is not appropriate in your evidence collection procedures and evaluation of this patient?

A. Estimating the age of the contusions based on their color
B. Measuring and documenting each visible injury on a diagram
C. Preserving the condition of the bite mark until after a forensic examination
D. Swabbing the bite mark with a sterile cotton-tipped applicator moistened with sterile water or saline
E. Taking photographs of the bite mark and each injury

Answer: A. When an acute bite mark is identified, take care that critical evidence is not washed away. The skin surface should first be swabbed with a sterile cotton-tipped applicator moistened with sterile saline. Swabbing the area may reveal the assailant's DNA present in dried saliva. Remember, a contusion's color is never a predictor of its age. The emergency clinician may be asked to render an opinion regarding the age of a contusion. Because contusions develop as a result of multiple variables, there is no reproducible standard for dating them.

e1.5. When managing a gunshot wound victim, which of the following is not important for forensic evidence collection?

A. Do not clean the hands with alcohol or Betadine.
B. If soot is noted on the hands of the victim, cover with paper bags.
C. Maintain a chain of evidence.
D. Place each article of clothing in a separate paper bag.
E. Use metal forceps to handle a bullet to prevent contamination.

Answer: E. Never remove a bullet with metal hemostats or pickups because metal tools can obliterate the microscopic markings (the telltale fingerprint) of the gun from which it was shot. A victim's clothing may hold the answer to critical questions, such as "How far away was the assailant who fired the weapon?" and "Which hole is the entrance and which the exit?" Articles of clothing removed from a wounded patient should be placed in separate paper bags to preserve the trace evidence on them and to avoid accidentally transferring evidence from one article to another (cross-contamination). Always cover a patient's hands with paper bags when the presence of soot is suspected. A gunshot residue test may determine whether a victim or suspect has been in close proximity to a weapon that has been fired. Factors that decrease the sensitivity of gunshot residue tests include washing the skin with alcohol or Betadine.

CHAPTER e2

Injury Prevention and Control*

Katherine Bakes

PRINCIPLES

History of Injury Prevention

Current State of Injury Prevention

Injury Epidemiology and Documentation

Risk Assessment

Motor Vehicle Collisions

Behavioral and Comorbid Risk Factors

Hospital-Based Violence Intervention Programs

Brief Emergency Department Interventions

SPECIFIC ISSUES AND DISORDERS

Acute Care

Firearm-Related Injuries

Emergency Medicine Leadership: Advocacy of Public Policy

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

KEY CONCEPTS

- The Haddon Matrix addresses injury prevention by focusing on the environment, agent inflicting harm, and at-risk populations. Key tenets to this injury prevention model include understanding of the following: (1) injuries are predictable; (2) they follow typical patterns (eg, by age or gender); and (3) reliance solely on human factors for prevention has significant limits.
- The E-code is a system for identifying the cause of injury according to the International Classification of Diseases, Clinical Modification, and allows for systematic tracking of harmful agents.
- Proper use of lap and shoulder belts reduces the risk of death and severe injury to front seat passengers by 50%.
- Ten percent of fatal motor vehicle collisions and 17% of injury collisions are associated with distractions.
- Hospital-based violence intervention programs have been shown to decrease recidivism to the emergency department for recurrent violent injuries and decrease recidivism to the criminal justice system; hospital-based violence intervention programs have been found to be cost-effective.
- Firearm-related injuries are more prevalent among countries with higher rates of gun ownership. The US has the highest rate of gun ownership, with 89 guns/100 persons and the highest mortality rate attributed to firearm injuries of developed countries (eg, 40 times higher than that of the UK).

CHAPTER e2

Injury Prevention and Control

Katherine Bakes

PRINCIPLES

Over 40 million people are treated in US emergency departments (EDs) for injuries annually, and approximately 30% of ED visits is injury-related.[1] Injury is the fourth leading cause of death for all age groups and the leading cause for those aged 1 to 44 years (Table e2.1). The major causes of injury include falls, motor vehicle collisions (MVCs), gunshots, suffocation, and poisonings. In addition to the emotional cost of disability and lost lives, the monetary cost of injury-related medical care in the United States is estimated at approximately $150 billion annually.[2] Because the emergency care system may be the injured patient's only contact with the health care system, emergency clinicians have an opportunity to provide interventions and secondary prevention services.

History of Injury Prevention

Decreasing personal injury is a goal of modern public health. However, until the 1950s, unintentional injuries were attributed primarily to human error, and prevention was based on educating people to act safely. Safety design flaws were not considered when manufacturing roads, motorized vehicles, and other consumer products. From a public health perspective, this is analogous to supplying untreated tap water to homes and relying on educating people to purify their drinking water to prevent cholera.

In the 1920s, attributing vehicle collisions to poor driver performance led to mandatory licensing of drivers. In the 1930s, when it was learned that vehicle collisions could be caused by mechanical factors, President Roosevelt called for automobiles to be made more "crashworthy." In 1942, Hugh DeHaven, a former World War I pilot turned physiologist, pondering his own survival in an airplane crash when another occupant had been killed, suggested structural provisions to vehicles that would reduce injuries in collisions. Also in the 1940s, an epidemiologist named John Gordon suggested that injuries have epidemic patterns, seasonal variation, long-term trends, and demographic distribution and can be examined with methodologies applied to infectious diseases. Gordon also believed that similar to other diseases, injury results from the interaction of the agent inflicting harm, host, and environment, a concept known as the epidemiologic triad.

In the 1960s, injury analysis began to consider three phases—preinjury, injury, and postinjury, allowing specific interventions to target specific phases. William Haddon, the first physician administrator for the National Highway Traffic Safety Administration (NHTSA), developed a comprehensive public health framework for injury prevention in 1970, referred to as the Haddon Matrix. In this model, modifiable factors include risk factors of the individual and the environment, as well as risks of the agent inflicting harm (eg, motor vehicles).

In 1985, the publication *Injury in America: A Continuing Public Health Problem,* by the National Research Council and Institute of Medicine, called on leaders in public health and the health care community to address the injury epidemic. With the establishment of the National Center for Injury Prevention and Control (NCIP) in the Centers for Disease Control and Prevention (CDC), injury prevention was adopted by the disease control community. In 2009, the NCIP published its research agenda, which included the need for acute care injury research.[3]

Current State of Injury Prevention

Prevention of injury requires principles that have been successfully applied to other diseases, necessitating a broad interdisciplinary approach, including the medical community, public health, policy makers, law enforcement, and educated citizens (Box e2.1). Similar to other disease models, risk of injury is dependent on host factors (eg, seat belt use), external human factors (eg, driver from another car runs a red light), and environmental factors (eg, an icy road). Effective injury prevention strategies include (1) decreasing environmental risk factors, (2) enhancing protective factors, and (3) removing or modifying physical risks (eg, gun control).

Injuries are preventable. Understanding the risks of injury is paramount for developing prevention strategies and improving outcomes. Individual risk factors comprise static (or fixed) and dynamic (or changeable) risk factors. Static factors include age, gender, size, current stage in development, and past traumatic events; dynamic factors include mental or behavioral dysfunction amenable to therapy, substance use, social influences (eg, positive or negative peer influences), and other lifestyle choices (eg, decision whether to own or carry a weapon). Risks for injury and death vary by age (see Table e2.1). Environmental factors can also be modified to reduce injury risk, such as implementing safer road designs and lighting to prevent MVC g-force, removing throw rugs to prevent falls, placing fences around pools and railings around elevated surfaces, and separating bicycle paths from roadways. For children, effective strategies to reduce the risk of any injury should take into account the child's developmental stage.

As defined above, the Haddon Matrix addresses injury prevention by focusing on the environment, agent inflicting harm, and at-risk populations. Table e2.2 illustrates use of the Haddon Matrix to reduce MVC injuries. Key tenets to this injury prevention model include understanding of the following: (1) injuries are predictable; (2) they follow typical patterns (eg, by age or gender); and (3) reliance solely on human factors for prevention has significant limits. After key collaborations are formed, injury countermeasures can be implemented using one of the three Es: ***e***ducation, ***e***nforcement of laws, and ***e***ngineering modification of hazardous devices and environmental conditions.

Traditionally, emergency clinicians have focused on treating the patient after an injury has occurred. However, injury control techniques can be incorporated into emergency medicine practice. Recognizing that the emergency department (ED) provides a unique opportunity to identify and intervene in high-risk behaviors, many EDs now provide targeted risk assessments and clinically based interventions. Some of these assessments and interventions are mandated by federal regulators (eg, The Joint Commission requires EDs to have written protocols in place for identifying and treating survivors of domestic violence). A

TABLE e2.1

Ten Leading Causes of Death by Age Group, United States, 2014

	AGE GROUPS										
RANK	**<1**	**1–4**	**5–9**	**10–14**	**15–24**	**25–34**	**35–44**	**45–54**	**55–64**	**65+**	**TOTAL**
1	Congenital Anomalies	Unintentional Injury	Unintentional Injury	Unintentional Injury	Unintentional Injury	Unintentional Injury	Unintentional Injury	Malignant Neoplasms	Malignant Neoplasms	Heart Disease	Heart Disease
	4,746	1,216	730	750	11,836	17,357	16,048	44,834	115,282	489,722	614,348
2	Short Gestation	Congenital Anomalies	Malignant Neoplasms	Suicide	Suicide	Suicide	Malignant Neoplasms	Heart Disease	Heart Disease	Malignant Neoplasms	Malignant Neoplasms
	4,173	399	436	425	5,079	6,569	11,267	34,791	74,473	413,885	591,699
3	Maternal Pregnancy Comp.	Homicide	Congenital Anomalies	Malignant Neoplasms	Homicide	Homicide	Heart Disease	Unintentional Injury	Unintentional Injury	Chronic Low. Respiratory Disease	Chronic Low. Respiratory Disease
	1,574	364	192	416	4,144	4,159	10,368	20,610	18,030	124,693	147,101
4	SIDS	Malignant Neoplasms	Homicide	Congenital Anomalies	Malignant Neoplasms	Malignant Neoplasms	Suicide	Suicide	Chronic Low. Respiratory Disease	Cerebrovascular	Unintentional Injury
	1,545	321	123	156	1,569	3,624	6,706	8,767	16,492	113,308	136,053
5	Unintentional Injury	Heart Disease	Heart Disease	Homicide	Heart Disease	Heart Disease	Homicide	Liver Disease	Diabetes Mellitus	Alzheimer's Disease	Cerebrovascular
	1,161	149	69	156	953	3,341	2,588	8,627	13,342	92,604	133,103
6	Placenta Cord. Membranes	Influenza & Pneumonia	Chronic Low. Respiratory Disease	Heart Disease	Congenital Anomalies	Liver Disease	Liver Disease	Diabetes Mellitus	Liver Disease	Diabetes Mellitus	Alzheimer's Disease
	965	109	68	122	377	725	2,582	6,062	12,792	54,161	93,541
7	Bacterial Sepsis	Chronic Low Respiratory Disease	Influenza & Pneumonia	Chronic Low Respiratory Disease	Influenza & Pneumonia	Diabetes Mellitus	Diabetes Mellitus	Cerebrovascular	Cerebrovascular	Unintentional Injury	Diabetes Mellitus
	544	53	57	71	199	709	1,999	5,349	11,727	48,295	76,488
8	Respiratory Distress	Septicemia	Cerebrovascular	Cerebrovascular	Diabetes Mellitus	HIV	Cerebrovascular	Chronic Low. Respiratory Disease	Suicide	Influenza & Pneumonia	Influenza & Pneumonia
	460	53	45	43	181	583	1,745	4,402	7,527	44,836	55,227
9	Circulatory System Disease	Benign Neoplasms	Benign Neoplasms	Influenza & Pneumonia	Chronic Low Respiratory Disease	Cerebrovascular	HIV	Influenza & Pneumonia	Septicemia	Nephritis	Nephritis
	444	38	36	41	178	579	1,174	2,731	5,709	39,957	48,146
10	Neonatal Hemorrhage	Perinatal Period	Septicemia	Benign Neoplasms	Cerebrovascular	Influenza & Pneumonia	Influenza & Pneumonia	Septicemia	Influenza & Pneumonia	Septicemia	Suicide
	441	38	33	38	177	549	1,125	2,514	5,390	29,124	42,773

HIV, Human immunodeficiency virus; *SIDS,* sudden infant death syndrome.
Data from the National Center for Health Statistics, National Vital Statistics System http://www.cdc.gov/injury/images/lc-charts/leading_causes_of_death_age_group_2014_1050w760h.gif.

BOX e2.1

Multidisciplinary Team Approach to Injury Control: Prevention, Acute Care, and Rehabilitation

PREVENTION
Epidemiology
Biomechanics
Education
Public policy
Law enforcement
Engineering
Outcomes research
Emergency preparedness

ACUTE CARE
Trauma system
Emergency medical services
Emergency department care
Hospital care
Clinical guidelines
Clinical prevention services
Outcomes research

REHABILITATION
Physical therapy
Occupational therapy
Mental health providers

BOX e2.2

Injury Control in Emergency Medicine Practice

CLINICAL PREVENTIVE SERVICES
Document injury information in the medical record.
Ensure that medical records of injury cases contain E codes.
Assess behavioral and comorbid risk factors for future injury.
Provide risk screening, counseling, and referral.
Assess biomechanical risk factors in individual patients.
Use biomechanical risk factors for directed evaluation of injured patients.
Provide systematized acute trauma care.

POPULATION HEALTH, RESEARCH, AND POLICY
Participate in and advocate for inclusive trauma systems.
Direct and advocate for rapid, competent emergency medical services response.
Lead efforts in policy development, implementation, and evaluation.
Lead efforts in educating high-risk groups.
Lead efforts to address and modify the environment to reduce risk of injury.
Collaborate in multidisciplinary research to reduce injury risk and to improve care.

TABLE e2.2

Typical Haddon Matrix (Constructed for Motor Vehicle Injury)

PARAMETER	HOST (DRIVER)	AGENT (CAR)	ENVIRONMENT
Pre-event (before the collision)	Alcohol use Fatigue Experience and judgment	Brake condition Tire quality Center of gravity Load weight	Visibility of hazards Road curvature and gradient Surface coefficient of friction Shoulder height
Event (during the collision)	Medications Motor skills Cognitive function Vision	Speed capacity Visual obstructions Speed at impact Vehicle size	Intersections, access control Weather Signalization Speed limits
Postevent (after the collision)	Age-related event processing Physical condition Medications Social situation	Load containment Deformation zones Fuel system integrity	911 access EMS response Triage and transfer protocols Nearby level 1 trauma center

EMS, Emergency medical services.
Adapted from Baker SP, O'Neill B, Ginsburg MJ, Li G: The injury fact book, ed 2, New York, 1992, Oxford University Press.

rational approach to improve injury control in a community (Box e2.2) requires that clinicians from a variety of specialties (eg, emergency clinicians, surgeons, pediatricians, psychiatrists) assume specific roles and activities in promoting injury control.

Injury Epidemiology and Documentation

Accurate data are essential to understanding the characteristics of a disease—its endemic populations, cyclic variations, geographic characteristics, and effectiveness of interventions. Consistent and comprehensive data should be gathered across the population of injured patients. Data can then be used for hypothesis testing, hypothesis generation, ongoing monitoring of disease patterns and characteristics, and understanding of outcomes of interventions.

Until recently, injury data were mostly limited to mortality data collected by coroners and medical examiners. For example, the Fatal Analysis Reporting System, a comprehensive data set on all car collision deaths in the United States, was established by the NHTSA in 1975 to examine the epidemiology of MVCs. Because death is uncommon compared with the large number of people injured, conclusions based solely on mortality data are limited. The advent of trauma center registries in the 1980s increased the availability of data. Because these data are skewed toward the most severe injuries, the conclusions based on these data are still limited when generalized to all injured people. Most injured patients (almost 90%) are treated and discharged from the ED.[4] Many of these patients experience significant morbidity and incur significant cost to society.

One of the most important data elements for understanding injury is the E code, which is documented in the medical record. The E code is a system for identifying the cause of injury according to the International Classification of Diseases, Clinical Modification, and allows for systematic tracking of harmful agents. Several states have mandated documentation of E codes for all emergency department discharges; however, the completeness of this documentation is variable due to incompletely documented patient records.[5]

E-coded hospital records can provide the who, what, and when of injury. Hospital records can help identify high-risk geographic areas for targeted prevention and intervention measures. However,

best practice would incorporate a comprehensive multiagency approach. Location of injury data may be available from emergency medical services (EMS), police, local government, and trauma registries. Statewide injury data linkages exist in some states and are available for surveillance information and research for unintentional and intentional injuries. For example, the Crash Outcome Data Evaluation System uses probabilistic linkage to create a database of police, hospital, EMS, and ED information for MVCs.[6]

Investigators in Wales have demonstrated the effectiveness of a collaborative approach. After discovering that only 50% of assaults presenting to their ED in the city of Cardiff matched police records, the Cardiff Violence Prevention Group worked to reconcile future missing assault data. ED staff collected information on location of assaults, sharing raw anonymous data with local police on a monthly basis.[7] Information was used to target violence prevention strategies in high-risk areas of the city, and violence rates over 5 years fell by almost one-third, compared to a rise of almost two-thirds in 14 similar cities.[7] This was recently validated in another English community,[8] and efforts to implement this program in the United States are ongoing.

Location data are also likely to be useful for environmental modification through engineering enhancements, police enforcement, or hazard removal. Linkage of these records to patient visits for specific research studies or surveillance is the next step in gaining a comprehensive understanding of the epidemiology of injury. Computer-based geographic information systems can be used to study injury locations with minimal training and resources, identifying areas with injury clusters for focused prevention efforts.

Risk Assessment

Ascertaining the forces released on the patient during a blunt injury (eg, car collision, fall) or penetrating injury (eg, gunshot, stabbing) leads to a directed approach to injury management. Extensive research has been done with crash dummies, mathematical models, and computer models to understand the mechanical forces applied in injury and human impact tolerance. Whether more accurate information regarding energy transfer (eg, actual kinetics of the collision from an on-board vehicle monitoring system vs. a first responder estimate of passenger space intrusion) will inform clinical decision making remains unclear.

Injury occurs when energy is delivered to the host in levels that exceed tissue and organ tolerance. This energy can be expressed in g-force. For example, the g-force that results from a MVC can be expressed by the following formula:

$$g = \Delta v^2/(\text{stopping distance} \times k)$$

where Δv is the change in velocity, stopping distance is the distance over which the change in velocity occurs, and k is a constant. The g-force is inversely related to stopping distance; doubling the stopping distance reduces the g-force by half, but halving it quadruples the force. Thus, less g-force is applied if a lower velocity reduction occurs—as in braking to slow the vehicle before impact—or the reduction occurs over increasing distance, a key focus of vehicle design that allows the vehicle to deform during a collision. This understanding has led to myriad engineering solutions, such as interior padding, collapsible steering columns, vehicle crumple zones, water barrel barriers at bridge abutments, and flexible guardrails. One of the best examples of this principle is vehicle air bags, which result in increased occupant stopping distance during a collision and were credited with saving nearly 40,000 lives by 2013.[9]

With any new safety countermeasure, there may be unintended consequences. First-generation air bags deploy with tremendous force at speeds of 140 to 200 mph. Such forces can be lethal to children in the front passenger seat, especially when unrestrained by safety belts, or when seated in rear-facing infant seats. A new generation of advanced, less forceful air bags has been in use since the late 1990s to reduce air bag–associated injuries.

Motor Vehicle Collisions

MVCs are the leading cause of death for children older than 24 months in the United States (see Table e2.1). Giving patients the necessary data for them to make an accurate self-assessment about their risks is the essence of patient behavioral interventions. When feasible, these messages should be part of every injured patient's encounter with the health care system. The three behavioral risk factors most likely to result in motor vehicle injuries are speeding, seat belt nonuse, and driving after drinking alcohol. Unfortunately, alcohol-impaired driving remains a challenge; in 2013, there were over 10,000 MVC fatalities involving a driver with a blood alcohol level of 0.08 or higher, representing over 30% of the total traffic fatalities for the year.[10]

Primarily due to increased seat belt use, motor vehicle fatality rates have declined by almost one-third, with fewer than 11 deaths/100,000 population between 2000 and 2012.[11] Seat belt use in 2016 was at 90%, up from 70% in 2000.[12] Proper use of lap and shoulder belts reduces the risk of death and severe injury to front seat passengers by 50%.[13] In 2012, 50% of occupant MVC fatalities involved individuals who were not restrained.[13] Proper restraint use in vehicles by occupants aged 5 years and older saved over 10,000 lives between 1975 and 2012.[13] Almost all states now have primary or secondary laws, although states with primary laws have seat belt use 11% higher than those with secondary laws.[12] New Hampshire has neither a primary nor secondary law.[14]

In recent years, driver distraction, especially by device use for talking or texting, has been recognized as a significant hazard. The NHTSA reported that in 2011, 10% of fatal collisions and 17% of injury collisions were associated with distractions.[15] National efforts continue to address this growing problem. For commercial truck and bus drivers, the US Department of Transportation banned texting in 2010 and all hand-held cell phone use in 2011.[16] For noncommercial drivers, 44 states and Washington DC ban text messaging, and 14 states and Washington DC prohibit hand-held cell phone usage for drivers of all ages.[17]

Age-appropriate child restraints reduce the risk of pediatric death in a MVC by 50%. Every pediatric visit is an opportunity to counsel parents on the safe transport of their children. In March 2011, the NHTSA revised its recommendations, stating that anyone younger than 13 years should ride only in the rear seat of a vehicle.[18] Infant seats should never be positioned in the front seat within range of the air bag, and federal rules allow for air bags to be disabled if there are circumstances necessitating that small children ride in the front seat. Increasingly, vehicles are equipped with sensors that turn off the airbag when certain weight thresholds are not met.

US collision data have shown that the odds of injury is over five times greater for children younger than 24 months who are restrained forward-facing as compared to those who are rear-facing. These data have prompted the American Academy of Pediatrics to strongly recommend keeping children younger than 24 months rear-facing.[19] The NHTSA recommends that infants 12 months and younger should always ride in a rear-facing car seat, and children 1 to 3 years of age should ride rear-facing until they outgrow the car seat manufacturer's specifications. At this point, they should be placed in a forward-facing seat until they are 7 years of age or outgrow the car seat manufacturer's specifications.[18] A booster seat should be used until children are 12 years old or big enough to fit in a seat belt properly. For a seat belt to fit properly, the lap belt must lie snugly across the upper thighs

and not compress the abdomen; the shoulder belt should lie snugly across the shoulder and chest, avoiding the neck and face.

Proper seat belt position is important for all ages. Although seatbelt use has saved hundreds of thousands of lives, seat belts can also be a source of injuries, particularly when they are not positioned appropriately. For example, wearing only a lap belt or having too much slack in the seatbelt can result in the body jackknifing over the belt, causing abdominal injuries, fractures, and dislocations. Alternatively, when automatic "passive" shoulder belts that require manual fastening of the lap portion were put on the market, people frequently did not fasten the lap portion of the belt. In a collision, this resulted in submarining of the torso under the shoulder belt, increasing the risk of liver, spleen, and lung injuries. Although these types of seat belts have been discontinued, older model cars with this feature are still in circulation. Emergency clinicians should advise patients (particularly those of small stature) about the need to sit with at least 10 inches between the sternum and an air bag. For more information on automobile safety, visit www.safercar.gov.

Behavioral and Comorbid Risk Factors

Recognition of patients at high risk of injury affords opportunity for intervention. Risk factors for all types of injury include male gender, low income, illicit drug involvement, previous arrest, and young age. Injury in children is a marker of increased risk for future injury. Emergency clinicians should identify risks of future injury and opportunities for intervention. A brief review of the incident may help providers and parents identify risks for future injury and opportunities for intervention.

An ED visit represents a teachable moment, when patients are aware of the consequences of their actions, to counsel patients about high risk behaviors.[20] Although these lessons can be reinforced by primary care providers, impact wanes as the time from injury passes. Risk factors for intentional injury are complex and involve behavioral, social, and environmental factors. A history of prior significant, violence-related injury is a strong predictor of injury recidivism. EDs should have protocols in place for the detection, reporting, and referral of patients likely to be victims of future injury, including victims of domestic violence and intentionally injured children.

Hospital-Based Violence Intervention Programs

Up to 40% of violently injured youth aged 15 to 24 years will return to the ED for violence-related injuries; up to 20% will be victims of homicide within 5 years, a mortality rate greatly exceeding that of many cancers in that age group.[20a] Youth 14 to 24 years of age presenting to an ED with assault-related injuries are twice as likely to return for a violent injury and twice as likely to die within 24 months when compared to those with nonassault injuries.[21] Hospital-based violence intervention programs reduce the risk of future injury, as well as recidivism to the criminal justice system.[22,23] Effective programs couple the teachable moment with culturally competent outreach workers who continue to case-manage and mentor youth as outpatients.[24] The National Network of Hospital-Based Violence Programs is now an international network, providing collaborative education, research, best practices, advocacy, and resources for hospital-based violence intervention programs (http://nnhvip.org).

Brief Emergency Department Interventions

The American College of Surgeons Committee on Trauma has recommended that all trauma centers screen for alcohol and provide interventions as a part of routine trauma care.[25] Alcohol-related collision injury is a national epidemic in the United States, with over 30% of all motor vehicle traffic fatalities involving an alcohol-impaired driver.[26] Patients with alcohol use disorders (AUDs) have higher rates of illness and MVC injury than the rest of the population, and patients with an AUD are more likely to drive after drinking. Reductions in alcohol-related deaths as a result of more stringent laws, public vigilance, and a societal shift toward the condemnation of driving while impaired have reduced impaired driving by social drinkers, but have not had significant effects on those with an AUD. Emergency clinicians have a unique role to play in the identification of high-risk patients. In particular, patients with AUD should be detected and referred for formal evaluation and treatment. A structured approach to detect and treat the disease should be brief and effective if it is to be used in a busy ED. Screening and brief intervention techniques have been validated in the ED, but likely require booster sessions after discharge.

SPECIFIC ISSUES AND DISORDERS

Acute Care

The acute care component of injury control involves trauma system planning, medical direction of out-of-hospital care, and provision of systematized resuscitative care after the injury. Local resources for management of the injured patient should be identified. To avoid secondary injury from delays in transfer or inappropriate care, algorithms and agreements to transfer severely injured patients to the highest level trauma center available should be established. EMS providers should recognize higher risk trauma patients and select the most appropriate destination.[27] For trauma centers, in-hospital triage criteria should be developed to align services and avoid unneeded overuse of trauma surgery teams.[25]

An inclusive trauma care system uses all acute care and rehabilitation facilities that treat injured patients. In an inclusive system, even patients remote from trauma centers are integrated into the system, and every hospital can play a role based on available resources, whether it is the expeditious transfer of patients to comprehensive major (level 1) trauma centers or the treatment of patients without subspecialist needs. Treatment at a level 1 trauma center can improve survival for severely injured trauma patients by 25%.

Out-of-hospital emergency care can be an integral part of injury control. EMS response, triage, and treatment are the first steps in injury control, and triage protocols should avoid unnecessary delays in definitive care. The Field Triage Decision Scheme, first developed by the American College of Surgeons and updated in collaboration with the CDC, is intended to help EMS providers identify patients who need the resources of a trauma center.[19,27] However, studies have consistently demonstrated that field triage protocols have a sensitivity less than 90% for identifying major trauma patients.[28] EMS providers can also be involved in primary injury prevention through injury risk identification, documentation of injury data, and safety education programs.

Firearm-Related Injuries

Firearm injuries are a major US public health issue, with over 30,000 deaths and over 180,000 nonfatal injuries annually.[29] In 2015, eight health organizations, including the American College of Emergency Physicians and the American Bar Association, published a position statement on firearm-related injuries in which they endorsed "universal background checks of gun purchasers, elimination of physician 'gag laws,' restricting the manufacture and sale of military-style assault weapons and large-capacity magazines by civilians, and research to support strategies for reducing firearm-related injuries and deaths."[30]

Emergency clinicians are at the front line of gun-related tragedies and have an obligation to educate their community on evidence-based risks of gun ownership. The United States has, by far, the highest private gun ownership rate of any developed or developing country, with 89 private guns/100 people (eg, compared to the United Kingdom, at 6 private guns/100 people). Risk of death by firearm is associated with rates of gun ownership. Gun deaths are 40 times higher in the United States than in the UK (10 vs. 0.25 annual deaths/100,000 population, respectively).[31] A systematic review and meta-analysis of studies has evaluated the impact of gun access on suicide and homicide victimization. Access to guns increased the odds of suicide by more than threefold and doubled the risk of being a victim of homicide.[32] Recent mass shooting have given a false impression of the association of gun-related deaths and mental illness. In fact, the attributable risk of violence associated with mental illness has been found to be only 4%. The vast majority of patients with mental illness are never violent, and the vast majority of people who commit gun-related homicides have never been diagnosed with a major mental health disorder.[33] Patients with depression are at increased risk of suicide, and those with access to firearms are more likely to die from suicide, irrespective of mechanism of death.

Emergency Medicine Leadership: Advocacy of Public Policy

As witnesses to daily preventable tragedies, emergency clinicians are uniquely qualified to advocate for effective measures to reduce injury rates. Most public health regulations and safety laws are under the jurisdiction of state legislatures and local governments. State and local policy makers are generally accessible to local physicians and other providers, who can provide expertise and advice on cost-effective, evidence-based injury prevention strategies. The American College of Emergency Physicians and National Association of EMS Physicians work on the national level to advocate for laws that will improve health and safety.

KEY CONCEPTS

- The Haddon Matrix addresses injury prevention by focusing on the environment, agent inflicting harm, and at-risk populations. Key tenets to this injury prevention model include understanding of the following: (1) injuries are predictable; (2) they follow typical patterns (eg, by age or gender); and (3) reliance solely on human factors for prevention has significant limits.
- The E-code is a system for identifying the cause of injury according to the International Classification of Diseases, Clinical Modification, and allows for systematic tracking of harmful agents.
- Proper use of lap and shoulder belts reduces the risk of death and severe injury to front seat passengers by 50%.
- Ten percent of fatal motor vehicle collisions and 17% of injury collisions are associated with distractions.
- Hospital-based violence intervention programs have been shown to decrease recidivism to the emergency department for recurrent violent injuries and decrease recidivism to the criminal justice system; hospital-based violence intervention programs have been found to be cost-effective.
- Firearm related injuries are more prevalent among countries with higher rates of gun ownership. The US has the highest rate gun ownership, with 89 guns/100 persons and the highest mortality rate attributed to firearm injuries of developed countries (eg, 40 times higher than that of the UK).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER e2: QUESTIONS & ANSWERS

e2.1. What percentage of injured patients seen in an emergency department are treated and discharged rather than admitted?
A. 59%
B. 65%
C. 76%
D. 88%
E. 98%

Answer: D. Approximately 88% of injured patients seeking medical care for injury are treated and discharged from the emergency department.

e2.2. What is the E code?
A. A system for identifying the cause of injury in a patient's medical record
B. A system for identifying the severity of injury in a patient's medical record
C. A system for indicating the type of injury in a patient's medical record
D. A system for predicting morbidity secondary to trauma in a patient's medical record
E. A system for predicting mortality secondary to trauma in a patient's medical record

Answer: A. The most crucial data element for the understanding of injury is the E code, a system for identifying the cause of injury in a patient's medical record, according to a classification published in the *International Classification of Diseases.* The "E" stands for external cause of injury, such as a motor vehicle collision, fall, or bicycle collision.

e2.3. Alcohol-related motor vehicle collisions account for what percentage of motor vehicle collision fatalities?
A. 7%
B. 19%
C. 31%
D. 68%
E. 87%

Answer: C. Alcohol-related collision injury is a national epidemic in the United States, accounting for 31% of all motor vehicle collision fatalities.

e2.4. What percentage of violent injuries can be attributed to patients with a major mental health diagnosis?
A. 4%
B. 24%
C. 44%
D. 84%

Answer: A. Only 4% of violent injuries are attributed to people with a major mental health diagnosis. The vast majority of patients with mental illness will never be violent.

CHAPTER e3

Global and Humanitarian Emergency Medicine*

Stephanie Kayden | *Shawn M. D'Andrea*

PRINCIPLES

SPECIFIC TYPES OF HUMANITARIAN EMERGENCIES

Natural Disasters

Armed Conflict

Disease Epidemics

Standards in Humanitarian Response

International Law

Humanitarian Principles and Codes of Conduct

Sphere Standards

Priorities in Global Humanitarian Emergencies

International Actors in Humanitarian Response

Individual Responders

Role of the Emergency Clinician

Coordination of Humanitarian Response

Tips for the Field

*For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.

KEY CONCEPTS

- A humanitarian emergency, or humanitarian crisis, is a critical threat to the health, safety, security, or well-being of a community or other large group of people, usually over a wide area.
- Demand for humanitarian responders is likely to rise in the future as global urbanization and an increase in climate-related disasters conspire to create more frequent and severe disasters. At the same time, the growing professionalization of humanitarian aid will move the field closer to a model of international standards and cooperation among relief agencies.
- Humanitarian responders should understand the organizational strengths and weakness of the nongovernmental organization (NGO) and the setting, mission, and likely hazards associated with the deployment.
- Emergency clinicians have a skill set well suited for humanitarian response. Those who seek appropriate training and experience will have the opportunity to expand their professional practice while providing an essential service to the world's most vulnerable populations.

CHAPTER e3

Global and Humanitarian Emergency Medicine

Stephanie Kayden | Shawn M. D'Andrea

PRINCIPLES

When a natural disaster or armed conflict forces thousands of people from their homes, a humanitarian emergency arises that requires a global response. Increasingly, emergency clinicians are called on to provide medical and organizational assistance in these humanitarian crises. Emergency clinicians contribute a unique skill set to the humanitarian environment, including an understanding of multiple medical specialties and expertise in managing within complex systems. Emergency clinicians have taken leadership roles in major humanitarian organizations, United Nations (UN) agencies, and national governmental disaster agencies. This chapter will provide an overview of global humanitarian emergencies and the role of the emergency clinician in humanitarian responses.

SPECIFIC TYPES OF HUMANITARIAN EMERGENCIES

A humanitarian emergency, or humanitarian crisis, is "a critical threat to the health, safety, security, or well-being of a community or other large group of people, usually over a wide area."[1] Humanitarian crises can be natural disasters (eg, floods, earthquakes, tsunamis), human-made disasters (eg, armed conflict, industrial accidents), or complex emergencies. A complex emergency occurs "where there is total or considerable breakdown of authority resulting from internal or external conflict and which requires an international response."[2] A key feature of humanitarian crises is the mass displacement of large numbers of people from their homes. Displaced populations are designated as internally displaced persons (IDPs) or refugees. An IDP is someone who has been forced from his or her home but who remains within the country of origin. If an IDP crosses an international border to seek help in another country, she or he becomes a refugee. The distinction is important. Whereas refugees enjoy protections and rights guaranteed by international treaty, IDPs must depend—in the absence of international aid—on their own government for help, even though the actions, or inaction, of their government may have caused their displacement.[3]

Another feature of humanitarian emergencies is the threat of excess mortality. Conflict, disaster, and displacement can lead to a lack of food, water, healthcare, and sanitation. A humanitarian crisis emerges when this lack of basic human needs leads to (or threatens) a mortality rate greater than twice the baseline and requires emergency measures to prevent excess death and disability.

Most of the disease burden in humanitarian emergencies is brought on by the displacement itself. Removed from their usual sources of medical care, displaced people suffer complications of untreated hypertension, diabetes, and other diseases. Women and young infants die from the lack of safe perinatal care. Infants and children may not receive lifesaving vaccinations. Densely packed refugee camps promote outbreaks of measles and other infectious diseases. Erosion of public health programs, proper sanitation, and the lack of clean water, latrines, washing facilities, proper shelter, and good nutrition are often the main causes of poor health among displaced people.

Natural Disasters

Natural disasters, often seen as random acts of nature, attract media attention and public sympathy that spur a robust aid response. The risk for and effects of natural disasters, however, are predictable, and the type of medical response needed varies by the type of disaster (Table e3.1). Damage to health facilities is common to human-made and natural disasters, and medical relief is often focused on immediate emergency stabilization and reestablishing primary care and basic health services. Different types of natural disasters have specific effects on the health care system. Some disasters disproportionally affect the public health infrastructure (eg, floods), whereas other types of disasters (eg, earthquakes) damage the curative health care system and hospitals.

Earthquakes cause uniquely high rates of complex injuries—fractures, crush injuries, burns, and even hypothermia. Search and rescue teams are designated to manage confined space medicine and emergent field amputations. Surgical field hospitals are often needed in the first hours and days after an earthquake to provide lifesaving neurosurgical or orthopedic care when the local medical system is overwhelmed with trauma cases. The need for inpatient postoperative wound care, rehabilitation services, and prosthesis care continues for months or even years. Rebuilding hospitals is a top priority. A rapid transition to capacity building of the health care system is important, even as relief organizations and foreign medical teams begin to provide initial services after an earthquake.

In contrast to earthquakes, most natural disasters produce less severe, more easily survivable injuries. Humanitarian efforts after floods, hurricanes and other weather-related events usually focus on restoring baseline health services. Surgical field hospitals, if needed at all, typically perform wound care and everyday emergency surgeries (eg, cesarean section, appendectomy). In disasters that produce high death rates—earthquakes, tsunamis, landslides, and volcanic eruptions—postmortem services may be needed emergently. Psychological first aid and mental health care are also vital to the population's health and are integral to the health response to sudden-onset natural disasters.

Unlike sudden-onset natural disasters, droughts develop slowly over months or years. Lack of water leads to crop shortages, skyrocketing food prices, and disruption of food markets. Poor or isolated populations can suffer a lack of access to food that if unchecked, leads to famine. Thus, acute medical needs in a drought often stem from severe malnutrition, especially in young children, and subsequent infections. Medical responses to acute and chronic malnutrition are complex and specialized. Special

TABLE e3.1

Predictable Effects of Natural Disasters

PARAMETER	EARTHQUAKES	HURRICANES	TSUNAMIS	FLOODS	LANDSLIDES	VOLCANOES
Deaths	+++	+	+++	+	+++	+++
Complex injuries	+++	++	+	+	+	+
Infectious diseases	Always a risk: increases with overcrowding, poor sanitation					
Damage to health care facilities	+++	+++	+++ (local)	+++ (equipment)	+++ (local)	+++
Damage to water systems	+++	+	+++	+	+++ (local)	+++
Food shortage	+	+	+++	+++	+	+
Mass displacement	Rare (heavily damaged cities)			Common (generally limited)		

Adapted from Pan American Health Organization: Natural disasters: protecting the public's health, Washington, DC, 2000, Pan American Health Organization, Pan American Sanitary Bureau, Regional Office of the World Health Organization, p 2.

training in therapeutic feeding programs and supplemental food distribution is needed for emergency clinicians responding to famine or to any emergency in which a population's baseline rate of severe malnutrition is high.[4]

Armed Conflict

Armed conflicts are a major contributor to global humanitarian crises. The changing nature of conflict, including the growth of intrastate wars and asymmetric warfare, have led to mass displacement of populations and growing civilian mortality due to war. Moreover, natural disasters sometimes occur in a setting of underlying armed conflict. For example, people in Aceh, Indonesia, were already coping with an ongoing insurgency when the 2004 Indian Ocean tsunami struck.

The primary driver of a population's medical needs in armed conflicts is not violent injury but rather, as in natural disasters, displacement from usual sources of medical care, home, and household income. People fleeing conflict lose access to clean water, food markets, and health clinics, making them vulnerable to injury and disease. For example, people living with chronic mild malnutrition who are driven from their household fields and wells can quickly develop severe malnutrition, suffer from infections, and die. When conflict disrupts basic health services, untreated acute illnesses and acute exacerbations of chronic illnesses lead to increased morbidity and mortality.

As in natural disasters, the medical response during armed conflicts focuses on providing basic health services. Unlike in most natural disasters, however, armed conflicts also tend to cause a prolonged breakdown in local security, political, and civil society structures, which can inhibit the restoration of health services and permanently displace large populations Responders must prepare for insecure environments and prolonged deployments. Violent injuries are typically limited to civilians who are trapped in active conflict zones or directly targeted by fighting forces. The number of civilians who suffer violent injuries is usually small in proportion to the total number of people displaced by armed conflicts.[5] Nevertheless, survivors of war wounds, building collapse, and sexual violence will require high-level medical care and culturally appropriate mental health services.

Disease Epidemics

Despite the experience of the 2014 outbreak of Ebola virus disease in West Africa, epidemics that result in humanitarian emergencies are rare, largely because most outbreaks of highly infectious, quickly fatal diseases such as Ebola have not typically spread beyond the rural areas where response agencies could contain them.[6] Nevertheless, the 2014 West Africa Ebola outbreak caused over 11,000 deaths and highlighted the need for more international aid agencies to be able to respond to large global epidemics. In addition to the catastrophic death toll of the virus itself, its impact on fragile national health systems, including hospital and clinic closures and the death or flight of medical professionals, led to a surge in untreated illness and avoidable deaths. Weak public health infrastructure allowed the unchecked spread of the Ebola virus in Guinea, Liberia, and Sierra Leone. This rapid spread was in contrast to containment of the virus in countries with more developed public health systems, such as Spain, Nigeria, and the United States. Future epidemics, especially those that spread to densely populated areas with an underdeveloped public health infrastructure, may require an international medical relief and health care development response.

Epidemics of infectious diseases more commonly complicate, rather than cause, humanitarian crises. This was the case after the 2010 earthquake that struck Port-au-Prince, Haiti, devastating that country's already weak health system. Ten months later after the earthquake, a cholera outbreak further strained health resources, increasing cholera transmission to displaced and nondisplaced populations and disrupting efforts to rebuild the health infrastructure damaged by the earthquake.[7]

Standards in Humanitarian Response

The variability in relief services in response to several recent humanitarian crises has led to a growing recognition of the value of standards in humanitarian aid. The international response community has developed practice guidelines that stem from research, international law, and expert consensus. These guidelines promote a standardized approach to improve the quality and efficiency of humanitarian aid. Responders should be familiar with these international laws and standards to ensure that their response efforts fulfill the rights of the people they are trying to help.

International Law

Humanitarian aid is the attempt to respect the rights to assistance that all civilians have during humanitarian crises. To fulfill these rights, responders must know what they are. Two bodies of international law set forth the rights of people in humanitarian crises, international humanitarian law (IHL) and human rights law.

IHL is often described as the law of war, and its core documents are the Geneva Conventions.[8] IHL gives special protections to people not taking part in conflict—civilians and soldiers rendered incapable of fighting due to injury, illness, surrender, or having been taken prisoner. It mandates that these noncombatants be treated humanely and be given food, water, shelter, and medical care. IHL not only ensures noncombatants the right to humanitarian assistance, but also grants humanitarian aid workers the right to offer that assistance. This means that humanitarian responders must be allowed to provide lifesaving aid uninterrupted and must not become war targets as long as they remain neutral in the conflict. Indeed, IHL is one of the primary tools used to ensure protection in conflict zones for aid workers who, as neutral actors, do not carry weapons. Humanitarian aid agencies often use IHL to negotiate with conflict commanders for safe access to civilian populations. Military leaders who do not respect the tenets of IHL can be individually prosecuted for IHL violations or war crimes.

Although IHL applies only during conflict, human rights law applies at all times. The 1948 Universal Declaration of Human Rights, the core document of human rights law, stated that "all human beings are born free and equal in dignity and rights" and are entitled to life, liberty, security of person, and "a standard of living adequate for… health and well-being."[9] The Declaration and other human rights laws enshrine specific civil, political, economic, social, and cultural rights, prohibit torture, genocide, and racial discrimination, and provide special protections for women, children, refugees, and internally displaced persons.[10-18]

IHL and human rights law govern the scope of activity of humanitarian response. More importantly, it is by virtue of these international laws that humanitarian responders legitimately can enter a sovereign country and intervene in the lives of its citizens.

Humanitarian Principles and Codes of Conduct

The four humanitarian principles—humanity, neutrality, impartiality, and independence—are the bedrock of humanitarian action. Table e3.2 provides definitions of these principles, to which all humanitarian responders must adhere. Violations of the humanitarian principles can impede access to affected populations and create security risks for aid workers.

Nongovernmental organizations (NGOs) use codes of conduct to specify behavioral, professional, interpersonal, and ethical standards for their personnel. The most widely used code of conduct is the one in Box e3.1, prepared by the International Federation of Red Cross and Red Crescent Societies and International Committee of the Red Cross for disaster responders.[19] Humanitarian response often requires long work hours in uncomfortable and insecure settings. Personnel must maintain appropriate conduct despite working in a high-stress setting. Maladaptive coping behaviors such as drug and alcohol abuse, inappropriate relations with national staff or locals staff, and security protocol violations put individuals and organizations at risk. Codes of conduct help establish behaviors necessary to ensure an ethical and effective response. Responders should be aware of, and abide by, the codes of conduct for their individual organizations.

Sphere Standards

The *Sphere Handbook*,[20] a collaborative project of humanitarian response experts, sets international standards for the provision of humanitarian aid. It is widely considered the "bible" of global humanitarian response. The *Sphere Handbook* begins with the Humanitarian Charter, which distills international law, humanitarian principles, and the humanitarian code of conduct into a five-page document that establishes the legal and ethical essence of the humanitarian imperative.

The *Sphere Handbook* provides minimum response standards for water and sanitation, food and nutrition, shelter, health care, and protection. It also sets forth certain core standards that apply to all sectors, such as involving beneficiaries in the response. These minimum standards are supplemented by specific indicators,

TABLE e3.2

Humanitarian Principles

HUMANITARIAN PRINCIPLE	DEFINITION
Humanity	Human suffering must be addressed wherever it is found. The purpose of humanitarian action is to protect life and health and ensure respect for human beings.
Neutrality	Humanitarian actors must not take sides in hostilities or engage in controversies of a political, racial, religious or ideologic nature.
Impartiality	Humanitarian action must be carried out on the basis of need alone, giving priority to the most urgent cases of distress and making no distinctions on the basis of nationality, race, gender, religious belief, class or political opinions.
Independence	Humanitarian action must be autonomous from the political, economic, military or other objectives that any actor may hold with regard to areas where humanitarian action is being implemented.

Adapted from United Nations Office for the Coordination of Humanitarian Affairs: Humanitarian principles. https://docs.unocha.org/sites/dms/Documents/OOM-humanitarianprinciples_eng_June12.pdf.

BOX e3.1

Code of Conduct for the International Red Cross and Red Crescent Movement and Nongovernmental Organizations (NGOs) in Disaster Relief

1. The humanitarian imperative comes first.
2. Aid is given regardless of the race, creed, or nationality of the recipients and without adverse distinction of any kind.
3. Aid priorities are calculated on the basis of need alone.
4. Aid will not be used to further a particular political or religious standpoint.
5. We shall endeavor not to act as instruments of government foreign policy.
6. We shall respect culture and custom.
7. We shall attempt to build disaster response on local capacities.
8. Ways shall be found to involve program beneficiaries in the management of relief aid.
9. Relief aid must strive to reduce future vulnerabilities to disaster as well as meeting basic needs.
10. We hold ourselves accountable to both those we seek to assist and those from whom we accept resources.
11. In our information, publicity and advertising activities, we shall recognize disaster victims as dignified humans, not hopeless objects.

Adapted from International Committee of the Red Cross: Code of conduct for International Red Cross and Red Crescent Movement and non-government organizations in disaster relief. https://www.icrc.org/eng/resources/documents/publication/p1067.htm.

numerical sign posts that help responders know when they are on track to meet the standards. For example, the first Sphere standard for water supply is that "all people have safe and equitable access to a sufficient quantity of water for drinking, cooking, and personal and domestic hygiene."[20] But how much water is that? Although the exact answer may vary depending on the context, the key indicator for this standard is at least 15 L of clean water per person per day.[20] Similar standards and indicators are given for other sectors of humanitarian aid. Box e3.2 highlights a few of the key indicators from the *Sphere Handbook*.

The *Sphere Handbook* provides a single set of uniform standards for aid agencies to follow in humanitarian response. The Sphere standards are the key measures whereby aid agencies evaluate their responses and, as such, are the basis of accountability for international response efforts.

Priorities in Global Humanitarian Emergencies

The goal of humanitarian response is to save lives, restore livelihoods, and rebuild communities. Effective humanitarian response centers around several key priorities.

BOX e3.2

Examples of *Sphere Handbook* Indicators of Minimum Standards

WATER, SANITATION, AND HYGIENE
- 15 L of water/person/day
- 250 people/water tap
- 10–20 L capacity water container for storage/household
- One toilet/20 people
- Toilets no more than 50 m from dwellings

FOOD SECURITY AND NUTRITION
- 2100 kcal/person/day
  - 10% of total energy from protein
  - 17% of total energy from fat
  - Adequate micronutrient intake
- >90% of people aged 6-59 mo live within 1 day's walk of a supplemental feeding program site

SHELTER, SETTLEMENT, AND NON-FOOD ITEMS
- 3.5 m^2/person of covered living space in shelters
- 45 m^2/person of total area of displacement camp
- 30-m firebreak between every 300 m of built-up area in camps
- Fuel-efficient stoves with required supply of fuel or domestic energy used by affected population.

HEALTH
- One doctor/50,000 people
- One nurse/10,000 people
- One midwife/10,000 people
- One basic health unit (health post)/10,000 people
- One health care center/50,000 people
- One district or rural hospital/250,000 people
- >10 inpatient and maternity beds/100,000 people
- <1 death/10,000 people/day, or less than double the baseline crude mortality rate
- Under 5-yr-old mortality rate less than double the baseline

When measles vaccination coverage is <90% or unknown, conduct a mass measles vaccination campaign for children aged 6 mo–15 yr

Adapted from Sphere Project: The Sphere Handbook: humanitarian charter and minimum standards in humanitarian response. www.spherehandbook.org.

Protection

The first priority—before food, water, shelter, or medical care—is the protection of people caught in the crisis. The humanitarian protection principles are outlined in the *Sphere Handbook* as follows[20]:

1. Avoid exposing people to further harm as a result of your actions.
2. Ensure people's access to impartial assistance—in proportion to need and without discrimination.
3. Protect people from physical and psychological harm arising from violence and coercion.
4. Assist people to claim their rights, access available remedies and recover from the effects of abuse.

The *Sphere Handbook* provides detailed guidance to help aid agencies adhere to these principles. Some protection measures are simple (eg, fences around refugee camps in insecure areas, good lighting near latrines); others are more complex (eg, issuing identification cards so that refugees can claim benefits, tracking unaccompanied children to help reunite families). Without adequate protection, other response measures may fail.

Rapid Assessment

A rapid assessment should always be conducted before large-scale aid operations begin. Taking time for an assessment may seem counterintuitive in times of urgent need, but rapid assessments are critical to ensuring that the right aid arrives in the right amount at the right time. Aid funds are always limited, and rapid assessments help avoid wasted resources. Most initial rapid assessments focus on needs over all response sectors, but some target specific areas such as health or shelter. Responders in the acute phase should be familiar enough with humanitarian aid to be able to participate in a multisector rapid assessment.

A rapid assessment takes from a few hours to a few days. Even in large-scale disasters, initial rapid assessments are complete by the end of the first week. Information gathered in a rapid assessment is shared with responding agencies to identify aid priorities and vulnerable populations. Priorities in different communities will vary, depending on the nature of the emergency. For example, flood waters may destroy homes in one community and food stores in another. Only after a rapid assessment can appropriate resources be mobilized to the neediest populations.

Food, Water, and Shelter

The major sectors of humanitarian response are water and sanitation, food, shelter, and health care. Although specific interventions will depend on the findings of the rapid assessment, most emergencies will require a response in each of these sectors.

Clean water, latrines, and washing facilities are among the most important public health measures in emergencies. If forced to choose, prioritize the provision of water quantity over quality. Lack of water causes people to stop washing, and poor hygiene is a major cause of disease in overcrowded refugee camps. Sanitation facilities must be provided to prevent fecal cross-contamination. Defecation fields, separated by gender, can be used until there is time to dig proper latrines.

Food distributions are necessary when food markets are disrupted and should be culturally appropriate, equitable, and organized. Nutritionally balanced dry rations of staple foods (eg, flour, beans, oil) are typically provided, but wet rations of prepared meals can be used if people cannot cook for themselves. Supplemental rations are given to pregnant and breast-feeding women, children, and sick or malnourished people. When local markets are functioning, allocations of cash or vouchers often replace food distributions.

Emergency shelter can be provided by housing displaced people with local host families, in vacant apartments, or—as a last resort—in tented camps. Careful camp planning is needed to reduce the impact of displaced populations on local communities and the environment, because camps can typically last not for weeks or months, but years or decades.

Health Care

Health care in humanitarian emergencies focuses on primary and preventive care, control of communicable diseases, and restoration of basic health services. Control of communicable disease and public health surveillance are two key interventions in displaced groups living in densely populated camps and who often have low baseline vaccination rates. The biggest killers of children are respiratory infections and diarrheal illness. In endemic regions, malaria is also a dominant infectious disease threat. Measles is a particular threat in undernourished populations that have not been appropriately immunized. Measles vaccination campaigns for children are often the first medical priority after disasters.

Most humanitarian emergencies do not require large numbers of foreign surgical teams. The utility for foreign surgical teams may be in the care of war wounded, but they are most likely deployed to compensate for chronic shortages of surgical services. When surgical teams are needed, they should be trained in emergency obstetric care in addition to general surgery. In disasters that produce complex surgical needs, such as earthquakes, surgical field hospitals can be deployed to address acute injuries. Less recognized, however, is the need for postsurgical follow-up care and rehabilitation services. After the 2010 earthquake in Haiti, for example, some foreign surgical teams arrived to perform amputations or place external fixators for complex fractures, but left Haiti without establishing solid plans for rehabilitation or follow-up care. Surgical field hospitals must plan in advance to provide inpatient wound care and physical therapy for 3 to 6 months after surgery to patients whose homes and local health services have been destroyed. Amputees requiring prosthetics may need to be followed for years. Surgical responders have a responsibility to ensure, singlehandedly or through agency partnerships, comprehensive postoperative care to all patients.

Transition and Exit

The decision to respond to a crisis is much simpler than knowing how and when to end the relief effort.

- When is a humanitarian crisis over?
- How should deployed services be removed from an area chronically lacking resources?

Withdrawing relief aid may leave gaps in medical care, employment for local workers, and support for local livelihoods. Rather than abruptly pulling out, a successful relief effort will transition many activities from the relief phase to the development phase. Planning for this transition and exit must start early in the response and often will require collaboration with other agencies.

International Actors in a Humanitarian Response

The government of a country affected by a humanitarian emergency or refugee crisis has the primary responsibility to provide aid. If that government cannot or does not respond sufficiently, the international community may offer assistance. If the government invites this assistance, a variety of government organizations and NGOs, often collectively referred to as humanitarian actors, will arrive to provide relief. Responders should understand the roles of the major humanitarian actors—response organizations, the UN, government funding agencies, and those in the military—in funding, coordinating, and carrying out the response.

Response Organizations: The International Humanitarian Architecture

Among international responders, NGOs do most of the actual aid provision. Humanitarian emergency clinicians typically work with these groups. NGOs sometimes have access to vulnerable populations that are off limits to government agencie, and thus play a critical role in a humanitarian response. Although many international NGOs offer a range of response services, some are known for expertise in certain sectors. Doctors Without Borders (Médecins Sans Frontières), for example, is known for its specialized medical care, the International Rescue Committee for refugee health, and Oxfam for food and water expertise.[21]

The International Committee of the Red Cross (ICRC) and International Federation of Red Cross and Red Crescent Societies also represent response organizations; however, the two groups have very different mandates. Founded in Switzerland in 1863, the ICRC is in fact neither a governmental organization nor NGO. Instead, the ICRC is a neutral body mandated by the international community to aid and protect civilians in violent emergencies under the tenets of international humanitarian law. The ICRC provides health care, water and sanitation support, and international legal advocacy for refugees and IDPs.[22] In contrast, the International Federation of Red Cross and Red Crescent Societies is comprised of 189 National Societies of the Red Cross and Red Crescent. The National Societies primarily work to support emergency preparedness and response in their own countries. A few of the National Societies, including the American Red Cross and Turkish Red Crescent, in coordination with the International Federation of Red Cross and Red Crescent Societies, also assist in emergencies outside their home countries.[23]

Despite the prominence of international groups in humanitarian emergencies, it is important to remember that most humanitarian aid comes from local sources—neighbors, community organizations, religious groups, and local government agencies. When international aid agencies arrive, they often partner with local community organizations that know the area well and have preexisting relationships with the people. This allows the international agency to provide efficient aid while helping to train and strengthen local organizations.

United Nations

The UN's primary role in humanitarian crises is to create policies, set policies, and coordinate the international response. The UN Office for the Coordination of Humanitarian Affairs (OCHA) is the agency that serves as the main coordinating body for humanitarian crises. OCHA leads the cluster approach (see later, "Coordination of Global Humanitarian Response"), which coordinates local and international humanitarian actors in each sector of the field response. Some UN agencies also provide services directly to disaster survivors or NGOs in the field. For example, the World Food Program, which feeds more than 80 million people in 75 countries,[24] provides logistic support for the transport and warehousing of NGO relief goods and food rations.

Foreign Governments

Although many aid agencies raise funds from private donors, the vast majority of funding for global humanitarian responses comes from foreign governments. Government funding agencies, such as the US Agency for International Development (USAID) or United Kingdom's Department for International Development, often send representatives to the field to assess the scale of the emergency

and to offer assistance. These foreign government funds—a total of US $16.4 billion worldwide in 2013[25]—go to the local government of the affected country, to the UN, or to NGOs to fund specific aid proposals. USAID, via its Office of US Foreign Disaster Assistance, also guides the use of US military forces in humanitarian response missions.

Militaries

International militaries increasingly are engaged in humanitarian activities. Although militaries can offer a range of services, the main gap they fill is in large-scale transport and logistic support. Unlike most NGOs, militaries can rebuild bridges, reopen damaged airports, and/or transport equipment by helicopter. The militaries of the US, Canada, Israel, and United Kingdom are common responders worldwide, typically working with the military of the local government. A government dictates the actions of its military in accordance with its national interest and may decide to respond to some crises but not others.

The services of foreign militaries may be offered to nations that are responding to natural disasters to provide rapid logistic support. Military humanitarian response may also be deployed within peace-building operations to promote stability and reconstruction. In the setting in which militaries are engaged in conflict and humanitarian action, the lines between military action and humanitarian action may be blurred. Militaries may not always be perceived as neutral parties by beneficiaries, and NGOs that work with militaries risk a similar perception. This loss of perceived neutrality may cause NGOs to be threatened or attacked, even in other countries far from the disaster. NGOs who partner with militaries must therefore work to ensure an accurate perception of their neutrality.

Individual Responders

Given the complex nature of humanitarian emergencies, there is little place for individual responders without the support of a well-established agency. Most lone responders arrive ill equipped to be truly self-sufficient, and ultimately siphon scarce resources (eg, lodging, food and water, ground transportation) away from the response. For this and many other reasons, individuals should not respond independently to humanitarian emergencies unless they do so as part of an experienced humanitarian relief organization. Would-be responders who cannot join an international NGO can be more effective by donating money, not material goods. This produces a triple benefit. NGOs use donated funds, which require no transport or warehousing, to buy culturally appropriate relief supplies in the exact quantities needed, which reduces waste and is best for survivors, often from local markets, which boosts the damaged economy and promotes faster recovery.

Role of the Emergency Clinician

Many people assume that humanitarian emergency clinicians spend most of their time treating trauma or serious injuries—fractures and crush injuries from earthquakes, infected flesh wounds in floods, or blast and penetrating injuries in conflict. Although this is true in some emergencies, the reality is that most of the time spent by an international medical responder is used to reinforce primary care and basic medical services that have been destroyed or bolster public health programs to prevent diseases in displaced populations.

Coordination of Humanitarian Response

Humanitarian relief can seem haphazard to the casual observer. In reality, global humanitarian response is carefully coordinated by the UN Cluster Approach, or cluster system, which is activated in large-scale international emergencies. Professional humanitarians are trained to coordinate with other NGOs via the cluster system to avoid duplication, omission, and inefficiency of humanitarian aid.

United Nations Cluster Approach

The cluster system was implemented in 2005 to increase coordination and accountability in relief aid. It is designed to accompany and advise, not supplant, the host government in its coordination of international response efforts. The cluster system divides humanitarian response into 11 sectors, or clusters (Fig. e3.1): camp management, early recovery, education, emergency telecommunications, food security, health, logistics, nutrition, protection, shelter, and water, sanitation, and hygiene.[26]

Each cluster is overseen by a UN agency or other response organization termed the *cluster lead,* which fills this role in every response; the World Health Organization (WHO) is always the health cluster lead. Cluster leads gather and share information, promote adherence to international standards, coordinate NGO activities, and report progress to OCHA. OCHA, led in the field by the Humanitarian Coordinator, is responsible for overall coordination among the clusters and with the larger international community. Cluster meetings, held daily in the early response and less frequently over time, are the mainstays of coordination. They are often co-led by representatives of the host government (perhaps the Minister of Health in health cluster meetings) and the cluster lead agency (WHO). Representatives from NGOs, government agencies, and other groups working in the sector attend cluster meetings to share information and plan next steps.

Ongoing Coordination

Between emergencies, the 11 clusters work together on an ongoing basis to improve future responses. These global clusters are standing bodies that work to improve response preparedness, disseminate best practices, and support in-country clusters during disasters. Leaders of the global clusters report to the UN Under-Secretary General for Humanitarian Affairs and Emergency Response Coordinator,[27] who also leads the Inter-Agency Standing Committee (IASC). The IASC brings together UN agencies, NGOs, ICRC and International Federation of Red Cross and Red Crescent Societies, World Bank, and International Organization for Migration to set policies and guidelines for effective humanitarian aid.

Emergency Clinician in Humanitarian Emergencies

Emergency clinicians are well suited for humanitarian response. They are comfortable working in stressful, chaotic environments. They can nimbly rearrange priorities and see the big picture in an ever-changing situation. They have uniquely broad medical skills that are useful in emergency response.

However, not all emergency clinicians make good humanitarian responders. They must consider whether relief work is right for them and be willing to seek training in the public health aspects of humanitarian response. Emergency clinicians should also be careful to choose an experienced aid agency with which to deploy.

Preparing for Humanitarian Response

Humanitarian response can be life-changing, usually for the better, sometimes for the worse. Humanitarian crises are stressful and unpredictable. To ensure an effective rewarding experience,

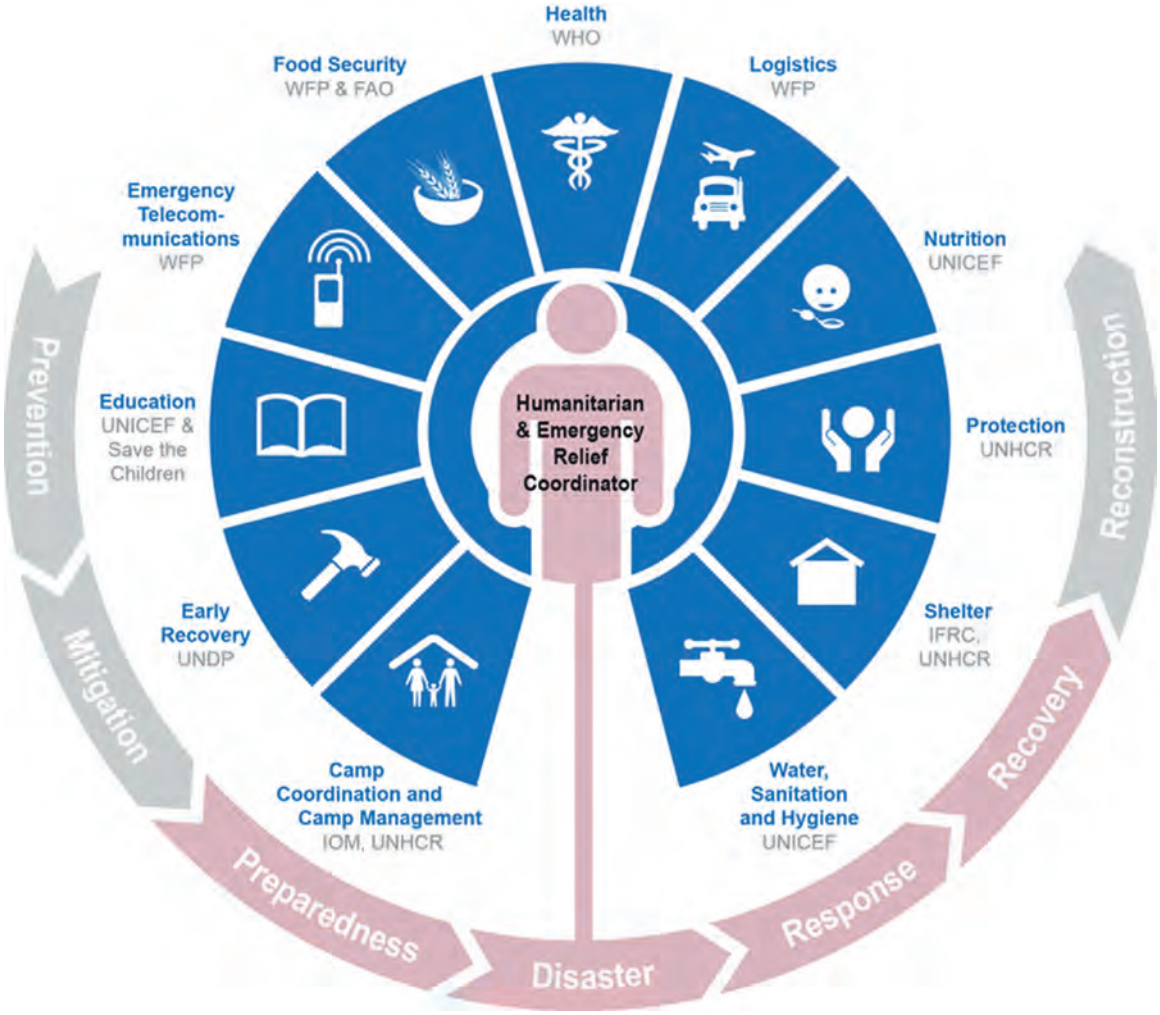

Fig. e3.1. Organization of the UN cluster approach. *FAO,* Food and Agriculture Organization of the United Nations; *IFRC,* International Federation of Red Cross; *IOM,* Institute of Medicine; *UNCHR,* United Nations High Commissioner for Refugees; *UNDP,* United Nations Development Programme; *UNICEF,* United Nations International Children's Emergency Fund; *WFP,* World Food Programme. (From United Nations Office for the Coordination of Humanitarian Affairs: Cluster coordination. www.unocha.org/what-we-do/coordination-tools/cluster-coordination.)

emergency clinicians should carefully consider whether they are properly prepared for humanitarian work.

Work in a humanitarian crisis often involves long hours, unfamiliar cultures, and uncomfortable accommodations. Electricity, running water, and mobile phone and Internet service may be unavailable. Insecure environments may require curfews and restriction to the NGO compound. Emergency clinicians who are new to austere living conditions might try backpacking in a low-income country before deploying to a humanitarian emergency.

The ability to cope with prolonged stress and personal discomfort is key. In a humanitarian response, toxic coping mechanisms (eg, drugs, alcohol, sex) can endanger you and your team. Music, journaling, movies, and exercise are better ways to relax. You will be living in close quarters with your teammates for weeks or months and should make every effort to keep morale high and conflicts to a minimum.

Medical resources are often limited in the field. It can be useful to review certain procedures that are more common in austere medical environments (eg, regional blocks instead of procedural sedation). It is also useful to provide on-site educational support which servicing abroad.

Humanitarian deployments can be a challenge for your personal relationships. It is important for emergency clinicians who have deployed abroad to understand that adjusting to normal activities of work and life after returning from mission may be challenging. After the deployment, you may find it difficult to readjust to the ED. Some emergency clinicians become frustrated with patients with minor complaints after witnessing so much suffering abroad. Remember that these feelings are common.

Training for Humanitarian Response

Humanitarian professionals are expected to be familiar with a large and growing body of literature, guidelines, and procedures. Emergency clinicians considering humanitarian work should seek additional training. Formal educational opportunities include humanitarian certification courses, fellowships, and graduate degrees. Certification courses in humanitarian aid are available through a number of universities and organizations. The Humanitarian Academy at Harvard[28] and Tufts University[29] offer nondegree courses in humanitarian assistance. International organizations also offer courses. The ICRC's Health Emergencies in Large Populations (HELP) course is taught in several locations around the world.[30] Lasting a few days to a few weeks, certification courses can be a most effective way to prepare for a deployment or explore a career in humanitarian aid.

BOX e3.3

Major Humanitarian Response Agencies

Action Against Hunger
CARE
Catholic Relief Services
Concern
Doctors Without Borders
International Committee of the Red Cross
International Medical Corps
International Rescue Committee
Islamic Relief
Mercy Corps
Oxfam
Save the Children
World Vision

Some fellowships in international emergency medicine (IEM) prepare clinicians for humanitarian response. Specialists in IEM work to develop emergency care and improve humanitarian response worldwide. Fellowships typically last 1 to 2 years; more information can be found at www.iemfellowships.com.

Humanitarian tracks exist in some graduate school degree programs, such as international affairs, engineering, and public health. A few programs, such as the Master of Arts in Humanitarian Assistance offered at Tufts University,[31] cover all aspects of humanitarian response. Emergency clinicians who wish to obtain mort intensive training than what is offered in certification courses, but need more flexibility than IEM fellowships offer, may enroll in a Master of Public Health program that specializes in humanitarian studies.

Choosing a Deployment

When seeking to start humanitarian work, look for a deployment that fits your skills and experience. Well-established NGOs are usually good at ensuring that applicants have the right experience. In general, large relief organizations such as those listed in Box e3.3 have extensive field experience and logistic capability. They provide proper accommodations, reliable transportation, and security and evacuation resources necessary for a safe deployment. Responders should also ask about an NGO's practices in the field to determine the right fit. Avoid NGOs that do not have robust logistic or security support in the field. Investigate each organization to determine whether their goals are aligned with yours.

Tips for the Field

Emergency clinicians new to humanitarian response can be challenged by field basics, sometimes with disastrous consequences. The following sections present some tips to help prepare for a humanitarian deployment.

Safety and Security

Humanitarian crises are often set in dangerous and insecure environments, with inadequate public safety and medical facilities. Responders should understand and adhere to their organization's safety protocols, even if the advice seems overcautious. Mandatory seat belt use, for example, helps prevent harm from the most common cause of unintentional injury to aid workers—road traffic accidents. Responders must be familiar with the basic tenets of personal security and travel safety to prepare for deployment in the field.

Unfortunately, attacks on humanitarian aid workers have increased in the past decade.[32] Modern conflicts often directly target civilians and aid workers, and hostage ransoms are an increasingly important source of revenue for some non–state-armed actors. Responders should be aware of how their own identity or the reputation of their NGO affects their level of risk. Although it is extremely unlikely that any single aid worker will be a victim of violence, responders should review insurance policies before deployment to an insecure area. Health, life, and disability policies, particularly if provided by your home hospital, may not cover death or injury while working in a humanitarian crisis. Responders can improve their awareness of field security via training programs such as the UN Department of Safety and Security Field Course (online).[33]

Ethical Dilemmas

Humanitarian emergency clinicians often face ethical dilemmas in the field that would never occur at home. At home, triage usually decides who gets care first; in a humanitarian crisis, triage often decides who gets care at all. This unfamiliar territory can lead emergency clinicians into ethical pitfalls in humanitarian medicine. A common pitfall is deciding to work outside of one's scope of clinical practice because of an incomplete understanding of referral capability. Nonsurgeons may attempt a makeshift emergency appendectomy, rationalizing that this care is "better than nothing." In our experience, this emergency clinician is usually unaware of surgical resources a few hours (or minutes) away. Even in disasters, humanitarian emergency clinicians have a responsibility to arrange a referral and transport system for patients needing higher care. In the few cases when referral is truly impossible, the patient and family must be fully informed of your lack of experience and given the option to refuse.

Many ethical dilemmas are better addressed by a group. Group consensus, especially when beneficiaries are represented, helps avoid war zone decision making and removes the burden of an emotional decision made by an individual.[34] Having a standard protocol for the use of prearranged ethics groups will allow for quick decisions.

What to Bring

First-time responders often wonder which items are most useful to pack for humanitarian work. Overpacking can mean leaving things behind in an emergency evacuation, when luggage is often restricted to a 12-kg carry-on. Box e3.4 provides suggestions for packing light while remembering the essentials.

BOX e3.4

Packing List for Humanitarian Deployments

DOCUMENTS
Passport (plus copy)[a]
Visa (plus copy)[a]
Immunization card (plus copy)[a]
Air ticket (plus copy)[a]
Letter of invitation by NGO[a]
Medical evacuation insurance card (plus copy)[a]
Health insurance card[a]
Trip cancellation insurance[a]
International calling card[a]
Driver's license (consider an international driver's license)[a]
ATM/credit cards (may not work)[a]
Cash (generally U.S. currency, but check with contacts)[a]
Copy of medical school diploma
Copy of medical license
CV/résumé
Hospital identification badge
Business cards
Extra passport photos
Address and contact list[a] (see below)

ADDRESS AND CONTACT LIST[a]
Field supervisor and local contacts
Arrival and airport contacts
Local embassy
Family, friends
Lost ATM, credit card reporting contacts
Medical evacuation company
Health insurance company
Local airline office
Travel agent

GEAR
Money belt[a]
Day pack
Alarm clock (that runs on batteries)
Headlamps, flashlights[a]
Mosquito net
Sunglasses
Sleep sack
Rain protection
Duct tape
Swiss Army knife *(not for carry-on)*
Sewing kit
Ear plugs
Pocket tissues (toilet paper)[a]
Baby wipes
Luggage locks (for hotel, not flight)
Quick-dry travel towel
Flip-flops, shower sandals
Bandana, scarf
Travel clothesline
Laundry detergent
Sink stopper
Ziploc bags
Water purifier or disinfection tablets
Phrasebook
Travel guide[a]
Stethoscope
White coat, surgical scrubs (where applicable)
Pocket medical references

ELECTRONICS
Laptop and power cord[a]
Electrical adapters, converter[a]
Surge protector
Flash drive[a]
Unlocked cell phone and charger[a]
Camera and memory cards[a]
Other cables and adapters
Extra batteries

FIRST-AID KIT
Sunscreen
Mosquito repellant
Antimalarial prophylaxis
HIV postexposure prophylaxis
Alcohol-based hand sanitizer
Traveler's diarrhea antibiotic(s)
Antidiarrheal
Laxative
Acetaminophen, ibuprofen
Decongestant
Antihistamine
Albuterol inhaler
Prednisone
Fluconazole
Bacitracin ointment
Antiemetic
Vitamins
Oral contraceptive, emergency contraceptive
Condoms
Adhesive bandages
Blister dressings
Alcohol wipes
Cloth tape
Wound closure strips
Safety pins
Tweezers
Spare eyeglasses, contact lenses
Sutures and needle driver
Nitrile gloves

TOILETRIES
Toothbrush, toothpaste
Dental floss
Shampoo, soap
Comb, brush
Razor, shaving cream
Deodorant
Contact lens kit
Eyeglasses (and spare)
Sunscreen
Makeup
Mirror
Lotions, creams
Lip balm
Tampons
Facecloth
Prescription medicines[a]

EXTRAS
Notebook, journal, pens
Gum, candy, protein bars
Instant coffee packages, teabags
Magazines, novels
Playing cards, games
Textbooks, equipment donations
Gifts for hosts

[a]In carry-on bag.
NGO, Nongovernmental organization.

KEY CONCEPTS

- A humanitarian emergency, or humanitarian crisis, is a critical threat to the health, safety, security, or well-being of a community or other large group of people, usually over a wide area.
- Demand for humanitarian responders is likely to rise in the future as global urbanization and an increase in climate-related disasters conspire to create more frequent and severe disasters. At the same time, the growing professionalization of humanitarian aid will move the field closer to a model of international standards and cooperation among relief agencies.
- Humanitarian responders should understand the organizational strengths and weakness of the nongovernmental organization (NGO) and the setting, mission, and likely hazards associated with the deployment.
- Emergency clinicians have a skill set well suited for humanitarian response. Those who seek appropriate training and experience will have the opportunity to expand their professional practice while providing an essential service to the world's most vulnerable populations.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER e3: QUESTIONS & ANSWERS

e3.1. A health crisis exists in a refugee population when the crude mortality rate (CMR) reaches how many times the baseline CMR?

A. 1.5
B. 2.0
C. 3.0
D. 5.0

Answer: B

e3.2. Which of the following medical responses is the highest priority in a nation with an underdeveloped health care infrastructure after a natural disaster causing mass population displacement into temporary shelters?

A. Immediate construction of temporary hospitals with surgical capability
B. Implementation of hand hygiene education programs
C. Rapid deployment of emergency surgical teams
D. Rapid initiation of measles vaccination campaign

Answer: D

e3.3. The *Sphere Handbook* provides what information for aid agencies?

A. Comprehensive catalogue of nongovernmental agencies' response capabilities for humanitarian crises
B. Most current set of standards for establishing and managing an Ebola treatment unit
C. Single set of uniform standards for aid agencies to follow in humanitarian response
D. Standardized approach to resolving ethical challenges in humanitarian crises for emergency clinicians

Answer: C

e3.4. For what activities should emergency clinicians deploying to a humanitarian crisis generally be expected to prepare?

A. Assist in the care of a large number of emergency surgical patients.

B. Gain experience practicing outside of one's usual scope of practice.

C. Provide care for a large number of chronically malnourished patients.

D. Provide mostly primary care and assist in restoration of basic health services.

Answer: D

CHAPTER e4

Tactical Emergency Medical Support and Urban Search and Rescue*

Nelson Tang | *Leah Bright*

PRINCIPLES

Background

Organizational Principles and Objectives

SPECIAL ISSUES

Tactical Emergency Medical Support Providers and Scopes of Practice

Medical Oversight of Tactical Emergency Medical Support

Casualty Care

Tactical Team Health

Integration with EMS Infrastructure

Active Shooter Incidents

Future Directions

URBAN SEARCH AND RESCUE

Components and Structure of an Urban Search and Rescue Team

Medical Team Operations in Urban Search and Rescue

Medical Team Tasks

Confined Space Rescue

Specific Medical Challenges

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

KEY CONCEPTS

- Tactical emergency medical support (TEMS) facilitates the overall success and safety of law enforcement missions during all phases of a tactical operation through the delivery of preventive, urgent, and emergency medical care.
- A fundamental principal in tactical medicine is that the medical mission may be subordinate to the overall law enforcement mission.
- Tactical combat casualty care (TCCC) has adapted civilian advanced life support principles to provide medical care during an effective hostile force encounter. Its goals are to treat the casualty, prevent additional casualties, and complete the mission.
- TCCC is divided into three phases of care—care under fire (CUF), tactical field care (TFC), and combat casualty evacuation care (CASEVAC).
- Tactical emergency casualty care (TECC) addresses casualty management during high-threat civilian tactical and rescue operations and is divided into three phases; direct threat, indirect threat, and evacuation care.
- Urban search and rescue (USAR) is the science of responding to, locating, reaching, medically treating, and safely extricating victims entrapped by collapsed structures. The primary role of the emergency clinician is support of the health and welfare of the team members, including canines.
- USAR teams often treat crush syndrome, particulate inhalation, hazardous materials exposures, and blast injuries.
- In crush syndrome, treatment with fluids begins prior to extrication to avoid life-threatening complications once the patient is extricated.

CHAPTER e4

Tactical Emergency Medical Support and Urban Search and Rescue

Nelson Tang | Leah Bright

PRINCIPLES

Background

A confluence of domestic incidents in the mid-1960s of unprecedented violence and scale demonstrated to law enforcement agencies in the United States that increased preparedness and specialized response teams were necessary. Today, law enforcement agencies in the United States have ready access to highly trained individuals and special equipment to respond to high risk, operationally complex situations. Often referred to as special weapons and tactics (SWAT), police tactical teams respond to rapidly evolving patterns of crime and violence, including the criminal use of military style weapons, taking of hostages, and increasingly organized terrorist activities.

National leaders within law enforcement, emergency medicine, and emergency medical services (EMS) have supported the development of dedicated medical support for tactical teams. Position papers from the National Tactical Officers Association, National Association of EMS Physicians, and American College of Emergency Physicians supported tactical emergency medical support (TEMS) as an essential component of law enforcement teams, which help maintain a healthy and safer environment for law enforcement and the public. Today, the breadth of law enforcement tactical missions commonly includes hostage or barricade situations, high-risk warrant service, active shooter incidents, violent felon apprehension, civil disturbances, dignitary and executive protection, maritime and dive operations, and explosive ordnance disposal.

Tactical emergency medical support (TEMS) is now viewed as an invaluable adjunct to law enforcement operations and public safety.[1,2] Professional practice in the area of TEMS continues to attain formal recognition, and physician competency is a newly established requirement of subspecialty certification in emergency medical services (EMS).[3,4] Furthermore, the efficacy of tactically trained medical providers and their roles have been described in a growing number of unconventional prehospital scenarios.[5]

Organizational Principles and Objectives

Tactical medicine augments high-risk law enforcement operations by providing scene commanders with medical threat assessments, delivering immediate emergency medical care, and promoting the safety and health of law enforcement personnel. Tactically trained medical personnel achieve their objectives through mission preplanning, implementation of clinical practices developed specifically for law enforcement applications, and provision of a critical interface between law enforcement personnel, conventional EMS, and existing emergency health care system infrastructure.

The broad goals of TEMS are to facilitate the overall success and safety of law enforcement missions during all phases of a tactical operation through the delivery of preventive, urgent, and emergency medical care. The basic approaches used by tactical medicine providers were initially developed by the military for small unit operations and have been widely applied to civilian law enforcement. The primary function of TEMS during a mission is to provide broad medical support, including injury prevention, resource identification and allocation, and rapid access to emergency medical care.

During law enforcement operations, medical activities and casualty movements are a coordinated effort between the command post, operational team leaders, and medical support element. Tactical physicians are often on scene to ensure that local medical resources, including conventional EMS, are properly staged, briefed, and ready to assist the operation as circumstances require and safety permits. During law enforcement operations of extended duration, the need for dedicated medical support resources is intensified.[6]

A fundamental principal in tactical medicine is that the medical mission may be subordinate to the overall law enforcement mission. In contrast to conventional EMS and hospital practices, in which the sole priority is usually the health and welfare of the patient, the essential priority in a tactical mission is the success of the law enforcement objective. When a casualty occurs during a tactical operation, medical providers may be directed to delay or modify medical care until the tactical commander determines that rendering care will not jeopardize the overall mission.

SPECIAL ISSUES

Tactical Emergency Medical Support Providers and Scopes of Practice

A fundamental consideration in TEMS concerns the level or type of medical provider to be deployed. Most commonly, tactical medical support is rendered by experienced emergency medical personnel with EMS backgrounds, trained in basic life support (BLS) or advanced life support (ALS). BLS providers are generally more plentiful, with fewer requirements for initial and continuous training, whereas ALS providers are typically less numerous, difficult to train, and more costly to maintain. Larger law enforcement agencies, especially at the federal and possibly state levels, may deploy BLS and ALS personnel. True multitiered programs in TEMS are rare, not accounting for the potential operational role of tactical physicians or the agency medical director.

Jurisdictional EMS standards may restrict many or all the interventions commonly found in the ALS scope of practice. Nevertheless, specialized BLS providers with focused expansions of practice have demonstrated real effectiveness in providing operational medical support for federal law enforcement.[7] TEMS medical directors have the authority to train BLS providers

judiciously, with enhanced skill sets required for clinical care in the tactical environment.

Given that the overall volume of patient encounters in tactical emergency medical support is relatively low, TEMS-specific protocols and training paradigms have often been developed with a paucity of data and based on anecdotal evidence. Although the impetus for many tactical medicine programs was the threat of traumatic injuries during law enforcement special operations, opportunities to provide more comprehensive medical support beyond the narrow scope of trauma care have emerged. Subsequently, there has been increasing evidence to justify broadened medical training, protocols, and expanded clinical skills sets for tactical medics.[7,8]

Two distinct subgroups of encounters occur in TEMS—low-frequency, high-acuity (eg, gunshot wound, cardiac arrest, and falls from height) and high-frequency, low-acuity (eg, musculoskeletal sprains and strains, environmental exposures, lacerations).[7] Management of low-frequency, high-acuity patient encounters requires proficiency in lifesaving interventions; however, advanced clinical skills are difficult to maintain in low-volume EMS systems. Furthermore, because TEMS providers typically serve as medics as well as law enforcement officers, resources, including time, funding, and opportunities to maintain clinical skills, are often limited.

By contrast, high-frequency, low-acuity patient encounters are not medically emergent or even urgent in many cases. However, because patient populations encountered in TEMS are very often law enforcement officers, the impact of these low-acuity issues on overall tactical team performance, capacity, or time can be significant. Unfortunately, the assessment and management of low-acuity medical complaints (eg, laceration repair, vaccination, muscle cramps) are often out of the scope of training and clinical practice of conventional EMS providers. The challenge for medical directors and law enforcement agencies is to ensure that protocols, training, and ultimately provider capabilities are sufficiently adept to manage types of clinical encounters in TEMS.

Medical Oversight of Tactical Emergency Medical Support

As a rapidly expanding subspecialty area of prehospital medical practice and law enforcement operations, TEMS programs carry special administrative and medical oversight requirements. Qualified physician leadership and medical control, as in conventional EMS, is an essential component of tactical emergency medical support. Unique qualifications and expanded responsibilities exist for medical directors. The ability to manage thoughtfully and proactively enhanced provider scopes of practice, adjuncts to conventional EMS interventions, and integration with existing health system and public safety infrastructure are equally important.

The successful integration of emergency medicine into law enforcement operations is a complex process that mandates effective medical leadership. All fundamental tenets of medical director accountability in EMS apply to tactical emergency medical support programs.[9] The added challenges of directing care in the law enforcement arena and potential need for augmented capacities of TEMS providers call for additional qualifications of emergency clinicians directing such programs.[10] Of foremost significance, the TEMS medical director must understand the central mission of the law enforcement agency. TEMS medical directors must formulate and implement clinical policies, protocols, and training sufficient for TEMS providers to deliver effective preventive, urgent, and emergent medical care in the dynamic law enforcement environment. Additionally, they must be proficient in the formulation of operational medical plans and have a functional understanding of special operations and tactical procedures.

Casualty Care

Tactical combat casualty care (TCCC) originated as a project within naval special warfare, and tactically appropriate battlefield trauma care guidelines were published in 1996. These were later continued by the US Special Operations Command and used today throughout the Department of Defense. TCCC adapted civilian ALS principles to provide medical care during an effective hostile force encounter. These combat trauma care guidelines combine advanced trauma care with good small-unit tactics, balancing the need to treat casualties against the risks of providing such treatment within the context of an ongoing operation.[11] The three major goals of TCCC are to treat the casualty, prevent additional casualties, and complete the mission.

The treatment principles of TCCC were developed based on the recognition that preventable deaths in combat scenarios occur from uncontrolled hemorrhage due to extremity wounds, tension pneumothorax, and airway compromise from maxillofacial trauma. TCCC recognizes that the tactical objective of neutralizing an effective hostile threat generally takes precedence over providing definitive medical care. TCCC divides the level of medical care provided during a hostile force encounter into three phases—care under fire (CUF), tactical field care (TFC), and combat casualty evacuation care (CASEVAC).

Care Under Fire

CUF is the first phase of casualty care that is rendered while tactical operators are under direct effective hostile fire (Fig. e4.1). CUF encourages the casualty to remain engaged in the operation, seeking cover and concealment, and returning fire, if possible. Immediate lifesaving maneuvers that may be rendered by a casualty ("self-aid) or a nearby tactical operator (buddy aid) are emphasized in this phase. Because uncontrolled hemorrhage from extremity wounds is a leading cause of preventable battlefield deaths, CUF emphasizes control of life-threatening bleeding with early use of a tourniquet. Airway management while under fire is preferentially deferred until the TFC phase. Both CPR and cervical

Fig. e4.1. Care under fire—direct threat phase of care. (Courtesy Nelson Tang, with permission)

spine immobilization are usually contraindicated in the presence of an ongoing hostile threat.

Tactical Field Care

TFC begins once operators, who remain at risk of injury, are no longer under direct effective hostile fire and is most often rendered by trained medical providers. Assessment and treatment priorities include assessing the casualty for unrecognized hemorrhage and controlling all sources of bleeding, including through the use of tourniquets and topical hemostatic agents (Fig. e4.2). Attention is directed toward establishing or maintaining an unobstructed airway by using simple maneuvers, such as inserting a nasopharyngeal airway and/or placing the casualty in a recovery position. Casualties with unilateral blunt or penetrating chest trauma in respiratory distress are rapidly evaluated for tension pneumothorax or sucking chest wounds and undergo needle decompression, if indicated, or are treated with an occlusive dressing, as necessary. When possible, intravenous (IV) or intraosseous access is established to administer fluids and/or medications. Grossly contaminated wounds, open fractures, or penetrating abdominal trauma may receive empirical IV antibiotics, especially if evacuation and transport times are prolonged. The need to perform a complete physical examination (secondary survey) is balanced against the risk of hypothermia, which should be actively managed using layered coverings and warmed IV fluids.

Combat Casualty Evacuation Care

CASEVAC is the care rendered while the casualty is being evacuated by ambulance or helicopter to undergo definitive care at a prestaged landing zone or casualty collection point (Fig. e4.3). Interventions and therapeutics during the CASEVAC phase most closely approximates conventional EMS care and includes continued ALS while en route to receiving facilities, most often trauma centers. The situational tempo, severity of specific injuries, numbers of casualties, and local system practices determine whether the TEMS provider accompanies an injured law enforcement officer to the hospital to act as the patient's advocate, as well as a liaison to tactical command.

Committee for Tactical Emergency Casualty Care

Whereas TCCC is widely accepted in the military combat setting, there are some data that question the applicability of TCCC to the civilian environment.[12] Recognizing this, a diverse group of first responder and tactical medicine experts, the Committee for Tactical Emergency Casualty Care was formed and, in May 2011, held their inaugural meeting to create the tactical emergency casualty care (TECC) guidelines, a set of best practice recommendations for casualty management during high-threat civilian tactical and rescue operations. Based on principles derived from TCCC, TECC guidelines consider differences in the civilian environment, including resources allocation, patient populations, and scopes of practice. TECC is applied in three phases—direct threat, indirect threat, and evacuation care.[12-14]

Direct Threat Care. To meet the specific operational scenarios and terminology used in the civilian sector, the first phase of care under TECC is termed *direct threat care*. The priorities of direct threat care emphasize mitigating the threat, moving the wounded to an area of relative safety, and managing massive hemorrhage by using tourniquets. Additionally, emphasis is placed on the importance of various rescue and patient movement techniques, as well as rapid airway opening and positioning techniques, if operationally feasible. Treatment and operational requirements are the same for all levels of providers during this phase of care.

Indirect Threat Care. Indirect threat care can be initiated once the casualty is in a relatively safe area, with proper cover and less chance of rescuers being injured or patients sustaining additional injuries. Similar to TCCC, assessment and treatment priorities in this phase focus on the preventable causes of death. Four different levels of providers are assigned to scope of practice and skill sets based on level of training and certification—law enforcement officer, emergency medical responder (or equivalent), emergency medical technician (EMT), and advanced EMT-paramedic.

Evacuation Care. The final phase of care under TECC is called evacuation care, when the casualty is moved to a definitive treatment facility. Most additional interventions during this phase of care are similar to those performed during normal EMS operations. However, reassessment of prior interventions and hypothermia management are emphasized.

Tactical Team Health

Historically developed to address the well-recognized potential for lethal injuries intrinsic to tactical operations, the initial focus of TEMS was training and preparation to render lifesaving trauma care. Tactical medicine today is much broader in scope, drawing

Fig. e4.2. Tactical field care—indirect threat phase of care. (Courtesy Nelson Tang, with permission)

Fig. e4.3. Combat casualty evacuation care—evacuation phase of care. (Courtesy Nelson Tang, with permission)

from clinical principles and practices of preventive, sports, occupational, and emergency medicine. The broad objectives of such programs are to support the overall success of the tactical mission by optimizing the health and wellness of the operational team as well as providing immediate emergency medical and trauma care. Core tactical medicine responsibilities include the health surveillance of law enforcement personnel and delivery of preventive and routine medical care. It is common today for TEMS providers to manage issues such as sleep-rest cycles, hydration and nutrition, vaccinations, environmental exposures, and preexisting medical conditions for the tactical teams. High-volume TEMS programs have demonstrated that tactical medics most frequently encounter law enforcement officers as patients, validating these programs as ones designed to protect the health and welfare of the team.[9-11]

Integration With Emergency Medical Services Infrastructure

TEMS programs generally operate within the framework of existing local EMS systems and abide by established mechanisms for administrative oversight. More often than not, TEMS may be a specialty function or service of the existing EMS system. Even if a law enforcement agency has intrinsic tactical medical assets and thereby jurisdictional authority to expand on established EMS protocols or scopes of practice, from quality and system-based perspectives, it is preferable for TEMS programs to operate in overall concert with the local infrastructure. Close working relationships contribute to quality of care and optimize transitions of care and mutual aid responses.

Although concepts of operational security (OPSEC) are basic to law enforcement and security personnel, they may be less familiar to EMS and other health care providers. OPSEC governs how sensitive information, even unclassified, is handled and protected. In the law enforcement context, there can be issues related to OPSEC that preclude full disclosure of all TEMS-related capabilities and activities in all cases. Nevertheless, focused outreach and effective communication on the part of the TEMS medical director can be tremendously valuable for system integration and interagency public safety cooperation.

EMS policies and protocols are typically administered at the state or regional level, thereby resulting in significant jurisdictional variation. In many cases, EMS protocols, provider certifications, duties, and scopes of practice are matters of legislative governance.[15] Specific local protocols, including the provision of TEMS care, is often guided by factors such as population, geography, resources, and medical oversight.[16] If expanded scopes of practice are invoked, it is the responsibility of the TEMS medical director to ensure that advanced procedures and protocols are justified to support force protection and mission safety.[10]

Due to the special requirements for operating in the austere tactical environment, TEMS providers are often trained and authorized to perform therapeutic procedures that may be unconventional when compared to standard EMS. Procedures such as supraglottic airways, needle thoracostomy, tourniquets, topical hemostatic agents, intraosseous vascular access, and field-expedient splinting and wound care are often deployed in TEMS for lifesaving care. Additionally, specialized capabilities such as medical threat assessment, remote patient assessment, forensics and evidence preservation, rapid decontamination, and hazardous materials management have all been described.

Active Shooter Incidents

The prevalence of hostile mass casualty events, such as school, workplace, and public venue shootings, seems to be an ever-increasing phenomenon worldwide. Determining potential strategies for prevention remains a massive undertaking for medicine and law enforcement alike. The destructive capacity of single or small numbers of individuals armed with conventional weapons is now well recognized and must be addressed using public safety and public health approaches.

Although ideally suited to function within the operationally austere conditions of law enforcement SWAT missions, TEMS remains a relatively small and selective component of the multidimensional response to a mass casualty, active shooter incident. Just as a SWAT team is not likely to be the first law enforcement element to arrive at such an incident, TEMS providers will generally not be the first medical responders on the scene. Additionally, TEMS providers are usually small in number and logistically embedded with the tactical team. Recent studies of active shooter events in the United States have characterized the brief duration of many such events, building consensus that first responders and conventional EMS must be capable of reaching casualties quicker and initiating lifesaving procedures sooner.[17,18] Consensus panels have been convened to formulate best practices from military and civilian TEMS lessons learned.[13,19,20] EMS systems have developed rescue task force models to enable its providers to respond to active hostile situations using personal protective equipment, with law enforcement officer providing security and deploying medical approaches adapted from TEMS principles.[21,22]

Future Directions

Despite rapidly growing recognition of its efficacy, the development of TEMS programs and capabilities remains a collateral responsibility for most law enforcement agencies around the country. TEMS programs often remain informal initiatives, existing under the auspices of ad hoc agreements between local law enforcement and a medical entity, with limited funding. Widespread medical acceptance of the TEMS mission and continued development of physician leadership remain as challenges.

URBAN SEARCH AND RESCUE

Urban search and rescue (USAR) is the science of responding to, locating, reaching, medically treating, and safely extricating victims entrapped by collapsed structures. USAR is a so-called multihazard discipline because it may be needed in a variety of emergencies, natural disasters such as earthquakes and hurricanes, and human-made disasters, including terrorist attacks, building and structure collapse, hazardous materials spills, and trench collapse.[23] Federal activation of USAR teams occurs when local and state resources have been overwhelmed during a disaster and there has been a request from a state governor to the President for the activation of federal response assets. For responding teams to be effective, they should be highly trained, quickly deployable, mobile, and self-sufficient.

In the 1980s Fairfax County Fire and Rescue (Virginia) and Metro-Dade County Fire Department (Florida) created elite search and rescue teams. These teams worked with the Office of Foreign Disaster Assistance and were deployed to disaster scenes internationally. In 1989, the Federal Emergency Management Agency (FEMA) established the National Urban Search and Rescue Response System after recognizing that there was a lack of teams for urban disasters. The model structures local emergency rescue personnel into response task forces. In 1991, USAR was incorporated into the National Response Plan (NRP), which is organized into 15 emergency support functions (ESFs) grouped under Homeland Security. Search and Rescue Annex is ESF 9. Any of the ESFs can be used during a disaster.

Components and Structure of an Urban Search and Rescue Team

The responding team must mobilize quickly, without placing additional demands on the already stressed infrastructure at the

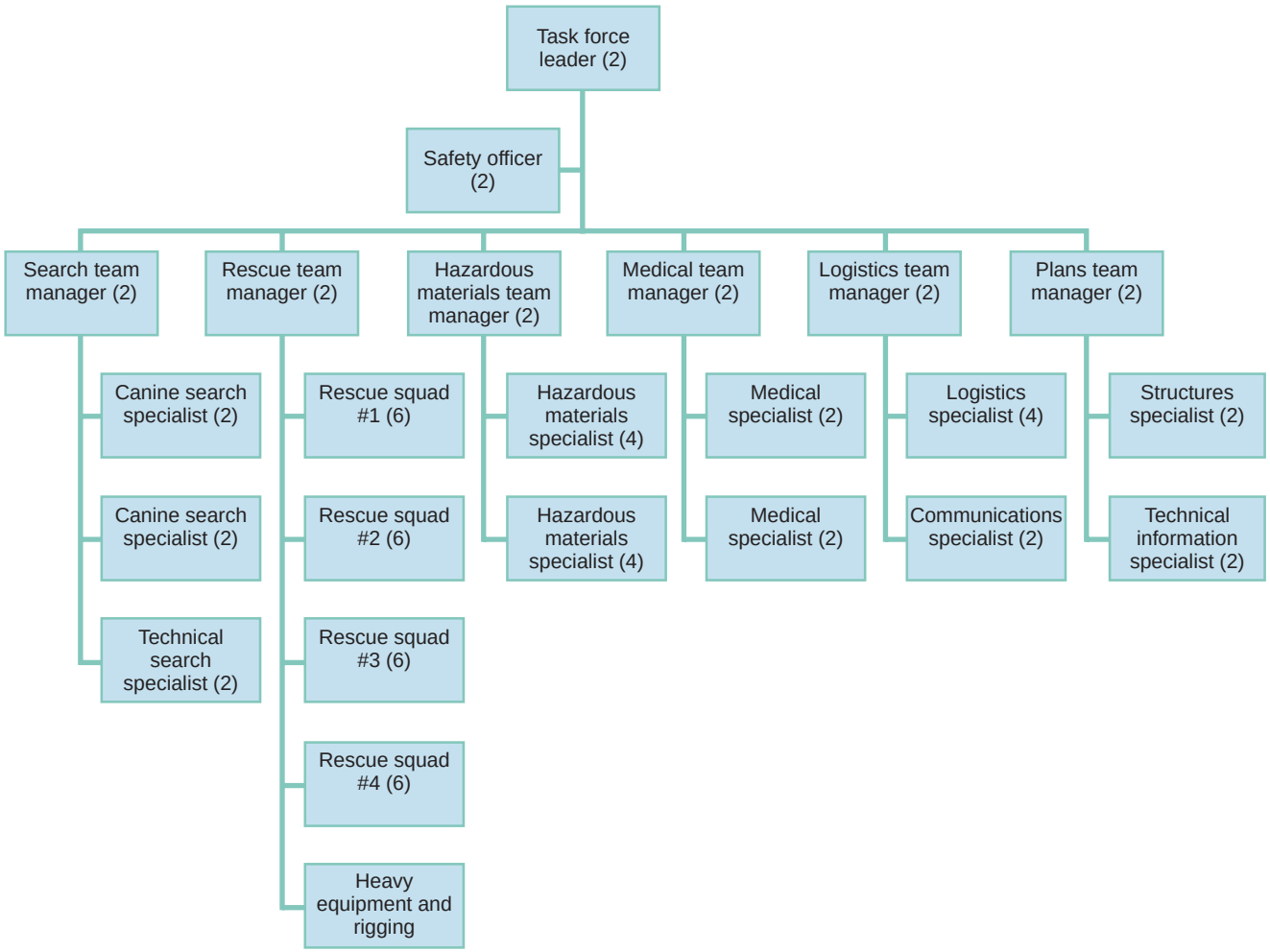

Fig. e4.4. Structure and organization of a Federal Emergency Management Agency (FEMA) urban search and rescue team.

area of deployment. Fig. e4.4 shows the organizational structure of a FEMA USAR team.[23] There are 28 FEMA USAR task forces throughout the continental United States that are trained and equipped to respond to a federal disaster. FEMA will deploy the three closest task forces within 6 hours of notification. Each task force consists of two 31-person teams, four canines, and a comprehensive equipment cache. USAR task force members work in four areas of specialization—search (discovering survivors after a disaster), rescue (safely rescuing and transporting victims from areas of high water or collapsed structures), technical (structural specialists shoring up structures so sites are safe for rescuers), and medical (caring for victims before and after a rescue, prior to being transferred to a disaster medical assistance team [DMAT] site). The length of deployment is typically 10 to 14 days. The search and rescue objective is for live search, not recovery of the deceased.

An effective USAR team has properly trained personnel and appropriate equipment. The equipment cache allows the task force to be totally self-sufficient for the first 72 hours and be capable of 24-hour operations for 10 days. The FEMA equipment cache is divided into five groups—rescue, medical, technical, communications, and logistics equipment. The medical equipment cache was designed to treat the unique medical needs of entrapped victims, as well as the medical needs of the team itself. The medical cache contains enough supplies to handle 10 critical cases, 15 moderate cases, and 25 minor cases. The cost of an entire cache is approximately $2 million.[23]

Coordination and cooperation with local resources and other teams is critical.[24] Thus, the USAR team is integrated into the Incident Command System (ICS) at the disaster.

The search team is responsible for developing and implementing a plan to search the area for victims. The search team can be subdivided into two teams, a canine search team and technical search team. The canine team uses specially trained dogs to locate trapped victims. The technical team uses specialized microphones, listening devices, cameras, and fiberoptic devices to locate victims in confined spaces. The search team is responsible for locating victims and identifying probable areas where victims may be found.

The rescue team is composed of rescue specialists. Once a victim or potential victim is located, the rescue team is responsible for creating a safe entrance and exit from the victim's position. The rescue team works with the technical team to shore and stabilize unstable walls.

The technical team includes structural specialists, hazardous materials specialists, heavy rigging and equipment specialists, technical information specialists, and communications specialists, who work collaboratively to ensure a safe and efficient operation. The logistics team is responsible for all the equipment needs, including inventory, issuing, and record keeping. Finally, the medical component is composed of personnel who are responsible for the medical needs of the task force personnel and victims. Typically, medical personnel consist of paramedics and two emergency clinicians.[24,25]

Medical Team Operations in Urban Search and Rescue

A number of unique considerations must be addressed for USAR. The emergency clinician on the team works with the team leader and managers of the other teams (eg, search, rescue). To do this efficiently, the emergency clinician should be familiar with the capabilities and training of all the members on the team and the ICS. Cross-training of team members is ideal, and team training sessions are required.[24-26] Often during a disaster, the medical team will join the search and rescue teams.

USAR team emergency clinicians have two primary objectives during a search and rescue. The first is to care for the medical team members, who will often be working to stabilize trapped victims medically for prolonged periods of time. Often, the emergency clinician may also be at the patient's side. The second objective is to provide medical care to other team members and canines. To prepare for this, USAR emergency clinicians participate in a week-long training course, which includes drills in confined space and learning about medical scenarios that will likely be encountered during a USAR deployment (Fig. e4.5).

Medical Team Tasks

Predeployment

The function of the medical team in the predeployment phase is to ensure that the entire team is fit and functional for deployment and that the medical equipment cache is organized and up to date.[25] The perceived medical threats in the deployed area must also be addressed (eg, endemic diseases, water contamination, insect threats, existing medical support), and medical intelligence information needs to be collected and addressed (Box e4.1). A plan is developed to transfer and transport victims and for fatality management.

Fig. e4.5. Training of emergency clinicians for urban search and rescue. (Courtesy Leah Bright, with permission)

Deployment

The medical action plan, which may include information regarding medical evacuation and local EMS resources, is critical for ensuring smooth operations and should be updated as conditions or knowledge changes.[23-25] The medical team must also assess the adequacy of team members' rest and sleep, as well as the psychological effects of the situation.[24,25] In addition, the USAR medical assets must be integrated with the overall medical response that is guided under ESF 8, "Public Health and Medical Services." This includes integration with existing medical resources, DMATs, TEMS resources, military resources, and public health. The medical team also undergoes basic veterinary training before deployment during their training.

Confined Space Rescue

A confined space is defined as any space with limited access and ventilation. The emergency clinician and medical team must be prepared to work in this setting and should be aware of issues related to team and victim safety, air purification, and structural dynamics related to collapse or impending collapse.[26,27] Medical providers may be asked for input on cessation of rescue operations based on the likelihood of finding survivors. The decision should be based on individual characteristics of the event and not rely on predefined time frames, as evidenced from the 2010 Haitian earthquake.[27]

Specific Medical Challenges

USAR teams will typically respond to the aftermath of earthquakes, collapsed structures, terrorist bombings, hurricanes, and other natural and human-made disasters.[27] Reviews of the literature have identified the types of medical problems and conditions that might be encountered.[24,25] Most of the medical conditions are those encountered in the emergency department and are managed similarly. The following clinical problems occur with much greater frequency in the USAR environment: crush syndrome, compartment syndrome, particulate inhalation, hazardous materials exposures, and blast injuries.[25]

Crush Injury and Crush Syndrome

Crush syndrome is defined as the systemic manifestations caused by crushed muscle tissue. This typically occurs when blood flow

BOX e4.1

Predeployment Medical Intelligence Gathering

Type of disaster and predicted numbers and types of potential victims
Capabilities of team to deal with medical aspects of the situation, including dealing with injured team members
Local emergency departments' level of functioning; trauma center status and location
Local EMS resources
Location of planned triage staging area
Communications with local resources (eg, EMS, police, emergency departments, fire and rescue)
Weather, environment, or hazardous materials issues
Availability of other resources (eg, military, NDMS, DMAT)

DMAT, Disaster medical assistance team; *EMS,* emergency medical services; *NDMS,* National Disaster Medical System.

is restored to the crushed tissue and toxins are released systemically. It is estimated that 3% to 20% of earthquake victims and up to 40% of survivors of multistory building collapses will have crush syndrome. Early hydration of the victim in the rubble before, during, and after extrication can mitigate the nephrotoxicity of crush syndrome. The amount of time required for crush syndrome to develop depends on the amount of pressure and patient factors. It can occur within 1 hour if the pressure is severe, but often takes 4 to 6 hours to develop.

The cause of muscle injury in crush injury is not fully understood and remains controversial. When the crushed area is released, there is a release of toxic intracellular contents into the systemic circulation. Victims may be trapped for days with a severe crush injury and appear stable when they are reached by rescuers, but deteriorate soon after being rescued. The major causes of early death due to crush syndrome are hypovolemia due to third spacing of fluid, dysrhythmias due to severe metabolic acidosis, and hyperkalemia. Delayed causes of death include renal failure, acute respiratory distress syndrome, sepsis, ischemic organ injury, disseminated intravascular coagulopathy, and electrolyte disturbances.

Early aggressive therapy is essential for the prevention of crush syndrome and should begin before extrication. All victims who have an obvious crush injury or are immobilized for 4 hours or more should be considered to have crush injury. The severity of the crush syndrome may be related to the number of extremities injured. In a Japanese study of earthquake victims, the incidence of acute renal failure due to crush syndrome was 50% for one, 75% for two, and 100% for three or more involved extremities. Once a victim is located, the medical component needs to be actively involved with the rescue process and treatment should be started before extrication. Continuous cardiac monitoring is recommended and can be performed in confined space. Hydration is started along with the usual management of hyperkalemia (eg, insulin or glucose, ion exchange resins, β-agonists,). Current FEMA guidelines recommend IV calcium only for arrhythmias or when there is documented severe hypocalcemia.[25] An average-sized adult may require up to 12 L/day of fluids to sustain a forced diuresis of 8 L/day to prevent renal complications. Continued monitoring of the patient's vital signs, hydration status, and urine output should be used to guide fluid administration.[26]

Airway Management

Another unique medical problem in USAR is dust and airway contamination. During earthquakes and building collapses, a tremendous amount of dust is released into the air. During the first 48 hours of rescue efforts at the World Trade Center, 90% of the 10,116 New York City Fire Department rescue workers evaluated at the site reported an acute cough, often accompanied by nasal congestion, chest tightness, and/or chest burning, but only three required hospitalization for respiratory symptoms. A cough was eventually found in 1561 (29.1%) firefighters at baseline and 1186 (22.1%) at follow-up, including 559 with delayed onset.[28] The victim of a collapsed structure should be assumed to have some sort of dust contamination. Evaluation of the airway for any evidence of burns or hazardous materials exposure is routine. During the extrication process, patients are fitted with dust and particle masks, and their airway is monitored for deterioration. If intubation is considered, it should be done early, before edema obstructs the airway and prior to a prolonged extrication, when accessing the victim may be difficult.

Hazardous Materials and Exposures

Chemical, explosive, and radiologic agents represent potential threats to the USAR team. Hazardous materials may be released from many sources, such as manufacturing plants or transportation vehicles. Explosions and fires from disrupted gas lines or other flammable and explosive gases and liquids present significant hazards. Radiation is a danger that may threaten search and rescue operations, as demonstrated by the Fukushima nuclear reactor radiation leak after the earthquake in Japan in 2011.

Medical teams are integral to the success of the USAR capability. USAR deployments are often highly challenging, and the prerequisite training is rigorous. The USAR emergency clinician must be prepared and specifically trained to work in confined spaces and other challenging situations.

KEY CONCEPTS

- Tactical emergency medical support (TEMS) facilitates the overall success and safety of law enforcement missions during all phases of a tactical operation through the delivery of preventive, urgent, and emergency medical care.
- A fundamental principal in tactical medicine is that the medical mission may be subordinate to the overall law enforcement mission.
- Tactical combat casualty care (TCCC) has adapted civilian advanced life support principles to provide medical care during an effective hostile force encounter. Its goals are to treat the casualty, prevent additional casualties, and complete the mission.
- TCCC is divided into three phases of care—care under fire (CUF), tactical field care (TFC), and combat casualty evacuation care (CASEVAC).
- Tactical emergency casualty care (TECC) addresses casualty management during high-threat civilian tactical and rescue operations and is divided into three phases; direct threat, indirect threat, and evacuation care.
- Urban search and rescue (USAR) is the science of responding to, locating, reaching, medically treating, and safely extricating victims entrapped by collapsed structures. The primary role of the emergency clinician is support of the health and welfare of the team members, including canines.
- USAR teams often treat crush syndrome, particulate inhalation, hazardous materials exposures, and blast injuries.
- In crush syndrome, treatment with fluids begins prior to extrication to avoid life-threatening complications once the patient is extricated.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER e4: QUESTIONS & ANSWERS

e4.1. Which of the following is a priority for the tactical emergency medical support (TEMS) provider in caring for a victim shot during a hostage incident?
- **A.** Bag-valve-mask ventilation
- **B.** Cervical spine stabilization
- **C.** Endotracheal intubation
- **D.** Intravenous access and fluid resuscitation
- **E.** Tourniquet application to bleeding extremity

Answer: E. This scenario describes care rendered by TEMS in the hot zone, or care under fire; thus, conventional care sequences do not apply. Priorities include mitigation of threats, tourniquet use for serious bleeding, and evacuation to a safer location.

e4.2. A 28-year-old man has been trapped under building debris for 6 hours following an urban explosion. A rescue team is actively working to extricate him. Both legs are pinned, but his torso is free. Which of the following statements is true?
- **A.** Aggressive fluid therapy should begin after extrication.
- **B.** Assessment for crush injury should occur after 2 hours of immobilization.
- **C.** Cardiac monitoring is indicated during extrication.
- **D.** Prophylactic calcium is indicated.
- **E.** The incidence of acute renal failure is approximately 30%.

Answer: C. The incidence of crush injury rises dramatically after 4 hours of immobilization. Continuous cardiac monitoring is indicated during extrication. Calcium is indicated only for refractory arrhythmias or documented hypocalcemia. Fluid resuscitation may help prevent the hypotension associated with release of the entrapped limb(s) and should be initiated before extrication. The incidence of acute renal failure is 50% with one-extremity and 75% with two-extremity crush injuries (Japanese earthquake victim data).

e4.3. The principles of TEMS have largely developed from which type of incidents?
- **A.** Civilian multicasualty events
- **B.** Military conflicts
- **C.** Natural disasters
- **D.** Pandemics

Answer: B. The principles of TEMS have largely developed from lessons learned during military conflicts and most closely emulate the medical support structure of military special operations units.

e4.4. Which of the following is incorrect with respect to the principles of tactical medicine?
- **A.** During a tactical operation, TEMS providers may be directed to delay medical care.
- **B.** During a tactical operation, medical care of a casualty may jeopardize the overall mission.
- **C.** None of these.
- **D.** The first priority is always the health and welfare of the patient.
- **E.** The medical mission may be subordinate to the overall law enforcement mission.

Answer: E. A fundamental principal in tactical medicine is that the medical mission may be subordinate to the overall law enforcement mission. In contrast to conventional EMS and hospital practices, in which the sole priority is usually the health and

welfare of the patient, the essential priority in a tactical mission is the success of the law enforcement objective. When a casualty occurs during a tactical operation, medical providers may be directed to delay or modify medical care until the tactical commander determines that rendering care will not jeopardize the overall mission.

e4.5. Which of the following is a primary responsibility of the USAR team emergency clinician?
A. Extrication of victims
B. Medical treatment of entrapped victims
C. Locating victims
D. Support the health and welfare of team members

Answer: D. The USAR team emergency clinician has a primary responsibility to the team members should they require medical attention.

CHAPTER e5

Emergency Ultrasound*

Heidi Harbison Kimberly | Michael B. Stone

PRINCIPLES

HISTORY

TRAINING, CREDENTIALING, AND ACCREDITATION

APPLIED ULTRASOUND PHYSICS AND INSTRUMENTATION

EQUIPMENT AND SAFETY

APPLICATIONS AND CATEGORIZATION

SPECIFIC ULTRASOUND USES

Trauma Ultrasound

Pelvic Ultrasound

Cardiac Ultrasound

Abdominal Vascular Ultrasound

Biliary Ultrasound

Urinary Tract Ultrasound

Deep Venous Thrombosis Ultrasound

Thoracic Ultrasound

Ocular Ultrasound

Soft Tissue Ultrasound

Musculoskeletal Ultrasound

Testicular Ultrasound

Bowel Ultrasound

Pediatric Emergency Ultrasound

Ultrasound for Procedural Guidance

Out-of-Hospital Ultrasound: Disasters And Remote Settings

INTEGRATION INTO EMERGENCY MEDICINE PRACTICE

KEY CONCEPTS

- Emergency ultrasound is performed and interpreted by the emergency clinician at the bedside.
- Emergency ultrasound is designed to answer focused clinical questions.
- The key to proficiency in emergency ultrasound is practice.
- Credentialing guidelines exist to guide emergency clinicians in the acquisition of this important skill.
- All emergency clinicians should be familiar with the resuscitative applications of emergency ultrasound, including focused assessment with sonography for trauma (FAST), focused cardiac ultrasound, abdominal aortic aneurysm assessment, and procedural guidance for central venous catheter placement.
- The "four Is" of emergency ultrasound are as follows: (1) identification of appropriate patients for whom emergency ultrasound is likely to be valuable; (2) image acquisition; (3) interpretation of the acquired images; and (4) integration of the ultrasound findings into patient management.

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

CHAPTER e5

Emergency Ultrasound

Heidi Harbison Kimberly | Michael B. Stone

PRINCIPLES

Emergency ultrasound (US) is the simultaneous performance and interpretation of a focused sonographic examination at the bedside of the patient for the diagnosis, resuscitation, monitoring, guidance, and treatment of emergency medical conditions.[1] Emergency US is, by definition, performed by the treating emergency clinician and consists of four essential components called the "four Is": (1) identification of appropriate patients for whom US is likely to be valuable; (2) image acquisition; (3) interpretation of the acquired images; and (4) integration of the ultrasound findings into patient management.

Although the operator is typically an emergency clinician, he or she may be an emergency clinician assistant, nurse practitioner, or trained emergency nurse or paramedic—all under the supervision of a trained, credentialed emergency clinician. Emergency US is typically performed in the emergency department (ED) but may also be performed in other areas of the hospital, free-standing EDs, out-of-hospital mobile transport (ground and/or air transport), disaster scenes, military engagements, international rescue work, resource-limited rural and international settings, and remote locations (eg, space, sea, or land centers with limited or no medical access).

As illustrated by the four Is, the emergency clinician performing an emergency US examination selects patients, acquires and interprets images, and integrates their findings directly into clinical care. This is the fundamental difference from the paradigm of traditional imaging specialties, in which a trained technologist typically performs the examination and a physician subsequently interprets, or reads, the images.

Emergency US examinations are focused examinations of an area of the body, organ system, physiologic pattern, or goal-directed investigations of an emergency symptom or sign. Essentially, emergency US is designed to answer a focused, often dichotomous, clinical question (eg, "Does this young female patient with vaginal bleeding have an intrauterine pregnancy?" or "Is there a pericardial effusion present in this dyspneic oncology patient?"). As such, emergency US examinations are neither sufficient nor intended to diagnose all of the broad range of pathologic processes encountered in emergency medicine. Technical limitations clearly exist, whether related to clinician experience, skill or confidence, or a patient's anatomic factors or pathologic condition. If the question of interest cannot be answered after an emergency US is performed, emergency clinicians should choose an alternative strategy to pursue a definitive answer. Despite its limitations, however, the main risk management issue associated with emergency US relates to failure to use this modality when it is available and appropriate.[2]

HISTORY

A half-century of international scientific innovation resulted in the initial medical use of US in the 1950s by physicians interested in its advantages over traditional imaging, including noninvasiveness, lack of ionizing radiation, and superior resolution. In the 1980s, emergency clinicians started to use US as a way to rule out emergent, so-called silent diagnoses, such as ectopic pregnancy, intraperitoneal hemorrhage, hemopericardium, cholelithiasis, renal colic, and aortic aneurysm. A model curriculum was created by the Society for Academic Emergency Medicine (SAEM) that initiated formal guidance for emergency US programs. Due in part to resistance from traditional imaging specialties, the American Medical Association House of Delegates, led by the American College of Emergency Physicians (ACEP), passed a resolution that hospital credentialing committees follow specialty-specific guidelines for US-based credentialing.[3]

Specialty-specific guidelines, created in 2001, updated in 2008 by ACEP, and endorsed by SAEM in 2010, specify emergency US scope of practice, primary applications, training pathways, number of procedures required for training before credentialing, quality assurance and documentation guidance, and training course outlines.[1] Today, more than 95% of emergency medicine residency programs teach US, approximately 30% to 60% of community hospitals have instituted bedside US performed by emergency clinicians, and emergency ultrasound is an integral component of the 2013 model of the clinical practice of emergency medicine.[4]

Since 2008, emergency US has been recognized by organizations outside emergency medicine, including the American Institute of Ultrasound in Medicine, with implementation of the focused assessment with sonography for trauma (FAST) examination, and American Society of Echocardiography, with application of focused cardiac US for shock, effusion, chest pain, and cardiac arrest.[5] Several other organizations have recognized emergency or point of care US, including the World Interactive Network Focused on Critical Ultrasound and Society of Medical Ultrasound in Medical Education.

TRAINING, CREDENTIALING, AND ACCREDITATION

Emergency US training occurs throughout all levels of practice. Medical student emergency US training has been defined by national organizations and, increasingly, medical schools are incorporating emergency US education into their curricula. Emergency US is now one of the competency assessments required of emergency medicine residents by the Residency Review Committee for Emergency Medicine, with defined requirements as set by national organizations.[4,6] US fellowships have become the most common postgraduate emergency medicine fellowship and provide advanced training in emergency US. For emergency clinicians in practice who did not receive residency training in emergency US, initial training often occurs through continuing medical education courses, followed by a period of proctoring or supervision. Recent educational advances, such as simulation, task trainers, Internet-based training, and nontraditional media (eg, electronic books, mobile device applications, social media) may all enhance US training.[7] As a result of the rapid proliferation of high-quality, nontraditional US educational materials, references to free online content (eg, websites, podcasts, videos) will be provided throughout this chapter, where appropriate.

US programs typically require some investment in education and hardware, but reimbursement for professional and hospital fees is adequate to meet a return on investment within years, depending on the number and types of US, payer mix, and documentation.

Credentialing for emergency US at the hospital level is based on specialty-specific national guidelines. See the ACEP ultrasound website (https://www.acep.org/ultrasound) for helpful references for program development and education.

APPLIED ULTRASOUND PHYSICS AND INSTRUMENTATION

A brief summary of relevant terminology is presented in Box e5.1. Readers seeking more in-depth reviews of ultrasound physics, machine controls, ultrasound modes, and instrumentation are encouraged to visit the Sonoguide website (http://www.sonoguide.com/). Relevant lectures on this topic can be accessed through the Academy of Emergency Ultrasound (AEUS) website.

EQUIPMENT AND SAFETY

Modern broadband frequency transducers can selectively use several available US frequencies to maximize tissue penetration or image quality, depending on the application. Transducer design and footprints (the actual transducer surface area touching the patient) can be divided into three categories—flat linear array transducers, curved linear array transducers, and phased array transducers.

- Flat linear array (high-frequency) transducers generate a square or rectangular image with excellent lateral resolution at the expense of width of field and are used for superficial examinations (eg, soft tissue, musculoskeletal) and as procedural guidance for vascular access.
- Curved linear array (low-frequency) transducers, which generate a wider field of view at the expense of lateral resolution, are usually used for applications requiring deep tissue penetration, such as evaluation for pregnancy or abdominal aortic aneurysm. The endocavitary transducer is a highly curved linear array (high-frequency) transducer that is generally used for endovaginal evaluation.
- Phased array (low-frequency) transducers offer a smaller footprint than curved linear array transducers and are ideal for cardiac evaluations, although they can also be used for abdominal examinations. Transesophageal echocardiographic and biplanar transducers have more recently been used in EDs exploring new imaging venues.

US biosafety includes use of the ALARA (***a***s ***l***ow ***a***s ***r***easonably ***a***chievable) principle, appropriate Doppler usage, and appropriate microbiologic disinfection of the ultrasound transducer and system.[8] US is kinetic energy, and users of this technology should observe the ALARA principle by performing procedures only when indicated and limiting the time of sonographic investigation. Doppler modes should be minimized over sensitive tissue, including early gestation and germinal, mucosal, ocular, and neural tissues. Surface transducers should be cleaned at the bedside with mechanical removal of gel and debris, followed by disinfection with an appropriate spray or wipe. Endocavitary transducers require more prolonged and substantial cleaning. Safety also includes the use of appropriate barriers over transducers, including condoms, gloves, or commercial barriers over endocavitary transducers and sterile transducer covers for sterile procedures. For nonsterile procedures, or for examination of obviously infected or disrupted skin surfaces, an adhesive dressing can be applied to minimize contamination of the transducer.

BOX e5.1

Common Definitions

Ultrasound (US)—sound waves with frequencies >20,000 Hz. Modern diagnostic US typically operates in the 1- to 18-MHz range
Window—soft tissue where transducer is placed to interrogate tissue in the body
B-mode or brightness mode (greyscale or two-dimensional)—graphs the amplitude of reflected US waves as shades of gray from black to white on a monitor screen
Gain—adjusts the amplitude of signals on the ultrasound display (brightness)
Time-gain compensation (TGC)—changes gain at specific depths
M-mode (motion mode)—displays reflected waves over time and distance; used to calculate rates (eg, fetal heart rate) and evaluate moving structures (eg, cardiac valves)
Color flow Doppler—displays direction and velocity of flow
Power Doppler (power angiography)—displays velocity of flow, but not direction
Pulsed wave Doppler—demonstrates velocity and direction of flow in a waveform display
Focus—image area where US beam is narrowest and lateral resolution is greatest
Near-field—area on display from transducer to focus
Far field—area on display from focus to the bottom of the display
Anechoic—without sounds (black)
Echogenic—with sounds (white)
Hyperechoic—with more reflected sounds than adjacent tissue (more echogenic)
Hypoechoic—with less sound than adjacent tissue (less echogenic)

APPLICATIONS AND CATEGORIZATION

In 1994, SAEM categorized US applications broadly into abdominal, cardiac, obstetric-gynecologic, and special applications. In 2001, ACEP developed guidelines that categorized applications more specifically to include trauma, pregnancy, abdominal aortic aneurysm, cardiac (for pericardial effusion and cardiac activity), biliary, renal, and procedural guidance. In 2008, ACEP added deep venous thrombosis (DVT), thoracic studies for pneumothorax and pleural effusion, soft tissue and musculoskeletal studies, and ocular examination as core applications.[1] Advanced applications at that time included testicular, adnexal, bowel, advanced echocardiography, transesophageal echocardiography, transcranial Doppler, and contrast studies. Grouping of US applications into categories of resuscitative, diagnostic, symptom- or sign-based, procedural guidance, and monitoring and therapeutic helps describe the uses of US in emergency medicine.[1]

The most common uses of emergency US include trauma, cardiac (eg, cardiac arrest, pericardial effusion), abdominal aortic aneurysm, pelvic, biliary, procedural, renal, and DVT. Emergency US is commonly used in clinical pathways or algorithms to identify or exclude emergency medical conditions rapidly. US guidance can also assist with the performance of percutaneous procedures, such as vascular access, diagnostic and/or therapeutic drainage (eg, thoracentesis, paracentesis, pericardiocentesis, arthrocentesis), lumbar puncture, abscess drainage, peripheral nerve blocks, foreign body localization and removal, airway management and others.

Common applications of emergency US are reviewed below, using the four Is approach to highlight critical components of specific examinations. Where available, links to open access educational content are provided for a more in-depth review of

examination-specific issues related to image acquisition and interpretation.

SPECIFIC ULTRASOUND USES

Trauma Ultrasound

Identification of Appropriate Patients

The trauma US examination, also called the focused assessment with sonography for trauma (FAST) examination, was originally developed as a noninvasive alternative to diagnostic peritoneal lavage in the evaluation for hemoperitoneum. As such, the FAST examination is most appropriate for patients with blunt abdominal trauma with hemodynamic instability. The EFAST (extended FAST) examination also includes the evaluation for potential pneumothorax, hemothorax, and pericardial effusion, and often plays a valuable role in the evaluation of patients with blunt or penetrating thoracoabdominal trauma.

Image Acquisition

The FAST technique uses a low-frequency broadband transducer (2–6 MHz) to evaluate dependent peritoneal spaces, pleural spaces, and the pericardium. A thorough evaluation of the potential spaces in the right upper quadrant includes the hepatorenal space (Morison's pouch), diaphragmatic space (including assessment of the thorax for pleural fluid and suprahepatic area for peritoneal fluid), and inferior edge of the liver and right kidney. In the left upper quadrant emergency clinicians should first evaluate the subdiaphragmatic space and tip of the spleen, because free intraperitoneal fluid tends to accumulate here before spilling over the splenorenal ligaments into the splenorenal space. The pelvis should be evaluated in the transverse and longitudinal planes, where fluid may be detected deep to the uterus (in females) or in the retrovesical space (in males). Emergency clinicians may choose to incorporate additional views of the paracolic gutters caudal to the upper quadrant views to detect free fluid surrounding the bowel. Pleural fluid is typically detected during the upper quadrant evaluations described above.

The most common cardiac FAST windows include subcostal (or subxiphoid) and parasternal windows (see below, "Cardiac Ultrasound"). Evaluation for pneumothorax typically uses a low-frequency transducer at a shallow depth or a high-frequency transducer, which provides better resolution, placed along the anterior and lateral chest wall.

Interpretation of the Acquired Images

Typically, fluid in the peritoneum, pericardium, and pleural cavity is anechoic, but it can have echogenicity if active extravasation, a blood clot, or bowel contents are present within the fluid. Compared with other fluid-filled structures in the abdomen and pelvis, peritoneal free fluid generally has sharp pointy edges and an irregular shape, whereas most visceral or vascular structures have intrinsically smooth oval or round contours, with less edge detail (Figs. e5.1, e5.2, and e5.3). The volume of fluid required for a positive US study depends on the site of injury, sonographic window, and experience of the operator, but 250 mL or more is generally visible, and nearly 600 mL of fluid is required for a positive upper quadrant window when fluid is infused from the pelvis.

Pericardial fluid is contained within the parietal and visceral pericardium. Once a certain volume is reached, the pressure in the pericardial space increases dramatically, resulting in cardiac tamponade. Generally, at least 50 mL of fluid is required to cause hemodynamic compromise in a patient without prior pericardial

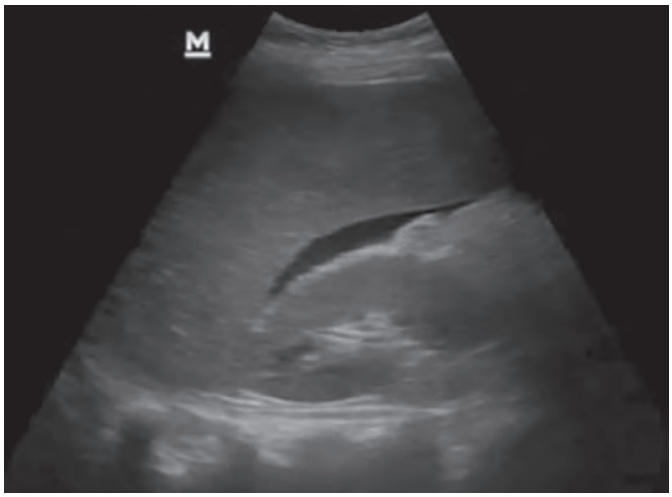

Fig. e5.1. Free fluid in the hepatorenal recess (Morison's pouch).

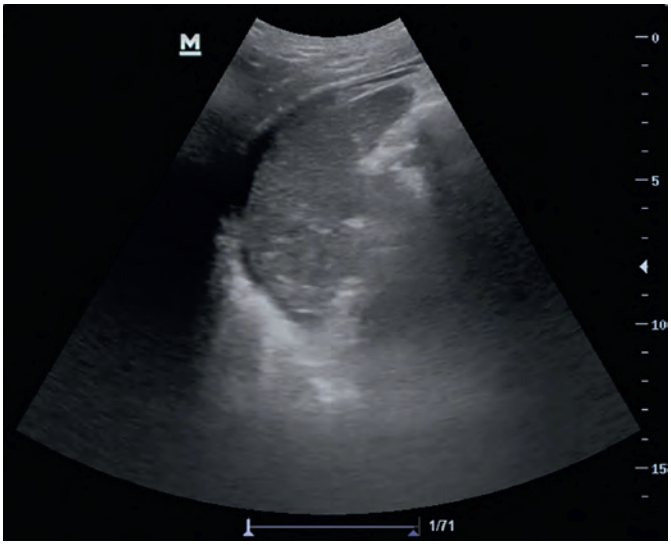

Fig. e5.2. Free fluid in the splenodiaphragmatic space.

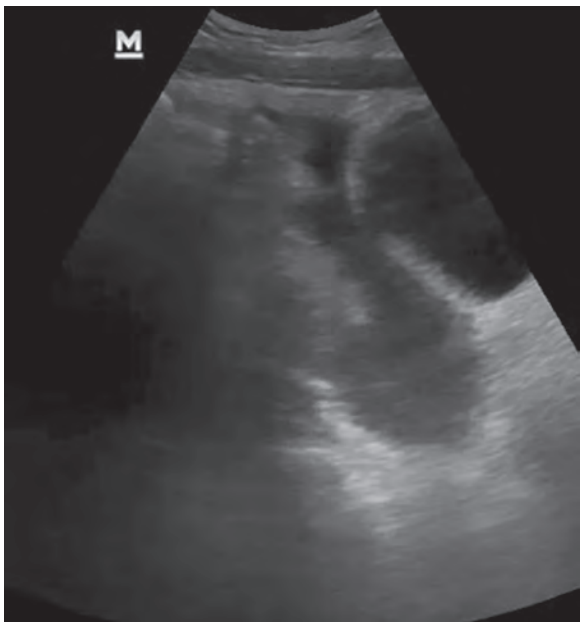

Fig. e5.3. Pelvic free fluid in a sagittal plane.

inflammation. Pleural fluid can also be detected using US, and assessment for hemothorax can be performed in the setting of blunt or penetrating trauma. US is an accurate modality for the evaluation of suspected traumatic pneumothorax through direct visualization of the sliding of the visceral and parietal pleural layers (see below, "Thoracic Ultrasound").

Integration of Ultrasound Findings Into Patient Management

The test characteristics of the FAST examination vary greatly among published studies, and depend on operator skill, patient acuity, and choice of gold standard used for each study, with clinical endpoints suggesting higher accuracy. The FAST does not identify every peritoneal injury, although the need for intervention in undetected injuries has not been studied. The use of US during resuscitation has been shown to decrease patient morbidity, time to operating room, and hospital charges.

Patients with traumatic pericardial effusions diagnosed by emergency US receive more rapid operative intervention and have lower mortality rates. US can also diagnose pneumothorax with excellent sensitivity and specificity compared with supine chest radiography, with accuracy often approaching that of computed tomography (CT).

The FAST examination is accurate and clinically relevant in patients with penetrating thoracic injury and hypotensive patients with blunt abdominal trauma. In contrast, a stable blunt trauma patient with a positive FAST examination will often still require CT imaging due to the growing trend for nonoperative or interventional management of blunt solid organ injury. In addition, FAST is insufficiently sensitive to exclude injuries in stable blunt trauma patients or patients with purely anterior penetrating abdominal trauma to the abdomen.

In pediatric patients, the FAST is not only less accurate but will more often be positive in the pelvis than in the right upper quadrant.[9] In obstetric patients, few observational studies have been performed demonstrating reasonable sensitivity and specificity, although abruption and fetal viability may necessitate an earlier operative course.

FAST is unreliable for the detection of hemoperitoneum in patients with pelvic fractures, and the detection of free fluid in an unstable patient with a pelvic fracture may be due to uroperitoneum from bladder injury rather than hemoperitoneum from vascular injury, clouding the decision for laparotomy versus pelvic embolization. In addition, retroperitoneal injuries to the genitourinary tract are not reliably assessed with the FAST examination.

Additional online educational content relevant to trauma ultrasound can be accessed as follows:

- Trauma Ultrasound eBook—iPad app
- Academic Life in Emergency Medicine—reference card
- Sonoguide website—text, image, video
- AEUS website—narrated lecture
- Emergency Ultrasonography website—video gallery

Pelvic Ultrasound

Identification of Appropriate Patients

Pelvic US by emergency clinicians is used to evaluate patients rapidly who are at risk for ectopic pregnancy.[10] Ultrasonography is used to confirm intrauterine pregnancy in early pregnancy, which indirectly excludes ectopic pregnancy in most patients. Indications for sonographic evaluation of the first-trimester pregnant patient include symptoms or signs that suggest an ectopic pregnancy, molar pregnancy, or fetal demise and dating of the pregnancy. Emergency US may also facilitate detection of fetal viability, incomplete abortion, ectopic pregnancy, and molar pregnancy. Pelvic US may also be used in nonpregnancy states to detect tuboovarian abscesses, masses, and hemoperitoneum in the hemodynamically unstable patient.

Image Acquisition

Pelvic US is performed by a transabdominal or endovaginal technique. The transabdominal technique uses a low-frequency transabdominal transducer placed over the lower abdomen in the suprapubic area. Ideally, the transabdominal examination is performed when the patient has a full bladder (an excellent sonographic window), but this may not be necessary if the uterus is large or the patient is thin. Advantages of the transabdominal technique include wider field of view, detection of large pelvic masses, and greater depth of field. In the endovaginal technique, the transducer is placed in the vagina, ideally with a near-empty bladder. Endovaginal transducers are high frequency, providing excellent axial resolution but poor penetration of distant structures. Early intrauterine yolk sacs and fetal poles within gestational sacs may be detected earlier, and ectopic pregnancies can be identified with more accuracy. Transabdominal and, if necessary, endovaginal US in the hemodynamically unstable patient has replaced culdocentesis for detection of ruptured ectopic pregnancy.

Interpretation of the Acquired Images

The diagnosis of intrauterine pregnancy is established when emergency clinicians confidently identify a gestational sac that contains a yolk sac and/or fetal pole and is located within the endometrium[10] (Fig. e5.4). Findings of an ectopic pregnancy include a chorionic ring or gestational sac containing a yolk sac or fetal pole outside the uterus or in an abnormal location in the uterus, such as the cornu or cervix (Fig. e5.5). Although ectopic pregnancy, molar pregnancy, embryonic demise, blighted ova, subchorionic hemorrhage, and other first-trimester diagnoses are best established by US, image interpretation should remain primarily focused on the search for an intrauterine pregnancy.

Integration of Ultrasound Findings Into Patient Management

Emergency clinician–performed pelvic US has reduced the morbidity of ectopic pregnancy by shortening the time to diagnosis and operating room treatment and has resulted in greater initial

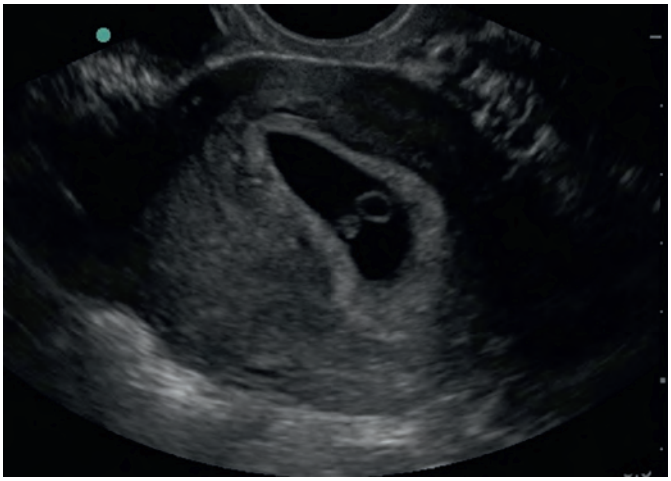

Fig. e5.4. Early intrauterine pregnancy with yolk sac and fetal pole using an endovaginal transducer.

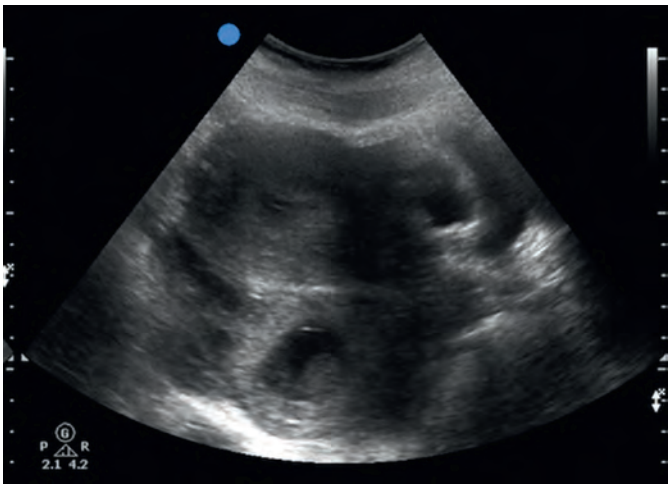

Fig. e5.5. Ectopic pregnancy posterior to the uterus.

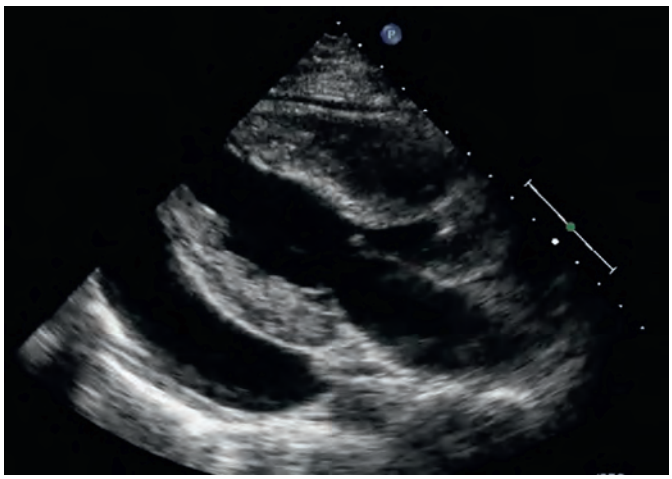

Fig. e5.6. Circumferential pericardial effusion in parasternal long axis.

detection of abnormal pregnancy, reduced ED patient throughput times, and increased patient satisfaction. The detection of live intrauterine pregnancy predicts a rate of 91% continuation past 20 weeks, except for those with vaginal bleeding, who drop to a rate of 86%. Emergency clinicians can also date pregnancies accurately by pelvic US with typical fetal biometry.[11] Heterotopic pregnancies can occur spontaneously at a rate of 1/5000, but occur up to 1 to 3/100 in patients receiving assisted reproductive therapy (ART). As a result, confirmation of an intrauterine pregnancy may not sufficiently exclude the presence of a concomitant ectopic pregnancy in patients receiving ART, and emergency clinicians should perform comprehensive ultrasound evaluations in this patient population, when possible.

Emergency clinicians are adept at the identification of ectopic pregnancies by transabdominal and endovaginal techniques.[10] Pelvic US in nonpregnancy states has good accuracy for a tuboovarian abscess and can lead to faster diagnosis for female patients with abdominal pain.

Additional online educational content relevant to pelvic ultrasound can be accessed as follows:

- Academic Life in Emergency Medicine—transabdominal, transvaginal reference cards
- Sonoguide website—text, image, video
- AEUS website—narrated lectures, parts I and II

Cardiac Ultrasound

Identification of Appropriate Patients

Cardiac ultrasound enables rapid assessment for pericardial effusion, global left ventricular systolic function, and right ventricular enlargement and may prove valuable in hemodynamic assessment and early detection of valvular or aortic emergencies. Emergency clinicians should consider cardiac ultrasound in patients with cardiac arrest, suspected pericardial effusion, trauma, chest pain, undifferentiated hypotension, or dyspnea.[1,5]

In a patient who presents with chest pain, US has been studied for the evaluation of pericardial tamponade, pulmonary embolus, cardiogenic shock, aortic dissection, pneumothorax, and bony chest wall fracture. Cardiac US can also be used to guide placement of transvenous pacer wires and for pericardiocentesis. Transvenous pacer wires are often placed through central veins, and it can be difficult to place them into the right ventricular apex. US facilitates placement by imaging the wires in real time as they pass through the tricuspid valve and approach the apex of the right ventricle.[12] US can also document ventricular capture.

Image Acquisition

Cardiac US is performed through the transthoracic and transabdominal windows with the use of small curvilinear or phased array transducers. Typical views include the subcostal four-chamber view, parasternal long-axis view, parasternal short-axis view, and apical four-chamber view. Although most emergency clinicians are comfortable with the subcostal view from the FAST examination, the parasternal views are excellent windows for left ventricular assessment. The apical four-chamber view is ideal for comparison of right and left ventricular sizes and function. The subcostal four-chamber view is ideal for assessment of pericardial effusion, whereas the long-axis subcostal view highlights the inferior vena cava and provides an alternative two-chamber view of the left and right ventricles in patients with poor parasternal windows.

Interpretation of the Acquired Images

Pericardial fluid is typically anechoic (Fig. e5.6), although it can contain internal echoes in cases of pericardial hemorrhage or infection. Large pericardial effusions are usually circumferential, although large loculated effusions can have important hemodynamic effects as well. As a result, assessment for pericardial effusion should include interpretation of the subcostal, parasternal, and apical windows, when feasible. Emergency clinicians should be familiar with the location and appearance of an epicardial fat pad to avoid mistaking it for a pericardial effusion. Although cardiac tamponade is a clinical diagnosis, there are several suggestive echocardiographic features, including diastolic collapse of the right ventricle (Fig. e5.7; Video e5.1), loss of inferior vena cava respiratory variation, and transvalvular flow velocity paradoxus.[13]

Assessment for global left ventricular (LV) systolic function can be performed with visual estimation and/or estimation of E-point septal separation (EPSS).[14,15] EPSS is the distance between the anterior leaflet of the mitral valve and ventricular septum measured using M-mode. A distance greater than 7 mm correlates with poor LV function. Emergency clinicians should recognize that accurate visual estimation of global LV systolic function requires experience and may prefer to categorize systolic function dichotomously as depressed or normal.

Integration of Ultrasound Findings Into Patient Management

Cardiac US performed by emergency clinicians shows good accuracy in the detection of medical and traumatic pericardial

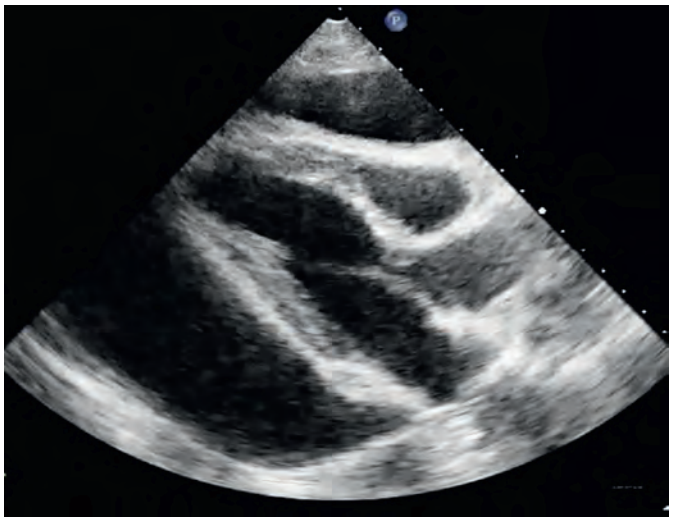

Fig. e5.7. Large pericardial effusion with diastolic collapse of the right ventricular free wall seen on parasternal long axis view (see Video e5.1).

Fig. e5.8. Abdominal aortic aneurysm with mural thrombus.

effusion, assessment of LV function, and evaluation of patients with undifferentiated shock. US has a role in cardiac arrest, where it can detect ventricular motion in asystole and pulseless electrical activity, confirm cardiac standstill and its associated poor prognosis, and detect ventricular capture when the patient is transcutaneously or transvenously paced.[16] There is a developing role for bedside transesophageal echocardiography in the evaluation of the periarrest patient[17]; advanced cardiac life support guidelines have suggested minimizing noncardiopulmonary resuscitation intervals.

Several US protocols have been developed to evaluate undifferentiated hypotension. Cardiac US windows with the addition of abdominal views can assess for effusion, global ventricular activity, ventricular chamber size, inferior vena cava size, respiratory changes, peritoneal fluid, and abdominal aortic aneurysm (AAA) to narrow the differential diagnosis.

Additional online educational content relevant to cardiac ultrasound can be accessed as follows:

- Academic Life in Emergency Medicine—reference card
- Sonoguide website—text, image, video
- AEUS website—narrated lecture parts I and II
- Emergency Ultrasonography website—video gallery

Abdominal Vascular Ultrasound

Identification of Appropriate Patients

Emergency clinicians use abdominal US to detect an AAA in patients with flank, abdominal, or back pain, and to evaluate unexplained hypotension in the older patient. The use of US to detect aortic dissection has also been described.

Image Acquisition

The examination is performed with a curvilinear array or phased array low-frequency transducer, and requires significant pressure to displace the overlying bowel gas, which can obscure the abdominal aorta. The technique involves imaging from the subxiphoid space to the umbilicus and visualizing the aorta from the diaphragm to its bifurcation in transverse and longitudinal planes. If an aneurysm is identified, a view of Morison's pouch and/or the splenorenal space may be obtained to assess for intraperitoneal or retroperitoneal fluid. Proximal iliac arteries may also be evaluated if technically feasible and indicated by clinical suspicion.

Fig. e5.9. Aortic dissection flap visualized on longitudinal view of the aorta.

Aortic dissection may be detected by a combination of abdominal and cardiac scanning, with the addition of a suprasternal notch view to the traditional cardiac windows.

Integration of Ultrasound Findings Into Patient Management

Emergency clinicians should visualize the abdominal aorta and measure its diameter from outside edge to outside edge, being careful to include any mural thrombus in the measurement. A diameter greater than 3 cm (Fig. e5.8) constitutes an abdominal aortic aneurysm, but risk of rupture increases with size and is rare with aneurysms smaller than 4.5 cm.

A linear echogenic flap, anywhere across the lumen of the aorta, is suggestive of aortic dissection (Fig. e5.9), and may be associated with a different Doppler flow pattern on either side of the flap. The cardiac US examination may demonstrate an unexplained pericardial effusion, a dilated aortic root (>4 cm); aortic insufficiency, and/or a linear echogenic flap in the ascending aorta, aortic arch (through the suprasternal notch view), descending thoracic, or abdominal aorta.

Integration of Ultrasound Findings Into Patient Management

Emergency clinician use of US for AAA detection has shown good accuracy compared with other imaging modalities. It also has

management implications in older patients with lower back pain, for whom the elimination of the presence of an AAA is important for medical decision making. Screening for AAA in the ED with US has been shown to be effective.

Although intraperitoneal and/or retroperitoneal hemorrhage may be detected, abdominal ultrasound is insufficiently sensitive to exclude a leaking AAA, and CT should be performed in patients with aneurysms in whom the clinical picture suggests the possibility of rupture. Likewise, emergency US may demonstrate evidence of an aortic dissection but should not be used to exclude this potentially life-threatening diagnosis.

Additional online educational content relevant to aorta ultrasound can be accessed as follows:

- Academic Life in Emergency Medicine—reference card
- Sonoguide website—text, image, video
- AEUS website—narrated lecture
  - Emergency Ultrasonography website—video gallery

Biliary Ultrasound

Identification of Appropriate Patients

Biliary US to detect gallstones and associated cholecystitis was one of the early applications of US in emergency medicine and should be considered in patients with right upper quadrant pain, epigastric pain, jaundice, and sepsis without a clear source.

Image Acquisition

The examination is performed with a low-frequency curved linear array or phased array transducer. Subcostal, intercostal, and flank windows will facilitate visualization of the gallbladder, which should be evaluated in two orthogonal (perpendicular) planes. A complete evaluation includes visualization and measurement of the common bile duct, typically located just cephalad to the gallbladder neck.

Interpretation of the Acquired Images

The diagnosis of cholelithiasis is made by identification of echogenic foci within the gallbladder lumen, with associated shadowing. Other image patterns include stones with indistinct shadow, sludge, and the wall-echo-shadow (WES) sign seen in a gallbladder full of gallstones. Signs of cholecystitis include a dilated gallbladder, increased gallbladder wall thickness (>3 mm), sonographic Murphy's sign, and pericholecystic fluid (Fig. e5.10). A nonmobile stone in the gallbladder neck is highly suggestive of eventual cholecystitis. A common bile duct larger than 6 mm in people younger than 60 years and larger than 10 mm in older patients may indicate choledocholithiasis.

Integration of Ultrasound Findings Into Patient Management

Biliary US is fast and accurate, with a reported sensitivity of 87% to 94% and specificity of 82% to 96% in the detection of gallstones, comparable to radiologic ultrasound.[18,19] Emergency clinicians should be aware that small stones may be difficult to visualize with the resolution available from a portable ultrasound system and that comprehensive radiologic ultrasound may be indicated in cases of high clinical suspicion and/or obese patients with challenging sonographic windows.

Additional online educational content relevant to biliary ultrasound can be accessed as follows:

- Academic Life in Emergency Medicine—reference card
- Sonoguide website—text, image, video
- AEUS website—narrated lecture
- Emergency Ultrasonography website—video gallery

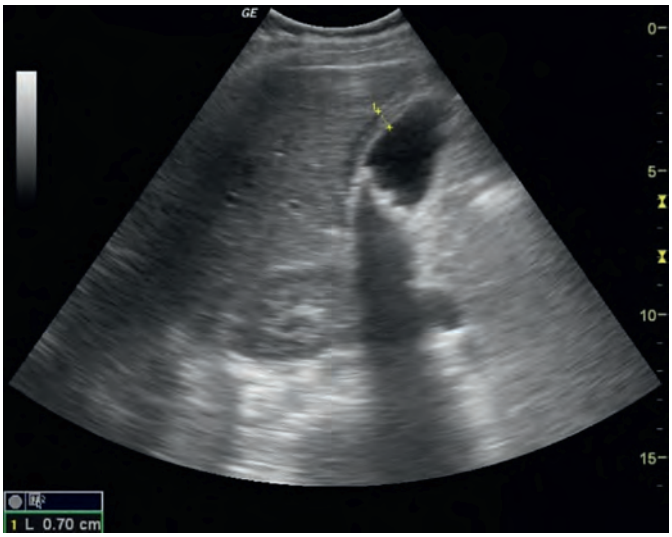

Fig. e5.10. Gallbladder with echogenic gallstones, thickened gallbladder wall, and pericholecystitic fluid consistent with acute cholecystitis.

Urinary Tract Ultrasound

Identification of Appropriate Patients

Renal and urinary tract US can detect hydronephrosis and/or urinary retention. The lack of ionizing radiation and rapidity of renal US make it an attractive option for the investigation of patients with unexplained flank, back, or groin pain.[20] In addition, bladder US is useful for the detection of a full bladder, presence and location of a Foley catheter, and guidance during suprapubic aspiration or Foley placement.

Image Acquisition

Renal US includes orthogonal views of the kidneys, with an emphasis on visualization of the renal pelvis. In addition, visualization of the bladder can diagnose secondary hydronephrosis from an obstructed bladder stone and may demonstrate nonobstructive ureteral jets through the use of Doppler US. The sonographic windows for the two kidneys are similar to those used in the trauma upper quadrant views, with the exception that the patient may be rolled toward the opposite side so that the transducer may be placed more posteriorly on the back, if necessary. The bladder view is performed from the suprapubic window, and calculations of volume may be made with on-machine calculators or by using the formula:

$$\text{Length} \times \text{width} \times \text{height} \times 0.52 = \text{volume}$$

Interpretation of the Acquired Images

Hydronephrosis is characterized by dilation and anechoic fluid accumulation within the renal pelvis and calyces (Fig. e5.11) and can range from mild to severe. Renal and/or ureteral calculi may be identified as echogenic foci with associated shadowing and are usually located within the kidney (nonobstructive) or in the renal pelvis, proximal ureter, or ureterovesicular junction. The use of color Doppler may help identify urolithiasis by visualization of twinkling artifact.

Integration of Ultrasound Findings Into Patient Management

A recent multicenter randomized controlled trial comparing CT to emergency US and radiologic US as the initial imaging modal-

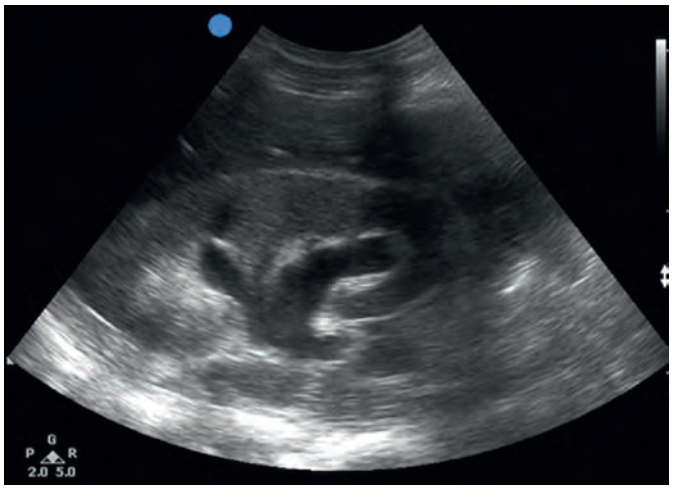

Fig. e5.11. Hydronephrosis with dilation of the calyces and renal pelvis.

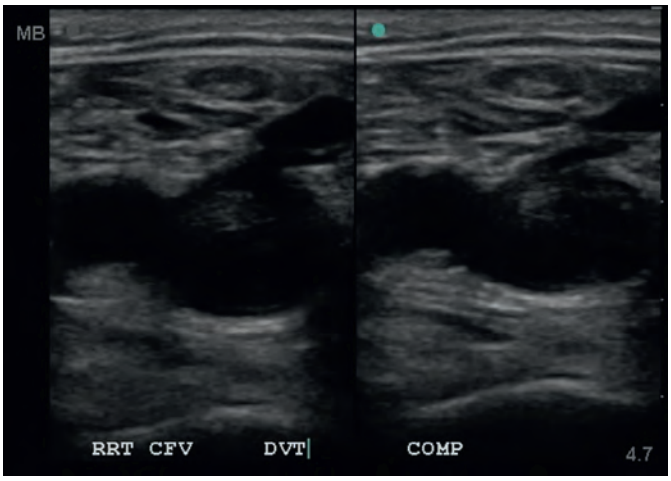

Fig. e5.12. Echogenic thrombus noted in the common femoral vein at the junction of the saphenous vein. The dual screen demonstrates lack of compressibility.

ity in suspected renal colic has found no difference in patient-oriented outcomes.[20]

Additional online educational content relevant to renal ultrasound can be accessed as follows:

- Sonoguide website—text, image, video
- AEUS website—narrated lecture
- Emergency Ultrasonography website—image gallery

Deep Venous Thrombosis Ultrasound

Identification of Appropriate Patients

Emergency clinicians should consider using emergency US to assess for DVT in patients with swollen or painful extremities. In some cases, evaluation for DVT may be indicated in patients with suspected pulmonary embolism because the presence of a DVT may facilitate initiation of anticoagulation prior to, or in lieu of, other imaging modalities.

Image Acquisition

Lower extremity venous compression ultrasound is typically performed with a high-frequency linear array transducer. The two-zone technique involves evaluating and compressing the common femoral vein from the saphenofemoral junction through the bifurcation of the femoral vein and the popliteal vein through its trifurcation. The three-zone technique adds the femoral vein from its origin through the distal thigh. Evaluation of upper extremity veins is less commonly performed by emergency clinicians; Doppler US is required for the subclavian vein, which is not compressible under the clavicle.

Interpretation of the Acquired Images

The lack of compressibility is the hallmark of deep venous thrombosis, although newer generation ultrasound systems commonly have sufficient resolution to allow direct visualization of echogenic thrombi as well[21] (Fig. e5.12).

Integration of Ultrasound Findings Into Patient Management

The accuracy of this technique ranges from 87% to 99%, depending on operator experience. Hospital charges and time in the ED are reduced for patients who have bedside venous US performed to rule out DVT. A large randomized trial has compared radiology performed via whole-leg ultrasound versus a two-point ultrasound in combination with a D-dimer test, which, if abnormal, required a 1-week follow-up visit. Both strategies were equally efficacious in the detection of symptomatic DVT and overall outcomes at 3-month follow-up. Most studies evaluating two-zone compression ultrasonography have been performed in an ambulatory outpatient population; therefore, bedridden, postoperative, or otherwise immobile patients may require more comprehensive imaging protocols to exclude DVT. Depending on the skill of the sonographer, patient characteristics, and availability of follow-up, ED US may guide lower extremity DVT institutional protocols.

Additional online educational content relevant to DVT ultrasound can be accessed as follows:

- Practical Ultrasound Series—deep venous thrombosis iBook
- Academic Life in Emergency Medicine—reference card
- Sonoguide website—text, image, video
- AEUS website—narrated lecture
- Emergency Ultrasonography website—video gallery

Thoracic Ultrasound

Identification of Appropriate Patients

Thoracic ultrasound should be considered in patients with chest pain and/or dyspnea in whom the emergency clinician suspects pleural effusion, pneumothorax, pneumonia, or pulmonary edema.[22]

Image Acquisition

Thoracic ultrasound is often performed with a low-frequency curvilinear array or phased array transducer, although visualization of lung sliding may be enhanced, if necessary, by the use of a high-frequency linear array transducer. The anterior, anterolateral, and posterolateral areas of the thorax are investigated, with an emphasis on visualization of lung sliding, A-lines, B-lines, consolidation, and effusion.

Interpretation of the Acquired Images

Lung sliding, a normal finding, is identified as the visceral and parietal pleura glide against each other during normal respiration (Video e5.2). A-lines, equally spaced horizontal echogenic artifacts deep to the pleural line, are also a normal finding.

The visualization of lung sliding excludes the presence of a pneumothorax at that location on the patient's chest wall. Although M-Mode and color Doppler techniques have been described as adjuncts to the evaluation of patients with suspected pneumothorax, neither is a necessary component of the examination. Absent lung sliding (Video e5.3) can result from a variety of causes in addition to pneumothorax, including pleural adhesions, pleurodesis, partial or complete pneumonectomy, and contralateral mainstem bronchus intubation. A lung point sign is identified at the border of the pneumothorax, where the image shows absent lung sliding until the lung moves into the interspace with respiration (Fig. e5.13).

Pulmonary edema is indicated by the presence of B-lines, which are hyperechoic reverberation artifacts that arise from the pleura, move with respiration, extend off the screen without fading, and erase the normal A-line pattern (Fig. e5.14). Normally found in small numbers in the dependent areas of the lung, the widespread distribution of these artifacts indicates increased interstitial and/or alveolar thickening due to fluid accumulation (edema) or scarring (fibrosis).[23]

Lobar pneumonia is visualized as echogenic so-called liver-like echogenicity as the lung accumulates fluid with consolidation. The dynamic air bronchogram, hyperechoic areas within bronchi that move with respiration, usually within consolidated lung, has been described as another sign of alveolar consolidation.

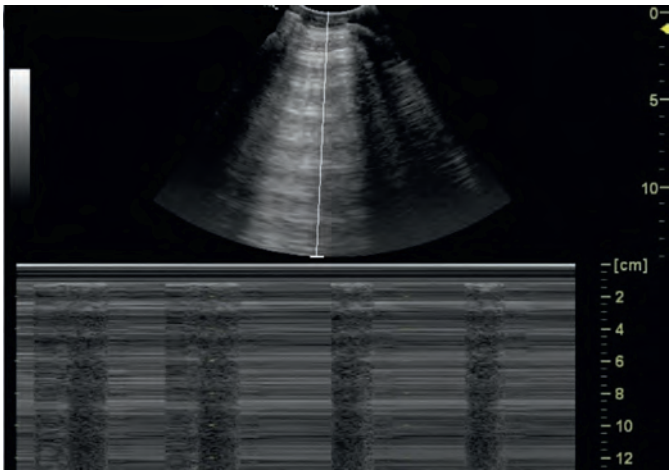

Fig. e5.13. M-mode image demonstrating lung point sign.

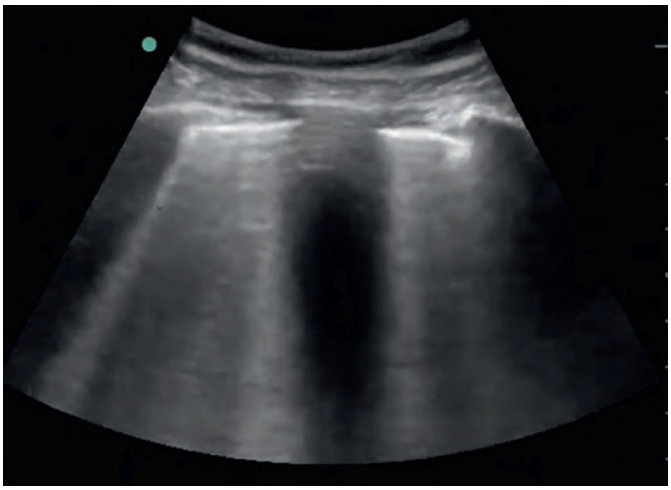

Fig. e5.14. B-line pattern on thoracic ultrasound.

Pleural fluid appears as an anechoic collection above the diaphragm (Fig. e5.15), although internal echoes may be present in cases of chronic, infected, or loculated effusions.

Integration of Ultrasound Findings Into Patient Management

The accuracy of US for the detection of pneumothorax (sensitivity, 100%; specificity, 98%) is better than that of plain chest radiography in the acute setting, with performance characteristics approaching that of thoracic CT scanning.[24] US evaluation of the acutely dyspneic patient has been associated with increased diagnostic accuracy as compared to traditional clinical, laboratory, and imaging protocols,[25,26] particularly for the identification of patients with a cardiogenic cause of acute dyspnea.

Additional online educational content relevant to thoracic ultrasound can be accessed as follows:

- Academic Life in Emergency Medicine—reference card
- AEUS website—narrated lecture
- Ultrasound podcast—narrated lectures, parts I and II
- Emergency Ultrasonography website—video gallery

Ocular Ultrasound

Identification of Appropriate Patients

Ocular US is a useful modality for intraocular diseases such as retinal detachment, retinal hemorrhage, vitreal hemorrhage, intraocular foreign body, dislocated lens, and retro-orbital hemorrhage. In addition, the globe, pupillary size, and extraocular movements can be examined, even in the presence of facial swelling.[27]

Image Acquisition

The structures of the eye provide an excellent acoustic window, and short-duration, B-mode US over a closed eyelid allows the anterior and the posterior chambers to be well visualized. An ocular preset should be selected to minimize the thermal exposure to the retina during the examination. The vitreous chamber is evaluated by scanning through the globe in orthogonal planes in low-gain and high-gain settings.

Fig. e5.15. Right pleural effusion with hyperechoic consolidated lung.

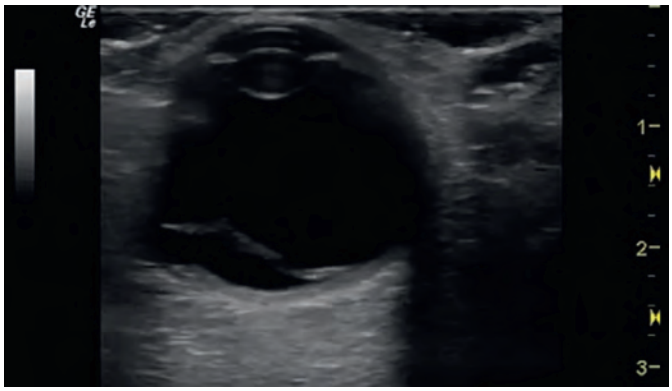

Fig. e5.16. Retinal detachment.

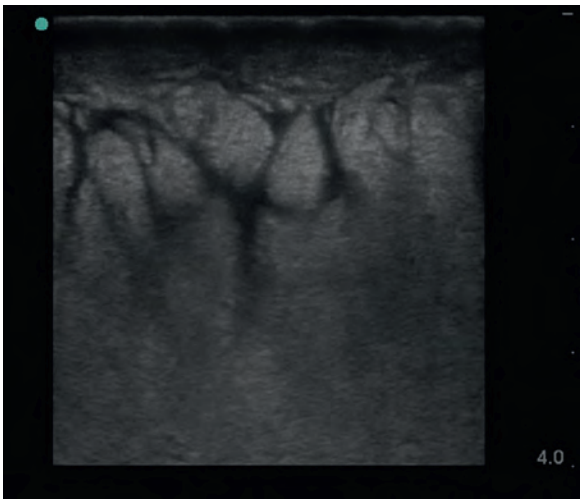

Fig. e5.17. Cobblestoning pattern of cellulitis or edema.

Interpretation of the Acquired Images

A linear echogenic structure in the vitreous chamber seen with low-gain imaging is suggestive of a retinal detachment (Fig. e5.16), whereas a thinner linear structure seen only with high-gain imaging is more consistent with a vitreous detachment. The diagnosis of vitreous hemorrhage, retinal detachment, and lens dislocation may all be facilitated through the use of kinetic echography, where the patient shifts the gaze in different directions during the examination.

Integration of Ultrasound Findings Into Patient Management

The reported sensitivity of ocular US for retinal detachment by emergency clinicians is 100%, and the specificity is 83% to 92%.[28]

Additional online educational content relevant to ocular ultrasound can be accessed as follows:

- Academic Life in Emergency Medicine—reference card
- Sonoguide website—text, image, video
- AEUS website—narrated lecture

Soft Tissue Ultrasound

Identification of Appropriate Patients

Soft tissue US is used to differentiate cellulitis from abscess, detect foreign bodies and hernias, and evaluate other soft tissue pathologic processes, including masses, pseudoaneurysms, and glands. US can also differentiate peritonsillar abscess from cellulitis and can be used to guide peritonsillar aspiration.[29]

Image Acquisition

A high-frequency linear transducer is used to visualize the entire affected area in two orthogonal planes. Evaluation for peritonsillar abscess is best performed with the endocavitary transducer.

Interpretation of the Acquired Images

Cellulitis or edema results in an echogenic pattern, with cobblestoning between fat lobules (Fig. e5.17). Abscesses are irregular hypoechoic to anechoic collections, typically located within the subcutaneous layer (Fig. e5.18), but may also connect with the skin surface. US is diagnostic in soft tissue disease for cellulitis, abscess and, in some case series, necrotizing fasciitis.[30]

The detection of foreign bodies is characterized by variable echogenicity in the tissue, with shadowing beneath the foreign body. Metal foreign bodies, such as bullets and intrauterine devices, have characteristically high-reflective echogenicity and ring-down artifacts. Use of a water bath may aid in the detection of superficial foreign bodies.

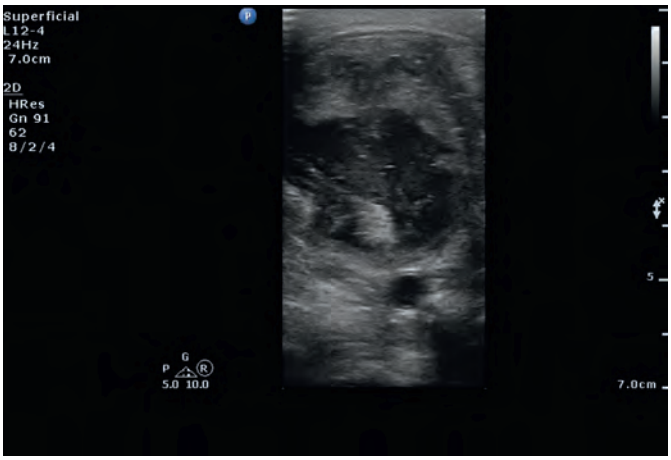

Fig. e5.18. Anterior neck abscess overlying carotid artery.

Integration of Ultrasound Findings Into Patient Management

Ultrasound has greater sensitivity and specificity than a clinical examination for the detection of soft tissue abscess. In other studies, the use of US changed management for 50% of adult patients and 22% of children with clinical cellulitis. One study has shown that incision and drainage are superior to US-guided aspiration in a cohort of patients with soft tissue infection with respect to resolution at 1 week (80% vs. 26%, respectively).[31]

Additional online educational content relevant to soft tissue ultrasound can be accessed as follows:

- Academic Life in Emergency Medicine—reference card
- Sonoguide website—text, image, video
- Emergency Ultrasonography website—video gallery

Musculoskeletal Ultrasound

Identification of Appropriate Patients

Patients with suspected joint effusion or muscular, tendinous, or ligamentous injury may benefit from US-guided evaluation.

Emergency US is excellent for the detection of fluid in joints, confirmation of effusions, and guidance of drainage procedures. In addition, the diagnosis of ligamentous injuries and muscle avulsion and hemorrhage has also been reported.

Image Acquisition

Musculoskeletal US is typically performed with a high-frequency linear array transducer with imaging of the affected joint, muscle, tendon, ligament, or bone in two orthogonal planes. As with the physical examination, US detection of tendon and muscle injury is often assisted by movement of the limb. Comparison with the contralateral side may also be helpful. Water bath techniques provide a better acoustic window for shallow tissue, such as fingers.

Interpretation of the Acquired Images

Joint effusions can be anechoic or echogenic, depending on type and age. Muscle and tendon abnormalities are detected by anechoic and heterogeneous abnormalities. Tendons and their anisotropic longitudinal fibrils can be visualized near joints, with pathologic tears appearing as a discontinuity of the tendon (Fig. e5.19). Muscles are hypoechoic and appear striated, with echogenic borders. Tears and hemorrhage are interruptions of this normal pattern.

The characteristic echogenic appearance of bony cortex with associated shadowing is used to identify normal bone and its contour. Fractures are seen as a defect in the bony cortex (Fig. e5.20).

Integration of Ultrasound Findings Into Patient Management

Ultrasound identification of tendon disruption is highly accurate in the knee extensors and Achilles tendon. Evaluation of the rotator cuff requires considerable experience but offers accuracy that rivals that of magnetic resonance imaging.

Additional online educational content relevant to Musculoskeletal Ultrasound can be accessed as follows:

- Sonoguide website—text, image, video
- AEUS website—narrated lecture

Testicular Ultrasound

Identification of Appropriate Patients

Although testicular scanning is an advanced US application, it can be incredibly valuable in patients with acute scrotal pain and/or swelling.

Image Acquisition

The scrotum is evaluated with a high-frequency linear transducer using B-mode to evaluate the echotexture of the normal and affected testes. Color Doppler and pulsed wave Doppler evaluation are also performed for the evaluation of normal venous and arterial flow.

Interpretation of the Acquired Images

Absent or decreased flow on the affected side indicates possible torsion (Fig. e5.21), whereas increased flow often indicates epididymitis and/or orchitis.

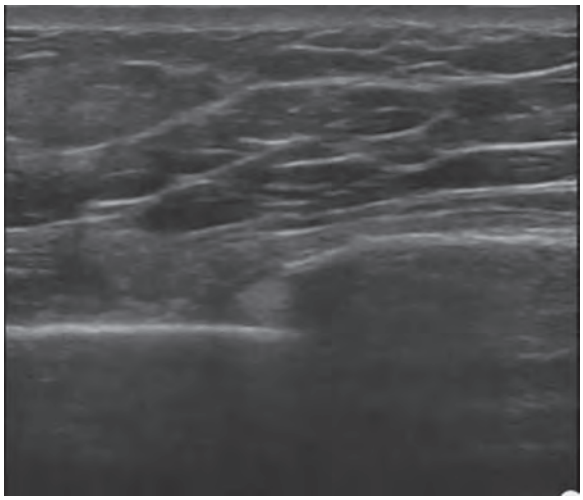

Fig. e5.20. Sternal fracture.

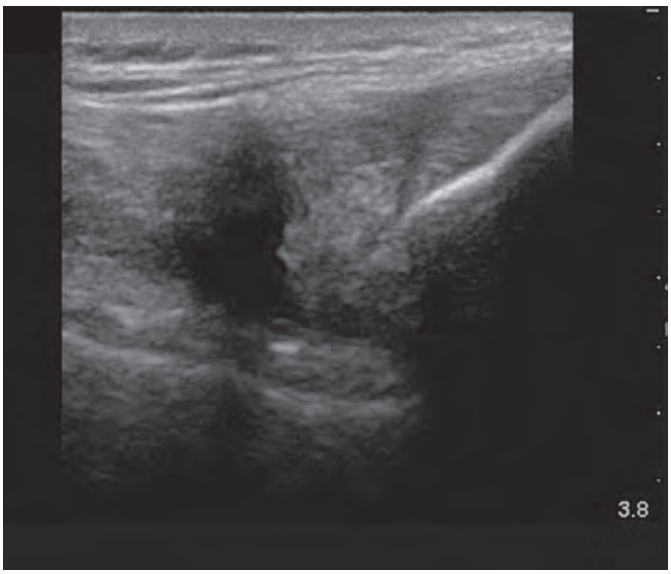

Fig. e5.19. Tendon disruption.

Fig. e5.21. Testicular torsion. Note the absent color power flow in the left testis (*right*).

Integration of Ultrasound Findings Into Patient Management

In small studies, experienced emergency clinicians have accurately diagnosed testicular pain with high sensitivity and specificity.

Additional online educational content relevant to testicular ultrasound can be accessed as follows:

- Academic Life in Emergency Medicine—reference card
  Sonoguide website—text, image, video

Bowel Ultrasound

The use of bedside US for the evaluation of appendicitis, small bowel obstruction and other bowel disease has been an area of increasing interest. There has been variable experience with the use of graded compression US to detect appendicitis (Figs. e5.22 and e5.23) and, although there has been considerable interest in an ultrasound-first approach to suspected appendicitis, the accuracy of emergency clinician–performed US for appendicitis has been equivocal. The use of US for diverticulitis, intussusception, volvulus, and small bowel obstruction has also been reported. Hernias may also be detected as masses in the ventral, inguinal, paramedian, femoral, and scrotal areas.

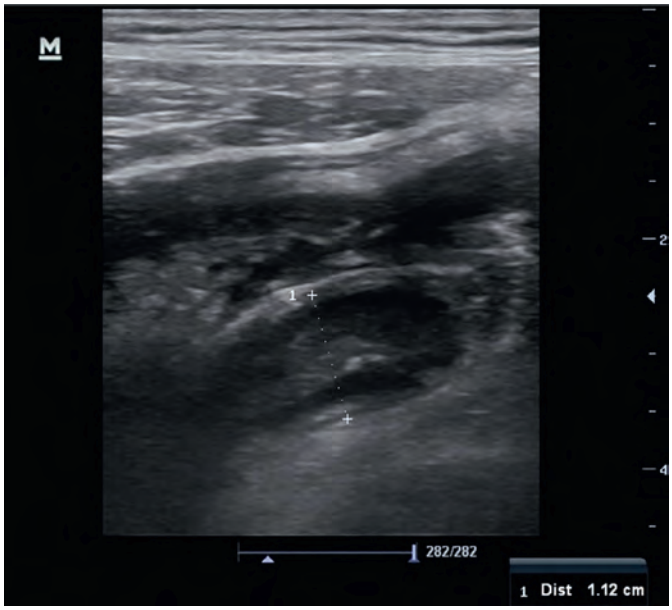

Fig. e5.22. Longitudinal view of a dilated appendix.

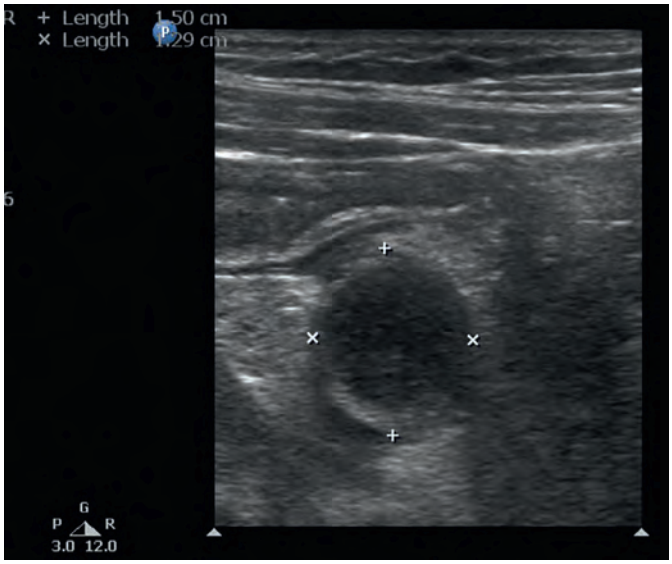

Fig. e5.23. Transverse view of a dilated appendix with a small amount of periappendiceal free fluid.

Additional online educational content relevant to bowel ultrasound can be accessed as follows:

- AEUS website—narrated lectures, parts I and II

Pediatric Emergency Ultrasound

The use of US for children in the ED has two paths, one that mirrors the applications that have been used for adults and another that explores the more specific pediatric abdominal applications.

The FAST examination for evaluation of abdominal trauma in children is specific (98%), but the sensitivity is only 20%, making it difficult to use without further imaging or other testing.[9] In addition, specific pediatric abdominal applications that are common in the radiology suite have been gaining in popularity, as evidenced by studies evaluating the role of emergency US in patients with suspected intussusception, appendicitis, and pyloric stenosis.

Ultrasound for Procedural Guidance

In 2001, in response to the Institute of Medicine report *To Err Is Human,* the Agency for Healthcare Research and Quality (AHRQ) sanctioned a report on actions that may improve patient safety. The report contained a recommendation for US guidance for internal jugular central line insertion that was reiterated in the revised 2013 report. Since the original report, the use of US for procedural guidance has expanded for many emergency procedures (Table e5.1), and is advocated for error reduction.

Procedural guidance can be static or dynamic. Static guidance suggests that US has been placed over the anatomic area, and the area has been marked after noting angle and distance information. Dynamic guidance describes procedures performed with real-time US visualization of the needle entering the anatomic area.

Additional online educational content relevant to procedural ultrasound can be accessed as follows:

- Sonoguide website—text, image, video
- AEUS website—narrated lectures, parts I and II

Vascular Access Procedures

There are two common approaches to vein cannulation—out of plane, in which the vein is imaged in short axis and appears as a circular structure on the screen, and in plane, in which the vein is imaged in long-axis and appears as a tubular structure traversing the width of the screen. In the out-of-plane approach, the needle bisects the transducer at its midpoint (Fig. e5.24). In the in-plane approach, the needle is introduced under the long axis of the transducer (Fig. e5.25). Although the out-of-plane approach is more popular with novices, the in-plane approach may be safer in experienced hands due to the continuous visualization of the needle tip during the entire procedure. In addition, an oblique axis in-plane technique has been described, where the vessels are imaged at an oblique angle while the needle is inserted in plane. Although there have been no large-scale trials evaluating this technique, it may offer the benefit of continuous needle visualization while offering improved visibility of surrounding structures not possible with use of the long-axis, in-plane technique.

The most studied and advocated use of US procedural guidance is for central venous catheter insertion. Both the AHRQ and National Institute for Health and Clinical Excellence have recommended US guidance for central line insertion. US guidance for

TABLE e5.1

Ultrasound-Guided Emergency Procedures

ULTRASOUND	PROCEDURE
Vascular access	Central venous access Internal jugular vein Subclavian vein Femoral vein Peripheral vein Intraosseous needle Arterial cannulation
Torso fluid collections	Paracentesis Thoracentesis Pericardiocentesis
Cardiac	Pacer placement
Musculoskeletal	Arthrocentesis Fracture reduction Foreign body removal Tendon sheath injection
Soft tissue	Abscess drainage Hernia reduction
Anesthesia	Brachial plexus Femoral or fascia iliaca Popliteal Sciatic Tibial Hematoma block
Airway	Endotracheal tube placement
Urinary bladder	Suprapubic aspiration and cystostomy Foley guidance
Neurologic	Lumbar puncture

Fig. e5.25. In-plane approach to vascular access.

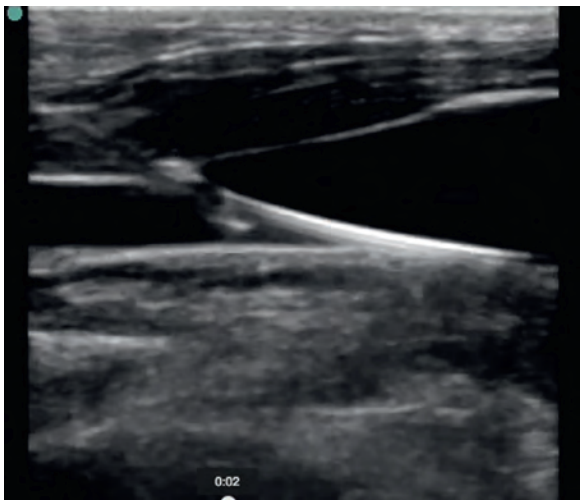

Fig. e5.26. Echogenic guidewire visualized in long-axis view of internal jugular vein.

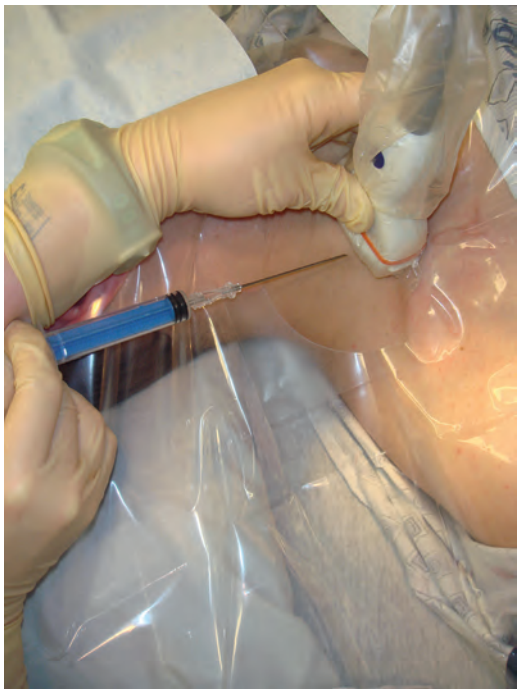

Fig. e5.24. Out-of-plane approach to vascular access.

internal jugular central line insertion can be recommended as a safe and best practice[32] (Fig. e5.26).

Ultrasound guidance enables the emergency clinician to assess the internal jugular for overlap with the carotid artery, vessel diameter, and presence of luminal clot or vessel obliteration (Videos e5.4 and e5.5). Internal jugular central line insertion has been studied in the ED, intensive care unit, and radiology suite. In the ED, US-guided internal jugular cannulation is associated with decreased time to vessel penetration and improved success in the difficult to stick patient, improved overall and first-attempt success rates, reduced time to insertion, and reduced complication rate. The Valsalva maneuver and Trendelenburg position may assist in increasing the cross-sectional area of the internal jugular vein.

US does not prevent posterior vein wall penetration, as reported in case reports and simulated models.[33] Adverse events (eg, hematoma, arterial cannulation, pneumothorax, unsuccessful placement) can occur in up to 20% of patients undergoing US-guided internal jugular catheterization.[34] US improves procedural success in subclavian vein cannulation, whether cannulated via the infraclavicular or supraclavicular subclavian approach.[35,36]

Emergency clinicians can also insert peripheral intravenous (IV) catheters successfully in patients with difficult access using

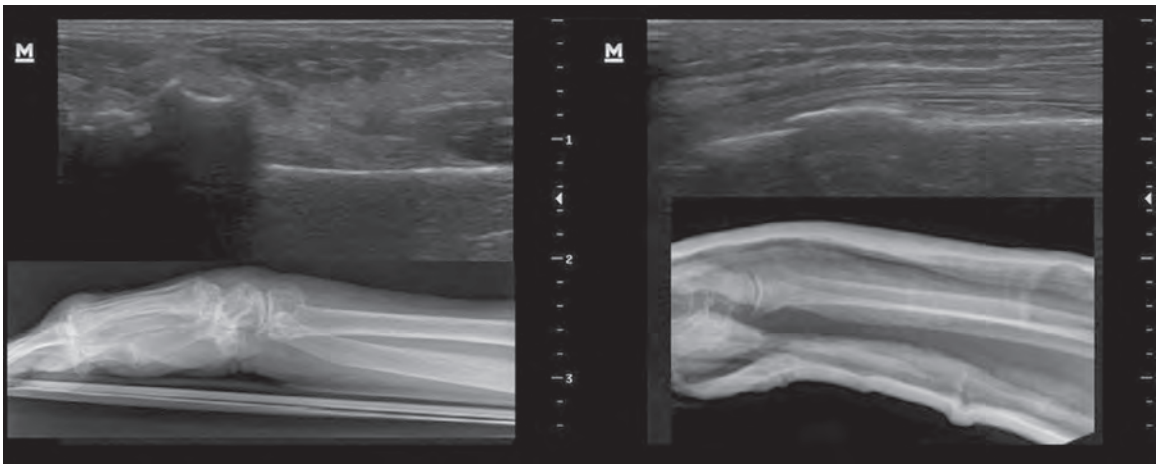

Fig. e5.27. Distal radius fracture before (*left*) and after (*right*) reduction.

emergency US,[37] with one study demonstrating a marked reduction in the need for central venous catheter placement in ED patients with poor IV access.[38] Only one randomized study has shown no differences in number of attempts, time to successful catheterization, or patient satisfaction. Veins that are large in width or at moderate depth (<1.6 cm) have a higher success rate. Nurses and ED technicians have also been taught to use US for peripheral venous guidance.[37,38]

Arterial access, including radial artery aspiration and cannulation, is more successful with US guidance. Sonographic confirmation of intraosseous needle placement has also been described based on the detection of extraosseous or intraosseous Doppler flow.

Torso Drainage Procedures

US can facilitate procedures such as paracentesis, thoracentesis, and pericardiocentesis by confirming the presence and amount of fluid as well as its relative location to key anatomic structures. Paracentesis, including US-guided diagnostic peritoneal lavage, can be performed with static or dynamic ultrasound guidance. US is useful for identifying the deepest location of ascites and presence of obstructing bowel loops or superficial vascular structures. Thoracentesis is assisted by considering the diaphragm as the most inferior anatomic landmark to avoid solid organ injury. The routine use of sonography has been associated with a reduced rate of pneumothorax and tube thoracostomy. Pericardiocentesis also can be facilitated by location of the best window—subcostal, apical, or parasternal long—and needle guidance into the pericardial space, lessening the likelihood of cardiac puncture.

Soft Tissue and Musculoskeletal Procedures

Foreign bodies can be identified and removed with the guidance of US. Static guidance marks the location, depth, and size of the foreign body. Dynamic guidance requires an incision remote from the overlying skin to allow the probe to monitor the procedure.

Arthrocentesis may be assisted by US to detect effusion, identify joint landmarks, and confirm the needle tip in the joint. Use of US reduces the number of attempts and increases the overall success rate for most joint aspirations, but has not shown benefit in knee joint aspiration. Arthrocentesis of the adult and pediatric hip, in addition to other joints, has been reported, with good success.

US may assist hematoma aspiration and blocks by directing the needle into the affected site. It can be used as an alternative to fluoroscopy for the guidance of fracture reduction because assessment of alignment can be performed before and after reduction[39,40] (Fig. e5.27).

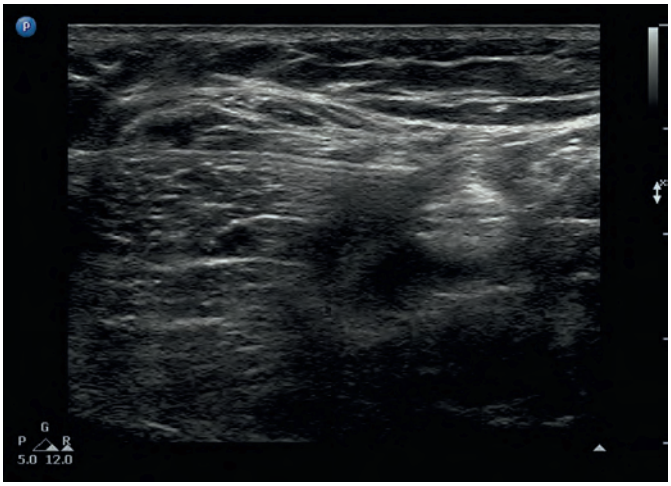

Fig. e5.28. Sciatic nerve block using in-plane approach.

Nerve Blocks

US-guided nerve blocks confirm needle placement adjacent to the target nerve and allow anesthetic to be delivered safely and effectively around the nerve (Fig. e5.28). Multiple US-guided nerve blocks have been described in the emergency medicine and anesthesia literature, and it is clear that most peripheral nerve blocks benefit from the assistance of US. US-guided femoral or fascia-iliaca blocks have an opioid-sparing effect in older patients with femur fractures and have been increasingly incorporated into standardized care protocols for geriatric orthopedic trauma.[41]

Lumbar Puncture

Ultrasound can be used to facilitate lumbar puncture by identification of the spinous processes in patients without palpable anatomic landmarks. This procedure is most often performed using a static technique, where an appropriate needle insertion site is identified and marked prior to sterile skin preparation, and the procedure is then performed without dynamic US guidance.

Out-of-Hospital Ultrasound: Disasters and Remote Settings

The use of ultrasound has been described in European and other settings by emergency clinicians and paramedics in the out-of-hospital arena, including ground, helicopter, air, and space, for FAST and abdominal aorta examinations.

The military has used US extensively in combat situations, including the frontline, combat support hospital, and tertiary hospital settings. US was used to facilitate the care of patients injured in the Haitian earthquake in 2010, Boston marathon bombing in 2013, and a number of other casualty situations.[42,43]

US interpretation may be enhanced by satellite and telesonography systems that allow remote guidance and interpretation. In remote and international low-resource settings, US has become the imaging test of choice for emergency care.[44]

INTEGRATION INTO EMERGENCY MEDICINE PRACTICE

US has been integrated into emergency medicine practice because of the need for effective, noninvasive, nonionizing portable imaging techniques. US, whether it is introduced in medical school, residency, or clinical practice, is a skill that requires constant attention, with hands-on practice and interpretation. Emergency US, the performance and interpretation of ultrasonographic examination at the bedside in the emergency setting, has enhanced many aspects of emergency care, making diagnosis and treatment more rapid, efficient, safe, and accurate.

KEY CONCEPTS

- Emergency ultrasound is performed and interpreted by the emergency clinician at the bedside.
- Emergency ultrasound is designed to answer focused clinical questions.
- The key to proficiency in emergency ultrasound is practice.
- Credentialing guidelines exist to guide emergency clinicians in the acquisition of this important skill.
- All emergency clinicians should be familiar with the resuscitative applications of emergency ultrasound, including focused assessment with sonography for trauma (FAST), focused cardiac ultrasound, abdominal aortic aneurysm assessment, and procedural guidance for central venous catheter placement.
- The "four Is" of emergency ultrasound are as follows: (1) identification of appropriate patients for whom emergency ultrasound is likely to be valuable; (2) image acquisition; (3) interpretation of the acquired images; and (4) integration of the ultrasound findings into patient management.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER e5: QUESTIONS & ANSWERS

e5.1. Emergency ultrasound (US) is defined by the physical location of the emergency patient.
A. True
B. False

Answer: B. Emergency US is not defined by location but by patient need. Patients may be in remote locations, prehospital, in the emergency department (ED), in the intensive care unit (ICU), or elsewhere in the hospital.

e5.2. Which are not typically involved with emergency US examinations?
A. Acute symptom
B. Comprehensive mapping of an organ
C. Emergency sign
D. Focused area of the body
E. Physiologic pattern

Answer: B. Comprehensive mapping of organs is not typical of emergency US examination. The other items are characteristics of US done for emergency and symptom-based examinations.

e5.3. Which frequency range defines US?
A. Less than 0.2 Hz
B. Over 2 Hz
C. Over 200 Hz
D. Over 20,000 Hz
E. Over 2 million Hz

Answer: D. US is defined as sound with frequency over 20,000 Hz.

e5.4. Which of the following performance characteristics is true for higher frequency probes?
A. Deeper penetration, higher resolution
B. Deeper penetration, poorer resolution
C. Superficial penetration, higher resolution
E. Superficial penetration, poorer resolution

Answer: C. Higher frequency probes penetrate in superficial areas but generally give good resolution.

e5.5. Which type of US has the best resolution when the probe is perpendicular to the object of interest?
A. Doppler US
B. Gray scale US

Answer: B.

e5.6. Which of the following is not considered safe practice for performing emergency US?
A. Cleaning surface probes with spray or wipe
B. Imaging over a body part continuously for 60 minutes
C. Special endovaginal cleaning
D. Use of the ALARA (***a***s ***l***ow ***a***s ***r***easonably ***a***chievable) principle
E. Transducer covers during sterile procedures

Answer: B. There are thermal effects to US over a long duration.

e5.7. Which of the following areas is not scanned during an EFAST examination?
A. Orbital space
B. Pericardial space
C. Peritoneal space
D. Pleural space

Answer: A. Orbital space is not typically part of the EFAST.

e5.8. Sensitivity is typically greater than specificity for FAST examination.
A. True
B. False

Answer: B. The FAST examination is typically more specific than sensitive.

e5.9. Which of the following is the most appropriate use for emergency pelvic US in early pregnancy?
A. To rule out adnexal masses
B. To rule out ectopic pregnancy
C. To rule out fibroids
D. To rule in intrauterine pregnancy

Answer: D. The most appropriate use of US is to rule in intrauterine pregnancy, which greatly decreases the chances for an ectopic pregnancy. Evaluation of the adnexa and detection of an ectopic pregnancy requires a higher level of equipment and training than reliably available in an emergency situation.

e5.10. Which of the following is an advantage of endovaginal US over using a transabdominal window?
A. Better ability to assess Morison's pouch
B. Deeper penetration of ultrasound
C. Greater field of view
D. Higher resolution for assessment of gestational structures

Answer: D. An endovaginal transducer allows imaging closer to the structures of interest and eliminates poor acoustic imaging due to body habitus or artifacts such as bowel gas.

e5.11. Which of the following is not a typical use of cardiac US by emergency clinicians?
A. Focal wall motion abnormalities
E. Global left ventricular function
C. Pericardial effusion
B. Pseudo-PEA (pulseless electrical activity)
D. Right ventricular dilation

Answer: A. Focal wall motion abnormalities are more difficult to detect than the other conditions.

e5.12. Which of the following has been demonstrated with the use of cardiac US?
A. Reduced time to central line in sepsis
B. Reduced time to computed tomography (CT) in blunt obstetric trauma
C. Reduced time to operating room (OR) for penetrating cardiac trauma
D. Reduced time to pelvic fixator in blunt pelvic trauma

Answer: C. Emergency cardiac US has been shown to reduce time to the OR for penetrating cardiac trauma and has greatly decreased the need for emergency thoracotomy in critical patients.

e5.13. Which of the following is not an indication for emergency US of the abdominal aorta?
B. Detecting aortic dissection
C. Detecting aortic occlusion
D. Placing aortic stents
A. Ruling out abdominal aortic aneurysm (AAA)

Answer: D. Ultrasound of the aorta is sensitive to detect AAAs and can rule out the condition with high accuracy. It is also useful to detect dissection and occlusion, but emergency clinicians do not place aortic stents.

e5.14. Which of the following is a typical use for biliary US by emergency clinicians?
A. Biliary stricture
B. Gallstones
C. Hepatic cyst detection
D. Hepatic hemangioma

Answer: B. Gallstones are a common finding that can direct emergency management and disposition. The other conditions are not easily detected and do not need to be diagnosed on an emergency basis.

e5.15. Which of the following is not a characteristic of sonographic cholecystitis?
A. Gallbladder septation
B. Gallbladder wall thickening
C. Gallstones
D. Pericholecystic fluid

Answer: A. All the findings provide evidence for cholecystitis except septation of the gallbladder.

e5.16. Dilation of which genitourinary (GU) structure(s) is typically seen with US?
A. Bladder
B. Midureter
C. Renal calyces
D. Renal pelvis

Answer: B. Midureter

e5.17. A typical emergency lower extremity deep venous thrombosis (DVT) protocol includes compression of which of the following veins?
A. Common femoral
B. Deep peroneal
C. Posterior tibial
D. Transcapular

Answer: A. Compression of the common femoral vein assists in the diagnosis of DVT.

e5.18. Which of the following is the correct order of imaging for the sensitivity of detecting a pneumothorax?
A. Chest x-ray (CXR) > CT > US
B. CT > CXR > US
C. CT > US > CXR
D. US > CT > CXR

Answer: C. CT > US > CXR is the correct order.

e5.19. Which of the following is not a common abnormal pattern detected by lung US?
A. Anechoic collection in the dependent pleural space
B. B-lines in the bases of the lung
C. Increased B-lines in the apices of the lung
D. Lack of sliding after penetrating chest trauma
E. Liver-like lesions with air bronchograms

Answer: B. B-lines in the bases of the lung are not common.

e5.20. Which of the following can be diagnosed by ocular ultrasound?
A. Glaucoma
B. Pterygium
C. Retinal detachment
D. Uveitis

Answer: C. Retinal detachment can be seen on ocular ultrasound. US is not useful for the detection of the other conditions listed.

e5.21. Which of the following is not true of soft tissue US in the ED?
A. US aspiration is superior to incision and drainage (I&D) in regard to resolution at 1 week.
B. US changes management of clinical cellulitis in 50% of adult patients.
C. US is more sensitive and specific than clinical examination.
D. Water baths may assist in the detection of superficial foreign bodies.

Answer: A. I&D is superior to US-guided aspiration in regard to abscess resolution at 1 week. The other statements are true.

e5.22. Which of the following has not been diagnosed by musculoskeletal US in the ED?
A. Cervical disk impingement
B. Fracture of long bones
C. Hematomas
D. Joint effusions
E. Tendon lacerations

Answer: A. Musculoskeletal US has been used for all the listed conditions except cervical disk impingement.

e5.23. Dynamic US guidance reflects sonographic real visualization of the needle tip into the particular anatomic region.
A. True
B. False

Answer: A. True

e5.24. During a US-guided procedure, which of the following is not a benefit of the long-axis approach to US guidance?
A. Depth information
B. Medial-lateral information
C. Visualization of the needle shaft tip
D. Visualization of the needle tip

Answer: B. Medial-lateral information is lacking because the plane of the US is aligned with the needle.

e5.25. Which of the following procedures is benefited by US guidance?
A. All of these
B. Arthrocentesis
C. Internal jugular guidance
D. Pericardiocentesis
E. US-guided nerve blocks

Answer: A. All the listed procedures benefit from US guidance.

Video e5.1. Pericardial effusion with tamponade. This subcostal cardiac view demonstrates a large circumferential pericardial effusion, with diastolic collapse of the right ventricle.

Video e5.2. Normal lung sliding. The hyperechoic pleural line is sliding normally in an interspace between two ribs.

Video e5.3. Absent lung sliding. The pleural line is visualized between two ribs but does not demonstrate normal sliding movement.

Video e5.4. Internal jugular vein, located anterior to the carotid artery, with normal compressibility.

Video e5.5. Internal jugular vein cannulation. During dynamic ultrasound-guided central line placement, the hyperechoic needle with a ring-down artifact is visualized in the internal jugular vein. Care must be taken to visualize the needle tip at all times to avoid posterior wall or carotid puncture.

CHAPTER e6

Observation Medicine and Clinical Decision Units*

Christopher W. Baugh | Louis Graff IV

PRINCIPLES OF OBSERVATION MEDICINE

THE OBSERVATION APPROACH

CLINICAL CONDITIONS

Evaluation of Critical Diagnostic Syndromes

Treatment of Emergency Conditions

SUMMARY

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

KEY CONCEPTS

- Hospitalization can often be avoided by providing short-term care (<24 hours) in observation units for certain medical disorders, such as chest pain, deep vein thrombosis (DVT), upper gastrointestinal (GI) bleeding, syncope, transient ischemic attack (TIA), trauma, asthma, atrial fibrillation, congestive heart failure (CHF), dehydration, pneumonia, and pyelonephritis.
- The use of observation units results in cost savings and improved patient satisfaction with care.
- Observation care is on an outpatient basis and is not necessarily delivered in a specific location.
- Observation is used to provide additional time for therapeutics and/or diagnostics for patients with an uncertain need for inpatient admission.
- Observation care is often influenced by payer policies and is congruent with recent national efforts to increase patient safety while also reducing unnecessary costs.
- Evidence-based observation care is delivered in a dedicated area for this purpose, using condition- or complaint-specific protocols of care.
- When used appropriately and at benchmark levels of quality and efficiency, observation visits can reduce the duration and thus the cost of hospital care for eligible patients while also reducing the incidence of unsafe discharges to home.
- The role of observation care is best studied in chest pain patients but, over the past several decades, patients with many other conditions have shown to be managed effectively using observation.
- Emergency clinicians should play a central role in identifying and managing observation patients.

CHAPTER e6

Observation Medicine and Clinical Decision Units

Christopher W. Baugh | Louis Graff IV

PRINCIPLES OF OBSERVATION MEDICINE

Observation services are an extension of emergency department (ED) services specifically designed to address unmet patient needs. They improve patient care by continuing the evaluation and management of selected patients who require further hospital care following an ED visit, but do not clearly need an inpatient admission. Observation is an outpatient service, can be delivered by any specialty, and is not tied to a specific site of care. However, protocol-driven observation care in a dedicated unit results in lower length of stay and cost, equivalent clinical outcomes, and even higher patient satisfaction versus routine inpatient management.[1] The benchmark rate of discharge to home from an observation unit is about 80%, with an average length of stay close to 15 hours.[2] The cost to evaluate and treat these patients is nearly half that incurred by routine inpatient admission, a savings of $1572, on average.[3] In addition, the threshold for extended evaluation (traditionally provided only with inpatient hospitalization) is lowered— emergency clinicians are no longer forced into a dichotomy of home versus admission. Patients with atypical signs and symptoms are more fully evaluated to rule out serious conditions, such as acute myocardial infarction or acute appendicitis. Thus, in addition to lower costs, there is also a simultaneous decrease in the inadvertent release home of patients with serious disease.

An ED observation unit is an area dedicated to provide these short-term services, typically for up to 24 hours but, in rare cases, care may extend beyond this time frame. In 2013, the Centers for Medicare & Medicaid Services introduced the 2 Midnight Rule, wherein patients with an expected hospital stay of less than two midnights should be designated observation patients.[4] Although this type of influential payer policy makes strict limits on observation length of stay less feasible, providers need to be wary of the threat of mission creep, resulting in prolonged stays that are out of scope for care by emergency emergency clinicians. Names given to observation units vary; they include chest pain unit, clinical decision unit, and rapid diagnostic treatment unit. An ED-based observation unit is not a holding unit. A holding unit stems from hospital overcrowding and is an area where patients admitted to the hospital are held passively until they can be transferred to an inpatient bed.

Two categories of patients benefit from extension of the usual 2- or 3-hour ED visit to up to 24 hours. One group is selected ED patients with a critical diagnostic syndrome (Box e6.1). These are patients whose diagnoses are unclear after the initial ED evaluation and who will benefit from further evaluation during observation. They are admitted if found to have a serious disease or otherwise released home. The second group is patients with selected emergency conditions for whom the diagnosis is not in doubt but an additional period of treatment or observation is deemed necessary.

THE OBSERVATION APPROACH

The traditional ED encounter lasts 2 or 3 hours. The emergency clinician performs a history and physical examination, orders laboratory and radiologic tests, and provides short-term care. When the test results return, the emergency clinician admits the patient to the hospital or discharges the patient home. The observation approach adds a third option at the completion of the ED evaluation. Additional time allows for further treatment and diagnostics. After the observation period, patients are then admitted to the hospital or discharged home.

Observation begins with the emergency clinician writing the observation orders, which include an order to "assign to observation" or "place in observation"; this order begins the observation visit. The patient is transferred to the observation unit from the main ED. An observation unit chart is started with treatment, and investigations are begun. The initial observation documentation also includes a note with the clinical impression, reason for observation, therapeutic evaluation plan, expected outcome, criteria and time frame for disposition, and health care provider responsible for the patient's care and disposition. The responsible provider may be the emergency clinician, patient's private physician, or a consultant.

Adequate staffing of the observation unit is crucial for the success of the program. The amount of nursing staff required is proportional to the type and intensity of treatments offered, number of beds, and patient acuity. The average staff to patient ratio is one registered nurse per four to six patients.

Staff nursing skills should be broad-based and include the ability to care for patients of all ages seen in the ED with a wide spectrum of conditions. They should have the ability to provide critical care when needed and perform on-demand phlebotomy and frequent assessments of patients under their care. Nurses should also be able to provide prolonged patient and family interactions, including hygiene care, meals, and emotional support. These skills are typically present in emergency nurses, who are optimal for observation services. When nonemergency nurses are recruited for the observation unit, they should be cross-trained, serving some shifts each month in the ED to develop the appropriate skill set to care for complex observation patients.

Additional emergency clinician staffing is also required for the observation unit. Managing ED patients in the observation unit for an additional 12 to 14 hours requires a doubling of the emergency clinician service for a single patient. Calculations of staffing for the amount of additional services amounts to approximately one full-time equivalent for every 2000 patients observed per year. In a model where the emergency clinician rounds on observation unit patients prior to an ED shift, about 6 to 9 minutes are needed per patient (ie, 60–90 minutes for a 10-bed unit, depending on patient complexity). As with the nurses,

BOX e6.1

Conditions Appropriate for Observation

EVALUATION: CRITICAL DIAGNOSTIC SYNDROMES

Abdominal pain
Back pain
Chest pain
Deep venous thrombosis
Gastrointestinal bleed
Syncope
Trauma
- Blunt abdominal
- Blunt chest
- Penetrating abdominal
- Penetrating chest
- Head injury

TREATMENT: EMERGENCY CONDITIONS

Allergic reaction
Asthma
Atrial fibrillation
Congestive heart failure
Dehydration
Headache
Renal colic
Infections
- Cellulitis
- Pneumonia
- Pyelonephritis

emergency clinicians in the observation unit must have broad-based knowledge and experience in the management of a wide variety of disease processes. In a closed unit, wherein all patients first pass through the ED and care is continued by emergency medicine staff, the emergency clinician is ultimately responsible for the care of the patient and needs to provide clear leadership at all times.

Patients and staff involved in the observation process should be well informed about the goals and benefits provided by the extended service. Well-written, condition-specific, observation protocols ensure a continuum of care, including the transfer of patient care at shift change. The services provided in an ED observation unit are equivalent to inpatient services, albeit at an accelerated pace. Consultants must be available to the observation unit as they would to any inpatient service, and agreements with consulting services may be made to expedite consultations to avoid admission.

The amount and type of ancillary personnel needed to staff an observation unit depend on the size and type of services offered in the unit. Most units require clerks and secretaries, medical assistants to assist nursing staff, and respiratory therapists. Observation units that offer chest pain or psychiatric evaluation may require staff with particular skill sets.

The structure of the observation unit will determine its clinical effectiveness and financial viability. Models for the structure of the observation unit have been described in the American College of Emergency Physicians textbook, Emergency Department Design.[5] An observation unit that is properly designed and located within or adjacent to the ED will create large cost savings compared with traditional hospital admission while providing equivalent or improved quality of patient care in less time.

BOX e6.2

Observation Criteria for Abdominal Pain[a]

EXCLUSIONS[b]

Severe dehydration
Hemodynamic instability
Na < 120 mEq; Na > 155 nEq
Concomitant acute severe medical condition (eg, acute renal failure or sepsis)
Acute peritonitis
Probability of discharge within 24 hours < 80%
High or moderate probability serious dangerous disease such as acute appendicitis, bowel obstruction or perforation

INCLUSIONS[c]

Inability to correct symptoms
Inability to take fluids by mouth
Possibility patient has serious dangerous cause of symptoms
Inability to control pain with oral medication

[a]**NOTE:** These criteria are based on our observation protocols.
[b]Any criterion indicates too high a risk for observation but patient should be admitted.
[c]Appropriate to refer to observation if patient meets all criteria.

CLINICAL CONDITIONS

Evaluation of Critical Diagnostic Syndromes

Abdominal Pain

Traditional Approach. Abdominal pain is one of the most frequent complaints seen in the ED and accounts for about 11% of all visits.[6] The typical ED evaluation of the abdominal pain patient includes a thorough history, physical examination, and appropriate diagnostic tests. Within the short time frame of 2 or 3 hours, patients are given a provisional diagnosis and are hospitalized or sent home.

Problem With Traditional Approach. The ED evaluation is inadequate for many patients and, in 40% of patients, the origin of abdominal pain is never determined. Acute appendicitis is the most common abdominal surgical emergency and illustrates the inadequacies of the traditional diagnostic approach. The diagnosis of acute appendicitis is missed in 20% to 30% of cases (false-negative decisions). In addition, 20% to 30% of patients taken to surgery for acute appendicitis are found to have no abnormality (false-positive decisions). Although abdominal CT scan imaging improves emergency clinician performance in identifying patients with acute appendicitis, there has been mounting concern regarding the amount of ionizing radiation exposure to patients due to increased utilization. Also, patients with early appendicitis may have a CT scan without an obvious acute finding but also have a concerning examination, warranting additional evaluation.

Observational Approach. With observation, the ED evaluation can be extended beyond the initial 2- or 3-hour evaluation for selected patients (Box e6.2). After the initial history and physical examination of the patient, the emergency clinician makes an estimate of the probability—via the Alvarado score—that the patient actually has appendicitis. Patients deemed to have a low probability of disease are ideal candidates for the observational approach. Patients who are difficult to assess clinically are also good candidates for observation, such as immunocompromised patients, pregnant women, and patients at the extremes of age.

During the period of observation, the patient is usually kept NPO and hydrated via the intravenous (IV) route. Serial abdominal examinations are repeated at 4-hour intervals, and laboratory tests are repeated, as appropriate. Imaging and consultations are also arranged during this time frame. For pregnant patients, abdominal magnetic resonance imaging (MRI) may be the best imaging choice. Patients are hospitalized if they have no improvement, worsening of their clinical findings, or surgical pathology diagnosed by testing.

In addition to patients with suspected appendicitis, the evaluation and care of other patients with abdominal pain improves with observation. Patients with abdominal pain often have accompanying symptoms, such as fever, vomiting, and diarrhea, resulting in metabolic disarray and dehydration. Time in observation for IV hydration and medications (eg, antiemetics, opioids), with repeat laboratory tests, provides the necessary time for the patient to recover and transition to an oral regimen of nutrition and medications prior to discharge. Consultation with the general surgery and/or gastroenterology service may be helpful in select cases. Advanced imaging, typically out of scope for an emergency department visit, can also be performed—for example, magnetic resonance cholangiopancreatography or hepatobiliary scintigraphy in patients with suspected biliary pathology. Trending laboratory tests also provide an opportunity to assess whether the patient is responding to treatments appropriately versus experiencing a progressive course of illness necessitating inpatient care. Providers should be cautious of using the observation unit for patients with acute on chronic abdominal pain because the time frame and available resources of a typical observation unit stay are unlikely to address the needs of these patients sufficiently.

Chest Pain

Traditional Approach. The role of the emergency clinician in evaluating in chest pain patients is twofold: (1) assessment of the probability that the patient has an acute myocardial infarction (AMI) or acute coronary ischemia (ACI); and (2) assessment of the risk of the patient having a life-threatening event. These two assessments help determine the appropriate setting for further testing and monitoring. The probability of AMI is traditionally assessed in the ED with a history, physical examination, electrocardiogram (ECG), and initial measurement of cardiac biomarkers.

Patients with clear evidence of AMI based on their history and ECG are potential candidates for immediate reperfusion therapy with thrombolytics or emergency angioplasty. Such patients are at risk for life-threatening events and are best managed in the coronary care unit.[7] Depending on the evaluating emergency clinician's threshold, chest pain patients without definite evidence of AMI at initial evaluation are traditionally admitted to the hospital to confirm or exclude (rule in or rule out) ACI or AMI. Patients who are judged to have a low probability of ACI after the initial evaluation are released home for outpatient follow-up.

Problem With Traditional Approach. The poor performance of initial diagnostic testing makes the evaluation of chest pain highly dependent on clinical judgment. The initial ECG is diagnostic in only 50% of AMI patients, and the initial biomarker measurement has a sensitivity of only 35%. Reliance on physician judgment and initial ED testing has resulted in as many as 2% to 5% of AMI or ACI patients being discharged home with inadvertent reassurance. The consequences of a missed AMI are significant. AMI patients not identified at the initial evaluation and released from the ED have up to a 25% risk of poor outcome. To avoid inadvertently releasing AMI or ACI patients, emergency clinicians often err on the side of admitting patients to the hospital, many who do not have an AMI or ACI. The increased sensitivity of a more liberal admission policy results in two-thirds of patients admitted for chest pain having a noncardiac cause for their symptoms, costing billions of dollars for these negative evaluation hospitalizations. Yet, despite this this approach, missed AMI is the leading cause for malpractice suits against emergency clinicians.[8]

BOX e6.3

Observation Criteria for Chest Pain[a]

EXCLUSIONS[b]

Diagnostic electrocardiographic changes or cardiac biomarkers consistent with acute myocardial injury
High probability of serious dangerous disease or risk of adverse event
Unstable vital signs

INCLUSIONS[c]

Atraumatic chest pain
Low to intermediate probability of serious dangerous disease or risk of adverse events
Stable vital signs

[a]**NOTE:** These criteria are based on our observation protocols.
[b]Any criterion indicates too high a risk for observation but patient should be admitted.
[c]Appropriate to refer to observation if patient meets all criteria.

Observational Approach. The emergency clinician can use the observation unit to extend the evaluation of selected patients with chest pain (Box e6.3). When used principally for such a purpose, the observation unit has been termed a *chest pain unit.* The chest pain unit has been successful in improving the sensitivity and specificity of the evaluation process and reducing unnecessary hospital admissions. Patients with a low and intermediate risk of AMI may be treated in the observation unit. Patients unsuitable for observation unit evaluation include those who have a high probability of acute myocardial ischemia, unstable vital signs, electrocardiographic findings of AMI, or persistent chest pain consistent with unstable angina.

The emergency clinician may identify patients with a low or intermediate probability for ACI by using one or more risk stratification tools. Most validated risk stratification tools widely used today incorporate some elements of risk factors, age, chest pain history, electrocardiographic findings, and troponin results. For example, the HEART score incorporates these elements and has performed well in subsequent validation studies (ie, negative predictive value > 98% for those with a low-risk score; Table e6.1).[9]

Patients assigned to the observation unit are first evaluated to rule out a myocardial infarction. They are serially tested with cardiac markers and ECGs. Conventional troponin level measurement on arrival and 6 hours after symptom onset is routine; with new, highly sensitive troponin assays currently available outside the United States. This time frame is accelerated in low-risk patients.[10] Recent evidence has suggested accelerated diagnostic protocols, such as a 2- or 3-hour repeat conventional troponin level assay without provocative stress testing may be appropriate for patients deemed low risk via a validated risk stratification tool, with undetectable troponins and nonischemic ECGs.[11,12]

Patients are monitored with continuous electrocardiographic monitors equipped with dysrhythmia alarms and memory storage capabilities. Low-risk patients and those who are pain-free do not require continuous telemetry.[13] However, in higher risk patients or those with ongoing pain, continuous monitoring can detect dynamic ST segment changes indicative of ischemia, which, when

TABLE e6.1

HEART Score for Risk Stratification in Chest Pain

PARAMETER	VALUE	POINTS
History	Highly suspicious (2) Moderately suspicious (1) Slightly suspicious (0)	0–2
Electrocardiogram	Significant ST depression (2) Nonspecific repolarization disturbance (1) Normal (0)	0–2
Age (yr)	≥65 (2) 45–64 (1) <45 (0)	0–2
Risk factors • Hypercholesterolemia • Hypertension • Diabetes mellitus • Cigarette smoking • Positive family history • Obesity	Three or more risk factors or history of atherosclerotic disease (2) One or two risk factors (1) No risk factors known (0)	0–2
Troponin	>3× normal limit (2) 1–3× normal limit (1) < Normal limit (0)	0–2

Risk Score	Risk Class	Treatment Site
0–3	Low	Outpatient or Observation
4–7	Intermediate	Observation
8–10	High	Inpatient

present, indicate an increased likelihood for an adverse cardiac event. After evaluation to exclude AMI, the patient is evaluated for possible ACI through some form of provocative testing. This may be performed before release of the patient from the observation unit or at follow-up evaluation within 72 hours of discharge.[10] The most common testing modality used is exercise stress testing. Patients who obtain their target heart rate without electrocardiographic evidence of ischemia can be released home. These patients have an annual mortality rate less than 1%. The performance of exercise testing depends on the ability of the patient to exercise adequately, gender (women have higher false-positive rates), interpretability of the resting ECG, and availability of the test. Other testing modalities include stress echocardiography, technetium (99mTc) sestamibi scanning, and coronary computed tomography (CT) angiography.[14,15]

Approximately one-third of ED chest pain patients are candidates for observation, with 80% to 85% released home after observation admission. This approach reduces hospitalization rates and cost of care. The Centers for Medicare & Medicaid Services began nationwide audits in 2010 by recovery audit contractors to deny payment for low probability of AMI chest pain patients who were admitted to the hospital rather than evaluated in the lower cost outpatient observation. The use of observation units for chest pain evaluation is thus becoming the standard in US hospitals.

Deep Vein Thrombosis

Traditional Approach. The primary objectives for the treatment of deep vein thrombosis (DVT) are to prevent pulmonary embolism (PE), reduce morbidity, and prevent or minimize the risk of developing postphlebitic syndrome. Patients with suspected DVT are usually hospitalized when diagnostic testing is unavailable in the ED, or the diagnosis has been confirmed and further management is required. Traditionally, anticoagulation with unfractionated heparin has been administered by continuous IV infusion for 5 to 7 days while oral anticoagulation is instituted.

Problem With Traditional Approach. New modalities for investigation and treatment have made it possible to manage DVT on an outpatient basis with lower costs rather than with hospitalization. There are newer, less invasive investigative tests and newer therapeutic agents that do not require monitoring of coagulation profiles.

Observational Approach. Observation units can be used to arrange diagnostic studies and initiate patient treatment and education. Patients often present during the night or on weekends when definitive tests for DVT (eg, Doppler ultrasonography) may not be available. The patient may have a positive D-dimer test finding, which requires a confirmatory definitive test in intermediate- to high-risk patients because of its poor specificity. In these circumstances, the patient can be anticoagulated for the short term with one dose of low-molecular-weight heparin (LMWH; eg, enoxaparin, 1 mg/kg SQ bid) or a novel oral anticoagulant (eg, rivaroxaban, 15 mg PO bid) until the diagnosis can be clarified. If the diagnosis is confirmed, the patient can be admitted or treated as an outpatient based on hospital protocol. Patients considered for outpatient management are instructed on how to administer the medication. They are educated about DVT and the possible complications and side effects of anticoagulation therapy. This approach has been shown to result in patients spending 67% less time in the hospital and having greater physical activity and social functioning than their standard heparin cohorts. Outpatient management is not recommended if the patient has proven or suspected concomitant high-risk pulmonary embolism, significant comorbidities, extensive iliofemoral DVT, active bleeding, renal failure, or poor follow-up compliance.

Upper Gastrointestinal Bleeding

Traditional Approach. Most patients with upper gastrointestinal bleeding (UGIB) are admitted to the hospital after initial ED assessment and stabilization.

Problem With Traditional Approach. UGIB is a common and potentially life-threatening condition, with an overall mortality rate of 6% to 10%. However, most cases of UGIB are self-limited, and 80% of patients have only one bleeding episode.

Observational Approach. Many patients with UGIB can be managed in an outpatient setting, although patients at high risk for further bleeding must be identified and monitored closely. Prognostic indicators include age, heart rate, systolic blood pressure, orthostatic changes in blood pressure or pulse, color of stool or emesis, anticoagulant use, and comorbid conditions. In an attempt to refine diagnostic accuracy, risk assessment, and disposition, several scoring systems have been developed. Some practitioners use hemodynamic stability, intensity of bleeding, and underlying health status as predictors of rebleeding, need for surgery, and mortality. Admitting patients to an observation setting with early endoscopy can identify patients who can be

discharged early. Patients found to have clean-based ulcers at endoscopy have a rebleeding rate of less than 2%, almost never require urgent intervention for recurrent bleeding, and can be released. Use of this approach has been proven to be safe and cost-effective.

Syncope

Traditional Approach. Syncope is caused by a wide spectrum of disease entities. ED evaluation includes a thorough history, physical examination, and electrocardiography. Patients with evidence of possible myocardial ischemia or cardiac cause of their syncope are usually admitted to the hospital because cardiac syncope has a high risk of death—up to one-third will have a poor outcome. On the other hand, patients with noncardiac syncope have a low risk of adverse events (<1%) and can be managed as outpatients.

Problem With Traditional Approach. Attempts to exclude a possible cardiac cause for syncope usually result in 25% to 40% of patients being hospitalized for further evaluation and management. The traditional ED evaluation identifies only 50% of patients with a serious cause of their syncope, which often results in high rates of hospitalization. Up to one-third of patients admitted after their ED evaluation are at very low risk of an adverse event (<2%) and would be appropriate for outpatient observation evaluation.

Observational Approach. Extending the ED care with a period of observation for select patients with syncope is a useful strategy to reduce unnecessary hospitalizations (Box e6.4). Patients with cardiac syncope have a poor prognosis and need to be identified with a high degree of sensitivity. Prolonged telemetry monitoring can point to a specific cause in up to 20% of patients, with 50% of all abnormalities detected in the first 24 hours.

The challenge for the emergency clinician is to risk-stratify patients into very low risk, who can be discharged home, intermediate risk, who are appropriate for outpatient observation, and high risk, who are appropriate for acute care hospitalization. Many factors have been found to correlate with adverse outcomes and should be considered in risk stratification; however, attempts to create simple, highly reliable decision rules have not been successful. The 1-year risk of dysrhythmia or death in syncope patients correlates with four factors: an abnormal ECG, history of ventricular dysrhythmia, history of heart failure, and age older than 45 years. Patients with none of these risk factors have only a 4.4% rate of adverse events at 1 year and may be appropriate for outpatient evaluation. In contrast, patients with three or four risk factors have a 58% adverse outcome rate and should be admitted to the hospital. Patients with one or two risk factors have intermediate risk and may be appropriate for outpatient evaluation with observation. The San Francisco syncope rule has been found to be sensitive for identifying patients who are at immediate risk for serious outcomes within 7 days, with ranges in different studies from 74% to 96%.[16] Its criteria are the absence of abnormal electrocardiographic findings, history of CHF, dyspnea, hematocrit level of less than 30%, or hypotension.[16]

The ***R***isk stratification ***O***f ***S***yncope in the ***E***mergency Department (ROSE) criteria suggest that an elevated B-type natriuretic peptide (BNP) level, hemoccult-positive stool, anemia, low oxygen saturation, and presence of Q waves on the ECG predict serious outcomes at 30 days.[17] These rules had an 87% sensitivity and 98.5% negative predictive value to help risk stratify patients. In this study, the isolated finding of BNP greater than 300 pg/mL was a major predictor of serious outcomes and was present in 89% of patients who died within 30 days. In one study, it was found that 6.1% of patients have severe outcomes within 10 days of syncope evaluation. The mortality rate was 0.7%, and 5.4% of patients were readmitted or experienced major therapeutic intervention. Risk factors associated with severe short-term outcomes included abnormal ECG, history of CHF, age older than 65 years, male gender, history of chronic obstructive pulmonary disease, structural heart disease, presence of trauma, and lack of prodromal symptoms.

The ***E***valuation of ***G***uidelines in ***SY***ncope ***S***tudy 2 (EGSYS 2) prospectively followed nearly 400 patients at 1 month and 2 years. The death rate was 2% at 1 month and 9% at 2 years. Patients with advancing age, presence of structural heart disease, and/or an abnormal ECG had higher risk.[18-20] Additional factors that would indicate a patient should be admitted rather than placed in outpatient observation include history of ventricular arrhythmia, low ejection fraction, abnormal neurologic findings, positive cardiac biomarkers, and loss of consciousness for longer than 15 minutes.

Because there are many factors that could be considered in the emergency clinician's risk stratification for patient disposition to observation or acute hospitalization (see Box e6.4), the best practice approach is to come to an institutional consensus on this risk stratification and codify this consensus in a syncope order set. This approach reduces health care provider variability in decision making by adopting evidence-based practices more uniformly, which improves the quality of patient care and use of health care resources.

During the observation period, serial examination of patients is carried out, including vital signs, with most patients safely discharged home without hospitalization. Continuous telemetry, consultation, serial cardiac enzyme level assays for those with a concern for AMI, and further tests, such as two-dimensional echography of the heart, should be arranged, when appropriate. The period of observation can also identify patients with cardiac dysrhythmias or sinus pauses who are candidates for more extensive diagnostic evaluation in the hospital. Typically, a 12-hour minimum duration of telemetry is used to evaluate a syncope patient in an observation unit, with longer monitoring more

BOX e6.4

Observation Criteria for Syncope[a]

EXCLUSIONS[b]

History of dyspnea or loss of consciousness >10 min or seizure
Past history of ventricular dysrhythmia
Abnormal laboratory hematocrit level <30%, elevated B-type natriuretic peptide (BNP) or pro-BNP, or positive cardiac biomarkers
Evidence of injury or ischemia on ECG or documented or highly suspected unstable dysrhythmia
Low oxygen saturation or unstable vital signs
Evidence of clinically significant gastrointestinal hemorrhage (ie, stool positive for blood in the setting of hematocrit drop)
New focal neurologic findings or persistently altered mental status
High or moderate probability of serious dangerous disease or adverse event
History of low ejection fraction (eg, <30%)
Clearly vasovagal episode (ie, candidate for immediate discharge home)

INCLUSIONS[c]

Possibility of pathologic cause of the syncope
Intermediate probability of serious dangerous disease or adverse event

[a]**NOTE:** These criteria are based on our observation protocols.
[b]Any criterion indicates too high a risk for observation but patient should be admitted.
[c]Appropriate to refer to observation if patient meets all criteria.

efficiently arranged via an outpatient continuous monitor (eg, Holter monitor) in patients for whom arrhythmia is an ongoing concern.[1]

Transient Ischemic Attack

Traditional Approach. More than 300,000 people suffer a transient ischemic attack (TIA) each year. For most patients, it is a transient event that will not recur if they take one aspirin each day. However, for 1 in 10 patients, it is a warning sign that they will suffer a stroke unless they are appropriately evaluated and treated. Traditionally, the patient is assessed in the ED with history, physical examination, laboratory tests, electrocardiography, and head CT scan. Most patients are then hospitalized for serial clinical evaluations, neurology consultation, carotid imaging, echocardiography, and cardiac monitoring.

Problem With Traditional Approach. The problem with the traditional approach is that most TIA patients are admitted primarily for expedited evaluation. After 3 days of evaluation, few will be found to have clinically significant carotid stenosis or structural heart disease requiring an intervention. As a result, there is a significant opportunity to develop a more cost-effective approach for the evaluation of TIA.

Observational Approach. Observation is an alternative to hospitalization for TIA patients with a negative ED evaluation for whom the emergency clinician still has concern. Currently, the ABCD^2 score is a validated risk-stratification tool that can help identity those patients most appropriate for an observation unit protocol (Table e6.2). Risk-stratification of TIA patients is discussed in Chapter 91. Patients at highest risk (ie, a score of 6 or 7) should be managed as inpatients, whereas intermediate- and low-risk patients are candidates for observation. This approach has been shown to decrease the cost of evaluation and has not resulted in adverse patient outcomes versus standard inpatient care.

TABLE e6.2

ABCD^2 Score for Risk Stratification in Transient Ischemic Attack

FACTOR	VALUE	POINTS
Age	≥60 yr	1
Blood pressure (mm Hg)	≥140/90 Initial reading: SBP ≥ 140 or DBP ≥ 90	1
Clinical features of episode	Unilateral weakness (2) Speech disturbance without weakness (1) Other symptoms (0)	0–2
Duration of symptoms (min)	<10 (0) 10–59 (1) ≥60 (2)	0–2
History of diabetes mellitus		1
Risk Score	**Risk Class**	**Treatment Site**
0–3	Low	Outpatient or Observation
4–5	Intermediate	Observation
6–7	High	Inpatient

DBP, Diastolic blood pressure; *SBP,* systolic blood pressure.

Trauma

There are more than 41 million trauma-related ED visits annually.[21] Patients with serious injuries require hospitalization for definitive therapy, whereas those with minor injuries can be discharged after treatment in the ED.

The problem with the traditional ED approach is that many patients have injury patterns or actual injuries that fall somewhere between the two scenarios just described. If these patients are released home, there is a risk that some will have poor outcomes as a result of missed injuries. On the other hand, because most of these patients do not have serious injuries, admitting this group to the hospital will result in a waste of scarce health care resources.

Observation units have been found to be an efficient and useful strategy for the evaluation and management of trauma victims. With observation, select patients can be evaluated further to determine the need for admission.

Blunt Abdominal Injury

Traditional Approach. Current ED management of blunt abdominal trauma (BAT) patients includes history taking, physical examination, blood analysis, plain radiography, bedside ultrasonography, and CT scanning. After initial stabilization and exclusion of other major injuries in the ED, most patients suffering BAT are admitted to the hospital for further evaluation and monitoring.

Problem With Traditional Approach. The initial evaluation is inadequate for the accurate disposition of many BAT patients. One-third of patients who do not have any symptoms or signs suggestive of intra-abdominal injury may actually have significant injury. Also, because none of the present modalities for investigating the presence of injury is 100% sensitive, many patients with initially negative investigations are hospitalized.

Observational Approach. BAT patients appropriate for observation include those who, after initial evaluation, have no clear evidence of serious injury on physical examination but remain at risk for serious injury because of the mechanism of the injury or his or her personal health (eg, anticoagulant use). Evaluations during an observation unit stay include repeat physical examinations, laboratory testing, imaging, and specialty consultations. Patients are hospitalized if their condition deteriorates during the observation period or if, after testing, they are found to have serious internal injury. CT alone is not adequate to rule out serious injury, with a sensitivity of only 80% to 95%. Observation alone in patients with BAT is not sufficient because up to 20% of patients with significant injury will not have abdominal tenderness or will develop it even after a short period of observation. Thus, the prudent approach to patients with significant BAT without clear evidence of intra-abdominal injury is the use of a diagnostic test, such as CT, together with a period of observation.

Penetrating Abdominal Injury

Traditional Approach. Most patients with penetrating abdominal injury are hospitalized for further evaluation, which may include wound exploration in the operating room and additional diagnostic testing.

Problem With Traditional Approach. Many of these hospitalizations are unnecessary because only two-thirds of patients with abdominal stab wounds have a breach of the peritoneum, and two-thirds of them do not sustain visceral injury.

Observational Approach. A period of observation can identify patients who do not require surgical intervention. Patients undergo serial examinations by the emergency clinician, further diagnostic testing, and specialty consultation. Those without evidence of peritoneal perforation or visceral injury after evaluation are sent home after proper wound care.

The conservative approach to penetrating abdominal wounds was developed in the 1970s. Those without peritoneal breach can be safely sent home after wound care and a period of observation, without the need for hospitalization. Those with stab wounds to the abdomen with peritoneal breach but a negative finding on diagnostic laparoscopy or imaging with CT or ultrasonography can be safely managed in an observation unit. Patients with significant intra-abdominal injuries identified during observation are admitted; the 70% to 90% of patients without such injuries are released home. Gunshot wounds are often more difficult to evaluate than stab wounds and usually require admission.

Blunt Chest Trauma

Traditional Approach. Many patients who have a history of blunt chest trauma (BCT) in high-velocity accidents are admitted to the hospital to rule out myocardial or pulmonary contusion.

Problem With Traditional Approach. Very few patients admitted to the hospital with BCT from high-velocity accidents without initial evidence of injury are found to have serious injury during hospital evaluation.

Observational Approach. Patients with isolated BCT who are otherwise stable, with a normal ECG, are suitable for a period of observation to exclude myocardial injury. During the period of observation, patients are monitored with continuous ECG, specifically assessing for dysrhythmias. Serial cardiac enzyme determinations, such as troponin level, are also carried out to detect evidence of myocardial injury. Patients with sternal fractures or other evidence of a higher risk of intrathoracic injury should be considered for transesophageal echocardiography. Those with negative evaluations during the period of observation are released home for outpatient follow-up.

Much of the period of observation in patients with BCT focuses on identifying the presence and prognosis of myocardial contusions. The overall incidence of cardiac-related complications in these patients is low (0.1%). Patients with blunt cardiac trauma who have complications usually have an abnormal ECG or abnormal troponin level at presentation. Conversely, normal ECG and troponin levels correlate with the lack of clinically significant complications. Patients who have isolated chest wall contusions and no abnormality of serial troponin levels, electrocardiographic abnormalities, or dysrhythmia during 6 to 12 hours of electrocardiographic monitoring are unlikely to have complications.

Penetrating Chest Injury

Traditional Approach. Patients with penetrating chest injury present with a spectrum of severity, ranging from a severe life-threatening injury requiring urgent operative intervention to hemodynamically stable patients with a negative initial evaluation. Most patients presenting with penetrating chest injuries are admitted to the hospital to exclude serious injury to the heart, lungs, and major blood vessels.

Problem With Traditional Approach. The accuracy of this approach is limited because many patients with evidence of injury are admitted but have no further deterioration or need for medical therapy. On the other hand, there are those without obvious evidence of serious injury who will have a negative outcome if released after the initial evaluation.

Observational Approach. A period of observation combined with diagnostic imaging can improve clinical decision making. Patients with evidence of a small pneumothorax or hemothorax can be monitored for deterioration. Those without evidence of serious injury but of concern to the emergency clinician can likewise be observed for complications. During the period of observation, patients are monitored for respiratory or hemodynamic compromise. Repeat chest radiographs can detect the development of hemothorax or pneumothorax. Patients who deteriorate during the period of observation require hospitalization.

The safety and efficacy of managing asymptomatic stab wound victims in the short-term observation unit have been clearly established. A total of 5% to 15% will require hospitalization because of the development of delayed pneumothorax, subcutaneous emphysema, hematemesis, or pneumopericardium. In addition, most stab wound victims with small pneumothoraces or hemothoraces will be treated solely with a chest tube, without further surgical intervention. Major trauma centers can manage many of these patients as outpatients without hospitalization by using a period of observation.

Patients with penetrating wounds to the cardiac area of the chest (between the nipples), region of the great vessels, or thoracoabdominal area usually require more intensive testing to exclude injury not only to the heart, major vessels, and lungs but also to the diaphragm and abdominal organs. Echocardiography may detect pericardial fluid or tamponade in patients with penetrating injury in close proximity to the heart. Patients with small effusions may be observed in a monitored setting with serial examinations, whereas patients with large effusions should be treated surgically. Patients with a negative echocardiogram can be observed in the observation unit. Even patients with small effusions may have sustained a serious injury, so the intensity of monitoring needs to be high.

Treatment of Emergency Conditions

Asthma

Traditional Approach. More than 25 million people in the United States are afflicted with asthma. Acute exacerbation of asthma is a common ED presentation, with estimated annual inpatient admissions with asthma listed as a primary discharge diagnosis exceeding 450,000.[22] Traditionally, therapy has been provided in the ED for 2 to 4 hours, consistent with national guidelines.[23] The initial assessment includes history, physical examination, oxygen saturation, and peak expiratory flow rate (PEFR) or forced expiratory volume in 1 minute. Treatment consists of beta agonists, magnesium sulfate, and steroids, where appropriate. Patients who do not improve after 3 or 4 hours of treatment are hospitalized for further management.

Problems With Traditional Approach. With this approach, one-third of patients are hospitalized. This translates into an estimated medical cost of $2.5 billion annually. Another pitfall in the traditional ED treatment of asthma is that short encounter times do not allow for identification and aggressive treatment of patients with a higher tendency for relapse. This leads to repeat ED visits, additional medical costs, and diminished quality of life.

Observational Approach. An alternative to hospitalization for patients failing ED treatment is the use of an extended, short-term intensive protocol for 8 to 12 hours in an observation unit for select patients (Box e6.5). With extended treatment, 80% of such patients can be discharged home. Inclusion criteria for observation unit management are failure of standard initial management with continued respiratory distress and a reasonable response to initial management. An increased risk of relapse is indicated by a history of numerous asthma-related ED or clinic visits within the past year, using more outpatient medications (including home nebulizers), and longer duration of symptoms. Exclusion criteria for observation include unstable vital signs, evidence of impending respiratory failure (increased work of breathing or evidence of fatigue), or severe airway restriction (PEFR < 80 L/min after first inhaled beta agonist treatment). Also considered during selection for observation are factors that correlate with unsuccessful treatment during observation. These

BOX e6.5

Observation Criteria for Asthma[a]

EXCLUSIONS[b]

Respiratory fatigue or failure (respiratory rate > 40 breaths/min, oximetry < 90%)
Inability to perform spirometry or peak flows
Peak flow after third beta agonist <30% of predicted
Concomitant illness (eg, pneumonia, heart failure)
Bronchospasm due to aspiration or foreign body
Temperature > 38.3° C (101° F)
Need for continuous nebulizer treatment, BiPAP, or heliox
Acute ischemic electrocardiographic changes or positive cardiac biomarkers

INCLUSIONS[c]

Shortness of breath
Mild to moderate use of accessory muscles
Wheezing
Fair to good air exchange
Stable vital signs
Normal mentation

[a]**NOTE:** These criteria are based on our observation protocols.
[b]Any criterion indicates too high a risk for observation but patient should be admitted.
[c]Appropriate to refer to observation if patient meets all criteria.

include a previous ED visit in the past 10 days, previous intensive care unit admission or intubation, hospitalization during the previous year, three or more ED visits in the past 6 months, use of oral steroids for more than half of the previous year, and peak flow after the third beta agonist treatment that is less than 32% of predicted.

Therapy in the observation unit is a continuation of ED treatment with nebulized beta agonists every 2 to 4 hours and repeated ipratropium at 6 hours after initial therapy. Intravenous magnesium is another useful treatment in this patient population. Patients are released from the observation unit when they are not in respiratory distress, have minimal residual symptoms, and have a PEFR of 70% or higher of predicted or personal best. Before discharge, there should also be patient educational activities and assessment of inhaler techniques. Patients should be initiated into keeping a daily diary, as well as a log of PEFR before and after treatment. Appropriate follow-up monitoring should also be arranged.

Observation unit patients also reported fewer problems with care received, communication, emotional support, physical comfort, and special needs. Observation has also been shown to have value in the management of pediatric patients with asthma. Of those who would otherwise require hospitalization, 30% to 70% can be successfully managed as outpatients with the observation unit.

Atrial Fibrillation

Traditional Approach. Atrial fibrillation is a relatively common condition that occurs in less than 3% of adults and is the most common sustained cardiac dysrhythmia in patients presenting to the ED. The goals for the management of acute atrial fibrillation are hemodynamic stabilization, symptom relief, prevention of thromboembolism, resolution of the dysrhythmia, and exclusion of serious pathologic causes of the dysrhythmia. Most patients who present to the ED with new-onset atrial fibrillation or acute atrial fibrillation are hospitalized.[24]

BOX e6.6

Observation Criteria for New-Onset Atrial Fibrillation[a]

EXCLUSIONS[b]

Evidence of new or acute on chronic CHF
Evidence of injury or ischemia on ECG or documented or highly suspected unstable dysrhythmia
Low oxygen saturation or unstable vital signs
New focal neurologic findings or persistently altered mental status
High or moderate probability of serious dangerous disease or adverse event
Poor candidate for outpatient anticoagulation

INCLUSIONS[c]

Low probability of serious dangerous disease or risk of adverse event
Stable vital signs

[a]**NOTE:** These criteria are based on our observation protocols.
[b]Any criterion indicates too high a risk for observation but patient should be admitted.
[c]Appropriate to refer to observation if patient meets all criteria.

Problem With Traditional Approach. Recently, the necessity of admitting most patients with acute atrial fibrillation has been questioned.[25,26] It is recognized that new-onset atrial fibrillation for most patients is a transient dysrhythmia, with no serious precipitants and a benign prognosis. One retrospective analysis of 216 patients admitted for atrial fibrillation found that one-third of patients did not actually require admission to the hospital.[27]

Observational Approach. The observational approach to new and acute atrial fibrillation has been validated in a number of clinical trials. The period of observation is usually 8 to 12 hours. During observation, patients are treated to correct their dysrhythmia and evaluated for serious precipitants of their condition. After observation, 80% to 90% of patients can be discharged home without hospitalization.

For select patients (Box e6.6), observation extends the ED evaluation of the patient for serious underlying medical conditions that may have precipitated the arrhythmia, such as AMI or hyperthyroidism. AMI is excluded as a precipitant with serial electrocardiographic and cardiac biomarker testing on arrivals and 6 hours later and an evaluation for unstable angina in the subset of patients with a presentation that raises concern for AMI (ie, chest pain). The period of observation is also used to detect structural heart disease with the use of echocardiography, where appropriate. Patients are excluded from observation if they exhibit hemodynamic instability, comorbid conditions, heart failure, or evidence of active coronary artery disease.

Observation is also used to extend the treatment period of the patient with atrial fibrillation. The spontaneous conversion rate for patients with acute atrial fibrillation is 50% to 70% within the first 24 hours. Patients who spontaneously convert have a low rate of structural heart disease. Those who present within a clear, 48-hour time of onset but do not spontaneously convert in the first 8 hours can be converted chemically or electrically. After cardioversion, the patient needs to be observed. This is especially true for patients converted with the newer class III antidysrhythmic agents (eg, ibutilide), which have the potential for serious side effects, such as torsades de pointes (5% of patients), sinus bradycardia, and sinus arrest. Currently, the CHA_2DS_2VASc score is used to determine the need for anticoagulation in patients discharged home after a cardioversion to normal sinus rhythm in the ED or observation unit (Table e6.3). Those with a score of 2 or higher

TABLE e6.3

CHA_2DS_2VASc Score for Anticoagulation in Patients With Atrial Fibrillation

FACTOR	VALUE	POINTS
Age (yr)	<65 (0) 65–74 (1) ≥75 (2)	0–2
Gender	Female (1) Male (0)	1
Congestive heart failure history		1
Hypertension history		1
Stroke, transient ischemic attack, thromboembolism history		1
Vascular disease history		1
History of diabetes mellitus		1
Risk Score	**Risk Class**	**Anticoagulation**
0–1	Low	No
≥2	Moderate to high	Yes

BOX e6.7

Observation Criteria for Heart Failure[a]

EXCLUSIONS[b]

Diagnostic electrocardiographic changes or cardiac biomarkers consistent with acute myocardial ischemia
Concomitant acute severe medical condition (eg, acute renal failure, sepsis)
Moderate or high probability of serious dangerous disease or risk of adverse event
Unstable vital signs
Chronic renal insufficiency
New onset heart failure
Severe anemia (Hgb < 8 g/dL; Hct < 24%)
Anasarca
New arrhythmia

INCLUSIONS[c]

High likelihood successful treatment within time frame of observation visit
Clear clinical diagnosis of recurrent CHF exacerbation (eg, shortness of breath, DOE, PND, lower extremity or abdominal edema, elevated JVD, S3 present, elevated BNP, pulmonary edema on chest x-ray)
Low probability of serious dangerous disease or risk of adverse event

[a]**NOTE:** These criteria are based on our observation protocols.
[b]Any criterion indicates too high a risk for observation but patient should be admitted.
[c]Appropriate to refer to observation if patient meets all criteria.
BNP, Brain natriuretic peptide; *CHF,* congestive heart failure; *DOE,* dyspnea on exertion; *Hct,* hematocrit; *Hgb,* hemoglobin; *JVD,* jugular venous distention; *PND,* paroxysmal nocturnal dyspnea.

should be started on an anticoagulant (ie, LMWH or factor Xa inhibitor), except for those with a contraindication to anticoagulation (ie, fall risk).[28] All patients managed with rate control alone and discharged while still in atrial fibrillation should be anticoagulated, barring contraindications. The outpatient follow-up and anticoagulation plan should be closely coordinated with the patient's outpatient providers.

Congestive Heart Failure

Traditional Approach. Patients who present to the ED with CHF undergo history taking, physical examination, and investigations, including chest radiography. Treatment is begun with oxygenation, diuretics, inotropic agents, and vasodilators, where appropriate. Most CHF patients treated in the ED are eventually hospitalized.

Problem With Traditional Approach. CHF is highly prevalent, affecting approximately 1% of people in their 50s and increasing progressively with age to afflict 10% of people in their 80s. It is an increasing problem; over 5 million Americans have the disease, and 550,000 new cases are diagnosed each year.[29] One-third of patients with CHF require hospitalization each year, one-third get readmitted each year, and one-third die within 2 years. The annual cost to the health care system of managing patients with heart failure admitted to the hospital has been estimated at $32 billion.[30] Between 80% and 87% of patients diagnosed with CHF are hospitalized.[29]

Observational Approach. Observation is a strategy to avoid hospital admission of patients with CHF, which results in cost savings. Selected patients can be safely managed in an observation unit (Box e6.7). Such patients include those with a high probability of successful treatment with short-term extension of the ED visit. Patients should also have a low severity of illness. They should not be hypoxic, have pulmonary edema or hypotension, and have objective evidence of AMI, hemodynamic instability, or serious comorbid conditions. BNP has been used to streamline decision making. Patients with BNP levels between 100 and 500 pg/mL are suitable candidates for observation unit care because a large proportion of these patients should be able to be discharged home. The test has a negative predictive value of greater than 95% and positive predictive value of 70% to 95%. It correlates with pulmonary capillary wedge pressure and because, its half-life is less than 30 minutes, serial measurements during observation can evaluate the effects of therapeutic interventions.

Therapy and evaluation are a continuation of the initial 2- or 3-hour ED visit for up to 23 hours. Continuous electrocardiographic monitoring for dysrhythmias is performed because up to 30% of CHF patients have dysrhythmias. Inotropic agents can be infused and the patient educated about preventable causes of the exacerbation. Therapy may include continuous infusion of a loop diuretic (0.05–0.1 mg/kg/hr) titrated hourly to a net fluid balance of −1 mL/kg/hr. In most patients with acute exacerbation of chronic CHF, the cause of their exacerbation is preventable, such as failure to take their medications or dietary indiscretion. The opportunity to provide patient education, medication review, and consultations with dietary and social services, where necessary, is fully used because this has been shown to improve compliance with therapy. Patients are discharged home when their symptoms are adequately controlled, all reversible causes of morbidity are treated or stabilized, and adequate outpatient support and follow-up care are arranged. With observation, the focus of ED care can shift from providing only episodic treatment for CHF patients to providing more comprehensive and preventive care. Compared with acute care hospitalization, observation has a much reduced length of stay and significantly lower costs.

Dehydration

Traditional Approach. Dehydration is often the presenting symptom of an underlying disease state and can affect the very

BOX e6.8

Observation Criteria for Dehydration[a]

EXCLUSIONS[b]

Severe dehydration
Moderate or high probability of serious dangerous disease or risk of adverse event
Unstable vital signs
Na < 120 mEq; Na > 155 nEq
Concomitant acute serious medical condition (eg, acute renal failure, sepsis)

INCLUSIONS[c]

Inability to correct symptoms in the emergency department during initial evaluation
Inability to take fluids orally

[a]**NOTE:** These criteria are based on our observation protocols.
[b]Any criterion indicates too high a risk for observation but patient should be admitted.
[c]Appropriate to refer to observation if patient meets all criteria.

BOX e6.9

Observation Criteria for Pneumonia[a]

EXCLUSIONS[b]

Moderate or high probability of serious dangerous disease or risk of adverse event
Unstable vital signs
Risk factors for poor outcome—immunocompromise, neuromuscular disorder, pulmonary tuberculosis, cystic fibrosis
Health care–associated pneumonia or hospital-acquired pneumonia
Concomitant acute serious medical condition (eg, acute renal failure, sepsis)

INCLUSIONS[c]

Stable vital signs
Normal mentation
Low risk by clinical judgment or severity index

[a]**NOTE:** These criteria are based on our observation protocols.
[b]Any criterion indicates too high a risk for observation but patient should be admitted.
[c]Appropriate to refer to observation if patient meets all criteria.

young to the very old. Patients are often admitted for IV hydration to correct fluid and electrolyte imbalances or for further diagnostic evaluation.

Problem With Traditional Approach. Patients with dehydration are often hospitalized because short ED visits do not allow for full correction of fluid and electrolyte disorders or extensive evaluation for underlying causes. A common cause of ED return visits is dehydration due to initially inadequate therapy and evaluation.

Observational Approach. The goals of observation unit therapy are adequate treatment of fluid and electrolyte abnormalities and identification of the underlying cause of symptoms. Appropriate patients for observation include those with acceptable vital signs and mild to moderate dehydration (Box e6.8). They should have self-limited or treatable causes not requiring hospitalization, with mild to moderate electrolyte abnormalities. Another group of patients appropriate for observation are those with hyperemesis gravidarum. Patients unsuitable for observation are those with unstable vital signs, cardiovascular compromise, underlying chronic medical illness, severe dehydration or electrolyte abnormalities, or associated conditions not amenable to short-term therapy (eg, bowel obstruction, diabetic ketoacidosis, sepsis). Interventions include IV rehydration, serial examination and vital signs, and antiemetics. The patient is released home when there are acceptable vital signs, resolution of symptoms, tolerance to oral fluids, and normal electrolyte levels. If the patient does not fulfill the discharge criteria or serious underlying pathology is found, she or he is admitted to the hospital.

Infections

Pneumonia

Traditional Approach. Each year, approximately 1,100,000 patients are hospitalized with pneumonia, at a cost of over $7 billion in the Medicare population alone.[22,31] Many of these patients are admitted after initial ED evaluation. Physicians often rely on subjective criteria such as clinical appearance when selecting patients for hospital admission.

Problem With Traditional Approach. There is great variation in the admission rates for pneumonia. Emergency clinicians tend to overestimate the risk of death in patients with pneumonia, which has resulted in many low-risk patients being hospitalized unnecessarily.

Observational Approach. Observational care is appropriate for patients with stable vital signs, normal mentation, and judged to be at low risk by clinical judgment or severity index (Box e6.9). The risk stratification of patients with pneumonia is discussed in Chapter 66. Patients who are not appropriate for observation include those who are immunocompromised or hypoxic, at risk for pulmonary tuberculosis, or suspected of having a PE (Table e6.4).

During observation, patients are treated with antibiotics, oxygen therapy, and pulse oximetry monitoring. Hydration is given orally or IV. After 10 to 12 hours of treatment in the observation unit, the patient is reevaluated, and a decision about disposition is made. Patients who deteriorate during the observation period or have an oxygen saturation of less than 90% on room air after observation should be admitted to the hospital.

Pyelonephritis

Traditional Approach. Pyelonephritis is a serious infection that frequently results in hospitalization for IV hydration and antibiotic administration.

Problem With Traditional Approach. Many patients with pyelonephritis are at very low risk for developing complications.

Observational Approach. Observation is appropriate for adult nonpregnant women who appear to have uncomplicated pyelonephritis. Patients receive an initial dose of IV antibiotic, IV fluids, antiemetic, and antipyretic. Laboratory tests include complete blood cell count, urinalysis, and urine and blood cultures. Patients who are clinically stable and able to tolerate oral fluids are released home after 12 hours of treatment.

Outpatient management of selected pyelonephritis patients with observation is safe and effective. Only 5% to 25% of patients require hospitalization after the period of observation. At a 3-week follow-up examination, 2% to 6% will have developed complications and require hospitalization. With a period of observation and careful follow-up evaluation, select patients with pyelonephritis can be successfully managed without hospital admission.

TABLE e6.4

Use of Pneumonia Severity Index (PSI) for Admission Decisions

STEP	QUESTION	ANSWER
1	Assess arterial oxygenation for all patients. Is pulse oximetry < 90% or Po_2 < 60 mm Hg?	Yes: Inpatient therapy recommended No: Go to step 2
2	Are any of the following present? • Patient ≥51 yr • Coexisting medical conditions listed in step 3 • Physical examination findings listed in step 3	Yes: Go to step 3 No: Risk class I, go to step 4
3	Compute risk score (sum of applicable points),	

Risk Factor	Points
• Demographic factors	
• Age, yr (age −10 yr for women)	
• Nursing home resident	10
• Coexisting medical conditions	
• Neoplastic disease	30
• Liver disease	20
• Congestive heart failure	10
• Cerebrovascular disease	10
• Renal disease	10
• Physical examination findings	
• Altered mental status	20
• Respiratory rate > 30 breaths/min	20
• Systolic blood pressure < 90 mm Hg	20
• Temperature < 35° C (95° F) or > 40° C (104° F)	15
• Pulse > 125 beats/min	10
• Laboratory and radiographic findings	
• Arterial pH < 7.35	30
• Blood urea nitrogen > 30 mg/dL	20
• Sodium < 130 mEq/L	20
• Glucose > 250 mg/dL	10
• Hematocrit < 30%	10
• Po_2 < 60 mm Hg or O_2 saturation < 90%	10
• Pleural effusion by chest x-ray	10
Total score (sum of all points)	
4	Recommended initial site of treatment

Risk Score	Risk Class	Treatment Site
Not applicable	I	Outpatient
<71	II	Outpatient
71–90	III	Observation
91–130	IV	Inpatient
>130	V	Inpatient

SUMMARY

Health care stakeholders will continue to demand improved outcomes at a lower cost as our current system evolves. This interest is best illustrated by Medicare's triple aim of improving the experience of care, improving the health of populations, and reducing per capita costs of health care. Care in a dedicated observation unit meets this challenge by shifting the site of care to less resource-intensive settings and embracing evidence-based protocols. As financial and operational pressures on the health care system persist, observation services will increasingly become integrated into the ED as a standard setting and model of care in the future.

KEY CONCEPTS

- Hospitalization can often be avoided by providing short-term care (<24 hours) in observation units for certain medical disorders, such as chest pain, deep vein thrombosis (DVT), upper gastrointestinal (GI) bleeding, syncope, transient ischemic attack (TIA), trauma, asthma, atrial fibrillation, congestive heart failure (CHF), dehydration, pneumonia, and pyelonephritis.
- The use of observation units results in cost savings and improved patient satisfaction with care.
- Observation care is on an outpatient basis and is not necessarily delivered in a specific location.
- Observation is used to provide additional time for therapeutics and/or diagnostics for patients with an uncertain need for inpatient admission.
- Observation care is often influenced by payer policies and is congruent with recent national efforts to increase patient safety while also reducing unnecessary costs.
- Evidence-based observation care is delivered in a dedicated area for this purpose, using condition- or complaint-specific protocols of care.
- When used appropriately and at benchmark levels of quality and efficiency, observation visits can reduce the duration and thus the cost of hospital care for eligible patients while also reducing the incidence of unsafe discharges to home.
- The role of observation care is best studied in chest pain patients but, over the past several decades, patients with many other conditions have shown to be managed effectively using observation.
- Emergency clinicians should play a central role in identifying and managing observation patients.

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CHAPTER e6: QUESTIONS & ANSWERS

e6.1. Which of the following is not a high risk factor for adverse events or death in patients with a syncopal event?

A. Abnormal electrocardiogram (ECG)
B. Advancing age
C. Female gender
D. History of heart failure
E. History of ventricular dysrhythmia

Answer: C. Female gender is not included in the factors to be considered in the risk stratification of patients for consideration of referral to outpatient observation for further evaluation and management of patients with syncope (see Box e6.4).

Additional factors that would indicate a patient is unsuitable for observation to evaluate their syncope episode include those who have a history of dyspnea, loss of consciousness for more than 10 minutes, trauma or seizure, past history of chronic obstructive pulmonary disease (COPD) or structural heart disease, abnormal laboratory results—hematocrit level < 30%, elevated brain natriuretic peptide (BNP) or ProBNP level, positive cardiac or abnormal electrolyte levels—electrocardiographic evidence of injury or ischemia, documented or highly suspected unstable dysrhythmia, low oxygen saturation or unstable vital signs, stool positive for blood, new focal neurologic findings or persistently altered mental status, and/or high or moderate probability of serious dangerous disease or adverse event.

e6.2. Which of the following criteria, when present in a patient with chest pain and a nondiagnostic electrocardiogram (ECG), is consistent with the decision to refer a chest pain patient to outpatient observation rather than admission to the acute care hospital?

A. Blunt chest trauma preceding pain
B. Cocaine-induced chest pain
C. History of three-vessel coronary artery bypass grafting (CABG)
D. Minimal elevation in troponin
E. Recurrent chest pain

Answer: B. Patients with a low risk of acute myocardial infarct (AMI) are candidates for referral to an outpatient chest pain observation unit rather than admission to the acute care hospital. Patients considered appropriate for placement in an outpatient chest pain observation unit include those with nontraumatic chest pain, low probability of disease or risk of adverse event, stable vital signs, normal cardiac biomarkers, and nondiagnostic ECG. Patients with cocaine-induced chest pain who meet the previous criteria may also be appropriately evaluated in a chest pain unit. Patients unsuitable for observation unit evaluation include those who have evidence of moderate to high risk, as shown by diagnostic electrocardiographic changes, positive cardiac biomarkers, clinical evidence of moderate or high probability of serious dangerous disease or risk of adverse event, continuing chest pain, and/or unstable vital signs.

e6.3. Which of the following parameters by itself makes inpatient admission the recommended emergency department (ED) disposition of a patient with the diagnosis of pneumonia?
A. Age > 65 years
B. Arterial pH < 7.35
C. Presence of congestive heart failure
D. Presence of neoplastic disease
E. Sao_2 less than 90%

Answer: E. See Table e6.1 for the Pneumonia Severity Index scoring system for admission decisions. Oxygenation is the first step in determining risk and hypoxia, regardless of any other findings, justifies inpatient care.

e6.4. All the following clinical scenarios are suitable candidates for ED observation unit admission except which one?
A. Atrial fibrillation with new onset of acute on chronic congestive heart failure
B. Chest pain with low probability of serious disease or adverse event
C. Congestive heart failure with BNP level of 400 pg/mL
D. Dehydration with moderate electrolyte abnormalities
E. Hyperemesis gravidarum

Answer: A. All the choices are acceptable observation candidates except for atrial fibrillation, with new onset of acute on chronic congestive heart failure. See Box e6.6 for observation criteria for new-onset atrial fibrillation.

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CHAPTER e7

Multiculturalism and Care Delivery*

James L. Thea | Morsal Tahouni

PRINCIPLES

RATIONALE FOR CULTURAL COMPETENCE

Changing Demographics: New Challenges for Emergency Clinicians

Racial and Ethnic Disparities in Health Care Access and Outcomes

Factors Contributing to Disparities in Health Outcomes

CULTURALLY COMPETENT APPROACH TO LANGUAGE BARRIERS

MULTICULTURALISM, CULTURE COMPETENCE, AND HEALTH DISPARITIES: PROGRESS TO DATE

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Care and Communication for Victims of Community Violence

Trauma-Informed Care

Role Expectations in Western Medicine: Opportunities for Misunderstanding

CULTURAL COMPETENCE AND PATIENT-CENTERED CARE: NEW MODELS

EDUCATION

RECOMMENDATIONS

SUMMARY

KEY CONCEPTS

- Changing demography and an evolving culture in the United States is changing emergency medicine practice.
- Disparities in health and health care delivery continue, despite efforts to improve care. Emergency clinicians and their institutions will need to be part of the solution—treating preventable conditions that become crises because of reduced access to primary care and specialists and acting as advocates for strategic system change to eliminate disparities in their institutions.
- Emergency departments (EDs) will contribute to breaking cycles of illness if they seize opportunities to establish treatment plans and interventions that focus on social determinants of health, health literacy, and empowerment of patients to participate in their care.
- Treatment plans that are created with patients and are based in what matters to them have the greatest opportunity for success.
- Emergency clinicians will improve the quality of care provided if they can meet federal standards for culturally and linguistically appropriate care, recognizing that patients with limited English proficiency have a right to medical interpretation.
- Culturally sensitive, patient-centered, and trauma-informed care will improve patient–emergency clinician communication and satisfaction, decrease medical errors, and promote patient follow-through with recommendations.

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CHAPTER e7

Multiculturalism and Care Delivery

James L. Thea | Morsal Tahouni

PRINCIPLES

In recent years, multiple high-profile incidents have put the role of multiculturalism and race in society on the forefront of public and medical discussion. These cases outline to an extent the distance that our society has come in understanding race relations but even more, delineate how much farther we have left to go. As a microcosm of the larger society, the medical institution, and by extension the practice of emergency medicine (EM), should develop a greater understanding and self-awareness of the role of multiculturalism and race in the delivery of medical care.

At baseline, the practice of emergency medicine is unique and challenging because most patients in the emergency department (ED) are unknown to providers. There is little time to establish a rapport, earn a patient's trust, make a correct diagnosis, and develop a treatment and discharge plan designed for that patient. EM provides opportunities that can teach emergency clinicians to listen and learn what matters to people, because treatment plans created with patients and based on what matters to them have the greatest opportunity for success. There is only a brief window of opportunity to optimize the physician-patient encounter. A multicultural physician and patient population present a dual and sometimes formidable barrier when providing appropriate and equal health care access.

Every day, emergency clinicians encounter a multitude of challenging cases that can be further complicated by subtle cultural differences. Providing effective care requires an appreciation of these differences, as well as an understanding of a provider's own biases. Lack of understanding of the role of cultural factors and provider bias can have an adverse effect on physician-patient communication and trust. Health outcomes can also be negatively affected, as demonstrated by an increasingly large body of literature on racial and ethnic disparities in interventions and health care. Race, culture, ethnicity, class, gender, economic conditions, spirituality, and sexual orientation define health and illness for patients and affect access to health care and the quality of services received. Missing these cues may lead to medical errors.[1-3]

The American College of Emergency Physicians (ACEP) supports cultural awareness and emergency care with policies that are updated as necessarily. These policies recognize that denial of emergency care or delay in providing emergency services on the basis of race, religion, ethnic background, social status, type of illness or injury, or ability to pay is unethical.[4]

The purpose of this chapter is to provide the knowledge base in cultural competence that is essential to meet patient needs, improve health outcomes, reduce racial and ethnic disparities, and achieve professional goals.

RATIONALE FOR CULTURAL COMPETENCE

Changing Demographics: New Challenges for Emergency Clinicians

Both the US population and the types of health problems seen by emergency clinicians are constantly changing. In 2010, the US Census Bureau estimated that 13.1% of the US population was foreign-born and that 21% spoke a language other than English at home.[5] According to most recent census estimates, 26% of the population identifies as other than solely "white," and 16.6% describe themselves as Hispanic or Latino.[6] It is projected that the proportion of all minorities will increase significantly from 37% in 2012 to 57% by 2060, and the United States will become a majority minority nation for the first time by 2043.[7]

These figures do not speak to the diversity within these groups. The category Hispanic, for example, is an ethnic grouping counted in the race category of the census, but it fails to capture the significant range of diversity represented by Spanish speakers. Hispanics may share some cultural practices and speak similar versions of the Spanish language, but they have major differences in vocabulary and dialect, history, socioeconomic status, cultural identity, what they call themselves (Hispanic or Latino), levels of acculturation, health beliefs, habits, access to care, and health outcomes. The changing cultural landscape will challenge EM providers to recognize, account for, and address these differences when providing care for their patients.

Racial and Ethnic Disparities in Health Care Access and Outcomes

In the past decade, financial and nonfinancial barriers to access for racial and ethnic minority populations have been thoroughly documented. These include high rates of noninsurance, lack of prenatal care, hospitalization for ambulatory-sensitive diagnoses (an indicator of reduced access to primary care), and concentration of minorities in areas of physician shortage.[8] In 2003, the Institute of Medicine (IOM) produced a report commissioned by Congress in which more than 100 studies assessing the quality of care for racial and ethnic US minorities were analyzed.[9] According to the IOM report, minorities received fewer needed services and procedures than whites after control for insurance status, income, and other access factors. These findings applied to a wide range of health conditions, such as cancer, cardiovascular disease, human immunodeficiency virus (HIV) infection and AIDS, diabetes, and mental illness. The findings identified cultural and linguistic barriers, fragmentation of the health care system, and differences in site of care delivery and insurance coverage as explanatory factors. The report concluded that "racial and ethnic disparities in health care exist, and because they are associated with worse outcomes in many cases, they are unacceptable."[9]

The IOM report also discussed important nonfinancial barriers to access, such as the unequal distribution of physicians in areas where minority populations live. In particular, it was noted that the number of racial and ethnic minorities living in medically underserved areas is three times the proportion of minorities in the general population. Poor urban communities with high African American and Hispanic representation, averaged 24 physicians/100,000 population compared with 69 physicians/100,000 in communities with low representation. Although minority physicians are more likely to serve patients with Medicaid or no insurance, they are still significantly

underrepresented in the medical profession when compared to the general population.[10,11] Despite initiatives to increase minority enrollment in health professions, in 2008 minority enrollment had only increased to 15.1%, whereas the percentage of minorities in the general population was nearly twice that.

The National Institutes of Health National Center on Minority Health and Health Disparities, created by Public Law 106-525 to oversee research in health care disparities, working in conjunction with the Centers for Disease Control and Prevention (CDC), has reported that improvements in health have not been universal during the past 2 decades. For example, life expectancy for blacks as a whole is 74.0 years versus 78.5 years for the white population, a gap of 4.5 years. Lower life expectancy for blacks is accompanied by higher rates of premature death from cardiovascular disease and stroke, drug-induced death, colorectal cancer, infant mortality, preterm birth, HIV infection, diabetes, obesity, intentional injury inflicted by others, sexually transmitted disease, and mental illness.[12]

Factors Contributing to Disparities in Health Outcomes

In the past decade, reports have been regularly published in major peer-reviewed journals regarding disparities in the use of diagnostic tests and procedures, access to appropriate treatment modalities, waiting times to receive care, and length of stay in the ED.[9,13-15] The Coalition to Reduce Racial and Ethnic Disparities in Cardiovascular Disease Outcomes, for example, has acknowledged racial and ethnic differences in cardiovascular comorbidities, use of evidence-based therapies, prolonged time to reperfusion, and a race-based invasive procedure gap for coronary intervention.[16]

Test and Treatment Disparity

Earlier studies documented clearly that Hispanics and African Americans receive fewer analgesics for extremity fractures and musculoskeletal pain than white patients in the ED setting, despite no evidence of difference across race and ethnicity in the ability to discriminate painful sensation.[17] Disparities in ED pain treatment continue to persist a decade after identification of racial and ethnic differences in analgesic administration.[18-20]

Evidence from other specialties corroborates that differences in provision of medically appropriate procedures and therapies are often related to race and ethnicity; the reasons can be complex and multifactorial.[21,22] Recent studies have shown that disparities in treatment and outcomes exist in areas of cancer care—screening, treatment, and outcomes.[23,24] Despite decades-old identification of these differences and regardless of the setting, health care disparities remain a real and pervasive threat to patient care.

Discrimination and Health Outcomes

Deleterious health consequences that result from racial discrimination have been well documented.[25] In states where respondents to a social survey indicated that blacks are intellectually inferior and lacked an innate ability to excel, there was an increase in age-adjusted black mortality that was considerably stronger than the correlation between mortality and socioeconomic status. Further studies found that even perceived discrimination had a significant effect on health.[26,27] Mechanisms used to cope with the stress of racism have been shown to backfire by adding to health risks, such as in regard to smoking, substance abuse, and overeating.[28-31] Racism-induced stress has been shown to be negatively associated with disease entities such as diabetes, hypertension, depression, and preterm birth. For example, a relationship between race consciousness and blood pressure has been shown. Findings of Brewer and colleagues have suggested that among black patients, race consciousness is associated with higher diastolic blood pressure (BP).[32] In contrast, among whites, there was no association between race consciousness and BP.[33] Similar experiences have been described for homosexuals in regard to homophobia.[34]

Race-Based Medical Decision Making

Racism, sexism, and homophobia can interfere with the establishment of trust and delivery of effective medical care if providers create or establish barriers on the basis of their own internal biases, prejudices, and negative reactions to racial or cultural characteristics, such as skin color or clothing styles.[35,36] In an early study, when primary care physicians viewed scripted video interviews with hypothetical patients with chest pain who had similar symptoms, risk factors, vital signs, and thallium stress test and electrocardiographic findings, they were less likely to refer African American women for cardiac catheterization than men and whites, even though the scripts varied only by race and gender. Similar disparities in treatment based on race and gender have been reaffirmed by early studies assessing the treatment of acute coronary syndrome. Furthermore, disparities in profiling can result in underdiagnosis and overdiagnosis and thus contribute to medical error.

Failure of Trust

Patients from minority communities have reason to be skeptical about the validity of medical research and appropriateness of medical recommendations. Participants in the Tuskegee study, for example, were not notified when effective treatment of syphilis became available because researchers wished to investigate the natural course of the disease.[37,38] African American patients often rate their physician interactions as longer, more participatory, and having more positive effects when their physician is of the same race.[39,40] However, this option for physician-patient congruence is rarely available to minority patients because only 4% of physicians are black, whereas 12% of the population is black.[9] In the Agency for Healthcare Research and Quality (AHRQ) *National Healthcare Disparities Report,* blacks and Hispanics were found to be more critical of the patient-provider relationship than whites. A higher percentage of adult blacks and Hispanics rated their health care at less than 6 on a scale of 1 to 10 in the year prior to the report and believed that they would have received better care if they were of a different race or ethnicity.[40]

Language and Effective Medical Care

According to the 2013 US Census estimates, 60 million Americans (21%) speak a language other than English at home, and 25.1 million speak English less than very well.[41] Patients with limited English proficiency are more likely to defer needed services, leave against medical advice, miss appointments, fail to adhere to treatment regimens, lack a regular provider, and report poorer health status.

A large body of literature has shown the importance of trained medical interpreters. Studies have shown that errors of ad hoc interpreters were more likely to result in clinically significant medical errors, such as omitting drug allergies and giving inaccurate instructions on dosing and route of administration.[42-44] Furthermore the use of untrained nonprofessional employees as interpreters resulted in serious translation errors, including omissions, additions, and substitutions for what the patient is trying to say, and the use of relatives, particularly children, may violate privacy and disrupt family norms of authority.[45-47]

Use of interpreters during clinical encounters can affect patient satisfaction.[48] Satisfaction ratings for patients using ad hoc

interpreters are lower, and rates are lowest when an interpreter should have been used but was unavailable. In one retrospective study of Spanish-, Haitian Creole–, and Portuguese Creole–speaking patients presenting to the ED with chest pain, headache, and abdominal pain, the investigators found that the use of trained interpreters was associated with increased intensity of ED services, reduced ED return rate, increased clinic use, and lower charges during the next 30 days, without any simultaneous increase in length of stay or cost of visit.[49]

CULTURALLY COMPETENT APPROACH TO LANGUAGE BARRIERS

A new standard of care has been established that requires institutions and practitioners to provide for medical needs in a patient's primary language and in a manner compatible with the patient's health beliefs and practices.[49] Health care institutions and providers are asked to collect data stratified by race, ethnicity, and language and to institute quality improvement efforts when cross-cultural differences in outcomes of care, process indicators, or patient satisfaction are detected. They are asked to develop culturally competent systems of care based on an assessment of the organization's mission, goals, policies, practices and services, staff training needs, and current diversity of the staff.

After the assessment process, health care organizations must identify opportunities to improve the cultural competence of the organization and its delivery of health care services to a diverse population. At the top of the list is the improvement of interpreter services. Hospitals are asked to establish minimum performance standards for interpreters, which includes training in the culturally specific medical language and code of ethics. These requirements have been codified as a set of standards for culturally and linguistically appropriate services (CLAS) by the Office of Minority Health and AHRQ and published in the Federal Register.[50]

The medical interview is the heart of the medical encounter between physician and patient yet, in an interpreted interaction, neither patient nor physician is in a position to judge the accuracy or completeness of a lay interpreter's translation. Clearly, omissions, additions, opinions, guesses, and distortions can lead to serious mistakes and unnecessary diagnostic procedures.

In a 2012 study, Flores and associates reported multiple mistakes made by professional interpreters in an analysis of audio recordings at two pediatric EDs. Mistakes included "addition, substitution and omission of words, use of phrases, idioms and language that did not exist in the patient's language." They reported that 18% of those involved potential clinical risks. Mistakes were found to be less frequent in professional interpreters with a minimum of 100 hours of training.[51]

Standards and certification for medical interpreters are needed to ensure consistency and quality. The Joint Commission (TJC) requires hospitals to provide professional interpretation services to every patient who needs it.[49] The Massachusetts Medical Interpreter Association recommends that standards cover interpretation, cultural interface, and ethical behavior. Because the meaning inherent in the message is rooted in culturally specific beliefs, values, assumptions, customs, and norms, and language is itself an expression of culture, it may be necessary for a medical interpreter to go beyond a literal interpretation to explain unstated assumptions and find new ways of communicating untranslatable words or concepts. In addition to maintaining confidentiality, the medical interpreter has an ethical burden to uphold the trust of both parties and to assure them that the considerable power associated with the interpreter's role will not be abused, and that information will be faithfully conveyed without interjection of the subjective opinions and thoughts of the interpreter. Even with such qualified interpreters, the emergency clinician still needs to monitor the flow of the interview and, from time to time, clarify meaning and ensure understanding. This can be done by having the interpreter repeat what he or she thought the patient meant and asking the patient to repeat what the interpreter said. It is important to observe the interaction for phrase length as an indication of material not translated or added by the translator.

Finally, failure to meet language and communication standards in clinical scenarios can lead to medical liability.[52] In a study of medical malpractice claims of a malpractice carrier that insures providers in four US states, researchers found that 2.5% of the carrier's total claims reviewed were related to language barriers, resulting in patient death or irreparable harm. The study reported that the carrier paid $2,289,000 in damages or settlements and $2,793,800 in legal fees between 2005 and 2009. In 32 of the 35 cases, the health care providers did not use competent interpreters. The following are examples of lack of provision of appropriate language services:

- Use of family members, friends, or children
- Failure to translate documents such as consent forms and discharge instructions
- Lack of documentation of a patient's need for an interpreter or English language limitations
- Lack of documentation of the use of an interpreter and background and qualifications of the interpreter

MULTICULTURALISM, CULTURE COMPETENCE, AND HEALTH DISPARITIES: PROGRESS TO DATE

The 2003 IOM report revealed disparities in health care in the United States based along lines of race and ethnicity.[9] The recommendations to reduce these health care disparities included "integration of cross-cultural education into the training of all current and future health professionals." Progress has been slow in actually reducing health disparities,[50] and gaps in economic resources between white and minority populations have actually widened,[53] increasing the barriers impeding access to timely and effective care.

Forward movement has primarily occurred in the form of the establishment of guidelines and standards at local, state, federal, public, and private levels. TJC's *A Roadmap for Hospitals* encourages hospitals to incorporate concepts from cultural competence, patient-centered care, and communication into their organizations.[49] These efforts include increasing awareness of health disparities, efforts to improve collection of race and ethnicity data across systems of care, quality improvement, community outreach, increasing workforce diversity, patient education, provider education, and increased availability of interpretation services. A policy system of checks and balancing now exists, with national performance monitoring affecting accreditation of health care organizations.

In 2011, patient-centered communication standards were included in TJC's *Comprehensive Accreditation Manual for Hospitals*.[54] After a period of monitoring hospitals for compliance of standards without any effect on accreditation, compliance has progressed as an expectation and is taken into account in the accreditation process.[55]

In another example of guideline development, the National Committee for Quality Assurance developed and released rigorous standards for monitoring and evaluating multicultural health care in 2010. Multicultural health care distinction is conferred on health care organizations that conform to acceptable practices regarding considerations of race and ethnicity in language data collection, access and availability of language services, practitioner network cultural responsiveness, programs for culturally and linguistically appropriate services, and overall efforts to reduce health care disparities. In a similar effort, the National Quality Forum released a report in 2011 on quality measures to assess cultural competence. In education, the Liaison Committee on

Medical School Education now includes cultural competency in its accreditation standards. Medical students should learn to recognize and appropriately address gender and cultural biases in themselves and others and in the process of health care delivery.

Disparities awareness has also been included in health care reform. The Patient Protection and Affordable Care Act (Health Care Reform Act) signed into law in March 2010 requires data collection on race, ethnicity, primary language, disability status, and gender. These data can identify areas of concern and provide opportunities for intervention. This law follows recommendations from the 2003 IOM report and raises awareness of culture and disparities. In addition to national activities, many states have taken action. For example, the New Jersey State Board of Medical Examiners requires that physicians licensed in New Jersey complete six credits in cultural competency (Rule NJAC 13:35-6.25).

Using Cultural Competence to Cross the Barrier of Different Beliefs, Values, and Life Experiences

Physicians and patients have a culture that they bring into the examining room. Differences between their cultures have an impact on the physician-patient encounter. Awareness of one's own values and those of others can enhance satisfaction and health outcomes. The Society for Academic Emergency Medicine task force report cautioned, however, that it is dangerous to hold strong preexisting assumptions about any cultural group because variations within cultures often exceed variations between them. A patient who is thoroughly acculturated into US society may be offended by a health care provider's attribution of traditional beliefs. Even in the context of a busy ED encounter, it is necessary and feasible to get to know the individual patient sufficiently to make a rough assessment about her or his level of acculturation or, at least to ask rather than assume.

In some cultures, the diagnosis of specific diseases can be particularly problematic. For example, in African American and Puerto Rican communities, cancer is often perceived as a fatal disease. Patients may therefore avoid initial evaluation or choose no treatment when they are diagnosed, even when the cancer is identified at an early stage and the prognosis is good. A health care provider who understands these health beliefs and concerns can work collaboratively with patients to provide health information in a format that the patient can accept.

Alternative healing systems have strong cultural roots. In 1997, the US population made an estimated 629 million visits to providers of alternative health care—approximately 243 million more visits than to conventional health care providers and an increase of 47% since 1990. The National Center for Complementary and Integrated Health maintains an extensive database of literature on alternative healing methodologies in the United States.[56-59]

Folk medicine is too diverse for providers to know all possible practices, but emergency clinicians need to be aware of the more common folk therapies. For example, more than a few physicians have called social workers to investigate children with apparent bruises caused by coining, which involves vigorous rubbing of the skin with coins and warm oil (tiger balm) to release the "bad wind" (reduce fever). These parents, who have attempted to help their children by using health care practices that are widely accepted in their communities of origin, feel accused, and the trust between the physician and family may be irrevocably lost. Similarly, herbal remedies can be effective or at least harmless, but they can occasionally be toxic, as in the case of clay ingestion by pregnant women, marijuana tea to treat asthma, and powders containing high concentrations of lead oxide to treat *empacho,* a condition in which it is believed that a substance (usually food or saliva) gets stuck to the walls of the stomach or intestines, causing an obstruction. Specific uses of folk medicine need to be elicited respectfully in a careful history and evaluated. Recommendations can then be presented nonjudgmentally, and alternative folk remedies that are benign can be prescribed along with needed allopathic medications.

The practitioner and patient will inevitably bring different beliefs and values to the medical encounter; the key to cultural competence is respectful negotiation of these differences without imposing the power of the physician's expertise, thus protecting the patient's autonomy. If patients are satisfied, they will carry out follow-up recommendations and return to the ED in the future when they need emergency care.

Interpreting the Culture of Medicine to Patients From Diverse Backgrounds

There are inherent conflicts between the culture of medical care and the cultures of many patients. Physicians are expert in diagnosis and treatment of diseases, which represent abnormal structures or functions of the human body (the pathophysiology of disease states). On the other hand, patients experience illness, a subjective feeling state that is interpreted through the lens of culture and has a personal and social meaning. The patient is an expert on his or her own illness and its effects on daily living, whereas a physician is expert on the effects of diseases on organ systems. Both ways of looking at the world have validity, but they are radically different. Unfortunately, the culture of medicine tends to recognize only its own interpretation and perspective. A culturally competent approach recognizes both and works to integrate the best of both worlds.

A patient may have very high blood pressure, HIV infection, or early cervical cancer and not experience symptoms. If patients do not feel sick and experience no alteration in functioning, they may not accept a physician's diagnosis. On the other hand, a patient may feel sick—be ill, weak, and dizzy, with extreme fatigue or abdominal pain—yet the physician is unable to diagnose a disease, despite a thorough history, physical examination, testing, and appropriate consultation. For example, *susto,* an illness recognized by Mexican Americans, causes listlessness, insomnia, depression, and anorexia and is believed to be caused by exposure to a frightening experience. Treatment requires the patient to speak openly about the events that led to the susto, followed by bed rest and a ritual that includes prayers, incantations, and *barridas*—sweeping of the body with an egg, candle, or herbal tea.[60]

To be most effective, physicians need to investigate how patients view the causality of their illnesses and how they experience them to negotiate a therapeutic intervention. Exploration might take the form of comments and questions, such as, "Help me see through your eyes how you understand this problem. Have you or someone you know experienced it before?" The role of the physician is to accept the patient's experience as uniquely his or hers or, when possible, to reframe it in terms of medical knowledge. Then both physician and patient will be satisfied with the outcome of the encounter.

Care and Communication for Victims of Community Violence

For several years, the CDC has proclaimed that "youth violence is a public health issue for individuals and communities." Annually, more than 5,000 young people between the ages of 15 and 24 years succumb to death by homicide, making homicide the second leading cause of death for this age group.[61] In 2011, more than 707,000 youths between the ages of 10 and 24 years were treated in US EDs for violent injuries.[62] Because urban black youth and other minorities are overrepresented among victims of violence in urban settings, racial and ethnic stereotyping can play a direct

role in trauma care. Assumptions of responsibility and guilt by emergency clinicians can produce a hostile environment for patients who have been shot or stabbed. Language that assumes blame ("What did you do?" instead of "What happened to you?" or "I'm sorry this happened to you") indicates a lack of understanding of the complexity of trauma, its neighborhood context, and the psychological impact of adverse childhood events, which are often at the epicenter of the cycle of violence.[62-65] Trauma can cause neurobiologic and psychosocial effects such as hyperarousability, hypervigilance, aggressive responses to fear and threat to safety, loss of empathy for others, withdrawal, anxiety and depression.[66-69] The emotional response to trauma of a victim of violent injury can be misinterpreted as negative behavior. A victim might be seen as ill-willed versus in need of care and healing. Providers and health care staff witnessing the responses of these violently injured youth have an opportunity to mitigate the trauma or inadvertently enhance it through retraumatization.

Trauma-Informed Care

A new construct, trauma-informed care,[70,71] is an alternative perspective that can enhance opportunities for productive encounters, self-reflection, and positive medical outcomes during a vulnerable time for an injured young person. The basic set of principles includes the creation of a safe physical and emotional environment that is sensitive to the needs of victims of violence, promotes recovery, and prevents revictimization. Symptoms are seen not as pathologic changes but primarily as attempts to cope and survive. Trauma-informed care can result in an injured youth's choosing "change" versus unsafe behavior that could result in injury, re-injury, or incarceration. Health care providers can contribute to positive outcomes and life choices of victims of violence. Understanding and maintaining an awareness of the comprehensive effects of trauma can help comprehend posttraumatic behavior and minimize revictimization. From providers, this respect, compassion, and familiarity with the manifestations of trauma.

One of the policies of the 2011 ACEP Revised Code of Ethics states that emergency clinicians have a "duty to promote the public health." The code states that "Emergency physicians have first-hand knowledge of the grave harms caused by firearms, motor vehicles, alcohol, and other causes of preventable illness and injury" and suggests that emergency clinicians have a responsibility to act: "Inspired by this knowledge, emergency physicians should participate in efforts to educate others."[3] EDs and inpatient trauma services present a unique opportunity for interventions to reduce youth violence and support communities. Several cities have established effective peer-model, hospital-based, violence intervention programs that use interventions geared specifically toward reducing recidivism among vulnerable and violently injured youth.[66,67] These programs can save hospitals and the criminal justice system millions of dollars through reducing retaliation and recidivism and, most importantly, saving lives.[72-76]

Role Expectations in Western Medicine: Opportunities for Misunderstanding

The culture of medicine, especially in EM, may have its own set of patient expectations, rules and regulations, language, and dress distinctions that reflect a hierarchy of authority, characterization of patients as good or bad, and different sets of behaviors toward patients, depending on the category to which they have been assigned. People from different cultures may find it impossible not to violate some of the unwritten negative and stereotypical rules and regulations of the ED. Every medical encounter is potentially a cross-cultural experience, and negotiation of the divide is a challenge for patients and providers. Cultural competence involves reframing many of these unstated rules because they prevent us from looking beneath the surface and addressing real problems. When a patient comes in with vague complaints, there may be a social stressor that has tipped the balance of mental health. There may be circumstances that the patient does not feel comfortable sharing with the provider because of cultural, racial, sexual orientation, or language barriers, or there may have been an overload of negative stimuli related to racial and ethnic discrimination—a crisis for the person and the body this person inhabits.[77,78] People from minority cultures experience stressful events daily that white providers, secure in their socioeconomic status and membership in the dominant majority, can only imagine. There is mounting evidence that these types of negative encounters engender clinical depression and anxiety and contribute to hypertension and other medical sequelae.

Studies have shown disparate patterns of ED use based on race and ethnicity. Nonwhite patients have been found to use the ED more as a source of care.[79,80] Patients who overuse or abuse the ED are seen as so-called bad patients, but the reasons patients give for using the ED are entirely rational. The ED does not require an appointment to receive care, provides sophisticated medical technology, operates 24 hours a day, provides services that are often covered by health insurance plans (whereas other options often are not), has a tradition of free care, and is often located close to inner city neighborhoods.

To practice good medicine in this health care and social environment, emergency clinicians should critically question and reframe the moralistic good patient–bad patient paradigm. We, like our patients, are at the whim of forces beyond our control, and patients and practitioners will experience higher levels of satisfaction if these issues are addressed directly. Patients must take responsibility for their own behaviors whenever possible, but physicians can and should work with health care institutions to adopt policies that improve access to culturally competent health care. These actions can help create a safe environment for practitioners and patients.

CULTURAL COMPETENCE AND PATIENT-CENTERED CARE: NEW MODELS

Models for cultural competence and patient-centered care have evolved separately yet in tandem. The goal of both is to improve the quality of the health care experience in a multicultural world, and there are areas of overlap.[81-85] Cultural competence evolved from the perspective of recognizing and respecting individual difference and the impact of individual interpretation on health, illness, and health care delivery. Patient centeredness addresses systems of health care delivery, improving access, and meeting patients where they are to maximize opportunities for successful health care.[83] Ideal health care systems should be designed to incorporate principles of cultural competence and patient centeredness. A health care system built on patient-centered principles represents the heart of cultural competence—seeing the problem and solution from the point of view of the patient.[85] Studies have suggested that patient-centered care might also be associated with improved clinical outcomes and patient satisfaction at reduced cost.[83]

EDUCATION

Education about the impact of culture on health care encounters is a key component for the development of culturally appropriate health care and is a requirement for organizational accreditation. Students and residents in training consistently express greater levels of comfort in multicultural environments when they have had preparatory training. Training also helps students and residents understand that their own culture also affects clinical

encounters and is equally participatory. Continued re-education raises awareness and imprints consciousness more permanently, establishing a conceptual norm for those interacting and working in multicultural environments. Linkage of cultural competence with ethical constructs of equal distribution of resources and social constructs of justice gives meaning to principles and context beyond the memorization of appropriate responses to model situations.

Medical schools are now required to include cultural competency training in their curriculum for accreditation. Faculty and students should demonstrate an understanding of the manner in which people of diverse cultures and belief systems perceive health and illness and respond to various symptoms, diseases, and treatments. Medical students should learn to recognize and appropriately address gender and cultural biases in themselves and others and in the process of health care delivery.[86,87]

Members of lesbian, gay, bisexual, transgender, questioning (LGBTQ) communities are among the many patients seeking emergency care.[88] Implicit and explicit bias against LGBTQ people exists in society and, by extension, in health care.[89-91] Medical literature suggests a need for enhanced education for trainees and providers to have knowledge and insight for the provision of optimal and appropriate care for this population.[92] Challenges and barriers to health care for LGBTQ are not widely known. LGBTQ patients identify lack of provider education as a barrier to care. Many LGBTQ patients avoid accessing the health care system, citing barriers such as discriminatory behavior and poor treatment from providers and other health care staff. Experiencing negative encounters causes patients to avoid seeking medical treatment, including emergency care. Social marginalization and inequality is associated with health disparities. Among the LGBTQ population there are disproportionate levels of substance abuse, tobacco use, psychiatric disorders, suicide, youth homelessness, obesity, and disease. Lesbian, bisexual, and transgendered women engage in less routine care and screenings than other women.[88-93]

Education and training in LGBTQ patient treatment and health is underdeveloped. A 2014 survey of EM residency programs found that only 26% included a specific LGBTQ lecture, and only 33% incorporated topics on LGBTQ health into their curriculum.[94] These findings suggest a paucity of education of EM residents on LGBTQ health needs. LGBTQ health education is not included in the most recent model of clinical practice in EM.[95] The need for cultural competency and provider education on LGBTQ health has been stated by the IOM, TJC, and Department of Health and Human Services.[96-98]

Making consistent upgrades in medical education is the best opportunity to cause a permanent shift in the paradigm of multicultural patient-physician clinical interactions in the future.

RECOMMENDATIONS

Diversity among the ED patient population poses a challenge to emergency clinicians. Recognition of cultural differences, knowledge about diverse cultures, awareness of the health impact of cultural beliefs and practices, and sensitivity to patients' needs can reduce access barriers and improve clinical outcomes and hospital-community relationships while reducing the number of repeated visits and costs of health care. Diversity education also creates a rich environment for conceptualizing and researching health problems.

There are many opportunities for EDs and their institutions to improve their care of multicultural communities. These include plans to address problems related to the following:

- Lack of protocols for patient care
- Lack of resources for translation and cross-cultural interpretation
- Incorrect perception that attention to cultural competence adversely affects flow and efficiency
- Lack of cross-cultural teaching guidelines and standards in medical education
- Inadequate recruitment and retention of minority residents, faculty, and practitioners
- Lack of pathways for communication and collaborative work with communities

Concrete recommendations, based on the CLAS standards, have been proposed for pediatric emergency settings and can be applied universally. Institutions should use trained medical interpreters and a diverse workforce. Pharmacies should label prescriptions and provide medical instructions in the patient's primary language. Administrators should post multilingual signs and ensure that handouts and forms are translated. Quality improvement programs should collect and analyze data and provide information to monitor outcomes based on race and ethnicity. A diverse group of patients should be enrolled in research studies to improve outcomes.

Recommendations from the IOM report for a series of additional legal, regulatory, and policy measures were highlighted in an *Academic Emergency Medicine* editorial and include the following:

- Patients in public managed care organizations should have the same patient bill of rights as patients in private health maintenance organizations.
- The number of health care providers who are members of racial and ethnic minority groups should be increased.
- Resources should be adequate to enforce penalties for civil rights violations.
- Incentives to promote disparities should be stringently limited.
- Health care professionals should have opportunities for cross-cultural education.
- Patient participation in decision making should be enhanced through education.
- Community health care workers and advocates should assist patients to negotiate the health care system successfully.
- The diversity of faculty and residents must be improved.
- A cross-cultural curriculum should be developed for residency training and continuing education.
- Physicians should educate themselves and the general public about the need to eliminate racial and ethnic disparities in health care.

SUMMARY

Changing demographic landscapes in EDs have set the stage for multicultural appropriate care. The process of change for the development of culturally competent medical systems has been slow, but progress is occurring. Evolution of culturally appropriate environments for patients and their families has begun on all levels and, with the development of new standards and performance-monitoring systems, assurance of established culturally competent systems will be an expectation. These expectations are important and tightly linked to safety and quality. The linkage of cultural competence to social justice broadens the depth of comprehension for the learner and provides opportunities for enhanced engagement with consumers and greater quality of care.

There is greater awareness of and movement toward a health care system that is rooted in cultural competence and patient centeredness. It is imperative that EDs invest in the development of their health care systems and educate all staff. ED patients are often unknown to providers, who have one window of opportunity to obtain accurate information and make a correct decision. Decisions are heavily based on one's ability to listen and learn what matters to patients and successfully engage with patients and

their families, engendering comfort, trust, and respect. Treatment plans that are created with patients and are based in what matters to them have the greatest opportunity for success. Continued education at all levels is key and should include everyone working in health care, especially those who engage with consumers. Multiculturalism education should be integrated into medical school curricula, physician training programs, allied health programs, new employee orientation, and staff in-service programs on a regular basis.

The process of creating a successful plan to move cultural competency from a theoretic model to one of action and implementation has been outlined in six principles that incorporate key points recommended by the IOM report of 2003 for systems aligned with new cultural competence standards and expectations:

- Community representation and feedback at all stages of implementation
- Cultural competency integrated into all systems of the health care organization, particularly quality improvement efforts
- Ensuring that changes made are manageable, measurable, and sustainable
- Making the business case for implementation of cultural competency policies
- Commitment from leadership
- Staff training on an ongoing basis

Essential cultural competence tools for providers include recognition of cultural differences, respect for individual opinions and perspectives about health and illness and, most importantly, ability and willingness to negotiate differences to offer the best opportunity for good health care outcomes. Culturally appropriate health care systems should be incorporated into EDs, which serve as the gateway to our health care institutions.

KEY CONCEPTS

- Changing demography and an evolving culture in the United States is changing emergency medicine practice.
- Disparities in health and health care delivery continue, despite efforts to improve care. Emergency clinicians and their institutions will need to be part of the solution—treating preventable conditions that become crises because of reduced access to primary care and specialists and acting as advocates for strategic system change to eliminate disparities in their institutions.
- Emergency departments (EDs) will contribute to breaking cycles of illness if they seize opportunities to establish treatment plans and interventions that focus on social determinants of health, health literacy, and empowerment of patients to participate in their care.
- Treatment plans that are created with patients and are based in what matters to them have the greatest opportunity for success.
- Emergency clinicians will improve the quality of care provided if they can meet federal standards for culturally and linguistically appropriate care, recognizing that patients with limited English proficiency have a right to medical interpretation.
- Culturally sensitive, patient-centered, and trauma-informed care will improve patient–emergency clinician communication and satisfaction, decrease medical errors, and promote patient follow-through with recommendations.

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CHAPTER e7: QUESTIONS & ANSWERS

e7.1. Which of the following factors has not been identified as a health care disparity for minorities?

A. High rates of no insurance or underinsurance
B. Lack of prenatal care
C. Likelihood of living in an area with adequate physician concentration
D. Lower life expectancy when compared to white populations
E. Relatively low number of minority providers

Answer: C

e7.2. Patients' cultural perceptions can have significant impact on how they perceive their provider and the care they are receiving. Which of the following methods can be used by providers to approach different cultural perceptions so as to enhance the provider-patient relationship?
- **A.** Being aware of one's own cultural values
- **B.** Developing assumptions of cultural perceptions base on patients' ethnicity or race
- **C.** Limiting participation of alternative therapies and folk medicine in the patient's care plan
- **D.** Maintaining the role of the physician as the decision maker, even when it may conflict with the patient's autonomy

Answer: A

e7.3. A helpful language translator can be essential in communication with a patient who is facing a language barrier. Which of the below methods are recommended for using an interpreter during a medical examination?
- **A.** Asking the patient to have friends or family translate discharge instructions for them
- **B.** Maintaining easy access to trained medical interpreters
- **C.** Only obtaining an interpreter if the patient requests it
- **D.** Using a family member is appropriate as long as they are older than 18 years
- **E.** Using health care staff members who are fluent in the patient's language

Answer: E

e7.4. Which of the following is not a benefit of using trauma-informed care when interacting with victims of violence?
- **A.** Decreased need for pain medications
- **B.** Decreased risk of injury or re-injury
- **C.** Decreased risk of long-term psychologic sequelae related to patient's injury
- **D.** Improved patient understanding of posttraumatic behavior

Answer: A

e7.5. Which of the following recommendations was not made by the Institute of Medicine to aid in decreasing disparities in health care?
- **A.** To create a different patient bill of rights for those in public versus private managed care organizations
- **B.** To create more opportunities for cross-cultural education for health care providers
- **C.** To have physicians educate the public regarding the necessity of eliminating racial and ethnic disparities in health care
- **D.** To increase the number of community health care workers and advocates who can assist patients in navigating the health care system
- **E.** To increase the number of health care providers from racial or minority groups

Answer: A

CHAPTER e8

The Geriatric Emergency Department*

Michael E. Stern

PRINCIPLES

Background

Older Patients in the Emergency Department

GERIATRIC EMERGENCY DEPARTMENT GUIDELINES

Staffing and Administration

Equipment and Supplies

Education

Policies, Procedures, and Protocols

Follow-Up and Transition of Care

Quality Improvement

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KEY CONCEPTS

- Physical and process characteristics of the current ED model can present a challenging environment for managing older patients and undermines the ability of the modern ED to serve as their care transition hub.
- Older patients are more likely to present with complex medical problems, receive a greater number of diagnostic tests and treatment regimens, have longer lengths of stay in the ED, require special needs during their visit, and be admitted more often.
- The new consensus-based GED guidelines were published to provide a standardized set of guidelines that can effectively improve the care of the geriatric population in the ED.
- The guidelines consist of 40 specific recommendations in 6 general categories: (1) staffing and administration; (2) equipment and supplies; (3) education; (4) policies, procedures, and protocols; (5) follow-up and transitions of care; and (6) quality improvement measures.
- The GED guidelines represent recommendations and are not intended as a mandate for every ED.

CHAPTER e8

The Geriatric Emergency Department

Michael E. Stern

PRINCIPLES

Background

The most significant demographic shift in the United States in the early twenty-first century is the rapid increase in the growth of the population aged 65 years and older. As a result of the baby boomers coming of age in 2011, this trend will continue for several decades. In addition, as a result of advances in health education, pharmacotherapy, and health-related technology, 20% of the US population, nearly 75 million people, will be aged 65 years and older in 2030, a dramatic increase from the current 13%.[1] Of particular significance, the most rapidly growing segment of the population is the oldest old, aged 85 years and older, who will represent nearly 25% of Medicare beneficiaries by 2050.

The US health care system has begun to recognize the complex challenges that exist in caring for this so-called silver tsunami. Federal, state, and community-based programs and initiatives have been put in place to improve the health and care of older adults. Changes in federal and state regulations and insurance reimbursement—the passage of the Affordable Care Act and new guidelines from the Centers for Medicare & Medicaid Services (CMS)—have begun to change the landscape of care provided to older patients by hospitals and individual providers. However, fewer physicians are choosing primary care and specialty training in geriatrics, despite older adults requiring more services.

Older Patients in the Emergency Department

The emergency department (ED) is increasingly shouldering the burden of the care of older adults. From 1993 to 2003, ED utilization rates by older adults increased from 12% to 16% of all ED visits, and there was a 34% increase in the visit rate/100,000 population of patients aged 65 years and older throughout the study period. As early as 2002, ED use was higher for older patients than for younger adults, with approximately 58% of 75-year-olds visiting the ED, as compared to 39% of those of all ages, and ED use increased with increasing age. In the Institute of Medicine's 2006 report, care for older adults was found to be increasingly sought in EDs. In the 2013 Rand Report, which evaluated the evolving role of hospital EDs in the US health care system, it was found that EDs are being increasingly used for complex evaluations, emergency clinicians are the principal decision makers for half of all hospital admissions, and hospital admissions of Medicare patients are growing faster than any other group, with 6 of 10 patients being admitted through the ED.[2]

Older patients are more likely to present with complex medical problems, receive a greater number of diagnostic tests and treatment regimens, have longer lengths of stay in the ED, require special needs during their visit, and be admitted more often. An ED presentation for any reason has been found to be a sentinel event for older adults, conferring an increased risk of functional decline, medical complications, and poorer health-related quality of life, as compared to before their visit. In one study, an ED return visit, hospitalization, or death within 3 months occurred in up to 27% of older adults after discharge to home from an initial ED visit.

The current model of care delivery in the ED is designed for rapid evaluation, treatment, and turnover of acutely ill and injured patients. The physical space and layout are designed for maximal use of resources and improved throughput at the expense of privacy and a quiet environment (eg, hallway beds, lack of space for family or caregivers). Choices in equipment and materials favor cost savings, space conservation, and ease of cleanup (eg, bright fluorescent lighting, thin, narrow mattresses, slippery vinyl flooring) over the special care needs of older adults. In addition, the care transition for older adults deemed safe to discharge from the ED is fraught with problems, including inadequate process for discharge instructions, suboptimal communication with primary care providers, and delayed or absent follow-up appointments. These physical and process characteristics of the current ED model can present a challenging environment for managing older patients and undermines the ability of the modern ED to serve as their care transition hub.[3]

The paradigm of the busy contemporary ED is ill-suited for typical geriatric patients, who have atypical presentations of disease and trauma, often vague complaints, polypharmacy, age-specific multifactorial syndromes (eg, falls and delirium), complicated comorbid disease burdens, and functional and cognitive impairments. Also, a general lack of geriatric specific training across all levels of providers and a dearth of focused geriatric emergency medicine research have contributed to limited evidence-based clinical protocols for older emergency medicine patients. As a result, care delivery in the current ED environment for this growing vulnerable population has been, in many settings, suboptimal.

GERIATRIC EMERGENCY DEPARTMENT GUIDELINES

In recognition of the pressing need for specialized care for older adults in response to this rapidly growing demographic, the first of several geriatric emergency departments (GEDs) opened in 2008 and 2009. These GEDs seek to provide care tailored to the special needs of geriatric patients in a setting that is conducive to appropriately care of older patients. Since then, competition among hospitals across the country has risen to attract older patients to use specific EDs for their care.

A surge in self-designated GEDs has taken place in the last few years, with over 90 hospitals nationwide now claiming to have GEDs. This has raised the salient question of exactly what sort of geriatric patient care is actually being delivered in these EDs, because very few of them are located in academic centers, and there are little data supporting their efficacy. In 2013, the first research study that systematically identified and qualitatively characterized the existence, locations, and features of GEDs across the United States was conducted and found significant variation in the capacities and components of a GED, indicating a need to address future standards for them.[4]

In an effort to provide a standardized set of guidelines that can effectively improve the care of the geriatric population in

the ED, new, consensus-based GED guidelines were published in early 2014. Representatives from the American College of Emergency Physicians (ACEP), Society of Academic Emergency Medicine (SAEM), American Geriatrics Society (AGS), and Emergency Nurses Association (ENA) collaboratively developed guidelines over a 2-year period, including academic and community providers. These guidelines are based on an 80% consensus among the representatives and were validated using existing literature.[5]

The GED guidelines were created to promote improved ED care for older adults while addressing the unique needs of this population. The guidelines consist of 40 specific recommendations in six general categories: (1) staffing and administration; (2) equipment and supplies; (3) education; (4) policies, procedures, and protocols; (5) follow-up and transitions of care; and (6) quality improvement measures.[6] This template outlines how to construct an effective GED program. It is important to note that the GED guidelines represent recommendations and are not intended as a mandate for every ED. Instead, the document provides the potential steps to be taken, rationale for these recommendations, and outline of the resources available to aid in their implementation in any ED. These recommendations target a coordinated care approach and focused resources on the most common needs of the typical geriatric ED patient. To create a GED, the specific GED guideline recommendations are categorically described.[7]

Staffing and Administration

The staffing and administration of the GED should be comprised of a multidisciplinary team of care providers who have specific geriatric training and education to focus on high-quality geriatric care. The GED guidelines recommend protocols to set qualifications and establish responsibilities for the GED medical director, GED nurse manager, staff physicians and nurses, medical staff specialists (including a geriatric consultation service) and provide accessibility to ancillary services (eg, social workers, geriatric case managers, pharmacists, physical and occupational therapists). The goal is the establishment of targeted ED and in-hospital staff and their coordination with local outpatient resources to improve ED, inpatient, and follow-up care for older adults.

Equipment and Supplies

Improved geriatric care requires a keen understanding of the specific needs and vulnerabilities of this unique patient population. Incorporating key concepts from the domain of environmental geriatrics, the development of a GED should adapt the physical space with structural modifications and introduce and implement equipment and supplies designed for the safe, comfortable, and effective evaluation and management of geriatric patients while decreasing iatrogenic complications. Enhancements that address issues of mobility, comfort, safety, and behavioral needs (including memory cues and sensory perception of vision and hearing) are desirable.

Suggested furniture improvements include reclining examination chairs that facilitate safe transferring, extra thick and soft gurney mattresses (or, even better, pressure-redistributing foam mattresses[8]) designed to decrease the possible development of pressure ulcers, and upholstery choices that are soft, moisture-proof, and easy to clean, designed to protect the fragile skin of older patients and reduce contamination by hospital-associated pathogens. Special equipment to equip a GED includes warm blankets, no-slip fall mats, bedside commodes, walking aids and devices, hearing aids, monitoring equipment, and condom catheters to reduce the risk of catheter-associated urinary tract infections (CAUTIs).

Visual orientation improvements include soft lighting, with a combination of ambient and spot lighting, designed to increase overall lighting and reduce glare. Patients should have control of the lighting in their respective rooms. Exposure to natural light is most desired because it has been shown to improve recovery times and decrease delirium.[9]

Color and pattern choices for facilities and structures should be made with an understanding of the vision and perception changes that accompany aging. Warm, light-colored walls (yellows and oranges) with a matte finish are preferable. Blues and greens are difficult to differentiate for many older patients. Avoid monochromatic color schemes and allow for colors to contrast between horizontal and vertical surfaces. Sharp, dominant contrast patterns may be disorienting and hinder movement.

Acoustic orientation improvements should provide better communication and decreased levels of anxiety and delirium. Private rooms and the use of sound-absorbing materials (eg, curtains, ceiling tiles) are preferred to reduce background noise and increase patient privacy. Portable hearing assist devices are helpful. Reduction in overhead paging and machine noise should be a targeted goal. A choice of music has been shown to reduce anxiety, heart rate, and blood pressure.[10,11] Enhanced signage is also helpful to improve communication.

Some miscellaneous safety enhancements include elimination of floor thresholds that separate spaces (eg, between a hallway and bathroom) because any elevation is a major falls risk. Doors should have handles and not round knobs for ease of use.

With minimal expense, the aforementioned equipment and supplies suggestions can help improve geriatric care. Although a dedicate, separate geriatric ED may be the ultimate goal, most hospitals can effectively implement a program to develop a GED by converting the existing space and beds into a geriatric-friendly environment with the equipment and supplies described.

Education

The education of a multidisciplinary staff regarding the specific needs of this unique population is a key component to the implementation and success of a GED program. Residency program curricula, ED staff training, and continuing medical education should incorporate the established geriatric emergency medicine core competencies[12] and provide specialty-specific training, focusing on contemporary, research-based, geriatric-specific material, with regular assessment for interdisciplinary core competencies. A number of instructional platforms can be used, including didactic lectures, Internet-based materials, case simulations, case-based conferences, journal clubs, and bedside clinical teaching. The GED educational program should be geared toward increasing and maintaining staff awareness and knowledge of the geriatric population's needs and implementation of specific policy and procedure initiatives. These should include didactic educational sessions, in-service sessions about geriatric-specific equipment, implementation of bedside assessment tools, and community awareness, involvement, and outreach, including emergency medical services (EMS) personnel, community-based organizations, and patient and family educational self-management materials.

Although individual EDs should tailor their educational content needs to their respective institutions, GED guidelines recommend the inclusion of the content outlined in Box e8.1.

Policies, Procedures, and Protocols

Specific policies, procedures, and protocol initiatives are an integral part of the application of GEM educational content and systematization of evidence-based clinical care for older adults. They are designed to implement a directed comprehensive

BOX e8.1

Geriatric Education Guideline Content

Atypical presentations of disease
Trauma, including falls and hip fracture
Cognitive and behavioral disorders
Modifications of emergent interventions for older patients
Medication management
Transitions of care and referrals to services
Pain management and palliative care
Effects of comorbid conditions
Functional impairments and disorders
Management of diseases peculiar to the geriatric adult
- Abdominal pain
- Weakness and dizziness
- Iatrogenic injuries
- Cross-cultural issues involving older patients in the emergency setting
- Elder abuse and neglect
- Ethical issues, including advance directives

approach to facilitate screening and assessment of geriatric patients for added needs, patient safety, and post-ED adverse outcomes, as well as (when possible) validated, ED-feasible screening tools for delirium and dementia, medication management, falls, use of urinary catheters, wound assessment and care, sedation and analgesia use, suspected elder abuse and neglect, transition of care and follow-up, provision of palliative care, and patient death.

The policies, procedures, and protocols listed by the GED guidelines are recommended to be comprehensive and adaptable to the specific needs of a particular ED. When possible, they are evidence-based and intended to become part of the routine care of patients. Sample policies and procedures are included in the GED guidelines manuscript.

Follow-Up and Transition of Care

The new CMS directive to reduce hospital admissions notwithstanding,[13] it has been known for some time that geriatric patients are particularly vulnerable to the deleterious consequences of hospitalization, including nosocomial infections, functional decline, increased rates of delirium, and iatrogenic complications. Reducing hospitalizations and providing safe discharge and outpatient follow-up and transition of care after an ED evaluation is an integral component of the establishment of a GED program.

The GED should establish discharge protocols that provide clear communication of relevant information, not only to patients and their families, but also to outpatient care providers, including primary care providers, specialty clinics, and nursing homes. As outlined by the GED guidelines, the essential clinical information required for the optimization of continuity of care includes presenting complaints, test results and interpretation, ED therapy and clinical response, consultation notes in the ED, working discharge diagnosis, ED physician notes, and new prescriptions and changes in long-term medications. The discharge processes ought to be designed to suit older adults (eg, large-font instructions) and should include a clear outpatient follow-up plan. To facilitate care following discharge, when appropriate, collaboration with community resources should be established to provide home health services and equipment and home safety assessment. Outpatient follow-up with provider-patient communication via telephone, telemedicine, texting, or direct contact is necessary. When required, the GED should use established relationships with community resources to facilitate, for example, short-term or long-term placement of the patient in a nursing home or rehabilitation facility.

Quality Improvement

As part of a GED program, outlined by the GED guidelines, a quality improvement (QI) system should be implemented to collect and monitor pertinent and prevalent geriatric emergency care indicators, including incidence of injurious falls and documentation of falls risk assessment, catheter use and CAUTIs, medication reconciliation, pharmacy oversight of adverse drug-related events and ED use of high-risk medications, and restraint use. Also, it should routinely review geriatric ED volume, admission and readmission rates, intensive care unit (ICU) admissions, ED return visits within 72 hours, completion of follow-up reevaluation for discharge patients, transfers to other facilities, suspected abuse or neglect, and deaths.

The QI program should be established and monitored by the GED medical director and GED nurse manager to ensure increased staff education and program success. It should include an interface with prehospital care, ED, trauma, and critical care services, alternative care facilities, and hospital-wide QI activities.

Criticisms of the GED guidelines have already been voiced by some emergency medicine (EM) providers. Specific concerns include a fear of partitioning the ED, as has occurred with pediatrics, an increase in cost and decreased efficiency, the need to maintain general expertise among EM physicians, the lack of evidence-based data on which the recommendations were made, the fact that some guidelines were extrapolated from evidence originally studied in other clinical settings, and the belief that these changes will be too logistically difficult and take too much time.[14]

Numerous factors have led to the advent of the GED, and the concept is likely here to stay. The goal to improve the evaluation and care of the increasing number of geriatric patients presenting to the ED is clearly exigent. Reliable tools, protocols, and guidelines must be developed, implemented, and studied to ensure diagnostic accuracy, decrease adverse events, and improve patient outcomes.[6] Fortunately, the new GED consensus guidelines are a sound and flexible starting point. They do not need to be wholly embraced, instead lending themselves to modifications and institution-specific adoptions. The so-called protocolization and implementation of the guidelines may ultimately improve patient flow, operational efficiency and, most importantly, the quality of care delivered to older adults. Although the GED guidelines have yet to be studied, they will hopefully effect substantive change in many EDs, improve the emergency care of older adults, and provide the foundation for future education and research.

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CHAPTER e8: QUESTIONS & ANSWERS

e8.1. What is the most rapidly growing segment of the US population according to age?
A. 5–10 years
B. 15–20 years
C. 55–60 years
D. 65–70 years
E. Older than 85 years

Answer: E. The most rapidly growing segment of the population is the "oldest old," aged 85 years and older, who will represent nearly 25% of Medicare beneficiaries by 2050.

e8.2. The geriatric ED (GED) guidelines developed by ACEP, SAEM, AGS, and ENA make recommendations in which of the following areas?
A. All of these
B. Education and patient care protocols
C. Follow-up and transitions of care
D. Quality improvement measures
E. Staffing, supplies, and administration

Answer: A. The GED guidelines consist of 40 specific recommendations in six general categories: (1) staffing and administration; (2) equipment and supplies; (3) education; (4) policies, procedures, and protocols; (5) follow-up and transitions of care; and (6) quality-improvement measures.

e8.3. The geriatric ED guidelines recommend older adult–specific educational content in which of the following areas?
A. All of these
B. Atypical presentations of disease
C. Cognitive and behavioral disorders
D. Medication management
E. Pain management and palliative care

Answer: A. See Box e8.1.

CHAPTER e9

End of Life*

Tammie E. Quest

PRINCIPLES

Palliative Care

Emergency Medicine and End-of-Life Care

End-of-Life Trajectories

Goals of Care as Central to Emergency Intervention and Care Planning

SPECIFIC DISORDERS AND CONCERNS

Out-of-Hospital Considerations

Field Death Pronouncement

Honoring Advance Directives to Withhold Resuscitation

Death in the Emergency Department

Treating Symptoms Requiring Palliation at the End of Life

Hospice Care and the Emergency Department

KEY CONCEPTS

- Palliative care is a physical, spiritual, psychological, and social support provided to patients and families at any stage of serious illness.
- Palliative care teams are specialized interdisciplinary teams that should be involved early in the course of illness.
- Hospice care is a care system for patients and families with a prognosis of 6 months or less if the disease runs its usual course; referral from the emergency department (ED) may be indicated.
- Patients at the end of life generally follow one of four terminal illness trajectories: sudden death, organ failure, cancer, or frailty.
- Functional status is a strong predictor of decline and progression to death in patients with advanced illness.
- Goals of care conversations that outline patient and family hopes and expectations of interventions should be carried out.
- Emergency clinicians should make recommendations for care plans, interventions, and treatment courses based on prognosis, goals of care, and expected benefit to meet the identified goals of care.
- Key communication skills include breaking bad news, death disclosure, and assessment of goals of care.
- Interpretation of an existing advance care plan or receipt of a prehospital order (eg, POLST— ***P***hysician ***O***rders for ***L***ife-***S***ustaining ***T***herapy) should factor into ED treatment plans in the context of the patient's illness trajectory.
- Advance care planning may occur in the ED in the form of goals of care assessment followed by recommendations and orders placed by the emergency clinician to implement the plan.
- Symptom management is critical at the end of life; common symptoms are dyspnea, pain, delirium and agitation, and secretion management.

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CHAPTER e9

End of Life

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PRINCIPLES

The Institute of Medicine's 2014 report, *Dying in America*,[1] highlights that patients nearing the end of life often experience multiple transitions between health care settings—including high rates of apparently preventable hospitalizations—which can fragment the delivery of care and create burdens for patients and families. The demand for family caregiving increases, and the types of tasks performed by family caregivers expand from personal care and household tasks to include medical and nursing tasks, such as medication management. Palliative care is associated with a higher quality of life, including better understanding and communication, access to home care, emotional and spiritual support, well-being and dignity, care at time of death, and lighter symptom burden. Most people live with some limitation in their ability for self-care for 2 to 4 years before they die.

Palliative Care

The World Health Organization defines palliative care as

> ….an approach that improves quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.

Palliative care is usually provided by an interdisciplinary team of experts that offers comprehensive care and support systems for patients and their health care providers at the end of life and when they are undergoing treatment for advanced illness. Some patients near the end of life are being treated with curative intent (eg, before transplantation) but are in palliative care. Palliative management is provided to inpatients through consultation; outpatient services are delivered at home, hospice, or long-term care facilities.

Hospice care is the component of palliative care for patients who are likely to be within 6 months of death. The hospice movement, which started in England in the 1950s, initially sought to provide a haven of medical care for persons dying of cancer. Home and inpatient hospice programs now exist throughout the United States and are funded through Medicare. If an emergency clinician would not be surprised if a patient died within 6 months, if the disease ran its natural course, a hospice evaluation might be appropriate.[2] The patient is hospice-eligible if the hospice patient's life span is likely to be less than 6 months and if Medicare will certify the patient for hospice. For adults, commercial insurers follow criteria for Medicare hospice benefit. Currently, hospice care is provided for an expanded spectrum of end-stage illness, including cancer, organ failure (eg, heart, liver, kidney), neurologic diseases, and terminal AIDS. Most patients who receive hospice care die with hospice care, and most have a cancer diagnosis. The median time from enrollment to death is 21 days, often leaving insufficient time for many of the services that hospice can offer.[3,4]

The palliative care movement has developed as an expansion of end-of-life care to include not only hospice-eligible patients but also patients with incurable, debilitating, chronic noncancer illnesses (eg, chronic obstructive pulmonary disease [COPD], congestive heart failure) that require symptom control, often in addition to some disease-modifying interventions, but with a less clear time frame to death. Consultation with palliative care specialists offers patients a mechanism to discuss and review management of symptoms and medical interventions that patients desire or wish to avoid.[5,6]

Emergency Medicine and End-of-Life Care

Emergency clinicians encounter death more frequently than other types of clinicians. Resuscitation and restoration to functional life is a primary goal of emergency practice, but seriously ill patients treated in the emergency department (ED) often present with important but less emergent complaints, and the emergency clinician often does have time to explore options for care with patients or family. Even when a patient has a severe chronic disease that is not curable, interventions are available that can improve the quality of life. Conversely, at the end of a course of chronic disease, death is not always unwelcome.

Addressing the needs of patients and their families in the ED at these critical times requires an important set of skills. In 2006, the American Board of Emergency Medicine joined with nine other specialty boards to cosponsor the American Board of Hospice and Palliative Medicine. This alliance has recognized the real need for emergency clinicians to address the wide range of interventions and management decisions that are relevant at the end of life. The integration of emergency medicine and palliative medicine has stimulated educational efforts to define the scope of ED-based palliative care and curriculum design.[7] Some evidence has suggested that on average, palliative care and hospice patients may live longer than similarly ill patients who do not receive such care.

In caring for patients with serious life-threatening illness, a number of palliative care skills are required of the emergency clinician (Table e9.1).[8] One important end-of-life skill is to determine the patient's wishes for interventions in a time of crisis rapidly. These wishes may be transmitted through written advance directives or direct conversation with a patient or proxy about general values or specific management choices that should guide ED management. Invasive interventions may carry greater risk and less benefit near the end of life. The patient's choices may include spiritual, economic, and community factors that the emergency clinician cannot know without clear rapid communication and the establishment of treatment goals.[6] The national Education in Palliative and End-of-Life Care for Emergency Medicine curriculum has been designed to help emergency clinicians prognosticate better, convey medical and technical choices, and discuss goals of care with patients and families at these critical times.

Subspecialty palliative care is the care provided by a specialized interdisciplinary care team that is focused on the physical,

TABLE e9.1

Sample Questions for Initiation of Discussion About End-of-Life Issues

DOMAIN	QUESTIONS[a]
Goals	Given the severity of your illness, what is most important for you to achieve? How do you think about balancing quality of life with length of life in terms of your treatment? What are your most important hopes? What are your biggest fears?
Values	What makes life most worth living for you? Would there be any circumstances under which you would find life not worth living? What do you consider your quality of life to be like now? Have you seen or been with someone who had a particularly good death or particularly difficult death?
Advance directives	If, with future progression of your illness, you are not able to speak for yourself, who would be best able to represent your views and values? (health care proxy) Have you given any thought to what kinds of treatment you would want (and not want) if you become unable to speak for yourself in the future? (living will)
Do-not-attempt-resuscitation order	If you were to die suddenly—that is, if you stopped breathing or your heart stopped—we could try to revive you by using cardiopulmonary resuscitation (CPR). Are you familiar with CPR? Have you thought about whether you would want it? Given the severity of your illness, CPR would in all likelihood be ineffective. I would recommend that you choose not to have it but that we continue all potentially effective treatments. What do you think?
Palliative care—pain and other symptoms	Have you ever heard of hospice (palliative care)? What has been your experience with it? Tell me about your pain. Can you rate it on a scale of 1 to 10? What is your breathing like when you feel at your best? How about when you are having trouble?
Palliative care: "unfinished business"	If you were to die sooner rather than later, what would be left undone? How is your family handling your illness? What are their reactions? Has religion been an important part of your life? Are there any spiritual issues you are concerned about at this point?

[a]It is important to give the patient an opportunity to respond to each question. Follow-up questions and responses should be based on careful listening to the patient, with use of the patient's own words whenever possible.
From Quill JE: Initiating end-of-life discussions with seriously ill patients: Addressing the "elephant in the room." JAMA 284:2502–2507, 2000.

spiritual, and psychological support of patients and families living with serious life-threatening and or terminal illness and is compatible with patients seeking curative therapies. In 2013, the American College of Emergency Physicians published, as part of the Choosing Wisely Campaign, the recommendation that emergency clinicians should engage patients who present to the emergency department (ED) with chronic or terminal illnesses, and their families, in conversations about palliative care and hospice services. Early referral from the ED to hospice and palliative care services can benefit select patients resulting in both improved quality and quantity of life.

End-of-Life Trajectories

With modern medical advances, chronic diseases are present during the last years of life for most people. Three diseases—heart disease, cancer, and stroke—are responsible most deaths, with less than 10% being accidental.[9] Four common trajectories of dying have been described (Fig. e9.1). Sudden death (due to cardiac arrest, trauma, or other sudden event) occurs in only 15% of people.[10] The other trajectories are more common and occur with roughly equal frequency. The predictable decline in patients with terminal illness during 6 months or less provides the basis for the hospice concept of managing the dying process for patients with cancer and terminal AIDS. In cases of organ failure (eg, COPD, heart failure, renal failure, other progressive, serious medical diseases), gradual decline is punctuated by intermittent exacerbations (entry-reentry decline). The fourth trajectory of gradual decline, or frailty, is associated with some form of dementia in 50% of affected persons and a lingering course that can extend for many years, stressing and wearing out caregivers and other support systems as decline in functional abilities progresses. As technology gives emergency clinicians the ability to stabilize

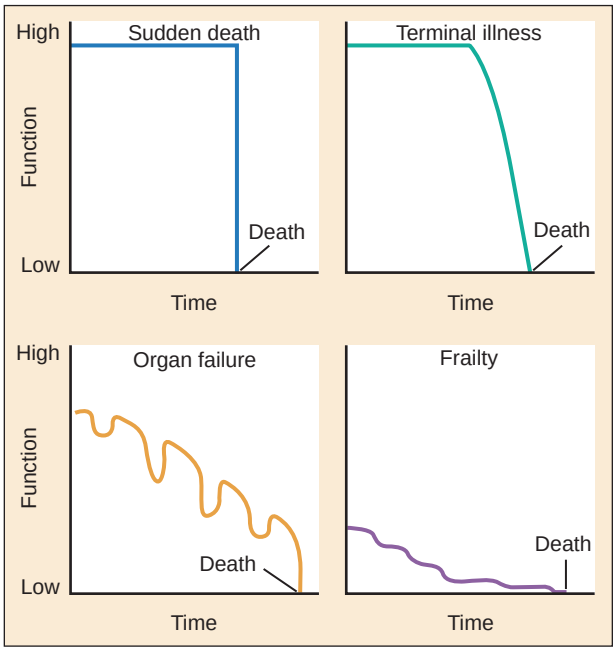

Fig. e9.1. Theoretic trajectories of dying. (From Lunney JR, Lynn J, Hogan C: Profiles of older Medicare decedents. J Am Geriatr Soc 50:1108–1112, 2002.)

patients with serious and incurable diseases and manipulate the timing of death, and as people increasingly exercise their autonomy to decide how and when their dying should occur, more conversations occur about what constitutes a good death. There is evidence that the quality of life for persons who live into their 80s is better

than it was 20 years ago. However, there are also serious deficiencies in end-of-life care. Whereas almost 95% of people express the wish to die at home, more than 70% die in an institution. The patient's priorities are often marginalized because they commonly include medical and nonmedical concerns.

Five concerns predominate in people who are dying:

- Having pain and other symptoms adequately relieved
- Avoiding inappropriate prolongation of dying
- Achieving control
- Relieving others of the burden of their dying
- Strengthening personal relationships

The medical profession has been slow to understand the broad scope of the patient's wishes and to honor them in planning and care.

In the ED, life-extending therapies are applied unless the patient's wishes to the contrary are clearly known, even though the number of patients completing some form of advance directive before nontraumatic death is now about 70%. Information that cardiopulmonary resuscitation (CPR), intubation, or other invasive treatments are not desired can be conveyed in the form of written advance directives, a state-authorized, no-CPR or do-not-attempt-resuscitation (DNAR) directive, clear indications from the person assigned the patient's durable power of attorney for medical affairs, or communication with the patient's physician through the newer POLST (***P***hysician ***O***rders for ***L***ife-***S***ustaining ***T***herapy) paradigm orders.[11] However, evidence of wishes from prior conversations between patients and family or physicians is rarely available in an emergency situation. Most people—patients and surrogates—do not understand what "do everything" means, and surrogates are poor at predicting care that their loved one would or would not want. A study comparing patient and surrogate choices about life support has shown that surrogates guessed patient wishes only 68% of the time.[12]

Goals of Care as Central to Emergency Intervention and Care Planning

Determination of the goals of care will dictate ED interventions and care planning. In a patient who lacks the ability for decision making, rapid determination of the patient's or surrogate's hopes and expectations for interventions based on the clinical scenario at a time of crisis is crucial. An ED visit alone does not suggest that patients or caregivers want interventions at the end of life, but they do want medical assessment and guidance based on expert opinion. Previously stated wishes may be transmitted through written advance directives or direct conversation with a patient or proxy about general values or specific management choices that should guide ED management. The patient's choices may include spiritual, economic, and community factors that the emergency clinician cannot know without clear, rapid communication and establishment of treatment goals.

Key components of goals of care conversations include sharing prognostic information, eliciting decision making preferences, understanding fears and goals, exploring views on trade-offs and impaired function, and wishes for family involvement.[13] Emergency clinicians are not required to offer treatments that are not beneficial. Unfortunately, information available in the out-of-hospital setting or the ED is often insufficient for making a judgment that a particular patient's condition is terminal or that treatment efforts would be futile. When cardiopulmonary arrest occurs, emergency clinicians proceed with full resuscitative measures unless there is a clear understanding that this is contrary to the patient's wishes. Assessment of the goals of care and patient's prognosis, once information is known, can guide the emergency clinician in determining if resuscitative efforts are not beneficial based on the goals of care.

SPECIFIC DISORDERS AND CONCERNS

Out-of-Hospital Considerations

Historically, out-of-hospital systems were designed to provide immediate resuscitation, stabilization, and transport of seriously ill or injured persons to EDs. Aggressive and early resuscitation, through CPR, airway management, defibrillation, fluid resuscitation, and trauma stabilization, has resulted in significant benefits and reduced mortality in patients with critical illness or injury for whom survival is time-dependent. However, emergency medical services (EMS) systems also are called to transport patients who have died or assist patients who are in extremis but whose death is expected. EMS is not infrequently activated for patients with acute decompensation of chronic medical conditions, such as heart failure or COPD, and for acute symptoms that occur in the context of terminal conditions when caregivers at the scene cannot cope.[14-16] Patients at the end of life may desire aggressive interventions for acute exacerbations of chronic illnesses, or they may prefer only supportive care or transportation to avoid unwanted interventions. In emergency situations, it may not be possible to determine the patient's underlying medical conditions or wishes. In some situations, a titrated response is possible, and noninvasive supportive care (eg, positioning, suctioning, oxygen, mask ventilation) during transport can buy time until the ED can further assess and clarify the patient's goals of care.

Several concerns about the validity of written advance directives persist. The patient's wishes can change over time, nonstandard forms of DNAR requests (eg, medical alert bracelets, notes on prescription pads, tattoos) cannot be recognized, and there is a theoretic concern that relatives or bystanders may not be accurately relaying the wishes of the patient. However, patients in the last 6 months of life increasingly have physician orders documenting their wishes (eg, POLST), and EMS providers need to ask for and honor these, as allowable by state laws.[17-19]

Field Death Pronouncement

Several physiologic circumstances have been identified in which out-of-hospital providers should not initiate or continue CPR because of uniformly poor outcomes and no benefit from intervention. American College of Emergency Physicians (ACEP) and American Heart Association (AHA) guidelines state that CPR should not be initiated in patients with nontraumatic cardiac arrest and signs of irreversible death, such as decapitation, dependent lividity, or rigor mortis.[20] ACEP policy recommends discontinuation of resuscitation in the out-of-hospital setting if the patient remains in asystole or wide-complex pulseless bradycardia after a trial of adequate resuscitation, including CPR, intubation, medications, defibrillation, and pacing. The National Association of EMS Physicians supports this approach. Termination of resuscitation efforts in nontraumatic cardiac arrest patients should be made in agreement with online medical direction and predicated on access to witnesses or family, provider comfort with death notification and grief counseling, and safety and logistic considerations.[21] In some systems, newer, physiology-based algorithms for the termination of resuscitation are being developed.[22] If questions arise about resuscitation, CPR and advanced cardiac life support measures should be initiated and the patient transported. It can be easier and is ethically more sound to withdraw care in the ED than to withhold care at the scene.

Honoring Advance Directives to Withhold Resuscitation

Honoring patients' wishes at the end of life should be a goal for out-of-hospital and ED personnel. Most out-of-hospital providers

think that end-of-life skills are important; 93% of Oregon EMS providers have found POLST orders are helpful in the event of a prehospital cardiac arrest, and two-thirds thought they were useful in patients who were not in arrest.[23] Significant gaps in training and knowledge about end-of-life issues have been noted among paramedics.[24]

Death in the Emergency Department

Delivering Bad News

Every emergency clinician will be required to communicate bad news to patients, family members, and caregivers. The manner in which this is done may make a difference in the course of subsequent grief and coping. Compassionate communication can strengthen trust and foster collaboration between the medical team and patient and family. Emergency clinicians have particular challenges in delivering bad news. They do not have ongoing relationships with their patients, and the bad news may be abrupt and unexpected. However, sometimes the lack of a prior relationship allows a more frank and open conversation about a patient's illness, prognosis, and wishes, particularly when the patient has a severe chronic disease.

The goal of skillfully breaking bad news is to reduce the severity and duration of stress and encourage engagement of coping mechanisms for emergency clinicians and for patients and their caregivers and family. Studies have shown that staff and clinician stress often peaks just before the transmission of the bad news, whereas patient or caregiver stress emerges after the delivery of bad news. Emergency clinician stress correlates directly with the severity of the news and feeling responsible for the outcome and inversely with the amount of experience in delivering bad news. Many emergency clinicians feel inadequately prepared for death disclosure or delivery of bad news about a new diagnosis or turn in health status for a patient with a life-limiting illness.[25] Feeling skilled in providing disclosures to families is key in managing external sources of provider stress. Anticipatory stress of delivering bad news may be reduced by use of a structured protocol, with practice, and by being intentional about the physical and social aspects of the setting.

Several initiatives to improve the delivery of bad news have been introduced. These encourage training in communication skills, explicit instructional sessions, role playing, use of standardized patients, and observing colleagues who are comfortable with this aspect of patient care. However, the best methods of increasing patient and family satisfaction with this important aspect of patient care have not been examined. Emergency clinicians who insulate themselves from stress may inadvertently increase stress for the receiver, whose needs should be primary; emergency clinicians should avoid the use of vague language, delegation to others, and delaying or rapidly disengaging from the encounter.

For the patient and family, the ED is typically the place where bad news is sudden and unexpected, thereby making the strain even more severe and overwhelming. Trust between ED caregivers and critically ill patients or their survivors does not come easily. Whereas emergency clinicians may focus on the content of the information they should convey, patients focus more on the process. Surveys of patients and families have identified the following factors as desirable for receiving bad news: privacy when receiving news, ability to express emotions safely, information that is free of unclear language or medical jargon, empathic and caring attitude, allowance for hope, and ability to ask for and receive good medical information. One proposal for encouraging provider empathy is to structure a conversation according to the NURSE pneumonic—the provider ***n***ames the emotions observed, confirms whether this ***u***nderstanding of the receivers' feelings is correct, expresses verbal and nonverbal ***r***espect for the receivers' feelings, ***s***upports them through expressions of concern, understanding, and willingness to help, and ***e***xplores additional concerns.

BOX e9.1

Delivering Bad News

The steps listed can help the emergency clinician think critically about how best to communicate at a time when stress is high. See the text for details about each step.

- Step 1: Clinician preparation
- Step 2: What does the patient know?
- Step 3: How much does the patient want to know?
- Step 4: Sharing the information
- Step 5: Responding to feelings
- Step 6: Planning and follow-up

Adapted from Buckman R: How to break bad news: a guide for health care professionals, Baltimore, 1992, Johns Hopkins University Press.

The steps listed in Box e9.1 and explained in detail in the following paragraphs are designed to shape the interaction to facilitate the patient's or survivor's coping. This six-step template was adapted from Buckman's work and adopted by the Education for Palliative and End-of-Life Care (EPEC) teaching project. Key to moving through the process of delivering bad news is the ask-tell-ask interactional framework, in which the emergency clinician is guided by the patient and family with regard to the pace, amount of information, and style that will work best to let them feel and hear what they need.

Step 1: Clinician Preparation. Before the emergency clinician interacts with the family or patient, preparatory steps are important. These include confirming all medical facts of the case, clarifying the name of the patient, being aware of any uncertainty about the patient's identity, and knowing the relationships between the patient and those with whom one will be talking. The physical site for the conversation should be quiet and allow private exchange of information and safe expression of emotions. This is sometimes difficult in the ED, but a family room or other quiet area usually is available. If the patient can be included, moving the patient to a private area is helpful, or key members of the patient's support group can be gathered around the bedside.

Emergency clinicians should identify themselves and their position, directly address the patient (when present) or the key persons receiving the news, and refer to the patient by name. Before beginning the discussion, the emergency clinician should sit down close to the patient, make direct eye contact with the patient (or close relatives), and be physically and mentally open to their concerns and needs.

Step 2: What Does the Patient Know? It is useful to know what the patient or family understands before the delivery of news. An introductory question can be used, such as, "What do you understand about your illness?" or "What have you been told happened to [name of spouse, sibling, other]?" This information helps the emergency clinician to see the event as the patient and family are seeing it and to adjust the mode of delivering this news to their understanding. When patients and families may expect the worst, this tactic can be perceived as delaying the news. In a less critical situation, asking about previous testing, conversations with other emergency clinicians, and understanding of the patient's illness can help the subsequently delivered information fit into the patient's perspective and expectations.

Step 3: How Much Does the Patient Want to Know? Every patient has the right to accept or to refuse medical treatment

on the basis of informed consent. This also is true for information. Most patients appreciate the direct simple truth about their condition and prognosis. There will, however, be some patients who do not want to receive the information themselves. These patients may wish to designate a friend or family member to represent them. This choice should be respected, if possible. People process information and make decisions in many different ways on the basis of their own cultural and religious views and previous experiences, and the Western principles of truth telling and individual decision making may be of lower priority to some families and communities.

Sometimes the family learns of a diagnosis and prognosis before the patient does and requests that the patient not be told. The emergency clinician's alliance with patient and family is important, although responsibility to the patient is primary. Physicians should explore why families do not want the patient told bad news:

- Is it a cultural tradition?
- Are they afraid of what harm it will cause the patient?
- Have they had previous bad experiences?

The emergency clinician is still required to ask the patient how much he or she would like to know. Sometimes it is helpful for the emergency clinician to invite family members to be present for this discussion. Important information should be shared with the use of an independent interpreter—rather than a family member—if the patient does not speak the same language as the clinician.

Step 4: Sharing the Information. In general, patients and families want to know bad news in a timely fashion. This is sometimes uncomfortable, particularly when information is incomplete, a common occurrence in the ED. At the very least, it is recommended that patients and family be given a preparatory warning after introductions, such as, "I am afraid I have some bad news." In delivering the information, it is important to use simple nonmedical language and make sure that the patient comprehends the information. Allow space for patients and family to absorb the news, react, and begin to ask questions. Typically the patient and family stress response will lag behind that of the emergency clinician because she or he has had at least a few minutes to adjust to the current situation, but the family has not.

Use of the phrase "I'm sorry" can be a reflection of empathy but, to avoid the implication that errors have occurred in treatment, some emergency clinicians have suggested the use of expressions such as "I wish things were different" instead. Survival data can sometimes be helpful, even when tentative. The emergency clinician's message should include some realistic hope and reassurance that the care team will not abandon the patient, even when cure or survival is unlikely.

Step 5: Responding to Feelings. The reaction to bad news is often unpredictable and can range from sadness to overt anger. It is important for emergency clinicians to be aware of the wide variety of responses that will be seen. The patient and family should be allowed to express their feelings, even if this is uncomfortable. Acute grief is painful but important. The emergency clinician should be prepared for those who turn inward and those who rage outwardly. Practicing and reflecting on these situations will allow the emergency clinician to deliver bad news and support the survivors. In the ED, it is helpful to invite other members of the care team into this meeting (eg, social worker, nurse, chaplain), especially those who will not be pulled away, so they can provide emotional support and help the family navigate through the early stages of grief, as well as the necessary technical details.

Step 6: Planning and Follow-Up. The ED is an entry point into the hospital if the patient survives. Family members should be encouraged to stay with the patient, particularly if it is possible that the end of life is near. Prognosticating may be difficult in view of the limited information obtained in the initial assessment. When initial management has stabilized a patient with an acute critical turn, it may be appropriate to look ahead to decompensation, which may occur later in the hospitalization. Some experts have suggested a "hope for the best and prepare for the worst" framework for conversation. The emergency clinician can share the success, however transient, of any ED interventions and the positive news and hope that this provides. At the same time, he or she can prepare the patient or family for the possibility of later setbacks and have them consider what actions may or may not be appropriate if the worst happens. If the patient does not have written advance directives, the emergency clinician can facilitate the conversation, initiate written wishes, or at least advise the patient that the admitting physician will need to have an early conversation about future plans and goals for the patient. The emergency clinician should inform the patient and family of the next steps, including hospital admission or discharge from the ED, consultation with specialists, support group referral, and chaplain services. It is important to make sure that the patient and family do not feel abandoned. When dying is near, active care and comfort are important medical tasks for the care team.

Death Notification

One particularly difficult form of bad news is death notification. Several algorithms exist to assist emergency clinicians in learning the steps. Practice can help emergency clinicians perform this task more smoothly (Box e9.2). In general, the format can follow the guidelines for delivery of bad news from Box e9.1. With death notification, however, diagnosis is certain, and specific actions will be required. Families do not have time to adjust or to think about options, and the news cannot be softened.

Telling in Person. Death notification usually occurs after an unsuccessful resuscitation attempt. Emergency clinicians should be sure that they are presentable and wear a name badge. If possible, ascertain beforehand the names of the persons who will receive the notification, their relation to the patient, and what they know about the patient's condition. Other members of the medical team may have met them already and can be a source of

BOX e9.2

Elements of an Empathic Death Disclosure

Introduce self and role.
Sit down.
Assume comfortable communication distance.
Use acceptable tone and rate of speech.
Make eye contact.
Maintain open posture.
Give advance warning of bad news.
Deliver news of death clearly (use dead or died).
Tolerate survivor's reaction.
Explain medical attempts to "save" patient.
Use no medical jargon; use language that is clear and easily understood.
Offer viewing of deceased.
Offer to be available to survivor.
Conclude appropriately.

Adapted from Quest TE, Otsuki JA, Banja J, et al: The use of standardized patients within a procedural competency model to teach death disclosure. Acad Emerg Med 9:1326–1333, 2002.

background information. Sometimes the family initiated the 9-1-1 call and recognized that their loved one had died at that time. On the other hand, a family summoned to the ED may have absolutely no idea that they are about to be informed that their loved one has been critically injured or has died. For this reason, it is useful to have a nurse or colleague advise the family briefly about the general nature of the event and the status of resuscitation as soon as possible. When giving the news, emergency clinicians should use clear "dead" or "died" terminology to be sure that there are no misunderstandings about the outcome being conveyed. Those at the scene should be assured that their responses to the emergency were appropriate, the medical care team did all that was possible, and the victim did not experience unnecessary discomfort. It is important to express appreciation for their presence in the ED or during the resuscitation attempts.

Telephone Notification. When the notification is to an individual who is more than an hour away or otherwise unable to come to the ED physically to receive the bad news, it needs to be given by phone. If the first contact with survivors of an ED death is by telephone, it is recommended that the survivor be told to come to the ED, if at all possible. Although family members may ask or even demand to know if death has occurred, allowing some time for the assimilation of news by delaying information about the final outcome may be more helpful for the grieving process. Nonphysician staff may be used to summon survivors and can inform them that the patient has been involved in an accident or is seriously ill without signs of improvement.

The emergency clinician should make sure that the relative has someone present in the room if possible, ask the relative to be seated, and name the person involved. It is best to start with brief information about the circumstances and provide a warning that bad news is coming before breaking it. Even a few seconds of preparation in these circumstances can serve to partially attenuate the acute psychic pain. As indicated by the perceived response, the clinician may need to ask, "Are you able to talk for a few minutes?" Some individuals may be unwilling or unable to continue after they hear the initial news, and they should be given an "out," but a definite time to reconnect should be established (eg, 10–15 minutes). Long-distance loved ones cannot view the body to facilitate confirmation and acceptance and inevitably have questions not addressed in the initial conversation. The relative should be given a telephone contact of someone who actually provided care for the patient. Otherwise, if a relative calls back, lack of information about what transpired on a prior shift may cause frustration or even feed the person's denial or false hope that the tragedy did not occur.

Viewing the Body

At some time immediately after death, the family should be offered an opportunity to view the body. This may be the first exposure to the body for the survivors and can make an abstract and unreal notification more concrete. Although most survivors find viewing of the body helpful, no attempt should be made to force this on them, and a few are not comforted by seeing the deceased.

If possible, the body should be moved to a small room, preferably away from the main treatment area. This not only ensures privacy but also makes the family feel more at ease. Family members should be warned of what to expect, such as color and temperature changes, injuries or invasive premortem procedures, and the presence of endotracheal and intravenous (IV) tubing or other medical devices.

A staff member should remain in the room or within close range at all times. This contact allows the staff to help make the viewing an important and supportive aspect of the grieving process. At times, it may be necessary to touch the body to assure the family that this is appropriate. Survivors should be allowed to remain with the body for as long as seems appropriate. When gross disfigurement has occurred, the viewers should be warned about this, and the body should be discreetly covered, when possible. Survivors may even find that helping to clean and prepare the body (particularly with a pediatric death), holding a loved one, or preparing for transport may allow a final expression of caring.

Family Presence During Resuscitation

It is increasingly common to invite a close family member to attend resuscitation attempts. Emerging evidence has suggested that presence during procedures and resuscitations may be beneficial to surviving patients and family members who choose to stay, and they are not harmed by the experience.[26,27] Less consensus exists among providers, and they often express discomfort with the concept, with nurses expressing less discomfort than physicians.[28-30] If resuscitation is to be witnessed by a family member, preferably a protocol is in place and a staff member who is dedicated to supporting that person should be present.[31] Processes and procedures should allow for the ED team to work effectively but also allow families the option of observing resuscitation.

Goals of Care

Establishing Goals of Care. A core skill in managing patients near the end of life is the ability to assess and establish goals of care. In a true emergency, where the patient lacks capacity and there is no legal surrogate or advance care plan, such conversations take a back seat to resuscitation interventions. Most patients with a serious illness will present with enough time to assess goals of care before interventions are required. In the ED setting, several approaches can be helpful to establish which treatments patients prefer near the end of life.

Initiating a Conversation on Goals of Care. Emergency clinicians see many sick patients who do not have written advance directives but are stable enough to have meaningful conversations about their needs and goals, their perception of where they are in the course of their disease, whether they wish to cure an intercurrent problem, which symptoms require management, and how much effort they wish to have undertaken if resuscitation is needed to preserve their life. Patients with a seemingly lethal condition may be aggressively pursuing curative or at least disease-modifying options. Conversely, the burden of suffering that some patients are experiencing may not be obvious until they are asked specifically about their illness and wishes. With or without written advance directives, the emergency clinician needs to ask about the patient's wishes. Key components of goals of care conversations include sharing prognostic information, eliciting decision making preferences, understanding fears and goals, exploring views on trade-offs and impaired function, and wishes for family involvement[13] (see Table e9.1). The start of the goals of care conversation most naturally begins with an assessment of the patient's global understanding of their illness, as well as their values ("What is most important?"), fears ("What are you most worried about?"), and expectations ("What are you expecting from your treatment?").[32,33] Any interventions need to be considered in the context of caring for the patient and enabling patients to achieve their goals. Common goals might be less interventions and desire to go home, life-extending interventions to buy time, with the understanding that this may limit other possibilities (eg, comfort or the ability to be at home), or the concept of the time-limited trial—try this to see if it can achieve goals and stop it if it cannot.[34]

Prognostication

Functional Status and the Value of the Surprise Question. ED patients invariably will present with signs and symptoms of deterioration, and the emergency clinician will need to formulate an opinion about where the patient is in their end-of-life trajectory. Common signs of deterioration include altered mental status, elevated heart rate or fever, and decreased oral intake. They may also present with an acute emergent condition such as acute myocardial infarction, stroke, or severe sepsis and will manifest multiple abnormalities, such as renal failure, electrolyte derangement, or infection. Patients, caregivers, and surrogates are typically frightened, confused, and chronically fatigued from the burden of illness. There may be those involved with home care systems that are in place, such as home health or hospice care, who may not understand the full nature of the patent's illness and life trajectory.

One way of formulating prognosis under these circumstances is the so-called surprise question[2,35]: "Would you be surprised if this patient died in the next _____ (hours, days, weeks, months, year)?" Those who are identified as not being surprised by a death within 1 year are appropriate for palliative care consultation that may occur in the ED, during hospital admission, or as an outpatient. Emergency clinicians may be hesitant to declare that a patient is in the last phase of decline from a terminal illness for fear of being wrong, but studies have shown that they are relatively accurate in formulating an accurate prognosis. Prognostic formulation should be done by using the time frames of hours to days, days to weeks, weeks to months, or months to years.

Functional Status in Relationship to Prognosis. In the context of limited information, functional status prior to ED presentation is the best predictor of postpresentation intervention outcomes. Prognostication in noncancer conditions remains complex but correlates with functional status.[22] Standard functional assessment is measured in oncology patients with the Eastern Cooperative Oncology Group (ECOG) scale and in nononcology patients with the Karnofsky Performance Scale (KPS; Table e9.2). Cancer patients with an ECOG score of 3 or 4 (capable of only limited self-care, confined to bed or chair more than 50% of waking hours) have a limited prognosis and are typically not recommended to have cancer-directed therapies; instead, they should have treatment aimed at symptom management.[36]

At the bedside, ask the key questions: "Tell me how you (your) loved one has been doing the last week or two? What have they been able to do for themselves? How much time do they spend up and out of bed in a day?" A patient who has metastatic cancer with brain metastasis, with relatively no symptoms, good functional status, and an acute sepsis presentation, is clinically distinct from the same patient who has been in bed for several weeks who has poor oral intake and is asleep for many hours of the day. In the former scenario, the patient is more likely to recover to hospital discharge with life-sustaining interventions such as antibiotics, vasopressor support, and intensive care unit admission than the latter. If not recognized in the context of normal progressive decline punctuated by a terminal fulminant event, the ED course may include comprehensive evaluation such as laboratory tests, IV fluids, radiographic evaluation, and emergent intervention, despite the patient not wanting these measures. Emergency clinicians should communicate where a patient is in the terminal illness trajectory, calm fears and anxieties, and create an emergent and contextually appropriate care plan.

Treating Symptoms Requiring Palliation at the End of Life

When a patient is suffering from a disease that is not curable, he or she may still want a variety of medical interventions as part of care, such as antibiotics for intercurrent infections, drainage of effusions that cause shortness of breath, wound care for decubitus ulcers, decompression of bowel obstructions, and pain management. The caregiver may encounter several unfamiliar principles when treating symptoms in someone near the end of life. One of the challenges for the emergency clinician is the treatment of symptoms without diagnosis of the underlying cause, even though this often is the appropriate option in palliative care. The emergency clinician may have concerns about drugging patients or overtreating them, but these are mostly unwarranted. Worry about unintended consequences may lead to underdosing of medications, leaving patients without desired relief. Concerns about respiratory depression arise when opioids are used, even

TABLE e9.2

Comparison of Eastern Cooperative Oncology Group (ECOG) Scale and Karnofsky Performance Status

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all predisease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or do active work
2—Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated, although death not imminent
4—Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

From ECOG-ACRIN Cancer Research Group: ECOG performance status. http://ecog-acrin.org/resources/ecog-performance-status.

though the risk of respiratory depression is minimal when the dose is titrated to the patient's desired endpoint.

Pain

Pain is a common complaint with terminal illness.[24,37] although typically considered in the setting of cancer, pain in the end-of-life phase is prevalent across many noncancer conditions, such as heart failure, COPD, and dementia. As patients become less mobile, they may suffer pain from contractures, wounds, or other conditions secondary to the primary illness. Patients suffering from malignant pain may need continuous infusions of opioids to obtain relief or rapid titration protocols, as well as an adjustment of chronic doses of analgesics in the ED.[38] Opioid use is appropriate for patients presenting with acute pain or chronic pain of moderate intensity (rated 5/10 or above; see Chapter 3). Obtain a thorough medication history to determine tolerance and dose adjustments that may be needed. Pain assessment is distinct for patients with chronic pain because they may not have abnormal vital signs or outward expressions of discomfort commonly observed with acute pain. Patients with advanced illness and pain may be tolerant to opioids and require high doses to achieve comfort. This may cause discomfort on the part of the provider.

Although not uniformly available, palliative care consultation can be helpful in guiding the treatment of malignant pain. Emergency clinicians should have a basic knowledge of how to treat severe pain at the end of life. Rapid opioid dose escalation is the most important intervention in cancer patients receiving opioids. Doubling the dose may be required until successful analgesia is reached. With IV administration of morphine, serum levels will be maximal in 5 to 15 minutes, so patients need to be reassessed and redosed promptly. Providing a stable analgesic effect is important; this is done by providing a long-acting formulation (eg, MS Contin) along with an immediate-release, short-acting agent for breakthrough pain. Side effects from opioids should be anticipated. Rising serum levels of opioids may stimulate the chemotactic trigger zone, causing nausea. Educating the patient that nausea will subside within days is helpful. Minimizing fluctuations by the use of long-acting agents, whenever possible, can limit this form of nausea. Constipation is a common effect of opioids, and tolerance to this symptom will not develop. Prevention is far easier than treatment, so a stimulant laxative should be part of all opioid prescriptions for malignant pain. The use of nonsteroidal antiinflammatory drugs may be helpful in potentiating the effects of opioids in cancer patients. Neuropathic pain can be treated with medications such as gabapentin. It is important to explain the proposed treatment plan clearly to the patient and caregivers, monitor the response to treatment and side effects, and coordinate changes in treatment regimens with the primary care physician.

Shortness of Breath

Dyspnea is a common symptom at the end of life. It is multifactorial and not defined by direct pathophysiology.[23,39] Shortness of breath can be part of the last stages of airway disease, cancer involving the lungs, or other advanced chronic diseases as patients become cachectic and immobile. Although the cause may not be found, several treatments may be helpful. Oxygen therapy is not harmful but may have limited effects.[40] In the actively dying patient, morphine and atropine can be used to dry secretions, slow breathing rates, and decrease the work of breathing. A safe starting doses of opioids for dyspnea is morphine, 2 mg IV q15min (or the equianalgesic equivalent of another opioid).[41] Shortness of breath is often accompanied by anxiety. Benzodiazepines are not recommended for dyspnea as a first-line treatment and have been shown to cause increased morbidity in dying patients.[42]

Imminent Death

Patients facing imminent death[43,44] often present with dyspnea, pain, and delirium. All are typically frightening for patients, caregivers, and surrogates. Signs of imminent death include irregular breathing, altered mental status (eg, agitation, stupor, coma), and/or mottling of extremities, with increased heart rate, increased temperature, or inability to handle secretions (death rattle). Although there is no evidence that secretions at the end of life are uncomfortable to patients, families are quite disturbed by them. In a patient who appears to have hours to days to live, the emergency clinician should consider initiating a goals of care discussion with a recommendation for hospice care, consultation with palliative care in the ED, and use of any ED resources to provide spiritual and psychosocial support to the patient and family. End-of-life symptom management includes medications for pain, dyspnea, delirium, and secretions. Nonsymptom management includes discontinuation of monitoring and consideration of oxygen therapy and IV fluids, when indicated.

Hospice Care and the Emergency Department

Hospice as a Care System

Hospice care is a set of services provided in the home, freestanding inpatient facility, hospital, or nursing home. Some hospice companies use wards or units within the hospital setting, and others use beds dispersed throughout the hospital; some use both. Hospice services are delivered by an interdisciplinary team. All patients enrolled in hospice care have a supervising physician who authorizes the medical plan of care. On a daily basis, the hospice field teams may consist of registered nurse case managers, certified nursing assistants, social workers, chaplains, and volunteers. After a physician certifies that a patient is hospice-eligible, that physician may choose not to retain responsibilities for the patient and instead transfer care to the medical director or another physician in the hospice facility. Although physicians may believe that they are acting in the best interest of the patient, this transition may make the patient and family feel that they have been abandoned. When a patient is receiving hospice care, the patient and surrogates agree that the goal is comfort care and that any services the hospice is expected to pay for must have prior approval of the hospice. If the hospice authorizes transfer to an ED for care, the hospice will usually cover all ED services. If a patient unilaterally decides to seek emergency services without partnering with the hospice, the patient may be at risk of losing hospice services because the hospice agency is the care plan manager.

Election of hospice care is not synonymous with "do not treat." Patients receiving hospice care frequently are treated for infections, receive artificial nutrition and hydration, undergo palliative invasive interventions aimed at improving quality of life, or receive palliative disease-directed therapy (eg, chemotherapy, radiation, home vasopressors, transfusion). These interventions need to be assessed and recommended based on the goals of care assessment. If not available to the hospice directly, arrangements can often be made under contractual relationship for the care to be provided. It does require that the hospice agency be involved in any changes to the care plan. Palliative care consultants may assist in negotiating goals of care or coordinating care.

Evaluation and Management of the Patient Enrolled in Hospice Care

Patients enrolled in hospice care may present to the ED for a variety of reasons, including panic regarding decline, uncontrolled symptoms, inability or lack of the hospice agency to respond to

BOX e9.3

Palliative Medical Treatment Options to Enhance Quality of Life

Pain control
Control of fluid and electrolyte imbalances
Nausea, vomiting, and constipation management
Radiation therapy for bone pain, cord compression, or hemorrhage from tumors
Drainage tubes for malignant effusions or obstructions
Treatment of intercurrent infections
Management of incontinence
Supplemental oxygen
Anxiolytics, antidepressants, and appetite stimulants, when appropriate

needs, desire by the patient or family to seek additional opinions regarding care, and concern regarding the care provided by the hospice agency (often a concern regarding the use of medications).[45] An ED visit does not mean that the patient no longer desires hospice care.[46] Although patients and families are instructed to call hospice before going to the hospital, this does not always occur. Patients and caregivers might tell emergency clinicians that they do not understand hospice care or may express concerns that the hospice agency is not providing enough intervention. It can be difficult for some patients and families to accept the comfort care philosophy of hospice; hospice care may be equated with giving up, and patients and caregivers may fear that they will die quickly if enrolled.[47] Despite patient or caregiver perceptions, hospice services may be able to meet their evolving needs, including antibiotics, artificial nutrition, hydration, arrangement of palliative procedures, and palliative radiation or cancer-directed therapy. Box e9.3 outlines the steps for evaluation of the hospice patient who presents to the ED.

Hospice Referral From the Emergency Department

Patients with a prognosis for death within 6 months or less if the disease runs its usual course, whose goals of care have been assessed to be comfort-oriented in nature, and in collaboration with the patient's treating physician, should be considered for referral to hospice from the ED. Because of the 24/7 nature of hospice care, all hospice agencies typically have on-call staff that can be reached at all hours; many of them can respond to the needs of the ED for emergent admissions. For some patients and families, the ability to avoid a regular hospital admission and its associated risk of a hospital death can be very meaningful. Increasingly, hospices have hospital-based services that are open to ED admission.[48,49] Steps for referral to hospice care for patients who present to the ED who have not been previously enrolled in hospice care are suggested in Boxes e9.4 and e9.5.

BOX e9.4

Management of Patients Receiving Hospice Care Who Present to the Emergency Department

1. Notify hospice staff as soon as possible. Under the Medicare Hospice Benefit, hospice agencies are legally and financially responsible for the patient's plan of care and all medical costs related to the terminal illness.
2. Determine the trigger for the ED visit, paying attention not only to the distressing signs and symptoms but also the emotional and psychosocial issues. Involve social services and chaplaincy personnel early if needs are identified. Contact the palliative care team for consultative advice if needed.
3. Treat distressing symptoms.
4. If deterioration is imminent and rapid decisions are needed regarding the use of life-sustaining treatments (eg, intubation for respiratory failure), a focused discussion around goals of care should occur in the ED.
5. If the patient is actively dying provide symptom management and spiritual (eg, call the cleric or lay representative) and social support.
6. Laboratory and diagnostic tests should be limited or withheld until discussion with the patient's hospice care team. Testing should be based on patient-defined goals of care. Generally, low-burden, noninvasive methods that may reveal reversible pathology or clarify prognosis should be used first.
7. Therapeutic modalities should be based on patient-defined goals of care rather than automatic ED indications (eg, antibiotics for pneumonia should only be used if they meet a patient- or surrogate-defined goal of care).
8. Disposition should be planned after discussion with hospice staff based on the patient's goals. Returning home or a direct admission to an inpatient hospice facility may be the best disposition, rather than hospital admission. At times, hospices can arrange 24-hour professional support in the home for patients with difficult to manage symptoms who wish to remain home.
9. Notify the inpatient palliative care service if the patient is to be admitted to the hospital. Hospice agencies may revoke a patient's enrollment in hospice care if care goals have changed or may continue a patient under hospice care during an admission for palliation.

Adapted from Lamba S, Quest TE, Weissman DE: Emergency department management of hospice patients #246. J Palliat Med 14:1345–1346, 2011.

KEY CONCEPTS

- Palliative care is a physical, spiritual, psychological, and social support provided to patients and families at any stage of serious illness.
- Palliative care teams are specialized interdisciplinary teams that should be involved early in the course of illness.
- Hospice care is a care system for patients and families with a prognosis of 6 months or less if the disease runs its usual course; referral from the emergency department (ED) may be indicated.
- Patients at the end of life general follow one of four terminal illness trajectories: sudden death, organ failure, cancer, or frailty.
- Functional status is a strong predictor of decline and progression to death in patients with advanced illness.
- Goals of care conversations that outline patient and family hopes and expectations of interventions should be carried out.
- Emergency clinicians should make recommendations for care plans, interventions, and treatment courses based on prognosis, goals of care, and expected benefit to meet the identified goals of care.
- Key communication skills include breaking bad news, death disclosure, and assessment of goals of care.
- Interpretation of an existing advance care plan or receipt of a prehospital order (eg, POLST— ***P***hysician ***O***rders for ***L***ife-***S***ustaining ***T***herapy) should factor into ED treatment plans in the context of the patient's illness trajectory.
- Advance care planning may occur in the ED in the form of goals of care assessment followed by recommendations and orders placed by the emergency clinician to implement the plan.
- Symptom management is critical at the end of life; common symptoms are dyspnea, pain, delirium and agitation, and secretion management.

BOX e9.5

Initiation of a Hospice Referral From the Emergency Department

1. Assess Medicare Hospice Benefit eligibility.
2. Discuss hospice as a disposition plan with the patient's physician. Contact the patient's personal physician—discuss the current condition, prognosis, and prior goals of care conversations. If you are considering hospice care, ask if the physician is willing to be the following physician for hospice services.
3. Assess whether the patient's goals are consistent with hospice care. Generally, this means a patient wants medical treatments and other support aimed at alleviating symptoms and maintaining quality of life, without life prolongation.
4. Introduce hospice to the patient and family or surrogates.
   - Discuss the core aspects of hospice care and how these features can help the patient and family (eg, 24/7 on-call assistance, home visits for symptom management, coordinated care with the patient's physician, emotional and spiritual or religious support).
   - Address concerns and clarify misconceptions.
   - Phrase your recommendation for hospice care in positive language, grounded in the patient's own care goals: "I think the best way to help you stay at home, avoid the hospital, and stay as fit as possible for whatever time you have left is to receive hospice care at your home…."
   - Discuss the location of hospice care. Usually, this is the patient's residence, such as a private home or long-term care facility. Direct admissions to hospice facilities can occur depending on bed availability and ability of local hospice agencies to arrange an immediate, direct facility admission. This is not available in all communities and requires a discussion with the hospice agency.
5. Make a referral and write orders.

Call a hospice agency; anticipate these questions:

- What is the terminal illness? Who will be the following physician (step 2)?
- What equipment will be needed immediately (eg, home oxygen)? Is there a caregiver at home?
- Code status (patients cannot be denied hospice enrollment if full code; however, the hospice team will need to know if code status needs to be addressed further).

Questions you need to ask the hospice agency include the following:

- How soon can you make an intake visit to the patient's home? Can you visit the patient immediately, even in the ED? (This is available in some communities.)
- How should I coordinate filling of new prescriptions I want the patient to have?

Examples of ED-initiated hospice referral orders:

- Evaluate and admit or enroll in hospice care.
- Terminal diagnosis: _____.
- Expected prognosis—terminal illness with less than 6-month survival likely if disease runs its normal expected course (or be more specific, if indicated).
- Physician who will follow patient: _____.

6. Ensure patient or surrogate understanding and secure the plan. Communicate the plan following ED discharge; provide the name and contact number for the hospice agency.
7. What if hospice enrollment is appropriate, but cannot be arranged in a timely manner? If the patient can be cared for at home safely for 1–2 days without extra services, send her or him home with appropriate prescriptions and care instructions. In most communities, patients can be enrolled in hospice care within 24–48 hours, even on weekends. If they cannot be cared for safely at home, observation versus inpatient admission is likely necessary until a safe discharge plan can be established.

Adapted from Lamba S, Quest TE, Weissman DE: Initiating a hospice referral from the emergency department #247. J Palliat Med 14:1346–1347, 2011.

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CHAPTER e9: QUESTIONS & ANSWERS

e9.1. Which of the following is expected to be the least likely cause of death for adults in the United States?
- **A.** Cancer
- **B.** Cardiovascular disease
- **C.** Heart disease
- **D.** Trauma

Answer: D. According to the Center for Disease Control, accidents are the 3rd leading cause of death in the United States. http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

e9.2. In a nondeath disclosure setting, deliverance of bad news should start with which of the following approaches?
- **A.** Allowing the patient to react to the news
- **B.** Asking the patient if he or she wants to know
- **C.** Making sure you keep the conversation going to provide comfort and thereby dull the emotional impact of the news
- **D.** Your knowledgeable of the complete medical implications and ramifications of the news

Answer: B. Respectful disclosure of breaking difficult news includes assessing the readiness and willingness of the patient to receive the news. Oncologist. 2000;5(4):302–11

e9.3. Mr. Jones is a 54-year -old man currently receiving hospice care at home for advanced colon cancer. His wife calls 911 when he becomes unresponsive. On presentation to the ED, his vital signs are blood pressure, 60/40 mm Hg; heart rate, 140 beats/min; temperature, 39.6°C (103.3°F); respiratory rate, 12 breaths/min. He is moaning with facial grimace. His wife, who is the legal decision maker, is at the bedside. Which of the following represents the best course of action?
- **A.** Initiate sepsis protocol, begin treatment for pain, and call the palliative care service.
- **B.** Initiate sepsis protocol, page the hospice nurse, and speak to his wife regarding goals of care.
- **C.** Page the hospice nurse, begin treatment for pain, and speak to his wife regarding the goals of care.
- **D.** Page the hospice nurse and speak to his wife regarding the goals of care.

Answer: C. Under the hospice benefit, the hospice agency is the care manager. The patient has lost capacity and his wife is his decision maker and she should be consulted regarding goals. Pain and non-pain symptoms should be addressed while other actions are being taken.

e9.4. Mrs. Smith is a 68 year-old woman with advanced heart failure who presents to the emergency department in cardiogenic shock with multiple previous admissions that state that she is currently optimized with all available therapies. You would like to initiate hospice care from the emergency department. Which of the following do you do next?
- **A.** Call the hospice liaison on call for the ED to speak with her family regarding their options.
- **B.** Call the palliative care service to discuss hospice care with the patient and her family.
- **C.** Conduct a goals of care discussion with the patient and her amily.
- **D.** Discuss the benefits of hospice care that would allow the patient to stay at home with her family.

Answer: C. Central to the discussion of hospice care is an assessment of the goals of care focused on care that addresses the distress of the illness and not the reversal of the primary illness.

e9.5. In performing a death disclosure, which of the following statements represents best practice when communicating news of death?
- **A.** "Your loved one didn't make it."
- **B.** "Your loved one has died."
- **C.** "Your loved one has gone to a better place."
- **D.** "Your loved one has passed on."

Answer: B. It is not recommended to use euphemism or unclear statements to communicate news of death as this can cause confusion and ambiguity for the receiver of the news.

e9.6. Mr. Stone is a 27 year-old man with glioblastoma multiforme. He has completed radiation and is on oral chemotherapy. Over the last week, he has become progressively weaker and is now in bed. He is no longer speaking and is dropping things. He is taking sips of clear liquids and coughs after swallowing. Which of the following is the strongest predictor of his death?
- **A.** Aspiration risk
- **B.** CT scan that shows progression
- **C.** Deterioration of speech
- **D.** Functional status

Answer: D.

e9.7. Mr. Samuels is a 46 year-old man with severe breathlessness and anxiety due to advanced chronic obstructive pulmonary disease. His vital signs are temperature, 36.8°C (98.2°F); blood pressure, 110/60 mm Hg; heart rate, 115 beats/min; respiratory rate, 34 breaths/min; oxygen saturation, 98% on room air. He is visibly anxious and reports dizziness and dyspnea. Which of the following is the best initial treatment?

A. IV fluids
B. Lorazepam
C. Morphine
D. Oxygen

Answer: C. In the absence of hypoxia, morphine has been shown to relieve the sensation of breathlessness. Benzodiazepines have not been shown to relieve breathlessness and may increase side effects.

CHAPTER e10

Bioethics*

Kenneth V. Iserson | Carlton E. Heine

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KEY CONCEPTS

- Bioethics is a method of using values and moral principles to come to defendable decisions for ethical dilemmas.
- Ethical dilemmas arise from conflicts between multiple good options or multiple bad options, not between good and bad choices.
- Individual rights come from another's duty to act.
- Values come from a variety of sources: community, culture, religion, and family.
- The values driving medical decisions should be the patient's values.
- Basic ethical principles include autonomy, beneficence, nonmaleficence, justice, and confidentiality.
- In emergency medicine, caregiver safety is an important value.
- A rapid ethical decision tool: Is there an established precedent? If not, apply the following three tests: the impartiality test, the universality test, and the interpersonal justifiability test.
- Consent requires decision-making capacity or appropriate surrogate decision makers.
- Futility, although an appropriate reason for withholding nonproductive interventions, is not an excuse for withholding compassionate care.
- There are many areas of emergency medicine with unique ethical issues, such as resuscitation research, disaster response, morality of triage, response to high-risk situations, and wilderness medicine.

CHAPTER e10

Bioethics

Kenneth V. Iserson | Carlton E. Heine

PRINCIPLES

The medical care we provide today bears little resemblance to what was available when the first edition of this book was published. What has not advanced as far or as fast is our system for deciding, in a moral and fair way, what treatments to provide. Scientific development has outpaced our social and ethical framework and often leaves clinicians struggling with moral dilemmas about the appropriateness of tests and procedures. This chapter is an introduction to our current tools for helping emergency clinicians approach ethical, rather than medical, dilemmas.

Definitions

Bioethics, a subset of ethics, is the application of values and moral rules to find reasoned and defensible solutions to actual or anticipated moral dilemmas facing clinicians. The moral precepts that underpin ethical decisions are derived from a variety of sources, including individual, cultural, and community value systems. Unlike the law, which is relatively rigid and can lag years or even decades behind modern developments, particularly in the case of scientific and medical issues, bioethical constructs allow a greater flexibility in decision-making. Emergency clinicians are often called on to identify a patient's personal, cultural, religious, or community values and to balance these values with their own personal and professional ethos. A working knowledge of bioethics greatly enhances the emergency clinician's ability to make reasonable, ethical decisions in the limited time frame common to the practice of emergency medicine.

In contrast to professional etiquette, which relates to standards governing the relationships and interactions between providers, bioethics deals with relationships between providers and patients, providers and society, and society and patients. Issues within the realm of professional etiquette include billing, referrals, advertising, competition, conflicts of interest, professional courtesy, and employment and supervision of auxiliary personnel. These are quite different from bioethics' concerns of basic moral values and patient-centered issues. Although the two areas occasionally overlap, each relies on different standards, values, and problem-solving methods.

Ethics and Emergency Medicine

In emergency medicine, the focus is inevitably on the inherent "medical" nature of each case; therefore, it should come as no surprise that ethical dilemmas often go unrecognized. Emergency clinicians may also misperceive ethics as embodying the dictates of secular or religious law or as a discipline that describes irresolvable issues.

This chapter addresses a number of ethical issues in emergency medicine. What follows are brief discussions of the relation of law to bioethics; bioethical values and principles; moral imperatives in emergency medicine; ethical oaths and codes; applying bioethics to clinical situations; bioethical dilemmas in emergency medicine; a rapid decision-making model for ethical dilemmas; advance directives; the relationship between consent, decision-making capacity, and surrogate decision makers; ethical issues in resuscitation; and ethical issues in public policy.

BIOETHICS AND THE LAW

Basic Considerations

Emergency clinicians often look to the law for answers to thorny dilemmas. Yet, except in the rare cases of "black-letter law," wherein specific actions are delineated, these issues are best served by turning to bioethical reasoning and using bioethics consultations. It is said that good ethics makes good law but that good law does not necessarily make good ethics. Societal values are incorporated both within the law and within ethical principles and decisions. Laws are rules of conduct established by legislatures, administrative agencies, courts, or other governing bodies. They often vary from locale to locale and are enforceable only in the jurisdiction where they prevail. By contrast, ethics is more universal within a culture, incorporating the broad values and beliefs of correct conduct. The primary differences between law and bioethics are shown in Table e10.1.

Modern bioethics developed because the law often has remained silent or inconsistent on matters vital to the biomedical community. The rapid increase in biotechnology, the failure of both the legal system and legislatures to deal with new and pressing issues, and the increasing liability crisis drove the medical community to seek answers to the difficult questions that practitioners have to work through on a daily basis.

Bioethical principles are not static and may evolve as societies change. The same evolution occurs within the law. For example, elective abortion, once illegal in most United States jurisdictions, is now legal in most circumstances and jurisdictions. Likewise, not all basic ethical principles have universal support, just as the values implicit in many legal changes have divided United States society.

Rights and Duties

Without a duty to act, there can be no rights. Both a moral and a logical connection exist between the rights and the duties of individuals; one cannot exist in the absence of the other. In general, a duty is an action required by the rights of others, the law, a higher authority, or one's conscience. This obligation to act can be based on an individual's personal values, professional position, or other commitments. For the physician, this duty to act is a role responsibility, at least specifically as a physician and possibly at all times. The role-duty link occurs whenever a person occupies a distinctive place or office in a social organization, to which specific duties are attached to provide for the welfare of others or to advance in some specific way the aims or purposes of the organization. In this circumstance, performance is predicated not on a guarantee of compensation but rather on a concern for

TABLE e10.1

Relationship Between Law and Bioethics

BIOETHICS	FUNCTION OR PRINCIPLE	LAW
✓	Case based (casuistic)	✓
✓	Has existed since ancient times	✓
✓	Changes over time	✓
✓	Strives for consistency	✓
✓	Incorporates societal values	✓
✓	Basis for health care policies	✓
	Some unchangeable directives	✓
	Formal rules for process	✓
	Adversarial	✓
✓	Relies heavily on individual values	
✓	Interpretable by medical personnel	
✓	Ability to respond rapidly to changing environment	

Modified from Iserson KV: Ethical principles—emergency medicine. In Schears RM, Marco CA, Mattu A, editors: Emergency medicine clinics of North America, Philadelphia, 2006, Elsevier/Saunders.

another person's welfare. The emergency clinician has not only such a moral duty but, because of the Emergency Medical Treatment and Active Labor Act (EMTALA), also a legal duty.

Significant overlap can exist between legal and ethical decision-making. Frequently, there is concurrence on basic issues. On occasion, clarity within the law can lead to clearer thinking in bioethics, and vice versa. Both law and bioethics, for example, use the term *rights,* as in "patients' rights" and "the right to die." This term, often used to advance an ethical argument about medical care, frequently is misunderstood or applied erroneously. A legal right is a demand that a person can make on another person, embodied in *in personam* rights, or against the state for recognition and enforcement of this demand. Most rights involved in bioethical discussions are *in rem* rights. These most often are negative rights, because they entail someone else's duty to refrain from doing something. A common source of ethical conflict is between "active rights," the right to act or not act as one chooses, and "passive rights," the right to not be acted on by others in certain ways.

VALUES

Values are the standards by which human behavior is judged. Values are learned, usually at an early age, through indoctrination into the birth culture, from observing behavior, and through secular (including professional) and religious education. Although many of these learned values overlap, each source often claims moral superiority over the others, whether the values are generic and cultural, legal norms, religious and philosophical traditions, or professional principles. Societal institutions incorporate and promulgate values, often attempting to solidify old values even in a changing society. In a pluralistic society, clinicians treat people with multiple and differing value systems, so they must be sensitive to alternative beliefs and traditions.

This section discusses the role of religious, patient, institutional, and professional values, including professional oaths and codes specific to emergency medicine.

BOX e10.1

Commonly Accepted Moral Rules

Moral rules govern actions on the basis of ethics and codes of conduct. These can justifiably be enforced and their violation punished. Although none of these rules is absolute, they all require one not to cause evil. Somewhat paradoxically, however, they may not require either preventing evil or doing good.

1. Do not kill.
2. Do not cause pain.
3. Do not disable.
4. Do not deprive of freedom.
5. Do not deprive of pleasure.
6. Do not deceive.
7. Keep your promise.
8. Do not cheat.
9. Obey the law.
10. Do your duty.

Modified from Gert B: Morality: a new justification of the moral rules. Oxford, 1988, Oxford University Press.

Society's Values

Organized religions see themselves as keepers of society's values. Even though various religions may appear dissimilar, most hold the golden rule, "Do unto others as you would have them do unto you," as a basic tenet. Other moral rules that are common to most religions are listed in Box e10.1. Problems surface in trying to apply religion-based rules to specific bioethical situations. For example, although "Do not kill" generally is accepted, the activities that constitute killing, active or passive euthanasia, or merely reasonable medical care vary with the interpretation of the world's religions as they do with the interpretations of various philosophers. As members of a democracy with significant populations practicing a number of religions, emergency clinicians should behave in a manner consistent with each patient's values. The most basic underlying question is: What is the patient's desired outcome for medical care?

Not only religious but also family, cultural, and other values contribute to patients' medical care decisions. Without asking, it is impossible to know what decision a specific person would make. An important point is that religion influences modern secular bioethics, which uses many religion-originated decision-making methods, arguments, and ideals. In addition, clinicians' personal spirituality may allow them to relate better to patients and families in crisis.

Good Versus Evil

The terms *good* and *evil* can be used to illustrate a stark dichotomy in ethical thought and values. The following is a current set of definitions that may help the physician find solutions to ethical problems. *Good* can be defined as what no rational person will avoid without a reason. Examples are freedom, pleasure, health, wealth, and knowledge. *Evil* can be defined as what all rational persons desire to avoid for themselves and for others they care about. Examples are untimely death, pain, disability, and loss of freedom or pleasure. Rational persons with deeply held religious beliefs may, for example, refuse a blood transfusion, choosing a likelihood of death over the permanent pain and anguish that they believe would ensue if they should violate their religious injunction. Conflicts that can be described as being between good and evil are not ethical dilemmas but rather moral temptations. Ethical dilemmas arise from conflicts between multiple good or multiple bad options.

Patient Values and Ethical Decisions

A key to making bedside ethical decisions is knowing the patient's values. Many people cannot answer the question: What are your values? However, physicians can get an operational answer by asking patients what they see as their goal of medical therapy and why they want specific interventions. The responses represent concrete expressions of patient values. In patients who are too young or are deemed incompetent to express their values, it may be necessary for physicians either to make general assumptions about what a normal person would want in a specific situation or to rely on surrogate decision-making. But with patients who are able to reason and communicate, care should be taken to discover what they hold as their own, uncoerced values.

Although each individual is entitled and perhaps even required to have a personal system of values, certain values have become generally accepted by the medical community, the courts, legislatures, and society at large. Autonomy and individual dignity, for example, are two such values; they have been considered fundamental and often are given overriding importance. Although some groups disagree about each of these values, this dissension has not affected their application to medical care.

BOX e10.2

Commonly Accepted Societal and Bioethical Values

Autonomy: Self-determination. A person's ability to make personal decisions, including those affecting personal medical care. Autonomy is the opposite of paternalism.
Beneficence: Doing good. A duty to confer benefits. Production of benefit.
Confidentiality: The presumption that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission.
Distributive justice: Fairness in the allocation of resources and obligations. This value is the basis of and is incorporated into society-wide health care policies.
Nonmaleficence: Not doing harm, prevention of harm, and removal of harmful conditions.
Personal integrity: Adhering to one's own reasoned and defensible set of values and moral standards.

FUNDAMENTAL BIOETHICAL PRINCIPLES

Nonmaleficence and Autonomy

The basic tenet that all medical students are taught is nonmaleficence: "First, do no harm." This credo, often stated in the Latin, *primum non nocere,* derives from the recognition that physicians can harm as well as help. With the physician's fallibility recognized, patient autonomy is and has been for several decades the overriding professional and societal bioethical value. Autonomy recognizes an adult person's right to accept or to reject recommendations for medical care, even to the extent of refusing all care, if that person has appropriate decision-making capacity. It is the counterweight to the medical profession's long-practiced paternalism (or parentalism), wherein the practitioner determines what is "good" for the patient, regardless of whether the patient agrees. Coupled with paternalism is coercion, the threat or use of violence to influence behavior or choice. The august figure in white combined with implied or explicit threats remains a potent force for counteracting patients' wishes. The thrust of modern bioethics is to respect patients by honoring their autonomy (Box e10.2).

Beneficence

At the patient's bedside, beneficence (doing good) and confidentiality (holding information in confidence) have been long-held and nearly universal tenets of the medical profession. Similarly, personal integrity (the adherence to one's own moral and professional standards) is basic to thinking and acting ethically.

Justice

The concept of comparative or distributive justice suggests that a society's comparable individuals and groups should share similarly in the society's benefits and burdens. Many society-wide decisions affecting thoughts and actions about the allocation of limited health care resources are based on this principle. Although it is important for physicians to be careful stewards of health care resources to maximize benefits, it is not appropriate for clinicians to limit or to terminate care on a case-by-case basis as an extrapolation of the perceived need to limit health care expenditures. Distributive justice is a social policy concept rather than a clinical model for individual physician/patient decisions.

Truth-Telling

Personal integrity involves adhering to one's own reasoned and defensible set of values and moral standards and is basic to ethical thought and action. Integrity includes a controversial value within the medical community: truth-telling. Some people think that the patient has the right to know the truth, no matter what the circumstances, and have championed absolute honesty. Yet many of these same people, when patients themselves, have been appalled by their physician's lack of sensitivity in relating unfavorable medical news. In this context, being honest does not mean being brutal; truth is best tempered with a modicum of compassion.

Physicians accept a lack of truth-telling, depending on the circumstances. When patient harm may result from failing to disclose the truth, such as happened in the infamous Tuskegee experiments, in which treatment was knowingly withheld from black men with syphilis, it is not only immoral but also probably illegal to withhold the information. Likewise, when failure to disclose information is strictly for the clinician's benefit, such as not telling a patient about a dismal prognosis or a medical error, the clinician's behavior suggests serious ethical and legal deficits. The issues become murkier when truth-telling, or lack thereof, involves a third party, such as a sex partner who has been exposed to an infectious disease.

Confidentiality Versus Privacy

Stemming at least from the time of Hippocrates, confidentiality is the presumption that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission. Health care workers have an obligation (duty) to maintain patient confidentiality. On occasion, the law, especially public health statutes, may conflict with this principle, because they require physicians to report specific diseases, injuries and injury mechanisms, and deaths. The Health Insurance Portability and Accountability Act (HIPPA) of 1996, a United States federal law designed to protect patient information, however, takes the principle of confidentiality to the extreme, resulting, paradoxically, in greater difficulty in obtaining crucial information needed to treat emergency department (ED) patients.

Privacy, which is often confused with confidentiality, is the right of patients to sufficient physical and auditory isolation so that they cannot be seen or heard by others during interactions

with medical personnel. ED overcrowding, patient and staff safety issues, and ED design limit patient privacy in many cases.

The increasing use of telemedicine to render advice and to guide procedures at remote sites also places a strain on both patient privacy and confidentiality. Suggested ethical guidelines for such practices can facilitate the use of these new technologies without sacrificing either patient rights or physician duties.

Another recent development has been filming of ED patients for public viewing. Such filming, whether for medical records, education, peer review, or "reality television," encroaches on ED patients' reasonable expectation of privacy and confidentiality, because the recording can easily be distributed or misused. Although good reasons exist to allow such filming with patient acquiescence, the standard is now to abstain from such filming for commercial purposes and to require patient or surrogate consent for educational purposes.

MEDICAL AND MORAL IMPERATIVES IN EMERGENCY MEDICINE

Professional Values

Emergency clinicians, in both the out-of-hospital and ED environments, operate with four imperatives: (1) to save lives when possible, (2) to relieve pain and suffering, (3) to comfort patients and families, and (4) to protect staff and patients from injury. All but the last of these are common imperatives of most other clinicians as well, although saving lives may occur more often and more dramatically in emergency medicine settings.

Safety: A Unique Value

The last imperative, safety, is nearly unique to emergency medicine. In both the out-of-hospital and ED settings, clinicians often encounter dangerous situations in which the environment, the patient, a friend, or a family member poses a threat. Violence against emergency care workers is well documented and unfortunately common. The ED routinely deals with psychotic and intoxicated patients and patients injured in human-on-human attacks, and those involved are often under extreme stress. Although most try to accommodate basic patient rights, clinicians' priority must be their own safety and the safety of their co-workers. This priority does not imply that clinicians should ignore patient safety but only that they should first ensure their own safety if they or their colleagues are at risk.

CODIFYING PROFESSIONAL VALUES: ETHICAL OATHS AND CODES

Conflicting Principles

In the abstract, bioethical principles often appear simple. However, clinicians adhere not only to basic bioethical principles but also, at least tacitly, to a number of professional, religious, and social organizations' ethical oaths, codes, and statements. This complexity can create a confusing array of potentially conflicting bioethical imperatives. Because bioethical principles seem to be neither universal nor universally applied, the principles that are most patient-centered normally hold sway.

Organizational and Institutional Values

Institutions, including health care facilities and professional organizations, have their own value systems. Health care facilities, although relatively well standardized under the requirements of regulatory bodies and government agencies, often have specific value-related missions. Religiously oriented or affiliated institutions may be the most obvious of these, but charitable, for-profit, and academic institutions also have specific role-related values. The values of professional organizations often are set forth in their ethical codes.

Professional Codes

Through the years, the medical profession has codified its ethics more rigorously than any other professional group, incorporating many standard bioethics principles into its ethical codes and oaths. For generations, the existing part of the Hippocratic Oath set the ethical standard for the medical profession. Yet its precepts clash with modern bioethical thinking, and many subsequent professional codes have included what may best be termed *economic guidelines* and *professional etiquette,* along with ethical precepts. Emergency clinician professional values have been incorporated into organization codes, such as the American College of Emergency Physicians' (ACEP) Code of Ethics, and into a more personal oath developed by the Society for Academic Emergency Medicine.

Most modern ethical codes do not require a higher level of duty or commitment for members than the same basic moral behavior that is expected of society at large. In fact, many of the ethical issues that would seem to be important to medical specialties usually are not addressed in their codes. Even when topics of inter-professional interactions are excluded, existing medical professional codes differ markedly (Table e10.2). All, however, try to give a "bottom line"—that is, minimally acceptable—course of action.

APPLYING BIOETHICS

Emergency Clinician/Patient Relationship

The emergency clinician has a markedly different relationship with patients from that of other health practitioners, especially those providing primary care (Table e10.3). Emergency clinicians care for patients who are unfamiliar to them and to the institution. Practitioners who either know their patients or who care for them in less acute settings often have the time and the mechanisms to make sound ethical decisions, but emergency clinicians have more limited options. A suggested method for rapid, ethical decision-making in the ED setting is outlined in Figure e10.1 and discussed in a later section.

Recognizing Ethical Problems

Although physicians like to reduce all clinical situations to "medical problems," today's increasingly complex medical environment often produces problems that are inexorably intertwined with fundamental bioethical dilemmas. Some are obvious, but many are more difficult to recognize.

Prioritizing Conflicting Principles

Once such dilemmas are recognized, applying bioethical principles to clinical situations can be confusing. When two or more seemingly equivalent principles or values seem to compel different actions, a bioethical dilemma exists. This situation is often described as being "damned if you do and damned if you don't," in which any potential action appears, on first reflection, to be an option between two seemingly equivalent goods or evils. In the following real case, taken from the book *Ethics in Emergency Medicine,* the attending physician can be said to be on the horns of a dilemma (involving two prickly but seemingly equal choices): although only two options for action may be available, both options involve a number of conflicting bioethical principles.[1]

TABLE e10.2

Comparison of Six Ethical Codes for Physician

PRINCIPLE OR CONCEPT	SOCIETY FOR ACADEMIC EMERGENCY MEDICINE	AMERICAN COLLEGE OF EMERGENCY PHYSICIANS	EMERGENCY MEDICINE RESIDENTS' ASSOCIATION	AMERICAN MEDICAL ASSOCIATION	AMERICAN OSTEOPATHIC ASSOCIATION	HIPPOCRATIC OATH
Protect patient confidentiality		x	x	x	x	x
Maintain professional expertise	x	x	x	x	x	x
Committed to serve humanity	x	x	x	x	x	
Patient welfare primary concern	x	x	x	x		x
Considerate to patients, colleagues	x	x	x	x		x
Respect human dignity	x	x	x	x		x
Safeguard public health	x	x	x	x		x
Protect vulnerable populations	x	x		x	x	x
Advance professional ideals	x	x	x	x		x
Honesty		x	x	x		
Report incompetent, dishonest, impaired physicians		x	x	x		
Moral sensitivity	x	x		x		
Obtain necessary consultation				x	x	x
Altruism in teaching	x					
Fairness to students, colleagues				x		x
Obey, respect the law			x	x	x	
Prudent resource use	x	x				
Work to change laws for patient benefit				x	x	
Not abuse privileges	x					x
Respect for students	x					x
Choose whom to serve except in emergencies				x	x	
Ensure beneficial research by employing competence, impartiality, compassion	x					
No abortions						x
No euthanasia						x
Do not compromise clinical judgment for money			x			
Universal access to health care				x		
Preserve human life						x

Modified from Iserson KV: Ethical principles—emergency medicine. In Schears RM, Marco CA, Mattu A, editors: Emergency medicine clinics of North America, Philadelphia, 2006, Elsevier/Saunders.

Case Example: Conflicting Bioethical Principles

A 60-year-old man stabbed himself in the abdomen because of intractable pain from terminal pancreatic cancer, unrelieved by any medical therapy. A well-meaning friend, who happened to be in the house when the event occurred, called the paramedics, who brought him to the ED. Although the man will obviously bleed to death if he is not given aggressive care, neither the patient, who is still alert and oriented, nor his wife, who is present, wants any treatment other than pain control. A review of his chart confirms that his physicians are at a loss as to how to alleviate his pain and that he is expected to die within the next several weeks. The physician believes in respecting a patient's autonomy yet usually questions patients' decision-making capacity when they attempt suicide. Such patients' actions seem to raise the question of whether, in fact, they have a right or an ability to be autonomous. This physician also believes strongly in beneficence—helping those in need, relieving pain, and saving lives when possible. Beneficence suggests two alternative courses of action: palliative care or therapeutic intervention. Merely using analgesics and other comfort measures will abet a suicide; initiating medical and surgical interventions will prolong a dying process that the physician's colleagues have found to be unresponsive to even palliative treatment. Which value takes precedence: patient autonomy or beneficence? If beneficence predominates, should it be aimed toward relieving suffering, prolonging life, or a third option that

TABLE e10.3

Relative Differences Between Emergency Practice and Primary Care Practice

EMERGENCY DEPARTMENT SETTING	PRIMARY CARE SETTING
Patient often is brought in by ambulance, police, or family.	Patient chooses to enter medical care system.
Patient does not choose physician.	Patient chooses physician.
ED personnel should gain patient's trust.	Physicians and nurses already enjoy patient's confidence and trust.
ED personnel do not know the patient, family, and their values.	Physicians and nurses often already know the patient, family, and their values.
Patient experiences an acute change in health status.	Patient has chronic medical problems.
Anxiety, pain, alcohol, and altered mental status are common.	Anxiety, pain, alcohol, and altered mental status are less common.
Decisions are made quickly.	There is usually time for reflection and deliberation.
Physician makes decisions independently.	Physician has greater opportunity to consult with patient, family, other physicians, ethics committees, lawyers, courts, and ethicists.
Physician represents institution and medical staff.	Physician represents self or medical group.
Work environment is open and less controlled.	Work environment is private and controlled.
ED personnel frequently have a stressful work schedule.	Work schedule often is set or canceled by physician.

Modified from Sanders AB: Unique aspects of ethics in emergency medicine. In Iserson KV, Sanders AB, Mathieu D: Ethics in emergency medicine, ed 2, Tucson, AZ, 1995, Galen Press.
ED, Emergency department.

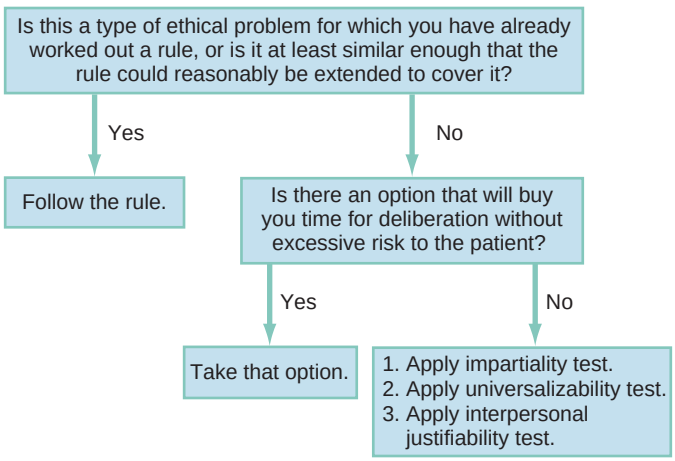

Fig. e10.1. A rapid approach to ethical problems in the emergency department (ED). (Modified from Iserson KV: An approach to ethical problems in emergency medicine. In Iserson KV, Sanders AB, Mathieu D: Ethics in emergency medicine, ed 2, Tucson, AZ, 1995, Galen Press.)

could include both? Bioethics deals with problems that are neither black nor white—only gray.

MEDICAL IMPERATIVES AND BIOETHICAL DILEMMAS

Clinicians have their own ethical values, as do professional organizations and health care institutions. Conscience clauses permit clinicians to "opt out" when they believe that they have a moral conflict with professionally, institutionally, or legally required actions. These conflicts, which may have a religious, philosophical, or practical basis, pose a barrier to use of the normal ethical decision-making algorithm. When such conflicts exist, it is morally and legally acceptable, within certain constraints, for the physician to follow a course of action based on his or her own value system. The constraint generally requires that timely and adequate medical care be provided for the patient, which may be particularly difficult to achieve in emergency medicine. When conflicts over values exist, however, it is essential for the practitioner to recognize the patient's identity, dignity, and autonomy to avoid the error of blindly imposing personal values on another.

Professional Value Conflicts

The imperative to save lives causes the most conflict between emergency clinicians and other clinicians. Emergency clinicians recognize that some of the intubations and resuscitations that they perform will be unwanted by patients or surrogates. Nearly all emergency clinicians have on occasion been berated by an irate intensivist or private practitioner for resuscitating a patient "who should not have been resuscitated." Nevertheless, the lifesaving imperative begins when the ambulance is called.

One classic dilemma is that posed by the exsanguinating adult patient, awake and still with medical decision-making capacity, who explicitly states a refusal to accept any blood or blood products based on religious beliefs. The physician, with a professional duty and moral commitment to preserve life, does not agree with the patient's decision. Yet society (through the benchmark of court decisions) has repeatedly sided with the patient. In this case, the patient's autonomy and right to practice his or her religion are recognized as the overriding values. The case becomes less clear when the patient does not have decision-making capacity, is a minor, or appears to be under external pressure to make a life-threatening decision.

Other examples of ethical problems and conflicts in emergency medical care include uncertainty about resuscitation efforts, especially when patients and families may not want such efforts; teaching, particularly in critical situations or using procedures performed on the newly deceased; emergency medical service (EMS) control, when administrative rules and good patient care conflict; helping others when one's own life may be placed at risk; and patient access, such as limited financial and personnel resources in the face of obvious patient need. Even if these problems do not fit into the classic form of a dilemma, they may be recognized as bioethical problems, because they require the clinician to make a choice between two (or more) accepted values.

RAPID ETHICAL DECISION-MAKING MODEL

The rapid ethical decision-making method of ethical case analysis, described in Figure e10.1, is designed as a way of avoiding an ethically incorrect course of action for the emergency clinician in need of a fast answer to an ethical dilemma. A decision based on a known precedent—the first step—is the most productive way to use this method. However, such decision-making requires advance planning, in-depth reading, and thought regarding ethical

problems. Just as with the indications for any emergency procedure, emergency clinicians should at the very least be prepared with a course of action for the most common ethical dilemmas they may face in the ED.

Even the prepared clinician, however, can encounter cases without relevant known precedents. With no precedent to rely on and no way to "buy time," the practitioner should select a possible course of action and test it for ethical validity. In such instances, three tests—the impartiality test, the universalizability test, and the interpersonal justifiability test—can be used. The *impartiality test* asks whether the practitioner would accept this action if he or she were in the patient's place. In essence, this is a form of the golden rule. The *universalizability test* asks whether the practitioner would be comfortable having all practitioners perform this action in all relevantly similar circumstances. This involves generalizing the action to all colleagues and then asking whether a rule for the contemplated behavior is reasonable. The *interpersonal justifiability test* asks whether the practitioner can supply good reasons to others for the action. Will peers, superiors, or the public be satisfied with the answers? If the answer to the question posed in each of the three tests is affirmative, the practitioner has identified a reasonable probability that the proposed action falls within the scope of ethically acceptable actions.

ADVANCE DIRECTIVES

The ethical principal of patient autonomy is the foundation for a range of documents that outline what care a patient wishes to receive if he or she is no longer able or competent to directly communicate those values. The term *advance directive* describes several types of legal and quasi-legal documents. Advance directives usually are written to avoid prolongation of an inevitable, often painful or non-sentient dying process. However, they can also be used to instruct surrogates and the patient's medical team to "do everything," whenever possible. Advance directives include the living will, durable power of attorney for health care, prehospital advance directive (Box e10.3), and mental health advance directive. Do not attempt resuscitation (DNAR), do not hospitalize, and out-of-hospital DNAR orders are not considered to be advance directives but rather are physician orders, because they are not patient or surrogate initiated. All play a role in emergency medicine.

Advance directives, DNAR orders, and other end-of-life considerations are discussed in Chapter e9.

CONSENT, DECISION-MAKING CAPACITY, AND SURROGATE DECISION MAKERS

Respect for patients, the basis for patient autonomy, requires that adults consent before undergoing medical interventions. To give consent, they must retain decision-making capacity. When patients cannot make their own health care decisions, others need to make such decisions for them. In such situations, three questions arise:

- What does "consent" mean in the ED?
- How can clinicians determine when patients lack such capability?
- Who then makes the decision?

Consent

Patients can provide three forms of consent: presumed, implied, and informed. Many patients may provide all three types of consent at different times during a single ED visit. Because clinicians use all three types of consent in EDs, and all are ethically and legally valid, clarifying the differences between them is in order.

The concept of *presumed consent* most commonly applies when patients are informed of what will occur and they do not refuse treatment. They allow themselves to be rolled on a gurney to the radiology suite to have a urethral catheter placed, and they remain still while being sutured. The more dramatic ED scenario involving presumed consent is the arrival of moribund patients with grave, often unstable conditions for which a reasonable person would be expected to want treatment. In those cases, clinicians "presume" that rational patients would want treatment. A question that must be raised, however, is whether those patients would want interventions even in the absence of a reasonable chance for meaningful (from the patient's standpoint) survival. Futility often is discussed from the clinician's perspective (see the Futility section later in this chapter); whether patients would give consent in these circumstances raises the question from the more valid patient's perspective.

Implied consent is operative when patients actively cooperate with the procedure, such as when they extend the arm for phlebotomy or lift the blouse so that leads can be placed for electrocardiography. Working under presumed or implied consent does not signify absence of patients' concern about the procedure or its complications. Rather, patients may (1) believe they know enough about the procedure to permit it or to cooperate with it without further questioning, (2) be in a condition (eg, unconscious) in which they are unable to communicate, or (3) feel too afraid (eg, of the clinician or hospital authority) or uncomfortable (eg, because of a language barrier) to ask.

Informed consent assumes that a patient who has decision-making capacity (eg, has been given all pertinent facts about the risks and benefits of a particular procedure) understands the risks and benefits and voluntarily agrees to undergo the procedure. Even if a patient with decisional capacity does not ask about a complex or potentially dangerous procedure, the clinician is obligated to provide information about the associated risks and benefits, unless the patient specifically asks not to be told. In those cases, the patient should be asked if he or she would like a relative or friend present in the ED to be told. This person need not be the patient's surrogate but may later help explain what occurred to the patient.

Informed consent relates to both law and ethics. Respect for persons is the requirement's ethical bulwark; statute and common law provide the legal rationale. Clinicians have a professional and moral obligation to provide their patients with the information necessary to make informed decisions. Communicating honestly with patients so that they may participate in decision-making is a recent rather than historical imperative. On the basis of a respect for patients, this cooperative physician/patient relationship reverses the paternalism that, since Hippocratic times, has guided physician interactions with patients.

Virtually all states, either in statute or by common law, now require physicians to inform patients about treatment choices and the associated risks and benefits. The legal standard for the information provided is either the community standard (also known as the *professional community standard* or the *reasonable physician standard*) or the materiality standard (also known as the *reasonable* or *prudent* or *subjective patient standard*). The former asks: What would a prudent physician in the same community, with the same background, training, and experience, have disclosed to a patient in the same or similar situation? The latter asks: What would a reasonable patient in the same or similar situation need to know to make an appropriate decision?

Note that great variability exists in the legal requirements. For example, although most of the nation's EDs require informed consent for many regional anesthetic blocks, closed fracture reductions, abscess incision and drainage, lumbar punctures ("spinal taps"), injection of radiocontrast agents and radionuclides for radiography, and nonemergency thoracostomy (chest

BOX e10.3

Guidelines for Development of an Out-of-Hospital Advance Directive Policy

POLICY SCOPE

To ensure maximum coherence and compliance, a comprehensive out-of-hospital DNAR policy should be endorsed by the widest possible jurisdiction, comprising local, regional, and state agencies and the medical community, including the EMS governing body. Whenever feasible, legislative support for such a policy should be sought.

POLICY GUIDELINES

1. Note the established fact that current basic and advanced life support interventions may not be appropriate or beneficial in certain clinical settings.
   - Develop a means to educate the public about the appropriate use of 911 after expected deaths.
   - Establish the fact that comfort care and palliative care are affirmative actions for patients with DNAR orders. These appropriate interventions, including hospice and respite care, do not require EMS activation and often can be arranged by calling the patient's physician in anticipation of death.
   - Develop a means to educate health care workers on topics of advance directives, including information on local out-of-hospital DNARs, community hospice alternatives, and bereavement services.
2. Establish consensus on the ideal identification device for DNAR directives to ensure continuity of care across settings.
3. Reiterate that initial resuscitative attempts usually are indicated when the patient's wishes are not known.
4. Define the conditions under which an out-of-hospital DNAR order can be considered, including its use in long-term care settings and in the emergency department (ED).
5. Define which patients have the decisional capacity to agree to a DNAR order and whether surrogates can sign such orders.
6. Establish a mechanism to determine the precedence of various directives, including living will, durable power of attorney for health care, and out-of-hospital advance directive (ie, DNAR order).
7. Develop a statutory prioritized list of surrogates to be used when there are no advance directives and the patient's decisional capacity is impaired.
8. Consider language acknowledging the growing home hospice movement as it concerns children, and incorporate provisions for document use in minors.
9. Establish that the decision not to attempt resuscitation must be an informed decision made by the patient or the surrogate.
10. Identify the information that should be contained in the DNAR order and the authority that will be responsible for development of such a mechanism.
11. Identify the clinical procedures that are to be provided and those withheld in the adherence to the DNAR order, or specify the authority that will verify adherence.
12. Define the exact manner in which the DNAR order is to be followed, including the role of online medical direction. Each system should ensure that a communication path to access online medical direction is immediately available, when necessary.
13. Establish legal immunity provisions for those who implement DNAR orders in good faith.
14. Establish data collection and protocol evaluation to perform periodic operational assessments.
15. Identify permissible exceptions to compliance with DNAR out-of-hospital directives. For example:
    - The patient is able to revoke a written directive at any time.
    - The EMS personnel can cancel the out-of-hospital DNAR order if there are doubts about the document's validity.

DNAR, Do not attempt resuscitation; *EMS,* emergency medical service.
Adapted from Schears RM, Marco CA, Iserson KV: "Do-not-attempt-resuscitation" (DNAR) policy in the out-of-hospital setting. Ann Emerg Med 44:68, 2004.

tube placement), Texas statutes eliminate any requirement to disclose the specific risks or hazards before these procedures are performed.

Decision-Making Capacity

Many ethical dilemmas in emergency medical care dissolve on ascertaining the patient's decision-making capacity, often linked with consent to (or, more commonly, refusal of) a medical procedure. A basic canon of both ethics and law, as stated by Justice Benjamin Cardozo, is that "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body."[2] These situations can often be clarified by an appreciation of what is meant by decision-making capacity and how it relates to consent.

Emergency clinicians must be prepared to decide quickly whether patients lack decision-making capacity. Although a lack of capacity is obvious in the unconscious or delirious patient, it often is less apparent when the patient remains verbal and at least somewhat coherent. Because such decisions in emergency situations are often time sensitive, unlike in other medical venues, bioethics consultations may not be readily available.

In clinical practice, the word *competence* is often used to mean *capacity*. *Competence* is a legal term and can be determined only by the court. *Capacity* refers to a patient's ability to make decisions about accepting health care recommendations. Capacity is always decision-relative rather than global. Although an inebriated person can have the capacity to refuse to have a small laceration sutured, especially if there is evidence of prior refusal without remorse, the same person may not have the capacity to agree to an elective operation or to refuse to have an emergent lifesaving procedure or operation. To have adequate decision-making capacity in any particular circumstance, the person must understand the options, the consequences of acting on those options, and the costs and benefits of consequences in relation to a relatively stable framework of personal values and priorities (Box e10.4). Disagreement with the physician's recommendation is not in itself grounds for determination that the patient is incapable of making a decision. In fact, even refusal of lifesaving medical care may not prove the person incapable of making valid decisions if it is done on the basis of firmly held religious beliefs, as in the case of a Jehovah's Witness patient who refuses a blood transfusion.

Surrogates

If patients lack capacity to participate in some decisions about their care, surrogate decision makers should then become involved. In most locales, the patient's advance directive may designate surrogates, or such persons or agencies may be detailed in institutional policy or law. Surrogates often include spouses, adult children, parents (of adults), and others, including the attending physician. On occasion, bioethics committees or the courts will need to intervene to help determine the decision maker.

Children represent a special case. Persons younger than the age of majority (or unemancipated minors) are usually deemed incapable of making independent medical decisions, although

BOX e10.4

Components of Decision-Making Capacity

Knowledge of the options
Awareness of consequences of each option
Appreciation of personal costs and benefits of options in relation to relatively stable values and preferences*

*As part of the assessment for capacity, the patient should be asked about why he or she made a specific choice.
Modified from Buchanan AE: The question of competence. In Iserson KV, Sanders AB, Mathieu D: Ethics in emergency medicine, ed 2, Tucson, AZ, 1995, Galen Press.

they are often asked to give their assent to the decision, allowing them to "buy in" to their medical treatment plan. In many cases, in determining whether a child has decision-making capacity, the same rules as those that apply to adult capacity are used. The more serious the consequences, the more the capacity to understand the options, consequences, and values involved is required of children to make a decision.

In the relatively rare case in which a patient has a court-appointed guardian for health care decisions, the guardian's decisions supersede those of both the patient and any other surrogates. Even if a parent is present, it is not always clear that the adult is acting in the best interest of the child. In such cases, child protective services may need to become involved. Disagreements between parents may, in extreme cases, require the involvement of bioethics committees or the courts.

Family

Traditionally, and usually in practice, the family, in particular the spouse, acts as a surrogate decision maker when the patient does not have the capacity to make medical decisions. Yet even when there is a strong family tie, emotional or fiscal costs may sway the surrogate decision maker from certain courses of action the patient would wish taken.

Surrogates make decisions on the basis of two distinct patterns: substituted judgment and best interests. *Substituted judgment* is used when there is an assumption that the surrogate knows enough about the patient's values to make a decision similar to that which the patient would make. It is not clear that anyone knows that much about a person to make decisions in every situation. Surrogates use the *best interest* standard when they do not know what the patient would want done in a particular situation, but, as in the case of Karen Ann Quinlan, in which life-prolonging measures were eventually discontinued against the wishes of some family members, they can use earlier statements and behavior to document the patient's values and then make a decision.[3] Some states may require explicit written directives for surrogates to follow. The best interest standard also applies in cases in which the patient has never had adequate decision-making capacity, as in the Saikewicz case, in which a court-appointed guardian for an elder who lacked decision-making capacity decided against treatment for leukemia after consultation with medical specialists because of a low likelihood of success in the face of debilitating side effects of treatment.[4] Unless there is already a court-appointed guardian, these situations often end up in court.

Surrogate Lists

If a patient lacks decision-making capacity and has no advance directive, many states stipulate that another person may automatically become the person's surrogate. In practice, this almost always means that the patient's spouse may act in that capacity. Some states now have a statutory surrogate list to simplify the process. The most extensive of such lists, which has worked well for nearly two decades, specifies surrogates in the following order: spouse (not divorced or legally separated), a majority of the adult children who can be reasonably contacted, parents (of an adult), domestic partner, sibling, close friend, and attending physician in consultation with a bioethics committee.

Bioethics Committees and Consultants

Multidisciplinary committees have been developed in most large hospitals to consult on cases with bioethical dilemmas and may also participate in surrogate decision-making. These committees usually have three main functions. First, they coordinate education on bioethical issues involving clinical care for the committee members, hospital physicians and staff, patients, families, and the local community. Second, they help institute mandatory or suggested policies or guidelines for health care professionals regarding decision-making processes in problematic cases and resource allocation. Third, they consult prospectively and retrospectively on clinical cases and offer advice and conclusions to those directly involved, most often concerning the treatment or nontreatment of patients who lack decision-making capacity. Ethics committees usually do not act as the primary decision makers. Rather, the members serve as consultants, providing information, advising, and supporting the primary decision-making role of the patient/family/physician triad. A common consultation relates to urgent decisions about withholding, withdrawing, or continuing life-sustaining medical care. A large part of ethics committee work consists of clarifying the facts and fostering communication. In 1995, the Joint Commission (formerly the Joint Commission for the Accreditation of Healthcare Organizations [JCAHO]) began requiring hospitals to ensure that ethics committees perform their functions.

Emergency Clinicians

In the past, clinicians made unilateral decisions for their patients, regardless of whether the patients had the capacity to decide for themselves. This still occurs, of course, especially for the acute illnesses and unexpected injuries seen in EDs. If the patient's decision-making capacity is questioned in the ED, the clinician is often forced to make a decision without assistance. But when it is possible to buy time, clinicians should consult with colleagues and, if possible, the hospital's bioethics committee (see Fig. e10.1). When making unilateral decisions, clinicians should recognize that they are not omniscient. Prognoses are often incorrect and medical knowledge is finite.

Courts

The courts often act as the final adjudicators of disagreements over medical care. They appoint legal guardians and, in a few select cases, set precedent that is followed as health law. The courts, however, usually are neither expeditious nor necessarily cognizant of bioethical principles. They are instructed only to follow the societal values codified in the law. Many courts have suggested that whenever possible, health care decisions should remain at the bedside rather than in legal chambers.

RESUSCITATION ETHICS

The most time-dependent of all activities, and arguably the best training periods in the ED, occur during resuscitations. The patients who require this care have implicitly been guaranteed that all appropriate medical knowledge and skill will be brought to bear in the attempt to save their lives. This implied promise leads to a dilemma. If the most proficient ED professional always leads

the resuscitations and performs procedures, the patient will receive the maximum beneficence, as well as nonmaleficence, as expected. Yet restricting ED practice in this manner also deprives future patients of trained clinicians who could bestow the same beneficence.

This controversy has raged for many years. The appropriate balance seems to be that training in EDs can ethically proceed, as it does in other areas of medicine, if safeguards are provided in the form of onsite supervision by experienced clinicians to ascertain that the patients receive the best possible and most appropriate care. It also has been suggested that medical students and residents be certified for cognitive and procedural skills in a manner similar to that of other hospital physicians. This certification would enable faculty to know when trainees are capable of performing resuscitations, as well as other medical procedures, on their own.

Rarely discussed, but a common practice in some teaching hospitals, has been the custom of allowing trainees with little skill or knowledge to learn and to practice procedures on those undergoing resuscitation only when a patient is deemed "unsalvageable." This practice does a disservice to the patient because prolongation of resuscitative attempts solely for this purpose may lead to a clinical state that prolongs dying. It also harms the family and society by making them pay for unnecessary procedures. (It may actually be less problematic to practice and to teach once a patient is dead, because the patient cannot be harmed and the family does not pay for these activities. See the Postmortem Teaching section later in this chapter.)

Futility

Emergency clinicians, nurses, and EMS personnel may, in some circumstances, believe that further medical interventions are "futile." Yet only three situations meet the most commonly accepted definition. The first such situation, which clinicians can identify in only a limited set of circumstances, is that in which the intervention is effective in less than 1% of identical cases, based on the medical literature. ED thoracotomy for blunt trauma is a well-documented example. Another common scenario with very low survival rates is that of the out-of-hospital cardiac arrest, either unwitnessed or in a patient who arrives from a long-term care facility. Individual clinicians should not rely on their own experiences to make such decisions, however, because they often are skewed owing to selective memory, limited numbers of similar cases, and other biases.

The second futile situation is physiologic futility, in which known anatomic or biochemical abnormalities will not permit successful medical interventions. Examples of such abnormalities generally accepted by EMSs as reasons not to intervene or to provide transport to hospitals are rigor mortis (muscle contraction after death), algor mortis (lowering of body temperature after death), burns so severe that the victim is beyond recognition, and injuries incompatible with life (eg, decapitation). These, along with prolonged normothermic resuscitative attempts without success or prolonged "down time" with an isoelectric electrocardiogram and pulseless electrical activity, are the criteria often used to help determine whether EMS personnel can pronounce death on the scene. In these instances, EMS need not expend valuable resources in a futile resuscitative effort.

The third situation is that in which the proposed intervention will not achieve the patient's goals for medical therapy in accordance with the patient's values. Recognizing this instance, the ACEP asserts, Physicians are under no ethical obligation to render treatments that they judge have no realistic likelihood of medical benefit to the patient. Because this course of action is based on knowing the patient's values related to medical treatment, it is necessary to have talked with the patient in advance (rare in the ED setting), to have received surrogate-supplied information or decisions, or to have access to the medical record. The danger is that differences in values between caregivers and patients may lead to overtreatment or undertreatment. Communication, if necessary with use of a third party, may help resolve these issues.

The futility concept should never be used to deny care to dying patients. Even terminal patients experience medical emergencies that require intervention. The goal is to ease pain and suffering. How that is accomplished depends on the patient, the medical condition causing discomfort, and the patient's value system.

Withholding Versus Withdrawal of Treatments

In emergency medicine, a significant difference *rightfully* exists between the withholding and the withdrawal of life-sustaining medical treatment. The justification for this distinction stems, in part, from the nature of the practice of emergency medicine and the unique manner in which emergency clinicians apply many ethical principles. Because emergency clinicians often lack vital information about their patients' identities, medical conditions, and goals for medical treatment, withholding of emergency medical treatment is more problematic than is later withdrawal of unwanted or useless interventions. Owing to the nature of emergency medicine, in both out-of-hospital and ED settings, higher standards are required to withhold medical treatment than to withdraw it.

Physicians should begin or continue resuscitation of those patients who arrive at the ED without sufficient evidence to determine that the resuscitation effort will be unsuccessful. The only reason to *withhold* cardiopulmonary resuscitation (CPR) is the availability of clear evidence, such as a standard advance directive, that the patient did not wish to have this done or of clinical evidence that further efforts would be futile. Without such information, the presumption must be to intervene.

Once the emergency clinician obtains information confirming a patient's wish not to be resuscitated or indicating a medical condition not amenable to resuscitation, resuscitative efforts and other medical treatment may appropriately be withdrawn. This information may be obtained from an advance directive, a patient surrogate, recent documentation in the medical chart, or EMS communication detailing the failed results of the ongoing resuscitative effort. With rare exceptions, such as after failed suicide attempts, resuscitative efforts should be withdrawn when information is provided either that the patient did not want such efforts or that the patient's medical condition precludes success.

Many factors influence the potential success of resuscitative efforts, including time to CPR, time to defibrillation, cause of the arrest, presence of comorbid illness, pre-arrest clinical status, and initial arrest rhythm. No combination of these factors, however, clearly predicts the outcome.

Three special situations should be noted:

- Cardiac arrest from blunt trauma is nearly uniformly fatal, so little benefit derives from performing chest compressions for any extended period after the airway is secured.
- When health care resources are limited (eg, during disasters), available resources (eg, time, personnel, and equipment) should be devoted to treatment of those patients with the greatest chance of benefiting. This principle may lead to withholding or more rapid discontinuation of resuscitative efforts than is standard in normal practice.
- It is unethical to prolong resuscitative efforts to practice or to teach procedures or to complete research protocols.

Palliative Care

Although lifesaving medical interventions may not be appropriate in all cases, emergency clinicians, whenever possible, should

provide patients with palliative care. Terminally ill and fatally injured patients have the right to receive state-of-the-art palliative care. Palliation often includes analgesics and may include diuretics, sedation, oxygen, paracentesis or thoracentesis, and other medications or procedures to alleviate suffering. Medical personnel should never withdraw or withhold care; only treatment should be withheld when it is appropriate. Although medical practitioners, surrogate decision makers, and sometimes patients find it emotionally easier to forgo new interventions than to withdraw ongoing treatment, no orders, policies, or directives should ever prevent emergency clinicians from alleviating discomfort.

The purpose of palliative interventions is not to prolong the dying process but rather, when death is inevitable, to make it as comfortable as possible for the patient. As patient advocates, emergency clinicians may need to "push" to have the patient admitted to a hospital, hospice, or nursing home or to get ancillary personnel (eg, social workers, home health nurses) to intervene for the patient.

Notifying Survivors

Death, especially when it is sudden and unexpected, shocks and devastates family and friends. For them, it is a life-changing event, with every nuance burned into their memories. Moreover, although they may not consciously acknowledge it, such losses may deeply affect ED personnel, despite their almost constant exposure to life's disasters. This makes death notifications and dealing with the survivors both vitally important and extremely difficult. Emergency clinicians, who deal with sudden death on a regular basis, are in a position to gain considerable knowledge of and to hone their skills in how to care for the survivors, their newest patients.

Even though notification of survivors of a sudden, unexpected death is one of the most difficult parts of the job for emergency clinicians, they and other professionals whose job includes delivery of such news are rarely taught the skills necessary to perform this task. Notification of survivors is emotionally draining; 70% of emergency clinicians find death notifications to be personally difficult. Perhaps this is because only half received any type of death-notification education in medical school, and only one-third received any such training during residency.

On occasion, physicians give the job of death notification to residents, medical students, or nurses. Although all three groups should be present to learn the techniques involved, to have an opportunity to hear what is said, and to observe an attending physician showing sensitivity, they should not be left to do death notifications on their own. That is a form of professional abandonment and, in a teaching hospital, the worst form of student abuse.

Viewing of Resuscitations

Traditionally, survivors have not been permitted to view resuscitation attempts. That attitude, however, is gradually giving way to a more enlightened view based, in part, on recognition that families gain enormous psychosocial benefits from being present and that they are also patients in need of appropriate support.

The argument against allowing survivor onlookers has been that resuscitations often involve large teams, unclear communications, and team leaders who are unwilling or unable to make firm, timely, and rational decisions. Having family members present, the argument goes, introduces the possibility of an onlooker fainting or otherwise becoming another patient. Survivors frequently misinterpret the team's discussions or actions, and team members may feel uncomfortable having family members judging their actions.

Yet studies in both the United States and Britain have shown that nearly all survivors who witnessed ED resuscitative efforts found the experience helpful. Seventy-six percent of survivors responded that their grieving was facilitated by having witnessed the resuscitation, and 64% thought that their presence was helpful to their dying family member. Psychological tests of survivors who witnessed resuscitation attempts, performed at 3 and 9 months after the event, showed that this group experienced fewer episodes of "intrusive imagery," such as flashbacks of the events leading to the death, compared with survivors not present at the resuscitation (relatives in the control group). They also had lower levels of anxiety, depression, post-traumatic avoidance behavior, and grief.[5]

The American Heart Association (AHA) now endorses giving family members the opportunity to be present so long as the patient has not previously objected. This position stems from the benefit families can derive from their presence during resuscitation attempts, the lack of harmful effects on them from viewing these resuscitations, and their quasi-right to be there based on the nature of their relationship to the patient.

The presence of these survivors does not hinder the resuscitative efforts and often leads to quieter, more effective team efforts. Experience has shown that survivors who witness ED resuscitative attempts never question whether the team "tried hard enough," do not ask whether the person is *really* dead, and spend less time in the ED trying to come to terms with the death. In addition, survivors may actually thank the ED team for their efforts, a situation that rarely occurs under other circumstances, and the ED staff never has to "notify" survivors of the death.

The general procedure is as follows:

- Ask survivors if they want to view resuscitative efforts.
- If they do, give them a quick briefing about what they will see, and have a knowledgeable staff member, usually a chaplain, social worker, or ED nurse who can answer their questions, accompany them.
- Provide a chair for elders and allow survivors to leave and to re-enter as they wish.
- Staff should attempt to cover as much of the patient as is compatible with effective resuscitative efforts.
- Team members should be advised that family is in the room.
- The survivors should be encouraged to talk to and to touch the patient.
- Decisions to pronounce the patient dead, although often discussed with the family, generally are communicated in the format of advising them that "we must stop now." They should never be asked whether to stop the resuscitative effort; this is a medical decision.
- If the family is present when it is clear that resuscitative efforts should cease, the situation should be explained to the family before supportive measures are discontinued. This provides them with a chance to "say good-bye" before death is pronounced. Dedicated pediatric EDs and pediatric resuscitation units in general EDs have adopted these procedures more often than others.

Postmortem Teaching

A less commonly discussed aspect of emergency medicine education programs is the use of recently deceased patients to teach or to practice emergency procedural techniques, such as intubations and central line placement. Although whether this practice is ethical is a matter of controversy, a reasonable argument might be that if medical treatment could not save the patient, then the emergency clinician's responsibility is to hone skills for the next patient in need of expertise in resuscitative techniques. This is not to condone the desecration of a body. Rather, it suggests that because clinicians learned the techniques used during the attempted resuscitation on other dead or living patients, this

(now dead) patient owes the next patient the same courtesy. No one would advocate practicing unneeded procedures on living patients, and many people argue against use of experimental animals. The religious or ethical beliefs of some ED personnel may make practicing or teaching of these procedures in such circumstances problematic.

Resuscitation Research

Physicians in a new and advancing specialty have an obligation to advance the knowledge base from which they practice. This can be done only through research, a significant component of which should necessarily be clinically based. In the United States, federally mandated institutional review boards (IRBs) must approve any research involving human subjects, including research in EDs and, possibly, in prehospital care. Increasingly, research ethics committees are being used to approve human subject research throughout the world. The IRBs try to guarantee that patients who are asked to participate in research review and sign an adequate informed consent document. Yet, even if the patient is conscious, it is unclear whether truly free and informed consent can be given in the midst of a medical emergency. In both trauma and cardiac resuscitation research, informed consent is, of course, not feasible. It is usually difficult, if not impossible, to obtain retrospective patient or, if appropriate, prospective surrogate consent. So as not to deny critically ill and injured patients the opportunity to participate in possibly beneficial research trials, the U.S. Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) issued regulations, which became effective in 1996, that allow "emergency research" without informed consent. These regulations contain extensive patient safeguards, including community consultation, public disclosure, and intensive oversight.

The ethical and legal basis for these regulations is presumed consent: If the research is not harmful and especially if it is potentially helpful, most "reasonable" patients would acquiesce to the research, given the basic values of good and evil (see Box e10.1). As routinely occurs in emergency medicine practice, persons suffering unexpected adverse events with a high probability of rapid death or serious morbidity generally demand that the physician deliver acute care interventions—immediately and without discourse. If there is a chance that the patient could benefit from a therapeutic course of action in such circumstances, most people would demand that it be used. Similar logic applies with acute care research, especially when accepted or standard therapy is futile and possibly when the investigators believe that equipoise (therapeutic equality) exists between the two tested forms of therapy. Protection for the patient in these cases rests with IRBs, which, among other considerations, must guard against the possibility of organ-specific success but failure to benefit the entire person, such as producing a patient in a persistent vegetative state after "successful" CPR.

Beyond IRB authorization for research is a moral responsibility for the individual researcher to ensure that the research protocol and its execution are ethical. This responsibility extends to the journals in which the research is published. Emergency medicine has an excellent record of ethical research, although a large percentage of human research studies published in the major emergency medicine journals fail to mention either IRB review or informed consent.[6]

PUBLIC POLICY AND BIOETHICS

Restricted Access to Emergency Medical Care

Society has acknowledged its moral obligation to ensure that everyone has reasonable access to adequate health care. People's need for health care is unequally distributed and highly unpredictable. Few could afford this care if left to their own devices, so mechanisms are in place to share the risk.

The ethical dilemma for emergency clinicians comes in basically two forms: one precipitated by the institution in which the ED is housed and one by outside third-party payers. Some institutions have refused care to patients coming to the ED, sending some away for clinic appointments at a later time. Institutions also have pressured emergency clinicians to limit treatment, ancillary tests, or hospital admission for patients without the ability to pay. Although such limitation may seem patently immoral, another question should be asked: Is there a moral obligation to the community to keep the health care institution financially viable? Hospitals have closed their doors because of financial losses, and many hospitals, especially in inner-city areas, are on the verge of bankruptcy.

Some prepaid health maintenance organizations (HMOs) use "gatekeepers" to keep patients in need of emergency medical care away from immediate assistance at institutions other than the HMO parent hospital. Moreover, the HMO's income may depend on *not* hospitalizing patients, *not* using ancillary tests, and *not* permitting ED visits. Nevertheless, it is prudent and ethical for emergency clinicians to err on the side of providing for the patient's needs.

Morality of Triage Decisions

In the aftermath of a massive natural or man-made disaster, triage officers face difficult decisions about who will receive scarce lifesaving treatment and who will be left to die without treatment. Even in "routine" ED triage, decisions about who should receive treatment priority and who can wait for treatment may, at least occasionally, have life-and-death consequences.

Triage provides a method to distribute health care resources when patient needs exceed available resources. Triage operates along a continuum of decreasing resources, social order, and the resource-to-patient ratio. Arrival patterns, triage methods, and the applicable ethical basis for triage vary along this continuum.

Most triage systems are designed to serve the values of human life, human health, efficient use of resources, and fairness. Nevertheless, because of the variety of specific triage settings and goals, no single "correct" way to perform or to justify triage can be identified. Routine triage in the relatively resource-rich setting of the modern hospital ED, for example, focuses appropriately on maximizing benefits for each individual patient, giving treatment priority to patients whose needs are most urgent. In triage after a massive disaster, when not all individual needs for lifesaving care can be met, the focus may shift from an individual to a group perspective, and triage officers may seek to save as many lives as possible with the limited resources at their disposal. In special circumstances (eg, times of war), military commanders may direct that triage systems devote scarce medical resources to achieve a nonmedical goal, namely, military victory. In situations of complete devastation, the lack of social order and minimal resources may make triage impossible.

Whether the choice of a triage system is justifiable depends on an evaluation of the specific system itself, its underlying values and principles, and the setting in which it is applied.

Physician Response to Risky Situations

Over the millennia, personal values have dictated whether a physician would remain with his or her patients during extreme or catastrophic circumstances. Physicians, even legends of medicine such as Galen, often fled to save their own lives. In the era of modern epidemics of unknown virulence and etiology, it remains a personal moral decision, especially for emergency clinicians who are on the frontline of these medical assaults.

How will physicians respond when a catastrophe involving personal risk strikes? The moral backbone of medical professionals may be tested as health care providers weigh multiple factors to determine whether to stay and carry out their professional roles or to step back and decrease their personal risk.

With incomplete information, providers may make decisions on the basis of heated emotions and panic rather than an accurate perception of risk. The decision to stay or to leave will ultimately depend on the individual practitioner's risk assessment and value system. Professional ethical statements about expected conduct establish important professional standards and norms, but each practitioner will interpret and apply them on the basis of his or her own situation and values. Recent historical precedent suggests that many physicians and other health care providers will dutifully care for the sick and needy, even at great risk to themselves. Although some emergency clinicians have worked in dangerous situations, most have not; nothing in day-to-day emergency medicine practice prepares emergency clinicians for the great opportunities and challenges that accompany a pandemic. Emergency clinicians can, however, reflect on their professional and personal responsibilities in crisis situations, and public and private institutions can create plans for effective communication and care when a disaster strikes. If this can be achieved before the next pandemic or disaster that includes personal risk to clinicians, emergency clinicians—who are inevitably among those at highest risk—can be encouraged to "stay and fight."

"Proactive Ethics": How Can Emergency Clinicians Change the Rules?

In every medical system, practitioners find that they repeatedly face identical ethical dilemmas. The normal outcome is an incomplete and often unsatisfactory decision made by administrators, lawyers, bioethics committees, or others. "Proactive ethics" involves changing the rules under which we operate. Easier done in some settings than in others, the process requires that all "stakeholders," those with a vested interest in an equitable solution, first come to the table and reach a compromise. Such groups often will include physicians, nurses, EMS personnel, lawyers, religious authorities, and representatives of affected groups (eg, an organization of elders in the case of issues involving the aged). Armed with this agreement or even sample legislation that they can present to politicians, it becomes easier to change laws or administrative rules to address recurrent ethical dilemmas. One such process led to a landmark out-of-hospital advance directive law, which markedly lessened unwanted EMS resuscitation attempts. It also led to an extensive statutory surrogate list and a simplified set of advance directives. Subsequently, physicians also spearheaded the similar, but less effective Physician Orders for Life-Sustaining Treatment.[7] Proactive ethics lies in the role of public policy—an arena in which emergency clinicians are well suited to play a pivotal role.

A Global Perspective

Emergency clinicians ever more frequently respond to acute and chronic "humanitarian catastrophes," those conflicts and calamities generating both widespread human suffering and destructive events. While struggling to provide care in these difficult situations and sometimes to do simultaneous research, health care workers must also apply standard bioethical concepts with sensitivity to local mores.[8]

Among the bioethical principles that directly apply to this work is that the humanitarian imperative comes first, meaning that action should be taken to prevent or alleviate human suffering arising out of disaster or conflict, and that nothing should override this principle. In addition, assistance is given regardless of the race, creed, or nationality of the recipients and without adverse distinction of any kind, with priorities based on need alone. This includes neither using offers of help to further government policy nor promoting political or religious views. Finally, physicians should be accountable, not only to the organizations with whom they work, but also to the local populations whom they are there to help.[9,10]

KEY CONCEPTS

- Bioethics is a method of using values and moral principles to come to defendable decisions for ethical dilemmas.
- Ethical dilemmas arise from conflicts between multiple good options or multiple bad options, not between good and bad choices.
- Individual rights come from another's duty to act.
- Values come from a variety of sources: community, culture, religion, and family.
- The values driving medical decisions should be the patient's values.
- Basic ethical principles include autonomy, beneficence, nonmaleficence, justice, and confidentiality.
- In emergency medicine, caregiver safety is an important value.
- A rapid ethical decision tool: Is there an established precedent? If not, apply the following three tests: the impartiality test, the universality test, and the interpersonal justifiability test.
- Consent requires decision-making capacity or appropriate surrogate decision makers.
- Futility, although an appropriate reason for withholding nonproductive interventions, is not an excuse for withholding compassionate care.
- There are many areas of emergency medicine with unique ethical issues, such as resuscitation research, disaster response, morality of triage, response to high-risk situations, and wilderness medicine.

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CHAPTER e10: QUESTIONS & ANSWERS

e10.1. "Confidentiality" is all of the following *except:*
- **A.** Describes the patient's right to sufficient physical and auditory isolation so that they cannot be seen or heard by others during interactions with medical personnel.
- **B.** Imposes a duty on health care workers.
- **C.** May conflict with the law, especially public health statutes.
- **D.** Presumes that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission.

Answer: A. While isolation of patients for confidentiality is a good goal the limited space and hectic nature of an ED would sometimes prevent timely and quality care.

e10.2. Which of the following can emergency clinicians always rely on for appropriate guidance when faced with ethical dilemmas?
- **A.** State laws and medical board policies
- **B.** The American College of Emergency Physicians' (ACEP) Code of Ethics
- **C.** The Hippocratic Oath
- **D.** None of the above.

Answer: D. All of these examples are great for guidance on ethical dilemmas none of them can "always" have guidance for every situation that can occur.

e10.3. To have adequate decision-making capacity in any particular circumstance, a person must understand all of the following *except:*
- **A.** The available options
- **B.** The consequences of acting on those options
- **C.** The costs and benefits of consequences in relation to a relatively stable framework of personal values and priorities
- **D.** The court's decision about their competency

Answer: D. To be deemed competent an individual must understand A, B, and C. Answer D is a legal issue and is not required for competency.

e10.4. Withholding treatment in the emergency department (ED):
- **A.** Legally differs from withdrawing treatment.
- **B.** Morally differs from withdrawing treatment.
- **C.** Requires clinical information that is often unavailable immediately.
- **D.** Should never be done.

Answer: C. In an emergency not all relevant information is available at the time important decisions must be made.

e10.5. When using the "rapid approach to ethical problems in the emergency department (ED)" to decide on a course of action:
- **A.** Always consult with the Bioethics Committee/ Consultant before acting.
- **B.** Assume that each ethical problem in the ED requires a unique solution.
- **C.** Test your chosen action against your religious values.
- **D.** When practicable and safe for the patient, buy time to consult on possible options.

Answer: D. Ethical problems can often take some time to work out, but a rapid approach rarely has enough time for a formal ethics consult. Buying some time so a reasonable solution can be derived is often the best that can be done.

CHAPTER e11

Emergency Medical Treatment and Active Labor Act and Medicolegal Issues*

Robert A. Bitterman

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SPECIFIC ISSUES—EMERGENCY MEDICAL TREATMENT AND ACTIVE LABOR ACT

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National Emergencies or Disasters

Sexual Assault Cases

Police-Requested Blood Alcohol Tests

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Ancillary Services as Part of the Medical Screening Examination

Policies, Procedures, and Practice Guidelines

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CONSENT FOR MEDICAL CARE

Informed Consent

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Informed Refusal

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Jehovah's Witnesses

REPORTING REQUIREMENTS

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

KEY CONCEPTS

- Emergency Medical Treatment and Active Labor Act (EMTALA) governs virtually every aspect of hospital-based emergency services. Hospitals and emergency clinicians need to address the following issues to ensure compliance with the law:
  - Adopt (and enforce) a hospital-wide EMTALA policy, as well as emergency department (ED)–specific policies.
  - Educate all appropriate hospital staff and medical staff.
  - Define the hospital's standard ED medical screening examination (MSE) process, including identifying "dedicated emergency departments" and designated "qualified medical personnel" to perform the MSE, as defined by the government.
  - Establish the hospital's patient stabilization procedures and documentation.
  - Do not delay access to the MSE, stabilizing care, on-call physicians, or transfer on account of or to inquire about the patient's insurance status (EMTALA's "no-delay" provision).
  - Address the ED/outpatient registration procedures and payment collection systems.
  - Implement processes and procedures regarding patient refusal of the MSE, stabilizing treatment, or transfer.
  - Implement an effective ED physician on-call system, with written duties and responsibilities.
  - Create a uniform system and "transfer packet" for transferring patients out of the hospital.
  - Create a system for accepting or rejecting patient transfers from other facilities.
  - Institute appropriate documentation requirements for ED medical records, a "central log" for patients presenting to the hospital, transfers, and on-call lists.
  - Post required "signs" in areas used for MSEs, including the ED, Labor and Delivery, and psychiatric intake centers.
  - Monitor and quality assurance review the hospital's EMTALA compliance.
  - Draft a policy and procedure to report suspected EMTALA violations to Centers for Medicare and Medicaid Services (CMS).
  - Review the potential application of EMTALA to the hospital's outlying facilities, such as Urgent Care Centers, or Ambulance/Helicopter EMS Services.
  - Review disaster plans and public health emergency responses for EMTALA issues.
  - Draft and use legally-approved EMTALA forms to achieve/document compliance.
- Whenever emergency clinicians are in doubt about the legality of a situation, they should "do what you believe to be in the patient's best interest and worry about the legal consequences later."
- Consent for minors in the ED is really a non-issue. Consent is a creature of state law; EMTALA pre-empts state law, and it requires the ED to provide a MSE and stabilizing treatment to all minors presenting to the ED.
- Emergency clinicians should be reticent to allow patients to leave the ED against medical advice. The capacity to make reasonable medical decisions can easily be affected by alcohol, drugs, pain, or any number of medical conditions. "When in doubt, don't let 'em out" should be the guiding principle. The courts (and public opinion) will bend over backward to protect clinicians who act in the best interests of the health and safety of their patients.

CHAPTER e11

Emergency Medical Treatment and Active Labor Act and Medicolegal Issues

Robert A. Bitterman

PRINCIPLES

Federal and state laws tightly control the practice of emergency medicine. The magnitude and complexity of the governing legal authority plus the significant penalties for noncompliance, such as criminal sanctions, civil lawsuits, civil monetary penalties, and exclusion from participation in Medicare and Medicaid, dictate that emergency clinicians acquire functional knowledge of these laws.

Federal law—the Emergency Medical Treatment and Active Labor Act (EMTALA), also known as the *antidumping statute*—governs how emergency clinicians must triage, register, examine, provide evaluation, treat or stabilize, discharge or transfer, use hospital resources, and involve medical staff expertise when caring for patients presenting to the ED.[1-3] State laws further control the practice of emergency medicine through such issues as consent, reporting requirements, confidentiality requirements, forensic and police matters, civil commitments, and emergency medical service (EMS) statutes.

SPECIFIC ISSUES—EMERGENCY MEDICAL TREATMENT AND ACTIVE LABOR ACT

EMTALA originally was enacted to prevent private hospitals from refusing to treat indigent patients with medical emergencies or transferring ("dumping") them in an unstable condition to public hospitals. Subsequent amendments to the law, government regulations, and court decisions greatly expanded the reach of EMTALA, such that the law now sets national standards for the provision of emergency services.[2-4] Today, emergency clinicians must have a solid understanding of EMTALA's statutory requirements and how the regulatory agencies and the courts interpret the three main aspects of the law: screening, stabilizing, and discharging or transferring ED patients.

Medical Screening Examination

Any person who comes to an ED requesting examination or treatment for a medical condition must be provided with an appropriate medical screening examination (MSE).[5] The purpose of the MSE is to determine whether the patient has an emergency medical condition (EMC).[6,7]

Emergency Medical Condition

EMTALA defines an EMC as "acute symptoms of sufficient severity (including severe pain) such that the absence of immediate medical attention could reasonably be expected to result in (1) placing the health of the individual (or, with respect to a pregnant woman, the health of the woman or her unborn child) in serious jeopardy, (2) serious impairment to bodily functions, or (3) serious dysfunction of any bodily organ or part."[6] In the case of a pregnant woman who is having contractions, an EMC is defined as one in which "there is inadequate time to effect a safe transfer to another hospital before delivery, or that transfer may pose a threat to the health or safety of the woman or the unborn child."[7]

If the MSE does not reveal an EMC, further care of that patient is not controlled by EMTALA, so the law's provisions governing stabilizing treatment, transfer of the patient, or involvement of on-call physicians cease to apply.[8] This interpretation emphasizes the critical importance of documenting the presence or absence of an EMC during a patient's initial ED evaluation. A checkbox to indicate such should be on every ED medical record.

Screening Each Individual Patient

Everyone who presents to the ED requesting care must be screened. Whether the patient is indigent, a member of a managed care plan, or covered by Medicare, Medicaid, or private insurance is irrelevant; the hospital must provide everyone who presents for care with an MSE.[5] This includes all populations of patients, such as illegal aliens, minors, and private patients of the hospital's medical staff, but excludes persons who are already patients of the hospital, such as inpatients or outpatients undergoing a scheduled procedure at the hospital who are brought to the ED for emergency care.[2,9] The screening of minors is discussed later in the Consent for Medical Care section.

Request for Examination or Treatment of a Medical Condition

Mere presence in the ED or on hospital property is not sufficient to trigger the hospital's duty to provide an MSE; a request for examination or treatment of a medical condition also is necessary. The request can be made by *anyone* on behalf of the patient, including EMS personnel, a police officer, or a babysitter; the request does not have to come from the patient, a family member, or a legal guardian.[5]

Also, if a person is unable to speak to request care, that person's behavior may constitute a request if the hospital's personnel are aware of the behavior and a prudent layperson would believe that the behavior indicated a need for examination or treatment.[2]

"Comes to the Emergency Department"

The Centers for Medicare and Medicaid Services (CMS) deems anyone on hospital property to have "come to the emergency department."[10,11] According to CMS, "hospital property" consists of the entire main hospital campus, including parking lots, sidewalks, and driveways, and any ambulance owned and operated by the hospital, even if the ambulance is not on hospital grounds.[10,11] CMS then divides hospital property into "dedicated emergency departments" and all other property that is not a dedicated ED.

A *dedicated* ED is defined as any department or facility of the hospital, whether on or off campus, that is licensed by the state as an ED; is held out to the public as a place that provides care for persons with EMCs on an unscheduled basis; or actually does provide care for persons with EMCs a certain percentage of the time.[2] Units qualifying as dedicated EDs include typical hospital EDs, labor and delivery units, and psychiatric intake centers. Urgent care centers generally fail to meet CMS's regulatory definition of a dedicated ED and therefore do not have to comply with EMTALA. However, urgent care centers legally structured as a hospital "department of the provider" need to review the EMTALA regulations to determine whether the EMTALA applies.[2]

CMS specifically exempts a number of on-campus areas from compliance with EMTALA—in general, those areas that typically do not provide emergency care, such as physicians' offices, skilled nursing facilities, other entities that participate separately under Medicare, and other nonmedical facilities on campus.[2] CMS also exempts application of the law to off-campus facilities and other "departments of a provider" that were never intended or structured to manage EMCs, such as dialysis centers, rehabilitation units, laboratories and radiology centers, and primary care clinics. However, these facilities must have written policies and procedures for appraisal of emergencies and arrangement of transfer when it is appropriate.[12,13]

Presentations to the hospital's dedicated ED require only a request for examination or treatment of a medical condition; it is not required that the presentation be for a medical condition that constitutes a true *emergency* to trigger EMTALA's screening duty. Presentations to hospital property other than to the dedicated ED do, however, require the request to be for an EMC before EMTALA applies.[2,3]

"Parking" of Patients Brought by Emergency Medical Services to the Emergency Department

Some overcrowded hospitals ignore ambulance patients, leaving EMS to care for them until the hospital "accepts" the patient, a practice termed EMS "parking." These hospitals erroneously believe that unless they accept responsibility for the patient, they have no EMTALA duty to provide care or to accommodate that patient. CMS deems a hospital's EMTALA obligation to begin the moment the patient "comes to the ED" and a request is made on behalf of the patient for examination or treatment of a medical condition, not when the hospital "accepts" the patient.[14] The practice of "parking" EMS patients also may violate other Medicare regulations, which require hospitals to "meet the emergency needs of patients in accordance with acceptable standards of practice."[15]

Under certain circumstances, such as an influx of multiple trauma victims, it is reasonable for the hospital to ask the EMS provider to stay with the patient until such time as ED staff becomes available to care for that person. However, CMS requires that "even if a hospital cannot immediately provide an MSE, it must still triage the individual's condition immediately upon arrival to ensure that an emergent intervention is not required and that the EMS provider staff can appropriately monitor the individual's condition."[16]

National Emergencies or Disasters

Under certain circumstances, the Secretary of Health and Human Services can exempt hospitals from EMTALA during times of national or local disasters or terrorist acts, bioterrorist events, or pandemic infectious disease.[17,18]

EMTALA still applies to individuals potentially exposed to Ebola virus, or other highly contagious diseases, who present to the hospital's ED (Box e11.1).

BOX e11.1

Centers for Medicare and Medicaid Services Resources for Emergency Medical Treatment and Active Labor Act Requirements and Implications Related to Ebola

CMS S&C: 15-10-Hospitals, November 21, 2014. Emergency Medical Treatment and Labor Act (EMTALA) Requirements and Implications Related to Ebola Virus Disease (Ebola): https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-15-10.pdf.

CMS S&C: 15-24-Hospitals, February 13, 2015. Emergency Medical Treatment and Labor Act (EMTALA) and Ebola Virus Disease (EVD)–Questions and Answers (Q+A): https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-15-24.pdf.

CMS, Centers for Medicare and Medicaid Services; *ED,* emergency department; *EMTALA,* Emergency Medical Treatment and Active Labor Act.

Sexual Assault Cases

If a person comes to the ED solely for the collection of evidence for a criminal investigation and is not requesting examination or treatment for a medical condition, no MSE is required. However, if the person complains of pain or injury or wants pregnancy or sexually transmitted disease prophylaxis, that person is requesting examination or treatment for a medical condition and must be provided with an MSE.[3,19,20]

Police-Requested Blood Alcohol Tests

For both medical and legal reasons, an MSE should be offered to all persons presenting to the ED for police-requested blood alcohol samples.[3] The police officer brought the patient because of aberrant behavior, suspected to be caused by alcohol intoxication. Many diseases mimic alcohol intoxication, including hypoglycemia, cerebral hypoxia, head injury, metabolic abnormalities, and other toxins. Medically, alcohol intoxication should not automatically be presumed as the cause of the patient's condition merely because it is so common. The emergency clinician should examine the person in custody to determine if an EMC exists.

The patient may refuse the MSE and request that only the blood be drawn. If the patient appears competent, this can be done. The refusal of the MSE must be documented, as noted for other testing done in the ED, with additional documentation of the risks and benefits of the offered MSE and careful notation of the patient's competence. If the patient is too intoxicated to make medical decisions, release from the ED should be delayed until the patient is competent enough to make rational decisions. Only physicians should assess and document a patient's competence; other ED personnel should not be allowed to make these decisions.[2]

Health Care Providers Qualified to Perform the Medical Screening Examination

EMTALA does not specify whether a physician, a nurse, or another health care provider must perform the MSE. CMS regulations require that the screening examination be done by "qualified medical personnel" and that the hospital's governing body formally designate, in writing, who is a qualified person to perform medical screening on behalf of the hospital.[21-23] Typically, the

designation is "physicians—credentialed members of the medical staff," and "physician assistants (PAs) or nurse practitioners (NPs) under the direction of an emergency clinician." CMS specifies that the hospital cannot allow the medical director of its ED to designate who is qualified to perform screenings on behalf of the hospital.[24]

Triage by a nurse does not constitute an MSE, even for "obvious" nonemergent conditions. Neither CMS nor the courts accept triage as adequate to determine whether an EMC exists.[2,3]

Ancillary Services as Part of the Medical Screening Examination

The law requires hospitals to provide the screening examination "within the capabilities of the hospital's emergency department, including ancillary services routinely available to the ED."[5] According to CMS, this means that the scope of an MSE may "range from a simple process involving only a brief history and physical examination to a complex process that also involves performing ancillary studies and procedures, such as (but not limited to) lumbar punctures, clinical laboratory tests, computed tomography (CT) scans, and/or diagnostic tests and procedures."[3]

Because the stated purpose of the MSE is to determine whether an EMC exists, CMS and the federal courts hold that the hospital must conduct whatever examination is necessary to make that determination.[3,25,26] It may take only a visual glance to rule out an EMC in a patient with a rash. However, if it takes a complete neurologic examination, CT scan, and lumbar puncture to decide whether a headache patient has a subarachnoid hemorrhage, then those procedures are considered part of the MSE.

Thus, if the ED usually has ultrasonography, CT, ventilation-perfusion scans, and similar tests available, it must use those resources *if necessary* to determine whether the patient has an EMC. However, the hospital is obligated to use only the resources ordinarily available to its ED.[5] Neither the statute nor the regulations mandate that hospitals expand resources or offer additional services to ED patients.[1-3]

CMS views the ancillary services available to the ED as including the services of on-call physicians if their expertise is required to decide whether the patient has an EMC.[2,27] If the emergency clinician cannot determine whether a patient has an EMC, the clinician must use the on-call physician services to help make that determination. For example, if it takes an on-call surgeon to decide whether a patient has an "acute abdomen," the surgical evaluation becomes an integral part of the hospital's MSE.

Policies, Procedures, and Practice Guidelines

An appropriate MSE has two components: (1) the examination must be "reasonably calculated to identify critical medical conditions," and (2) the "exact same level of screening must be uniformly provided to all patients who present with substantially similar complaints."[25,26] In other words, a hospital satisfies the requirements of EMTALA if it conducts standard screening procedures, uniformly, for all patients with similar complaints and circumstances.

Each hospital determines its own standard screening policies and procedures. By necessity, each hospital's standard will be individualized because each hospital ED has its own capabilities and different ancillary services available. Once a hospital defines its standard screening process, however, it must apply that process uniformly to all patients presenting with similar complaints, and material departure from its standard screening procedure constitutes inappropriate screening under EMTALA. Because motive is not a relevant issue in the federal courts (except the Sixth Circuit Court) or during CMS investigations, liability may result from any material deviation of the hospital's screening process, regardless of the hospital's motive and regardless of the reason for the deviation. For example, a Florida hospital's screening policy stated that triage would be conducted within 3 minutes after a patient's arrival at the ED. In one instance, a patient was not triaged until 45 minutes after arrival; this delay constituted a violation of the law because the hospital did not follow its own policy. Once hospitals define their own standard screening process, they will be held to that standard, by both plaintiffs and the government enforcers. Investigators and plaintiff attorneys will subpoena and closely examine the hospital's policies and procedures, medical staff bylaws, ED rules and regulations, practice guidelines, and other written information on the screening process. They will compare the written process to what actually transpired. These hospital documents must be drafted very carefully to avoid unintended liability.

Registration Process, Collections or Insurance Information, and Authorization

CMS does allow hospitals to conduct reasonable registration procedures in the ED, including collection of insurance data at the time of registration, as long as the process does not delay the MSE. A reasonable registration process may obtain demographic data and the name of the patient's physician and determine whether the patient is insured and the type of insurance. During the registration process, the patient can sign the hospital's usual "informed consent to be examined" form and a routine form that holds the patient financially accountable for any charges not covered by the patient's insurance carrier.[2]

The key is to create parallel tracks for medical and financial issues and to ensure that the financial track never interferes with the medical care in any way. "Bedside registration" is probably necessary under the existing regulatory scheme to avoid "no-delay" violations because CMS would consider any delay in access to the MSE due to diversion to the registration area to be against the law. Waiting for examination and treatment because the ED is overwhelmed is not a violation, but waiting for examination because the registration clerks are collecting insurance information probably is a violation.[2,3]

CMS warns hospitals not to coerce patients into leaving before they receive their federally guaranteed MSE, stating "reasonable registration processes may not unduly discourage individuals from remaining for further evaluation."[2,3] Moreover, since enactment of the Affordable Care Act, CMS now considers collection of co-payments, down payments, advanced beneficiary notifications, or signatures on managed care financial forms to constitute such "economic coercion" and therefore prohibited.[28]

Hospitals also should ensure that staff behavior does not create a hostile environment or constructive denial of the MSE.

Furthermore, hospitals should never delay a patient's MSE to obtain prior authorization from a managed care organization (MCO). CMS explicitly bans prior authorization for managed care plans before completion of the MSE and commencement of stabilizing treatment.[2,28] Hospitals may obtain authorization for payment from insurance entities only "concurrently" with stabilization of the patient.[2,3,28] Hospitals are legally obligated to provide the MSE, and they will be held to that standard regardless of the financial pressures placed on them by MCOs.[3,28]

Regardless of managed care status, "very important person (VIP)" status, private patient status, or any other classification, all patients should be processed in the same manner.[3,29,30] In addition, the triage team, emergency clinician and nursing staff, and all clinical personnel should not know the patient's insurance status throughout the initial screening and stabilizing treatment. This removes insurance status as an issue should the government later claim that the staff was motivated in some way or treated the patient disparately on the basis of financial class. It is easier to

prove that actions were not predicated on the patient's financial status when the staff lacked knowledge of that status than to prove that the actions were medically appropriate despite knowledge that the patient had no insurance.

After the MSE and initiation of stabilizing treatment, insurance status and ability to pay can be considered in determining the patient's future care, such as hospital admission, transfer, or discharge and follow-up.

Documentation

Compliance with EMTALA's technicalities requires proper documentation. Furthermore, clinical outcomes are irrelevant under government enforcement, and compliance is not presumed; hospitals must prove compliance through documentation.

Central Log

Hospitals must maintain a central log of all patients presenting to the ED requesting examination or treatment. The log must contain the name and disposition of the patient, including whether the patient refused treatment, whether the hospital refused to provide an MSE or treatment, and whether the patient was treated and stabilized, admitted, transferred, or discharged.[31] The purpose of the log is to permit CMS and state surveyors to select and review individual records to investigate whether the hospital is in compliance with the law.[3]

The log must include all persons presenting to the hospital's dedicated EDs, whether on or off campus.[3,27,32] These areas include the typical ED, ambulatory care or fast-track areas contained within the ED, freestanding emergency centers, labor and delivery suites, and psychiatric intake centers.[2] The logs are not required to be collated into a single document but must be retrievable at CMS's request.

Medical Record

All areas of the hospital used to conduct the MSE must create a medical record for the patient and keep a log of those presenting for examination and treatment.[33] If members of the hospital medical staff see their patients in the ED, on either a scheduled or an unscheduled basis, the hospital must create a medical record and require the physician to document the care provided in that record. The physician's private office records documenting care provided at the hospital are insufficient.

Most important, the emergency clinician should document whether an EMC was determined to exist for *every* patient seen in the ED, even if the initial chief complaint is seemingly trivial. The legal purpose of the required MSE is to determine if an EMC is present. To facilitate documentation, ED charts should include two checkboxes: one labeled "EMTALA EMC present" and the other "EMTALA EMC absent." The person performing the MSE should check the appropriate box for each patient, and completion of this documentation should be a prime part of the ED's quality improvement monitoring program.

Stabilization Requirements

Once the hospital determines that an individual has an EMC, EMTALA requires the hospital either to stabilize the EMC or, if it lacks the capability to stabilize the patient, to transfer the patient to another medical facility that can provide the necessary treatment.[34] A sample form for use in documenting such transfers and patient consent to transfer is shown in Figure e11.1.

When and if the patient is "stabilized" has significant ramifications for hospitals and physicians, because once patients are stabilized, EMTALA no longer applies.[35] After stabilization, hospitals are free to refuse to provide further treatment or to transfer stabilized patients for purely financial reasons. On-call clinicians can refuse to treat or to admit stable patients or insist that stable patients be transferred owing to their lack of or type of insurance. An MCO can refuse further payment to the hospital and request that the stabilized patient be transferred to one of its contracting facilities.[3]

However, other federal, state, or local standards may govern further treatment or transfer of ED patients. For example, state laws often prohibit hospitals from transferring patients for any reason except that they are incapable of handling the patient's medical problem.

Two elements must be present to trigger EMTALA's stabilization requirement: (1) the patient must have an EMC, as defined by law, and (2) the hospital must determine that an EMC exists. That an EMC exists is not sufficient to invoke the duty to stabilize; the hospital also must have actual knowledge that the EMC is present. *Actual knowledge* is a legal term that means the examining emergency clinician subjectively *determined* that an EMC existed. It is not the commonly understood objective standard used in malpractice cases, wherein liability is predicated on whether the physician knew or reasonably *should have known* that the patient had an emergency condition. Whether the physician's judgment was negligent, or even grossly negligent, is irrelevant under EMTALA. The *subjective perception* of the examining emergency clinician controls whether EMTALA's stabilization requirement is triggered.

The appellate courts have uniformly held that if an EMC is not detected, the hospital has no stabilization duty and cannot be charged with failure to stabilize the patient's condition.[8,31,36] Furthermore, consideration or suspicion that an EMC may exist does not rise to the level of actual knowledge. If the hospital fails to detect an EMC through its standard screening procedures, the patient has only a state malpractice claim of "failure to diagnose" and not a federal cause of action for "failure to stabilize" the emergency condition. Once the physician or hospital does diagnose an EMC, however, the courts will allow a failure-to-stabilize claim to be brought in federal or state court under EMTALA.

This aspect of EMTALA is distinctly different from ordinary malpractice. Documentation in the medical record of "no EMC present" eliminates all further civil liability under EMTALA; understanding and use of this distinction should be part of every ED's risk management program.

The screening section of EMTALA mandates the hospital to provide only those services within the capability of the *ED*, including ancillary services routinely available to that department.[5] The stabilization section, however, requires the level of services within the capabilities of staff and facilities available at the *hospital*.[1,2,37]

The capabilities of the hospital staff include whatever intensity of care the personnel of the hospital can provide within the training and scope of their professional licenses and hospital privileges.[24] To ensure that hospitals can stabilize patients, Congress mandated that Medicare-participating hospitals maintain a list of on-call physicians available to provide treatment necessary to stabilize a patient with an EMC.[38]

Thus, whenever the ED determines that a patient has an EMC, the hospital must use the full capabilities of its staff, facilities, and on-call physicians to stabilize the patient.[2,37] If the hospital is unable to stabilize the patient, a physician must certify that a transfer is medically indicated and arrange an "appropriate" transfer to a higher level facility.

The treating emergency clinician needs to decide whether a patient's EMC is stable or unstable. If two clinicians disagree about whether the patient is stable but only one of the clinicians is at the bedside caring for the patient, the on-site clinician should

PHYSICIAN

Emergency Medical Condition (EMC) Identified: (*Mark appropriate box(s), then go to Section II)* **[Dr. Bitterman - 2015]**

I. MEDICAL CONDITION: Diagnosis_____

☐ **No Emergency Medical Condition Identified:** This patient has been examined and an EMC has not been identified.

☐ **Patient Stable -** The patient has been examined and any medical condition stabilized such that, within reasonable clinical confidence, no material deterioration of this patient's condition is likely to result from or occur during transfer.

☐ **Patient Unstable -** The patient has been examined, an EMC has been identified and patient is not stable, but the transfer is medically indicated and in the best interest of the patient.

I have examined this patient and based upon the reasonable risks and benefits described below and upon the information available to me, I certify that the medical benefits reasonably expected from the provision of appropriate medical treatment at another facility outweigh the increased risk to this patient's medical condition that may result from effecting this transfer.

II. REASON FOR TRANSFER: ☐ Medically Indicated ☐ Patient Requested _____

☐ On-call physician refused or failed to respond within a reasonable period of time.

Physician Name: _____Address _____

III. RISK AND BENEFIT FOR TRANSFER:

Medical Benefits :	**Medical Risks :**
☐Obtain level of care/ service NA at this facility. Service _____ ☐Benefits outweigh risks of transfer	☐Deterioration of condition in route _____ ☐Worsening of condition or death if you stay here. There is always risk of traffic delay/accident resulting in condition deterioration.

IV. Mode/Support/Treatment During Transfer As Determined by Physician– (Complete Applicable Items):

Mode of transportation for transfer: ☐ BLS ☐ ALS ☐ Helicopter ☐ Neonatal Unit ☐ Private Car ☐Other_____

Agency:_____ Name/Title accompany hospital employee:_____

Support/Treatment during transfer: ☐ Cardiac Monitor ☐ Oxygen – (Liters): _____ ☐ Pulse Oximeter ☐ IV Pump ☐ IV Fluid: _____ Rate: _____ ☐ Restraints – Type: _____ ☐Other:_____ ☐ None

Radio on-line medical direction control *(If necessary):* ☐Transfer Hospital ☐ Destination Hospital ☐ Other

V. Receiving Facility and Individual: __The receiving facility has the capability for the treatment of this patient (including adequate equipment and medical personnel) and has agreed to accept the transfer and provide appropriate medical treatment.

Receiving Facility/Person accepting transfer: _____Time: _____

Receiving MD_____

Transferring Physician Signature_____ Date/Time_____

Per Dr. _____ by _____RN/Qualified Medical Personnel _____ Date/Time

NURSING

VI. ACCOMPANYING DOCUMENTATION– sent via: ☐Patient/Responsible Party ☐Fax ☐Transporter
☐ Copy of Pertinent Medical Record ☐ Lab/ EKG/ X-Ray ☐ Copy of Transfer Form ☐ Court Order
☐ Advanced Directive ☐ Other _____

Report given (Person/title):_____

Time of Transfer: _____Date: _____ Nurse Signature: _____Unit:_____

Vital Signs Just Prior to Transfer: T_____ Pulse _____ R _____ BP _____ Time: _____

PATIENT

VII. PATIENT CONSENT TO "MEDICALLY INDICATED" OR "PATIENT REQUEST" TRANSFER:

☐ I hereby **CONSENT TO TRANSFER** to another facility. I understand that it is the opinion of the physician responsible for my care that the benefits of transfer outweigh the risks of transfer. I have been informed of the risks and benefits upon which this transfer is being made.

☐ I hereby **REQUEST TRANSFER** to _____. I understand and have considered the hospital's responsibilities, the risks and benefits of transfer, and the physician's recommendation. I make this request upon my own suggestion and not that of the hospital, physician, or anyone associated the hospital.
The reason I request transfer is: _____

Signature of ☐ Patient ☐ Responsible Person_____ Relationship _____
Witness_____ Witness_____

TRANSFER FORM

White:-Receiving facility; **Yellow:** Medical Record; **Pink:**-QA

Patient Name:

Date of Birth:

Medical Record Number:

Fig. e11.1. Emergency Medical Treatment and Active Labor Act (EMTALA) hospital transfer form.

make the decision.[2] It is *not* appropriate for an on-call physician, a "managed care gatekeeper" physician, a physician at a receiving facility, or even the patient's regular attending physician to disagree with the decision of the on-site physician over the phone. If one of these outside physicians wants to overrule the determination of the on-site clinician, he or she must come to the hospital and personally examine the patient.

EMTALA defines the term *stabilized* as follows: "no material deterioration in the condition is likely, within reasonable medical probability, to result from or occur during the transfer of the individual from a facility."[39] For a pregnant woman having contractions who has an EMC, *stabilized* means that delivery (including the placenta) has occurred.[40]

This is a *legal* definition of stabilization, not a medical definition. The standard of care for any patient diagnosed with an EMC will be judged by this legal definition, not by the usual medical malpractice standards. This is a national standard under federal law, not a local standard under state malpractice law.[9,40]

The question of "stabilization" typically arises only when the patient deteriorates during or after the transfer and experiences an adverse medical result. It is likely to appear, particularly in hindsight, that the patient was not completely stabilized before transfer. Health care providers should remember that their compliance usually will be judged by an unsympathetic jury, aided by hindsight, in the context of impairments suffered by the patient in an adverse medical outcome. Unfortunately, the court system, not the health care system, will ultimately determine when a patient with an EMC is legally "stabilized."[40]

Furthermore, the U.S. Supreme Court, in the case of *Roberts v Galen,* ruled that a plaintiff need not show improper motive for a transfer to prevail on a failure-to-stabilize claim under EMTALA. The plaintiff merely must prove that the patient was not properly stabilized before the transfer.[41]

EMTALA's requirement to provide on-call physicians no longer extends to inpatients diagnosed with an EMC.[2] Other Medicare conditions of participation govern inpatient care, and hospitals certainly should implement policies and procedures to provide emergency specialty services to patients in whom an EMC develops after admission to the inpatient setting.[2]

Disposition Issues Under Emergency Medical Treatment and Active Labor Act

Admission

Once the emergency clinician determines that a patient needs to be hospitalized, the patient's physician or the appropriate on-call physician should be contacted. If the admitting or on-call physician disagrees with the emergency clinician's judgment, it is incumbent on the admitting or on-call physician to come to the ED to personally examine the patient. This fact should be mutually understood by the entire medical staff and the hospital administration and should be written into hospital policy and procedure.

CMS does not apply the law to *inpatients* regardless of whether they are directly admitted to the unit, directly admitted by way of the ED, or "boarded" in the ED awaiting bed placement. Even if the inpatient is brought down to the ED, the law does not apply.[2,3,21] According to CMS, once a hospital admits the individual in good faith (ie, the admission is not a ruse to avoid liability under the law) as an inpatient for further treatment, the hospital's obligation under EMTALA ends.[31,42]

An *inpatient* is defined as "an individual who is admitted to a hospital for bed occupancy for purposes of receiving inpatient hospital services … with the expectation that he or she will remain at least overnight."[2] It does not matter if the situation changes later and the patient can be discharged or transferred to another hospital and does not actually use the bed overnight. The key element is that the patient be formally admitted with a documented admission order. An emergency clinician's intent to admit or a level of acuity indicating that the patient "obviously will be admitted" is not enough to satisfy the definition. Documentation is critical.[2,21]

CMS does not consider patients admitted to "observation" status to meet the regulatory definition of admitted patients (not admitted for purposes of receiving inpatient services), so EMTALA still applies to the care of observation patients, such as patients managed in ED chest pain or observation units.[2,21] Therefore, under existing government regulations, persons who were directly admitted and sent through or held in the ED from a physician's office, from a nursing home, or in transfer from another ED or another hospital inpatient setting are no longer covered by EMTALA, even though they have "come to the hospital's emergency department."

However, in 2009 the Sixth Circuit Court of Appeals in the case of *Moses v Providence Hospital* rejected CMS's interpretation, giving no deference to the agency's rulemaking authority. It overruled CMS's regulation that EMTALA ended when the hospital admitted the patient in good faith.[43] The court determined that the rule was contrary to EMTALA's plain language, which requires a hospital to "provide … for such further medical examination and such treatment as may be required to stabilize the medical condition."[44,45] Therefore, the Sixth Circuit Court held that the hospital was required under EMTALA not just to admit the patient into an inpatient unit for further care but to actually treat him such that he was stabilized before discharge.[45] Subsequently, the U.S. Supreme Court declined to review the controversial Sixth Circuit decision in *Moses,* so presently in the states of Michigan, Ohio, Tennessee, and Kentucky, EMTALA applies to inpatients, at least for civil litigation purposes, even if CMS will not apply that law to inpatients for regulatory purposes.[45-48]

"Discharge" or "Transfer" to Home

Because EMTALA defines any patient movement away from the hospital as a transfer, all patients discharged from an ED are legally considered to have been transferred.[47] Sending a patient home after treatment in the ED who is retrospectively determined to be unstable is considered to represent a transfer of an unstable patient and, as such, a violation of the law. This exposes the hospital to civil litigation under EMTALA for failure of its emergency clinicians to stabilize patients with known emergency conditions before discharge ("transfer") home.[1,41]

To avoid such retrospective analyses, emergency clinicians should document that no emergency condition was found or that the patient was stable on discharge. If the patient leaves without permission, the hospital has not legally transferred the patient.[47]

"Discharge" or Transfer From the Emergency Department to an on-Call Physician's Office

Because all discharges from the ED are defined as transfers under EMTALA, so too are discharges from the ED sent directly to an on-call physician's office for acute intervention. CMS looks askance at transfer of patients away from the hospital to a physician's office for acute procedures that could have been done in the ED or in the hospital.[3,49] Ophthalmologist services may constitute an exception because although the ED may have rudimentary eye tools; ophthalmologists typically have much better equipment in their offices for examination of patients with eye complaints to determine whether an EMC is present or to treat emergency conditions. In essence, movement to the office in these cases becomes a medically indicated transfer to receive a higher level

of services than the hospital can provide. CMS accepts such movement, so long as the ED arranges a formal transfer in compliance with EMTALA, as noted later.

CMS's view is extremely unsatisfactory, particularly to orthopedic surgeons. It is standard practice in most hospitals for the emergency clinician to splint various displaced fractures and send the patient to the on-call orthopedic surgeon's office for reduction of the fracture and further necessary treatment. CMS believes that the orthopedic surgeon should perform the reduction and treatment at the hospital in each case because the surgeon's office has no resources that the hospital lacks.

However, EMTALA applies only if the EMC is unstable at the time of transfer.[1,49] If the ED "stabilizes" the fracture, EMTALA's obligations end. Thus it is reasonable to send patients to the office for further treatment, so long as they meet the legal definition of "stable at the time of discharge" from the ED. The determination of whether the patient is stable for transfer to the orthopedist's office rests solely on the judgment of the examining emergency clinician. If the patient has accompanying injuries or is too uncomfortable to be moved, or if the emergency clinician believes the injury is such that the patient should not travel, then the orthopedic surgeon should be asked to care for the patient in the ED.

Follow-Up Care

If the patient does not have an EMC or is stable at the time of discharge, EMTALA does not apply from that point forward, and the on-call physician has no legal duty *under EMTALA* to see the patient in the office.

The real ED follow-up issue is the level of commitment the hospital and medical staff are willing to make to the community. If the administration, the board, and the medical staff are comfortable with their decision and if they have acted in the best interests of the patients that they serve, they should have no trouble defending their actions to CMS or any other entity.

Whatever decision the hospital and physicians make about ED follow-up duties, they should explicitly define those responsibilities in the medical staff bylaws or hospital rules and regulations so that all personnel understand, *prospectively*, what it means to be "on call" for the ED at that hospital.

ED discharge instruction sheets also should include a *fail-safe clause* advising patients to return to the ED if their condition deteriorates before seeing the referral specialist or if the follow-up arrangements disintegrate for any reason. Such a statement could help the hospital avoid liability when the on-call specialist fails to implement the prescribed follow-up plan.[50]

Transfers to Other Acute Care Hospitals

Before transferring a patient out of the ED, the emergency clinician must first determine whether the patient is stable, as defined by law. EMTALA regulates the transfer of unstable patients only; it does not apply to the transfer of stable patients.[2,49] If no emergency condition is found, the patient is considered stable. The determination of whether a patient is stable must be made at the time of transfer to be valid under the law.[49] Unstable patients can be transferred for only one of two reasons: if the transfer is medically indicated, or if the patient requests the transfer.[1,2]

Patients usually are transferred out of the ED because the transferring facility lacks the capability or the resources necessary to treat the identified emergency condition. Examples of patients best served by transfer are the head-injured patient in a hospital without a neurosurgeon on staff, the pregnant woman who needs the services of a high-risk obstetric center, and the multiple-trauma patient treated initially in a rural ED who requires treatment at a level 1 trauma center.

EMTALA defines such transfers as medically indicated transfers because the purpose of each transfer is to obtain a higher level of medical care necessary to treat the patient's condition that is not available at the transferring facility.[34] EMTALA governs almost every aspect of medically indicated transfers, including requiring hospitals to adopt and to enforce policies to ensure compliance with federal transfer laws and mandating specific actions by the transferring and receiving hospitals (summarized in Boxes e11.2 to e11.4).[1-3,51-53]

Some states have enacted their own transfer laws.[54] Most state laws parallel EMTALA, but some are even more restrictive, so emergency clinicians responsible for patient transfers should be aware of the controlling laws and regulations in their own state as well as under federal law.

Duty to Accept Appropriate Transfers From Other Hospitals

Medicare-participating hospitals that have specialized capabilities or facilities are required by EMTALA to accept appropriate transfers of patients who require such capabilities or facilities, if the hospital has the capacity to treat the patient.[55]

The duty to accept patients in transfer is a problematic issue for many larger, tertiary care, or academic hospitals as a result of

BOX e11.2

Recommended Procedures for the Transferring Facility

- Stabilize the patient whenever possible.
- Complete a physician certificate of transfer, including the risks and benefits of transfer.
- Obtain the patient's informed consent to the transfer.
- Arrange for another hospital and physician to accept the patient in transfer.
- Send appropriate data to the accepting facility (eg, medical records, test results, transfer forms).
- Arrange the transfer through qualified personnel with use of appropriate transportation equipment.
- Maintain records of all transfers for 5 years.

BOX e11.3

Invalid Reasons for Refusal of an Appropriate Patient Transfer

- Lack of insurance or out-of-network managed care plan
- Lack of citizenship
- Veteran status
- Patient's physician not on staff
- Transferring hospital is out of network or outside hospital's defined referral area
- "We are not an affiliated hospital."
- "We are not a specialty hospital."
- "We are a specialty hospital, but that's not our specialty."
- "We are not a 'trauma center'"
- Transfer originating out of county or out of state (including transfer of out-of-state Medicaid patients)
- EMS bypassed closer hospital
- Another hospital refused the transfer in violation of the law
- Another hospital's on-call physician refused to respond to its ED in violation of the law

ED, Emergency department; *EMS,* emergency medical service.

BOX e11.4

Recommendations for the Facility Asked to Accept the Patient in Transfer

- Accept all appropriate requests for transfer, regardless of whether the patient is an ED patient or an inpatient of the hospital.
- Have a formal system for accepting or rejecting transfer requests and document the reasons for any refusal to accept a patient in transfer.
- Maintain records of all transfers for 5 years.
- Report all EMTALA transfer violations to CMS.

CMS, Centers for Medicare and Medicaid Services; *ED,* emergency department; *EMTALA,* Emergency Medical Treatment and Active Labor Act.

the on-call specialty coverage crisis in the United States. Numerous hospitals have lost full or partial on-call coverage for specialties, such as neurosurgery, orthopedic surgery, maxillofacial surgery, neurology, plastic surgery, and hand surgery, increasing the number of patient transfers.[56-58]

Specialty hospitals also enticed physicians away from acute care hospitals, in part because the physicians could decrease their on-call burden. However, CMS now requires specialty hospitals to accept appropriate transfers even if the specialty hospital lacks an ED.[59]

When Must a Receiving Hospital Accept a Patient in Transfer? A Medicare-participating hospital must accept medically indicated transfers if it has "specialized capabilities or facilities" and the "capacity" to care for the patient.[1] *Specialized capabilities* or *facilities* are essentially any resources, other than a routine admission bed, or physician services available at an accepting hospital but not available at the transferring hospital. *Capacity* is rather generously defined by CMS to include whatever a hospital customarily does to accommodate patients in excess of its occupancy limits. For example, if a hospital customarily moves patients to other units or calls in additional staff, it has in fact demonstrated the ability to provide services to patients in excess of its occupancy limits.[49,60]

Who Accepts Patients on Behalf of the Hospital? The duty to accept appropriate transfers is a hospital duty, not a physician duty, and EMTALA does not require that a physician accept the patient.[1,2] Each hospital must create a formal system designating who is authorized to accept or to reject patients on its behalf. It is strongly recommended that hospitals do not use the individual physician on call for each specialty *alone* to accept or to reject patients in transfer. Hospitals should involve an administrative person or an emergency clinician in addition to or instead of the on-call physician to avoid inappropriate refusals. Because the duty to accept rests with the hospital, any inappropriate refusal by an uninformed or rogue on-call physician subjects the hospital to termination from Medicare, civil monetary penalties, or civil liability if the patient is harmed because of the refusal to accept the patient in transfer.

The hospital should define the resources and capacity of the institution and the times during which those resources are available. When capacity or necessary resources are not available, the hospital should in a timely manner inform the persons charged with accepting or rejecting transfers. The hospital also should educate appropriate personnel in its known referral facilities on the proper procedure to transfer patients into its system, including informing them of who is and who is not authorized to accept patients in transfer on behalf of the hospital. The hospital is required to educate its medical staff, particularly its on-call physicians and emergency clinicians, about their responsibilities under EMTALA, including the responsibility to accept patients in transfer from other facilities on behalf of the hospital.[61]

Does a Hospital Have to Accept Transfers of Inpatients From Other Hospitals? Current CMS-issued regulations state that no hospital has a legal duty under EMTALA to accept an inpatient in transfer from another hospital.[2] Therefore, even if a requested hospital could treat an inpatient's emergency condition that the transferring hospital is unable to treat, it may refuse the transfer for any reason, including an economic reason, and not be in violation of EMTALA.

However, the issue is certain to be litigated and decided by the courts. It is inevitable that an inpatient will develop an EMC and proceed to die or suffer severe damages because no other hospital would accept the patient in transfer due to of lack of insurance. The patient or family will sue the hospital that refused to accept the patient in transfer, claiming that the hospital had a federal duty under EMTALA to accept appropriate transfers of patients with emergency conditions if the transferring hospital could not treat the emergency. The transfer acceptance section of EMTALA was not part of the law when it was originally enacted. Congress later amended the law, calling it the "nondiscrimination" section, because tertiary and academic referral hospitals were refusing to accept patients in transfer from other hospitals, leaving the patients to die in community EDs.[62] This issue was not specifically addressed in the Sixth Circuit opinion in the *Moses* case, although the court's ruling applying EMTALA to inpatients strongly suggests that it would also apply EMTALA's transfer acceptance section to inpatients as well as to ED patients.[45] Thus it still remains to be seen if the courts will ultimately interpret EMTALA contrary to Congress's nondiscrimination intent for patients with life-threatening emergencies.

When Can a Hospital Refuse to Accept a Patient in Transfer? There are only five reasons for which a hospital can refuse a request for transfer under EMTALA.

First, if the transfer is not a medically indicated transfer, a hospital can decline the transfer.[1,2,49] Non–medically indicated transfers include patient-requested transfers and lateral transfers for any reason (*lateral* meaning that both hospitals have the same ability to handle the patient's EMC), such as managed care transfers or family- or physician-requested transfers. Any time the sending facility can handle the patient's EMC, a hospital requested to accept the patient in transfer can lawfully decline.

Second, if the hospital does not have the capacity, as defined by CMS, to accept the patient in transfer, it may and generally should refuse the transfer.[1,2,60]

Third, if the transferring hospital is located outside the boundaries of the United States, the hospital has no legal obligation under EMTALA to accept the transfer.[63] No other territorial limits are imposed on the duty to accept transfers; out of county, out of state, and out of the hospital's designated referral area all are invalid reasons to refuse patients in transfer under EMTALA. Moreover, a hospital cannot refuse to accept a transfer just because the sending hospital is "skipping over" other hospitals to send the patient its way.

Fourth, if the transfer is not "appropriate," the hospital may refuse to accept the patient in transfer at that time.[1,2] This more vague reason takes into account the patient's condition at the time of transfer and the time, distance, and skipping over of other hospitals necessary to reach a receiving hospital. For example, a trauma patient may need intubation and a chest tube inserted before the transfer is appropriate, or traveling 100 miles with hypotension from a ruptured abdominal aneurysm may not be appropriate if closer hospitals are capable of repairing the aneurysm.

Fifth, the patient has been "admitted" to the hospital as defined by CMS (except in hospitals under the jurisdiction of the federal Sixth Circuit Court of Appeals, at least with respect to civil liability, as noted earlier in this chapter).[1,2,45,49]

There are no other reasons for which a hospital may refuse a request to accept a patient in transfer from another acute care hospital under EMTALA. Furthermore, no "contingencies" are allowed to be placed on the acceptance of a transfer. The receiving hospital may not condition acceptance of the patient on the transferring hospital's agreeing to take the patient back once the emergency condition is resolved, may not require that the transferring hospital have additional consultations completed before the emergency clinician transfers the patient, and may not require the transferring hospital to use the receiving hospital's transport ambulance or helicopter service as a condition for accepting the patient.[64]

Also, refusals of appropriate transfers on the basis of the patient's insurance status or delay of appropriate transfers until the transferring hospital obtains authorization for payment from the patient's managed care plan are definitely illegal under EMTALA.[65]

Duty to Report Transfer Violations. Any time a hospital has reason to believe it may have received a patient transferred in an unstable condition from another hospital, in violation of EMTALA, it must report the transferring hospital to CMS.[66] The duty to report rests with the hospital, so emergency clinicians who receive unstable patients in transfer should inform the hospital (risk management or the hospital's legal counsel), which then can determine the appropriate action.

CONSENT FOR MEDICAL CARE

Informed Consent

The doctrine of *informed consent* is a fundamental principle of the American legal system.[67,68] Emergency clinicians may not examine or treat any person without consent, and that consent must be informed. This means that the patient must be given all pertinent ("material") information concerning the nature, risk, and alternatives of the treatment before that patient can be deemed to have effectively consented to the medical intervention.

Clinicians should endeavor to obtain informed consent yet remain cognizant of the significant limitations on and multiple exceptions to the doctrine, especially in the ED setting. Delaying treatment in an emergency to obtain informed consent is a much more serious and common medicolegal problem than failure to obtain proper informed consent.

The law of informed consent contains a great deal of uncertainty, with many gray areas. Different states have different views, either in their statutory laws (legislation) or in their common law (judge-made law or precedent), on the meaning of "informed consent" in the care of the ED patient. Most cases are unique and depend on the specific circumstances.

Emergency clinicians rarely have time to seek legal consultations, let alone wait for a court to render a decision concerning the legal nuances of consent issues. In these situations, it is helpful for emergency clinicians to use a *when-in-doubt rule* to guide their immediate actions. This rule simply states that when emergency clinicians are in doubt about the legality of a situation, "they should do what they believe to be in the patient's best interest and worry about the legal consequences later." Although emergency clinicians risk criminal and civil charges of false imprisonment, battery, and even negligence for failure to obtain appropriate informed consent, the courts almost universally rule in favor of physicians who act in good faith on behalf of their patients in emergency situations. Successful civil litigation regarding an issue of consent theory against an emergency clinician acting reasonably, and consistent with the appropriate standard of care, is extremely rare. An emergency clinician is much more likely to be sued for failure to treat while waiting for consent than for providing reasonable treatment without consent.

Federal Versus State Laws

Both federal laws (eg, EMTALA) and state laws govern consent.[5,34] EMTALA comes into play primarily in the evaluation of minors and with patient refusal of stabilizing treatment or transfer. State consent laws vary widely and may be set by statutes or case law, or both. The concepts discussed next are generally applicable to emergency medical care, but all emergency clinicians should learn the consent laws specific to their own state.

The law presumes that an adult is mentally competent to make medical decisions and that the competent adult is entitled to sufficient information to make an informed decision concerning the physician's proposed course of examination and treatment. Under the doctrine of informed consent, clinicians have the duty to disclose the following information to patients[69]:

- The patient's condition or diagnosis
- The nature and purpose of the proposed treatment, including the likelihood of success in the clinician's practice
- Reasonable alternative measures related to the diagnosis and treatment, including the probable outcome of those alternatives
- The particular known inherent risks that are material to make an informed decision about whether to accept or to reject the proposed treatment, including the consequences of refusing that treatment

Reasonable Person Versus Professional Disclosure Standard

The states are split on the standard used to determine what should be disclosed for patients to make informed decisions, but most require the reasonable person standard of disclosure. Under this standard, a clinician is required to disclose all of the information that a reasonable person would require to make a decision under the facts and circumstances of the case. The less frequent standard, the professional disclosure standard, requires the physician to provide the same information that other physicians in the community would provide to patients in the same or similar circumstances. This is less stringent than the reasonable person standard.[69]

Clinicians are not required to disclose every remote risk associated with a procedure or risks that are common knowledge or obvious to the patient, such as the risk of infection after wound repair.[70] The law requires disclosure only of risks that are material, as judged by their seriousness or chance of occurrence. Courts define *material information* as information that "the physician knows or should know would be regarded as significant by a reasonable person in the patient's position when deciding to accept or reject the recommended medical procedure."[71]

Some states legally require clinicians to disclose specific risks, such as death.[70] Some states statutorily require a clinician to meet both the reasonable person standard and the professional disclosure standard.[72,73]

Emergency Clinician Role in the Consent Process

The emergency clinician who proposes to undertake the procedure must be the one to obtain the patient's informed consent. The duty to obtain consent cannot be delegated, so clinicians cannot ask nurses or other health care providers to obtain patients' consent on their behalf. The emergency clinician who will care for

the patient is best qualified to discuss the treatment and its risks and benefits with the patient. Nurses as well as physicians not skilled in performing the procedure cannot obtain valid informed consent.[74]

The clinician should write or dictate into the patient's medical record a summary of the discussion held with the patient and family concerning the elements of informed consent. Particular attention should be made to documentation of those material risks discussed with the patient before the patient's consent is obtained.

Consent is a *process,* not a signature. A written, signed, separate consent form is not legally required under the doctrine of informed consent; however, hospitals may require emergency clinicians to complete standardized consent forms and to obtain the patient's signature. The signed form is not a substitute for the consent process. It cannot replace the exchange of information that occurs between the physician and the patient and family, the answering of questions, and the ultimate agreement of the patient to undergo the medical or surgical intervention.[74]

A signed, written consent form, however, does constitute some evidence of a valid consent. In some states, a signed consent form is presumed to represent valid consent unless that presumption is rebutted by proof that the consent was obtained by fraud, deceit, or misrepresentation of material fact.[75]

Implied Consent in Emergency Situations

If an unconscious or incapacitated patient cannot express consent, the law will assume the patient consented to treatment for the emergency situation. Implied legal consent is premised on two principles: (1) duty to obtain informed consent is excused if death or irreparable harm may result if the clinician delays treatment, and (2) the law presumes that a reasonable, competent, lucid adult would consent to lifesaving treatment.[76]

The emergency treatment allowed is limited to the circumstances of the emergency, however, and only treatment required to resolve the emergency should be undertaken without consent. Similarly, the emergency condition must require immediate medical attention, with insufficient time to inform the patient or to seek consent from another person.

Courts differ on the definition of a "true emergency," and whether the emergency exception applies in a given case depends on the definition accepted by the court and the application of that definition to the particular set of facts. Fortunately, the courts generally will stretch the doctrine to protect clinicians who act in good faith in caring for a patient with a perceived emergency condition.[77] This is one situation in which use of the when-in-doubt rule and documentation of the clinician's concerns will weigh greatly in the court's determination of whether the clinician acted appropriately without obtaining informed consent. Clinicians can further protect themselves by obtaining a second opinion that a true emergency exists.

Minors

Minors Accompanied by a Parent or Legal Guardian

Parents and legal guardians have the right to consent on behalf of their minor children. However, they need to act reasonably and in the best interests of their children. If they do not, their right to consent can be abrogated by the state or the courts.[78] Parents are not allowed to refuse treatment for a child with a life-threatening emergency condition. The management of children with emergency conditions whose parents refuse to give their consent to treatment is discussed later.

Either natural parent of the minor child may provide legally binding consent. If one parent agrees with a proposed treatment and the other does not, consent may be accepted from the agreeing parent. Even if separated or divorced, either parent may give consent unless one parent has been judicially granted sole legal custody of the child, in which case only the custodial parent may consent. The child's biologic father, even if never married to the mother, also may consent for his child.

Unaccompanied Minors

EMTALA mandates that all persons presenting to an ED requesting care be examined to determine whether an emergency condition exists.[5] Because EMTALA is federal law, it takes precedence over all state consent laws regarding the initial evaluation of a minor child. In essence, the child's mere presence at an ED requesting examination or treatment constitutes legal consent to examination of the child to determine whether an emergency condition is present. Furthermore, the hospital should not delay this initial screening evaluation to wait for consent from a parent or legal guardian (and nurse triage does not qualify as the required medical screening, no matter how non-urgent the child's condition appears to the nurse).

If an emergency condition is discovered through the initial screening examination, the clinician may treat the emergency under either state or federal legal theories.[5,34] First, under state laws, the standard emergency exception doctrine applies. State laws allow clinicians to proceed with treatment whenever an emergency exists. Although no uniform legal definition of emergency exists among the states, state laws tend to define an emergency liberally, such as "any threat to the minor's life or health." The courts almost always affirm a clinician's judgment about an emergency condition and rarely question the treatment given to a minor without parental consent.[78] Preserving life, preventing permanent disability, alleviating pain and suffering, and avoiding eventual harm have been used as guidelines for emergency treatment without consent.[74] Any minor presenting to the ED should be triaged and provided with an MSE to determine whether an emergency condition exists.

Under EMTALA, if an emergency condition is present, the hospital and emergency clinicians are required to provide "stabilizing treatment."[1] Federal law also gives the clinician broad discretion to decide what treatment should be performed and in what time frame it should be accomplished. The stabilization requirement includes transfer as necessary to an institution capable of handling the minor's emergency condition. Thus, under federal law, a minor could be examined, stabilized, or transferred to another institution without consent ever being obtained from the family; in this instance, the care would be not only in the patient's best interest but also legally mandated.[5,34,49]

In general, if the MSE does not reveal an emergency condition, clinicians need to obtain proper consent from the minor's parents or legal guardian. However, state laws and the courts have applied a number of exceptions to allow minors to seek treatment on their own without parental consent. These exceptions (such as the *mature minor* and the *emancipated minor* exceptions) vary widely from state to state, and most are applied through an analysis of facts and circumstances on a case-by-case basis by the courts.[79,80] In addition, most states have statutory reasons, such as sexually transmitted diseases, pregnancy, or domestic violence injuries that allow minors to seek care without the consent of their parents.[81]

Incompetent or Incapacitated Adults

If a person has been declared legally incompetent by a court, consent must be obtained from the person's court-appointed legal guardian. In addition, people may appoint legal surrogates to make legal decisions for them should they become incompetent. State-sanctioned living wills, advance directives, and durable

medical power of attorney documents all transfer consent powers from a person who becomes incompetent to a legally appointed surrogate.[68]

If an incompetent adult lacks a legal guardian or an appointed surrogate, emergency clinicians typically look to the patient's family for consent to treatment. However, consent to treatment by a family member, even the patient's spouse, generally is not acceptable under American law unless the spouse or family member has been appointed legal guardian by a court of proper jurisdiction.[82] Marriage does not confer one spouse the legal capacity to consent to medical treatment for the other spouse, even when the ill or injured spouse is incompetent.

Some states recognized this problem and enacted "family consent statutes," which outline a hierarchy of family members who can legally provide consent when the family member becomes incapacitated.[83] However, even when families have no legal standing to consent for the incompetent relative, it is wise to involve family in the medical decision-making process. Communication and concern for the family will avoid misunderstandings, surprise, and anger, which are the primary sources of litigation. Fortunately, if an emergency exists, no authorization from family is necessary to provide such reasonable care as is necessary to correct the life-threatening situation. Once the emergency is resolved, consent should be obtained from someone authorized to act on behalf of the incompetent patient. If there is no appointed legal guardian or surrogate and no state statute on family consent, the emergency clinician should seek consent authorization from the courts. The courts may appoint a guardian at that time, generally a family member, or after judicial review of the issues, the court itself may grant consent on behalf of the incapacitated person.

Other Special Populations of Patients

Prisoners

Competent prisoners generally do not surrender the right to consent by virtue of being incarcerated. However, a state or court may compel treatment on the basis of interests perceived as paramount to the prisoner's interests.[84,85]

Alcohol-Intoxicated Patients

Alcohol intoxication itself may not render a patient incompetent to give informed consent.[86] The emergency clinician should evaluate each situation individually to determine whether the patient is incapacitated by alcohol to the extent that he or she is no longer able to understand the proposed treatment, risks and benefits, and rational alternatives. In essence, the general rules for determination of whether a patient is competent to make informed decisions cannot be disregarded just because the person is intoxicated with alcohol. However, the when-in-doubt rule is particularly applicable in these cases because alcohol intoxication often is associated with occult serious illness or injury.

Alcohol intoxication, especially if it is documented by a measured blood alcohol concentration (BAC), is strongly suggestive to courts and juries of impaired mental status, even though health care workers recognize that many alcoholics are entirely rational and competent at fairly high BACs. Conversely, low BACs do not guarantee competence because other processes (eg, hypoglycemia, blood loss, impairment from other illicit substances) may cause the patient to be incompetent. Thus the patient's clinical capacity is more important than the specific level of alcohol in determining competence.

One advantage of obtaining a BAC is that some states allow blood samples drawn solely for medical purposes to be subpoenaed later by the prosecutor for use against the driver in a driving-while-intoxicated prosecution or other criminal charges.[87]

The state "legal limit" of intoxication is not a measure of a patient's competence. The legal level for driving has little if anything to do with the capacity to make informed medical decisions. However, this distinction is sometimes difficult for judges and juries to understand, and the emergency clinician can actually use the blood level to support a judgment that the patient was not competent to make informed decisions in a particular instance. At other times, it is better not to have a "number" so that the only relevant criterion for determination of the patient's competence is the clinician's judgment.

Patients Given Pain Medications

As with alcohol intoxication, the mere fact that a patient has been given narcotic analgesia does not render that patient incapable of consenting to invasive diagnostic procedures or surgery. Plaintiff attorneys can always argue "the patient was too snowed with drugs to give consent;" on the other hand, they can equally argue that the patient was "in too much pain to consent and would have agreed to anything to stop the pain." Accordingly, when consent is sought from a patient who has received pain medication, the patient's ability to understand the ramifications pertaining to the procedure should be assessed and taken into consideration, involving the family in the process if possible. The emergency clinician should document that the patient's pre-medicated state was considered in judging the patient's competence to make an informed decision.

REFUSAL OF MEDICAL CARE

Informed Refusal

The corollary to a patient's right to give informed consent is the patient's right to refuse medical care, even if such refusal results in death. The U.S. Supreme Court holds that a competent adult has a constitutionally protected right to refuse medical care.[88] However, that right is not absolute. Under particular circumstances, courts will consider countervailing compelling state interests, such as preventing suicide, preserving life, and protecting innocent third parties.

Physicians who honor a competent patient's decision to refuse treatment are not liable for any resulting bad outcome.[89] In fact, emergency clinicians are more likely to be successfully sued for treating patients over their objections or without their consent, even when the treatment is lifesaving.

When a competent adult refuses indicated medical intervention, it often is because of fear, anger, misunderstanding, or some other failure in communication in the clinician/patient relationship. Before allowing a patient to refuse care, the emergency clinician should try to determine and resolve the underlying reasons behind the patient's refusal.

The attending physician must always be involved when a patient refuses medical care or expresses the intent to leave against medical advice.

As with consent, refusal of medical care is a process, not a signature. It must be an informed refusal; merely having the patient sign an "informed consent to refuse examination, treatment, or transfer" form or an "against medical advice" form is not sufficient. There are four essential components of the refusal process: determining competence, ensuring an informed decision, involving others, and documenting appropriately.

Determining Competence

The emergency clinician must determine that the patient is competent to make decisions. Normal findings on the mental status

examination without evidence of diminished mental capacity from closed head injury, severe pain, hypoxia, hypotension, alcohol intoxication, mental retardation, or mind-altering substances constitute good evidence of competency. Noting the patient's rationale for refusing care, even if it is not reasonable, provides additional evidence of competency.[74]

Ensuring an Informed Decision

To be legally binding, a decision to refuse a test or treatment or to sign out against medical advice must be an informed decision. The emergency clinician should explain the severity of the patient's condition, the potential complications, and the alternative treatments available. The emergency clinician should use terms that the patient can understand and provide the patient an opportunity to ask questions. The patient should understand that the risks of refusing care include the possibility of permanent disability and death. Ideally, a witness should be present when the clinician informs the patient and any family members.

Involving Others

The patient's family, friends, and personal physician should be involved whenever possible. These persons should hear the same message as that conveyed to the patient, because they may be able to persuade the patient to accept the recommended therapy. If the patient expressly forbids the emergency clinician to speak with others, as is the patient's legal right, this should be explained to them and documented in the medical record.

Documenting Appropriately

Appropriate documentation of the refusal process is necessary to protect the physician and hospital from inappropriate litigation.[90] The patient should be asked to sign the refusal form.[2,74,78] Figure e11.2 shows a sample leaving against medical advice form.

If the patient refuses to sign the form, that fact should be documented and the form signed by a hospital representative who witnessed the patient's refusal. The medical record should reflect the patient's mental status examination findings and competency to make informed decisions, the risks and benefits of recommended treatments, the available alternatives, and the participating family or friends. Documentation of the patient's rationale for refusing treatment, that the patient was treated to the extent allowed by the patient, and that the patient was invited to return for care at any time offers added protection.[78,90]

Federal Rules

EMTALA requires hospitals to take and to document specific actions when patients refuse medical screening, treatment and stabilization, or transfer. The government and the federal courts presume that the patient requested emergency care and place the burden of proof on the hospital to demonstrate that the patient voluntarily refused care.[2,49,91]

There are essentially two scenarios in which patients leave the ED after refusing examination or treatment. First, some patients simply pick up and leave, without the knowledge of anyone affiliated with the hospital. If the patient's departure is witnessed, the patient does not respond to requests to return for the examination or to discuss the issues with the hospital staff. These patients are generally referred to as those who "leave without being seen" (LWBS) or "leave before examination." In the second scenario, the hospital personnel are aware that the patient is about to leave and have an opportunity to interact before the patient leaves. Hospitals generally refer to this as "leaving against medical advice." The Office of the Inspector General and CMS refer to both of these scenarios as "voluntary withdrawal" of the patient's request for evaluation or treatment.[49,92]

Leaving Without Being Seen

If a patient walks out before the MSE and later has an adverse medical result, the burden will be on the hospital to prove that the person left voluntarily and was not denied examination or treatment by the hospital.[22,49]

Hospitals need to have a policy and practice for LWBS patients that adequately document pertinent findings and protect the hospital from liability. In most hospitals, the staff calls the patient and checks the waiting area at least three times before declaring that the patient has left the department. These serial checks, with time of day performed, should be documented on the patient's record, and once it is evident that the patient is no longer present, the record should be reviewed on a timely basis by the emergency clinician on duty. If the reviewing clinician discovers something of concern regarding the patient's chief complaint or triage data, the person can be contacted and encouraged to return to the ED. The registration papers, triage records, nursing documentation at triage, and emergency clinician's review and documentation of that review should be kept in the patient's permanent record. These records should be retained for a minimum of 5 years to protect the institution should the interaction ever be the subject of a retrospective EMTALA investigation or litigation on behalf of the LWBS patient.[2,49]

Leaving Against Medical Advice

If hospital personnel are aware that a patient intends to leave before completion of the MSE or stabilizing treatment for whatever reason (eg, tired of waiting, changes mind, concerned about cost of care), the hospital should handle and document the interaction carefully to avoid EMTALA or medicolegal liability (Box e11.5).[49,93,94] In each case, the following steps should be taken:

1. *Inform the patient of the hospital's obligation under the law.* The ED staff should inform patients of their rights under the EMTALA to receive medical screening and any necessary stabilizing treatment from the hospital, regardless of their ability to pay for that service.
2. *Determine the patient's competence.* Only legally competent persons can refuse necessary medical care. For example, alcohol-intoxicated patients who present to the hospital with medical complaints cannot be allowed to leave the hospital without examination and treatment until it is determined that they are legally competent to make such a decision.
3. *Explain the risks and the benefits to the patient.* For patients to make an informed consent to voluntarily withdraw their request for services, they need to understand the benefits and the risks of withdrawal before refusing examination and treatment. These risks and benefits should be specific to the patient's chief complaint.
4. *Secure the patient's written informed consent to refuse care.* The hospital should take all reasonable steps to secure the patient's written and informed consent (ie, obtain a signature) to refuse medical care. A standard form should be used that contains space for documentation of the patient's competence, the risks and benefits discussed, and whether the patient's family was available to be involved in the discussions. If the patient refuses to sign the form and simply walks out after the interaction with the hospital, the person who discussed the issues with the patient and witnessed the patient's refusal should sign the form and document the interaction.
5. *Offer alternative care within the scope allowed by the patient.* It is outside professional practice standards to respond angrily, to act vindictively, or to punish patients when they decide

INFORMED CONSENT TO REFUSE EXAMINATION, TREATMENT, OR TRANSFER

I understand that the hospital has offered: (Check all that apply).

A. To examine me (the patient) to determine whether I have an emergency medical condition, or

B. To provide medical treatment or to provide stabilizing treatment for my emergency condition, or

C. To provide a medically appropriate transfer to another medical facility.

The hospital and physician have informed me that the ***benefits*** that might reasonably be expected from the offered services are: _____

_____

and the ***risks*** of the offered services are: _____

_____

Physician Documentation

The patient appears competent and capable of understanding risks and benefits.

Alternative treatments discussed with the patient.

Patient's family involved. Family not available. Patient does not want family involved.

Signature of Physician _____

Patient or Legally Responsible Person Documentation

I have declined to have the physician fully explain to me the risks, benefits, and alternatives to leaving the hospital against medical advice. I knowingly and willingly take and assume the responsibility for all risks incurred.

or

The physician has fully explained to me the risks and benefits but I choose to refuse the offered services. I understand that my refusal is against medical advice, and that my refusal may result in a worsening of my condition and could pose a threat to my life, health, and medical safety. I understand that I am welcome to return at any time.

Signature/Patient or Legally Responsible Person _____

Print Name _____ Address _____

City _____ State/Zip _____ Date _____ Time _____

Witness/Signature _____ Print Name _____

The patient or person legally responsible for the patient was offered but refused to sign form after explanation of their rights and the risks and benefits of the services offered.

Hospital representative who witnessed refusal to sign: _____

Date _____ Time _____

Informed Consent to Refuse Examination Form [Hospital Addressograph or Sticker Goes Here]
White/Patient Record Yellow/Transfer With Patient Pink/Q/A [Robert A. Bitterman, MD JD - 2015]

Fig. e11.2. Leaving against medical advice form: Informed consent to refuse examination, treatment, or transfer.

to leave against advice by refusing to provide alternative treatments, medications, analgesics, or discharge instructions. Patients always get to define the scope of medical services that they are willing to accept. Accordingly, an appropriate strategy is to negotiate and cajole them into allowing the best possible care under the circumstances that they define. Negotiation aims for the best alternative that the patient is willing to accept, even if that means providing less than optimal treatment.

Pain medications should never be withheld because the patient will not accept the recommended treatment plan. This "strategy" is cruel, further alienates the patient, and serves

BOX e11.5

Protocol for Management of Leaving Against Medical Advice Cases in the Emergency Department

- Always involve the emergency clinician.
- Involve the family or the patient's personal physician whenever possible.
- Explain the risks and benefits specific to the patient's condition; "You could die" alone is too generic.
- Explain any alternative treatment options to the patient.
- Ascertain the patient's capacity to make informed medical decisions: "When in doubt, don't let 'em out!"
- Have the patient and at least one witness sign the leaving against medical advice form.
- If the patient refuses to sign the leaving against medical advice form, a member of the hospital staff should sign the form stating that the patient refused to sign the form.
- Always still provide the best possible treatment within the scope allowed by the patient, including antibiotics and analgesics when warranted.
- Provide appropriate discharge instructions and welcome the patient to return to the ED at any time if he or she reconsiders and decides to accept the recommended care.
- Document discussions with the patient, the risks explained, and the patient's medical decision-making capacity and understanding of the ramifications of leaving against medical advice in the medical record (and in real time, not hours after the patient has left the ED).

ED, Emergency department.

no useful purpose. Moreover, patients should always be invited to return to the ED (or encouraged to see their private physician) if they change their mind and become willing to accept the recommended treatment.

A patient's refusal of the more appropriate treatments as well as communication of offers to provide treatment within the circumstances proscribed by the patient should be delineated.

6. *Document the interaction in the patient's hospital record.* The medical record, preferably a dictated and transcribed medical record, should accurately relate the interaction between the hospital and the individual refusing ED care. The record reflects the hospital's conformity to the law and the patient's leaving of his or her own accord—specifically, the risks of refusing the examination and the reasons for the patient's refusal. Documentation of the reasons for refusal provides evidence that the hospital did not economically coerce or in any way financially deter the patient from remaining for the MSE. The chart should clearly indicate that the patient did not leave the department on the basis of a "suggestion" by the hospital concerning any financial issues.

Parent or Guardian Who Refuses Care or Blood Transfusions for a Minor

In general, state laws support parental control of health issues affecting their children. However, the state will not allow parents to deny children needed emergency medical care under the doctrine of *parens patriae,* the state's paternalistic interest in children.[78] All states empower emergency clinicians to intercede under their child abuse and child neglect laws. When a child's injuries are potentially life-threatening, the emergency clinician can take custody of the child under the child abuse laws and provide indicated treatment, including blood transfusions. In deciding whether to act, the when-in-doubt rule definitely applies, and all jurisdictions statutorily protect clinicians from criminal and civil liability for acting in good faith to protect children.[78]

The courts have specifically addressed the issue of Jehovah's Witness parents attempting to refuse emergency blood transfusions for their minor children. All jurisdictions hold that a parent's right to freedom of religion does not include the right to deny life-sustaining medical intervention for that person's children.[95,96] Some states specifically address the issue of overriding parental refusal of indicated medical intervention by statute. In North Carolina, for example, if the parents refuse to consent to treatment and the delay to obtain a court order would seriously worsen the child's physical condition or endanger the child's life, and if a second clinician agrees that the procedure is necessary to prevent immediate harm, an emergency clinician can render treatment without parental consent. If a second clinician cannot be contacted before treatment is initiated, the emergency clinician may still perform the indicated therapeutic intervention without parental consent.[97]

Conversely, courts refuse to rule against the parents' wishes when the child's medical condition is not serious or life-threatening. If there is no life threat or potential for serious impairment, the parents' refusal should be respected. Parental refusal of indicated nonemergency medical treatment is usually statutorily defined as "child neglect," which is not legally sufficient to take custody of the child. Child neglect should still be reported to the appropriate authorities; treatment for the child can then be obtained under a court order.[78]

Jehovah's Witnesses

Adult Blood Transfusions

Jehovah's Witnesses and the issue of blood transfusion present difficult medicolegal issues in the ED.[98] State courts may have widely divergent views on the issue, and no clear-cut answers exist. However, the current trend is granting patients greater autonomy to refuse blood, even when the state asserts compelling interests to override a person's refusal.

General principles of consent and the when-in-doubt rule apply, but hospitals and medical staff also should develop policies and procedures in advance to resolve potential conflicts with the Jehovah's Witness patients in the community; coordinate the management of each case with hospital legal counsel, in contact with a judge who can issue court orders when appropriate, if time allows; have other clinician consultants write notes of agreement regarding the need to give blood; and communicate effectively with patients and family, in advance when possible.

Competent Adult

The courts have found that "the competent adult has the right to refuse a transfusion regardless of whether his refusal to do so arises from fear of adverse reaction, religious belief, recalcitrance, or cost."[99] This applies "even though we may consider a patient's beliefs unwise, foolish, or ridiculous."[99,100] However, even this right is not absolute. If the patient's refusal conflicts with compelling state interests such as the preservation of life, the prevention of suicide, or the protection of innocent third parties, the courts may order transfusions despite the person's objections.[78,98] Previously, typical scenarios in which the courts overrode a competent person's refusal included cases involving pregnant women to protect the life of the fetus, mothers of young children to promote the general welfare of the children, and a sole supporting father or mother to prevent offspring from becoming wards of the state.[101] Some courts, however, have significantly restricted the hospital's

or state's ability to assert compelling interests challenging a competent person's right of self-determination.[102]

Unconscious or Medically Incompetent Adult

In an emergency, if the Jehovah's Witness's beliefs are unknown, physicians may transfuse the patient because consent will be implied under the emergency doctrine. It is irrelevant if the spouse, mother, or other family members adamantly refuse to allow the transfusion for religious reasons. The state's compelling interest in preserving life outweighs the family's expression of the patient's religious preferences.[98,103]

When a Jehovah's Witness's beliefs and transfusion preferences are known in advance but the patient is incompetent at the time of the emergency, the courts tend to accept objective evidence of the patient's wishes. For example, a signed card carried by the patient that identifies him or her as a member of the Jehovah's Witnesses and sets out the religious objection to blood transfusion may be accepted as adequate evidence of the patient's intent. Like a form of advanced directive, it is binding on hospitals and emergency clinicians. In a number of states, if the card is dated and signed before two witnesses, it is statutorily valid.[104] Even if the blood refusal card does not conform to a state's advance directive statute, it should be considered strong evidence but not necessarily determinative of the Jehovah's Witness's wishes. Advance directives are merely a means to express an individual's rights and are not the exclusive means to express those rights legally.[98] Jehovah's Witnesses increasingly use state statutorily defined advance directive methods to legally express their intentions.[98,105] Emergency clinicians should, naturally, be certain the card or advance directive actually belongs to the patient.

REPORTING REQUIREMENTS

All states require hospital EDs to report certain events, such as deaths, violent acts, animal bites, or child abuse; or illnesses, particularly those of epidemiological concern, to local public health authorities. The state's primary intent is to prevent the spread of communicable diseases, to protect its citizens from disease and violence, and to prosecute criminal acts. In each instance, the state statute overrides patients' rights of confidentiality. The statutes typically also provide clinicians with immunity from civil liability or criminal prosecution if the reporting is done in good faith.

All EDs should maintain up-to-date lists of diseases and incidents that must be reported to the state. The process and responsibility for appropriate reporting should be clearly articulated in departmental policy.

KEY CONCEPTS

- Emergency Medical Treatment and Active Labor Act (EMTALA) governs virtually every aspect of hospital-based emergency services. Hospitals and emergency clinicians need to address the following issues to ensure compliance with the law:
  - Adopt (and enforce) a hospital-wide EMTALA policy, as well as emergency department (ED)–specific policies.
  - Educate all appropriate hospital staff and medical staff.
  - Define the hospital's standard ED medical screening examination (MSE) process, including identifying "dedicated emergency departments" and designated "qualified medical personnel" to perform the MSE, as defined by the government.
  - Establish the hospital's patient stabilization procedures and documentation.
  - Do not delay access to the MSE, stabilizing care, on-call physicians, or transfer on account of or to inquire about the patient's insurance status (EMTALA's "no-delay" provision).
  - Address the ED/outpatient registration procedures and payment collection systems.
  - Implement processes and procedures regarding patient refusal of the MSE, stabilizing treatment, or transfer.
  - Implement an effective ED physician on-call system, with written duties and responsibilities.
  - Create a uniform system and "transfer packet" for transferring patients out of the hospital.
  - Create a system for accepting or rejecting patient transfers from other facilities.
  - Institute appropriate documentation requirements for ED medical records, a "central log" for patients presenting to the hospital, transfers, and on-call lists.
  - Post required "signs" in areas used for MSEs, including the ED, Labor and Delivery, and psychiatric intake centers.
  - Monitor and quality assurance review the hospital's EMTALA compliance.
  - Draft a policy and procedure to report suspected EMTALA violations to Centers for Medicare and Medicaid Services (CMS).
  - Review the potential application of EMTALA to the hospital's outlying facilities, such as Urgent Care Centers, or Ambulance/Helicopter EMS Services.
  - Review disasters plans and public health emergency responses for EMTALA issues.
  - Draft and use legally-approved EMTALA forms to achieve/document compliance.
- Whenever emergency clinicians are in doubt about the legality of a situation, they should "do what you believe to be in the patient's best interest and worry about the legal consequences later."
- Consent for minors in the ED is really a non-issue. Consent is a creature of state law; EMTALA pre-empts state law, and it requires the ED to provide a MSE and stabilizing treatment to all minors presenting to the ED.
- Emergency clinicians should be reticent to allow patients to leave the ED against medical advice. The capacity to make reasonable medical decisions can easily be affected by alcohol, drugs, pain, or any number of medical conditions. "When in doubt, don't let 'em out" should be the guiding principle. The courts (and public opinion) will bend over backward to protect clinicians who act in the best interests of the health and safety of their patients.

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CHAPTER e11: QUESTIONS & ANSWERS

e11.1. Which of the following is a common source of liability for failure to comply with the Emergency Medical Treatment and Active Labor Act (EMTALA):
- **A.** Failure to comply with written hospital policies and procedures.
- **B.** Failure to diagnose an emergency medical condition (EMC).
- **C.** Failure to properly treat an admitted patient who is boarded in the emergency department (ED) while waiting for an intensive care unit (ICU) bed to become available.
- **D.** Failure to stabilize a patient after admission to an inpatient unit.
- **E.** All of the above.

Answer: A. Hospital policies become the hospital's standard under EMTALA. Thus, failure to comply with written policies, what Dr. Bitterman terms "failure to follow your own rules," becomes an EMTALA violation when the policies are related to the medical screening and stabilization of patients in the ED.

e11.2. Which of the following violates the Emergency Medical Treatment and Active Labor Act (EMTALA):
- **A.** A 7-hour wait after triage to be medically screened by the emergency clinician.
- **B.** Boarding an admitted patient in the emergency department (ED) for 72 hours after the patient's physician has accepted the patient for admission.
- **C.** Delaying the patient's access to an ED bed by declining to promptly accept the patient from an arriving emergency medical service (EMS) unit or by failing to *immediately* triage or evaluate the patient to determine if the patient can wait on a stretcher with the EMS folks until a bed becomes available.
- **D.** Delaying the patient's medical screening examination (MSE) in the ED to triage the patient, and then for the emergency clinician to see the patients in the order based on the triage nurse's perception of the patients' acuity.

Answer: C. Centers for Medicare and Medicaid Services (CMS) guidelines require the hospital to *immediately* triage ambulance patients arriving to the hospital's ED.

e11.3. A 73-year-old woman is brought by private ambulance to the emergency department (ED) for shortness of breath. Due to ED overcrowding, there are several ambulance stretchers in line ahead of her at triage. At what point does the hospital "accept responsibility" for this patient?
- **A.** When she was placed in the ambulance
- **B.** When the ambulance arrived at her home
- **C.** When the ambulance arrived on hospital property
- **D.** When the patient is seen by the emergency clinician
- **E.** When the patient is seen by triage personnel

Answer: C. The Emergency Medical Treatment and Active Labor Act (EMTALA) defines the time of acceptance of responsibility as when the patient "comes to the ED." In its EMTALA regulations, the Centers for Medicare and Medicaid (CMS) defines the term "comes to the ED" to include anywhere on hospital property, so the hospital's duty and responsibility for the patient is triggered when the ambulance arrives on hospital property.

e11.4. A physician on-call for the hospital's emergency department (ED) has a duty *under the Emergency Medical Treatment and Active Labor Act (EMTALA)* to come to the ED under which of the following circumstances?
- **A.** If asked to help stabilize a patient in the ED who has an emergency medical condition (EMC)
- **B.** To help transfer a stable patient to another acute care hospital that has a specialist available that is not available at the transferring hospital
- **C.** When asked to consult on a patient who has been stabilized in the ED and is being admitted by the patient's primary care physician
- **D.** Whenever requested to come to the ED by the emergency clinician on-duty
- **E.** All of the above

Answer: A. Under the EMTALA, the on-call physician only has duty to come to the ED if needed to help determine whether the patient has an EMC or to stabilize an EMC. Any other requirements concerning when the on-call physician must come to the ED are governed by state law and/or by the hospital's medical staff by-laws, not by EMTALA.

e11.5. According to the Centers for Medicare and Medicaid Services (CMS), which of the following patients may a hospital with specialized capabilities and available capacity refuse to accept in transfer solely because the patient is uninsured?
- **A.** A patient with an unstable emergency condition admitted to observation at another hospital that is unable to stabilize the patient's condition
- **B.** Any patient the hospital chooses to reject
- **C.** An emergency department (ED) patient with an unstable emergency condition who is at another hospital that is unable to stabilize the patient
- **D.** An inpatient with an unstable emergency condition at another hospital that is unable to stabilize the patient

Answer: D. CMS guidelines state that hospitals do not have to accept an "inpatient," as defined by CMS, in transfer from another hospital under any circumstances, even if its decision to decline to accept the patient in transfer will result in the patient's death.

CHAPTER e12

Process Improvement and Patient Safety*

Shawna J. Perry | *Robert L. Wears*

PRINCIPLES

Background

Socio-technical Work Systems

SOURCES OF FAILURE IN EMERGENCY CARE

Communication and Interruptions

Workspace Design

Crowding

Information Gaps

Performance-Shaping Factors

Violation-Producing Factors

Teamwork

Efficiency/Thoroughness Trade-Off

Authority Gradients

Cognitive Processes

Fatigue and Shift Work

PROBLEM AREAS IN EMERGENCY CARE

Triage

Technical Procedures

Laboratory Tests

Radiology Studies

Transitions in Patient Care

Orphaned Patients

Medications

SUMMARY

KEY CONCEPTS

- Be cognizant that the work of health care occurs within a complex socio-technical system composed of five interrelated components: people, tasks, technology and tools, physical environment, and organizational conditions. A change in even one component has an impact on other parts of the work system and, ultimately, safety.
- Don't count errors. Patient safety and mitigation of risk emerges from multifactorial interactions within the clinical work system. Incidents of patient or staff harm are most often the result of system failures, not individual human error.
- Process improvements to clinical care often have "unintended consequences" elsewhere within the work system. Partner with cognitive, behavioral, social scientists and engineers to reduce the likelihood of this and improve adoption by workers.
- Don't set up reporting systems without the resources to fully analyze the reports.
- Safety is a complex dynamic "non-event" requiring minute-to-minute risk mitigation. Don't look for technological "quick fixes" for creating safety within health care.

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CHAPTER e12

Process Improvement and Patient Safety

Shawna J. Perry | Robert L. Wears

PRINCIPLES

Background

The overall process of an episode of patient care in the emergency department (ED) begins with the initial decision by the patient (or caregiver or family) to seek emergency assistance and ends with the patient's disposition and follow-up. The care process is highly complex, with many separate components, people, and interfaces with other processes in the health care organization. This complexity provides many opportunities for process failures and adverse outcomes.

Although adverse events and failures in health care have been studied for decades, most health care professionals were largely unaware of it. This unawareness began to change in the early 1990s when the Harvard Medical Practice Study reported that almost 4% of hospitalized patients suffered significant adverse events during their care and attributed a large proportion of those to "human error." Although that study noted that failures in ED care accounted for only approximately 3% of all adverse events in hospitals, the authors (who did not have ED experience) judged more than 90% of ED events to be preventable. This study and others ultimately led the Institute of Medicine (IOM) to issue a report in 2000 titled *To Err Is Human: Building a Safer Health System*. This report provoked the interest of the media and the general public, and it thrust the issue of safety in health care onto the national agenda. The major accomplishment of the IOM report was the introduction of some of the fundamental concepts regarding safety in complex systems for the first time into the world of health care. The most transforming concept was the idea that most failures in care are not the result of bad decisions or bad individuals but instead are intrinsic properties of the processes of care in the health care system. Thus efforts to reduce these failures should be focused on changing the processes of care rather than on identifying, retraining, or punishing the workers.

The response within health care was mixed. Most health care professionals focused on the projected number of deaths, arguing that they were either too high or too low; and a third, smaller group argued that the concept of error is essentially contestable and thus an approach aimed at counting errors is fundamentally flawed. The transforming concept of "system failure" rather than "human error" gradually gained acceptance, despite going against the natural human tendency to believe that individuals cause outcomes. This viewpoint is problematic because it undermines a clinician's sense of free agency; health care providers prefer not to view themselves as trapped in a system that is moving inexorably toward a poor outcome. In addition, although systems rhetoric is abundant in discussions of patient safety, the majority of safety efforts to date still focus squarely on the individual practitioner (eg, "wash your hands, use the checklist, perform a timeout"). This reductionist view of how safety is created tends to perpetuate the longstanding practice of assigning responsibility solely to those working closest to the patient, at the "sharp end of care," while not coincidentally removing those farther away—managers at the "blunt end" of care.[1]

Thus current solutions remain largely focused on rooting out "human error," resulting from the actions of a few aberrant practitioners who were not sufficiently accountable or attentive to safety. The prominence of educational efforts as responses to root cause analyses of adverse events testifies to the persistence of this "blame and train" mentality. Punitive measures, such as suspension, termination, or in extreme situations, criminal indictment of health professionals caught up in a medical mishap, are still all too common.[2,3]

This chapter takes a different perspective. It views safety in health care as an emergent property of a complex, adaptive system, consisting of multiple interdependent components that are strongly interactive, such that a change in any one reverberates throughout the entire system at a speed and in ways that are difficult to predict in advance. Especially in the ED, safety is a dynamic activity; it ebbs and flows from minute to minute as it is being constantly created and destroyed by the dynamic nature of risk in emergency care and the performance adjustments and adaptations of staff.

Socio-Technical Work Systems

Health care today has evolved far away from its origins in independent practitioners acting as isolated agents. Today's socio-technical work system requires the integration of humans, tools, technologies, and context to deliver of a wide variety of clinical care in numerous settings from hospitals to free standing EDs. The interactions among workers, technologies and the organization determine the work outcome of the system, and in most cases the interactions among components are more important than the components themselves.

For example, unexpected downtime of two dialysis machines for several days in a dialysis unit markedly delays patients' treatments, increasing the risk of cardiac and respiratory complications from hyperkalemia and fluid overload. This results in an increased number of blood draws to check potassium levels, with increasing risk of needle sticks for workers, as well as the risk of internal shortages of medications for managing hyperkalemia. There may also be organizational consequences, such as overtime pay for dialysis staff to accommodate patients whose treatments were delayed. Finally, there is also the potential for intensive care unit (ICU) admissions for patients who become unstable awaiting dialysis. Hence, any change in a work system, no matter how small, has implications for the system as a whole. This is encapsulated in the systems thinking adage that in a complex system, you cannot change only one thing.

Carayon and colleagues' Systems Engineering Initiative for Patient Safety (SEIPS) model (Fig. e12.1) is a useful representation of health care as a socio-technical work system and its relationship to patient safety. This model views work systems as composed of five interrelated components: *People* who do the work (or who are being worked on); these people perform a range of *tasks* using

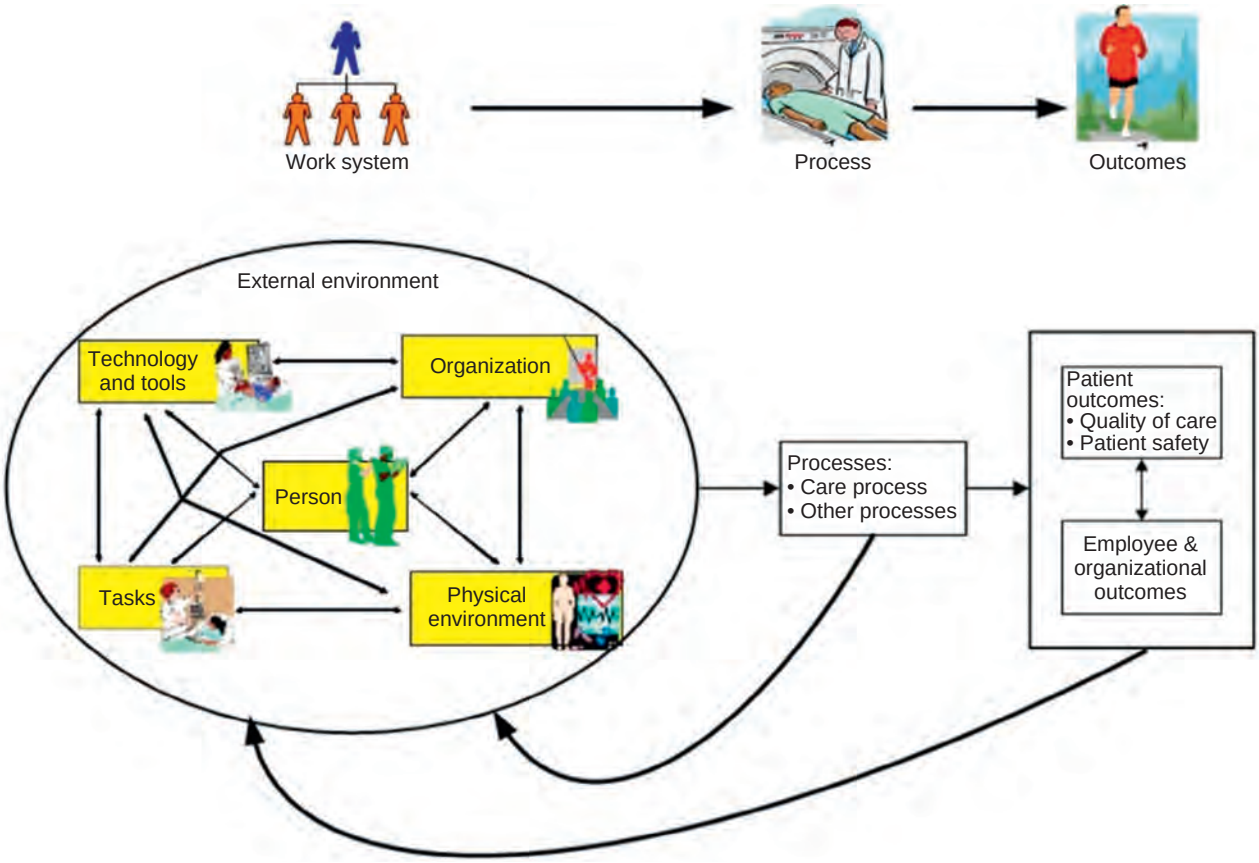

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Fig. e12.1. Systems Engineering Initiative for Patient Safety (SEIPS) model of work systems and patient safety. (From Carayon P, Hundt AS, Karsh BT, et al: Work system design for patient safety: the SEIPS model. Qual Saf Health Care 15[Suppl 1]:i50-i58, 2006; Carayon P, Wetterneck TB, River-Rodriguez AJ, et al: Human factors system approach to healthcare quality and patient safety. Applied Ergonomics 45[1]:14-25, 2014.)

technologies and tools. The performance of these tasks occurs in a *physical environment* under specific *organizational conditions.* The interaction of these five components produces the various outcomes that we desire.

The bi-directional arrows among the five components of the work system demonstrate their interdependence and reciprocal influences on each other. For instance, a failure of a blood analyzer *(technologies and tools)* in the laboratory results in a delay in reporting of laboratory results. This in turn causes a delay for clinical workers and patients *(people)* in need of final results for discharges. The delay in discharges results in further delays in moving admitted ED patients to the wards, resulting in boarding *(people* and *physical environment).* In turn, this increases the ED workload *(tasks)* and causes overcrowding that requires ED workers to deal with an overcrowded workspace *(physical environment).* The problem then requires action by the *organization* to forestall dissatisfaction, loss of reputation, and staff turnover (see Fig. e12.1).

The SEIPS model represents the hydraulic nature of interactions among components in a work system, in that changes in any component have varying degrees of impact on the others. This systems-based view of clinical work has several implications. First, safety and performance are ultimately functions of how well the work system as a whole is able to adapt and compensate for perturbations arising from numerous internal and external sources. Second, because the components are coupled, there are no isolated, "silver bullet" fixes; every change will have both direct and indirect effects on other components, which can be difficult to predict. Third, because of this coupling, such systems cannot be directly controlled. However, all is not lost, because even though they cannot be controlled in a mechanical, linear sense, they can be influenced; actions taken by managers and workers in the system can set the stage for desirable or undesirable outcomes to emerge, even though they do not directly cause them to occur.

Safety and Risk in Dynamic Work Systems

Safety is commonly thought of in terms of a lack of danger and risk or the absence of something going wrong. This is predicated on the hidden assumption that safety is somehow the natural and normal state of the system and that adverse events are aberrancies that must have some special cause.[4] This assumption is common in health care and has led to an emphasis on reporting systems and incident counting efforts to measure safety.

This perspective as been widely embraced, because it fits well with rationalized, linear notions about how clinical work is (or should be) done (ie, patient flow is registration → triage → waiting room → treatment room → nurse assessment, and so on). This view of work-as-imagined (WAI) assumes that clinical tasks can be standardized and managed by sets of rules, policies, and procedures. It also assumes that unsafe situations are the result of failure or deviation from policy, procedures, and protocols, and so reducing these deviations is the key to safety: If workers just follow the rules, then patients will be safe.

The fallacy here is that work as actually performed (work-as-done [WAD]) always deviates in some degree from WAI.[5] This is because the conditions of work are variable and underspecified, particularly in a dynamic, uncertain workplace, such as the ED. It is made worse by the need to resolve goal conflicts—speed versus thoroughness, for example. The job of the frontline ED workers is to detect these variations and conflicts, and then adapt their activities to make them effective in reaching their goals as best they can, given their local constraints. These adaptations produce variability in performance, which is the cause of usual success, and because the adaptations are necessarily incomplete, they sometimes result in occasional failure. After the fact, observers correctly note performance variability but incorrectly infer that it is the cause of the failure when in fact it is adaptive performance that mitigates risk.

Resilience

WAD often involves resilient behaviors that respond to current or potential problems that increase risk or delay completing the clinical work.[6] For example, on a busy day a clinician asks for an intravenous (IV) line on a patient she has just seen before she goes to a resuscitation. The ED technician, seeing no labs had been ordered "draws a rainbow," where he obtains blood from the patient and places a sample in every color of laboratory blood tube available. Organizational policy, however, requires blood not to be drawn until an order has been placed and a lab sticker generated to label each tube. The technician draws a rainbow without orders because he: (1) knows that the patient is a difficult stick and does not want to have her suffer through another painful blood draw; (2) anticipates that he may not be able to get back and perform another draw once orders are in because he might be pulled to another area; and (3) believes the patient looks ill, so the physician is likely order a number of tests when she returns.

This fairly simple workaround is an example of resilient behavior. The ED technician's decision to draw the blood despite the organizational policy requiring orders for drawing blood addresses a number of existing and potential obstacles for the patient's care. The technician's modification of work processes contributes to the patient's care and the ED's overall effectiveness. The majority of resilient performances in the ED are hidden (in part because they may involve bending the rules) and are done without any special thinking that "it's time to be resilient." Interestingly, seasoned nurses, technicians, and physicians can frequently be overheard orienting new staff to similar workarounds, because they have proven to help with workload management and to benefit patient care.[7]

Resilient performances can also occur across microsystems and specialties as illustrated in the following case[8]:

> *A 24-year-old non–English-speaking sailor presents to the ED with 3 days of intermittent pain and numbness in his left leg with recurrent short episodes of dizziness and low blood pressure. Upon physical examination, the emergency clinician notes a pectus excavatum deformity; a dramatically abnormal chest radiograph and intermittent hypotension made the diagnosis of aortic dissection almost a certainty. A page to cardiovascular surgery goes unanswered, an atypical occurrence in this ED. Based on a hunch that perhaps the cardiovascular team was in the operating room, she turns to the unorthodox solution of calling the operating room and asks the nurse to pull up the patient's chest x-ray on the computer in the operating room, thinking this will most easily and effectively alert the surgeon to the need. This novel method for escalating an urgent case gets the patient into the operating room shortly after his arrival in the ED.*

This case demonstrates resilient behavior not only by the emergency clinician but also by the surgical team in the operating room. Members of the team, including the surgeon, were open to participating in an unorthodox method of consultation, a workaround that deviated markedly from prescribed protocols for consultation and escalation. This is an important example of a "workaround" strategy and how "extra steps" contribute to resilience.[9]

SOURCES OF FAILURE IN EMERGENCY CARE

Many characteristics of emergency medical practice make it vulnerable to failures (Table e12.1). Safety research in emergency care demonstrates a wide range of known and unknown contributors to patient safety and highlights the importance of the work processes that overlay this complex work environment. For instance, Morey reported that specific training of emergency clinicians and nurses to work together in teams led to reductions in failures and improved performance. Perry and Fairbanks identified a number of unexpected yet highly consequential failures of information technology (IT) that were difficult to detect, some occurring during emergency resuscitations.[7] Wears and Perry noted ergonomic shortcomings in the workplace and pointed out their potential to contribute to failures in care. Hall identified significant delays related to ED layout, with time to assessment of chest pain patients being longer for patients placed behind a door or who were 25 feet or farther away from the physicians assigned to

TABLE e12.1

Performance Shaping Characteristics of the Emergency Department

INTRINSIC[A]	EXTRINSIC[B]
Limitations of human cognition	High communication load
High levels of uncertainty	Poor teamwork
High decision density	Overcrowding
High cognitive load	Production pressures
Narrow windows of opportunity	High ambient noise levels
Multiple interruptions or distractions	Information gaps
Low signal-to-noise ratio[c]	Report delays
Surge phenomena[d]	Inadequate staffing
Novel or infrequently occurring conditions	Poor feedback
Patient factors (eg, acuity, language, delirium)	Inexperience Inadequate supervision Sleep deprivation or sleep debt Fatigue Multiple transitions of care Poorly designed procedures ED layout

[a]Intrinsic factors are intimately part of the nature of emergency care and as such are not amenable to change but instead must be compensated for.
[b]Extrinsic factors are in principle manageable and typically relate to resource constraints.
[c]Low signal-to-noise ratio refers to the low likelihood of a critical diagnosis compared with a benign diagnosis for similarly presenting symptoms and findings (eg, subarachnoid hemorrhage vs. tension headache).
[d]Surge phenomena are the rapid changes in volume and acuity routinely experienced in many EDs.
ED, Emergency department.

care. This section focuses on some of the principal factors that contribute to adverse outcomes and how they might be better managed to improve safety.

Communication and Interruptions

Chisholm reported that emergency clinicians are interrupted, on average, approximately once every 6 minutes and that two-thirds of those interruptions cause a change in task; this is important because both interruptions and task switching frequently lead to process failures. Fordyce reported that self-detected errors occurred in almost 20% of all ED cases but that only 2% were associated with adverse events. Fordyce's work emphasizes that errors are ubiquitous but only rarely combined with other factors to produce adverse events, and it supports the notion that focusing on eliminating errors is not likely to be a productive strategy for improvement.

Workspace Design

Two frequently overlooked contributors to lowered safety in any work environment are (1) the design of the workspace and (2) the engineering of the tools, technology, and procedures used to perform the work. This is especially true for EDs, because the majority were not designed for the work currently being done in them. ED caregivers are required to adapt to the space by creating "workarounds" to cope with the limitations and impediments of the workspace.

Consistency is rarely found in equipment across or between areas. For instance, the monitors in the ED are often not the same as those used in the radiology department or ICU. In addition, tools and technology are seldom developed or assessed for their "user-centered design" or ability to be integrated into existing workspace and the associated hazards for doing so. This is most apparent with regard to health IT, which is often introduced for improvement of safety and quality; however, embedded latent features that can produce clinical failures that are "hard to see" have been demonstrated.[10-12] A study of computerized physician order entry by Koppel showed that the software facilitated 22 types of medication error risks, such as displays that prevented a coherent view of the patients' medications or inflexible ordering formats that led to wrong orders. Other contributors to IT failure within health care are the lack of usability testing and failure to reassess the impact of the new technology and changes in clinical work after implementation.

The contribution of poor design to the difficulty in maintaining safety in a health care environment is generally overlooked by staff members who cope with these difficulties as "part of the job." Vigilance is the common solution, but despite caregivers' best efforts it cannot be sustained, given competing demands for their attention. This increases the risk that a failure not being recognized will be linked to the workplace, the procedures, or the equipment, despite being "tightly coupled" to any or all of these.

Crowding

ED crowding has long been recognized as a major source of time-delay failures and a threat to patient safety. Such delays are not simply an inconvenience to the patient but may give rise to significant adverse events. For example, patients with atypical presentations of severe illness who have been mis-triaged to low levels of acuity may experience inordinate and, occasionally, fatal delays. In other cases, such as community-acquired pneumonia, cellulitis, and lacerations, more expedient care may significantly improve the outcome of the illness. A significant proportion of patients who leave the ED without being seen may have serious illness and incur delays in diagnosis and treatment. At the other end of the process, when the patient is ready for admission to the hospital from the ED, further time-delay errors may occur. Not only do such delays create throughput problems and contribute to crowding, but they also create discontinuities in care and may lead to adverse events that are difficult to identify, because they manifest after the patient has left the ED. The need to adapt to the cognitive overload posed by crowding contributes to greater use of mental shortcuts and less accurate decisions in an efficiency/thoroughness trade-off (see later).

Information Gaps

Missing information is common in emergency care and can significantly affect quality of care. Hospital records, especially discharge summaries, details of past medical history, and other important information are often difficult to access in an expedient manner; and even with electronic medical records, pertinent information may be difficult to locate. Referral notes sent by family physicians with the patient may not reach the emergency clinician or may not contain relevant or significant details. In these situations, clinicians make decisions and take action on the basis of incomplete, limited, or erroneous information. Emergency clinicians often end up not seeking additional or clarifying information because of time pressures, patient volume, or limited methods to obtain more information (eg, the referring physician's office is closed), essentially accommodating to this "gap" in continuity of care and the associated increase in patient risk.

Performance-Shaping Factors

A wide variety of ambient, systemic conditions contribute to the majority of adverse events and near misses that occur in the ED (see Table e12.1). Some performance-shaping factors are an "intrinsic," part of the milieu of emergency medicine and thus not amenable to direct control (eg, cognitive workload, multiple distractions and interruptions, and high acuity). These factors must be managed by strategies to buffer or to mitigate their effects. In contrast, other "extrinsic" performance-shaping factors typically reflect limitations of resources (eg, staffing ratios, production pressure, and ED layout).

Violation-Producing Factors

Although at first one might think that violations of organizational policies, rules, and procedures would always be causes of failures and adverse events, the modern approach to safety has pointed out that some violations are actually necessary for the safe functioning of the system, and others fall somewhere in between.[47] Aside from recklessness, drug use on the job, moral failings, and other egregious acts, research in other domains has identified other factors that are associated with the occurrence of rule and safety violations (Box e12.1). The "normalization of deviance" is an accumulated acceptance of small variances from safe operating conditions that develops over time, ultimately compromising safety. This is evidenced in overtaxed EDs coping with crowding of patients (eg, examining and managing of patients in hallways). Violations can also occur in response to perceptions of authority. They may occur through a directive supporting violation from an authority figure (eg, nursing supervisors order admitted patients moved to inpatient beds without calling to report if there are delays in reaching inpatient nurses), the absence of a disapproving authority (eg, physicians leaving shifts early but the medical director does not address the behavior), or an individual's self-perception that he or she is authorized to disregard or to deviate from prescribed procedures (eg, ED electrocardiograms done on patients in chairs because there are no available stretchers). It is important to note that violations differ from workarounds in that

BOX e12.1

Violation-Producing Factors

Gender
Mood
Ill health
Risk seeking or risk aversion
Normalization of deviance
Maladaptive group pressures (groupthink)
Maladaptive copying behavior
Under-confidence or overconfidence
Perceived authorization to deviate
Authority gradient effects (obeying authority figure or absence of disapproving authority figure)
Likelihood of detection

Based on an original schema by Williams JC: Assessing and reducing the likelihood of violation behavior—preliminary investigation. Proceedings of an International Conference on the Commercial and Operations Benefits of Probabilistic Safety Assessment. Edinburgh, Institute of Nuclear Engineers, 1997.
Modified for emergency medicine in Croskerry PG, Wears RL: Safety in emergency medicine. In Markovchick V, Pons P, editors: Emergency medicine secrets, ed 3, Philadelphia, 2003, Hanley & Belfus. A summary can also be found in Reason J: Managing the risks of organizational accidents, Aldershot, UK, 1997, Ashgate.

violations tend to undermine safety and increase risk, whereas workarounds and extra steps are resilient actions in support of safety and mitigation of risk.

Fluctuations in mood can also contribute to violations for a variety of reasons and will result in inconsistent clinical performance; for instance, men are more likely to break safety rules and to engage in more risk-taking behavior than women. Risk-seeking and risk-averse attitudes are associated aspects of decision-making in the ED.

Teamwork

Good teamwork is essential to the safe practice of emergency medicine, but emergency caregivers are not trained or evaluated as teams. Teamwork training in other fields, such as aviation, has been successful in reducing failures related to poor communication, cross-monitoring (observing others' behaviors to reduce risk of failure and share workload), and authority gradients (both within and between professions). Work on transferring teamwork training principles to emergency medicine suggested that teamwork failures are involved in approximately 40% of malpractice cases. The lack of cross-monitoring across team members and the failure of advocacy or assertion on behalf of the patient by caregivers to avoid patient harm were two of the factors most frequently identified. A multidisciplinary teamwork training course implemented in eight EDs showed a significant improvement in quality of team behaviors and a sixfold decrease in observed clinical errors. Teamwork is not a specific fix for any one type of error, but it should be viewed as one type of adaptable human factor intervention; a set of teachable skills and behaviors capable of increasing system resilience and safety, which are hallmarks of high-reliability organizations.

Teamwork training requires institutional and ED leadership to be fully committed to the process embarking on a training program. Resistance to behavioral change is common, and it will be necessary to demonstrate the clinical relevance of this training. High-fidelity medical simulation supported by audiovisual feedback offers an educational methodology to help clinicians and staff understand the necessity of behavioral change. A major unanswered question is how to embed teamwork behaviors into medical training and how to sustain the behaviors over time.

Efficiency/Thoroughness Trade-Off

EDs are under constant pressure to reduce waiting time and speed the throughput of patients. This risk forces a trade-off between improving efficiency and thoroughness referred to as the *efficiency/thoroughness trade-off principle.* This tradeoff is seldom directly acknowledged in official policies, but it can invariably be observed in the ED, especially when the volume is high. For example, the question "What is the one thing you are most worried about?" posed by a caregiver to a patient may indicate that efficiency is the priority and send a message that there will not be an opportunity to address all of the patient's concerns or medical complaints. Although efficiency/thoroughness trade-off decisions are often not articulated explicitly, organizations and regulators implicitly and explicitly demonstrate the importance of efficiency in their monitoring of throughput goals, length of stay, patients leaving prematurely, and staffing and supply levels. Thoroughness in most settings often only arises from the hindsight bias that follows an adverse event. Although simultaneous improvements in efficiency and thoroughness are sometimes possible, eventually every work system hits a hard limit where improving one dimension degrades the other.

Authority Gradients

Humans in groups invariably sort themselves by degrees of authority. This hierarchy can be based on profession (physicians have greater authority than nurses) or organizational rank (attending physicians have greater authority than residents). These authority gradients can impede the free flow of information among team members if low-authority members are inhibited by differences in seniority, stature, expertise, profession, or social status. There are clear examples of cases in which authority gradients have been responsible for adverse events. A work environment in which all team members feel comfortable expressing their viewpoint, especially if it is a dissenting one, requires a cultural change that can begin with the physicians who occupy the highest authority position in the clinical setting. Authority figures can support a flattened hierarchy by openly recognizing the value of perspectives other than their own and eliciting them from other clinicians and staff (eg, asking a nurse what he thinks might be going on with a patient). Senior clinicians are in a powerful position to bridge gradients by fostering open communication through multidisciplinary rounds, demonstrating that they are approachable (eg, acknowledging staff by name), and using clinical narratives from their own experience that illustrate near misses and judgment failures.

Cognitive Processes

Patient care in the ED is a process of making clinical sense out of multiple sets of unfolding, fragmented, tangential, ambiguous, and interrupted stimuli. The goal of this process is an accurate diagnosis if possible or, much more commonly, a characterization of the problem, which can usefully guide actions, management, and disposition. Although many diagnoses, such as lacerations, dislocations, fractures, and foreign bodies, are self-evident, others (eg, chest pain, fever, headache, abdominal pain, and syncope) are often associated with high levels of ambiguity and uncertainty and are more likely to lead to problems. Cognitive biases can frequently be identified in retrospect after diagnostic failures,[57] but the problem of hindsight bias makes this identification problematic.

Fatigue and Shift Work

Both fatigue and shift work contribute to performance failures, but relatively little research has been directed to their respective

BOX e12.2

Effects of Sleep Deprivation

Longer reaction time
Lapses in attention or concentration
Lost information
Errors of omission
Poor short-term memory
Poor mood (increased confusion, stress, and irritability)
Reduced motivation
Distractibility
Sleepiness
Poor psychomotor performance
At circadian low points
When sedentary
On long, difficult, or externally paced tasks with no feedback
In unchanging surroundings, particularly with reduced light or sound, or with low motivation, interest, or novelty

Modified from Bonnet MH: Sleep deprivation. In Kryger M, Roth T, Dement WC, editors: Principles and practice of sleep medicine, Philadelphia, 2000, WB Saunders, pp 53-71.

impacts on clinical performance in the unique milieu of the ED. Although the two are often considered together, they are different entities and exert both qualitatively and quantitatively different effects on performance. Fatigue has a number of determinants separate from those associated with shift work (see Fig e12.1).

Shift work has extensive, well-documented, detrimental effects on health that in turn have an impact on well-being and job performance. Importantly, it leads to disruption of circadian rhythms that inevitably result in sleep deprivation. Circadian dys-synchronicity largely occurs through missing sleep in the *anchor period,* approximately midway through the sleep phase when core temperature and arousal level are at their lowest. It has been stated that the performance degradation of someone who has been up all night is roughly equal to that of a person with a blood alcohol level of 0.1% (Box e12.2).

The acute effects of sleep deprivation are well known, but the chronic effects are less appreciated. Invariably, working a night shift results in less sleep the following day, and subsequent sleep is often disrupted and fragmented in the struggle to restore the circadian rhythm before the night-shift cycle repeats itself. This results in the accumulation of a *sleep debt* that has a significant impact on performance. A study of anesthesia residents on a normal work schedule, with no on-call duty in the preceding 48 hours, showed daytime sleepiness scores comparable to those of patients with narcolepsy or sleep apnea. The on-call schedule of these subjects (five periods per month) entailed considerably less sleep deprivation and fragmentation than an average emergency clinician's schedule. Increasing age is associated with decreased tolerance for sleep deprivation.

Performance declines as work hours increase, but the optimal shift length in the ED is unknown and difficult to delineate for several reasons. The relationship with workload or acuity is not well appreciated, and some workers exhibit contradictory incentives, such as preferring to work longer shifts to get more days off. More recovery time between shifts might be expected to enhance job performance, but these issues remain relatively unexplored. A survey of emergency clinicians found a preference for 8-hour over 12-hour shifts, but it is not known whether job satisfaction in the ED translates into improved clinical performance and fewer adverse events. Other conditions within the ED, competing commitments outside the ED, age, ill health, and other factors contribute to fatigue, with evidence pointing toward additional health implications for clinicians.

BOX e12.3

Rational Approaches to Shift Work

Optimize circadian-friendly schedules
Forward rotating (clockwise with circadian rhythms)
Rapid changes
Minimize consecutive nights (1 or 2)
24 to 48 hours off after nights
Allow social time, including some weekends
8-hour shifts (absolute maximum 12 hours)
Institute regular, predictable template
Practice proper sleep hygiene
Use a sleep-friendly room: Room-darkening blinds, "white noise" (eg, electric fan) or earplugs, no phones, family aware
Maintain a regular sleep routine
Try anchor sleep
Avoid caffeine, alcohol, and drugs
Prophylactic naps
Modulate circadian rhythms
Exercise
Consider bright light
Eat healthy
Eat a balanced diet
Avoid junk food
Keep regular mealtimes
Promote a healthy lifestyle and work style
Promote a personal healthy lifestyle
Educate friends and family about shift work issues
Educate colleagues about shift work issues
Advocate for department improvements in working conditions
Advocate for shift worker–friendly community services
Avoid pharmaceuticals
Use caffeine in moderation, prn
Do not use sedatives or stimulants
Avoid alcohol before sleep

Modified from Jha AK, Duncan BW, Bates DW: Fatigue, sleepiness, and medical errors. In Making health care safer: a critical analysis of patient safety practices. Evidence Report/Technology Assessment No. 43, AHRQ publication 01-E058. Rockville, MD, 2001, Agency for Healthcare Research and Quality; and Frank JR, Ovens H: Shiftwork and emergency medicine practice. CJEM 4:421, 2002.

The appropriate management of shift work and fatigue to improve patient safety is not well understood, and further research is needed in this area. In most high-hazard industries, the assumption is that fatigue and long, aberrant work hours lead to poor performance; however, in the health care industry, issues about discontinuity of care and difficulties in changing medical culture have obscured these concerns. Given that medical personnel, like all human beings, function suboptimally when they are fatigued, efforts to reduce fatigue and sleepiness should be undertaken, and the burden of proof should be in the hands of the advocates of the current system to demonstrate that it is safe. In the meantime, shift scheduling should be optimized to reduce the impact of circadian disruption, and ED personnel should practice good sleep hygiene. Some basic approaches are listed in Box e12.3.

PROBLEM AREAS IN EMERGENCY CARE

The mechanisms of failure in emergency care are remarkably variable, with a cadre of known and unknown contributors. Areas of consistent concern include triage, technical procedures, laboratory and radiographic tests, transitions in patient care, orphaned patients, and medications.

Triage

Triage, or sorting by acuity, is by definition an abbreviated decision-making process that can never be completely safe because of the limited information available, the lack of time invested, and the variety of presentations of illness and injury. Also, there is a low "signal-to-noise" ratio for a number of serious conditions (ie, when the incidence of a serious condition is far exceeded by that for a benign condition, but the clinical presentations are similar). Inevitably, the triage process involves tradeoffs between sensitivity and specificity. Under-triage for a particular patient would have a greater potential for an adverse event than over-triage, whereas over-triage affects resource utilization and may have an impact on the care of other patients.

Triage assessments are important contributors to process failures and adverse events. Beyond treatment delays, which can occur with under-triage or be produced by over-triage, an incorrect assessment may be the triggering event that initiates a chain of failures. Geography can become destiny, and an inappropriate triage to a specific treatment area may create a bias in the minds of the treating clinicians and staff. The use of five-level triage systems for adults and children, with excellent inter-rater reliability, offers an opportunity to reduce the risk associated with under-triage.

Technical Procedures

The practice of emergency medicine requires proficiency in a wide range of procedures with varying degrees of difficulty. Patients who require procedures are at greater risk for adverse events.[25] Contributors to this higher risk include problems with proficiency and a low frequency for use of higher risk procedures. Critical procedures, such as cricothyrotomy, pericardiocentesis, and endotracheal intubation, are rarely or less commonly performed; when they are needed, they are highly consequential events involving significant time pressure. An important challenge in emergency medicine is the acquisition and especially the maintenance of a requisite level of skill. Simulation techniques have considerable potential to ameliorate skill degradation, but require both capital and human investment to be effective.

Laboratory Tests

The interface between the ED and its ancillary services is critically important. Failures can occur at three phases of laboratory processes. Pre-analytic errors mostly occur through inappropriate collection of specimens because of lapses in technique, timing, and identification of both patient and specimen. Analytic errors refer to those that arise directly from the testing process. Post-analytic errors occur after the test result has been obtained and can take many forms (eg, keyboard entry errors, overlooked or lost data, and failure of results to reach the physician). Studies of a blood bank and a STAT laboratory found that the majority of failures occurred in the pre-analytic and post-analytic stages, with less than 5% in the analytic stage. Overall, the laboratory defect rate is less than 1%, but the number of exposures is large. Of the failures that do occur, up to 50% may have a moderate impact and up to 8% a severe impact on patient care.

Radiology Studies

Radiographic imaging is a critical aspect of diagnosis and management in the ED. Although patient identification and wrong-side problems are important sources of failure, the majority lie in interpretation. Assuming the radiologist's interpretation to be the criterion standard, the rate of errors in interpretation by emergency clinicians may be as high as 16% for plain radiographs and more than double that rate for computed tomography scans. Clearly, not all misinterpretations are consequential, and emergency clinicians typically seek the advice of the radiologist when they recognize difficult interpretations. The introduction of digital imaging and picture archiving communications systems has resulted in new patient safety issues related to usability, the effect of monitor resolution on interpretation, and reconciliation of ED clinician and radiology readings. Significant interpretation errors can be detected with prompt review of all films by the emergency clinician and radiologist, but effective procedures are required to ensure that timely and appropriate feedback and review occur. This approach has been demonstrated to substantially reduce the rate of clinically important misinterpretations.

Transitions in Patient Care

The need for 24-hour access to care and the fragmented nature of health care delivery require the occurrence of transitions of care between providers, either within the ED (at shift changes) or between the ED and other care areas (when patients are admitted, transferred, or discharged). The shift "sign-over," "sign-out," or "handoff" is generally thought of as a communication activity performed for the transfer of clinical information, but it also embodies the transfer of responsibility and authority from one provider to another. The sign-over also conveys general situational awareness (eg, the state of the department, hospital, and city) and provides a forum for review of decision-making and treatment plans.

Although transitions of care have been studied in recent years, few of these efforts have engaged with the cognitive, behavioral, and social sciences essential to a deep and systematic understanding of the problem.[13] When viewed superficially, sign-overs seem highly variable in their content, the number of individuals involved, the physical configuration (eg, walking, stationary, and at bedside), the tools used to facilitate the transition (eg, white boards, medical records, and written notes), and the length of the transition process; however, they have a fundamentally similar deep structure.[14] Although widely regarded as providing a major contribution to adverse events, sign-overs also provide an opportunity for review of decision-making by clinicians and may provide opportunities for rescue and recovery by bringing "fresh eyes" to a patient's case. Potential threats to effective transitions include:

- Interruptions during the turnover (eg, phone calls and sidebar conversations) can cause a loss of focus and lead to the omission of important information.
- Lack of consistent structure to the turnover: Although the traditional case presentation narrative is often followed (chief complaint, history, physical examination, initial laboratory results, impression, and plan), the case presentation format may not provide opportunities for noting pending or as yet uncompleted tasks.
- Patients are commonly "marked" in ways that can sometimes be helpful but sometimes harmful, especially for at-risk groups, such as the homeless, psychiatric patients, alcoholics, and drug abusers.

Common sense and well-meaning approaches, such as standardizing verbal content and compulsory use of sign-over checklists, risks extinguishing inherent latent safety features when implemented without deeper research of this complex and vital work tool for emergency medicine and health care overall.

Orphaned Patients

Orphaned patients are those who have suffered temporary loss or diminished supervision or accountability for their ED care. This may occur at several stages in the process. Patients who are seen

and assessed at triage and then wait in the waiting area are temporarily orphaned. Those who are brought in by paramedics sometimes remain on stretchers for hours before being admitted to the ED. Patients who leave without being seen or before treatment is completed have "orphaned" themselves. Patients can also be temporarily orphaned out of the ED for radiographic studies or other special tests. On occasion, patients get "lost in the shuffle" and are overlooked at shift change, or they may get "lost" after one or more consultations with other services. With prolonged wait times, occult conditions can progress to serious and potentially catastrophic levels. A significant cause of orphaning in some EDs is the "boarding" of admitted patients because no inpatient beds are available. In such cases, patients may be put in holding areas in or adjacent to the ED and receive sporadic care from a succession of caregivers who know increasingly less about their conditions. The risk of harm to patients caught in this "gap" within the ED is not well studied.

Medications

Medication errors constitute the largest proportion of failures in most studies, with failures occurring in all six steps of the process (prescription, transcription, dispensing, administration, monitoring, and discharge). Some EDs take on the dispensing role, obviating input from the pharmacy, where many errors are corrected. In addition, team communication errors can contribute to many failures—missed medications, wrong medications, and duplicate dosing. Pediatric patients are at higher risk; drug errors are no more common than in adults, but they are typically more serious.

The presence of a pharmacist on the clinical team has been shown to reduce medication errors in several settings. There is great interest in the potential for computer technologies, such as bar coding and computerized physician order entry, to enhance medication safety. However, despite this potential, there is evidence that such systems introduce new problems to replace old ones. The Institute for Safe Medication Practices has recommended that certain problem practices be avoided in writing orders or prescriptions. Success in this area will require more than just individual attentiveness; nurses, unit secretaries, and pharmacists will have to feel comfortable challenging improper use by physicians.

SUMMARY

The safe management of patients in the ED depends on a multiplicity of processes. All appear vulnerable to failure, yet all have the potential for improvement through judicious process management. Efforts by front-line workers will not be sufficient; considerable effort will be required at the administrative or "blunt end" of the system.

Safety in complex dynamic environments is itself dynamic. *Safety is a "non-event," because it is evidenced by the absence of things that should not or do not occur,* such as administration of a medication to the correct rather than wrong patient. It cannot be banked for future use but is created by workers in a well-designed and supportive organizational environment. Achieving safe performance in settings such as the ED is analogous to fighting a guerilla war: There are no dramatic victories, but there are occasional horrific defeats, with no end in sight. Sources of risk are ubiquitous with the human factor critical to its mitigation on a minute-to-minute basis.

The establishment and maintenance of successful safety cultures within health care requires constancy of purpose by health care organizations, willingness to adopt new ideas and tools from outside of health care, and commitment to continued effort and investment.

KEY CONCEPTS

- Be cognizant that the work of health care occurs within a complex socio-technical system composed of five interrelated components: people, tasks, technology and tools, physical environment, and organizational conditions. A change in even one component has an impact on other parts of the work system and, ultimately, safety.
- Don't count errors. Patient safety and mitigation of risk emerges from multifactorial interactions within the clinical work system. Incidents of patient or staff harm are most often the result of system failures, not individual human error.
- Process improvements to clinical care often have "unintended consequences" elsewhere within the work system. Partner with cognitive, behavioral, social scientists and engineers to reduce the likelihood of this and improve adoption by workers.
- Don't set up reporting systems without the resources to fully analyze the reports.
- Safety is a complex dynamic "non-event" requiring minute-to-minute risk mitigation. Don't look for technological "quick fixes" for creating safety within health care.

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CHAPTER e12: QUESTIONS & ANSWERS

e12.1. Teamwork failures in emergency medicine are involved in approximately what percentage of malpractice cases?
A. 10%
B. 20%
C. 30%
D. 40%
E. 50%

Answer: D. The lack of cross-monitoring by team members and the failure to demonstrate advocacy or assertion on behalf of the patient by caregivers in avoidance of harm are two of the most frequent factors cited.

e12.2. A 27-year-old woman presents with complaints of back pain. She has been to the emergency department (ED) a number of times for this same complaint. On the way to the medical screening examination, the emergency clinician is heard to mutter, "She's a drug seeker." This is an example of which potentially negative process?
A. Authority gradient
B. Cognitive framing
C. Countertransference
D. Fatigue and shift work
E. Visceral bias

Answer: E. In addition to cognitive mental properties and the effects of fatigue/shift work, the emotional state of the physician can affect his or her decision making. This has been referred to as *visceral bias.* Health care workers are often less aware of the presence/function of factors such as economy of perception that may lead to stereotyping and adversely affect clinical interactions.

e12.3. Rational approaches to shift work include all of the following *except:*
A. Exercise
B. Forward rotating schedules
C. Sedatives
D. Use of sleep-friendly rooms (eg, dark cloth or blinds, white noise, ear plugs, family awareness of need to sleep)

Answer: C. Sedatives. The use of sedatives and/or alcohol should be avoided because each affects the effectiveness of sleep between shifts and therein the overall risk of medical errors and patient harm while working shift hours due to fatigue.

e12.4. Factors that affect emergency department (ED) performance and increase vulnerability to failure *include:*
A. Low-density decision-making, poor teamwork, low workload, hunger
B. Overcrowding, high levels of uncertainty, fatigue, ED layout
C. Overstaffing, low cognitive load, production pressure, low numbers of transitions in care
D. Physician salaries, consultation rates, multiple interruptions, medication shortages

Answer: B. Many intrinsic and extrinsic factors affect an ED's performance, undermining its functioning and making it more at risk for a medical mishap or patient harm (see Table e12.1). Although each choice contains at least one of these performance-affecting factors, only choice B contains four of the factors.

CHAPTER e13

Wellness, Stress, and the Impaired Physician*

Julius (Jay) A. Kaplan | Lori Weichenthal

PRINCIPLES

SPECIFIC ISSUES RELATED TO EMERGENCY CLINICIAN WELLNESS

Stress

Burnout

Compassion Fatigue

Resilience

CONSEQUENCES OF LACK OF WELLNESS AND THE IMPAIRED PHYSICIAN

WELLNESS STRATEGIES

Professional

Personal

For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.

KEY CONCEPTS

- Stress is a part of the human experience. The practice of emergency medicine, because of its unpredictable and chaotic nature, and because matters of life and death occur every shift, includes more stressors than most other professions.
- Emergency clinicians experience high rates of burnout and compassion fatigue, which threatens the future of the specialty.
- The approach to preventing burnout and promoting resilience must be multifaceted and involve institutional, professional, and personal strategies. Only by being specific and concrete in proactively creating a more supportive, efficient, and fulfilling work environment will health care institutions be successful in promoting physician wellness.
- At the departmental level, emergency medicine leaders should educate physicians, whether in practice, in residency, or in medical school, to cultivate resilience to meet the challenges that they will face.
- Emergency clinicians should take personal responsibility and develop the skills that they need in order to have long and satisfying careers in emergency medicine.

CHAPTER e13

Wellness, Stress, and the Impaired Physician

Julius (Jay) A. Kaplan | Lori Weichenthal

PRINCIPLES

The National Wellness Institute defines wellness as an active process through which people become aware of, and make choices toward, a more successful existence.[1] Wellness is complex and multifaceted and includes a person's physical, mental, and emotional health and wellbeing.[2] Multiple recent studies suggest that physicians as a group, and emergency clinicians in particular, are unwell.[3-7] In fact, emergency clinicians have the highest rate of burnout when compared to other specialties.[3] Burnout can have a serious impact on a physician's personal life and lead to chemical dependence, broken relationships, depression, and suicidal ideation.[3,8,9] Of concern to the health care system as a whole, there is mounting evidence that burnout impacts patient care and satisfaction.[2,10,11] Furthermore, physicians who experience burnout are more likely to change careers or retire early, amplifying the physician workforce shortage.[5] This chapter outlines concepts related to wellness, discusses consequences of the lack of wellness and the impaired physician, and explores strategies for promoting wellness at the institutional, professional, and personal level.

SPECIFIC ISSUES RELATED TO EMERGENCY CLINICIAN WELLNESS

Stress

Stress is a nonspecific response of the body to any demand, and it can have both positive and negative effects. Without any demand, performance suffers. With too much stress, anxiety and exhaustion lead to poor performance (Fig. e13.1). Although all human beings experience stress, emergency clinicians face unique stressors, due to the nature of their work. The emergency department (ED) is a diverse and frequently chaotic environment. Patients arrive at any time of the day or night in an unscheduled manner, and the numbers, types, and acuities are unpredictable and can change at any moment. Patients are frequently in distress when they present to the ED, and many are dealing with life-threatening illness or injury. Patients do not come to the ED with their joy; rather, they arrive with their pain and anxiety, often severe. Some have language barriers, mental health issues, or alterations in their mentation that make them difficult to evaluate and present challenges for communication.

Emergency clinicians deal with death and dying on a daily basis and generally do not have time to process their feelings regarding these losses due to patient load and the need "to move on" to the next patient. Personal safety is also a major issue while working in the ED environment where exposure to acts of violence, verbal abuse, and risk of exposure to potentially life-threatening diseases are higher than in other practice settings. Add to all of the aforementioned stresses, the pressure for perfection, with the ever-present possibility of a missed diagnosis, with the attendant risk of a medical negligence lawsuit, and the continued focus on patient satisfaction, with the threat of a patient complaint and punitive action related to this, it is not difficult to understand how physicians feel burdened and constantly under pressure.

The 24/7 nature of emergency medicine also creates unique physiologic stress on the emergency clinician due to changing shifts and its impact on circadian rhythms. Shift work has been shown to lead to poor quality of sleep, fatigue, and mood disturbance; challenges to maintaining relationships; and difficulty coping with the demands of daily life.[12,13]

Faced with decreased hospital and community resources and growing public demand for emergency services, EDs frequently are stretched beyond capacity by sheer patient load and the boarding of admitted patients.[14] This is further complicated by commonplace workforce shortages, nursing under-staffing, and the lack of availability of on-call specialists. These issues have been shown to correlate with poorer patient outcomes and have led to a new culture where efficiency is often viewed as more important than providing safe, compassionate care.[15]

The introduction of electronic medical records (EMRs) has added a new stressor to emergency clinicians. Recent studies suggest that EMRs lead to increased administrative burden (more time charting, order entry, and so on) and less face-time with patients, resulting in decreased job satisfaction.[16-18] The EMR also interferes with physician/nurse collaboration and the fulfilling sense of being part of a team and working together, as communication moves from face-to-face personal interaction to an electronic interface.

Burnout

The term *burnout* was first used by Herbert Freudenberger in 1974. It is defined as a prolonged response to chronic stressors, on the job, defined by three dimensions: emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment. Eric Gentry and Anna Baranowsky described burnout as "the chronic condition of perceived demands outweighing perceived resources." Although not all emergency clinicians will develop burnout during the course of their careers, the particular aforementioned stresses place them at increased risk.

Compassion Fatigue

Compassion fatigue has been described as burnout plus secondary traumatization. Secondary traumatic stress, which some describe as synonymous with compassion fatigue, is defined as the emotional and physical burden created by the additive trauma of helping others in distress that results in a reduced capacity and interest in being empathetic toward future suffering (Fig. e13.2).[19] Risk factors for emergency clinicians developing compassion fatigue include being in situations where they are a "first responder" or when they share some identity with the people that they are providing care for.[20] Along with leading to decreased empathy, compassion fatigue can also lead to sadness, grief, somatic complaints, detachment, anger, and changes in belief

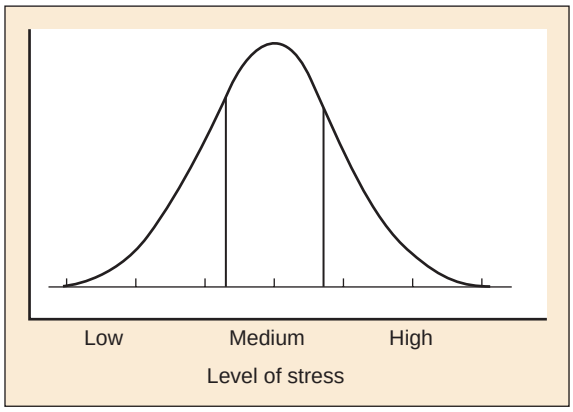

Fig. e13.1. The Yerkes-Dodson human performance and stress curve. (Yerkes RM, Dodson JD: The relation of strength of stimulus to rapidity of habit-formation. J Compar Neuro Psych 18:459-482, 1908.)

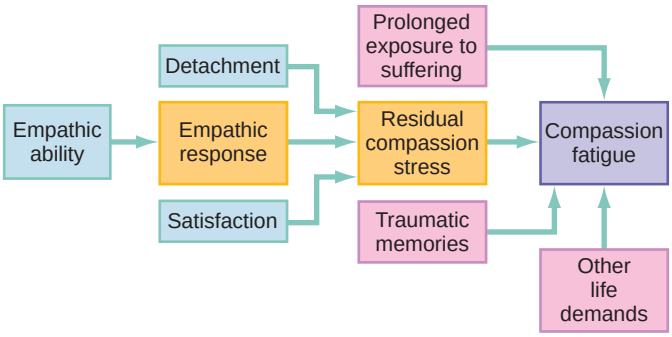

Fig. e13.2. Model of compassion fatigue. (Modified from Figley CR: Compassion fatigue as secondary traumatic stress: an overview. In Figley CR, editor: Compassion fatigue: coping with secondary traumatic stress disorder, New York, 2005, Bruner/Mazel.)

systems, which is similar to post-traumatic stress disorder (PTSD).[19] Recent studies have shown that compassion fatigue impacts both residents and attending residents in emergency medicine and may influence the desire of attending residents to seek early retirement.[19,20]

Resilience

Resilience is defined as the process of adapting well in the face of adversity, trauma, or significant stress; it is an antidote to stress.[21] Multiple studies, including those of at-risk youth and survivors of the September 11, 2001, terrorist attacks, support that resilience is ordinary, not extraordinary. It is a characteristic that can be cultivated and supported by an appropriate environment. Four main aspects of physician resilience include: (1) attitudes and perspectives, which include valuing the physician role, maintaining interest, developing self-awareness, and accepting personal limitations; (2) balance and prioritization, which include setting limits, taking effective approaches to continuing profession development, and honoring the self; (3) good practice management style; and (4) supportive relations, including positive personal relationships, effective professional relationships, and good communication.

CONSEQUENCES OF LACK OF WELLNESS AND THE IMPAIRED PHYSICIAN

Lack of wellness and resilience of emergency clinicians can have a significant impact on the care that they provide and the health care system as a whole. Stress, job dissatisfaction, and burnout have been shown to negatively impact quality of care and patient safety. Firth-Cozens and Greenhalgh examined physicians' perceptions of the connection between work-related stress and patient care. Physicians perceived that work-related stress led to reduced standards of patient care (eg, taking shortcuts and not following procedures), increased irritability and anger at work, and increased errors related to patient care.[11] Burnout is also associated with reduced workplace productivity due to increased absenteeism, job turnover and early retirement, probability of ordering unnecessary tests, and decreased time with patients.[2]

At the far end of the spectrum of physician lack of wellness is physician impairment. The Federation of State Medical Boards defines an impaired physician as one who is unable to practice medicine with reasonable skill and safely due to mental or physical illness; due to a condition that adversely affects cognitive, motor, or perceptive skills; or due to substance abuse. Substance abuse has been described as a direct consequence of work stress and burnout for physicians.[8]

WELLNESS STRATEGIES

Lack of wellness is a major problem for emergency clinicians and one that can have a huge impact on their personal lives, their families, the profession, and the health care system. Although there is a growing body of literature on the problem of burnout and compassion fatigue, the research surrounding how to address these problems is still in its infancy. What little literature does exist supports a multifaceted approach to the problem at the institutional, professional, and personal levels.[16] The focus should be on preventing burnout and impairment, not just on identifying the impaired clinician and providing treatment.

Hospitals and other institutions could benefit from recognizing the impact of burnout and make wellness a priority. Studies have suggested that metrics for institutional success should include physician satisfaction and wellbeing.[2,22] Tools exist to assess physician wellness and satisfaction at a systems-level; instruments have also been developed that measure the overall health of an organization. The development of wellness committees, not just to deal with impaired physicians, but to monitor and respond to such metrics, have been successful at institutions, including Stanford University and the Permanente Medical Group of Kaiser Permanente.[23] Many health care systems recognize that physician wellness is related to creating an efficient and fulfilling practice environment. Some have made "Physician Quality of Life" a regular agenda item at their medical executive, departmental, and board of trustee meetings.

Incorporation of mindfulness and teamwork training for physicians has also been recommended by some research. A study by West and colleagues found that a 9-month bi-weekly 1-hour facilitated discussion group incorporating elements of mindfulness, reflection, and shared experiences improved work meaning and engagement and reduced depersonalization even 12 months after the intervention.[23] The physical health of physicians has also been the focus of some institutions. A study out of the Mayo Institute demonstrated that an incentivized exercise program increased physical activity and quality of life for residents and fellows who participated in the program versus those who did not.[24] When more than 2000 physicians were asked how their institution could help with stress and burnout, the top requests included the following: more ancillary support to help with charting (eg, scribes); onsite exercise facilities or classes; wellness initiatives; and education on managing stress and burnout.[18]

Institutions can also provide monitoring programs for at-risk physicians and should have resources to help impaired physicians. Physicians themselves are not especially good at detecting their own burnout or impairment. Employee assistance programs or wellness committees can serve this role. Referral to state

impaired-physician programs may also have a role in helping physicians salvage a career threatened by impairment or addiction. Programs to detect and treat physician impairment exist in every state of the United States.

Professional

Multiple studies have identified the fact that burnout and increased rates of depression begin early in the professional development of physicians, with rates of depression and burnout increasing as early as the third year of medical school.[25-28] This has led to a call for early education in wellness and stress management for medical students and residents. A few medical schools have experimented with wellness programs, and some success has been observed with interventions such as self-development groups and the respiratory one method for relaxation.[26]

Wellness interventions in emergency medicine residency programs are less well-studied. The core content of emergency medicine includes wellbeing curriculum topics, including fatigue and impairment, time management/organizational skills, work/life balance, and work dysphoria (burnout). Some emergency medicine residency programs have developed wellness initiatives, including faculty mentors, big sibling programs, yearly retreats, self-reflection exercises, monitoring of wellness (eg, administration of the Maslach burnout scale and Jefferson Empathy Scale), mindfulness programs, compassion practices, and stress management programs.

As important as early education in wellness is, continuing education in wellness and stress management are equally important. Professional organizations should be at the vanguard of this mission. The American College of Emergency Physicians (ACEP) provides several lectures at their annual conference with regard to physician wellness and also provides wellness activities, including the Wellness Booth. ACEP has an online Wellness Handbook (updated in 2015) with every chapter devoted to different aspects of avoiding burnout and promoting wellness.

Personal

As important as institutional and professional responses to the wellness crisis in medicine are, the commitment to wellness ultimately is the responsibility of the individual physician. The majority of physicians enter the practice of medicine with an authentic desire to care for and heal fellow human beings. This initial altruistic desire can be eroded by the stress of training and the reality of the current health care environment. To adequately address the issue of wellness, physicians need to recognize that they are an important resource that needs nurturing and care.[27]

As with any procedural skill, physicians must look at the skills needed to remain emotionally and physically well. Self-care is essential and necessary for physicians to continue to show up and be present for the needs of their patients. At the very basis of self-care is the apparently obvious, but at times difficult to obtain, measures of getting enough sleep, obtaining adequate exercise, and adhering to a healthy diet. Time off that allows for reconnection with the aspects of life that are important to the individual is also essential.

A good personal practice is to self-monitor wellness on a regular basis. This can be done in many ways, including measuring one's level of burnout, empathy, and level of satisfaction using established tools, such as the mini-Maslach, Jefferson empathy score, and/or the Adult APGAR score, all of which are available online. By tracking one's responses on a regular basis, any drift toward burnout can be noted and serve as notice to pay more attention to self-care and wellness.

Frequently reassessing life priorities assures that one is making choices and living life in a manner aligned with what is personally important. Self-monitoring should occur on a regular basis (every 6 months to 12 months), as well as with any major life change (marriage, birth of a child, change of workplace, and so on).

A sense of connection with a community, whether it is with colleagues, family, or friends is important, because isolation is a key component related to lack of wellness and burnout. Mindfulness and compassion practices can further enhance physicians' resilience to burnout (Boxes e13.1 and e13.2).

Identifying specific and simple strategies to help emergency clinicians remain well is crucial to decreasing the frequency of burnout and compassion fatigue and, consequently, to the future of the specialty. Some of these tactics employed to maintain wellness include:

1. Be clear about what you want: Take time to write a personal mission statement. Too often a physician is not clear about priorities and what is important to him/her. There are many examples online of how to write a personal mission statement. Priorities may be educational, financial, oriented toward special interests or hobbies, family-oriented, or oriented to others. Writing down the list and putting them in order of importance will prevent the feelings of: "Where did all the time go? This is not what I really wanted."
2. Join a group/find a practice where you are treated as a person, and feel appreciated. The best work environments are places that feel like both a family and a school—a family in the sense that people feel supported and surrounded by like-minded colleagues and a school in that people feel that they can continue to grow and expand their capabilities. Ensure that the group you join supports your strengths and helps you grow through your opportunities.
3. Make sure you create a renewal investment plan. Almost all physicians have a financial plan and an investment advisor,

BOX e13.1

Example of a Mindfulness Meditation Practice

MINDFULNESS MEDITATION

Find a comfortable seated position. Allow your spine to lengthen. If it is comfortable for you, close your eyes. Rest your hands on your knees or thighs. Take notice of your breath without attempting to change it. You might find it easiest to notice your breath as it comes in an out at your nostrils, or you may find it easier to be in touch with your breath as your belly rises and falls. Whatever technique works best for you, use your breath as an anchor to keep you present in the moment. It is natural that your mind will continue to have thoughts. When you notice yourself being carried away by your thoughts, just say to yourself, "thinking" without judgment and return to your breath.

Try this practice initially for 5 minutes, and try to increase it to 20 to 30 minutes a day.

BOX e13.2

Example of Compassion Meditation Practice

COMPASSION PRACTICE

Take a comfortable seat, and tune into your breath for several minutes. Once you feel grounded, begin by focusing on a beloved one. Picture them in your mind and say silently to them, "May you be happy, may you be healthy, may your life be easy," or similar phrases that convey similar wishes to your beloved. Next send similar wishes to yourself, a neutral person in your life (eg, the grocery clerk, a person you pass on the street, and so on), someone who you have difficulty with in your life, and then to all sentiment beings.

yet few have a formal renewal investment plan where they write down a specific action-oriented stepwise approach to remaining well.

4. Exercise regularly, eat right, and sleep more. Optimal exercise is 3 to 5 times a week for at least 45 minutes, and daily exercise does not have to be at one time (45 minutes can be split 15/15/15 depending on availability of time). No one diet is right for everyone, and breakfast is an important meal. If sleep is less than 6 hours a night, there is a 48% increase in the risk of heart disease and a 15% increase in the risk for stroke. Set an alarm for when it is time to go to bed, not just when to wake up.
5. Be more than just a shift worker. Physicians who contribute to their specialty, who become integral to the social fabric of their medical staff, and who attend their department meetings, develop a greater sense of control over their workplace and a greater sense of contribution to their community.
6. Help create your team. Ask colleagues and staff: "What can I do to help you have a great day in working with me?" Say *thank you* more. It takes three compliments to one criticism to create a positive work environment.
7. Take time away from the electronic interface. To truly let down, it is necessary to disconnect from electronic devices. This is important on days off and especially important on vacations.
8. Take more deep breaths. As mentioned previously, there are mindfulness techniques that can help physicians stay balanced even while in the chaotic highly stressed ED environment.
9. Stay connected to why you decided to do what you are doing, to others, to your spirit. Most physicians entered the profession to make a difference in people's lives. This connection has to be remembered. The human connection is crucial to the healing process and to remaining well when giving care.
10. Practice gratitude. Every morning wake up and say thank you for something, even if it is just the opportunity to be present for another day. Consider keeping a gratitude journal where you write each day what you are most thankful for.
11. Spend time in nature every day (or as often as possible). Most EDs are boxes with no windows or exposure to the outside world. We need, as human beings to experience the sun, rain, and wind and to stay connected to the natural world around us.
12. Laugh every day. Laughter is truly great medicine. Spend time with people who make you happy or enjoy a movie, book, or Internet site that elicits laughter.
13. Hug and touch often. Human touch is paramount to health, wellness, and happiness. We live in a world and profession where the importance of touch has been minimized, and where there is even fear of touching due to concerns about it being inappropriate. Remember that human babies will die if they are not touched, so reach out to those who you are comfortable with (family, friends, your children, and so on) and share the power of physical connection.

KEY CONCEPTS

- Stress is a part of the human experience. The practice of emergency medicine, because of its unpredictable and chaotic nature, and because matters of life and death occur every shift, includes more stressors than most other professions.
- Emergency clinicians experience high rates of burnout and compassion fatigue, which threatens the future of the specialty.
- The approach to preventing burnout and promoting resilience must be multifaceted and involve institutional, professional, and personal strategies. Only by being specific and concrete in proactively creating a more supportive, efficient, and fulfilling work environment will health care institutions be successful in promoting physician wellness.
- At the departmental level, emergency medicine leaders should educate physicians, whether in practice, in residency, or in medical school, to cultivate resilience to meet the challenges that they will face.
- Emergency clinicians should take personal responsibility and develop the skills that they need to have long and satisfying careers in emergency medicine.

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